Supporting Information for:

Direct access to vicinally functionalized and N-trifluoroacetylated (bicyclic)ketopiperazines using a readily affordable N-heterocyclic anhydride

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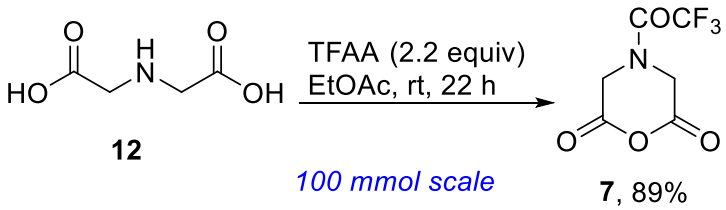
Contents:

2. Experimental Section

All experiments involving air and moisture sensitive reagents such as palladium precatalysts and 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 $KMnO_4$ stain. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using DMSO-d_6, CD_3OD or $CDCl_3$ as 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).

General Procedure A: Synthesis of anhydride 7



To an oven-dried 500 mL round bottomed flask equipped with stir bar was added diacid **12** (13.30 g 100 mmol, 1 equiv) and dry ethyl acetate (250 mL). Trifluoroacetic anhydride (30.8 mL, 220 mmol, 2.2 equiv) was added slowly under nitrogen. The cloudy mixture was stirred at room temperature for 22 h (as judged by TLC and GCMS). The mixture was concentrated under reduced pressure and washed three times with ice-cold petroleum ether to afford the anhydride, which was used without further purification.

General Procedure B: Cycloaddition with anhydride 7

A 5 mL screw-cap vial was flame-dried, evacuated and flushed with nitrogen. A solution of the lactim ether/imidoyl chloride/amine/azadiene (1.0 mL, 0.10 M in freshly distilled toluene) was added to the vial at room temperature followed by anhydride **7** (1 equiv). The contents were placed in a pre-heated oil bath thermostatted at the desired temperature (usually 100 °C). After complete conversion (as judged by TLC and NMR), the mixture/suspension was cooled to room temperature

and washed several times with petroleum ether, then concentrated under reduced pressure to afford the crude cycloadduct.

Methyl esterification of cycloadduct

To a stirring suspension of the acid (1 mmol), dissolved in DMF (5 mL), and K_2CO_3 (3 equiv) was added methyl iodide (2 equiv) under nitrogen atmosphere. The reaction mixture was stirred for about 12 h (TLC monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the desired ester, which was purified by flash chromatography on silica.

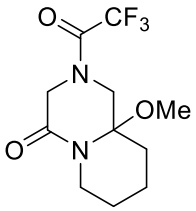
General Procedure C: Vilsmeier-Haack reaction

To a solution of DMF (6 mmol, 6 equiv) in CH_2Cl_2 (5 mL) at 0 ^oC was added dropwise, phosphorus oxychloride (3 mmol, 3 equiv). The resulting pale yellow mixture was refluxed for 40 min. A solution of the lactam (1 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was cooled to room temperature and stirred for the indicated time period (TLC and LC-MS monitoring was used to follow the extent of the reaction). Upon completion, the mixture was poured into a large flask containing crushed ice. After stirring at rt for 60 min, the layers were separated. Powdered K_2CO_3 was added slowly to the mixture and the flask was swirled after each addition (***Caution***: it bubbles vigorously). The addition/swirling was continued until persistent cloudiness was observed. The neutralized/slightly basic mixture was extracted three times with CH_2Cl_2 and washed with brine. The combined organic layers were dried over Na_2SO_4 for 30 min. The mixture was filtered and concentrated under reduced pressure to give the desired product as an oil.

General Procedure D: Catalytic hydrogenation

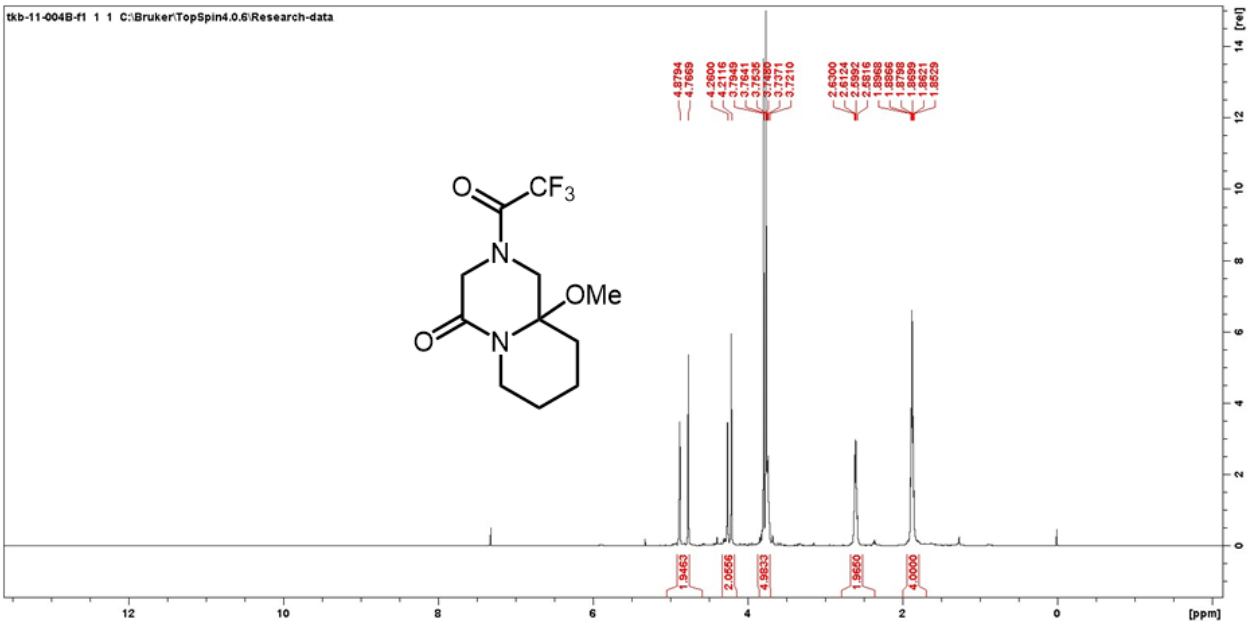
EtOAc (10 mL) was added to a flask containing 10% Pd/C (100 mg) at room temperature. The flask was degassed and placed under an inert atmosphere of nitrogen. A solution of the unsaturated lactam in EtOAc (10 mL) was added. After complete addition, the nitrogen line was cut off and then replaced with a balloon of hydrogen. After complete consumption of the unsaturated lactam (based on LC-MS and TLC monitoring), the mixture was filtered through a plug of Celite and concentrated under reduced pressure.

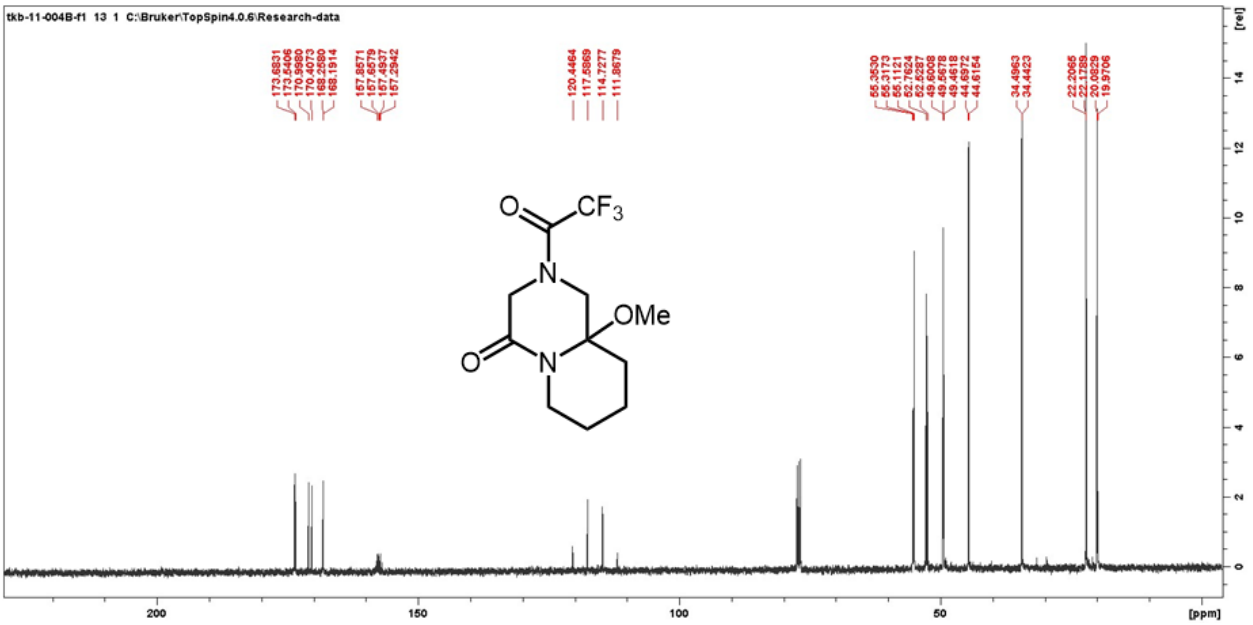
Reaction with lactim ethers



8a, 88%

Prepared from **2a** (113.3 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. T = 110 ºC, time = 22 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 247 mg, 88%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.67 (d, *J* = 1.6 Hz, 1H), 4.56 (s, 1H), 4.08 – 4.03 (m, 2H), 3.63 – 3.49 (m, 5H), 2.45 – 2.36 (m, 2H), 1.73 – 1.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.69, 173.54, 171.00, 170.41, 168.26, 168.20, 157.86, 157.66, 157.50, 157.30, 156.93, 120.45, 117.59, 114.73, 111.87, 55.36, 55.32, 55.12, 52.77, 52.53, 49.61, 49.57, 49.47, 44.70, 44.62, 34.50, 34.45, 22.21, 22.18, 20.09, 19.98. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{11}H_{15}F_3N_2O_3$ 280.1035; found 280.1042.

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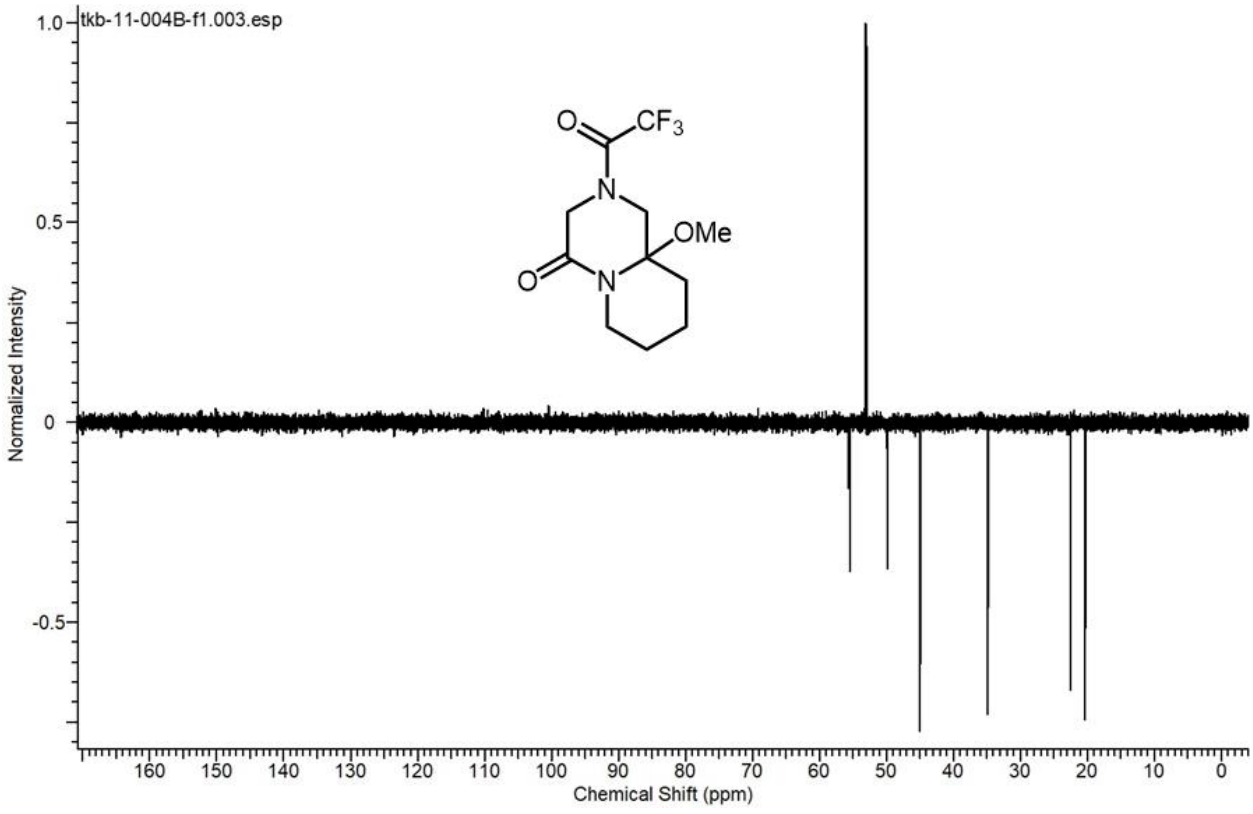
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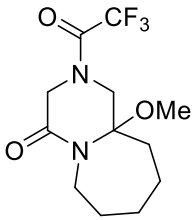
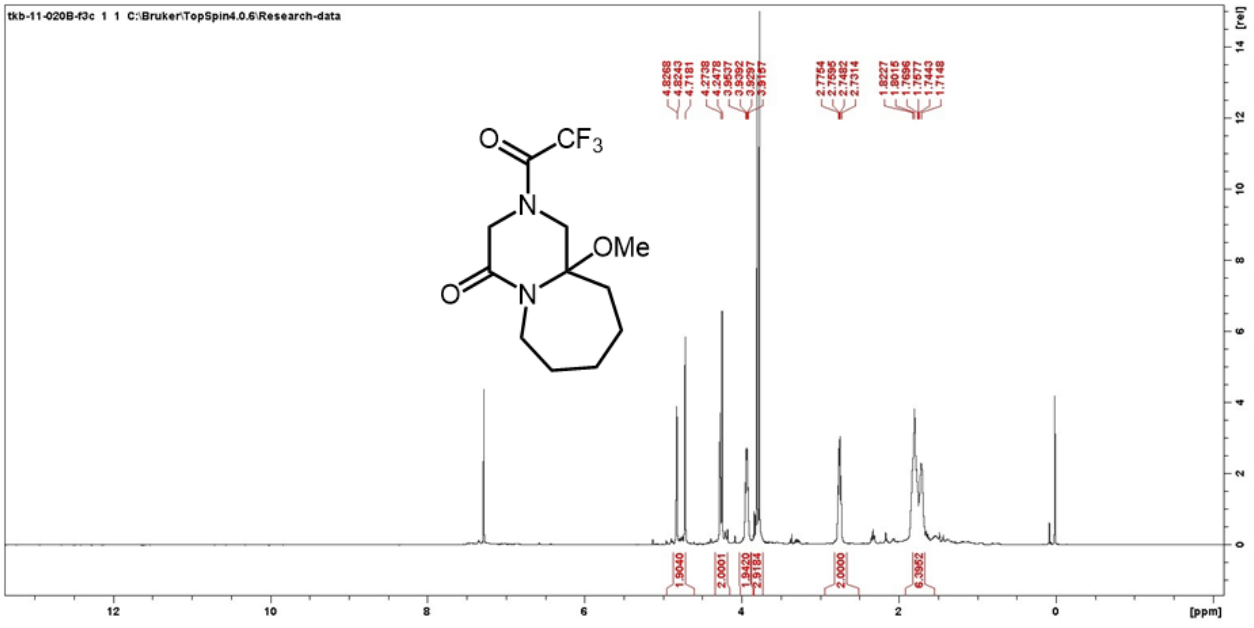
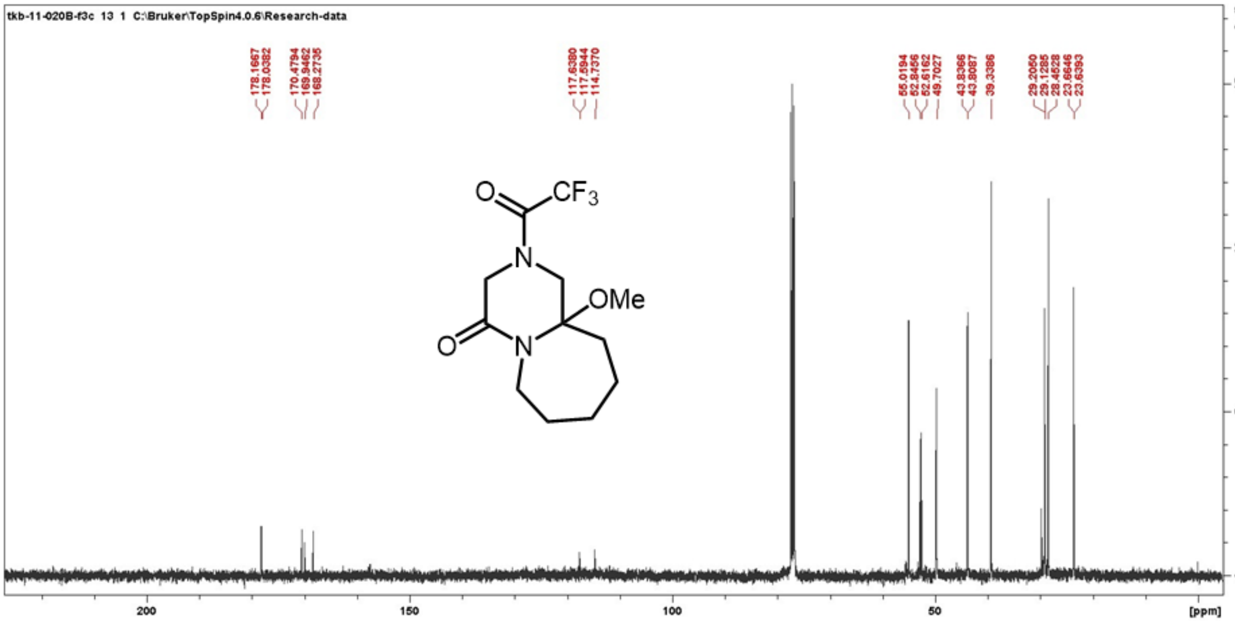


8b, 83%

Prepared from **2b** (127.5 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. T = 110 ºC, time = 22 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 244 mg, 83%. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 4.66 (s, 2H), 4.13 – 3.99 (m, 2H), 3.77 (q, J = 5.5 Hz, 2H), 3.62 (s, 3H), 2.58 (m, 2H), 1.70 – 1.64 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.17, 178.04, 170.48, 169.95, 168.28, 117.64, 117.60, 114.74, 55.02, 52.85, 52.62, 49.71, 43.84, 43.81, 39.34, 29.80, 29.21, 29.13, 28.46, 23.67, 23.64. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{12}H_{17}F_3N_2O_3$ 294.1191; found 294.1198.

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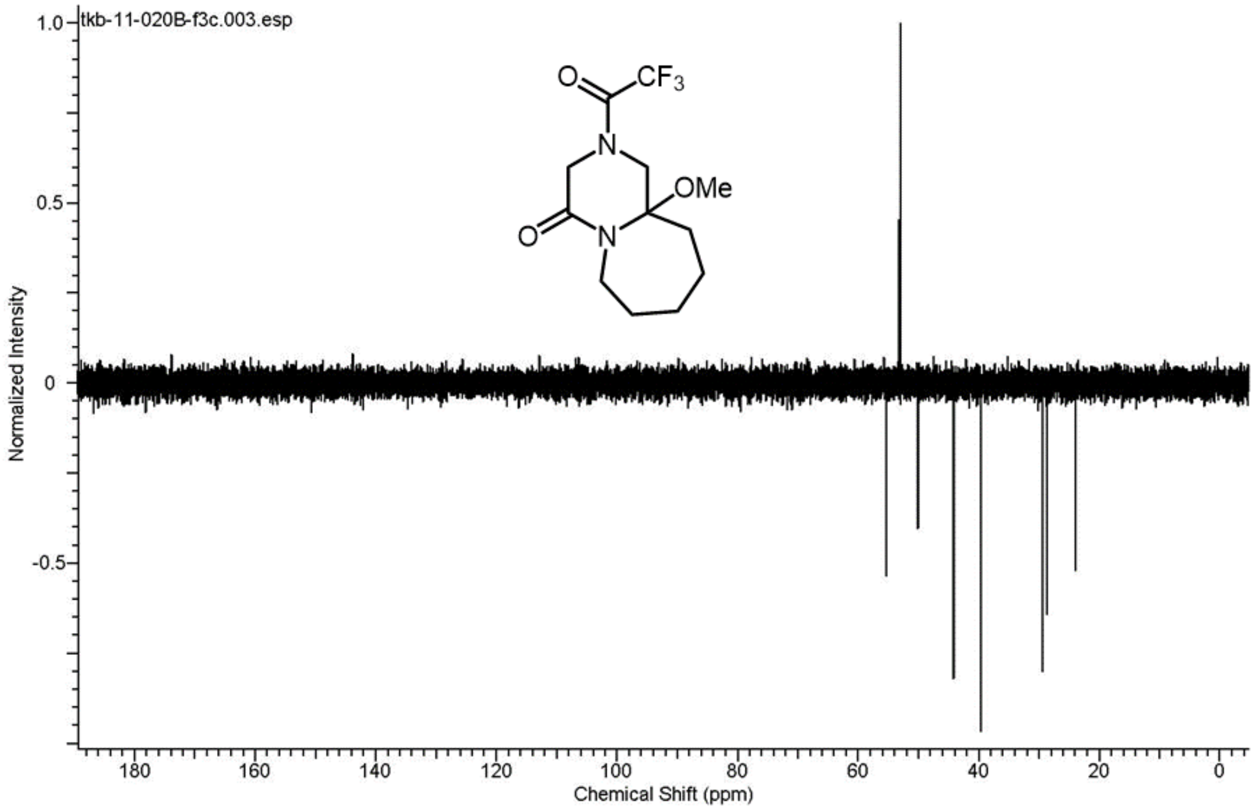
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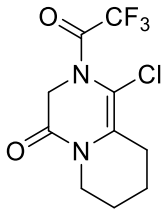
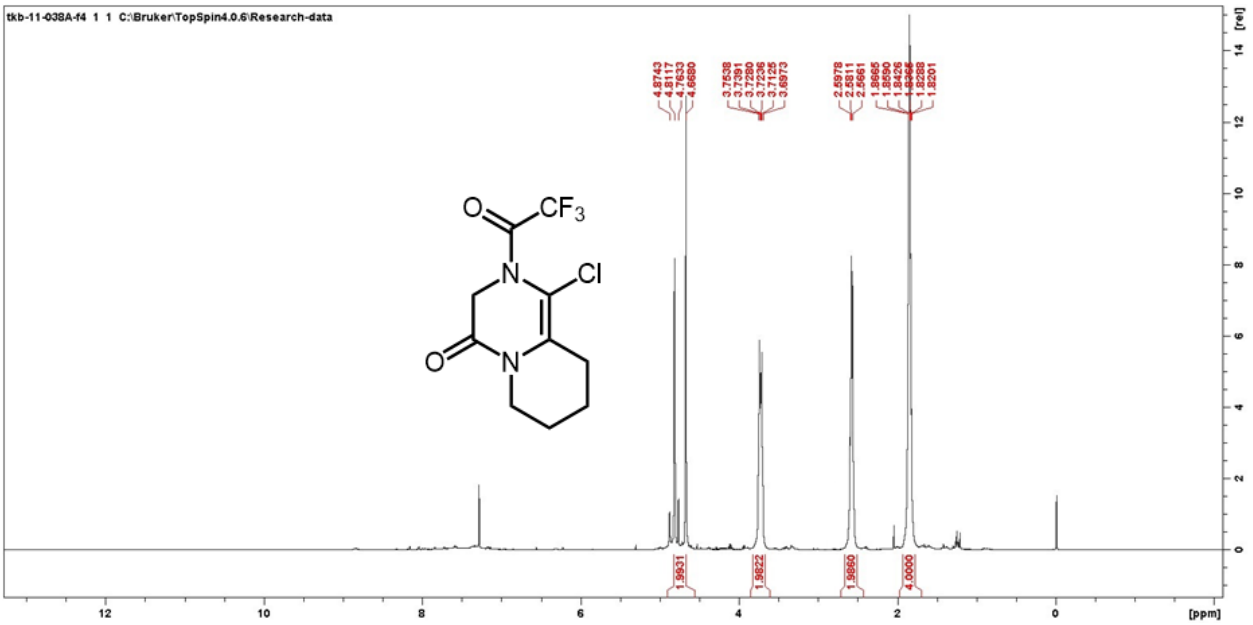
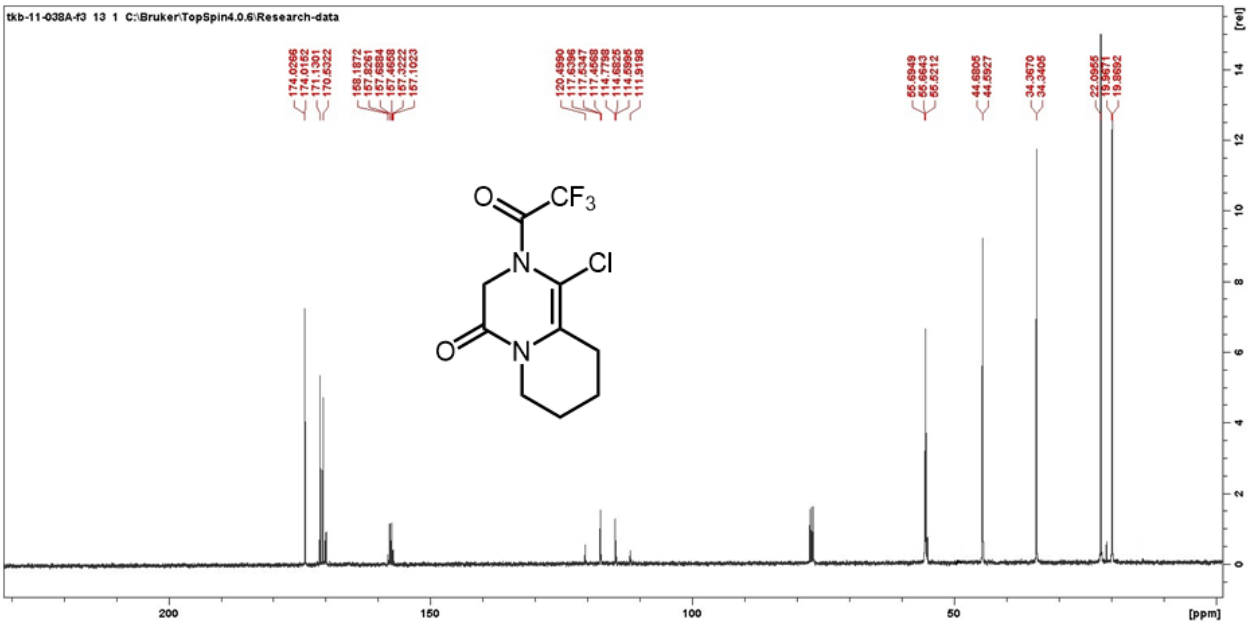


8c, 85%

Prepared from **2c** (117.6 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. T = 100 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 240 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.65 (d, *J* = 1.6 Hz, 1H), 4.50 (s, 1H), 3.57 (dq, *J* = 10.2, 3.5 Hz, 2H), 2.41 (dq, *J* = 7.2, 3.0 Hz, 2H), 1.68-1.60 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.03, 174.01, 171.28, 171.13, 170.54, 170.07, 169.95, 157.83, 157.47, 157.33, 157.11, 120.50, 117.64, 114.78, 111.92, 55.70, 55.67, 55.52, 44.68, 44.60, 34.37, 34.34, 22.10, 22.08, 19.97, 19.87. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{10}H_{10}ClF_3N_2O_2$ 282.0383; found 282.0388.

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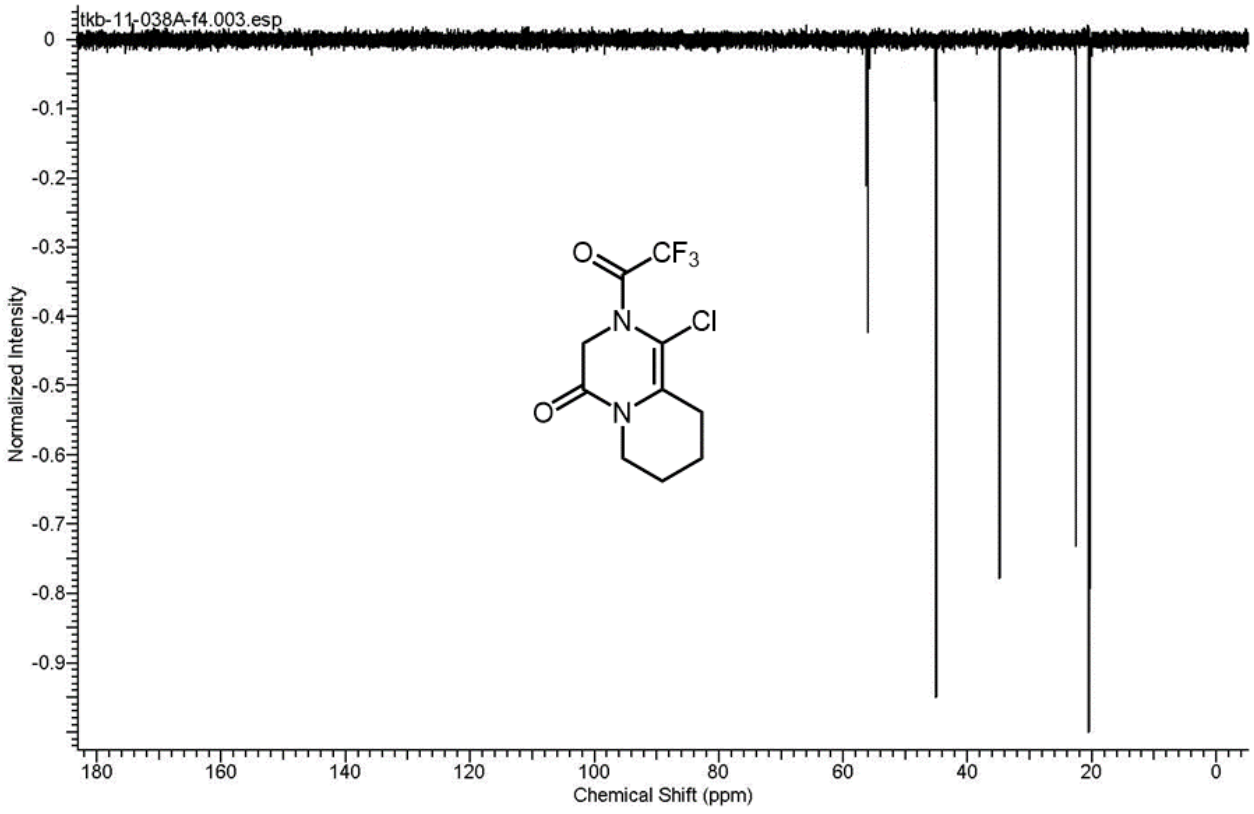
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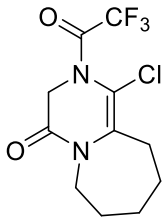
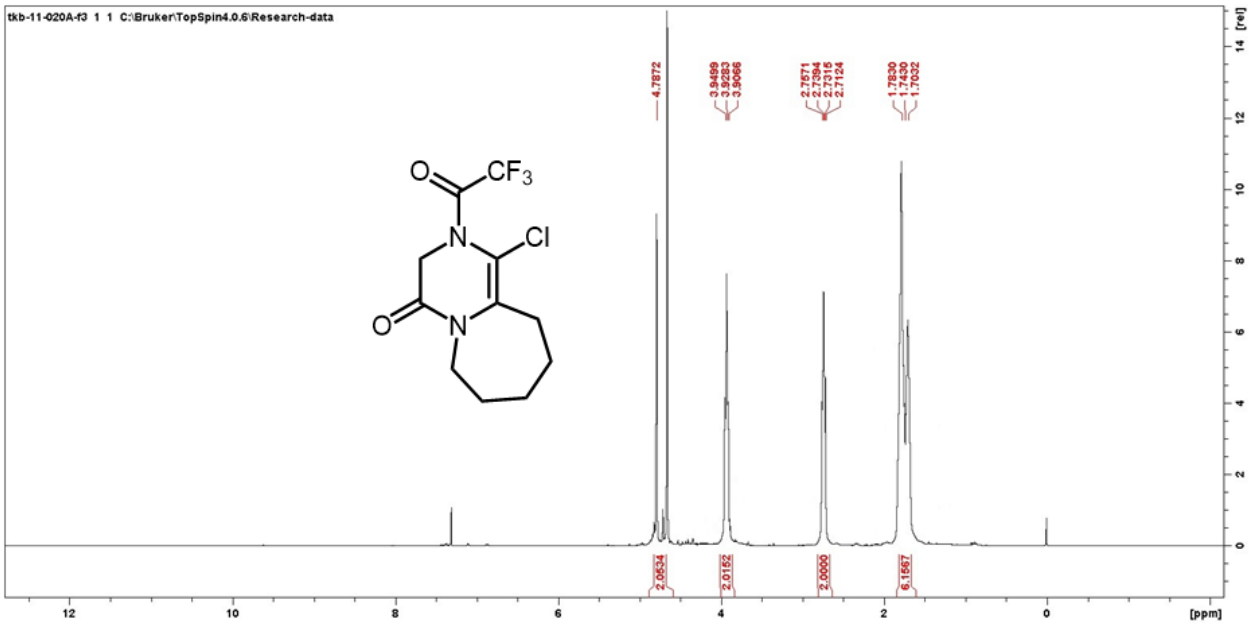
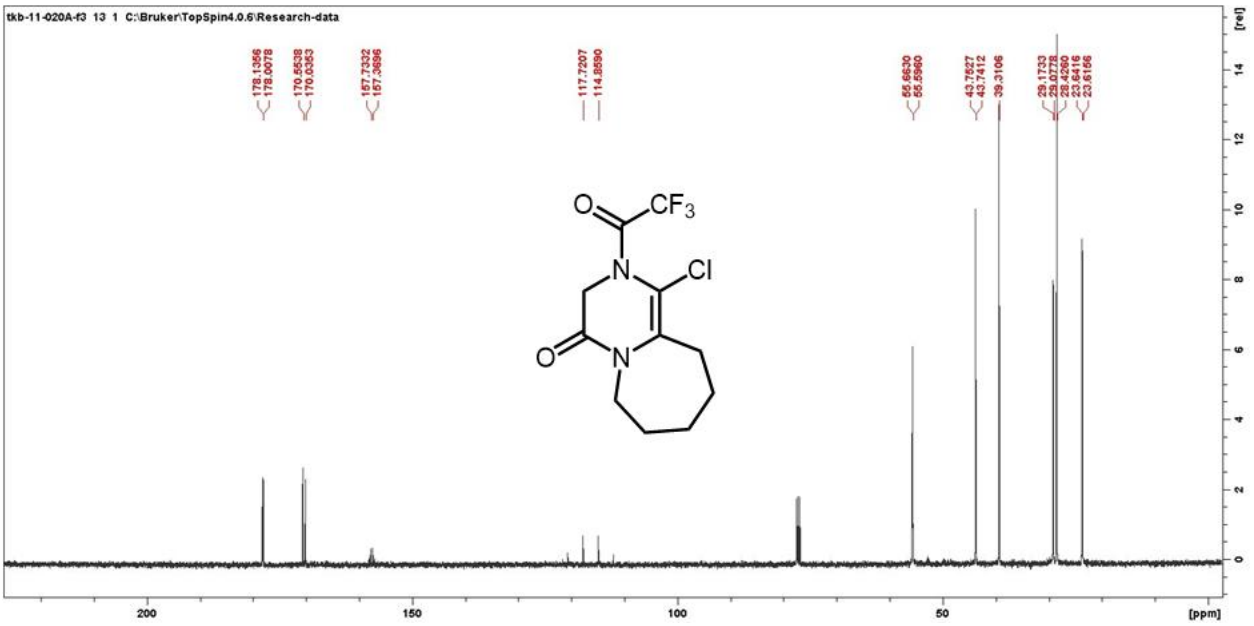


8d, 87%

Prepared from **2d** (131.7 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. T = 100 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 258 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.60 (d, *J* = 1.8 Hz, 1H), 4.47 (s, 1H), 3.78 – 3.68 (m, 2H), 2.55 (dt, *J* = 10.9, 5.5 Hz, 2H), 1.60 – 1.51 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.14, 178.01, 170.56, 170.04, 157.74, 157.37, 120.59, 119.66, 117.72, 114.86, 112.00, 55.67, 55.60, 55.57, 43.76, 43.74, 39.31, 29.18, 29.08, 28.43, 23.65, 23.62. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{11}H_{12}ClF_3N_2O_2$ 296.0539; found 296.0545.

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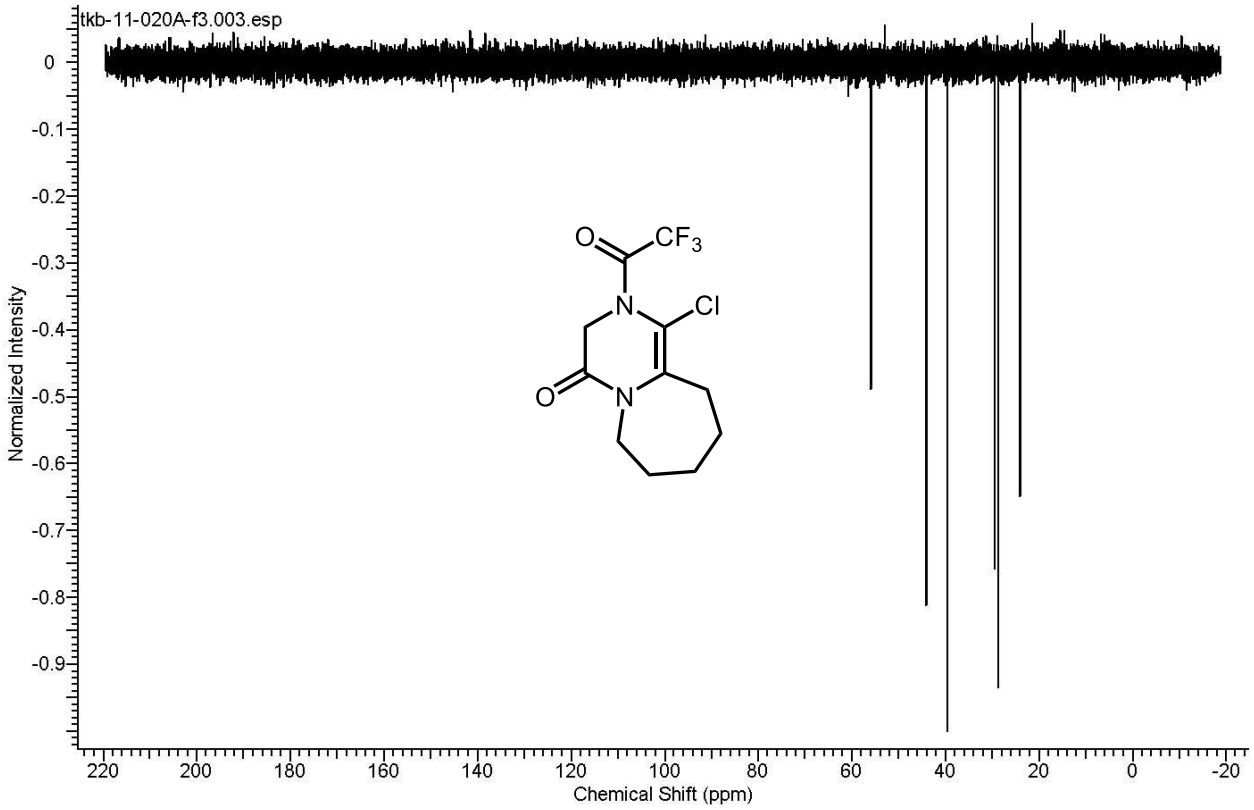
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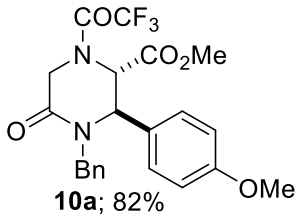
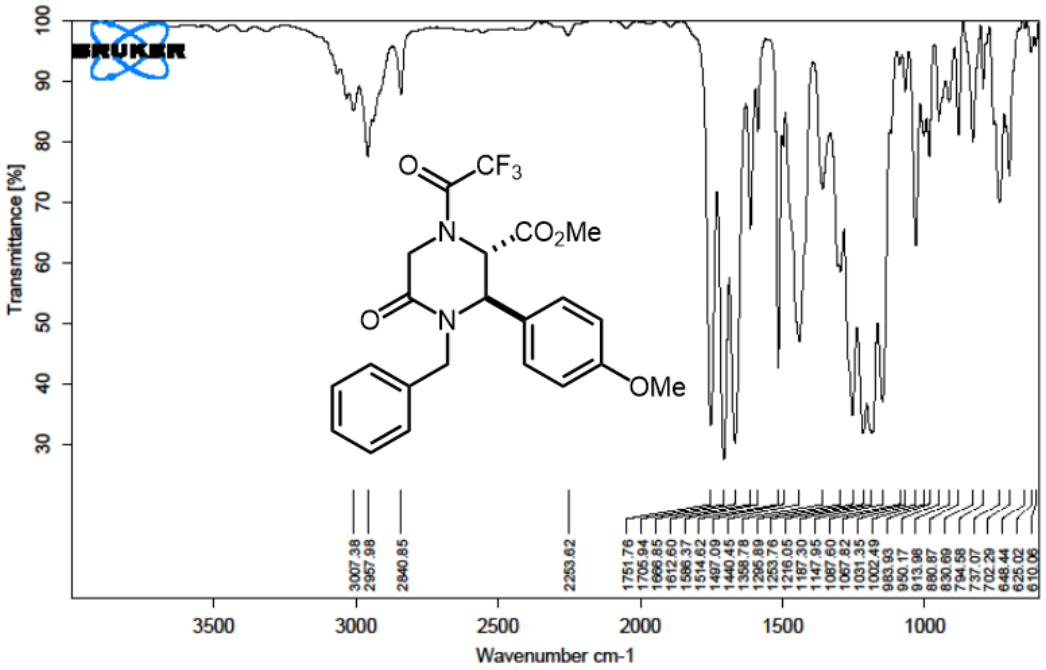


10a; 82%

Prepared from the imine (225 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 369 mg, 82%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.03 (m, 3H), 7.02 (ddd, *J* = 6.8, 4.6, 2.0 Hz, 2H), 6.97 – 6.87 (m, 2H), 6.81 – 6.71 (m, 2H), 5.44 (dd, *J* = 14.5, 11.7 Hz, 1H), 4.77 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.54 – 4.39 (m, 2H), 4.20 – 4.09 (m, 1H), 3.64 (s, 3H), 3.35 – 3.19 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 167.1, 163.8, 162.9, 160.2, 160.2, 157.3, 157.1, 156.7, 156.5, 156.3, 156.1, 155.9, 155.8, 155.4, 135.6, 135.4, 128.9, 128.8, 128., 128.56, 128.4, 128.2, 127.5, 127.3, 127.2, 127.1, 120.1, 119.8, 117.5, 117.3, 117.0, 115.2, 114.9, 114.9 111.5, 111.2, 61.1, 59.1, 58.3, 55.4, 53.2, 53.0, 52.8, 52.6, 48.8, 48.2, 46.6, 46.0. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{22}H_{21}F_3N_2O_5$ 450.1403; found 450.1408.



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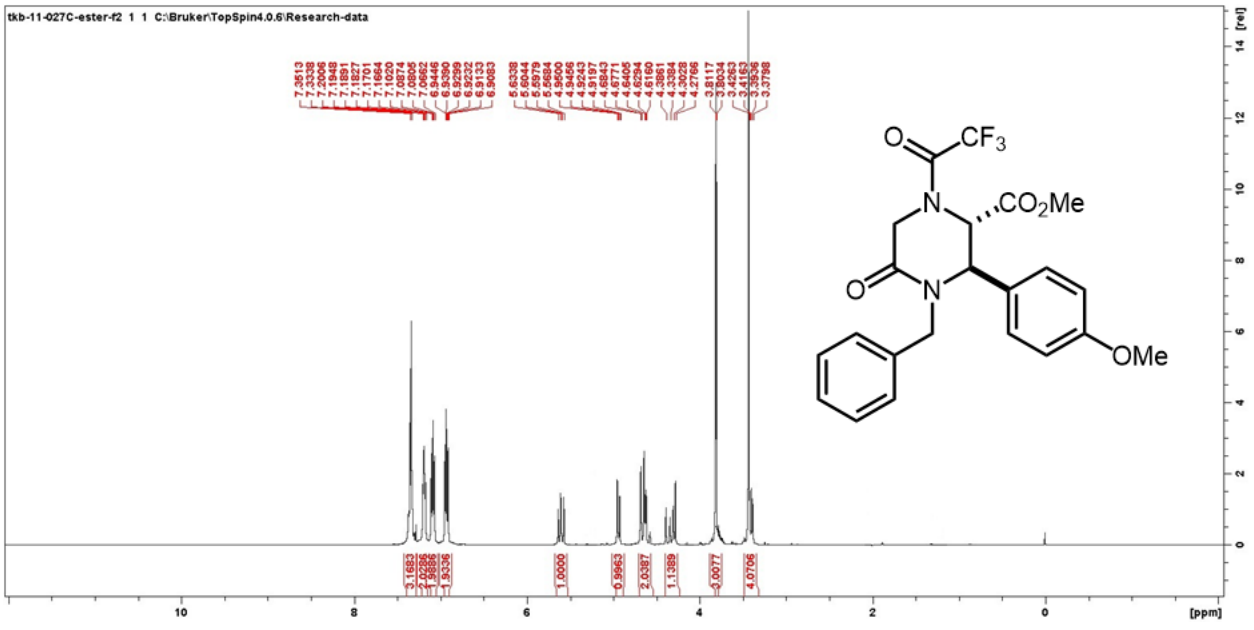

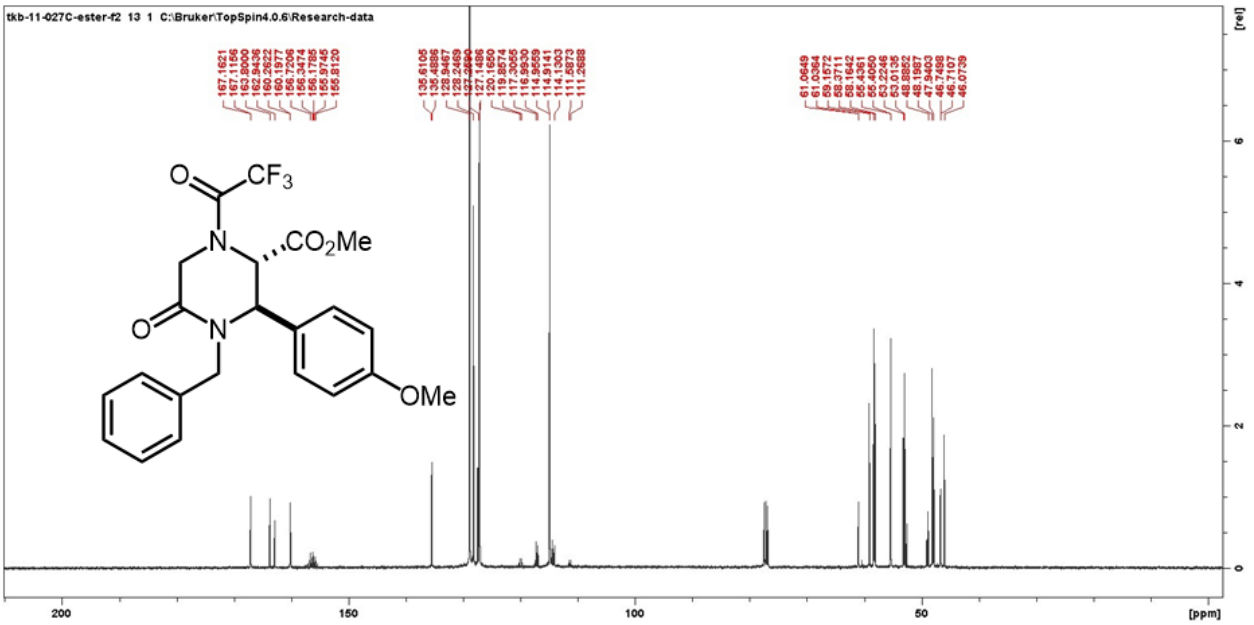
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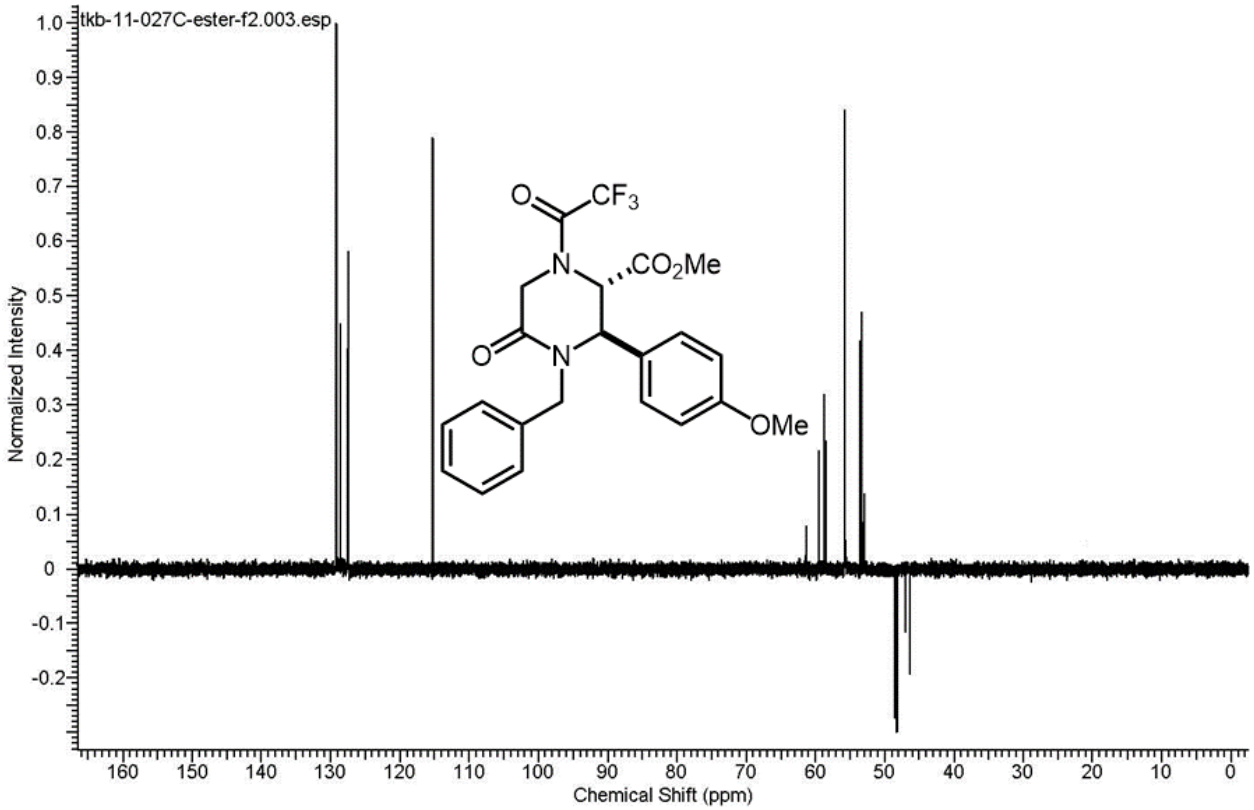
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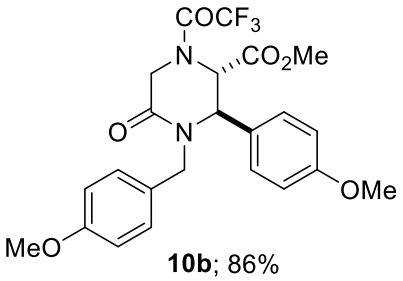

10b; 86%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Yield = 413 mg, 86%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 6.90 – 6.83 (m, 4H), 6.78 – 6.61 (m, 4H), 5.33 (dd, *J* = 14.4, 11.2 Hz, 1H), 4.76 (dd, *J* = 9.2, 2.1 Hz, 1H), 4.52 – 4.34 (m, 2H), 4.14 – 4.06 (m, 1H), 3.70 – 3.51 (m, 6H), 3.27 (s, 3H), 3.18 (dd, *J* = 14.4, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 168.1, 168.0, 167.1, 167.1, 163.6, 162.8, 160.2, 160.1, 159.6, 156.6, 156.2, 156.1, 155.7, 130.2, 130.2, 127.5, 127.5, 127.4, 127.2, 127.1, 127.1, 117.3, 116.9, 114.8, 114.1, 61.0, 58.9, 58.1, 55.3, 55.3, 53.2, 53.0, 52.8, 52.5, 48.9, 47.3, 46.6, 46.0. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{23}H_{23}F_3N_2O_6$ 480.1508; found 480.1514.

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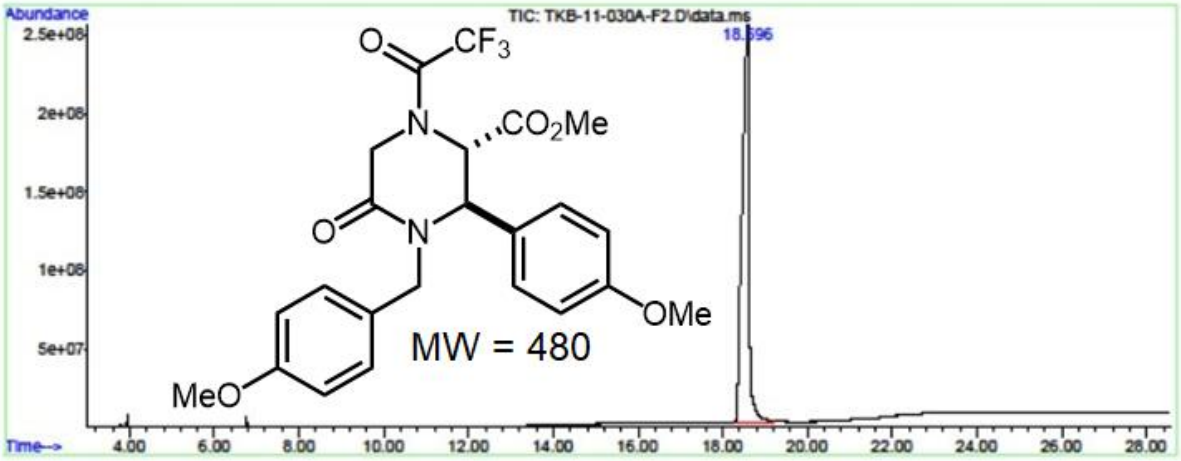

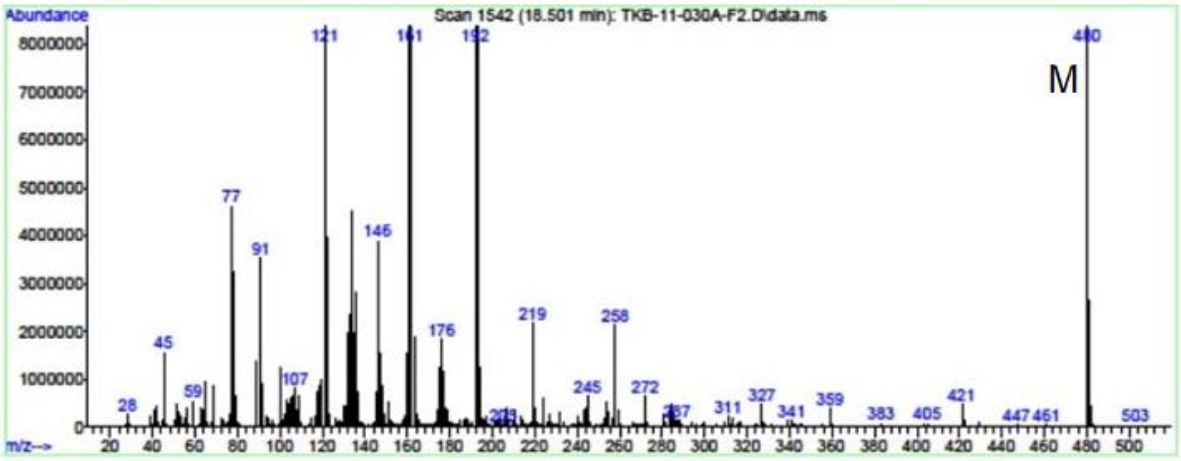

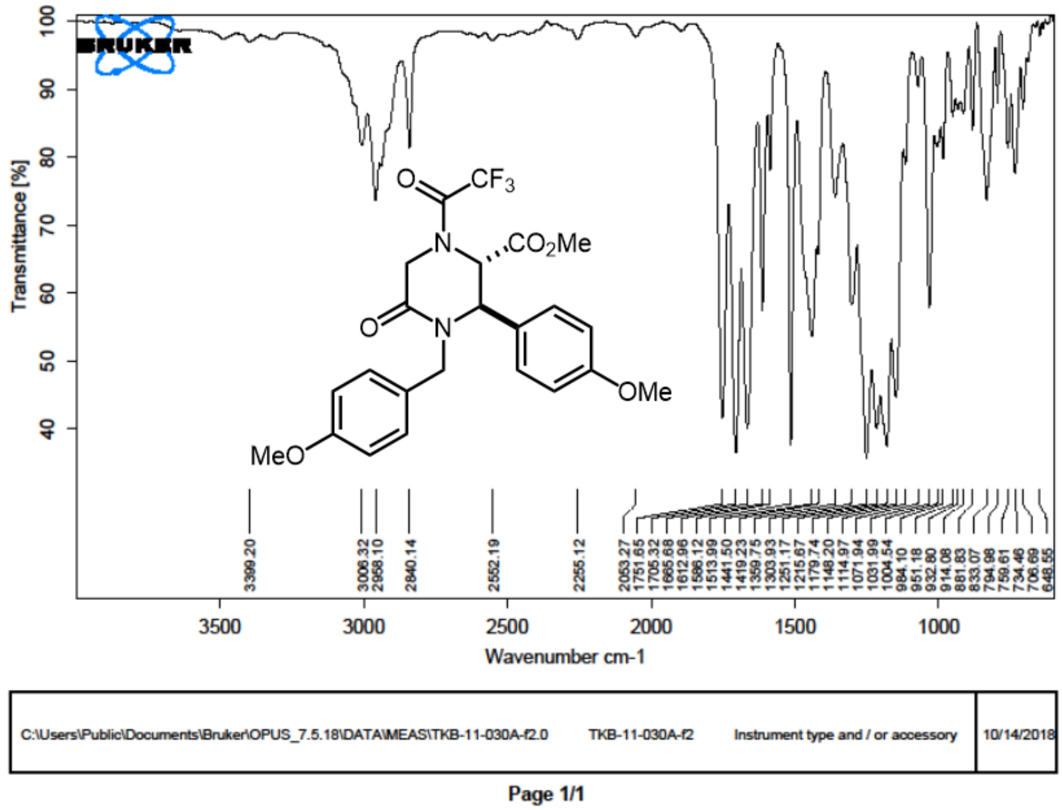

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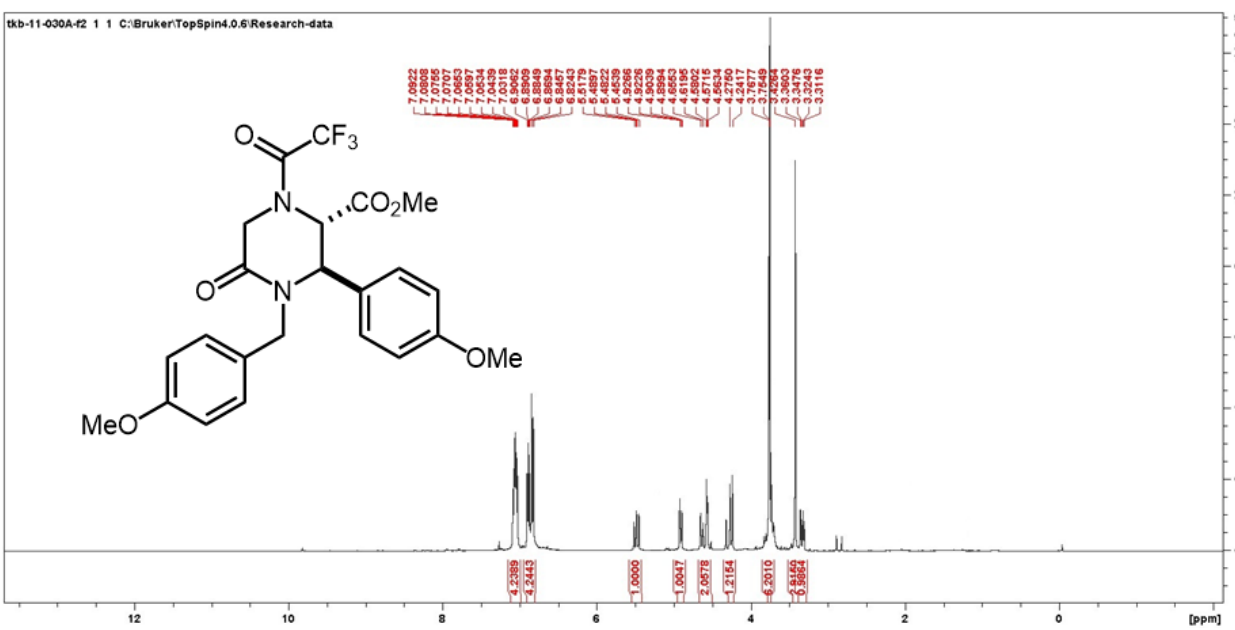
Instrument type and / or accessory
10/14/2018
Page 1/1



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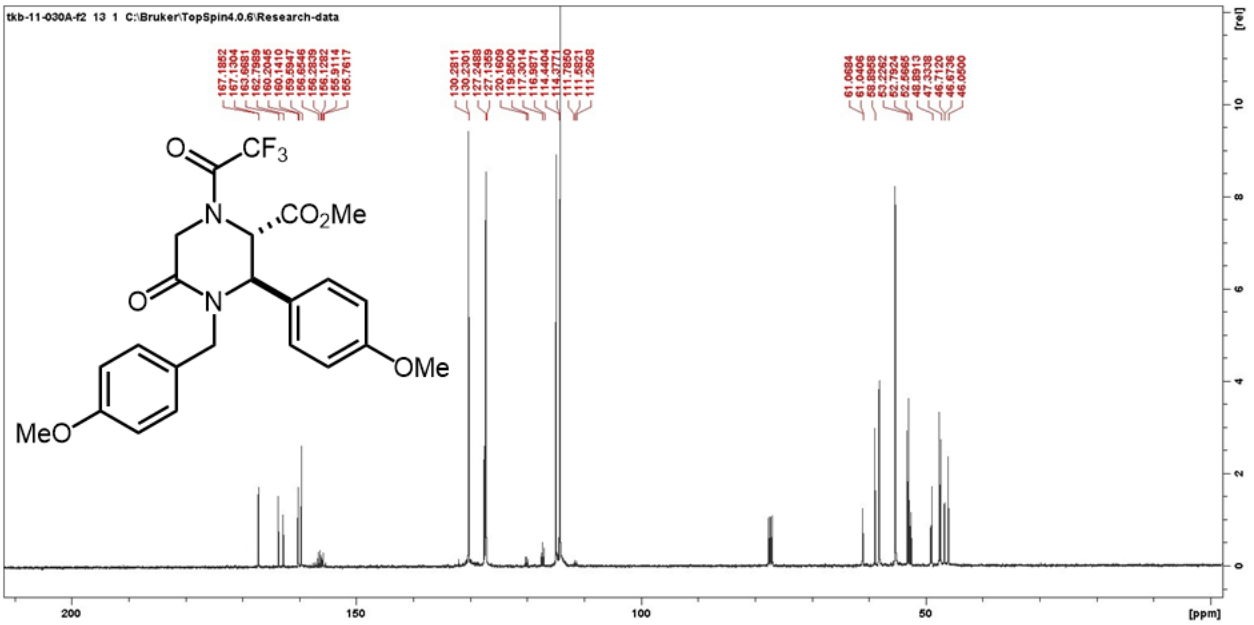
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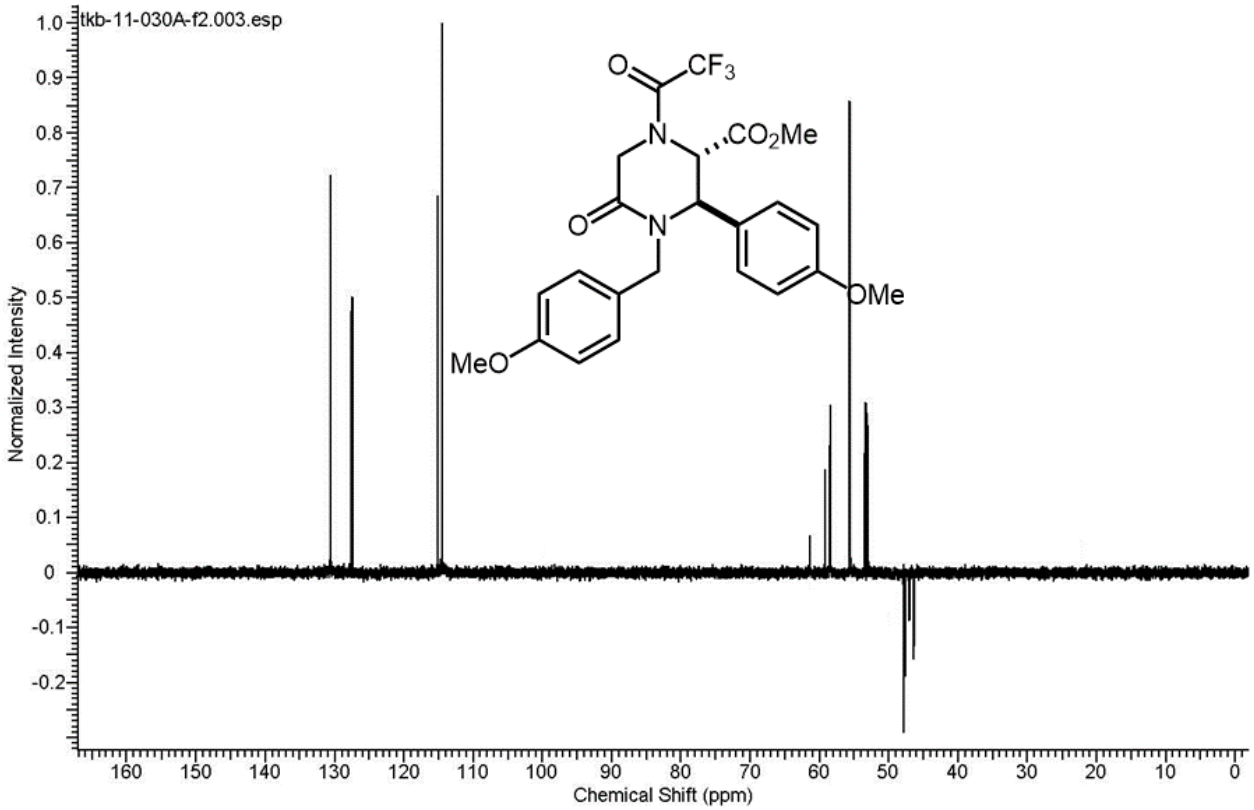
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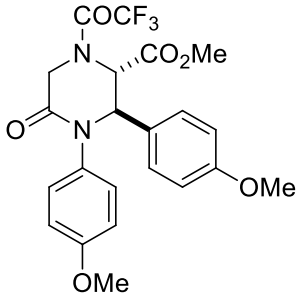

10c; 63%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Yield = 294 mg, 63%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.02 (dd, *J* = 8.7, 3.6 Hz, 6H), 6.93 – 6.83 (m, 2H), 6.81 – 6.71 (m, 2H), 6.75 – 6.61 (m, 2H), 5.31 (dd, *J* = 10.8, 2.3 Hz, 1H), 4.56 (dd, *J* = 18.6, 10.5 Hz, 1H), 4.43 (d, *J* = 17.9 Hz, 1H), 3.73 – 3.60 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.7, 163.7, 162.9, 160.1, 160.0, 159.0, 159.0, 156.7, 156.31, 155.9, 133.2, 133.1, 128.1, 127.8, 127.5, 127.4, 121.6, 117.3, 114.7, 114.21, 114.1, 67.1, 64.8, 63.9, 61.8, 61.7, 58.8, 55.5, 55.3, 54.0, 53.7, 47.1, 46.5. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{22}H_{21}F_3N_2O_6$ 466.1352; found 466.1358.

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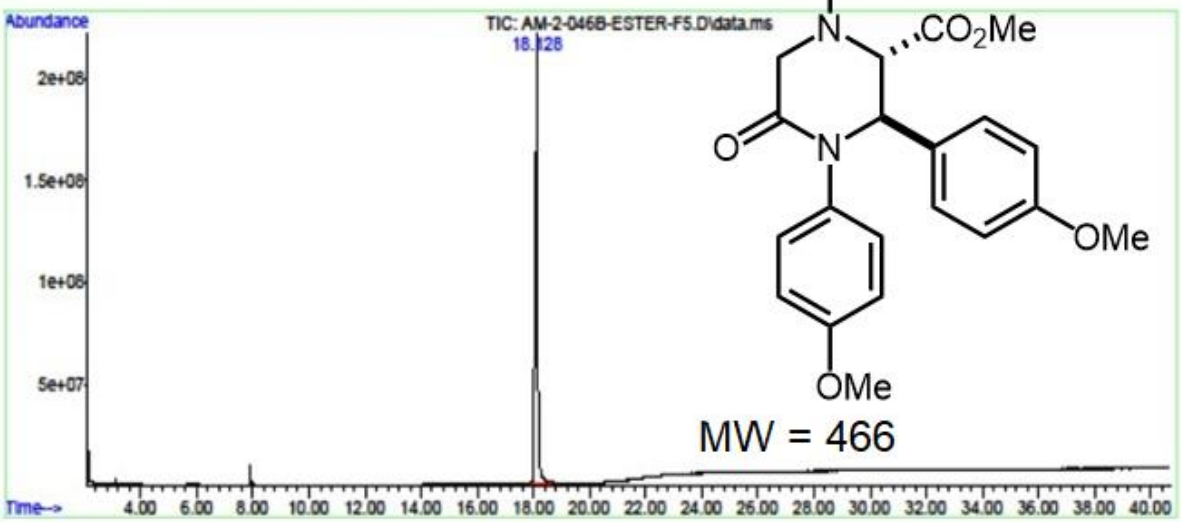

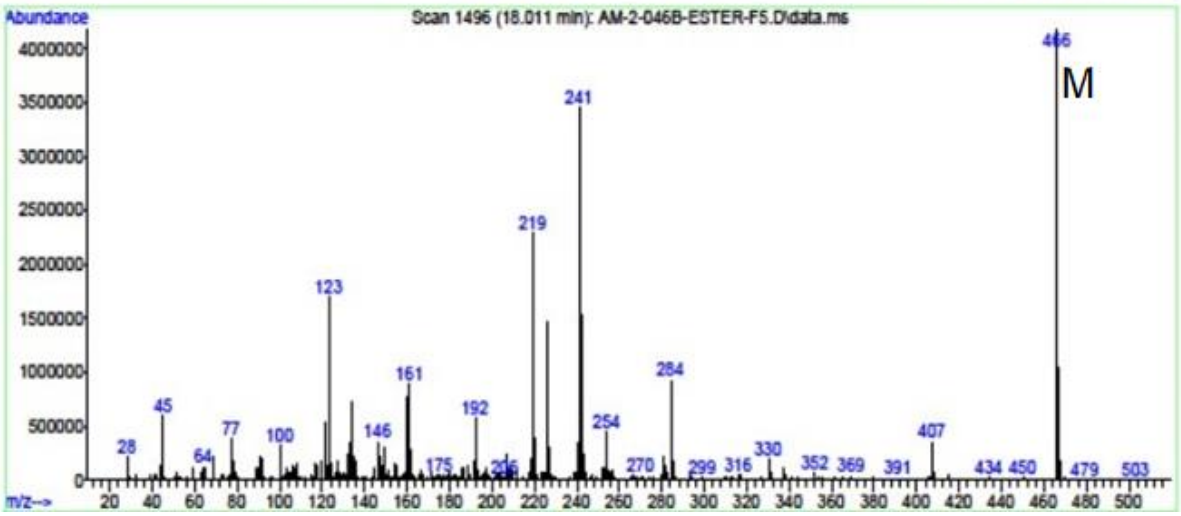

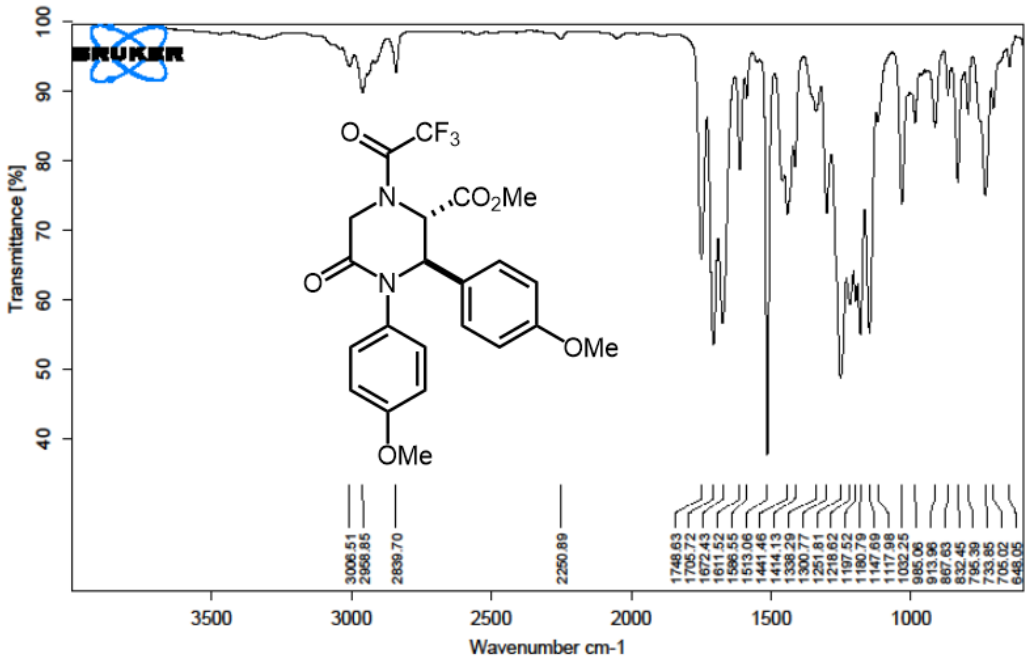
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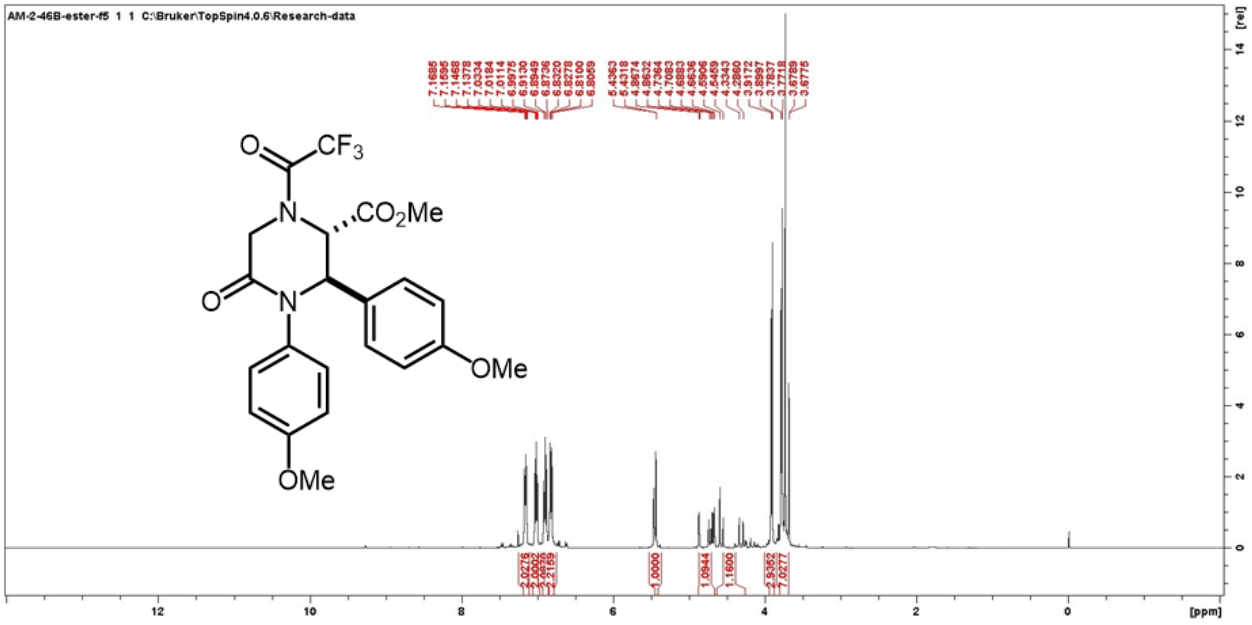
Instrument type and / or acc
11/10/2018
Page 1/1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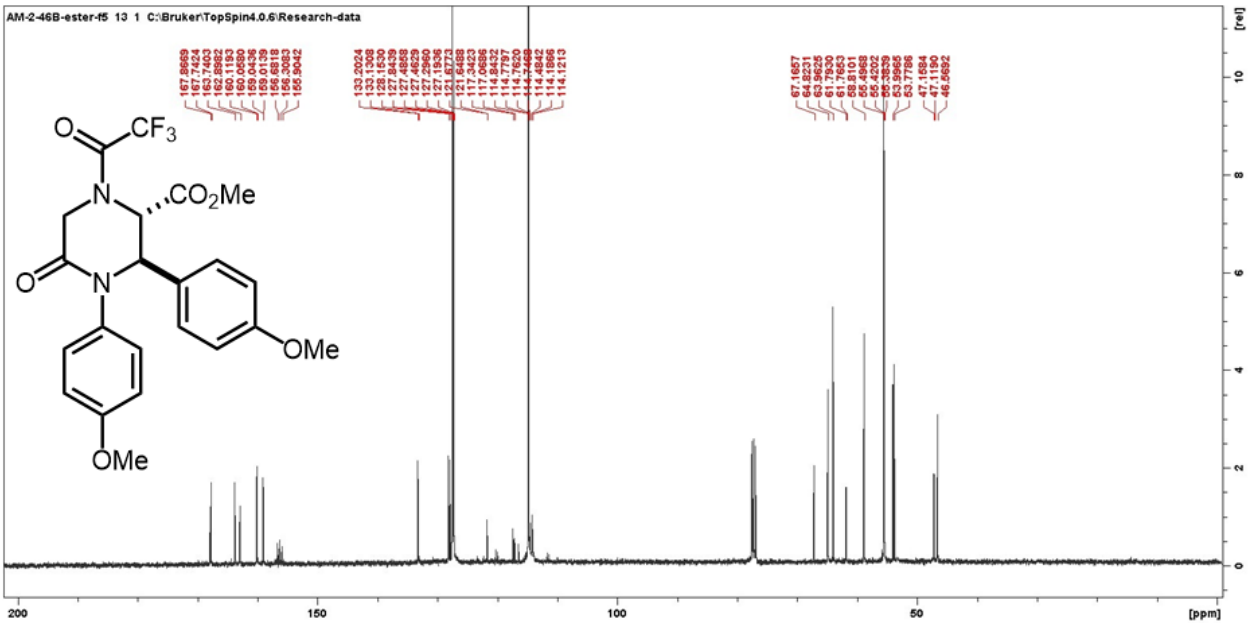
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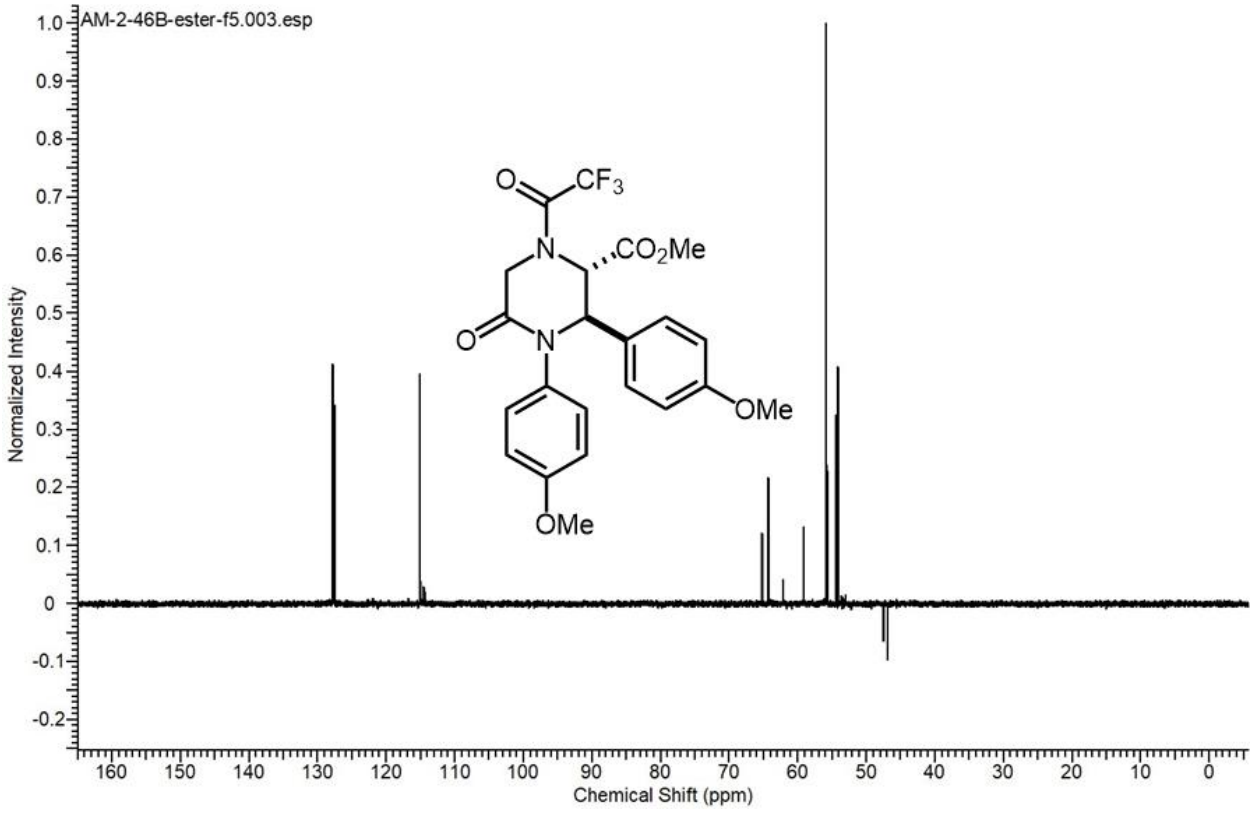
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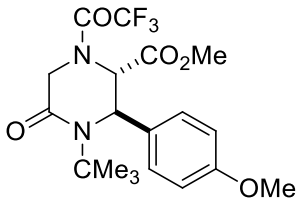
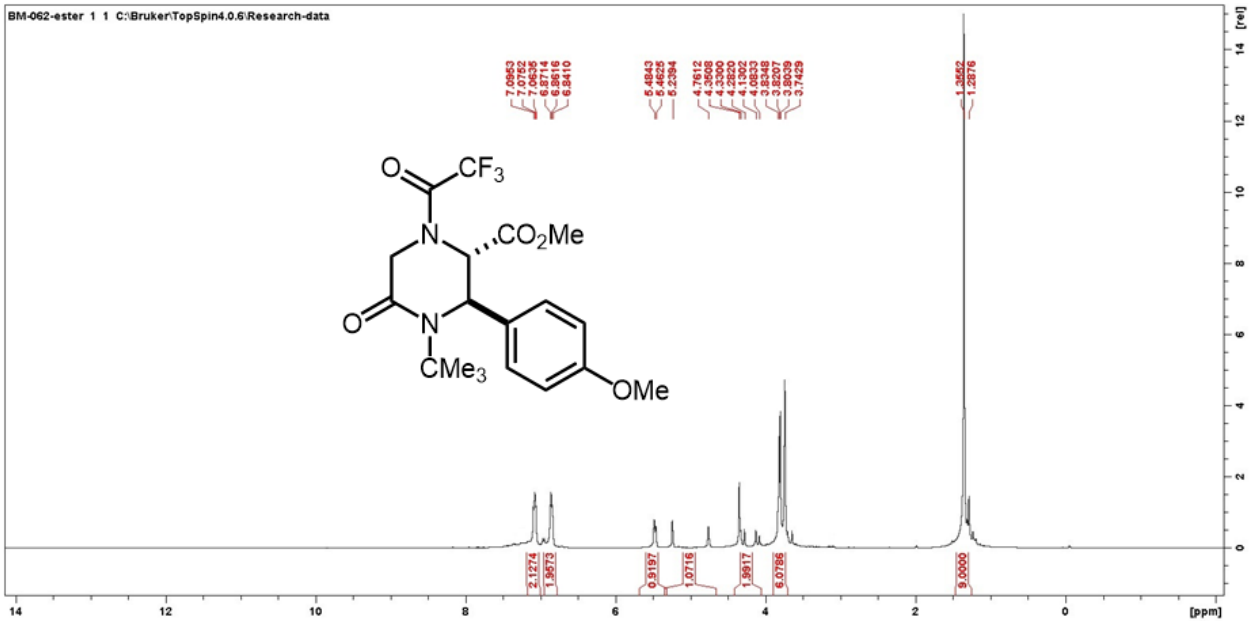
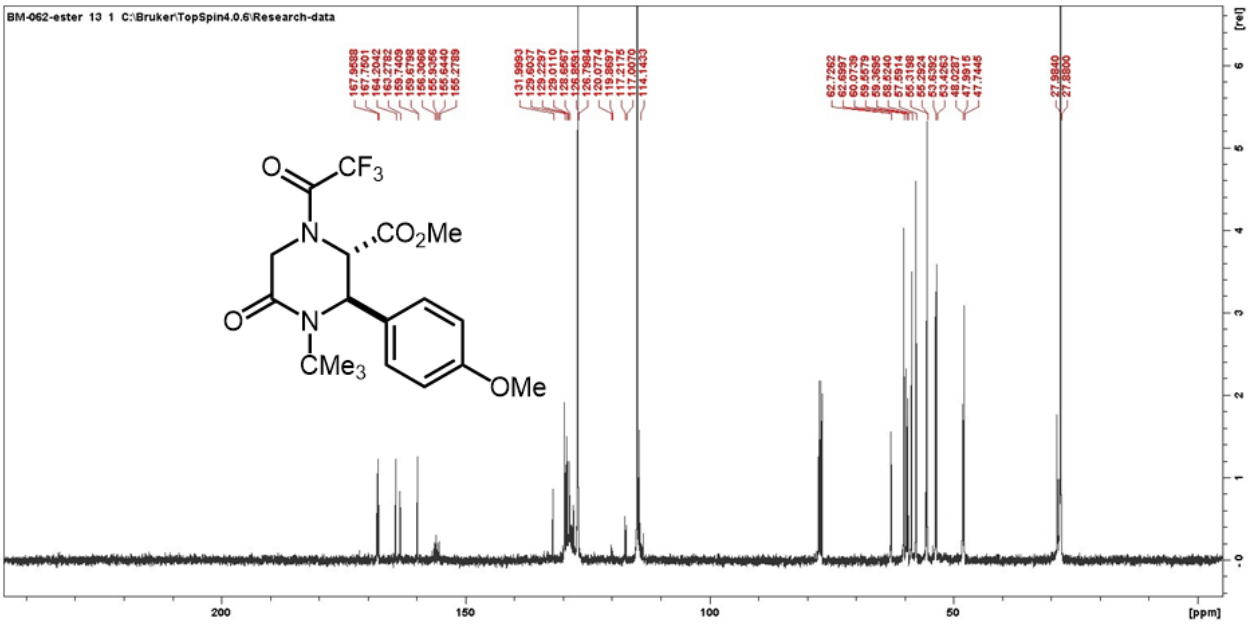


10d; 77%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 320 mg, 77%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (dd, *J* = 8.6, 4.8 Hz, 2H), 6.86 (dd, *J* = 8.5, 4.4 Hz, 2H), 5.48 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.24 + 4.76 (d, *J* = 2.8 Hz, 1H), 4.32 – 4.11 (m, 2H), 3.89 – 3.68 (m, 6H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.7, 164.2, 163.2, 159.75, 159.68, 155.94, 155.65, 132.0, 129.6, 129.2, 128.6, 126.8, 117.2, 114.7, 62.7, 60.0, 59.5, 59.3, 58.5, 57.5, 55.3, 53.6, 53.4, 48.0, 47.9, 47.7, 28.7, 27.9. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{19}H_{23}F_3N_2O_5$ 416.1559; found 416.1567.

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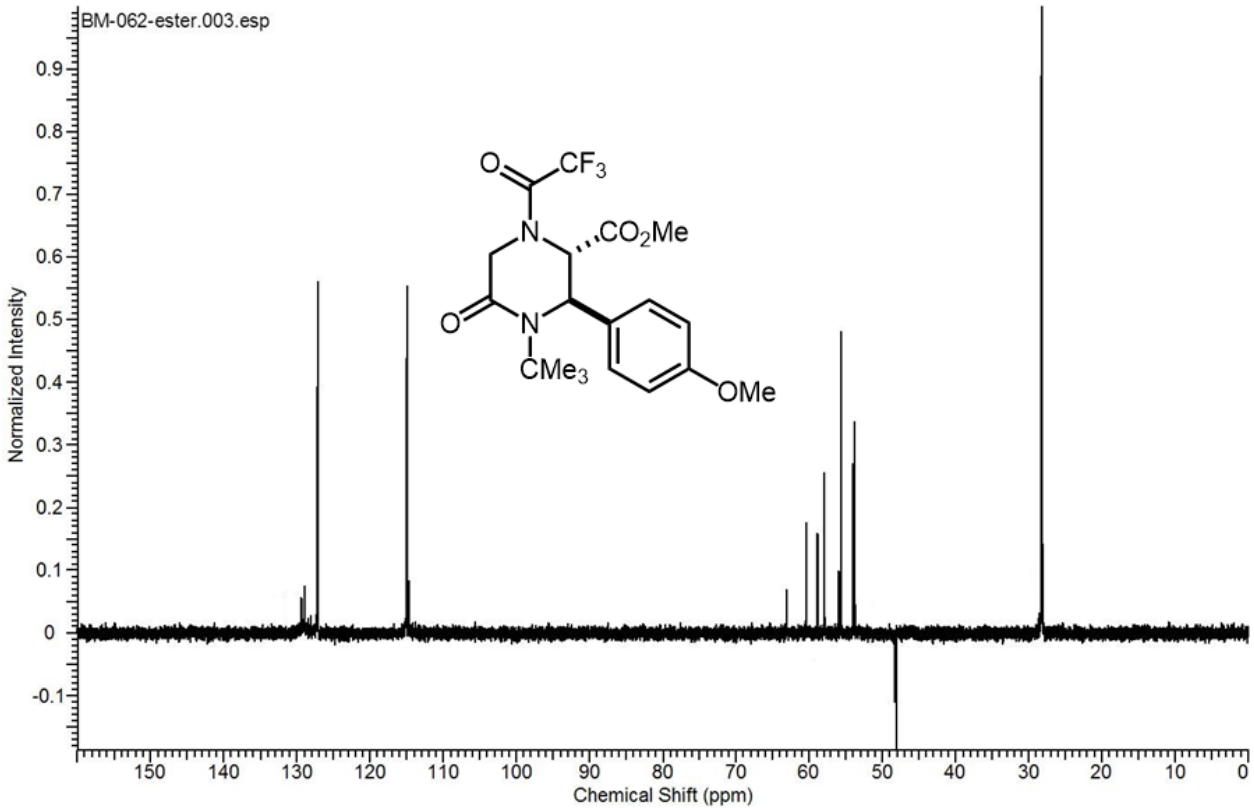
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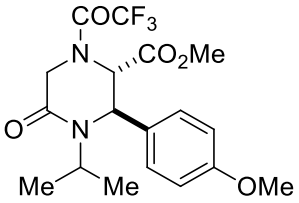
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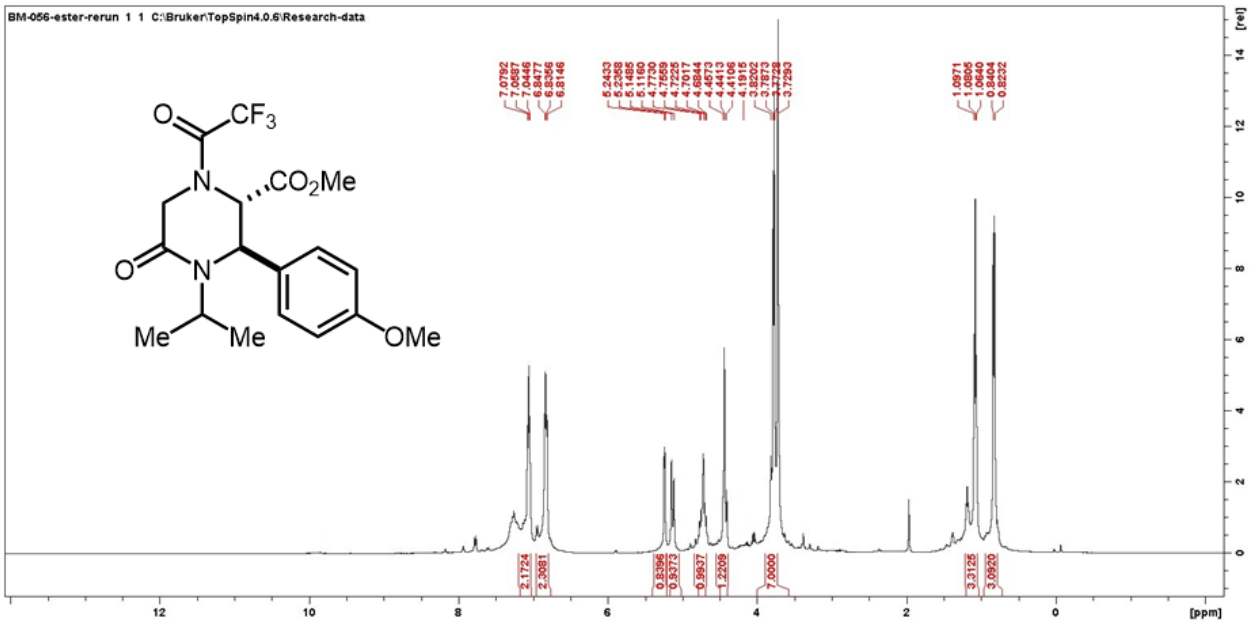
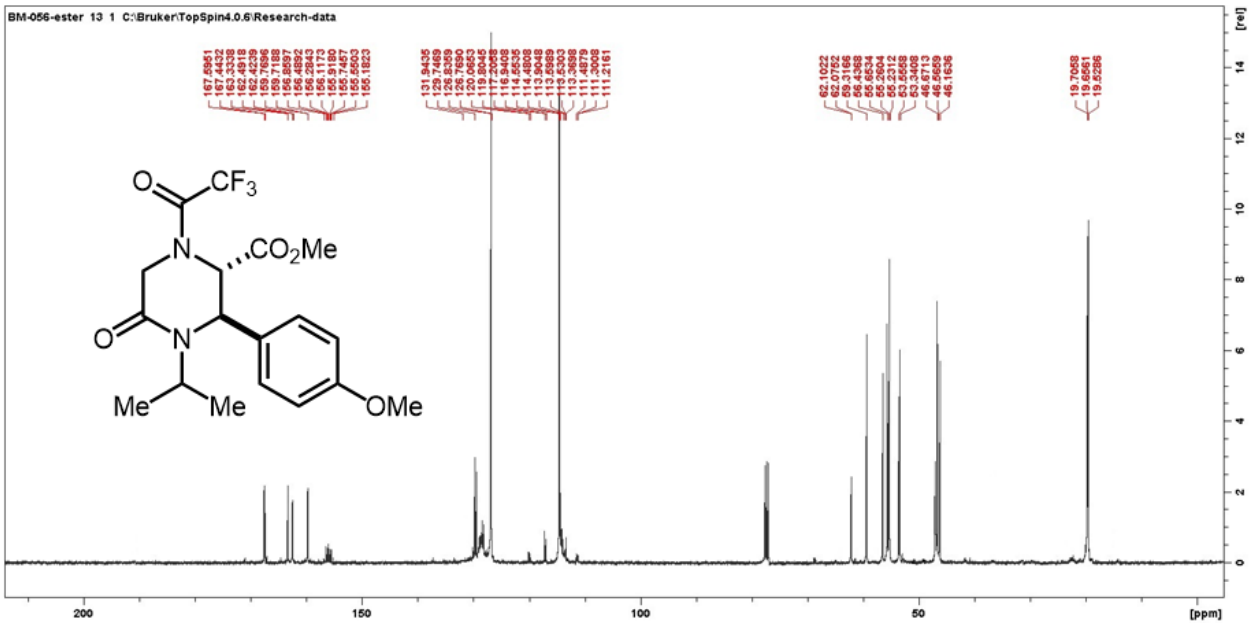
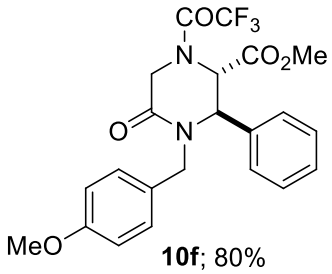
10e; 75%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Yield = 302 mg, 75%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) 7.06 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.98 – 6.79 (m, 2H), 5.27 – 5.21 (m, 1H), 5.13 (dd, *J* = 12.8, 2.5 Hz, 1H), 4.82 – 4.64 (m, 1H), 4.43 (d, *J* = 12.3 Hz, 1H), 3.82 – 3.69 (m, 6H), 1.08 (t, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 167.4, 163.3, 162.4, 159.7, 156.5, 156.2, 155.6, 131.9, 130.9, 129.8, 129.4, 128.4, 126.84, 126.7, 117.2, 116.9, 114.1, 113.3, 58.0, 56.4, 55.6, 55.3, 53.6, 53.3, 47.0, 47.0, 46.9, 46.6, 46.6, 46.1, 19.7, 19.7, 19.5, 19.5. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{18}H_{21}F_3N_2O_5$ 402.1403; found 402.1409.







10f; 80%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 360 mg, 80%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.19 (m, 3H), 7.17 – 6.95 (m, 2H), 7.06 – 6.87 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 5.37 (dd, *J* = 14.4, 10.4 Hz, 1H), 4.83 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.55 – 446 (m, 2H), 4.12 (d, *J* = 11.3 Hz, 2H), 3.51 (s, 3H), 3.31 (s, 3H), 3.21 (dd, *J* = 14.5, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.1, 163.8, 162.9, 159.6, 157.6, 156.7, 156.3, 155.7, 135.8, 135.4, 130.3, 129.6, 129.1, 127.4, 125.9, 117.27, 114.6, 114.0, 60.9, 59.4, 58., 55.39, 53.3, 52.8, 49.1, 48.9, 47.7, 46.7, 46.7, 46.1. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{22}H_{21}F_3N_2O_5$ 450.1403; found 450.1408.

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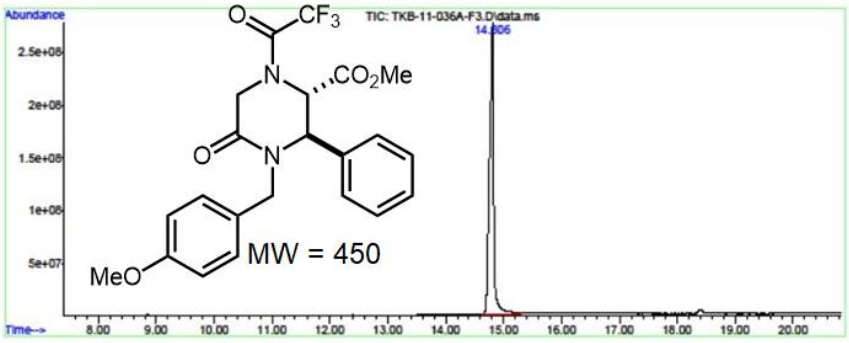

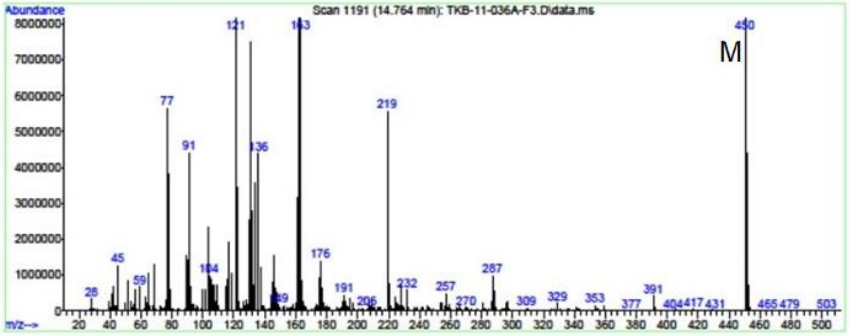

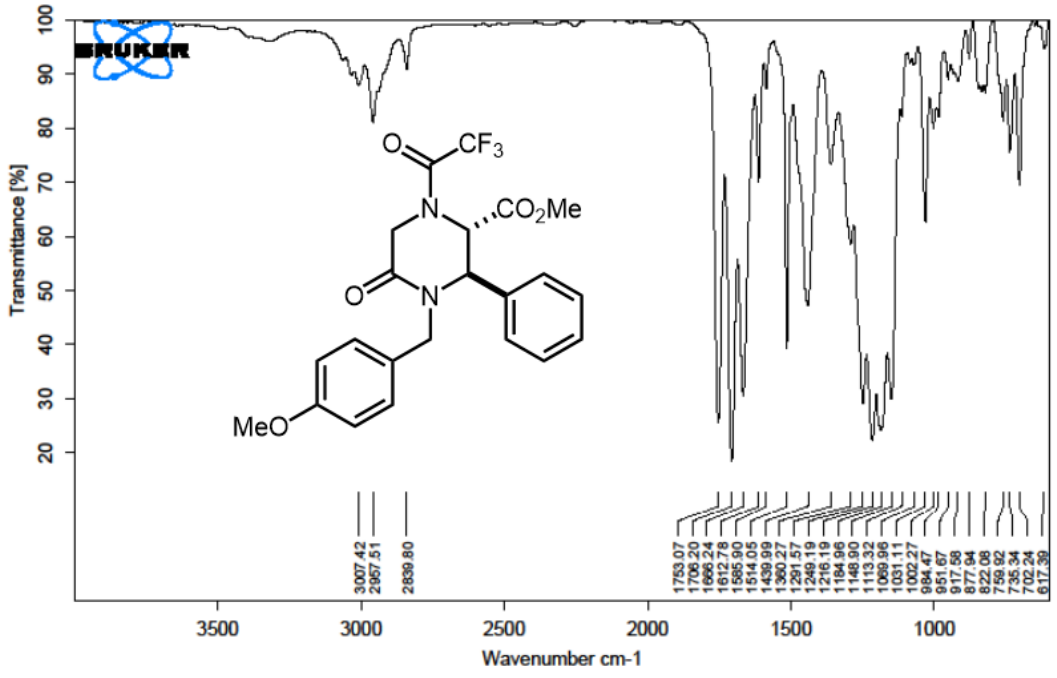

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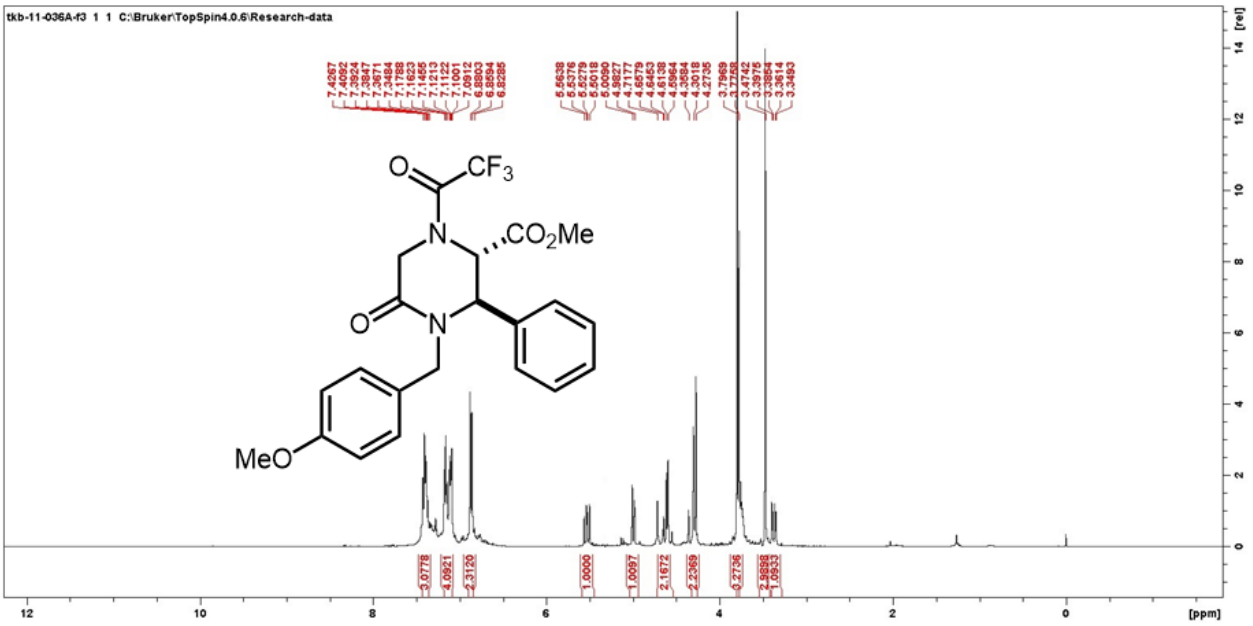
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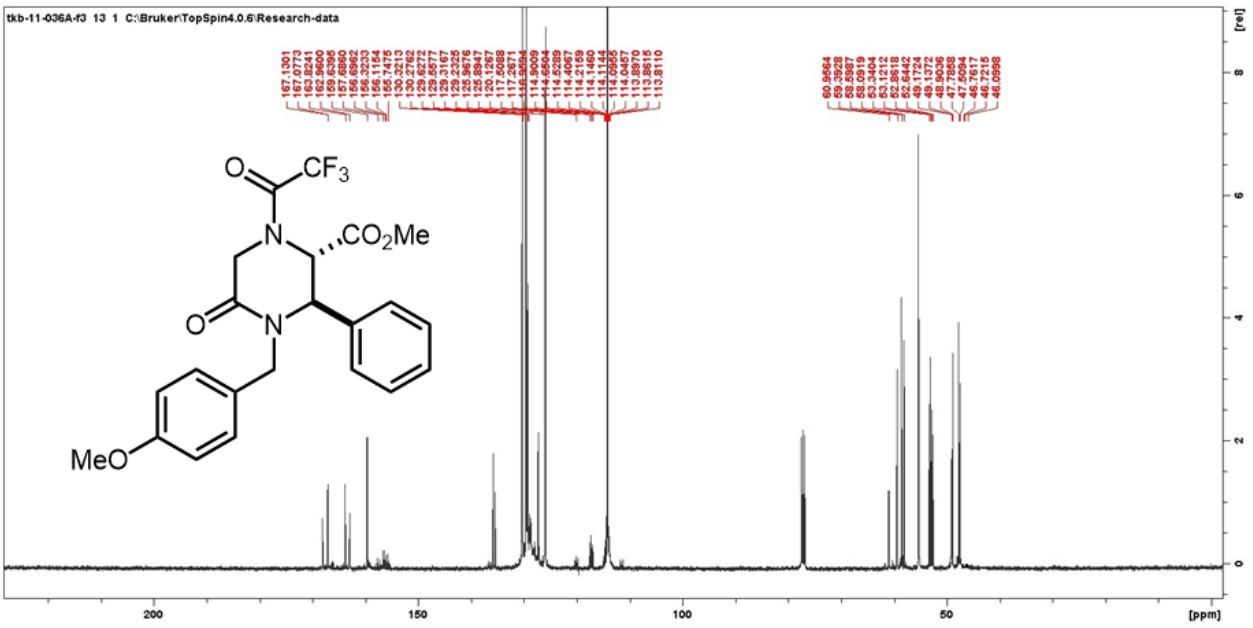
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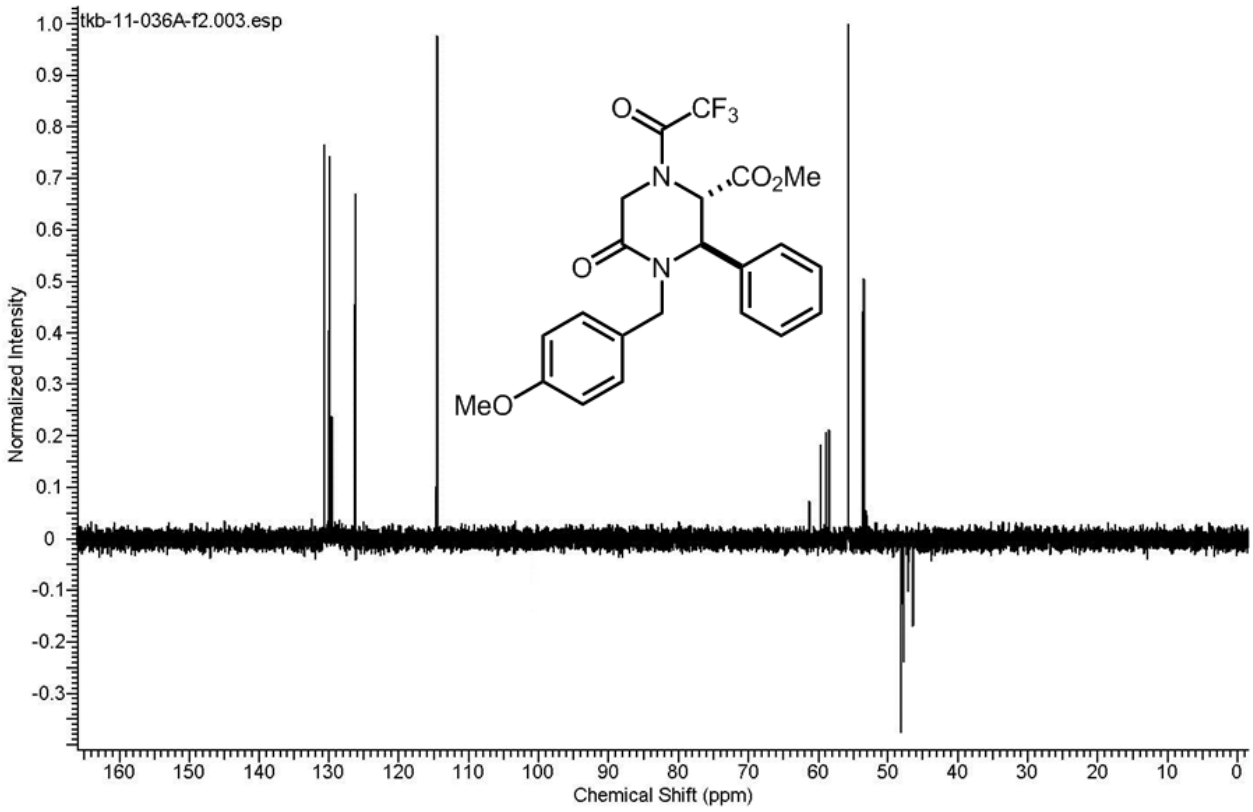

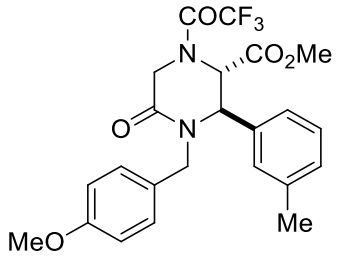

10g; 84%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 390 mg, 84%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.16 – 7.06 (s, 1H), 6.98 – 6.85 (m, 3H), 6.73 – 6.55 (m, 4H), 5.36 (t, *J* = 14.7 Hz, 1H), 5.12 – 5.04 (m, 1H), 4.78 (dd, *J* = 5.3, 2.1 Hz, 1H), 4.52 – 4.29 (m, 2H), 3.54 (m, 3H), 3.28 (s, 3H), 3.20 (d, *J* = 14.4 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 163.8, 162.9, 162.6, 159.6, 156.6, 139.5, 139.4, 135.7, 135.3, 130.3, 130.2, 129.8, 129.4, 127.5, 126.5, 122.9, 117.3, 116.9, 114.4, 61.0, 61.0, 59.3, 58.5, 58.1, 55.3, 55.2, 53.2, 53.0, 47.5, 46.7, 46.1, 21.5, 21.4. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{23}H_{23}F_3N_2O_5$ 464.1559; found 464.1566.

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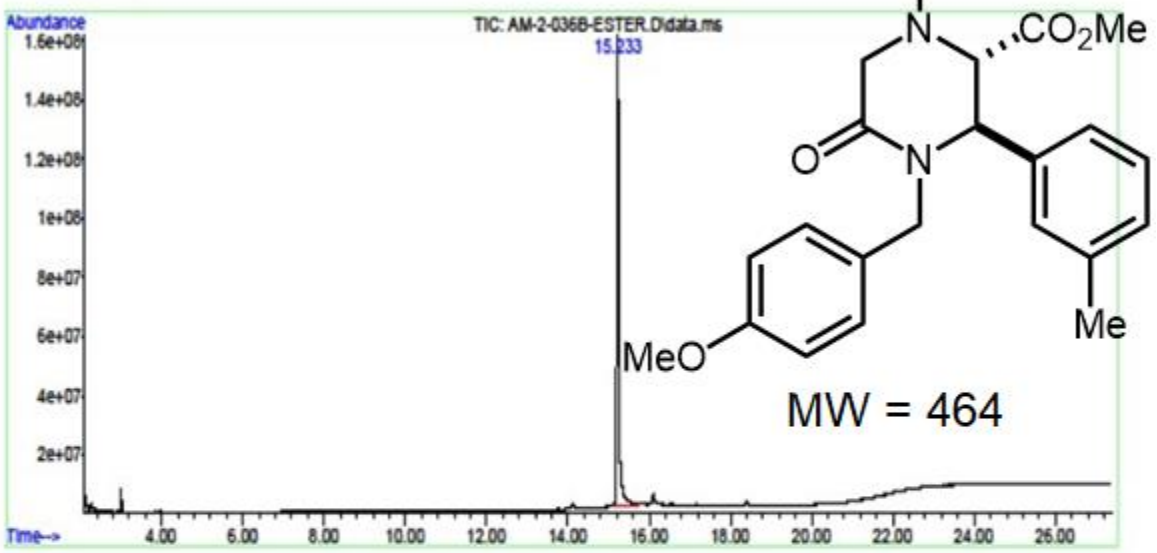

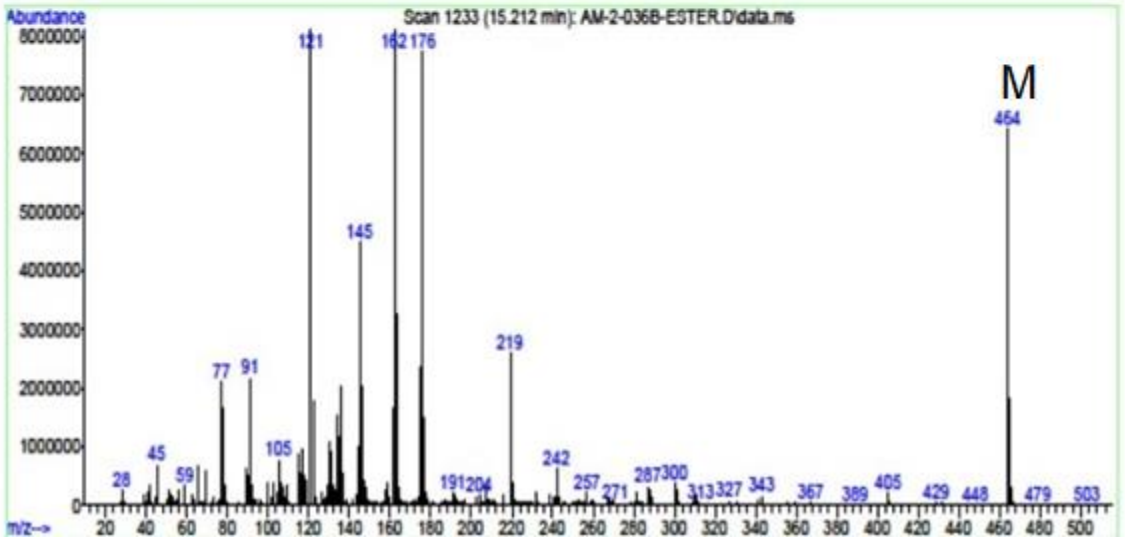

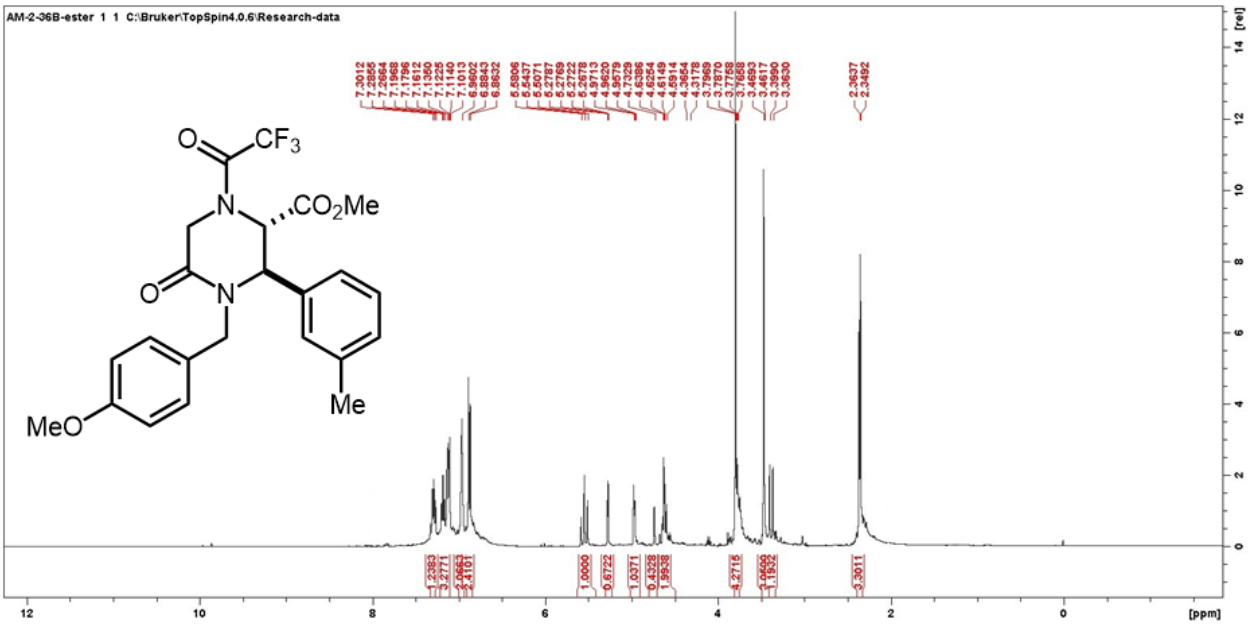
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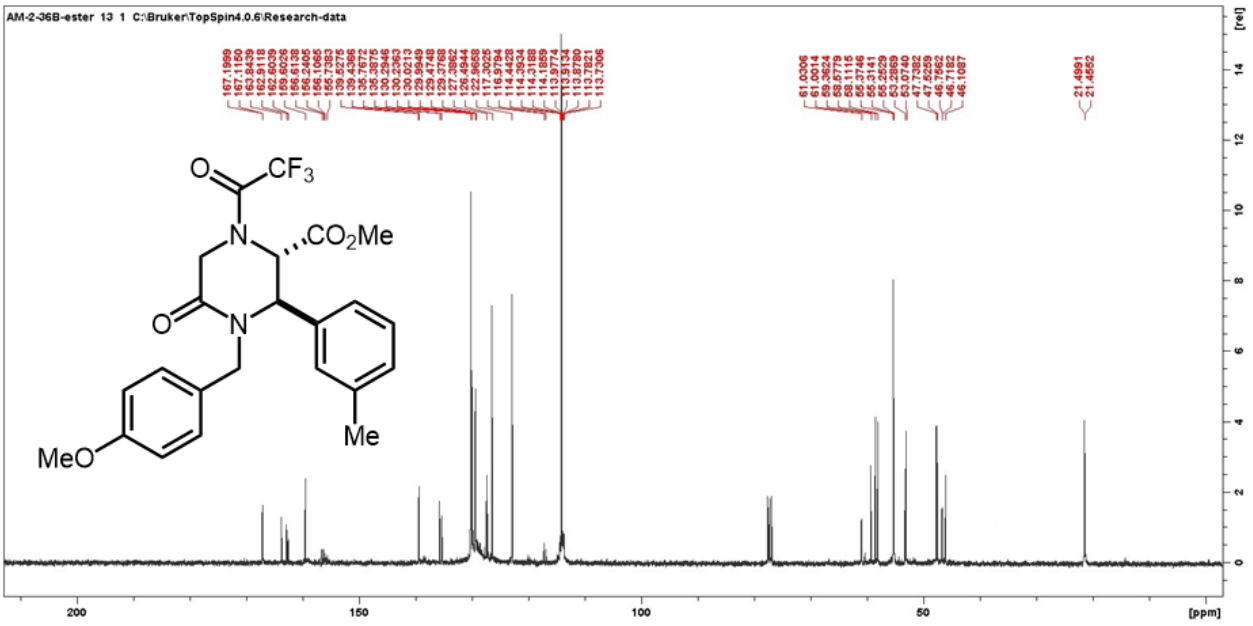
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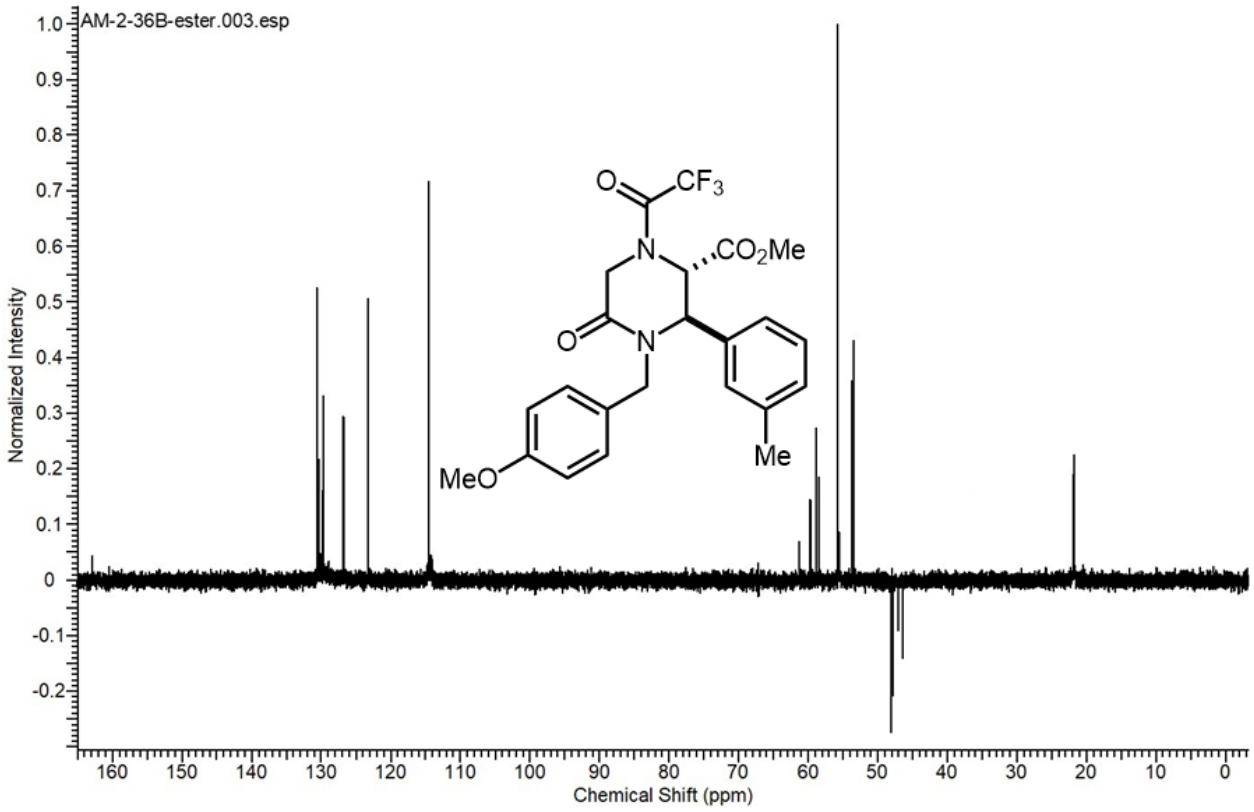
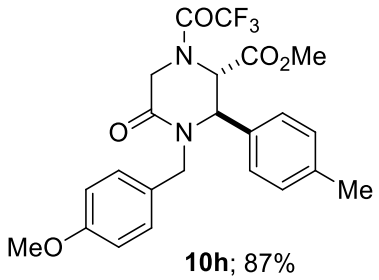
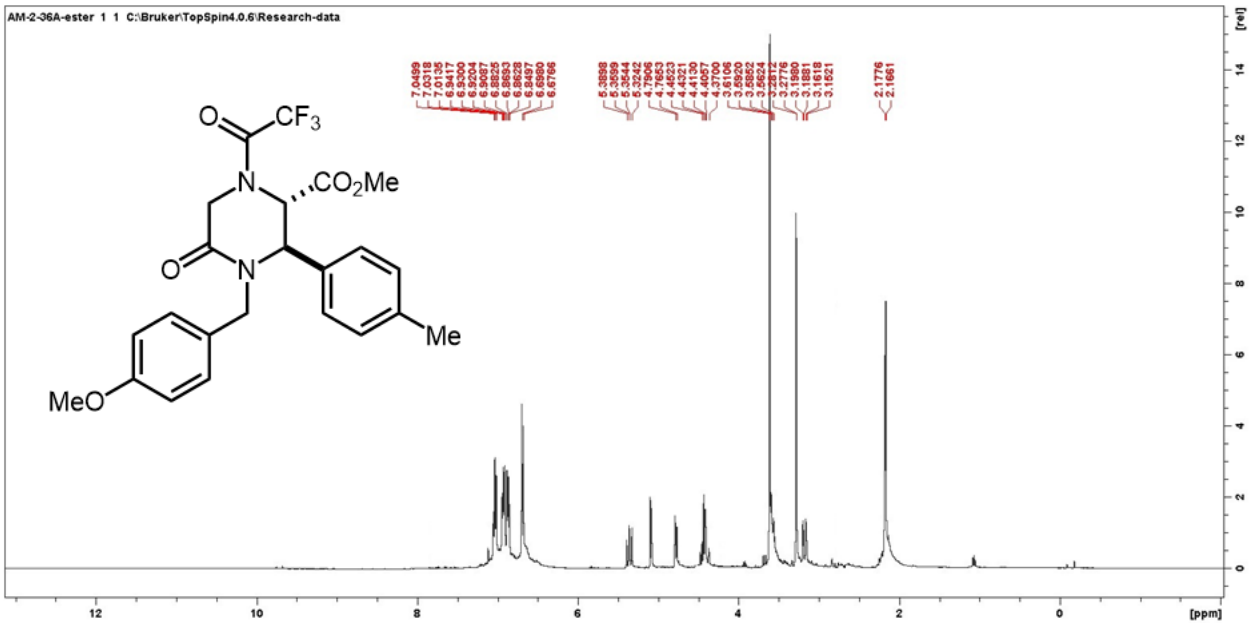




10h; 87%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 404 mg, 87%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 6.98 – 6.77 (m, 6H), 6.73 – 6.57 (m, 2H), 5.36 (dd, *J* = 14.4, 11.9 Hz, 1H), 5.12 – 5.06 (m, 1H), 4.78 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.55 – 4.41 (m, 1H), 4.44 – 4.32 (m, 1H), 3.50 (s, 3H), 3.28 (s, 3H), 3.18 (dd, *J* = 14.5, 4.0 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 163.8, 162.9, 162.6, 159.6, 156.6, 155.7, 139.2, 139.1, 132.7, 132.3, 130.2, 130.2, 130.2, 130.2, 130.1, 127.5, 127.3, 125.8, 125.7, 117.2, 114.2, 61.3, 61.0, 59.1, 58.3, 58.1, 55.3, 53.2, 53.0, 47.6, 46.7, 46.1, 21.8, 21.4. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{23}H_{23}F_3N_2O_5$ 464.1559; found 464.1566.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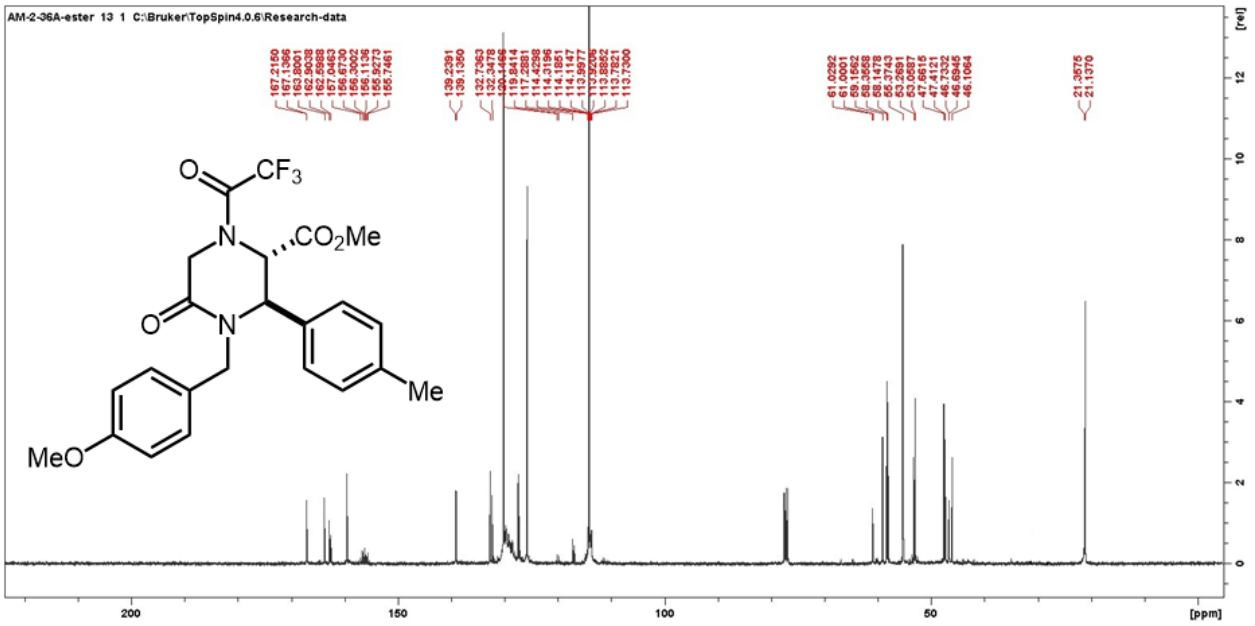
N
CO2Me
O
N
Me
MeO
[ppm]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O
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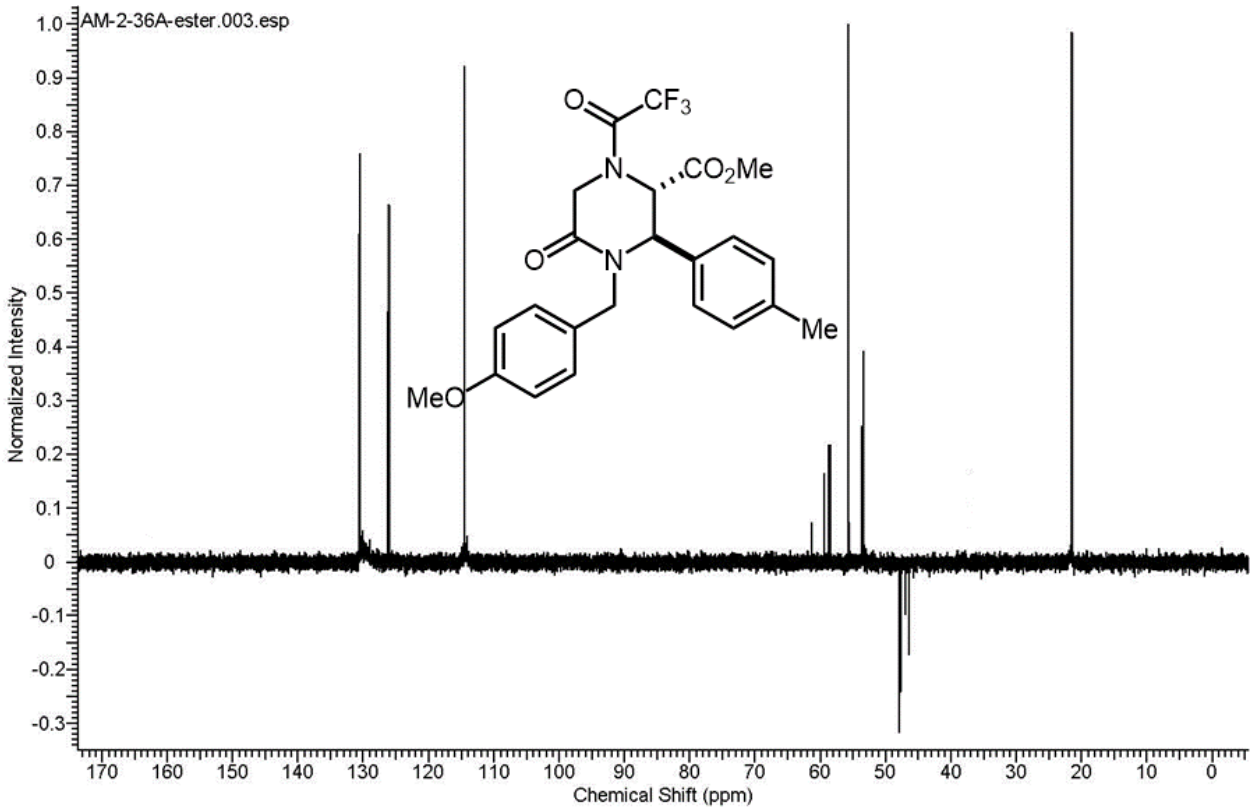
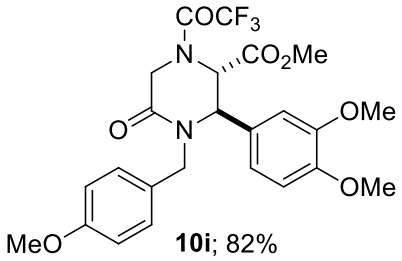
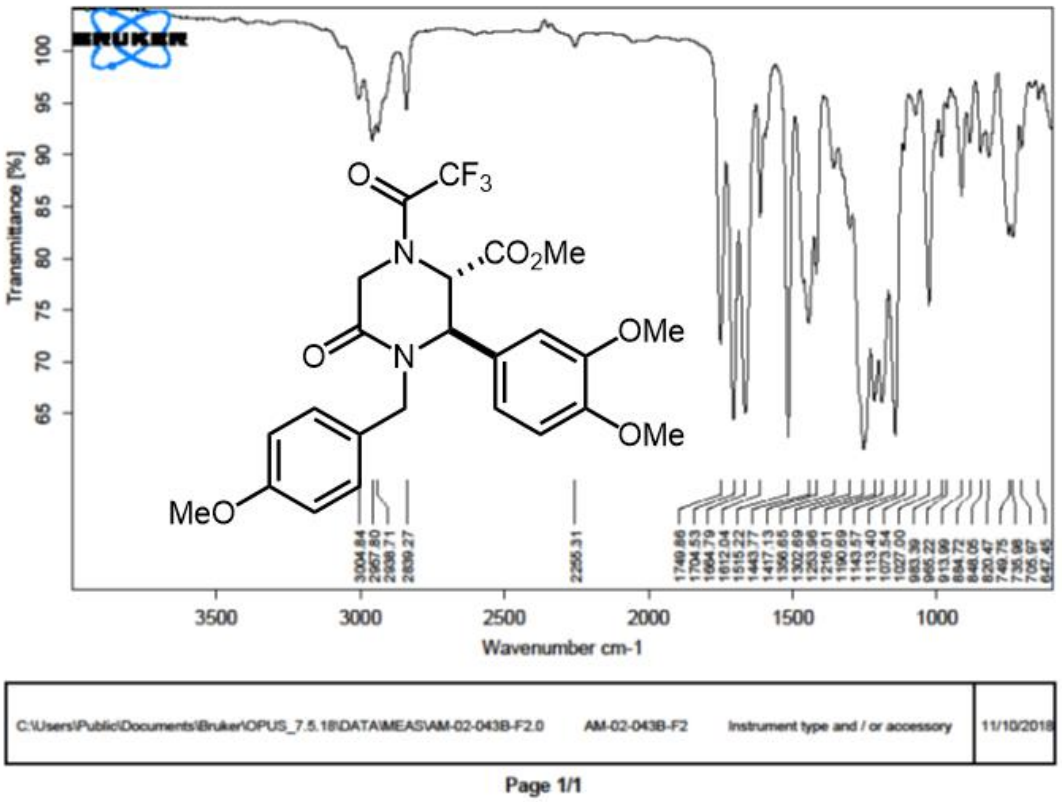




10i; 82%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 418 mg, 82%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 6.89 (ddq, *J* = 8.1, 5.8, 2.8 Hz, 2H), 6.66 (dd, *J* = 8.4, 5.2 Hz, 3H), 6.49 (td, *J* = 8.0, 2.3 Hz, 1H), 6.40 (dd, *J* = 4.8, 2.2 Hz, 1H), 5.29 (t, *J* = 14.1 Hz, 1H), 5.07 (d, *J* = 2.1 Hz, 1H), 4.72 (dd, *J* = 7.8, 2.1 Hz, 1H), 4.41 (dd, *J* = 18.3, 3.6 Hz, 2H), 3.71 – 3.59 (m, 6H), 3.58 (s, 3H), 3.27 (s, 3H), 3.20 (dd, *J* = 14.5, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 167.0, 163.6, 162.7, 159.5, 156.5, 156.2,, 149.9, 149.6, 130.2, 128.0, 127.6, 127.4, 118.2, 117.2, 116.9, 111.6, 108.8, 61.0, 60.9, 59.1, 58.3, 58.0, 56.0, 55.9, 55.9, 55.3, 53.2, 53.0, 47.7, 47.5, 46.7, 46.6, 45.9. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{24}H_{25}F_3N_2O_7$ 510.1614; found 510.1614.


Transmittance [%]
Wavenumber cm-1
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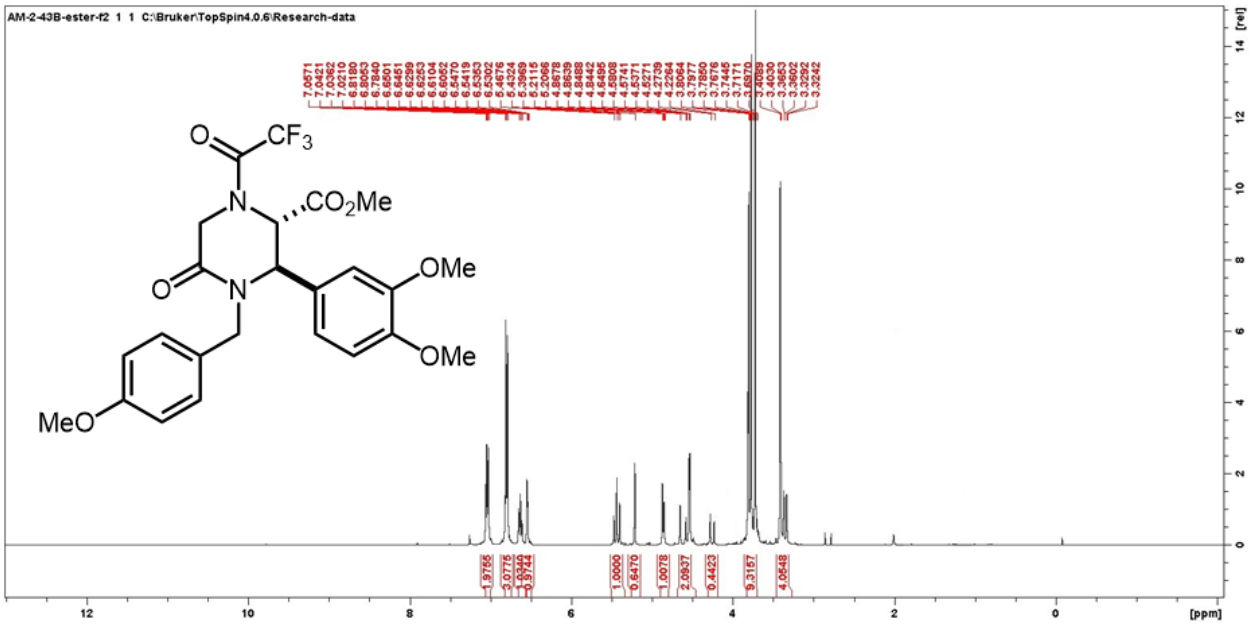
AM-02-043B-F2
Instrument type and / or accessory
11/10/2018
Page 1/1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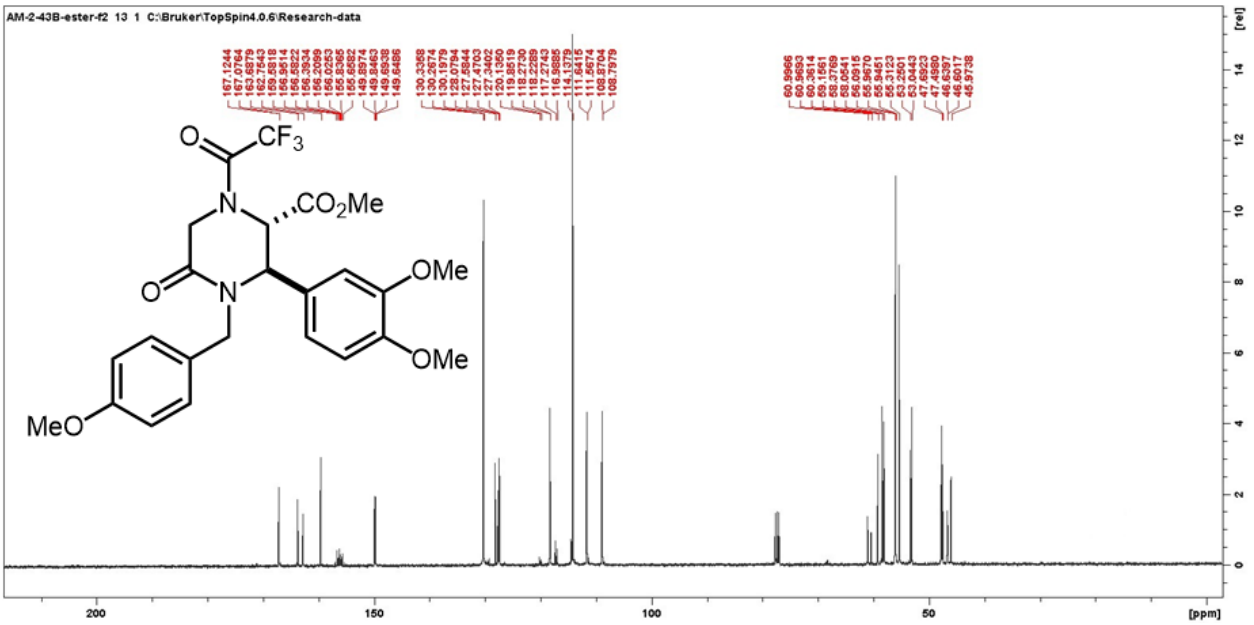
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CO2Me
O
N
OMe
OMe
MeO
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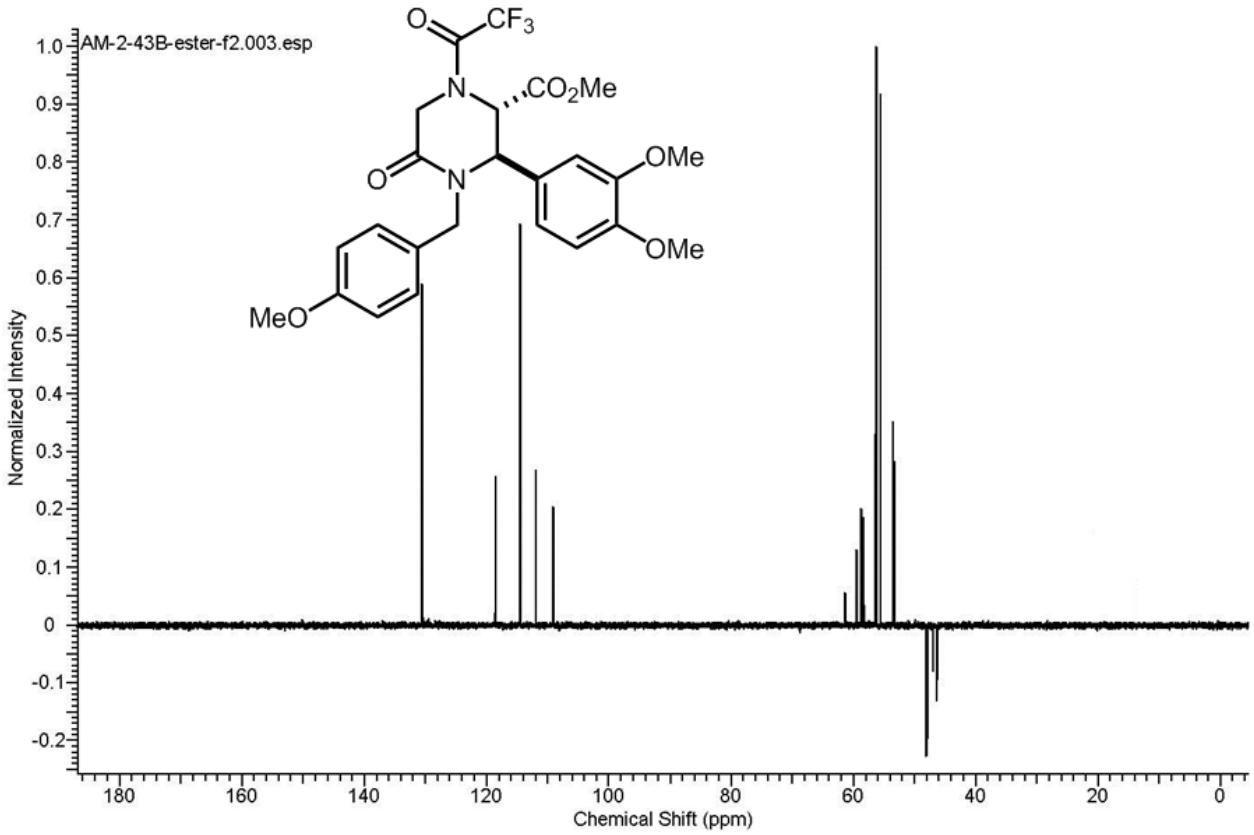
150
100
50
[ppm]


AM-2-43B-ester-f2.003.esp
O
CF3
N
CO2Me
O
N
OMe
OMe
MeO
Normalized Intensity
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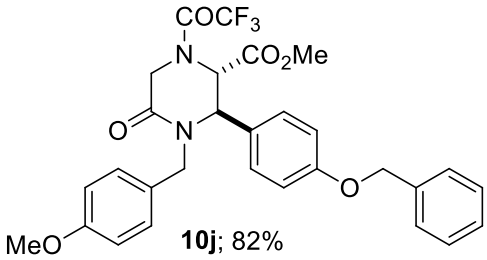
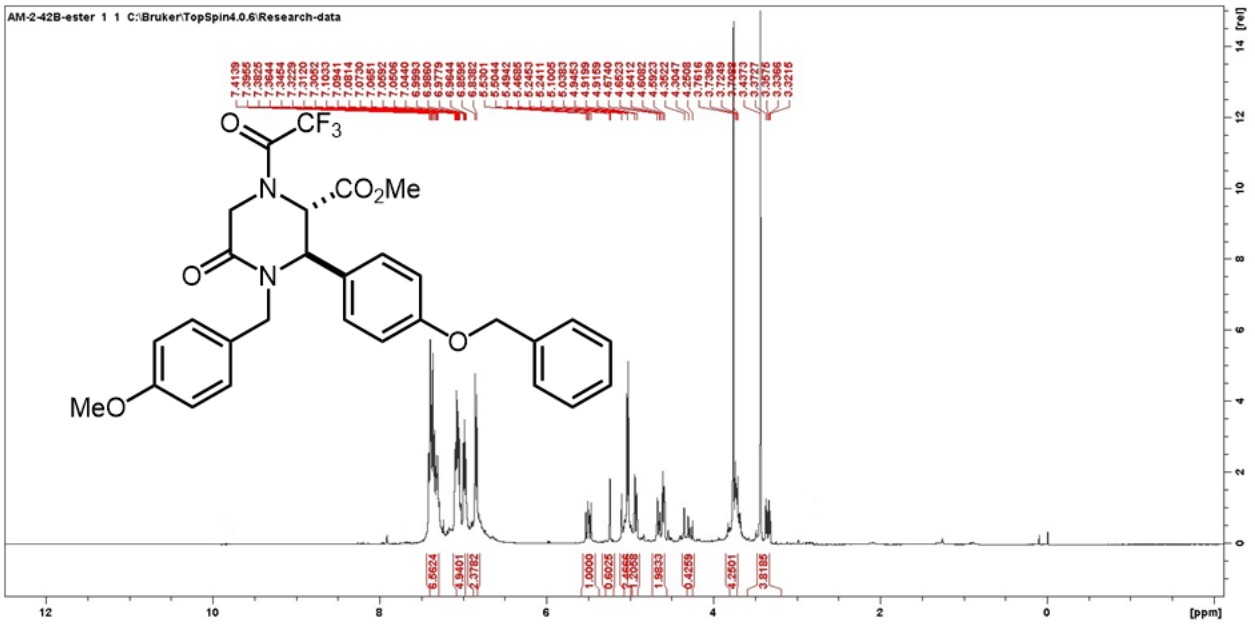
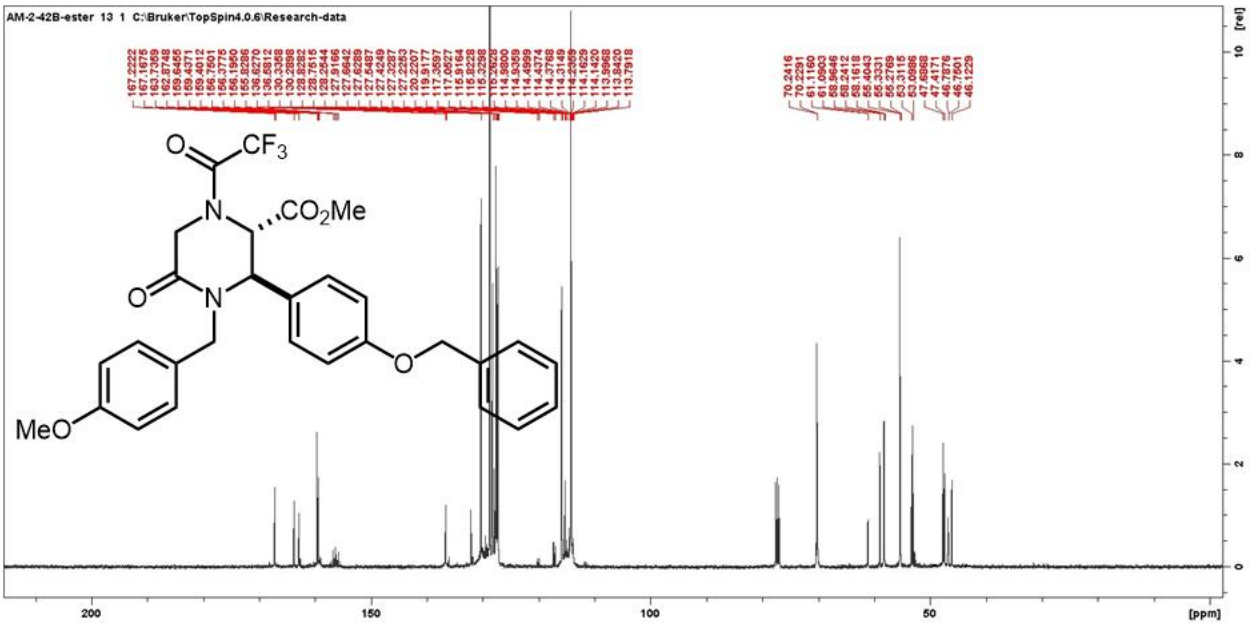
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



10j; 82%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Yield = 456 mg, 82%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.36 – 7.22 (m, 6H), 6.96 – 6.79 (m, 5H), 6.68 (d, 2H), 5.38 (dd, *J* = 14.4, 10.2 Hz, 1H), 5.02 – 4.88 (m, 2H), 4.91 – 4.77 (m, 1H), 4.59 – 4.39 (m, 2H), 3.52 (s, 3H), 3.31 (s, 3H), 3.22 (dd, *J* = 14.4, 6.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 163.7, 162.8, 159.6, 159.4, 156.7, 156.3, 136.6, 132.1, 130.3, 128.8, 128.7,, 128.4, 127.9, 127.6, 127.61, 127.5, 127.4, 127.3, 127.2, 115.92 115.8, 115.2, 114.28, 114.1, 70.3, 70.2, 58.9, 58.2, 58.1, 55.4, 53.3, 53.1, 47.6, 47.4, 46.1. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{29}H_{27}F_3N_2O_6$ 556.1821; found 556.1827.

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CO2Me
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N
O
MeO
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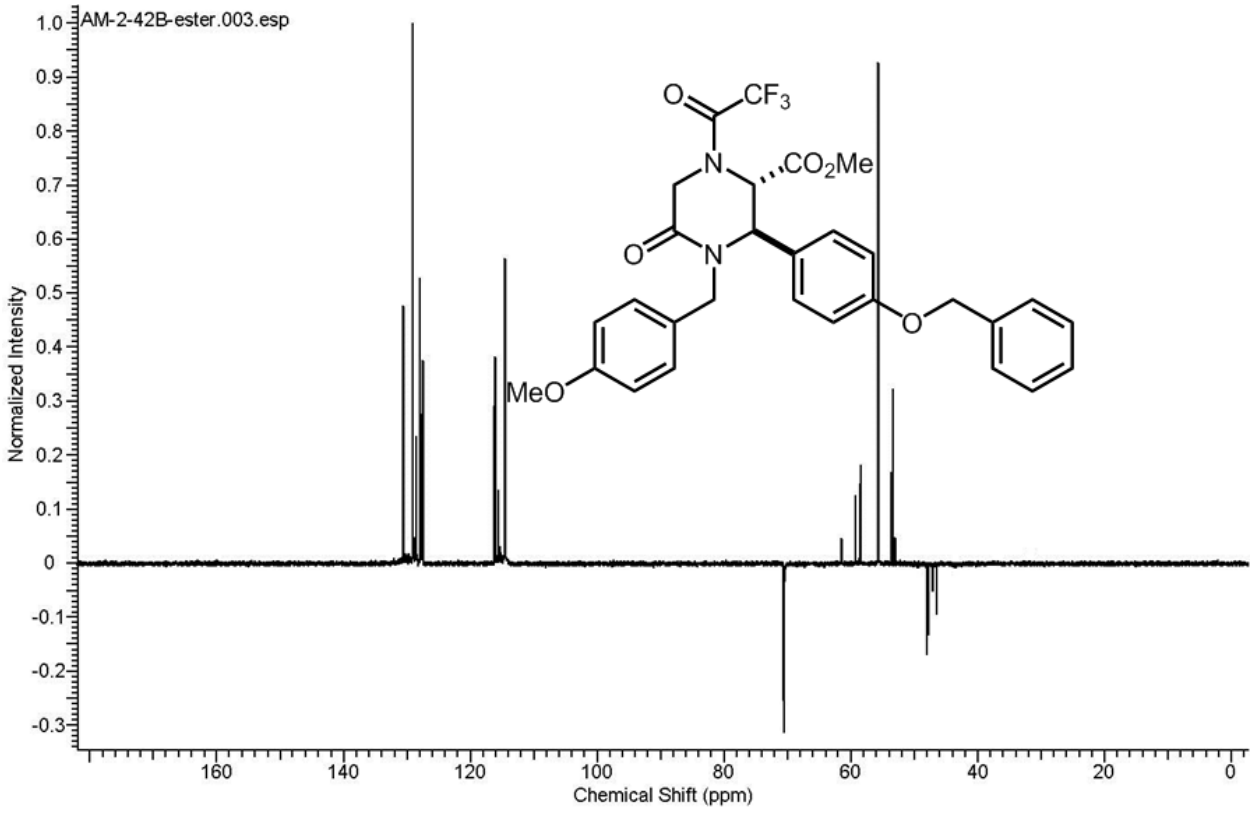
150
100
50
[ppm]


AM-2-42B-ester.003.esp
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0.6
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0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
O
CF3
N
CO2Me
O
N
O
MeO
160
140
120
100
80
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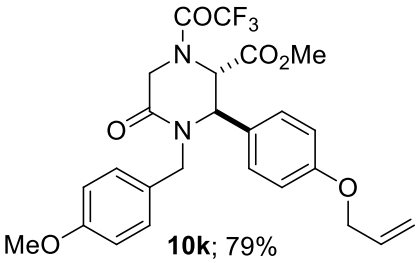
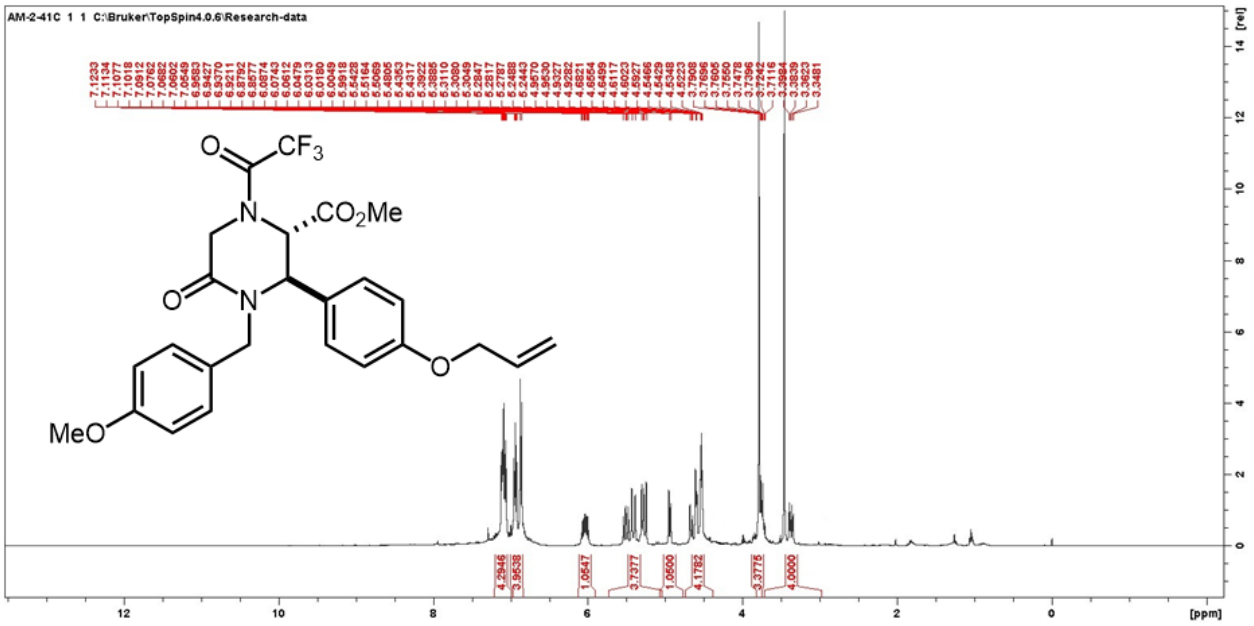
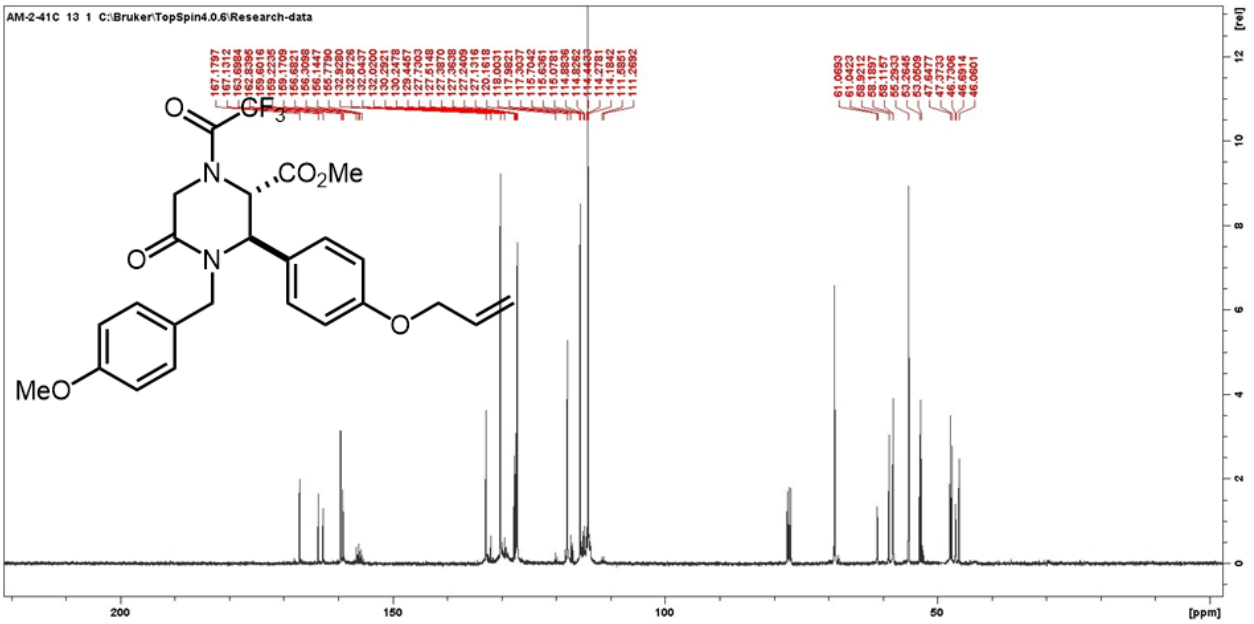
40
20
0
Chemical Shift (ppm)



10k; 79%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Yield = 400 mg, 79%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 6.89 – 6.80 (m, 4H), 6.72 – 6.61 (m, 4H), 5.86 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.33 – 5.04 (m, 4H), 4.77 (dd, *J* = 9.8, 2.1 Hz, 1H), 4.53 – 4.42 (m, 4H), 3.61 (s, 3H), 3.28 (s, 3H), 3.20 (dd, *J* = 14.4, 5.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 163.7, 162.8, 159.6, 159.2, 156.6, 156.3, 156.15, 132.9, 130.3, 127.7, 127.52 127.3, 127.1, 118.0, 117.9, 115.7, 115.0, 114.8, 114.2, 114.1, 68.9, 61.0, 61.0, 58.9, 58.19, 58.12, 55.36, 55.30, 53.27, 53.05, 47.65, 47.38, 46.74, 46.6. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{25}H_{25}F_3N_2O_6$ 506.1665; found 506.1672.

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CO2Me
MeO
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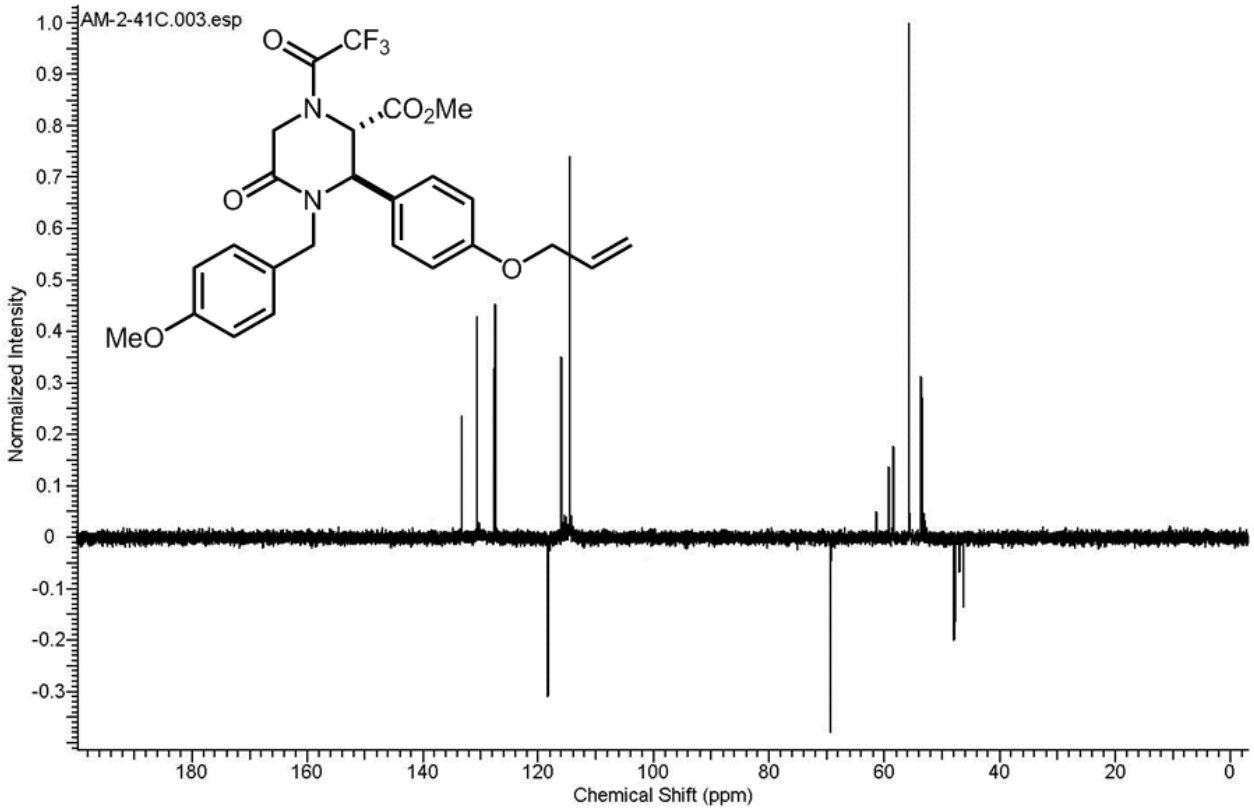
150
100
50
[ppm]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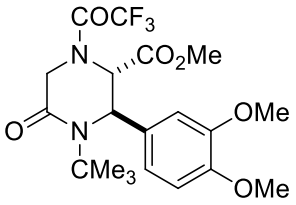
CF3
CO2Me
MeO
Normalized Intensity
Chemical Shift (ppm)



10l; 75%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 335 mg, 75%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 6.66 (dd, *J* = 8.3, 3.1 Hz, 1H), 6.55 (ddd, *J* = 8.1, 5.6, 2.2 Hz, 1H), 6.47 (t, *J* = 2.6 Hz, 1H), 5.31 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.19 (s, 1H), 4.17 – 4.06 (m, 2H), 3.69 – 3.63 (m, 9H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 167.7, 164.2, 163.3, 156.3, 155.9, 155.5, 155.2, 149.6, 149.2, 149.1, 130.1, 129.6, 118.1, 111.5, 111.4, 108.6, 108.4, 62.7, 62.6, 60.0, 59.6, 58.7, 57.7, 56.0, 55.9, 53.7, 53.4, 52.8, 52.6, 48.8, 47.7, 28.0, 27.9. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{20}H_{25}F_3N_2O_6$ 446.1665; found 446.1669.

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Instrument :    Instrument #1
Sample Name:
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Vial Number: 1
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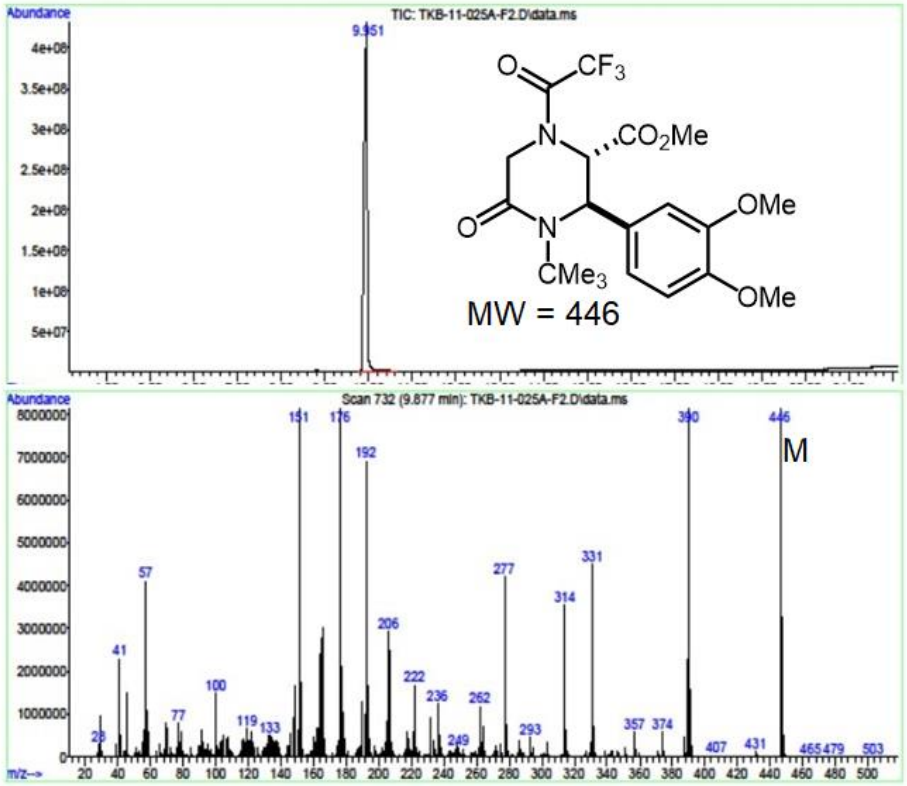

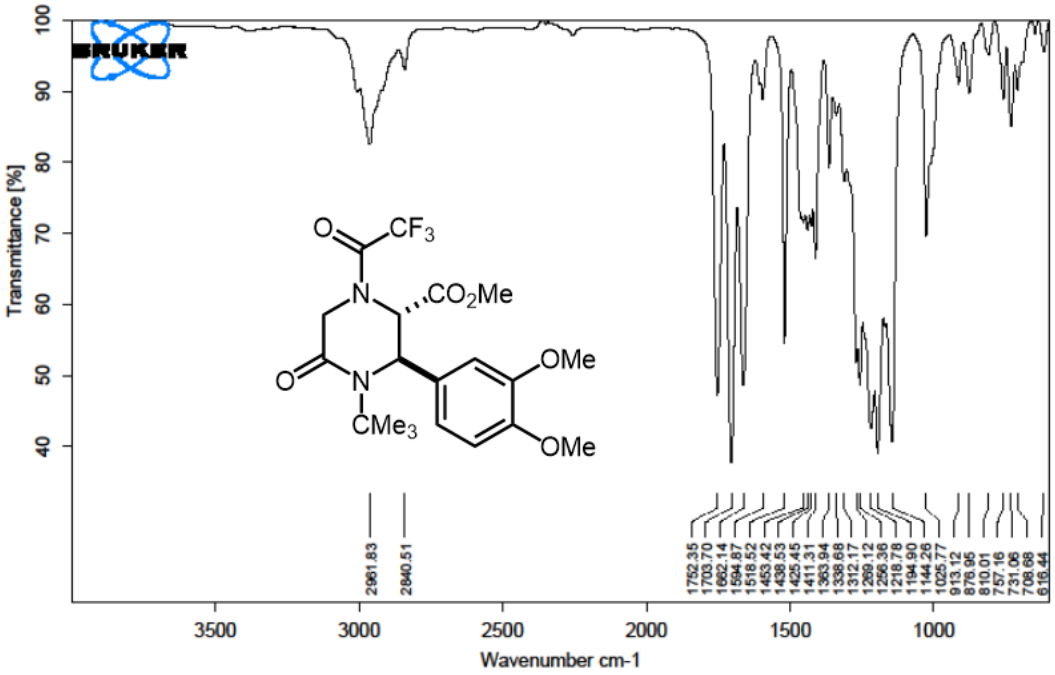

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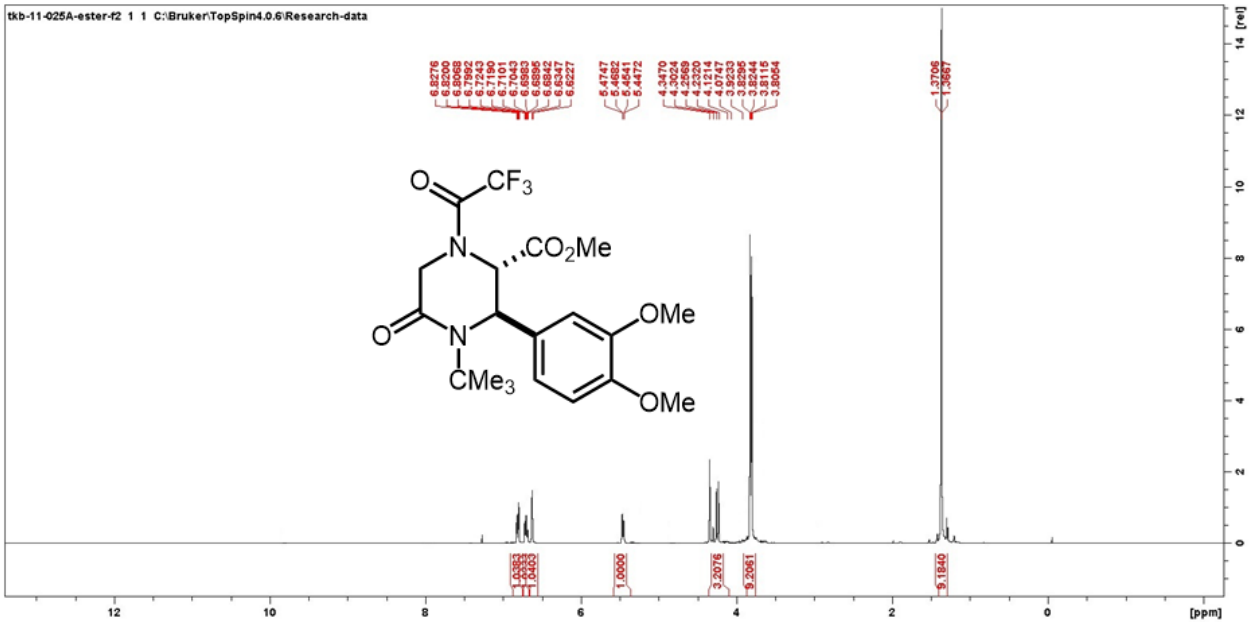
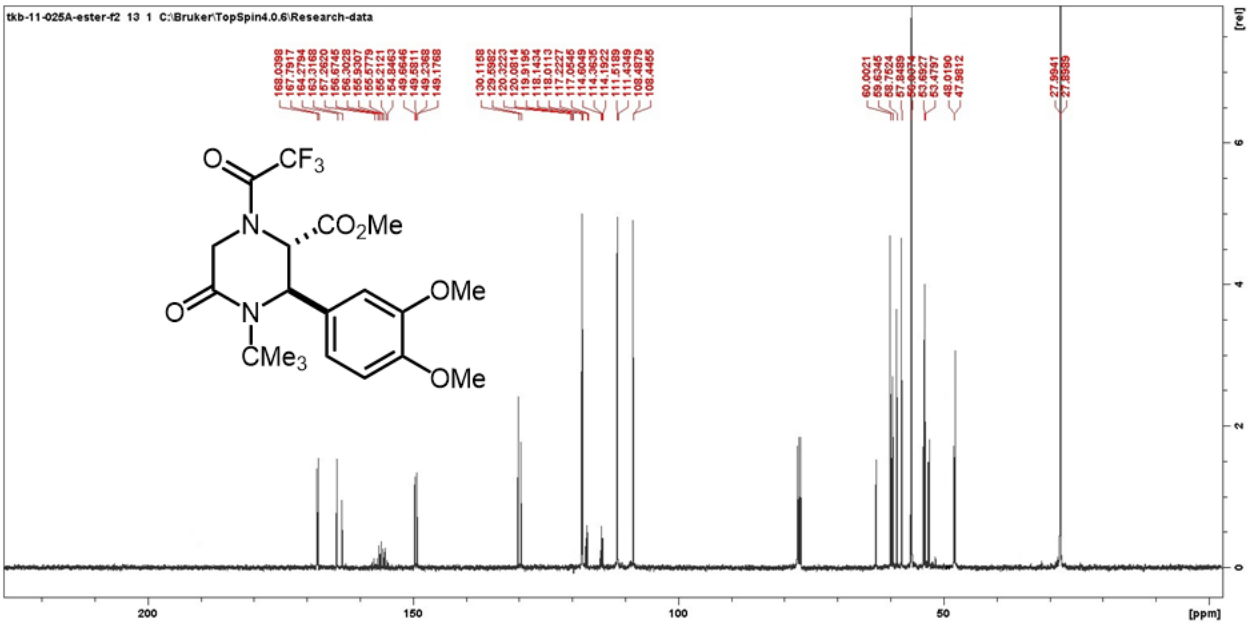
Page 1/1

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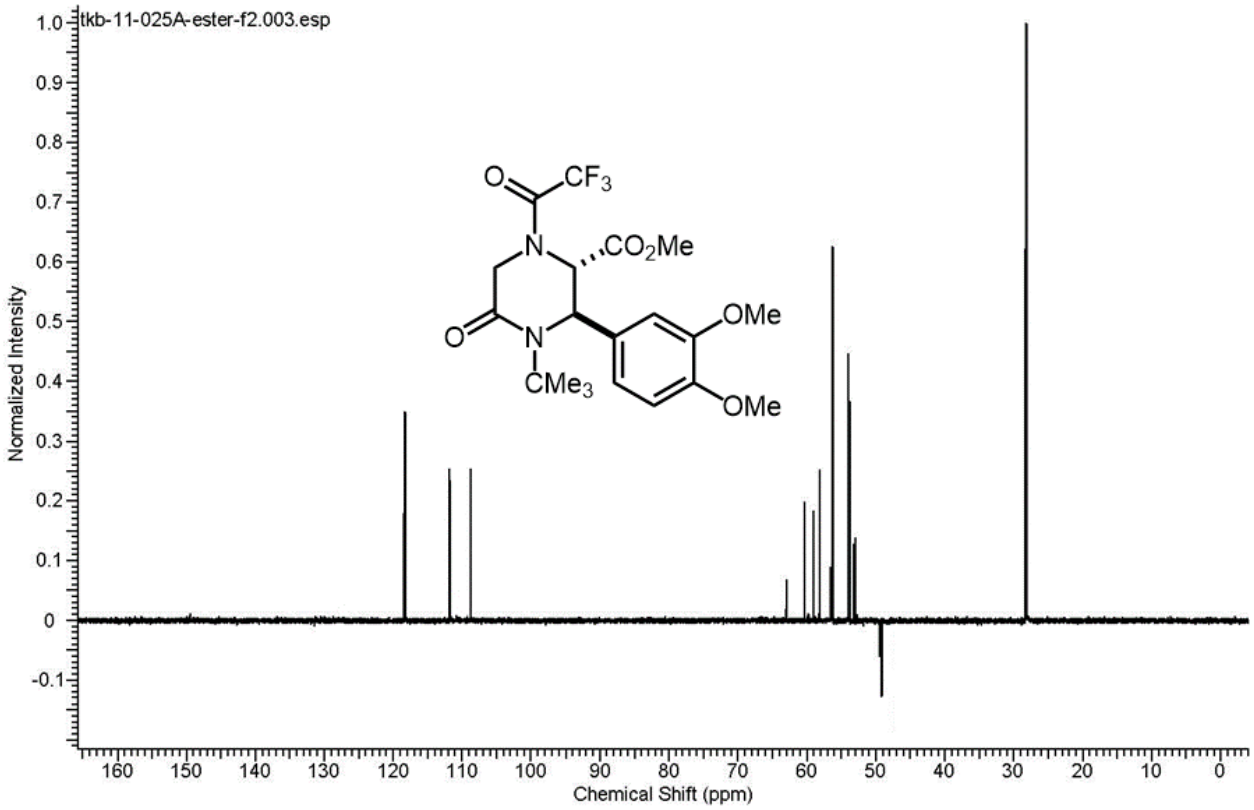
[ppm]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0.5
0.4
0.3
0.2
0.1
0
-0.1
O
CF3
N
CO2Me
O
N
CMe3
OMe
OMe
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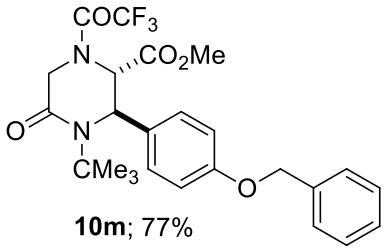
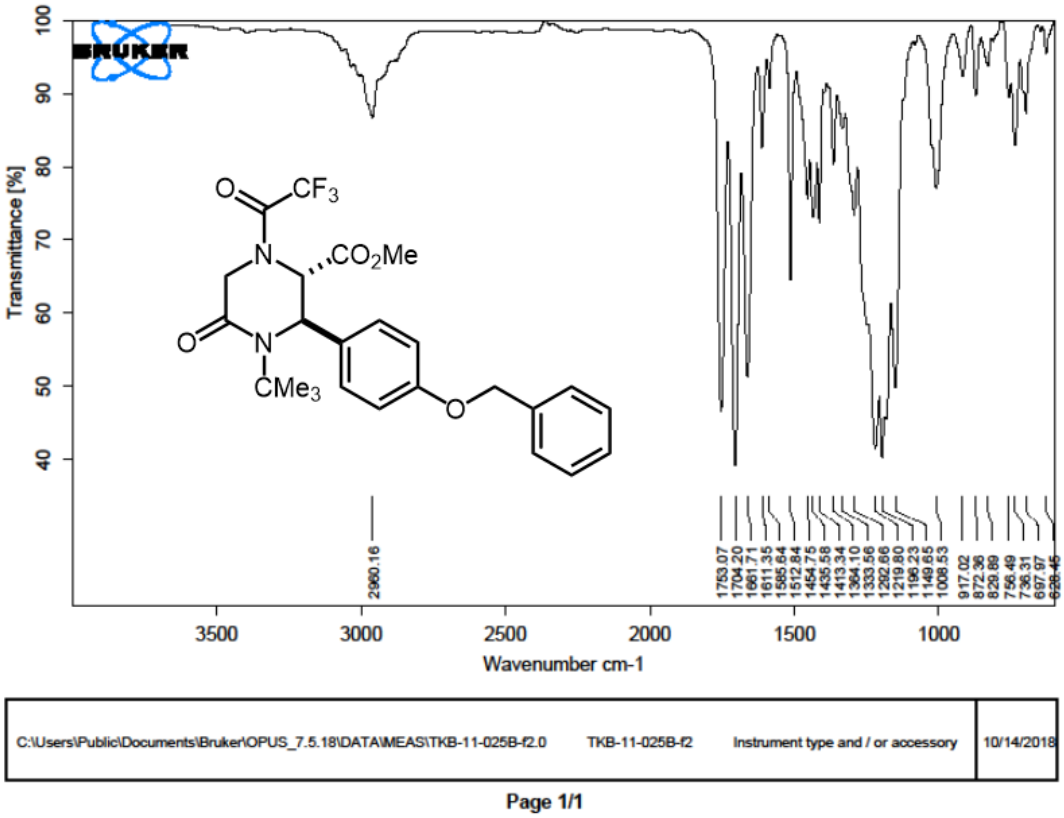
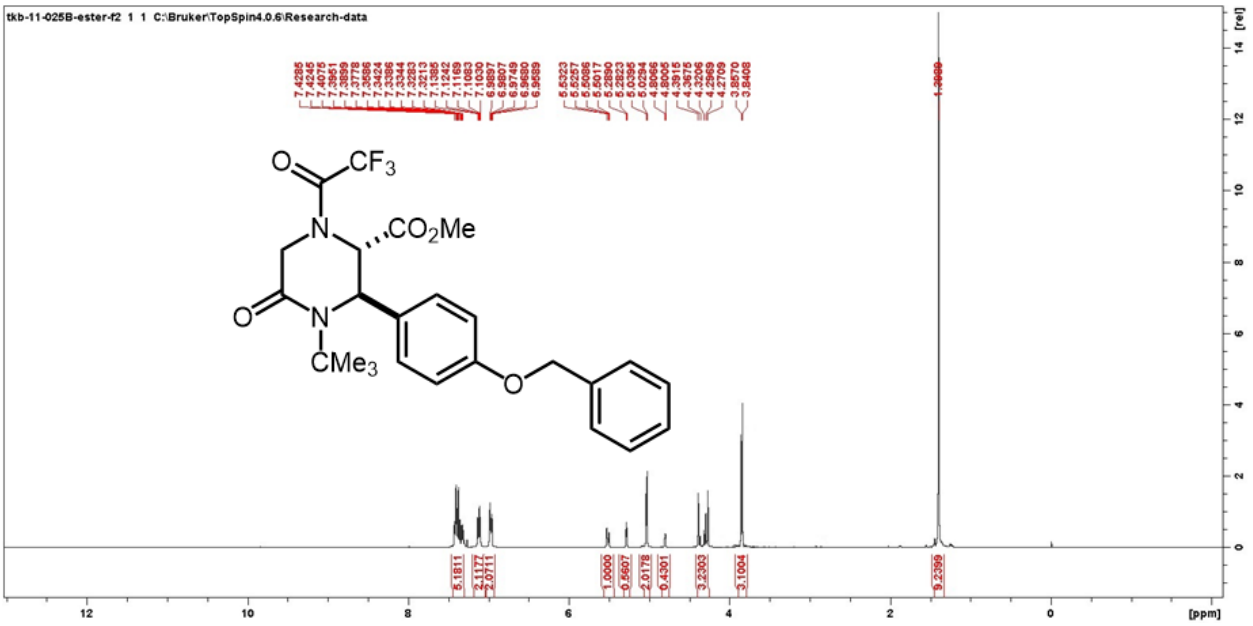
Chemical Shift (ppm)



10m; 77%

Prepared in 5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 1.895 g, 77%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.30 – 7.21 (m, 5H), 7.02 – 6.92 (m, 2H), 6.87 – 6.78 (m, 2H), 5.36 (d, J = 9.6 Hz, 1H), 4.88 (d, J = 4.0 Hz, 2H), 4.26 – 4.10 (m, 3H), 3.70 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 167.8, 164.2, 163.3, 159.0, 158.9, 156.4, 156.0, 136.6, 136.5, 129.9, 128.7, 127.6, 126.9, 117.1, 115.5, 114.6, 114.42, 70.3, 70.2, 62.7, 60.1, 59.6, 59.4, 58.6, 57.6, 53.7, 52.8, 48.9, 47.8, 28.0, 27.9. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{25}H_{27}F_3N_2O_5$ 492.1872; found 492.1877.

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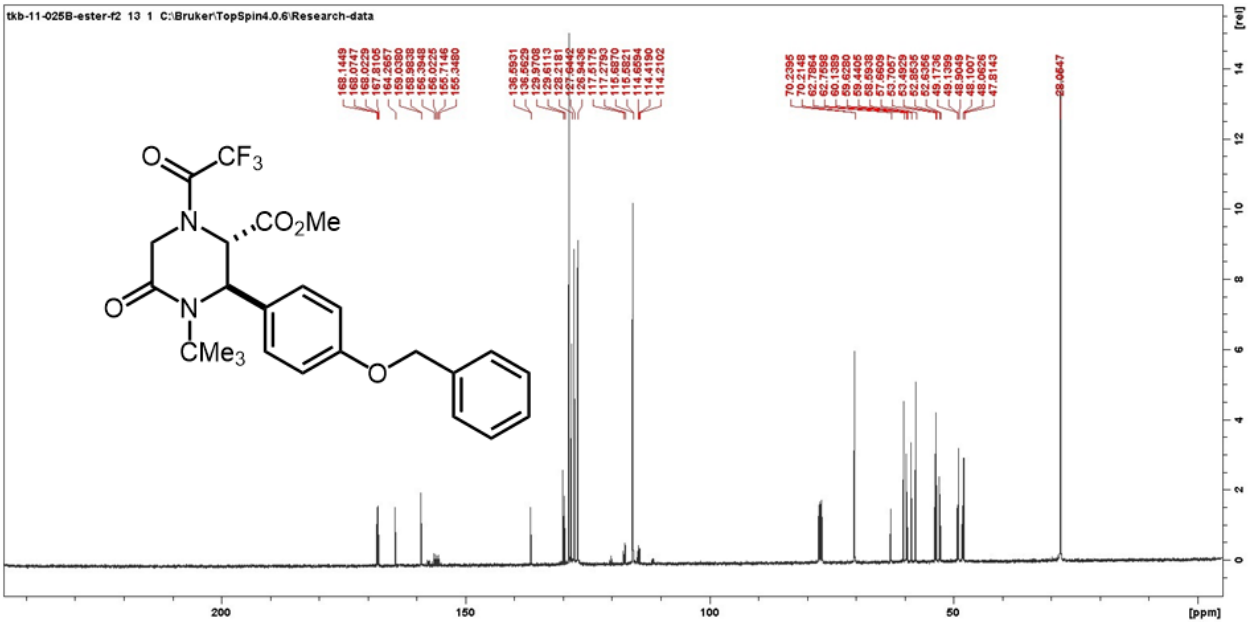
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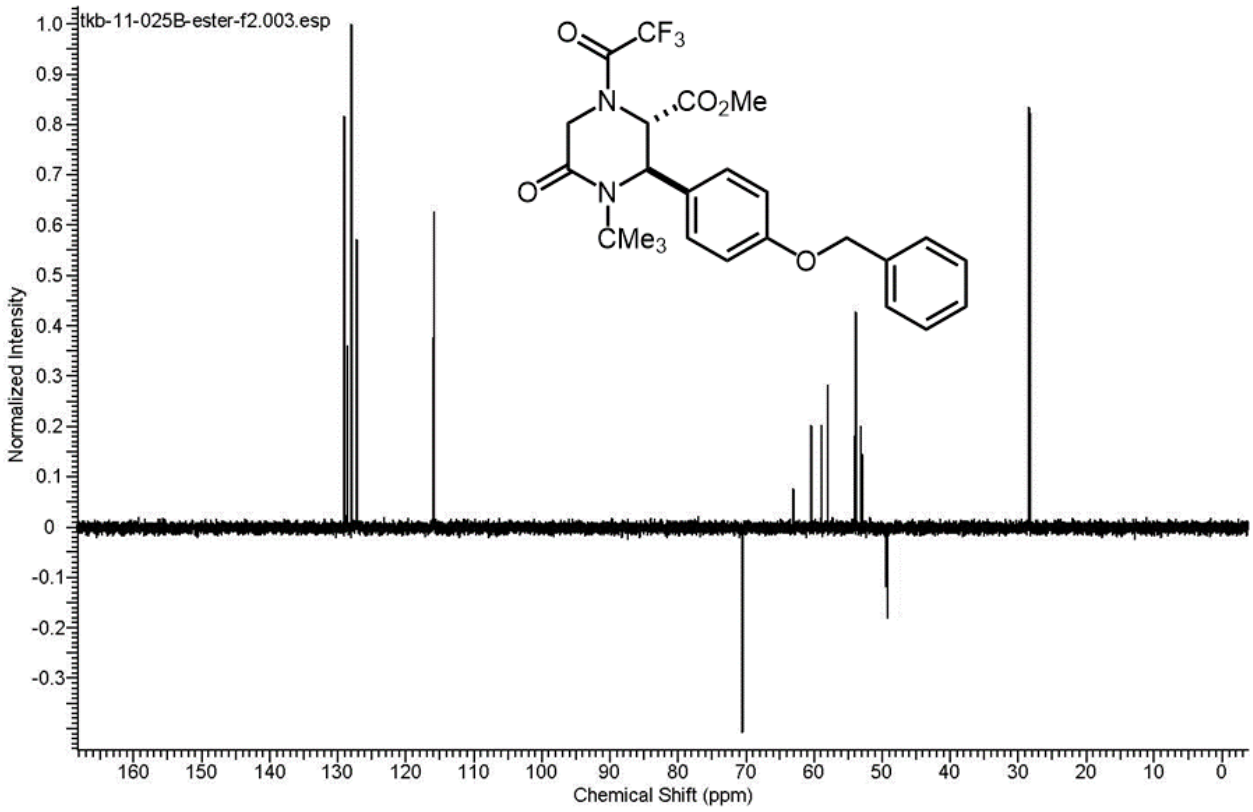
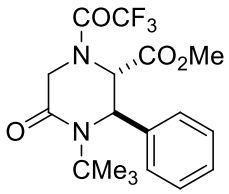
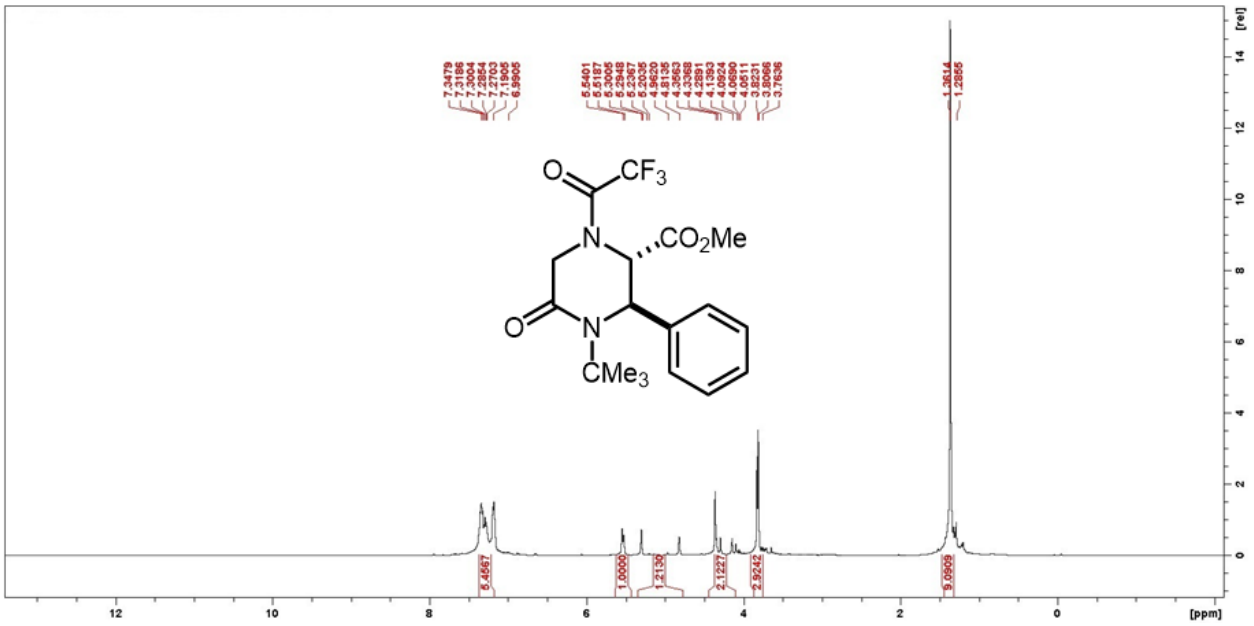




10n; 72%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 278 mg, 72%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 7.36 – 7.23 (m, 5H), 5.53 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.30 (d, *J* = 2.8 Hz, 0.5H), 4.82 (d, *J* = 2.8 Hz, 0.5H), 4.32 – 4.01 (m, 2H), 3.81 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.6, 164.2, 163.1, 156.26, 155.8, 155.6, 155.2, 137.8, 137.5, 129.3, 129.3, 128.7, 128.6, 125.6, 125.5, , 118.7, 117.1, 116.3, 62.6, 62.6, 60.00, 59.6, 59.0, 58.0, 53.7, 53.4, 48.0, 47.7, 28.0, 27.9. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{18}H_{21}F_3N_2O_4$ 386.1453; found 386.1459.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1.2865
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CF3
N
CO2Me
O
N
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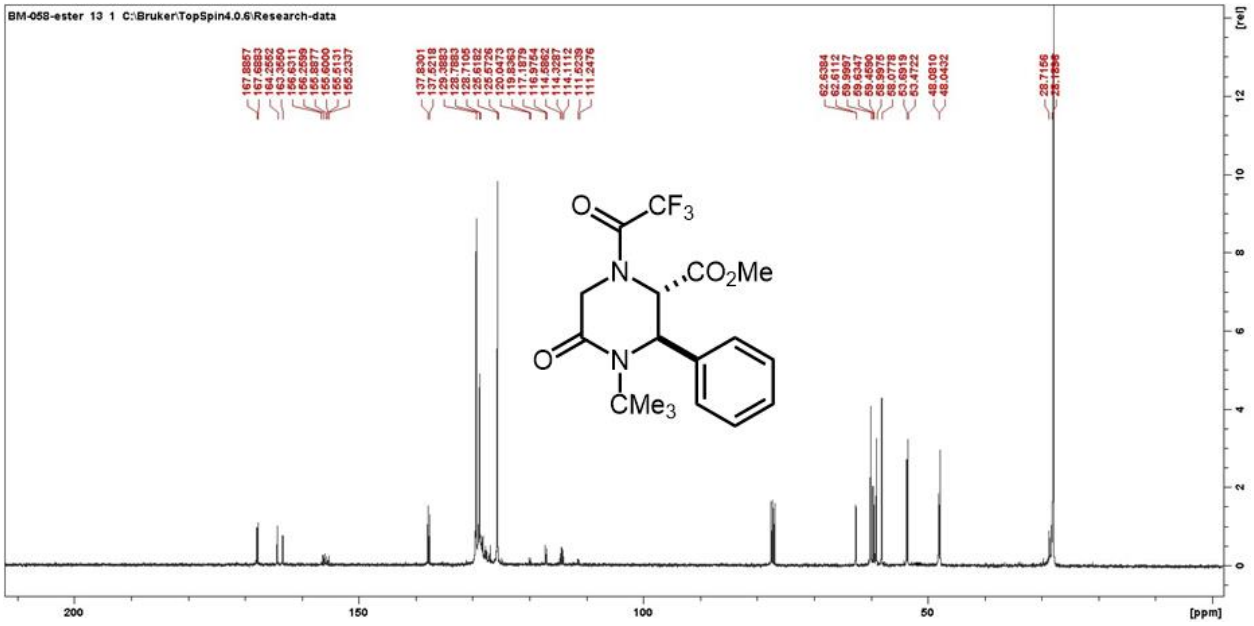
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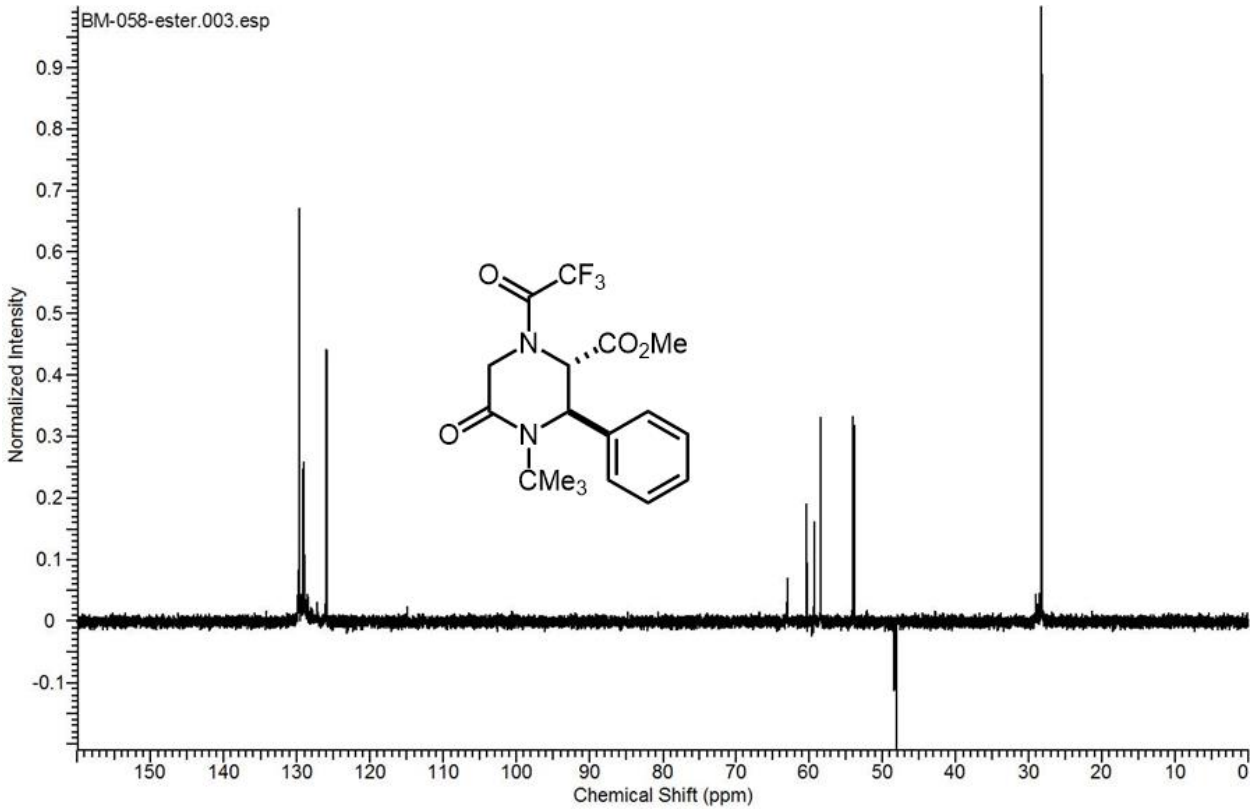
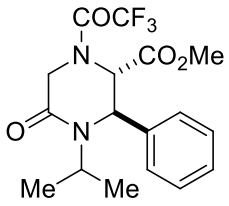
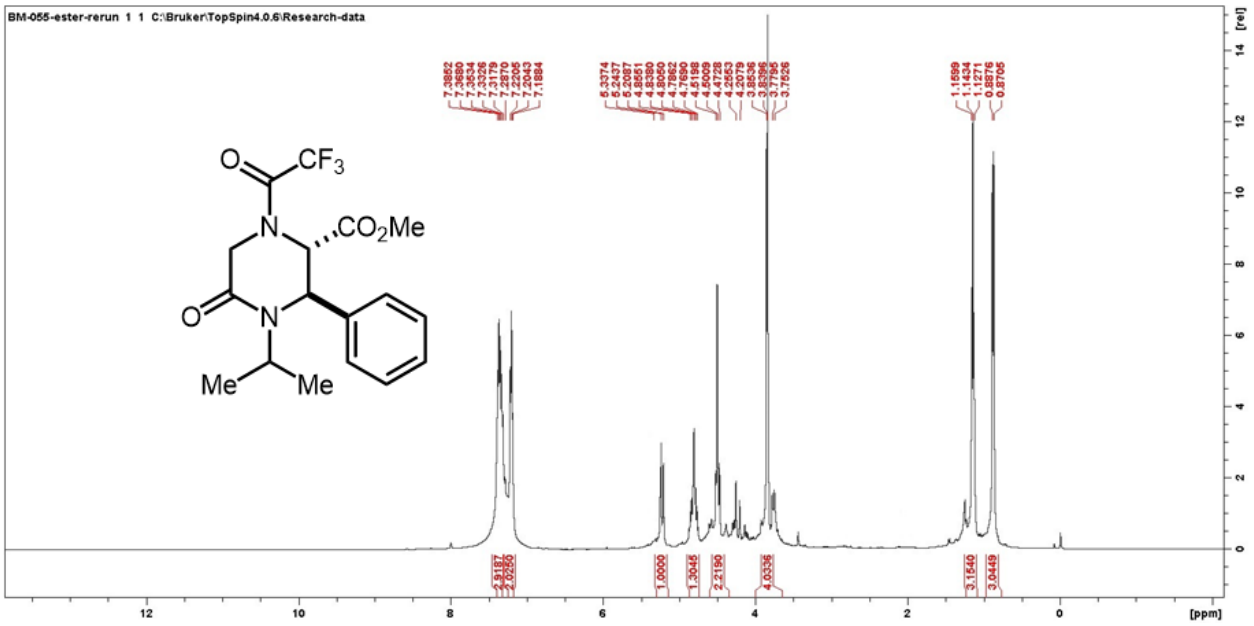




10o; 70%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 260 mg, 70%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 7.31 – 7.09 (m, 5H), 5.20 (dd, *J* = 13.8, 2.4 Hz, 1H), 4.78 (td, *J* = 14.3, 12.4, 6.9 Hz, 1H), 4.46 (d, *J* = 11.2 Hz, 2H), 4.23 (t, *J* = 18.5 Hz, 1H), 3.63 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 167.4, 163.5, 162.6, 155.9, 137.9, 137.7, 129.3, 129.2, 128.9, 128.8, 128.6, 128.3, 125.8, 125.6, 125.6, 119.7, 117.2, 116.9, 114.3, 114.1, 62.1, 62.0, 59.3, 56.9, 56.1, 53.7, 53.5, 47.1, 47.1, 47.0, 46.7, 46.6, 46.1, 19.8, 19.7, 19.6. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{17}H_{19}F_3N_2O_4$ 372.1297; found 372.1291.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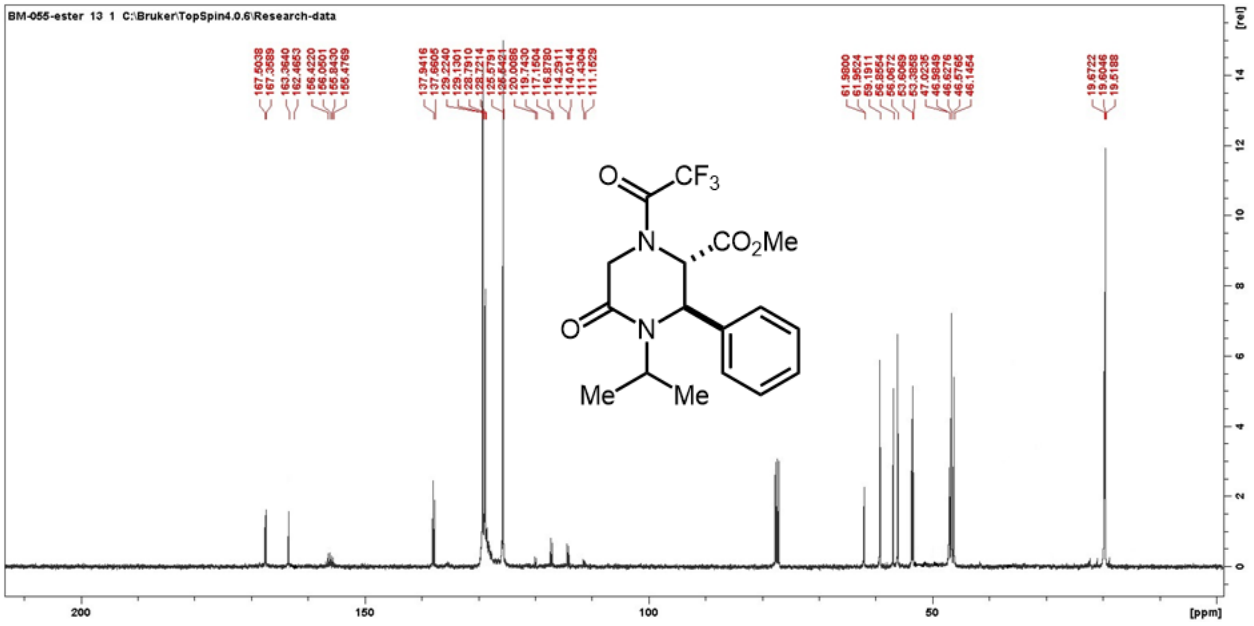
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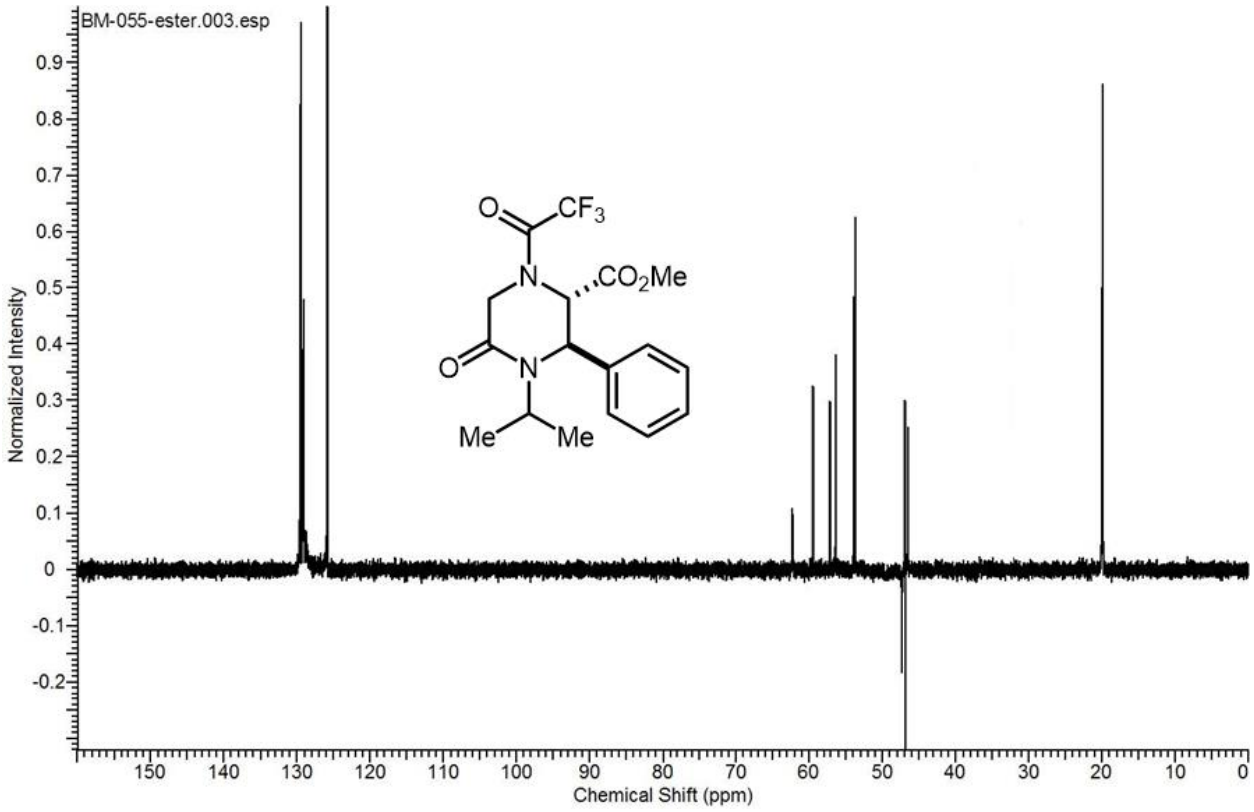

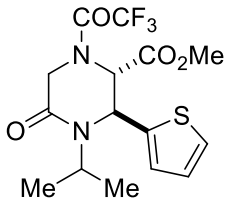

10p; 79%

Prepared in 1 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 299 mg, 79%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 7.11 (td, *J* = 4.6, 1.8 Hz, 1H), 6.80 (qd, *J* = 4.9, 4.2, 2.8 Hz, 2H), 5.29 (dd, *J* = 17.0, 2.5 Hz, 1H), 4.54 (dp, *J* = 28.8, 6.9 Hz, 1H), 4.41 – 4.25 (m, 2H), 4.15 – 4.05 (m, 1H), 3.66 (d, *J* = 5.7 Hz, 3H), 3.59 (d, *J* = 10.5 Hz, 2H), 0.97 (dd, *J* = 9.0, 6.8 Hz, 3H), 0.82 (dd, *J* = 7.0, 3.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.2, 162.9, 162.0, 161.1, 157.2, 156.9, 156.5, 156.1, 155.7, 141.9, 141.5, 127.4, 127.2, 126.2, 126.2, 125.8, 120.1, 119.4, 117.4, 117.2, 114.63, 114.21, 111.55, 62.2, 59.3, 53.7, 53.2, 52.8, 52.6, 52.6, 46.9, 46.7, 46.6, 19.7, 19.6, 19.5, 19.4. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{15}H_{17}F_3N_2O_4S$ 378.0861; found 378.0869.

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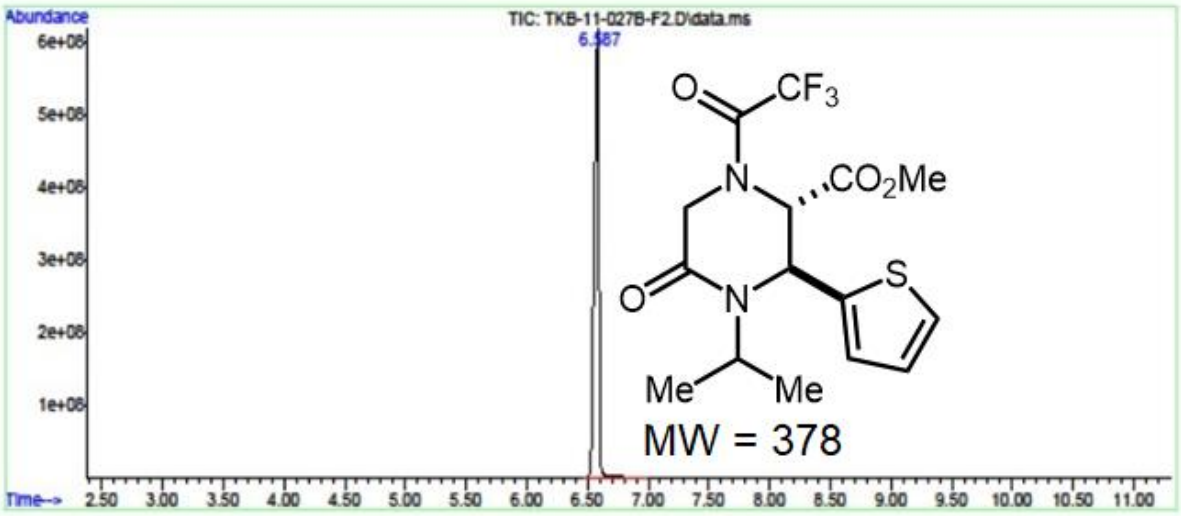

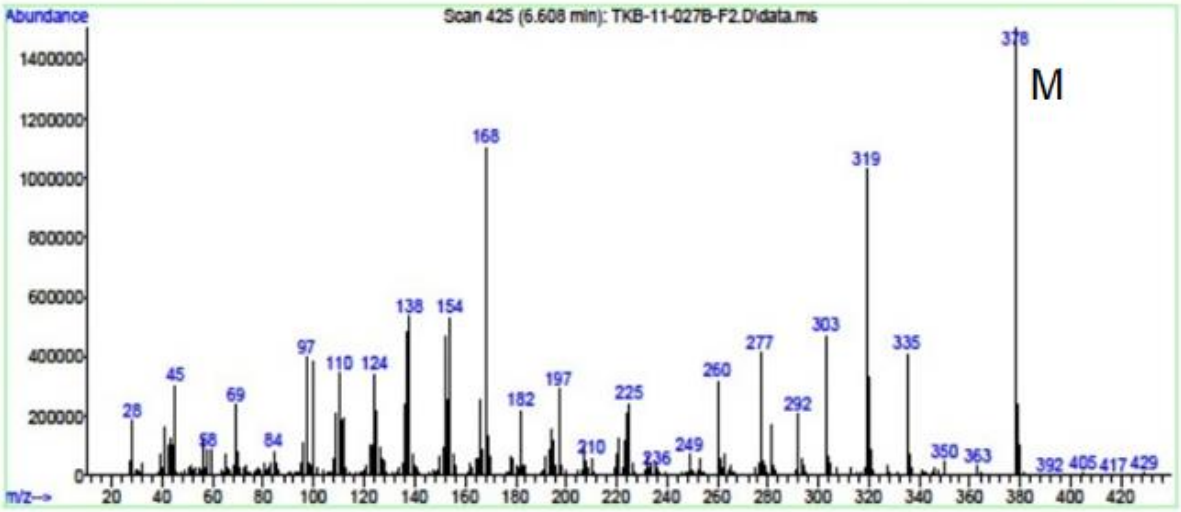

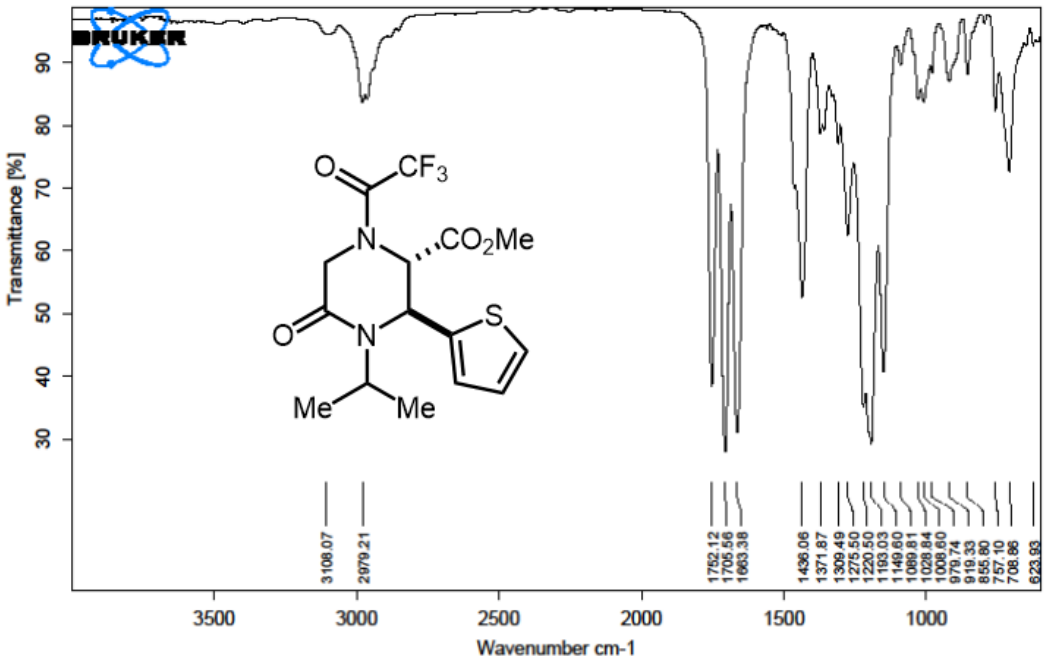
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919.33
855.80
757.10
708.86
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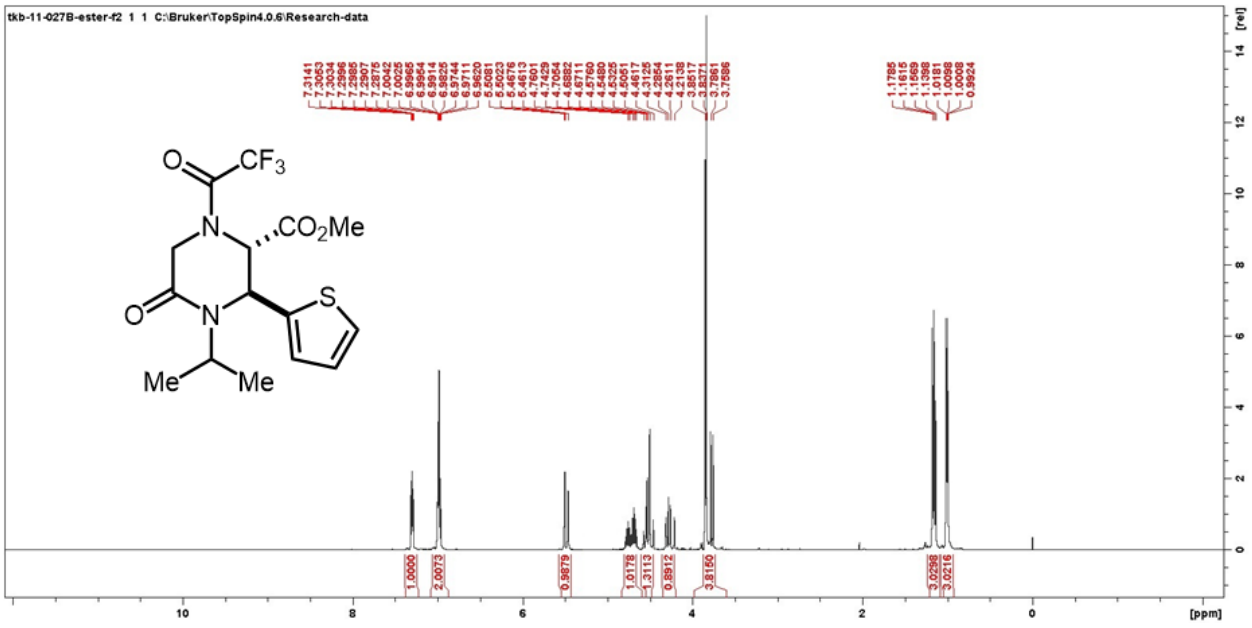
TKB-11-027B-f2
Instrument type and / or accessory
10/14/2018
Page 1/1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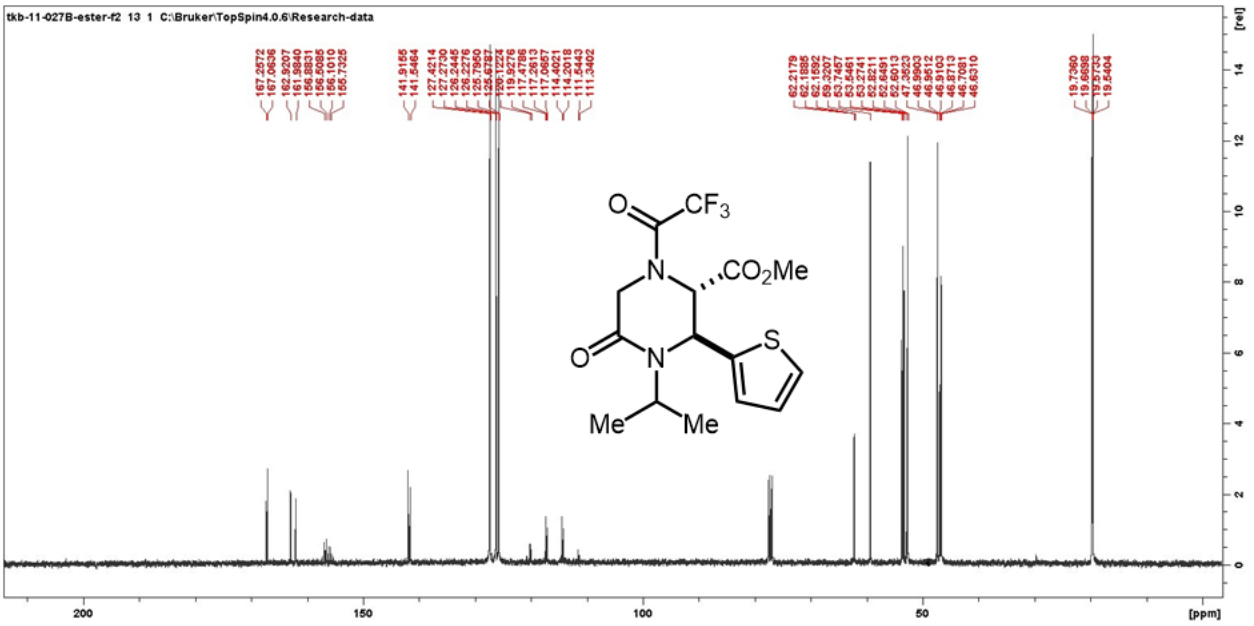
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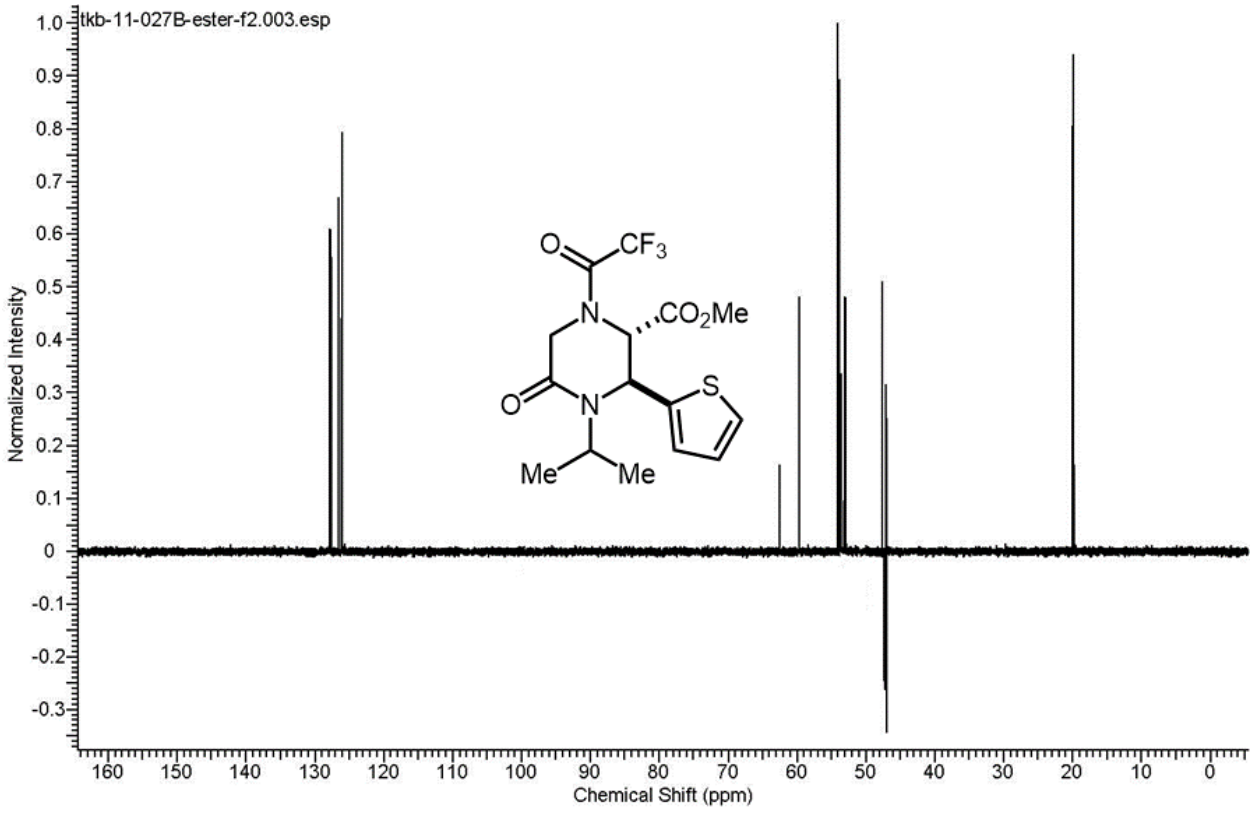
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-0.3
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CF3
N
CO2Me
O
N
S
Me
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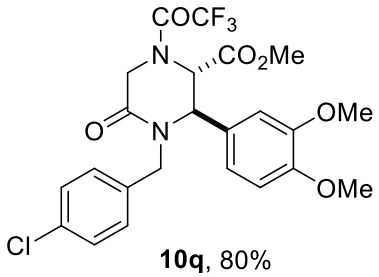
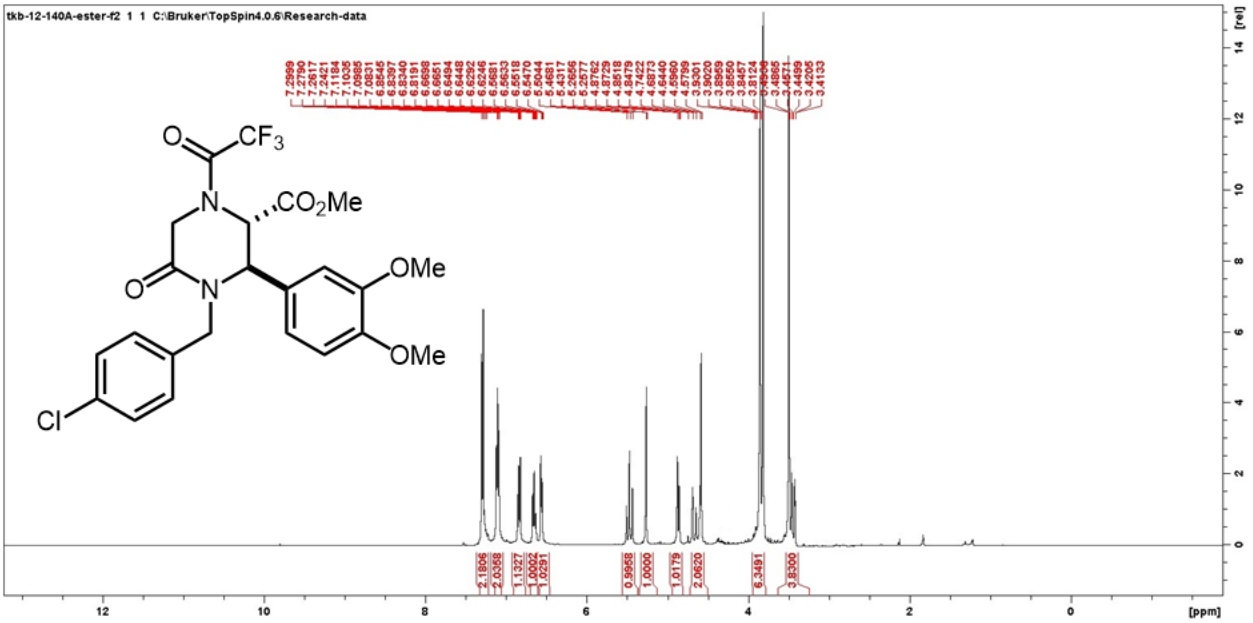
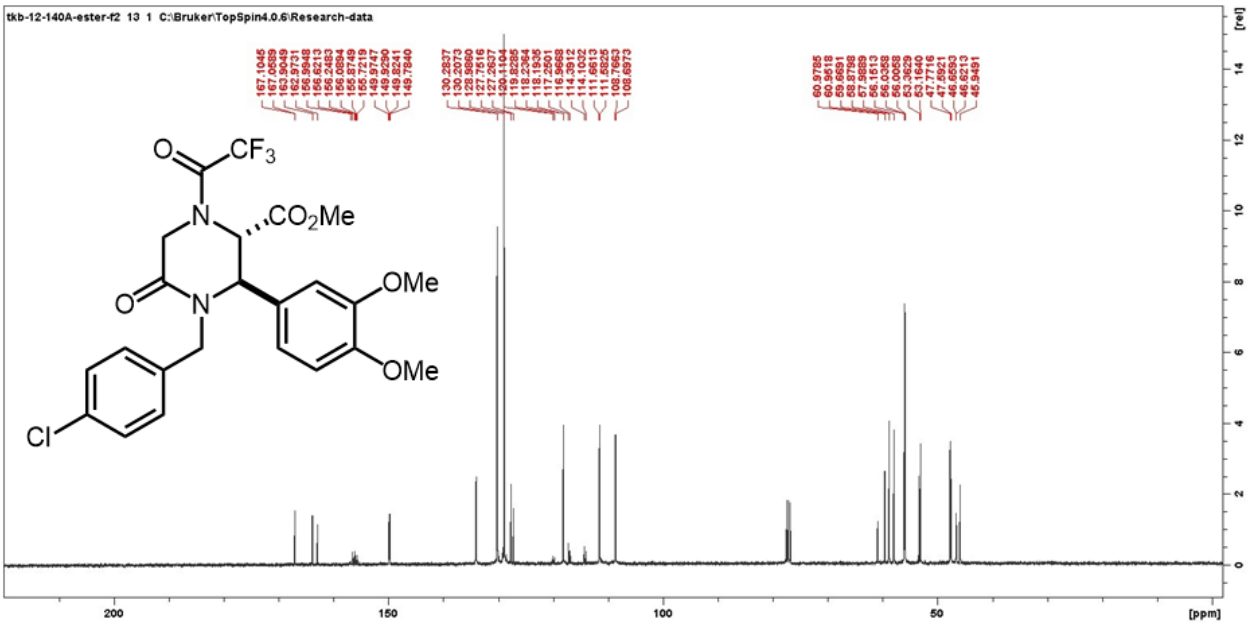


10q, 80%

Prepared in 0.5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (20:80). Yield = 206 mg, 80%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.29 – 7.24 (m, 2H), 7.20 – 7.07 (m, 2H), 6.85 (dd, *J* = 8.3, 5.9 Hz, 1H), 6.67 (td, *J* = 8.2, 2.2 Hz, 1H), 6.57 (dd, *J* = 6.6, 2.2 Hz, 1H), 5.51 (t, *J* = 14.6 Hz, 1H), 5.35 – 5.28 (m, 1H), 4.91 (dd, *J* = 9.9, 2.1 Hz, 1H), 4.75 – 4.66 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.53 (s, 3H), 3.48 (dd, *J* = 14.6, 3.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 167.1, 167.0, 163.9, 162.9, 156.6, 156.2, 156.0, 155.7, 149.9, 149.8, 134.2, 134.0, 130.3, 130.2, 129.0, 127.8, 127.3, 120.1, 118.2, 117.2, 116.9, 114.4, 114.1, 111.7, 111.6, 108.8, 108.7, 61.0, 60.9, 59.6, 58.8, 57.9, 56.2, 56.1, 56.0, 53.3, 53.1, 47.7, 47.6, 46.7, 46.6, 45.9. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{23}H_{22}ClF_3N_2O_6$ 514.1118; found 514.1123.

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OMe
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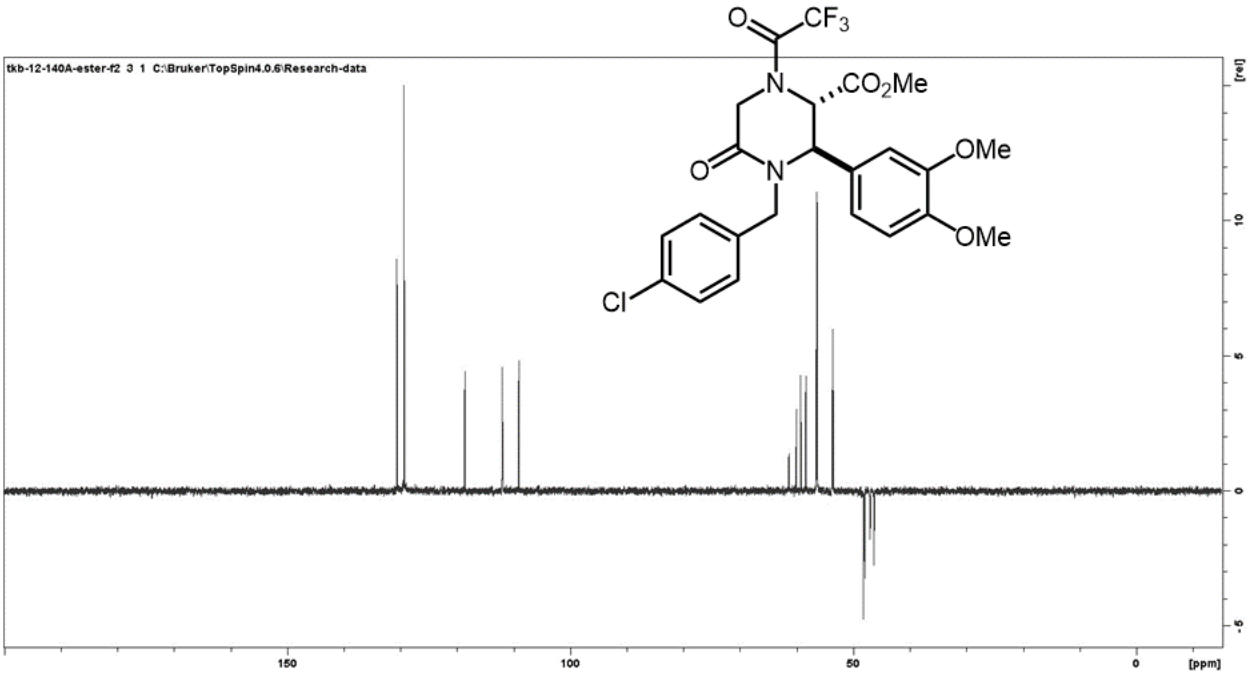
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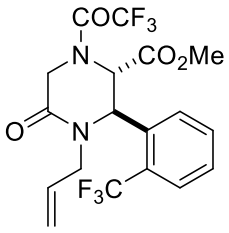
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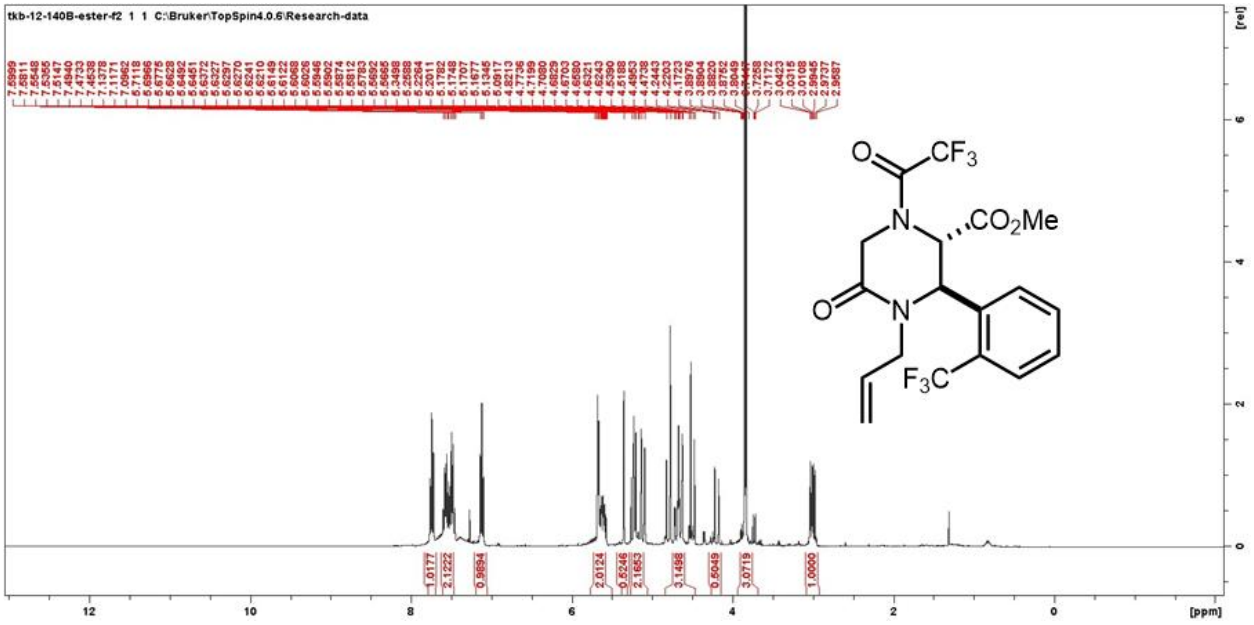
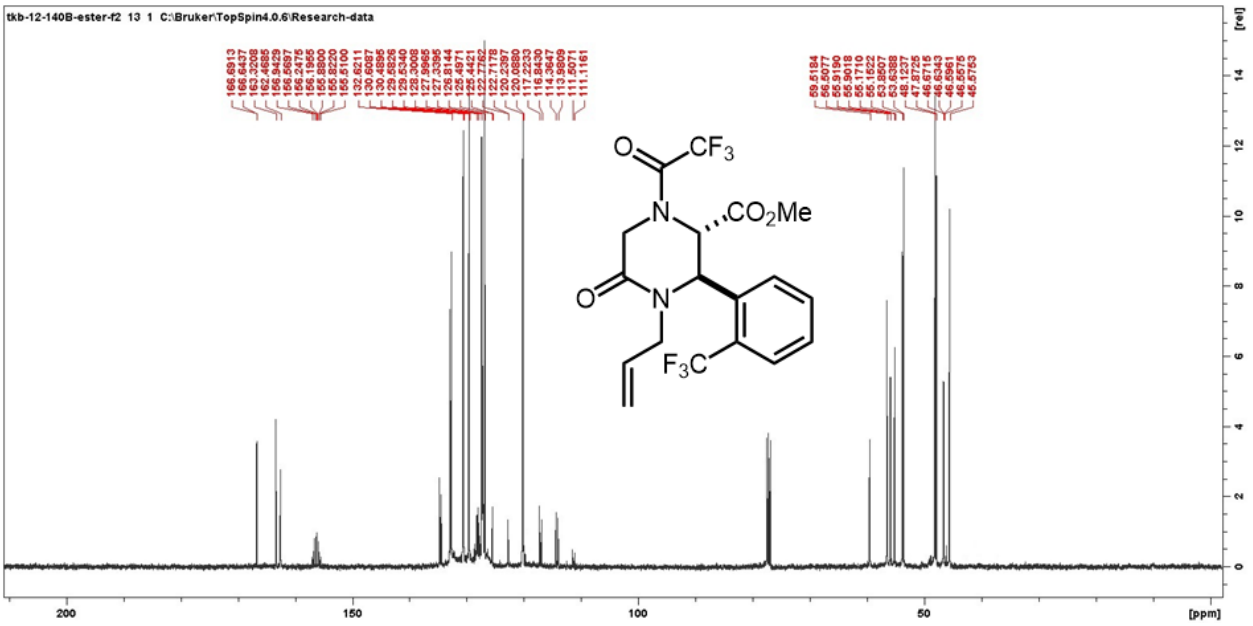
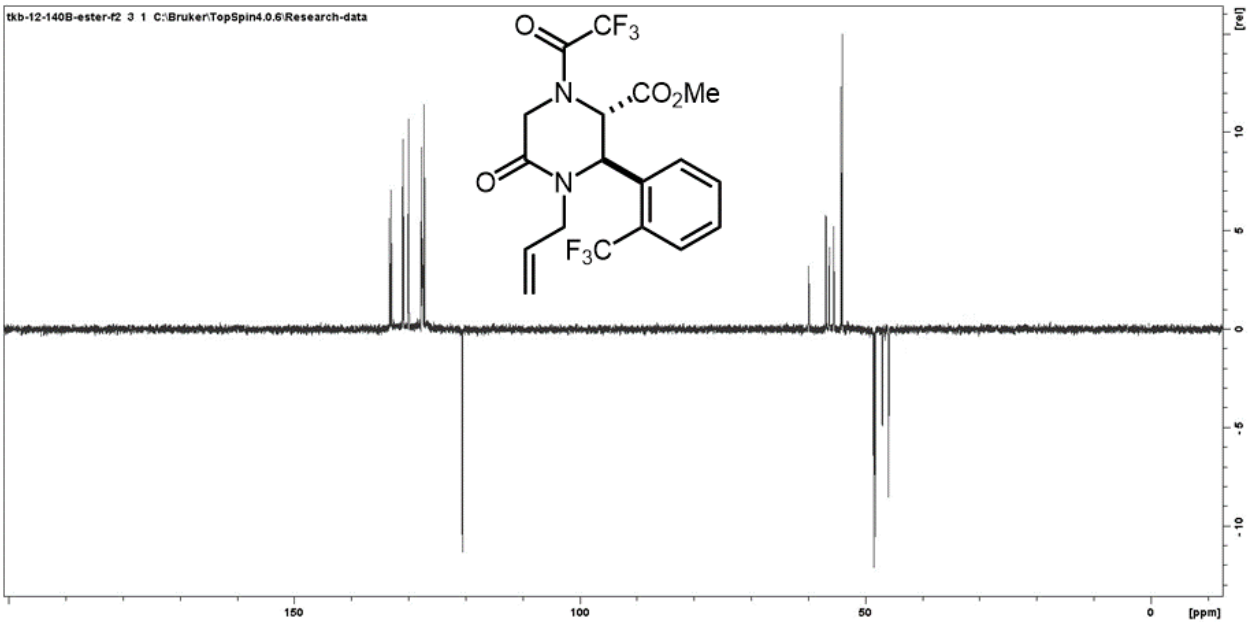
CO2Me
O
N
F3C

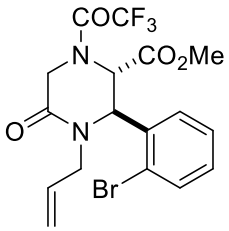
10r, 61%

Prepared in 0.5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 133.7 mg, 61%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.74 (ddd, *J* = 9.4, 7.8, 1.4 Hz, 1H), 7.69 – 7.37 (m, 2H), 7.12 (t, *J* = 8.3 Hz, 1H), 5.70 – 5.54 (m, 2H), 5.37 (s, 0.5H), 5.30 – 5.18 (m, 2H), 4.75 – 4.56 (m, 3H), 4.31 – 4.20 (m, 0.5H), 3.84 (s, 3H), 3.08 – 2.94 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 166.7, 166.6, 163.3, 162.5, 156.9, 156.5, 156.3, 156.2, 155.9, 155.8, 155.5, 134.7, 134.4, 132.9, 132.6, 130.6, 130.5, 129.6, 129.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.3, 127.2,127.1, 127.0, 126.8, 125.5, 125.4, 122.8, 122.7, 120.2, 120.1, 119.0, 117.2, 116.9, 114.4, 113.9, 111.5, 111.1, 59.5, 59.4, 56.5, 55.9, 55.2, 55.18, 55.15, 55.13, 53.9, 53.6, 48.1, 47.9, 46.6, 45.6. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{18}H_{16}F_6N_2O_4$ 438.1014; found 438.1018.





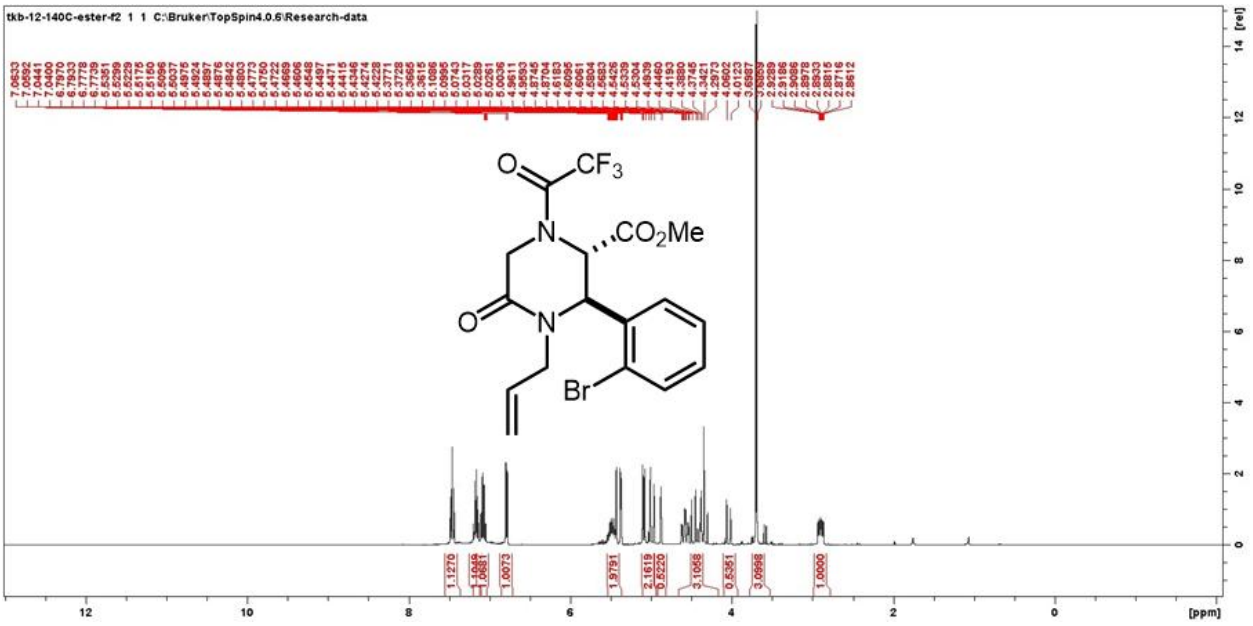


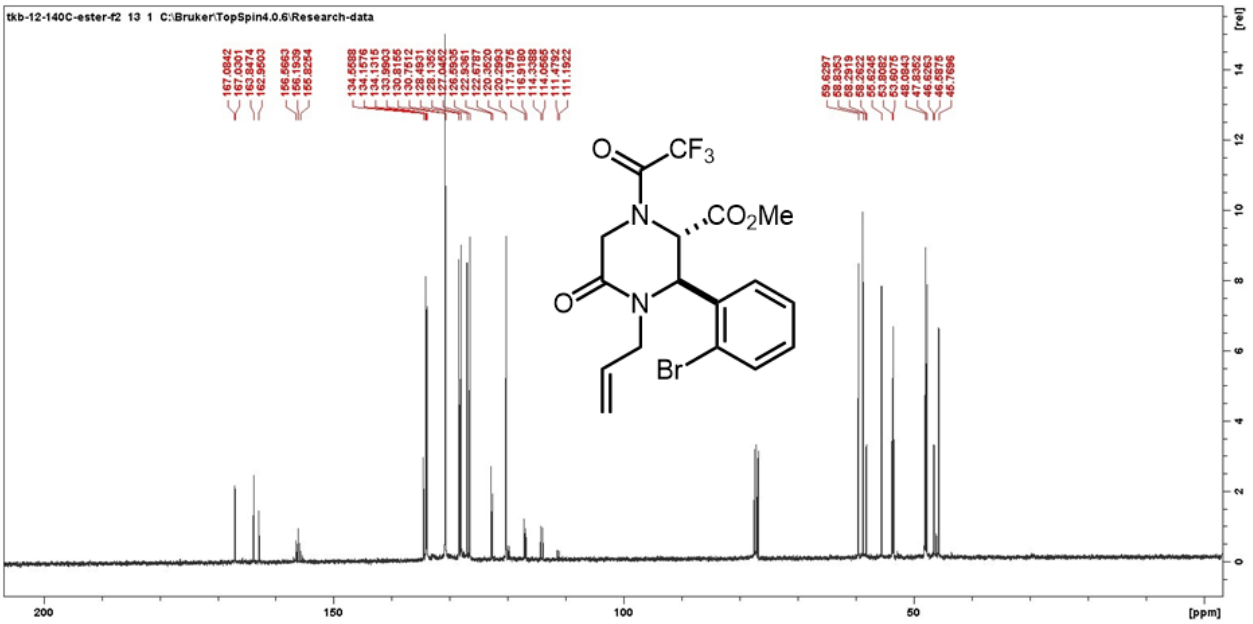


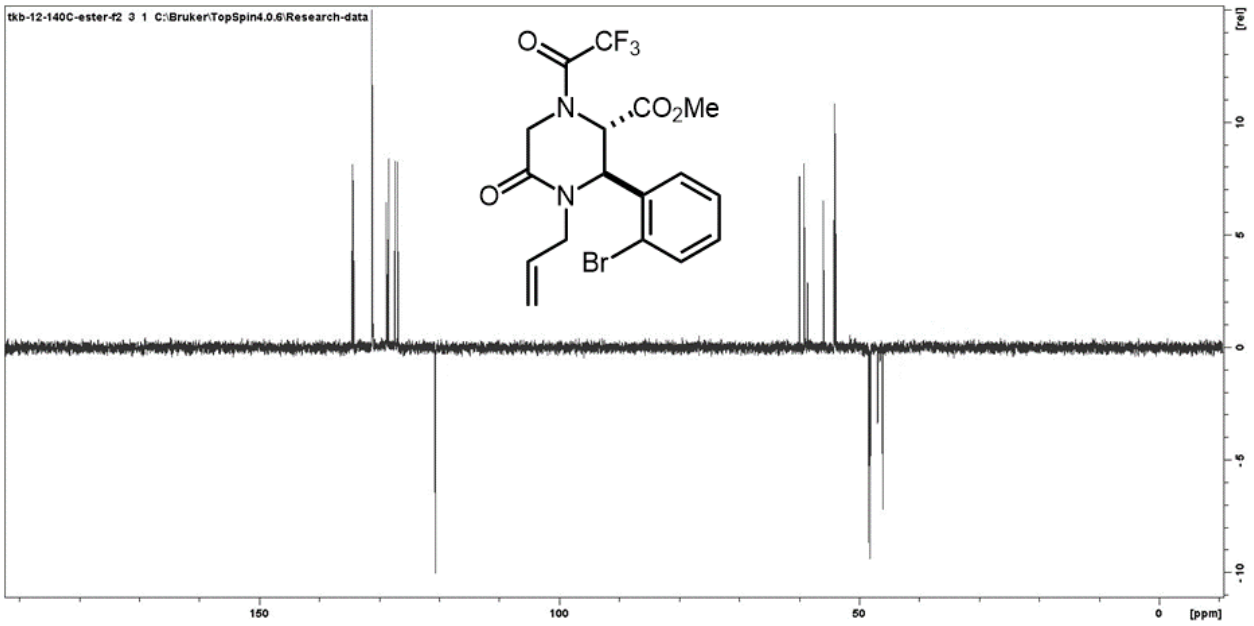
10s, 65%

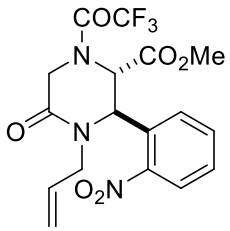
Prepared in 0.5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Yield = 146 mg, 65%, 95:5 dr. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.46 (td, *J* = 8.0, 1.3 Hz, 1H), 7.23 – 6.97 (m, 2H), 6.79 (dd, *J* = 7.7, 1.7 Hz, 1H), 5.57 – 5.40 (m, 2H), 5.15 – 4.90 (m, 2H), 4.87 (d, *J* = 2.0 Hz, 0.5H), 4.65 – 4.31 (m, 3H), 4.01 (d, *J* = 1.1 Hz, 0.5H), 3.69 (s, 3H), 2.95 – 2.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.09, 167.03, 163.85, 162.96, 156.57, 156.20, 155.83, 134.56, 134.16, 134.13, 133.99, 130.88, 130.82, 130.76, 130.68, 128.50, 128.14, 127.05, 126.60, 122.94, 122.68, 120.36, 120.30, 119.18, 117.20, 116.92, 114.34, 114.06, 111.48, 111.20, 59.63, 58.84, 58.29, 58.26, 55.63, 53.81, 53.61, 48.09, 47.84, 46.63, 46.59, 45.77. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{17}H_{16}BrF_3N_2O_4$ 448.0246; found 448.0242.



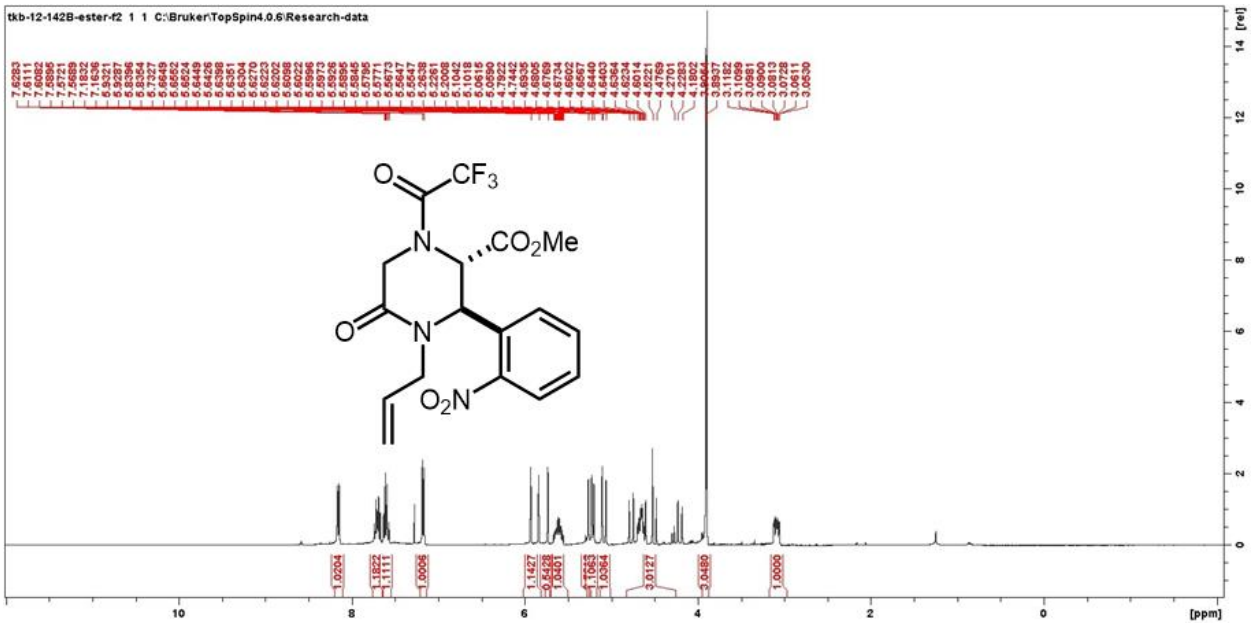






10t, 58%

Prepared in 0.5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Yield = 120.4 mg, 58%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.72 – 7.58 (m, 2H), 7.21 (dt, *J* = 7.9, 1.5 Hz, 1H), 5.96 (d, *J* = 1.7 Hz, 1H), 5.72 – 5.56 (m, 1H), 5.32 – 5.18 (m, 2H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.75 – 4.21 (m, 3H), 3.93 (s, 3H), 3.22 (ddd, *J* = 14.9, 8.0, 3.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.64, 163.84, 163.02, 156.58, 156.31, 156.21, 155.94, 148.17, 148.15, 134.61, 134.27, 131.77, 131.43, 130.69, 130.56, 130.54, 130.48, 127.99, 127.46, 126.46, 126.20, 120.57, 120.50, 120.06, 119.77, 117.20, 116.91, 114.34, 114.05, 111.48, 59.20, 59.17, 56.45, 56.32, 55.65, 54.00, 53.80, 48.43, 48.18, 46.73, 46.70, 45.65. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{17}H_{16}F_3N_3O_6$ 415.0991; found 415.0996.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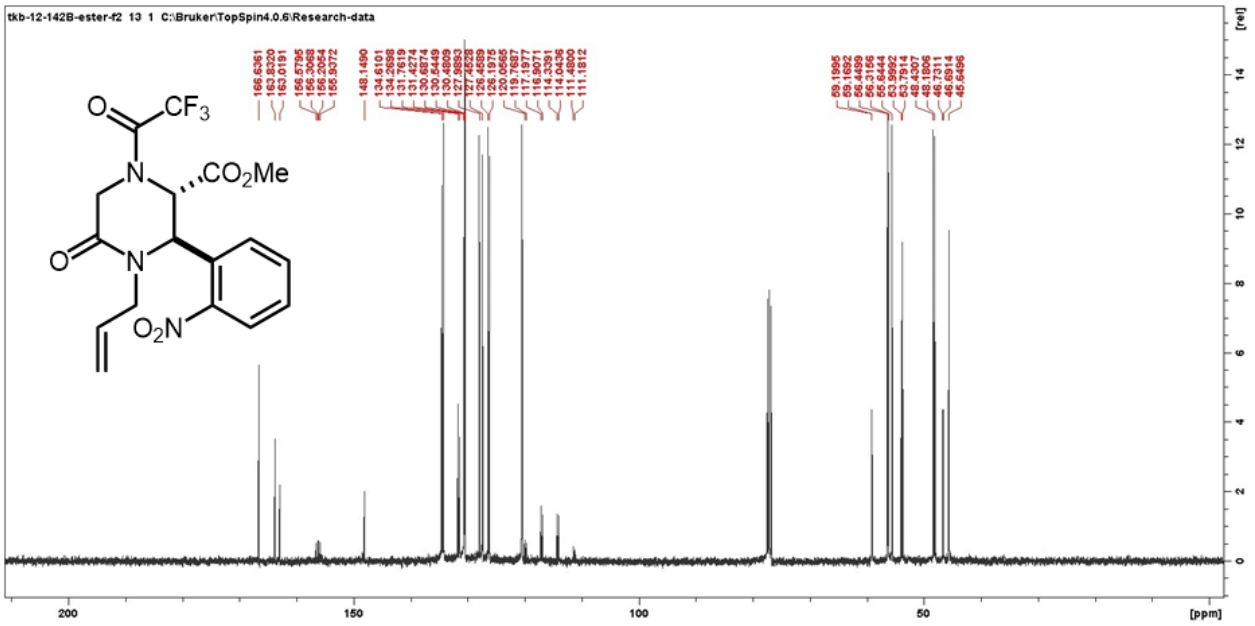
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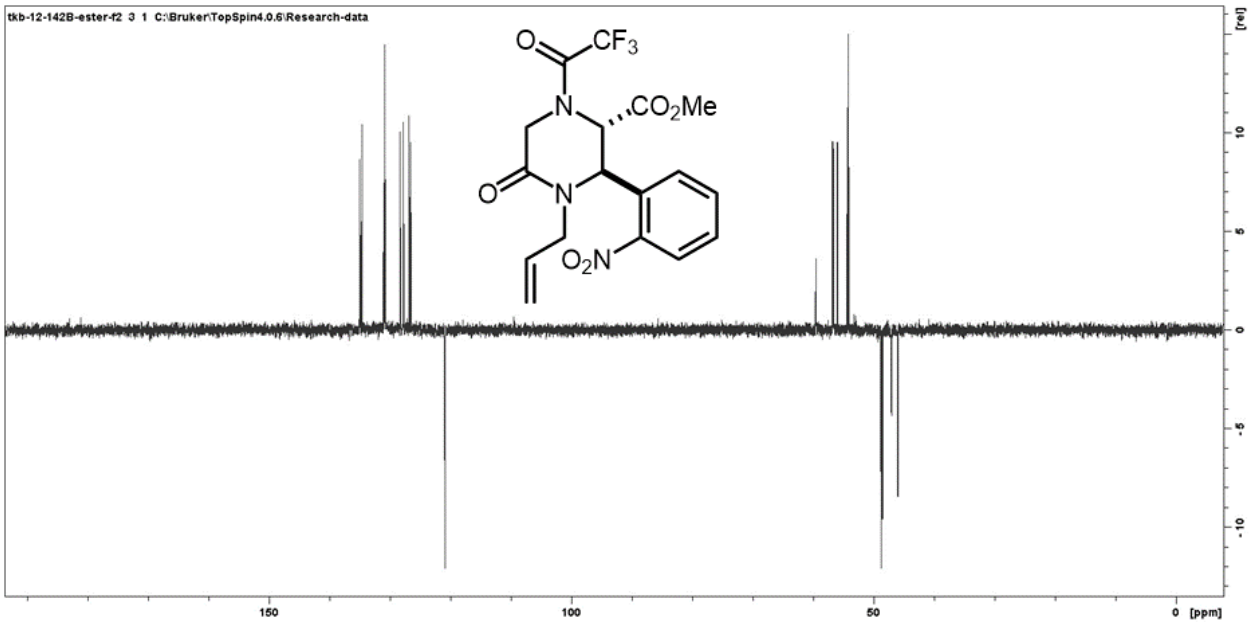
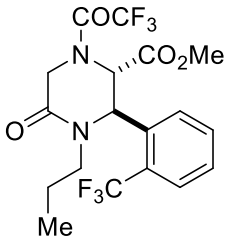
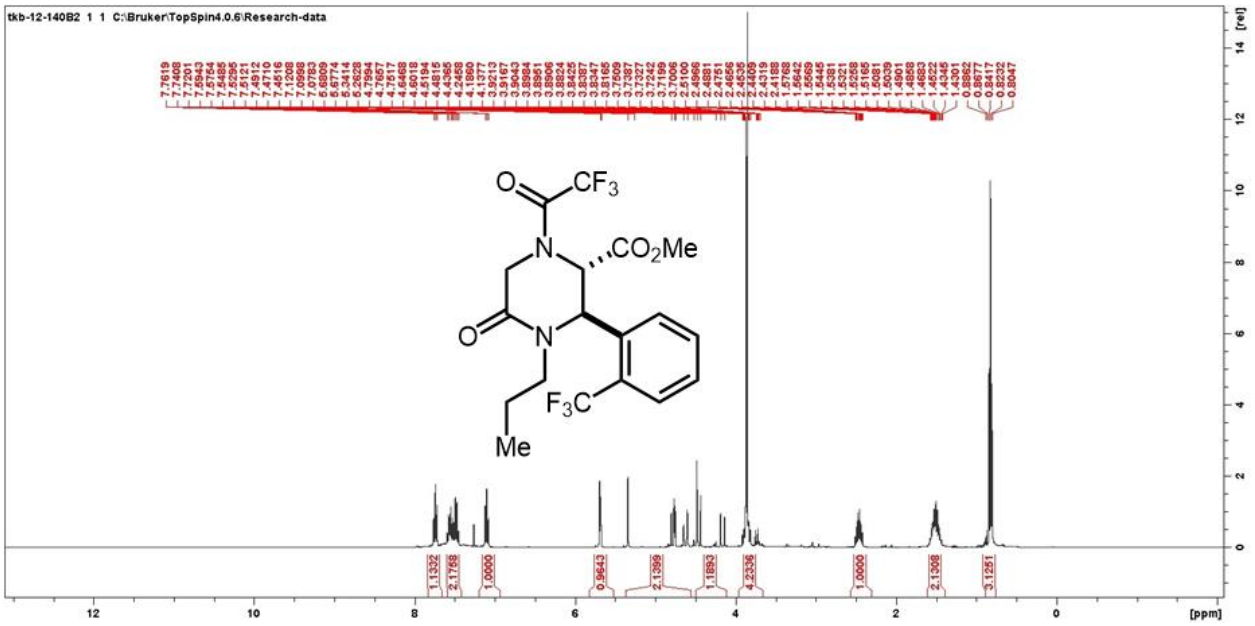




10u, 63%

Prepared in 0.5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 138.7 mg, 63%, 95:5 dr. H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.79 – 7.70 (m, 1H), 7.70 – 7.34 (m, 2H), 7.10 (t, *J* = 8.5 Hz, 1H), 5.69 (dd, *J* = 5.9, 1.8 Hz, 1H), 5.37 (s, 0.5H), 4.82 – 4.53 (m, 1.5H), 4.46 + 41.8 (d, *J* = 18.0 Hz, 1H), 3.94 – 3.79 (m, 4H), 2.46 (m, 1H), 1.63 – 1.39 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 166.75, 166.72, 163.49, 162.59, 156.61, 156.24, 155.91, 155.54, 134.99, 134.71, 132.90, 132.63, 129.56, 129.51, 128.29, 128.08, 127.99, 127.78, 127.32, 127.20, 127.14, 127.12, 127.08, 127.06, 127.02, 127.00, 126.94, 126.79, 125.58, 125.52, 122.86, 122.80, 120.10, 119.72, 117.24, 116.86, 114.38, 114.00, 111.52, 111.14, 59.52, 56.47, 56.44, 56.42, 55.59, 55.57, 55.55, 53.98, 53.76, 47.59, 47.36, 46.58, 46.54, 45.52, 20.03, 19.99, 11.06, 11.03. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{18}H_{18}F_6N_2O_4$ 440.1171; found 440.1176.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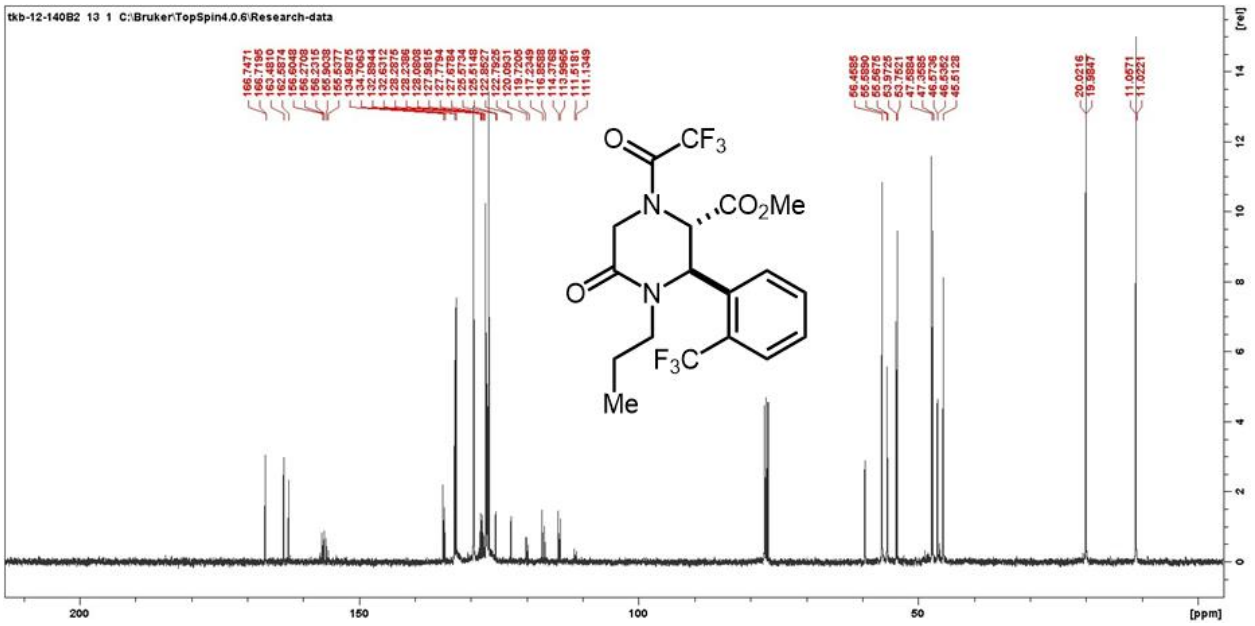
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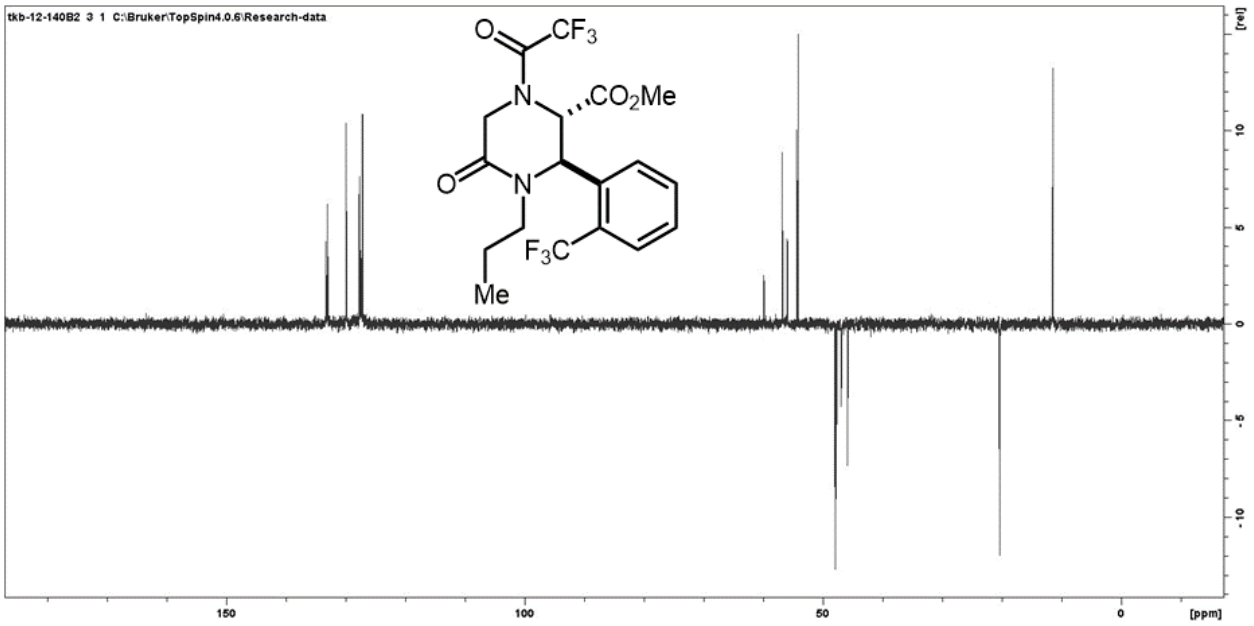
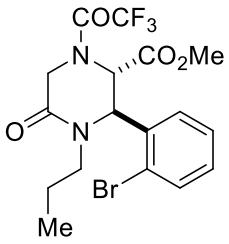
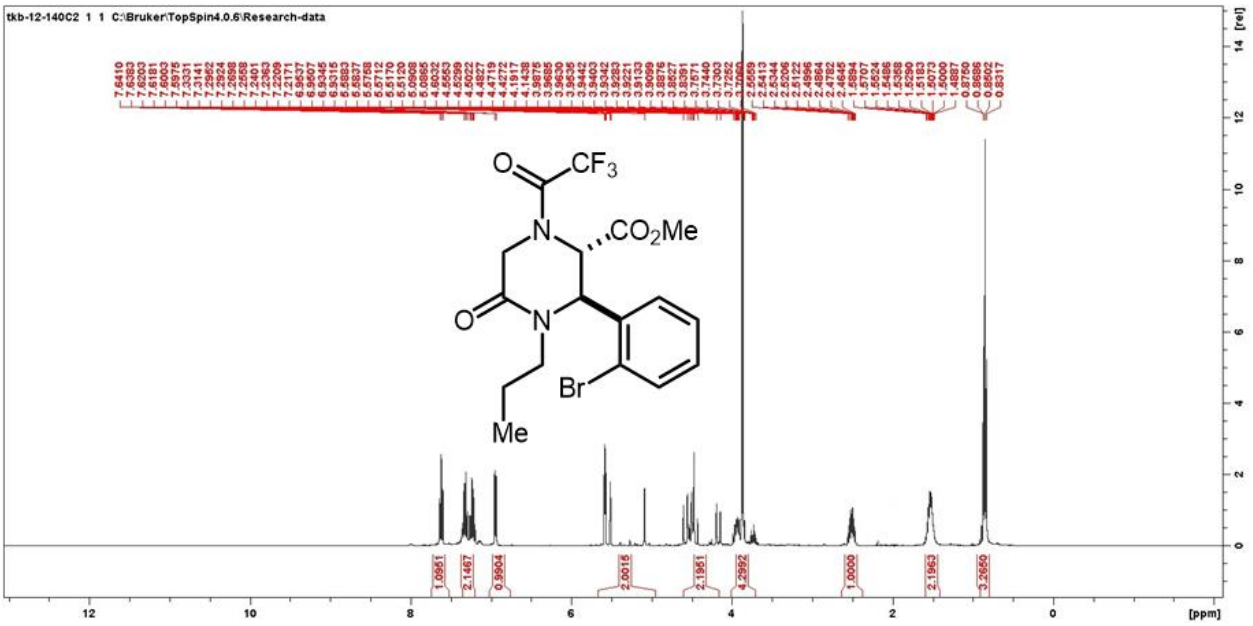




10v, 67%

Prepared in 0.5 mmol scale using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Yield = 151.2 mg, 67%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.62 (td, *J* = 8.1, 1.3 Hz, 1H), 7.41 – 7.08 (m, 2H), 6.94 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.61 – 5.09 (m, 2H), 4.64 – 4.19 (m, 2H), 4.01 – 3.88 (m, 4H), 2.51 (m, 1H), 1.63 – 1.44 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 167.19, 167.10, 164.19, 163.28, 156.57, 156.19, 155.81, 134.74, 134.32, 134.13, 133.97, 130.87, 130.81, 128.52, 128.15, 127.05, 126.59, 122.89, 122.65, 120.05, 119.80, 117.19, 116.93, 114.33, 114.07, 111.47, 111.21, 60.55, 59.69, 58.29, 58.26, 55.61, 53.90, 53.68, 47.84, 47.58, 46.56, 46.52, 45.74, 20.28, 20.22, 11.14, 11.11. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{17}H_{18}BrF_3N_2O_4$ 450.0402; found 450.0408.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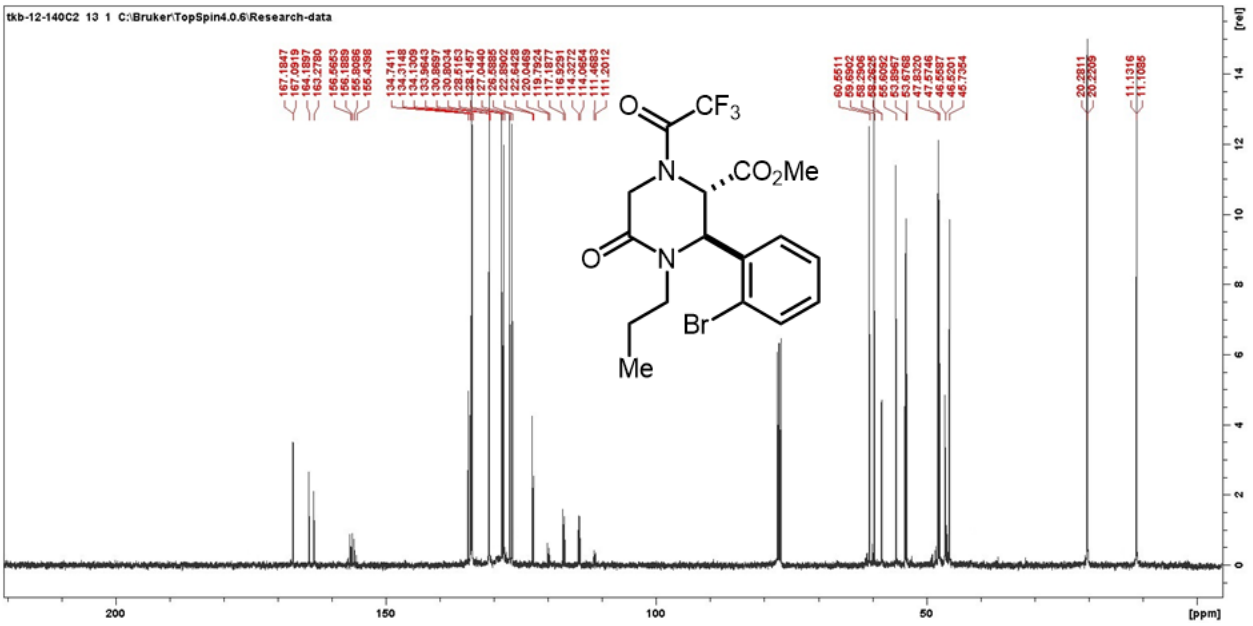
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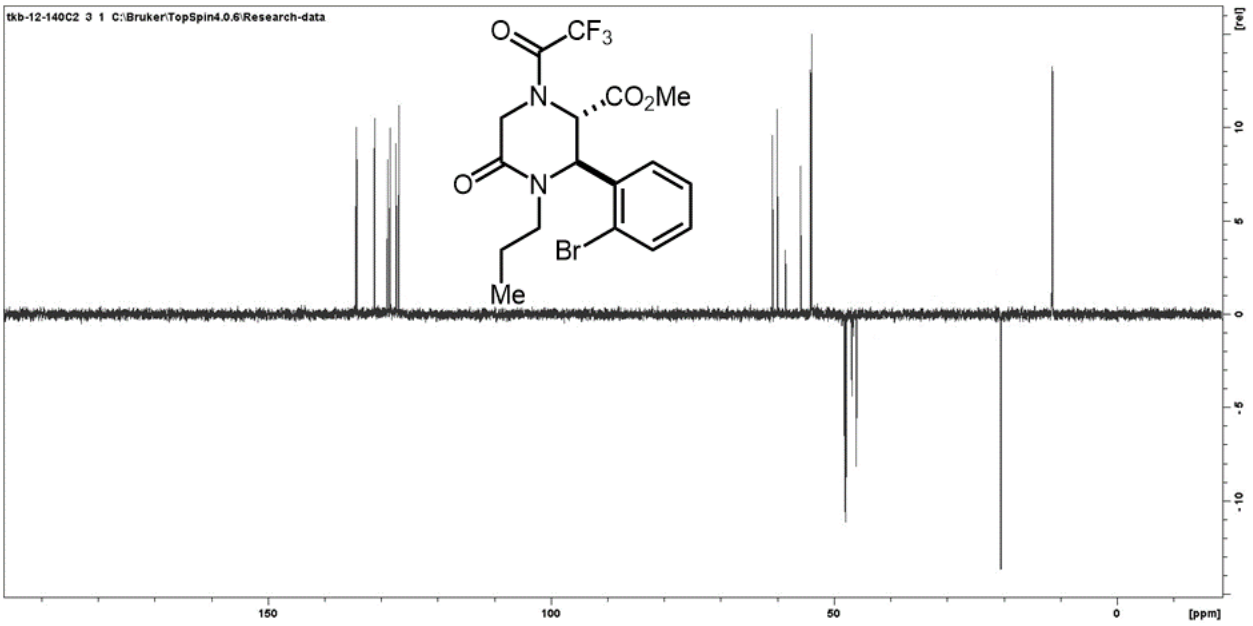
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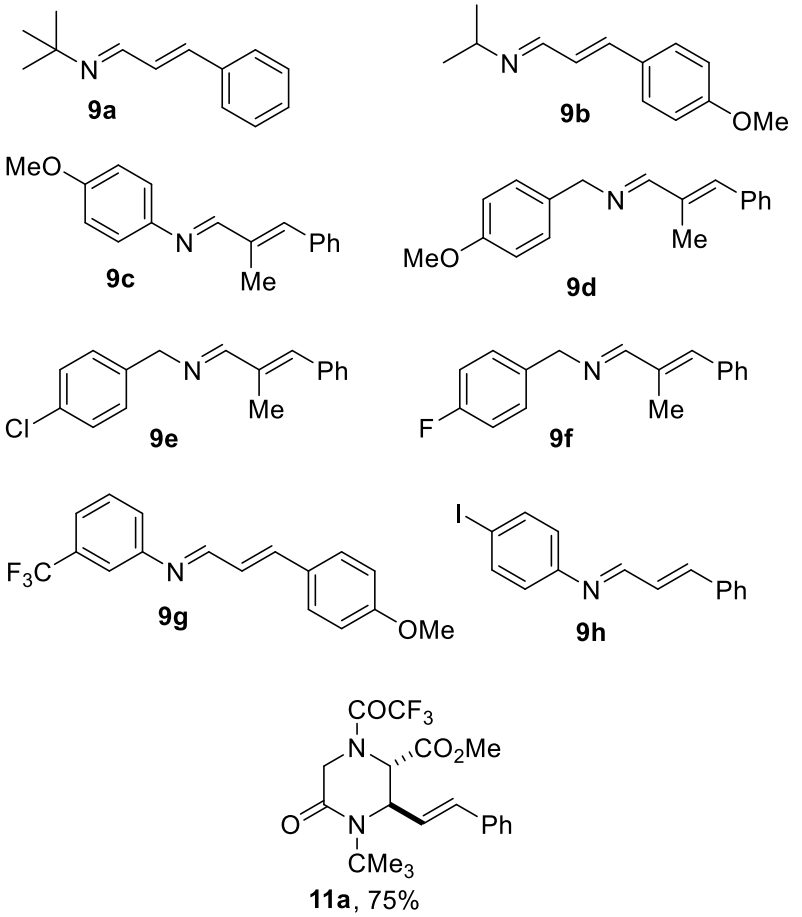
With 1,3-azadienes



11a, 75%

Prepared from 1,3-azadiene **9a** (936.5 mg, 5.0 mmol) and anhydride **7** (1.056 g, 1.0 equiv) using General Procedure B. T = 100 °C, time = 8 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 1.463 g, 75%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 7.35 – 7.23 (m, 5H), 6.65 – 6.53 (m, 1H), 6.10 (ddd, *J* = 15.9, 5.2, 2.8 Hz, 1H), 5.25 (d, *J* = 2.7 Hz, 1H), 5.15 – 5.05 (m, 1H), 4.35 (q, *J* = 17.0 Hz, 1H), 4.18 (d, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 165.0, 164.8, 161.0, 160.2, 153.4, 152.3, 132.0, 131.0, 130.5, 125.8, 125.7, 123.6, 122.6, 114.31, 111.45, 56.0, 55.8, 55.3, 52.8, 50.5, 50.3, 44.9, 44.9, 25.0, 24.9. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{20}H_{23}F_3N_2O_4$ 412.1610; found 412.1616.

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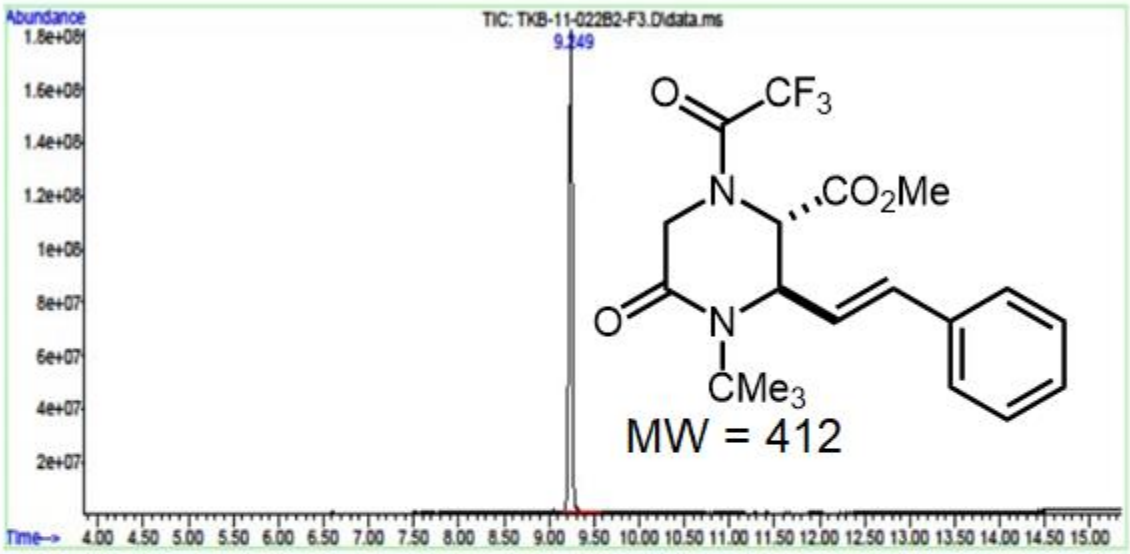

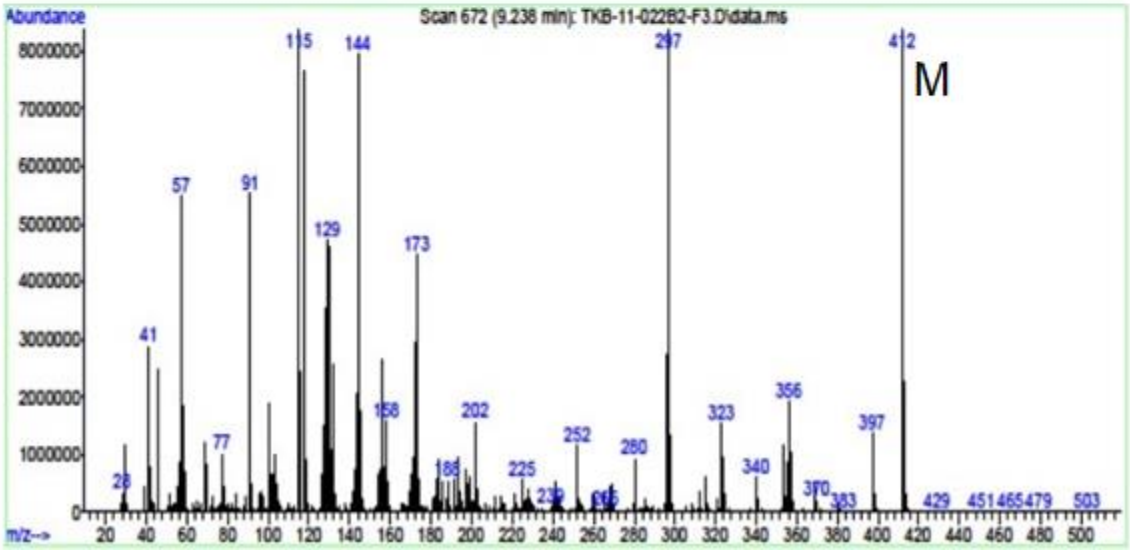

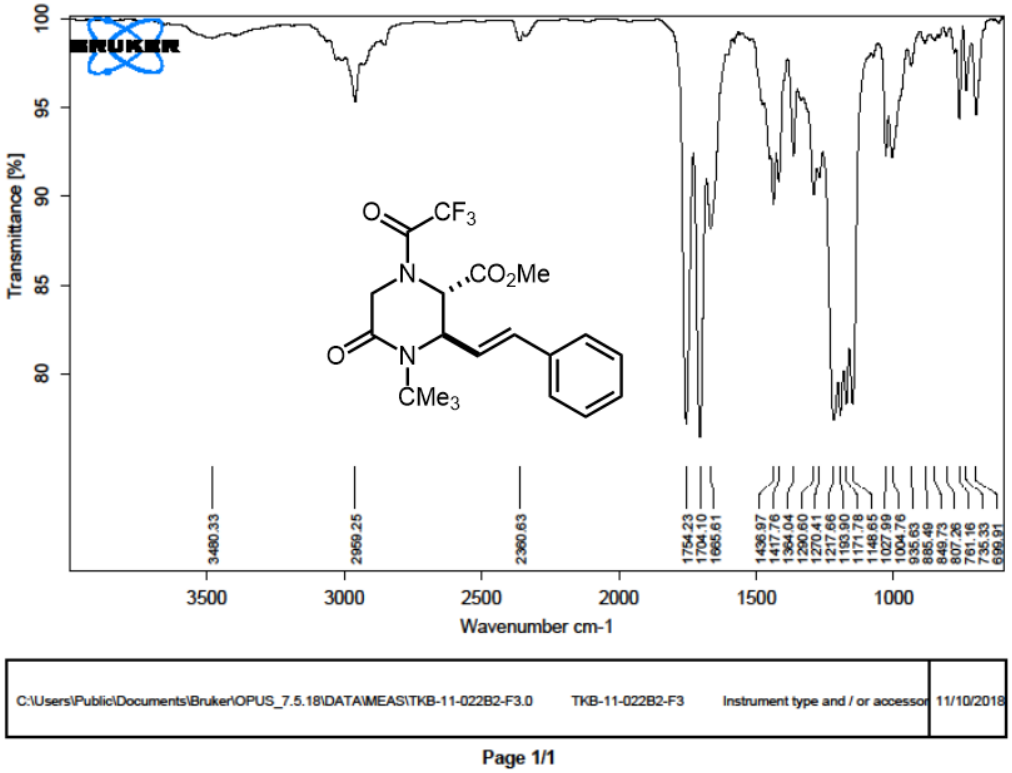
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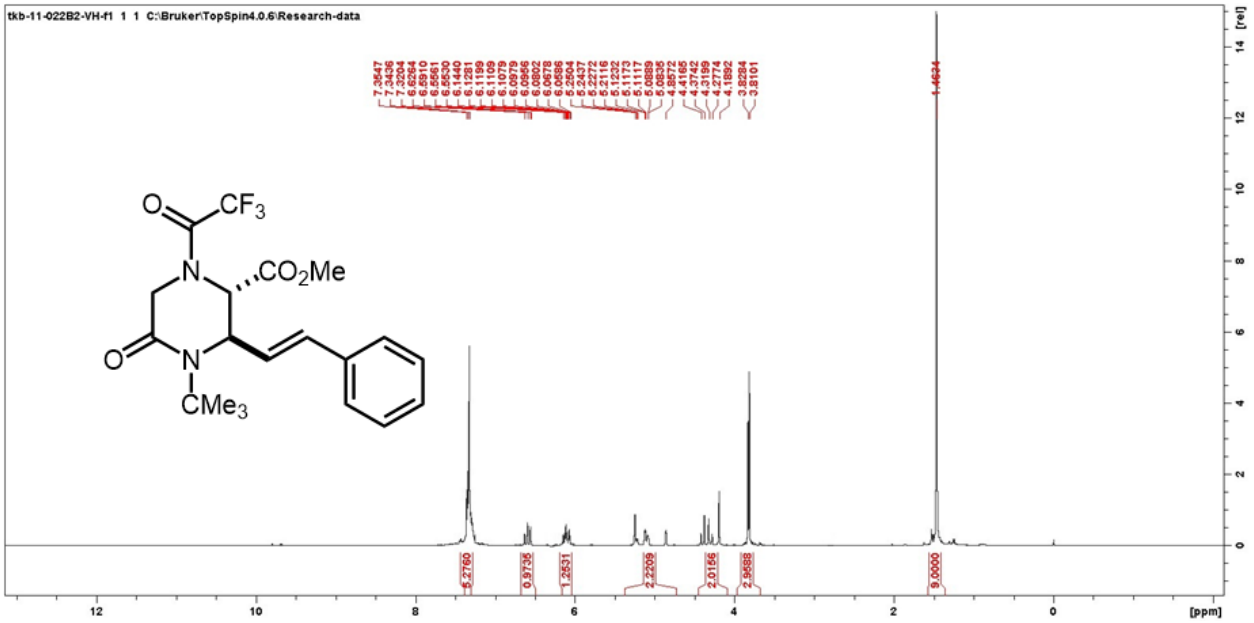
11/10/2018
Page 1/1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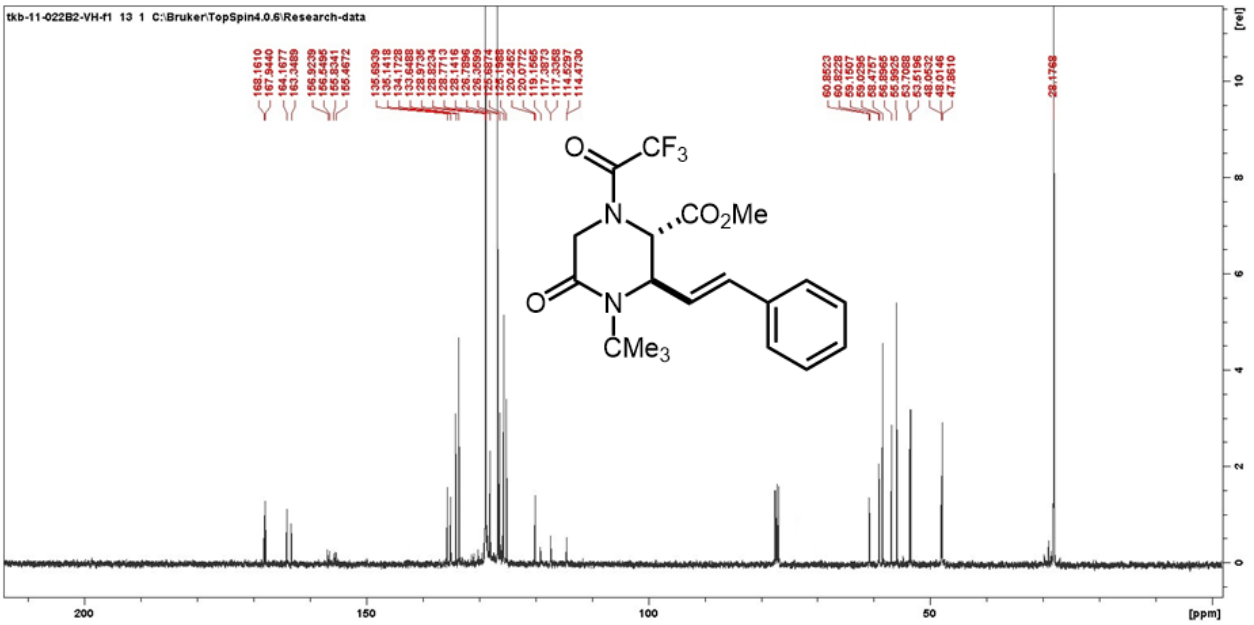
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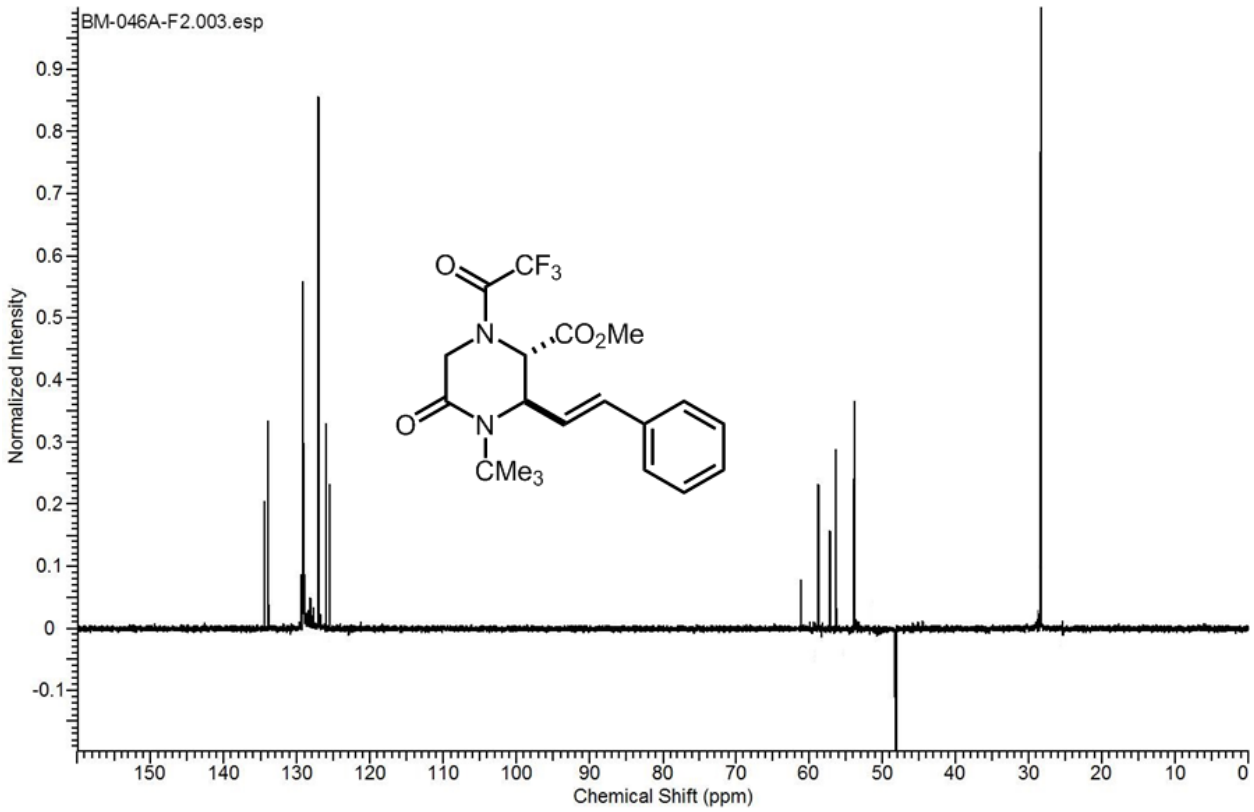
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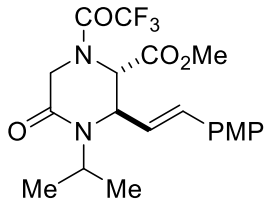
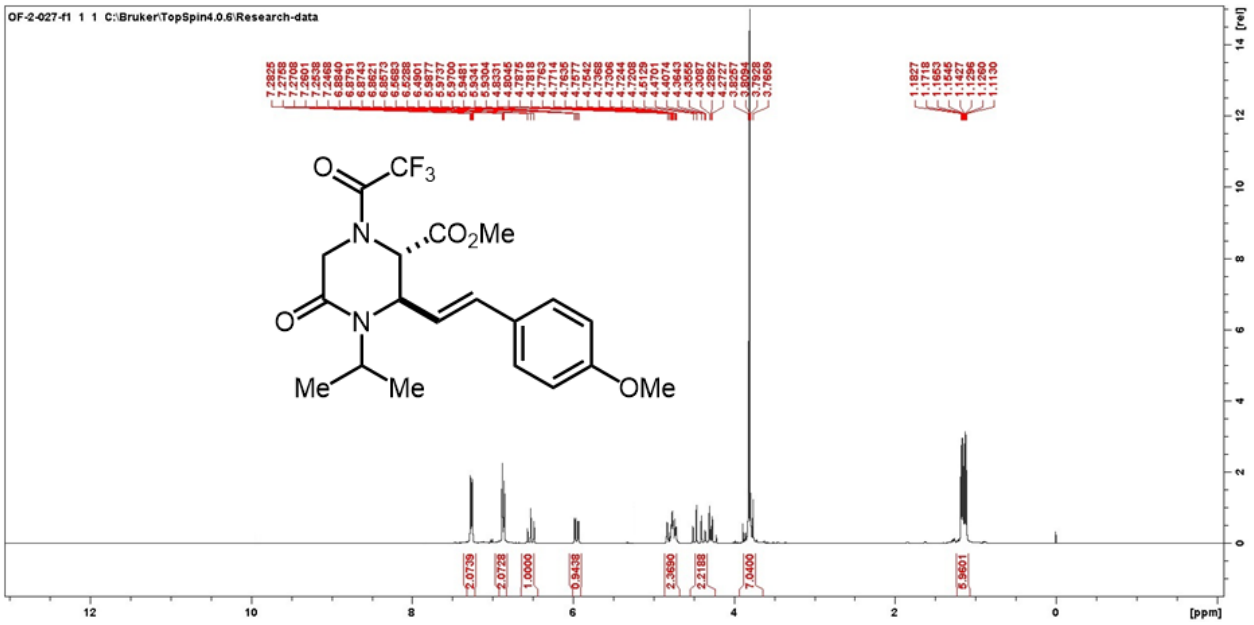
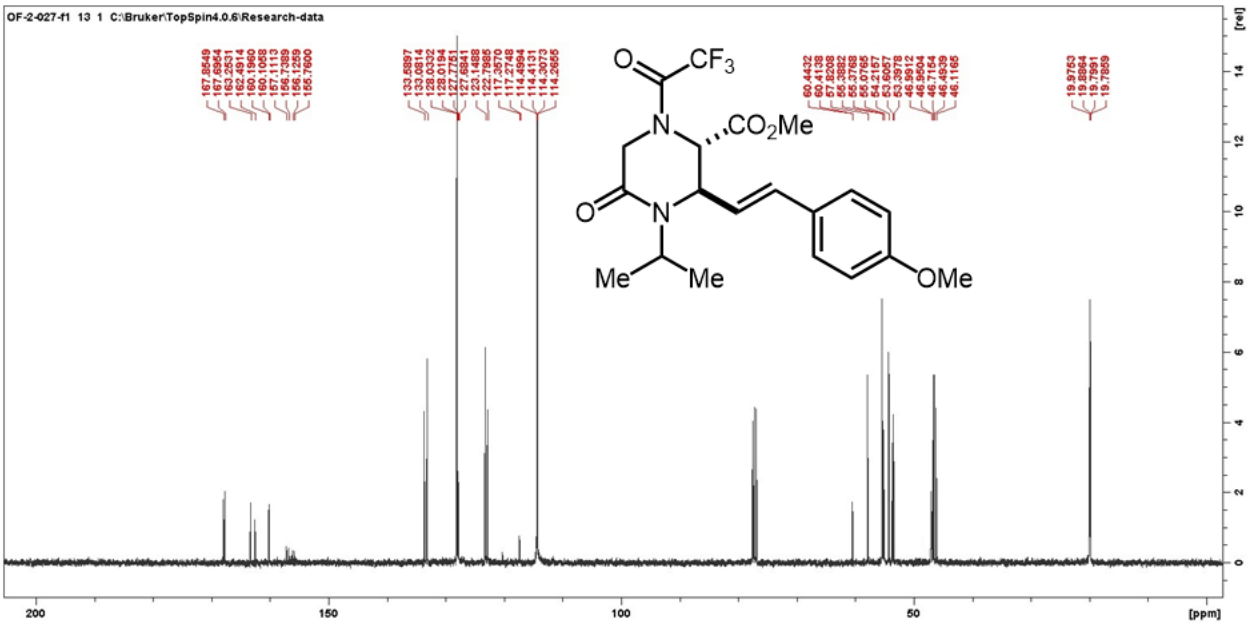


11b, 79%

Prepared from 1,3-azadiene **9b** (1016.5 mg, 5.0 mmol) and anhydride **7** (1055.5 mg, 1.0 equiv) using General Procedure B. T = 100 ºC, time = 8 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 1.63 g, 79%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.33 – 7.22 (m, 2H), 6.94 – 6.80 (m, 2H), 6.53 (td, *J* = 15.8, 1.3 Hz, 1H), 5.96 (ddd, *J* = 15.8, 5.9, 1.4 Hz, 1H), 4.83 – 4.68 (m, 2H), 4.43 – 4.20 (m, 2H), 3.92 – 3.73 (m, 9H), 1.15 (dd, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.7, 163.2, 162.5, 160.2, 160.1, 157.1, 156.7, 133.5, 133.0, 128.0, 128.0, 123.1, 122.8, 114.3, 114.2, 60.4, 60.4, 57.8, 55.3, 55.0, 54.2, 53.6, 53.4, 47.0, 46.9, 46.5, 46.1, 20.1, 19.9, 19.8, 19.79. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{20}H_{23}F_3N_2O_5$ 428.1559; found 428.1554.

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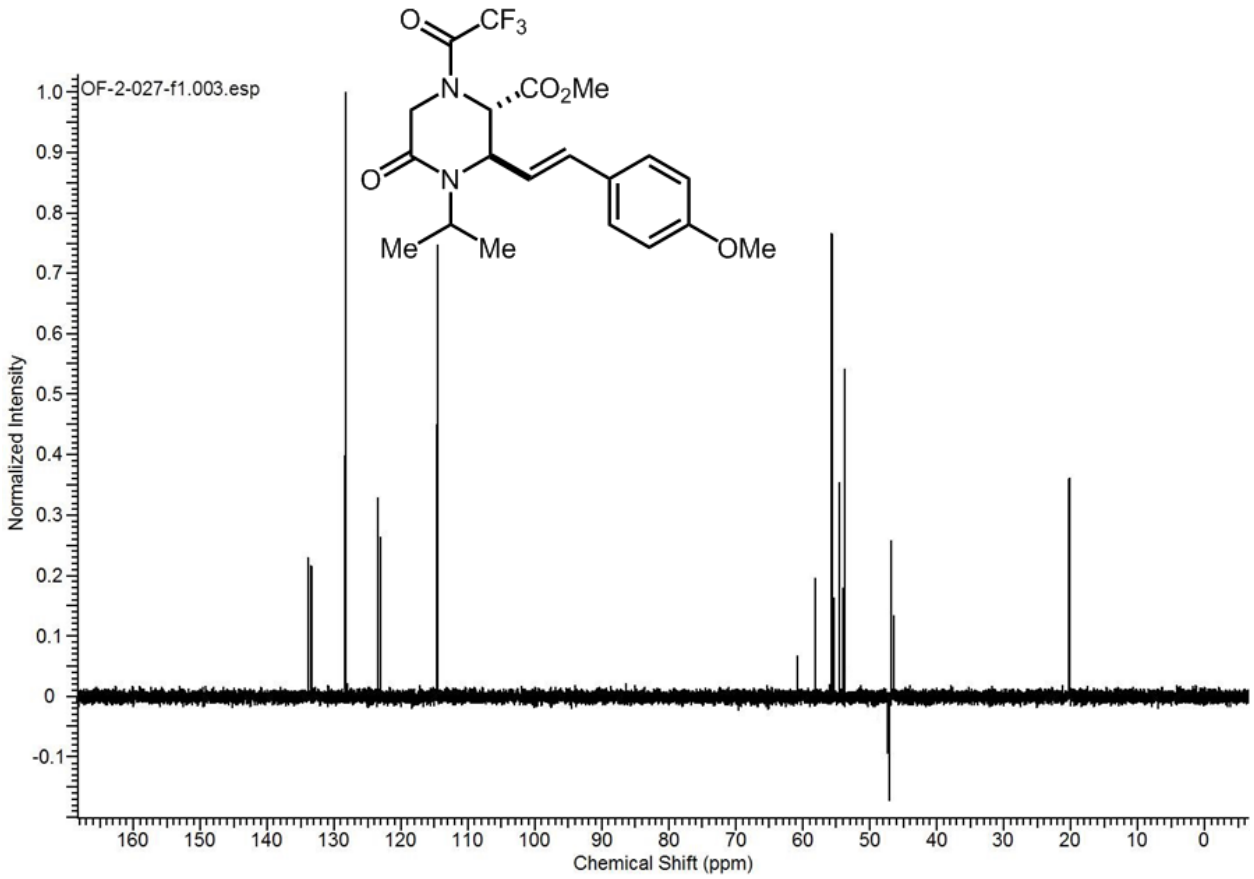
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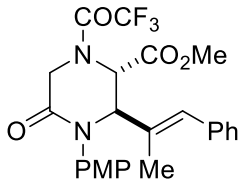

11c, 71%

Prepared from 1,3-azadiene **9c** (251 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Yield = 338.1 mg, 71%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.29 – 7.05 (m, 7H), 6.87 – 6.72 (m, 2H), 6.46 (s, 1H), 4.74 (dt, *J* = 15.5, 1.7 Hz, 1H), 4.55 – 4.36 (m, 2H), 4.22 – 4.12 (m, 1H), 3.74 – 3.60 (m, 6H), 1.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 168.0, 163.8, 163.0, 159.0, 157.6, 156.9, 156.5, 135.9, 133.3, 132.4, 129.0, 128.9, 128.5, 128.4, 127.6, 127.5, 127.3, 127.2, 120.3, 117.5, 114., 114.77, 114.6, 114.6, 68.1, 67.3, 58.1, 58.1, 55.5, 54.0, 53.7, 52.6, 49.2, 48.9, 47.0, 46.9, 16.3, 16.2. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{24}H_{23}F_3N_2O_5$ 476.1559; found 476.1566.

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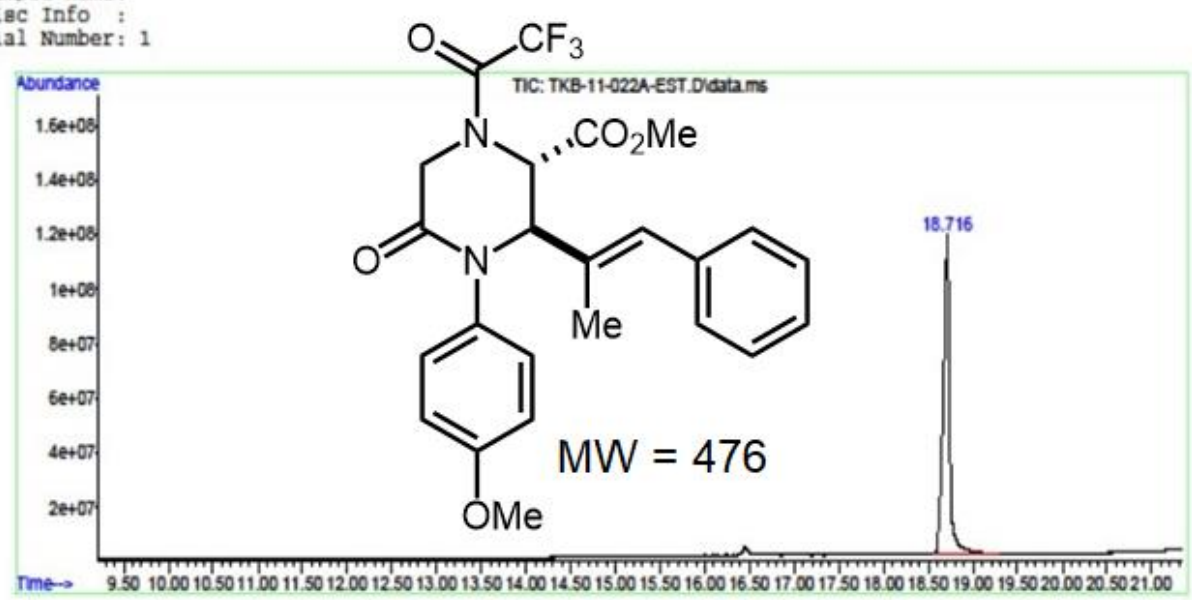

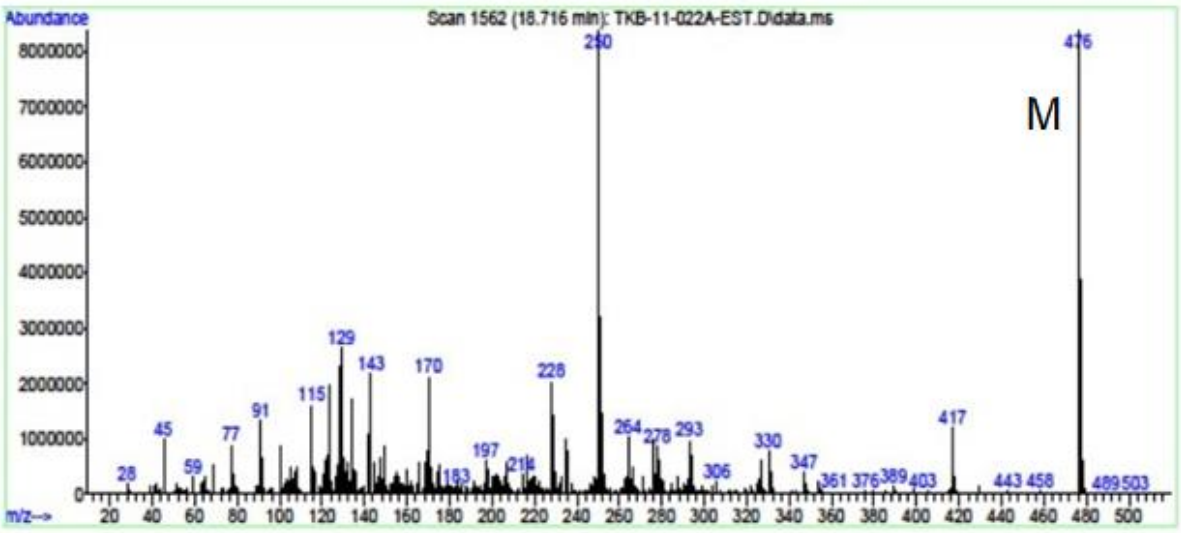

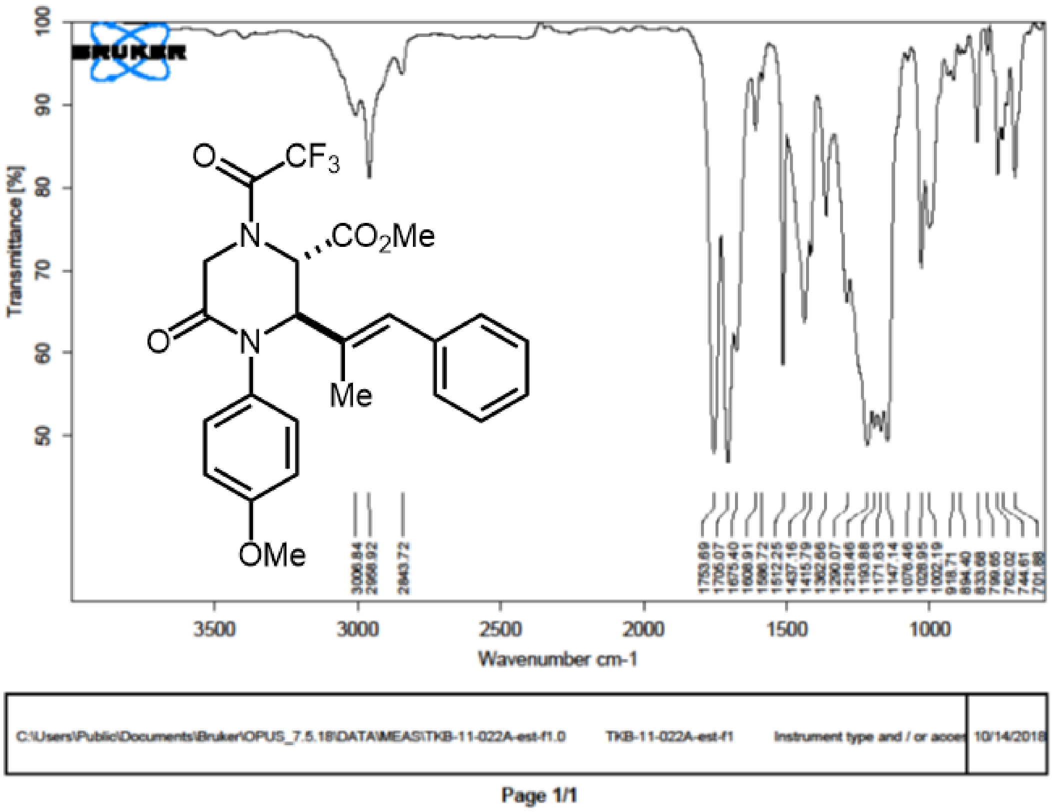

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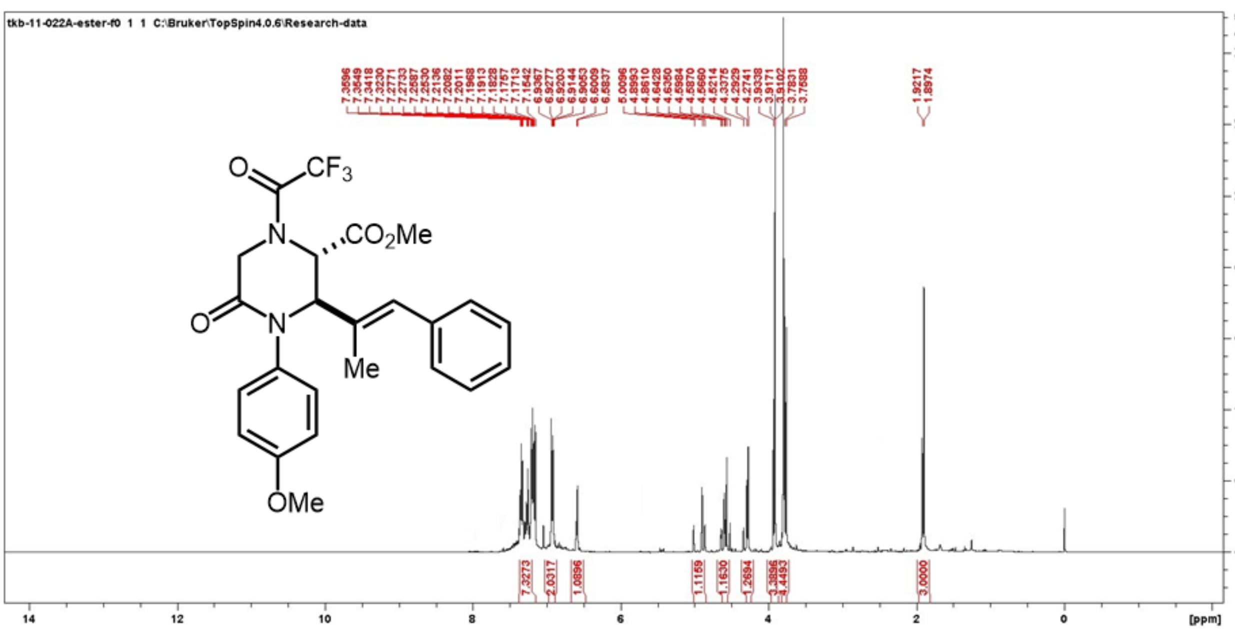
Instrument type and / or acces
10/14/2018
Page 1/1



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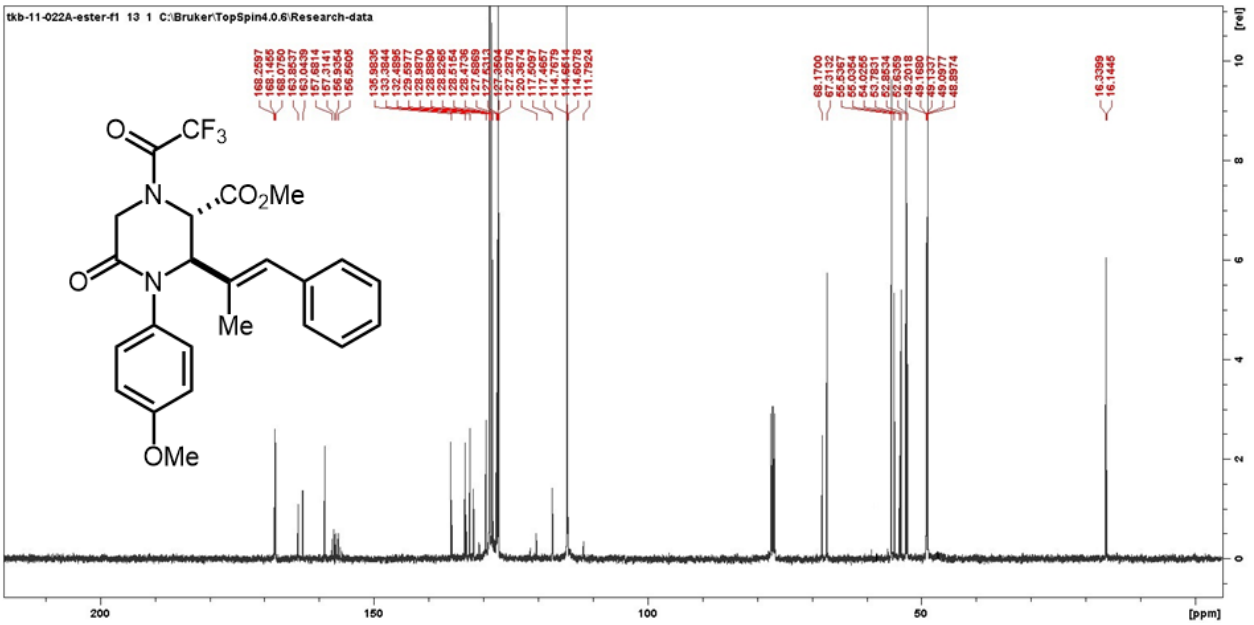
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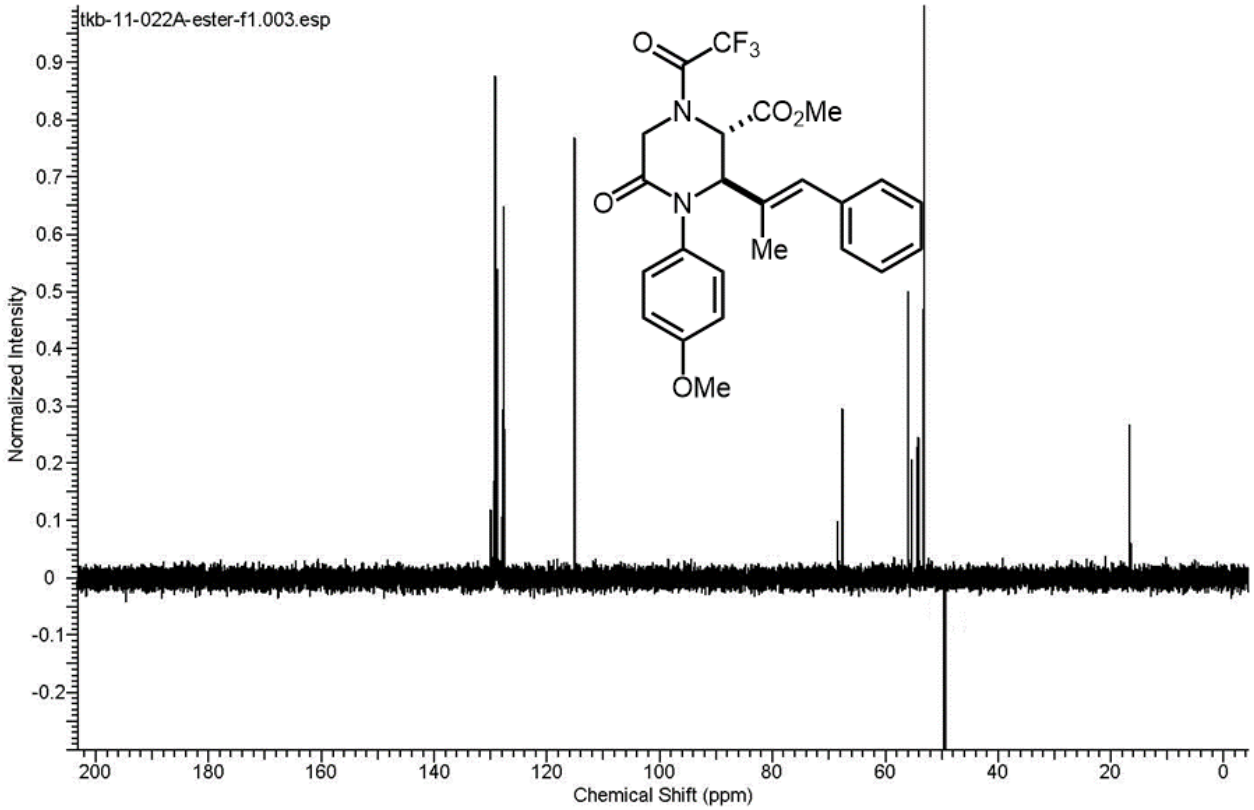
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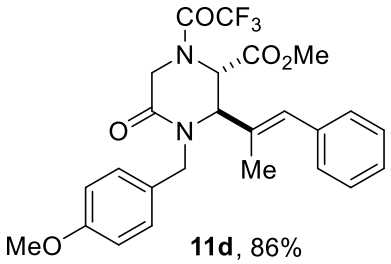
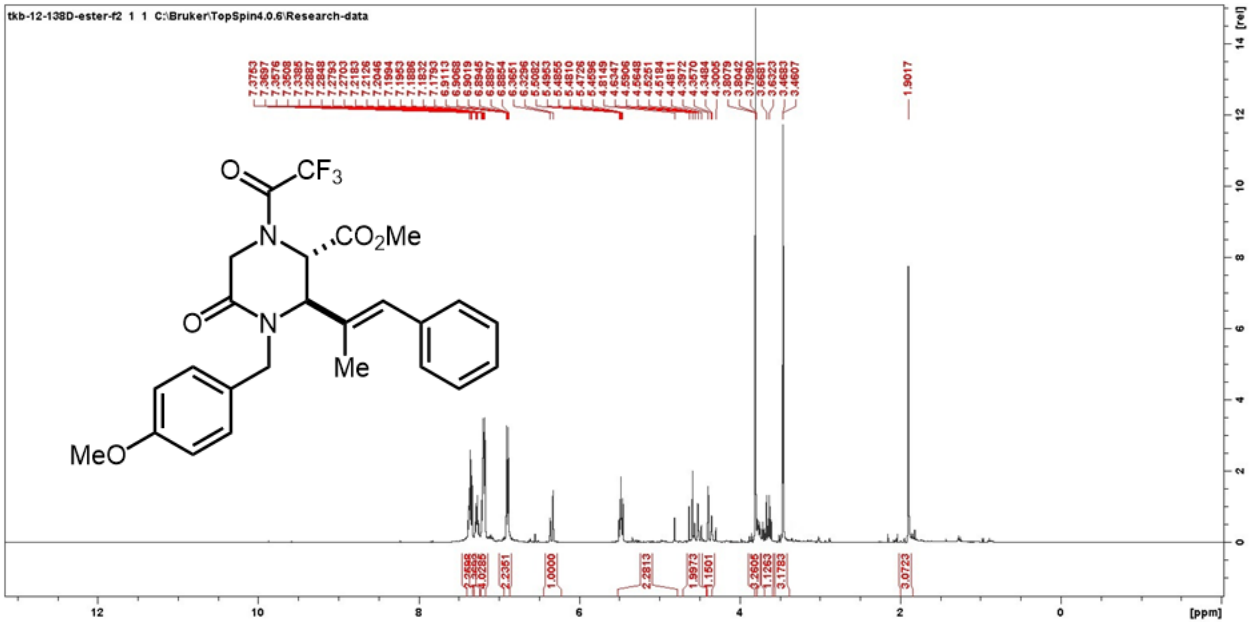
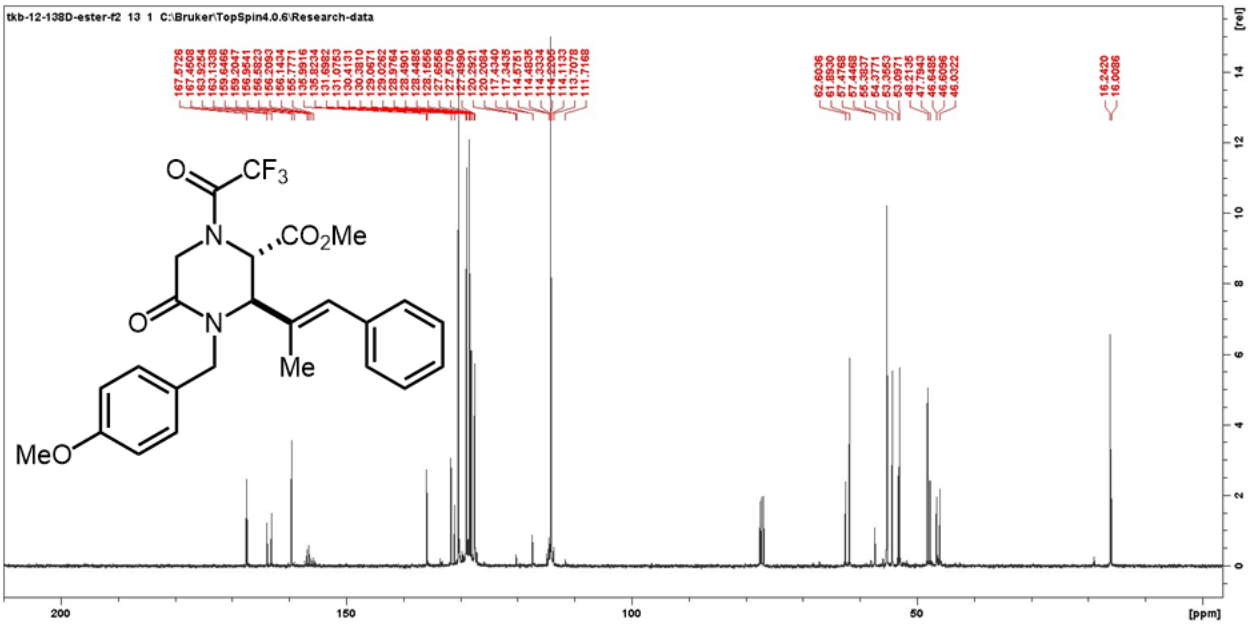


11d, 86%

Prepared from 1,3-azadiene **9d** (1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 421.8 mg, 86%, 95:5 dr. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{25}H_{25}F_3N_2O_5$ 490.1716; found 490.1722.

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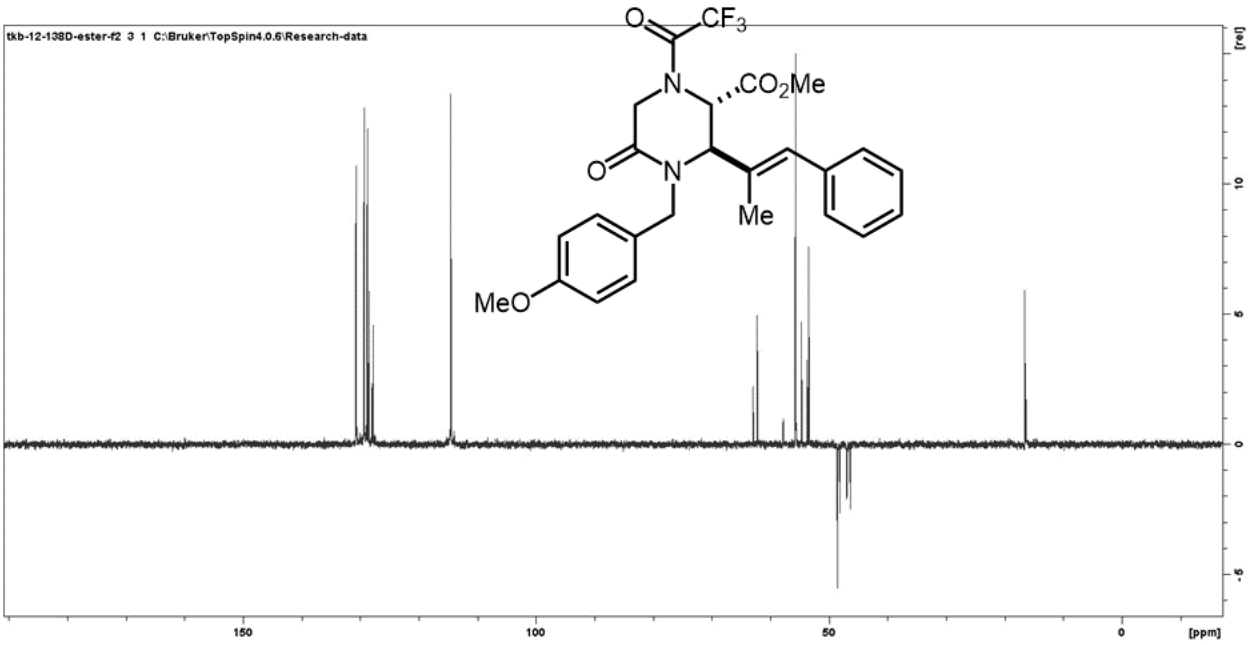
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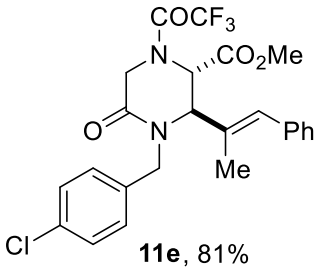
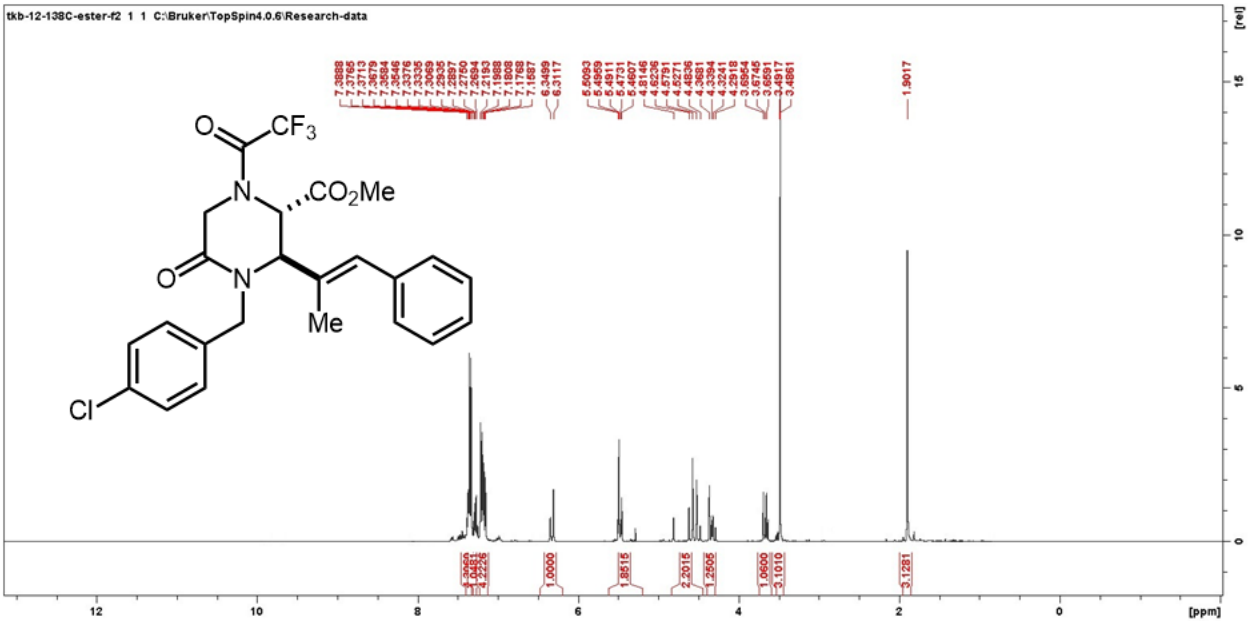
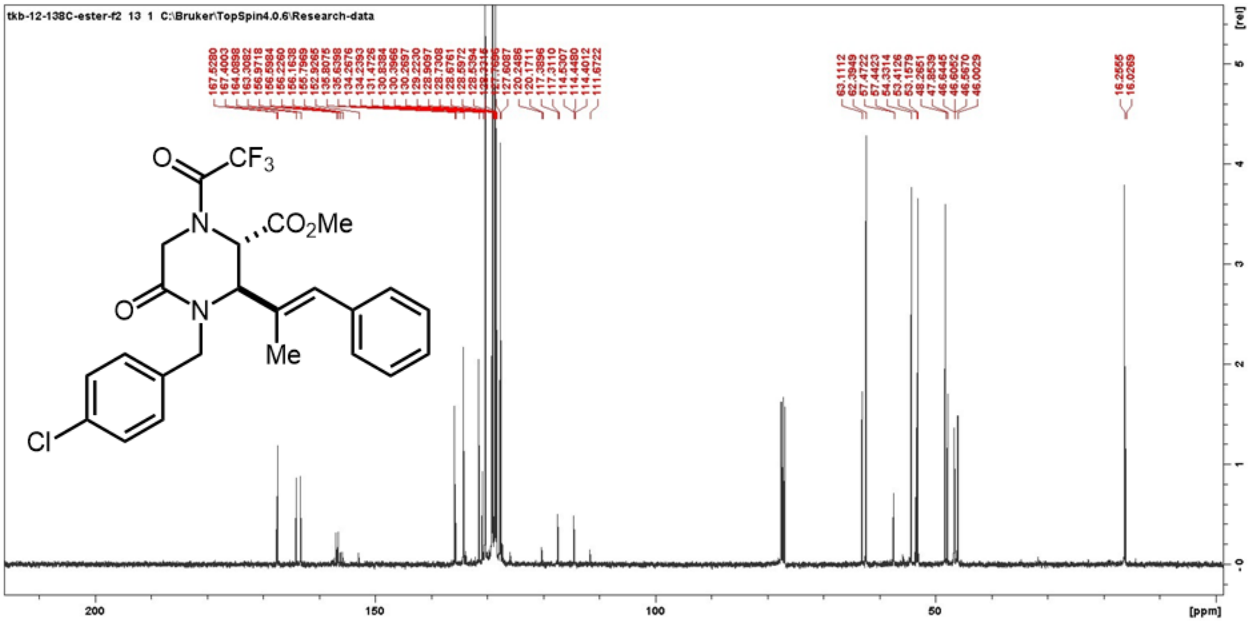


11e, 81%

Prepared from 1,3-azadiene **9e** (0.5 mmol) and anhydride **7** (105.6 mg, 1.0 equiv) using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yield = 200.4 mg, 81%, 95:5 dr. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{24}H_{22}ClF_3N_2O_4$ 494.1220; found 494.1225.

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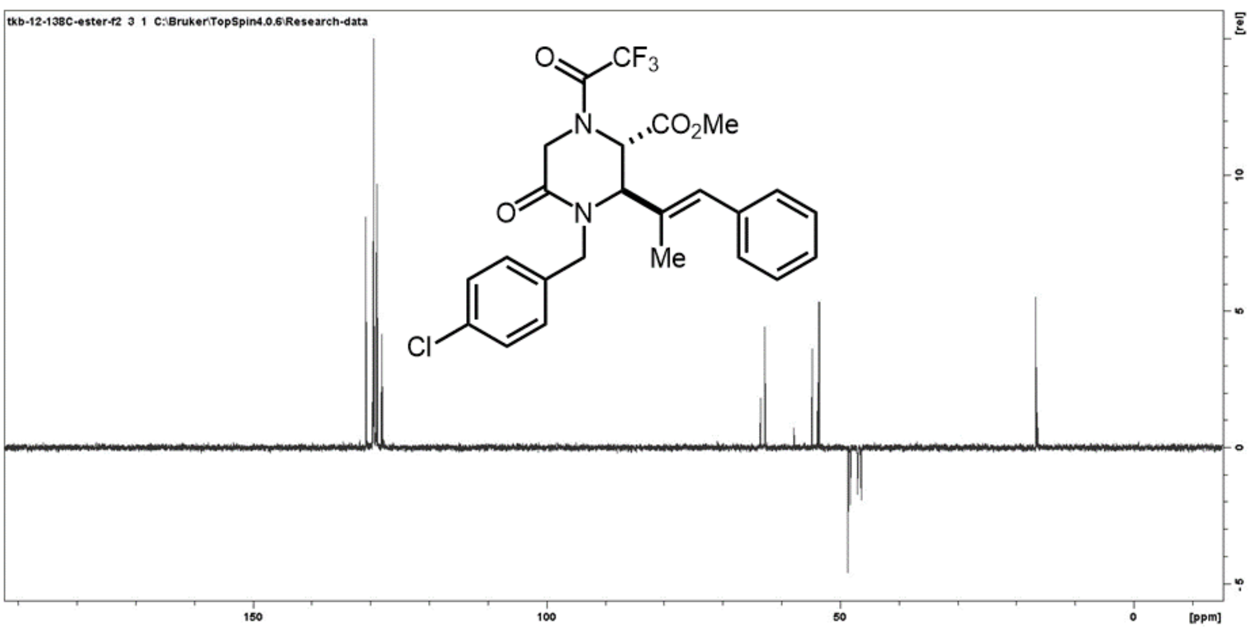
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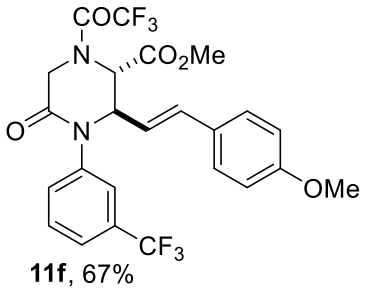

11f, 67%

Prepared from 1,3-azadiene **9f** (305.3 mg, 1.0 mmol) and anhydride **7** (211.1 mg, 1.0 equiv) using General Procedure B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yield = 355.2 mg, 67%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.38 – 7.24 (m, 4H), 7.21 – 7.16 (d, *J* = 8.7, 2H), 6.73 (d, *J* = 8.7, 2H), 6.41 (dd, *J* = 15.8, 9.8 Hz, 1H), 5.87 (td, *J* = 16.3, 6.3 Hz, 1H), 4.98 – 4.77 (m, 1H), 4.54 – 4.40 (m, 2H), 3.76 (s, 3H), 3.74 – 3.58 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 167.6, 163.3, 162.6, 160.5, 160.4, 157.2, 156.8, 156.0, 140.7, 140.6, 135.0, 134.4, 130.2, 129.8, 128.2, 127.4, 127.3, 124.8, 123.1, 123.1, 120.4, 120.1, 114.8, 114.4, 63.3, 62.5, 60.0, 57.1, 55.4, 54.0, 53.8, 47.1, 46.6. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{24}H_{20}F_6N_2O_5$ 530.1276; found 530.1268.

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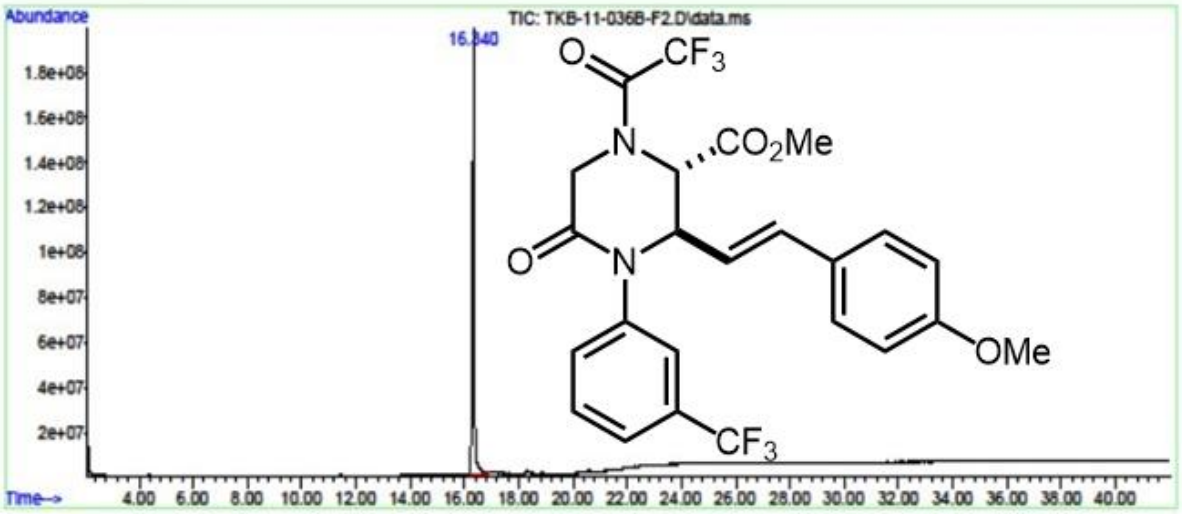

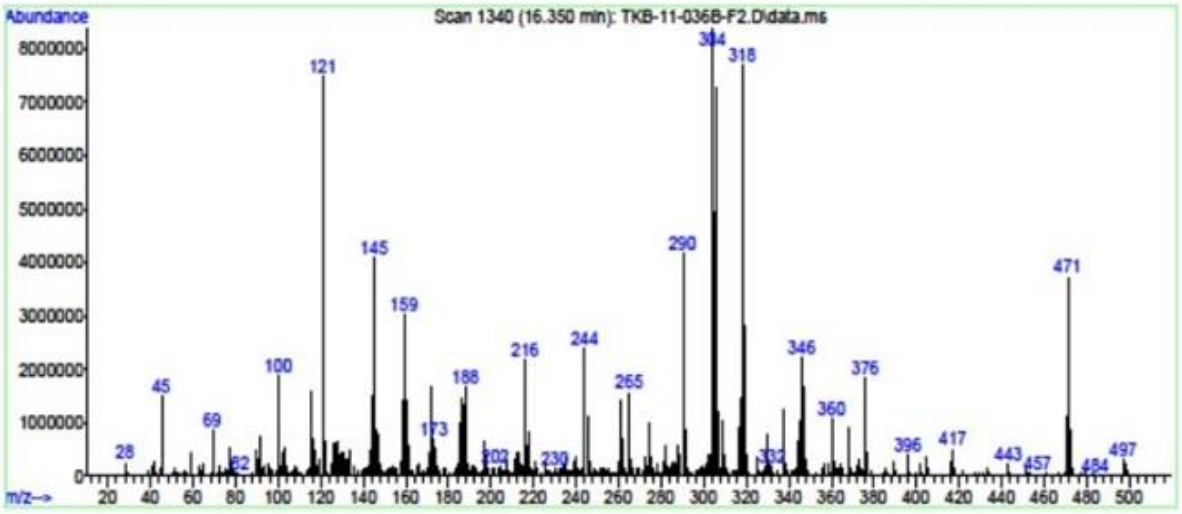

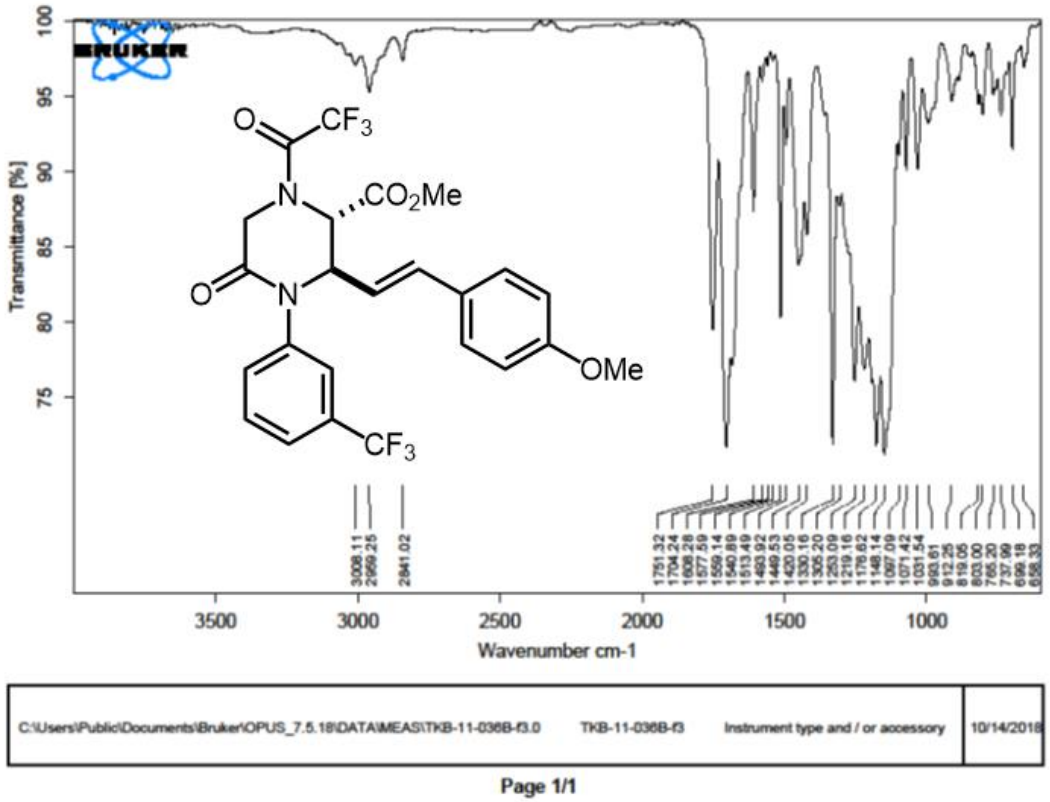
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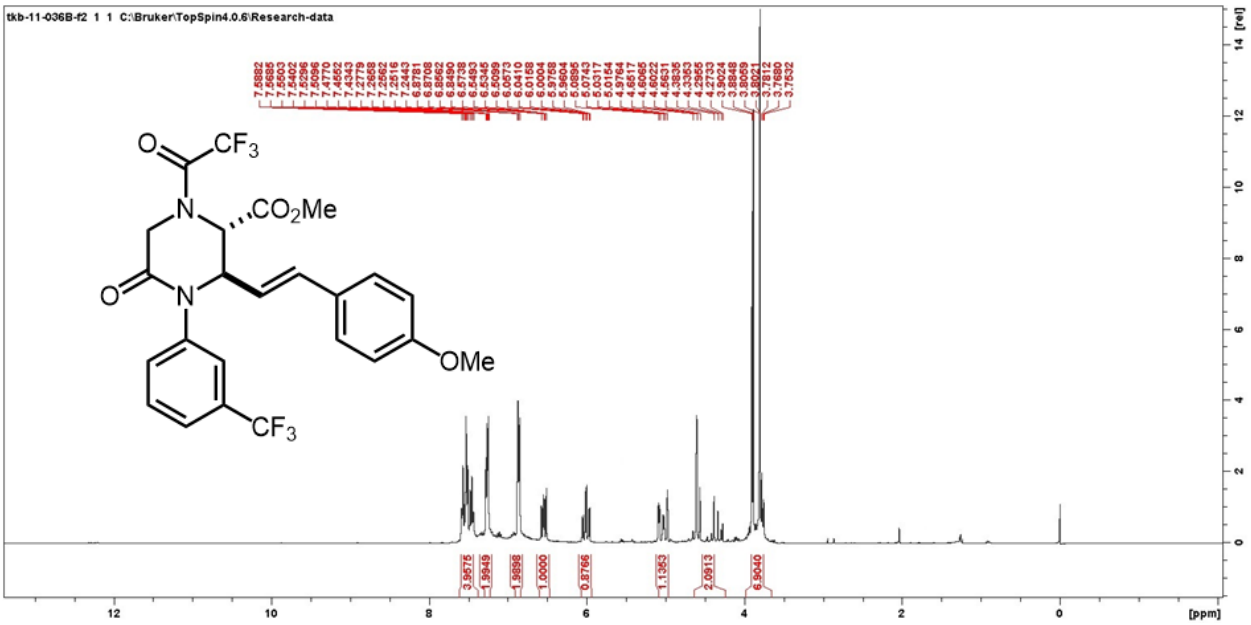
10/14/2018
Page 1/1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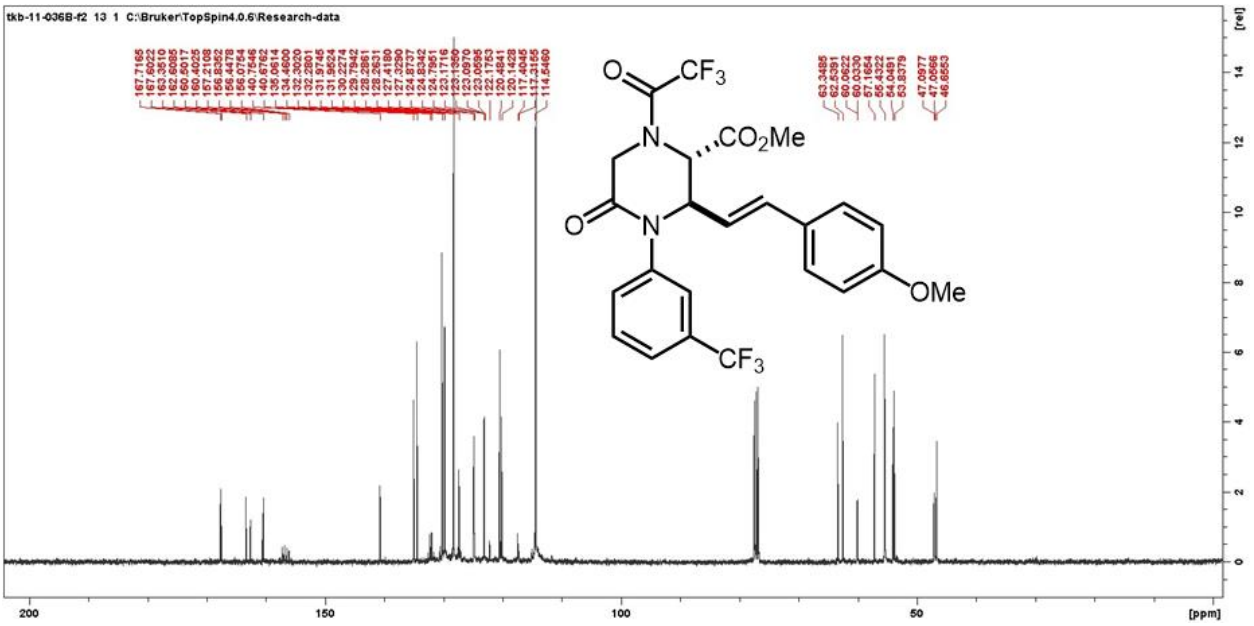
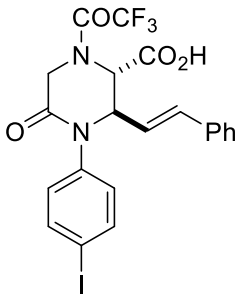
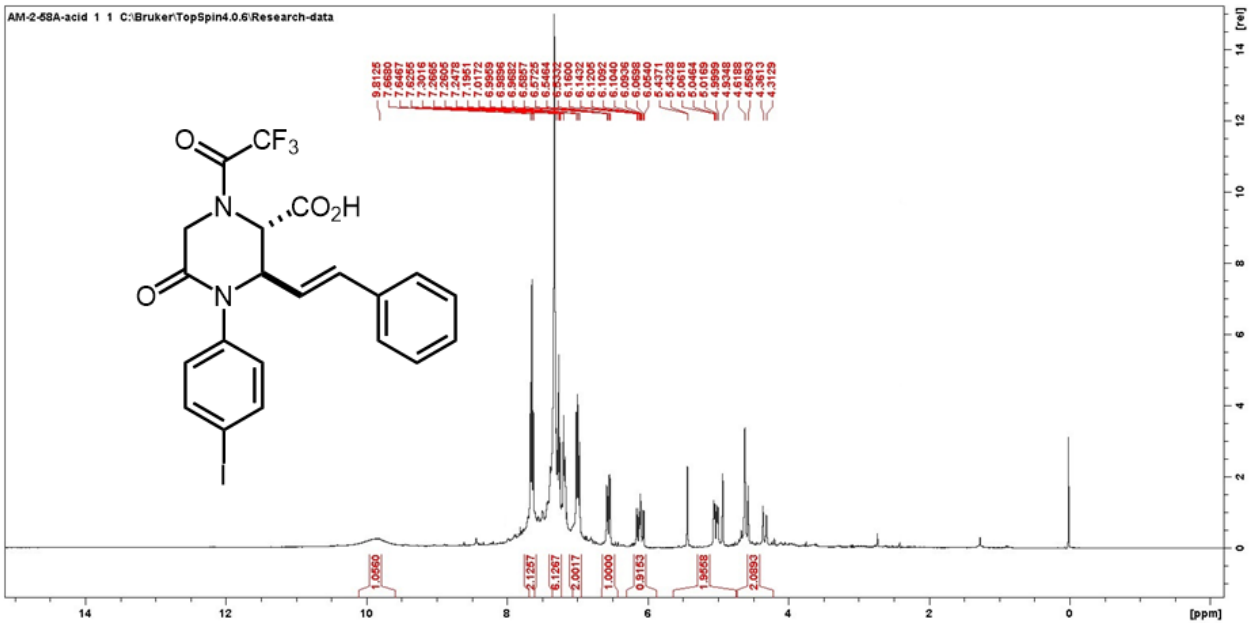




11g, 70%*

Prepared from 1,3-azadiene **9g** (0.5 mmol) and anhydride **7** (105.6 mg, 1.0 equiv) using General Procedure B but without performing the methylation. Purification: Flash chromatography on silica eluting with hexane/EtOAc (20:80). Yield = 190.5 mg, 70%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 9.81 (br. s, 1H), 7.67 (t, *J* = 8.4 Hz, 2H), 7.30 – 7.24 (m, 6H), 6.95 (dd, *J* = 11.2, 8.3 Hz, 2H), 6.58 (dd, *J* = 15.7, 5.4 Hz, 2H), 6.15 (dd, *J* = 15.7, 6.5 Hz, 2H), 5.43 – 4.93 (m, 2H), 4.63 – 4.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 169.21, 169.11, 164.50, 163.47, 157.21, 156.83, 156.66, 156.29, 139.61, 139.47, 138.86, 135.38, 134.89, 134.82, 129.17, 129.11, 129.06, 129.00, 128.96, 128.48, 128.39, 128.35, 126.95, 123.04, 122.70, 120.30, 117.44, 117.33, 114.58, 114.47, 93.75, 93.72, 63.49, 62.57, 59.84, 56.86, 47.01, 46.62. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{21}H_{16}F_3IN_2O_4$ 544.0107; found 544.0113.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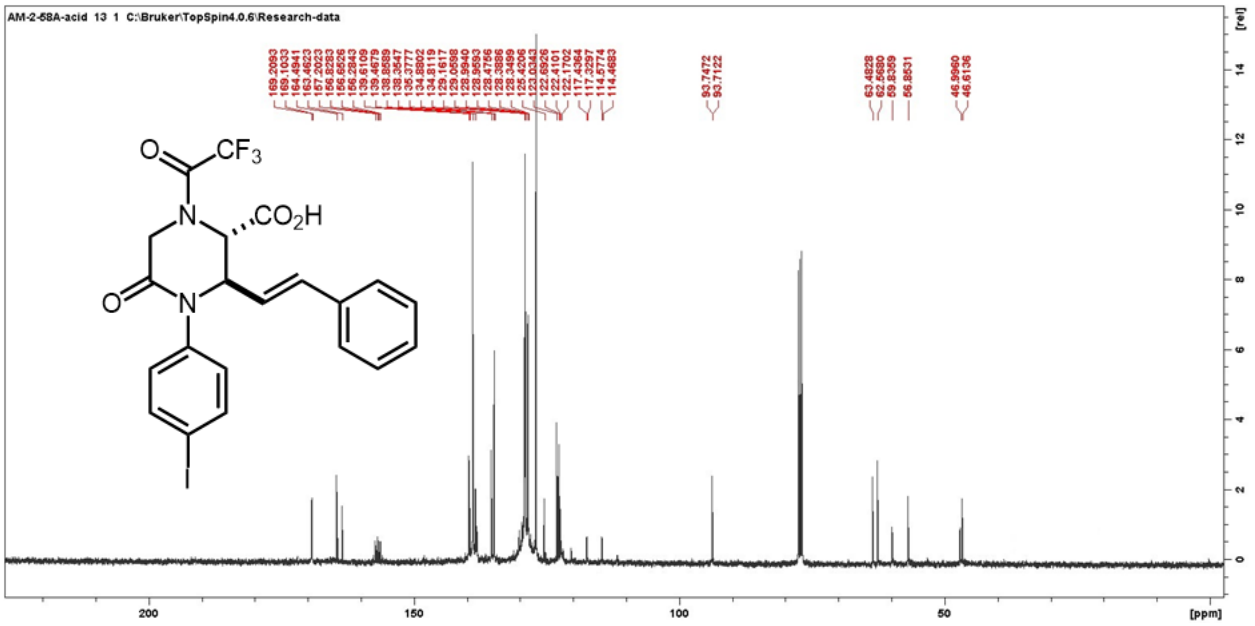
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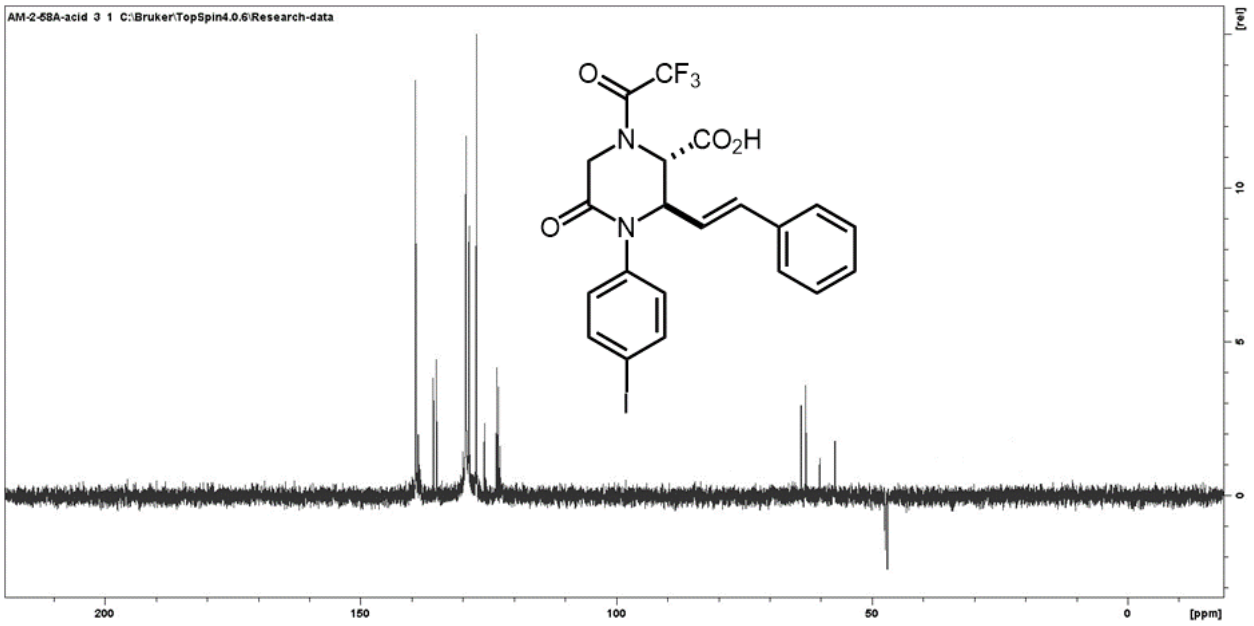
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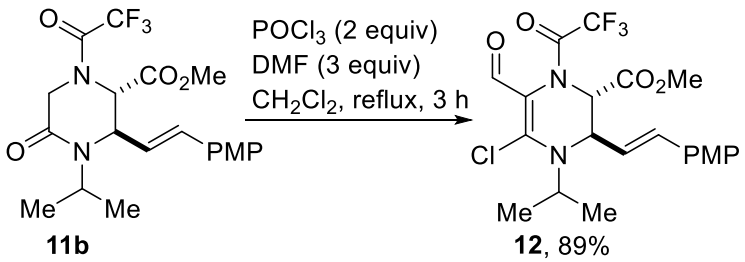
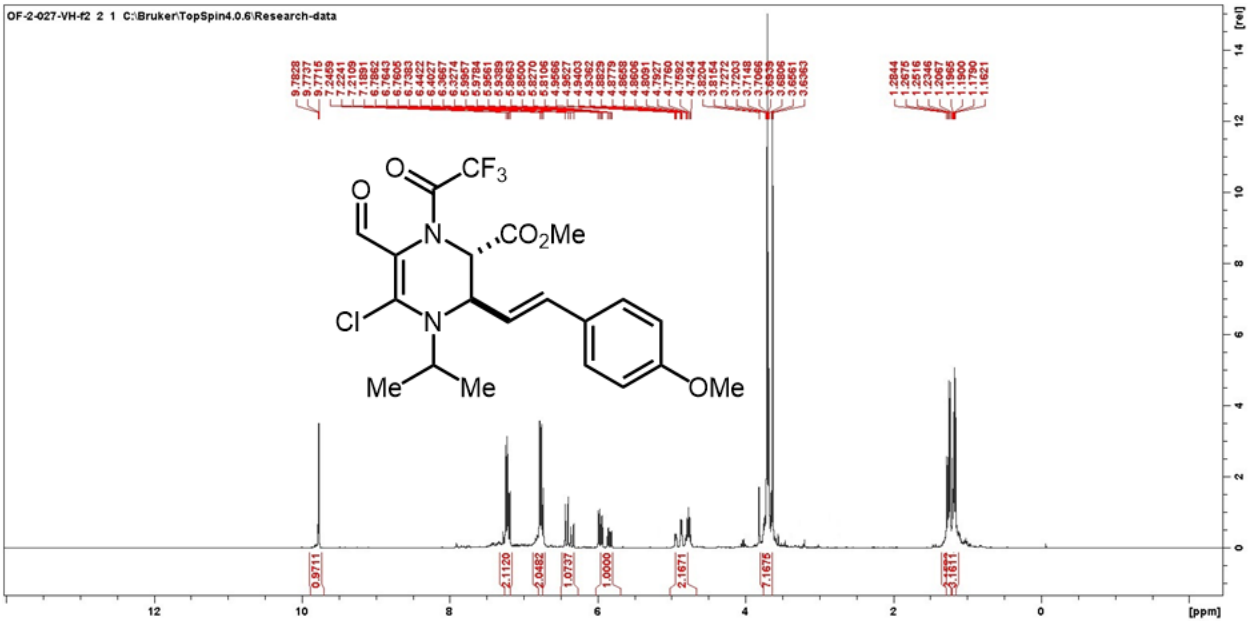
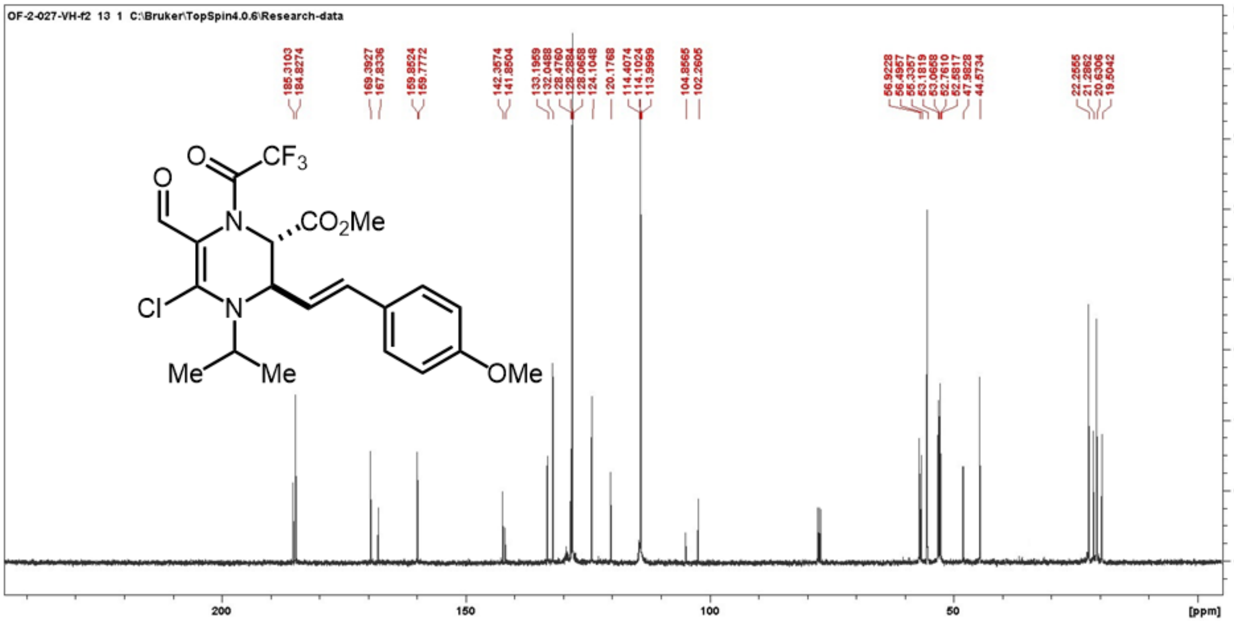
Synthetic Applications



Prepared from **11b** (214.2 mg, 0.50 mmol) using General Procedure C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 211.3 mg, 89%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 9.81 (s, 1H), 7.30 (d, 2H), 6.85 (d, 2H), 6.35 (d, *J* = 15.4 Hz, 1H), 5.97 & 5.84 (dd, *J* = 15.8, 6.6 Hz, 1H), 4.95 & 4.87 (ddd, *J* = 7.0, 2.9, 1.1 Hz, 2H), 4.84 – 4.70 (m, 1H), 3.82 (dd, *J* = 2.9, 1.1 Hz, 1H), 3.80 – 3.66 (m, 6H), 1.31 – 1.17 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3, 184.8, 169.3, 167.8, 159.8, 159.7, 142.3, 141.8, 133.2, 132.0, 128.2, 128.0, 124.1, 120.1, 114.1, 114.0, 104.8, 102.3, 56.9, 56.5, 55.3, 53.1, 53.0, 52.7, 52.5, 47.9, 44.5, 22.2, 21.2, 20.6, 19.5. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{22}ClF_3N_2O_5$ 474.1169; found 474.1173.

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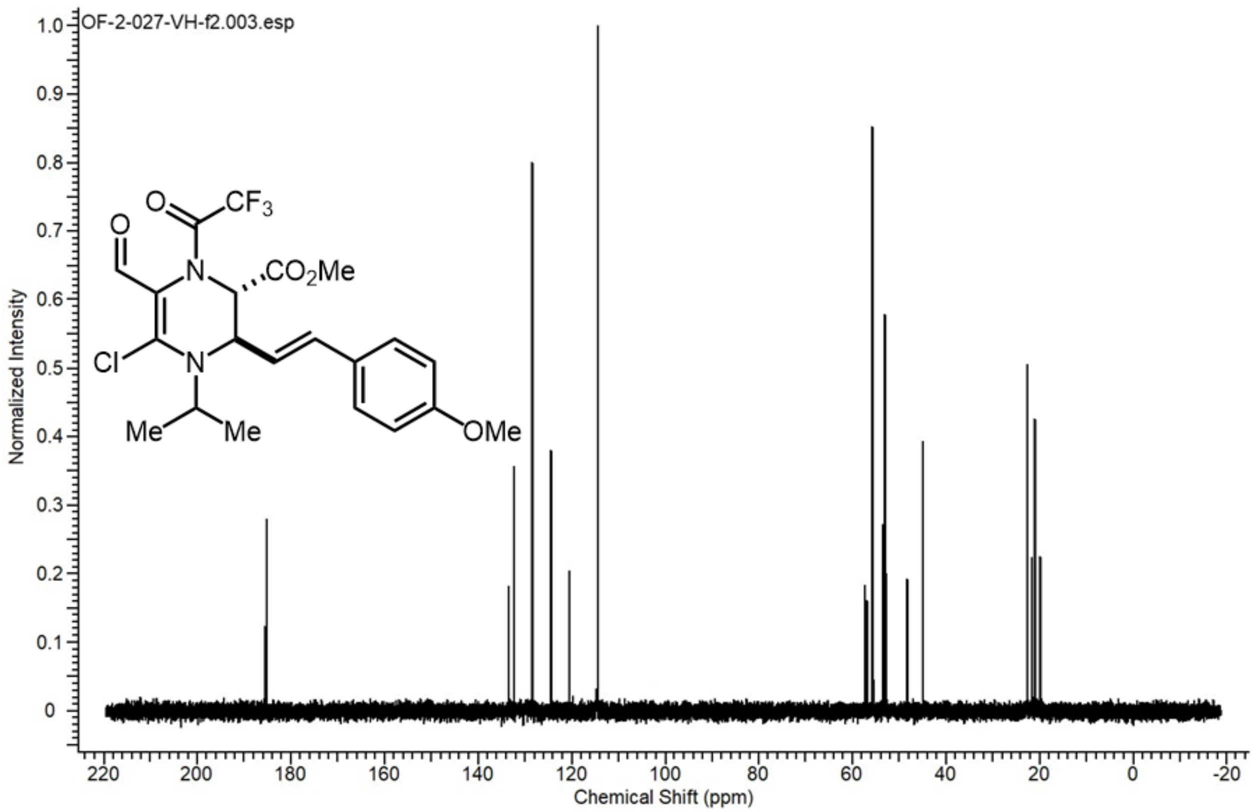
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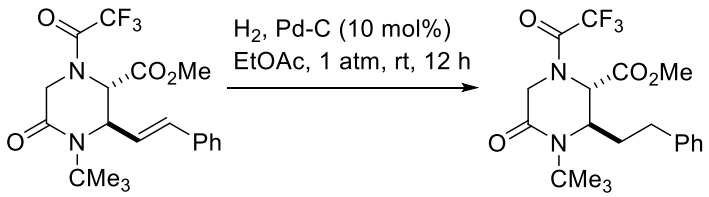

Prepared from **11a** (206.2 mg, 0.50 mmol) using General Procedure D. Yield = 201.3 mg, 97%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.22 – 6.95 (m, 5H), 5.18 + 4.74 (dd, *J* = 2.9, 1.4 Hz, 1H), 4.18 – 4.02 (m, 3H), 3.63 (s, 3H), 2.58 (ddt, *J* = 18.7, 8.8, 4.0 Hz, 1H), 2.47 – 2.32 (m, 1H), 1.88 – 1.62 (m, 2H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 168.6, 163.4, 162.4, 157.1, 156.7, 156.3, 155.9, 139.4, 139.2, 129.0, 128.9, 128.3, 126.9, 126.8, 120.3, 117.5, 117.4, 114.6, 114.5, 58.7, 58.6, 57.6, 57.6, 55.2, 54.4, 53.6, 53.4, 47.6, 47.4, 36.1, 35.7, 32.3, 32.0, 28.3, 28.2. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{20}H_{25}F_3N_2O_4$ 414.1766; found 414.1769.

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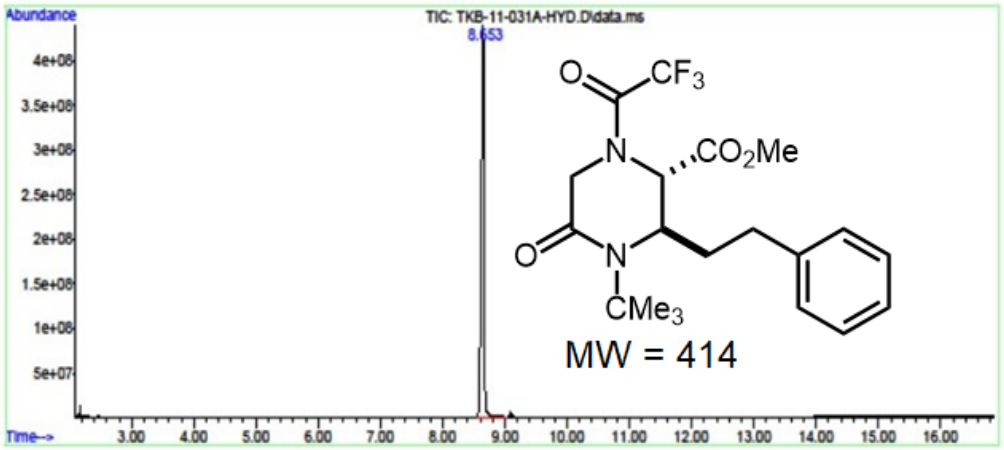

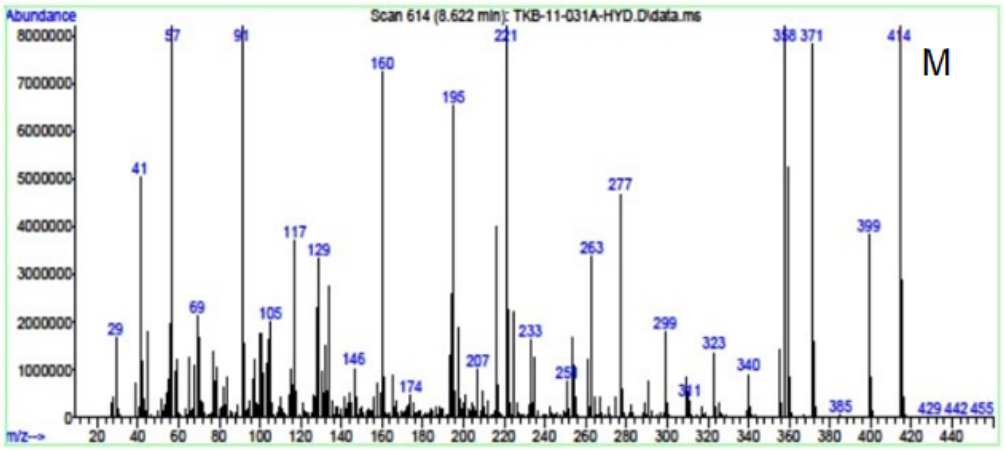

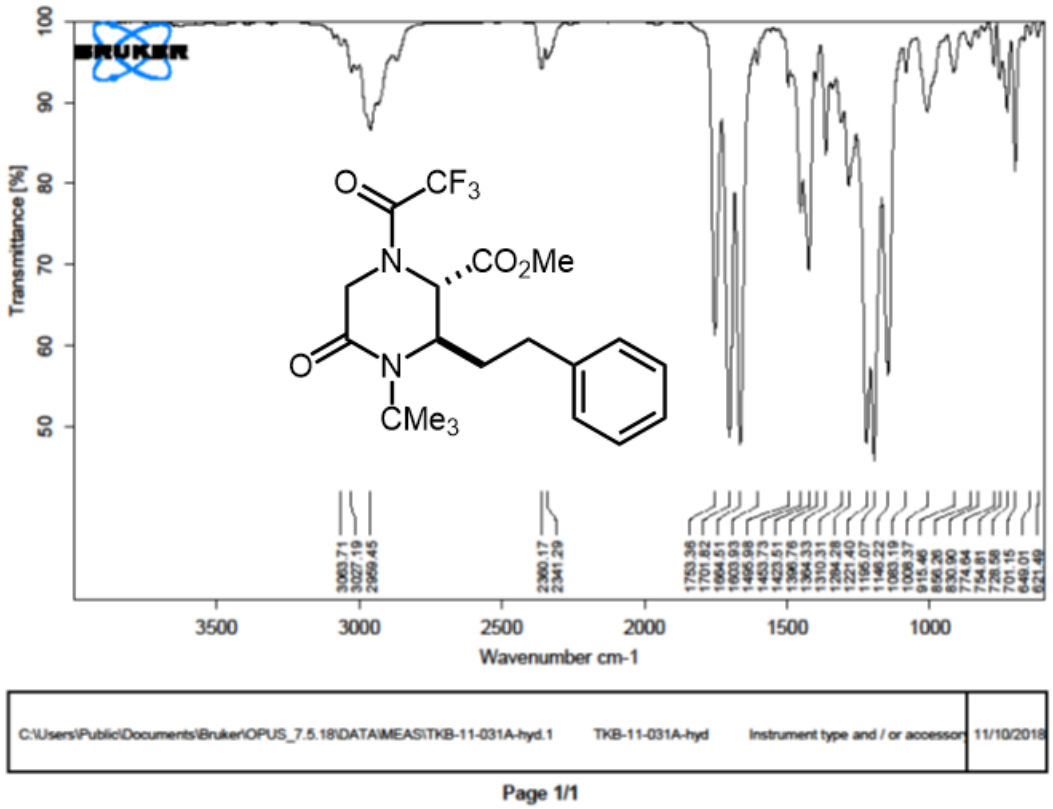
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11/10/2018
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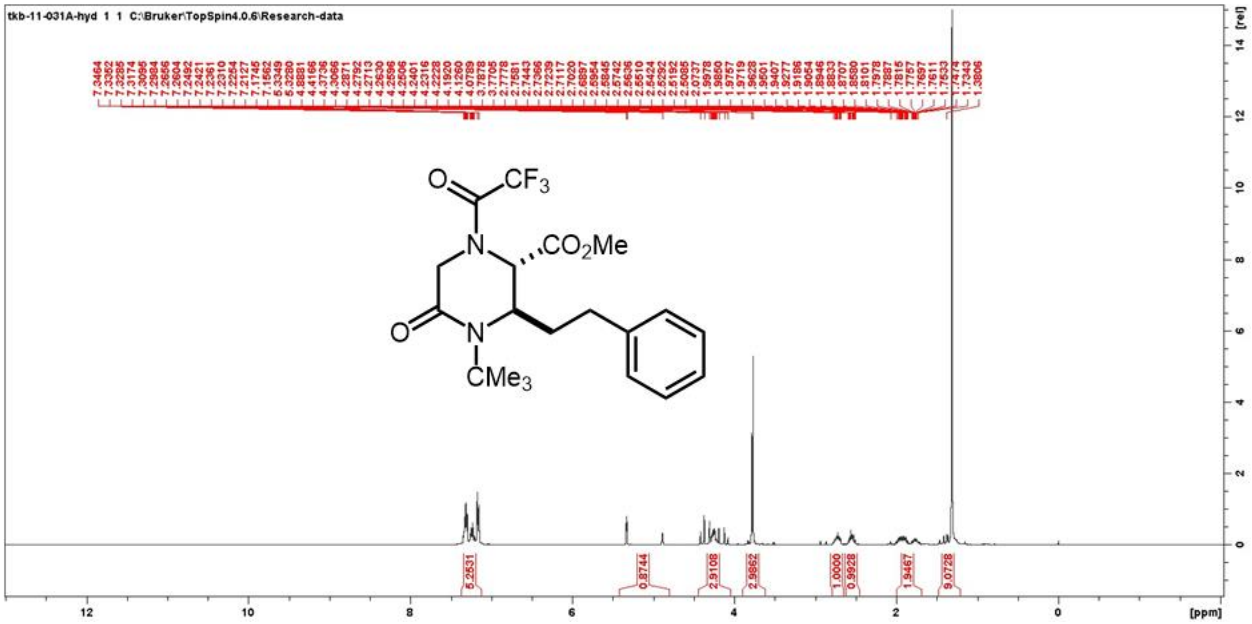
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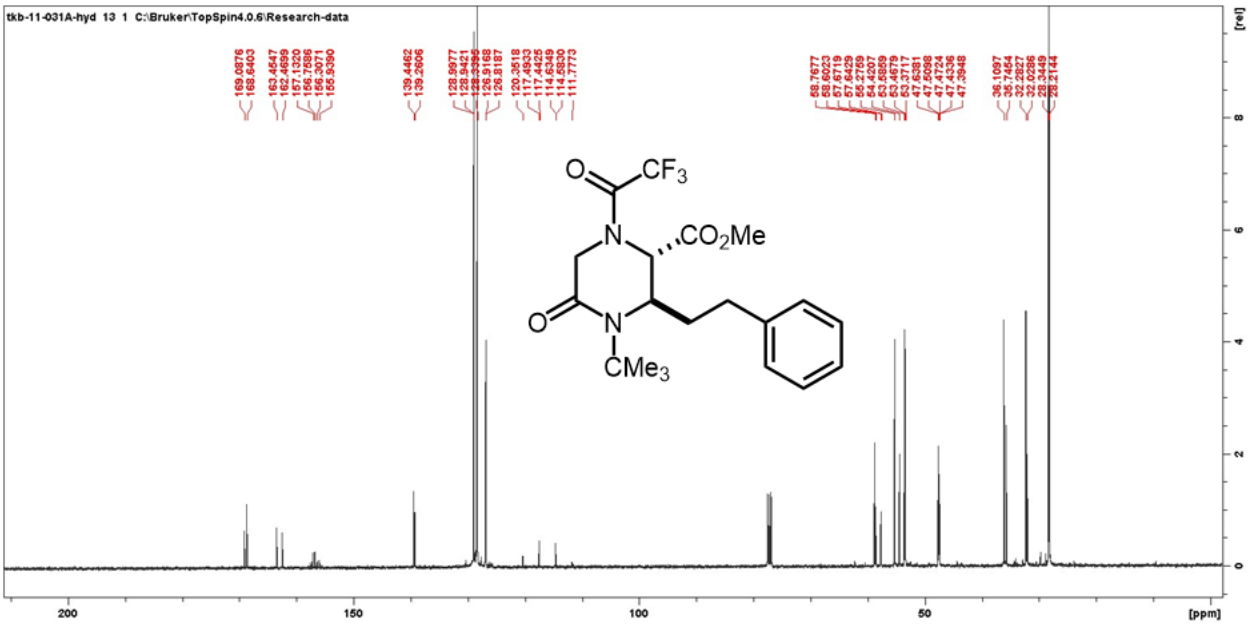
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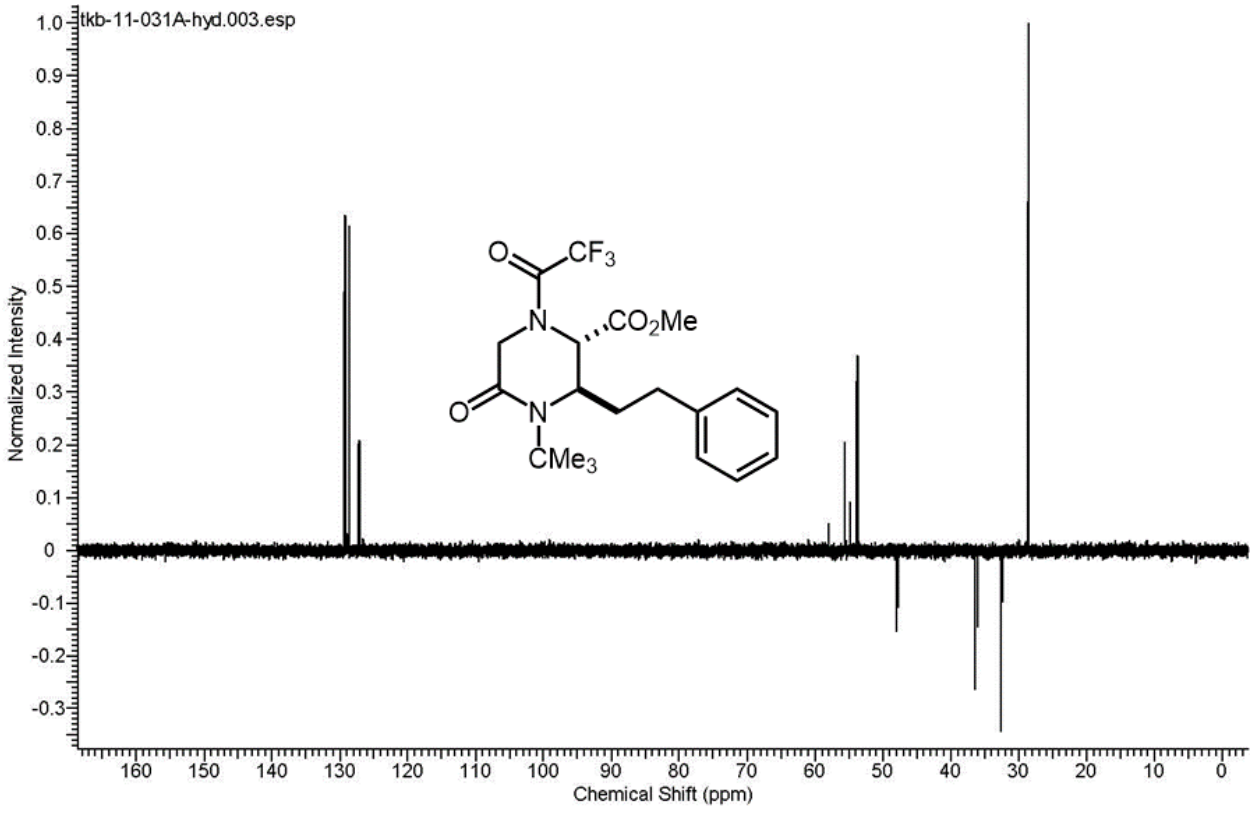
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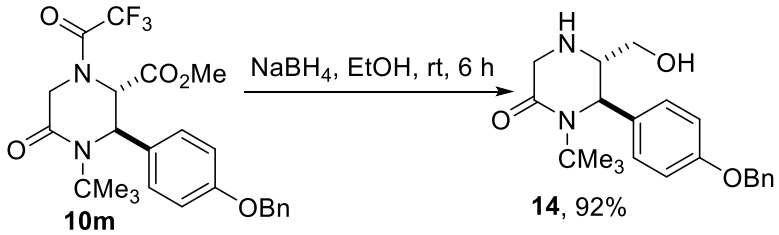
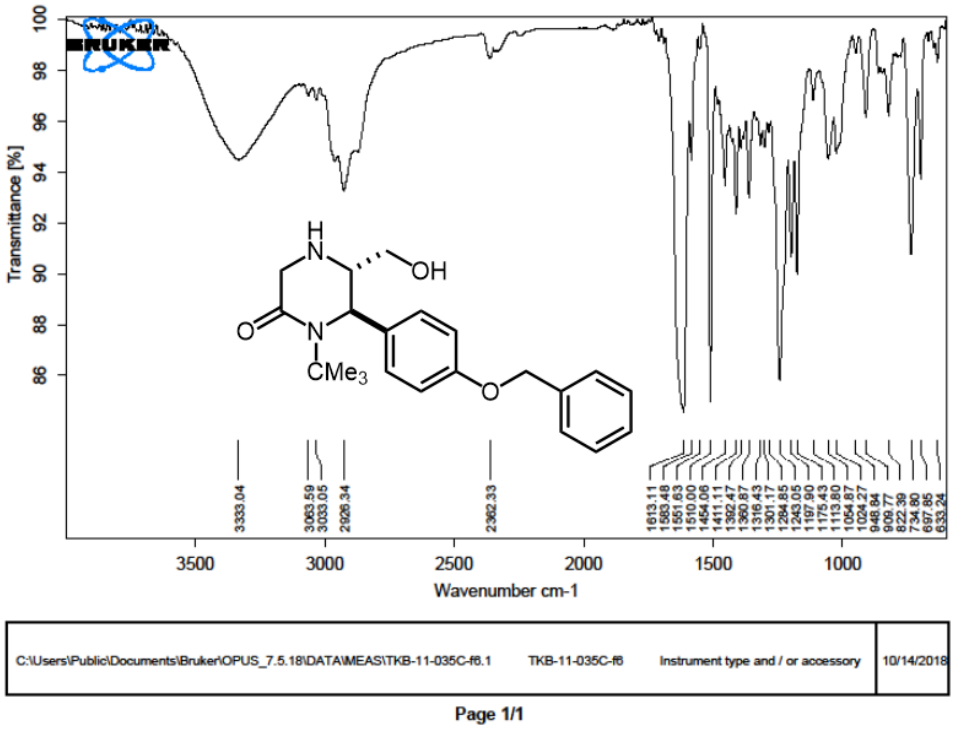
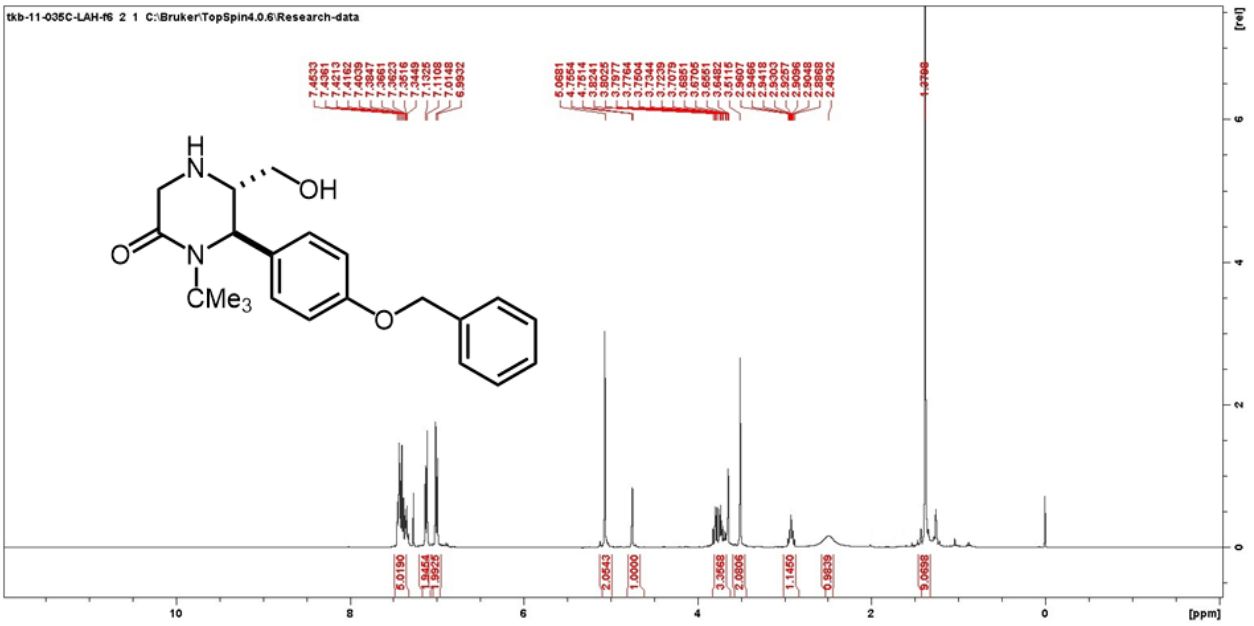

NaBH4, EtOH, rt, 6 h
10m
14, 92%

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 ester **10m** (197 mg, 0.40 mmol) and ethanol (5 mL). $NaBH_4$ (122 mg, 3.2 mmol, 8 equiv) was then added portion-wise. The reaction mixture was allowed to warm to room temperature overnight (judged complete by GC-MS analysis). After this time, the reaction mixture was cooled to 0 °C and diluted with Et_2O (10 mL), then quenched by slow addition of a solution of 2 N $NaOH_{(aq)}$ (2 mL). The organic layer was washed successively with sat NH_4Cl and brine, then dried over anhydrous Na_2SO_4. It was filtered and concentrated *in vacuo* to yield the alcohol as a pale yellow oil. Yield = 136 mg, 92%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.15 (m, 5H), 7.03 – 6.94 (m, 2H), 6.94 – 6.81 (m, 2H), 4.92 (s, 2H), 4.60 (d, J = 2.1 Hz, 1H), 3.71 – 3.46 (m, 3H), 3.36 (s, 2H), 2.83 – 2.71 (m, 1H), 1.26 (q, J = 16.4 Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 158.4, 136.8, 134.6, 128.7, 128.2, 127.6, 127.3, 115.3, 70.2, 60.8, 60.0, 58.9, 58.0, 46.9, 28.3. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{22}H_{28}N_2O_3$ 368.2100; found 368.2106.

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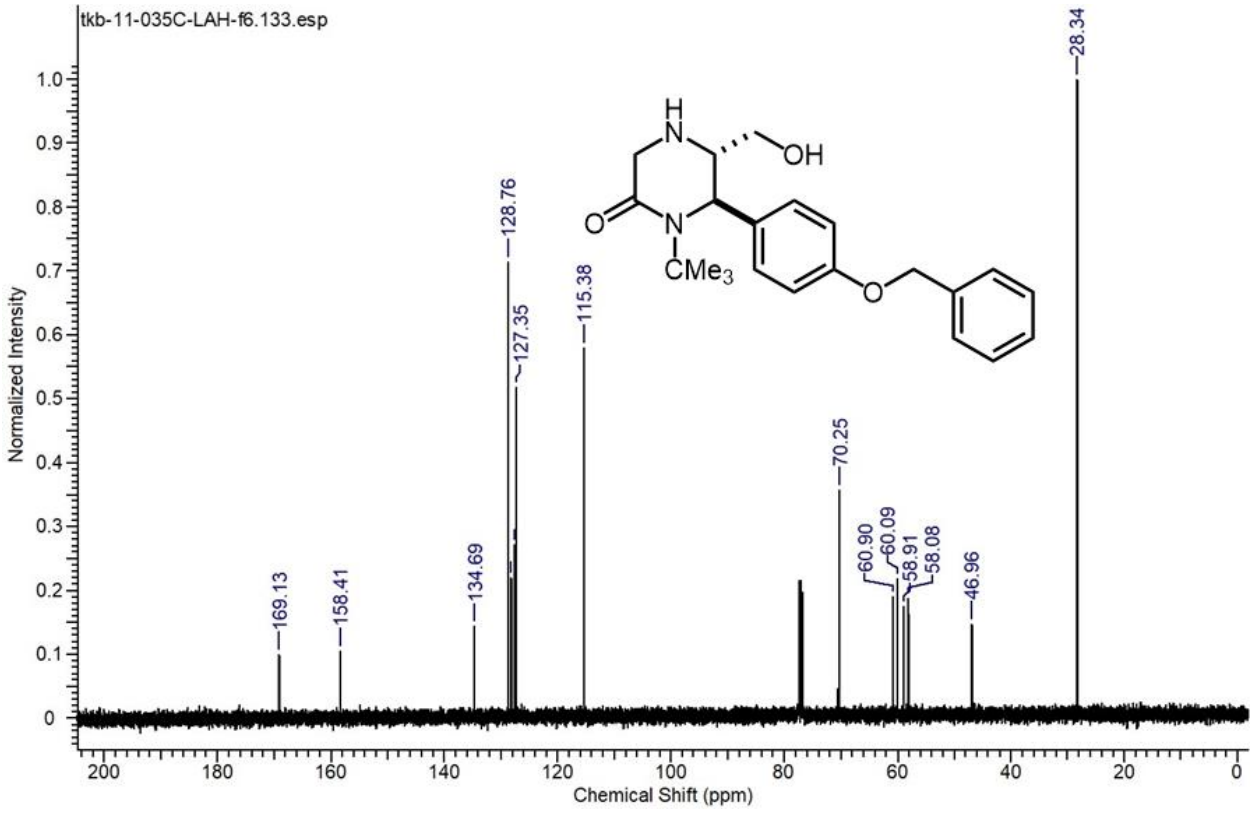
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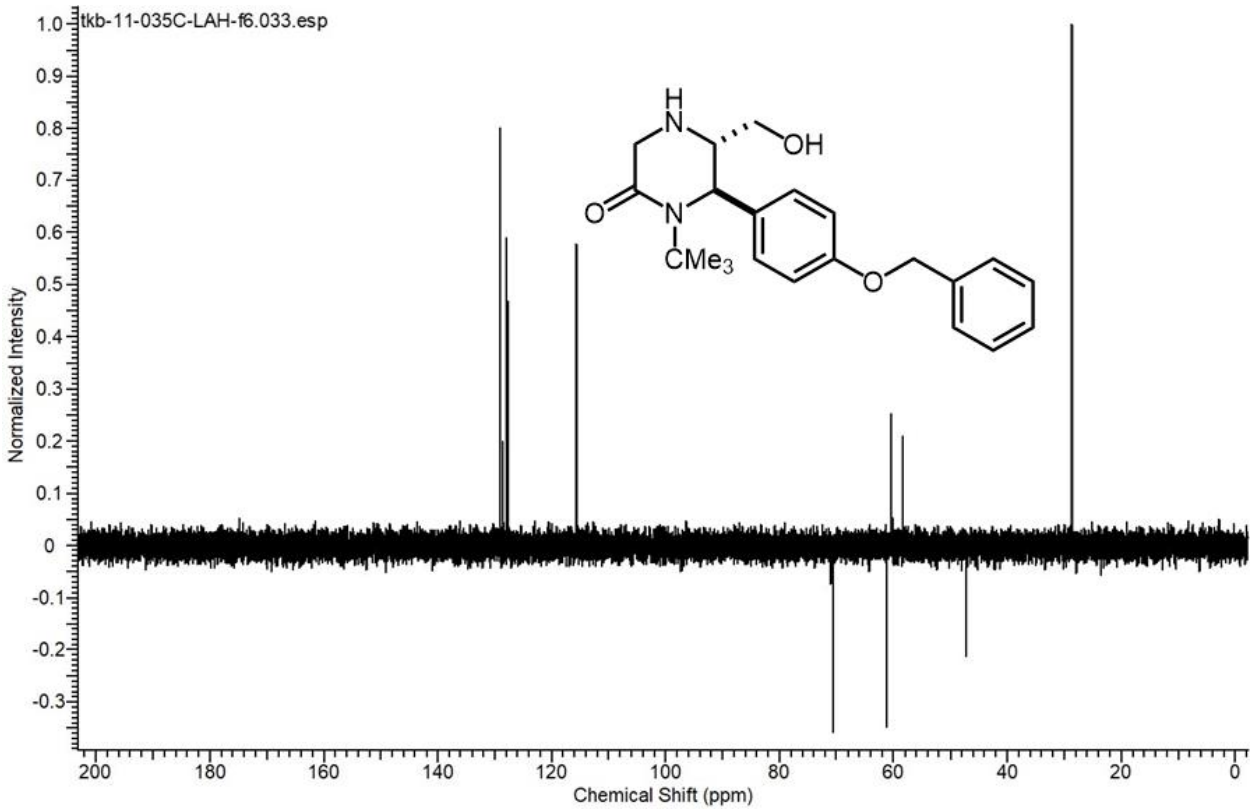
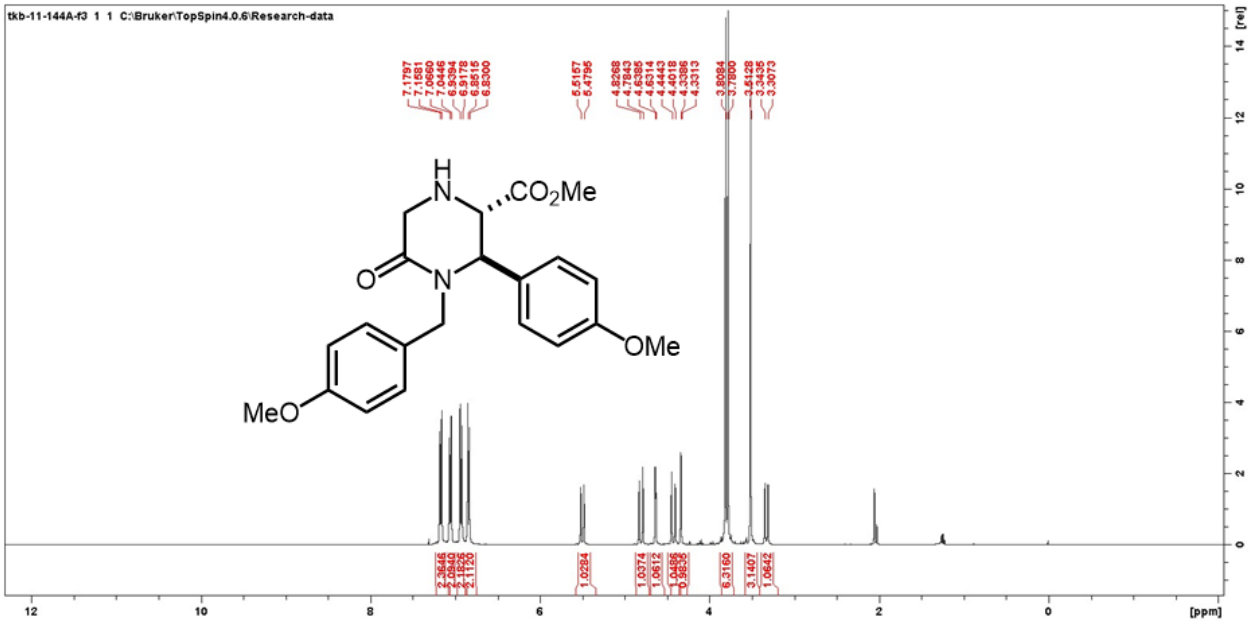
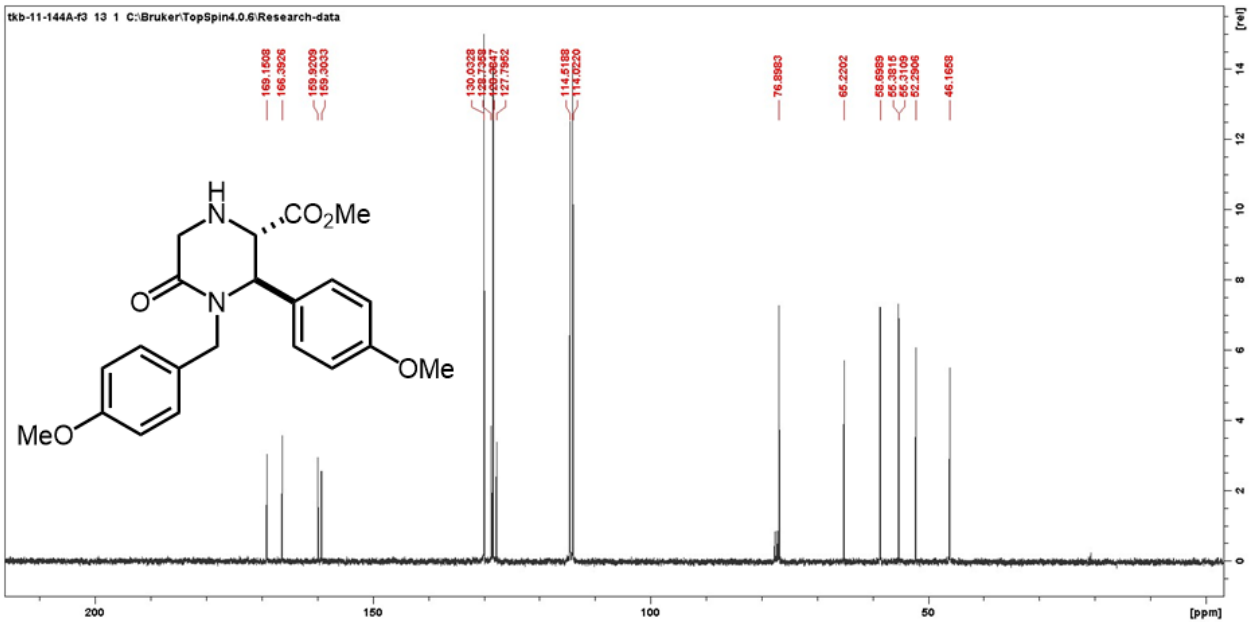
O
CMe3

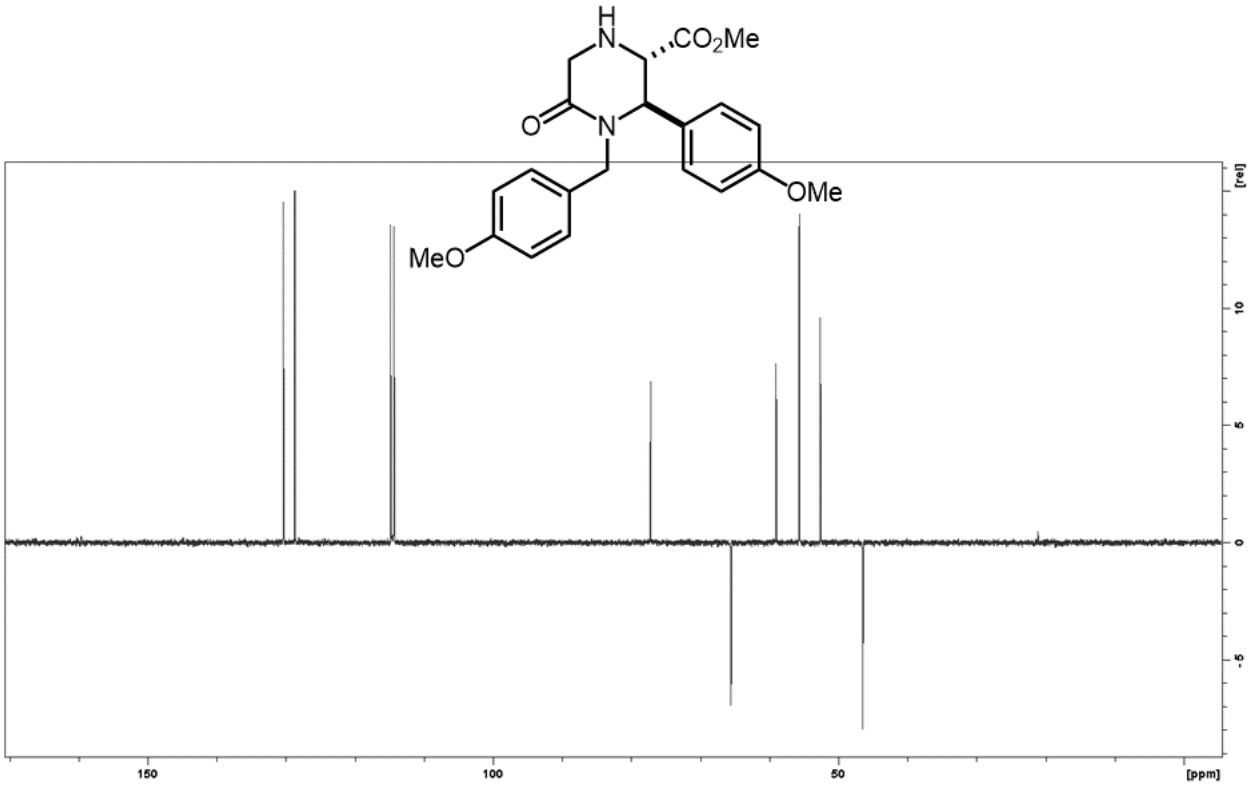


To a 10 mL round-bottomed flask equipped with a magnetic stir bar under a nitrogen atmosphere, at room temperature, was added ester **10b** (240 mg, 0.50 mmol) dissolved in DCM (5 mL) by means of a syringe. Pyrrolidine (71.1 mg, 1.0 mmol, 2 equiv) was then added. The reaction mixture was allowed to stir at room temperature until complete conversion (as judged by GC-MS and TLC analyses). The mixture was concentrated *in vacuo* to yield the amino ester as a pale yellow oil, which was purified by flash column chromatography on silica gel eluting with DCM:MeOH (1:1) Yield = 186 mg, 97%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 6.8 Hz, 2H), 7.11 (d, J = 7.2 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 6.81 (d, J = 6.8 Hz, 2H), 5.50 (d, J = 14.4 Hz, 1H), 4.70 (d, J = 17.0 Hz, 1H), 4.63 (d, J = 3.0 Hz, 1H), 4.42 (d, J = 17.0 Hz, 1H), 4.33 (d, J = 3.0 Hz, 1H), 3.79 (overlapping singlets, 6H), 3.51 (s, 3H), 3.32 (d, J = 14.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.15, 166.40, 159.92, 159.31, 130.04, 128.74, 128.39, 127.80, 114.52, 114.03, 76.90, 65.22,

58.70, 55.38, 55.31, 52.30, 46.17. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{21}H_{24}N_2O_5$ 384.1685; found 384.1693.



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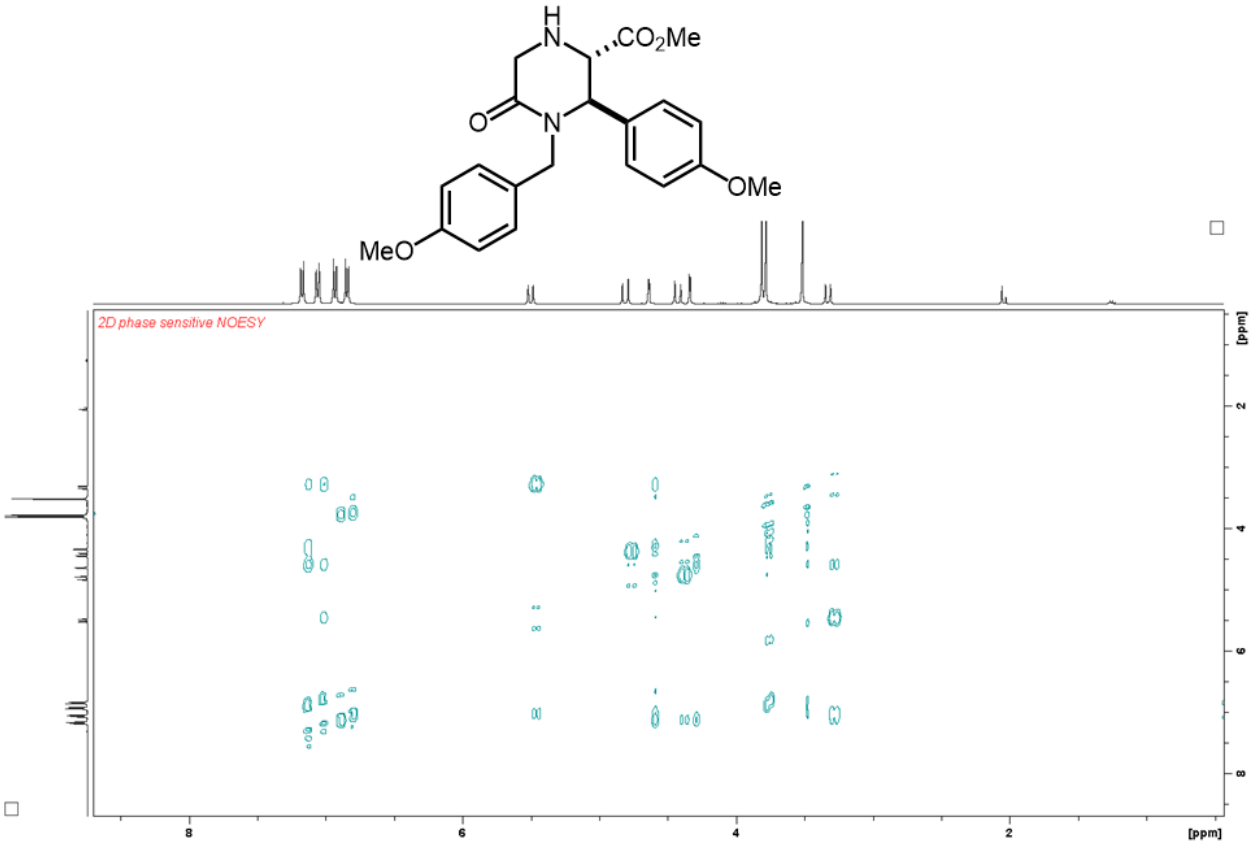
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References

(1) Dar'in, D.; Bakulina, O.; Chizhova, M.; Krasavin, M. *Org. Lett.* **2015**, *17*, 3930.
(2) Beng, T. K.; Bassler, D. P. *Tetrahedron Lett.* **2014**, *55*, 6662.
(3) Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R. *Org. Lett.* **2014**, *16*, 916.