Supporting Information for:

Harnessing the 1,3-azadiene-anhydride reaction for the regioselective and stereocontrolled synthesis of lactam-fused bromotetrahydropyrans by bromoetherification of lactam-tethered trisubstituted tertiary alkenols

*Ifeyinwa S. Anosike and Timothy K. Beng**

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 were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Freshly purchased toluene and DMF were stored under 4 A^{o} molecular sieves for several days prior to use. THF and 2-MeTHF were distilled from sodium benzophenone ketyl. All other solvents were used as purchased. All amines, enals, Grignard reagents, and N-bromosuccinimide were newly purchased and used without further purification. 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). Unless otherwise indicated, NMR spectral data were acquired using $CDCl_3$ as solvent, at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^{+} data were obtained using either electron spray 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 alkenols were prepared using reported procedures.[1,2]

General Procedure A: Bromoetherification of lactam-tethered alkenol 1: An oven-dried vial was equipped with a stir bar and a solution of **1** (1.00 mmol) in dichloromethane (5 mL) was added to the vial followed by deionized water (1 mL) and *N*-bromosuccinimide (1.10 mmol, 1.1 equiv) at room temperature. After stirring for 3 days at the same temperature, the reaction mixture diluted by the addition of dichloromethane (20 mL) and quenched by the addition of saturated sodium thiosulfate solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography to afford the lactam-fused bromotetrahydropyran.

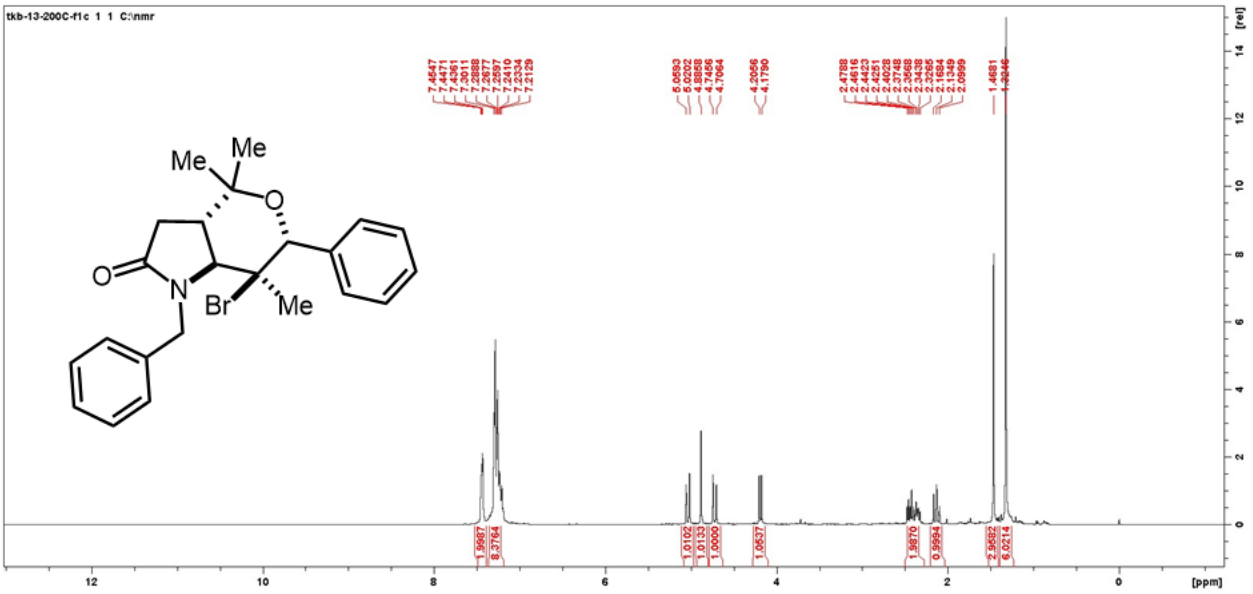
Typical Procedure A: To a solution of alkenol **1a** (349.5 mg, 1.00 mmol) in dichloromethane (10 mL) was added *N*-bromosuccinimide (195.8 mg, 1.10 mmol) at room temperature. After stirring for 3 days at the same temperature, the reaction mixture diluted by the addition of dichloromethane (20 mL) and quenched by the addition of saturated sodium thiosulfate solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and

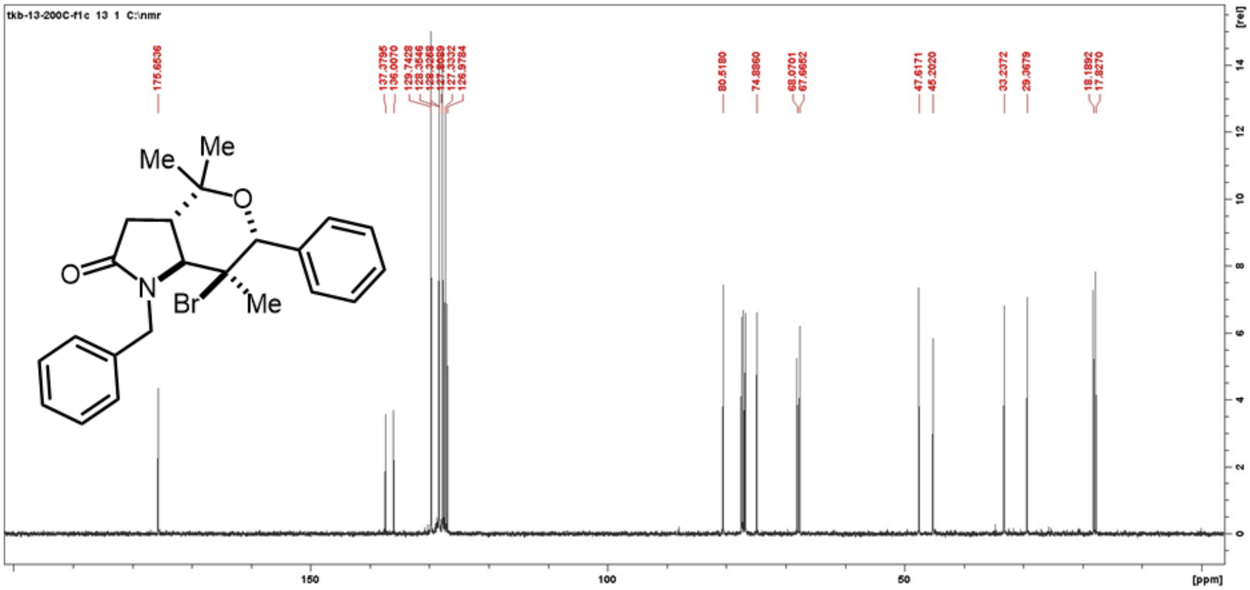
concentrated *in vacuo*. The residue was purified by flash column chromatography as indicated below to afford **4a** in 93% yield and 95:5 dr.

Scheme 1 Results

Compound 4a

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Yellowish oil. Yield = 398.4 mg, 93%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.39 – 7.14 (m, 8H), 5.04 (d, *J* = 15.7 Hz, 1H), 4.89 (s, 1H), 4.73 (d, *J* = 15.7 Hz, 1H), 4.19 (d, *J* = 10.8 Hz, 1H), 2.51 – 2.30 (m, 2H), 2.19 – 2.08 (m, 1H), 1.47 (s, 3H), 1.33 (s,s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.66, 137.38, 136.01, 129.75, 128.36, 128.33, 127.81, 127.34, 126.98, 80.52, 74.89, 68.08, 67.67, 47.62, 45.20, 33.24, 29.37, 18.19, 17.83. **HRMS-EI$^+$** (*m/z*): calc for $C_{23}H_{26}BrNO_2$ $[M]^+$ 427.1147, found 427.1153. FTIR (KBr): 2965.4, 1727.5, 1696.3, 1604.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1298.7, 1247.5, 1179.3, 1135.9, 1031.8, 905.8, 839.0.

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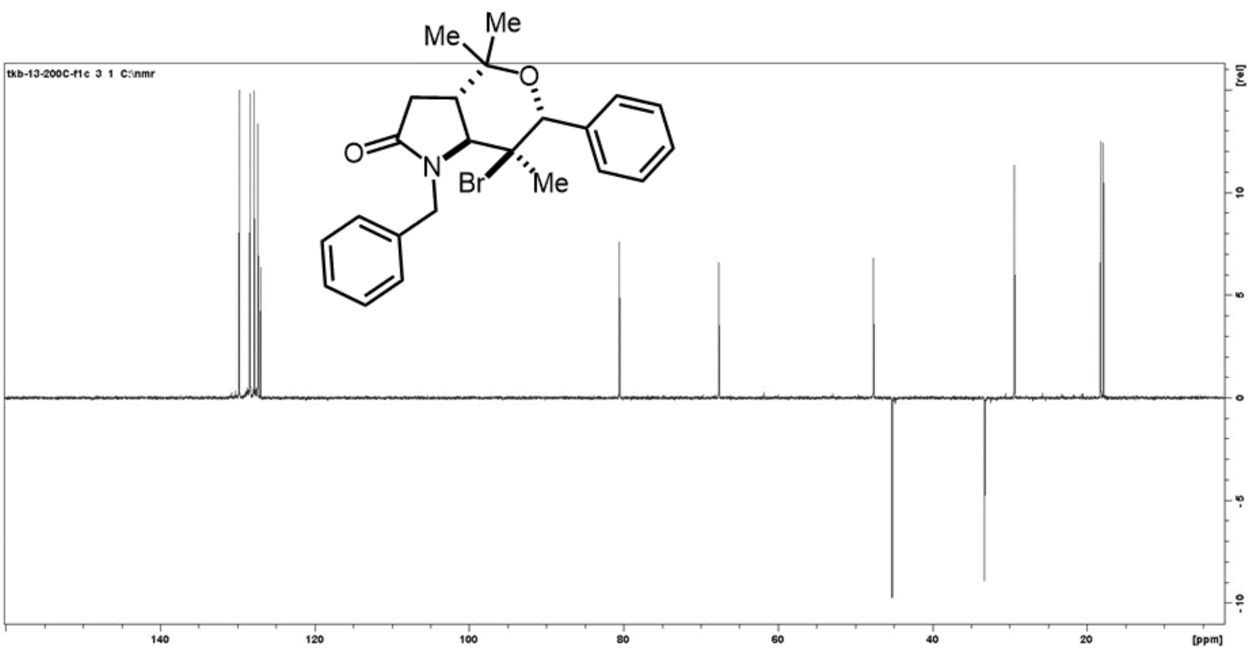
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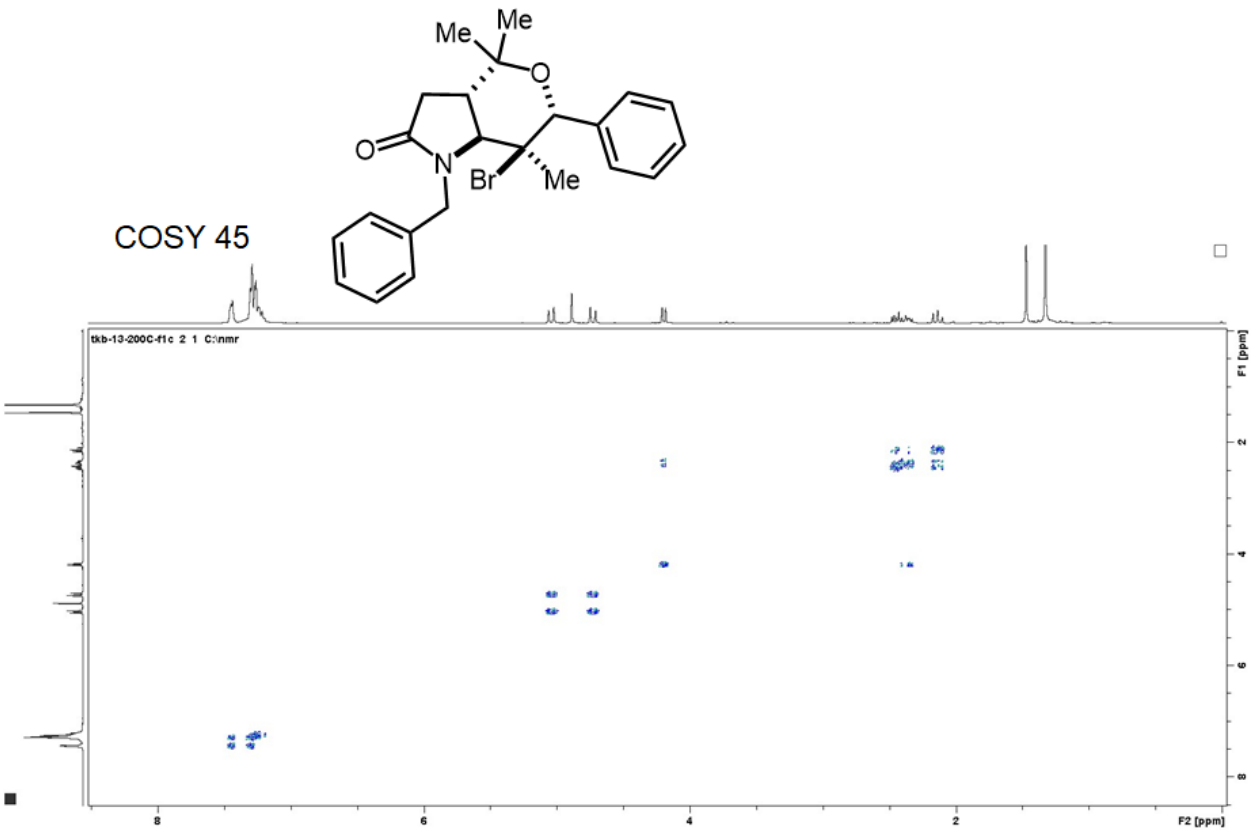
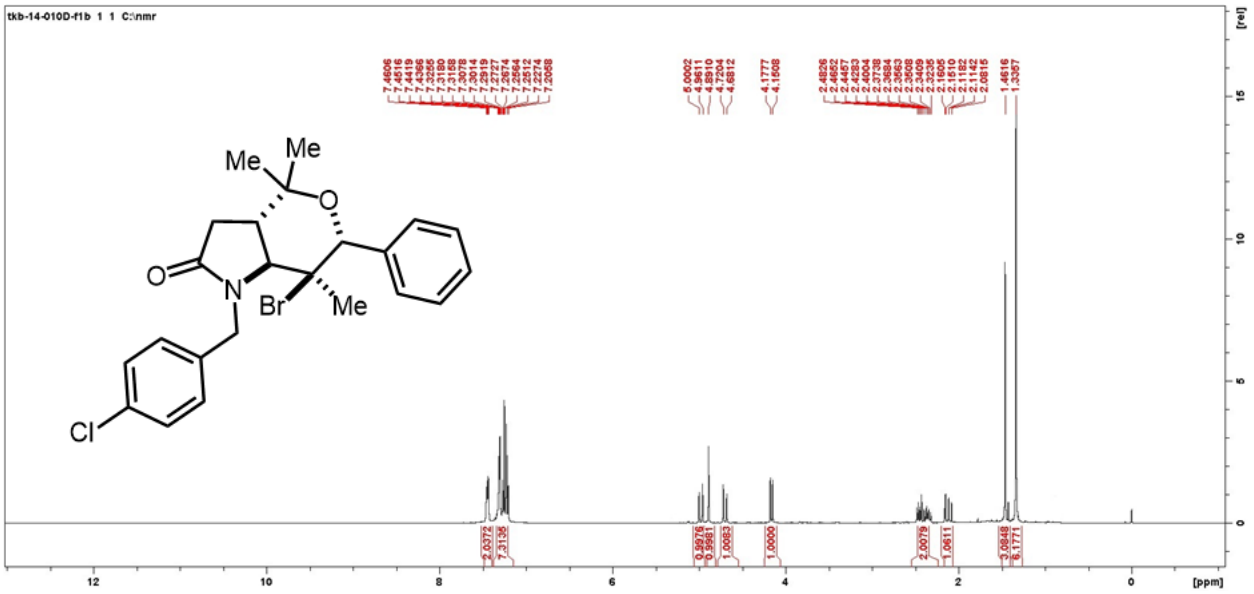


Compound 4b

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Yellowish oil. Yield = 416.5 mg, 90%, 95:5 dr (*anti*:*syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.44 (dt, J = 5.9, 3.5 Hz, 2H), 7.38 – 7.18 (m, 7H), 4.98 (d, J = 15.7 Hz, 1H), 4.89 (s, 1H), 4.70 (d, J = 15.7 Hz, 1H), 4.16 (d, J = 10.7 Hz, 1H), 2.51 – 2.30 (m, 2H), 2.18 – 2.06 (m, 1H), 1.46 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.70, 136.01, 135.85, 132.84, 129.70, 129.38, 128.50, 128.37, 127.35, 80.50, 74.87, 68.20, 67.77, 47.60, 44.64, 33.17, 29.32, 18.22, 17.79. **HRMS-EI^{+}** (*m/z*): calc for $C_{23}H_{25}BrClNO_2$ $[M]^{+}$ 461.0757, found 461.0761. FTIR (KBr): 2985.4, 1737.5, 1691.2, 1644.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1298.7, 1247.5, 1179.3, 1002.8, 925.8, 791.0.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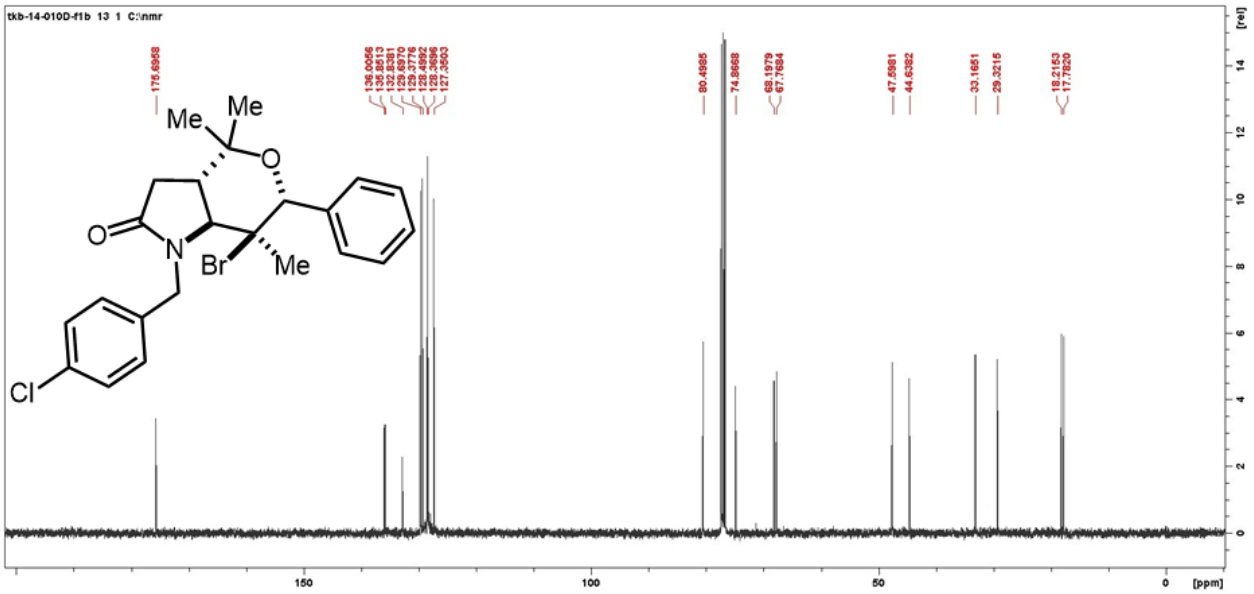
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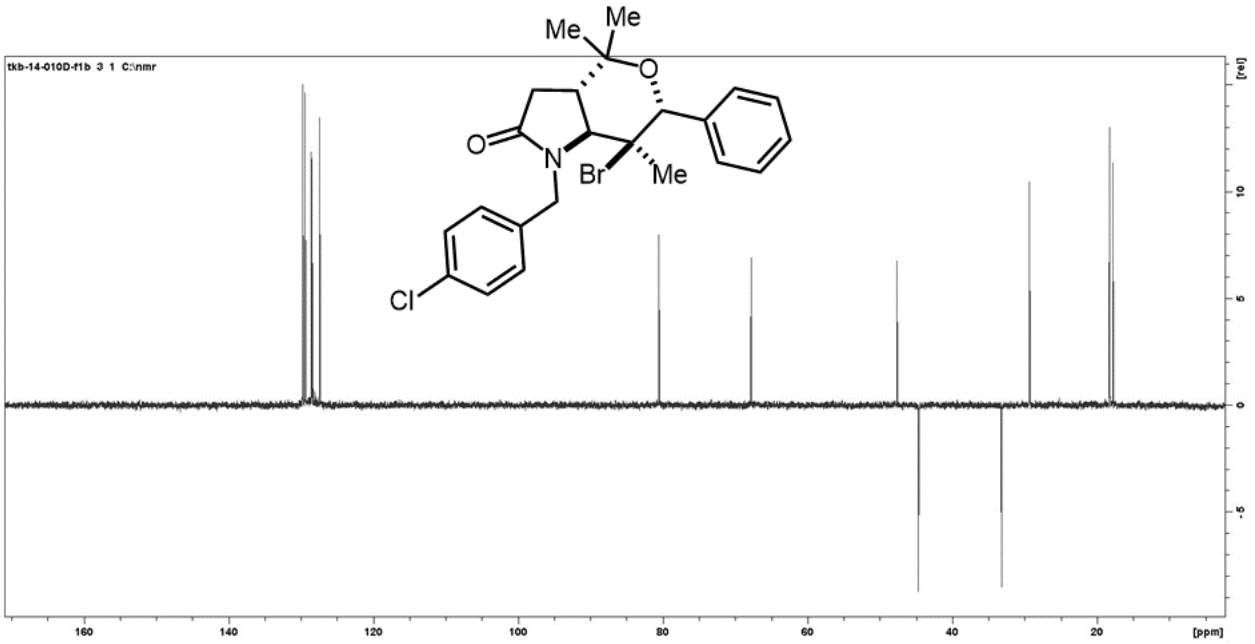
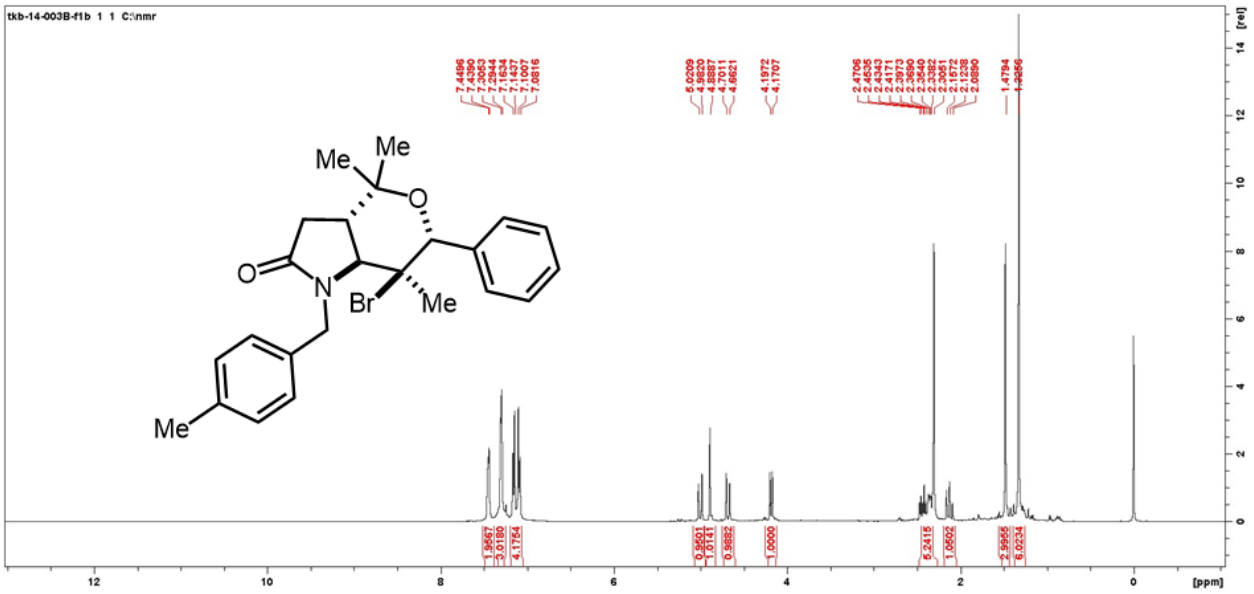


Compound 4c

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 420.3 mg, 95%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (q, J = 3.0 Hz, 2H), 7.30 (dd, J = 4.6, 2.4 Hz, 3H), 7.19 – 7.12 (m, 2H), 7.09 (d, J = 7.8 Hz, 2H), 5.00 (d, J = 15.6 Hz, 1H), 4.89 (s, 1H), 4.68 (d, J = 15.6 Hz, 1H), 4.22 – 4.11 (m, 1H), 2.49 – 2.26 (m, 5H), 2.18 – 2.07 (m, 1H), 1.47 (s, 3H). 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.61, 136.47, 135.98, 134.25, 130.21, 129.70, 129.37, 128.99, 128.27, 127.90, 127.77, 127.67, 127.28, 80.47, 74.84, 68.05, 67.53, 47.55, 44.86, 33.23, 29.32, 21.09, 18.17, 17.77. **HRMS-EI^{+}** (*m/z*): calc for $C_{24}H_{28}BrNO_2$ $[M]^{+}$ 441.1303, found 441.1300. FTIR (KBr): 2939.4, 1723.5, 1696.3, 1604.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1298.7, 1247.5, 1179.3, 1135.9, 1031.8, 985.8, 833.0.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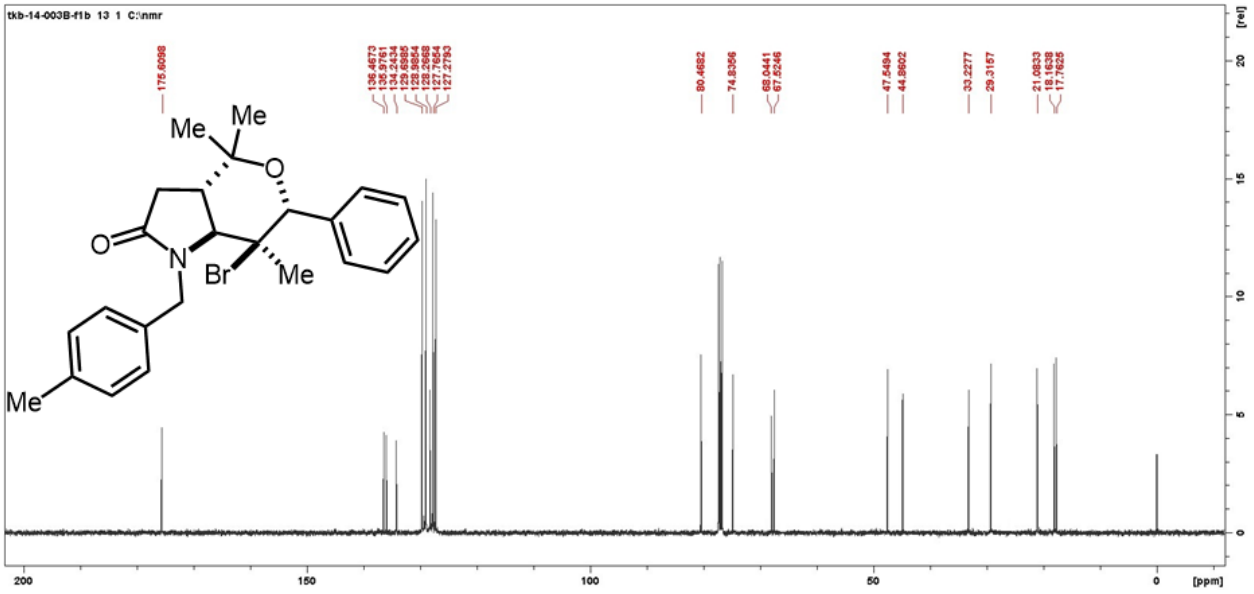
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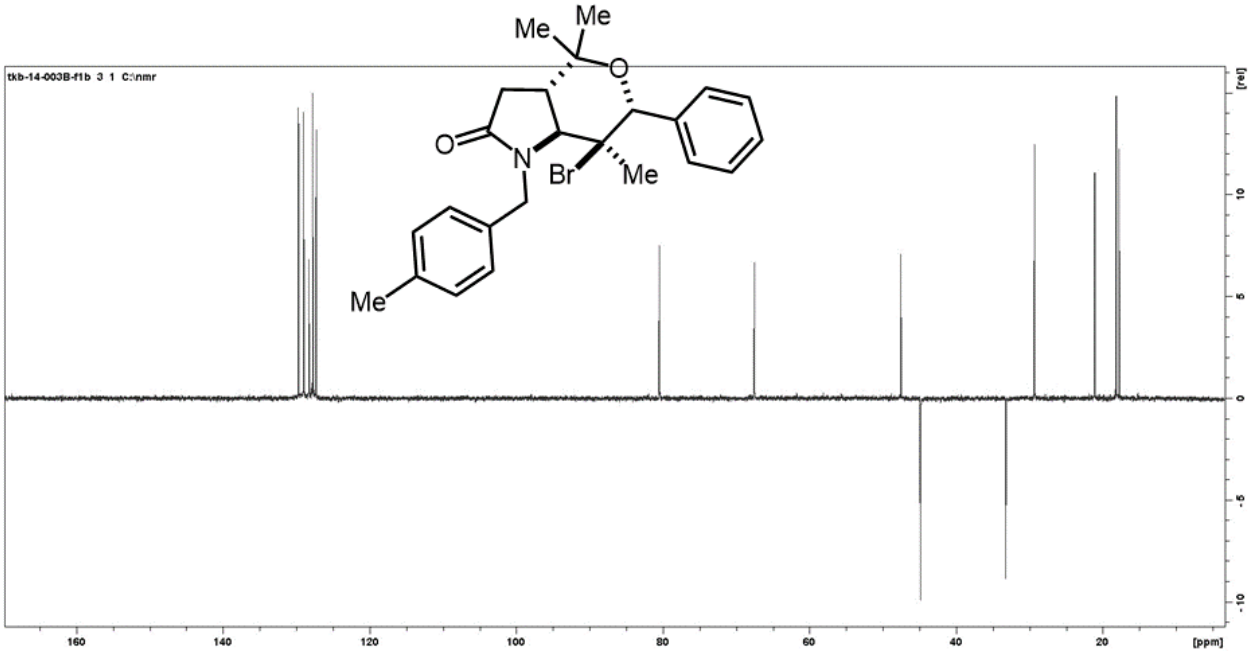
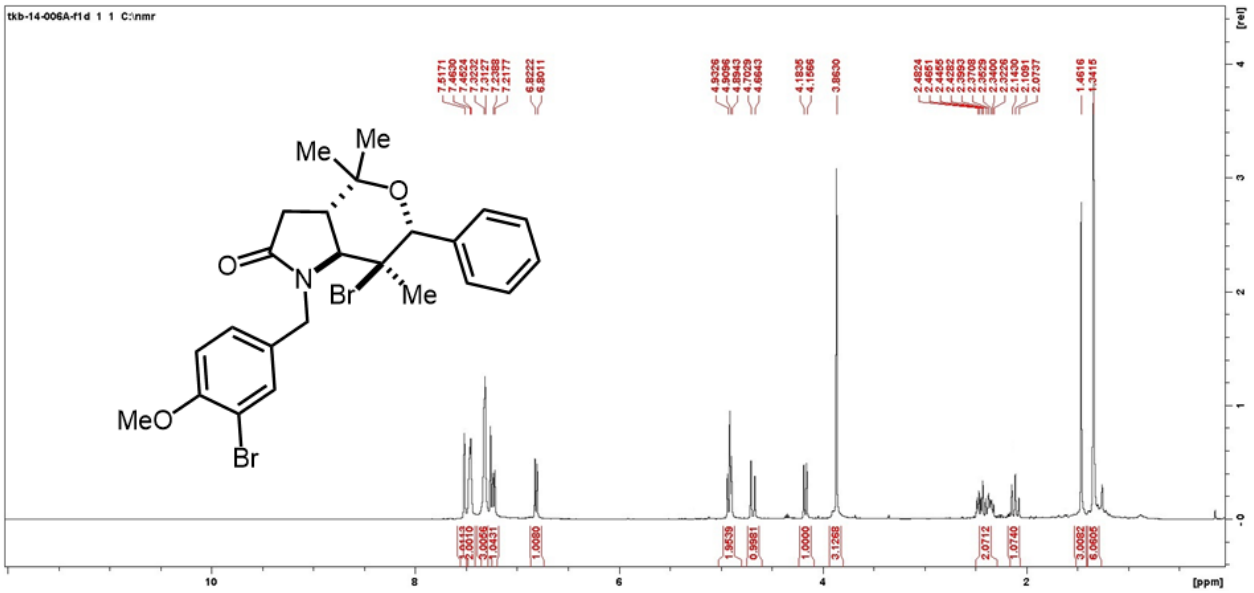


Compound 4d

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 427.8 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.52 (s, 1H), 7.46 (q, J = 2.9 Hz, 2H), 7.32 (dd, J = 4.6, 2.4 Hz, 3H), 7.28 – 7.19 (m, 2H), 6.81 (d, J = 7.5 Hz, 1H), 4.91 (t, J = 7.7 Hz, 2H), 4.68 (d, J = 15.4 Hz, 1H), 4.17 (d, J = 10.7 Hz, 1H), 3.86 (s, 3H), 2.52 – 2.30 (m, 2H), 2.19 – 2.05 (m, 1H), 1.46 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.70, 154.96, 135.91, 133.09, 131.28, 129.73, 128.40, 128.38, 127.36, 111.65, 80.53, 74.89, 68.35, 67.87, 56.23, 47.59, 44.13, 33.19, 29.33, 18.25, 17.80. **HRMS-EI^{+}** (*m/z*): calc for $C_{24}H_{27}Br_2NO_3$ $[M]^{+}$ 535.0358, found 535.0362. FTIR (KBr): 2984.1, 1733.5, 1654.3, 1606.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1299.7, 1242.5, 1179.3, , 1031.8, 994.9, 823.7, 735.2.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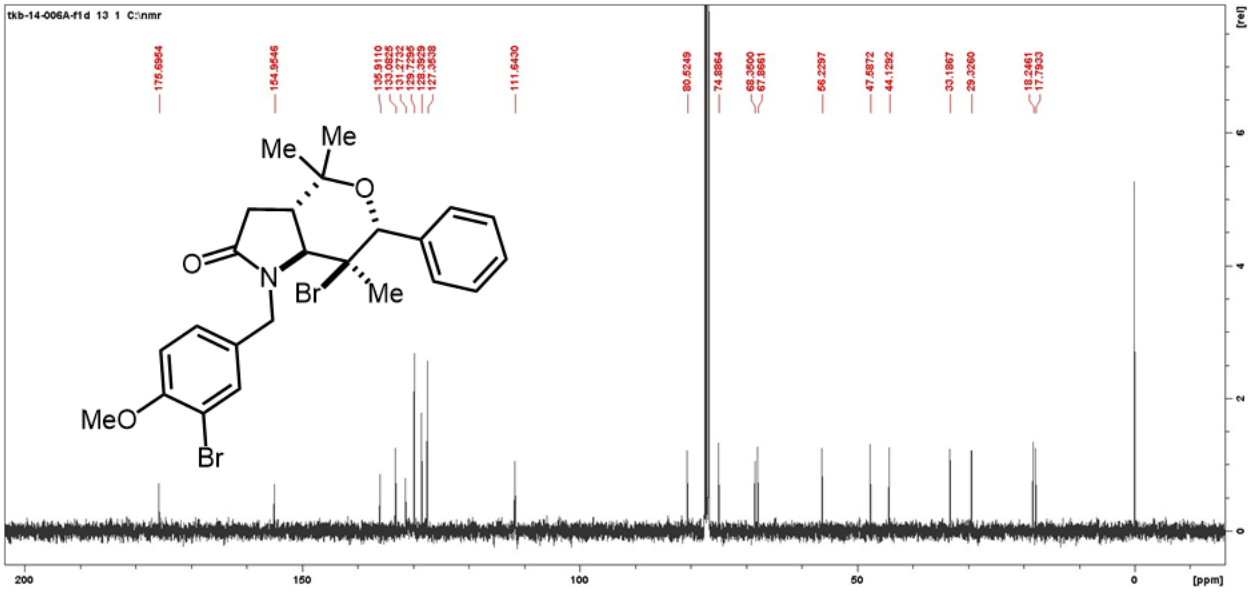
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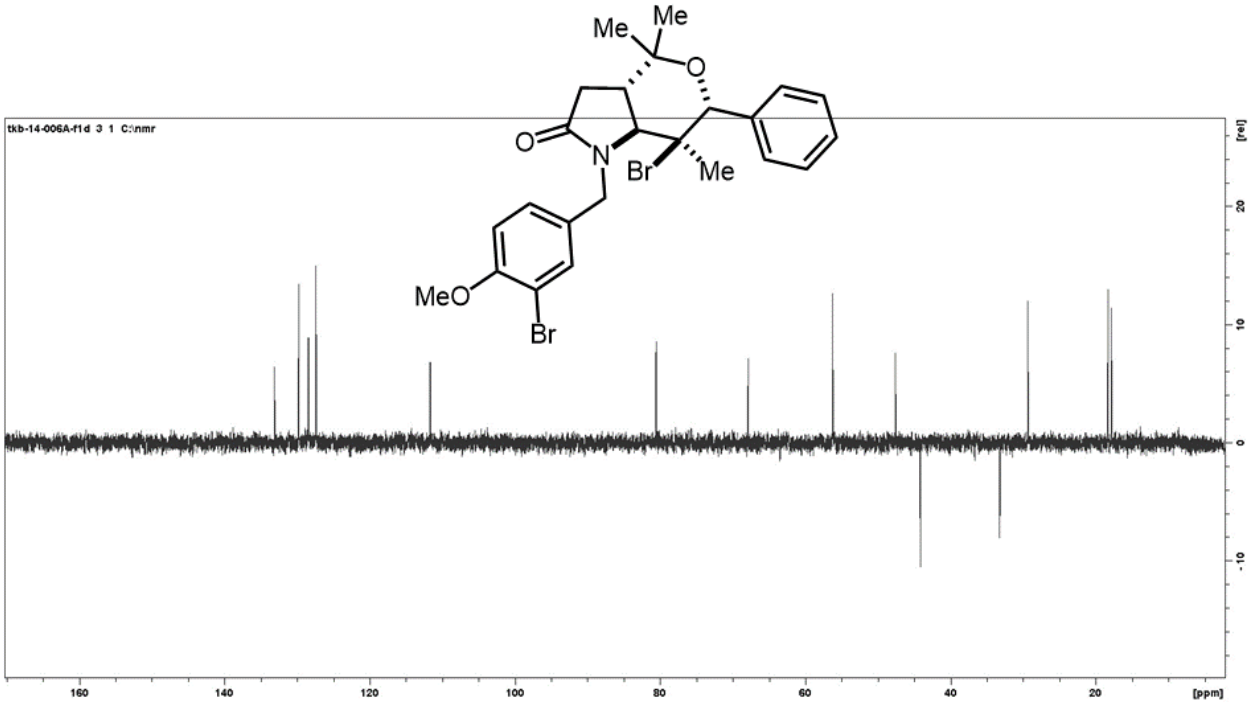
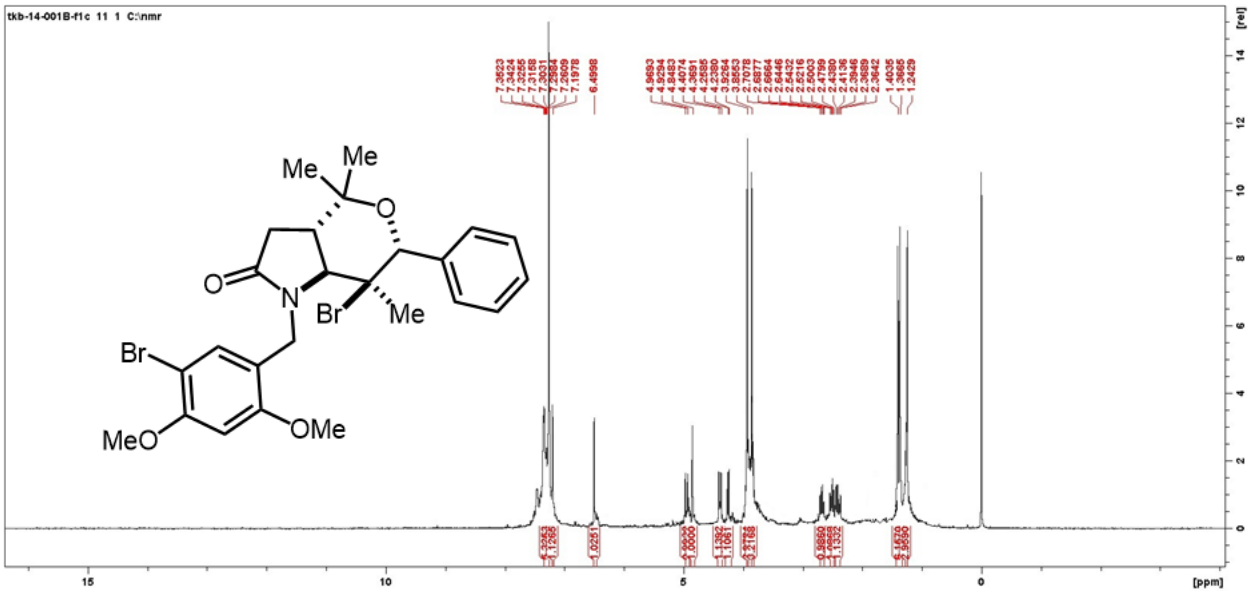


Compound 4e

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 482.2 mg, 85%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.35 – 7.20 (m, 6H), 6.50 (s, 1H), 4.94 (d, J = 15.4 Hz, 1H), 4.85 (s, 1H), 4.39 (d, J = 15.4 Hz, 1H), 4.25 (d, J = 8.1 Hz, 1H), 3.92 – 3.85 (m, 6H), 2.71 – 2.64 (m, 1H), 2.55 – 2.31 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H), 1.24 (s, 3H).^{13}C NMR (101 MHz, CDCl3) δ 175.62, 157.68, 156.10, 137.67, 132.16, 130.19, 128.29, 127.67, 118.16, 102.12, 96.71, 87.91, 81.13, 69.64, 61.62, 56.51, 55.79, 48.93, 39.62, 32.44, 30.48, 25.71, 21.13. **HRMS-EI^{+}** (*m/z*): calc for $C_{25}H_{29}Br_2NO_4$ $[M]^{+}$ 565.0463, found 565.0468. FTIR (KBr): 2994.1, 1763.4, 1669.4, 1608.2, 1511.1, 1431.8, 1414.7, 1344.9, 1298.4, 1135.3, 1031.8, 996.7, 706.4.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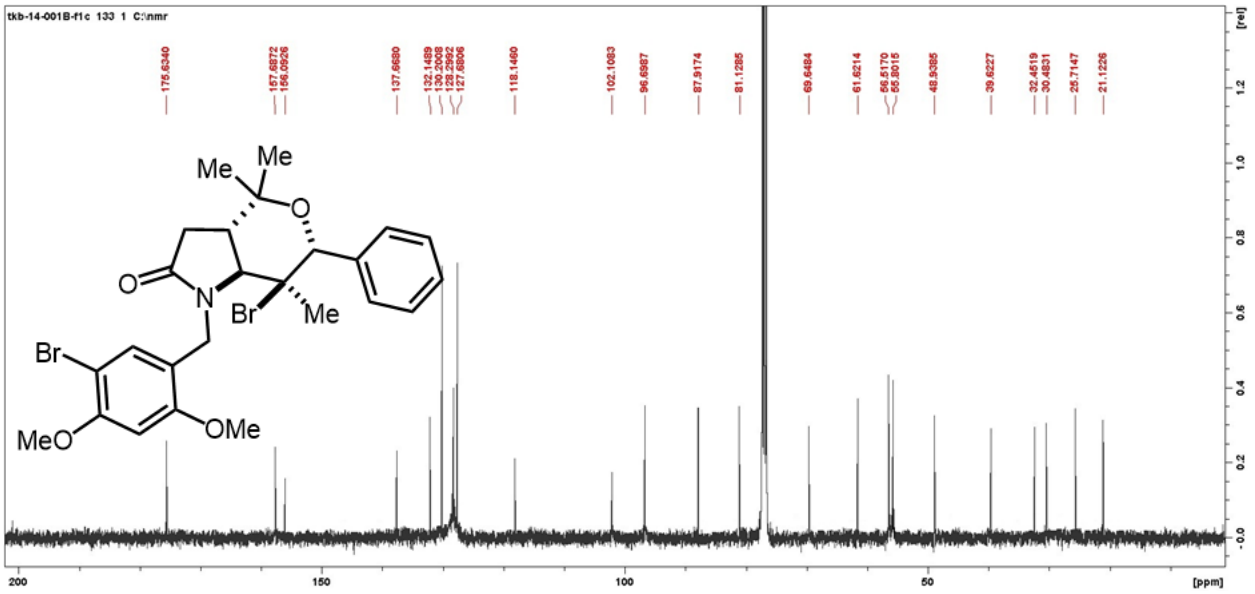
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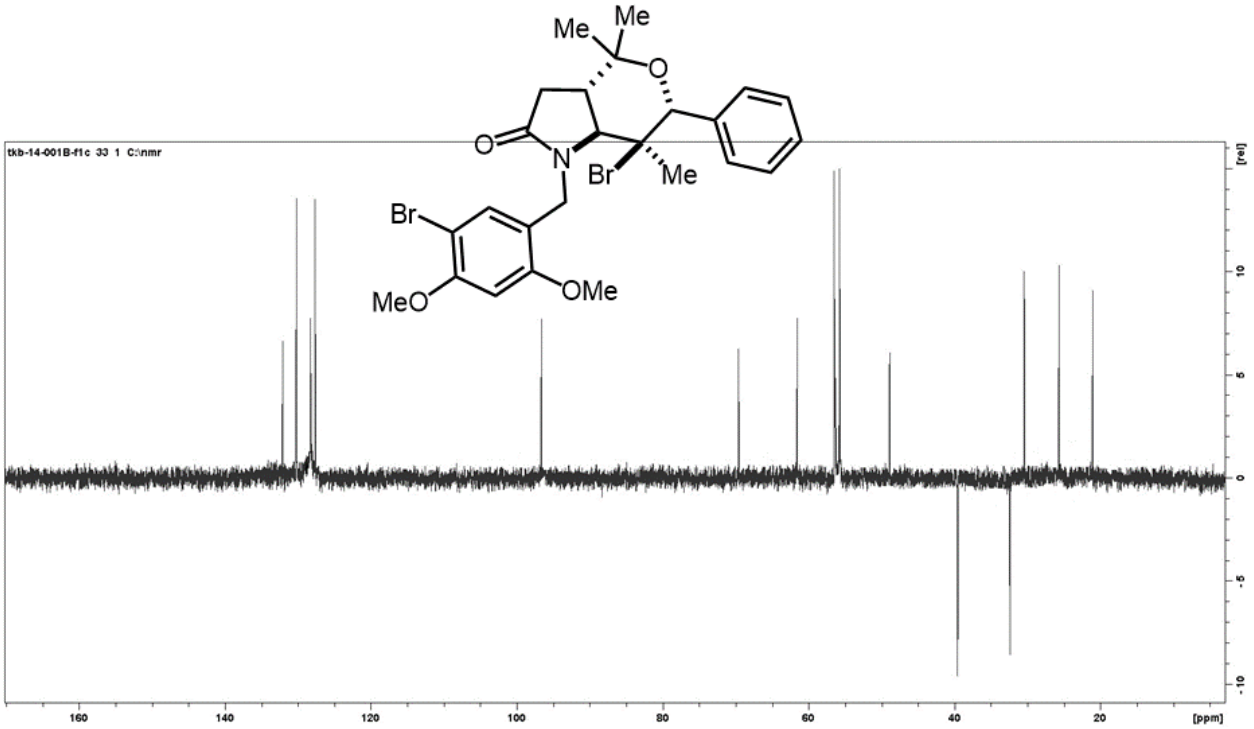
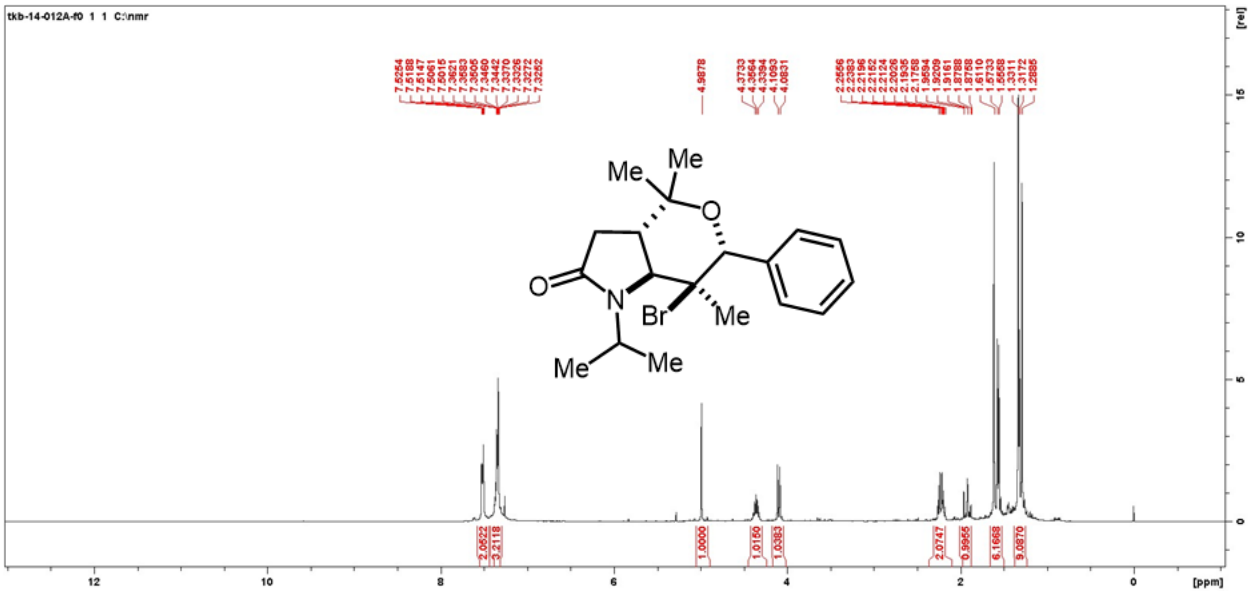


Compound 4f

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 349.9 mg, 92%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.51 (dq, J = 8.3, 2.8 Hz, 2H), 7.43 – 7.28 (m, 3H), 4.99 (s, 1H), 4.36 (hept, J = 6.6 Hz, 1H), 4.09 (d, J = 11.6 Hz, 1H), 2.28 – 2.15 (m, 2H), 1.98 – 1.85 (m, 1H), 1.61 – 1.56 (m, 6H), 1.31 – 1.28 (m, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 175.29, 136.11, 129.92, 128.33, 127.37, 80.51, 74.65, 69.24, 67.46, 48.01, 46.26, 34.20, 29.23, 20.56, 17.93, 17.77, 16.64. **HRMS-EI^{+}** (*m/z*): calc for $C_{19}H_{26}BrNO_2$ $[M]^{+}$ 379.1147, found 379.1153.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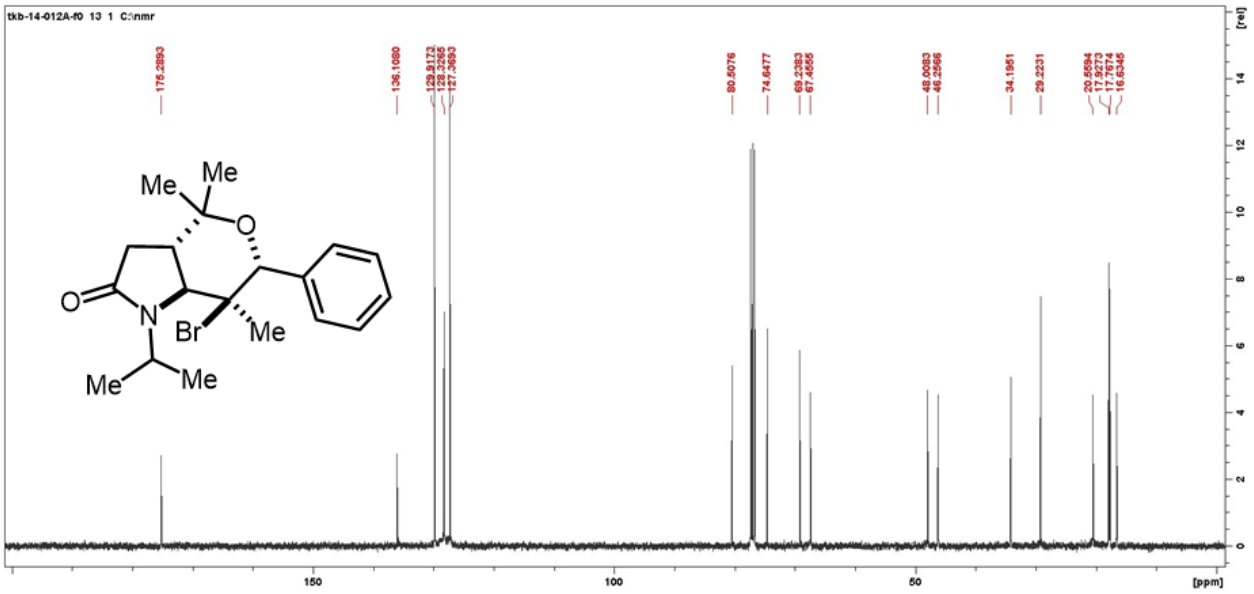
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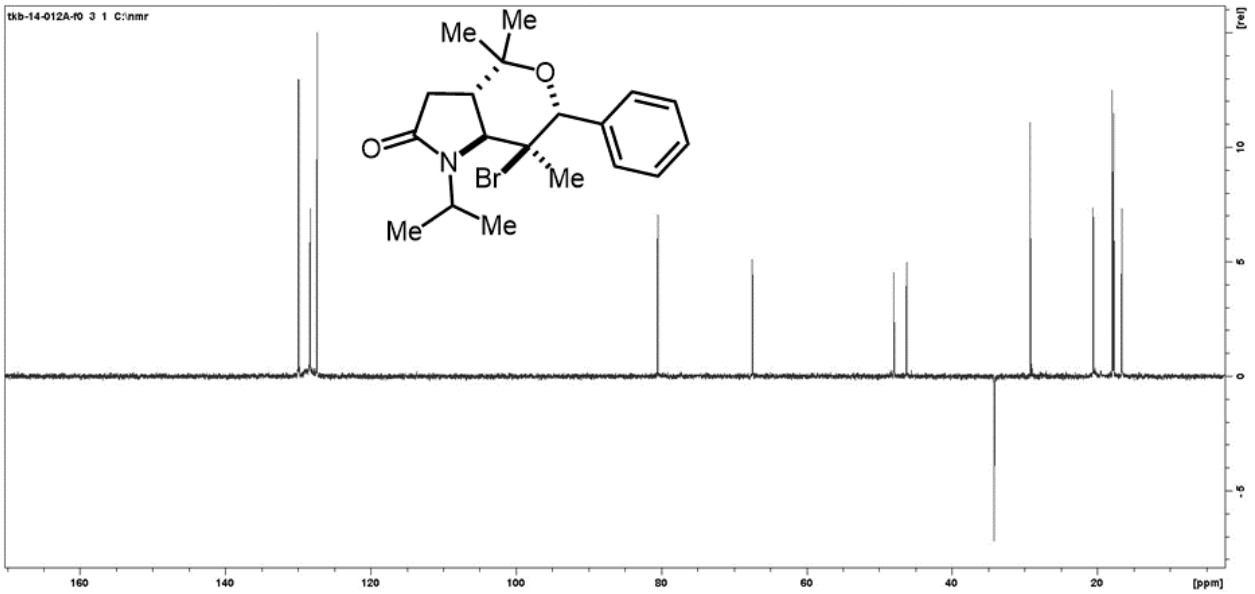
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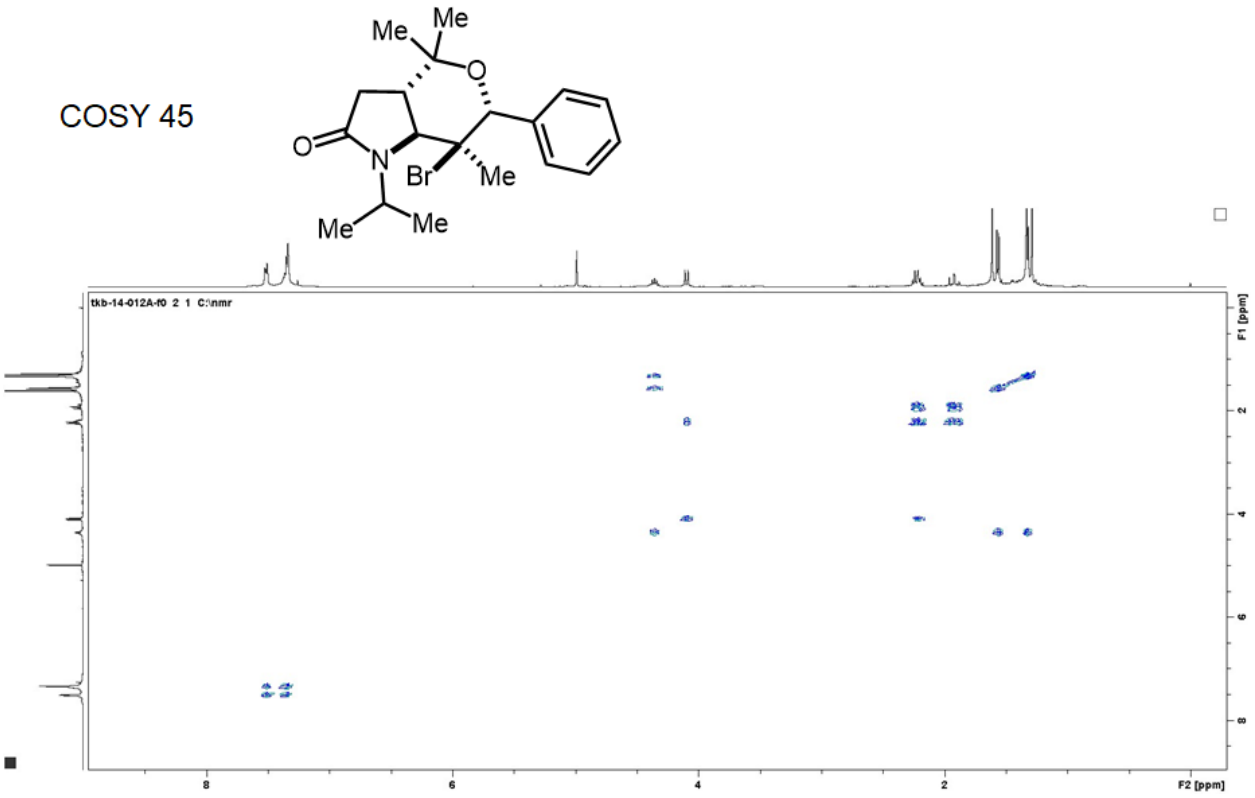
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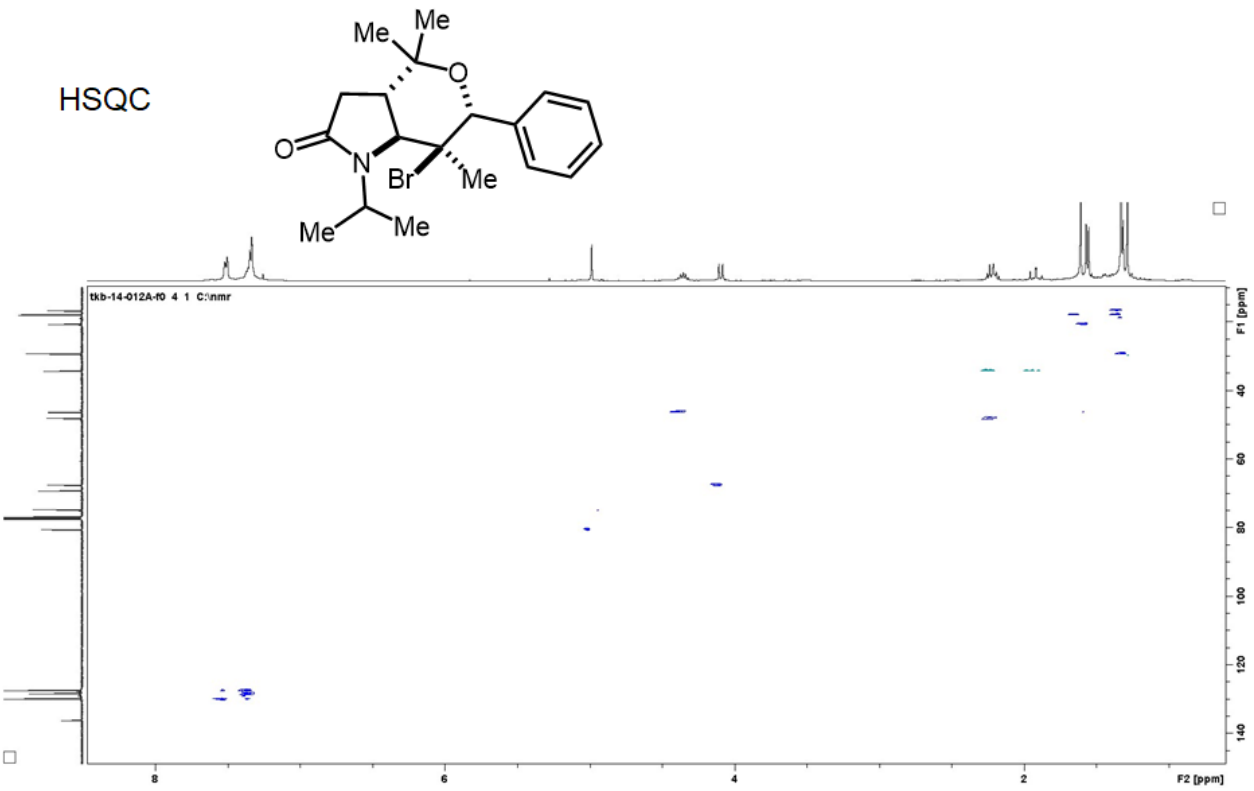
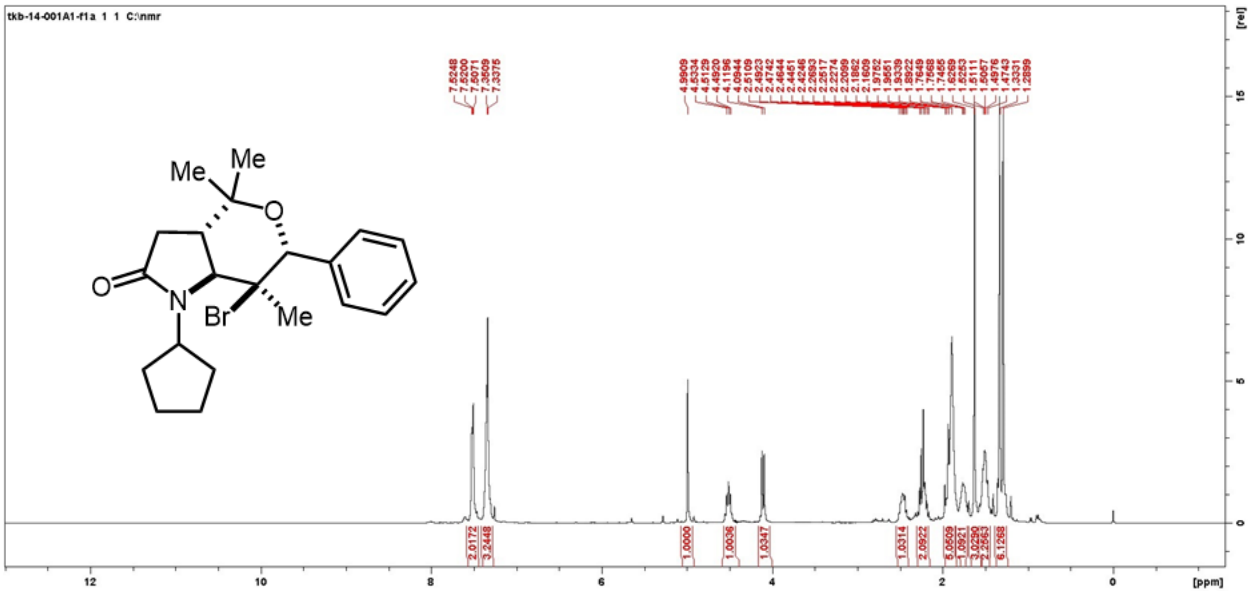


Compound 4g

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 361.7 mg, 89%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.55 – 7.44 (m, 2H), 7.40 – 7.28 (m, 3H), 4.99 (s, 1H), 4.51 (p, J = 8.3 Hz, 1H), 4.11 (d, J = 10.1 Hz, 1H), 2.46 (dp, J = 14.9, 7.2 Hz, 1H), 2.35 – 2.14 (m, 2H), 2.00 – 1.90 (m, 5H), 1.77 – 1.74 (m, 1H), 1.62 (m, 3H), 1.33 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 174.63, 136.12, 129.92, 128.32, 127.38, 80.55, 74.66, 69.37, 68.32, 55.10, 48.12, 34.23, 29.21, 28.64, 27.57, 25.55, 24.96, 17.85, 17.78. **HRMS-EI^{+}** (*m/z*): calc for $C_{21}H_{28}BrNO_2$ $[M]^+$ 405.1303, found 405.1307.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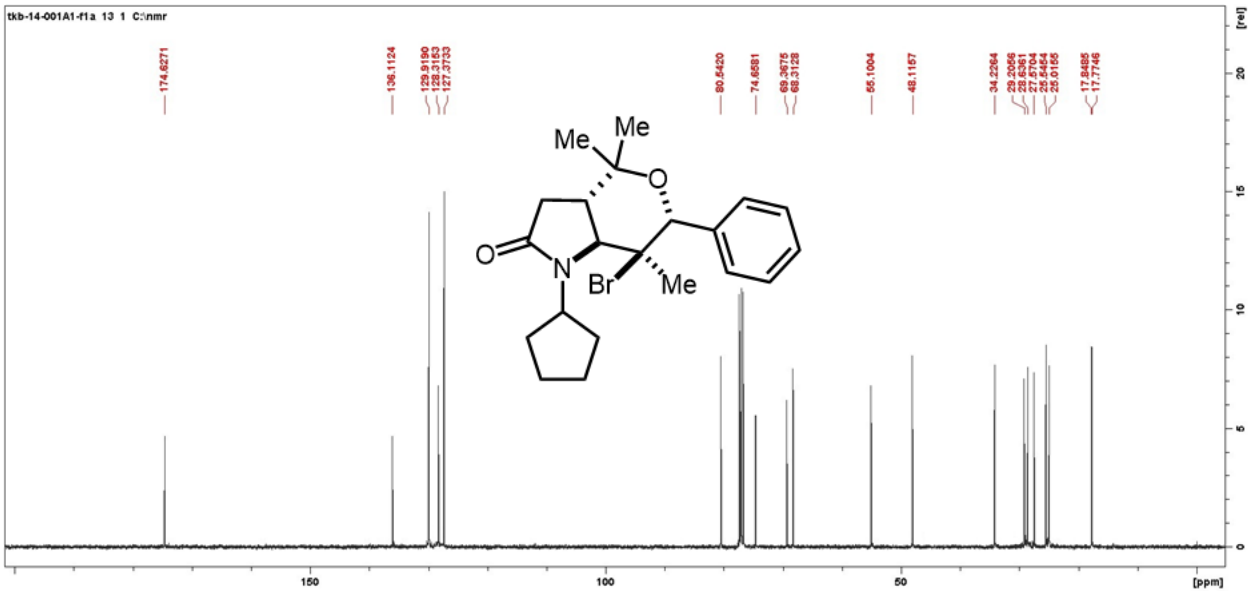
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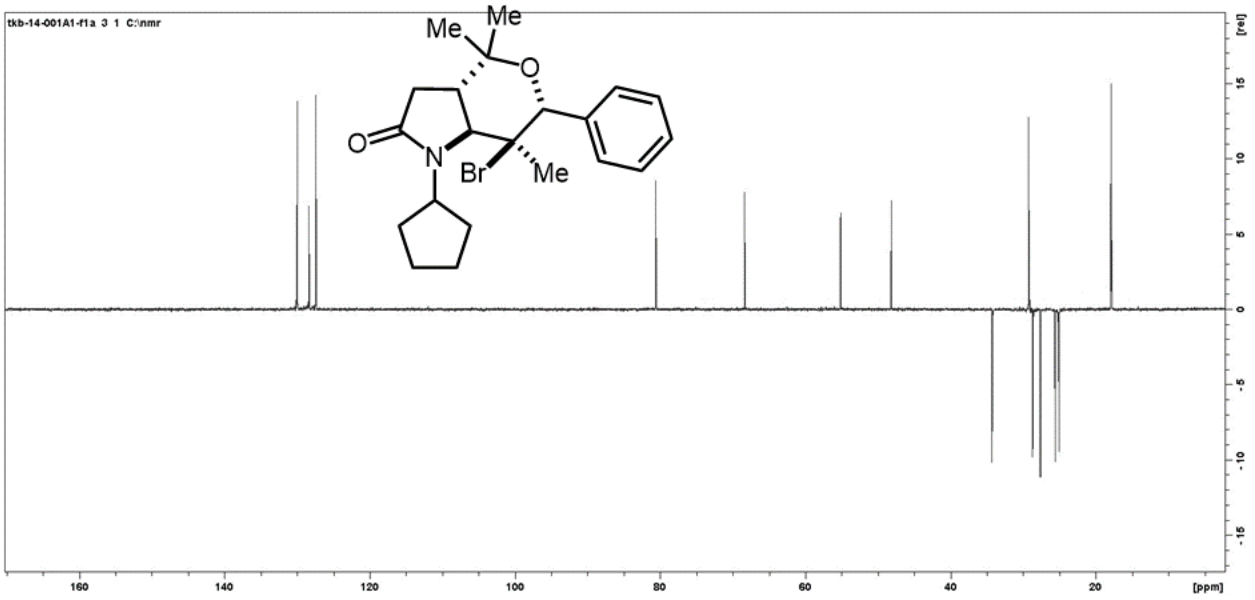
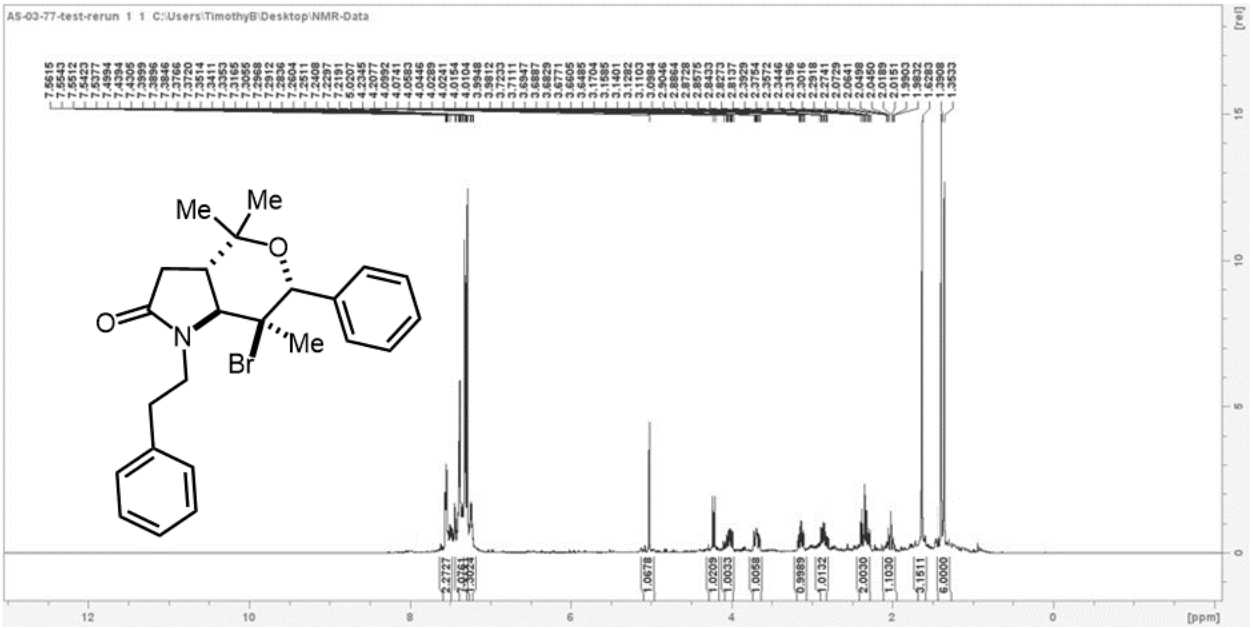


Compound 4h

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 60:40). Amorphous solid. Yield = 380.5 mg, 86%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 2H), 7.50 – 7.27 (m, 7H), 7.30 – 7.19 (m, 1H), 5.02 (s, 1H), 4.23 (d, *J* = 11.0 Hz, 1H), 4.13 – 3.96 (m, 1H), 3.69 (ddd, *J* = 13.7, 11.3, 4.8 Hz, 1H), 3.19 – 2.69 (m, 2H), 2.50 – 2.25 (m, 2H), 2.15 – 1.93 (m, 1H), 1.63 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.03, 138.72, 135.96, 129.76, 129.09, 128.46, 128.41, 127.42, 126.41, 80.55, 74.89, 68.68, 66.78, 47.56, 43.37, 33.32, 32.62, 29.33, 18.07, 17.77. **HRMS-EI$^+$** (*m/z*): calc for $C_{24}H_{28}BrNO_2$ $[M]^+$ 441.1303, found 441.1308.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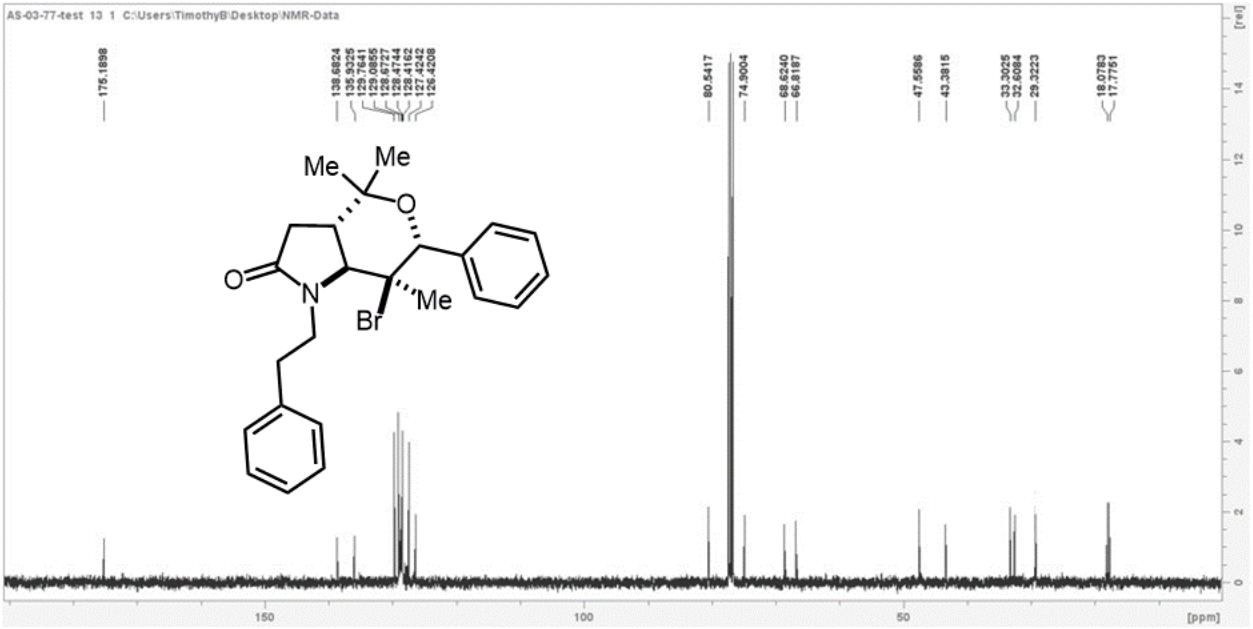
Me
O
N
O
Br
Me
[ppm]


AS-03-77-test 13 1 C:\Users\TimothyB\Desktop\NMR-Data
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126.4208
80.5417
74.9004
68.6240
66.8187
47.5586
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32.6084
29.3223
18.0783
17.7751
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Me
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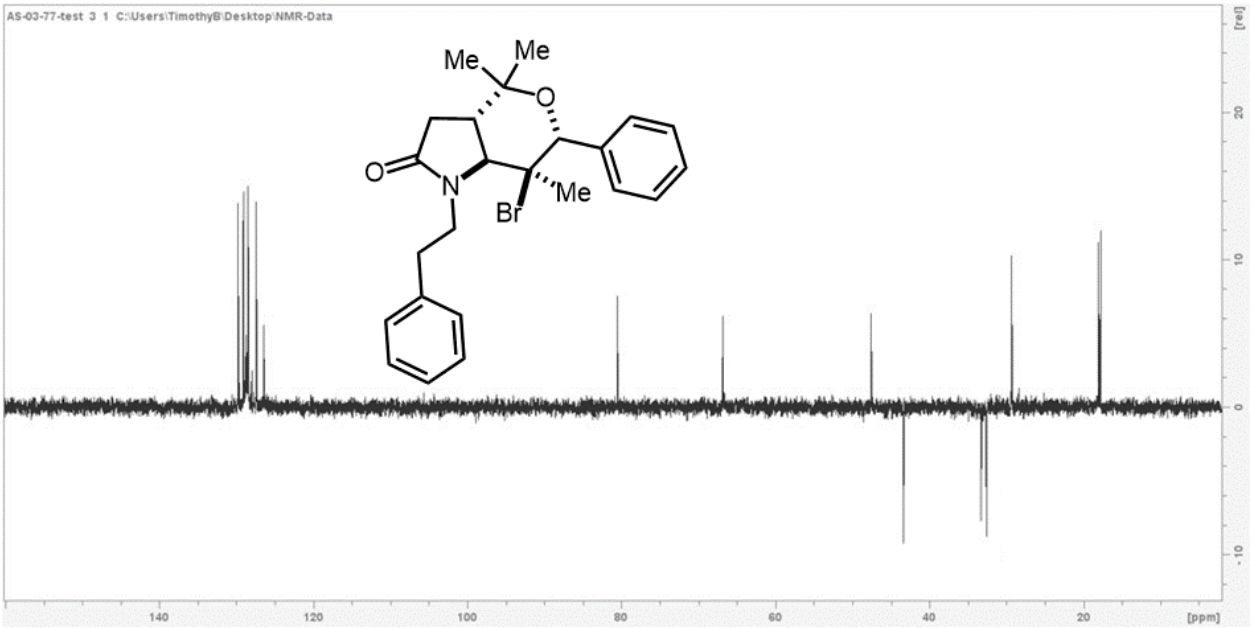
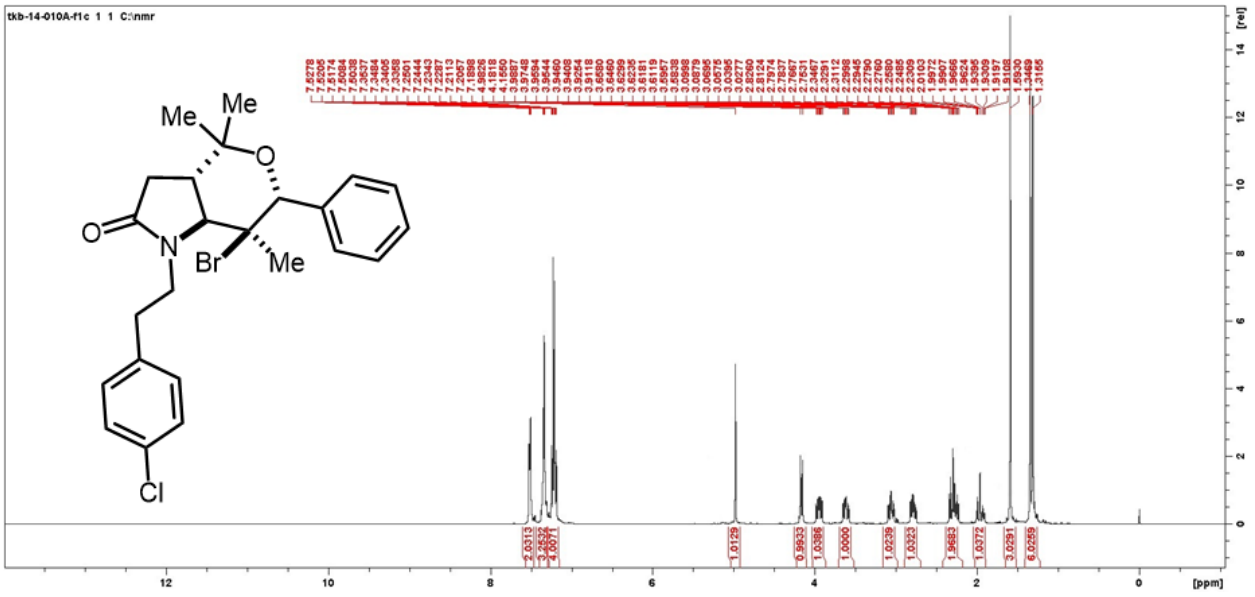
N
O
Br
Me
[ppm]



Compound 4i

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 60:40). Amorphous solid. Yield = 419.6 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.56 – 7.47 (m, 2H), 7.40 – 7.29 (m, 3H), 7.33 – 7.15 (m, 4H), 4.98 (s, 1H), 4.17 (d, J = 11.6 Hz, 1H), 3.95 (ddd, J = 13.7, 11.6, 5.5 Hz, 1H), 3.62 (ddd, J = 13.7, 11.1, 4.8 Hz, 1H), 3.06 (td, J = 12.0, 4.8 Hz, 1H), 2.79 (ddd, J = 12.6, 11.2, 5.5 Hz, 1H), 2.37 – 2.21 (m, 2H), 2.05 – 1.88 (m, 1H), 1.59 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 175.01, 137.20, 135.92, 132.21, 130.42, 129.76, 128.88, 128.61, 128.44, 128.38, 127.51, 127.44, 80.54, 74.88, 68.92, 66.85, 47.58, 43.19, 33.28, 32.06, 29.33, 18.09, 17.76. **HRMS-EI^{+}** (*m/z*): calc for $C_{24}H_{27}BrClNO_2$ $[M]^{+}$ 475.0914, found 475.0917.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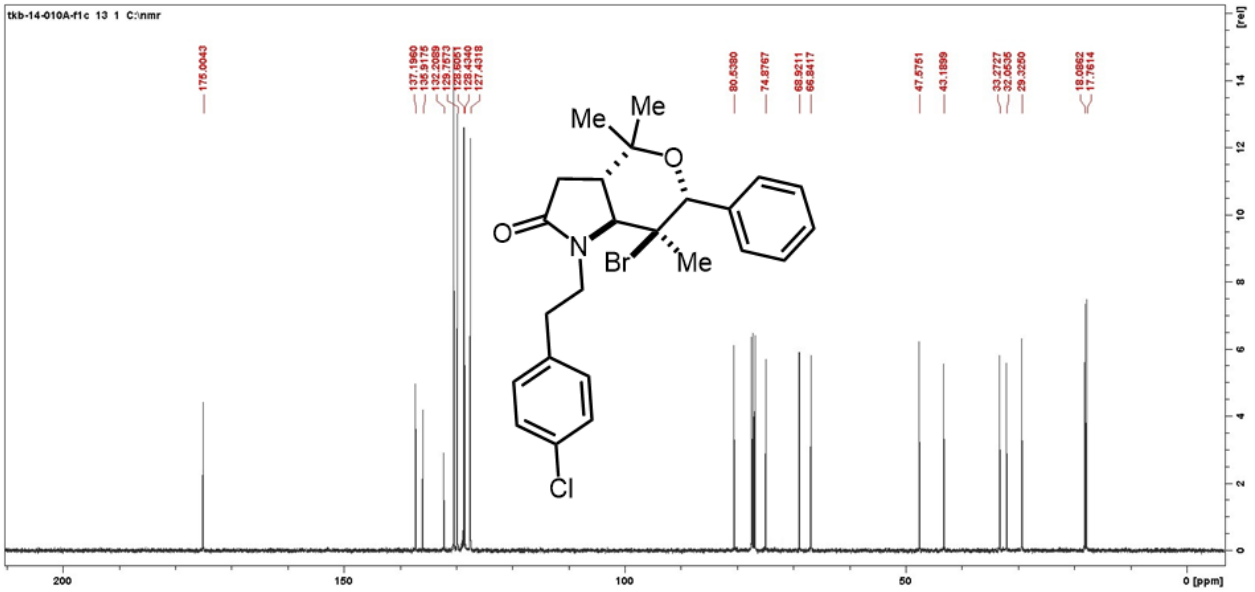
Me
O
O
N
Br
Me
Cl
[rel]
[ppm]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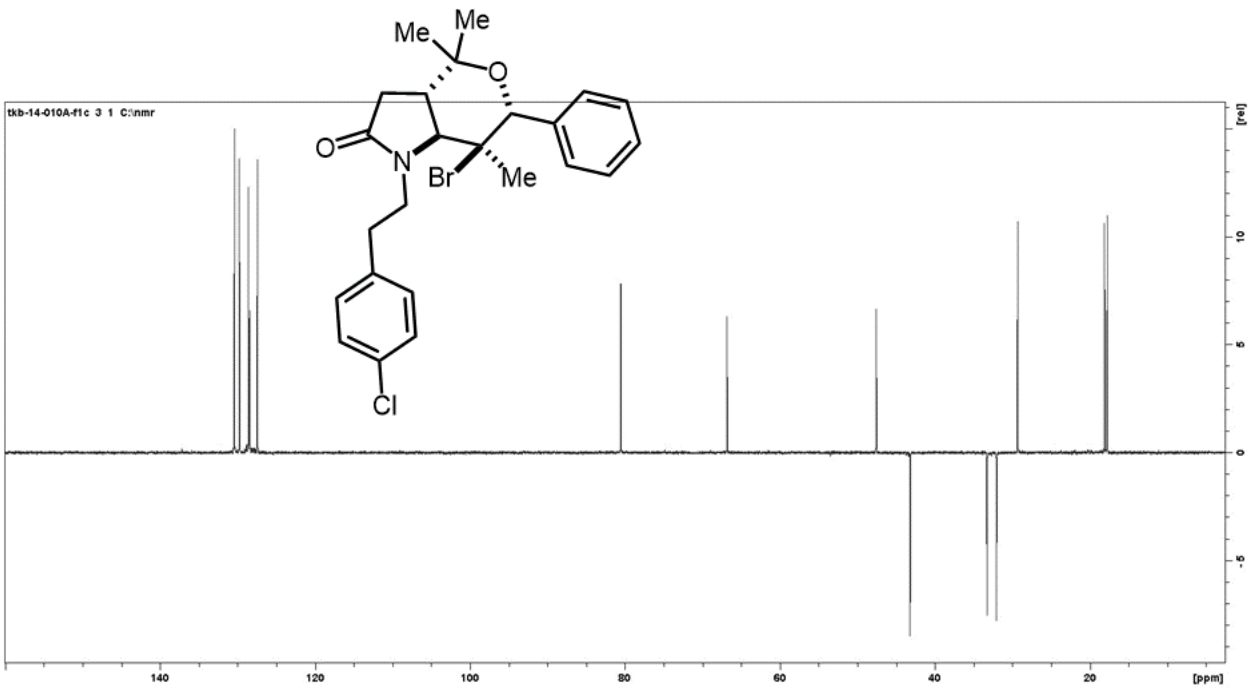
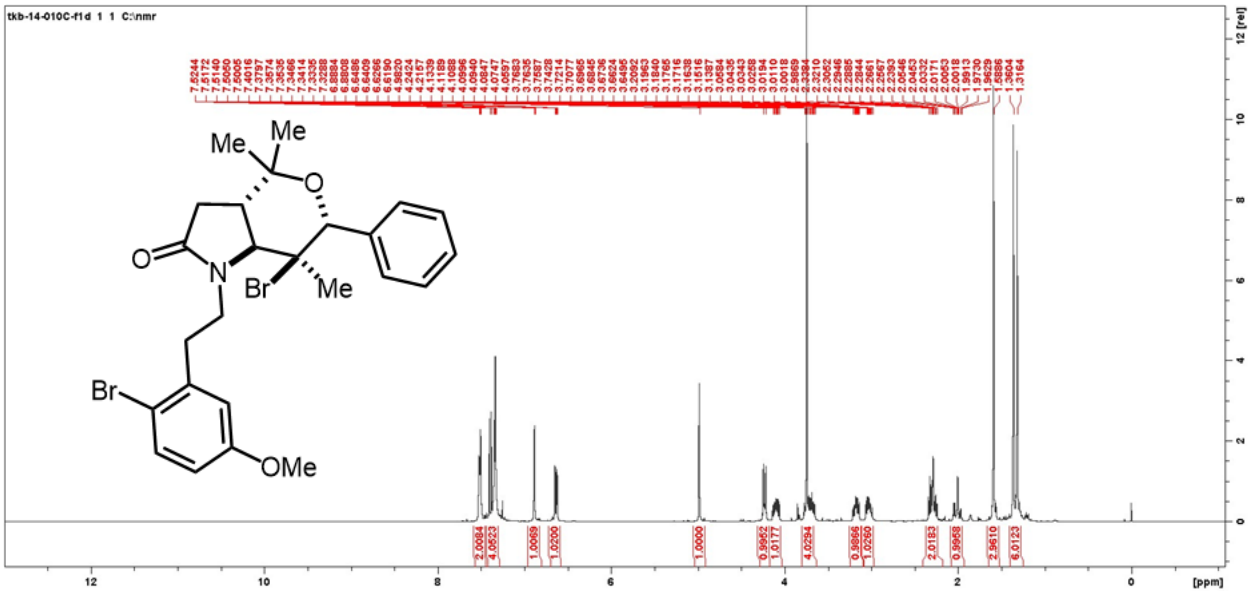
Me
O
O
N
Br
Me
Cl
[rel]
[ppm]



Compound 4j

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 60:40). Amorphous solid. Yield = 496.1 mg, 90%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.51 (dq, J = 5.2, 3.0 Hz, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.39 – 7.28 (m, 3H), 6.88 (d, J = 3.1 Hz, 1H), 6.63 (dd, J = 8.8, 3.0 Hz, 1H), 4.98 (s, 1H), 4.23 (d, J = 11.1 Hz, 1H), 4.10 (ddd, J = 13.7, 10.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.69 (ddd, J = 13.7, 9.8, 5.3 Hz, 1H), 3.17 (ddd, J = 13.0, 10.0, 5.2 Hz, 1H), 3.02 (ddd, J = 13.0, 9.6, 5.9 Hz, 1H), 2.36 – 2.22 (m, 2H), 2.09 – 1.93 (m, 1H), 1.59 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 175.05, 158.96, 139.53, 136.00, 133.34, 129.77, 128.39, 127.39, 116.47, 115.19, 113.96, 80.55, 74.91, 68.51, 66.99, 55.44, 47.66, 41.78, 33.26, 33.19, 29.33, 18.06, 17.78. **HRMS-EI^{+}** (*m/z*): calc for $C_{25}H_{29}Br_2NO_3$ $[M]^+$ 549.0514, found 549.0510.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Me
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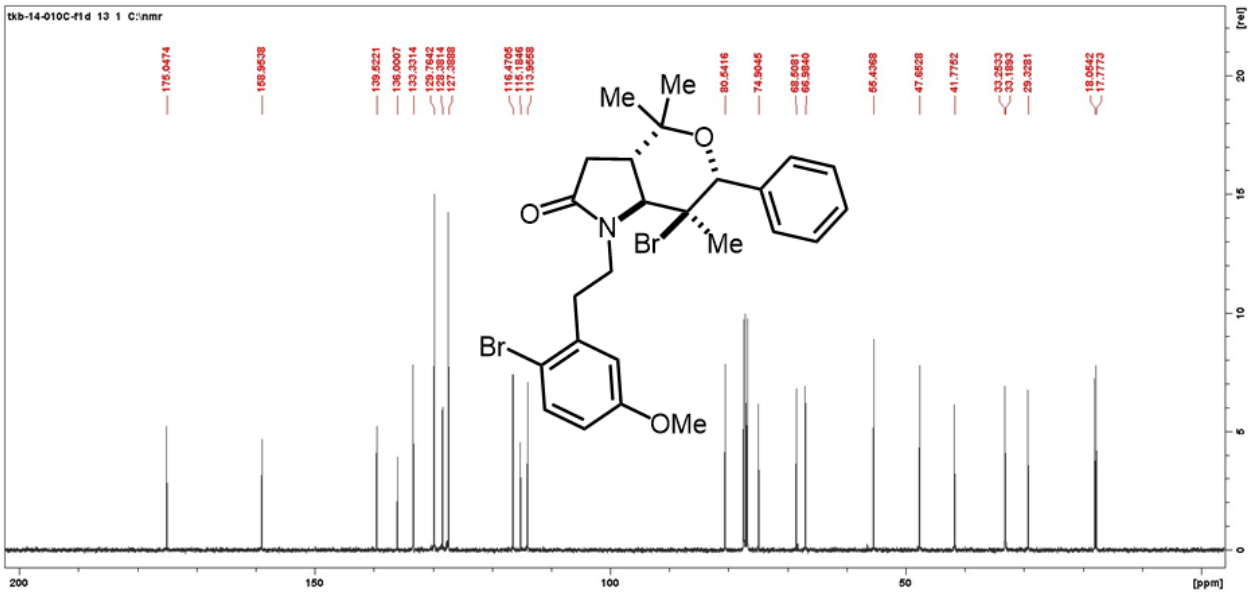
O
N
Br
Me
Br
OMe
[ppm]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74.9045
68.5081
66.3840
55.4368
47.6528
41.7752
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Br
OMe
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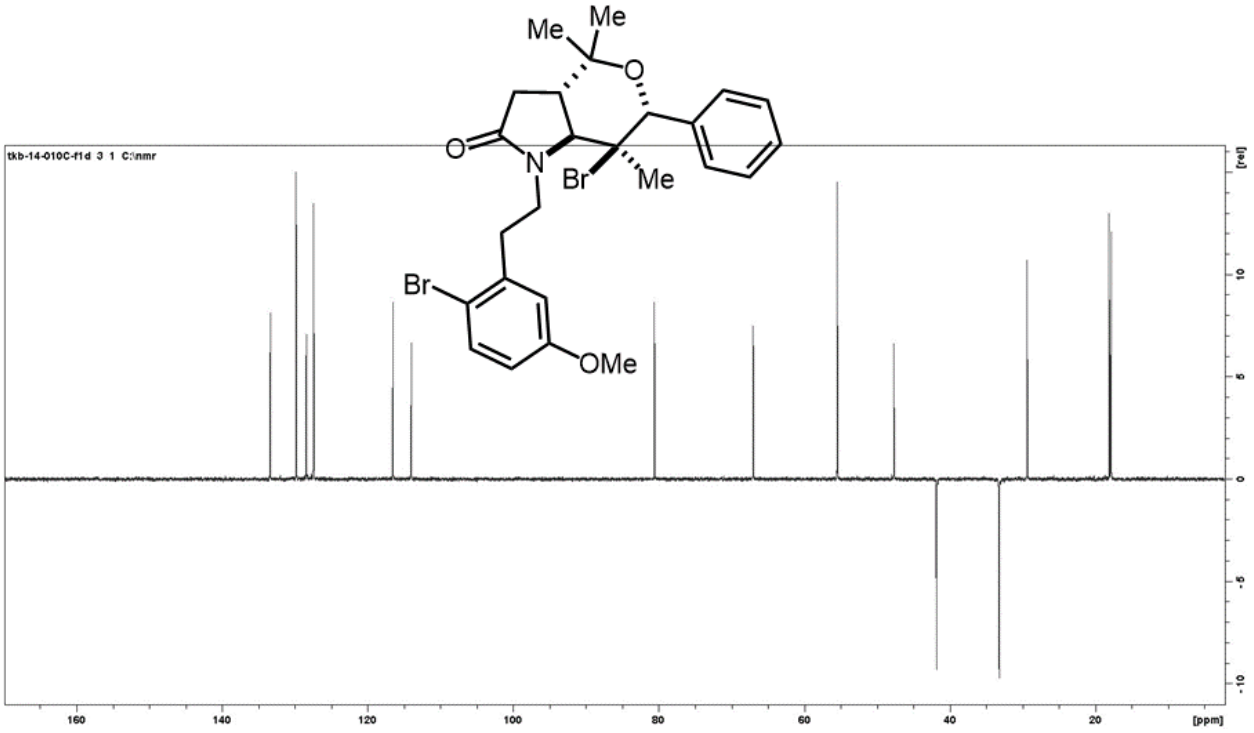
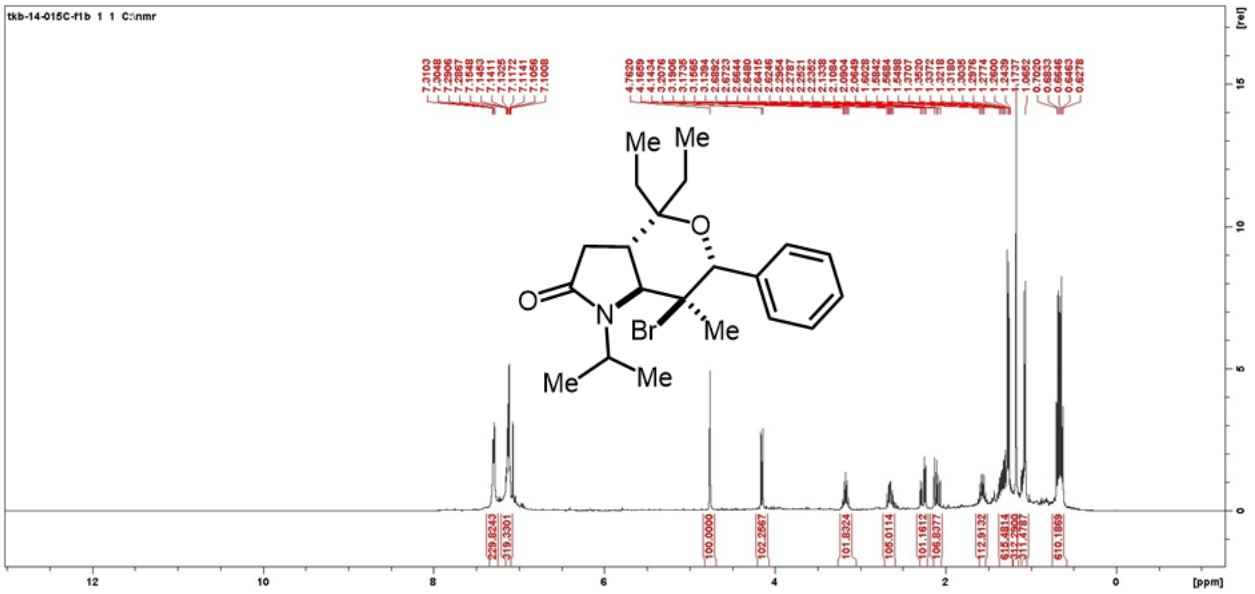


Compound 4k

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Greenish-yellow oil. Yield = 367.6 mg, 90%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.35 – 7.19 (m, 2H), 7.18 – 7.01 (m, 3H), 4.76 (s, 1H), 4.15 (d, J = 9.0 Hz, 1H), 3.17 (hept, J = 6.5 Hz, 1H), 2.71 – 2.54 (m, 1H), 2.27 (dd, J = 17.3, 6.7 Hz, 1H), 2.10 (dd, J = 17.4, 10.2 Hz, 1H), 1.60 – 1.54 (m, 1H), 1.37 – 1.13 (m, 12H), 0.66 (dt, J = 14.8, 7.4 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 176.59, 138.05, 129.90, 129.66, 128.56, 128.47, 128.27, 127.85, 87.37, 86.27, 71.24, 63.04, 48.40, 47.23, 33.71, 31.10, 22.27, 19.80, 18.37, 8.95, 8.00. **HRMS-EI^{+}** (*m/z*): calc for $C_{21}H_{30}BrNO_2$ $[M]^{+}$ 407.1460, found 407.1466.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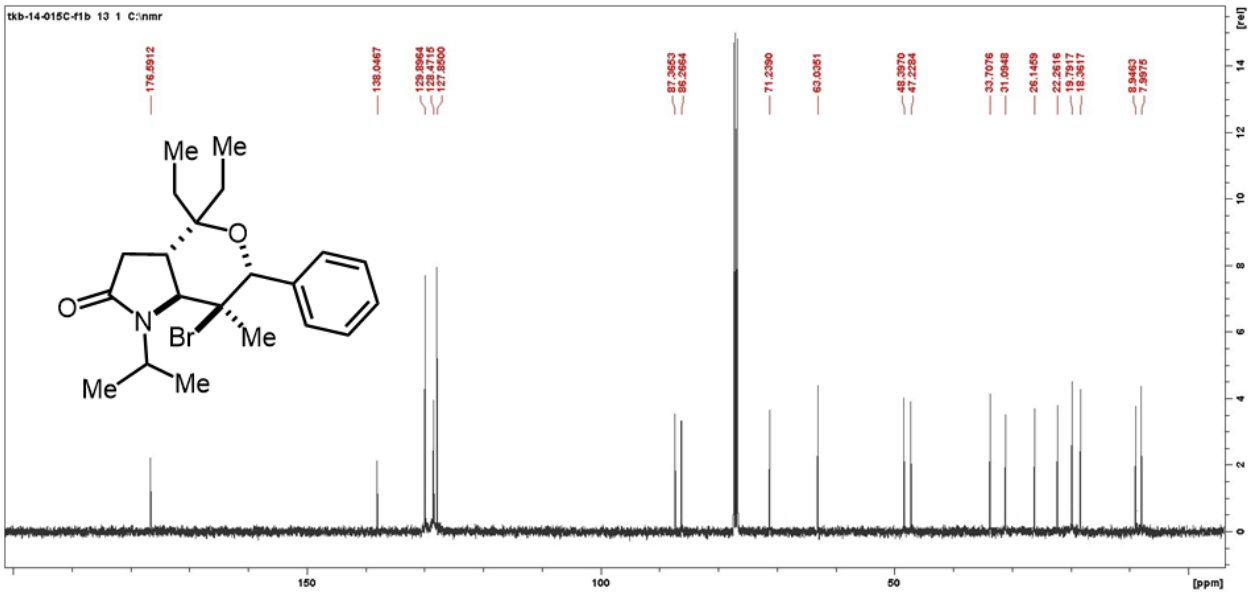
[ppm]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26.1459
22.2616
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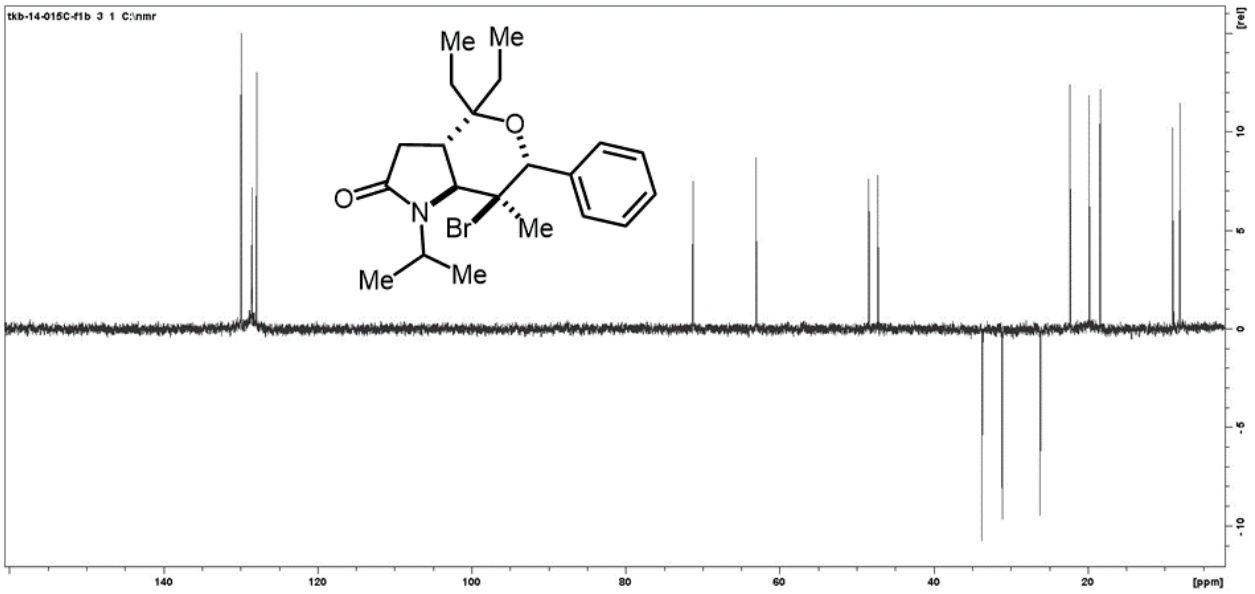
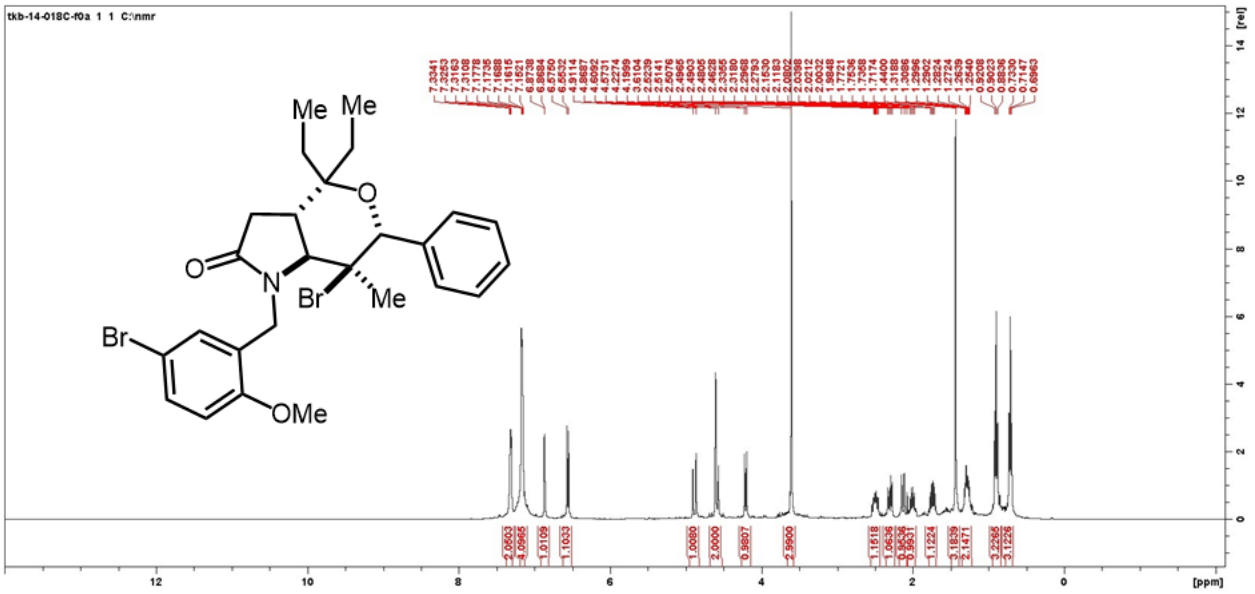


Compound 4l

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Greenish-yellow oil. Yield = 502.9 mg, 89%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.32 (dt, J = 6.3, 3.6 Hz, 2H), 7.27 – 7.06 (m, 4H), 6.87 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 4.89 (d, J = 17.0 Hz, 1H), 4.64 – 4.55 (m, 2H), 4.21 (d, J = 11.0 Hz, 1H), 3.61 (s, 3H), 2.50 (ddd, J = 13.6, 10.9, 7.1 Hz, 1H), 2.31 (dd, J = 15.5, 7.0 Hz, 1H), 2.19 – 1.94 (m, 2H), 1.75 (dq, J = 14.8, 7.4 Hz, 1H), 1.44 (s, 3H), 1.27 (dddd, J = 16.9, 13.0, 8.7, 4.9 Hz, 2H), 0.90 (t, J = 6.7 Hz, 3H), 0.72 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 175.84, 155.98, 136.22, 130.41, 129.62, 129.54, 129.36, 128.24, 127.65, 127.25, 112.73, 112.25, 79.93, 77.80, 67.22, 55.63, 43.84, 40.21, 32.73, 29.76, 21.99, 18.22, 7.44, 6.60. **HRMS-EI^{+}** (*m/z*): calc for $C_{26}H_{31}Br_2NO_3$ $[M]^{+}$ 563.0671, found 563.0677.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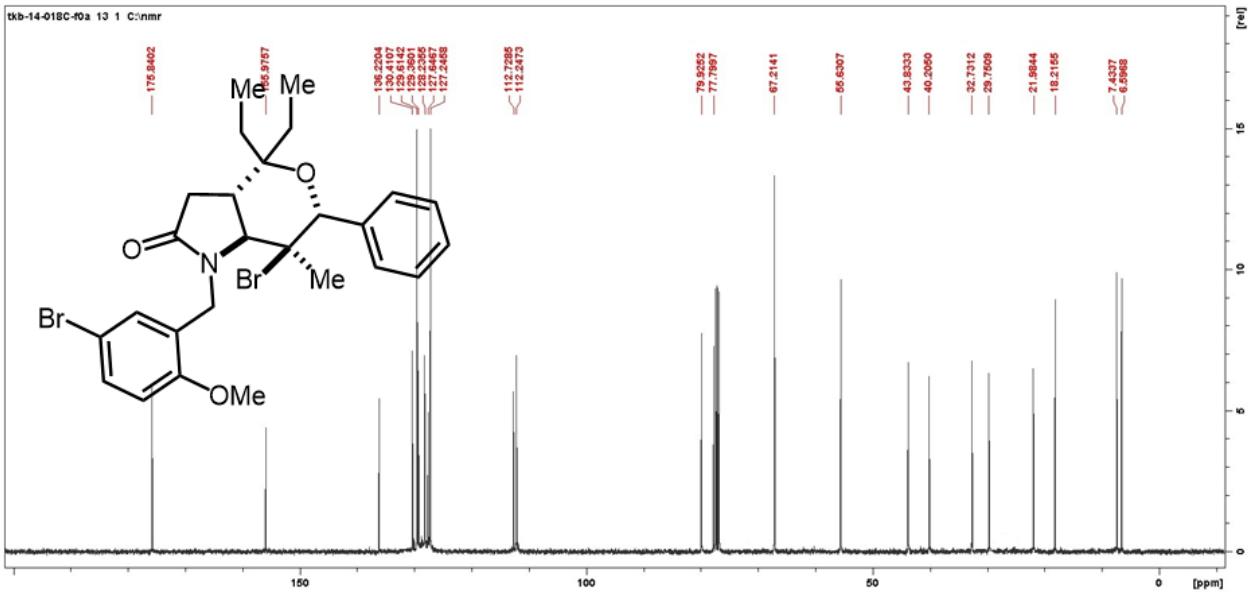
Br
OMe
[ppm]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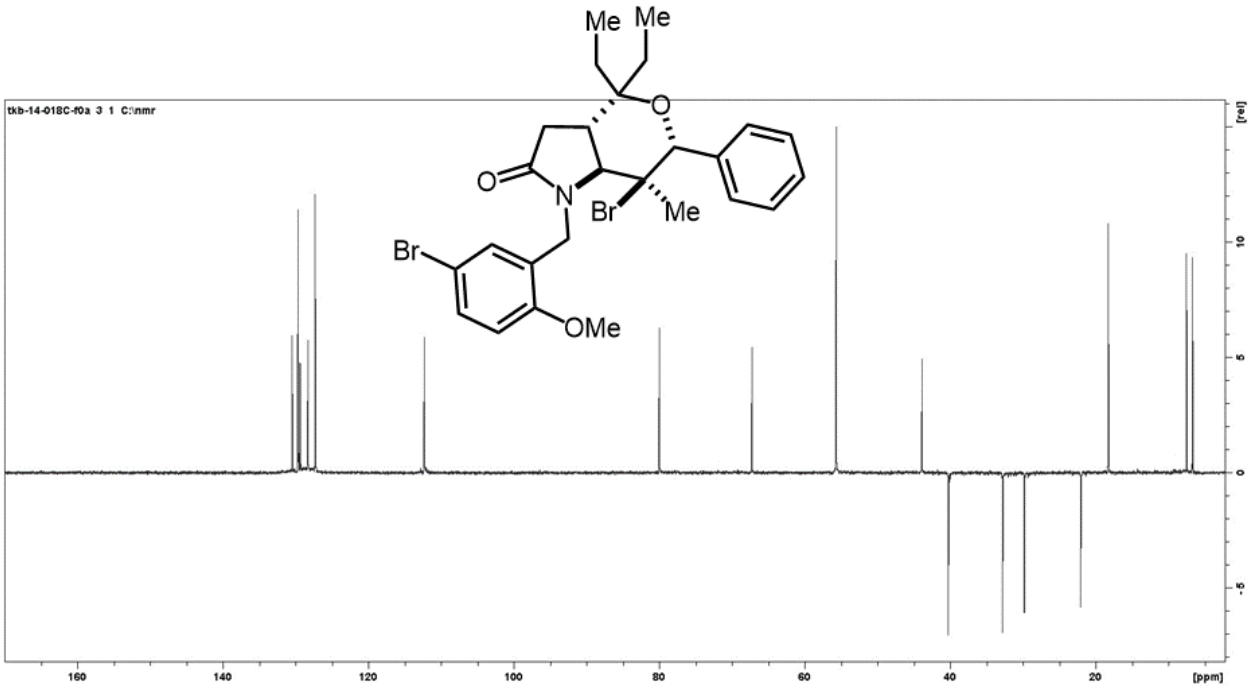
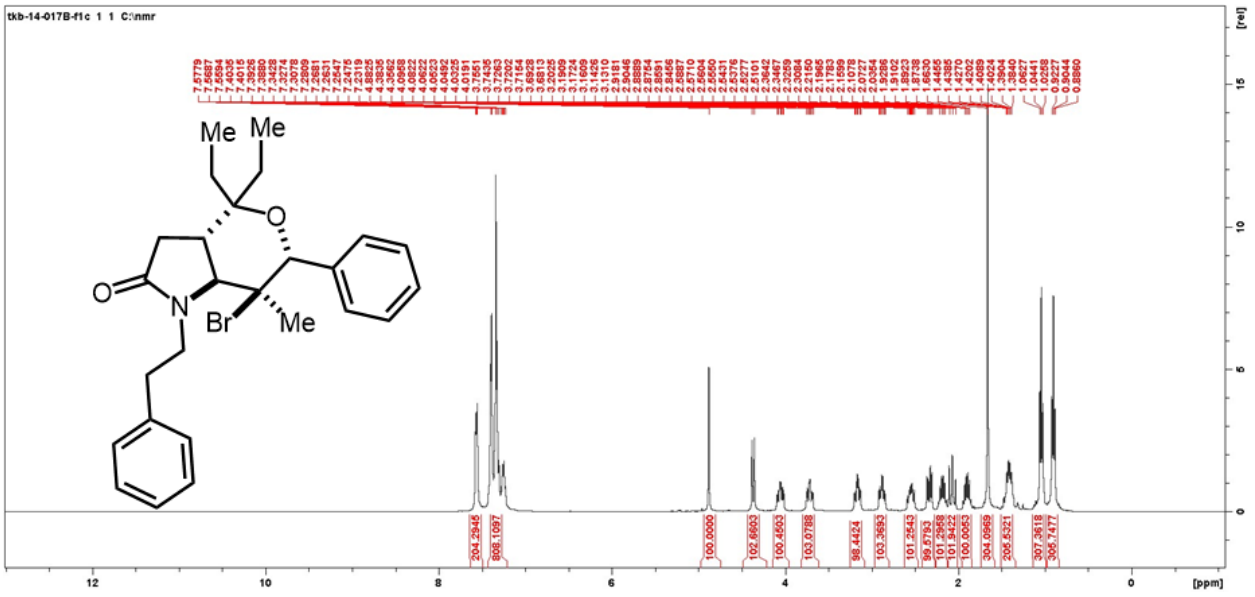
Br
OMe
[ppm]



Compound 4m

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Greenish-yellow oil. Yield = 409.3 mg, 87%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.56 (dt, J = 6.1, 3.8 Hz, 2H), 7.45 – 7.19 (m, 8H), 4.88 (s, 1H), 4.37 (d, J = 10.9 Hz, 1H), 4.06 (ddd, J = 13.6, 11.7, 5.5 Hz, 1H), 3.72 (ddd, J = 13.6, 11.2, 4.7 Hz, 1H), 3.17 (td, J = 12.0, 4.7 Hz, 1H), 2.88 (td, J = 11.8, 5.4 Hz, 1H), 2.55 (ddd, J = 13.4, 10.9, 6.9 Hz, 1H), 2.34 (dd, J = 15.3, 7.0 Hz, 1H), 2.26 – 2.03 (m, 2H), 1.90 (dq, J = 14.8, 7.4 Hz, 1H), 1.66 (s, 3H), 1.45 (ddd, J = 10.4, 7.7, 4.2 Hz, 1H), 1.43 – 1.29 (m, 1H), 1.04 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 175.21, 138.80, 136.31, 129.72, 129.12, 128.51, 128.35, 127.38, 126.44, 80.01, 68.65, 66.43, 43.59, 43.41, 32.88, 32.69, 29.67, 22.02, 18.14, 7.38, 6.65. **HRMS-EI^{+}** (*m/z*): calc for $C_{26}H_{32}BrNO_2$ $[M]^{+}$ 469.1616, found 469.1612.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Br
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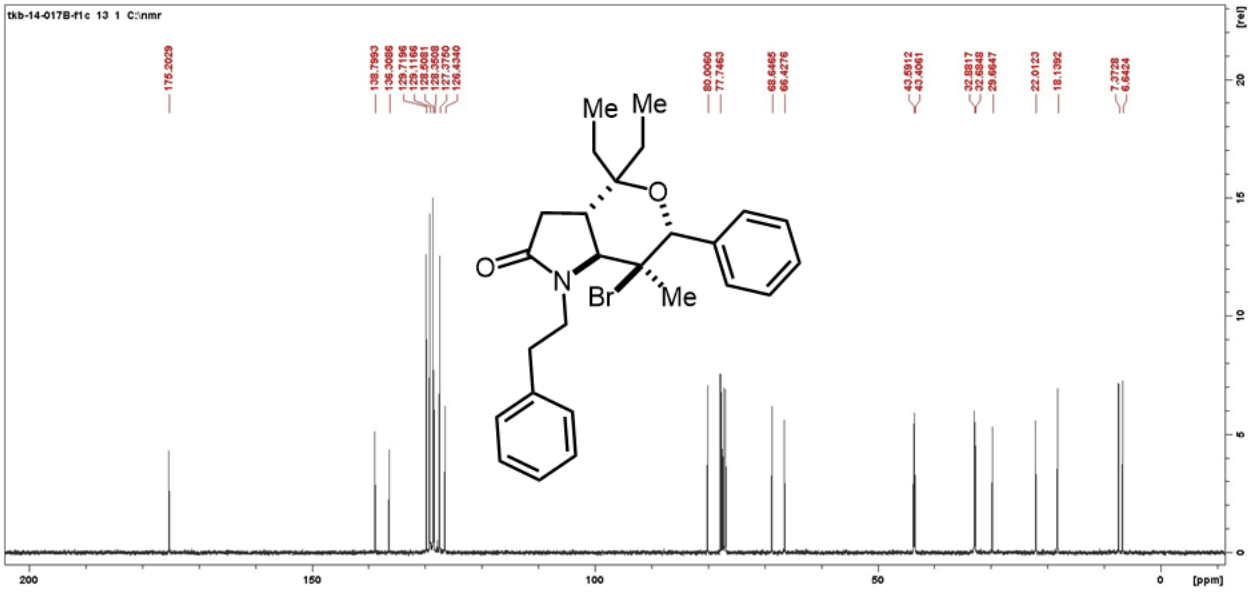
[ppm]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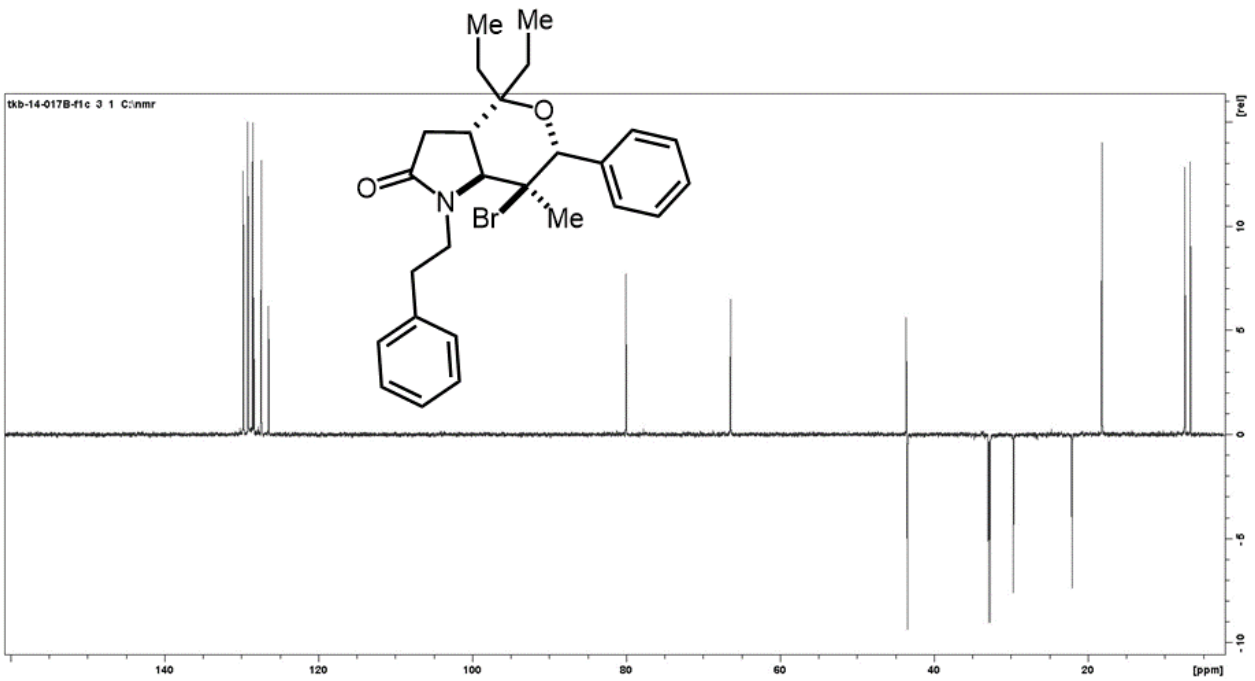
[ppm]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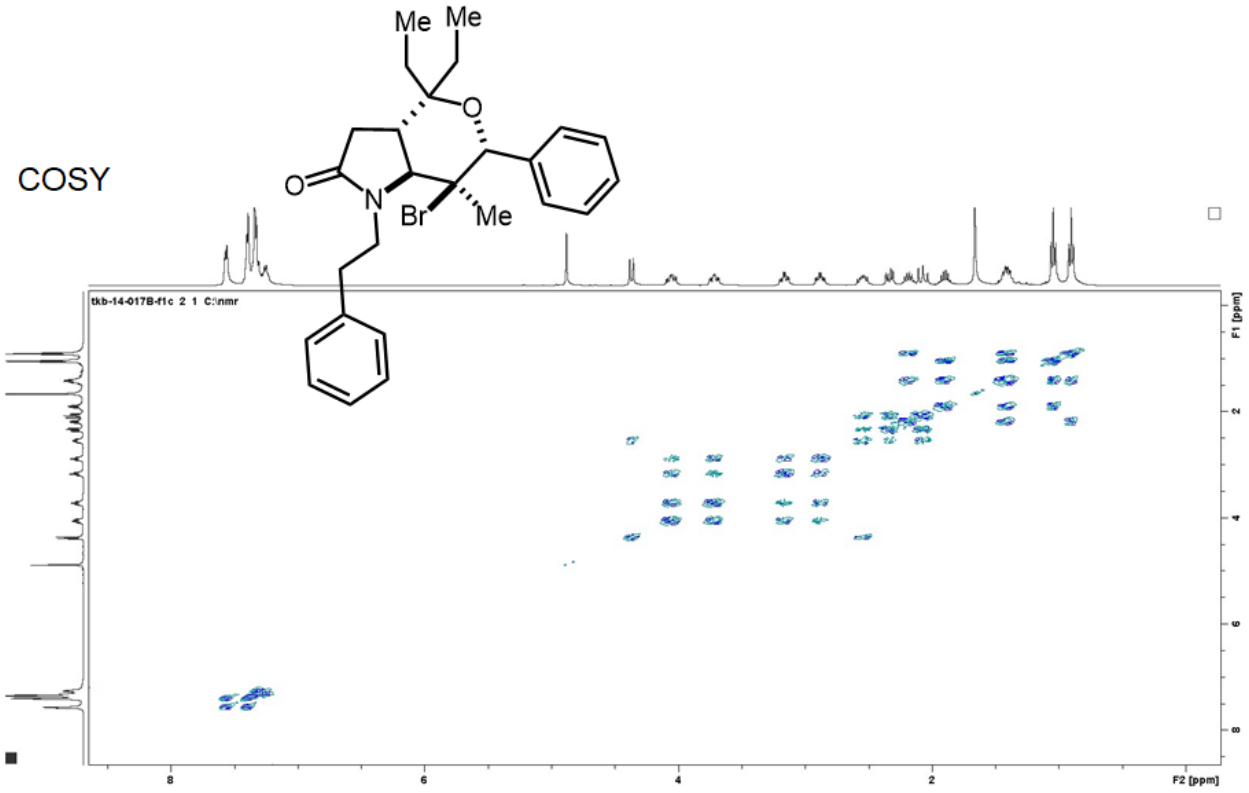
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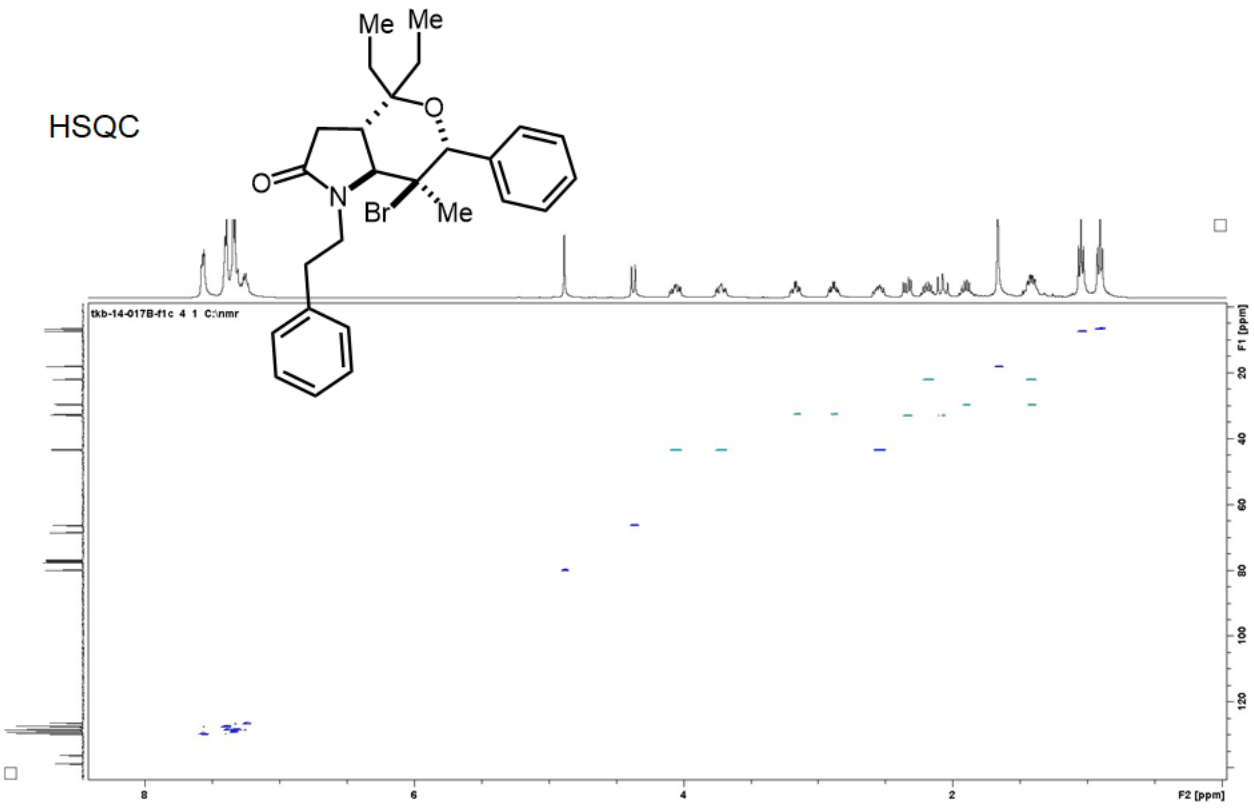
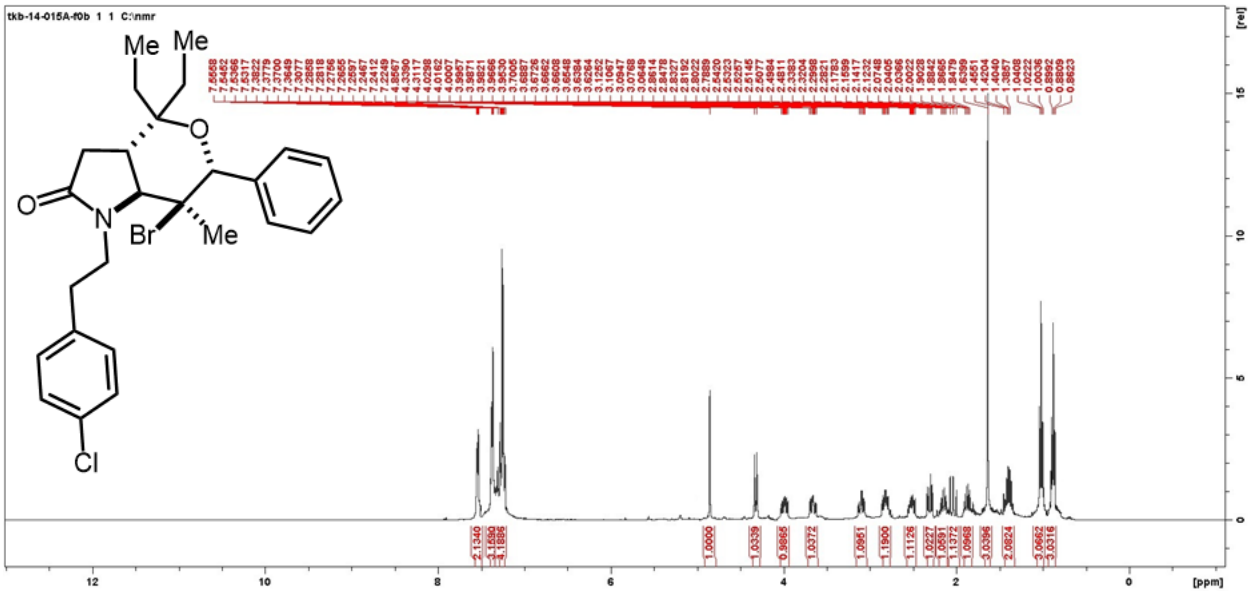
6
8
8
6
4
2
F2 [ppm]



Compound 4n

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 459.4 mg, 91%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.56 – 7.53 (m, 2H), 7.38 – 7.22 (m, 7H), 4.86 (s, 1H), 4.32 (d, J = 9.7 Hz, 1H), 4.04 (dddd, J = 37.6, 13.7, 10.6, 5.7 Hz, 1H), 3.66 (ddd, J = 13.8, 11.2, 4.8 Hz, 1H), 3.09 (tt, J = 10.4, 5.2 Hz, 1H), 2.88 – 2.72 (m, 1H), 2.60 – 2.45 (m, 1H), 2.38 – 2.26 (m, 1H), 2.26 – 1.98 (m, 2H), 1.94 – 1.77 (m, 1H), 1.64 (s, 3H), 1.59 – 1.24 (m, 2H), 1.05 – 0.86 (m, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.23, 137.24, 136.22, 132.20, 130.42, 130.38, 130.32, 130.11, 129.68, 128.66, 128.61, 128.36, 127.77, 127.73, 127.36, 86.16, 79.99, 68.80, 66.53, 43.66, 43.21, 32.82, 32.08, 29.68, 21.97, 18.13, 7.35, 6.61. **HRMS-EI^{+}** (*m/z*): calc for $C_{26}H_{31}BrClNO_2$ $[M]^+$ 503.1227, found 503.1222.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Me
Cl
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10
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4
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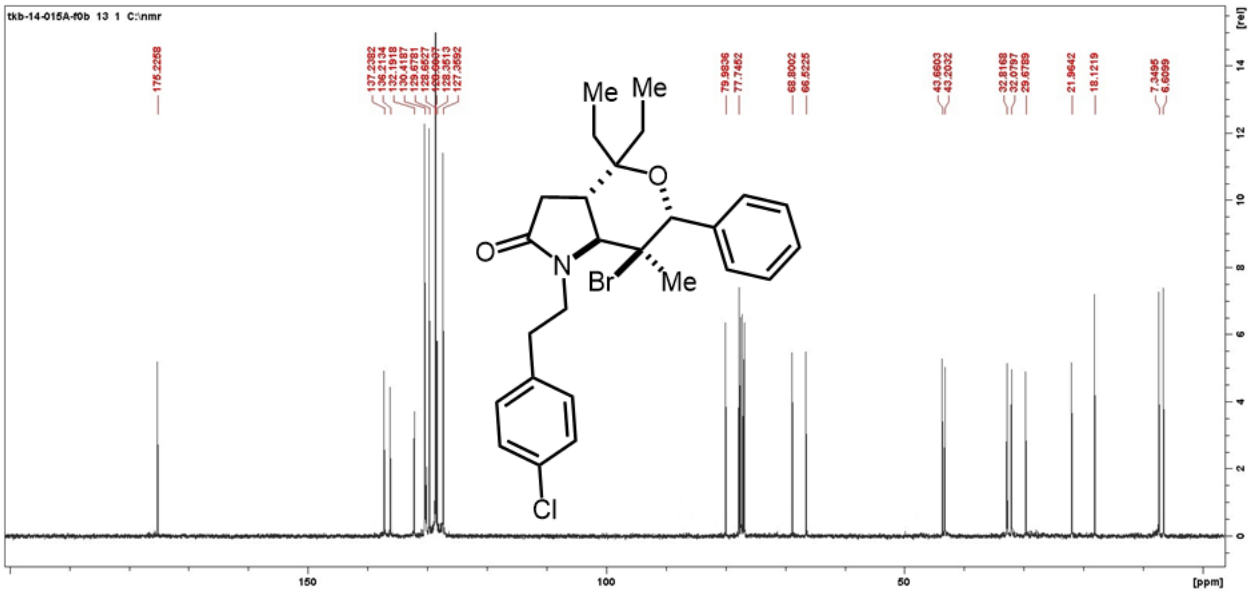
0
[ppm]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43.2032
32.8168
32.0707
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N
Br
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Cl
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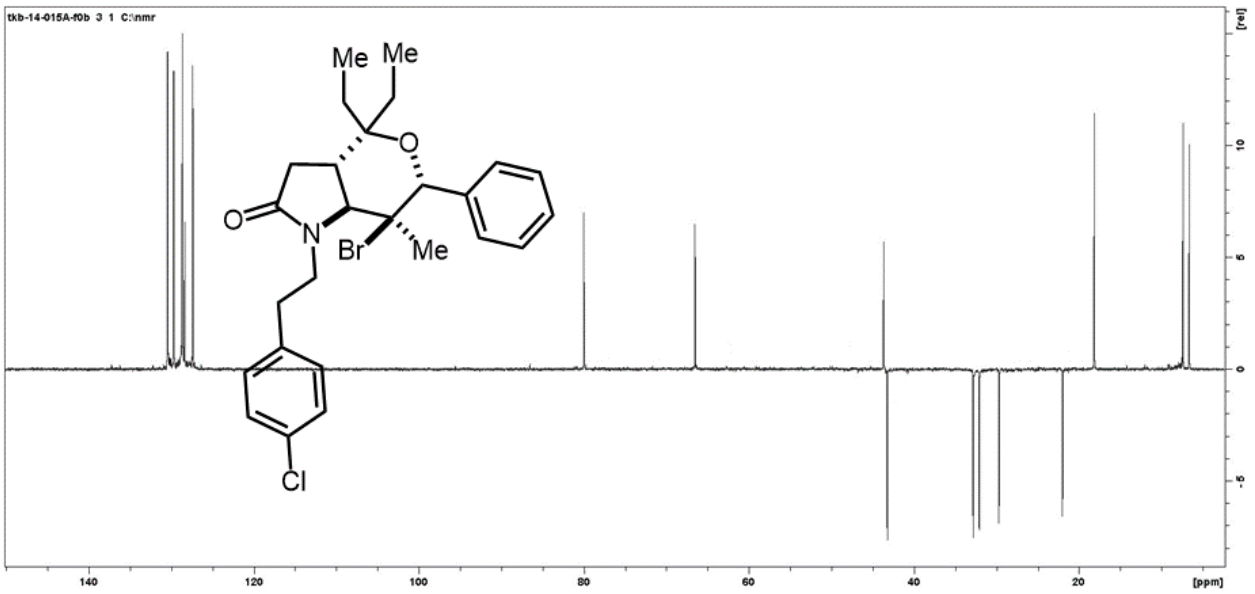
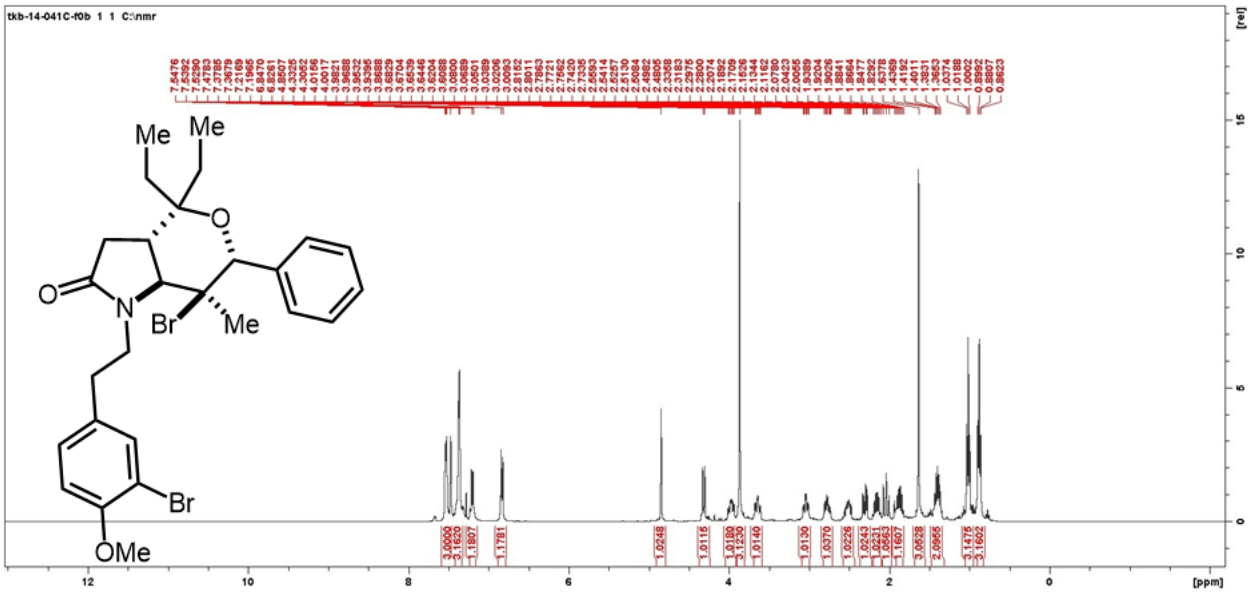


Compound 4o

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 492.5 mg, 85%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.53 (dt, J = 5.7, 3.6 Hz, 2H), 7.48 (d, J = 2.1 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.21 (dd, J = 8.4, 2.1 Hz, 1H), 6.84 (dd, J = 8.4, 3.8 Hz, 1H), 4.85 (s, 1H), 4.37 – 4.21 (m, 1H), 3.98 (ddd, J = 13.4, 11.2, 5.5 Hz, 1H), 3.87 (s, 3H), 3.71 – 3.59 (m, 1H), 3.04 (td, J = 11.9, 4.7 Hz, 1H), 2.78 (ddt, J = 15.8, 9.5, 4.8 Hz, 1H), 2.61 – 2.46 (m, 1H), 2.31 (dd, J = 15.4, 7.0 Hz, 1H), 2.16 (dq, J = 14.7, 7.4 Hz, 1H), 2.04 (t, J = 14.5 Hz, 1H), 1.88 (tt, J = 15.0, 7.5 Hz, 1H), 1.64 (3, 2H), 1.56 – 1.33 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 175.17, 154.52, 136.23, 133.76, 132.41, 130.01, 129.67, 129.09, 128.34, 127.35, 113.91, 112.07, 111.47, 79.99, 68.75, 66.47, 56.28, 43.63, 43.26, 32.82, 31.45, 29.66, 21.98, 18.12, 7.33, 6.60. **HRMS-EI^{+}** (*m/z*): calc for $C_{27}H_{33}Br_2NO_3$ $[M]^{+}$ 577.0827, found 577.0821.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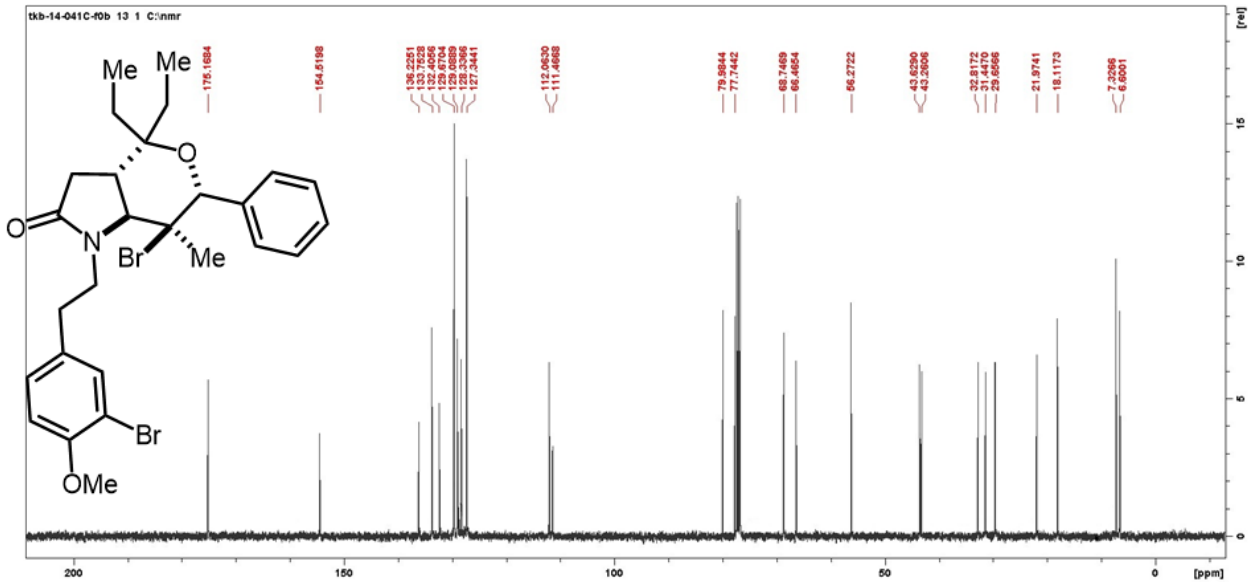
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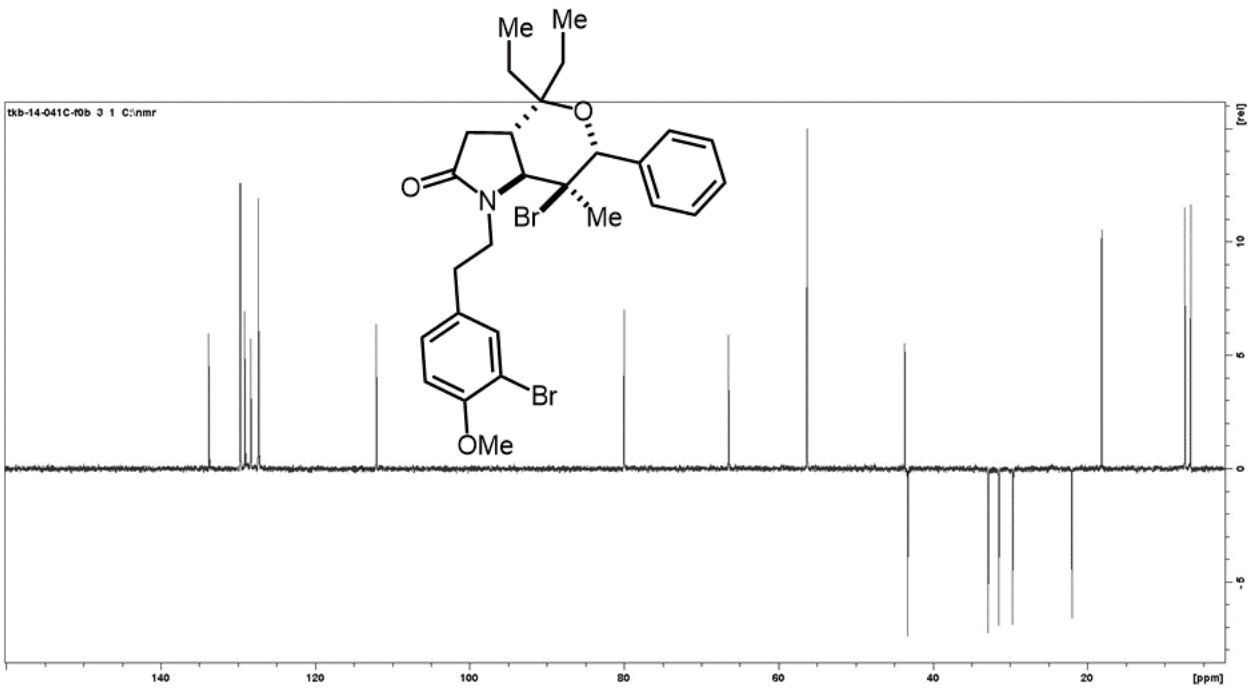
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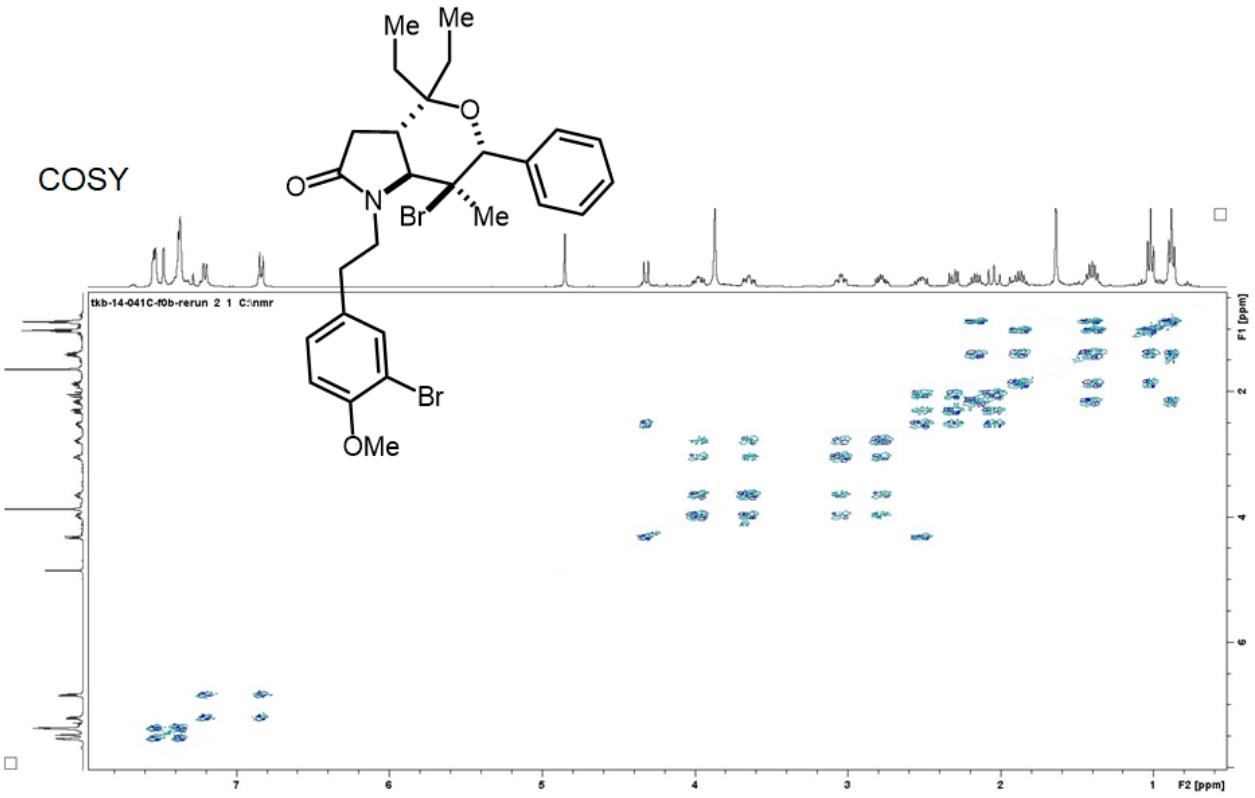
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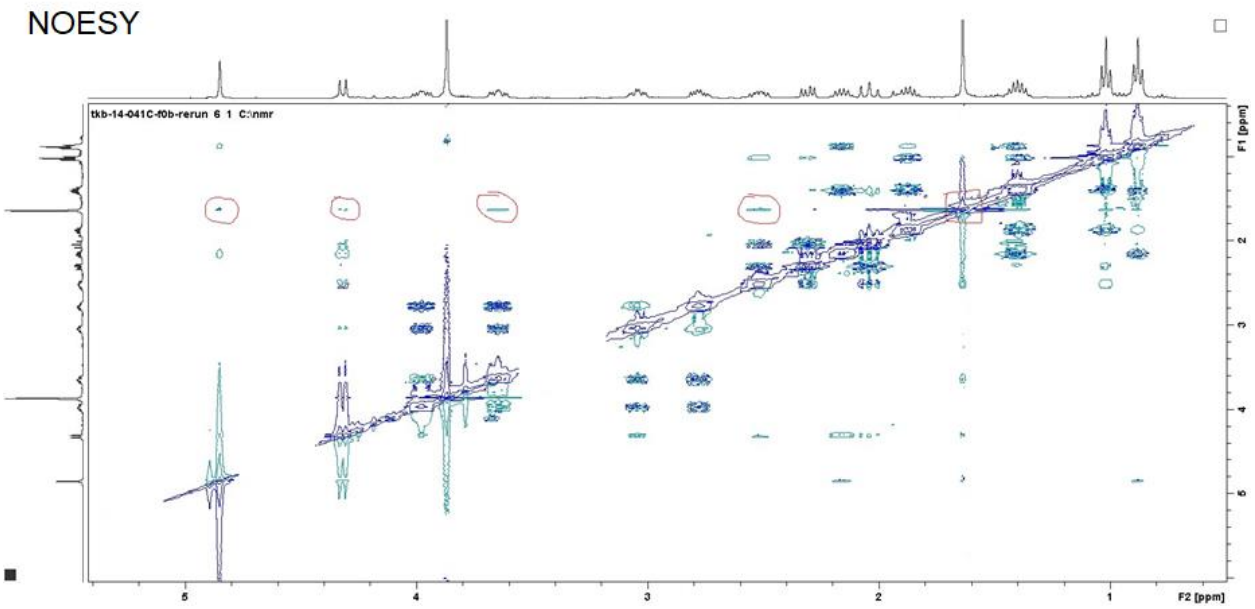
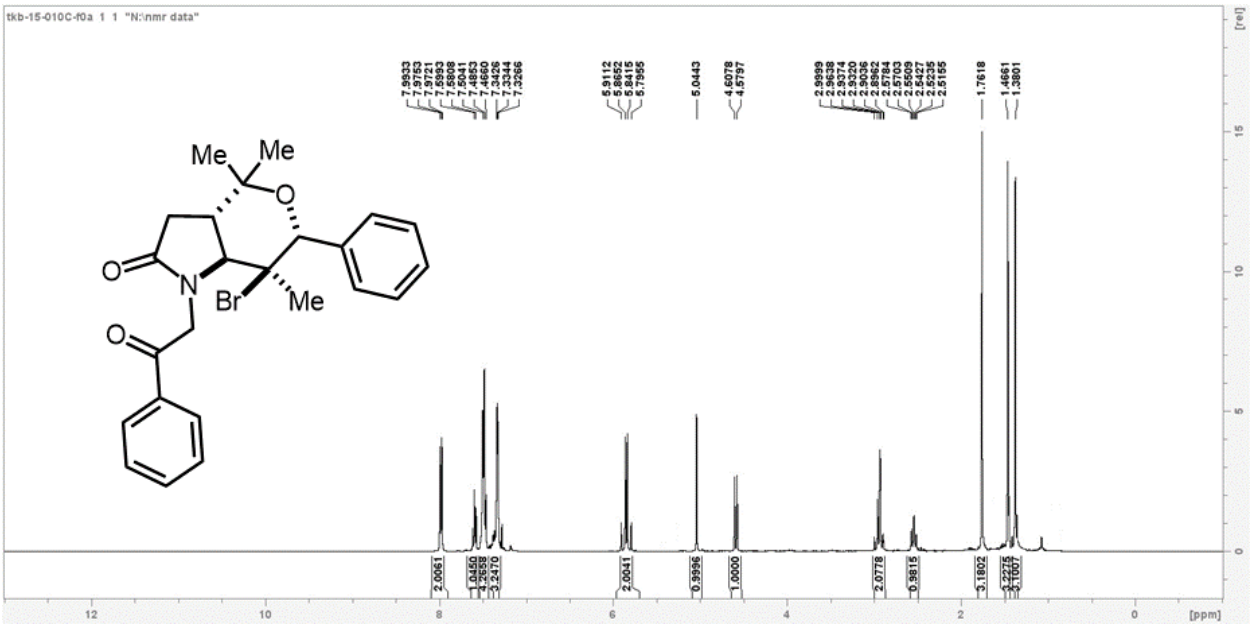


Compound 4p

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 401.6 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.66 – 7.56 (m, 1H), 7.55 – 7.44 (m, 4H), 7.43 – 7.28 (m, 3H), 5.85 (d, *J* = 9.5 Hz, 2H), 5.04 (s, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 3.02 – 2.87 (m, 2H), 2.55 (td, *J* = 11.0, 3.3 Hz, 1H), 1.76 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.59, 167.99, 136.45, 135.19, 133.72, 130.27, 128.82, 128.44, 128.03, 127.32, 79.90, 74.49, 70.37, 67.44, 57.81, 51.91, 46.67, 44.78, 28.53, 18.75, 18.34. **HRMS-EI$^+$** (*m/z*): calc for $C_{24}H_{26}BrNO_3$ $[M]^+$ 455.1096, found 455.1093.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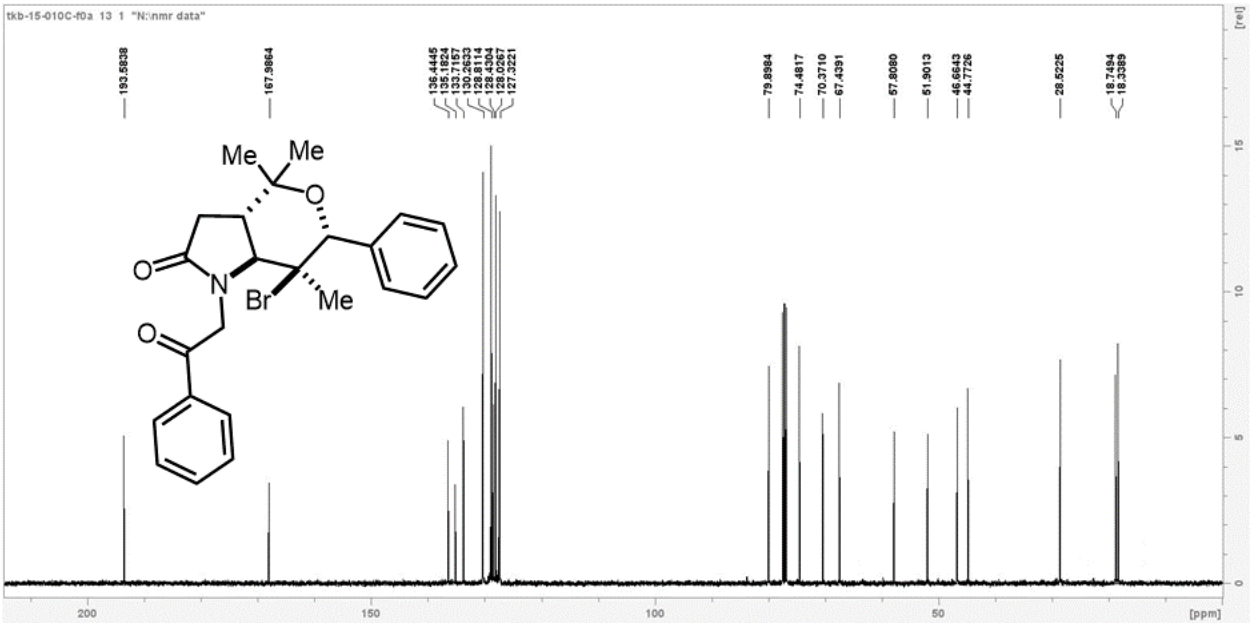
[ppm]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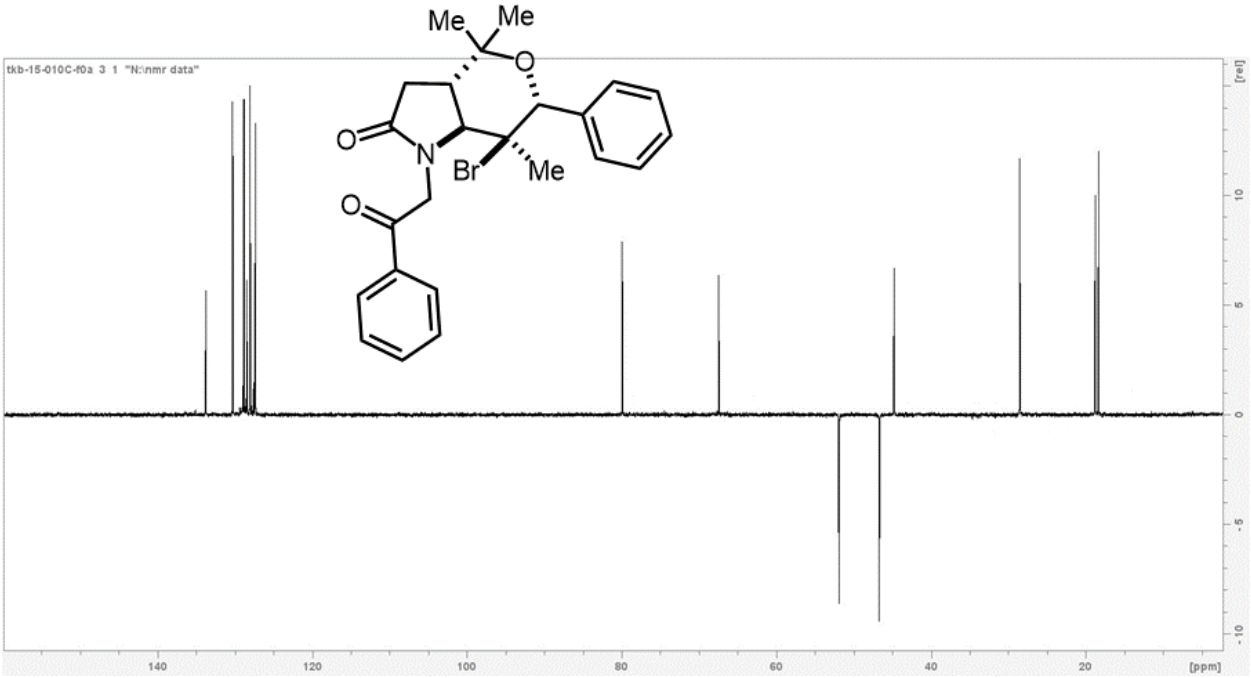
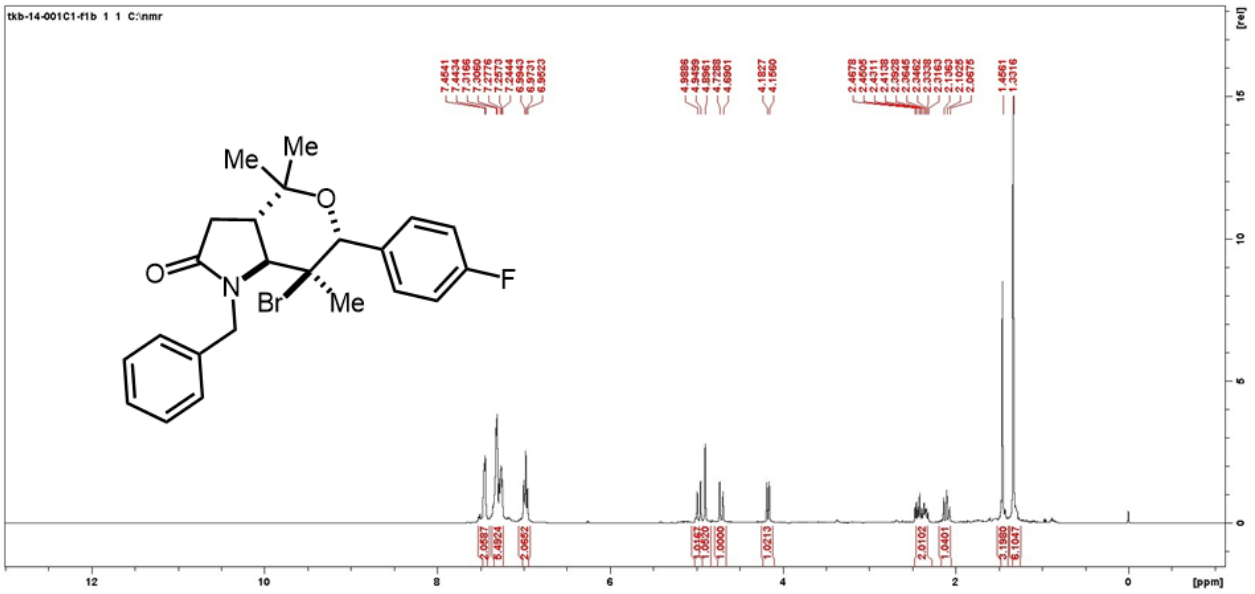


Compound 4q

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 392.5 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7. 47 – 7.44 (m, 2H), 7.31 – 7.24 (m, 5H), 7.00 – 6.95 (m, 2H), 4.97 (d, J = 15.5 Hz, 1H), 4.90 (s, 1H), 4.71 (d, J = 15.4 Hz, 1H), 4.17 (d, J = 10.7 Hz, 1H), 2.49 – 2.29 (m, 2H), 2.10 (dd, J = 14.8, 12.9 Hz, 1H), 1.46 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.77, 163.14, 160.70, 135.88, 133.23, 133.19, 129.72, 129.69, 129.61, 128.76, 128.37, 128.29, 128.27, 127.96, 127.59, 127.36, 115.28, 115.07, 80.51, 74.87, 68.25, 67.80, 47.60, 44.54, 33.18, 29.32, 18.20, 17.79. **HRMS-EI^{+}** (*m/z*): calc for $C_{23}H_{25}BrFNO_2$ $[M]^{+}$ 445.1053, found 445.1053.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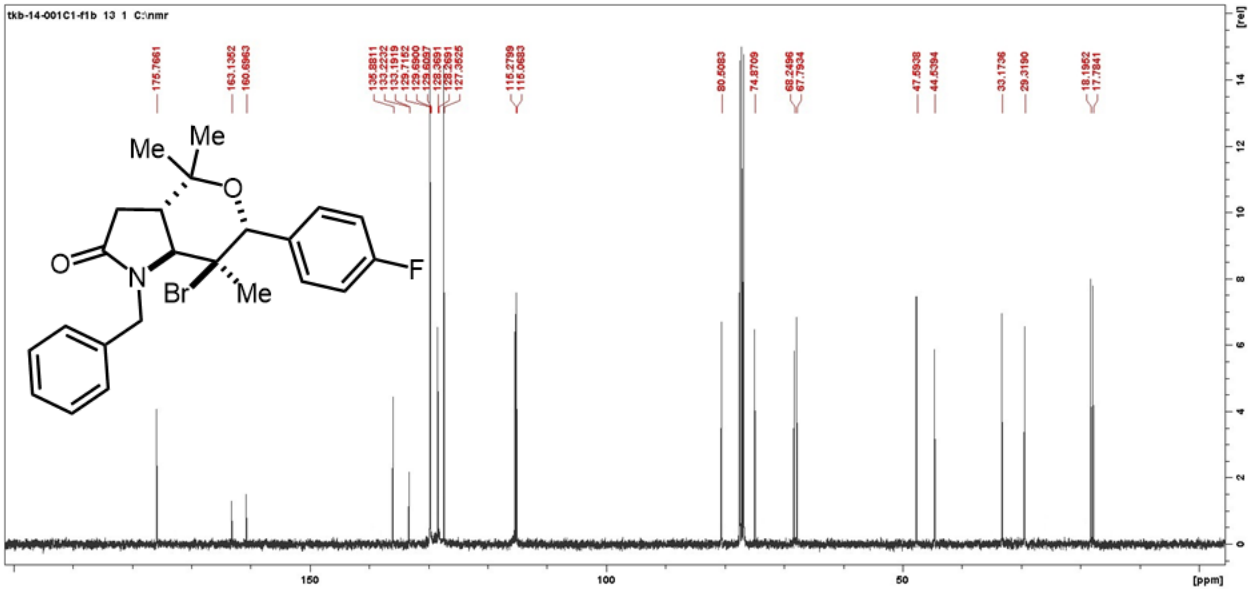
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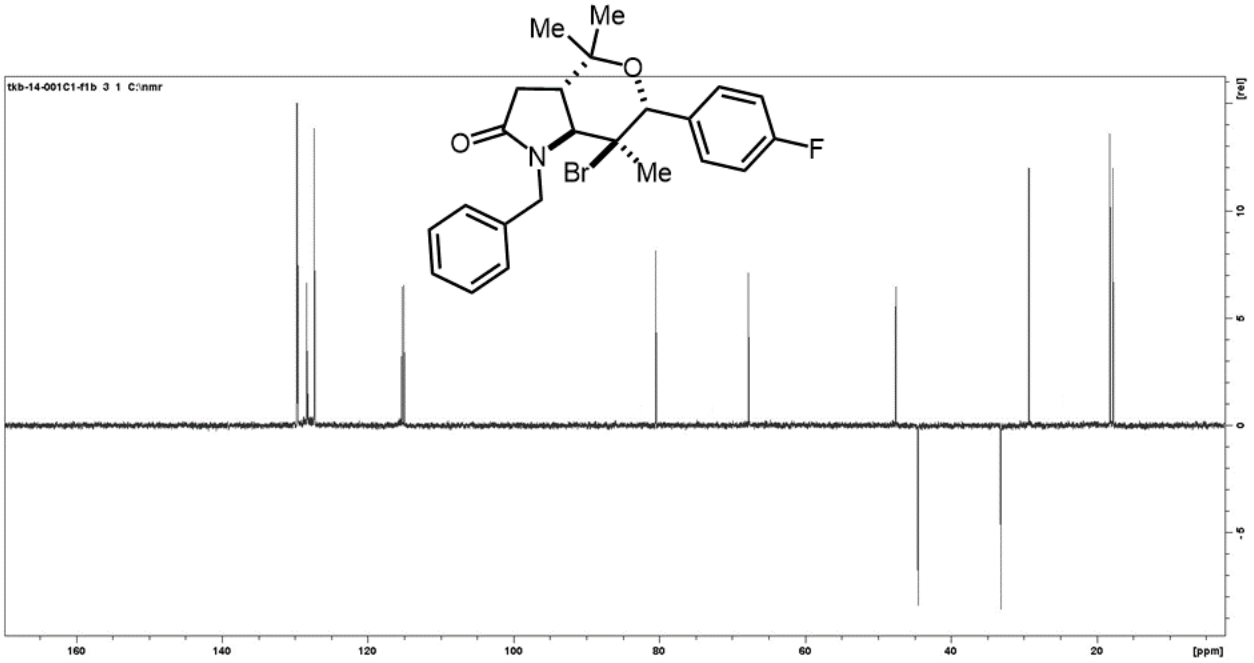
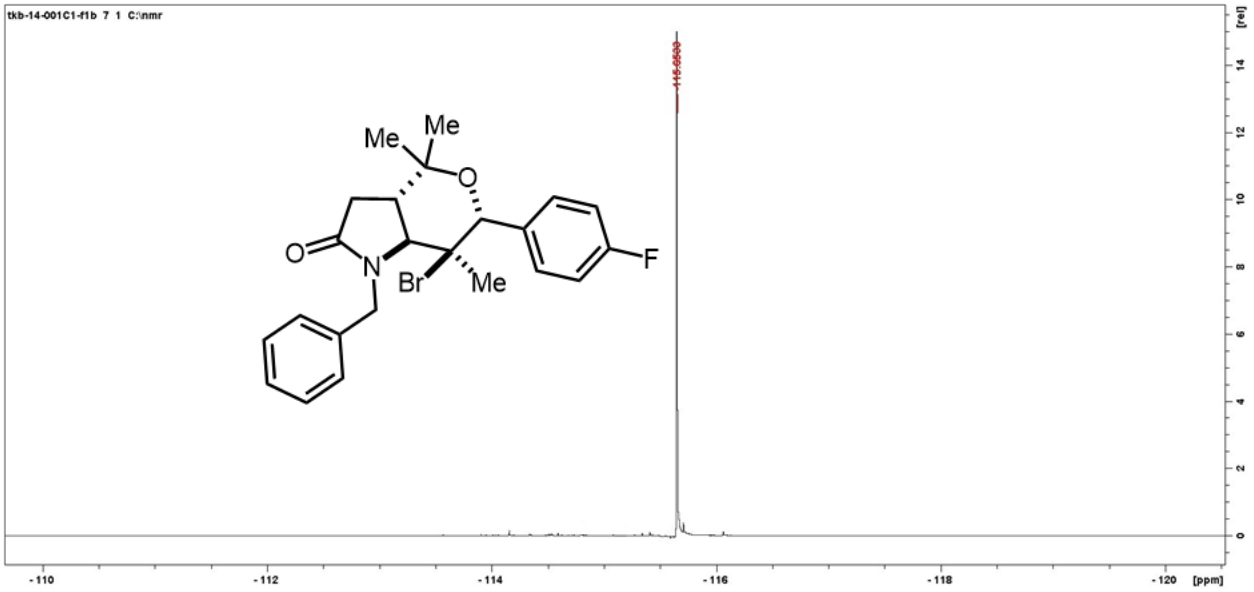


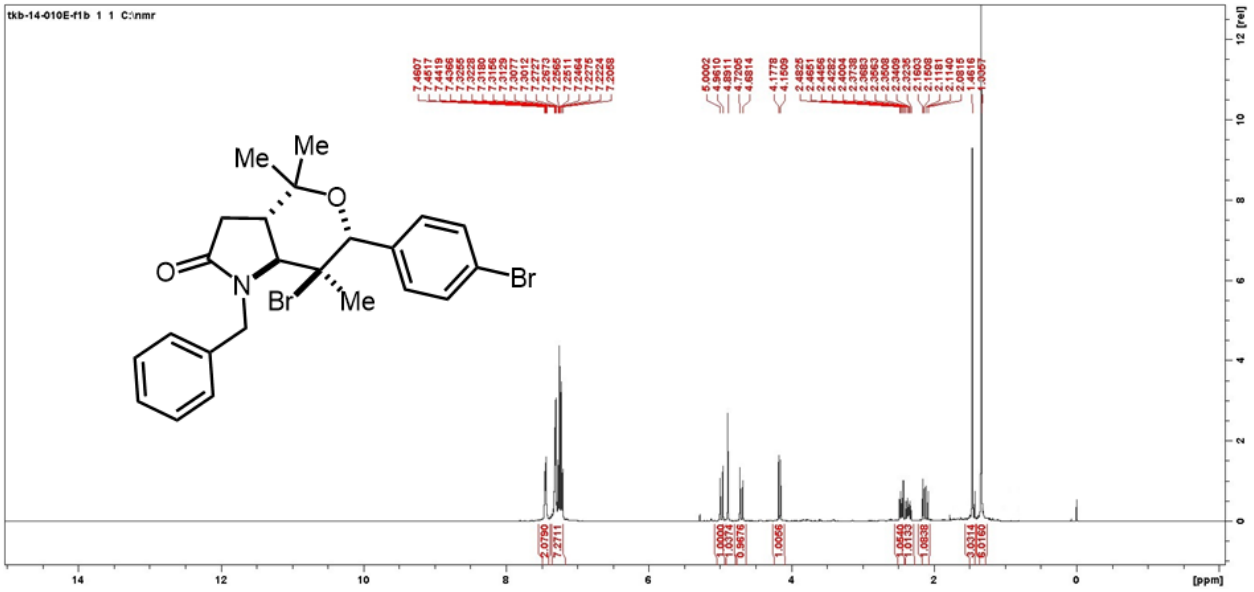
^{19}F NMR

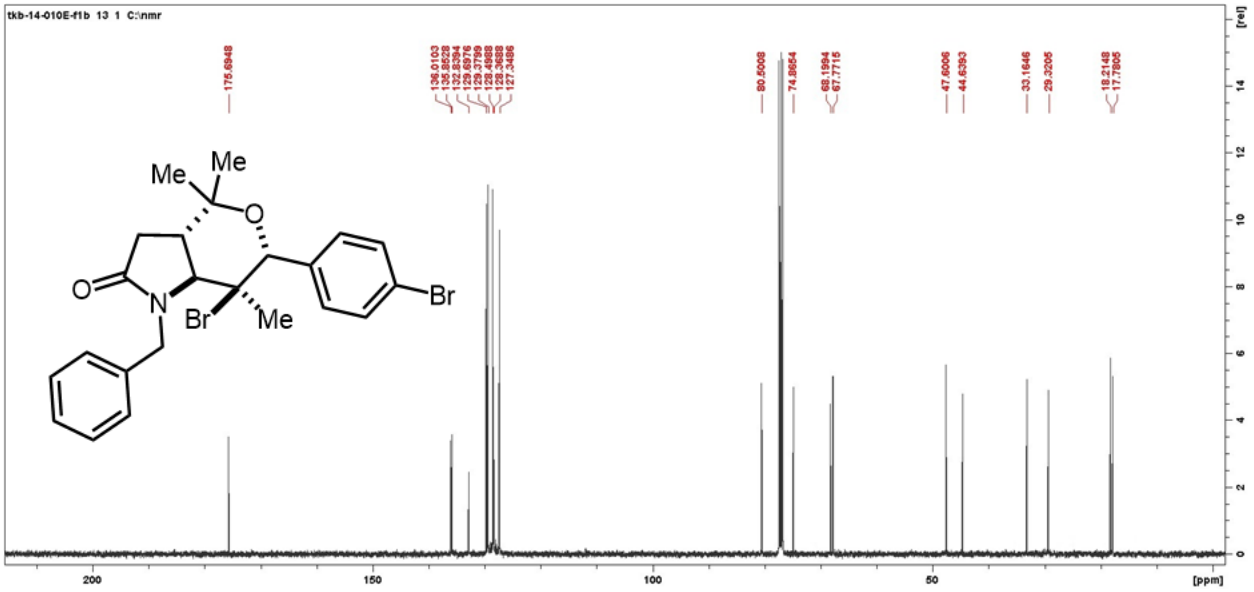


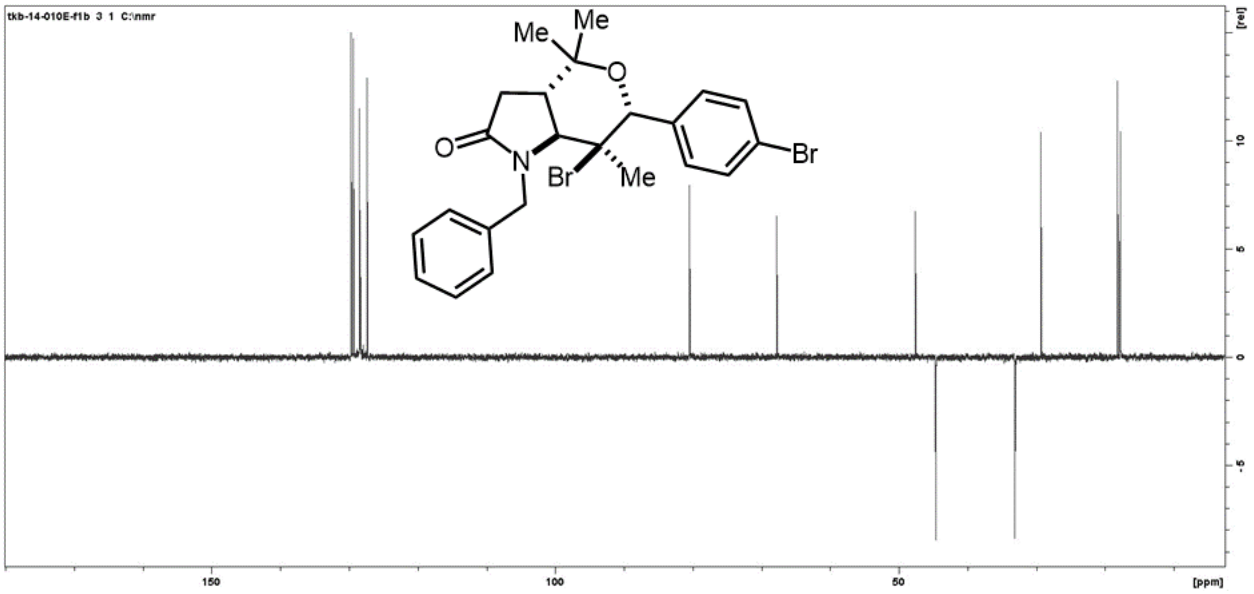
Compound 4r

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 431.2 mg, 85%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.45 (dtt, J = 5.8, 3.6, 1.5 Hz, 2H), 7.32 – 7.20 (m, 7H), 4.98 (d, J = 15.7 Hz, 1H), 4.89 (s, 1H), 4.70 (d, J = 15.7 Hz, 1H), 4.16 (d, J = 10.7 Hz, 1H), 2.51 – 2.30 (m, 2H), 2.18 – 2.06 (m, 1H), 1.46 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.70, 136.01, 135.86, 132.84, 129.70, 129.38, 128.50, 128.37, 127.35, 80.50, 74.87,

68.20, 67.78, 47.60, 44.64, 33.17, 31.59, 29.32, 22.65, 18.22, 17.78, 14.11. **HRMS-EI$^+$** (*m/z*): calc for $C_{23}H_{25}Br_2NO_2$ $[M]^+$ 505.0252, found 505.0257.

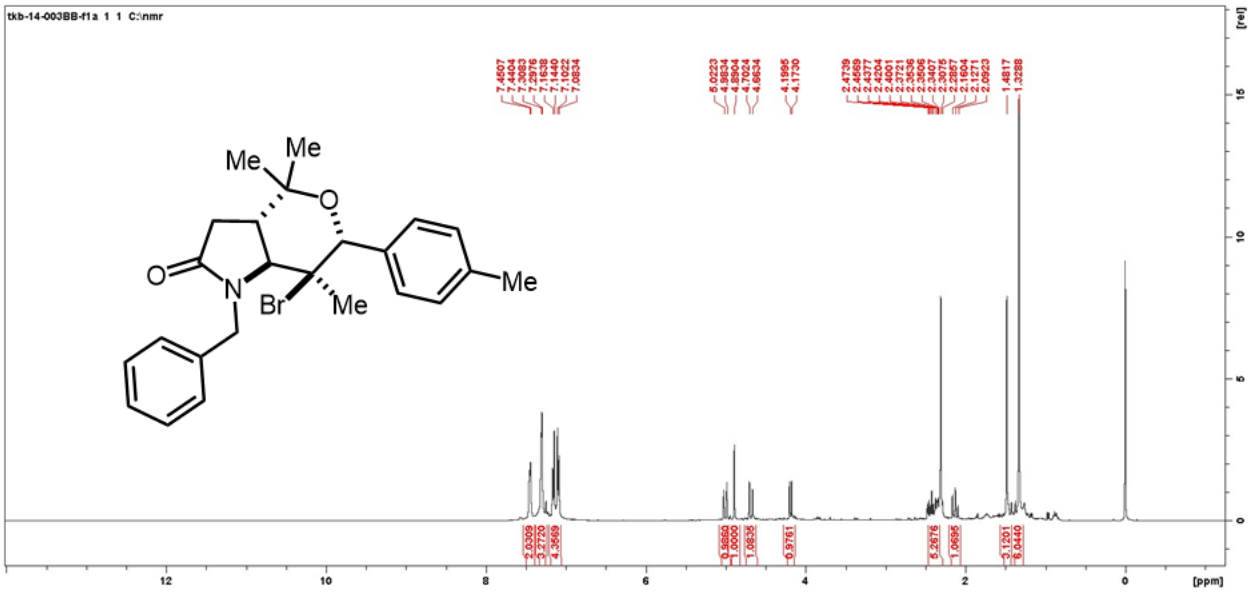


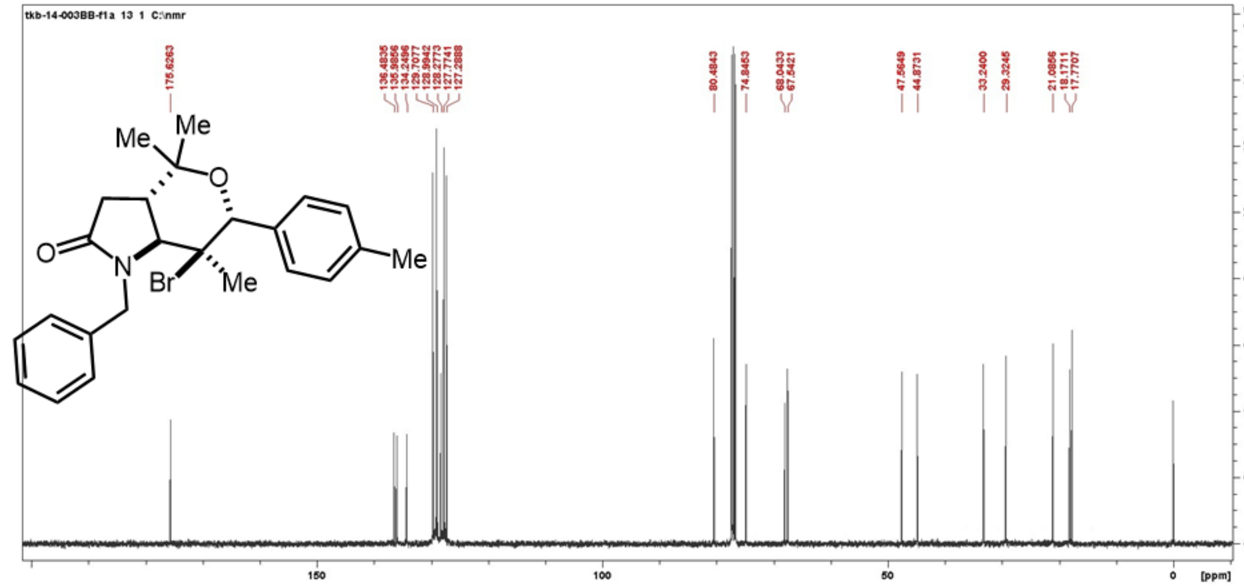




Compound 4s

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 398.2 mg, 90%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.45 (q, J = 3.0 Hz, 2H), 7.30 (d, J = 4.4 Hz, 3H), 7.16 – 7.08 (m, 4H), 5.00 (d, J = 15.5 Hz, 1H), 4.89 (s, 1H), 4.68 (d, J = 15.5 Hz, 1H), 4.23 – 4.12 (m, 1H), 2.47 – 2.28 (m, 5H), 2.13 (dd, J = 14.7, 12.8 Hz, 1H), 1.48 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.63, 136.49, 135.99, 134.25, 129.71, 129.00, 128.28, 127.78, 127.29, 80.49, 74.85, 68.05, 67.55, 47.57, 44.88, 33.24, 29.33, 21.09, 18.17, 17.77. **HRMS-EI^{+}** (*m/z*): calc for $C_{24}H_{28}BrNO_2$ $[M]^+$ 441.1303, found 441.1306.

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33.2400
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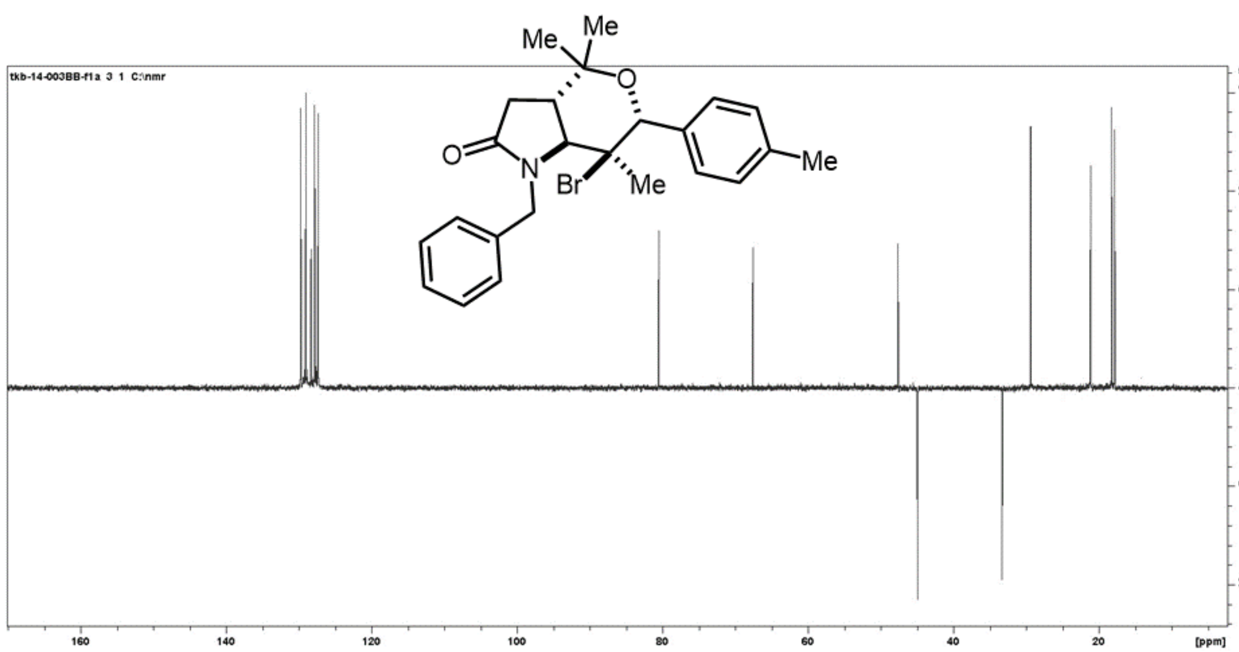
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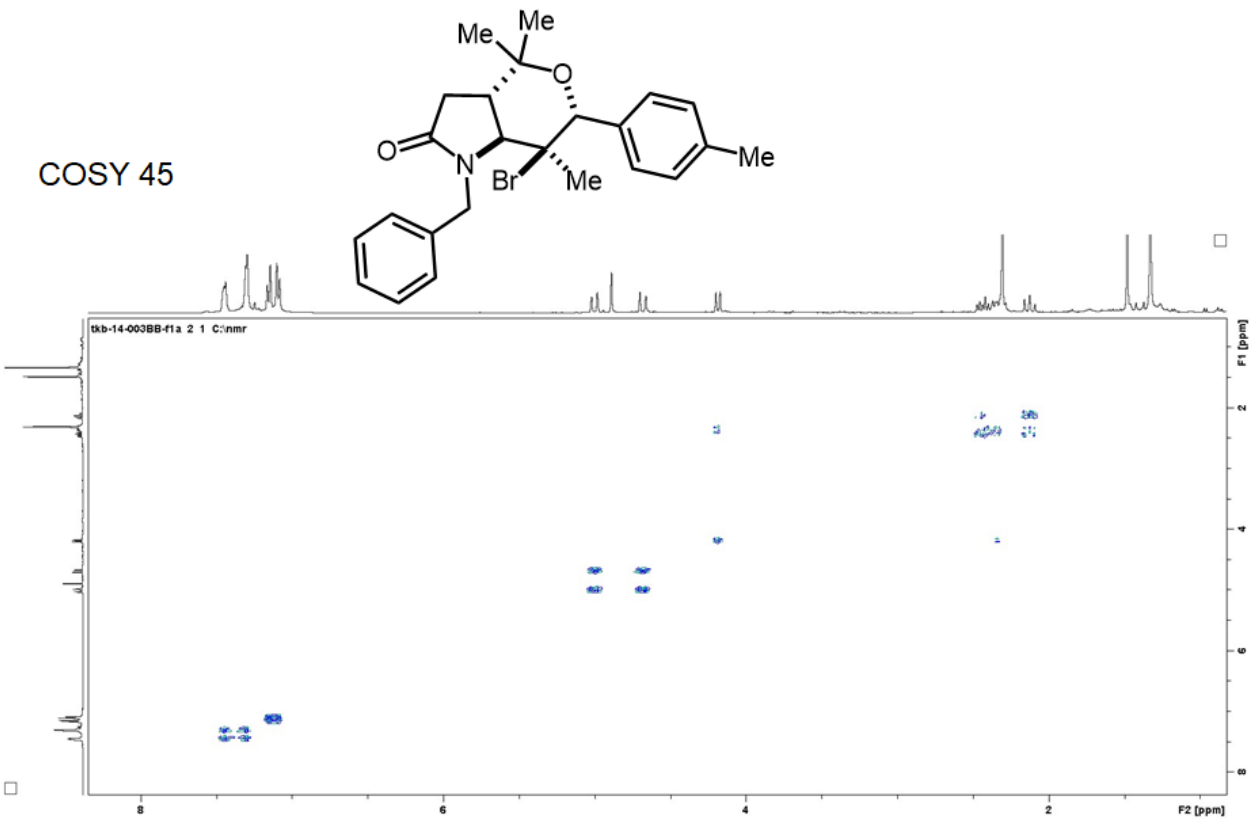
COSY 45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F2 [ppm]

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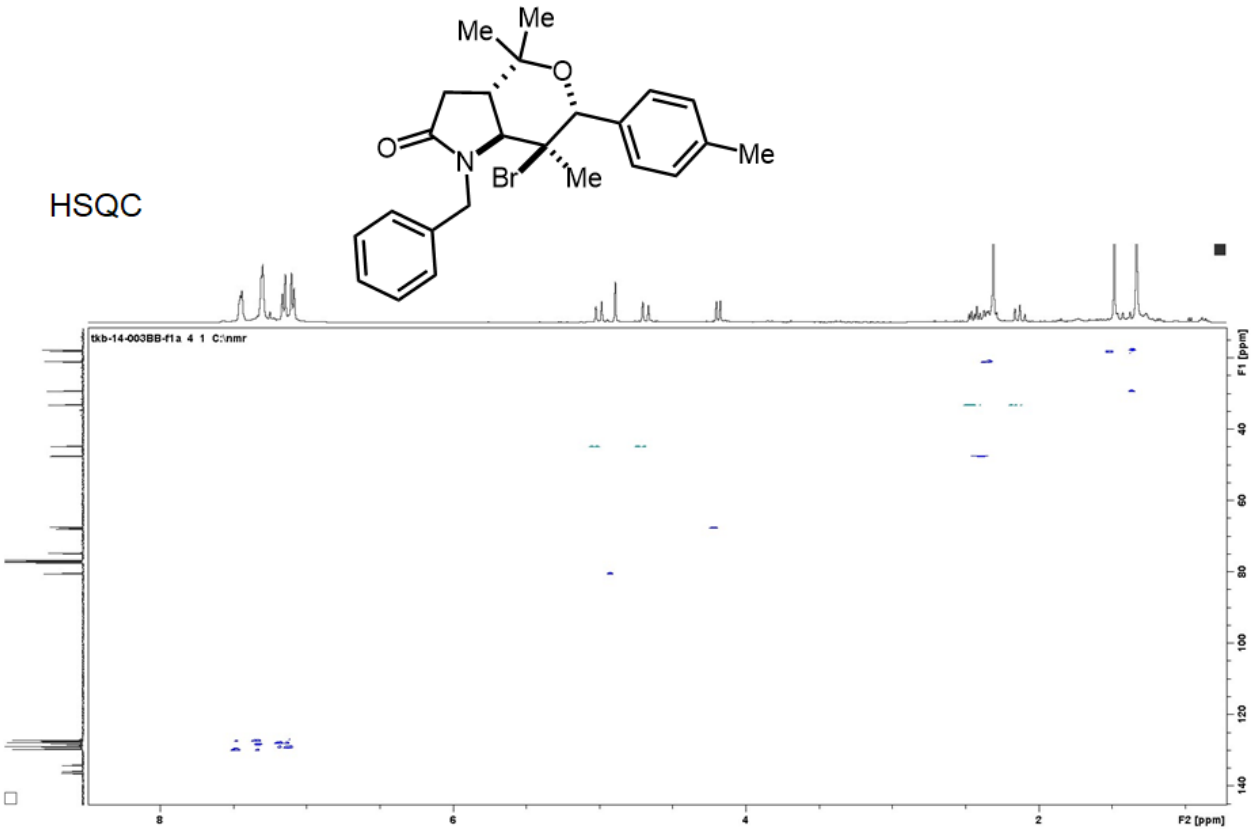
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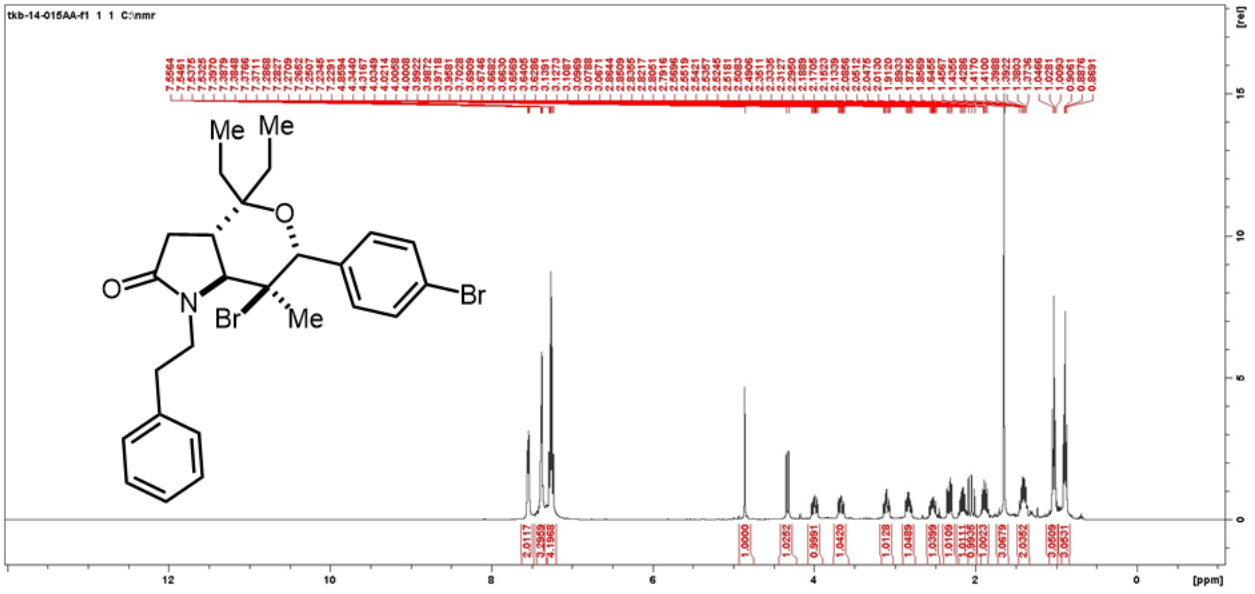
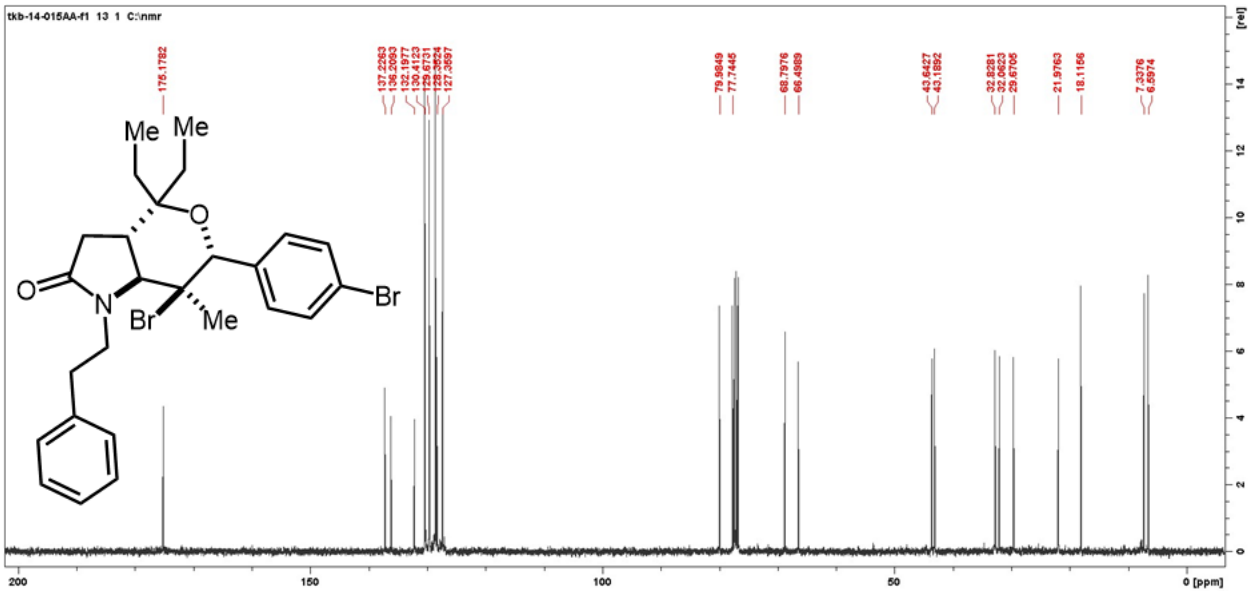
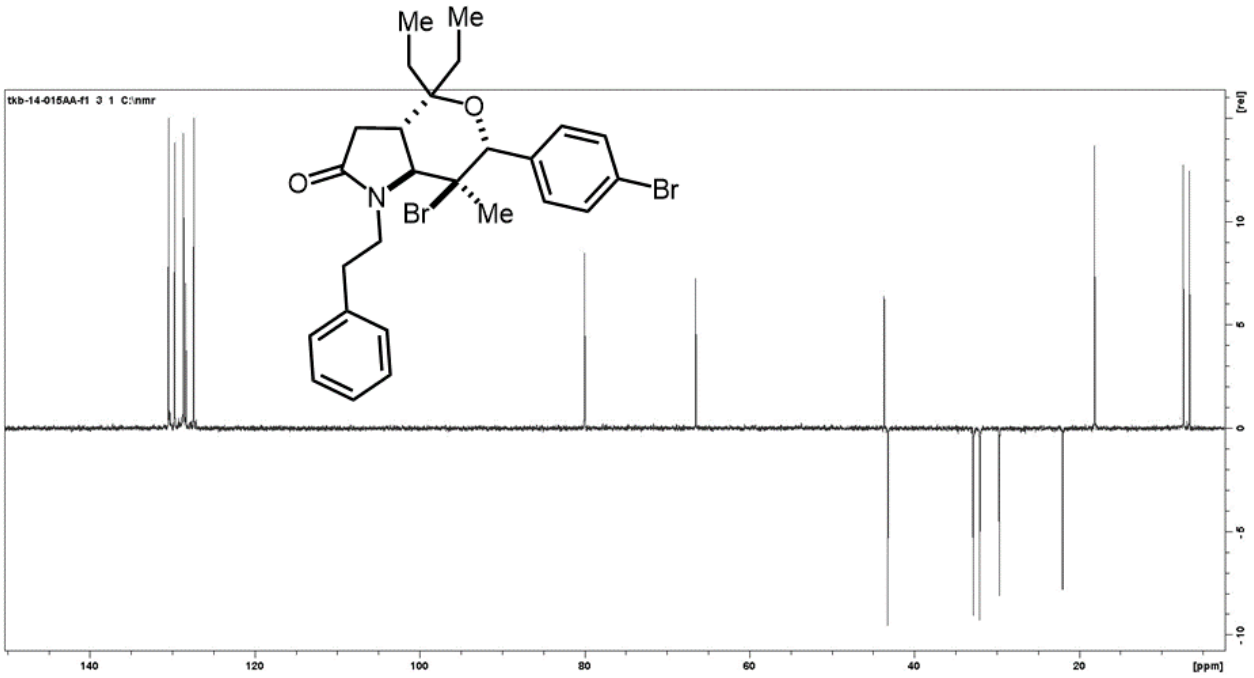
Compound 4t

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 461.4 mg, 84%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.56 – 7.53 (m, 2H), 7.38 – 7.22 (m, 7H), 4.86 (s, 1H), 4.32 (d, J = 9.7 Hz, 1H), 4.04 (dddd, J = 37.6, 13.7, 10.6, 5.7 Hz, 1H), 3.66 (ddd, J = 13.8, 11.2, 4.8 Hz, 1H), 3.09 (tt, J = 10.4, 5.2 Hz, 1H), 2.88 – 2.72 (m, 1H), 2.60 – 2.45 (m, 1H), 2.38 – 2.26 (m, 1H), 2.26 – 1.98 (m, 2H), 1.94 – 1.77 (m, 1H), 1.64 (s, 3H), 1.59 – 1.24 (m, 2H), 1.05 – 0.86 (m, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 175.23, 137.24, 136.22, 132.20, 130.42, 130.38, 130.32, 130.11, 129.68, 128.66, 128.61, 128.36, 127.77, 127.73, 127.36, 86.16, 79.99, 68.80, 66.53, 43.66, 43.21, 32.82, 32.08, 29.68, 21.97, 18.13, 7.35, 6.61. **HRMS-EI^{+}** (*m/z*): calc for $C_{26}H_{31}Br_2NO_2$ $[M]^+$ 547.0722, found 547.0726.



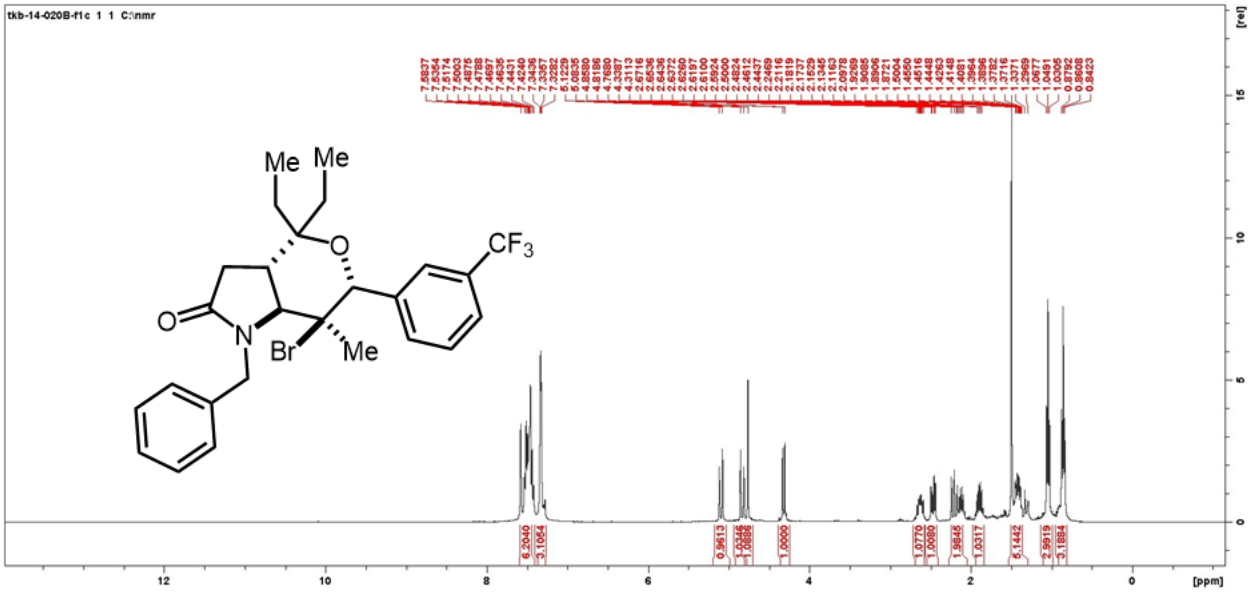


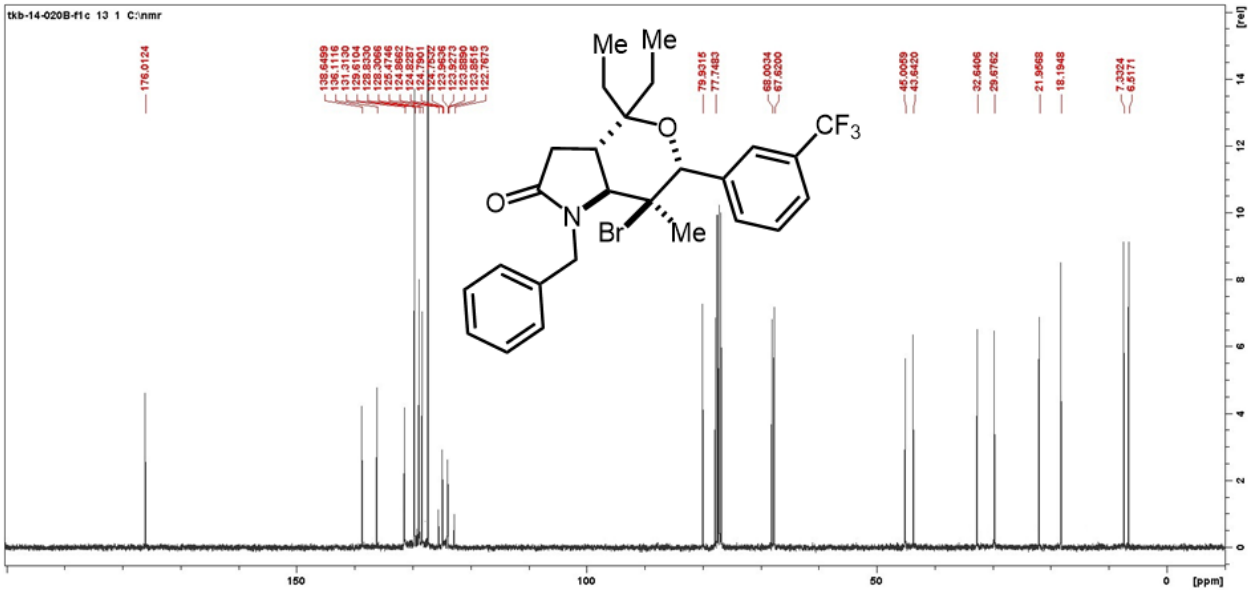


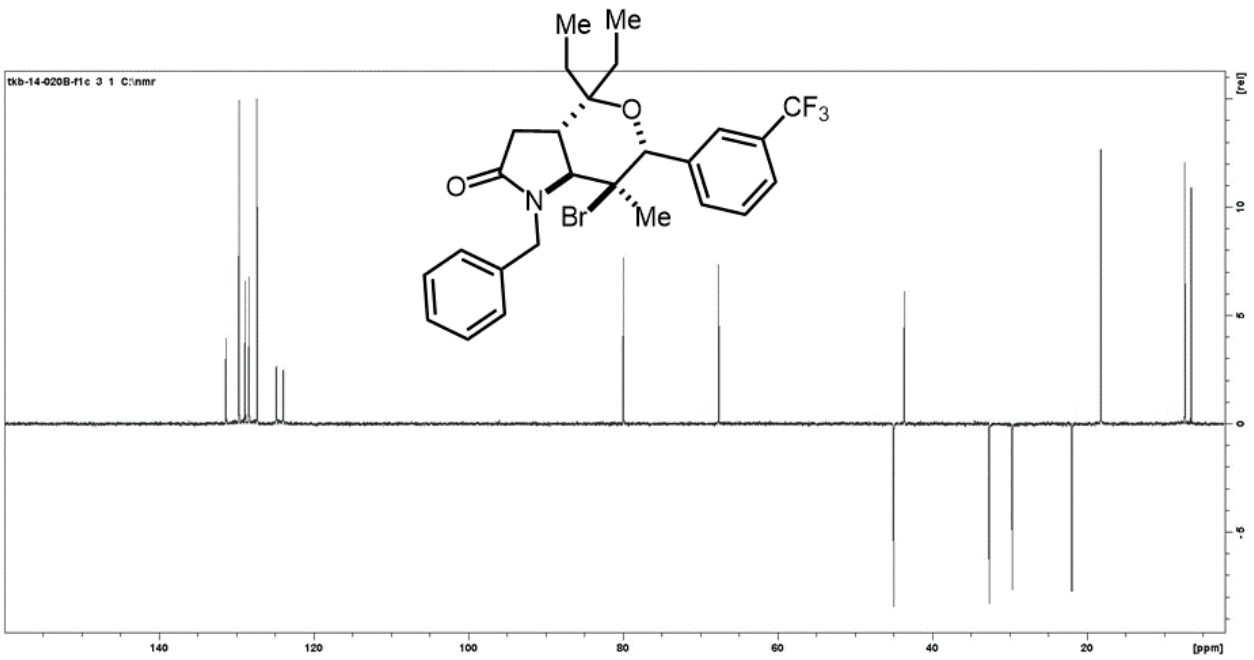
Compound 4u

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 466.7 mg, 89%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.58 – 7.42 (m, 5H), 7.34 – 7.31 (m, 3H), 5.10 (d, J = 15.8 Hz, 1H), 4.84 (d, J = 15.8 Hz, 1H), 4.77 (s, 1H), 4.33 (d, J = 11.0 Hz, 1H), 2.63 (ddd, J = 13.5, 10.8, 7.0 Hz, 1H), 2.47 (dd, J = 15.5, 7.0 Hz, 1H), 2.27 – 2.06 (m, 2H), 1.90 (dq, J = 14.9, 7.4 Hz, 1H), 1.49 – 1.39 (m, 5H), 1.04 (t, J = 6.8 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101

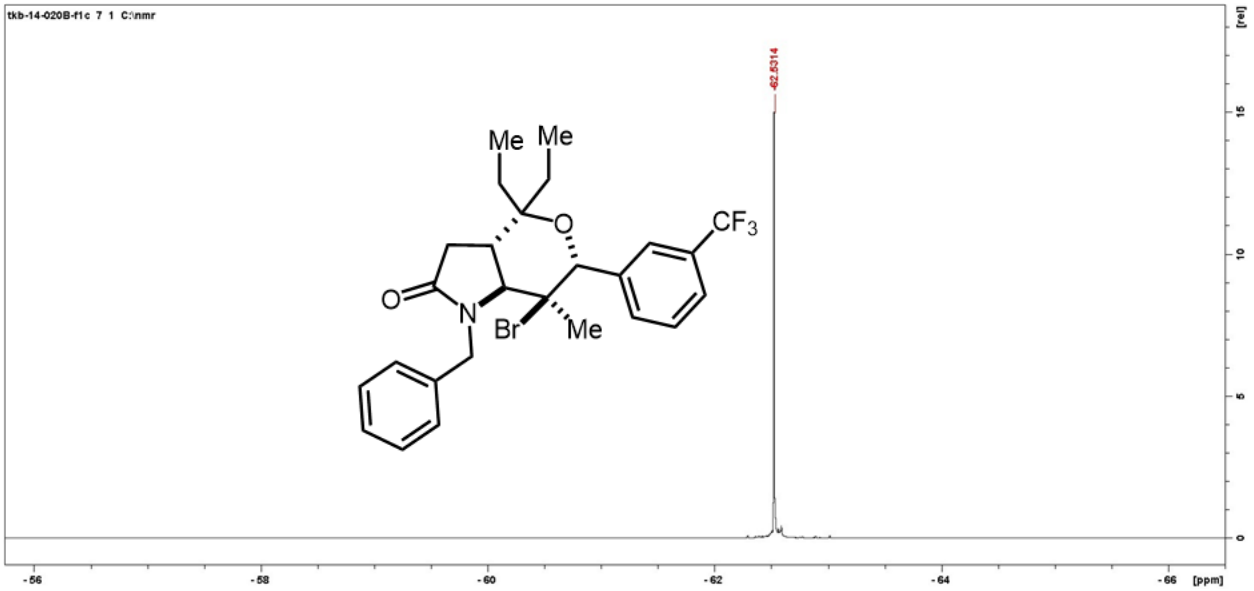
MHz, CDCl3) δ 176.02, 138.65, 136.11, 131.33, 131.31, 130.84, 130.53, 129.61, 128.84, 128.31, 127.29, 125.48, 124.83, 124.79, 124.76, 123.93, 123.89, 123.85, 79.93, 68.01, 67.62, 45.01, 43.64, 32.64, 29.68, 21.96, 18.20, 7.34, 6.52. **HRMS-EI**$^{+}$ (*m/z*): calc for $C_{26}H_{29}BrF_3NO_2$ $[M]^{+}$ 523.1334, found 523.1338.







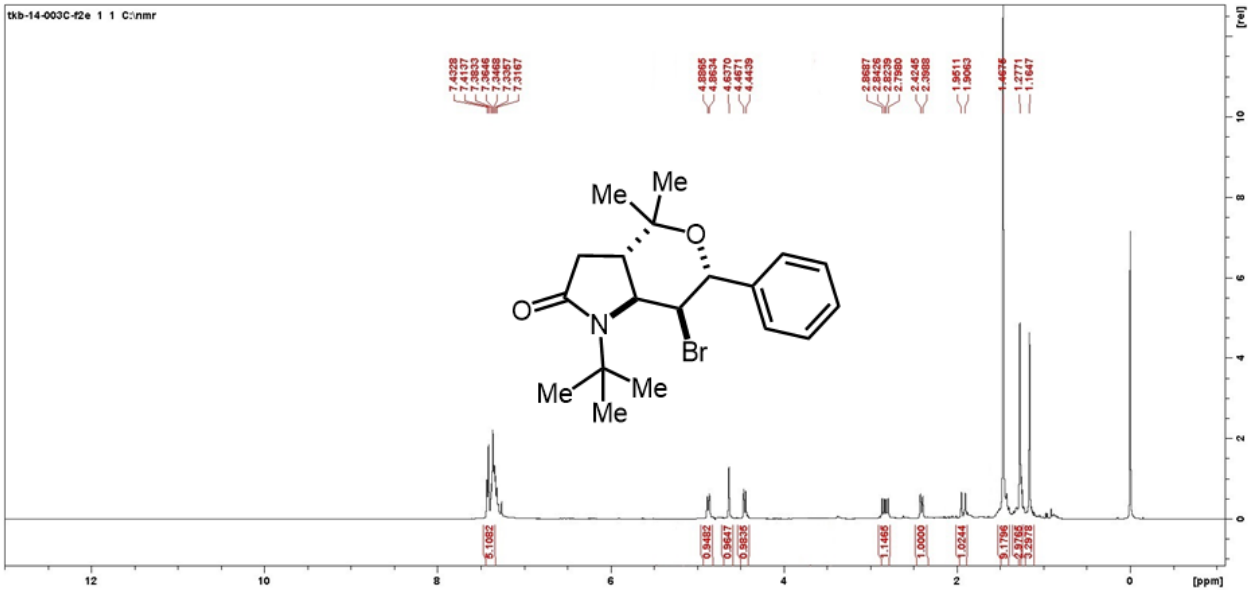
^{19}F NMR

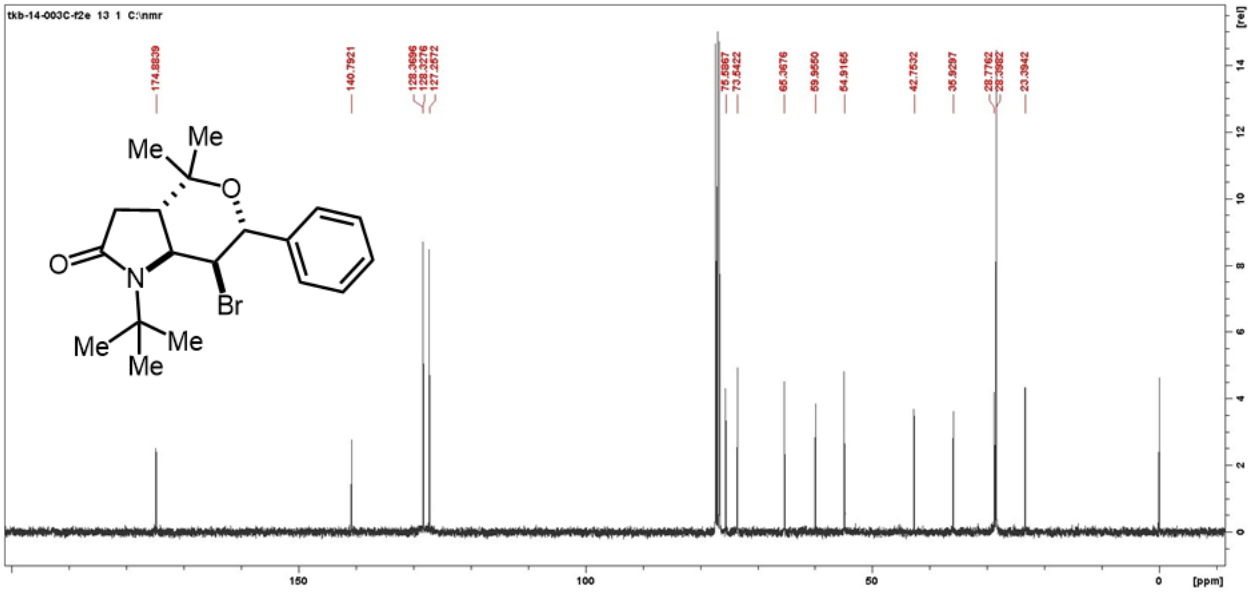


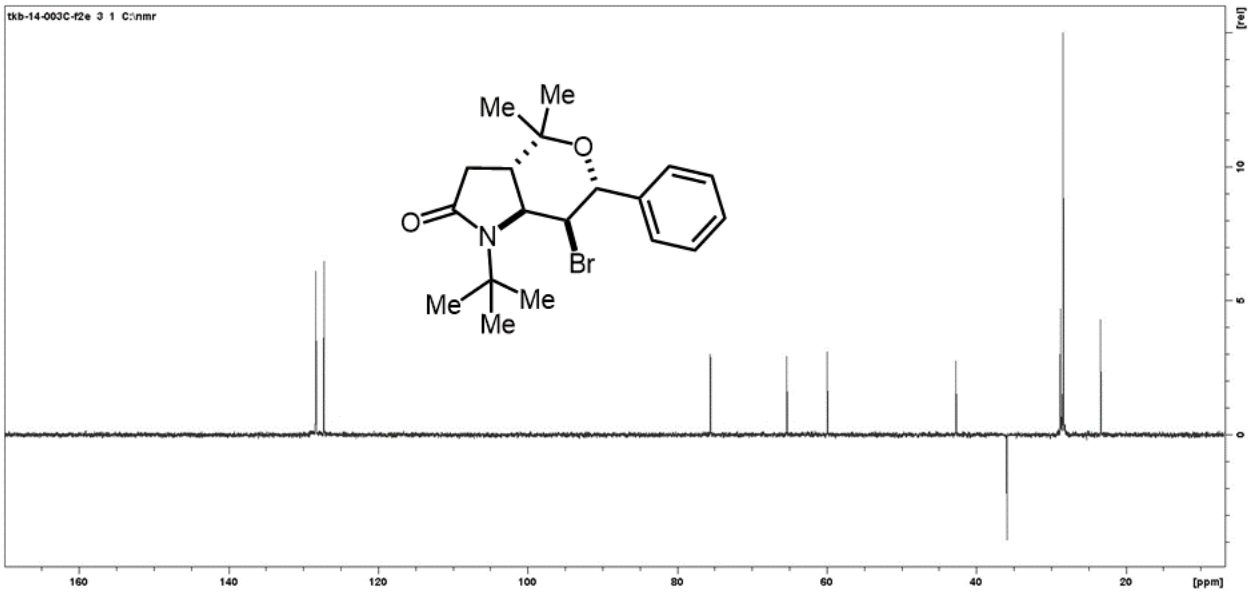
Compound 4v

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 308.0 mg, 81%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.43 – 7.32 (m, 5H), 5.36 (s, 1H), 4.89 (d, J = 9.4 Hz, 1H), 4.64 (s, 1H), 4.49 – 4.40 (m, 1H), 2.83 (dd, J = 17.9, 10.5 Hz, 1H), 2.41 (d, J = 10.3 Hz, 1H), 1.98 – 1.82 (m, 1H), 1.47 (s, 9H), 1.28 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (101 MHz, CDCl3)

δ 174.89, 140.80, 128.37, 128.33, 128.31, 127.26, 75.59, 73.55, 65.37, 59.96, 54.92, 42.76, 35.93, 28.74, 28.40, 23.40. **HRMS-EI$^+$** (*m/z*): calc for $C_{19}H_{26}BrNO_2$ $[M]^+$ 379.1147, found 379.1144.

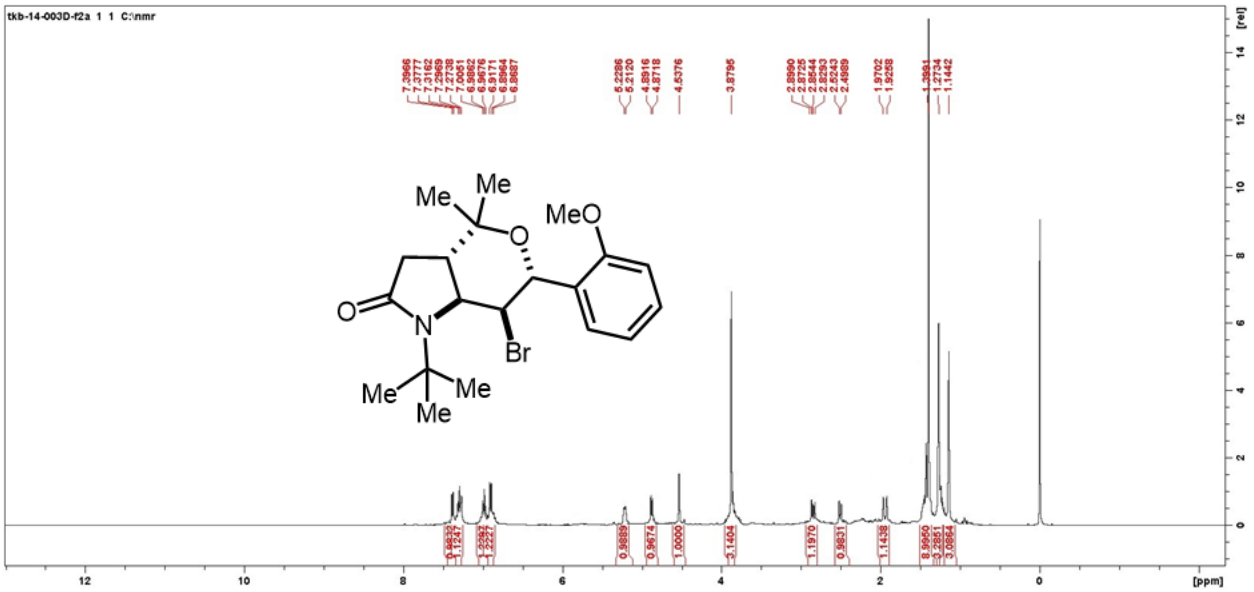


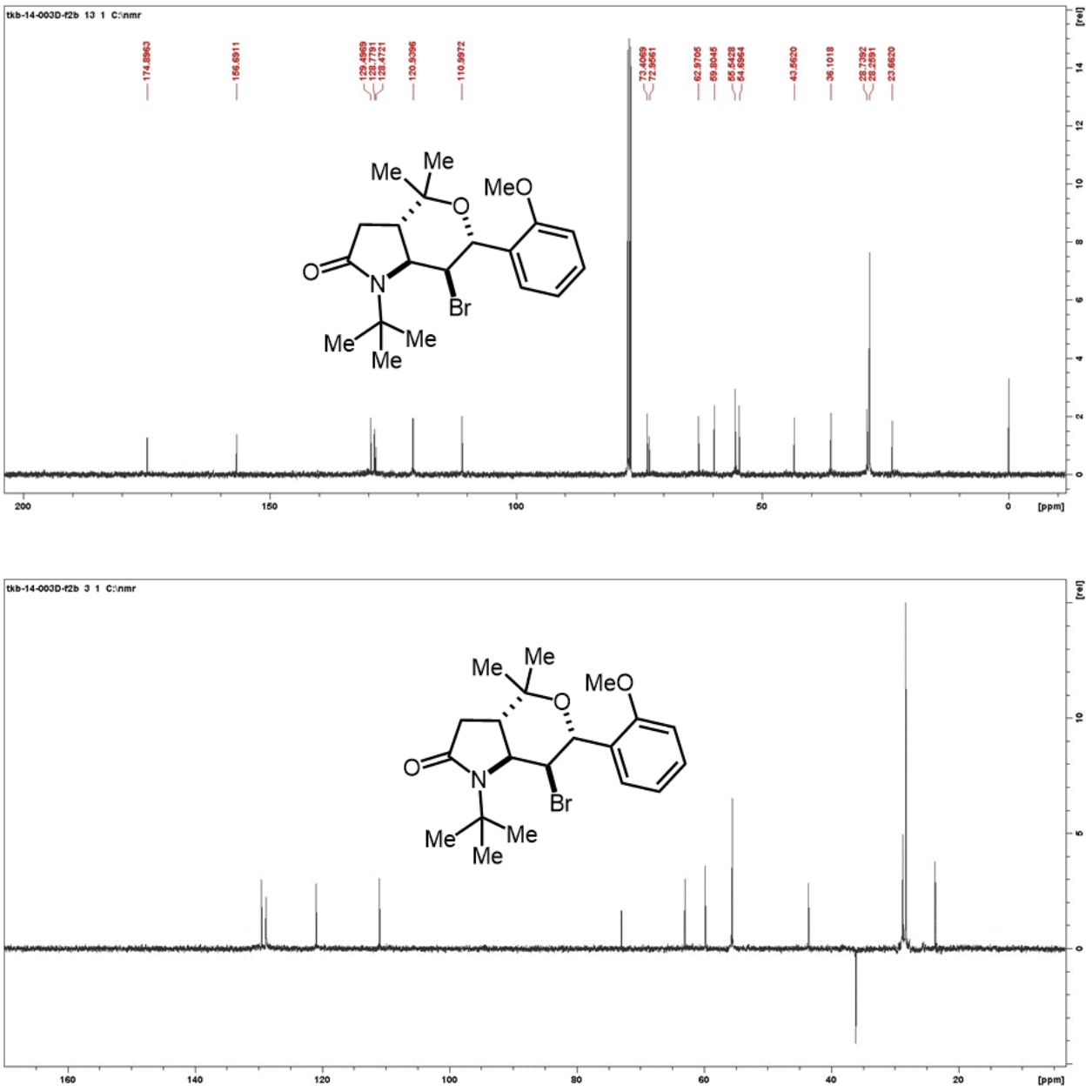




Compound 4w

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 324.1 mg, 79%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.38 – 7.27 (m, 2H), 7.00 – 6.87 (m, 2H), 5.22 (m, 1H), 4.88 (d, J = 8.0 Hz, 1H), 4.54 (s, 1H), 3.87 (s, 3H), 2.86 (qd, J = 17.1, 10.4 Hz, 1H), 2.55 – 2.42 (m, 1H), 1.95 (dd, J = 17.9, 2.4 Hz, 1H), 1.40 (s, 9H), 1.27 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 174.99, 156.68, 129.45, 128.68, 128.59, 120.92, 110.97, 73.30, 72.84, 63.05, 59.83, 55.55, 54.70, 43.61, 36.08, 28.71, 28.25, 23.57. **HRMS-EI^{+}** (*m/z*): calc for $C_{20}H_{28}BrNO_3$ $[M]^{+}$ 409.1253, found 409.1255.

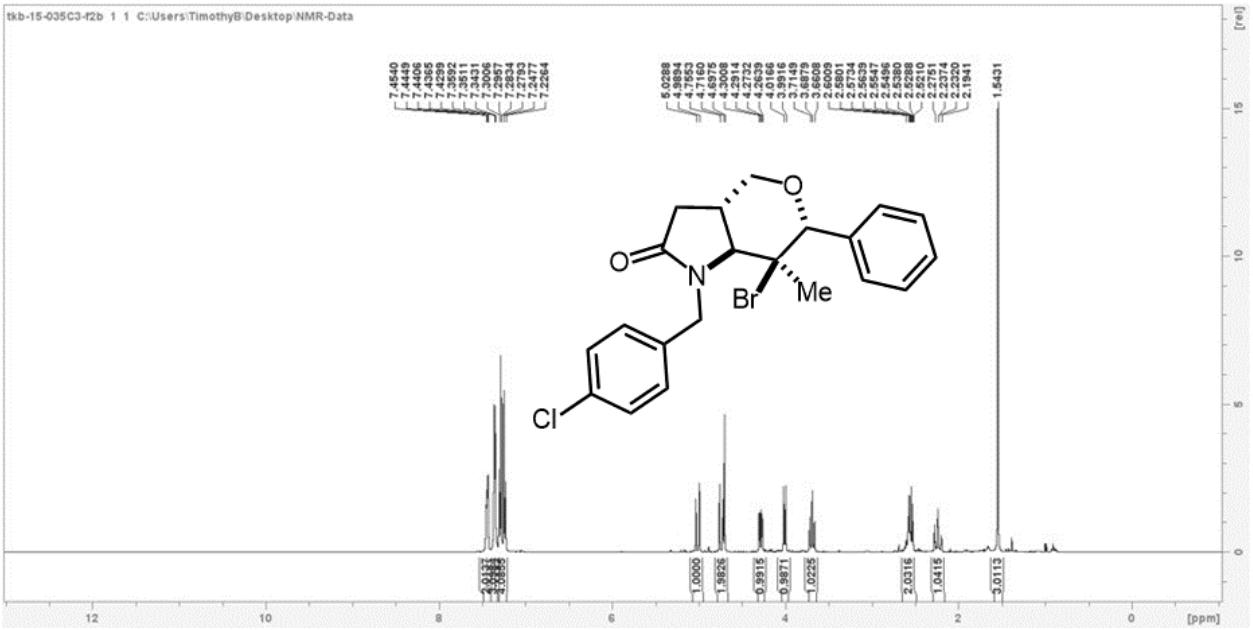


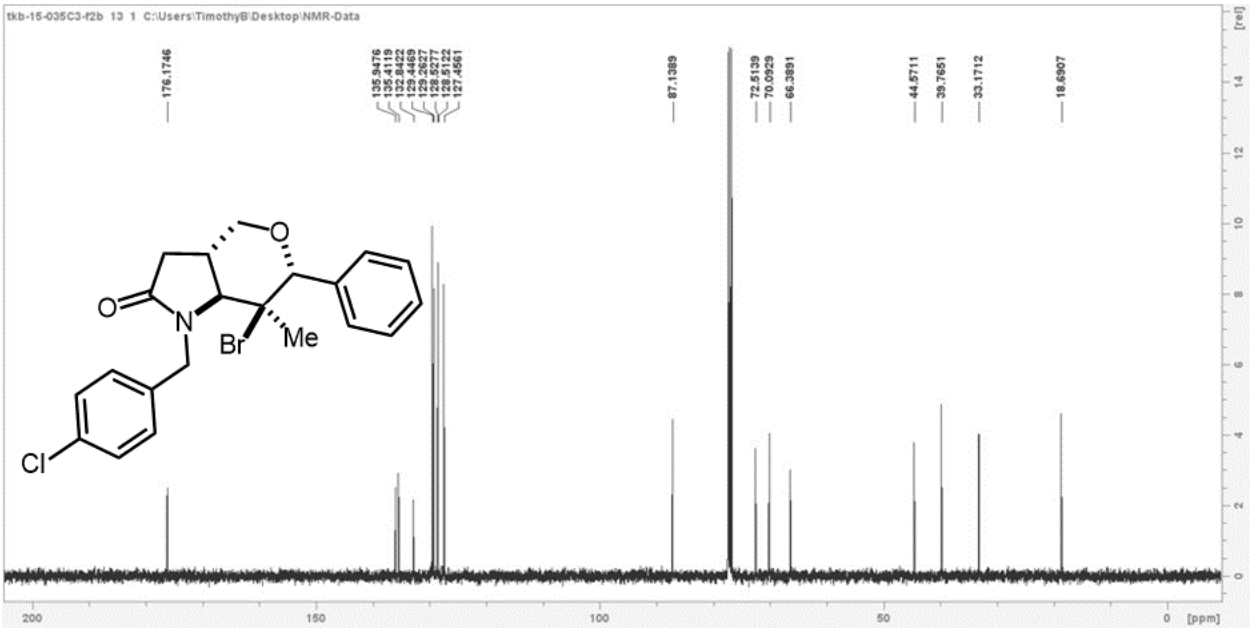


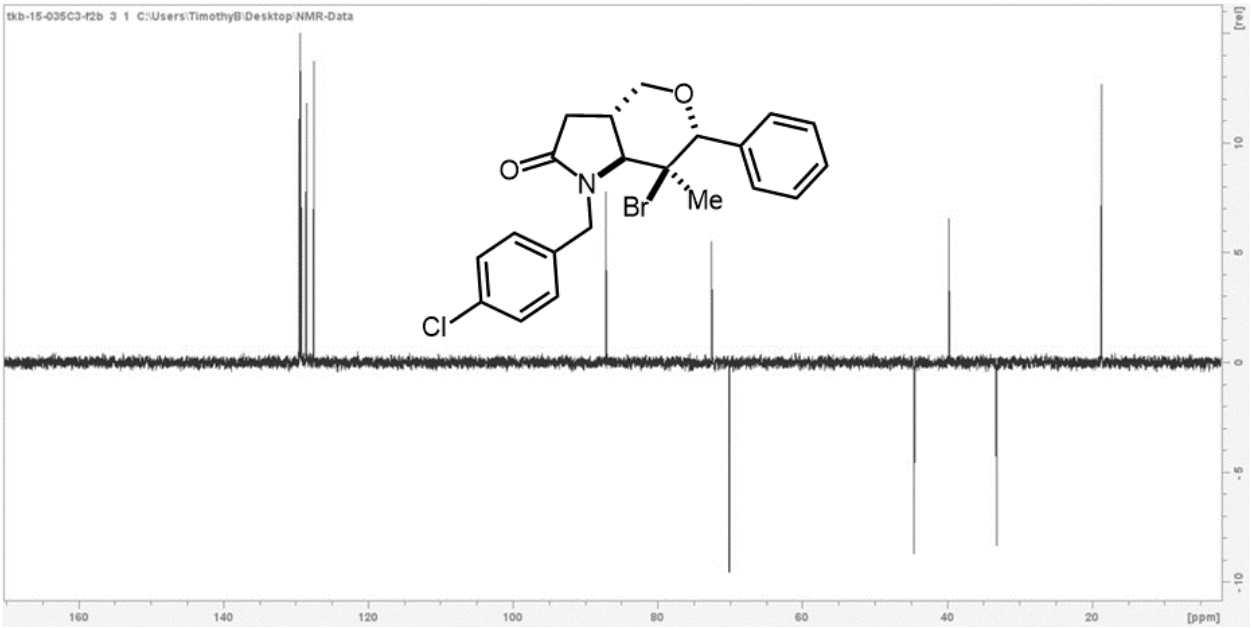
Compound 4x

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 60:40). Yellowish oil. Yield = 304.3 mg, 70%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.40 – 7.20 (m, 7H), 5.01 (d, *J* = 15.7 Hz, 1H), 4.78 – 4.68 (m, 2H), 4.28 (dd, *J* = 11.0, 3.7 Hz, 1H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.69 (t, *J* = 10.8 Hz, 1H), 2.65 – 2.49 (m, 2H), 2.31 – 2.17 (m, 1H), 1.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.18, 135.95, 135.42, 132.85, 129.45, 129.27, 128.53, 128.52, 127.46, 87.14,

77.05, 76.73, 72.52, 70.10, 66.39, 44.58, 39.77, 33.17, 18.69. **HRMS-EI**$^+$ (*m/z*): calc for $C_{21}H_{21}BrClNO_2$ $[M]^+$ 433.0444, found 433.0449.

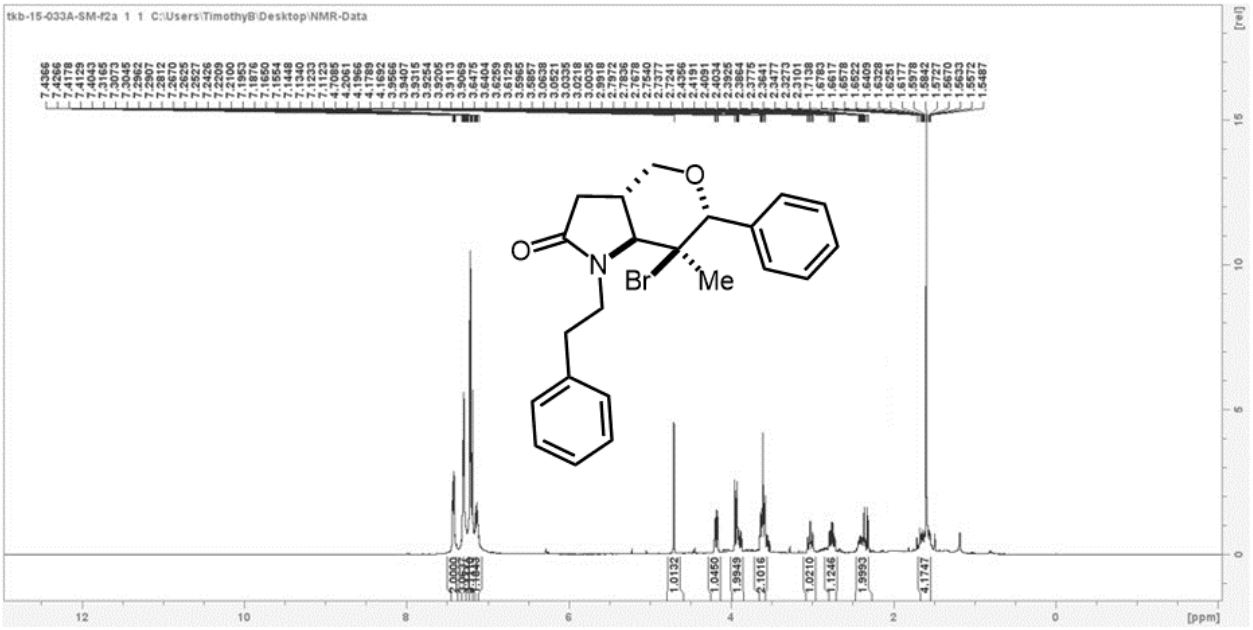






Compound 4y

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Yellowish oil. Yield = 281.7 mg, 68%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 2H), 7.30 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.22 (d, *J* = 4.4 Hz, 4H), 7.13 (dt, *J* = 8.8, 4.3 Hz, 1H), 4.71 (s, 1H), 4.19 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.69 – 3.51 (m, 2H), 3.03 (td, *J* = 12.1, 4.7 Hz, 1H), 2.89 – 2.70 (m, 1H), 2.49 – 2.29 (m, 2H), 1.62– 1.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.50, 138.71, 135.54, 129.52, 129.04, 128.56, 128.49, 127.51, 126.41, 87.23, 71.63, 70.17, 66.93, 43.45, 39.74, 33.34, 32.58, 18.53. **HRMS-EI$^+$** (*m/z*): calc for $C_{22}H_{24}BrNO_2$ $[M]^+$ 413.0990, found 413.0994.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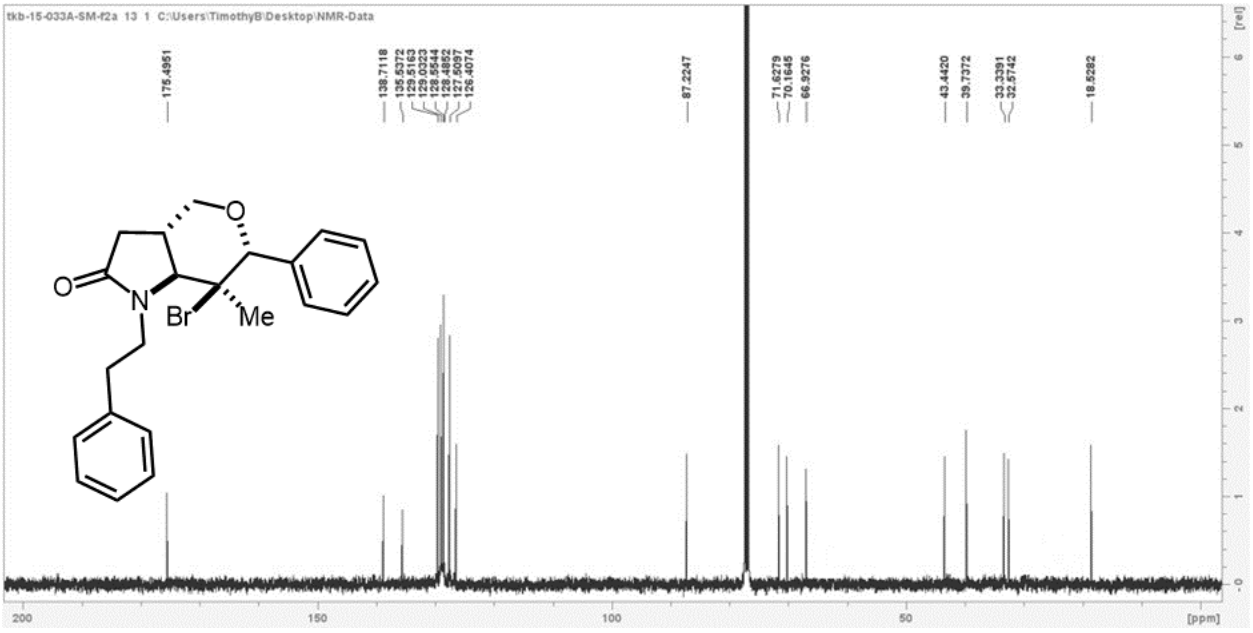
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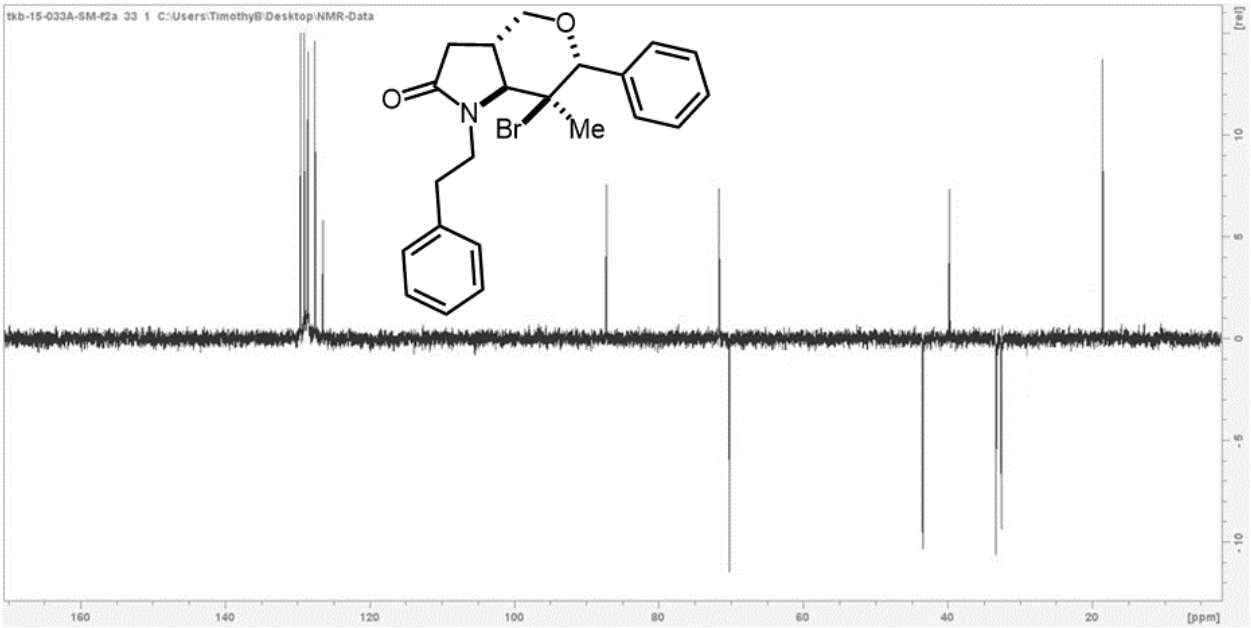
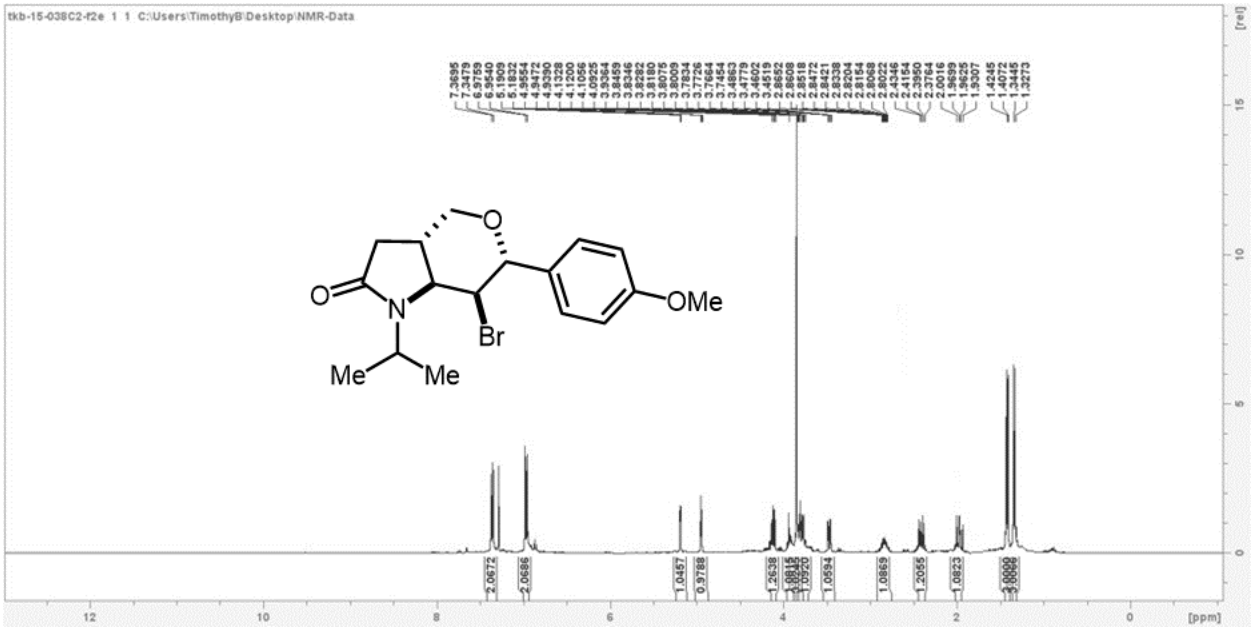


Compound 4z

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Yellowish oil. Yield = 195.2 mg, 53%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 4.95 (t, *J* = 3.3 Hz, 1H), 4.14 – 4.02 (m, 1H), 3.95 – 3.85 (m, 1H), 3.85 (s, 3H), 3.81 (dq, *J* = 6.7, 3.2 Hz, 1H), 3.47 (dd, *J* = 10.4, 3.4 Hz, 1H), 2.83 (dddd, *J* = 21.3, 10.8, 7.6, 5.3 Hz, 1H), 2.52 – 2.27 (m, 1H), 2.05 – 1.90 (m, 1H), 1.46 – 1.25 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.18, 159.36, 130.24, 127.04, 114.42, 80.44, 66.73, 59.61, 55.35, 53.44, 45.58, 34.47, 33.08, 20.12, 19.86. **HRMS-EI^{+}** (*m/z*): calc for $C_{17}H_{22}BrNO_3$ $[M]^{+}$ 367.0783, found 367.0788.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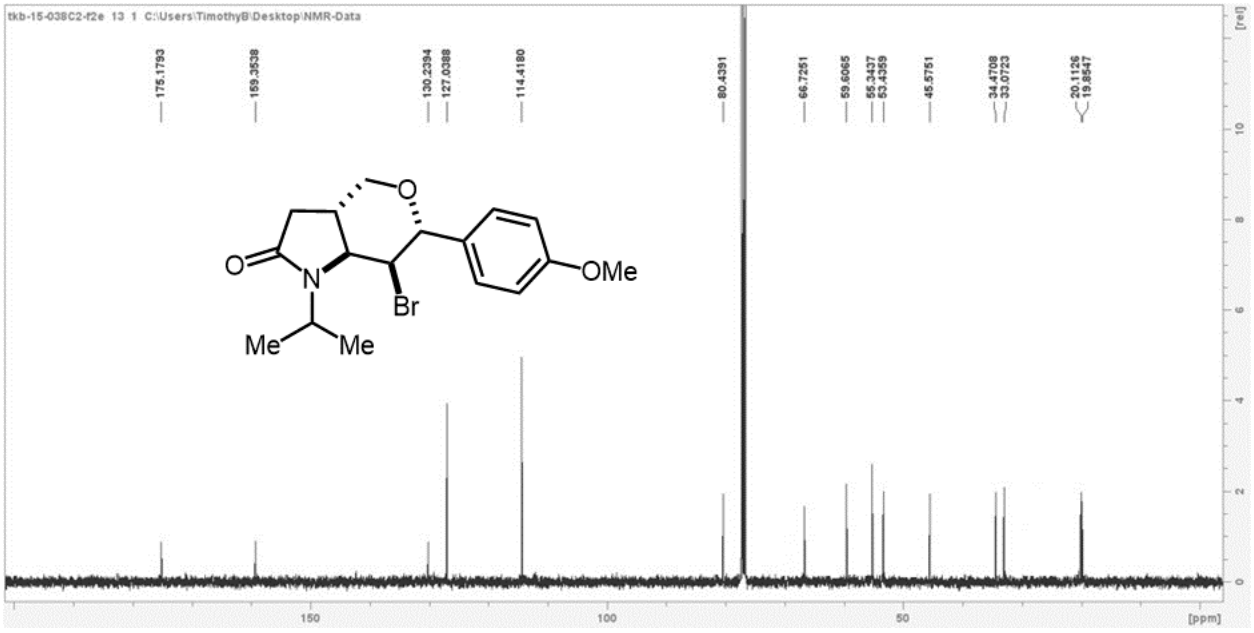
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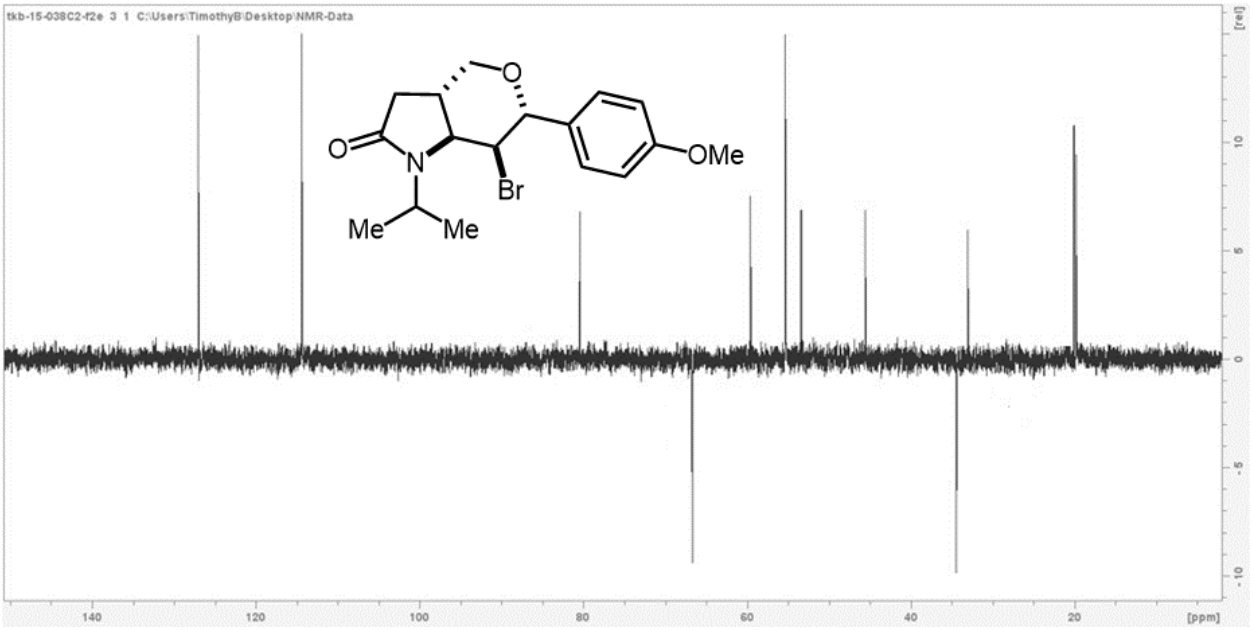
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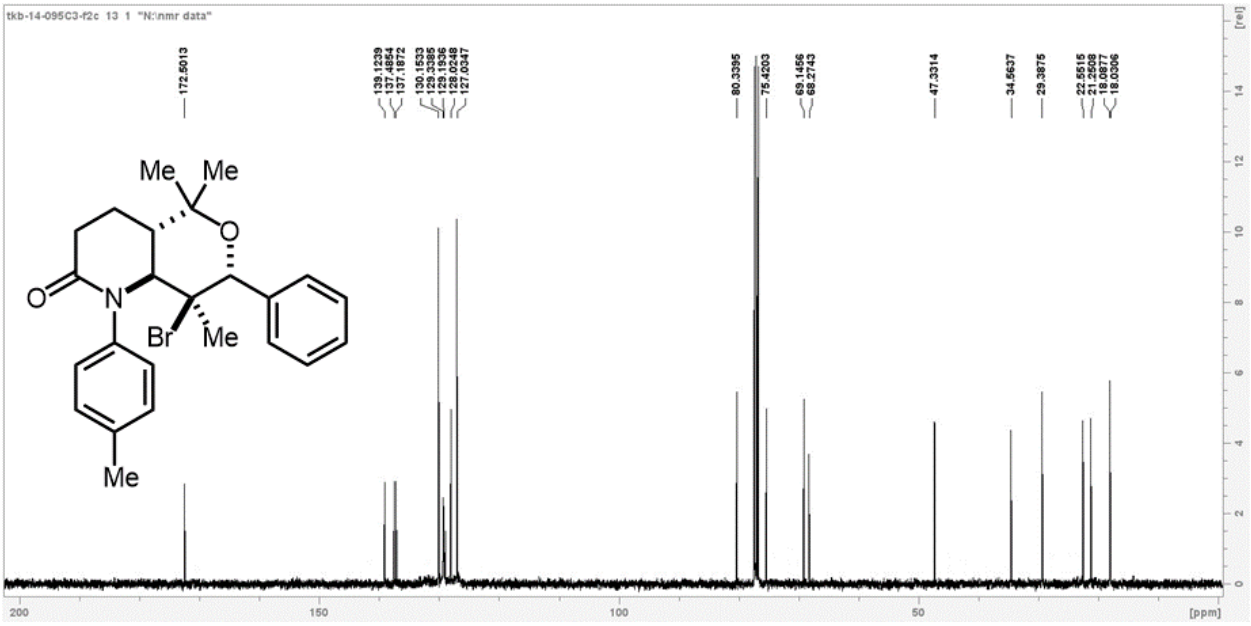
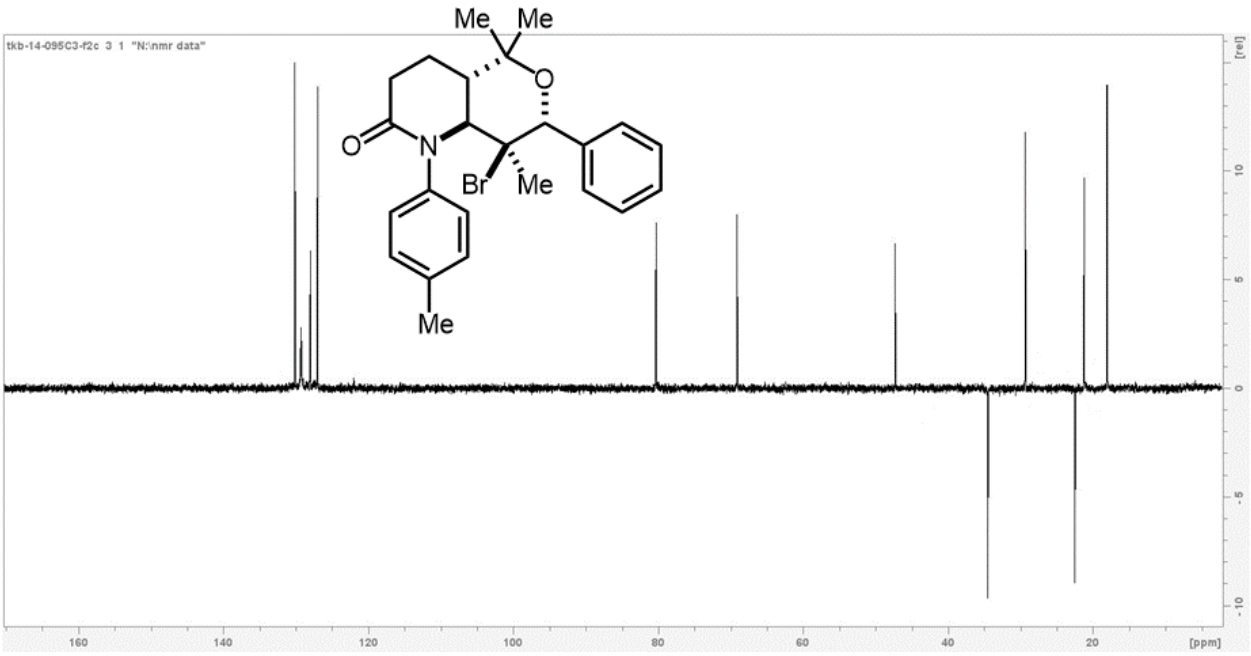
[ppm]

Valerolactam-fused tetrahydropyrans

Compound 5a

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 362.8 mg, 82%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.45 (dt, J = 5.8, 3.6 Hz, 2H), 7.30 – 7.26 (m, 3H), 7.19 – 7.12 (m, 4H), 4.96 (s, 1H), 4.52 (d, J = 11.1 Hz, 1H), 2.77 (ddd, J = 17.7, 4.6, 2.0 Hz, 1H), 2.62 (ddd, J = 17.6, 13.4, 5.7 Hz, 1H), 2.36 (s, 3H), 2.10 (td, J = 11.8, 2.0 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.75 (s, 3H), 1.72 – 1.59 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 172.51, 139.12, 137.50, 137.19, 130.15, 129.34, 129.20, 128.03, 127.04, 80.34, 75.42, 69.15, 68.27, 47.33, 34.57, 29.39, 22.56, 21.25, 18.09, 18.03. **HRMS-EI^{+}** (*m/z*): calc for $C_{24}H_{28}BrNO_2$ $[M]^{+}$ 441.1303, found 441.1307.

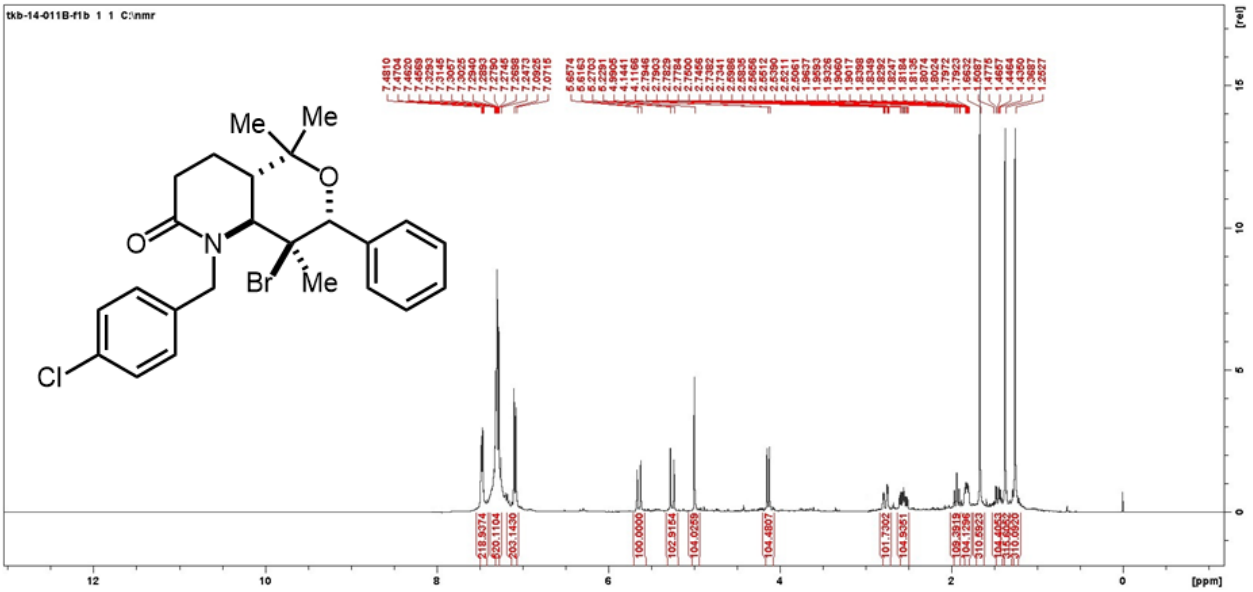


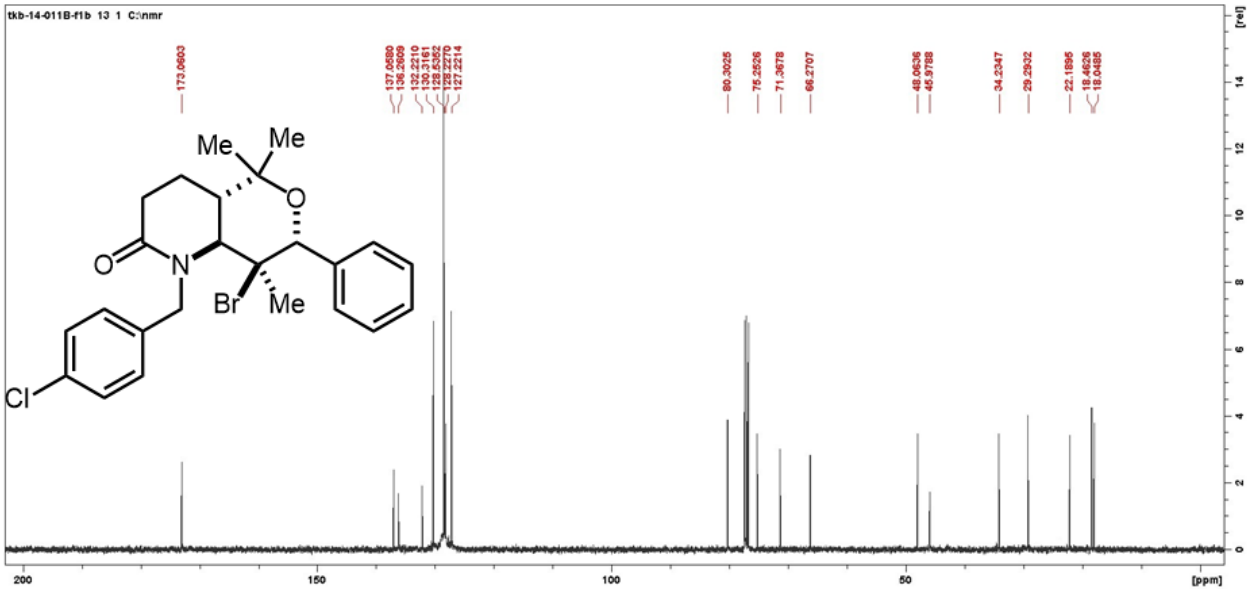


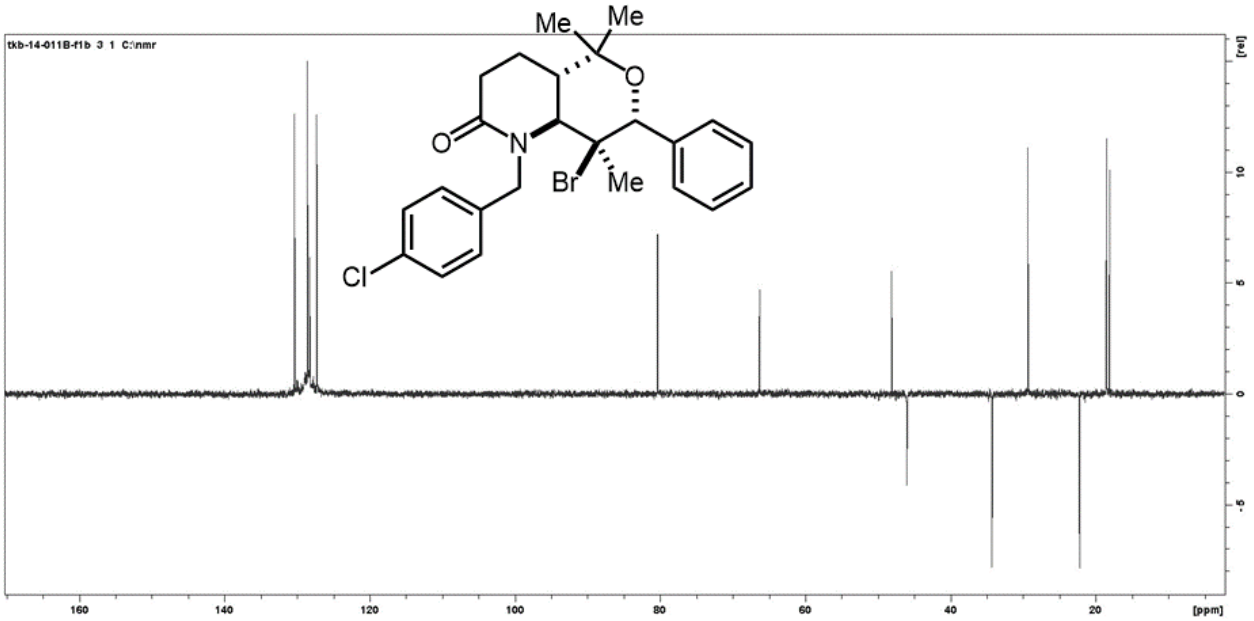
Compound 5b

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 452.9 mg, 95%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.52 – 7.41 (m, 2H), 7.41 – 7.20 (m, 5H), 7.14 – 7.01 (m, 2H), 5.64 (d, J = 16.5 Hz, 1H), 5.25 (d, J = 16.5 Hz, 1H), 4.99 (s, 1H), 4.13 (d, J = 11.0 Hz, 1H), 2.76 (ddd, J = 17.8, 4.9, 2.0 Hz, 1H), 2.55 (ddd, J = 18.2, 13.2, 6.0 Hz, 1H), 1.93 (td, J =

11.6, 2.1 Hz, 1H), 1.82 (ddt, J = 10.3, 6.0, 2.0 Hz, 1H), 1.66 (s, 3H), 1.51 – 1.43 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 173.06, 137.06, 136.26, 132.23, 130.32, 128.97, 128.81, 128.54, 128.48, 128.23, 127.22, 80.31, 75.25, 71.37, 66.27, 48.07, 45.98, 34.24, 29.30, 22.19, 18.47, 18.05. **HRMS-EI$^+$** (*m/z*): calc for $C_{24}H_{27}BrClNO_2$ $[M]^+$ 475.0914, found 475.0918.

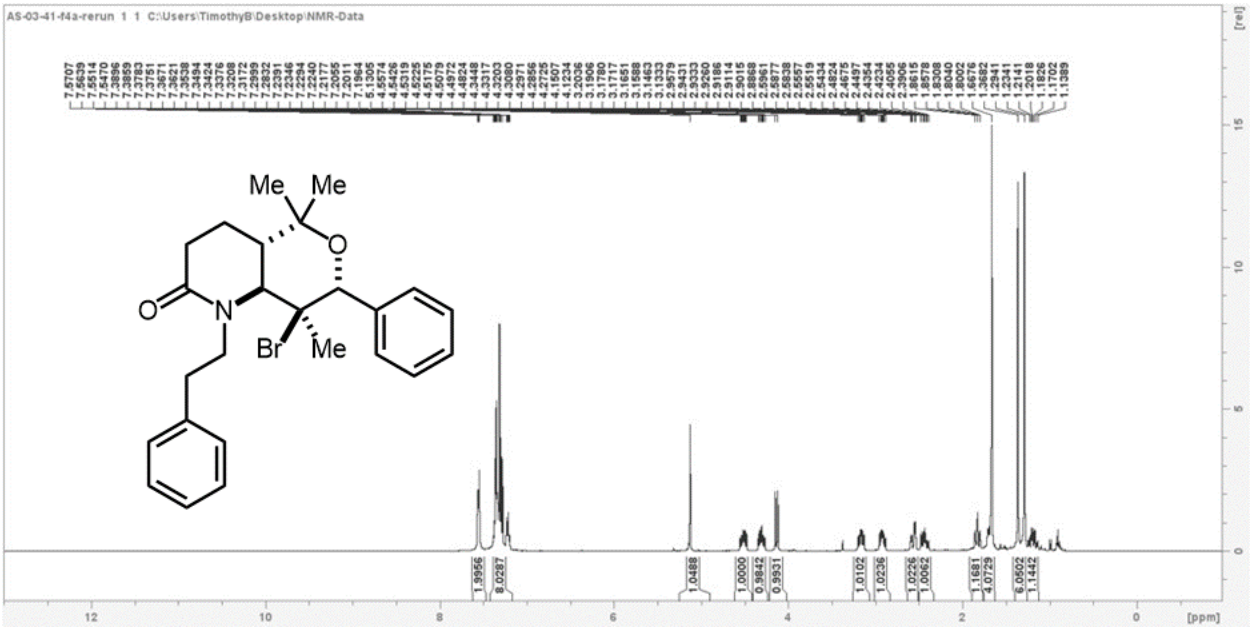






Compound 5c

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 438.1 mg, 96%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 2H), 7.39 – 7.20 (m, 8H), 5.13 (s, 1H), 4.52 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 4.31 (ddd, *J* = 14.3, 9.8, 5.2 Hz, 1H), 4.14 (d, *J* = 10.9 Hz, 1H), 3.17 (ddd, *J* = 12.7, 10.2, 5.2 Hz, 1H), 2.92 (ddd, *J* = 12.8, 9.8, 5.9 Hz, 1H), 2.57 (ddd, *J* = 17.7, 5.0, 1.9 Hz, 1H), 2.44 (ddd, *J* = 18.0, 13.1, 6.0 Hz, 1H), 1.83 (ddd, *J* = 12.6, 11.0, 2.0 Hz, 1H), 1.70 (ddd, *J* = 8.8, 4.4, 2.0 Hz, 1H), 1.37 (s, 3H), 1.29 (s, 3H), 1.31 – 1.08 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.56, 172.95, 130.36, 129.25, 128.34, 128.23, 127.24, 126.26, 80.38, 77.40, 77.08, 76.76, 75.26, 72.17, 66.30, 47.90, 45.32, 34.31, 33.44, 29.60, 29.25, 22.12, 18.44, 18.00. **HRMS-EI$^+$** (*m/z*): calc for $C_{25}H_{30}BrNO_2$ $[M]^+$ 455.1460, found 455.1465.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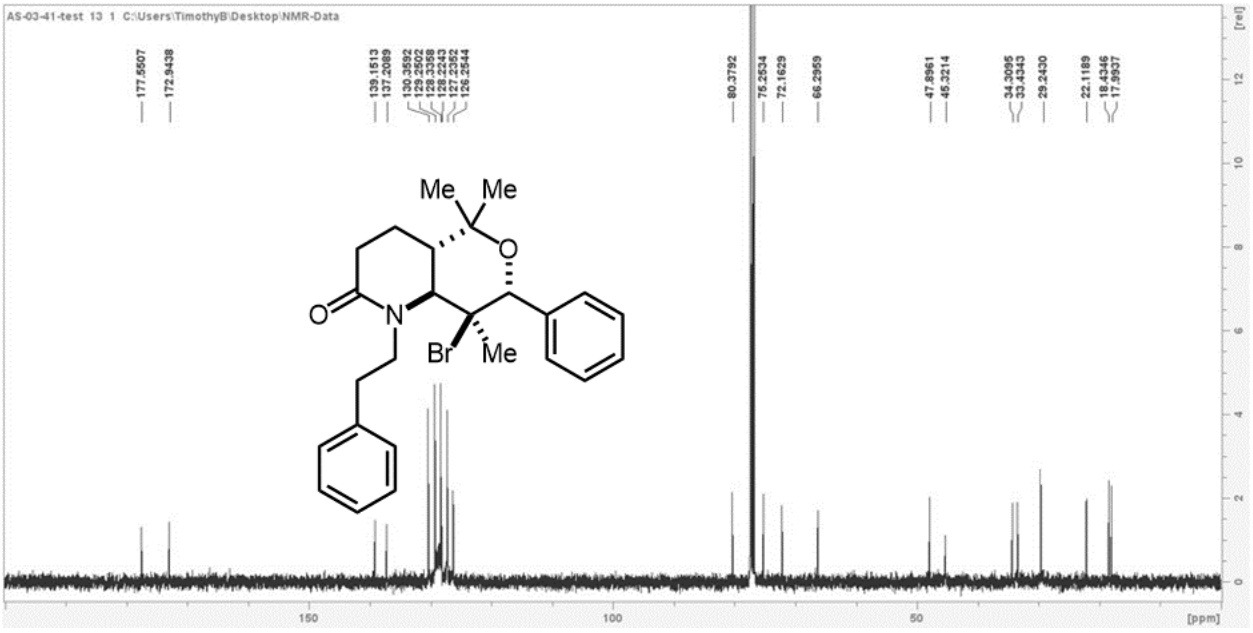
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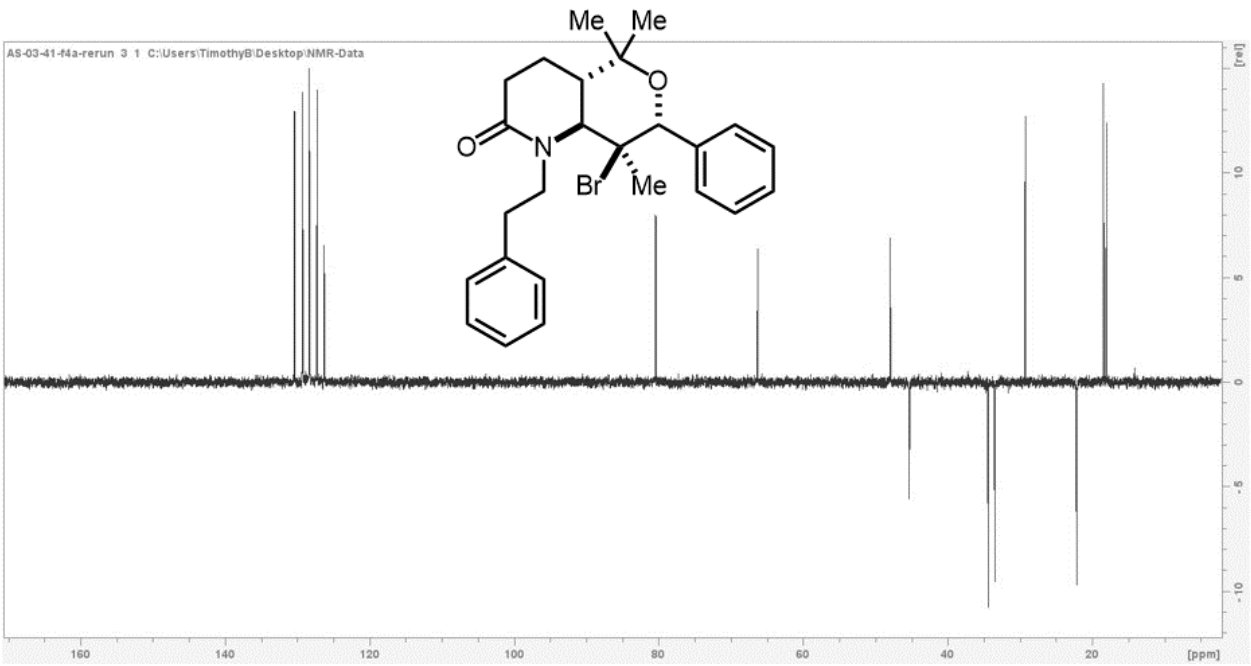
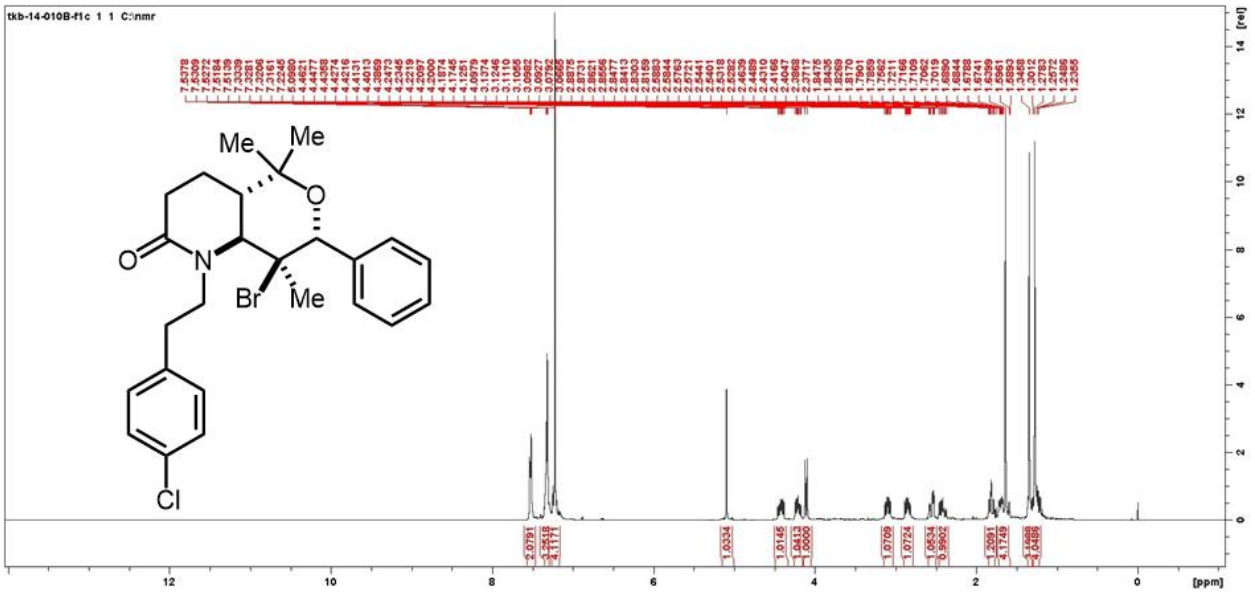


Compound 5d

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 451.6 mg, 92%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 7.51 (m, 2H), 7.33 – 7.22 (m, 7H), 5.10 (s, 1H), 4.42 (ddd, J = 13.8, 10.5, 5.7 Hz, 1H), 4.21 (ddd, J = 13.9, 10.1, 5.1 Hz, 1H), 4.11 (d, J = 10.9 Hz, 1H), 3.10 (ddd, J = 12.7, 10.4, 5.1 Hz, 1H), 2.85 (ddd, J = 12.7, 10.1, 5.7 Hz, 1H), 2.56 (ddd, J = 17.8, 5.0, 1.9 Hz, 1H), 2.42 (ddd, J = 18.1, 13.2, 6.0 Hz, 1H), 1.88 – 1.65 (m, 2H), 1.64 (s, 3H), 1.35 (s, 3H), 1.34 – 1.22 (m, 4H). ^{13}C NMR (101 MHz, CDCl3) δ 172.66, 137.73, 137.17, 132.00, 130.53, 130.35, 128.45, 128.25, 127.24, 80.39, 75.24, 72.35, 66.55, 47.98, 45.36, 34.28, 32.94, 29.25, 22.31, 18.39, 18.01. **HRMS-EI^{+}** (*m/z*): calc for $C_{25}H_{29}BrClNO_2$ $[M]^{+}$ 489.1070, found 489.1075.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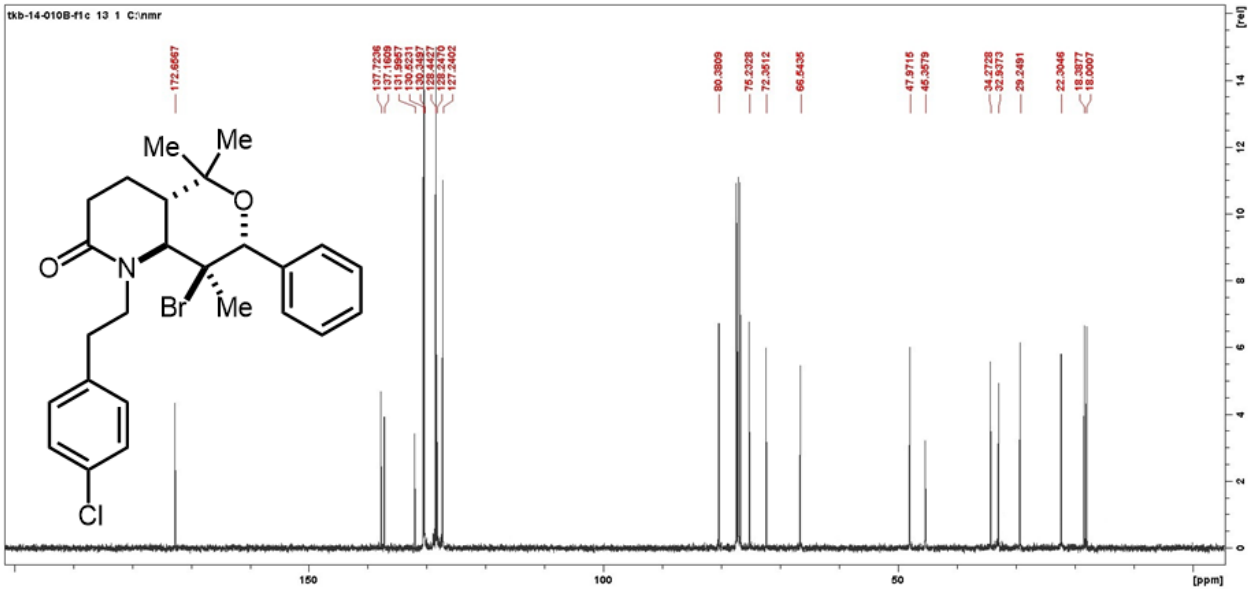
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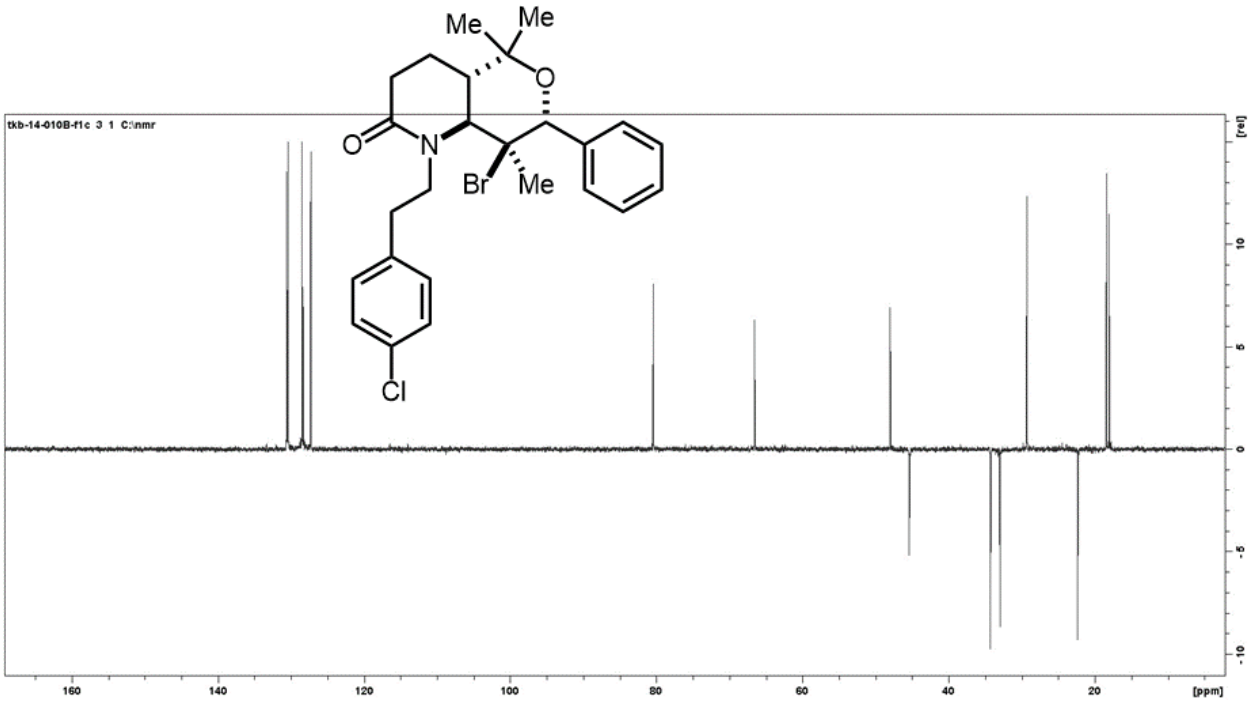
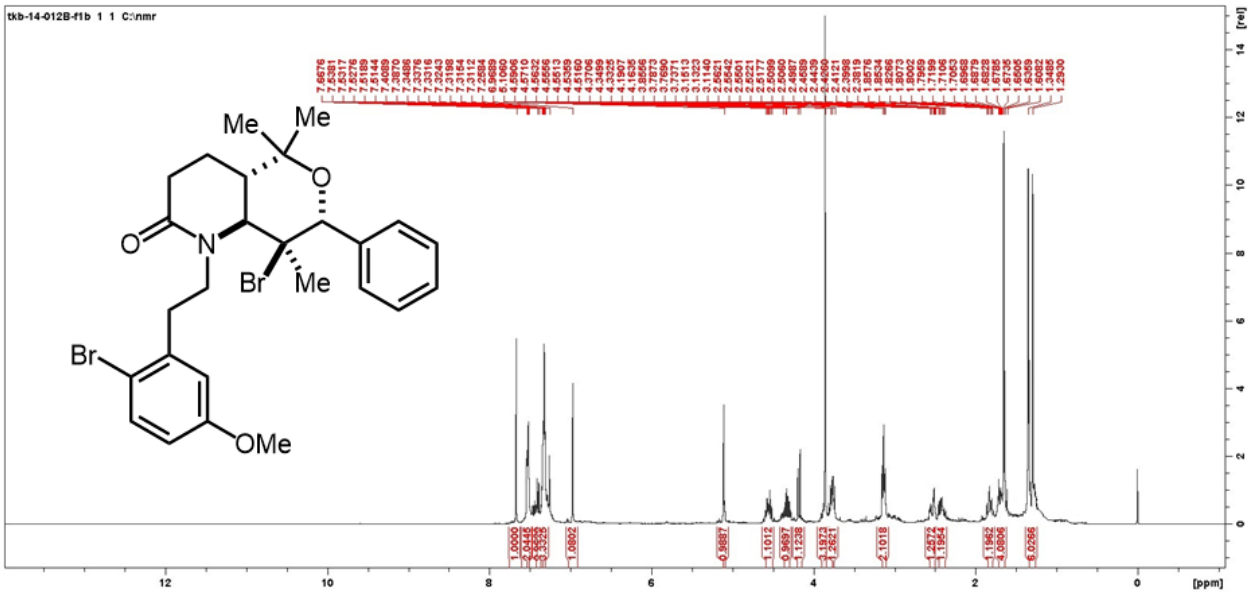


Compound 5e

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 497.5 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.67 (s, 1H), 7.54 – 7.51 (m, 2H), 7.40 – 7.25 (m, 4H), 6.97 (s, 1H), 5.10 (d, J = 5.0 Hz, 1H), 4.64 – 4.45 (m, 1H), 4.43 – 4.22 (m, 1H), 4.16 (d, J = 10.9 Hz, 1H), 3.86 (s, 3H), 3.84 – 3.71 (m, 1H), 3.24 – 3.10 (m, 2H), 2.56 – 2.38 (m, 2H), 1.86 – 1.79 (m, 1H), 1.71 – 1.60 (m, 4H), 1.35 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 172.91, 155.22, 139.79, 137.23, 135.97, 133.21, 130.33, 128.26, 127.25, 127.21, 115.17, 114.27, 110.08, 80.42, 75.30, 72.21, 66.42, 56.47, 48.06, 43.80, 34.47, 33.57, 29.26, 22.14, 18.49, 17.94. **HRMS-EI^{+}** (*m/z*): calc for $C_{26}H_{31}Br_2NO_3$ $[M]^{+}$ 563.0671, found 563.0677.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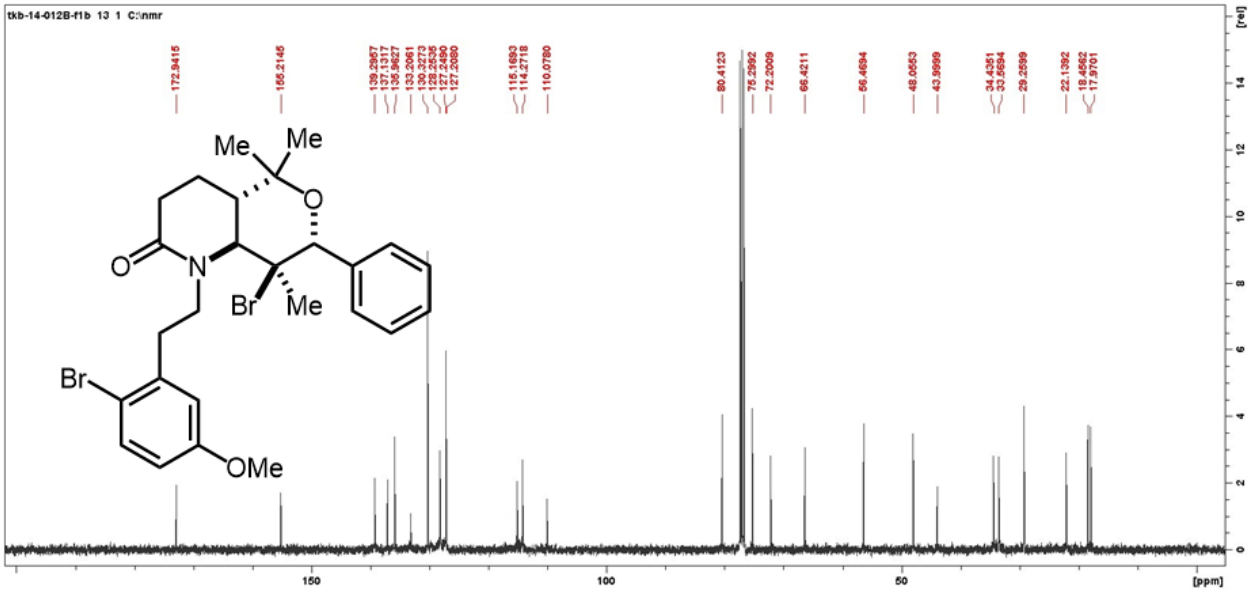
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133.2061
130.3273
128.2536
127.2490
127.2060
115.1693
114.2718
110.0780
80.4123
76.2992
72.2009
66.4211
56.4694
48.0553
43.9999
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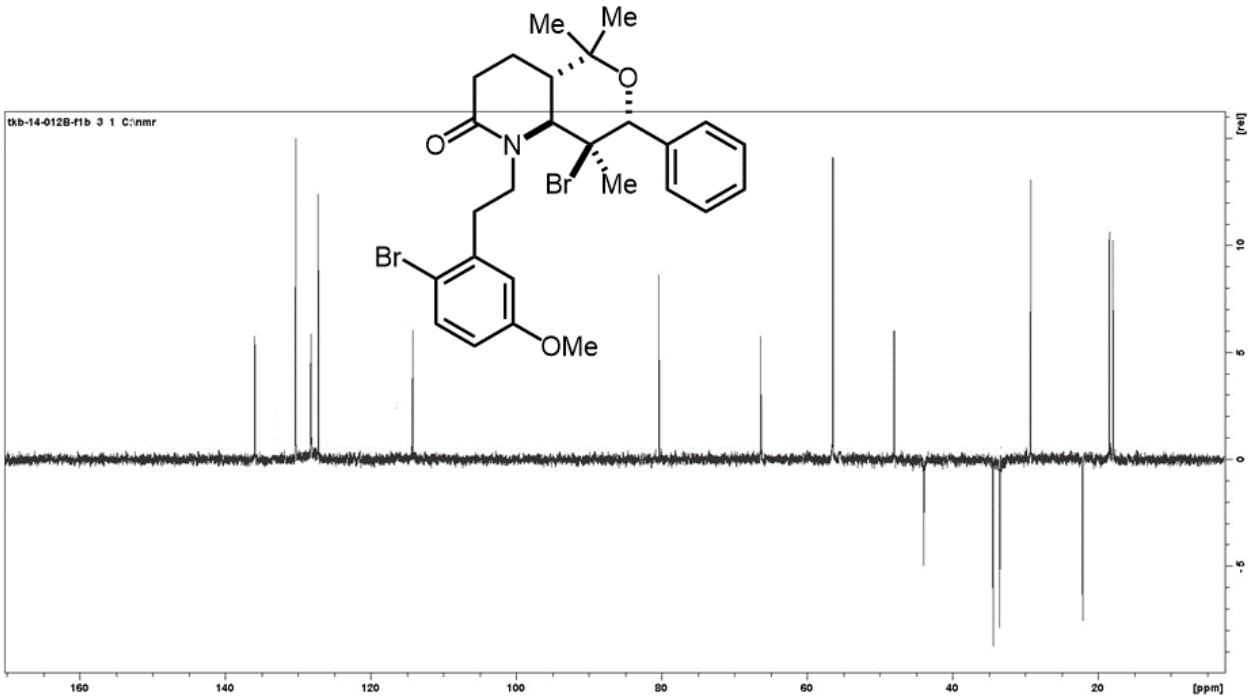
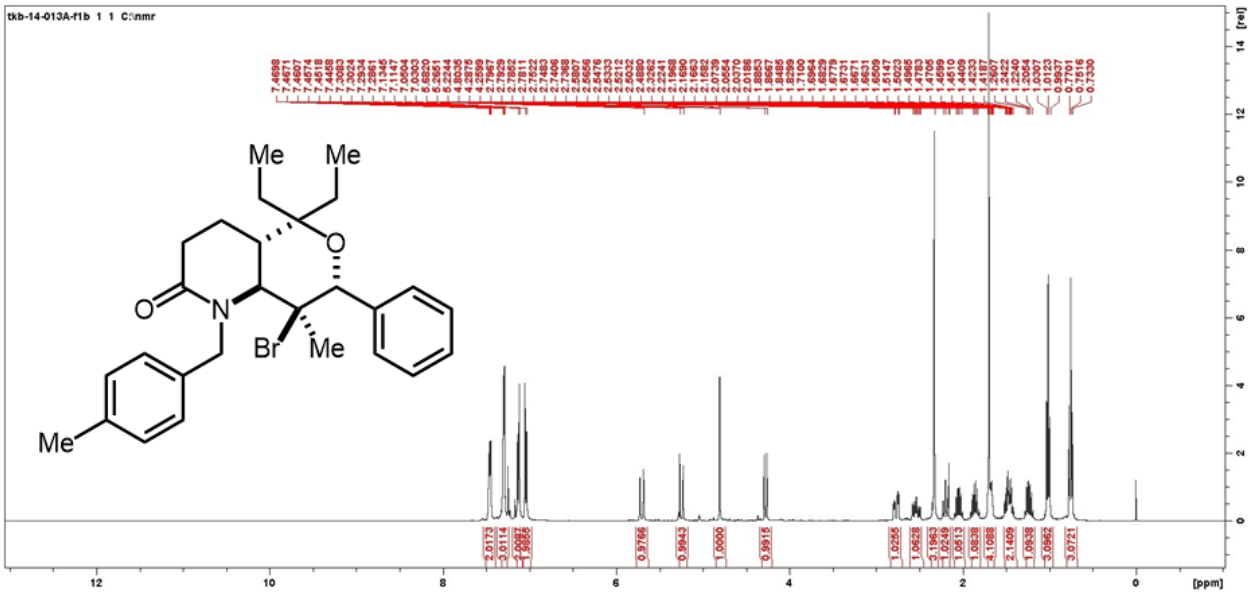


Compound 5f

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 440.9 mg, 91%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.50 – 7.41 (m, 2H), 7.35 – 7.20 (m, 3H), 7.12 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 5.68 (d, J = 16.3 Hz, 1H), 5.23 (d, J = 16.3 Hz, 1H), 4.80 (s, 1H), 4.27 (d, J = 11.1 Hz, 1H), 2.77 (ddd, J = 17.9, 4.8, 1.9 Hz, 1H), 2.53 (ddd, J = 18.4, 13.3, 6.2 Hz, 1H), 2.25 – 2.14 (m, 1H), 2.05 (dq, J = 14.8, 7.4 Hz, 1H), 1.86 (dq, J = 14.8, 7.4 Hz, 1H), 1.70 (s, 3H), 1.74 – 1.61 (m, 1H), 1.54 – 1.38 (m, 2H), 1.23 (dq, J = 14.8, 7.5 Hz, 1H), 1.01 (t, J = 7.4 Hz, 3H), 0.75 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 173.09, 137.50, 135.99, 134.48, 130.22, 129.10, 128.08, 127.13, 127.05, 79.74, 71.18, 65.30, 45.96, 42.51, 34.56, 28.30, 22.80, 21.11, 21.10, 18.58, 7.03, 6.21. **HRMS-EI^{+}** (*m/z*): calc for $C_{27}H_{34}BrNO_2$ $[M]^{+}$ 483.1773, found 483.1777.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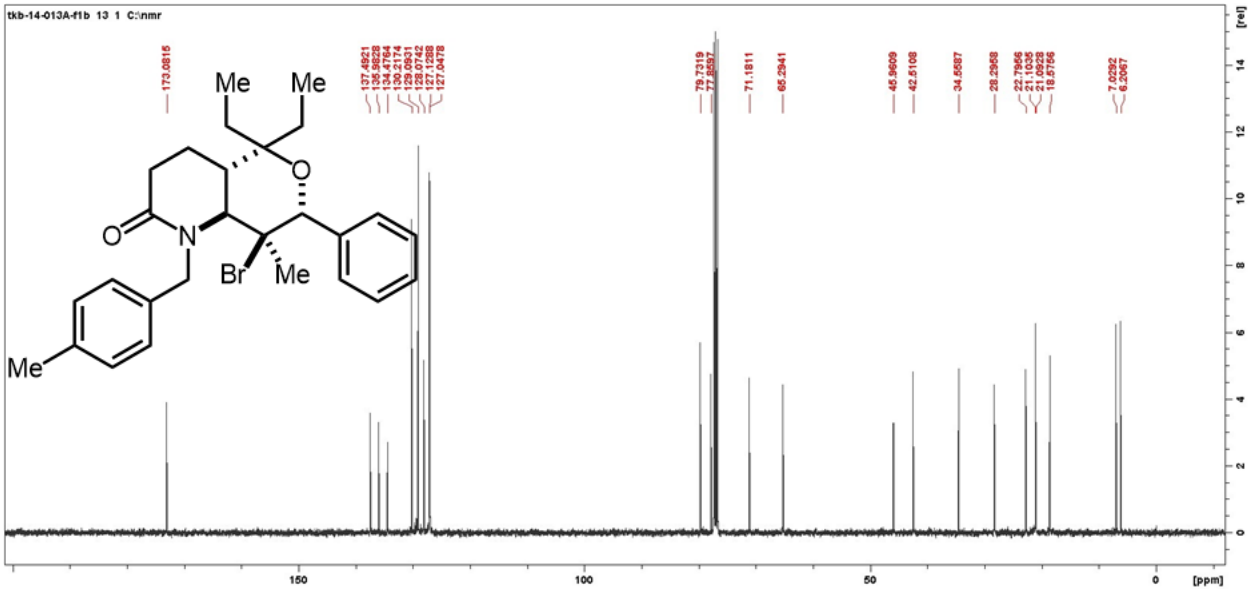
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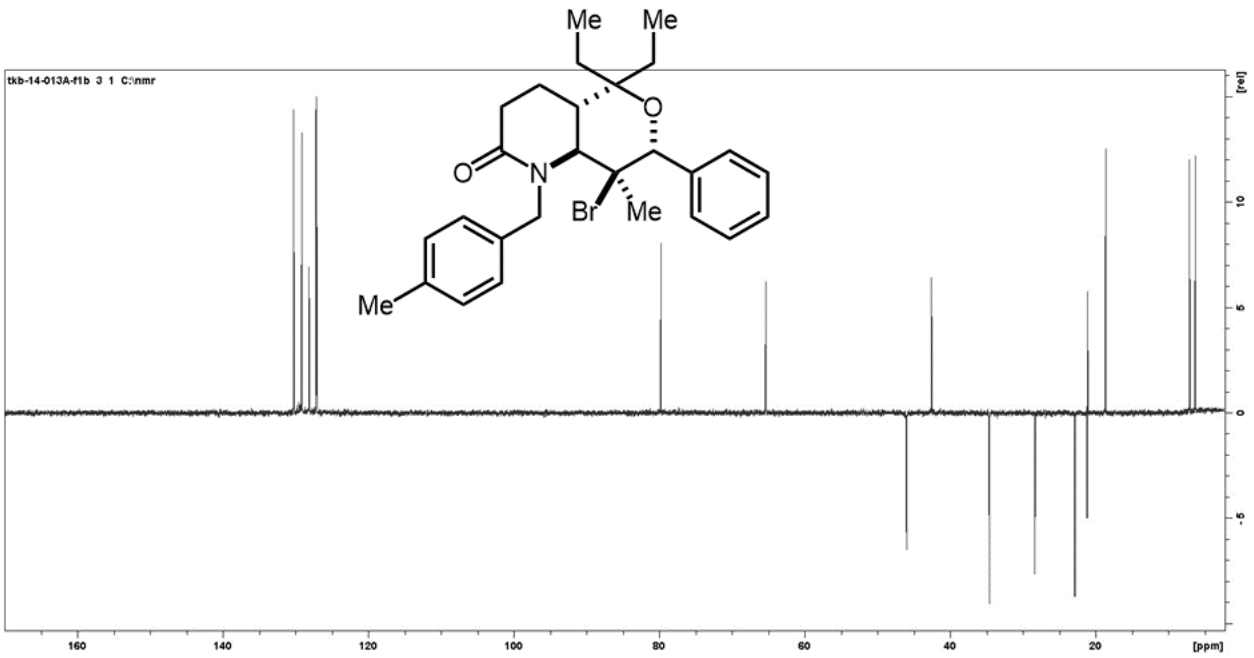
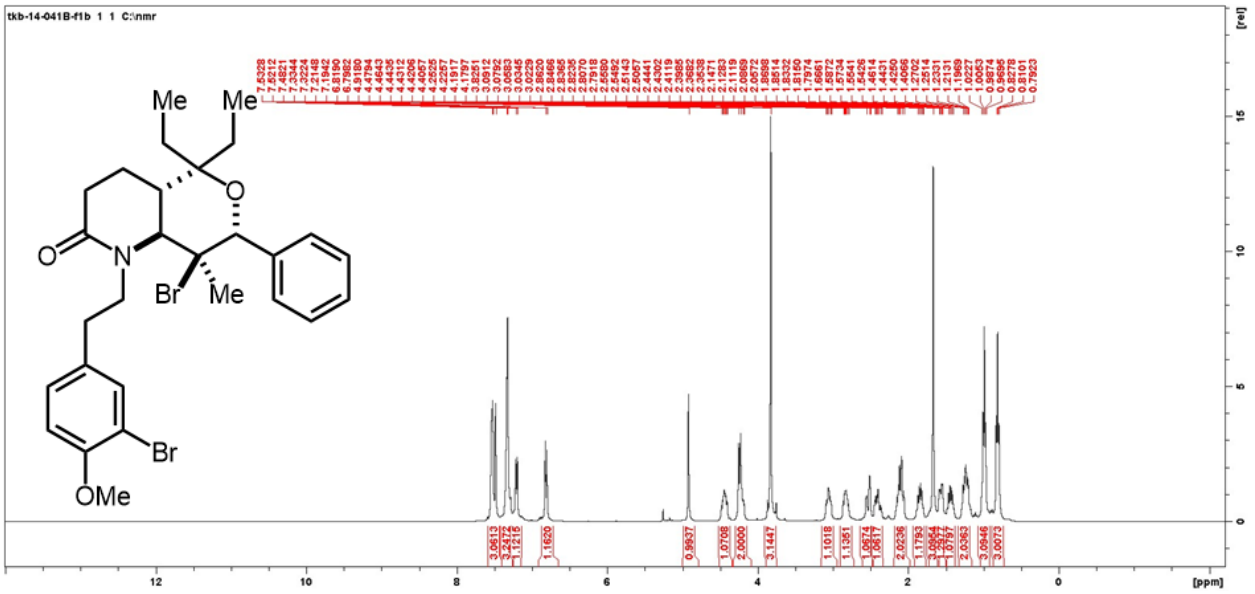


Compound 5g

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 504.4 mg, 85%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.53 – 7.48 (m, 3H), 7.33 (d, J = 5.6 Hz, 3H), 7.20 (dd, J = 8.4, 2.1 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.92 (s, 1H), 4.44 (ddd, J = 15.5, 10.5, 5.9 Hz, 1H), 4.22 (dd, J = 12.4, 7.6 Hz, 2H), 3.83 (s, 3H), 3.06 (ddd, J = 14.7, 10.3, 5.0 Hz, 1H), 2.83 (ddd, J = 12.5, 9.8, 5.9 Hz, 1H), 2.53 (dd, J = 17.8, 4.7 Hz, 1H), 2.40 (ddd, J = 18.1, 13.0, 6.0 Hz, 1H), 2.11 (dt, J = 22.0, 9.7 Hz, 2H), 1.84 (dq, J = 14.7, 7.3 Hz, 1H), 1.56 (dd, J = 13.2, 5.8 Hz, 1H), 1.44 (dp, J = 14.7, 8.0 Hz, 1H), 1.22 (tq, J = 13.1, 6.2 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 172.67, 154.37, 137.47, 133.85, 132.94, 130.26, 129.21, 128.17, 127.20, 112.01, 111.30, 79.77, 72.24, 65.94, 56.27, 45.38, 42.33, 34.44, 32.35, 28.18, 22.77, 21.20, 18.49, 7.05, 6.37. **HRMS-EI^{+}** (*m/z*): calc for $C_{28}H_{35}Br_2NO_3$ $[M]^{+}$ 591.0984, found 591.0988.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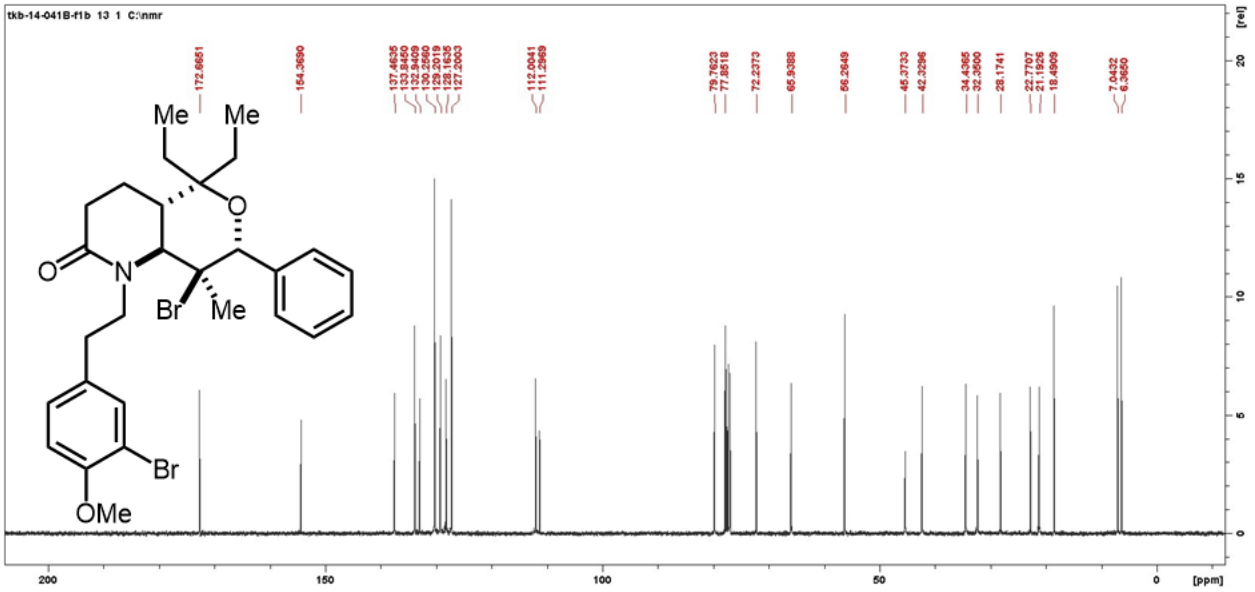
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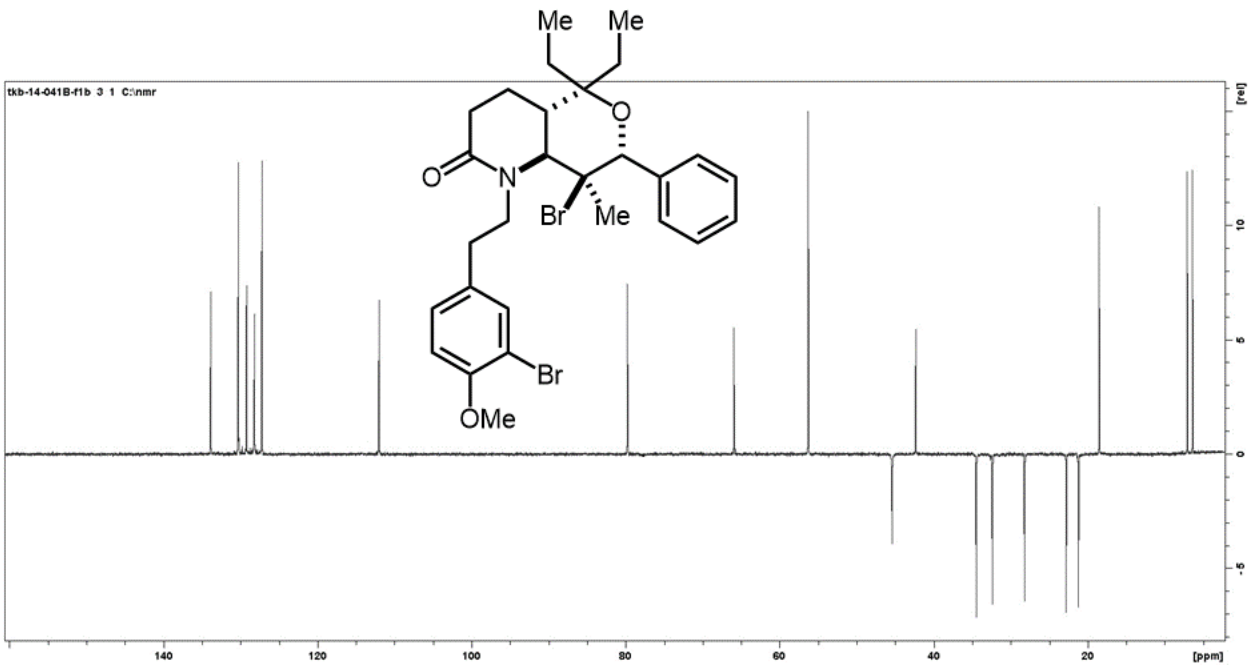
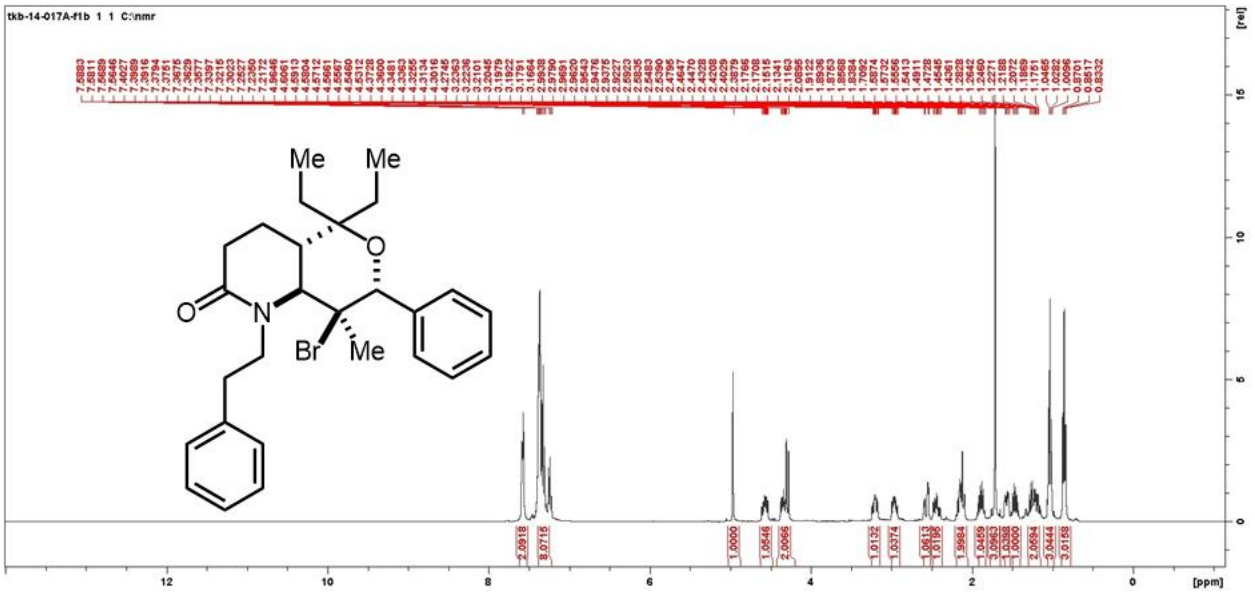


Compound 5h

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 75:25). Amorphous solid. Yield = 426.3 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.59 – 7.56 (m, 2H), 7.39 – 7.22 (m, 8H), 4.96 (s, 1H), 4.57 (ddd, J = 13.8, 10.2, 5.9 Hz, 1H), 4.40 – 4.25 (m, 2H), 3.20 (ddd, J = 12.6, 10.2, 5.1 Hz, 1H), 2.96 (ddd, J = 12.7, 9.8, 5.9 Hz, 1H), 2.57 (ddd, J = 17.8, 5.0, 1.8 Hz, 1H), 2.43 (ddd, J = 18.0, 13.0, 6.0 Hz, 1H), 2.21 – 2.06 (m, 2H), 1.88 (dq, J = 14.7, 7.3 Hz, 1H), 1.70 (s, 3H), 1.62 – 1.40 (m, 2H), 1.37 – 1.10 (m, 2H), 1.04 (q, J = 6.5 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 172.77, 139.26, 137.55, 130.31, 129.30, 128.38, 128.19, 127.24, 126.29, 79.80, 72.12, 65.83, 45.36, 42.31, 34.56, 33.57, 28.21, 22.79, 22.74, 21.18, 18.54, 7.08, 6.41. **HRMS-EI^{+}** (*m/z*): calc for $C_{27}H_{34}BrNO_2$ $[M]^{+}$ 483.1773, found 483.1777.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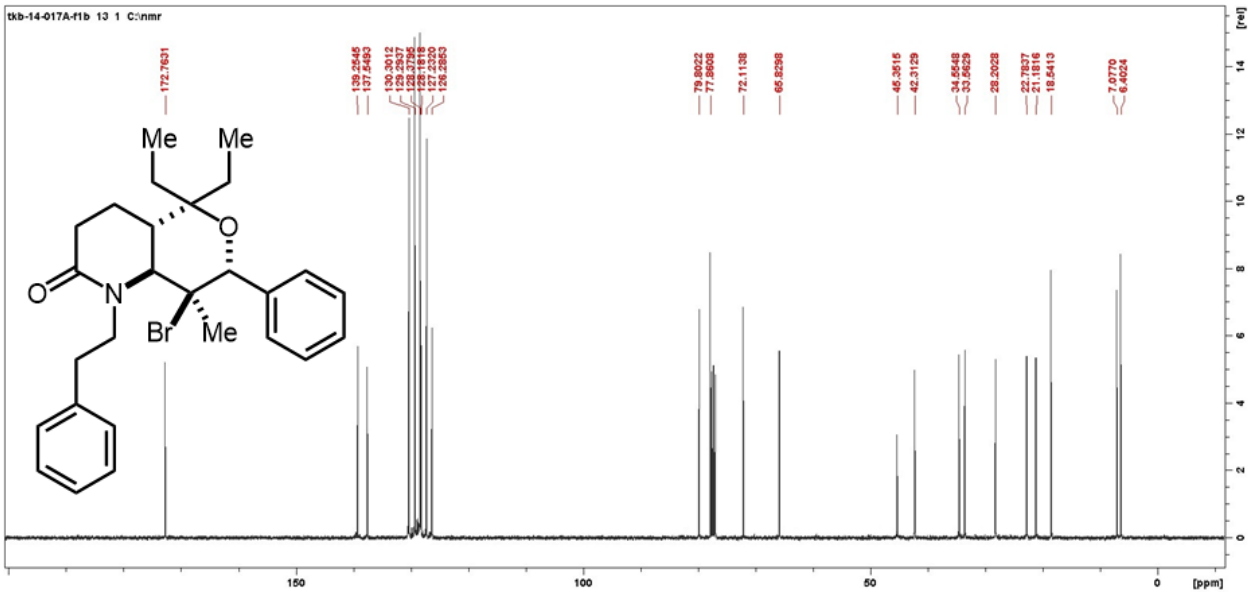
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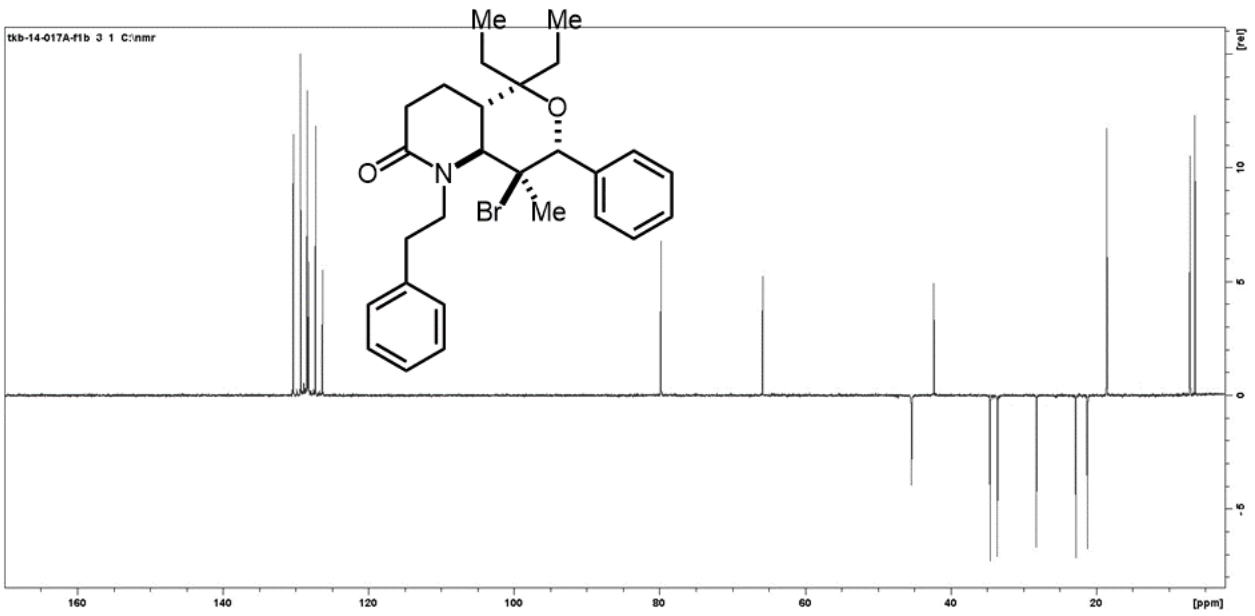
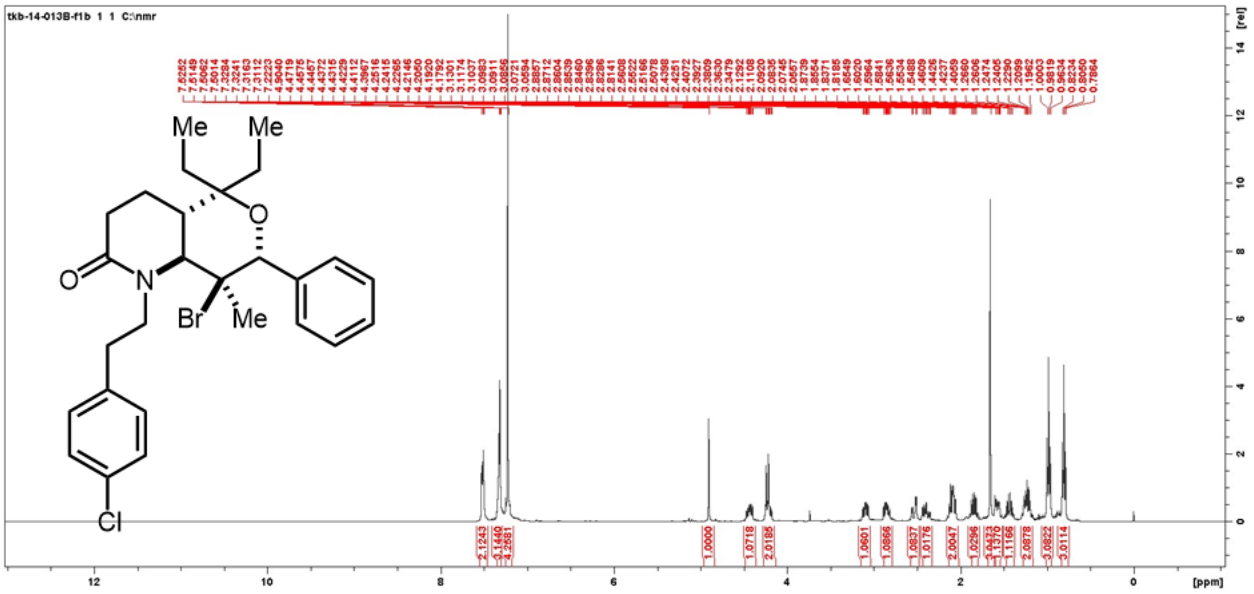


Compound 5i

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 467.0 mg, 90%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dq, *J* = 5.9, 3.4 Hz, 2H), 7.32 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.31 – 7.16 (m, 4H), 4.90 (s, 1H), 4.43 (ddd, *J* = 13.8, 10.5, 5.8 Hz, 1H), 4.27 – 4.16 (m, 2H), 3.09 (ddd, *J* = 12.8, 10.5, 5.1 Hz, 1H), 2.85 (ddd, *J* = 12.8, 10.1, 5.8 Hz, 1H), 2.53 (ddd, *J* = 17.8, 5.1, 1.8 Hz, 1H), 2.39 (ddd, *J* = 18.0, 13.1, 5.9 Hz, 1H), 2.17 – 2.02 (m, 2H), 1.85 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.62 – 1.51 (m, 1H), 1.43 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.32 – 1.14 (m, 2H), 1.13 – 0.92 (m, 3H), 0.92 – 0.75 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.69, 137.77, 137.43, 131.99, 130.54, 130.25, 128.44, 128.18, 127.20, 79.80, 77.86, 72.19, 66.08, 45.33, 42.40, 34.44, 32.97, 28.21, 22.79, 21.30, 18.47, 7.00, 6.33. **HRMS-EI^{+}** (*m/z*): calc for $C_{27}H_{33}BrClNO_2$ $[M]^{+}$ 517.1383, found 517.1387.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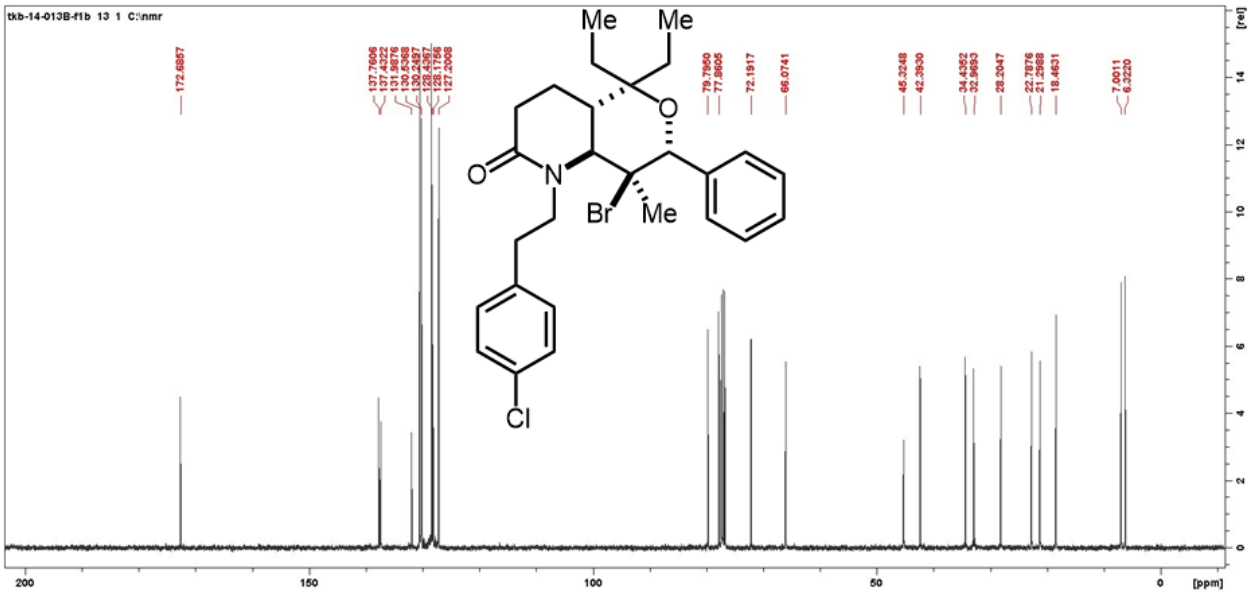
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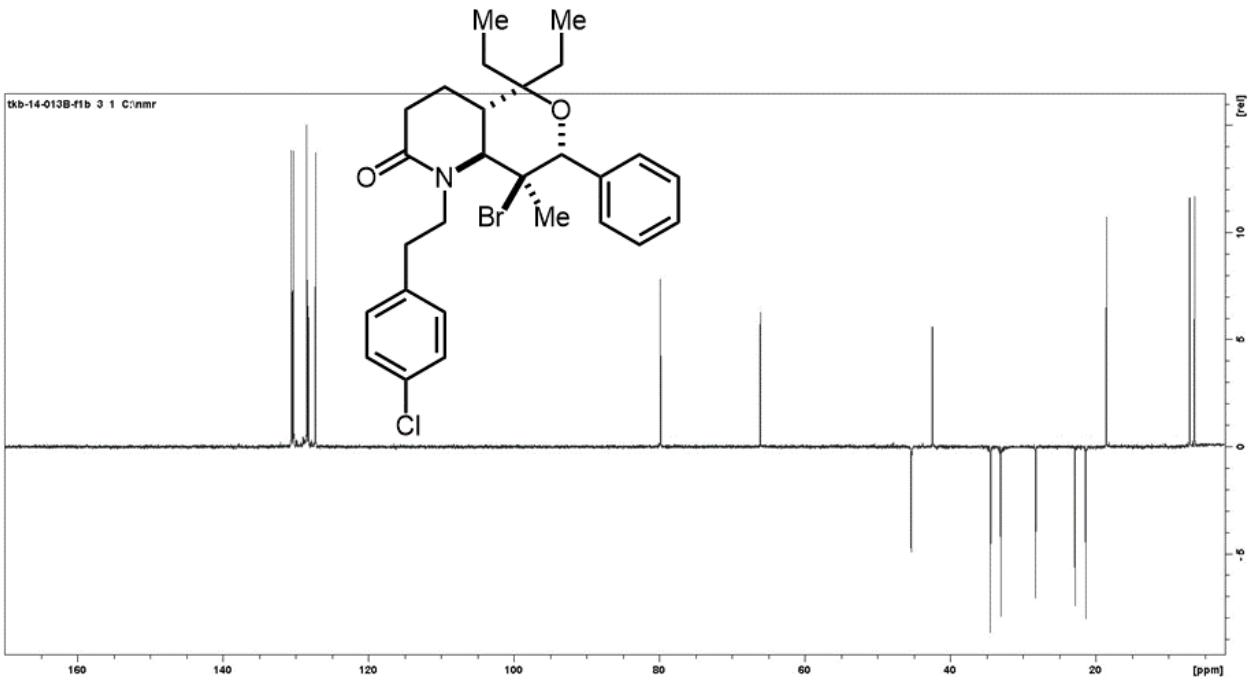
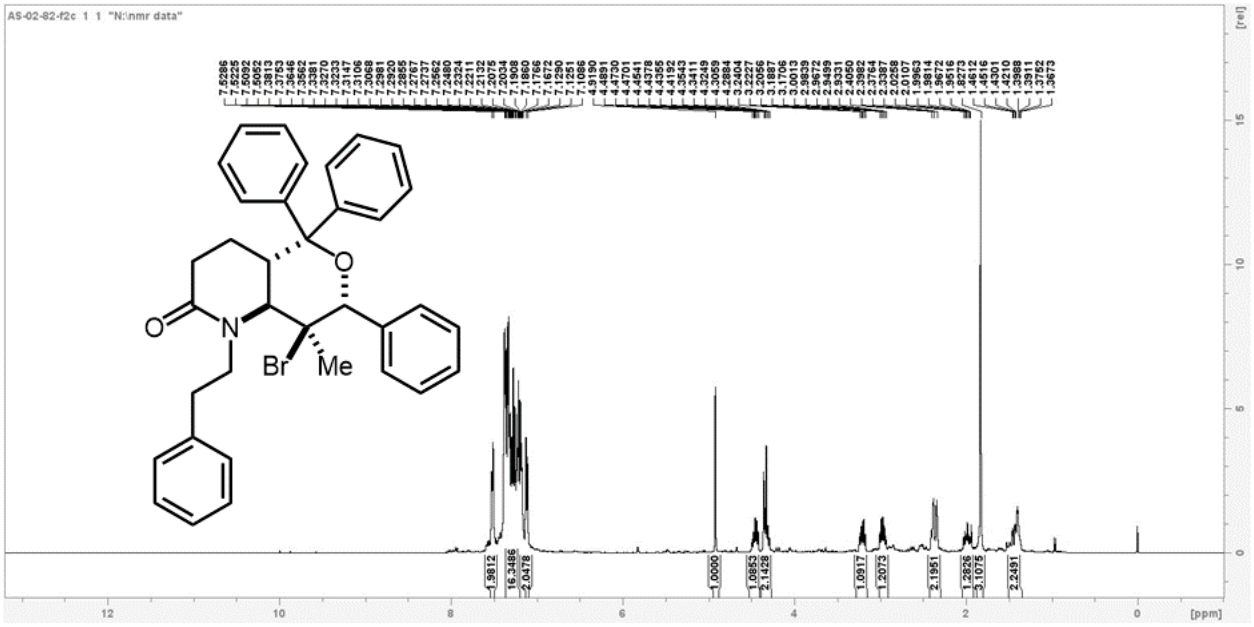
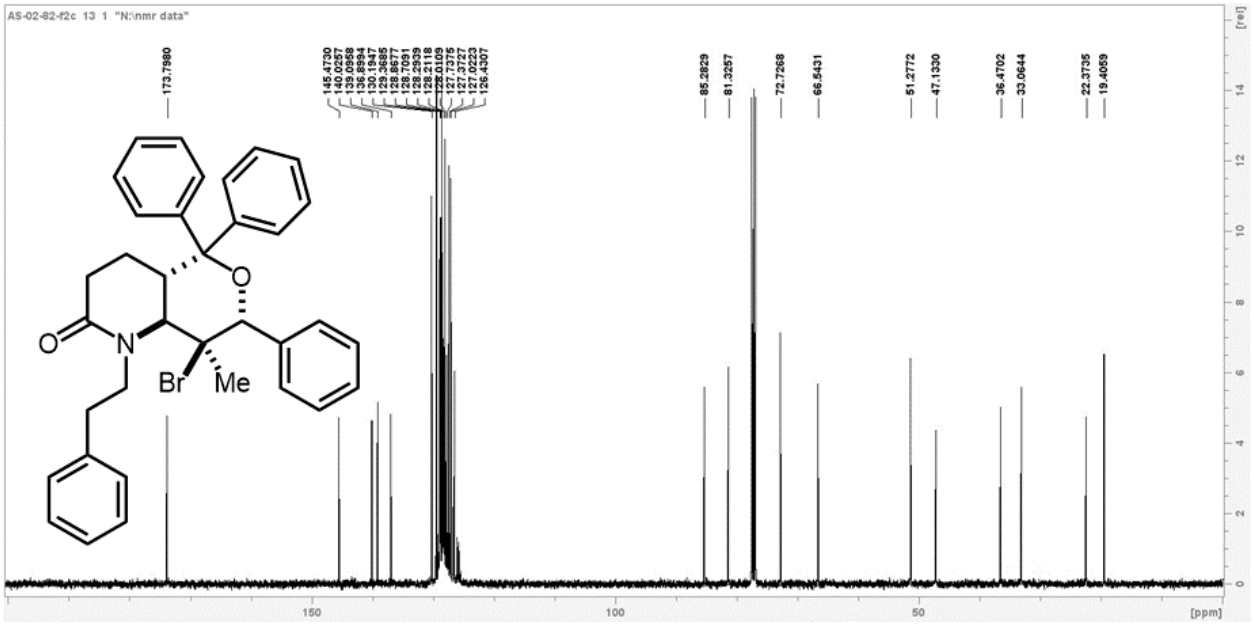


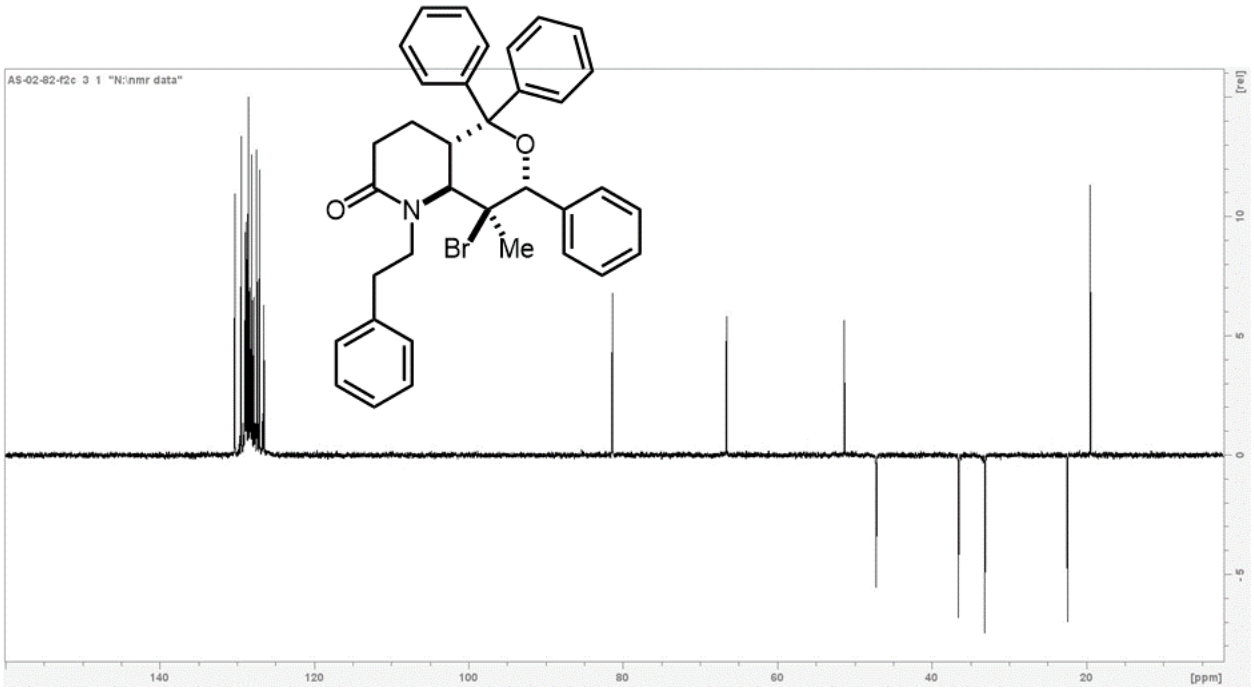
Compound 5j

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 464.5 mg, 80%, 95:5 dr (*anti:syn*).

HRMS-EI$^+$ (*m/z*): calc for $C_{35}H_{34}BrNO_2$ $[M]^+$ 579.1773, found 579.1778.



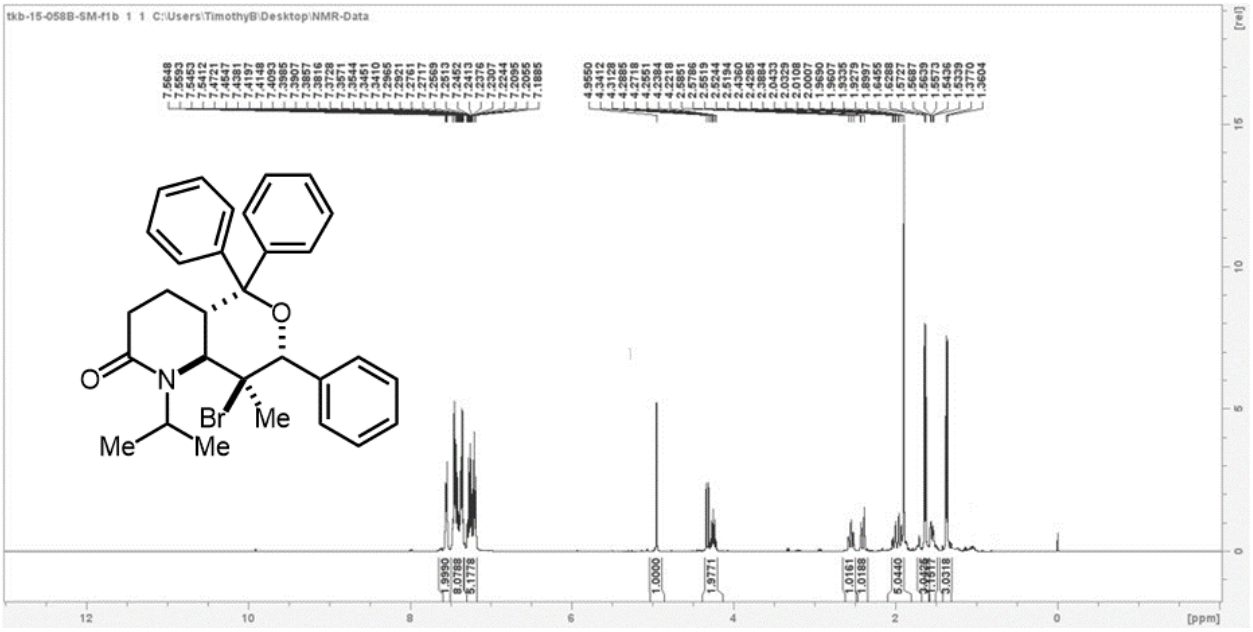


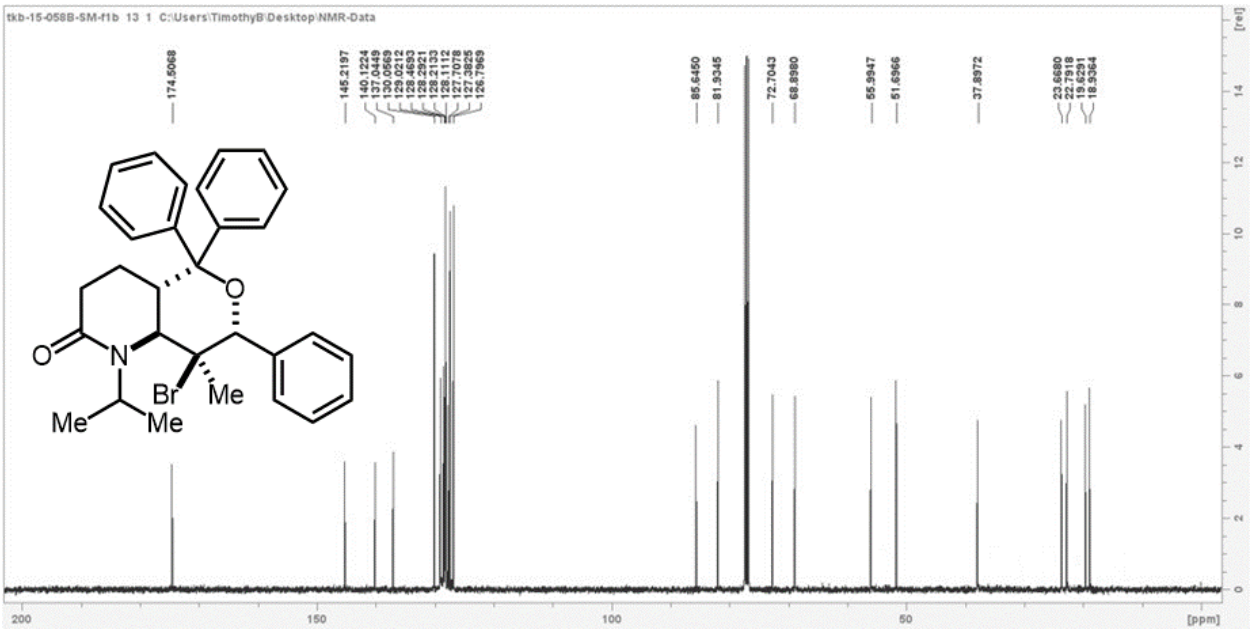


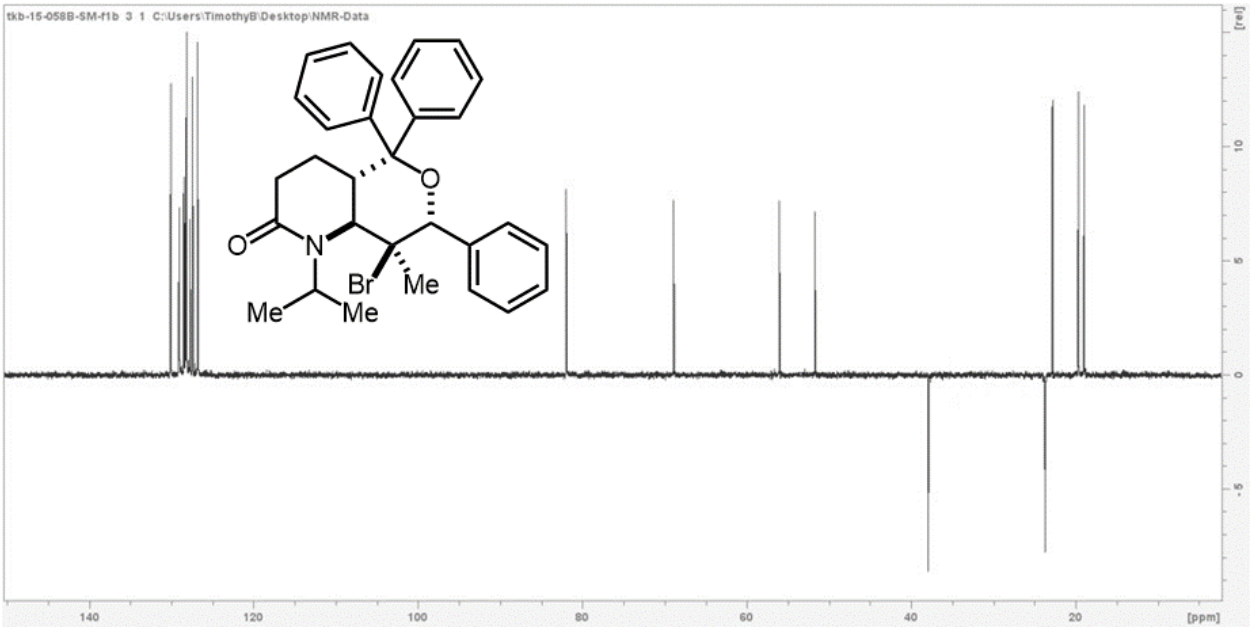
Compound 5k

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 60:40). Amorphous solid. Yield = 414.8 mg, 80%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.50 – 7.31 (m, 8H), 7.31 – 7.16 (m, 5H), 4.96 (s, 1H), 4.33 (d, J = 11.4 Hz, 1H), 4.25 (h, J = 6.7 Hz, 1H), 2.55 (ddd, J = 13.4, 11.3, 2.7 Hz, 1H), 2.41 (dt, J = 16.8, 2.9 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.90 (s, 3H), 1.64 (d,

J = 6.7 Hz, 3H), 1.61 – 1.48 (m, 1H), 1.37 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.51, 145.22, 140.13, 137.05, 130.06, 129.02, 128.47, 128.30, 128.22, 128.11, 127.71, 127.39, 126.80, 85.65, 81.94, 72.71, 68.90, 56.00, 51.70, 37.90, 23.67, 22.80, 19.63, 18.94. **HRMS-EI$^+$** (*m/z*): calc for $C_{35}H_{33}Br_2NO_2$ $[M]^+$ 657.0878, found 657.0872.







Compound 5l

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 540.4 mg, 80%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 2H), 7.45 – 7.14 (m, 15H), 6.90 (d, J = 8.4 Hz, 1H), 5.70 (d, J = 15.4 Hz, 1H), 5.20 (d, J = 15.4 Hz, 1H), 4.87 (s, 1H), 4.51 (d, J = 11.5 Hz, 1H), 3.97 (s, 3H), 2.71 – 2.54 (m, 2H), 2.17 (ddd, J = 17.4, 12.9, 4.8 Hz, 1H), 2.01 – 1.84 (m, 1H), 1.91 (s, 3H), 1.59 – 1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.21, 145.23, 139.69, 136.72, 132.65, 131.44, 130.08, 129.29, 128.81, 128.40, 128.31, 128.10, 128.07, 127.74, 127.36, 126.90, 111.87, 85.48, 81.61, 72.93, 64.17, 56.31, 51.41, 47.01, 36.40, 22.68, 19.62. **HRMS-EI^{+}** (*m/z*): calc for $C_{36}H_{35}Br_2NO_3$ $[M]^+$ 687.0984, found 687.0988.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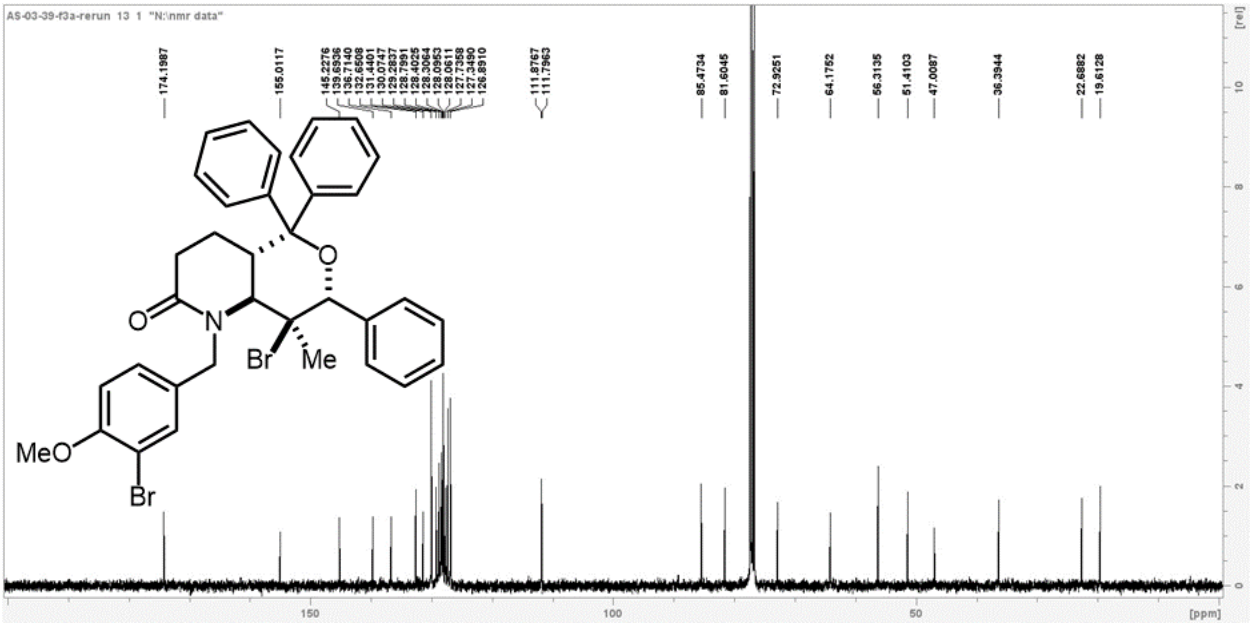
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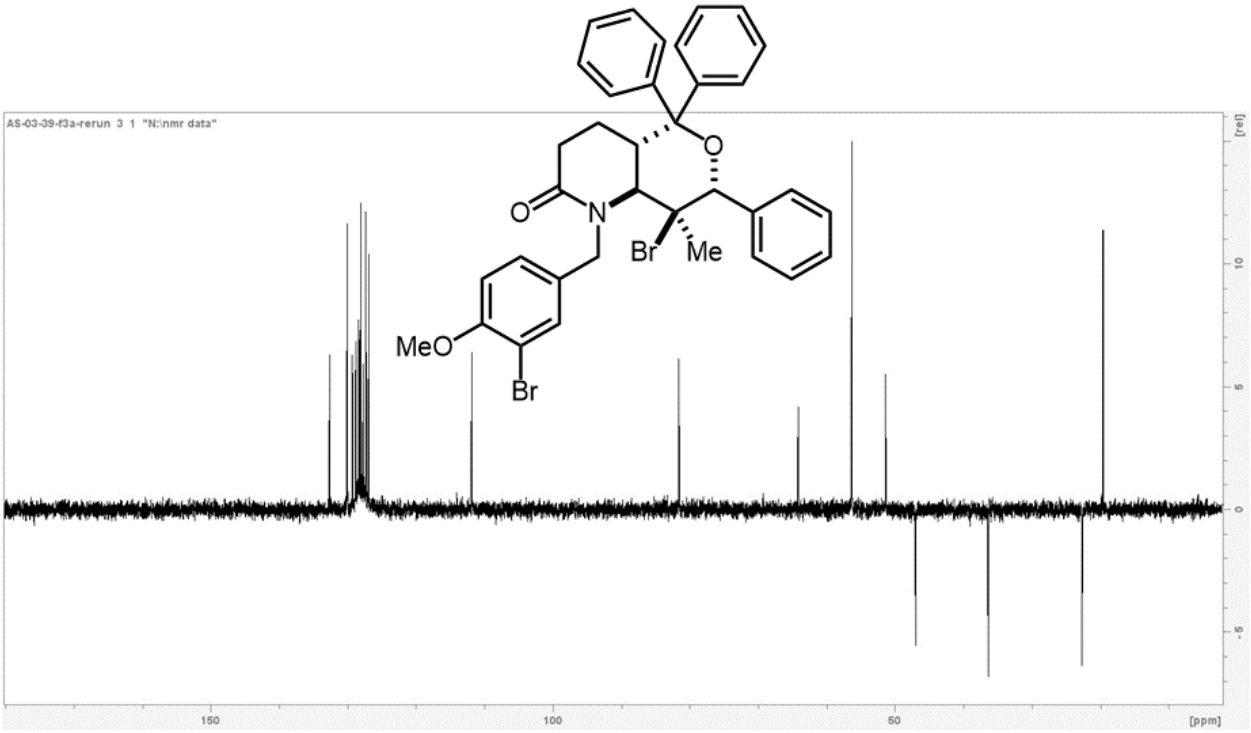
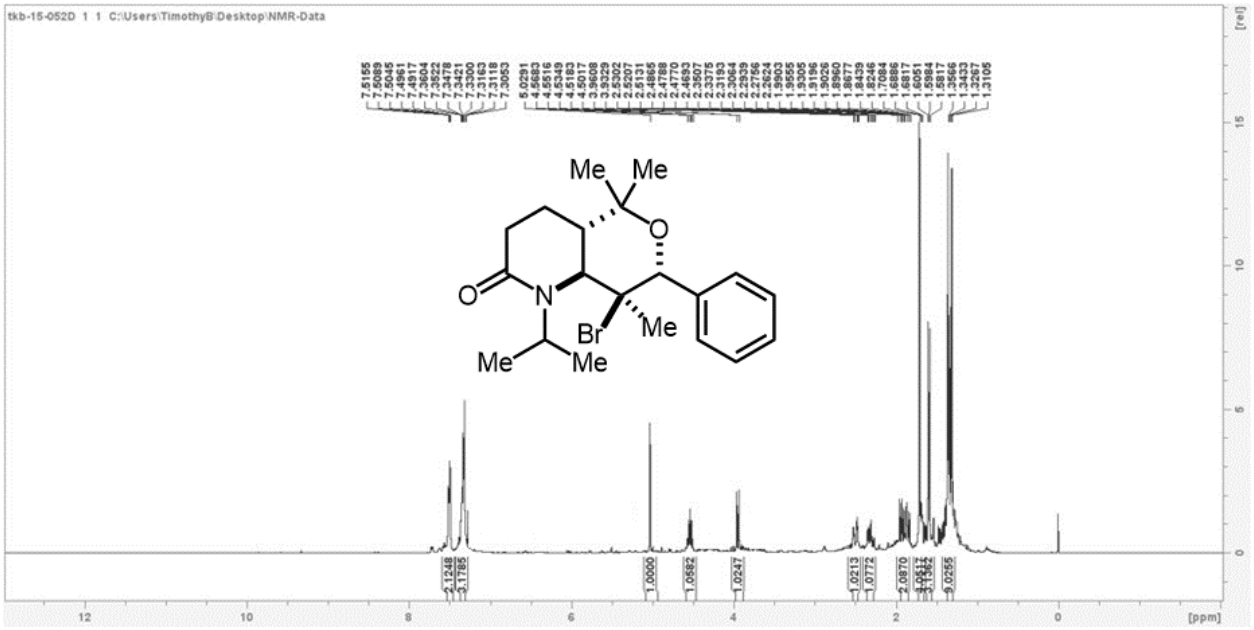


Compound 5m

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 347.0 mg, 88%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 2H), 7.40 – 7.27 (m, 3H), 5.03 (s, 1H), 4.53 (hept, *J* = 6.6 Hz, 1H), 3.95 (d, *J* = 11.1 Hz, 1H), 2.50 (ddd, *J* = 17.5, 4.3, 2.8 Hz, 1H), 2.31 (ddd, *J* = 17.7, 12.7, 5.3 Hz, 1H), 1.93 – 1.65 (m, 2H), 1.60 (dd, *J* = 6.8, 4.5 Hz, 6H), 1.40 – 1.31 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.70, 137.36, 130.19, 128.18, 127.21, 80.90, 75.72, 72.35, 68.57, 53.89, 48.21, 36.44, 29.53, 22.85, 22.03, 19.03, 18.93, 17.67. **HRMS-EI$^+$** (*m/z*): calc for $C_{20}H_{28}BrNO_2$ $[M]^+$ 393.1303, found 393.1306.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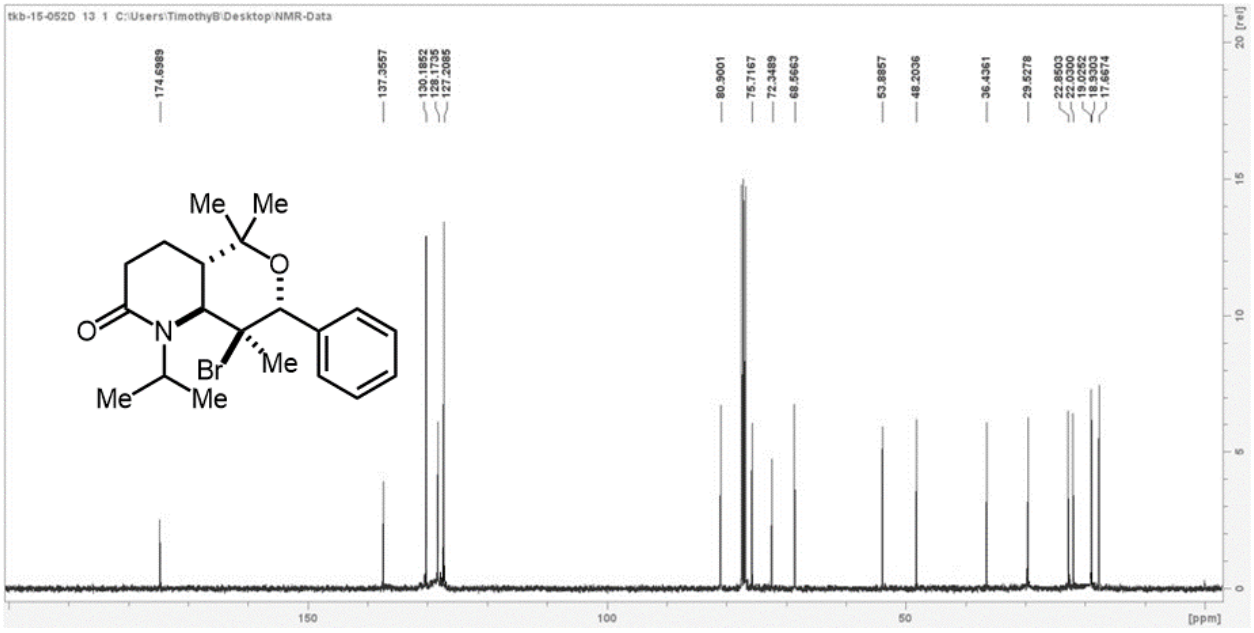
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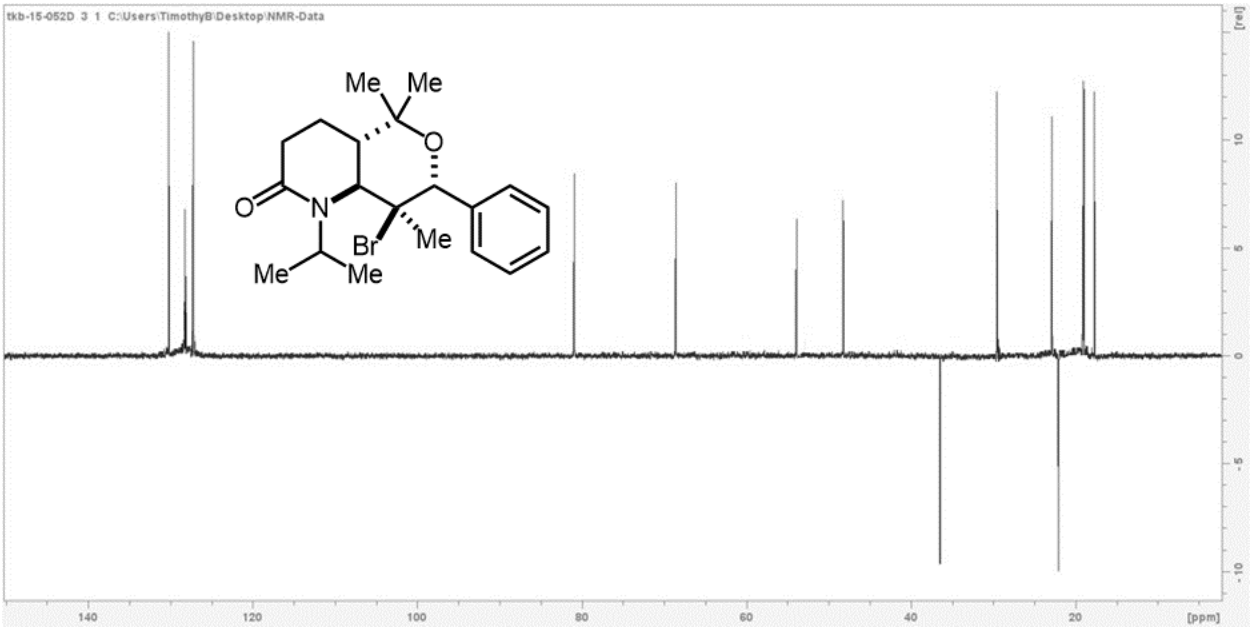
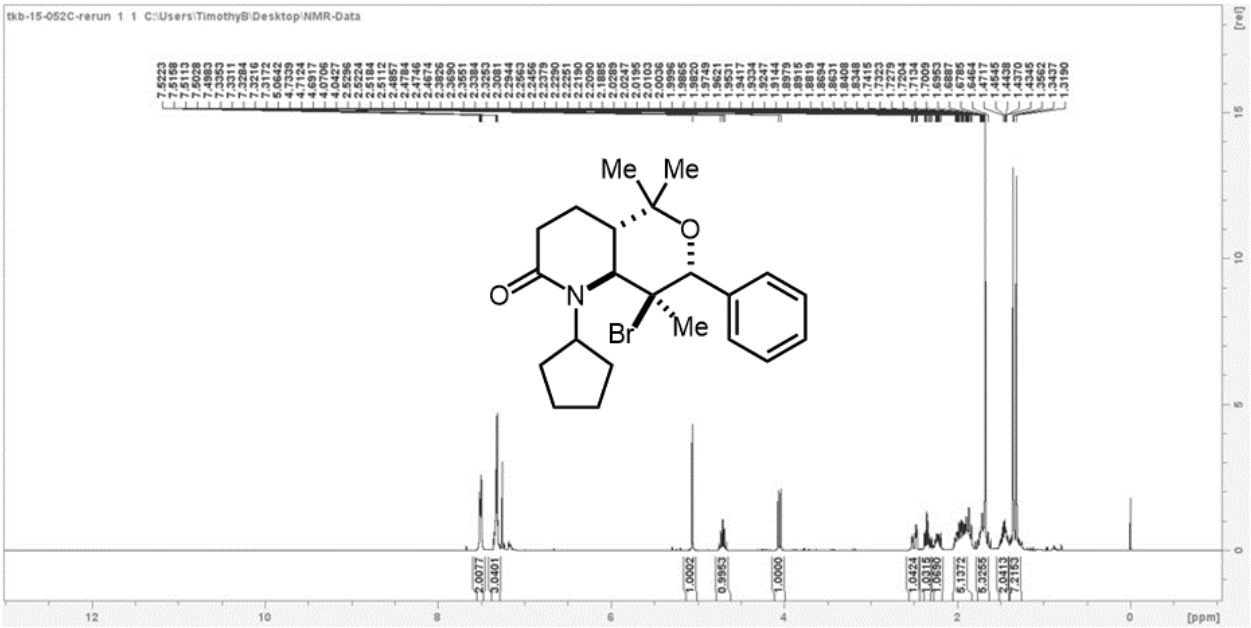


Compound 5n

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 70:30). Amorphous solid. Yield = 357.3 mg, 85%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H), 7.38 – 7.22 (m, 3H), 5.06 (s, 1H), 4.78 – 4.65 (m, 1H), 4.06 (d, J = 11.1 Hz, 1H), 2.50 (ddd, J = 17.6, 4.7, 2.9 Hz, 1H), 2.41 – 2.17 (m, 2H), 2.07 – 1.80 (m, 3H), 1.84 – 1.59 (m, 2H), 1.68 (s, 3H), 1.53 – 1.35 (m, 2H), 1.34 (d, J = 14.9 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.71, 137.34, 130.24, 128.17, 127.22, 80.84, 75.63, 72.68, 68.68, 61.80, 48.33, 36.32, 30.81, 29.48, 28.34, 25.85, 25.42, 21.87, 18.90, 17.71. **HRMS-EI$^+$** (*m/z*): calc for $C_{22}H_{30}BrNO_2$ $[M]^+$ 419.1460, found 419.1466.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N
O
Br
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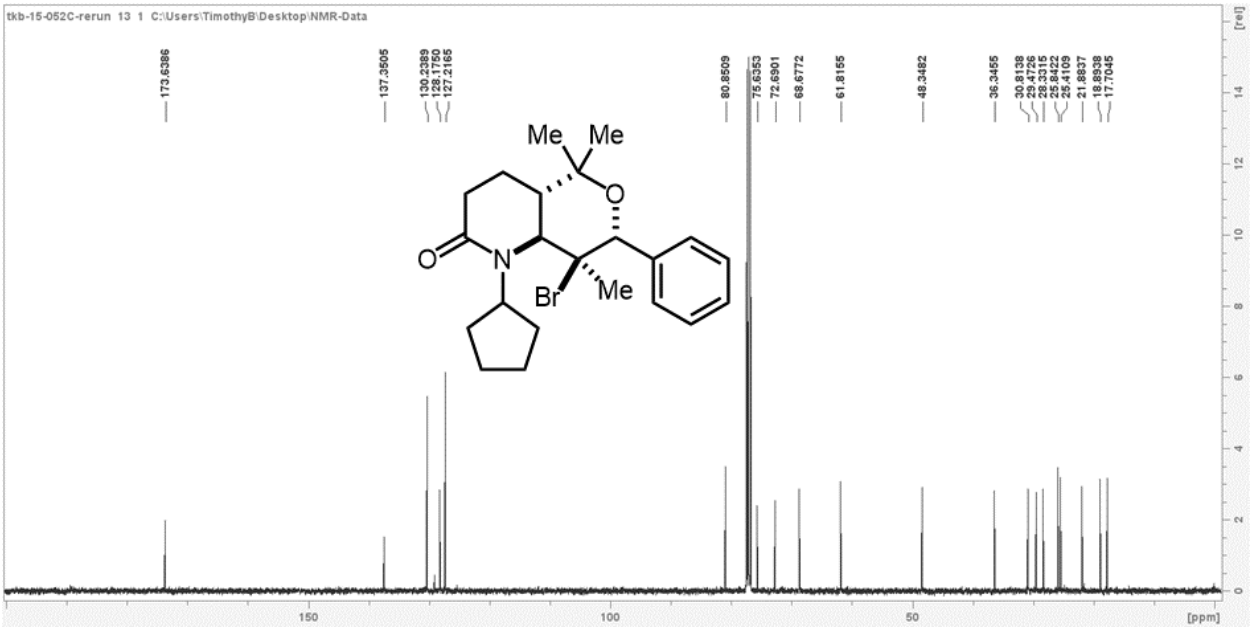
[ppm]


tkb-15-052C-rerun 13 1 C:\Users\TimothyB\Desktop\NMR-Data
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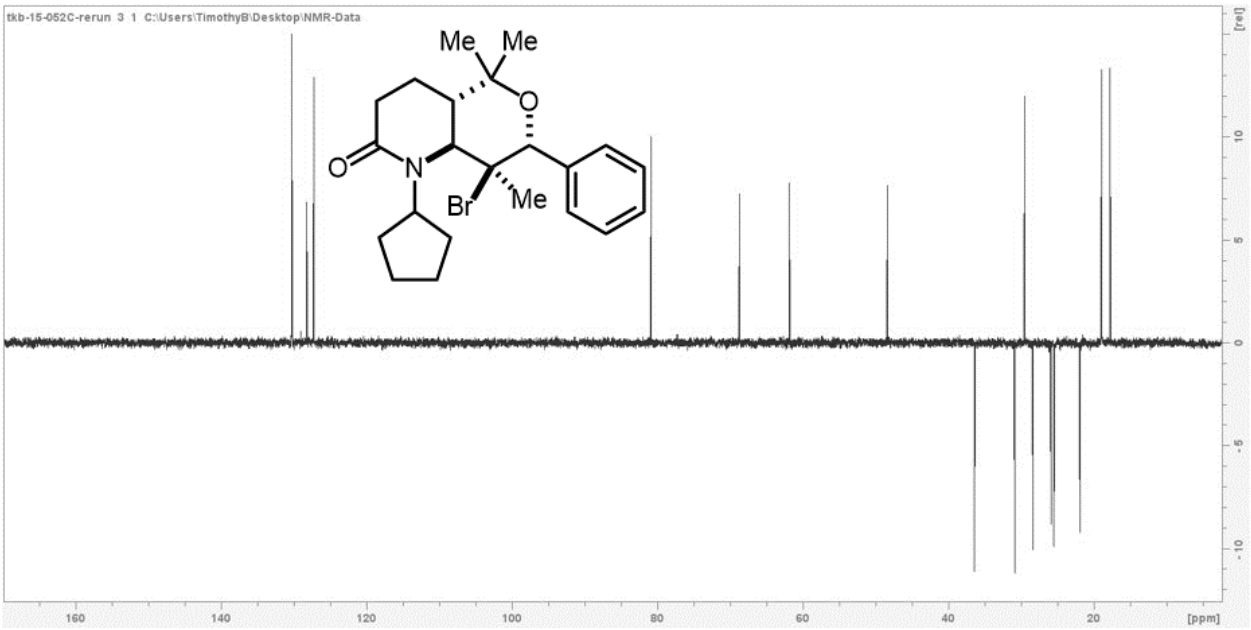
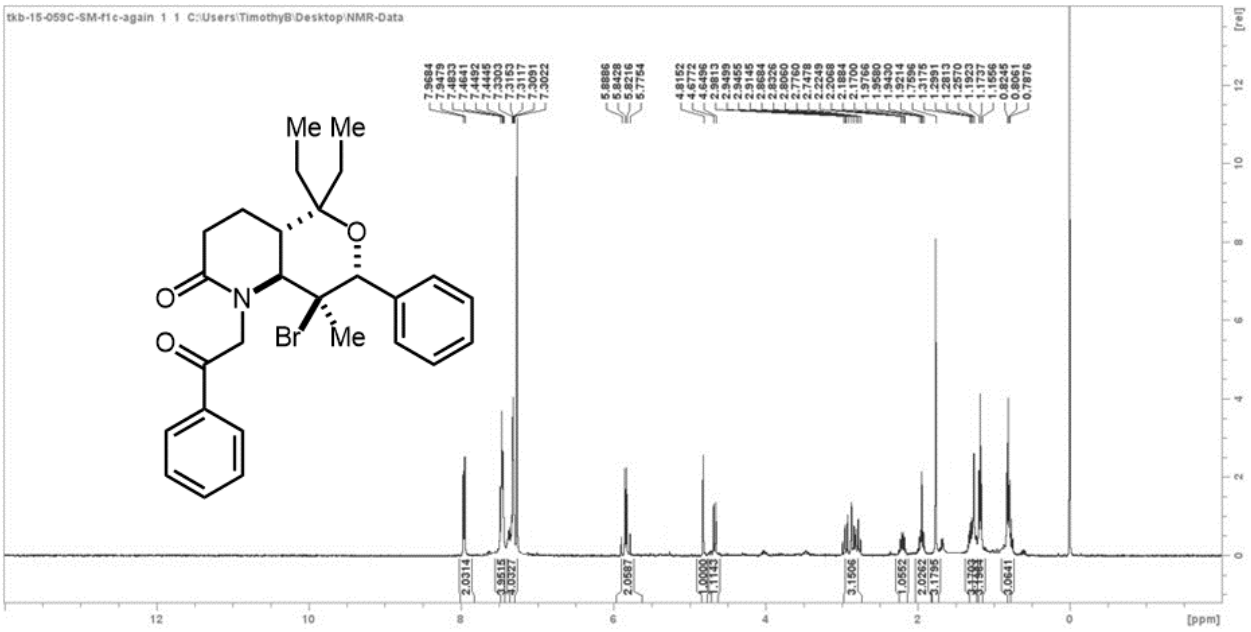
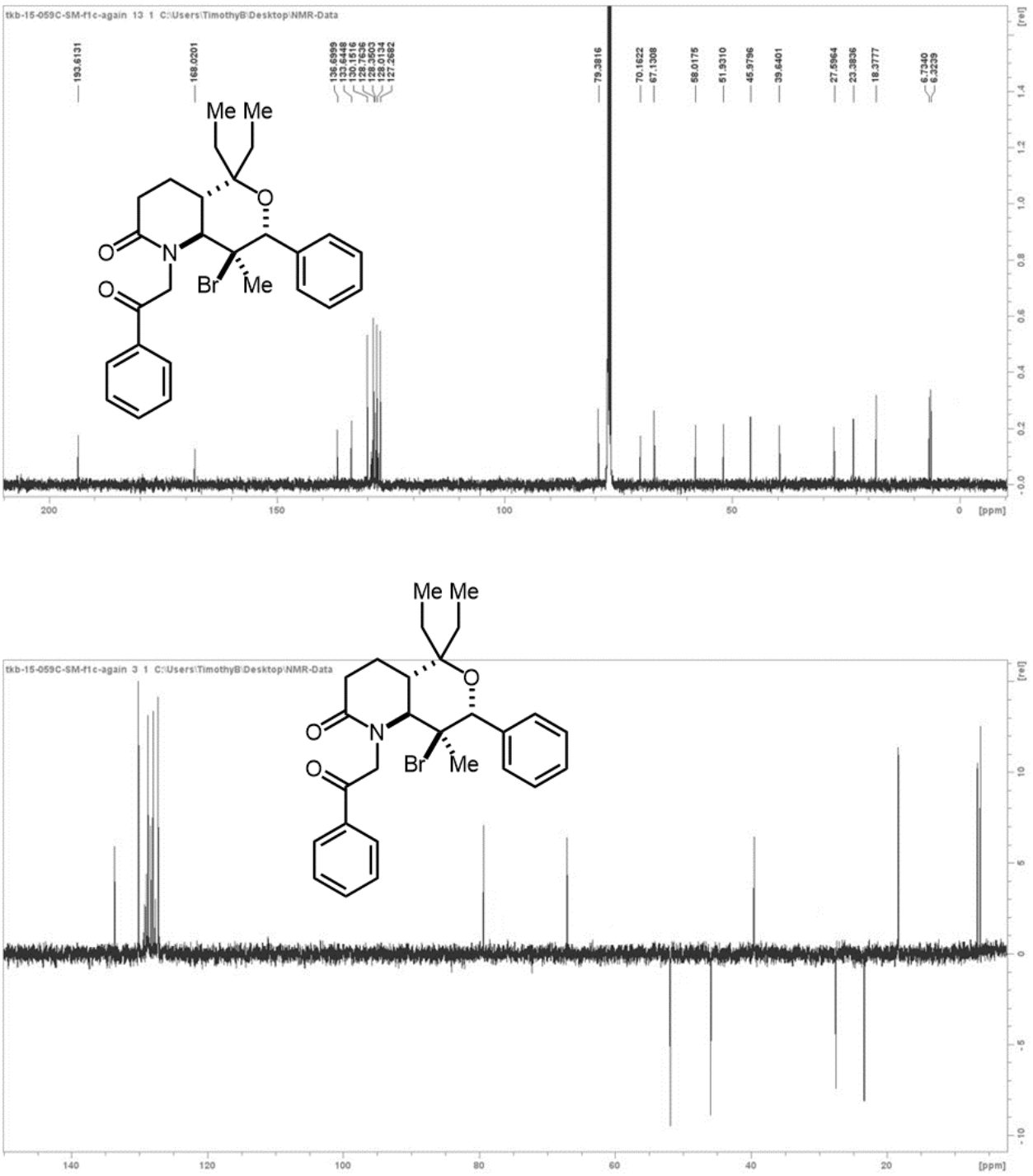
O
Br
Me
[ppm]



Compound 5o

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Yellowish oil. Yield = 357.3 mg, 89%, 95:5 dr (*anti:syn*).

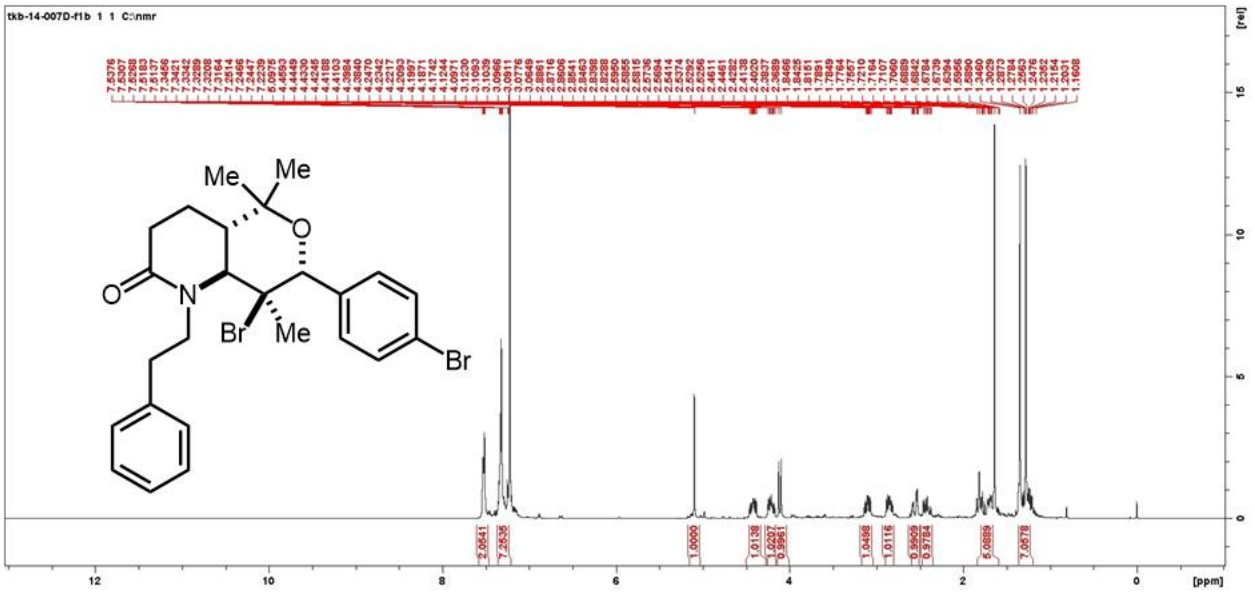


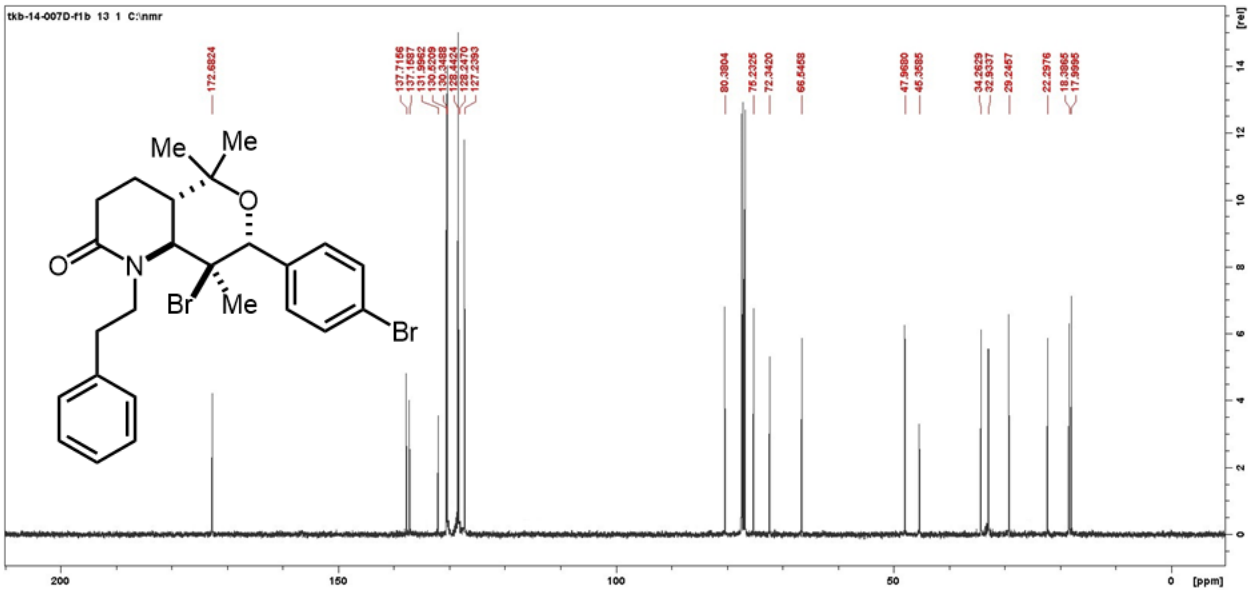


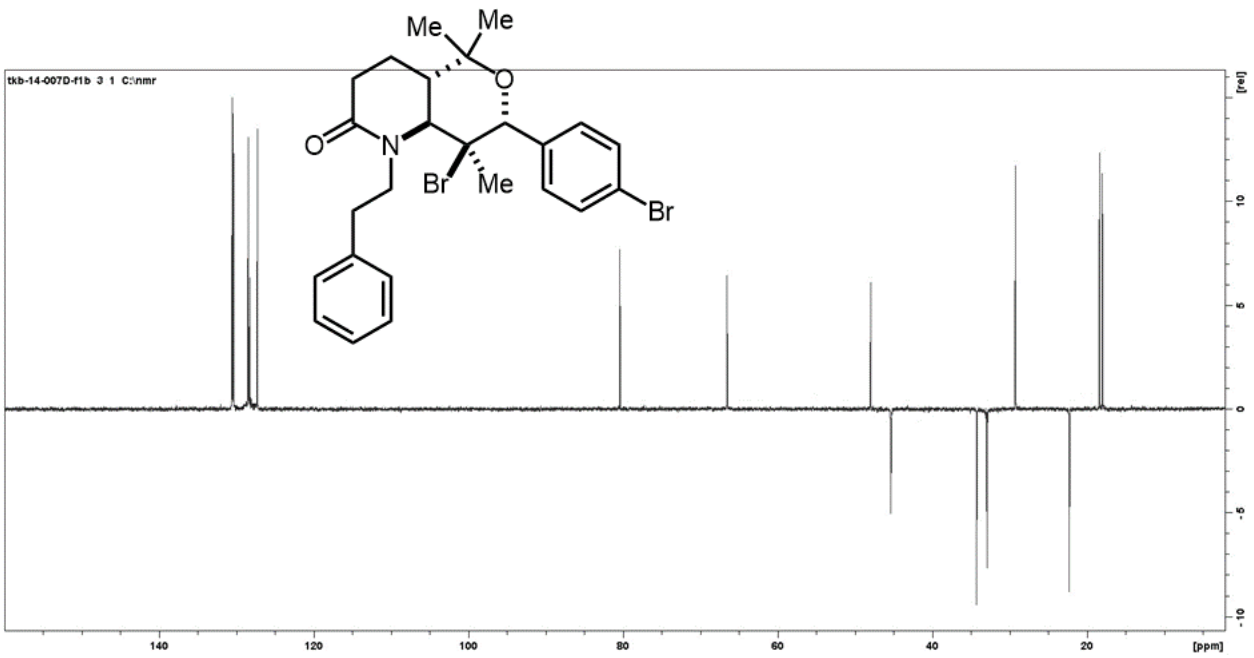
Compound 5p

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 492.5 mg, 92%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 7.51 (m, 2H), 7.33 – 7.22 (m, 7H), 5.10

(s, 1H), 4.42 (ddd, J = 13.8, 10.5, 5.7 Hz, 1H), 4.21 (ddd, J = 13.9, 10.1, 5.1 Hz, 1H), 4.11 (d, J = 10.9 Hz, 1H), 3.10 (ddd, J = 12.7, 10.4, 5.1 Hz, 1H), 2.85 (ddd, J = 12.7, 10.1, 5.7 Hz, 1H), 2.56 (ddd, J = 17.8, 5.0, 1.9 Hz, 1H), 2.42 (ddd, J = 18.1, 13.2, 6.0 Hz, 1H), 1.88 – 1.65 (m, 2H), 1.64 (s, 3H), 1.35 (s, 3H), 1.34 – 1.22 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.66, 137.73, 137.17, 132.00, 130.53, 130.35, 128.45, 128.25, 127.24, 80.39, 75.24, 72.35, 66.55, 47.98, 45.36, 34.28, 32.94, 29.25, 22.31, 18.39, 18.01. **HRMS-EI$^+$** (*m/z*): calc for $C_{25}H_{29}Br_2NO_2$ $[M]^+$ 533.0565, found 533.0569.

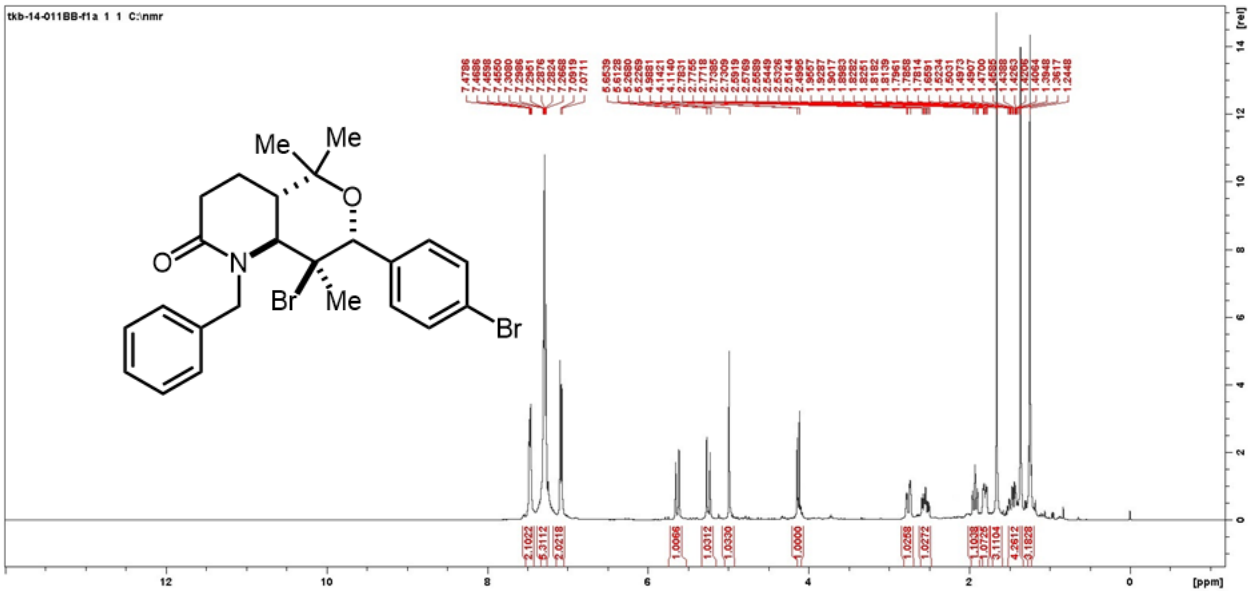






Compound 5q

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 453.5 mg, 87%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, CDCl3) δ 7.52 – 7.41 (m, 2H), 7.41 – 7.20 (m, 5H), 7.14 – 7.01 (m, 2H), 5.64 (d, J = 16.5 Hz, 1H), 5.25 (d, J = 16.5 Hz, 1H), 4.99 (s, 1H), 4.13 (d, J = 11.0 Hz, 1H), 2.76 (ddd, J = 17.8, 4.9, 2.0 Hz, 1H), 2.55 (ddd, J = 18.2, 13.2, 6.0 Hz, 1H), 1.93 (td, J = 11.6, 2.1 Hz, 1H), 1.82 (ddt, J = 10.3, 6.0, 2.0 Hz, 1H), 1.66 (s, 3H), 1.51 – 1.43 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 173.06, 137.06, 136.26, 132.23, 130.32, 128.97, 128.81, 128.54, 128.48, 128.23, 127.22, 80.31, 75.25, 71.37, 66.27, 48.07, 45.98, 34.24, 29.30, 22.19, 18.47, 18.05. **HRMS-EI^{+}** (*m/z*): calc for $C_{24}H_{27}Br_2NO_2$ $[M]^{+}$ 519.0409, found 519.0403.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Br
Me
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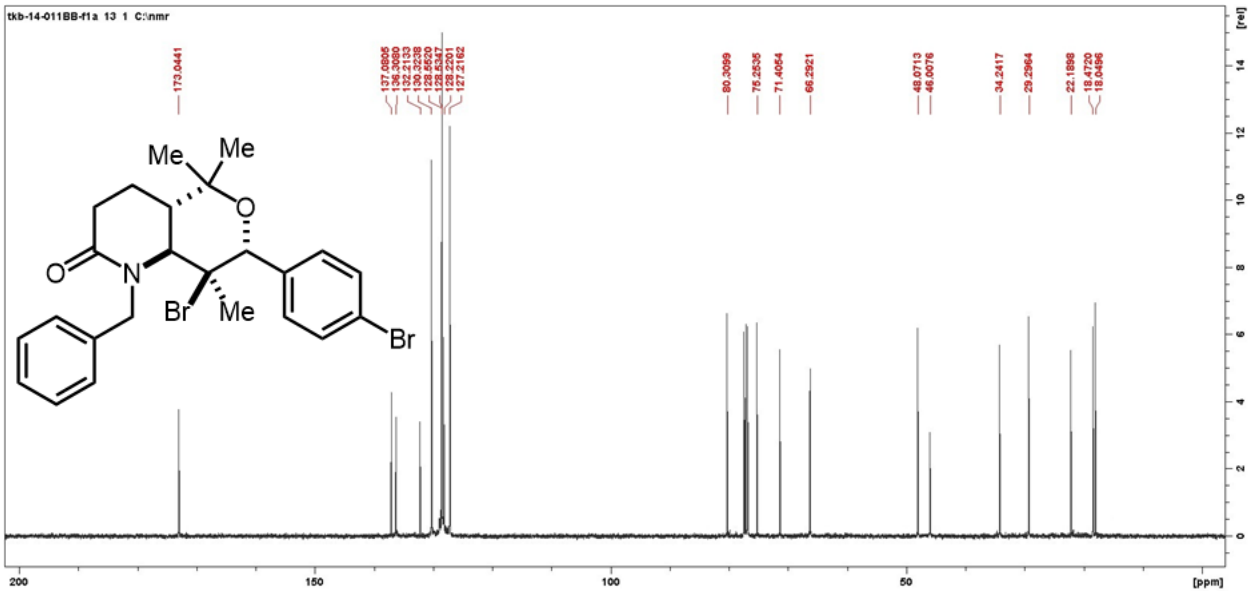
[rel]
[ppm]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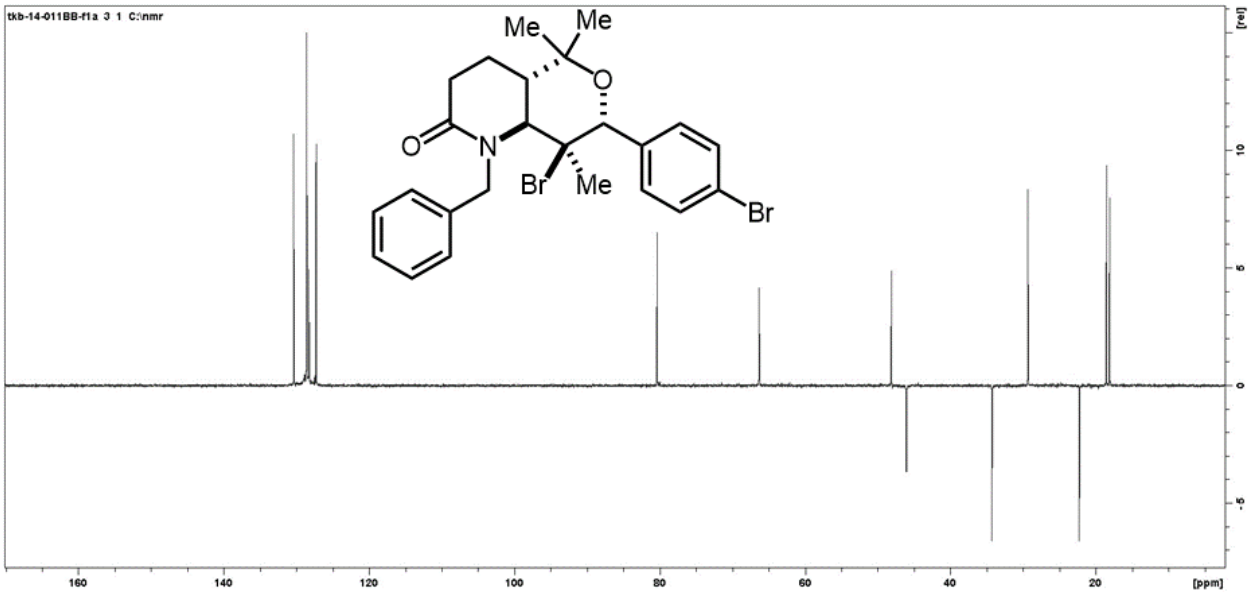
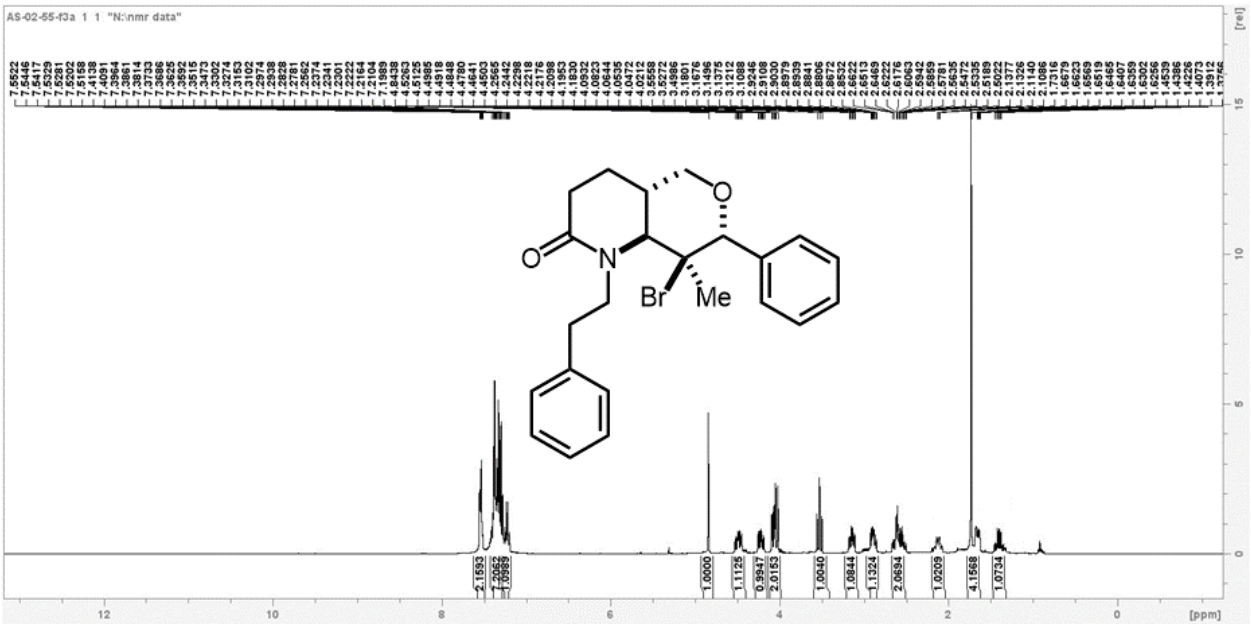


Compound 5r

Prepared in 1.0 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 312.7 mg, 73%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dp, *J* = 6.9, 2.2 Hz, 2H), 7.47 – 7.22 (m, 7H), 7.26 – 7.17 (m, 1H), 4.84 (s, 1H), 4.55 – 4.35 (m, 1H), 4.22 (ddd, *J* = 13.8, 10.6, 4.9 Hz, 1H), 4.13 – 3.95 (m, 2H), 3.53 (t, *J* = 11.4 Hz, 1H), 3.20 – 3.09 (m, 1H), 2.95 – 2.83 (m, 1H), 2.69 – 2.46 (m, 2H), 2.12 (tddd, *J* = 12.6, 10.8, 4.5, 2.5 Hz, 1H), 1.73 (s, 3H), 1.72 – 1.58 (m, 1H), 1.48 – 1.26 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.14, 139.21, 136.68, 130.19, 129.18, 128.41, 128.37, 127.36, 126.24, 88.00, 71.71, 69.99, 69.85, 44.49, 39.42, 33.31, 33.11, 22.08, 18.50. **HRMS-EI$^+$** (*m/z*): calc for $C_{23}H_{26}BrNO_2$ $[M]^+$ 427.1147, found 427.1133.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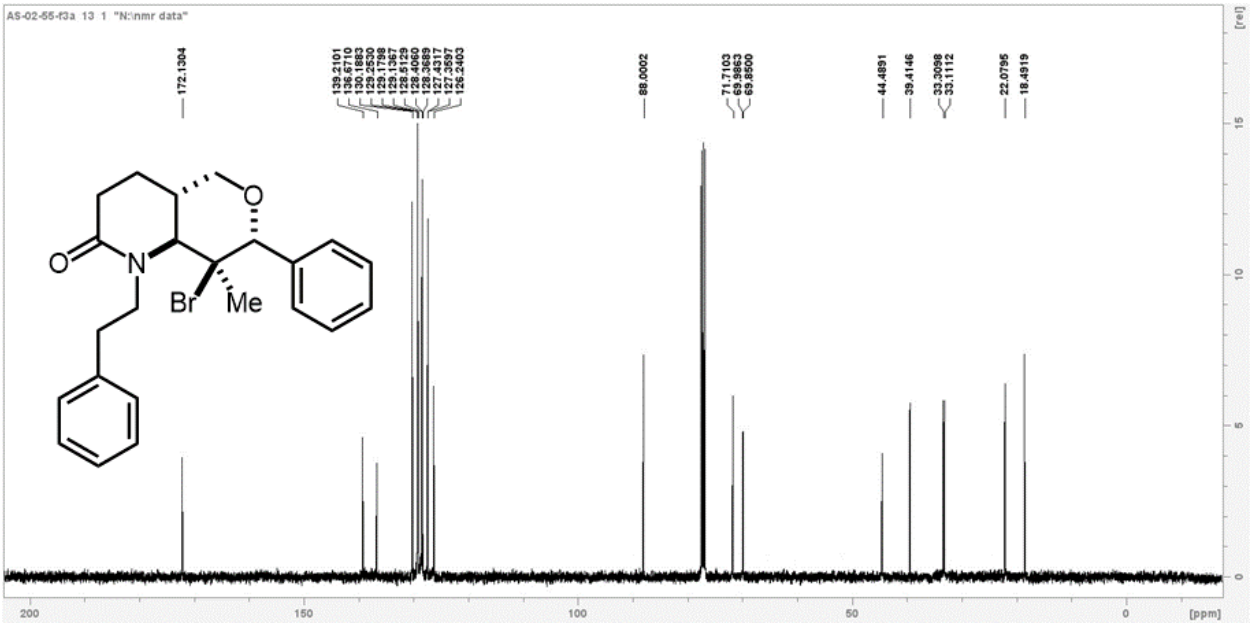
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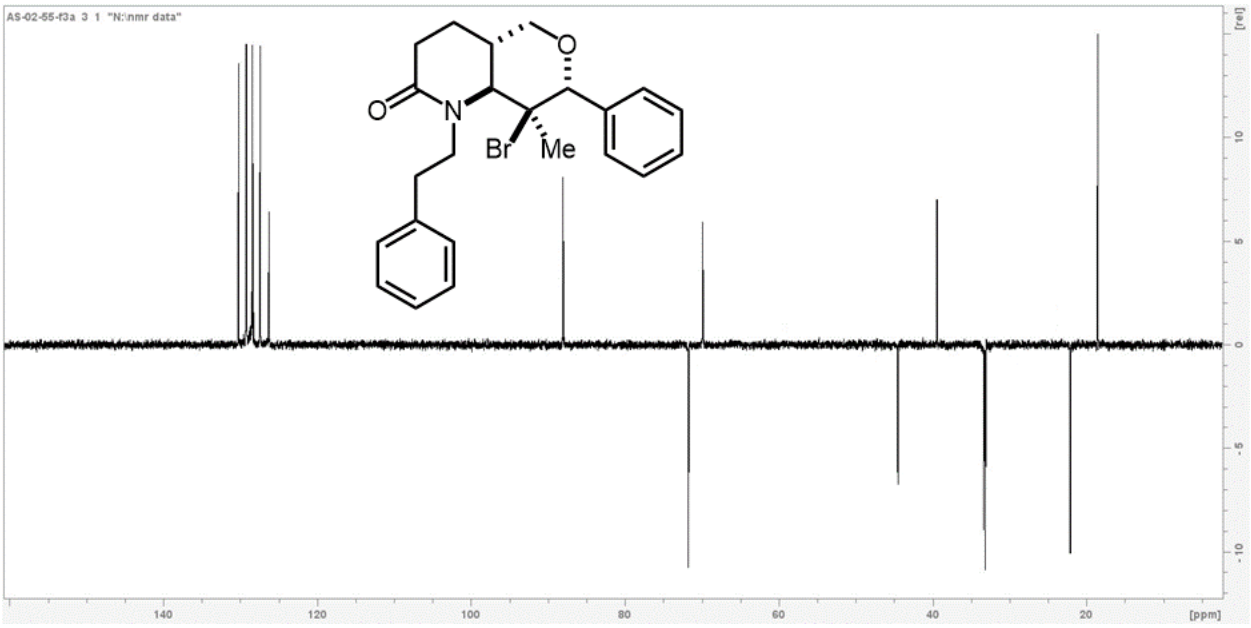
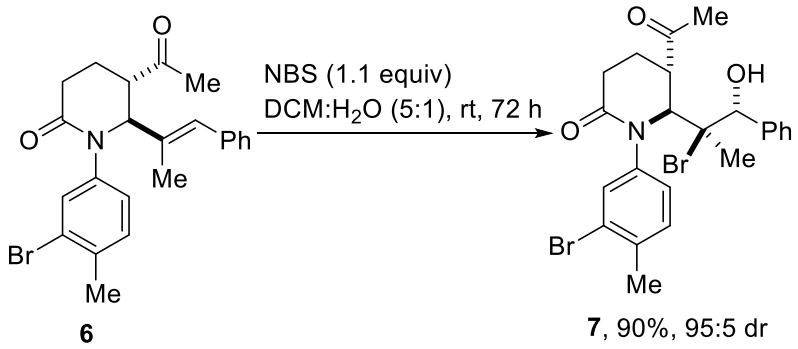
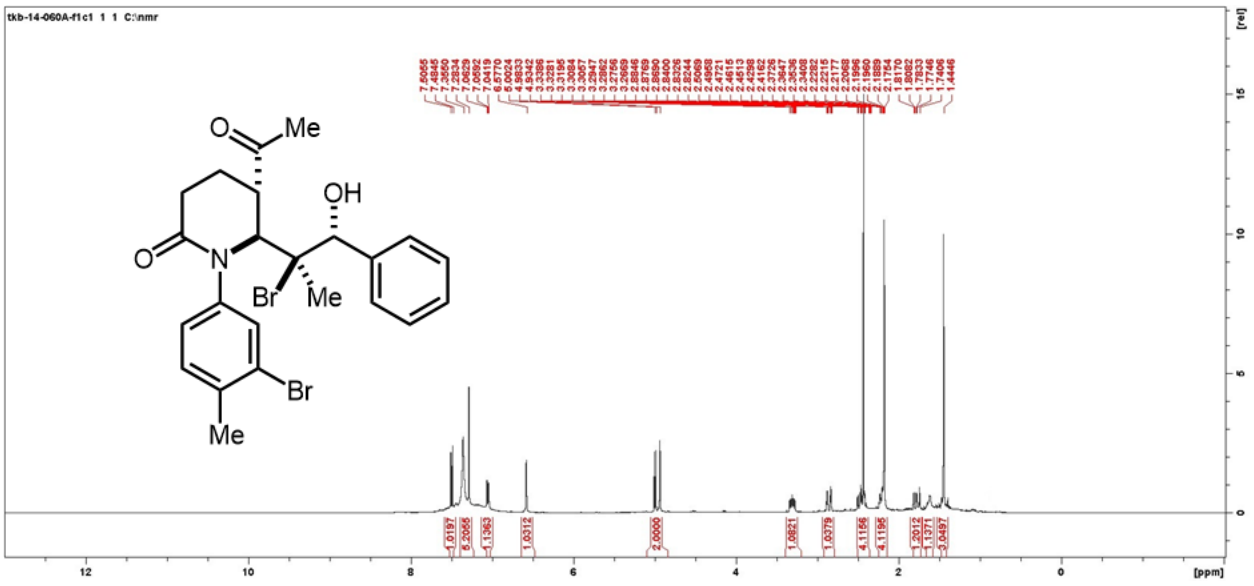




Compound 7

Prepared from **6** (213.2 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/acetone (90:10 to 50:50). Amorphous solid. Yield = 235.5 mg, 90%, 95:5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.05 (dd, J = 8.4, 2.1 Hz, 1H), 6.57 (s, 1H), 4.99 (d, J = 7.6 Hz, 1H), 4.93 (s, 1H), 3.31 (ddd, J = 13.4, 7.7, 4.2 Hz, 1H), 2.85 (ddd, J = 17.9, 3.6, 2.6 Hz, 1H), 2.53 – 2.43 (m, 4H), 2.28 – 2.17 (m, 4H), 1.80 – 1.58 (m, 1H), 1.58 – 1.38 (m, 1H), 1.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.75, 170.76, 139.26, 135.41, 135.22, 130.56, 130.33, 127.78, 127.62, 124.97, 70.91, 64.73, 60.80, 50.99, 32.86, 28.76, 23.89, 21.56, 20.91. **HRMS-EI$^+$** (*m/z*): calc for $C_{23}H_{25}Br_2NO_3$ $[M]^+$ 521.0201, found 521.0207.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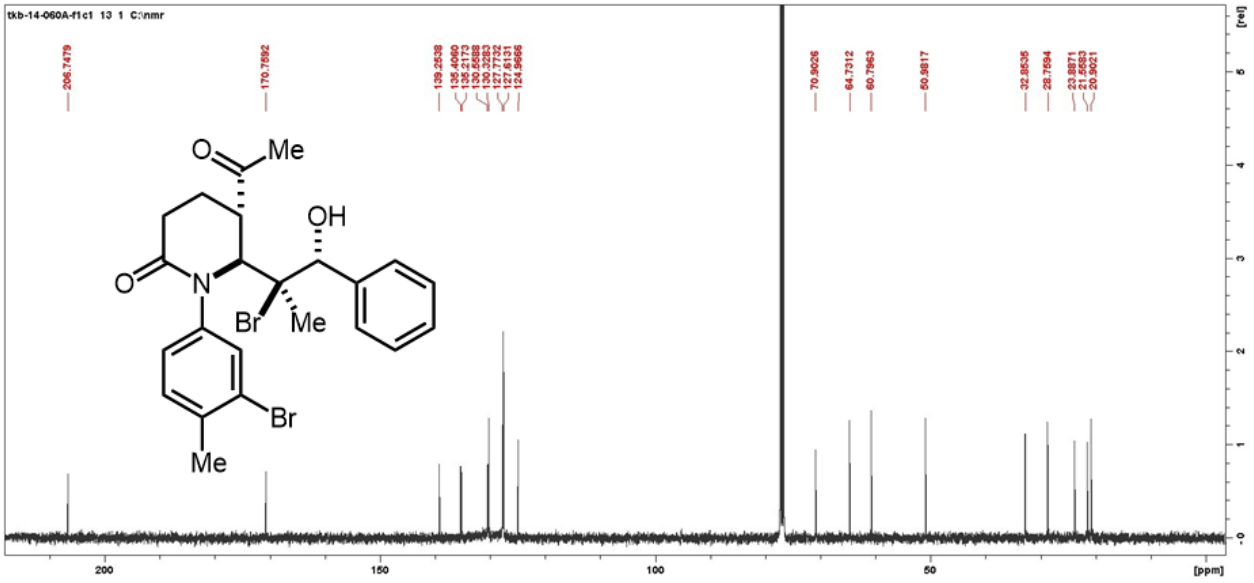
[ppm]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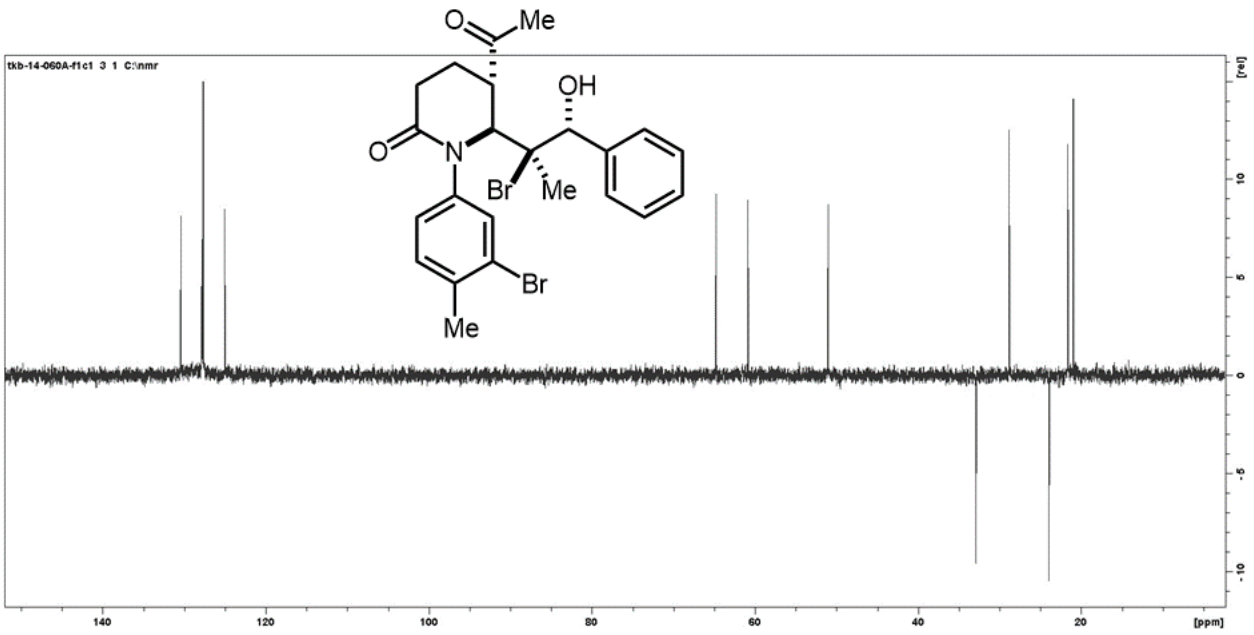

References

1 H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864-8872.

2 K. Hovenkotter, H. Braunstein, S. Langevin and T. K. Beng, *Org. Biomol. Chem.*, 2017, **15**, 1217-1221.