Electronic Supplementary Material (ESI) for Chemical Communications

Asymmetric synthesis of a structurally and stereochemically complex spirooxindole pyran scaffold through an organocatalytic multicomponent cascade reaction

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Supporting Information

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1. General methods

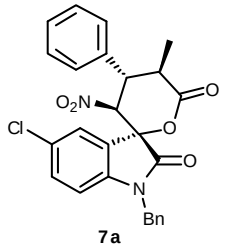
NMR data was obtained for ^{1}H at 400 MHz, and for ^{13}C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2. In each case, enantiomeric ratio was determined by HPLC analysis on chiral column in comparison with authentic racemates, using a Daicel Chiralpak AD-H Column (250 x 4.6 mm) or Kromasil AmyCoat Column (250 x 4.6 mm). UV detection was monitored at 220 nm or 254 nm. Optical rotation data were examined in CH_2Cl_2 solution at 20 °C. Column chromatography was performed on silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light and I_2 were used to visualize products. Melting points were determined on a Mel-Temp apparatus and are uncorrected. All chemicals were used without purification as commercially available unless otherwise noted. The catalysts were synthesized according to the literature procedures. [1]

[1]. (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jøgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayasi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

2. General procedure for the asymmetric synthesis of spirooxindole δ-lactone 7

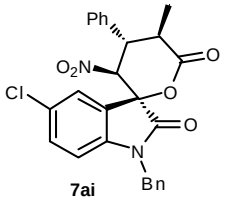
The reaction was carried out with saturated aldehyde **1** (0.4 mmol) and nitroolefin **2** (0.36 mmol) in the presence of catalyst **3** (13 mg, 0.04 mmol), acetic acid (2.4 mg, 0.04 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 3 h to afford the Michael adduct **4**. When the reaction was complete, the reaction mixture was cooled to 0 ^{o}C, after which isatin **5** (0.2 mmol), K_2CO_3 (0.8 mmol in 0.4 mL H_2O) and TBAB (0.02 mmol) were added in one-pot. The reaction mixture was stirred at 0 ^{o}C for a specified reaction time (about 1h) until the reaction completed (monitored by TLC). Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give hemiacetal **6**.

Hemiacetal **6** were oxidized to the stable corresponding spirooxindole δ-lactone **7**. To a solution of **6** in methylene chloride (2 mL) was added PCC (107.8 mg, 0.5 mmol). The mixture was stirred for 2 h at 50 ^{o}C. The solid was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residual was purified by column chromatography (petroleum ether/ethyl acetate = 30:1) to give spirooxindole δ-lactone **7** and its minor isomer **7i**.



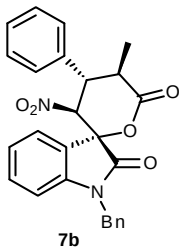
7a

7a was obtained as a white solid in 82% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column (20% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 14.48 min, t_{major} = 31.32 min. m.p. 178-180 °C; $[\alpha]_D^{20}$ -119.6 (*c* = 0.48 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (s, 1H), 7.42-7.24 (m, 10H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 4.50 (t, *J* = 11.6 Hz, 1H), 3.09-3.02 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 170.2, 141.8, 135.0, 133.4, 132.0, 129.0, 128.9, 128.6, 128.6, 127.7, 127.3, 126.7, 124.8, 123.0, 111.3, 89.2, 78.2, 45.0, 44.3, 41.4, 14.4 ppm; ESI HRMS: calcd. For $C_{26}H_{21}ClN_2O_5$+Na 499.1037, found 499.1039.



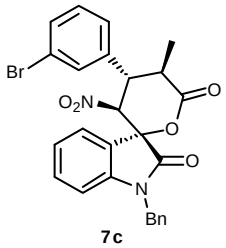
7ai

The minor isomer **7ai:** m.p. 149-151 °C; $[\alpha]_D^{20}$ -18.1 (*c* = 0.47 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 7.42-7.25 (m, 12H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 11.2 Hz, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 4.84 (d, *J* = 15.6 Hz, 1H), 3.86 (dd, *J* = 13.2 Hz, *J* = 11.2 Hz, 1H), 3.61-3.52 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 170.6, 141.3, 136.1, 133.5, 132.0, 129.5, 129.4, 129.0, 128.6, 128.1, 127.7, 126.8, 125.6, 124.2, 111.4, 89.9, 79.4, 46.7, 44.5, 38.4, 14.0 ppm; ESI HRMS: calcd. For $C_{26}H_{21}ClN_2O_5$+Na 499.1037, found 499.1034.



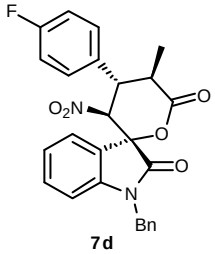
7b

7b was obtained as a white solid in 80% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 20.01 min, t_{major} = 25.83 min. m.p. 176-178 °C; $[\alpha]_D^{20}$ -86.4 (*c* = 0.38 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (d, *J* = 7.2 Hz, 1H), 7.40-7.24 (m, 11H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.59 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 4.53 (t, *J* = 11.6 Hz, 1H), 3.09-3.04 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 169.9, 143.0, 136.3, 134.1, 132.1, 129.4, 129.0, 128.6, 128.1, 127.9, 127.0, 125.2, 124.1, 122.8, 110.5, 90.4, 79.9, 44.5, 44.0, 43.2, 14.1 ppm; ESI HRMS: calcd. For $C_{26}H_{22}N_2O_5$+Na 465.1426, found 465.1425.



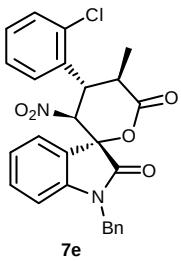
7c

7c was obtained as a white solid in 84% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 98% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 15.47 min, t_{major} = 21.09 min. m.p. 185-187 °C; $[\alpha]_D^{20}$ -96.2 (*c* = 0.51 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): 7.51-7.49 (m, 3H), 7.37-7.25 (m, 8H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.54 (d, *J* = 12.8 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 4.51 (t, *J* = 11.6 Hz, 1H), 3.05-2.97 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.8, 143.8, 138.2, 134.3, 132.6, 132.2, 131.0, 130.8, 129.0, 128.1, 127.2, 126.8, 124.8, 124.0, 123.5, 121.7, 110.8, 89.5, 78.9, 45.2, 44.7, 41.9, 14.9 ppm; ESI HRMS: calcd. For $C_{26}H_{21}BrN_2O_5$+Na 543.0532, found 543.0530.



7d

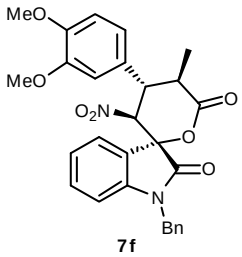
7d was obtained as a white solid in 76% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 17.60 min, t_{major} = 30.68 min. m.p. 168-169 °C; $[\alpha]_D^{20}$ -104.2 (*c* = 0.72 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, *J* = 7.6 Hz, 1H), 7.36-7.24 (m, 8H), 7.09-7.04 (m, 3H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.59 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 4.54 (t, *J* = 11.6 Hz, 1H), 3.03-2.99 (m, 1H), 1.43 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 171.1, 162.8 (d, J_{CF} = 247 Hz), 143.8, 134.3, 132.5, 131.6 (d, J_{CF} = 4 Hz), 129.6 (d, J_{CF} = 9 Hz), 129.0, 128.0, 127.2, 124.9, 124.0, 121.8, 116.5 (d, J_{CF} = 22 Hz), 110.8, 89.8, 79.0, 44.8, 44.7, 42.1, 14.9 ppm; ESI HRMS: calcd. For $C_{26}H_{21}FN_2O_5$+Na 483.1332, found 483.1330.



7e

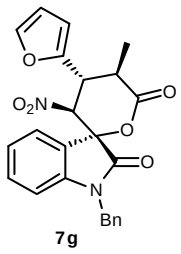
7e was obtained as a white solid in 78% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 21.58 min, t_{major} = 34.76 min. m.p. 175-176 °C; $[\alpha]_D^{20}$ -88.4 (*c* = 0.39 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): 7.49 (d, *J* = 2.0 Hz, 1H), 7.42-7.30 (m, 9H), 7.26-7.23 (m, 2H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 16.0 Hz, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 4.50 (dd, *J* = 12.0 Hz, *J* = 11.2 Hz, 1H), 3.09-3.02 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 170.9, 143.9, 135.8, 134.7, 134.3, 134.0,

132.5, 131.9, 130.5, 129.8, 129.0, 128.0, 127.3, 124.7, 123.8, 121.8, 110.8, 89.1, 79.0, 44.7, 43.2, 39.8, 14.6 ppm; ESI HRMS: calcd. For $C_{26}H_{21}ClN_2O_5$+Na 499.1037, found 499.1034.



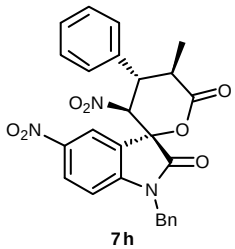
7f

7f was obtained as a white solid in 72% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 19.22 min, t_{major} = 27.35 min. m.p. 184-186 °C; $[\alpha]_D^{20}$ -96.2 (*c* = 0.54 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.6 Hz, 1H), 7.36-7.24 (m, 6H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.88-6.83 (m, 2H), 6.76 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.56 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 16.0 Hz, 1H), 4.45 (t, *J* = 11.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.05-3.01 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 171.2, 149.4, 149.2, 143.7, 134.2, 132.4, 129.0, 128.0, 127.9, 127.0, 124.8, 123.8, 121.8, 119.9, 111.6, 110.8, 110.7, 89.9, 78.9, 56.0, 55.8, 45.1, 44.6, 42.1, 14.9 ppm; ESI HRMS: calcd. For $C_{28}H_{26}N_2O_7$+Na 525.1638, found 525.1635.



7g

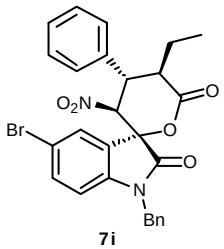
7g was obtained as a white solid in 68% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 94% by HPLC on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 15.32 min, t_{major} = 18.92 min. m.p. 162-164 °C; $[\alpha]_D^{20}$ -82.4 (*c* = 0.39 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.44 (m, 2H), 7.34-7.26 (m, 6H), 7.13-7.09 (m, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.34-6.29 (m, 2H), 5.63 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 16.0 Hz, 1H), 4.74-4.63 (m, 2H), 3.27-3.23 (m, 1H), 1.50 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 170.8, 147.9, 143.5, 134.3, 132.5, 129.0, 128.0, 127.1, 124.8, 123.9, 121.7, 110.7, 110.6, 87.6, 44.6, 39.7, 39.2, 15.0 ppm; ESI HRMS: calcd. For $C_{24}H_{20}N_2O_6$+Na 455.1219, found 455.1216.



7h

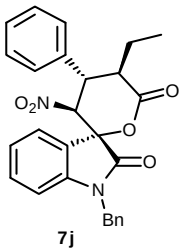
7h was obtained as a white solid in 70% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 13.31 min, t_{major} = 21.15 min. m.p. 174-176 °C; $[\alpha]_D^{20}$ -69.8 (*c* = 0.24 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 8.20 (d, *J* =

8.4 Hz, 1H), 7.42-7.33 (m, 10H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.74-5.68 (m, 1H), 5.20 (d, *J* = 15.6 Hz, 1H), 4.77 (d, *J* = 15.6 Hz, 1H), 4.48 (t, *J* = 11.6 Hz, 1H), 3.17-3.13 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.5, 149.3, 143.9, 135.2, 133.2, 129.6, 129.3, 129.2, 129.0, 128.5, 127.9, 127.2, 123.0, 121.0, 110.6, 89.3, 78.1, 45.5, 45.1, 41.9, 14.9 ppm; ESI HRMS: calcd. For $C_{26}H_{21}N_3O_7$+Na 510.1277, found 510.1273.



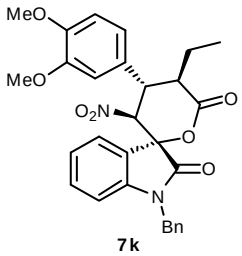
7i

7i was obtained as a white solid in 75% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 98% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 16.46 min, t_{major} = 20.55 min. m.p. 177-178 °C; $[\alpha]_D^{20}$ -76.8 (*c* = 0.35 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 1H), 7.41-7.26 (m, 11H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 4.77 (t, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 3.12-3.07 (m, 1H), 2.10-2.03 (m, 1H), 1.67-1.61 (m, 1H), 1.11 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 169.7, 142.7, 135.4, 135.3, 133.8, 129.5, 129.1, 129.0, 128.1, 128.0, 127.7, 127.1, 123.9, 116.4, 112.2, 90.3, 78.6, 47.1, 44.7, 41.9, 21.6, 10.1 ppm; ESI HRMS: calcd. For $C_{27}H_{23}BrN_2O_5$+Na 557.0688, found 557.0685.



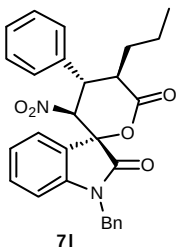
7j

7j was obtained as a white solid in 80% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 20.43 min, t_{major} = 25.97 min. m.p. 180-181 °C; $[\alpha]_D^{20}$ -89.4 (*c* = 0.49 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.6 Hz, 1H), 7.39-7.23 (m, 11H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.54 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 4.80 (t, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 3.13-3.08 (m, 1H), 2.10-2.04 (m, 1H), 1.67-1.59 (m, 1H), 1.11 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.2, 143.7, 135.7, 134.3, 132.4, 129.4, 128.9, 128.8, 127.9, 127.7, 127.1, 124.7, 123.8, 122.0, 110.6, 90.5, 78.9, 47.1, 44.6, 42.0, 21.6, 10.2 ppm; ESI HRMS: calcd. For $C_{27}H_{24}N_2O_5$+Na 479.1583, found 479.1586.



7k

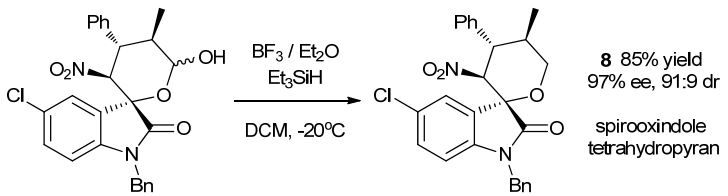
7k was obtained as a white solid in 74% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 98% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 19.18 min, t_{major} = 34.40 min. m.p. 171-173 ^{o}C; $[\alpha]_D^{20}$ -85.7 (*c* = 0.41 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.6 Hz, 1H), 7.36-7.23 (m, 6H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.88-6.83 (m, 2H), 6.76 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 4.75-4.69 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.08-3.03 (m, 1H), 2.09-2.03 (m, 1H), 1.71-1.65 (m, 1H), 1.11 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 170.3, 149.5, 149.2, 143.6, 134.3, 132.4, 128.9, 127.9, 127.8, 127.0, 124.7, 123.8, 122.0, 119.9, 111.6, 110.6, 90.6, 78.9, 56.0, 55.8, 47.3, 44.5, 41.7, 21.7, 10.3 ppm; ESI HRMS: calcd. For $C_{29}H_{28}N_2O_7$+Na 539.1794, found 539.1792.



7l

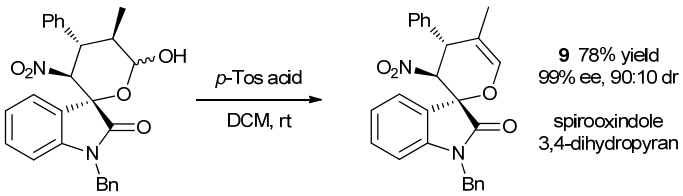
7l was obtained as a white solid in 78% yield for two steps after flash chromatography and the enantiomeric excess was determined to be 98% by HPLC on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 12.63 min, t_{major} = 19.17 min. m.p. 174-175 ^{o}C; $[\alpha]_D^{20}$ -91.8 (*c* = 0.47 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.6 Hz, 1H), 7.41-7.24 (m, 11H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 4.77-7.71 (m, 2H), 3.14-3.09 (m, 1H), 1.94-1.87 (m, 1H), 1.74-1.47 (m, 3H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.5, 143.7, 135.8, 134.3, 132.4, 129.4, 129.0, 128.9, 127.9, 127.7, 127.1, 124.7, 123.8, 122.0, 110.7, 90.5, 78.9, 46.1, 44.6, 42.8, 31.1, 19.2, 14.1 ppm; ESI HRMS: calcd. For $C_{28}H_{26}N_2O_5$+Na 493.1739, found 493.1737.

3. Synthetic transformations to access diverse pirooxindole pyran scaffolds

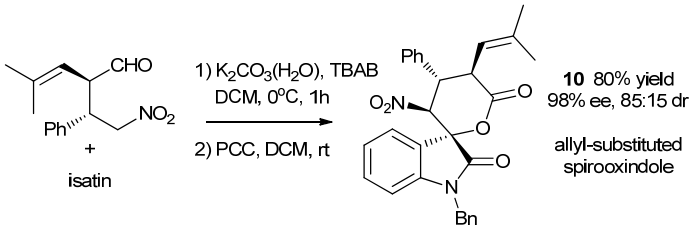


To a solution of **6a** (47.9 mg, 0.1 mmol) and triethyl silane (34.8 mg, 0.3 mmol) in DCM (3 mL) was added $BF_3{\cdot}Et_2O$ (42 μL, 0.33 mmol). The mixture was stirred at room temperature for 12 h.

The reaction was quenched with aqueous $NaHCO_3$, extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 40:1). The spirooxindole tetrahydropyran derivative **8** was obtained as a white solid in 85% yield and the enantiomeric excess was determined to be 97% by HPLC on Kromasil AmyCoat column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, t_{minor} = 6.13 min, t_{major} = 15.28 min. m.p. 157-158 ^{o}C; $[\alpha]_D^{20}$ -65.8 (*c* = 0.34 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (s, 1H), 7.37-7.26 (m, 10H), 7.18-7.16 (m, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.75-4.67 (m, 2H), 4.18 (t, *J* = 11.6 Hz, 1H), 3.88 (dd, *J* = 11.6 Hz, *J* = 5.2 Hz, 1H), 2.43-2.31 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 141.8, 136.4, 134.6, 131.2, 129.1, 129.0, 128.9, 128.2, 127.9, 127.2, 126.7, 124.6, 111.0, 92.9, 75.4, 68.0, 46.7, 44.0, 36.1, 14.0 ppm; ESI HRMS: calcd. For $C_{26}H_{21}ClN_2O_5$+Na 485.1244, found 485.1241.

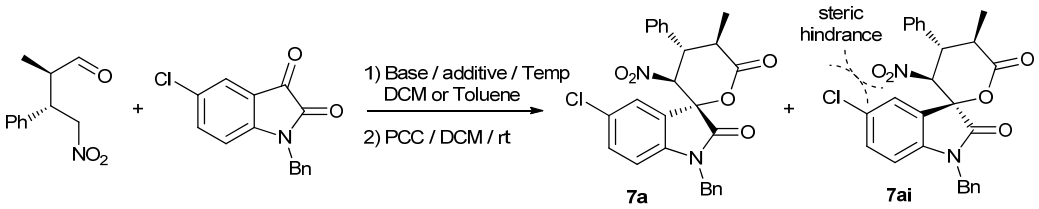


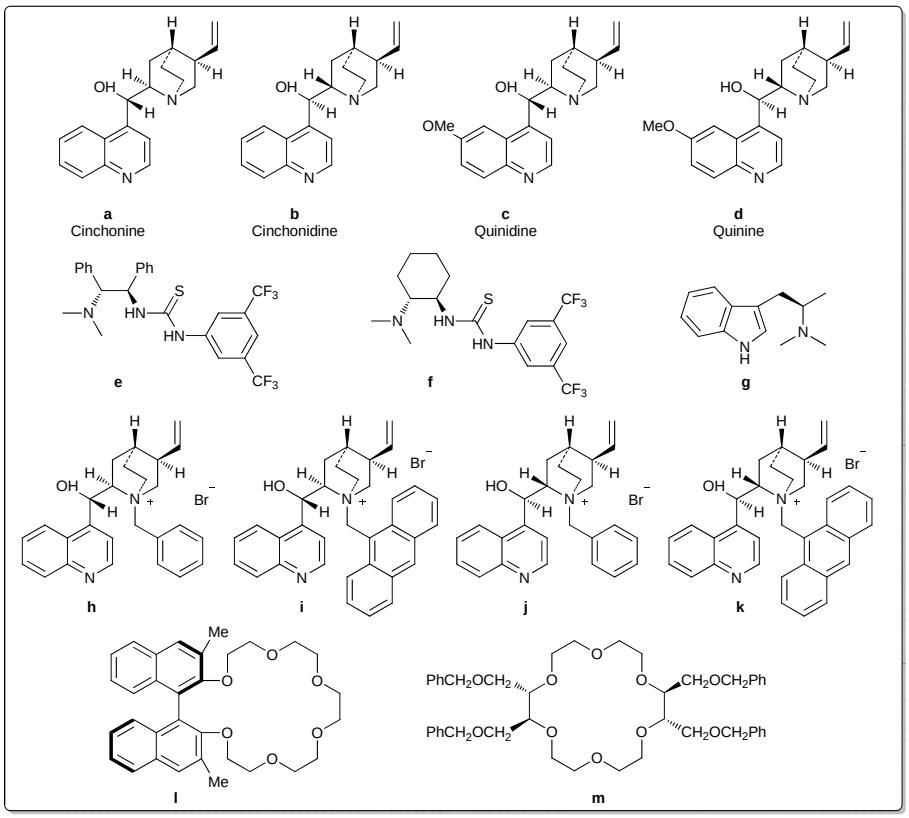
To a solution of **6b** (44.4 mg, 0.1 mmol) in methylene chloride (2 mL) was added *p*-toluene sulfonic acid (34.4 mg, 0.2 mmol). The mixture was stirred for 8 h at room temperature. When the reaction was complete, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 40:1). 3,4-Dihydropyran derivative **9** was obtained as a white solid in 78% yield and the enantiomeric excess was determined to be 99% by HPLC on Chiralpak AD column (10% 2-propanol/hexane, 1 mL/min), UV 220 nm, t_{minor} = 11.22 min, t_{major} = 12.98 min. m.p. 151-152 ^{o}C; $[\alpha]_D^{20}$ -47.8 (c = 0.39 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.23 (m, 12H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.41 (s, 1H), 5.33 (d, *J* = 11.2 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.80-4.73 (m, 2H), 1.49 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 143.9, 135.8, 134.7, 134.0, 132.5, 131.9, 130.5, 129.8, 129.0, 127.9, 127.3, 127.0, 124.7, 123.8, 121.8, 110.8, 89.1, 79.0, 47.5, 43.2, 15.9 ppm; ESI HRMS: calcd. For $C_{26}H_{22}N_2O_4$+Na 449.1477, found 449.1479.



The reaction was carried out with 4-methylpent-2-enal (39.2 mg, 0.4 mmol) and nitrostyrene (53.6 mg, 0.36 mmol) in the presence of catalyst **3** (13 mg, 0.04 mmol), acetic acid (2.4 mg, 0.04 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 3 h to afford the Michael adduct. When the reaction was complete, the reaction mixture was cooled to 0 ^oC, after which *N*-benzyl-protected isatin (0.2 mmol), K_2CO_3 (0.8 mmol in 0.4 mL H_2O) and TBAB (0.02 mmol) were added in one-pot. The reaction mixture was stirred at 0 ^oC for 1h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give hemiacetal intermediate. To a solution of hemiacetal in methylene chloride (2 mL) was added PCC (107.8 mg, 0.5 mmol). The mixture was stirred for 2 h at 50 ^oC. The solid was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residual was purified by column chromatography (petroleum ether/ethyl acetate = 30:1). Allyl-substituted oxa-spirooxindole **10** was obtained as a white solid in 80% yield and the enantiomeric excess was determined to be 98% by HPLC on Chiralpak AD column (30% 2-propanol/hexane, 1 mL/min), UV 254 nm, t_{minor} = 24.80 min, t_{major} = 55.07 min. m.p. 162-164 ^oC; $[\alpha]_D^{20}$ -79.2 (c = 0.61 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 7.2 Hz, 1H), 7.35-7.26 (m, 11H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.70 (d, *J* = 12.4 Hz, 1H), 5.49 (d, *J* = 9.2 Hz, 1H), 5.14 (d, *J* = 15.6 Hz, 1H), 4.61-4.55 (m, 1H), 4.58 (t, *J* = 11.6 Hz, 1H), 3.83 (t, *J* = 10.0 Hz, 1H), 1.68 (s, 3H), 1.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 170.0, 143.8, 138.9, 135.6, 134.3, 132.5, 129.1, 129.0, 128.6, 128.1, 128.0, 127.1, 124.8, 123.9, 121.8, 118.3, 110.7, 89.1, 79.0, 47.1, 44.9, 44.7, 25.5, 17.7 ppm; ESI HRMS: calcd. For $C_{29}H_{26}N_2O_5$+Na 505.1739, found 505.1741.

4. Screening studies to improve the yield of stereoisomer 7ai

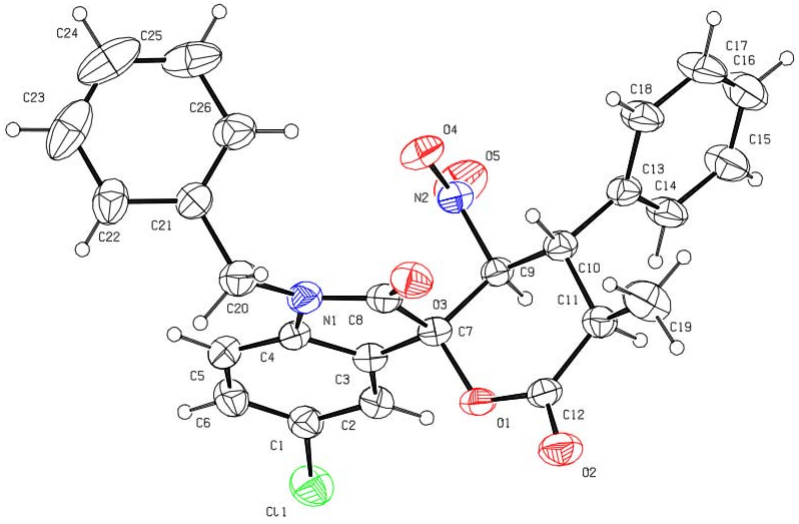


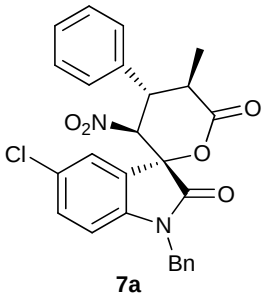


entry	Base	additive	temp	Total yield (%)	**7a**:**7ai**
1	**a**	-	rt	66	85:15
2	**b**	**-**	**rt**	**73**	**52:48**
3	**c**	-	rt	68	80:20
4	**d**	-	rt	65	58:42
5	**e**	-	rt	45	81:19
6	**f**	-	rt	30	80:20
7	**g**	-	rt	65	75:25
8	K_2CO_3/H_2O	**h**	0 ^oC	54	78:22
9	K_2CO_3/H_2O	**i**	0 ^oC	58	80:20
10	K_2CO_3/H_2O	**j**	0 ^oC	62	72:28
11	K_2CO_3/H_2O	**k**	0 ^oC	60	65:35
12	K_2CO_3/H_2O	**l**	0 ^oC	35	75:25
13	K_2CO_3/H_2O	**m**	0 ^oC	45	68:32

The diastereoisomer **7ai**, despite obvious steric crowding, was obtained in moderate yield when cinchonidine was used as the chiral base in the Henry reaction cascade.

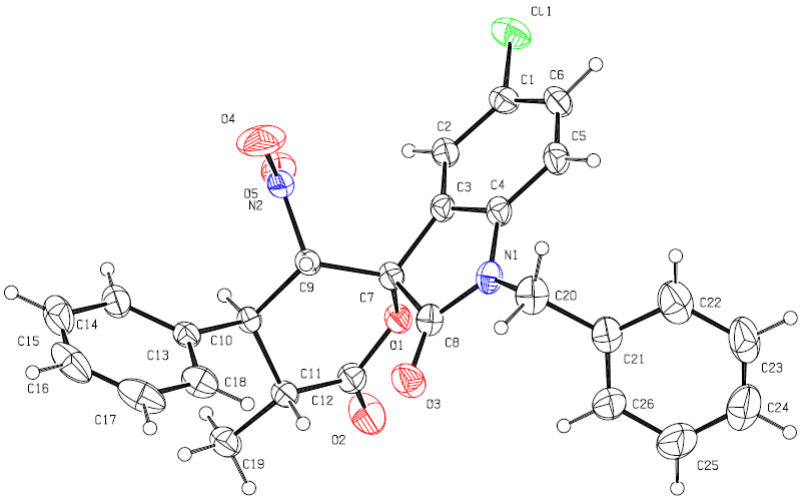
5. Crystal data of 7a and 7ai

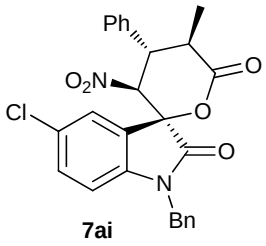




7a

Identification code	120530_s2_oyl
Empirical formula	$C_{26}H_{21}ClN_2O_5$
Formula weight	476.90
Temperature/K	293.15
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.7125(6)
b/Å	11.9908(6)
c/Å	22.8948(13)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	2391.8(2)
Z	4
ρ_{calc}mg/mm^3	1.324
m/mm^{-1}	0.199
F(000)	992.0
Crystal size/mm^3	0.37 × 0.29 × 0.26
2Θ range for data collection	5.78 to 52.74°
Index ranges	$-8 \le h \le 10$, $-14 \le k \le 9$, $-28 \le l \le 28$
Reflections collected	10633
Independent reflections	4879[R(int) = 0.0899]
Data/restraints/parameters	4879/0/308
Goodness-of-fit on F^2	1.007
Final R indexes [I>=2σ (I)]	R_1 = 0.0697, wR_2 = 0.1537
Final R indexes [all data]	R_1 = 0.1111, wR_2 = 0.1862
Largest diff. peak/hole / e Å^{-3}	0.32/-0.20
Flack parameter	0.02(12)

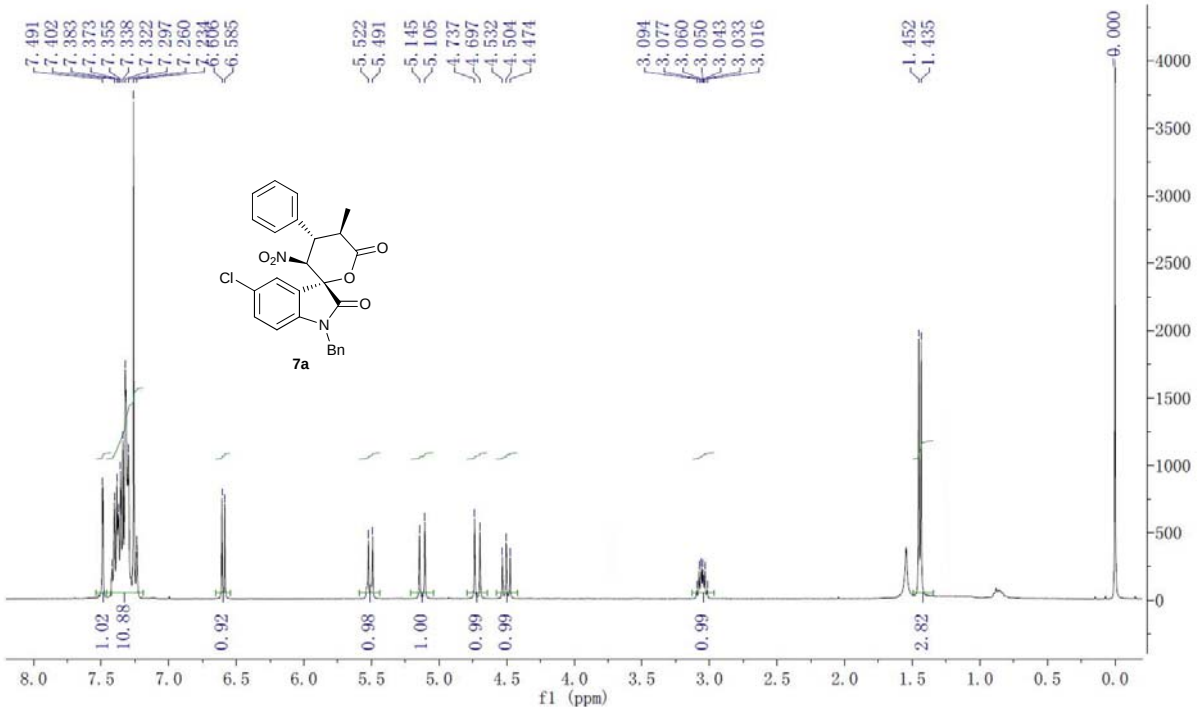


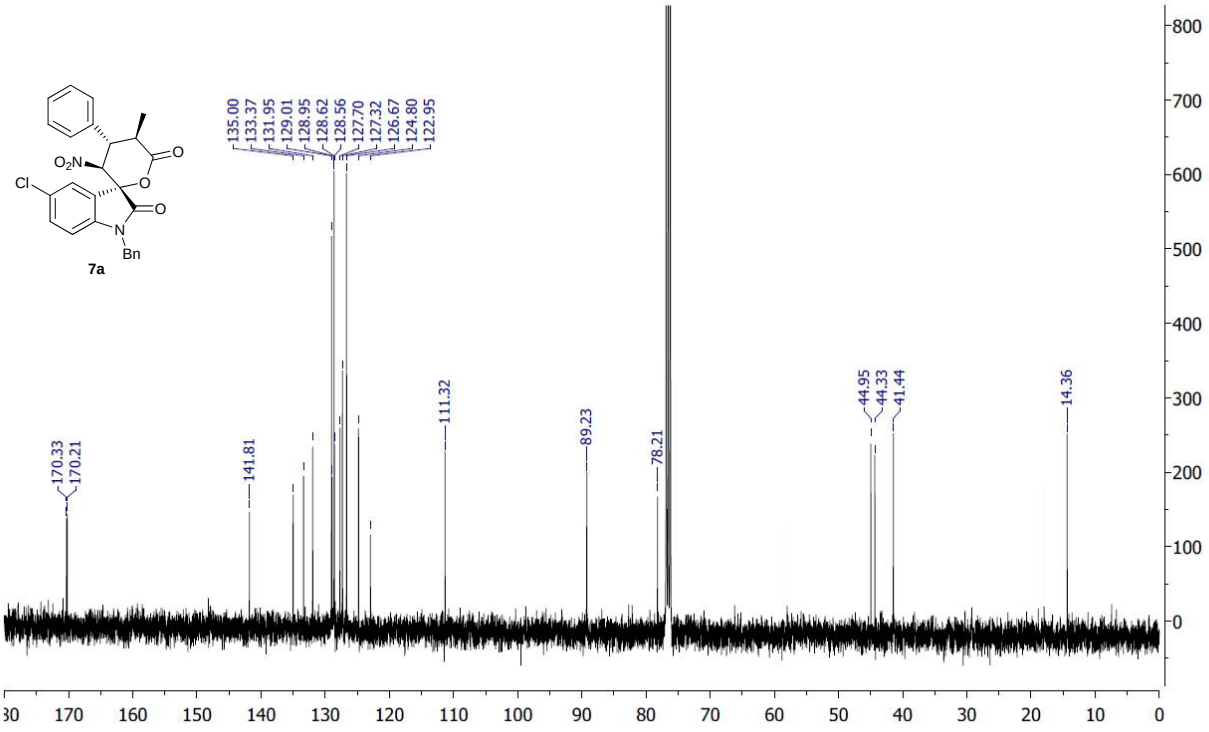


7ai

Identification code	120530_s3_oyl
Empirical formula	$C_{26}H_{21}ClN_2O_5$
Formula weight	476.90
Temperature/K	293.15
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.9973(3)
b/Å	16.3475(6)
c/Å	19.9730(8)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	2284.68(15)
Z	4
ρ_{calc}mg/mm^3	1.386
m/mm^{-1}	0.209
F(000)	992.0
Crystal size/mm^3	0.36 × 0.29 × 0.26
2Θ range for data collection	6.16 to 52.74°
Index ranges	$-7 \le h \le 8$, $-19 \le k \le 20$, $-24 \le l \le 14$
Reflections collected	6181
Independent reflections	3910[R(int) = 0.0220]
Data/restraints/parameters	3910/0/308
Goodness-of-fit on F^2	1.015
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.0737
Final R indexes [all data]	R_1 = 0.0798, wR_2 = 0.0830
Largest diff. peak/hole / e Å^{-3}	0.18/-0.19
Flack parameter	0.01(8)

6. NMR spectra and HPLC chromatograms





Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
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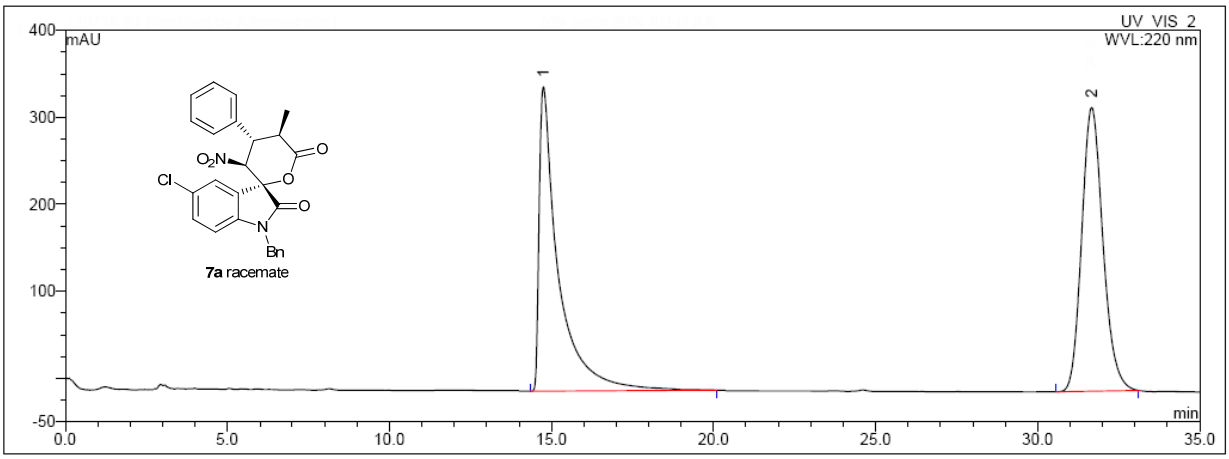

Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
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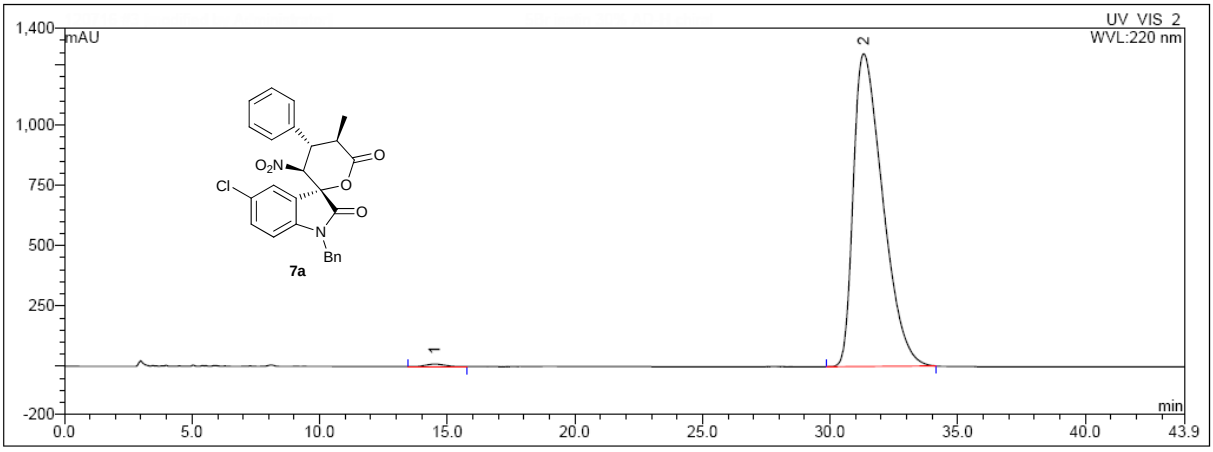

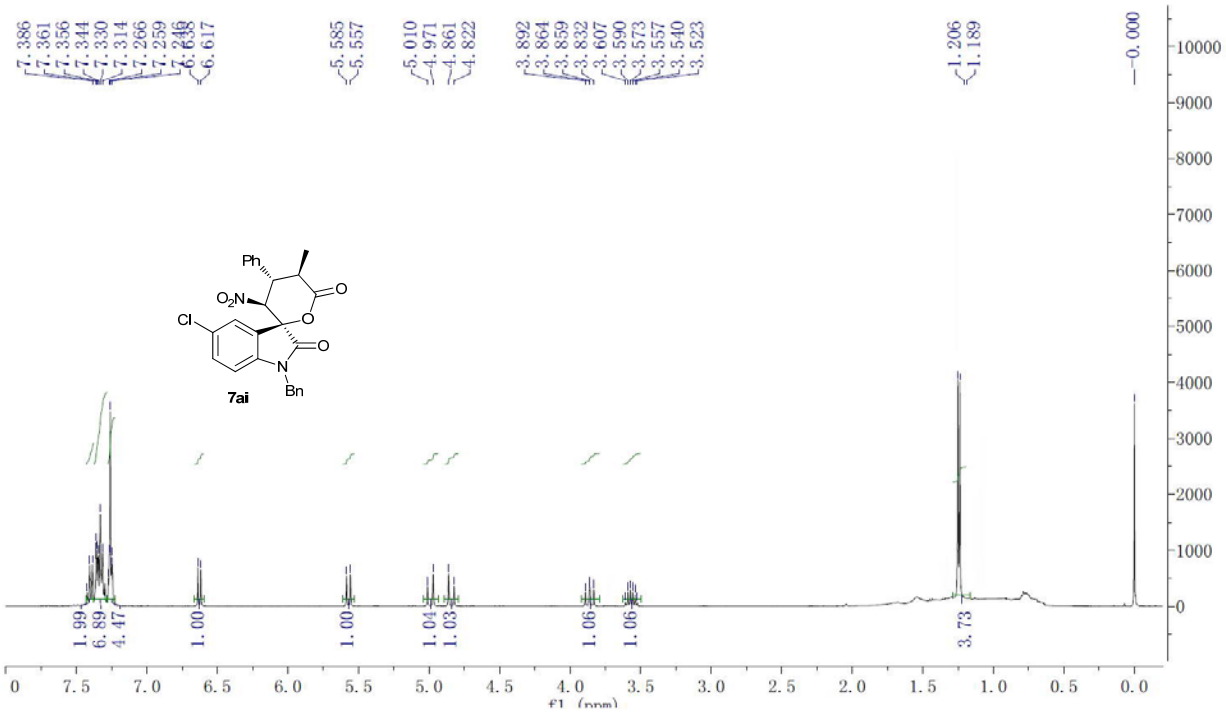

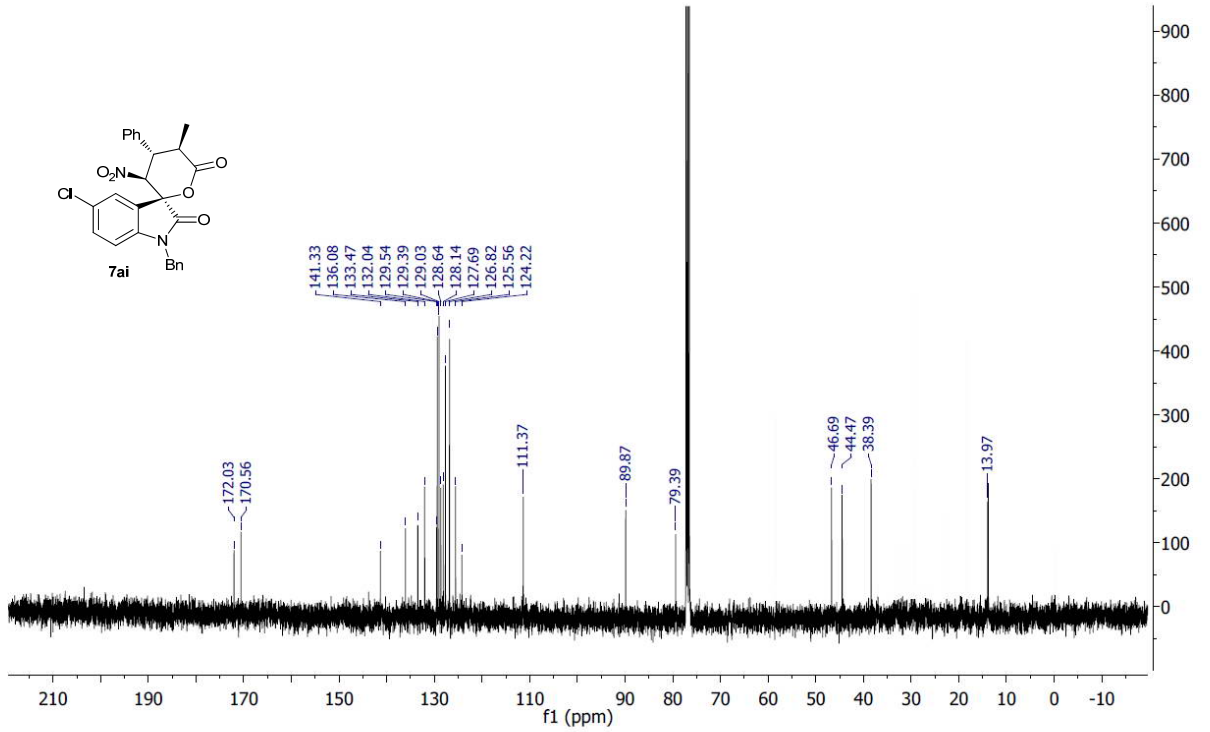

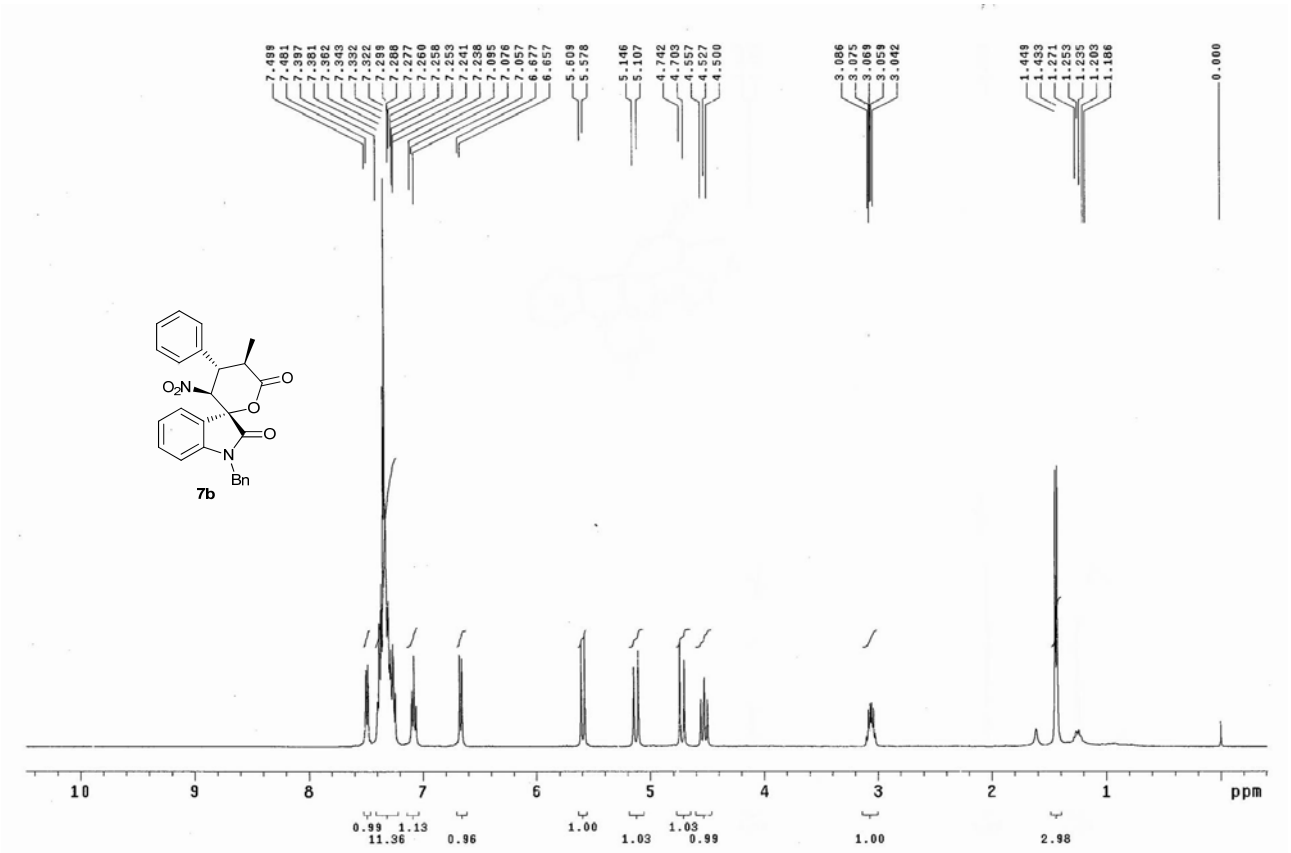
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7.238
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6.657
5.609
5.578
5.146
5.107
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3.075
3.069
3.059
3.042
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1.433
1.271
1.253
1.235
1.203
1.186
0.000
O2N
O
O
O
N
Bn
7b
10
9
8
7
6
5
4
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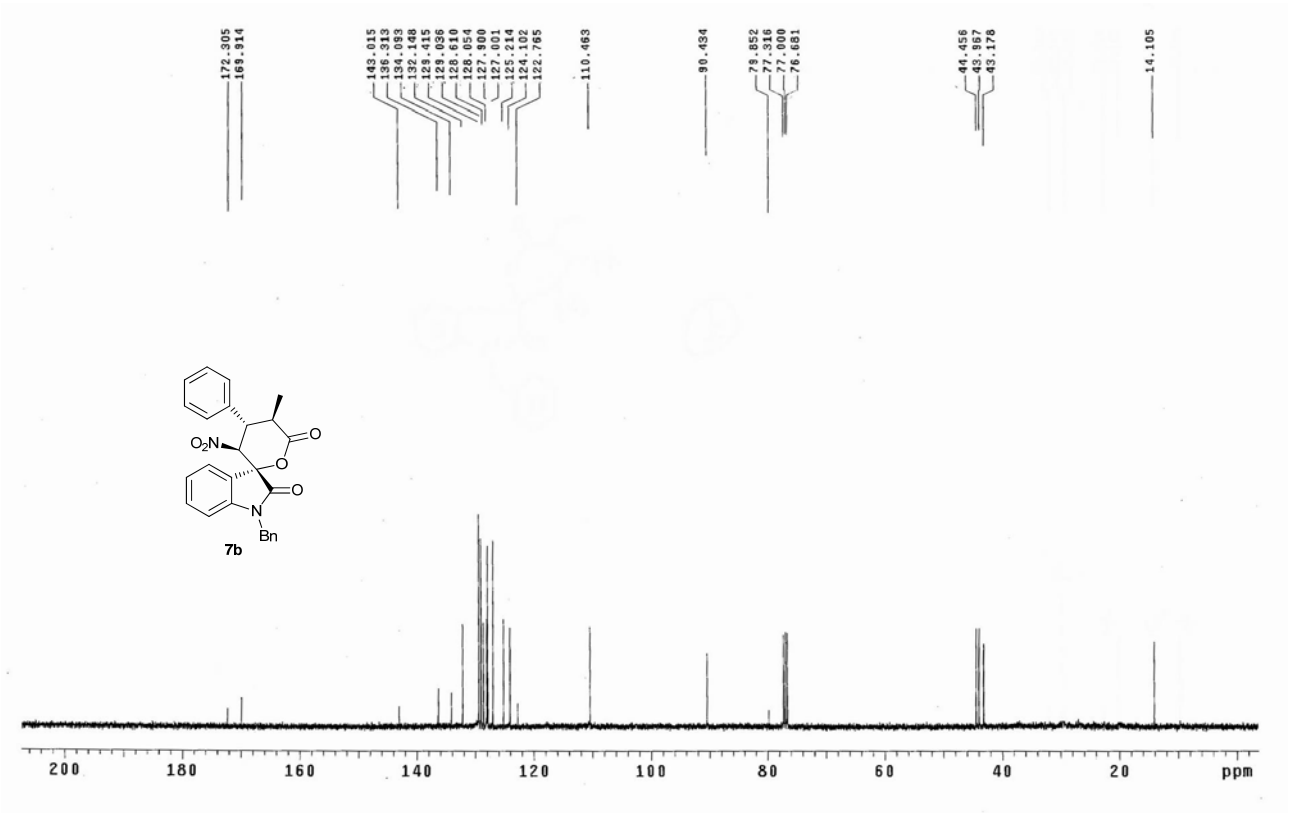
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125.214
124.102
122.765
110.463
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78.852
77.316
77.000
76.681
44.456
43.967
43.178
14.105
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O
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O
N
Bn
7b
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180
160
140
120
100
80
60
40
20
ppm

Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
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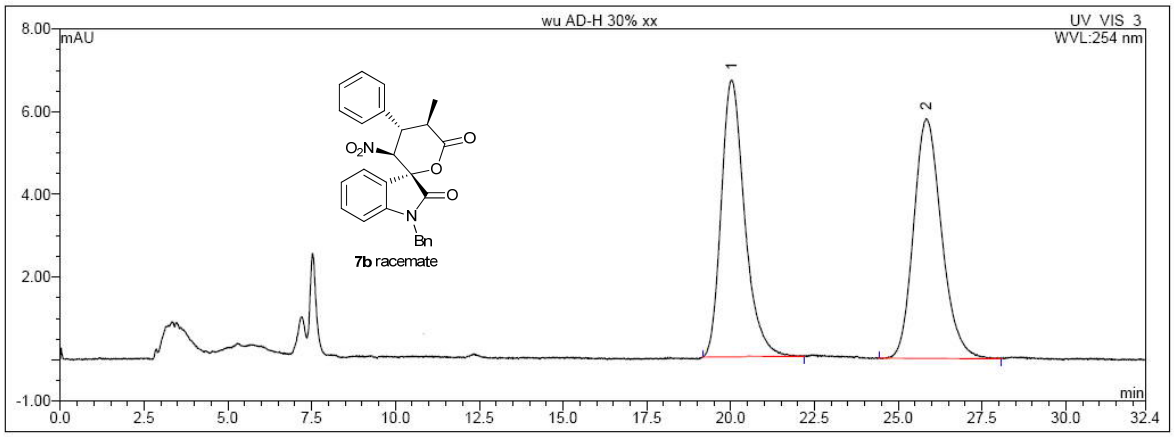

Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
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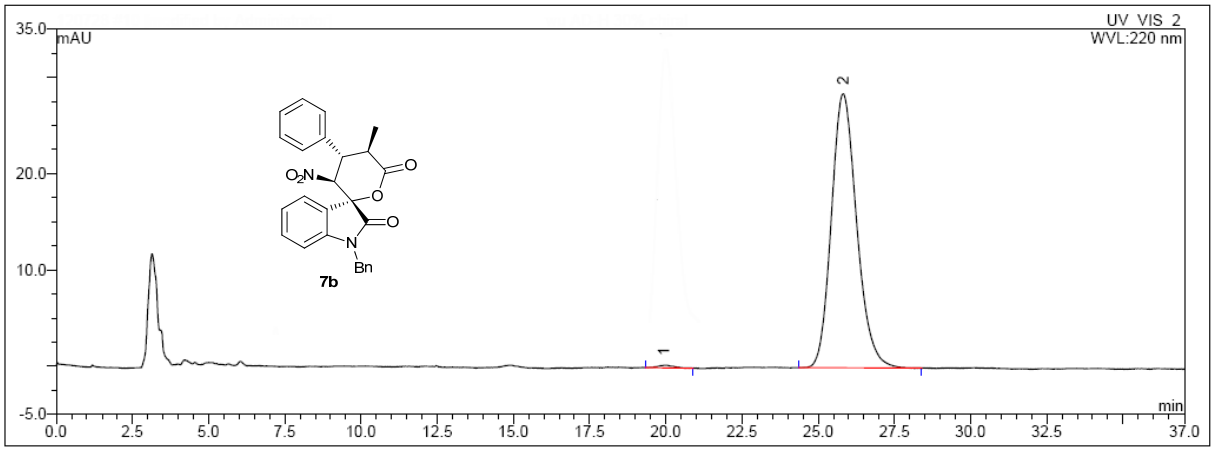

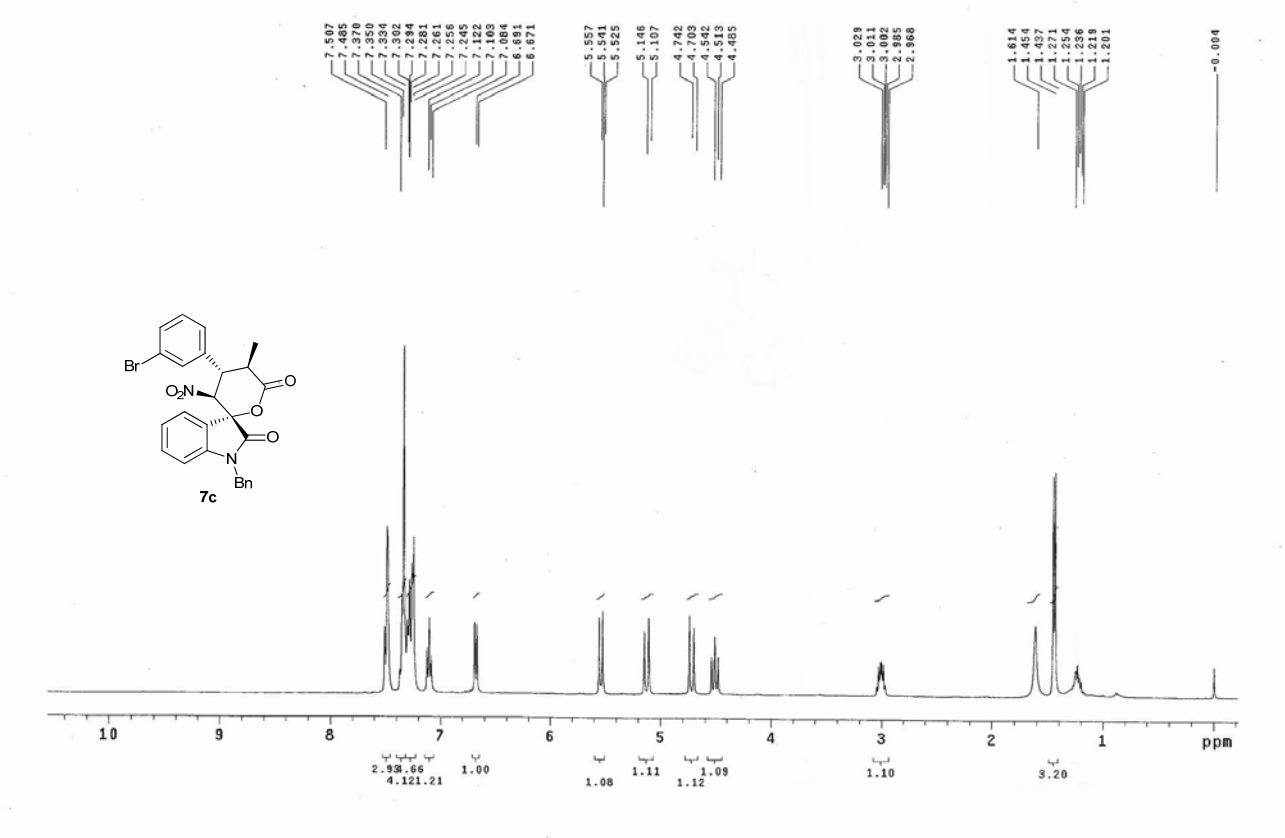

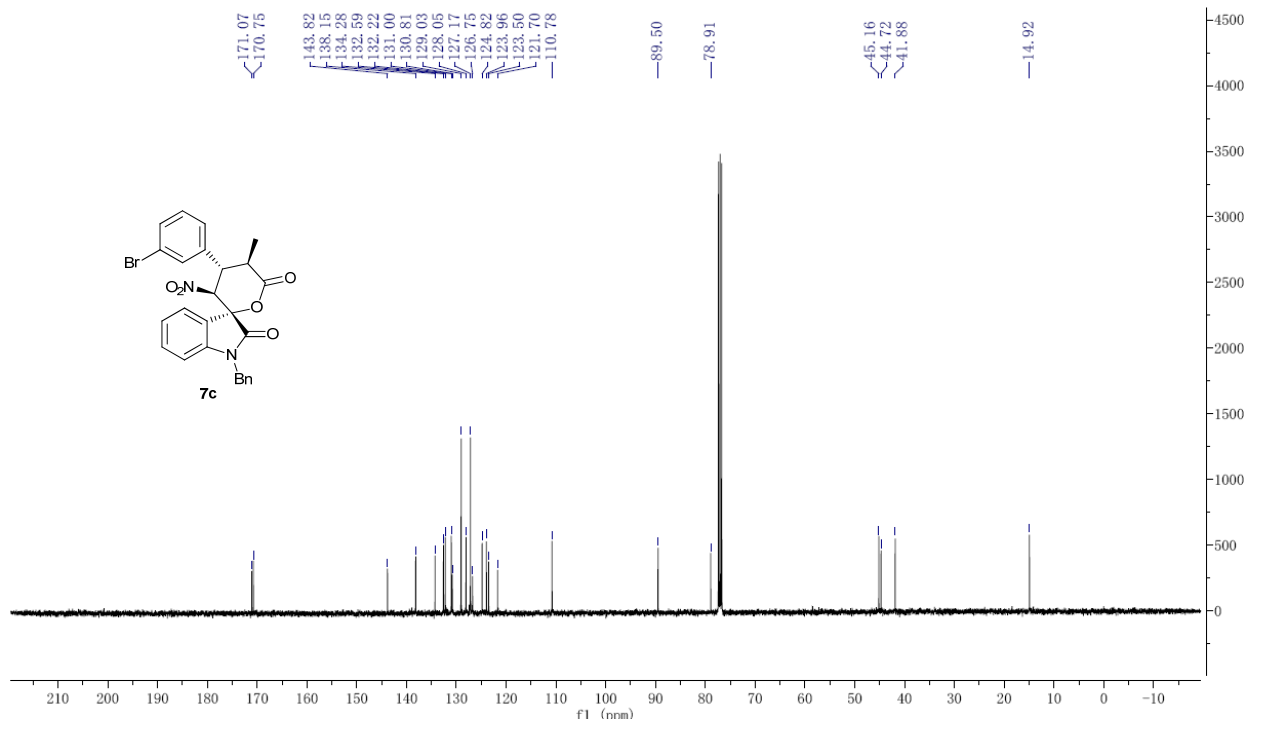

Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
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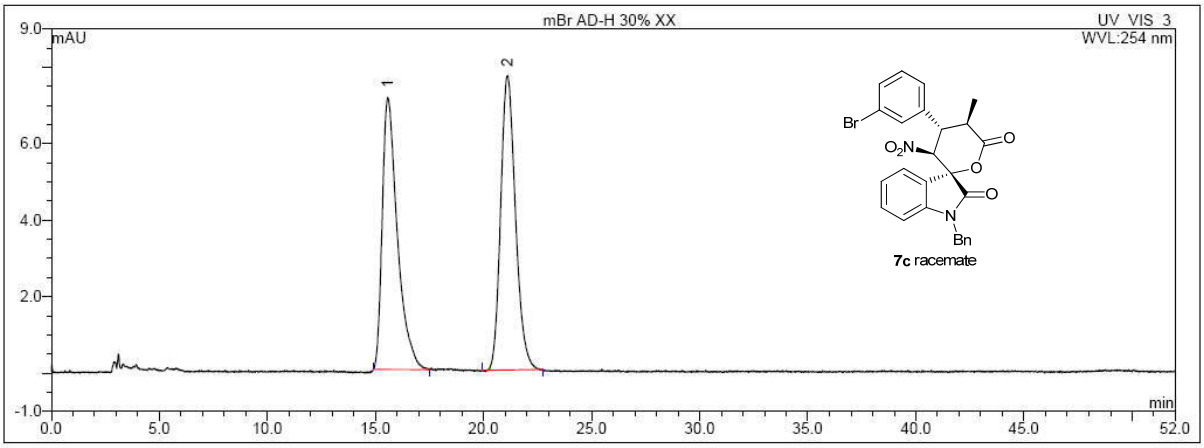
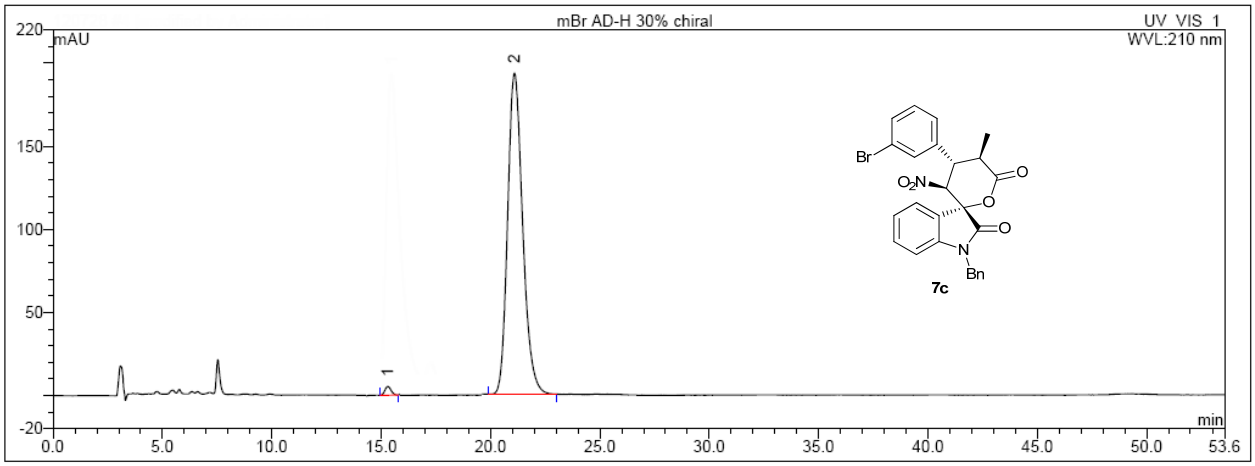
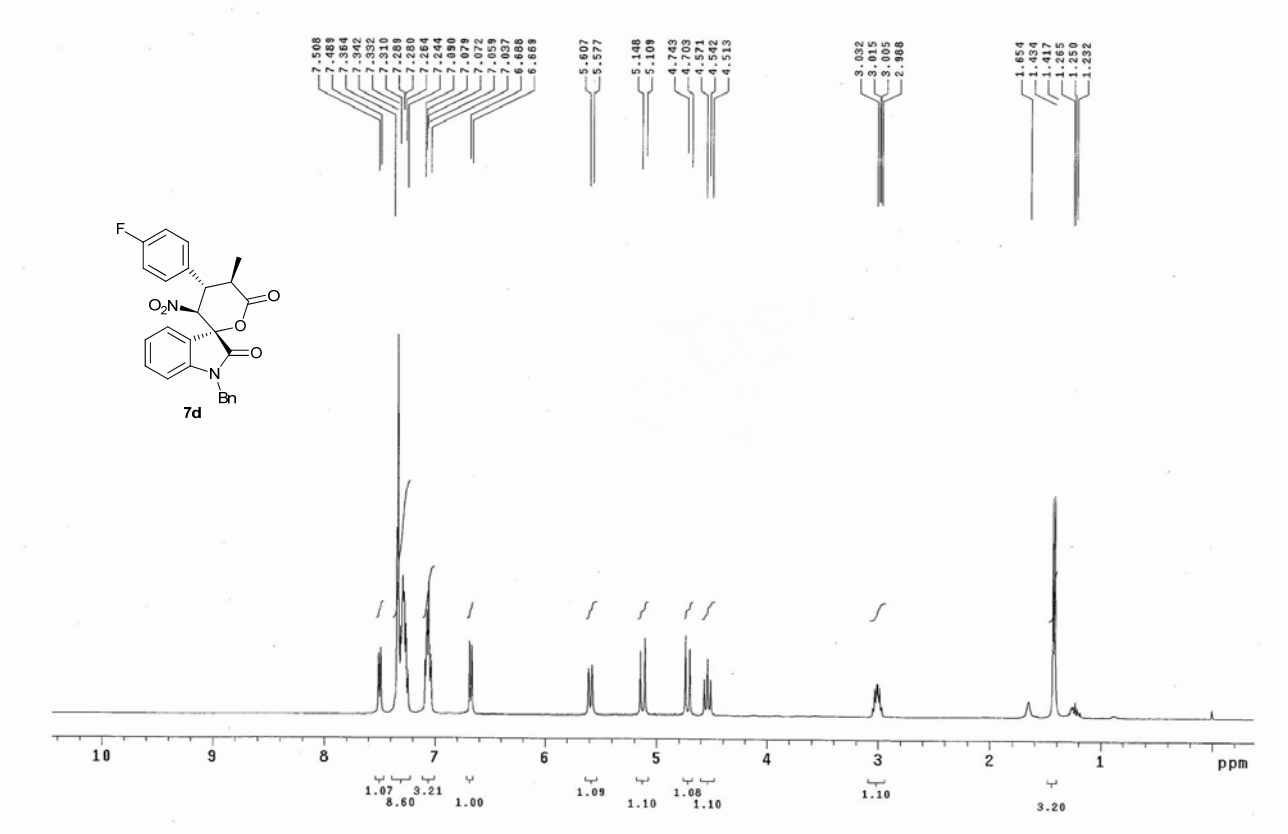
1	n.a.	15.57	6.222	50.51	7.119	n.a.
2	n.a.	21.11	6.095	49.49	7.699	n.a.

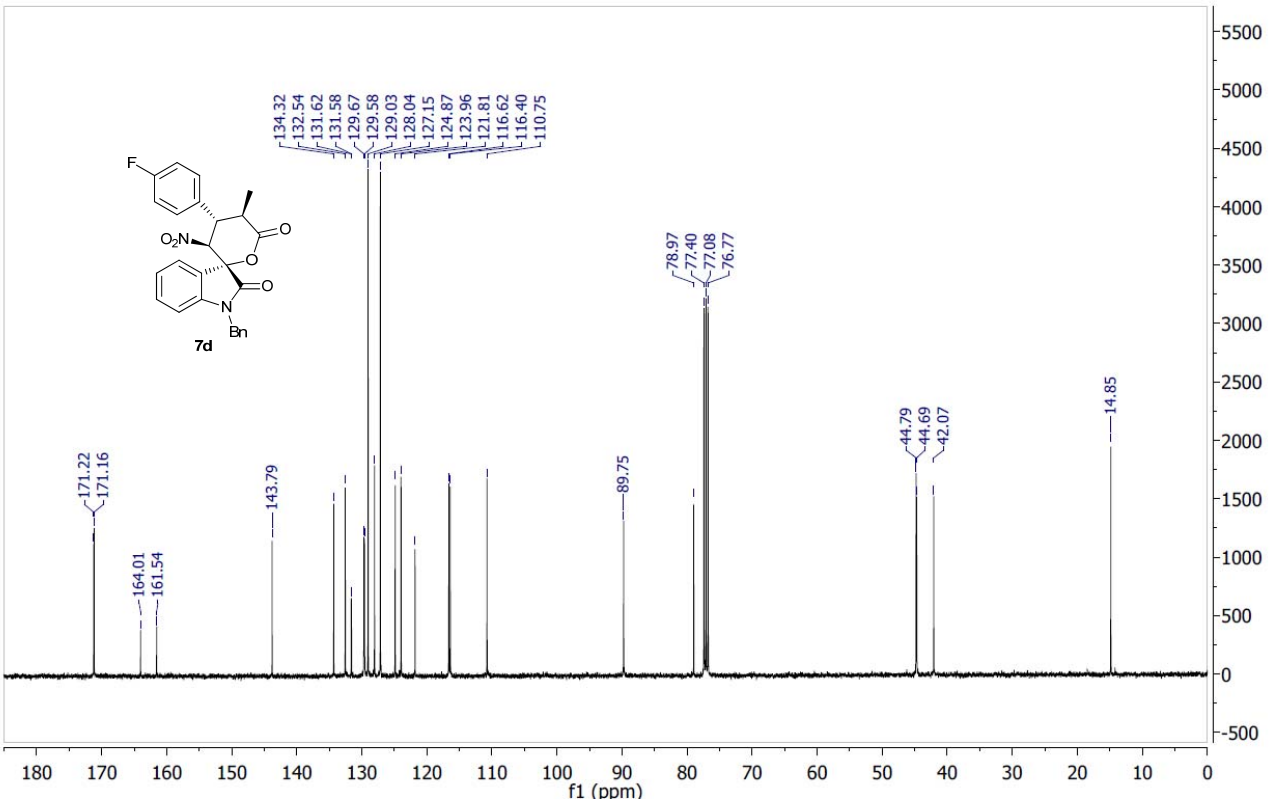


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	15.47	1.699	1.09	5.242	n.a.
2	n.a.	21.09	154.056	98.91	193.306	n.a.

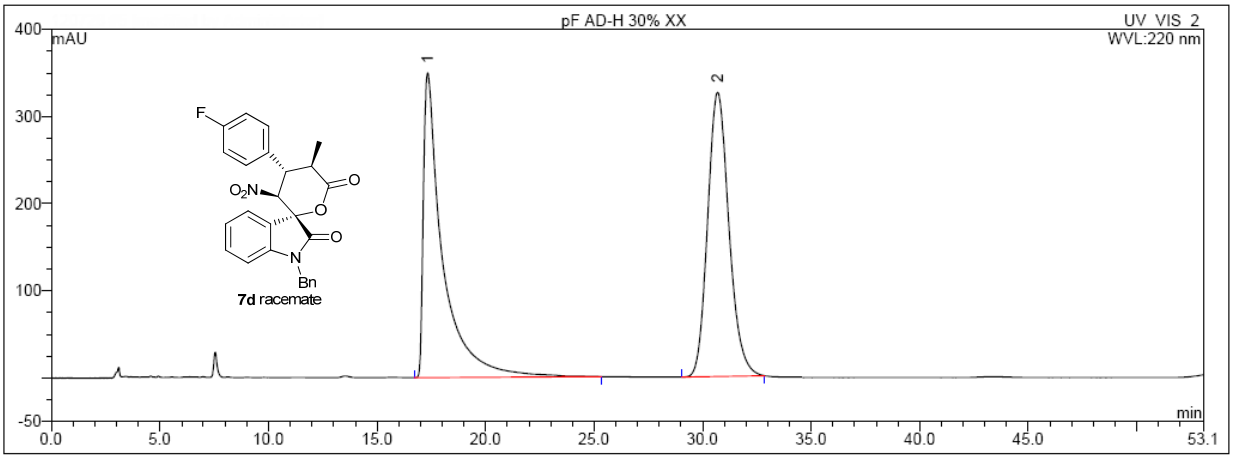






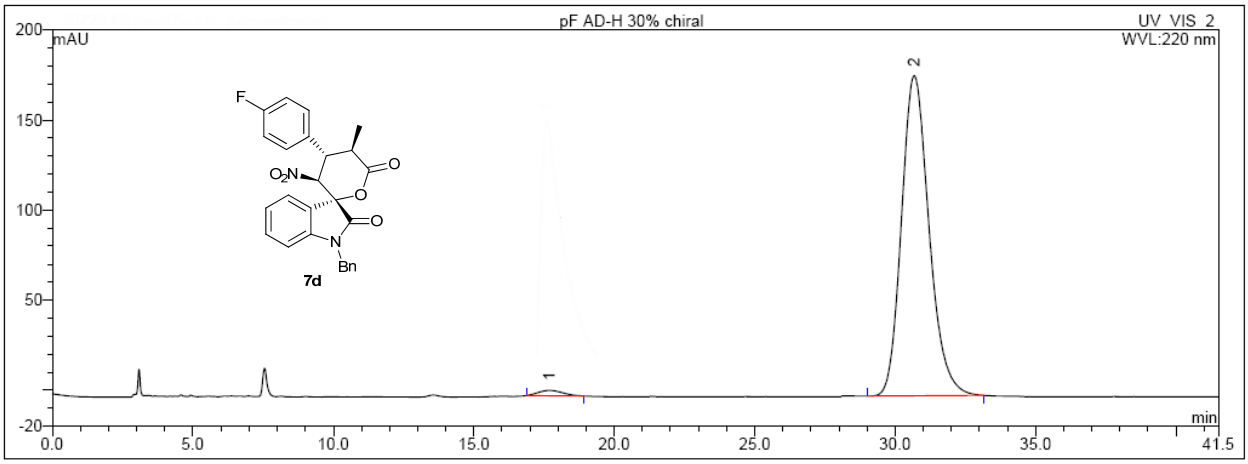
Peak Analysis Report

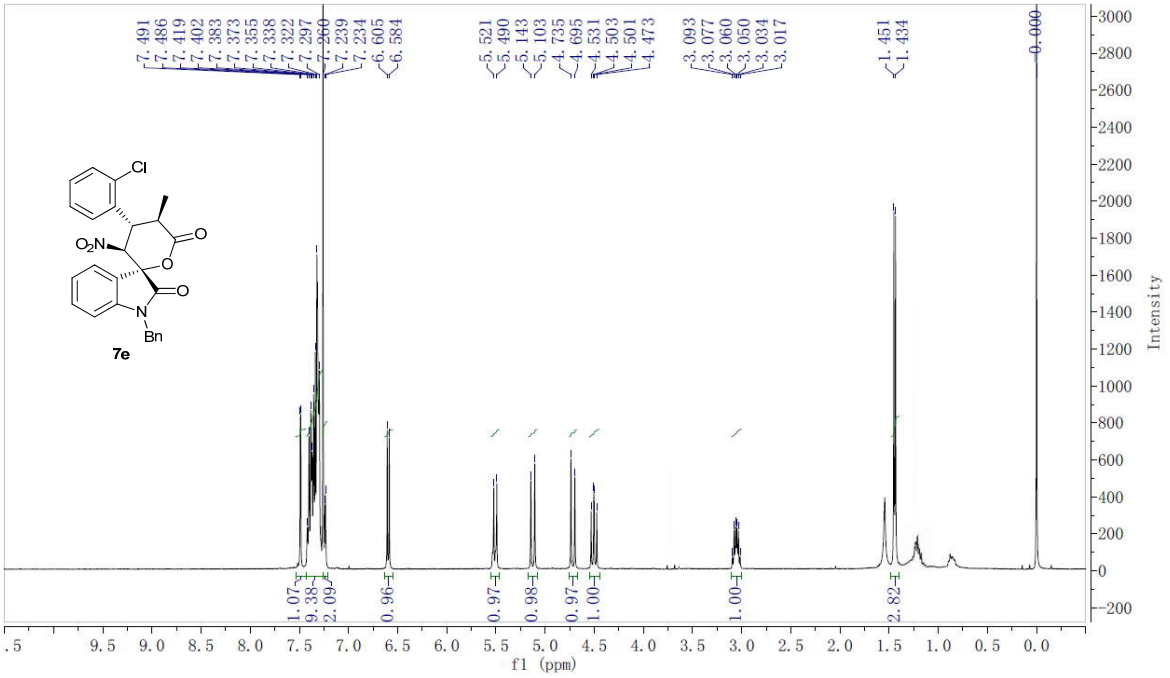
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	17.33	359.367	49.20	349.846	n.a.
2	n.a.	30.69	371.096	50.80	326.237	n.a.

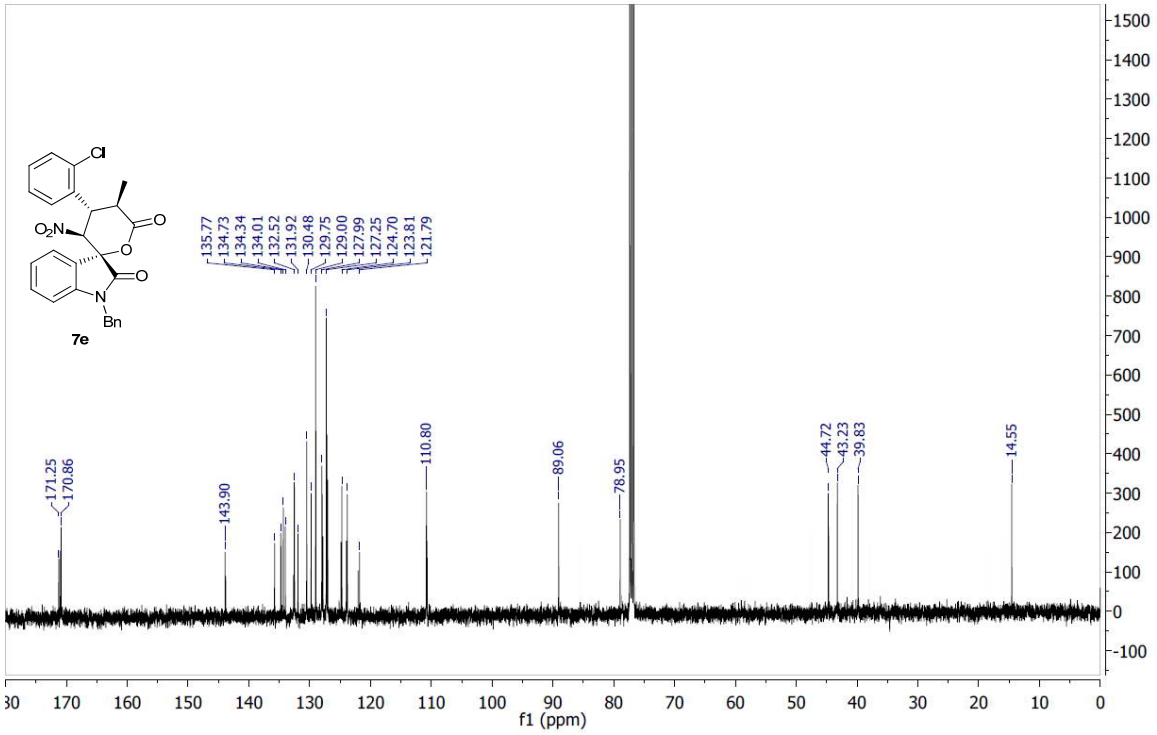


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	17.60	2.938	1.43	2.973	n.a.
2	n.a.	30.68	201.975	98.57	177.653	n.a.

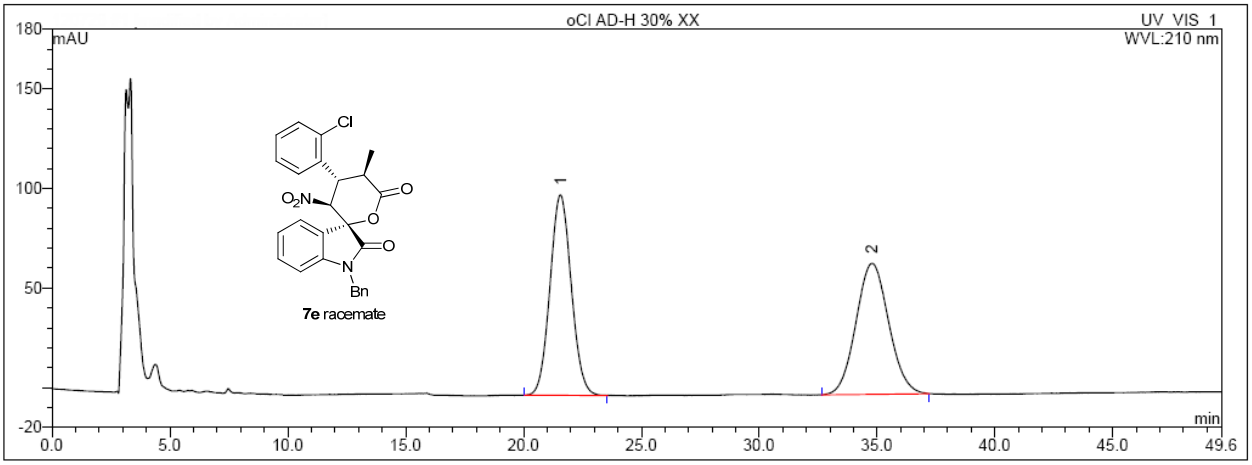






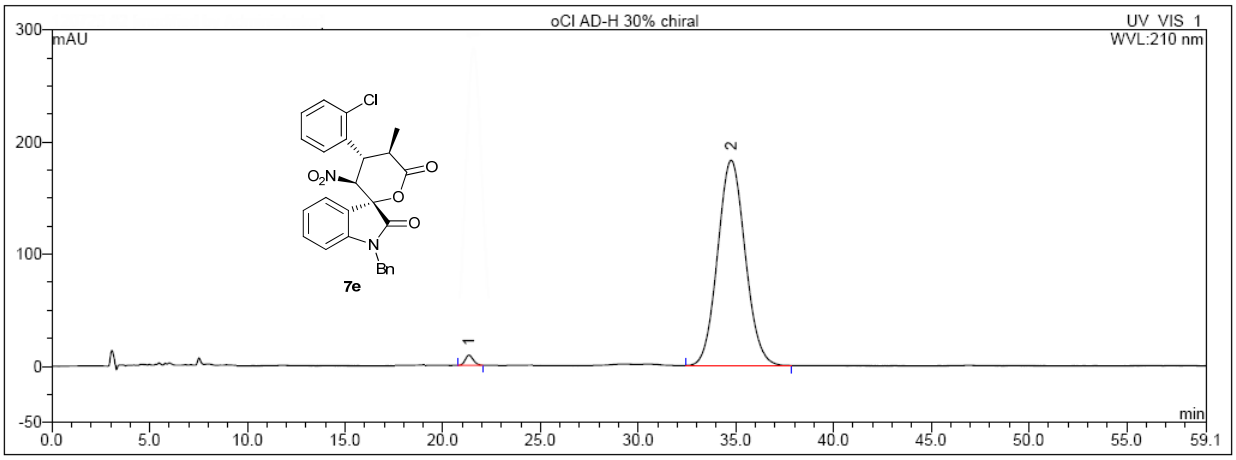
Peak Analysis Report

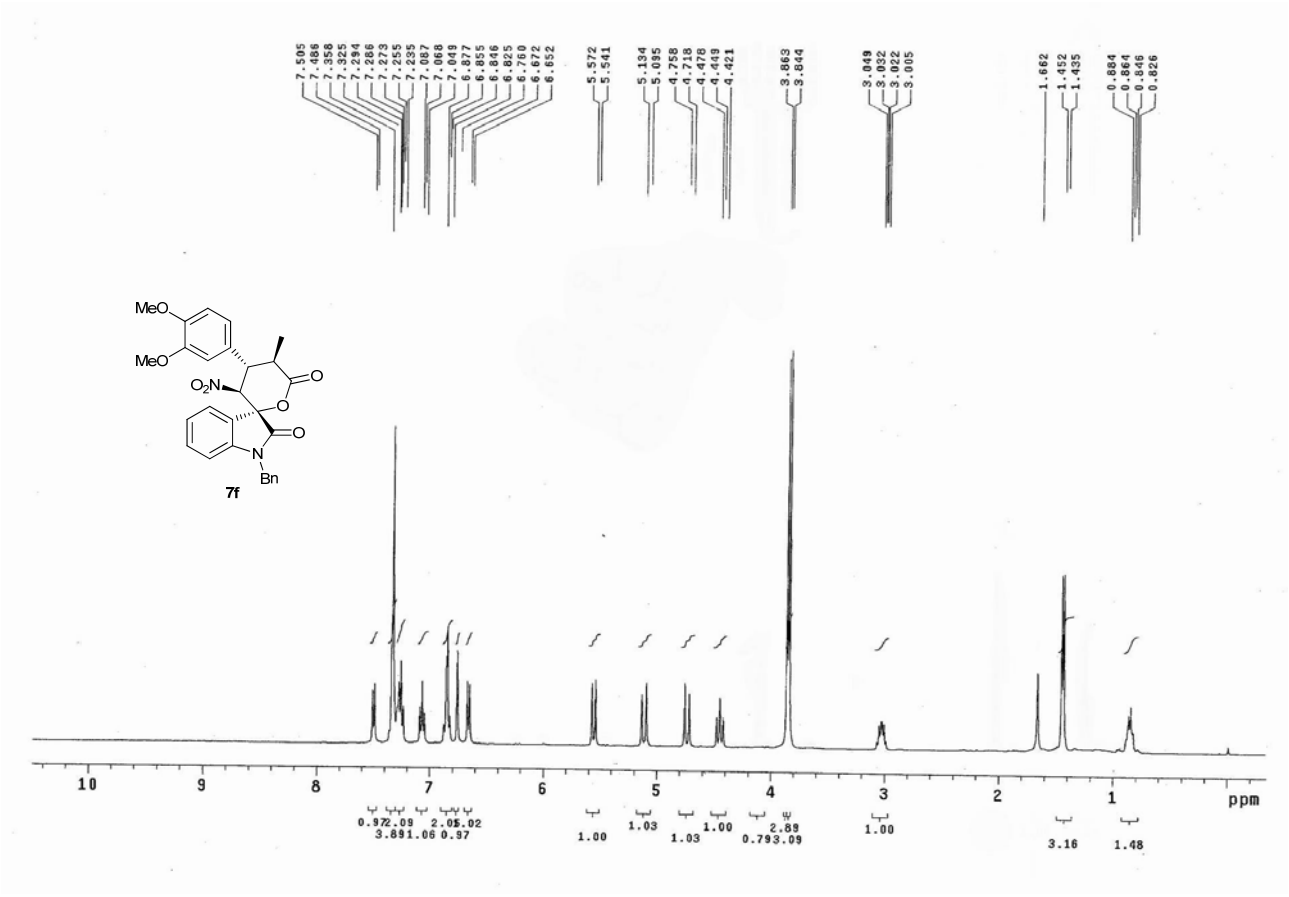
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	21.58	105.436	49.93	100.675	n.a.
2	n.a.	34.78	105.742	50.07	65.780	n.a.

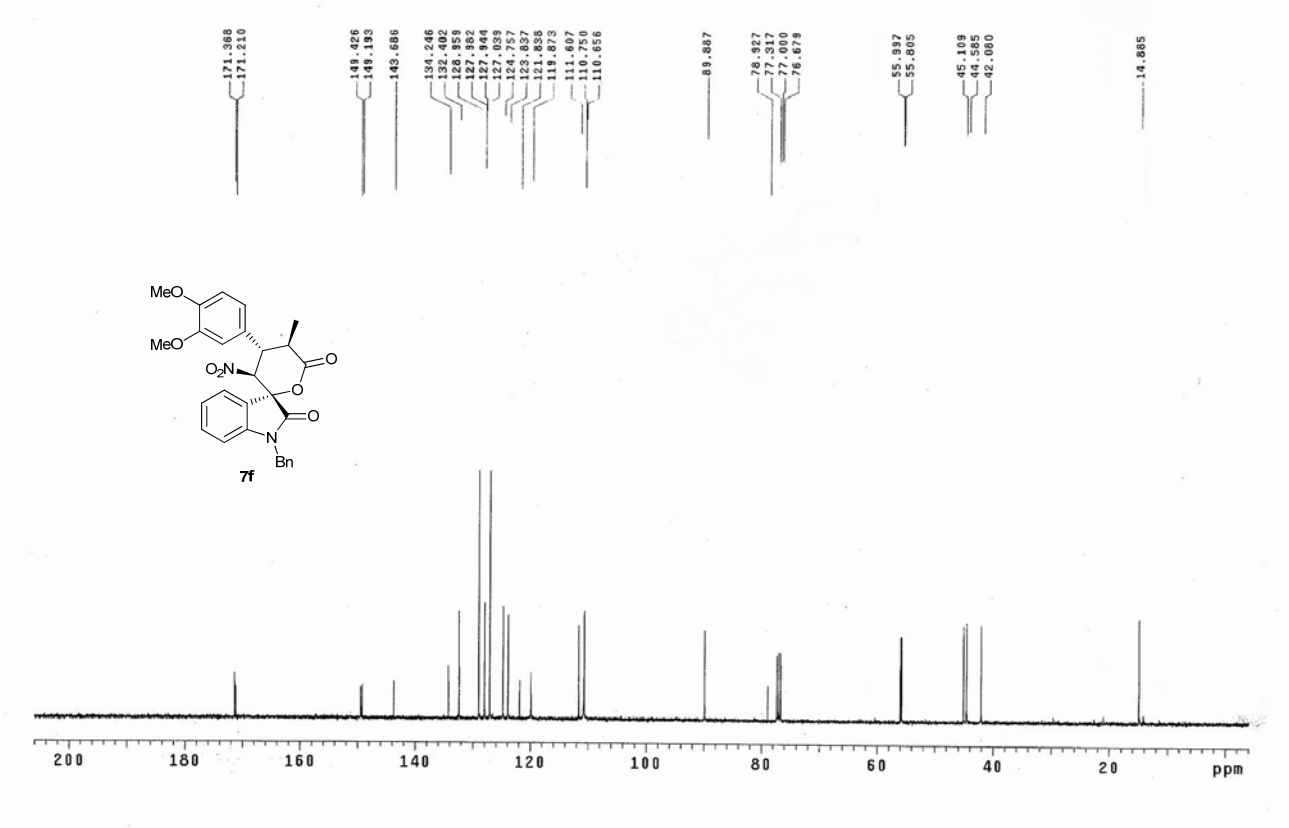


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	21.58	4.275	1.41	9.046	n.a.
2	n.a.	34.76	299.435	98.59	183.143	n.a.

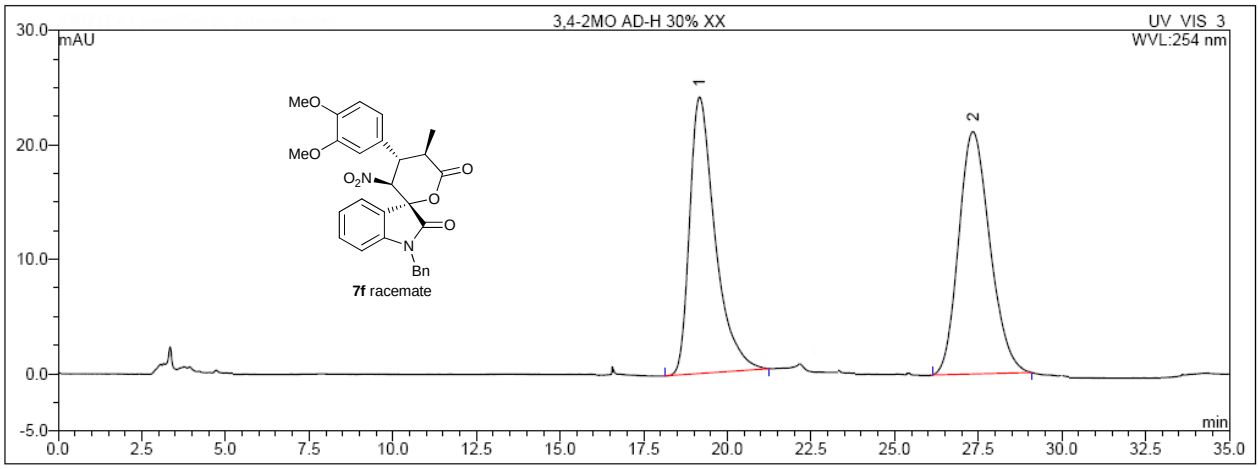






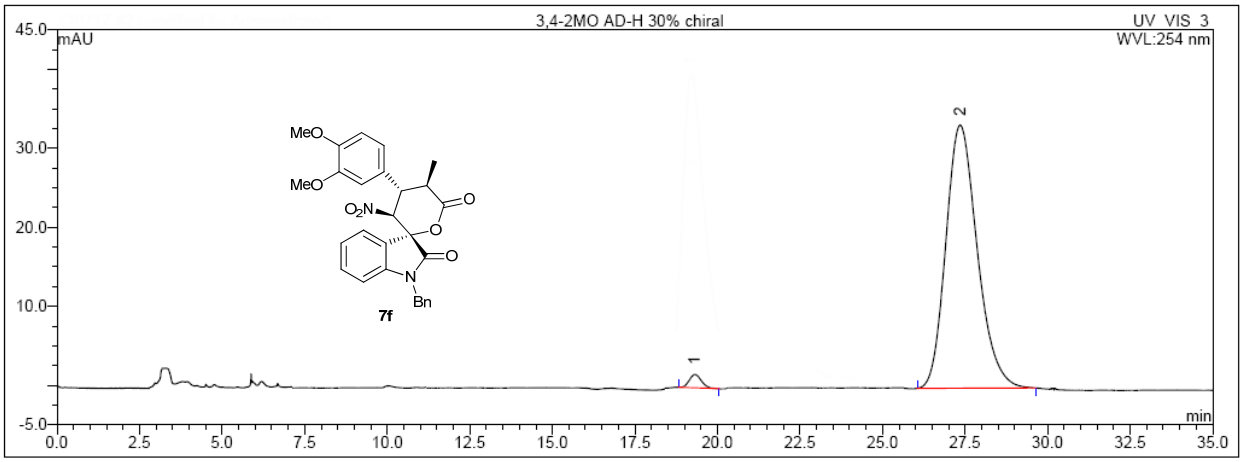
Peak Analysis Report

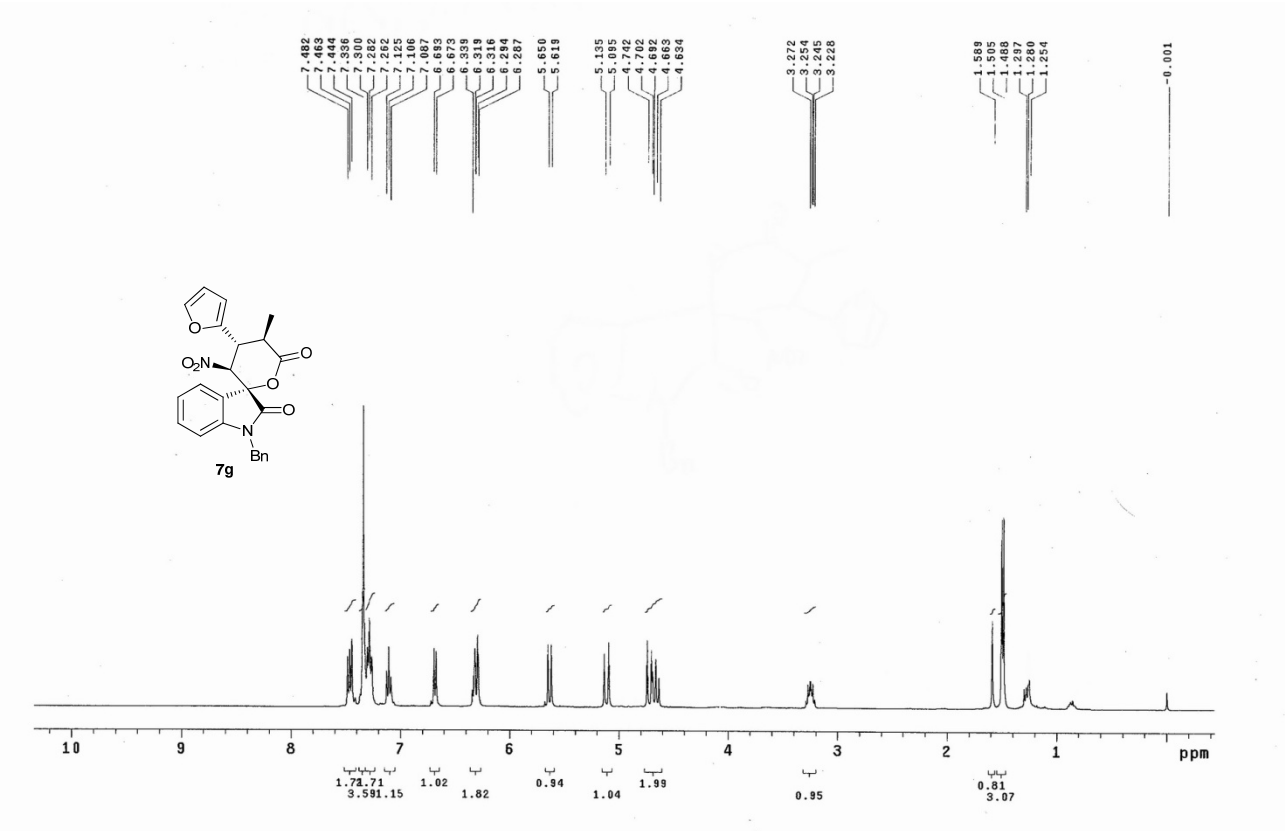
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	19.17	21.302	48.20	24.155	n.a.
2	n.a.	27.35	22.895	51.80	21.169	n.a.

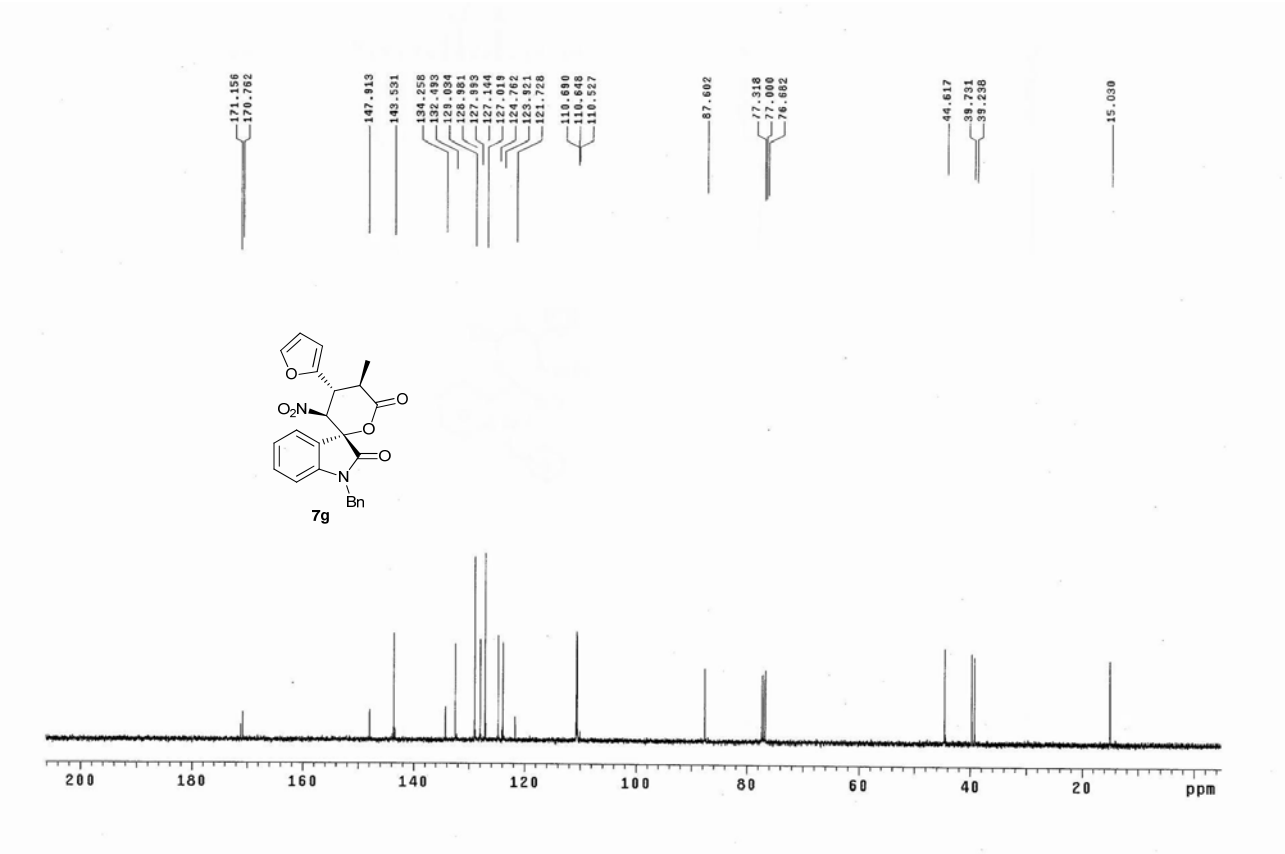


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	19.22	0.715	1.91	1.694	n.a.
2	n.a.	27.35	36.707	98.09	33.325	n.a.

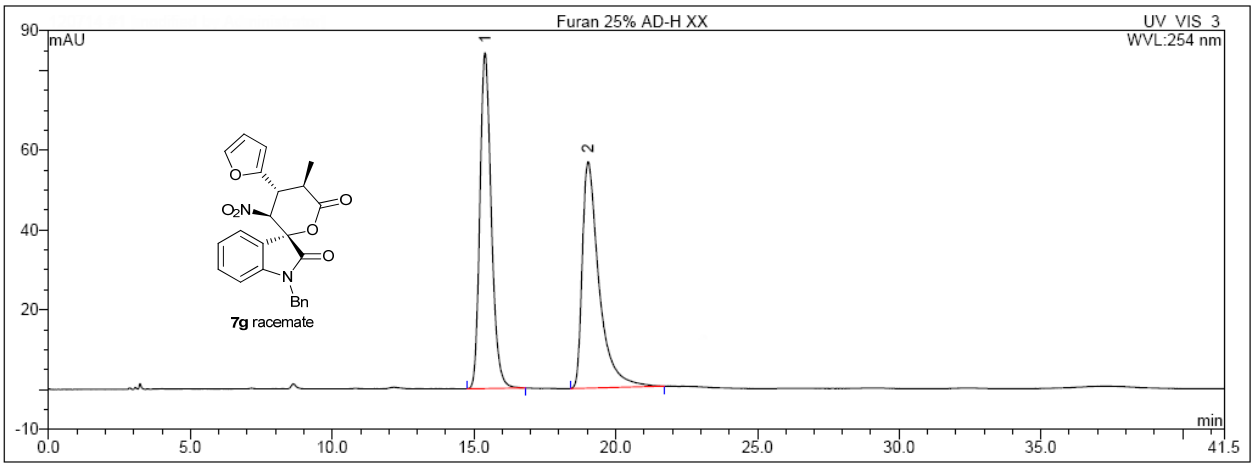






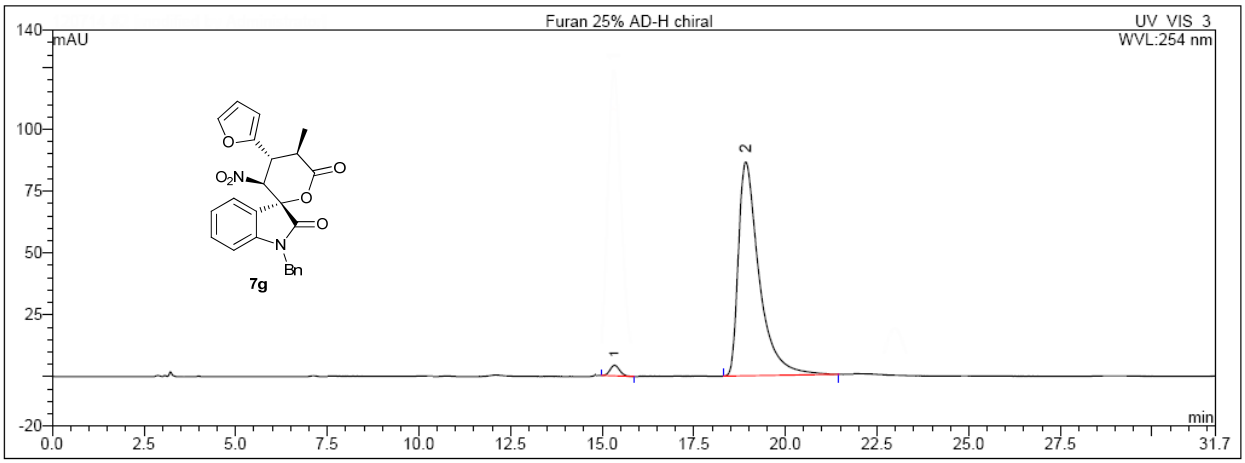
Peak Analysis Report

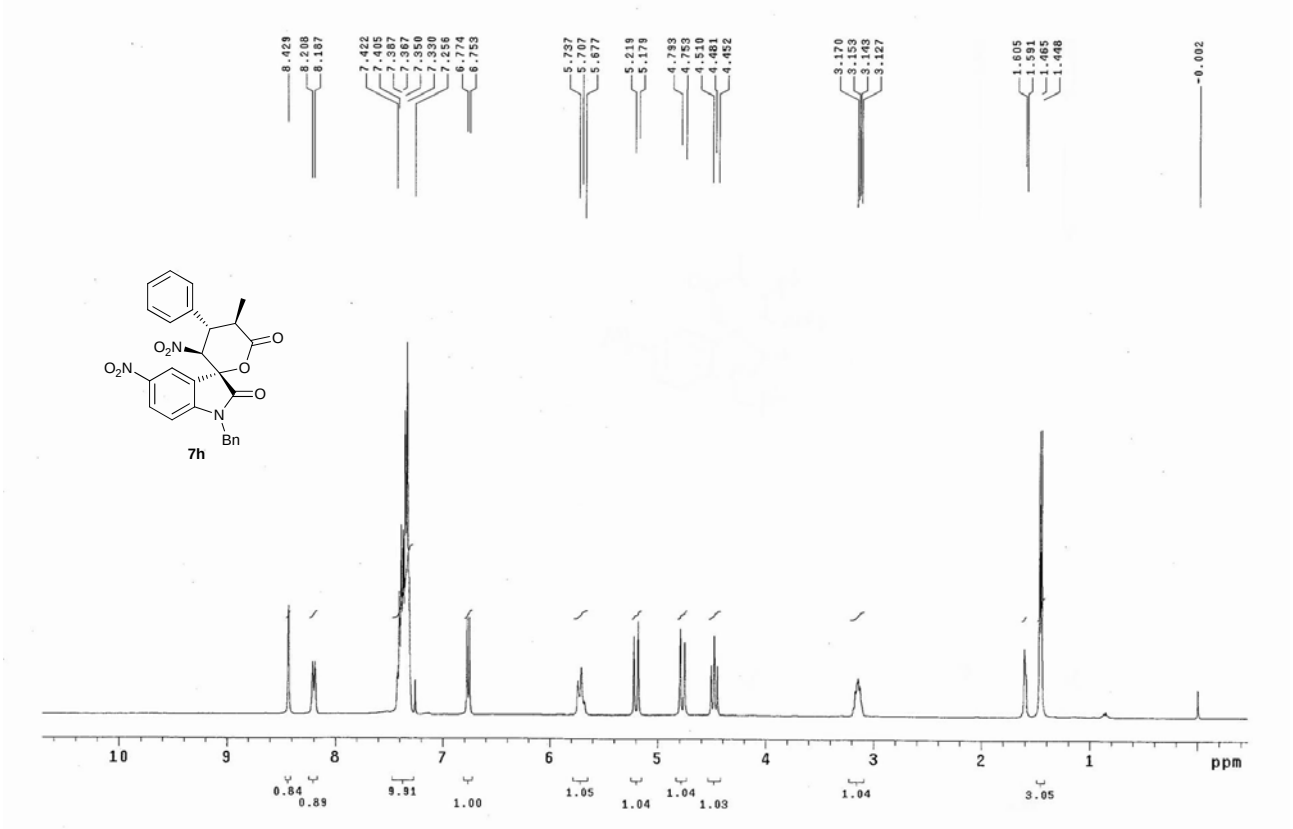
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	15.39	39.256	50.28	84.166	n.a.
2	n.a.	19.03	38.824	49.72	56.744	n.a.

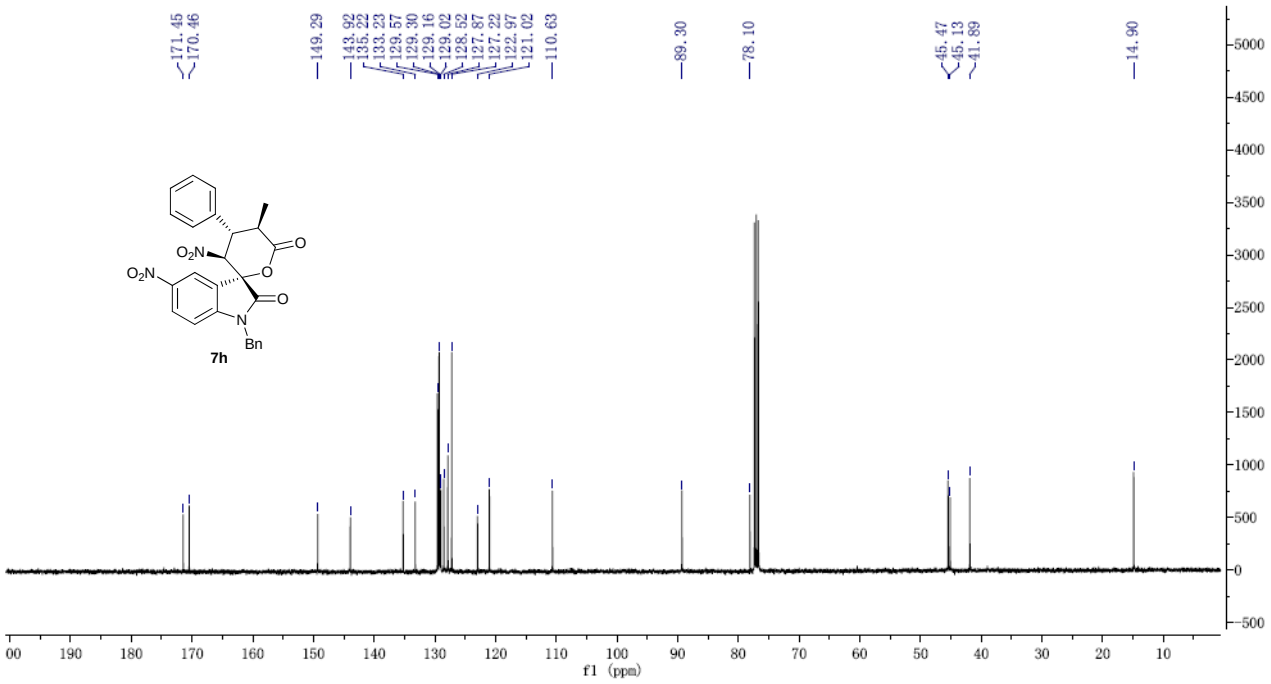


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	15.32	1.882	3.20	15.632	n.a.
2	n.a.	18.92	56.884	96.80	86.436	n.a.

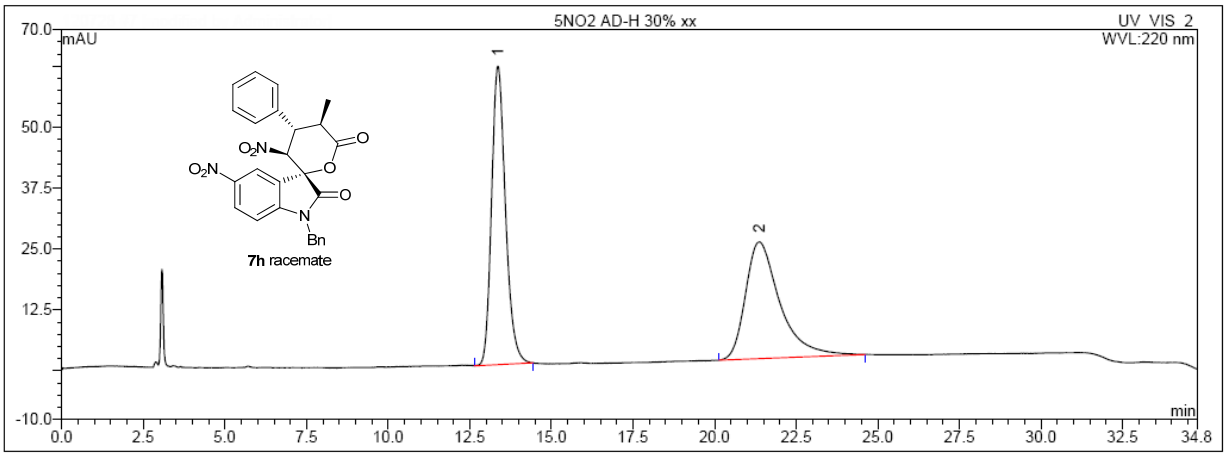






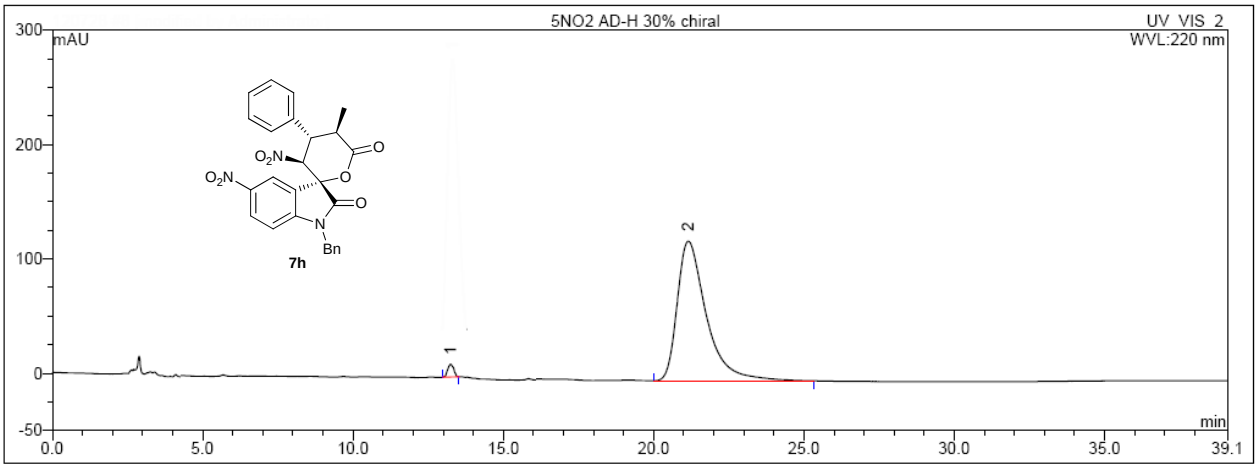
Peak Analysis Report

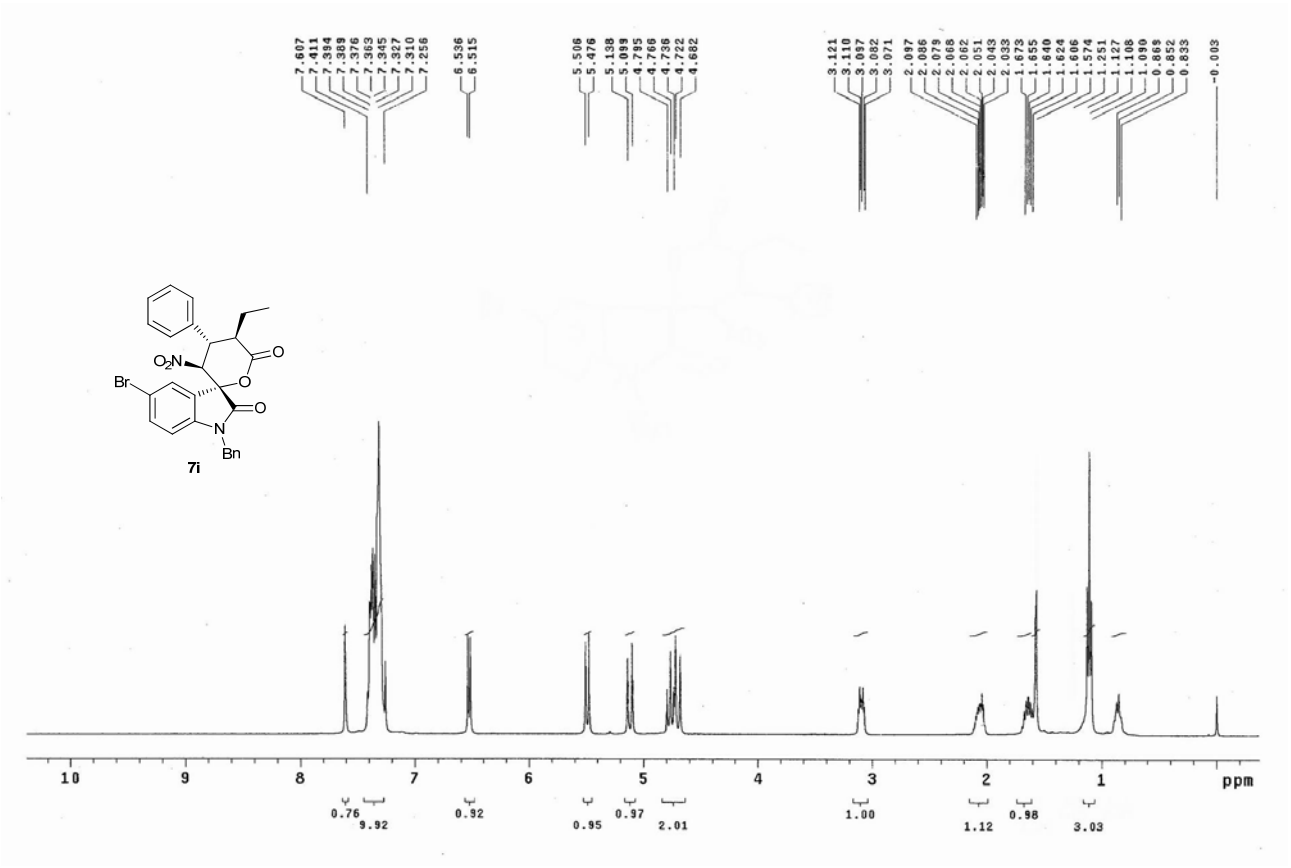
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	13.36	30.356	50.93	61.288	n.a.
2	n.a.	21.38	29.246	49.07	23.959	n.a.

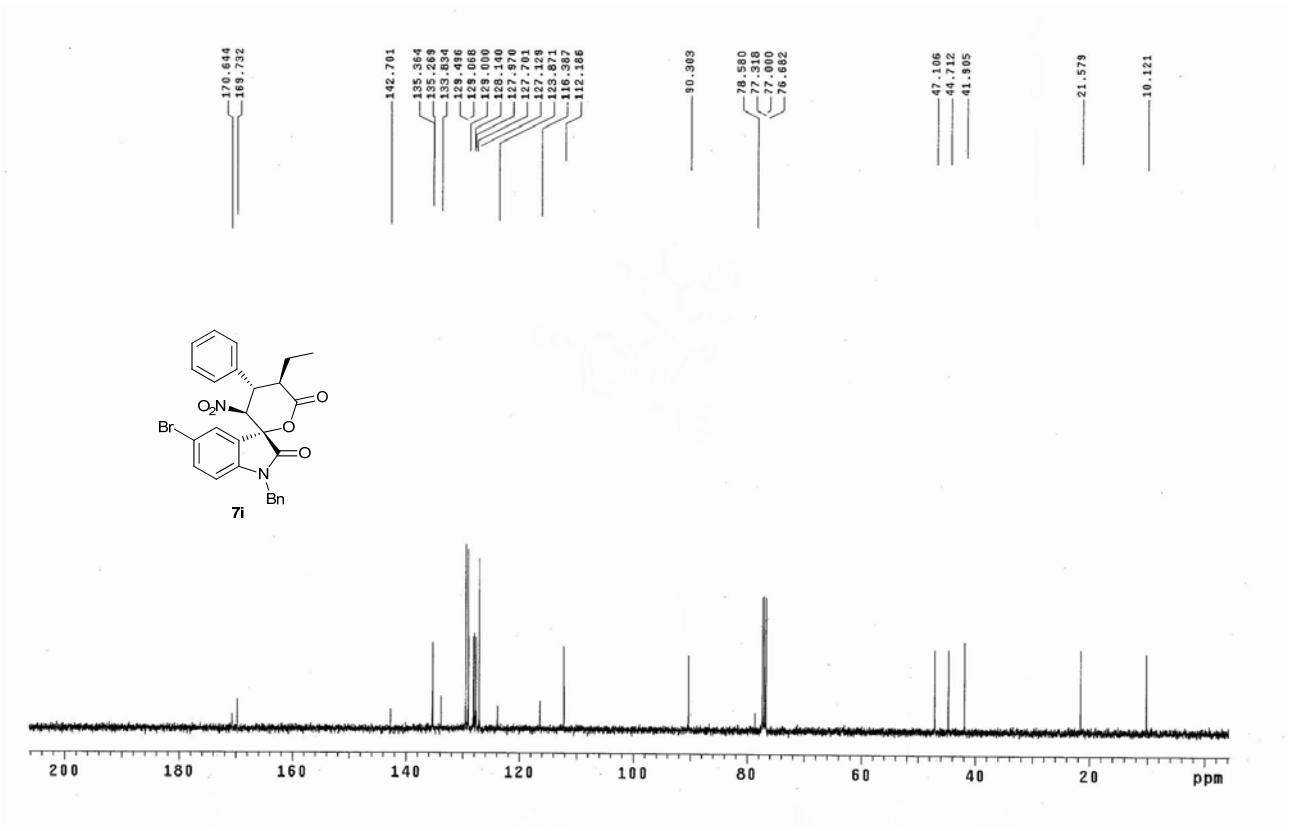


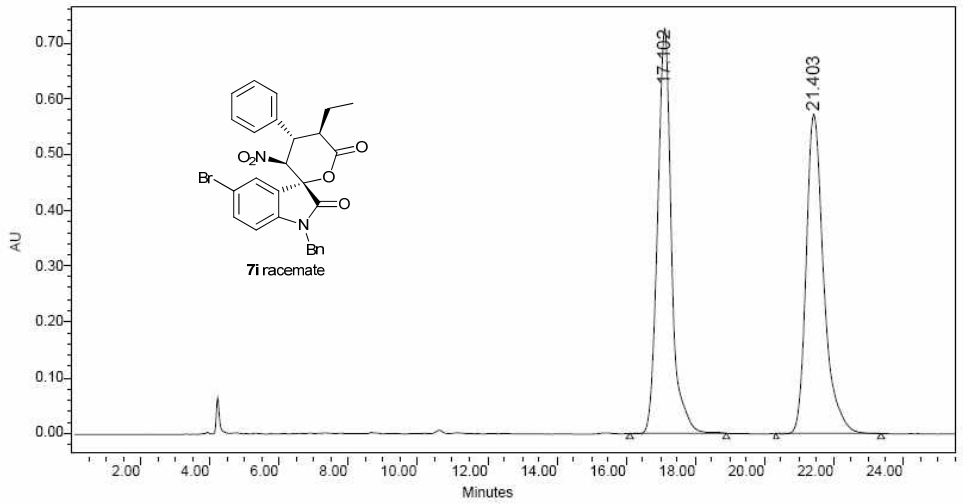
Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	13.31	2.538	1.82	11.019	n.a.
2	n.a.	21.15	137.081	98.18	122.062	n.a.

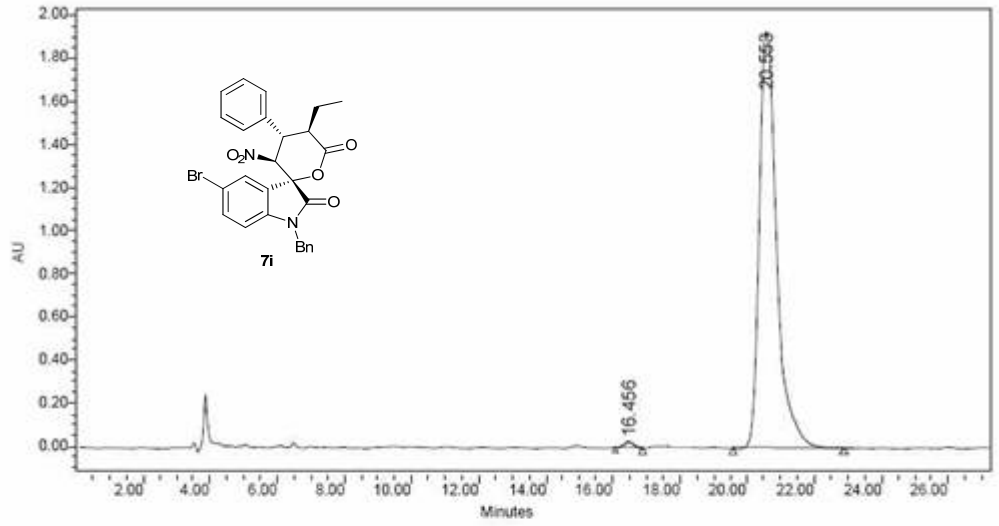




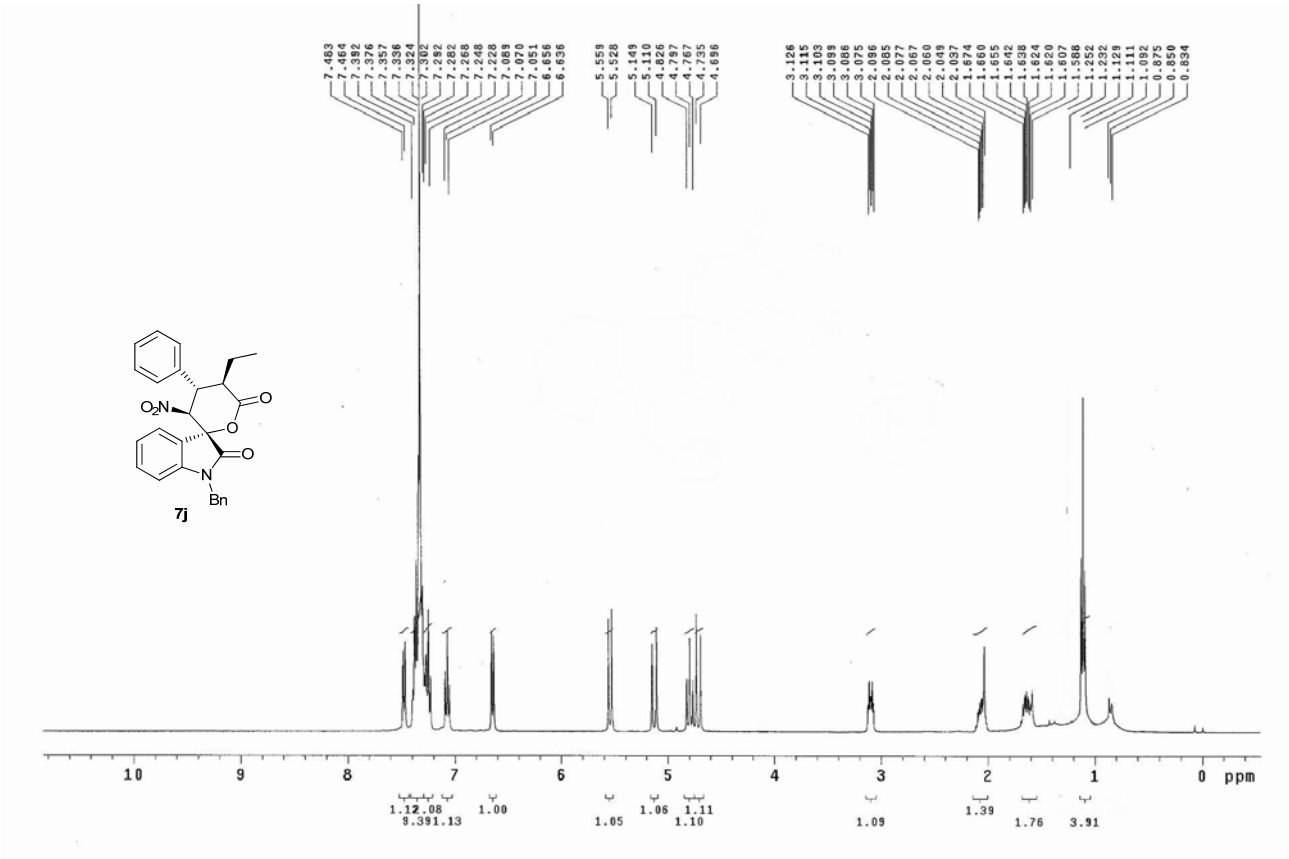


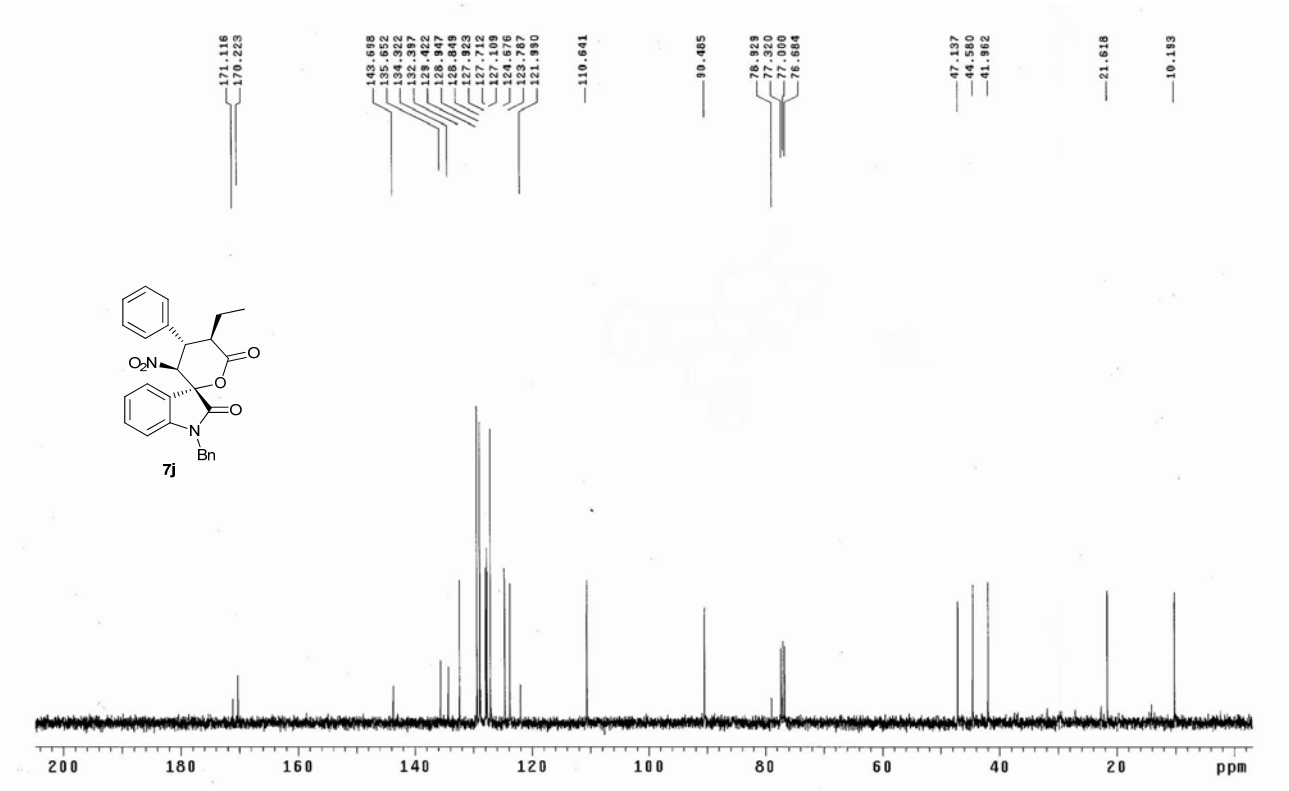


	RT (min)	Area (V *sec)	% Area	Height (V)	% Height
1	17.102	20121873	49.97	724532	55.91
2	21.403	20147282	50.03	571327	44.09



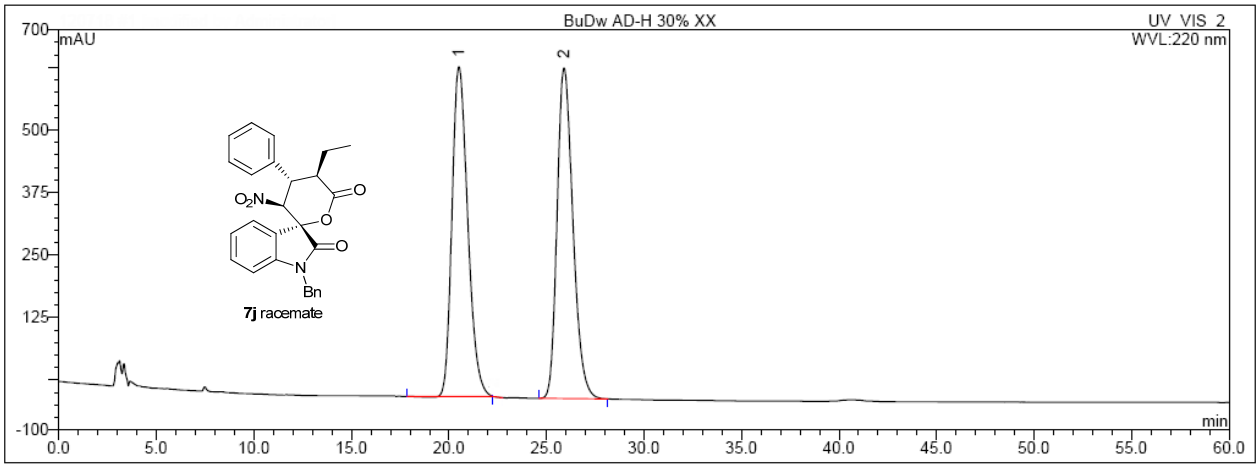
	RT (min)	Area (V *sec)	% Area	Height (V)	% Height
1	16.456	567105	0.80	27628	1.41
2	20.553	70556253	99.20	1930934	98.59





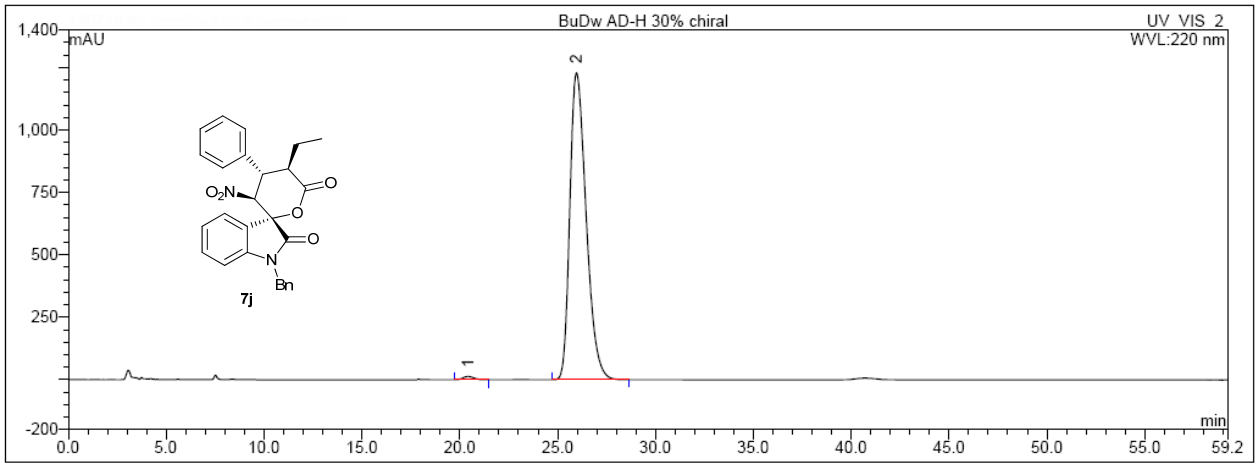
Peak Analysis Report

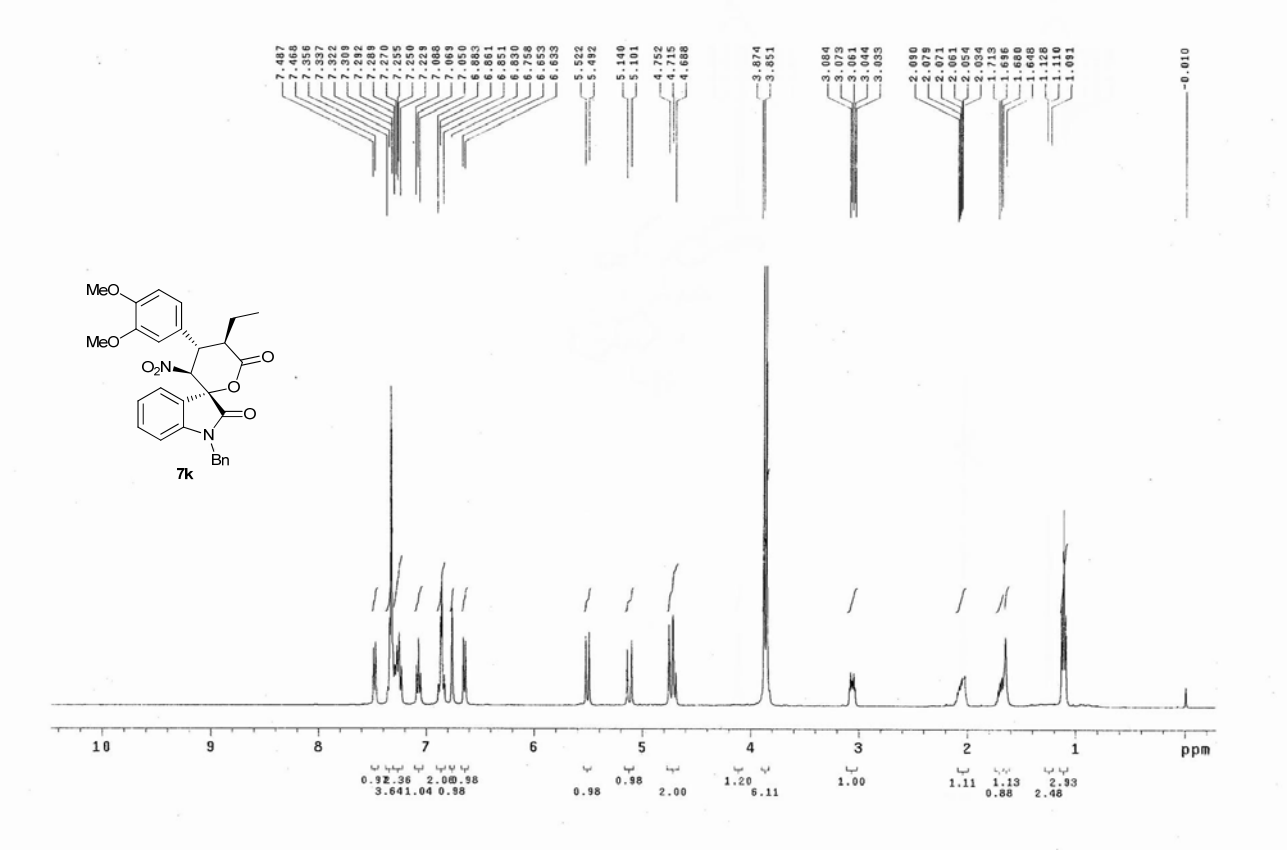
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	20.36	615.454	49.20	658.971	n.a.
2	n.a.	25.90	622.966	50.80	660.837	n.a.

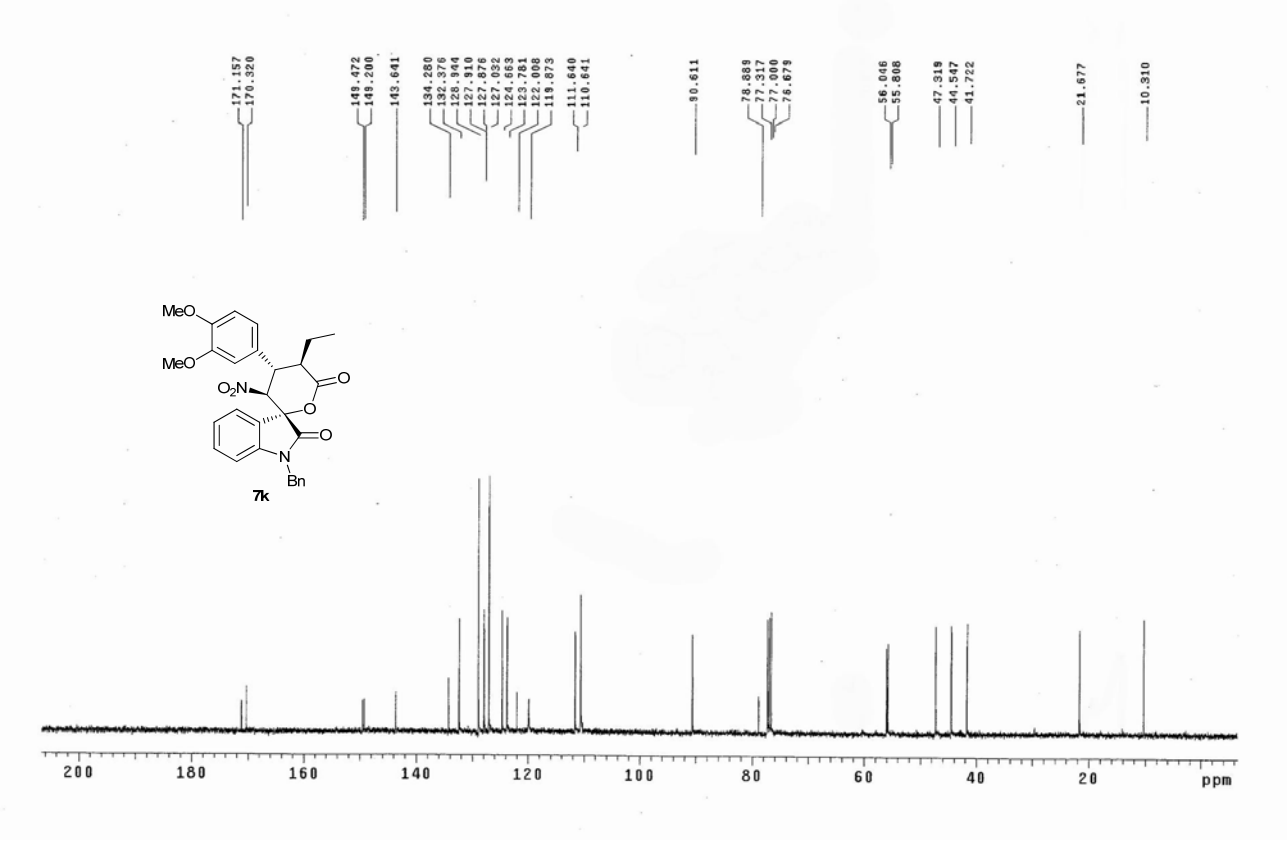


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	20.43	8.507	0.71	13.438	n.a.
2	n.a.	25.97	1187.532	99.29	1229.430	n.a.

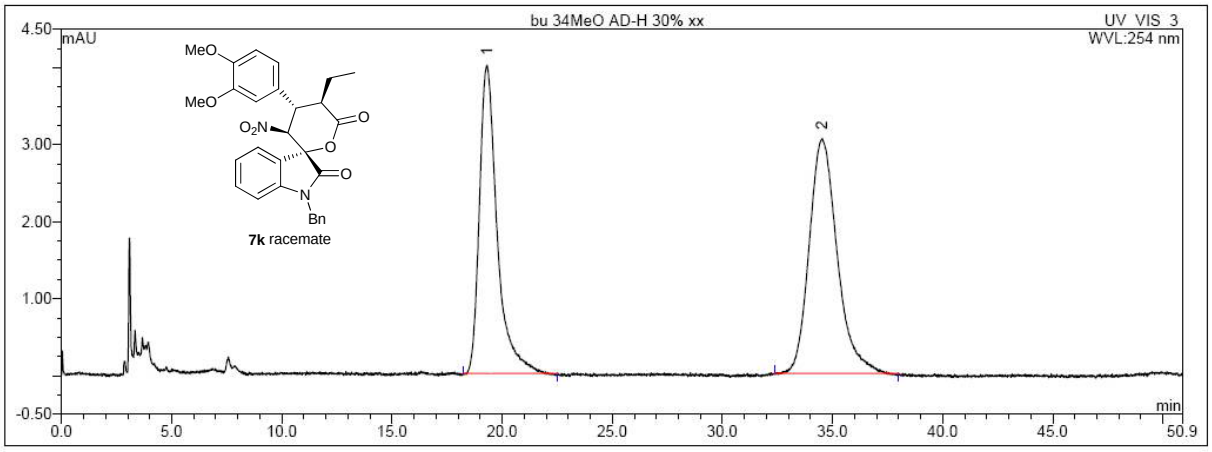






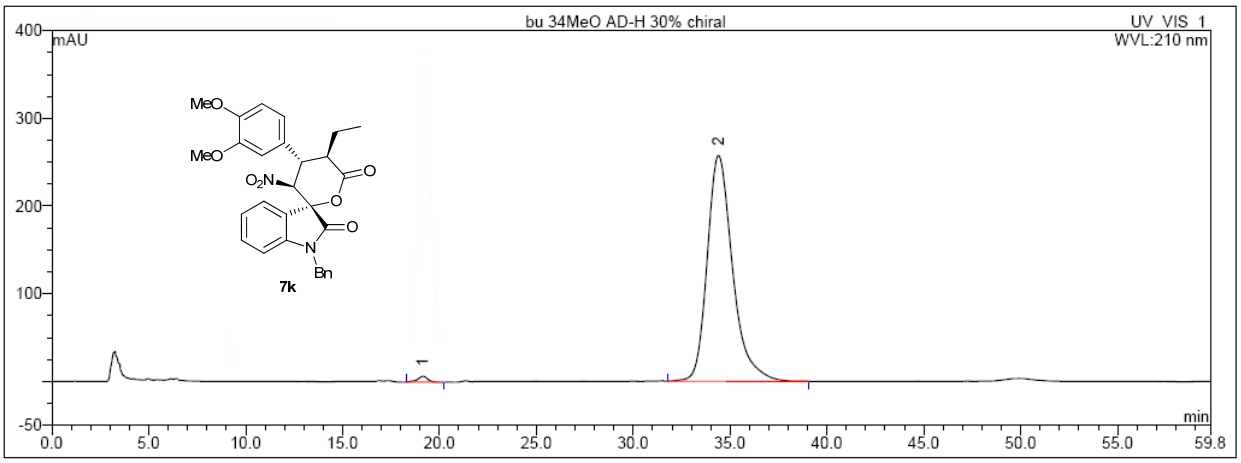
Peak Analysis Report

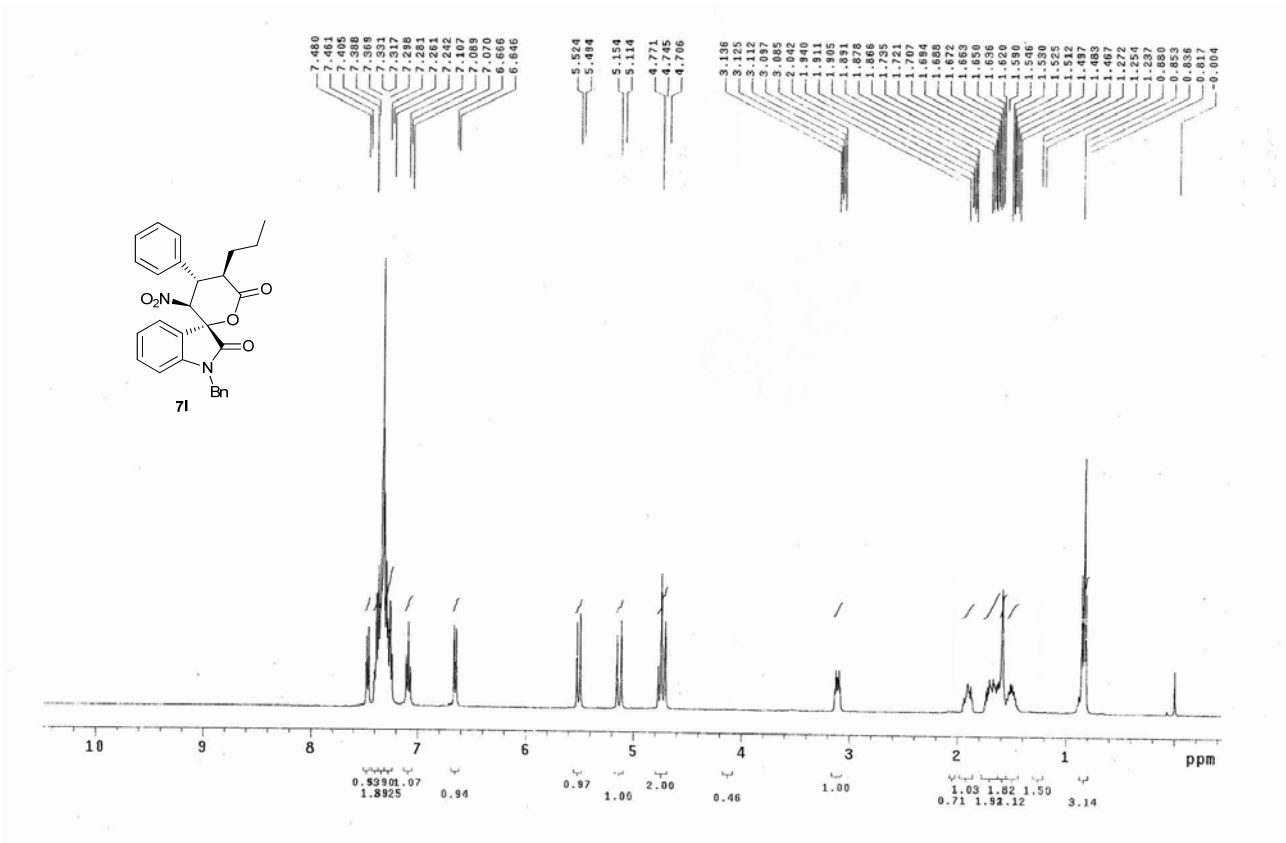
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	19.32	3.974	49.07	4.007	n.a.
2	n.a.	34.53	4.124	50.93	2.976	n.a.



Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	19.18	3.953	1.00	6.644	n.a.
2	n.a.	34.40	391.655	99.00	257.411	n.a.

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7l
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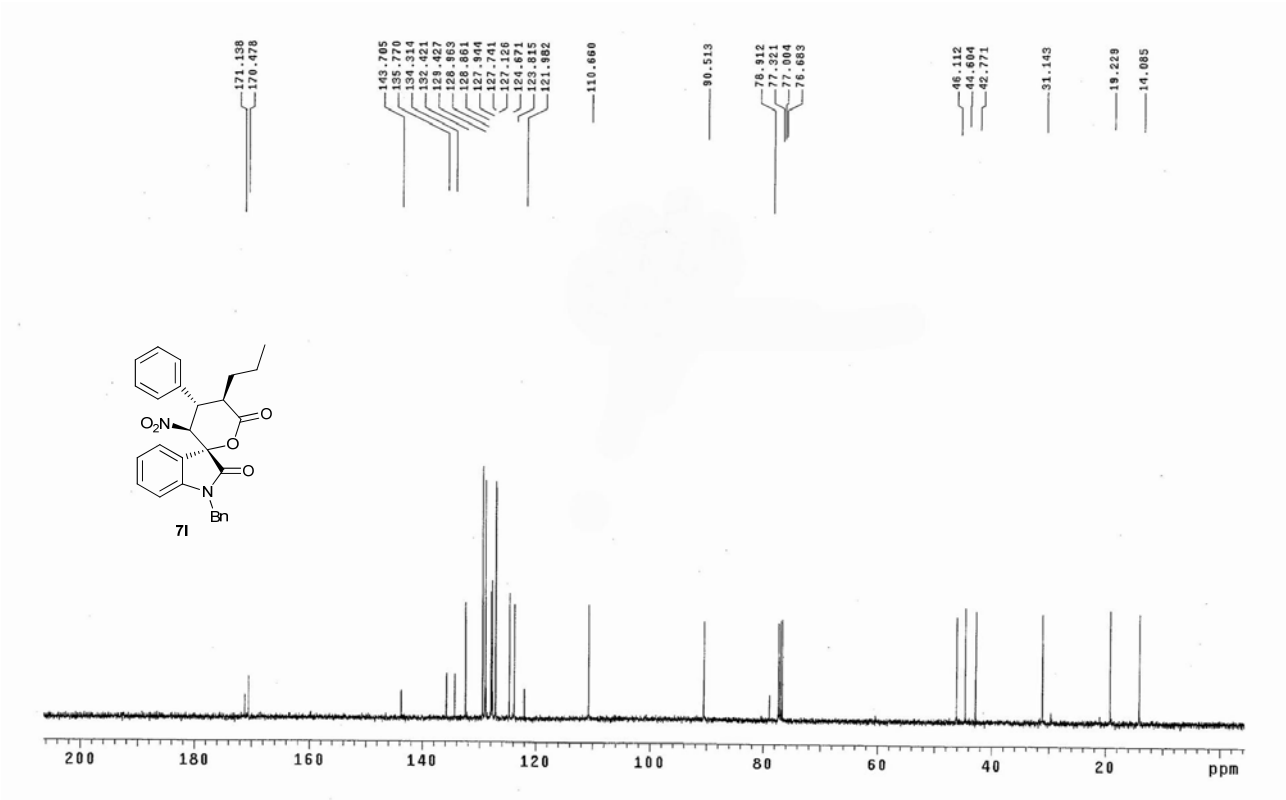
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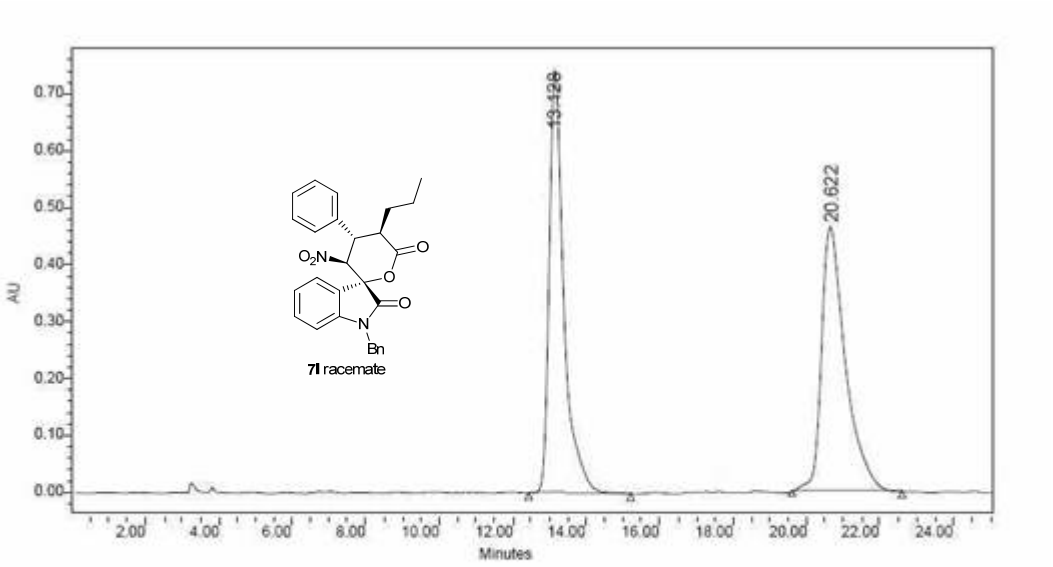
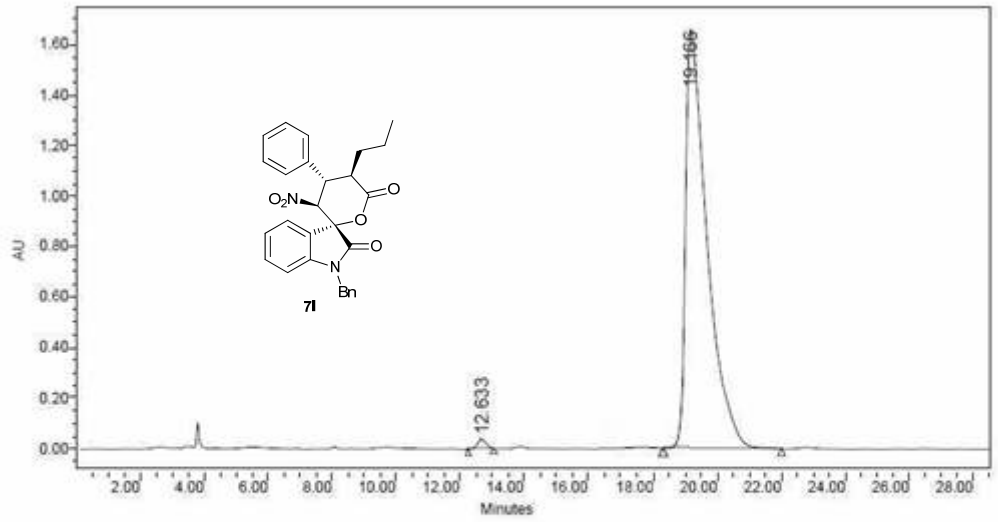
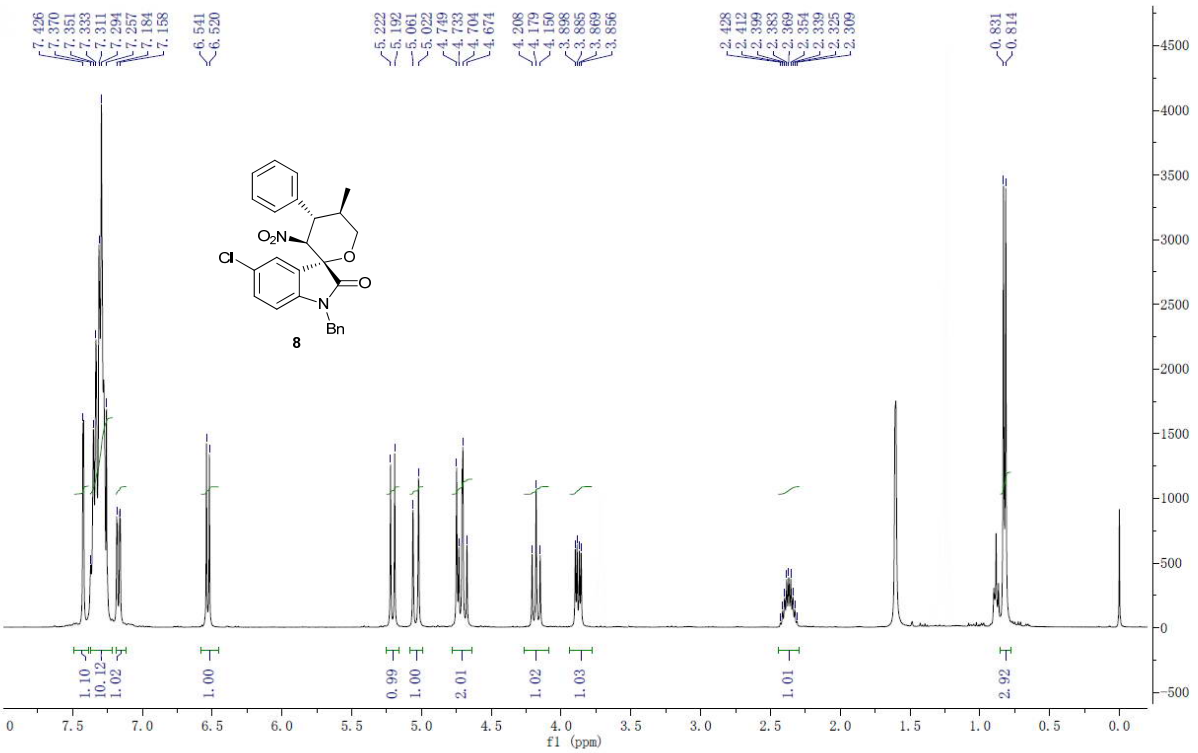


	RT (min)	Area (V *sec)	% Area	Height (V)	% Height
1	13.128	21217528	50.22	740293	61.52
2	20.622	21028713	49.78	463067	38.48



	RT (min)	Area (V *sec)	% Area	Height (V)	% Height
1	12.633	717463	0.89	36952	2.18
2	19.166	79492705	99.11	1659145	97.82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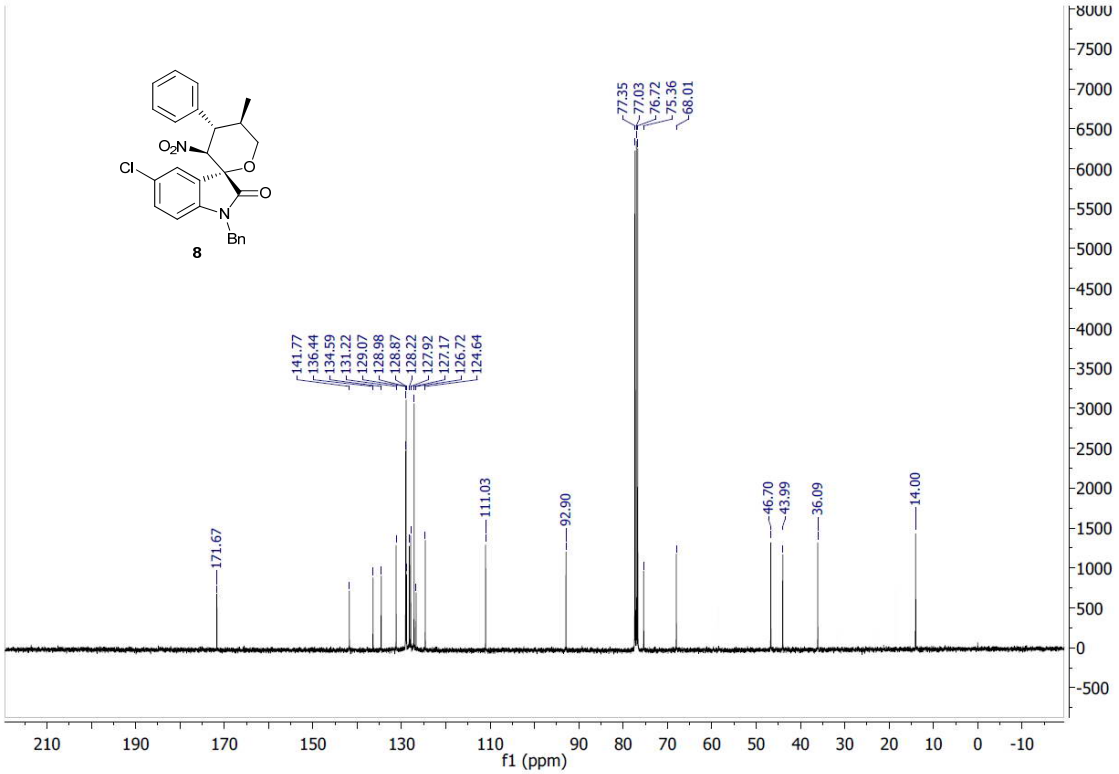
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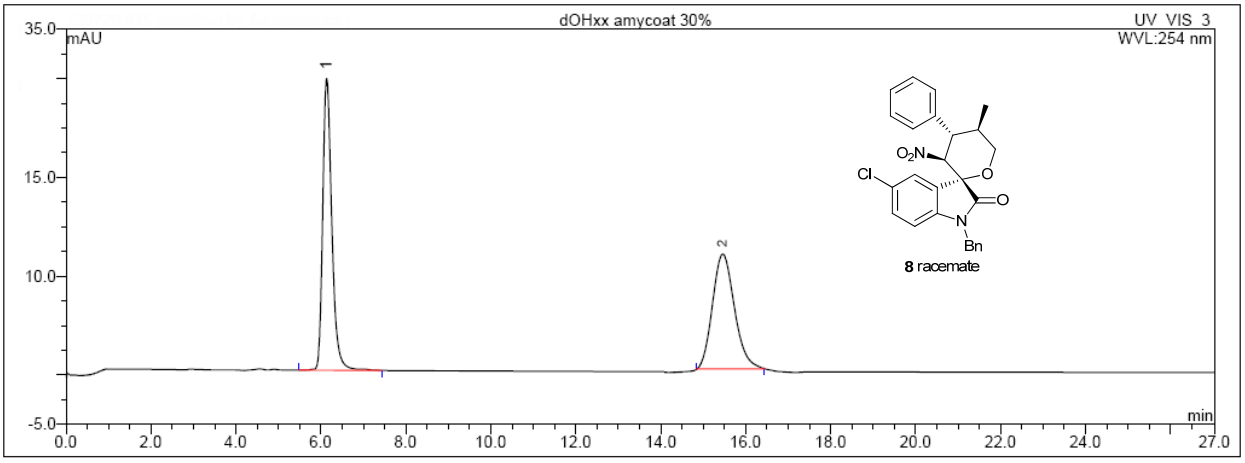
141.77
136.44
134.59
131.22
129.07
128.98
128.87
128.22
127.92
127.17
126.72
124.64
171.67
111.03
92.90
46.70
43.99
36.09
14.00
f1 (ppm)

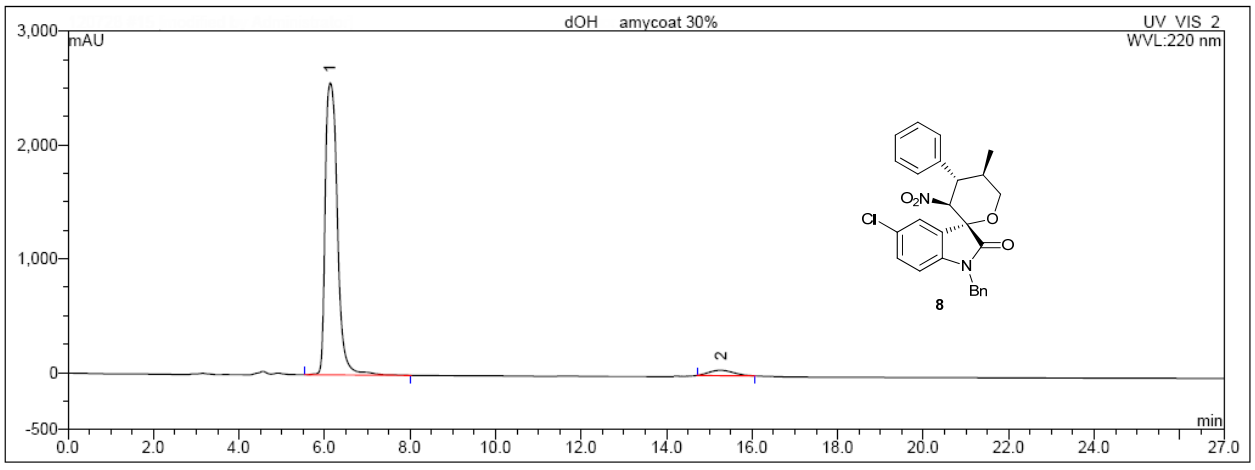
Peak Analysis Report

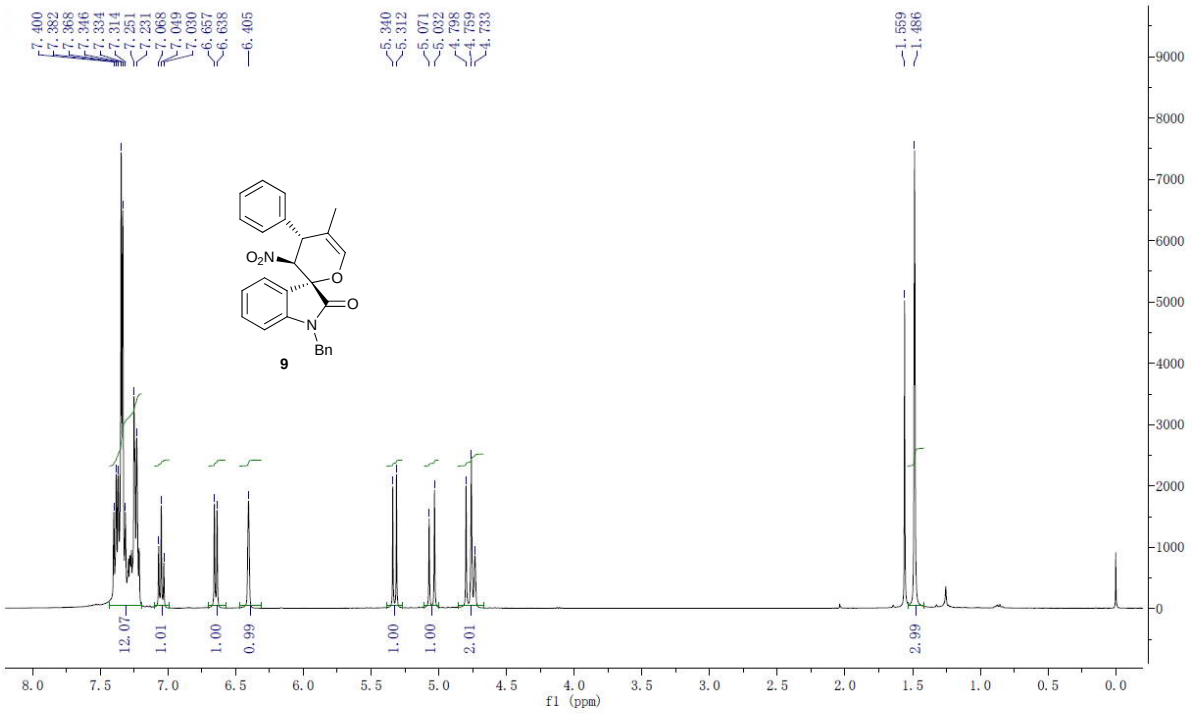
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	6.13	19.656	48.84	19.707	n.a.
2	n.a.	15.28	20.588	51.16	14.639	n.a.

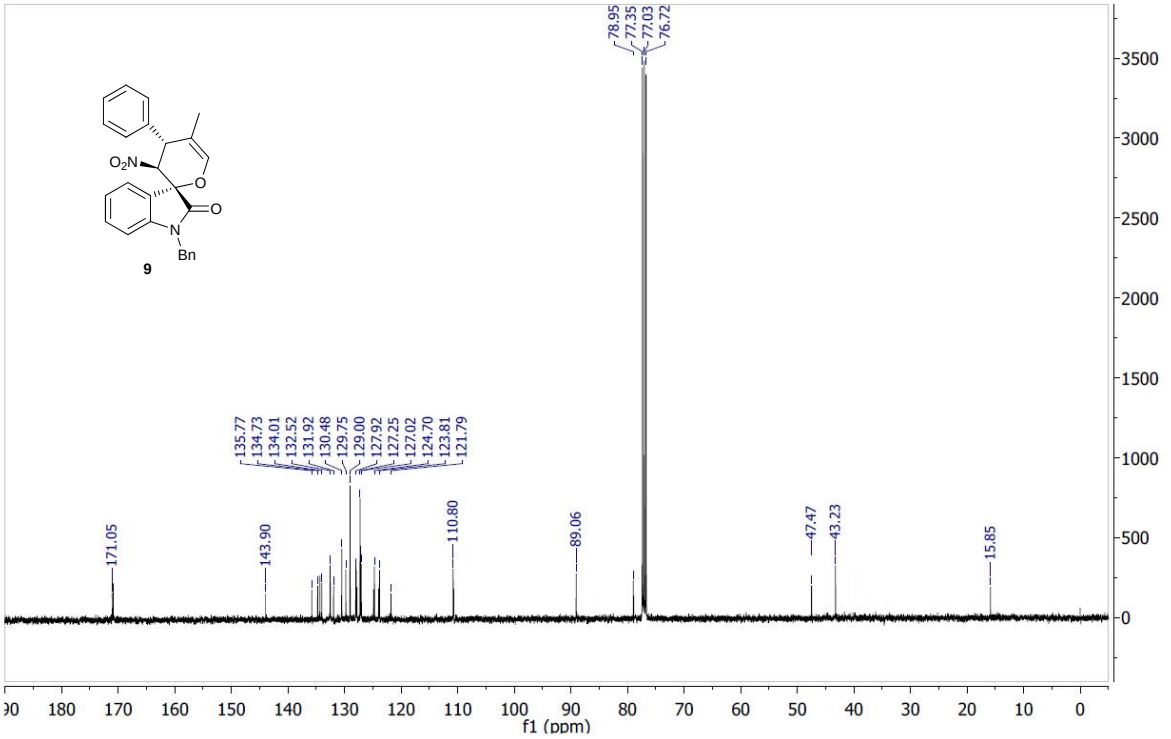


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	6.13	844.699	98.59	2565.716	n.a.
2	n.a.	15.31	12.052	1.41	23.440	n.a.

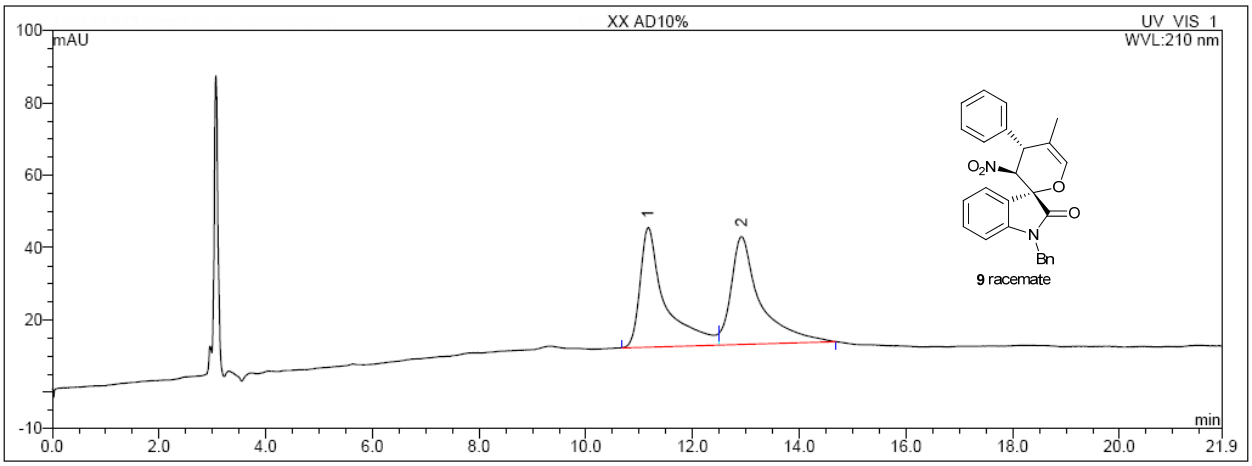



7.400
7.382
7.368
7.346
7.334
7.314
7.251
7.231
7.068
7.049
7.030
6.657
6.638
6.405
5.340
5.312
5.071
5.032
4.798
4.759
4.733
1.559
1.486
O2N
O
O
N
Bn
9
12.07
1.01
1.00
0.99
1.00
1.00
2.01
2.99
f1 (ppm)


78.95
77.35
77.03
76.72
135.77
134.73
134.01
132.52
131.92
130.48
129.75
129.00
127.92
127.25
127.02
124.70
123.81
121.79
171.05
143.90
110.80
89.06
47.47
43.23
15.85
O2N
O
O
N
Bn
9
f1 (ppm)

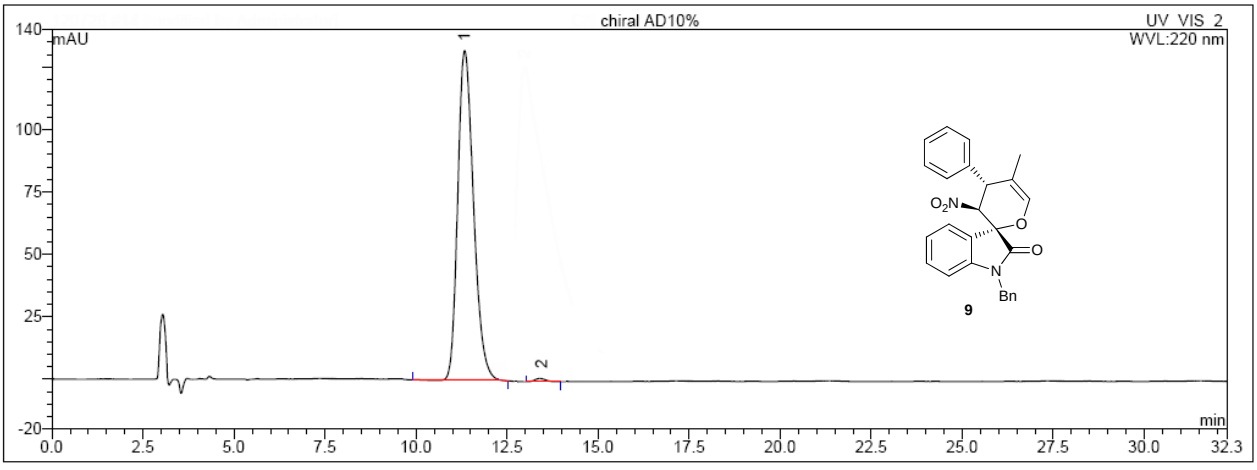
Peak Analysis Report

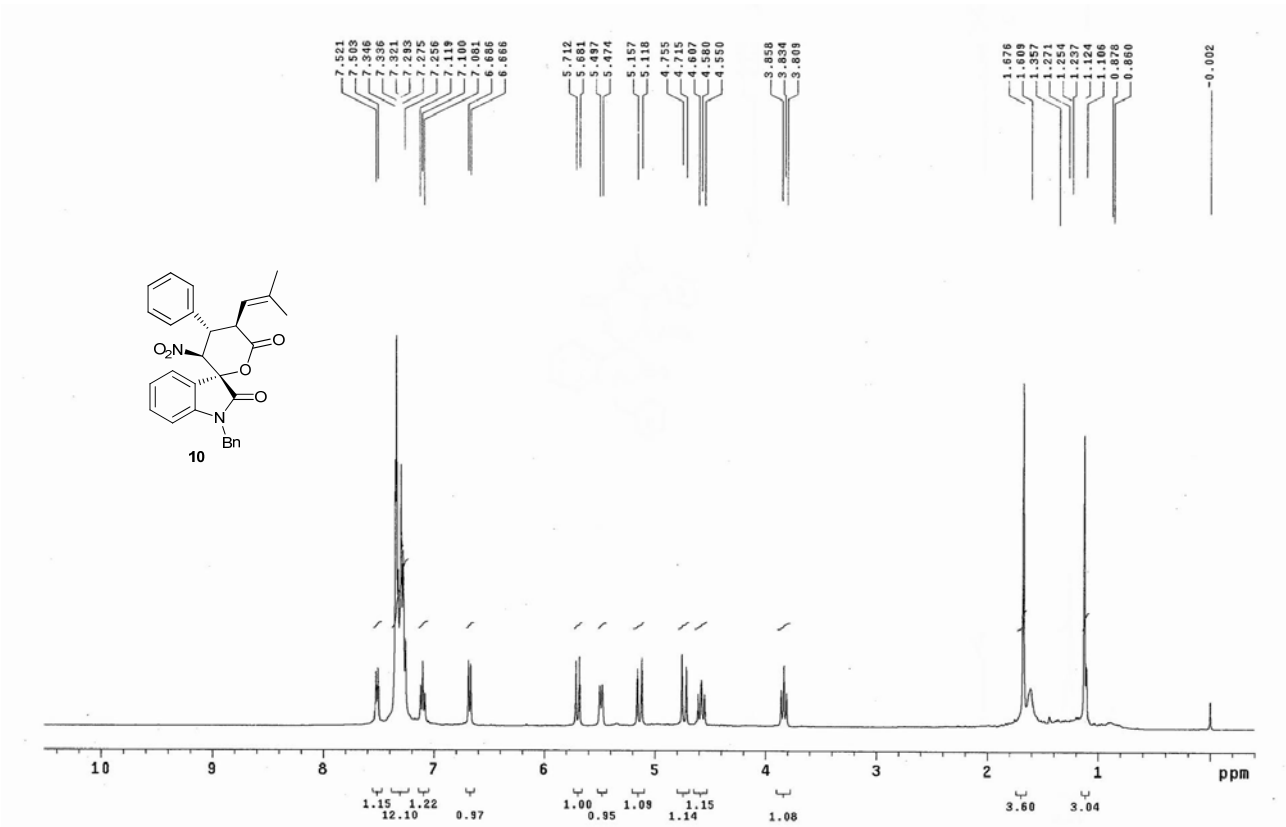
No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	11.17	18.054	49.04	33.008	n.a.
2	n.a.	12.92	18.759	50.96	29.807	n.a.

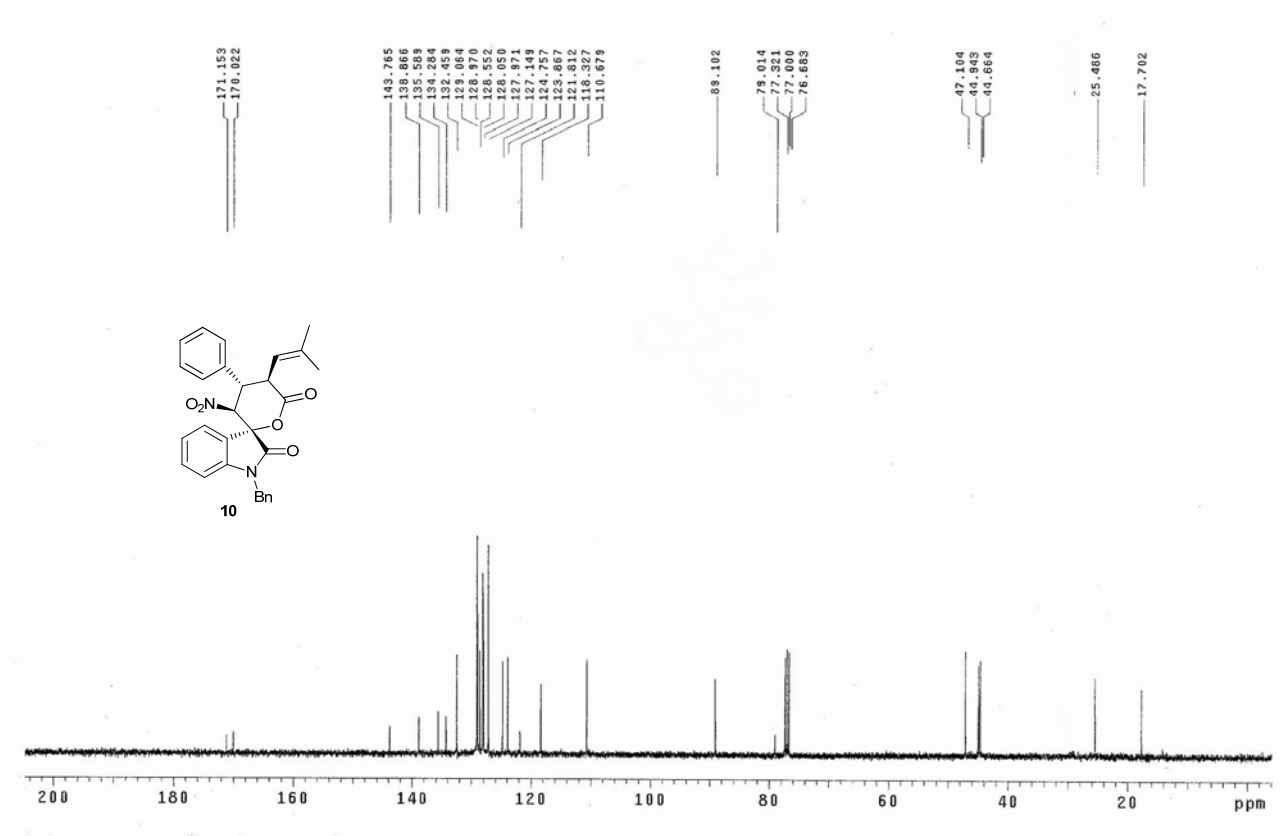


Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	11.22	76.891	99.37	124.374	n.a.
2	n.a.	12.98	0.485	0.63	1.403	n.a.

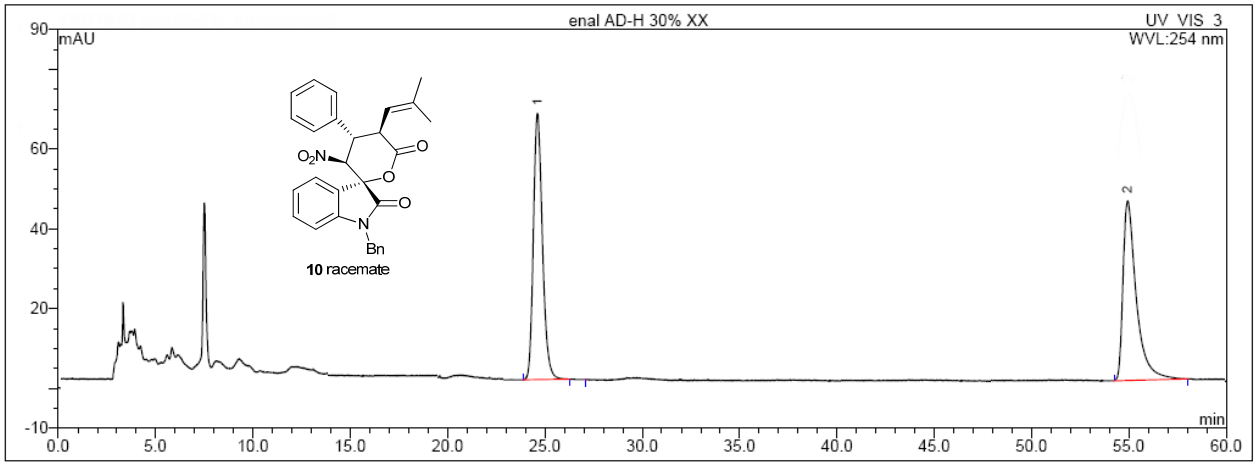






Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	24.76	39.256	49.22	84.166	n.a.
2	n.a.	55.00	38.824	50.78	56.744	n.a.



Peak Analysis Report

No.	Peak Name	Ret.Time (detected)	Area	Rel.Area	Height	Amount
		min	mAU*min	%	mAU	
1	n.a.	24.80	0.444	1.12	0.277	n.a.
2	n.a.	55.07	39.102	98.88	18.200	n.a.