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# Organocatalytic Cascade Reactions: Diversity-Oriented Synthesis for the Construction of Hydroisoquinoline Scaffolds

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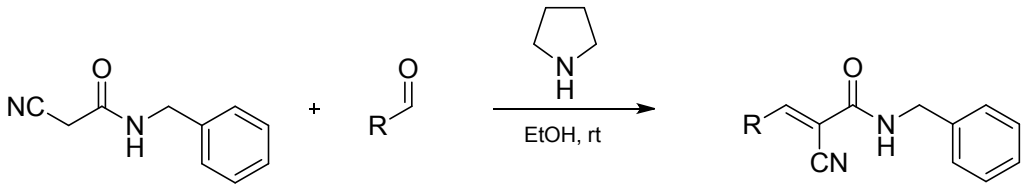
**1. GENERAL METHODS**

The NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$. Chemical Shifts ($\delta$) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for $^{1}H$ NMR and 77.0 for $^{13}C$ NMR). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; bd, broad doublet. $^{13}C$ NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorder on a Bruker MicroTOF-Q High performance LC- MS system. Analytical thin layer chromatography (TLC) was performing using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ stain. Optical rotations were measured on a Bellingham+Stanley ADP440+ polarimeter and $[\alpha]_D$ values are given in $deg \cdot cm \cdot g^{-1} \cdot dm^{-1}$; concentration *c* is listed in $g \cdot (100\ mL)^{-1}$. The enantiomeric excess (ee) of the products were determined by Ultra Performance Convergence Chromatography ($UPC^2$) using Daicel Chiralpak IA-3, IB-3, IC-3 and ID-3 columns as chiral stationary phases. Unless otherwise noted, analytical grade solvents and commercially reagents were used without further purification. For flash chromatography (FC) silica gel ($SiO_2$ 60, 230-400 mesh, Fluka) was used. Racemic samples were prepared using a mixture of enantiomers of **3g** (20 mol%) in combination with *p*-nitrobenzoic acid (20 mol%) in dioxane.

## 2. STARTING MATERIALS

Dienals **1a, m, o-q and n, r** were prepared from the corresponding alkenyl bromides following the procedure reported by Cacchi *et al.*[1] Aldehyde **1d**,**h** were prepared according the procedure reported in literature.[2]

### 2.1 Synthesis of cyanoacrylamides

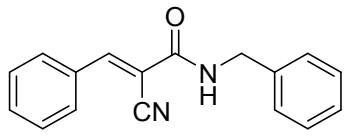



**2**

**General procedure**

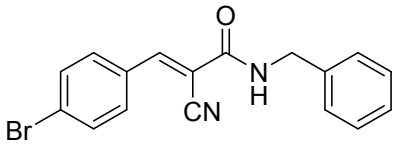
To a solution of *N*-benzyl-2-cyanoacetamide[3] (11.4 mmol) in EtOH (35 mL) was added pyrrolidine (20 mol%) followed by the addition of the aldehyde (11.4 mmol). The mixture was stirred vigorously at rt. After 1 h the solvent was removed and the obtained solid was recrystallized from $CH_2Cl_2$:pentane.

**(*E*)-*N*-Benzyl-2-cyano-3-phenylacrylamide 2a**



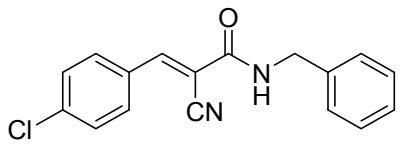

Following the general procedure the compound **2a** was obtained in 90% yield as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.57 – 7.46 (m, 3H), 7.40 – 7.28 (m, 5H), 6.74 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.5, 153.6, 137.4, 133.1, 132.0, 130.9 (2C), 129.5 (2C), 129.2 (2C), 128.2 (3C), 117.2, 104.1, 44.8. HRMS calc. for $C_{17}H_{14}N_2OH^+$ 263.1179 $[M+H]^+$, found 263.1177.

**(*E*)-*N*-Benzyl-2-cyano-3-(4-bromophenyl)acrylamide 2b**




Following the general procedure the compound **2b** was obtained in 78% yield as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.29 (m, 5H), 6.65 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.2, 137.2, 132.9 (2C), 132.2 (2C), 130.9, 129.2 (2C), 128.3, 128.2 (2C), 128.0, 117.0, 104.7, 45.0. HRMS calc. for $C_{17}H_{13}BrN_2OH^+$ 341.0286 $[M+H]^+$, found 341.0286.

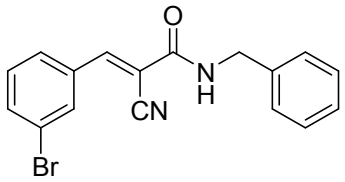
**(*E*)-*N*-Benzyl-3-(4-chlorophenyl)-2-cyanoacrylamide 2c**




Following the general procedure the compound **2c** was obtained in 86% yield as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.28 (m, 5H), 6.70 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.0, 139.4, 137.3, 132.1 (2C), 130.5, 129.9 (2C), 129.2 (2C), 128.3, 128.2 (2C), 117.0, 104.6, 44.9. HRMS calc. for $C_{17}H_{13}ClN_2OH^+$ 297.0789 $[M+H]^+$, found 297.0791.

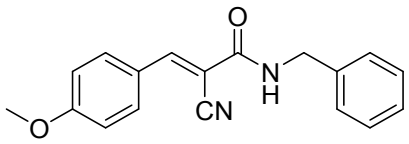

1 G. Battistuzzi, S. Cacchi, G. Fabrizi, *Org. Lett*. 2003, **5**, 777. All spectroscopy data agree with those reported.
2 Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc*. 2011, **133**, 15212.
3 Z. Zhang, T. Song, X. Li, Z. Wu, Y. Feng, F. Xie, C. Liu, J. Qin, H. Chen, *Eur. J. Med. Chem*. 2013, **141**, 149.

**(*E*)-*N*-Benzyl-3-(3-bromophenyl)-2-cyanoacrylamide 2d**



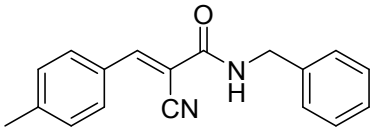
Following the general procedure the compound **2d** was obtained in 76% yield as a white solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.01 (bs, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.29 (m, 6H), 6.71 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.9, 151.8, 137.2, 135.8, 133.9, 133.6, 131.0, 129.2 (2C), 129.0, 128.3, 128.2 (2C), 123.6, 116.7, 105.7, 44.9. HRMS calc. for $C_{17}H_{13}BrN_2OH^+$ 341.0284 $[M+H]^+$, found 341.0282.

**(*E*)-N-Benzyl-2-cyano-3-(4-methoxyphenyl)acrylamide 2e**



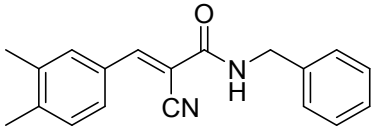
Following the general procedure the compound **2e** was obtained in 95% yield as a pale green solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.28 (m, 5H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.62 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.1, 153.0, 137.6, 133.4 (2C), 129.2 (2C), 128.2 (2C), 128.2, 124.9, 118.0, 115.0 (2C), 100.5, 55.9, 44.8. HRMS calc. for $C_{18}H_{16}BrN_2O_2H^+$ 293.1285 $[M+H]^+$, found 293.1288.

**(*E*)-*N*-Benzyl-2-cyano-3-(*p*-tolyl)acrylamide 2f**



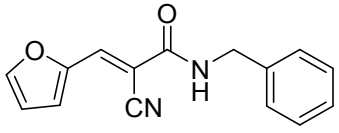
Following the general procedure the compound **2f** was obtained in 88% yield as a white solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.27 (m, 7H), 6.65 (bs, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.8, 153.6, 144.4, 137.5, 131.1 (2C), 130.3 (2C), 129.4, 129.2 (2C), 128.2 (2C), 117.6, 102.7, 77.2, 44.9, 22.1. HRMS calc. for $C_{18}H_{16}N_2OH^+$ 277.1335 $[M+H]^+$, found 277.1335.

**(*E*)-*N*-Benzyl-2-cyano-3-(3,4-dimethylphenyl)acrylamide 2g**



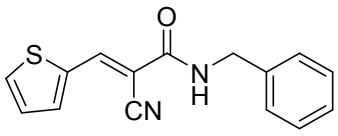
Following the general procedure the compound **2g** was obtained in 62% yield as a white solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.76 – 7.70 (m, 2H), 7.42 – 7.31 (m, 5H), 7.28 (s, 1H), 6.69 (bs, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 2.35 (s, 3H), 2.34 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.9, 153.8, 143.2, 138.0, 137.5, 132.3, 130.8, 129.8, 129.2 (2C), 128.7, 128.2 (2C), 128.2, 117.6, 102.4, 44.8, 20.5, 20.0. HRMS calc. for $C_{19}H_{18}N_2OH^+$ 291.1492 $[M+H]^+$, found 291.1495.

**(*E*)-*N*-Benzyl-2-cyano-3-(furan-2-yl)acrylamide 2h**



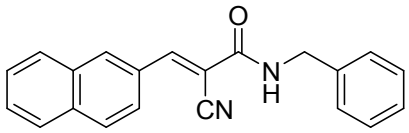
Following the general procedure the compound **2h** was obtained in 59% yield as a red solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.72 (bs, 1H), 7.40 – 7.27 (m, 5H), 7.19 (d, *J* = 3.6 Hz, 1H), 6.64 (bs, 1H), 6.63 (dd, *J* = 3.4, 1.5 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.6, 149.3, 148.0, 137.9, 137.4, 129.2 (2C), 128.2 (3C), 121.5, 117.0, 113.8, 100.0, 44.8. HRMS calc. for $C_{15}H_{12}N_2O_2H^+$ 253.0972 $[M+H]^+$, found 253.0973.

**(*E*)-*N*-Benzyl-2-cyano-3-(thiophen-2-yl)acrylamide 2i**



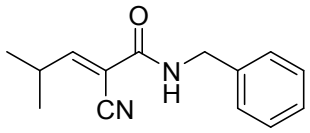
Following the general procedure the compound **2i** was obtained in 91% yield as a gray solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.78 (d, *J* = 3.6 Hz, 1H), 7.76 (d, *J* = 5.2 Hz, 1H), 7.43 – 7.28 (m, 5H), 7.23 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.60 (bs, 1H), 4.60 (d, *J* = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.7, 145.4, 137.5, 136.9, 136.6, 134.4, 129.2 (2C), 128.8, 128.2 (3C), 117.3, 100.6, 44.8. HRMS calc. for $C_{15}H_{12}N_2OSH^+$ 269.0743 $[M+H]^+$, found 269.0742.

**(*E*)-*N*-Benzyl-2-cyano-3-(naphthalen-2-yl)acrylamide 2j**



Following the general procedure the compound **2j** was obtained in 90% yield as a pale yellow solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.32 (s, 1H), 8.14 – 8.09 (m, 1H), 7.96 – 7.85 (m, 3H), 7.65 – 7.56 (m, 2H), 7.41 – 7.29 (m, 5H), 6.77 (bs, 1H), 4.64 (d, *J* = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.6, 153.5, 137.4, 135.5, 133.9, 133.1, 129.6, 129.4, 129.2 (2C), 129.1, 128.2 (4C), 128.1, 127.4, 125.3, 117.5, 103.8, 44.9. HRMS calc. for $C_{21}H_{16}N_2OH^+$ 313.1335 $[M+H]^+$, found 313.1338.

**(*E*)-*N*-benzyl-2-cyano-4-methylpent-2-enamide 2k**



Following the general procedure the compound **2k** was obtained in 40% yield as a pale yellow solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 10.6 Hz, 1H), 7.31 – 7.15 (m, 5H), 6.46 (bs, 1H), 4.46 (d, *J* = 5.8 Hz, 2H), 2.93 – 2.80 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.04, 159.56, 137.15, 128.87 (2C), 127.93 (2C), 127.90, 115.00, 108.07, 44.31, 31.74, 21.46 (2C). HRMS calc. for $C_{14}H_{16}N_2OH^+$ 229.1335 $[M+H]^+$, found 229.1335.

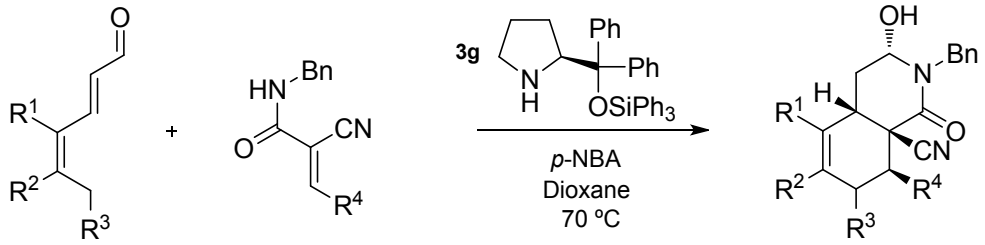
**2.2 Synthesis of the catalysts.**

Catalysts **3a-d** are commercially available, while the catalysts **3e-f** were synthesized according to the procedure reported in the literature.[4]

4 a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed*. 2005, **44**, 4212; b) U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru, *Helv. Chim. Acta.* 2009, **92**, 1225; c) R. López, M. Zalacain, C. Palomo, *Chem.-Eur. J.* 2011, **17**, 2450.

## 3. PROCEDURES AND PRODUCTS

### 3.1 Organocatalytic asymmetric Diels-Alder-aldol reactions of cyanoacrylamides with 2,4-dienals.

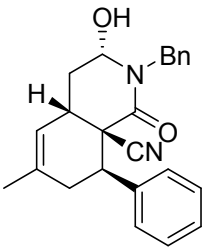



1 2 4

**General procedure**

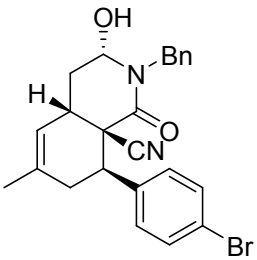
A normal glass vial equipped with a magnetic stirring bar was charged with the catalyst (0.02 mmol, 0.2 equiv) in dioxane (0.5 mL). The aldehyde **1** was added (0.2 mmol, 2 equiv) followed by the cyanoacrylamide **2** (0.1 mmol, 1 equiv) and *p*-nitrobenzoic acid (0.02 mmol, 0.2 equiv). The reaction mixture was stirred at 70 °C until the reaction was complete and then directly purified by FC on silica gel to afford the corresponding adduct.

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-6-methyl-1-oxo-8-phenyl-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4a**



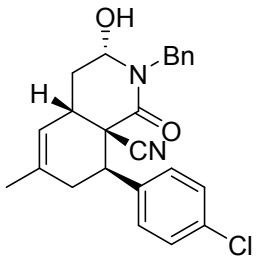
Following the general procedure the compound **4a** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 80% yield as a brown foam. $[\alpha]^{25}_{D}$ -61.2 (*c* 0.95, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 10H), 5.61 (s, 1H), 5.11 (d, *J* = 14.8 Hz, 1H), 4.78 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.26 (d, *J* = 14.8 Hz, 1H), 4.09 (d, *J* = 6.4 Hz, 1H), 2.73 (bs, 1H), 2.56 (d, *J* = 11.2 Hz, 1H), 2.49 (bd, *J* = 21.6 Hz, 1H), 2.35 (dt, *J* = 15.2, 4.4 Hz, 1H), 2.21 – 2.12 (m, 2H), 1.81 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 139.8, 136.9, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.6, 128.2, 128.1 (2C), 128.0, 121.9, 119.4, 79.5, 48.4, 47.8, 41.9, 32.8, 32.7, 32.2, 23.9. HRMS calc. for $C_{24}H_{24}N_2O_2H^+$ 373.1911 $[M+H]^+$, found 373.1911. UPC$^2$ IC-3, $CO_2$/MeOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.73 min; $t_{minor}$ = 4.15 min (95% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-8-(4-bromophenyl)-3-hydroxy-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4b**



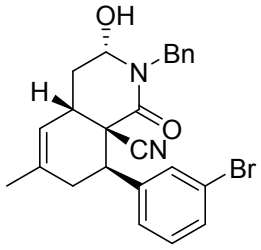
Following the general procedure the compound **4b** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 69% yield as a brown foam. $[\alpha]^{25}_{D}$ -8.9 (*c* 1.65, $(CH_3)_2CO$). $^1$H NMR (400 MHz, $C_6D_6$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.10 (m, 4H), 7.05 – 6.99 (m, 3H), 5.08 (s, 1H), 5.03 (d, *J* = 14.8 Hz, 1H), 4.46 (d, *J* = 2.0 Hz, 1H), 4.23 (d, *J* = 14.8 Hz, 1H), 4.07 – 4.02 (m, 1H), 2.54 (bs, 1H), 2.35 – 2.24 (m, 2H), 1.98 (dt, *J* = 15.0, 4.4 Hz, 1H), 1.77 (d, *J* = 18.4 Hz, 1H), 1.56 (dd, *J* = 15.0, 1.6 Hz, 1H), 1.33 (s, 3H). $^{13}$C NMR (100 MHz, $C_6D_6$) δ 164.3, 139.5, 137.8, 136.9, 132.2 (2C), 131.2 (2C), 129.2 (2C), 128.6, 128.4, 128.2, 122.7, 122.4, 119.7, 79.4, 48.5, 48.0, 41.8, 33.2, 33.0, 32.3, 23.3. HRMS calc. for $C_{24}H_{23}BrN_2O_2H^+$ 451.1016 $[M+H]^+$, found 451.1017. UPC$^2$ IC-3, $CO_2$/MeOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.72 min; $t_{minor}$ = 4.17 min (93% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-8-(4-chlorophenyl)-3-hydroxy-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4c**



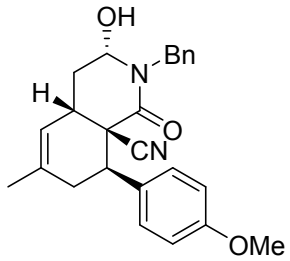

Following the general procedure the compound **4c** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 79% yield as a brown foam. $[\alpha]^{25}_{D}$ -58.3 (*c* 0.49, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 9H), 5.65 (s, 1H), 5.14 (d, *J* = 14.8 Hz, 1H), 4.82 (dd, *J* = 11.2, 3.3 Hz, 1H), 4.29 (d, *J* = 14.8 Hz, 1H), 4.11 (d, *J* = 6.4 Hz, 1H), 2.73 (bs, 1H), 2.52 (bd, *J* = 19.6 Hz, 1H), 2.45 (d, *J* = 11.2 Hz, 1H), 2.39 (dt, *J* = 14.8, 4.4 Hz, 1H), 2.21 – 2.12 (m, 2H), 1.83 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.7, 138.8, 138.3, 136.8, 134.2, 130.4 (2C), 129.1 (2C), 129.1 (2C), 128.2 (2C), 128.0, 122.0, 119.3, 79.5, 48.4, 47.6, 41.4, 32.8, 32.7, 32.2, 23.9. HRMS calc. for $C_{24}H_{23}ClN_2O_2H^+$ 407.1521 $[M+H]^+$, found 407.1523. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.70 min; $t_{minor}$ = 4.65 min (94% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-8-(3-bromophenyl)-3-hydroxy-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4d**



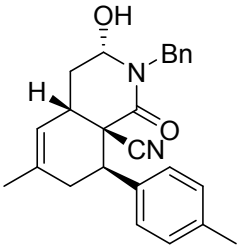

Following the general procedure the compound **4d** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 85:15) in 64% yield as a light brown foam. $[\alpha]^{25}_{D}$ -46.0 (*c* 0.84, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.16 (m, 9H), 5.70 (s, 1H), 5.15 (d, *J* = 14.9 Hz, 1H), 4.87 (dd, *J* = 10.8, 3.1 Hz, 1H), 4.35 (d, *J* = 14.9 Hz, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 2.80 (bs, 1H), 2.62 – 2.49 (m, 2H), 2.44 (dt, *J* = 15.0, 4.4 Hz, 1H), 2.30 – 2.14 (m, 2H), 1.88 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.5, 142.0, 138.4, 136.6, 131.4, 131.3, 130.2, 129.0 (2C), 128.0 (3C), 127.9, 122.8, 121.9, 119.0, 79.3, 48.3, 47.4, 41.5, 32.7, 32.5, 31.9, 23.7. HRMS calc. for $C_{24}H_{23}BrN_2O_2H^+$ 451.1016 $[M+H]^+$, found 451.1013. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.18 min; $t_{minor}$ = 5.22 min (91% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-8-(4-methoxyphenyl)-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4e**



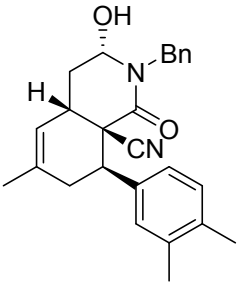

Following the general procedure the compound **4e** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 80% yield as a brown foam. $[\alpha]^{25}_{D}$ -42.3 (*c* 0.95, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 7H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.65 (s, 1H), 5.16 (d, *J* = 14.8 Hz, 1H), 4.83 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.31 (d, *J* = 14.8 Hz, 1H), 4.11 (d, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 2.78 (bs, 1H), 2.60 (d, *J* = 11.2 Hz, 1H), 2.53 (d, *J* = 19.2 Hz, 1H), 2.41 (dt, *J* = 15.2, 4.4 Hz, 1H), 2.23 – 2.15 (m, 2H), 1.85 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.1, 159.5, 139.0, 136.9, 131.8, 130.1 (2C), 129.1 (2C), 128.2 (2C), 127.9, 121.9, 119.6, 114.2 (2C), 79.6, 55.5, 48.3, 48.0, 41.2, 32.9, 32.7, 32.4, 23.9. HRMS calc. for $C_{25}H_{26}N_2O_3H^+$ 403.2016 $[M+H]^+$, found 403.2015. UPC$^2$ IC-3, $CO_2$/MeOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.82 min; $t_{minor}$ = 4.28 min (96% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-6-methyl-1-oxo-8-(p-tolyl)-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4f**



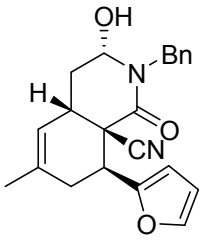
Following the general procedure the compound **4f** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 60% yield as a brown foam. $[\alpha]^{25}_{D}$ -44.2 (*c* 0.7, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 7H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.68 (s, 1H), 5.19 (d, *J* = 14.8 Hz, 1H), 4.85 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.26 (d, *J* = 14.8 Hz, 1H), 4.13 (d, *J* = 6.0 Hz, 1H), 2.80 (bs, 1H), 2.53 (d, *J* = 11.6 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.43 (dt, *J* = 15.2, 4.4 Hz, 1H), 2.33 (s, 3H), 2.26 – 2.18 (m, 2H), 1.87 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 139.1, 137.9, 136.9, 136.8, 129.5 (2C), 129.1 (2C), 128.8 (2C), 128.2 (2C), 128.0, 121.9, 119.5, 79.6, 48.3, 47.9, 41.6, 32.9, 32.7, 32.3, 23.9, 21.4. HRMS calc. for $C_{25}H_{26}N_2O_2H^+$ 387.2067 $[M+H]^+$, found 387.2068. UPC$^2$ IC-3, $CO_2$/MeOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.63 min; $t_{minor}$ = 4.07 min (96% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-8-(3,4-dimethylphenyl)-3-hydroxy-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4g**



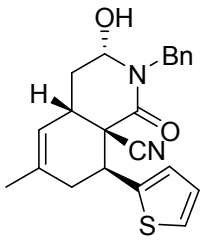
Following the general procedure the compound **4g** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 8:2) in 74% yield as a brown foam. $[\alpha]^{25}_{D}$ -52.9 (*c* 0.76, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.03 (m, 8H), 5.68 (s, 1H), 5.18 (d, *J* = 14.9 Hz, 1H), 4.85 (dd, *J* = 11.2, 3.4 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 4.10 (d, *J* = 6.2 Hz, 1H), 2.83 (bs, 1H), 2.62 (d, *J* = 11.2 Hz, 1H), 2.54 (bd, *J* = 15.0 Hz, 1H), 2.43 (dt, *J* = 15.0, 4.4 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 1.87 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 139.0, 137.1, 136.8, 136.7, 136.4, 130.3, 129.9, 128.9 (2C), 128.0 (2C), 127.8, 125.9, 121.7, 119.4, 79.4, 48.2, 47.7, 41.4, 32.7, 32.6, 32.2, 23.8, 20.1, 19.5. HRMS calc. for $C_{26}H_{28}N_2O_2H^+$ 401.2224 $[M+H]^+$, found 401.2227. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.30 min; $t_{minor}$ = 6.03 min (93% ee).

**(3*S*,4a*S*,8*S*,8a*S*)-2-Benzyl-8-(furan-2-yl)-3-hydroxy-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4h**



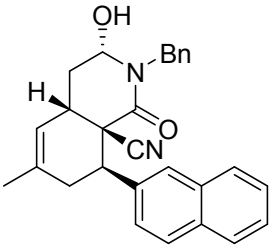
Following the general procedure the compound **4h** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 85:15) in 73% yield as a brown foam. $[\alpha]^{25}_{D}$ -54.0 (*c* 0.73, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 6H), 6.34 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.28 (d, *J* = 3.2 Hz, 1H), 5.60 (s, 1H), 5.20 (d, *J* = 14.8 Hz, 1H), 4.84 (dd, *J* = 11.4, 2.8 Hz, 1H), 4.37 – 4.26 (m, 2H), 2.96 (bs, 1H), 2.66 (d, *J* = 11.4 Hz, 1H), 2.52 – 2.38 (m, 2H), 2.28 – 2.16 (m, 2H), 1.82 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.3, 153.2, 142.3, 137.4, 136.6, 128.9 (2C), 128.1 (2C), 127.8, 120.9, 119.2, 110.52, 108.2, 79.4, 48.1, 46.5, 37.1, 33.7, 32.6, 30.8, 23.8. HRMS calc. for $C_{22}H_{22}N_2O_3H^+$ 363.1703 $[M+H]^+$, found 363.1706. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.91 min; $t_{minor}$ = 7.16 min (93% ee).

**(3*S*,4a*S*,8*S*,8a*S*)-2-Benzyl-3-hydroxy-6-methyl-1-oxo-8-(thiophen-2-yl)-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4i**



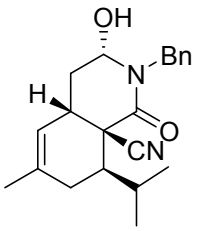

Following the general procedure the compound **4i** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 74% yield as a brown foam. $[\alpha]^{25}_{D}$ -52.6 (*c* 0.86, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 5H), 7.16 (d, *J* = 5.2 Hz, 1H), 7.13 (d, *J* = 3.6 Hz, 1H), 6.96 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.66 (s, 1H), 5.20 (d, *J* = 14.8 Hz, 1H), 4.83 (dd, *J* = 11.4, 3.2 Hz, 1H), 4.52 (d, *J* = 5.6 Hz, 1H), 4.27 (d, *J* = 14.8 Hz, 1H), 3.03 (bs, 1H), 2.60 (d, *J* = 11.6 Hz, 1H), 2.51 (d, *J* = 18.4 Hz, 1H), 2.39 (dt, *J* = 14.8, 4.0 Hz, 1H), 2.25 (dd, *J* = 15.2, 1.6 Hz, 1H), 2.19 (d, *J* = 18.4 Hz, 1H), 1.83 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.5, 141.4, 138.0, 136.7, 129.1 (2C), 128.3, 128.3 (2C), 128.1, 126.9, 125.2, 122.3, 119.5, 79.5, 48.4, 47.9, 39.1, 33.4, 33.2, 32.6, 24.1. HRMS calc. for $C_{22}H_{22}N_2O_2SH^+$ 379.1475 $[M+H]^+$, found 379.1475. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.89 min; $t_{minor}$ = 5.90 min (95% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-6-methyl-8-(naphthalen-2-yl)-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4j**



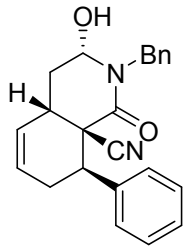

Following the general procedure the compound **4j** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 80% yield as a brown foam. $[\alpha]^{25}_{D}$ -9.7 (*c* 1.23, $(CH_3)_2CO$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 4H), 7.55 – 7.44 (m, 3H), 7.38 – 7.25 (m, 5H), 5.76 (s, 1H), 5.22 (d, *J* = 14.8 Hz, 1H), 4.87 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 4.36 (d, *J* = 6.8 Hz, 1H), 2.87 (bs, 1H), 2.66 (bd, *J* = 18.8 Hz, 1H), 2.53 (d, *J* = 11.6 Hz, 1H), 2.44 (dt, *J* = 15.2, 4.4 Hz, 1H), 2.35 (d, *J* = 18.0 Hz, 1H), 2.24 (dd, *J* = 15.2, 2.0 Hz, 1H), 1.95 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 139.1, 137.4, 136.9, 133.6, 133.2, 129.1 (2C), 128.5, 128.4, 128.2 (2C), 128.0, 127.8, 127.8, 127.1, 126.4, 126.4, 122.1, 119.4, 79.6, 48.4, 47.9, 42.0, 32.9, 32.8, 32.4, 24.0. HRMS calc. for $C_{28}H_{26}N_2O_2H^+$ 423.2067 $[M+H]^+$, found 423.2065. UPC$^2$ IC-3, $CO_2$/iPrOH 80:20, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 5.35 min; $t_{minor}$ = 13.79 min (97% ee).

**(*3S*,4a*S*,8*R*,8a*R*)-2-Benzyl-3-hydroxy-8-isopropyl-6-methyl-1-oxo-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4k**



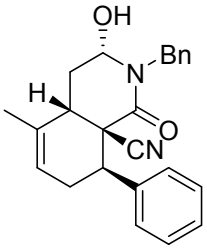

Following the general procedure the compound **4k** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 85:15) in 48% yield as a brown oil. $[\alpha]^{25}_{D}$ 29.2 (*c* 0.40, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.17 (m, 5H), 5.46 (s, 1H), 5.15 (d, *J* = 14.7 Hz, 1H), 4.81 (dt, *J* = 11.1, 4.4 Hz, 1H), 4.33 (d, *J* = 14.7 Hz, 1H), 2.99 (bs, 1H), 2.68 (dt, *J* = 8.8, 4.4 Hz, 1H), 2.57 (d, *J* = 11.1 Hz, 1H), 2.45 (dt, *J* = 14.8, 4.4 Hz, 1H), 2.21 – 2.06 (m, 2H), 2.04-1.99 (m, 2H), 1.75 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.6, 138.6, 136.8, 128.9 (2C), 128.2 (2C), 127.8, 120.7, 120.3, 79.1, 47.9 (2C), 41.5, 34.8, 33.4, 28.7, 27.3, 24.0, 23.7, 18.8. HRMS calc. for $C_{21}H_{26}N_2O_2H^+$ 339.2067 $[M+H]^+$, found 339.2067. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 5.04 min; $t_{minor}$ = 5.26 min (70% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-1-oxo-8-phenyl-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4l**



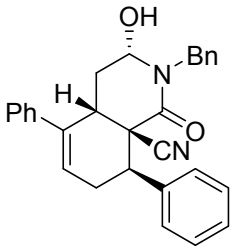

Following the general procedure the compound **4l** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 78% yield as a brown foam. $[\alpha]^{25}_{D}$ -33.3 (*c* 1.23, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.4 Hz, 2H), 7.32 – 7.18 (m, 8H), 6.20 – 6.10 (m, 1H), 5.94 (d, *J* = 10.2 Hz, 1H), 5.15 (d, *J* = 14.9 Hz, 1H), 4.80 (dd, *J* = 5.6, 3.2 Hz, 1H), 4.26 (d, *J* = 14.9 Hz, 1H), 4.09 (d, *J* = 6.4 Hz, 1H), 2.75 (bs, 1H), 2.64 – 2.52 (m, 2H), 2.42 – 2.31 (m, 2H), 2.18 (dd, *J* = 14.8, 2.0 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 139.7, 136.7, 130.7, 129.1 (2C), 129.0 (2C), 128.8 (2C), 128.3, 128.2 (2C), 128.0, 127.9, 119.3, 79.3, 48.2, 48.0, 41.3, 32.8, 32.4, 27.5. HRMS calc. for $C_{23}H_{22}N_2O_2H^+$ 359.1754 $[M+H]^+$, found 359.1755. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.11 min; $t_{minor}$ = 4.69 min (94% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-5-methyl-1-oxo-8-phenyl-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4m**



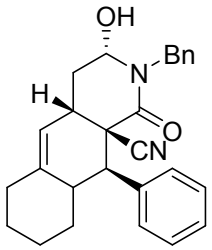

Following the general procedure the compound **4m** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 77% yield as a dark brown foam. $[\alpha]^{25}_{D}$ -34.1 (*c* 1.08, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 10H), 5.74 (s, 1H), 4.90 (d, *J* = 14.6 Hz, 1H), 4.80 (dt, *J* = 8.8, 4.4 Hz, 1H), 4.33 (d, *J* = 14.6 Hz, 1H), 3.81 (t, *J* = 4.8 Hz, 1H), 2.67 – 2.49 (m, 4H), 2.35 (dt, *J* = 15.0, 4.7 Hz, 1H), 2.26 – 2.15 (m, 1H), 1.83 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.6, 139.4, 137.0, 133.3, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.6 (2C), 128.2, 128.0, 124.9, 119.6, 79.2, 50.0, 47.9, 41.6, 38.1, 31.4, 28.9, 21.9. HRMS calc. for $C_{24}H_{24}N_2O_2H^+$ 373.1911 $[M+H]^+$, found 373.1910. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.75 min; $t_{minor}$ = 5.03 min (96% ee).

**(3*S*,4a*S*,8*R*,8a*R*)-2-Benzyl-3-hydroxy-1-oxo-5,8-diphenyl-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4n**



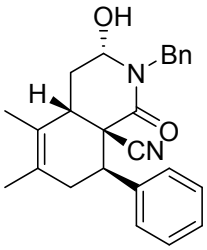

Following the general procedure the compound **4n** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 75:25) in 75% yield as a brown foam. $[\alpha]^{25}_{D}$ -38.3 (*c* 1.03, $(CH_3)_2CO$). $^1$H NMR (400 MHz, DMSO) δ 7.65 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.46 – 7.32 (m, 11H), 6.39 (d, *J* = 8.4 Hz, 1H), 6.30 (dd, *J* = 4.4, 2.4 Hz, 1H), 4.97 (dd, *J* = 14.4, 8.4 Hz, 1H), 4.55 (d, *J* = 14.8 Hz, 1H), 4.40 (d, *J* = 14.8 Hz, 1H), 3.88 (dd, *J* = 4.4, 3.6 Hz, 1H), 3.72 (dd, *J* = 11.2, 5.2 Hz, 1H), 2.91 (dd, *J* = 18.4, 12.0 Hz, 1H), 2.61 (dt, *J* = 19.1, 5.2 Hz, 1H), 2.22 – 2.16 (m, 1H), 2.11 – 2.02 (m, 1H). $^{13}$C NMR (100 MHz, DMSO) δ 164.3, 139.2, 138.7, 137.9, 136.9, 128.7, 128.5, 128.0 (2C), 127.9 (3C), 127.6, 127.3, 126.6, 125.7 (2C), 124.6, 119.5, 78.9, 59.8, 50.7, 46.4, 40.1, 37.2, 34.0, 31.2, 20.8, 14.1. HRMS calc. for $C_{29}H_{26}N_2O_2H^+$ 435.2067 $[M+H]^+$, found 435.2070. UPC$^2$ IC-3, $CO_2$/iPrOH 80:20, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 7.59 min; $t_{minor}$ = 8.88 min (98% ee).

**(3*S*,4a*S*,10*R*,10a*S*)-2-Benzyl-3-hydroxy-1-oxo-10-phenyl-2,3,4,4a,6,7,8,9,9a,10-decahydrobenzo[g]isoquinoline-10a(1*H*)-carbonitrile 4o**



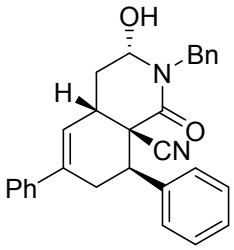
Following the general procedure the compound **4o** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 8:2) in 48% yield as a white foam. $[\alpha]^{25}_{D}$ -46.9 (*c* 0.64, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 10H), 5.53 (s, 1H), 4.85 (dt, *J* = 9.2, 4.8 Hz, 1H), 4.72 (d, *J* = 14.4 Hz, 1H), 4.49 (d, *J* = 14.4 Hz, 1H), 3.40 (d, *J* = 6.4 Hz, 1H), 2.90-2.77 (m, 2H), 2.61 – 2.49 (m, 1H), 2.41 (dt, *J* = 14.8, 4.8 Hz, 1H), 2.35 (d, *J* = 13.3 Hz, 1H), 2.13 (t, *J* = 13.3 Hz, 1H), 2.01 (ddd, *J* = 14.8, 9.2, 6.4 Hz, 1H), 1.82 (br d, *J* = 12.4 Hz, 1H), 1.76-1.56 (m, 2H), 1.40-1.08 (m, 2H), 0.93 (qd, *J* = 12.9, 3.5 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.8, 144.5, 139.3, 137.0, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.0, 127.7, 119.6, 118.3, 79.6, 49.1, 48.8, 47.9, 42.8, 35.6, 35.0, 34.8, 34.1, 27.8, 26.4. HRMS calc. for $C_{27}H_{28}N_2O_2H^+$ 413.2224 $[M+H]^+$, found 413.2226. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 5.26 min; $t_{minor}$ = 5.76 min (93% ee).

**(3*S*,4a*S*,8*R*,8a*R*)-2-Benzyl-3-hydroxy-5,6-dimethyl-1-oxo-8-phenyl-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4p**



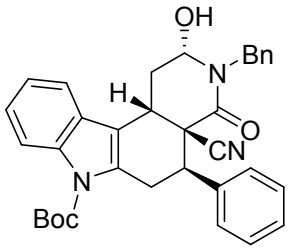
Following the general procedure the compound **4p** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 8:2) in 74% yield as a white foam. $[\alpha]^{25}_{D}$ -47.3 (*c* 0.63, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 10H), 4.88 (d, *J* = 14.6 Hz, 1H), 4.82 (dt, *J* = 9.2, 4.8 Hz, 1H), 4.41 (d, *J* = 14.6 Hz, 1H), 3.72 (t, *J* = 6.1 Hz, 1H), 2.75 (d, *J* = 9.2 Hz, 1H), 2.53 (br s, 1H), 2.49-2.26 (m, 3H), 2.12-2.04 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.6, 139.2, 136.9, 129.9, 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.0, 127.7, 125.1, 119.6, 79.2, 50.2, 47.7, 41.8, 39.5, 35.2, 31.9, 19.7, 17.2. HRMS calc. for $C_{25}H_{26}N_2O_2H^+$ 387.2067 $[M+H]^+$, found 387.2070. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.82 min; $t_{minor}$ = 5.23 min (91% ee).

**(3*S*,4a*S*,8*R*,8a*S*)-2-Benzyl-3-hydroxy-1-oxo-6,8-diphenyl-2,3,4,4a,7,8-hexahydroisoquinoline-8a(1*H*)-carbonitrile 4q**



Following the general procedure the compound **4q** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 66% yield as a brown foam. $[\alpha]^{25}_{D}$ -80.6 (*c* 0.95, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.20 (m, 15H), 6.33 (s, 1H), 5.05 (d, *J* = 15.0 Hz, 1H), 4.96 (dd, *J* = 9.3, 3.5 Hz, 1H), 4.44 (d, *J* = 15.0 Hz, 1H), 4.34 (d, *J* = 5.6 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.85 – 2.78 (m, 1H), 2.59 – 2.50 (m, 2H), 2.35 (dd, *J* = 15.0, 1.5 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 139.7, 139.6, 139.3, 136.8, 129.1 (4C), 129.0 (2C), 128.9 (2C), 128.7, 128.3, 128.0 (2C), 127.9, 125.6 (2C), 124.1, 119.4, 79.6, 48.9, 47.8, 42.0, 33.1, 33.0, 29.5. HRMS calc. for $C_{29}H_{26}N_2O_2H^+$ 435.2067 $[M+H]^+$, found 435.2074. UPC$^2$ IC-3, $CO_2$/MeOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 4.10 min; $t_{minor}$ = 4.61 min (94% ee).

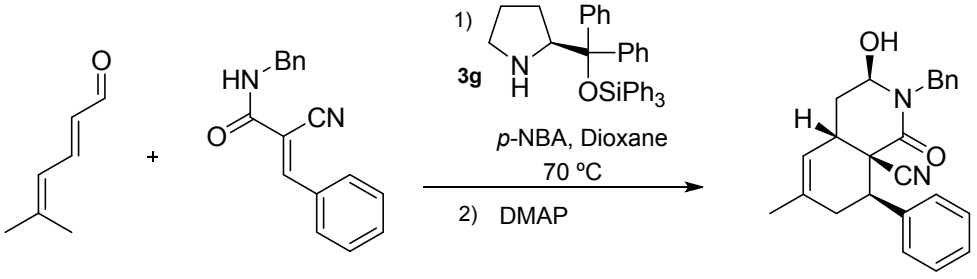
***tert*-butyl (2*S*,4a*R*,5*R*,11c*S*)-3-Benzyl-4a-cyano-2-hydroxy-4-oxo-5-phenyl-1,2,3,4,4a,5,6,11c-octahydro-7*H*-pyrido[3,4-c]carbazole-7-carboxylate 4r**



Following the general procedure the compound **4r** was obtained as a single diastereoisomer after FC on silica gel (pentane:EtOAc 7:3) in 56% yield as a brown foam. $[\alpha]^{25}_{D}$ -127.4 (*c* 0.96, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.14 (m, 12H), 5.09 (d, *J* = 13.9 Hz, 1H), 4.87 – 4.79 (m, 1H), 4.39 – 4.25 (m, 2H), 3.50 – 3.37 (m, 3H), 2.97 (bs, 1H), 2.74 (dt, *J* = 8.7, 4.1 Hz, 1H), 1.94 (d, *J* = 11.3 Hz, 1H), 1.67 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.5, 150.2, 138.8, 136.8 (2C), 135.8, 129.0 (7C), 128.9 (3C), 128.5, 128.4, 128.0, 127.0, 125.2, 123.7, 119.2, 116.4, 114.2, 85.3, 78.8, 77.5, 49.6, 48.1, 42.6, 28.5 (3C). HRMS calc. for $C_{34}H_{33}N_3O_4H^+$ 548.2544 $[M+H]^+$, found 548.2543. UPC$^2$ IC-3, $CO_2$/iPrOH 80:20, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 6.90 min; $t_{minor}$ = 4.60 min (96% ee).

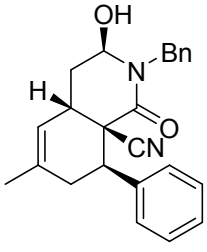
**3.2 Synthetic transformations**

**a) Inversion of the configuration at C-3**



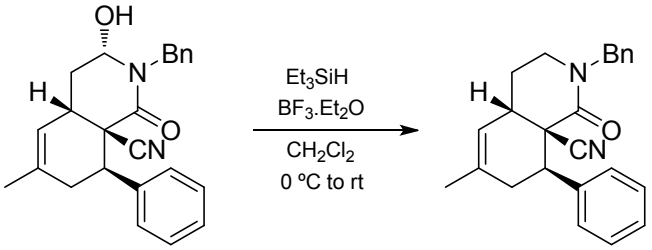

**1a** **2a** **5**

A normal glass vial equipped with a magnetic stirring bar was charged with the catalyst (0.02 mmol, 0.2 equiv) in dioxane (0.5 mL), the aldehyde **1a** was added (0.2 mmol, 2 equiv) followed by the cyanoacrylamide **2a** (0.1 mmol, 1 equiv) and *p*-nitrobenzoic acid (0.02 mmol, 0.2 equiv). After 3 h of stirring at 70 °C, DMAP (0.15 mmol, 1.5 equiv) was added and the mixture was allowed stirring for an additional 20 h. When the reaction was complete, the crude product was directly purified by FC on silica gel to afford the corresponding adduct.



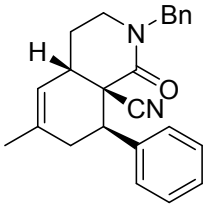
Following the general procedure the compound **5** was obtained as a single diastereoisomer in 82% yield as a golden foam. $[\alpha]^{25}_{D}$ -20.7 (*c* 1.1, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21 (ddd, *J* = 21.0, 9.0, 4.4 Hz, 8H), 7.12 – 7.08 (m, 2H), 5.22 (s, 1H), 5.12 (d, *J* = 14.6 Hz, 1H), 4.58 – 4.52 (m, 1H), 4.27 (d, *J* = 14.6 Hz, 1H), 3.84 (dd, *J* = 6.0, 2.4 Hz, 1H), 3.23 (d, *J* = 10.6 Hz, 1H), 2.66 (bs, 1H), 2.38 – 2.27 (m, 1H), 2.23 – 2.16 (m, 2H), 2.00 (ddd, *J* = 14.0, 8.4, 3.5 Hz, 1H), 1.62 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.4, 139.8, 138.0, 136.8, 129.1 (2C), 128.8 (2C), 128.7 (4C), 128.1, 127.8, 120.4, 119.7, 77.7, 67.4, 48.1, 45.8, 42.7, 34.9, 32.2, 23.3. HRMS calc. for $C_{24}H_{24}N_2O_2H^+$ 373.1911 $[M+H]^+$, found 373.1907. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 5.05 min; $t_{minor}$ = 5.39 min (96% ee).

**b) Reduction of the adduct 4a**



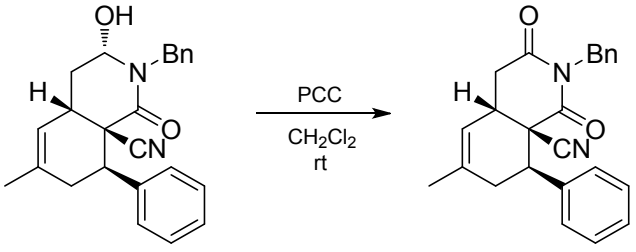

**4a** **6**

To a solution of adduct **4a** (0.141 mmol, 1 equiv) in 0.5 mL of $CH_2Cl_2$ at 0 °C, was added $Et_3SiH$ (0.282 mmol, 2 equiv) followed by $BF_3{\cdot}Et_2O$ (0.564 mmol, 4 equiv). The mixture was stirred starting at 0 °C to rt for 75 min. The reaction was quenched with water and extracted three times with $CH_2Cl_2$, the combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The obtained solid was recrystallized from $Et_2O$.



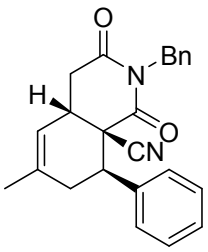

Following the procedure the compound **6** was obtained as a single diastereoisomer in 86% yield as a brown solid. $[\alpha]^{25}_{D}$ -21.1 (*c* 1, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.1 Hz, 2H), 7.37 – 7.27 (m, 6H), 7.15 (d, *J* = 7.0 Hz, 2H), 5.38 (s, 1H), 4.98 (d, *J* = 14.7 Hz, 1H), 4.26 (d, *J* = 14.7 Hz, 1H), 4.15 (d, *J* = 6.7 Hz, 1H), 3.23 – 3.14 (m, 2H), 2.65 (bs, 1H), 2.54 (dd, *J* = 18.9, 3.5 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.14 (d, *J* = 18.4 Hz, 1H) 1.88 – 1.81 (m, 1H), 1.80 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.2, 140.3, 138.6, 136.6, 129.2 (2C), 129.0 (2C), 128.7 (2C), 128.0, 127.9 (3C), 120.7, 120.2, 51.8, 47.8, 44.7, 42.2, 33.5, 32.5, 25.2, 23.6. HRMS calc. for $C_{24}H_{24}N_2OH^+$ 357.1961 $[M+H]^+$, found 357.1963. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 6.12 min; $t_{minor}$ = 9.13 min (94% ee).

**c) Oxidation of the adduct 4a**



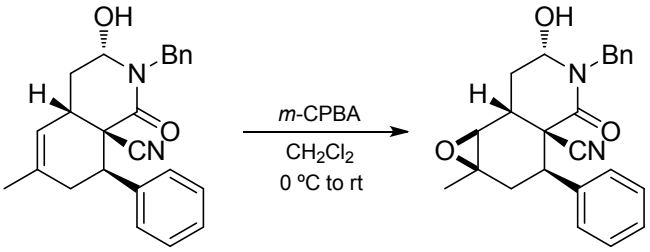

**4a** **7**

$CH_2Cl_2$ (0.5 mL) was added to an argon flushed vial containing compound **4a** (0.04 mmol, 1 equiv) and PCC (0.06 mmol, 1.5 equiv). The reaction mixture was stirred for 4 h at rt followed by filtration over silica gel (pentane:EtOAc 85:15) and concentrated in vacuo to afford the pure product.



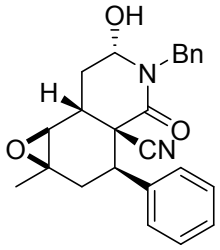
Following the general procedure the compound **7** was obtained as a single diastereoisomer in 99% yield as a white foam. $[\alpha]^{25}_{D}$ 1.5 (*c* 0.80, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.14 (m, 10H), 5.30 (s, 1H), 5.06 (d, *J* = 14.1 Hz, 1H), 4.91 (d, *J* = 14.1 Hz, 1H), 3.99 (d, *J* = 6.2 Hz, 1H), 3.05 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.90 – 2.76 (m, 2H), 2.34 (br d, *J* = 19.1 Hz, 1H), 2.18 (d, *J* = 19.1 Hz, 1H), 1.63 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.6, 139.7, 138.7, 136.4, 128.9 (4C), 128.6 (2C), 128.4, 128.2 (2C), 127.7, 120.1, 117.2, 48.1, 44.0, 42.2, 36.3, 32.4, 30.8, 23.1. HRMS calc. for $C_{24}H_{22}N_2O_2H^+$ 371.1754 $[M+H]^+$, found 371.1755. UPC$^2$ IC-3, $CO_2$/iPrOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.71 min; $t_{minor}$ = 4.27 min (92% ee).

**d) Epoxidation of adduct 4a**



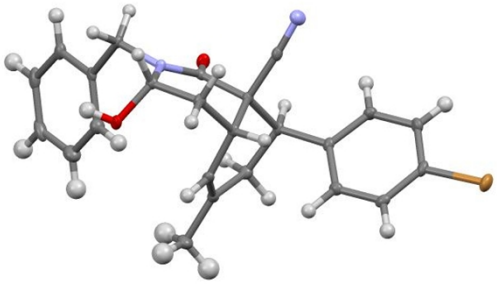

**4a** **8**

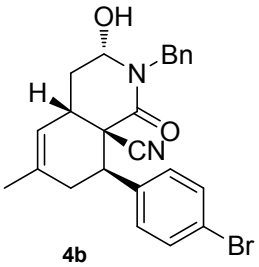
A solution of *m*-chloroperoxybenzoic acid (≤77%, 0.161 mmol, 2 equiv) in $CH_2Cl_2$ (0.2 mL), was added at 0 °C to a stirred solution of compound **4a** (0.080 mmol, 1 equiv) in $CH_2Cl_2$ (0.3 mL). The reaction mixture was stirred for 4 h, starting at 0 °C and increasing the temperature to r.t. When the reaction was complete, water was added and extracted with $CH_2Cl_2$, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was directly purified by FC on silica gel (pentane:EtOAc 6:4) to afford the pure product.



Following the procedure the compound **8** was obtained as a single diastereoisomer in 72% yield as a white foam. $[\alpha]^{25}_{D}$ -16.2 (*c* 0.48, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 10H), 5.24 (d, *J* = 14.8 Hz, 1H), 4.77 (ddd, *J* = 12.3, 4.8, 1.4 Hz, 1H), 4.21 (d, *J* = 14.9 Hz, 1H), 3.91 (dd, *J* = 6.9, 1.5 Hz, 1H), 3.80 (d, *J* = 12.4 Hz, 1H), 3.26 (d, *J* = 1.4 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.55 – 2.45 (m, 2H), 2.19 (dt, *J* = 15.2, 2.0 Hz, 1H), 2.12 (dd, *J* = 16.0, 1.6 Hz, 1H), 1.53 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.4, 139.8, 136.9, 129.3 (2C), 129.1 (4C), 128.3 (3C), 127.9, 119.1, 77.7, 62.9, 61.9, 47.5, 46.1, 40.0, 32.1, 31.2, 31.0, 24.2. HRMS calc. for $C_{24}H_{24}N_2O_3H^+$ 389.1860 $[M+H]^+$, found 389.1859. UPC$^2$ IC-3, $CO_2$/MeOH Gradient 99:1 to 60:40, 3 mL·min$^{-1}$, 40 °C, 120 bar; $t_{major}$ = 3.50 min; $t_{minor}$ = 3.58 min (96% ee).

4. X-Ray structure

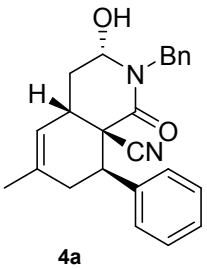





**4b**

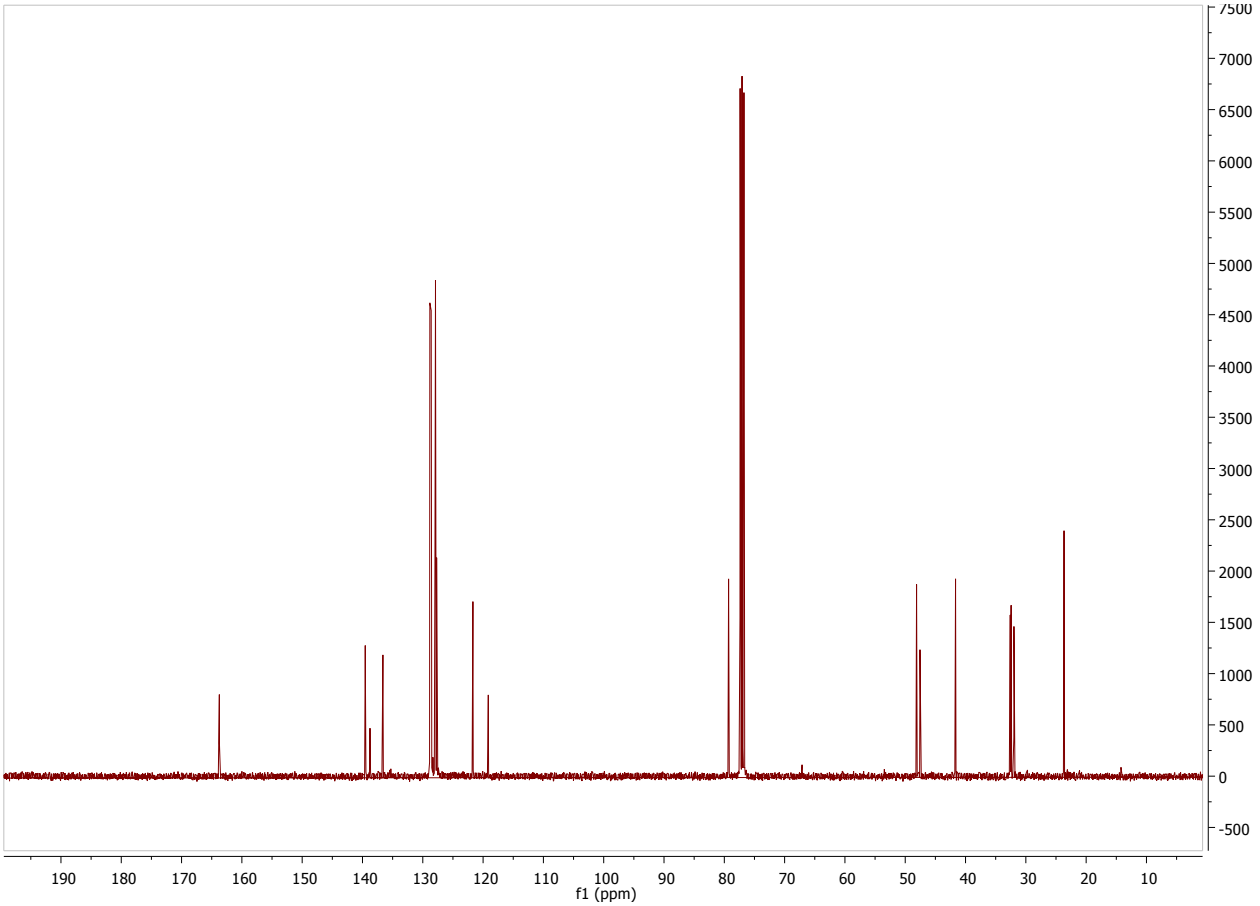
Crystal data for [**1**]: $C_{24}H_{23}BrN_2O_2$, $M$ = 451.35, orthorhombic, Space group P 21 21 21 (no. 115), $a$ = 10.6176(8) Å, $b$ = 11.3209(7) Å, $c$ = 17.5317(10) Å, $V$ = 2107.3(2) Å$^3$, $T$ = 100 K, $Z$ = 4, $d_c$ = 1.423 g cm$^{-3}$, $\mu$(Mo Kα, λ = 0.56085 Å) = 1.063 mm$^{-1}$, 28770 reflections collected, 5611 unique [$R_{int}$ = 0.0341], which were used in all calculations. Refinement on $F^2$, final R(F) = 0.0283, $R_w$(F2) = 0.0554. CCDC number 984677.

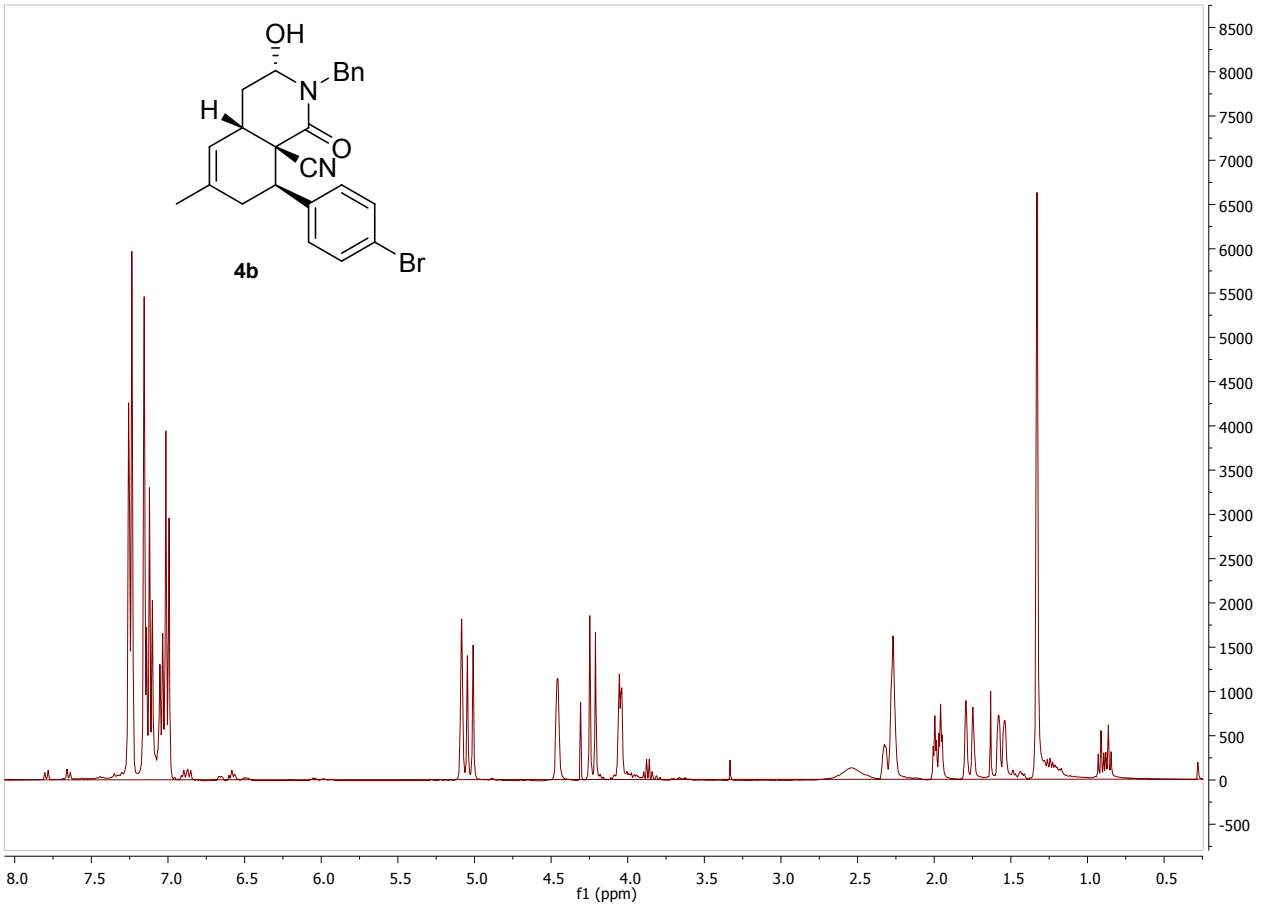
5. $^{1}H$ and $^{13}C$ NMR spectra.




**4a**

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Bn
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H
O
CN
Br
4b
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8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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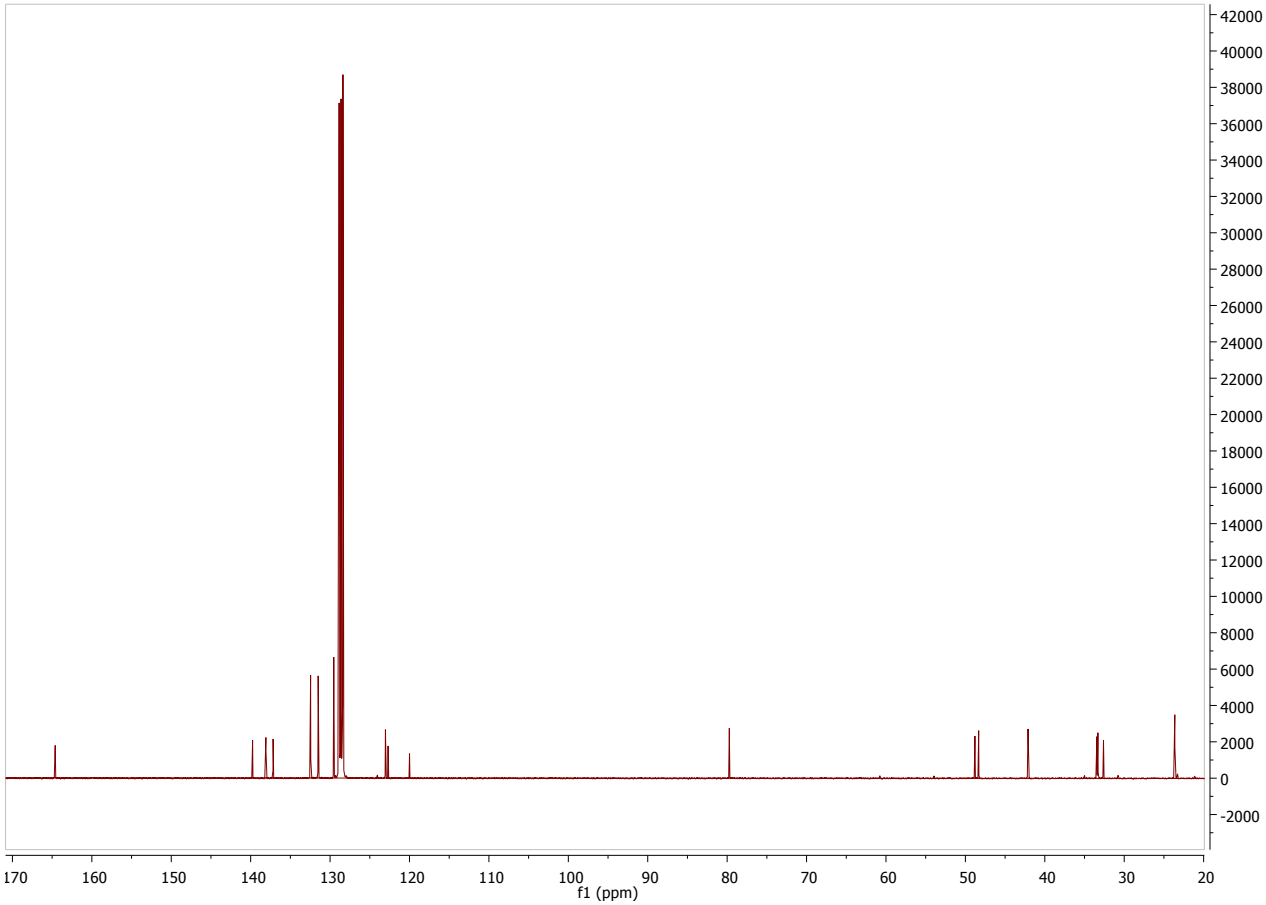
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
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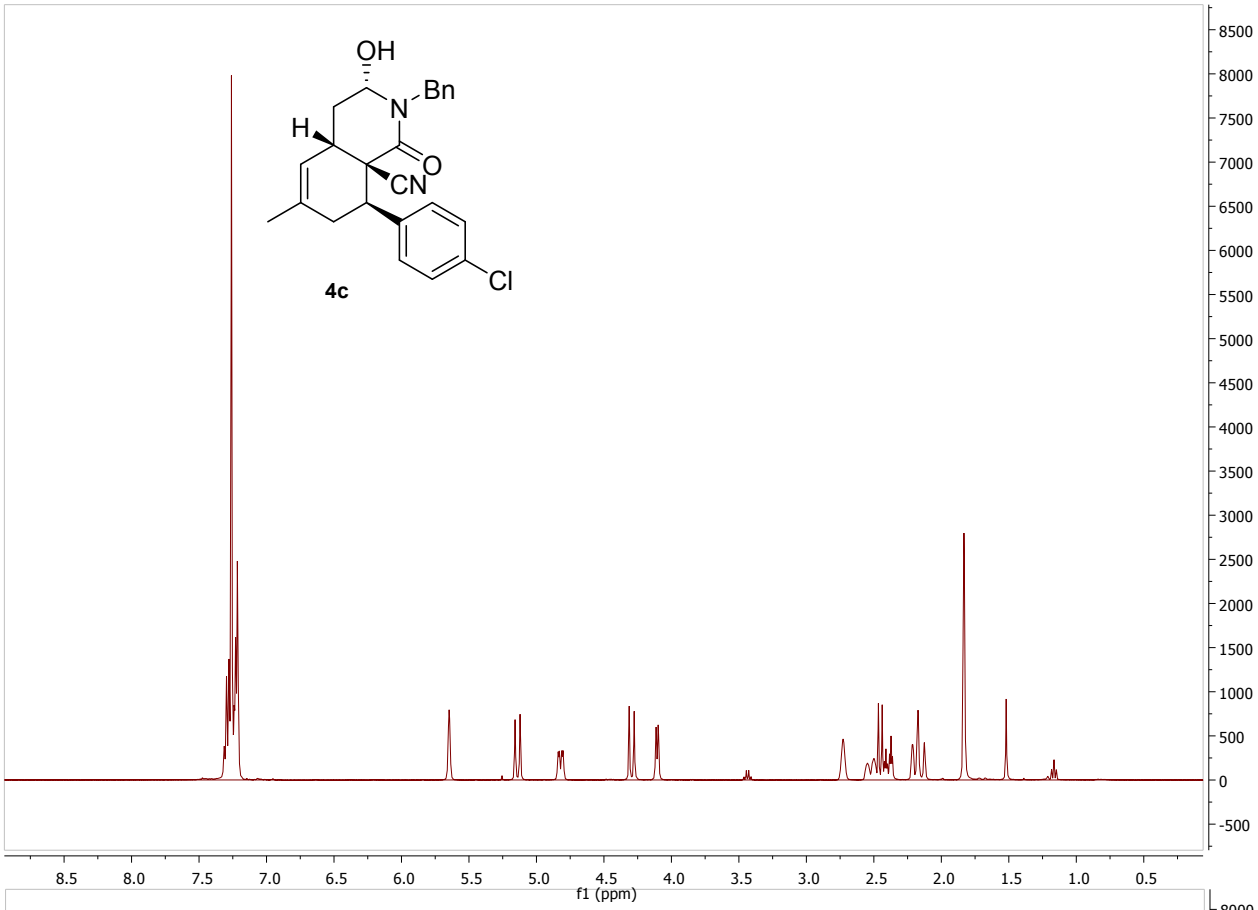
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


OH
Bn
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H
O
CN
Cl
4c
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7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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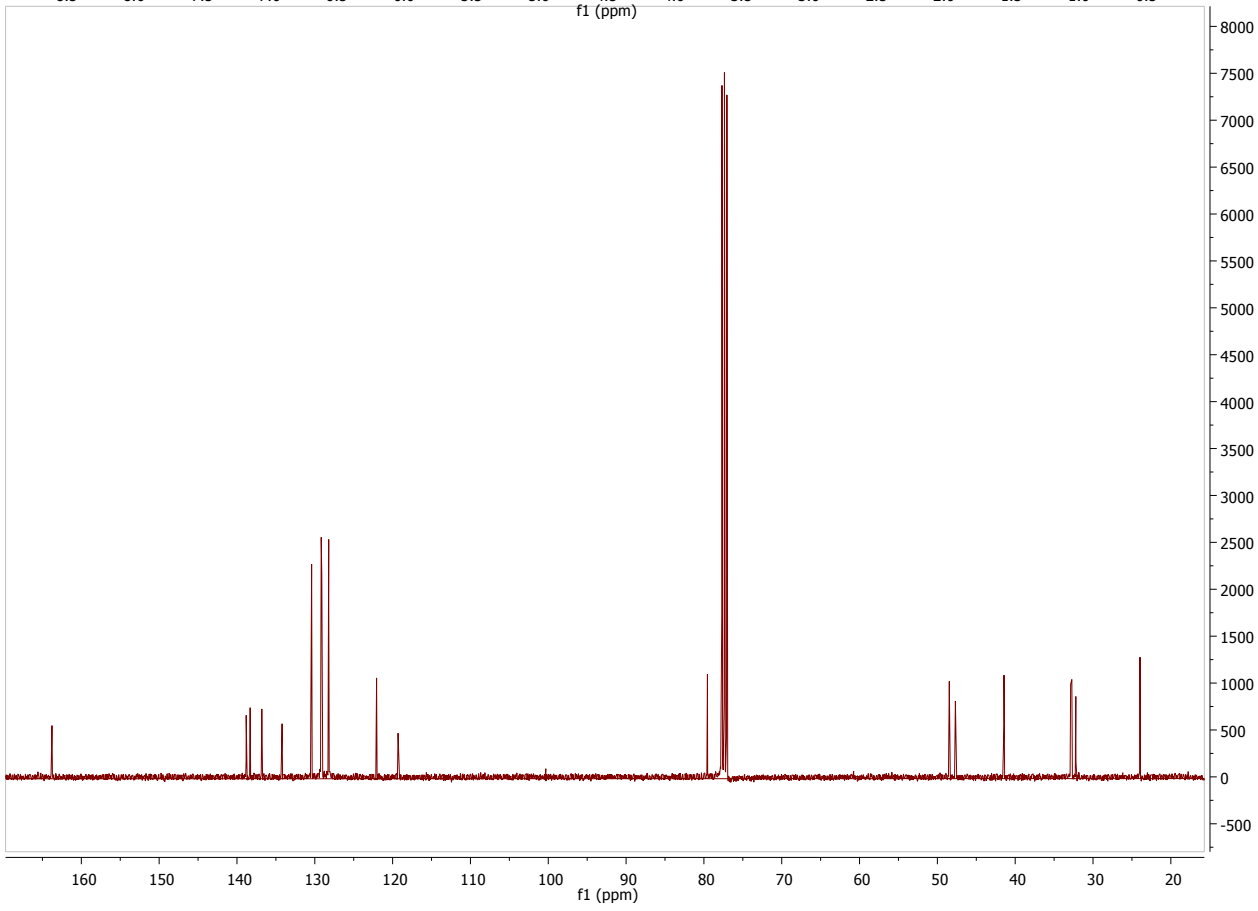
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


8000
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6000
5500
5000
4500
4000
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3000
2500
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1500
1000
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150
140
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110
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90
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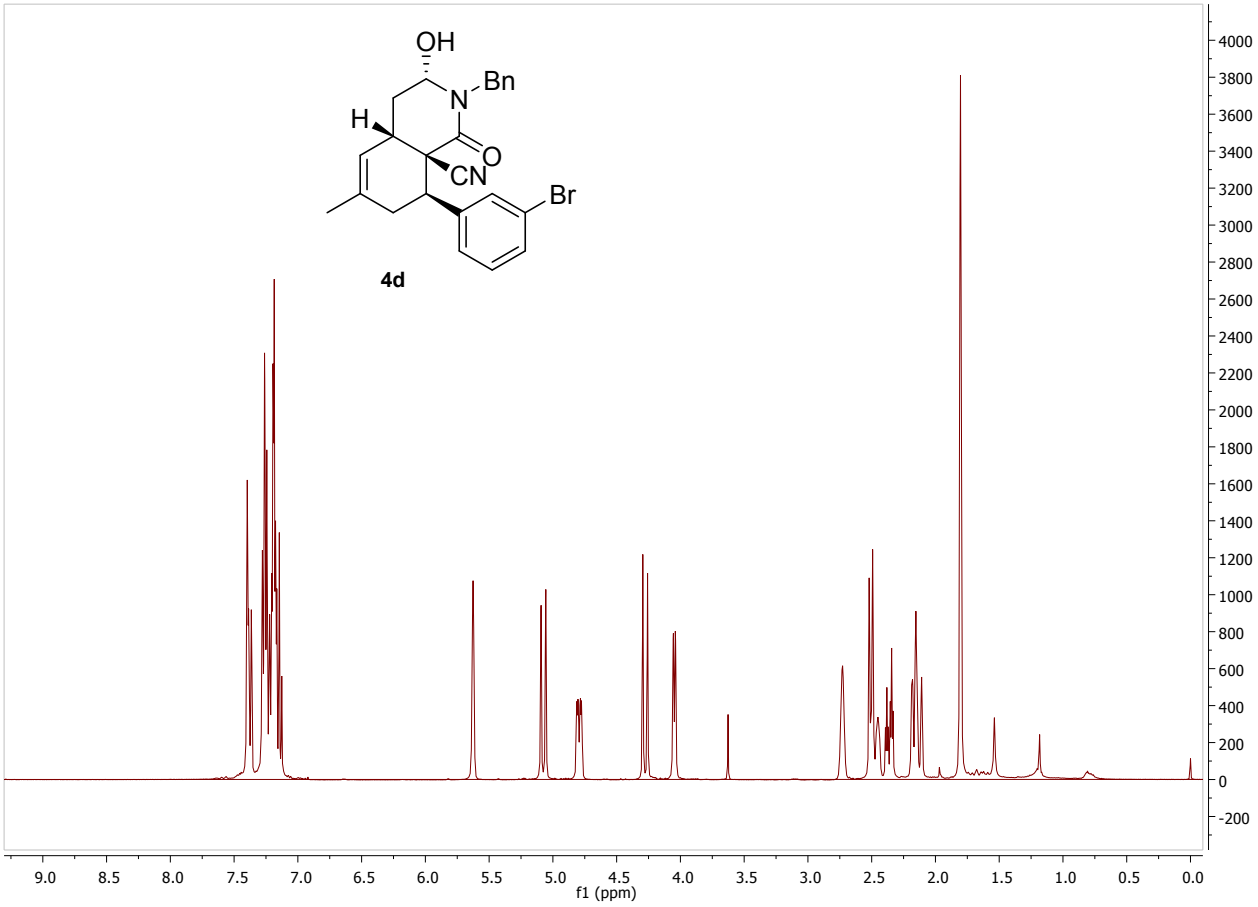
70
60
50
40
30
20
f1 (ppm)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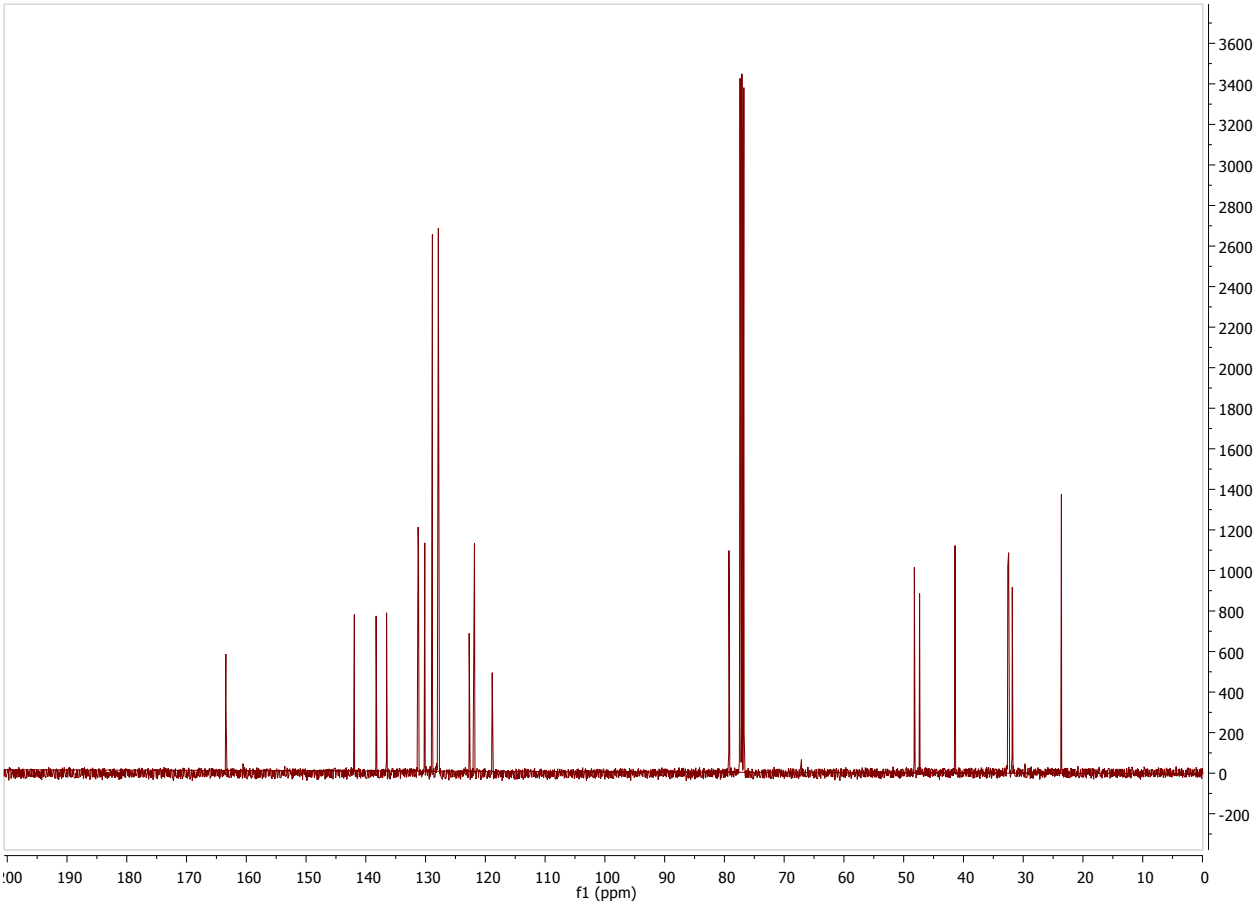
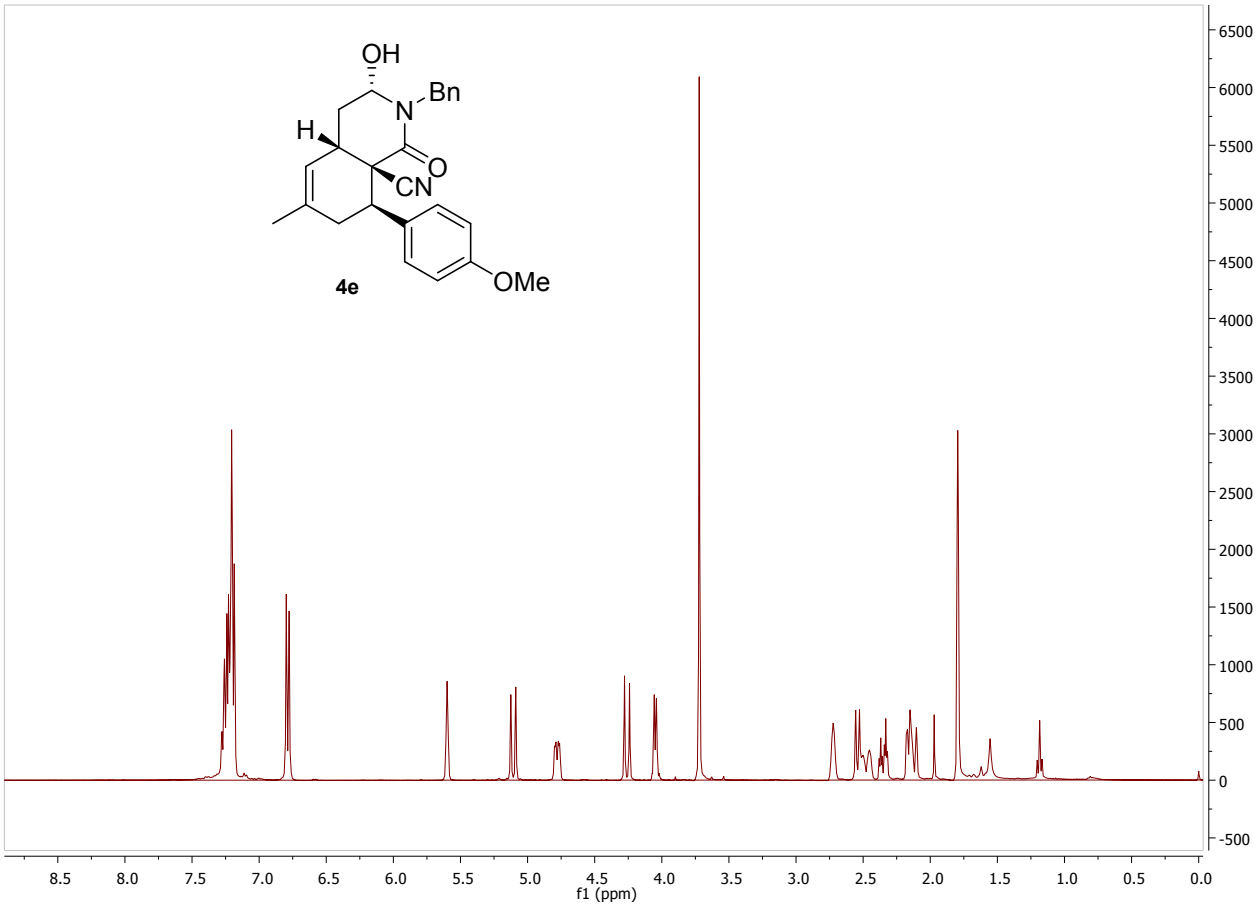
N
H
O
CN
Br
4d
f1 (ppm)


f1 (ppm)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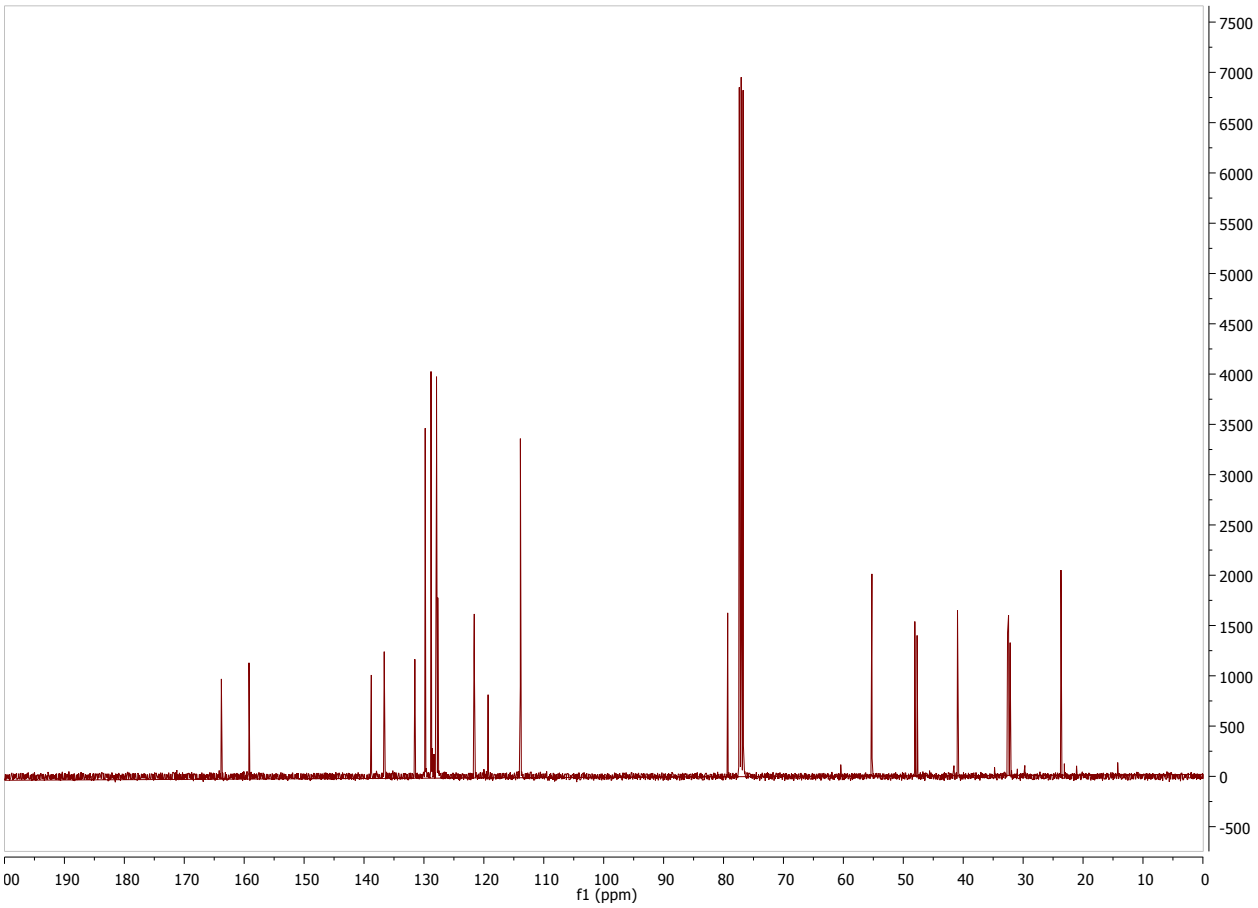
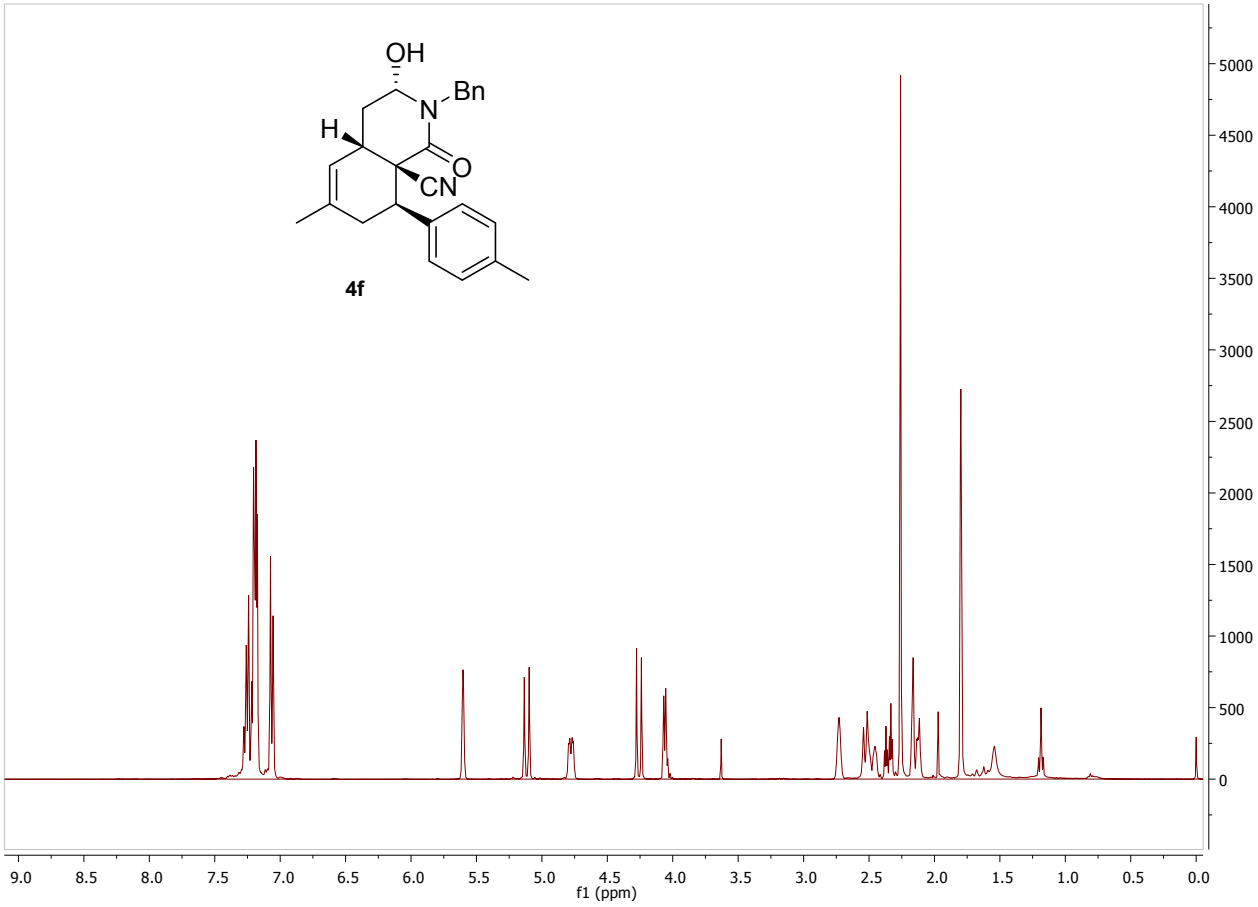
N
H
O
CN
OMe
4e
f1 (ppm)


f1 (ppm)


OH
Bn
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H
O
CN
4f
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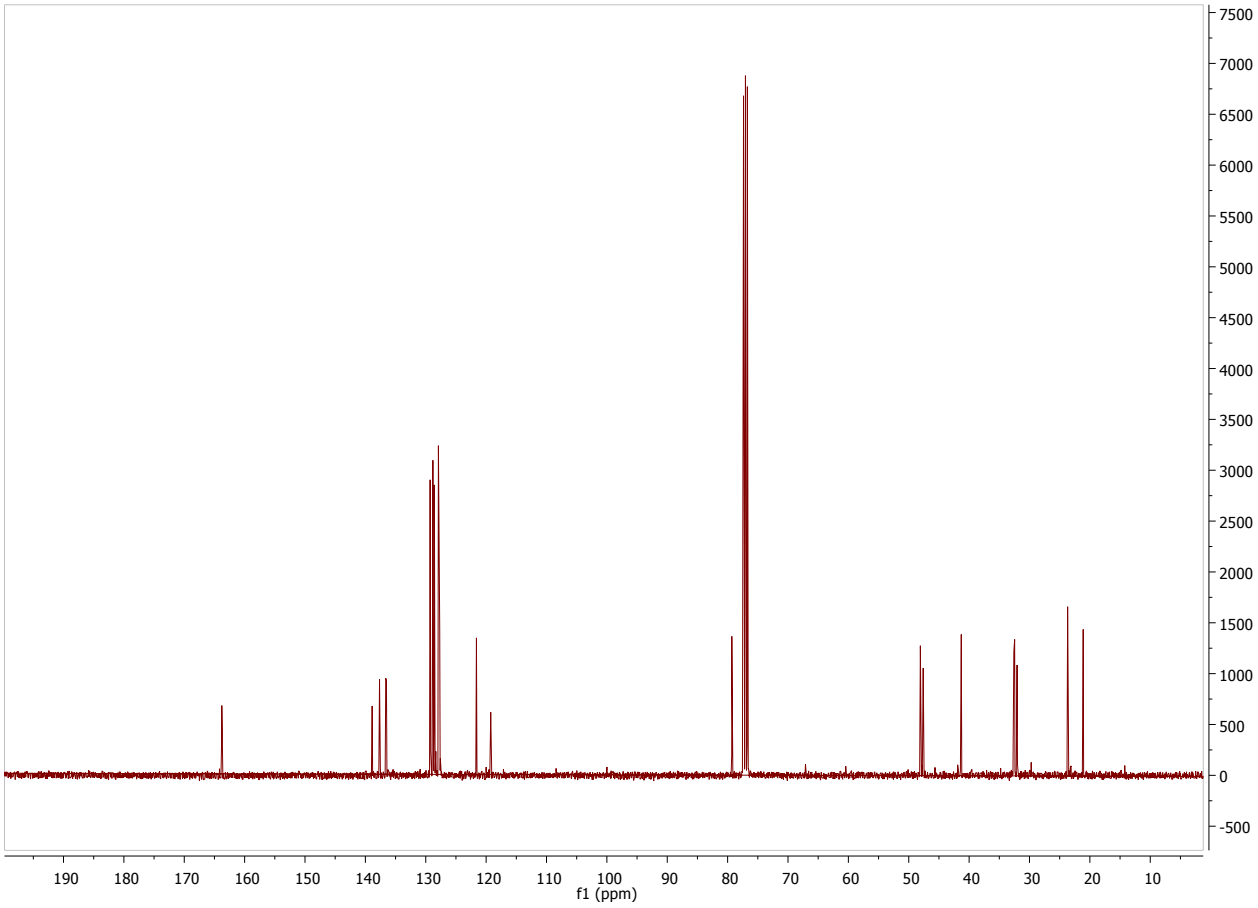
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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7000
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6000
5500
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3500
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2500
2000
1500
1000
500
0
-500
190
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160
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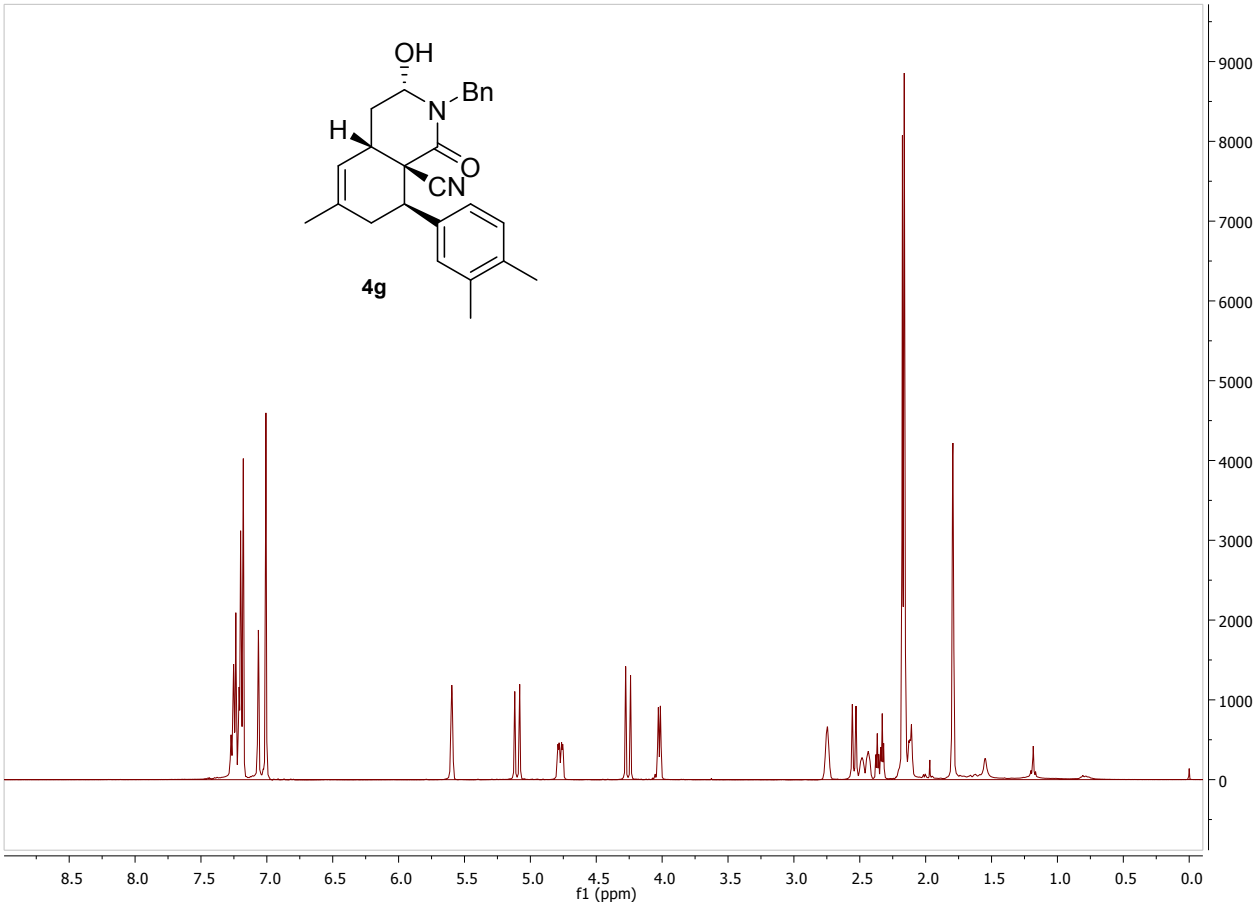
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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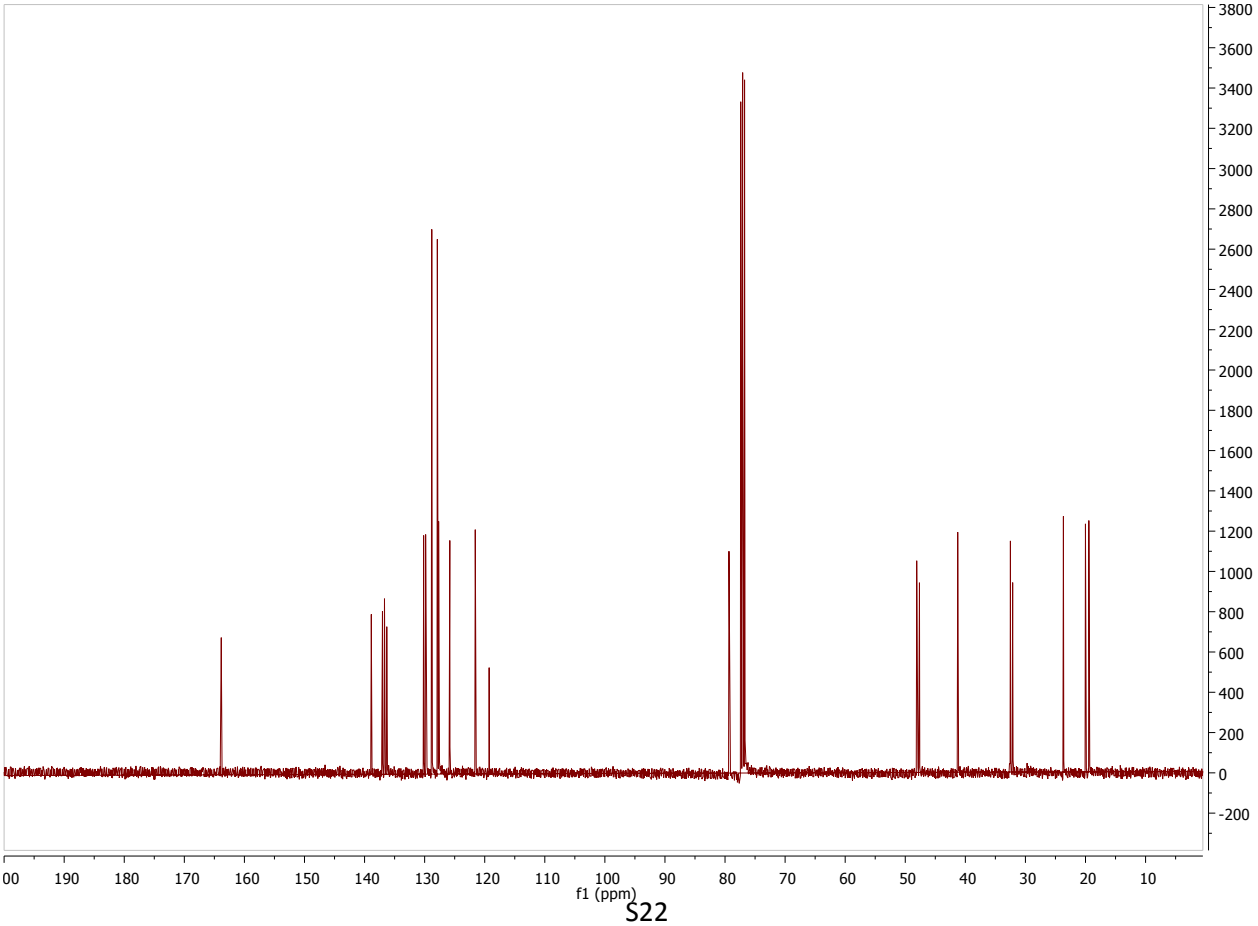
Bn
N
H
O
CN
4g
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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3200
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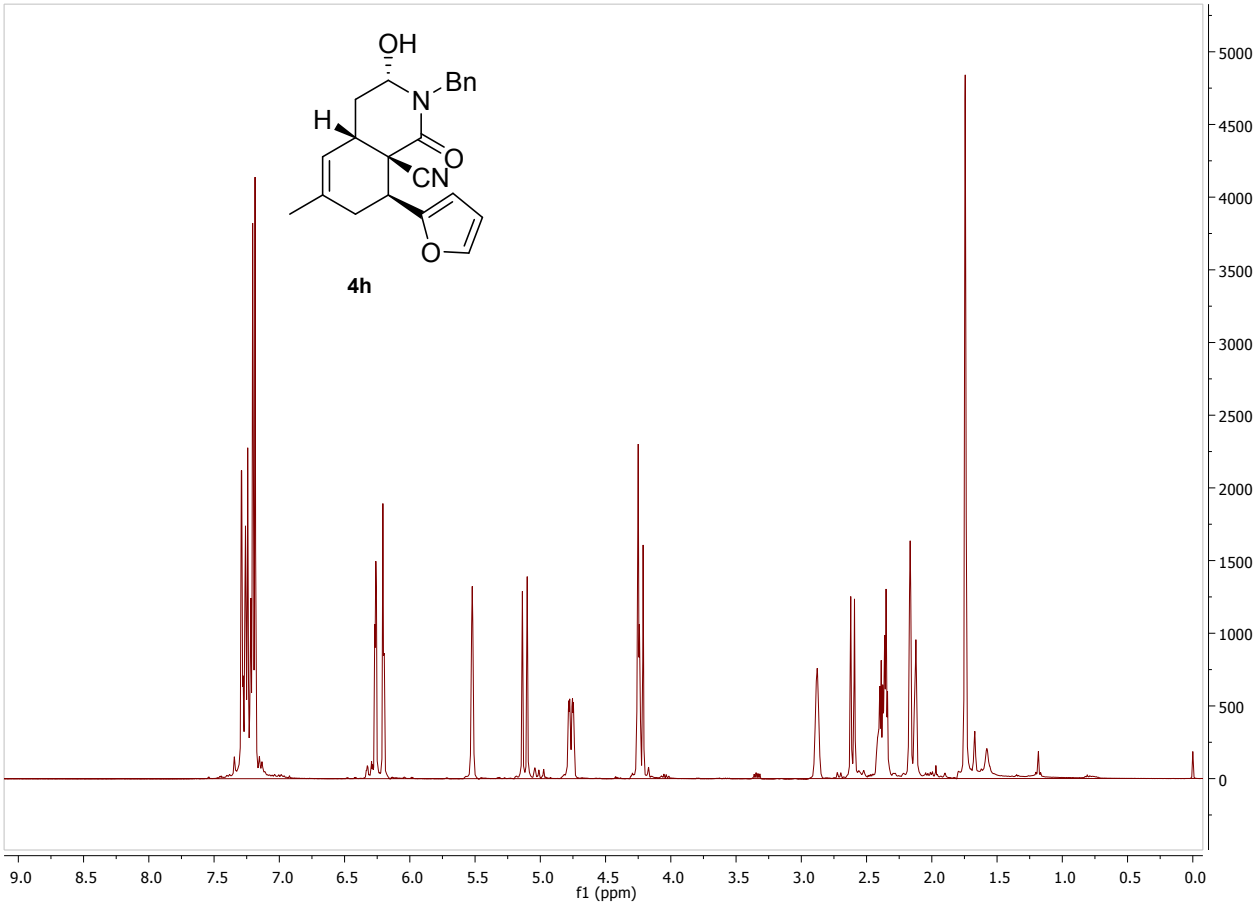
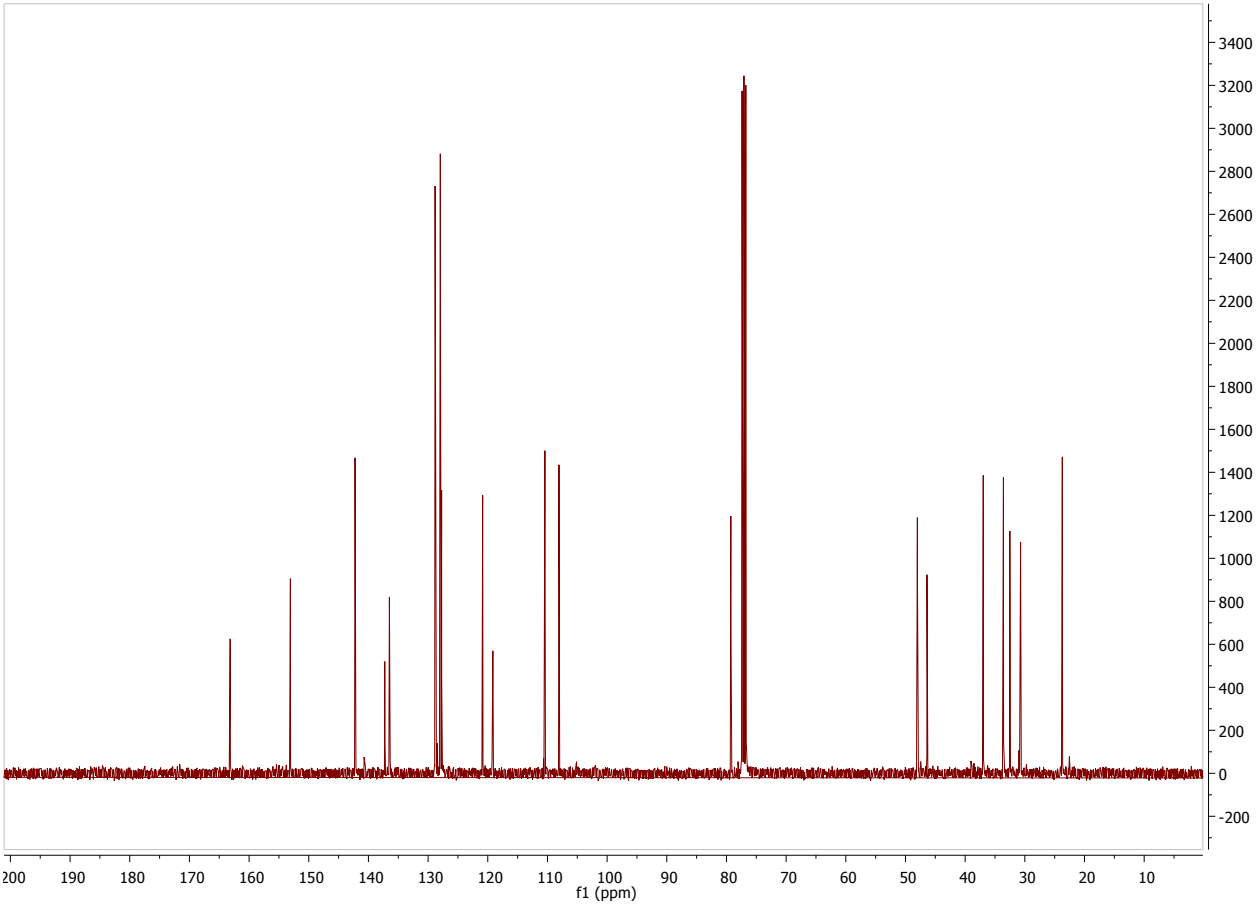
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OH
Bn
N
H
O
CN
O
4h
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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2800
2600
2400
2200
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1800
1600
1400
1200
1000
800
600
400
200
0
-200
200
190
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140
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100
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80
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60
50
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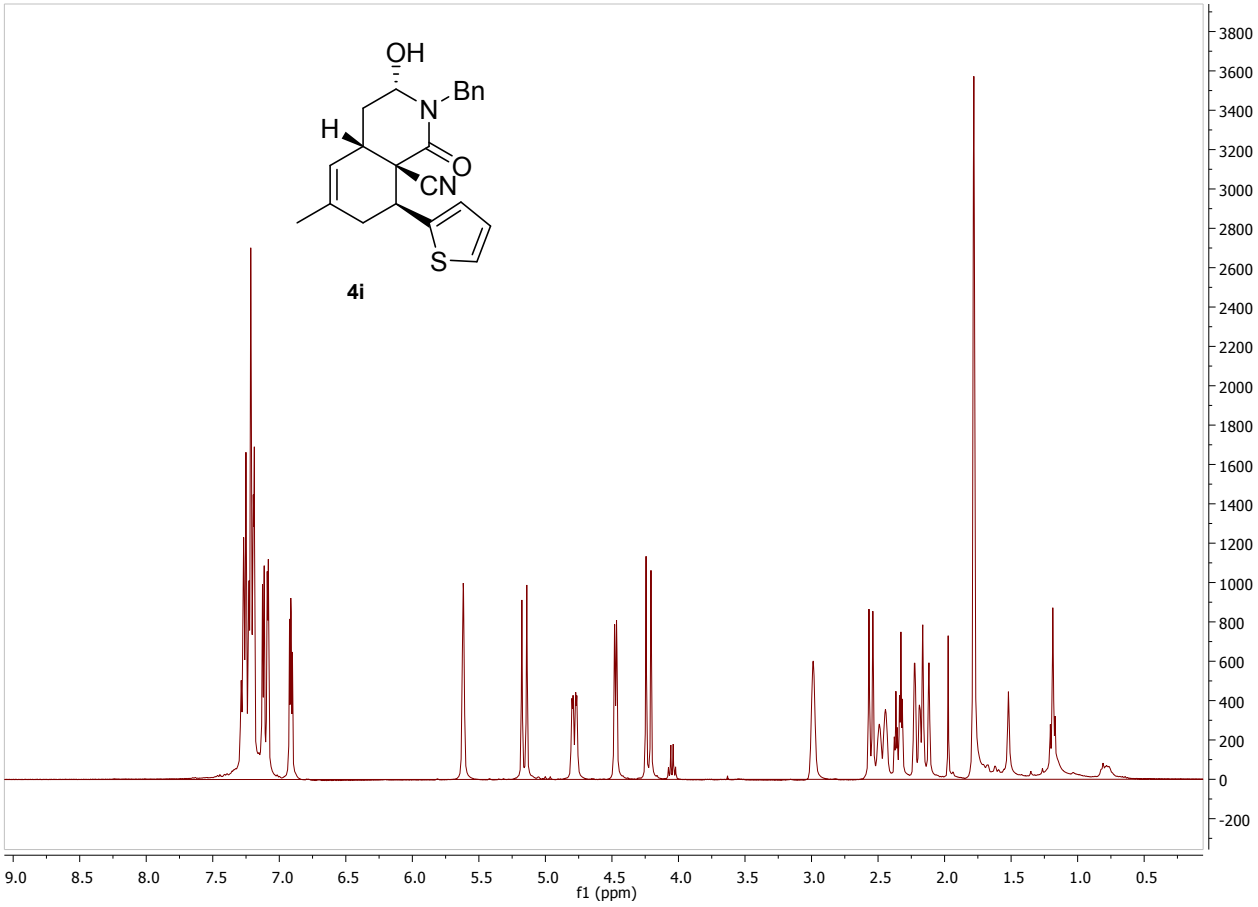
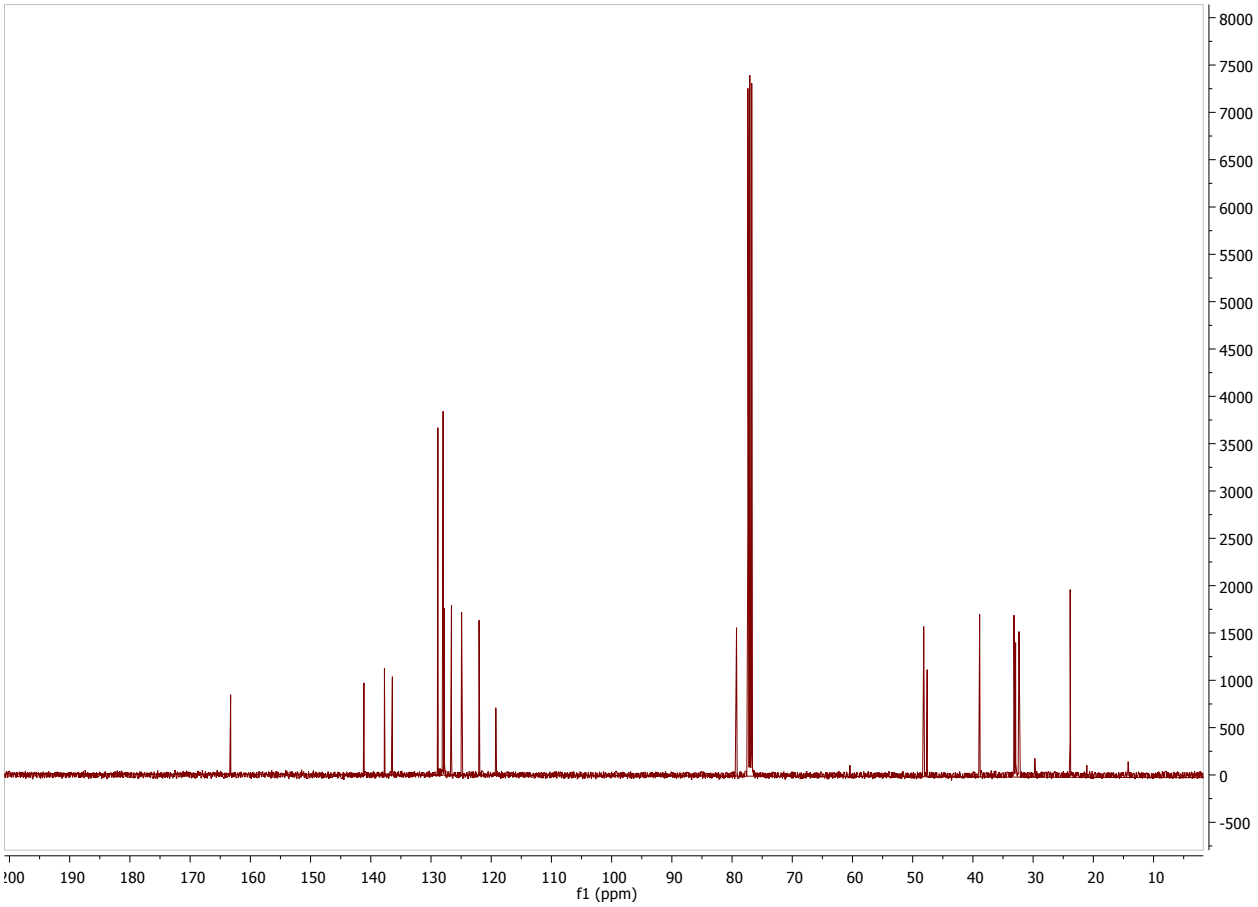
20
10
f1 (ppm)


OH
Bn
N
H
O
CN
S
4i
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


8000
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7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
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160
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140
130
120
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100
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80
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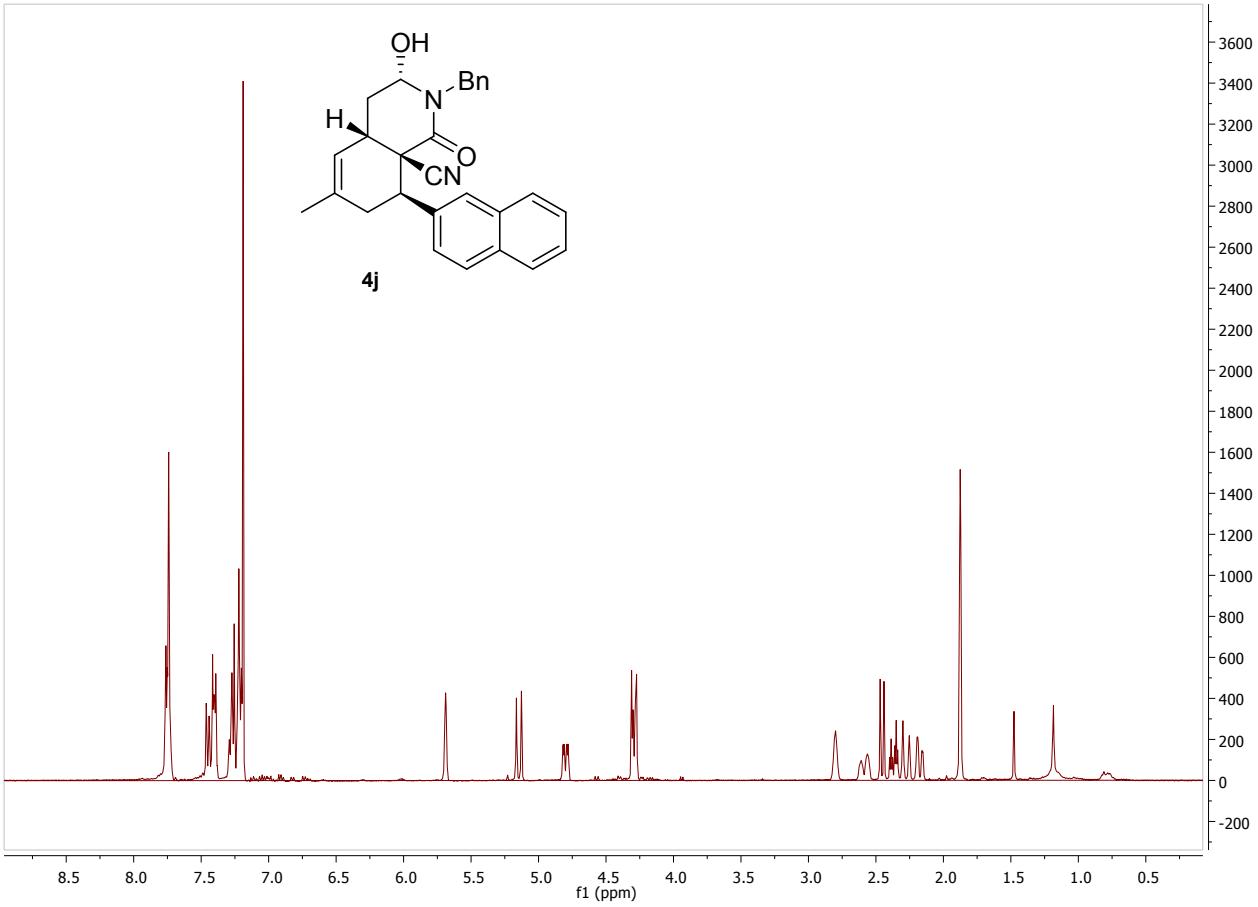
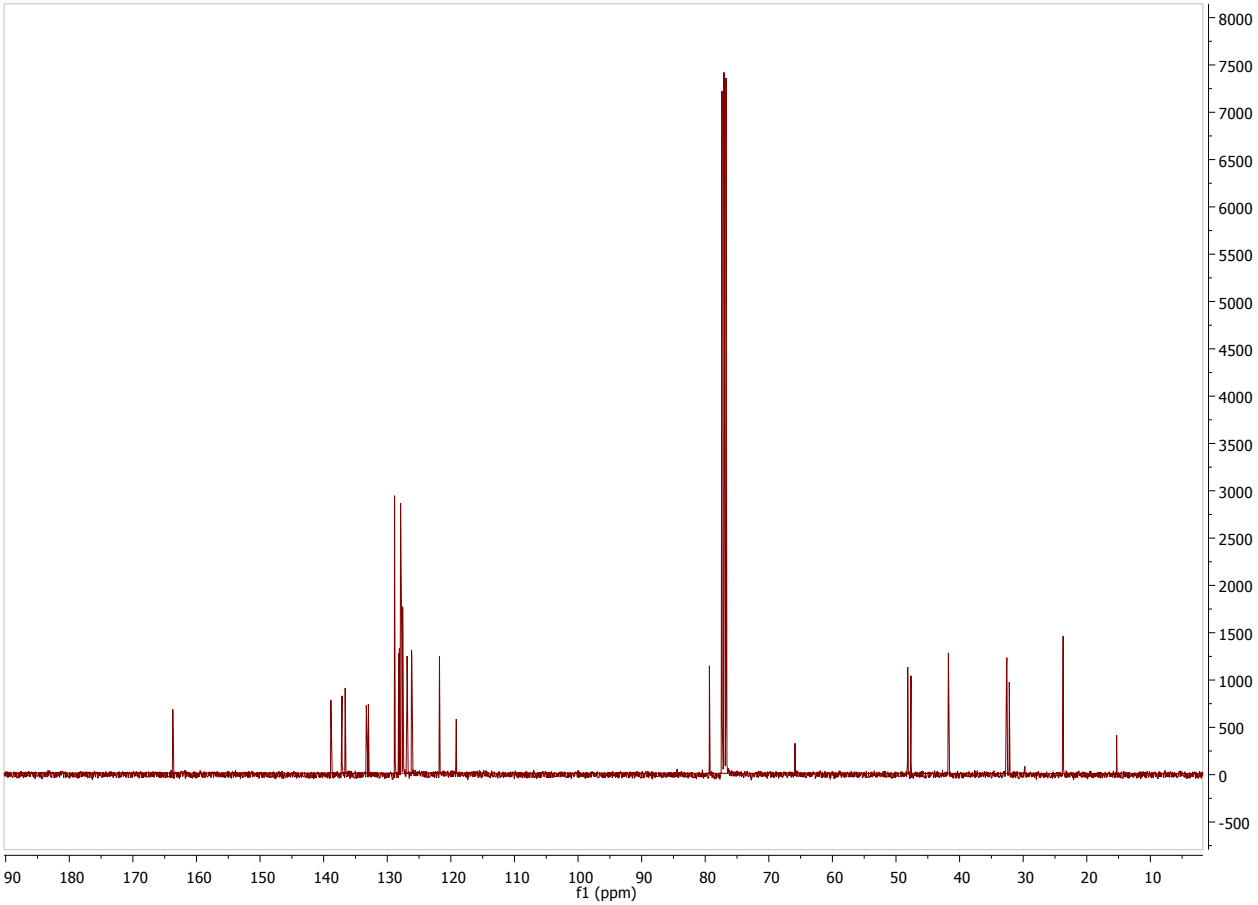
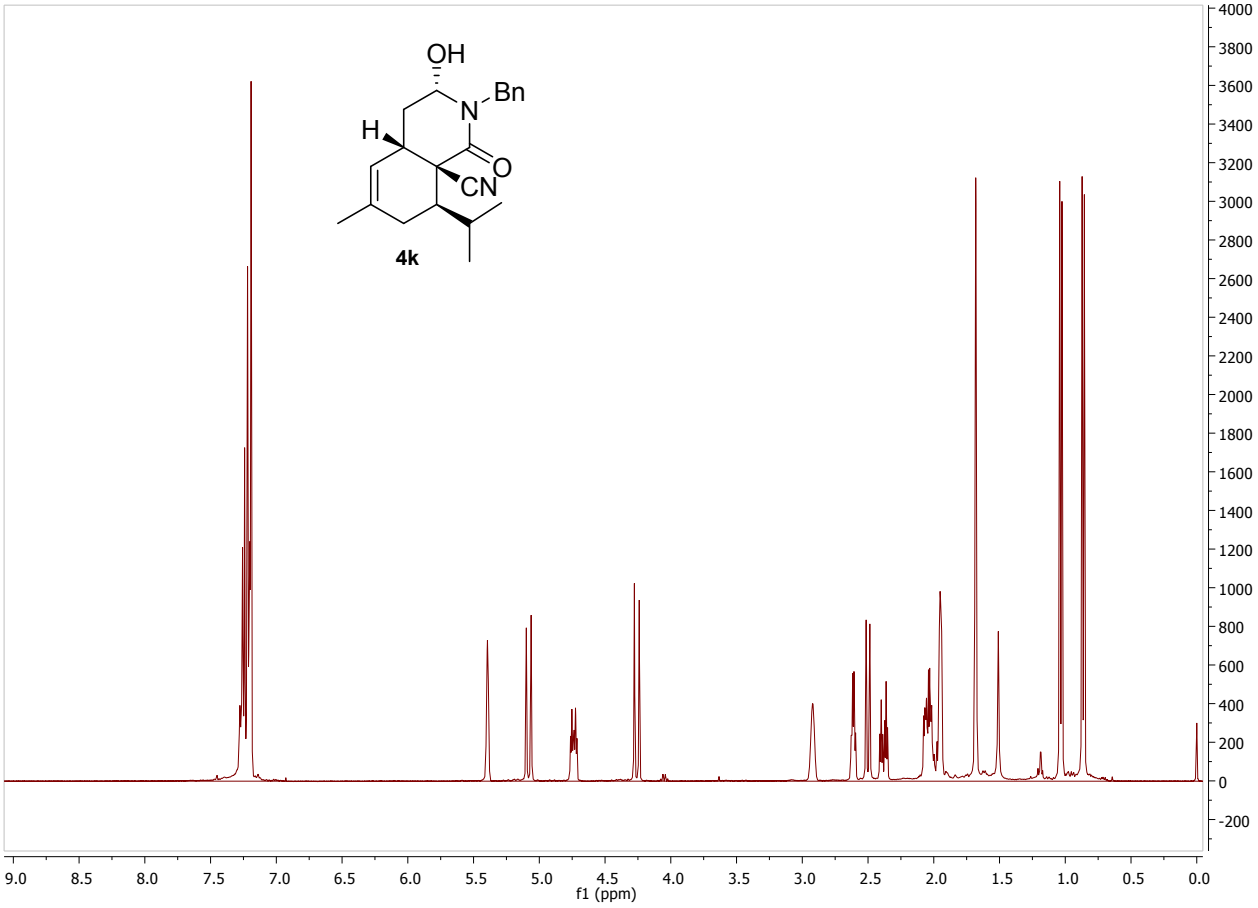
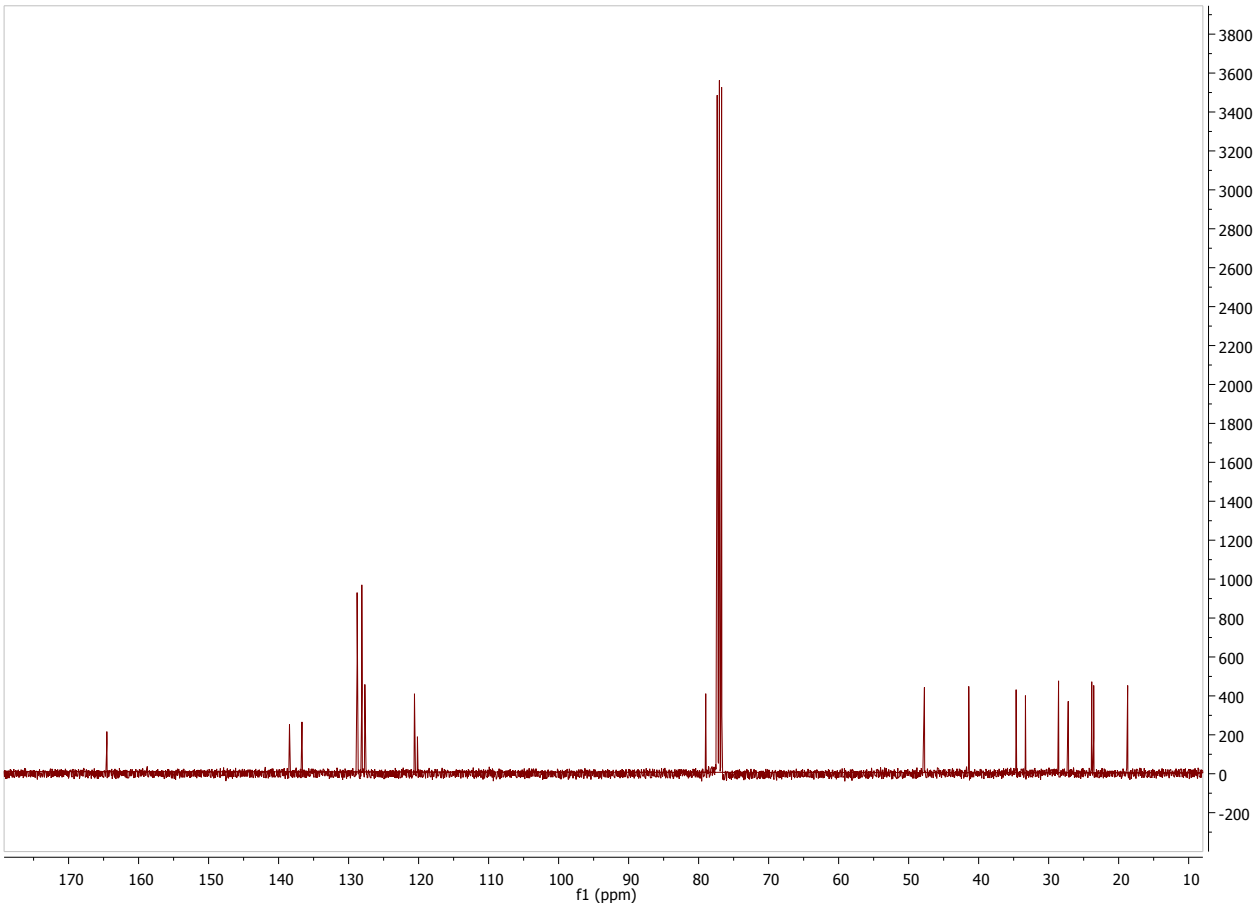
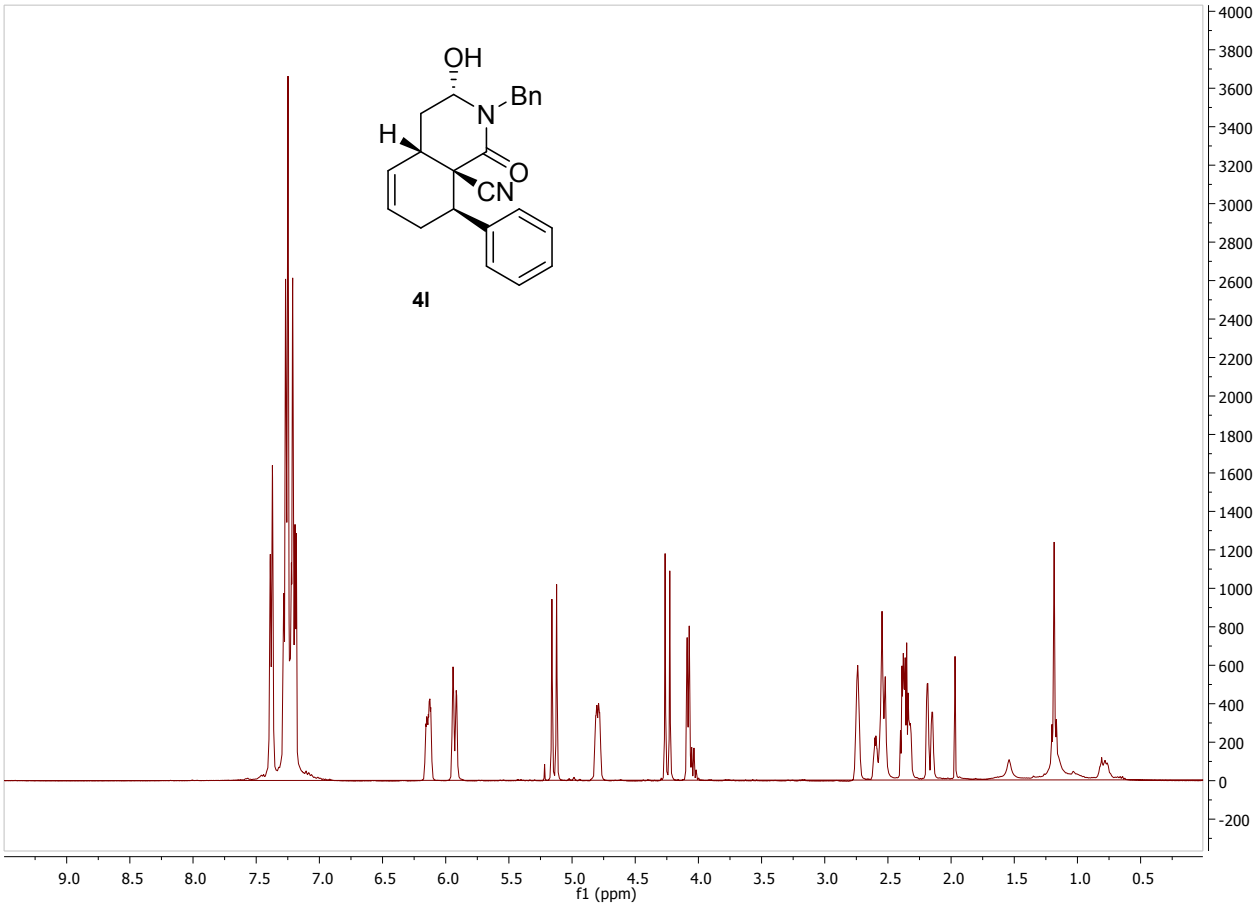
60
50
40
30
20
10
f1 (ppm)

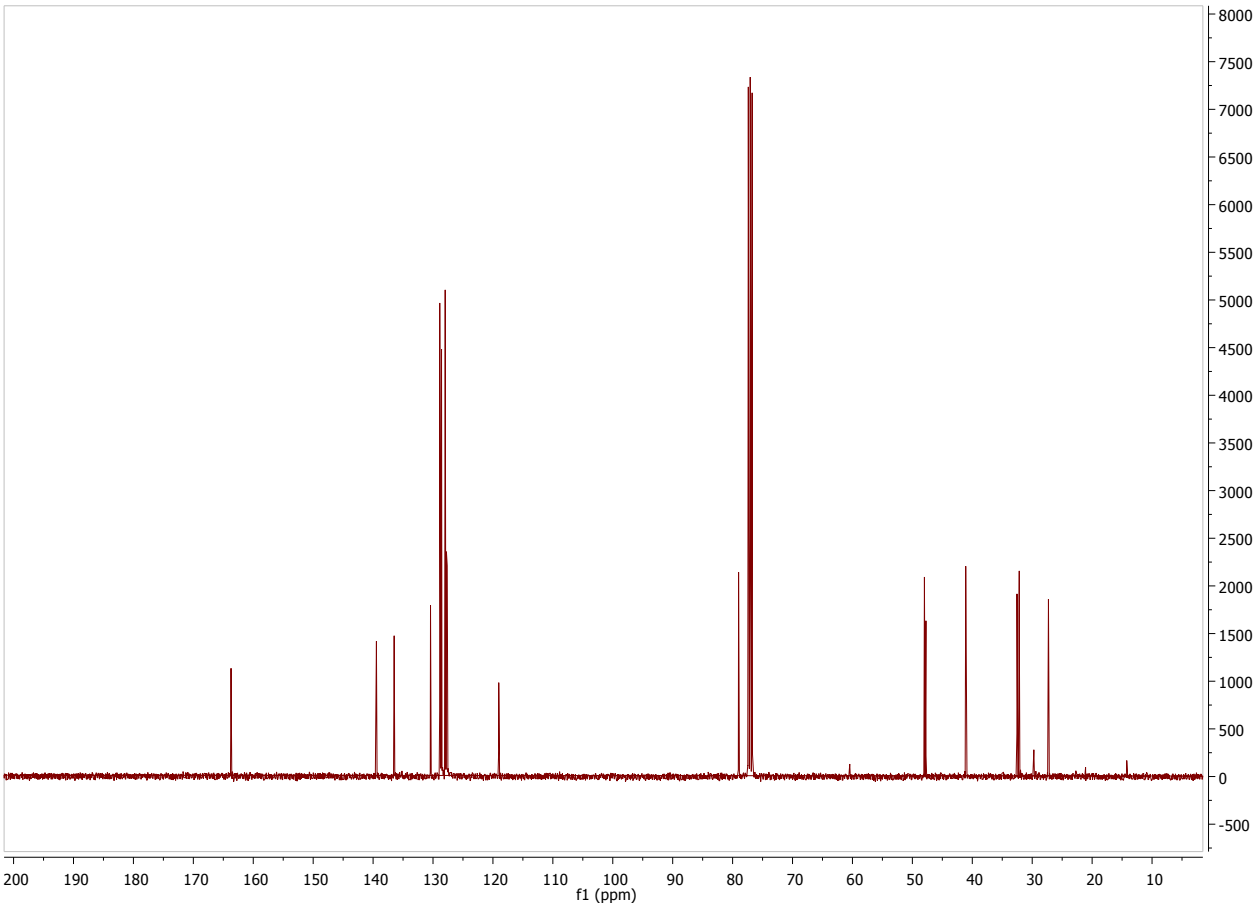

OH
Bn
N
H
O
CN
4j
f1 (ppm)

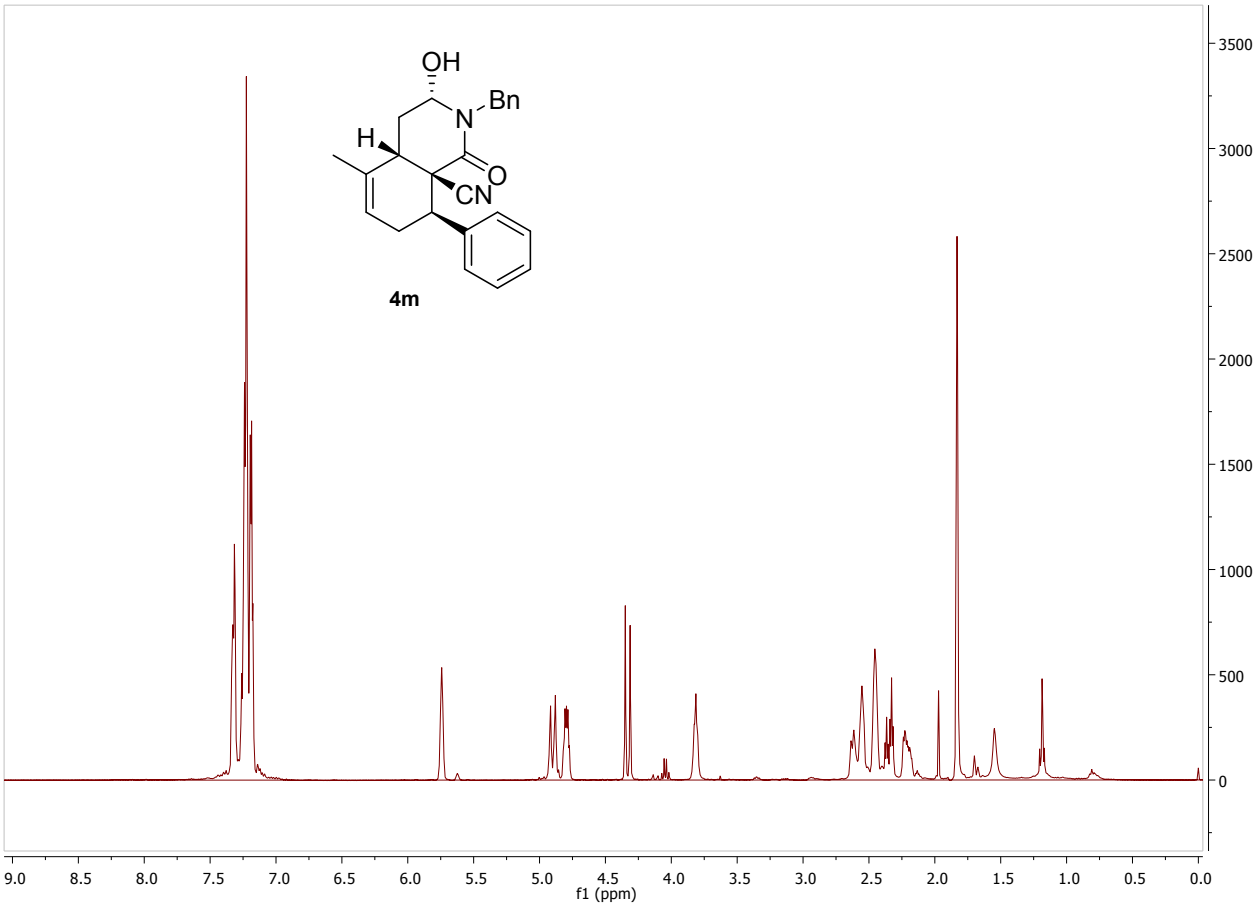

f1 (ppm)


OH
Bn
N
H
O
CN
4k
f1 (ppm)


f1 (ppm)


OH
Bn
N
H
O
CN
4l
f1 (ppm)


f1 (ppm)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N
H
O
CN
4m
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3000
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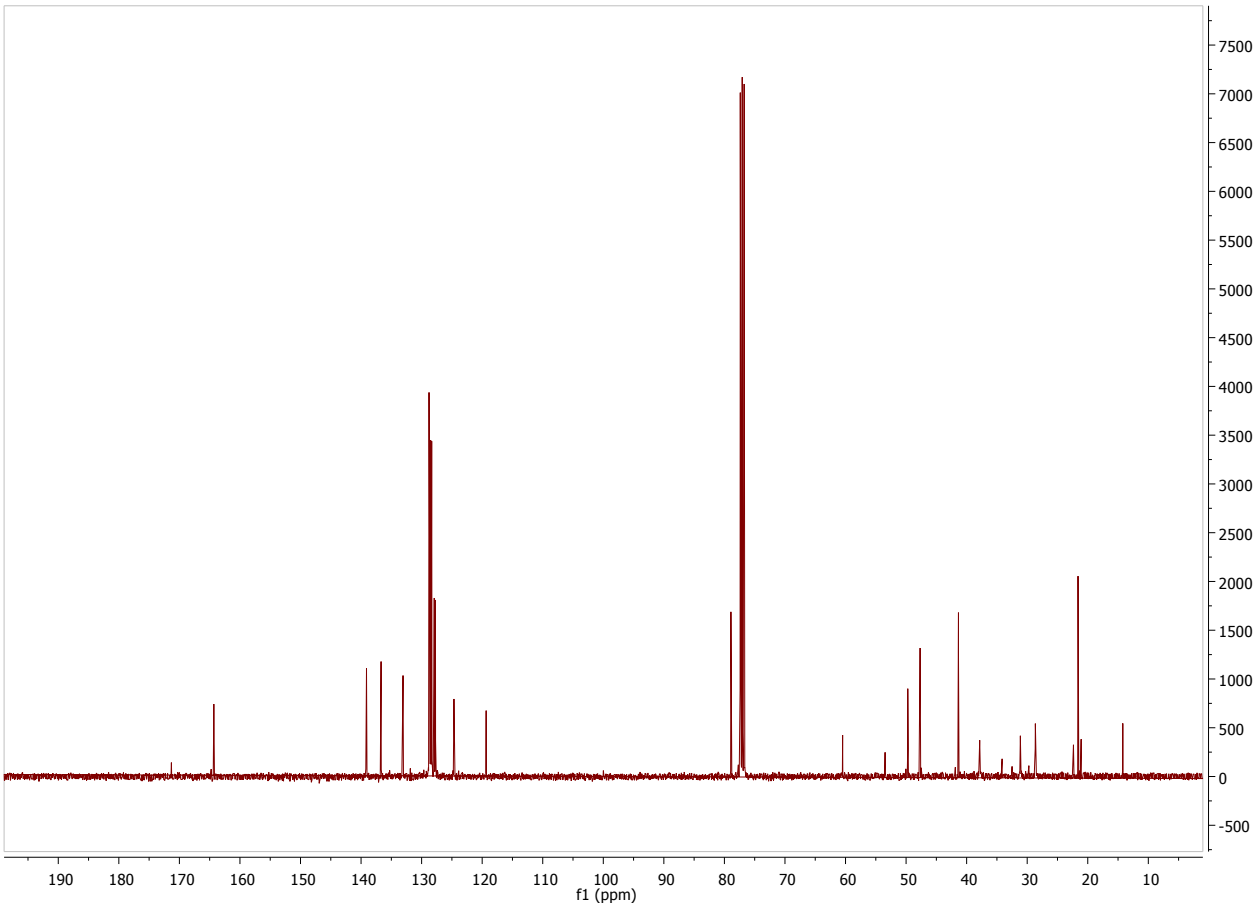
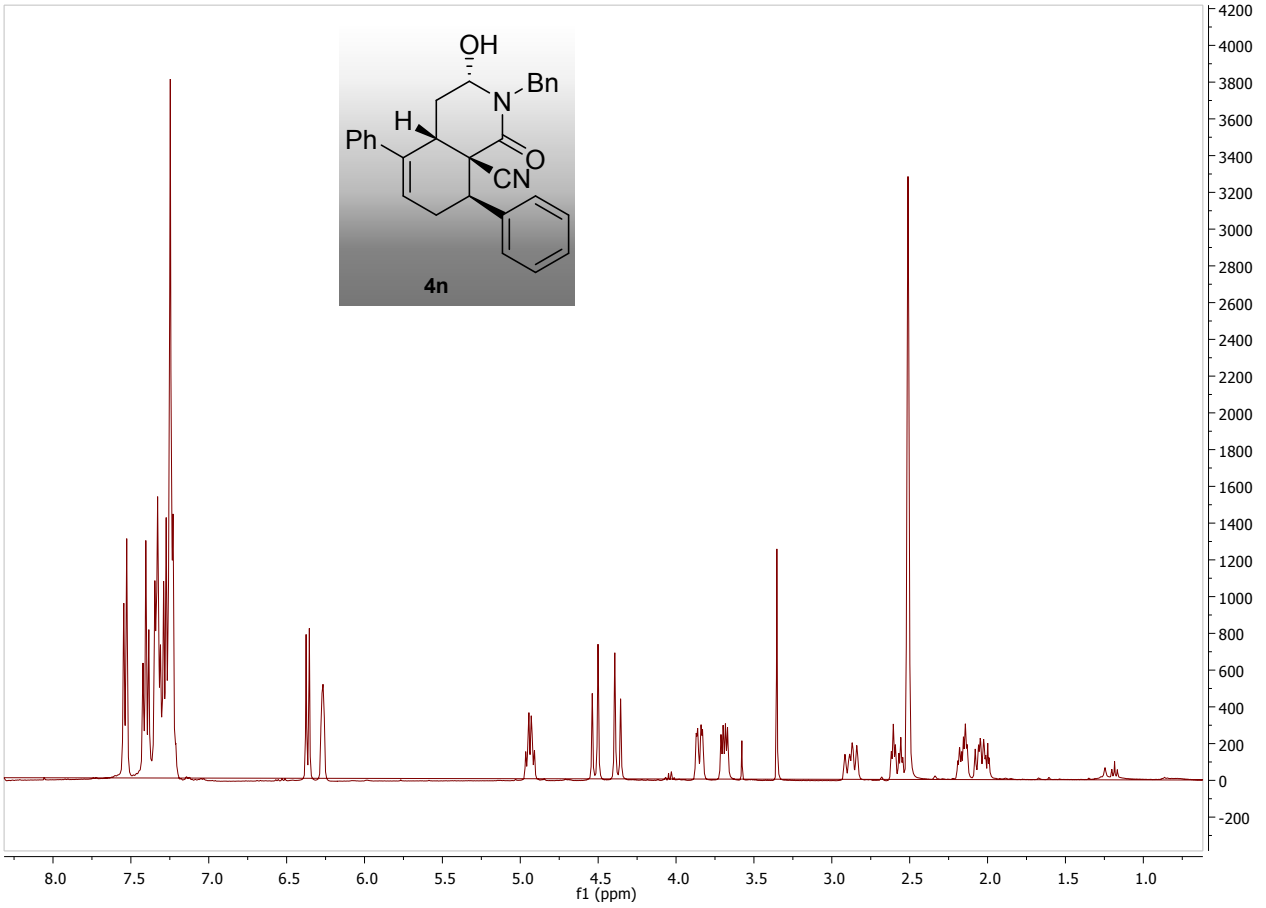
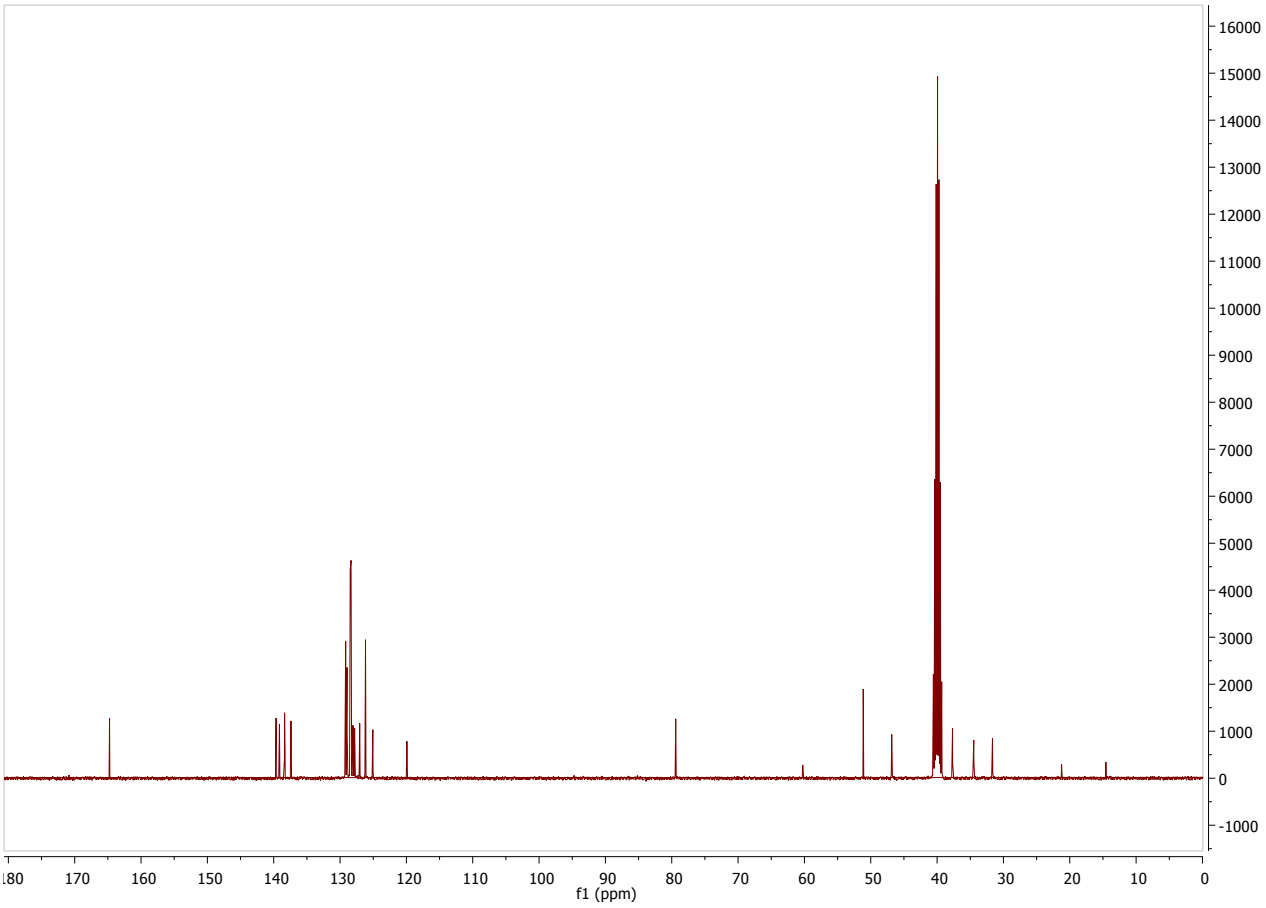
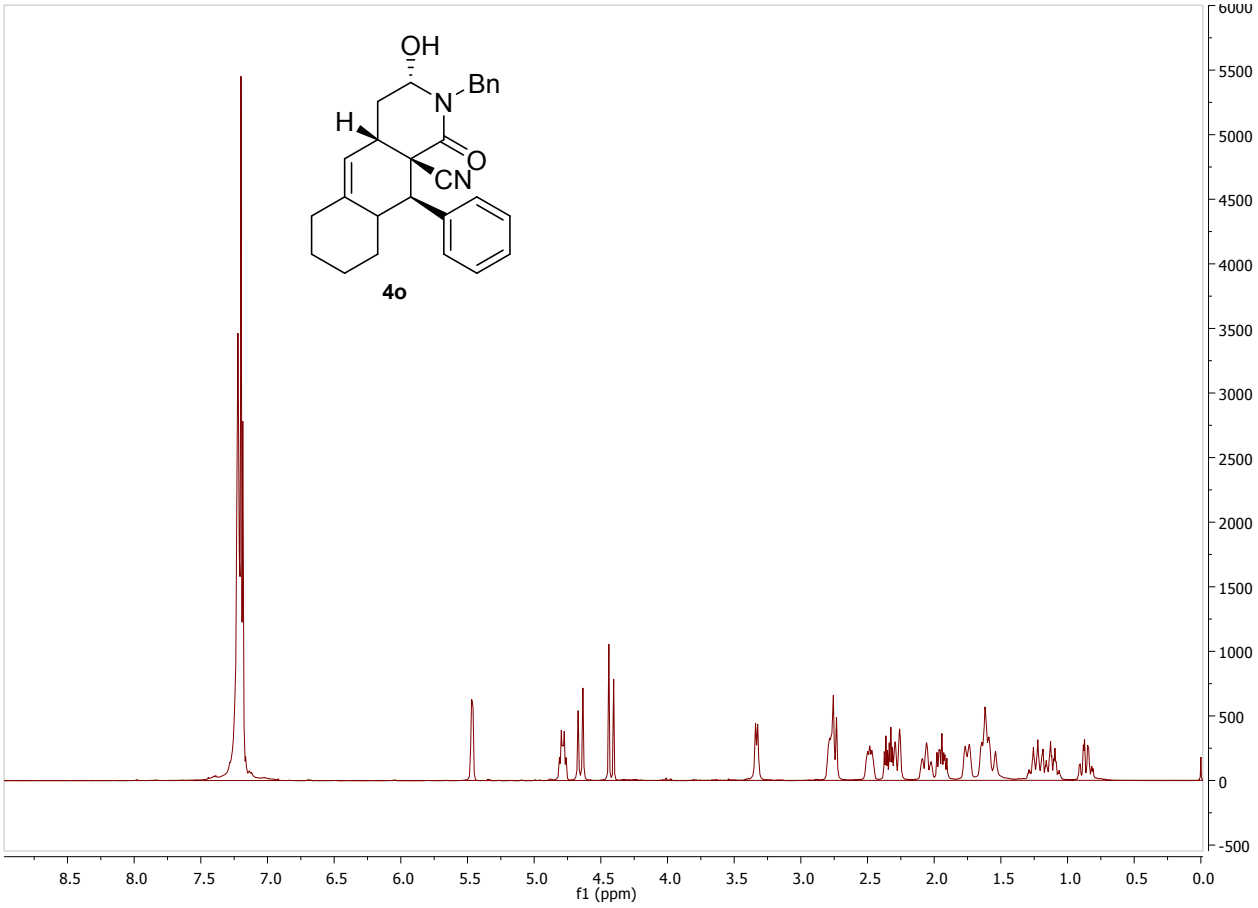
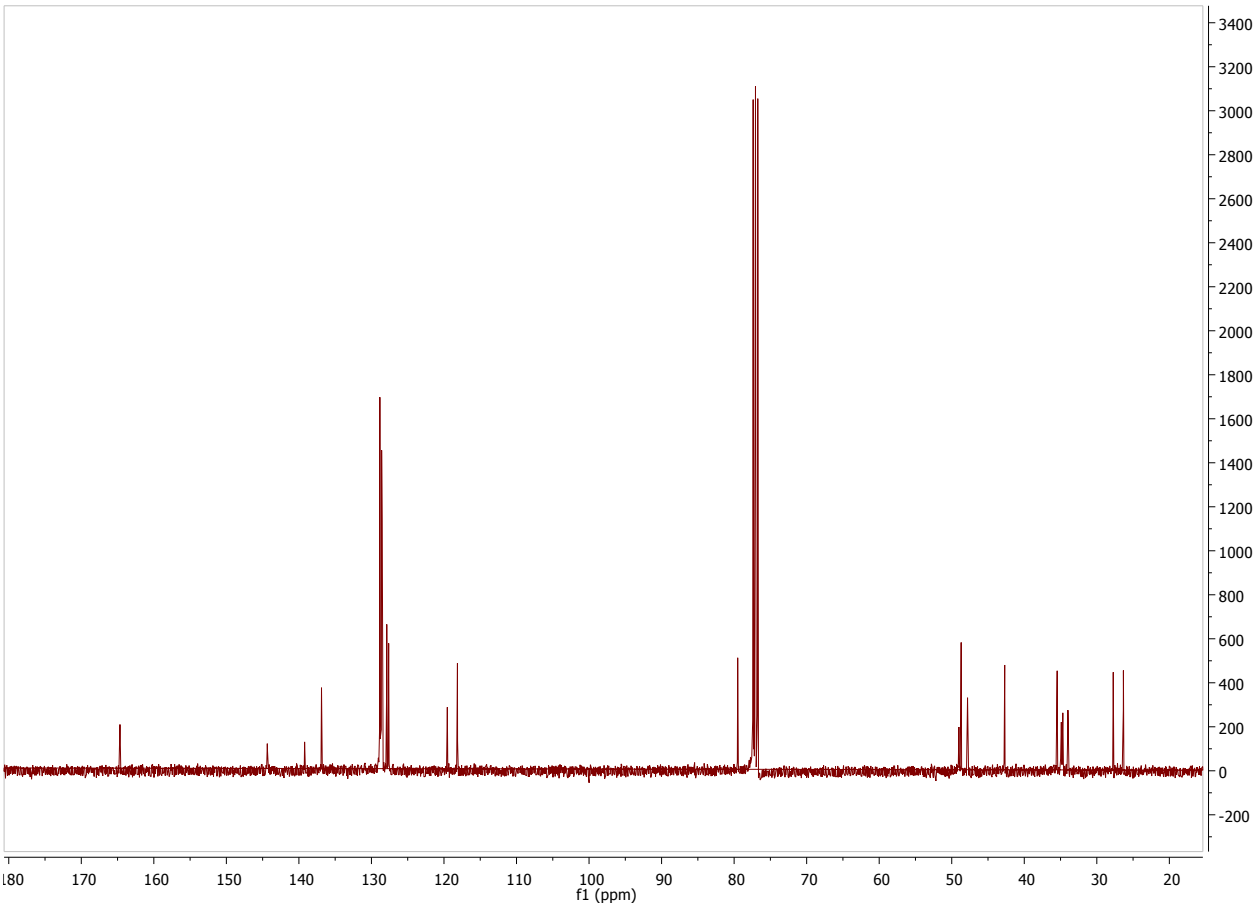
2000
1500
1000
500
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OH
Bn
N
H
Ph
O
CN
4n
f1 (ppm)


f1 (ppm)


OH
Bn
N
H
O
CN
4o
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500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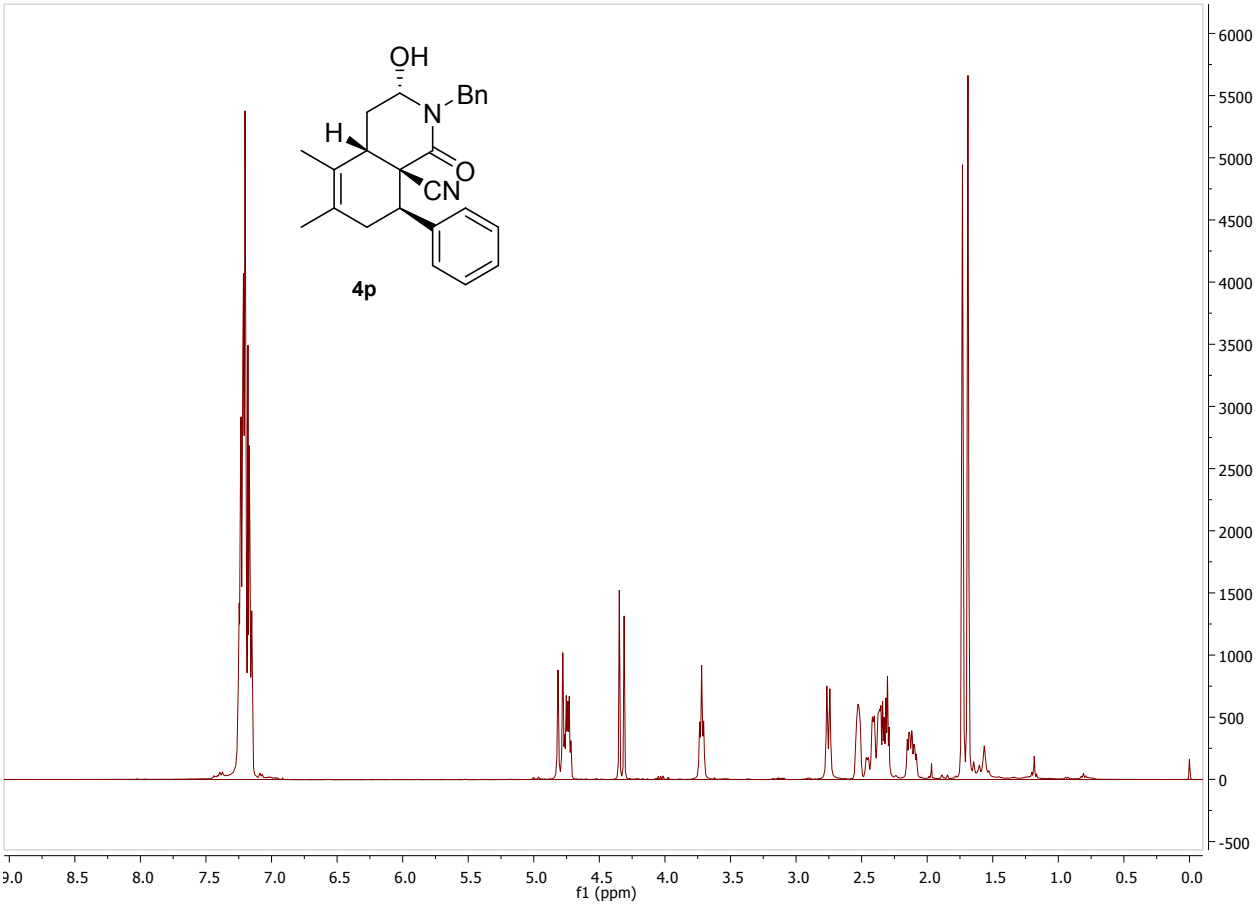
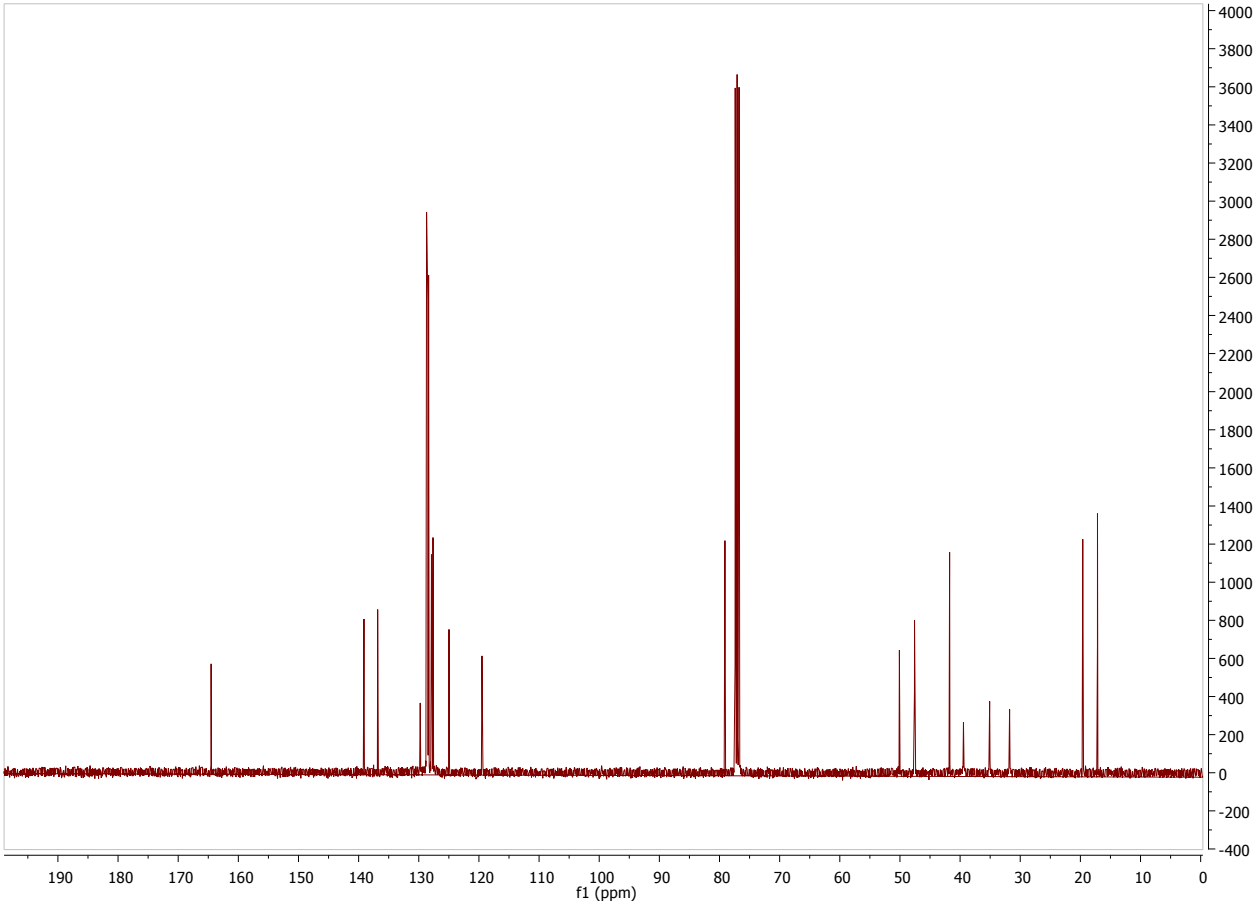
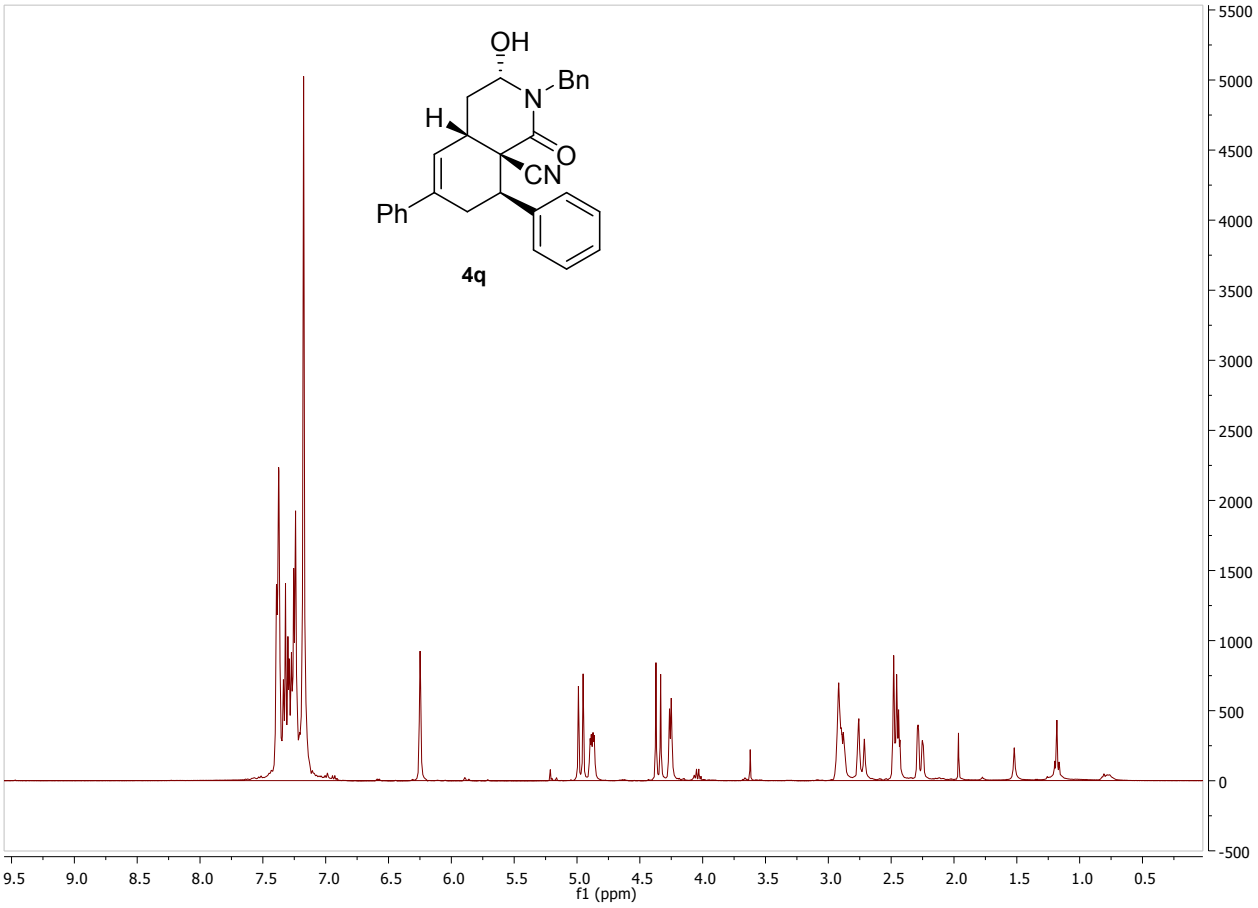
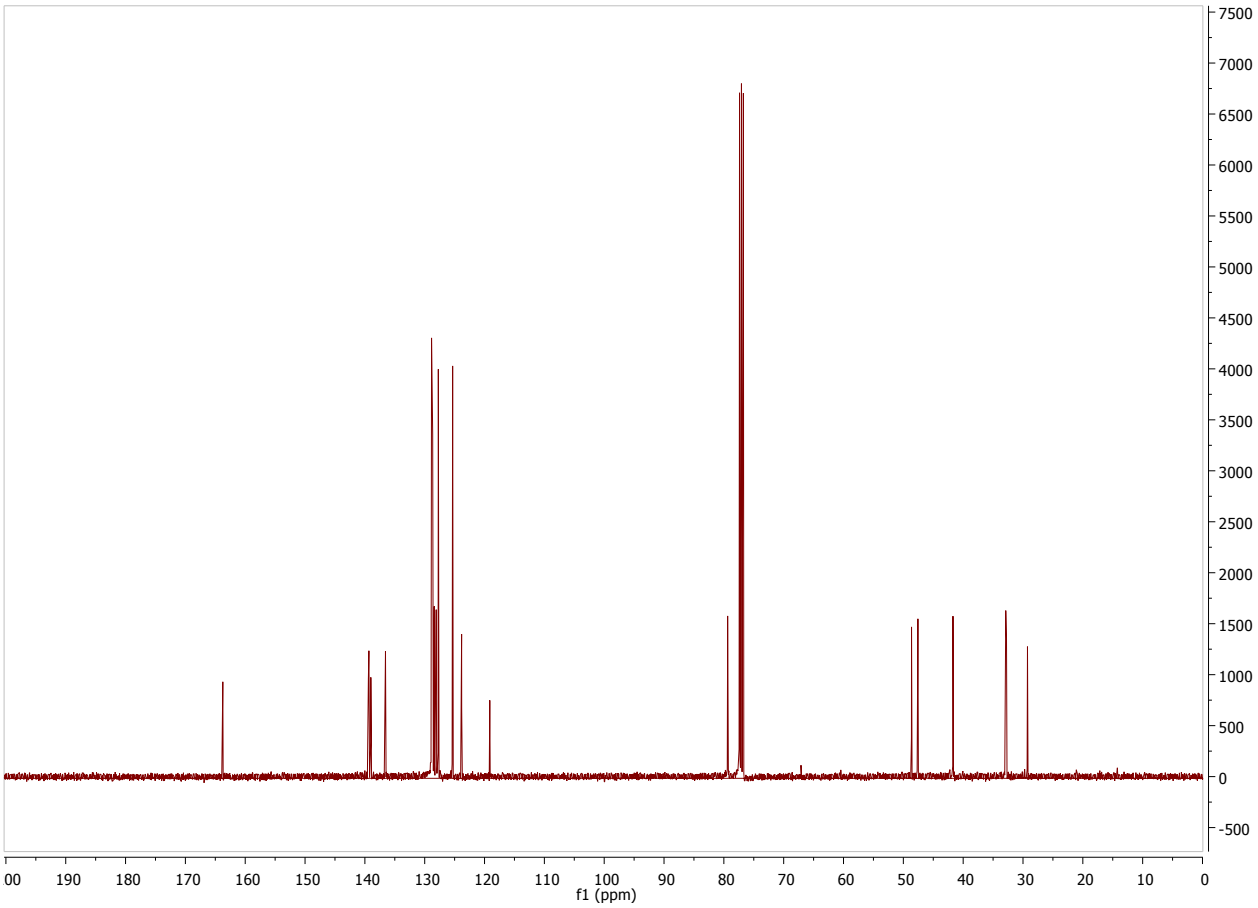
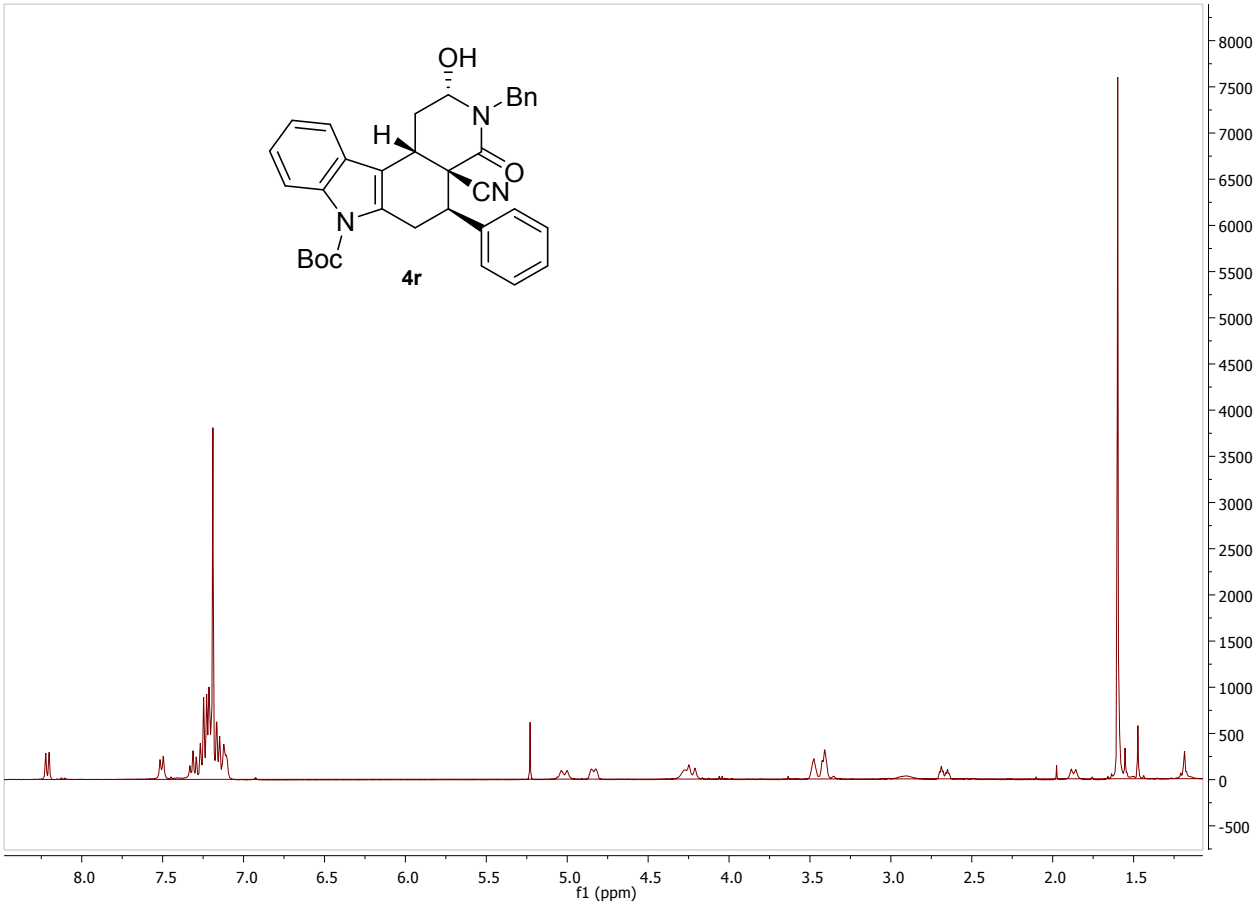
f1 (ppm)
3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200


OH
Bn
N
H
O
CN
4p
f1 (ppm)


f1 (ppm)


OH
Bn
N
H
O
CN
Ph
4q
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
Bn
N
H
O
CN
N
Boc
4r
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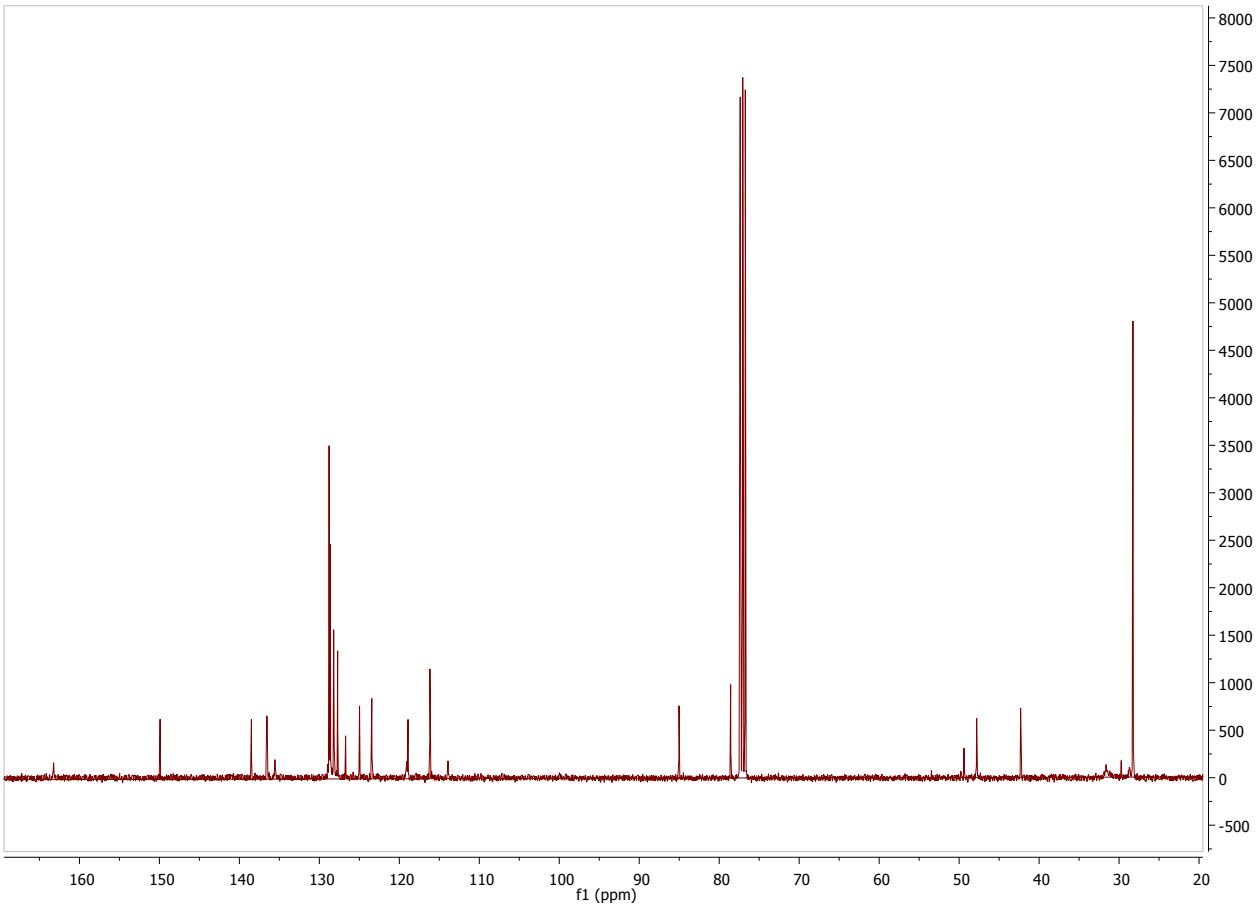
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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150
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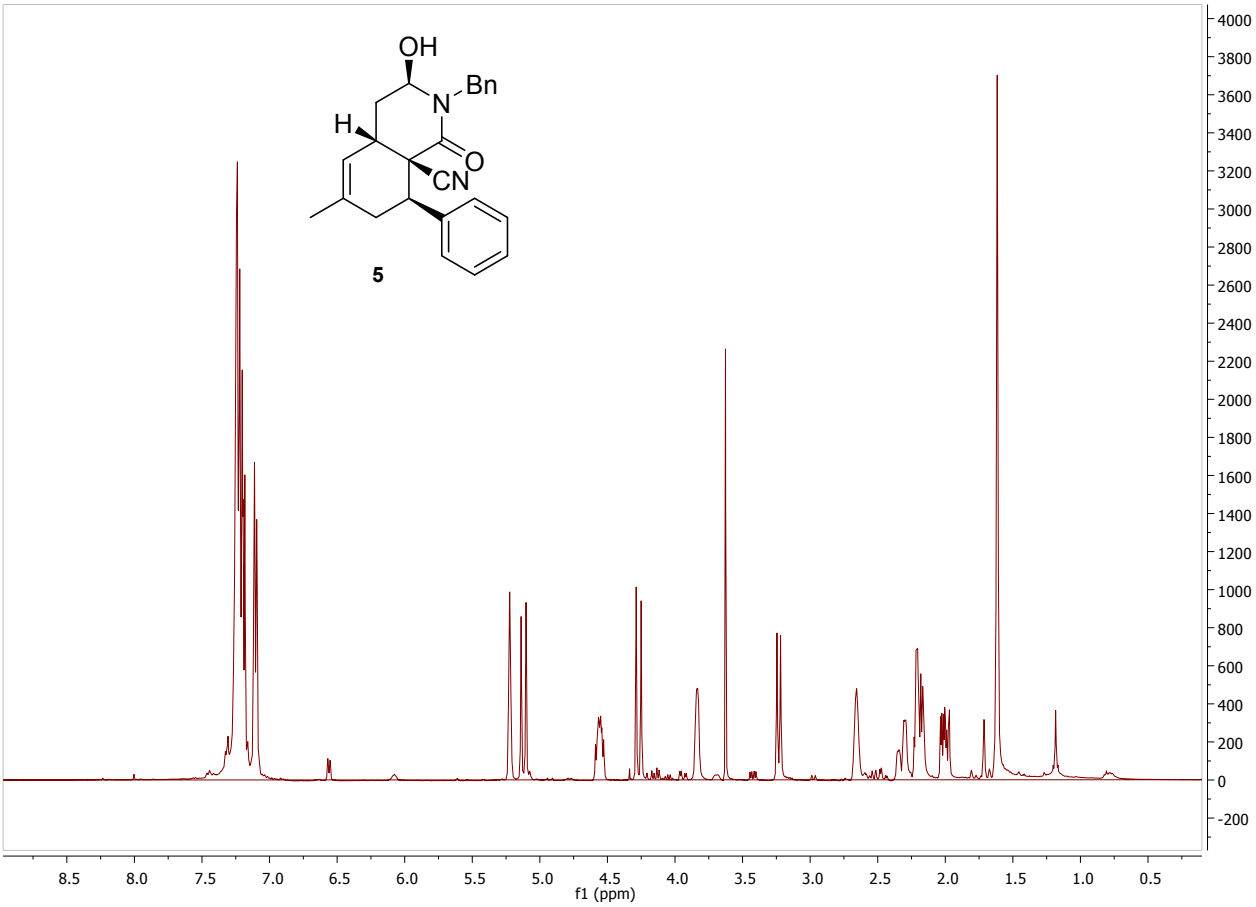
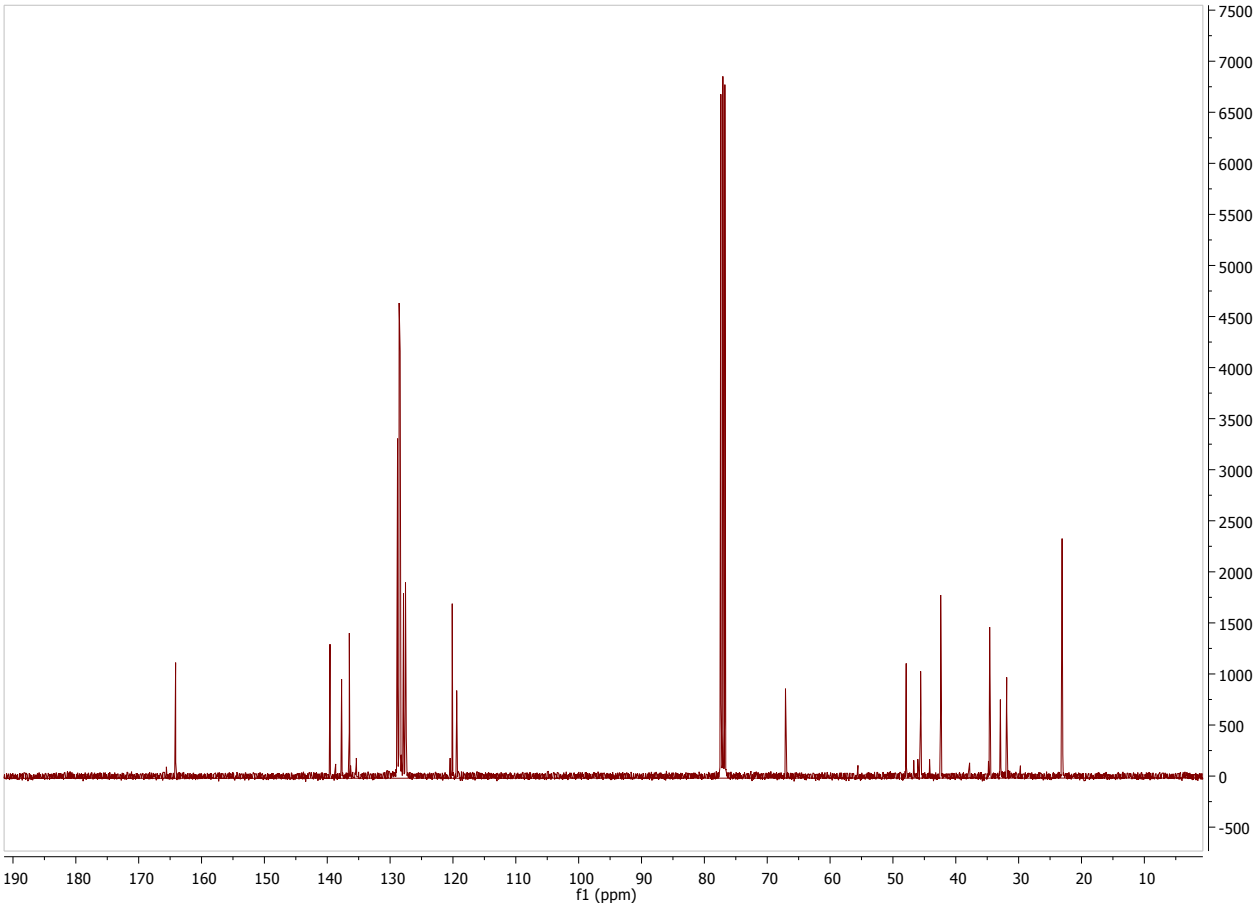
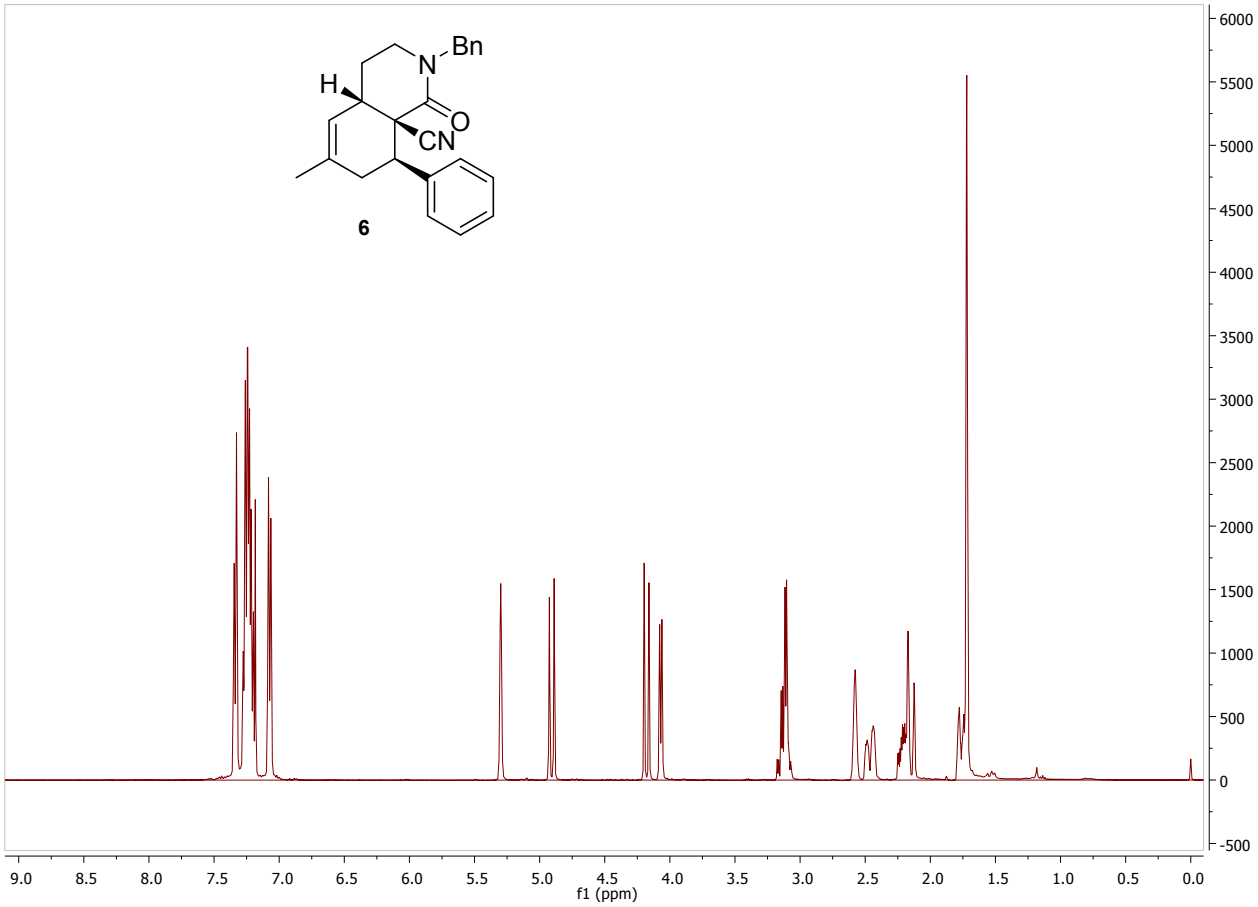
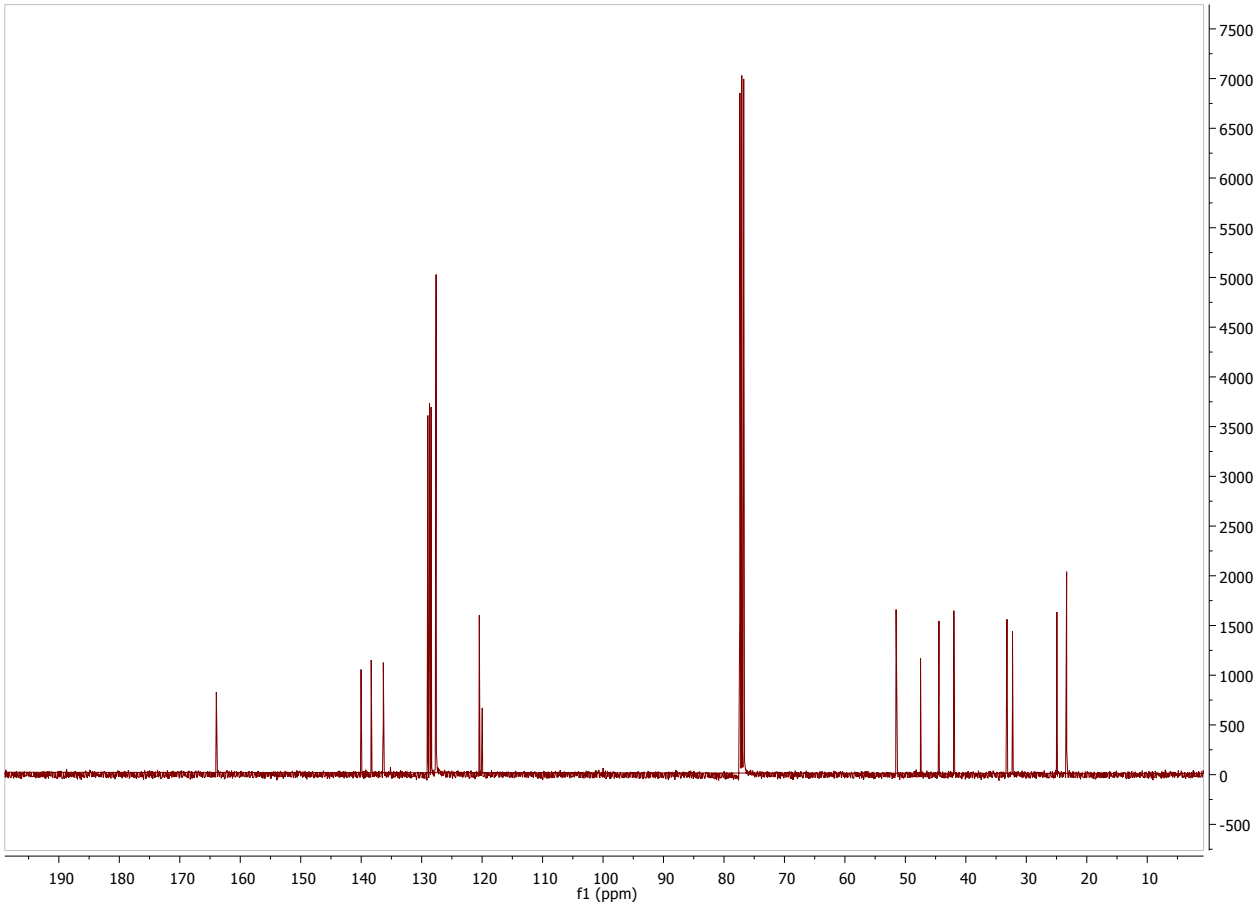
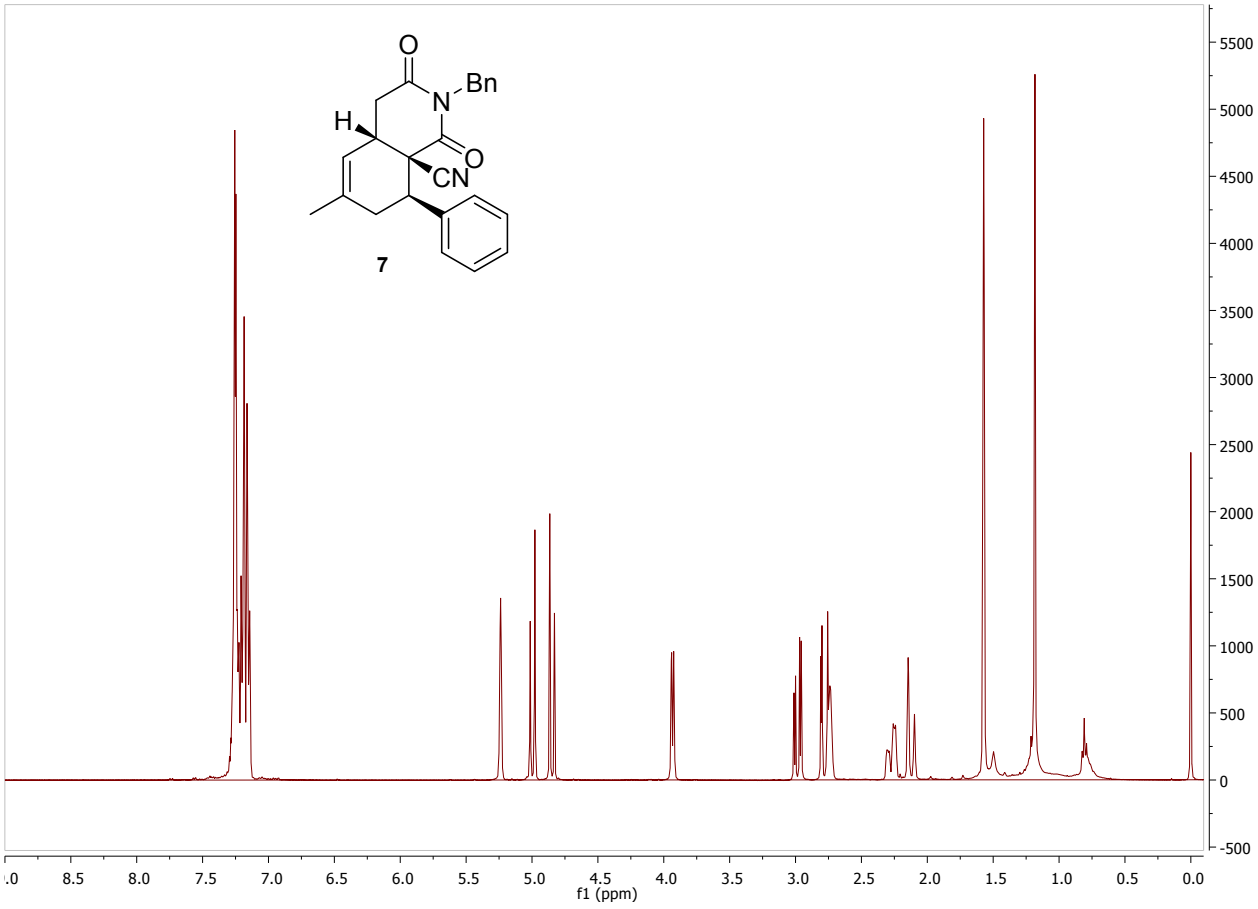
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

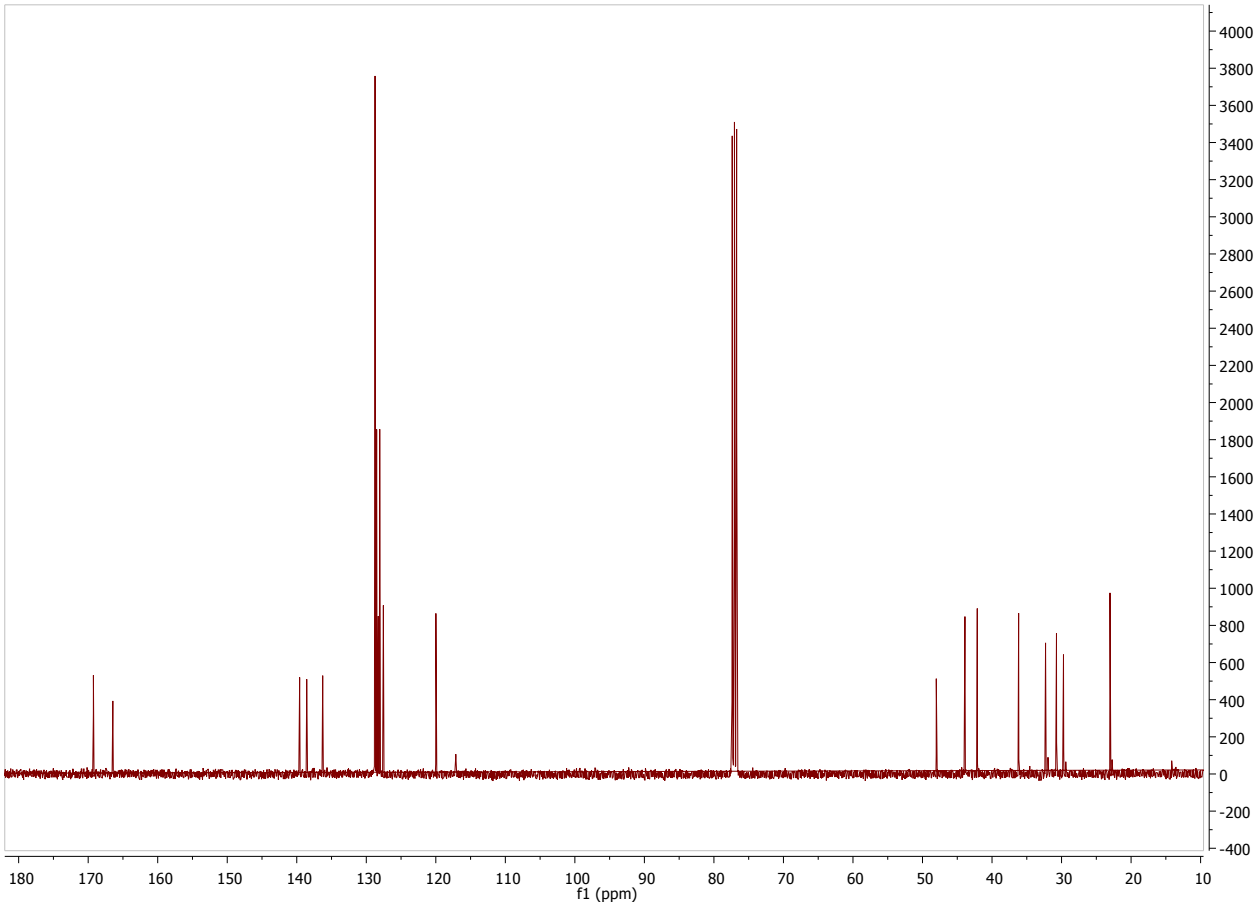

OH
Bn
N
H
O
CN
5
f1 (ppm)

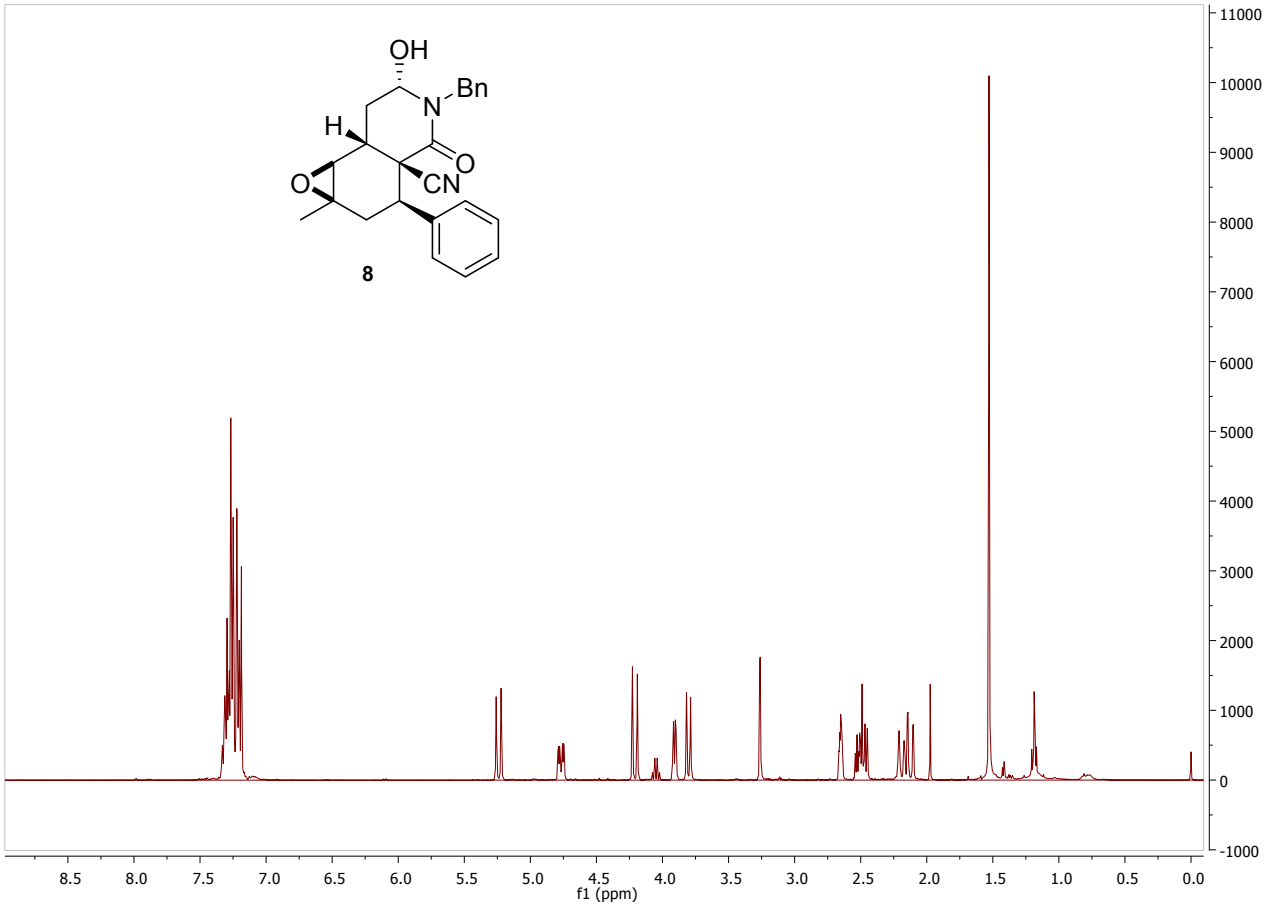

f1 (ppm)

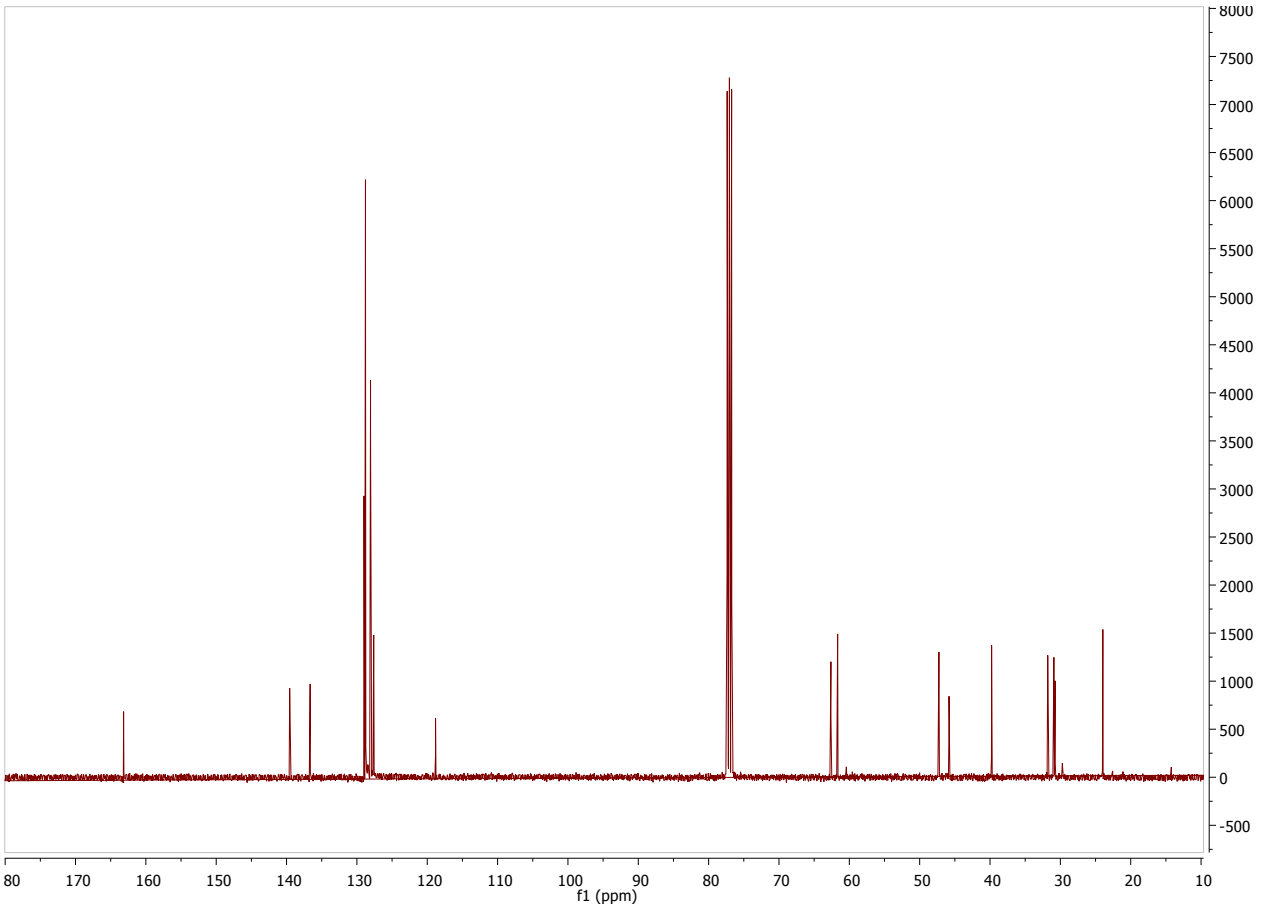

Bn
N
H
O
CN
6
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

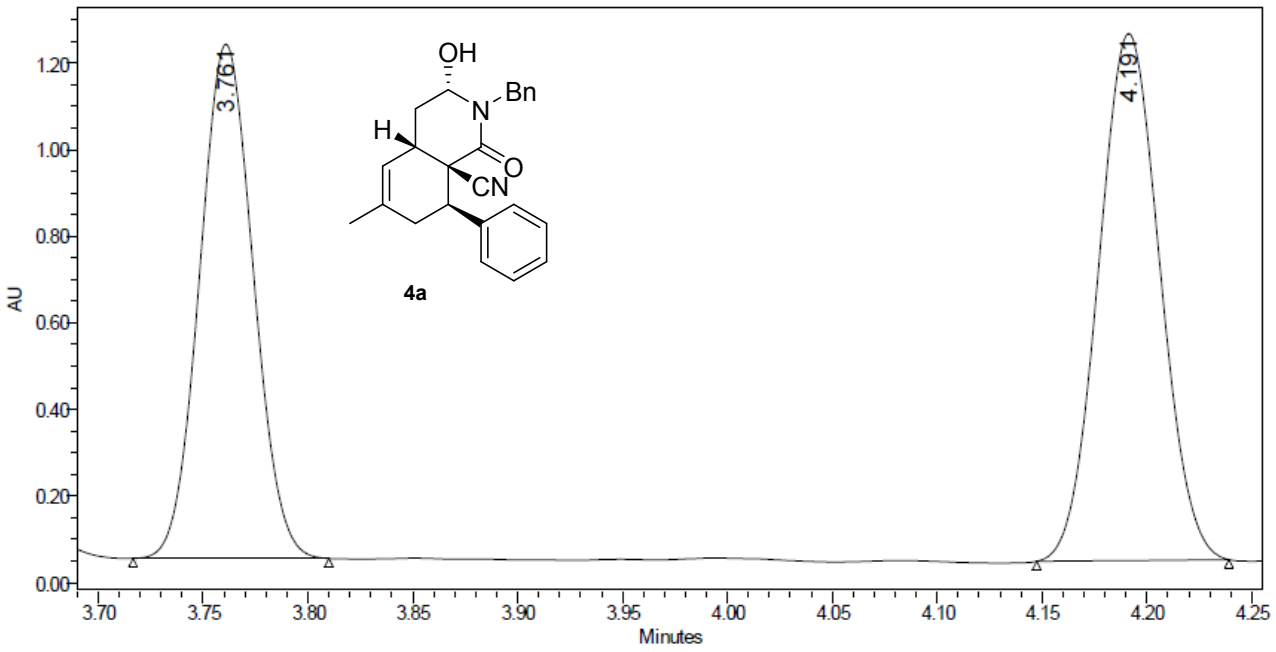

O
Bn
N
H
O
CN
7
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

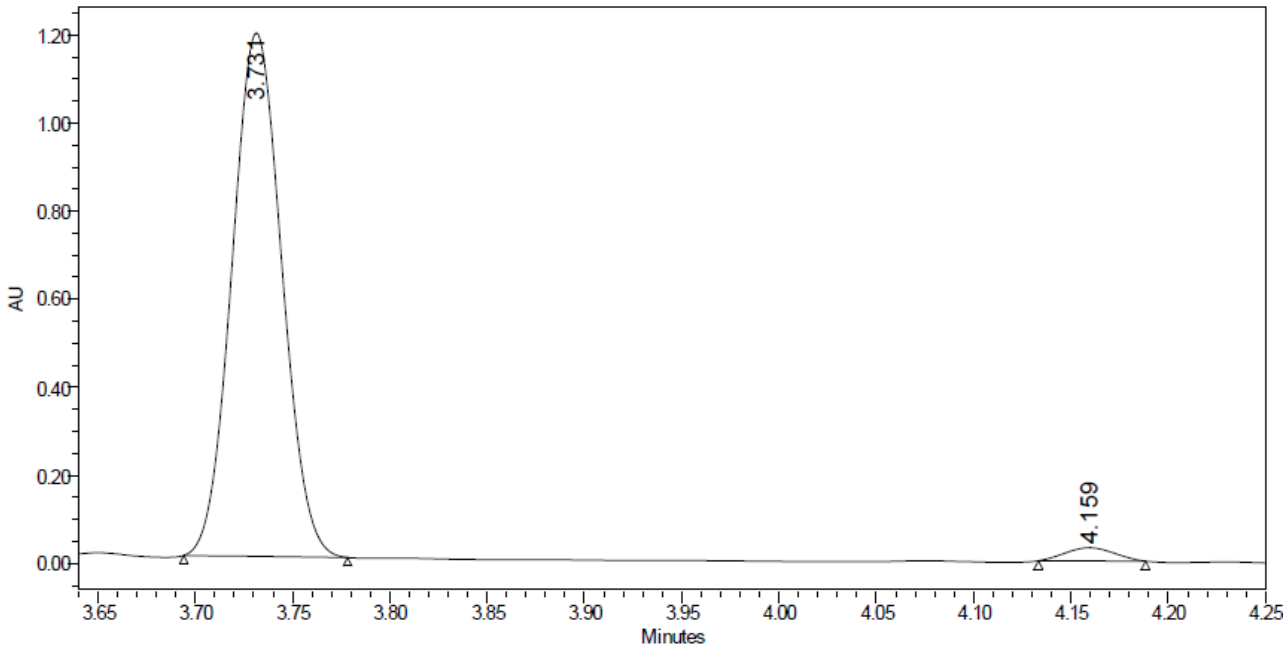

OH
Bn
N
H
O
O
CN
8
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

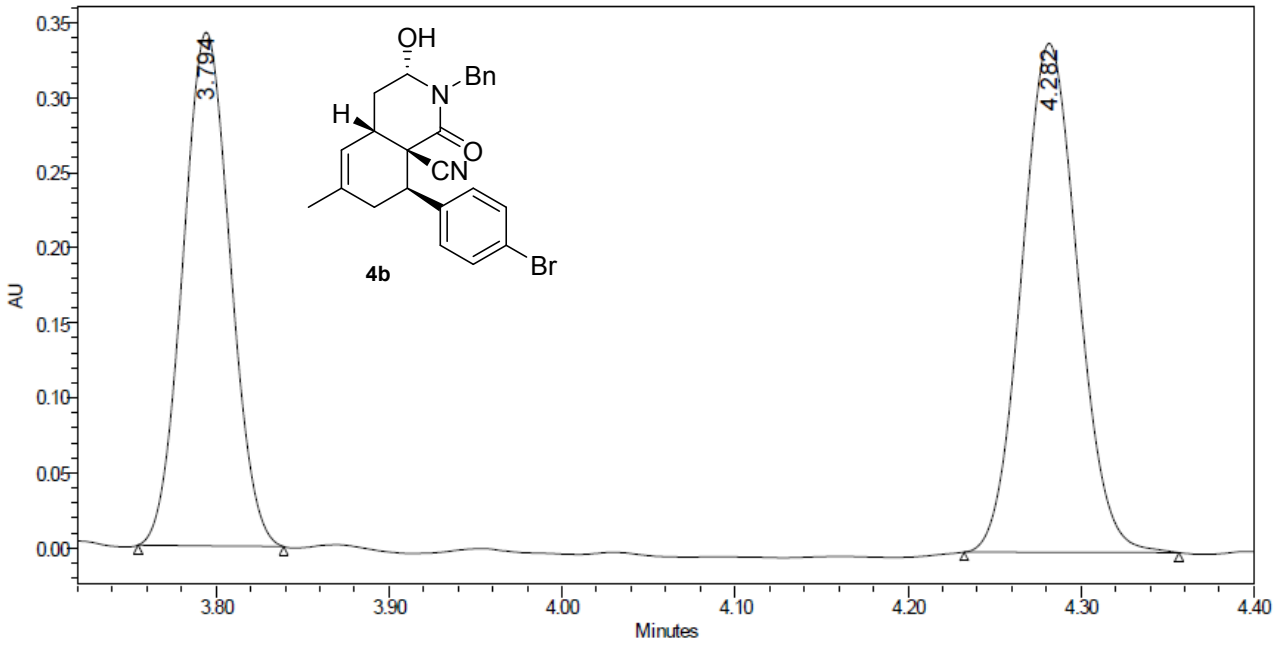
6. UPC$^2$ traces



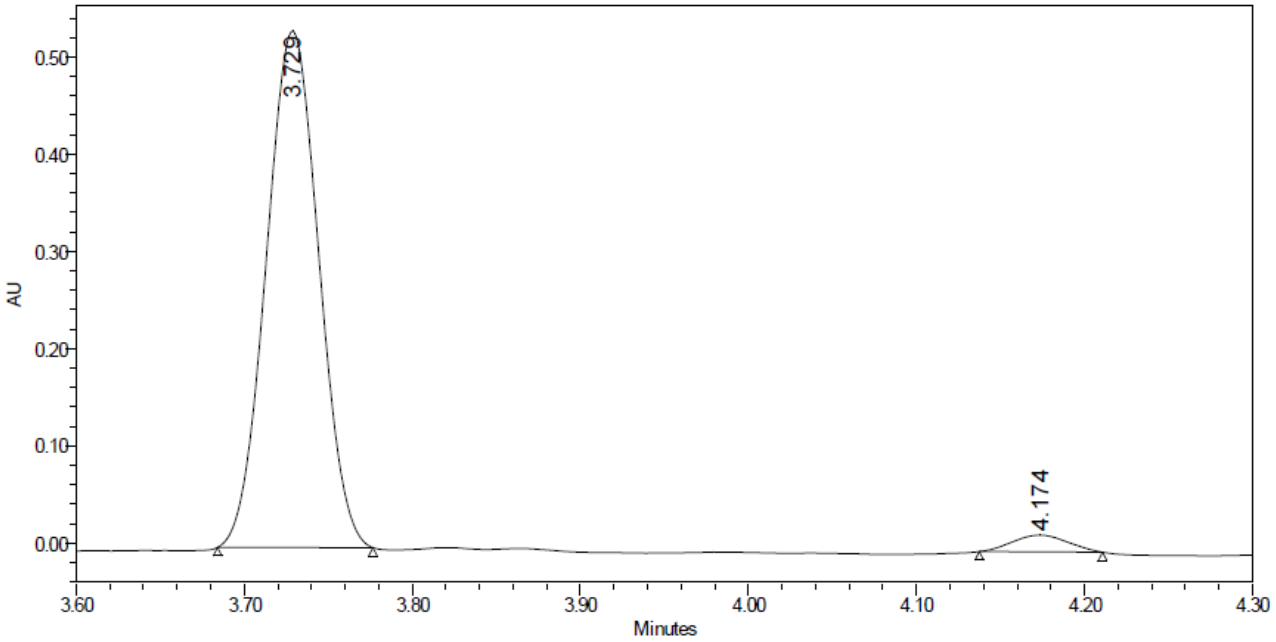

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.761 | 46.11 |
| 2 | 4.191 | 53.89 |



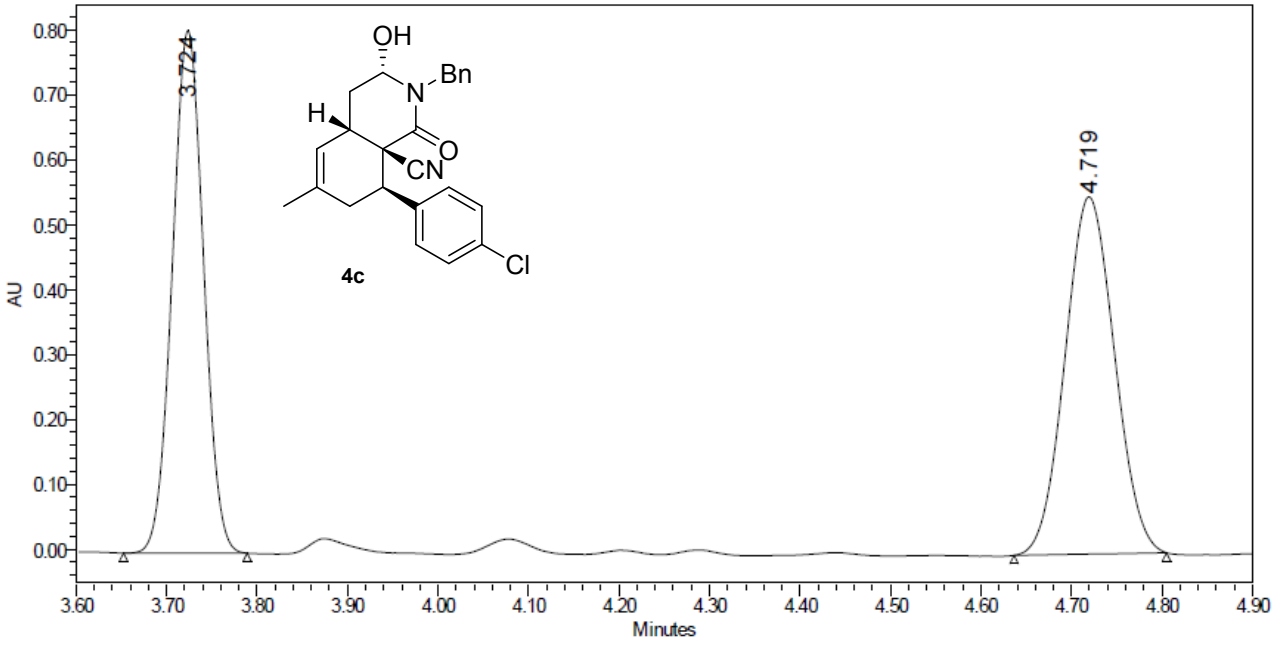

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.731 | 97.60 |
| 2 | 4.159 | 2.40 |



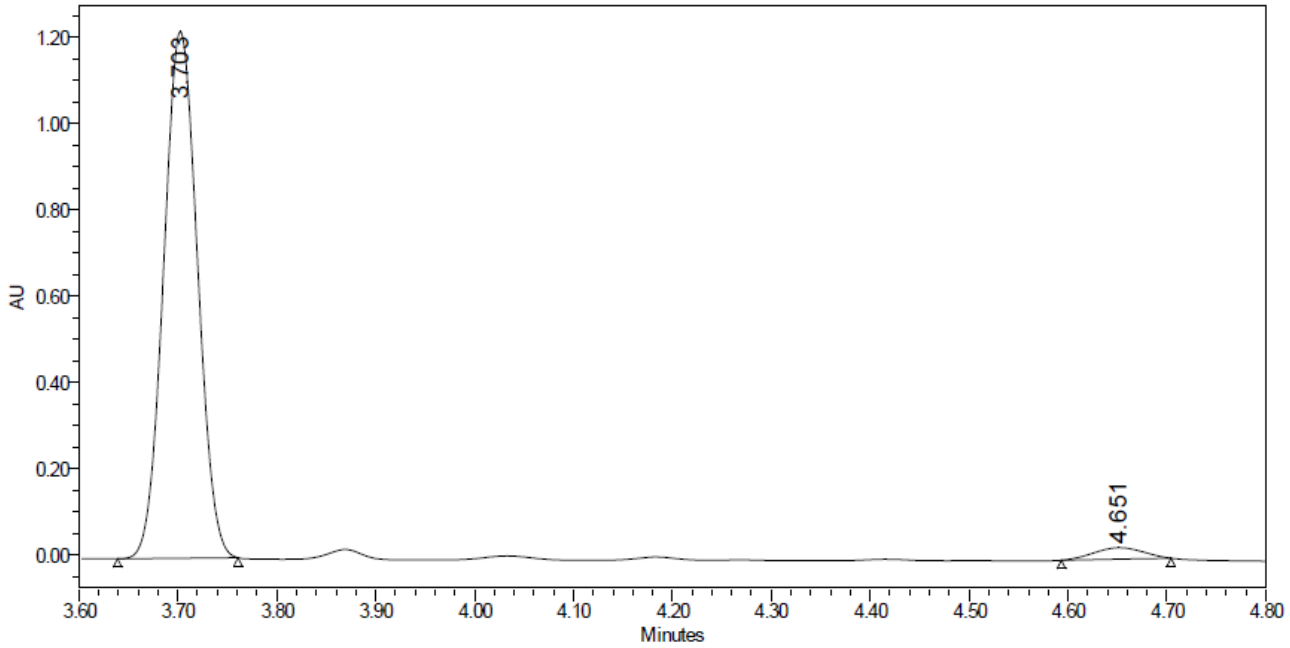

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.794 | 46.01 |
| 2 | 4.282 | 53.99 |



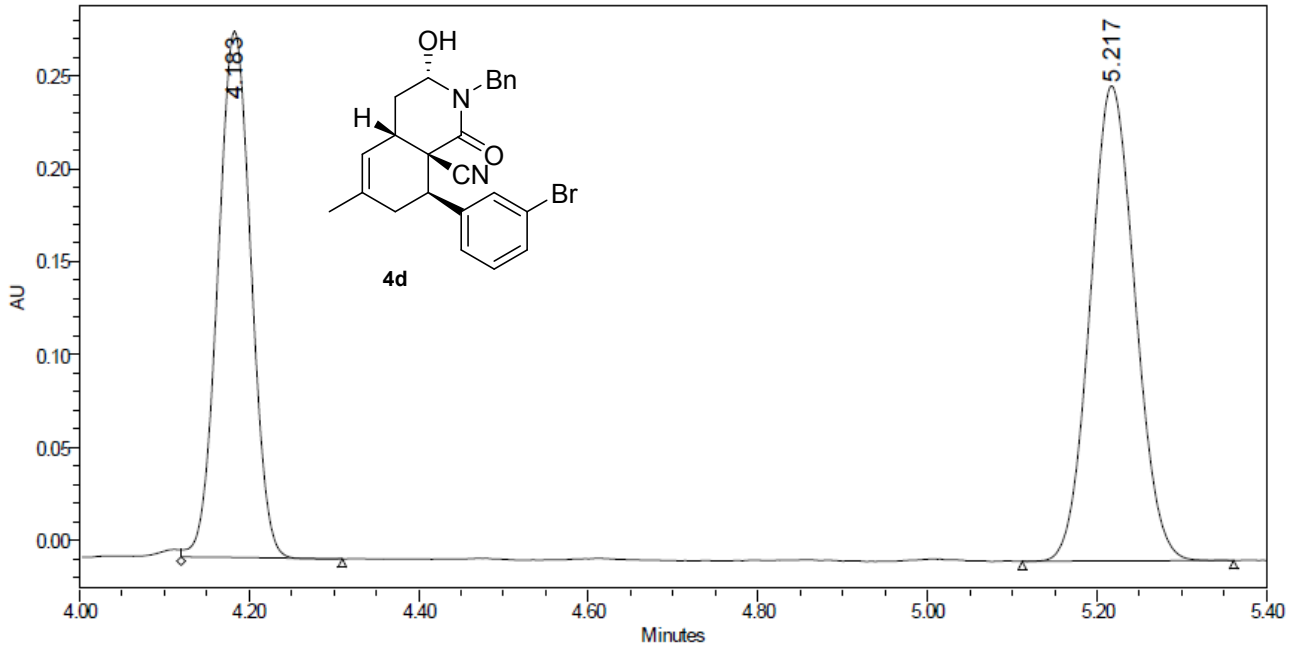

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.729 | 96.70 |
| 2 | 4.174 | 3.30 |



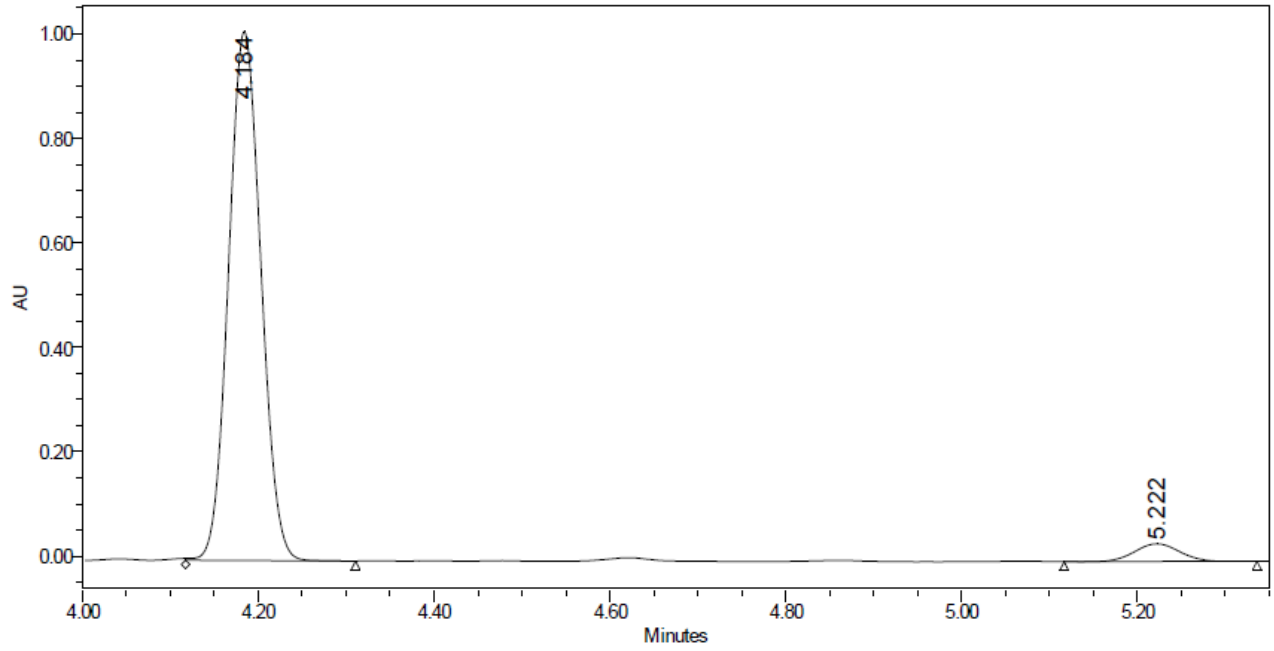

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.724 | 48.08 |
| 2 | 4.719 | 51.92 |



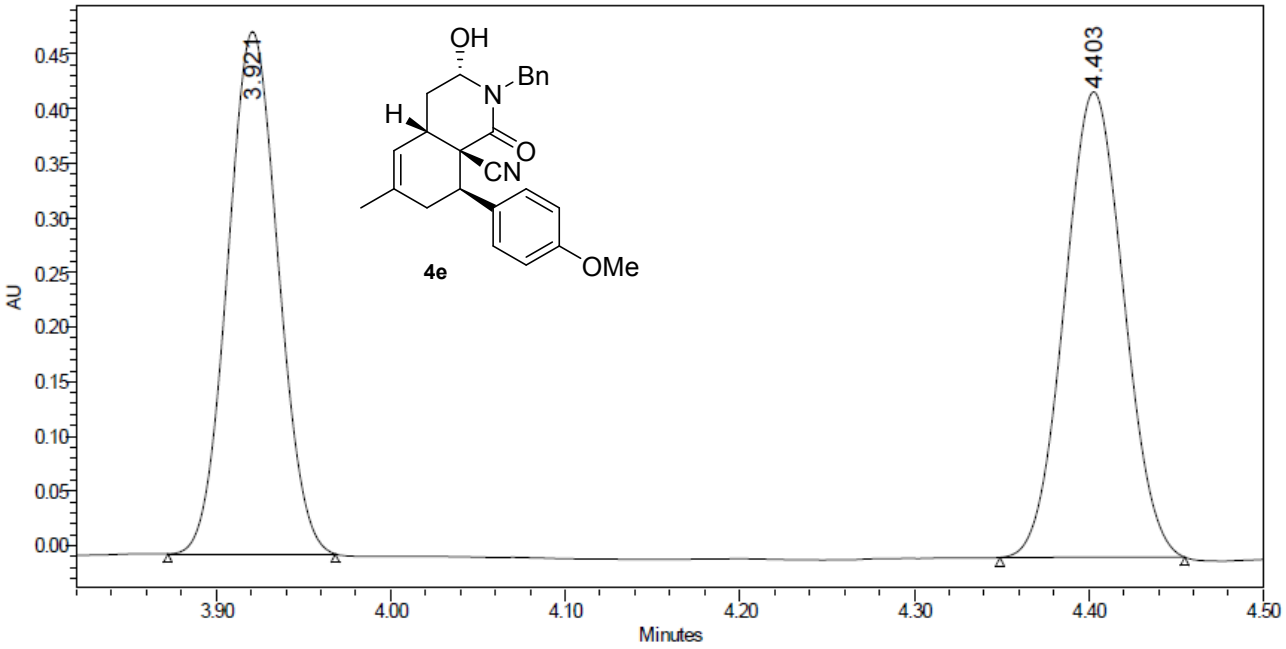

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.703 | 96.94 |
| 2 | 4.651 | 3.06 |



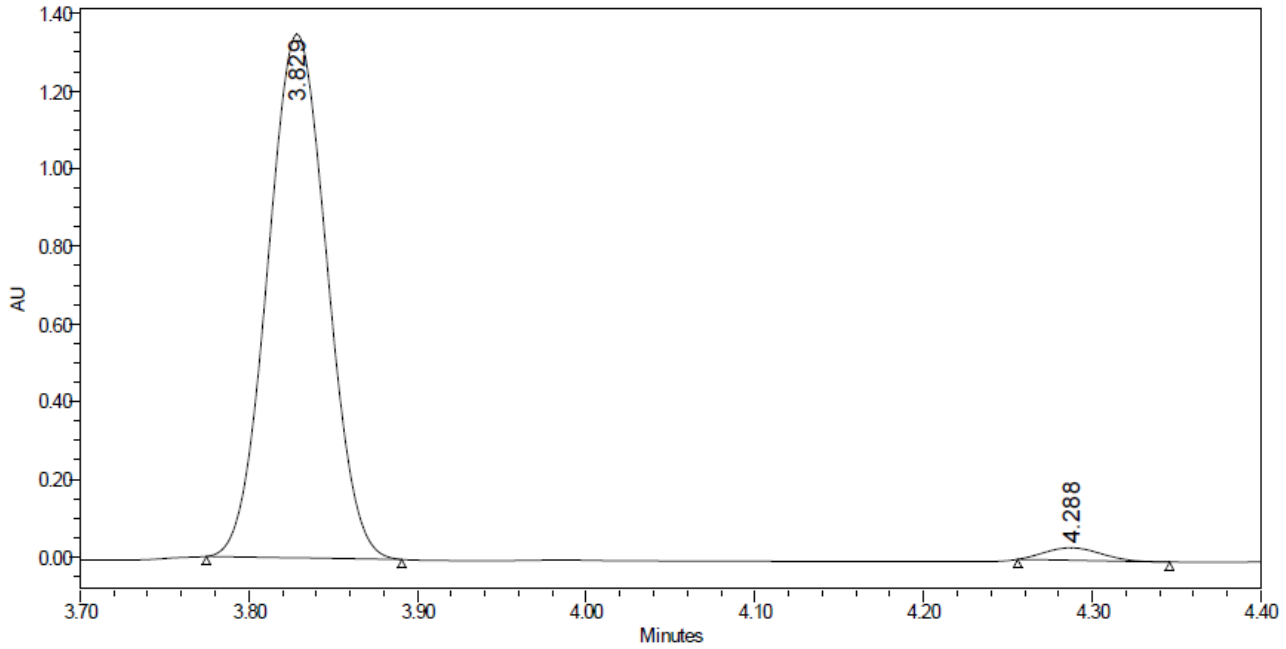

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.183 | 44.92 |
| 2 | 5.217 | 55.08 |



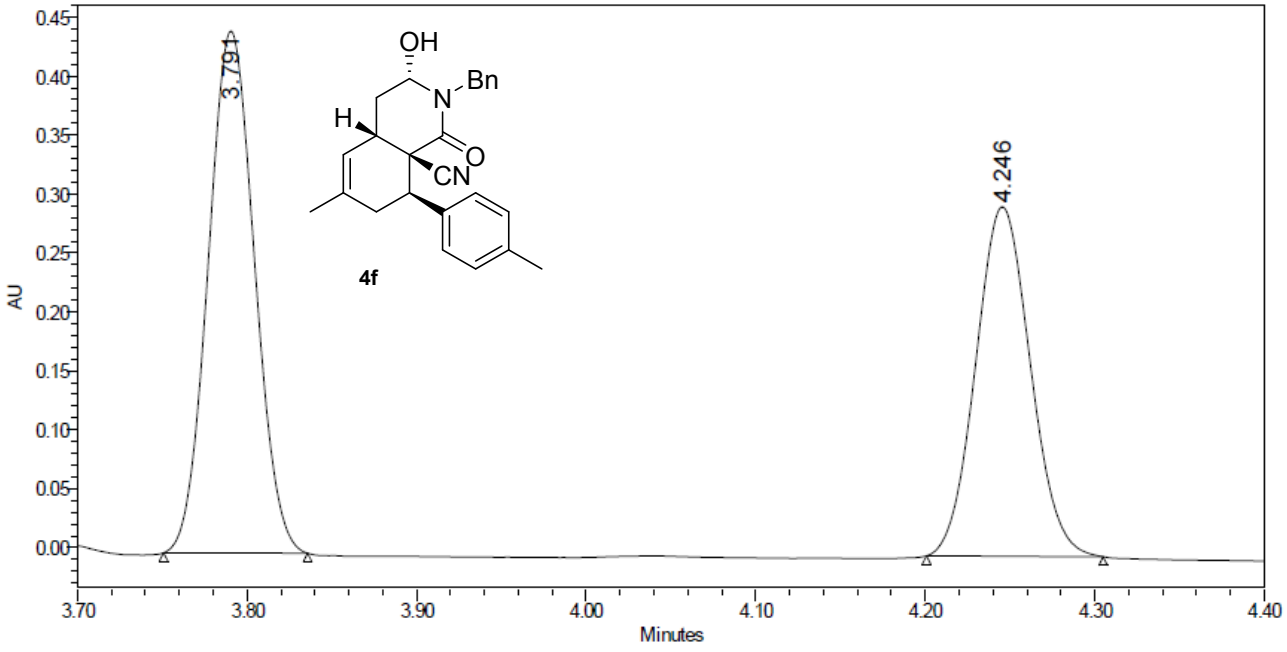

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.184 | 95.55 |
| 2 | 5.222 | 4.45 |



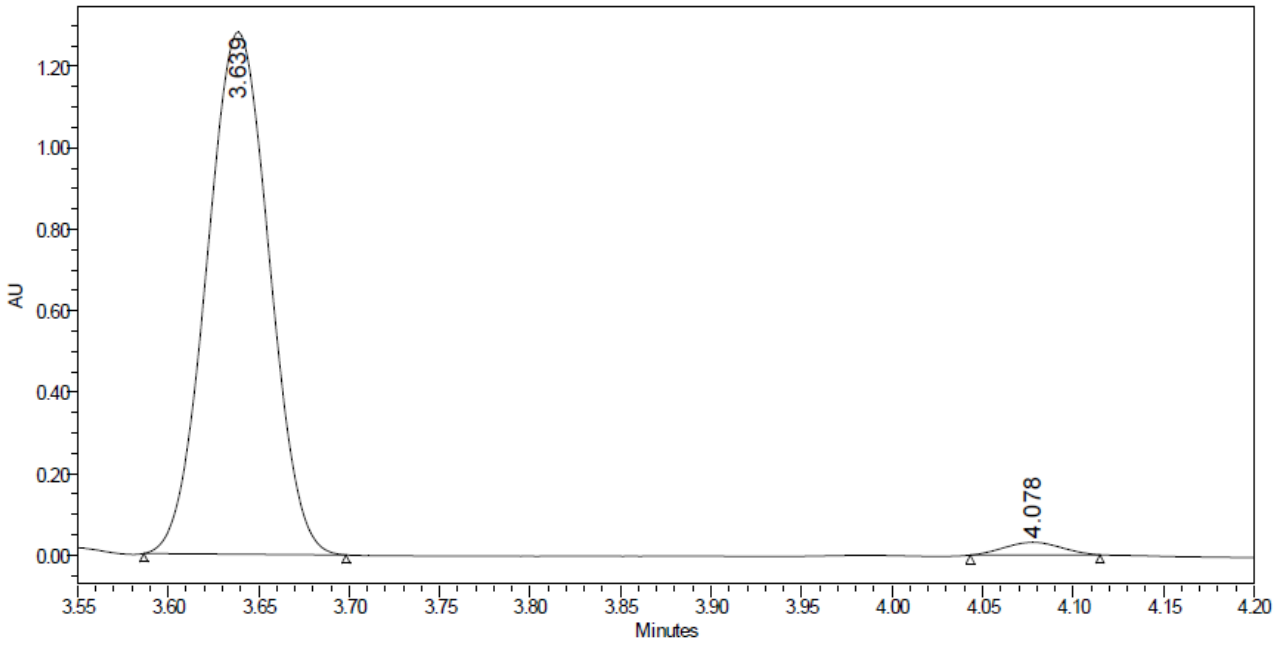

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.921 | 48.96 |
| 2 | 4.403 | 51.04 |



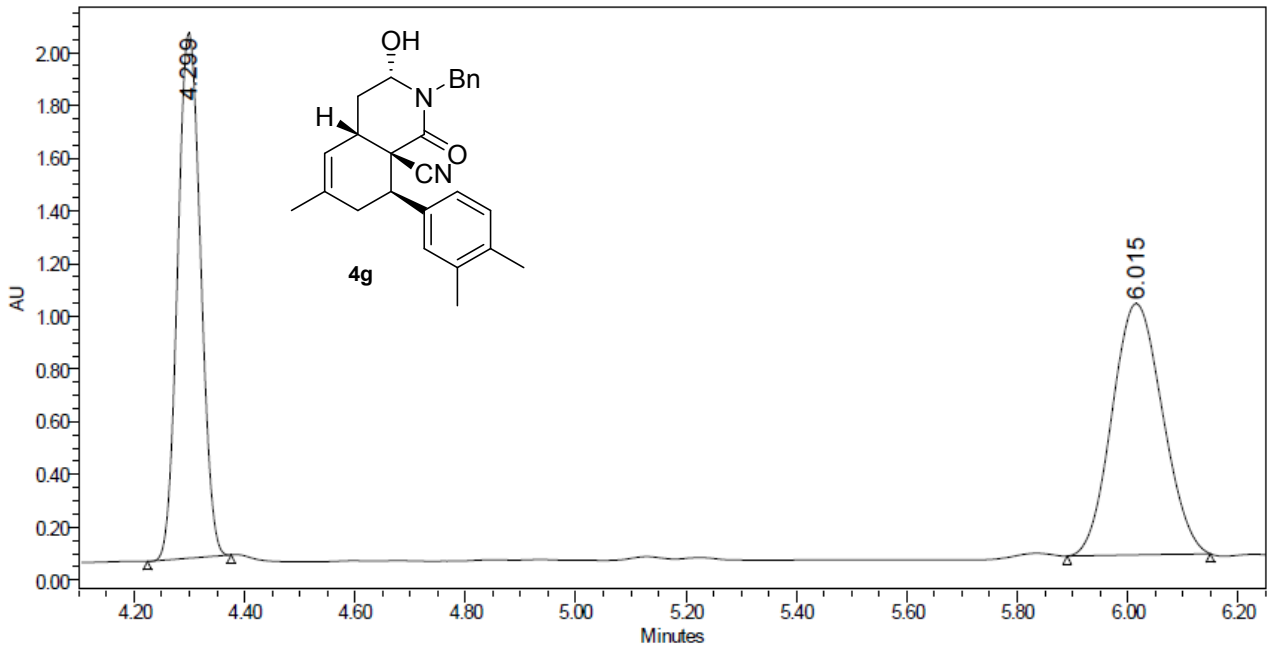

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.829 | 97.80 |
| 2 | 4.288 | 2.20 |



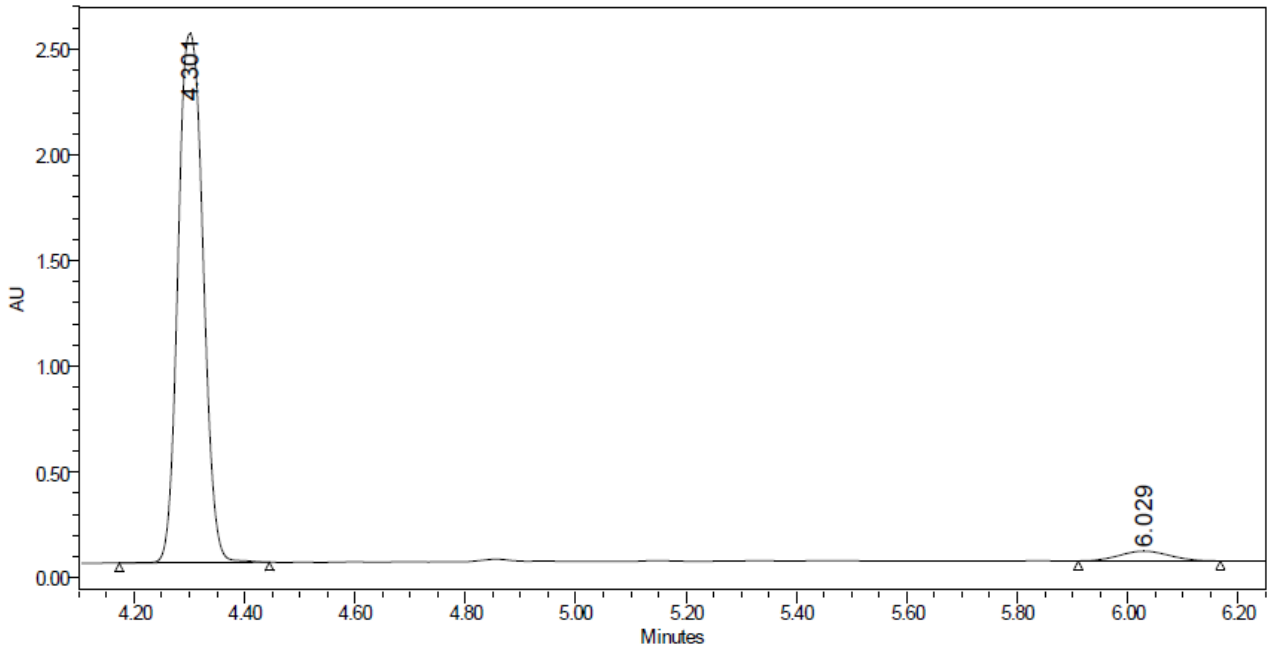

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.791 | 55.93 |
| 2 | 4.246 | 44.07 |



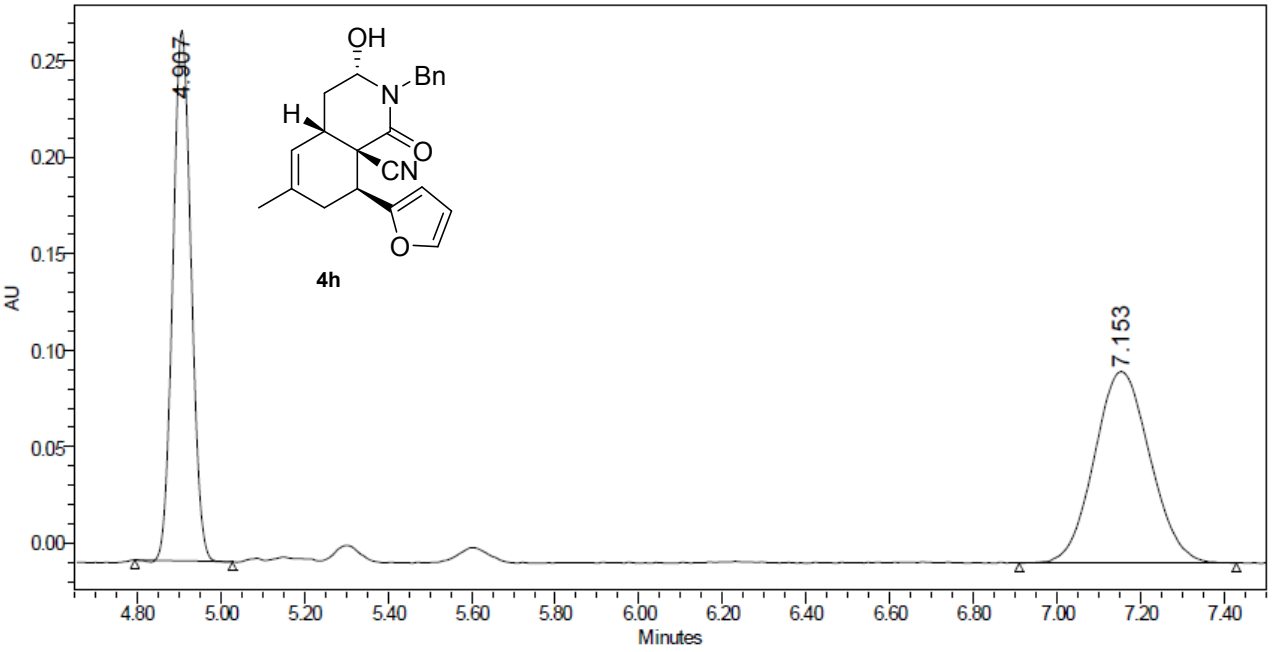

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.639 | 97.86 |
| 2 | 4.078 | 2.14 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.299 | 48.71 |
| 2 | 6.015 | 51.29 |

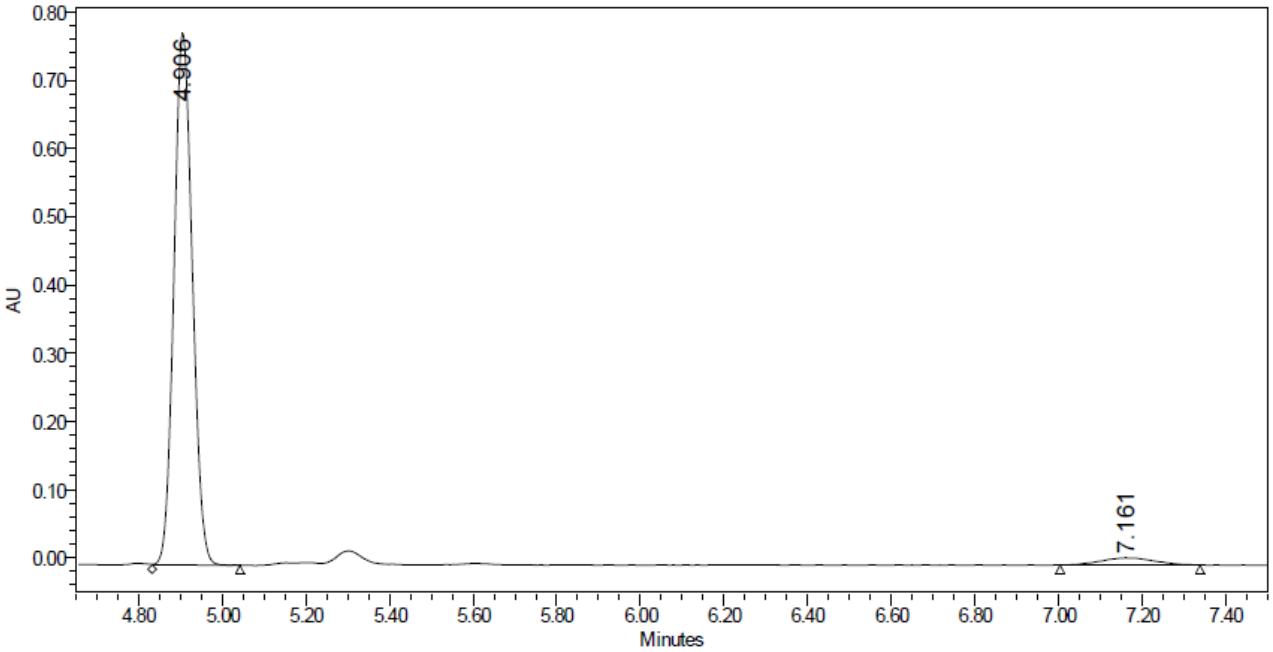



| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.301 | 96.41 |
| 2 | 6.029 | 3.59 |

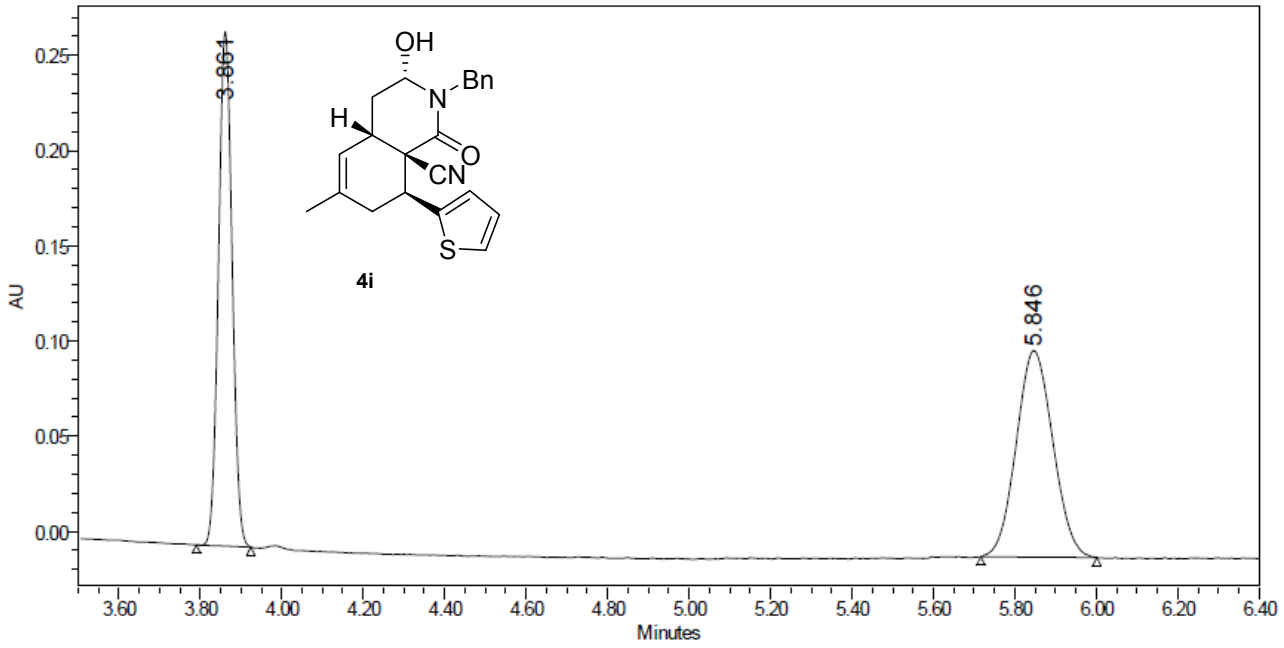



4h

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.907 | 47.59 |
| 2 | 7.153 | 52.41 |

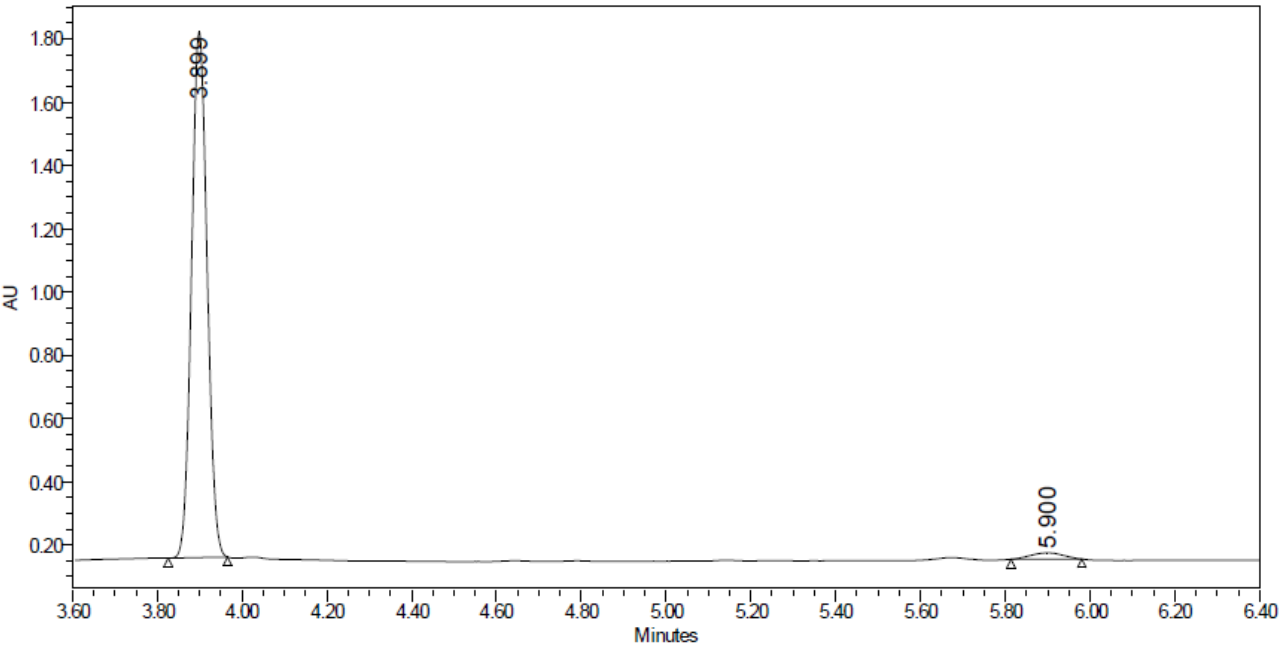



| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.906 | 96.28 |
| 2 | 7.161 | 3.72 |

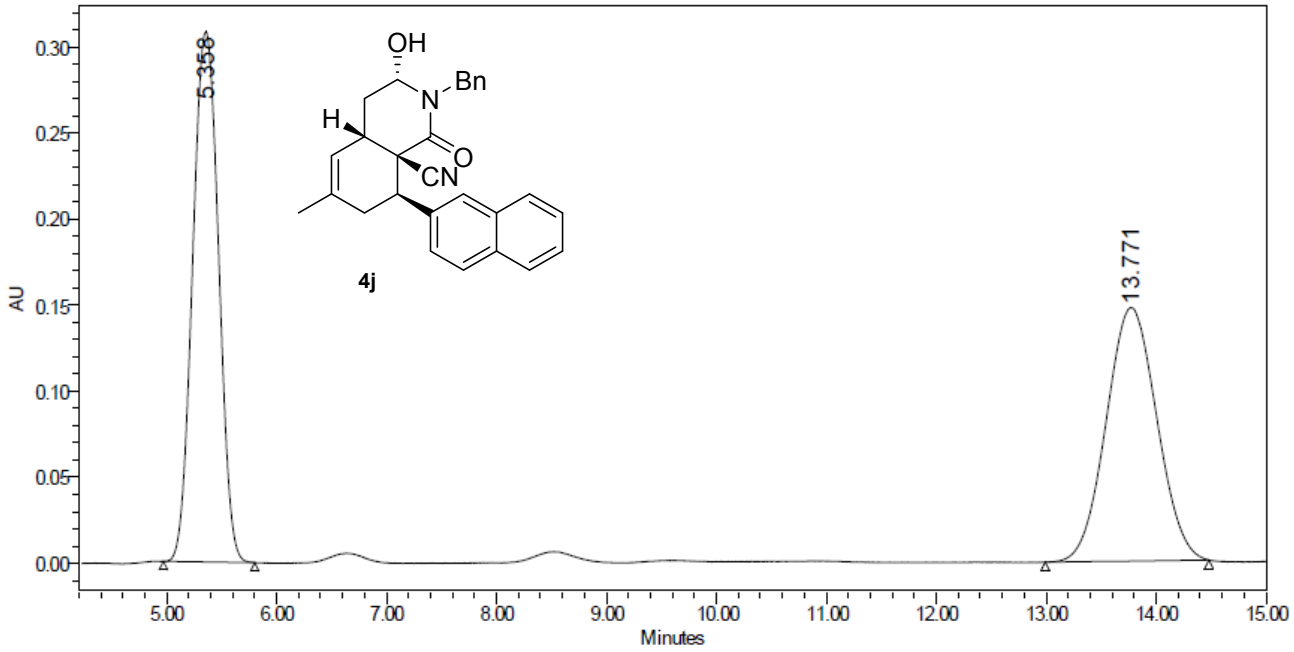



**4i**

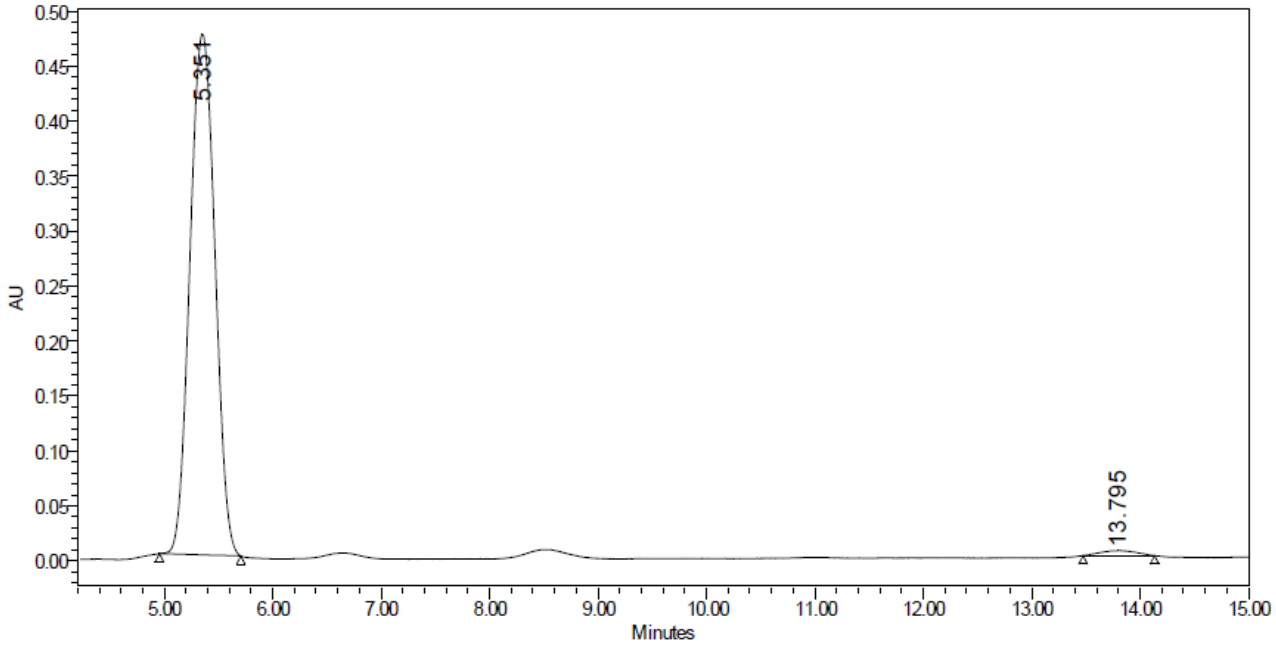
| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.861 | 48.02 |
| 2 | 5.846 | 51.98 |



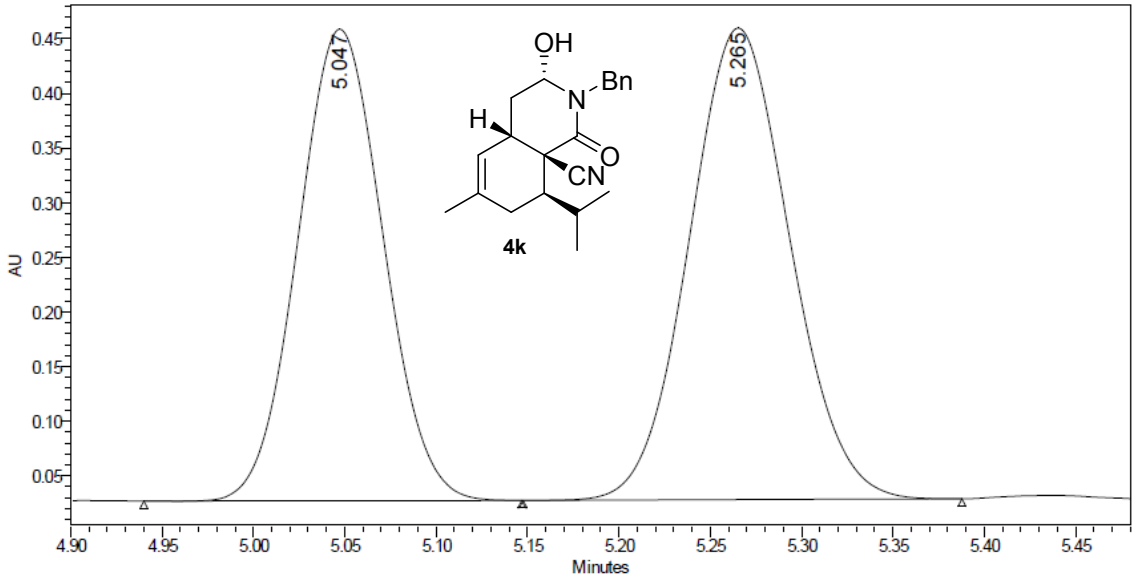

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.899 | 97.54 |
| 2 | 5.900 | 2.46 |



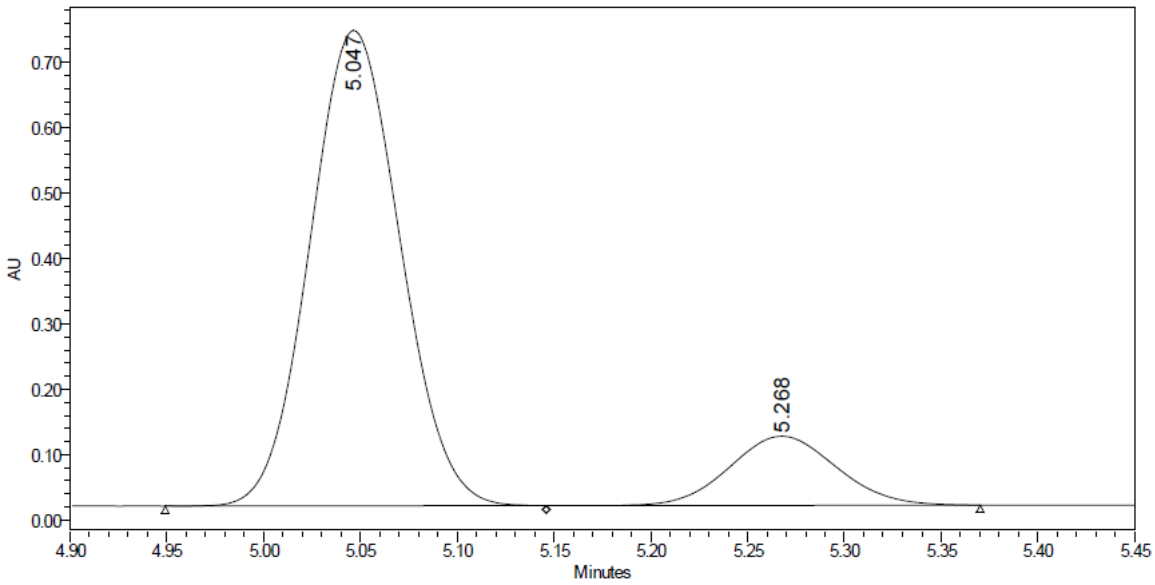

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.358 | 51.70 |
| 2 | 13.771 | 48.30 |



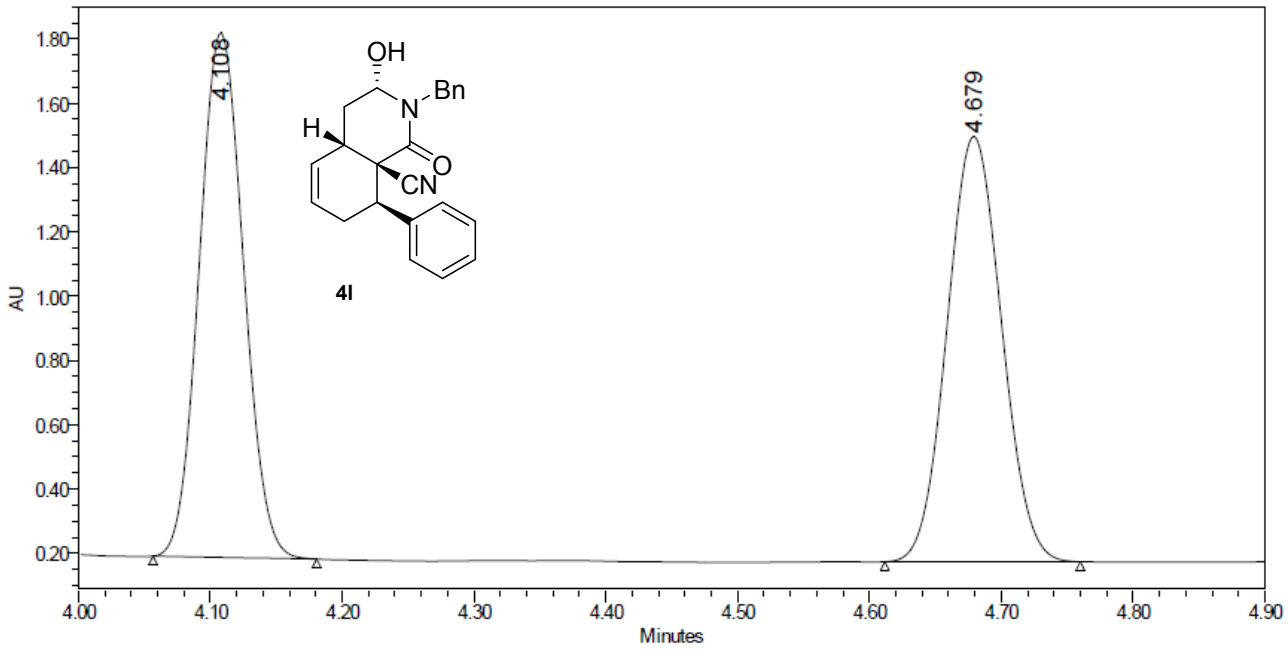

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.351 | 98.67 |
| 2 | 13.795 | 1.33 |



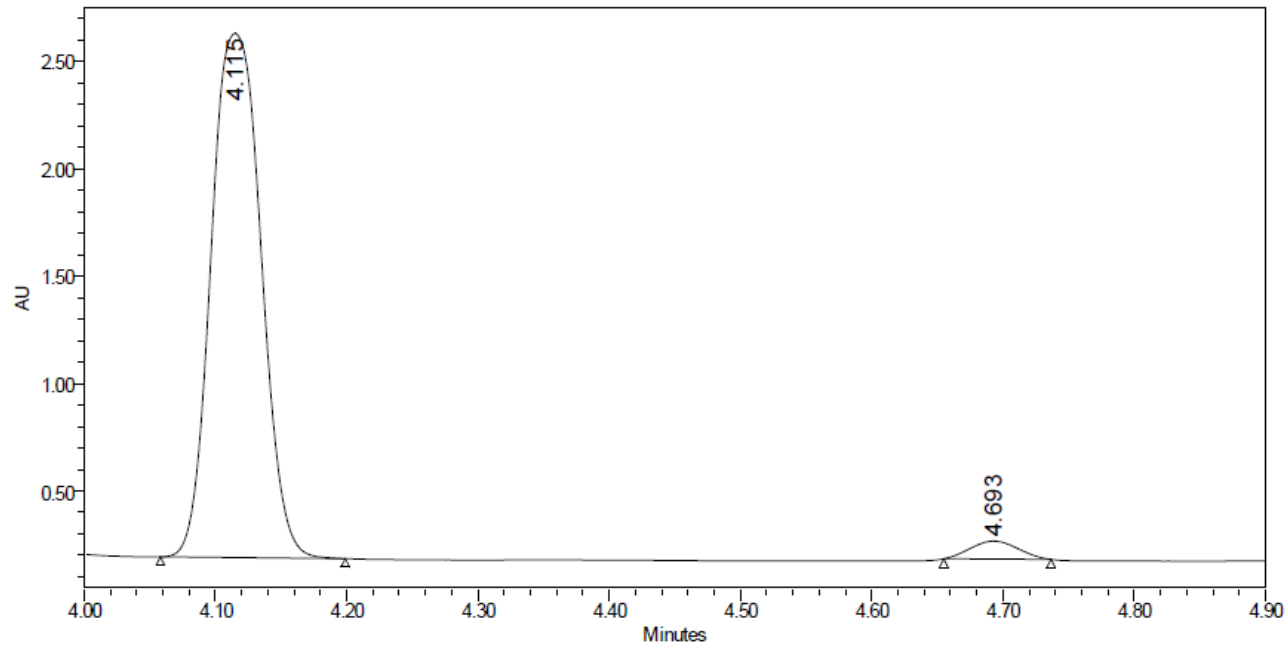

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.047 | 45.83 |
| 2 | 5.265 | 54.17 |



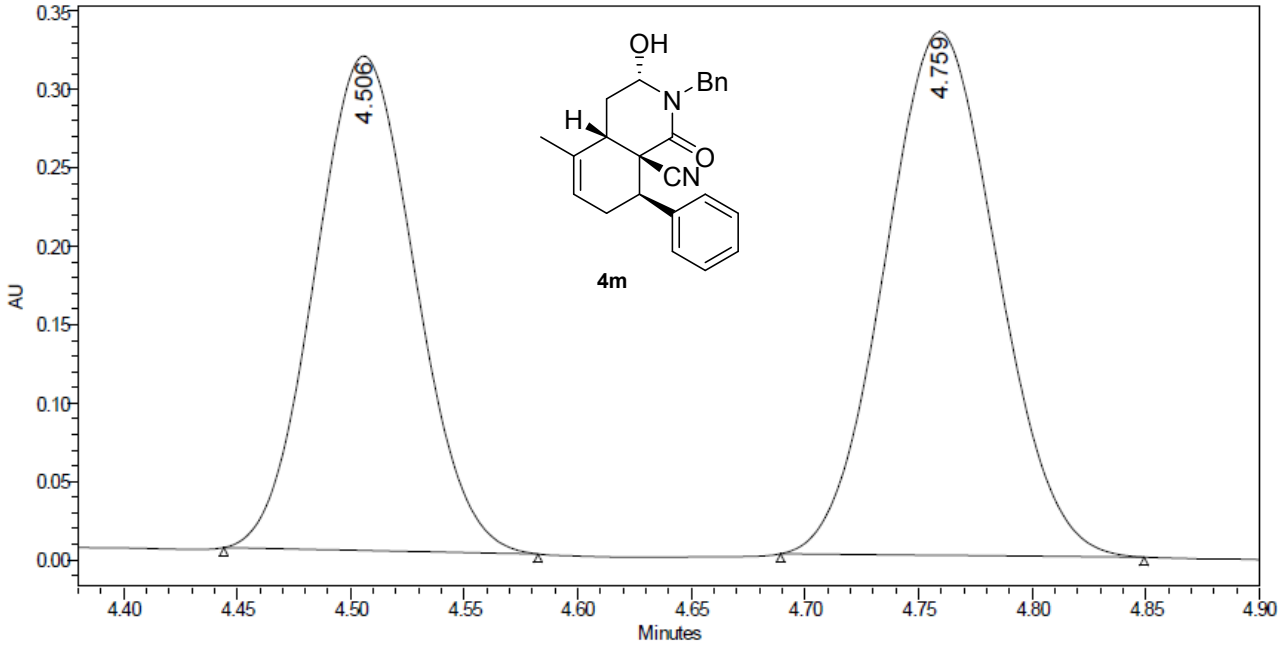

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.047 | 85.28 |
| 2 | 5.268 | 14.72 |



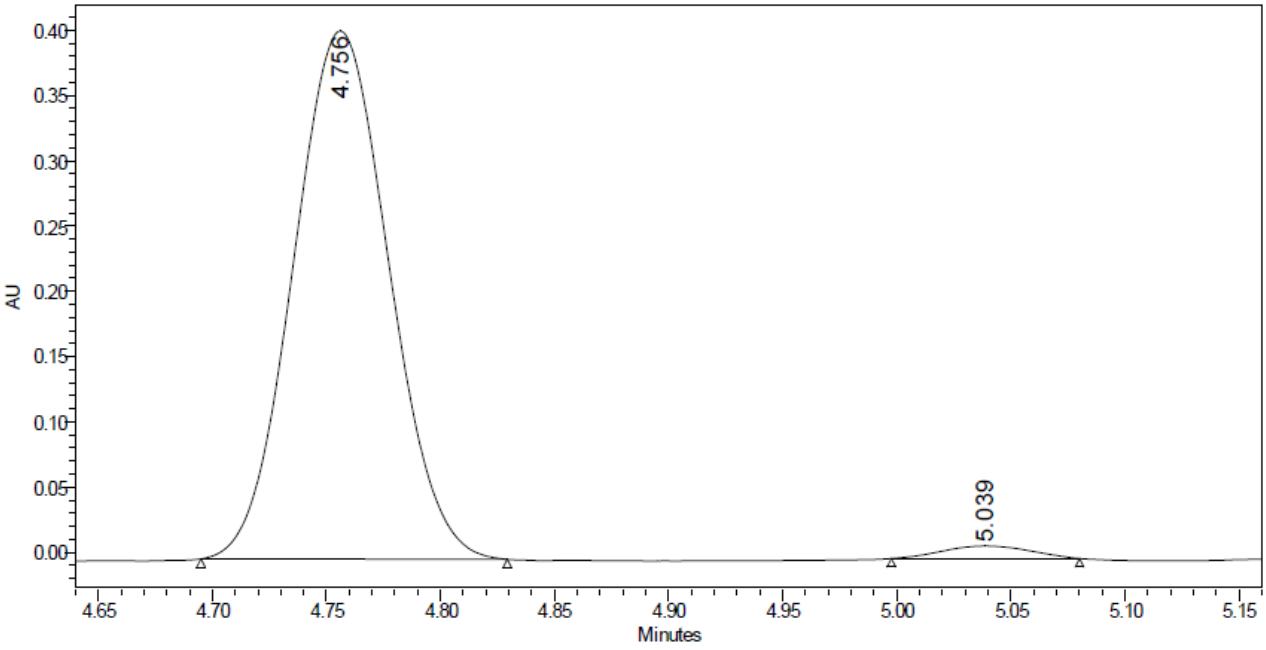

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.108 | 50.07 |
| 2 | 4.679 | 49.93 |



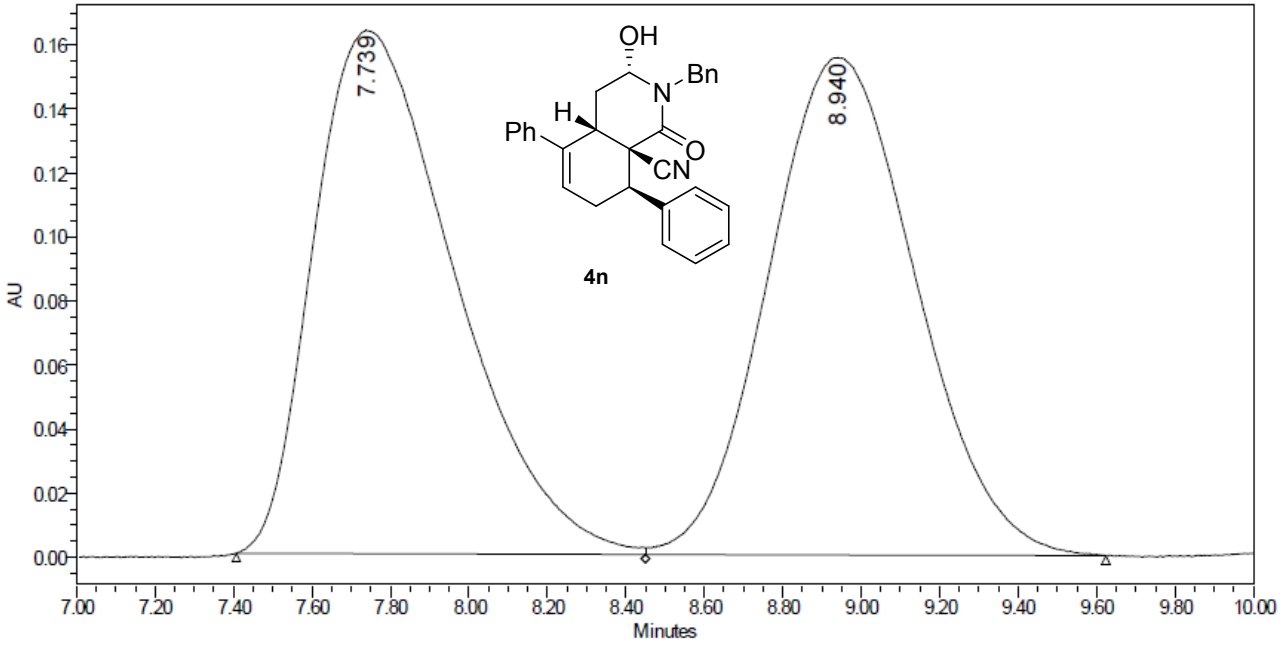

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.115 | 96.83 |
| 2 | 4.693 | 3.17 |



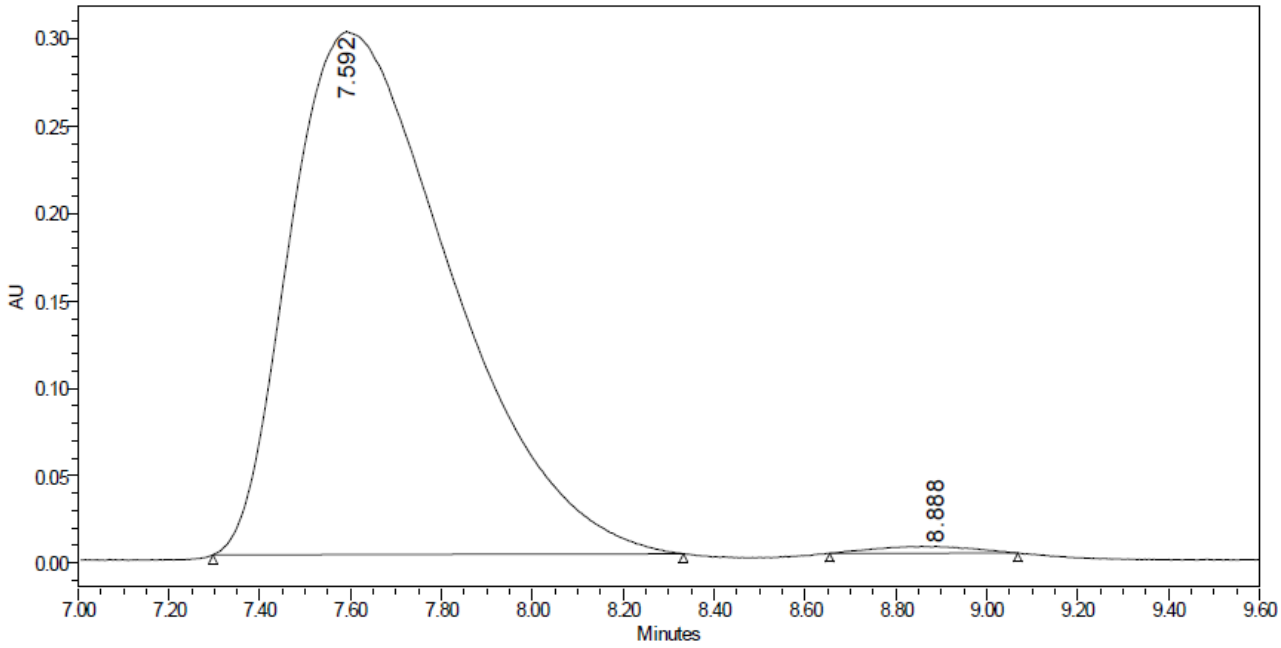

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.506 | 45.73 |
| 2 | 4.759 | 54.27 |



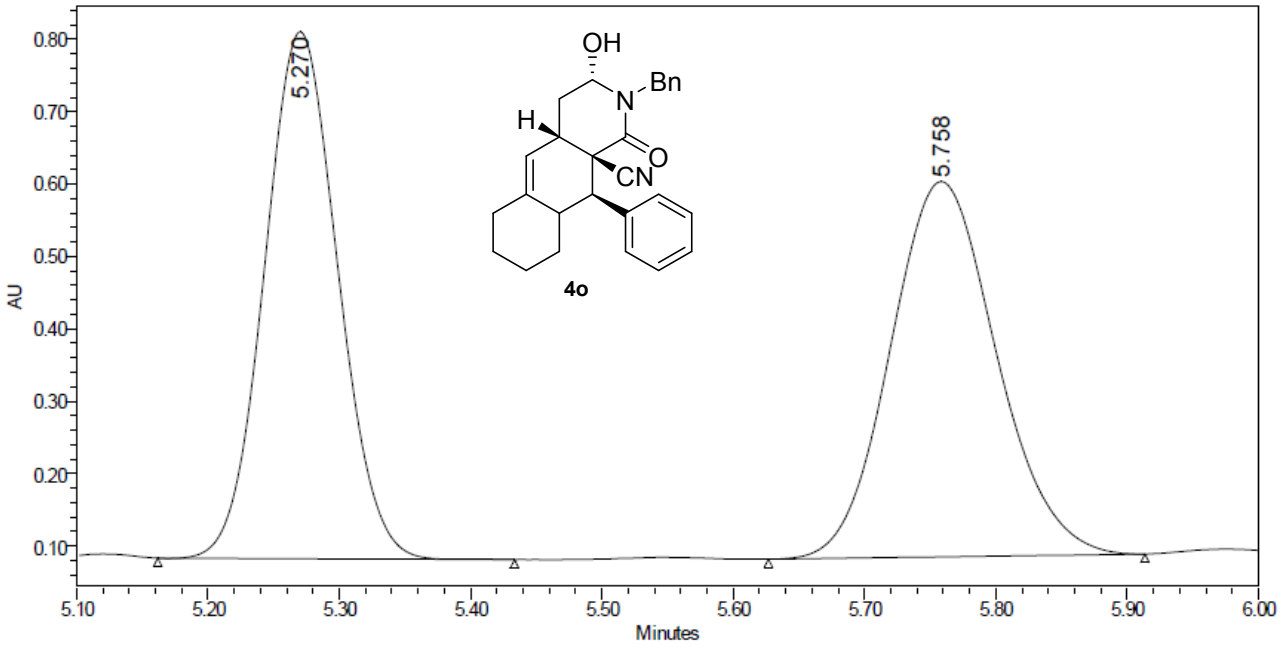

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.756 | 97.86 |
| 2 | 5.039 | 2.14 |



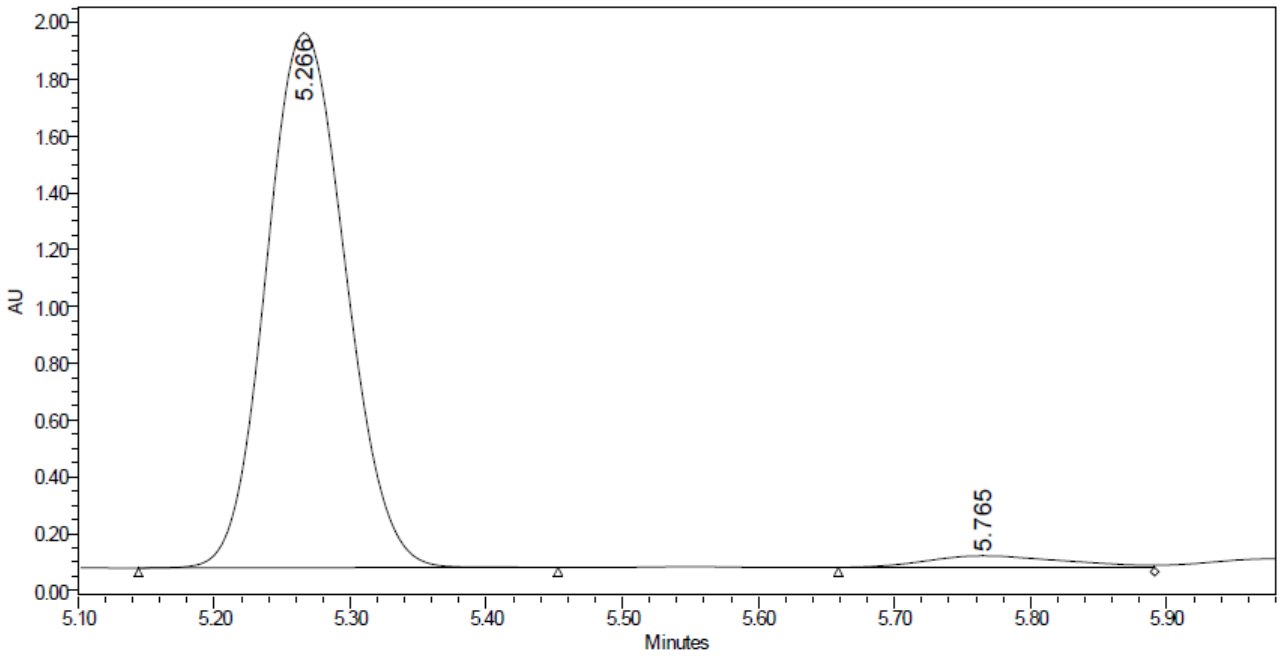

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 7.739 | 50.11 |
| 2 | 8.940 | 49.89 |



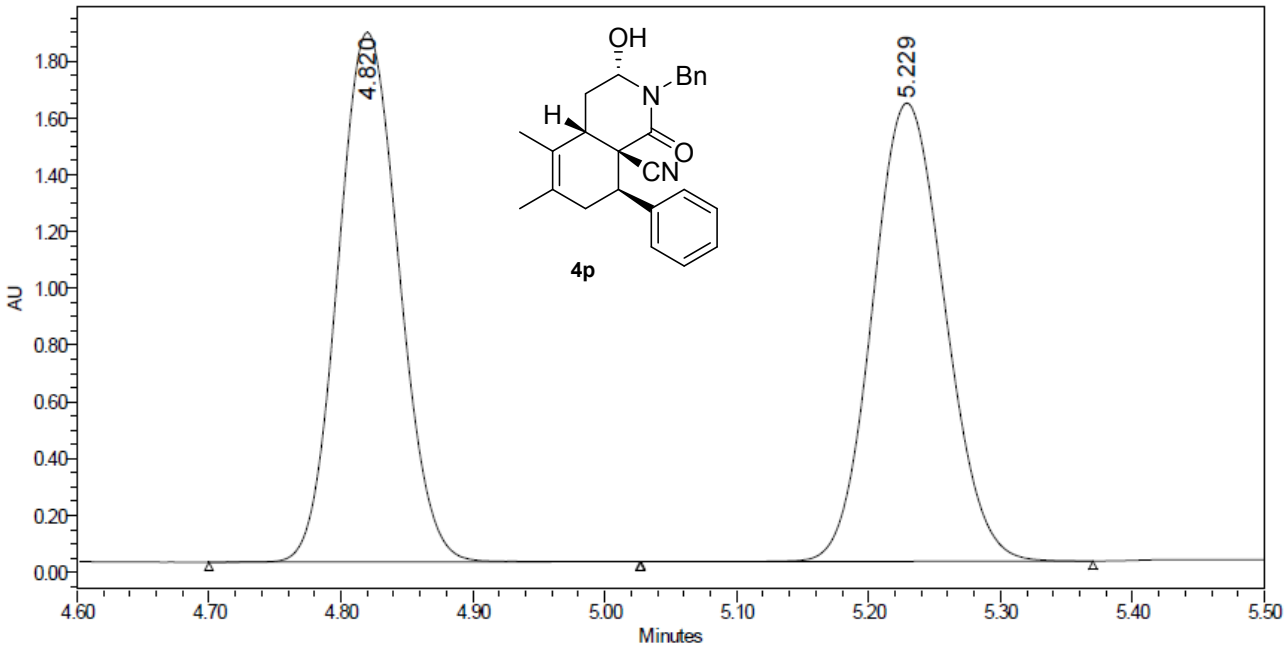

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 7.592 | 99.21 |
| 2 | 8.888 | 0.79 |



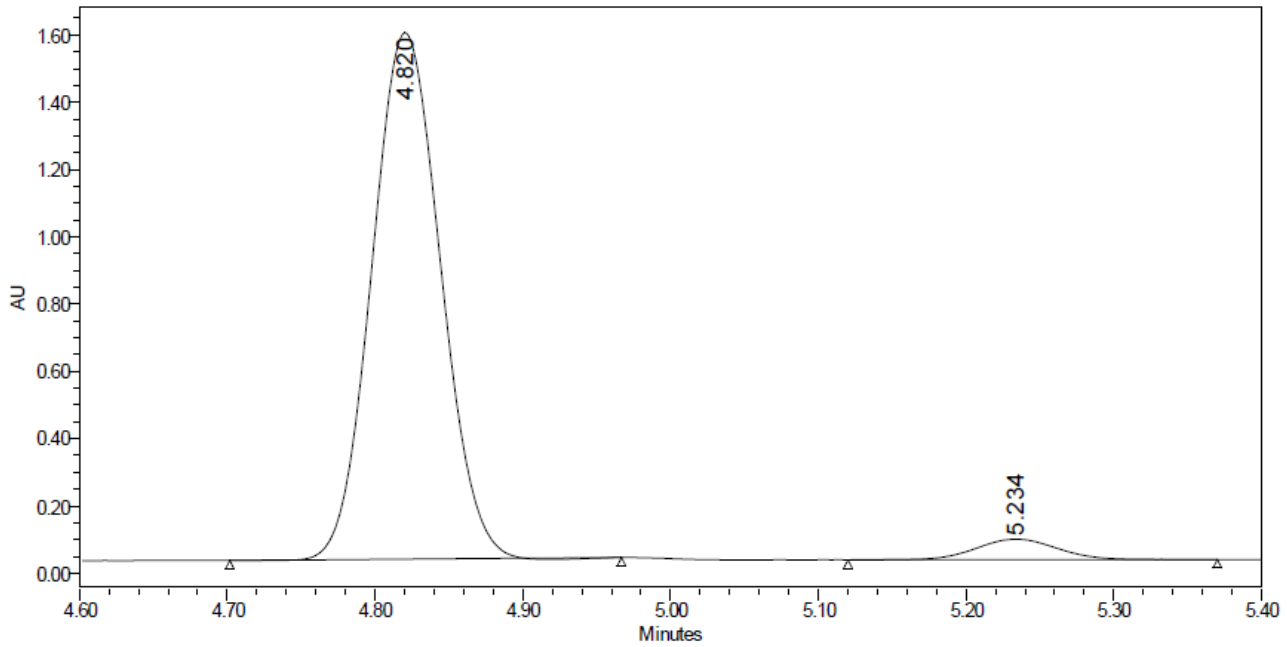

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.270 | 49.31 |
| 2 | 5.758 | 50.69 |



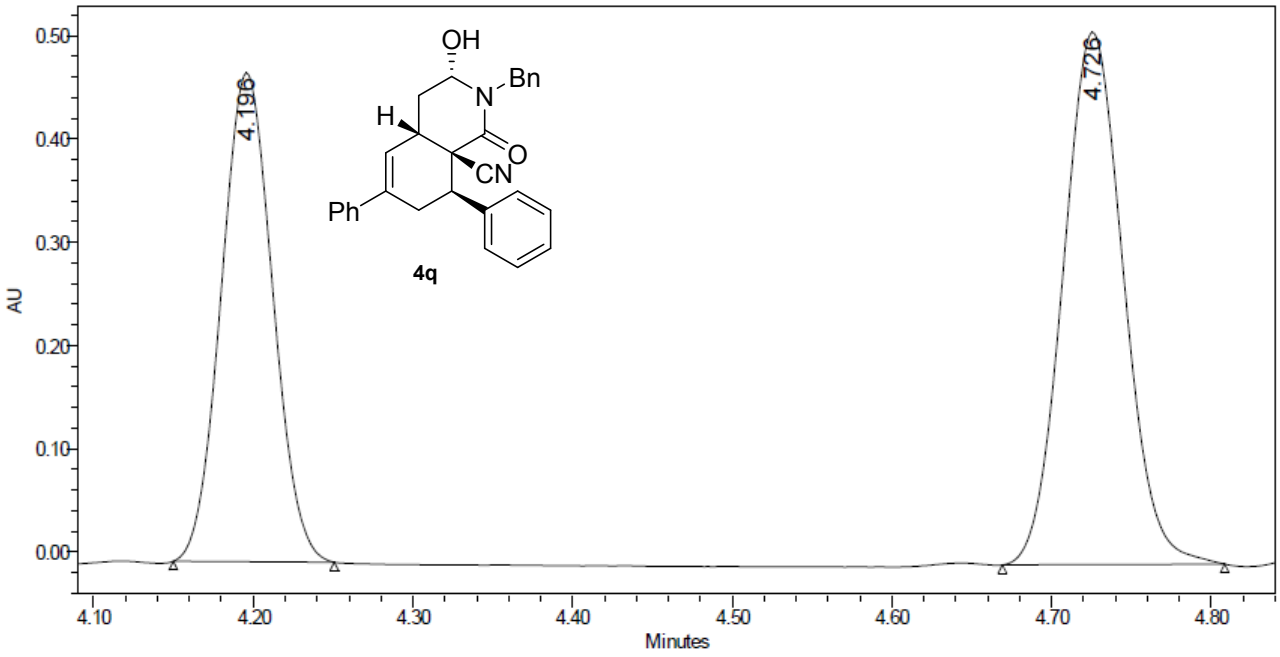

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.266 | 96.38 |
| 2 | 5.765 | 3.62 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.820 | 49.37 |
| 2 | 5.229 | 50.63 |

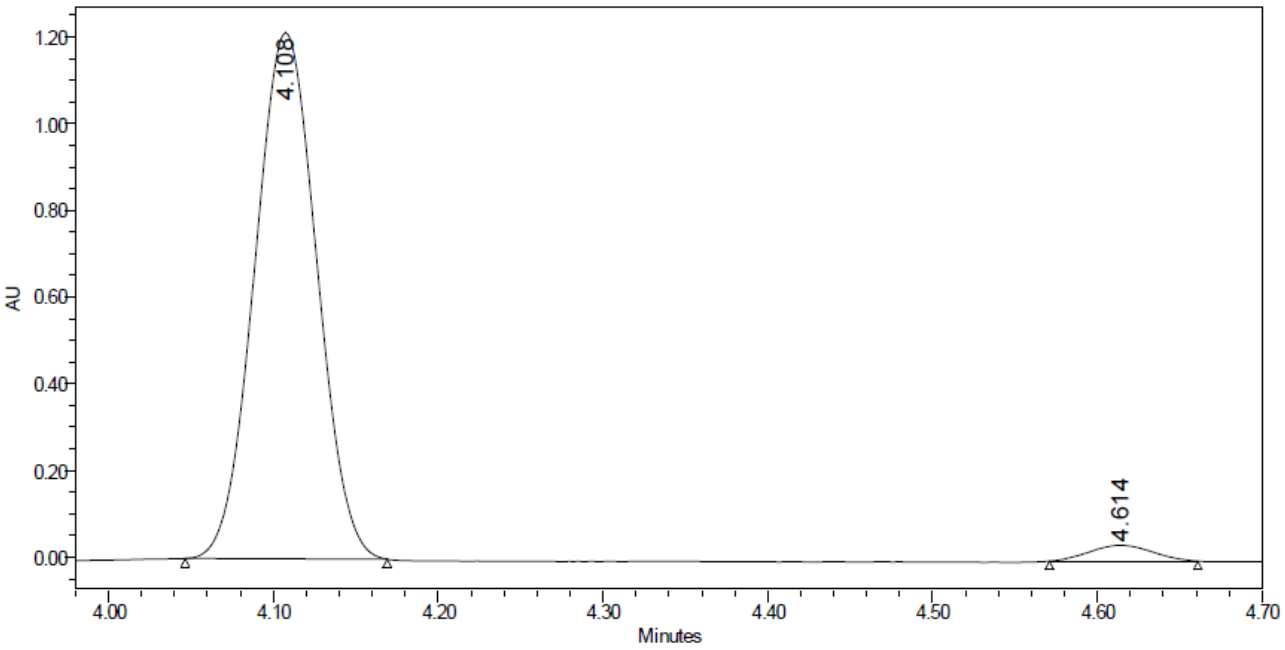



| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.820 | 95.59 |
| 2 | 5.234 | 4.41 |

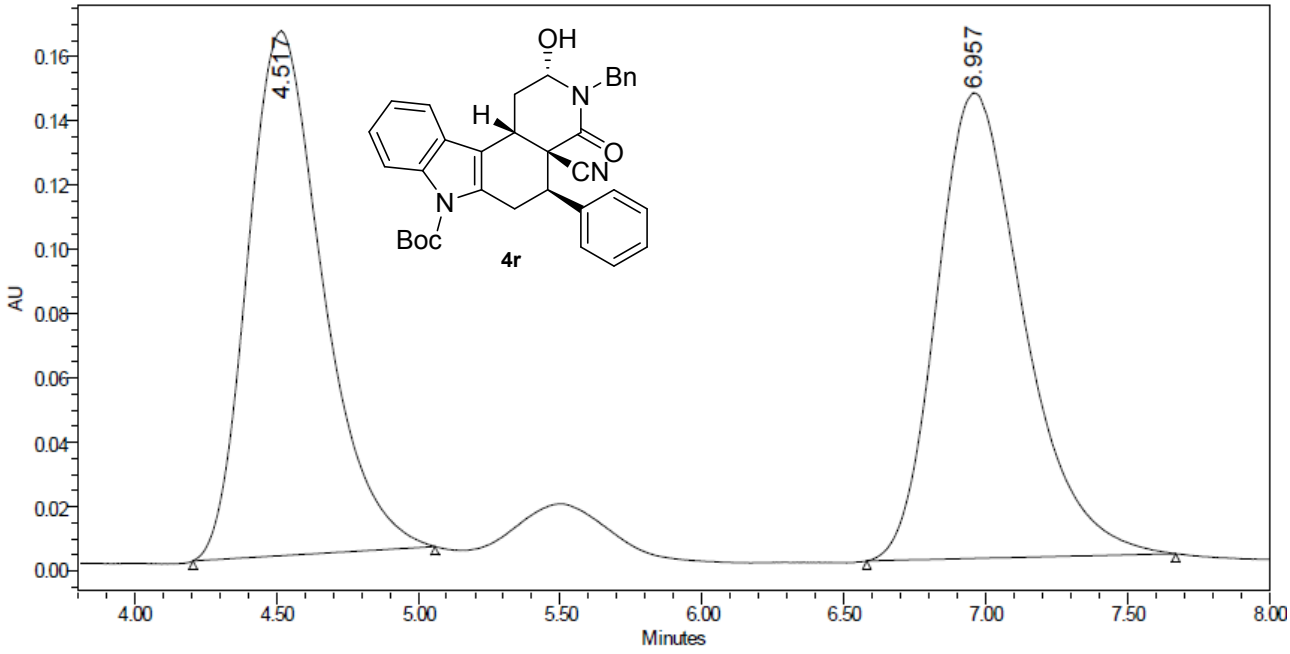



4q

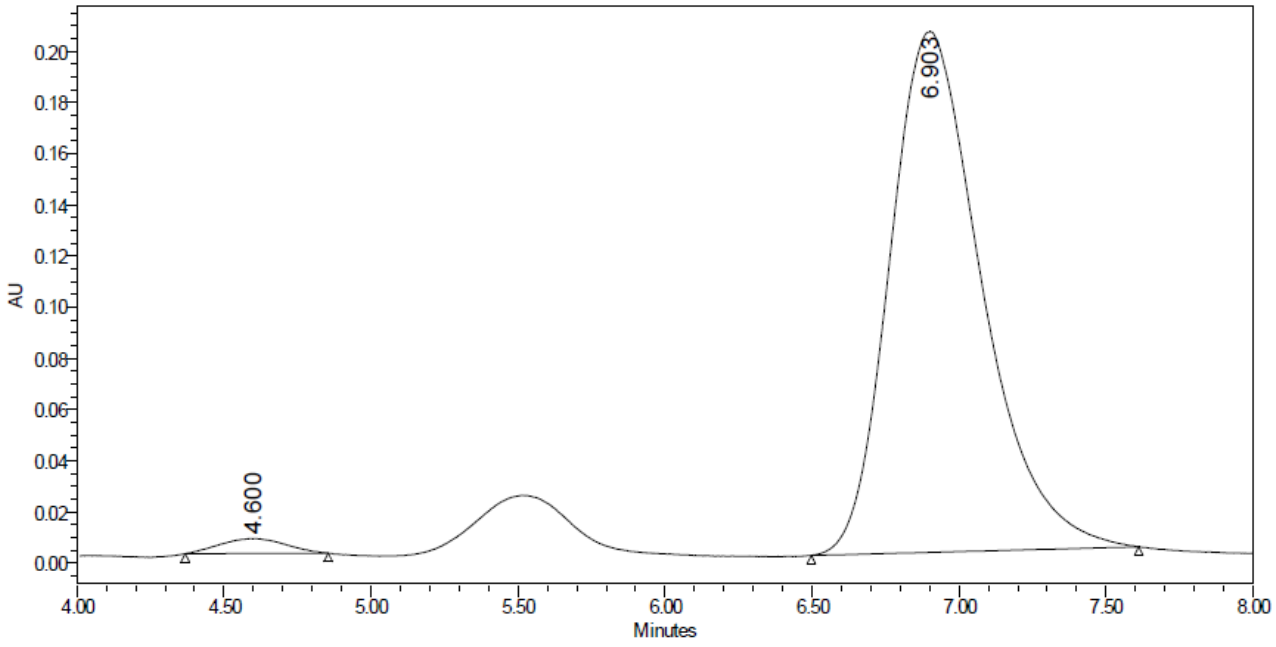
| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.196 | 43.88 |
| 2 | 4.726 | 56.12 |



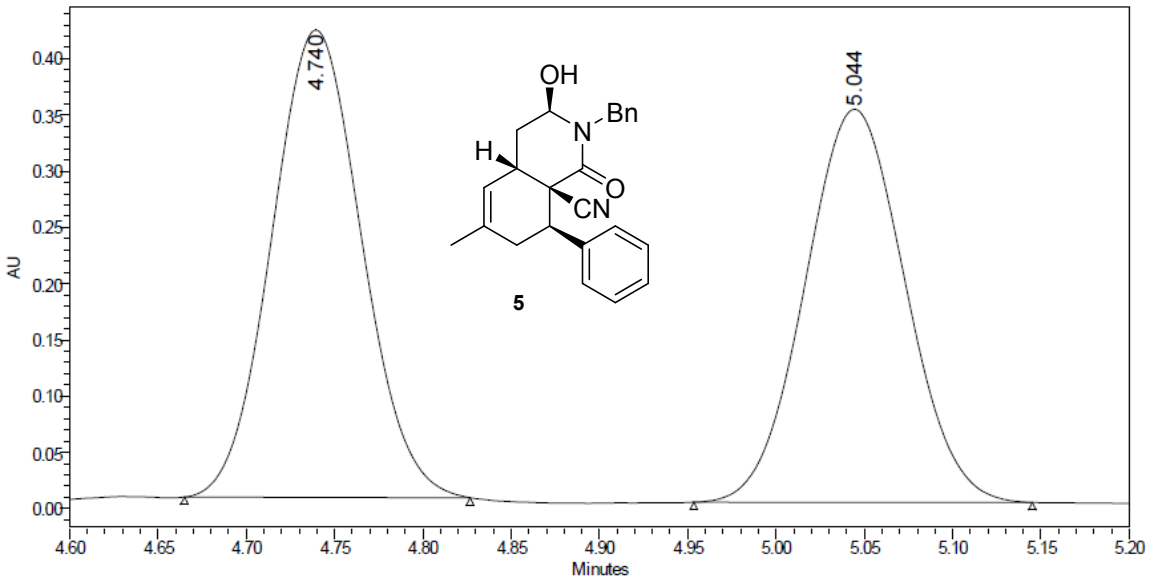

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.108 | 97.04 |
| 2 | 4.614 | 2.96 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.517 | 49.26 |
| 2 | 6.957 | 50.74 |

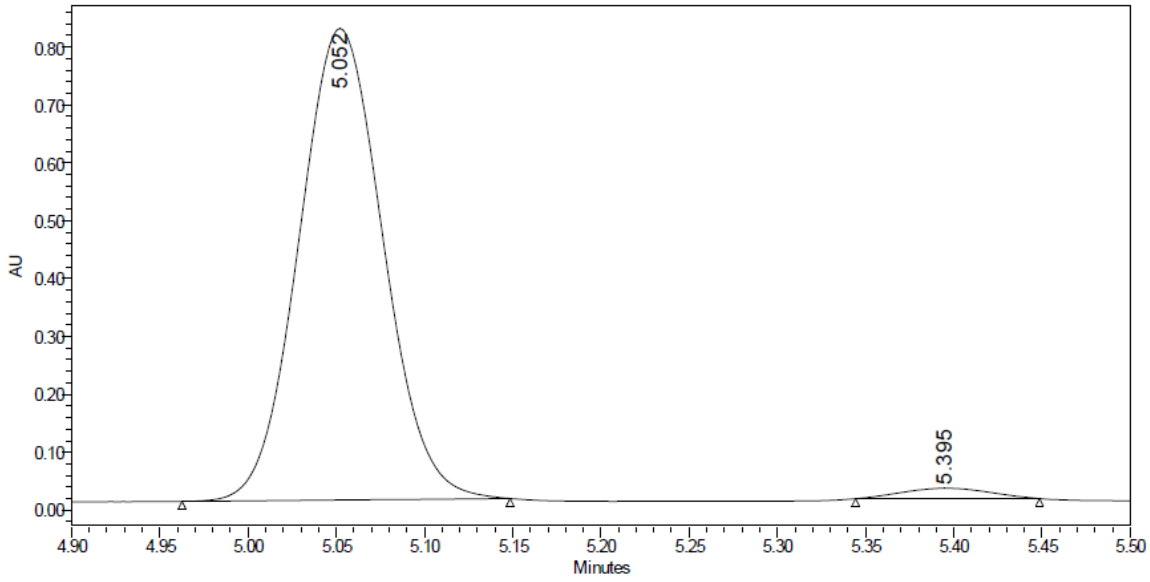



| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.600 | 2.01 |
| 2 | 6.903 | 97.99 |

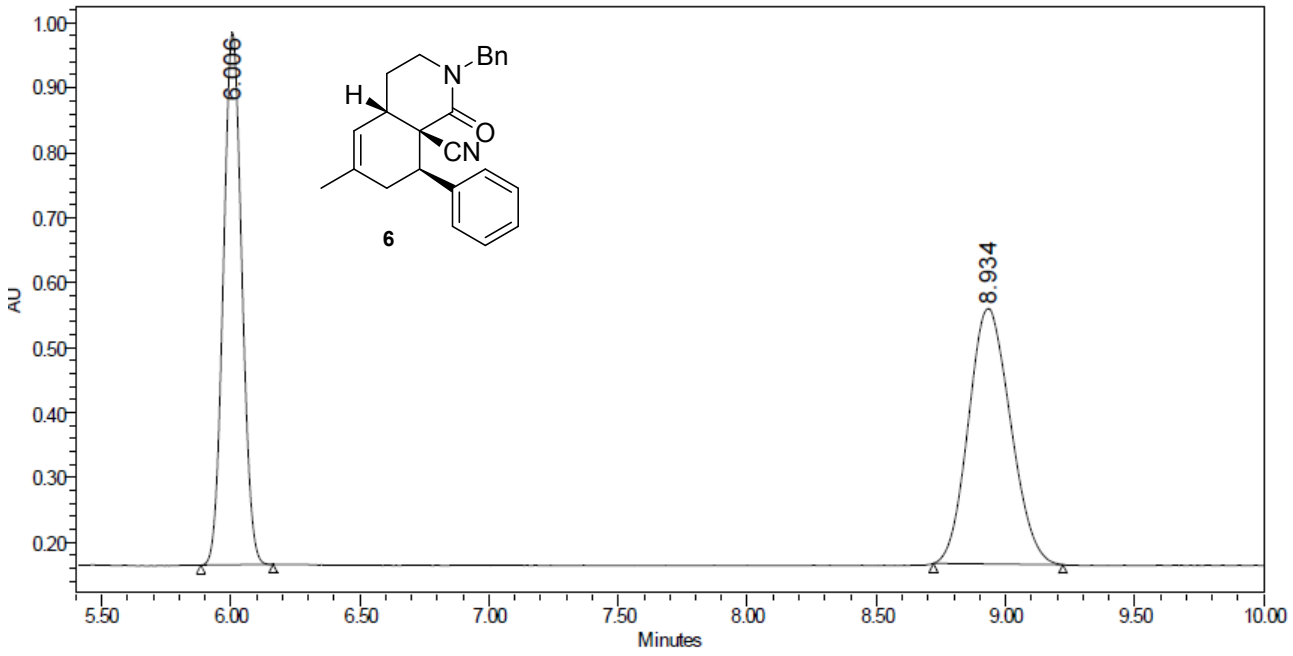



**5**

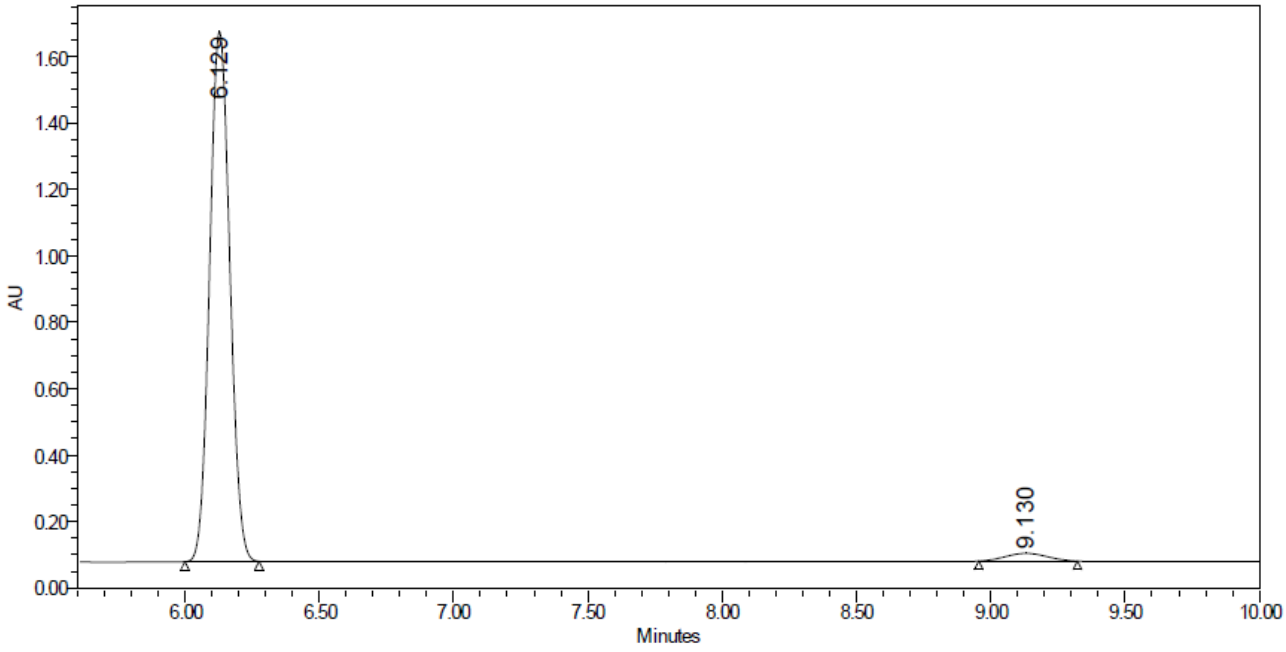
| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 4.740 | 51.65 |
| 2 | 5.044 | 48.35 |



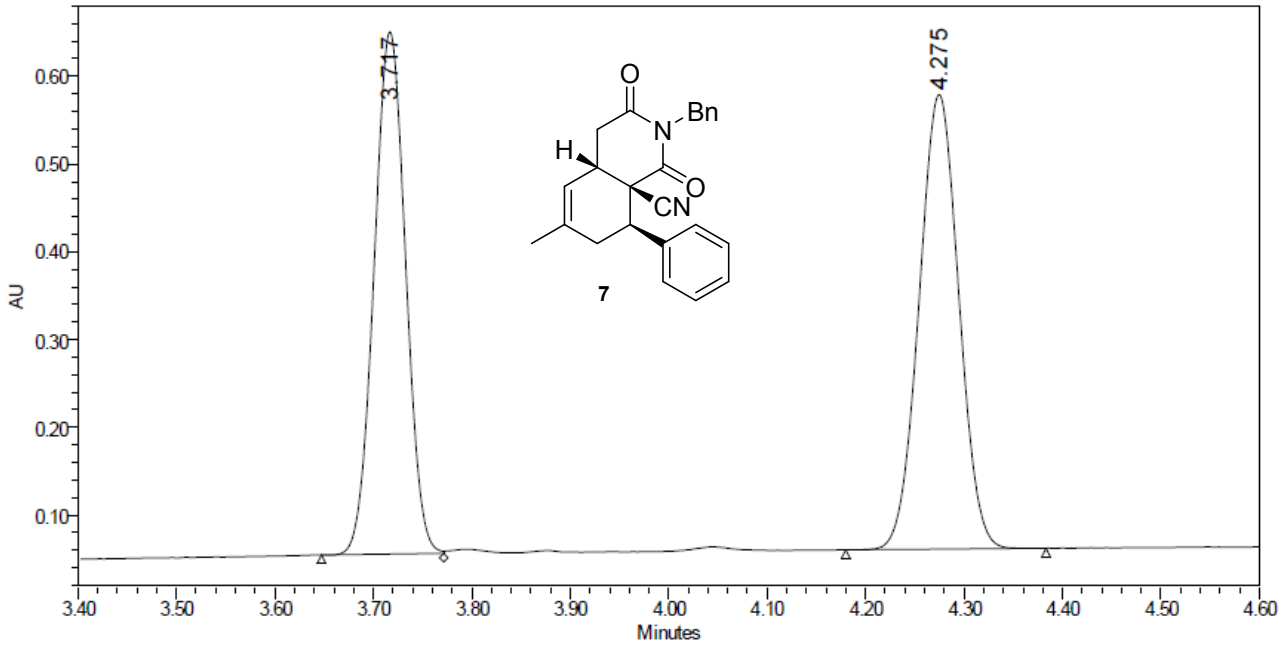

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.052 | 97.77 |
| 2 | 5.395 | 2.23 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 6.006 | 47.78 |
| 2 | 8.934 | 52.22 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 6.129 | 97.09 |
| 2 | 9.130 | 2.91 |

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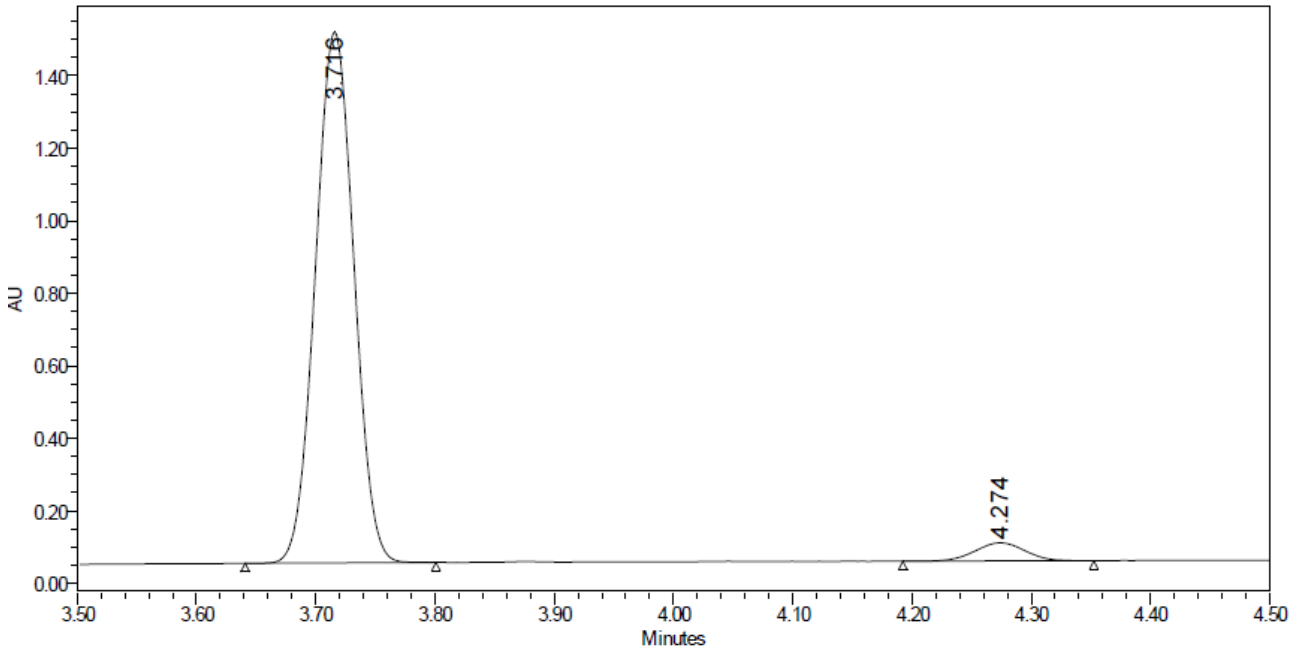
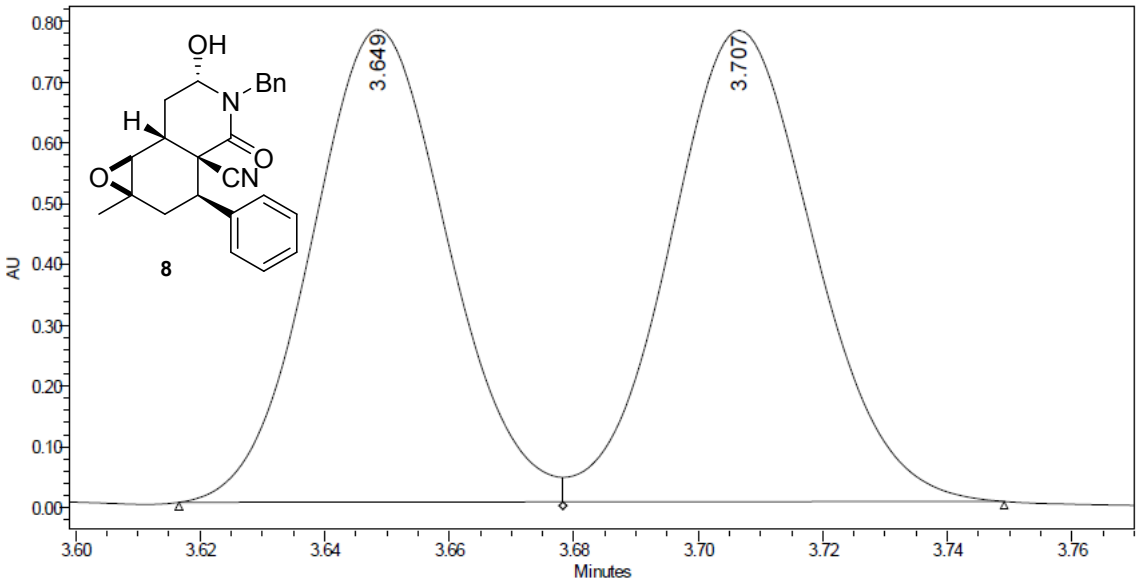
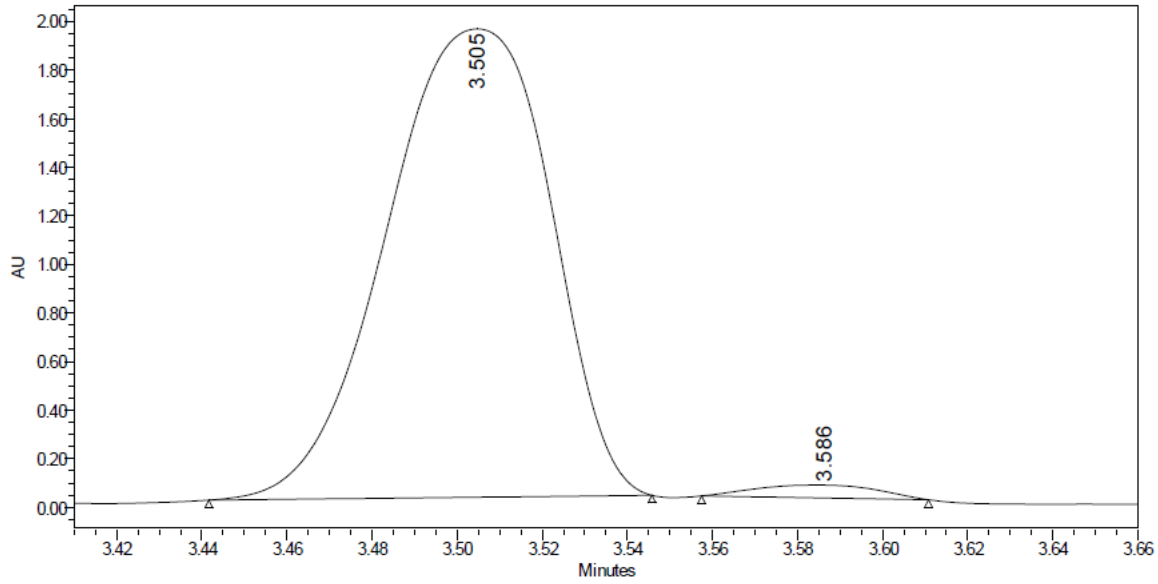
| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.717 | 47.69 |
| 2 | 4.275 | 52.31 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.716 | 95.79 |
| 2 | 4.274 | 4.21 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.649 | 48.62 |
| 2 | 3.707 | 51.38 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.505 | 97.99 |
| 2 | 3.586 | 2.01 |