Asymmetric [3+2] Cycloaddition of Vinyl Cyclopropanes and α,β-Unsaturated Aldehydes by Synergistic Palladium and Organocatalysis

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SUPPORTING INFORMATION

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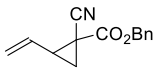
1. General methods

NMR spectra were acquired on a Bruker AVANCE III HD spectrometer running at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 376 MHz for ^{19}F. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.16 ppm for ^{13}C NMR). For ^{19}F NMR $CFCl_3$ was used as internal standard. The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired in broad band decoupled mode. ^{19}F NMR spectrum was acquired in proton decoupled mode. Mass spectra were recorded on a Bruker Maxis Impact mass spectrometer using electrospray (ES^+) ionization (referenced to the mass of the charged species). Dry solvents were obtained from a MBraun MB SPS-800 solvent purification system. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by UV radiation or $KMnO_4$ stain. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Sigma-Aldrich) was used. Optical rotations were measured on a Bellingham+Stanley ADP440+ polarimeter, α values are given in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$; concentration c in g $(100\ mL)^{-1}$. The diastereomeric ratio (dr) of products was evaluated by ^{1}H NMR analysis of the crude mixture. The enantiomeric excess (ee) of products was determined by chiral stationary phase Waters ACQUITY UPC^2 (Daicel Chiralpak). Reference samples for UPC^2 analysis were prepared using a mixture of products obtained from reactions with cat **3** and *ent*-cat **3**. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.

2. Synthesis of starting materials

Vinyl cyclopropanes **1** were synthesized according to previously reported methods. Characterization data for **1a,b** matched those reported in the literature.[1] Characterization data for **1c** is provided below. Vinyl cyclopropanes **1b**,**c** were achieved and applied in the reaction as a diastereomeric mixture. α,β-Unsaturated aldehydes **2** were either purchased from commercial sources or made by previously reported methods. Characterization data matched those reported in the literature.[2] All other reagents were purchased from commercial sources.

Benzyl 1-cyano-2-vinylcyclopropane-1-carboxylate, 1c



1c

Isolated in 38% yield (0.86 g) as a colorless oil by FC on silica using EtOAc/pentane 1:8 as eluent (3:1 diastereomeric mixture after purification). For NMR characterization * denotes the minor diastereoisomer, + denotes overlap of signals of both diastereoisomers, whereas no sign denotes the major diastereoisomer. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.43-7.31$^+$ (m, 10H), 5.70-5.58$^+$ (m, 2H), 5.43$^+$ (d, *J* = 16.9 Hz, 2H), 5.38$^+$ (d, *J* = 10.5 Hz, 2H), 5.29-5.19$^+$ (m, 4H), 2.64* (q, *J* = 8.9 Hz, 1H), 2.59 (q, *J* = 8.5 Hz, 1H), 2.00 (dd, *J* = 9.0; 5.1 Hz, 1H), 1.99-1.88* (m, 2H), 1.67 (dd, *J* = 7.9; 5.1 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 167.1, 165.1*, 134.8*, 134.7, 132.0, 130.4*, 128.72$^+$ (3C), 128.67 (2C), 128.6*, 128.2 (2C), 128.1* (2C), 121.6*, 121.0, 118.5*, 116.5, 68.4, 68.2*, 36.0*, 34.0, 24.1, 22.7*, 21.2, 20.4*. **HRMS** (ESI+) *m*/*z* calcd. for $C_{14}H_{13}NO_2$ [M+Na]$^+$: 250.0838; found: 250.0841.

[1] (a) Wu, J.-Q.; Qiu, Z.-P.; Zhang, S.-S.; Liu, J.-G.; Lao, Y.-X.; Gu, L.-Q.; Huang, Z.-S.; Li, J.; Wang, H. *Chem. Commun.* **2015**, *51*, 77. (b) Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. *J. Am. Chem. Soc.* **2012**, *134*, 5048.
[2] Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.

3. General procedure for the asymmetric [3+2] cycloaddition

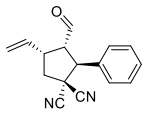
Procedure:

A glass vial equipped with a magnetic stirring bar was charged with vinyl cyclopropane **1** (0.20 mmol, 1.0 equiv.), α,β-unsaturated aldehyde **2** (0.30 mmol, 1.5 equiv.), aminocatalyst **3** (0.02 mmol, 0.10 equiv.), $PhCO_2H$ (0.02 mmol, 0.10 equiv.) and MeCN (0.5 mL). $Pd(dba)_2$ (0.006 mmol, 0.03 equiv.) was then added. The mixture was stirred for 16 h at ambient temperature. The crude product was concentrated *in vacuo* and then loaded onto the column using CH_2Cl_2. FC on silica gel yielded product **4**.

NOTE: No precautions were taken to exclude moisture or air when setting up the reaction.

Characterization data for new compounds:

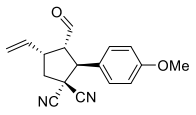
(2S,3S,4R)-3-formyl-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile, 4a



4a

Isolated in 90% yield (45 mg) as a colorless oil by FC on silica using EtOAc/pentane 1:11 as eluent. $[\alpha]_D^{22}$ = –21.2 (*c* 1.5, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.67 (d, *J* = 1.3 Hz, 1H), 7.46-7.40 (m, 5H), 5.72 (ddd, *J* = 16.9; 10.0; 8.3 Hz, 1H), 5.35 (d, *J* = 16.9 Hz, 1H), 5.28 (d, *J* = 10.0 Hz, 1H), 4.26 (d, *J* = 9.5 Hz, 1H), 3.81-3.67 (m, 2H), 2.83 (dd, *J* = 13.4; 6.4 Hz, 1H), 2.36 (dd, *J* = 13.3; 10.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.9, 133.8, 133.2, 129.5, 129.3 (2C), 128.3 (2C), 119.8, 114.8, 114.1, 55.7, 53.6, 43.60, 43.55, 41.7. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{14}N_2O$ $[M+H]^+$: 251.1179; found: 251.1182. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4a'**. **UPC^2**: IA, CO_2/MeOH gradient, 3.0 mL·min^{-1}; t_{major} = 2.79 min; t_{minor} = 2.64 min.

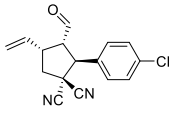
(2S,3S,4R)-3-Formyl-2-(4-methoxyphenyl)-4-vinylcyclopentane-1,1-dicarbonitrile, 4b



4b

Isolated in 89% yield (50 mg) as a yellow solid by FC on silica using EtOAc/pentane 1:10 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –19.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (d, *J* = 1.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.71 (ddd, *J* = 16.7; 10.0; 8.1 Hz, 1H), 5.34 (d, *J* = 16.7 Hz, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 4.23-4.18 (m, 1H), 3.80 (s, 3H), 3.77-3.63 (m, 2H), 2.85-2.77 (m, 1H), 2.38-2.29 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.1, 160.4, 133.9, 129.5 (2C), 125.0, 119.7, 114.9, 114.7 (2C), 114.3, 55.9, 55.4, 53.3, 43.5, 43.4, 42.0. **HRMS** (ESI+) *m/z* calcd. for $C_{17}H_{16}N_2O_2$ $[M+Na]^+$: 303.1104; found: 303.1106. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCO_2Bn to form the corresponding unsaturated ester **4b'**. **UPC^2**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.60 min; t_{minor} = 3.41 min.

(2S,3S,4R)-2-(4-Chlorophenyl)-3-formyl-4-vinylcyclopentane-1,1-dicarbonitrile, 4c

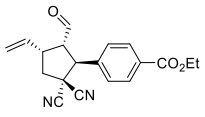


4c

Isolated in 89% yield (50.7 mg) as a yellow solid by FC on silica gel using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –27.1 (*c* 0.3, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.68 (s, 1H), 7.47-7.34 (m, 4H), 5.77-5.64 (m, 1H), 5.42-5.26 (m, 2H), 4.27-4.17 (m, 1H), 3.80-3.66 (m, 2H), 2.85 (ddd, *J* = 13.3; 6.8; 3.1 Hz, 1H), 2.41-2.28 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 198.6, 135.7, 133.7, 131.7, 129.6 (4C), 120.2, 114.5, 114.0, 55.8, 53.1, 43.6, 43.5, 41.6. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{13}N_2OCl$ $[M+H]^+$: 285.0789; found: 285.0792. Enantiomeric excess was measured after Wittig reaction

with Ph_3PCHCN to form the corresponding unsaturated nitrile **4c'**. UPC^2: IA, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.05 min; t_{minor} = 2.98 min.

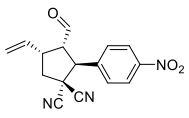
Ethyl 4-((1S,4R,5S)-2,2-dicyano-5-formyl-4-vinylcyclopentyl)benzoate, 4d



4d

Isolated in 84% yield (54.1 mg) as a pale yellow solid by FC on silica gel using EtOAc/pentane 1:20 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –29.0 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.69 (s, 1H), 8.11 (dd, *J* = 11.4; 4.8 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 5.72 (ddd, *J* = 17.0; 10.0; 8.4 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.78 (dq, *J* = 19.8; 10.9 Hz, 2H), 2.86 (dd, *J* = 13.4; 6.5 Hz, 1H), 2.36 (dt, *J* = 18.6; 9.3 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 198.6, 165.9, 138.0, 133.6, 131.7, 130.5 (2C), 128.4 (2C), 120.2, 114.5, 113.9, 61.4, 55.7, 53.4, 43.66, 43.61, 41.5, 14.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{19}H_{18}N_2O_3$ $[M+H]^+$: 323.1390; found: 323.1391. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCO_2Bn to form the corresponding unsaturated ester **4d'**. **UPC^2**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 4.13 min; t_{minor} = 3.95 min.

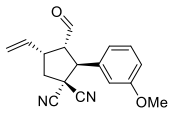
(2S,3S,4R)-3-Formyl-2-(4-nitrophenyl)-4-vinylcyclopentane-1,1-dicarbonitrile, 4e



4e

Isolated in 92% yield (54.3 mg) as a yellow solid by FC on silica gel using EtOAc/pentane 1:5 as eluent. $[\alpha]_D^{22}$ = –67.3 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.70 (s, 1H), 8.36-8.25 (m, 2H), 7.71-7.60 (m, 2H), 5.77-5.64 (m, 1H), 5.46-5.31 (m, 2H), 4.41-4.26 (m, 1H), 3.89-3.72 (m, 2H), 2.94-2.86 (m, 1H), 2.39 (ddd, J = 10.2; 8.0; 3.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 198.1, 148.7, 140.3, 133.4, 129.5 (2C), 124.5 (2C), 120.6, 114.2, 113.7, 55.8, 53.0, 43.6, 43.4, 41.2. **HRMS** (ESI+) *m*/*z* calcd. for $C_{16}H_{13}N_3O_3$ $[M+H]^+$: 296.1030; found: 296.1033. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4e'**. **UPC^2**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.30 min; t_{minor} = 3.17 min.

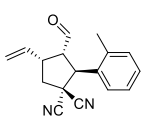
(2S,3S,4R)-3-Formyl-2-(3-methoxyphenyl)-4-vinylcyclopentane-1,1-dicarbonitrile, 4f



4f

Isolated in 89% yield (49.9 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –16.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (d, *J* = 1.3 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.05-6.89 (m, 3H), 5.71 (ddd, *J* = 16.8; 10.1; 8.3 Hz, 1H), 5.34 (d, *J* = 16.8 Hz, 1H), 5.27 (d, *J* = 10.1 Hz, 1H), 4.22 (d, *J* = 9.5 Hz, 1H), 3.84-3.64 (m, 2H), 3.82 (s, 3H), 2.82 (dd, *J* = 13.3; 6.4 Hz, 1H), 2.35 (dd, *J* = 13.3; 10.1 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.0, 160.1, 134.7, 133.8, 130.3, 120.3, 119.8, 114.84, 114.82, 114.16, 114.13, 55.7, 55.4, 53.5, 43.6, 43.5, 41.6. **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{16}N_2O_2$ $[M+H]^+$: 281.1285; found: 281.1287. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4f'**. **UPC^2**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.15 min; t_{minor} = 3.25 min.

(2S,3S,4R)-3-Formyl-2-(o-tolyl)-4-vinylcyclopentane-1,1-dicarbonitrile, 4g

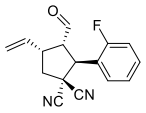


4g

Isolated in 82% yield (43.3 mg) as a pale yellow solid by FC on silica gel using EtOAc/pentane 1:20 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –13.8 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (s, 1H), 7.49-7.41 (m, 1H), 7.33-7.21 (m, 3H), 5.74 (ddd, *J* = 17.1; 10.0; 8.4 Hz, 1H), 5.44-5.25 (m, 2H), 4.76 (d, *J* = 8.9 Hz, 1H), 3.85-3.65 (m, 2H), 2.88-2.79 (m, 1H), 2.61 (s, 3H), 2.39 (dd, *J* = 13.2;

10.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.3, 138.0, 133.7, 132.2, 131.4, 129.1, 127.0, 126.8, 119.9, 115.1, 114.5, 58.3, 47.9, 44.2, 44.1, 40.7, 20.1. **HRMS** (ESI+) *m/z* calcd. for $C_{17}H_{16}N_2O$ $[M+H]^+$: 265.1335; found: 265.1338. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4g'**. **UPC²**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 2.95 min; t_{minor} = 2.90 min.

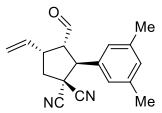
(2R,3S,4R)-2-(2-Fluorophenyl)-3-formyl-4-vinylcyclopentane-1,1-dicarbonitrile, 4h



4h

Isolated in 62% yield (33.3 mg) as a pale yellow solid by FC on silica gel using EtOAc/pentane 1:20 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –37.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.68 (d, *J* = 0.9 Hz, 1H), 7.49-7.35 (m, 2H), 7.24-7.13 (m, 2H), 5.77 (ddd, *J* = 17.0; 10.1; 8.4 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 10.1 Hz, 1H), 4.65 (d, *J* = 9.2 Hz, 1H), 3.79 (dt, *J* = 15.8; 9.6 Hz, 2H), 2.85 (dd, *J* = 13.3; 6.4 Hz, 1H), 2.40 (dd, *J* = 13.3; 10.1 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 198.8, 161.4 (d, $^1J_{C\text{-}F}$ = 248.9 Hz), 133.5, 131.3 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 129.3 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 125.0 (d, $^3J_{C\text{-}F}$ = 3.7 Hz), 120.9 (d, $^2J_{C\text{-}F}$ = 13.1 Hz), 120.1, 116.6 (d, $^2J_{C\text{-}F}$ = 22.4 Hz), 114.6, 114.2, 56.0 (d, $^4J_{C\text{-}F}$ = 2.3 Hz), 46.9, 43.9, 43.6, 40.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ –113.95. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{13}N_2OF$ $[M+H]^+$: 269.1085; found: 269.1086. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4h'**. **UPC²**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 2.56 min; t_{minor} = 2.65 min.

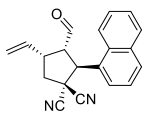
(2S,3S,4R)-2-(3,5-Dimethylphenyl)-3-formyl-4-vinylcyclopentane-1,1-dicarbonitrile, 4i



4i

Isolated in 83% yield (46.2 mg) as a pale yellow solid by FC on silica gel using EtOAc/pentane 1:20 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –35.4 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.68 (d, *J* = 1.2 Hz, 1H), 7.03 (s, 3H), 5.73 (ddd, *J* = 17.0; 10.0; 8.4 Hz, 1H), 5.35 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 10.0 Hz, 1H), 4.18 (d, *J* = 9.5 Hz, 1H), 3.81-3.64 (m, 2H), 2.82 (dd, *J* = 13.3; 6.5 Hz, 1H), 2.35-2.32 (m, 7H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.2, 138.9, 133.9, 133.1 (2C), 131.3, 126.0 (2C), 119.8, 114.9, 114.2, 55.9, 53.6, 43.76, 43.75, 41.8, 21.5 (2C). **HRMS** (ESI+) *m/z* calcd. for $C_{18}H_{18}N_2O$ $[M+H]^+$: 279.1492; found: 279.1494. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4i'**. **UPC²**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 2.55 min; t_{minor} = 2.45 min.

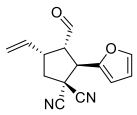
(2S,3S,4R)-3-Formyl-2-(naphthalen-1-yl)-4-vinylcyclopentane-1,1-dicarbonitrile, 4j



4j

Isolated in 86% yield (51.7 mg) as a white solid by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –26.3 (*c* 2.0, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.69 (d, *J* = 1.3 Hz, 1H), 7.93-7.85 (m, 4H), 7.58-7.52 (m, 3H), 5.73 (ddd, *J* = 16.9; 10.1; 8.7 Hz, 1H), 5.36 (d, *J* = 16.9 Hz, 1H), 5.29 (d, *J* = 10.1 Hz, 1H), 4.44 (d, *J* = 10.0 Hz, 1H), 3.93-3.88 (m, 1H), 3.76 (tdd, *J* = 11.3; 10.1; 1.4 Hz, 1H), 2.85 (dd, *J* = 11.3; 10.1 Hz, 1H), 2.39 (dd, *J* = 13.3; 10.6 Hz, 1H) . **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.0, 133.8, 133.6, 133.3, 130.6, 129.3, 128.3, 128.0, 127.8, 127.0, 126.8, 125.3, 119.8, 114.8, 114.2, 55.8, 53.8, 43.64, 43.59, 41.7. **HRMS** (ESI+) *m/z* calcd. for $C_{20}H_{16}N_2O$ $[M+H]^+$: 301.1335; found: 301.1338. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4j'**. **UPC²**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.60 min; t_{minor} = 3.73 min.

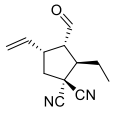
(2R,3S,4R)-3-Formyl-2-(furan-2-yl)-4-vinylcyclopentane-1,1-dicarbonitrile, 4k



4k

Isolated in 91% yield (43.7 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –44.4 (*c* 1.3, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.70 (d, *J* = 1.2 Hz, 1H), 7.45 (dd, *J* = 1.8; 0.8 Hz, 1H), 6.43 (d, 3.3 Hz, 1H), 6.38 (dd, *J* = 3.4; 1.9 Hz, 1H), 5.70 (ddd, *J* = 16.9; 10.1; 8.6 Hz, 1H), 5.36 (d, *J* = 16.9 Hz, 1H) 5.28 (d, *J* = 10.1 Hz, 1H), 4.42 (d, *J* = 9.2 Hz, 1H), 3.81-3.76 (m, 1H), 3.73-3.63 (m, 1H), 2.77 (dd, *J* = 13.3; 6.5 Hz, 1H), 2.29 (dd, *J* = 13.3; 10.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 198.7, 147.5, 143.8, 133.4, 120.1, 114.7, 113.8, 110.9, 109.6, 54.7, 47.4, 43.5, 43.1, 39.8. **HRMS** (ESI+) *m*/*z* calcd. for $C_{14}H_{12}N_2O_2$ $[M+Na]^+$: 263.0791; found: 263.0794. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4k'**. **UPC^2**: IC, CO_2/ *i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.01 min; t_{minor} = 3.14 min.

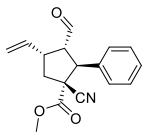
(2R,3S,4R)-2-Ethyl-3-formyl-4-vinylcyclopentane-1,1-dicarbonitrile, 4l



4l

Isolated in 89% yield (36 mg) as a clear oil by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –27.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.70 (d, *J* = 1.5 Hz, 1H), 5.66 (ddd, *J* = 16.9; 10.1; 8.4 Hz, 1H), 5.29 (d, *J* = 16.9 Hz, 1H), 5.24 (d, *J* = 10.1 Hz, 1H), 3.52-3.39 (m, 1H), 3.07 (q, *J* = 8.0 Hz, 1H), 3.02-2.95 (m, 1H), 2.64 (dd, *J* = 13.1; 6.2 Hz, 1H), 2.20 (dd, *J* = 13.1; 11.8 Hz, 1H), 1.90-1.78 (m, 1H), 1.74-1.62 (m, 1H), 1.06 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 200.0, 133.5, 119.7, 115.6, 114.0, 57.3, 50.0, 44.1, 43.2, 38.6, 25.4, 12.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{12}H_{14}N_2O$ $[M+Na]^+$: 225.0998; found: 225.1005. Enantiomeric excess was measured after Wittig reaction with $Ph_3PCHCOPh$ to form the corresponding unsaturated ketone **4l'**. **UPC^2**: IC, CO_2/ *i*-PrOH 90:10, 3.0 mL·min^{-1}; t_{major} = 3.85 min; t_{minor} = 3.46 min.

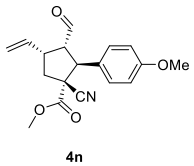
Methyl (1R,2S,3S,4R)-1-cyano-3-formyl-2-phenyl-4-vinylcyclopentane-1-carboxylate, 4m



4m

Isolated in 87% yield (49.3 mg) as a yellow solid by FC on silica using EtOAc/pentane 1:11 as eluent. $[\alpha]_D^{22}$ = –36.6 (*c* 1.0, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.67 (d, *J* = 1.5 Hz, 1H), 7.35-7.29 (m, 5H), 5.78 (ddd, *J* = 16.7; 10.1; 8.3 Hz, 1H), 5.30 (dd, *J* = 16.7; 0.7 Hz, 1H), 5.21 (dd, *J* = 10.1; 0.8 Hz, 1H), 4.31 (d, *J* = 10.0 Hz, 1H), 3.75 (s, 3H), 3.73-3.69 (m, 2H), 2.63 (dd, *J* = 13.3; 6.9 Hz, 1H), 2.35 (dd, *J* = 13.3; 9.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 200.3, 168.2, 135.4, 135.1, 128.9 (2C), 128.7, 128.2 (2C), 118.7, 117.9, 57.1, 55.4, 53.9, 52.5, 43.7, 43.2. **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{17}NO_3$ $[M+H]^+$: 284.1281; found: 284.1276. Enantiomeric excess was measured after reduction with $NaBH_4$ (3 equiv.) to form the corresponding diol **4m'** (both aldehyde and ester moiety were reduced). **UPC^2**: ID, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.44 min; t_{minor} = 3.52 min.

Methyl (1R,2S,3S,4R)-1-cyano-3-formyl-2-(4-methoxyphenyl)-4-vinylcyclopentane-1-carboxylate, 4n

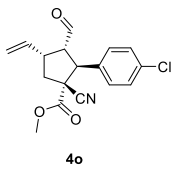


4n

Isolated in 87% yield (54.5 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –32.3 (*c* 2.0, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (d, *J* = 1.4 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.78 (ddd, *J* = 16.8; 10.0; 8.5 Hz, 1H), 5.30 (d, *J* = 16.8 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 4.26 (d, *J* = 10.2 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.69-3.67 (m, 2H), 2.65-2.60 (m, 1H), 2.37-2.31 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 200.4, 168.3, 159.7, 135.4, 129.3 (2C), 126.9, 118.6, 118.0, 114.3 (2C), 57.2, 55.5, 55.3, 53.9, 52.0, 43.5, 43.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{18}H_{19}NO_4$ $[M+H]^+$: 314.1387; found: 314.1386. Enantiomeric excess was

measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4n'**. **UPC²**: IA, CO_2/ *i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.26 min; t_{minor} = 3.33 min.

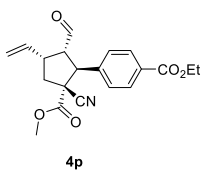
Methyl (1R,2S,3S,4R)-2-(4-chlorophenyl)-1-cyano-3-formyl-4-vinylcyclopentane-1-carboxylate, 4o



4o

Isolated in 88% yield (55.9 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –37.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.67 (d, *J* = 1.3 Hz, 1H), 7.38-7.19 (m, 4H), 5.82-5.69 (m, 1H), 5.32 (d, *J* = 16.9 Hz, 1H), 5.23 (d, *J* = 10.1 Hz, 1H), 4.28 (d, *J* = 10.1 Hz, 1H), 3.88-3.62 (m, 2H), 3.78 (s, 3H), 2.65 (dd, *J* = 13.3; 6.9 Hz, 1H), 2.32 (dd, *J* = 13.3; 9.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.9, 168.0, 135.2, 134.7, 133.7, 129.7 (2C), 129.2 (2C), 119.0, 117.8, 57.2, 55.2, 54.0, 51.7, 43.5, 43.2. **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{16}N_3OCl$ $[M+Na]^+$: 340.0711; found: 340.0712. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4o'**. **UPC²**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.04 min; t_{minor} = 3.10 min.

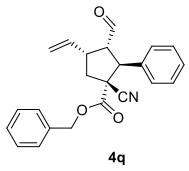
Ethyl 4-((1S,2R,4R,5S)-2-cyano-5-formyl-2-(methoxycarbonyl)-4-vinylcyclopentyl)benzoate, 4p



4p

Isolated in 80% yield (56.9 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –28.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.68 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 5.82-5.70 (m, 1H), 5.32 (d, *J* = 16.9 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.41-4.29 (m, 3H), 3.78-3.70 (m, 1H), 3.76 (s, 3H), 2.70-2.59 (m, 1H), 2.38-2.28 (m, 1H), 1.62-1.55 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.9, 168.0, 166.2, 140.1, 135.2, 130.9, 130.2 (2C), 128.3 (2C), 119.0, 117.7, 61.2, 57.1, 55.1, 54.1, 52.1, 43.6, 43.3, 14.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{20}H_{21}NO_5$ $[M+H]^+$: 356.1492; found: 356.1496. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4p'**. **UPC²**: ID, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 2.84 min; t_{minor} = 2.99 min.

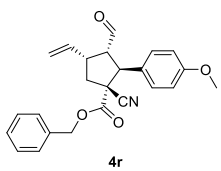
Benzyl (1R,2S,3S,4R)-1-cyano-3-formyl-2-phenyl-4-vinylcyclopentane-1-carboxylate, 4q



4q

Isolated in 88% yield (63.2 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –33.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.67 (d, *J* = 1.5 Hz, 1H), 7.36-7.18 (m, 10H), 5.83-5.71 (m, 1H), 5.29 (d, *J* = 17.0 Hz, 1H), 5.20 (d, *J* = 11.4 Hz, 1H), 5.19 (s, 2H), 4.27 (d, *J* = 10.0 Hz, 1H), 3.75-3.65 (m, 2H), 2.67-2.59 (m, 1H), 2.40-2.31 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 200.3, 167.6, 135.4, 135.0, 134.5, 128.9 (2C), 128.8 (2C), 128.62, 128.60, 128.4 (2C), 128.3 (2C), 118.7, 117.9, 68.7, 57.3, 55.5, 52.6, 43.7, 43.1. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{21}NO_3$ $[M+Na]^+$: 382.1414; found: 382.1413. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4q'**. **UPC²**: IA, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 2.86 min; t_{minor} = 2.75 min.

Benzyl (1R,2S,3S,4R)-1-cyano-3-formyl-2-(4-methoxyphenyl)-4-vinylcyclopentane-1-carboxylate, 4r

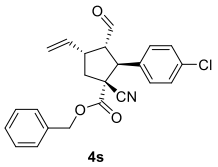


4r

Isolated in 87% yield (67.8 mg) as a yellow oil by FC on silica using EtOAc/pentane 1:10 as eluent. $[\alpha]_D^{22}$ = –27.9 (*c* 2.0, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.65 (d, *J* = 1.5 Hz, 1H), 7.35-7.33 (m, 3H), 7.24-7.16 (m, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H) 5.82-5.73 (m, 1H), 5.28 (d, *J* = 16.6 Hz, 1H), 5.30-5.16 (m, 3H), 4.23 (d, *J* = 10.1 Hz, 1H), 3.77 (s, 3H), 3.68-3.66 (m, 2H), 2.65-2.60 (m, 1H), 2.38-2.33 (m, 1H). **^{13}C NMR (100**

MHz, $CDCl_3$): δ 200.3, 167.6, 159.7, 135.5, 134.5, 129.3 (2C), 128.7 (2C), 128.4 (2C), 126.8, 118.5, 118.0, 114.2 (3C), 68.5, 57.3, 55.6, 55.3, 52.1, 43.5, 42.9. **HRMS** (ESI+) *m*/*z* calcd. for $C_{24}H_{23}NO_4$ $[M+H]^+$: 390.1700; found: 390.1708. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCO_2Bn to form the corresponding unsaturated ester **4r'**. **UPC²**: IC, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.95 min; t_{minor} = 4.13 min.

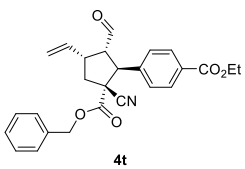
Benzyl (1R,2S,3S,4R)-1-cyano-3-formyl-2-(4-methoxyphenyl)-4-vinylcyclopentane-1-carboxylate, 4s



4s

Isolated in 92% yield (72.3 mg) as a yellow oil by FC on silica gel using EtOAc/pentane 1:20 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –37.3 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.65 (d, *J* = 1.3 Hz, 1H), 7.38-7.32 (m, 3H), 7.24-7.12 (m, 6H), 5.74 (ddt, *J* = 16.9; 10.0; 5.6 Hz, 1H), 5.30 (d, *J* = 16.9 Hz, 1H), 5.25-5.13 (m, 3H), 4.21 (d, *J* = 10.1 Hz, 1H), 3.73-3.61 (m, 2H), 2.67-2.59 (m, 1H), 2.36-2.28 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.9, 167.3, 135.3, 134.5, 134.4, 133.5, 129.6 (2C), 129.1 (2C), 128.9, 128.8 (2C), 128.5 (2C), 118.9, 117.7, 68.7, 57.2, 55.2, 51.8, 43.5, 42.9. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{20}NO_3Cl$ $[M+H]^+$: 394.1204; found: 394.1207. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4s'**. **UPC²**: IA, CO_2/*i*-PrOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.12 min; t_{minor} = 3.03 min.

Ethyl 4-((1S,2R,4R,5S)-2-((benzyloxy)carbonyl)-2-cyano-5-formyl-4-vinylcyclopentyl)benzoate, 4t

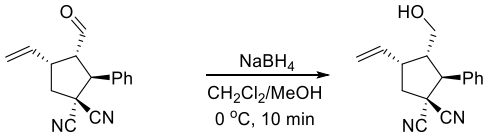


4t

Isolated in 97% yield (83.7 mg) as a yellow oil by FC on silica gel using EtOAc/pentane 1:20 -> 1:5 as eluent. $[\alpha]_D^{22}$ = –26.6 (*c* 0.3, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.42-7.17 (m, 7H), 5.85-5.68 (m, 1H), 5.31 (d, *J* = 16.8 Hz, 1H), 5.25-5.13 (m, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.29 (d, *J* = 9.9 Hz, 1H), 3.78-3.67 (m, 2H), 2.68-2.60 (m, 1H), 2.38-2.28 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 199.8, 167.3, 166.2, 140.0, 135.2, 134.4, 130.7, 130.1 (2C), 128.9, 128.8 (2C), 128.6 (2C), 128.3 (2C), 119.0, 117.6, 68.8, 61.2, 57.2, 55.2, 52.2, 43.6, 43.1, 14.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{26}H_{25}NO_5$ $[M+H]^+$: 432.1805; found: 432.1808. Enantiomeric excess was measured after Wittig reaction with Ph_3PCHCN to form the corresponding unsaturated nitrile **4t'**. **UPC²**: ID, CO_2/MeOH gradient, 3.0 mL·min^{-1}; t_{major} = 3.10 min; t_{minor} = 3.03 min.

4. Synthetic transformations

Reduction to form alcohol S1:



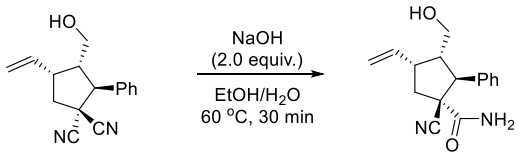
4a → **S1**
75% yield
>95:5 dr

Procedure:

Aldehyde **4a** (0.20 mmol, 1.0 equiv.) was dissolved in a mixture CH_2Cl_2/MeOH (1:1) mixture (2 mL) in a glass vial equipped with a magnetic stirring bar and cooled to 0 °C. $NaBH_4$ (0.3 mmol, 1.5 equiv.) was added. After stirring for 10 min., the reaction mixture was diluted with CH_2Cl_2 and washed with NH_4Cl (sat. aq.), H_2O and brine. The organic phase was dried over Na_2SO_4, concentrated *in vacuo* and then subjected to purification by FC.

Isolated in 75% yield (37.8 mg) as a white solid by FC on silica using EtOAc/pentane 1:5 as eluent. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{22}}$ = +29.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50-7.34 (m, 5H), 6.04 (ddd, *J* = 8.5; 5.4; 2.8 Hz, 1H), 5.27 (d, *J* = 7.4 Hz, 1H), 5.24 (s, 1H), 3.73-3.64 (m, 2H), 3.52 (d, *J* = 11.3; 5.5 Hz, 1H), 3.33 (dq, *J* = 9.8; 7.5 Hz, 1H), 2.89-2.75 (m, 2H), 2.44 (dd, *J* = 13.2; 9.9 Hz, 1H). 1.41 (t, *J* = 5.1 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 136.2, 133.8, 129.3, 129.2 (2C), 128.6 (2C), 118.4, 115.6, 114.7, 60.2, 56.1, 46.4, 43.8, 43.1, 41.8. **HRMS** (ESI+) *m*/*z* calcd. for $C_{16}H_{16}N_2O$ $[M+Na]^+$: 275.1155; found: 275.1159.

Hydrolysis to form amide 5:



S1
>95:5 dr → **5**
70% yield
>95:5 dr

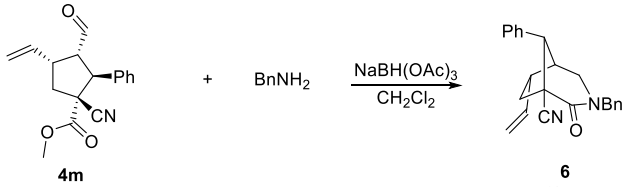
Procedure:

In a 10 mL round bottom flask equipped with a magnetic stirring bar, alcohol **S1** (0.3 mmol, 1.0 equiv.) was dissolved in an EtOH/H_2O (1:1) mixture (5 mL) at 60 °C. Then, NaOH (0.6 mmol, 2.0 equiv.) was added and the reaction mixture stirred at 60 °C for 30 min. Once the reaction was completed, the mixture was diluted with EtOAc (30 mL), washed with brine (2 x 25 mL), dried over Na_2SO_4 concentrated *in vacuo* and then subjected to purification by FC.

Isolated in 70% yield (56.8 mg) as an off-white solid by FC on silica gel using EtOAc/pentane 1:1 as eluent. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{22}}$ = +17.4 (*c* 0.6, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.29 (m, 5H), 6.08 (ddd, *J* = 17.1; 10.0; 9.2 Hz, 1H), 5.95 (s, 1H), 5.77 (s, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 5.20 (dd, *J* = 10.1; 1.1 Hz, 1H), 3.63 (d, *J* = 11.7 Hz, 1H), 3.58 (t, *J* = 5.4 Hz, 2H), 3.35-3.24 (m, 1H), 2.89 (ddd, *J* = 16.1; 11.2; 5.5 Hz, 1H), 2.50 (qd, *J* = 13.5; 8.3 Hz, 2H), 1.64 (t, *J* = 5.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 168.6, 137.8, 135.9, 128.9 (2C), 128.60 (2C),

128.58, 120.4, 117.5, 61.5, 55.9, 54.9, 48.0, 43.1, 42.4. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{18}N_2O_2$ $[M+H]^+$: 271.1441; found: 271.1441.

Reductive amination/cyclization to form lactam 6:

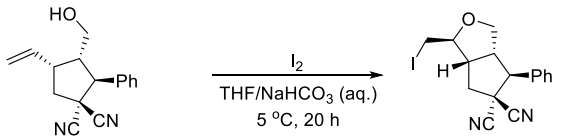


4m **6**
60% yield
>95:5 dr

Procedure:
A glass vial equipped with a magnetic stirring bar was charged with aldehyde **4m** (0.10 mmol, 1.0 equiv.), benzylamine (0.15 mmol, 1.5 equiv.) and CH_2Cl_2 (0.4 mL). Sodium triacetoxyborohydride (0.16 mmol, 1.6 equiv.) was then added. The mixture was stirred for 16 h at ambient temperature. The crude product was then loaded directly onto the column. FC on silica gel yielded product **6**.

Isolated in 60% yield (20.5 mg) as a pale grey oil by FC on silica using EtOAc/pentane 1:5 as eluent. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = –36.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42-7.28 (m, 10H), 5.35 (ddd, *J* = 17.0; 10.2; 7.8 Hz, 1H), 5.01 (d, *J* = 17.0 Hz, 1H), 4.99 (d, *J* = 10.2 Hz, 1H), 4.67 (d, *J* = 14.1 Hz, 1H), 4.45 (d, *J* = 14.1 Hz, 1H), 3.70 (s, 1H), 3.33-3.16 (m, 3H), 2.78-2.61 (m, 2H), 2.31 (dd, *J* = 14.4; 5.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 167.6, 137.0, 136.3, 136.1, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.2, 128.0, 127.7 (2C), 118.0, 117.8, 53.3, 51.3, 50.2, 48.9, 45.4, 41.8, 40.5. **HRMS** (ESI+) *m/z* calcd. for $C_{23}H_{22}N_2O$ $[M+H]^+$: 343.1805; found: 343.1806.

Iodoetherification to form 7:



S1
>95:5 dr

7
73% yield
>95:5 dr

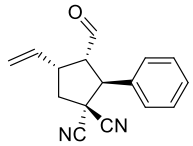
Procedure:
Alcohol **S1** (0.20 mmol, 1.0 equiv.) was dissolved in a THF/$NaHCO_3$ (sat. aq.) (3:1) mixture (1.6 mL) in a glass vial equipped with a magnetic stirring bar and cooled to 5 °C. Iodine was then added 0.5 equiv. at the time every hour until a total amount of 3.0 equiv. had been added. The mixture was kept at 5 °C and stirred overnight. The reaction mixture was then quenched with H_2O and extracted with EtOAc (x 3). The organic phase was washed with $Na_2S_2O_3$ (sat. aq.), H_2O and brine. The organic phase was dried over Na_2SO_4, concentrated *in vacuo* and then subjected to purification by FC.

Isolated in 73% yield (55.2 mg) as a white crystalline solid by FC on silica using EtOAc/pentane 1:10 as eluent. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +48.0 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50-7.40 (m, 5H), 4.17 (ddd, *J* = 8.5; 5.4; 2.8 Hz, 1H), 3.99 (dd, *J* = 9.9; 5.8 Hz, 1H), 3.73 (dd, *J* = 9.9; 1.9 Hz, 1H), 3.50-3.36 (m, 2H), 3.25 (d, *J* = 10.0; 5.4 Hz, 1H), 3.20-3.04 (m, 3H), 2.42-2.32 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 132.7, 129.7, 129.4 (2C), 128.6 (2C), 114.4, 114.3, 86.1, 70.5, 59.7, 48.7, 47.5, 44.4, 44.2, 6.8. **HRMS** (ESI+) *m/z* calcd. for $C_{16}H_{15}N_2OI$ $[M+Na]^+$: 401.0121; found: 401.0125.

5. Determination of the absolute and relative configuration in products

Determination of absolute configuration in products 4:

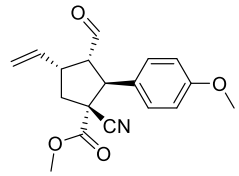
Compounds **4a**,**m**,**n**,**o** are described in the literature and our characterization data for these compounds were in agreement with those previously reported.[3] Absolute configuration was assigned based on comparison of measured values for optical rotation for **4a**,**n** as shown below. The absolute stereochemistry of the remaining products **4** was assigned by analogy.



4a

$[\alpha]_D^{22}$ = -20.4 (*c* 1.7, $CHCl_3$) (experimental value)

$[\alpha]_D^{22}$ = -16.6 (*c* 1.7, $CHCl_3$) (literature value)[3]



4n

$[\alpha]_D^{22}$ = -39.0 (*c* 0.5, $CHCl_3$) (experimental value)

$[\alpha]_D^{22}$ = -41.8 (*c* 1.0, $CHCl_3$) (literature value)[3]

Determination of relative configuration in product 5:

Colorless single crystals were obtained from a recrystallized sample of **5** with a minimum amount of chloroform. Stereochemical configuration of the newly formed stereocenter in **5** was determined by X-ray crystallography analysis. X-ray crystal structure of **5** (Figure S1) shows that primary amide moiety is positioned *syn* with respect to the allylic moiety and allows for determination of the relative stereochemical configuration at the center in question.

[3] Ma, G.; Afewerki, S.; Deiana, L.; Palo-Nieto, C.; Liu, L.; Sun, J.; Ibrahem, I.; Córdova, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 6050.

Figure S1. Ortep diagram of compound 5 (with thermal ellipsoids drawn at 50% probability).

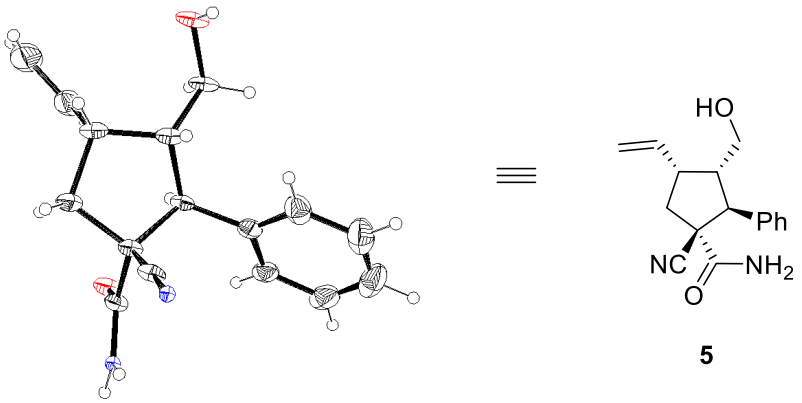


Table S1. Crystal data and refinement details for compound 5.

Item	Value
Molecular formula	C16 H18 N2 O2
Formula weight	270.33
Crystal system	monoclinic
Space Group	P 1 2 1
a (Å)	8.94706
b (Å)	11.2291
c (Å)	14.9983
α (°)	90
β (°)	102.552
γ (°)	90
Volume (Å3)	1470.82
Z	4
T (K)	100
ρ (g cm-1)	1.2207
λ (Å)	0.71073
μ (mm-1)	0.081
# measured refl	16869
# unique refl	6730
R_{int}	0.0401
# parameters	378
R(F2), all refl	0.067
R_w(F2), all refl	0.1187
Goodness of fit	1.051

Crystal data for [**5**]: $C_{16}H_{18}N_2O_2$, M = 270.33, monoclinic, Space group P 1 2 1 (no. 3), a = 8.94706(18) Å, b = 11.2291(3) Å, c = 14.9983(3) Å, β = 102.552(2)°, Flack parameter = 8.38, V = 1470.82(6) Å^3, T = 100 K, Z = 4, d_c = 1.2207 g cm^{-3}, μ(Mo Kα, λ = 0.71073 Å) = 0.081 mm^{-1}, 16869 reflections collected, 6730 unique [R_{int} = 0.0401], which were used in all calculations. Refinement on F^2, final R(F) = 0.067, R_w(F2) = 0.1187. CCDC number 1458670.

Determination of relative configuration in product 7:

The stereochemical configuration of the newly formed stereocenter in **7** was determined by detailed NMR analysis. First, all hydrogen signals were assigned based on COSY NMR analysis. Subsequently, NOESY NMR analysis revealed the relative configuration of the new stereocenter as shown below.

Figure S2. 1D ^{1}H NMR of 7 (zoom of relevant region) with assigment of signals. Assignment was made with the aid of COSY (Figure S3) and NOESY (Figure S4) spectra.

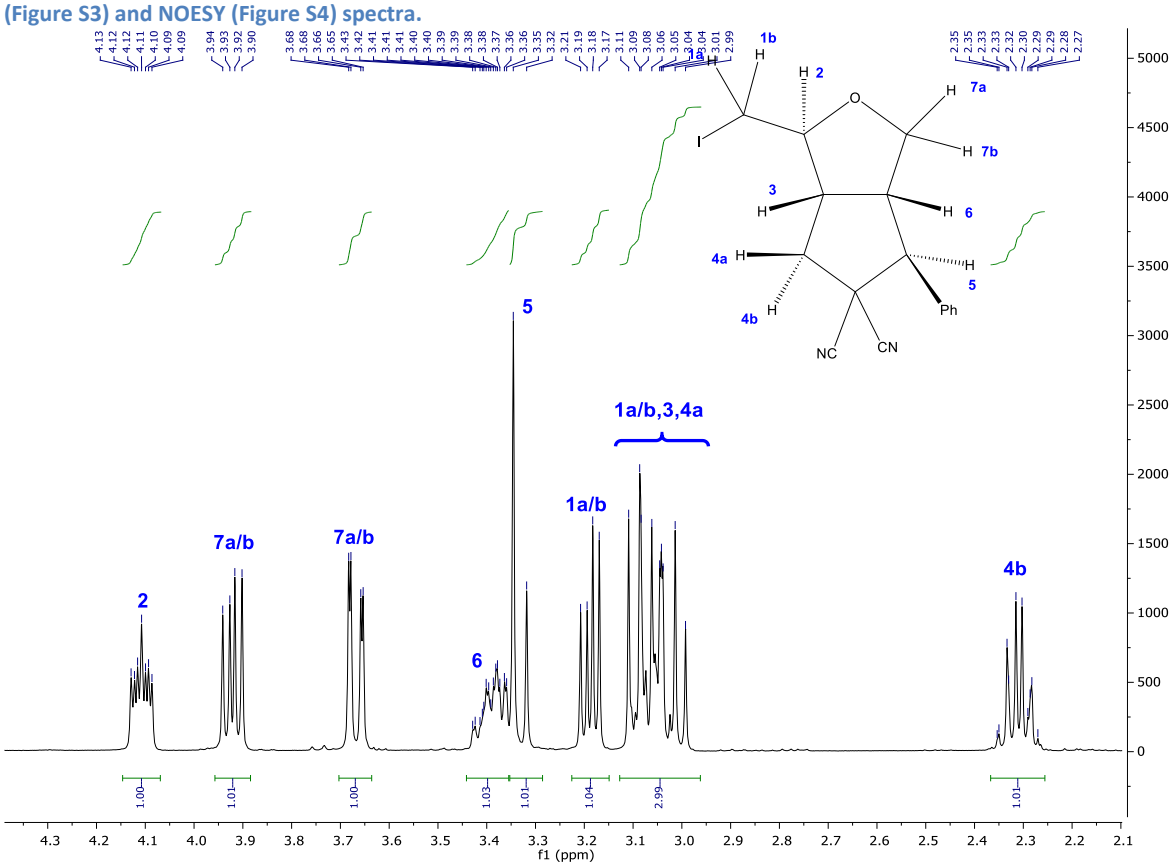


Figure S3. COSY spectrum of 7 (zoom of relevant region).

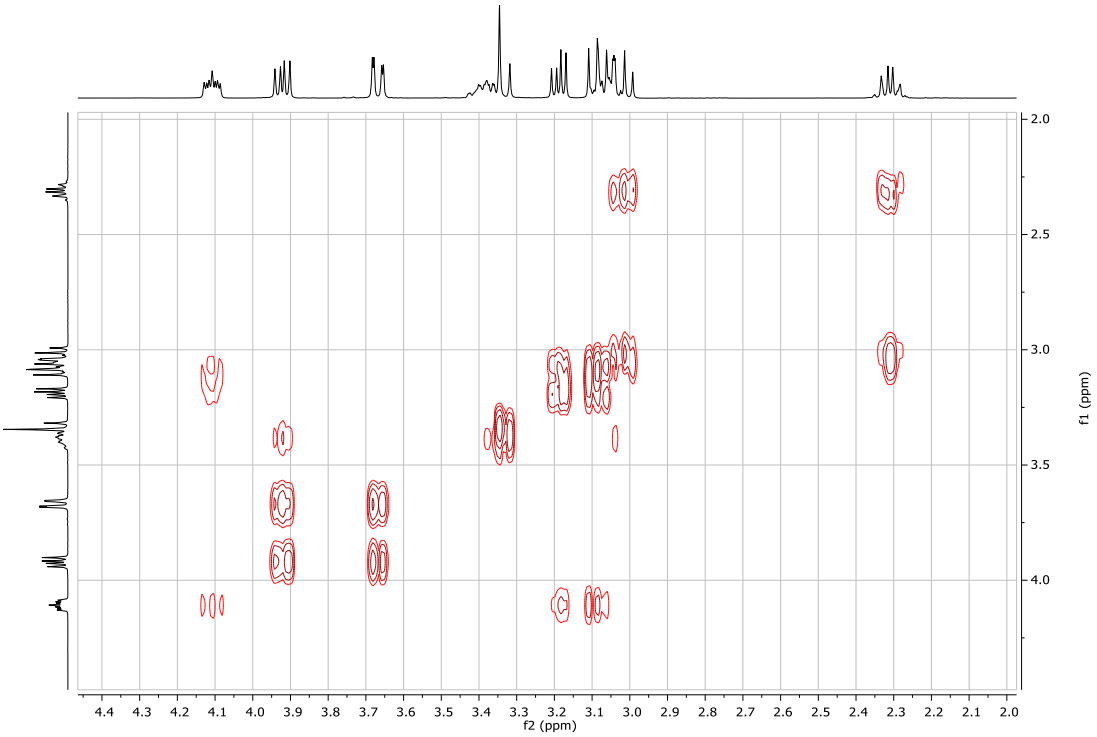


Figure S4. NOESY spectrum of 7 (zoom of relevant region). Relevant couplings marked with green circles.

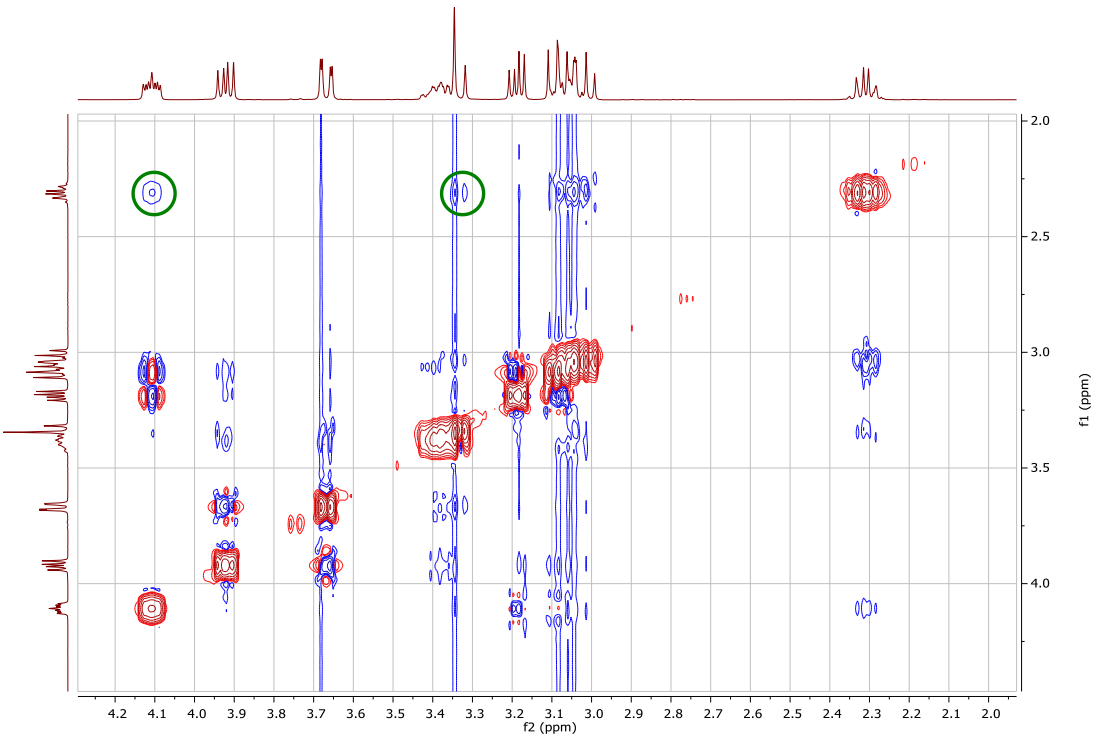
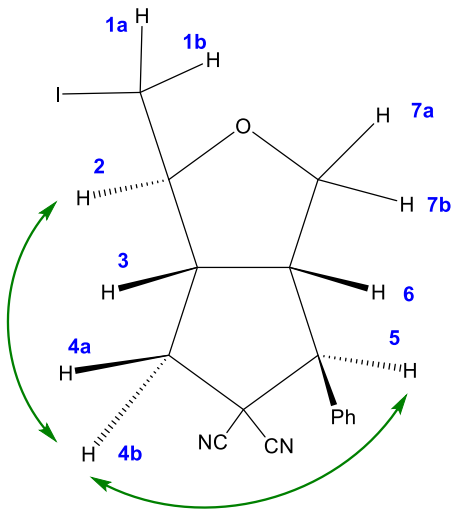
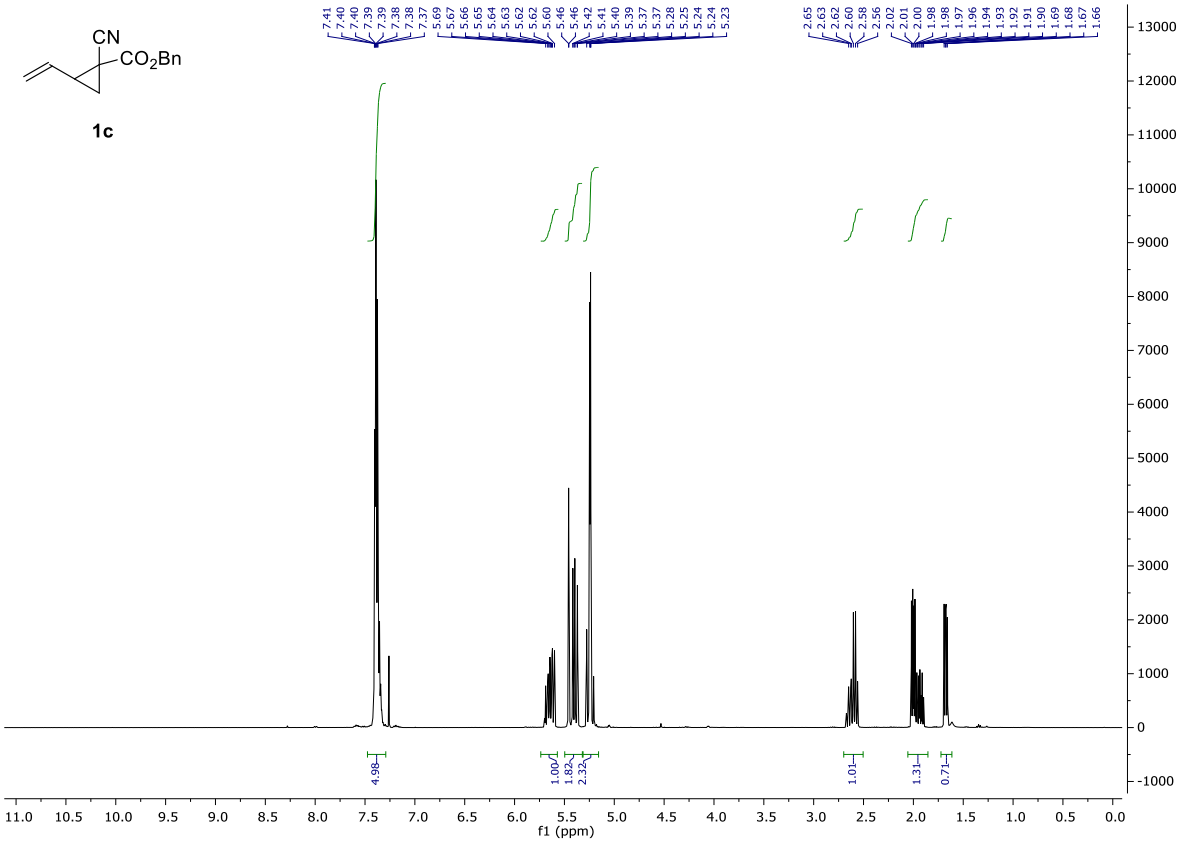


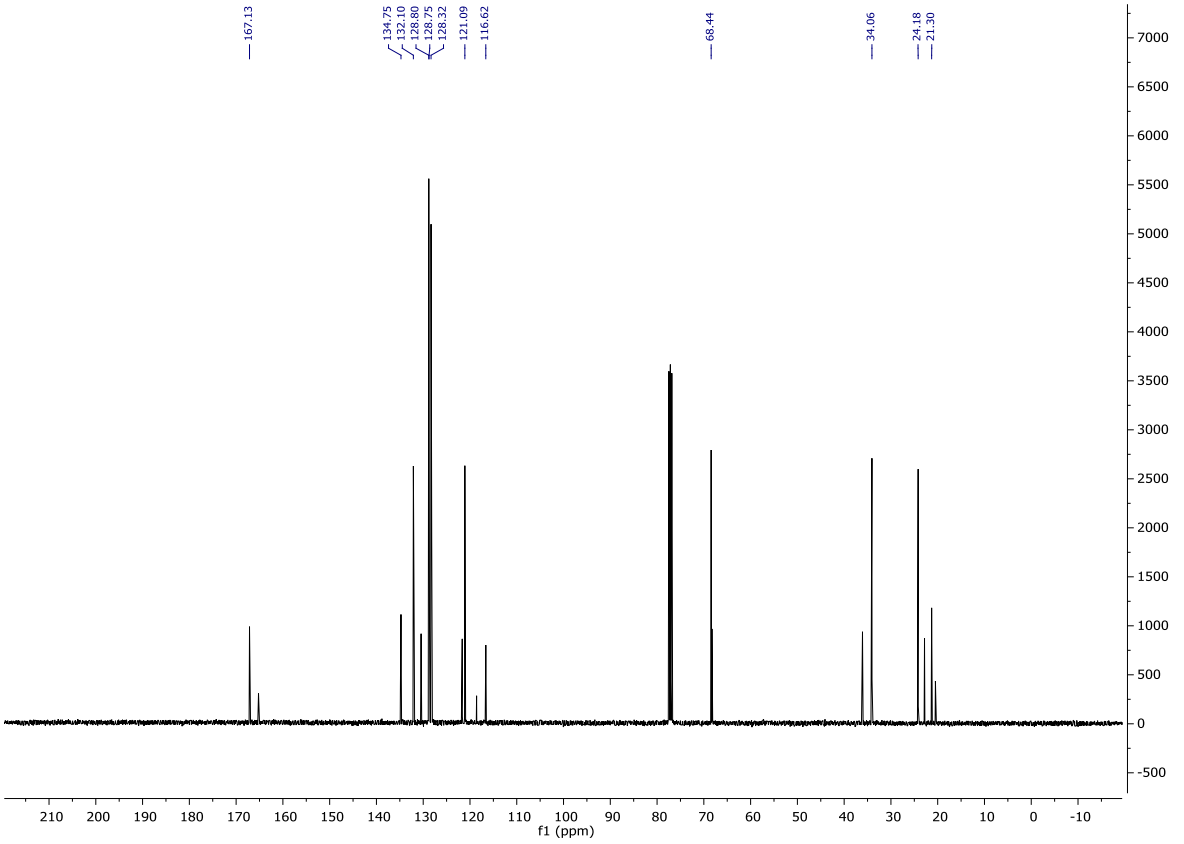
Figure S5. Overview of relevant cross-peaks observed in NOESY spectrum.

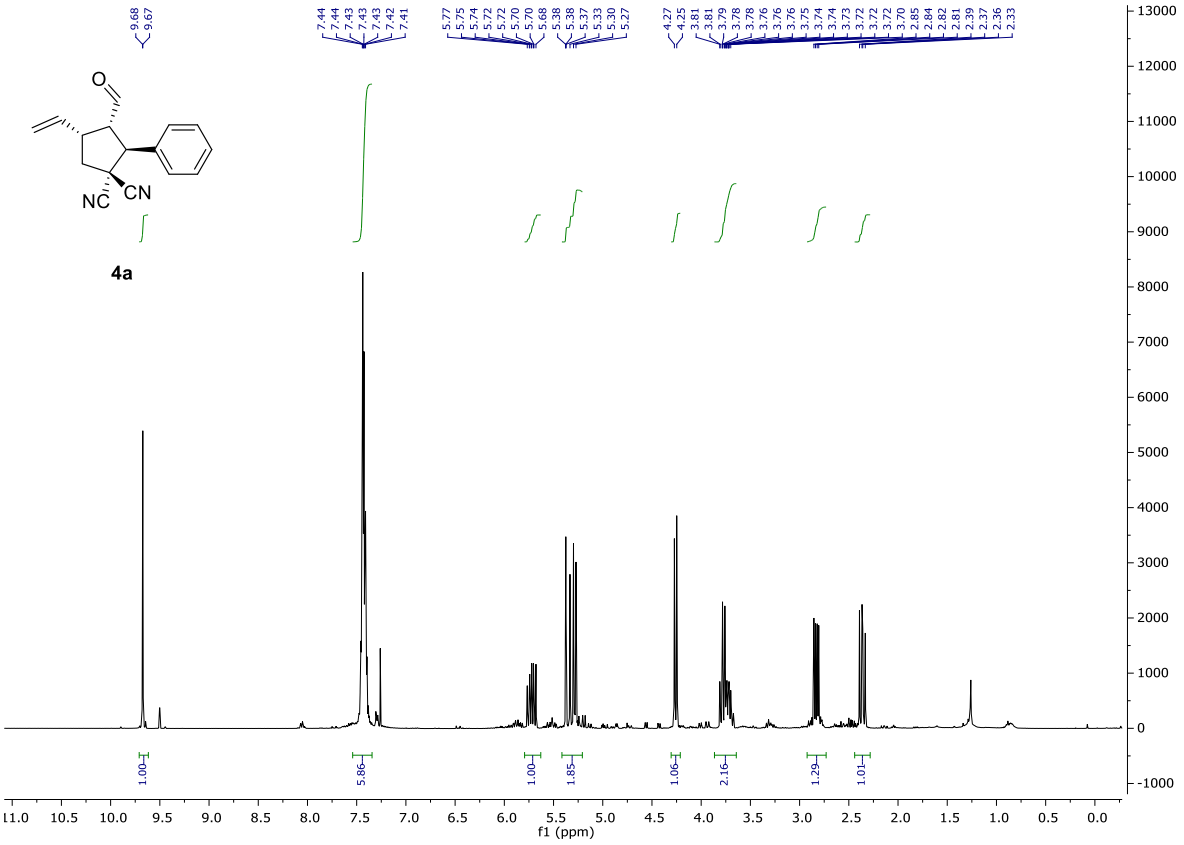


The spectra were interpreted as follows: From analysis of the 1D ^{1}H NMR and COSY spectra, hydrogen signals could be assigned. Notably, the signal at ~2.3 ppm must originate from one of the diastereotopic protons **4a** or **4b**. This signal was assigned to arise from **4b** from the NOESY spectrum since a correlation to proton **5** can be detected. The correlation between **4b** and **2** allow for determination of the stereochemical configuration at the center in question.

6. NMR spectra






9.68
9.67
7.44
7.44
7.43
7.43
7.43
7.42
7.41
5.77
5.75
5.74
5.72
5.72
5.70
5.70
5.68
5.38
5.38
5.37
5.33
5.30
5.27
4.27
4.25
3.81
3.81
3.79
3.78
3.78
3.76
3.76
3.76
3.75
3.74
3.74
3.73
3.72
3.72
3.72
3.70
2.85
2.84
2.82
2.81
2.39
2.37
2.36
2.33
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CN
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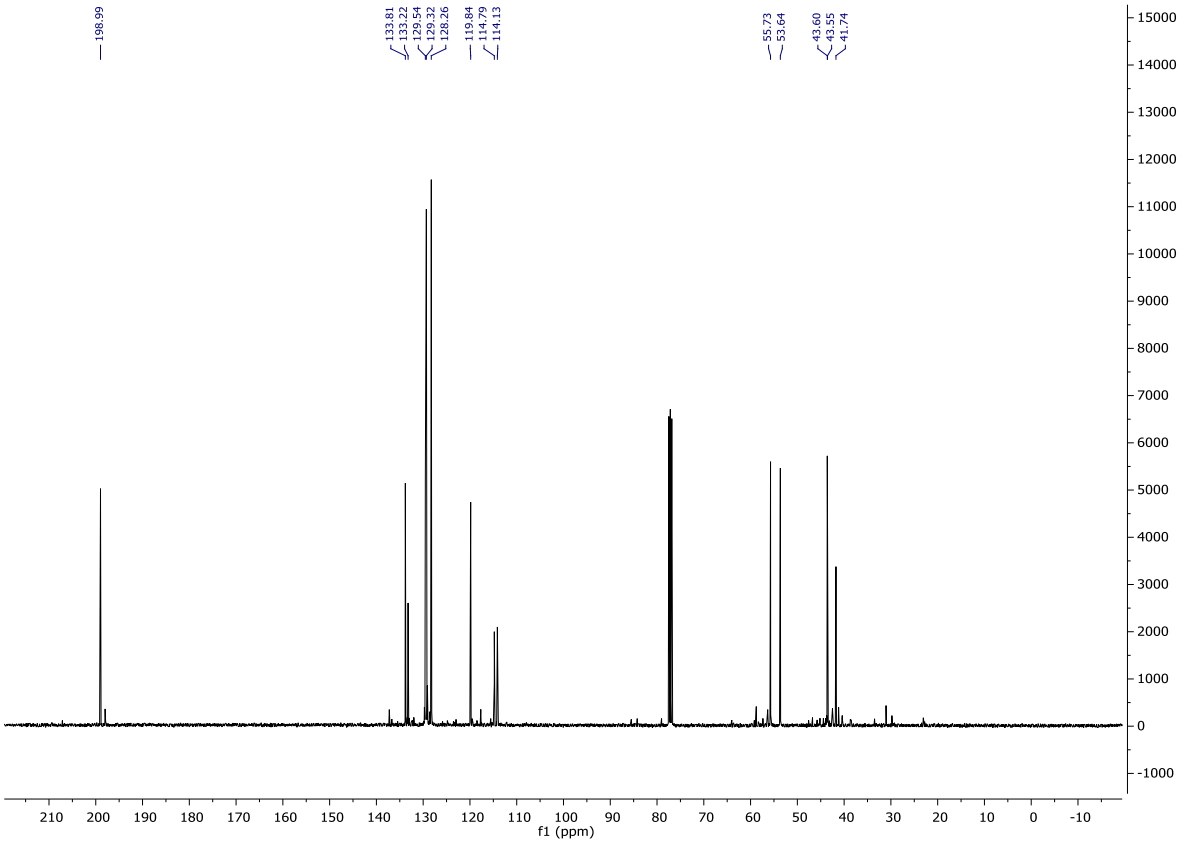
1.00
1.85
1.06
2.16
1.29
1.01
f1 (ppm)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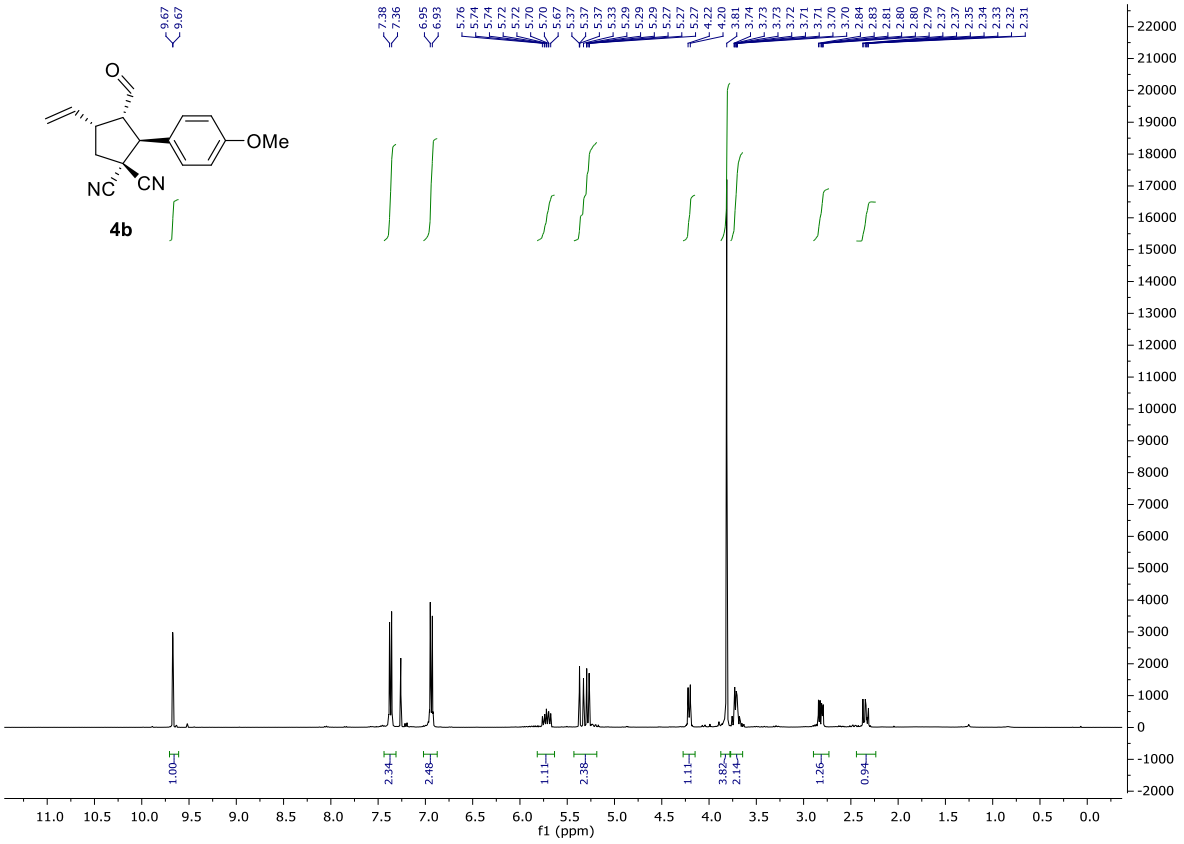
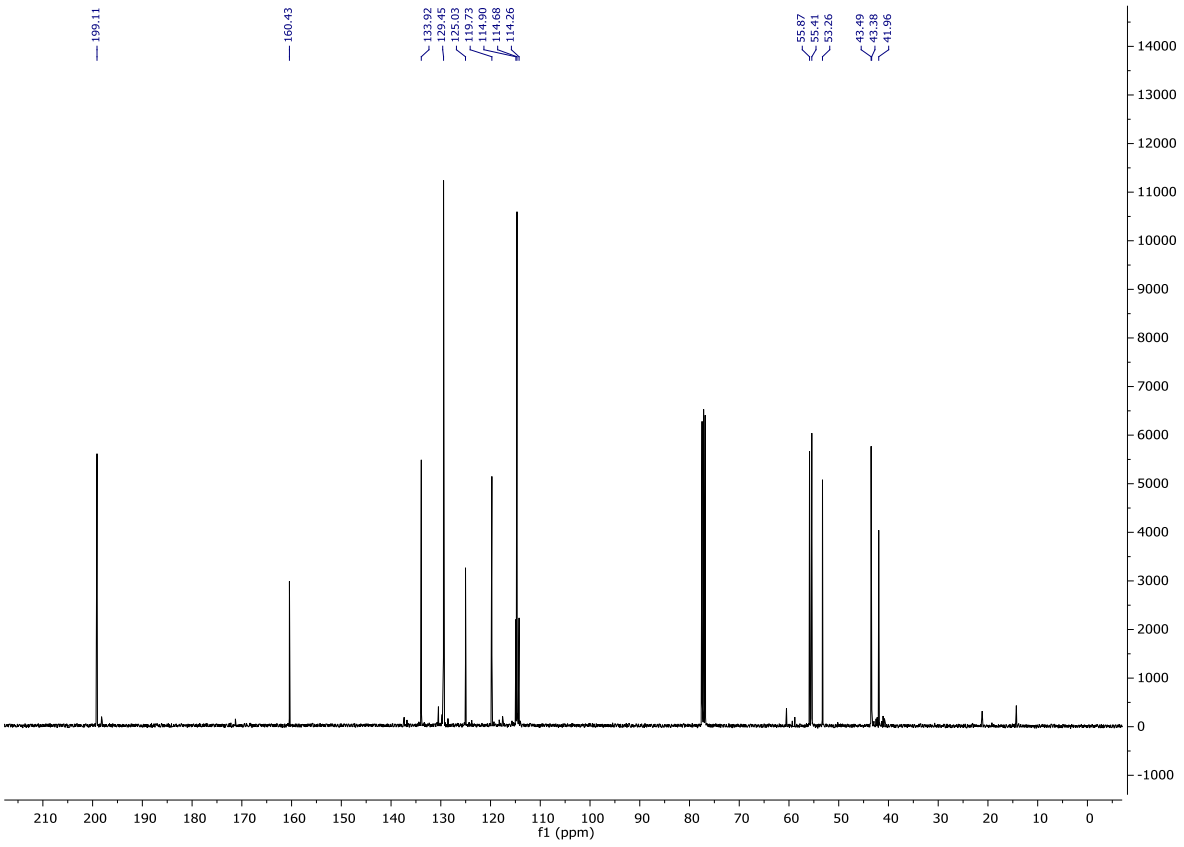
129.32
128.26
119.84
114.79
114.13
55.73
53.64
43.60
43.55
41.74
f1 (ppm)


O
OMe
NC
CN
4b
f1 (ppm)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160.43
133.92
129.45
125.03
114.73
114.60
114.68
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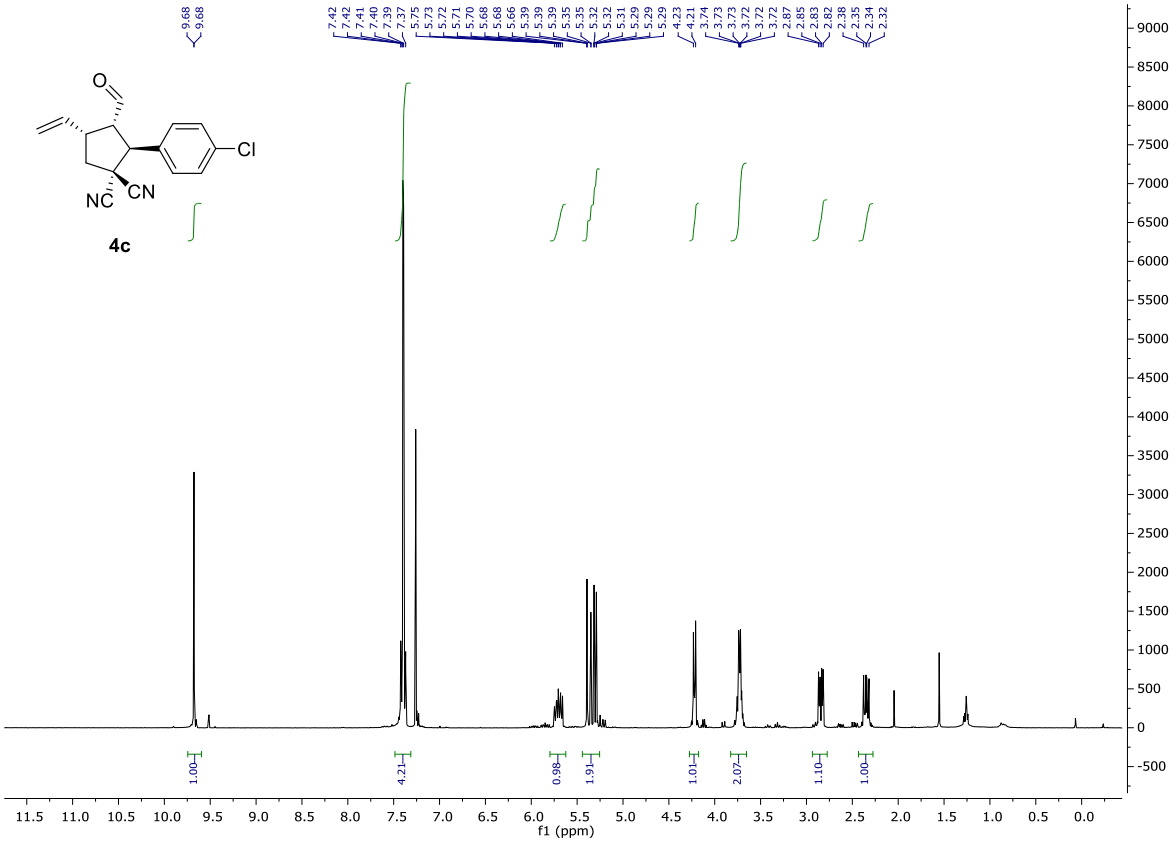
55.87
55.41
53.26
43.49
43.38
41.96
f1 (ppm)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2.85
2.83
2.82
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2.35
2.34
2.32
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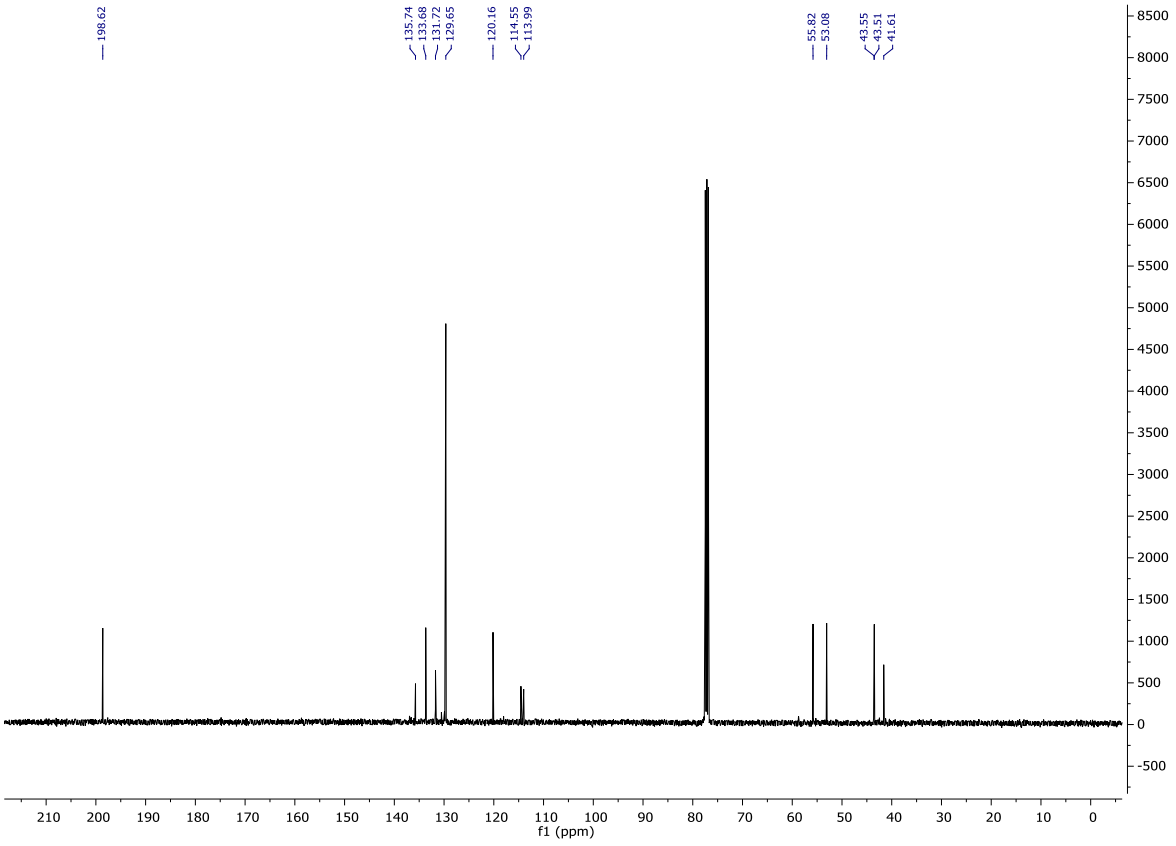
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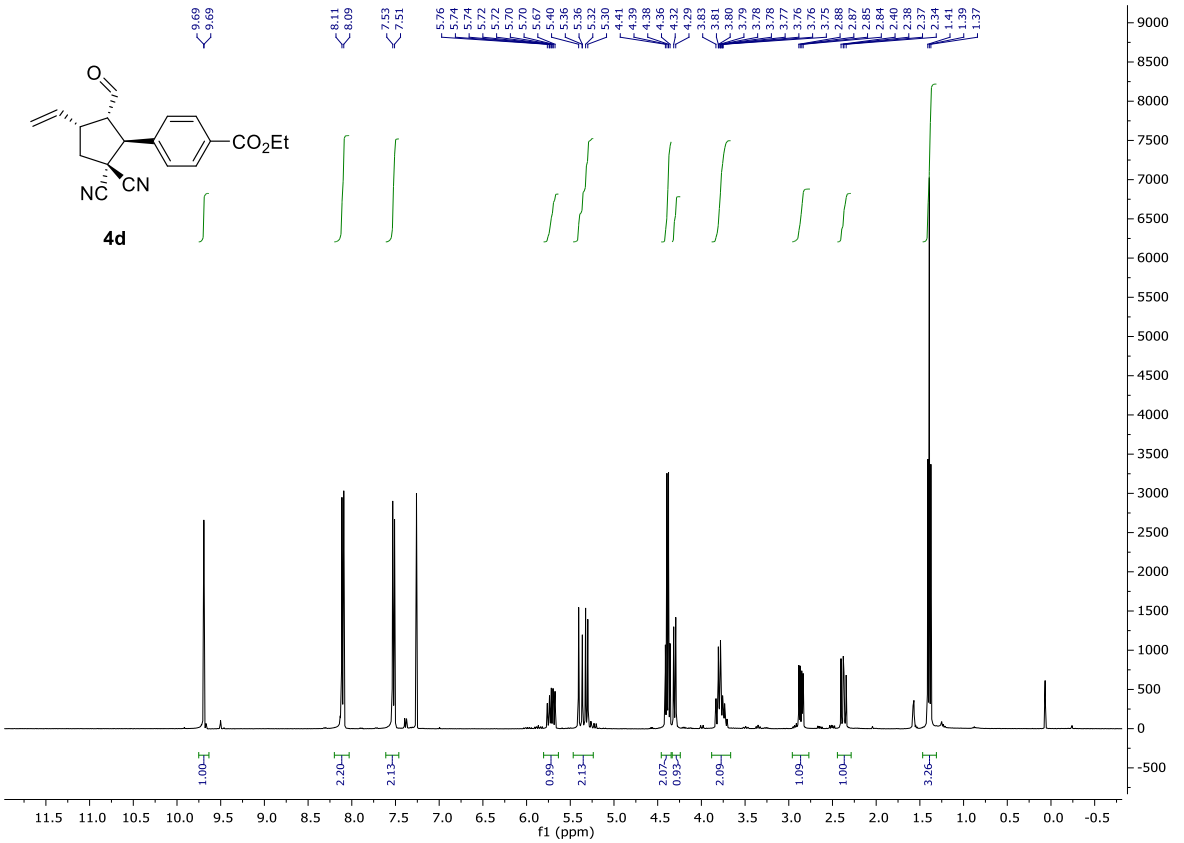
f1 (ppm)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5.72
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2.37
2.34
1.41
1.39
1.37
O
CO2Et
NC
CN
4d
1.00
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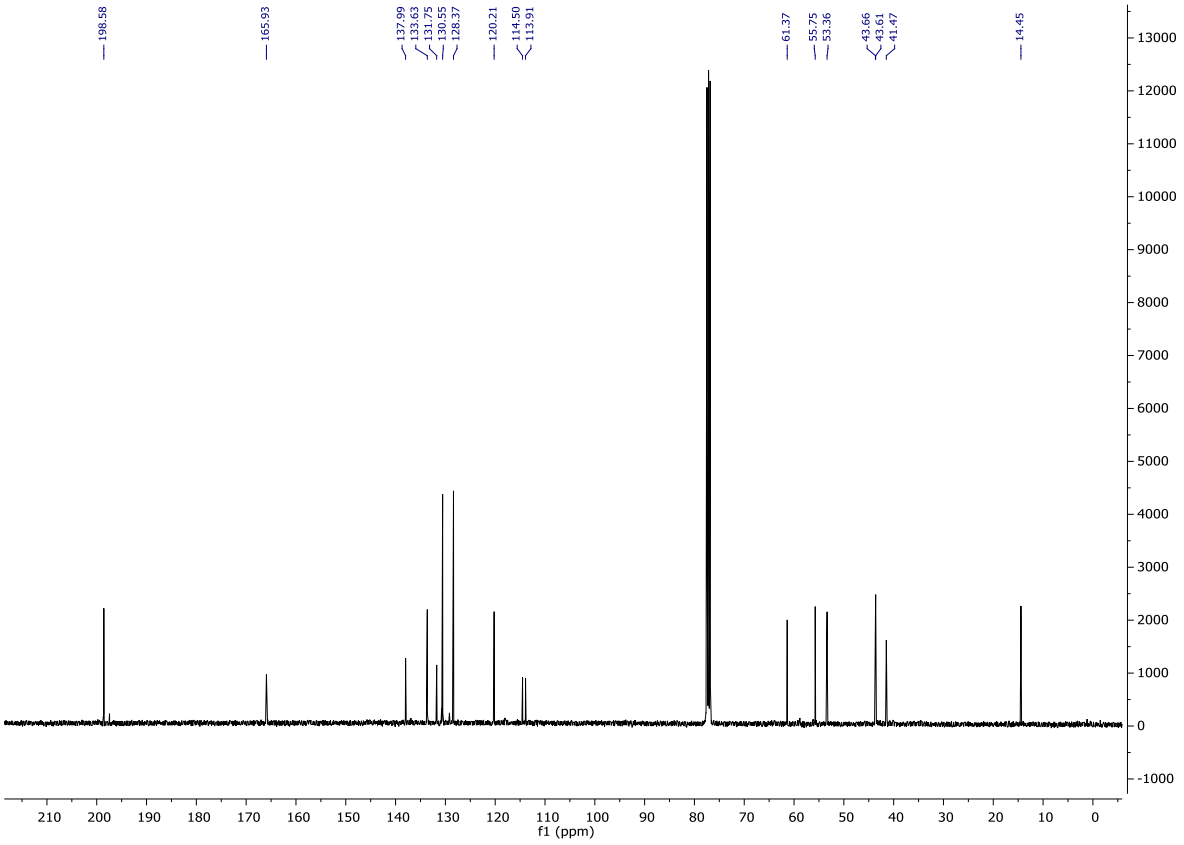
2.13
0.99
2.13
2.07
0.93
2.09
1.09
1.00
3.26
f1 (ppm)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131.75
130.55
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55.75
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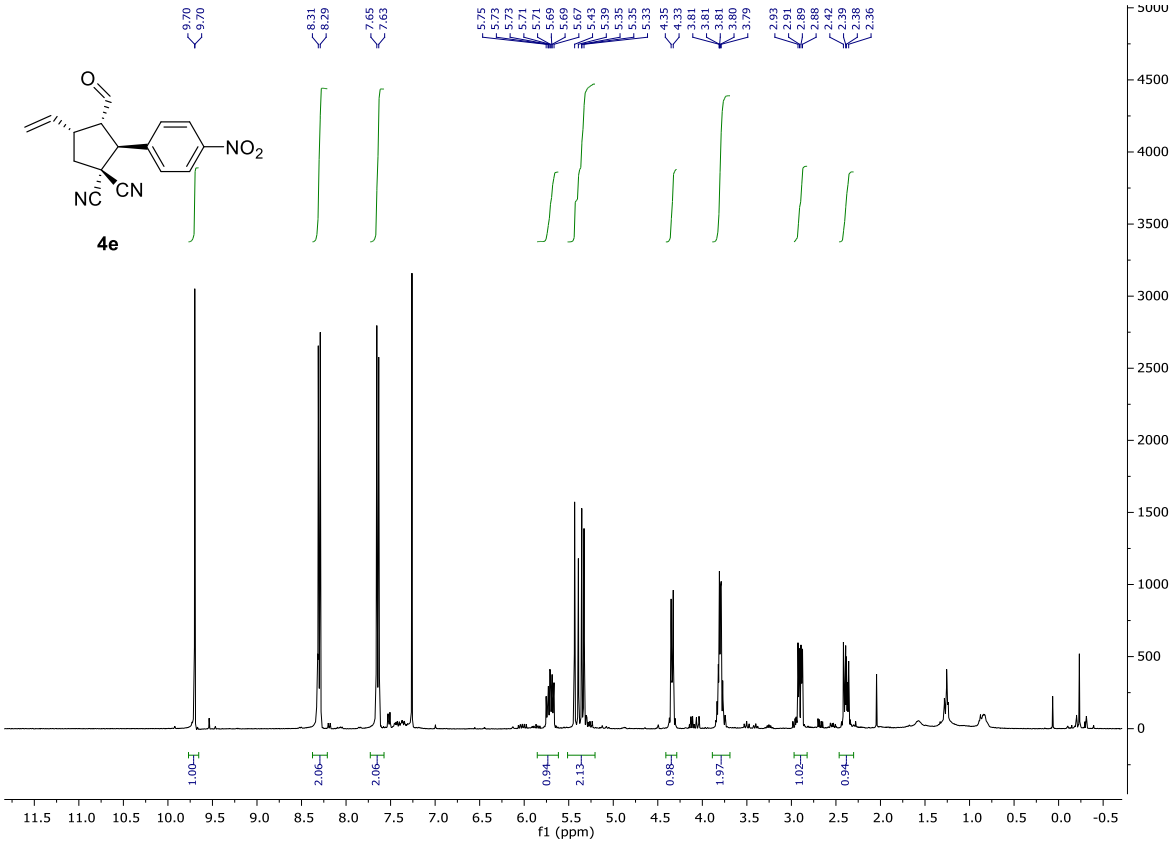
43.66
43.61
41.47
14.45
f1 (ppm)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5.73
5.71
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2.42
2.39
2.38
2.36
O
NO2
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CN
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2.06
0.94
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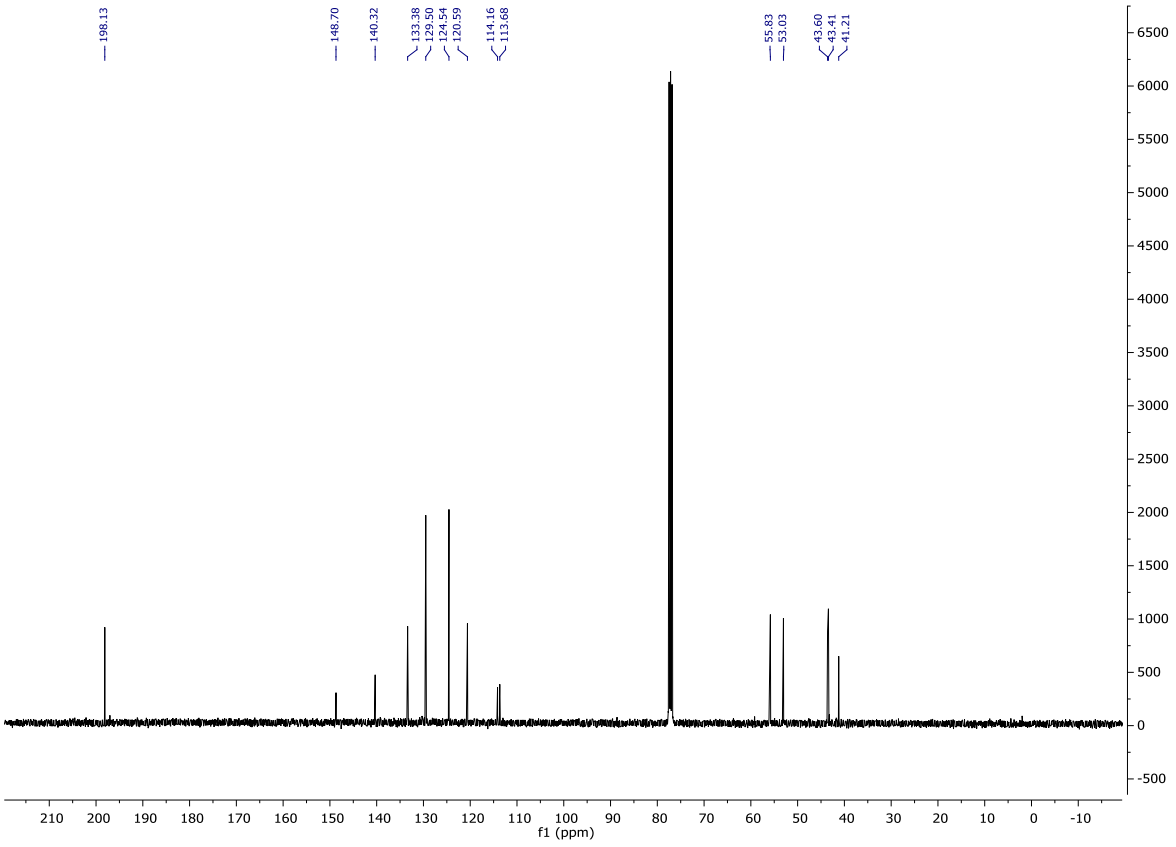
1.97
1.02
0.94
f1 (ppm)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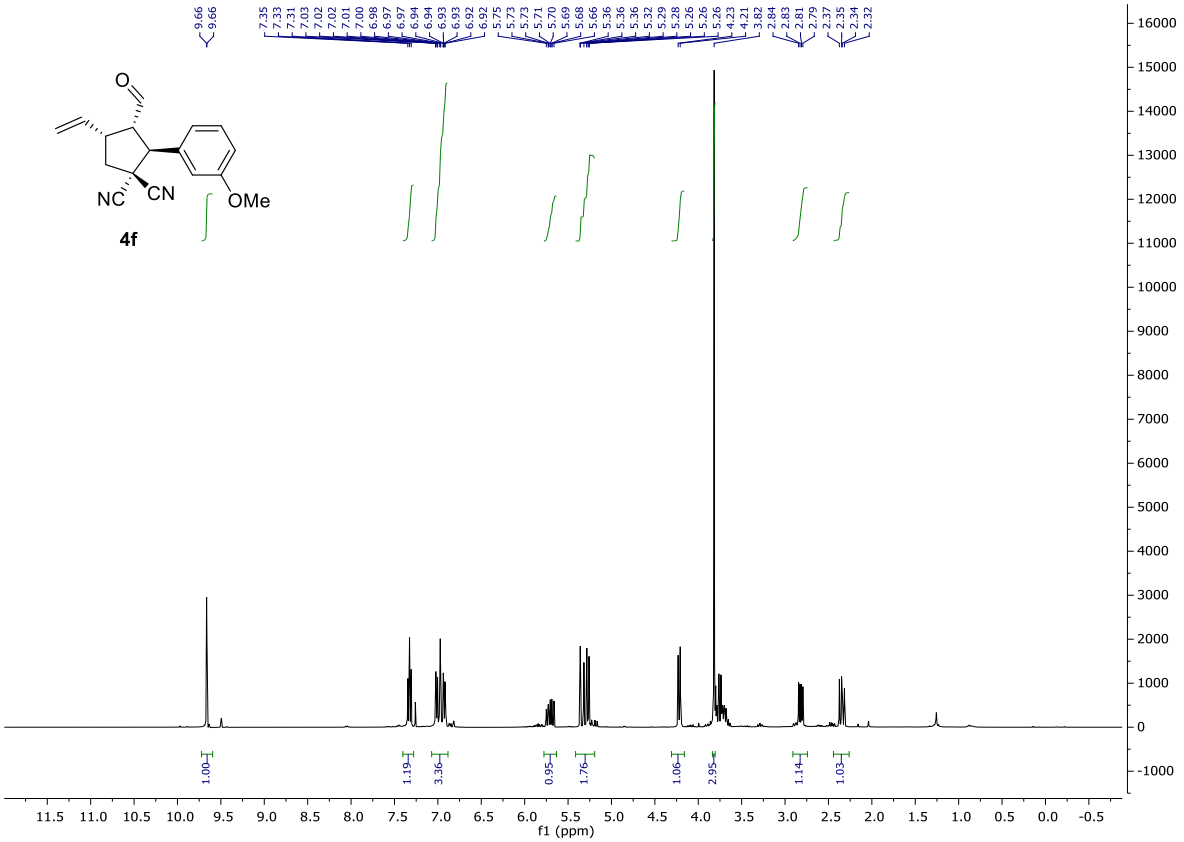
41.21
f1 (ppm)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5.68
5.66
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5.36
5.36
5.32
5.29
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5.26
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NC
CN
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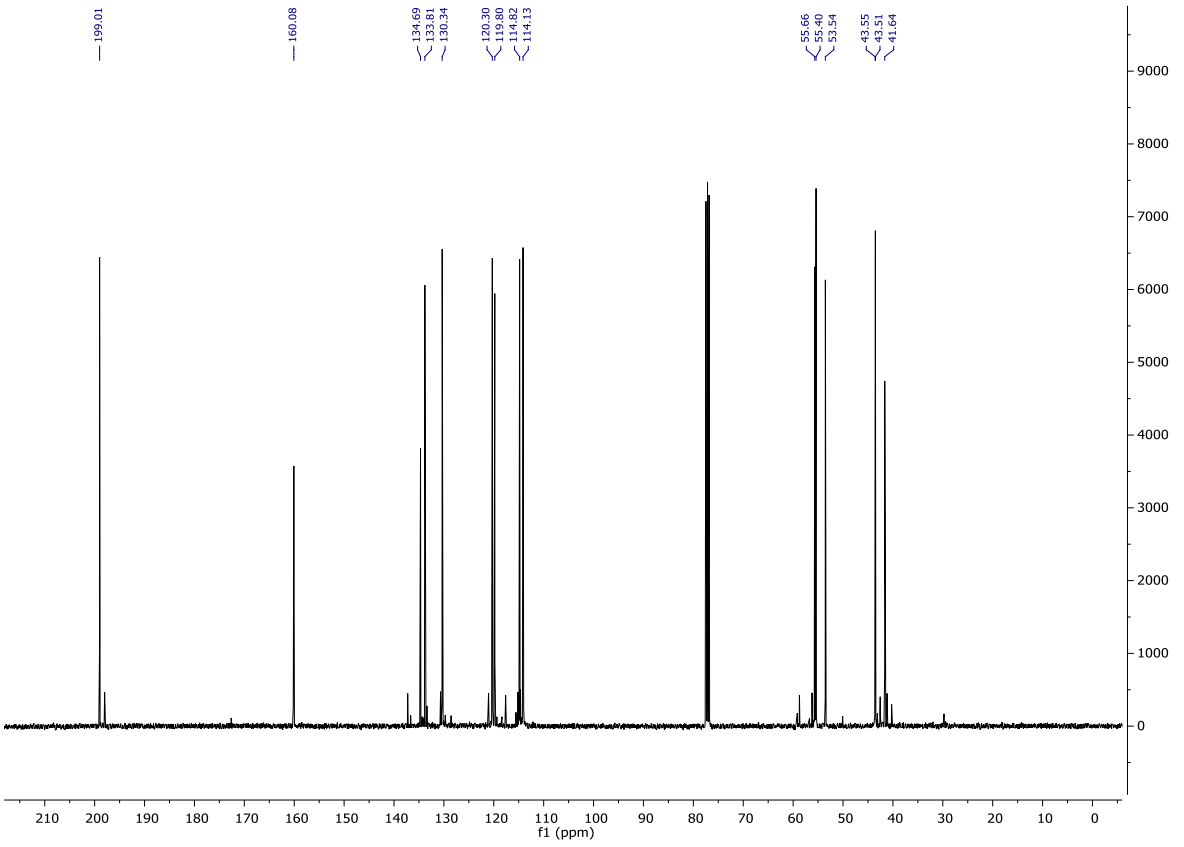
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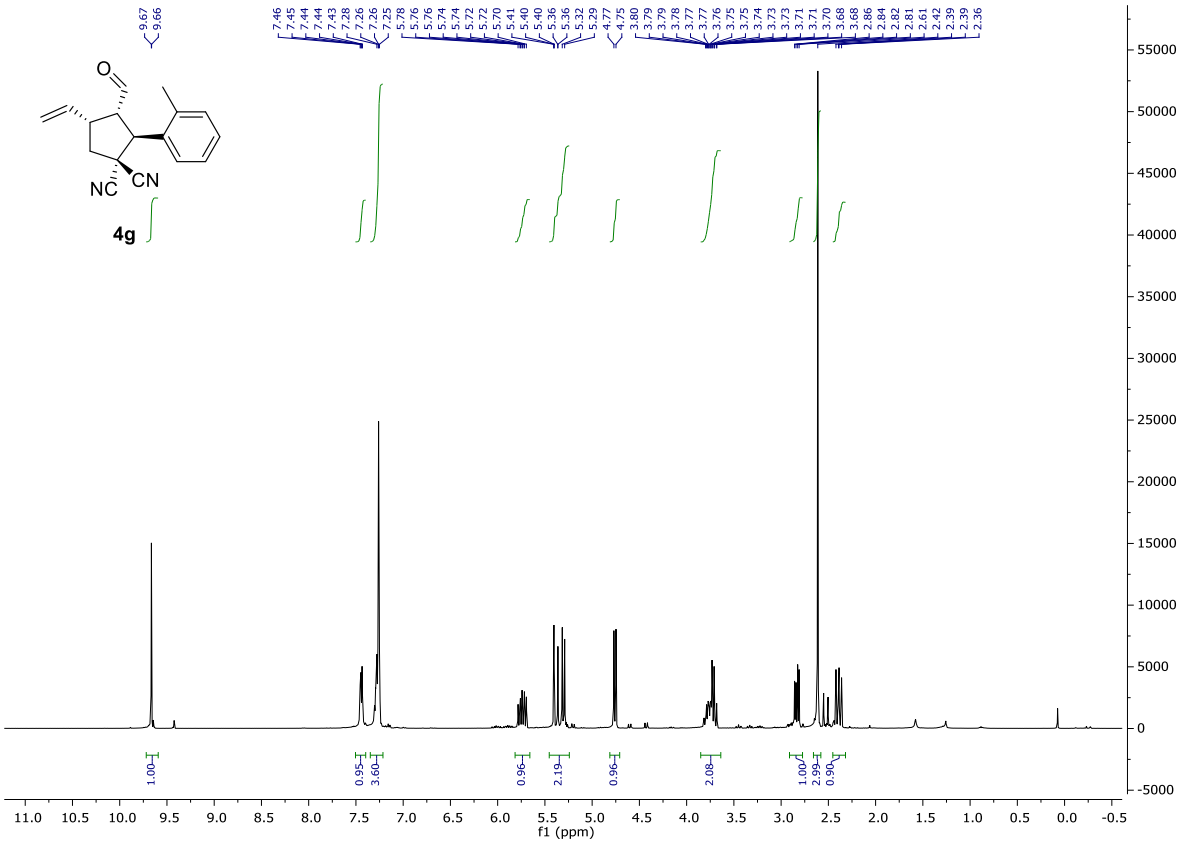
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CN
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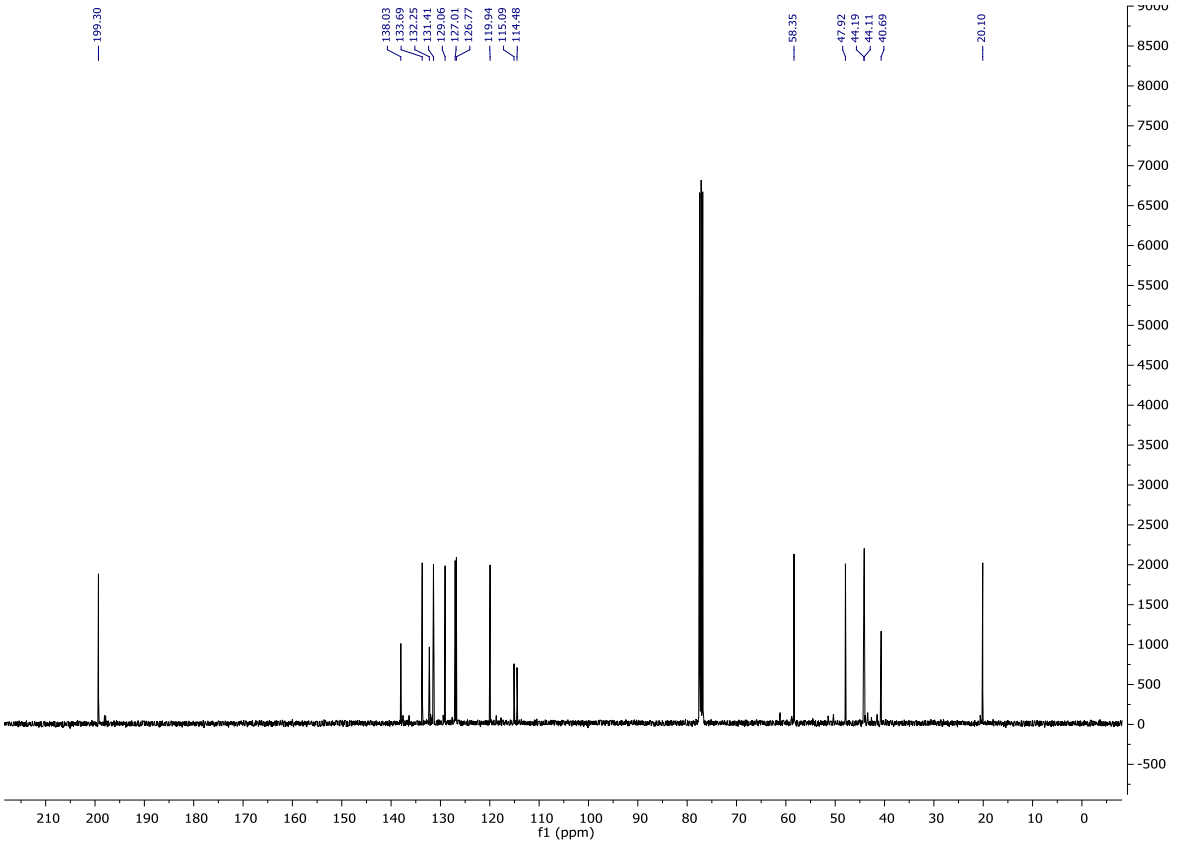
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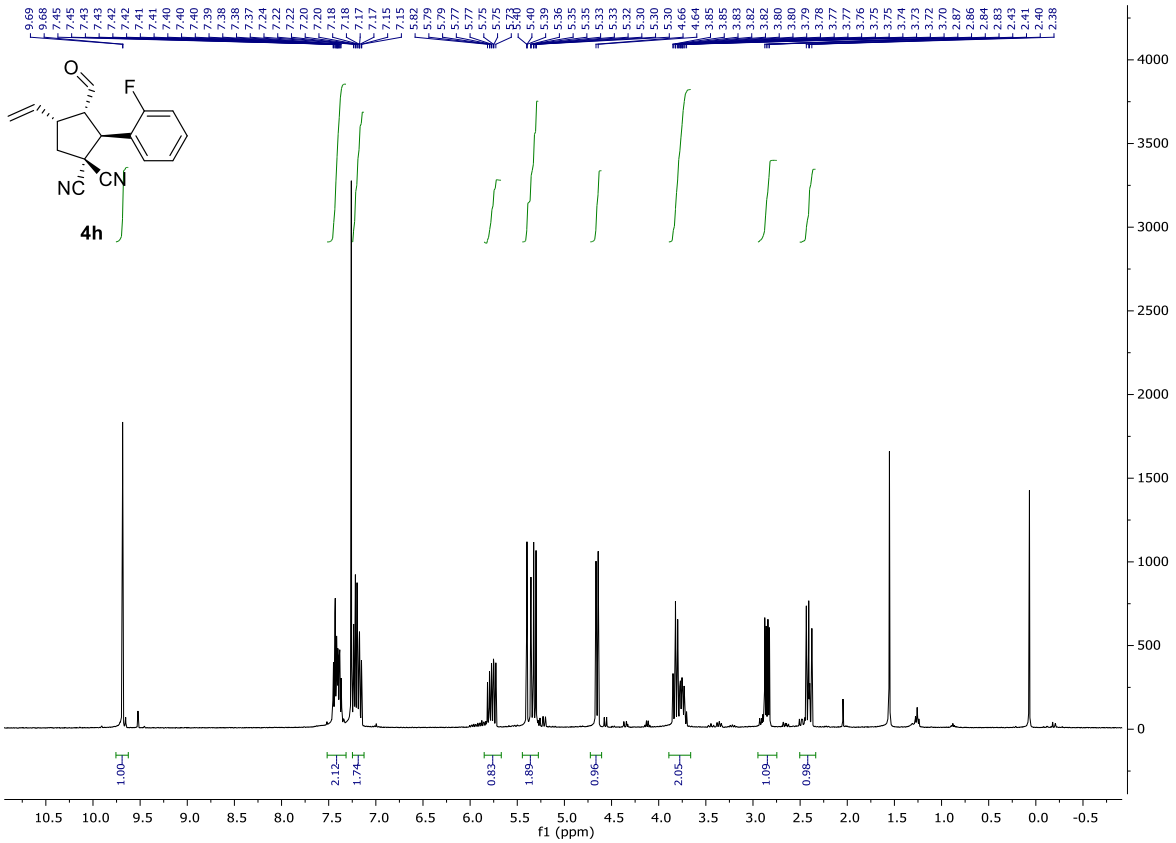
f1 (ppm)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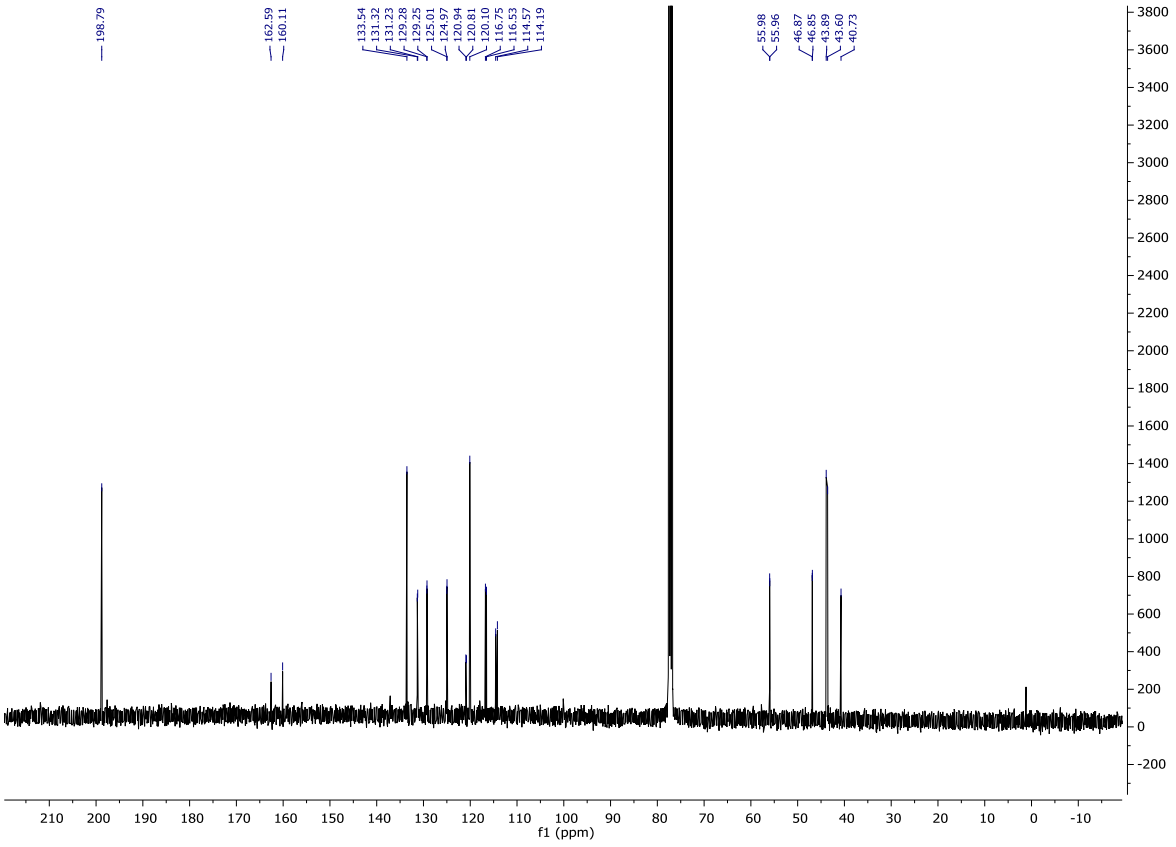
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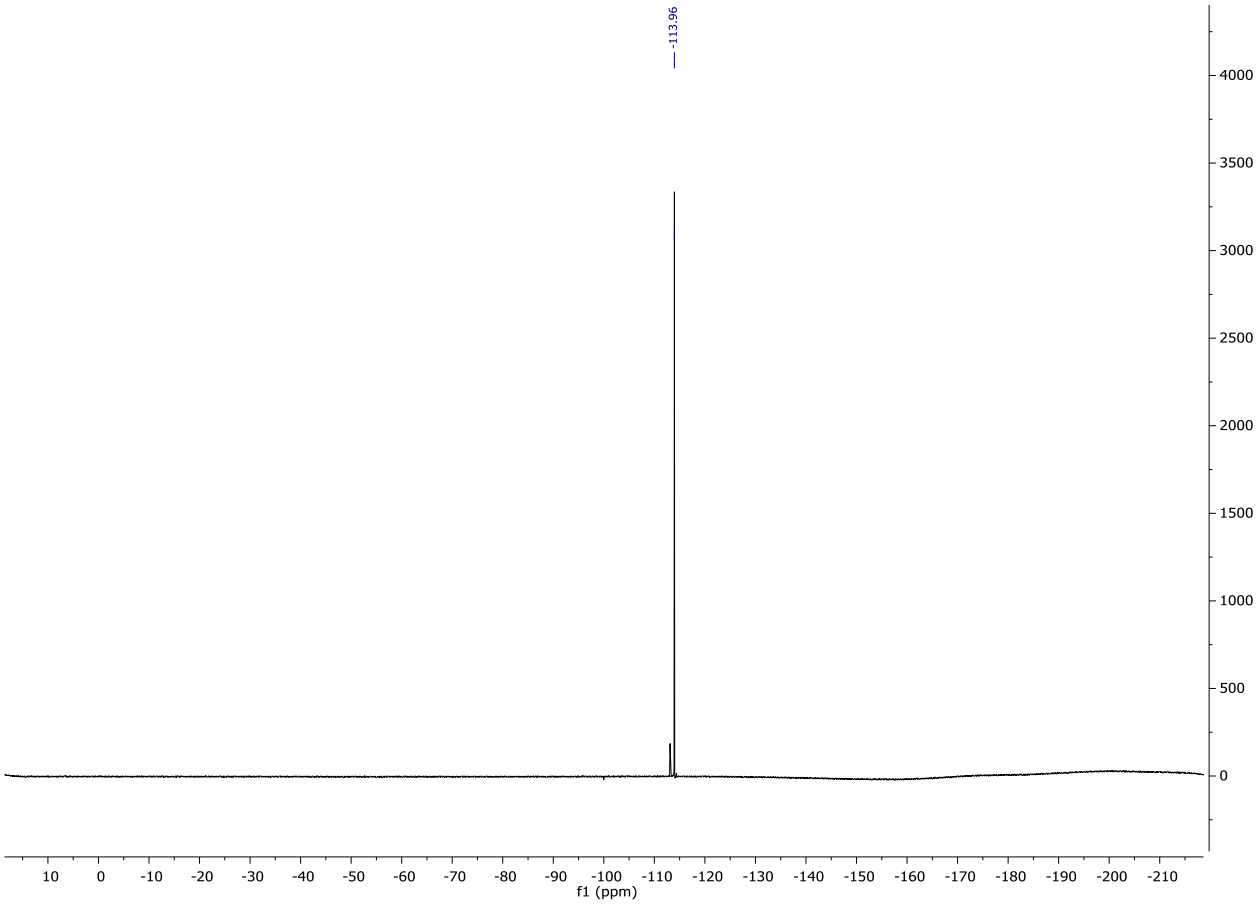
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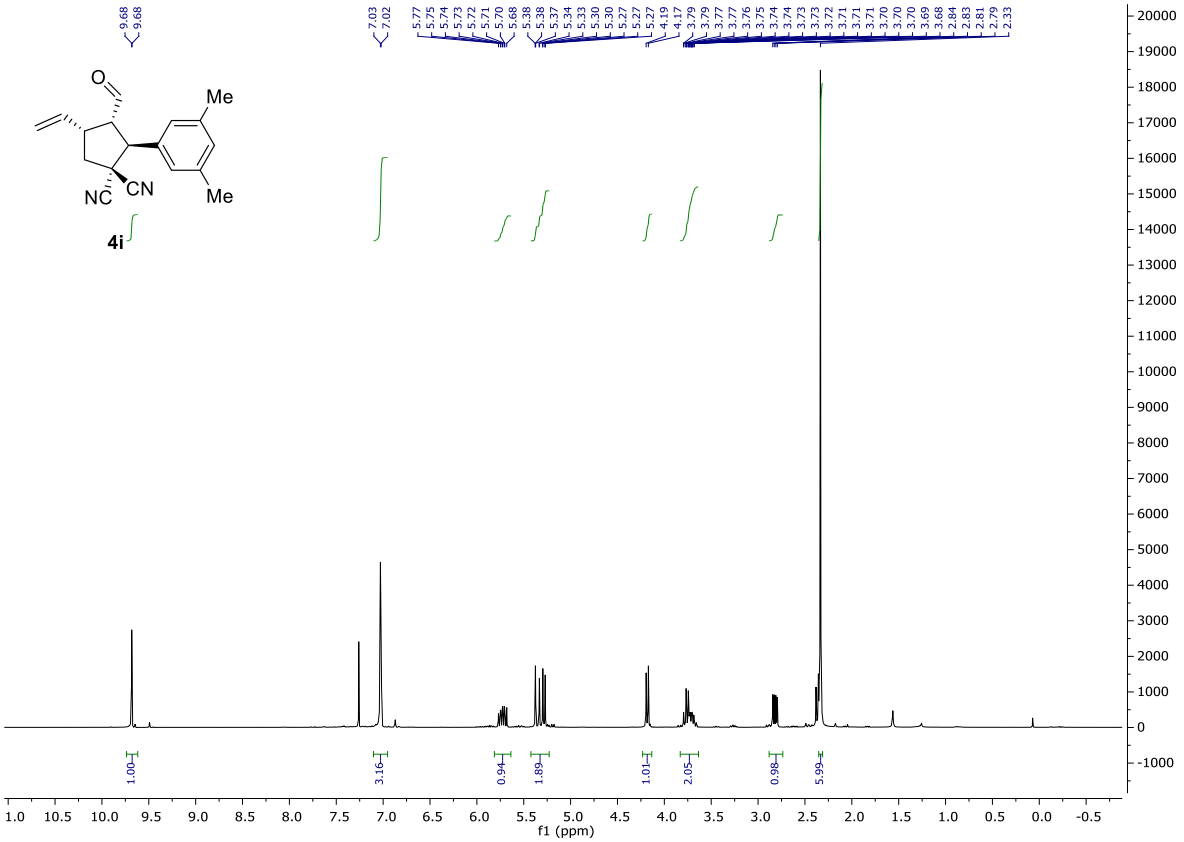
f1 (ppm)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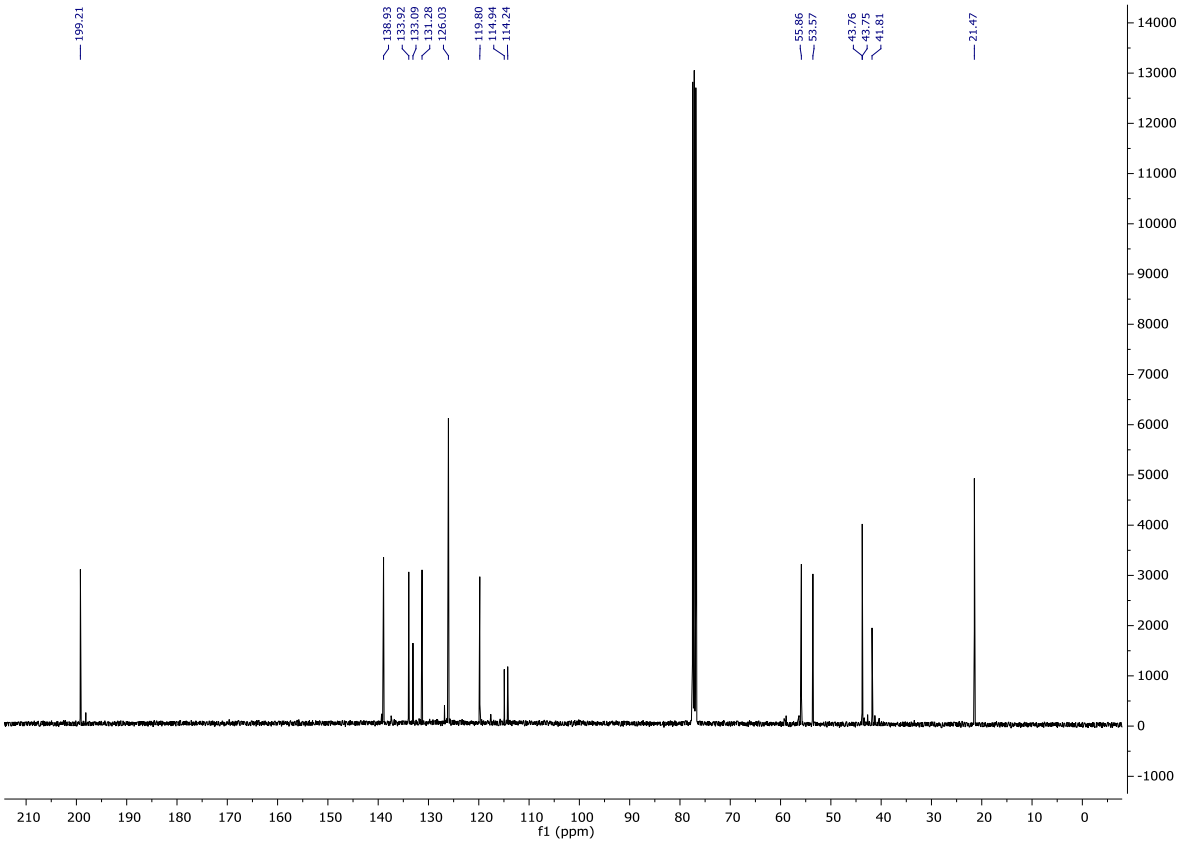
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21.47
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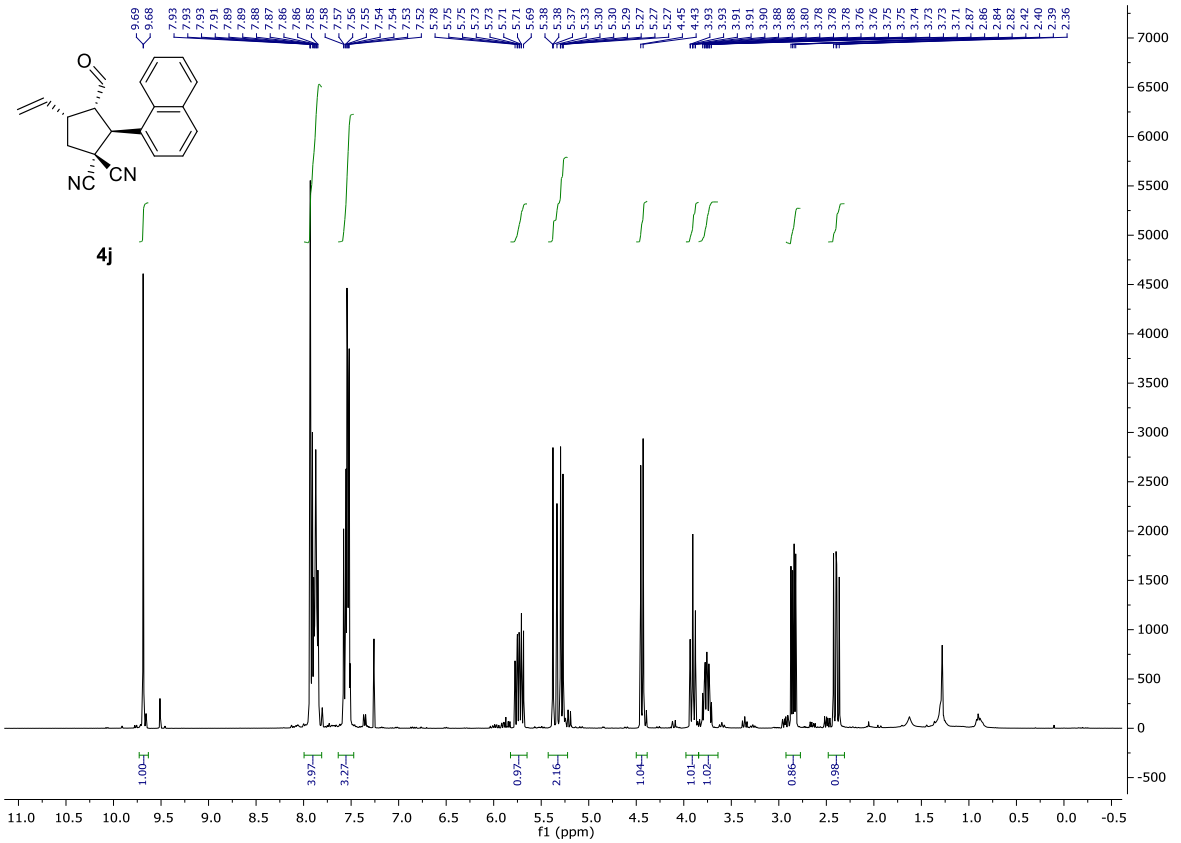
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NC
CN
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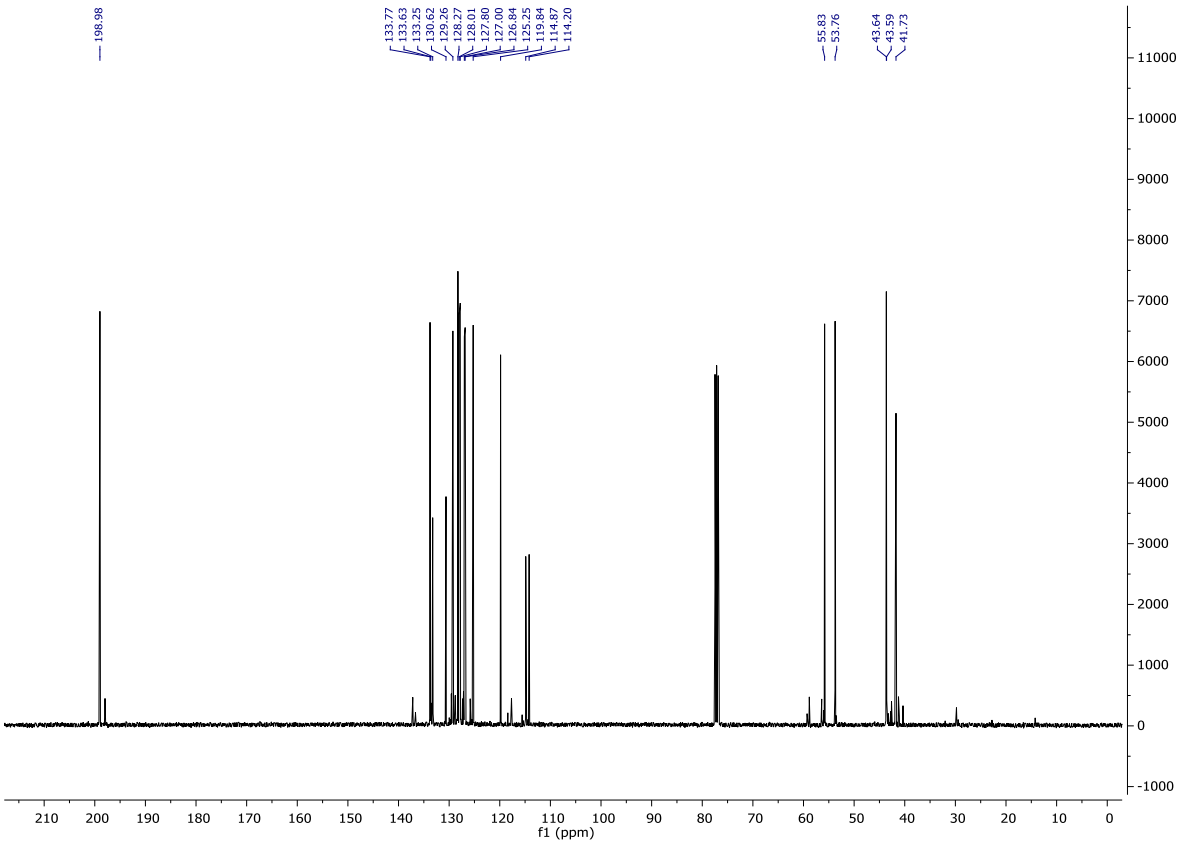
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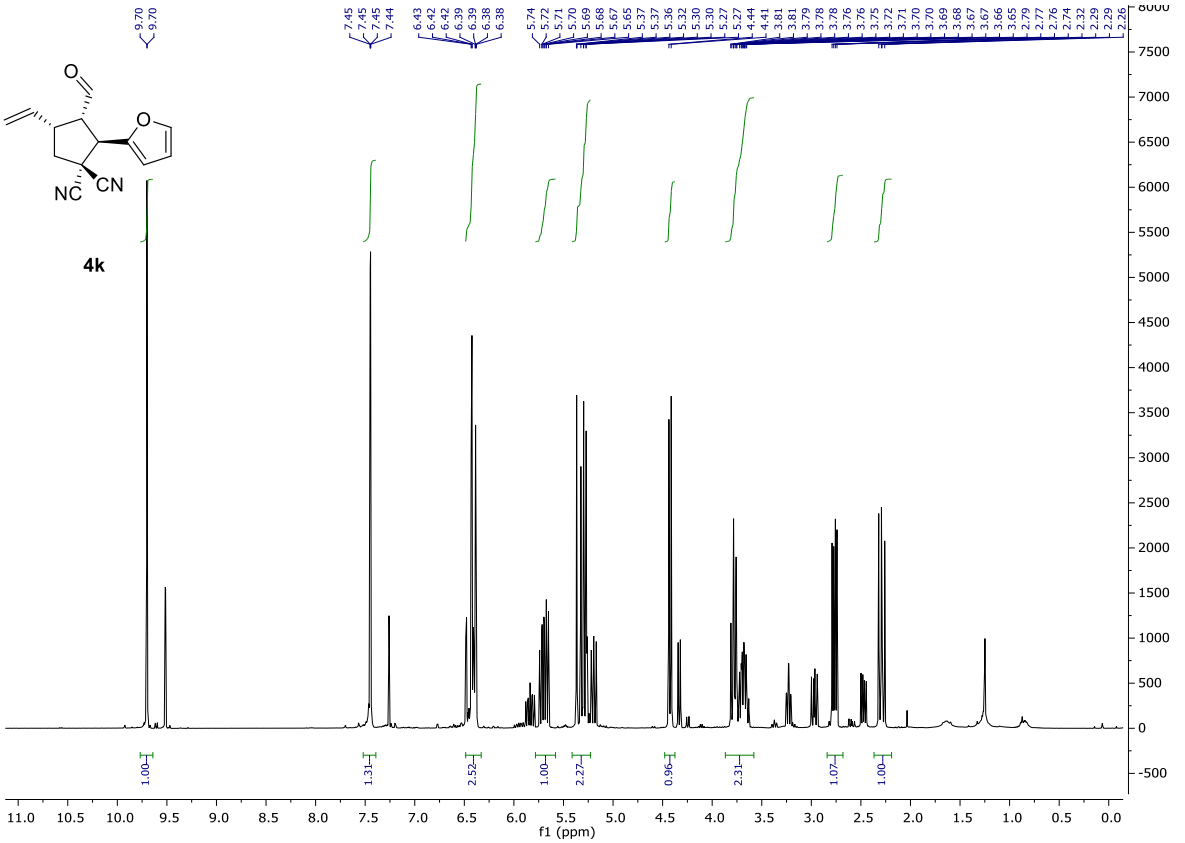
43.59
41.73
f1 (ppm)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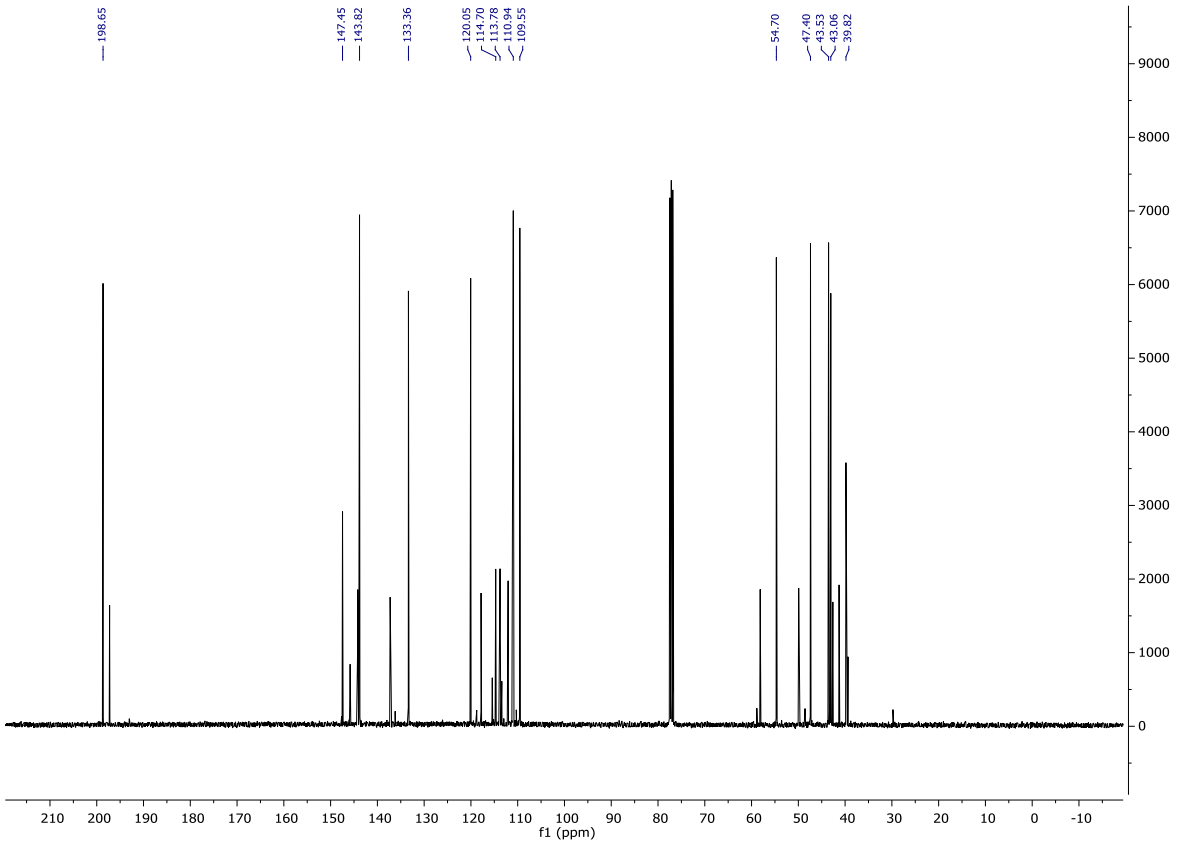
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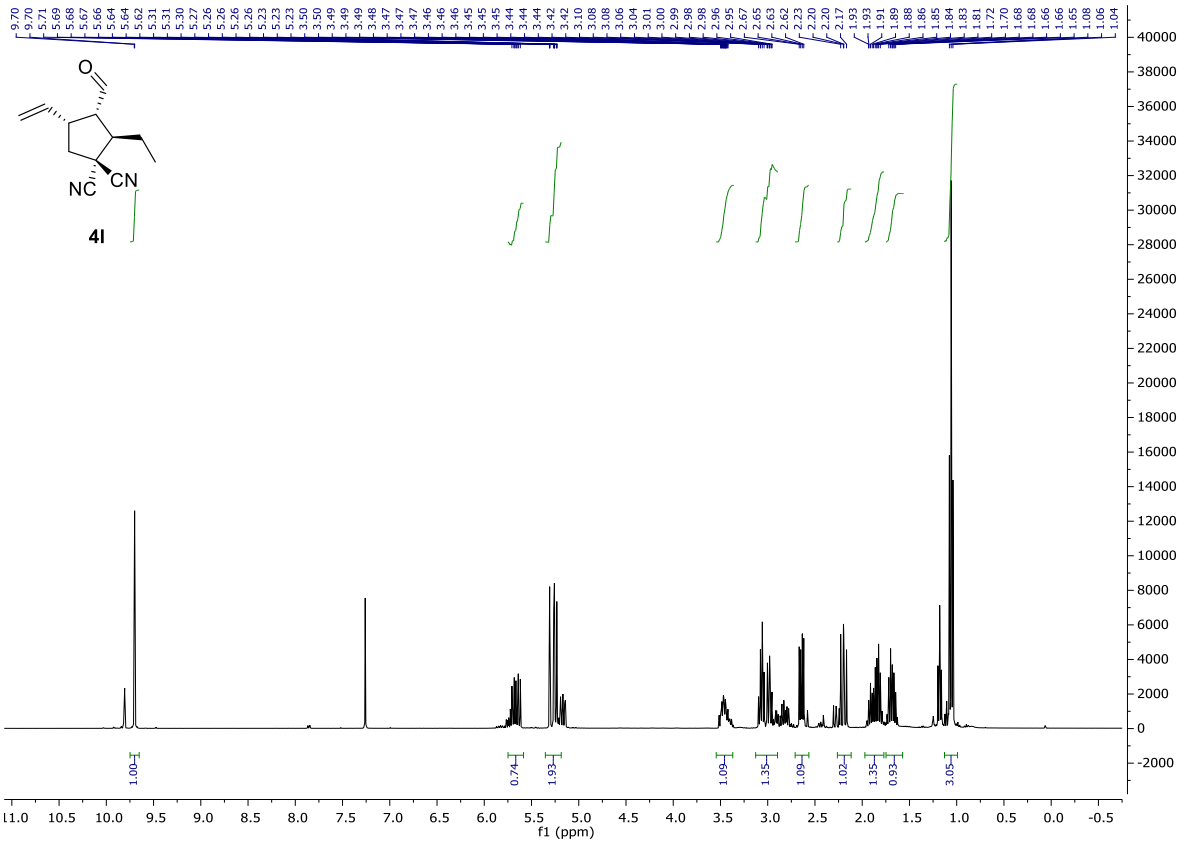
O
NC
CN
4l
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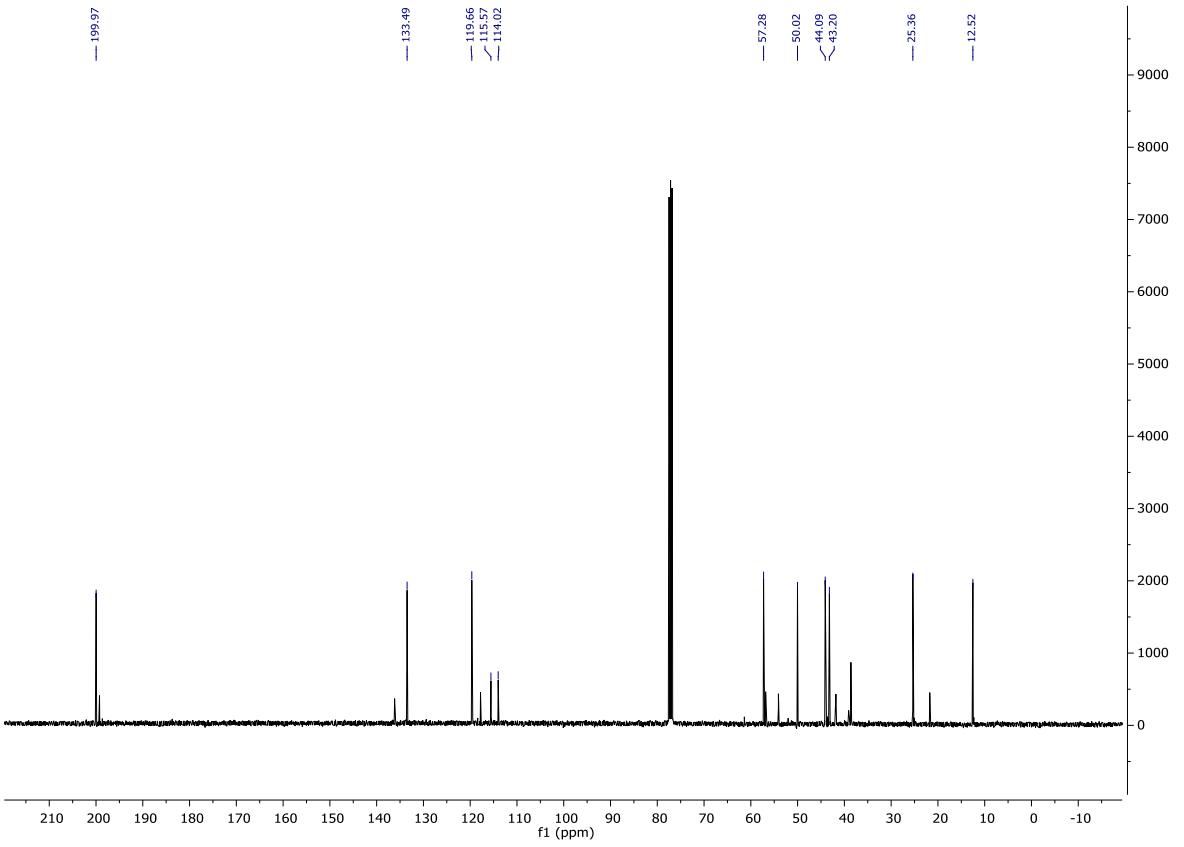
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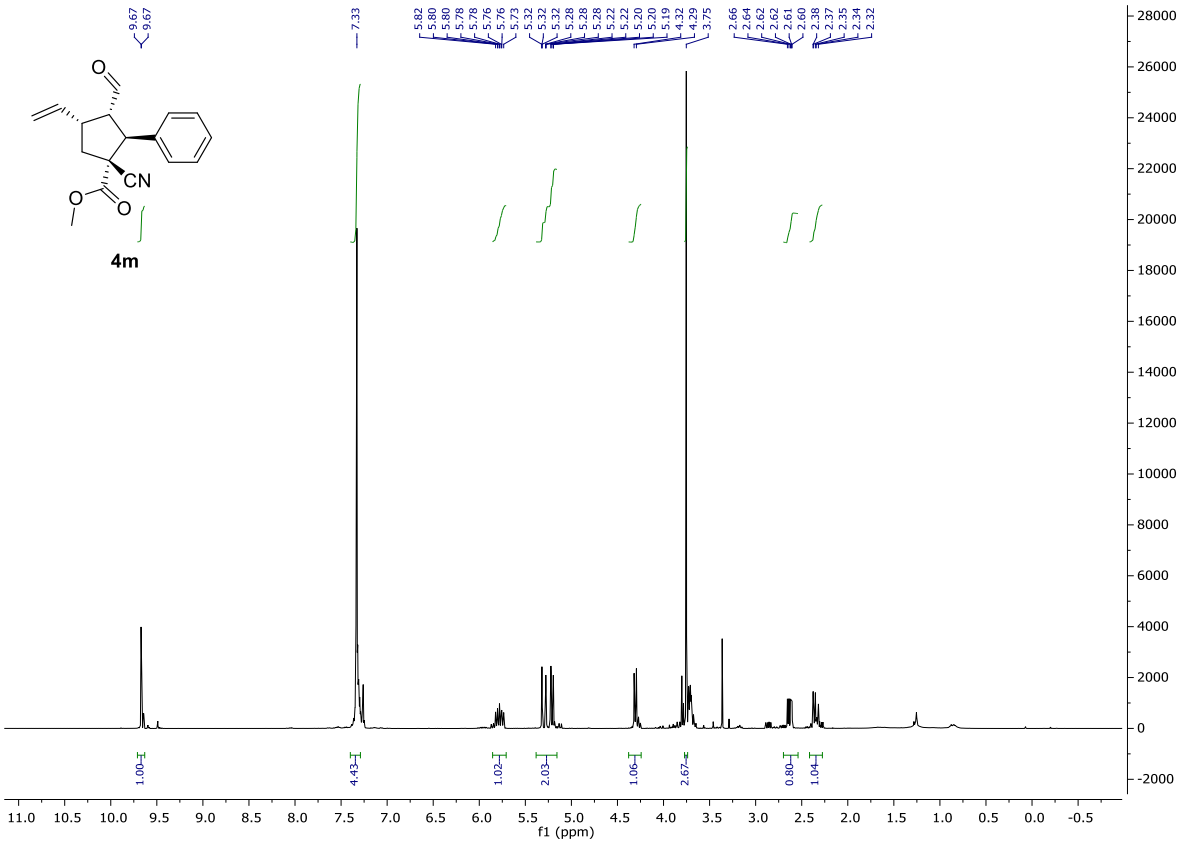
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2.38
2.37
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2.34
2.32
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1.04
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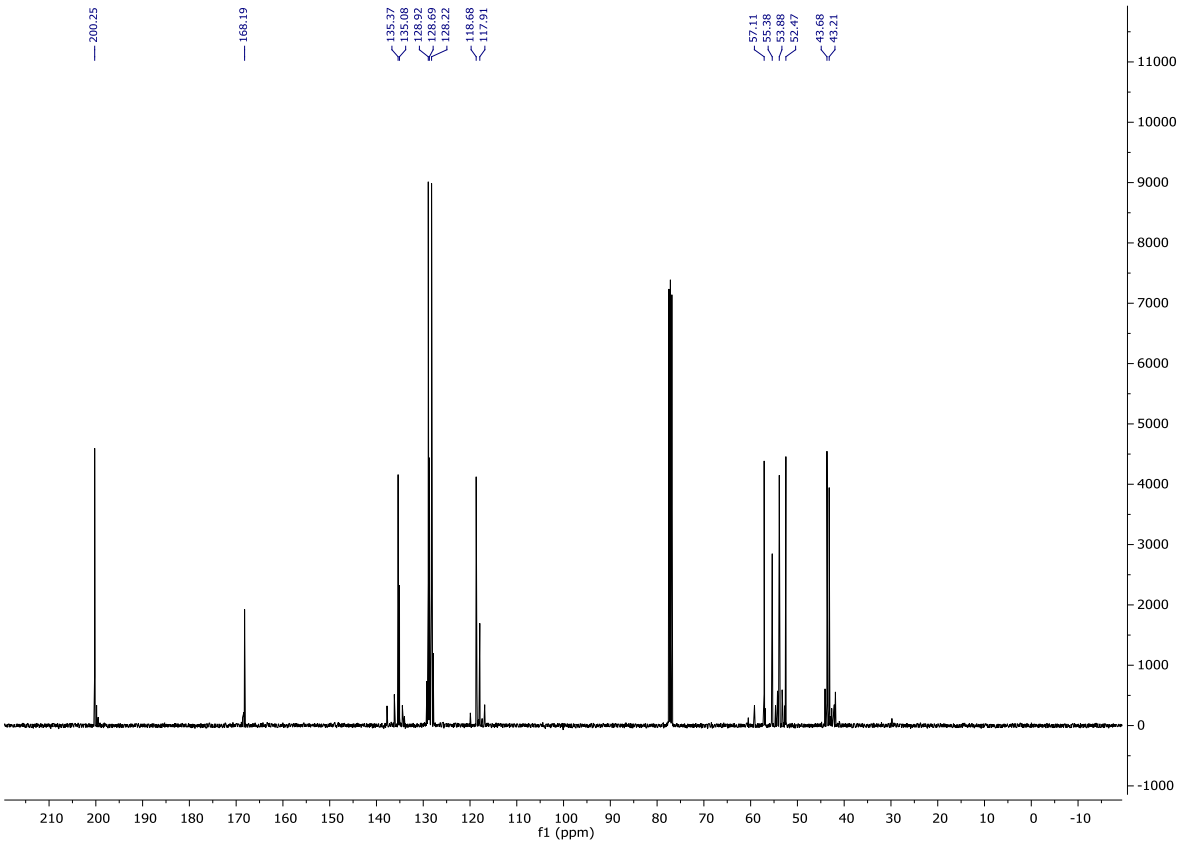
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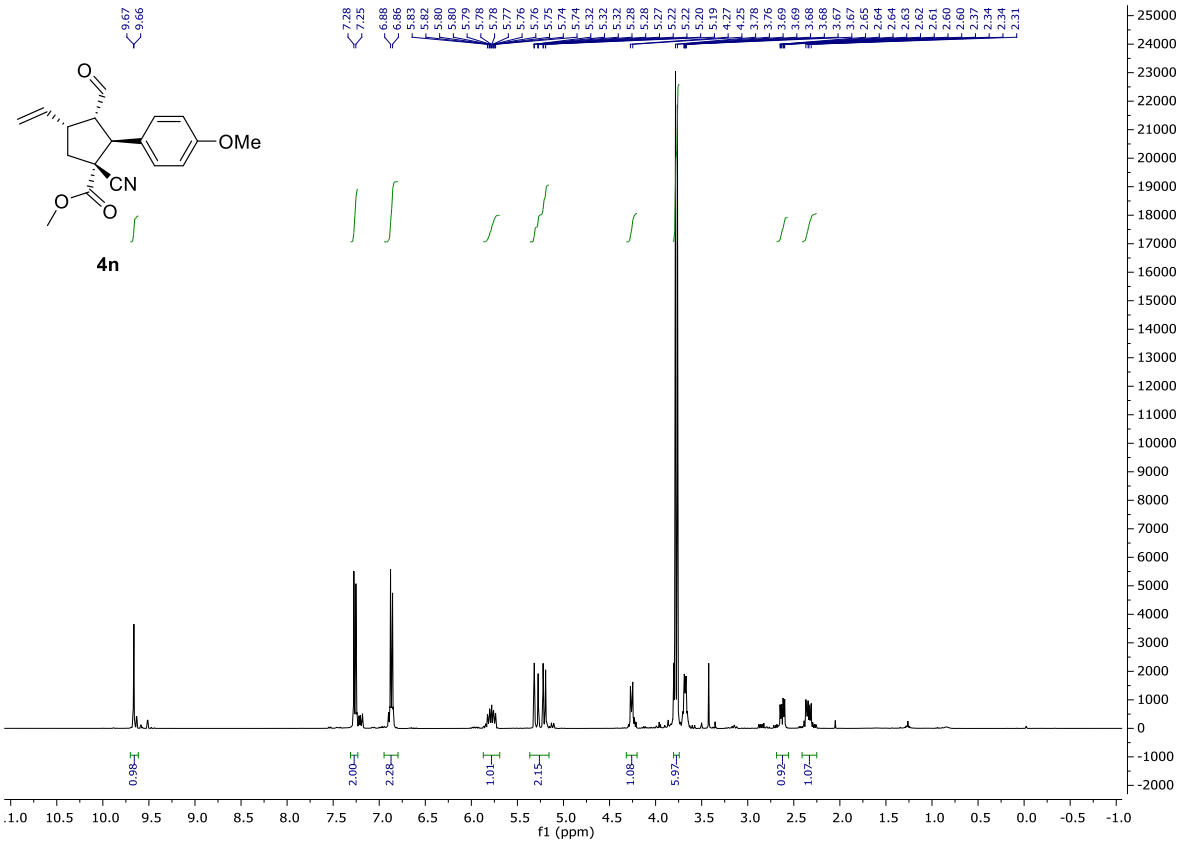
f1 (ppm)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OMe
CN
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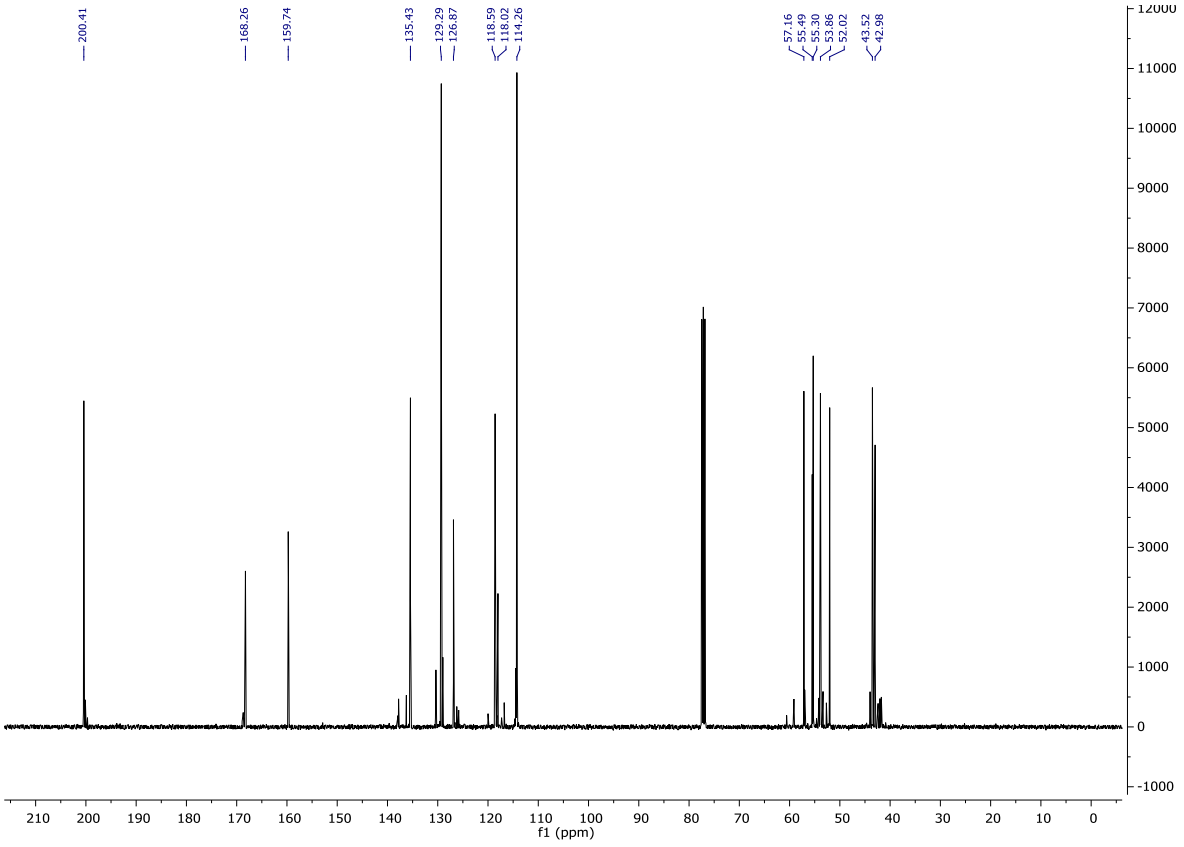
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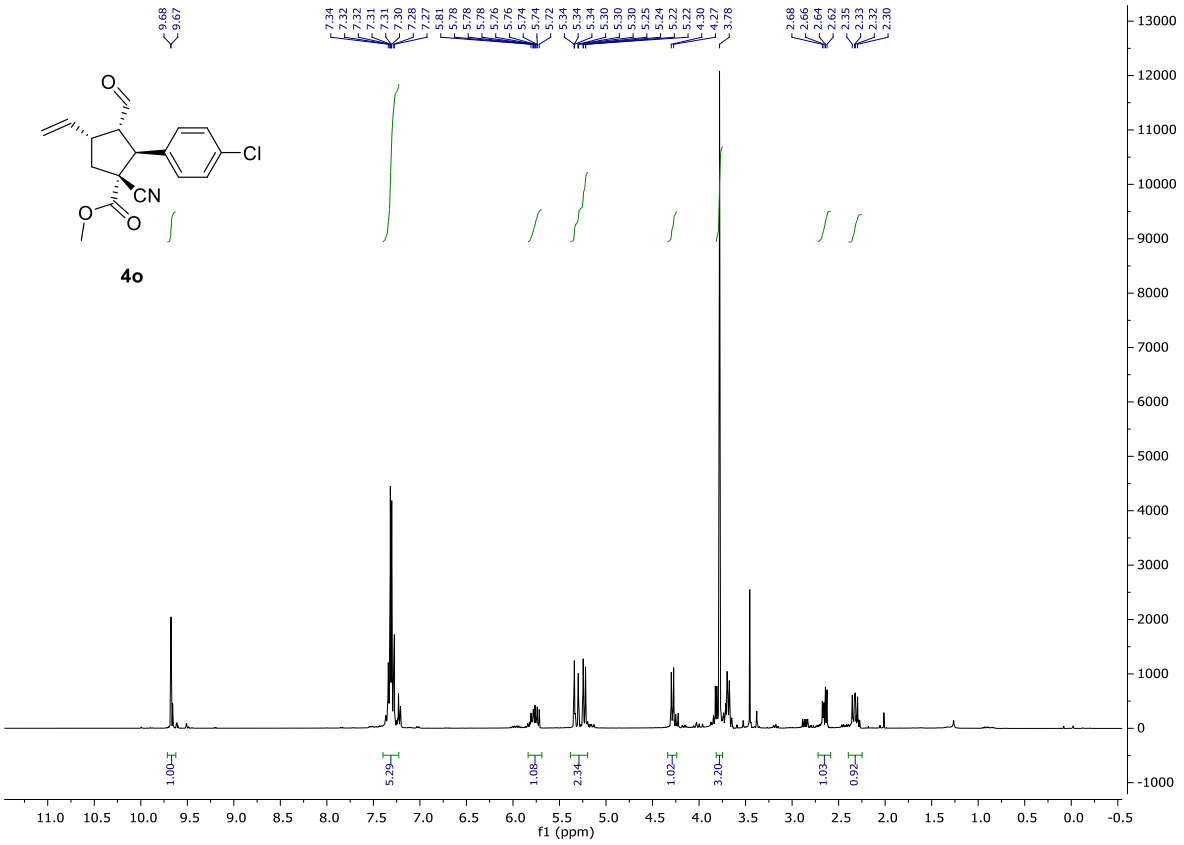
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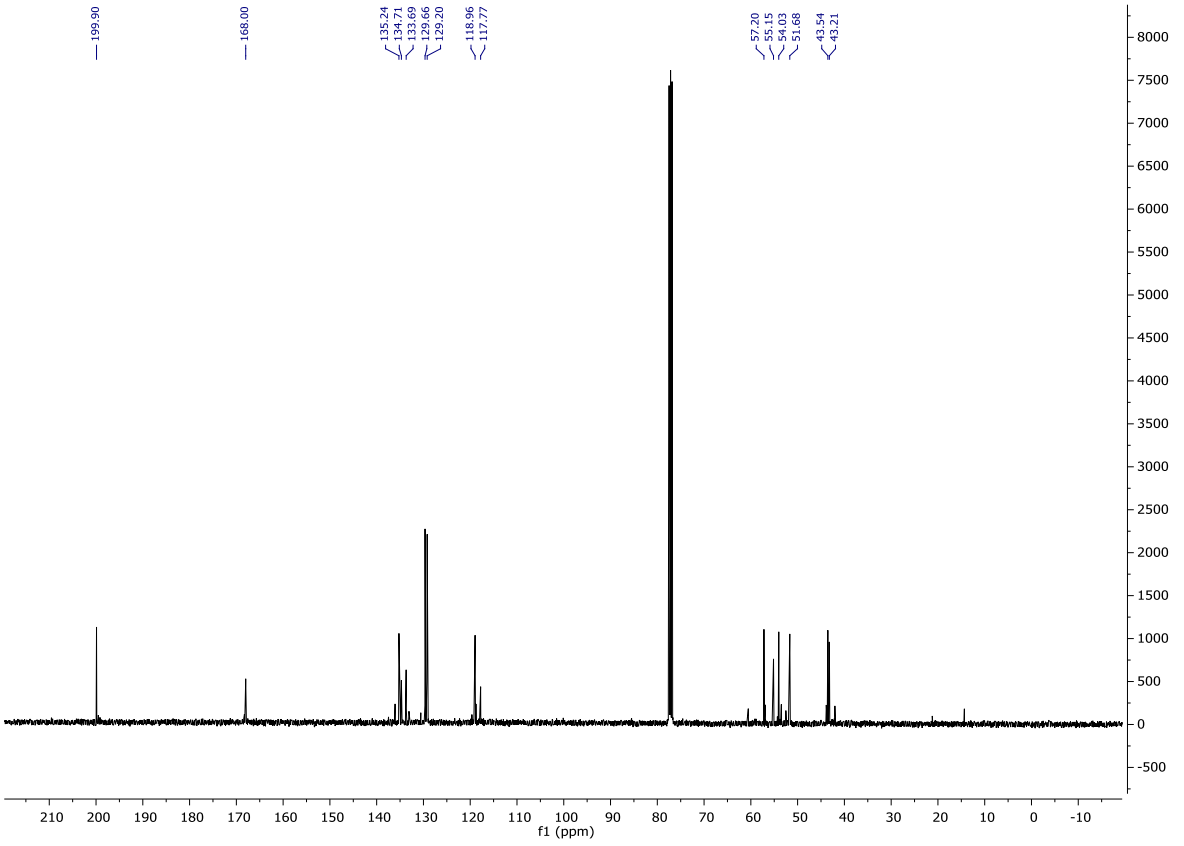
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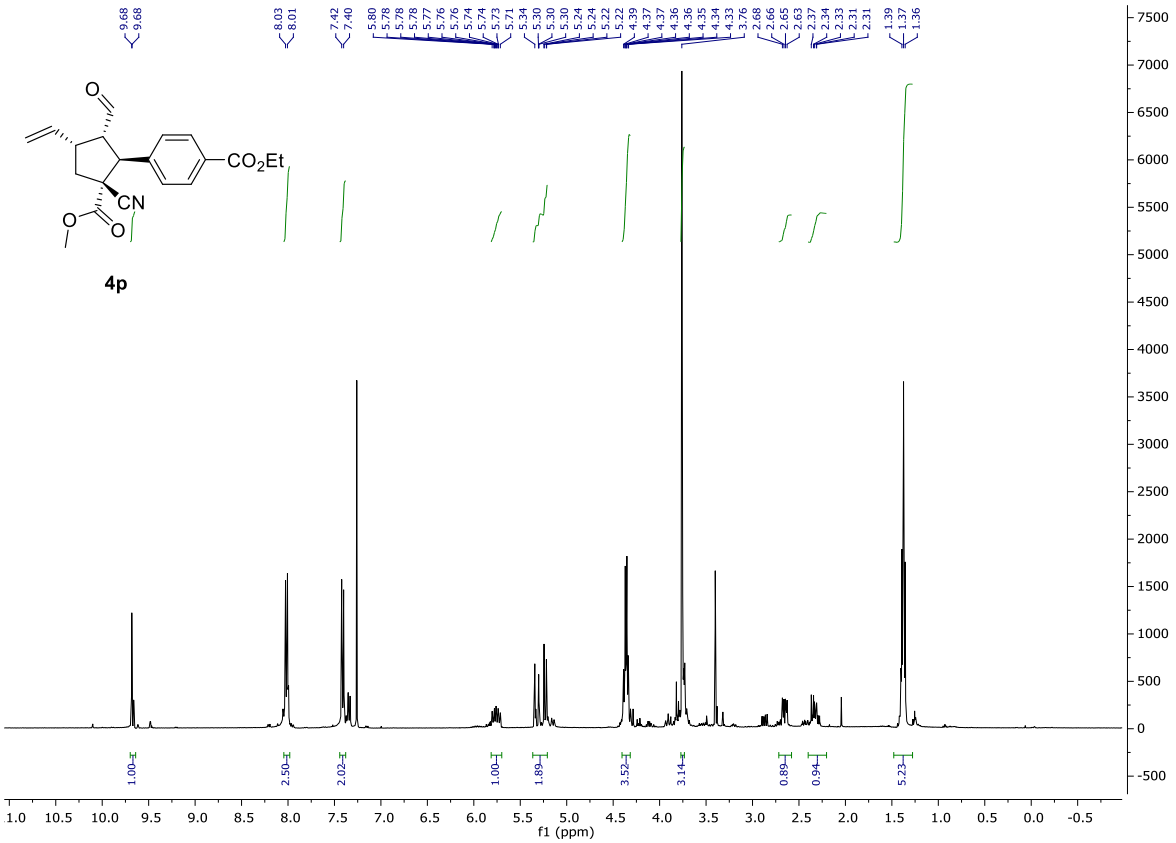
f1 (ppm)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O
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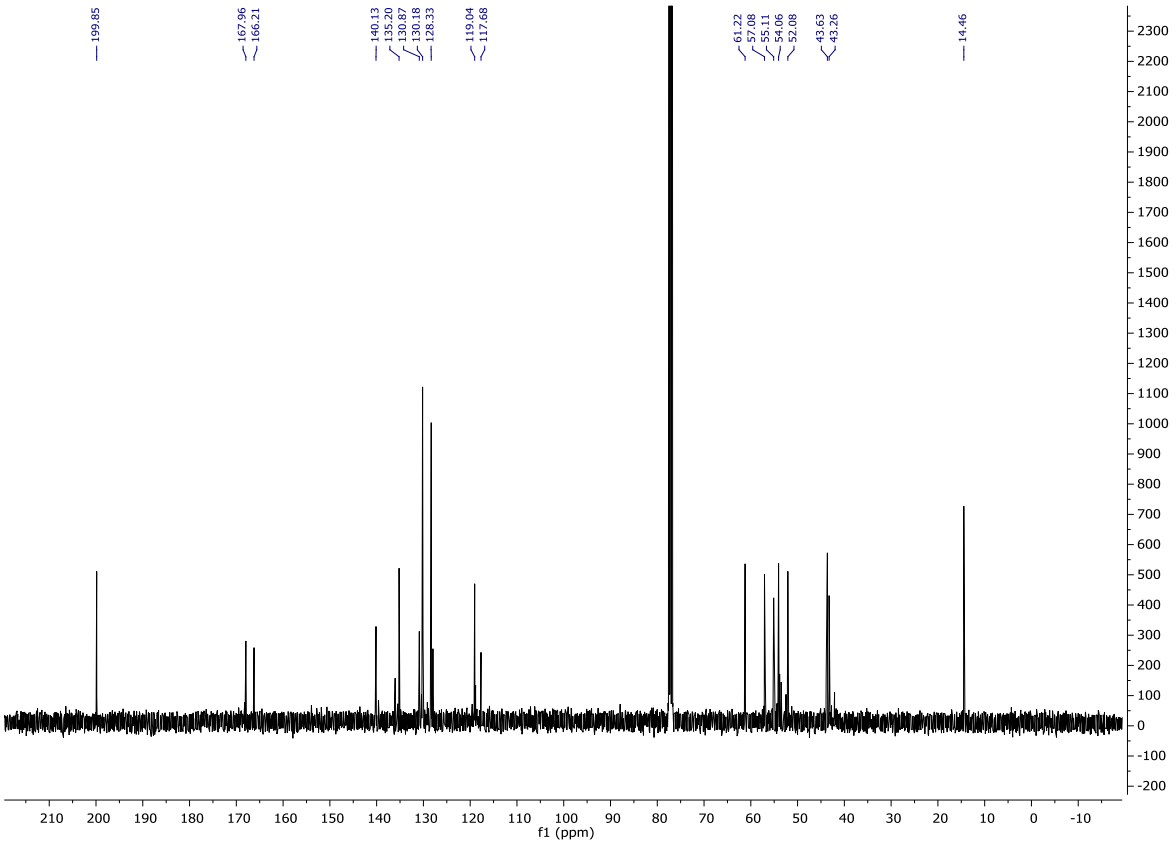
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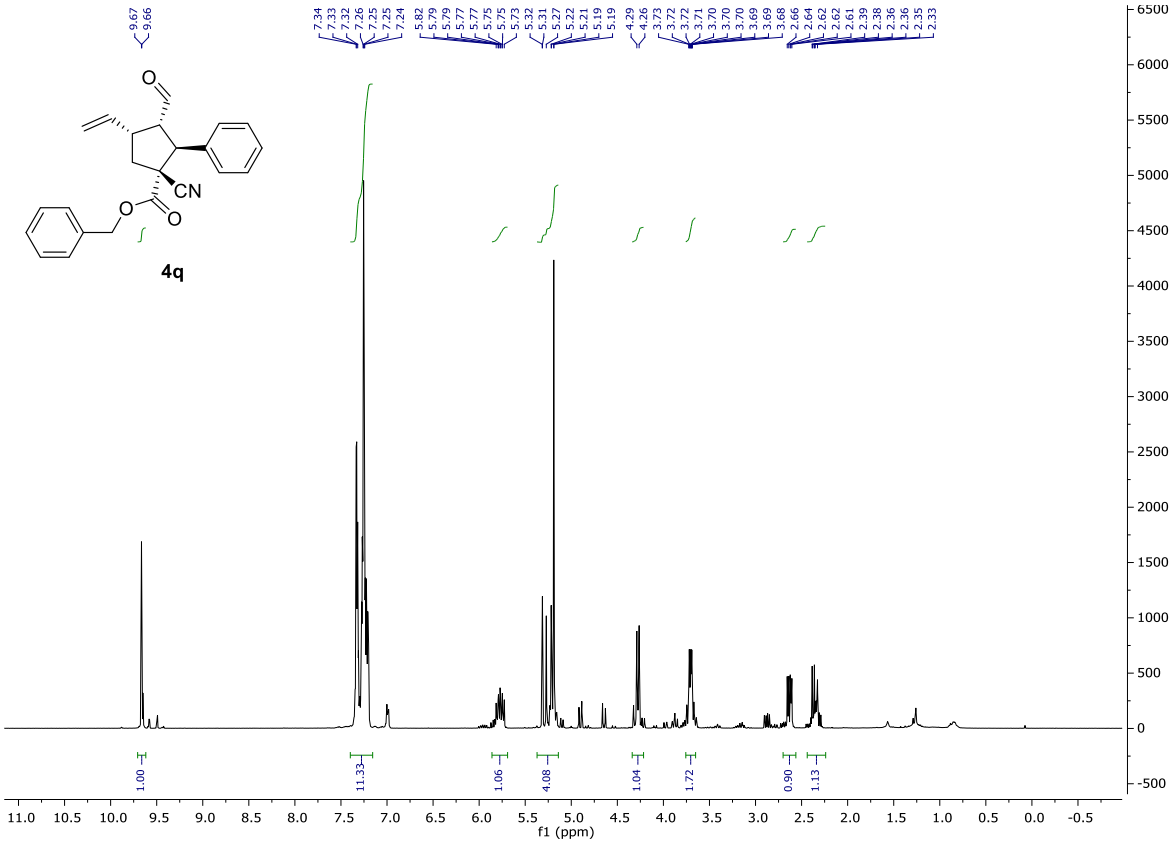
f1 (ppm)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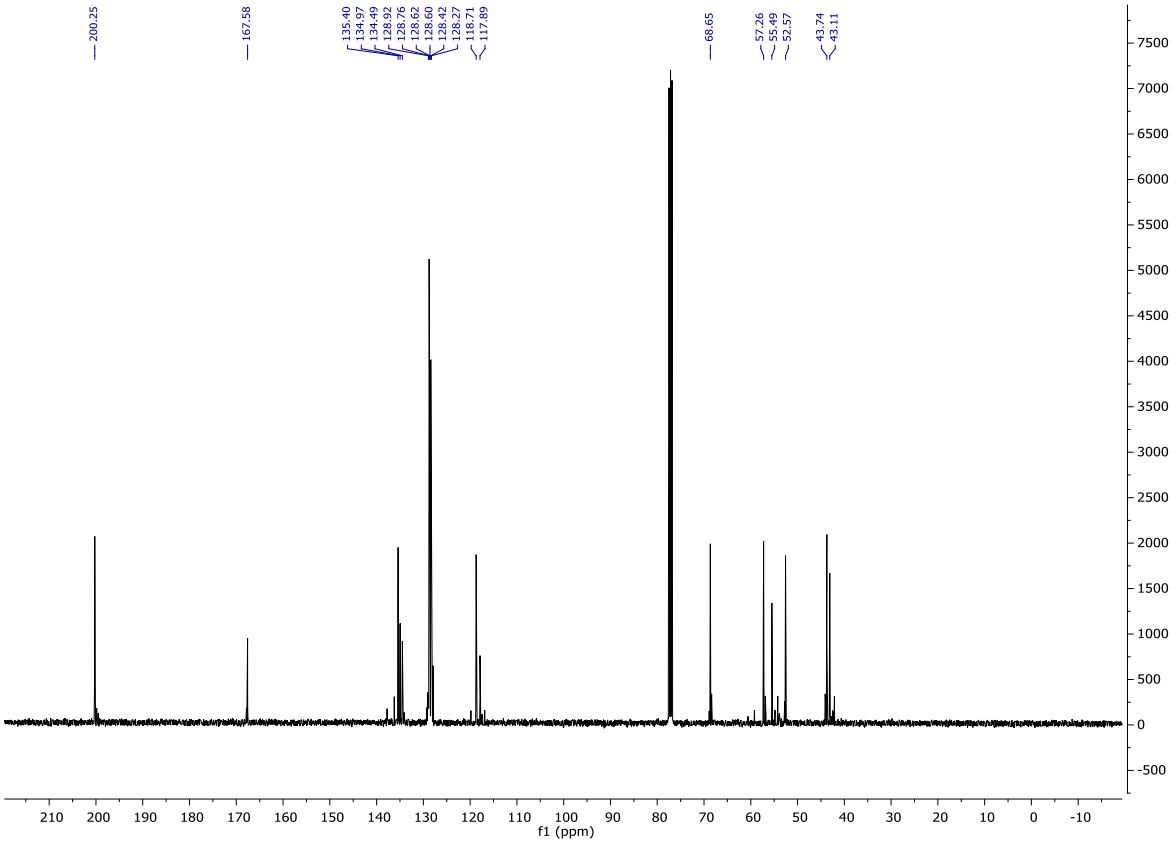
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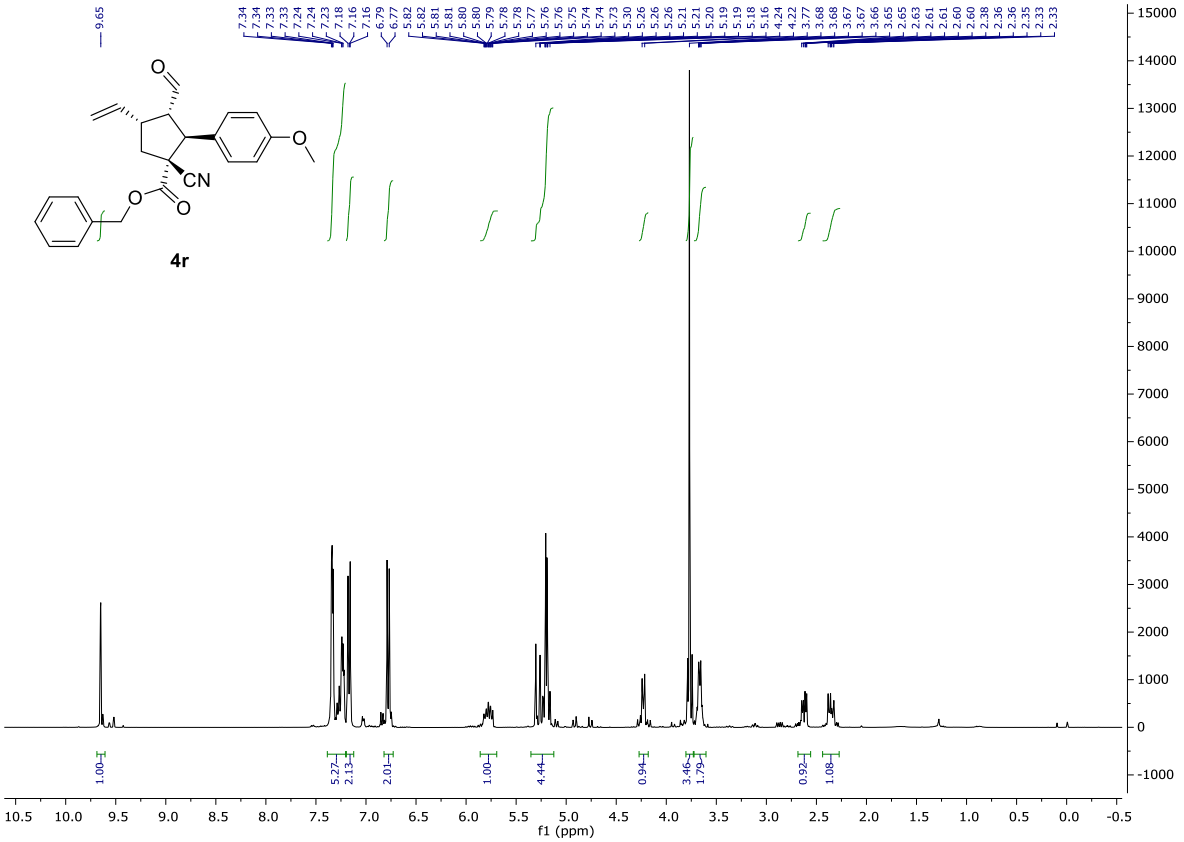
43.11
f1 (ppm)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O
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CN
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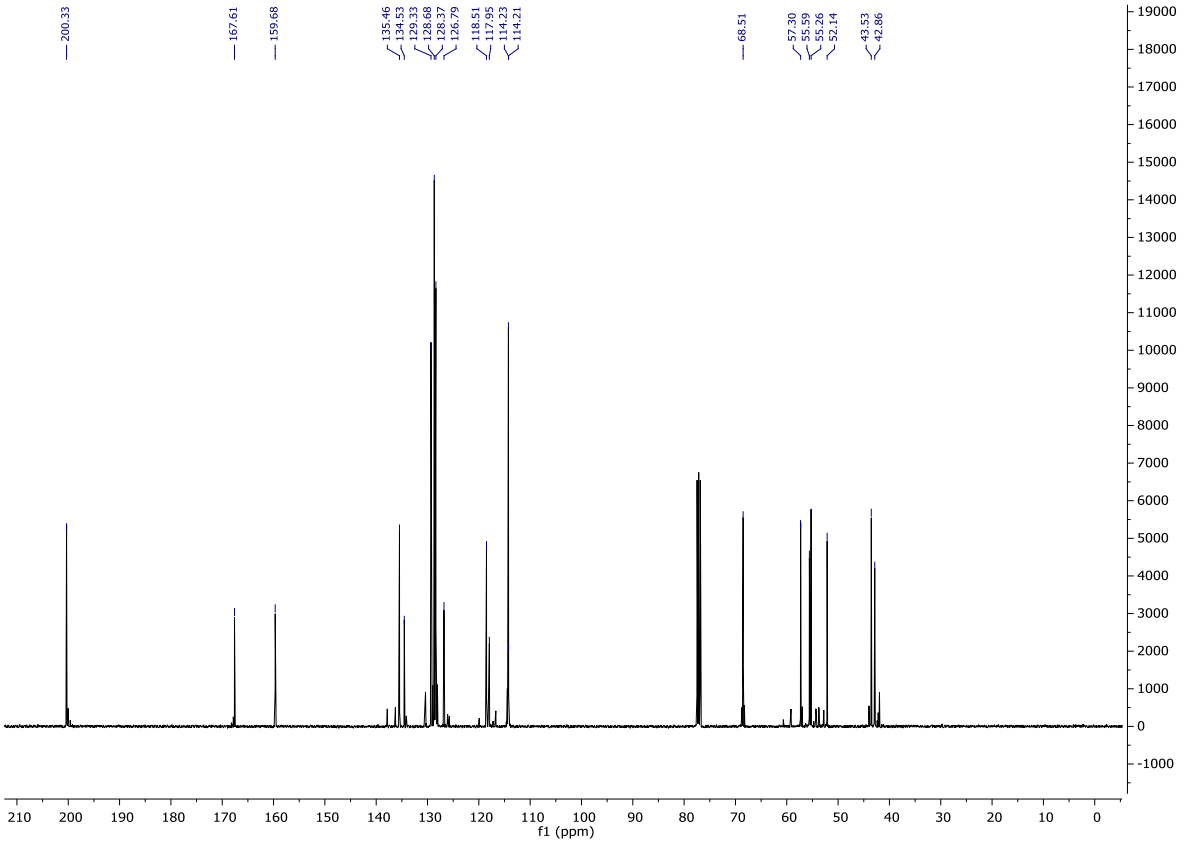
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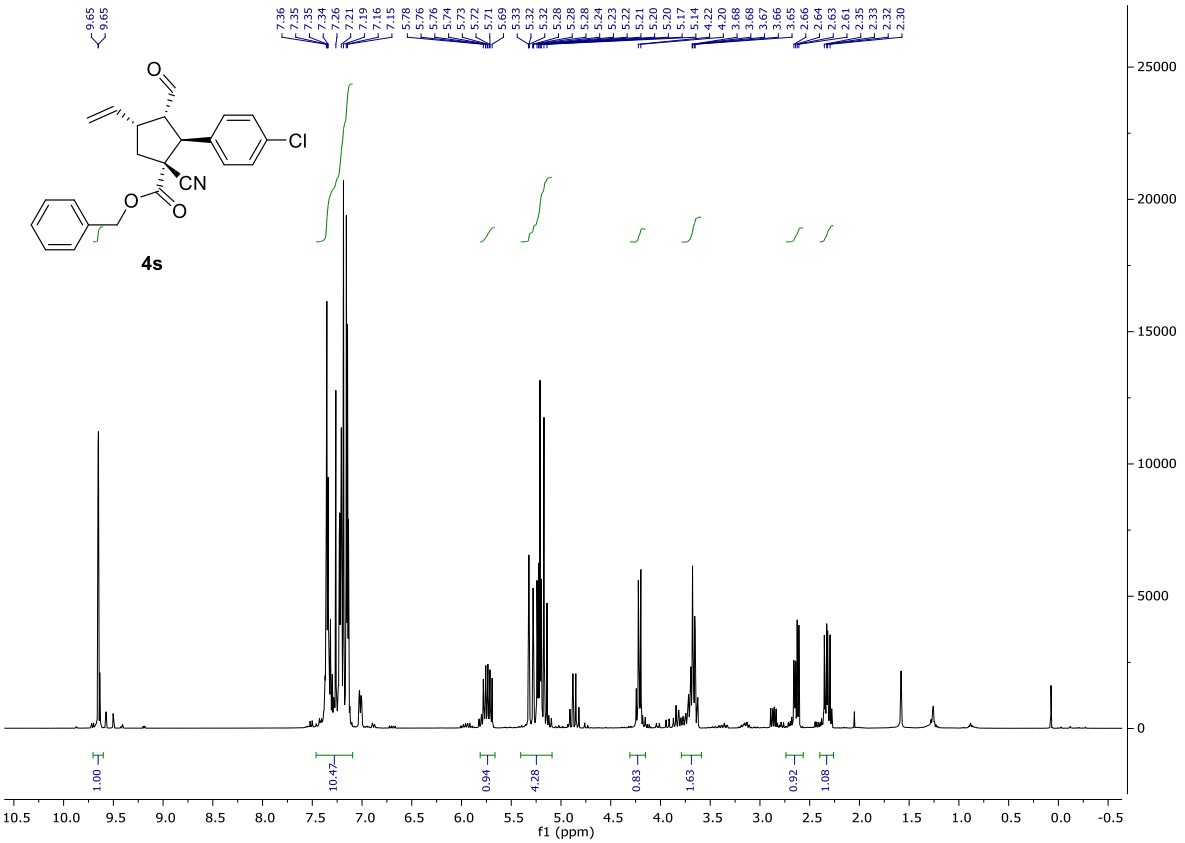
42.86
f1 (ppm)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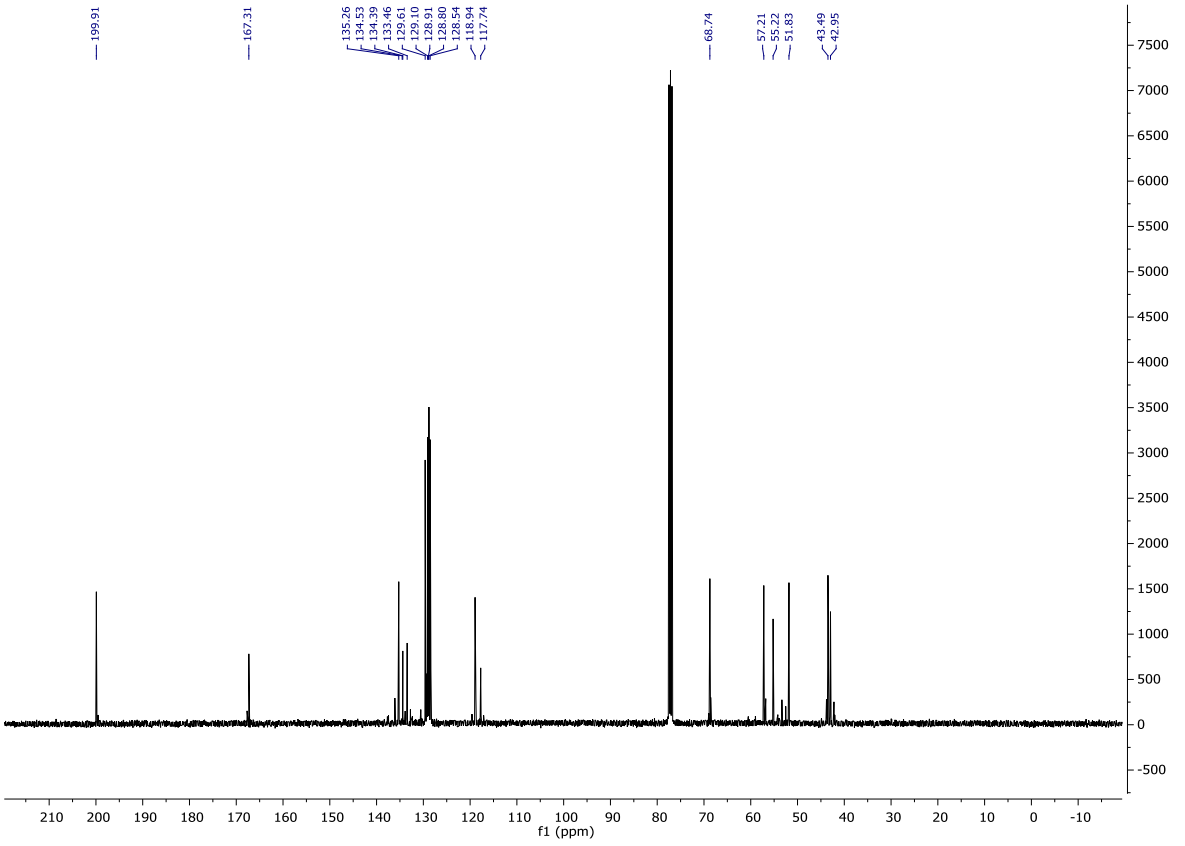
f1 (ppm)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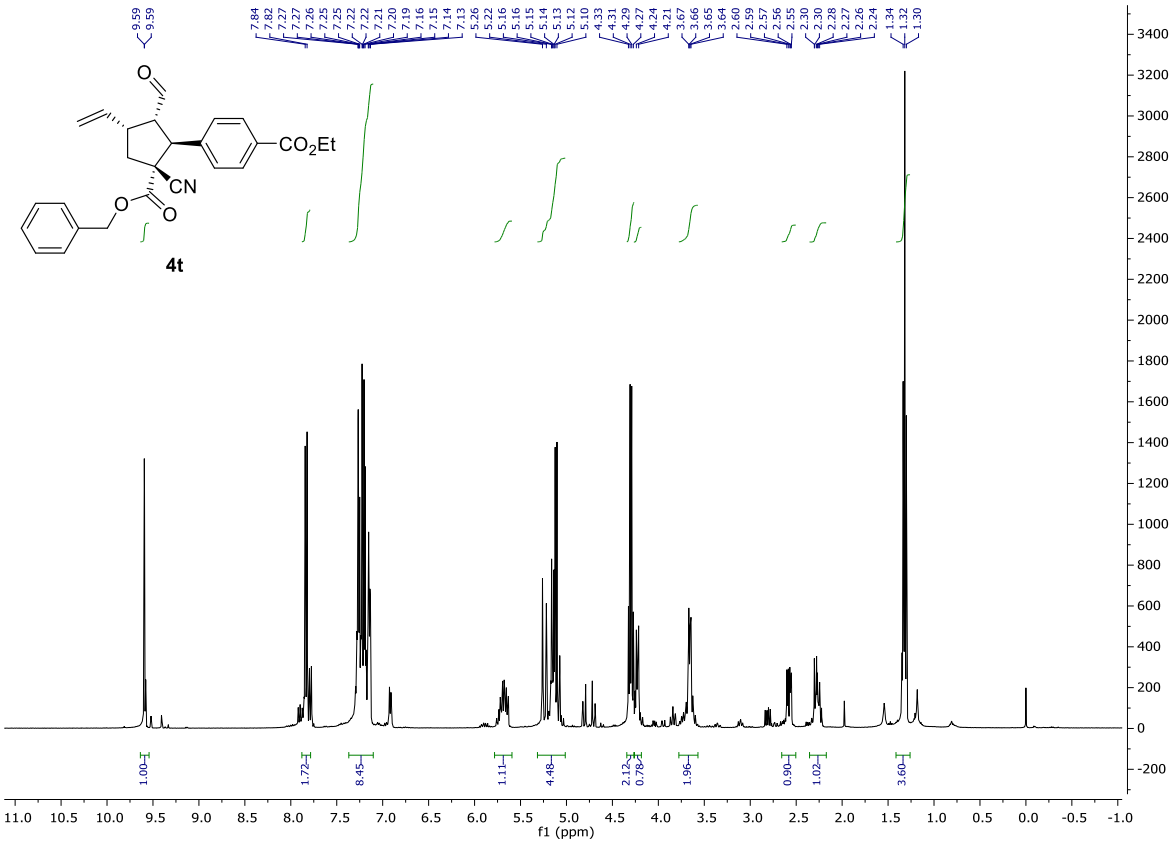
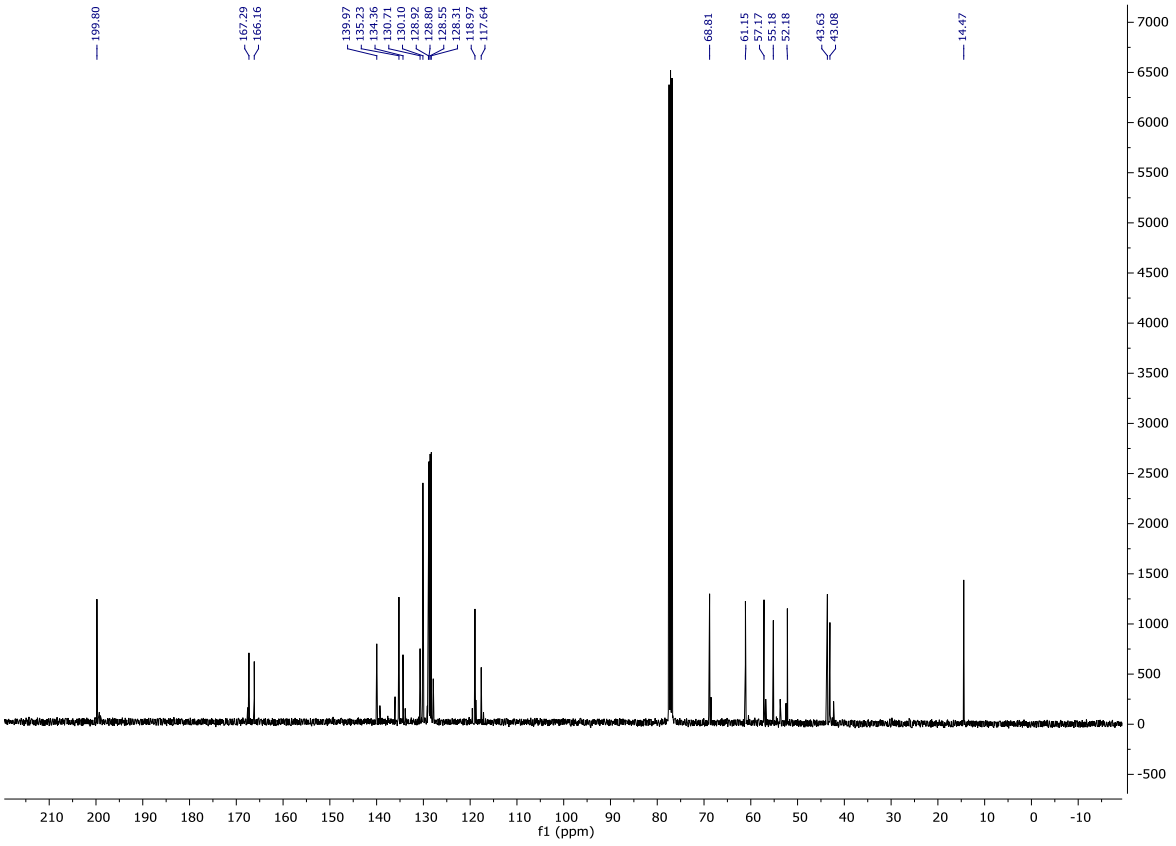
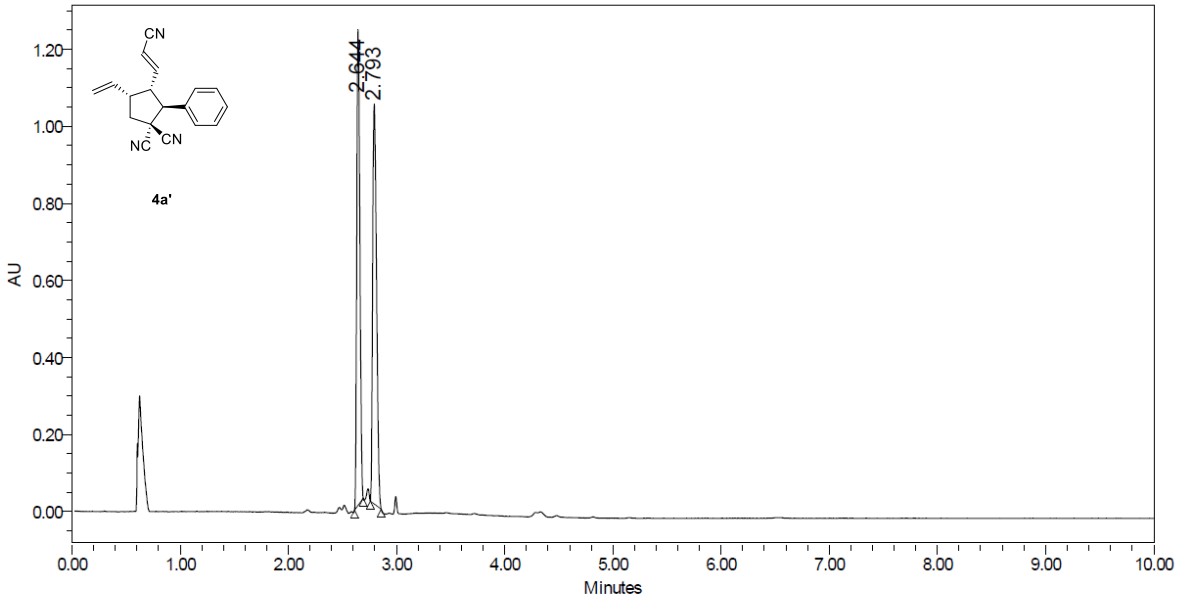
42.95
f1 (ppm)


4t
f1 (ppm)

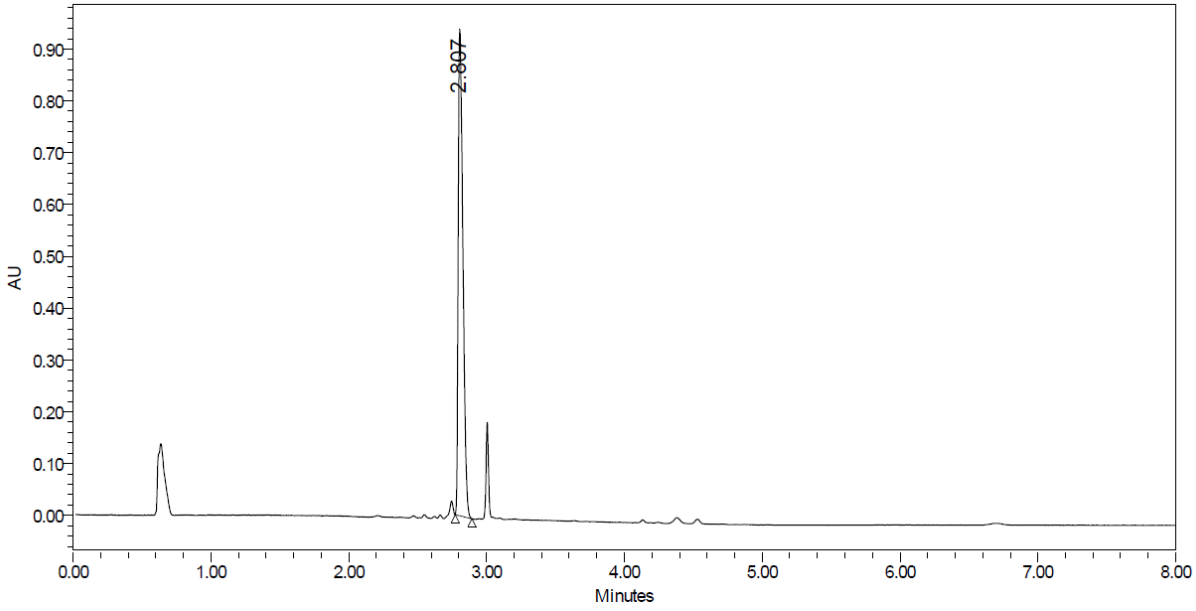

f1 (ppm)

7. UPC^2 traces

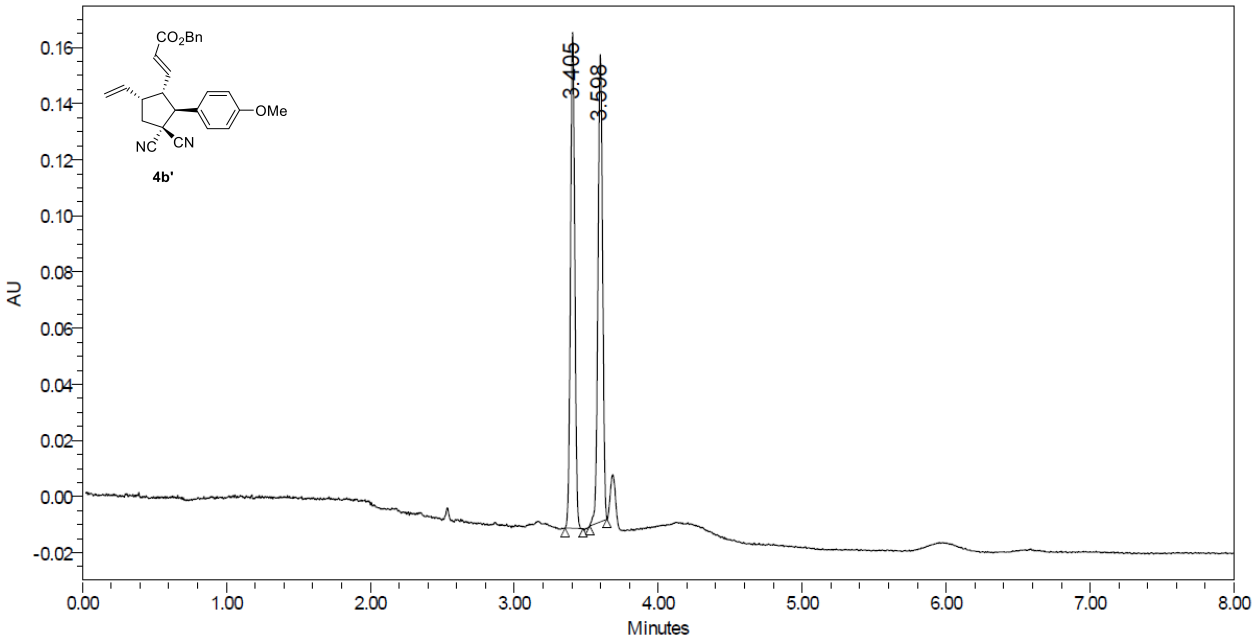
Enantiomeric excesses of compounds **4** were measured on the corresponding Wittig olefination products (**4a'**-**l'**, **4n'**-**t'**) or on the corresponding diol **4m'**.



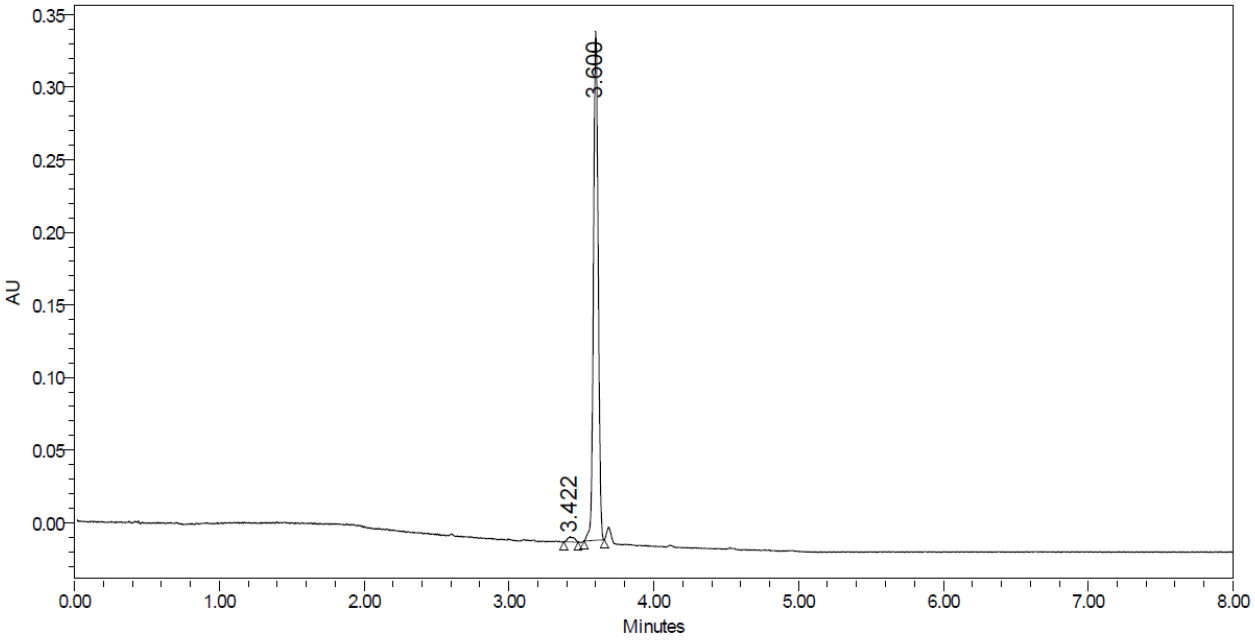
	Retention Time (min)	% Area
1	2.644	48.69
2	2.793	51.31



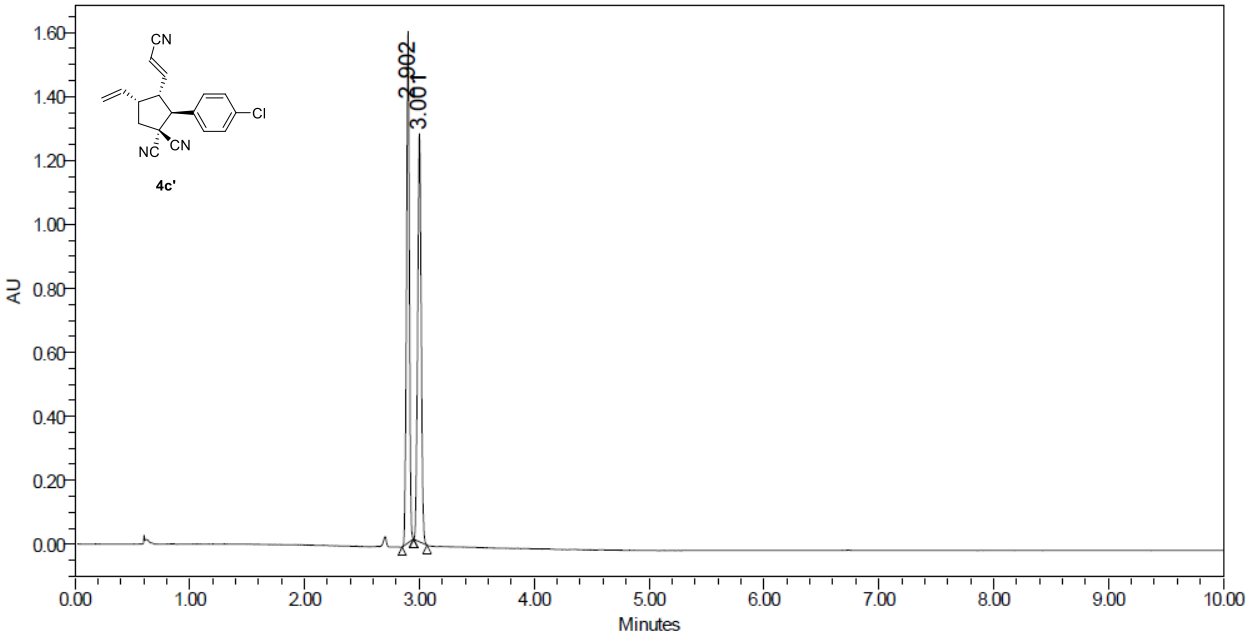
	Retention Time (min)	% Area
1	2.807	100.00



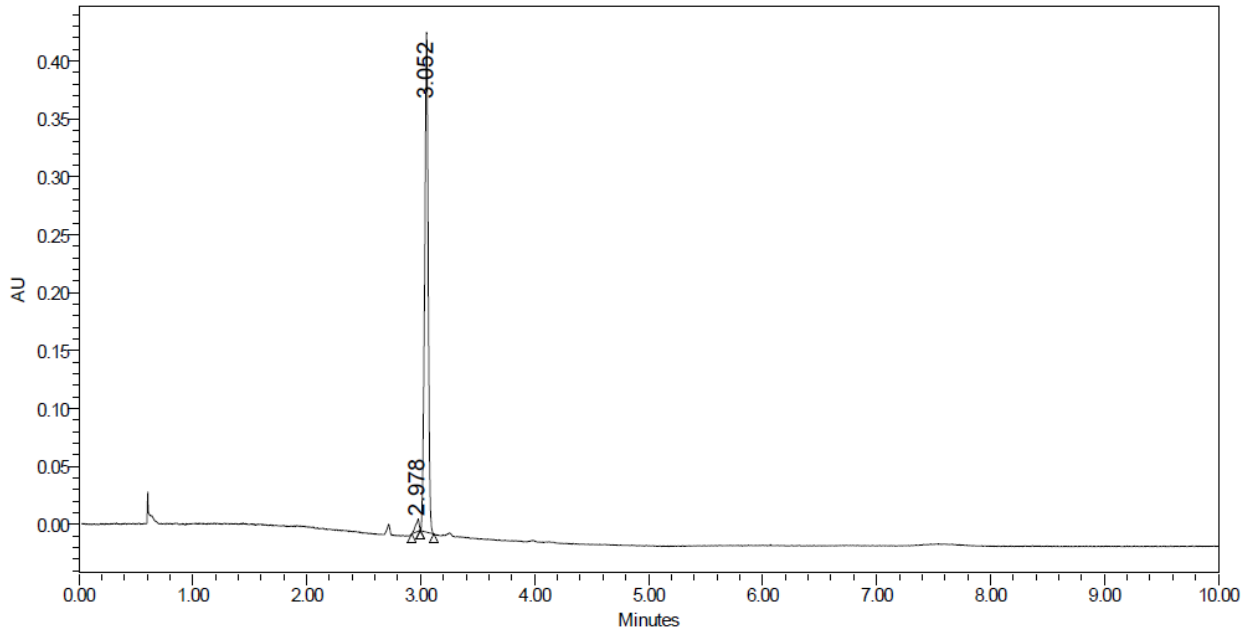
	Retention Time (min)	% Area
1	3.405	49.54
2	3.598	50.46



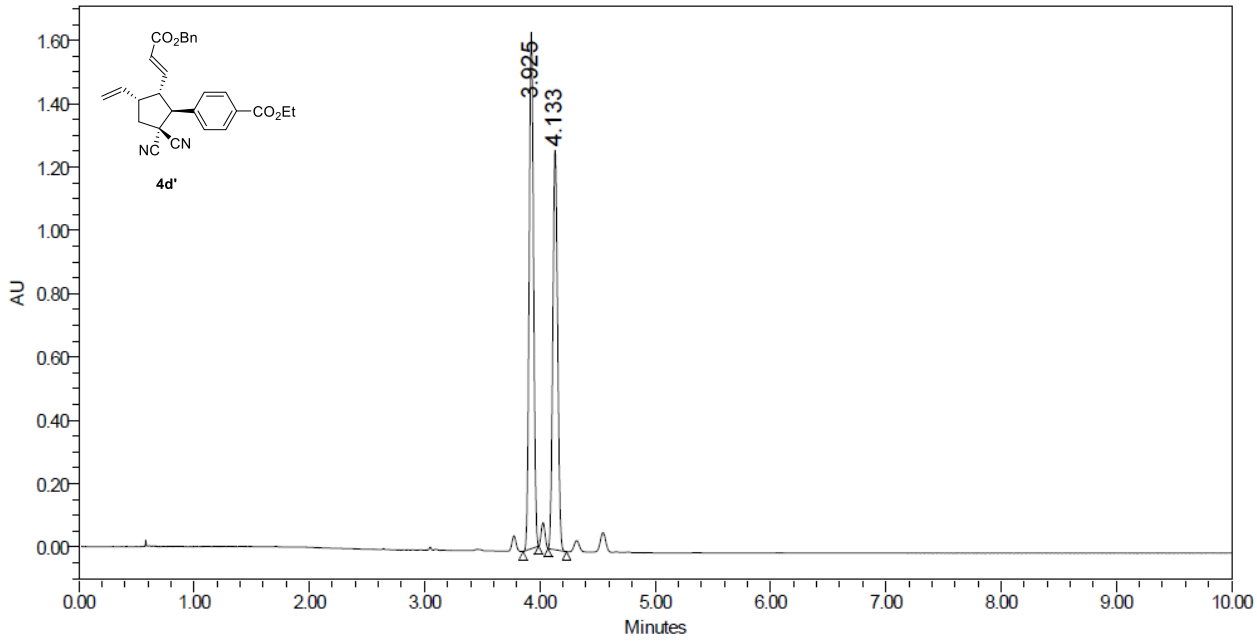
	Retention Time (min)	% Area
1	3.422	1.41
2	3.600	98.59



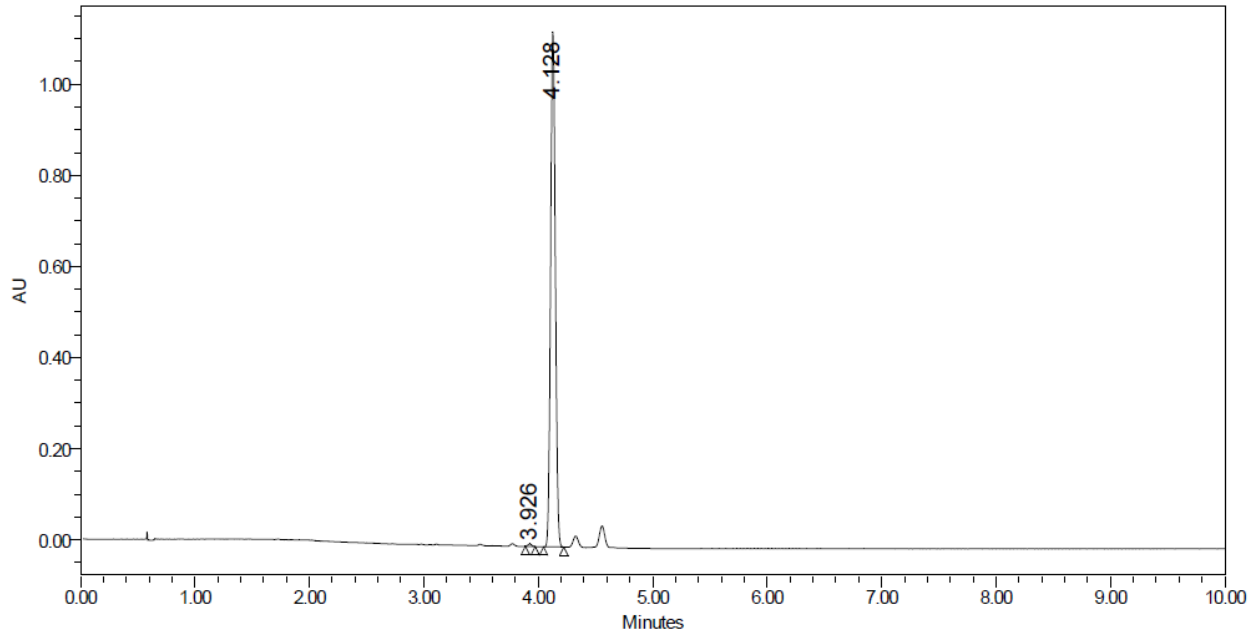
	Retention Time (min)	% Area
1	2.902	49.92
2	3.001	50.08



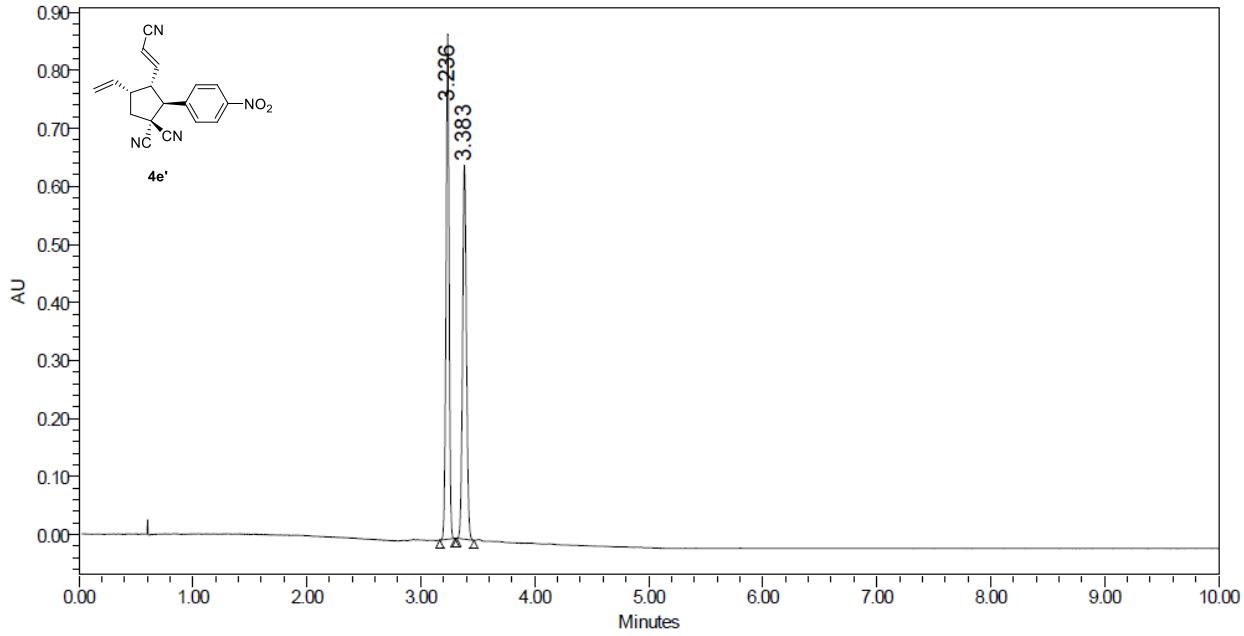
	Retention Time (min)	% Area
1	2.978	2.31
2	3.052	97.69



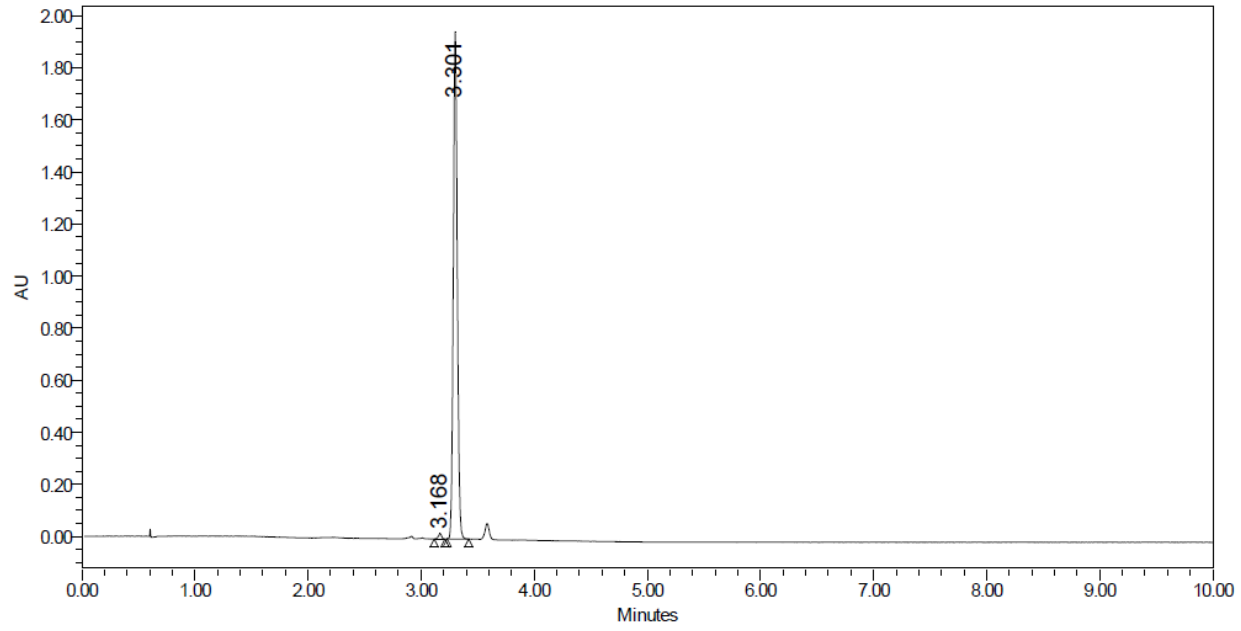
	Retention Time (min)	% Area
1	3.925	54.14
2	4.133	45.86



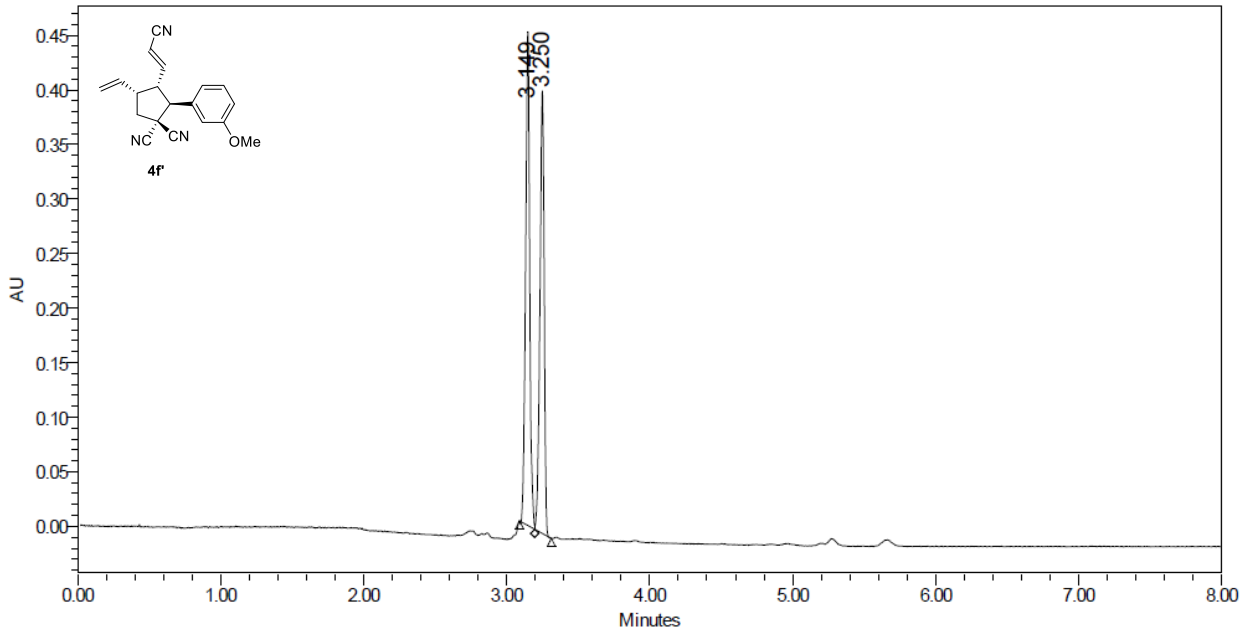
	Retention Time (min)	% Area
1	3.926	0.39
2	4.128	99.61



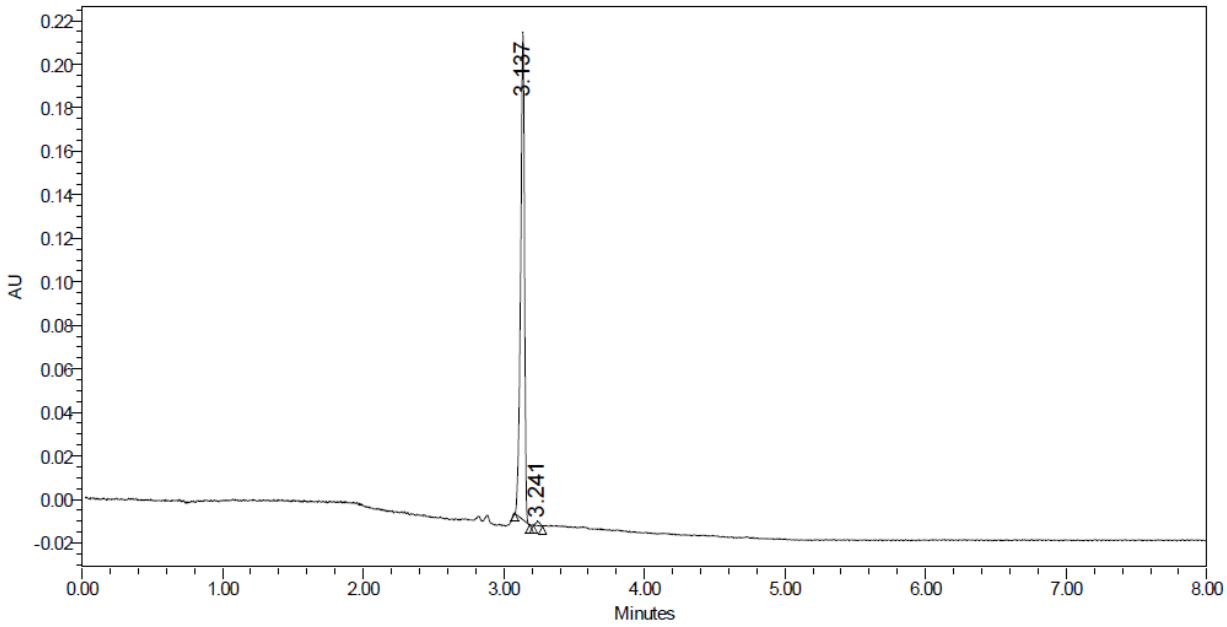
	Retention Time (min)	% Area
1	3.236	51.24
2	3.383	48.76



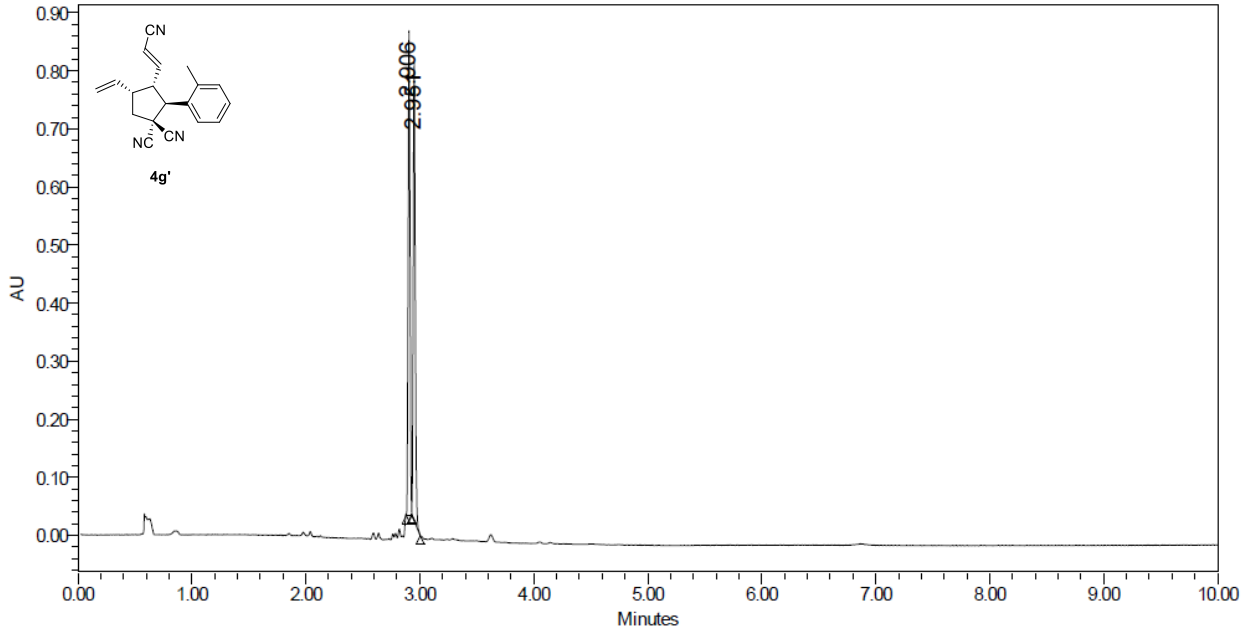
	Retention Time (min)	% Area
1	3.168	0.85
2	3.301	99.15



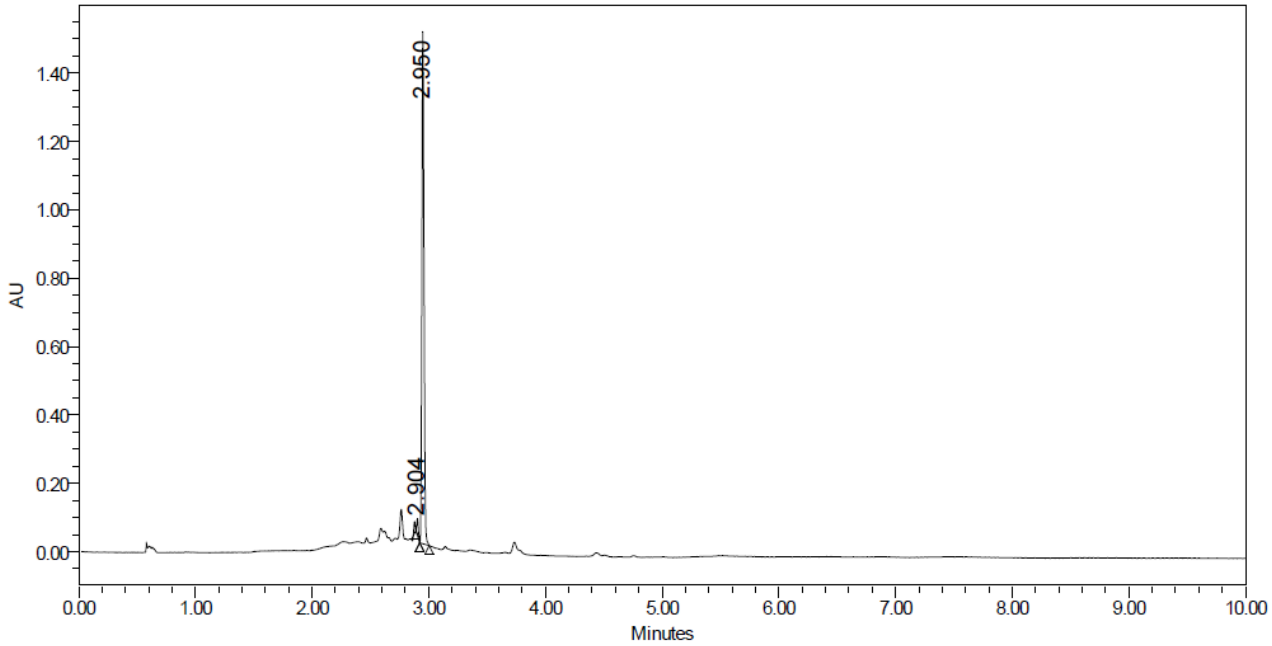
	Retention Time (min)	% Area
1	3.149	52.08
2	3.250	47.92



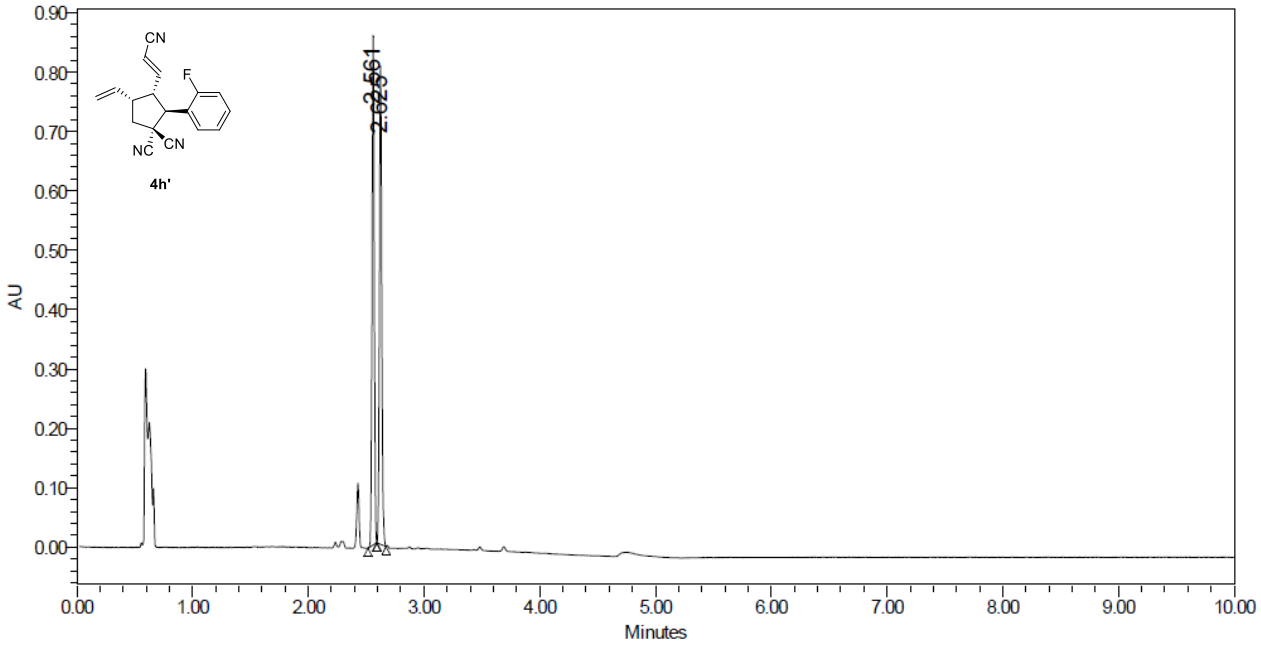
	Retention Time (min)	% Area
1	3.137	99.15
2	3.241	0.85



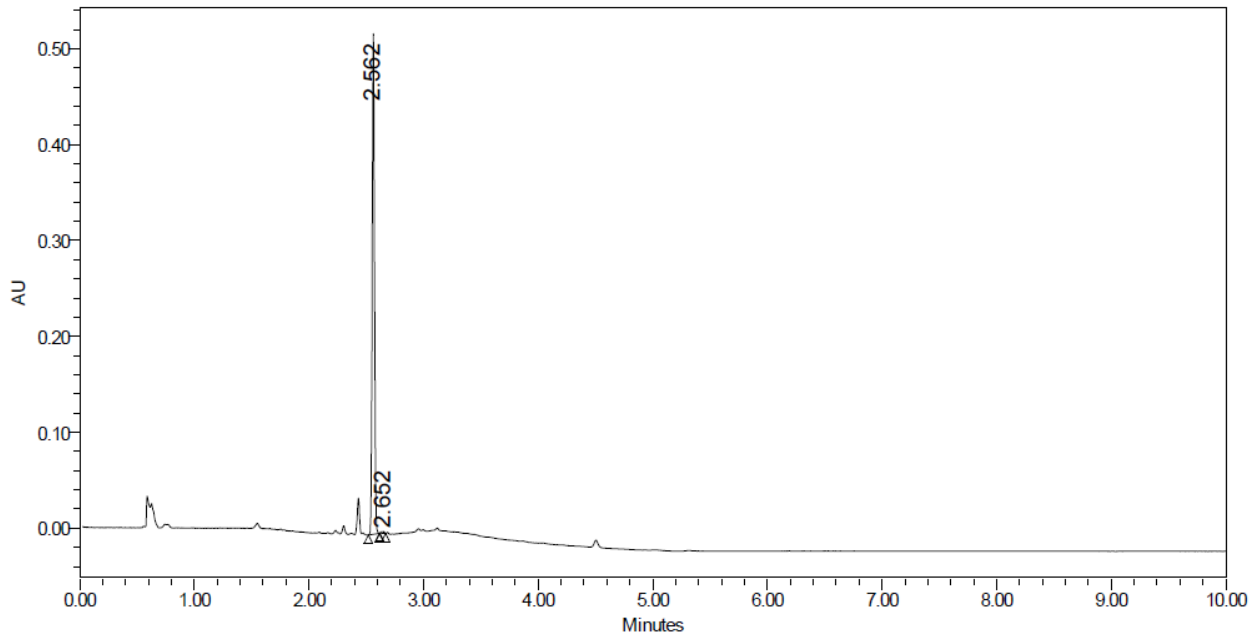
	Retention Time (min)	% Area
1	2.906	49.31
2	2.951	50.69



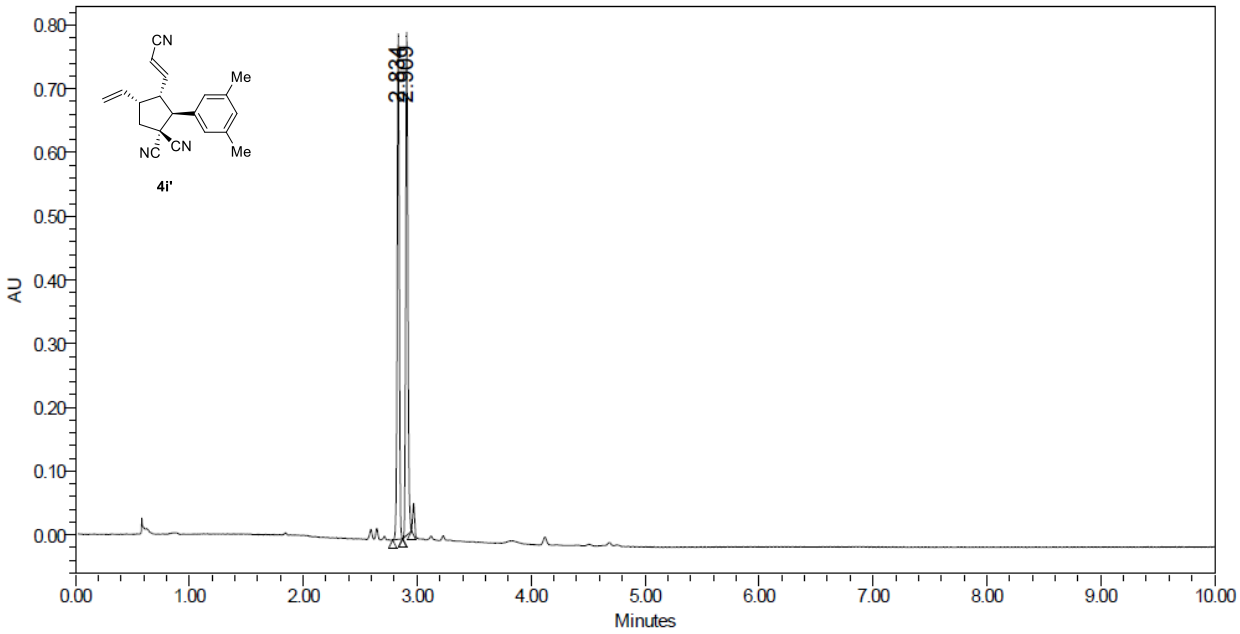
	Retention Time (min)	% Area
1	2.904	2.44
2	2.950	97.56



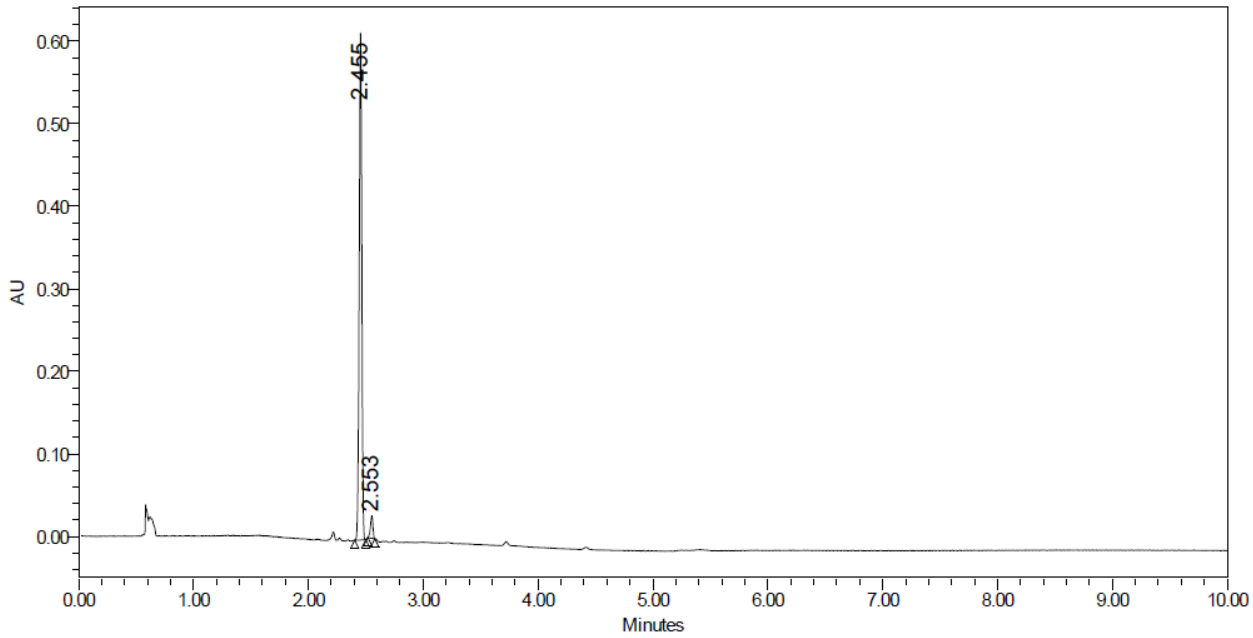
	Retention Time (min)	% Area
1	2.561	50.20
2	2.625	49.80



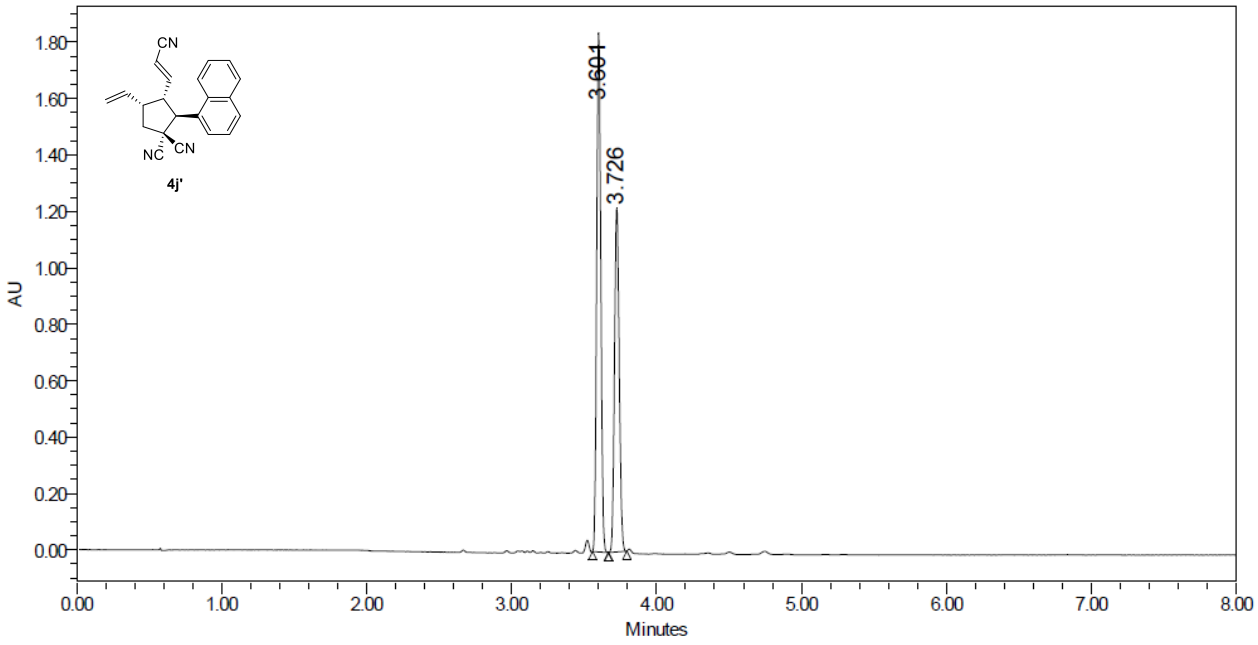
	Retention Time (min)	% Area
1	2.562	99.51
2	2.652	0.49



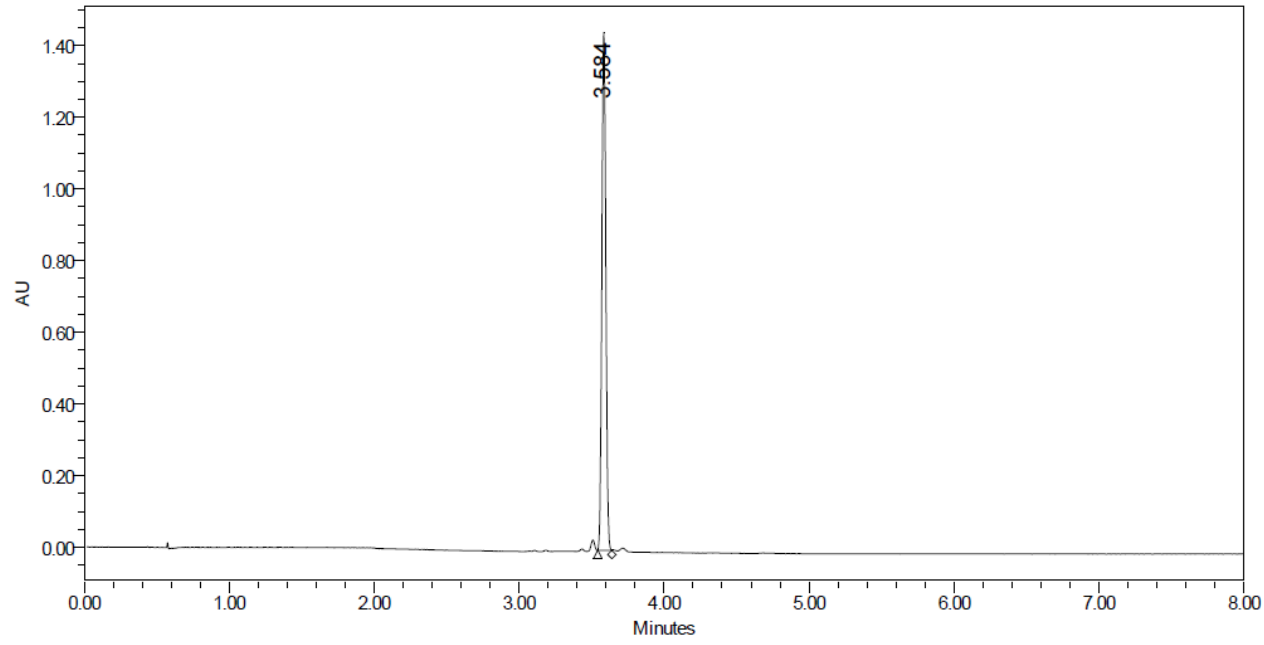
	Retention Time (min)	% Area
1	2.834	48.78
2	2.909	51.22



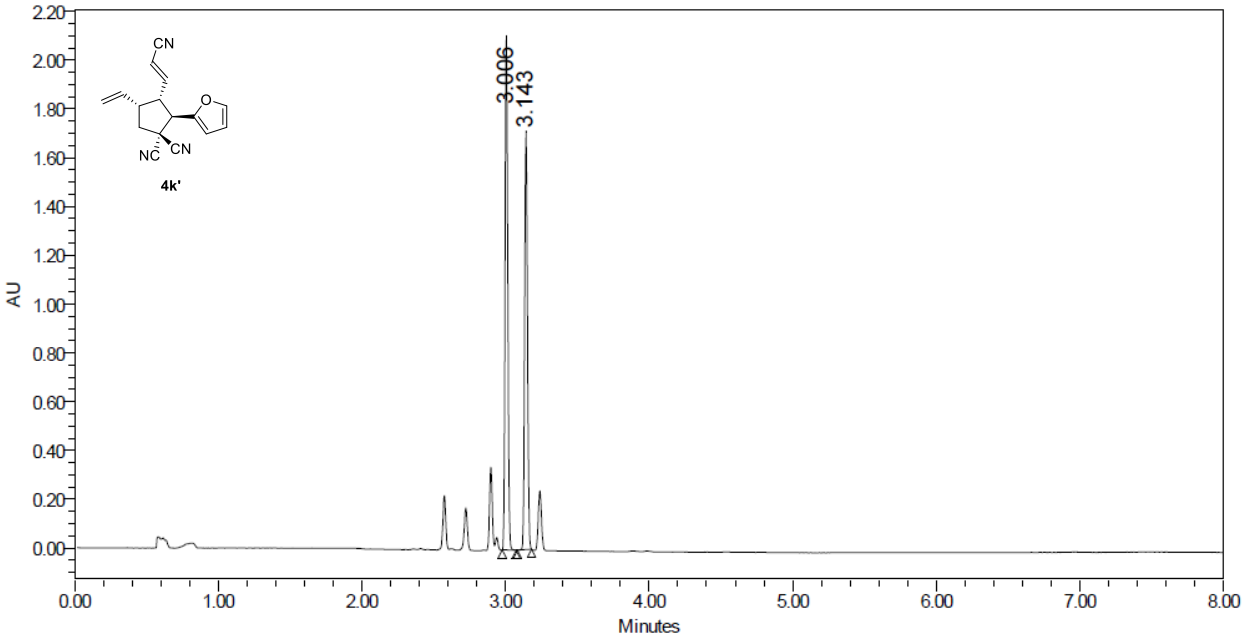
	Retention Time (min)	% Area
1	2.455	95.95
2	2.553	4.05



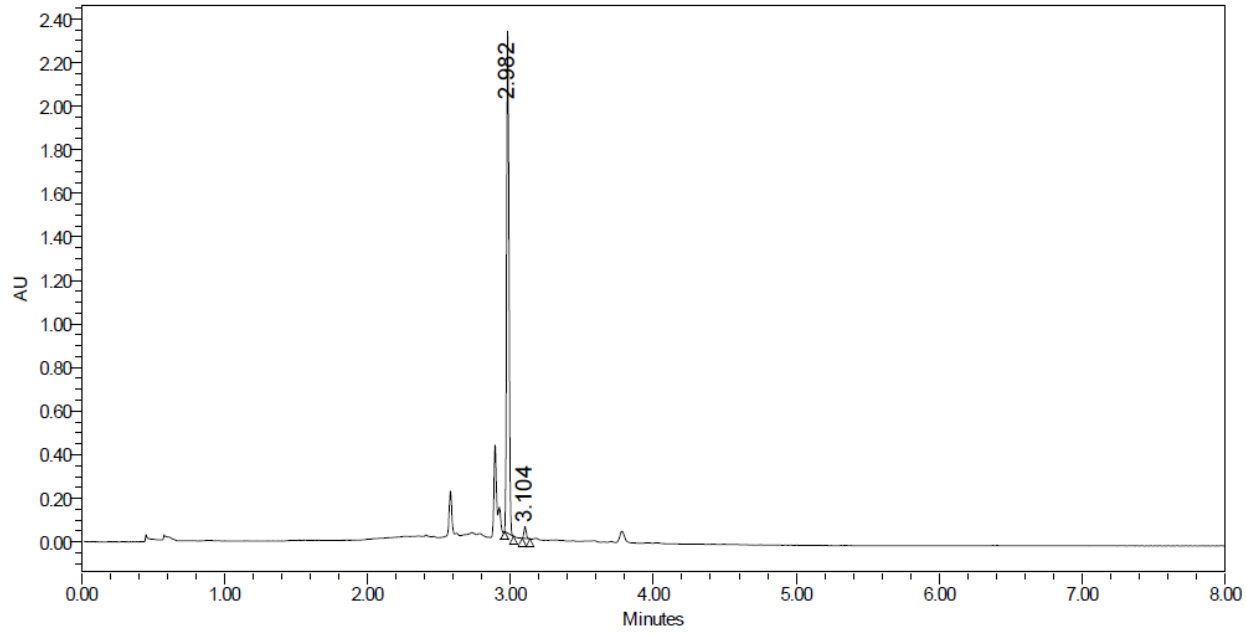
	Retention Time (min)	% Area
1	3.601	56.97
2	3.726	43.03



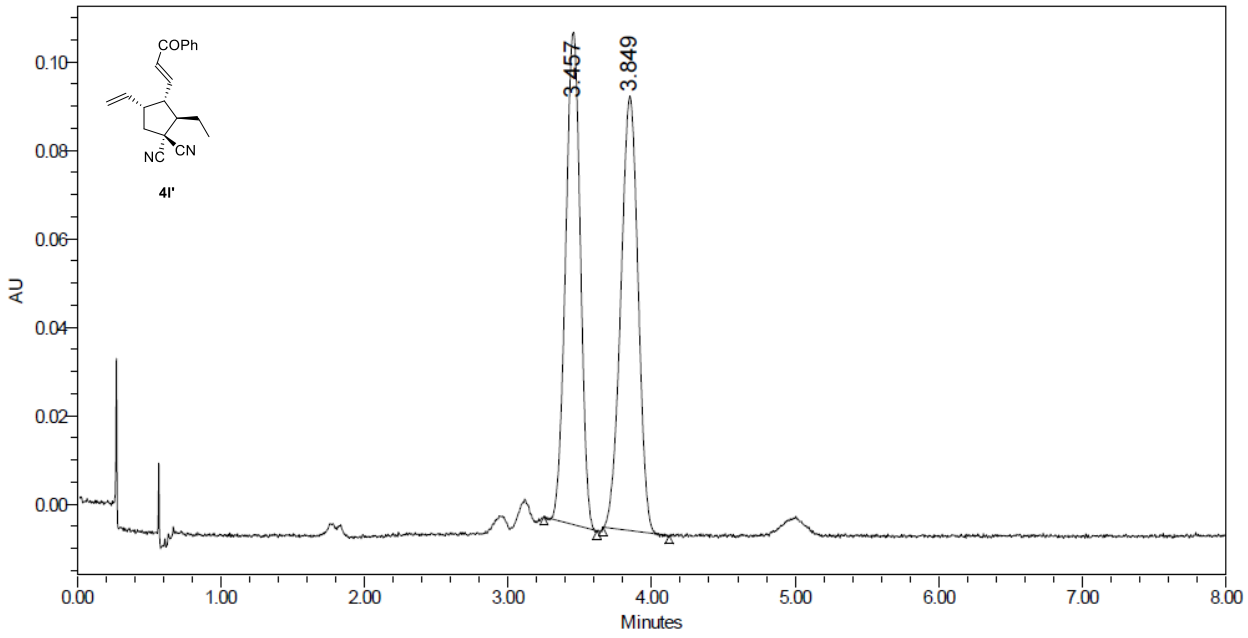
	Retention Time (min)	% Area
1	3.584	100.00



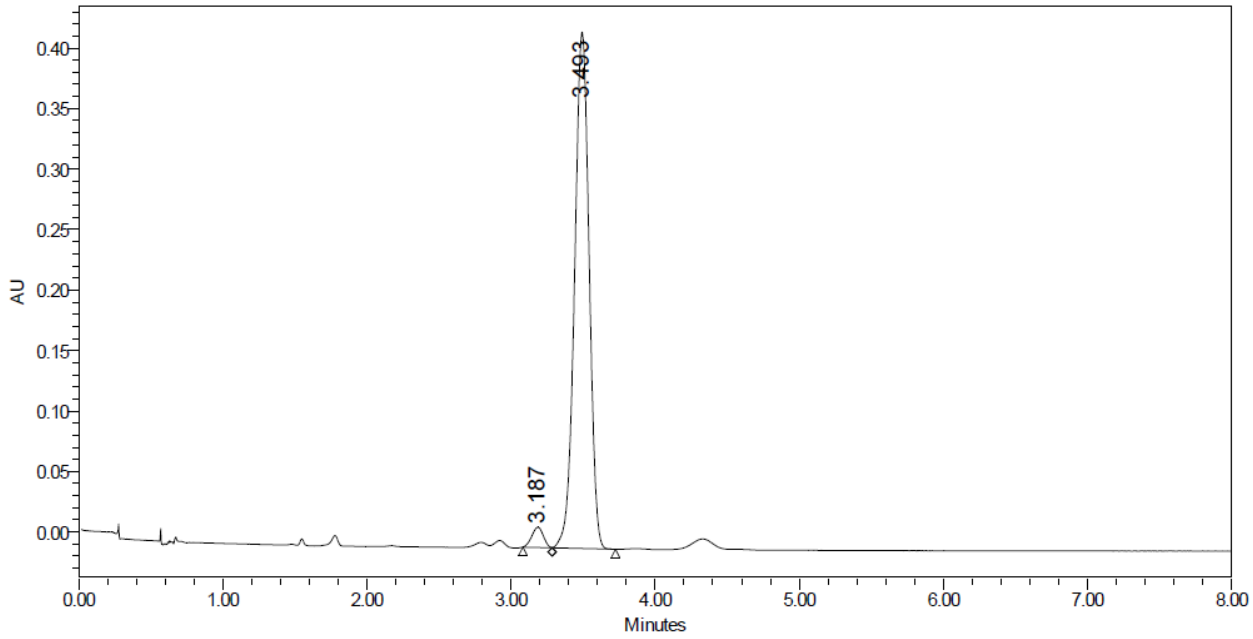
	Retention Time (min)	% Area
1	3.006	53.89
2	3.143	46.11



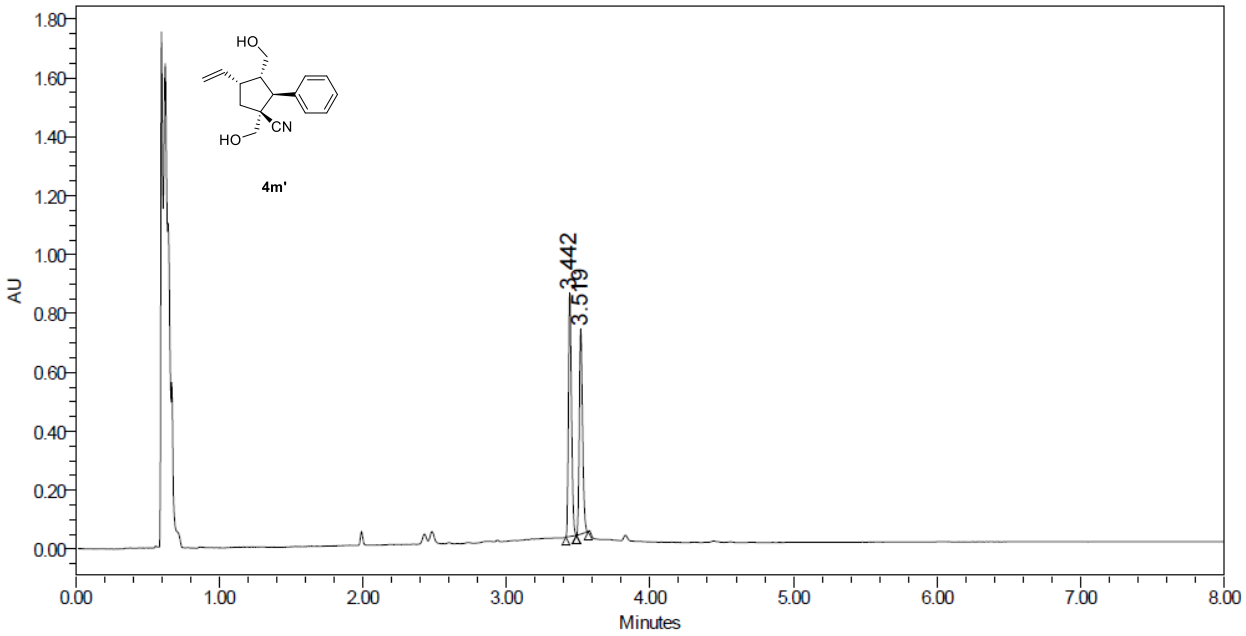
	Retention Time (min)	% Area
1	2.982	97.87
2	3.104	2.13



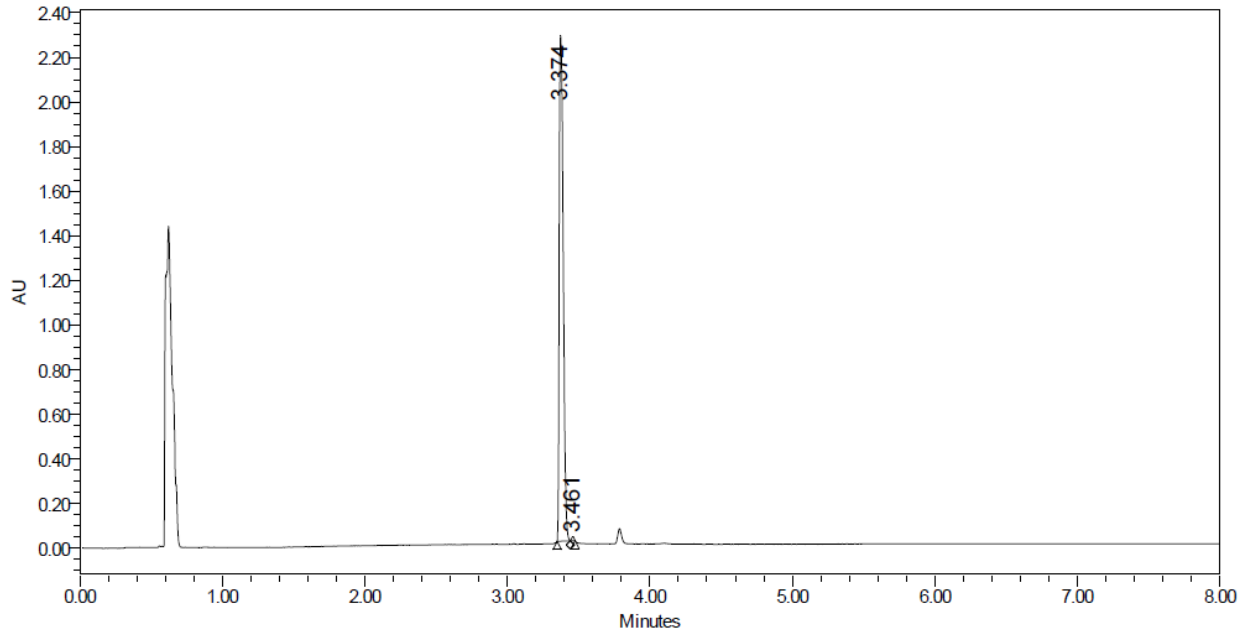
	Retention Time (min)	% Area
1	3.457	49.12
2	3.849	50.88



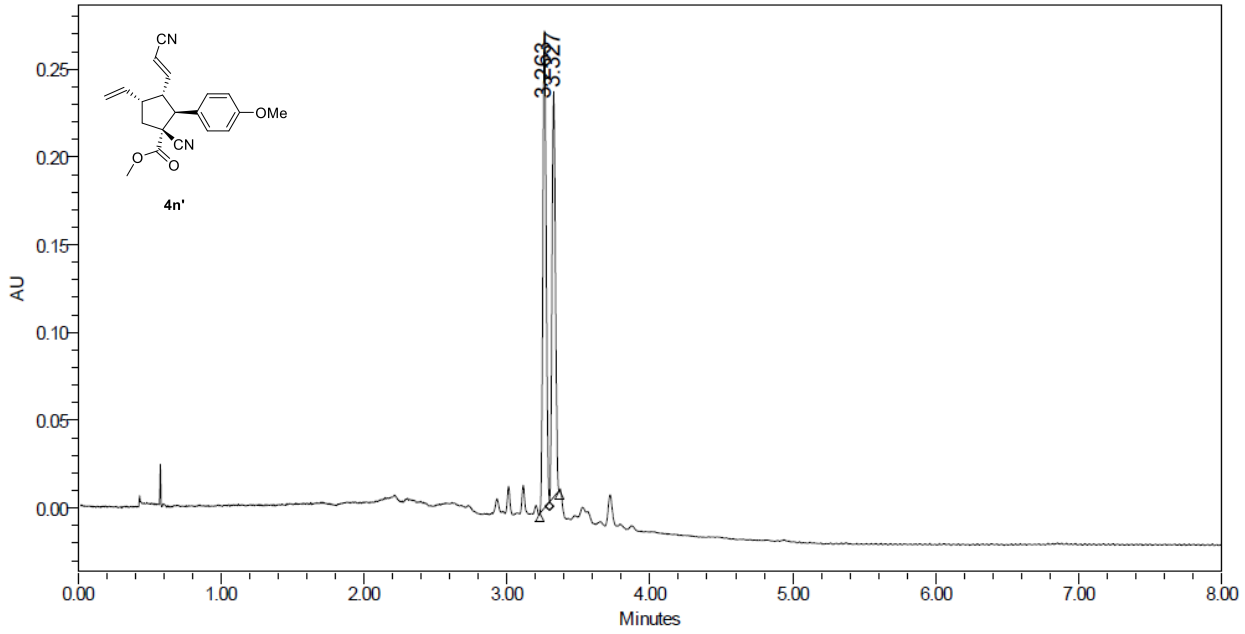
	Retention Time (min)	% Area
1	3.187	3.00
2	3.493	97.00



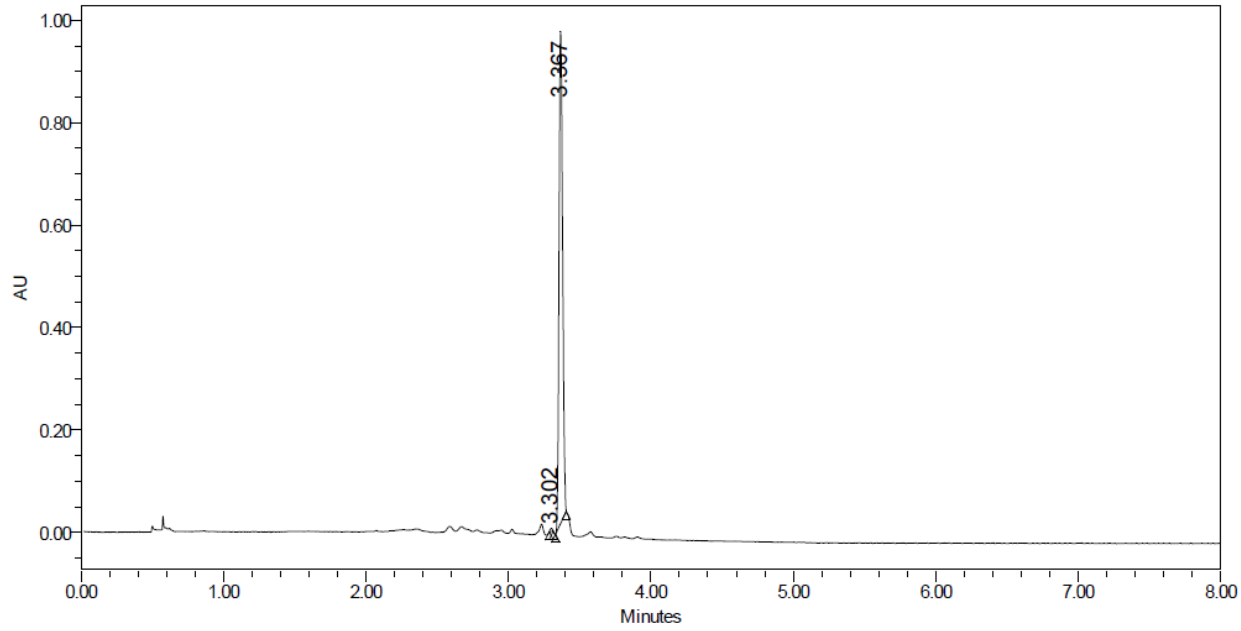
	Retention Time (min)	% Area
1	3.442	52.77
2	3.519	47.23



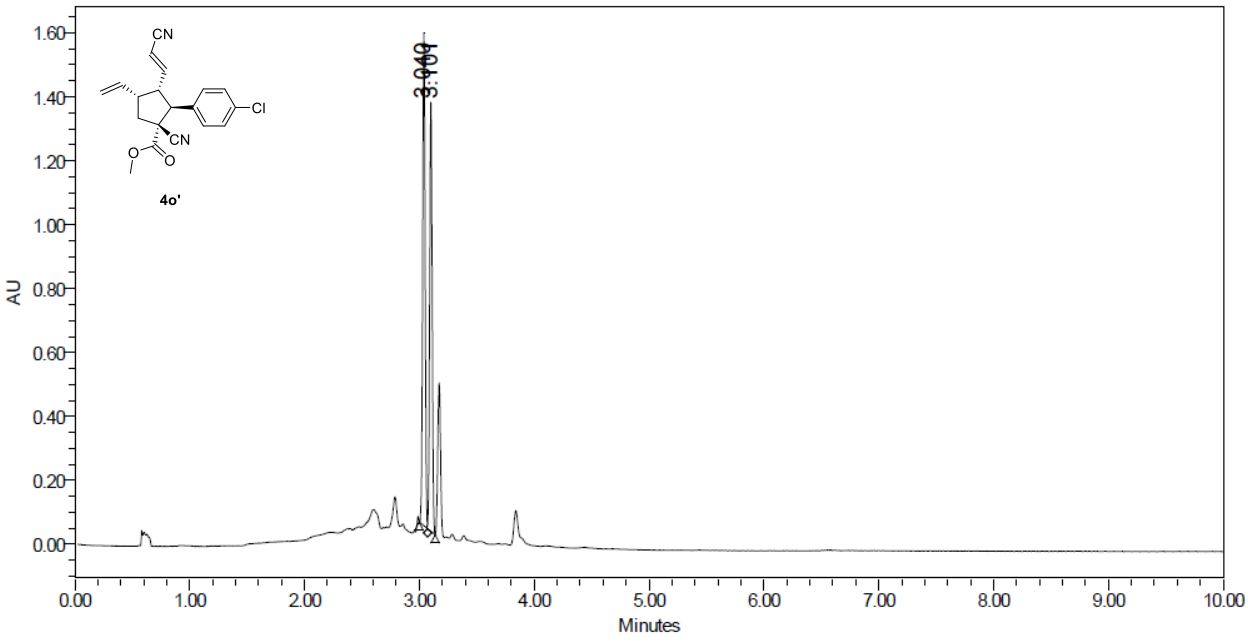
	Retention Time (min)	% Area
1	3.374	99.51
2	3.461	0.49



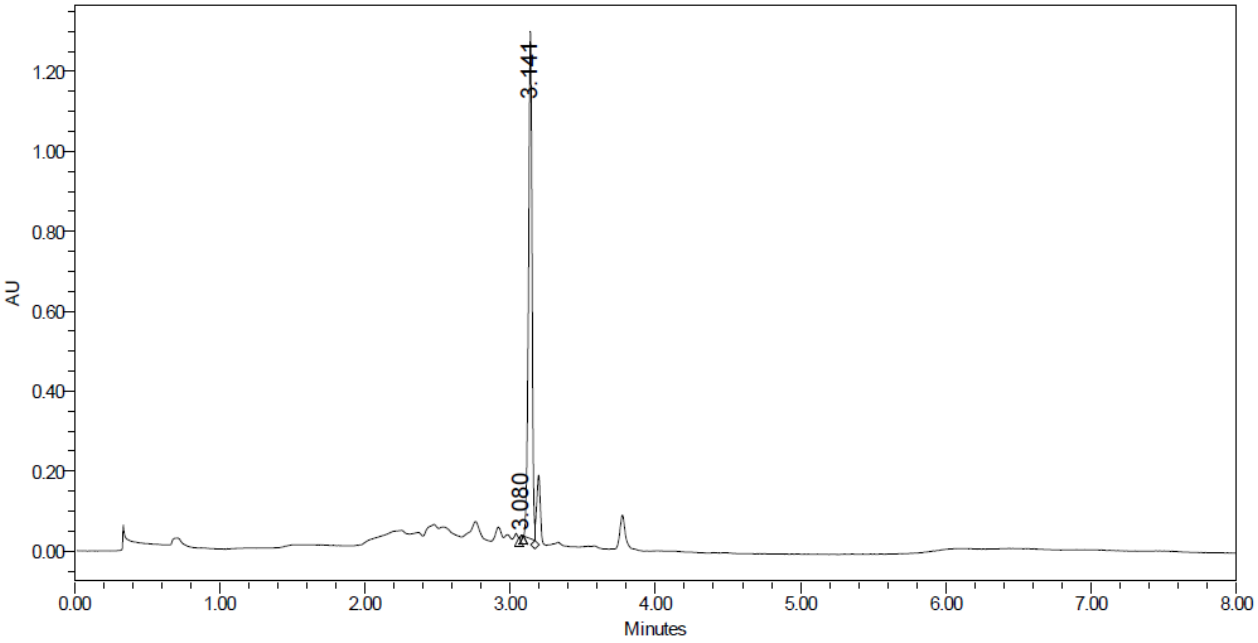
	Retention Time (min)	% Area
1	3.263	53.29
2	3.327	46.71



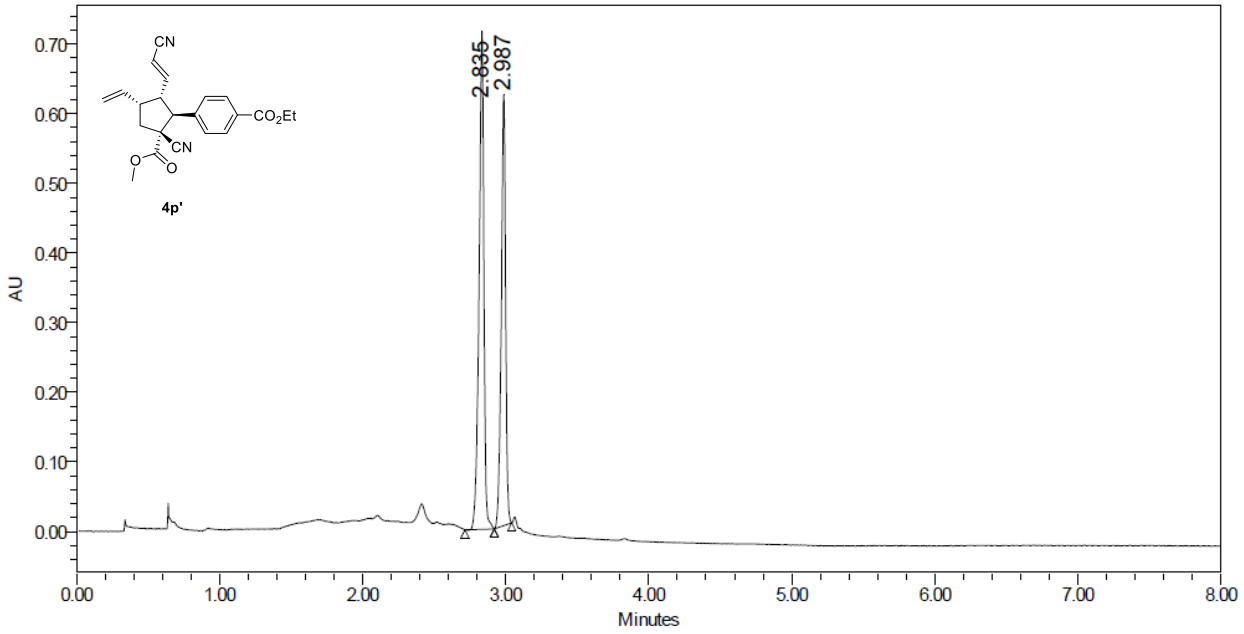
	Retention Time (min)	% Area
1	3.302	0.40
2	3.367	99.60



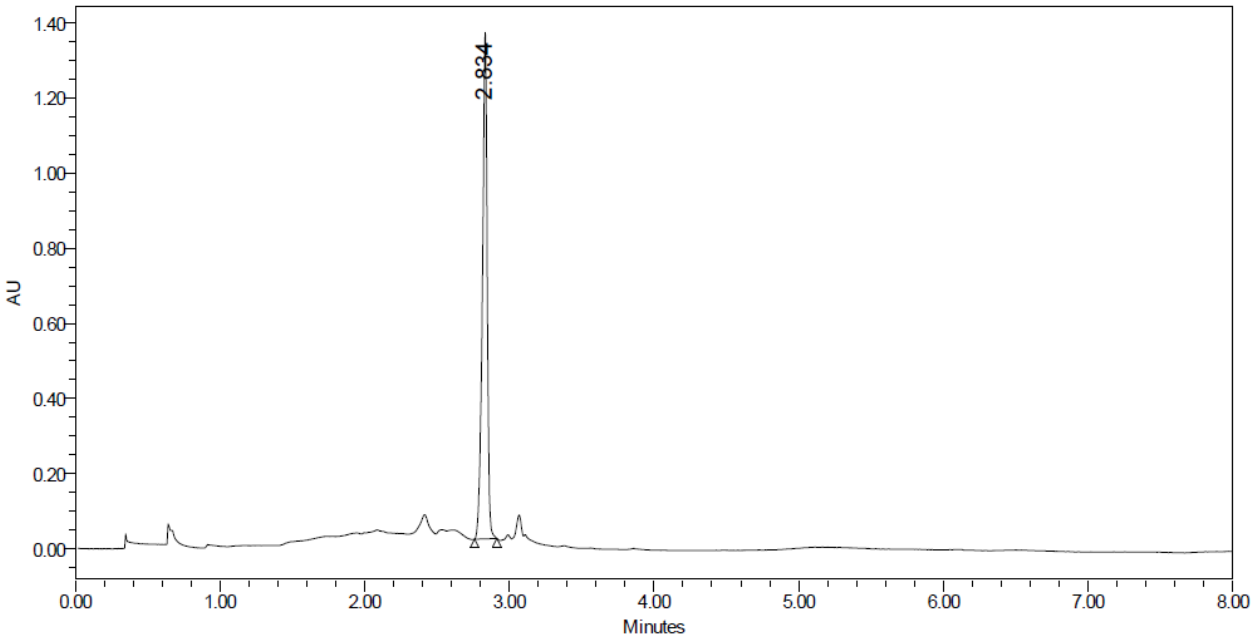
	Retention Time (min)	% Area
1	3.040	53.14
2	3.101	46.86



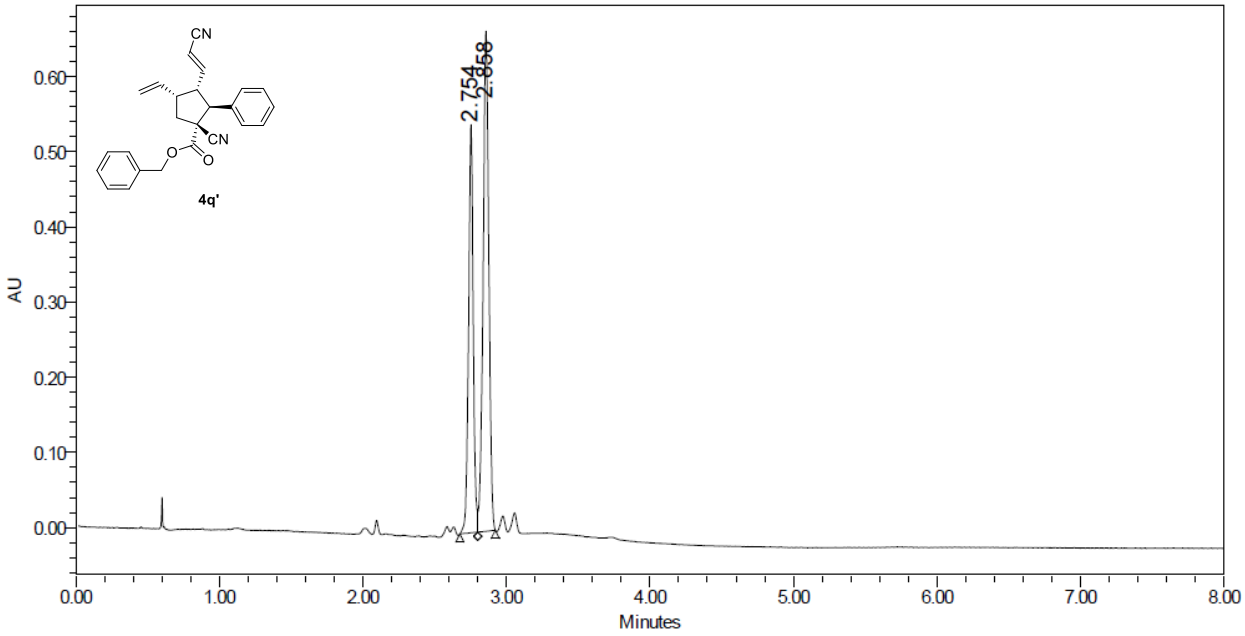
	Retention Time (min)	% Area
1	3.080	0.17
2	3.141	99.83



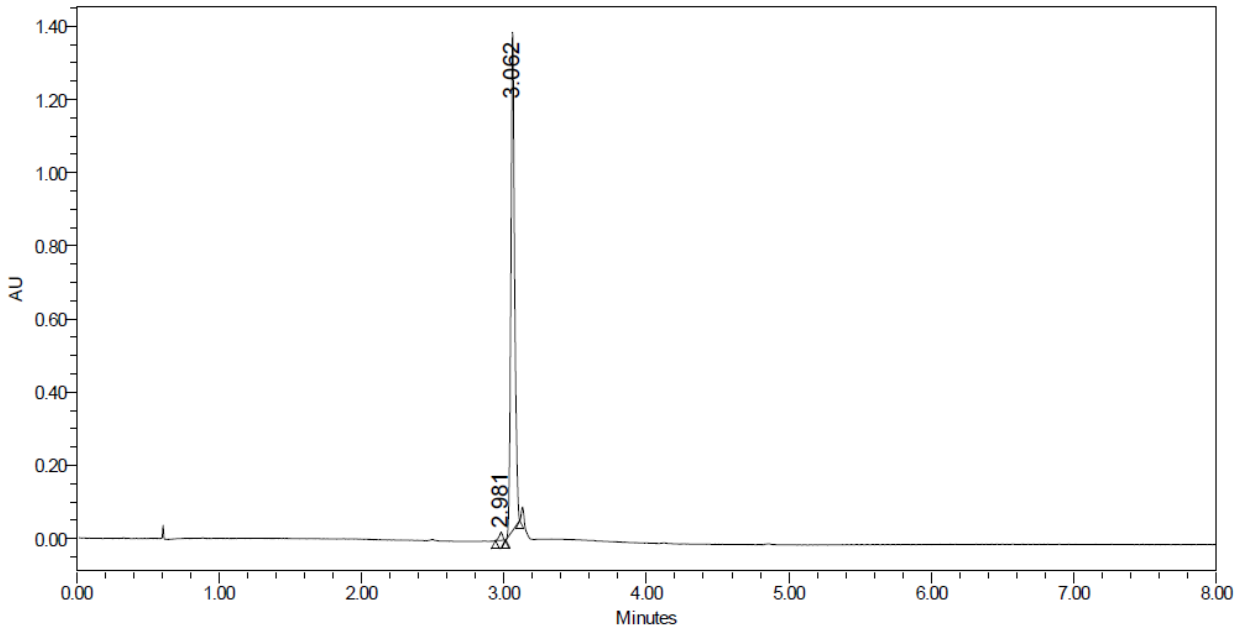
	Retention Time (min)	% Area
1	2.835	56.39
2	2.987	43.61



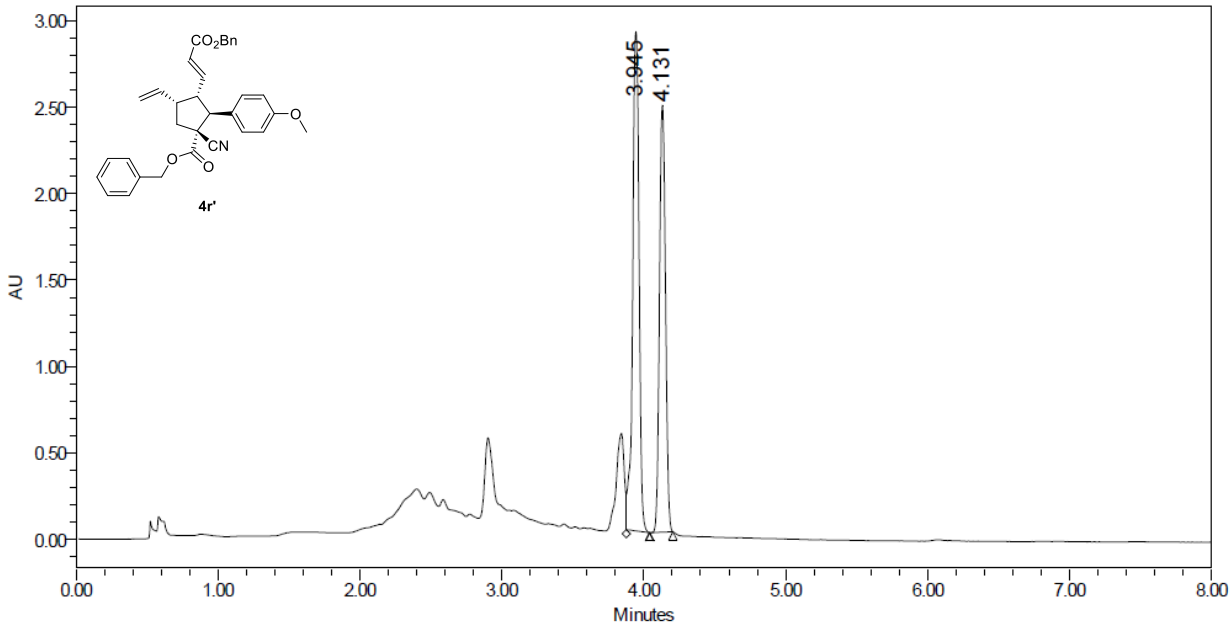
	Retention Time (min)	% Area
1	2.834	100.00



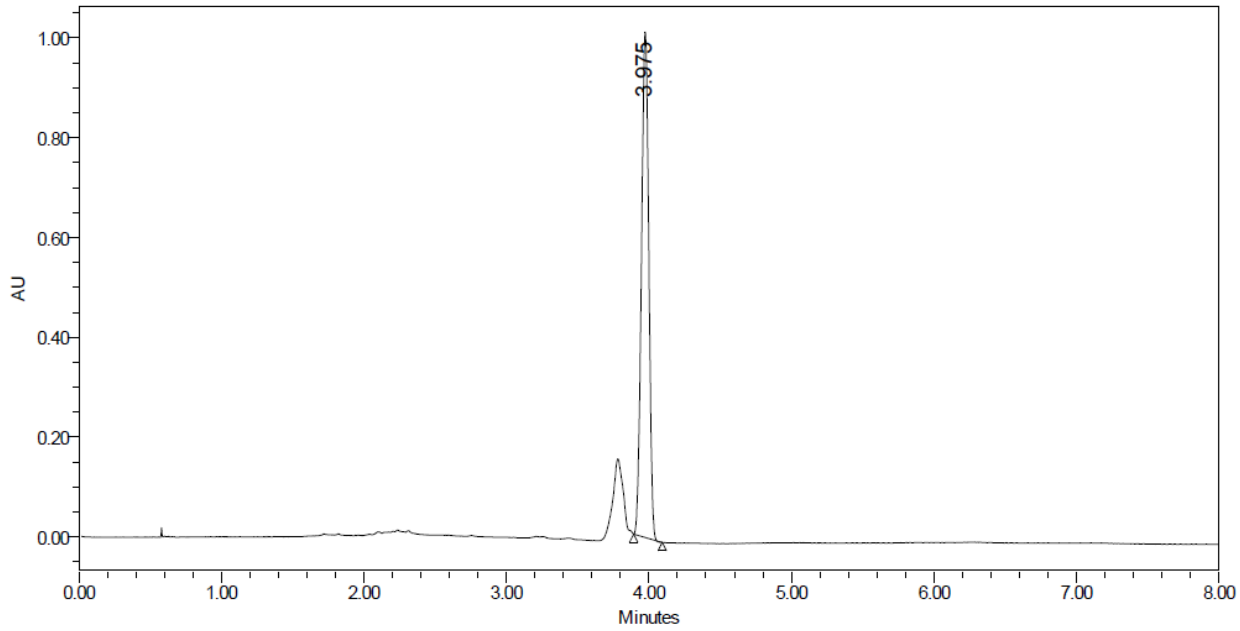
	Retention Time (min)	% Area
1	2.754	40.17
2	2.858	59.83



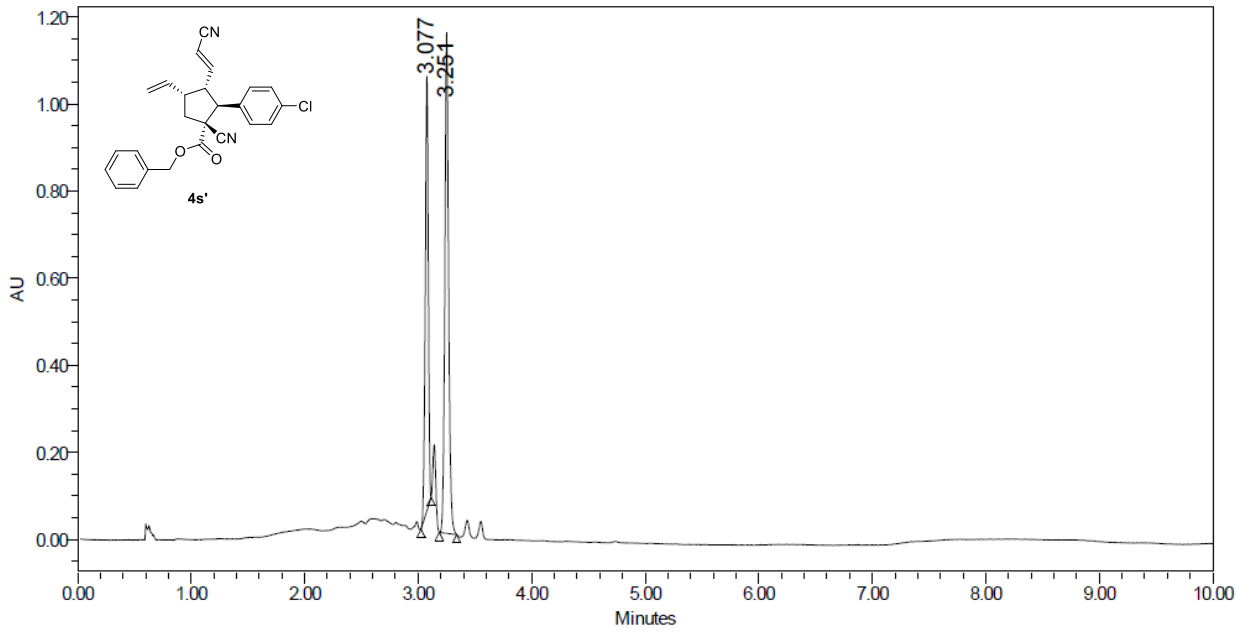
	Retention Time (min)	% Area
1	2.981	1.46
2	3.062	98.54



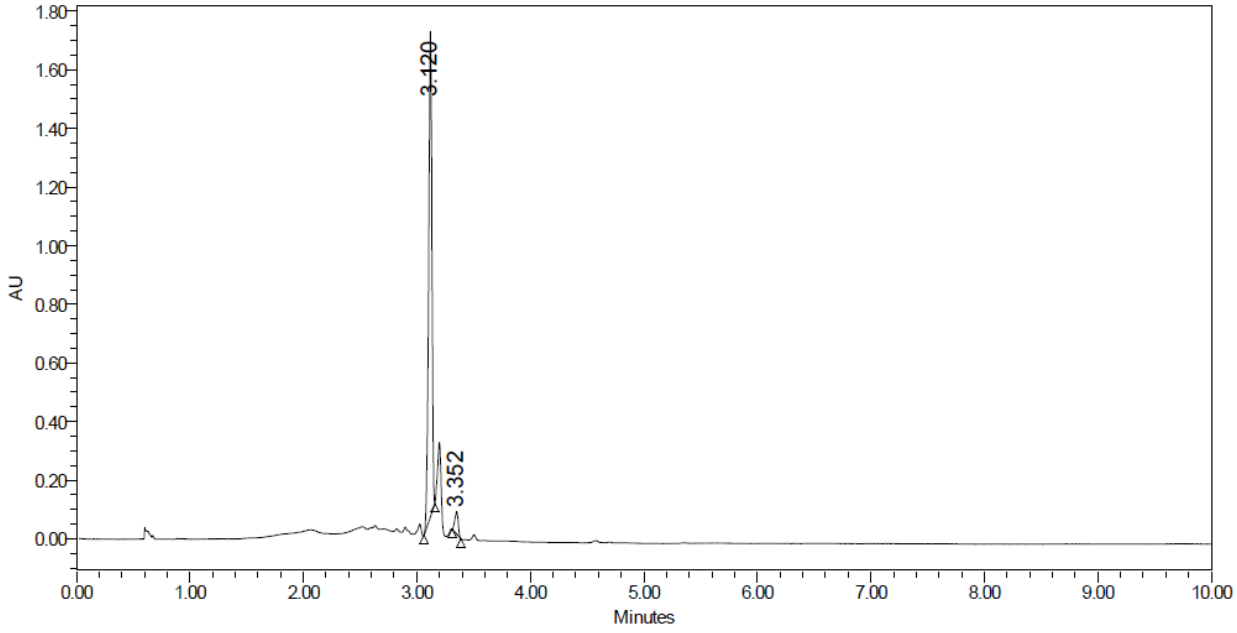
	Retention Time (min)	% Area
1	3.945	55.28
2	4.131	44.72



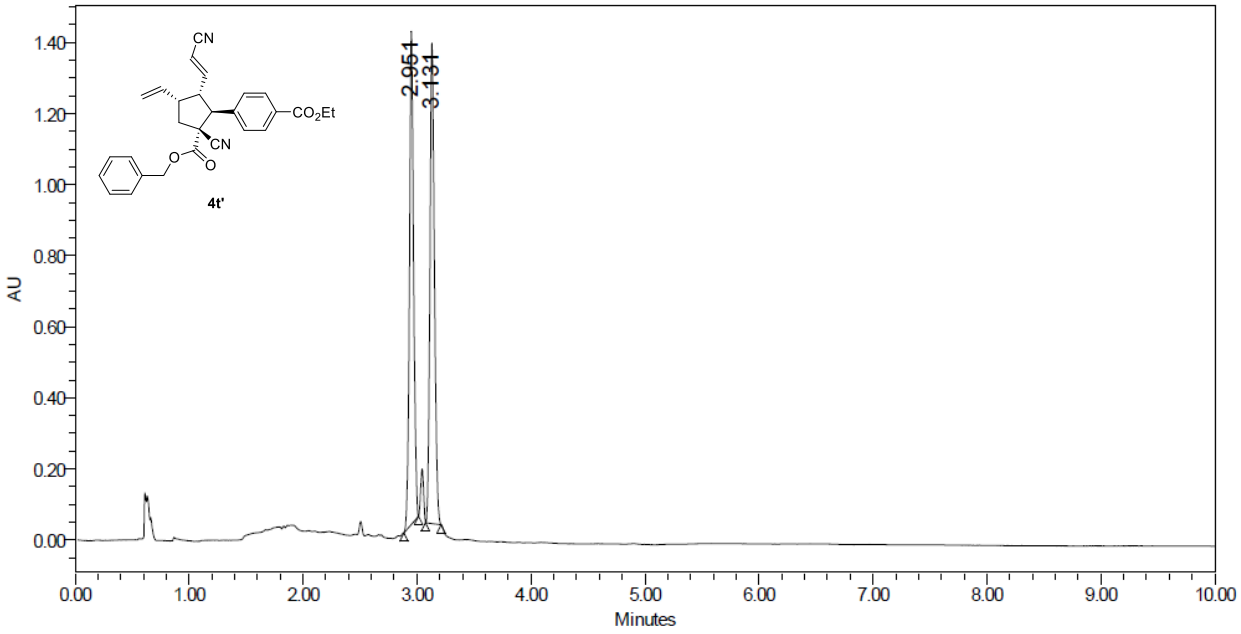
	Retention Time (min)	% Area
1	3.975	100.00



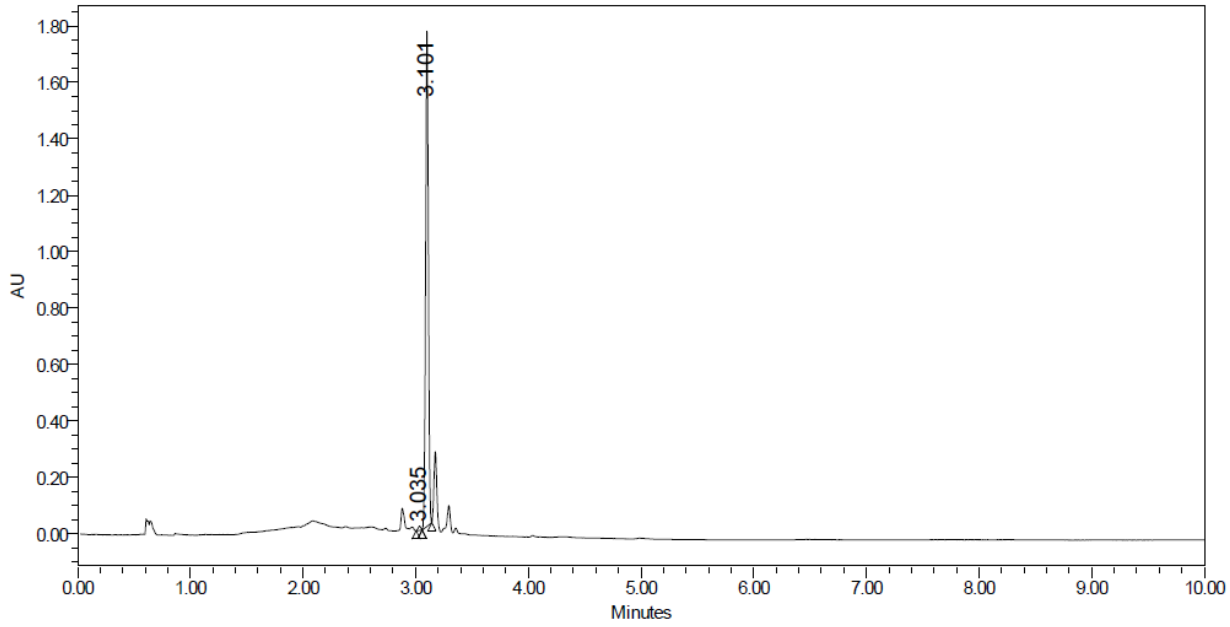
	Retention Time (min)	% Area
1	3.077	41.20
2	3.251	58.80



	Retention Time (min)	% Area
1	3.120	95.61
2	3.352	4.39



	Retention Time (min)	% Area
1	2.951	48.54
2	3.131	51.46



	Retention Time (min)	% Area
1	3.035	0.81
2	3.101	99.19