

Supporting Information

Stereoselective Synthesis of 1,3-Disubstituted Dihydroisoquinolines via L-Phenylalanine-Derived Dihydroisoquinoline N-Oxides

Jesús Flores-Ferrándiz, Nicholas Carter, Maria José González-Soria, Malgorzata Wasinska, Daniel Gill, Beatriz Maciá* and Vittorio Caprio*,

Division of Chemistry & Environmental Science, Manchester Metropolitan University

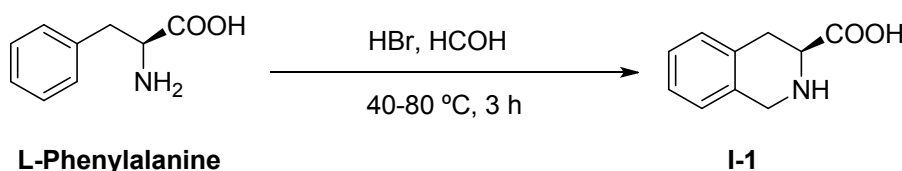
Oxford Road, M1 5GD, Manchester, UK

Table of contents

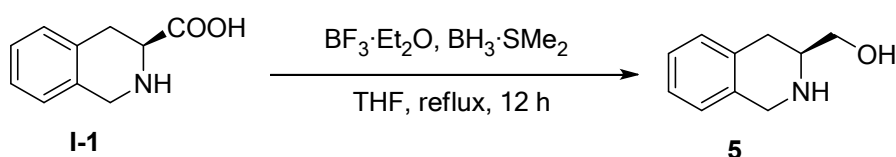
Experimental procedures for precursors S-1

NMR spectra for new compounds S-3

Experimental procedures for precursor compounds:



(S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (I-1): To a stirred mixture of *L*-phenylalanine (2.0 g, 12.1 mmol) in HBr (10 mL) at 40 °C, formaldehyde (1.8 mL, 48.9 mmol) was added dropwise over 15 min. The reaction mixture was stirred for 3 h at 70–80 °C until a white precipitate was formed. The reaction was cooled to room temperature and the white precipitate was collected by filtration and washed with cold ethanol (2 × 20 mL) to give the title compound (1.32 g, 86%) as a white powder. m.p decomposes T > 300 °C (lit.¹ 295 – 300 °C with decomposition). NMR spectral data is consistent with the literature.¹

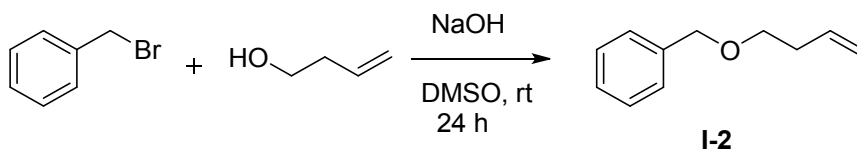


(S)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (5): The procedure was adapted from the literature.² To a stirred solution of **I-2** (3.0 g, 17.0 mmol) in dry THF (25 mL), BF₃·OEt₂ (6.4 mL, 51.0 mmol) was added dropwise over 10 min. The reaction mixture was then allowed to stir for 1 h under reflux. BH₃·SMe₂ (5.6 mL, 59.5 mmol) was added slowly over 15 min. and the mixture stirred under reflux overnight. The reaction mixture was then allowed to cool to r.t. and water (2 mL), followed by NaOH_(aq) (10 M, 22 mL) was added. The resulting two-phase system was stirred vigorously at reflux for 2 h and allowed to cool down to r.t. The reaction mixture was concentrated under reduced pressure and the residue was extracted with CH₂Cl₂ (3 × 35 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was crystallized from EtOAc to afford the title compound (1.18 g, 61%) as a white solid. m.p. 118 °C (lit.² 117–118 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.15–6.99 (m, 4H), 4.00 (s, 2H), 3.92 (br s, 2H), 3.69 (dd, *J* = 10.9, 3.4 Hz, 1H), 3.49 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.01–2.94 (m, 1H), 2.66–2.53 (m, 2H). ¹³C

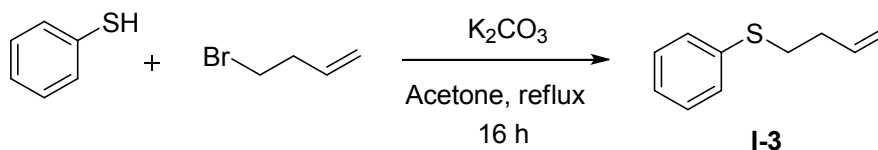
¹ Chalepo, M. P.; Pawar, S. A.; Sokhela, M. K.; Govender, T.; Kruger, H. G.; Maguire, G. E. M. *Eur. J. Med. Chem.*, **2013**, *66*, 407–414.

² Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2883–2889.

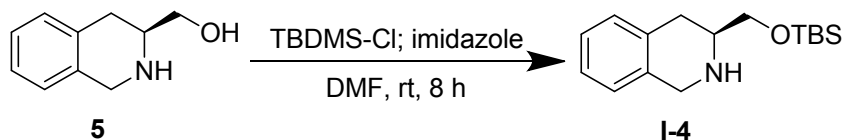
NMR (101 MHz, CDCl₃) δ : 135.6, 133.9, 129.3, 126.29, 126.28, 125.8, 65.8, 55.1, 47.8, 30.9. NMR spectral data is consistent with the literature.³



3-Benzyloxybut-1-ene (I-2): Benzyl bromide (594 μ L, 5 mmol) was added to a solution of allyl alcohol (340 μ L, 5 mmol) and aq NaOH (2 M, 5 mL, 10 mmol) in DMSO (20 mL) and the reaction mixture was stirred at room temperature for 24 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 \times 30 mL). The organic layers were washed with water (10 mL) and brine (10 mL), then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (95:5) as eluent to give the title compound (184 mg, 47%) as a colourless oil. NMR spectral data is consistent with the literature.⁴



But-3-en-1-yl(phenyl)sulfane (I-3): K₂CO₃ (690 mg, 5 mmol) and 4-bromobutene (305 μ L, 3 mmol) were added to a solution of thiophenol (275 mg, 2.5 mmol) in acetone (10 mL). The reaction mixture was stirred under reflux overnight then concentrated under reduced pressure. EtOAc (15 mL) was added and the organic phase was washed with water (10 mL) then dried over MgSO₄ and concentrated under reduced pressure to give the title compound (393 mg, 96%) as a colorless oil. NMR spectral data is consistent with the literature.⁵



Synthesis of (S)-1,2,3,4-tetrahydro-3-tert-butylidimethylsilyloxymethylisoquinoline (I-4). Imidazole (0.41 g, 6.0 mmol) and *tert*-butyldimethylsilylchloride (0.90 g, 6.0 mmol) were added to a solution of **5** (0.66 g, 4.0 mmol) in DMF (10 mL). The mixture was stirred for 72 h at r.t. and then concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate (3 \times 25 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexane-EtOAc (10:1) as eluent to give the title compound (0.258 g, 77% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.03 (m, 4H), 4.13–4.05 (m, 2H), 3.77 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.61 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.06–2.99 (m, 1H), 2.69–2.60 (m, 2H), 2.11 (br s, 1H), 0.92 (s, 9H), 0.10 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ : 135.8, 134.9, 129.4, 126.3, 126.2, 125.8, 67.1, 55.1, 48.4, 31.2, 26.1, 18.5, –5.20, –5.24. NMR spectral is consistent with the literature.⁶

³ Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakkar, K.; Bidlack, J. M. *J. Org. Chem.*, **1998**, *63*, 7795–7804.

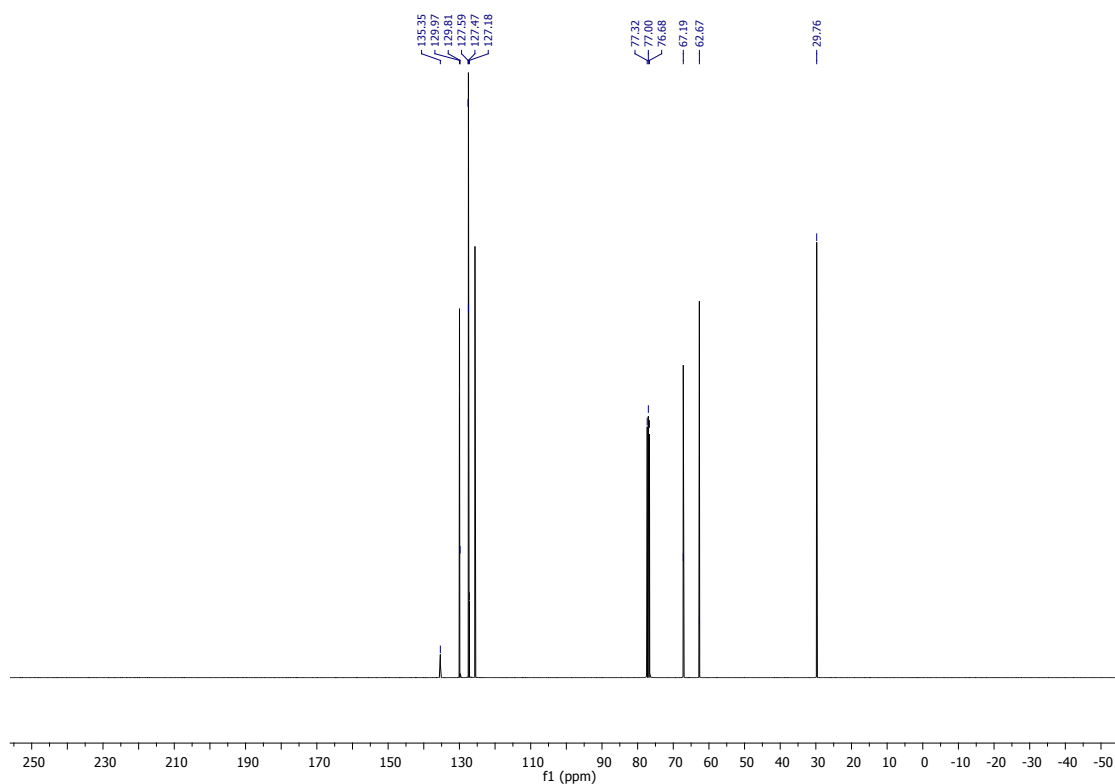
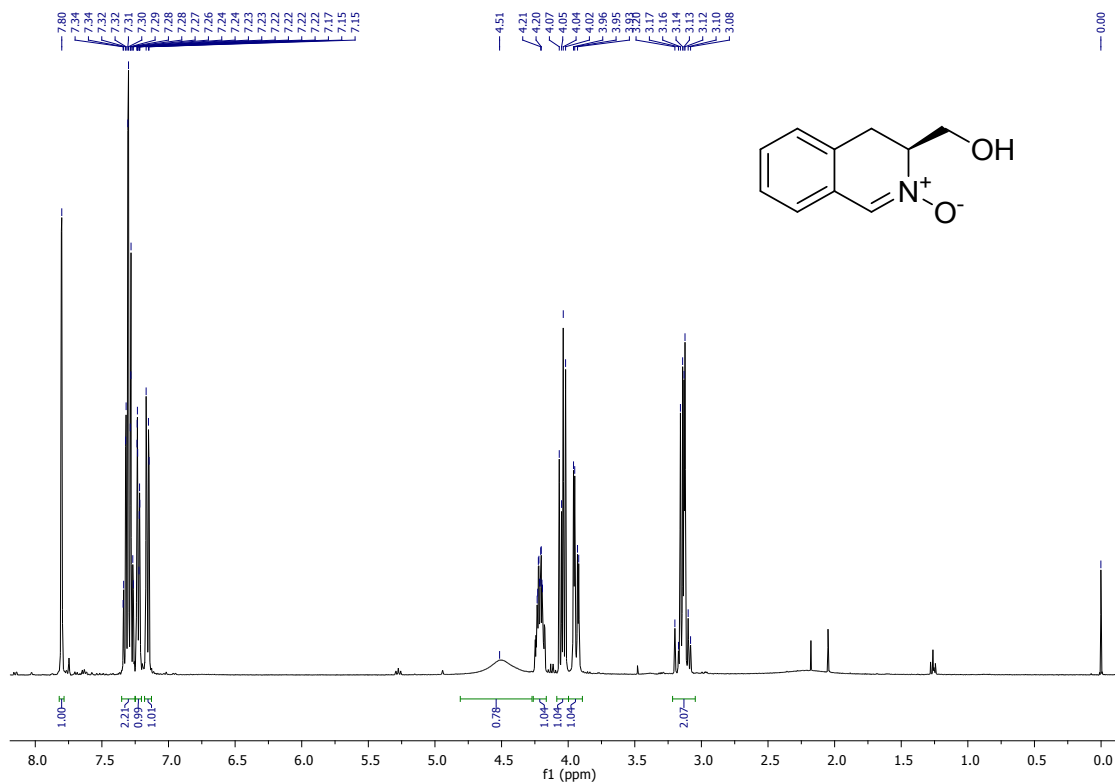
⁴ Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Eriksson, C. *Org. Lett.*, **1999**, *1*, 1599–1602.

⁵ Leicht, H.; Göttker-Schnetmann, I.; Mecking, S. *J. Am. Chem. Soc.*, **2017**, *139*, 6823–6826.

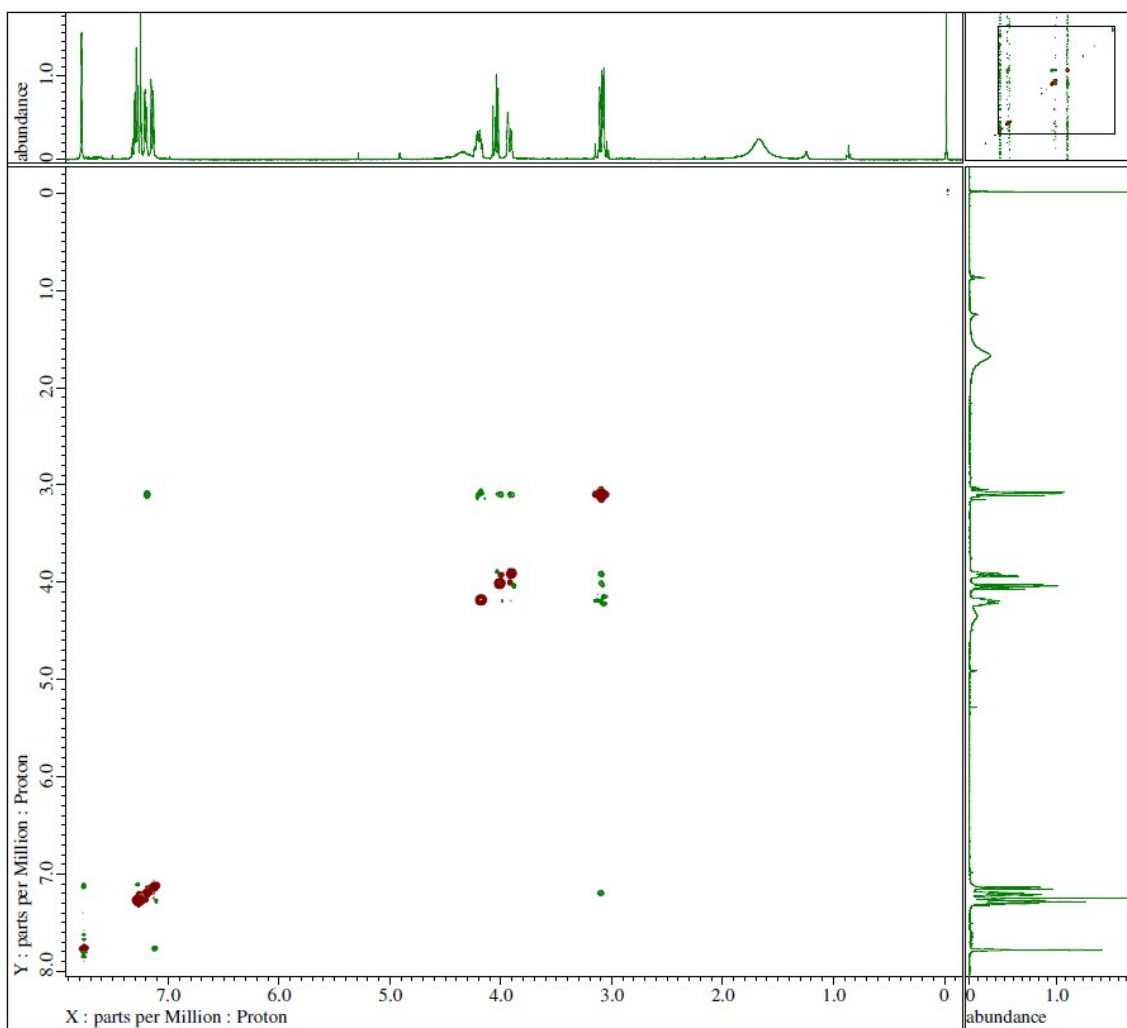
⁶ Page, D.; Naismith, A.; Schmidt, R.; Coupal, R.; Labarre, E.; Gosselin, M.; Bellemare, D.; Payza, K.; Brown, W. *J. Med. Chem.* **2001**, *44*, 2387–2390.

NMR spectra for new compounds

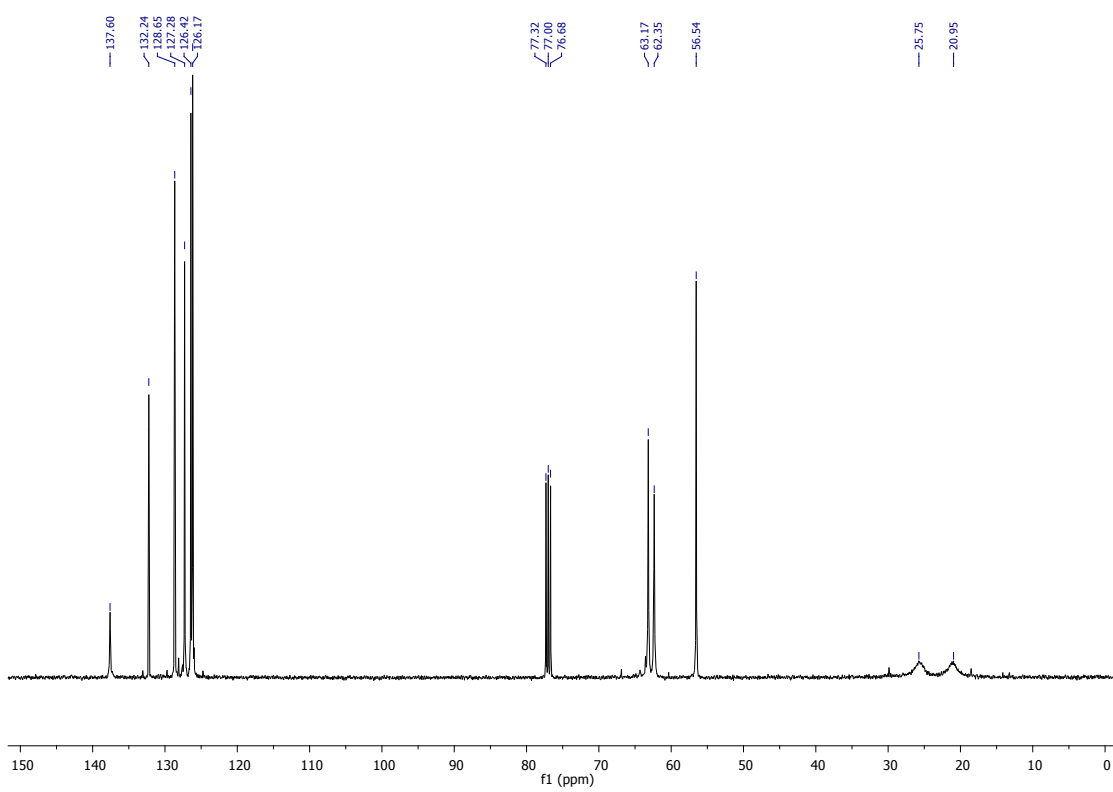
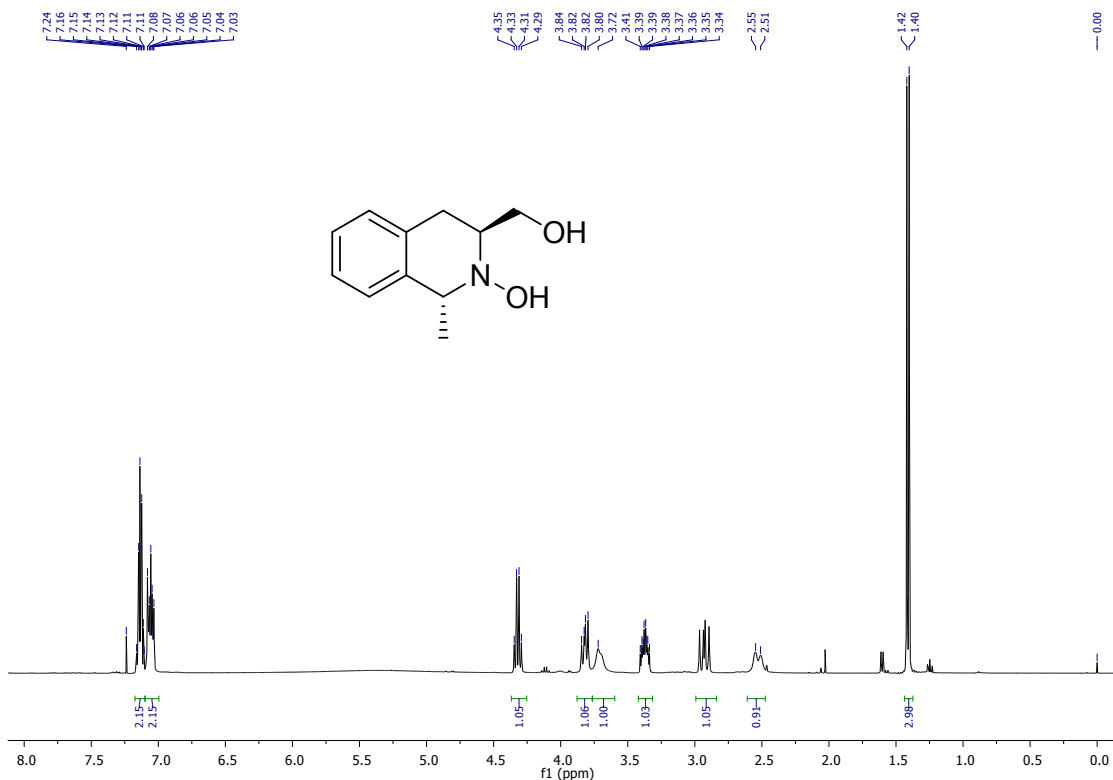
(S)-3-(hydroxymethyl)-3,4-dihydroisoquinoline 2-oxide (3)



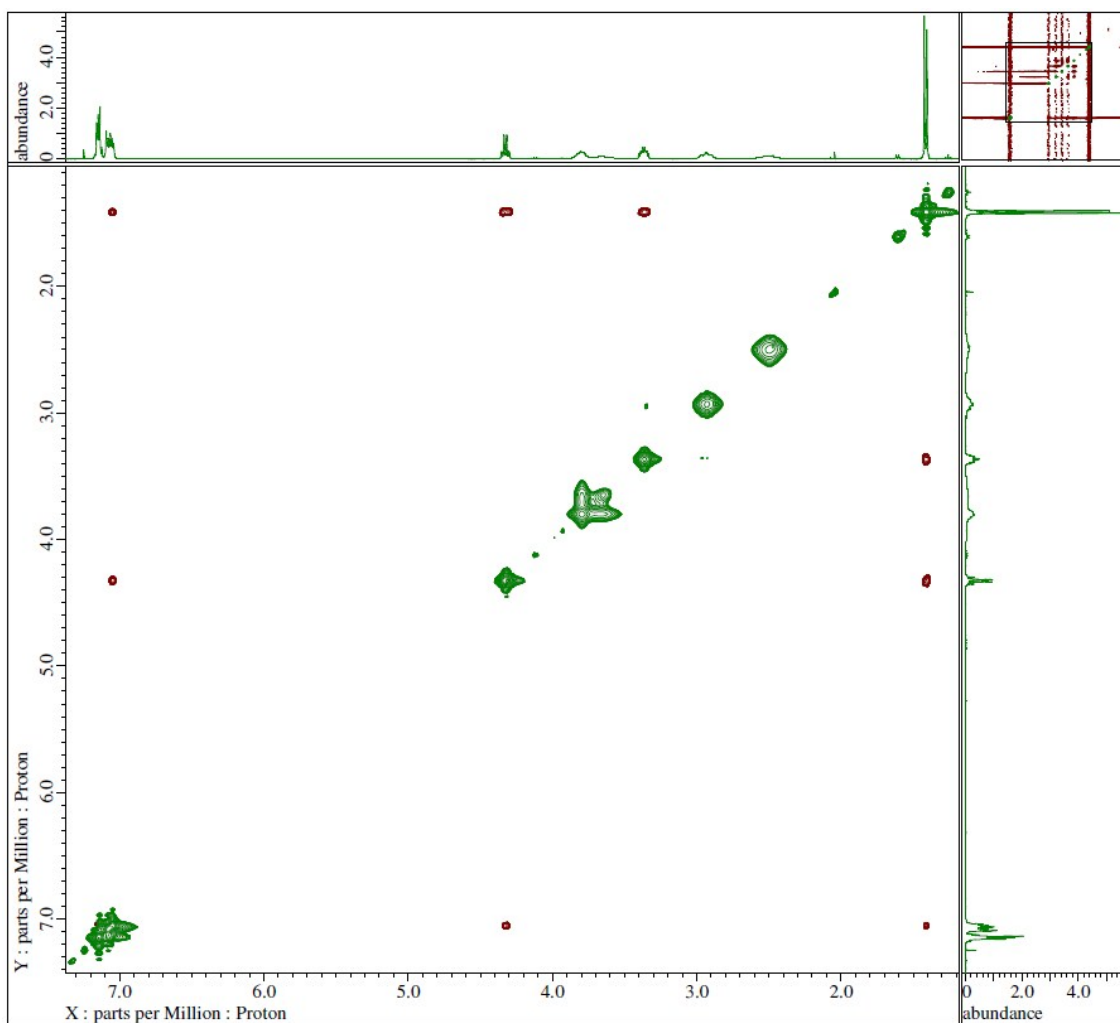
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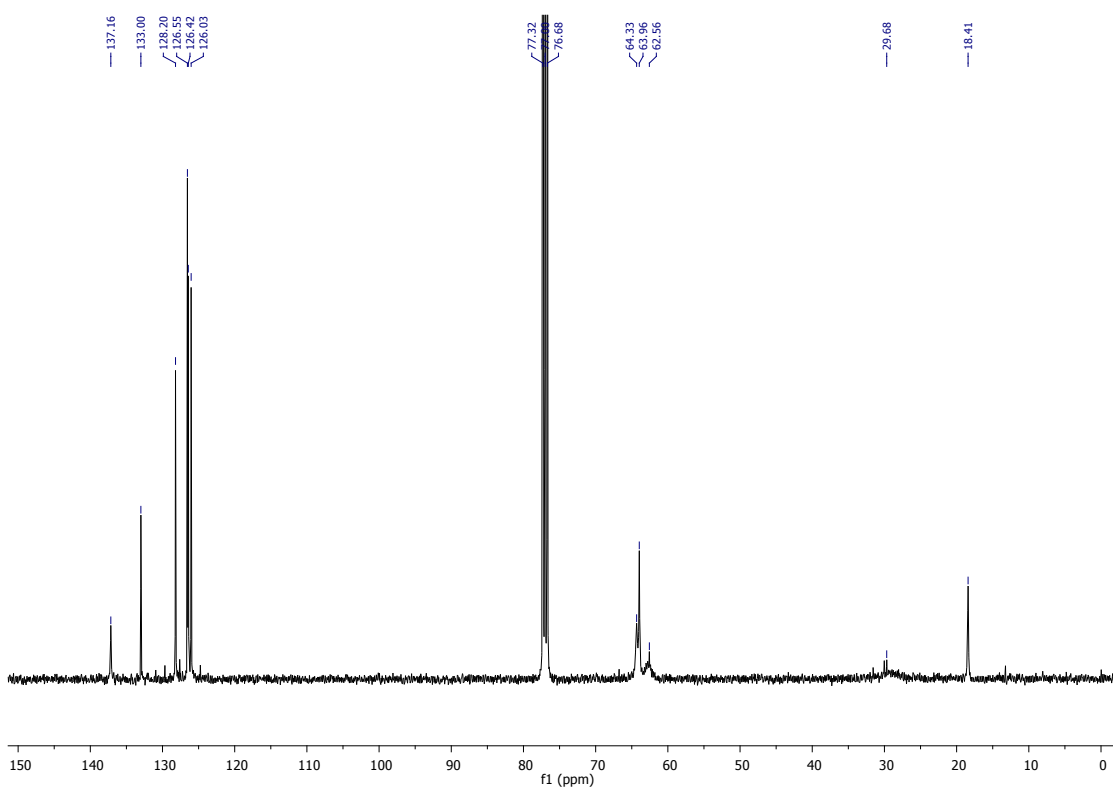
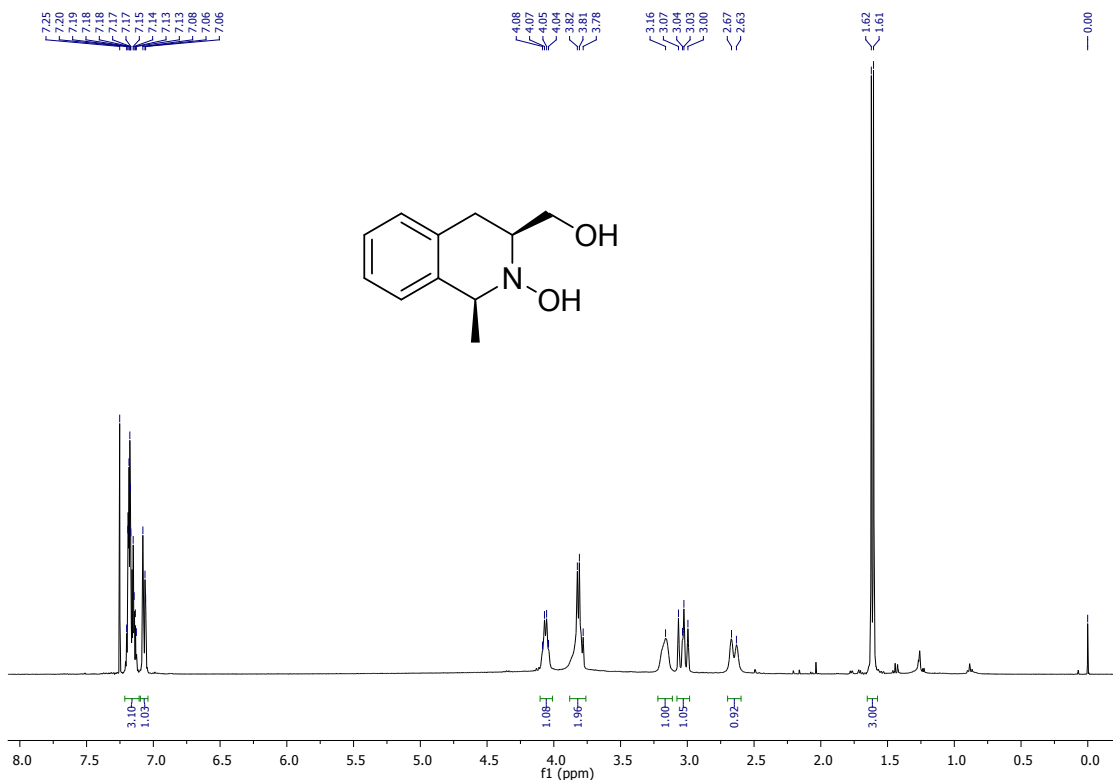
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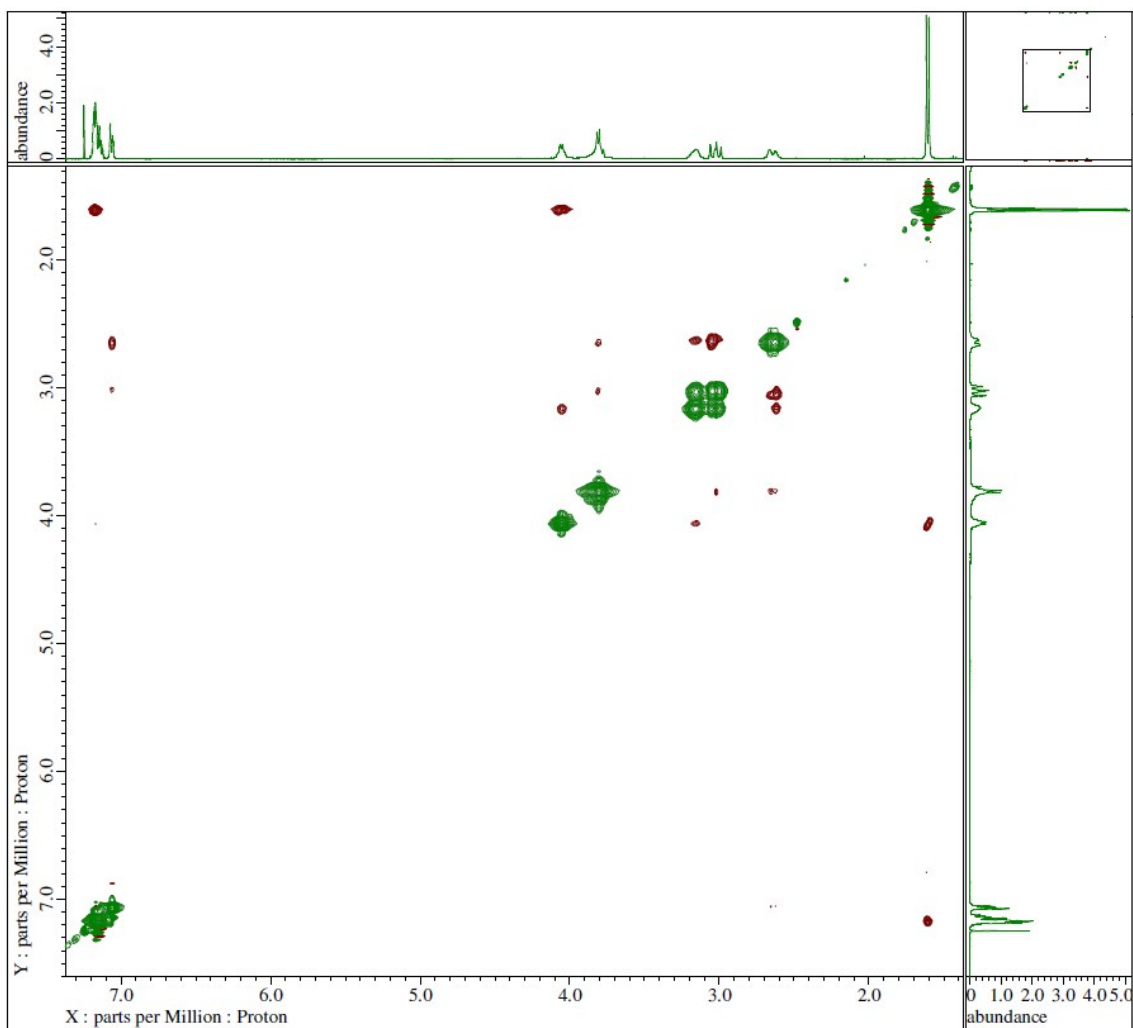
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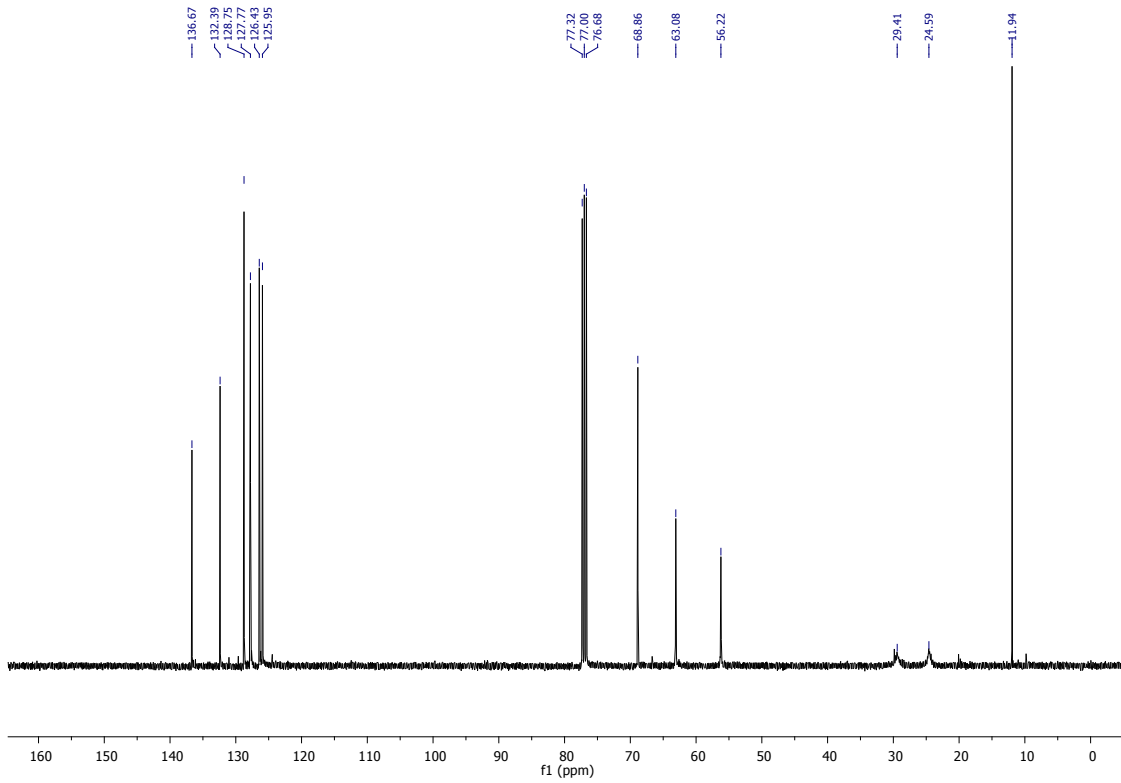
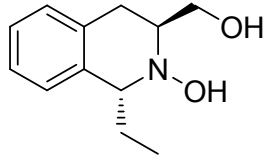
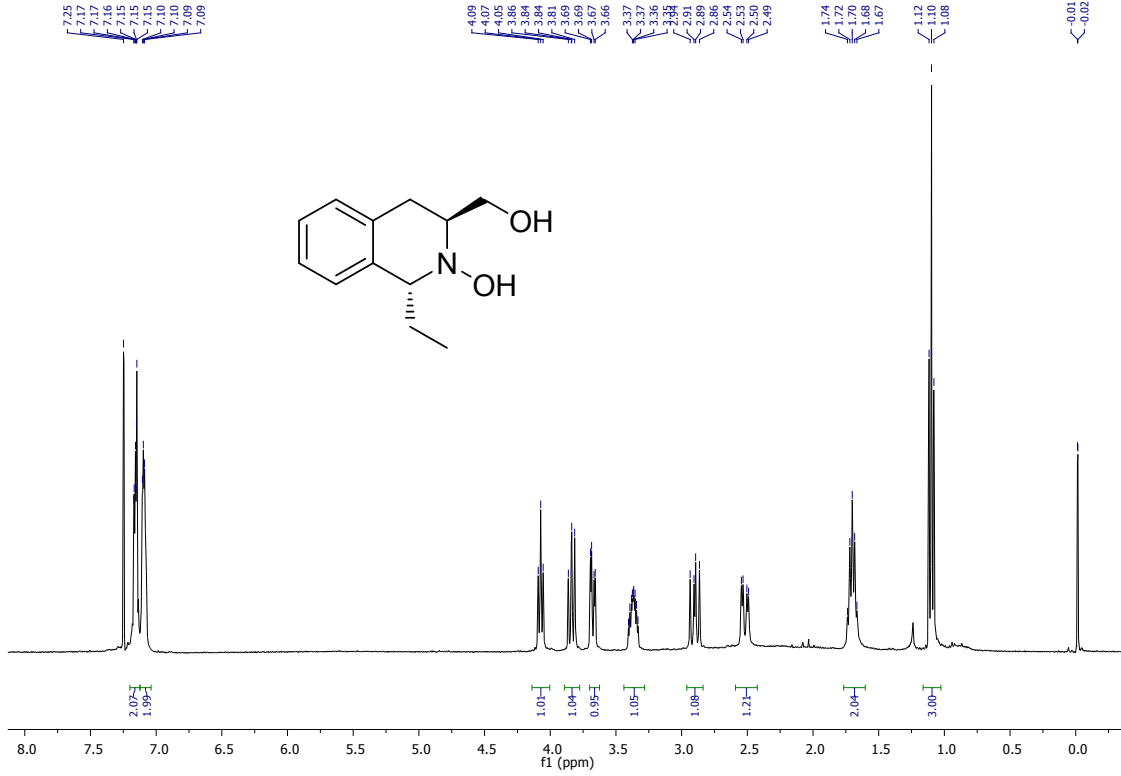
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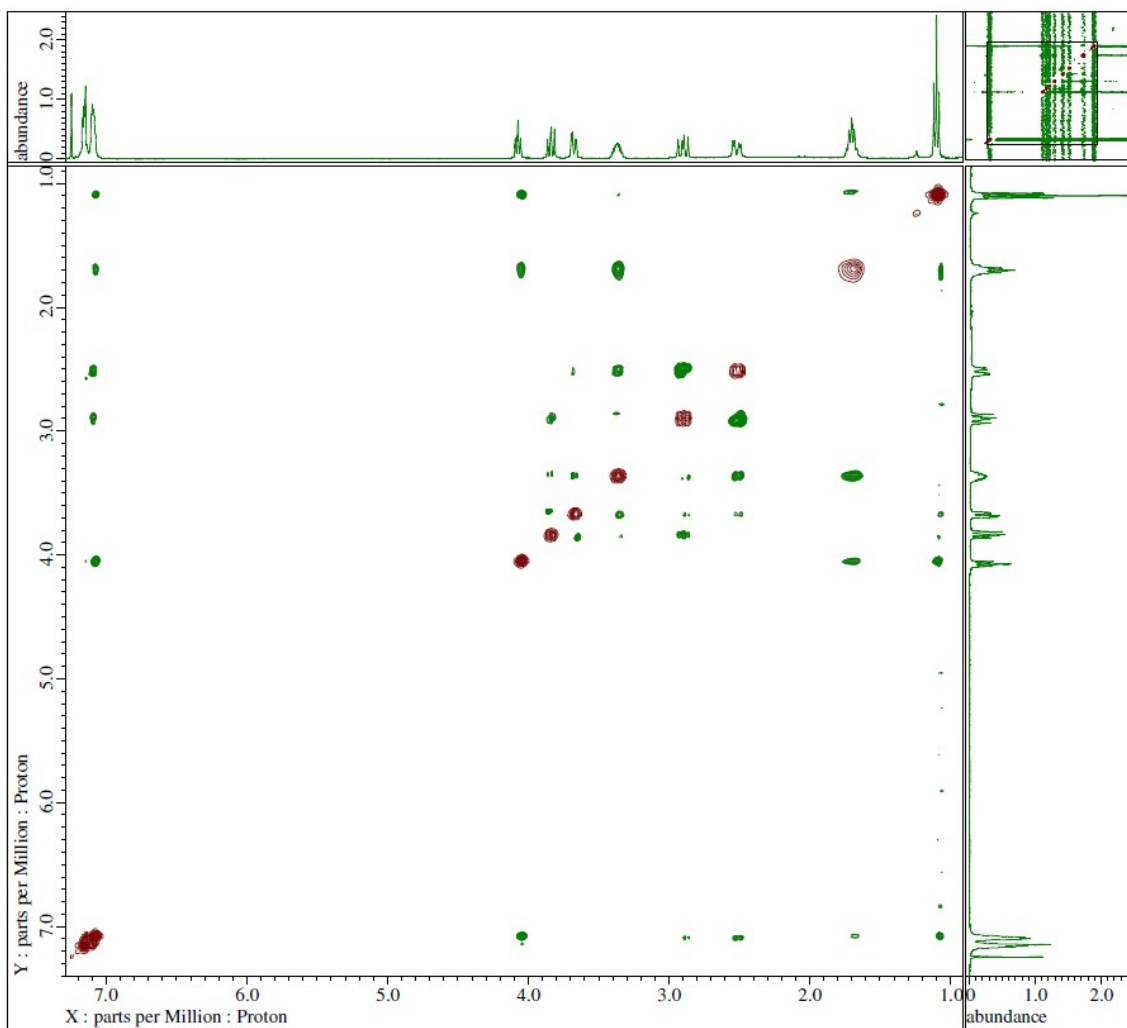
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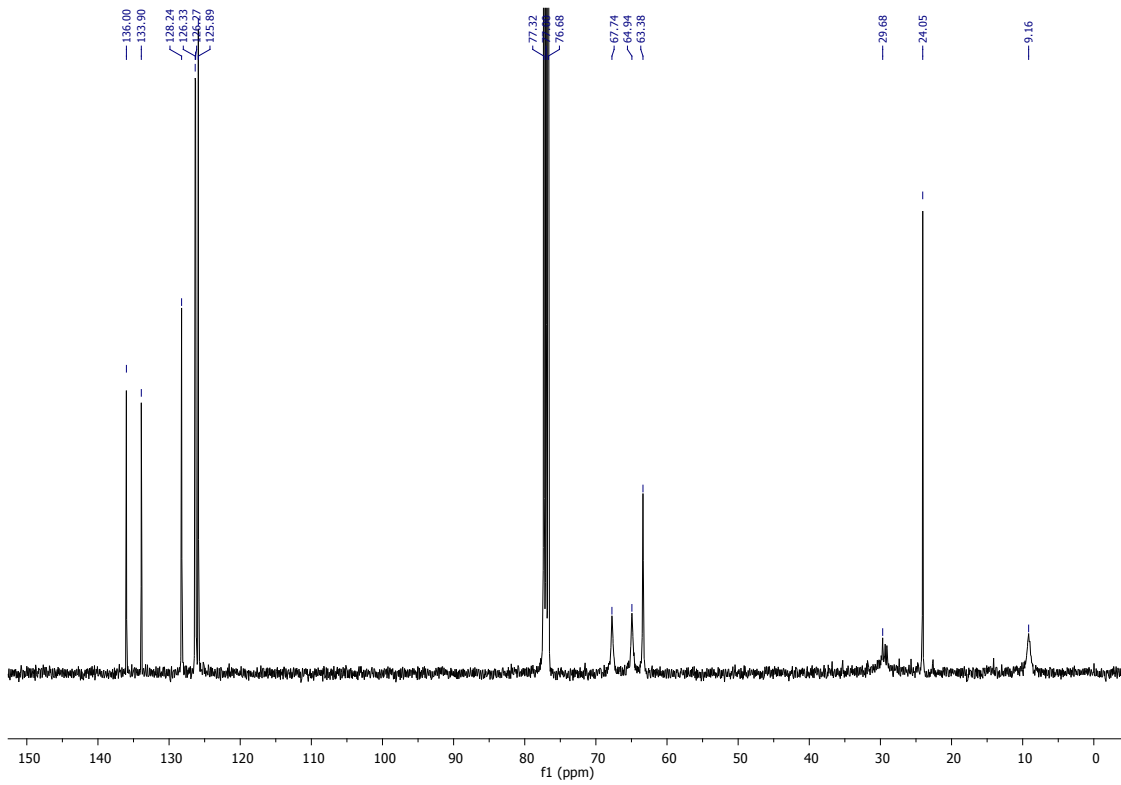
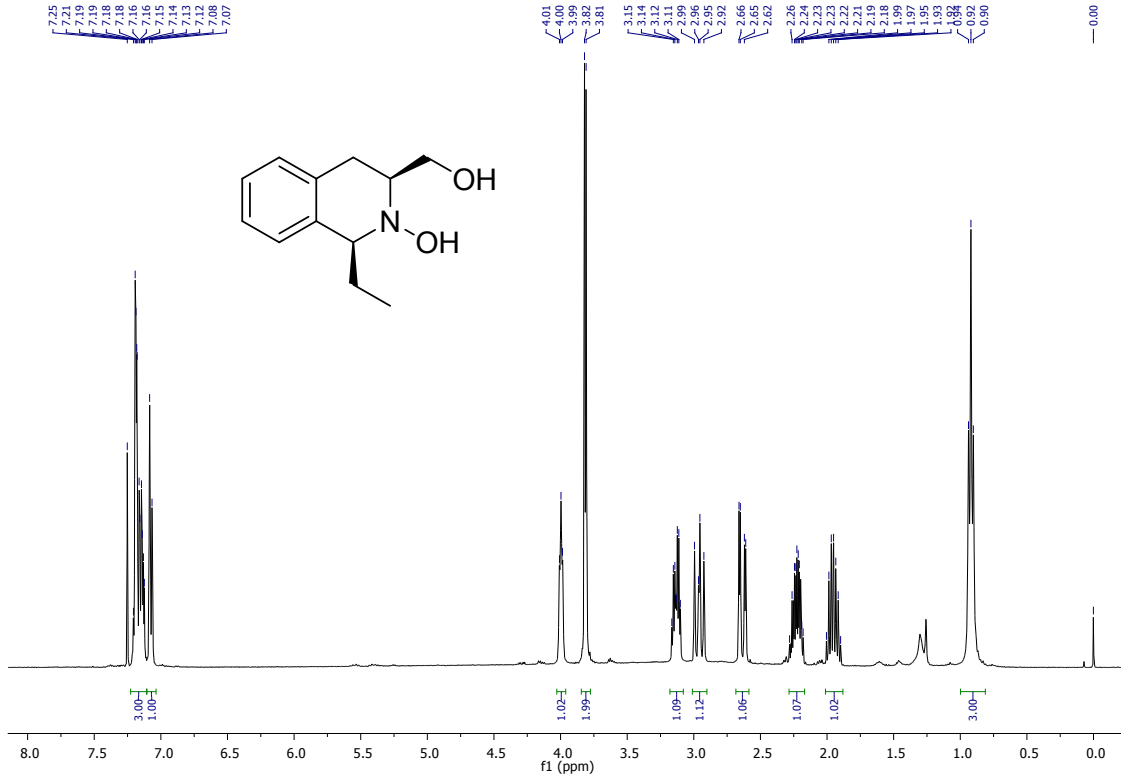
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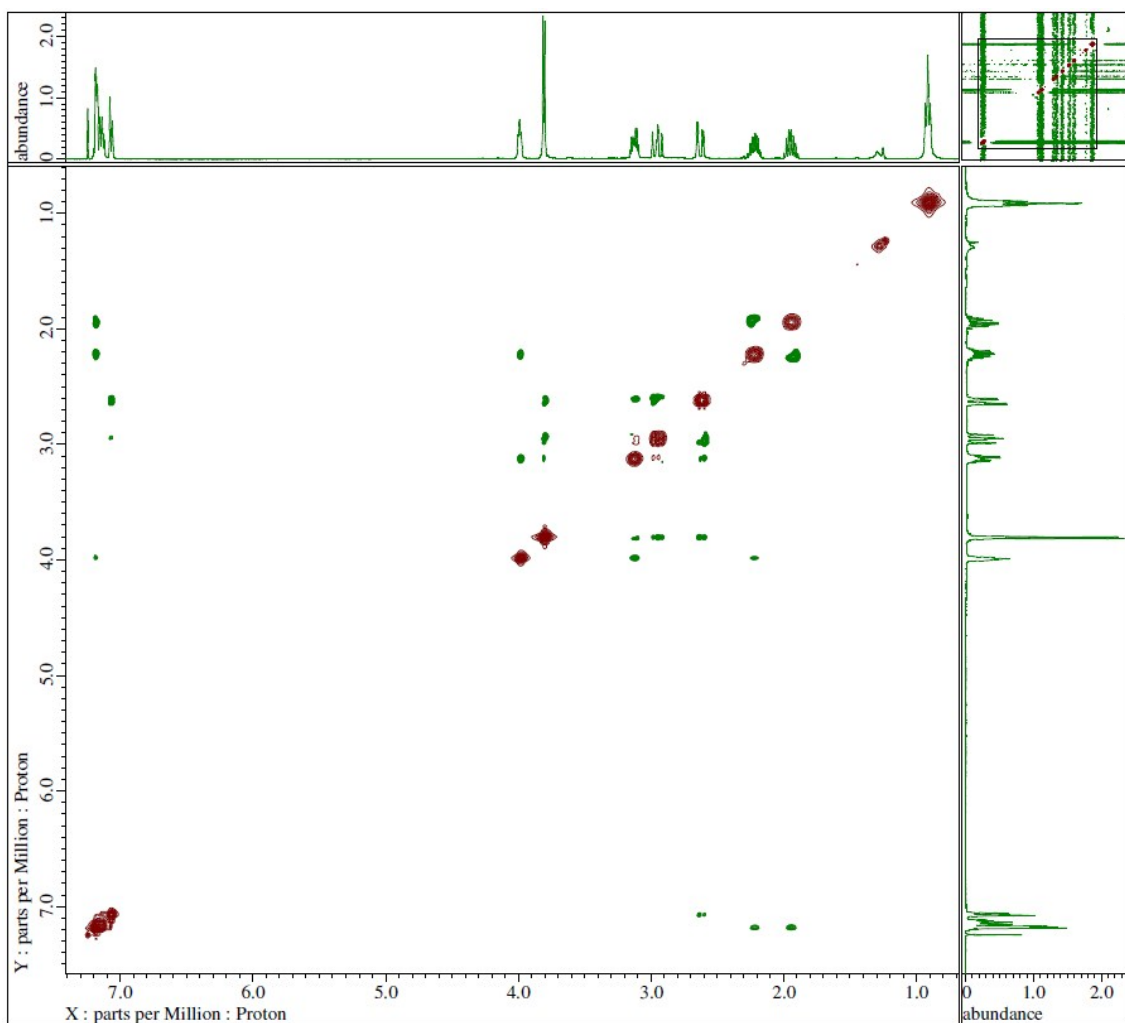
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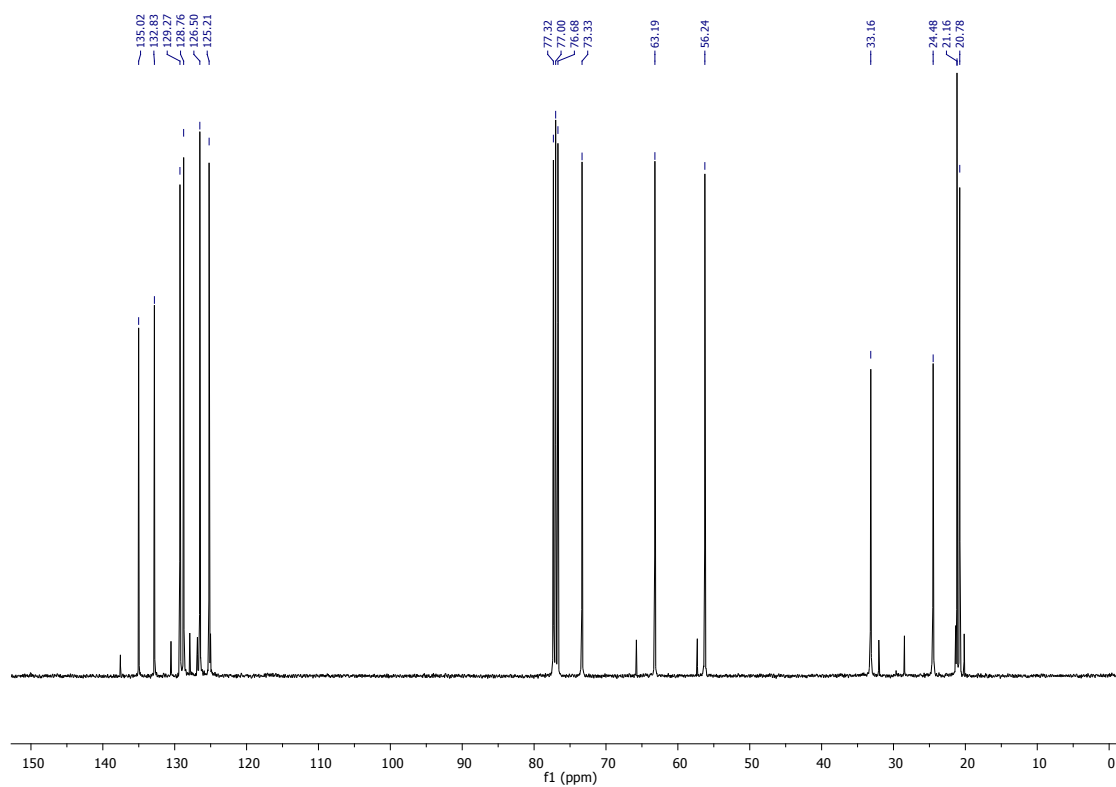
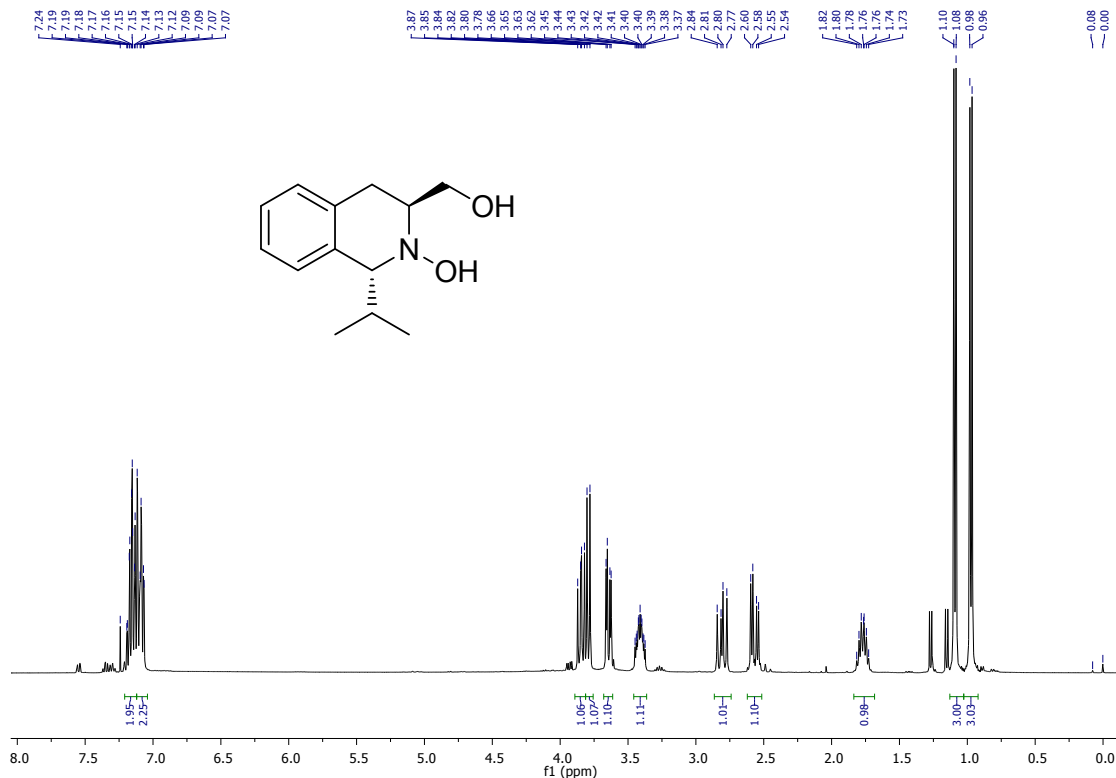
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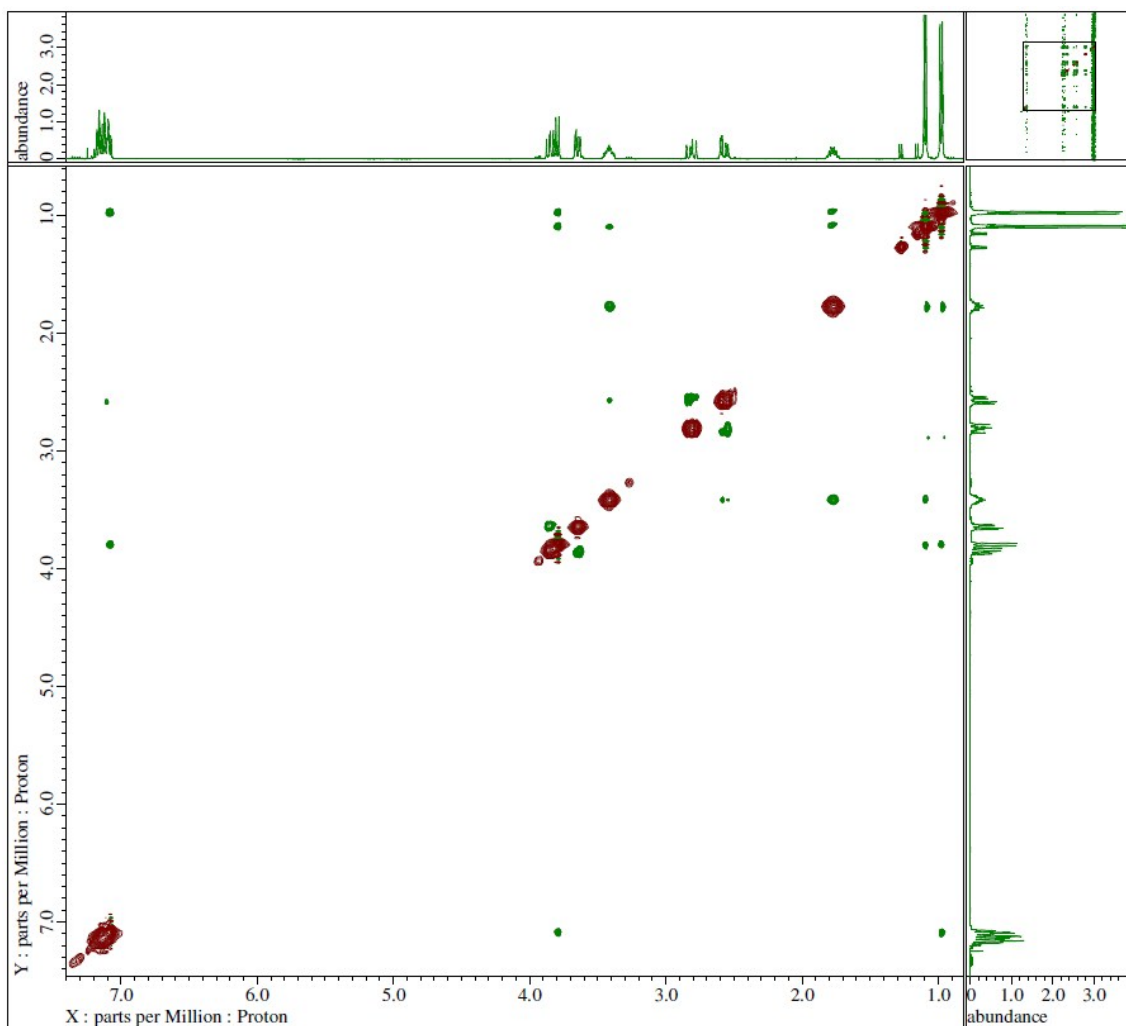
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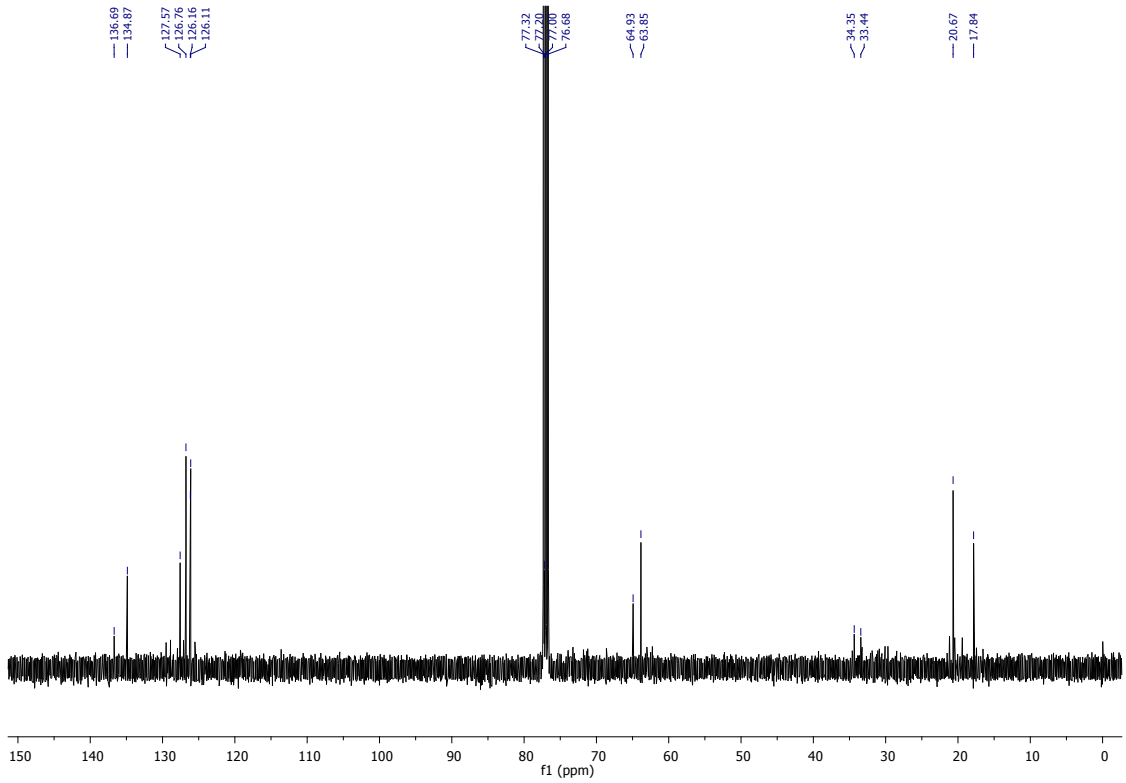
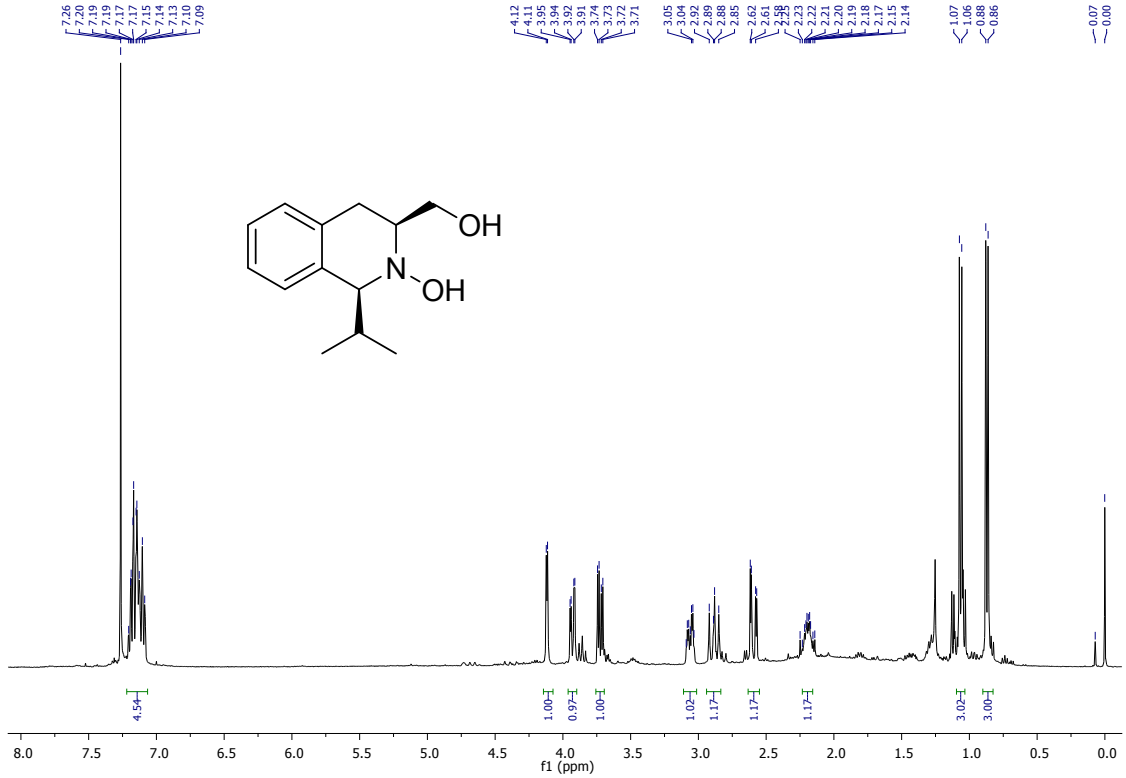
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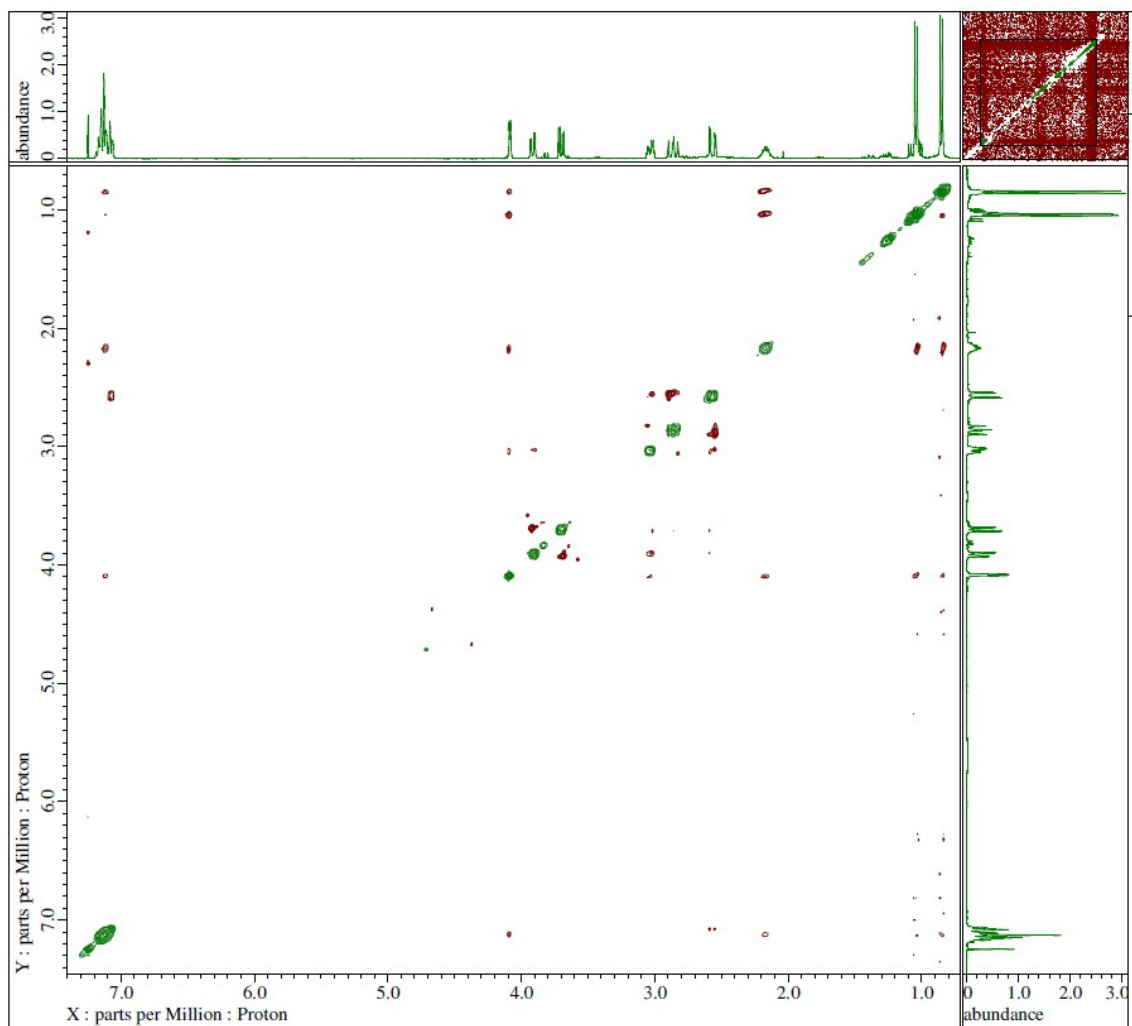
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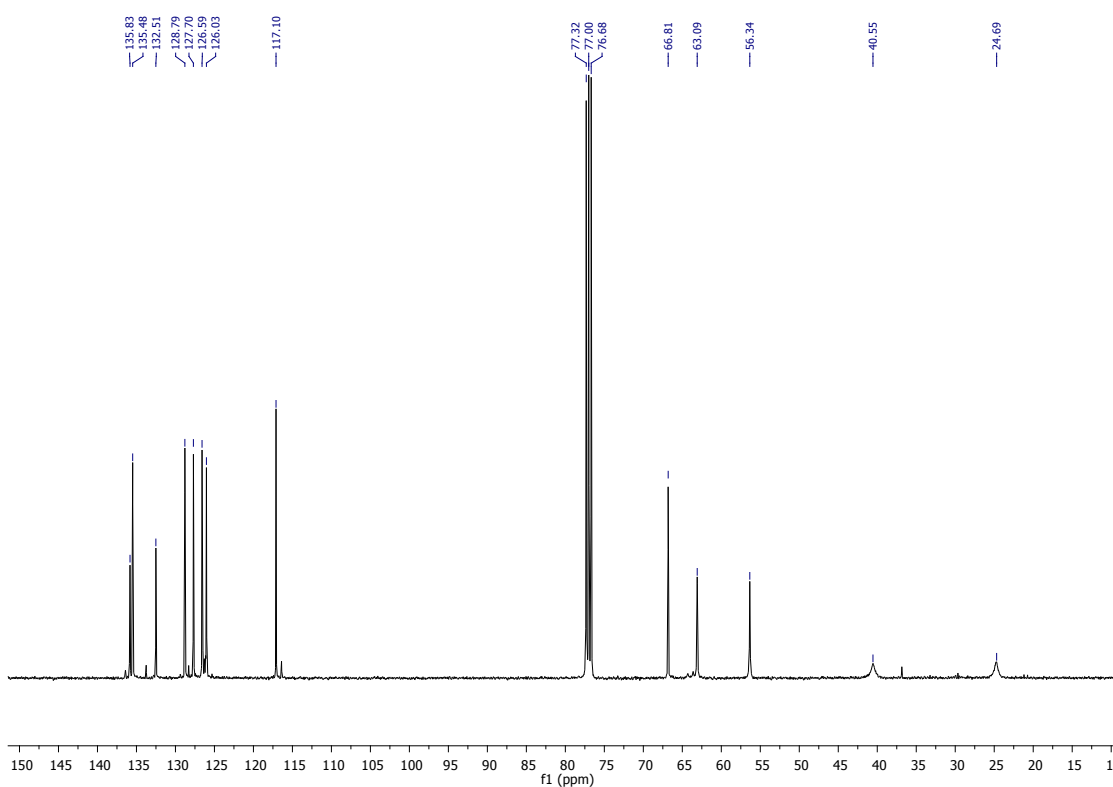
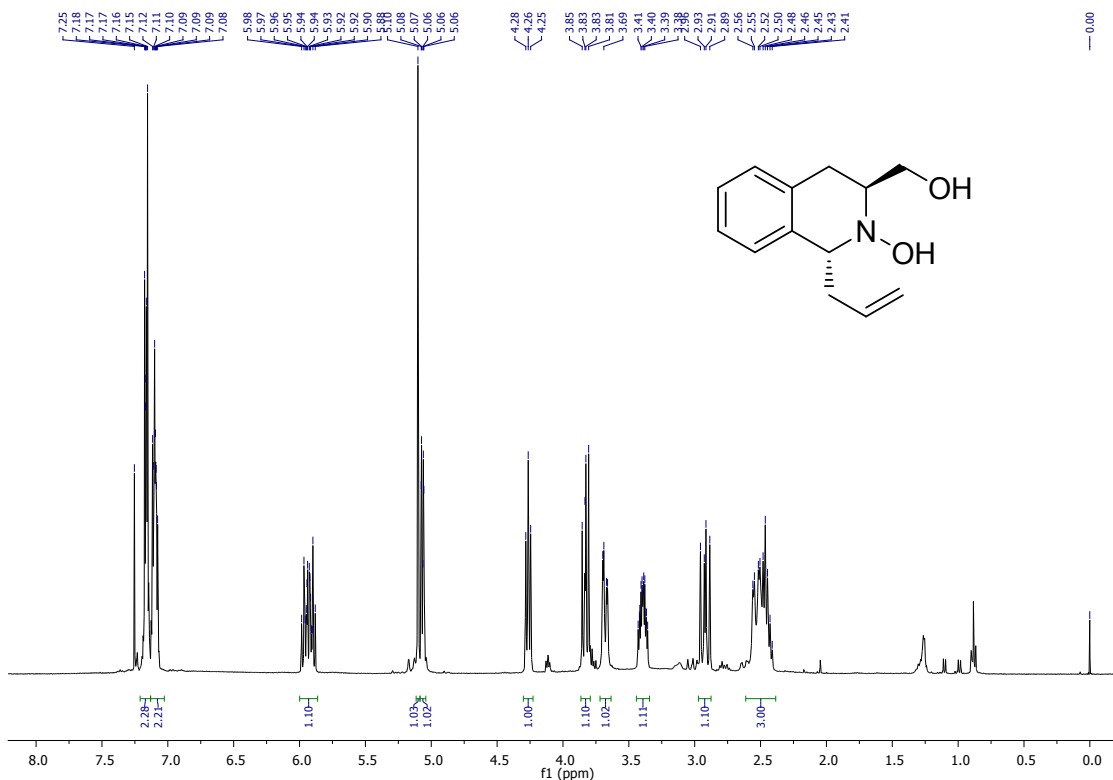
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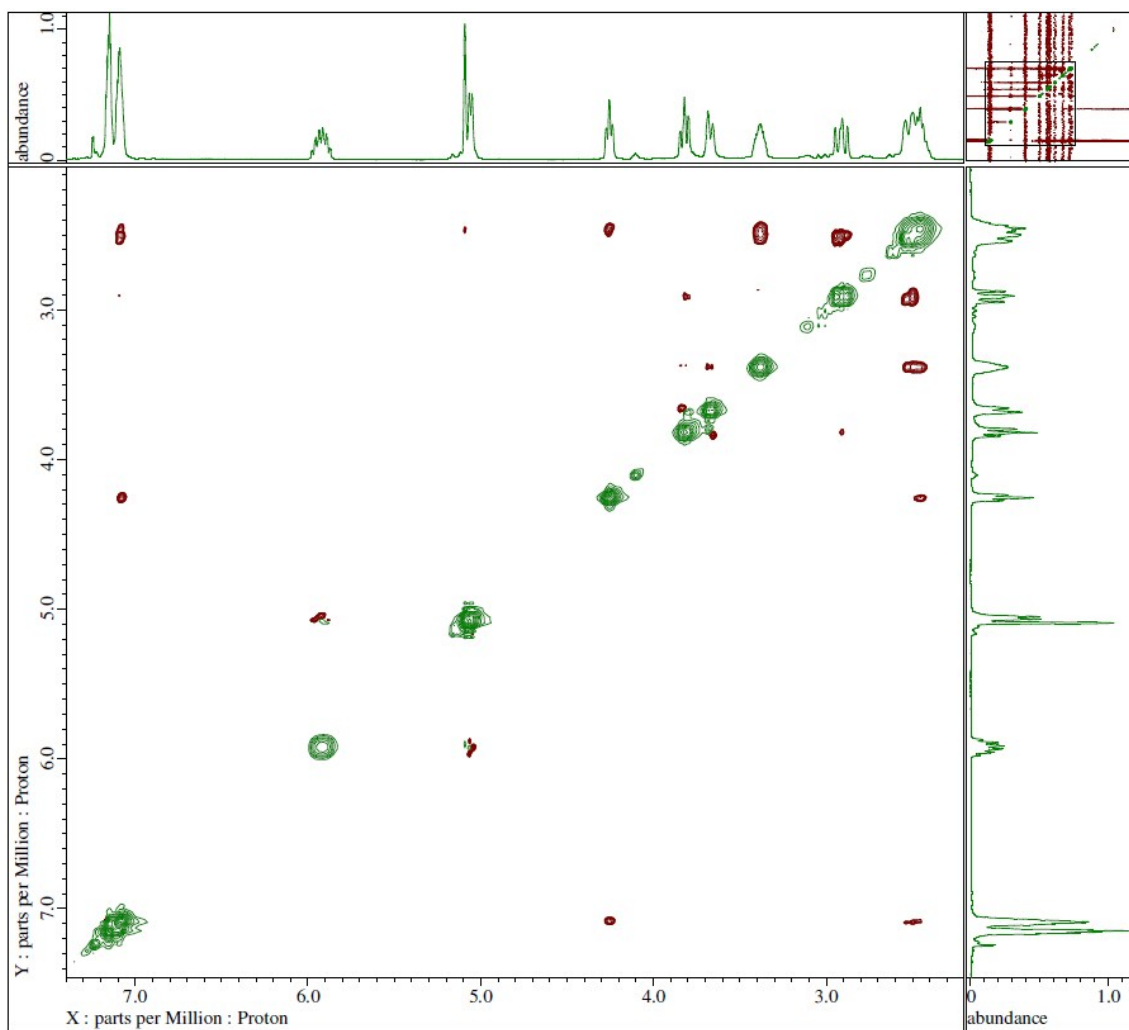
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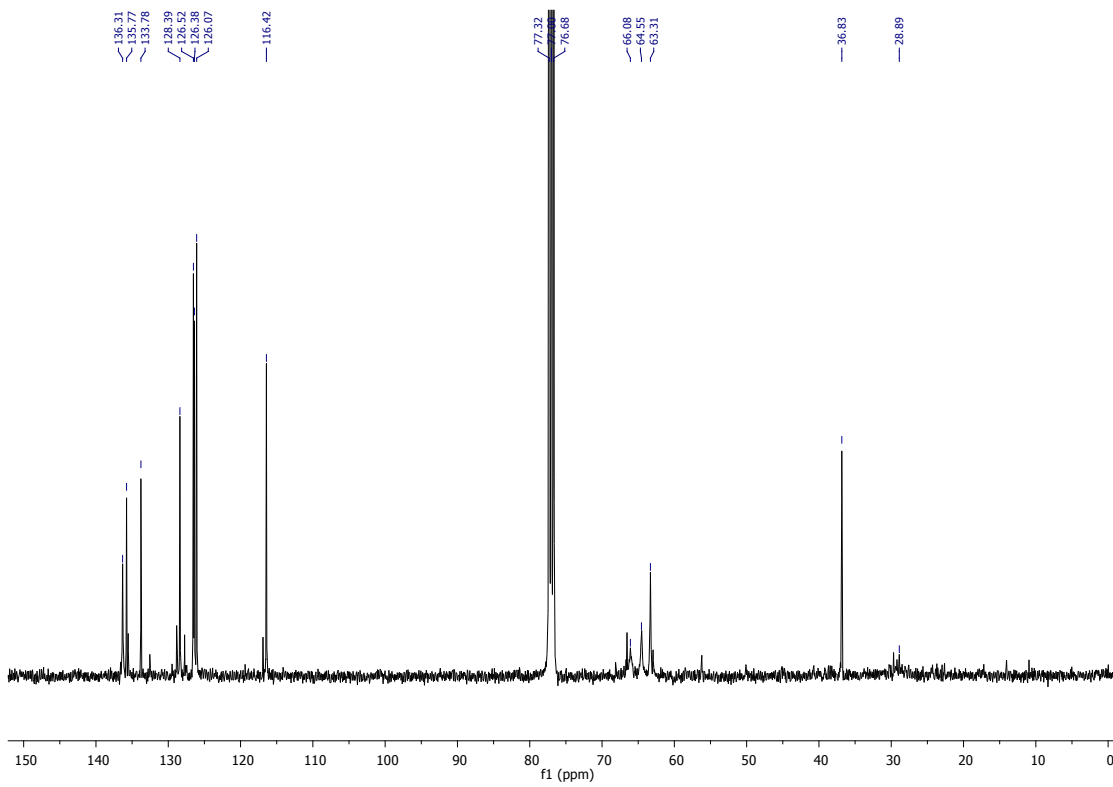
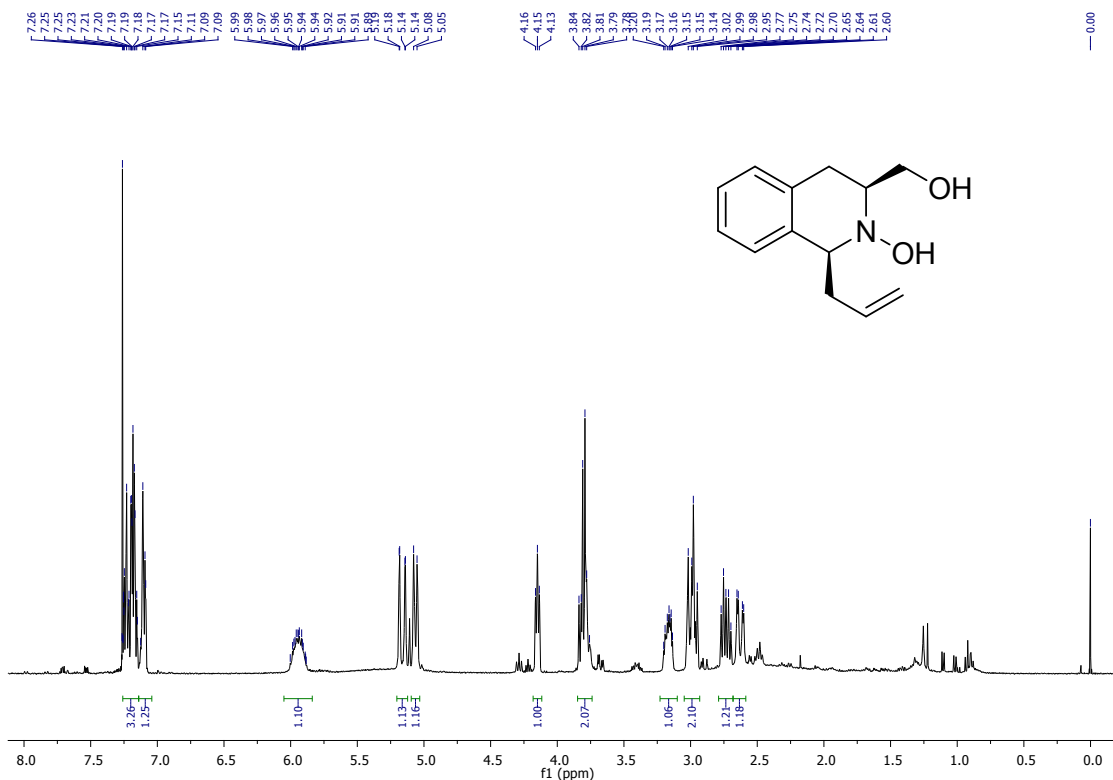
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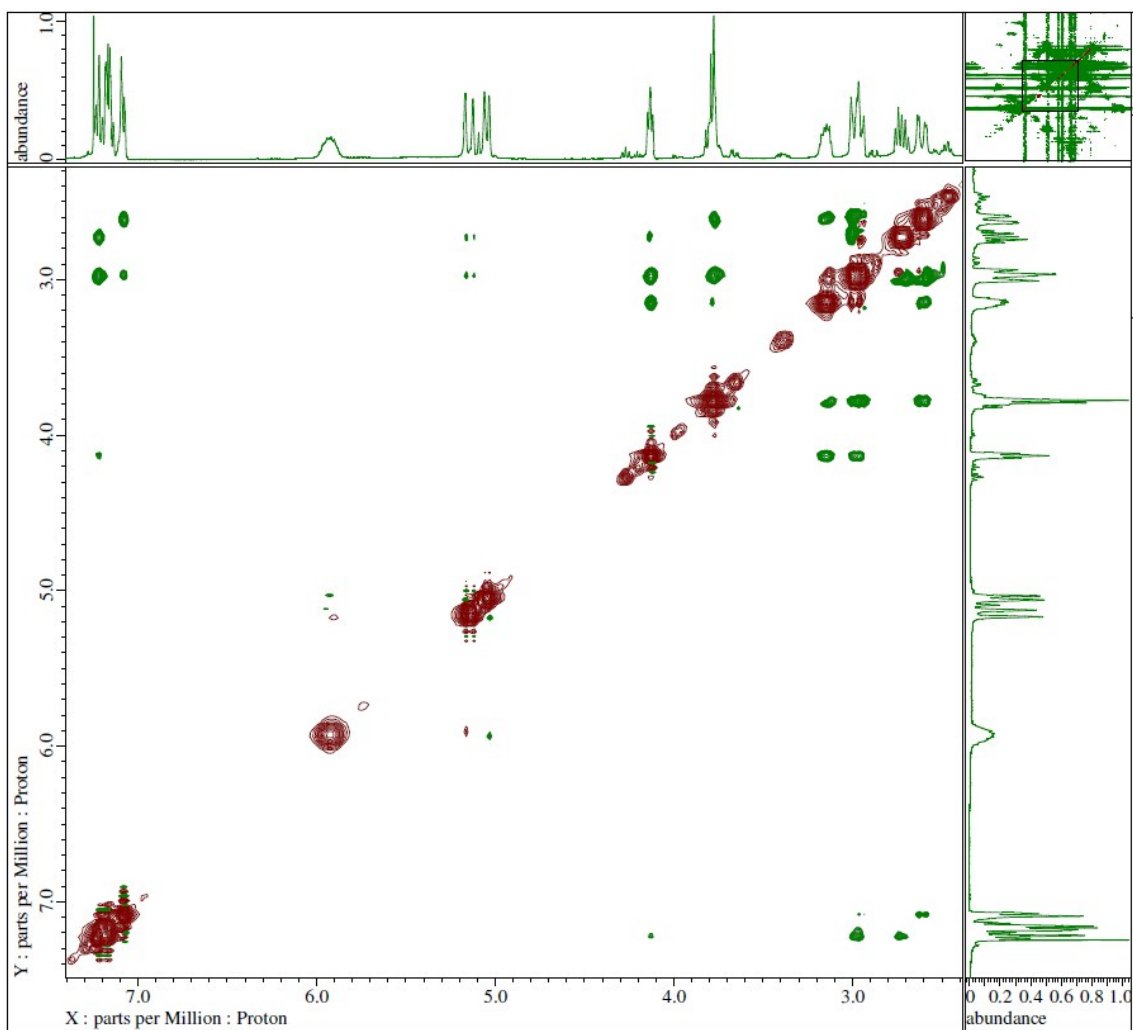
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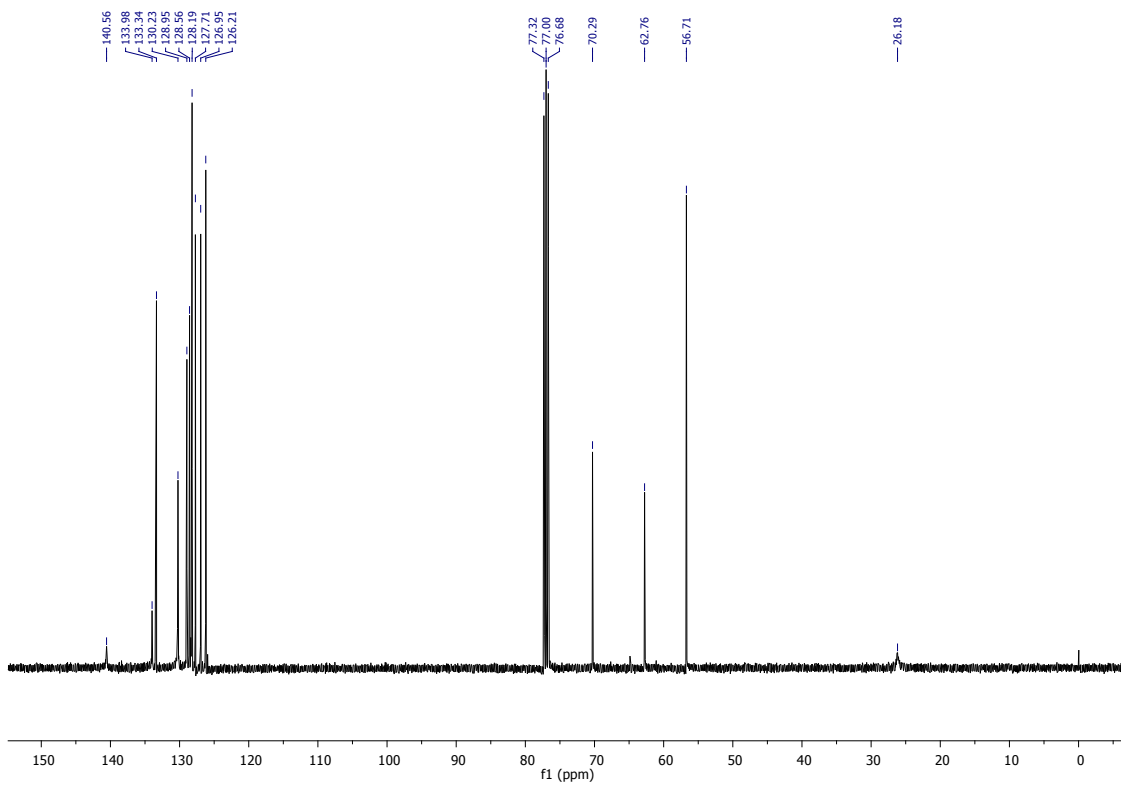
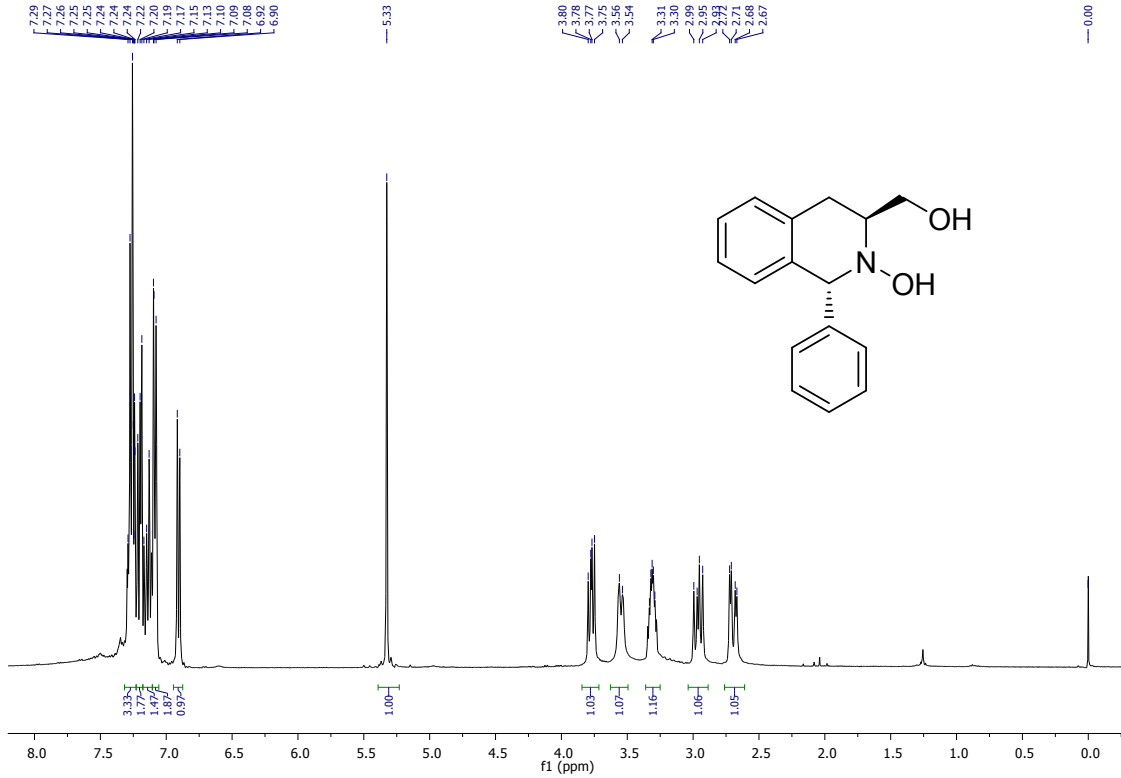
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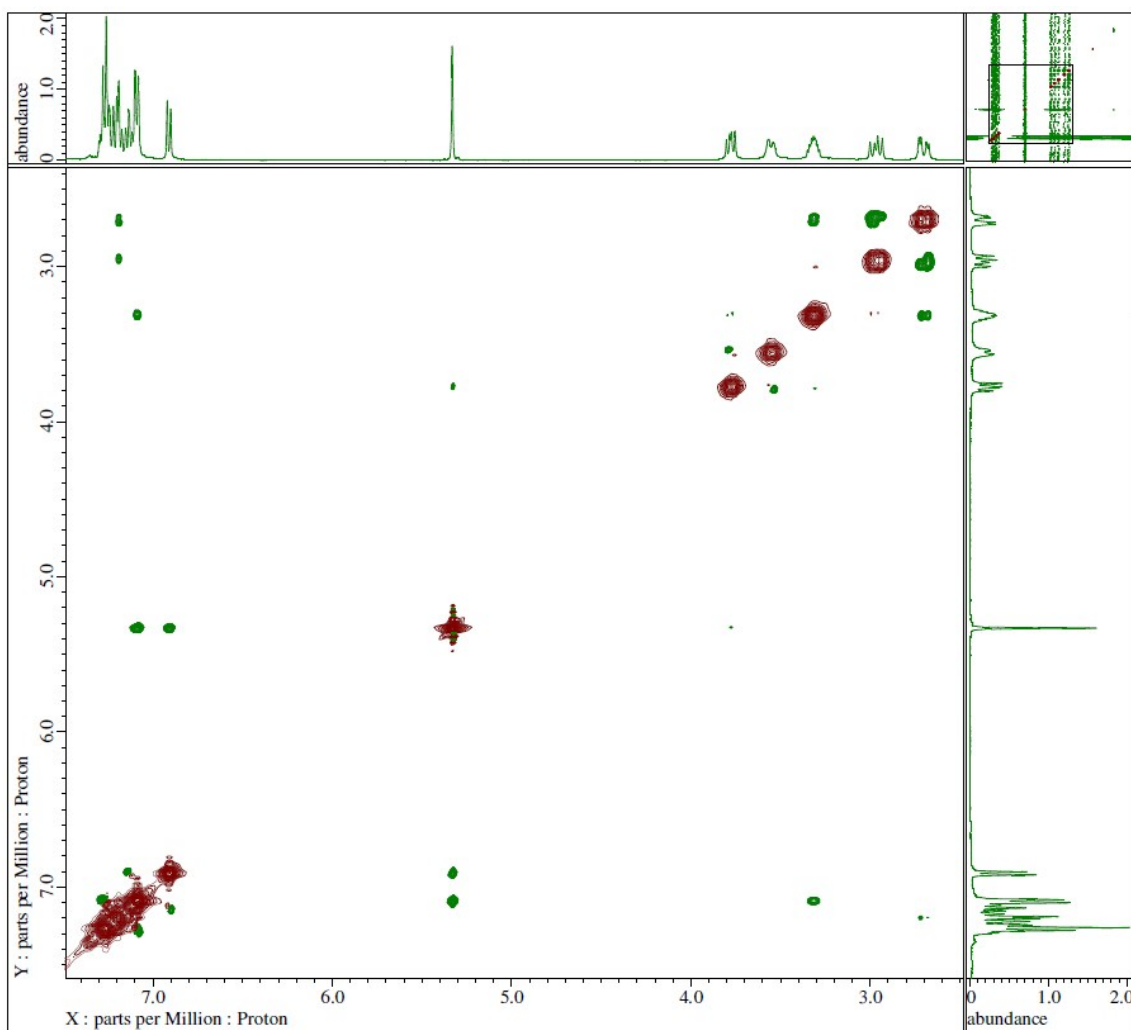
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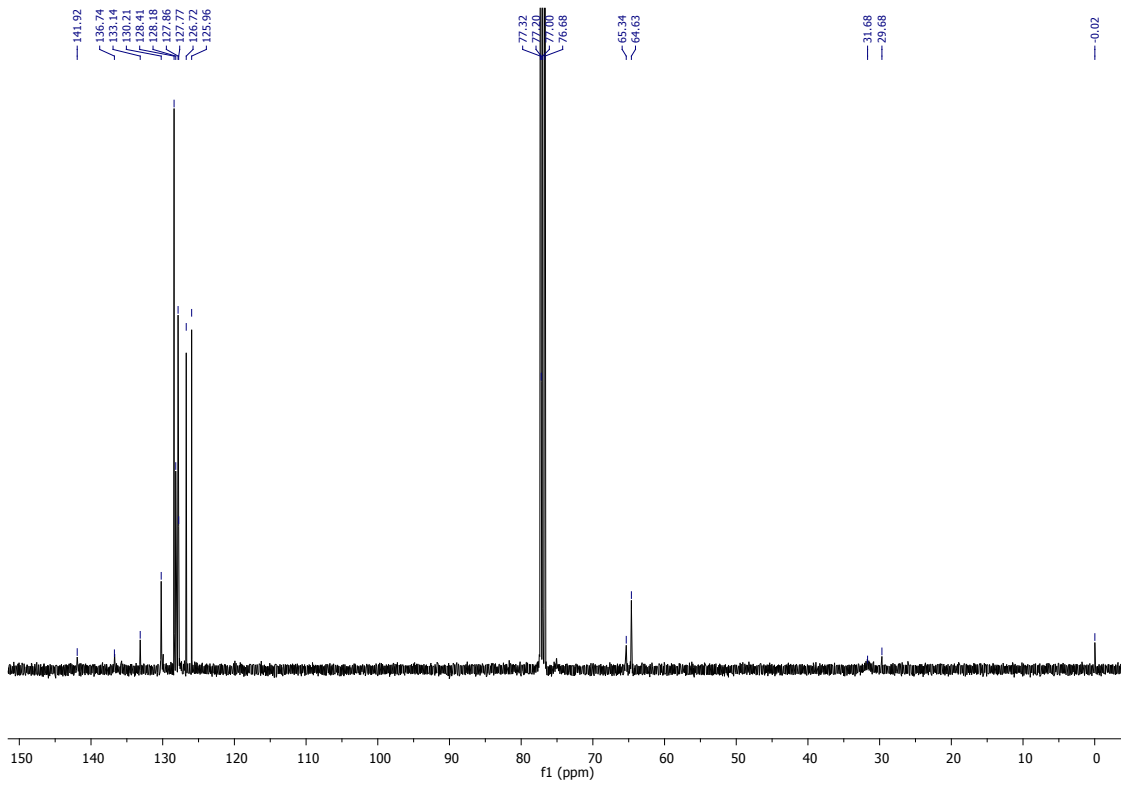
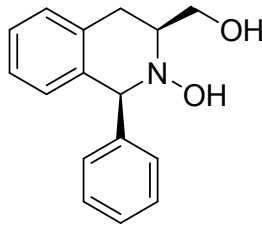
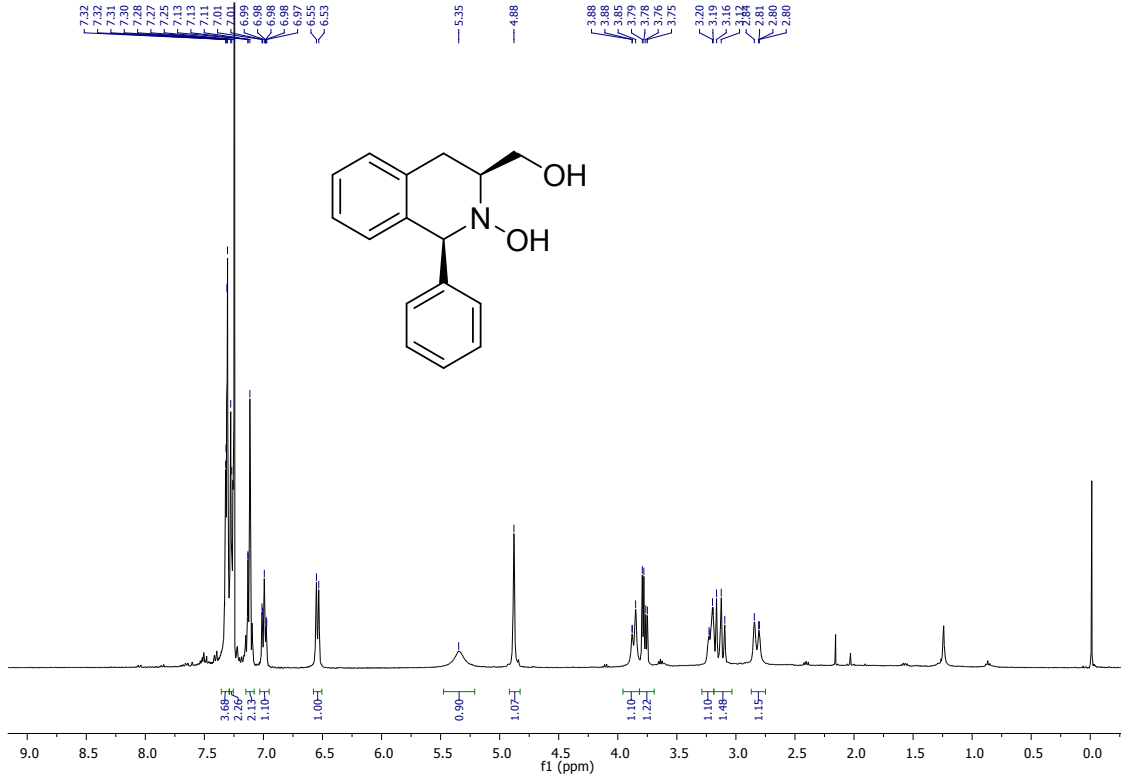
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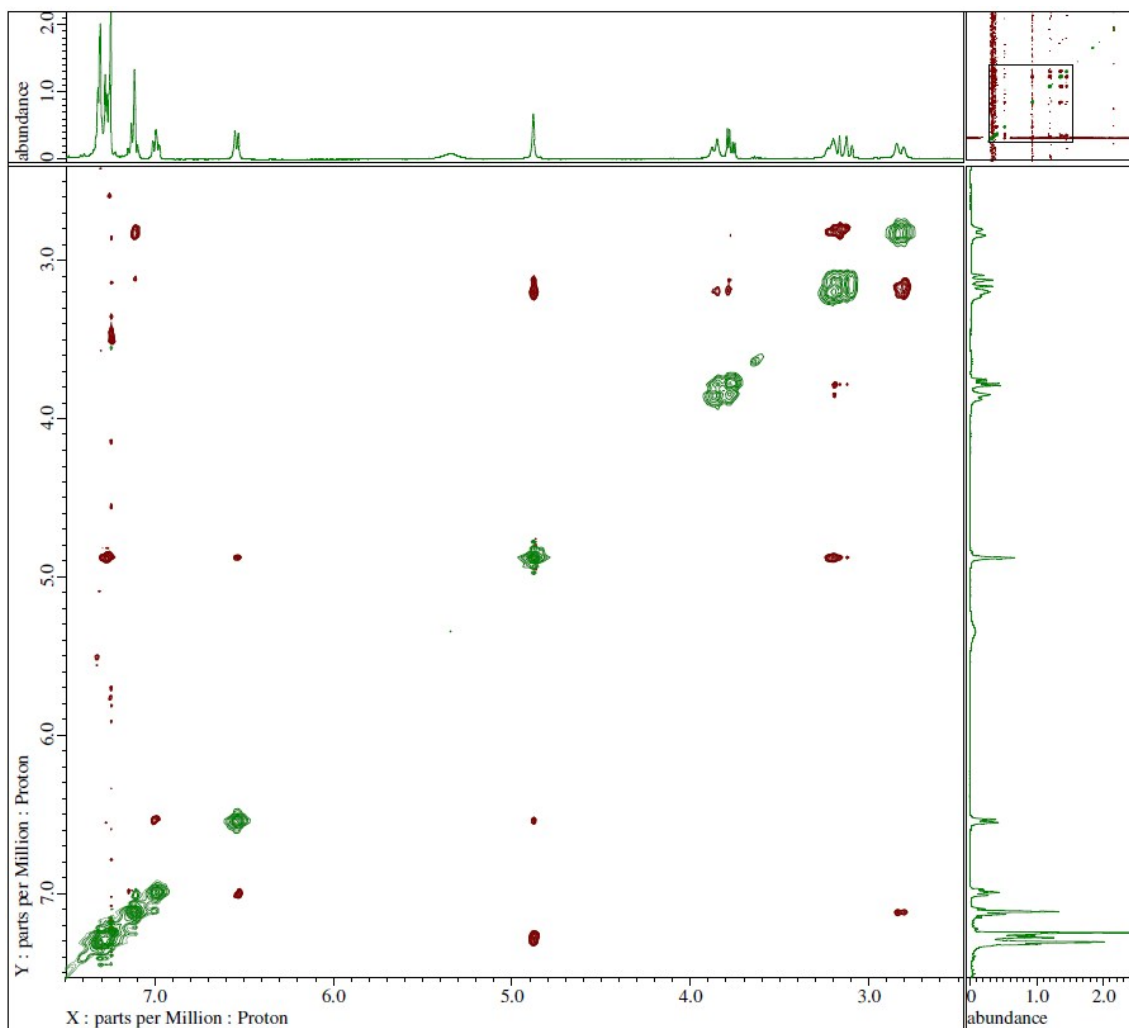
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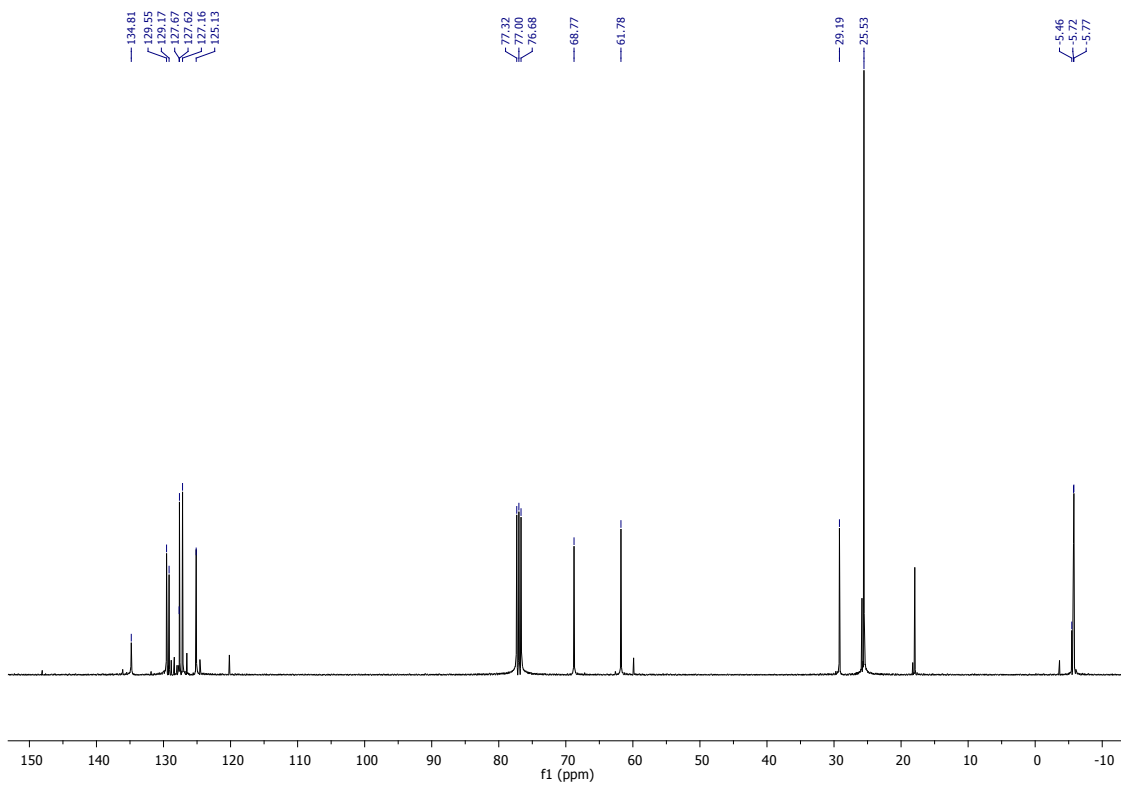
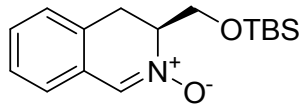
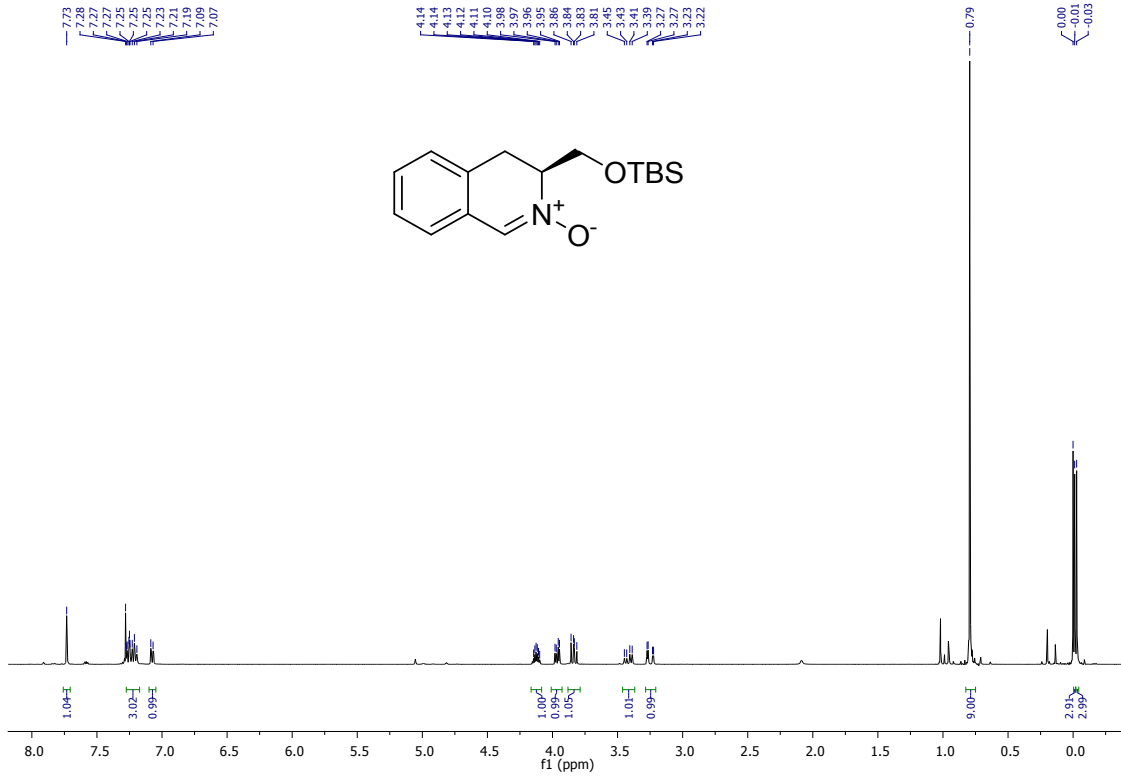
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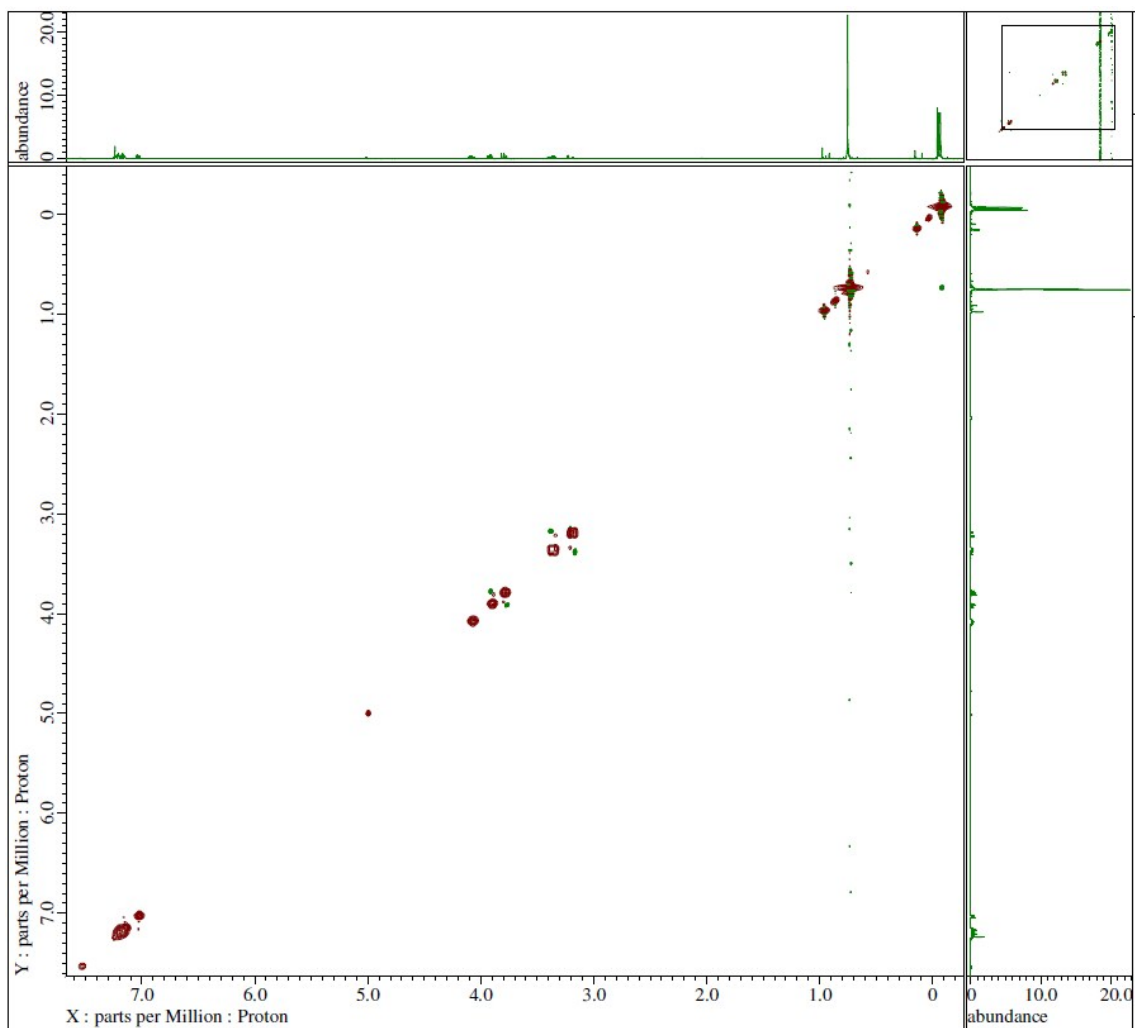
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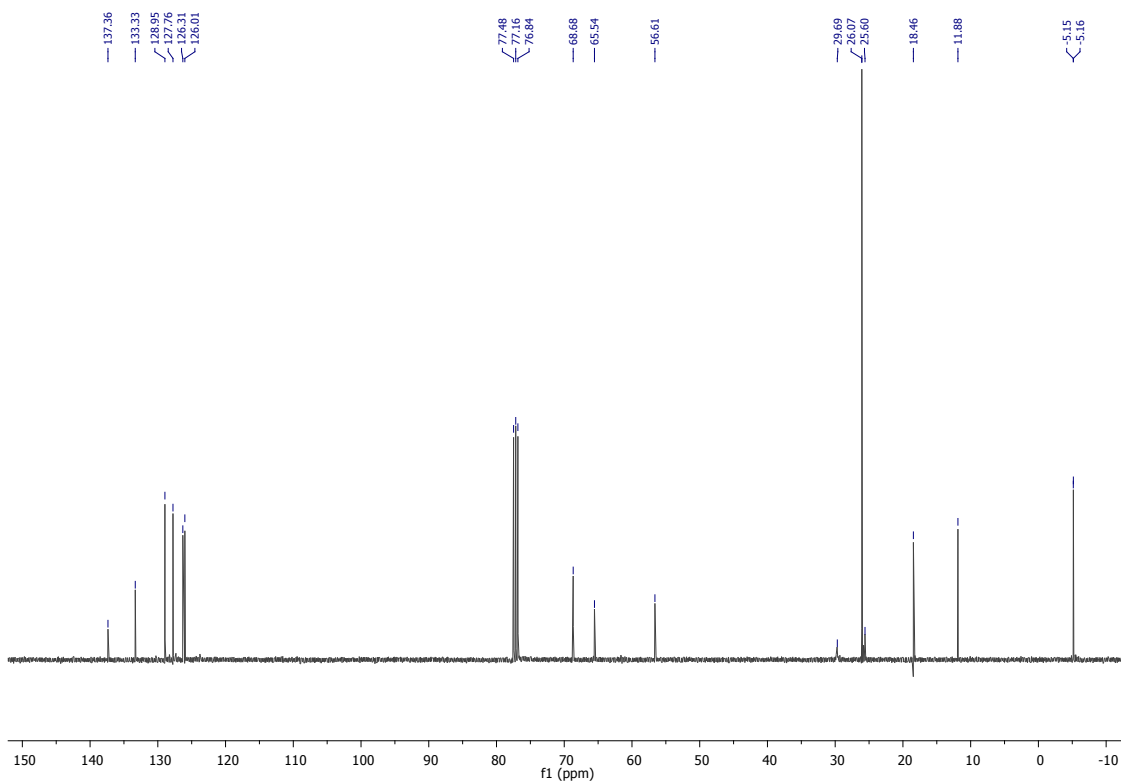
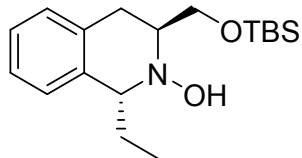
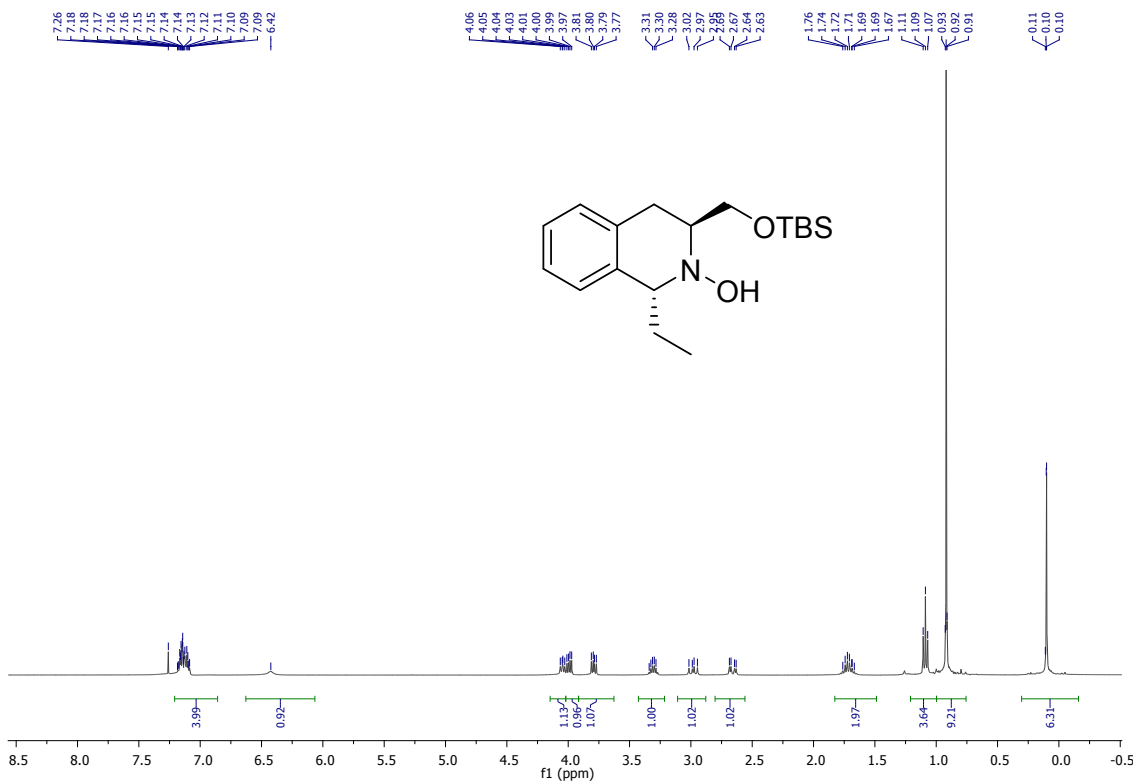
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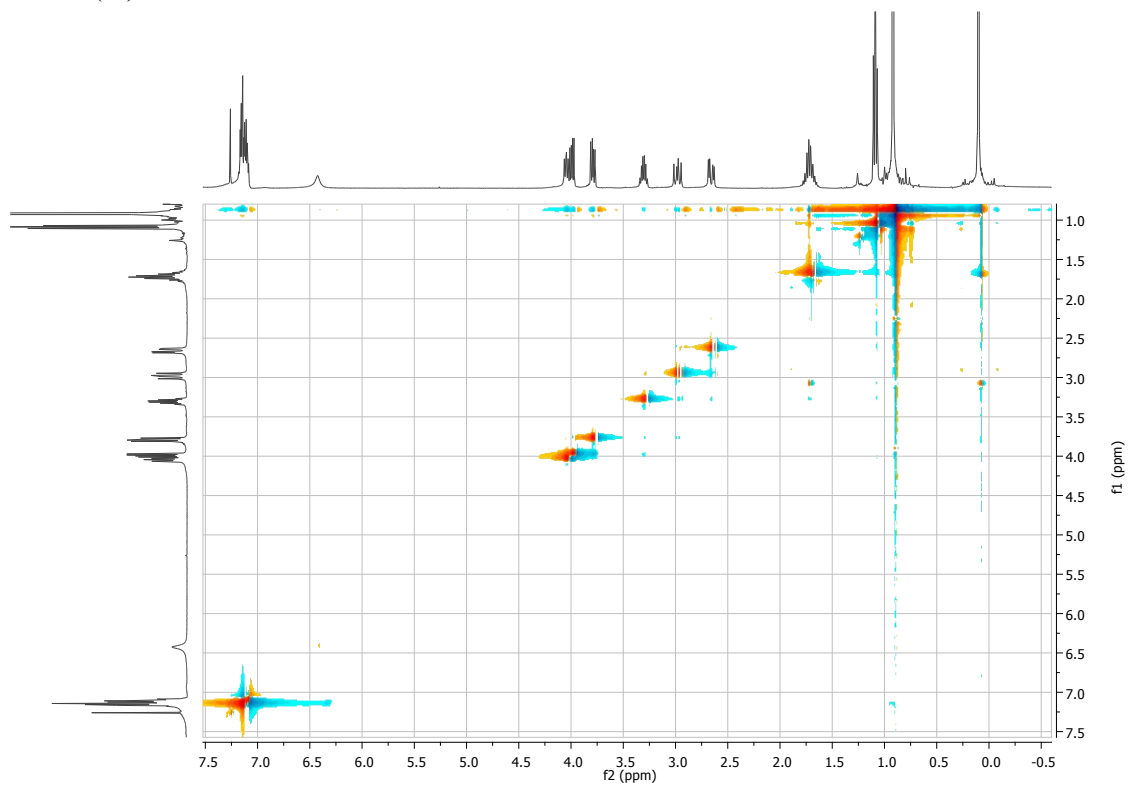
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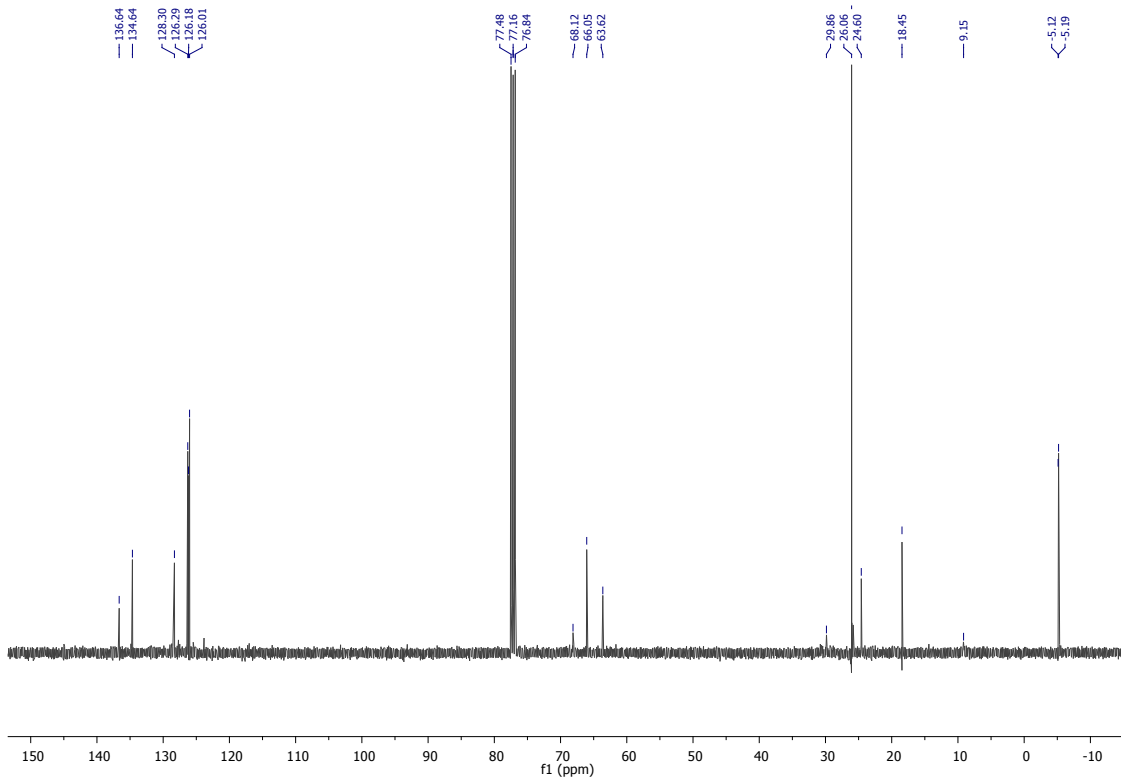
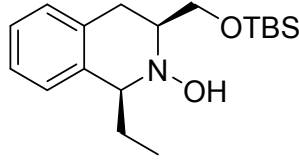
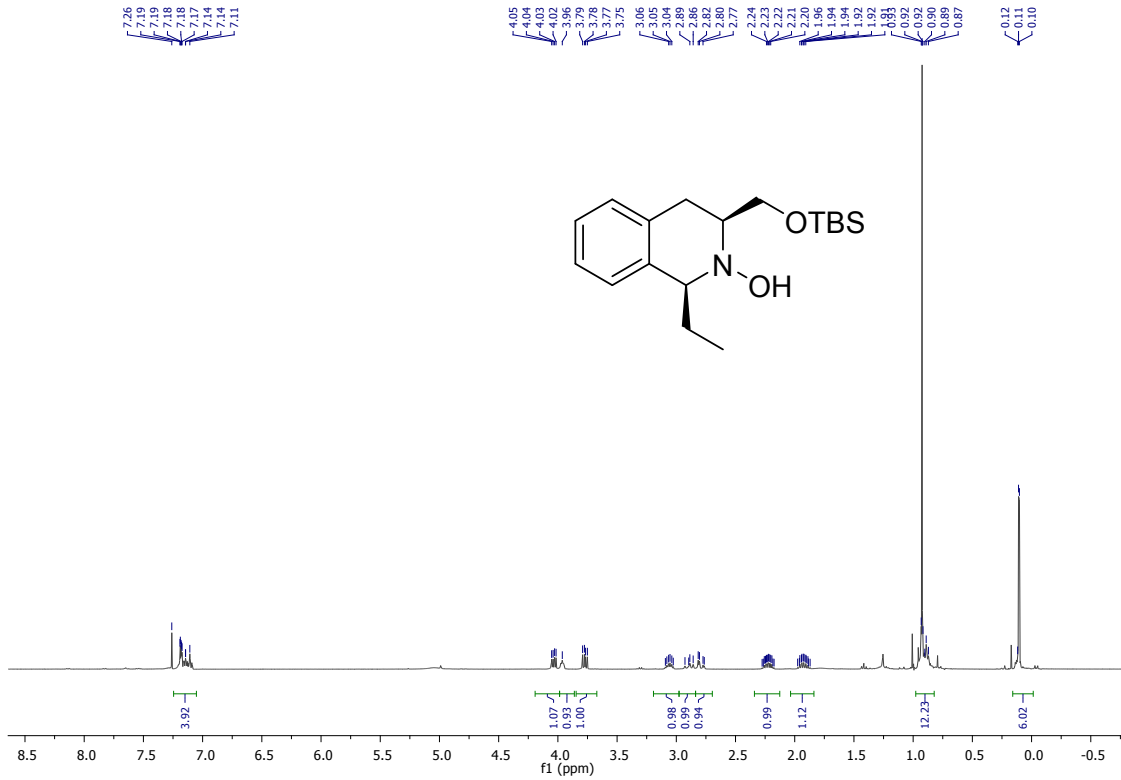
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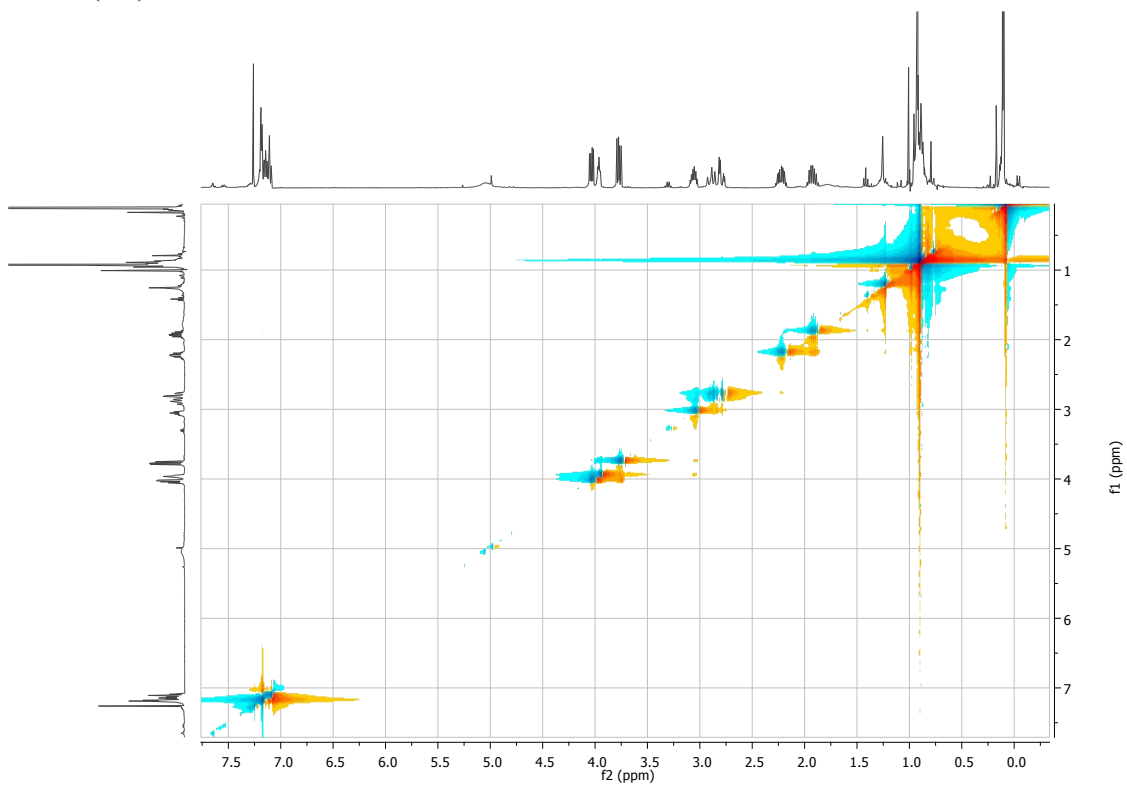
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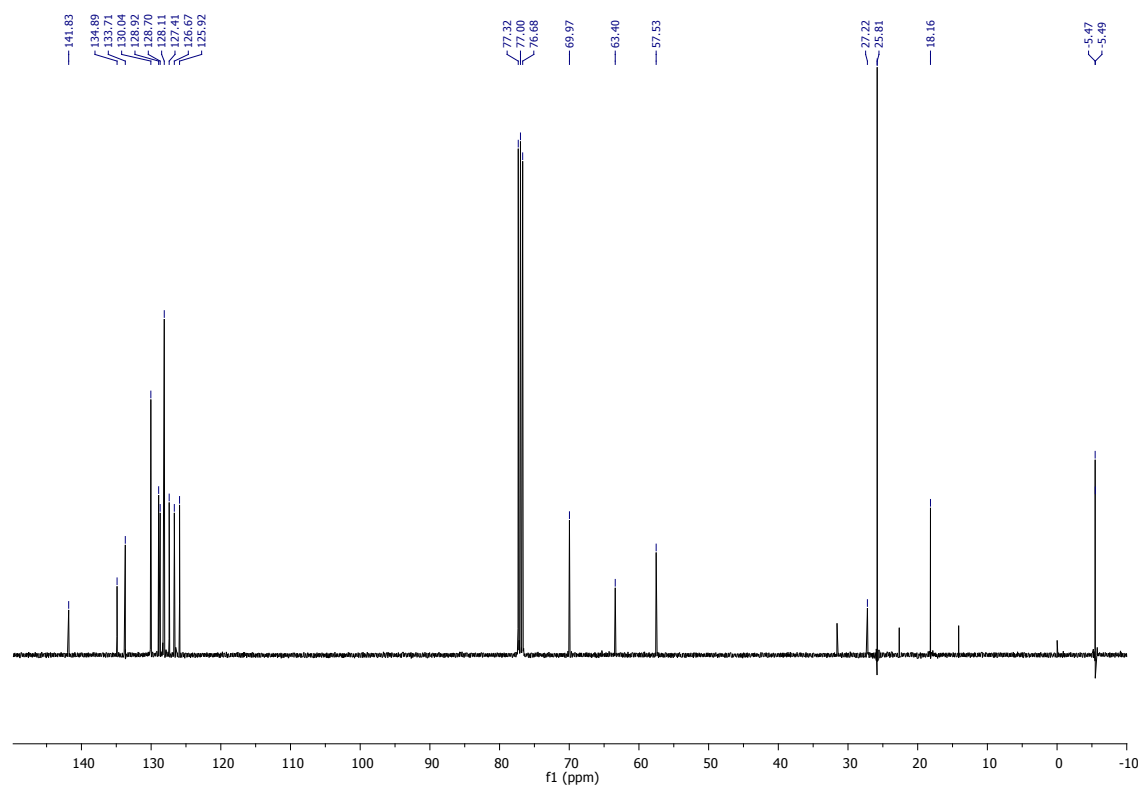
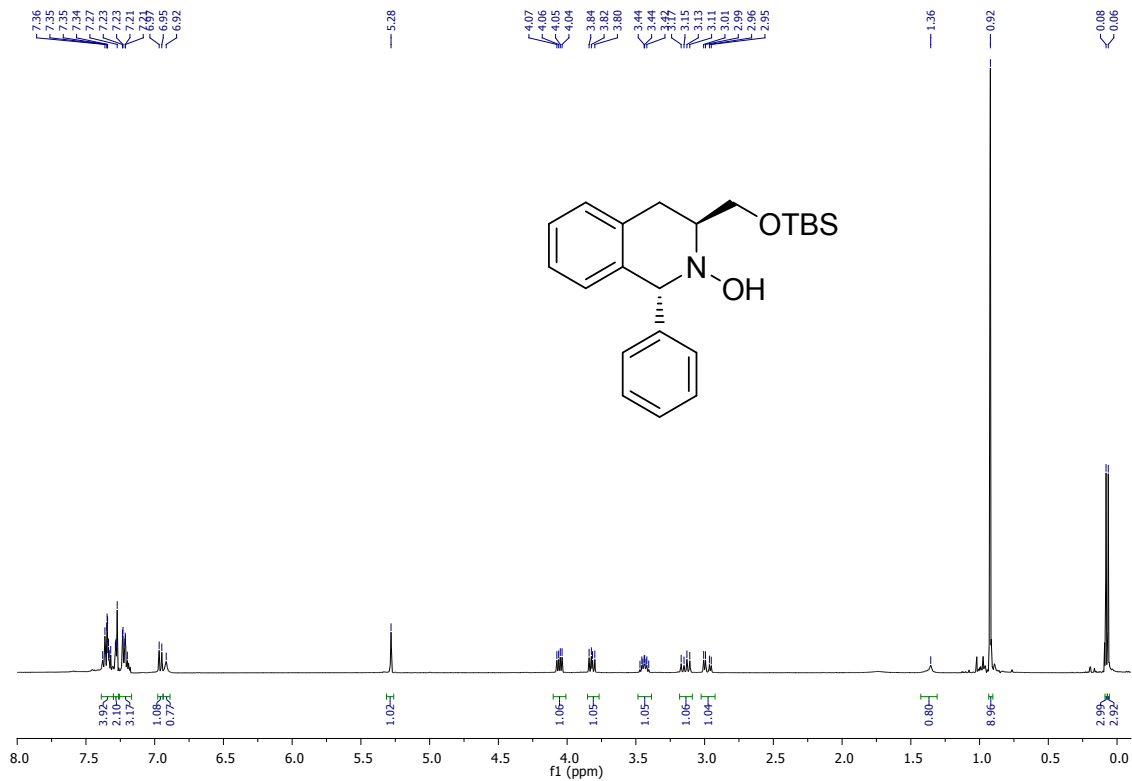
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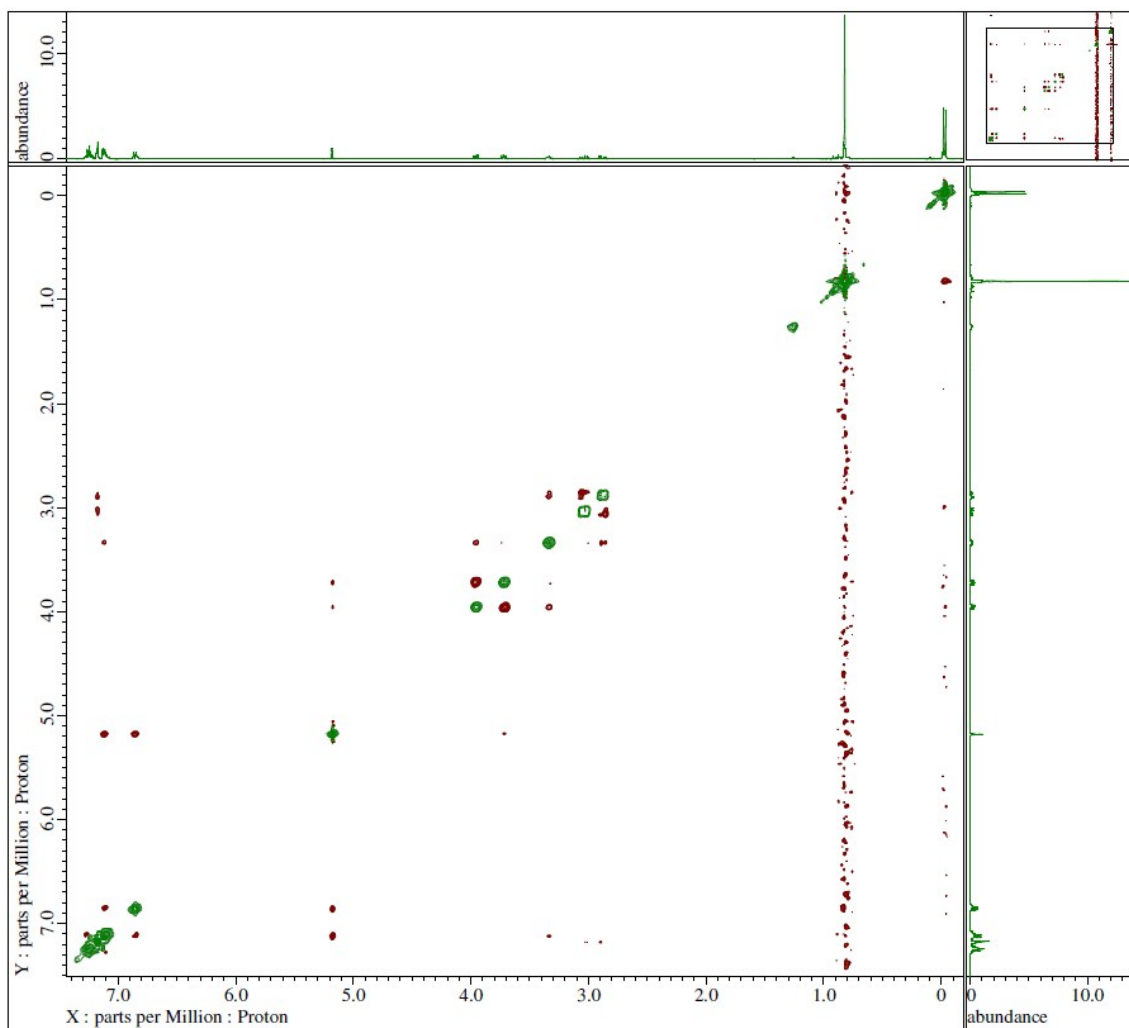
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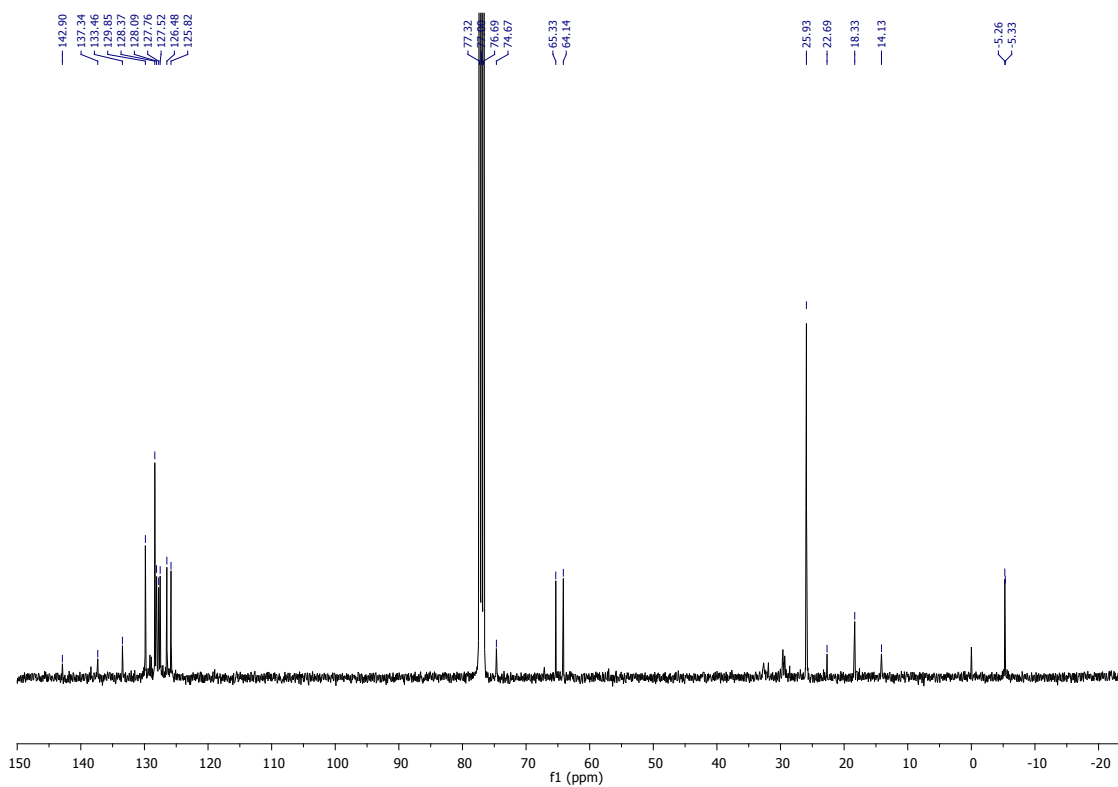
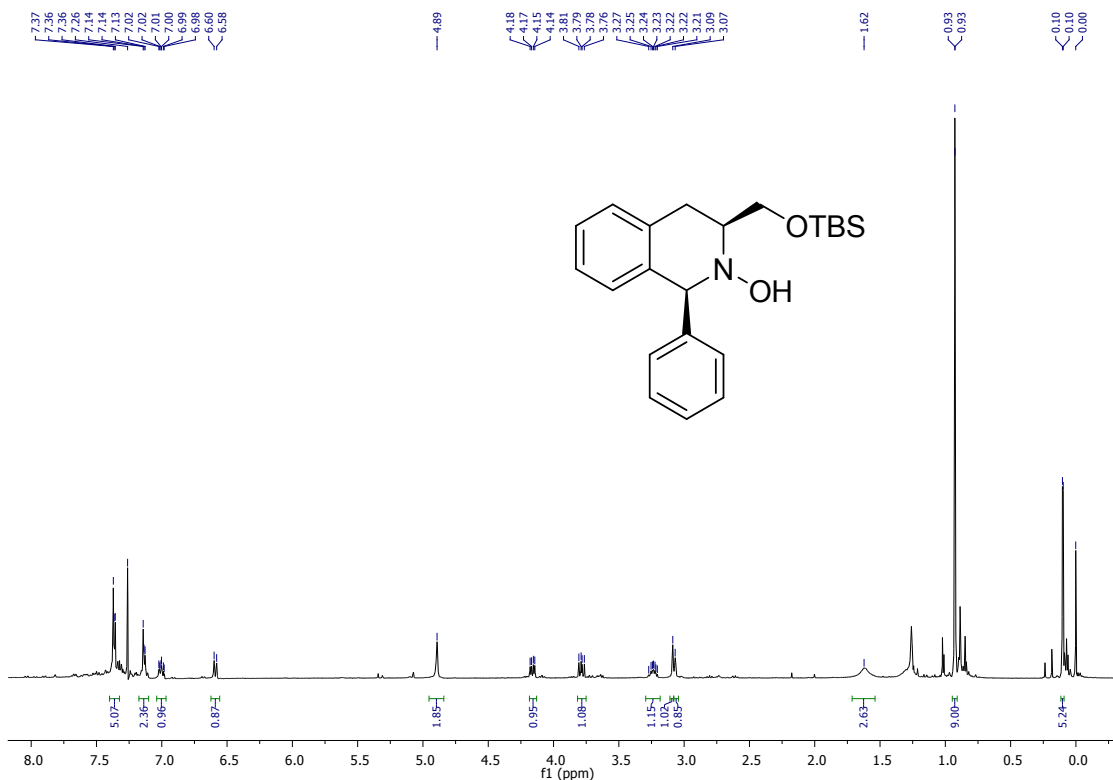
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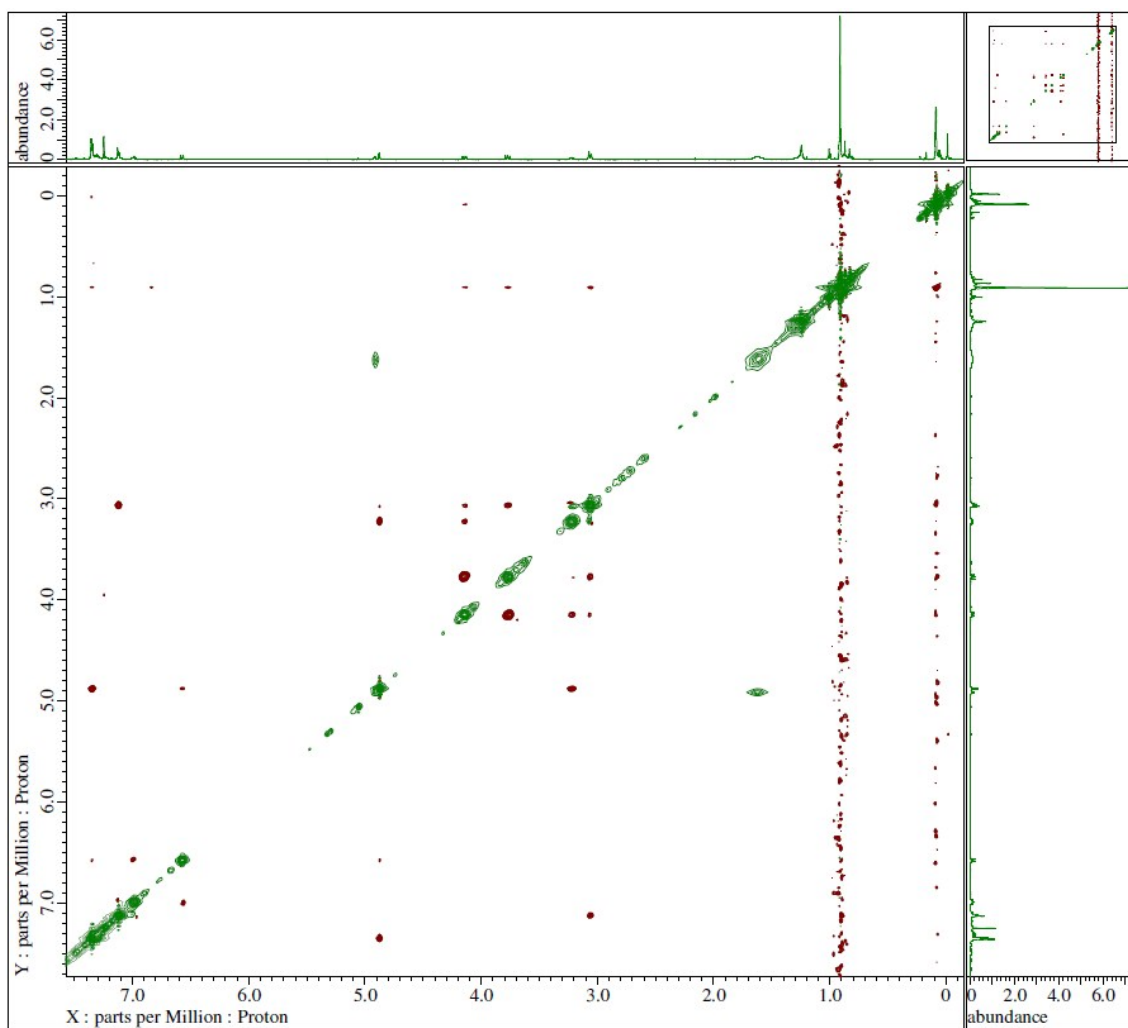
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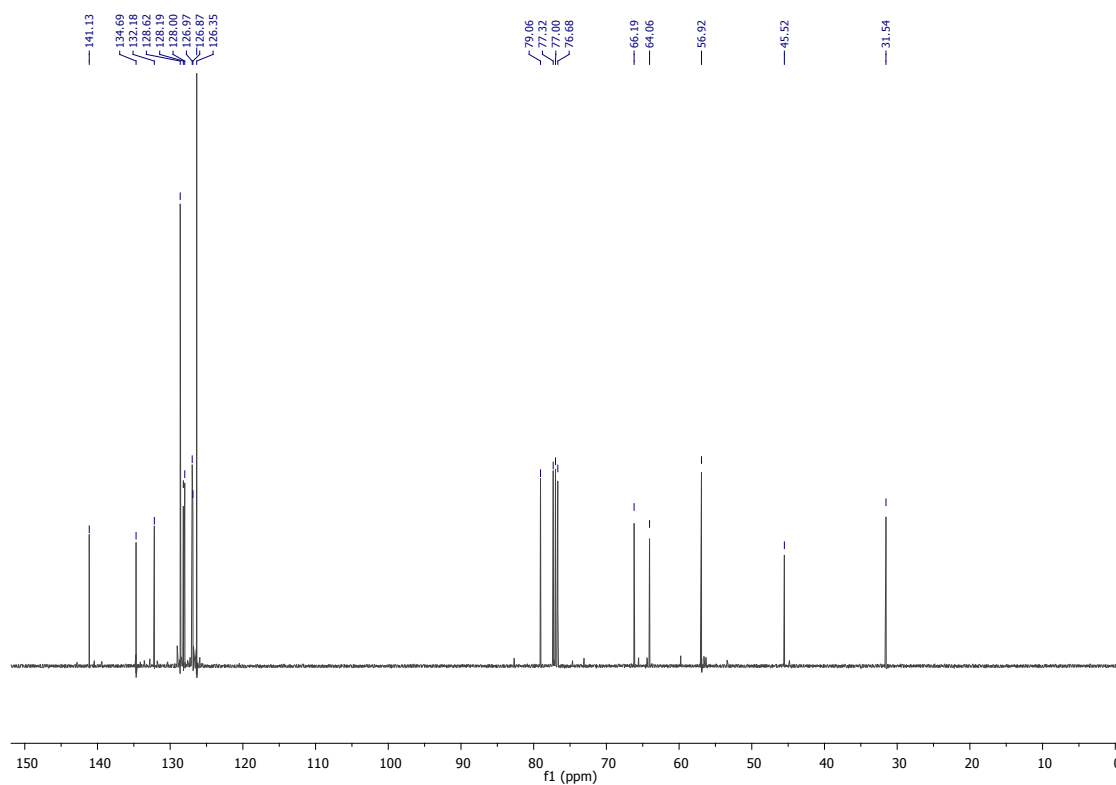
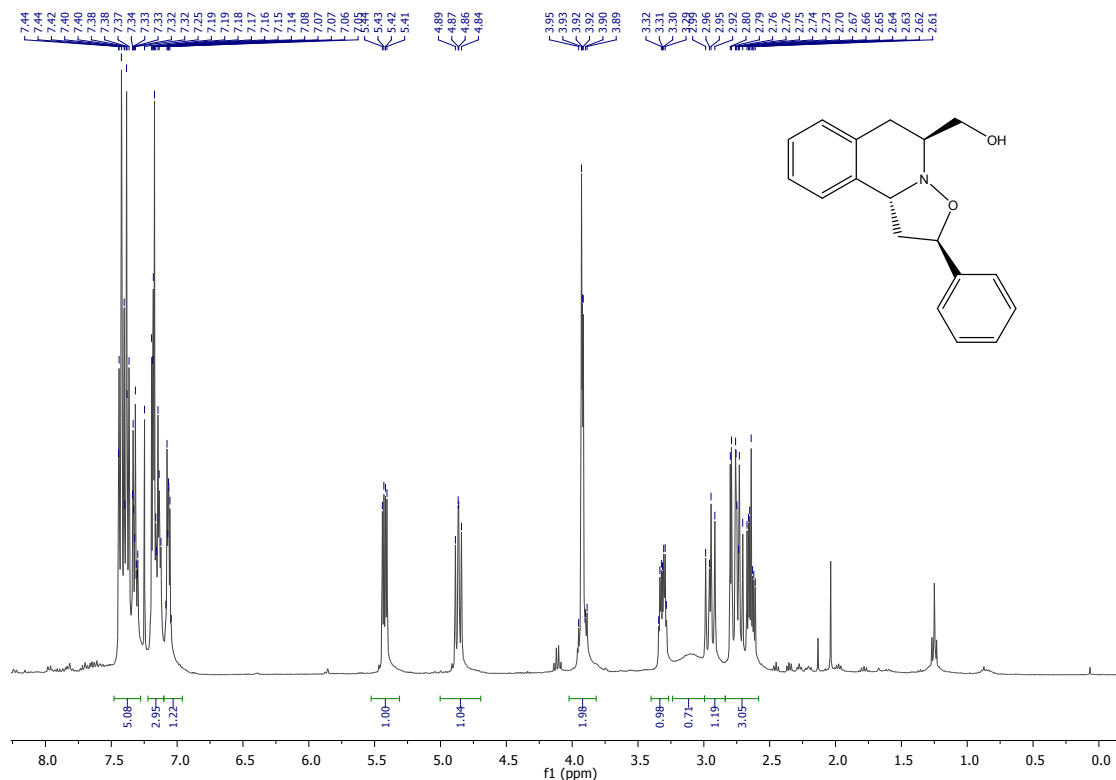
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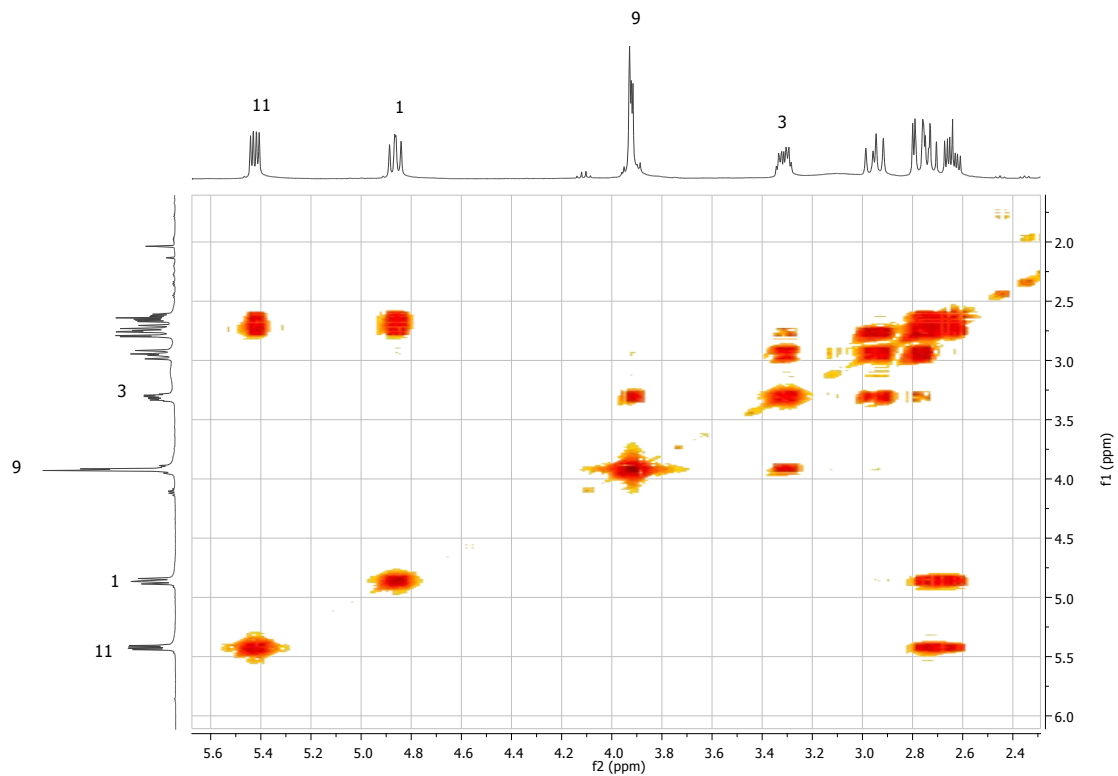
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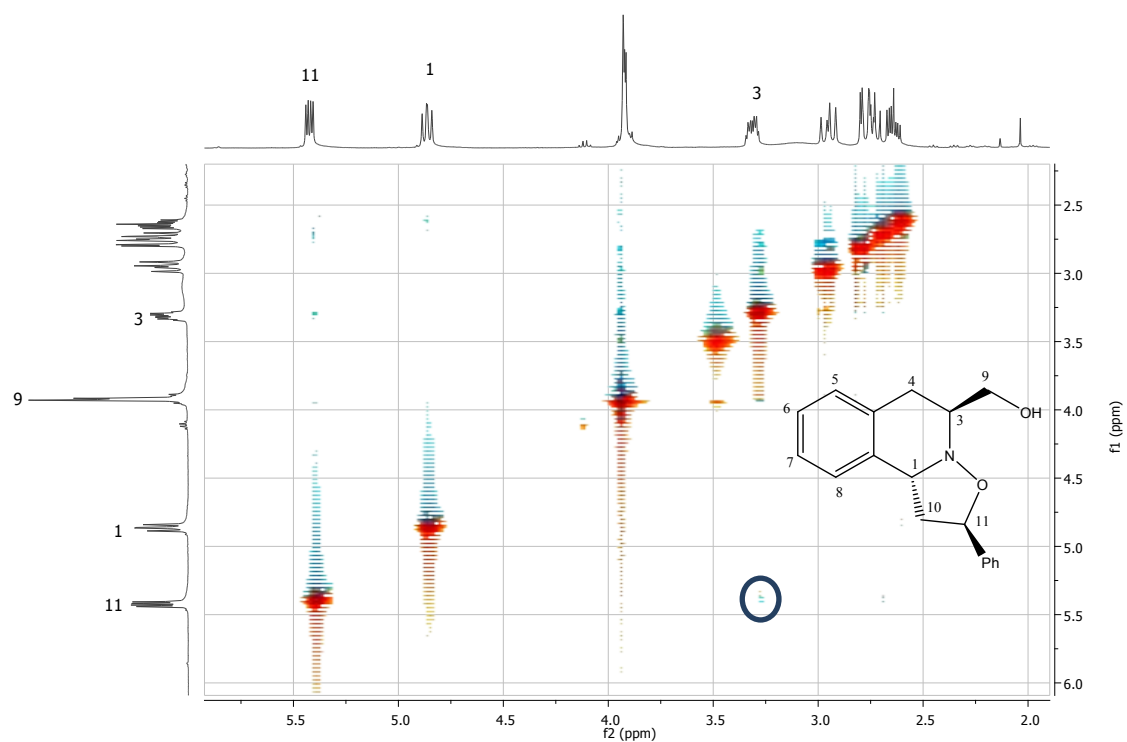
((2*R*,5*S*,10*bR*)-2-phenyl-1,5,6,10*b*-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinolin-5-yl)methanol (11a)



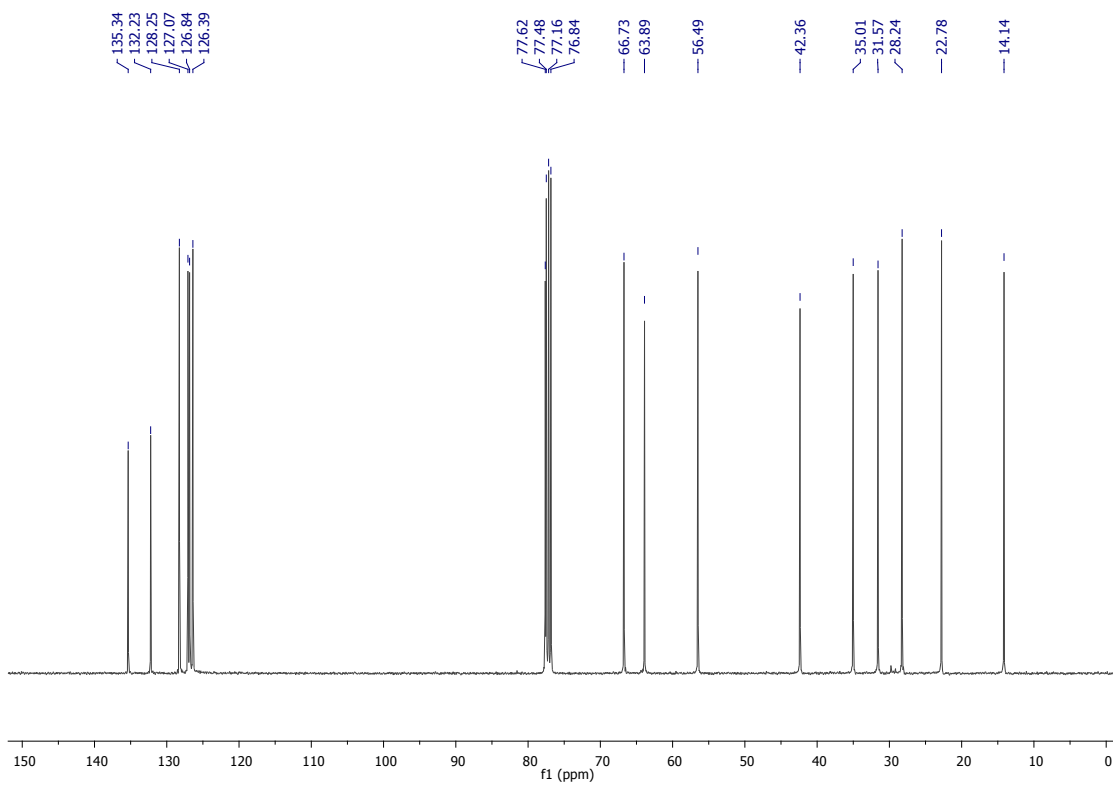
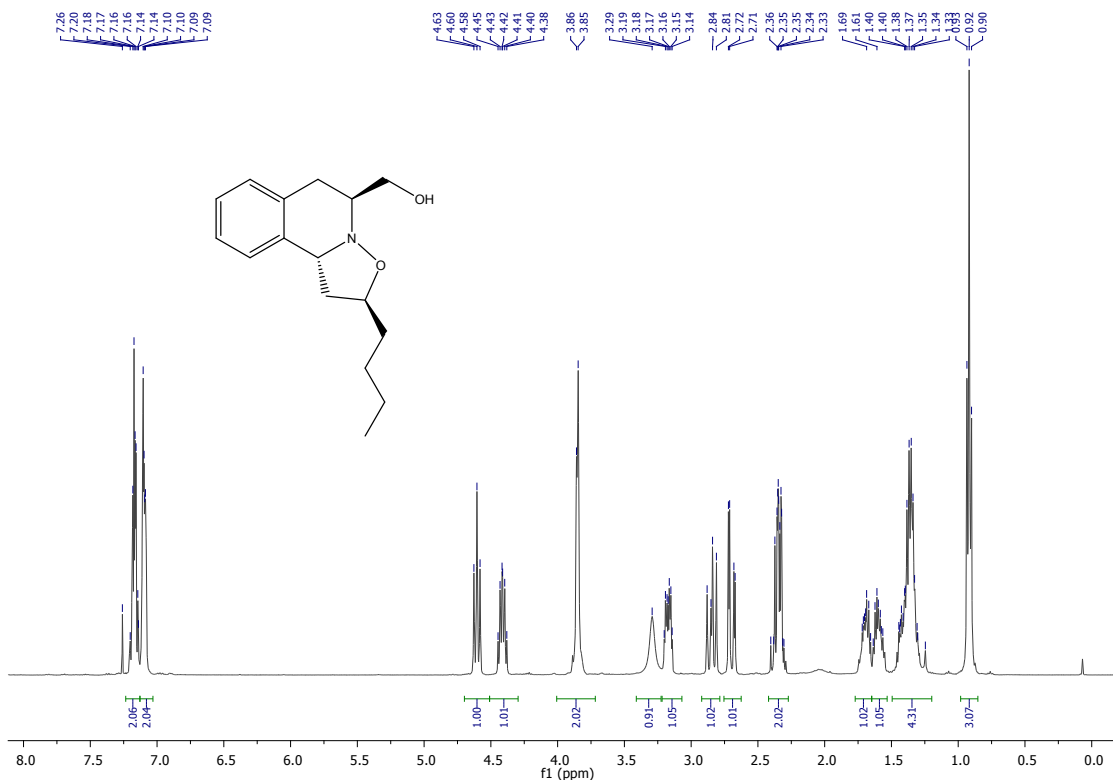
COSY (11a)



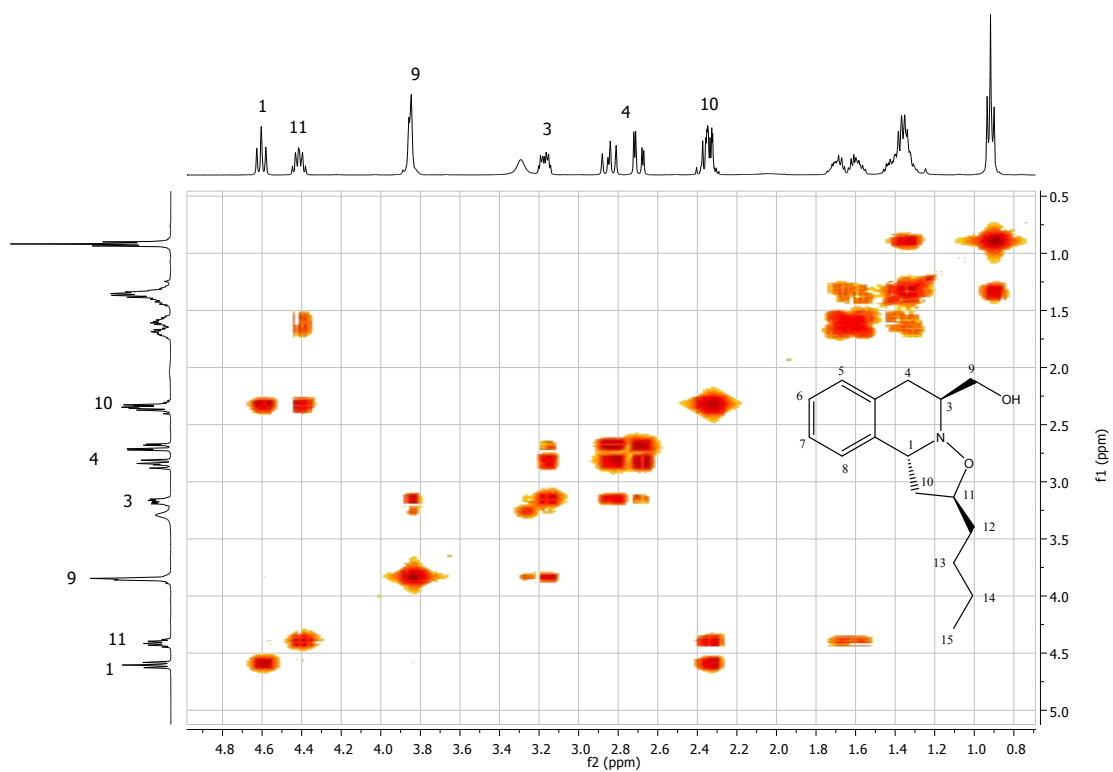
NOESY (11a)



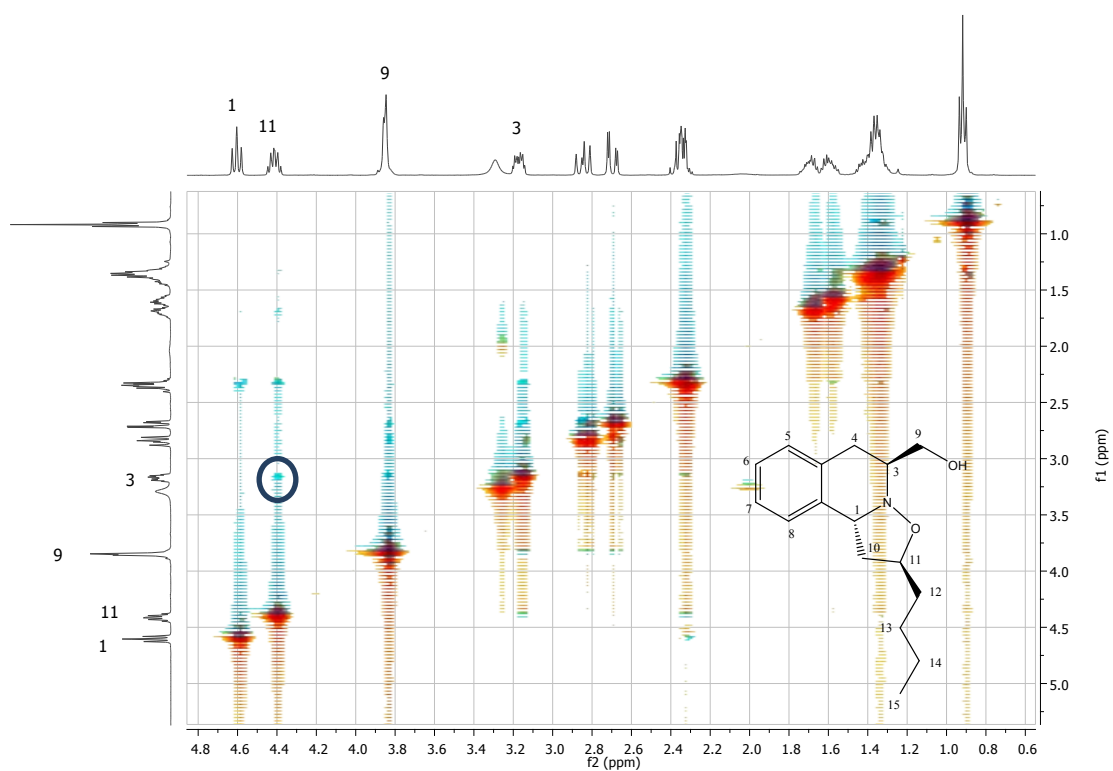
((2*S*,5*S*,10*BR*)-2-butyl-1,5,6,10*b*-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinolin-5-yl)methanol (11b)**



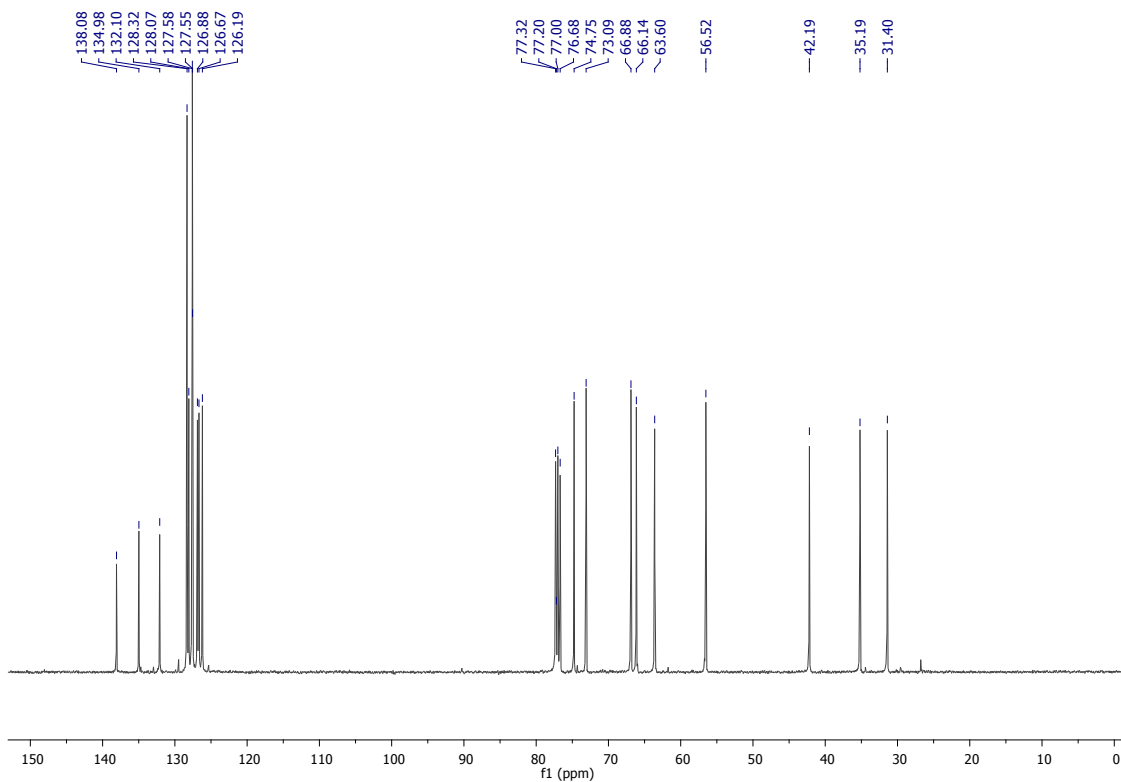
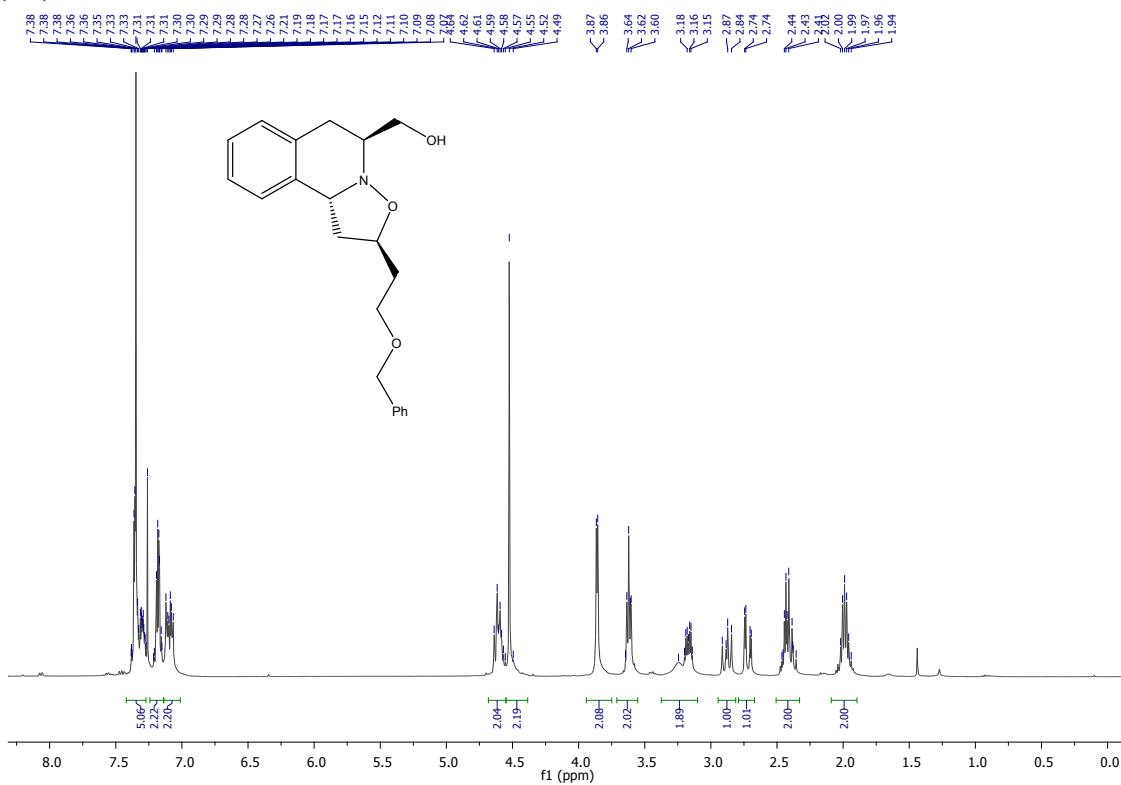
COSY (11b)



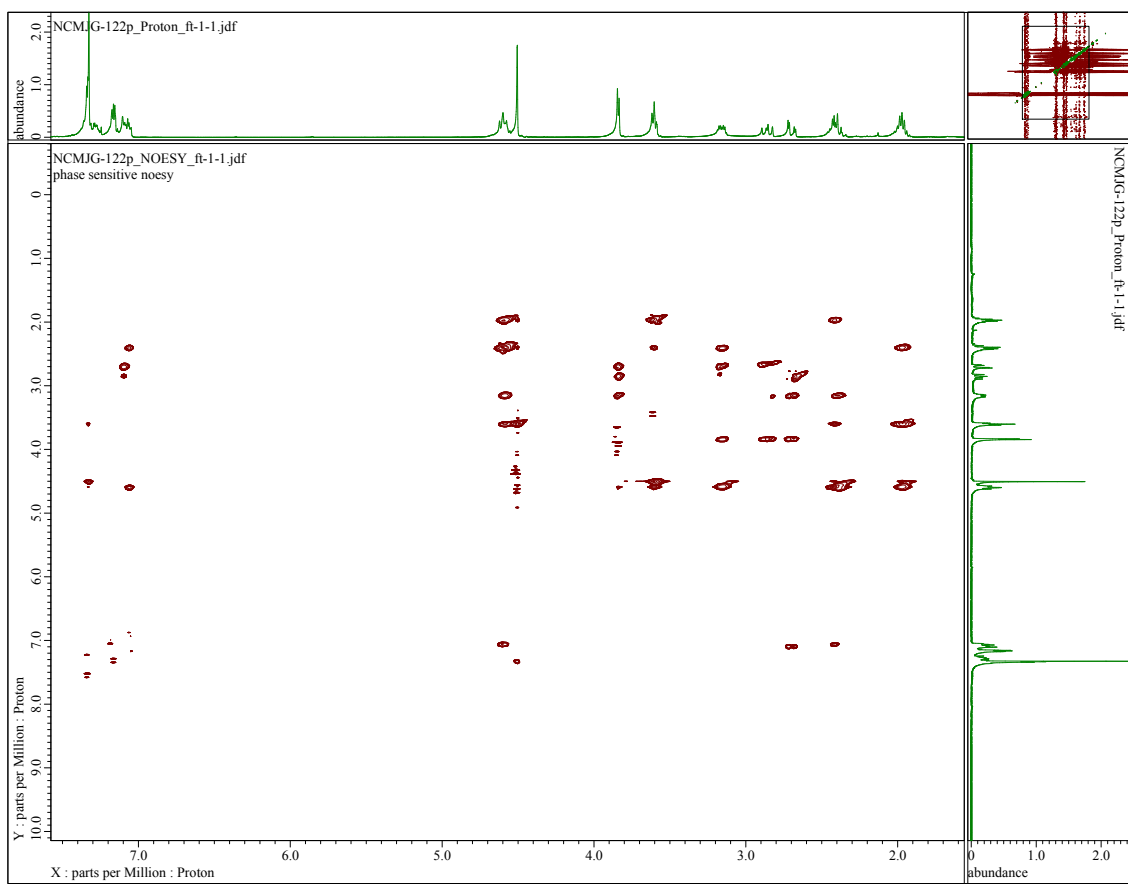
NOESY (11b)



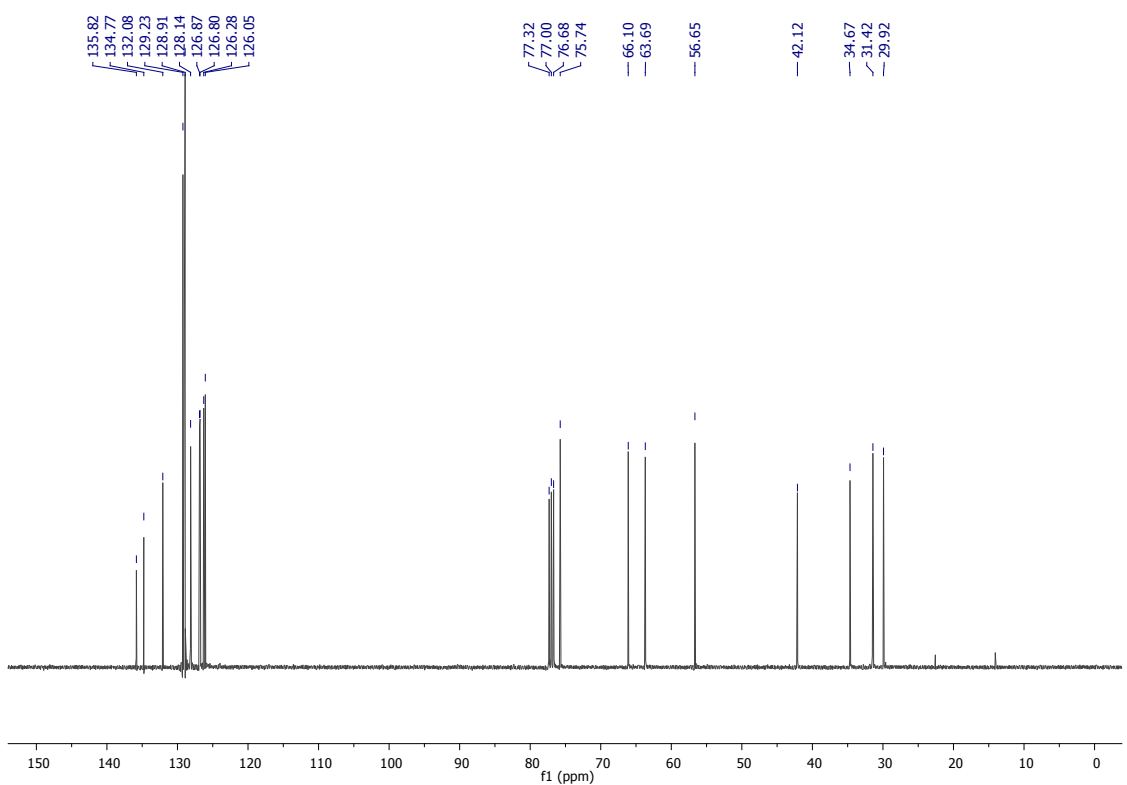
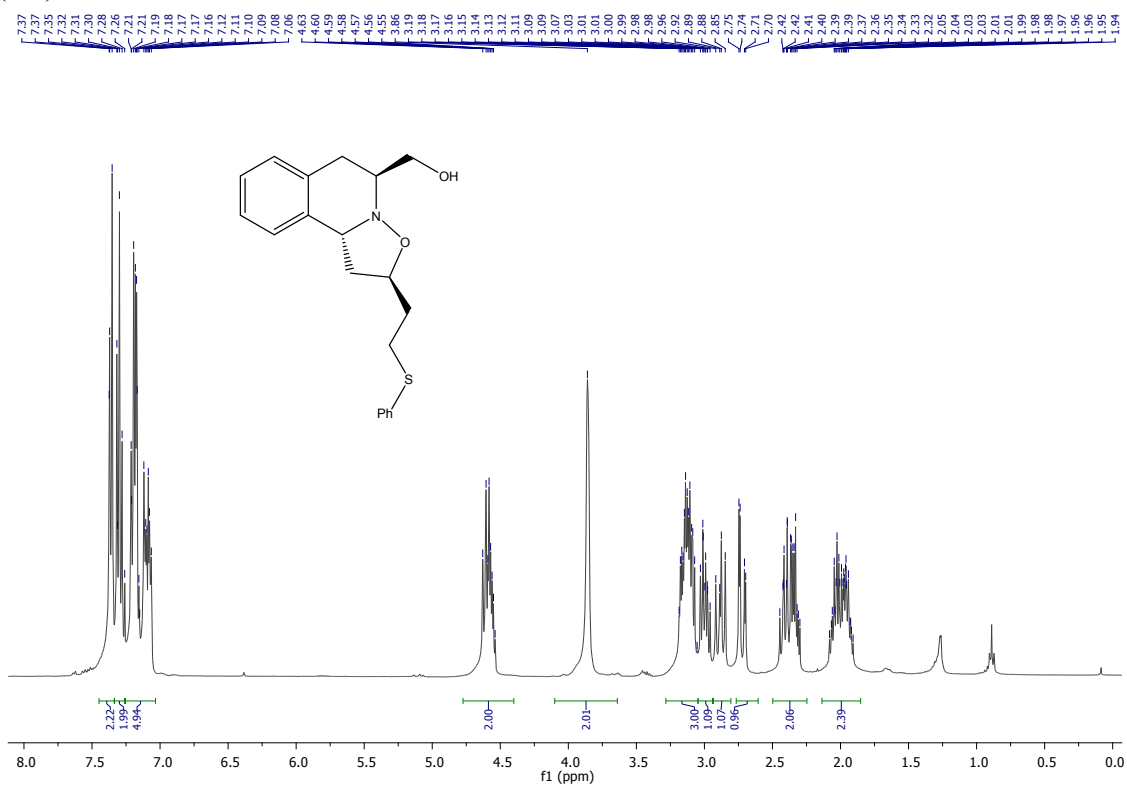
((2*R*,5*S*,10*bR*)-2-(2-(benzyloxy)ethyl)-1,5,6,10*b*-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinolin-5-yl)methanol (11c)



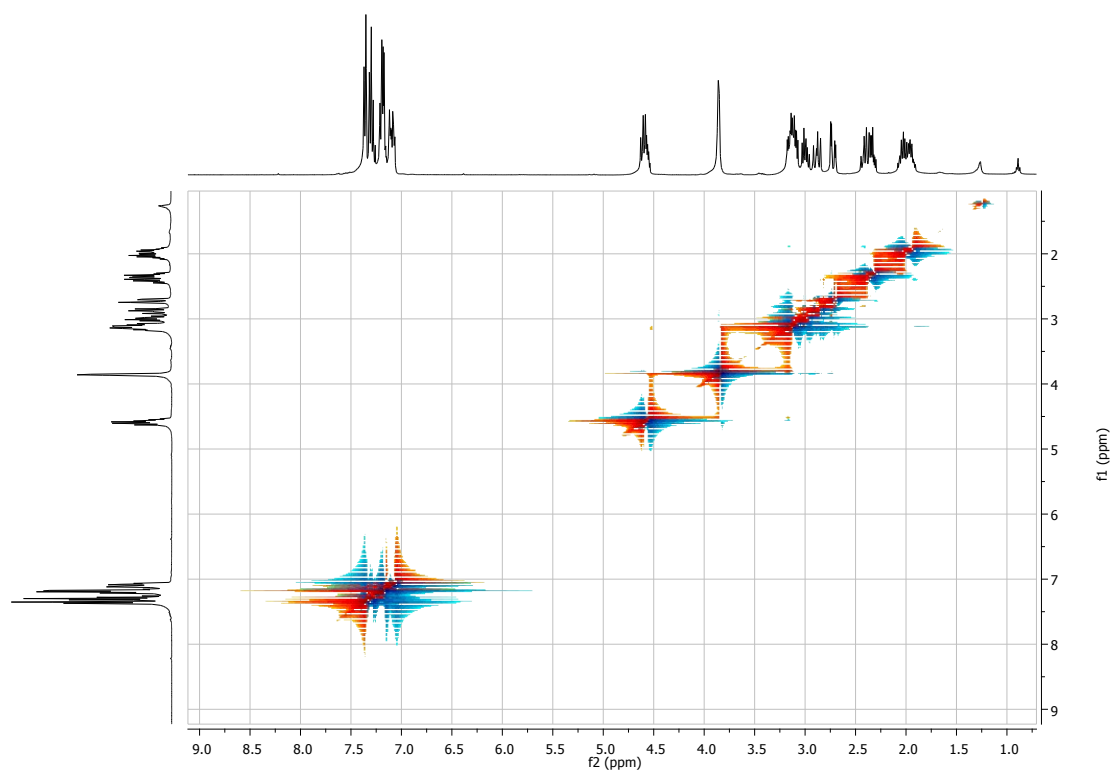
NOESY (11c)



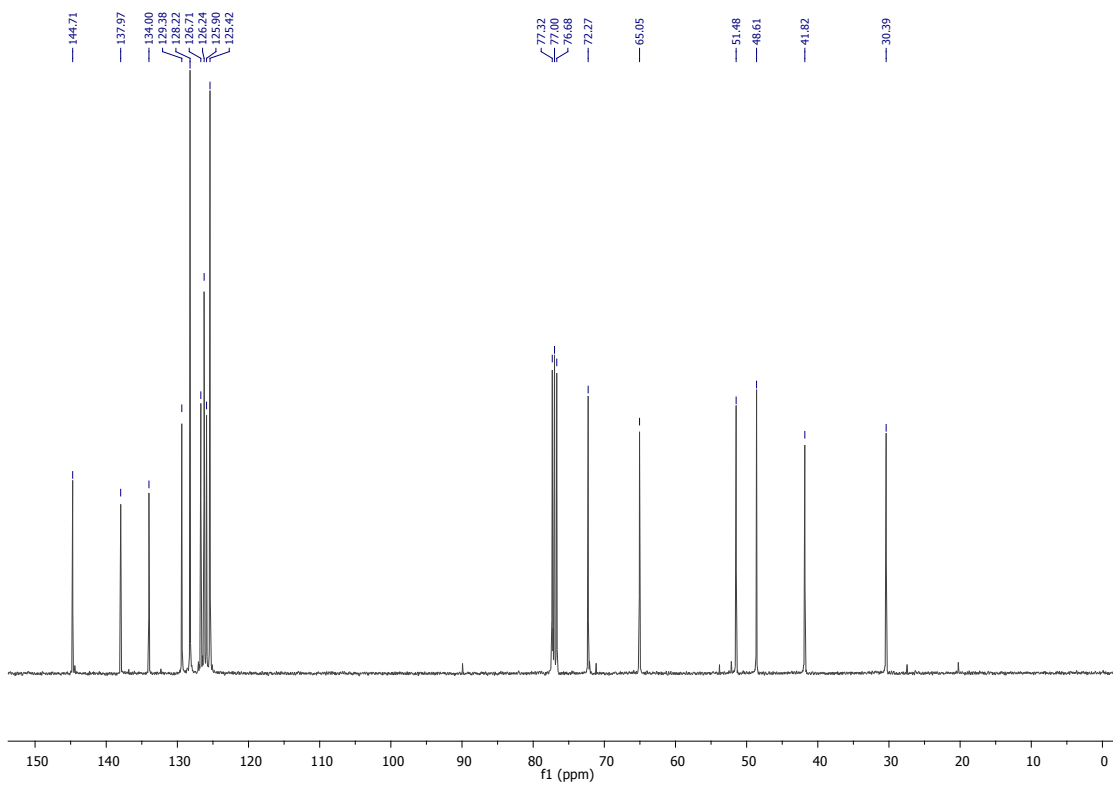
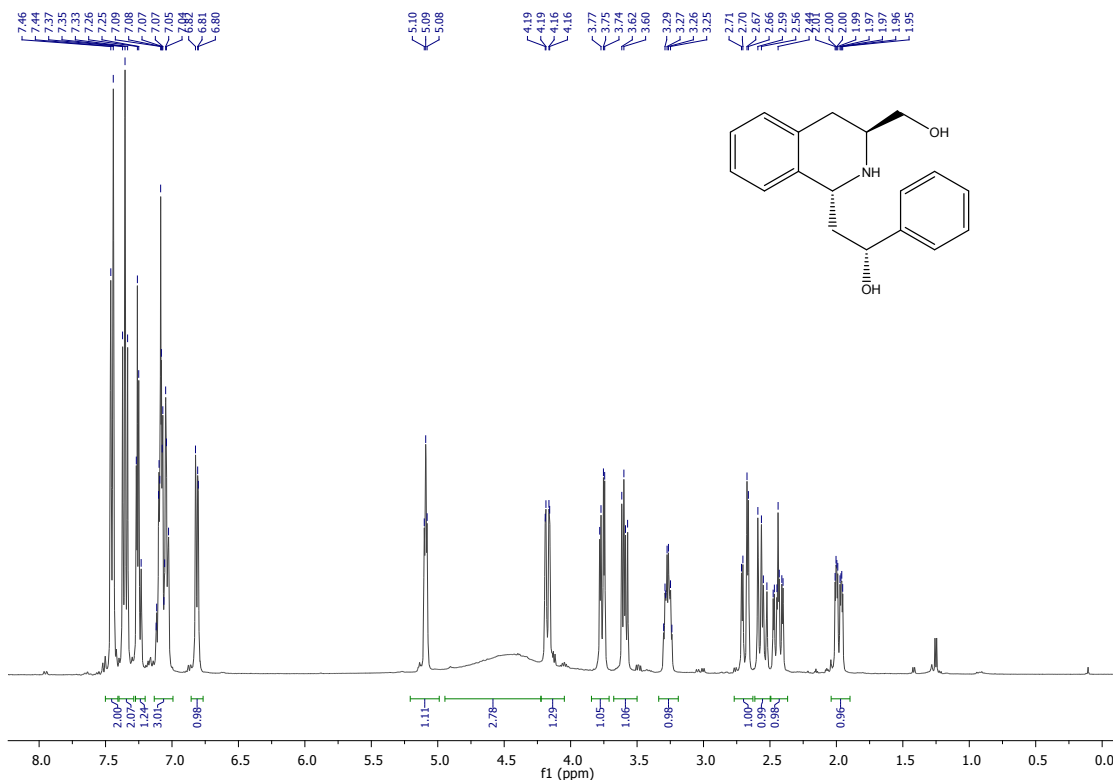
((2*R*,5*S*,10*bR*)-2-(2-(phenylthio)ethyl)-1,5,6,10*b*-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinolin-5-yl)methanol (11d)



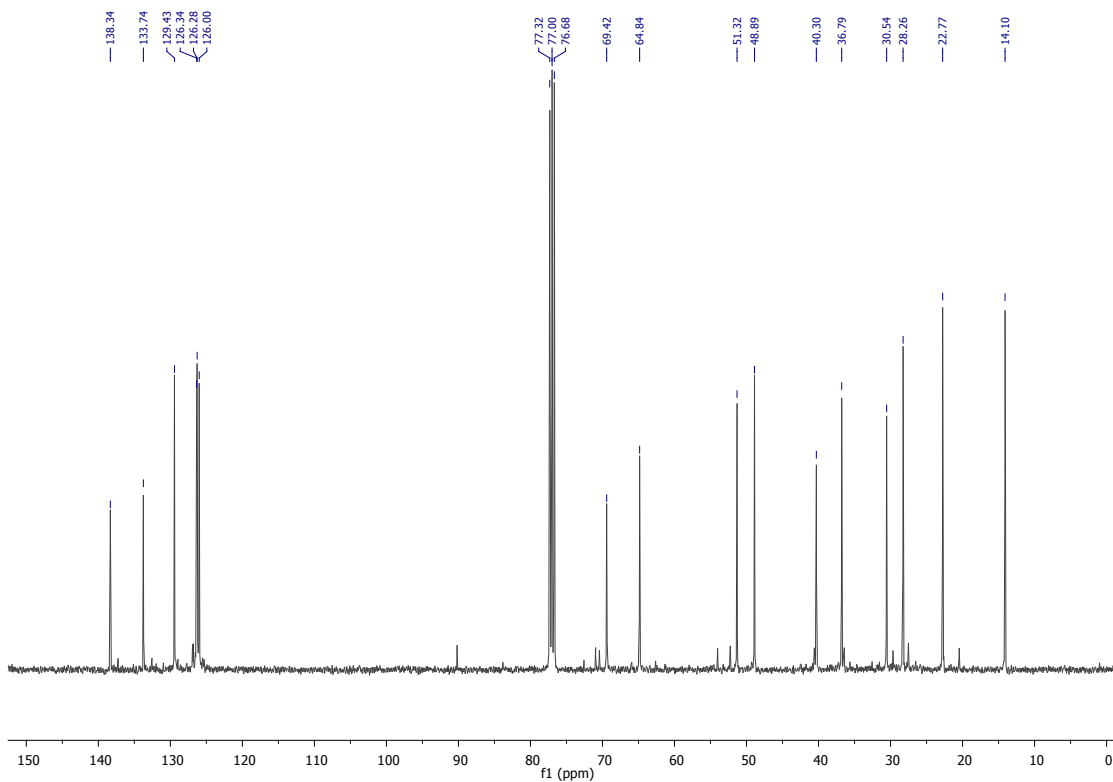
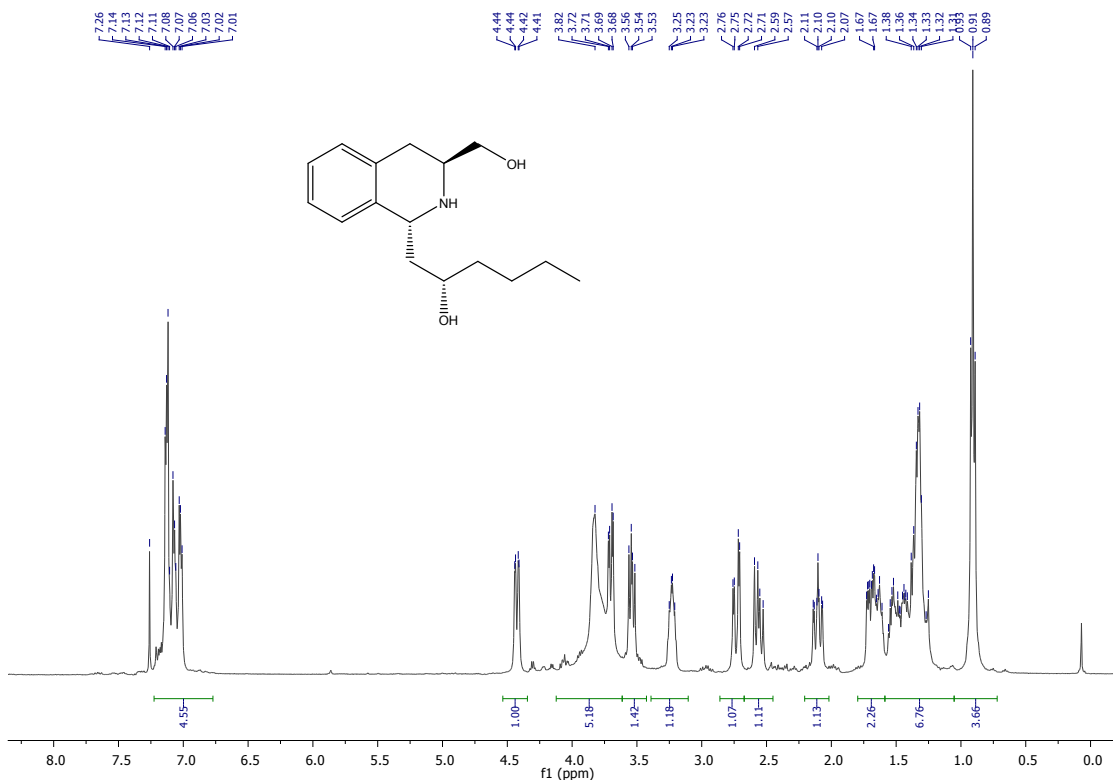
NOESY (11d)



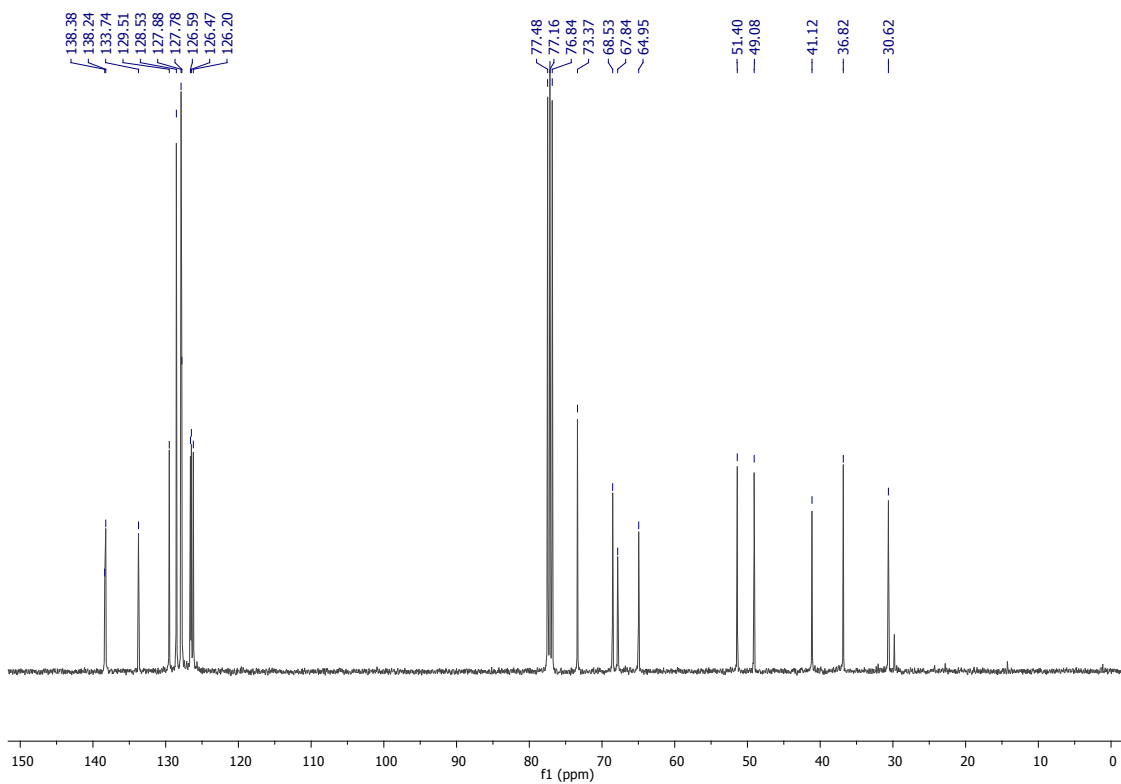
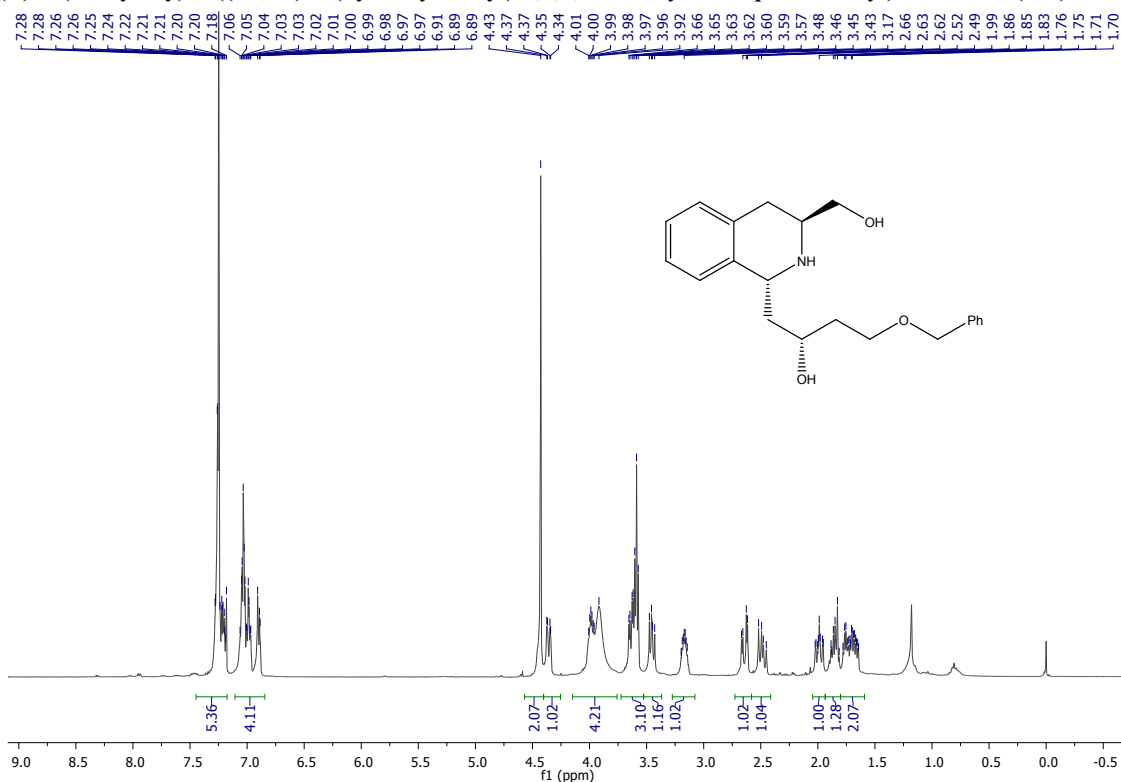
(R)-2-((1R,3S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanol (12a)



(S)-1-((1R,3S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)hexan-2-ol (12b)



(R)-4-(benzyloxy)-1-((1R,3S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-ol (12c)



(R)-1-((1R,3S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-4-(phenylthio)butan-2-ol (12d)

