Electronic Supplementary Information

Trienamine catalyzed asymmetric synthesis and biological investigation of a cytochalasin B-inspired compound collection

Magnus Sellstedt[1], Melanie Schwalfenberg[1], Slava Ziegler[1], Andrey P. Antonchick[1], and Herbert Waldmann[1,2,*]

[1] Max-Planck-Institute für Molekulare Physiologie, Otto-Hahn-Strasse 11, 44227 Dortmund (Germany), E-mail: herbert.waldmann@mpi-dortmund.mpg.de
[2] Technische Universität Dortmund, Otto-Hahn-Strasse 6, 44221 Dortmund (Germany)

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Methods

All reactions were performed under argon atmosphere under dry conditions unless otherwise stated. The reactions were followed by thin layer chromatography using $KMnO_4$ staining to visualize the products. Optical rotations were measured at 589 nm. NMR spectra were calibrated against the residual peeks of solvent as internal standard ($CHCl_3$ δ_H 7.26 ppm, $CDCl_3$ δ_C 77.16 ppm, C_6HD_5 δ_H 7.16 ppm). The catalysts **C1**, **C3**, **C4**, and **C5**, were purchased from Sigma-Aldrich and the catalysts **C2**,[S1] **C6**,[S2] **C7**,[S3] and **C8**[S4] were prepared according to literature procedures. The dienals **2** were prepared as previously described.[S5] While dienal **2a**, could be stored cold for a few months, the dienals **2b-d** were prepared and used in the next step the same day to minimize decomposition. In some NMR spectra isomeric products are visible. The data is given for the major isomer. Racemic material of compounds **3-7** for ee determination were obtained by following the general procedures, but using a mixture of 10+10 mol% of *R*- and *S*-diphenylprolinol trimethylsilyl ethers as catalysts. *p*-Tolylsulfinic acid was freshly prepared prior to use by dissolving the corresponding sodium salt in water and then precipitating the sulfinic acid by addition of conc. HCl(aq.). The sulfinic acid was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to afford a white solid. (*E*)-hepta-2,6-dienoic acid was prepared as previously described,[S6] but further purified with reversed phase HPLC using a 21x150 mm C18 column, a gradient of 5-60% MeCN + 0.1% TFA over 40 min, and a flow rate of 20 mL/min.

General procedure I

The catalysts, acids, solvents, temperatures, and reactions times used are stated in table 1. *N*-Methyl maleimide (13.3 mg, 0.12 mmol), dienal **2a**, (23 mg, 0.13 mmol), the chiral catalyst (0.024 mmol, 0.20 equiv.), and the acid (0.024 mmol, 0.20 equiv.) were dissolved in 1.2 mL of solvent and stirred in a sealed flask at 40 °C or at -10 °C for the indicated time. The reaction mixture was concentrated under reduced pressure and the residue was purified with silica gel chromatography using hexanes: ethyl acetate 6:1 → 4:1 to give the product as colorless sticky foam.

2-((3a*S*,4*R*,7a*R*)-2-methyl-1,3-dioxo-5-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetaldehyde (3)

By following the general procedure I, using catalyst **C8** (14.7 mg, 0.024 mmol), 2-F-benzoic acid (3.4 mg, 0.024 mmol), with $CHCl_3$ as solvent at -10 °C for 120 h. 27 mg **3** (79%) was isolated. $[\alpha]_D^{20}$ –35 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 9.79 (t, *J* = 0.9 Hz, 1H), 7.51-7.42 (m, 3H), 7.27-7.22 (m, 2H), 6.11 (ddd, *J* = 6.3, 4.6, 1.8 Hz, 1H), 3.67-3.59 (m, 1H), 3.51 (dd, *J* = 9.0, 5.7 Hz, 1H), 3.40 (ddd, *J* = 9.0, 7.9, 3.6 Hz, 3H), 3.37 (ddd, *J* = 18.5, 8.3, 0.9 Hz, 1H), 3.15 (s, 1H), 2.95 (ddd, *J* = 15.6, 6.3, 3.6 Hz, 1H), 2.92 (ddd, *J* = 18.5, 6.1, 0.9 Hz, 1H), 2.67 (dddd, *J* = 15.6, 7.9, 4.6, 1.4 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 200.5, 179.6, 178.8, 143.7, 139.5, 128.3 (2C), 127.6 (2C), 127.4, 125.7, 43.6, 43.3, 40.0, 32.6, 24.8, 24.6 ppm; IR(ATR) λ 1772, 1686, 1435, 1382, 1279, 759, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{18}O_3N$ $[M + H]^+$ 284.1281, found 284.1281.

General procedure II

The maleimide (1.0 equiv.), catalyst **C8** (0.20 equiv.), and benzoic acid (0.20 equiv.), were dissolved in a solution of the appropriate dienal (1.5 equiv.) in $CHCl_3$ (10 mL / mmol maleimide) and stirred at room temperature for the time indicated in table 3. (Ethoxycarbonylmethylene)-triphenylphosphorane (1.5 equiv.) was added and the reaction was stirred for 20-24 h at room temperature and then concentrated under reduced pressure. The residue was purified with silica gel chromatography and then further purified with preparative HPLC using a 125x10mm C4-column to afford the products as colorless oils, or

solids (compounds **4c** and **7d**). The HPLC chromatography employed a gradient of 15-90% aqueous acetonitrile + 0.1% TFA over 18 minutes with a flow rate of 6 mL/min.

(*E*)-ethyl 4-((3a*S*,4*R*,7a*R*)-1,3-dioxo-5-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)but-2-enoate (4a)

By following the general procedure II, maleimide (14.6 mg, 0.15 mmol), and dienal **2a** (26 mg, 0.15 mmol) were converted to 19 mg (37%) of compound **4a**. Hexanes: ethyl acetate 5:1→2:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ +10 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 8.66 (bs, 1H), 7.33-7.15 (m, 5H), 6.71 (dt, *J* = 15.6, 7.6 Hz, 1H), 6.06 (t, *J* = 5.2 Hz, 1H), 5.77 (bd, *J* = 15.6 Hz, 1H), 4.10 (q (sp.), *J* = 7.1 Hz, 2H), 3.29 (dd (sp.), *J* = 9.4, 6.0 Hz, 1H), 3.25-3.18 (m, 1H), 3.14 (dt, *J* = 6.0, 7.1 Hz, 1H), 2.76-2.63 (m, 2H), 2.60-2.51 (m, 1H), 2.36 (ddd, *J* = 14.4, 7.6, 7.1 Hz, 1H), 1.21 (t (sp.), *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 180.1, 178.7, 166.2, 146.0, 143.8, 139.9, 128.5 (2C), 127.6, 127.1 (2C), 124.9, 123.9, 60.4, 44.8, 40.8, 38.2, 31.9, 23.8, 14.3 ppm; IR(ATR) λ 1775, 1700, 1168, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{22}O_4N$ $[M + H]^+$ 340.1543, found 340.1546.

(*E*)-ethyl 4-((3a*S*,4*R*,7a*R*)-2-benzyl-1,3-dioxo-5-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol -4-yl)but-2-enoate (4b)

By following the general procedure II, *N*-benzyl maleimide (28.1 mg, 0.15 mmol), and dienal **2a** (39 mg, 0.23 mmol) were converted to 46 mg (71%) of compound **4b**. Hexanes: ethyl acetate 8:1→5:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –16 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.39-7.33 (m, 2H), 7.28-7.19 (m, 6H), 7.02-6.94 (m, 2H), 6.68 (ddd, *J* = 15.6, 8.1, 7.2 Hz, 1H), 5.96 (ddd, *J* = 5.7, 5.2, 0.9 Hz, 1H), 5.70 (dt, *J* = 15.6, 1.3 Hz, 1H), 4.70 (d, *J* = 14.0 Hz, 1H), 4.60 (d, *J* = 14.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.22 (dd, *J* = 9.2, 5.7 Hz, 1H), 3.17 (ddd, *J* = 17.5, 9.2, 4.7 Hz, 1H), 3.06 (dt, *J* = 5.7, 7.2 Hz, 1H), 2.70 (ddd, *J* = 15.9, 5.2, 4.7 Hz, 1H), 2.62-2.47 (m, 2H), 2.23 (ddt, *J* = 14.2, 1.3, 7.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.5, 178.0, 166.2, 146.1 (CH), 144.0, 139.8, 135.8, 128.9 (2 CH), 128.7 (2 CH), 128.3 (2 CH), 128.1 (CH), 127.4 (CH), 127.2 (2 CH), 125.0 (CH), 123.8 (CH), 60.3 (CH_2), 43.3 (CH), 42.6 (CH_2), 39.7 (CH), 38.5 (CH), 31.7 (CH_2), 24.2 (CH_2), 14.3 (CH_3) ppm; IR(ATR) λ 1696, 1431, 1167, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{28}O_4N$ $[M + H]^+$ 430.2013, found 430.2014.

(*E*)-ethyl 4-((3a*S*,4*R*,7a*R*)-1,3-dioxo-2,5-diphenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)but-2-enoate (4c)

By following the general procedure II, *N*-phenyl maleimide (26.0 mg, 0.15 mmol), and dienal **2a** (39 mg, 0.23 mmol) were converted to 47 mg (75%) of compound **4c**. Hexanes: ethyl acetate 7:1→5:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –19 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.50-7.44 (m, 2H), 7.42-7.38 (m, 1H), 7.34-7.23 (m, 5H), 7.23-7.18 (m, 2H), 6.75 (dt, *J* = 15.4, 7.4 Hz, 1H), 6.12 (t, *J* = 5.4 Hz, 1H), 5.80 (d, *J* = 15.4 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.41 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.34 (ddd, *J* = 9.5, 8.4, 4.9 Hz, 1H), 3.24 (dt, *J* = 5.9, 7.4 Hz, 1H), 2.84-2.74 (m, 2H), 2.65 (ddd, *J* = 16.2, 8.4, 5.4 Hz, 1H), 2.42 (ddt, *J* = 14.2, 1.2, 7.4 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 178.8, 177.4, 166.1, 145.8, 143.9, 139.9, 131.9, 129.3 (2 CH), 128.8 (CH), 128.5 (2 CH), 127.6 (CH), 127.1 (2 CH), 126.5 (2 CH), 125.0 (CH), 124.0 (CH), 60.3 (CH_2), 43.5 (CH), 39.7 (CH), 38.6 (CH), 31.9 (CH_2), 24.3 (CH_2), 14.3 (CH_3) ppm; IR(ATR) λ 1703, 1495, 1379, 1267, 1159, 756, 692 cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{26}O_4N$ $[M + H]^+$ 416.1856, found 416.1857.

(*E*)-ethyl 4-((3a*S*,4*S*,8a*S*,8b*R*)-2-methyl-1,3-dioxo-1,2,3,3a,4,6,7,8,8a,8b-decahydrocyclopenta[e]isoindol-4-yl)but-2-enoate (5a)

By following the general procedure II, *N*-methyl maleimide (16.7 mg, 0.15 mmol), and dienal **2b** (31 mg, 0.23 mmol) were converted to 16 mg (34%) of compound **5a**. Hexanes: ethyl acetate 8:1→5:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –35 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.01 (dt, *J* = 15.7, 7.5 Hz, 1H), 5.97 (dt, *J* = 15.7, 1.6 Hz, 1H), 5.46-5.42 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.16 (t, *J* = 8.4 Hz, 1H), 3.04 (dd, *J* = 8.4,

5.5 Hz, 1H), 2.92 (ddt, *J* = 14.8, 1.6, 7.5 Hz, 1H), 2.87 (s, 3H), 2.75 (ddt, *J* = 14.8, 1.6, 7.5 Hz, 1H), 2.55-2.45 (m, 1H), 2.41-2.07 (m, 4H), 2.01-1.90 (m, 1H), 1.62 (quin, *J* = 6.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 178.0, 177.8, 166.7, 148.3, 147.2 (CH), 123.3 (CH), 120.2 (CH), 60.4 (CH_2), 44.7 (CH), 43.0 (CH), 40.0 (CH), 36.6 (CH), 34.1 (CH_2), 31.5 (CH_2), 28.0 (CH_2), 26.7 (CH_2), 24.7 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1689, 1435, 1382, 1284, 1032, 734 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{24}O_4N$ $[M + H]^+$ 318.1700, found 318.1703.

(*E*)-ethyl 4-((3a*S*,4*S*,8a*S*,8b*R*)-2-benzyl-1,3-dioxo-1,2,3,3a,4,6,7,8,8a,8b-decahydrocyclopenta[e]isoindol-4-yl)but-2-enoate (5b)

By following the general procedure II, *N*-benzyl maleimide (28.1 mg, 0.15 mmol), and dienal **2b** (31 mg, 0.23 mmol) were converted to 15 mg (25%) of compound **5b**. Hexanes: ethyl acetate 9:1→6:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –46 (*c* 0.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.29-7.20 (m, 5H), 7.01 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.97 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.45-5.41 (m, 1H), 4.6 (d, *J* = 14.3 Hz, 1H), 4.51 (d, *J* = 14.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.15 (t, *J* = 8.4 Hz, 1H), 3.06 (dd, *J* = 8.4, 5.1 Hz, 1H), 2.93 (dddd, *J* = 14.9, 7.5, 7.2, 1.5 Hz, 1H), 2.79 (dddd, *J* = 14.9, 8.7, 7.2, 1.5 Hz, 1H), 2.49 (q, *J* = 8.4 Hz, 1H), 2.41-2.31 (m, 1H), 2.24-2.11 (m, 2H), 1.98-1.84 (m, 2H), 1.53 (d quin, *J* = 12.5, 7.0 Hz, 1H), 1.39 (d quin, *J* = 12.5, 6.9 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 177.6, 177.3, 166.7, 148.4, 147.2 (CH), 136.0, 128.6 (2 CH), 128.2 (2 CH), 127.8 (CH), 123.3 (CH), 120.3 (CH), 60.4 (CH_2), 44.7 (CH), 43.0 (CH), 42.1 (CH_2), 40.1 (CH), 36.8 (CH), 34.1 (CH_2), 31.4 (CH_2), 27.8 (CH_2), 26.6 (CH_2), 14.4 (CH_3) ppm; IR(ATR) λ 1692, 1397, 1174, 1031, 733, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{24}H_{28}O_4N$ $[M + H]^+$ 394.2013, found 394.2007.

(*E*)-ethyl 4-((3a*S*,4*S*,8a*S*,8b*R*)-1,3-dioxo-2-phenyl-1,2,3,3a,4,6,7,8,8a,8b-decahydrocyclopenta[e]isoindol-4-yl)but-2-enoate (5c)

By following the general procedure II, *N*-phenyl maleimide (26.0 mg, 0.15 mmol), and dienal **2b** (31 mg, 0.23 mmol) were converted to 26 mg (46%) of compound **5c**. Hexanes: ethyl acetate 9:1→6:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –61 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.46-7.39 (m, 2H), 7.38-7.32 (m, 1H), 7.17-7.11 (m, 2H), 7.03 (dt, *J* = 15.6, 7.3 Hz, 1H), 6.00 (bd, *J* = 15.6 Hz, 1H), 5.56 (bs, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.32 (dd, *J* = 8.8, 8.6 Hz, 1H), 3.22 (dd, *J* = 8.6, 5.0 Hz, 1H), 2.97 (dt, *J* = 14.8, 7.3 Hz, 1H), 2.81 (dt, *J* = 14.8, 7.3 Hz, 1H), 2.61 (q, *J* = 8.8 Hz, 1H), 2.51-2.40 (m, 1H), 2.36-2.18 (m, 3H), 2.01 (ddt, *J* = 13.2, 8.8, 6.8 Hz, 1H), 1.68 (quin, *J* = 6.8 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 177.0, 176.7, 166.7, 148.2, 147.1 (CH), 132.0, 129.2 (2 CH), 128.7 (CH), 126.7 (2 CH), 123.5 (CH), 120.6 (CH), 60.4 (CH_2), 44.8 (CH), 43.1 (CH), 40.2 (CH), 36.9 (CH), 34.1 (CH_2), 31.6 (CH_2), 28.0 (CH_2), 26.9 (CH_2), 14.4 (CH_3) ppm; IR(ATR) λ 1701, 1381, 1181, 734, 691 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{26}O_4N$ $[M + H]^+$ 380.1856, found 380.1860.

(*E*)-ethyl 4-((3a*S*,4*R*,7*R*,7a*R*)-2-benzyl-5,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)but-2-enoate (6a)

By following the general procedure II, *N*-benzyl maleimide (24.4 mg, 0.13 mmol), and dienal **2c** (25 mg, 0.23 mmol) were converted to 29 mg (58%) of compound **6a**. Hexanes: ethyl acetate 8:1→6:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –83 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.30-7.18 (m, 5H), 7.03 (dt, *J* = 15.7, 7.8 Hz, 1H), 6.02 (bd, *J* = 15.7 Hz, 1H), 5.30 (bs, 1H), 4.58 (d, *J* = 14.3 Hz, 1H), 4.52 (d, *J* = 14.3 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.11-3.00 (m, 2H), 2.90 (dd, *J* = 8.0, 6.9 Hz, 1H), 2.78-2.73 (m, 1H), 2.48-2.31 (m, 2H), 1.59 (s, 3H), 1.37 (d, *J* = 7.3 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 177.5, 177.1, 166.6, 147.3 (CH), 138.3, 136.1, 129.1 (CH), 128.6 (2 CH), 128.2 (2 CH), 127.7 (CH), 123.8 (CH), 60.4 (CH_2), 45.4 (CH), 43.7 (CH), 42.1 (CH_2), 38.9 (CH), 31.6 (CH), 30.8 (CH_2), 19.1 (CH_3), 16.7 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1693, 1396, 1170, 734, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{28}O_4N$ $[M + H]^+$ 382.2013, found 382.2020.

(*E*)-ethyl 4-((3a*S*,4*R*,7*R*,7a*R*)-5,7-dimethyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)but-2-enoate (6b)

By following the general procedure II, *N*-phenyl maleimide (22.5 mg, 0.13 mmol), and dienal **2c** (24 mg, 0.19 mmol) were converted to 37 mg (78%) of compound **6b**. Hexanes: ethyl acetate 8:1→5:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –120 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.45-7.39 (m, 2H), 7.38-7.32 (m, 1H), 7.17-7.11 (m, 2H), 7.07 (ddd, *J* = 15.6, 8.4, 6.3 Hz, 1H), 6.06 (bd, *J* = 15.6 Hz, 1H), 5.50 (bs, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.23 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.15 (ddd, *J* = 14.7, 8.4, 1.2 Hz, 1H), 3.09 (dd, *J* = 8.2, 7.2 Hz, 1H), 2.80 (ddt, *J* = 14.7, 1.6, 6.3 Hz, 1H), 2.57-2.41 (m, 2H), 1.78 (s, 3H), 1.42 (d, *J* = 7.3 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 177.0, 176.4, 166.6, 147.2 (CH), 138.7, 132.0, 129.2 (2C), 128.9 (CH), 128.6 (CH), 126.7 (2 CH), 124.1 (CH), 60.4 (CH_2), 45.4 (CH), 43.8 (CH), 39.0 (CH), 31.7 (CH), 30.9 (CH_2), 19.3 (CH_3), 16.8 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1703, 1378, 1178, 751, 691 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{26}O_4N$ $[M + H]^+$ 368.1856, found 368.1864.

(*E*)-ethyl 4-((3a*S*,4*S*,7a*R*)-2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)but-2-enoate (7a)

By following the general procedure II, *N*-methyl maleimide (16.6 mg, 0.15 mmol), and dienal **2d** (25 mg, 0.23 mmol) were converted to 31 mg (71%) of compound **7a**. Hexanes: ethyl acetate 10:1→6:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –1 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.98 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.95 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.32 (bs, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.10 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 3.03 (dd, *J* = 8.6, 6.0 Hz, 1H), 2.89 (s, 3H), 2.82 (ddt, *J* = 14.8, 1.4, 7.2 Hz, 1H), 2.63-2.54 (m, 1H), 2.55 (bd, *J* = 15.0 Hz, 1H), 2.41-2.31 (m, 1H), 2.16 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.69 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.7, 178.0, 166.6, 146.9 (CH), 137.3, 124.9 (CH), 123.4 (CH), 60.4 (CH_2), 42.8 (CH), 40.6 (CH), 35.8 (CH), 33.9 (CH_2), 29.5 (CH_2), 24.9 (CH_3), 23.2 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1688, 1437, 1382, 1282, 1175, 1025, 735 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{22}O_4N$ $[M + H]^+$ 292.1543, found 292.1546.

(*E*)-ethyl 4-((3a*S*,4*S*,7a*R*)-2-benzyl-6-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol -4-yl)but-2-enoate (7b)

By following the general procedure II, *N*-benzyl maleimide (28.2 mg, 0.15 mmol), and dienal **2d** (25 mg, 0.23 mmol) were converted to 32 mg (58%) of compound **7b**. Hexanes: ethyl acetate 8:1→6:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.30-7.20 (m, 5H), 6.98 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.95 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.28 (bs, 1H), 4.60 (d, *J* = 14.3 Hz, 1H), 4.55 (d, *J* = 14.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.11 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 3.04 (ddd, *J* = 8.7, 5.8 Hz, 1H), 2.82 (ddt, *J* = 14.8, 1.4, 7.2 Hz, 1H), 2.60 (dddd, *J* = 14.8, 8.5, 7.2, 1.4 Hz, 1H), 2.53 (bd, *J* = 15.0 Hz, 1H), 2.41-2.30 (m, 1H), 2.17 (dd, *J* = 15.0, 7.1 Hz, 1H), 1.60 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.3, 177.6, 166.6, 146.9 (CH), 137.4, 135.9, 128.6 (2 CH), 128.2 (2 CH), 127.8 (CH), 125.1 (CH), 123.4 (CH), 60.4 (CH_2), 42.9 (CH), 42.4 (CH_2), 40.6 (CH), 36.0 (CH), 33.8 (CH_2), 29.8 (CH_2), 23.0 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1694, 1432, 1168, 734, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{26}O_4N$ $[M + H]^+$ 368.1856, found 368.1869.

(*E*)-ethyl 4-((3a*S*,4*S*,7a*R*)-6-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol -4-yl)but-2-enoate (7c)

By following the general procedure II, *N*-phenyl maleimide (25.9 mg, 0.15 mmol), and dienal **2d** (25 mg, 0.23 mmol) were converted to 30 mg (57%) of compound **7c**. Hexanes: ethyl acetate 8:1→5:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ –14 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.47-7.41 (m, 2H), 7.40-7.34 (m, 1H), 7.19-7.14 (m, 2H), 7.02 (dt, *J* = 15.6, 7.3 Hz, 1H), 5.99 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.45 (bs, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.29 (ddd, *J* = 8.9, 7.0, 1.8 Hz, 1H), 3.22 (dd, *J* = 8.9, 5.9 Hz, 1H), 2.89 (ddt, *J* = 14.8, 1.4, 7.3 Hz, 1H), 2.71-2.61 (m, 2H), 2.52-2.42 (m, 1H), 2.28 (dd, *J* = 14.9, 7.0 Hz, 1H), 1.79 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 178.8, 177.0,

166.7, 146.8 (CH), 137.6, 132.0, 129.2 (2 CH), 128.8 (CH), 126.6 (2 CH), 125.1 (CH), 123.6 (CH), 60.4 (CH_2), 43.0 (CH), 40.7 (CH), 36.2 (CH), 33.9 (CH_2), 30.0 (CH_2), 23.2 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1703, 1499, 1381, 1181, 691 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{24}O_4N$ $[M + H]^+$ 354.1700, found 354.1704.

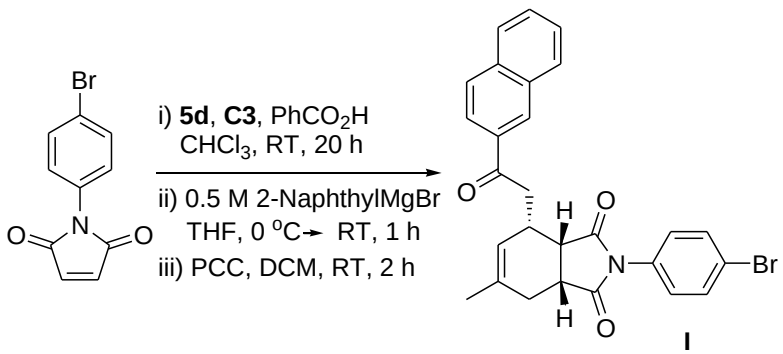
(*E*)-ethyl 4-((3a*S*,4*S*,7a*R*)-3a,6-dimethyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)but-2-enoate (7d)

By following the general procedure II, 2-methyl-*N*-phenyl maleimide (28.2 mg, 0.15 mmol), and dienal **2d** (25 mg, 0.23 mmol) were converted to 14 mg (25%) of compound **7d**. Hexanes: ethyl acetate 9:1→7:1 was used as eluent during silica gel chromatography. $[\alpha]_D^{20}$ +42 (*c* 0.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.47-7.41 (m, 2H), 7.39-7.34 (m, 1H), 7.21-7.16 (m, 2H), 6.92 (ddd, *J* = 15.7, 8.0, 6.0 Hz, 1H), 5.88 (bd, *J* = 15.7 Hz, 1H), 5.40 (bs, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.87 (dd, *J* = 6.3, 2.5 Hz, 1H), 2.85-2.77 (m, 1H), 2.68 (dd, *J* = 15.1, 2.5 Hz, 1H), 2.43-2.33 (m, 1H), 2.30 (dd, *J* = 15.1, 6.3 Hz, 1H), 2.14 (bd, *J* = 11.5 Hz, 1H), 1.79 (s, 3H), 1.52 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.9, 177.7, 166.6, 147.6 (CH), 138.4, 132.1, 129.2 (2 CH), 128.7 (CH), 126.5 (2 CH), 124.9 (CH), 123.1 (CH), 60.5 (CH_2), 49.5 (CH), 47.5 (CH), 42.9 (CH), 32.8 (CH_2), 29.3 (CH_2), 23.3 (CH_3), 23.1 (CH_3), 14.4 (CH_3) ppm; IR(ATR) λ 1703, 1388, 1371, 1180, 691 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{26}O_4N$ $[M + H]^+$ 368.1856, found 368.1864.

ethyl 2-((3a*R*/*S*,7*S*/*R*,7a*S*/*R*,9*S*/*R*)-2-benzyl-5-methyl-1,3-dioxo-1,2,3,4,7,7a-hexahydro-3a,7-ethanoisoindol-9-yl)acetate (8)

7b, (36.8 mg, 0.10 mmol), and cesium carbonate, (32.7 mg, 0.10 mmol), were taken up in 1 mL DMSO and stirred at room temperature for 24 h. The mixture was quenched with 1 M aqueous HCl and extracted with ethyl acetate. The organic phase was washed once with a small portion of water and then dried over anhydrous $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified with silica gel chromatography using hexanes: ethyl acetate 8:1 → 6:1 as eluent, which afforded 21 mg (57 %) of compound **8** as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.44-7.38 (m, 2H), 7.33-7.23 (m, 3H), 5.69-5.64 (m, 1H), 4.59 (s, 2H), 4.12-3.98 (m, 2H), 2.99-2.94 (m, 1H), 2.70 (s, 1H), 2.58-2.48 (m, 2H), 2.37 (d, *J* = 16.7 Hz, 1H), 2.22-2.10 (m, 2H), 1.67 (s, 3H), 1.7-1.60 (m, 1H), 1.35 (ddd, *J* = 13.0, 9.1, 4.2 Hz, 1H), 1.24-1.18 (m, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 178.1, 176.0, 171.8, 136.1, 133.4, 129.4 (2 CH), 128.8 (2 CH), 128.1 (CH), 127.3 (CH), 60.6 (CH_2), 56.3 (CH), 52.8, 44.0 (CH), 42.1 (CH_2), 41.4 (CH_2), 41.0 (CH_2), 36.4 (CH), 36.2 (CH_2), 22.7 (CH_3), 14.3 (CH_3) ppm; A NOESY spectrum were recorded in C_6D_6, which revealed a cross-peak between the C9-H (2.58-2.48 ppm) and its closest C4-H (2.15 ppm). ^{1}H-NMR (400 MHz, C_6D_6): δ= 7.55 (d, *J* = 7.8 Hz, 2H), 7.15-7.10 (m, 2H), 7.08-7.02 (m, 1H), 5.25-5.20 (m, 1H), 4.43 (s, 2H), 3.98-3.83 (m, 2H), 2.72-2.66 (m, 1H), 2.58-2.48 (m, 1H), 2.25 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.15 (d, *J* = 16.7 Hz, 1H), 2.07-1.96 (m, 3H), 1.65 (dd, *J* = 16.2, 9.5 Hz, 1H), 1.34-1.25 (m, 1H), 1.30 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm; IR(ATR) λ 1732, 1704, 1383, 1337, 1159, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{26}O_4N$ $[M + H]^+$ 368.1856, found 368.1870.

Confirmation of the absolute configuration by preparation of I



I

(3a*S*,4*S*,7a*R*)-2-(4-bromophenyl)-6-methyl-4-(2-(naphthalen-2-yl)-2-oxoethyl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (l)
N-(4-Bromophenyl)maleimide, (126 mg, 0.50 mmol), catalyst **C3** (37 mg, 0.10 mmol), and benzoic acid (12 mg, 0.10 mmol) were dissolved in 5 mL $CHCl_3$. Dienal **2d** (83 mg, 0.75 mmol) was added and the solution was stirred at room temperature for 20h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtrated and concentrated from toluene. The residue was dissolved in 5 mL THF and cooled to 0 °C. 0.5 M 2-Naphthylmagnesiumbromide in THF (1.7 mL, 0.85 mmol) was added slowly and the reaction was then stirred at room temperature for 1h. The reaction was quenched with aqueous saturated NH_4Cl, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated and concentrated. Non-polar side products were removed by passing the residue through a small silica plugusing CH_2Cl_2 as eluent. Further elution with CH_2Cl_2:ethyl acetate 1:1 afforded an impure mixture of products that contain a 5:4 diasteremeric mixture of the desired alcohols. Without further purification, the product mixture was dissolved in 5 mL of CH_2Cl_2. Crushed 3Å molecular sieves (220 mg) and pyridinium chlorochromate (162 mg, 0.75 mmol) were added and the mixture was stirred at room temperature 2h and then concentrated under reduced pressure. Silica gel chromatography using hexanes: ethyl acetate 8:1→4:1 gave 85 mg (35%) of **l** as a white solid. NMR data is in agreement with previously published data.[S7] $[\alpha]^{20}_{D}$ –5.3 (*c* 0.5, ethyl acetate)

(*E*)-6-methoxy-2-methylhexa-1,3-diene (9a)
5-Methyl-3,4-hexadienol,[S8] (999 mg, 8.91 mmol) was dissolved in 35.6 mL THF and cooled to 0 °C. NaH (washed with pentane), (256 mg, 10.7 mmol) was added and the mixture was then stirred at room temperature for 30 minutes before addition of methyl iodide (0.67 mL, 10.8 mmol). The reaction was stirred at room temperature overnight and then quenched by addition of saturated aqueous NH_4Cl. The product was extracted with pentane and concentrated at room temperature to ~65 mbar and then purified with silica gel chromatography using pentane: DCM 2:1 as eluent. After concentration at room temperature to ~65 mbar 494 mg **9a** (44 %) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.20 (bd, *J* = 15.7 Hz, 1H), 5.65 (dt, *J* = 15.7, 7.0 Hz, 1H), 4.88 (s, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.35 (s, 3H), 2.42-2.35 (m, 2H), 1.83 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 142.1, 134.8, 126.9, 115.1, 72.5, 58.8, 33.3, 18.8 ppm; IR(ATR) λ 1742, 1610, 1454, 1379, 1119, 965, 882 cm^{-1}; HRMS (ESI) Calcd. for $C_8H_{15}O$ $[M + H]^+$ 127.1117, found 127.1119.

(*E*)-6-(allyloxy)-2-methylhexa-1,3-diene (9b)
5-Methyl-3,4-hexadienol,[S8] (1.096 g, 9.77 mmol) was dissolved in 5 mL THF and cooled to 0 °C. NaH (washed with pentane), (355 mg, 14.8 mmol) was added and the mixture was then stirred at room temperature for 30 minutes before addition of allyl bromide (1.27 mL, 14.7 mmol). The reaction was stirred at room temperature overnight and then quenched by addition of saturated aqueous NH_4Cl. The product was extracted with pentane and concentrated at room temperature to ~65 mbar and then purified with silica gel chromatography using pentane: DCM 4:1 as eluent. After concentration at room temperature to ~65 mbar 745 mg **9b** (50 %) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.21 (d, *J* = 15.7 Hz, 1H), 5.97-5.86 (m, 1H), 5.67 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.31-5.24 (m, 1H), 5.20-5.15 (m, 1H), 4.88 (s, 2H), 3.99 (m, 2H), 3.49 (t, *J* = 6.9 Hz, 2H), 2.41 (q, *J* = 6.9 Hz, 2H), 1.83 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 142.1, 135.1, 134.7, 126.9, 117.0, 115.0, 72.0, 70.0, 33.4, 18.8 ppm; IR(ATR) λ 1086, 977 916, 731 cm^{-1}; HRMS (ESI) Calcd. for $C_{10}H_{17}O$ $[M + H]^+$ 153.1274, found 153.1270.

***N*-(2-(trimethylsilyl)ethyl)-maleimide (1g)**
2-trimethylsilylethanol, (237 mg, 2.00 mmol), and maleimide, (214 mg, 2.20 mmol), were dissolved in 8.0 mL THF and cooled to 0 °C. Diethylazodicarboxylate, (1.00 mL, 40% in toluene, 2.2 mmol), was added followed by slow addition of a solution of triphenylphosphine,

(577 mg, 2.20 mmol) in 2.0 mL THF. The reaction was stirred overnight allowing the mixture to reach room temperature. The reaction was concentrated and the residue was purified with silica gel chromatography using hexanes: ethyl acetate 1:0 → 20:1 as eluent. Compound **1g**, 224 mg (57 %) was obtained as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 6.59 (s, 2H), 3.49-3.41 (m, 2H), 0.86-0.79 (m, 2H), -0.05 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 170.6 (2C), 134.1 (2C), 34.2, 17.0, -1.9 (3C) ppm; IR(ATR) λ 1692, 1407, 1349, 1246, 1136, 1017, 691 cm^{-1}; LCMS (ES^{+}) Calcd. for $C_9H_{16}NO_2Si$ [M + H]$^{+}$ 198, mass not found.

***N*-(*tert*-butyldimethylsilyl)-maleimide (1h)**
Maleimide, (971 mg, 10.0 mmol), 4-dimethylaminopyridine, (122 mg, 1.0 mmol), and dimethyl-*tert*-butylsilylchloride, (1.969 g, 13.0 mmol) were taken up in 10 mL ethyl acetate. Triethylamine, (1.80 mL, 13.0 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was concentrated onto silica and purified with silica gel chromatography using hexanes: ethyl acetate 20:1 as eluent. 1.630 g (77%) **1h** was obtained as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 6.63 (s, 2H), 0.88 (s, 9H), 0.39 (s, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 176.5 (2C), 136.3 (2C), 26.3 (3C), 18.9, -4.5 ppm; IR(ATR) λ 1697, 1326, 1252, 1144, 998, 848, 823, 694 cm^{-1}; LCMS (ES^{+}) Calcd. for $C_{10}H_{18}O_2NSi$ [M + H]$^{+}$ 212, found 212.

General procedure III

Maleimide **1a**, **1f**, **1g**, or **1h**, (1.0 equiv.) and diene **9a** or **9b** (1.1 equiv.) were dissolved in toluene (2 mL / mmol maleimide) and heated at 110 °C for 1.5-3.5h and then concetrated under reduced pressure. The residue was purified with silica gel chromatography to give the compounds **10** as colorless oils.

(3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-3a,4,7,7a-tetrahydro-4-(2-methoxyethyl)-2,6-dimethyl-2*H*-isoindole-1,3-dione (10a)
By following general procedure **III**, *N*-methyl maleimide, (278 mg, 2.50 mmol), and **9a**, (348 mg, 2.76 mmol), were converted to 502 mg (85%) **10a** after 3 h of heating. Hexanes: ethyl acetate 8:1 → 2:1 were used as eluent during the chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 5.24 (bs, 1H), 3.54-3.46 (m, 1H), 3.43-3.36 (m, 1H), 3.22 (s, 3H), 3.03-2.92 (m, 2H), 2.77 (s, 3H), 2.42 (d, *J* = 15.0 Hz, 1H), 2.33 (bs, 1H), 2.14-1.98 (m, 2H), 1.88-1.78 (m, 1H), 1.59 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 179.7, 178.1, 136.4, 125.6, 70.5, 58.5, 42.6, 40.5, 32.9, 31.0, 29.3, 24.6, 23.0 ppm; IR(ATR) λ 1692, 1433, 1382, 1284, 1115, 1003 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_{20}O_3N$ [M + H]$^{+}$ 238.1438, found 238.1438.

(3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-2-(4-methoxybenzyl)-3a,4,7,7a-tetrahydro-4-(2-methoxyethyl)-6-methyl-2*H*-isoindole-1,3-dione (10b)
By following general procedure **III**, *N*-(4-methoxybenzyl) maleimide, (98 mg, 0.45 mmol), and **9a**, (62 mg, 0.49 mmol), were converted to 130 mg (84%) **10b** after 3.5 h of heating. Hexanes: ethyl acetate 10:1 → 3:1 were used as eluent during the chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.18 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.27 (bs, 1H), 4.51 (d, *J* = 14.2 Hz, 1H), 4.47 (d, *J* = 14.2 Hz, 1H), 3.74 (s, 3H), 3.62-3.55 (m, 1H), 3.51-3.44 (m, 1H), 3.31 (s, 3H), 3.10-2.98 (m, 2H), 2.49 (bd, *J* = 14.8 Hz, 1H), 2.40 (bs, 1H), 2.21-2.07 (m, 2H), 1.99-1.88 (m, 1H), 1.59 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 179.6, 178.0, 159.1, 136.6, 129.7 (2C), 128.4, 126.0, 113.8 (2C), 70.7, 58.7, 55.3, 42.8, 41.7, 40.7, 33.3, 31.2, 29.7, 23.1 ppm; IR(ATR) λ 1695, 1515, 1399, 1248, 1177, 1116 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{26}O_4N$ [M + H]$^{+}$ 344.1856, found 344.1860.

(3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-3a,4,7,7a-tetrahydro-4-(2-methoxyethyl)-6-methyl-2-(2-(trimethylsilyl)ethyl)-2*H*-isoindole-1,3-dione (10c)
By following general **III**, **1g**, (296 mg, 1.50 mmol), and **9a**, (208 mg, 1.65 mmol), were converted to 409 mg (84%) **10c** after 1.5 h of heating. Hexanes: ethyl acetate 15:1 → 6:1

were used as eluent during the chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 5.34 (bs, 1H), 3.65-3.58 (m, 1H), 3.54-3.47 (m, 1H), 3.44-3.37 (m, 2H), 3.34 (s, 3H), 3.08-2.96 (m, 2H), 2.52 (bd, *J* = 15.0 Hz, 1H), 2.42 (bs, 1H), 2.23-2.11 (m, 2H), 2.01-1.91 (m, 1H), 1.69 (s, 3H), 0.81-0.73 (m, 2H), 0.02 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.7, 178.2, 136.6, 125.9, 70.8, 58.8, 42.8, 40.7, 35.3, 33.3, 31.3, 29.7, 23.2, 16.4, -1.7 (3C) ppm; IR(ATR) λ 1692, 1249, 1119, 859, 837 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{30}O_3NSi$ $[M + H]^+$ 324.1990, found 324.1996.

(3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-2-(*tert*-butyldimethylsilyl)-3a,4,7,7a-tetrahydro-4-(2-methoxyethyl)-6-methyl-2*H*-isoindole-1,3-dione (10d)

By following general procedure **III**, **1h**, (317 mg, 1.50 mmol), and **9a**, (208 mg, 1.65 mmol), were converted to 392 mg (77%) **10d** after 2 h and 15 min of heating. Hexanes: ethyl acetate 20:1 → 8:1 were used as eluent during the chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 5.37 (bs, 1H), 3.60 (ddd, *J* = 9.8, 6.8, 5.2 Hz, 1H), 3.50 (ddd, *J* = 9.8, 6.8, 5.2 Hz, 1H), 3.33 (s, 3H), 3.08 (ddd, *J* = 9.1, 6.6, 1.9 Hz, 1H), 3.01 (dd, *J* = 9.1, 6.2 Hz, 1H), 2.51 (bd, *J* = 14.8 Hz, 1H), 2.39 (bs, 1H), 2.18-2.08 (m, 2H), 1.98-1.88 (m, 1H), 1.72 (s, 3H), 0.82 (s, 9H), 0.36 (s, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 185.9, 184.3, 137.2, 126.2, 70.8, 58.8, 44.7, 43.1, 33.4, 31.4, 30.0, 26.3 (3C), 23.4, 18.9, -4.1, -4.2 ppm; IR(ATR) λ 1689, 1317, 1172, 1118, 845 cm^{-1}; LCMS (ES^+) Calcd. for $C_{18}H_{32}O_3NSi$ $[M + H]^+$ 338, found 338.

(3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-2-(*tert*-butyldimethylsilyl)-4-(2-(allyloxy)ethyl)-3a,4,7,7a-tetrahydro-6-methyl-2*H*-isoindole-1,3-dione (10e)

By following general procedure **III**, **1h**, (940 mg, 4.45 mmol), and **9b**, (745 mg, 4.89 mmol), were converted to 1222 mg (76%) **10e** after 2 h of heating. Hexanes: ethyl acetate 20:1 → 10:1 were used as eluent during the chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 5.74-5.63 (m, 1H), 5.39 (bs, 1H), 5.11-5.01 (m, 2H), 4.04-3.99 (m, 2H), 3.82 (ddd, *J* = 10.4, 6.7, 5.6 Hz, 1H), 3.74 (ddd, *J* = 10.4, 6.7, 5.6 Hz, 1H), 3.11 (ddd, *J* = 8.7, 7.1, 1.9 Hz, 1H), 3.04 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.55 (bd, *J* = 14.8 Hz, 1H), 2.51-2.42 (m, 1H), 2.18 (dd, *J* = 14.8, 7.1 Hz, 1H), 2.14-2.04 (m, 1H), 1.95-1.84 (m, 1H), 1.70 (s, 3H), 0.87 (s, 9H), 0.038 (s, 3H), 0.036 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.5, 177.8, 136.5, 130.9, 126.4, 117.1, 61.2, 43.0, 40.8, 40.7, 34.2, 33.0, 29.7, 26.1 (3C), 23.2, 18.4, -5.2 (2C, splitted) ppm; IR(ATR) λ 1690, 1316, 1173, 845 cm^{-1}; LCMS (ES^+) Calcd. for $C_{20}H_{34}O_3NSi$ $[M + H]^+$ 364, found 364.

(3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-4-(2-(allyloxy)ethyl)-3a,4,7,7a-tetrahydro-2,6-dimethyl-2*H*-isoindole-1,3-dione (10f)

By following general procedure **III**, *N*-methyl maleimide, (400 mg, 3.60 mmol), and **9b**, (603 mg, 3.96 mmol), were converted to 799 mg (84%) **10f** after 2h of heating. Hexanes: ethyl acetate 9:1 → 4:1 were used as eluent during the chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 5.84-5.73 (m, 1H), 5.25 (bs, 1H), 5.18-5.11 (m, 1H), 5.07-5.02 (m, 1H), 3.89-3.84 (m, 2H), 3.56 (ddd, *J* = 9.8, 6.8, 5.4 Hz, 1H), 3.46 (ddd, *J* = 9.8, 6.8, 5.4 Hz, 1H), 3.03-2.92 (m, 2H), 2.77 (s, 3H), 2.42 (bd, *J* = 14.9 Hz, 1H), 2.36 (bs, 1H), 2.13-2.00 (m, 2H), 1.90-1.79 (m, 1H), 1.59 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 179.7, 178.0, 136.3, 134.8, 125.7, 116.6, 71.6, 68.0, 42.6, 40.5, 33.0, 31.2, 29.2, 24.5, 23.0 ppm; IR(ATR) λ 1686, 1435, 1382, 1284 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{22}O_3N$ $[M + H]^+$ 264.1594, found 264.1592.

General procedure IV

The compound **10**, (1.0 equiv.) was dissolved in DCM (10 mL/mmol **10**) and the solution was cooled to -78°C. Diisobutylaluminiumhydride (1.2 M in toluene, 1.25 mL / mmol **10**) was added slowly and then stirred for 1 h. The reaction was placed in a 0 °C ice-bath and a room-temperated solution of *p*-tolylsulfinic acid, (625 mg / mmol **10**, 4.0 equiv.) in DCM (5 mL / mmol **10**) and trimethylsilyl trifluoromethylsulfonate, (0.452 mL / mmol **10**, 2.5 equiv.), was immediately added and the mixture was stirred 25 minutes. The reaction was then quenched

with saturated aqueous $NaHCO_3$ and extracted with DCM. The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The resulting sulfone was concentrated once from toluene and then dissolved in THF (10 mL / mmol **10**) and cooled to 0 °C. A separate flask was charged with $ZnBr_2$, (450 mg / mmol **10**, 2.0 equiv.) and THF (4 mL / mmol **10**) and cooled to 0 °C. The Grignard-reagent, (1 M in diethylether, 4 mL / mmol **10**) was added slowly and the mixture was stirred for 30 minutes. A syringe was then used to transfer the produced reagent to the flask containing the sulfone-solution, leaving as much as possible of the precipitated salts behind. The resulting mixture was stirred overnight, allowing the reaction to reach room temperature. The reaction was quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, extracted with ethyl acetate and then concentrated under reduced pressure. The resulting residue was purified with silica gel chromatography, and if necessary with reversed phase HPLC.

(3*S*/*R*,3a*R*/*S*,7*S*/*R*,7a*S*/*R*)-3-benzyl-2,3,3a,4,7,7a-hexahydro-7-(2-methoxyethyl)-2,5-dimethylisoindol-1-one (11a)

By following general procedure **IV**, compound **10a**, (475 mg, 2.00 mmol) and benzyl magnesium chloride were reacted to give compound **11a**, 257 mg (41%) as colorless oil. Hexanes: ethyl acetate 4:1 → 1:1 was used as eluent in the silica gel chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.34-7.28 (m, 2H), 7.27-7.22 (m, 1H), 7.18-7.13 (m, 2H), 5.43-5.38 (m, 1H), 3.53-3.41 (m, 2H), 3.31 (s, 3H), 3.26-3.20 (m, 1H), 3.03 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.80 (s, 3H), 2.63 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.60 (dd, *J* = 8.9, 5.9 Hz, 1H), 2.46-2.39 (m, 1H), 2.39-2.30 (m, 1H), 2.16-2.06 (m, 1H), 1.93 (dd, *J* = 16.4, 8.0 Hz, 1H), 1.88-1.78 (m, 1H), 1.61 (s, 3H), 1.52 (dd, *J* = 16.4, 4.3 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 175.8, 137.1, 134.6, 129.4 (2C), 128.8 (2C), 126.9, 125.8, 71.1, 68.7, 58.6, 42.9, 39.2, 36.3, 33.3, 32.6, 31.2, 28.4, 23.8 ppm; IR(ATR) λ 1678, 1453, 1398, 1114, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{28}O_2N$ $[M + H]^+$ 314.2115, found 314.2120.

(3*S*/*R*,3a*R*/*S*,7*S*/*R*,7a*S*/*R*)-2-(4-methoxybenzyl)-3-benzyl-2,3,3a,4,7,7a-hexahydro-7-(2-methoxyethyl)-5-methylisoindol-1-one (11b)

By following general procedure **IV**, compound **10b**, (546 mg, 1.59 mmol) and benzyl magnesium chloride were reacted to give compound **11b**, 340 mg (51%) as colorless oil. Hexanes: ethyl acetate 6:1 → 2:1 was used as eluent in the silica gel chromatography. Mixed fractions were further purified with HPLC employing a 21x150 mm C4-column, a gradient of 15-100% MeCN over 35 min, and a flow rate of 20 mL/min. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.32-7.20 (m, 3H), 7.09-7.03 (m, 4H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.42 (bs, 1H), 5.07 (d, *J* = 14.8 Hz, 1H), 3.80 (s, 3H), 3.69 (d, *J* = 14.8 Hz, 1H), 3.60-3.46 (m, 2H), 3.33 (s, 3H), 3.07-3.01 (m, 1H), 2.96 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.66 (dd, *J* = 8.6, 5.0 Hz, 1H), 2.59 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.44-2.36 (m, 1H), 2.36-2.21 (m, 2H), 2.12-2.01 (m, 1H), 1.90 (dd, *J* = 16.3, 8.0 Hz, 1H), 1.50 (s, 3H), 1.30 (dd, *J* = 16.3, 3.5 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 175.1, 159.1, 137.4, 134.9, 129.6 (2C), 129.3 (2C), 128.7 (2C), 128.5, 126.8, 126.0, 114.1 (2C), 71.1, 64.7, 58.6, 55.4, 43.7, 42.9, 38.7, 36.0, 33.8, 32.8, 31.3, 23.7 ppm; IR(ATR) λ 1714, 1512, 1243, 1175, 1111, 1031, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{34}O_3N$ $[M + H]^+$ 420.2533, found 420.2533.

(3*S*,3a*R*,7*S*,7a*S*)-3-benzyl-2,3,3a,4,7,7a-hexahydro-7-(2-methoxyethyl)-5-methyl-2-(2-(trimethylsilyl)ethyl)isoindol-1-one (11c)

By following general procedure **IV**, compound **10c**, (387 mg, 1.20 mmol) and benzyl magnesium chloride were reacted to give compound **11c**, 267 mg (56%) as colorless oil. Hexanes: ethyl acetate 10:1 → 5:1 was used as eluent in the silica gel chromatography. $[\alpha]_D^{20}$ +16 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.33-7.28 (m, 2H), 7.26-7.21 (m, 1H), 7.18-7.14 (m, 2H), 5.38 (bs, 1H), 3.70 (dt, *J* = 13.6, 4.5 Hz, 1H), 3.56-3.42 (m, 2H), 3.39-3.34 (m, 1H), 3.31 (s, 3H), 2.93 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.72 (dt, *J* = 13.6, 4.5 Hz, 1H), 2.63 (dd, *J* = 13.6, 8.2 Hz, 1H), 2.59 (dd, *J* = 8.4, 5.6 Hz, 1H), 2.42-2.31 (m, 2H), 2.26-2.16 (m, 1H), 2.03-1.89 (m, 2H), 1.61 (s, 3H), 1.58 (dd, *J* = 16.6, 4.6 Hz, 1H), 0.82 (dt, *J* =

13.6, 4.5 Hz, 1H), 0.59 (dt, *J* = 13.6, 4.5 Hz, 1H), -0.01 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.5, 137.7, 134.0, 129.3 (2C), 128.8 (2C), 126.8, 125.9, 71.1, 65.0, 58.6, 42.6, 39.1, 36.5, 36.2, 33.7, 32.5, 31.3, 23.7, 15.3, -1.7 (3C) ppm; IR(ATR) λ 1677, 1248, 1117, 860, 834, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{24}H_{38}O_2NSi$ $[M + H]^+$ 400.2666, found 400.2662.

(3*S*,3a*R*,7*S*,7a*S*)-7-(2-(allyloxy)ethyl)-3-benzyl-2,3,3a,4,7,7a-hexahydro-2,5-dimethylisoindol-1-one (11d)

By following general procedure **IV**, compound **10f**, (632 mg, 2.40 mmol) and benzyl magnesium chloride were reacted to give compound **11d**, 325 mg (40%) as colorless oil. Hexanes: ethyl acetate 6:1 → 2:1 was used as eluent in the silica gel chromatography. The material was further purified with HPLC employing a 21x150 mm C18-column, a gradient of 20-90% MeCN + 0.1% TFA over 35 min, and a flow rate of 20 mL/min. $[\alpha]_D^{20}$ +43 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.35-7.29 (m, 2H), 7.28-7.22 (m, 1H), 7.19-7.14 (m, 2H), 5.95-5.84 (m, 1H), 5.40 (bs, 1H), 5.28-5.21 (m, 1H), 5.18-5.12 (m, 1H), 3.97-3.92 (m, 2H), 3.60-3.47 (m, 2H), 3.24-3.18 (m, 1H), 3.02 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.79 (s, 3H), 2.63 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.58 (dd, *J* = 8.9, 6.0 Hz, 1H), 2.45-2.33 (m, 2H), 2.21-2.11 (m, 1H), 1.98-1.83 (m, 2H), 1.61 (s, 3H), 1.53 (dd, *J* = 16.4, 4.2 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 175.4, 137.4, 135.2, 134.4, 129.4 (2C), 128.8 (2C), 126.9, 126.0, 116.8, 71.8, 68.8, 68.5, 42.7, 39.1, 36.3, 33.4, 32.6, 31.4, 28.3, 23.8 ppm; IR(ATR) λ 1679, 1398, 1087, 734, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{30}O_2N$ $[M + H]^+$ 340.2271, found 340.2279.

(3*S*/*R*,3a*R*/*S*,7*S*/*R*,7a*S*/*R*)-7-(2-(allyloxy)ethyl)-2,3,3a,4,7,7a-hexahydro-3-isobutyl-2,5-dimethylisoindol-1-one (11e)

By following general procedure **IV**, compound **10f**, (158 mg, 0.60 mmol) and *iso*-butyl magnesium bromide were reacted to give compound **11e**, 37 mg (20%) as colorless oil. Hexanes: ethyl acetate 6:1 → 3:1 was used as eluent in the silica gel chromatography. The material was further purified with HPLC employing a 10x150 mm C18-column, a gradient of 20-100% MeCN + 0.1% TFA over 35 min, and a flow rate of 6 mL/min. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 5.95-5.83 (m, 1H), 5.43 (bs, 1H), 5.28-5.20 (m, 1H), 5.16-5.11 (m, 1H), 3.97-3.93 (m, 2H), 3.64-3.49 (m, 2H), 2.95 (dt, *J* = 9.8, 3.4 Hz, 1H), 2.73 (dd, *J* = 8.7, 5.7 Hz, 1H), 2.71 (s, 3H), 2.43 (bs, 1H), 2.38-2.30 (m, 1H), 2.25-2.15 (m, 2H), 1.95-1.85 (m, 1H), 1.83 (dd, *J* = 16.3, 4.7 Hz, 1H), 1.77-1.66 (m, 1H), 1.68 (s, 3H), 1.47 (ddd, *J* = 13.2, 9.2, 3.7 Hz, 1H), 1.27 (ddd, *J* = 13.2, 9.5, 4.6 Hz, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.9, 135.3, 134.1, 126.1, 116.7, 71.8, 68.8, 65.5, 42.5, 42.0, 37.2, 33.8, 32.6, 31.4, 28.0, 25.1, 24.0, 23.9, 22.2 ppm; IR(ATR) λ 1682, 1428, 1399, 1093, 920 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{32}O_2N$ $[M + H]^+$ 306.2428, found 306.2434.

(3*S*/*R*,3a*R*/*S*,7*S*/*R*,7a*S*/*R*)-3-benzyl-2,3,3a,4,7,7a-hexahydro-7-(2-methoxyethyl)-5-methylisoindol-1-one (11f)

By following general procedure **IV**, compound **10d**, (371 mg, 1.10 mmol) and benzyl magnesium chloride were reacted to give compound **11f**, 150 mg (46%) as colorless solid. Hexanes: ethyl acetate 4:1 → 1:2 was used as eluent in the silica gel chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.32-7.27 (m, 2H), 7.25-7.19 (m, 1H), 7.17-7.13 (m, 2H), 6.05 (bs, 1H), 5.50-5.45 (m, 1H), 3.55-3.41 (m, 2H), 3.30 (s, 3H), 3.29-3.24 (m, 1H), 2.83 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.72-2.64 (m, 2H), 2.57-2.42 (m, 1H), 2.44-2.35 (m, 1H), 2.17-2.06 (m, 2H), 1.85-1.74 (m, 2H), 1.68 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 178.0, 137.7, 134.8, 129.1 (2C), 128.8 (2C), 126.8, 125.9, 71.1, 62.3, 58.5, 43.0, 42.7, 39.4, 32.5, 32.1, 31.3, 24.0 ppm; IR(ATR) λ 1688, 1436, 1117, 749, 694 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{26}O_2N$ $[M + H]^+$ 300.1958, found 300.1966.

(3*S*/*R*,3a*R*/*S*,7*S*/*R*,7a*S*/*R*)-7-(2-(allyloxy)ethyl)-3-benzyl-2,3,3a,4,7,7a-hexahydro-5-methylisoindol-1-one (11g)

By following general procedure **IV**, compound **10e**, (218 mg, 0.60 mmol) and benzyl magnesium chloride were reacted to give compound **11g**, 85 mg (44%) as colorless oil that solidified upon standing. Hexanes: ethyl acetate 3:1 → 1:1 was used as eluent in the silica gel chromatography. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.31-7.25 (m, 2H), 7.23-7.18 (m, 1H), 7.17-7.12 (m, 2H), 6.31 (bs, 1H), 5.94-5.81 (m, 1H), 5.49-5.44 (m, 1H), 5.27-5.19 (m, 1H), 5.15-5.09 (m, 1H), 3.96-3.90 (m, 2H), 3.59-3.45 (m, 2H), 3.31-3.24 (m, 1H), 2.80 (dd, *J* = 13.5, 5.6 Hz, 1H), 2.69 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.65 (dd, *J* = 9.3, 6.2 Hz, 1H), 2.55-2.46 (m, 1H), 2.41 (bs, 1H), 2.17-2.03 (m, 2H), 1.84-1.72 (m, 2H), 1.66 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 178.1, 137.6, 125.1, 124.6, 129.1 (2C), 128.7 (2C), 126.7, 125.8, 116.6, 71.7, 68.7, 62.3, 43.0, 42.5, 39.3, 32.4, 32.1, 31.4, 23.9 ppm; IR(ATR) λ 1685, 1434, 1087, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{28}O_2N$ $[M + H]^+$ 326.2115, found 326.2123.

(1*S*/*R*,3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-*tert*-butyl 1-benzyl-3a,4,7,7a-tetrahydro-4-(2-methoxyethyl)-6-methyl-3-oxo-1*H*-isoindole-2(3*H*)-carboxylate (11h)

Compound **11f**, (60 mg, 0.20 mmol), and 4-dimethylaminopyridine, (12 mg, 0.10 mmol), was dissolved in a small amount of DCM and then concentrated, leaving a residue that contained approximately 8 mg DCM. Di-*tert*-butyl dicarbonate, (87 mg, 0.40 mmol), was added and the mixture was stirred at room temperature 1h and then diluted with DCM, quenched with aqueous saturated NH_4Cl, extracted with DCM and concentrated under reduced pressure. The residue was purified with silica gel chromatography using hexanes: ethyl acetate 10:1→6:1 as eluent. 70 mg **11h** (87%) was obtained as colorless oil that solidified upon standing. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.34-7.29 (m, 2H), 7.27-7.19 (m, 3H), 5.30 (bs, 1H), 3.89 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.57-3.45 (m, 2H), 3.33 (s, 3H), 3.15 (dd, *J* = 13.3, 3.6 Hz, 1H), 2.80 (dd, *J* = 6.8, 5.9 Hz, 1H), 2.75 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.54-2.45 (m, 1H), 2.34-2.22 (m, 2H), 2.06-1.96 (m, 2H), 1.75-1.66 (m, 1H), 1.59-1.56 (m, 3H), 1.55 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.1, 150.6, 137.7, 132.6, 129.3 (2C), 128.8 (2C), 126.9, 124.7, 82.9, 70.7, 65.3, 58.7, 42.3, 37.9, 33.51, 33.49, 31.8, 31.4, 28.2 (3C), 23.4 ppm; IR(ATR) λ 1776, 1744, 1712, 1367, 1295, 1147 cm^{-1}; HRMS (ESI) Calcd. for $C_{24}H_{34}O_4N$ $[M + H]^+$ 400.2482, found 400.2487.

(1*S*/*R*,3a*S*/*R*,4*S*/*R*,7a*R*/*S*)-*tert*-butyl 4-(2-(allyloxy)ethyl)-1-benzyl-3a,4,7,7a-tetrahydro-6-methyl-3-oxo-1*H*-isoindole-2(3*H*)-carboxylate (11i)

Compound **11g**, (75 mg, 0.23 mmol), and 4-dimethylaminopyridine, (14 mg, 0.11 mmol), was dissolved in a small amount of DCM and then concentrated, leaving a residue that contained approximately 8 mg DCM. Di-*tert*-butyl dicarbonate, (101 mg, 0.46 mmol), was added and the mixture was stirred at room temperature 1h, and then concentrated from DCM. Another 30 mg di-*tert*-butyl dicarbonate, (0.14 mmol), was added and the mixture was stirred another 30 min and then diluted with DCM, quenched with aqueous saturated NH_4Cl, extracted with DCM and concentrated under reduced pressure. The residue was purified with silica gel chromatography using hexanes: ethyl acetate 10:1→8:1 as eluent. 75 mg **11i** (76%) was obtained as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.33-7.28 (m, 2H), 7.26-7.18 (m, 3H), 5.97-5.85 (m, 1H), 5.31-5.23 (m, 2H), 5.19-5.14 (m, 1H), 3.98-3.94 (m, 2H), 3.89 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.62-3.51 (m, 2H), 3.15 (dd, *J* = 13.4, 3.6 Hz, 1H), 2.82 (dd, *J* = 6.8, 5.8 Hz, 1H), 2.74 (dd, *J* = 13.4, 10.0 Hz, 1H), 2.58-2.48 (m, 1H), 2.34-2.24 (m, 2H), 2.06-1.96 (m, 2H), 1.70 (dd, *J* = 17.5, 7.4 Hz, 1H), 1.58-1.55 (m, 3H), 1.55 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.0, 150.6, 137.7, 135.1, 132.5, 129.2 (2C), 128.8 (2C), 126.8, 124.7, 116.7, 82.8, 65.2, 42.2, 37.8, 33.5, 33.4, 31.8, 31.4, 28.2 (3C), 23.4 ppm; IR(ATR) λ 1776, 1745, 1711, 1367, 1297, 1147 cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{36}O_4N$ $[M + H]^+$ 426.2639, found 426.2642.

(3*S*/*R*,3a*S*/*R*,7*S*/*R*,7a*R*/*S*)-3-benzyl-2,3,3a,4,7,7a-hexahydro-7a-hydroxy-7-(2-methoxyethyl)-2,5-dimethylisoindol-1-one (12a)

Compound **11a**, (63 mg, 0.20 mmol), was dissolved in 2.0 mL THF and cooled to -78 °C. Lithium diisopropylamide, (1.00 mL, 0.50 mmol, 0.5 M in THF, freshly prepared from 1.6M

BuLi (hex) and diisopropylamine), was added slowly and the solution was stirred for 20 minutes. Triethylphosphite, (0.14 mL, 0.82 mmol), was added and the reaction was moved to 0 °C. After a few minutes, dry O_2(g) was bubbled through the solution for 20 minutes and the reaction was then quenched by addition of saturated aqueous NH_4Cl, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. Silica gel chromatography using hexanes: ethyl acetate 4:1 → 1:2 afforded 27 mg (41%) of the more polar hydroxylated isomer **12a** as a colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.34-7.29 (m, 2H), 7.28-7.23 (m, 1H), 7.22-7.17 (m, 2H), 5.35-5.30 (m, 1H), 4.08 (s, 1H), 3.55-3.48 (m, 1H), 3.43-3.36 (m, 1H), 3.34 (s, 3H), 3.20 (dd, *J* = 13.0, 4.8 Hz, 1H), 3.11-3.05 (m, 1H), 2.83 (s, 3H), 2.59 (dd, *J* = 13.0, 9.2 Hz, 1H), 2.36-2.20 (m, 3H), 1.97 (dd, *J* = 16.1, 6.9 Hz, 1H), 1.59 (s, 3H), 1.51-1.42 (m, 1H), 1.29 (dd, *J* = 16.1, 3.2 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 175.0, 137.1, 136.1, 129.4 (2C), 128.9 (2C), 127.0, 124.5, 78.7, 72.0, 65.3, 58.6, 46.3, 43.1, 40.8, 31.5, 29.8, 28.3, 23.6 ppm; IR(ATR) λ 3389, 1667, 1055, 741, 699 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{28}O_3N$ $[M + H]^+$ 330.2064, found 330.2067.

(1*S*/*R*,3a*R*/*S*,4*S*/*R*,7a*S*/*R*)-*tert*-butyl 1-benzyl-3a,4,7,7a-tetrahydro-3a-hydroxy-4-(2-methoxyethyl)-6-methyl-3-oxo-1*H*-isoindole-2(3*H*)-carboxylate (12b)

Compound **11h**, (72 mg, 0.18 mmol), was dissolved in 3.6 mL THF and cooled to -78 °C. Lithium diisopropylamide, (0.72 mL, 0.36 mmol, 0.5 M in THF, freshly prepared from 1.6M BuLi (hex) and diisopropylamine), was added slowly and the solution was stirred 15 min and then cooled in an etanol/N_2(l) bath until the solution started to freeze. 2-(Phenylsulfonyl)-3-phenyl-oxaziridine,[S9] (99 mg, 0.38 mmol), in 1.8 mL THF was added rapidly and the mixture was moved back to -78 °C and stirred 45 min. The reactions was quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate and then concentrated under reduced pressure. The residue was passed through a silica plug using hexanes: ethyl acetate 6:1 → 3:1 as eluent and then further purified with preparative TLC using hexanes: ethyl acetate 2:1 as eluent. Compound **12b**, 34 mg (45%), was obtained as a colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.35-7.29 (m, 2H), 7.28-7.21 (m, 3H), 5.19 (bs, 1H), 5.13 (bs, 1H), 3.69 (dt, *J* = 10.3, 3.4 Hz, 1H), 3.66-3.58 (m, 1H), 3.48 (dt, *J* = 3.3, 9.8 Hz, 1H), 3.40 (s, 3H), 3.36 (dd, *J* = 12.8, 3.4 Hz, 1H), 2.95 (dd, *J* = 12.8, 10.3 Hz, 1H), 2.77-2.65 (m, 1H), 2.37-2.29 (m, 1H), 2.27-2.21 (m, 1H), 2.21-2.12 (m, 1H), 1.63-1.58 (m, 4H), 1.57 (s, 9H), 1.48 (dd, *J* = 16.3, 3.8 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.8, 150.3, 137.9, 135.4, 129.8 (2C), 128.8 (2C), 126.7, 124.8, 83.2, 78.6, 72.5, 65.1, 58.6, 43.8, 41.9, 40.9, 34.5, 29.7, 28.3 (3C), 23.2 ppm; IR(ATR) λ 1781, 1750, 1714, 1368, 1297, 1150, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{24}H_{34}O_5N$ $[M + H]^+$ 416.2432, found 416.2435.

(1*S*/*R*,3a*R*/*S*,4*S*/*R*,7a*S*/*R*)-*tert*-butyl 4-(2-(allyloxy)ethyl)-1-benzyl-3a,4,7,7a-tetrahydro-3a-hydroxy-6-methyl-3-oxo-1*H*-isoindole-2(3*H*)-carboxylate (12c)

Compound **11i**, (68 mg, 0.16 mmol), was dissolved in 3.2 mL THF and cooled to -78 °C. Lithium diisopropylamide, (0.56 mL, 0.28 mmol, 0.5 M in THF, freshly prepared from 1.6M BuLi (hex) and diisopropylamine), was added slowly and the solution was stirred 15 min and then cooled in an etanol/N_2(l) bath until the solution started to freeze. 2-(Phenylsulfonyl)-3-phenyl-oxaziridine,[S9] (84 mg, 0.32 mmol), in 1.6 mL THF was added rapidly and the mixture was moved back to -78 °C and stirred 45 min. The reactions was quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate and then concentrated under reduced pressure. The residue was passed through a silica plug using hexanes: ethyl acetate 8:1 → 5:1 as eluent and then further purified with preparative TLC using hexanes: ethyl acetate 4:1 as eluent. Compound **12c**, 31 mg (44%), was obtained as a colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.35-7.29 (m, 2H), 7.28-7.22 (m, 3H), 5.96-5.85 (m, 1H), 5.33-5.25 (m, 1H), 5.23-5.17 (m, 2H), 4.89 (bs, 1H), 4.10 (ddt, *J* = 12.8, 5.5, 1.4 Hz, 1H), 3.99 (ddt, *J* = 12.8, 5.8, 1.4 Hz, 1H), 3.72-3.64 (m, 2H), 3.51 (dt, *J* = 3.8, 9.8 Hz, 1H), 3.37 (dd, *J* = 12.8, 3.5 Hz, 1H), 2.92 (dd, *J* = 12.8, 10.3 Hz, 1H), 2.70-2.58 (m, 1H), 2.38-2.30 (m, 1H), 2.28-2.22 (m, 1H), 2.14 (dd, *J* = 16.5, 7.8 Hz, 1H), 1.63-1.59 (m, 4H), 1.57 (s, 9H), 1.47 (dd, *J* = 16.5, 3.9 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.8, 150.2, 137.8, 135.4, 134.3, 129.8 (2C), 128.8 (2C), 126.8, 124.7, 117.6, 83.3, 78.7, 71.8, 69.7, 64.8, 43.7, 42.1, 40.9, 34.2, 29.8,

28.3 (3C), 23.3 ppm; IR(ATR) λ 1778, 1716, 1296, 1149, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{36}O_5N$ $[M + H]^+$ 442.2588, found 442.2591.

(3S,3aS,7S,7aR)-7-(2-(allyloxy)ethyl)-3-benzyl-2,3,3a,4,7,7a-hexahydro-7a-hydroxy-2,5-dimethylisoindol-1-one (12d)

Compound **11d**, (44 mg, 0.13 mmol), was dissolved in 1.3 mL THF and cooled to -78 °C. Lithium diisopropylamide, (0.65 mL, 0.33 mmol, 0.5 M in THF, freshly prepared from 1.6M BuLi (hex) and diisopropylamine), was added slowly and the solution was stirred for 20 minutes. Triethylphosphite, (0.09 mL, 0.52 mmol), was added and the reaction was moved to 0 deg C. After a few minutes, dry O_2(g) was bubbled through the solution for 20 minutes and the reaction was then quenched by addition of saturated aqueous NH_4Cl, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. Silica gel chromatography using hexanes: ethyl acetate 4:1 → 1:2 as eluent, followed by preparative TLC using hexanes: ethyl acetate 1:4 as eluent afforded 12.5 mg (27%) of the more polar hydroxylated isomer **12d** as a colorless solid. $[\alpha]_D^{20}$ +121 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.35-7.29 (m, 2H), 7.28-7.23 (m, 1H), 7.22-7.18 (m, 2H), 5.95-5.83 (m, 1H), 5.37-5.32 (m, 1H), 5.29-5.22 (m, 1H), 5.18-5.13 (m, 1H), 4.06-3.91 (m, 3H), 3.62-3.55 (m, 1H), 3.48-3.40 (m, 1H), 3.21 (dd, *J* = 13.0, 4.7 Hz, 1H), 3.13-3.06 (m, 1H), 2.84 (s, 3H), 2.59 (dd, *J* = 13.0, 9.1 Hz, 1H), 2.33-2.22 (m, 3H), 1.96 (dd, *J* = 16.1, 6.8 Hz, 1H), 1.59 (s, 3H), 1.53-1.45 (m, 1H), 1.28 (dd, *J* = 16.1, 3.3 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 174.9, 137.1, 136.0, 134.7, 129.4 (2C), 128.9 (2C), 127.0, 124.5, 117.2, 78.7, 71.9, 69.5, 65.1, 46.4, 43.1, 40.8, 31.4, 29.9, 28.3, 23.7 ppm; IR(ATR) λ 3367, 1672, 1057, 737, 700 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{30}O_3N$ $[M + H]^+$ 356.2220, found 356.2227.

(2*E*)-(1*S*/*R*,3a*R*/*S*,4*S*/*R*,7a*S*/*R*)-1-benzyl-2,3,3a,4,7,7a-hexahydro-4-(2-methoxyethyl)-2,6-dimethyl-3-oxo-1*H*-isoindol-3a-yl 4-hydroxybut-2-enoate (13a)

(*E*)-4-(*tert*-butyldimethylsilyloxy)-but-2-enoic acid,[S10] (38 mg, 0.18 mmol), was dissolved in THF and cooled to 0 °C. Ghosez's reagent, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, (23 µL, 0.17 mmol), was added and the mixture was stirred 2.5h at 0 °C to generate the corresponding acid chloride. In a separate flask compound **12a**, (16.5 mg, 0.050 mmol), was dissolved in 1 mL THF and 60% sodium hydride in mineral oil, (16 mg, 0.40 mmol), was added. The mixture was stirred at room temperature 20 min and then the previously prepared acid chloride solution was added using a syringe and the reaction was stirred another 75 min. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The resulting residue was dissolved in 1 mL methanol and (+)-10-camphorsulfonic acid, (17.5 mg, 0.075 mmol), was added. The reaction was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was dissolved in DCM, washed with saturated aqueous $NaHCO_3$, and extracted with DCM. The combined organic extracts were concentrated under reduced pressure and purified with silica gel chromatography using hexanes: ethyl acetate 2:1 → 1:6. Compound **13a**, 6.3 mg (30 %), was obtained as a colorless film. Compound **12a**, 8.5 mg (52 %) was also reisolated. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.35-7.29 (m, 2H), 7.28-7.23 (m, 1H), 7.22-7.17 (m, 2H), 7.05 (dt, *J* = 15.7, 3.9 Hz, 1H), 6.12 (dt, *J* = 15.7, 2.1 Hz, 1H), 5.38-5.32 (m, 1H), 4.34 (dd, *J* = 3.9, 2.1 Hz, 2H), 3.48-3.40 (m, 2H), 3.30 (s, 3H), 3.26 (dd, *J* = 12.7, 4.5 Hz, 1H), 3.09-3.02 (m, 1H), 2.87 (s, 3H), 2.81 (dd, *J* = 12.7, 10.1 Hz, 1H), 2.71-2.65 (m, 1H), 2.55-2.47 (m, 1H), 2.25-2.15 (m, 1H), 1.90-1.75 (m, 2H), 1.61 (s, 3H), 1.60-1.50 (m, 1H), 1.16 (dd, *J* = 15.5, 3.5 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 170.3, 165.7, 148.0, 137.5, 129.5 (2C), 128.9 (2C), 126.9, 123.4, 120.4, 85.7, 71.3, 65.1, 62.0, 58.5, 43.4, 39.4, 39.3, 31.8, 28.9, 28.4, 23.9 ppm; IR(ATR) λ 3401, 1686, 1262, 1169, 1105, 1029,737, 702 cm^{-1}; HRMS (ESI) Calcd. for $C_{24}H_{32}O_5N$ $[M + H]^+$ 414.2275, found 414.2274.

(2*E*)-(1*S*/*R*,3a*R*/*S*,4*S*/*R*,7a*S*/*R*)-1-benzyl-2,3,3a,4,7,7a-hexahydro-4-(2-methoxyethyl)-6-methyl-3-oxo-1*H*-isoindol-3a-yl 4-hydroxybut-2-enoate (13b)

(*E*)-4-(*tert*-butyldimethylsilyloxy)-but-2-enoic acid,[S10] (43 mg, 0.20 mmol), was dissolved in 1 mL THF and cooled to 0 °C. Ghosez's reagent, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, (27 µL, 0.20 mmol), was added and the mixture was stirred 2.5h at 0 °C to generate the corresponding acid chloride. In a separate flask compound **12b**, (21 mg, 0.051 mmol), was dissolved in 1.0 mL THF and sodium hydride, (60% in mineral oil, 12 mg, 0.30 mmol), was added and the mixture was stirred at room temperature for 20 min. Then the acid chloride solution was transferred to the second flask and the mixture was stirred at room temperature for 70 min and then quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. The residue was passed through a silica plug using hexanes: ethyl acetate: methanol 12:1:0 → 0:100:2 which afforded a mixture of TBS-protected and TBS-deprotected product. This material was then dissolved in 1.0 mL MeOH and 1*S*-camphor-10-sulfonic acid, (5 mg, 0.02 mmol) was added. The reaction was stirred at room temperature 1h, and then concentrated under reduced pressure. The residue was dissolved in 0.54 mL DCM and 0.06 mL TFA was added. The reaction was stirred another hour at room temperature and concentrated under reduced pressure. The crude product was purified with silica gel chromatography using hexanes: ethyl acetate: methanol 1:1:0 → 10:40:1, which gave 7.0 mg (35%) of **13b** as a colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.35-7.29 (m, 2H), 7.27-7.18 (m, 3H), 7.11-7.04 (m, 1H), 6.18-6.11 (m, 1H), 5.63 (bs, 1H), 5.47-5.40 (m, 1H), 4.36 (dd, *J* = 3.9, 2.2 Hz, 2H), 3.51-3.44 (m, 2H), 3.31 (s, 3H), 3.10 (dt, *J* = 5.7, 7.1 Hz, 1H), 2.96 (d, *J* = 7.1 Hz, 2H), 2.91-2.86 (m, 1H), 2.61-2.53 (m, 1H), 2.29-2.20 (m, 2H), 1.80-1.68 (m, 5H), 1.61-1.51 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 172.4, 165.7, 148.1, 137.7, 136.9, 129.2 (2C), 129.1 (2C), 127.1, 123.4, 120.3, 85.4, 71.1, 62.0, 59.2, 58.5, 45.8, 42.1, 39.0, 31.4, 29.1, 24.2 ppm; IR(ATR) λ 3279, 1708, 1263, 1168, 1107, 1032 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{30}O_5N$ $[M + H]^+$ 400.2119, found 400.2113.

(2E)-(1*S*/*R*,3a*R*/*S*,4*S*/*R*,7a*S*/*R*)-1-benzyl-2,3,3a,4,7,7a-hexahydro-4-(2-methoxyethyl)-6-methyl-3-oxo-1*H*-isoindol-3a-yl but-2-enoate (13c)

Compound **12b**, (10.5 mg, 0.025 mmol), was dissolved in 0.5 mL THF and cooled to 0 °C. 60 % Sodium hydride in mineral oil (5 mg, 0.13 mmol) was added and the mixture was stirred 30 min. Trans-crotonyl chloride, (5 µL, 0.05 mmol), was added and after 1h at 0 °C, more 60 % sodium hydride (6 mg, 0.15 mmol) was added and the mixture was stirred at room temperature for 10 min. Trans-crotonyl chloride, (7 µL, 0.08 mmol), was added and the reaction was stirred 25 min at room temperature and then quenched with saturated aqueous NH_4Cl. The intermediate Boc-protected product was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, and then again extracted with ethyl acteate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was passed through a silica plug using hexanes: ethyl acetate 12:1 → 8:1 to afford 7 mg of the intermediate product. This material was dissolved in 0.27 mL DCM and cooled to 0 °C. 0.03 mL TFA was added and the reaction was then stirred at room temperature for 1h. The mixture was diluted with toluene and concentrated under reduced pressure to remove the TFA and the residue was purified with silica gel chromatography using hexanes: ethyl acetate 3:1 → 1:2. Compound **13c**, 5.0 mg (52 %), was obtained as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.35-7.28 (m, 2H), 7.26-7.18 (m, 3H), 7.07-6.96 (m, 1H), 5.92-5.84 (m, 1H), 5.59 (bs, 1H), 5.46-5.40 (m, 1H), 3.51-3.45 (m, 2H), 3.31 (s, 3H), 3.08 (dt, *J* = 5.7, 7.2 Hz, 1H), 2.96 (d, *J* = 7.2 Hz, 2H), 2.91-2.86 (m, 1H), 2.60-2.52 (m, 1H), 2.30-2.19 (m, 2H), 1.89 (d, 3H), 1.79-1.72 (m, 4H), 1.62-1.51 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 172.5, 165.8, 145.7, 137.8, 136.9, 129.2 (2C), 129.0 (2C), 127.0, 123.4, 123.0, 85.1, 71.2, 59.2, 58.5, 45.8, 42.1, 39.0, 31.4, 29.1, 24.2, 18.2 ppm; IR(ATR) λ 1710, 1179, 1114, 1101, 1034, 802, 743 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{30}O_4N$ $[M + H]^+$ 384.2169, found 384.2179.

(1*S*/*R*,3a*R*/*S*,4*S*/*R*,7a*S*/*R*)-*tert*-butyl 3a-((*E*)-hepta-2,6-dienoyloxy)-4-(2-(allyloxy)ethyl)-1-benzyl-3a,4,7,7a-tetrahydro-6-methyl-3-oxo-1*H*-isoindole-2(3*H*)-carboxylate (13d)

(*E*)-hepta-2,6-dienoic acid, (35 mg, 0.28 mmol), was dissolved in 1.6 mL THF and cooled to 0 °C. Ghosez's reagent, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, (37 µL, 0.28 mmol), was added and the mixture was stirred 2.5 h at 0 °C to generate the corresponding acid chloride. In a separate flask compound **12c**, (35 mg, 0.079 mmol), was dissolved in 1.6 mL THF and sodium hydride, (60% in mineral oil, 19 mg, 0.48 mmol), was added. The mixture was stirred at room temperature 20 min and then the previously prepared acid chloride solution was added using a syringe and the reaction was stirred another 75 min. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified with silica gel chromatography using hexanes: ethyl acetate 15:1 → 10:1 as eluent and then preparative TLC using hexanes: ethyl acetate 6:1 as eluent. Compound **13d**, 5.5 mg (13%), was obtained as a colorless film. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.34-7.28 (m, 2H), 7.26-7.20 (m, 3H), 7.02 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.95-5.75 (m, 3H), 5.37-5.32 (m, 1H), 5.28-5.21 (m, 1H), 5.17-5.11 (m, 1H), 5.10-5.00 (m, 2H), 4.00-3.89 (m, 2H), 3.57-3.46 (m, 4H), 2.95-2.85 (m, 1H), 2.60-2.47 (m, 2H), 2.37-2.16 (m, 5H), 1.86 (dd, *J* = 15.2, 5.4 Hz, 1H), 1.63 (s, 3H), 1.59-1.54 (m, 10H), 1.12 (dd, *J* = 15.2, 3.3 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 170.0, 165.7, 150.1, 149.8, 137.8 (2C), 137.1, 135.2, 129.6 (2C), 128.8 (2C), 126.8, 123.1, 121.4, 116.6, 115.8, 85.3, 83.2, 71.6, 68.8, 62.9, 41.4, 40.1, 39.7, 32.8, 32.1, 31.7, 28.8, 28.3 (3C), 23.9 ppm; IR(ATR) λ 1791, 1760, 1716, 1369, 1350, 1256, 1155 cm^{-1}; HRMS (ESI) Calcd. for $C_{33}H_{44}O_6N$ $[M + H]^+$ 550.3163, found 550.3170.

(2*E*)-(1*S*,3a*R*,4*S*,7a*S*)-4-(2-(allyloxy)ethyl)-1-benzyl-2,3,3a,4,7,7a-hexahydro-2,6-dimethyl-3-oxo-1*H*-isoindol-3a-yl hepta-2,6-dienoate (13e)

(*E*)-hepta-2,6-dienoic acid, (22 mg, 0.17 mmol), was dissolved in 1.0 mL THF and cooled to 0 °C. Ghosez's reagent, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, (24 µL, 0.18 mmol), was added and the mixture was stirred 2.5 h at 0 °C to generate the corresponding acid chloride. In a separate flask compound **12d**, (18 mg, 0.051 mmol), was dissolved in 1.0 mL THF and sodium hydride, (60% in mineral oil, 7 mg, 0.18 mmol), was added. The mixture was stirred at room temperature 20 min and then the previously prepared acid chloride solution was added using a syringe and the reaction was stirred another 70 min. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, and concentrated under reduced pressure. The residue was passed through a silica plug using hexanes: ethyl acetate 10:1 → 1:1 as eluent and then purified with reversed phase HPLC using a 10x150 mm C18-column, a gradient of 20-100% MeCN + 0.1% TFA over 40 min, and a flow rate of 6 mL/ min. Compound **13e**, 3.2 mg (14%), was obtained as a colorless film. $[\alpha]_D^{20}$ +210 (*c* 0.25, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 7.35-7.29 (m, 2H), 7.28-7.18 (m, 3H), 6.98 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.95-5.75 (m, 3H), 5.39-5.33 (m, 1H), 5.29-5.21 (m, 1H), 5.17-5.11 (m, 1H), 5.10-4.98 (m, 2H), 4.00-3.88 (m, 2H), 3.56-3.45 (m, 2H), 3.26 (dd, *J* = 12.7, 4.5 Hz, 1H), 3.09-3.01 (m, 1H), 2.87 (s, 3H), 2.81 (dd, *J* = 12.7, 10.1 Hz, 1H), 2.68 (td, *J* = 5.6, 3.5 Hz, 1H), 2.56-2.48 (m, 1H), 2.36-2.27 (m, 2H), 2.27-2.17 (m, 3H), 1.86 (dd, *J* = 15.4, 5.6 Hz, 1H), 1.61 (s, 3H), 1.60-1.53 (m, 1H), 1.16 (dd, *J* = 15.4, 3.5 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 170.3, 165.9, 149.3, 137.6, 137.2, 137.0, 135.3, 129.5 (2C), 128.8 (2C), 126.9, 123.6, 121.9, 116.6, 115.7, 85.6, 71.6, 69.0, 65.1, 43.4, 39.5, 39.3, 32.1, 31.9, 31.7, 29.2, 28.4, 23.9 ppm; IR(ATR) λ 1701, 1263, 1173, 1082, 1031, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{38}O_4N$ $[M + H]^+$ 464.2795, found 464.2801.

(1*R*/*S*, 4*E*, 8*E*, 14*S*/*R*, 18*S*/*R*)-19-benzyl-16-methyl-20-aza-2,11-dioxa-tricyclo[12.7.0.0^{1,18}]henicos-4,8,15-trien-3,21-dione (14a)

Compound **13d**, (2.1 mg, 3.8 µmol), was dissolved in a 0.3 mM solution of Grubbs 1st generation catalyst in DCM, (0.76 mL, 0.23 µmol), and stirred in a sealed tube at 35 °C for 22 h. The solution was concentrated under reduced pressure and the residue was then dissolved in a 0.2 mM solution of Grubbs 1st generation catalyst in DCM, (0.76 mL, 0.15 µmol), and stirred in a sealed tube at room temperature for 24 h. TFA, (42 µL, 0.55 mmol),

was added and the reaction was stirred at room temperature 1 h and then concentrated under reduced pressure. Preparative TLC using hexanes: ethyl acetate 1:1 afforded 0.9 mg (56%) of **14a** as a colorless film. ^{1}H-NMR (600 MHz, $CDCl_3$): *δ*= 7.34-7.30 (m, 2H), 7.26-7.23 (m, 1H), 7.20-7.17 (m, 2H), 6.99 (ddd, *J* = 15.9, 8.1, 7.1 Hz, 1H), 5.74 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.68-5.62 (m, 1H), 5.59 (bs, 1H), 5.53 (ddd, *J* = 15.3, 8.2, 6.0 Hz, 1H), 5.24-5.21 (m, 1H), 4.06-3.99 (m, 2H), 3.70 (td, *J* = 9.0, 5.9 Hz, 1H), 3.44 (ddd, *J* = 9.0, 8.5, 5.7 Hz, 1H), 2.99-2.91 (m, 3H), 2.84 (td, *J* = 4.4, 2.4 Hz, 1H), 2.59-2.54 (m, 1H), 2.43-2.29 (m, 5H), 2.26-2.18 (m, 1H), 1.76-1.74 (m, 3H), 1.74-1.69 (m, 2H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$): *δ*= 171.7, 165.2, 150.1, 138.2, 137.8, 133.5, 131.2, 129.1 (2C), 129.0 (2C), 127.0, 125.2, 122.4, 86.3, 72.0, 69.0, 58.6, 47.4, 42.3, 39.5, 32.1, 31.9, 31.8, 29.9, 24.2 ppm; IR(ATR) λ 1713, 1456, 1259, 1087 cm^{-1}; HRMS (ESI) Calcd. for $C_{26}H_{32}O_4N$ $[M + H]^+$ 422.2326, found 422.2323.

(1*R*, 4*E*, 8*E*, 14*S*, 18*S*)-19-benzyl-16,20-dimethyl-20-aza-2,11-dioxa-tricyclo[12.7.0.0^{1,18}]henicos-4,8,15-trien-3,21-dione (14b)

Compound **13e**, (2.2 mg, 4.7 µmol), was dissolved in a 0.3 mM solution of Grubbs 1st generation catalyst in DCM, (0.95 mL, 0.29 µmol), and stirred in a sealed tube at 35 °C for 22 h. The solution was concentrated under reduced pressure and the residue was then dissolved in a 0.2 mM solution of Grubbs 1st generation catalyst in DCM, (0.95 mL, 0.19 µmol), and stirred in a sealed tube at room temperature for 24 h and then concentrated under reduced pressure. Preparative TLC using hexanes: ethyl acetate 1:1 afforded 1.1 mg (53%) of **14b** as a colorless film. $[\alpha]_D^{20}$ +108 (*c* 0.12, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): *δ*= 7.34-7.29 (m, 2H), 7.26-7.23 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 2H), 6.94 (dt, *J* = 15.9, 7.6 Hz, 1H), 5.73-5.69 (m, 1H), 5.63 (ddd, *J* = 15.2, 7.9, 6.0 Hz, 1H), 5.51 (ddd, *J* = 15.2, 7.9, 6.2 Hz, 1H), 5.16-5.12 (m, 1H), 4.06 (dd, *J* = 12.1, 6.0 Hz, 1H), 3.99 (dd, *J* = 12.1, 7.9 Hz, 1H), 3.76 (td, *J* = 9.1, 5.8 Hz, 1H), 3.38 (td, *J* = 9.1, 5.3 Hz, 1H), 3.23 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.93 (dt, *J* = 10.1, 4.5 Hz, 1H), 2.85 (s, 3H), 2.77 (dd, *J* = 12.6, 10.1 Hz, 1H), 2.71-2.67 (m, 1H), 2.51-2.45 (m, 1H), 2.43-2.32 (m, 4H), 2.24-2.17 (m, 1H), 2.05 (bd, *J* = 14.7 Hz, 1H), 1.73-1.67 (m, 1H), 1.62 (s, 3H), 1.09-1.04 (m, 1H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$): *δ*= 169.5, 165.3, 149.8, 138.0, 137.5, 133.5, 131.2, 129.5 (2C), 128.8 (2C), 126.9, 125.1, 122.7, 86.6, 72.0, 69.1, 64.3, 44.7, 39.7, 39.3, 32.1, 31.94, 31.90, 30.1, 28.4, 23.9 ppm; IR(ATR) λ 1699, 1256, 1030, 735, 702 cm^{-1}; HRMS (ESI) Calcd. for $C_{27}H_{34}O_4N$ $[M + H]^+$ 436.2482, found 436.2486.

General procedure V

The maleimide to be reacted, (1.0 equiv.), benzoic acid, (24 mg / mmol maleimide, 0.20 equiv.), and catalyst **C8**, (122 mg / mmol maleimide, 0.20 equiv.), were dissolved in chloroform, (10 mL / mmol maleimide). Dienal **2d**, (165 mg / mmol maleimide, 1.5 equiv.), was added and the reaction was stirred at room temperature for 21 h and then concentrated under reduced pressure. The residue was dissolved in methanol, (10 mL / mmol maleimide), and saturated aqueous $NaHCO_3$, (0.2 mL / mmol maleimide), was added and the mixture was cooled to 0 °C. Sodium borohydride, (57 mg / mmol maleimide, 1.5 equiv.), was added and the reaction was moved to room temperature and stirred for 30 min. The reaction was quenched with ice and 1 M HCl(aq.) and then diluted with brine and extracted with DCM. The organic extract was concentrated under reduced pressure and the residue was purified with silica gel chromatography.

(3a*S*,4*S*,7a*R*)-3a,4,7,7a-tetrahydro-4-(2-hydroxyethyl)-6-methyl-2-(2-(trimethylsilyl)ethyl)-2*H*-isoindole-1,3-dione (15a)

Maleimide **1g**, (197 mg, 1.00 mmol), was converted to 253 mg (82%) **15a** by following the general procedure **V**. Hexanes: ethyl acetate 6:1→1:1 was used as eluent in the chromatography and the product was obtained as a slightly yellowish oil. $[\alpha]_D^{20}$ +13 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 5.31 (bs, 1H), 3.94-3.85 (m, 1H), 3.80-3.72 (m, 1H), 3.44-3.37 (m, 2H), 3.17 (dd, *J* = 8.6, 6.5 Hz, 1H), 3.05 (ddd, *J* = 8.6, 6.8, 1.9 Hz, 1H), 2.54 (bd, *J* = 15.0 Hz, 1H), 2.34 (bs, 2H), 2.22-2.10 (m, 2H), 1.98-1.87 (m, 1H), 1.69 (s, 3H), 0.80-

0.72 (m, 2H), 0.01 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 179.6, 178.8, 136.8, 125.9, 61.6, 42.8, 40.7, 35.4, 34.1, 34.0, 29.5, 23.2, 16.4, -1.7 (3C) ppm; IR(ATR) λ 3439, 1686, 1402, 1349, 1249, 1150, 860, 836 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{28}O_3NSi$ $[M + H]^+$ 310.1833, found 310.1841.

(3a*S*,4*S*,7a*R*)-3a,4,7,7a-tetrahydro-4-(2-hydroxyethyl)-2,6-dimethyl-2*H*-isoindole-1,3-dione (15b)

N-Methyl maleimide, (389 mg, 3.50 mmol), was converted to 681 mg (87%) **15b** by following the general procedure **V**. Hexanes: ethyl acetate 4:1→1:2 was used as eluent in the chromatography and the product was obtained as a yellowish oil. $[\alpha]_D^{20}$ +24 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ*= 5.29 (s, 1H), 3.89-3.82 (m, 1H), 3.77-3.69 (m, 1H), 3.18 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.11-3.05 (m, 1H), 3.87 (s, 3H), 2.55-2.36 (m, 3H), 2.19-2.06 (m, 2H), 1.94-1.83 (m, 1H), 1.67 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*= 180.0, 179.0, 136.8, 125.8, 61.4, 42.8, 40.8, 34.1, 33.7, 29.4, 24.8, 23.1 ppm; IR(ATR) λ 3445, 1682, 1435, 1383, 1284, 1055, 1004 cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{18}O_3N$ $[M + H]^+$ 224.1281, found 224.1282.

(3a*S*,4*S*,7a*R*)-3a,4,7,7a-tetrahydro-4-(2-methoxyethyl)-6-methyl-2-(2-(trimethylsilyl)ethyl)-2*H*-isoindole-1,3-dione ((+)-10c)

Compound **15a**, (217 mg, 0.701 mmol), was dissolved in 2.8 mL DCM and cooled to 0 °C. 50% aqueous HBF_4, (0.09 mL, 0.71 mmol), was added and to the stirring mixture was 2 M TMS-diazomethane in Et_2O, (0.35 mL, 0.70 mmol), added slowly over 5 min. After 30 min another 0.35 mL TMS-diazomethane solution was added over 5 min and after another 30 min 0.18 mL TMS-diazomethane solution was added over 5 min. After 30 min the reaction was quenched with 1 M HCl(aq.), extracted with DCM, dried over anhydrous $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was dissolved in 2.8 mL DCM and cooled to 0 °C. 50% aqueous HBF_4, (44 μL, 0.35 mmol), was added and to the stirring mixture was 2 M TMS-diazomethane in Et_2O, (0.18 mL, 0.36 mmol), added slowly over 5 min. After 30 min, another 0.17 mL TMS-diazomethane solution was added slowly over 5 min. After 30 min the reaction was quenched with 1 M HCl(aq.), extracted with DCM, and concentrated under reduced pressure. Silica gel chromatography using hexanes: ethyl aceate 10:1 → 6:1 as eluent gave 168 mg (74%) **(+)-10c** as colorless oil. $[\alpha]_D^{20}$ +7 (*c* 1.0, $CHCl_3$); NMR-data was identical to the racemic material.

(3a*S*,4*S*,7a*R*)-4-(2-(allyloxy)ethyl)-3a,4,7,7a-tetrahydro-2,6-dimethyl-2*H*-isoindole-1,3-dione ((+)-10f)

Compound **15b**, (223 mg, 1.00 mmol), and allyl-*tert*-butyl carbonate,[S11] (238 mg, 1.50 mmol), triphenylphosphine, (11 mg, 0.04 mmol), were dissolved in 3.0 mL THF and degassed by evacuation and refilled with argon three times. Palladium-tetrakis(triphenylphosphine), (11.5 mg, 0.010 mmol), was added and the mixture was evacuated and refilled with argon once more. The reaction was vigorously refluxed for 2.5 h, and then concentrated under reduced pressure. Silica gel chromatography using hexanes: ethyl acetate 8:1 → 5:1 as eluent gave 207 mg (79%) **(+)-10f** as a slightly yellow oil. $[\alpha]_D^{20}$ +12 (*c* 0.5, $CHCl_3$); NMR-data was identical to the racemic material.

Biological evaluation

Cell lines

Human colon carcinoma HCT116 (obtained from DSMZ, DMSZ-no. ACC-581) and human cervix carcinoma HeLa (obtained from ATCC, ATCC-no. CCL-2) cell lines were cultured in Dulbecco's Modified Eagle's medium (DMEM, high glucose) supplemented with 10% fetal bovine serum, L-glutamine, penicillin and streptomycin. Cell lines were maintained at 37°C in a 5% CO_2 humidified atmosphere.

2-Deoxy-D-glucose (2DG) uptake assay

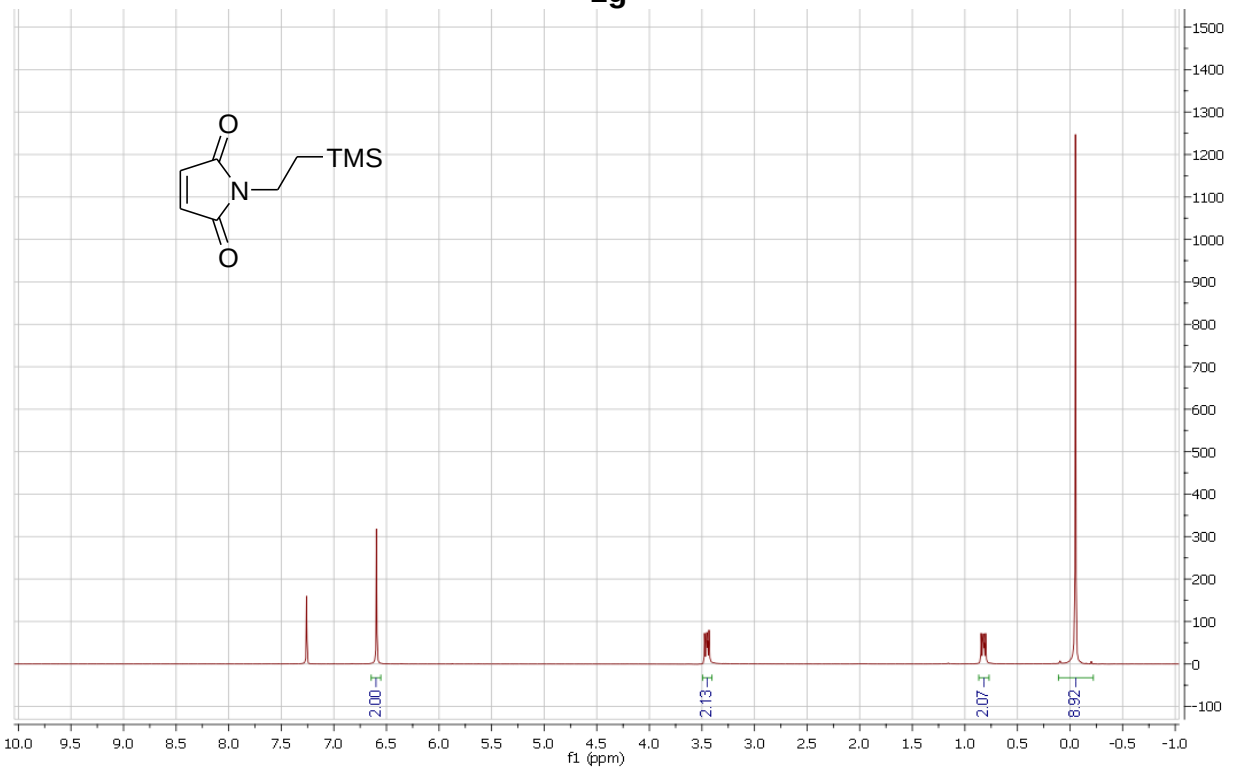
40000 HCT116 cells/well were seeded in 96-well microtiter plates and incubated overnight. 2DG uptake in presence of compounds was determined as previously reported[S12] with minor modifications. Briefly, cells were incubated with compounds or DMSO and 1mM 2DG in glucose-free KRB buffer (20mM HEPES, 5mM KH_2PO_4, 1mM $MgSO_4$, 1mM $CaCl_2$, 136mM NaCl, 0.1% BSA, pH 7.4) buffer for 30 min. Cells were then washed and lysed. The amount of 2DG in the lysate was determined based on resorufin fluorescence as described by Yamamoto et al.[12] Fluorescence intensity was measured at ex/em 535/590 nm with a Tecan Infinite 200 plate reader (Tecan, Switzerland. Blank values were subtracted from all readings and values were normalized to the DMSO control.

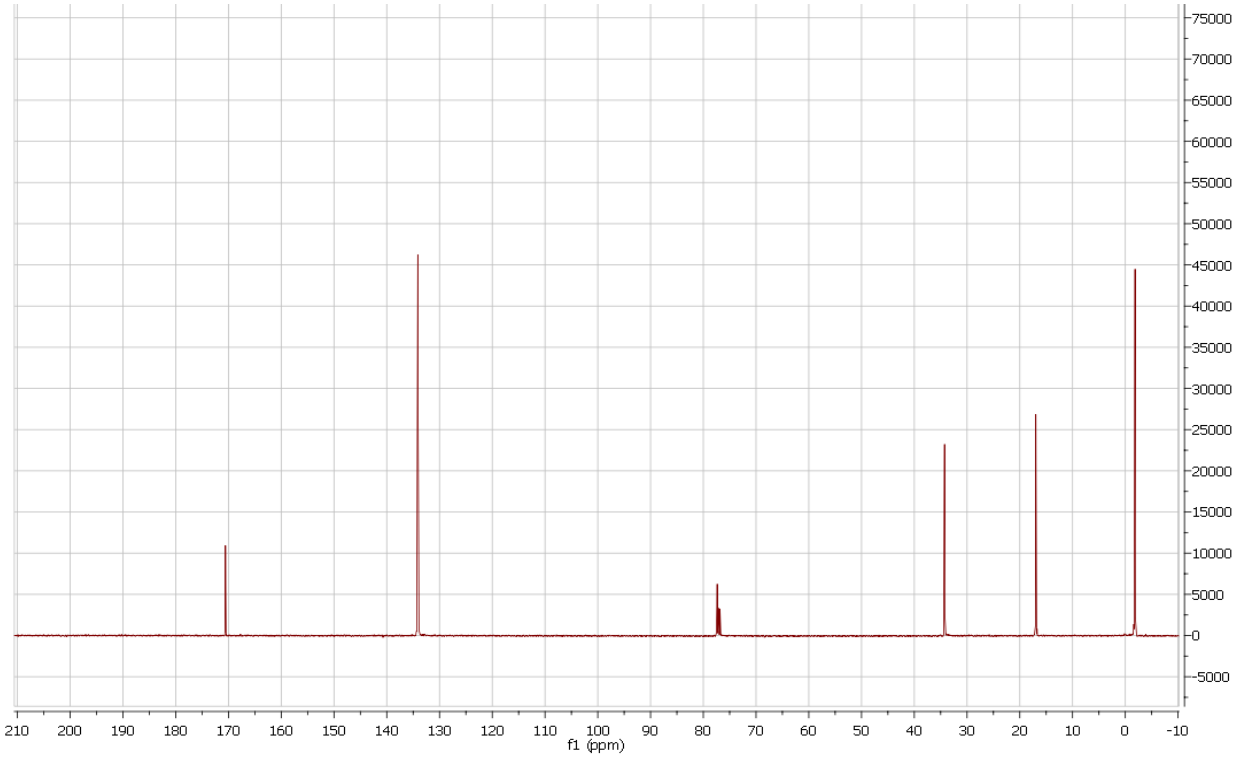
Immunocytochemistry

Hela cells were seeded on cover slips and incubated overnight. After treatment with the compounds at a concentration of 180 µM for 1 hour cells were fixed with formaldehyde and permeabilized with Triton X-100. Cells were then stained for actin with TRITC-phalloidin. Coverslips were then washed again and mounted onto glass slides. Samples were examined by means of fluorescence microscopy using the Zeiss Observer Z1 (Carl Zeiss, Germany) and a Plan-Apochromat 63x/1.40 Oil DIC M27 objective.

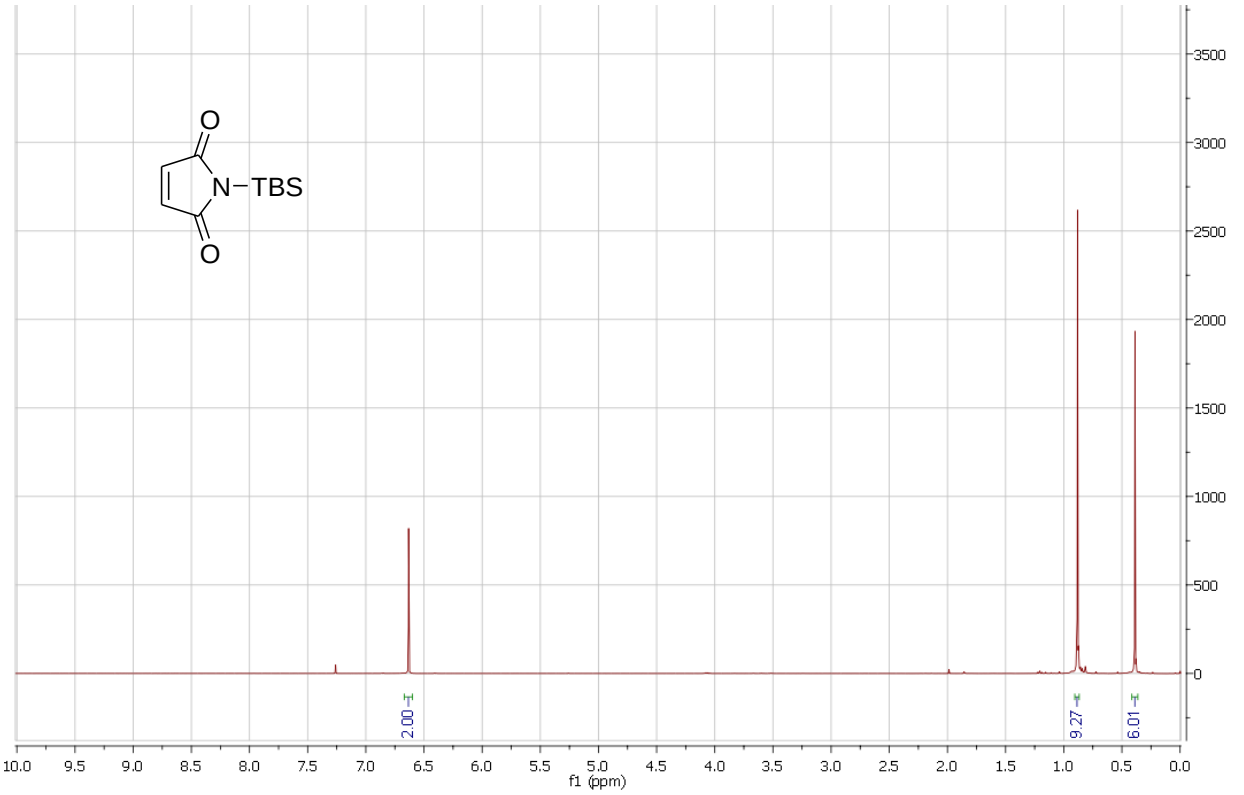
NMR spectra

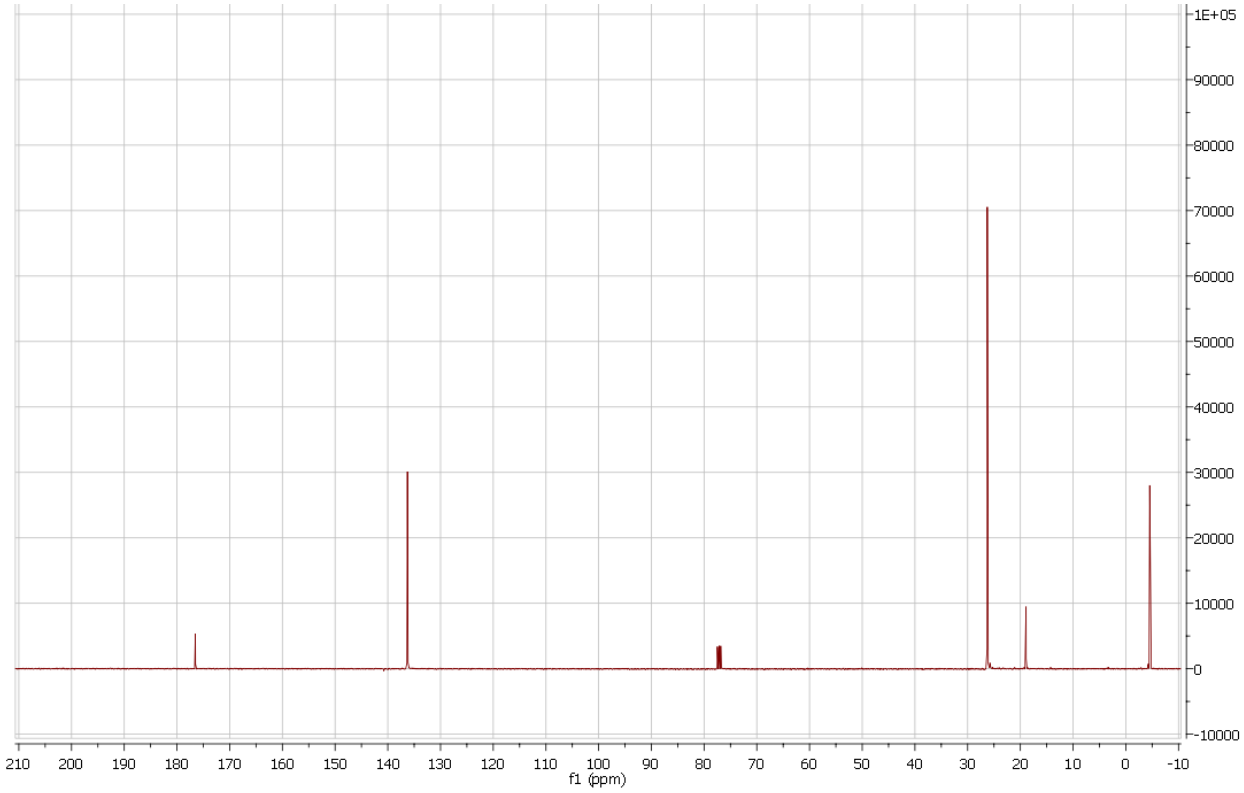
1g





1h





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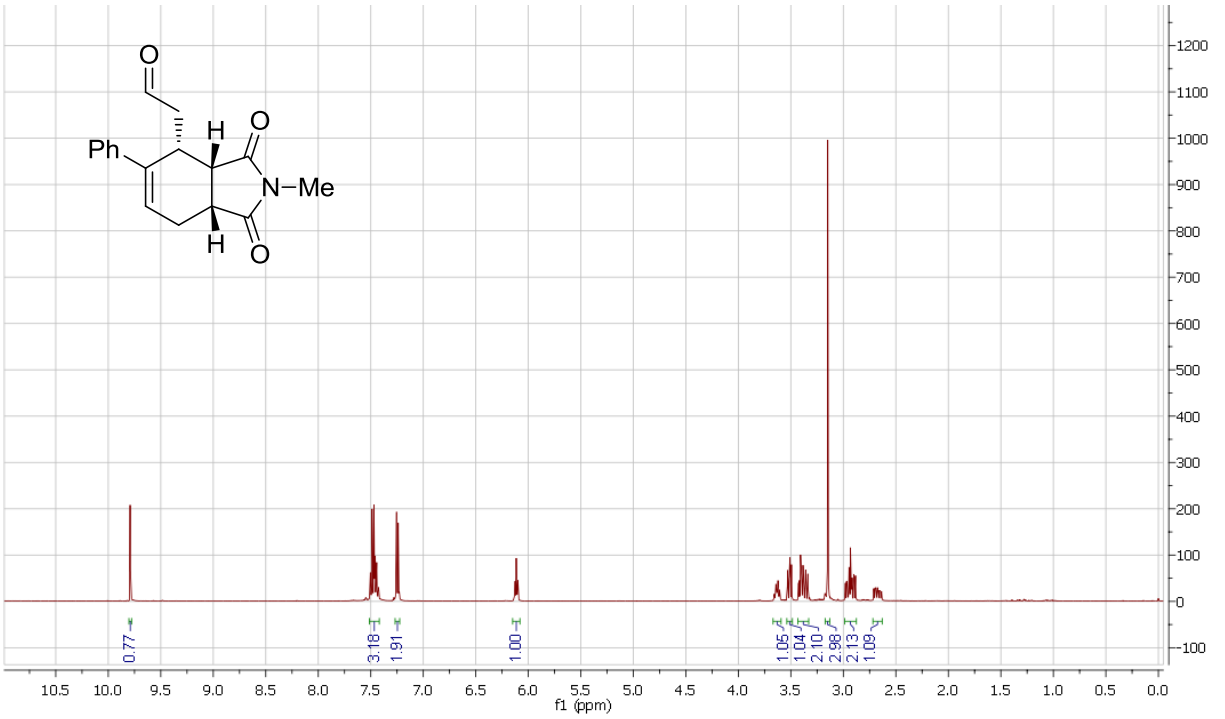
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Ph
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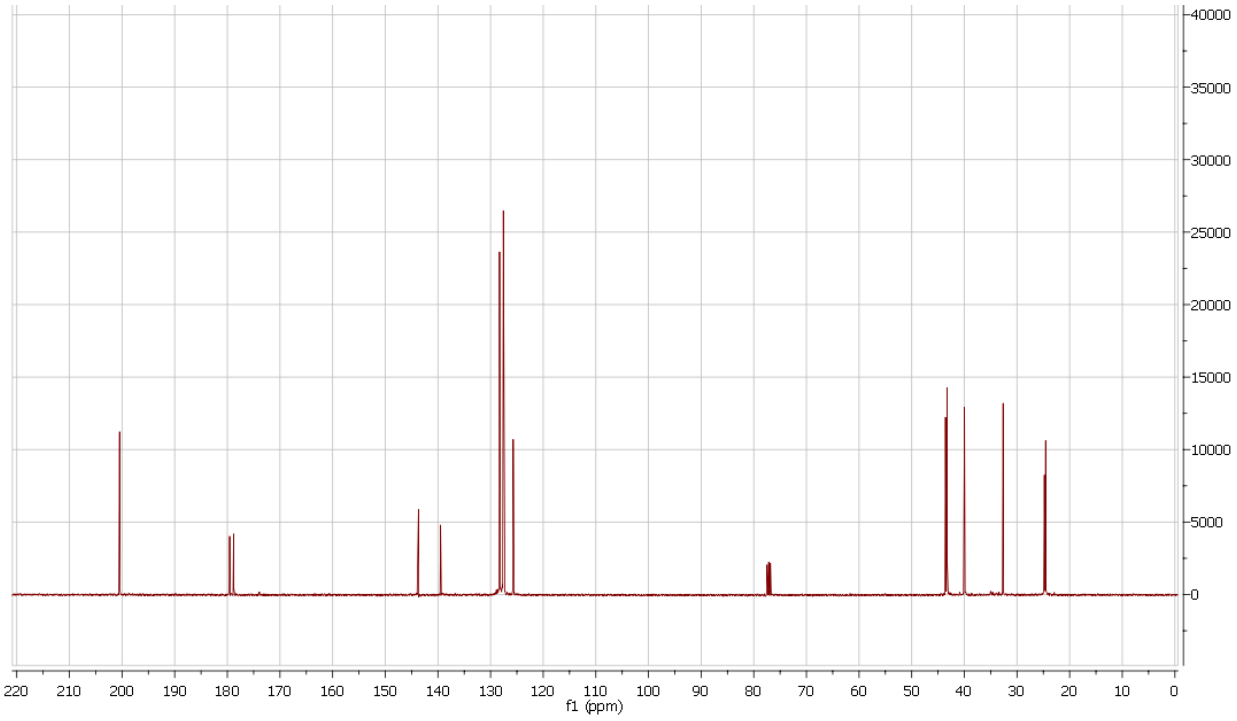
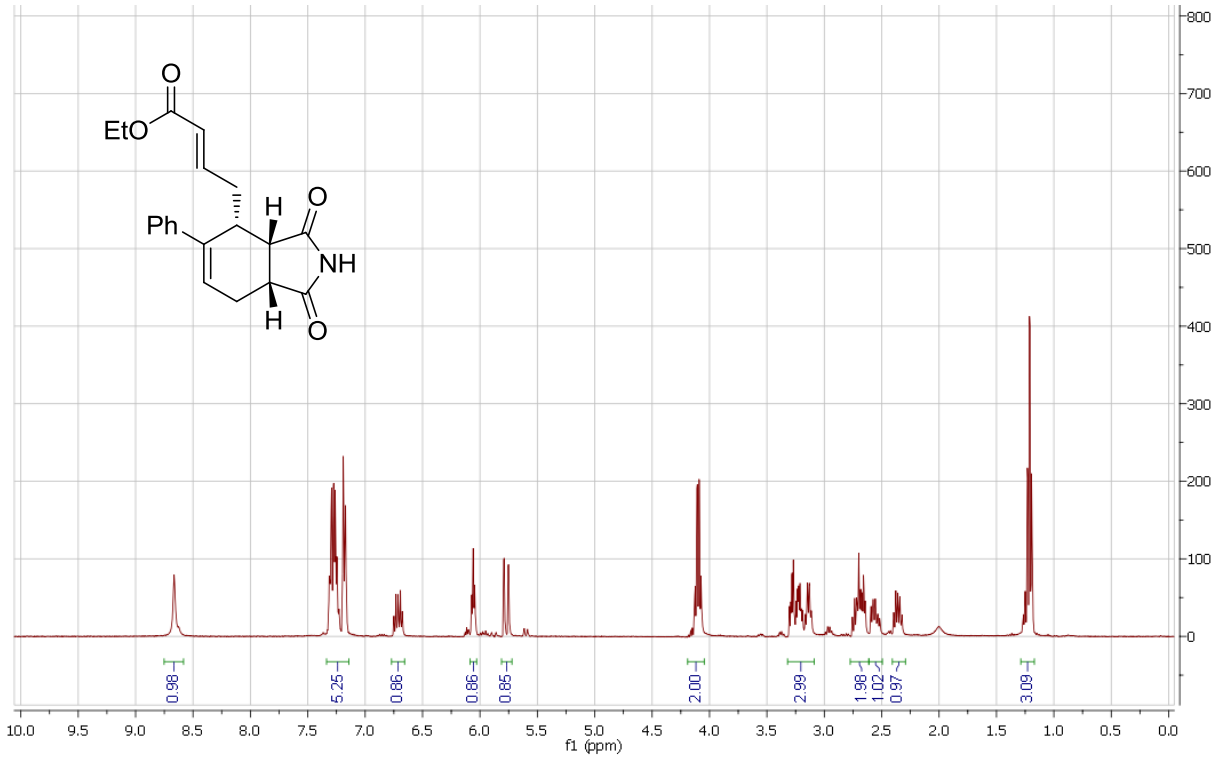
1.09
f1 (ppm)


f1 (ppm)

4a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Ph
NH
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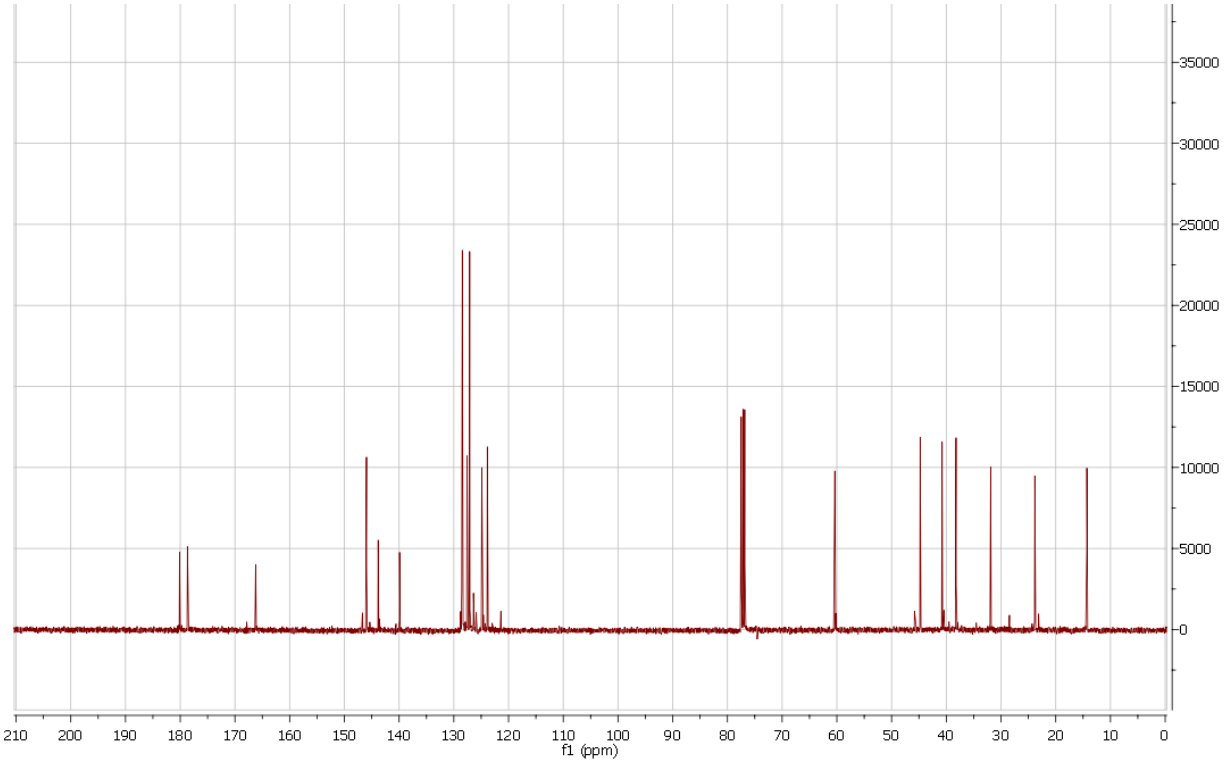
3.09
f1 (ppm)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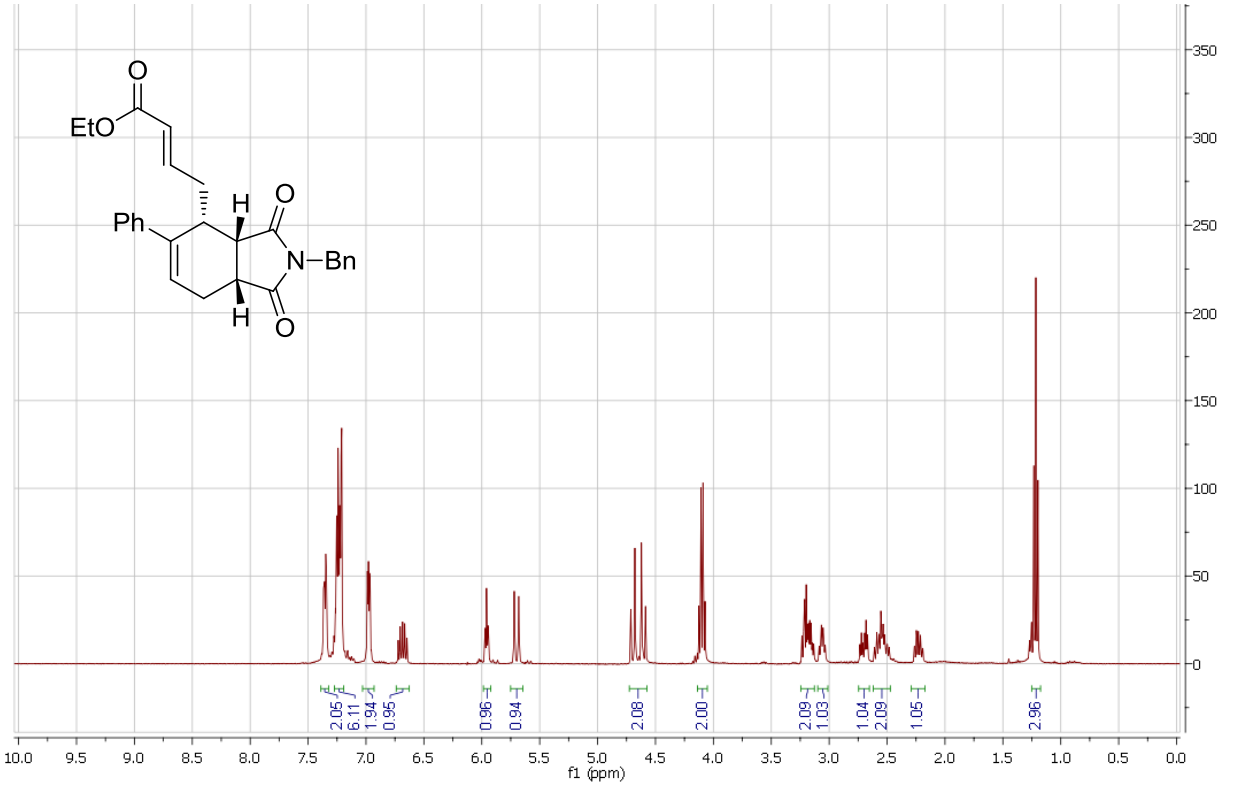
4b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Ph
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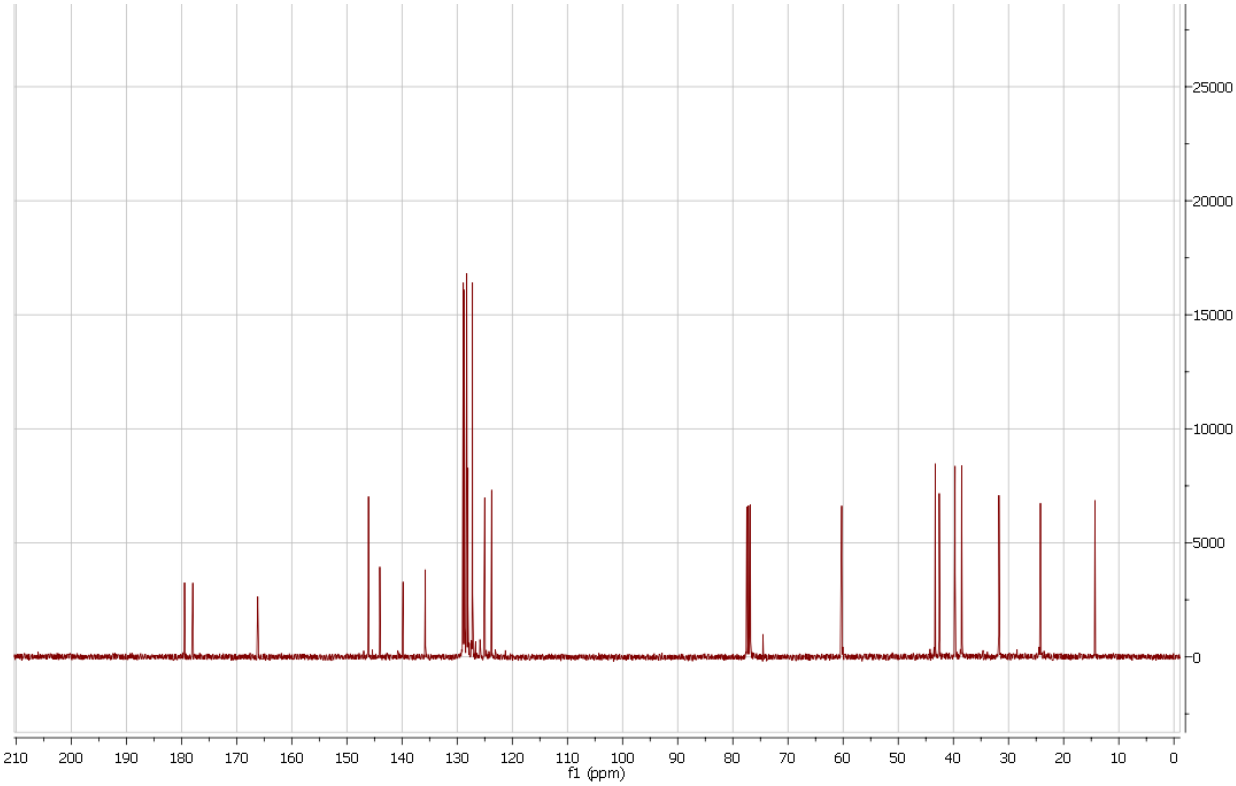
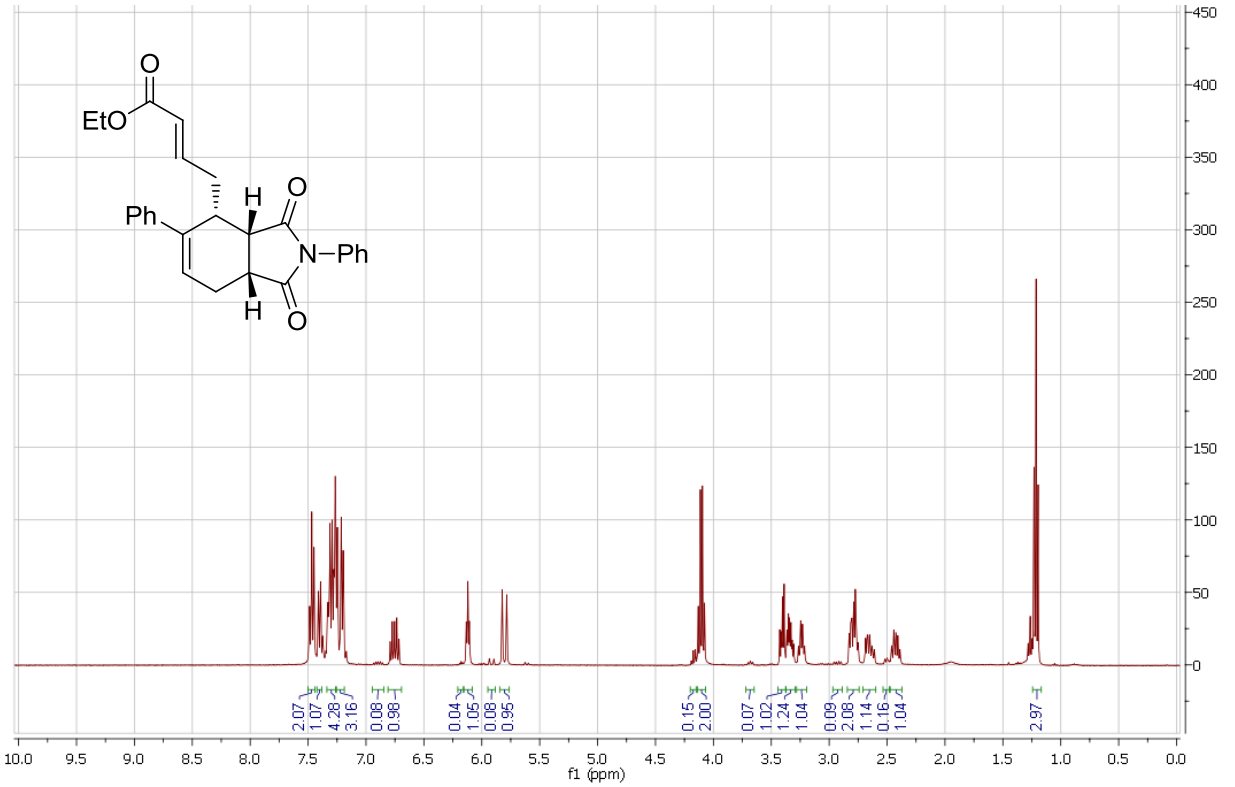
2.09
1.05
2.96
f1 (ppm)


f1 (ppm)

4c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O
Ph
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H
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1.05
0.08
0.95
0.15
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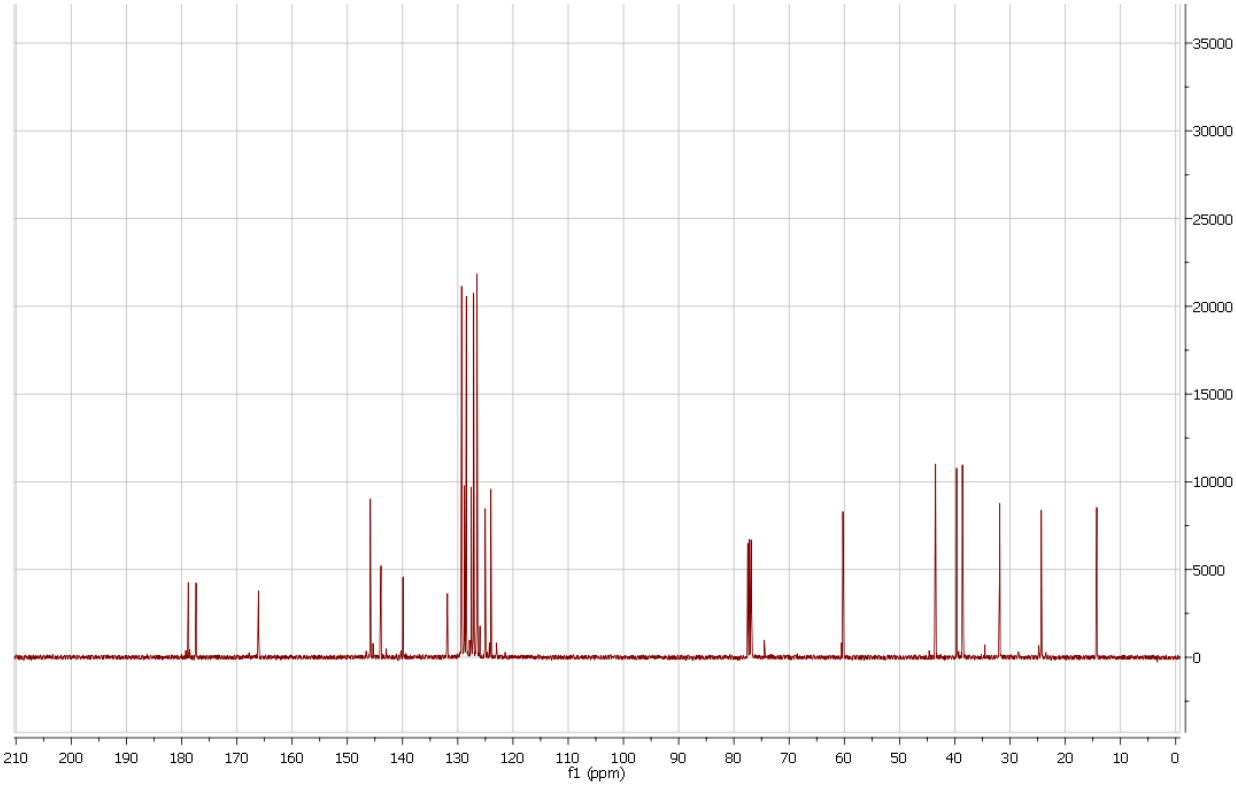
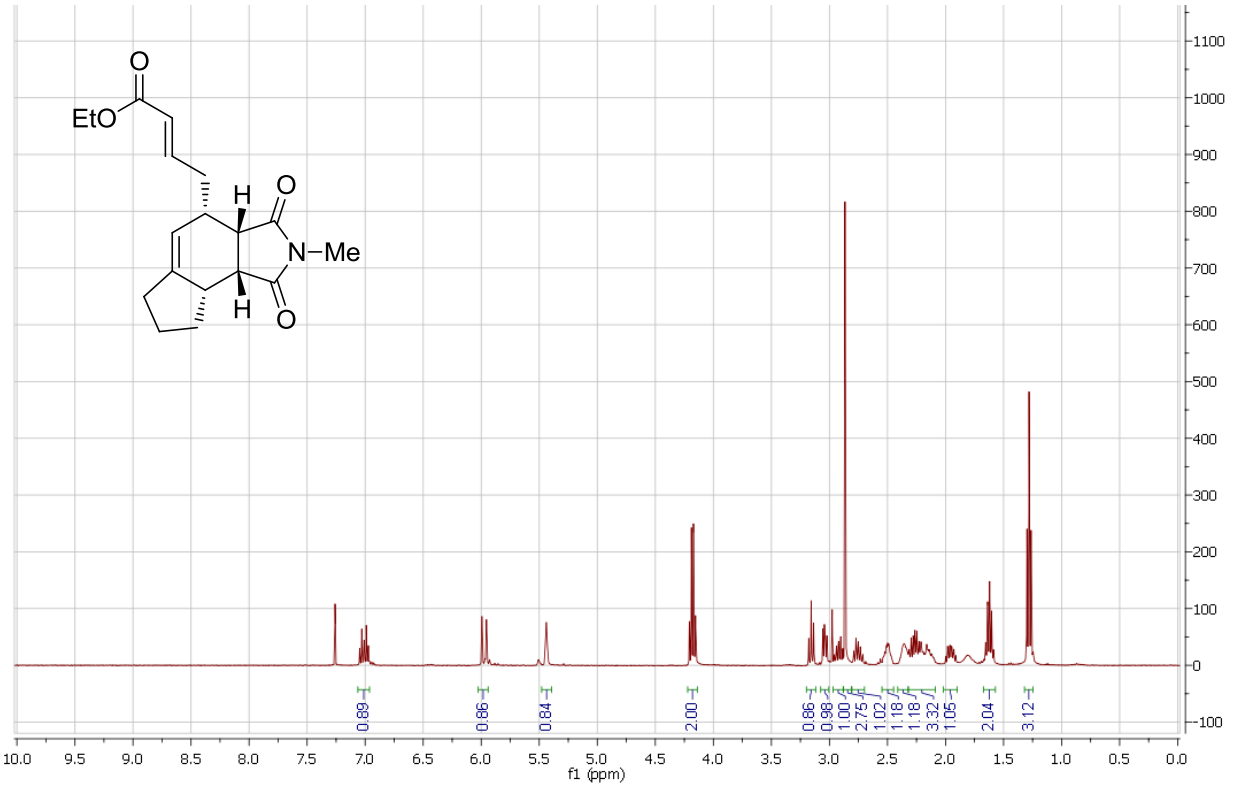
0.09
2.08
1.14
0.16
1.04
2.97
f1 (ppm)


f1 (ppm)

5a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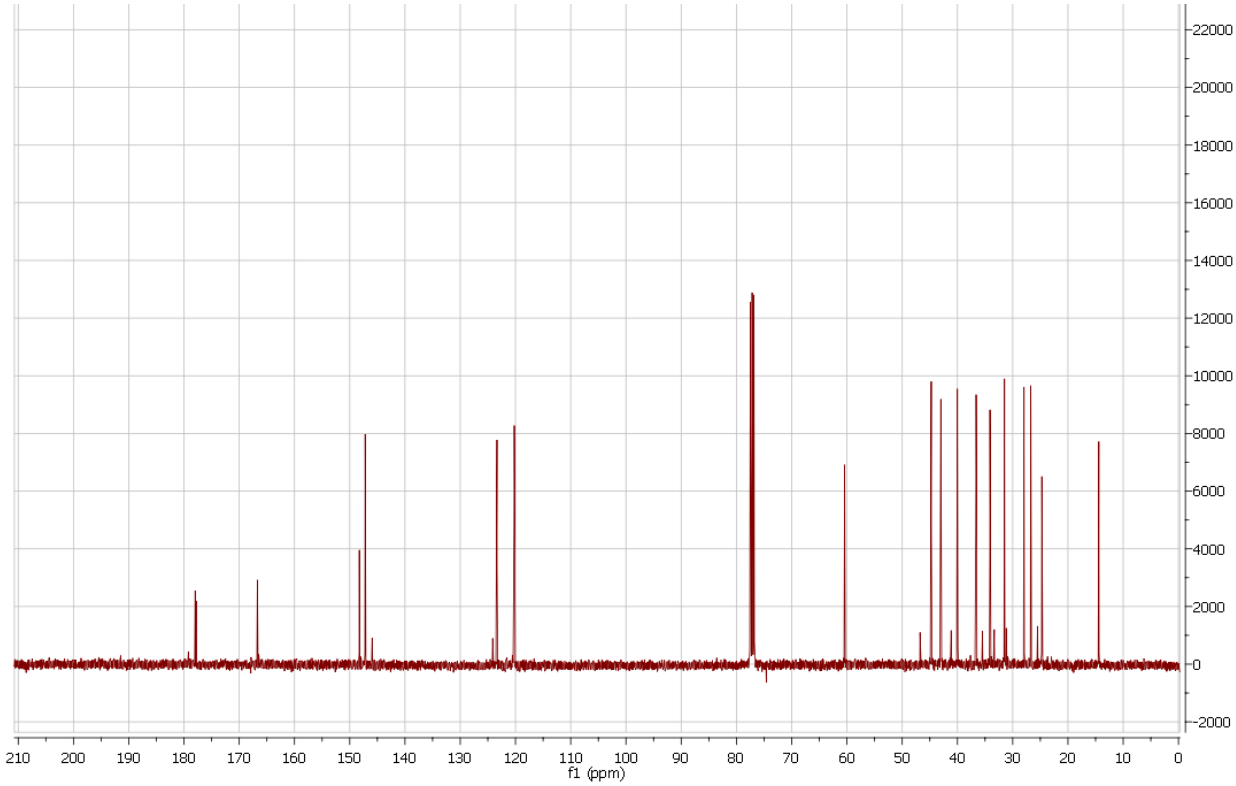
3.12
f1 (ppm)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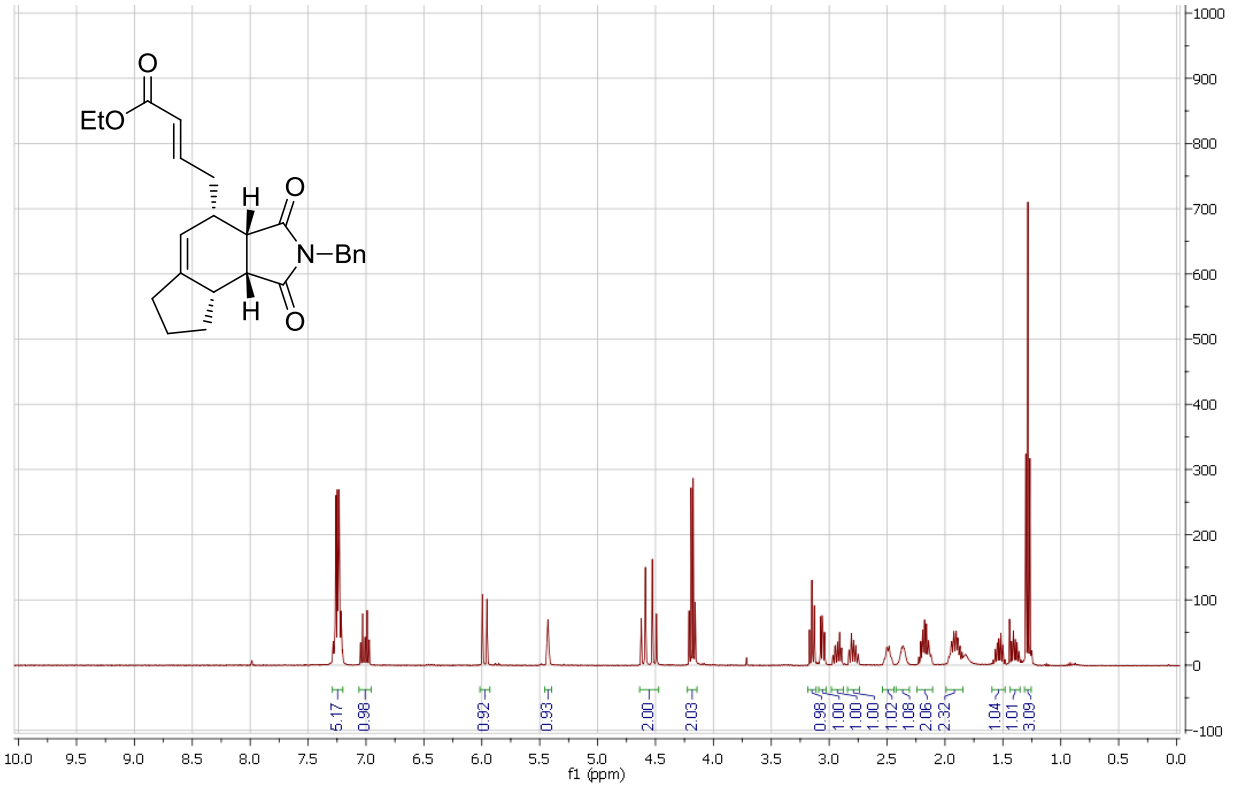
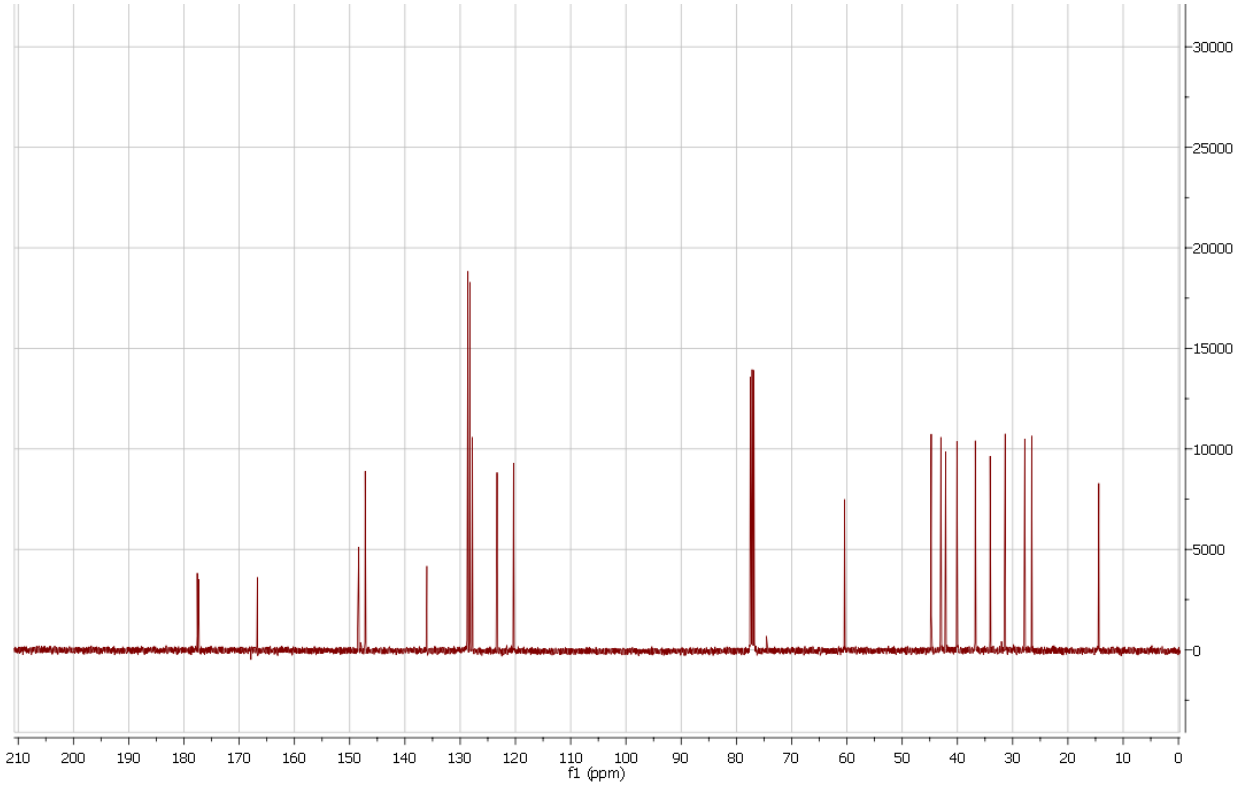
5b





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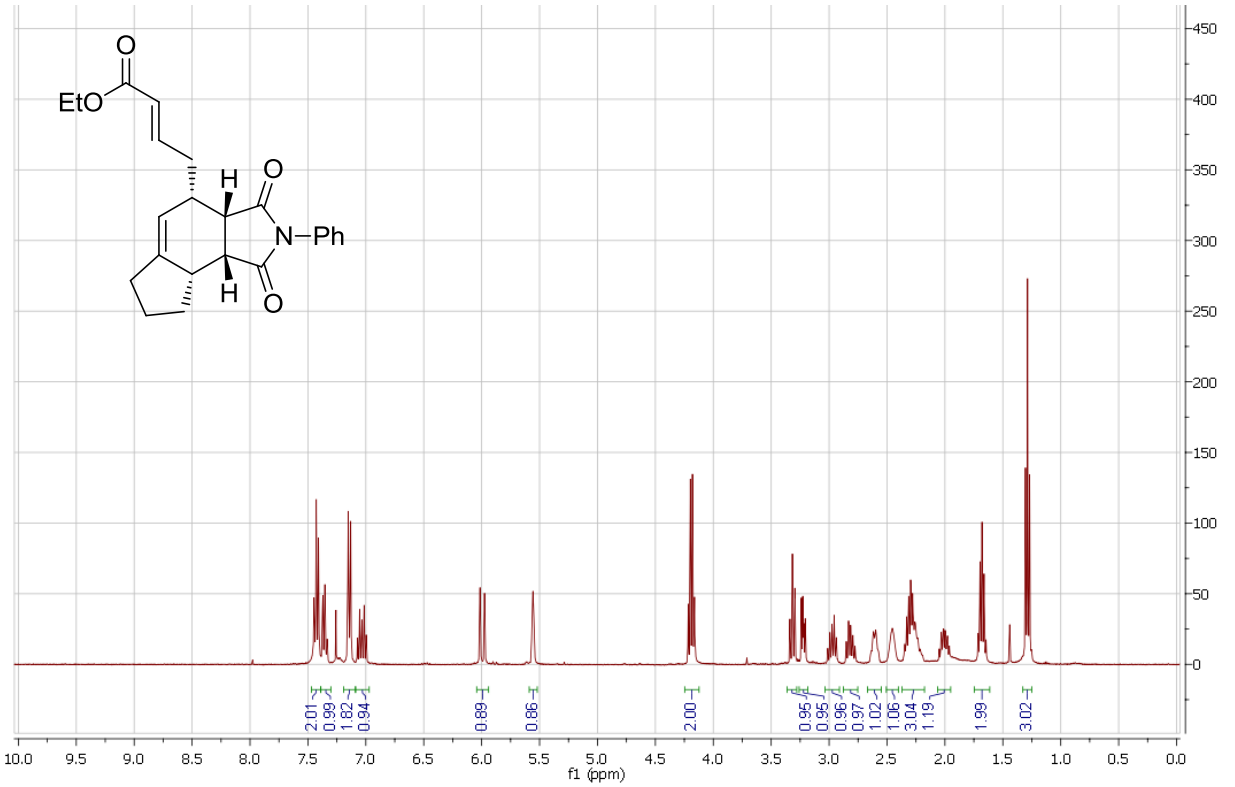
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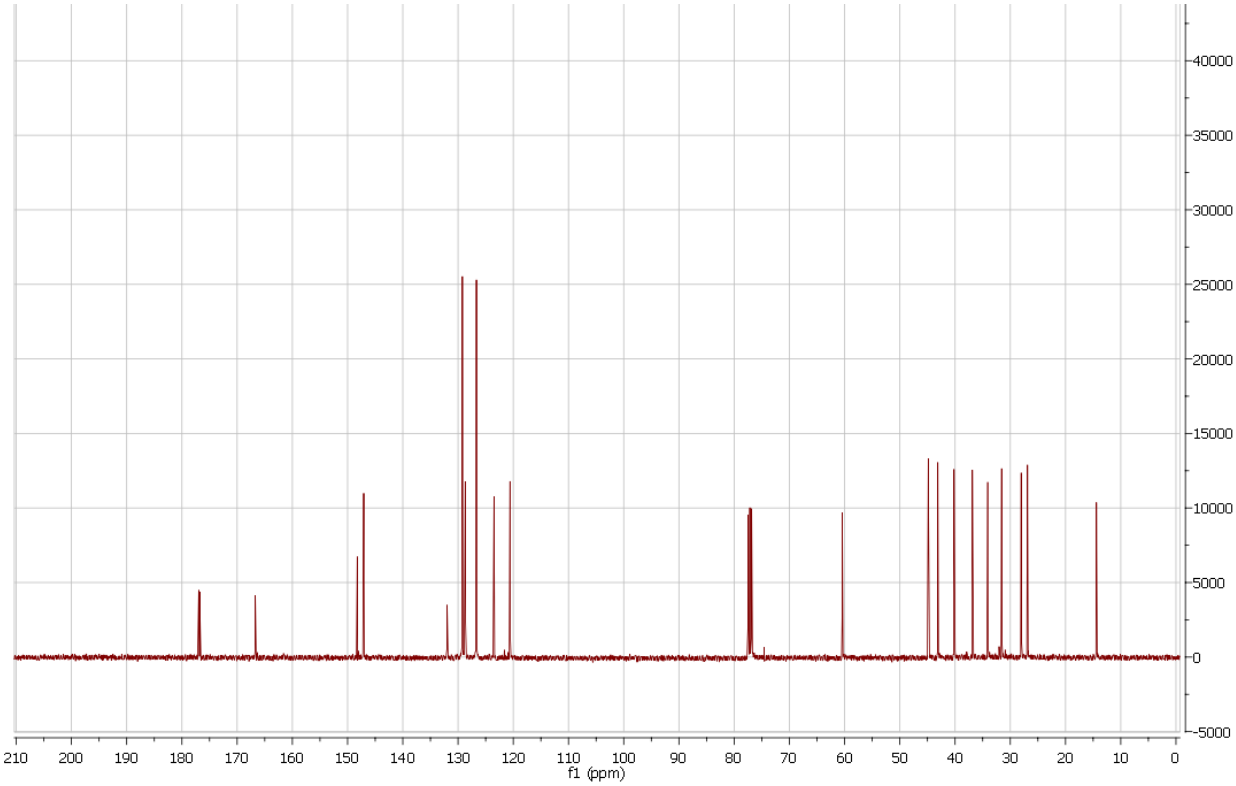
1.19
1.99
3.02
f1 (ppm)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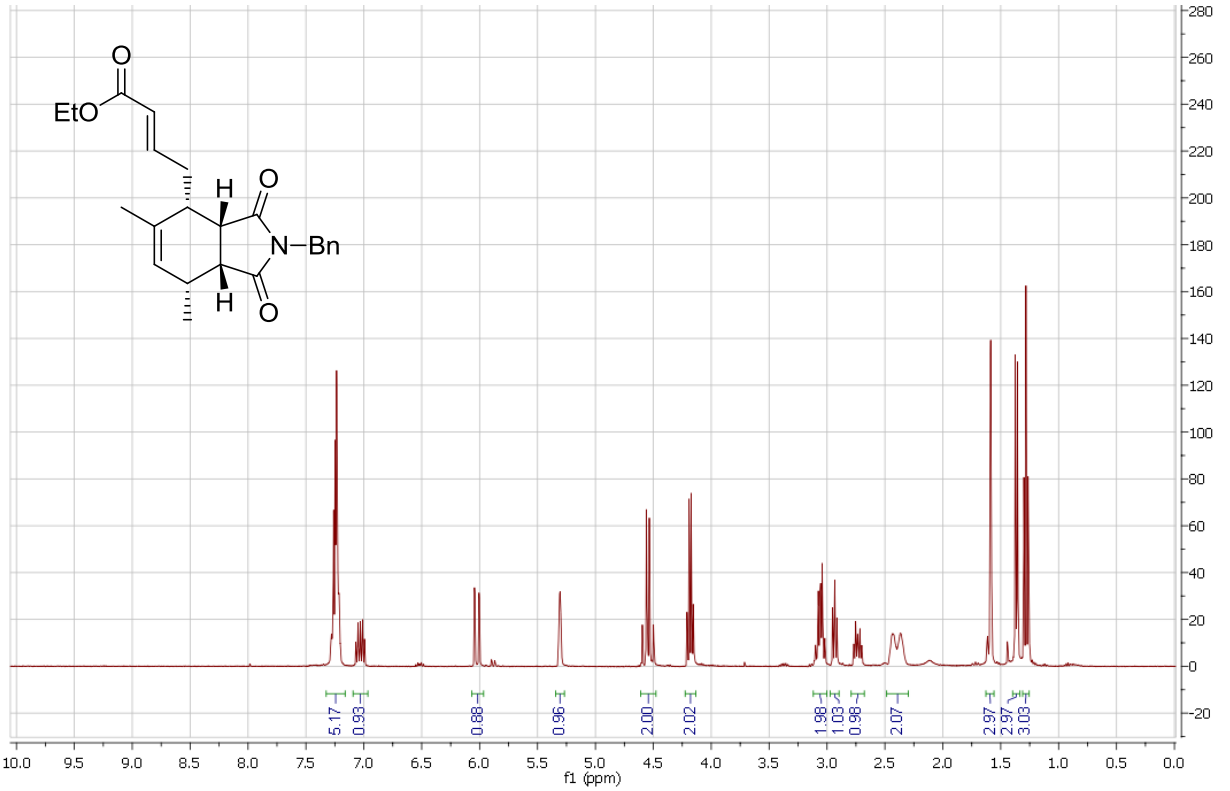
6a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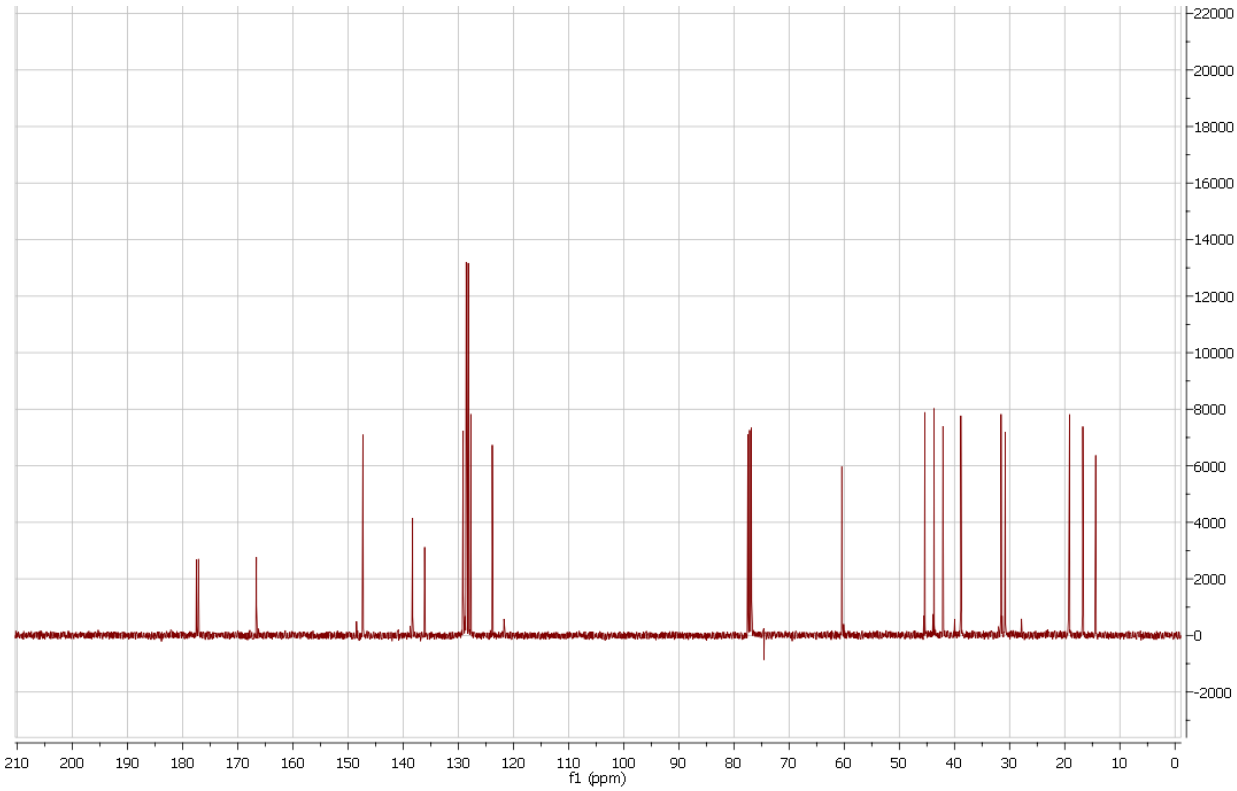
2.07
2.97
2.97
3.03
f1 (ppm)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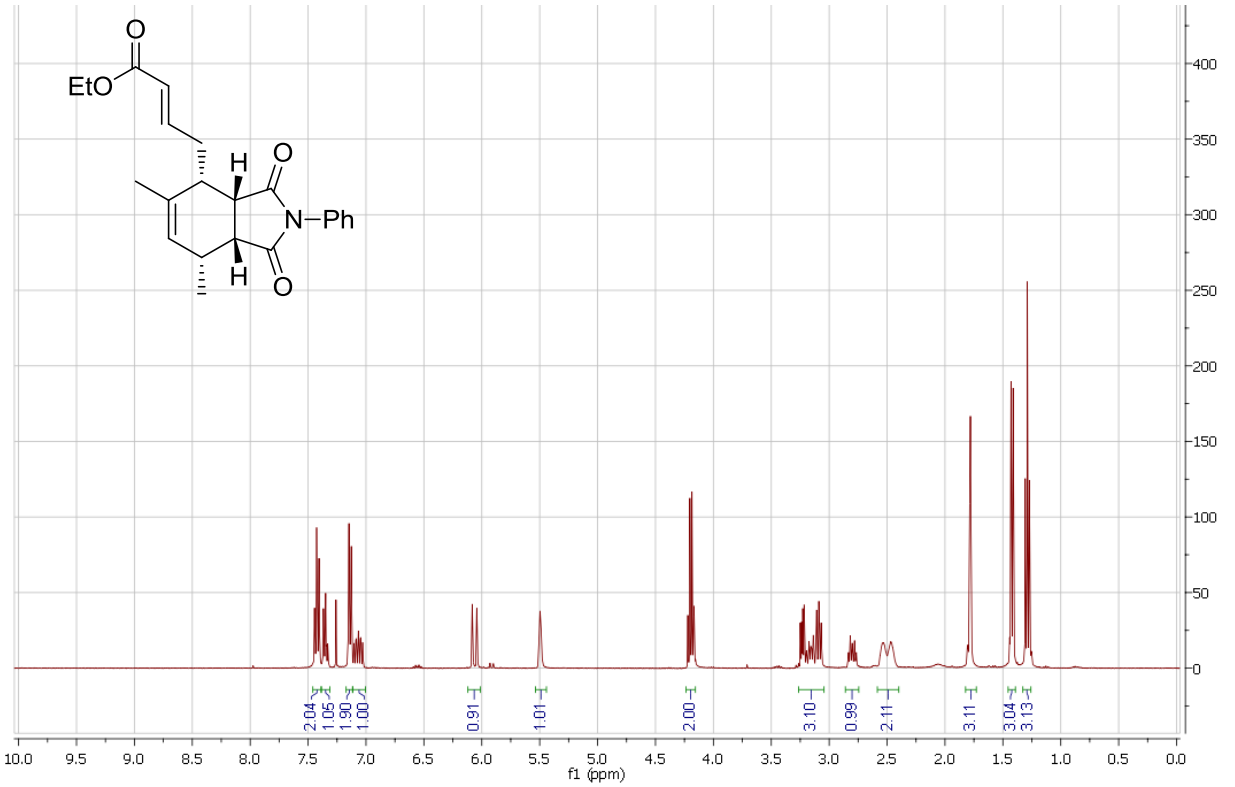
6b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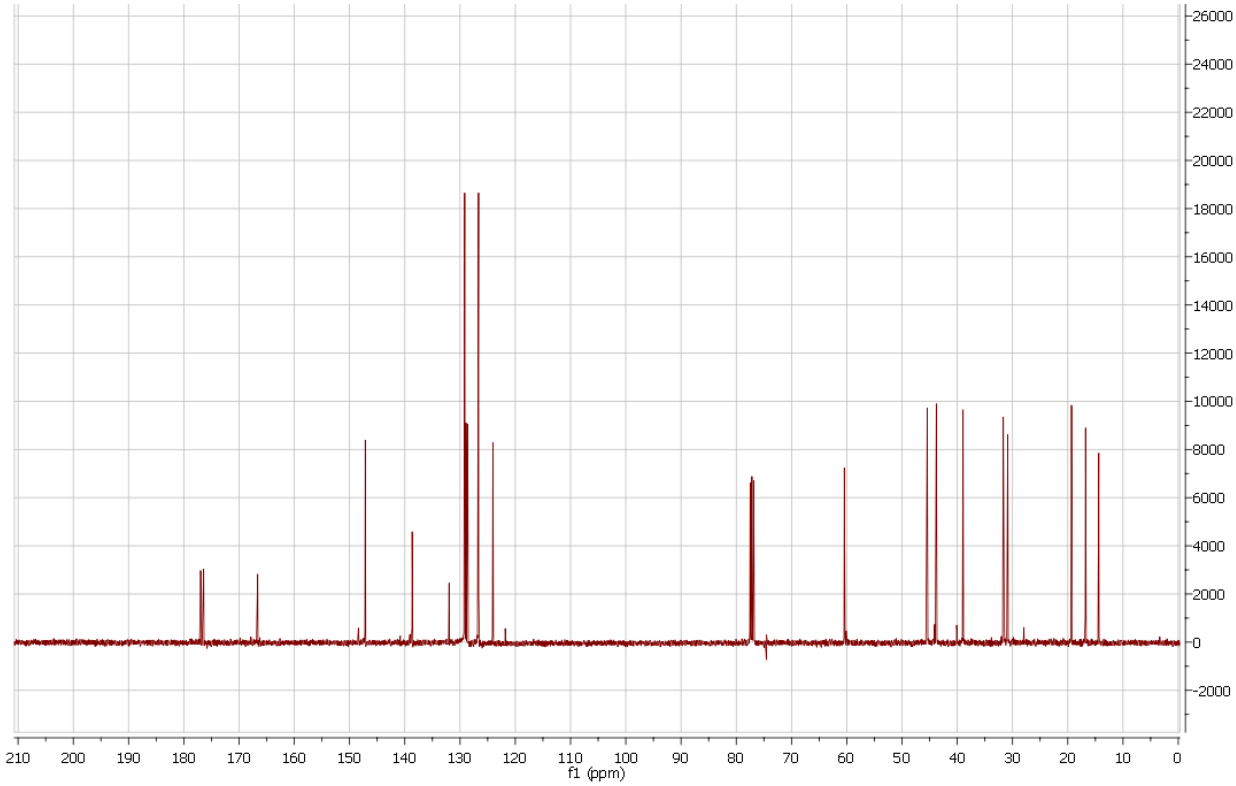
3.13
f1 (ppm)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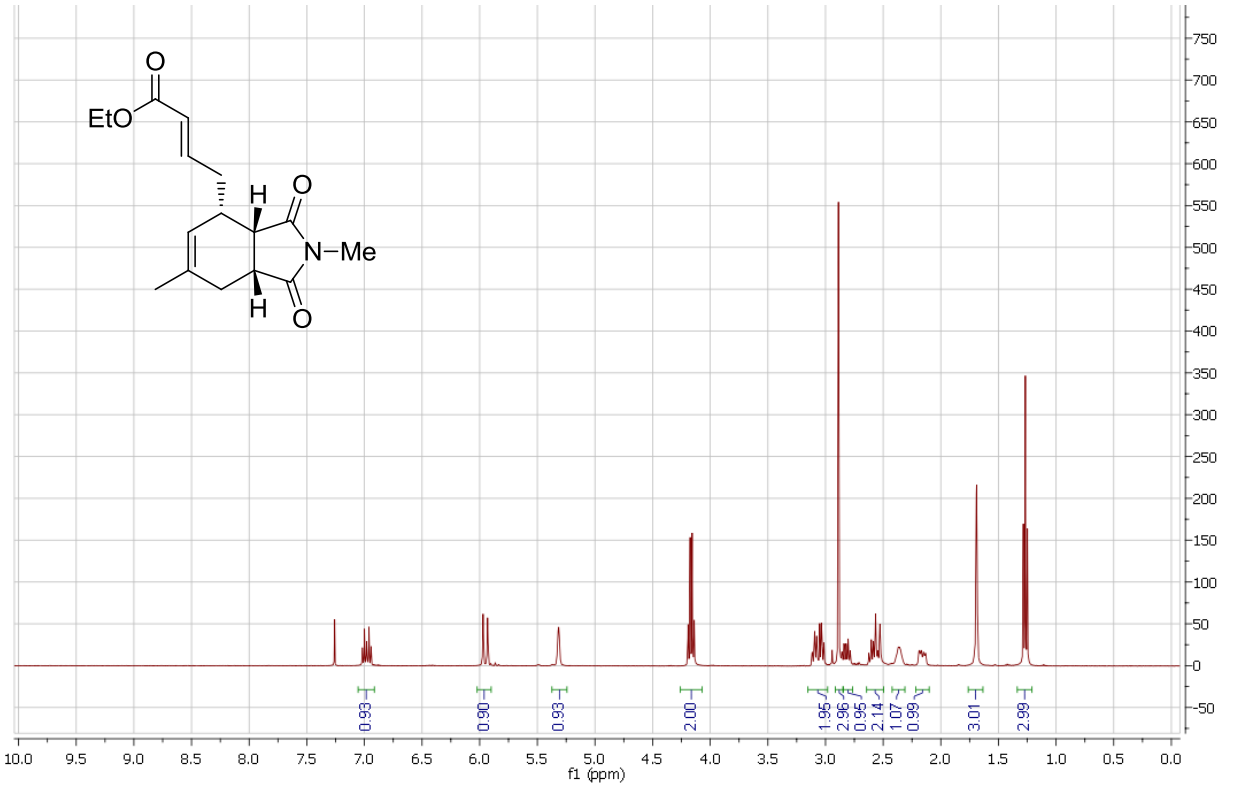
7a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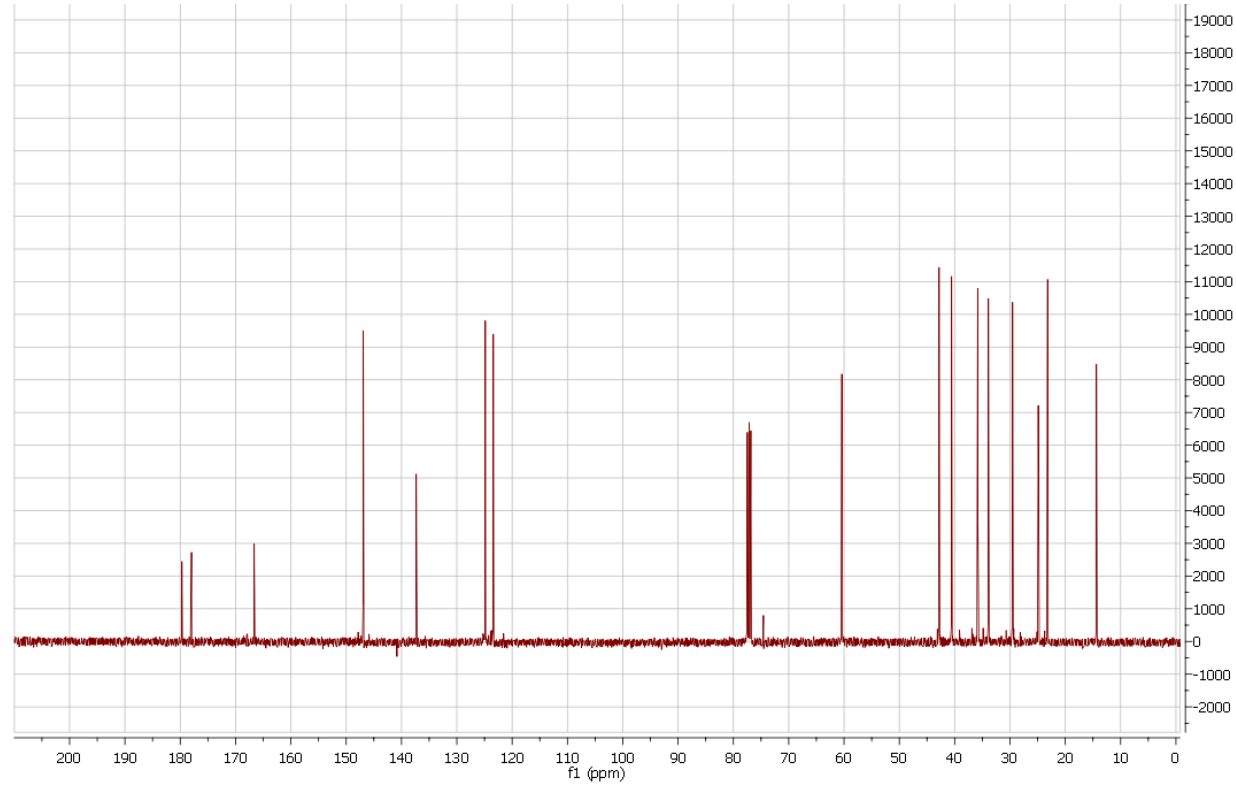
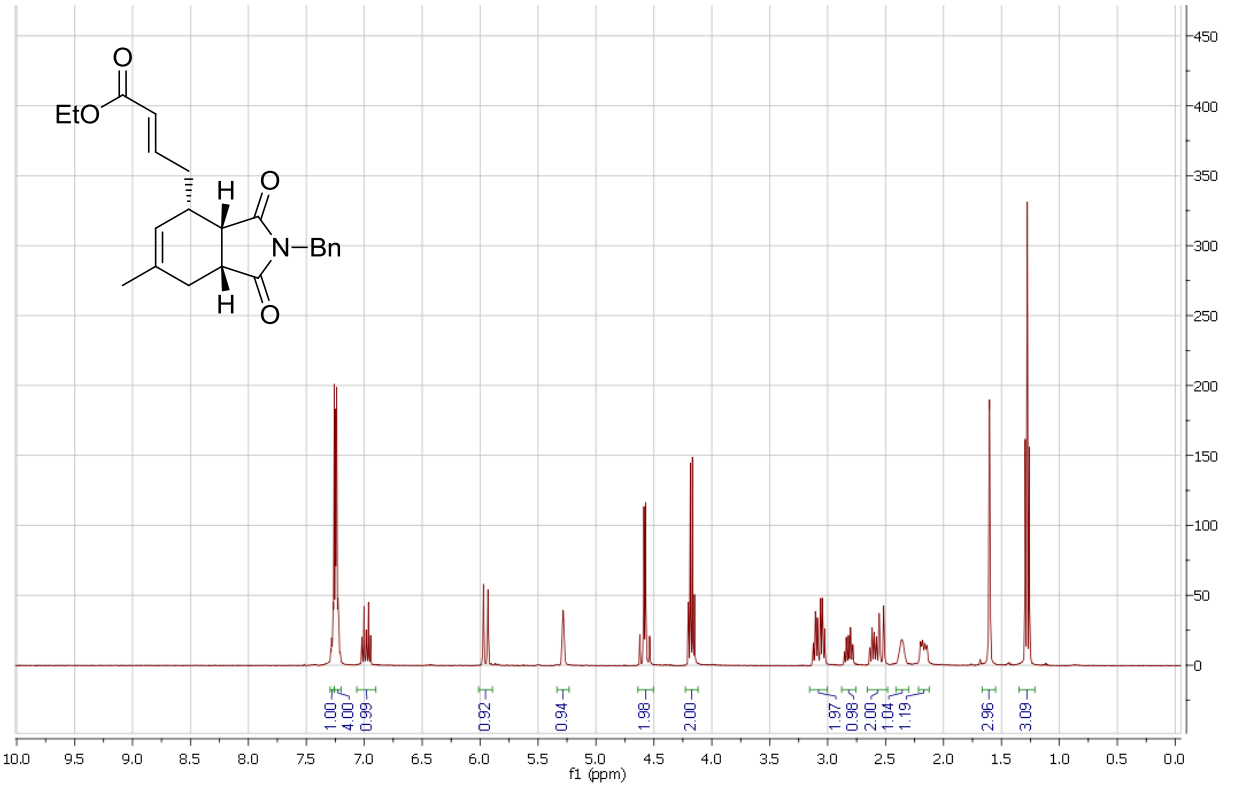
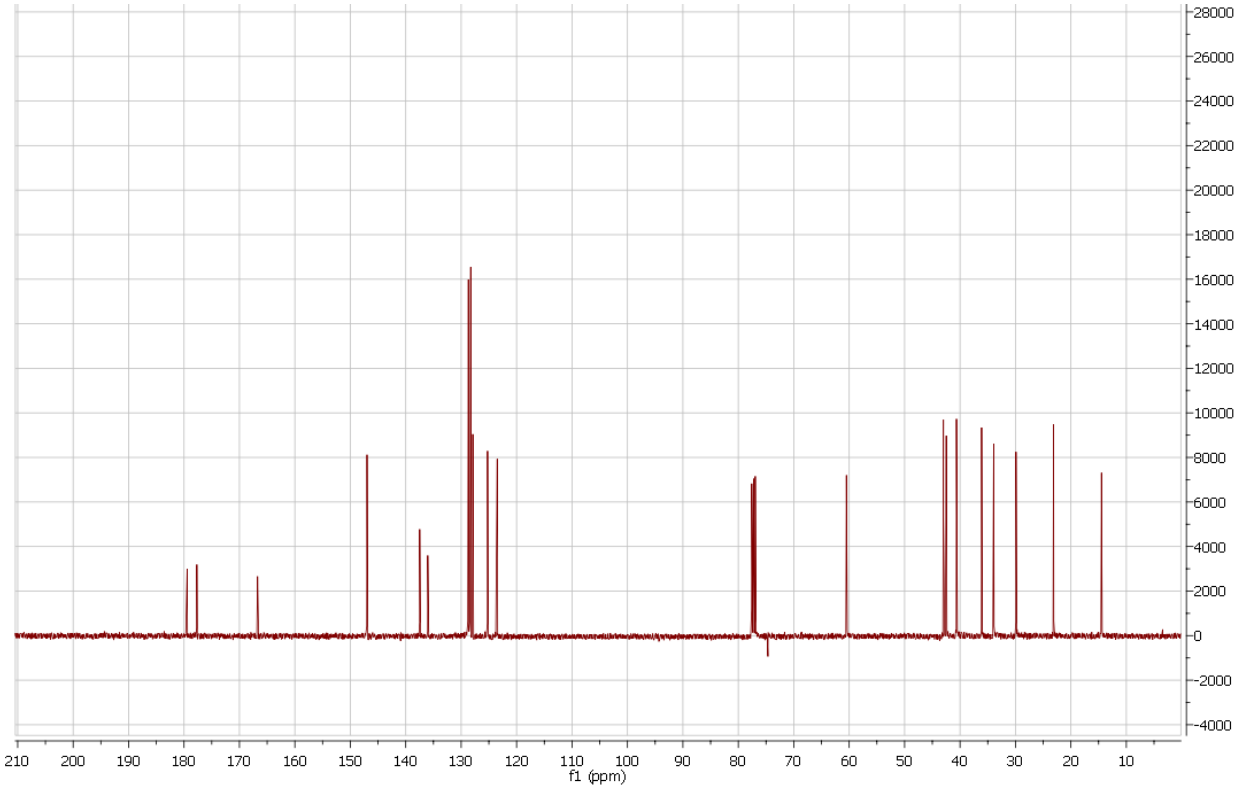
0.99
3.01
2.99
f1 (ppm)

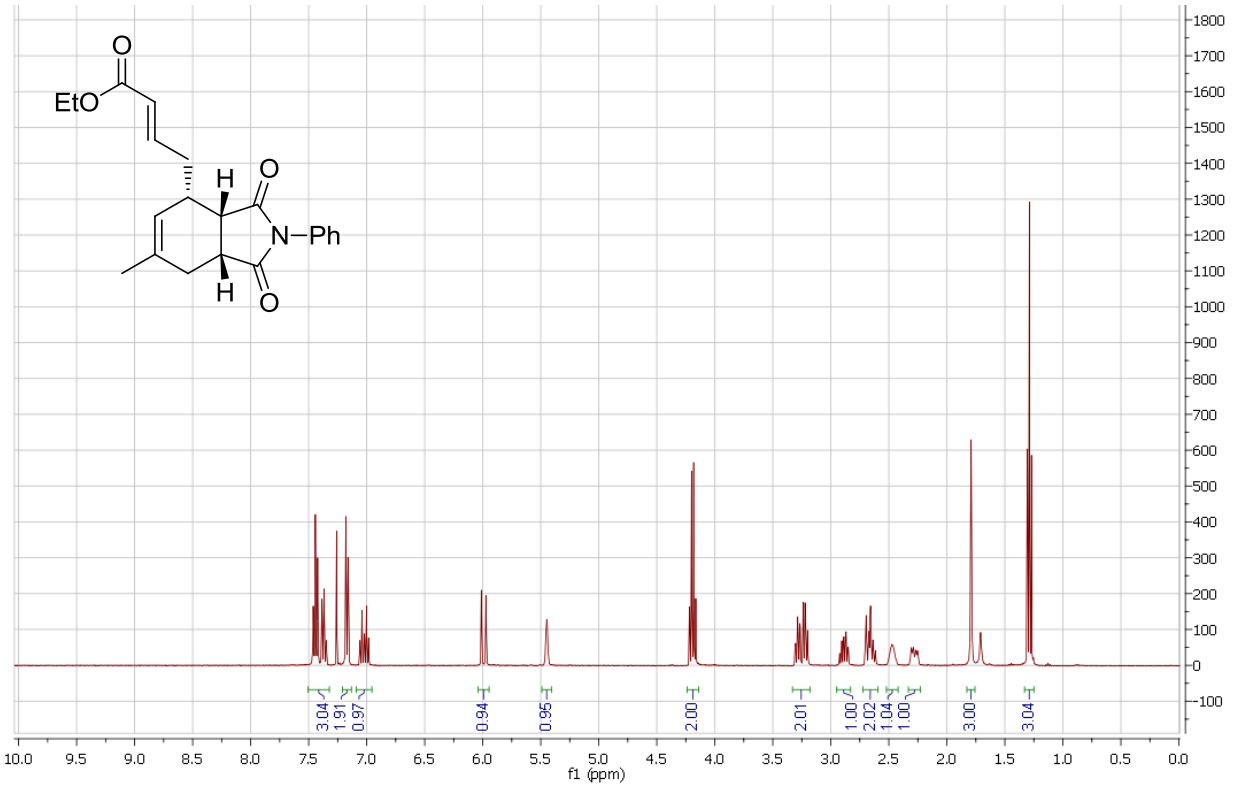

f1 (ppm)

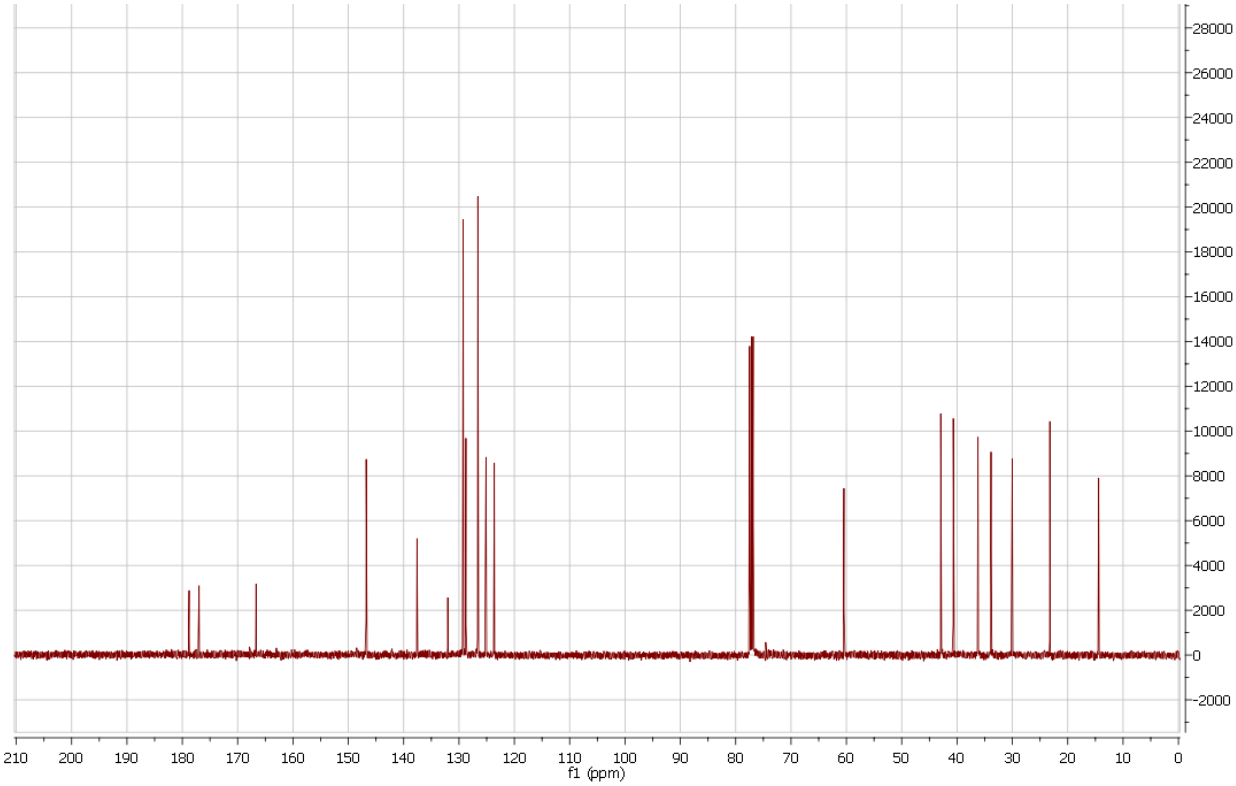
7b


EtO
O
H
O
N–Bn
H
O
1.00
4.00
0.99
0.92
0.94
1.98
2.00
1.97
0.98
2.00
1.04
1.19
2.96
3.09
f1 (ppm)

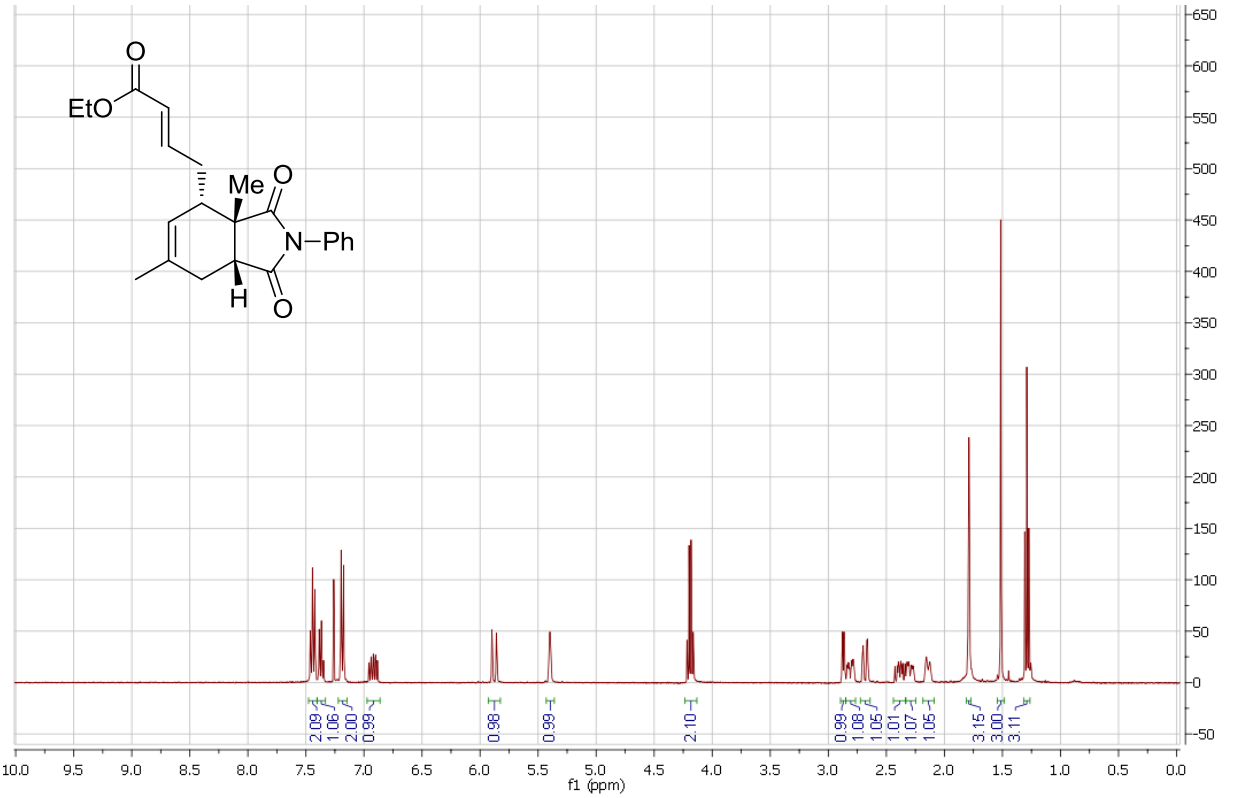

f1 (ppm)

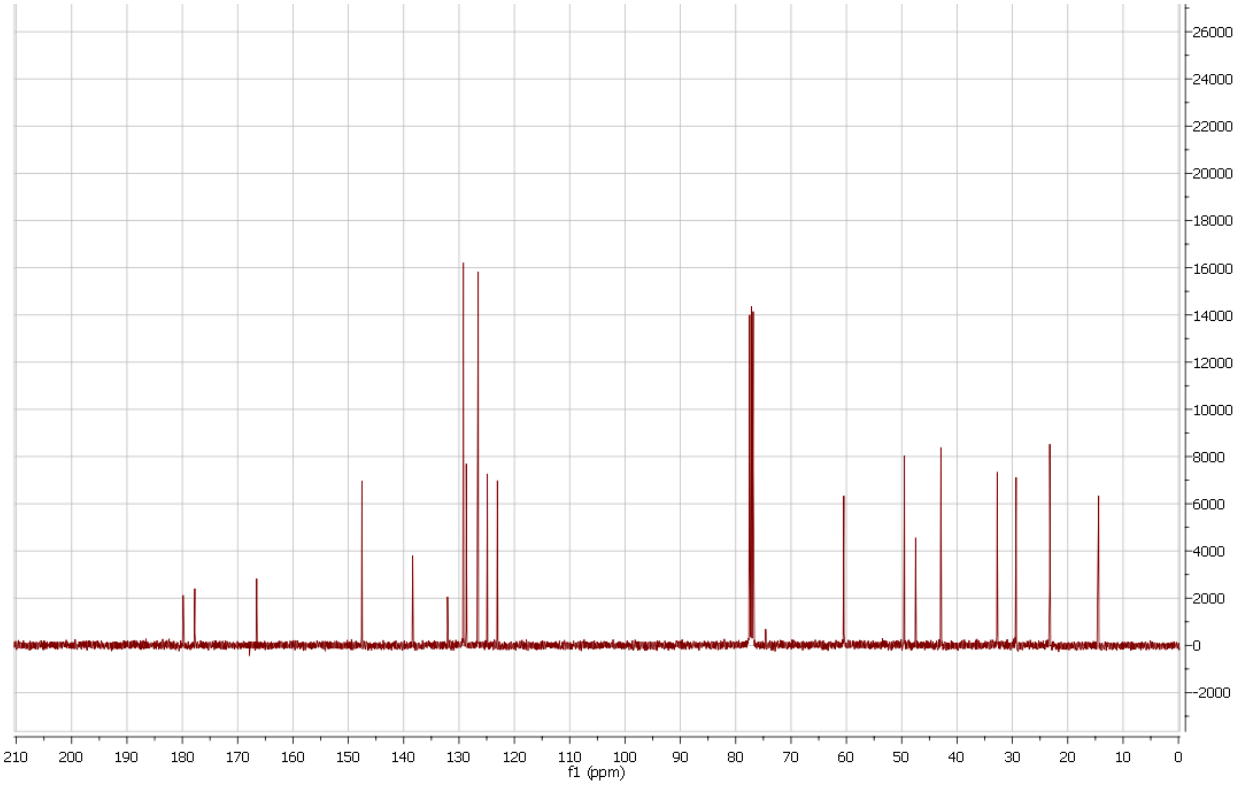
7c


O
EtO
H
O
N–Ph
H
O
3.04
1.91
0.97
0.94
0.95
2.00
2.01
1.00
2.02
1.04
1.00
3.00
3.04
f1 (ppm)

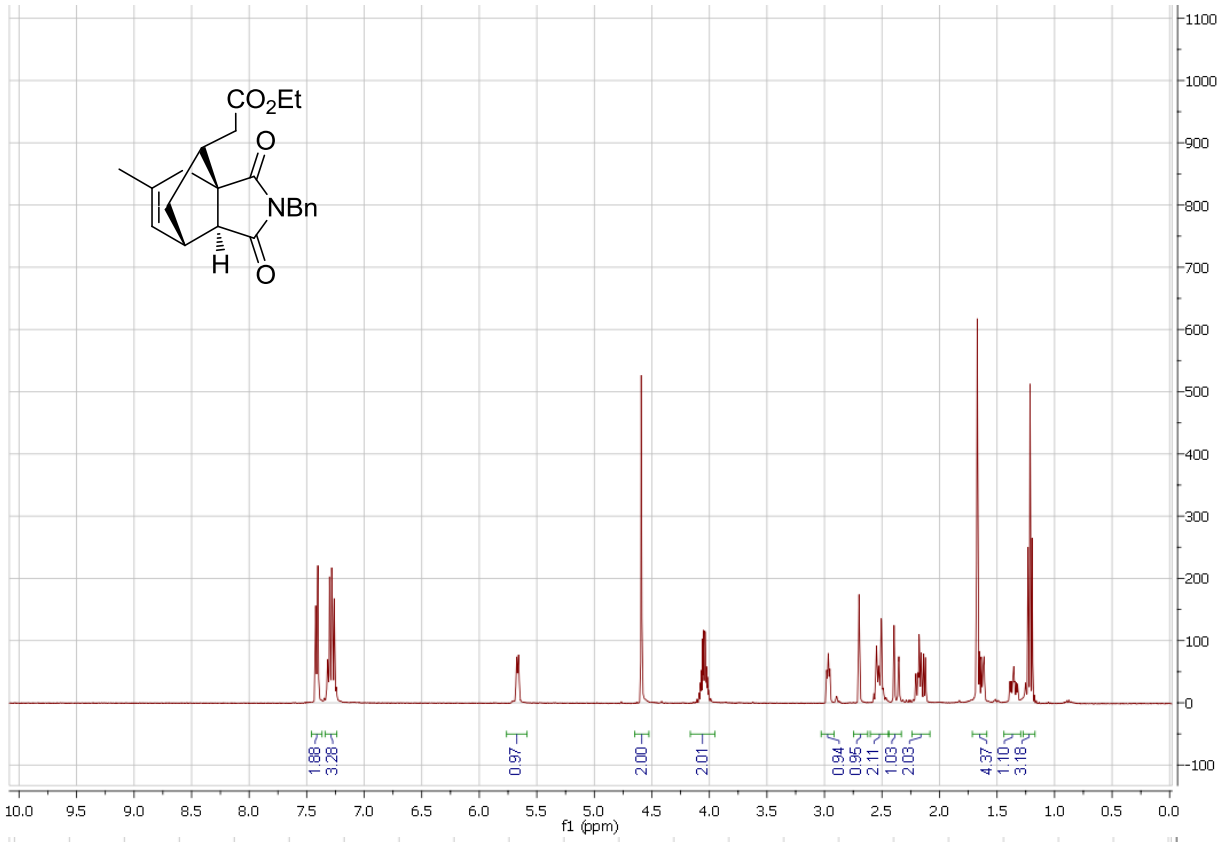

f1 (ppm)

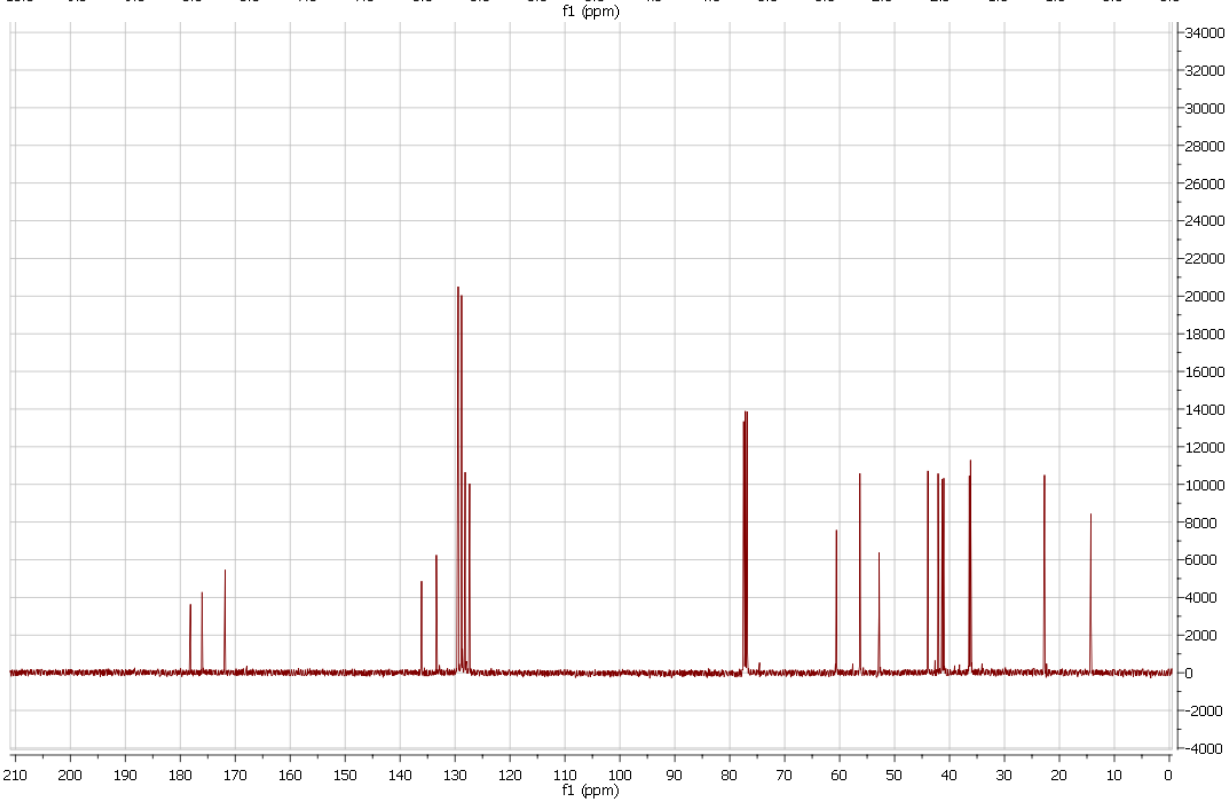
7d


O
EtO
Me
O
N–Ph
H
O
2.09
1.06
2.00
0.99
0.98
0.99
2.10
0.99
1.08
1.05
1.01
1.07
1.05
3.15
3.00
3.11
f1 (ppm)

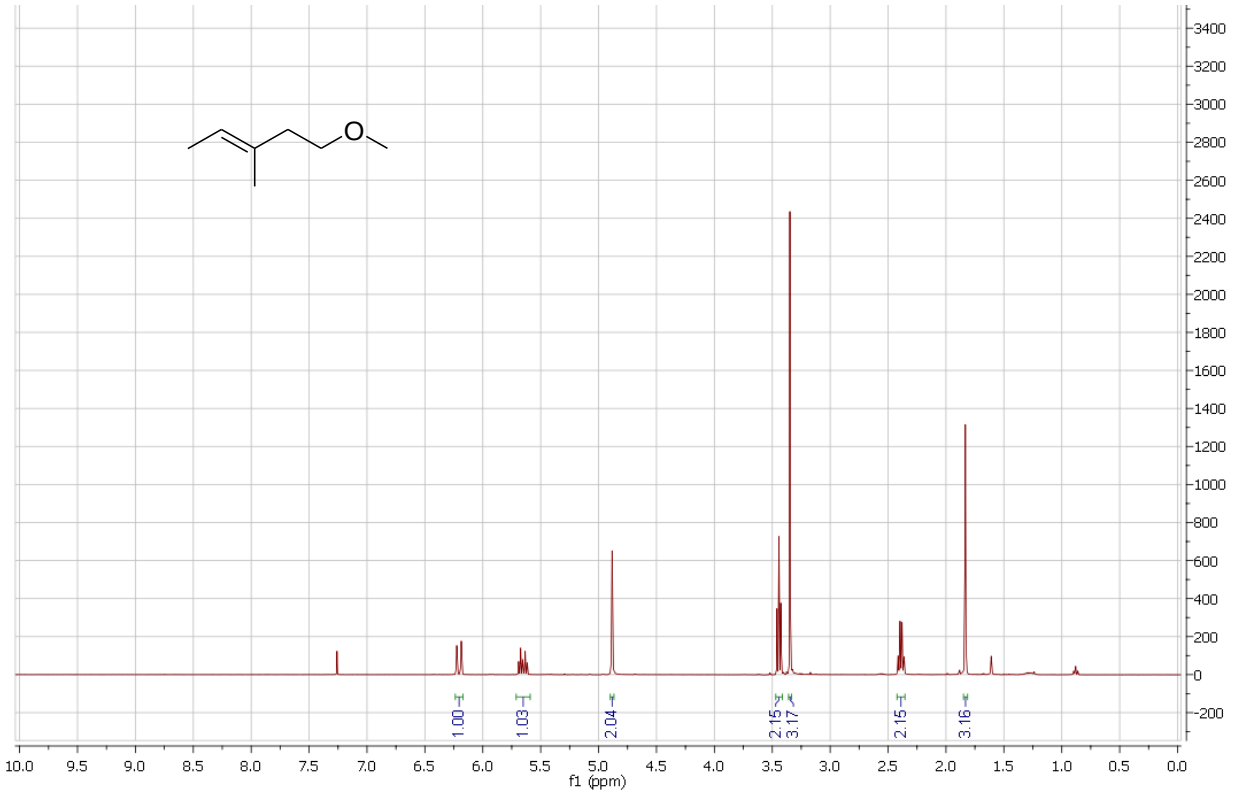

f1 (ppm)

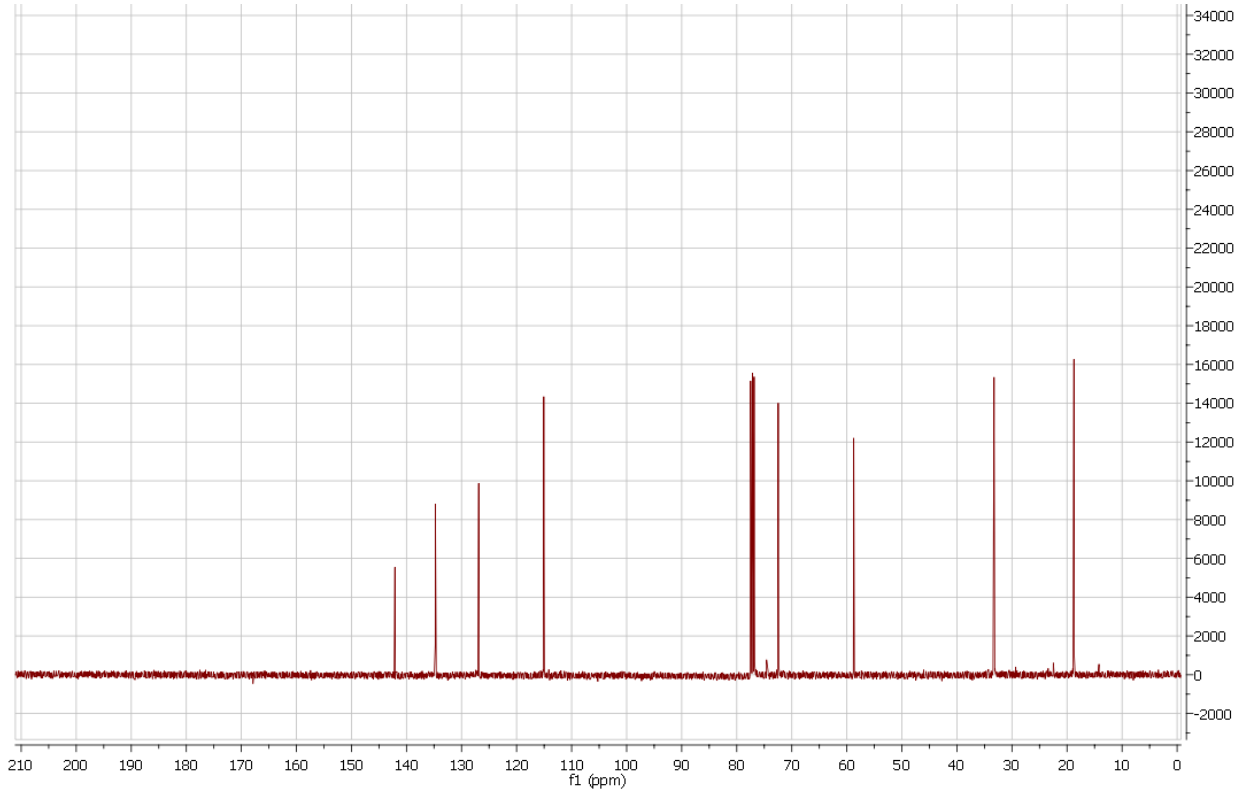
8


CO2Et
O
NBn
H
O
1.88
3.28
0.97
2.00
2.01
0.94
0.95
2.11
1.03
2.03
4.37
1.10
3.18
f1 (ppm)

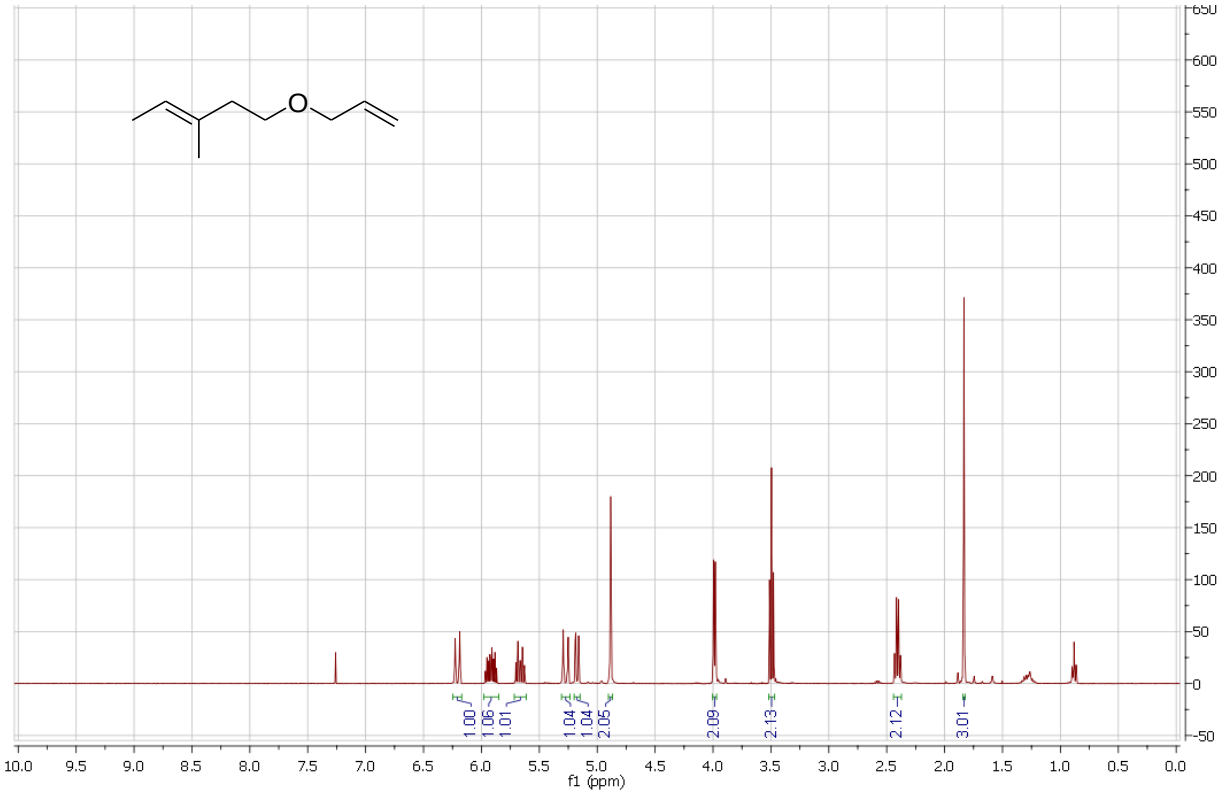

f1 (ppm)

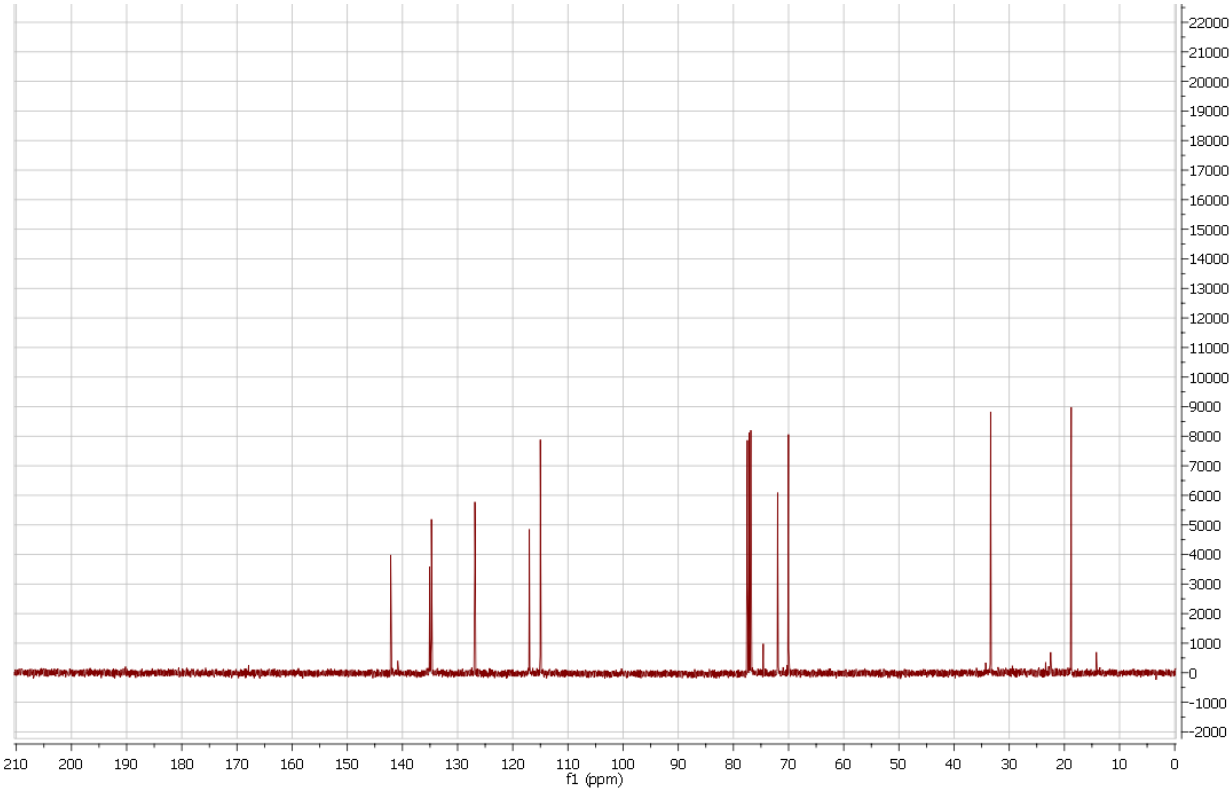
9a



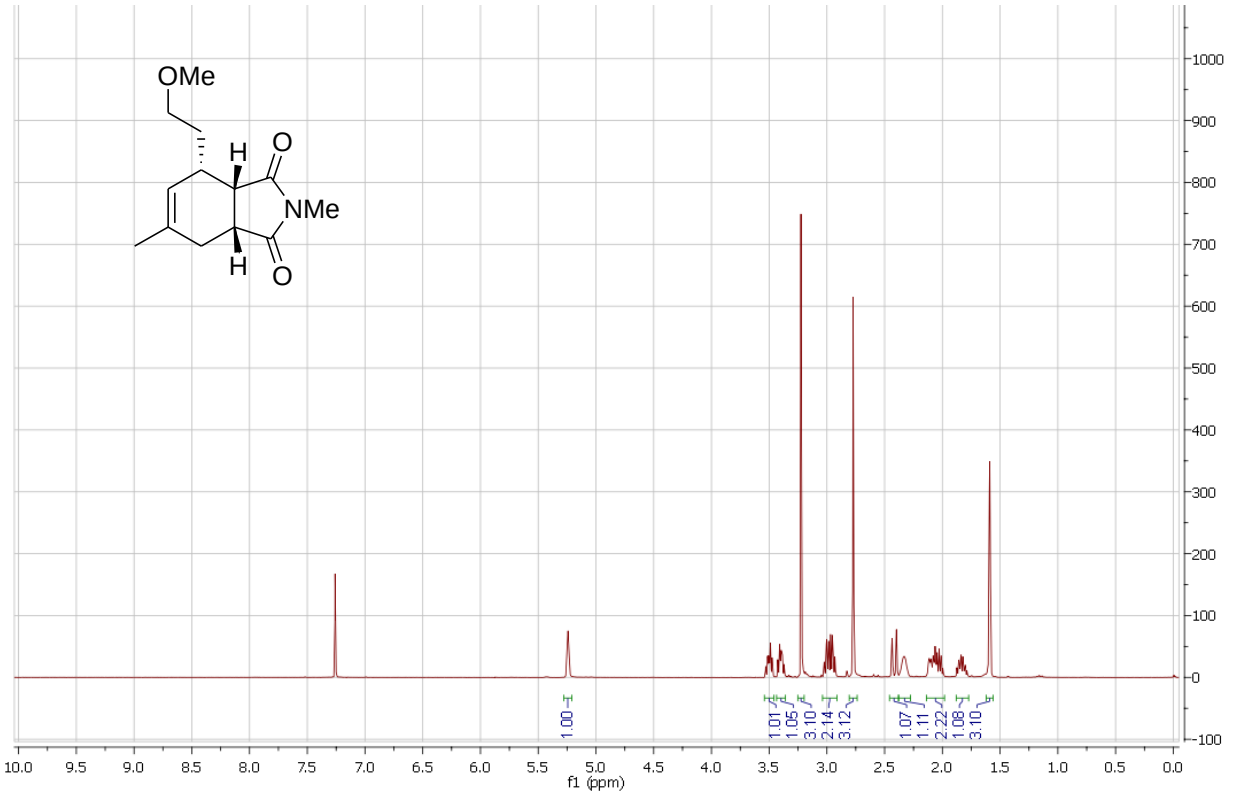


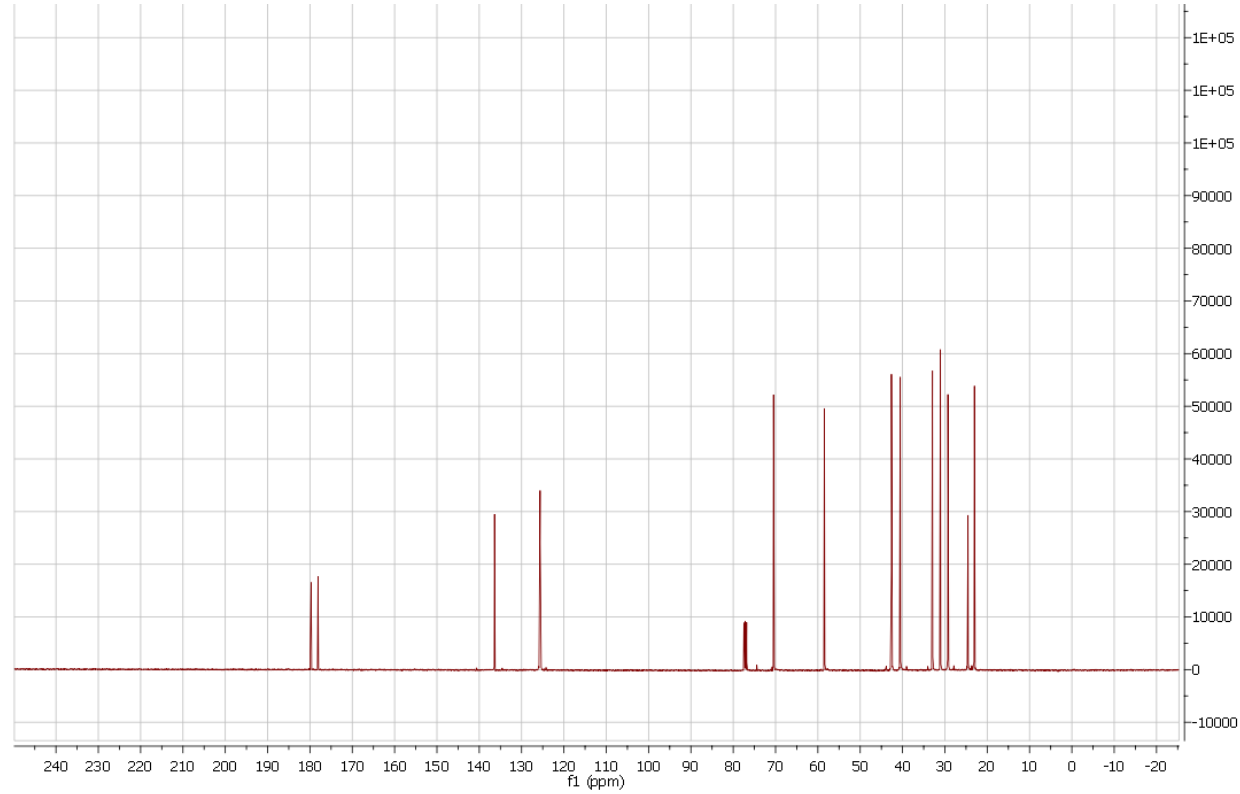
9b



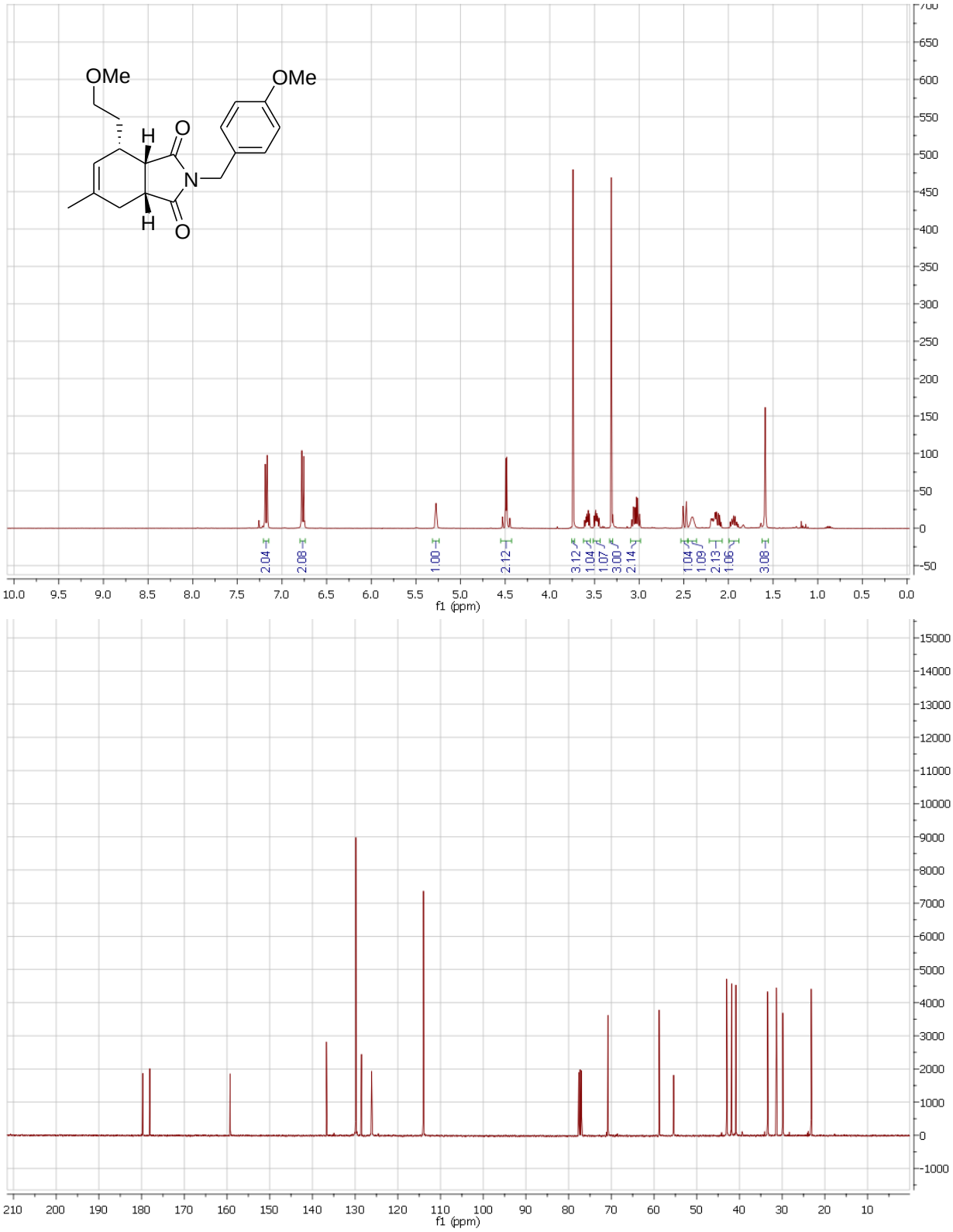


10a

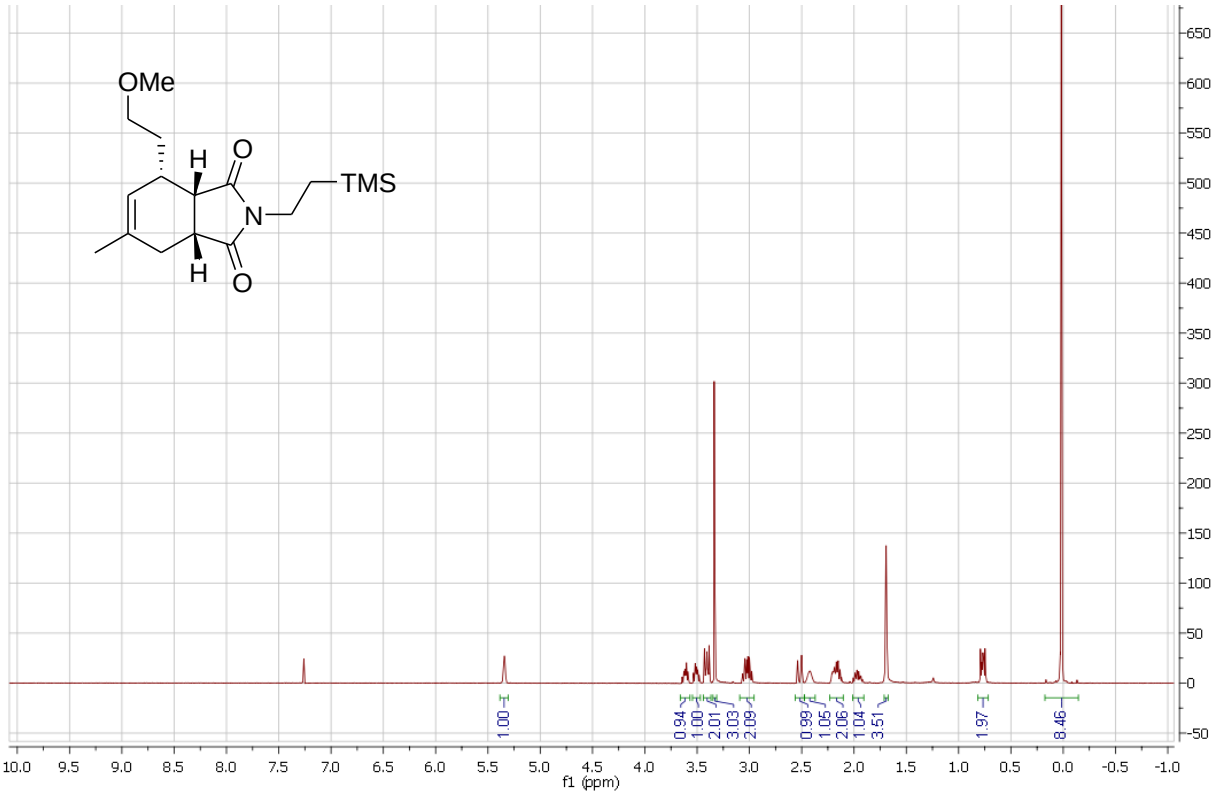

OMe
H
O
NMe
H
O
1.00
1.01
1.05
3.10
2.14
3.12
1.07
1.11
2.22
1.08
3.10
f1 (ppm)

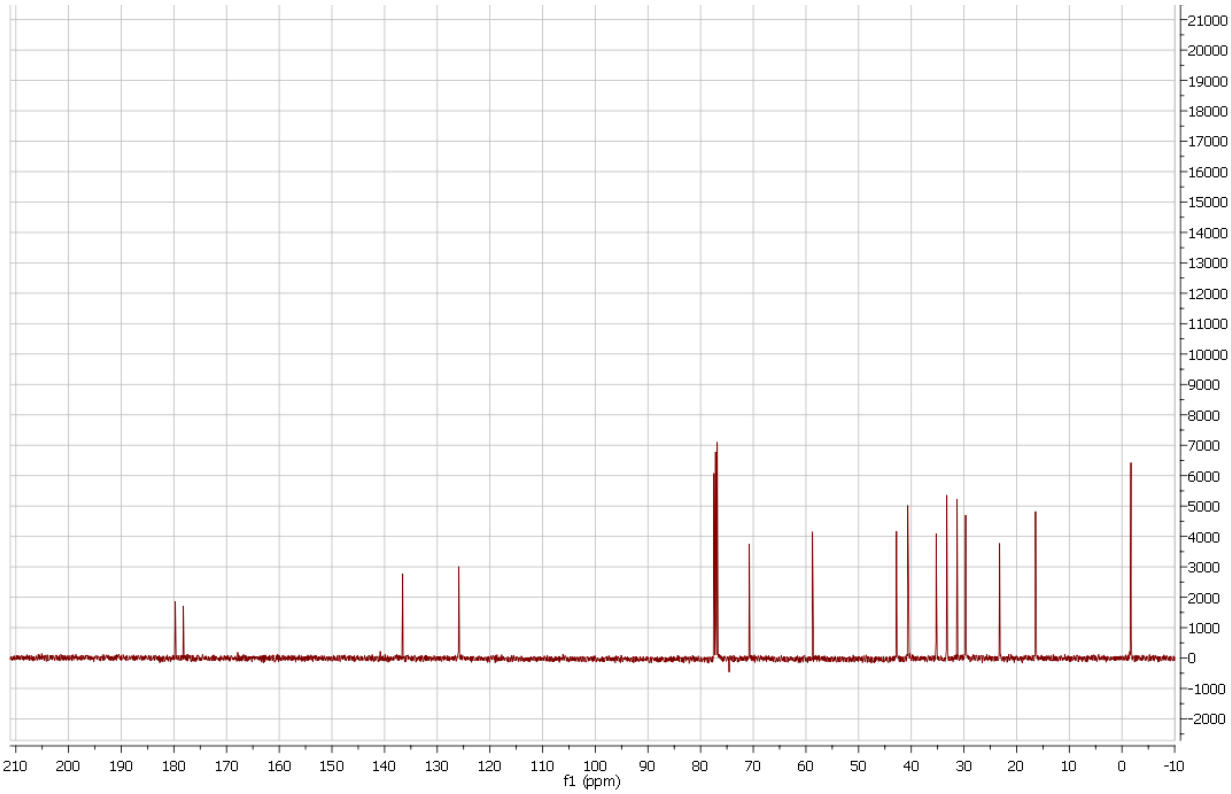

f1 (ppm)

10b

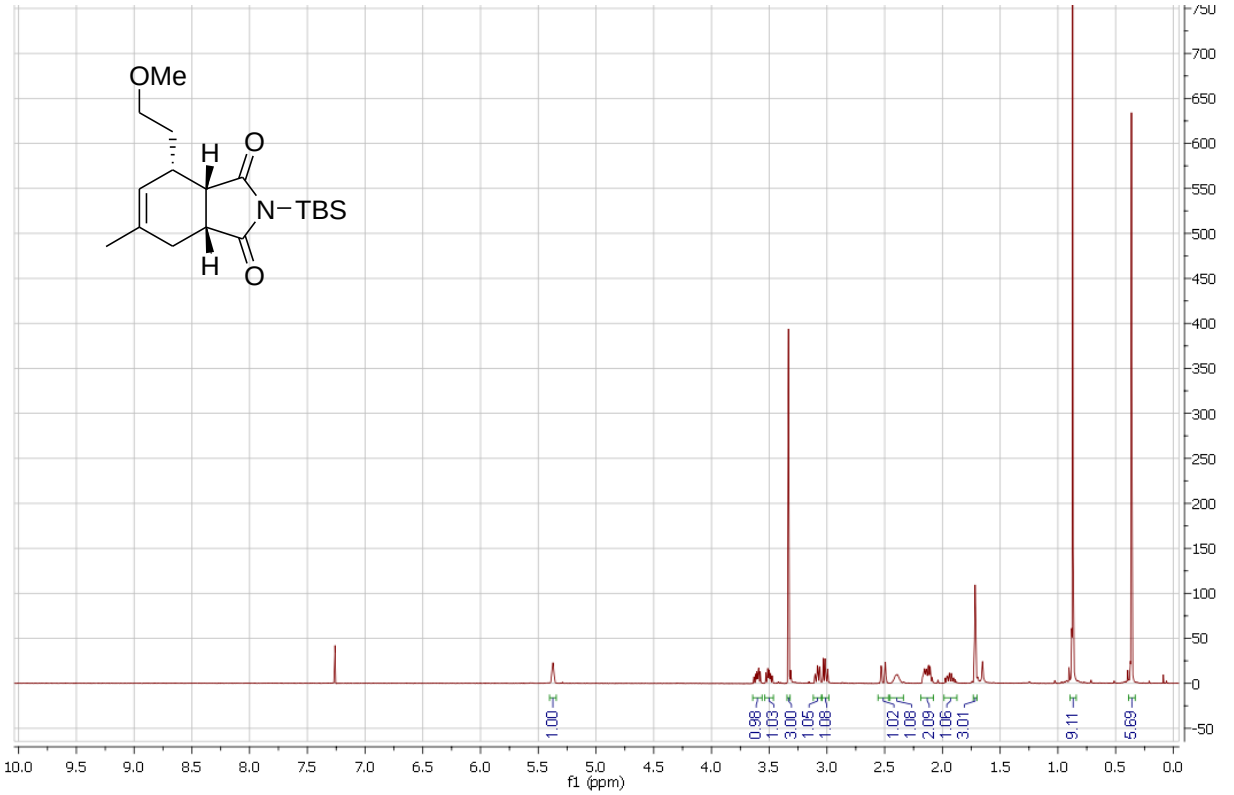

OMe
OMe
H
O
N
H
O
2.04
2.08
1.00
2.12
3.12
1.04
1.07
3.00
2.14
1.04
1.09
2.13
1.06
3.08
f1 (ppm)
f1 (ppm)

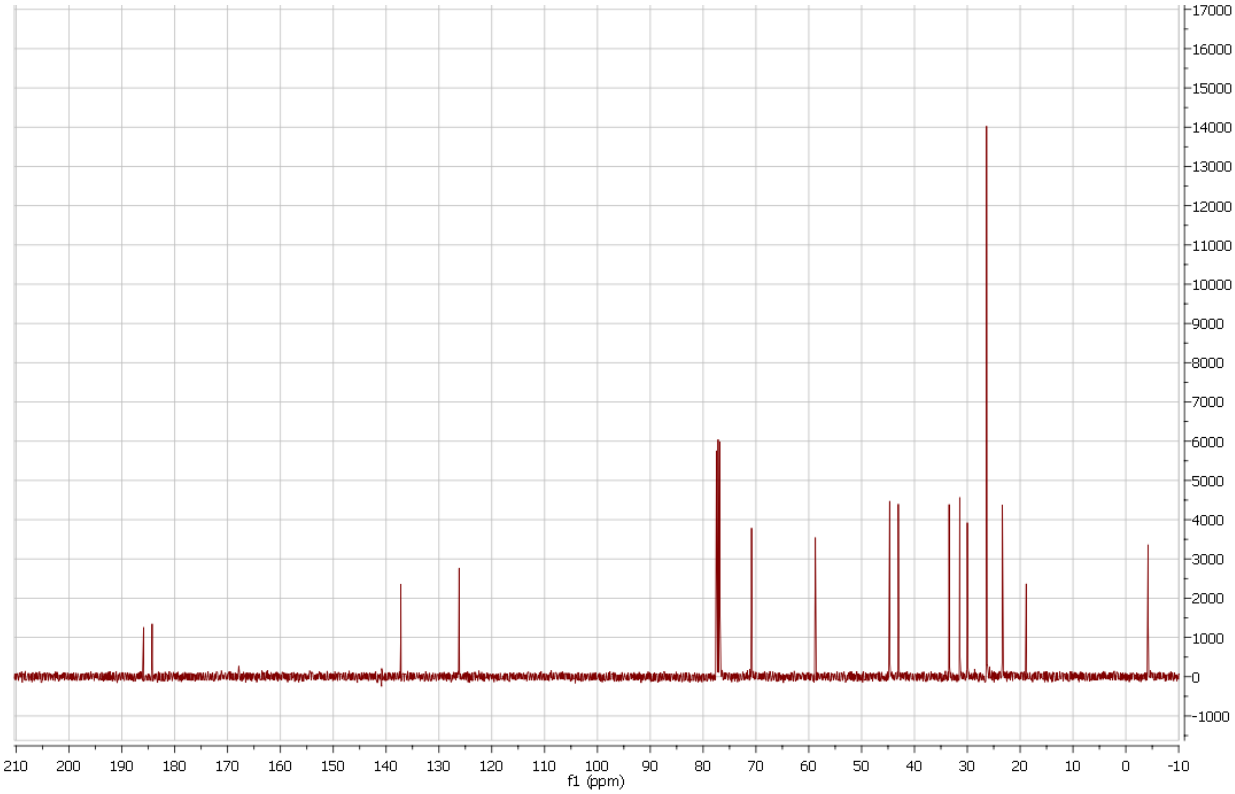
10c


OMe
H
O
TMS
N
H
O
1.00
0.94
1.00
2.01
3.03
2.09
0.99
1.05
2.06
1.04
3.51
1.97
8.46
f1 (ppm)

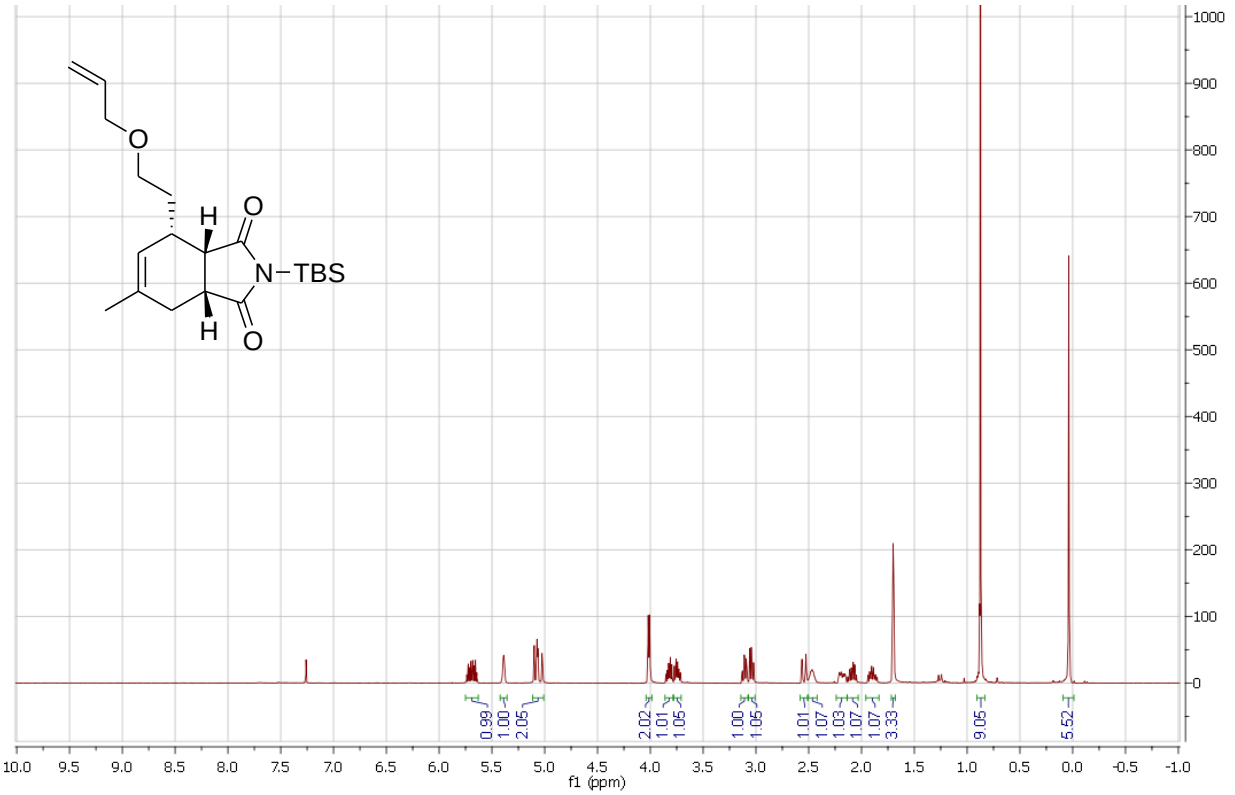

f1 (ppm)

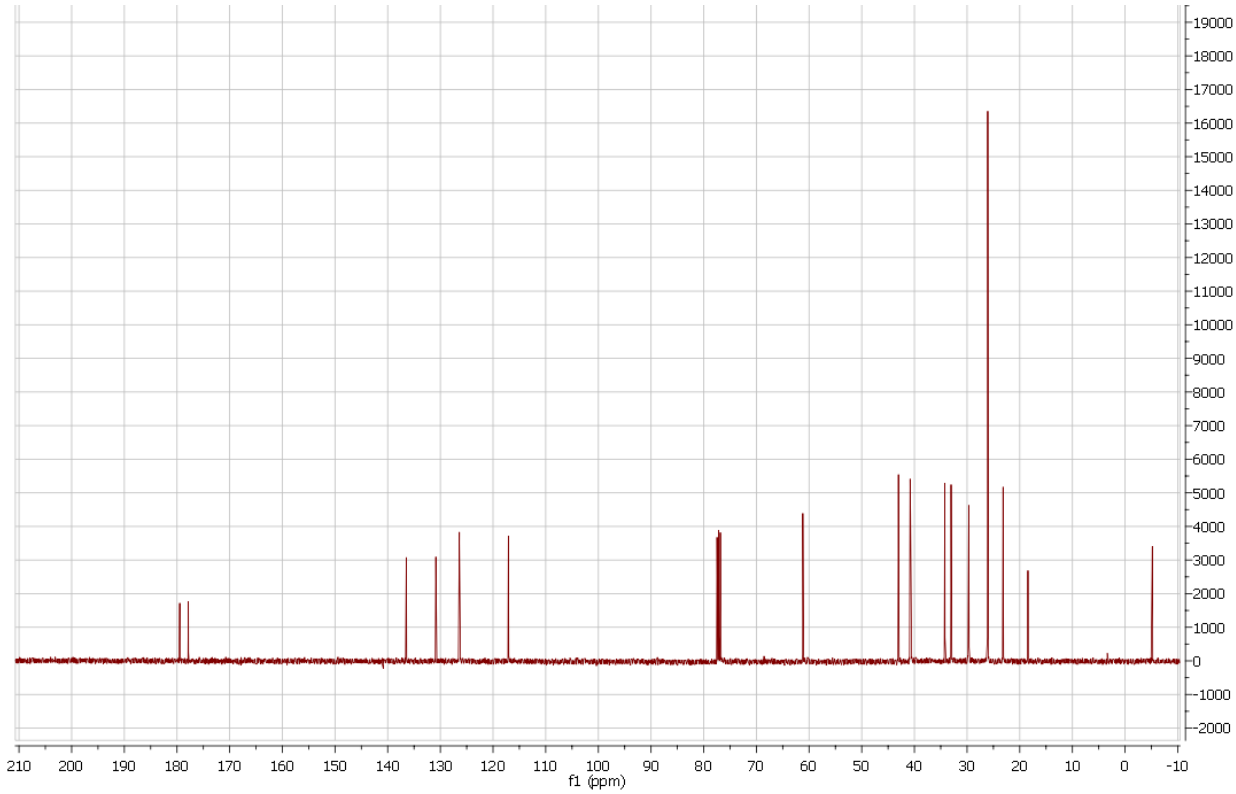
10d


OMe
H
O
N−TBS
H
O
1.00
0.98
1.03
3.00
1.05
1.08
1.02
1.08
2.09
1.06
3.01
9.11
5.69
f1 (ppm)

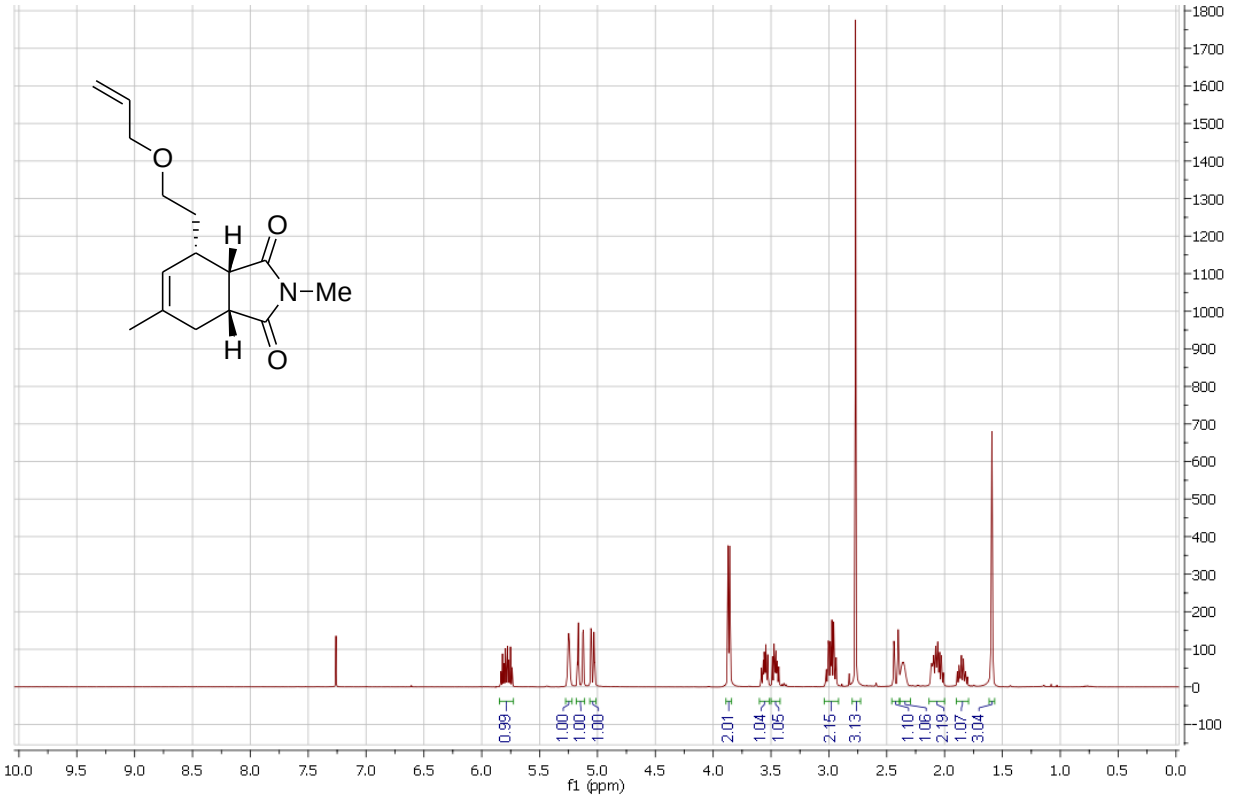

f1 (ppm)

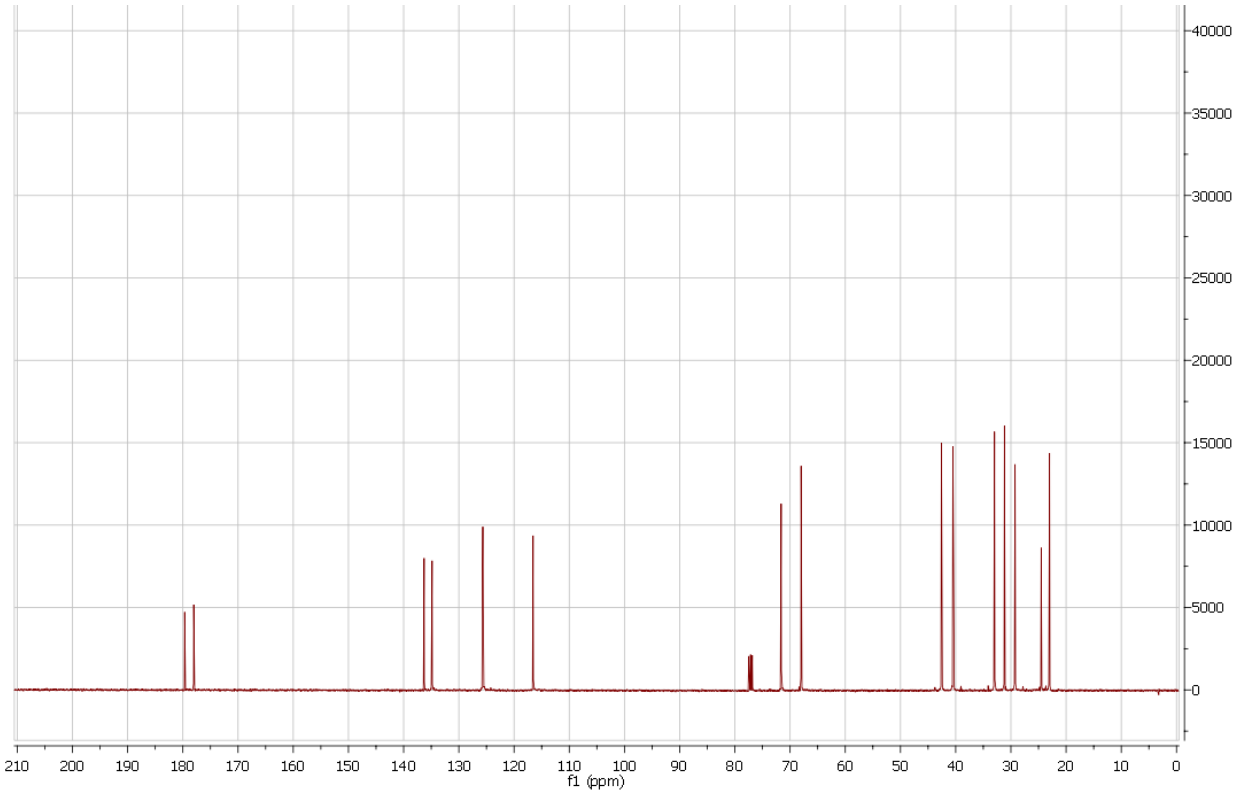
10e


O
H
O
N−TBS
H
O
0.99
1.00
2.05
2.02
1.01
1.06
1.00
1.05
1.01
1.07
1.03
1.07
1.07
3.33
9.05
5.52
f1 (ppm)

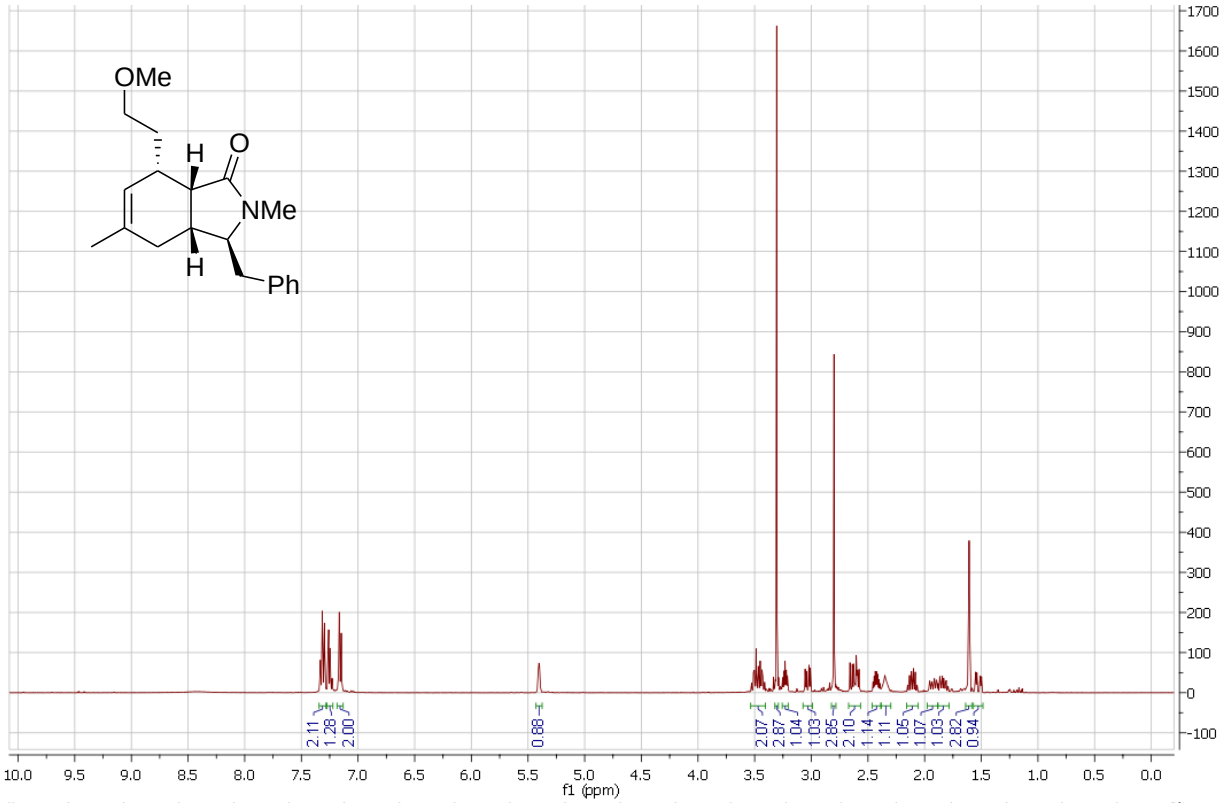

f1 (ppm)

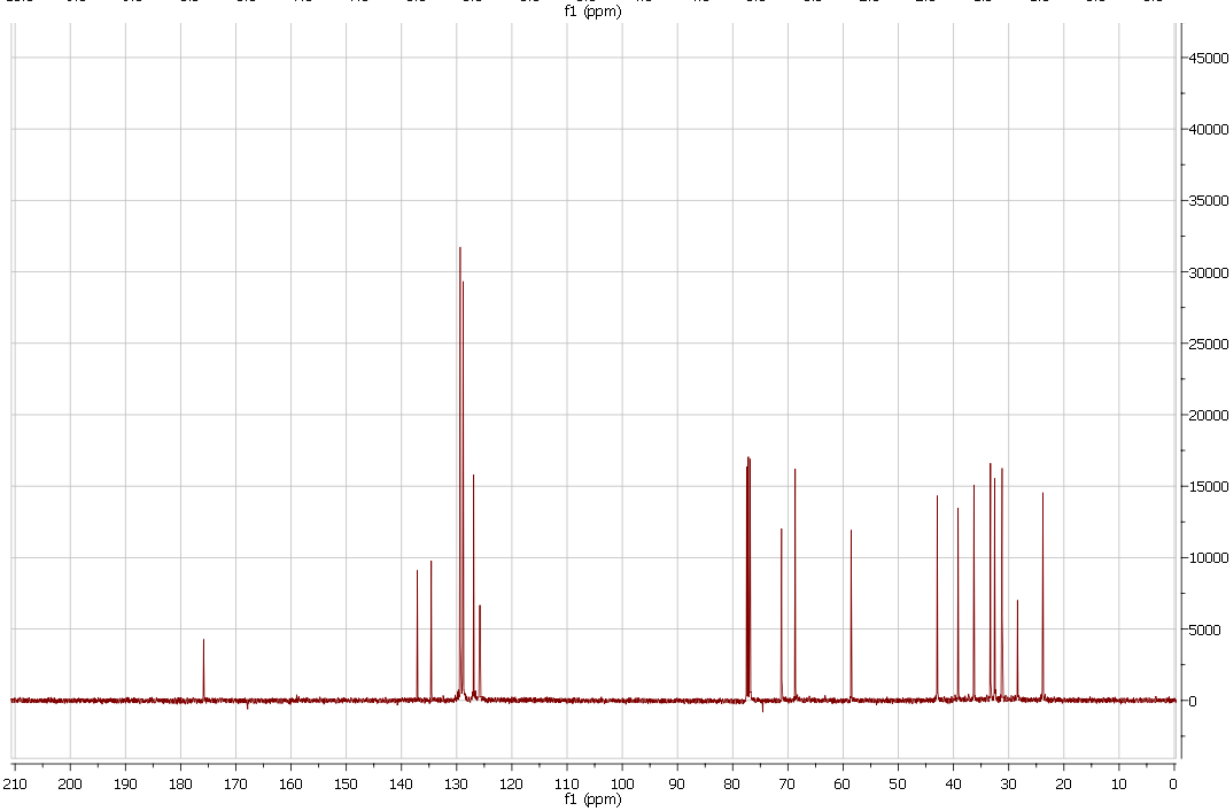
10f


O
H
O
N−Me
H
O
0.99
1.00
1.00
1.00
2.01
1.04
1.05
2.15
3.13
1.10
1.06
2.19
1.07
3.04
f1 (ppm)

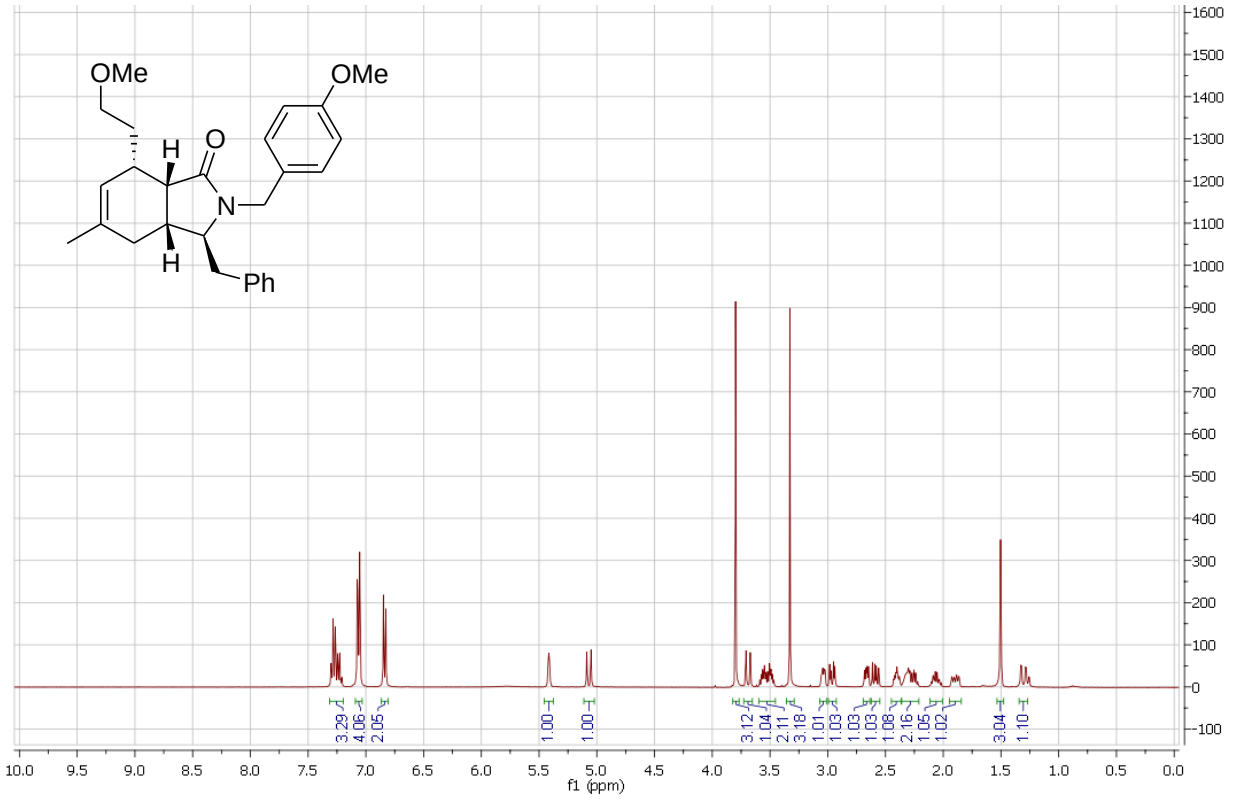

f1 (ppm)

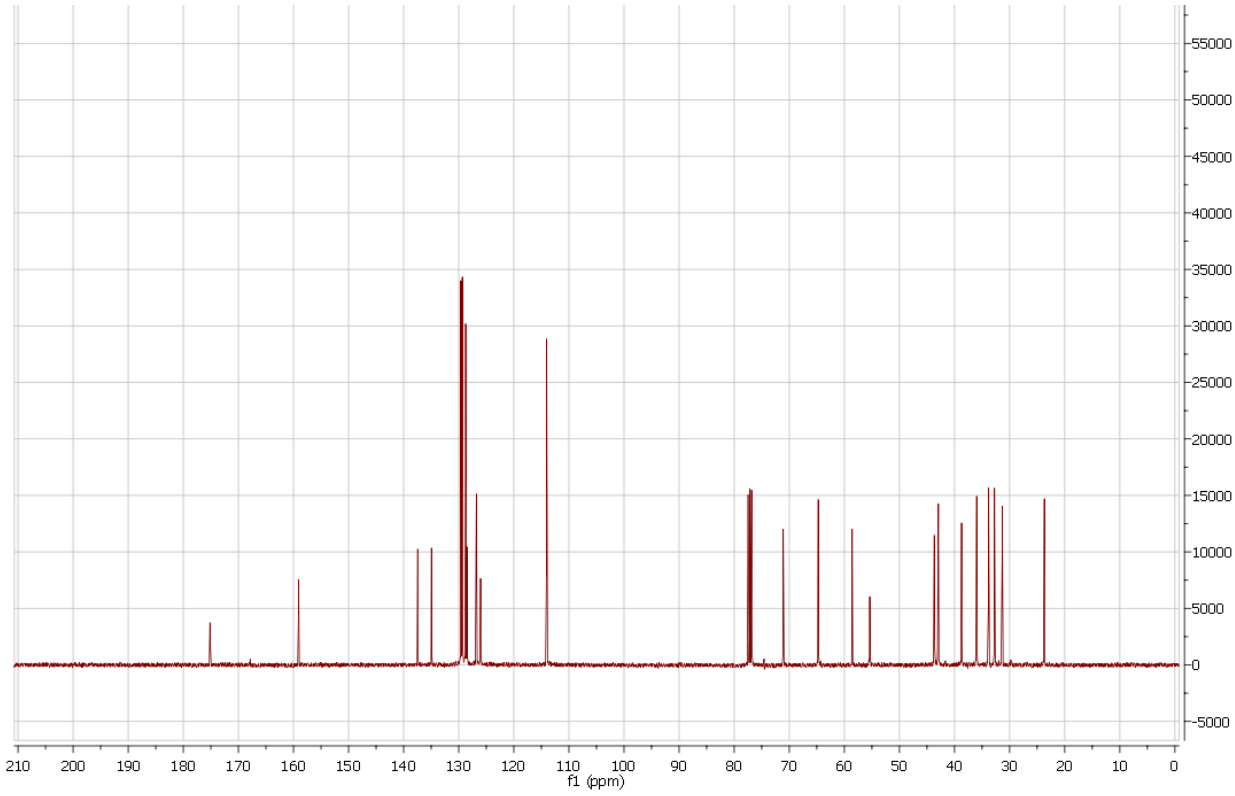
11a


OMe
H
O
NMe
H
Ph
2.11
1.28
2.00
0.88
2.07
2.87
1.04
1.03
2.85
2.10
1.14
1.11
1.05
1.07
1.03
2.82
0.94
f1 (ppm)

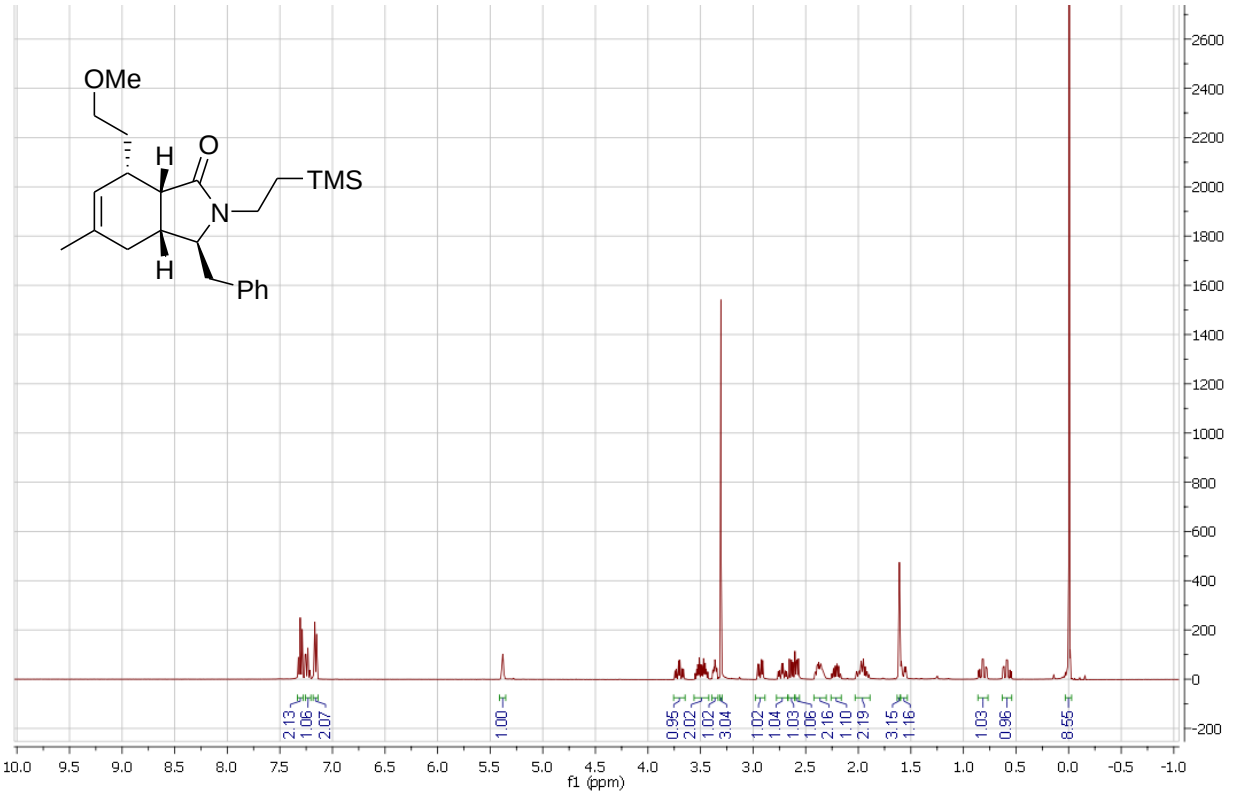

f1 (ppm)

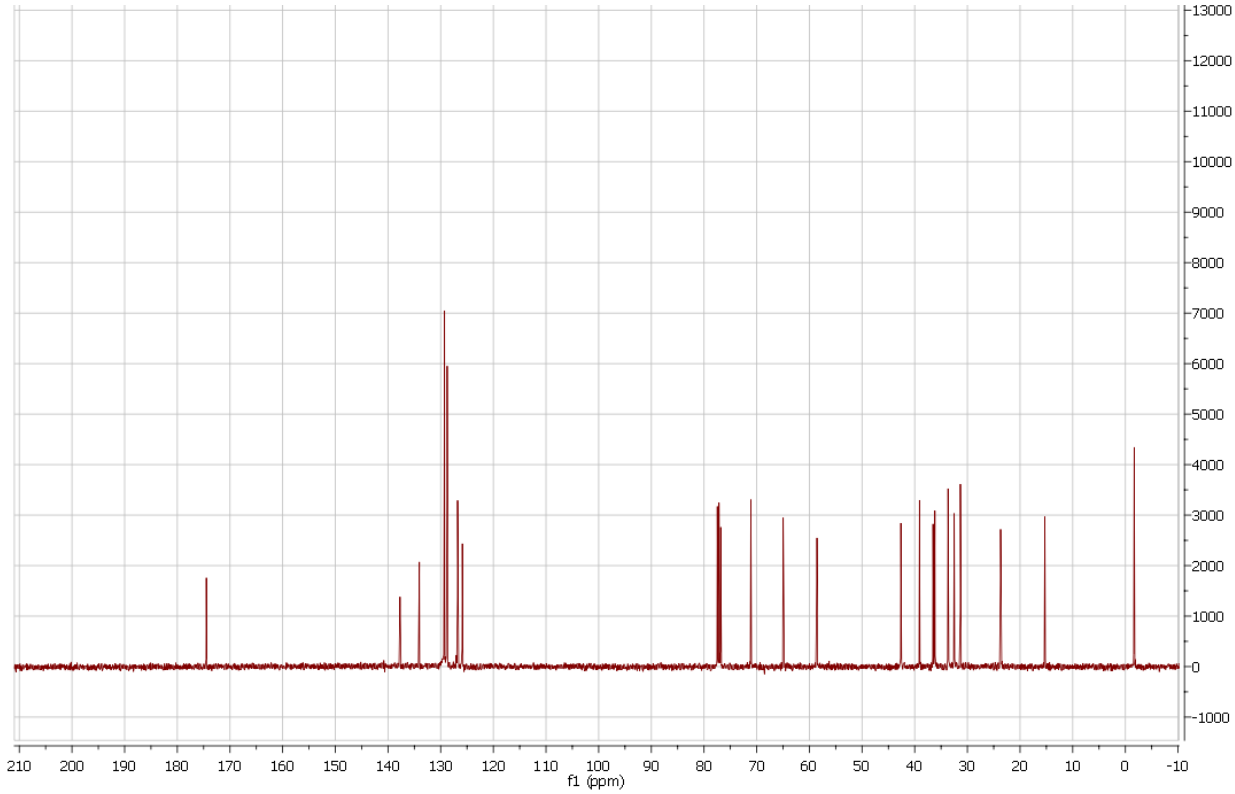
11b


OMe
OMe
H
O
N
H
Ph
3.29
4.06
2.05
1.00
1.00
3.12
1.04
2.11
3.18
1.01
1.03
1.03
1.08
2.16
1.05
1.02
3.04
1.10
f1 (ppm)

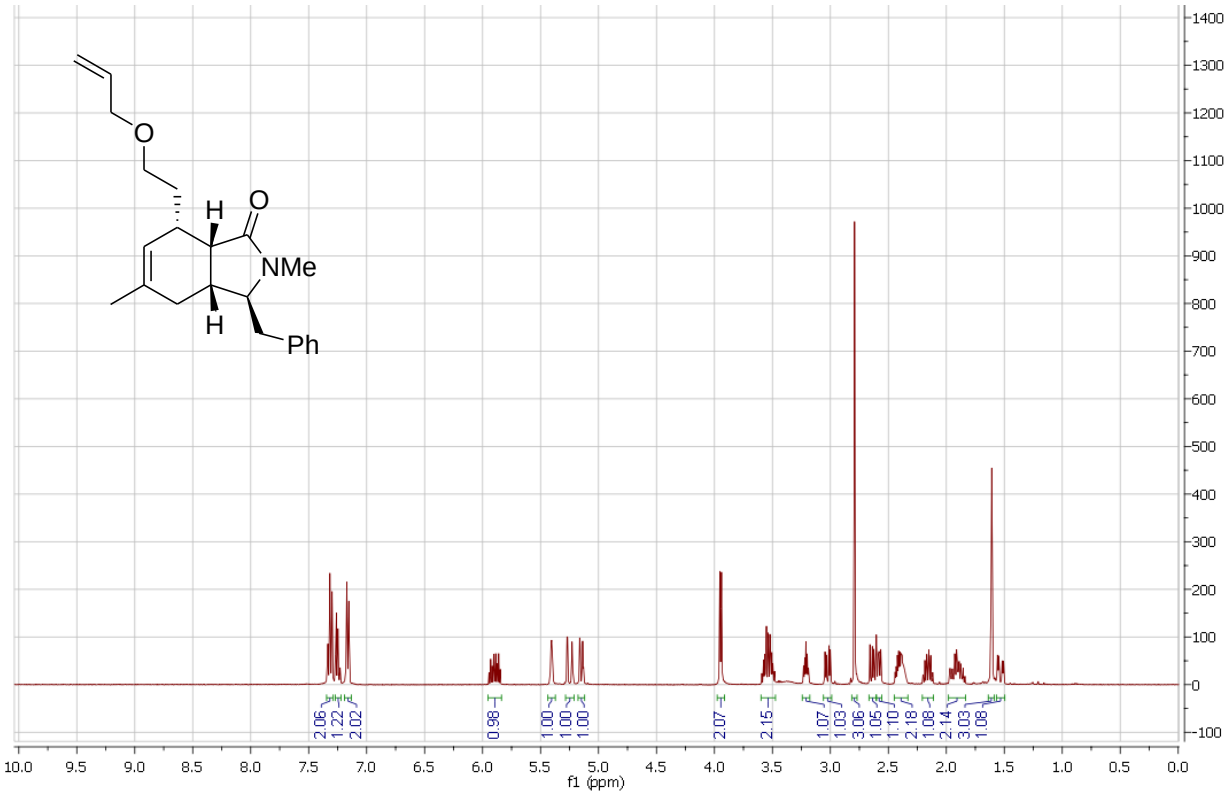

f1 (ppm)

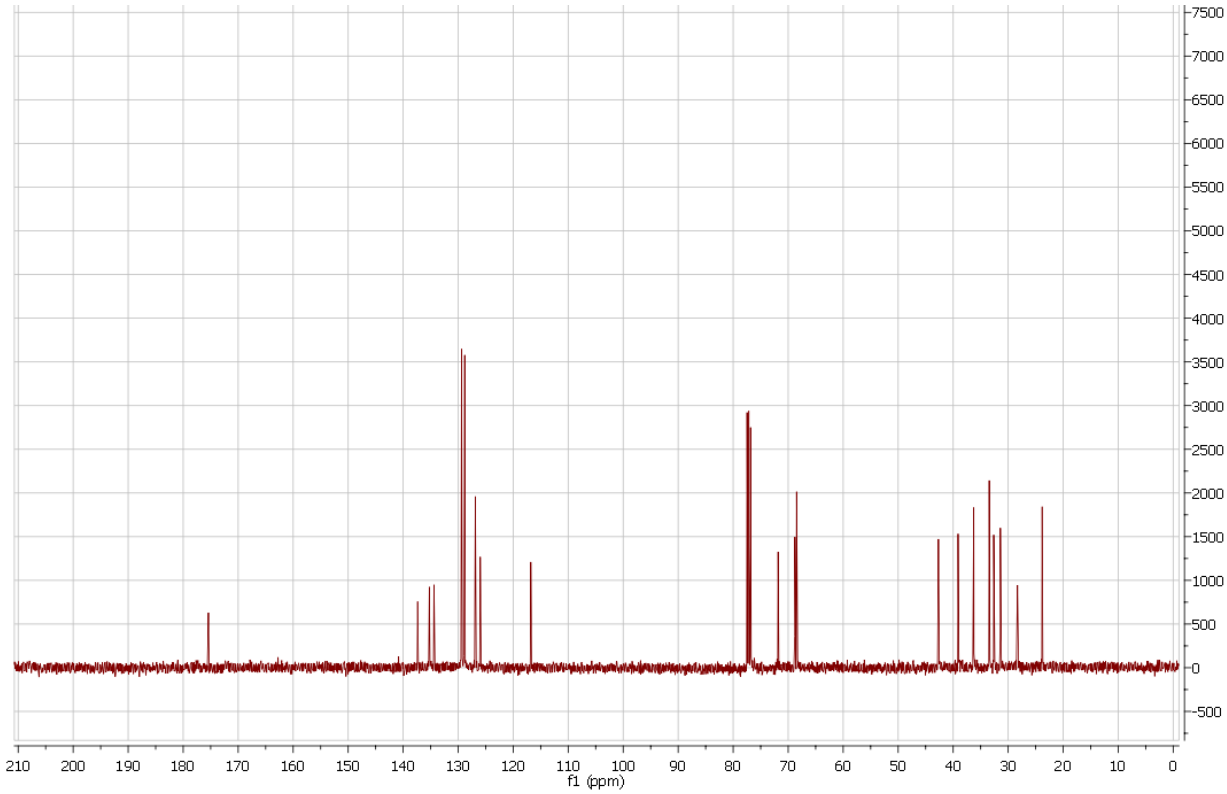
11c



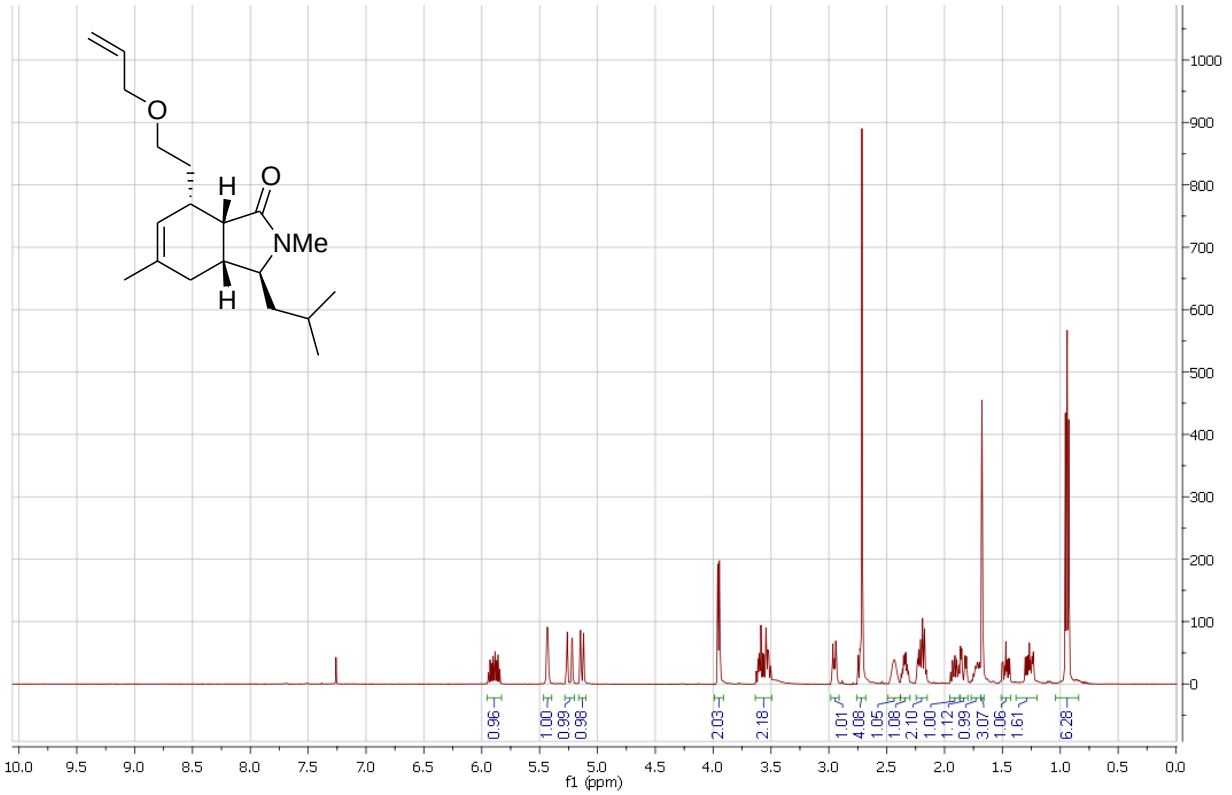


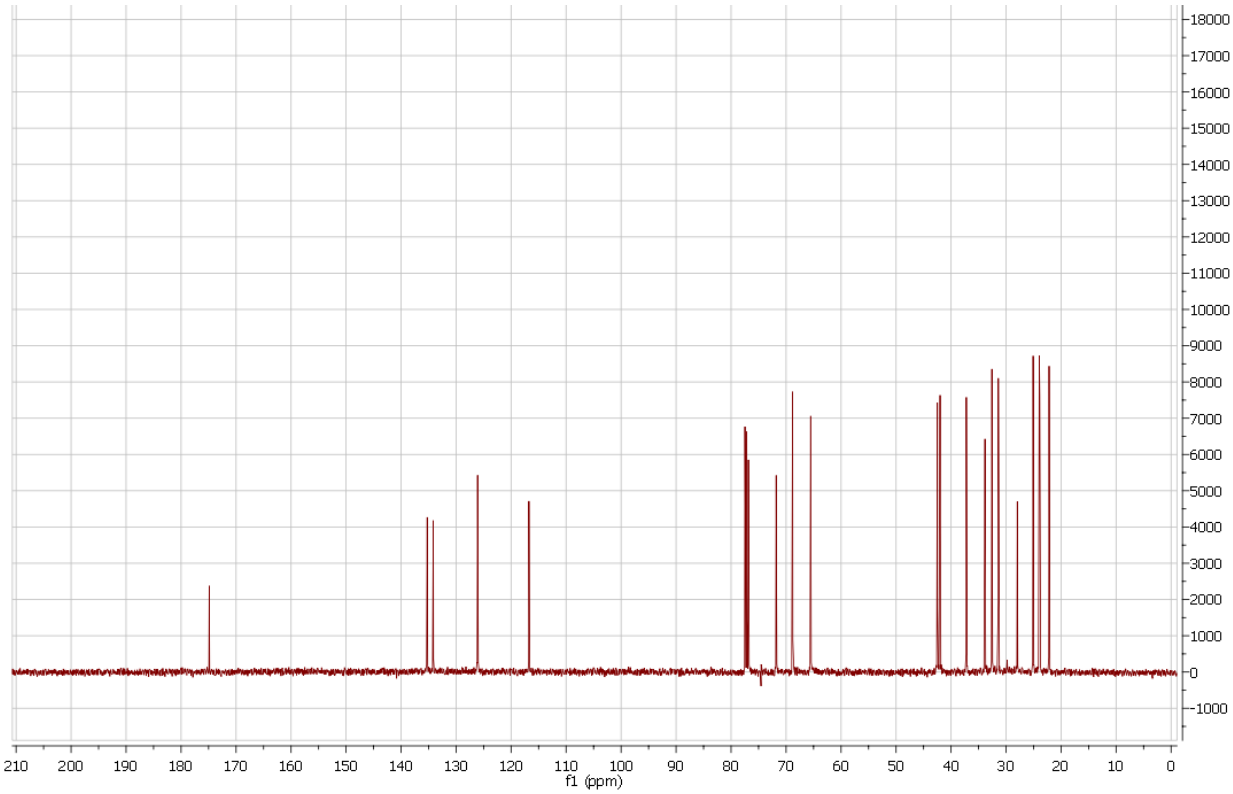
11d



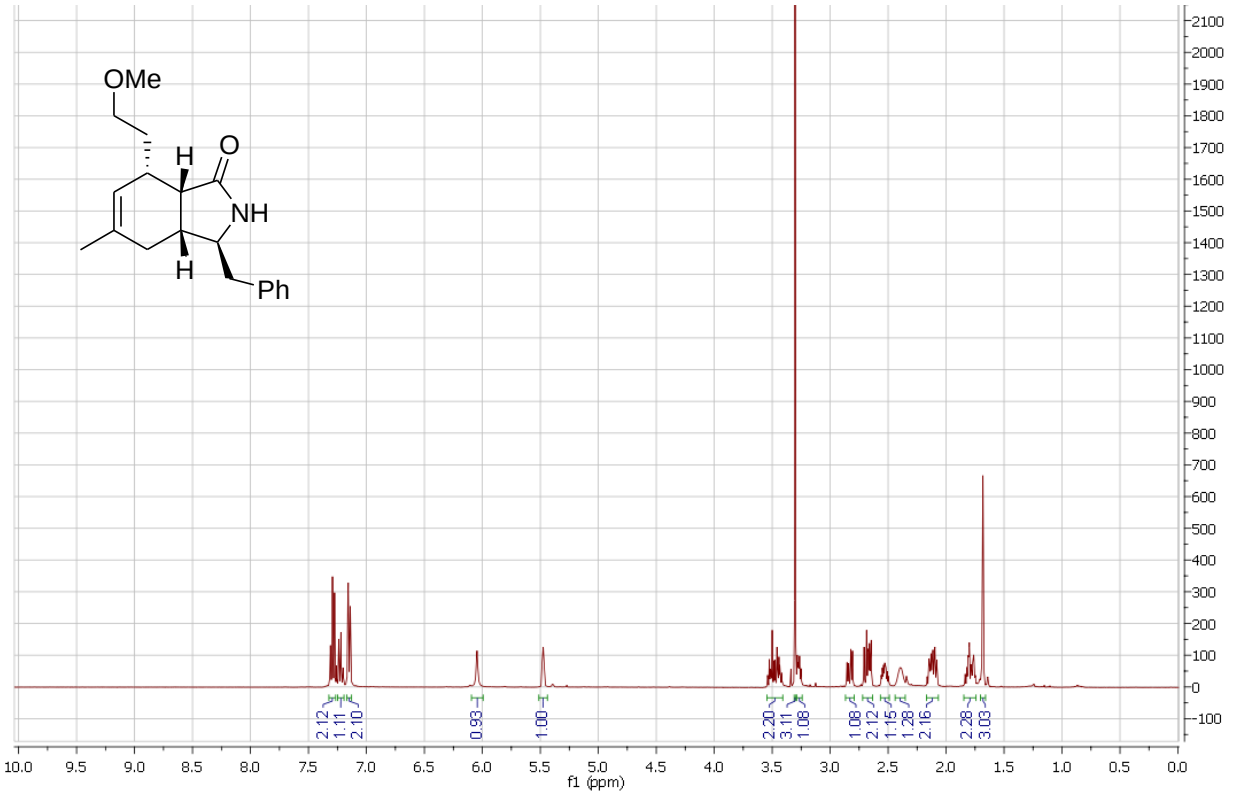


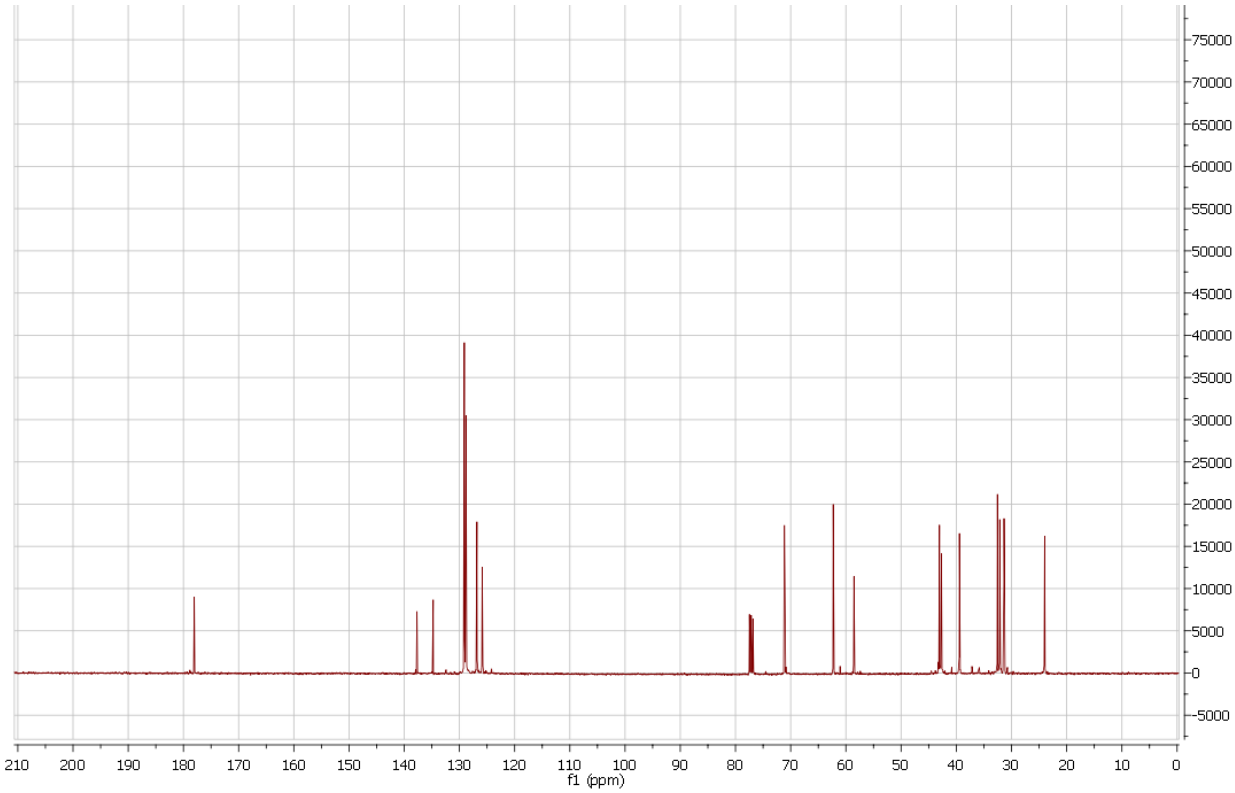
11e


O
H
O
NMe
H
0.96
1.00
0.99
0.98
2.03
2.18
1.01
4.08
1.05
1.08
2.10
1.00
1.12
0.99
3.07
1.06
1.61
6.28
f1 (ppm)

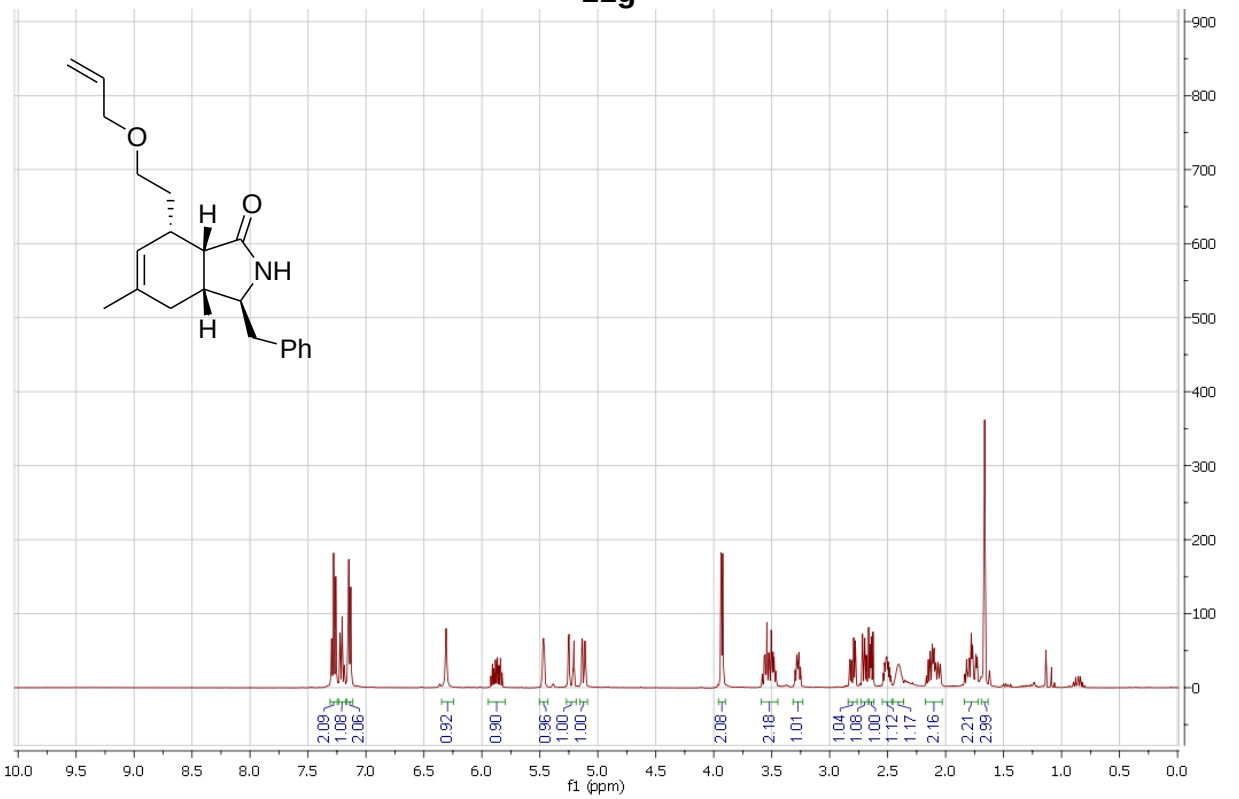

f1 (ppm)

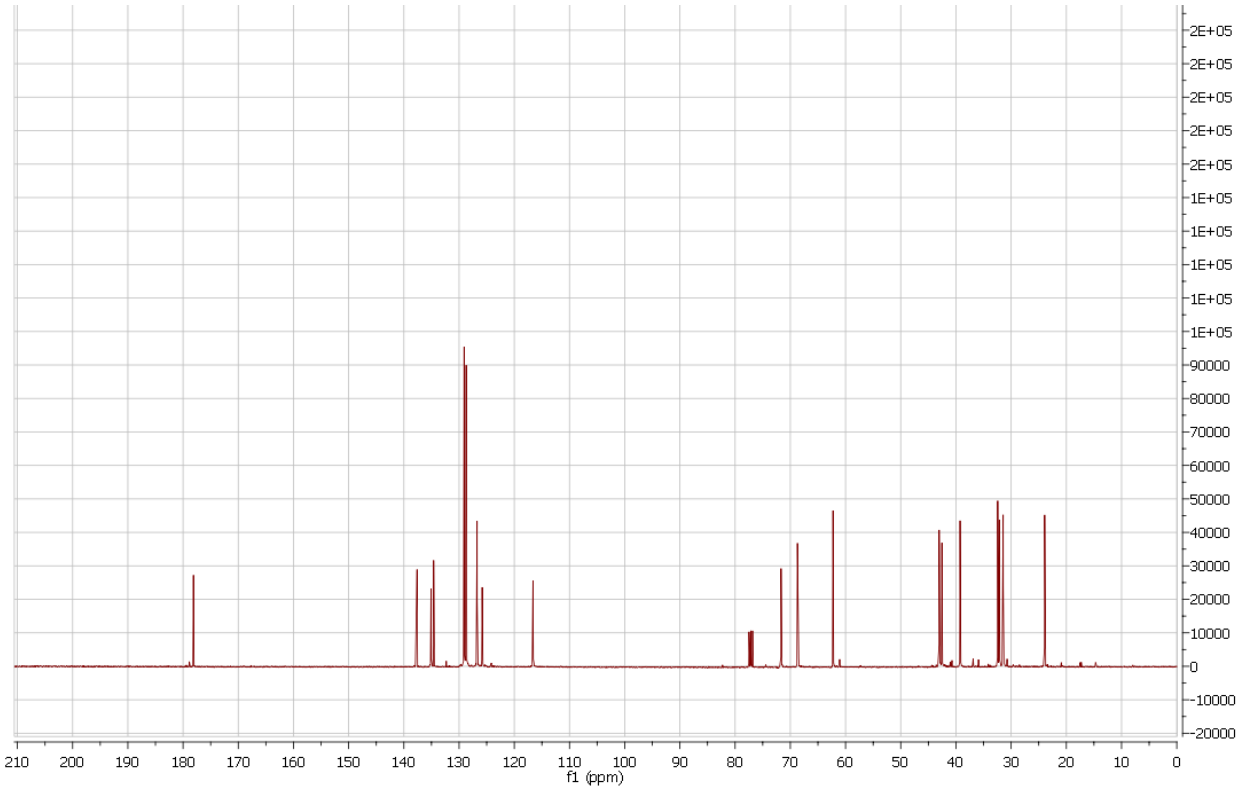
11f


OMe
H
O
NH
H
Ph
2.12
1.11
2.10
0.93
1.00
2.20
3.11
1.08
1.08
2.12
1.15
1.28
2.16
2.28
3.03
f1 (ppm)

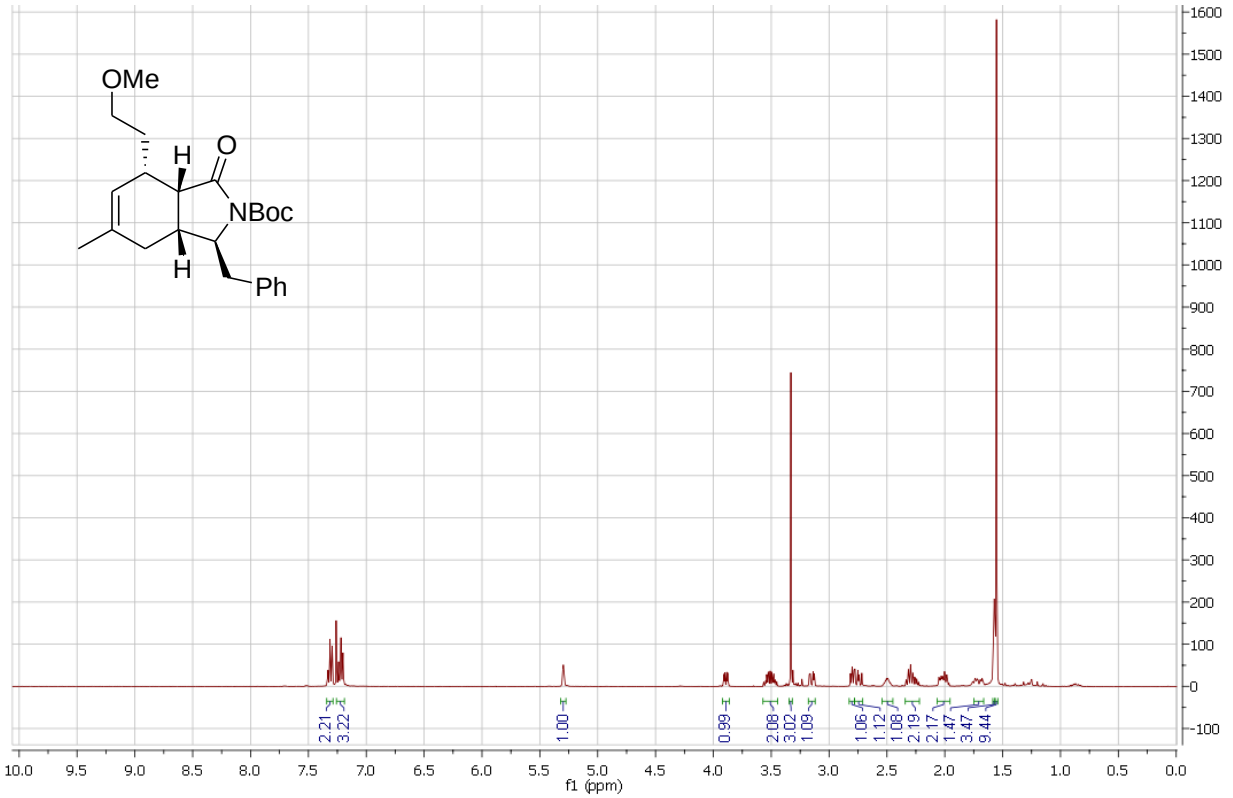

f1 (ppm)

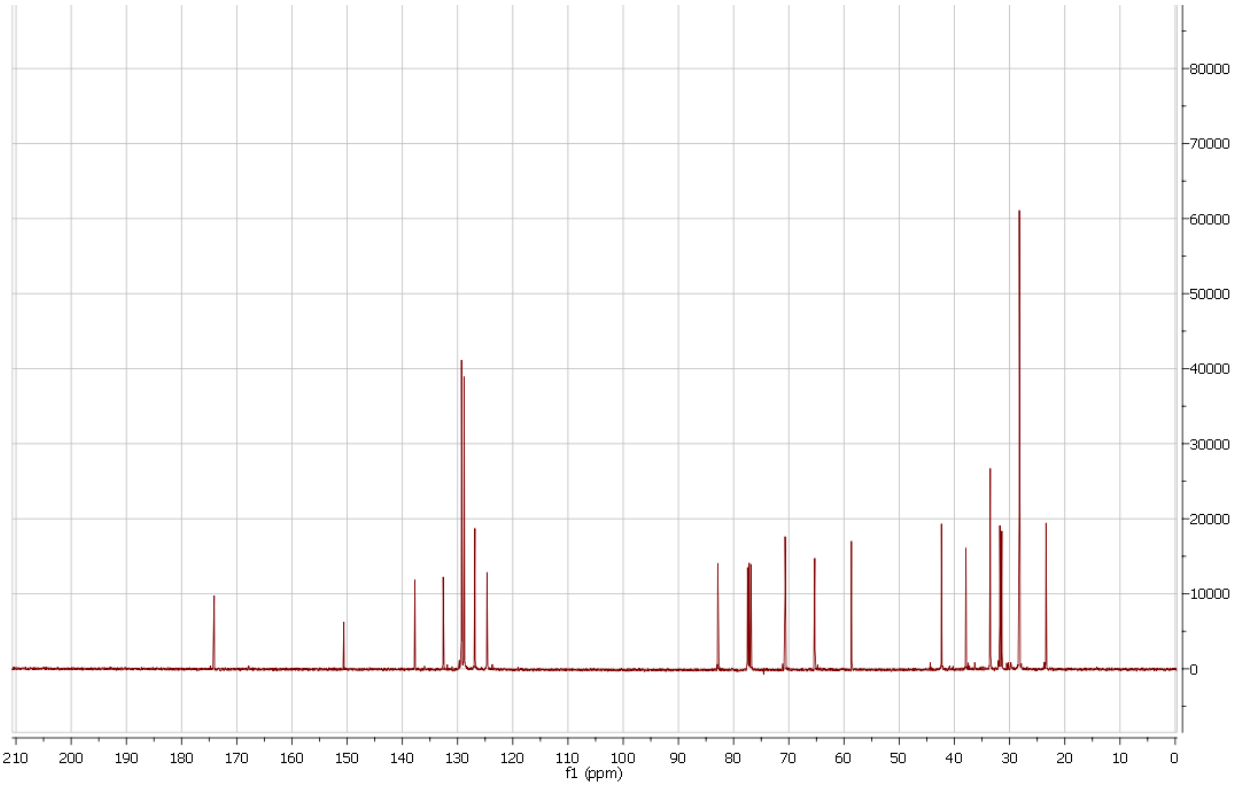
11g


O
H
O
NH
H
Ph
2.09
1.08
2.06
0.92
0.90
0.96
1.00
1.00
2.08
2.18
1.01
1.04
1.08
1.00
1.12
1.17
2.16
2.21
2.99
f1 (ppm)

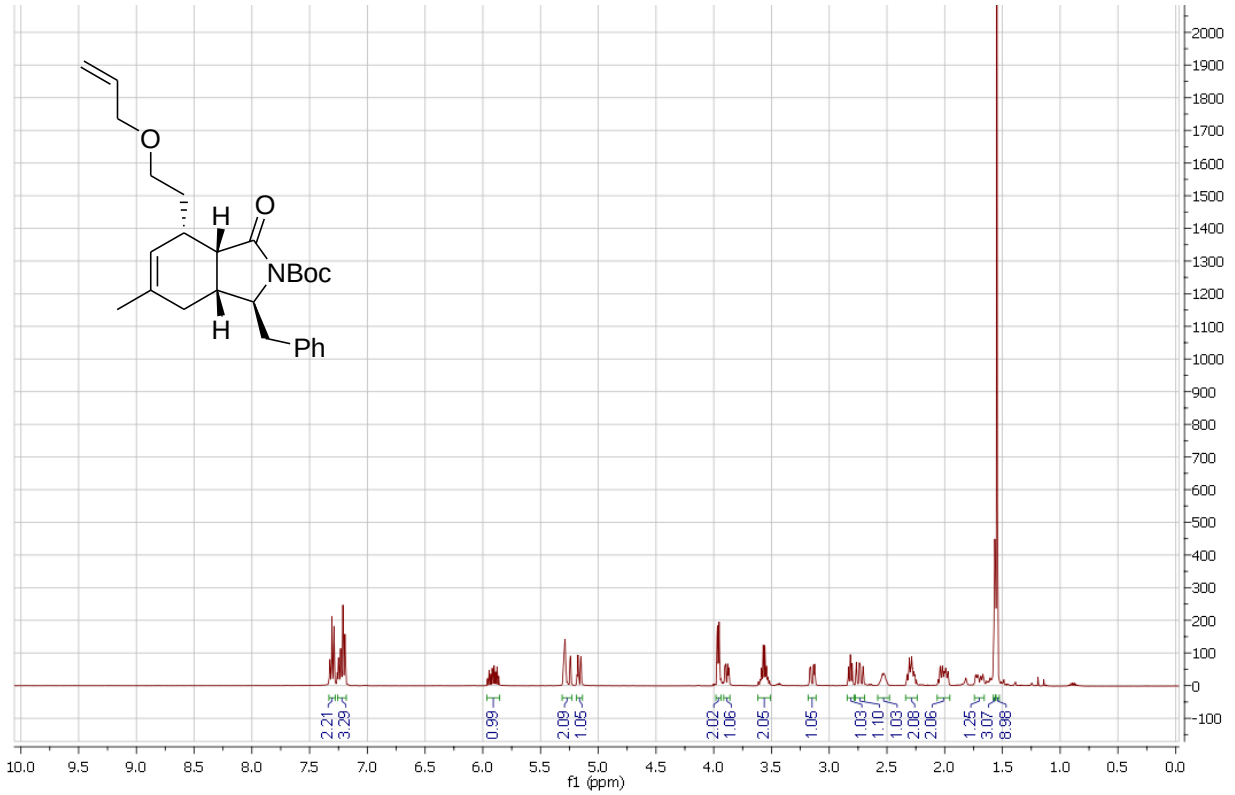

f1 (ppm)

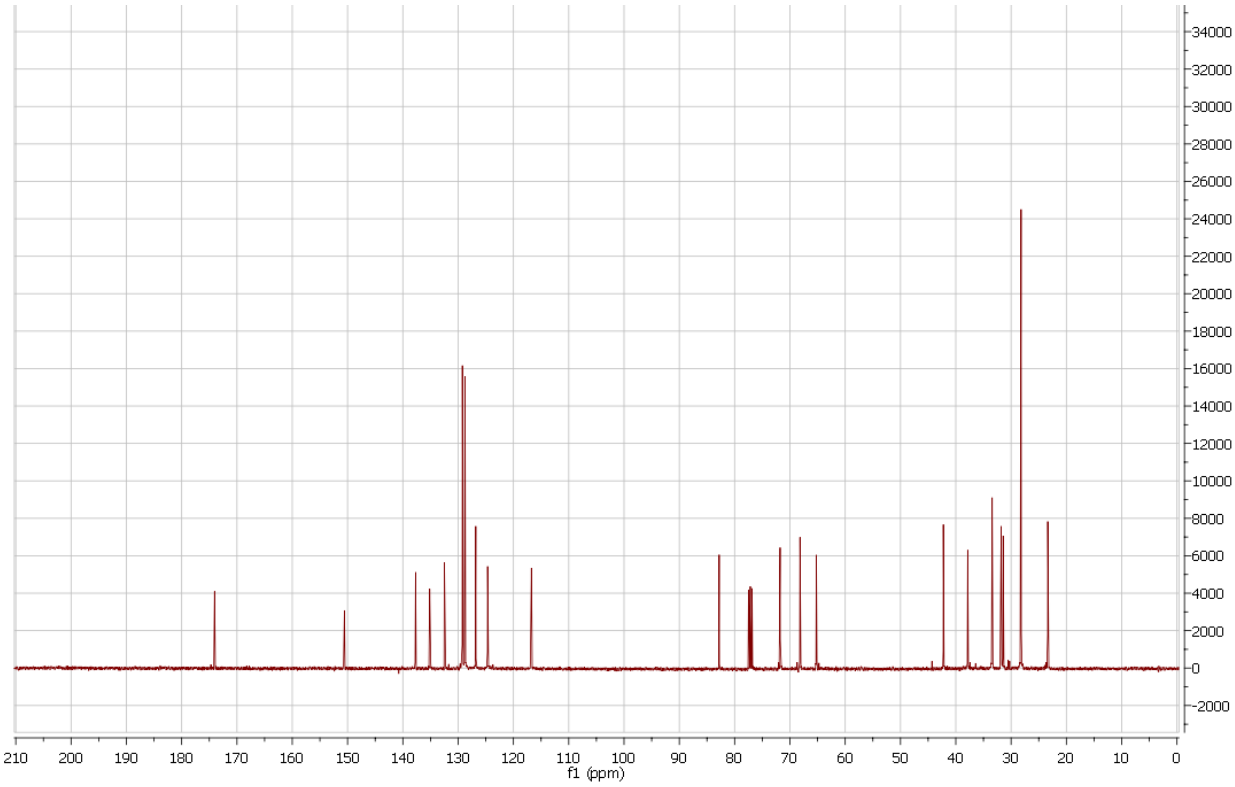
11h


OMe
H
O
NBoc
H
Ph
2.21
3.22
1.00
0.99
2.08
3.02
1.09
1.06
1.12
1.08
2.19
2.17
1.47
3.47
9.44
f1 (ppm)

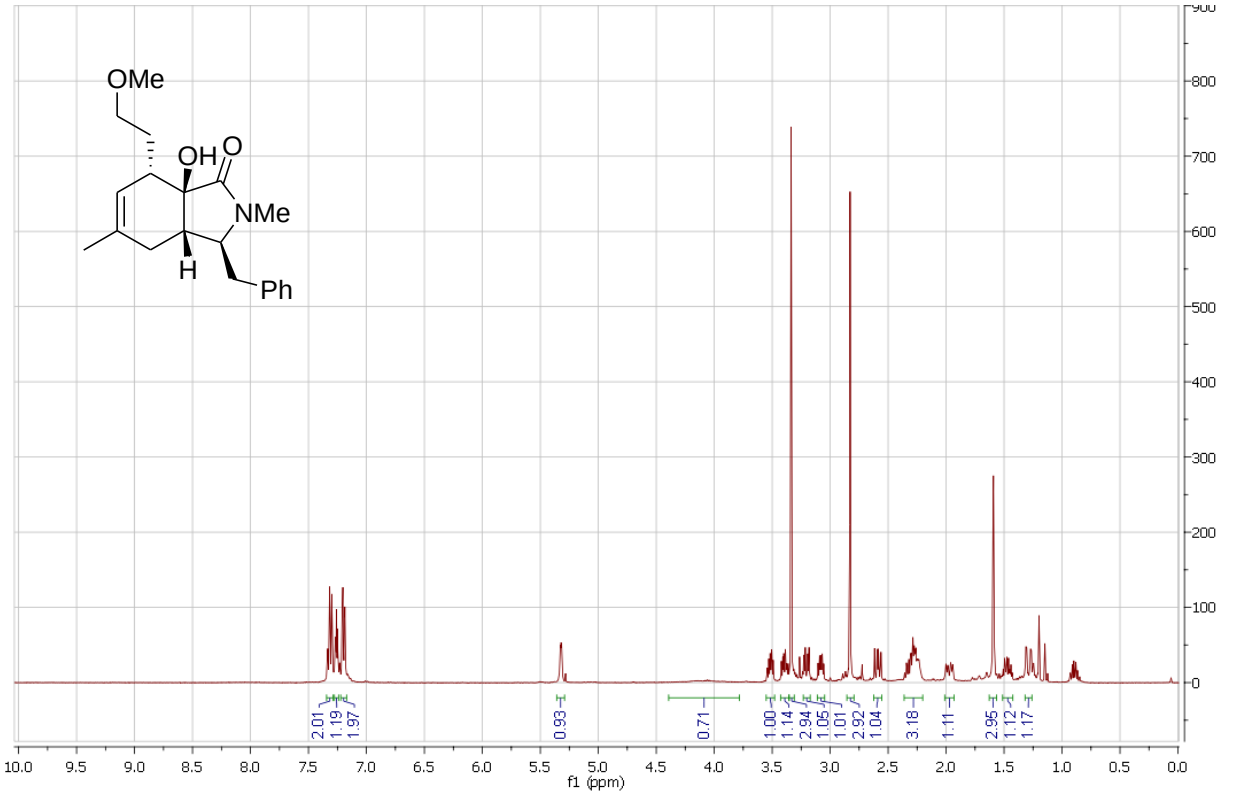

f1 (ppm)

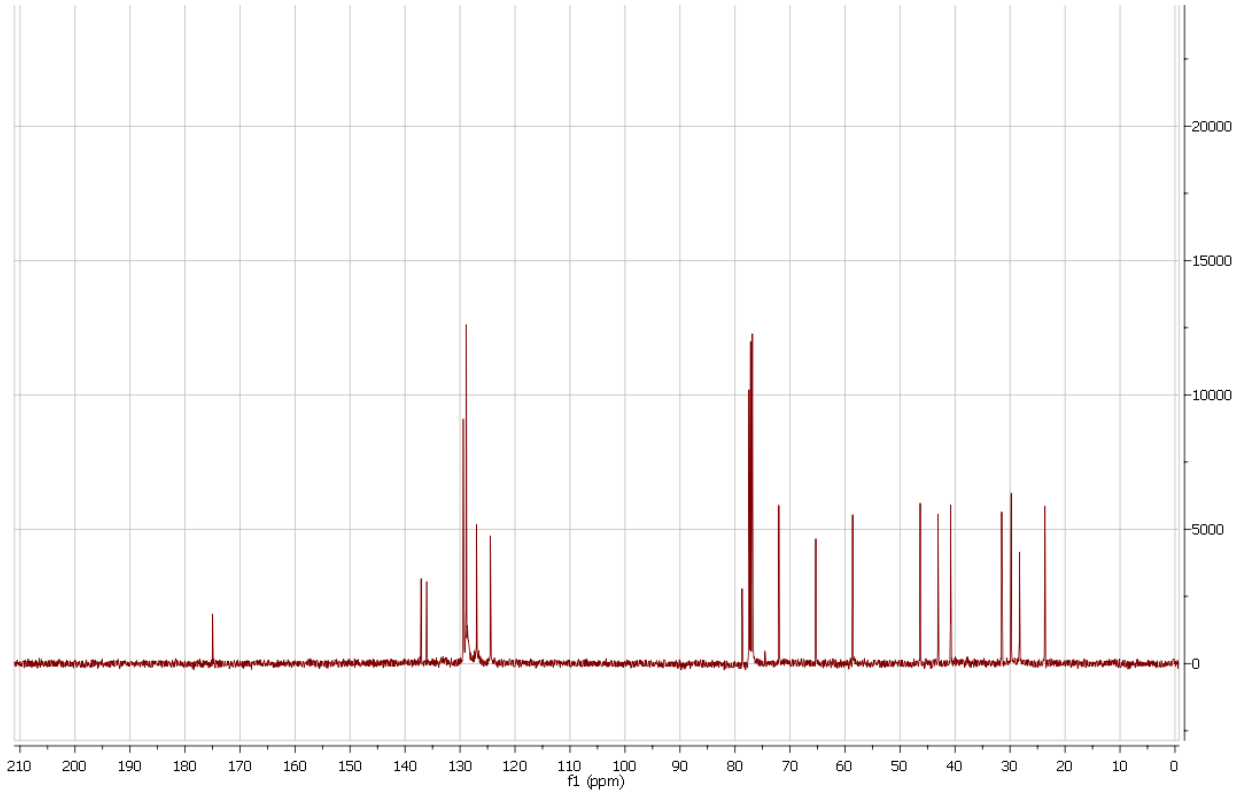
11i


O
H
O
NBoc
H
Ph
2.21
3.29
0.99
2.09
1.05
2.02
1.06
2.05
1.05
1.03
1.10
1.03
2.08
2.06
1.25
3.07
8.98
f1 (ppm)

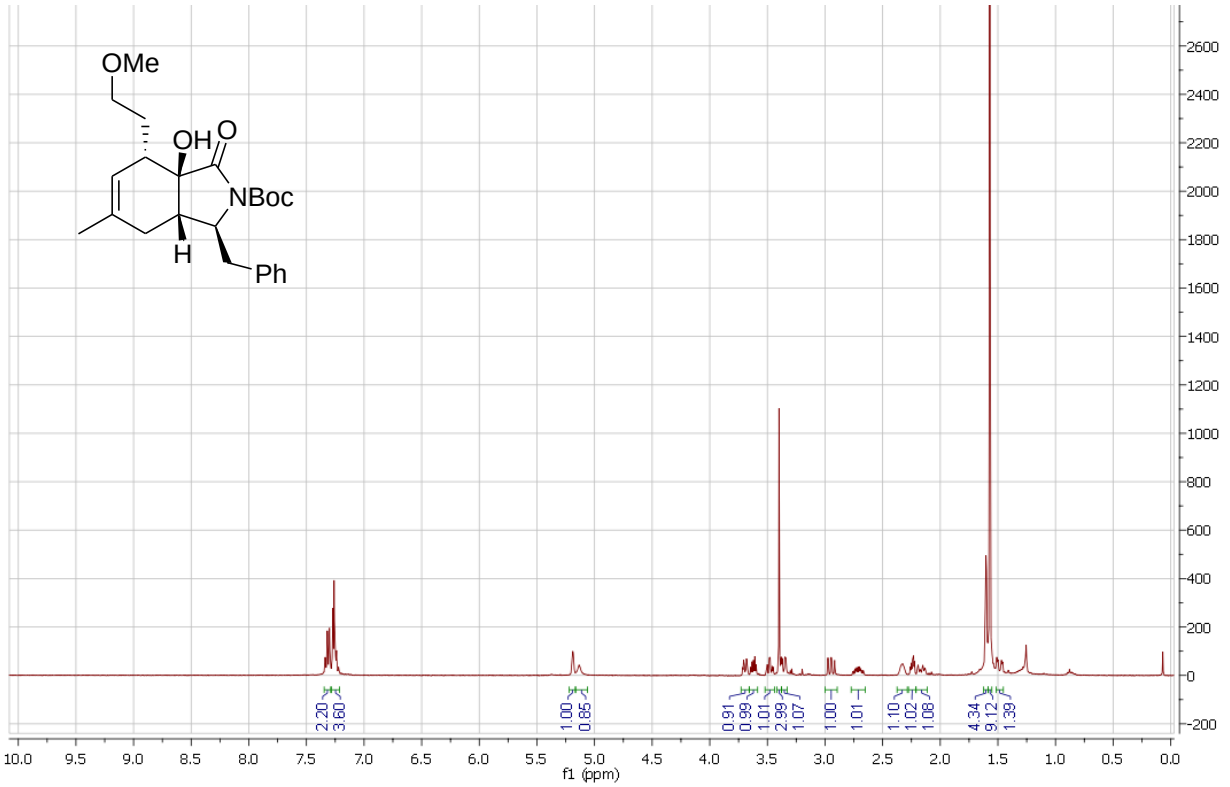

f1 (ppm)

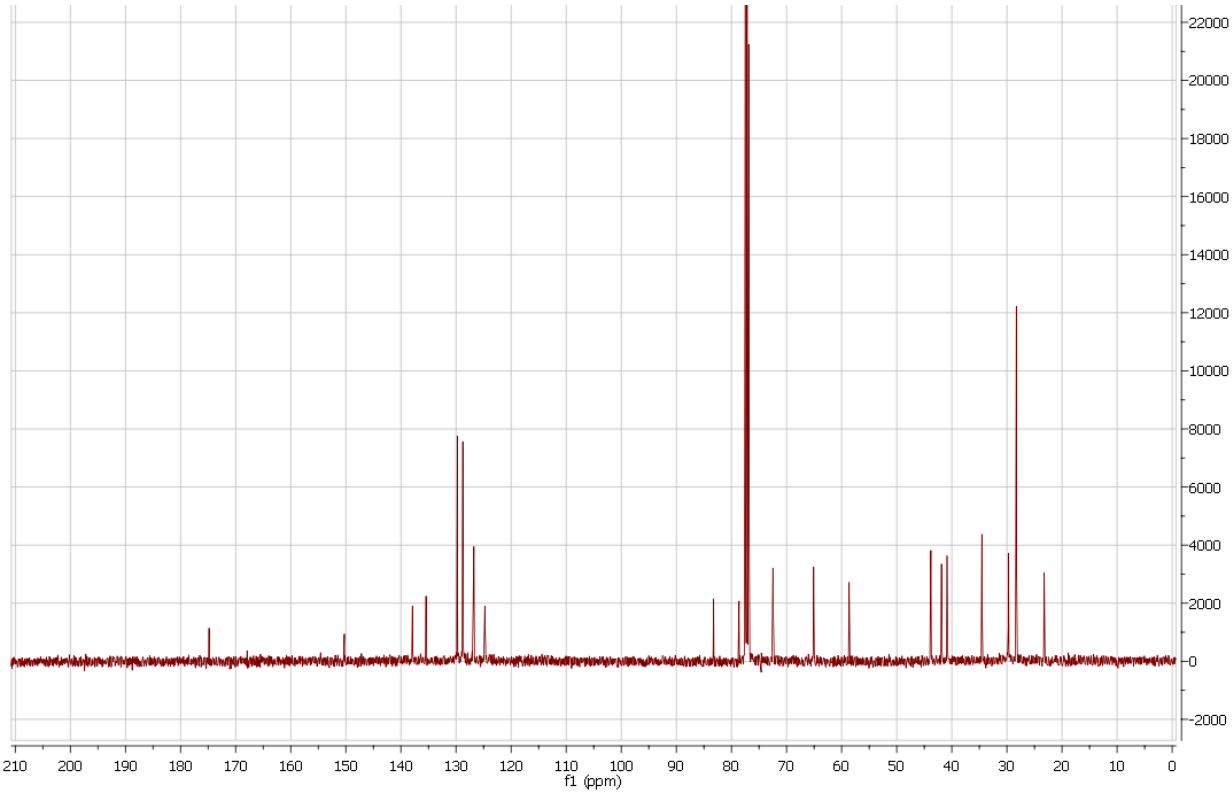
12a


OMe
OH
O
NMe
H
Ph
2.01
1.19
1.97
0.93
0.71
1.00
1.14
2.94
1.05
1.01
2.92
1.04
3.18
1.11
2.95
1.12
1.17
f1 (ppm)

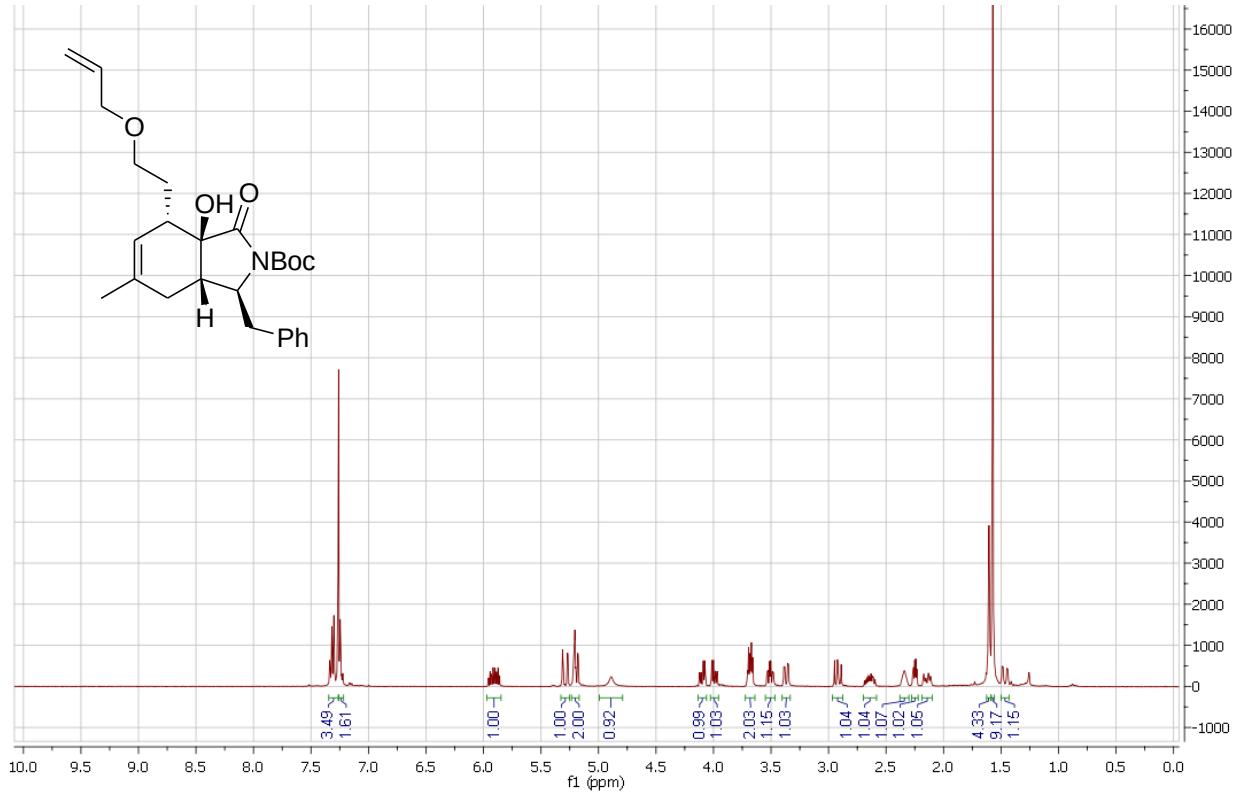

f1 (ppm)

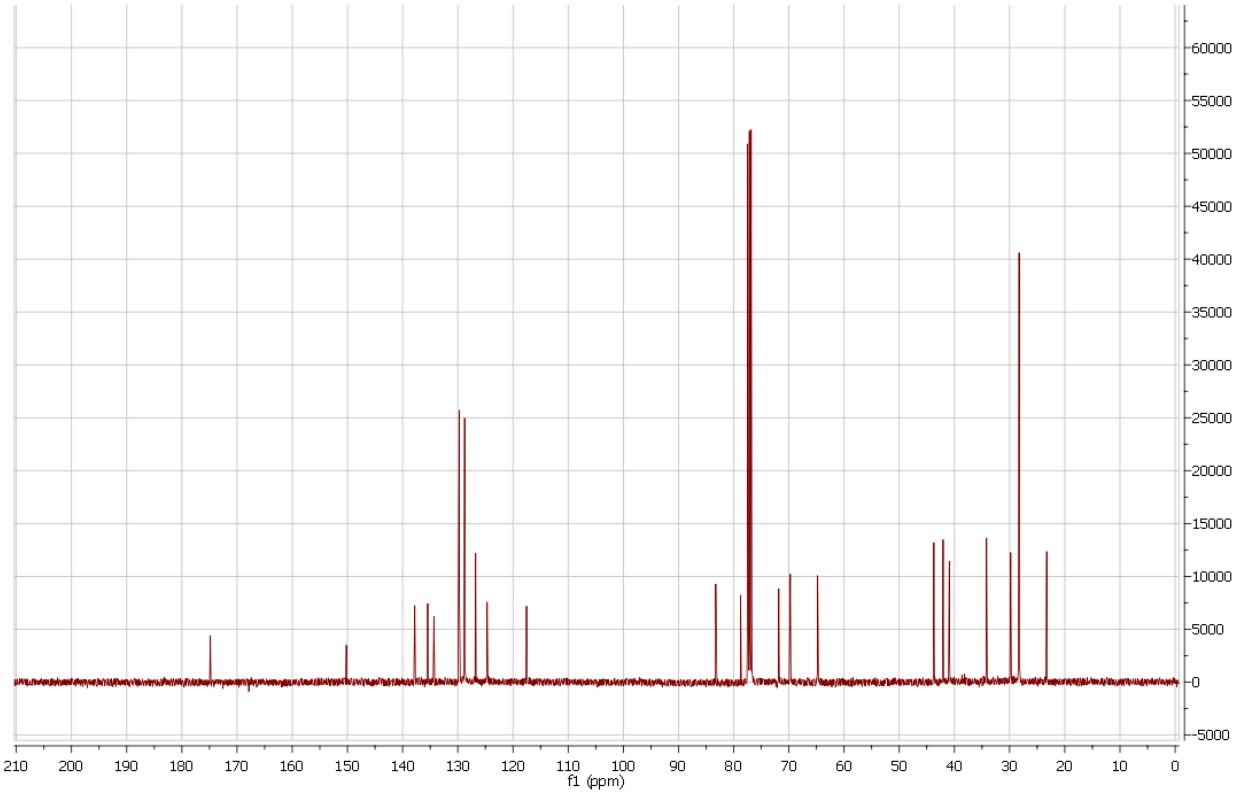
12b


OMe
OH
O
NBoc
H
Ph
2.20
3.60
1.00
0.85
0.91
0.99
1.01
2.99
1.07
1.00
1.01
1.10
1.02
1.08
4.34
9.12
1.39
f1 (ppm)

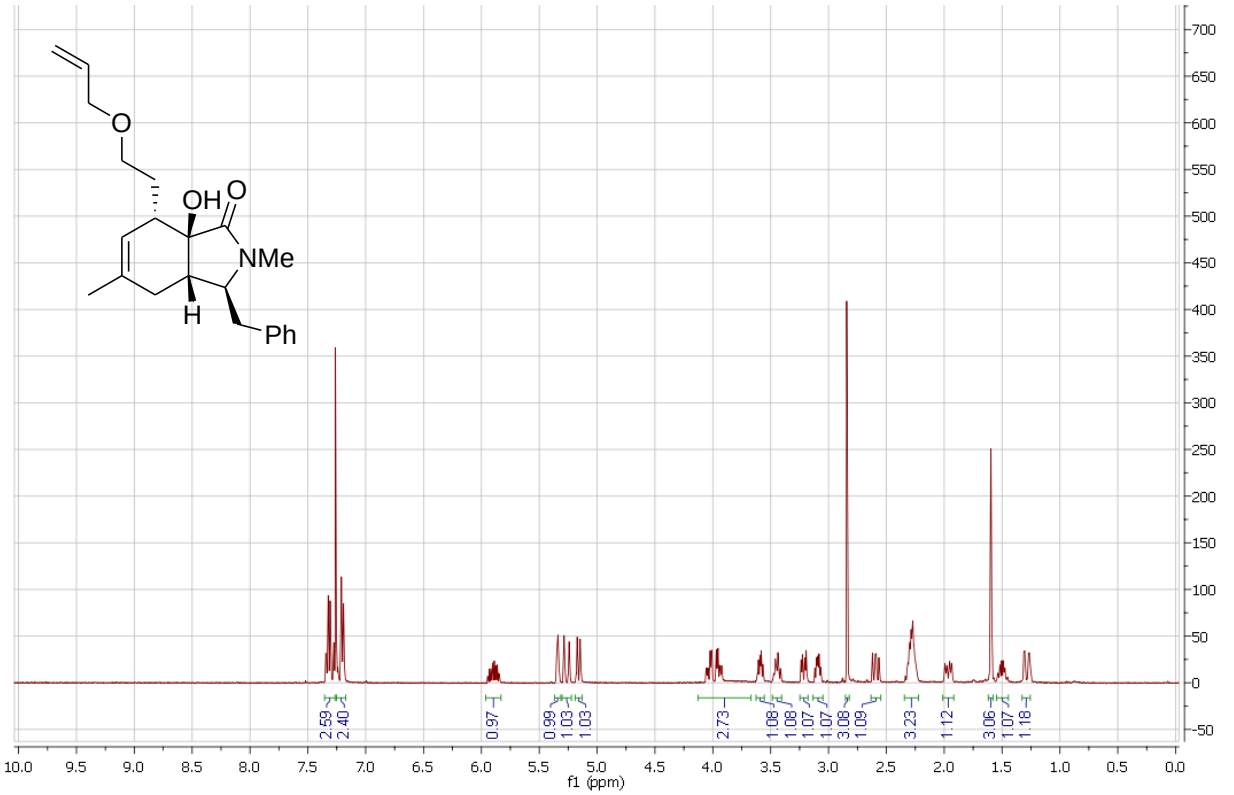

f1 (ppm)

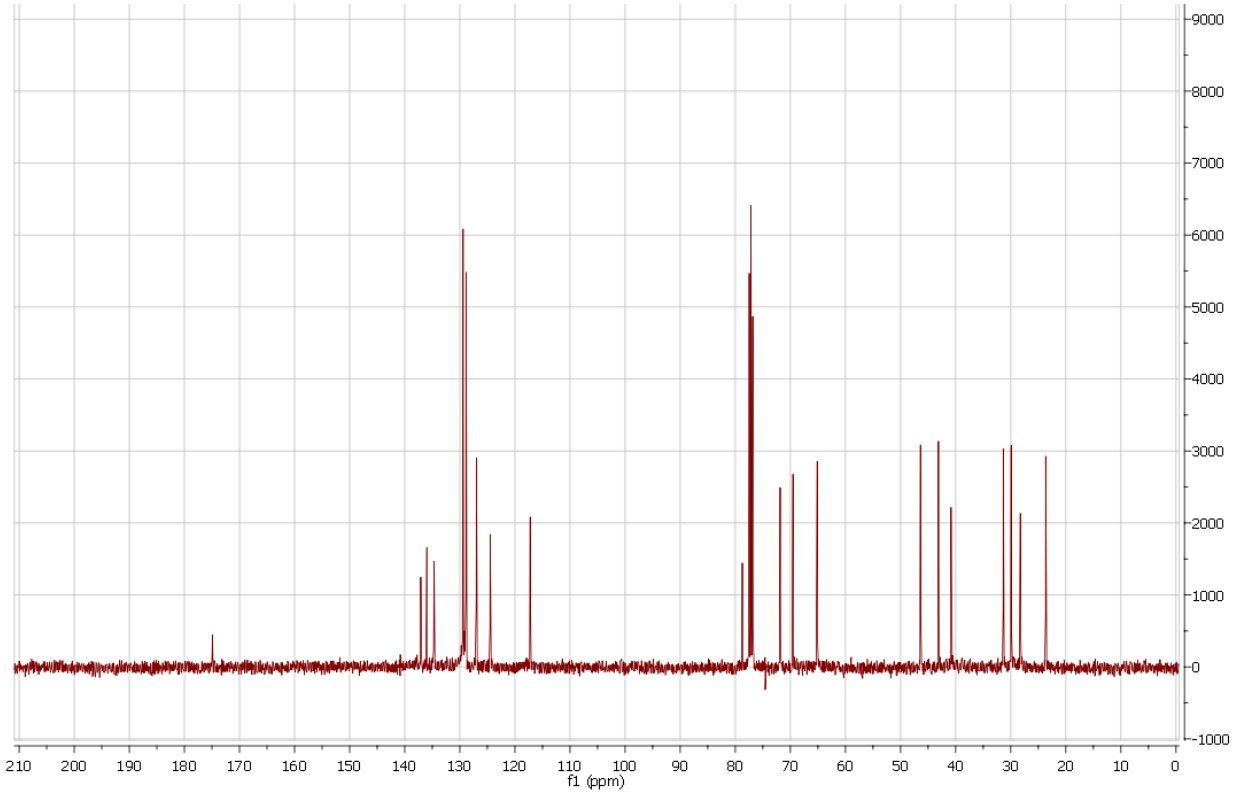
12c


O
OH
O
NBoc
H
Ph
3.49
1.61
1.00
1.00
2.00
0.92
0.99
1.03
2.03
1.15
1.03
1.04
1.04
1.07
1.02
1.05
4.33
9.17
1.15
f1 (ppm)

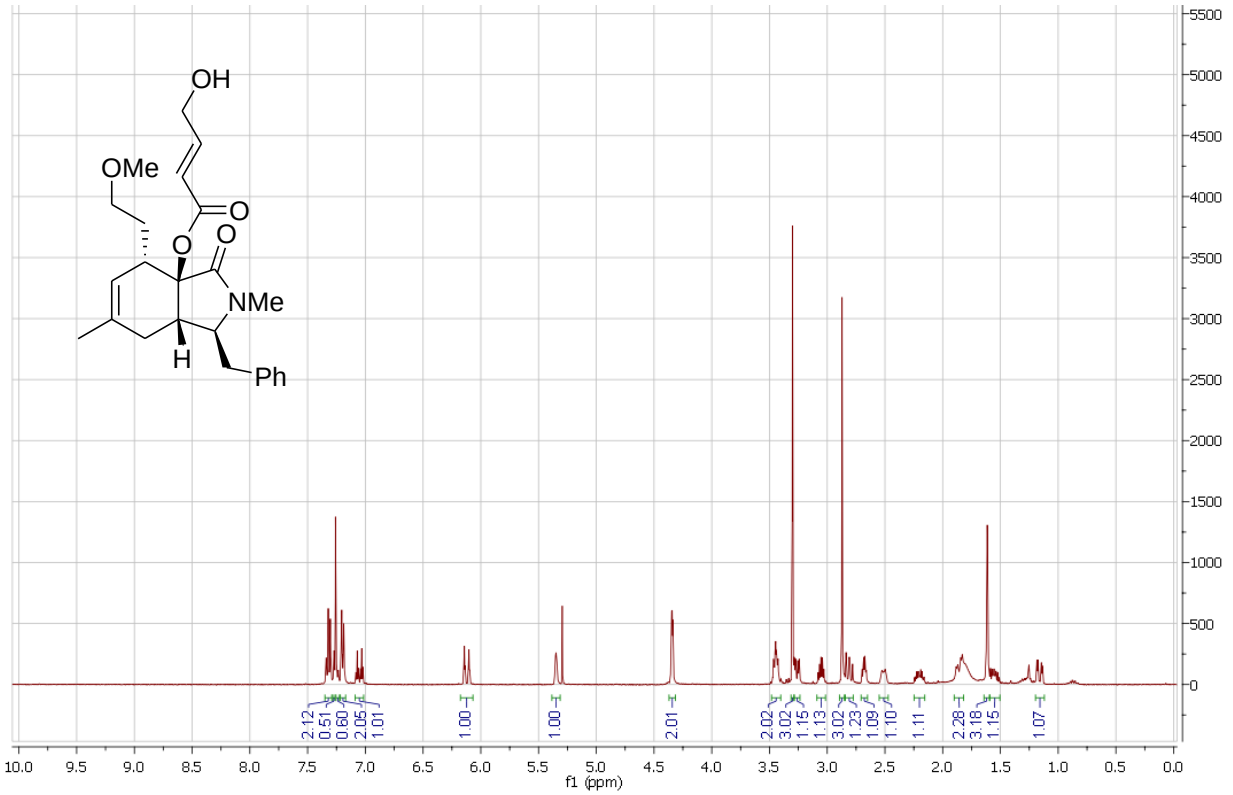

f1 (ppm)

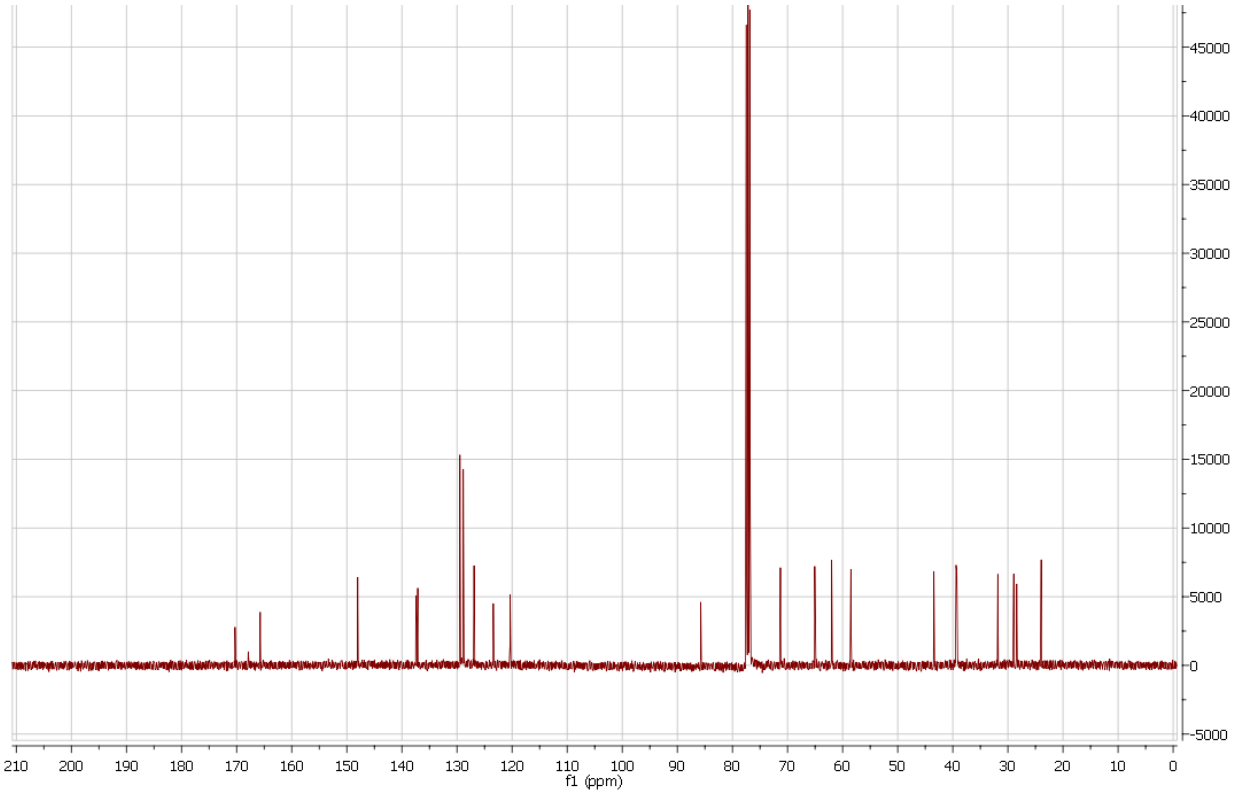
12d


O
OH
O
NMe
H
Ph
2.59
2.40
0.97
0.99
1.03
1.03
2.73
1.08
1.08
1.07
1.07
3.08
1.09
3.23
1.12
3.06
1.07
1.18
f1 (ppm)

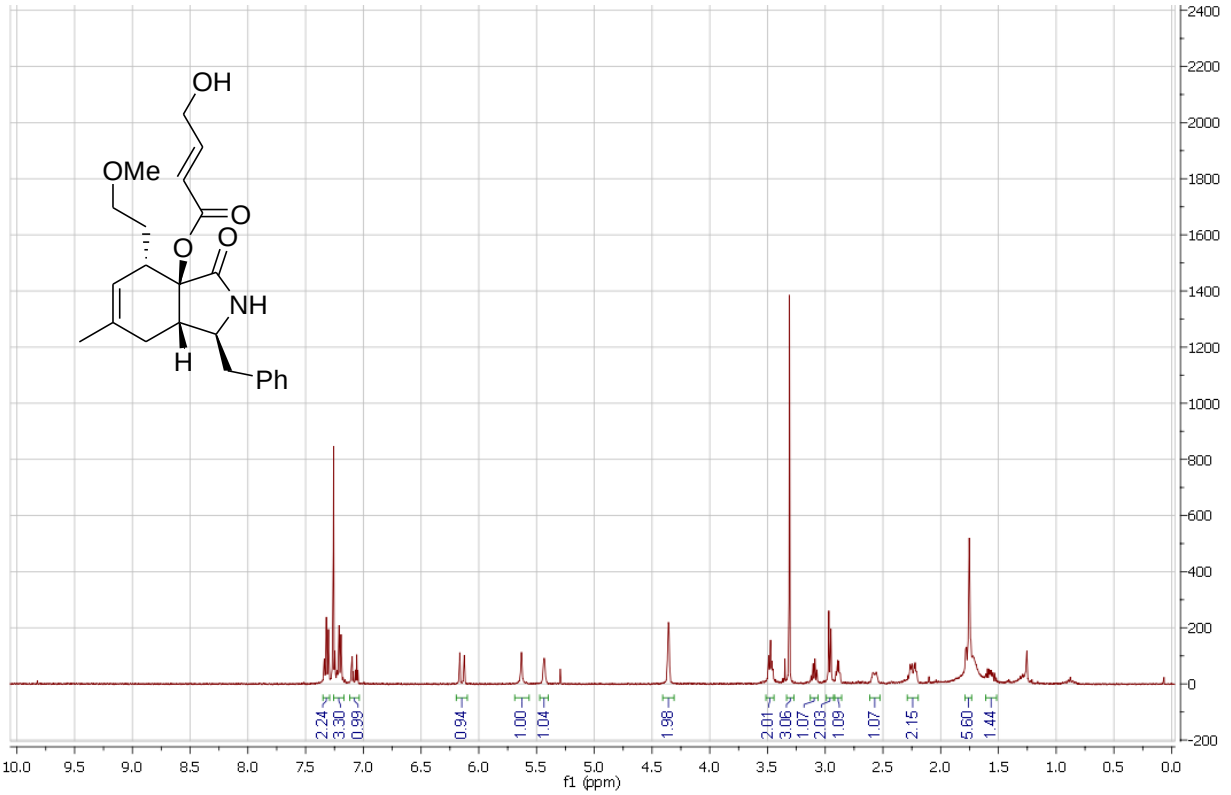

f1 (ppm)

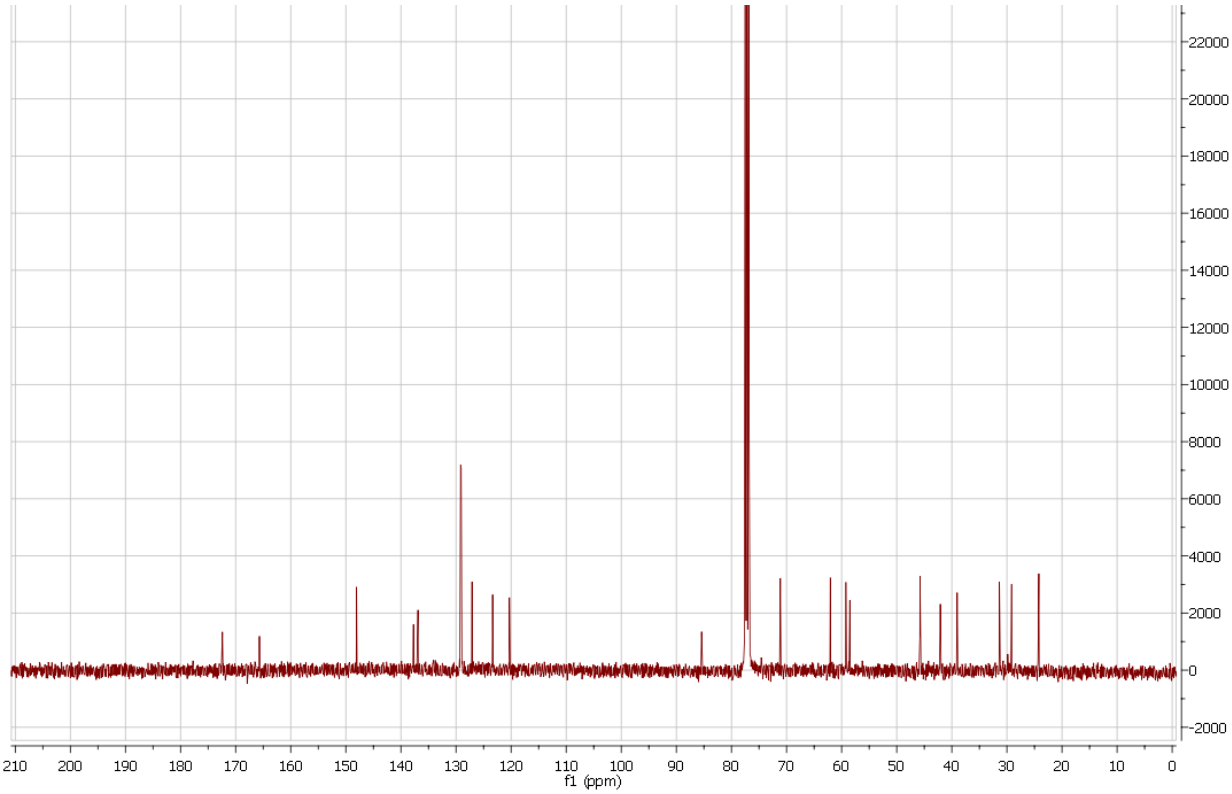
13a



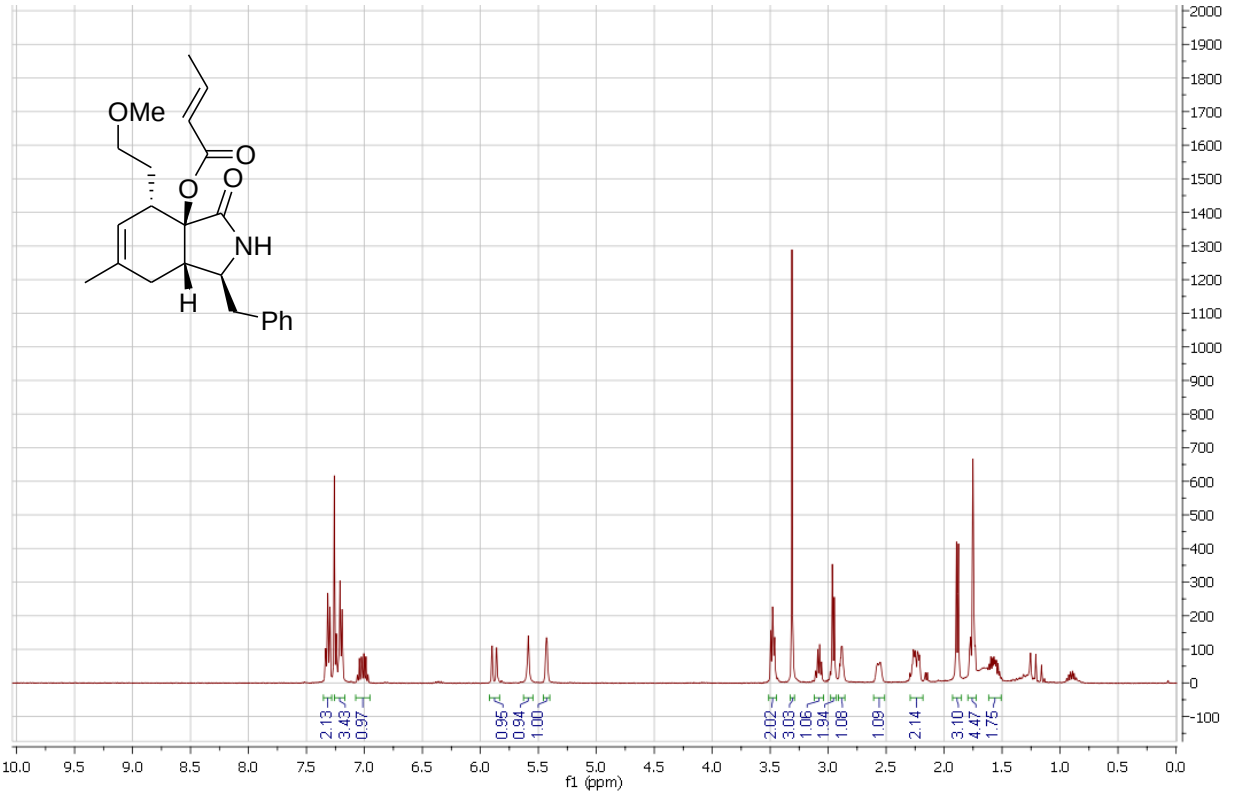


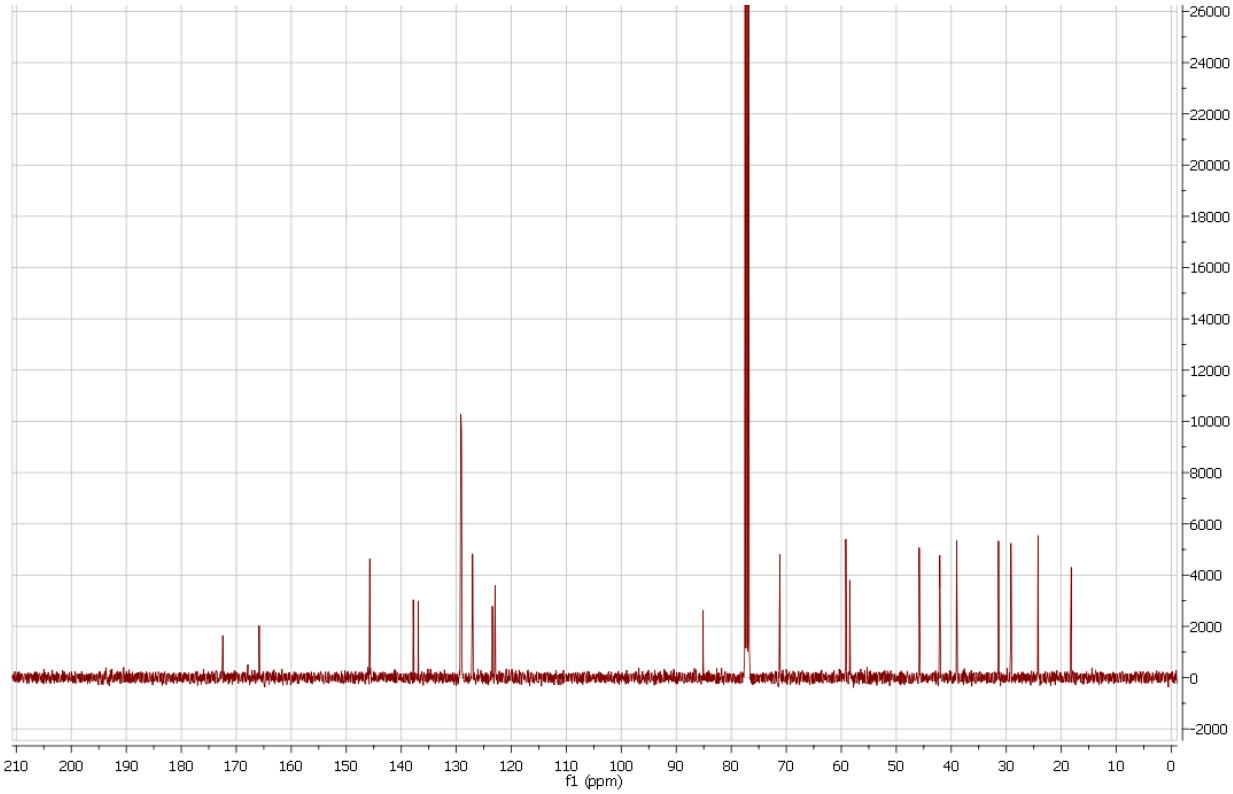
13b


OH
OMe
O
O
O
NH
H
Ph
2.24
3.30
0.99
0.94
1.00
1.04
1.98
2.01
3.06
1.07
2.03
1.09
1.07
2.15
5.60
1.44
f1 (ppm)

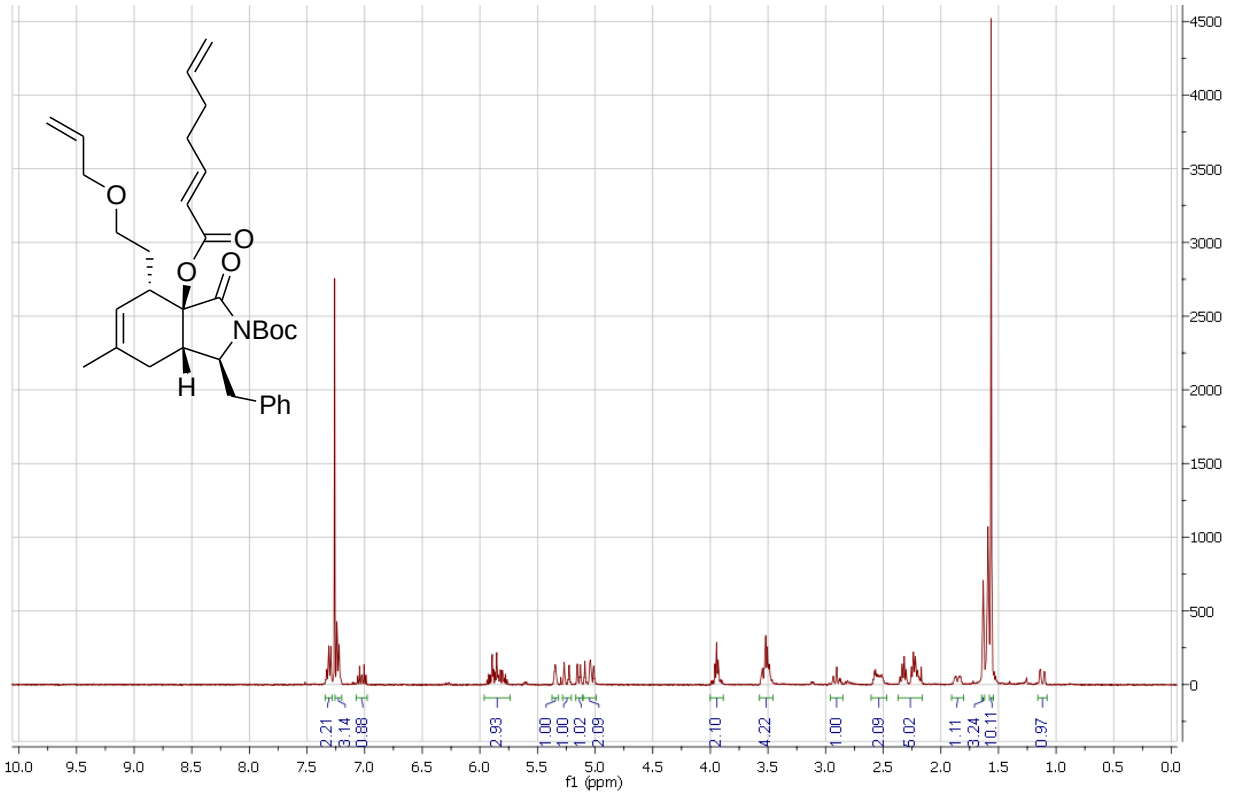

f1 (ppm)

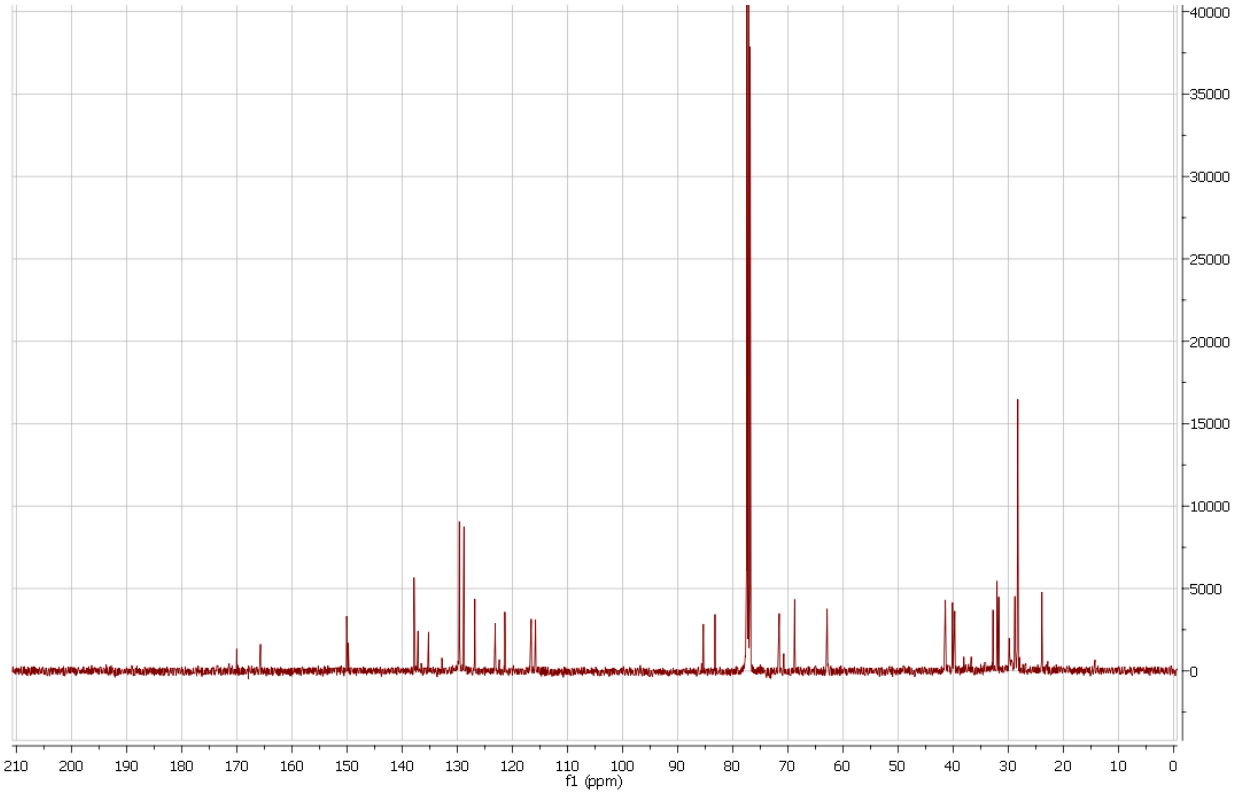
13c


OMe
O
O
O
NH
H
Ph
2.13
3.43
0.97
0.95
0.94
1.00
2.02
3.03
1.06
1.94
1.08
1.09
2.14
3.10
4.47
1.75
f1 (ppm)

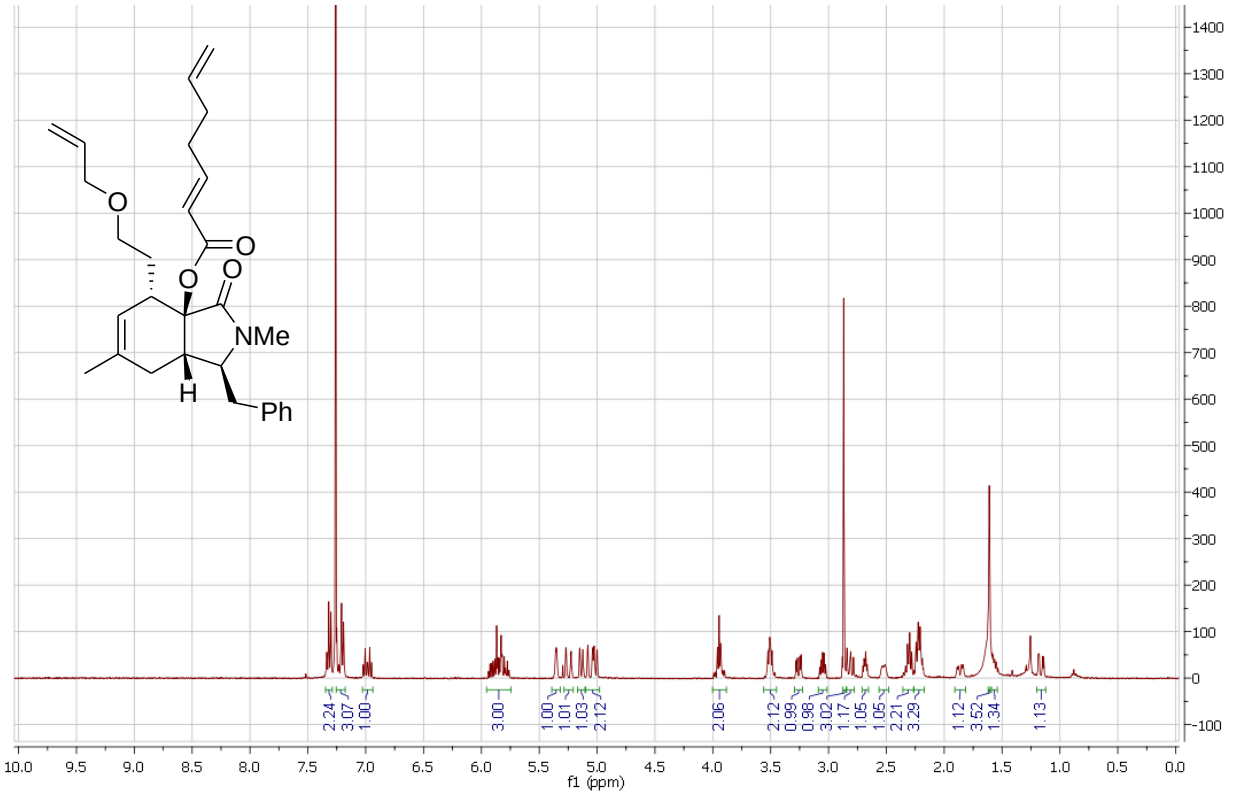

f1 (ppm)

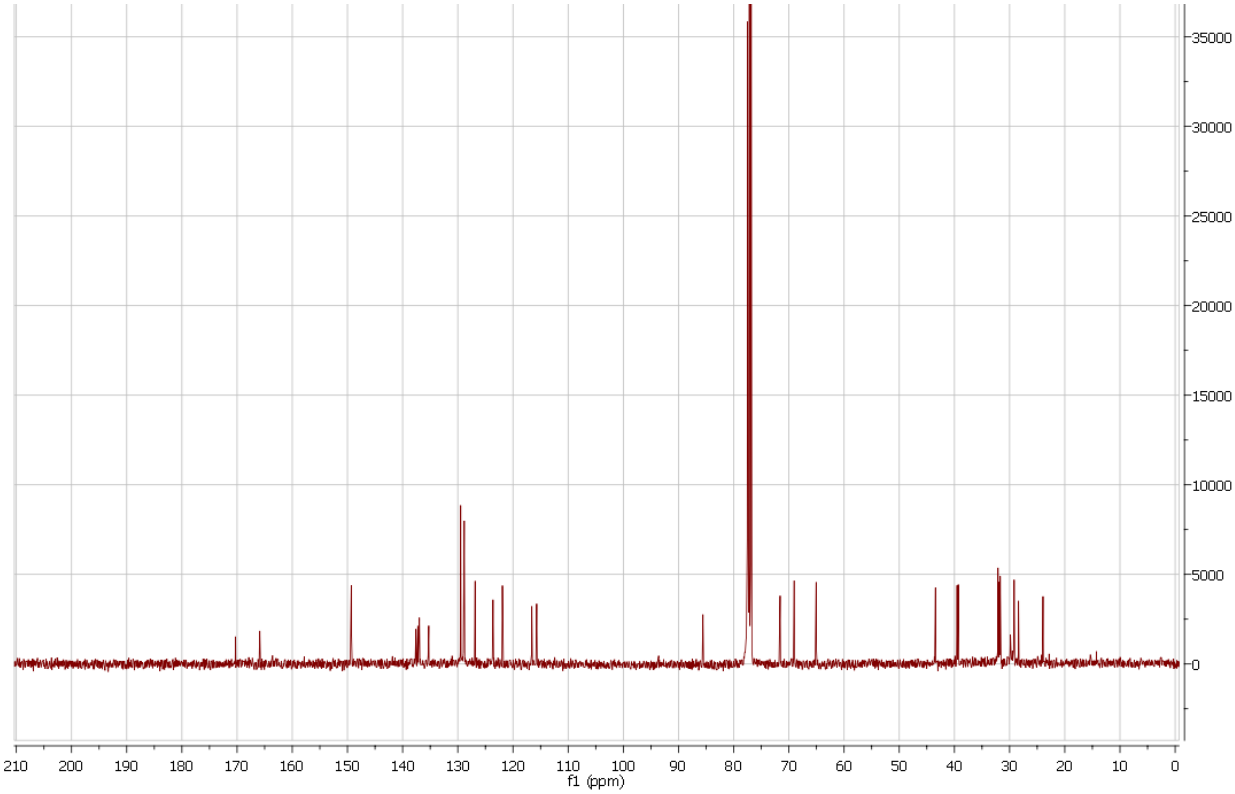
13d


O
O
O
O
NBoc
H
Ph
2.21
3.14
0.88
2.93
1.00
1.00
1.02
2.09
2.10
4.22
1.00
2.09
5.02
1.11
3.24
10.11
0.97
f1 (ppm)

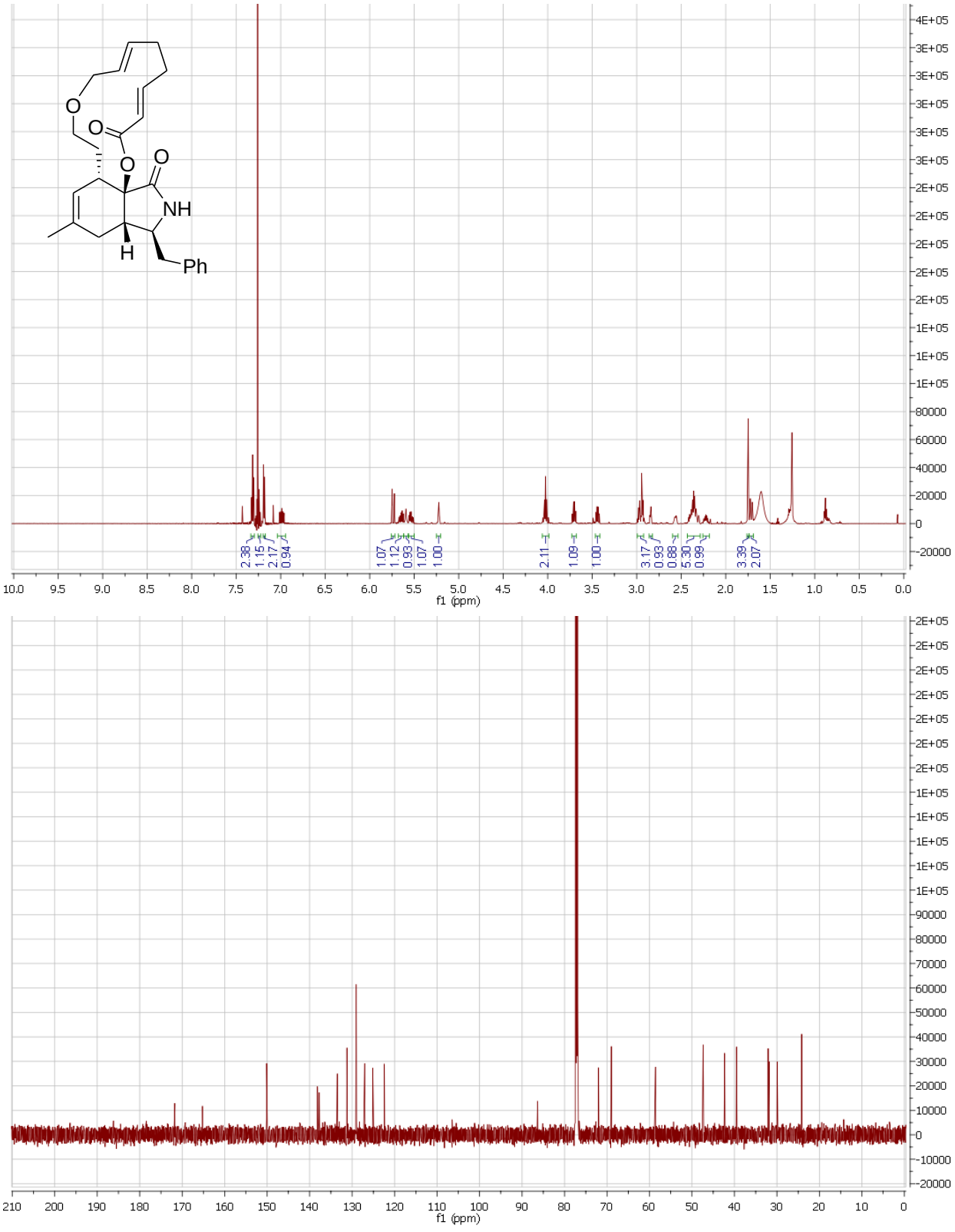

f1 (ppm)

13e

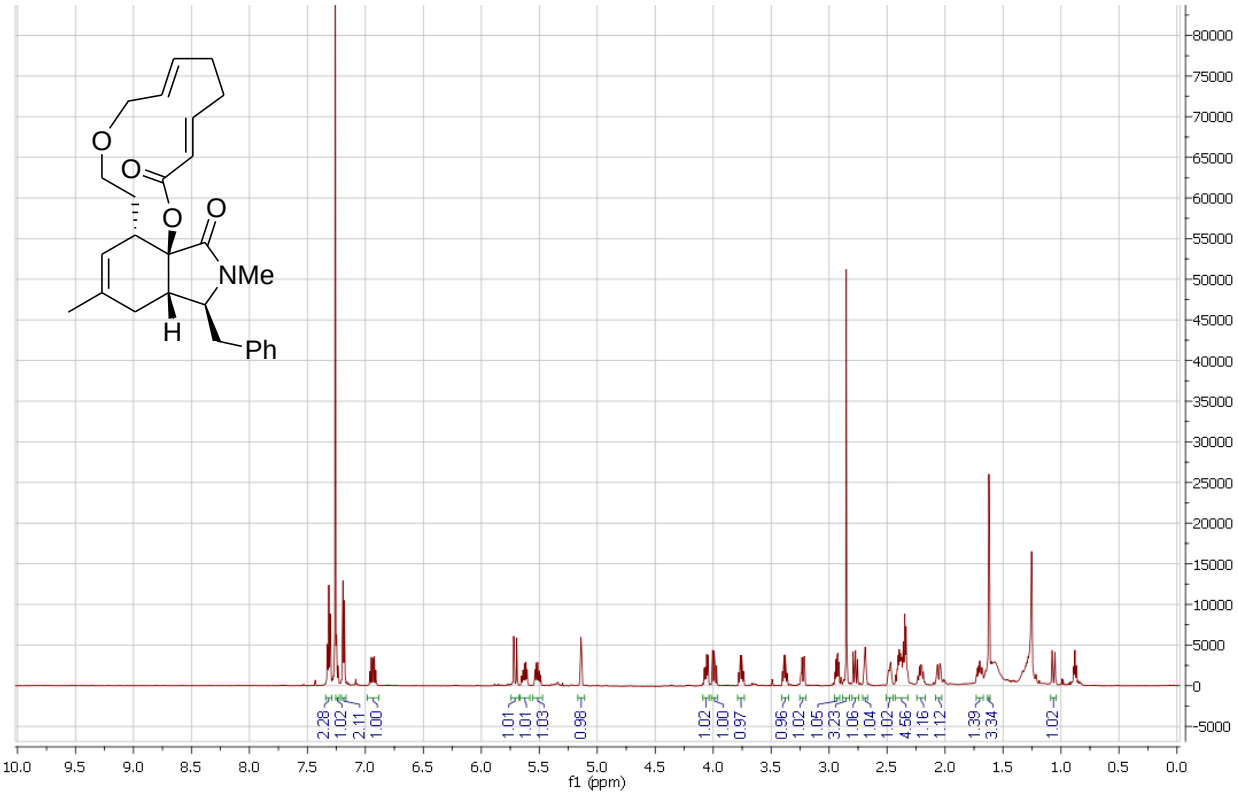

O
O
O
O
NMe
H
Ph
2.24
3.07
1.00
3.00
1.00
1.01
1.03
2.12
2.06
2.12
0.99
0.98
3.02
1.17
1.05
1.05
2.21
3.29
1.12
3.52
1.34
1.13
f1 (ppm)

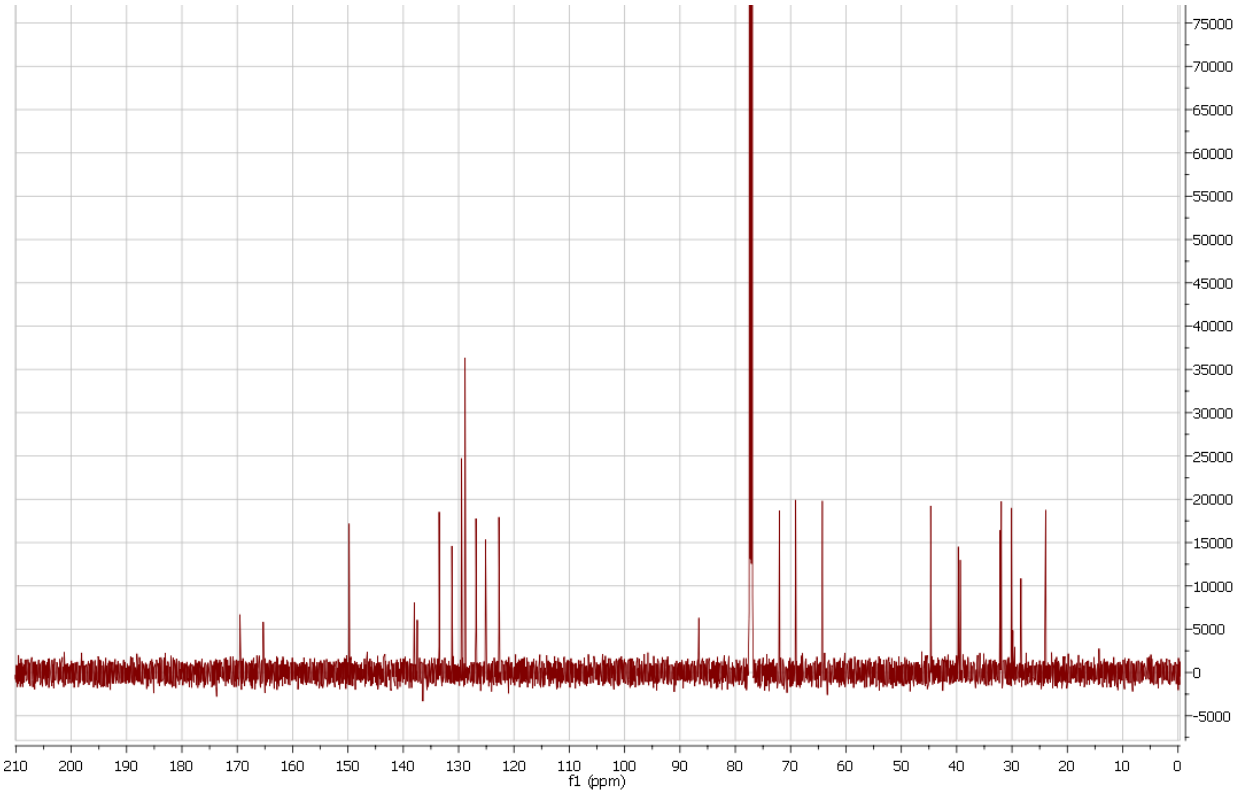

f1 (ppm)

14a

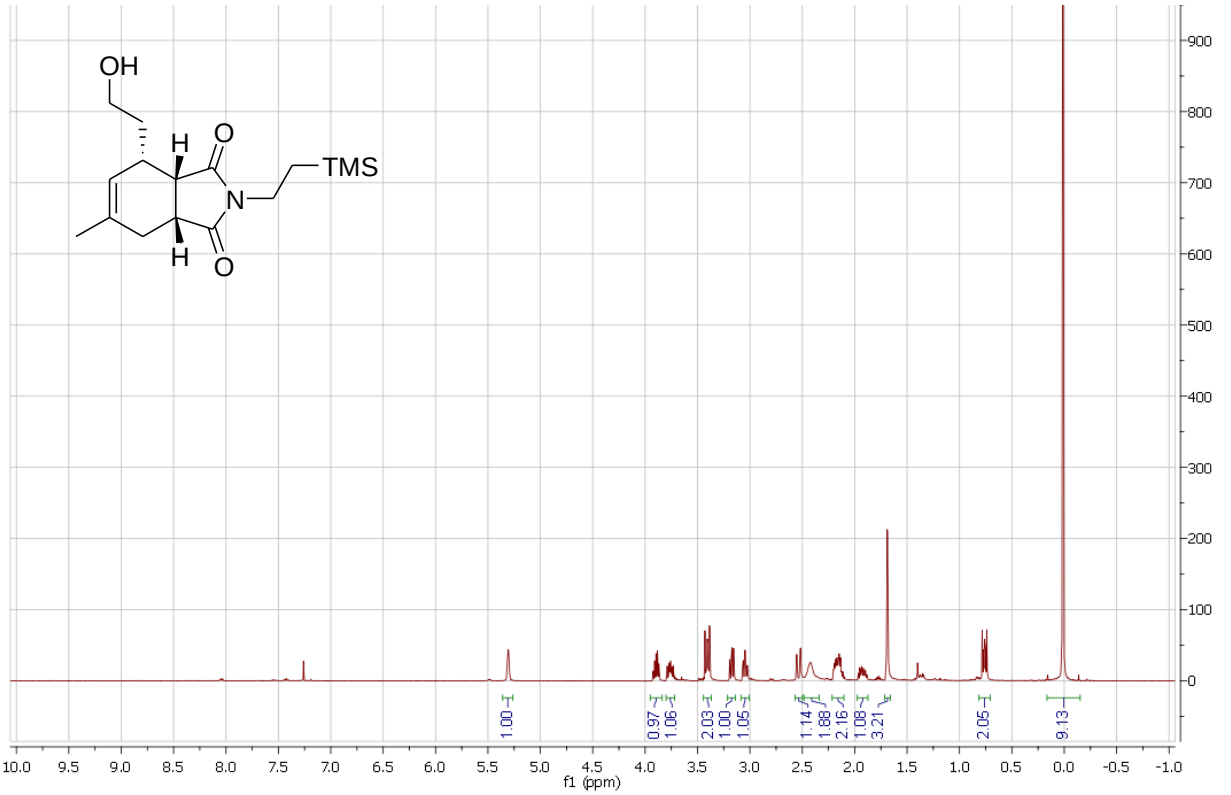


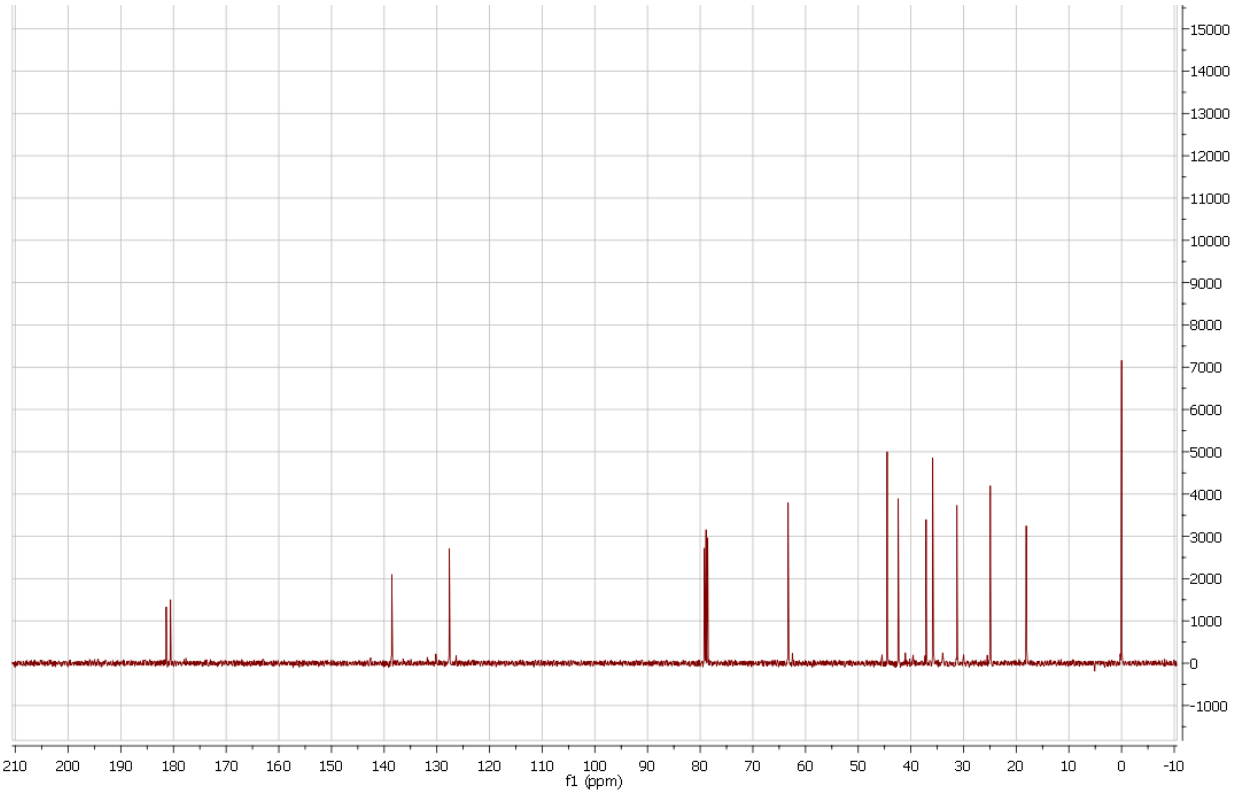
14b


O
O
O
O
NMe
H
Ph
2.28
1.02
2.11
1.00
1.01
1.01
1.03
0.98
1.02
1.00
0.97
0.96
1.02
1.05
3.23
1.06
1.04
1.02
4.56
1.16
1.12
1.39
3.34
1.02
f1 (ppm)

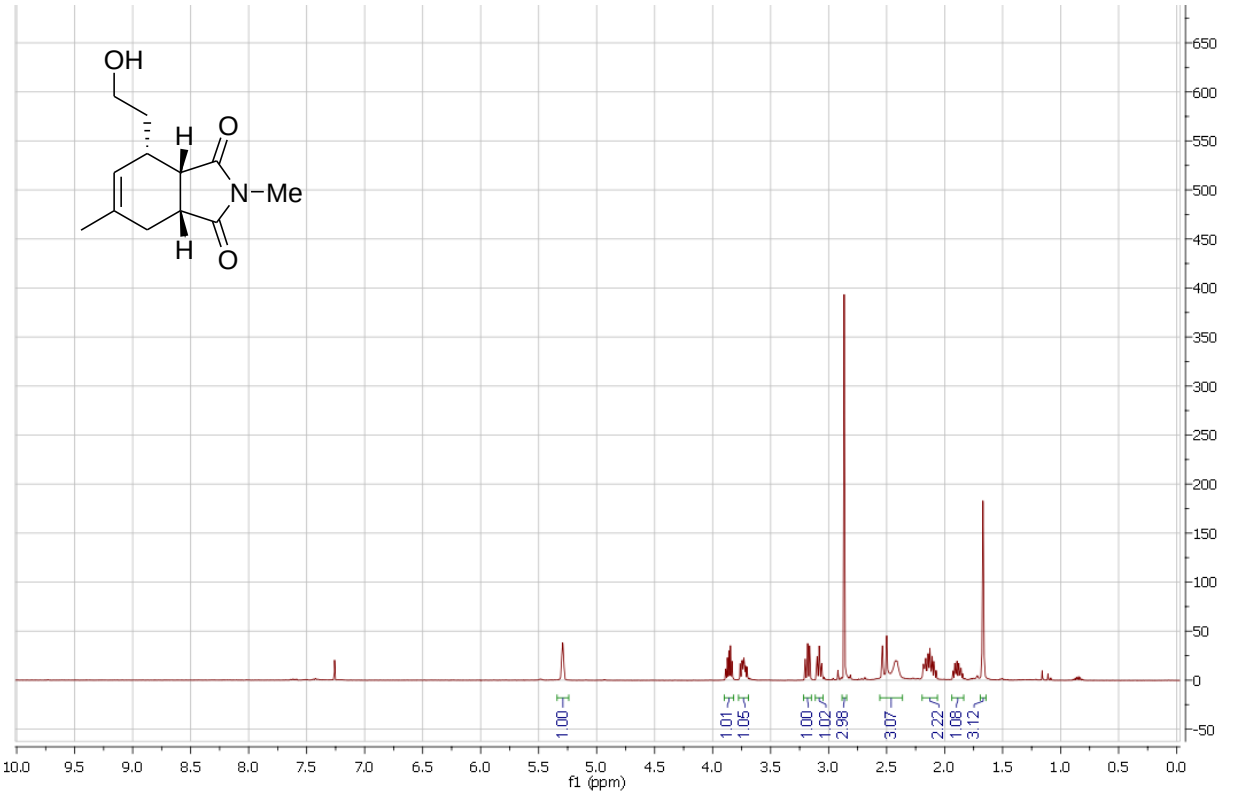

f1 (ppm)

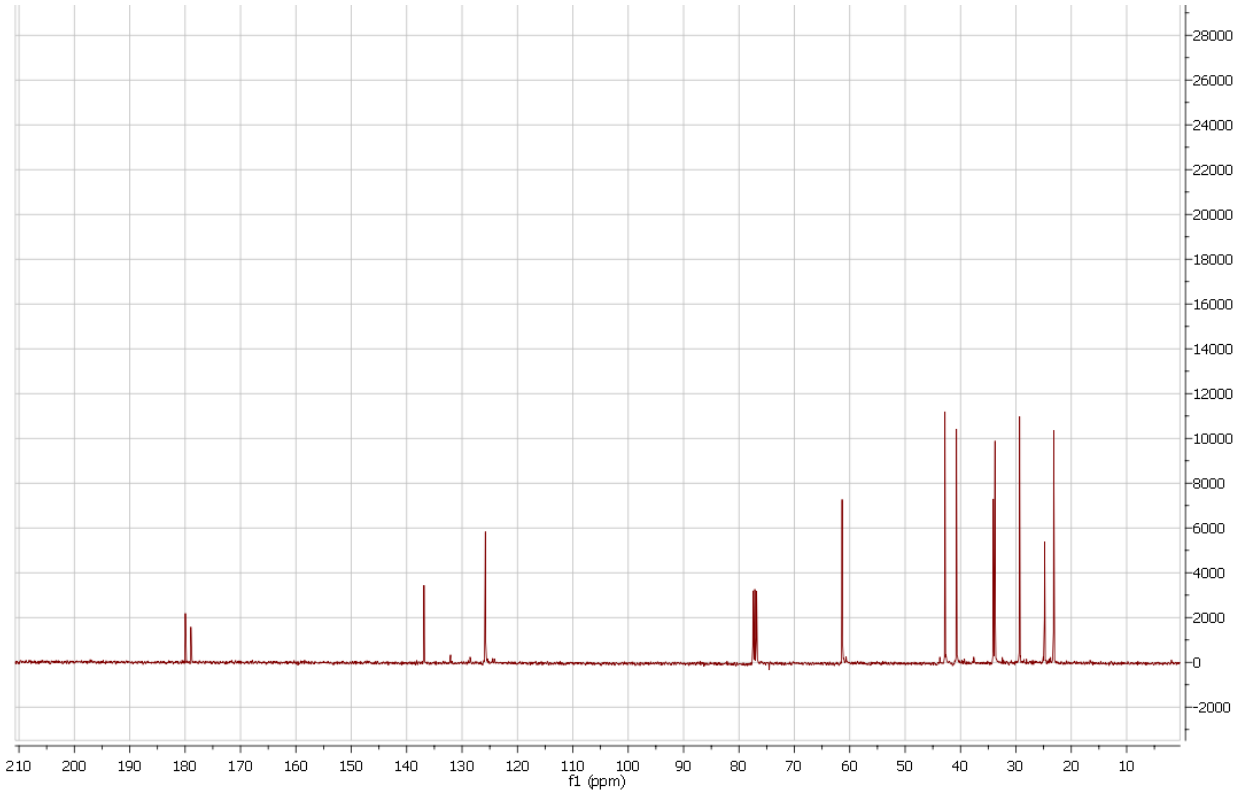
15a


OH
H
O
N
TMS
H
O
1.00
0.97
1.06
2.03
1.00
1.05
1.14
1.88
2.16
1.08
3.21
2.05
9.13
f1 (ppm)


f1 (ppm)

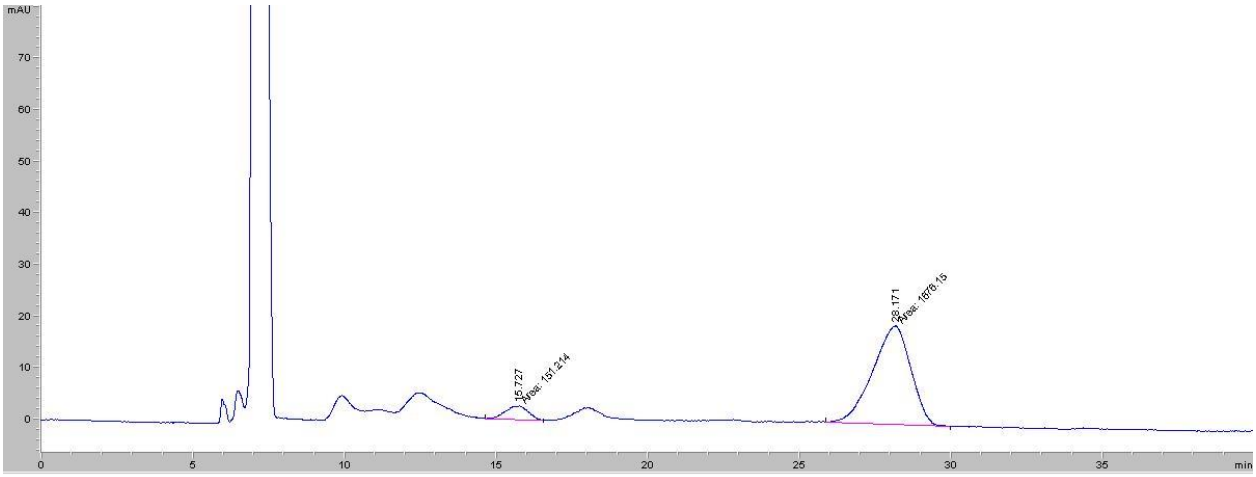
15b



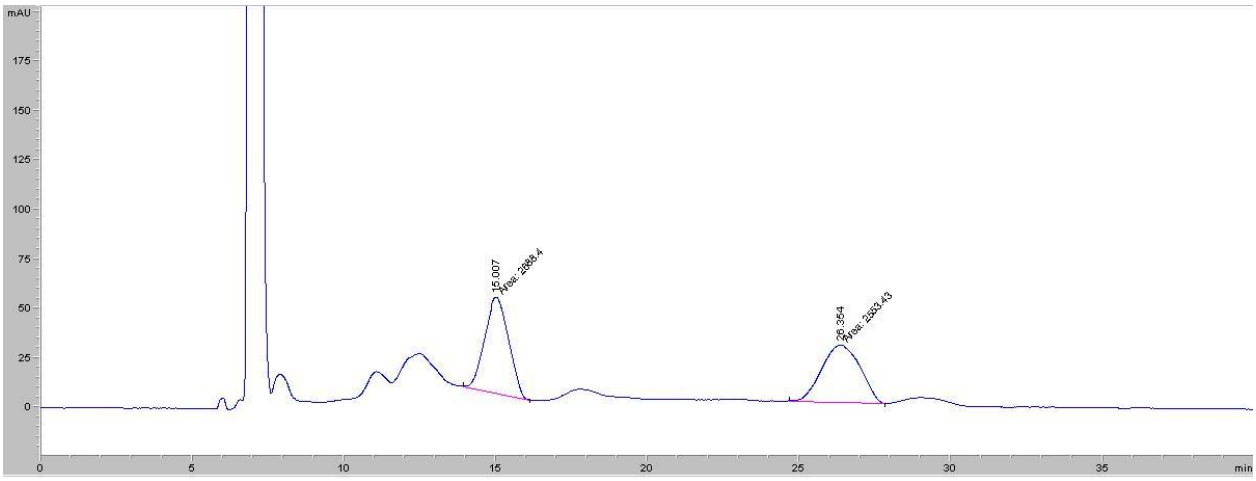


Determination of enantiomeric excesses

3

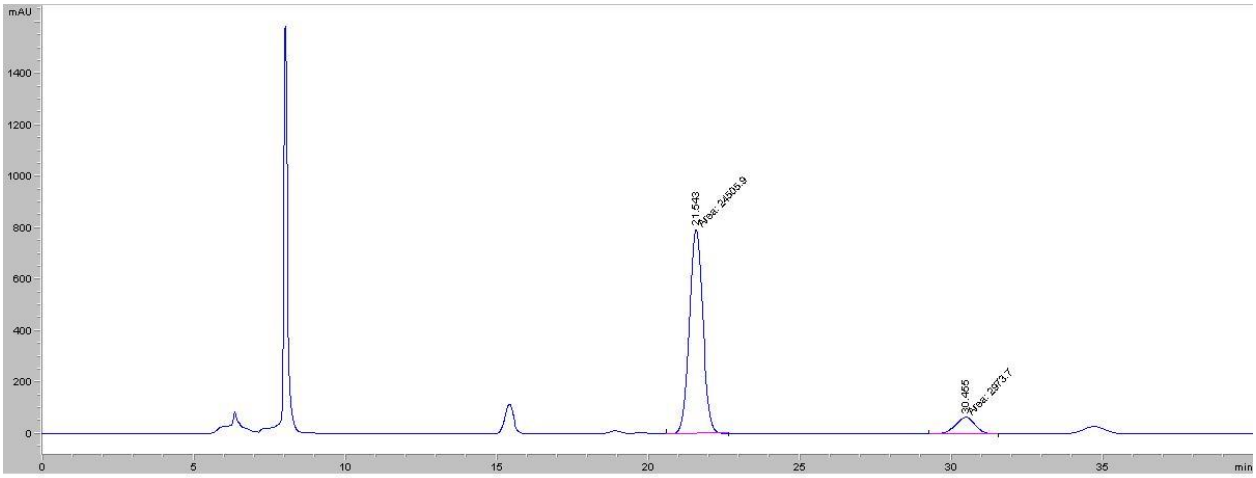


***rac*-3**

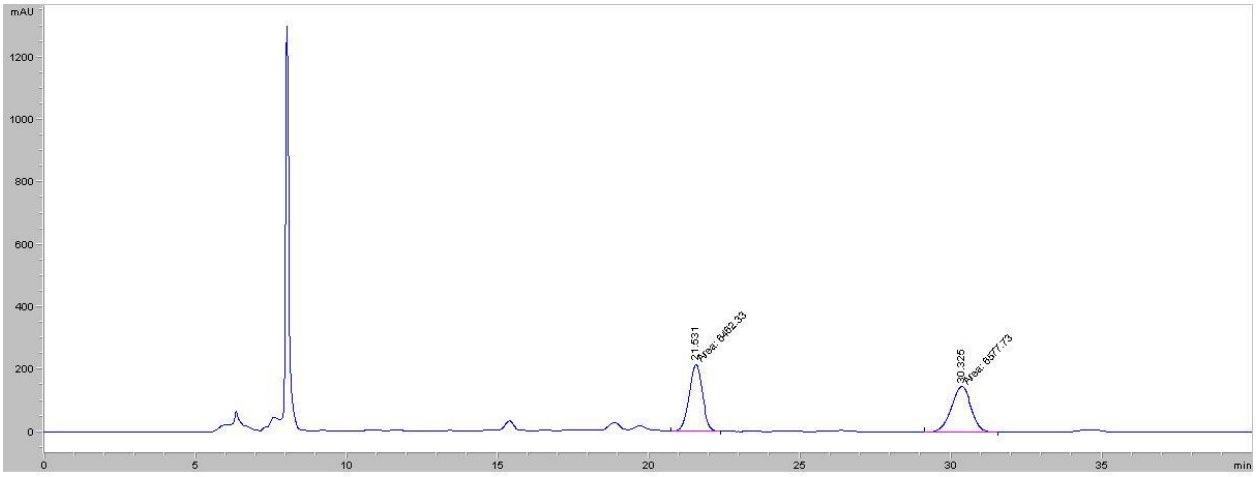


Column: Chiralpak® IA, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 7:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 230 nm
ee: 83%

4a

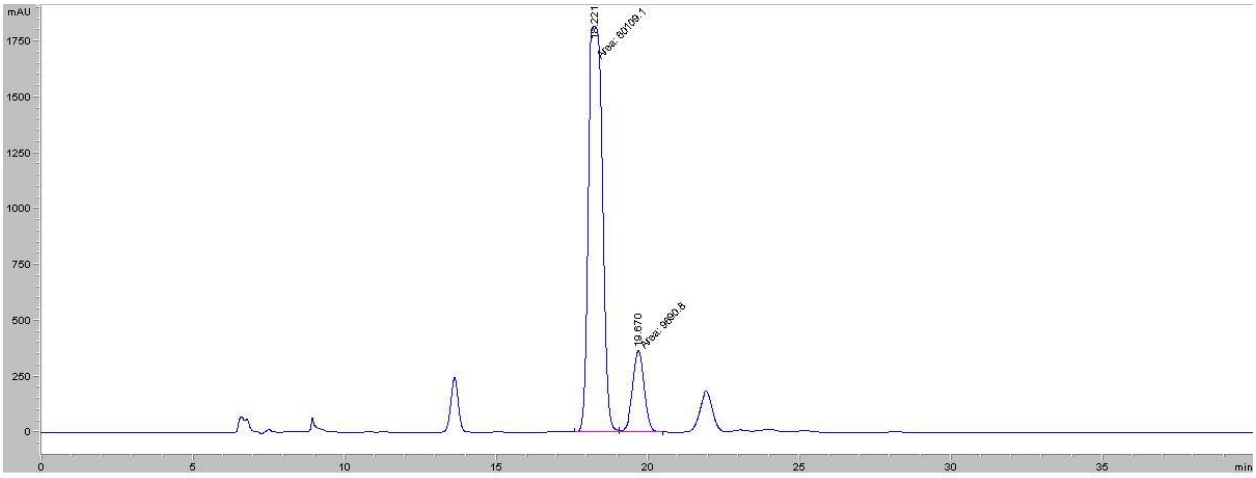


***rac*-4a**

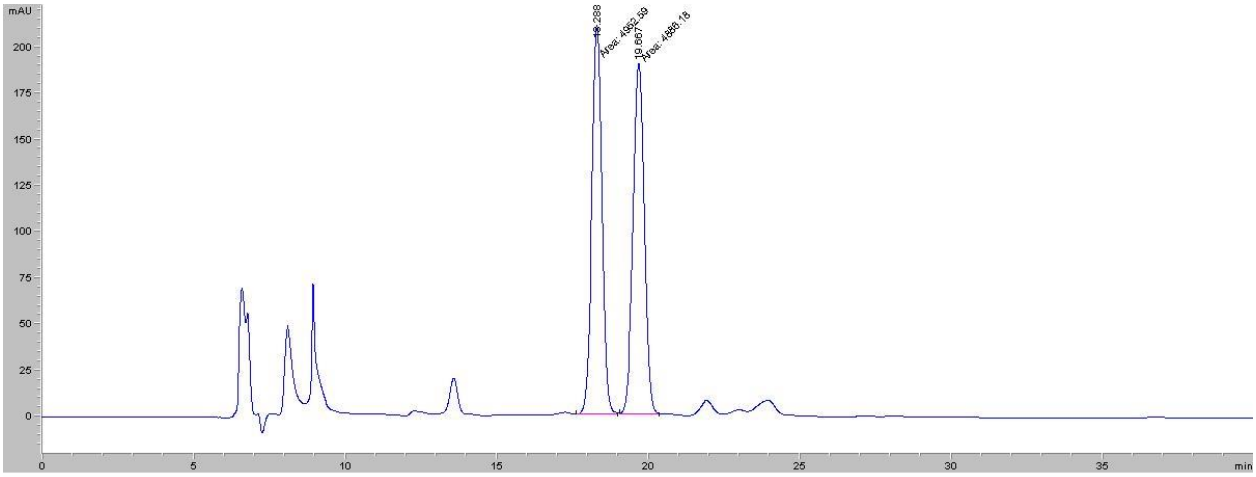


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 7:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 78%

4b

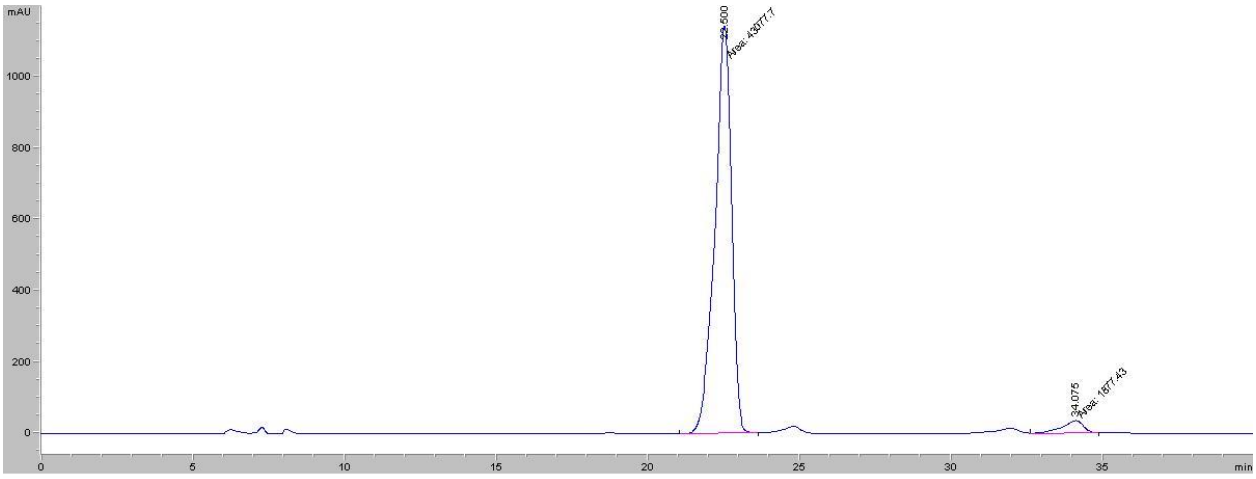


***rac*-4b**

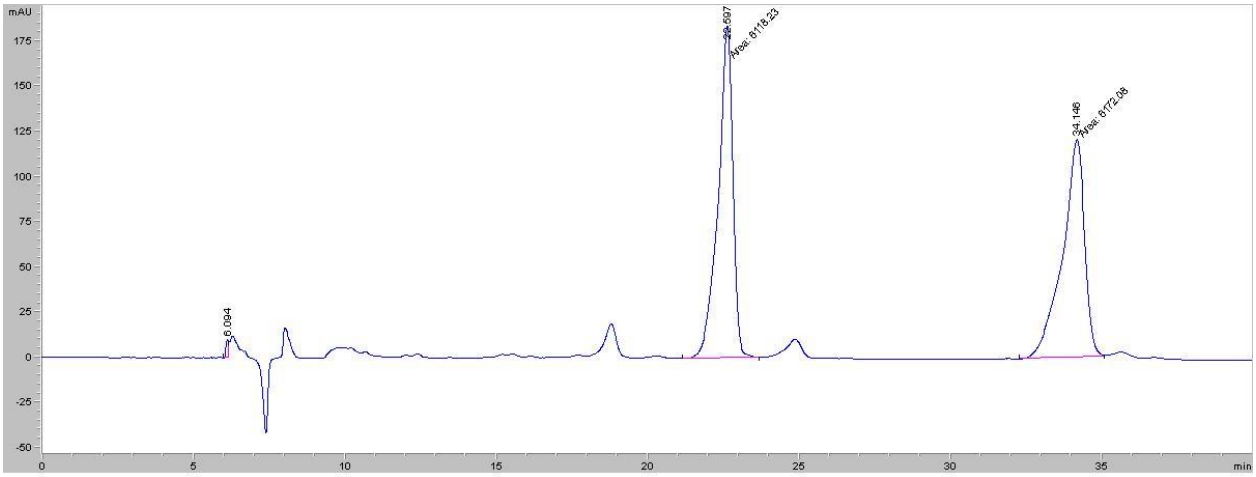


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 72%

4c

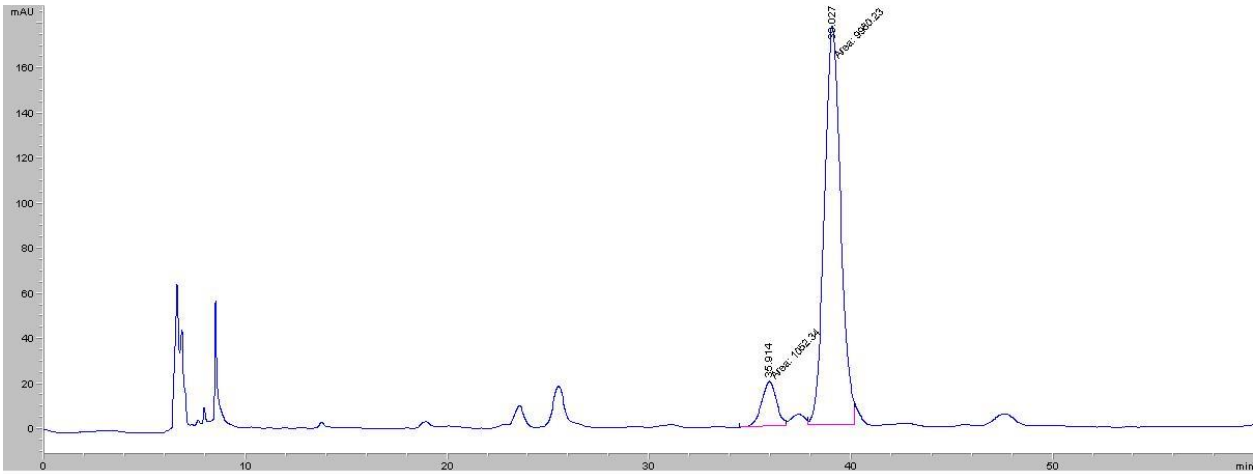


***rac*-4c**

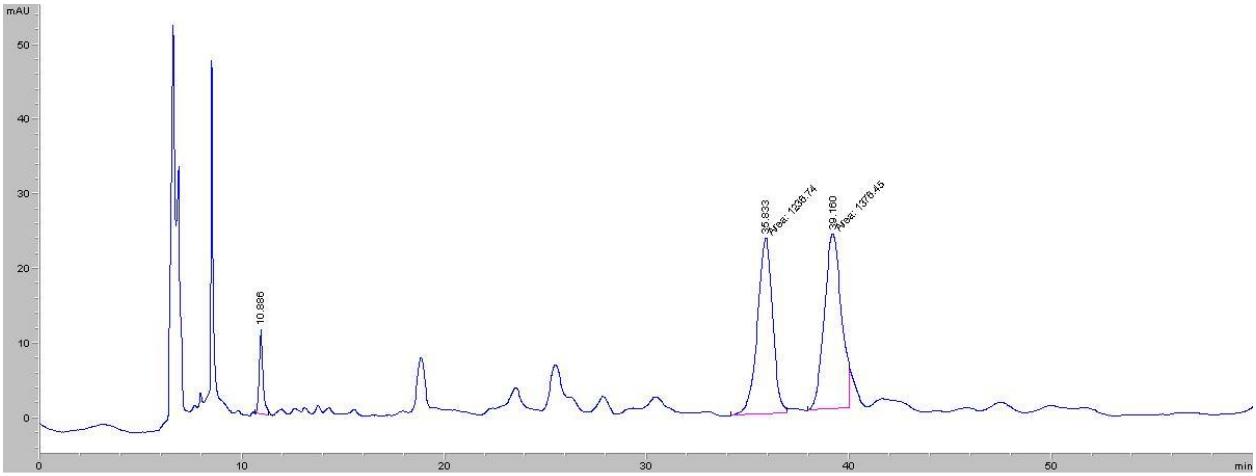


Column: Chiralpak® IA, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 230 nm
ee: 92%

5a

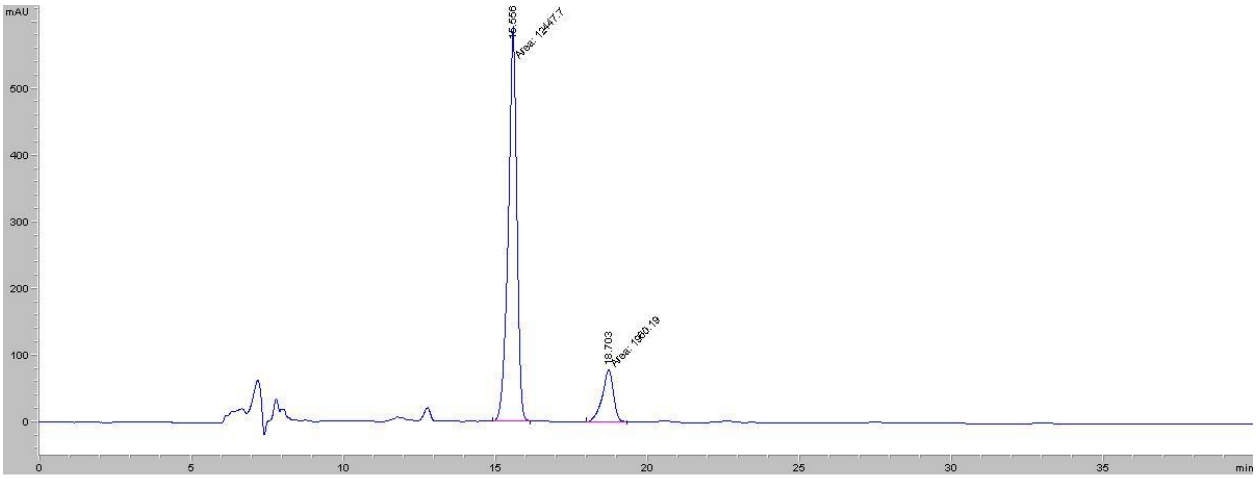


***rac*-5a**

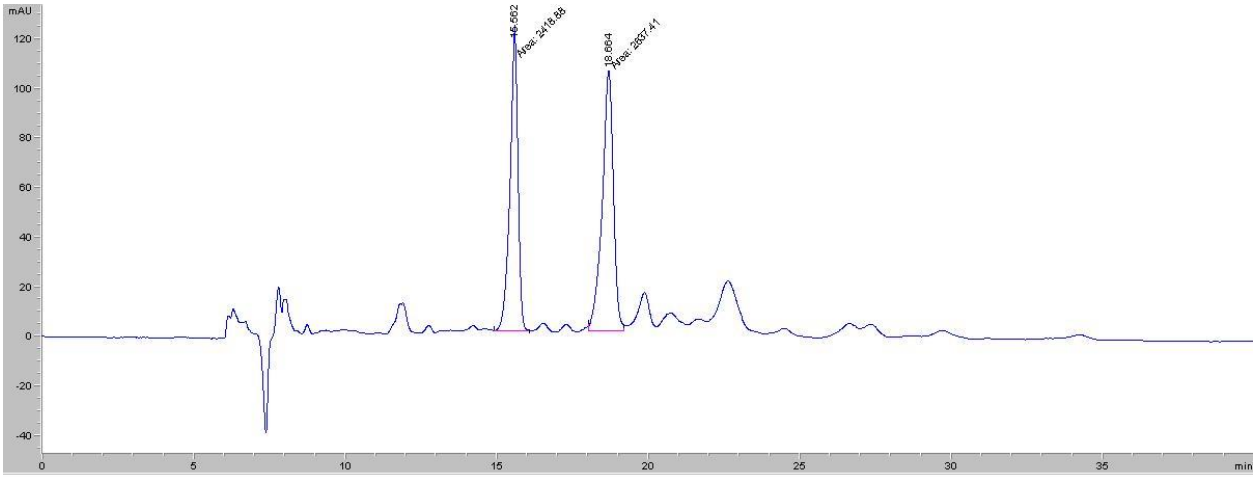


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH 4:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 81%

5b

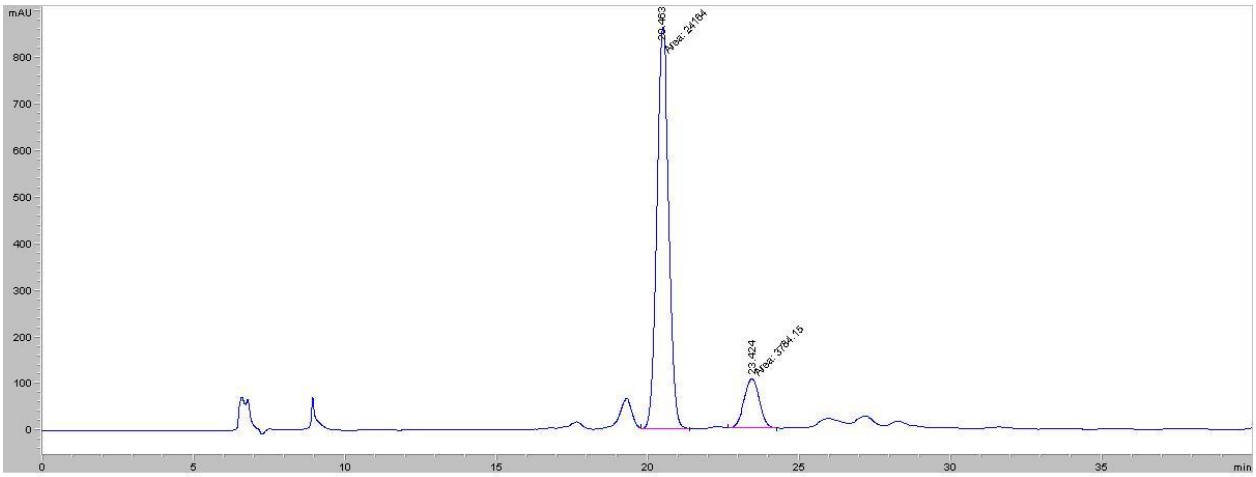


***rac*-5b**

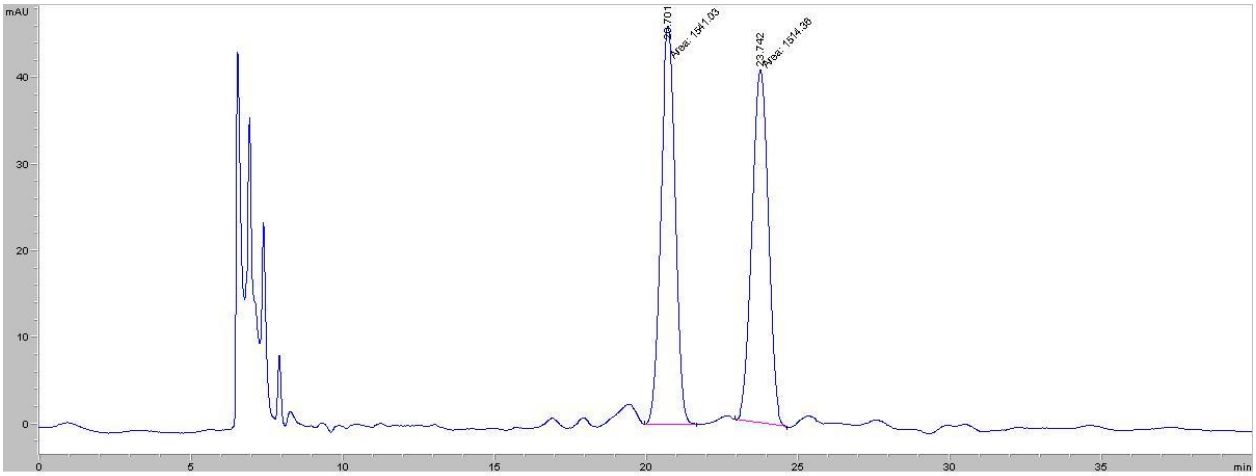


Column: Chiralpak® IA, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 230 nm
ee: 73%

5c

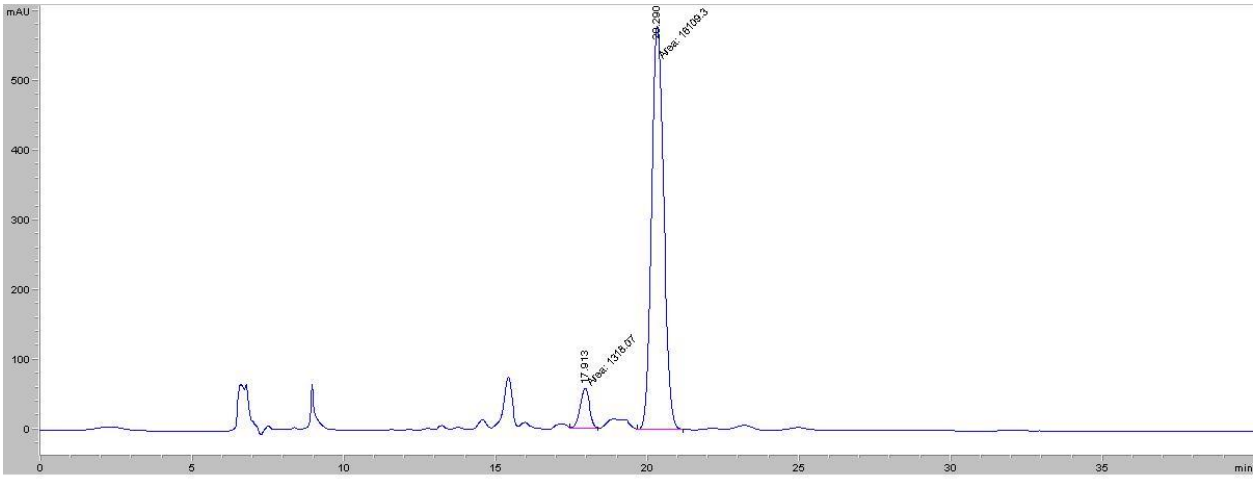


***rac*-5c**

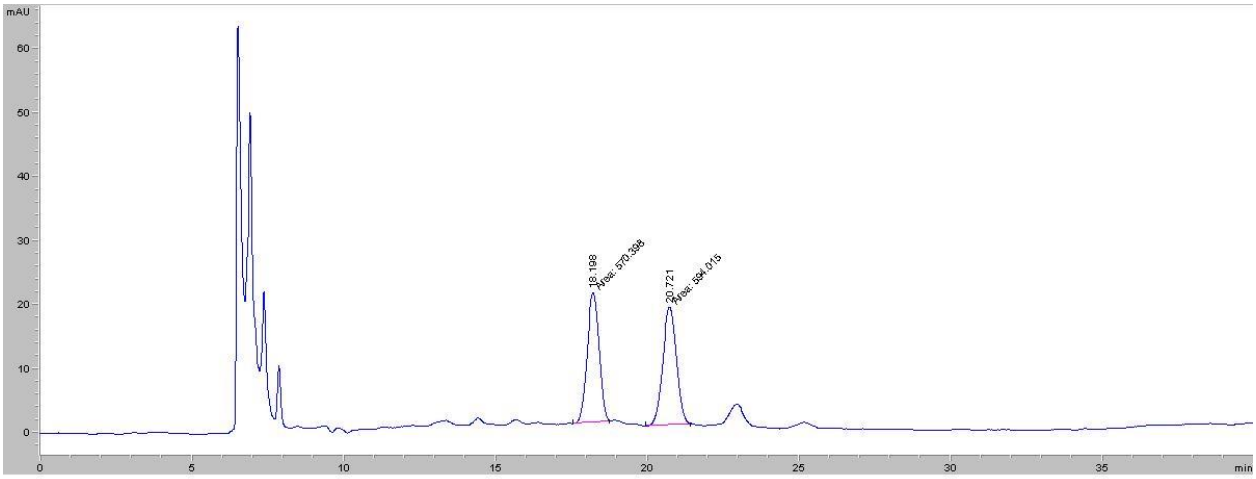


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 73%

6a

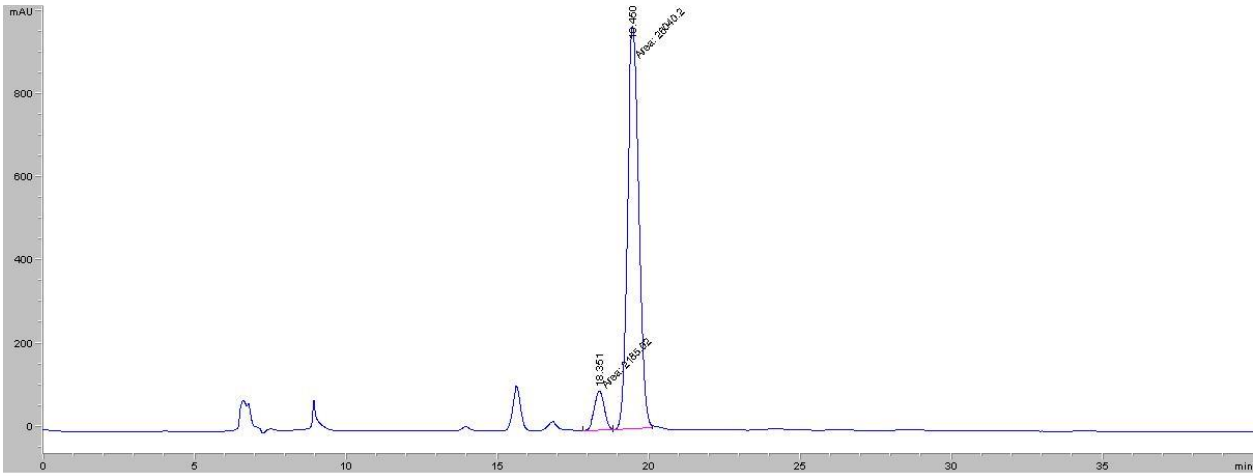


***rac*-6a**

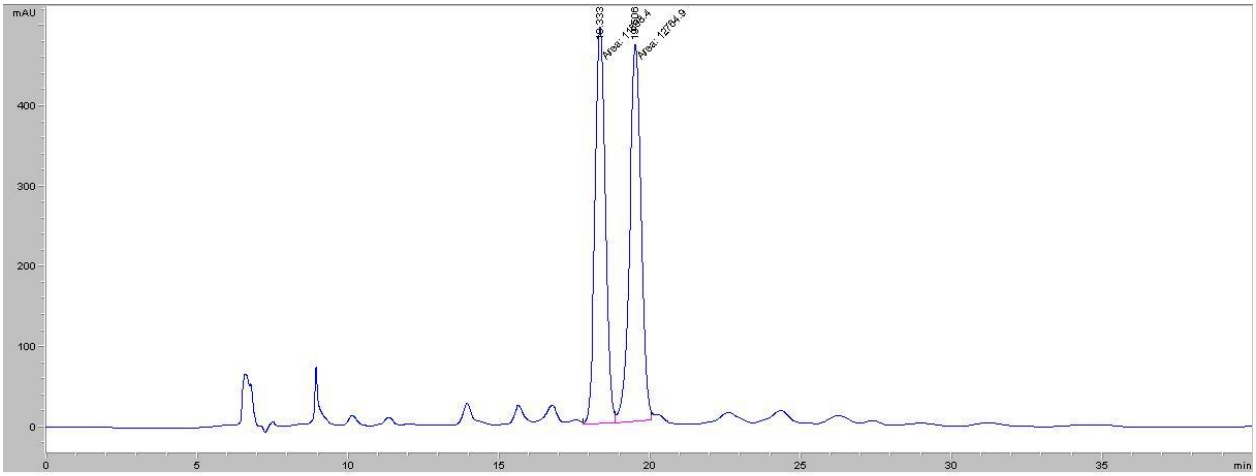


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 85%

6b

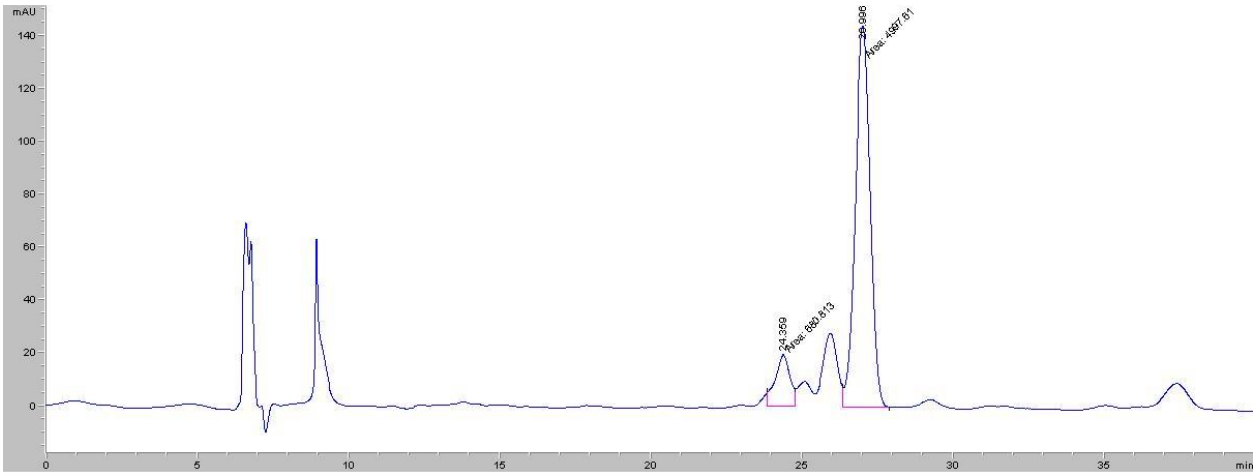


***rac*-6b**

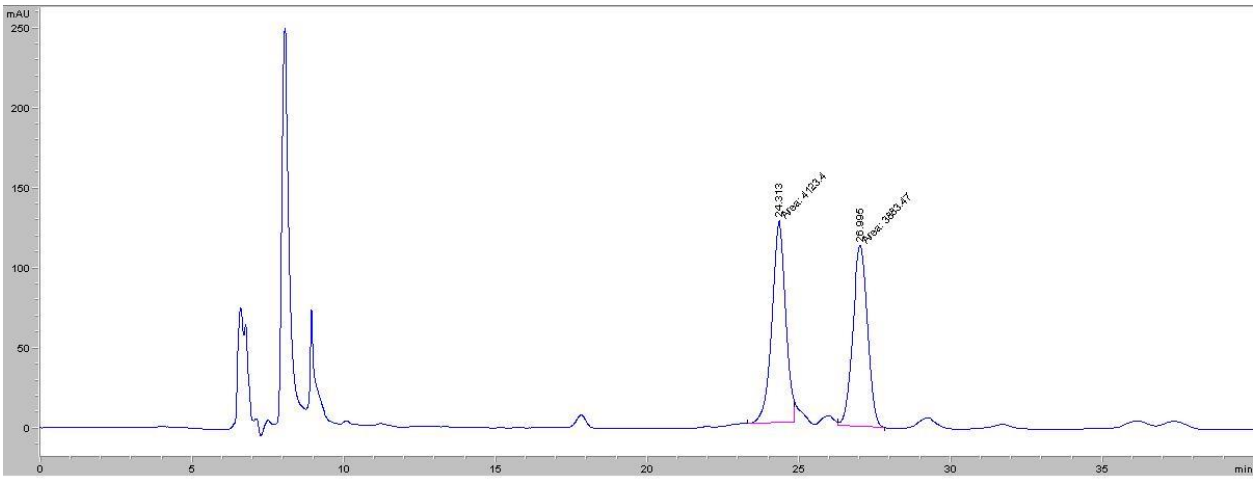


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 85%

7a

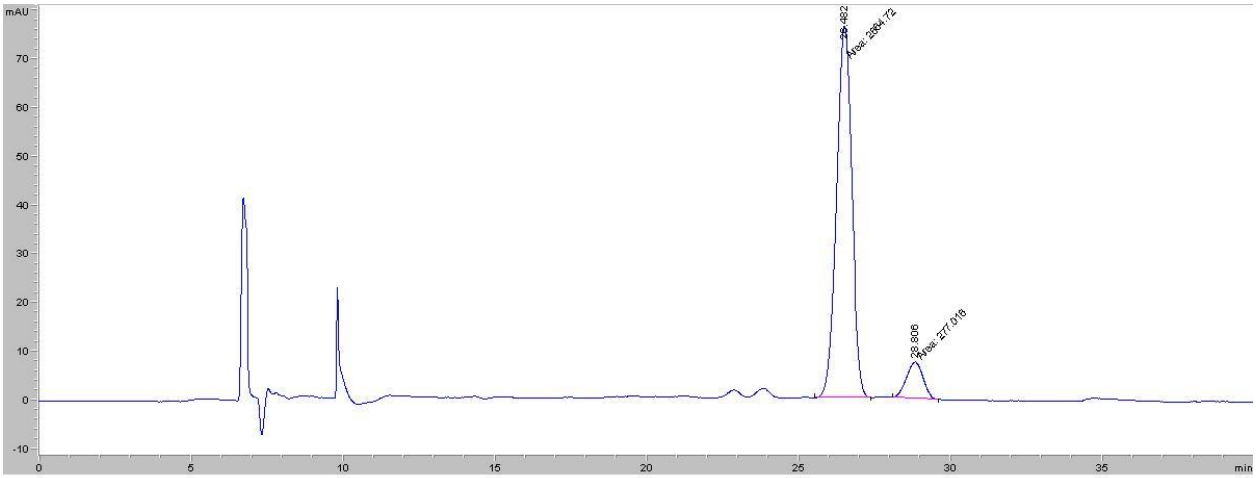


***rac*-7a**

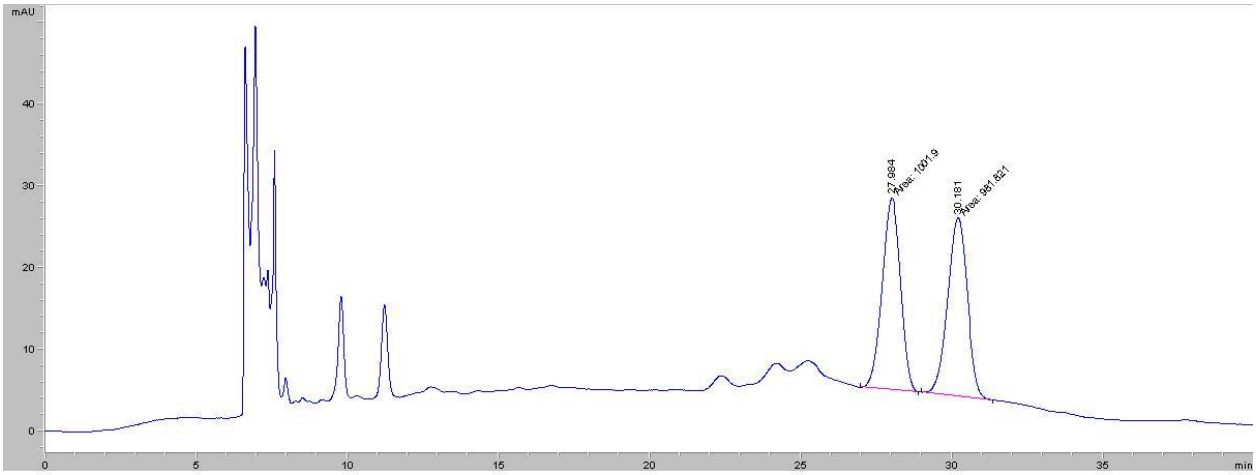


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 76%

7b

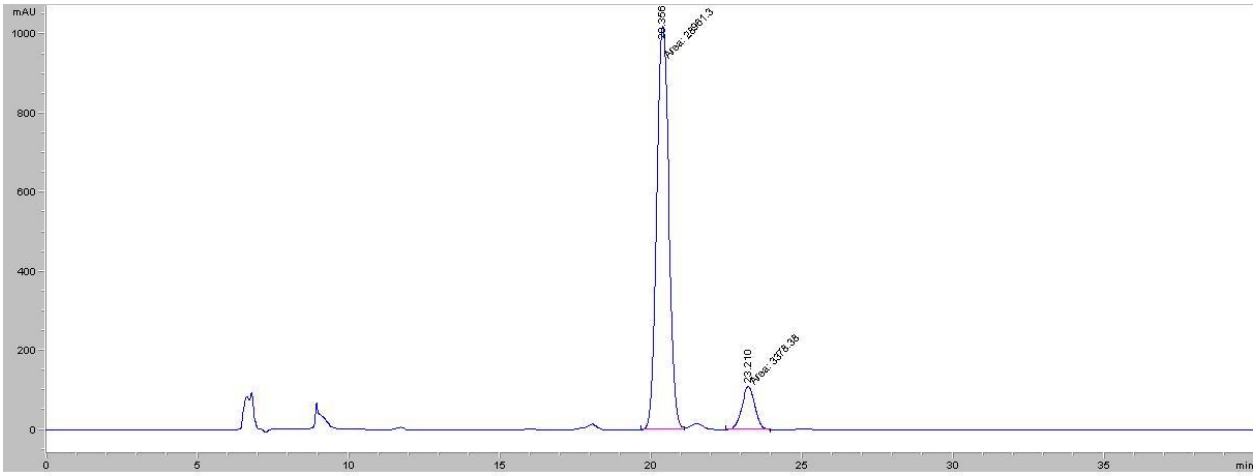


***rac*-7b**

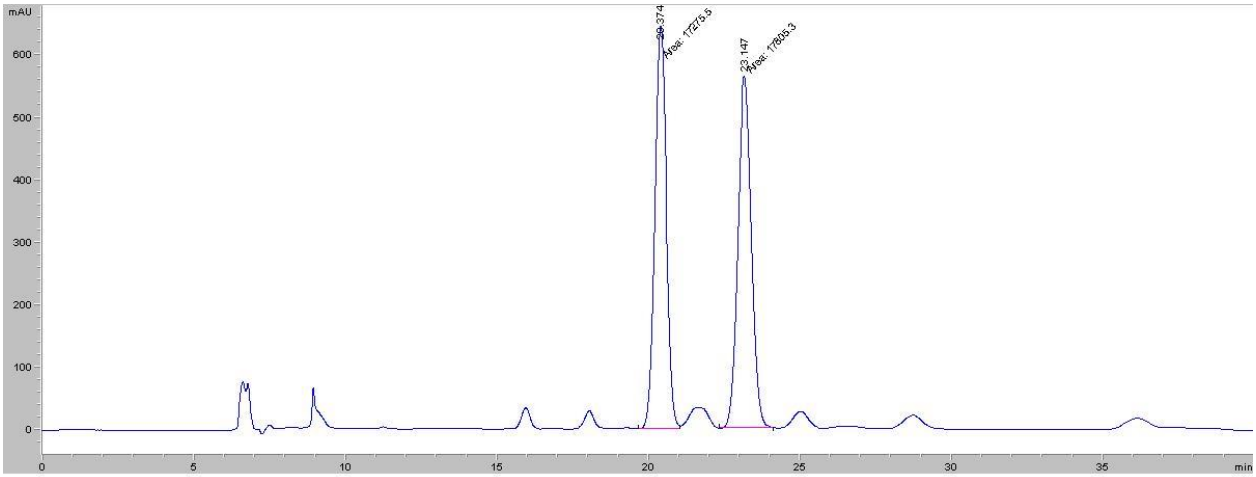


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 17:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 81%

7c

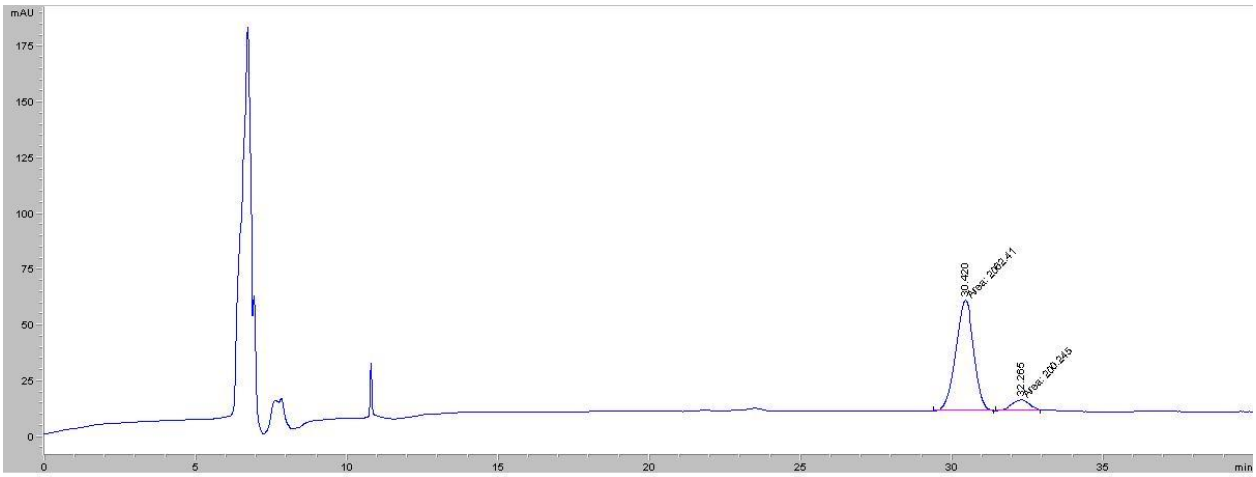


***rac*-7c**

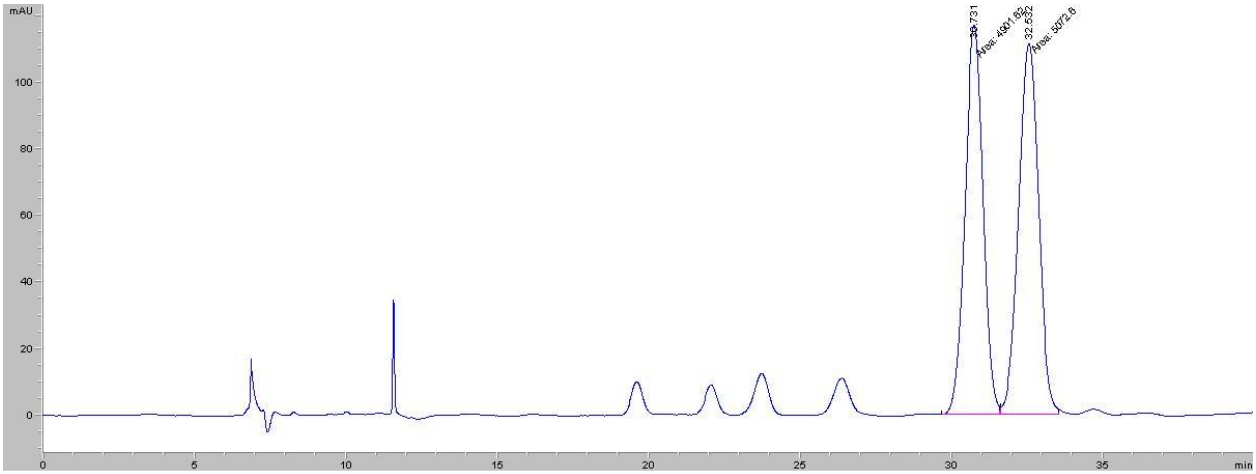


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 12:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 79%

7d

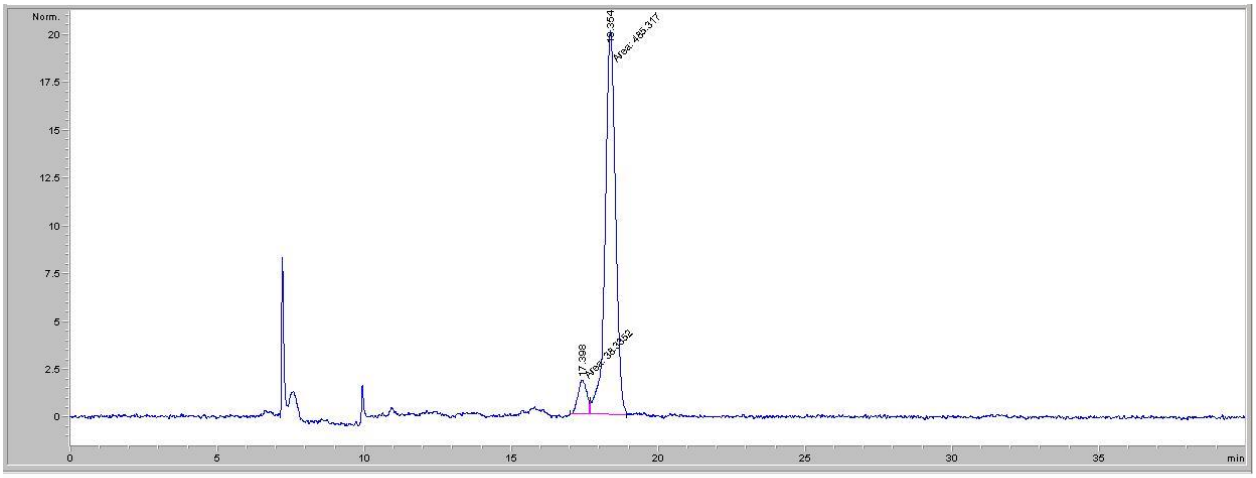


***rac*-7d**

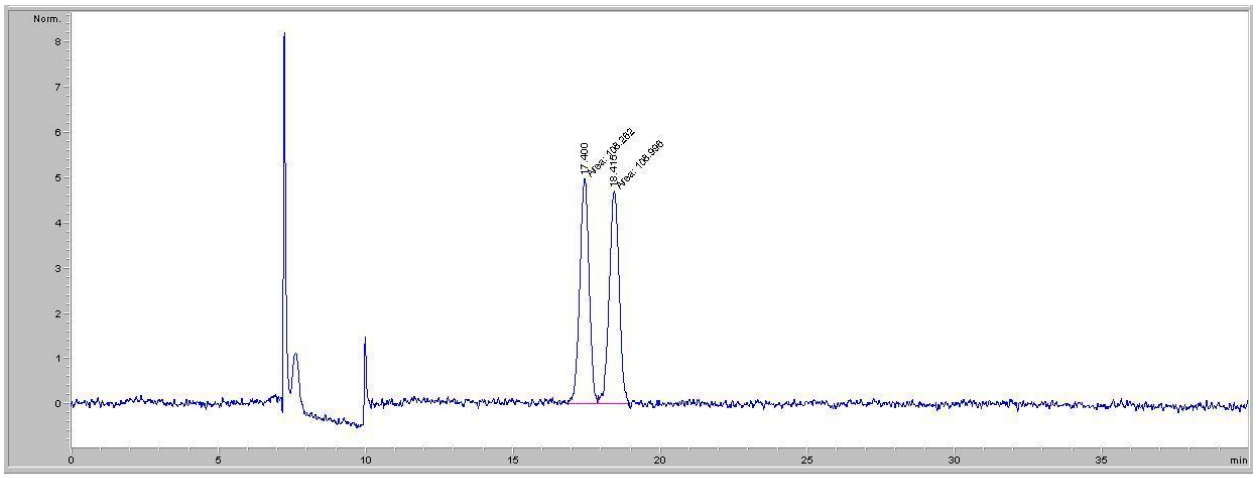


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 27:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 235 nm
ee: 82%

(+)-10c

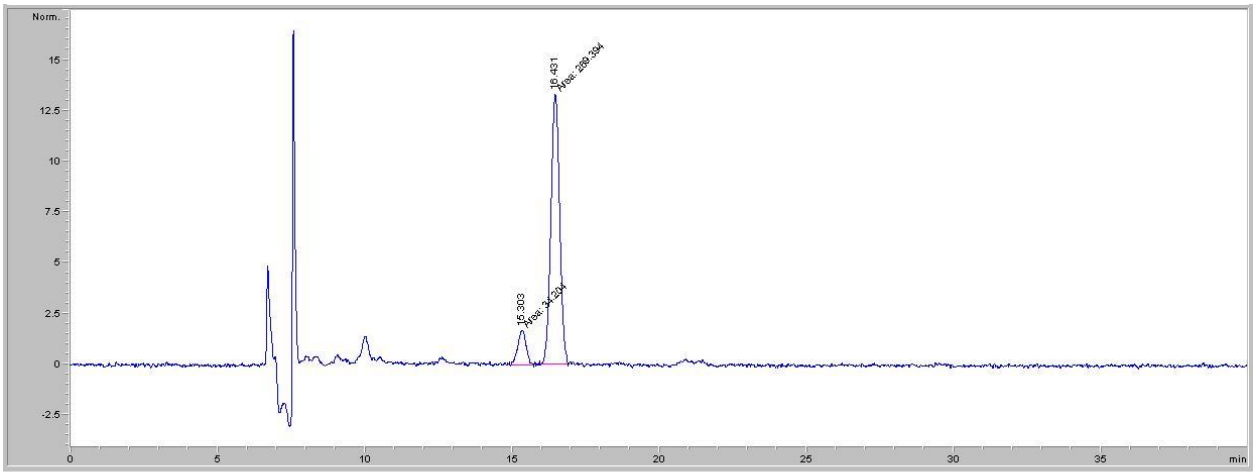


***rac*-10c**

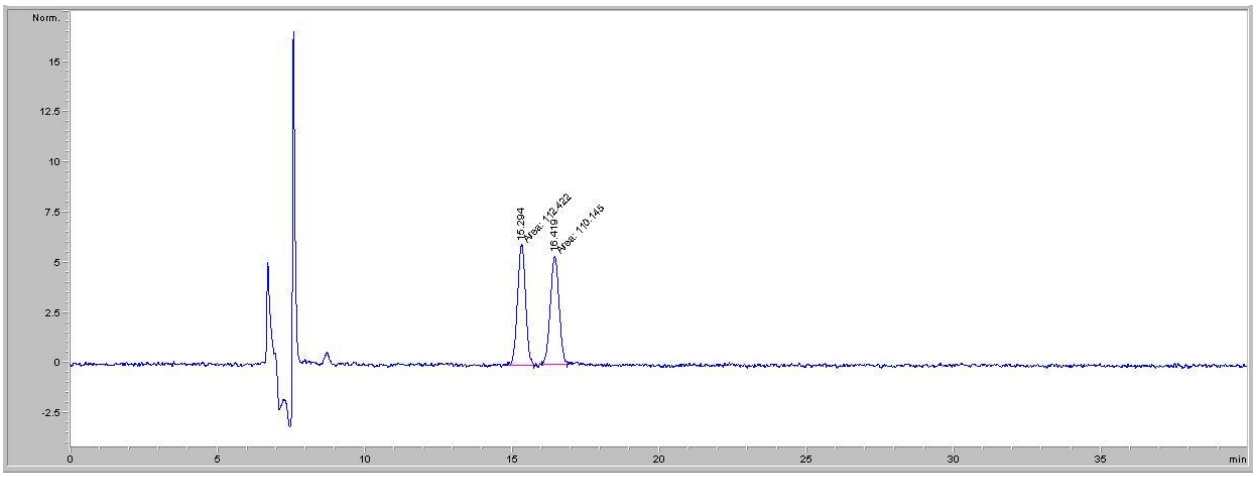


Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 72:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 254 nm
ee: 85%

(+)-10f



***rac*-10f**



Column: Chiralpak® IC, 4.6x250 mm, 5 µm particle size
Mobile phase: Hexanes:EtOH:CH_2Cl_2 17:2:1
Flow rate: 0.5 mL/min
Detection wavelength: 254 nm
ee: 77%

Supplementary references

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