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Supplementary Information

Formal Enantioslective Syntheses of Oseltamivir and Tamiphosphor

Saúl Silva and Christopher D. Maycock*

Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, EAN, 2780-157 Oeiras, Portugal and Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

* Email: maycock@itqb.unl.pt

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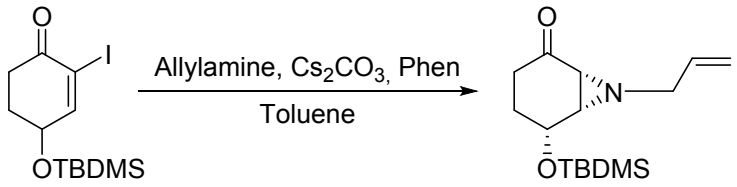
General Procedures

All chemicals used were of reagent grade. All solvents were dried by established methods.[1] Flash chromatography was performed on Kieselgel 60, particle size 0.032–0.063 mm. Analytical TLC: Aluminium-backed silica gel Merck 60 F_{254}. Infrared (IR) spectra were obtained using commercial FT-IR spectrophotometer and are in cm^{-1}. Specific rotations were measured using an automatic polarimeter and are reported as follows: $[\propto]_D^T$ (c= g/100mL; solvent). Melting points were determined with a capillary apparatus and are uncorrected. HRMS was recorded on a commercial apparatus (ESI Source). NMR spectra were obtained with a commercial 400 MHz (^{1}H NMR) instrument, 101 MHz (^{13}C NMR) and 162 MHz (^{31}P NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million relative to TMS (^{1}H and ^{13}C) or phosphoric acid (^{31}P) and coupling constants in hertz. The chemical shift assignments of all compounds were carried out with the help of 2D NMR experiments such as COSY, HMQC and HMBC. Chiral HPLC analysis was carried out by using a Chiralpak® AD-H (250 x 4.6 mm) column in a Waters system: 515 pump and 2485 dual λ absorbance detector.

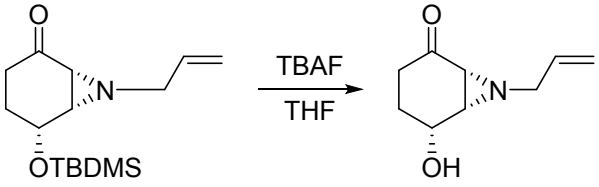
(±)-(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one (7)



(±)-**7**

In a flask under argon a mixture of racemic 4-((tert-butyldimethylsilyl)oxy)-2-iodocyclohex-2-en-1-one[2] (1.1 g, 3.1 mmol), anhydrous caesium carbonate (1.2 g, 1.1 eq.), anhydrous 1,10-phenantroline (590 mg, 1.0 eq.), allylamine (370 µL, 1.5 eq.) and dry toluene (7 mL) was stirred at room temperature. After 4 hours the reaction mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with hexane/ethyl acetate (9:1), afforded 770 mg (88%) of the pure compound as a colourless oil.

(±)-(1*R*,5*R*,6*S*)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one (8)

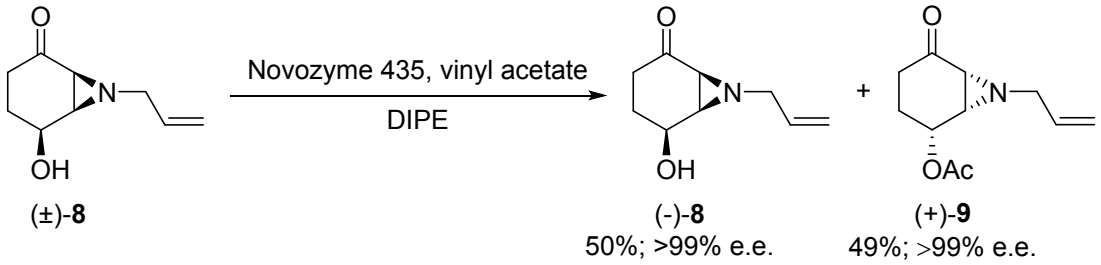


(±)-**7** (±)-**8**

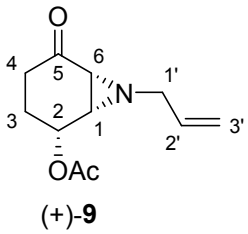
To a stirred solution of **(±)-7** (1.9 g, 6.75 mmol) in dry tetrahydrofuran (30 mL) under argon was added tetrabutylammonium fluoride (12.2 mL, 1 M in THF, 1.8 eq.). After 30

minutes the reaction mixture was diluted with dichloromethane (30 mL) and washed with water (30 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with hexane/ethyl acetate (1:1), afforded 1.15 g (100%) of the pure compound as colourless oil.

(+)-(1*S*,2*R*,6*R*)-5-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-yl acetate (9)

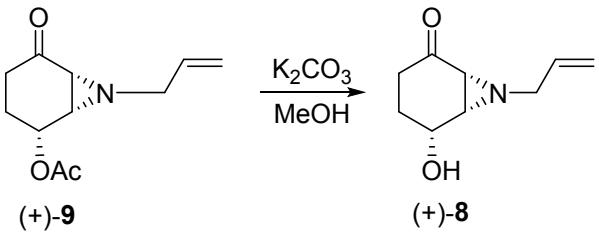


A mixture of **(±)-8** (1.36 g, 2.9 mmol), vinyl acetate (1.3 mL, 5 eq.), novozym 435 (680 mg) and diisopropyl ether (30mL) was agitated (700 r.p.m.) in a closed tube for 4 hours at 24°C. The solid-supported enzyme was then removed by decantation and the organic solution was evaporated to dryness. Purification by flash column chromatography, eluting with hexane/ethyl acetate (1:1), afforded 829 mg of **(+)-(9)** (49%) and 685 mg of **(-)-(8)** (50%, >99% e.e. HPLC), both as colourless oils.

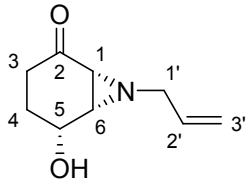


^{1}H RMN δ: 5.87 (1H, ddt, $J_{2',3'}$=17.3, $J_{2',3'}$=10.6, $J_{2',1'}$=5.4, H-2'); 5.29 (1H, dq, $J_{3',2'}$=17.3, ^{2}J=$J_{3',1'}$=1.5, H-3'); 5.16 (1H, dq, $J_{3',2'}$=10.6, ^{2}J=$J_{3',1'}$=1.3, H-3'); 5.12 (1H, ddd, $J_{2,3}$=9.9, $J_{2,3}$=5.3, $J_{2,1}$=2.3, H-2); 3.19 (1H, dd, ^{2}J=14.2, $J_{1',2'}$=5.4, H-2'); 2.86 (1H, dd, ^{2}J=14.2, $J_{1',2'}$=5.6, H-2'); 2.53-2.44 (2H, m, H-1, H-4); 2.28-2.06 (3H, m, H-3, H-4, H-6); 2.11 (3H, s, CH_3 Ac); 1.85-1.75 (1H, m, H-3). ^{13}C RMN δ: 204.4 (C-5); 170.8 (C=O Ac); 134.0 (C-2'); 117.0 (C-3'); 69.2 (C-2); 61.6 (C-1'); 46.5 (C-6); 43.9 (C-1); 34.8 (C-4); 22.8 (C-3); 21.1 (CH_3 Ac). IR: 1736, 1706 (C=O st.); 1235 (C-O-C st.); 1027 (C-O-C st.). $[\propto]_D^{20^oC}$ = +184 (c=1.3; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{17}NO_3$ 210.1125; Found 210.1120.

(+)-(1*R*,5*R*,6*S*)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one 8



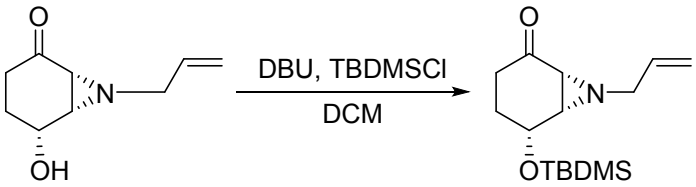
To a stirred solution of **(+)-9** (540 mg, 2.58 mmol) in methanol (5 mL) was added potassium carbonate (37 mg, 10 mol%). After 1 hour ammonium chloride (40 mg) was added. The salts were then filtered and the solution evaporated to dryness. 425 mg of alcohol (99%,>99% e.e. HPLC) were obtained as a colourless oil.



(+)-**8**

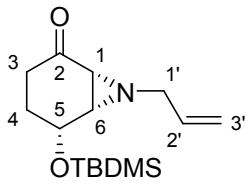
^{1}H RMN δ: 5.91 (1H, ddt, $J_{2',3'}$=17.0, $J_{2',3'}$=10.4, $J_{2',1'}$=5.9, H-1'); 5.26 (1H, dq, $J_{3',2'}$=17.2, ^2J=$J_{3',1'}$=1.5, H-3'); 5.19 (1H, dq, $J_{3',2'}$=10.3, ^2J=$J_{3',1'}$=1.2, H-3'); 4.17-4.14 (1H, m, H-5); 3.11 (1H, dd, ^2J=13.8, $J_{1',2'}$=5.8, H-1'); 2.99 (1H, dd, ^2J=13.8, $J_{1',2'}$=5.9, H-1'); 2.56-2.47 (2H, m, H-3, H-6);2.45 (1H, s br, OH); 2.19 (1H, d, $J_{1,6}$=5.9, H-1); 2.09-1.96 (2H, m, H-3, H-4); 1.86-1.77 (1H, m, H-4). ^{13}C RMN δ: 206.2 (C-2); 133.9 (C-2'); 117.9 (C-3'); 64.5 (C-5); 62.1 (C-1'); 48.1 (C-6); 47.4 (C-1); 33.8 (C-3); 29.7 (C-4). IR: 3400 (OH st); 1694 (C=O st.); 1054 (C-O st.); 924 (CH bend). $[\propto]_D^{20^oC}$ = +126 (c=0.8; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{14}NO_2$ 168.1019; Found 168.1015.

(+)-(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-2-one (7)



(+)-**8** (+)-**7**

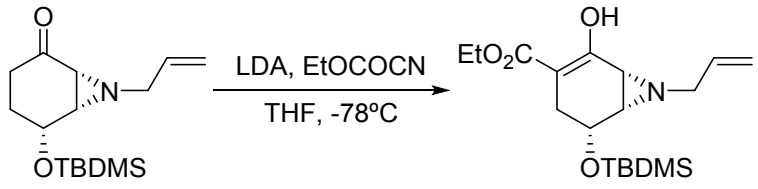
To a stirred solution of **(+)-8** (50 mg, 0.30 mmol) in dry dichloromethane (1 mL) under argon was added DBU (54 µL, 1.2 eq.) and *tert*-butyldimethylsilyl chloride (50 mg, 1.1 eq.) at 0^{o}C. After 1 hour the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL). The mixture was then extracted with dichloromethane (3x5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with hexane/ethyl acetate (95:5), afforded 80 mg (95%) of the pure compound as colourless oil.



(+)-**7**

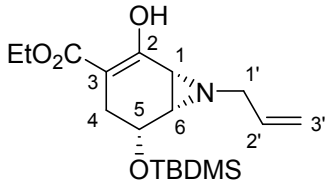
^{1}H RMN δ: 5.88 (1H, ddt, $J_{2',3'}$=17.1, $J_{2',3'}$=10.5, $J_{2',1'}$=5.3, H-2'); 5.37 (1H, dq, $J_{3',2'}$=17.3, ^2J=$J_{3',1'}$=1.6, H-3'); 5.14 (1H, dq, $J_{3',2'}$=10.5, ^2J=$J_{3',1'}$=1.5, H-3'); 4.10 (1H, ddd, $J_{5,4}$=10.4, $J_{5,4}$=5.0, $J_{5,6}$=1.8, H-5); 3.25 (1H, ddt, ^2J=14.5, $J_{1',2'}$=5.3, $J_{1',3'}$=1.5, H-1'); 2.82 (1H, ddt, ^2J=14.5, $J_{1',2'}$=5.1, $J_{1',3'}$=1.5, H-1'); 2.42 (1H, ddd, ^2J=18.2, $J_{3,4}$=5.0, $J_{3,4}$=2.5, H-3), 2.21-2.00 (4H, m, H-1, H-3, H-4, H-6); 1.66-1.59 (1H, m, H-4); 0.92 (9H, s, ^{t}Bu TBDMS); 0.11 (3H, s, Me TBDMS); 0.10 (3H, s, Me TBDMS). ^{13}C RMN δ: 205.8 (C-2); 134.1 (C-2'); 116.8 (C-3'); 67.7 (C-5); 61.8 (C-1'); 47.6, 46.8 (C-1, C-6); 35.4 (C-3); 25.9 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); -4.58 (Me TBDMS); -4.63 (Me TBDMS). IR: 1712 (C=O st.), 1095 (Si-O st.), 838 (Si-O-C bend.). $[\propto]_D^{20^oC}$ = +147 (c=0.8; DCM). Anal. Calcd for $C_{15}H_{27}NO_2Si$: C 64.01; H 9.67; N 4.98. Found: C 64.21; H 9.46; N 4.81.

Ethyl (-)-
(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (10)



(+)-**7** (-)-**10**

To a solution of diisopropylamine (350 µL, 1.6 eq.) in THF (2.5 mL) under argon at 0°C was added *n*-butyllithium (1.46 mL, 1.6 M in hexanes, 1.5 eq.) drop by drop, and the reaction mixture was stirred at this temperature for 15 minutes, then cooled at –78 °C and a solution of **(+)-7** (440 mg, 1.56 mmol) in THF (2.5 mL) was slowly added. Stirring at –78 °C was continued for further 30 minutes and ethyl cyanoformate (150 µL, 1.2 eq.) was then added. The reaction mixture was stirred at –78 °C for 1 hour. The reaction was quenched with saturated ammonium chloride aqueous solution (5mL). The mixture was then extracted with dichloromethane (3 x 5 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. Purification by flash column chromatography, eluted with hexane/ethyl acetate (95:5), afforded 440 mg (80%) of the pure compound as a colourless oil.



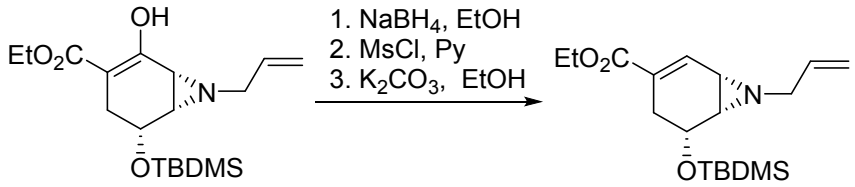
(-)-**10**

Although the two ketone tautomers can be observed in the ^{1}H and ^{13}C NMR spectra, only the enol is described.

^{1}H RMN δ: 12.30 (1H, s, OH); 5.80 (1H, ddt, $J_{2',1'}$=17.2, $J_{2',1'}$=10.5, $J_{2',3'}$=5.2, H-2'); 5.37 (1H, dq, $J_{3',2'}$=17.3, ^2J=$J_{3',1'}$=1.6, H-3'); 5.14 (1H, dq, $J_{3',2'}$=10.4, ^2J=$J_{3',1'}$=1.5, H-3'); 4.26-4.11 (2H, m, CH_2 Et); 3.97 (1H, ddd, $J_{5,4}$=9.6, $J_{5,4}$=6.4, $J_{5,6}$=2.4, H-5); 3.29 (1H, dd, ^2J=14.5, $J_{1',2'}$=5.2, H-1'); 2.74 (1H, dd, ^2J=14.5, $J_{1',2'}$=5.2, H-1'); 2.44 (1H, ddd, ^2J=14.9, $J_{4,5}$=6.6, J=1.5, H-4); 2.20-2.11 (2H, m, H-4, H-6); 2.07 (1H, d, $J_{1,6}$=6.5, H-1); 1.27 (3H, t, ^3J=7.1, CH_3 Et); 0.91 (9H, s, ^{t}Bu TBDMS); 0.11 (6H, s,

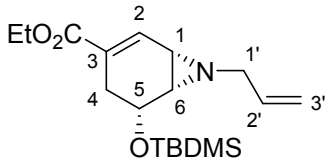
2x Me TBDMS). ^{13}C RMN δ: 201.5 (C-2); 169.3 (C=O CO_2Et); 134.2 (C-2'); 116.7 (C-3'); 101.6 (C-3); 67.2 (C-5); 61.5 (C-1'); 60.5 (CH_2 Et); 47.4 (C-6), 39.8 (C-1); 27.2 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 14.3 (CH_3 Et); -4.59 (Me TBDMS); -4.63 (Me TBDMS). IR: 1651 (C=O st.); 1277, 1254, 1229 (C-O-C st, C-O st.); 1090 (Si-O st.), 837 (Si-O-C bend.). $[\propto]_D^{20^oC}$ = -29 (c=0.7; DCM). Anal. Calcd for $C_{18}H_{31}NO_4Si$: C 61.15; H 8.84; N 3.96. Found: C 61.35; H 8.40; N 3.77.

Ethyl (-)-(1*S*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (11)



(-)-**10** (-)-**11**

To a stirred solution of **10** (400 mg, 1.13 mmol) in ethanol abs. (3.5 mL) at 0ºC was added sodium borohydride (43 mg, 1 eq.) portionwise. After 1 hour the reaction was quenched with a saturated ammonium chloride aqueous solution (3.5mL) and the mixture was extracted with dichloromethane (2x 5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The obtained crude (400 mg) was dissolved in dry pyridine (3.5 mL) under argon and mesyl chloride (175 µL, 2 eq.) was added at 0ºC. After 1 hour of stirring at room temperature the reaction mixture was diluted with dichloromethane (5 mL) and washed with water (5mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. The obtained crude (515 mg) was dissolved in ethanol abs. (3.5 mL) and potassium carbonate (310 mg, 2 eq.) was added. After 1 hour ammonium chloride (310 mg) was added. The salts were then filtered and the solution evaporated to dryness. Purification by flash column chromatography, eluted with hexane/ethyl acetate (9:1), afforded 190 mg (50%) of the pure compound as colourless oil.

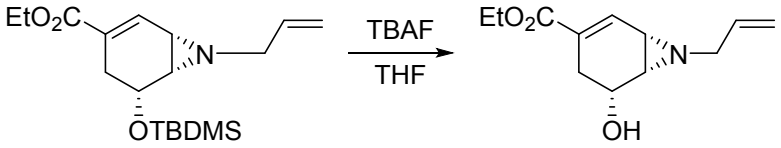


(-)-**11**

^{1}H RMN δ: 7.12 (1H, dd, $J_{2,1}$=4.6, $J_{2,4}$=3.3, H-2); 5.88 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.3, H-2'); 5.35 (1H, dq, $J_{3',2'}$=17.2, ^2J=$J_{3',1'}$=1.7, H-3'); 5.11 (1H, dq, $J_{3',2'}$=10.5, ^2J=$J_{3',1'}$=1.4, H-3'); 4.17 (2H, q, ^3J=7.1, CH_2 Et); 4.00 (1H, ddd, $J_{5,4}$=9.4, $J_{5,4}$=6.8, $J_{5,6}$=2.3, H-5); 3.21 (1H, ddt, ^2J=14.4, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'); 2.77 (1H, ddt, ^2J=14.5, $J_{1',2'}$=5.1, $J_{1',3'}$=1.5, H-1'); 2.67 (1H, dd, ^2J=16.5, $J_{4,5}$=6.5, H-4); 2.20 (1H, ddd, ^2J=16.4, $J_{4,5}$=9.7, $J_{4,2}$=3.1, H-4); 2.08 (1H, dt, $J_{6,1}$=6.3, $J_{6,5}$= $J_{6,4}$=2.0, H-6); 2.00 (1H, dd, $J_{1,6}$=6.1, $J_{1,2}$=4.9, H-1); 1.27 (3H, t, ^3J=7.1, CH_3 Et); 0.92 (9H, s, ^{t}Bu TBDMS); 0.11 (6H, s, 2x Me TBDMS). ^{13}C RMN δ: 166.3 (C=O CO_2Et); 135.8 (C-2); 134.6 (C-2'); 130.7 (C-3); 116.5 (C-3'); 67.1 (C-5); 61.9 (C-1'); 60.5 (CH_2 Et); 47.6 (C-6), 37.1 (C-1); 30.5 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 14.3 (CH_3 Et); -4.56 (Me TBDMS); -4.61 (Me TBDMS). IR: 1712 (C=O st.); 1250

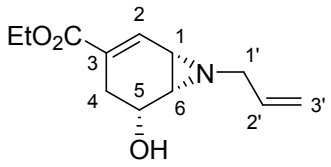
(C-O-C st); 1070 (Si-O st.), 836 (Si-O-C bend.). $[\propto]_D^{20^oC}$ = -70 (c=0.7; DCM). Anal. Calcd for $C_{18}H_{31}NO_3Si$: C 64.05; H 9.26; N 4.15. Found: C 64.08; H 9.37; N 4.21.

Ethyl (-)-(1*S*,5*R*,6*S*)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (12)



(-)-**11** (-)-**12**

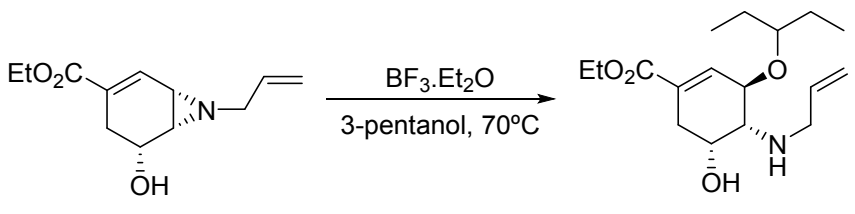
To a stirred solution of **11** (100 mg, 0.296 mmol) in dry tetrahydrofuran (3 mL) under argon was added tetrabutylammonium fluoride (530 µL, 1 M in THF, 1.8 eq.). After 1 hour the reaction mixture was diluted with dichloromethane (3 mL) and washed with water (3 mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with hexane/ethyl acetate (1:1), afforded 66 mg (100%) of the pure compound as white solid.



(-)-**12**

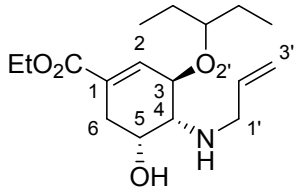
^{1}H RMN δ: 7.14 (1H, dd, $J_{2,1}$=4.6, $J_{2,4}$=3.3, H-2); 5.92 (1H, ddt, $J_{2',3'}$=16.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.8, H-2'); 5.26 (1H, dq, $J_{3',2'}$=17.2, ^2J=$J_{3',1'}$=1.6, H-3'); 5.16 (1H, dq, $J_{3',2'}$=10.4, ^2J=$J_{3',1'}$=1.2, H-3'); 4.18 (2H, q, ^3J=7.1, CH_2 Et); 4.00 (1H, tdd, $J_{5,4}$=$J_{5,OH}$=8.8, $J_{5,4}$=6.6, $J_{5,6}$=2.3, H-5); 3.06 (1H, dd, ^2J=13.9, $J_{1',2'}$=5.4, H-1'); 2.95 (1H, dd, ^2J=14.0, $J_{1',2'}$=5.7, H-1'); 2.86 (1H, ddd, ^2J=16.4, $J_{4,5}$=6.6, $J_{4,6}$=1.3, H-4); 2.30 (1H, dt, $J_{6,1}$=6.3, $J_{6,5}$=$J_{6,4}$=2.0, H-6); 2.14-2.04 (2H, m, H-1, H-4); 1.66 (1H, d, $J_{OH,5}$=8.6, OH); 1.27 (3H, t, ^3J=7.1, CH_3 Et). ^{13}C RMN δ: 166.1 (C=O CO_2Et); 135.5 (C-2); 134.7 (C-2'); 130.5 (C-3); 117.2 (C-3'); 66.1 (C-5); 62.1 (C-1'); 60.7 (CH_2 Et); 46.7 (C-6); 37.9 (C-1); 30.5 (C-4); 14.2 (CH_3 Et). IR: 3400 (OH st.); 1705 (C=O st.); 1242 (C-O-C st., C-O st.); 1036 (C-O-C st.). $[\propto]_D^{20^oC}$ = -140 (c=0.7; DCM). M.p. = 82ºC. Anal. Calcd for $C_{12}H_{17}NO_3$: C 64.55; H 7.67; N 6.27. Found: C 64.67; H 7.87; N 6.50.

Ethyl (-)-(3*R*,4*R*,5*R*)-5-hydroxy-3-(pentan-3-yloxy)-4-[(prop-2-en-1-yl)amino]cyclohex-1-ene-1-carboxylate (13)



(-)-**12** (-)-**13**

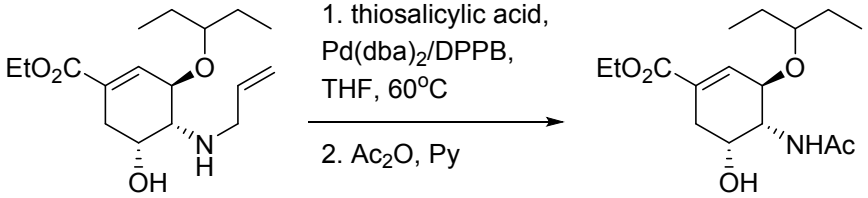
To a stirred solution of **12** (120 mg, 0.54 mmol) in 3-pentanol (3.5 mL) under argon was added boron trifluoride diethyl etherate (100 µL, 1.5 eq.). After 30 minutes of stirring at 70ºC the reaction was quenched with a saturated sodium bicarbonate aqueous solution (5mL) and the mixture was extracted with ethyl acetate (3x5mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with ethyl acetate, afforded 150 mg (90%) of the pure compound as white solid.



(-)-**13**

^{1}H RMN δ: 6.86 (1H, q, $J_{2,3}$=$J_{2,6}$=1.9, H-2); 5.90 (1H, dddd, $J_{2',3'}$=16.8, $J_{2',3'}$=10.3, $J_{2',1'}$=6.3, $J_{2',1'}$=5.4, H-2'); 5.22 (1H, dq, $J_{3',2'}$=17.2, ^{2}J=$J_{3',1'}$=1.5, H-3'); 5.12 (1H, dq, $J_{3',2'}$=10.3, ^{2}J=$J_{3',1'}$=1.4, H-3'); 4.20 (2H, q, ^{3}J=7.1, CH_2 Et); 4.17-4.14 (1H, m, H-5); 4.03 (1H, dq, $J_{3,4}$=8.1, $J_{3,2}$= $J_{3,6}$=2.2, H-3); 3.39-3.32 (2H, m, H-1', CH pentyl); 3.23 (1H, ddt, ^{2}J=14.2, $J_{1',2'}$=6.4, $J_{1',3'}$=1.2, H-1'); 2.72 (1H, dd, $J_{4,3}$=8.1, $J_{4,5}$=2.5, H-4); 2.58 (1H, ddt, ^{2}J=18.8, $J_{6,5}$=3.1, $J_{6,2}$=$J_{6,3}$=1.6, H-6); 2.48 (1H, ddt, ^{2}J=18.9, $J_{6,5}$=4.9, $J_{6,2}$=$J_{6,3}$=2.6, H-6); 2.40 (2H, s br, OH, NH); 1.64-1.44 (4H, m, CH_2 pentyl); 1.28 (3H, t, ^{3}J=7.1, CH_3 Et); 0.94 (3H, t, ^{3}J=7.4, CH_3 pentyl); 0.92 (3H, t, ^{3}J=7.5, CH_3 pentyl). ^{13}C RMN δ: 166.6 (C=O CO_2Et); 136.4 (C-2'); 136.3 (C-2); 128.5 (C-1); 116.1 (C-3'); 81.0 (CH pentyl); 73.2 (C-3); 63.8 (C-5); 60.8 (C-4); 60.6 (CH_2 Et); 49.3 (C-1'); 29.9 (C-6); 26.5, 25.6 (2xCH_2 pentyl); 14.2 (CH_3 Et); 9.7, 9.5 (2xCH_3 pentyl). IR: 3400 (OH st., NH st.); 1715 (C=O st.); 1251 (C-O-C st.); 1054 (C-O-C st.). $[\propto]_D^{20^oC}$ = -123 (c=1.0; DCM). M.p. = 95-95.5ºC. Anal. Calcd for $C_{12}H_{17}NO_3$: C 65.57; H 9.39; N 4.50. Found: C 65.83; H 9.61; N 4.75.

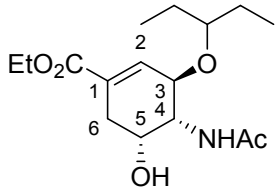
Ethyl (-)-(3*R*,4*R*,5*R*)-4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (14)



(-)-**13** (-)-**14**

In a flask under argon a mixture of bis(dibenzylideneacetone)palladium(0) (26 mg, 10 mol%), 1,4-Bis(diphenylphosphino)butane (20 mg, 10 mol%) and dry tetrahydrofuran (1 mL) was stirred at room temperature for 15 minutes. This mixture was then added to a stirred solution of **13** (140 mg, 0.45 mmol) in tetrahydrofuran (1 mL) under argon followed by addition of thiosalicylic acid (143 mg, 2 eq.). After 30 minutes of stirring at 60ºC the reaction was cooled to 0ºC and pyridine (180 µL, 5 eq.) and acetic anhydride (47 µL, 1.1 eq.) were added. After additional 15 minutes of styring at room temperature the reaction was quenched with a

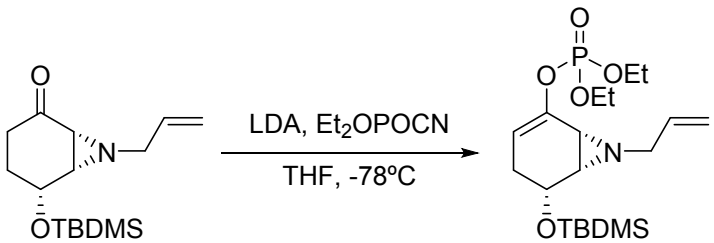
saturated sodium bicarbonate aqueous solution (2mL) and the mixture was extracted with ethyl acetate (3x 2mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with ethyl acetate, afforded 117 mg (83%) of the pure compound as white solid.



(-)-**14**

^{1}H RMN δ: 6.84 (1H, dt, $J_{2,3}$=3.3, $J_{2,6}$=1.8, H-2); 5.93 (1H, d, $J_{NH,4}$=7.0, NH); 4.30 (1H, td, $J_{5,6}$=4.9, $J_{5,4}$=2.3, H-5); 4.25-4.21 (1H, m, H-3); 4.21 (2H, q, ^{3}J=7.1, CH_2 Et); 3.90 (1H, td, $J_{4,3}$=$J_{4,NH}$=7.2, $J_{4,5}$=2.3, H-4); 3.40 (1H, p, ^{3}J=5.8, CH pentyl); 2.69 (1H, ddt, ^{2}J=18.5, $J_{6,5}$=4.3, $J_{6,2}$=$J_{6,3}$=2.1, H-6); 2.43 (1H, ddt, ^{2}J=18.5, $J_{6,5}$=5.3, $J_{6,2}$=$J_{6,3}$=1.3, H-6); 2.04 (3H, s, CH_3 Ac); 1.58-1.48 (4H, m, 2xCH_2 pentyl); 1.29 (3H, t, ^{3}J=7.1, CH_3 Et); 0.92 (6H, t, ^{3}J=7.4, 2xCH_3 pentyl). ^{13}C RMN δ: 171.7 (C=O Ac); 166.5 (C=O CO_2Et); 136.0 (C-2); 129.3 (C-1); 81.9 (CH pentyl); 72.6 (C-3); 67.1 (C-5); 60.9 (CH_2 Et); 55.1 (C-4); 31.5 (C-6); 26.3, 26.0 (2xCH_2 pentyl); 23.5 (CH_3 Ac); 14.2 (CH_3 Et); 9.6, 9.5 (2xCH_3 pentyl). IR: 3300 (OH st., NH st.); 1714 (C=O st. ester); 1651 (C=O st. amide); 1545 (Amide II); 1250 (C-O-C st.); 1092, 1054 (C-O-C st.). $[\propto]_D^{20^oC}$ = -100 (c=1.7; AcOEt) [lit: $[\propto]_D^{25^oC}$ = -104 (c=3.0; AcOEt)]. M.p. = 132ºC (lit: 131.9-132.2ºC).

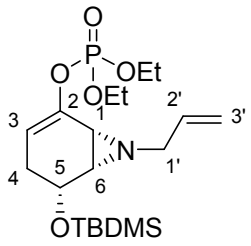
(+)-(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-2-yl diethyl phosphate (15)



(+)-7 **(+)-15**

To a solution of diisopropylamine (600 µL, 1.6 eq.) in THF (5 mL) under argon at 0°C was added *n*-butyllithium (2.5 mL, 1.6 M in hexanes, 1.5 eq.) drop by drop, and the reaction mixture was stirred at this temperature for 15 minutes, then cooled at –78 °C and a solution of **(+)-7** (750 mg, 2.7 mmol) in THF (5 mL) was slowly added. Stirring at –78 °C was continued for further 30 minutes and diethyl cyanophosphonate (480 µL, 1.2 eq.) was then added. The reaction mixture was stirred at –78 °C for 1 hour. The reaction was quenched with saturated ammonium chloride aqueous solution (10mL). The mixture was then extracted with dichloromethane (3 x 10 mL), the combined organic phases were dried ($MgSO_4$), and the

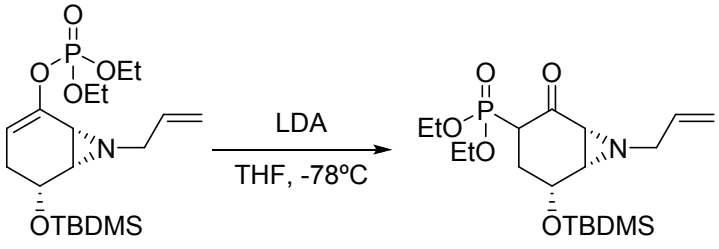
solvent evaporated. Purification by flash column chromatography, eluted with hexanes/ethyl acetate (2:1), afforded 962 mg (80%) of the pure compound as colourless oil.



(+)-15

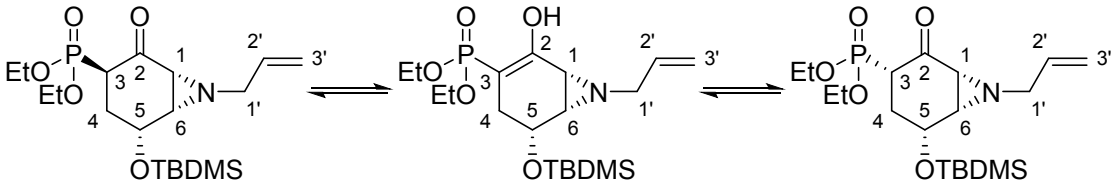
^{1}H RMN δ: 5.89 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.5, $J_{2',1'}$=5.3, H-2'); 5.37 (1H, dq, $J_{3',2'}$=17.3, ^{2}J=$J_{3',1'}$=1.7, H-3'); 5.29-5.23 (1H, m, H-3); 5.11 (1H, dq, $J_{3',2'}$=10.5, ^{2}J=$J_{3',1'}$=1.5, H-3'); 4.22-4.13 (4H, m, 2xCH_2 Et); 4.04 (1H, t, J=8.0, H-5); 3.25 (1H, ddt, ^{2}J=14.5, $J_{1',2'}$=5.2, $J_{1',3'}$=1.5, H-1'); 2.69 (1H, ddt, ^{2}J=14.6, $J_{1',2'}$=5.2, $J_{1',3'}$=1.4, H-1'); 2.23-2.03 (4H, m, H-1, H-4, H-6); 1.37 (3H, td, ^{3}J=7.1, $^{4}J_{H,P}$=1.0, CH_3 Et); 1.36 (3H, td, ^{3}J=7.1, $^{4}J_{H,P}$=1.0, CH_3 Et); 0.91 (9H, s, ^{t}Bu TBDMS); 0.09 (3H, s, Me TBDMS); 0.07 (3H, s, Me TBDMS). ^{13}C RMN δ: 145.5 (d, $^{2}J_{C,P}$=9, C-2); 134.6 (C-2'); 116.4 (C-3'); 107.6 (d, $^{3}J_{C,P}$=5, C-3); 66.6 (C-5); 64.44 (d, $^{2}J_{C,P}$=6, CH_2 Et); 64.38 (d, $^{2}J_{C,P}$=6, CH_2 Et); 61.5 (C-1'); 46.7 (C-6), 39.1 (d, $^{3}J_{C,P}$=6, C-1); 29.3 (C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 16.1 (d, $^{3}J_{C,P}$=7, CH_3 Et); -4.63 (Me TBDMS); -4.66 (Me TBDMS). ^{31}P RMN δ: -6.2. IR (neat): 1033 (P-O-C st). $[\alpha]_D^{20^oC}$ = +45 (c=1.1; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{37}NO_5PSi$ 418.2173; Found 418.2177.

Diethyl (+)-[(1*R*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-oxo-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]heptan-3-yl]phosphonate (16)



(+)-15 **(+)-16**

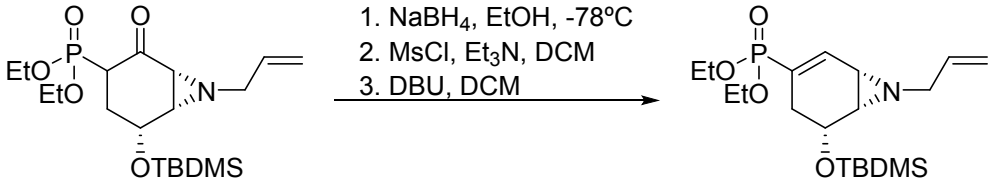
To a solution of diisopropylamine (875 µL, 2.4 eq.) in THF (5 mL) under argon at 0°C was added *n*-butyllithium (3.6 mL, 1.6 M in hexanes, 2.2 eq.) drop by drop, and the reaction mixture was stirred at this temperature for 15 minutes, then cooled at –78 °C and a solution of **15** (1.1 g, 2.6 mmol) in THF (5 mL) was slowly added. After 30 minutes of stirring at this temperature the reaction was quenched with saturated ammonium chloride aqueous solution (10mL). The mixture was then extracted with dichloromethane (3 x 10 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. Purification by flash column chromatography, eluted with hexanes/ethyl acetate (2:1), afforded 996 mg (91%) of the pure compound as colourless oil.



16(I) **16(II)** **16(III)**

^{1}H NMR δ: 10.92 (0.1H, s, OH II), 5.93-5.81 (1H, m, H-2'); 5.40-5.34 (1H, m, H-3'); 5.29-5.23 (1H, m, H-3); 5.13 (1H, d, $J_{3',2'}$=10.5, H-3'); 4.56-4.51 (0.5H, m, H-5 I); 4.3-3.9 (4.5H, m, 2xCH_2 Et, H-5); 3.31-3.12 (1H, m, H-1'); 2.99-2.69 (1.9H, m, H-3, H-1'); 2.54 (0.4H, p, ^{2}J=$^{3}J_{H,P}$=$J_{4,3}$= $J_{4,2}$=12.4, H-4 II); 2.39-1.85 (3.6H, H-1, H-4, H-6); 1.36-1.31 (3H, m, CH_3 Et); 0.926, 0.914, 0.910 (9H, s, ^{t}Bu TBDMS); 0.13, 0.103, 0.095 (6H, s, Me TBDMS).^{13}C NMR δ: 200.2 (d, $^{2}J_{C,P}$=7, C-2 III); 199.7 (d, $^{2}J_{C,P}$=5, C-2 I); 168.0 (d, $^{2}J_{C,P}$=7, C-2 II); 134.4 (II), 134.0 (I), 133.8 (III) (C-2'); 116.9 (I), 116.8 (III), 116.5 (II) (C-3'); 84.5 (d, $^{1}J_{C,P}$=183, C-3 II); 67.5 (d, $^{3}J_{C,P}$=4, C-5 II); 67.5 (d, $^{3}J_{C,P}$=11, C-5 II); 67.4 (d, $^{3}J_{C,P}$=18, C-5 III); 65.1 (d, $^{3}J_{C,P}$=1, C-5 I); 63.0 (d, $^{2}J_{C,P}$=7), 62.6 (d, $^{2}J_{C,P}$=6), 62.4 (d, $^{2}J_{C,P}$=7), 61.7 (d, $^{2}J_{C,P}$=4) (CH_2 Et); 61.9 (I), 61.5 (II), 61.2 (III) (C-1'); 48.3 (d, $^{4}J_{C,P}$=1, C-6 III); 48.1 (d, $^{3}J_{C,P}$=4, C-1 III); 46.8 (C-6 I); 46.5 (d, $^{3}J_{C,P}$=1, C-1 III); 46.3 (d, $^{4}J_{C,P}$=2, C-6 III); 45.5 (d, $^{1}J_{C,P}$=126, C-3 I); 44.9 (d, $^{1}J_{C,P}$=134, C-3 III); 40.6 (d, $^{3}J_{C,P}$=19, C-1 II); 27.5 (d, $^{3}J_{C,P}$=5, C-4 II); 27.4 (d, $^{3}J_{C,P}$=3, C-4 III); 27.0 (d, $^{3}J_{C,P}$=6, C-4 I); 25.8, 25.7 (3xMe ^{t}Bu); 18.14 (II), 18,10 (I), 18.0 (III) (C_q ^{t}Bu); 16.43, 16.37, 16.34, 16.28, 16.21, 16.19, 16.14 (CH_3 Et); -4.65, -4.67, -4.73 (Me TBDMS). ^{31}P NMR δ: 26.1; 22.9; 21.4. FTIR (neat): 1705 (C=O st.); 1253 (P=O st.; Si-C st.); 1094, 1052, 1026 (P-O-C st, Si-O-C st.); 838 (Si-O-C bend.); 774 (P-O-C st.). $[\propto]_D^{20^oC}$ = +71 (c=1.2; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{37}NO_5PSi$ 418.2173; Found 418.2169.

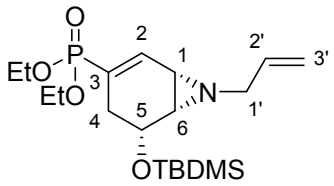
Diethyl (-)-[(1*S*,5*R*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-3-yl]phosphonate (17)



(+)-16 **(-)-17**

To a stirred solution of **16** (750 mg, 1.8 mmol) in ethanol abs. (7 mL) under argon at -78ºC was added sodium borohydride (68 mg, 1 eq.) portionwise. After 1 hour the reaction was quenched with a saturated ammonium chloride aqueous solution (7mL) and the mixture was extracted with dichloromethane (3x 10mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The obtained crude (750 mg) was dissolved in dry dichloromethane (7 mL) under argon and triethylamine (920 µL, 3 eq.) and mesyl chloride (280 µL, 2 eq.) were added at 0ºC. After 3 hour of stirring at room temperature the reaction mixture was quenched with water (10mL) and then extracted with dichloromethane (3x 10mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. The obtained

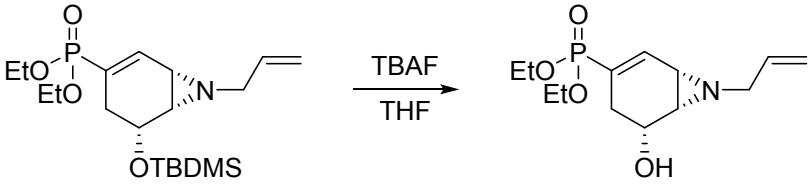
crude (1.2 g) was dissolved in dry dichloromethane (7 mL) under argon and DBU (400 µL, 1.5 eq.) was added at 0ºC. After 1 hour of stirring at room temperature the reaction was treated using the same procedure above. Purification by flash column chromatography, eluted with hexanes/ethyl acetate (1:2), afforded 339 mg (47%) of the pure compound as colourless oil.



(-)-17

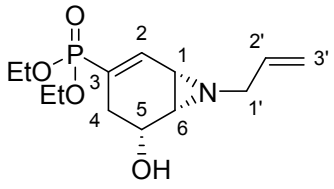
^{1}H RMN δ: 6.91 (1H, ddd, $^{3}J_{H,P}$=20.0, $J_{2,1}$=4.3, $J_{2,5}$=3.2, H-2); 5.87 (1H, ddt, $J_{2',3'}$=17.2, $J_{2',3'}$=10.4, $J_{2',1'}$=5.2, H-2'); 5.33 (1H, dq, $J_{3',2'}$=17.2, ^{2}J=$J_{3',1'}$=1.7, H-3'); 5.11 (1H, dq, $J_{3',2'}$=10.5, ^{2}J=$J_{3',1'}$=1.5, H-3'); 4.10-3.95 (5H, m, H-5, 2xCH_2 Et); 3.10 (1H, ddt, ^{2}J=14.6, $J_{1',2'}$=5.3, $J_{1',3'}$=1.4, H-1'); 2.85 (1H, ddt, ^{2}J=14.6, $J_{1',2'}$=5.0, $J_{1',3'}$=1.6, H-1'); 2.38-2.20 (2H, m, H-4); 2.04 (1H, dt, $J_{6,1}$=6.3, $^{5}J_{H,P}$=$J_{6,5}$=1.8, H-6); 1.98 (1H, dt, $^{4}J_{H,P}$=10.9, $J_{1,6}$=$J_{1,2}$=4.8, H-1); 1.31 (3H, t, ^{3}J=7.0, CH_3 Et); 1.30 (3H, t, ^{3}J=7.0, CH_3 Et); 0.92 (9H, s, ^{t}Bu TBDMS); 0.11 (3H, s, Me TBDMS); 0.10 (3H, s, Me TBDMS). ^{13}C RMN δ: 140.0 (d, $^{2}J_{C,P}$=10, C-2); 134.7 (C-2'); 128.3 (d, $^{1}J_{C,P}$=184, C-3); 116.3 (C-3'); 66.6 (d, $^{3}J_{C,P}$=12, C-5); 61.9 (C-1'); 61.8 (d, $^{2}J_{C,P}$=5, CH_2 Et); 61.6 (d, $^{2}J_{C,P}$=5; CH_2 Et); 46.7 (d, $^{4}J_{C,P}$=2, C-6), 37.8 (d, $^{3}J_{C,P}$=24, C-1); 30.9 (d, $^{2}J_{C,P}$=8, C-4); 25.8 (3xMe ^{t}Bu); 18.1 (C_q ^{t}Bu); 16.3 (d, $^{3}J_{C,P}$=6, CH_3 Et); -4.6 (2xMe TBDMS). ^{31}P RMN δ: 18.2. IR (neat): 1250 (P=O st.; Si-C st.); 1090, 1069, 1054, 1026, 965 (P-O-C st, Si-O-C st.); 837 (Si-O-C bend.); 777 (P-O-C st.). $[\propto]_D^{20^oC}$ = -1 (c=1.0; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{37}NO_4PSi$ 402.2224; Found 402.2230.

Diethyl (-)-[(1*S*,5*R*,6*S*)-5-hydroxy-7-(prop-2-en-1-yl)-7-azabicyclo[4.1.0]hept-2-en-3-yl]phosphonate (18)



(-)-17 **(-)-18**

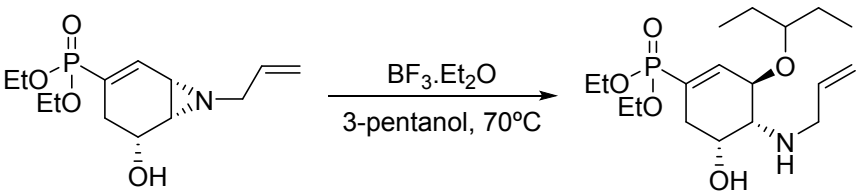
To a stirred solution of **17** (330 mg, 0.82 mmol) in dry tetrahydrofuran (3 mL) under argon was added tetrabutylammonium fluoride (1.5 mL, 1 M in THF, 1.8 eq.). After 1 hour of stirring at room temperature the reaction mixture was quenched with water (5mL) and then extracted with ethyl acetate (3x 5mL). The organic layer was dried with magnesium sulfate and evaporated to dryness. Purification by flash column chromatography, eluted with dichloromethane/methanol (95:5), afforded 238 mg (100%) of the pure compound as colourless oil.



(-)-18

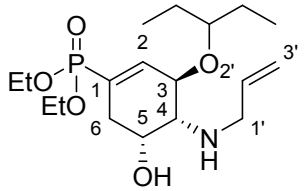
^{1}H RMN δ: 6.93 (1H, dt, $^{3}J_{H,P}$=20.0, $J_{2,1}$=$J_{2,5}$=3.1, H-2); 5.90 (1H, ddt, $J_{2',3'}$=16.6, $J_{2',3'}$=11.0, $J_{2',1'}$=5.5, H-2'); 5.25 (1H, d, $J_{3',2'}$=17.2, H-3'); 5.15 (1H, d, $J_{3',2'}$=10.4, H-3'); 4.16-3.95 (5H, m, H-5, 2xCH_2 Et); 3.02 (1H, dd, ^{2}J=14.3, $J_{1',2'}$=3.5, H-1'); 2.96 (1H, dd, ^{2}J=14.2, $J_{1',2'}$=5.6, H-1'); 2.54 (1H, ddd, ^{2}J=16.3, $^{3}J_{H,P}$=11.1, $J_{4,5}$=5.7, H-4); 2.26 (1H, d, $J_{6,1}$=6.0, H-6); 2.16-1.96 (1H, m, H-1, H-4, OH); 1.31 (3H, t, ^{3}J=6.4, CH_3 Et); 1.30 (3H, t, ^{3}J=6.1, CH_3 Et). ^{13}C RMN δ: 139.6 (d, $^{2}J_{C,P}$=10, C-2); 134.8 (C-2'); 128.3 (d, $^{1}J_{C,P}$=185, C-3); 117.0 (C-3'); 65.7 (d, $^{3}J_{C,P}$=11, C-5); 62.0 (C-1'); 61.9 (d, $^{2}J_{C,P}$=6, CH_2 Et); 61.8 (d, $^{2}J_{C,P}$=6; CH_2 Et); 45.8 (C-6), 38.4 (d, $^{3}J_{C,P}$=23, C-1); 30.9 (d, $^{2}J_{C,P}$=8, C-4); 16.4 (d, $^{3}J_{C,P}$=6, CH_3 Et); 16.3 (d, $^{3}J_{C,P}$=6, CH_3 Et). ^{31}P RMN δ: 17.8. IR (neat): 3370 (O-H st.); 1227 (P=O st.); 1021, 966 (P-O-C st, C-OH st.). $[\propto]_D^{20^oC}$ = -37 (c=0.5; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{23}NO_4P$ 288.1359; Found 288.1358.

Diethyl (-)-[(3*R*,4*R*,5*R*)-5-hydroxy-3-(pentan-3-yloxy)-4-[(prop-2-en-1-yl)amino]cyclohex-1-en-1-yl]phosphonate (19)



(-)-18 **(-)-19**

To a stirred solution of **18** (150 mg, 0.52 mmol) in 3-pentanol (3.5 mL) under argon was added boron trifluoride diethyl etherate (100 µL, 1.5 eq.). After 30 minutes of stirring at 70ºC the reaction was quenched with a saturated sodium hydrogencarbonate aqueous solution (5mL) and the mixture was extracted with ethyl acetate (3x 5mL). The combined organic phases were dried with sodium sulfate and evaporated to dryness, affording 200 mg (100%) of the pure compound as colourless oil.

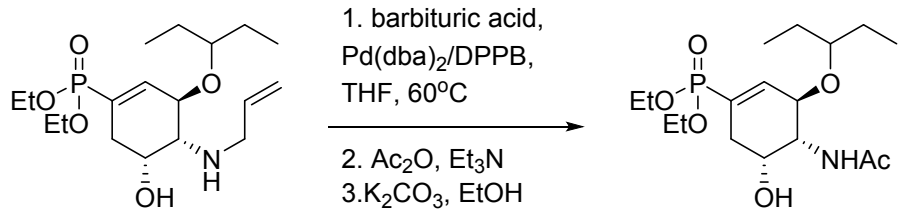


(-)-**19**

^{1}H RMN δ: 6.66 (1H, d, $^{3}J_{H,P}$=21.8, H-2); 5.93 (1H, dd, $J_{2',3'}$=16.7, $J_{2',3'}$=11.1, $J_{2',1'}$=5.6, H-2'); 5.27 (1H, d, $J_{3',2'}$=17.2, H-3'); 5.18 (1H, d, $J_{3',2'}$=10.0, H-3'); 4.22 (1H, br s, H-5); 4.12-4.03 (5H, m, H-3,

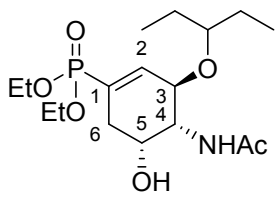
2xCH_2 Et); 3.47-3.33 (3H, m, H-1', CH pentyl); 2.79 (1H, br d, *J*=7.8, H-4); 2.51-2.38 (2H, m, H-6); 1.63-1.40 (4H, m, 2xCH_2 pentyl); 1.32 (6H, td, ^3J=7.1, $^4J_{H,P}$=3.0, 2xCH_3 Et); 0.92 (3H, t, ^3J=7.7, CH_3 pentyl); 0.91 (3H, t, ^3J=7.5, CH_3 pentyl). ^{13}C RMN δ: 139.9 (d, $^2J_{C,P}$=7, C-2); 135 (br, C-2'); 126.4 (d, $^1J_{C,P}$=181, C-1); 118 (br, C-3'); 80.8 (CH pentyl); 72.7 (d, $^3J_{C,P}$=21, C-3); 63.8 (d, $^3J_{C,P}$=12, C-5); 62.0 (d, $^2J_{C,P}$=5; CH_2 Et); 61.9 (d, $^2J_{C,P}$=6; CH_2 Et); 60.8 (C-4); 49.4 (H-1'); 30.0 (d, $^3J_{C,P}$=79, C-6); 26.4, 25.4 (2x CH_2 pentyl); 16.4 (d, $^3J_{C,P}$=6, 2xCH_3 Et); 9.7, 9.4 (2xCH_3 pentyl). ^{31}P RMN δ: 18.1. IR (neat): 3370 (O-H st., NH st.); 1226 (P=O st.); 1091, 1052, 1024, 969 (P-O-C st, C-OH st., C-O-C st.). $[\alpha]_D^{20^oC}$ = -107 (c=0.9; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{35}NO_5P$ 376.2247; Found 376.2257.

Diethyl (-)-
[(3*R*,4*R*,5*R*)-4-acetamido-5-hydroxy-3-(pentan-3-yloxy)cyclohex-1-en-1-yl]phosphonate (20)



(-)-19 **(-)-20**

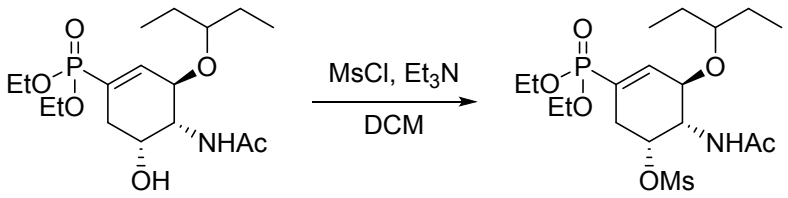
In a flask under argon a mixture of bis(dibenzylideneacetone)palladium(0) (11.5 mg, 10 mol%), 1,4-Bis(diphenylphosphino)butane (8.7 mg, 10 mol%) and dry tetrahydrofuran (0.5 mL) was stirred at room temperature for 15 minutes. This mixture was then added to a stirred solution of **19** (75 mg, 0.20 mmol) in tetrahydrofuran (0.5 mL) under argon followed by addition of 1,3-dimethylbarbituric acid (62 mg, 2 eq.). After 30 minutes of stirring at 60°C the reaction was cooled to 0°C and triethylamine (170 µL, 6 eq.) and acetic anhydride (80 µL, 4 eq.) were added. After additional 60 minutes of styring at room temperature the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL) and the mixture was extracted with ethyl acetate (3x 2mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The obtained crude was dissolved in ethanol abs. (1 mL) and potassium *tert*-butoxide (4.4 mg, 20 mol%) was added. After 1 hour ammonium chloride (5 mg) was added. The salts were then filtered and the solution evaporated to dryness. Purification by flash column chromatography, eluted with dichloromethane:methanol (93:7), afforded 53 mg (70%) of the pure compound as colourless oil.



(-)-**20**

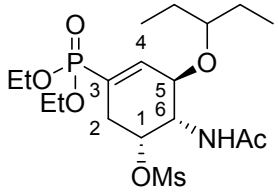
^{1}H RMN δ: 6.66-6.60 (1H, br s, NH); 6.58 (1H, d, $^{3}J_{H,P}$=22.0, H-2); 4.21 (1H, br s, H-5); 4.16 (1H, br d, *J*=6.5, H-3); 4.12-4.03 (4H, m, 2xCH_2 Et); 3.96 (1H, br t, *J*=7.5, H-4); 3.7 (1H, br s, OH); 3.35 (1H, p, ^{3}J=5.5,CH pentyl); 2.51 (1H, br d, ^{2}J=17.8, H-6); 2.36 (1H, dt, ^{2}J=18.0, *J*=4.6, H-6); 2.03 (3H, s, CH_3 Ac); 1.54-1.47 (4H, m, 2xCH_2 pentyl); 1.33 (6H, t, ^{3}J=7.1, 2xCH_3 Et); 0.90 (6H, t, ^{3}J=7.5, 2xCH_3 pentyl). ^{13}C RMN δ: 171,6 (C=O Ac); 140.2 (C-2); 126.5 (d, $^{1}J_{C,P}$=185, C-1); 82.0 (CH pentyl); 73.0 (d, $^{3}J_{C,P}$=21, C-3); 67.4 (d, $^{3}J_{C,P}$=12, C-5); 62.3 (d, $^{2}J_{C,P}$=6; CH_2 Et); 62.1 (d, $^{2}J_{C,P}$=6; CH_2 Et); 54.6 (C-4); 31.8 (d, $^{3}J_{C,P}$=9, C-6); 26.3, 25.8 (2xCH_2 pentyl); 23.3 (CH_3 Ac); 16.3 (d, $^{3}J_{C,P}$=6, 2xCH_3 Et); 9.54, 9.45 (2xCH_3 pentyl). ^{31}P RMN δ: 17.6. IR (neat): 3300 (O-H st., NH st.); 1652 (C=O st.); 1553 (amide II); 1230 (P=O st.); 1087, 1052, 1022, 965 (P-O-C st, C-OH st., C-O-C st.). $[\propto]_D^{20^oC}$ = -132 (c=0.7; DCM). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{32}NO_6P$ 378.2040; Found 378.2055.

(-)-
(1*R*,5*R*,6*S*)-3-(diethoxyphosphoryl)-6-acetamido-5-(pentan-3-yloxy)cyclohex-3-en-1-ylmethanesulfonate (21)



(-)-20 **(-)-21**

To a stirred solution of **20** (40 mg, 0.11 mmol) in dry dichloromethane (1 mL) under argon was added triethylamine (30 µL, 2 eq.) and mesyl chloride (12 µL, 1.5 eq.) at 0ºC. After 1 hour of stirring at room temperature the reaction was quenched with a saturated sodium bicarbonate aqueous solution (2mL) and the mixture was extracted with ethyl acetate (3x 2mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness, affording 48 mg (99%) of the pure compound as a white solid.



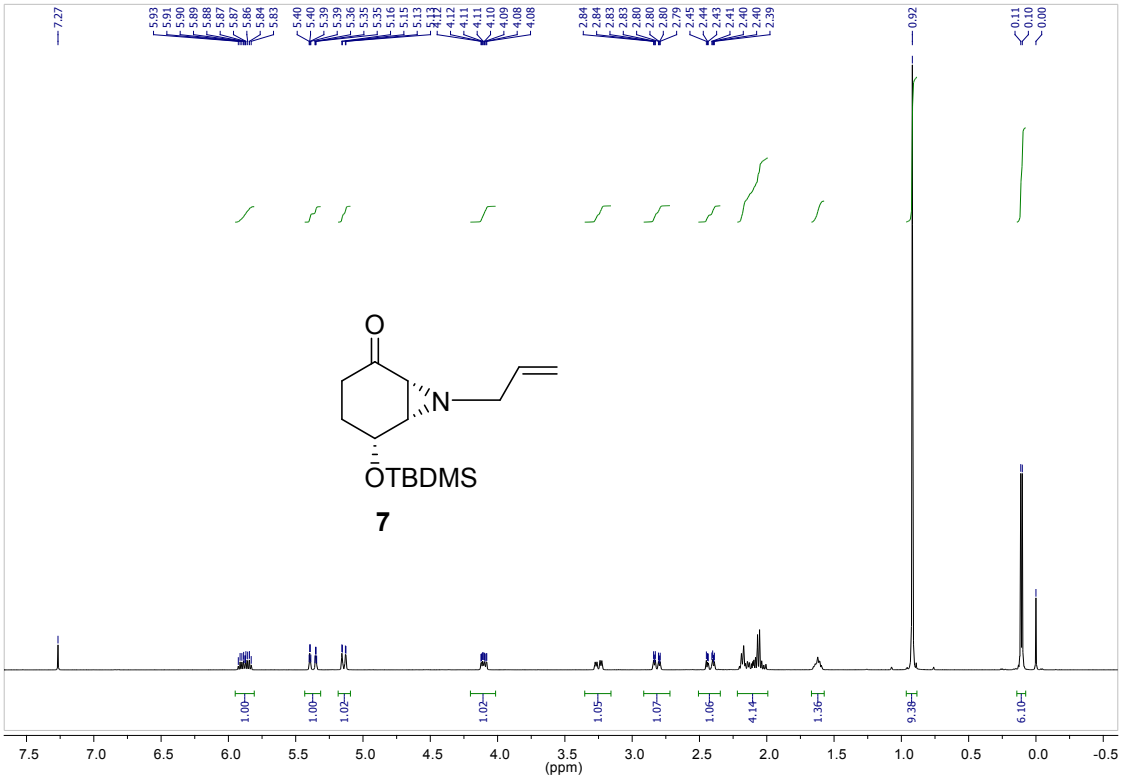
(-)-21

^{1}H RMN δ: 6.67 (1H, d, $^{3}J_{H,P}$=21.6, H-4); 5.83 (1H, d, $J_{NH,6}$=8.1, NH); 5.24-5.20 (1H, m, H-1); 4.31 (1H, td, $J_{6,NH}$=$J_{6,5}$=8.2, $J_{6,1}$=2.2, H-6); 4.14-4.05 (4H, m, 2xCH_2 Et); 4.01 (1H, dm, *J*=8.2, H-5); 3.36 (1H, p, ^{3}J=5.4, CH pentyl); 3.05 (3H, s, CH_3 Ms); 2.77-2.61 (2H, m, H-2); 2.03 (3H, s, CH_3 Ac); 1.56-1.48 (4H, m, 2xCH_2 pentyl); 1.34 (6H, td, ^{3}J=7.1, $J_{H,P}$=0.7, 2xCH_3 Et); 0.91 (3H, t, ^{3}J=7.4, CH_3 pentyl); 0.90 (3H, t, ^{3}J=7.4, CH_3 pentyl). ^{13}C RMN δ: 170,7 (C=O Ac); 140.7 (d, $^{2}J_{C,P}$=7, C-4); 125.7 (d, $^{1}J_{C,P}$=184, C-3); 82.3 (CH pentyl); 78.1 (d, $^{3}J_{C,P}$=13, C-1); 72.7 (d, $^{3}J_{C,P}$=20, C-5); 62.4 (d, $^{2}J_{C,P}$=6; CH_2 Et); 62.2 (d, $^{2}J_{C,P}$=6; CH_2 Et); 51.6 (d, $^{4}J_{C,P}$=2, C-6); 38.6 (CH_3 Ms); 29.9 (d, $^{3}J_{C,P}$=10, C-2); 26.3, 25.8 (2xCH_2 pentyl); 23.2 (CH_3 Ac); 16.3 (d, $^{3}J_{C,P}$=6, 2xCH_3 Et); 9.43, 9.38 (2xCH_3 pentyl). ^{31}P RMN

δ: 16.3. IR (neat): 3276 (NH st.); 1658 (C=O st.); 1549(amide II); 1354 (O=S=O st.); 1234 (P=O st.); 1176 (O=S=O st.); 1093, 1051, 1022, 970, 906 (P-O-C st, S-O-C st., C-O-C st.). $[\propto]_D^{20^oC}$ = -110 (c=1.2; AcOEt) [lit: $[\propto]_D^{22^oC}$ = -102.5 (c=0.4; AcOEt)]. M.p. = 106-108°C.

References

(**1**) W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, **2003**, p.
(**2**) M. T. Barros, C. D. Maycock and M. R. Ventura, *Journal of the Chemical Society, Perkin Transactions 1* **2001**, 166-173.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2.39
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0.11
0.10
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O
N
OTBDMS
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1.00
1.00
1.02
1.02
1.05
1.07
1.06
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1.36
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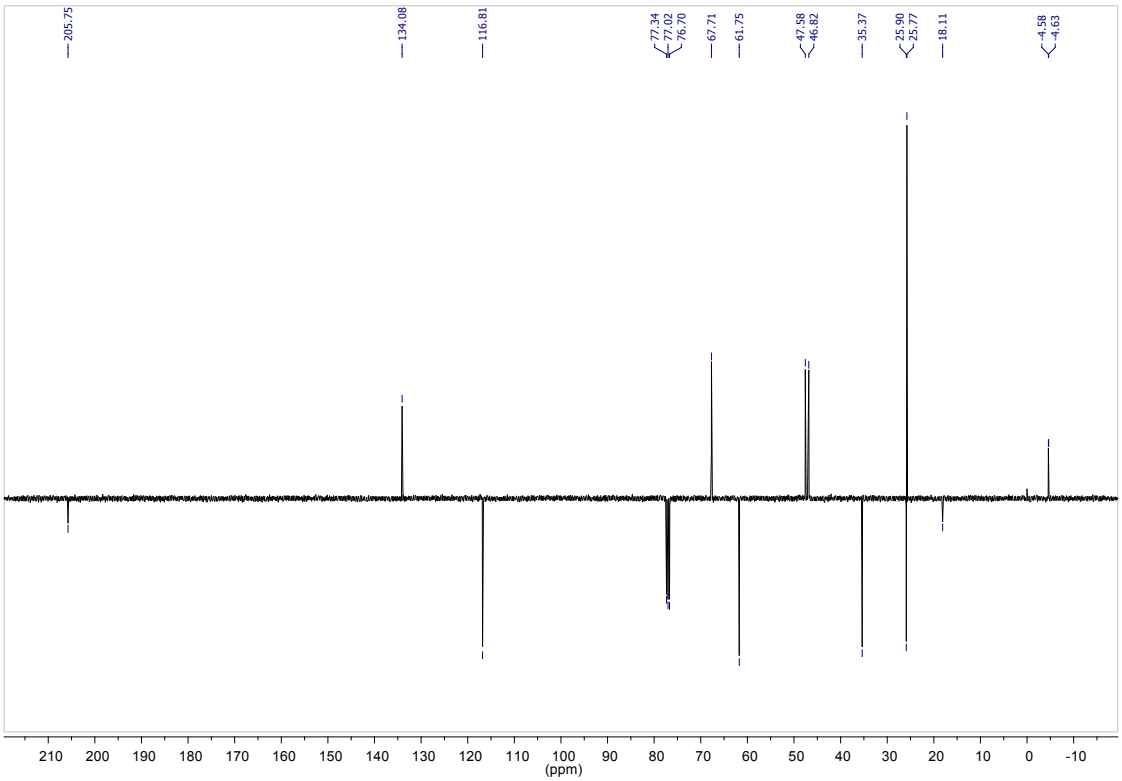
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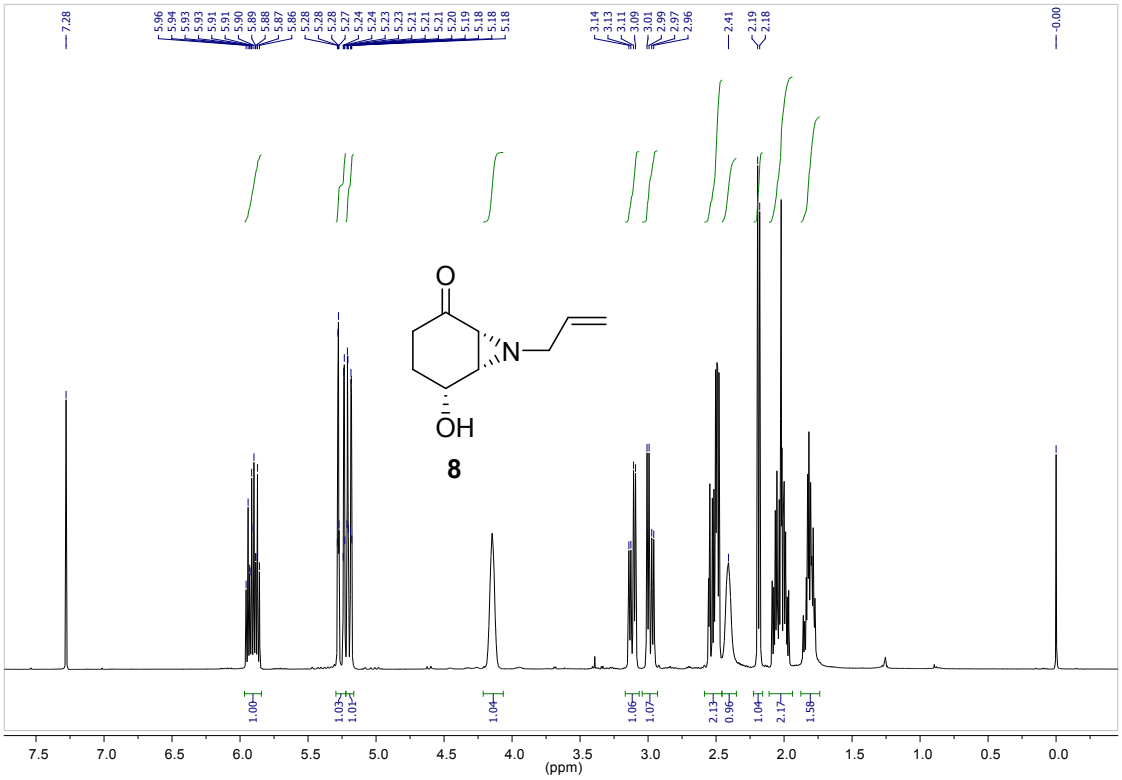
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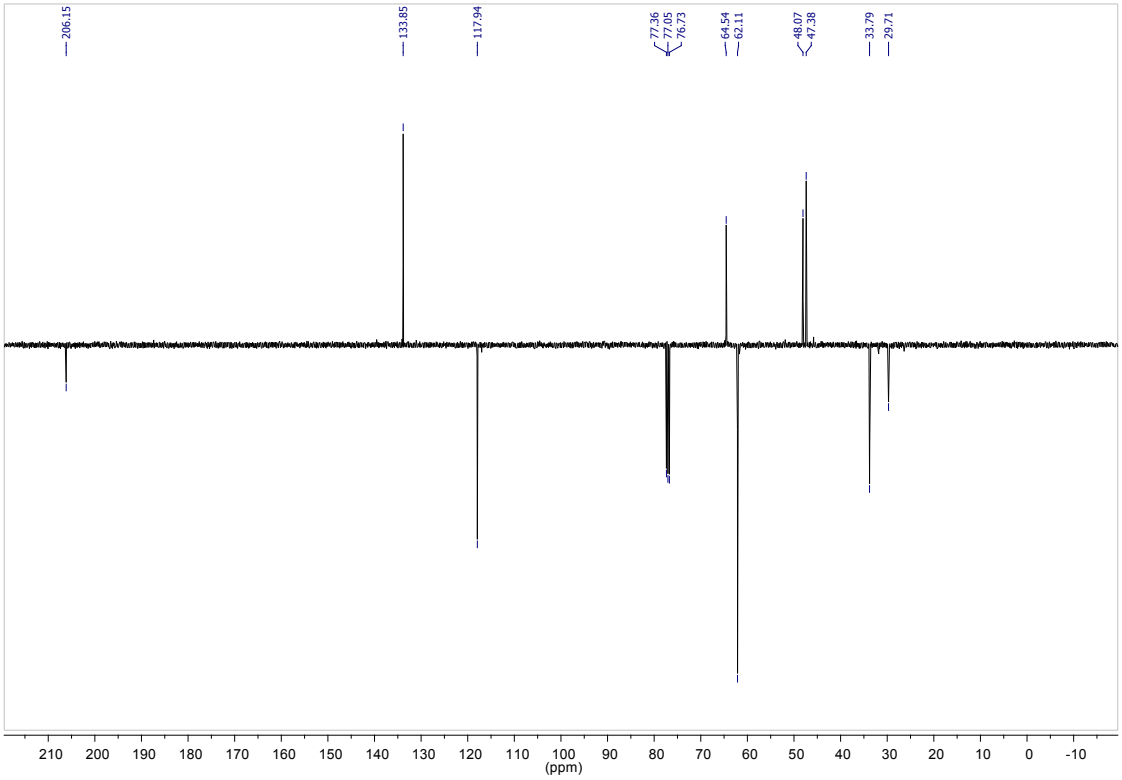
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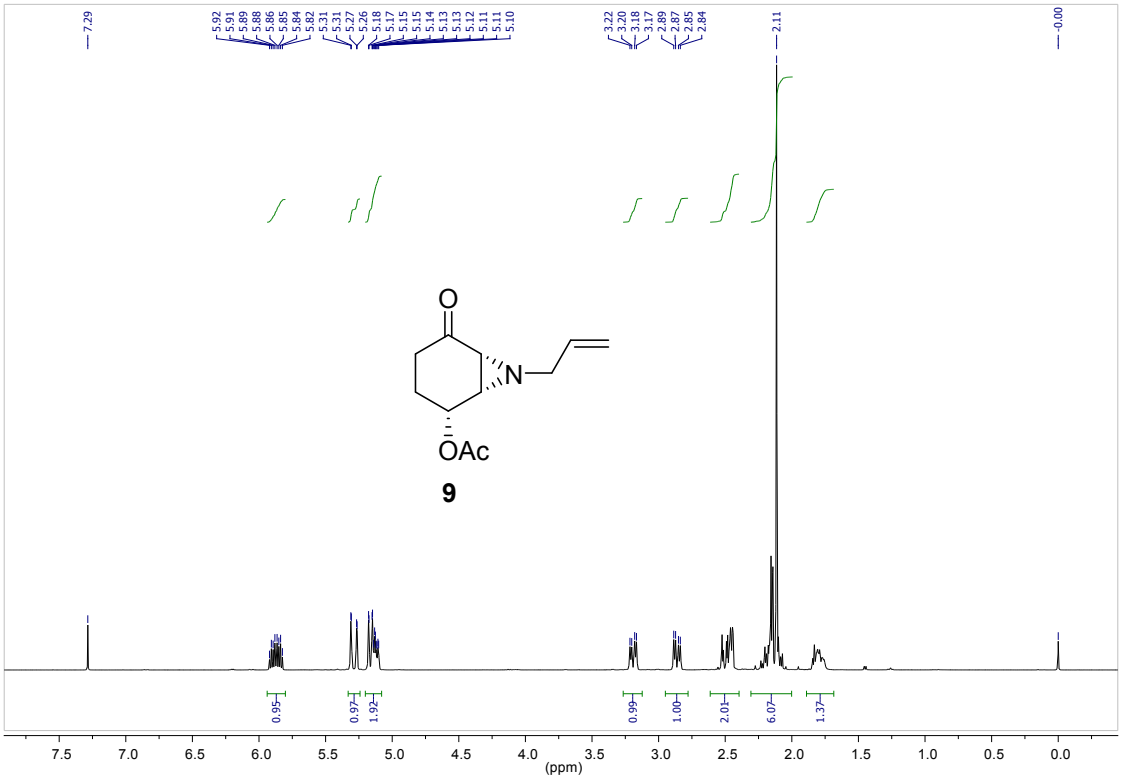
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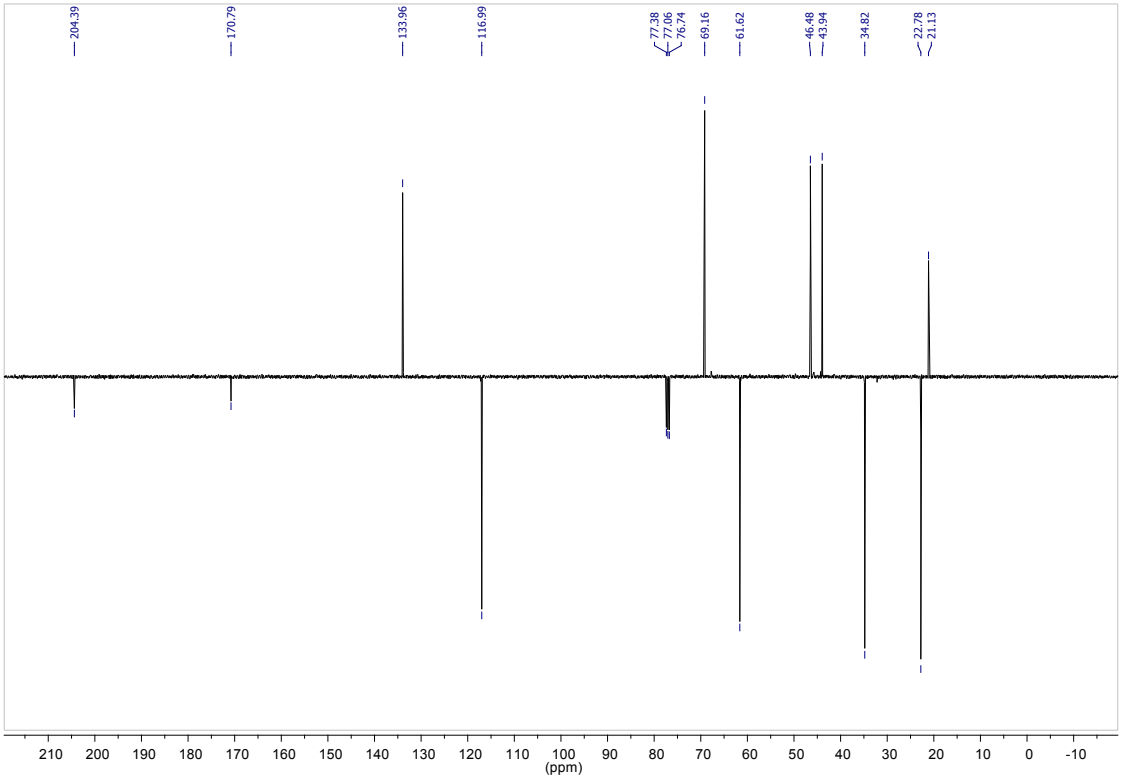
(ppm)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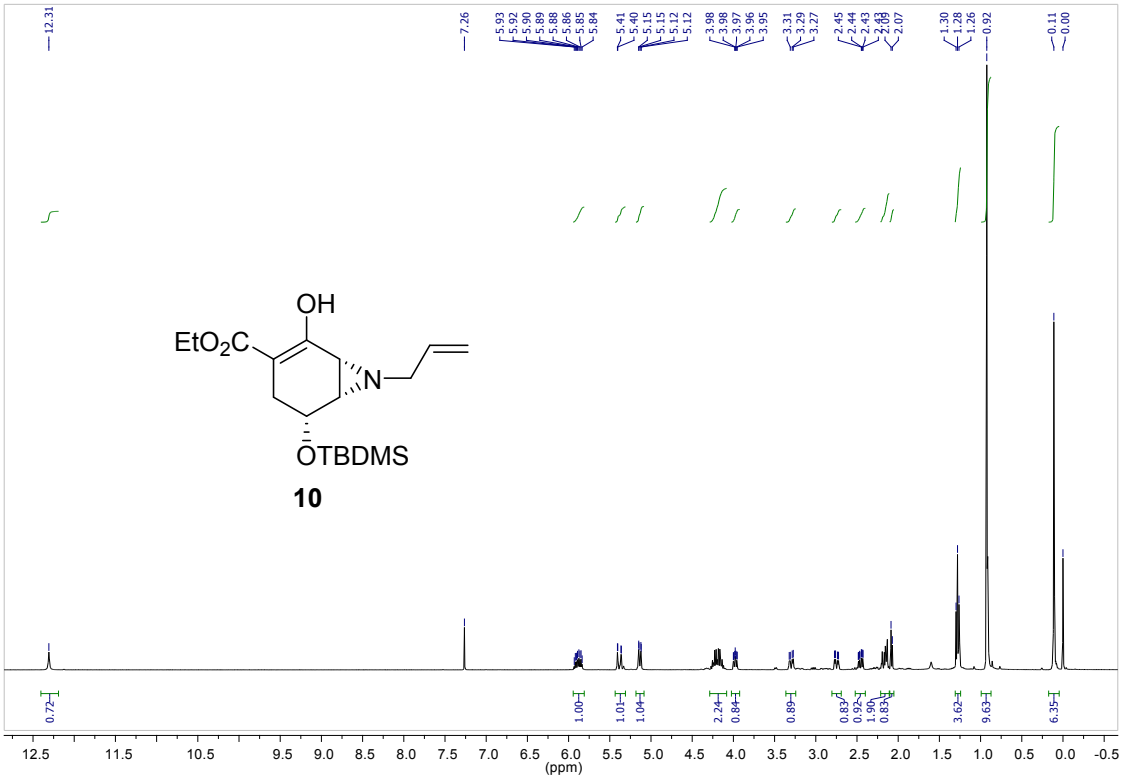
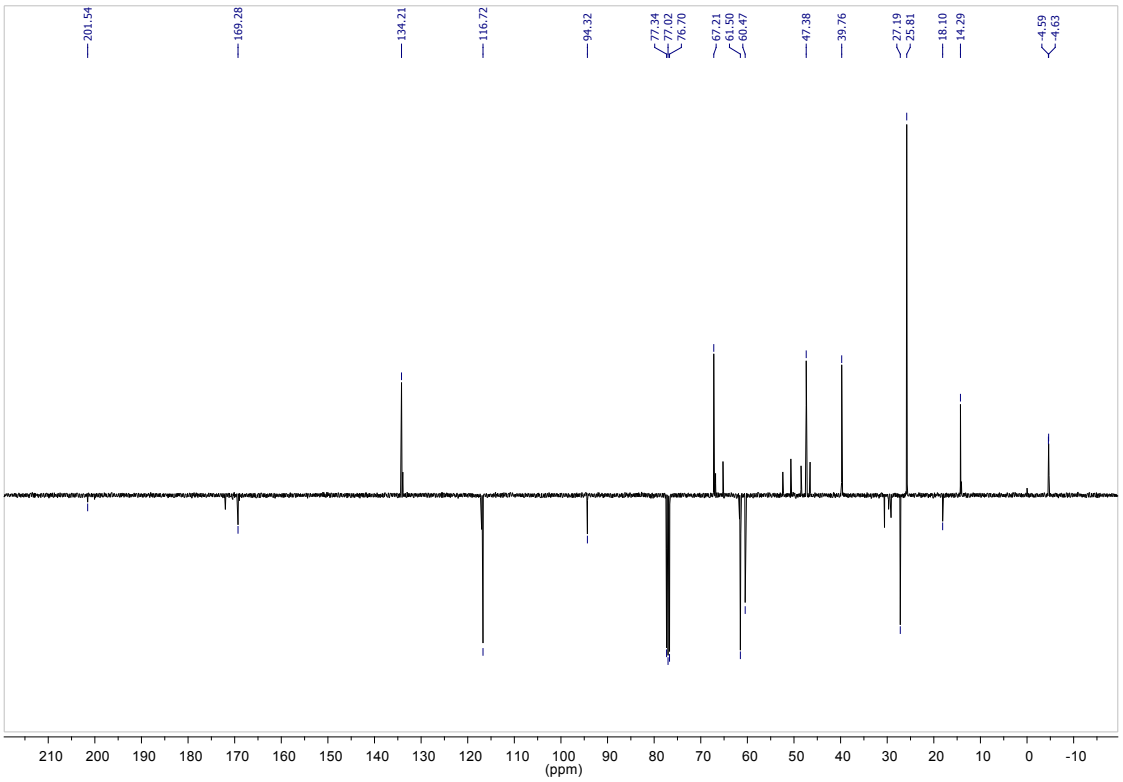
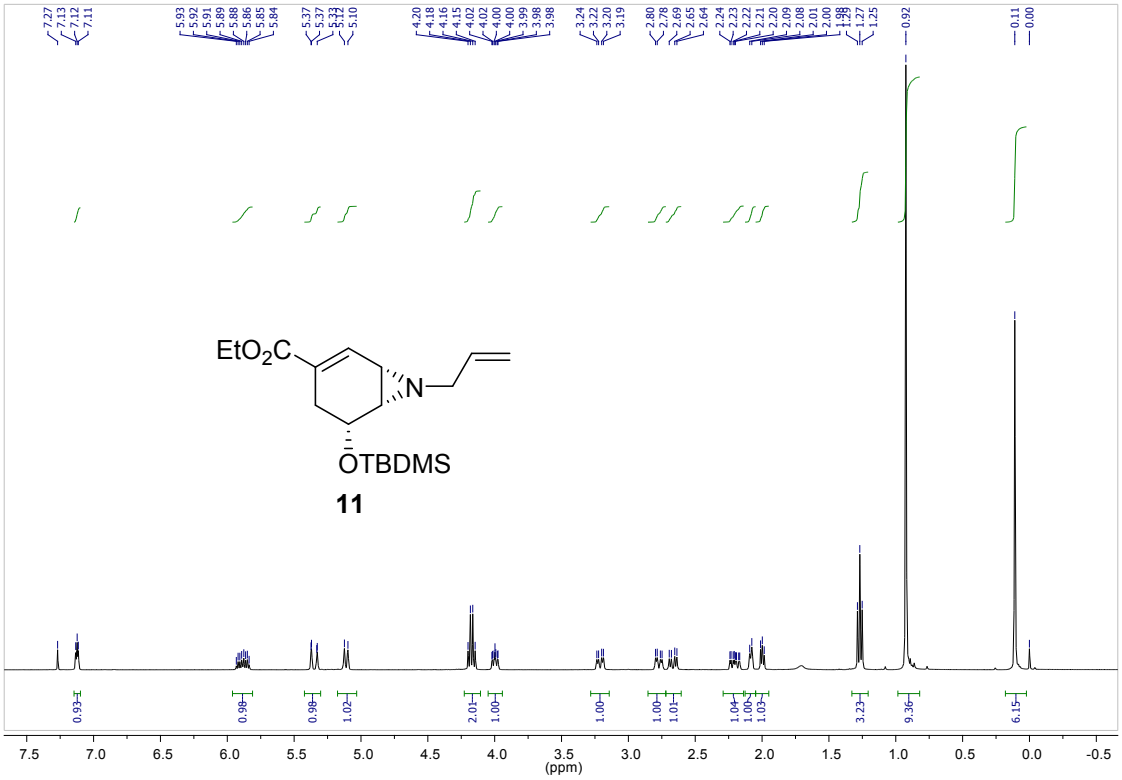
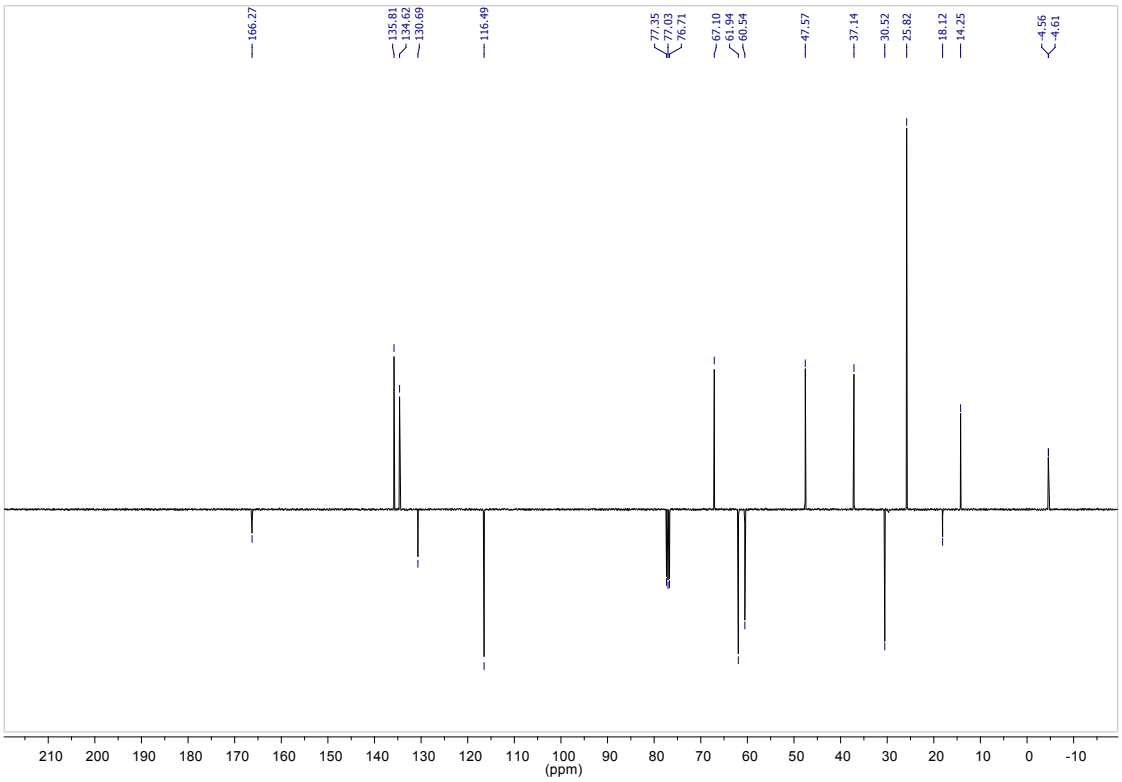
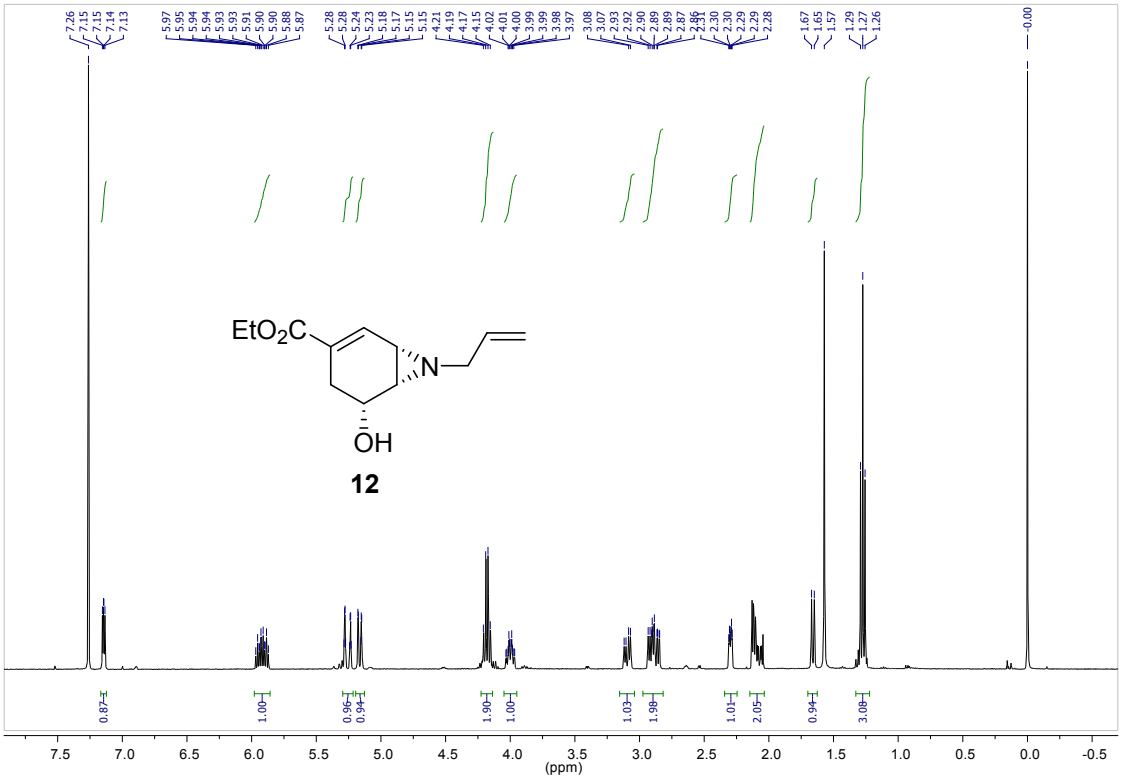
170.79
133.96
116.99
77.38
77.06
76.74
69.16
61.62
46.48
43.94
34.82
22.78
21.13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

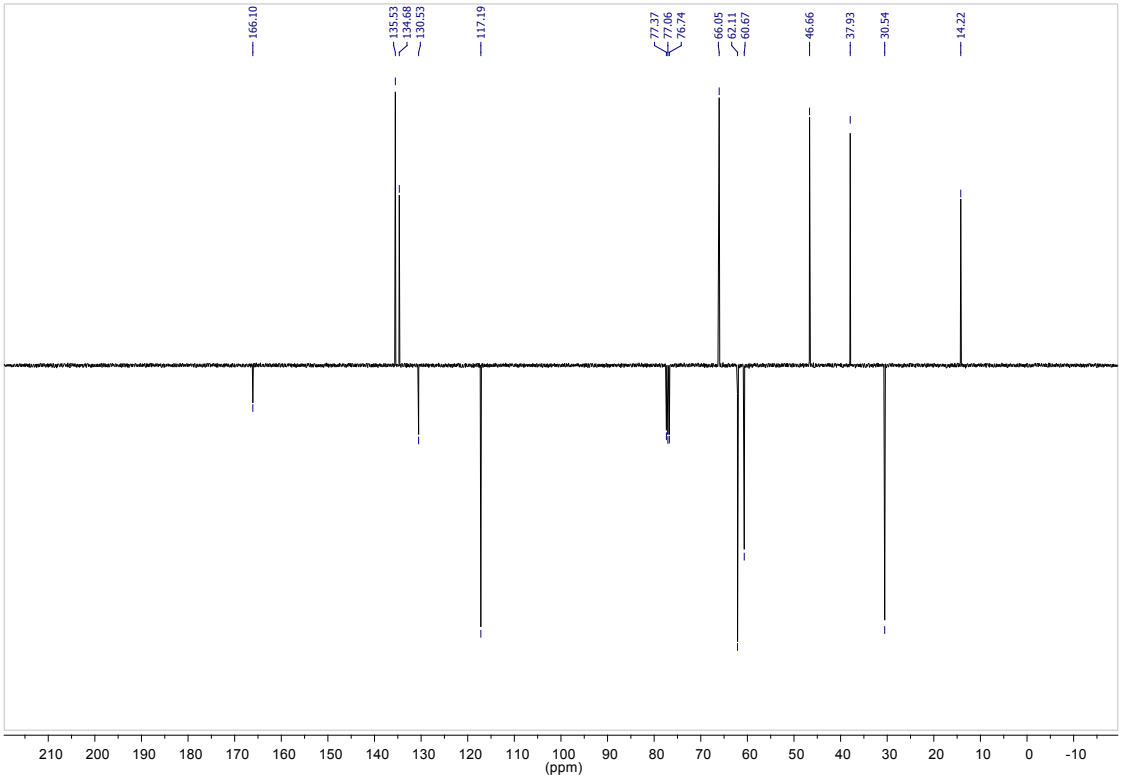

OH
EtO2C
N
OTBDMS
10
(ppm)


(ppm)


EtO2C
N
OTBDMS
11
(ppm)


(ppm)


EtO2C
N
OH
12
(ppm)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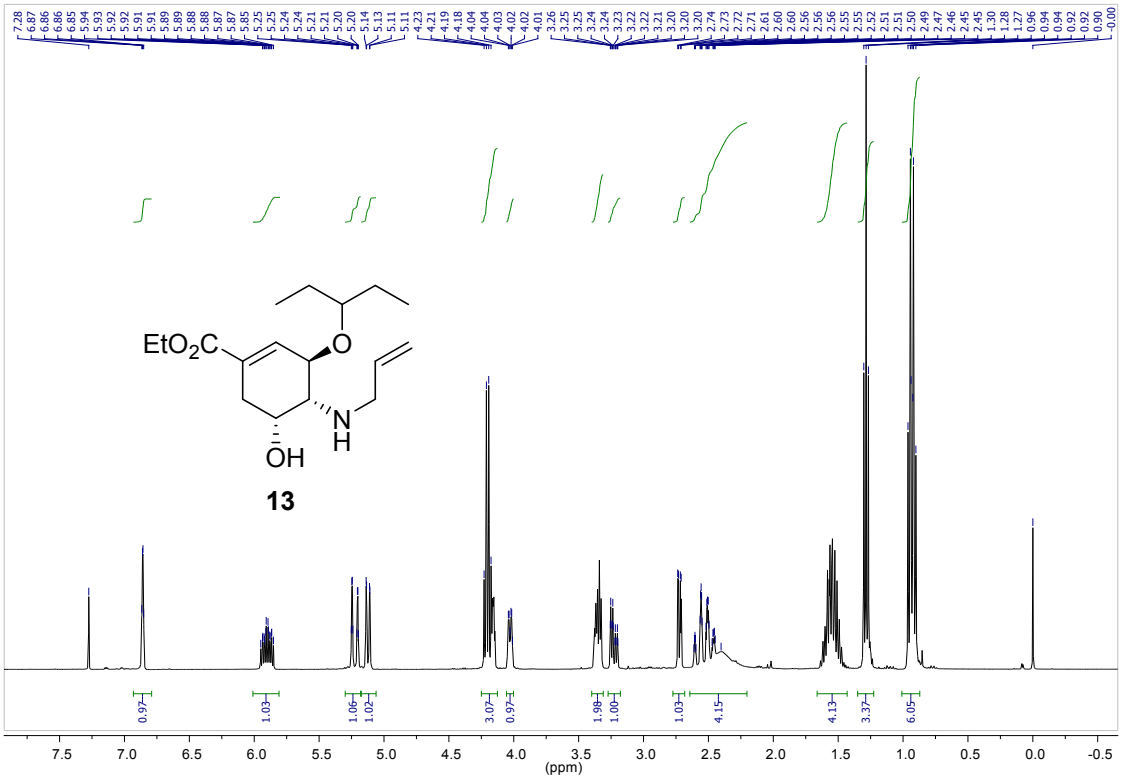
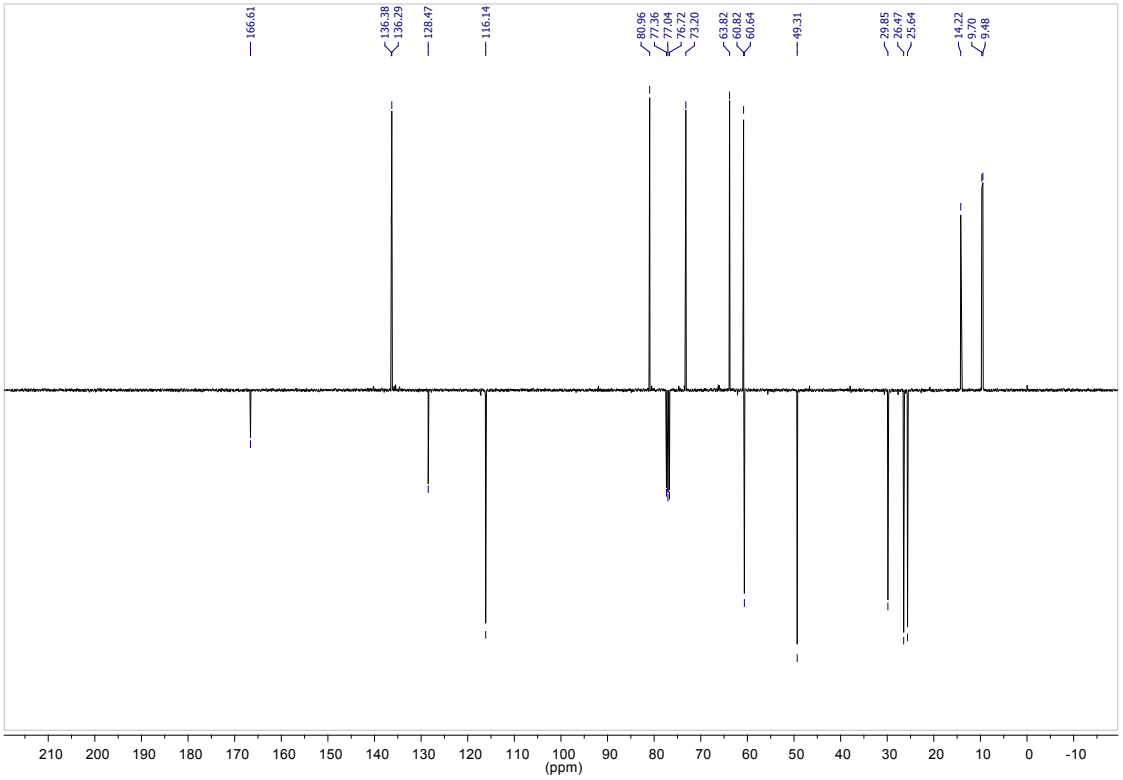
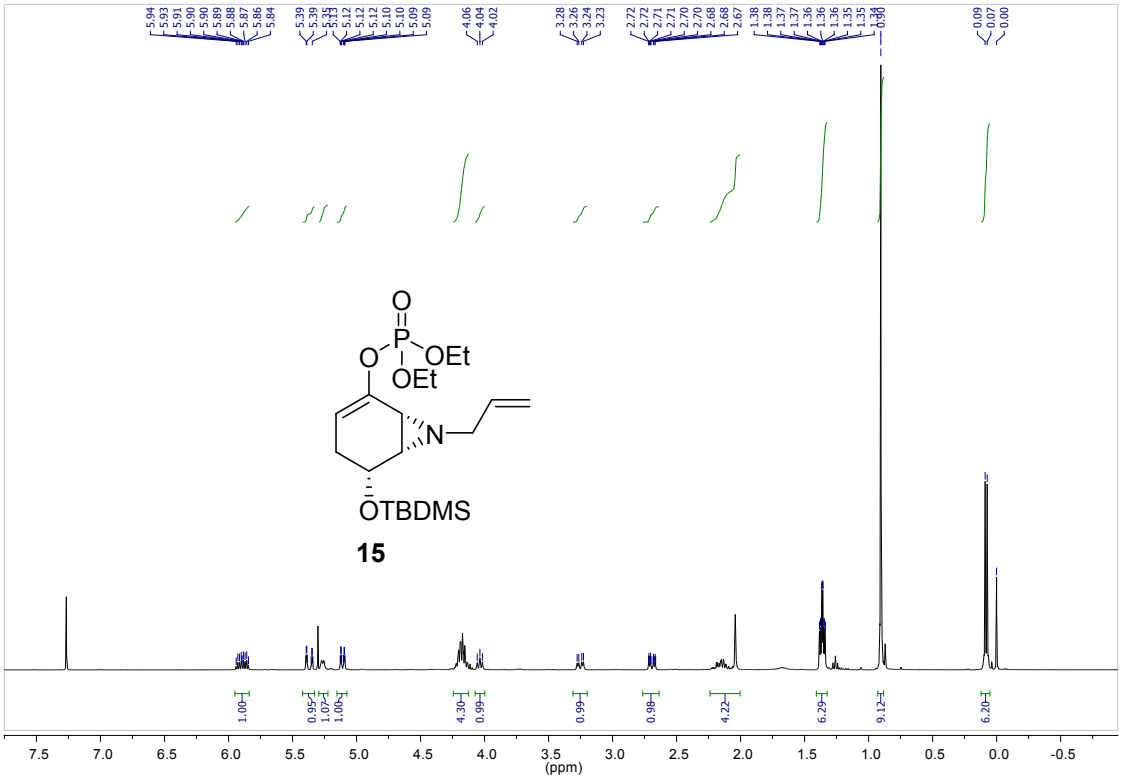
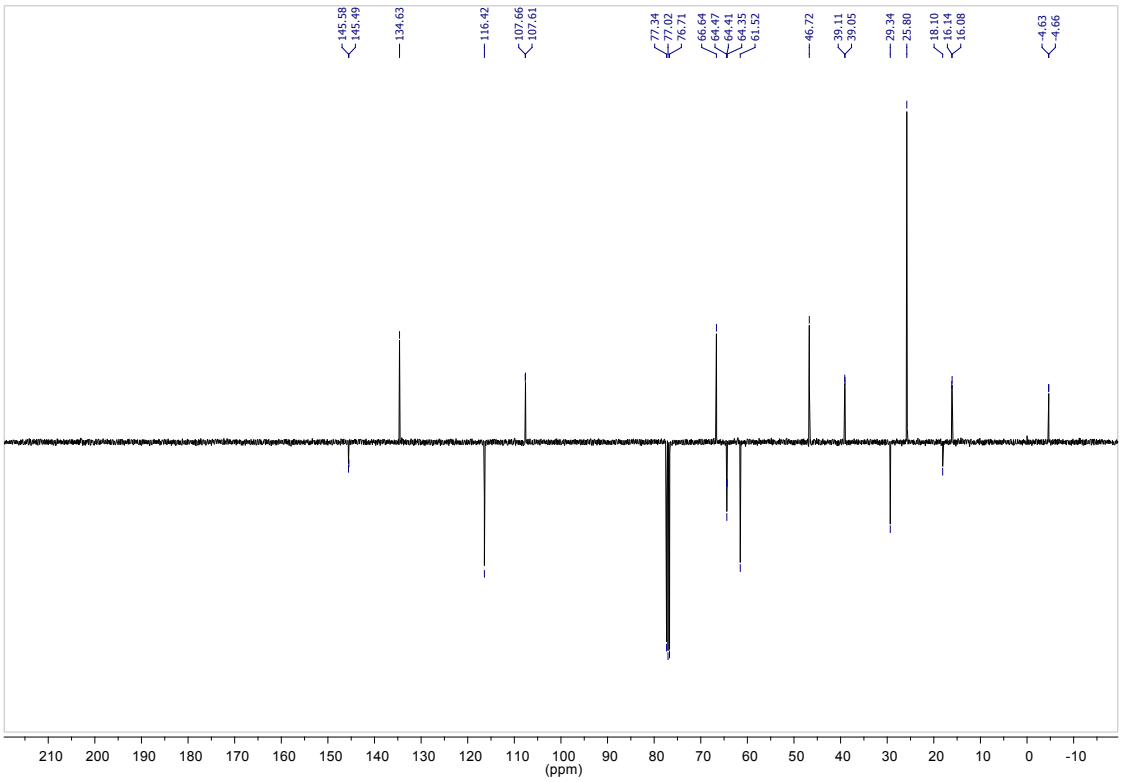
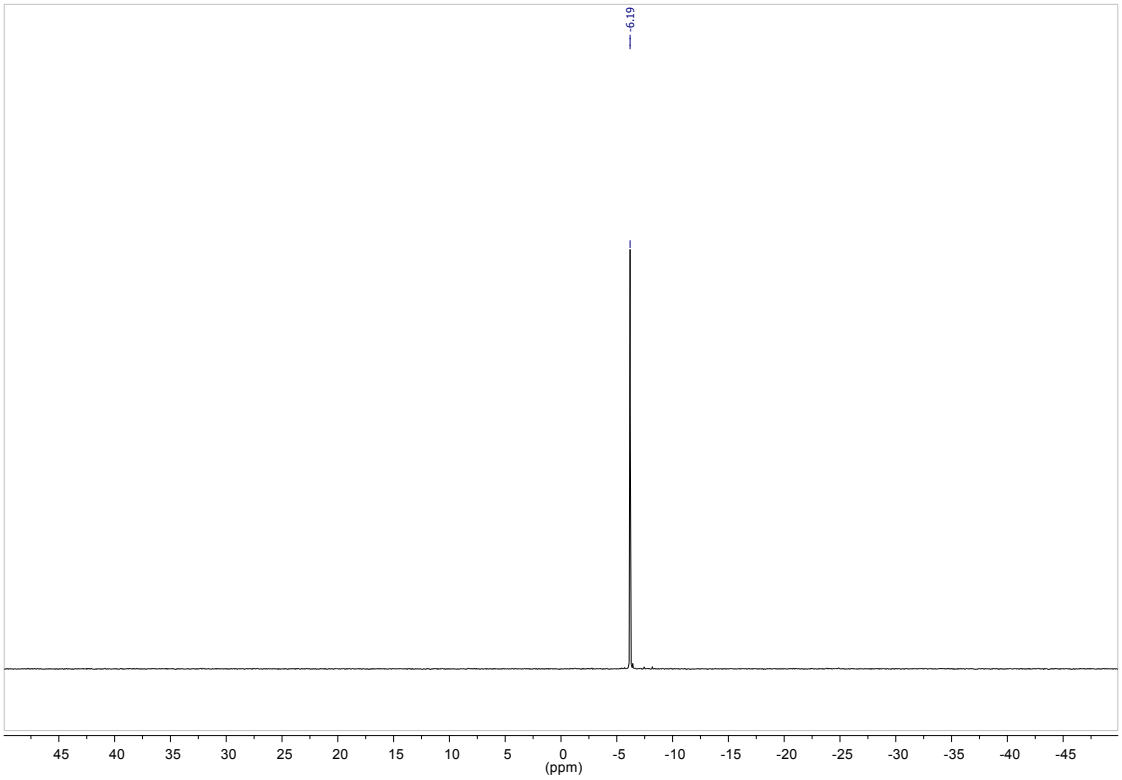
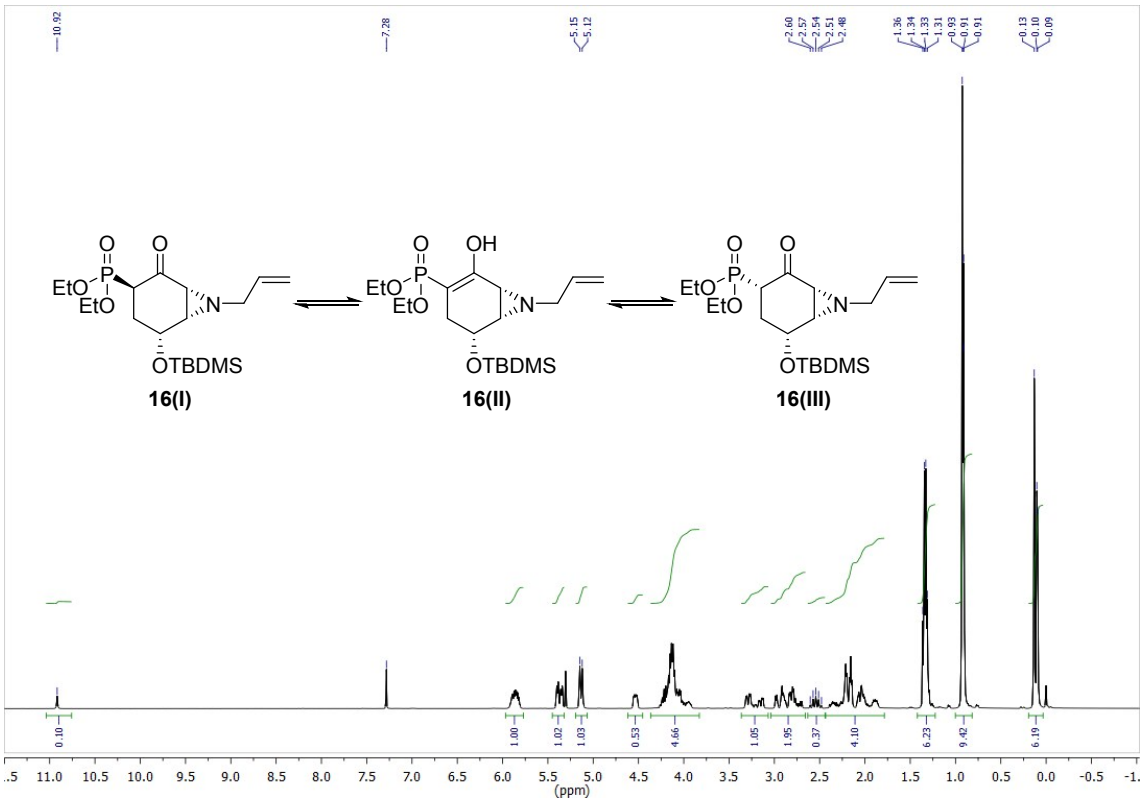

EtO2C
O
N
H
OH
13
(ppm)

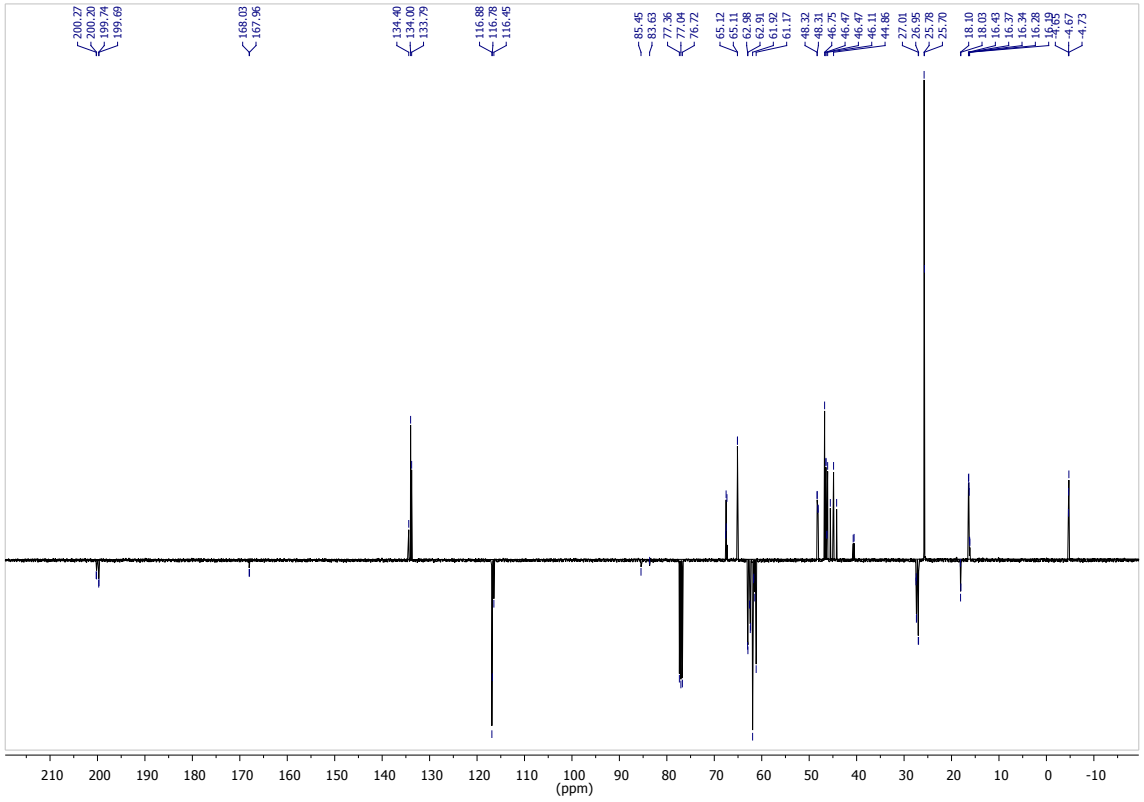

166.61
136.38
136.29
128.47
116.14
80.96
77.36
77.04
76.72
73.20
63.82
60.82
60.64
49.31
29.85
26.47
25.64
14.22
9.70
9.48
(ppm)

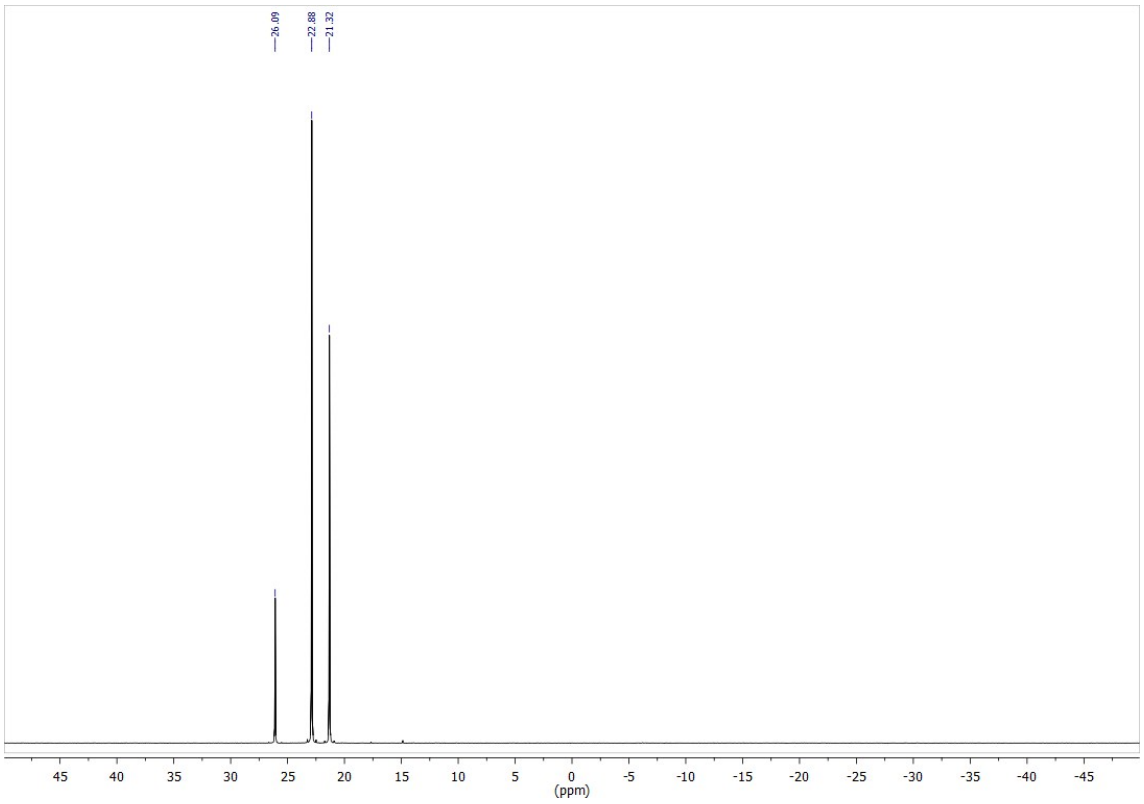

OEt
OEt
N
OTBDMS
15
(ppm)

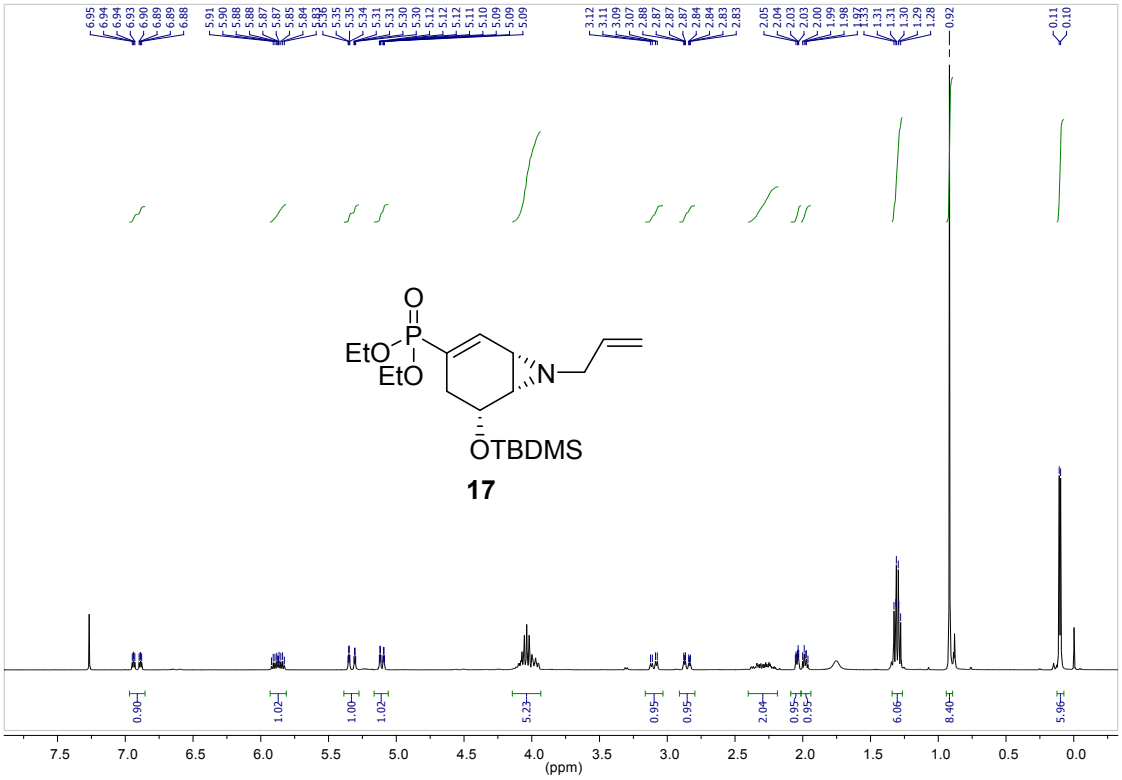

(ppm)

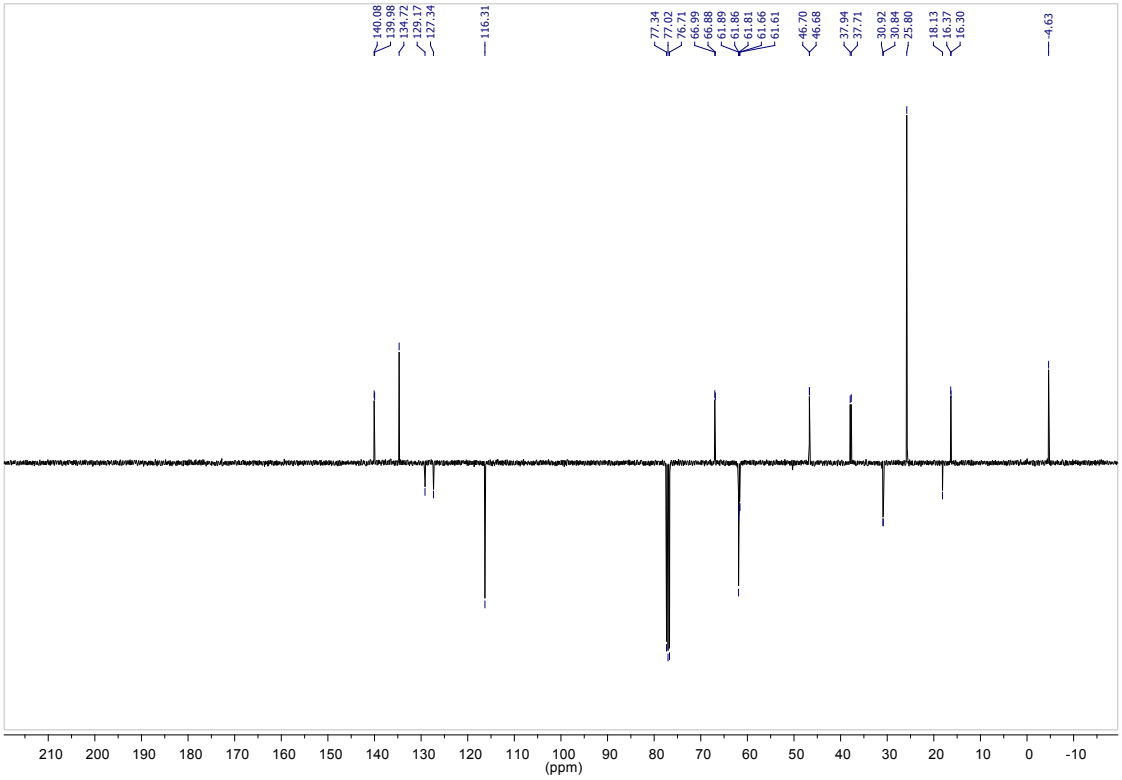

-6.19
45
40
35
30
25
20
15
10
5
0
(ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45

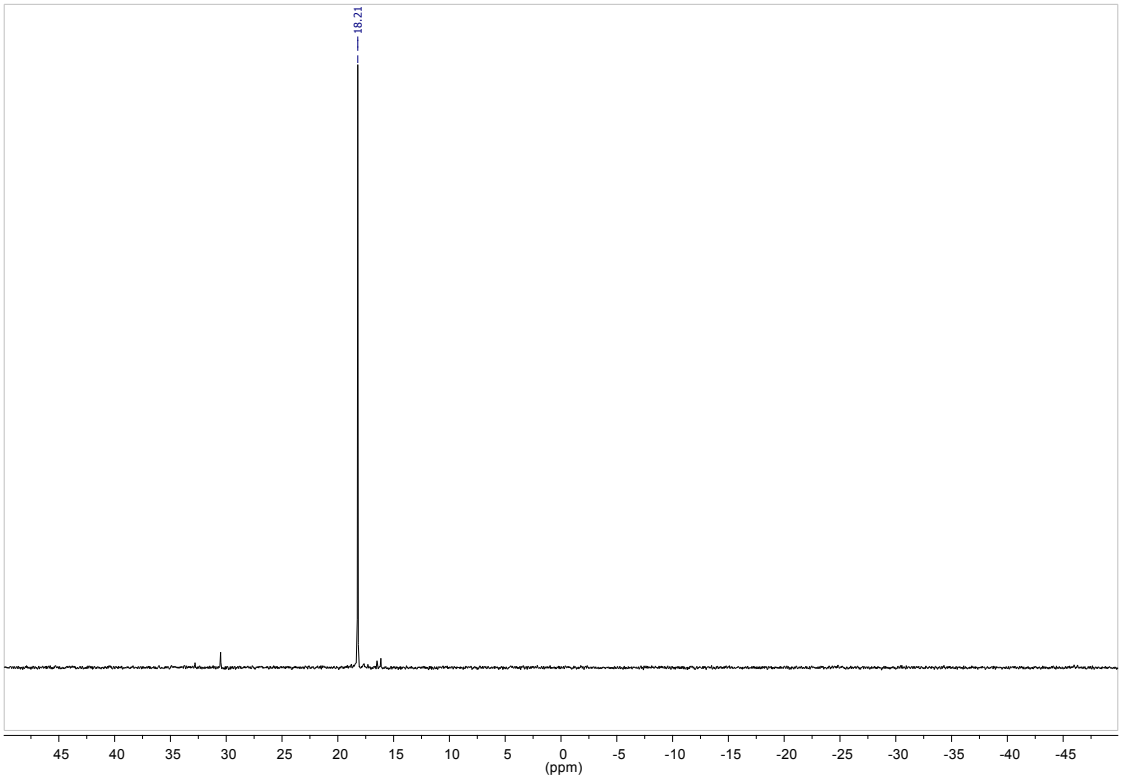

EtO
EtO
OTBDMS
16(I)
16(II)
16(III)
(ppm)

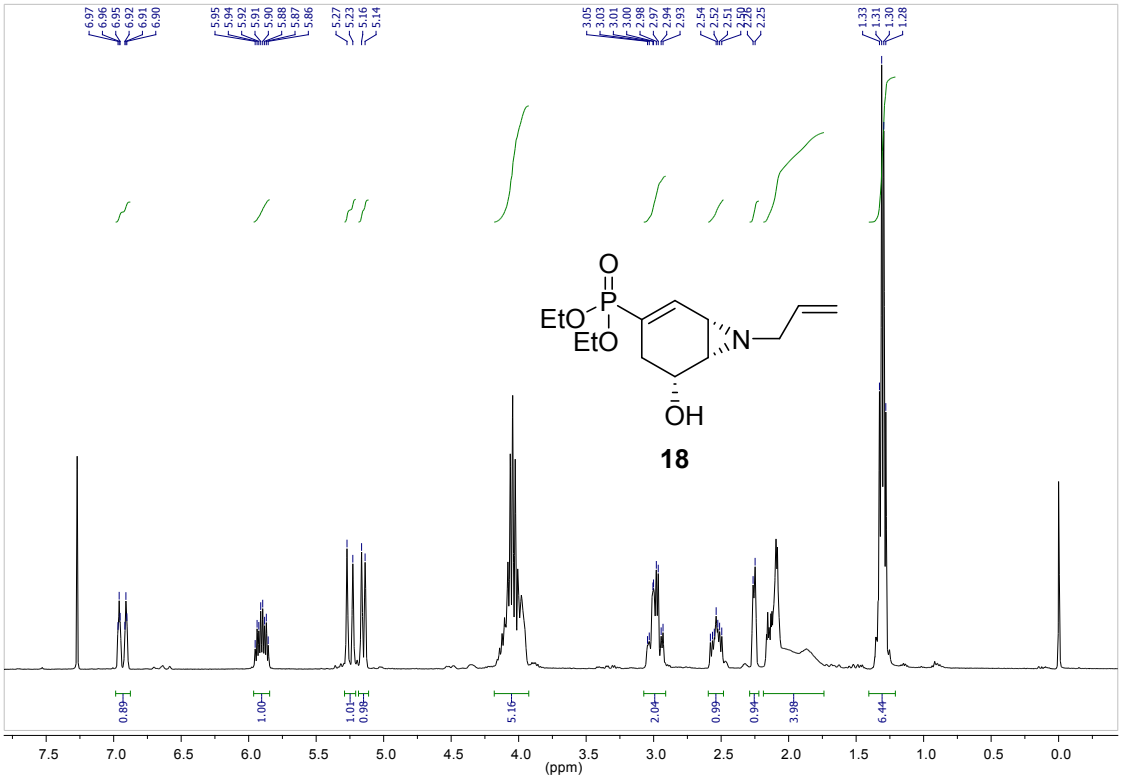

(ppm)

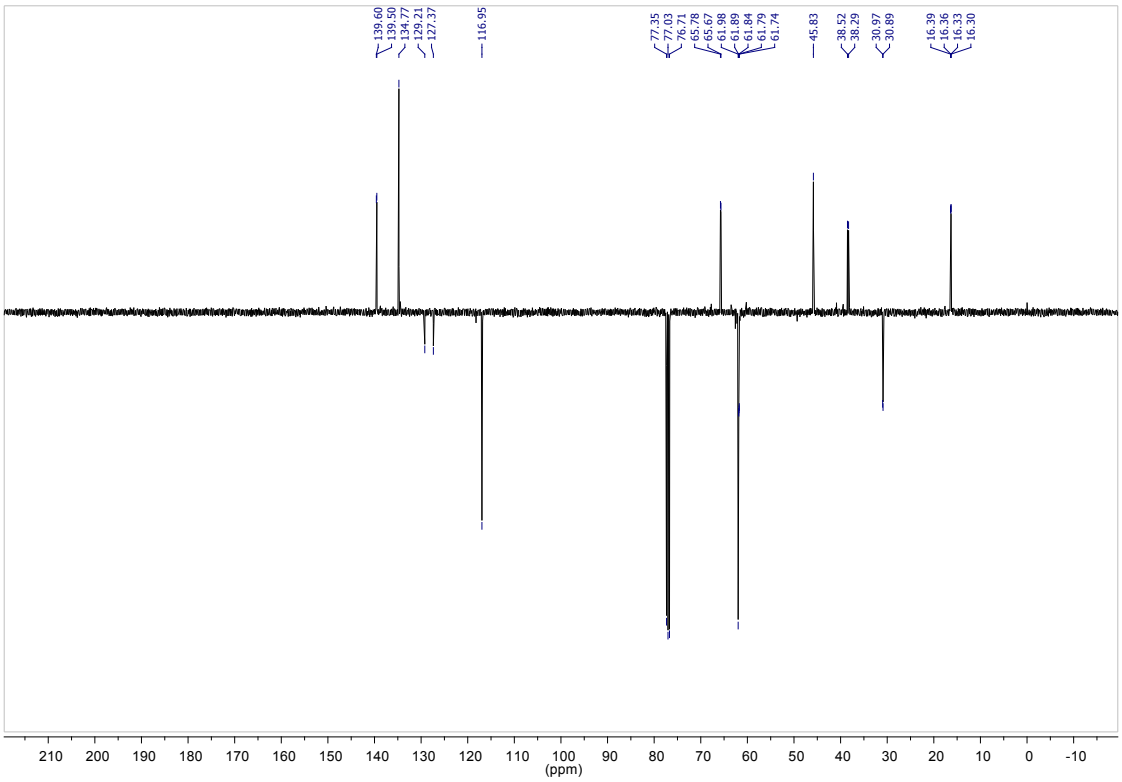

26.09
22.88
21.32
45
40
35
30
25
20
15
10
5
0
(ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45

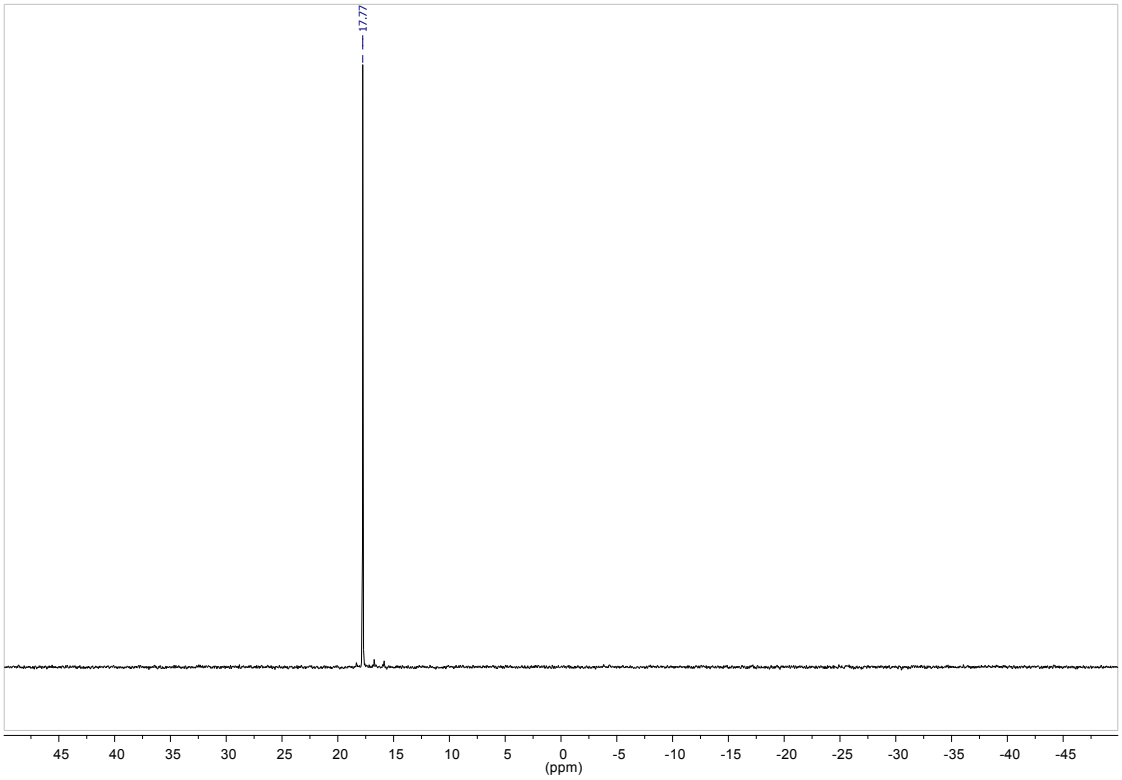

O
P
EtO
EtO
N
OTBDMS
17
(ppm)

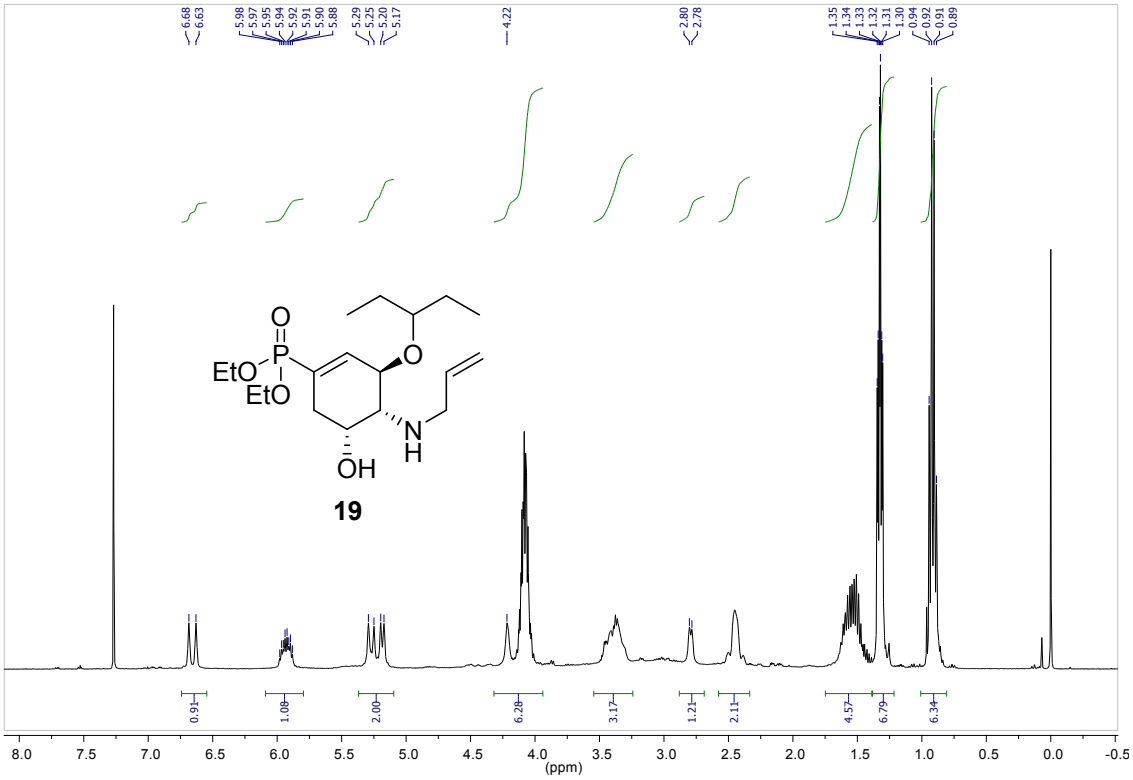

(ppm)

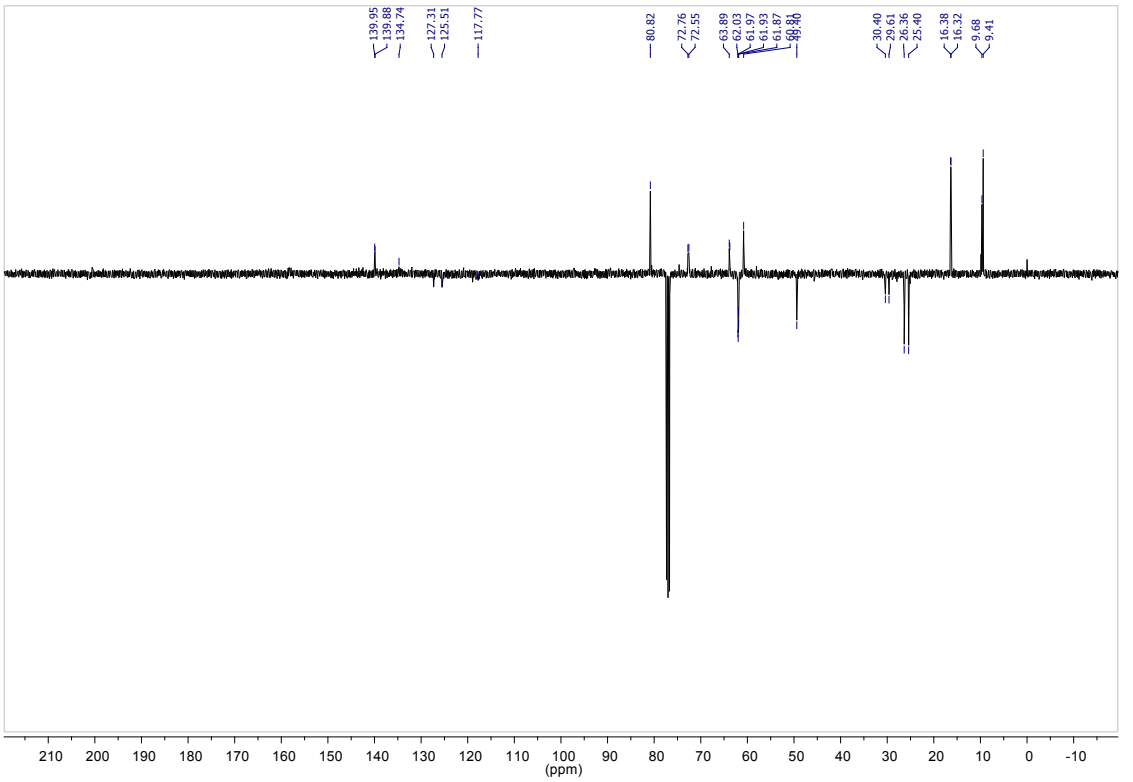

18.21
45
40
35
30
25
20
15
10
5
0
(ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45

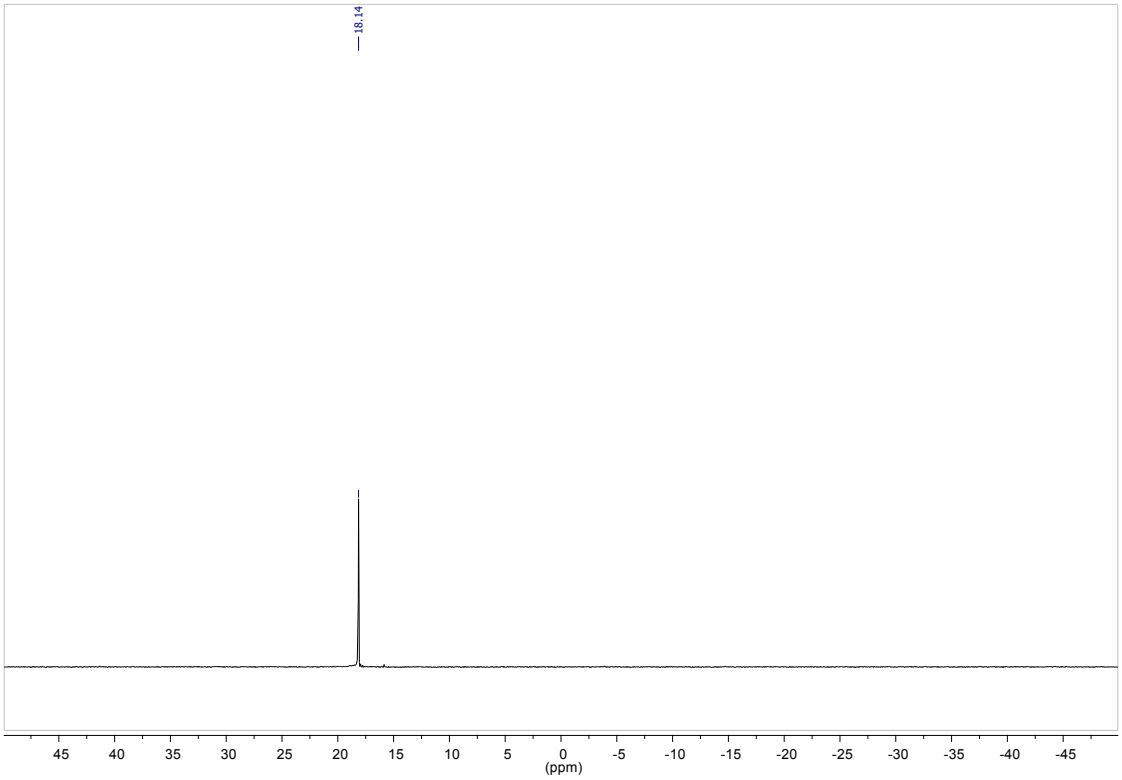

6.97
6.96
6.95
6.92
6.91
6.90
5.95
5.94
5.92
5.91
5.90
5.88
5.87
5.86
5.27
5.23
5.16
5.14
3.05
3.03
3.01
3.00
2.98
2.97
2.94
2.93
2.54
2.52
2.51
2.50
2.28
2.25
1.33
1.31
1.30
1.28
O
P
EtO
EtO
N
OH
18
0.89
1.00
1.01
0.98
5.16
2.04
0.99
0.94
3.98
6.44
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

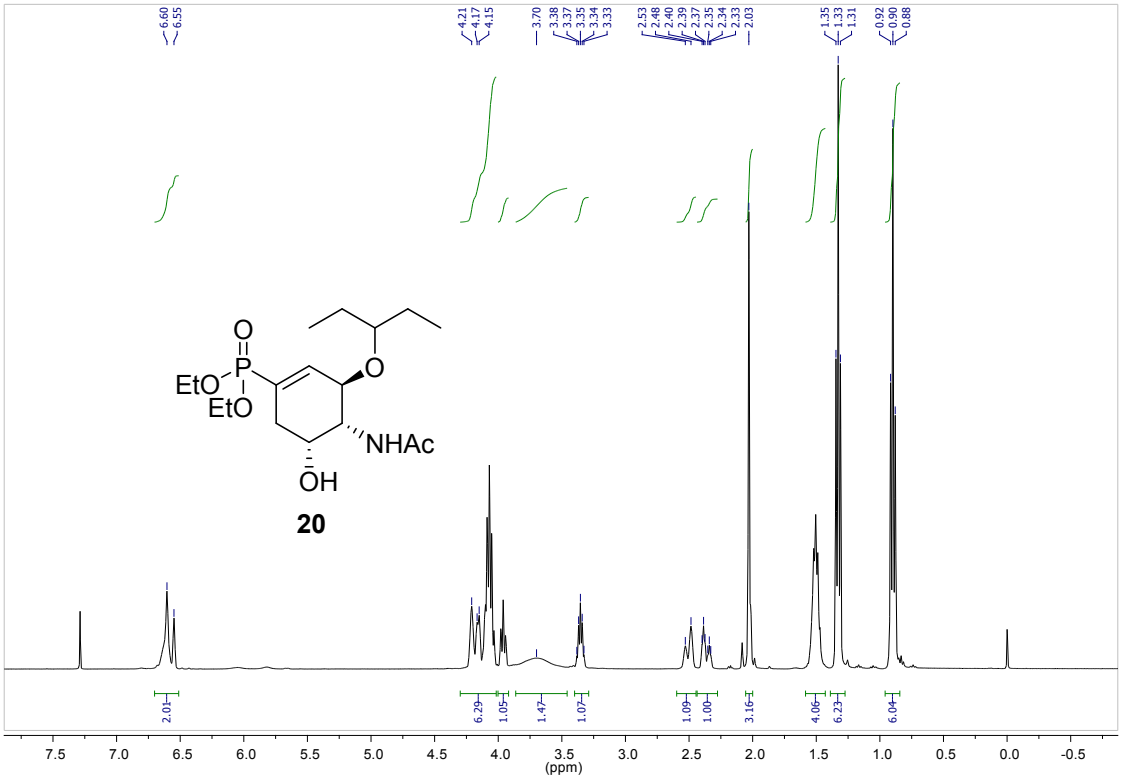

139.60
139.50
134.77
129.21
127.37
116.95
77.35
77.03
76.71
65.78
65.67
61.98
61.89
61.84
61.79
61.74
45.83
38.52
38.29
30.97
30.89
16.39
16.36
16.33
16.30
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)


17.77
45
40
35
30
25
20
15
10
5
0
(ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45

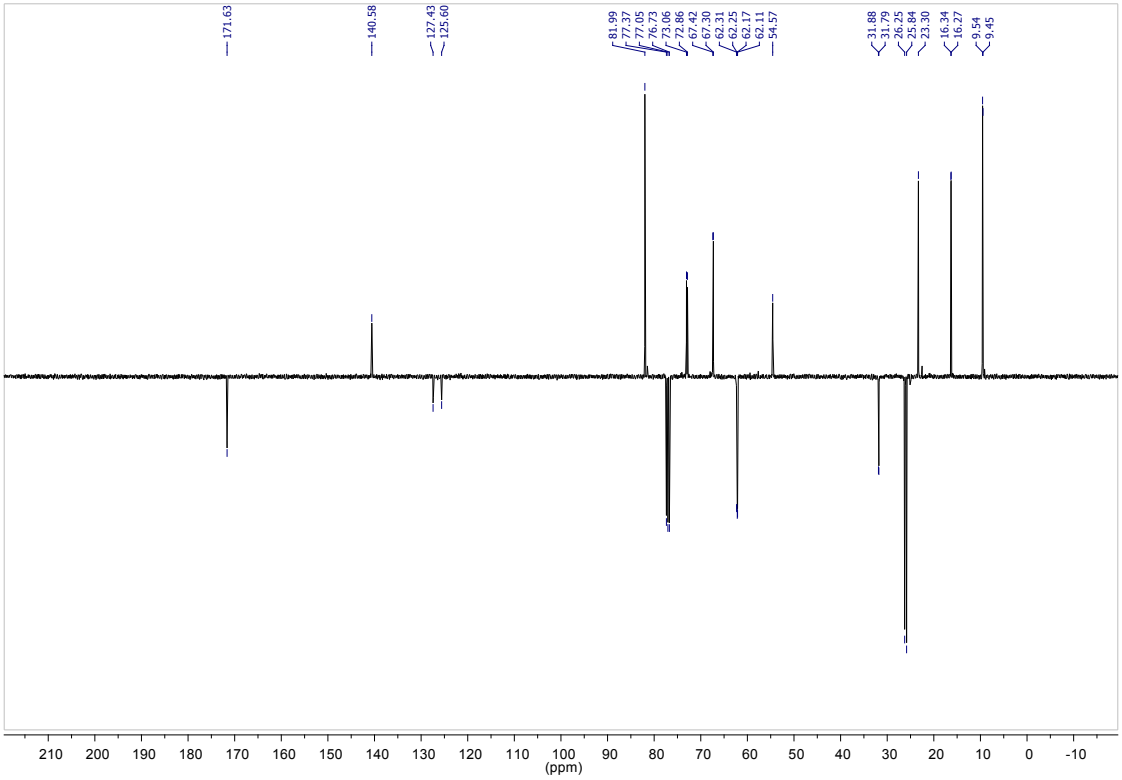

6.68
6.63
5.98
5.97
5.95
5.94
5.92
5.91
5.90
5.88
5.29
5.25
5.20
5.17
4.22
2.80
2.78
1.35
1.34
1.33
1.32
1.31
1.30
0.94
0.92
0.91
0.89
O
P
EtO
EtO
O
N
H
OH
19
0.91
1.08
2.00
6.28
3.17
1.21
2.11
4.57
6.79
6.34
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

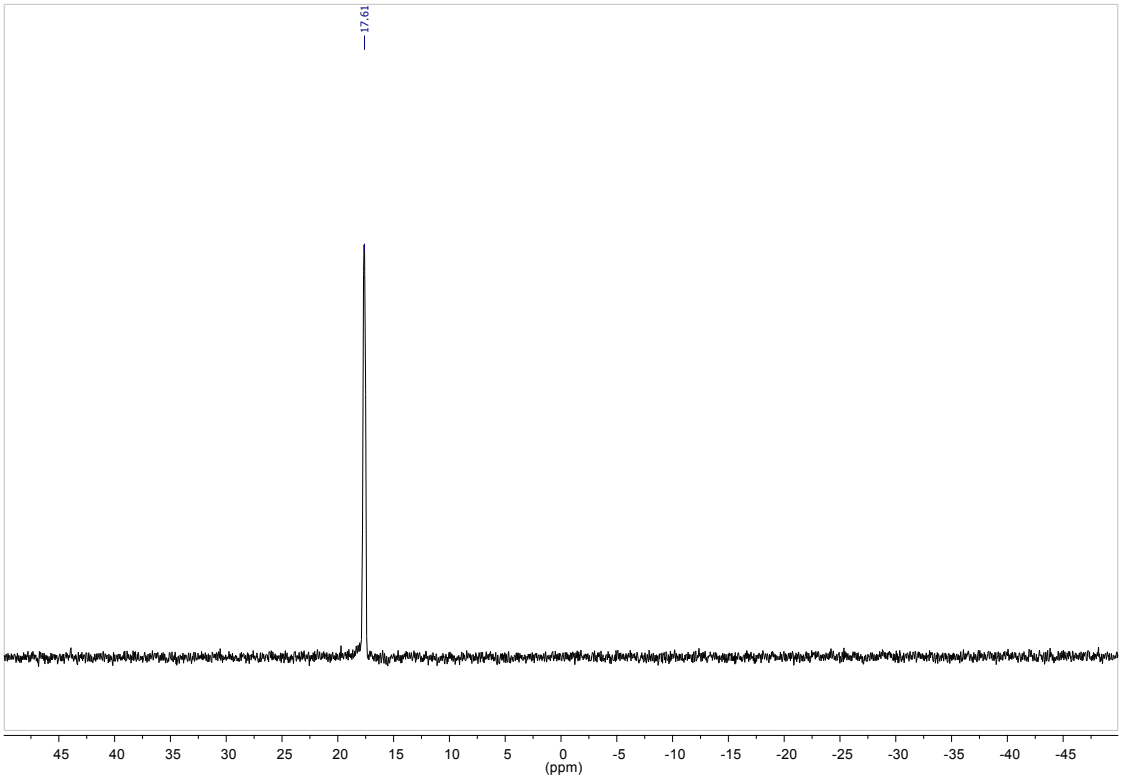

139.95
139.88
134.74
127.31
125.51
117.77
80.82
72.76
72.55
63.89
62.03
61.97
61.93
61.87
30.40
29.61
26.36
25.40
16.38
16.32
9.68
9.41
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

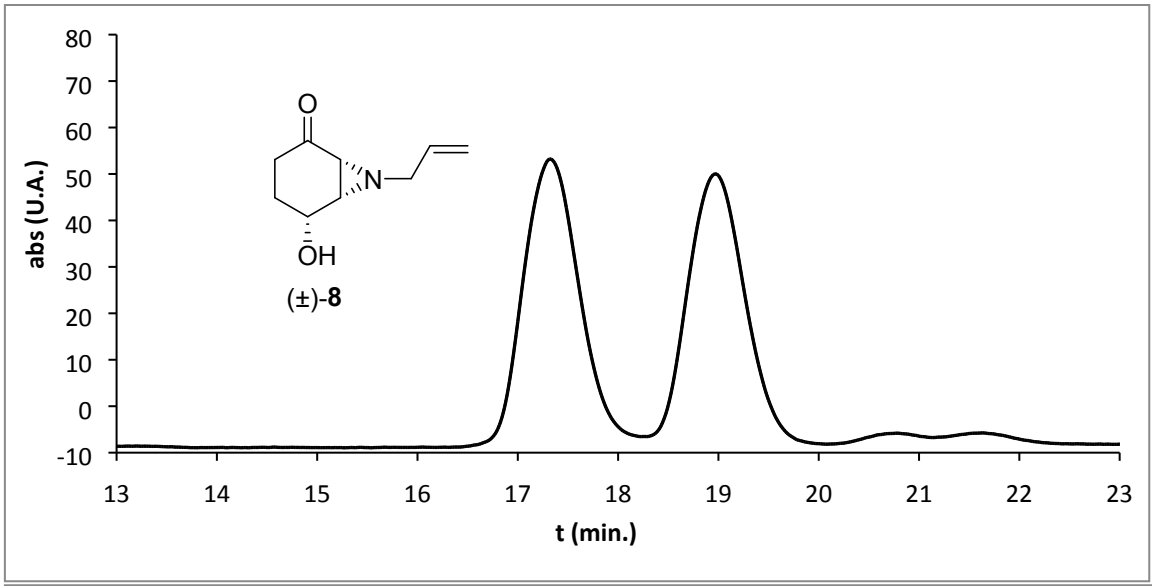

18.14
45
40
35
30
25
20
15
10
5
0
(ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45

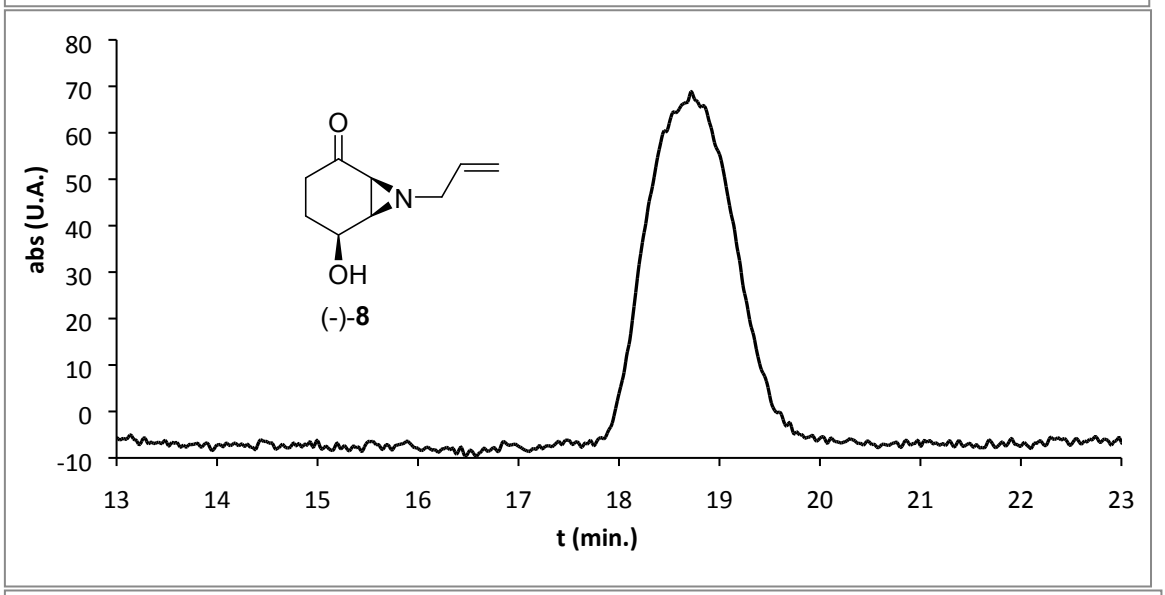

6.60
6.55
4.21
4.17
4.15
3.70
3.38
3.37
3.35
3.34
3.33
2.53
2.48
2.40
2.39
2.37
2.35
2.34
2.33
2.03
1.35
1.33
1.31
0.92
0.90
0.88
O
P
EtO
EtO
O
NHAc
OH
2.01
6.29
1.05
1.47
1.07
1.09
1.00
3.16
4.06
6.23
6.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

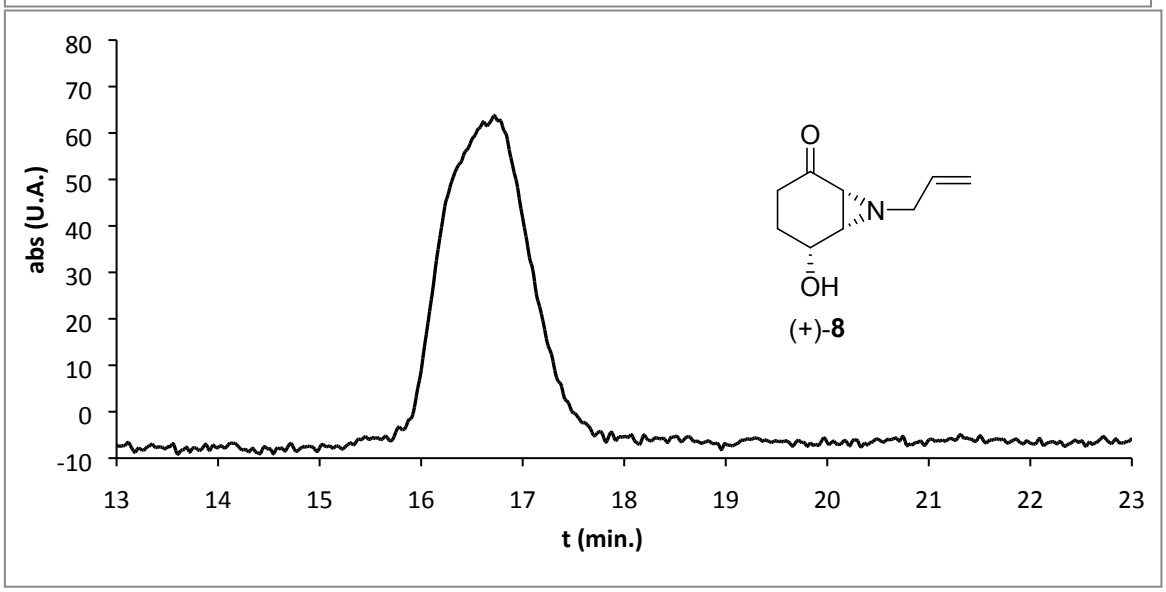
20


171.63
140.58
127.43
125.60
81.99
77.37
77.05
76.73
73.06
72.86
67.42
67.30
62.31
62.25
62.17
62.11
54.57
31.88
31.79
26.25
25.84
23.30
16.34
16.27
9.54
9.45
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)


17.61
45
40
35
30
25
20
15
10
5
0
(ppm)
-5
-10
-15
-20
-25
-30
-35
-40
-45







Elution conditions: AD-H; 95:5 hexane:isopropanol; 1.0ml.min^{-1}; 210nm.