Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Design and Synthesis of a Tetracyclic Tripeptide Mimetic Frozen in a Polyproline Type II (PP2) Helix Conformation

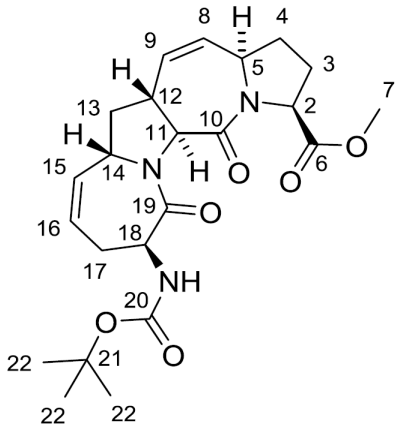
Supporting Information

1. Assigned NMR data for compounds 1, 14, 15, 16, 17, 19 and 20 ..... S2

2. Depicted NMR spectra S7

3. Crystal structure and structure refinement data S19

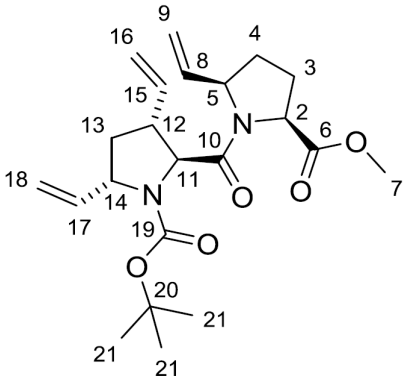
1.1. Assigned NMR data for compound 1 (Boc-[ProM-19]-OMe)



^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.86 – 5.79 (m, 2H, H-9, H-16), 5.70 – 5.65 (m, 1H, H-15), 5.61 – 5.56 (m, 1H, H-8), 4.78 – 4.67 (m, 3H, H-2, H-11, H-5/14), 4.64 – 4.59 (m, 1H, H-5/14), 4.34 – 4.29 (m, 1H, H-18), 2.99 – 2.90 (m, 1H, H-12), 2.73 (br, 1H, NH), 2.61 – 2.54 (1H, H-17), 2.42 (dt, J = 11.6, 5.7 Hz, 1H, H-13), 2.36 – 2.29 (m, 1H, H-4), 2.17 – 2.00 (m, 2H, H-3), 1.95 – 1.80 (m, 1H, H-4), 1.72 – 1.63 (m, 1H, H-13), 1.45 (s, 10 H, H-17, H-22).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 172.5 (s, C-6), 170.8 (s, C-19), 168.7 (s, C-18), 155.4 (s, C-20), 130.0(d, C-8), 128.8 (d, C-15), 128.0 (d, C-9, C-16), 79.7 (s, C-21), 64.6 (d, C-11), 59.4 (d, C-2), 57.5; 57.3 (d, C-5, C-14), 52.3 (q, C-7), 40.1 (t, C-13), 37.5 (d, C-12), 33.0 (t, C-4), 29.2 (t, C-17), 28.3 (q, C-22), 27.0 (d, C-3).

1.2. Assigned NMR data for compound 14

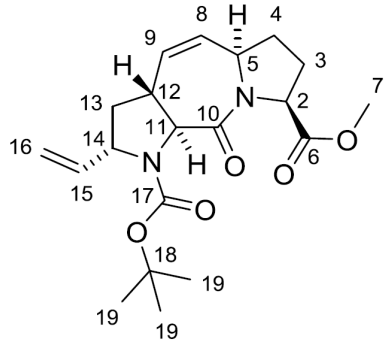


^{1}H NMR (600 MHz, $CDCl_3$; mixture of rotamers): δ (ppm) = 5.95 – 5.88 (m, 1H, H-8), 5.87 – 5.75 (m, 1H, H-15), 5.82 – 5.74 (m, 1H, H-17), 5.45 (m, 1H, H-9), 5.13 (m, 1H, H-9), 5.02 (m, 1H, H-1), 5.02 (m, 1H, H-18), 4.97 (m, 2H, H-16, H-18), 4.90 – 4.84 (t, 0.65H, H-5_{rot1}), 4.57 – 4.55 (m, 0.7H, H-5_{rot2}, H-14_{rot2}), 4.52 – 4.47 (m, 1H, H-2), 4.41 – 4.38 (m, 0.65H, H-14_{rot1}), 4.34 (m, 0.65H, H-11_{rot1}), 4.30 (m, H-11_{rot2}), 3.74; 3.72 (2x s, 3H, H-7), 2.85 – 2.79 (m, 1H, H-12), 2.73 – 2.64 (m, 1H, H-13), 2.27 – 2.11 (m, 2H, H-3, H-4), 2.01 – 1.80 (m, 2H, H-3, H-4), 1.64 – 1.60 (m, 1H, H-13), 1.39; 1.37 (2x s, 9H, H-21).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 172.8; 172.6; 172.5; 172.2 (s, C-6, C-10), 154.9; 153.9 (s, C-19), 141.0; 140.5 (d, C-17), 139.9; 139.7 (d, C-15), 138.6; 138.2 (d, C-8), 117.2; 116.7

(t, C-9), 115.1 (t, C-16), 114.1; 113.8 (t, C-18), 79.8 (s, C-20), 63.5; 63.2 (d, C-11), 61.2; 61.0 (d, C-14), 60.8, 60.7 (d, C-5), 60.0; 59.8 (d, C-2), 52.2; 52.0 (q, C-7), 46.7; 45.7 (d, C-12), 37.5; 36.2 (t, C-13), 32.9; 32.6 (t, C-4), 28.5; 28.3; 28.2 (q, C-21), 26.9; 26.9 (t, C-3).

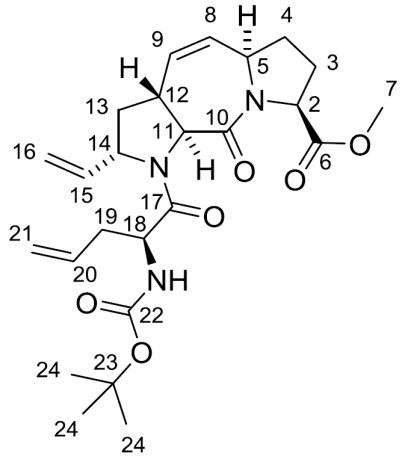
1.3. Assigned NMR data for compound 15



^{1}H NMR (500 MHz, $CDCl_3$; mixture of rotamers): δ (ppm) 5.85 – 5.74 (m, 1.25H, H-9, H-15$_{rot2}$), 5.66 (ddd, J = 17.0, 10.1, 8.3 Hz, 0.75H, H-15$_{rot1}$), 5.55 (ddd, J = 11.2, 2.9, 1.6 Hz, 1H, H-8), 5.26 – 4.97 (m, 2H, H-16), 4.80 (dd, J = 7.8, 2.8 Hz, 0.75H, H-2$_{rot1}$), 4.73 – 4.62 (m, 1.25H, H-2$_{rot2}$, H-5), 4.50 (dd, J = 25.5, 10.6 Hz, 1H, H-11), 4.32 (ddd, J = 10.5, 8.1, 5.6 Hz, 0.25H, H-14$_{rot2}$), 4.25 (ddd, J = 10.3, 8.3, 5.7 Hz, 0.75H, H-14$_{rot1}$), 3.69 (s, 0.75H, H-7$_{rot2}$), 3.68 (s, 2.25H, H-7$_{rot1}$), 2.99 – 2.85 (m, 1H, H-12), 2.39 – 2.25 (m, 1H, H-4), 2.28 – 2.17 (m, 1H, H-13), 2.11 – 1.97 (m, 2H, H-3), 1.96 – 1.80 (m, 1H, H-4), 1.59 – 1.46 (m, 1H, H-13), 1.41 (s, 6H), 1.38 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$; mixture of rotamers): δ (ppm) = 172.5; 172.3 (s, C-6), 169.7/169.1 (s, C-10), 154.2/153.0 (s, C-17), 140.0/138.8 (d, C-15), 129.6/129.3 (d, C-8), 128.9/128.6 (d, C-9), 115.1/114.7 (t, C-16), 80.0/79.6 (s, C-18), 63.2/62.8 (d, C-11), 61.8/61.5 (d, C-14), 59.5/59.4 (d, C-2), 57.1 (d, C-5), 52.3/52.1 (q, C-7), 39.7/39.5 (t, C-13), 39.2/39.1 (d, C-12), 33.1/33.0 (t, C-4), 28.3/28.1 (q, C-19), 27.2/27.0 (t, C-3).

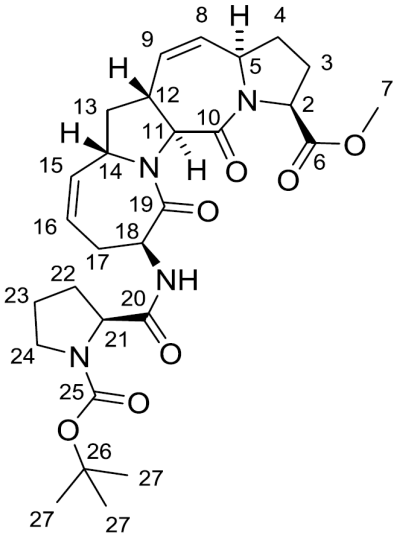
1.4. Assigned NMR data for compound 16



^{1}H NMR (500 MHz, $CDCl_3$, data for main rotamer): δ (ppm) = 5.97 – 5.84 (m, 1.4H, H-15, H-20), 5.79 (dt, J = 11.2, 2.2 Hz, 1H, H-9), 5.75 – 5.64 (m, 0.6H, H-15, H-20), 5.63 – 5.54 (m, 1H, H-8), 5.43 – 5.22 (m, 2H, H-16), 5.18 – 5.04 (m, 2H, H-21), 4.93 – 4.89 (m, 1H, H-18), 4.78 – 4.76 (m, 1H, H-2), 4.74 – 4.70 (m, 2H, H-5, H-11), 4.42 – 4.37 (m, 1H, H-14), 3.74 – 3.67 (m, 3H, H-7), 2.99 – 2.91 (m, 1H, H-12), 2.55 – 2.50 (m, 1H, H-19), 2.41 – 2.31 (m, 3H, H-4, H-13, H-19), 2.11 – 2.00 (m, 2H, H-3), 1.91 – 1.80 (m, 1H, H-4), 1.70 – 1.65 (m, 1H, H-13).

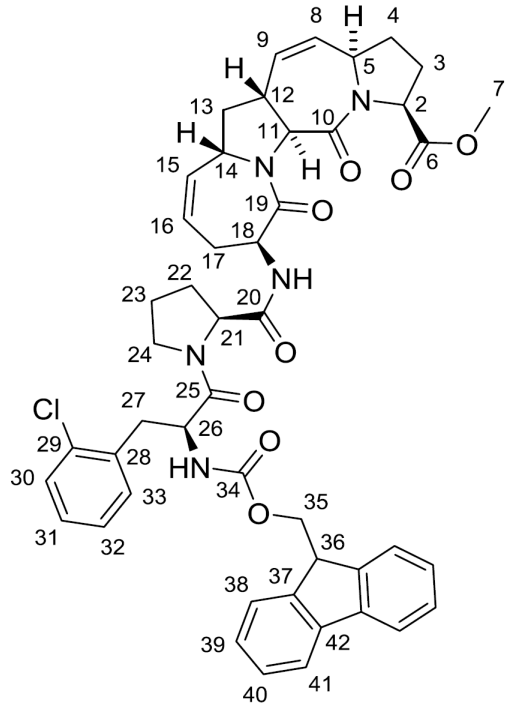
^{13}C NMR (125 MHz, $CDCl_3$, data for main rotamer): δ (ppm) = 172.3 (s, C-6), 172.1 (s, C-17), 168.4 (s, C-10), 155.5 (s, C-22), 137.9 (d, C-15), 133.5 (d, C-20), 130.0 (d, C-8), 128.1 (d, C-9), 118.2 (t, C-16, C-21), 79.0 (s, C-23), 63.9 (d, C-11), 62.9 (d, C-14), 59.3 (d, C-2), 57.2 (d, C-5), 52.3 (q, C-7), 51.7 (d, C-18), 40.9 (t, C-13), 38.1 (d, C-12), 37.1 (t, C-19), 32.8 (t, C-4), 28.4 (q, C-24), 27.2 (t, C-3).

1.5. Assigned NMR data for peptide 17



^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) = 7.67 (d, J = 7.6 Hz, 1H, NH), 6.04 – 5.55 (m, 4H, H-8, H-9, H-15, H-16), 4.82 – 4.15 (m, 6H, H-2, H-5, H-11, H-14 H-18, H-21), 3.69 (s, 3H, H-7), 3.54 – 3.22 (m, 2H, H-24), 2.98 – 2.90 (m, 1H, H-12), 2.71 – 1.61 (m, 12H, H-3, H-4, H-13, H-17, H-22, H-24), 1.42 (s, 9H, H-27).

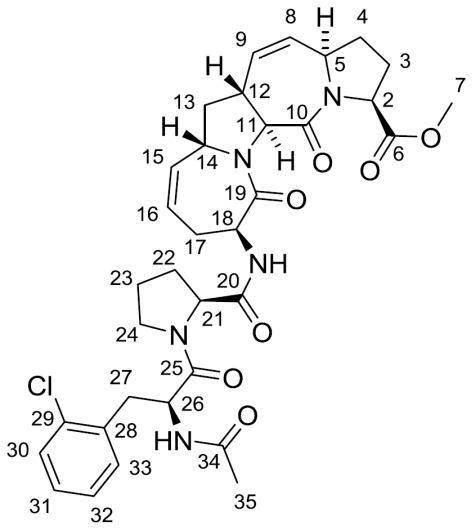
1.6. Assigned NMR data for peptide 19



^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) = 7.74 – 7.72 (m, 2H, H-41), 7.53 – 7.11 (m, 8.3H, H-30, H-31, H-32, H-33, H-38, H-39, H-40, NH, $CO2NH_{rot2}$), 4.89 (td, J = 9.1, 5.3 Hz, 0.7H, H-26_{rot1}), 4.82 – 4.49 (m, 6.3H, H-2, H-5, H-11, H-14, H-18 H-21, H- 26_{rot2}), 5.90 – 5.67 (m, 3.7H, H-9, H-15, H-16, CO_2NH_{rot1}), 5.61 – 5.54 (m, 1H, H-8), 4.89 (td, J = 9.1, 5.3 Hz, 0.7H, H-26_{rot1}), 4.75 – 4.50 (m, 6.3H, H-2, H-5, H-11, H-14, H-18, H-21, 26_{rot2}), 4.26 (dd, J = 10.5, 7.2 Hz, 1H, H-35), 4.15 (dd, J = 10.5, 7.4 Hz, 1H, H-35), 4.11 – 4.03 (m, 1H, H-36), 3.68 (s, 3H, H-7), 3.71 – 3.44 (m, 0.3H, H-24_{rot2}), 3.53 – 3.44 (m, 0.7H, H-24_{rot1}), 3.31 (dd, J = 13.3, 6.7 Hz, 0.3H, H-27_{rot2}), 3.20 (dd, J = 13.8, 5.3 Hz, 0.7H H-27_{rot1}),3.08 (dd, J = 13.1, 7.7 Hz, 0.3H H-27_{rot2}), 2.99 (dd, J = 13.8, 9.3 Hz, 0.7H H-27_{rot1}), 2.96 (br, 1H, H-12), 2.67 – 2.55 (m, 2H, H-17), 2.47 (dt, J = 11.6, 5.7 Hz, 1H, H-13), 2.41 – 1.81 (m, 8H, H-3, H-4, H-22, H-23),1.69 (q, J = 12.2 Hz, 1H, H-13).

^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) = 172.4 (s, C-6), 171.2 (s, C-25), 170.5/170.1 (s, C-19, C-20), 168.4 (s C-10), 155.6 (s, C-34), 143.8/143.7 (s, C-37), 141.1 (s, C-42), 134.4/133.9 (s, C-28, C-29), 131.9 (d, C-33), 129.9/129.6/129.5/128.6/127.9 (d, C-8, C-9, C-15, C-16, C-30, C-32, C-33), 127.6 (d, C-40), 126.9 (d, C-39), 126.8 (d, C-31), 125.1; 125.0 (d, C-38), 119.9 (d, C-41), 66.9 (t, C-35), 64.5 (d, C-11), 60.0 (d, C-21), 59.3(d, C-2), 57.3; 57.0 (d, C-5, C-14), 53.6 (d, C-18), 52.2 (q, C-7), 51.9 (d, C-26), 47.4 (t, C-24), 47.0 (d, C-36), 40.1 (t, C-13), 37.4 (d, C-12), 37.0 (t, C-27), 32.9 (t, C-4), 29.1 (t, C-17), 27.5/27.0 (t, C-3, C-22), 25.0 (t, C-23).

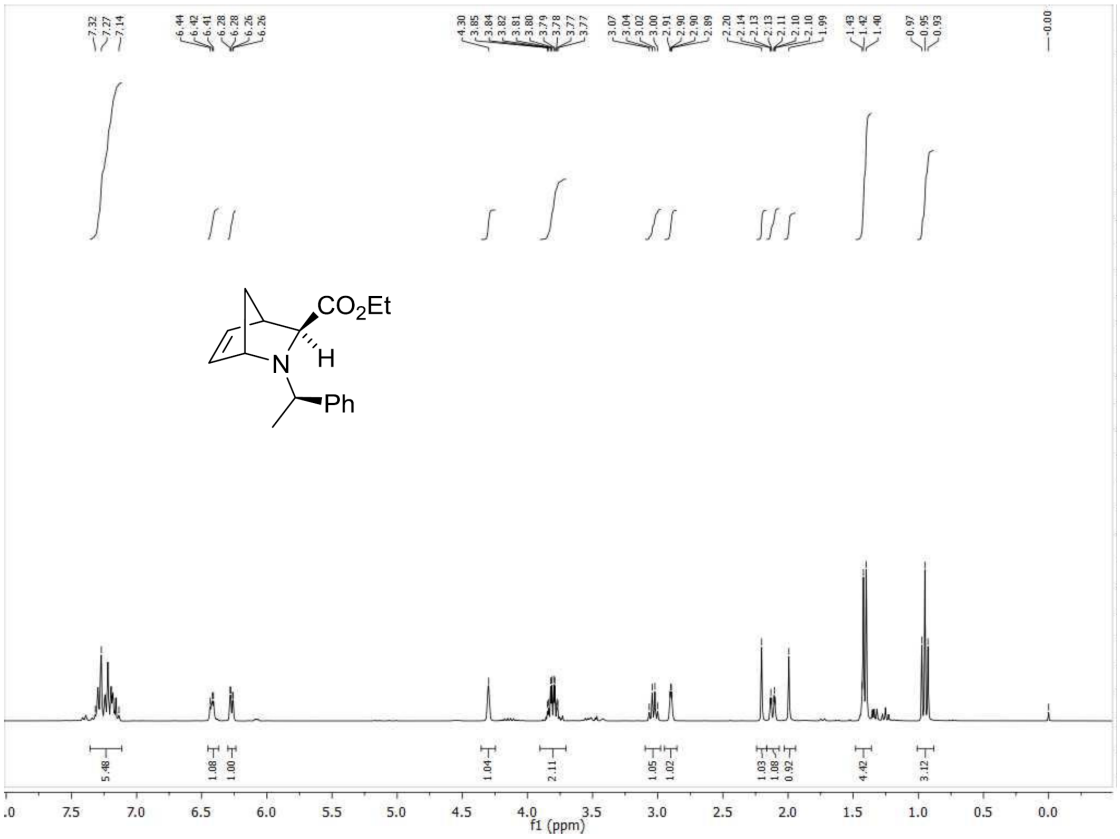
1.7. Assigned NMR Data for peptide 20

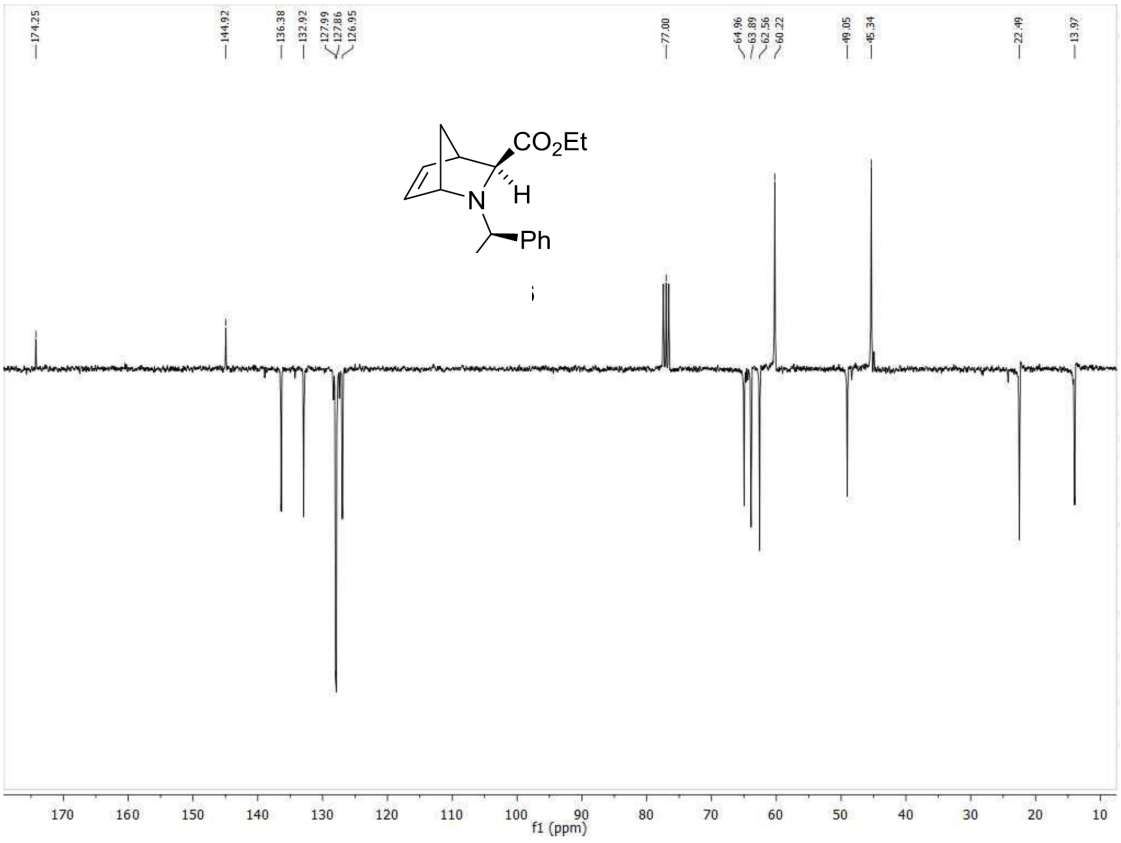


^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) = 7.62 (d, J = 9.6 Hz, 0.3H, NH-Ac_{rot2}), 7.43 (d, J = 7.2 Hz, 0.7 H, NH_{rot1}), 7.37 – 7.32 (m, 0.7H, Ar_{rot2}), 7.23 – 7.15 (m, 2.6H, Ar), 7.15 – 7.08 (m, 0.7H, Ar), 6.98 (d, J = 8.5 Hz, 0.3H, NH_{rot2}), 6.36 (d, J = 8.5 Hz, 0.7H, NH-Ac_{rot1}), 5.90 – 5.79 (m, 2H, H-9, H-16), 5.78 – 5.68 (m, 1H, H-15), 5.65 – 5.55 (m, 1H, H-8), 5.09 (td, J = 8.7, 5.5 Hz, 0.7H, H-26_{rot1}), 5.01 (td, J = 9.7, 5.0 Hz, 0.3H, H-26_{rot2}), 4.80 – 4.67 (m, 4H, H-2, H-5, H-11, H-14, H-18_{rot2}), 4.61 (td, J = 7.2, 3.3 Hz, 0.7H, H-18_{rot1}), 4.56 – 4.48 (m, 1H, H-5_{rot2} or H-14_{rot2}, H-21_{rot1}), 4.28 (d, J = 8.1 Hz, 0.3H, H-21_{rot2}), 3.72 (q, J = 8.3 Hz, 0.7H, H-24_{rot1}), 3.67 (s, 2.1H, H-7_{rot1}), 3.59 (s, 0.9H, H-7_{rot2}), 3.56 (m, 0.6H, H-24_{rot2}), 3.50 – 3.40 (m, 1H, H-24_{rot1}, H-27_{rot2}), 3.15 (dd, J = 13.9, 5.5 Hz, 0.7H, H-27_{rot1}), 3.05 – 2.91 (m, 1.7H, H-12, H-27_{rot1}), 2.80 (dd, J = 13.6, 9.7 Hz, 0.3H, H-27_{rot2}), 2.70 – 2.52 (m, 2H, H-17), 2.48 (m, 1H, H-13), 2.41 – 2.27 (m, 2H, H-4, H-22), 2.25 – 1.80 (m, 8.1H, H-3, H-4, H-22 H-23, H-35_{rot1}), 1.77 – 1.63 (m, 1.9H, H-13, H-35_{rot2}).

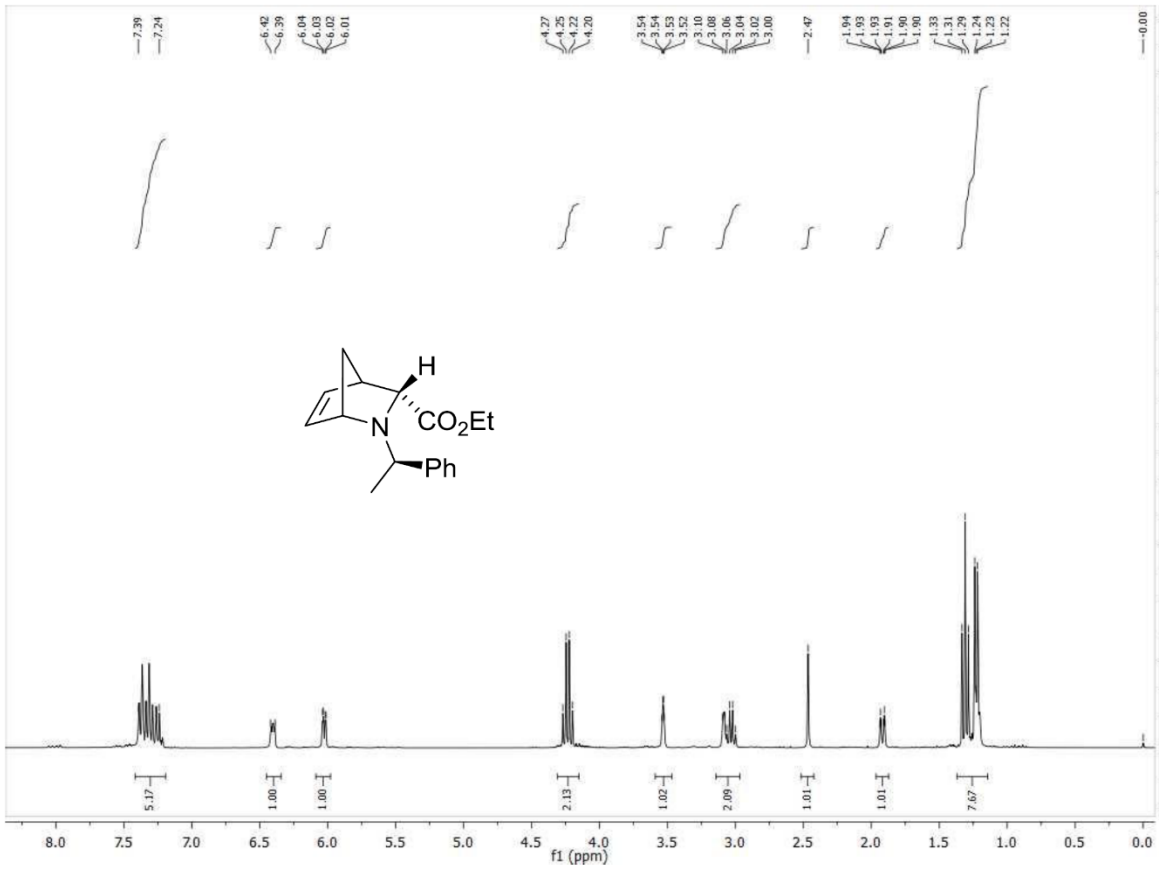
^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) = 172.4/171.8 (s, C-6), 171.3/171.3 (s, C-25), 170.5/170.4 (s, C-19), 171.1/ 170.1 (s, C-20), 170.1/169.5 (s, C-34), 169.1/168.4 (s, C-10), 135.4/134.0 (s, C-28), 134.4/134.4 (s, C-29), 132.0/131.7 (d, C-33), 130.0/129.8 (d, C-8), 129.5/129.5/129.3/128.6/128.1/127.9/127.8/127.5/126.8/ 126.2 (d, C-9, C-15, C-16, C-30, C-31, C-32), 64.7/64.5 (d, C-11), 60.7/60.1 (d, C-21), 59.6/ 59.3 (d, C-2), 57.7/57.4/57.1 (d, C-5, C-14), 53.7/52.7 (d, C-18), 52.4/52.2 (q, C-7), 51.0/50.2 (d, C-26), 47.5 (t, C-24), 40.3/40.1 (t, C-13), 37.4/37.3 (d, C-12), 36.4/35.9 (t, C-27), 32.9/ 32.8 (t, C-4), 29.7/29.1 (t, C-17), 27.5 (t, C-22), 27.0 (t, C-3), 25.0 (t, C-23), 23.0, 22.2 (t, C-35).

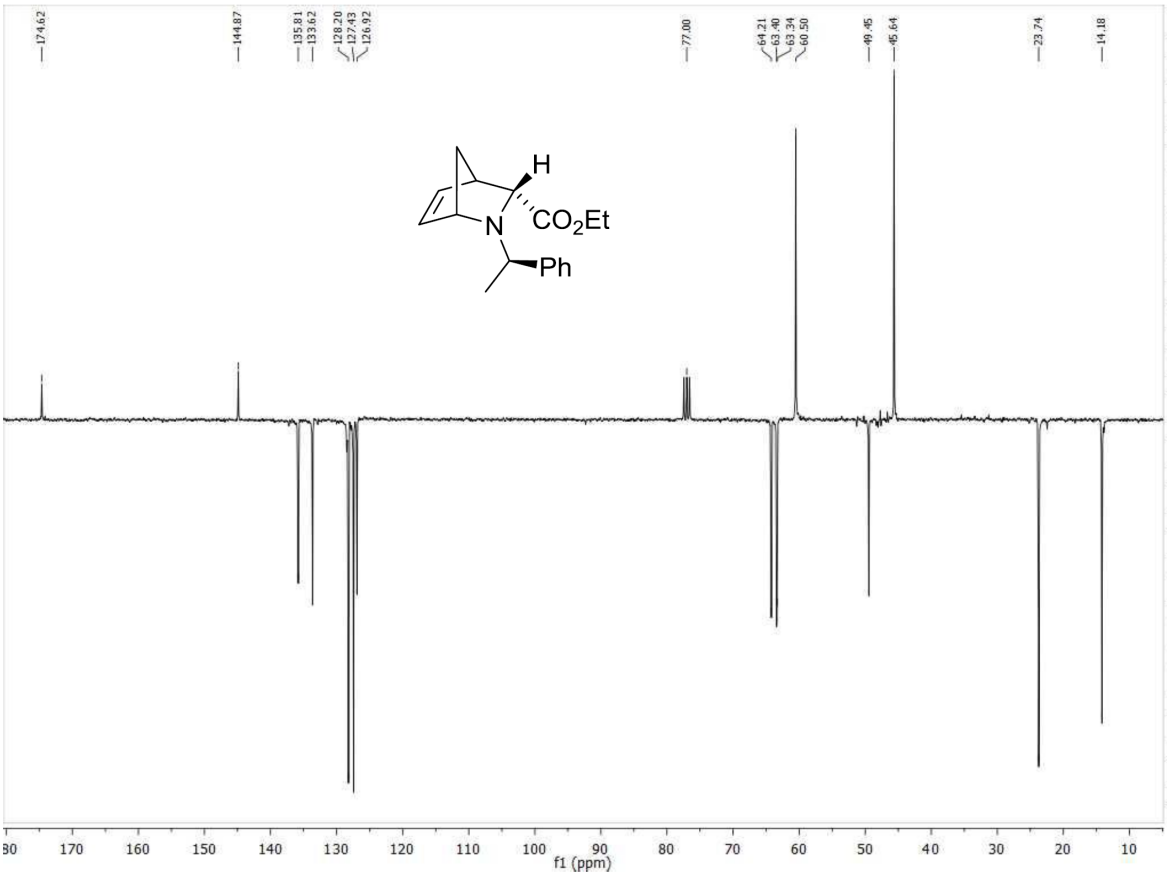
2.1. ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of 7a.



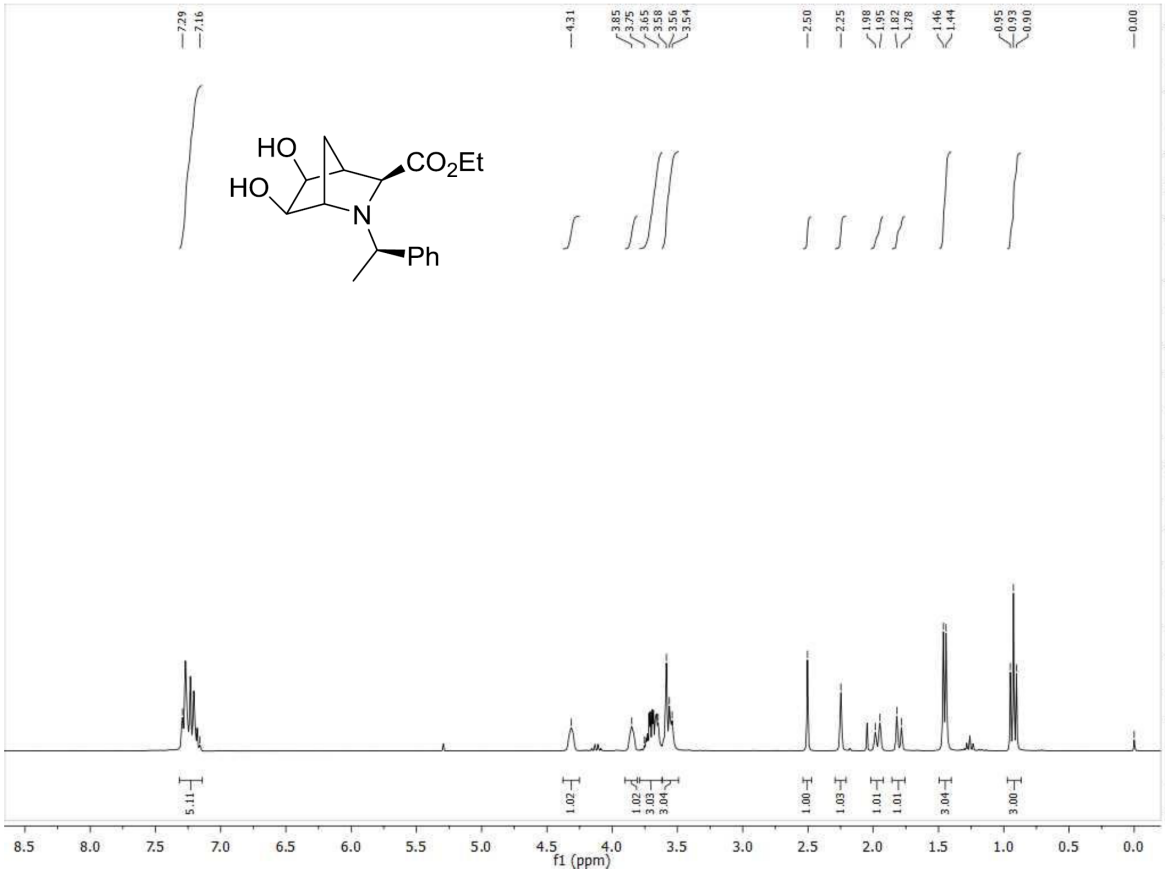


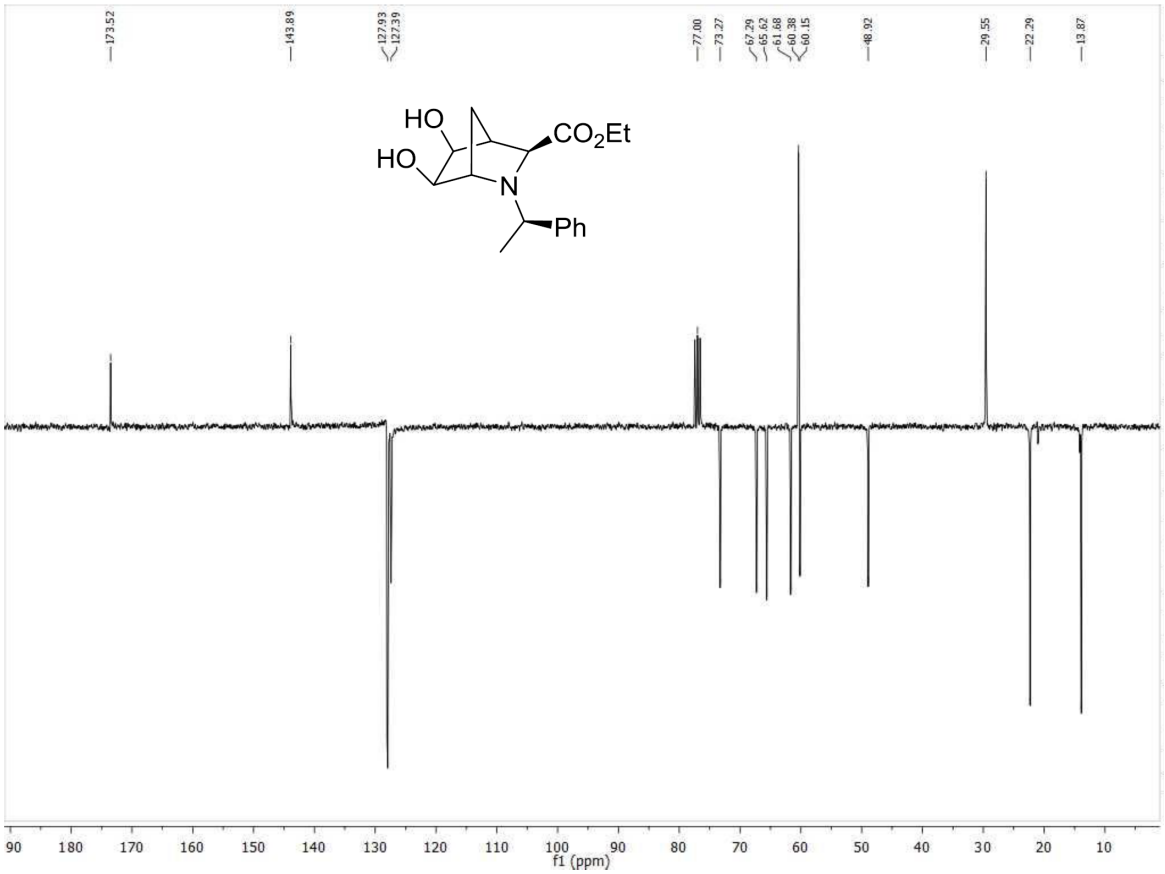
2.2. ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of 7b.



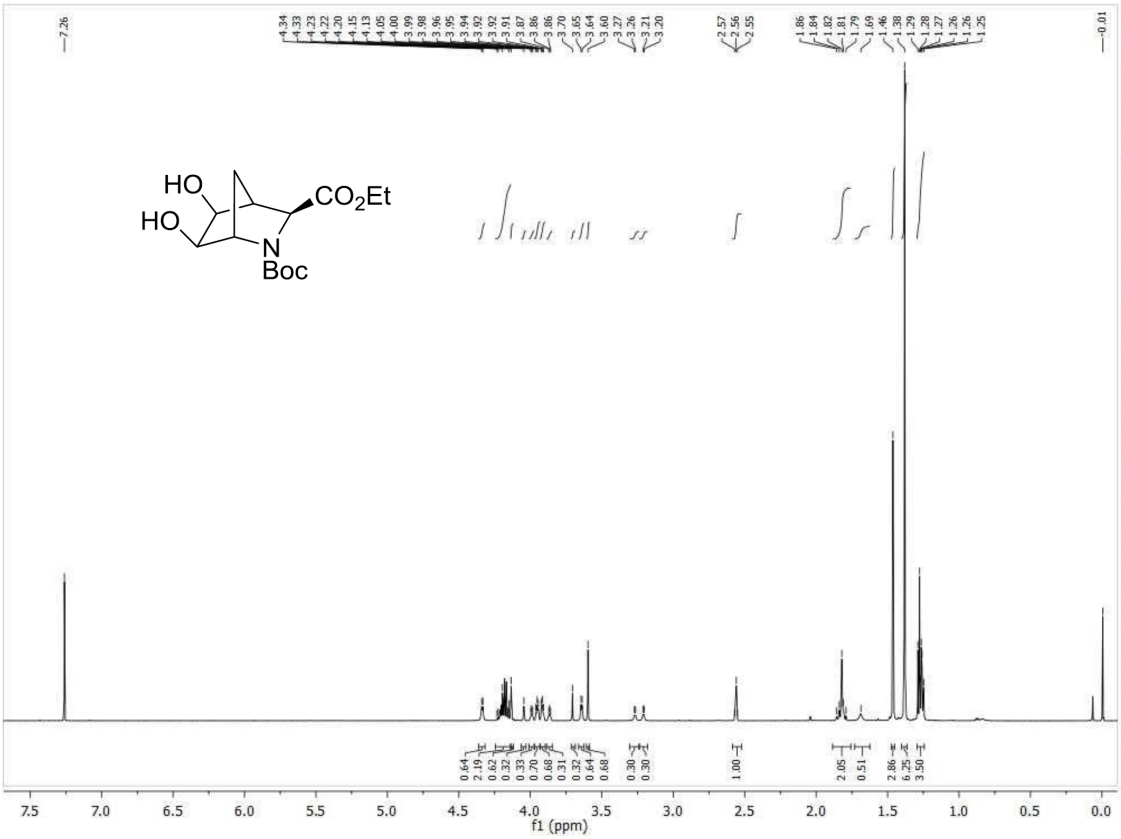


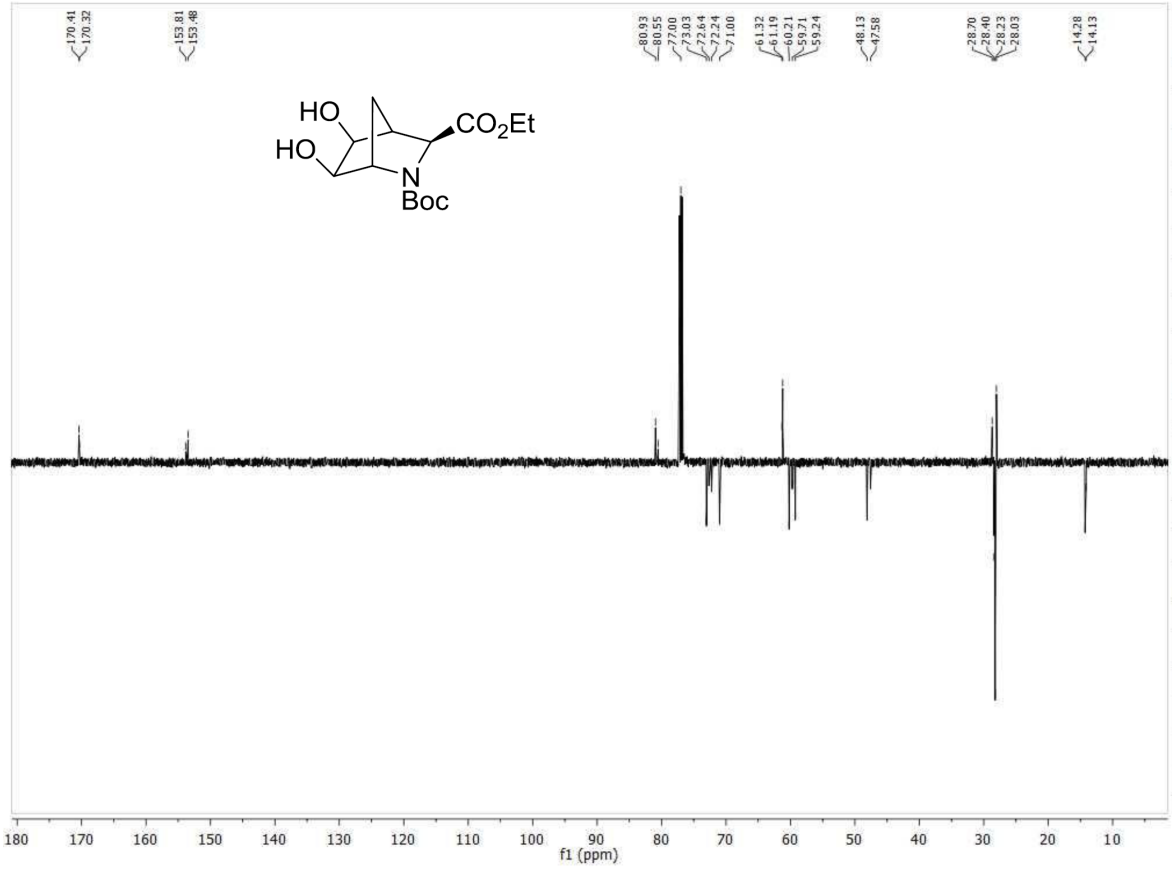
2.3. ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of 8.



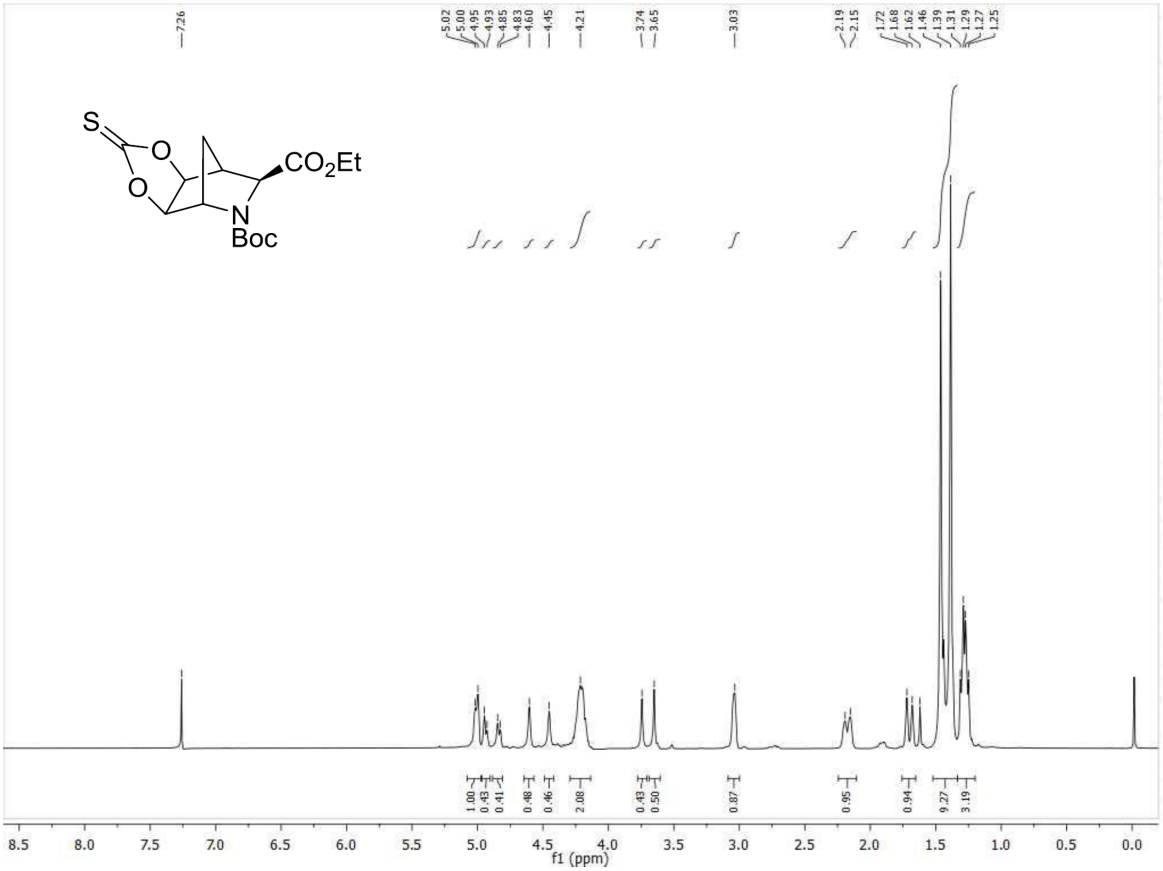


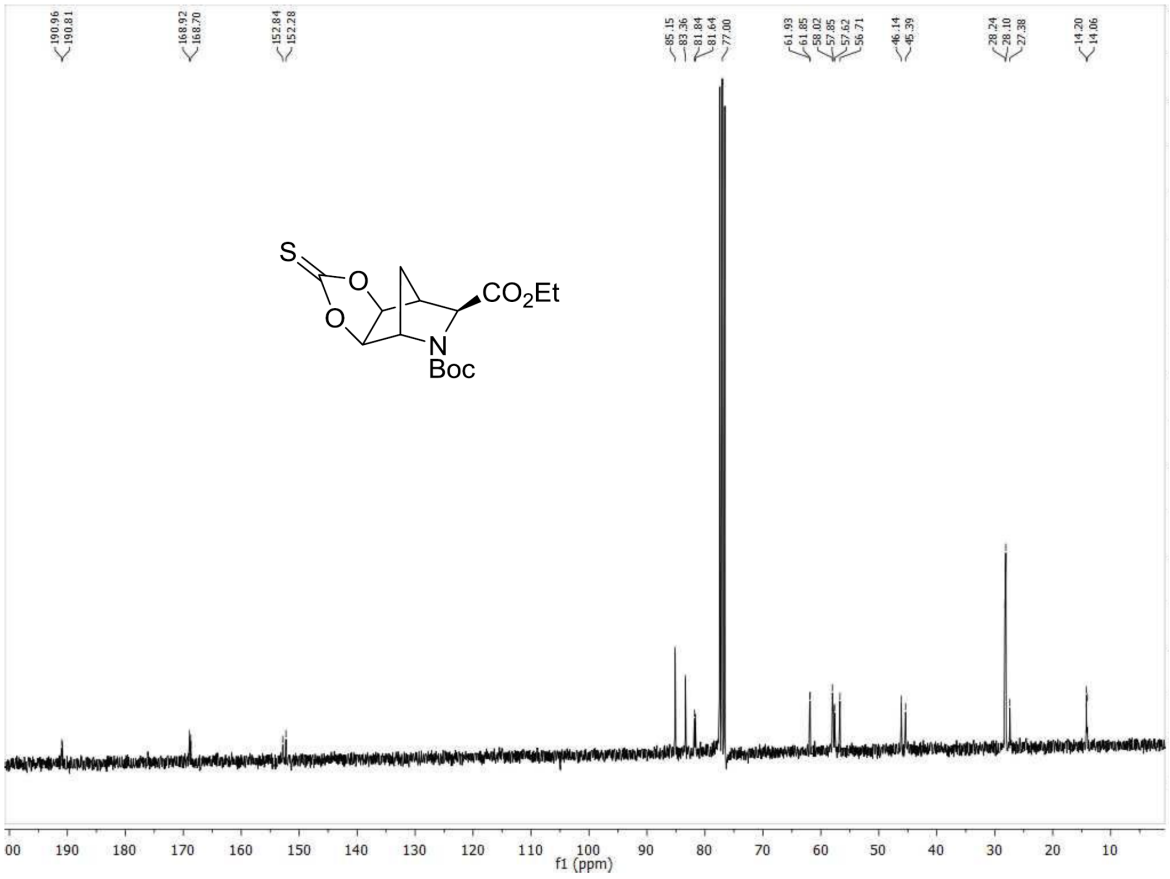
2.4. ^{1}H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz, $CDCl_3$) spectra of 9.



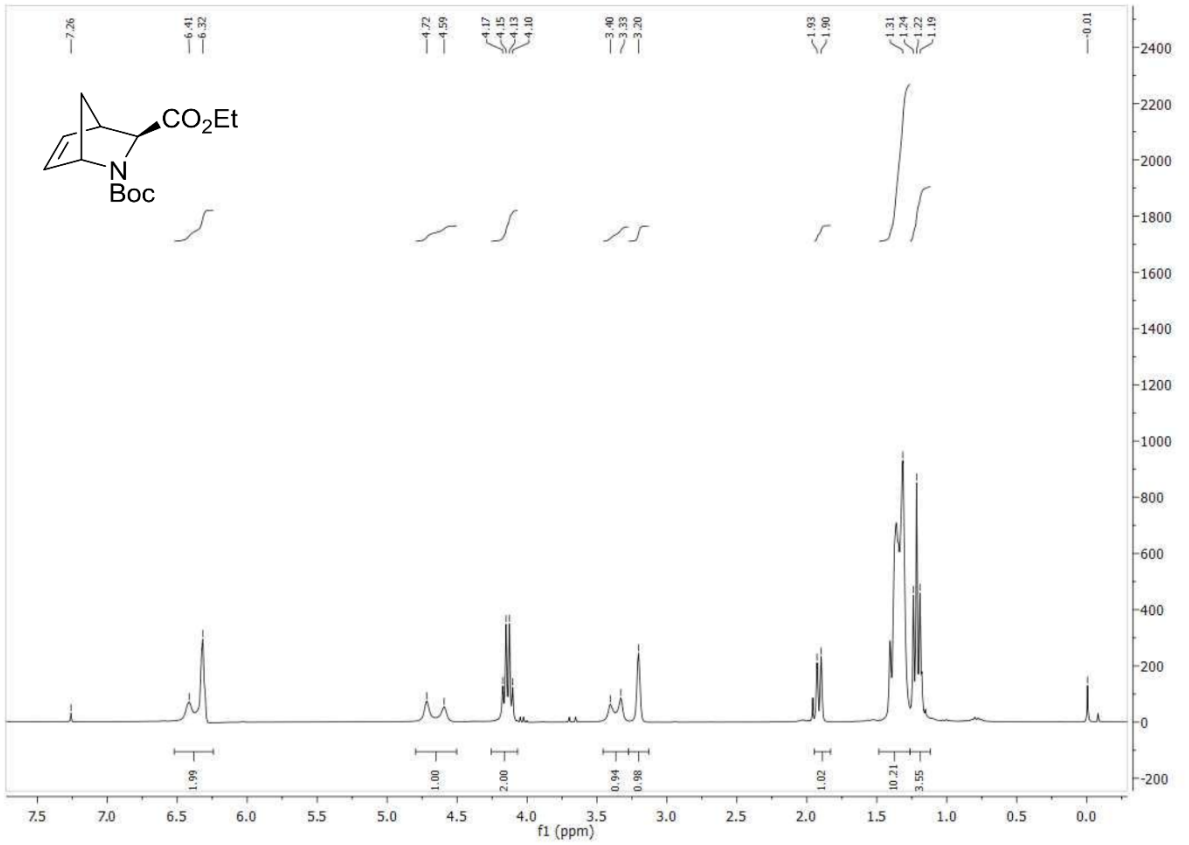


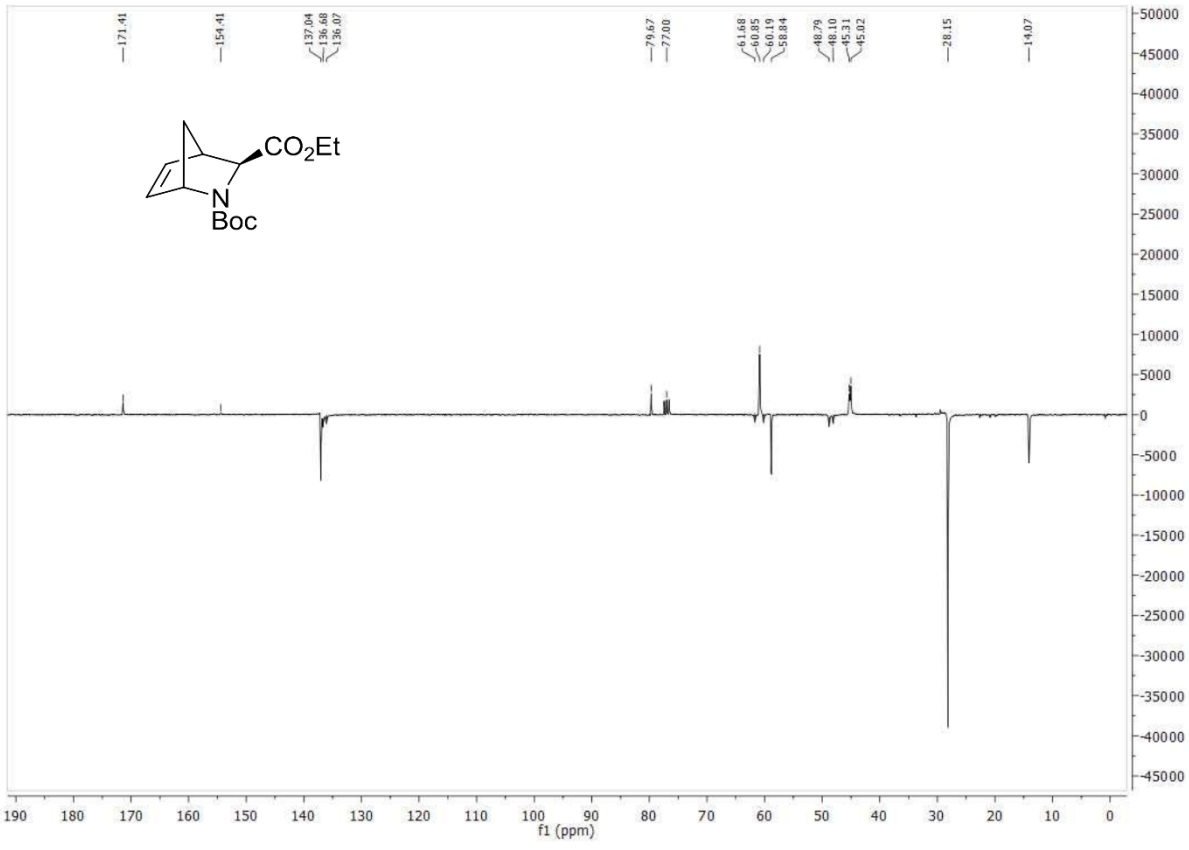
2.5. ^{1}H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz, $CDCl_3$) spectra of 10.



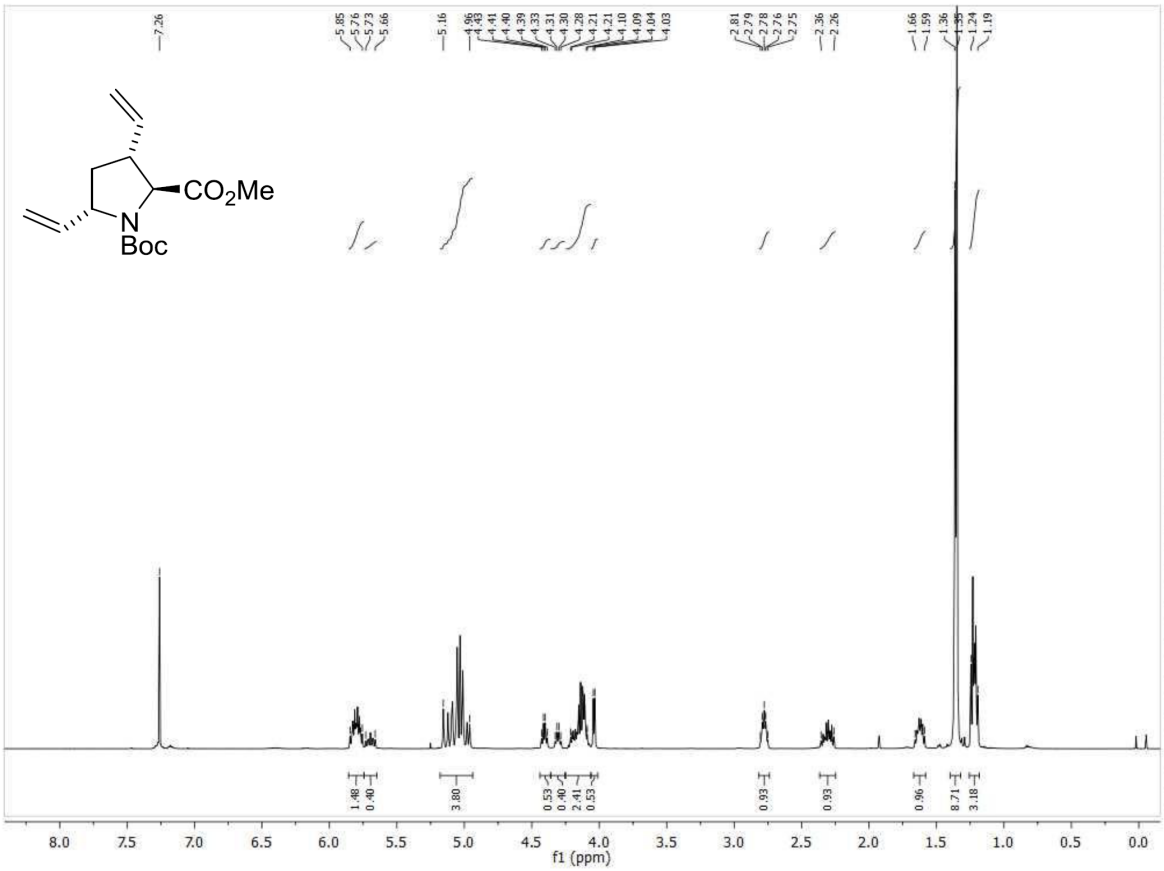


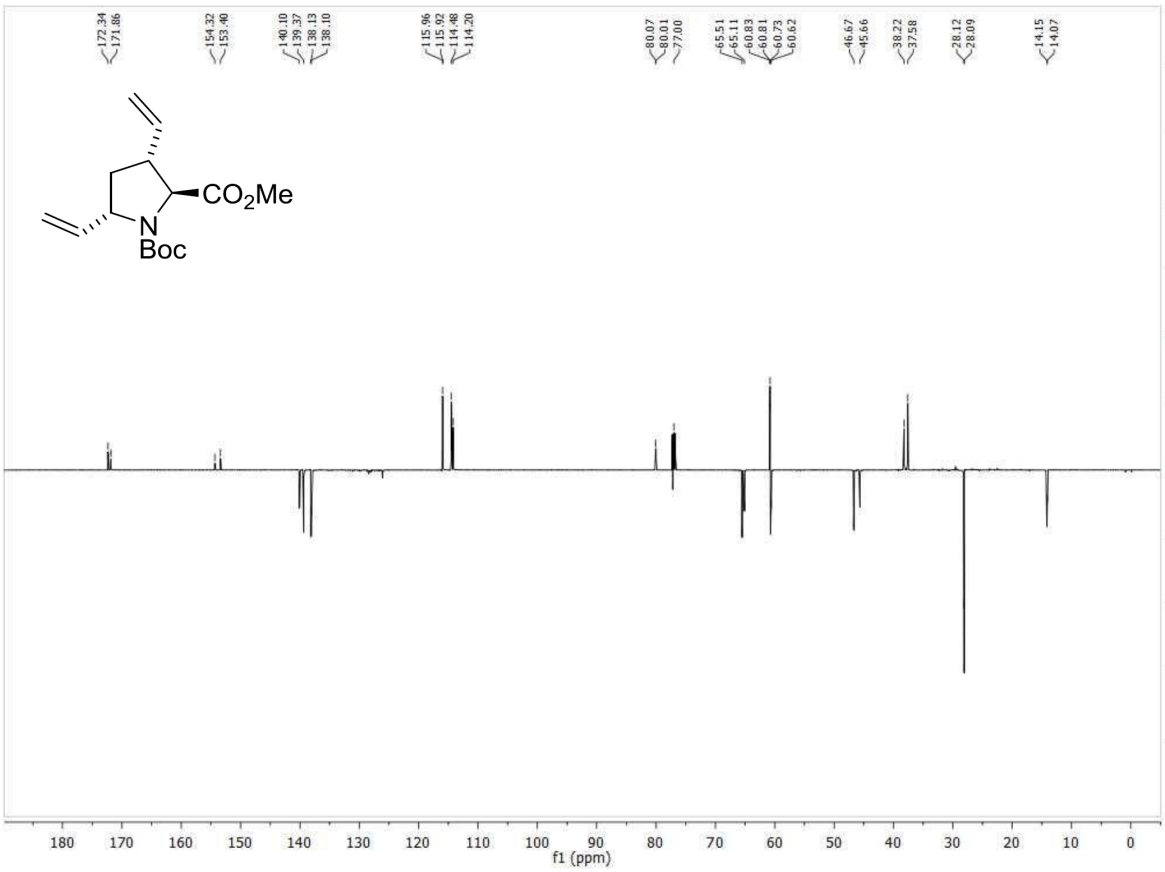
2.6. ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of 11.



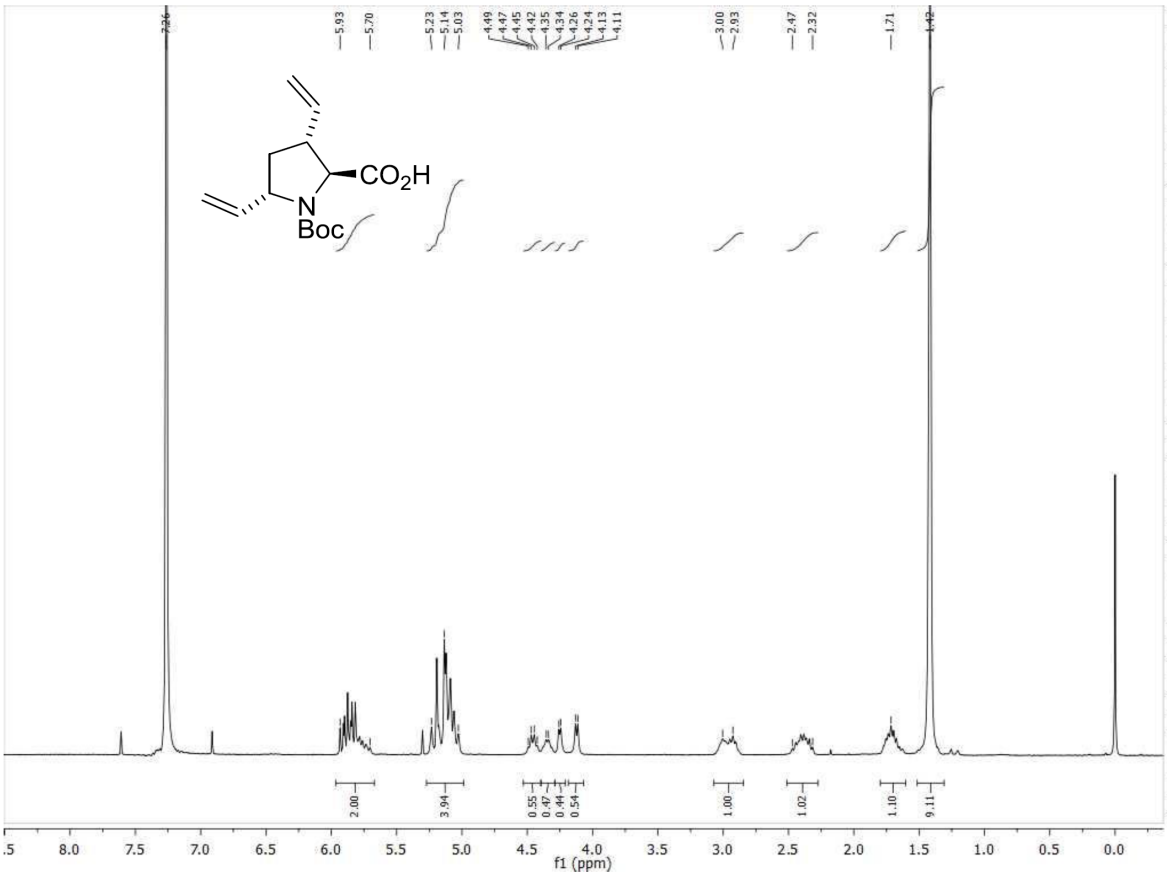


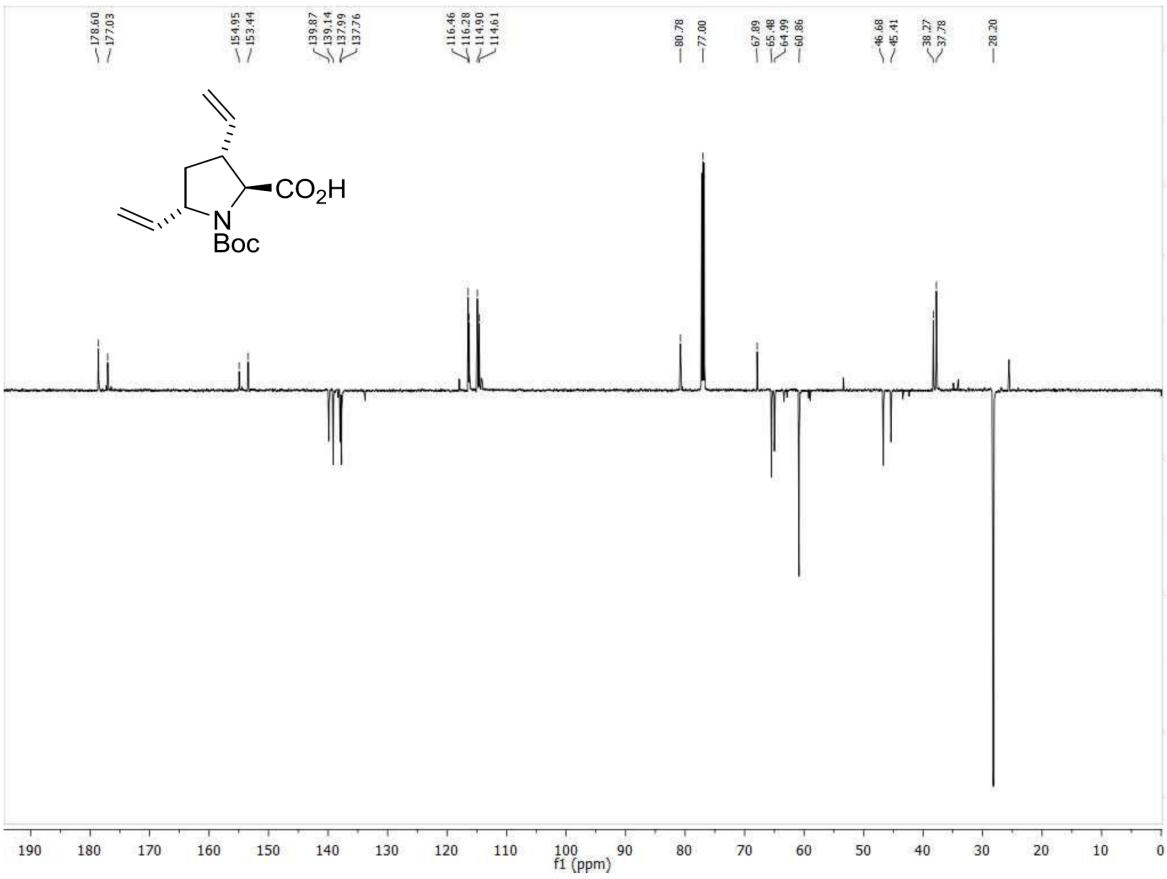
2.7. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) spectra of 12.



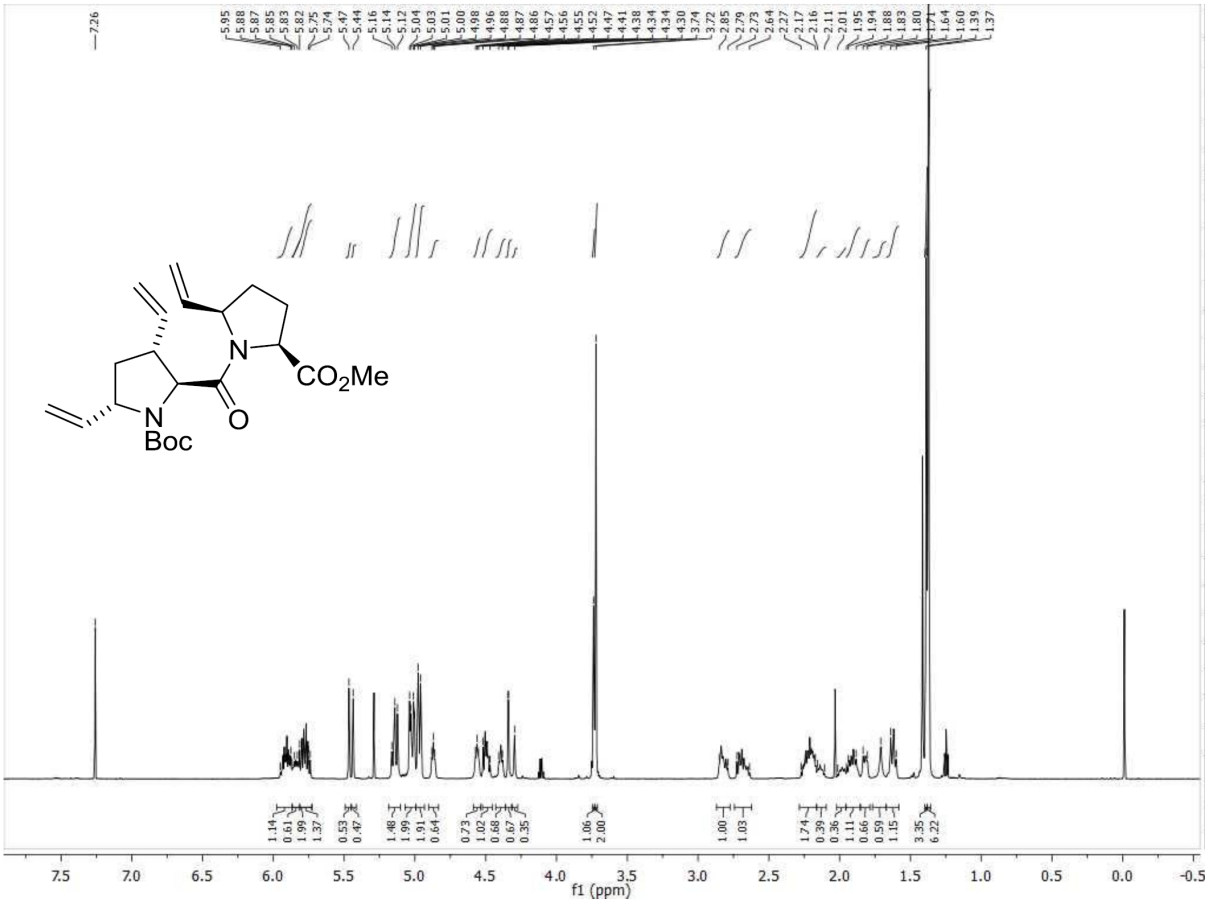


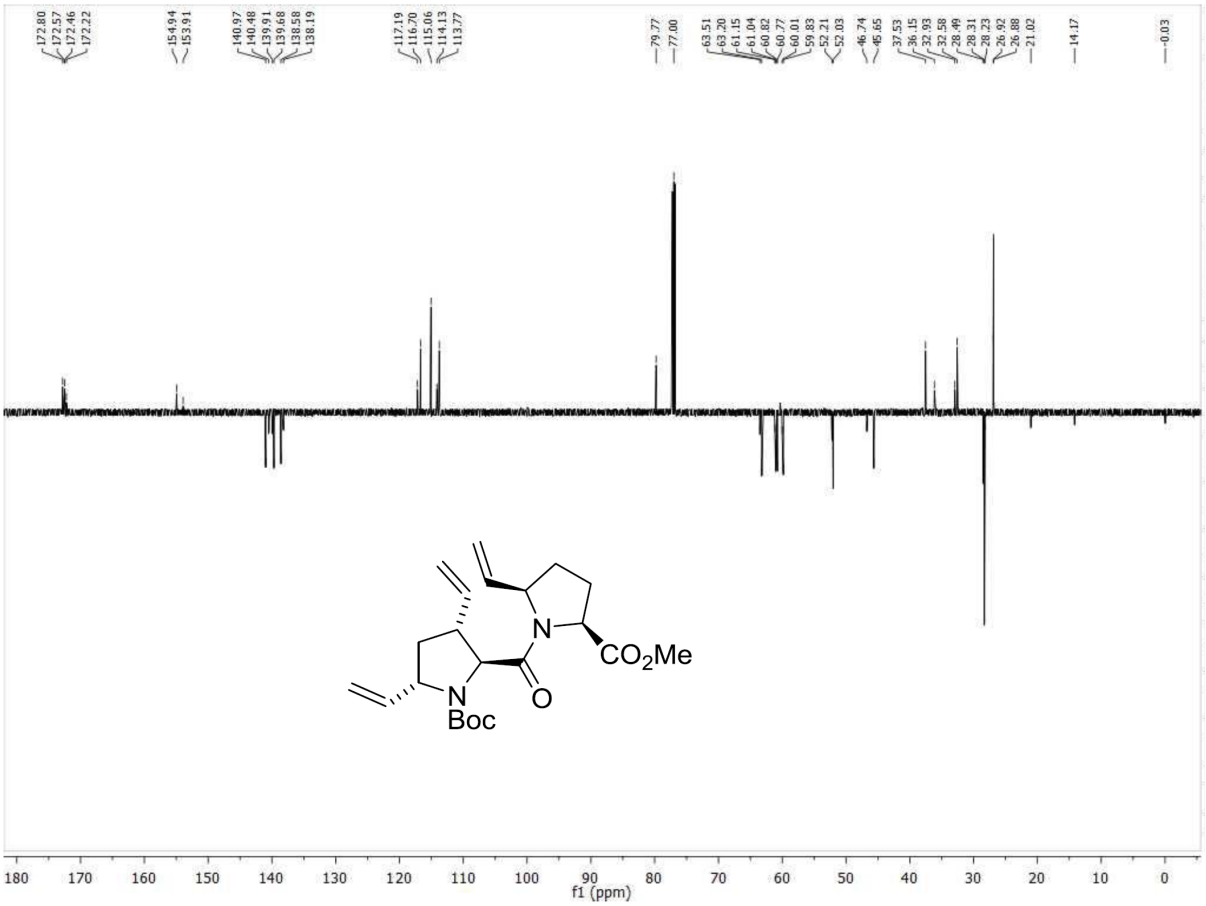
2.8. ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of 13.



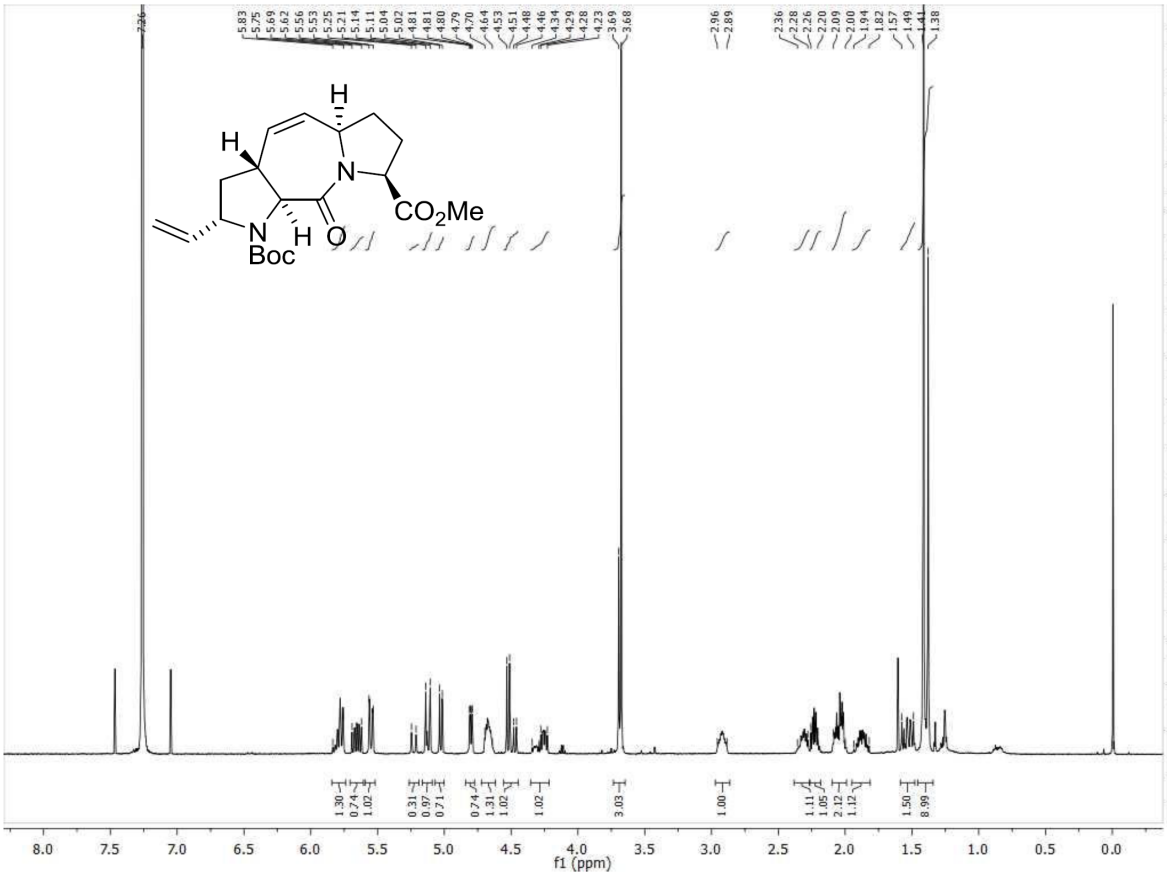


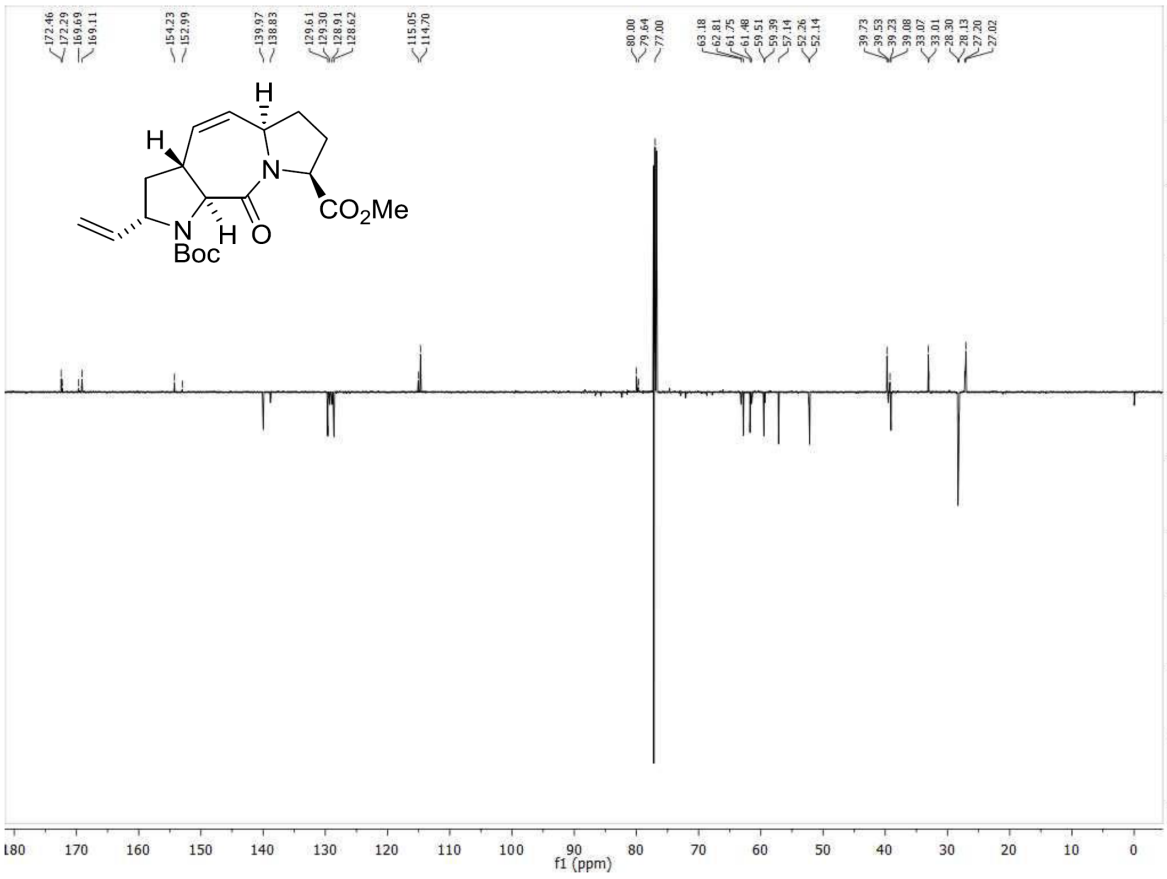
2.9. ^{1}H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz, $CDCl_3$) spectra of 14.



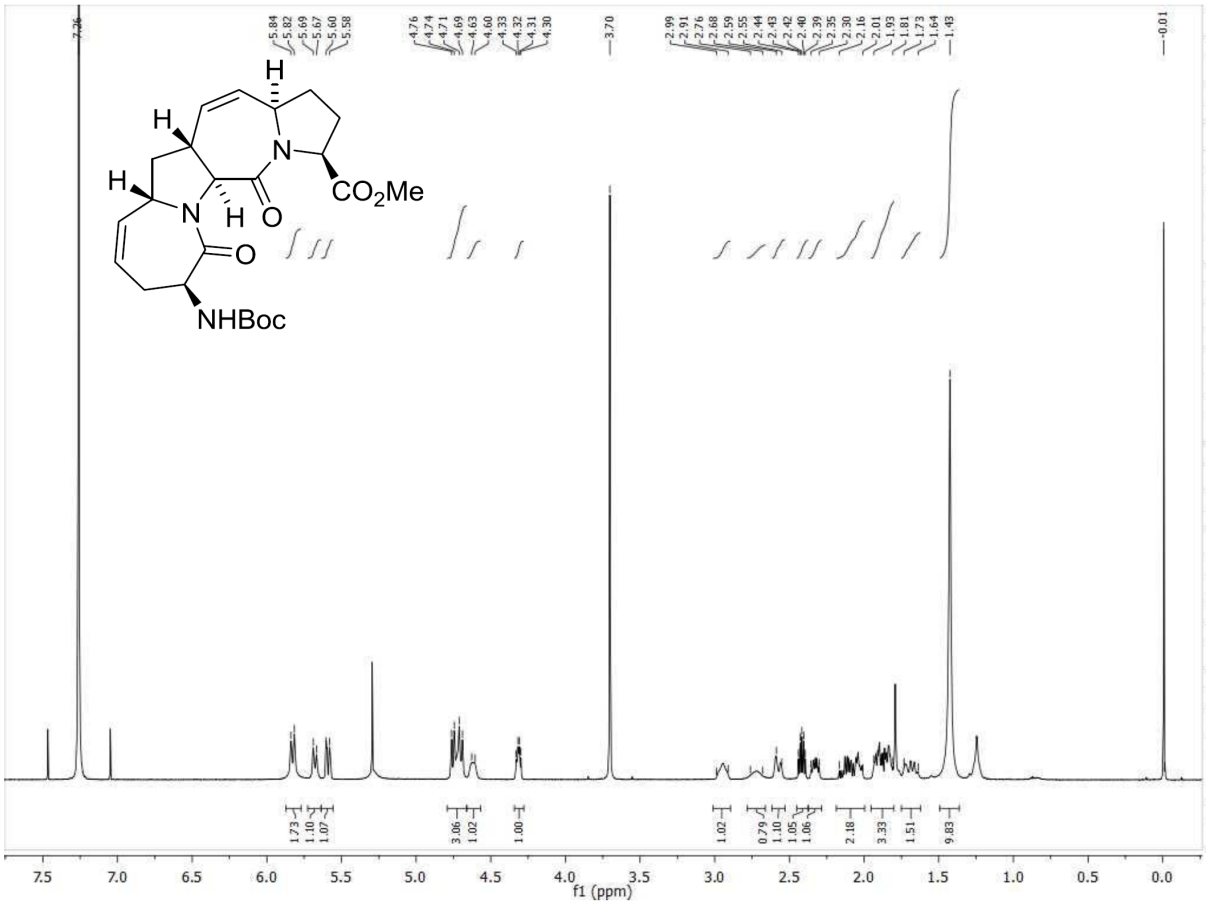


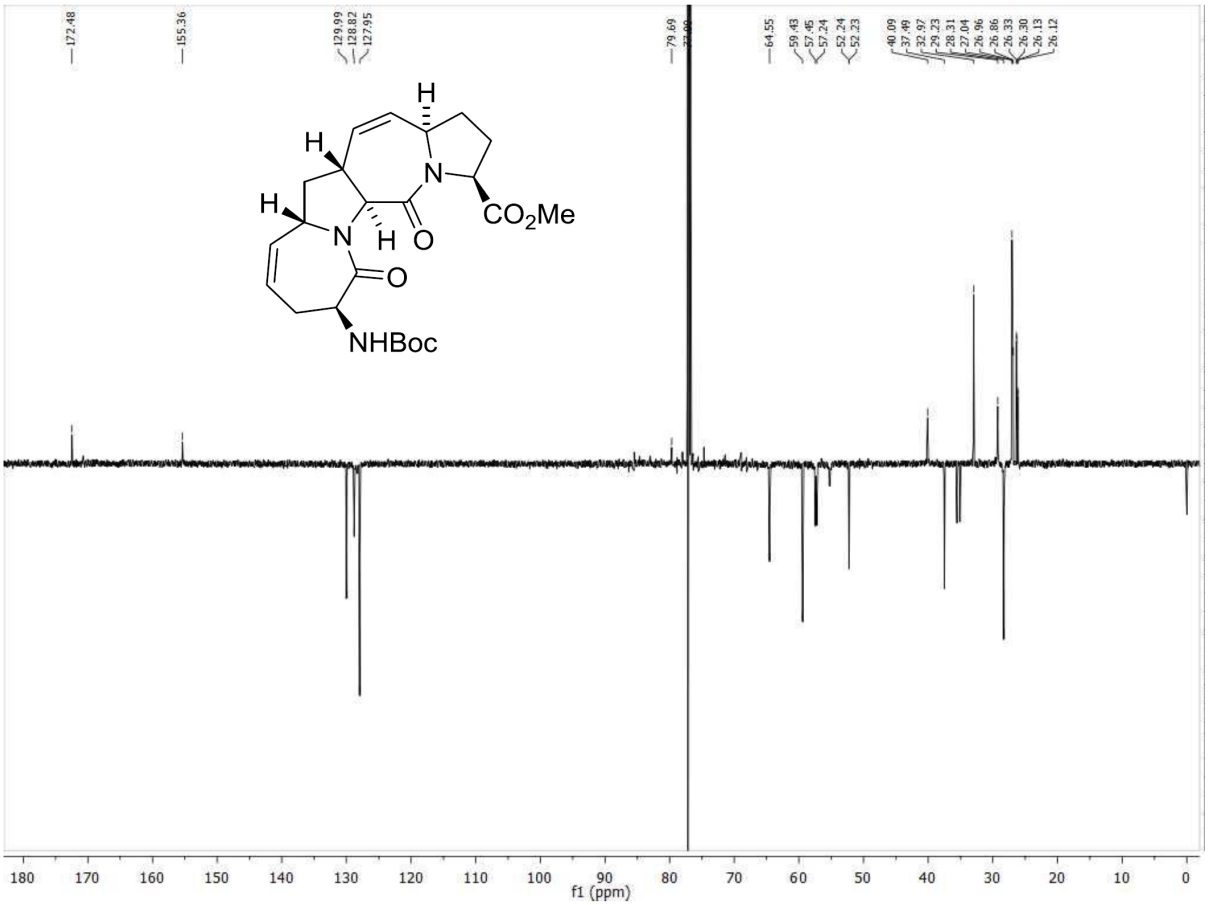
2.10. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) spectra of 15.



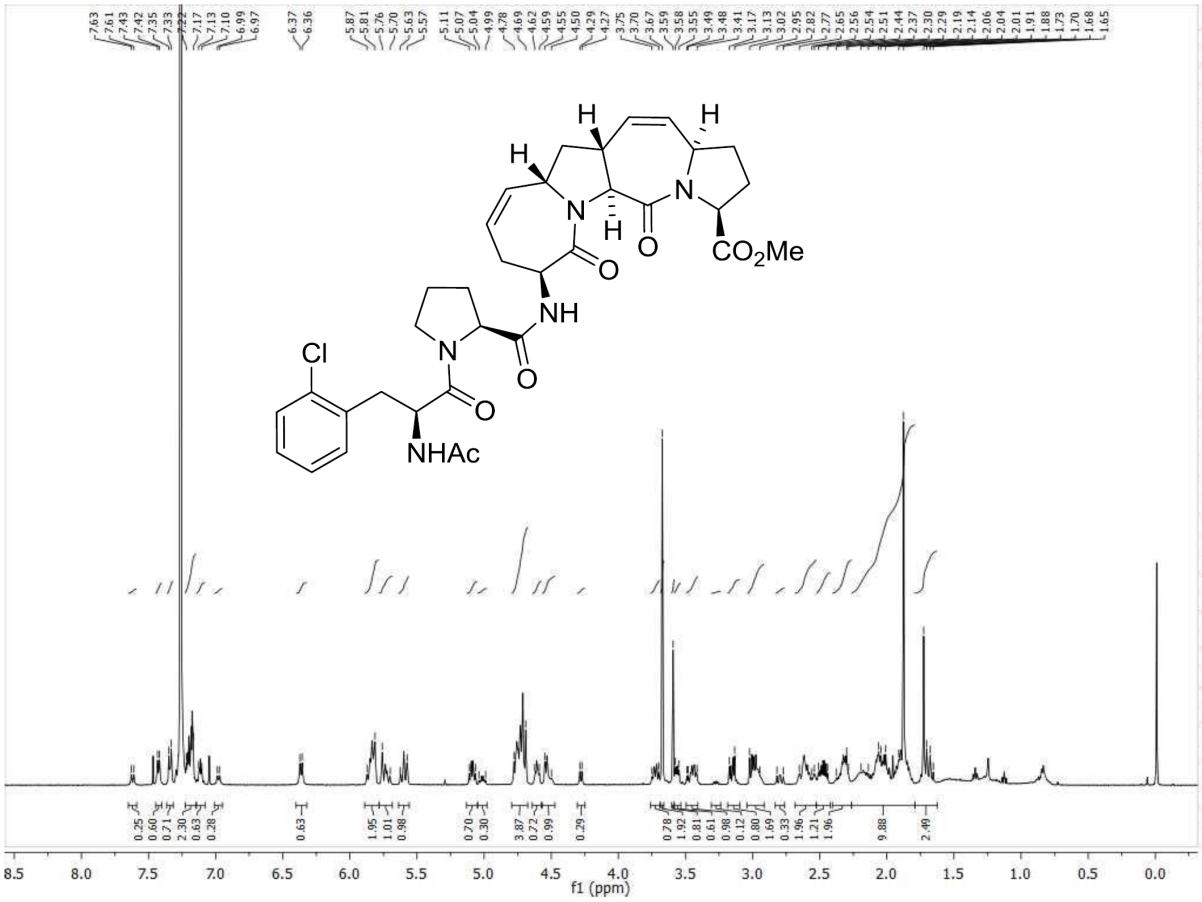


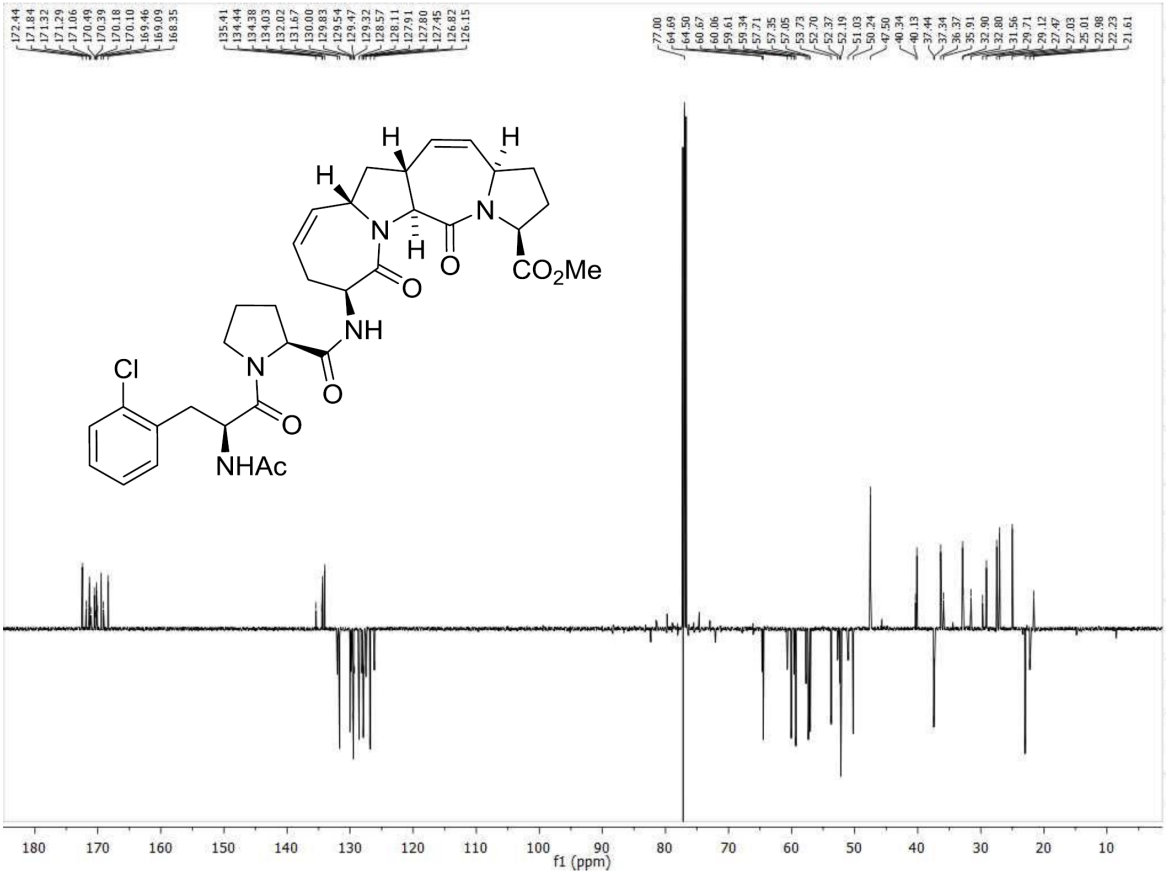
2.11. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) spectra of 1.



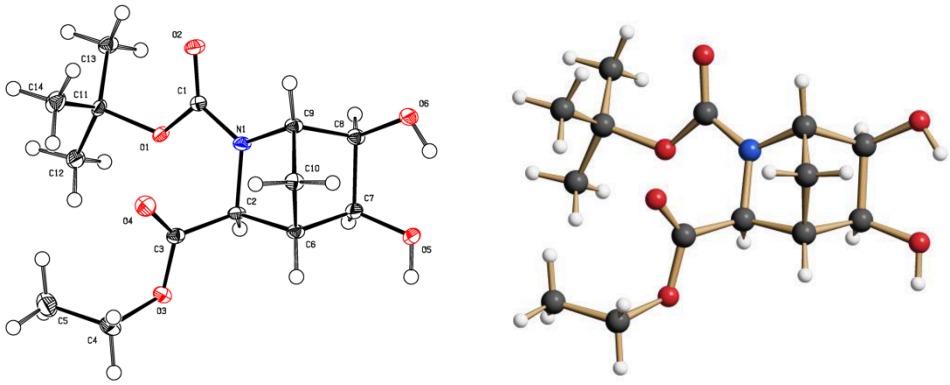


2.12. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) spectra of 20.





3.1. Crystal structure data and structure refinement for diol 9



Identification code	mtk120n	
Empirical formula	C14 H23 N O6	
Moiety formula	C14 H23 N O6	
Formula weight	301.33	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.0019(3) Å	α= 90°.
	b = 10.5127(4) Å	β= 90°.
	c = 17.2834(6) Å	γ = 90°.
Volume	1453.91(9) $Å^3$	
Z	4	
Density (calculated)	1.377 Mg/m^3	
Absorption coefficient	0.900 mm^{-1}	
F(000)	648	
Crystal size	0.200 x 0.150 x 0.070 mm^3	
Theta range for data collection	4.924 to 71.961°.	
Index ranges	-9<=h<=9, -12<=k<=12, -21<=l<=21	
Reflections collected	24294	
Independent reflections	2851 [R(int) = 0.0373]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7535 and 0.5505	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2851 / 0 / 202	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0644	
R indices (all data)	R1 = 0.0258, wR2 = 0.0646	
Absolute structure parameter	0.07(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.152 and -0.184 $e.Å^{-3}$	