Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Enantioselective total synthesis of pyrrolo-[2,1-*c*][1,4]-benzodiazepine monomers (*S*)-( )-barmumycin and (*S*)-(+)-boseongazepine B

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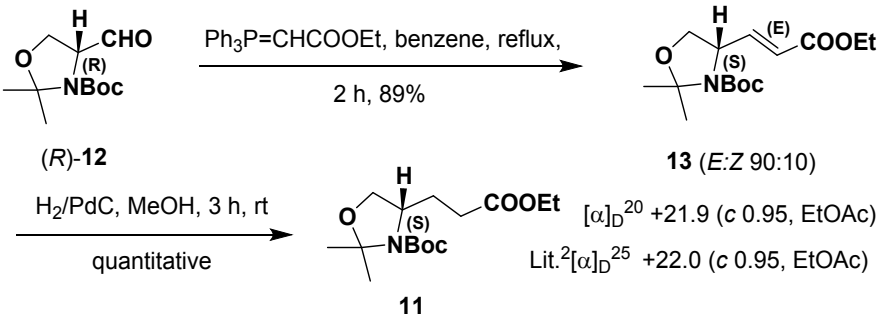
Experimental section

General Experimental Details

All reagents were obtained from commercial suppliers unless otherwise stated and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. All moisture sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) E. Merck 0.25 mm silica gel 60 F254. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or Ninhydrin stain/ or a solution of PMA followed by heating with a heat gun. Chromatography was performed using silica gel (100-200 mesh) with solvents distilled prior to use. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material. All spectra were recorded at 25 °C. 1H NMR spectra's were recorded on 400 MHz spectrometers and ^{13}C NMR spectra were obtained at 400 (101 MHz) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in 1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Chemical shifts were recorded in ppm, and coupling constants (*J*) were in Hz. HRESIMS were taken on Bruker Impact HD quadrupole plus ion trap at CIF S. P. Pune University. Infrared spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet dd: doublet of doublet for proton spectra. Optical rotations were measured on a digital polarimeter.

Synthesis of ester (11) from Garner's aldehyde [12]

An alternative route for the synthesis of ester (**11**) from commercially available Garner's aldehyde (**12**) is described here in **Scheme 1**. (*E*)-Enoate (**13**) was synthesized from Garner's aldehyde (*R*)-(**12**) with 90:10-(E/Z) selectivity and without any degradation of chiral integrity, however the degradation was reported in literature.[1] Further palladium catalysed hydrogenation of unsaturated ester (**13**) afforded desired ester (**11**) in quantitative yield [$[\alpha]_D^{20}$ = +21.9 (*c* 0.95, EtOAc)] [Lit.[2] $[\alpha]_D^{25}$ = +22.0 (*c* 0.95, EtOAc)].



Scheme 1 Synthesis of ester (**11**) from (*R*)-Garner's aldehyde (**12**)

***tert*-Butyl (*S*)-4-(3-ethoxy-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate** [**11**]: A mixture of conjugate ester (**13**) (1 g, 3.34 mmol) and 20% Pd/C in dry MeOH (20 mL) was stirred under a hydrogen

atmosphere at room temperature for 3 h. The reaction mixture was filtered through celite. After evaporation of the solvent, crude unsaturated ester was obtained. The residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as the eluant afforded the title compound (**11**).

[Spectral data of 11]: $[\alpha]_D^{20}$ = +21.9 (*c* 0.95, EtOAc); Lit.[2] $[\alpha]_D^{25}$ +22.0 (c 0.95, EtOAc)

IR (neat, cm^{-1}): 3027, 2983, 2937, 2881, 1715;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 4.18 – 4.11 (m, 2H), 4.07 – 3.83 (m, 2H), 3.74 (t, *J* = 8.1 Hz, 1H), 2.41 – 2.32 (m, *J* = 4.8 Hz, 2H), 2.06 (d, *J* = 13.6 Hz, 1H), 1.96 – 1.87 (m, 1H), 1.68 – 1.54 (m, 3H), 1.53 – 1.41 (m, 12H), 1.27 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 173.0, 152.6, 93.6, 80.0, 66.9, 60.4, 56.5, 31.0, 28.9, 28.4, 26.7, 24.3, 23.1, 14.1 ;

HRMS (ESI$^+$): calcd. for $C_{15}H_{27}NNaO_5$ [M+Na$^+$]: 324.1787, found: 324.1790.

Benzyl (*S*,*E*)-1-(1-(benzyloxy)-5-ethoxy-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate [10]: To a cooled solution of dibenzylazodicarboxylate (DBAD) (1.3653 g, 4.57 mmol) and L-proline (0.115 g, 1.37 mmol) in CH_3CN (35 mL) at 0 °C was added aldehyde (**9**) (0.900 g, 5.48 mmol) and the mixture was stirred for 2 h at 0 °C and cooled to 10 °C, further for 1 h. This was followed by addition of lithium chloride (0.302 g, 7.24 mmol), triethyl phosphonoacetate (1.427 mL, 7.24 mmol) and dropwise addition of DBU (0.833 mL, 5.48 mmol) in sequence and the whole mixture was stirred at 0 °C for 45 min. Solution was quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was purified over column chromatography (petroleum ether: ethyl acetate: 80:20) afforded titled compound (**10**) as a white solid (2.47 g, yield 85%).

[Spectral data of 10]: $[\alpha]_D^{20}$ = +1.98 (*c* 0.2, MeOH);

IR (neat, cm^{-1}): 1720, 1657;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 7.58 – 7.17 (m, 15H), 6.90 (d, *J* = 13.3 Hz, 1H), 6.64 (bs, 1H), 6.12 – 6.05 (m, 1H), 5.18 (bs, 5H), 4.49 (bs, 2H), 4.23 4.18 (m, 2H), 3.71-3.58 (m, 2H), 1.30 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 165.9, 156.3, 155.7, 141.7, 137.4, 135.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 126.9, 124.1, 73.0, 68.4, 67.9, 65.3, 60.5, and 14.2;

HRMS (ESI$^+$): calcd. for $C_{30}H_{30}N_2NaO_6$ [M+Na$^+$]: 537.2002, found:537.2007.

***tert*-Butyl (*S*)-4(3-ethoxy-3-oxopropyl) 2,2-dimethyloxazolidine-3-carboxylate [11]:** The solution of hydrazino conjugate ester (**10**) (2.0 g, 3.3 mmol) in MeOH (12 mL) and acetic acid (8 drops) was treated with Raney nickel (4.5 g, excess) under H_2 (70 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated under vacuo afforded crude amino alcohol, which was further treated with triethylamine (0.93 mL, 6.7 mmol) and Boc anhydride (1.2 mL, 5.1 mmol) in dry CH_2Cl_2 (15 mL) for 2 h. Ice flakes were added to the reaction mixture and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure afforded crude *N*-Boc derivative. The crude *N*-Boc derivative was dissolved in acetone (15 mL) and 2,2 DMP (10 mL) to which $BF_3.Et_2O$ (0.1 mL) was added at 0 °C. The resulting solution was stirred at rt for 3h. After TLC check solvent was removed under *vacuum,* residual oil was taken in to CH_2Cl_2 (100 mL) and resulting

solution was washed with $NaHCO_3$ and H_2O (1:1, 30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography over silica gel (petroleum ether: ethyl acetate: 90:10) to afford **11** (0.970 mg, 83%). All spectral data was matched with previously obtained ester (**11**).

[Spectral data of 11]: $[\alpha]_D^{20} = +21.4$(*c* 0.95, EtOAc); Lit.[2] $[\alpha]_D^{25}$ +22.0 (c 0.95, EtOAc)

IR (neat, cm^{-1}): 3027, 2983, 2937, 2881, 1712;

^{1}H and ^{13}C NMR is similar to 11 prepared from 12 above

HRMS (ESI$^+$): calcd. for $C_{15}H_{27}NNaO_5$ [M+Na$^+$]: 324.1787, found: 324.1790.

***tert*-Butyl(*S,E*)-4-(2-(ethoxycarbonyl)but-2-en-1-yl)-2,2dimethy-loxazolidine-3-carboxylate [14]:** A solution of diisopropylamine (348 µL, 2.46 mmol) in 4 mL of THF was cooled to 0 °C and treated dropwise with a 1.6 M solution of *n*-BuLi in hexanes (1.49 mL, 2.38 mmol). After the mixture was stirred for 10 min at the same temperature, a solution of (**11**) (250 mg, 0.793 mmol) in 2 mL of THF was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and then cooled to −78 °C and treated with acetaldehyde (445µL, 7.93 mmol). After it was stirred for 20 min at −78 °C, the reaction mixture was quenched by dropwise addition of saturated aqueous NH_4Cl, warmed to room temperature, and extracted with EtOAc (3 x 15 mL). The organic layers were combined washed with 1 M aqueous HCl, dried over anhydrous Na_2SO_4, and concentrated under vacuo. The crude alcohol was then taken up in 10 mL of CH_2Cl_2, cooled to 0 °C, and treated with NEt_3 (442 µL, 3.17 mmol) and methane sulfonyl chloride (184 µL, 2.38 mmol). Further it was cooled to room temperature and stirred for 1 h. Then reaction mixture was diluted with CH_2Cl_2, washed with 1 M aqueous HCl, dried over anhydrous Na_2SO_4, and concentrated under vacuo. The crude mesylate was then dissolved in 2.5 mL of toluene and treated with DBU (237 µL, 1.59 mmol). The reaction mixture was stirred at 60 °C for 4 h and then at room temperature for 16 h. The reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl, dried over anhydrous Na_2SO_4, and concentrated under vacuo and purification by flash chromatography over silica gel (5% EtOAc/ hexanes) afforded (**14**) (94:6 *E:Z* mixture) as an thick oil (188 mg, 69%, 3 steps).

[Spectral data of 14]: $[\alpha]_D^{20} = +1.024$ (*c* 0.5, MeOH);

IR (neat, cm^{-1}): 3026, 2984, 2938, 2881, 1715;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 7.07 – 6.94 (m, 1H, transe), 6.09 (bs, 1H, cis), 4.21 (q, *J* = 7.1 Hz, 2H), 4.14 – 4.04 (m, 1H), 3.85 – 3.68 (m, 2H), 2.79 – 2.61 (m, 1H), 2.57 – 2.51 (m, 1H), 2.01 – 1.88 (m, 3H), 1.67 – 1.57 (m, 3H), 1.59 – 1.44 (s, 9H), 1.37 – 1.29 (m, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 167.7, 167.4, 152.2, 152.0, 140.2, 139.6, 130.0, 129.7, 94.0, 93.3, 79.7, 66.3, 60.4, 60.3, 60.1, 57.1, 56.3, 28.4, 27.4, 26.9, 23.2, 22.6, 14.7, 14.2, 14.09;

HRMS (ESI$^+$): calcd. for $C_{17}H_{29}NNaO_5$[M+Na$^+$]:350.1943 found:. 350.1945.

***tert*-Butyl(*S,E*)-4-(2-(hydroxymethyl)but-2-en-1-yl)-2,2dimethyl-oxazolidine-3-carboxylate [15]:** A solution of ester (**14**) (350 mg, 1.07 mmol) in 10 mL of CH_2Cl_2 at -30 °C under an N_2 atmosphere was treated with a 1 M solution of DIBAL in toluene (2.60 mL, 2.60 mmol) and stirred for further 3 h. Then reaction mixture was quenched with saturated tartaric acid, diluted with CH_2Cl_2, and stirred vigorously for 2 h at room temperature. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under vacuo afforded **15** (94:6 *E:Z* mixture) as a colourless oil (267 mg, 86% yield).

[Spectral data of 15]: $[\alpha]_D^{20} = +11.60$ (*c* 0.4, MeOH);,

IR (neat, cm^{-1}): 3546, 2922, 2885;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 5.88 – 5.73 (m, 1H), 4.21 – 4.00 (m, 3H), 3.86 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.80 – 3.67 (m, 1H), 2.72 – 2.43 (m, 2H), 1.75 (d, *J* = 7.9 Hz, 3H), 1.67–1.57 (m, 9H), 1.27 (bs, 6H);
^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 152.7, 136.4, 124.0, 93.6, 79.7, 67.3, 60.4, 56.6, 28.3, 27.6, 24.3, 22.6, 13.8;
HRMS (ESI^+): calcd. for $C_{15}H_{27}NNaO_4$ $[M+Na^+]$: 308.1838, found: 308.1842.

Ethyl (*S,E*)-4-((tert-butoxycarbonyl)amino)-2-ethylidene-5-hydroxypentanoate [17]: The ester (**14**) (300 mg, 916 µmol) in 2.5 mL of MeOH at 0 °C was treated with *p*-TsOH·H_2O (126 mg, 667 µmol) and stirred from 0 °C to room temperature over 5 h. The reaction mixture was concentrated under reduced pressure and purification by flash chromatography over silica gel (20−35% EtOAc/hexane) afforded alcohol (**17**) (94:6 E:Z mixture) as a liquid (253 mg, 96% yield).
[Spectral data of 17]: $[\alpha]_D^{20}$ = +4.75 (*c* 0.4, MeOH);
IR (neat, cm^{-1}): 3555, 2937, 2880, 1715, 1693;
^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 7.05 (q, *J* = 7.2 Hz, 1H), 5.19 (s, 1H, exchangeable with D_2O), 4.23 (q, *J* = 7.1 Hz, 2H), 3.71 – 3.49 (m, 3H), 2.64 – 2.47 (m, 2H), 2.02 – 1.88 (m, 3H), 1.45 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H)**.**
^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 169.0, 155.8, 141.6, 129.0, 79.3, 63.5, 61.1, 52.1, 28.3, 27.5, 14.7, 14.1;
HRMS (ESI^+): calcd. for $C_{14}H_{25}NNaO_5$ $[M+Na]^+$: 310.1630 found: 310.1628

***tert*-Butyl (*S,E*)-(1-((tert-butyldimethylsilyl)oxy)-4-(hydroxy-methyl)hex-4-en-2-yl) carbamate [18]:** The solution of alcohol (**17**) (200 mg, 696.00 µmol) and imidazole (72 mg, 1.04 mmol) in 5 mL of DMF was cooled to 0 °C and to this cooled solution TBSCl (136.37 mg, 904.80 µmol) was added portion wise. After completion of reaction (TLC Check), water (10 mL) was added, then reaction mixture was further diluted with EtOAc (50 mL) and washed with 0.5 M aqueous HCl, dried over anhydrous Na_2SO_4, and concentrated under vacuo afforded crude TBS-ether. To the solution of above crude TBS-ether in dry CH_2Cl_2 (10 mL), 1M DIBAL in toluene (2.2 mL) was added drop wise at -5 °C and stirred for another 2 h. The reaction mixture was then quenched with saturated tartaric acid, diluted with CH_2Cl_2, and stirred vigorously for 1 h at room temperature. The organic layers were separated and dried over anhydrous Na_2SO_4 and concentrated under vacuo and purification by flash chromatography over silica gel (15−20% EtOAc/hexane) afforded alcohol (**18**) as colourless thick oil (210 mg, 84% yield, over 2 steps).
[Spectral data of 18]: $[\alpha]_D^{20}$ = +17.30 (*c* 0.2, MeOH);
IR (neat, cm^{-1}): 3541, 2930, 2887, 1691;
^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 5.61 (q, *J* = 6.7 Hz, 1H), 4.88 (d, J = 8.0 Hz, 1H), 4.07 (s, 2H), 3.94 (bs, 1H), 3.71 – 3.58 (m, 3H), 2.71 – 2.51 (t, *J* = 5.1 Hz, 1H), 2.15 (dd, *J* = 13.1, 4.7 Hz, 1H), 1.66 (d, *J* = 6.7 Hz, 3H), 1.44 (s, 9H), 0.94 (s, 9H), 0.09 (s, 6H);
^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 136.4, 136.0, 125.8, 124.7, 79.4, 69.5, 65.1, 64.8, 51.7, 31.2, 28.3, 25.8, 18.2, 13.9, 13.5, -5.4;
HRMS (ESI^+): calcd. for $C_{18}H_{37}NNaO_4Si$ $[M+Na]^+$: 382.2390 found: 382.2395.
***tert*-Butyl (*S,E*)(1(tert-butyldimethylsilyl)oxy)4(chloromethyl)-hex4en2yl)carbamate[19]:**
A solution of the above allylic alcohol (**18**) (100 mg, 2.78 µmol) in 3 mL of CH_2Cl_2 at room temperature was treated with triethylamine (0.280 mL, 1.94 mmol) and MsCl (0.125 mL, 1.67 mmol). After being

stirred at room temperature for 18 h, the reaction mixture was washed with 1 M aqueous HCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum afforded allyl chloride (**19**) as thick oil, was used in next step without any chromatographic purification.

[Spectral data of 19]: $[\alpha]_D^{20}$ = -0.64 (*c* 0.9, MeOH);

IR (neat, cm^{-1}): 1697, 1582;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 5.77 (q, *J* = 6.8 Hz, 1H), 4.66 (bs, 1H), 4.26 – 4.15 (m, 1H), 4.06 (d, *J* = 11.1 Hz, 1H), 3.80 (bs, 1H), 3.70 – 3.57 (m, 2H), 2.52 – 2.37 (m, 2H), 1.72 (d, *J* = 13.6 Hz, 3H), 1.44 (s, 9H), 0.92 (s, 9H), 0.09 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 155.4, 133.6, 128.4, 79.1, 64.4, 50.5, 50.3, 29.4, 28.3, 25.8, 18.2, 13.8, -5.4, 5.4;

HRMS (ESI$^+$): calcd. for $C_{18}H_{36}ClNNaO_3Si$ $[M+Na]^+$: 400.2051 found: 400.2051.

***tert*-Butyl (*S,E*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-4-ethylidenepyrrolidine1carboxylate [20]:** To the suspension of NaH (14.0 mg, 556.20 µmol) in DMF (2 mL) was treated with the solution of allylic alcohol (**19**) in DMF (2 mL) at 0 °C. After stirred at same temperature for 3 h, the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuo urification by flash chromatography over silica gel (10−15% EtOAc/hexanes) afforded *N*-Boc derivative (**20**) as thick oil 80 mg (84% over 2 steps).

[Spectral data of 20]: $[\alpha]_D^{20}$ = -17.9 (*c* 0.2, MeOH);

IR (neat, cm^{-1}): 1694, 1585;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 5.42– 5.35 (m, 1H), 4.08 – 3.97 (m, 2H), 3.81 (dd, *J* = 14.5, 1.7 Hz, 1H), 3.71 – 3.32 (m, 2H), 2.67 – 2.63 (m, 1H), 2.56 – 2.45 (m, 1H), 1.64 (d, *J* = 6.2 Hz, 3H), 1.48 (s, 9H), 0.89 (s, 9H), 0.04 (bs, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 154.1, 136.9, 116.3, 79.3, 63.9, 58.3, 51.6, 50.9, 30.4, 29.8, 28.5, 25.8, 18.1, 14.3, and 5.4;

HRMS (ESI$^+$): calcd. for $C_{18}H_{35}NNaO_3Si$ $[M+Na^+]$: 364.2284 found:. 364.2285.

***tert*-Butyl (*S,E*)-4-ethylidene-2-(hydroxymethyl)pyrrolidine-1-carboxylate [21]:** The solution of compound (**20**) (92.0 mg, 234 µmol) in THF (2.0 mL) at 0 °C was treated with 1M TBAF (1.5 mL) and stirred for 2.0 h and warmed to room temperature. The reaction was diluted with water (2 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated vacuo and purification by flash chromatography over silica gel (20−35% EtOAc/hexanes) to afford *N*-Boc prolinol derivative (**21**) as thick oil 49 mg (91%).

[Spectral data of 21]: $[\alpha]_D^{20}$ = -13.70 (*c* 0.8, MeOH);

IR (neat, cm^{-1}): 3585, 1580;

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 5.39 (s, 1H), 4.34 (bs, 1H, OH), 4.23 – 3.96 (m, 2H), 3.90 (t, *J* = 13.6 Hz, 1H), 3.59 (s, 2H), 2.78 – 2.55 (m, 1H), 2.38 – 2.17 (m, 1H), 1.66 – 1.59 (m, 3H), 1.47 (s, 9H);

^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers)**:** δ 156.59, 134.9, 116.7, 80.3, 67.1, 59.6, 51.7, 51.3, 30.48, 28.4, 14.3;

HRMS (ESI$^+$): calcd. for $C_{12}H_{21}NNaO_3$ $[M+Na^+]$: 250.1419 found:. 250.1421.

(*S*)-((–)-Barmumycin [5]: To the solution of compound (**21**) (30.0 mg, 132 µmol) in 2.0 mL of 15% TFA/ CH_2Cl_2 at 0 °C was stirred for 2.5 h and warmed to room temperature. The solvent was removed under reduced pressure, and the residue obtained was subjected for coupling. The PyBOP (86 mg, 158 µmol) was added to a solution of DIEA (0.057 mL, 330 µmol) and vanillic acid (27 mg, 158 µmol) in THF (5mL), and the mixture was stirred for 10 min. After this time, a solution of above Boc deprotected compound in THF was added, and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ and saturated NH_4Cl. The crude residue was purification by column chromatography over silca gel with MeOH gave (*S*)-(–)-barmumycin (**5**) as yellowish solid 25 mg (68%).
[Spectral data of 5]: $[\alpha]_D^{25}$ = -50.8° (*c* 0.25, CH_2Cl_2) [Lit.[3] $[\alpha]_D^{25}$ = -51.2° (*c* 0.25, CH_2Cl_2) ;
IR (neat, cm^{-1}): 3292, 1605, 1585;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 7.04 (d, *J* =7.84 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.39 (bs, 1H), 4.67 (bs, 1H), 4.22 – 4.02 (m, 2H), 3.93 (s, 3H), 3.74 (bs, 2H) 2.77 – 2.62 (m, 1H), 2.36 – 2.21 (m, 1H), 1.62 (d, *J* = 6.7 Hz, 3H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 147.8, 146.6, 134.5, 128.0, 120.9, 117.4, 113.8, 110.5, 67.0, 60.4, 56.1, 55.0, 30.0, 14.3;
HRMS (ESI$^+$): calcd. for $C_{15}H_{20}NO_4$ [M+H$^+$]: 278.1387 found:. 278.1385.

(*S,E*)-1-(*tert*-Butoxycarbonyl)-4-ethylidenepyrrolidine-2 carboxylic acid [22]: To a solution of (**21**) (40 mg, 0.17 mmol) in anhydrous DMSO (1.0 mL) was added NEt_3 (0.24 mL, 0.21 mmol) immediately followed by SO_3·pyridine (65 mg, 0.40 mmol) in anhydrous DMSO (1.0 mL). The resulting yellow-orange solution was stirred at room temperature for 30 min. The reaction mixture was neutralized with 2N HCl and extracted with EtOAc (3 x 15 ml). The organic layer was washed with brine solution (1 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in* vacuo to afford desired crude aldehyde. To a stirring solution of above crude aldehyde in *t*BuOH (1.5 mL) was added 2-methyl-2-butene (0.75 mL). In a separate vial, NaH_2PO_4 (227 mg, 1.60 mmol) and NaO_2Cl (96 mg, 1.07 mmol) were added and dissolved in water (1.2 mL). The *t*BuOH solution was cooled to 0 °C and the bleach solution was added dropwise. The resulting yellow solution was stirred at 0 °C for 2 hr then quenched with saturated $Na_2S_2O_3$ solution until cloudy and acidified to pH 4. The aqueous solution was extracted with EtOAc (3 X 25 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo* afforded the desired acid (**22**) as yellowish foam (29 mg, 68% yield), which used for next step without any further chromatographic purifation.
[Spectral data of 22]:
IR (neat, cm^{-1}): 3136, 3043, 1709, 1403;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (bs, 1H, COOH), 5.45 – 5.34 (m, 1H), 4.19 – 3.86 (m, 3H), 2.67 – 2.60 (m, 1H), 2.51 – 2.45 (m, 1H), 1.63 (d, *J* = 6.3 Hz, 3H), 1.47 (s, 9H);
^{13}C NMR (101 MHz, $CDCl_3$): δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 156.5, 139.3, 116.6, 80.2, 66.1, 51.6, 29.7, 28.3, 14.2;
HRMS (ESI$^+$): calcd. for $C_{12}H_{20}NO_4$ [M+H]: 242.1392 found:. 242.1390.

Boseongazepine B [7a]: To the freshly prepared methanolic HCl (5 mL) was added acid (**22**) (20 mg) at 0 °C and later on mixture was refluxed for 5 h. After complete conversion of starting material, MeOH was evaporated under vacuum to get desired crude proline ester salt (**23**), which

subjected to coupling reaction. To a stirred solution of anthranilic acid (2 equiv.), BOP reagent (2 equiv.) and HOBt (2 equiv) in anhyd DMF (10 mL) was added NEt_3 (10 equiv.). After stirring for 25 min, proline ester hydrochloride (1 equiv.) was added and the resultant mixture was stirred for 24 h. The volatiles were removed under vacuum and the residue was partitioned between CH_2Cl_2 and brine. The organic phase was dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The flash column chromatography purification in (EtOAc–MeOH) afforded Boseongazepine B as yellowish amorphous solid (16 mg, 71% yield, two steps).

[Spectral data Boseongazepine B]: $[\alpha]_D^{25}$ = +533.3° (*c* 0.01, MeOH) [Lit.[4] $[\alpha]_D^{30}$ = +419.4° (*c* 0.001, MeOH)];

IR (neat, cm^{-1}): 1615, 1587;

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.53 (S, 1H), 7.36 – 7.19 (m, 3H), 5.50 (bs), 4.30 (dd, *J* = 2.0, 9.5Hz), 4.20 (d, *J* = 15.7 Hz, 1H), 4.04 (d, *J* = 15.8 Hz, 1H), 3.86 (s, 3H), 3.24 (d, *J* = 16.8 Hz, 1H), 2.66 – 2.55 (m, 1H), 1.66 (d, *J* = 5.8 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 169.8, 164.2, 149.9, 133.8, 127.9, 125.6, 124.8, 121.2, 116.8, 113.7, 56.4, 56.2, 51.0, 27.2, 14.2;

HRMS (ESI$^+$): calcd. for $C_{15}H_{17}N_2O_3$[M+H]: 273.1239 found:. 273.1236;

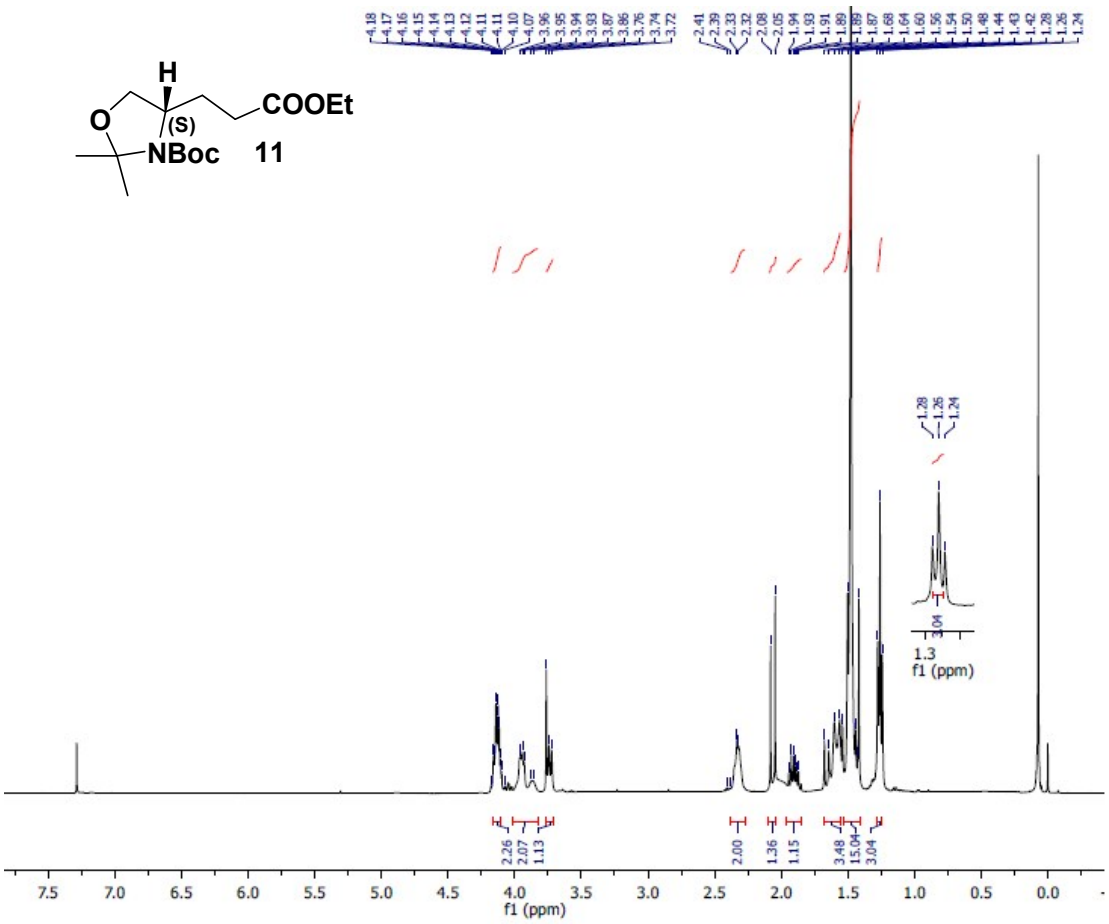
References

1 M. Passiniemi, A. M. P. Koskinen, *Beilstein J. Org. Chem*., 2013, **9**, 2641–2659.

2 X. Feng, E. D. Edstrom *Tetrahedron: Asymmetry*, 1999, **10**, 99–105.

3 G. Smits, Z. Ronalds, *Org. Lett.,* 2013, **15**, 4406-4409.

4 M. Oh, J. H. Jang, S. J. Choo, S. O. Kim, J. W. Kim, S. K. Ko, N. K. Soung, J. S. Lee, C. J. Kim, H. Oh, Y. S. Hong, M. Uek, H. Hirota, H. Osada, B. J. Kim, J. S. Ahn, *Bioorg. Med. Chem. Lett.,* 2014, **24**, 1802-1804.



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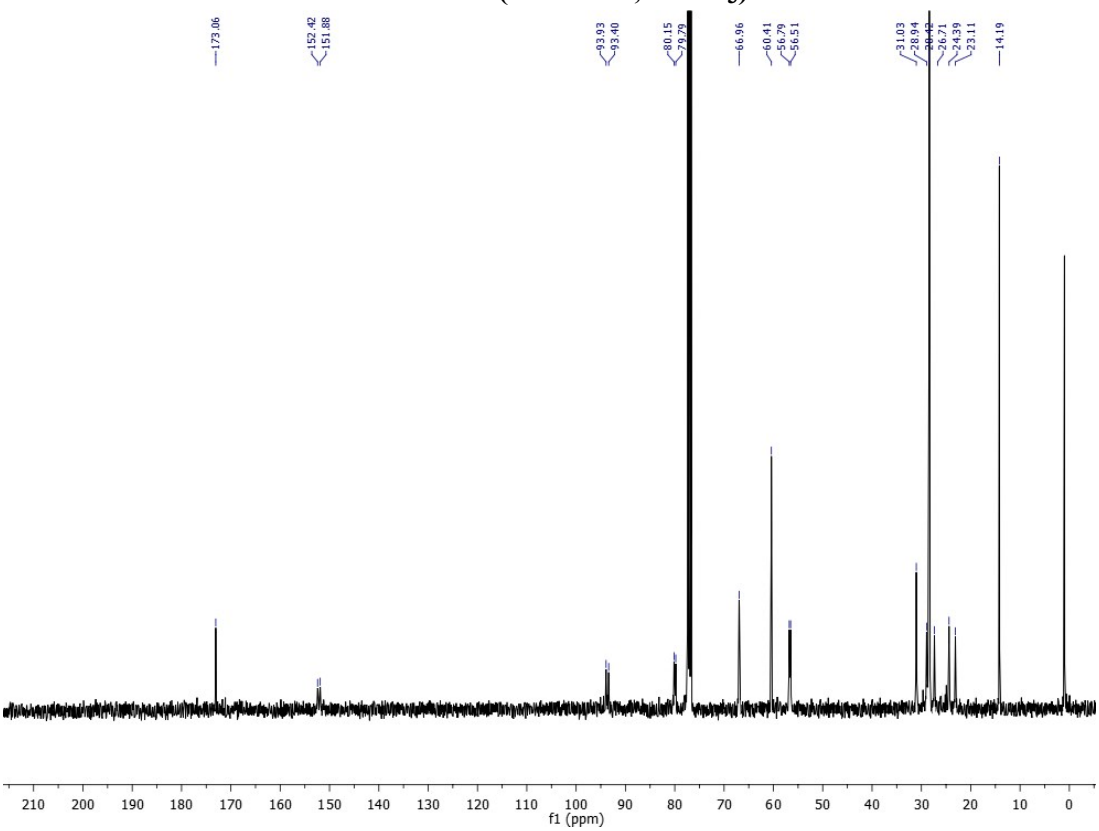

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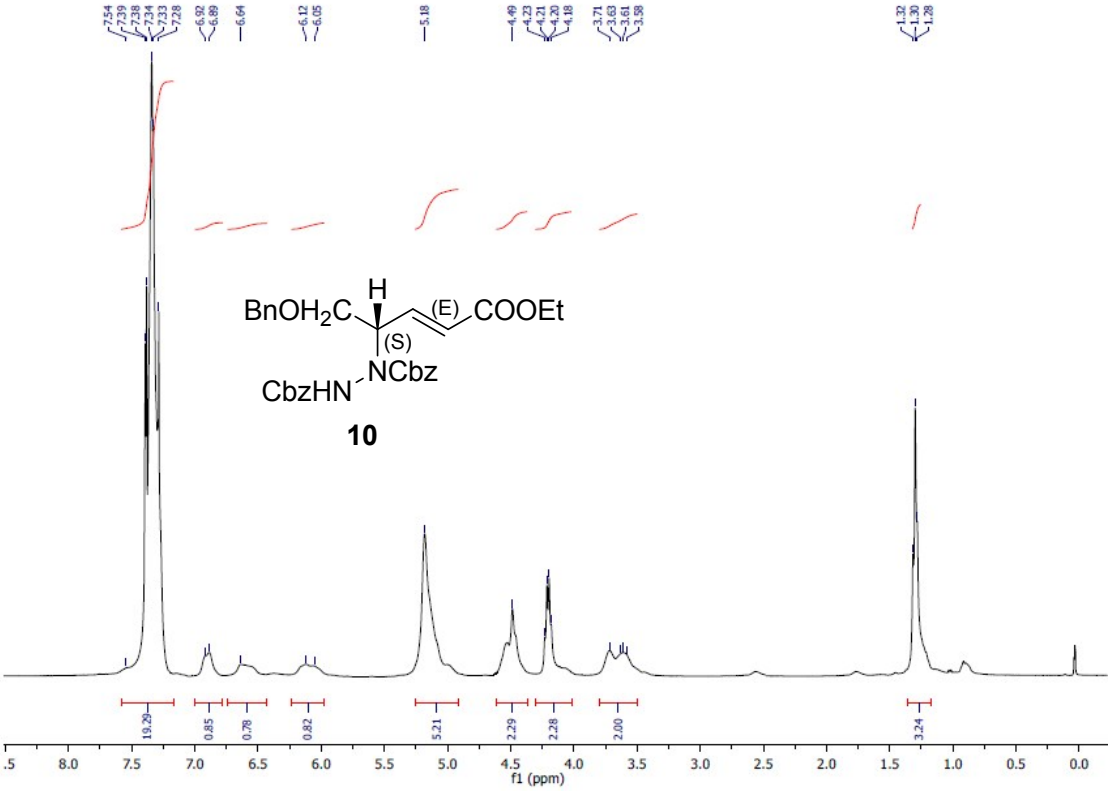

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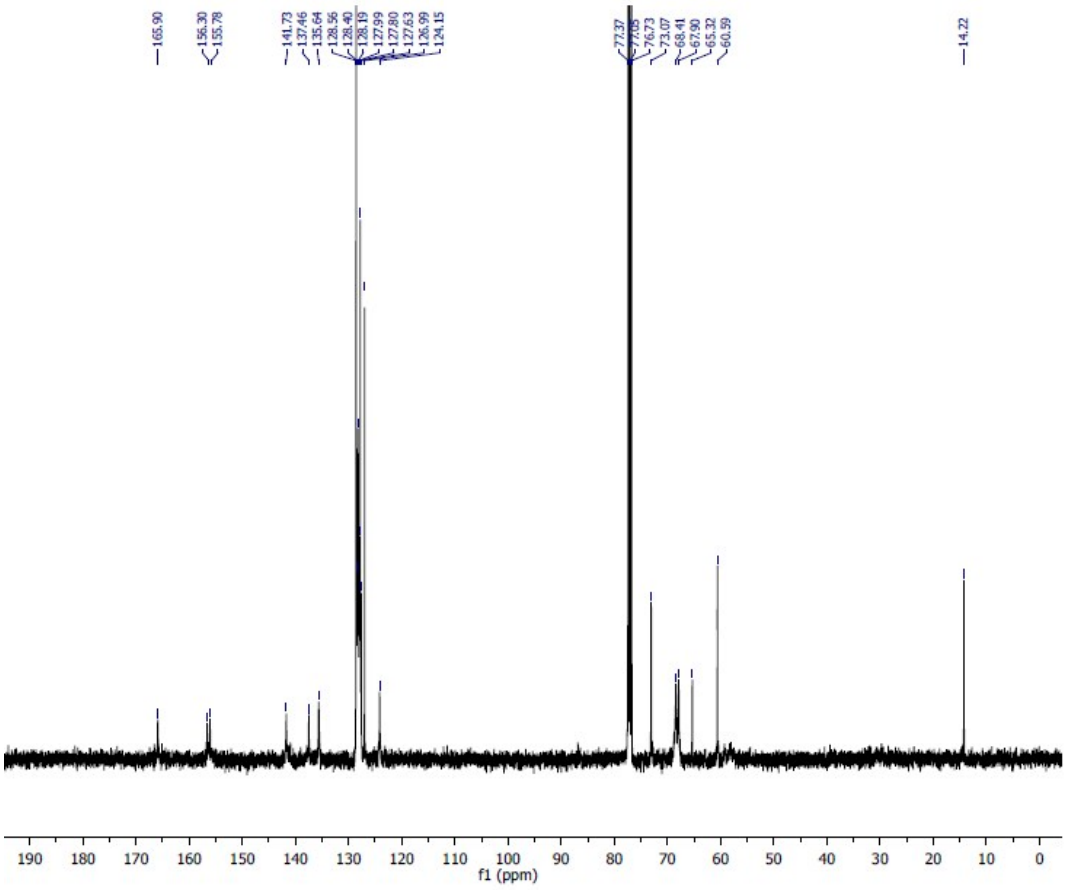

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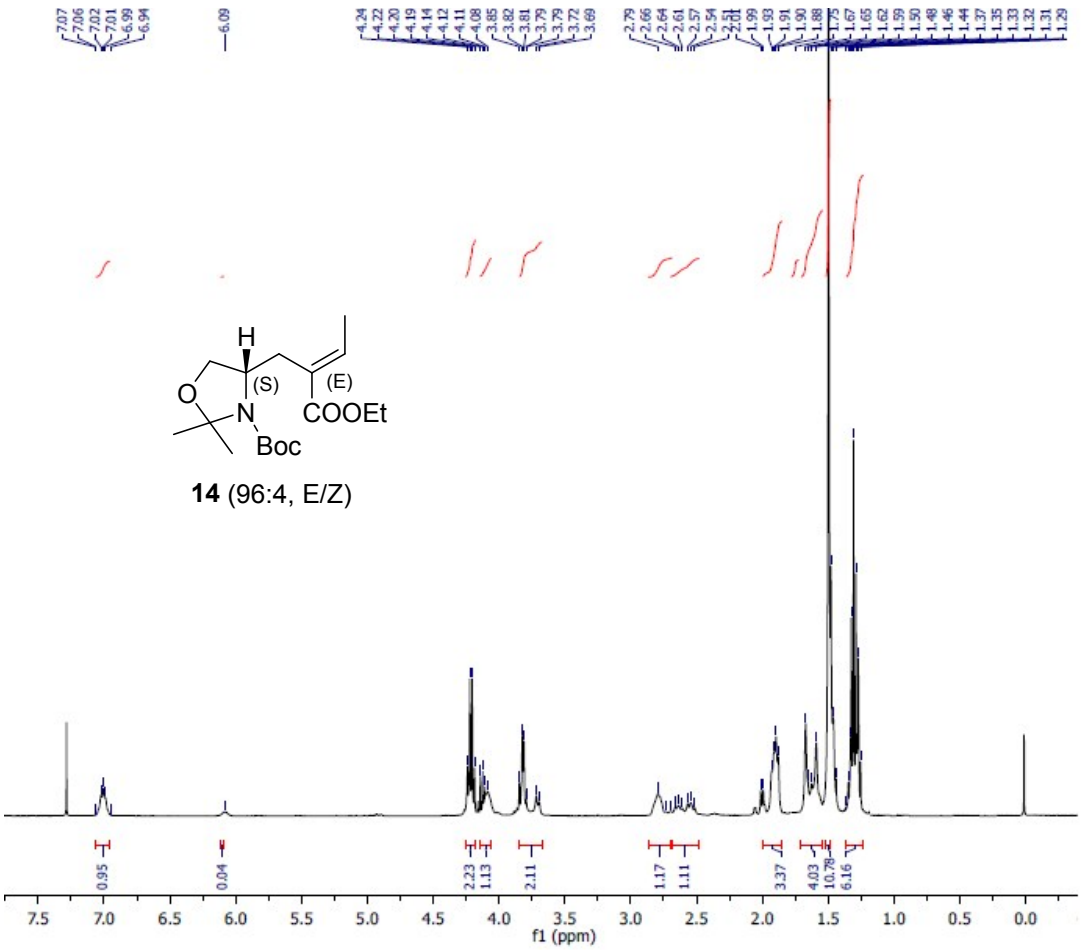

14 (96:4, E/Z)

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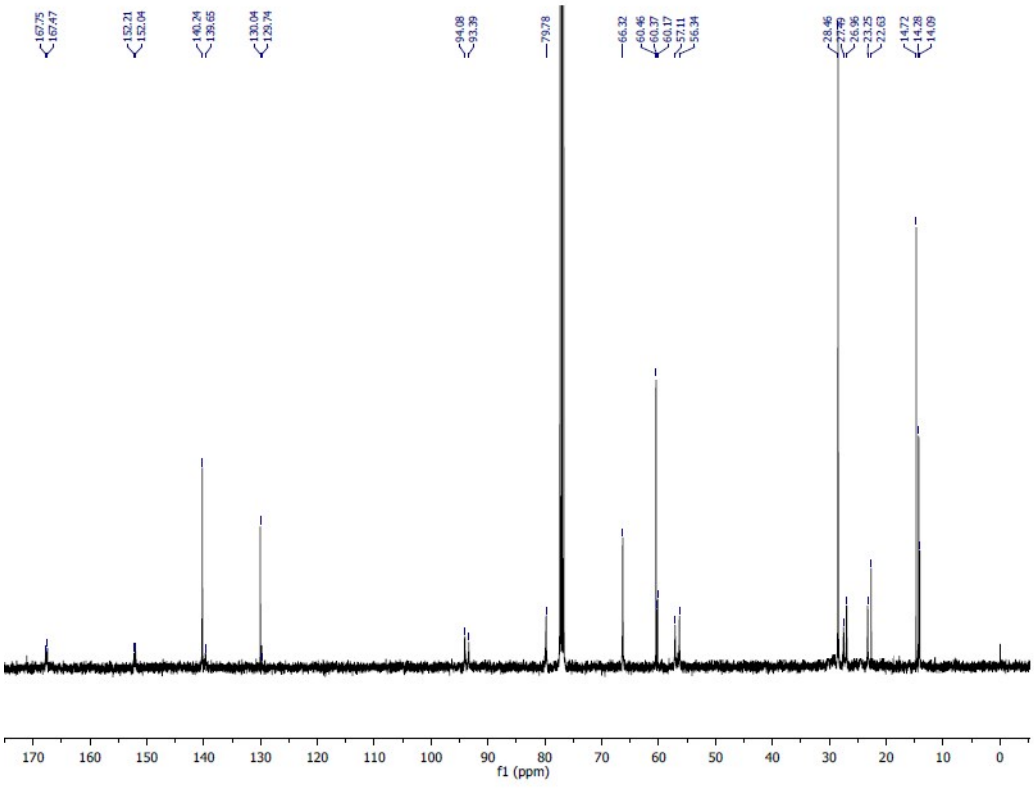

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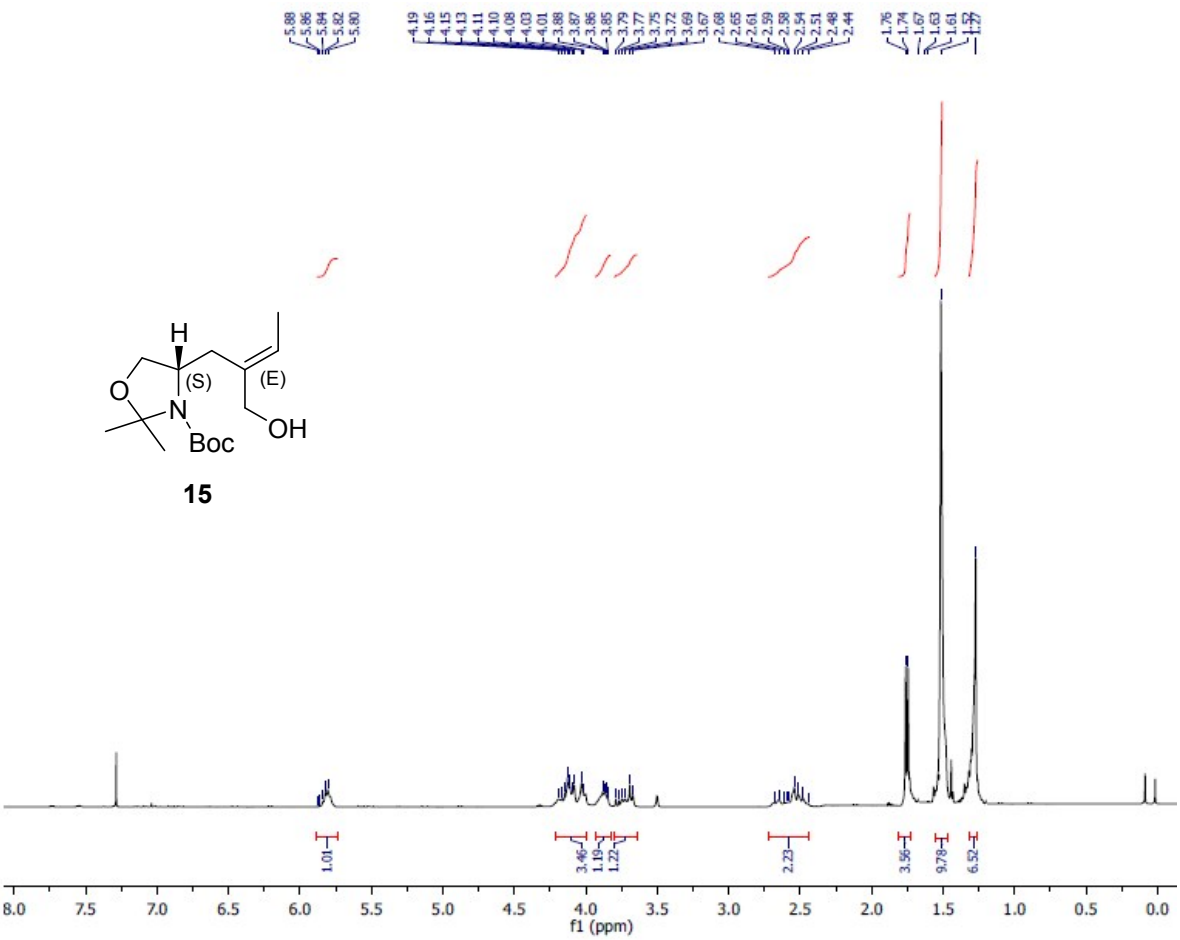

15

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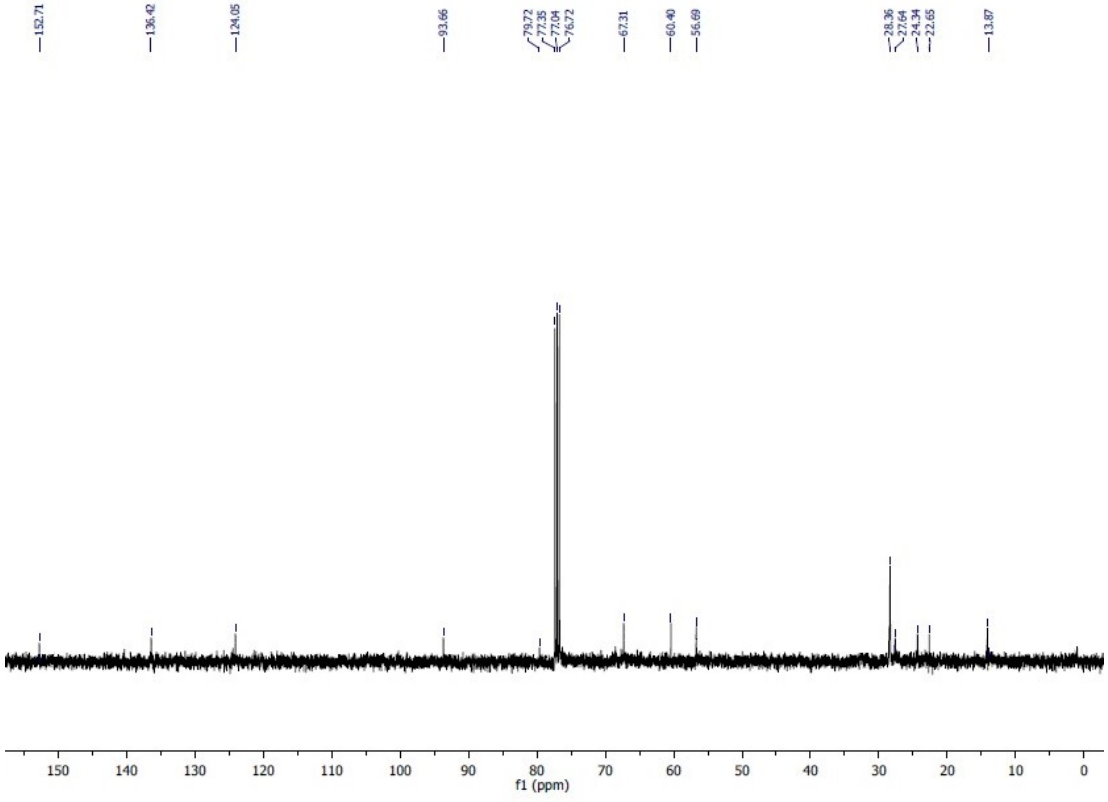

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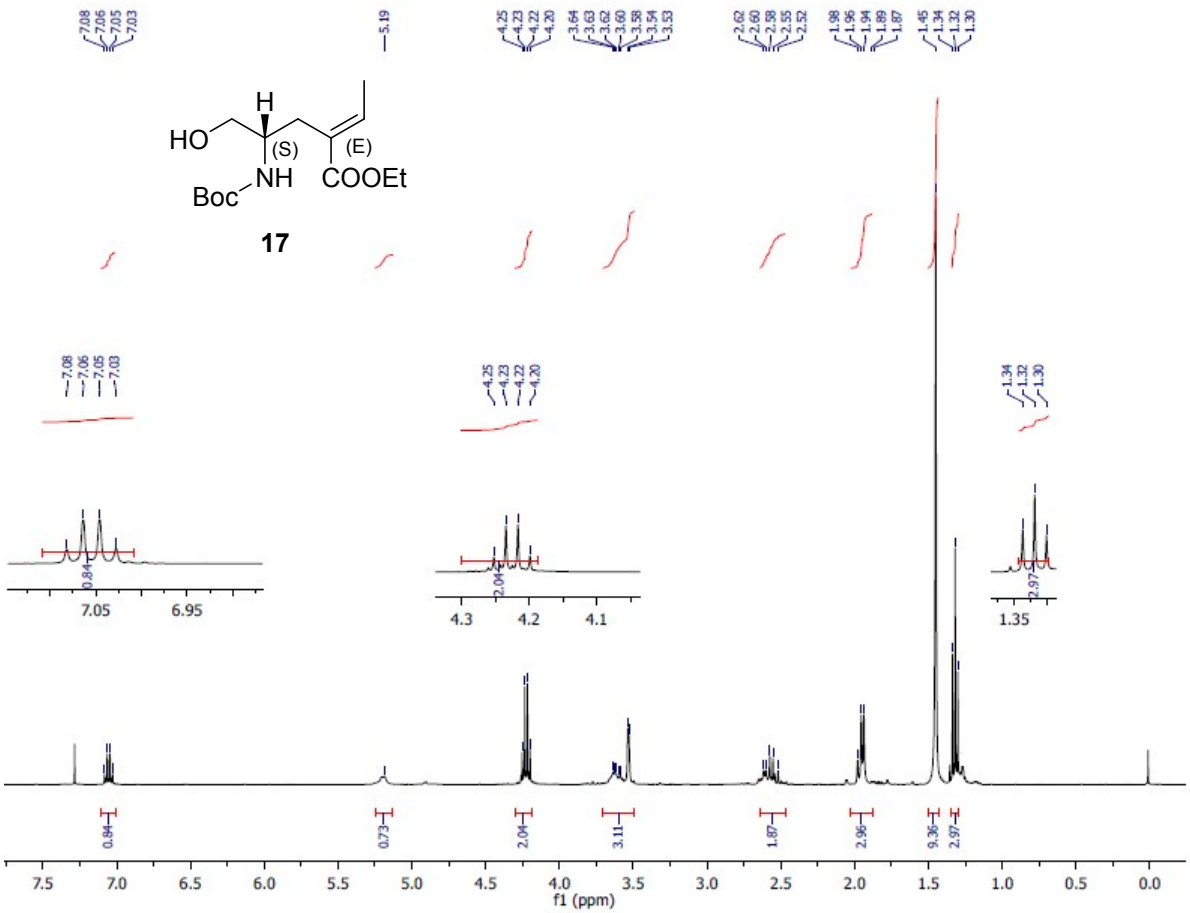

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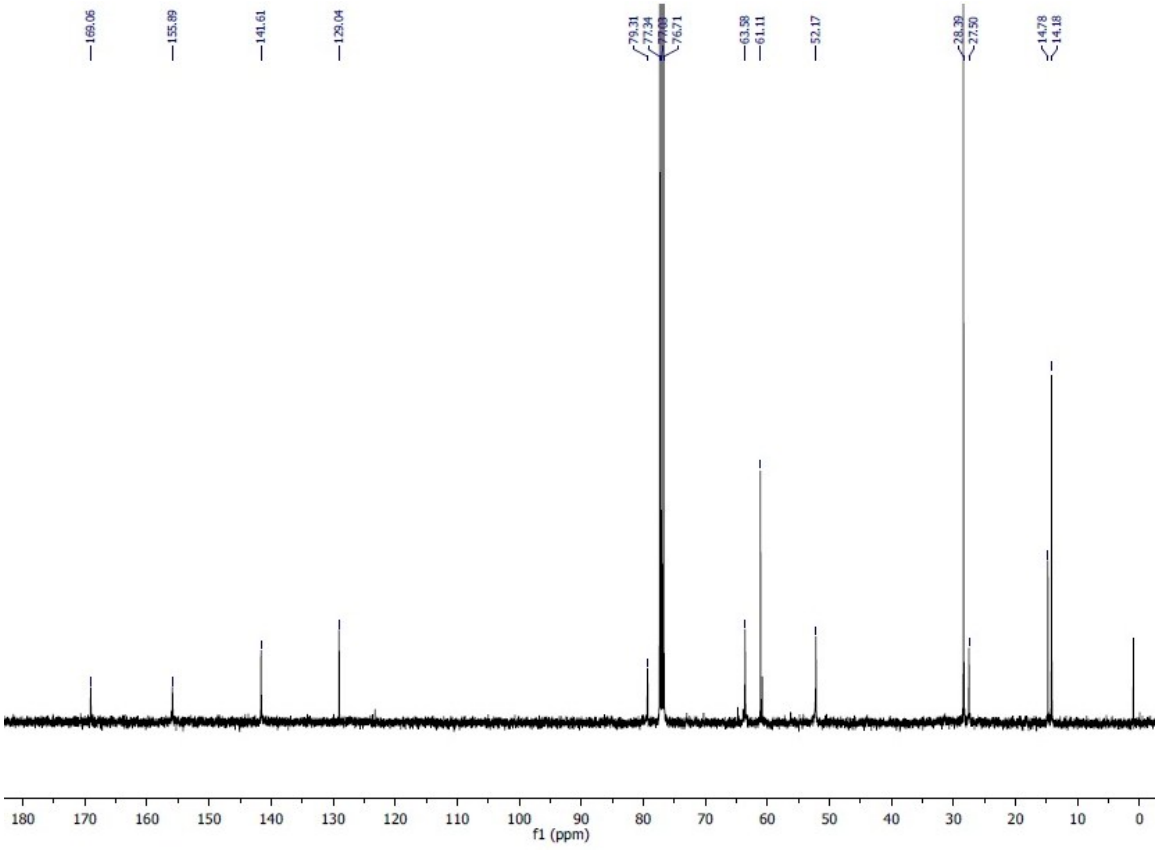

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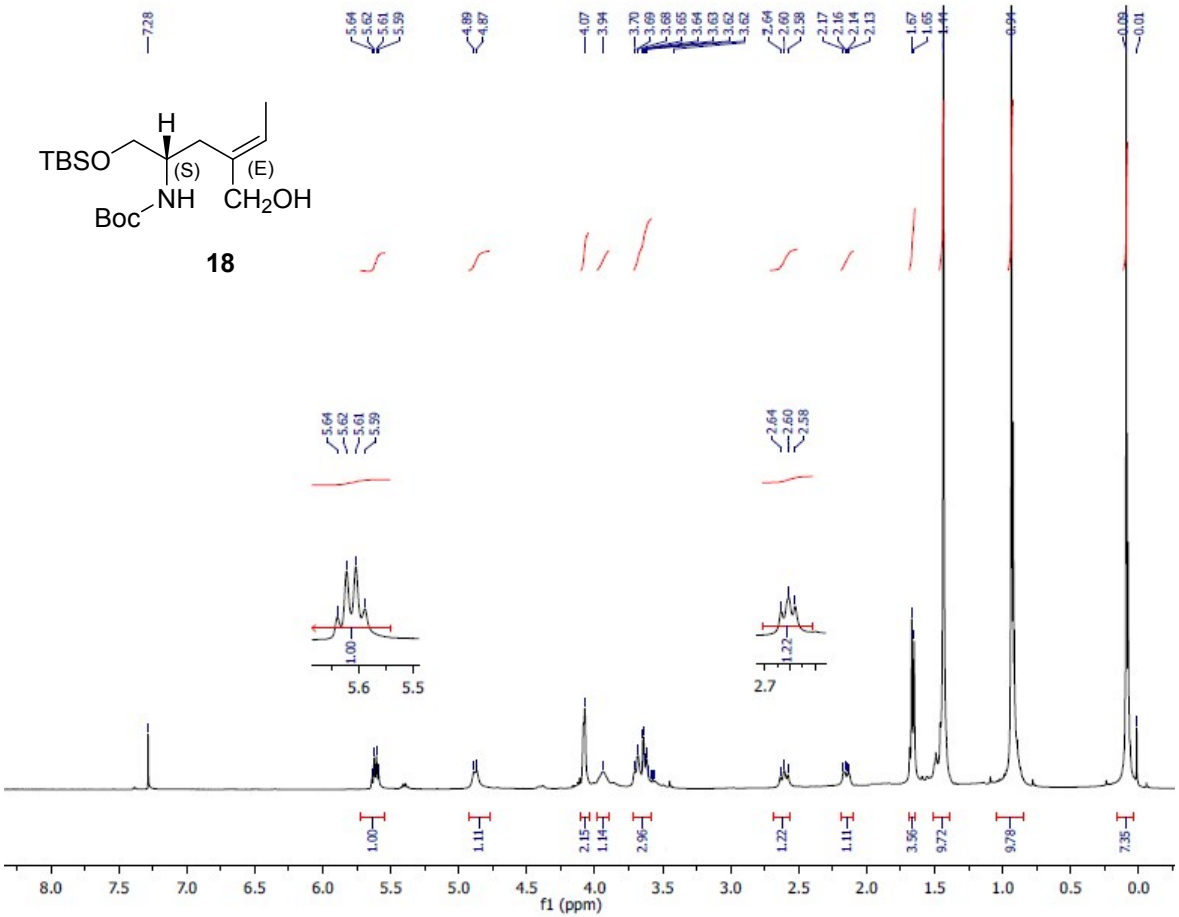

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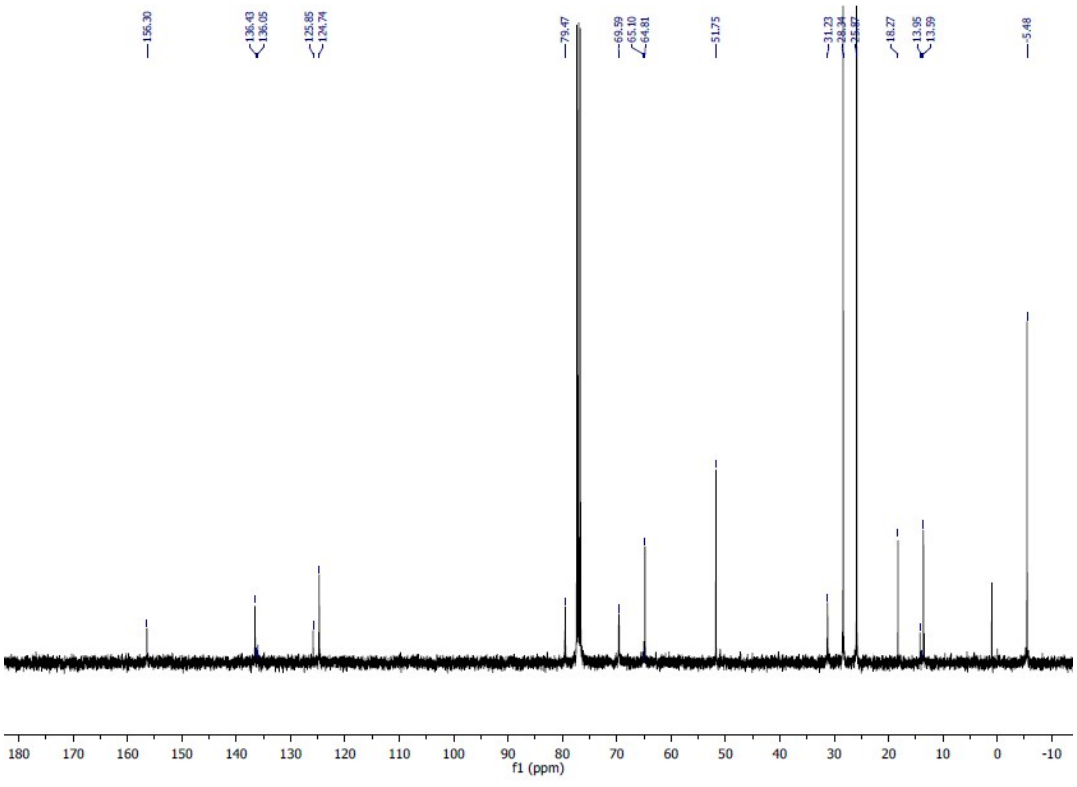

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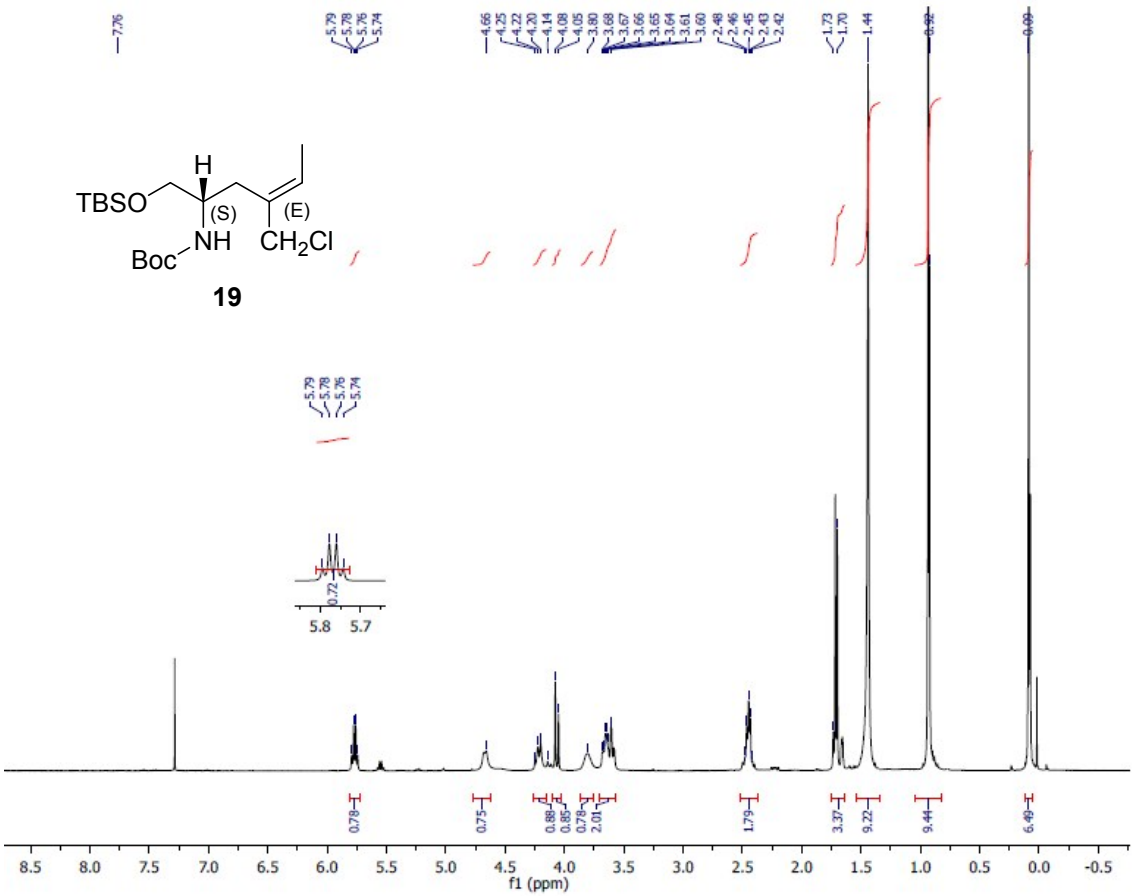

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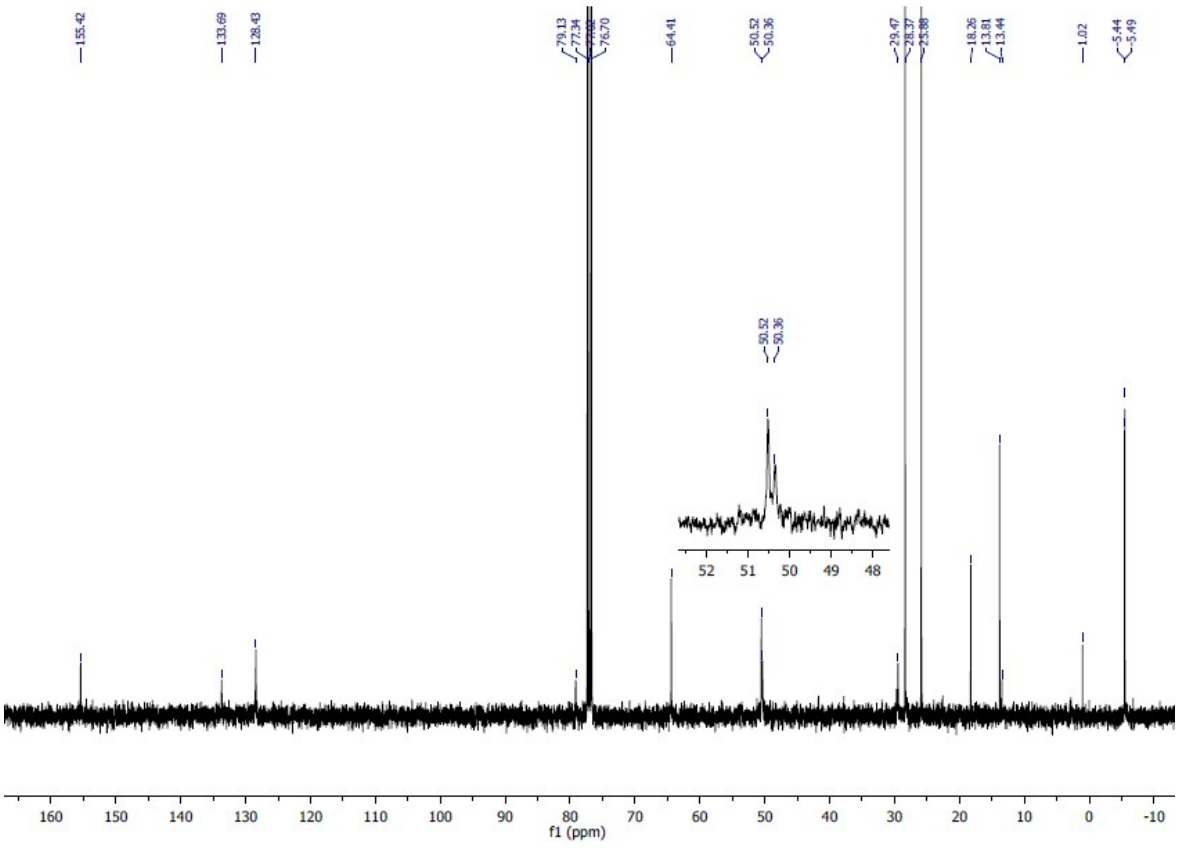

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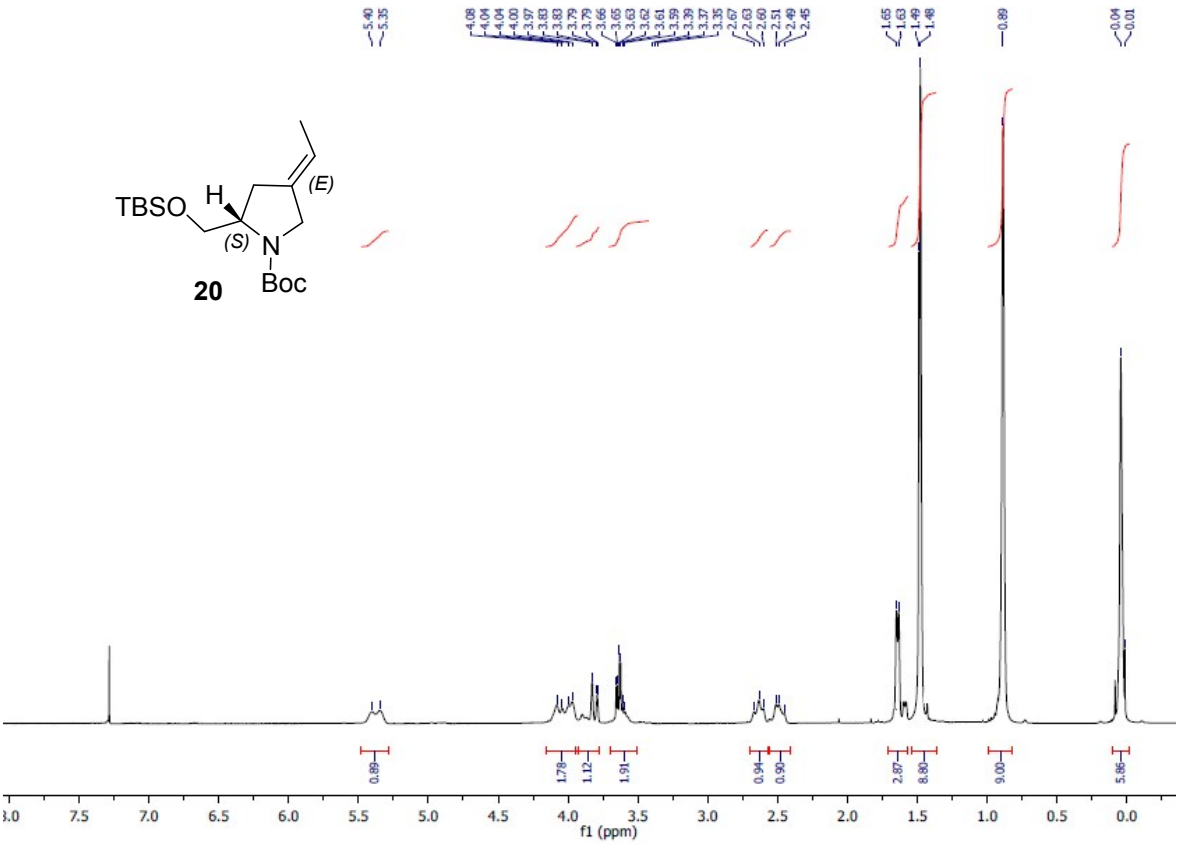

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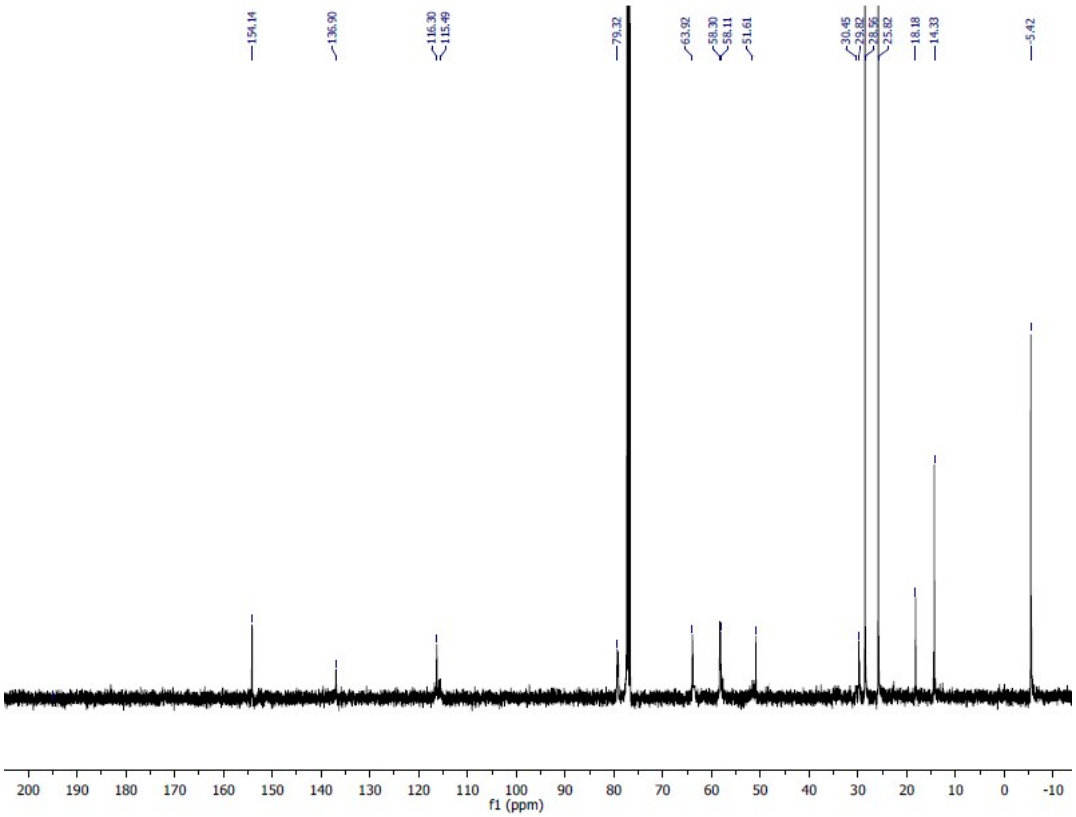

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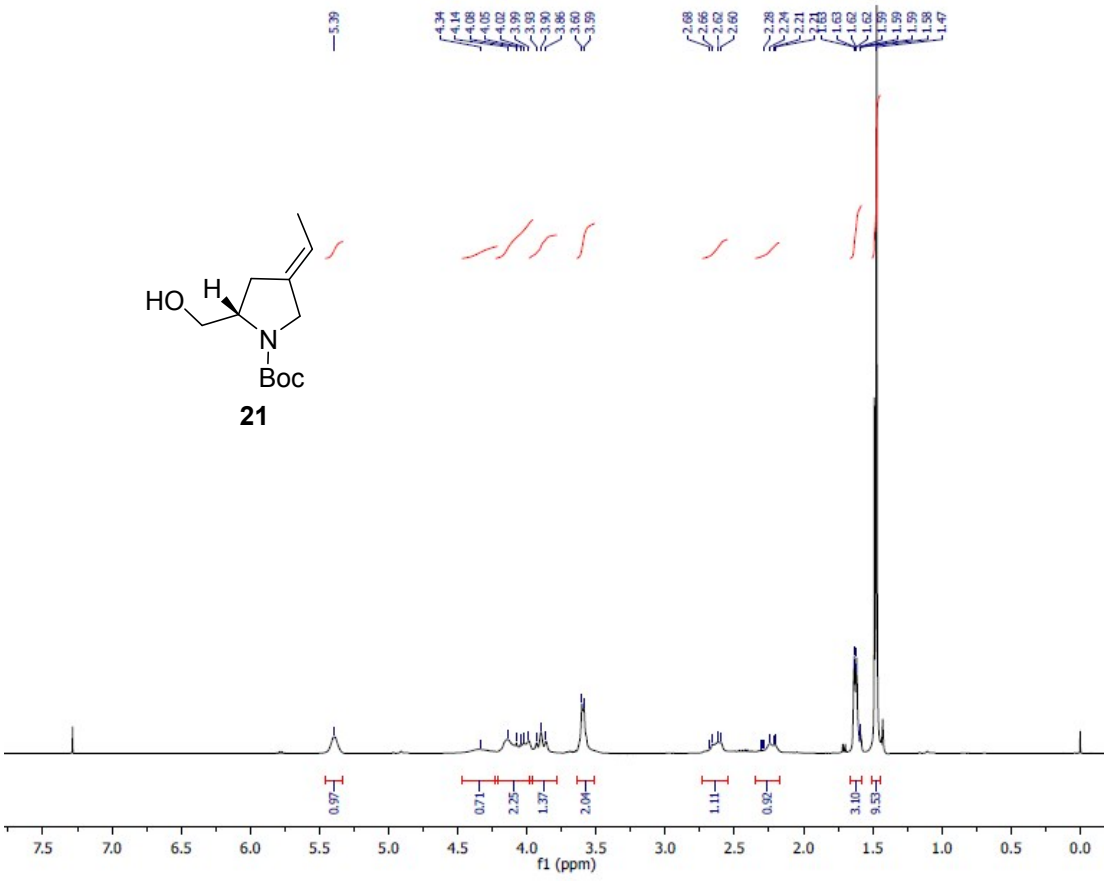

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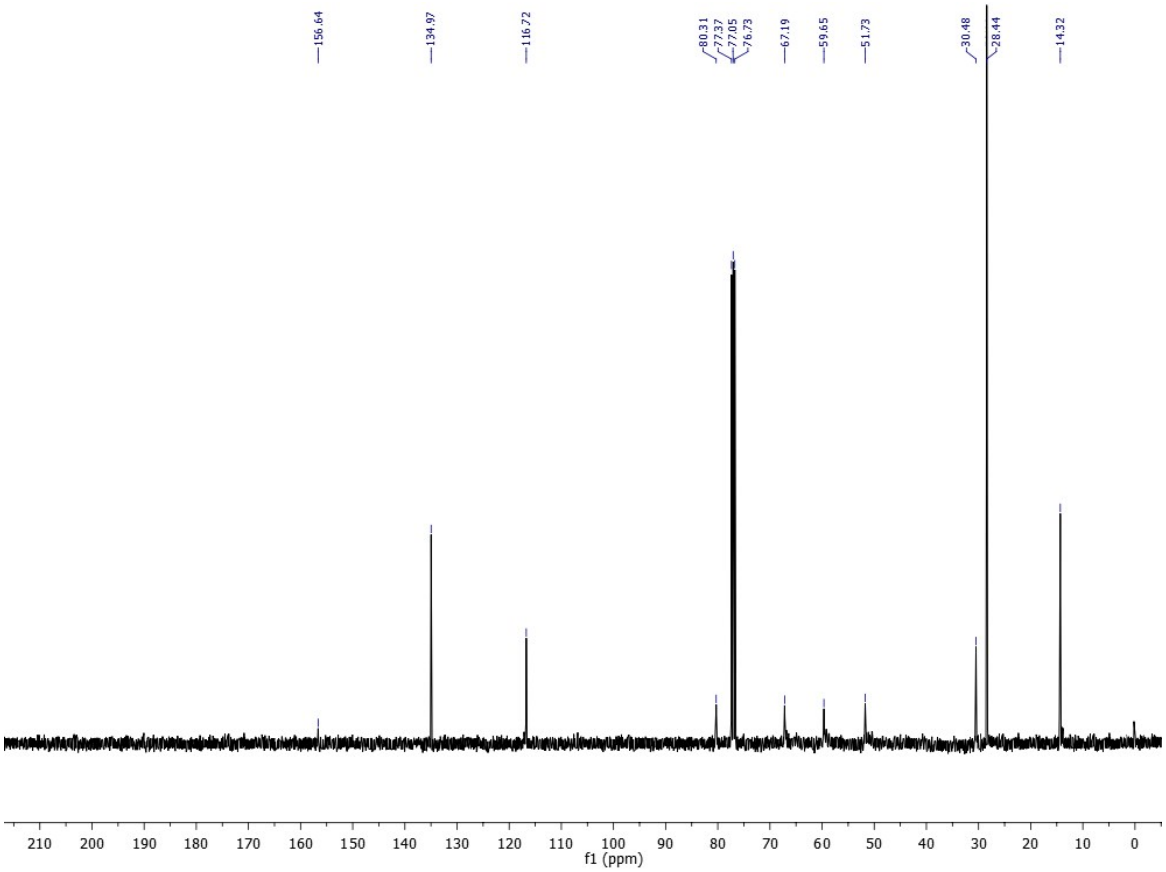

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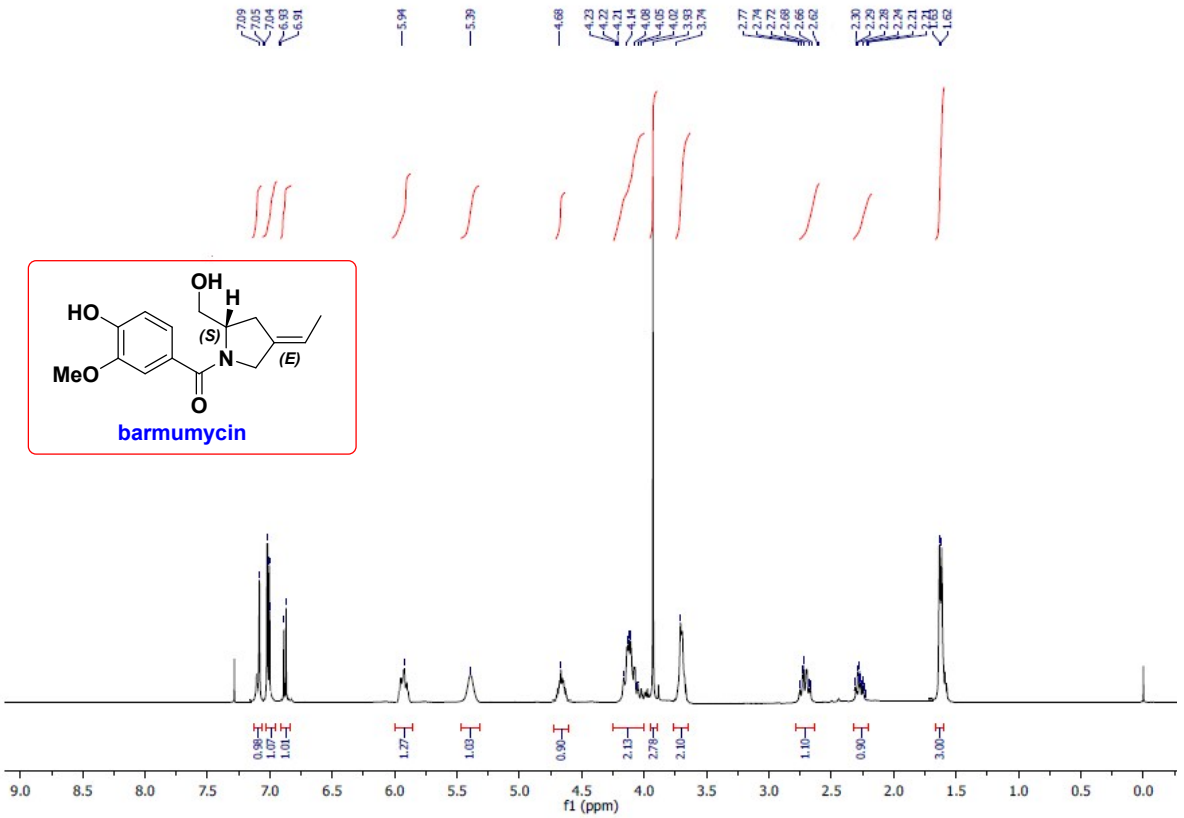

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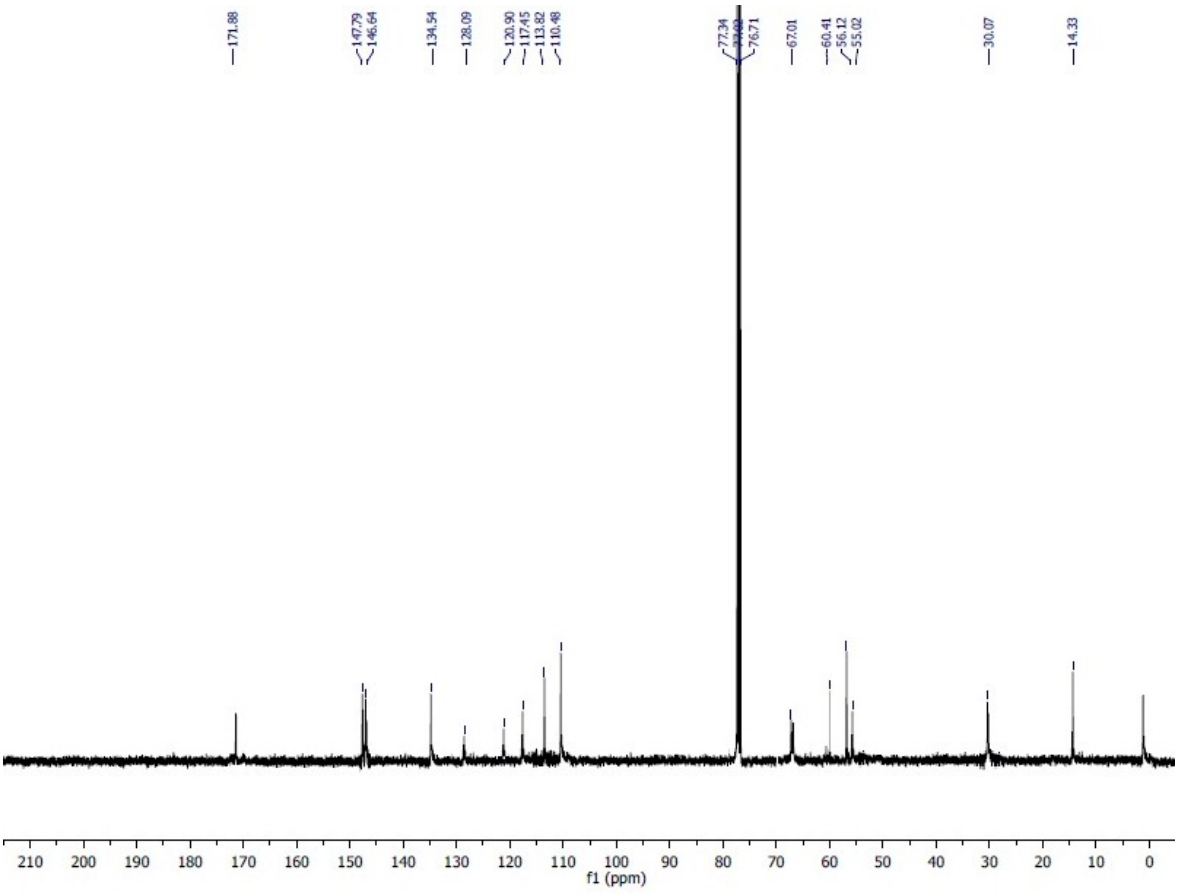

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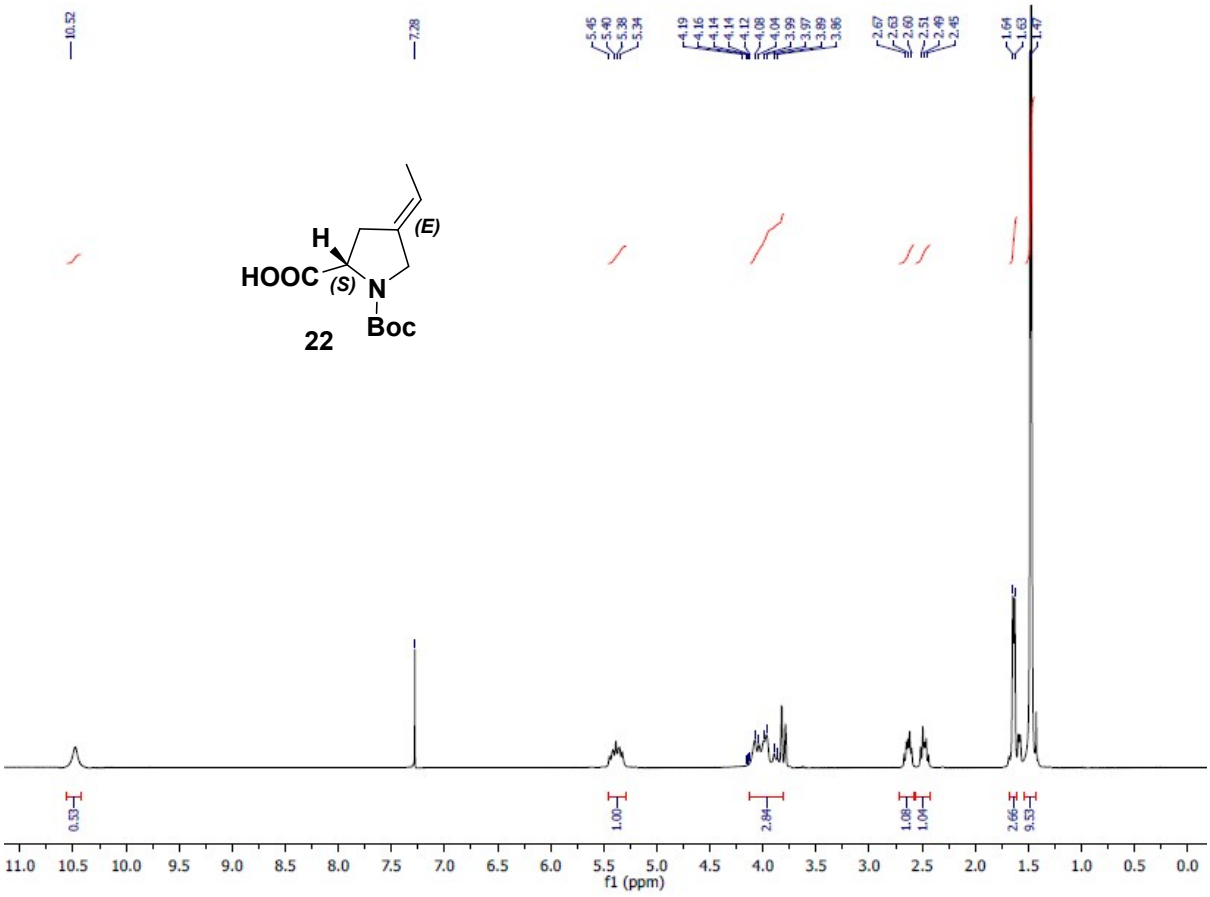

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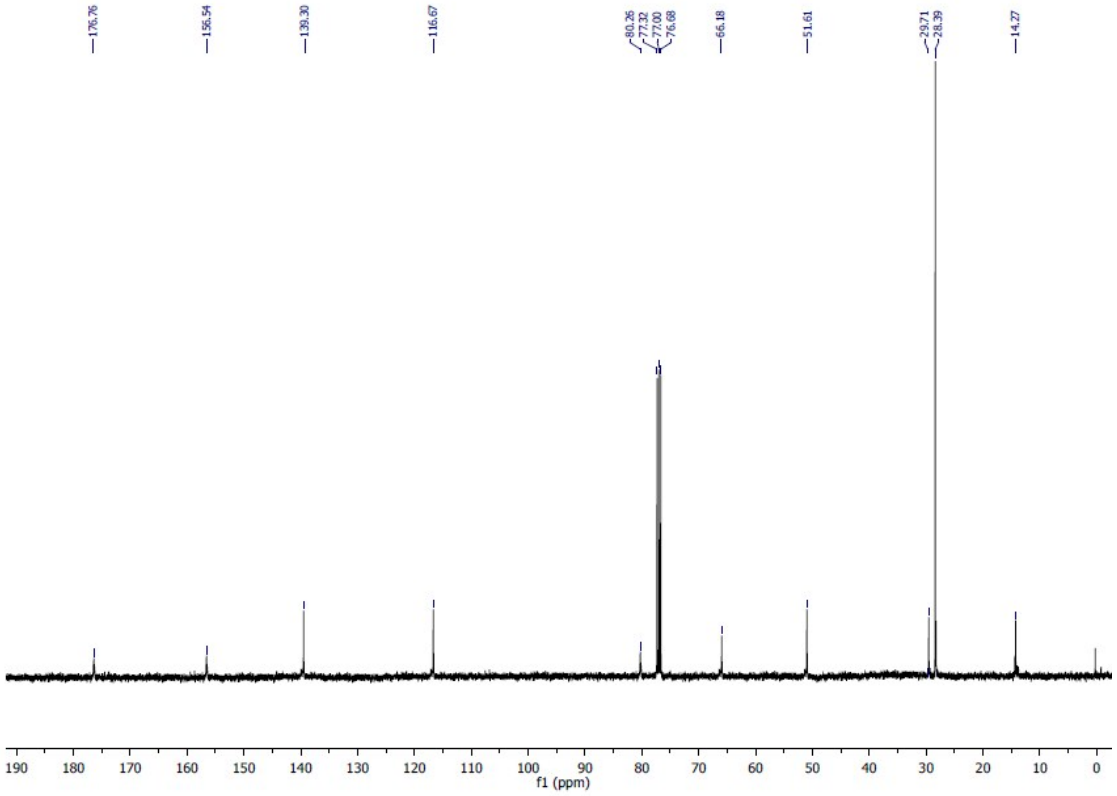

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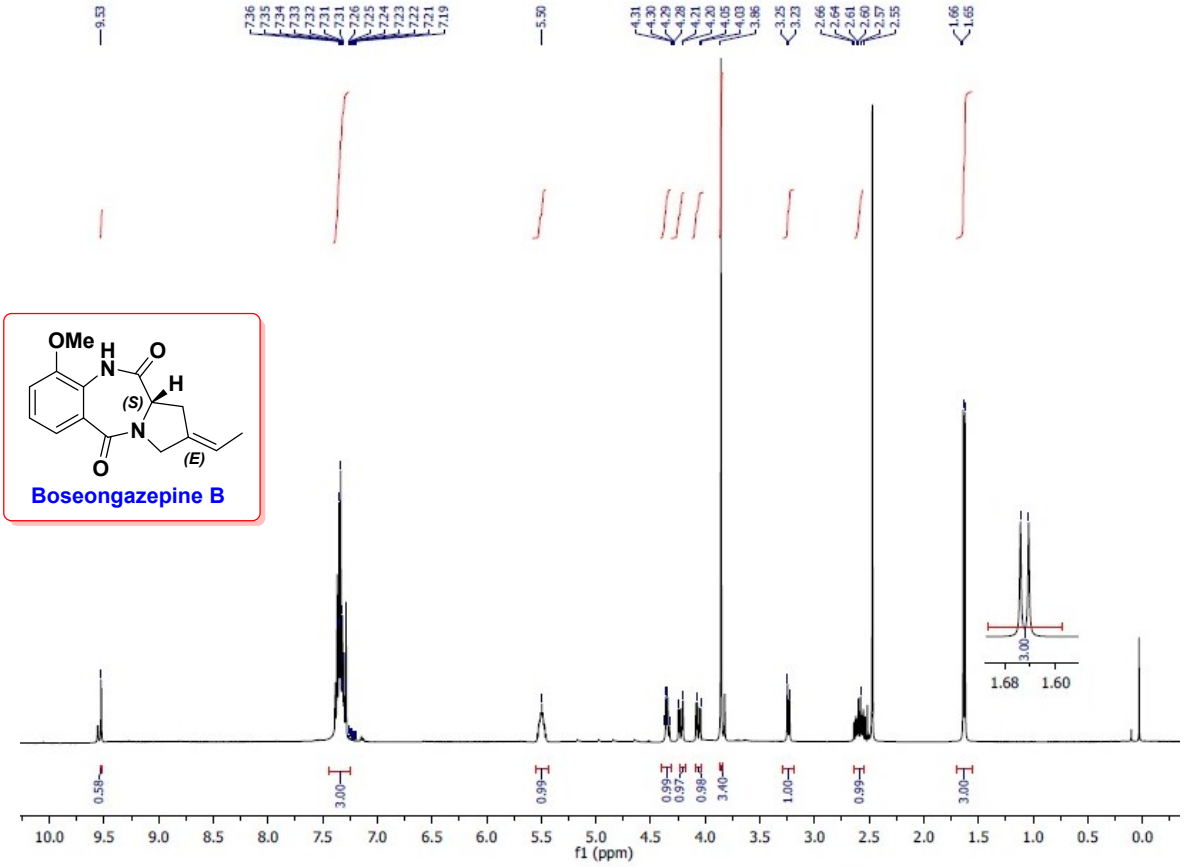

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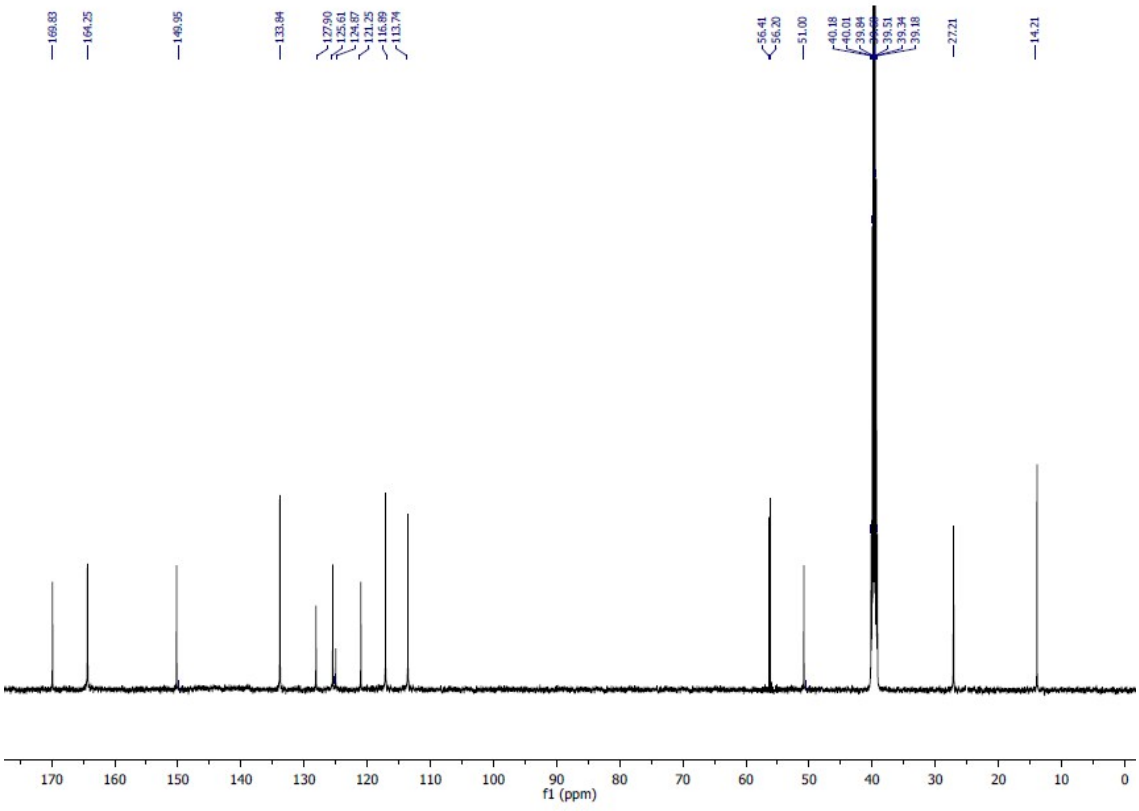

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