Supporting Information

Microwave-Assisted Synthesis of Peptidomimetic *trans*-Delta-Aminopent-3-enoic Acid and Derivatives†

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† Dedicated to **Prof. P. Balaram** on his 75th Birthday

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General information

1. Materials and methods

Trans-*β*-hydromuconic acid, Sodium azide were purchased from Aldrich**,** Fmoc-OSu and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) were purchased from GL Biochem (Pittsburgh, PA), 1-hydroxy benzotriazole (HOBt), N, N'-diisopropylethylamine (DIPEA), solvents are THF, Toluene, 1,2-Dichloromethane (DCM), Trifluoroacetic acid (TFA), N-methyl-2-pyrrolidone (NMP) and N, N'-dimethylformamide (DMF) were obtained from Spectrochem and used to dried over sodium and distilled immediately prior to use and Water, Acetonitrile was HPLC grade, Diethyl ether, *t*-butyl methyl ether were obtained from Rankem. Sodium chloride, Sodium sulphate/Magnesium sulphate were purchased from Sigma Aldrich. The chemicals used for peptide synthesis has very high purity and the glassware's taken during the course of synthesis was cleaned and sterilized in the oven. Analytical thin-layer chromatography (TLC) was performed using aluminium plates precoated with silica gel (0.25 mm, 60 Å pore-size) impregnated with a fluorescent indicator (254 nm). Visualization on TLC was achieved by the use of UV light (220 nm), treatment with 10% ninhydrin in ethanol or stained with Iodine. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on JEOL 300 Bruker (300 MHz). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26 and CD_3OD, δ 3.31). The following abbreviations were used to describe peak patterns when appropriate: *br* = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet. Coupling constants, *J*, were reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on JEOL 300 Bruker (75 MHz) and was fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the centre line at a 77.0 and 49.0 ppm of $CDCl_3$ and CD_3OD. Melting points were determined using a manual one side fused micro melting point tube (Automatic, PLC control, 5 ^{o}C above ambient to 360 ^{o}C, 1.4 mm to 2.0 mm, +, - 2 ^{o}C) were purchase for Guna melting point apparatus. ATR-FTIR spectra of the samples were recorded by using an Attenuated Total Reflectance-Fourier Transformation Infrared spectroscopy (Thermo scientific Nicolet 6700) instrument from 4500 to 450 cm^{-1}, and the purified pure samples were dispersed using the powder/solution phase technique. ESI-MS analysis was carried out using a Thermo Fisher Scientific instrument LTQ Fleet Ion Trap Mass Spectrometer using a C_{18} column (XTerra - 5µ) with a flow rate of 0.8 mL/min. (0.01 mol ammonium acetate buffer and acetonitrile) at the

absorption wavelength of 220 nm. The ability to generate such accurate information can be extremely useful for protein identification and characterization. This technique will give information about the mass/charge ratio of the ionized peptide species. High Pressure Liquid Chromatography is used to identify the formation of product and the purity of the compound. A High-Performance Liquid Chromatography equipped with gradient elution capability, UV/PDA detector and Data handling system (Agilent 1220 Infinity LC). A stainless-steel column of length 150 mm, internal diameter 4.6 mm) particles of 5 µ diameter. (Zorbax SB-C_{18} (150 x 4.6) mm, 5 µ. Data handling system: (Chem station chromatographic software). Programme run for 35 min with a flow rate 1mL/min, injection volume 25µL was programmed in the RP-HPLC for the sample analysis. Solvent system-A (water), B (Acetonitrile) Gradient – Acetonitrile and Water using a gradient of 95-5% where buffer A was 0.1% TFA in H_2O and buffer B was 0.1% TFA in CH_3CN and detection at 220 nm. Examining standard HPLC chromatograms, reveals that the peptide purity was greater than 80%. Peptides were purified *via* flash chromatography using a Buchi Pure C-815 instrument with UV/ELSD detector, UV-Vis/UV scanning and pre-packed column Grace® Reveleris® Flash cartridges (HP Silica 20 µm, Max pressure rating 200 psi, 40mg-8g, flow rate 40 ml/min) and various solvent system. Solution phase synthesis of (*trans*-δ-Apa) amino acid and peptides under MW-irradiation reactions were carried out on a CEM Discover® microwave reactor equipped with a 10mL and/or RB flask glass reaction closed/open vessel reaction and conventional reaction methods.

Abbreviations and symbols follow the recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur*. *J*. *Biochem*. 1984, 138, 9). In addition the following abbreviations are used: DIC, 1,3-diisopropylcarbodiimide; HONB, *N*-hydroxy-5-norbornene-*endo*-2,3-dicarboximide; Bom, benzyloxymethyl; Bzl, benzyl; Mtr, 4-methoxy-2,3,6-trimethyl-benzenesulfonyl; TBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; HOBt, 1-hydroxy-benzo-triazole; PyBOP, benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate; HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HCTU, 2-(6-chloro-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; EDC.HCl, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; CDI, 1,1'carbonyldiimidazole; Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (o-NosylOXY); DIEA, *N,N*-diisopropylethylamine.

2. Experimental procedure (Solution phase peptide synthesis protocols)

2.1. General Procedure for the Synthesis of (*E*)-5-Aminopent-3-enoic Acid (*trans*-δ-Apa) (conventional method)

Trans-β-hydromuconic acid (1.4 g, 10 mmol) was dissolved in THF/$CHCl_3$ (40 mL) at 45 °C under stirring. Concentrated H_2SO_4 (4 mL) was then added, followed by small portions of NaN_3 (0.65 g, 10 mmol) over a period of 35 min. The viscous solution was stirred for 5 h at 45 °C and further overnight at RT. The resulting solution was extracted with H_2O (3*10 mL) and the combined aqueous layers were diluted with H_2O (50 mL) to dissolve small floating particles. Meanwhile, Dowex resin 50WX8-100 (about 100 mL) was washed with de-ionized H_2O (100 mL) and HCl (1 M, 100 mL). The resulting resin was then loaded with the aqueous extract, rinsed with deionized H_2O until pH 7 about 100 mL. The product was finally eluted with pyridine (1M, 150 mL). All washings and elations were performed under atmospheric pressure. The fractions with the desired product were concentrated. The resulting white precipitate was filtered, rinsed with *i*PrOH/water (80:20 v/v) and dried under vacuum (0.589 g, 56%), m.p. 165-167 °C, as white needles.

2.2. General Procedure for the Synthesis of (*E*)-5-Aminopent-3-enoic Acid (Microwave method)

Trans-β-hydromuconic acid (1.4 g, 10 mmol) was suspended in tetrahydrofuran/chloroform (40 mL), and concentrated sulfuric acid (4 mL) added. Sodium azide (0.65 g, 10 mmol) was added in small amounts over 5 min while the mixture was stirred rapidly. Mixture was subjected to MW-irradiation (CEM Discover® microwave reactor) with gas cooling (pressure of 60 psi was maintained during irradiation) for 30 min at 100 W with magnetic stirring, and a temperature limit of 60 °C (reaction time refers to the hold time at the desired set temperature). After a further 35 min at 50 °C the chloroform layer was decanted from the viscous residue which was washed again with chloroform (30 mL). The acid layer was dissolved in water (150 mL) and HCl (50 mL), filtered and added to a column of Dowex 50W (H^+) ion-exchange resin (50 mL). The column was washed with water (150 mL) to neutral pH and then the amino acid eluted with aqueous pyridine (150 mL, 1M). Evaporation of the solvent afforded oil which slowly solidified. Recrystallization from isopropanol/water (80:20 v/v) gave (*E*)-5-aminopent-3-enoic acid (0.793 g, 74%), m.p. 166-167 °C, as white needles.

2.3. General procedure for the N^{α}-PG of *trans*-δ-Apa under microwave condition

N^{α}-Terminal protecting groups (1.67 g, 7.4 mmol) in *t*BuOH/THF (3.2 mL) was added to a solution of amine (0.92 g, 8.3 mmol) and 2.1 N aqueous NaOH/10% Na_2CO_3 (4 mL, 8.1 mmol) in *t*BuOH/THF (2.3 mL). The solution was stirred under microwave condition, Power 120 W, Temp 45 ºC, Pres 50 psi, 5 min, then 2.1 N aqueous NaOH/10% Na_2CO_3 (4.8 mL, 9.7 mmol) was added. The mixture was subsequently stirred for an additional 25 min. The solution was concentrated under reduced pressure, and the residue was acidified with 6 N aqueous HCl until pH 3 was reached. The aqueous phase was extracted with Et_2O (3*20 mL). The combined organics extracts were dried over Na_2SO_4, filtrated and concentrated to give the title compound as a white solid (1.94 g, 95%).

2.4. General procedure for the N^{α}, C-PG of *trans*-δ-Apa under microwave condition

0.4 g of and Boc-protected amino acid and 0.3 g of amine are dissolved in an RB flask using Dichloromethane and N, N-dimethyl formamide. 0.5 g of coupling reagent and 0.4 g of auxiliary nucleophile and hunig's base were added to the reaction vessel under microwave condition, Power 120 W, Temp 50 ºC, Pres 75 psi, Time 40 min. After ran the TLC which was confirmed the formation of the product and no more reactants are present. The organic layer was washed three times with sodium carbonate solution, for each wash 30-35 mL of base is used. Then it was washed three with 2N HCl, for acid wash also 30-35 mL of acid was used. After each wash the organic and aqueous layers were collected separately the aqueous layer is placed aside and only the organic layer is used for further washes. This procedure was same for both acid and base wash. Finally, the organic layer is washed with Brine solution. The organic layer was dried over sodium sulphate. The solvent was removed using rotavapor. 0.870 g of product was obtained.

2.5. General procedure for the C-PG of *trans*-δ-Apa under microwave condition

C-Terminal protecting groups was taken in a round bottom flask in ice bath, then thionyl chloride ($SOCl_2$) was added drop by drop in stirred condition and H-(*trans*-δ-Apa)-OH was added. The round bottom flask was closed with guard tube ($CaCl_2$). The solution mixture was then stirred for overnight RT or Microwave condition. Methanol was removed by distillation. After cooling the round bottom flask, diethyl ether was added. Compound was colourless.

2.6. General experimental procedure for dipeptides

In a 10 mL MW vial equipped with a magnetic stir bar, H-*trans*-δ-Apa-NHMe (2.2 mmol) was dissolved in DMF (2 mL). *t*Boc-*trans*-δ-Apa-OH (3.3 mmol) was added followed by HBTU (3.7 mmol) and HOBt (3.8 mmol). Mixture was subjected to MW-irradiation (CEM Discover® microwave reactor) with gas cooling (pressure of 75 psi was maintained during irradiation) for 45 min at 100 W with magnetic stirring, and a temperature limit of 60 ºC (reaction time refers to the hold time at the desired set temperature). DMF was evaporated and the reaction mixture was purified on automated flash column chromatography system to give *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe. The purity of the all the peptides were analysed by reversed-phase RP-HPLC.

2.7. General procedure for the deprotection of *t*Boc-Group

*t*Boc-*trans*-δ-Apa-NHMe was dissolved in DCM and then treated with trifluroacetic acid. The solution was stirred for 2-3 hours in ice bath. The solvent was evaporated in vacuum. Then Sodium carbonate was added slowly to the aqueous solution to make the pH 9-10. The Solution was then extracted with ethyl acetate (50ml three times). The organic layer consisting of free amino group was then concentrated in vacuum. The free amine was directly used for the coupling without any other further purification.

2.8. General method for the removal of methyl ester group

To a suspension of the desired peptide (1 equiv) in ethyl alcohol (7 mL) was added potassium carbonate (1.6 equiv), and the mixture was stirred for 60 min at 35 °C. The solvent of reaction mixture was removed under reduced pressure.

2.9. General method for the removal of benzyl ester/benzyl ether/Z groups

To a suspension of the desired peptide (1 equiv), 10% Pd-C (12 equiv) in ethyl alcohol (5 mL) was added ammonium formate (7.5 equiv), and the mixture was heated with stirring at 60 ºC for 16 h. The reaction mixture was filtered through a celite pad, and solvent was removed under reduced pressure. The resulting residue was purified on a preparative RP-HPLC using a Buchi-C-815 Flash system. Method: 40 min gradient, 5-90% CH_3CN-H_2O-0.1% CF_3CO_2H at 220 nm.

2.10. General method for the workup of peptides

On completion of chemical synthesis of the peptide chain, the final step is the extraction or precipitation. Depending on the solubility of the peptide, extraction or precipitation method was used. The solvents used for extraction or precipitation includes diethyl ether, ethyl acetate,

and glacial acetic acid. Many different approaches to this problem have been established, but the procedure most widely used for peptides has been treatment with cold ether. After completion of synthesis, ether was added directly to the reaction vessel, and peptide mixture was stirred or 30-45 min. The mixture was filtered and residue was washed three times with cold ether. The purity of crude peptide was analysed using analytical RP-HPLC and if peptide was more than 90% pure, then lyophilization was performed directly for final storage. Otherwise, isolation or purification (using Flash and RP-HPLC chromatography) of the crude peptide followed by lyophilization is the final step in this process.

3. Graphical experiment

3.1. Representative small-scale procedure

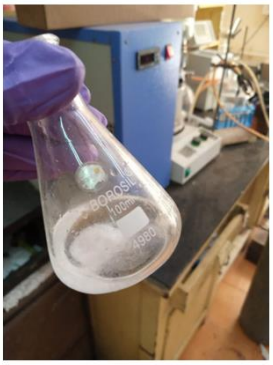
Describing a chemical synthesis process involving the reaction of a diacid, sodium azide, and sulfuric acid in a solvent such as acetonitrile or chloroform, followed by purification using ion-exchange chromatography. The resin used in the chromatography process can be regenerated and reused for multiple cycles, with regeneration involving treatment with a strong acid like hydrochloric or sulfuric acid.

Step-1

Step-2

Step-3

Step-4



Step-5

Step-6

Step-7

Step-8

The process involves several steps:

Step-1, 2

Reaction: The diacid, sodium azide, and sulfuric acid react in the chosen solvent under microwave conditions.

Step-3, 4, 5

Workup: After the reaction, an aqueous workup is performed to extract the product from the reaction mixture.

Step-6

Chromatography: The crude reaction mixture is then subjected to ion-exchange column chromatography using resin. This helps in purifying the product.

Regeneration: The resin used in chromatography can be regenerated for reuse. This involves treating the resin with a strong acid (hydrochloric or sulfuric acid) to exchange the ions and restore its functionality. The process may include backwashing, treatment with the regenerant chemical for a specific period and flow rate, followed by rinsing.

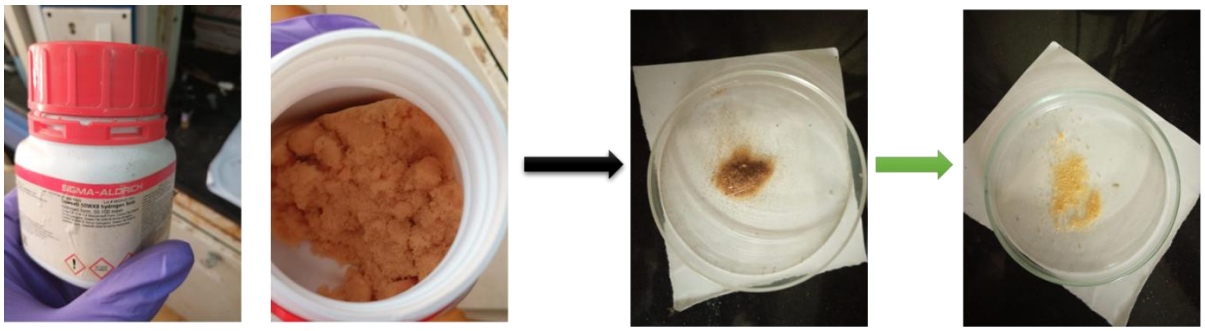
Recycling: The regenerated resin can be reused for multiple cycles, typically up to five cycles, while still maintaining a moderate output.

Handling: The ion-exchange method simplifies the purification process and makes it easy to handle. This process seems to be well-structured and efficient for the synthesis and purification of the desired product. It's important to ensure proper safety measures are in place when handling strong acids and other chemicals involved in the process.

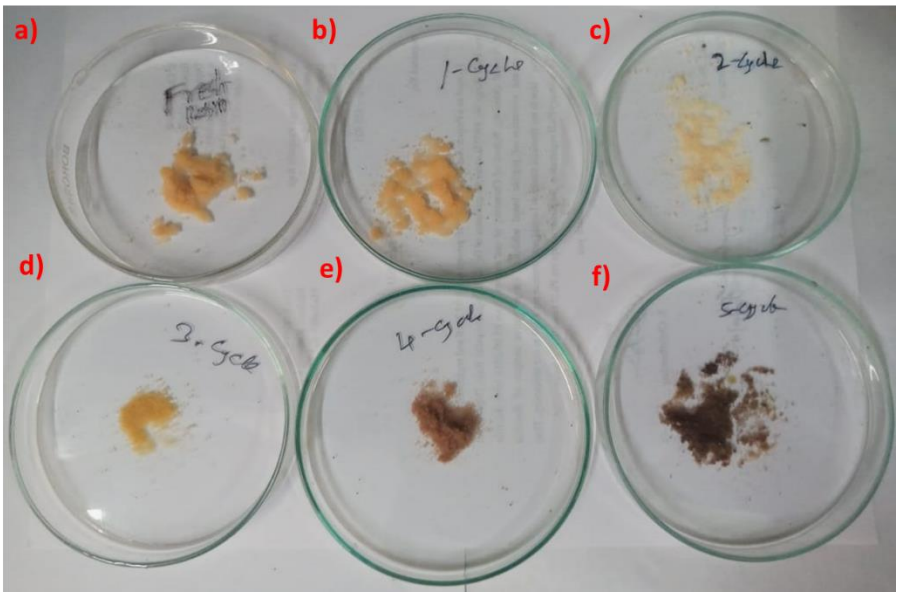
Step-7, 8

Pure product isolated as a white solid after chromatography.

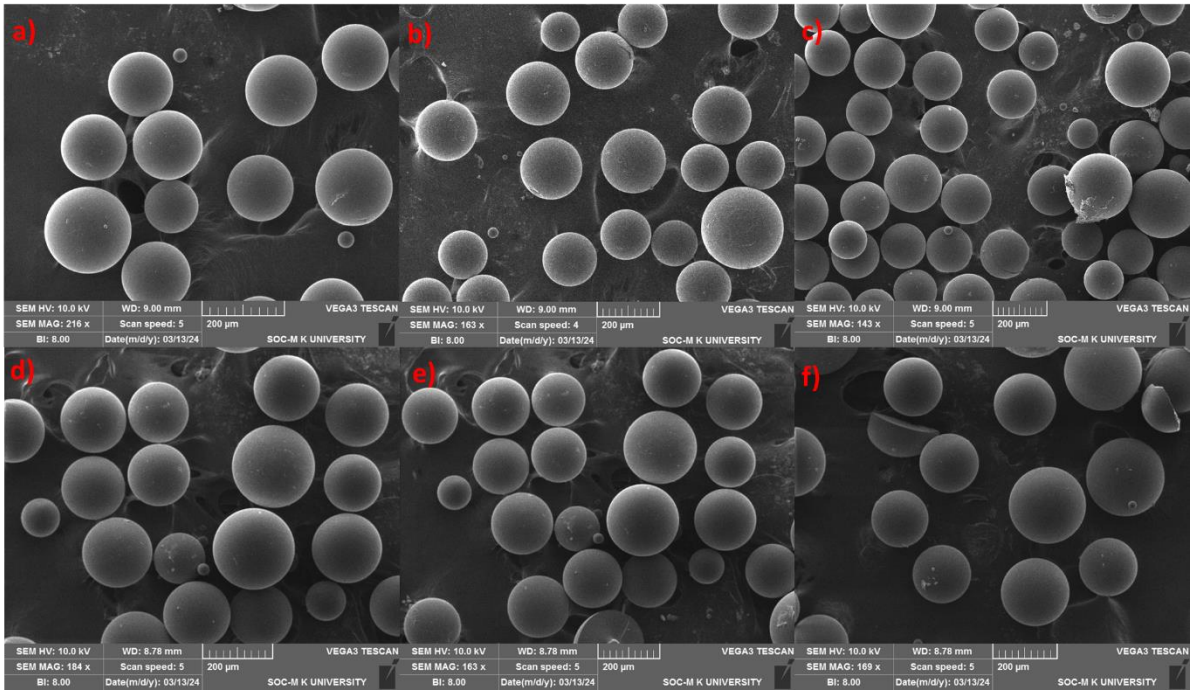
3.2. Resin regeneration



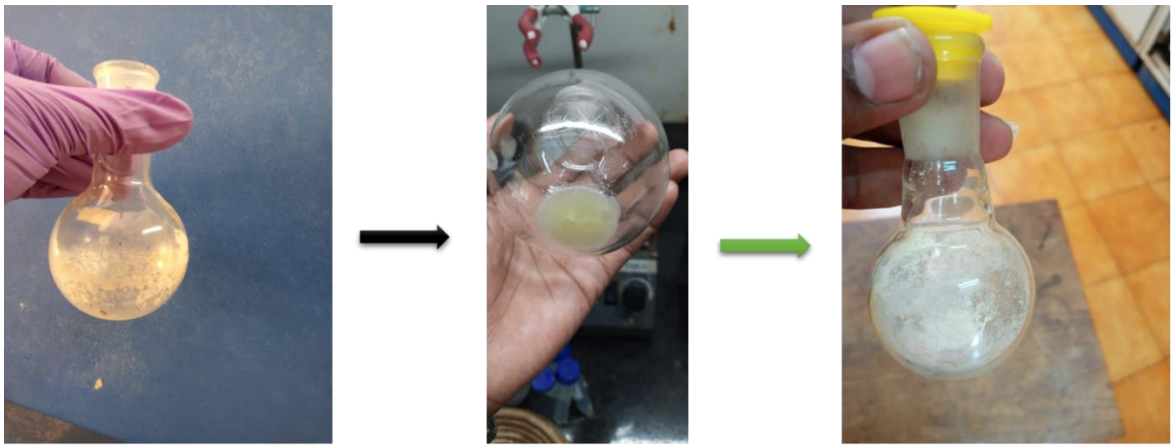
3.3. Resin recycles



3.4. SEM pictures



3.5. Recrystallization Process



trans-Delta amino acid

After Recrystallization

Transferred into RB flask

4. Reaction condition optimization

Table S1: Exploration of various solvent systems to synthesise *trans*-δ-Apa under microwave irradiation condition

Entry	Reagent (equiv.)[a]	Dry Solvent (mL)[b]	Yield (%)[c]
1	$NaNO_2$/Conc.H_2SO_4	Tetrahydrofuran	42
2	$NaNO_2$/Conc.H_2SO_4	Acetonitrile	44
3	$NaNO_2$/Conc.H_2SO_4	1,2-Dichloromethane	39
4	$NaNO_2$/Conc.H_2SO_4	Acetone	nr
5	$NaNO_2$/Conc.H_2SO_4	Dimethylformamide	36
6	$NaNO_2$/Conc.H_2SO_4	Dimethyl sulfoxide	nr
7	$NaNO_2$/Conc.H_2SO_4	Toluene	31
8	$NaNO_2$/Conc.H_2SO_4	Ethyl acetate	nr
9	$NaNO_2$/Conc.H_2SO_4	1,2-Dichloroethane	40
10	$NaNO_2$/Conc.H_2SO_4	1,4-Dixane	43
11	$NaNO_2$/Conc.H_2SO_4	Benzene	45
12	$NaNO_2$/Conc.H_2SO_4	Water	nr
13	$NaNO_2$/Conc.H_2SO_4	Chloroform	64
14	**$NaNO_2$/Conc.H_2SO_4**	**THF/$CHCl_3$[d]**	**74**
15	$NaNO_2$/Conc.H_2SO_4	THF/$CHCl_3$	67
16	$NaNO_2$/Conc.H_2SO_4	ACN/$CHCl_3$	59
17	$NaNO_2$/Conc.H_2SO_4	DMF/$CHCl_3$	45
18	$NaNO_2$/Conc.H_2SO_4	CCl_4	nr
19	$NaNO_2$/Conc.H_2SO_4	Cyclohexane	nr
20	$NaNO_2$/Conc.H_2SO_4	Xylene	54
21	$NaNO_2$/Conc.H_2SO_4	Chloroform[e]	54
22	$NaNO_2$/Conc.H_2SO_4	THF/$CHCl_3$[f]	56
23	$NaNO_2$/Conc.H_2SO_4	Chloroform[g]	49

Reaction conditions: Diacid (20.8 mmol), [b]Dry solvent (90 mL), [a]Reagent of conc.H_2SO_4 (9 mL), sodium azide (20.8 mmol) in nitrogen atmosphere at over period of 35 min, power 100 W, at 50 °C than pressure 60 psi for microwave-assisted synthesis. Meanwhile loaded with the aqueous extract. Ion-exchange chromatography. [c]Isolated yields. Solvent is used as a dry. [d]Bold letters indicate the optimized conditions. [e,f]Our report conventional methods initial 5 h at 45 °C further to overnight RT. [g]Pervious report conventional method initial 5 h at 45 °C further to overnight RT.[21]

Table S2: Comparison of peptide synthesis in conventional and microwave method

Coupling reagent	Yield (%)[a]	
	Conventional method[b]	Microwave method[c]
HBTU, HOBt	68	91
o-Nosyloxy	63	84
HATU/HOAt	60	79
EDCl.HCl	60	76
Oxyma	59	71

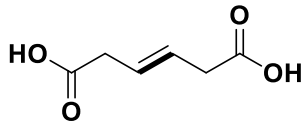
Reaction conditions: Synthesis of dipeptide; Each reaction carried out in 0.1 mmol scale (Solvent: v/v, DMF/DCM), [a]Isolated yields after chromatography, [b]Conventional method (Magnetic stirrer with RT), [c]CEM Discover® microwave reactor apparatus (closed/open vessel).

Table S3: Each amine experiment will be carried out in ion-exchange column

S.No	Amine	MW	Density	Pka	ppm (for 0.1 N)	Yield (%)	ppm (for 0.2 N)	Yield (%)	ppm (for 0.5 N)	Yield (%)	ppm (for 0.005 N)	Yield (%)	Regulatory Limits	Recommended Limits	Immediately Dangerous to Life or Health (IDLH)
1	TEA	101.193	0.72	10.8	1.39	62	2.78	65	6.95	64	0.69	65	25	15	200
2	Pyr	79.1	0.98	9.52	0.8	74	1.6	73	4	70	0.4	71	5	5	1000
3	DIPEA	129.247	0.74	11.4	1.74	58	3.48	60	8.7	59	0.87	60	5	5	200
4	Pyrrolidine	71.123	0.86	11.3	0.82	55	1.64	57	4.1	54	0.41	58	NA	NA	NA
5	DBU	152.241	1.01	13.5	1.49	42	2.98	43	7.45	41	0.74	42	NA	NA	NA
6	Imidazole	68.077	1.23	6.95	0.68	39	1.36	40	3.4	39	0.34	37	NA	NA	NA
7	Piperazine	86.138	0	9.8	0.86	54	1.72	55	4.3	52	0.43	50	NA	NA	NA
8	DEA	73.139	0.7	11	0.73	58	1.46	60	3.65	61	0.36	54	25	10	200
9	Piperdine	85.15	0.68	11.2	0.85	42	1.7	44	4.25	40	0.42	40	NA	NA	NA
10	TMA	59.112	670	4.19	0.59	40	1.18	41	2.95	38	0.29	40	NA	NA	10

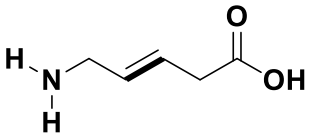
5. Characterization of Compounds

Synthesis of *trans-3-Hexenedioic acid*



Diacid: m.p. 195-196 ºC, RP-HPLC R_t =9.474 min 98%. ATR FT-IR (cm^{-1}): 3374, 2974, 1720, 1658, 1597, 1541, 1490, 1417, 1370, 1290, 1170, 1108, 980, 575 cm^{-1}; ESI-MS m/z: calcd for $C_6H_8O_4$.Na $[M+Na]^+$ 167.03, found 167.89.

Synthesis of (*E*)-*5-aminopent-3-enoic acid (1)*

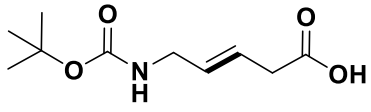


Yield 74 %, m.p. 165-167 ºC, RP-HPLC R_t =4.254 min 97%. ^{1}H NMR (400 MHz, CD_3OD, TMS, ppm): δ_H 5.86 (dt, *J* = 15.75 Hz 1H), 5.50 (dt, *J* = 15.60 Hz 1H), 3.45 (d, *J* = 6.5 Hz, 2H), 2.87 ppm (d, *J*= 7 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD, TMS, ppm): δ_C 180.0, 132.8, 123.0, 40.8 ppm; ATR FT-IR (cm^{-1}): 2800, 1630, 1560, 1490, 1370, 980 cm^{-1}; ESI-MS m/z: calcd for $C_5H_9NO_2$.Na 138.13 $[M+Na]^+$ found 138.17, $C_{10}H_{18}N_2O_4$.Na 253.23 $[2M+Na]^+$ found 253.27.

(*E*)-5-Aminopent-3-enoic acid: Yield 74 %; m.p. 165-167 ºC; RP-HPLC R_t = 4.254 min 97 %; ^{1}H NMR (400 MHz D_2O, ppm): δ_H 6.05-5.98 (dt, *J* = 15.43, Hz, 1H, =CH), 5.59-5.54 (dt, *J* = 15.41, Hz, 1H CH=), 3.49-3.48 (d, *J* = 6.9 Hz, 2H, NCH_2), 2.98-2.96 (d, *J* = 7.3 Hz, 2H, CH_2CO); ^{13}C NMR (100 MHz, D_2O, ppm): δ_C 183.52 (CO_2), 134.18 (CH=CH), 124.55, 42.71, 41.24 (CH_2); ATR FT-IR (cm^{-1}): 2800, 1630, 1560, 1490, 1370, 980 cm^{-1}; HRMS m/z: calcd for $C_5H_9NO_2$ 116.0681 $[M+H]^+$ found 116.0712, $C_5H_9NO_2$.Na 138.1201 $[M+Na]^+$ found 138.0531.

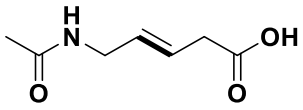
***N*$^{\alpha}$-terminal protecting group (*trans*-δ-Apa)**

Synthesis of *(E)-5-((tert-butoxycarbonyl) amino) pent-3-enoic acid (2a)*



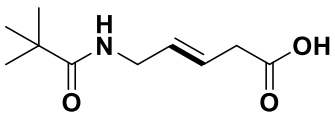
Yield 96 %, M.p 59-61 ºC, RP-HPLC R_t = 17.306 min, 95%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ_H 9.39 (br, 1H), 5.75–5.65 (m, 2H), 4.36 (br, 1H), 3.75 (br, 2H), 3.10 (d, J = 6.0 Hz, 2H), 1.45 ppm (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS, ppm): δ_C 176.8, 154.5, 130.8, 122.8, 81.0, 41.3, 37.0, 27.6; ^{13}C NMR, (75 MHz, DMSO-d_6, TMS): δ_C 174.1, 156.9, 130.2, 123.6, 78.6, 41.4, 36.9, 27.3; ATR FT-IR (cm^{-1}): 3335, 3010, 1718, 1645, 1526, 1258, 1178, 1019, 970, 877; ESI-MS m/z: calcd for $C_{10}H_{17}NO_4$ $[M+Na]^+$ 238.14, found 238.11.

Synthesis of *(E)-5-acetamidopent-3-enoic acid (2b)*



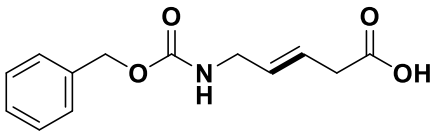
Yield 90 %, M.p 68-70 ºC, RP-HPLC R_t = 27.813 min, 67%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ_H 8.81 (s, 1H), 6.04-5.85 (m, 1H), 5.63-5.55 (m, 1H), 4.22 (br, 2H), 3.73-3.59 (d, J = 12 Hz, 2H), 3.04-2.98 (d, J = 15.6 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, ppm): δ_C 176.57, 171.79, 128.13, 122.27, 45.40, 35.98, 25.40; ATR FT-IR (cm^{-1}): 3478, 3012, 2941, 1720, 1681, 1615, 1542, 1420, 1382, 1278, 1102, 1007, 810; ESI-MS m/z: calcd for $C_7H_{11}NO_3$ $[M+H]^+$ 158.16, found 158.85.

Synthesis of *(E)-5-pivalamidopent-3-enoic acid (2c)*



Yield 90 %, M.p 72-75 ºC, RP-HPLC R_t = 19.251 min, 90%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ_H 8.4 (br, 1H), 5.81 (br, 1H), 5.69-5.60 (m, 1H), 5.58-51 (m, 1H), 3.82-3.78 (d, J = 12, 2H), 3.05-3.03 (d, J = 6 Hz, 2H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS, ppm): δ_C 178.58, 172.57, 127.31, 121.77, 40.16, 39.98, 35.29, 29.01, 25.26; ATR FT-IR (cm^{-1}): 3420, 3102, 2780, 1710, 1637, 1685, 1621, 1578, 1465, 1320, 1220, 1174, 1005, 852; ESI-MS m/z: calcd for $C_{10}H_{17}NO_3$ $[M+H]^+$ 200.25, found 200.62.

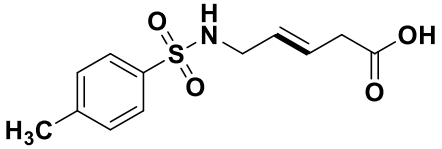
Synthesis of *(E)-5-(((benzyloxy)carbonyl)amino)pent-3-enoic acid (2d)*



Yield 91 %, M.p 97-99 ºC, RP-HPLC R_t = 28.489 min, 96%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS, ppm): δ_H 7.34-7.31 (d, J = 9 Hz, 2H), 7.30-7.28 (d, J = 8 Hz, 2H), 7.21-7.18 (d, J = 9 Hz, 1H), 6.38-6.28 (m, 1H), 6.07-5.84 (m, 1H), 4.06-3.92 (m, 3H), 2.36-2.35 (d, J = 3 Hz, 2H), 2.29-

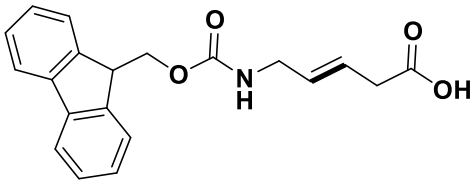
2.23 (t, J = 18 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, ppm): δ_C 178.57, 155.90, 134.25, 127.15, 129.77, 121.34, 63.21, 44.09, 35.89; ATR FT-IR (cm^{-1}): 3420, 3028, 2841, 1765, 1678, 1601, 1547, 1420, 1235, 1270, 1101, 1084, 997; ESI-MS m/z: calcd for $C_{13}H_{15}NO_4$ $[M+H]^+$ 249.10, found 248.99.

Synthesis of *(E)-5-((4-methylphenyl)sulfonamido)pent-3-enoic acid (2e)*



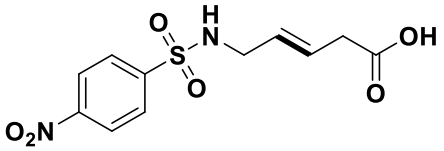
Yield 92 %, M.p 157-159 ºC, RP-HPLC R_t = 18.955 min, 94%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ_H 7.62-7.64 (d, 9 Hz, 2H, 7.24-7.22 (d, J = 6 Hz, 2H), 6.81 (br, 1H), 5.67-5.59 (m, 1H), 5.42-5.35 (m, 1H), 4.49 (b, 1H), 3.40-3.38 (d, 6 Hz, 2H), 3.89-3.87 (d, J = 6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ_C 176.71, 142.38, 138.84, 129.71, 128.43, 127.79, 125.36, 46.02, 34.98, 26.31; ATR FT-IR (cm^{-1}): 3512, 3257, 2870, 1754, 1670, 1614, 1530, 1473, 1398, 1243, 1185, 1020, 885; ESI-MS m/z: calcd for $C_{12}H_{15}NO_4S$ $[M+H]^+$ 292.31, found 292.45.

Synthesis of *(E)-5-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-3-enoic acid (2f)*



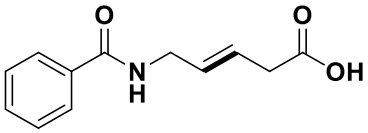
Yield 97 %, M.p 121-126 ºC, RP-HPLC R_t = 22.457 min, 91%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.75 (d, 2H, J = 7.4 Hz), 7.58 (d, 2H, J = 7.4 Hz), 7.43-7.38 (m,2H),7.34-7.29 (m, 2H), 5.74-5.60 (m, 2H), 4.91 (br, 2H), 4.41 (d, 2H, J = 6.2 Hz), 4.21 (t, 1H, J = 8.7 Hz), 3.82-3.74 (m, 2H), 3.11 (d, 2H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 176.4, 143.9, 141.3, 130.8, 127.7, 127.1, 125.0, 123.6, 120.0, 66.7, 47.2, 42.5, 37.1; ATR FT-IR (cm^{-1}): 3416, 3487, 3017, 2394, 1670, 1524, 1487, 1318, 1125, 1020, 987, 812; ESI-MS m/z: calcd for $C_{20}H_{19}NO_4$ $[M+Na]^+$ 360.37, found 360.17.

Synthesis of *(E)-5-((4-nitrophenyl)sulfonamido)pent-3-enoic acid (2g)*



Yield 95 %, M.p 146-148 ºC, RP-HPLC R_t = 11.738 min, 95%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 9.49 (br, 1H), 8.18-8.16 (d, J = 6 Hz, 2H), 7.99-7.97 (d, J = 6 Hz, 2H), 4.24-4.09 (m, 1H), 3.65-3.60 (d, J = 15 Hz, 1H), 3.07-3.04 (d, J = 9.4 Hz, 1H), 2.27-2.24 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 177.57, 152.01, 141.05, 132.25, 130.21, 128.28, 125.38, 122.49, 121.19, 45.19, 36.89; ATR FT-IR (cm^{-1}): 3520, 3014, 2986, 1716, 1635, 1558, 1467, 1320, 1220, 1178, 1007, 997; ESI-MS m/z: calcd for $C_{11}H_{12}N_2O_6S$ $[M+Na]^+$ 323.28, found 323.19.

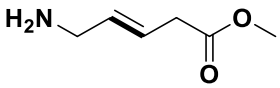
Synthesis of *(E)-5-benzamidopent-3-enoic acid (2h)*



Yield 91 %, M.p 90-93 ºC, RP-HPLC R_t = 25.764 min, 92%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 8.02 (s, 1H), 7.80-7.78 (d, J = 6 Hz, 1H), 7.61-7.58 (d, J = 3.7 Hz, 1H), 7.30-7.28 (m, 1H), 7.25-7.23 (m, 1H), 5.91-5.87 (m, 1H), 5.71-5.69 (m, 1H), 4.34 (br, 1H), 3.66-3.61 (m, 2H), 3.11-3.06 (m, 1H), 2.88-86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 176.57, 168.51, 137.12, 132.28, 128.74, 122.77, 43.92, 34.89; ATR FT-IR (cm^{-1}): 3523, 3210, 2975, 1735, 1647, 1558, 1377, 1260, 1170, 995; ESI-MS m/z: calcd for $C_{12}H_{13}NO_3$ $[M+H]^+$ 220.09, found 220.26.

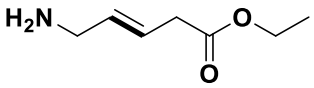
C-terminal protecting group (*trans*-δ-Apa)

Synthesis of *methyl (E)-5-aminopent-3-enoate (3a)*



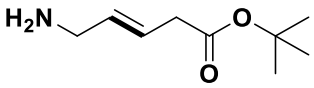
Yield 88 %, M.p 78-80 ºC, RP-HPLC R_t = 16.601 min, 82%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 5.51-5.48 (m, 2H), 4.29 (b, 1H), 4.22 (s, 3H), 4.00-3.96 (m, 1H), 3.42 (b, 1H), 2.88-2.86 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 176.01, 132.91, 116.23, 53.82, 44.60, 34.98; ATR FT-IR (cm^{-1}): 3587, 3026, 2847, 1738, 1630, 1582, 1471, 1382, 1192, 1021, 995; ESI-MS m/z: calcd for $C_6H_{11}NO_2$ $[M+Na]^+$ 152.16, found 152.75.

Synthesis of *ethyl (E)-5-aminopent-3-enoate (3b)*



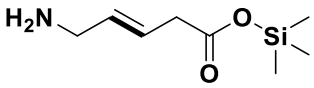
Yield 85 %, M.p 85-87 ºC, RP-HPLC R_t = 2.915 min, 90%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 5.80-5.74 (m, 1H), 5.66-5.61 (m, 1H), 4.26-4.14 (m, 1H), 3.42-3.31 (m, 2H), 2.97-2.94 (m, 2H), 1.38-1.34 (d, J = 12 Hz, 3H), 1.22-1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 174.55, 133.90, 114.32, 63.18, 45.60, 36.29, 19.28; ATR FT-IR (cm^{-1}): 3478, 1797, 1720, 1658, 1520, 1468, 1368, 1108, 1008, 773; ESI-MS m/z: calcd for $C_7H_{13}NO_2$ $[M+Na]^+$ 166.18, found 166.25.

Synthesis of *tert-butyl (E)-5-aminopent-3-enoate (3c)*



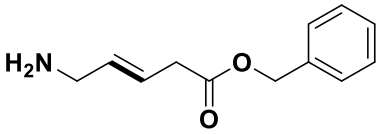
Yield 91 %, M.p 81-83 ºC, RP-HPLC R_t = 18.581 min, 89%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.23-722 (m, 1H), 5.90-5.89 (m, 1H), 5.87-5.79 (m, 1H), 4.39-4.30 (d, J = 16.2 Hz, 2H), 4.02-3.90 (d, J = 6 Hz, 1H), 3.18-3.13 (d, J = 15 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 171.97, 132.09, 115.23, 83.26, 44.06, 35.87, 28.25, 25.31; ATR FT-IR (cm^{-1}): 3571, 3257, 2907, 1709, 1645, 1530, 1480, 1398, 1243, 824; ESI-MS m/z: calcd for $C_9H_{17}NO_2$ $[M+Na]^+$ 194.24, found 194.18.

Synthesis of *trimethylsilyl (E)-5-aminopent-3-enoate (3d)*



Yield 84 %, M.p 62-67 ºC, RP-HPLC R_t = 24.359 min, 90%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 5.56-5.49 (m, 1H), 5.34-5.30 (m, 1H), 4.42-4.38 (t, J = 12 Hz, 2H), 3.67-3.58 (m, 2H), 3.08-3.07 (d, J = 3.9 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 172.16, 133.92, 115.23, 45.6, 36.18, 32.65, 21.08; ATR FT-IR (cm^{-1}): 3201, 2876, 1707, 1776, 1672, 1596, 1367, 1125, 930; ESI-MS m/z: calcd for $C_8H_{17}NO_2Si$ $[M+Na]^+$ 210.31, found 210.54

Synthesis of *benzyl (E)-5-aminopent-3-enoate (3e)*

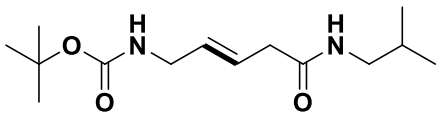


Yield 90 %, M.p 92-99 ºC, RP-HPLC R_t = 32.093 min, 91%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.46-7.44 (m, 1H), 7.23-7.21 (m, 1H), 7.14-7.11 (m, 1H), 7.07-7.04 (d, J = 9.7 Hz, 2H),

5.80-5.78 (m, 1H), 5.57-5.46 (m, 1H), 4.71 (br, 1H), 4.36-4.31 (d, J = 15 Hz, 2H), 3.99-3.95 (t, J = 12 Hz, 2H), 3.49-3.46 (m, 2H), 2.12-2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 173.71, 139.32, 130.09, 127.15, 125.23, 117.58, 44.60, 32.92; ATR FT-IR (cm^{-1}): 3520, 2810, 1798, 1664, 1617, 1547, 1468, 1391, 1201, 1082, 932; ESI-MS m/z: calcd for $C_{12}H_{15}NO_2$ $[M+H]^+$ 206.25, found 206.85.

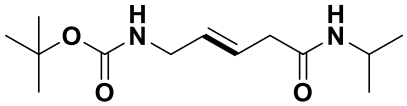
N^{α} and C-terminal protecting group (*trans*-δ-Apa)

Synthesis of *tert-butyl (E)-(5-(isobutylamino)-5-oxopent-2-en-1-yl)carbamate (4a)*



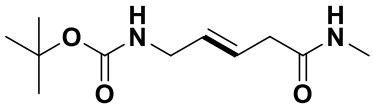
Yield 84 %, M.p 115-119 ºC, RP-HPLC R_t = 14.498 min, 85%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.74 (s, 2H), 6.61 (m, 1H), 5.97-5.80 (m, 1H), 5.27 (br, 1H), 4.64-4.61 (d, J = 10.2 Hz, 2H), 3.98-3.94 (m, 2H), 3.54-3.43 (m, 2H), 2.92-2.88 (m, 2H), 2.22-2.10 (m, 1H), 1.39 (s, 9H), 1.16-0.98 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 176.76, 159.03, 1366.78, 117.19, 80.68, 49.07, 42.41, 35.60, 28.31, 27.81, 22.02; ATR FT-IR (cm^{-1}): 3511, 3468, 3321,3125, 3007, 2985, 2870, 1770, 1665, 1410, 1511, 1472, 1301, 1212, 1112, 1007, 965, , 912, 823, 811; ESI-MS m/z: calcd for $C_{14}H_{26}N_2O_3$ $[M+Na]^+$ 270.37, found 270.18.

Synthesis of *tert-butyl (E)-(5-(isopropylamino)-5-oxopent-2-en-1-yl)carbamate (4b)*



Yield 85 %, M.p 118-120 ºC, RP-HPLC R_t = 10.824 min, 95%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.28-7.27 (s, 1H), 7.24-7.21 (s, 1H), 5.99-5.91 (m, 1H), 5.90-5.89 (m, 1H), 4.67 (s, 1H), 4.15-4.14 (d, J = 3.8 Hz, 1H), 4.12-4.10 (d, J = 5.9 Hz, 1H), 3.45-3.40 (d, J = 15 Hz, 1H), 2.70-2.67 (d, J = 12.1 Hz, 2H), 1.80-1.77 (m, 1H), 1.40 (s, 9H), 1.26-1.23 (t, J = 9.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 172.90, 154.39, 126.07, 42.33, 40.17, 40.11, 27.49, 22.8; ATR FT-IR (cm^{-1}): 3347, 3310, 2962, 1745, 1688, 1647, 1529, 1472, 1360, 1270, 1117, 1058, 987, 865; ESI-MS m/z: calcd for $C_{13}H_{24}N_2O_3$ $[M+Na]^+$ 276.34, found 276.11.

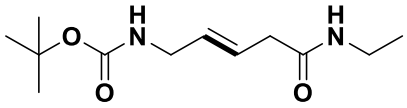
Synthesis of *tert-butyl (E)-(5-(methylamino)-5-oxopent-2-en-1-yl)carbamate (4c)*



Yield 91 %, RP-HPLC R_t = 18.288 min, 90%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 6.56 (b, 1H), 5.99 (b, 1H), 5.68-5.63 (m, 1H), 5.49-5.44 (m, 1H), 5.17 (b, 1H), 3.63 (b, 2H), 2.95 (b,

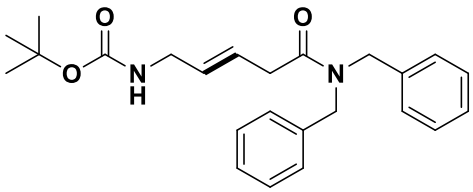
1H), 2.83-2.79 (m, 1H), 2.74-2.68 (d, J = 16.7 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 177.05, 157.30, 133.78, 118.91, 81.55, 42.28, 35.78, 28.29, 26.26; ATR FT-IR (cm^{-1}): 3530, 3461, 2975, 2920, 2855, 1780, 1610, 1587, 1320, 1230, 1120, 980, 830; ESI-MS m/z: calcd for $C_{11}H_{20}N_2O_3$ $[M+Na]^+$ 252.29, found 252.00.

Synthesis of *tert-butyl (E)-(5-(ethylamino)-5-oxopent-2-en-1-yl)carbamate (4d)*



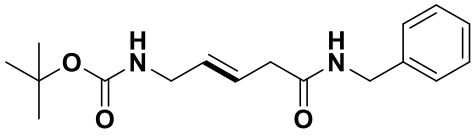
Yield 89 %, RP-HPLC R_t = 14.429 min, 88%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.23 (s, 1H), 7.03-7.01 (m, 1H), 5.87-5.82 (m, 1H), 5.70-5.59 (m, 1H), 4.19-4.10 (q, J = 7.9 Hz, 2H), 3.82-3.70 (d, J = 16 Hz, 2H), 3.09-3.00 (d, J = 12 Hz, 2H), 2.98-2.93 (d, J = 15 Hz, 1H), 1.47 (s, 9H), 1.26-1.21 (d, J = 15 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 172.68, 156.31, 132.55, 122.57, 61.20, 42.21, 39.65, 28.18; ATR FT-IR (cm^{-1}): 3470, 3359, 2982, 2945, 1739, 1721, 1657, 1514, 1463, 1361, 1249, 1128, 1082, 921, 827; ESI-MS m/z: calcd for $C_{12}H_{22}N_2O_3$ $[M+Na]^+$ 263.31, found 263.18.

Synthesis of *tert-butyl (E)-(5-(dibenzylamino)-5-oxopent-2-en-1-yl)carbamate (4e)*



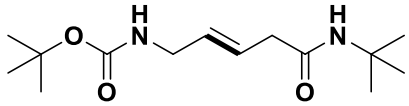
Yield 90 %, M.p 132-134 ºC, RP-HPLC R_t = 21.365 min. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.57 (s, 1H), 7.48-7.30 (m, 1H), 7.14-7.05 (m, 2H), 6.98-6.95 (m, 2H), 6.89-6.81 (s, 2H), 6.68-6.60 (d, J = 14 Hz, 1H), 6.54-6.49 (d, J = 15 Hz, 1H), 5.37-5.31 (m, 2H), 3.93-3.82 (t, J = 12.2 Hz, 1H), 3.78-3.73 (m, 2H), 3.22 (s, 4H), 2.99-2.93 (d, J = 16 Hz, 1H), 2.05-188 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 174.66, 158.30, 137.70, 136.32, 131.17, 129.46, 128.14, 126.30, 118.65, 82.98, 47.35, 45.87, 36.21, 27.8, 26.57, 25.21; ATR FT-IR (cm^{-1}): 3523, 3355, 2925, 2871, 1710, 1675, 1555, 1463, 1341, 1221, 1162, 1117, 932, 812; ESI-MS m/z: calcd for $C_{24}H_{30}N_2O_3$ $[M+H]^+$ 393.51, found 393.09

Synthesis of *tert-butyl (E)-(5-(benzylamino)-5-oxopent-2-en-1-yl)carbamate (4f)*



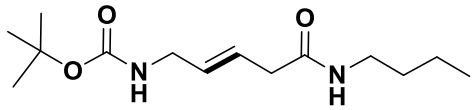
Yield 92 %, M.p 137-138 ºC, RP-HPLC R_t = 18.874 min, 87%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 8.40 (s, 1H), 7.43-7.41 (m, 1H), 7.35-7.32 (m, 2H), 7.29-7.28 (m, 1H), 7.27 (m, 1H), 6.48 (br, 1H), 5.89-5.80 (m, 1H), 5.77-5.67 (m, 1H), 4.43 (br, 1H), 4.41-4.39 (d, J = 6 Hz, 1H), 4.24-4.22 (d, J = 6 Hz, 2H), 3.48-3.45 (t, J = 11.3 Hz, 2H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, SMSO-d_6, ppm): δ_C 176.25, 159.03, 138.58, 131.78, 129.30, 127.83, 117.19, 82.36, 44.79, 42.44, 35.06, 28.52, 25.30; ATR FT-IR (cm^{-1}): 3520, 3312, 2985, 2920, 2871, 1760, 1640, 1518, 1410, 1245, 1172, 1110, 998, 872; ESI-MS m/z: calcd for $C_{17}H_{24}N_2O_3$ $[M+H]^+$ 306.39, found 306.39.

Synthesis of *tert-butyl (E)-(5-(tert-butylamino)-5-oxopent-2-en-1-yl)carbamate (4g)*



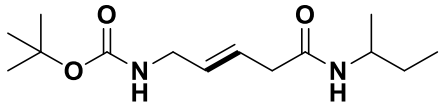
Yield 93 %, M.p 127-129 ºC, RP-HPLC R_t = 18.743 min, 91%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.20 (s, 1H), 6.25-6.18 (m, 1H), 5.98-5.78 (m, 3H), 4.67-4.65 (d, J = 15 Hz, 1H), 4.15-4.12 (br, 3H), 4.09-4.05 (br, 2H), 3.45-3.40 (m, 1H), 1.38 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 172.98, 157.03, 131.78, 117.19, 83.71, 55.94, 41.27, 37.85, 28.56, 27.03; ATR FT-IR (cm^{-1}): 3410, 3362, 2971, 2933, 2862, 1718, 1685, 1518, 1412, 1380, 1255, 1170, 1107, 970, 873; ESI-MS m/z: calcd for $C_{14}H_{26}N_2O_3$ $[M+H]^+$ 271.34, found 271.48.

Synthesis of *tert-butyl (E)-(5-(butylamino)-5-oxopent-2-en-1-yl)carbamate (4h)*



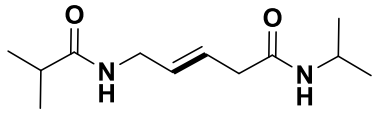
Yield 90 %, M.p 117-119 ºC, RP-HPLC R_t = 10.811 min, 96%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.49 (m, 1H), 7.32-7.28 (m, 1H), 6.32-6.23 (m, 1H), 6.03-6.00 (m, 1H), 5.98-5.86 (m, 1H), 4.58 (br, 1H), 4.24-4.21 (d, J = 9 Hz, 3H), 3.97 (br, 1H), 3.56-3.50 (m, 1H), 3.49-3.47 (d, J = 6 Hz, 1H), 2.87 (m, 1H), 1.68-1.66 (br, 1H), 1.47-1.46 (m, 2H), 1.38 (s, 9H), 1.33-1.29 (m, 3H), 0.95-0.91 (t, J = 12 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 173.39, 158.38, 131.78, 117.19, 82.56, 42.15, 40.87, 37.84, 31.78, 30.56, 28.91, 25.31, 22.02, 18.63; ATR FT-IR (cm^{-1}): 3472, 3355, 2962, 2855, 1781, 1620, 1570, 1411, 1355, 1211, 1178, 954, 812; ESI-MS m/z: calcd for $C_{14}H_{26}N_2O_3$ $[M+H]^+$ 272.37, found 272.32.

Synthesis of *tert-butyl (E)-(5-(sec-butylamino)-5-oxopent-2-en-1-yl)carbamate (4i)*



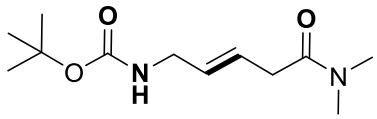
Yield 95 %, M.p 113-115 ºC, RP-HPLC R_t = 18.591 min, 96%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.32-7.30 (m, 1H), 6.30-6.23 (m, 1H), 5.99-5.93 (m, 1H), 5.89-5.81 (m, 1H), 4.56-4.51 (d, J = 15 Hz, 3H), 4.43-4.41 (br, 1H), 4.25-4.22 (d, J = 9 Hz, 1H), 4.08 (br, 1H), 3.51-3.43 (d, J = 12.4 Hz, 1H), 2.19-2.09 (br, 1H), 1.84-1.80 (d, J = 12 Hz, 1H), 1.78-1.63 (br, 1H), 1.47 (s, 2H), 1.44 (s, 9H), 1.31-1.28 (t, J = 9 Hz, 3H), 0.94-0.91 (t, J = 9.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 172.64, 157.30, 131.78, 117.19, 82.56, 47.44, 41.32, 36.82, 32.20, 30.84, 29.85, 28.95, 21.74, 20.35, 18.63; ATR FT-IR (cm^{-1}): 3520, 3431, 3350, 3034, 2987, 2941, 1758, 1712, 1652, 1525, 1410, 1365, 1287, 1178, 1092, 1010, 982, 853, 724; ESI-MS m/z: calcd for $C_{14}H_{26}N_2O_3$ $[M+Na]^+$ 293.37, found 293.14.

Synthesis of *(E)-5-isobutyramido-N-isopropylpent-3-enamide (4j)*



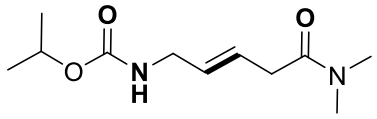
Yield 82 %, M.p 162-164 ºC, RP-HPLC R_t = 21.016 min, 85%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 8.15 (br, 1H), 7.87 (br, 1H), 6.14-6.12 (m, 1H), 5.62-5.55 (m, 1H), 4.43 (br, 1H), 3.99 (br, 1H), 3.86-3.84 (d, J = 6 Hz, 2H), 3.24-3.18 (d, J = 16.2 Hz, 2H), 2.66-2.63 (d, J = 13.2 Hz, 3H), 2.57-2.54 (d, J = 7.4 Hz, 3H), 1.46-1.43 (d, J = 6.7 Hz, 6H), 1.42-1.39 (d, J = 9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 178.10, 168.88, 132.57, 124.36, 45.57, 41.25, 37.85, 34.21, 31.55, 27.63, 22.77; ATR FT-IR (cm^{-1}): 3451, 3293, 1745, 1647, 1634, 1547, 1459, 1240, 1178, 1107, 980, 896; ESI-MS m/z: calcd for $C_{12}H_{22}N_2O_2$ $[M+H]^+$ 226.32, found 225.19.

Synthesis of *tert-butyl (E)-(5-(dimethylamino)-5-oxopent-2-en-1-yl)carbamate (4k)*



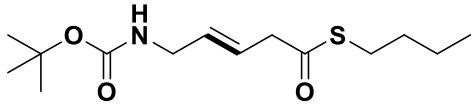
Yield 96 %, RP-HPLC R_t = 23.907 min, 85%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 5.91-5.87 (m, 1H), 5.70-5.61 (m, 1H), 4.34 (br, 1H), 3.65-3.61 (m, 2H), 3.10-3.08 (d, J = 6.5 Hz, 2H), 2.80 (s, 6H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 169.30, 154.57, 132.65, 131.80, 43.91, 38.12, 34.30, 28.63, 24.58; ATR FT-IR (cm^{-1}): 3512, 3418, 1732, 1672,1637, 1587, 1482, 1355, 1271, 1192, 1058, 963, 861; ESI-MS m/z: calcd for $C_{12}H_{22}N_2O_3$ $[M+K]^+$ 280.31, found 280.27.

Synthesis of *isopropyl (E)-(5-(dimethylamino)-5-oxopent-2-en-1-yl)carbamate (4l)*



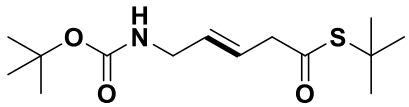
Yield 81 %, M.p 106-111 ºC, RP-HPLC R_t = 23.947 min, 81%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.06 (br, 1H), 5.68-5.53 (m, 3H), 4.81 (br, 1H), 4.10-4.05 (br, 2H), 3.50-3.44 (d, J = 15.4 Hz, 2H), 2.95-2.93 (s, 6H), 2.38 (sep, J = 7.65 Hz, 1H), 1.13-1.06 (d, J = 11.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 178.25, 168.88, 132.54, 128.07, 42.68, 37.21, 34.29, 31.87, 21.86; ATR FT-IR (cm^{-1}): 3425, 3293, 3120, 1723, 1602 1647, 1651, 1547, 1459, 1307, 1234, 1170, 1052, 971, 856; ESI-MS m/z: calcd for $C_{11}H_{20}N_2O_3$ $[M+Na]^+$ 251.19, found 251.25.

Synthesis of *S-butyl (E)-5-((tert-butoxycarbonyl)amino)pent-3-enethioate (4m)*



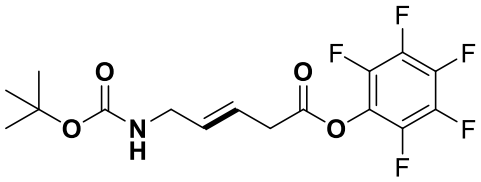
Yield 81 %, RP-HPLC R_t = 12.812 min, 88%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.36-7.30 (d, J = 16.8 Hz, 1H), 6.30-6.23 (m, 1H), 5.99-5.81 (m, 1H), 4.56-4.51 (br, 1H), 4.43-4.24 (br, 1H), 4.22-4.08 (br, 1H), 3.51-3.43 (d, J = 8.9 Hz, 1H), 2.49-2.41 (t, J = 7.4 Hz, 1H), 1.86-1.80 (m, 1H), 1.47 (s, 1H), 1.44 (s, 9H), 1.31-1.28 (m, 2H), 0.94-0.91 (t, J = 9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 182.65, 158.12, 132.64, 125.20, 78.11, 48.25, 41.74, 32.58, 31.55, 25.68; ATR FT-IR (cm^{-1}): 3362, 3051, 2750, 1732, 1628, 1547, 1498, 1370, 1210, 1102, 1087, 987, 887; ESI-MS m/z: calcd for $C_{14}H_{25}NO_3S$ $[M+Na]^+$ 310.55, found 310.16.

Synthesis of *S-(tert-butyl) (E)-5-((tert-butoxycarbonyl)amino)pent-3-enethioate (4n)*



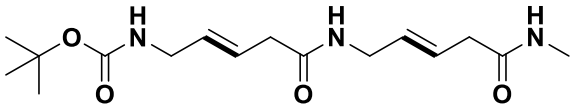
Yield 81 %. M.p 127-129 ºC, RP-HPLC R_t = 24.501 min 82%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.17-7.11 (m, 1H), 6.18-6.11 (m, 1H), 5.89-5.72 (m, 1H), 4.47 (b, 1H), 4.10-4.05 (d, J = 15 Hz, 2H), 3.66-3.60 (d, J = 14.9 Hz, 2H), 3.21 (m, 1H), 1.32 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 179.8, 157.32, 132.70, 127.16, 82.56, 47.64, 45.52, 32.18, 30.15, 28.68; ATR FT-IR (cm^{-1}): 3452, 3025, 2847, 2214, 1740, 1715, 1635, 1689, 1570, 1515, 1420, 1354, 1228, 1140, 1090, 973, 810; ESI-MS m/z: calcd for $C_{14}H_{25}NO_3S$ $[M+H]^+$ 288.41, found 288.72.

Synthesis of *perfluorophenyl (E)-5-((tert-butoxycarbonyl)amino)pent-3-enoate (4o)*



Yield 76 %. M.p 157-160 °C, RP-HPLC R_t = 12.510 min, 84%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ_H 7.20 (s, 1H), 5.95-5.87 (m, 1H), 5.83-5.77 (m, 1H), 4.49 (br, 1H), 4.16-4.12 (d, J = 12 Hz, 1H), 4.10 (br, 1H), 3.43-3.38 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ_C 171.34, 155.21, 153.87, 153.98, 153.21, 151.25, 140.30, 123.58, 122.71, 82.74, 42.57, 36.81, 9.64; ATR FT-IR (cm^{-1}): 3478, 3302, 3251, 2978, 1712, 1670, 1612, 1598, 1420, 1463, 1302, 1271, 1011, 945, 880; ESI-MS m/z: calcd for $C_{16}H_{16}F_5NO_4$ $[M+H]^+$ 381.18, found 381.22.

Synthesis of *tert-butyl ((E)-5-(((E)-5-(methylamino)-5-oxopent-2-en-1-yl)amino)-5-oxopent-2-en-1-yl)carbamate (5)*



Yield 88%, M.p 173-178 °C, R_t = 31.621 min, 92%. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ_H 8.03(br, 1H), 7.00-6.93 (d, J = 2.8 Hz, 1H), 6.80-6.78 (d, J = 3.2 Hz,1H), 5.8-5.5 (m, 4H), 4.71-4.64 (b, 2H), 3.57 (d, J = 3.5 Hz, 2H), 3.10-3.07 (m, 1H) 3.02-3.0 (s, 3H), 2.87-2.86 (d, J = 2.8 Hz, 1H), 2.66-2.60 (m, 1H), 2.57-2.54 (d, 1H), 2.35-2.33 (d, J = 3.0 Hz, 2H), 1.43 ppm (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ_C 173.53, 171.02, 155.93, 145.95, 130.67, 130.57, 125.28, 124.25, 78.06, 41.82, 40.50, 37.96, 32.43, 29.45, 28.69, 25.96. ATR FT-IR (cm^{-1}): 3243, 3046, 2501, 1738, 1615, 1470, 1449, 1393, 1357, 1285, 1222, 1157, 1108, 998, 985; ESI-MS m/z: calcd for $C_{16}H_{27}N_3O_4$ $[M+H]^+$ 325.40, found 325.20

6. Purification procedure – Column chromatography, RP-HPLC & Flash chromatography details

Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (0.25 mm, 60 Å pore-size) impregnated with a fluorescent indicator. Visualization on TLC was achieved by the use of UV light (220 nm), treatment with 10% ninhydrin in ethanol, or staining with iodine. Each derivative was purified by column chromatography using silica gel (60-120, 100-200, 240-400 mesh) as the stationary phase and

an ethyl acetate and petroleum ether mixture as the eluent. Peptides were purified via flash chromatography using a Buchi Pure C-815 instrument with a UV/ELSD detector, UV-Vis/UV scanning, and a prepacked column with various solvent systems. The purities of the peptides were confirmed by analytical reversed-phase HPLC on a High-Pressure Liquid Chromatography is used to identify the formation of the product and the purity of the compound. A High-Performance Liquid Chromatography system equipped with gradient elution capability, a UV/PDA detector, and a data handling system (Agilent 1220 Infinity LC) was employed. A stainless-steel column of length 150 mm and internal diameter 4.6 mm, with particles of 5 µ diameter (Zorbax SB-C18 (150 x 4.6) mm, 5 µ), was used. The data handling system utilized the ChemStation chromatographic software. The program was run for 35 and 60 min with a flow rate of 1 mL/min, and an injection volume of 25 µL was programmed in the RP-HPLC for the sample analysis. The solvent system used was A (water) and B (acetonitrile) with a gradient of acetonitrile and water using i) 95-5%, where buffer A was 0.1% TFA in H_2O and buffer B was 0.1% TFA in CH_3CN, ii) A = 9:1 H_2O/CH_3CN, 0.05% TFA; B = 1:9 H_2O/CH_3CN, 0.05% TFA, and detection at 220 nm. Examining standard HPLC chromatograms reveals that the peptide purity was greater than 90%. The peptide yield was calculated as the ratio between the obtained weight (mg) and the theoretical weight multiplied by the purity (% area) of the main peak. Each compound was characterized by mass spectrometry (LCQ Thermoquest-Ion Trap), and the data were consistent with the considered structures.

7. **Analytical spectral data of** *trans*-δ-Apa **amino acid, protected** *trans*-δ-Apa **amino acid derivatives and** *t*Boc-(*trans*-δ-Apa)$_2$-NHMe **dipeptide**

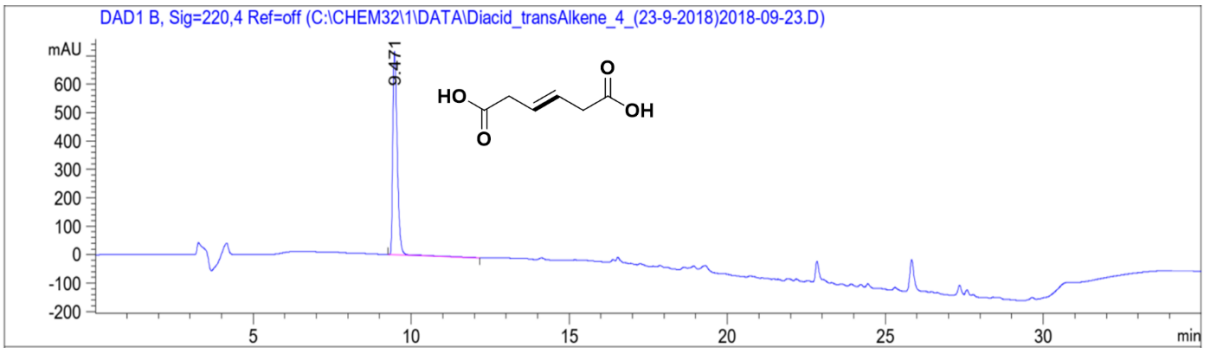


Figure S1: RP-HPLC Chromatogram of HO-*trans*-δ-Apa-OH

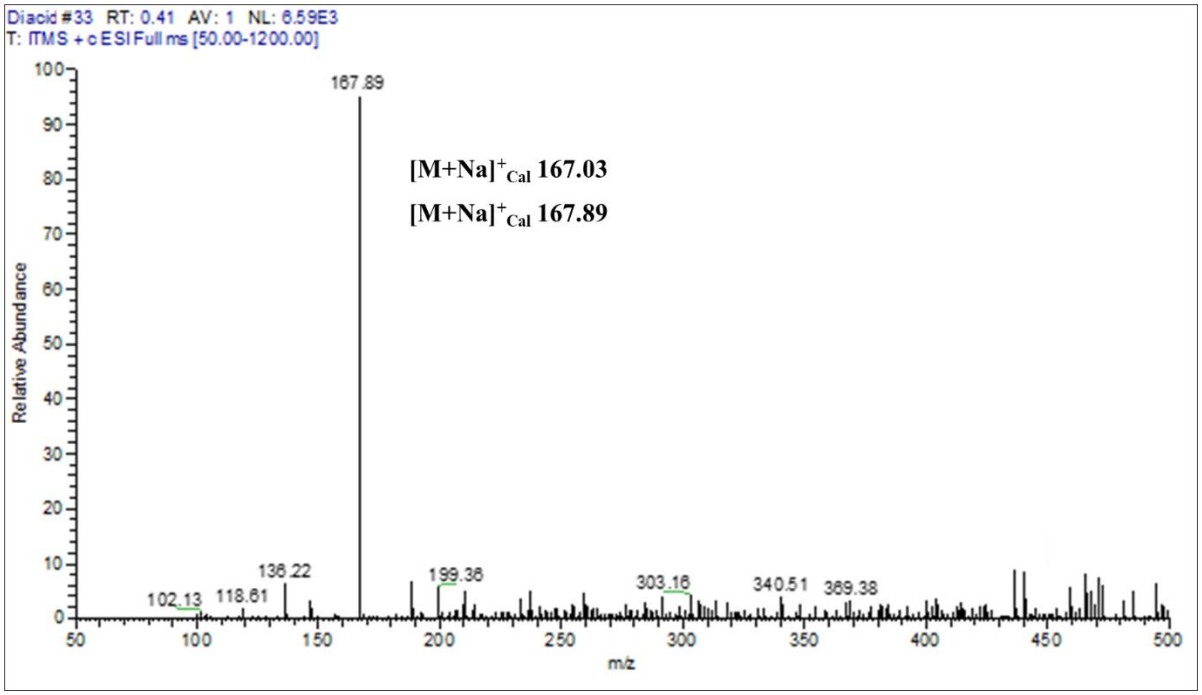


Figure S2: ESI-MS spectrum of HO-*trans*-δ-Apa-OH

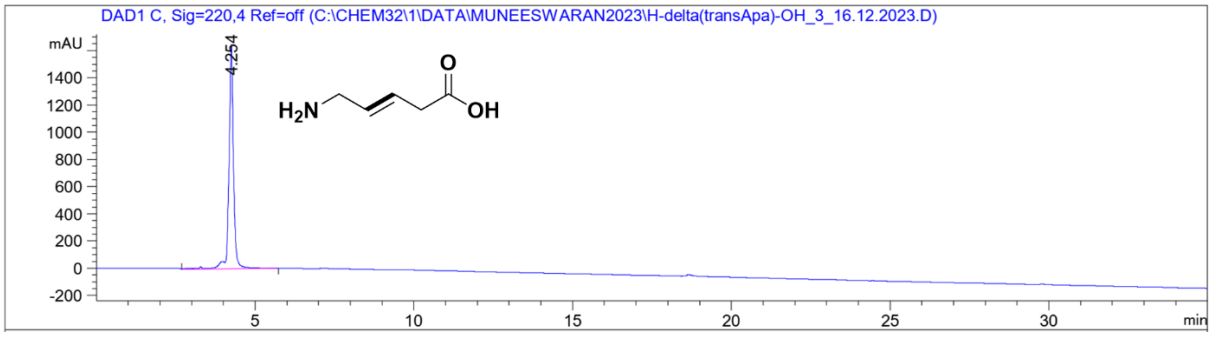


Figure S3: RP-HPLC Chromatogram of H-*trans*-δ-Apa-OH

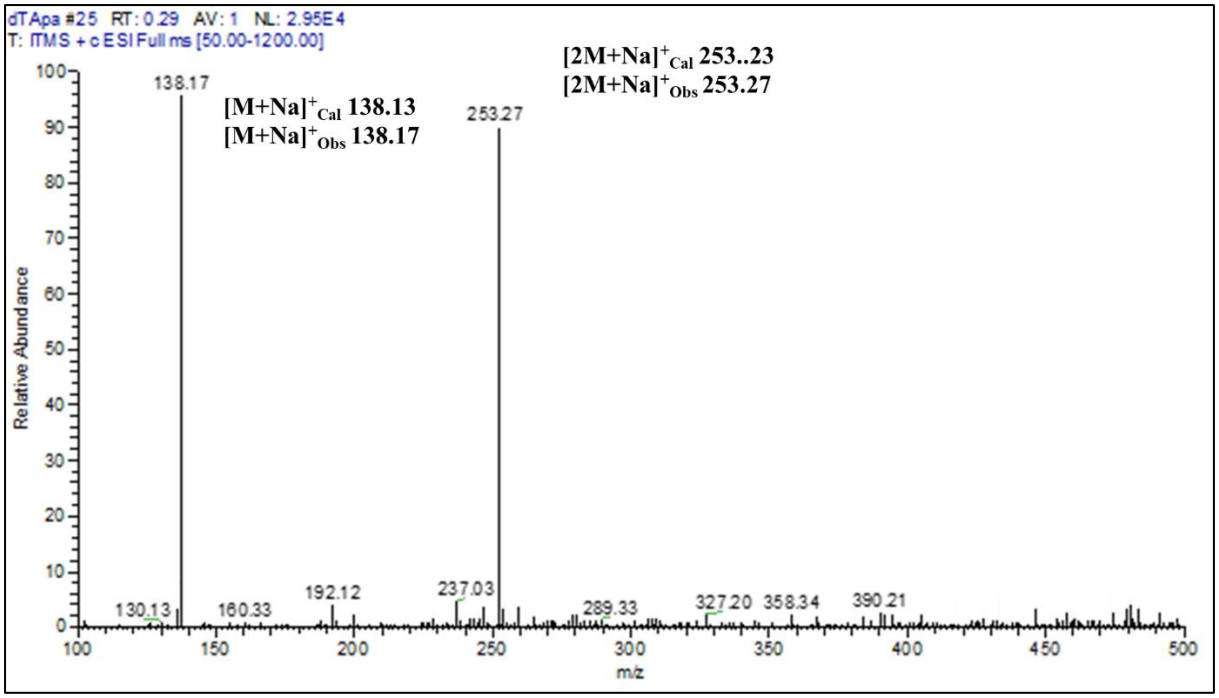


Figure S4: ESI-MS spectrum of H-*trans*-δ-Apa-OH

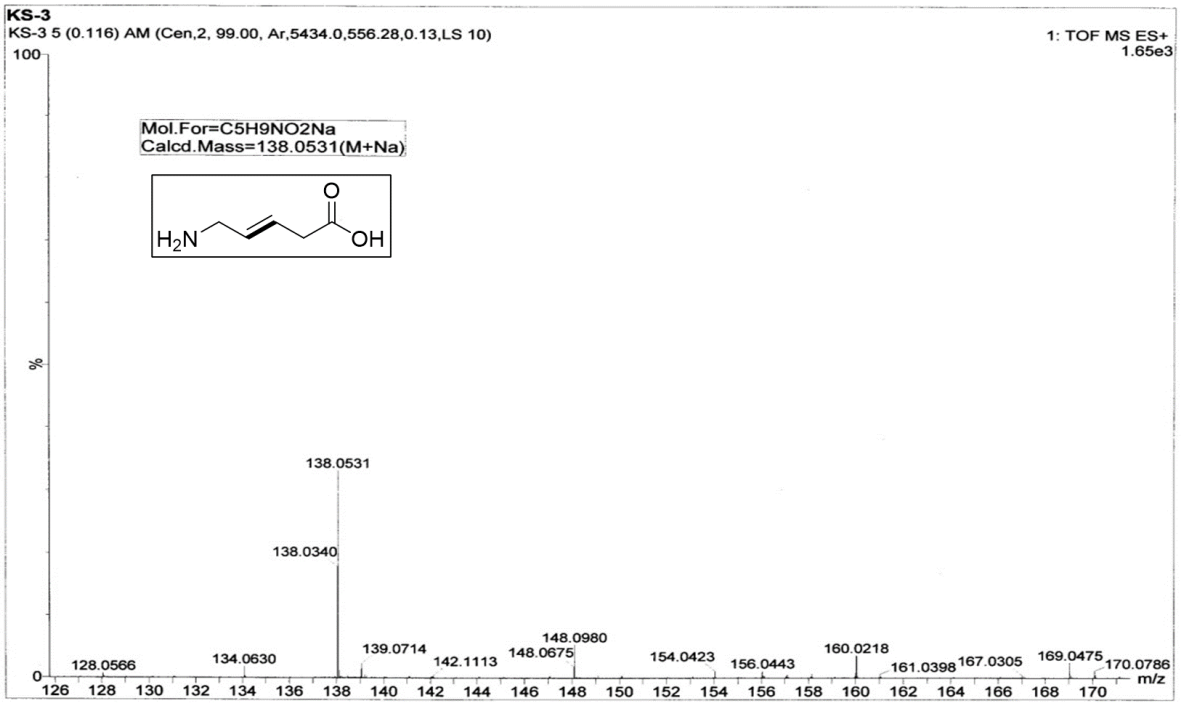


Figure S5: HRMS spectrum of H-*trans*-δ-Apa-OH

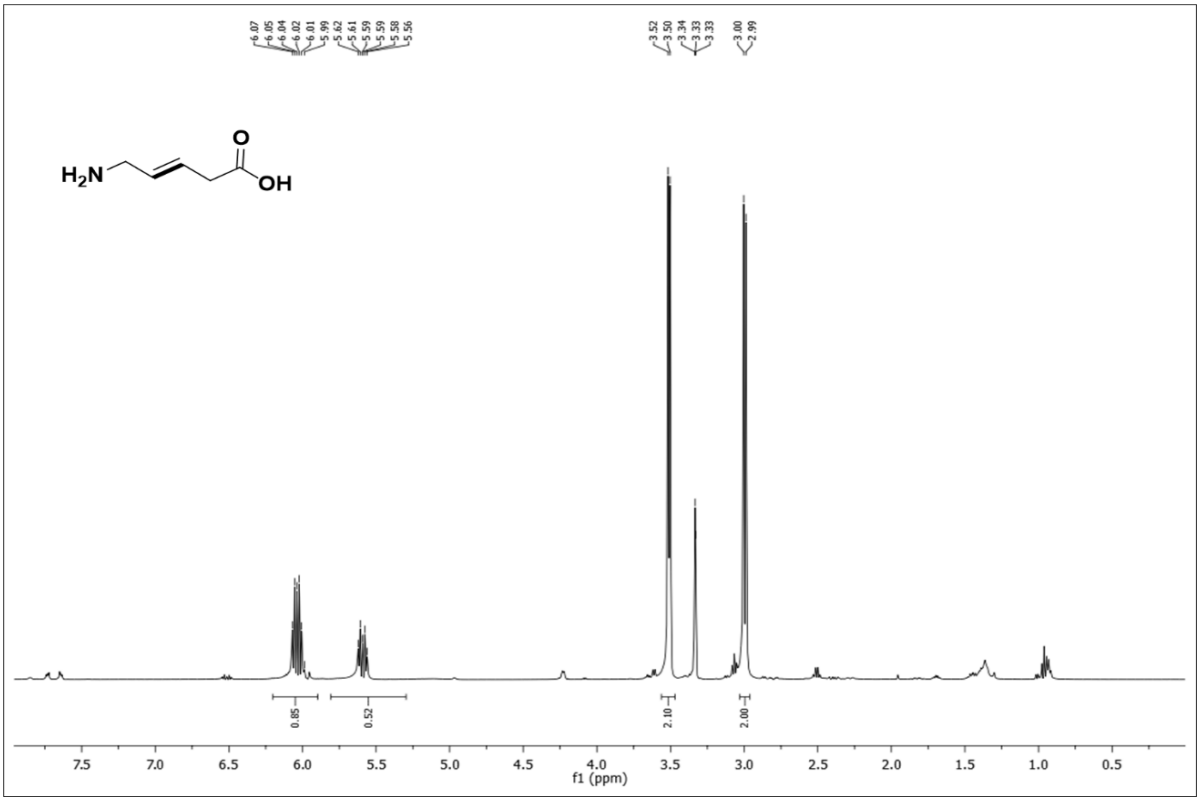


Figure S6: 400 MHz ^{1}H-NMR spectrum of H-*trans*-δ-Apa-OH in CD_3OD

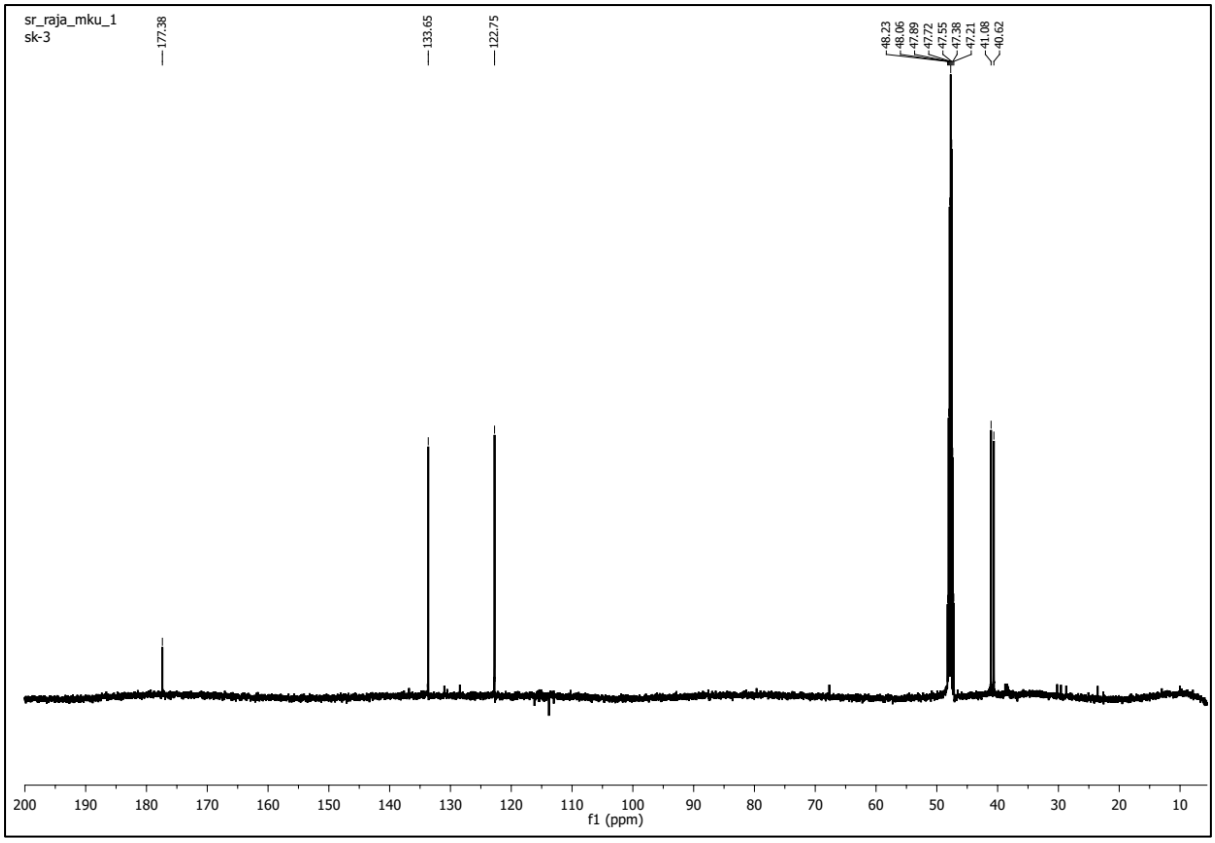


Figure S7: 100 MHz ^{13}C-NMR spectrum of H-*trans*-δ-Apa-OH in CD_3OD

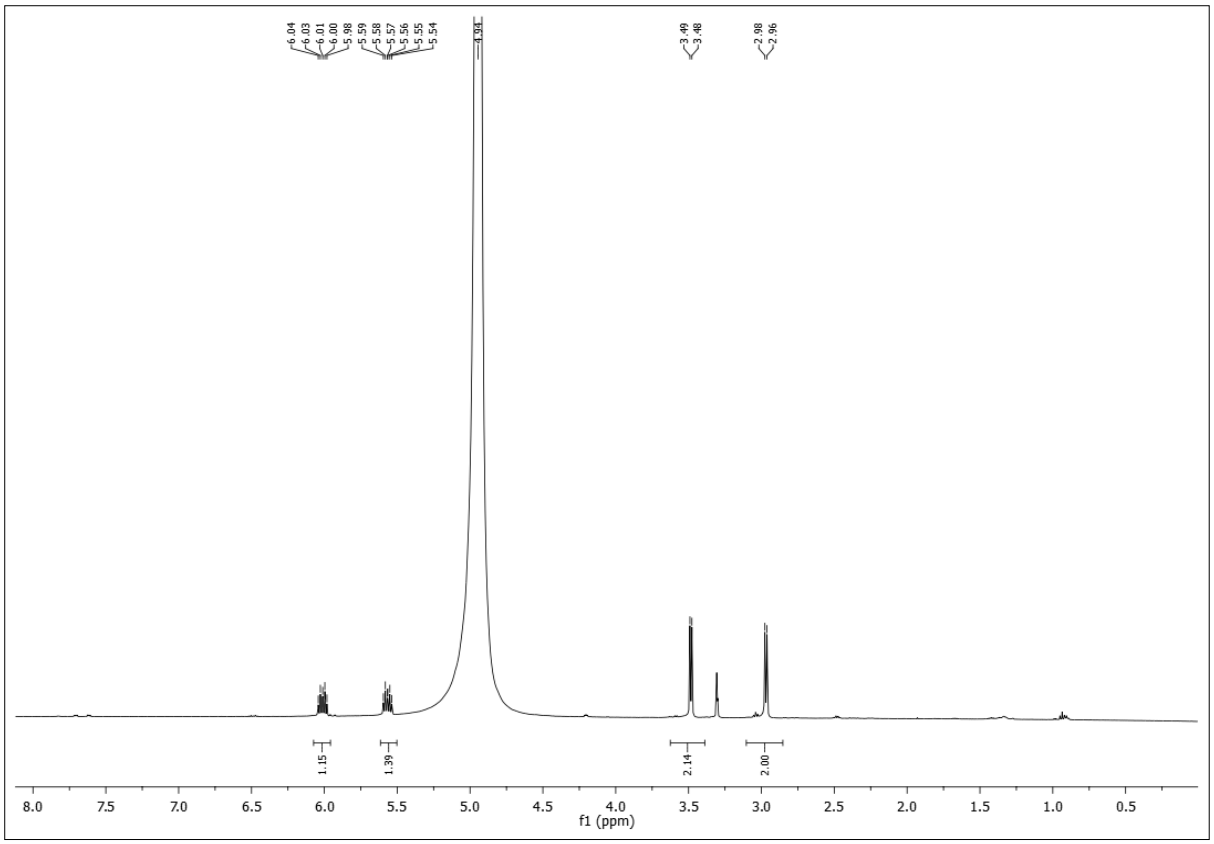


Figure S8: 400 MHz ^{1}H-NMR spectrum of H-*trans*-δ-Apa-OH in D_2O

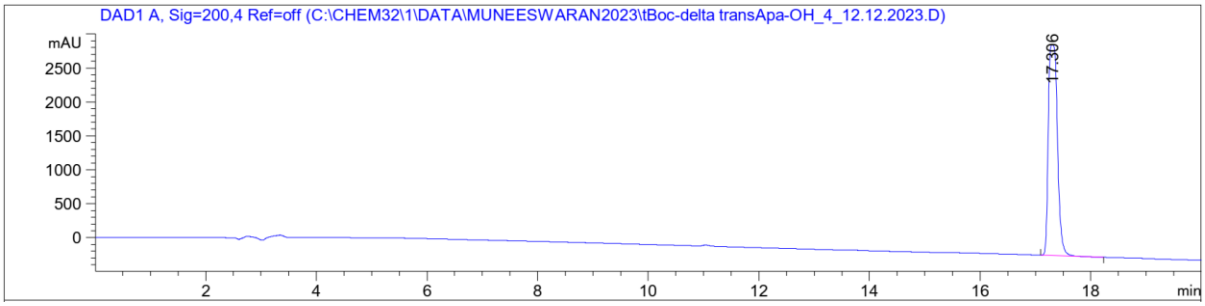


Figure S9: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-OH

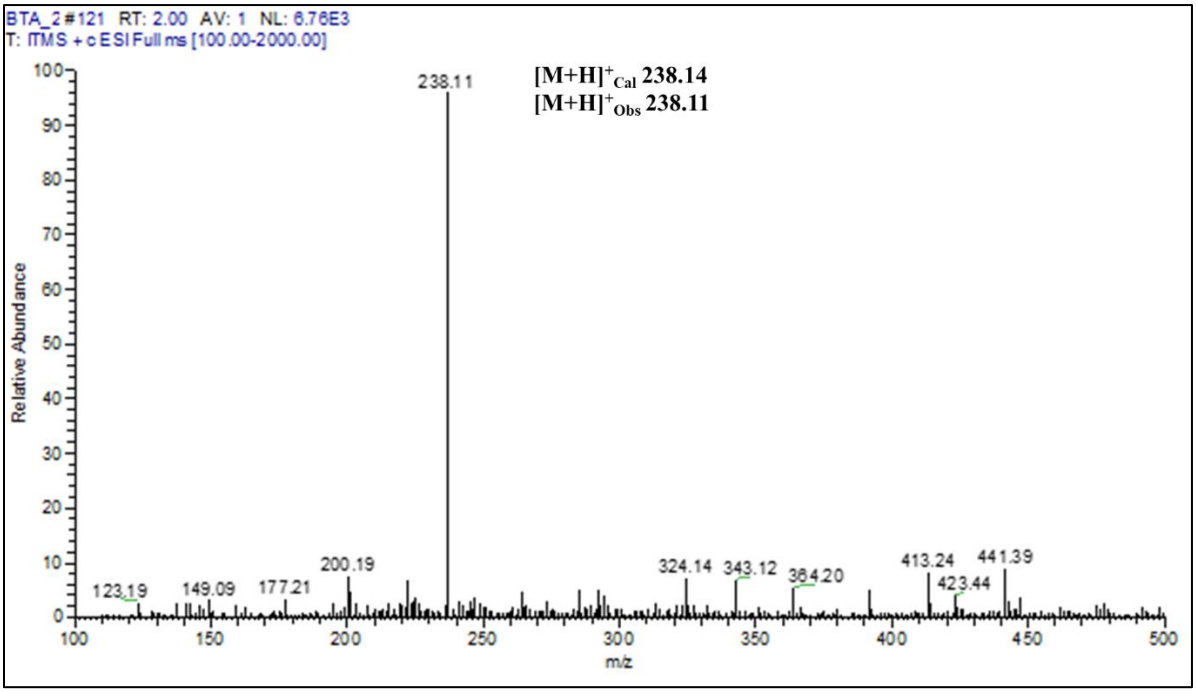


Figure S10: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-OH

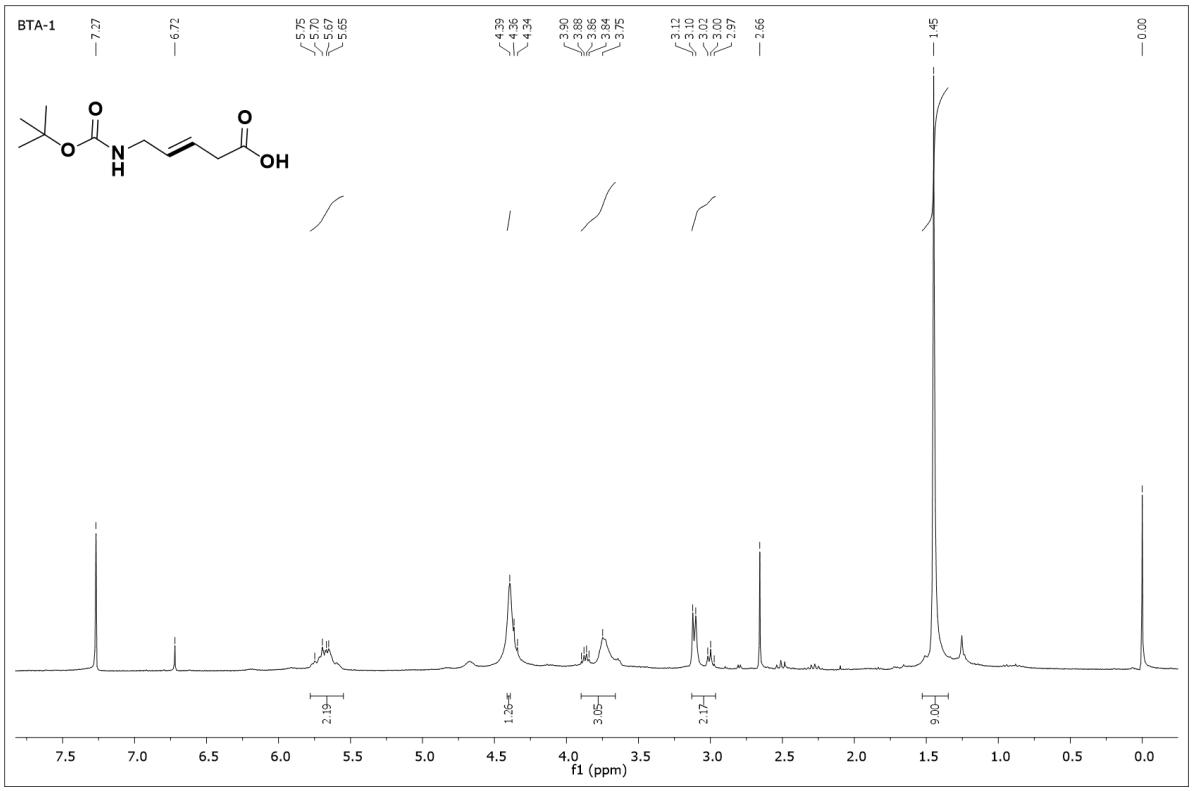


Figure S11: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-OH in $CDCl_3$

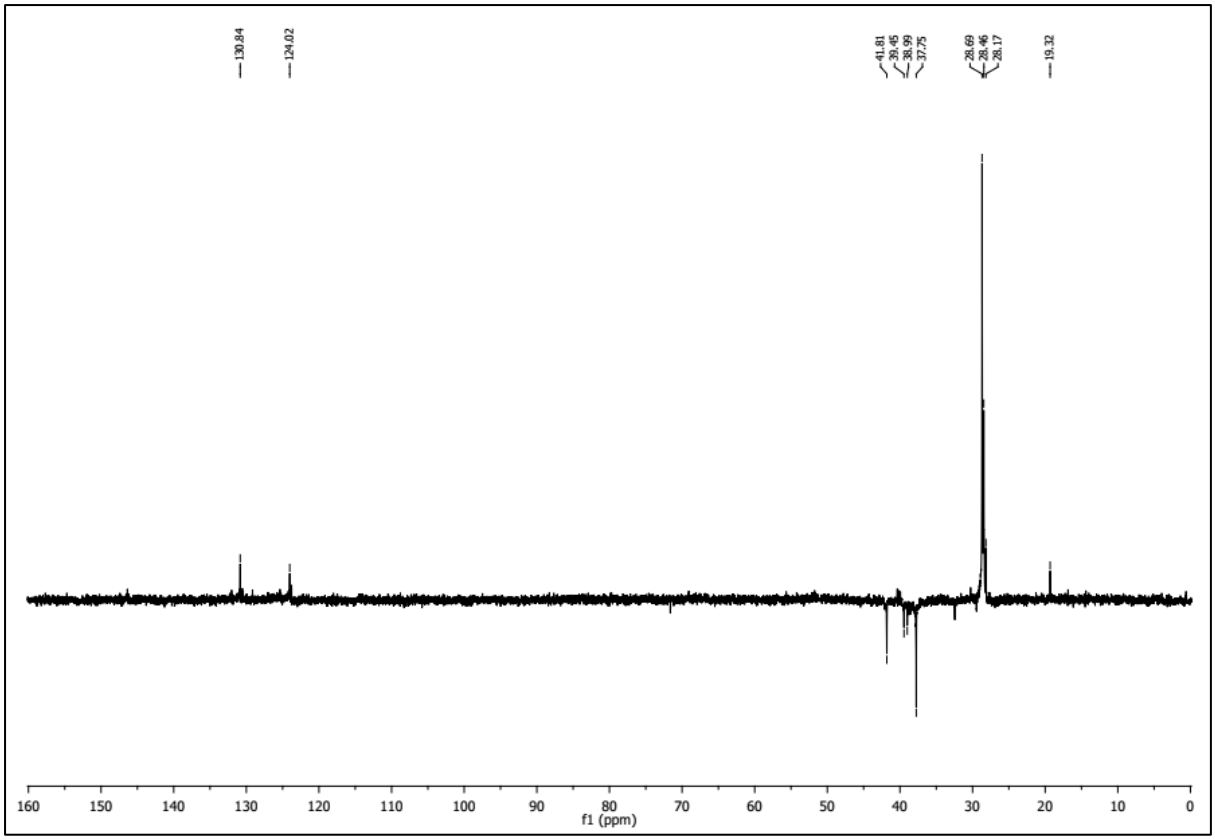


Figure S12: 300 MHz DEPT135-NMR spectrum of *t*Boc-*trans*-δ-Apa-OH in $CDCl_3$

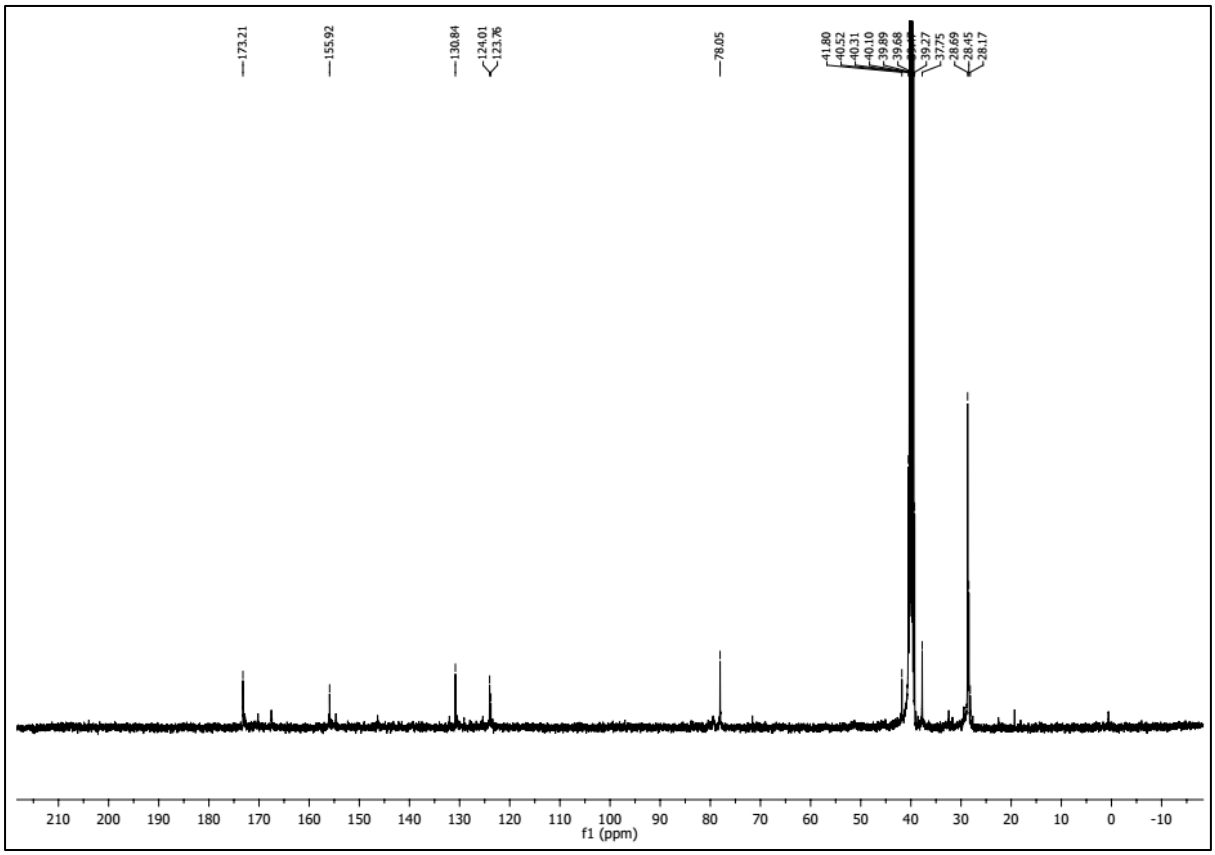


Figure S13: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-OH in DMSO-d_6

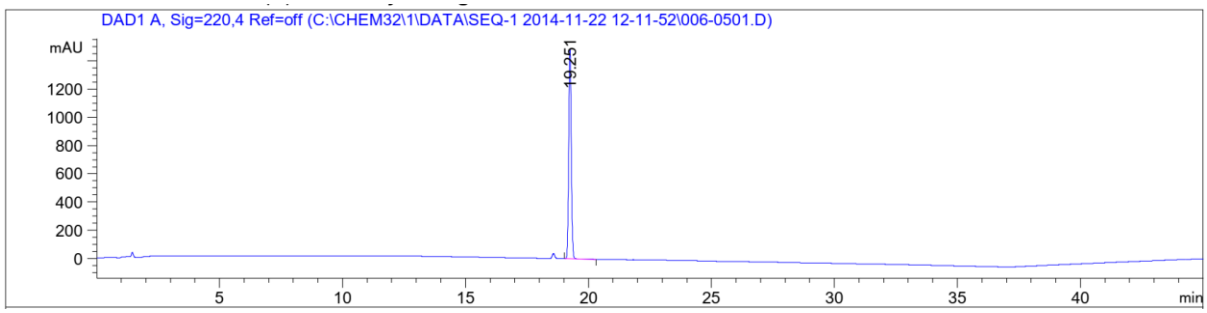


Figure S14: RP-HPLC Chromatogram of Pivaloyl-*trans*-δ-Apa-OH

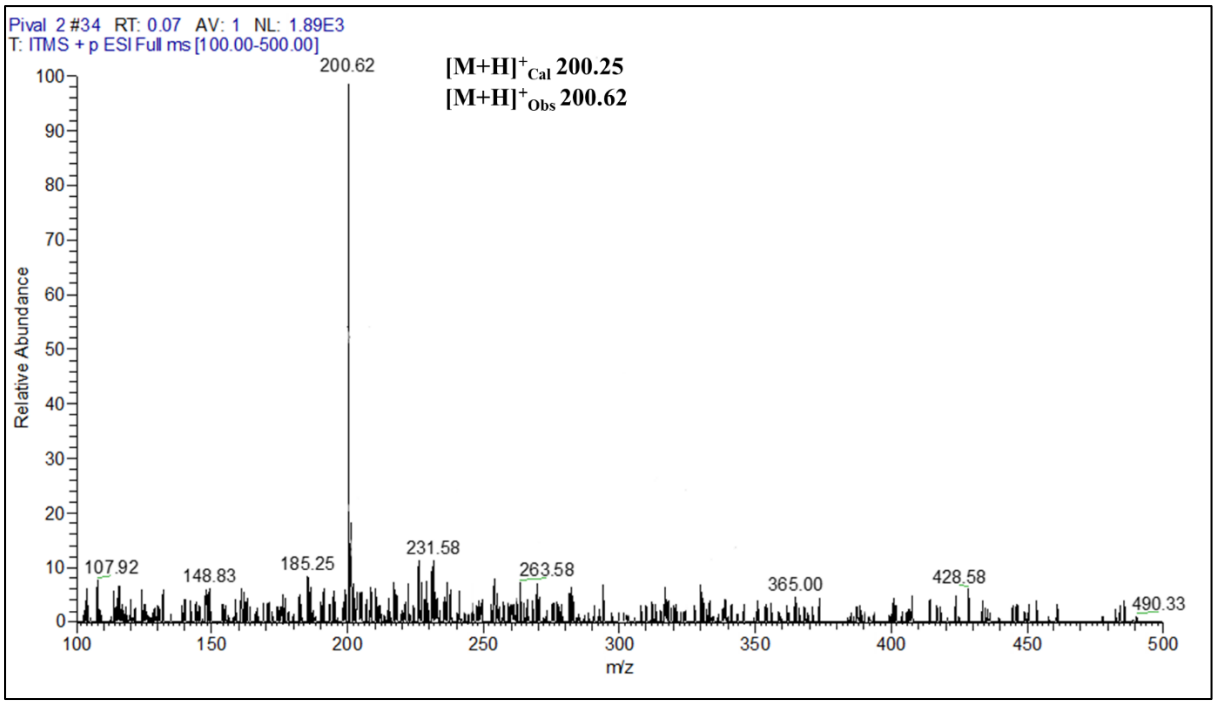


Figure S15: ESI-MS spectrum of Pivaloyl-*trans*-δ-Apa-OH

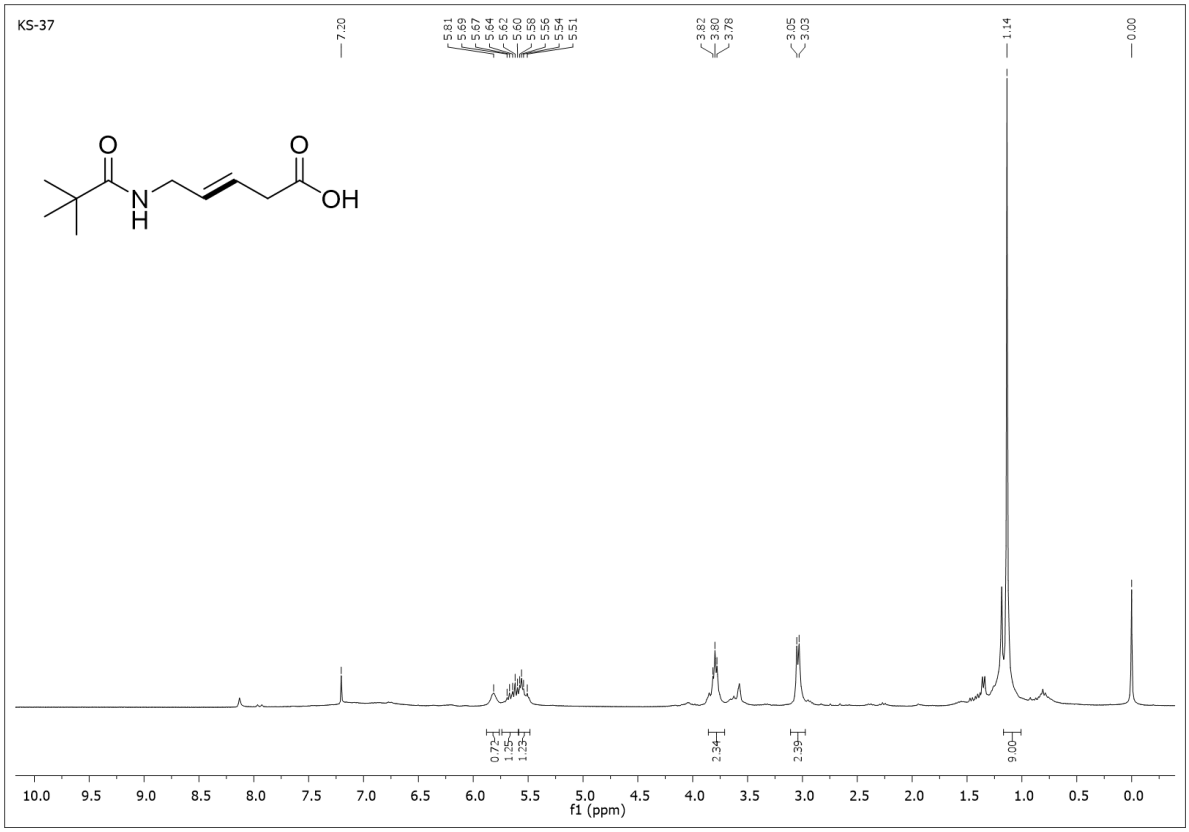


Figure S16: 300 MHz ^{1}H-NMR spectrum of Pivaloyl-*trans*-δ-Apa-OH in $CDCl_3$

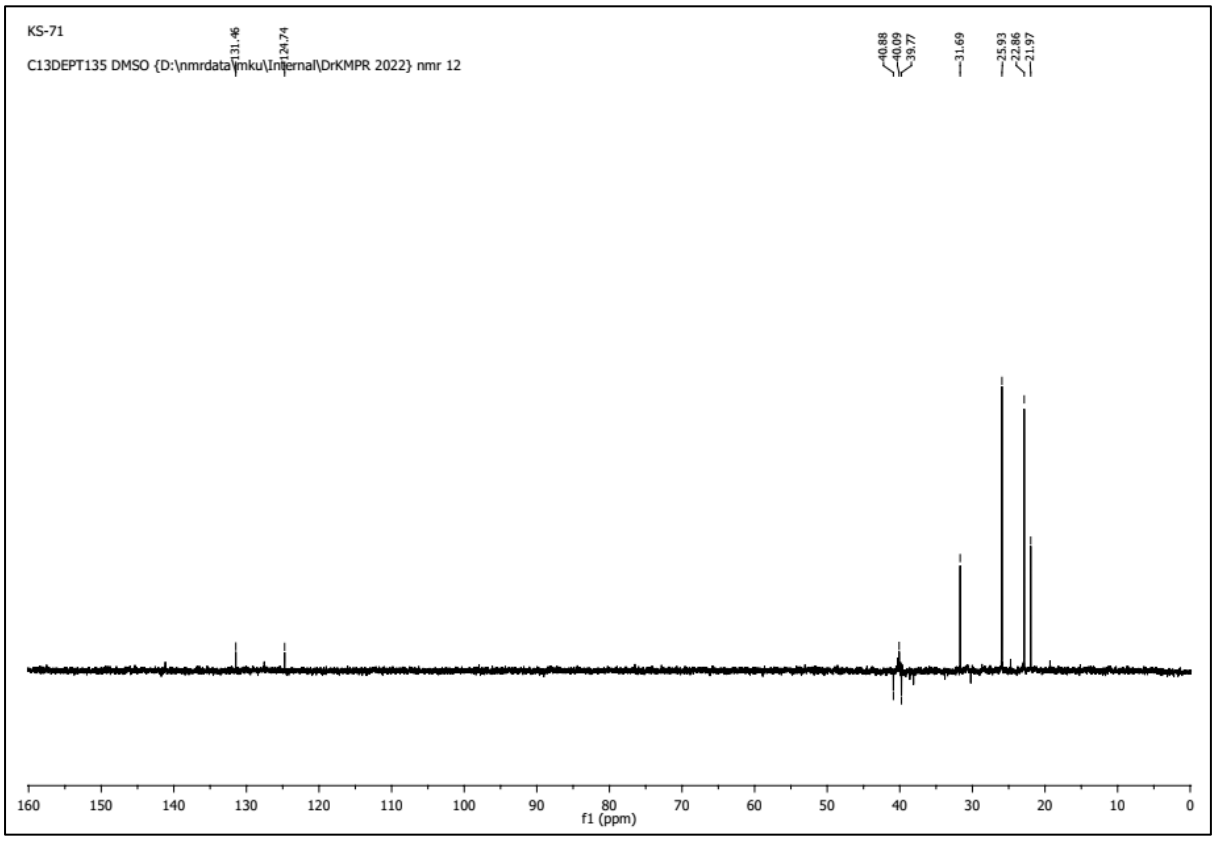


Figure S17: 300 MHz DEPT-135-NMR spectrums of Pivaloyl-*trans*-δ-Apa-OH in $CDCl_3$

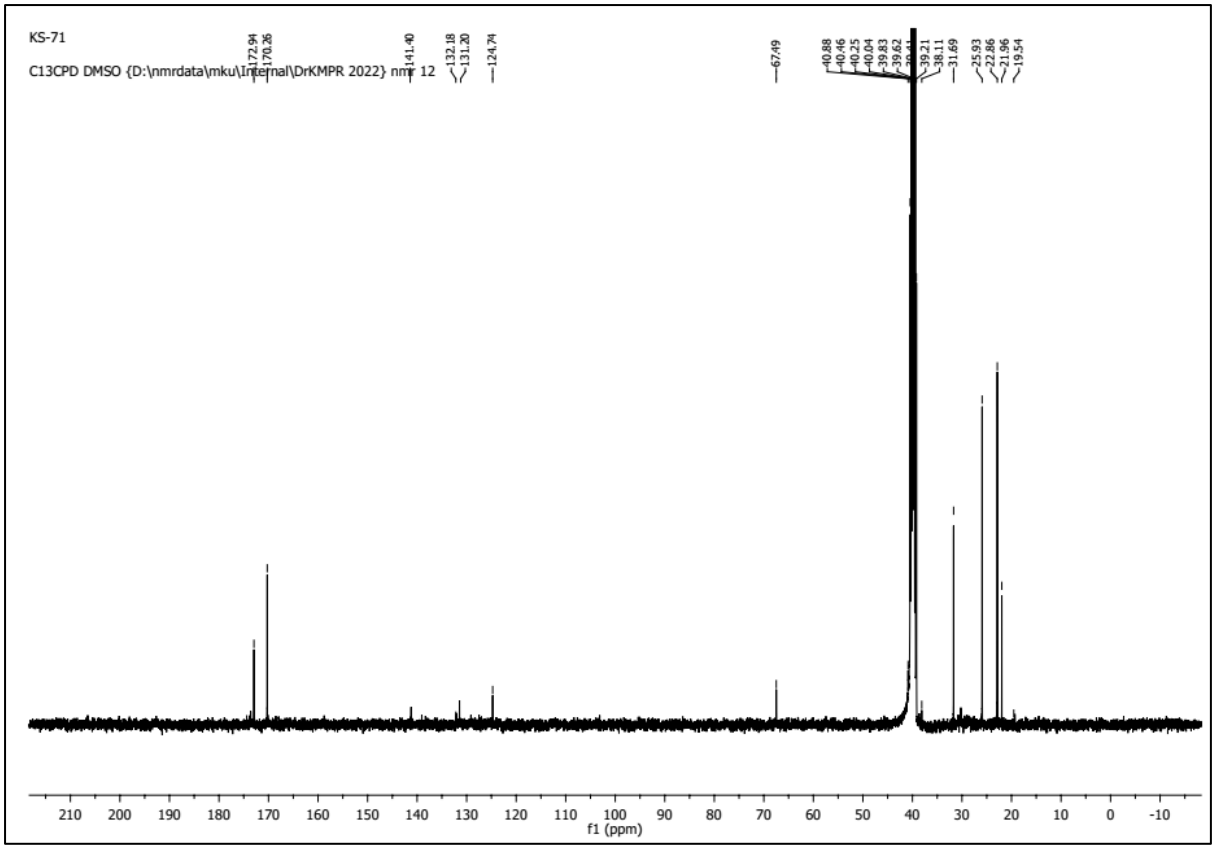


Figure S18: 75 MHz ^{13}C-NMR spectrum of Pivaloyl-*trans*-δ-Apa-OH in DMSO-d_6

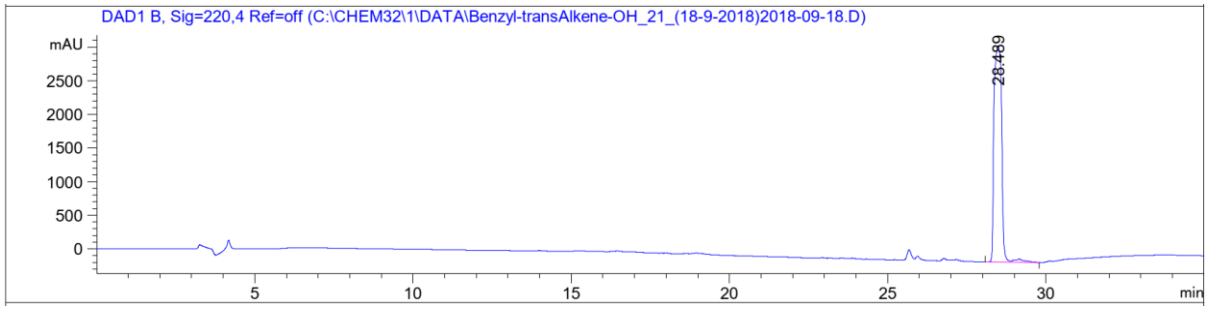


Figure S19: RP-HPLC Chromatogram of Cbz-*trans*-δ-Apa-OH

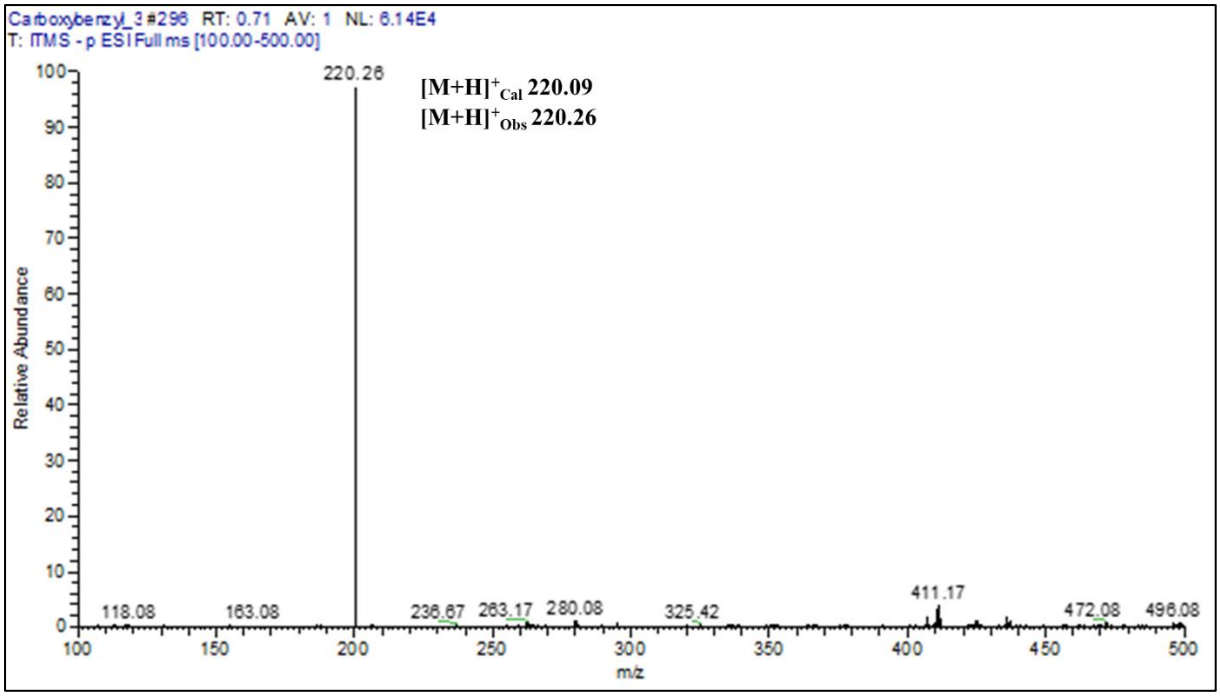


Figure S20: ESI-MS spectrum of Cbz-*trans*-δ-Apa-OH

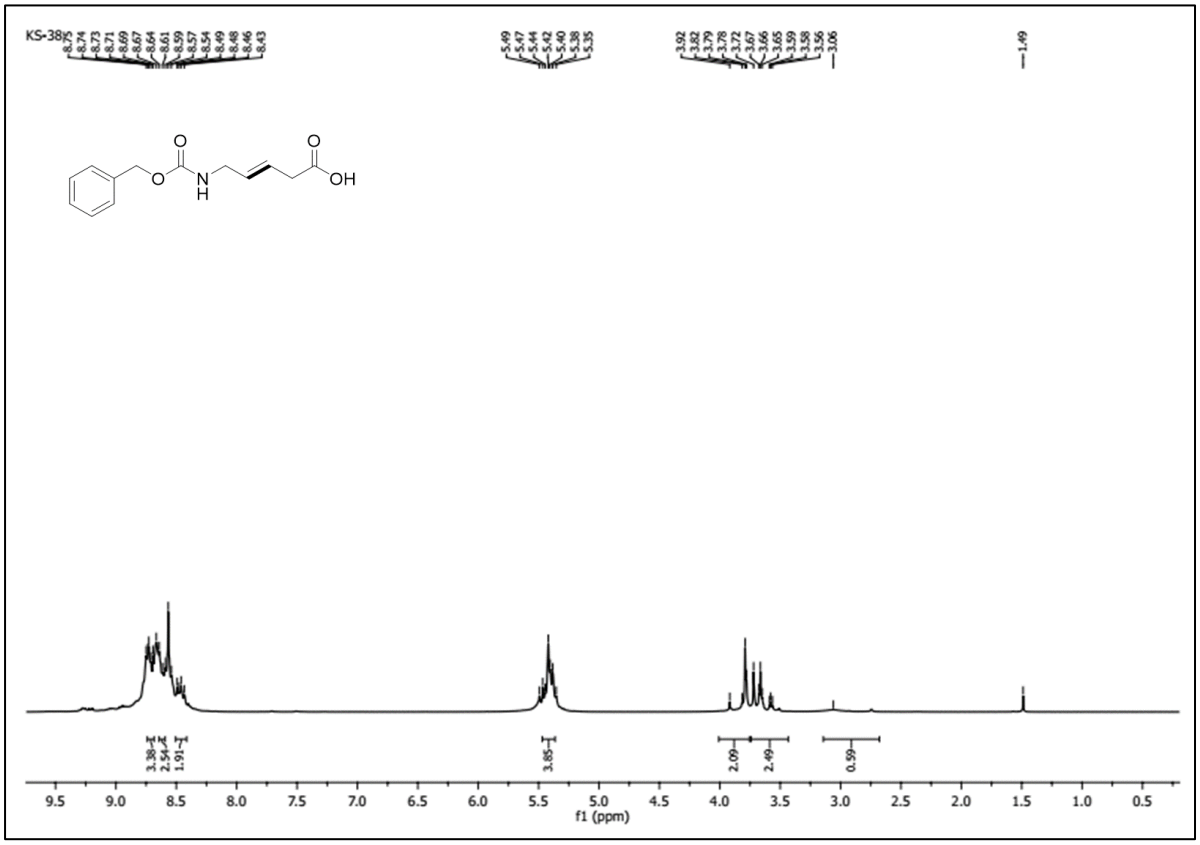


Figure S21: 300 MHz ^{1}H-NMR spectrum of Cbz-*trans*-δ-Apa-OH in $CDCl_3$

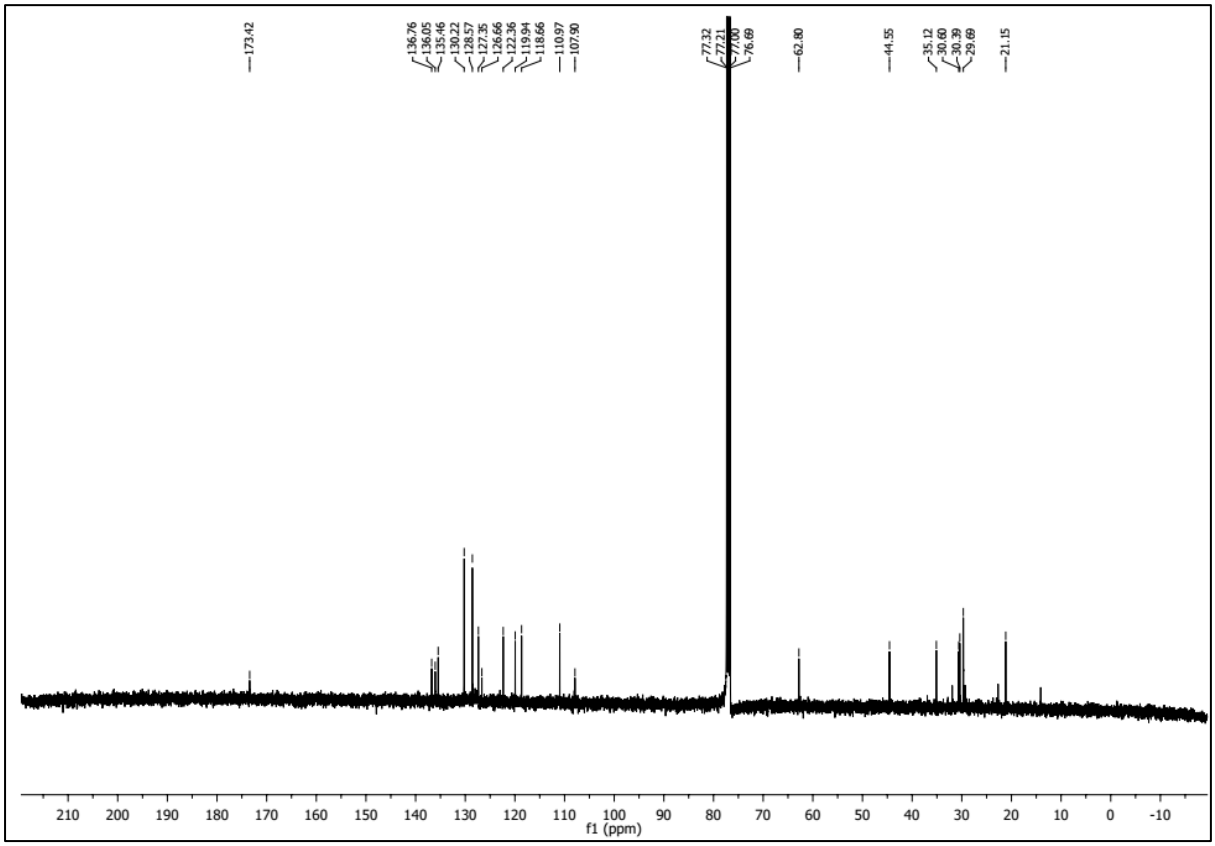


Figure S22: 75 MHz ^{13}C-NMR spectrum of Cbz-*trans*-δ-Apa-OH in $CDCl_3$

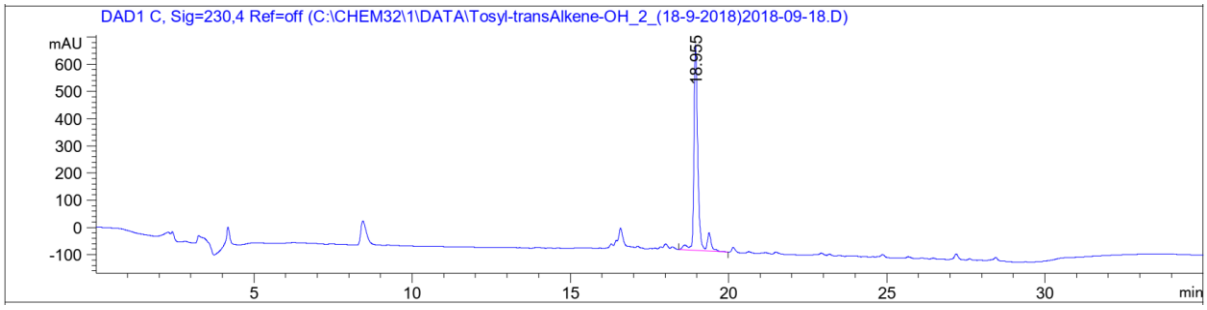


Figure S23: RP-HPLC Chromatogram of Tosyl-*trans*-δ-Apa-OH

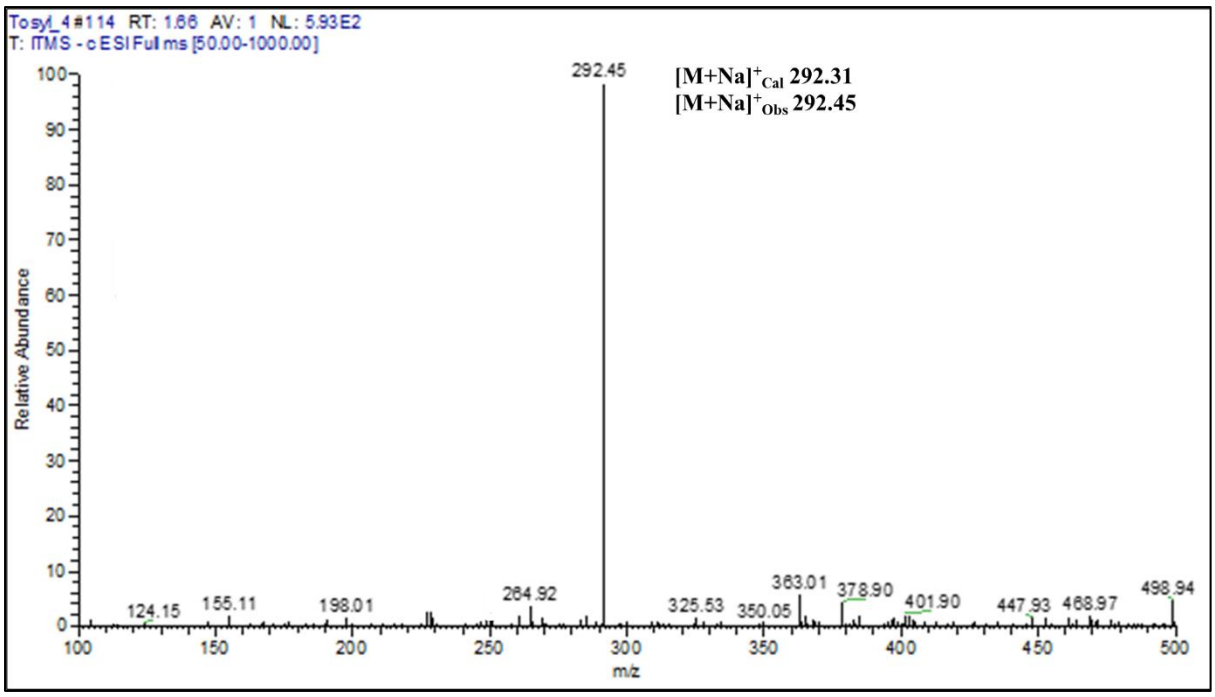


Figure S24: ESI-MS spectrum of Tosyl-*trans*-δ-Apa-OH

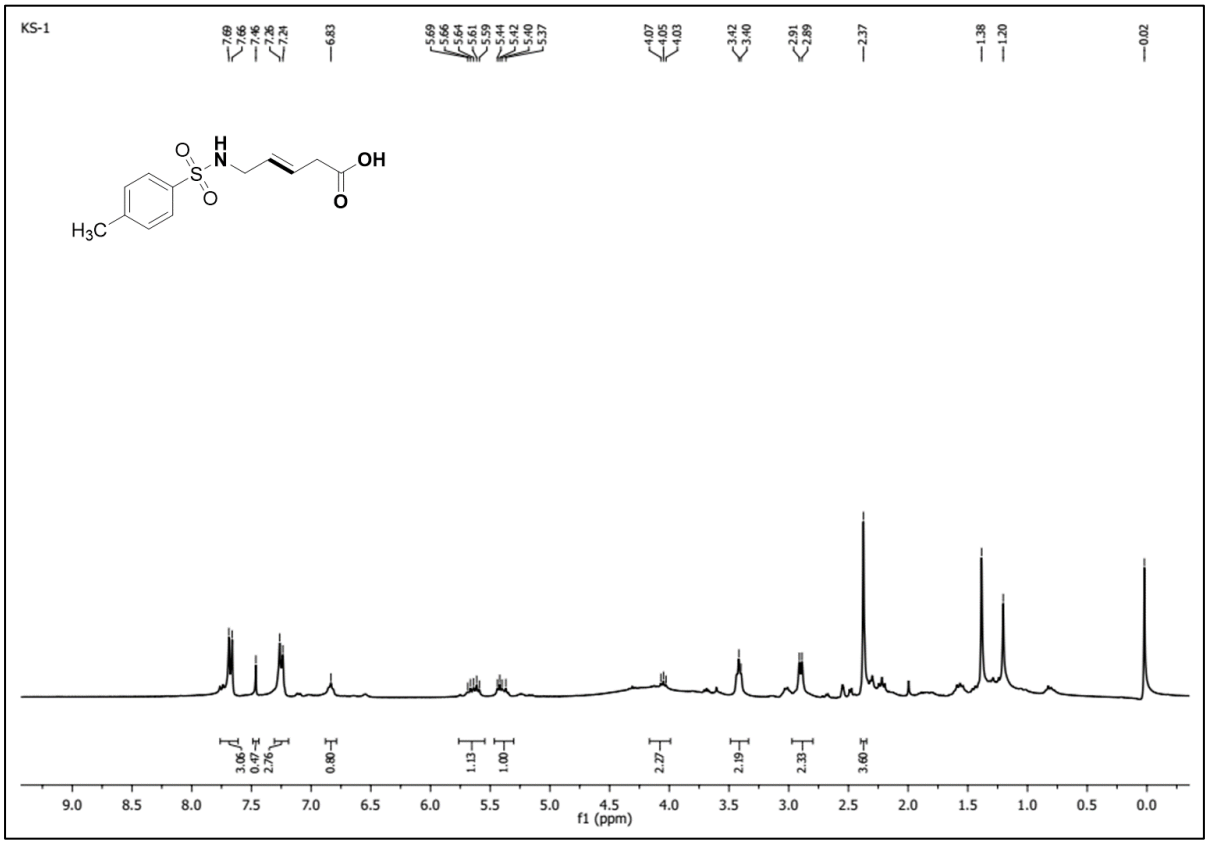


Figure S25: 300 MHz ^{1}H-NMR spectrum of Tosyl-*trans*-δ-Apa-OH in $CDCl_3$

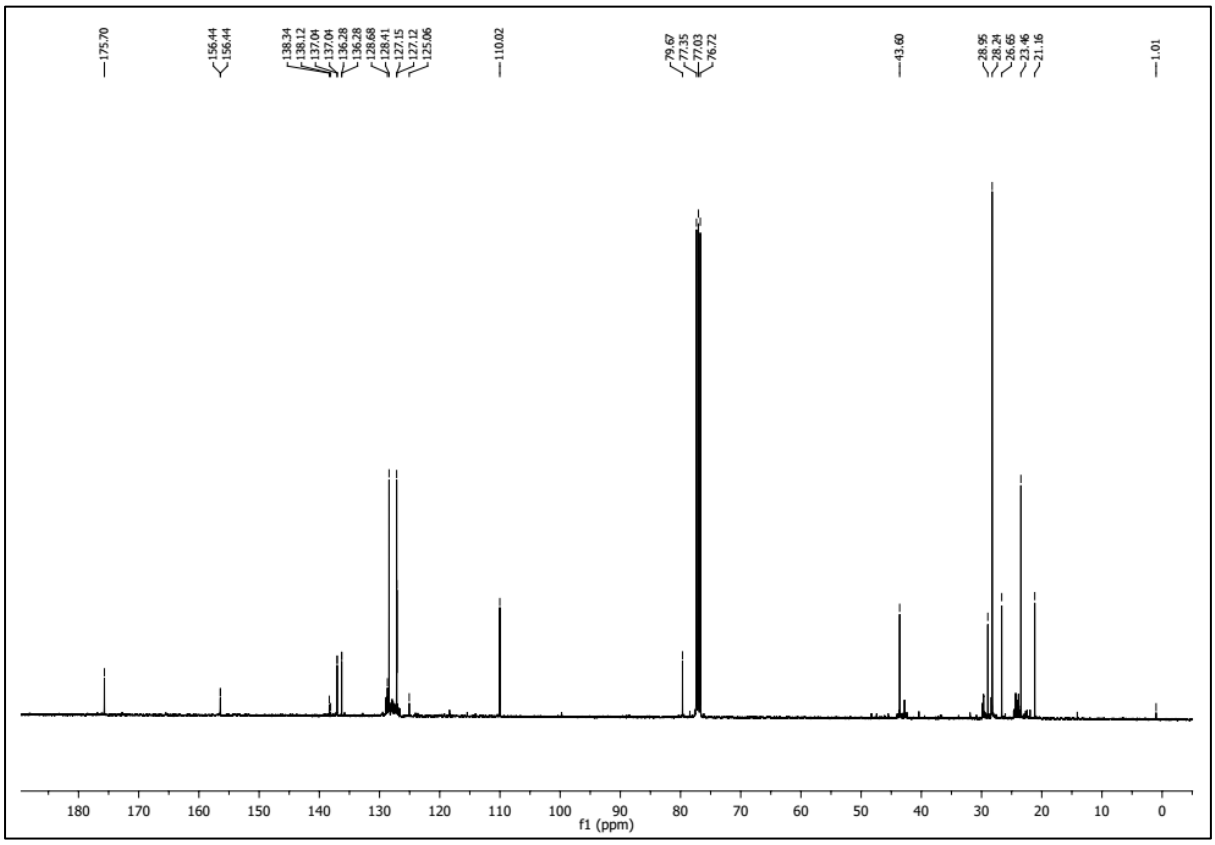


Figure S26: 75 MHz ^{13}C-NMR spectrum of Tosyl-*trans*-δ-Apa-OH in $CDCl_3$

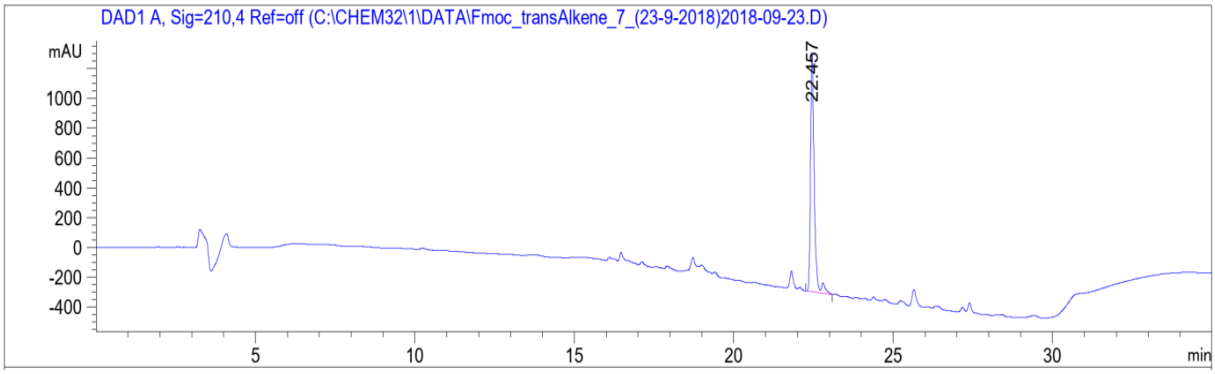


Figure S27: RP-HPLC Chromatogram of Fmoc-*trans*-δ-Apa-OH

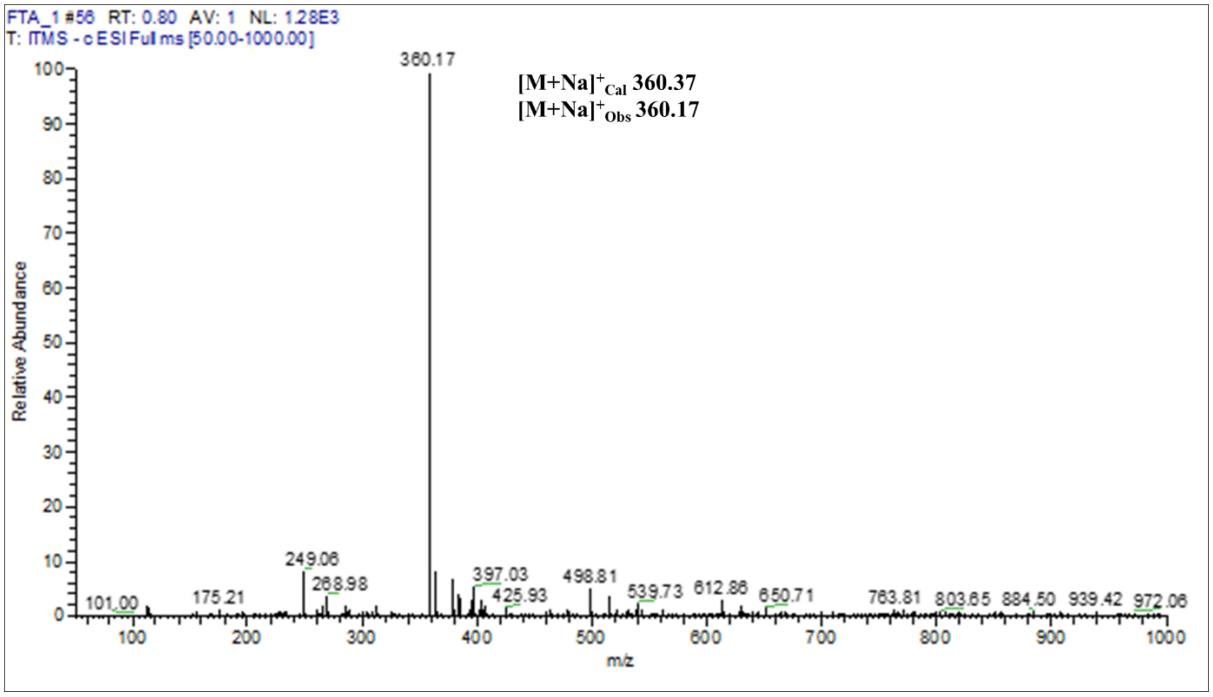


Figure S28: ESI-MS spectrum of Fmoc-*trans*-δ-Apa-OH

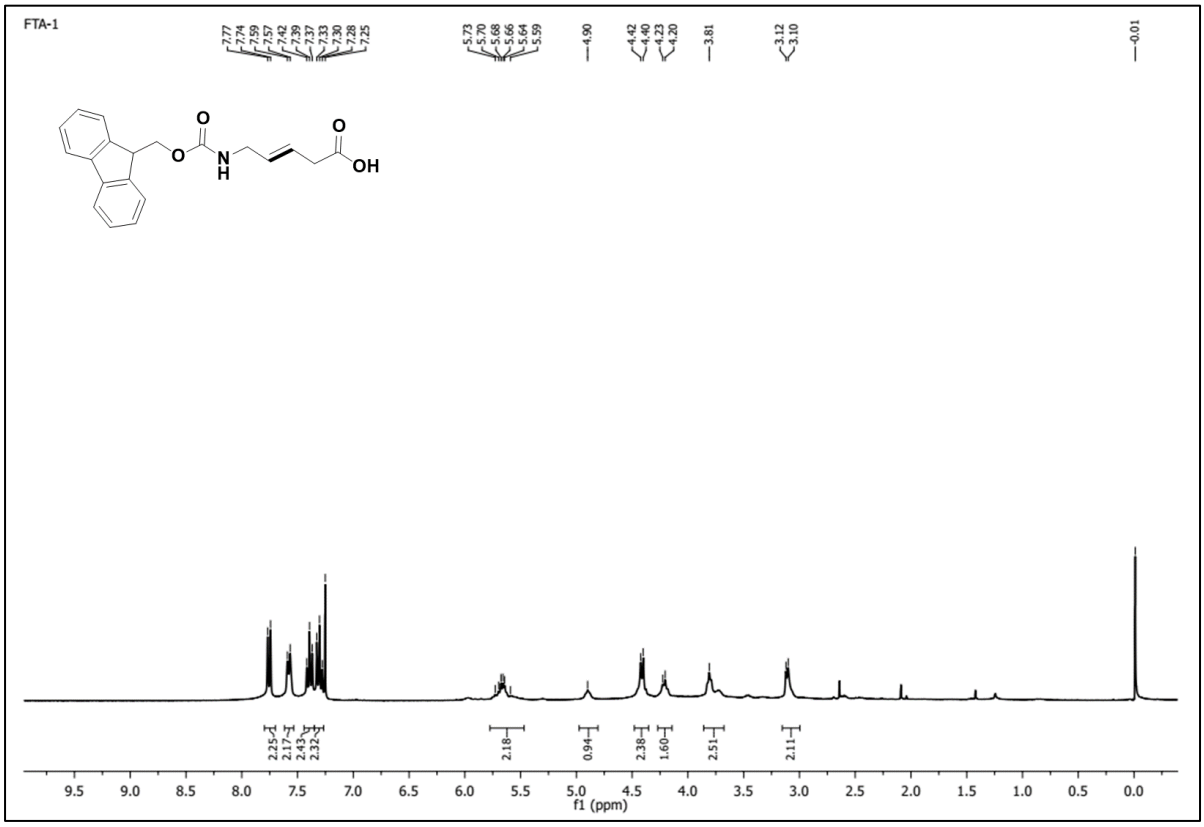


Figure S29: 300 MHz ^{1}H-NMR spectrum of Fmoc-*trans*-δ-Apa-OH in $CDCl_3$

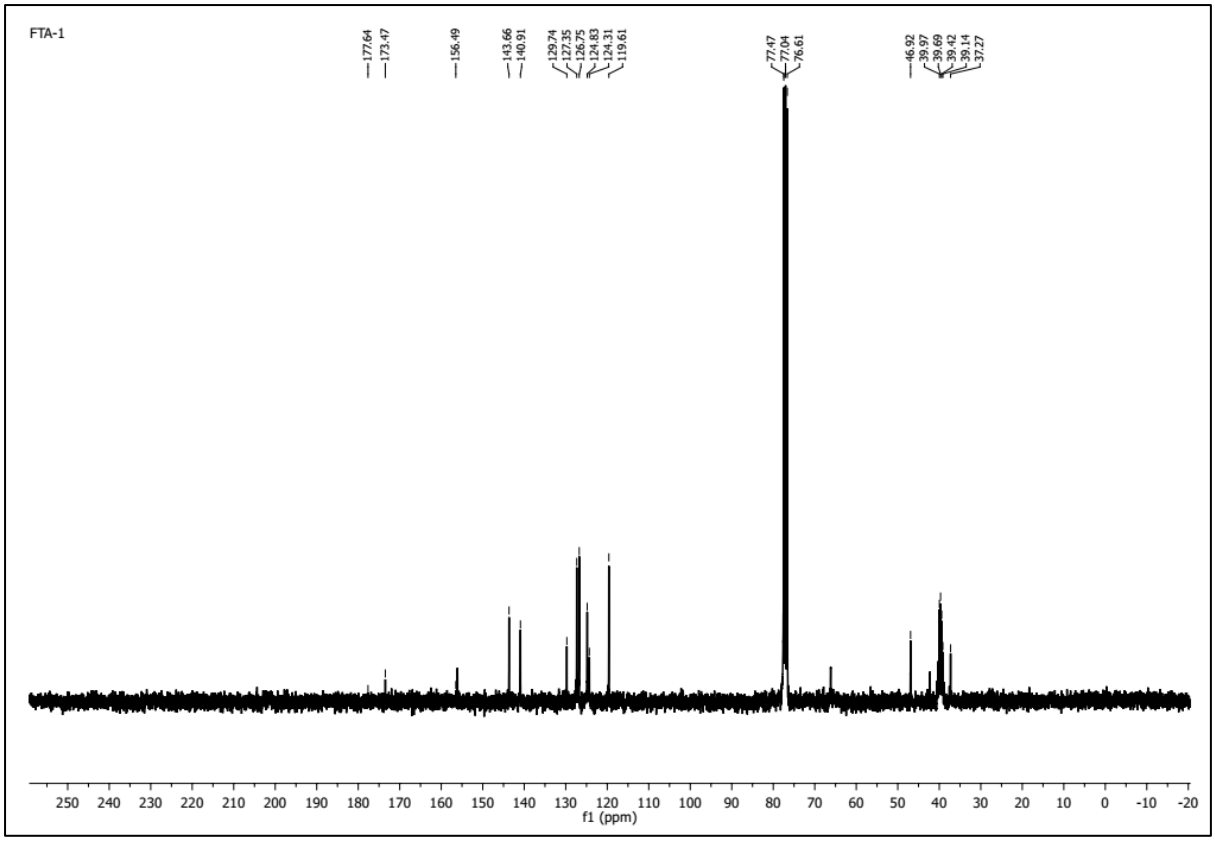


Figure S30: 75 MHz ^{13}C-NMR spectrum of Fmoc-*trans*-δ-Apa-OH in $CDCl_3$

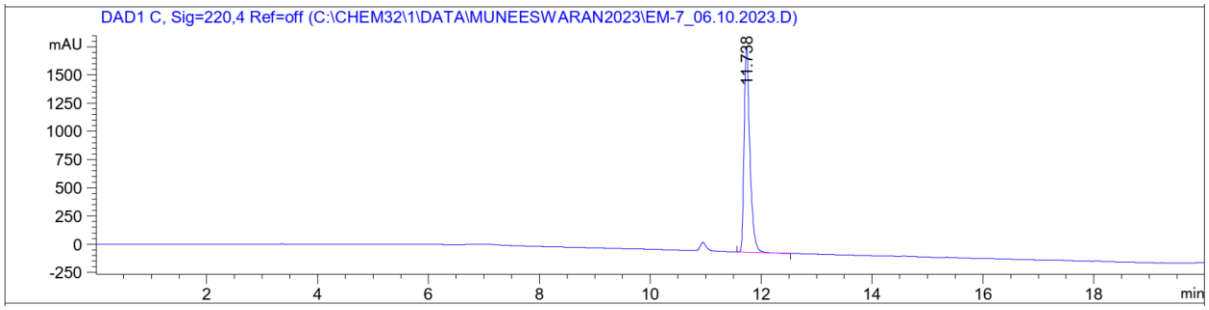


Figure S31: RP-HPLC Chromatogram of Nitro sulfonyl-*trans*-δ-Apa-OH

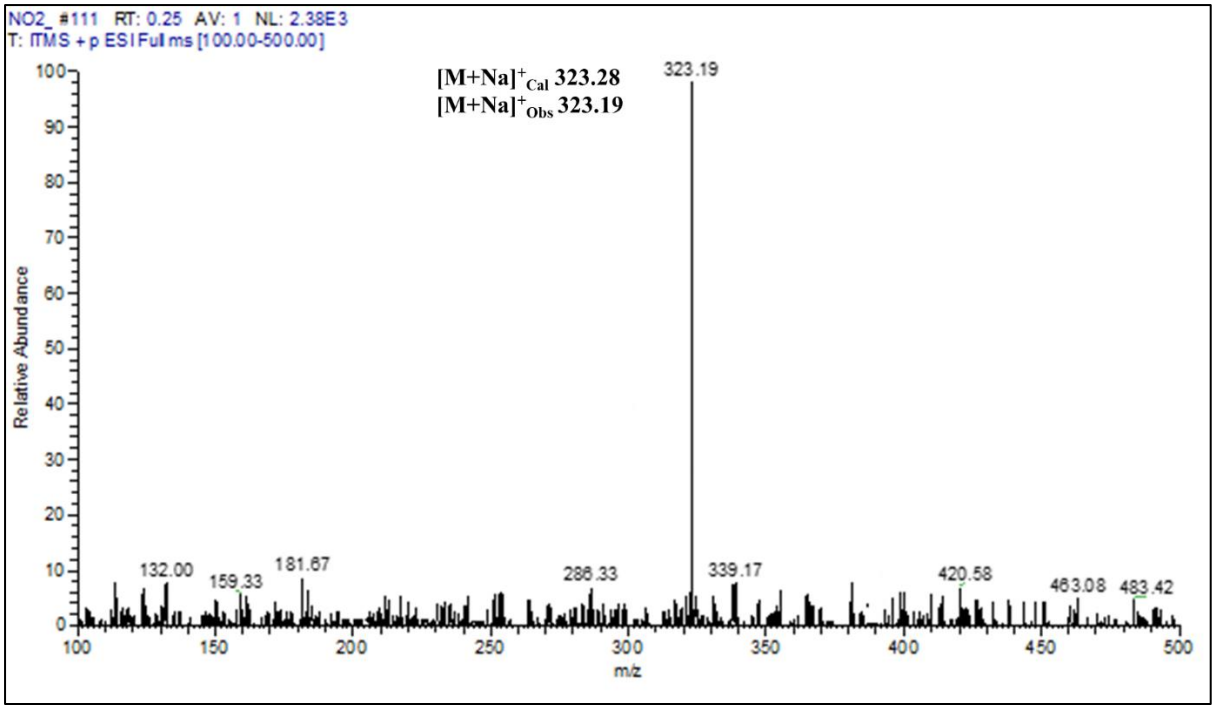


Figure S32: ESI-MS spectrum of Nitro sulfonyl-*trans*-δ-Apa-OH

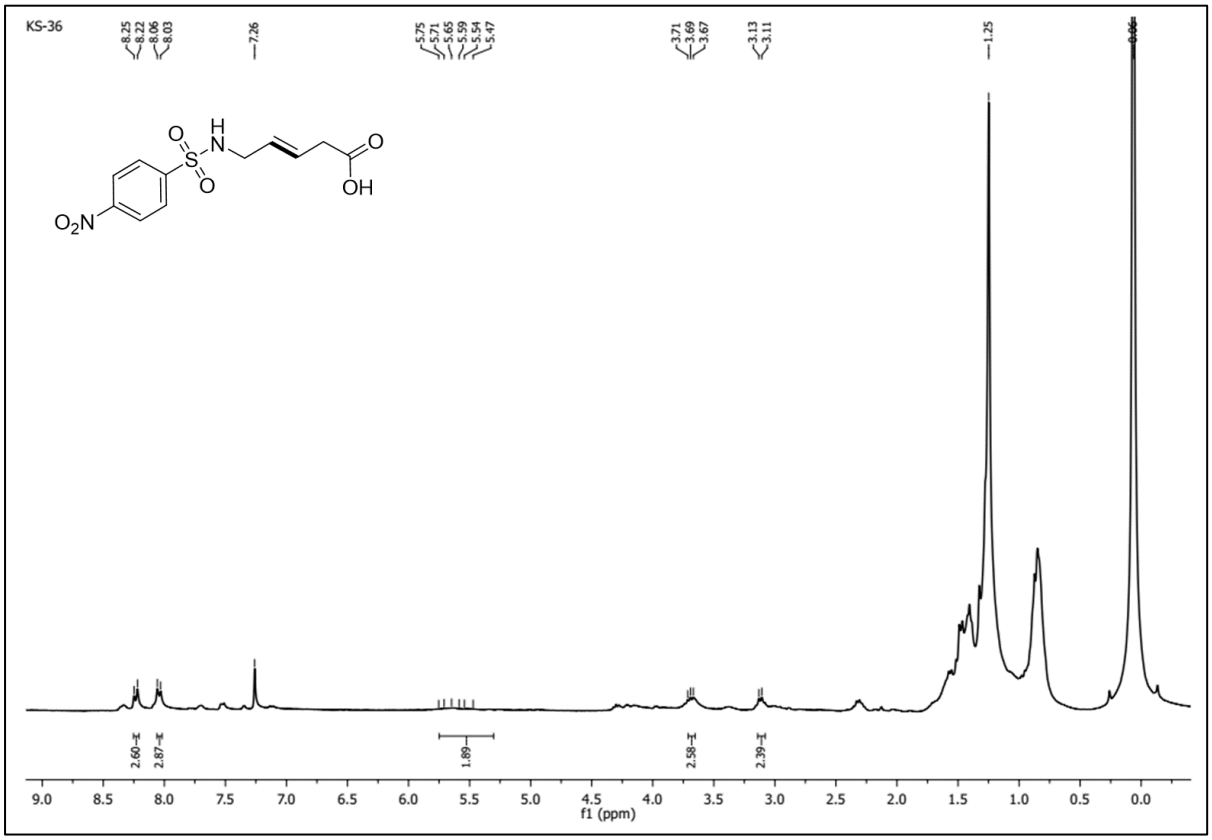


Figure S33: 300 MHz ^{1}H-NMR spectrum of Nitro sulfonyl-*trans*-δ-Apa-OH in $CDCl_3$

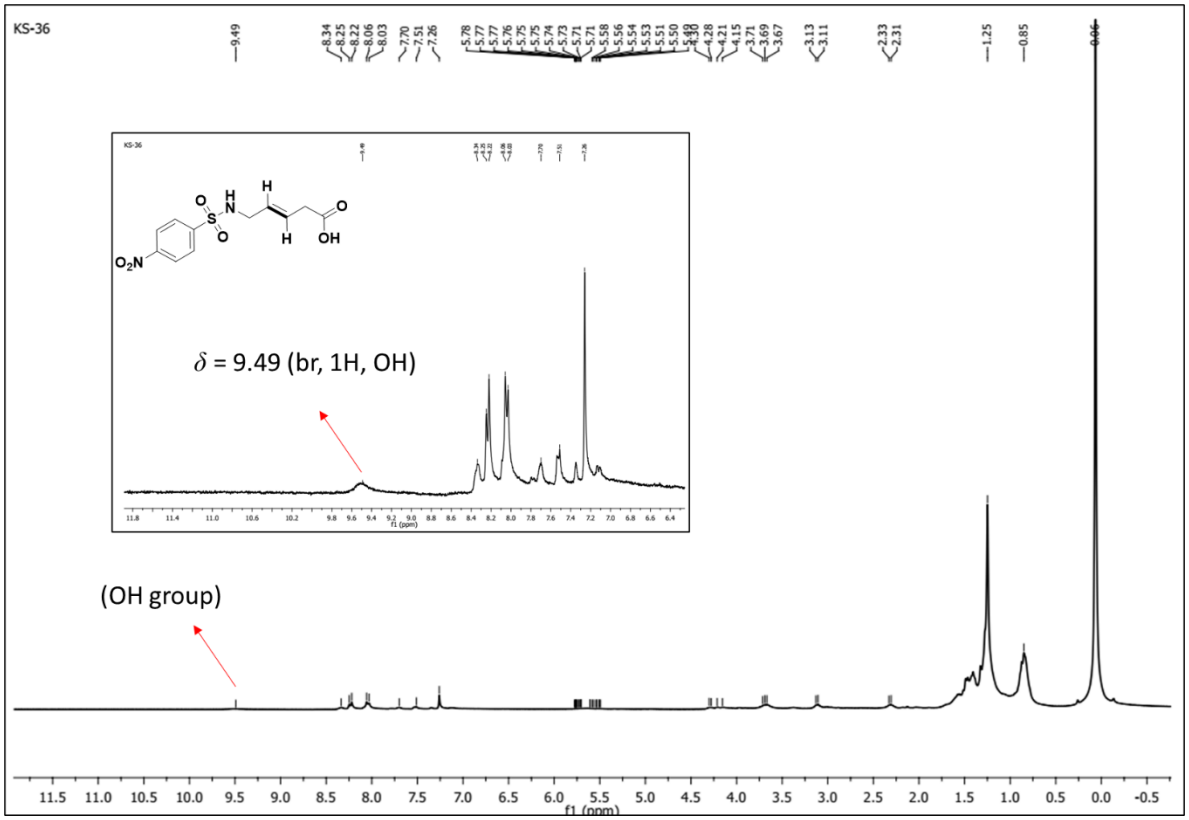


Figure S34: 300 MHz ^{1}H-NMR spectrum of Nitro sulfonyl-*trans*-δ-Apa-OH in $CDCl_3$

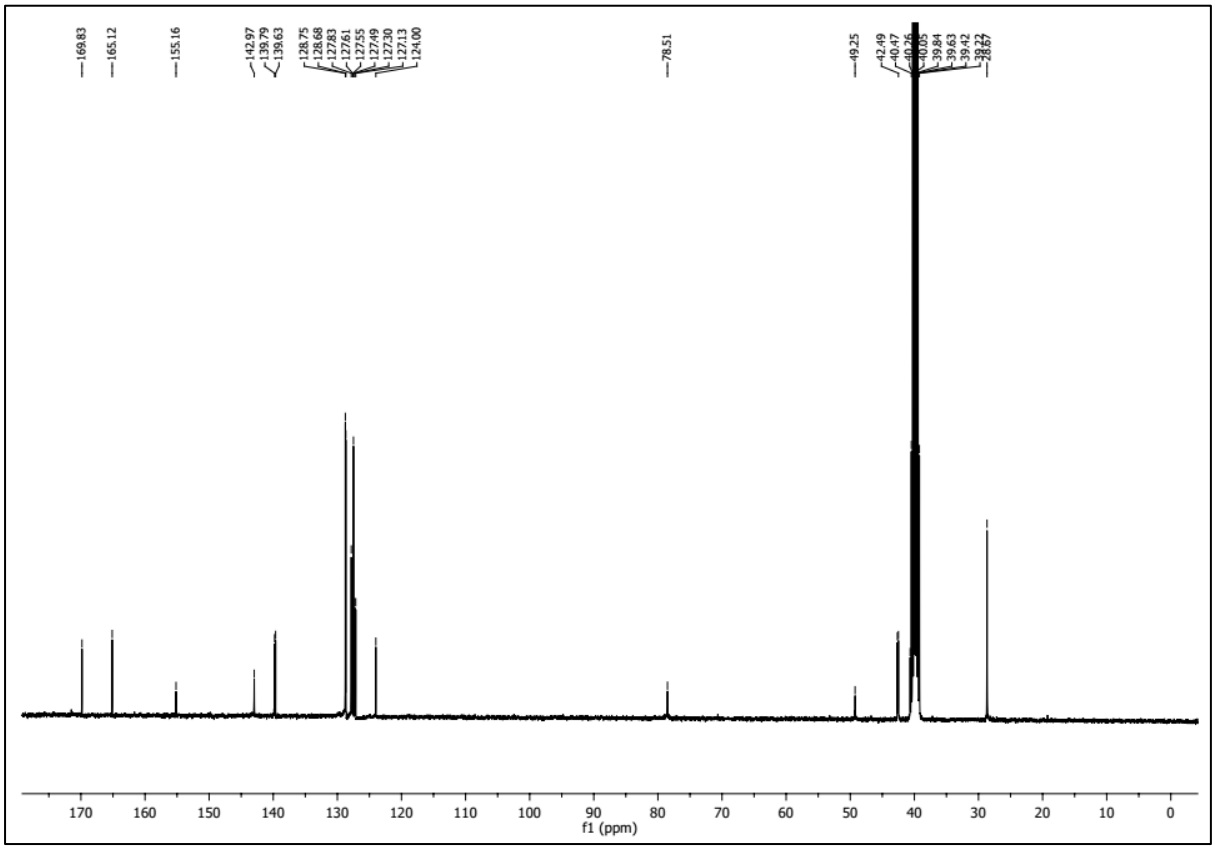


Figure S35: 75 MHz ^{13}C-NMR spectrum of Nitro sulfonyl-*trans*-δ-Apa-OH in DMSO-$_6$

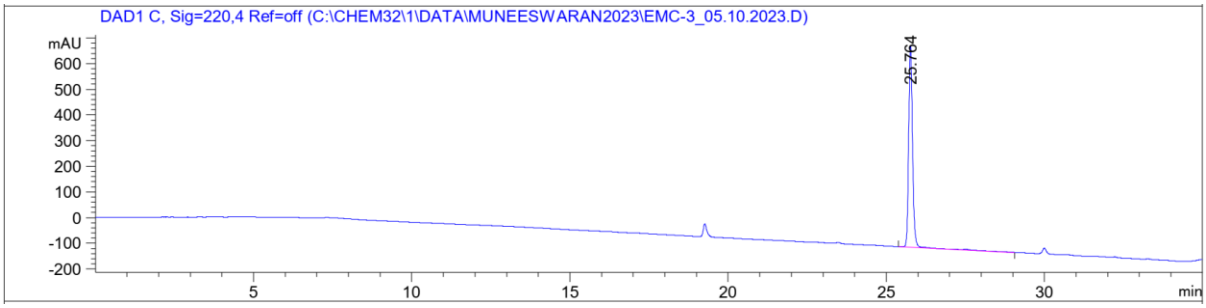


Figure S36: RP-HPLC Chromatogram of Bn-*trans*-δ-Apa-OH

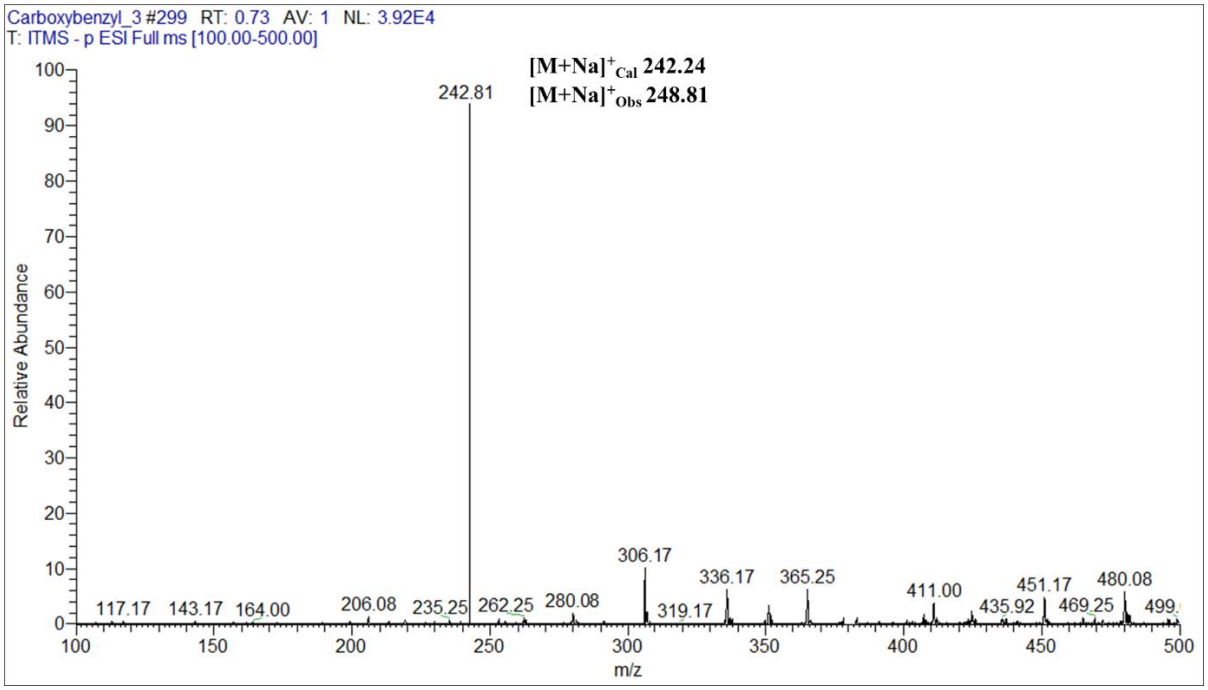


Figure S37: ESI-MS spectrum of Bn-*trans*-δ-Apa-OH

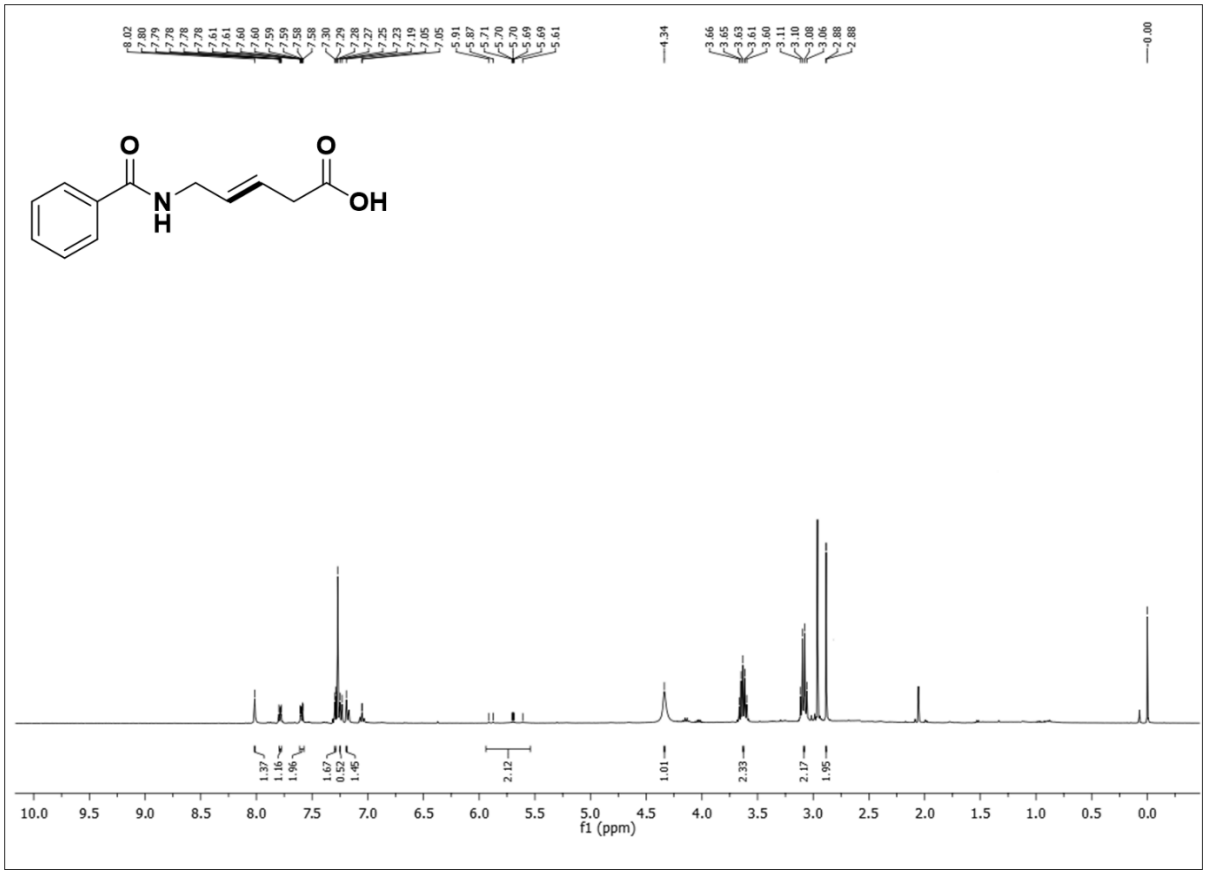


Figure S38: 300 MHz ^{1}H-NMR spectrum of Bn-*trans*-δ-Apa-OH in $CDCl_3$

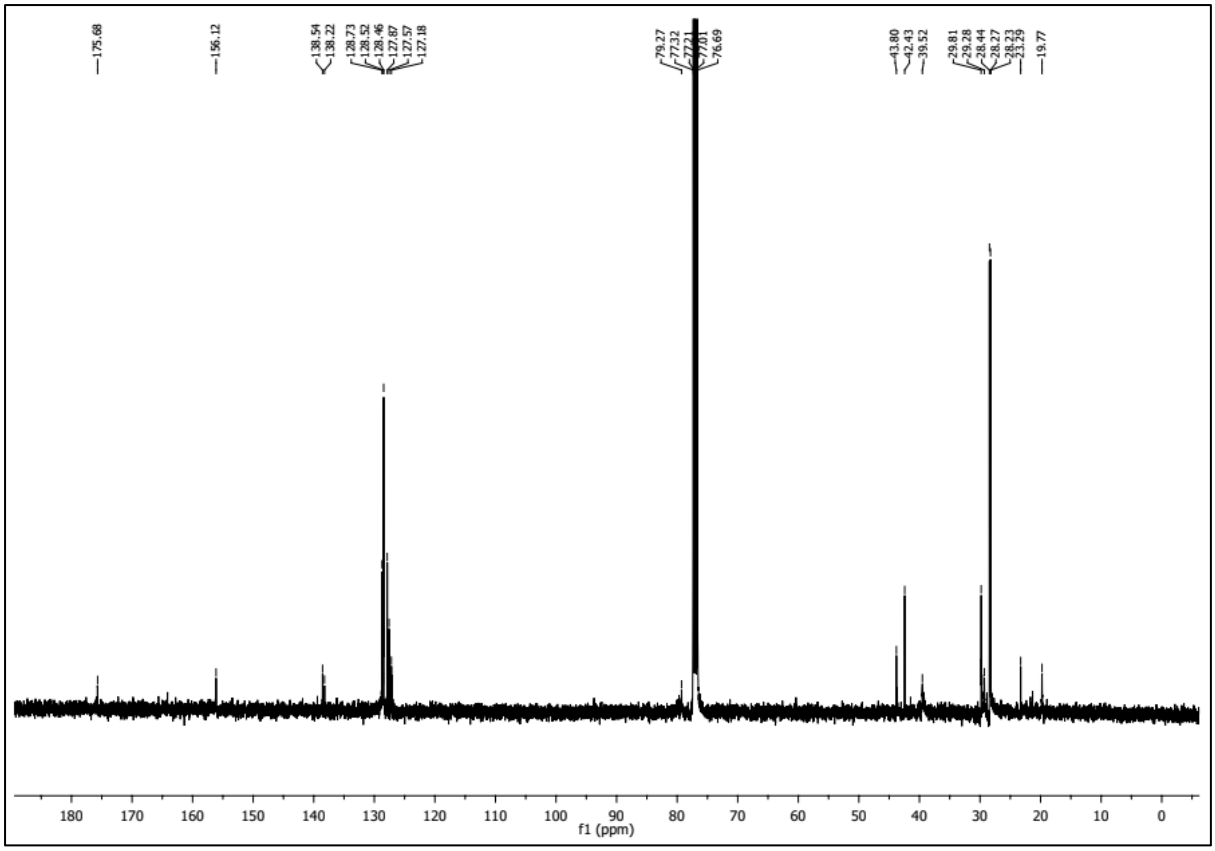


Figure S39: 75 MHz ^{13}C-NMR spectrum of Bn-*trans*-δ-Apa-OH in $CDCl_3$

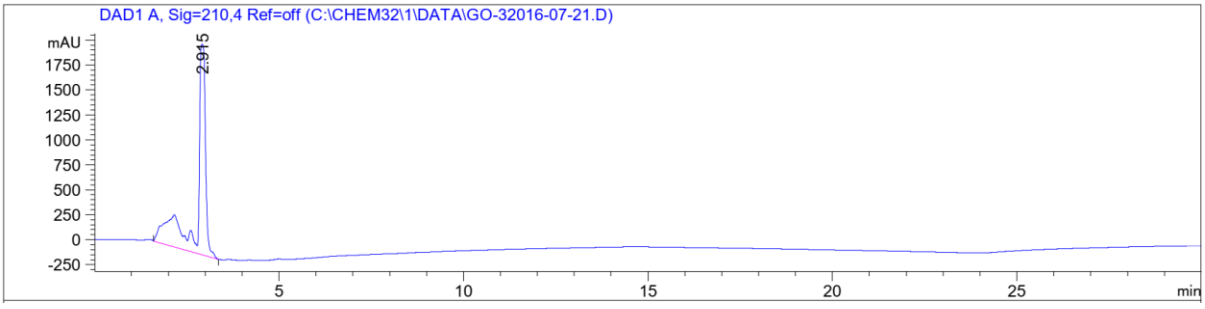


Figure S40: RP-HPLC Chromatogram of H-*trans*-δ-Apa-OEthyl

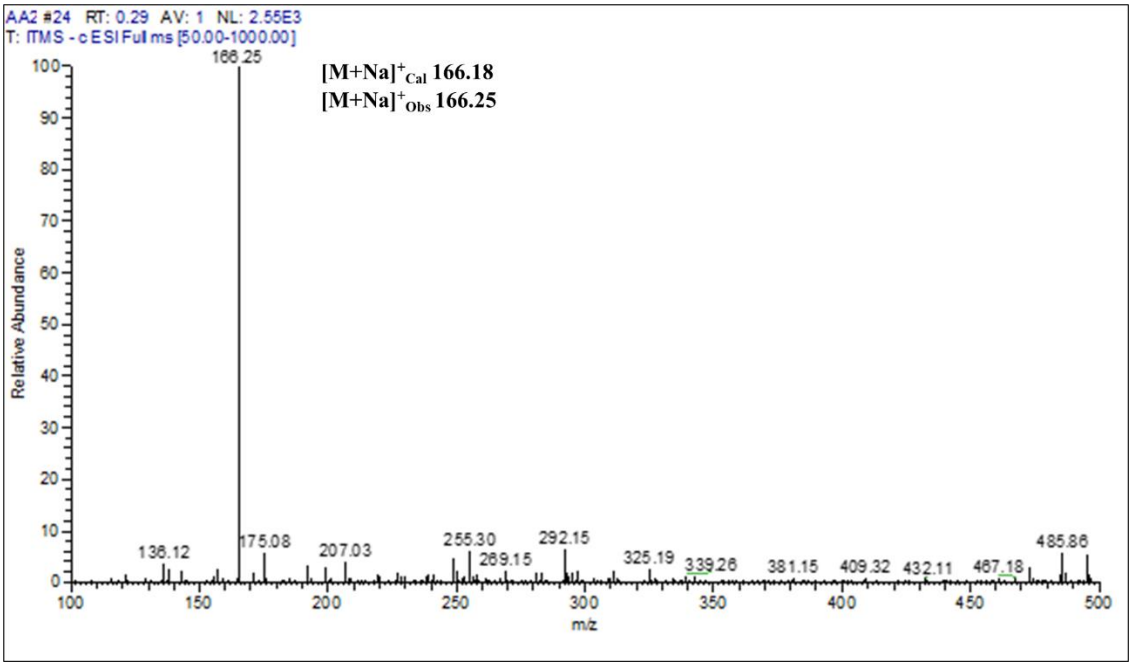


Figure S41: ESI-MS spectrum of H-*trans*-δ-Apa-OEthyl

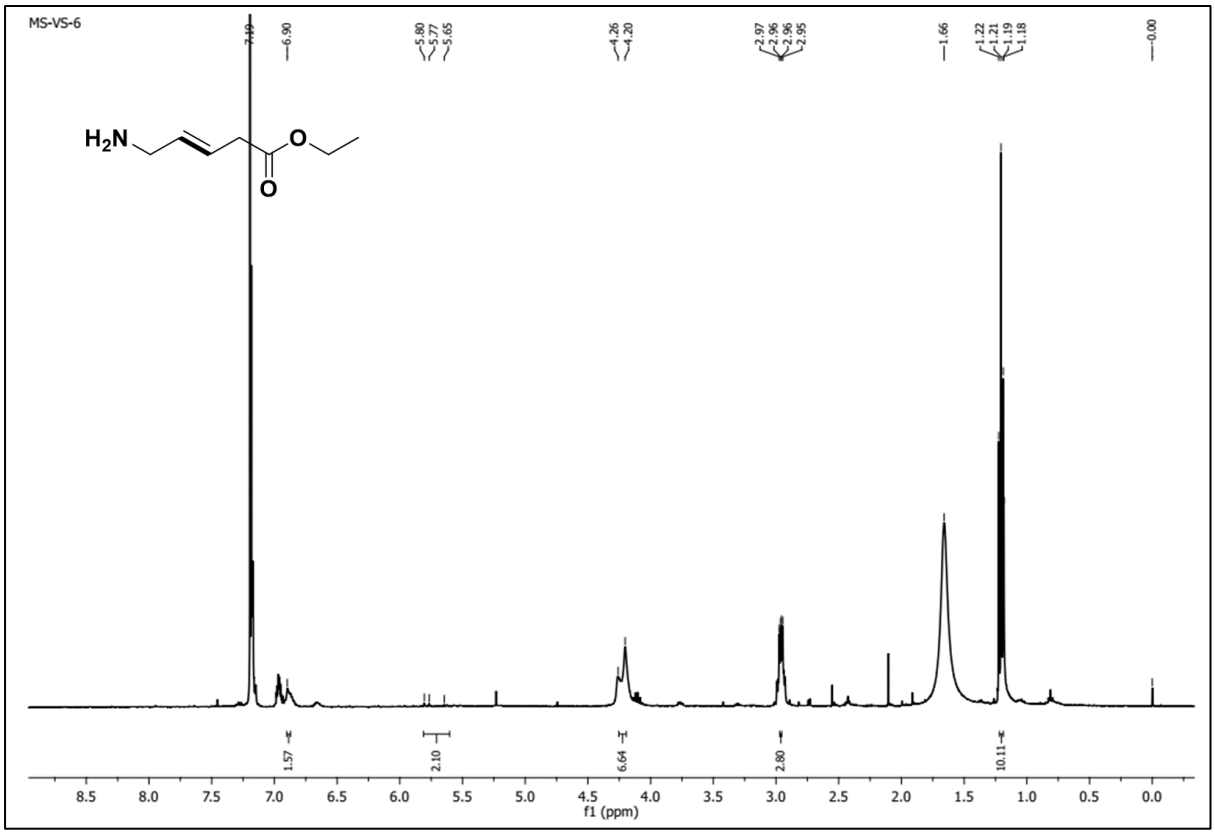


Figure S42: 300 MHz ^{1}H-NMR spectrum of H-*trans*-δ-Apa-OEthyl in $CDCl_3$

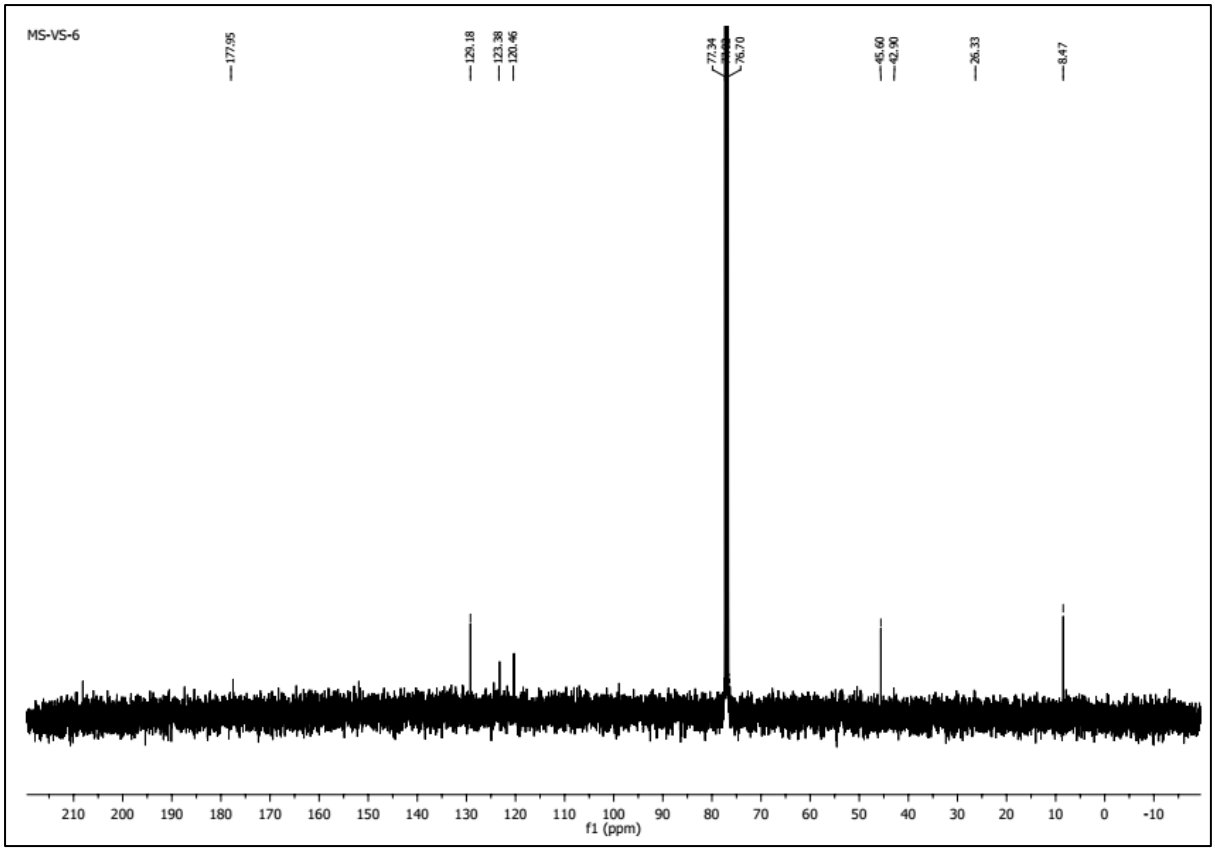


Figure S43: 75 MHz ^{13}C-NMR spectrum of H-*trans*-δ-Apa-OEthyl in $CDCl_3$

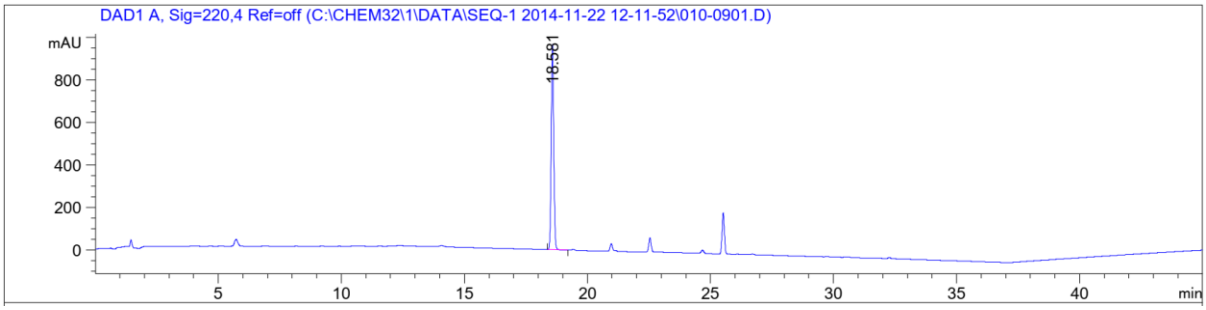


Figure S44: RP-HPLC Chromatogram of H-*trans*-δ-Apa-*tert*-butyl

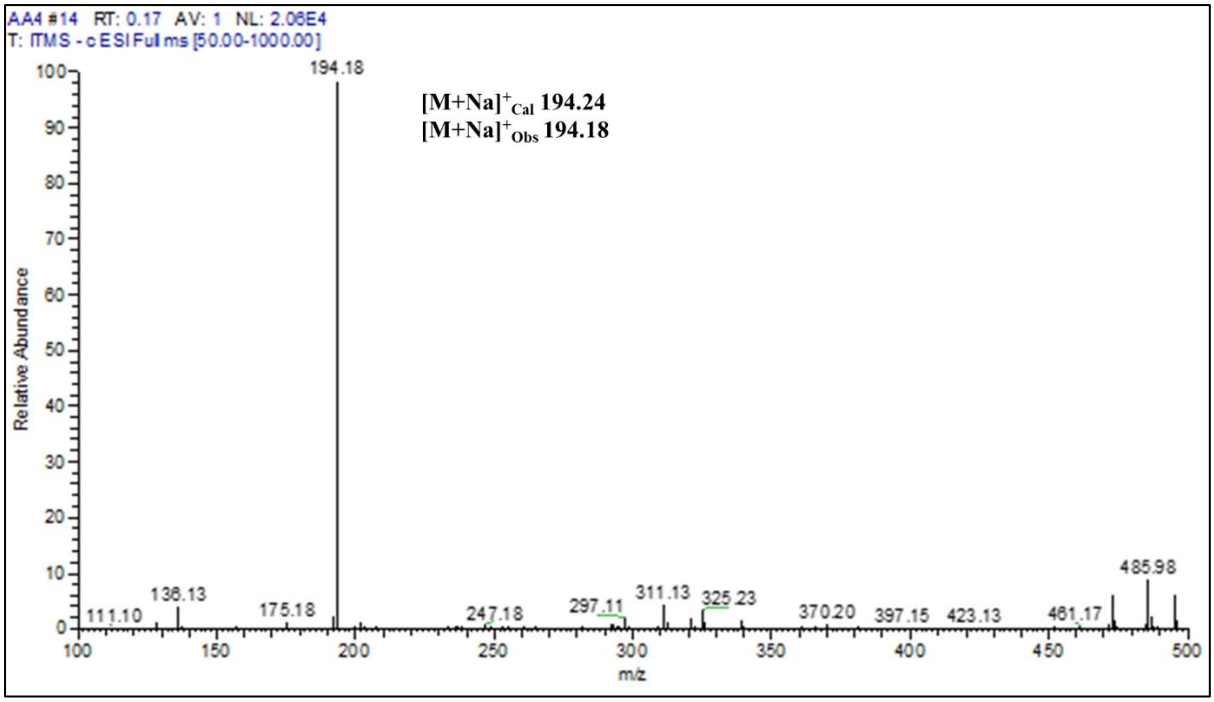


Figure S45: ESI-MS spectrum of H-*trans*-δ-Apa-*tert*-butyl

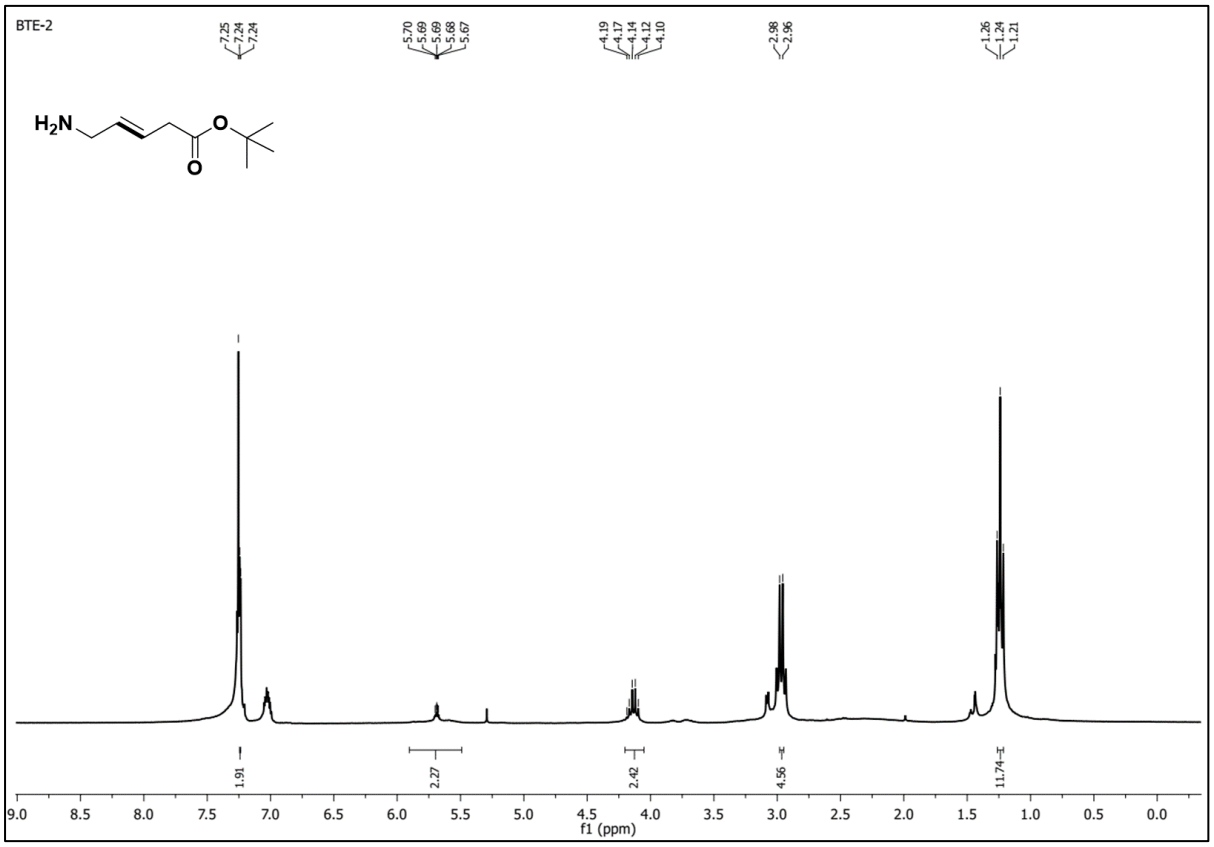


Figure S46: 300 MHz ^{1}H-NMR spectrum of H-*trans*-δ-Apa-*tert*-butyl in $CDCl_3$

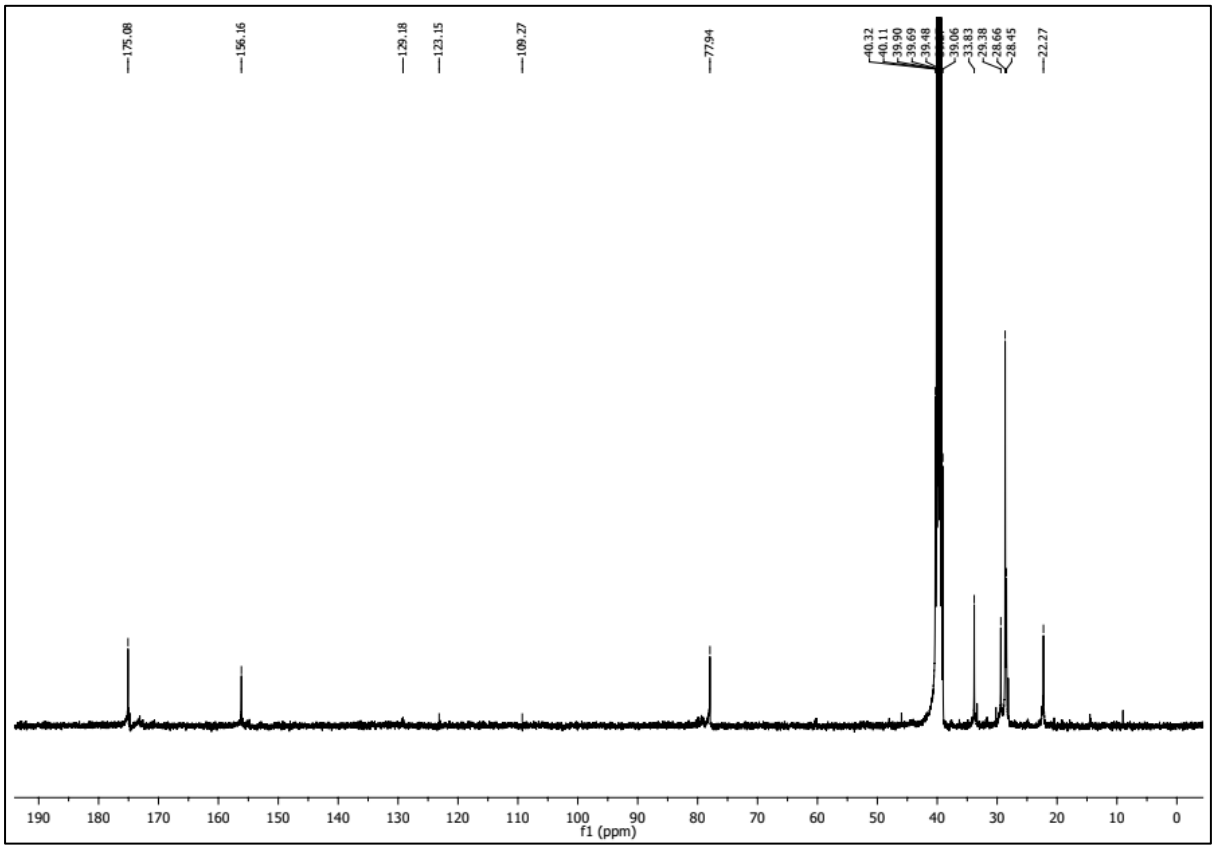


Figure S47: 75 MHz ^{13}C-NMR spectrum of H-*trans*-δ-Apa-*tert*-butyl in DMSO-d_6

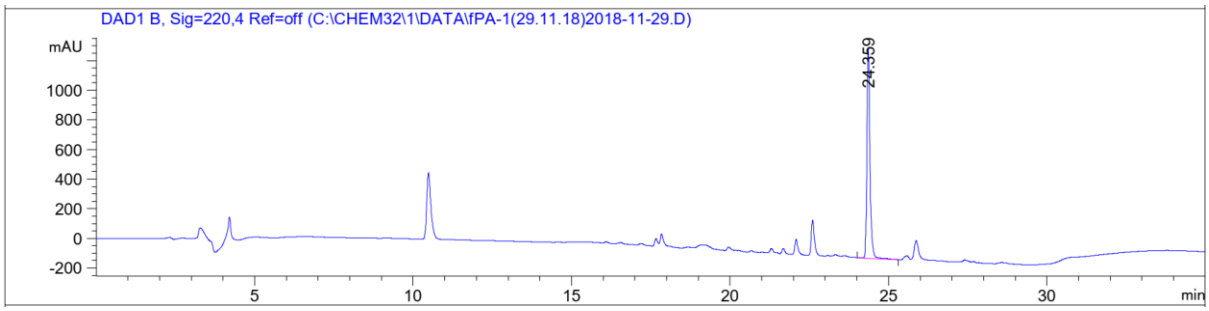


Figure S48: RP-HPLC Chromatogram of H-*trans*-δ-Apa-Silyl

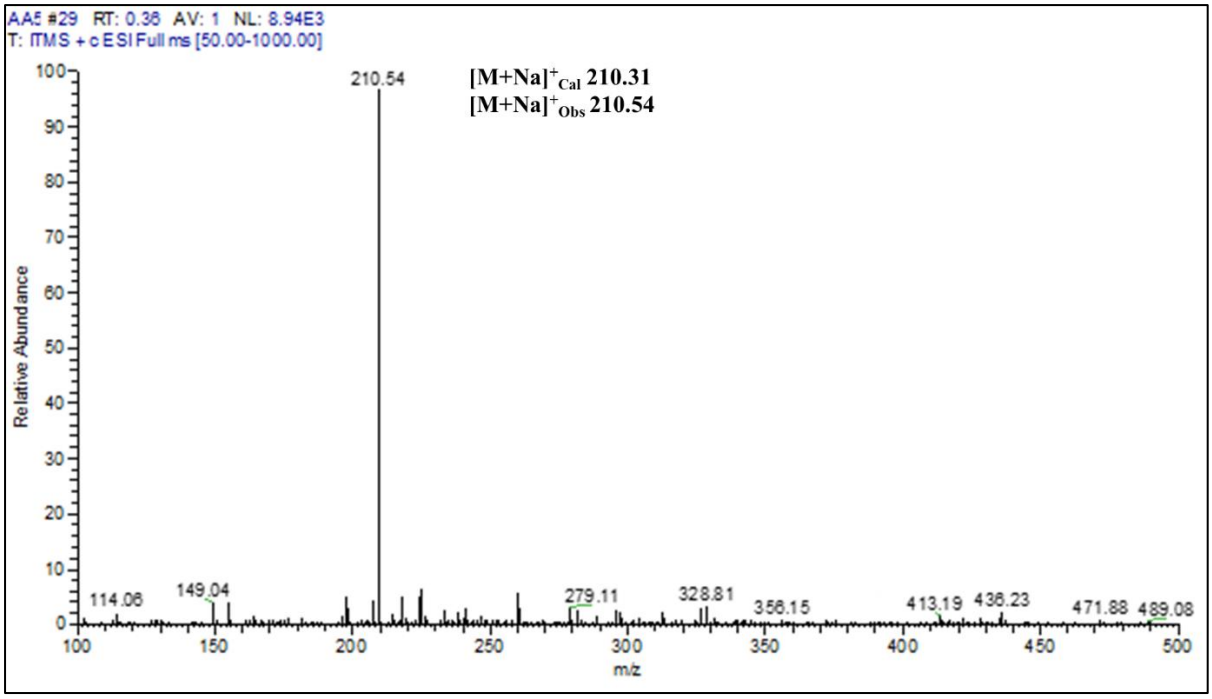


Figure S49: ESI-MS spectrum of H-*trans*-δ-Apa-Silyl

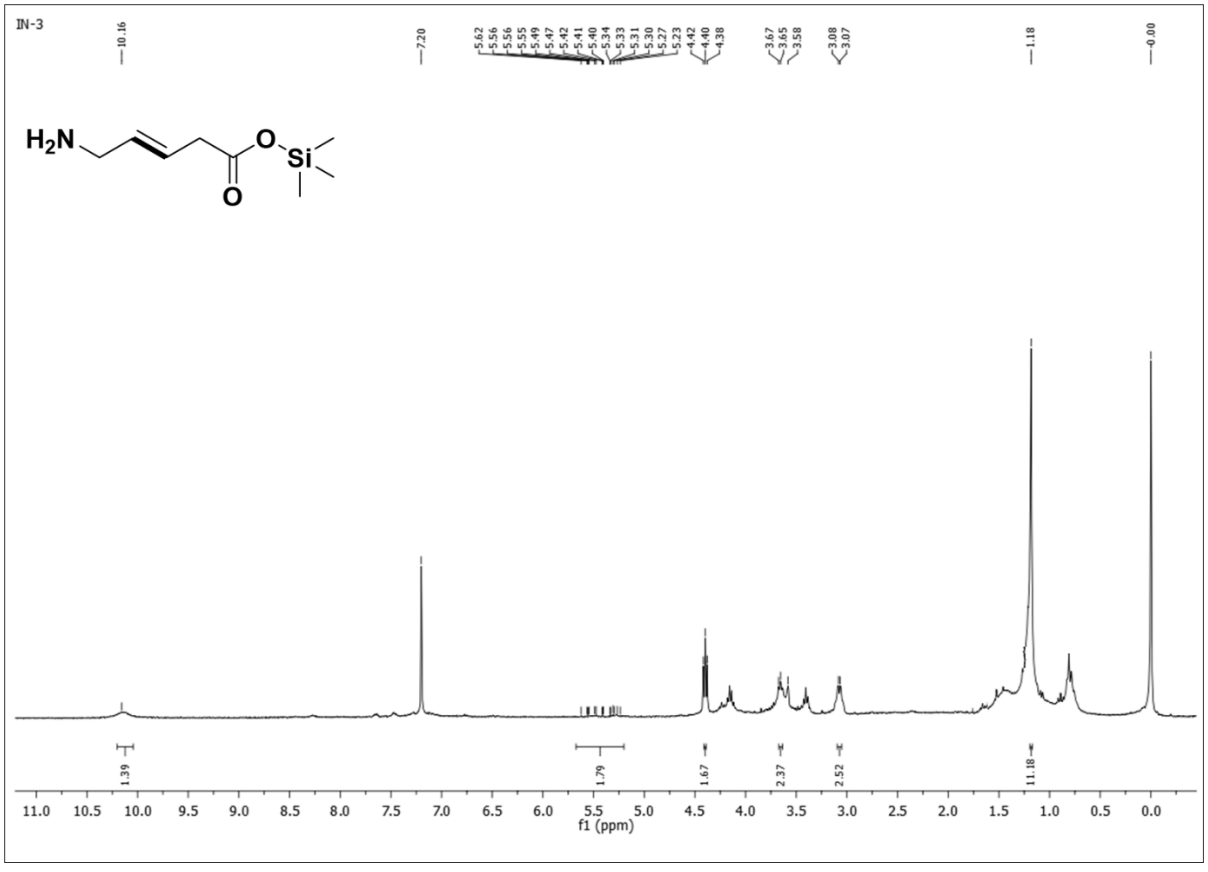


Figure S50: 300 MHz ^{1}H-NMR spectrum of H-*trans*-δ-Apa-Silyl in $CDCl_3$

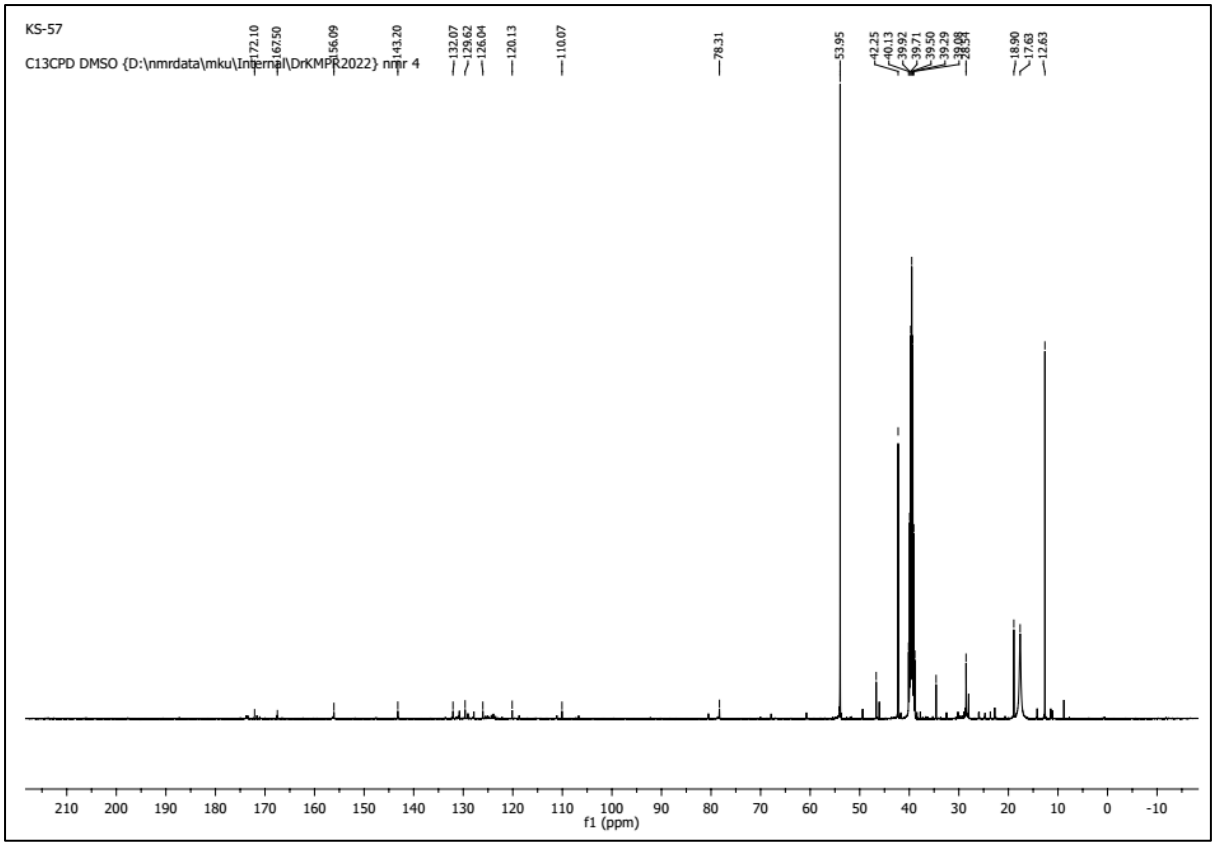


Figure S51: 75 MHz ^{13}C-NMR spectrum of H-*trans*-δ-Apa-Silyl in DMSO-d_6

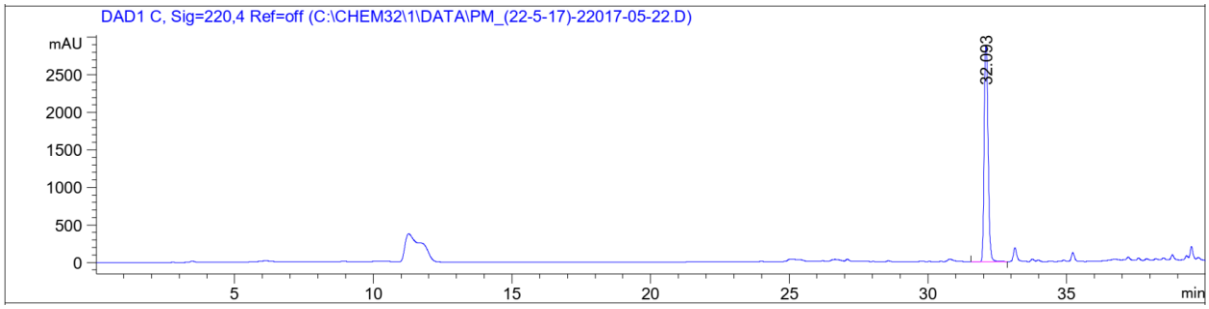


Figure S52: RP-HPLC Chromatogram of H-*trans*-δ-Apa-benzyl

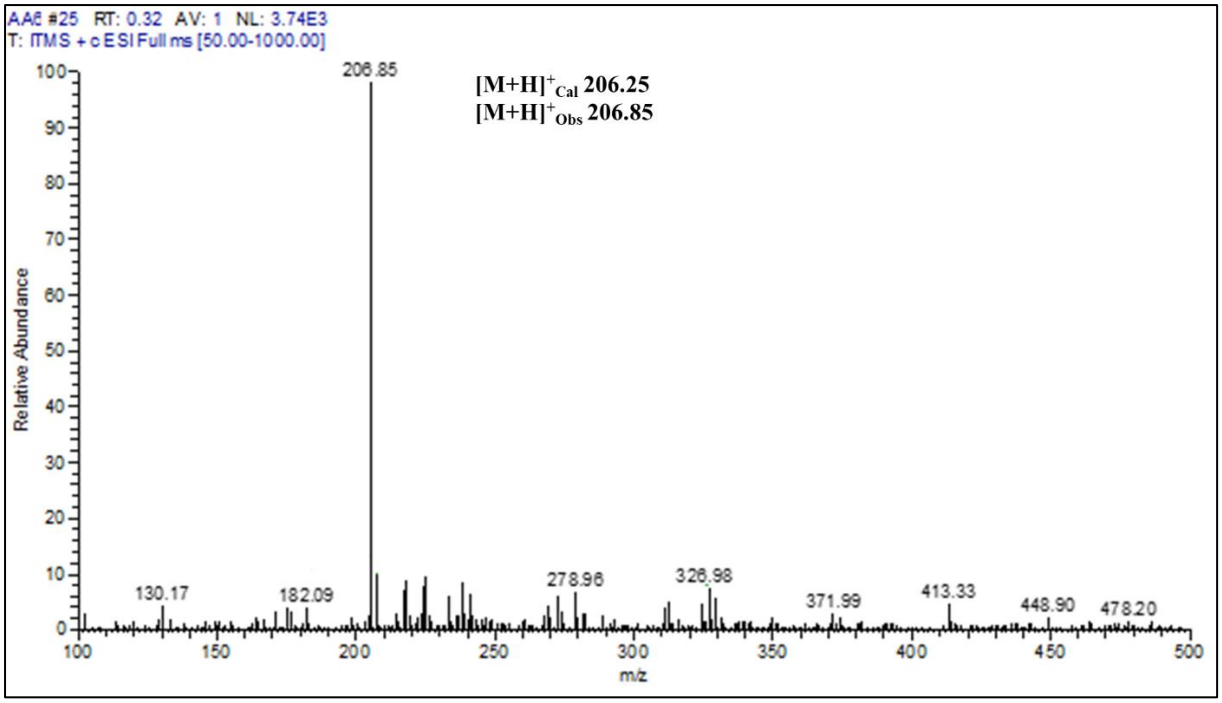


Figure S53: ESI-MS spectrum of H-*trans*-δ-Apa-benzyl

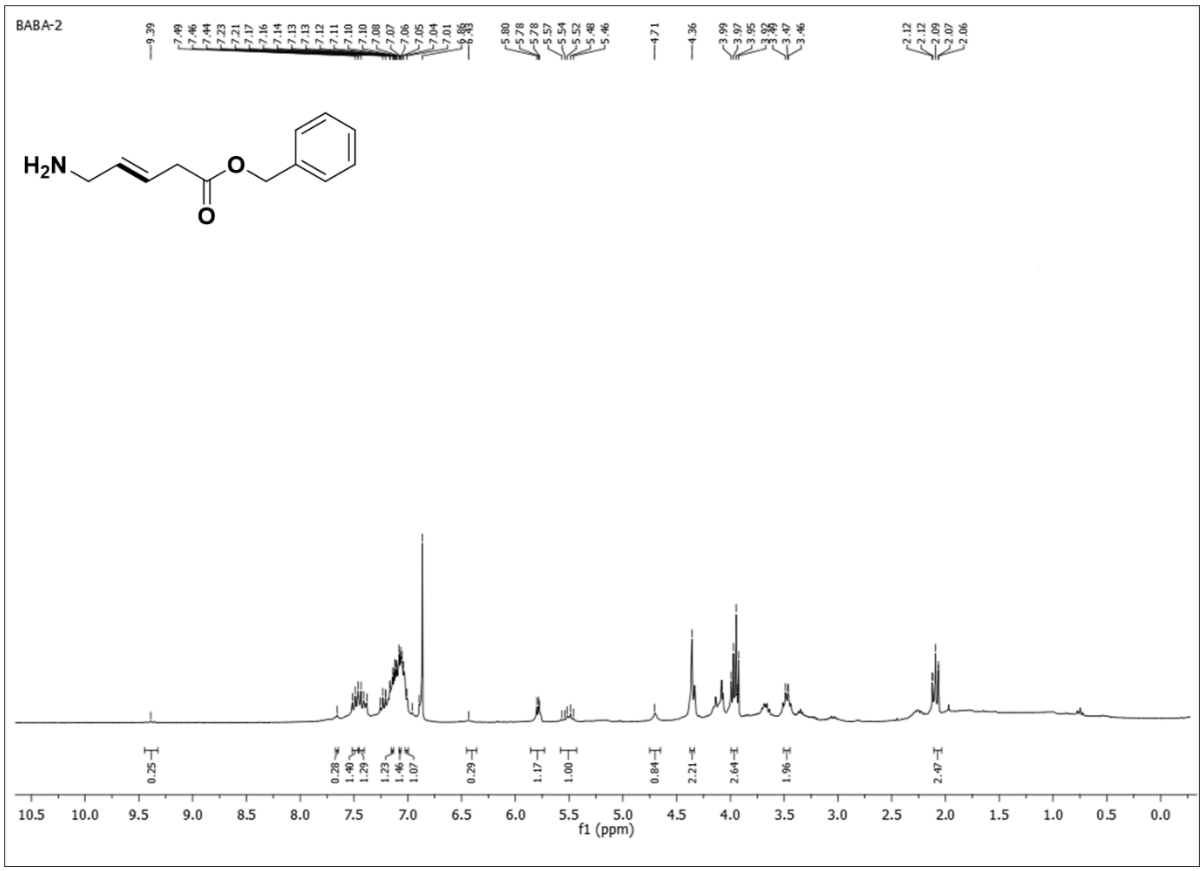


Figure S54: 300 MHz ^{1}H-NMR spectrum of H-*trans*-δ-Apa-benzyl in $CDCl_3$

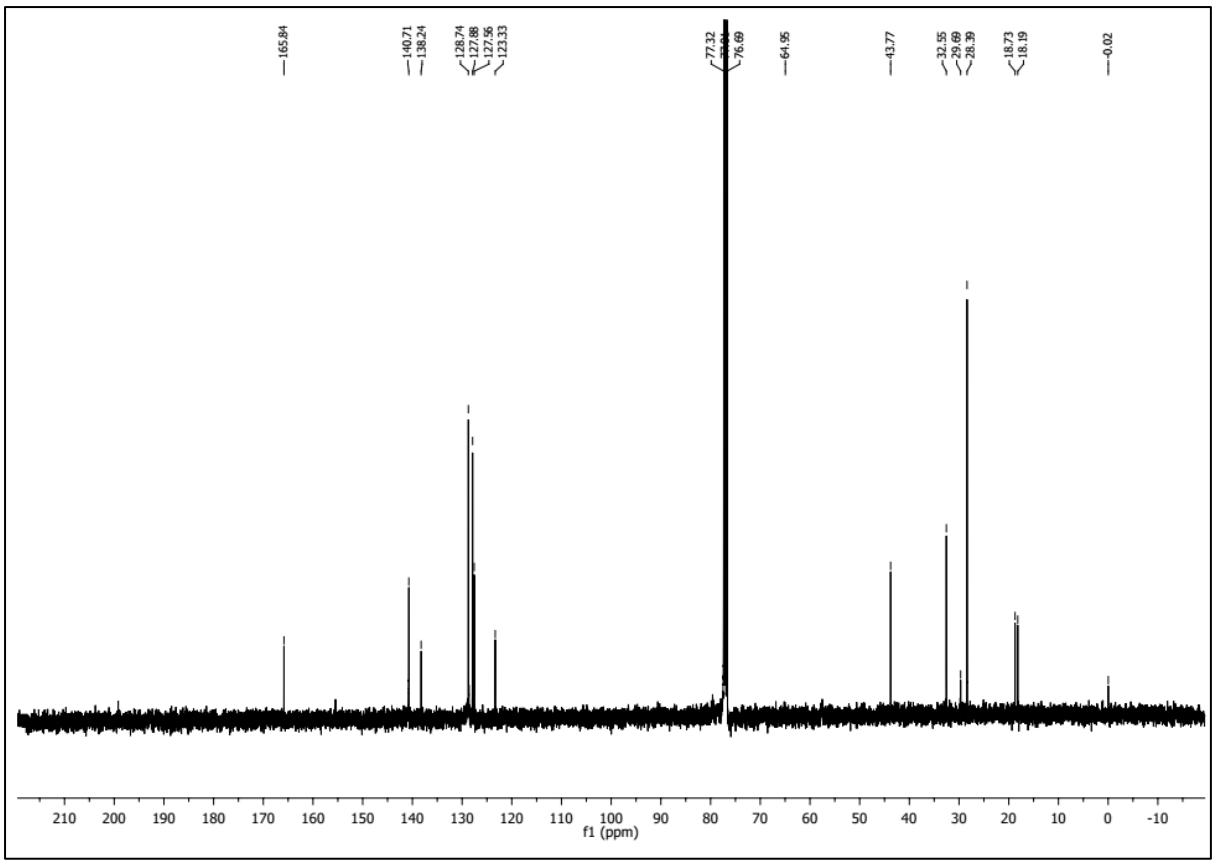


Figure S55: 75 MHz ^{13}C-NMR spectrum of H-*trans*-δ-Apa-benzyl in $CDCl_3$

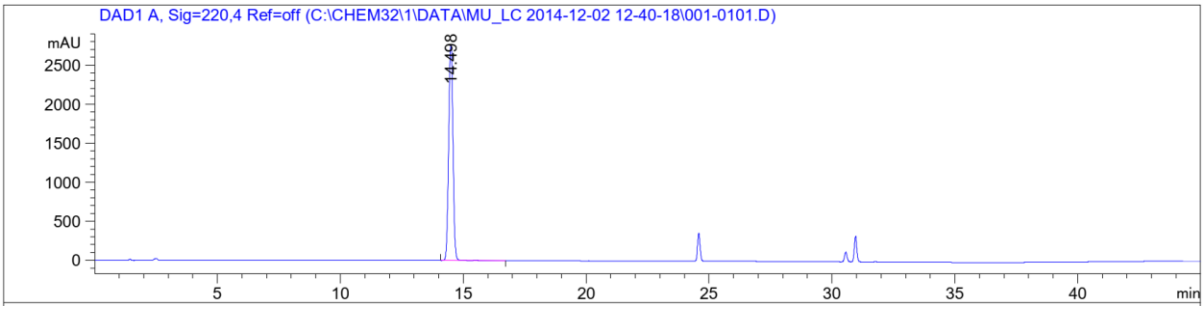


Figure S56: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NH*iso*butyl

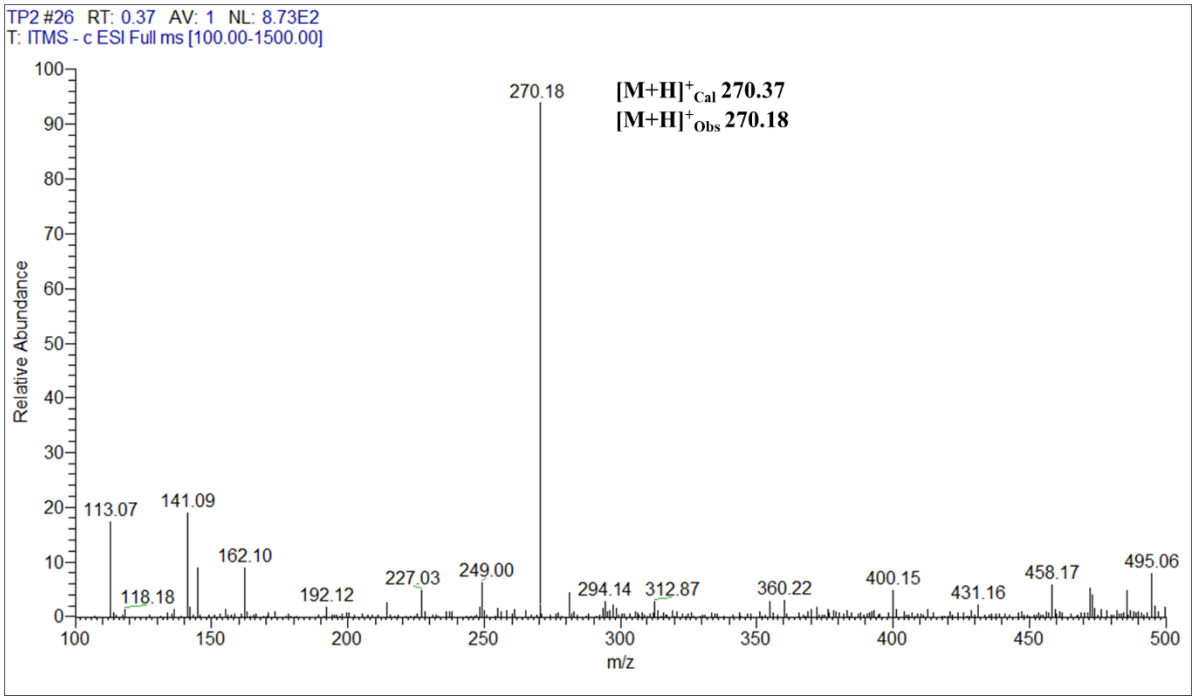


Figure S57: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*butyl

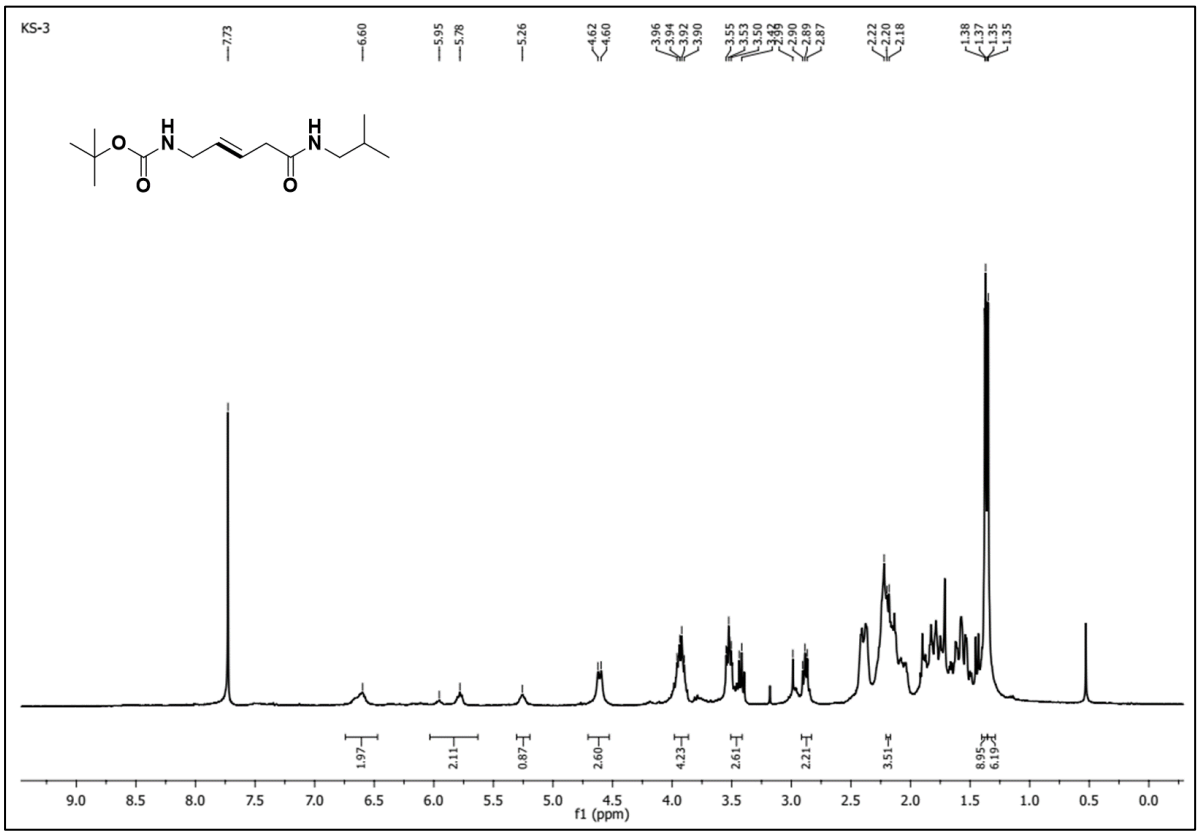


Figure S58: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*butyl in $CDCl_3$

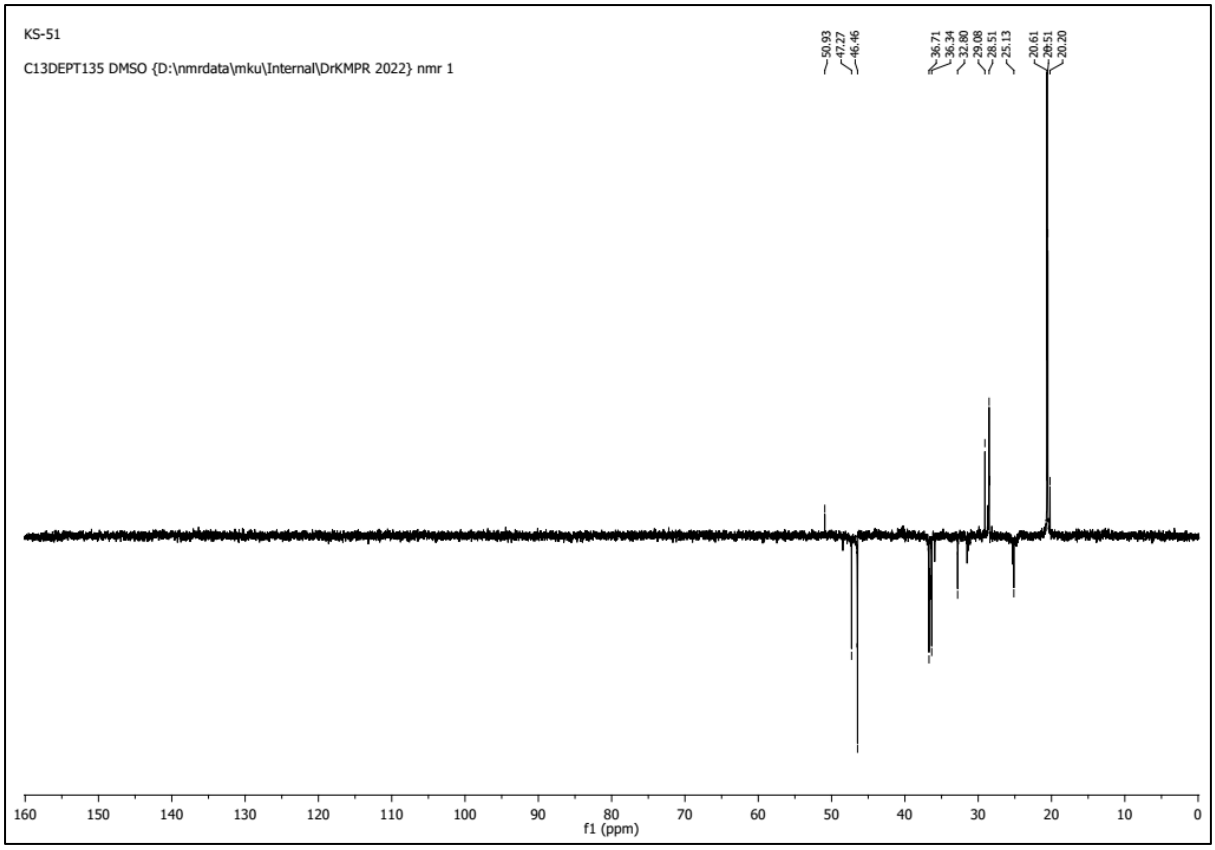


Figure S59: 300 MHz DEPT135-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*butyl in $CDCl_3$

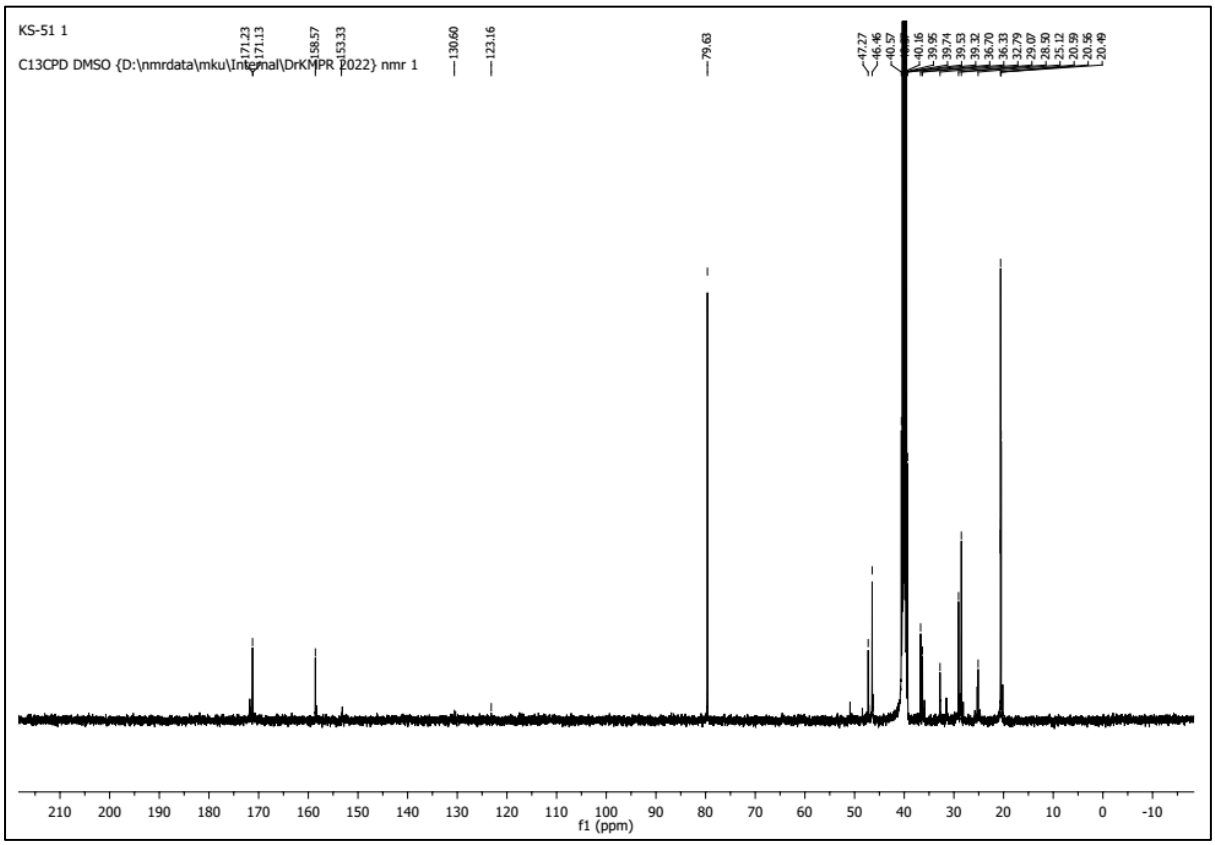


Figure S60: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*butyl in DMSO-d_6

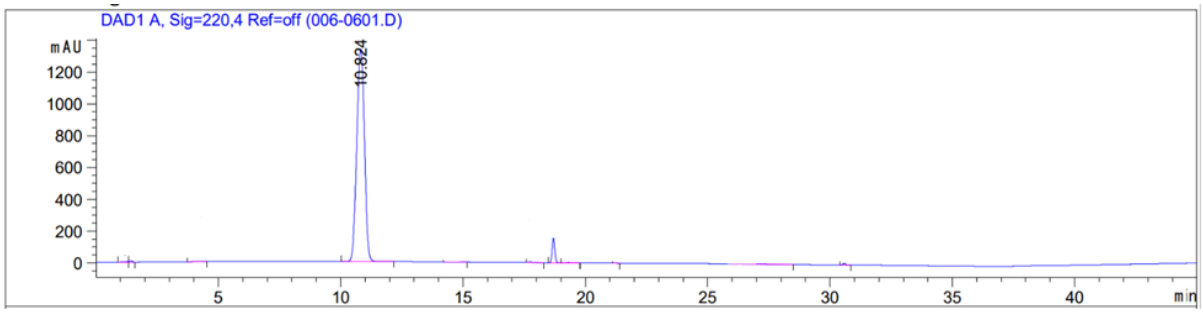


Figure S61: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NH*iso*Propyl

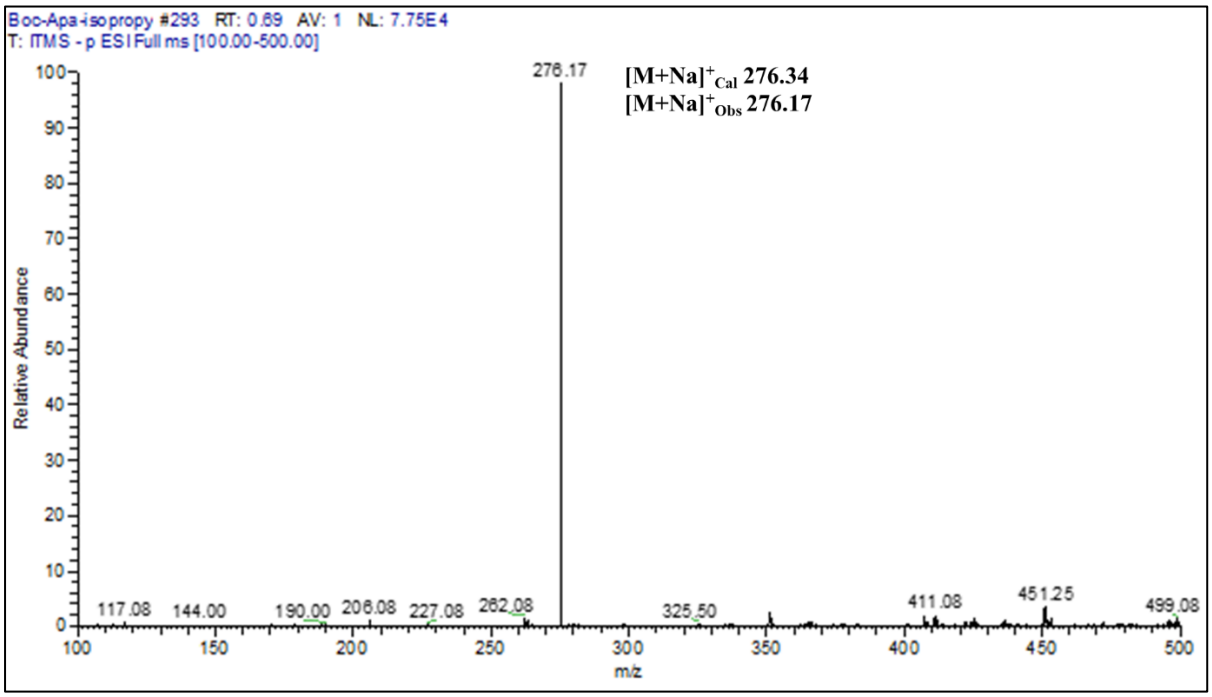


Figure S62: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*Propyl

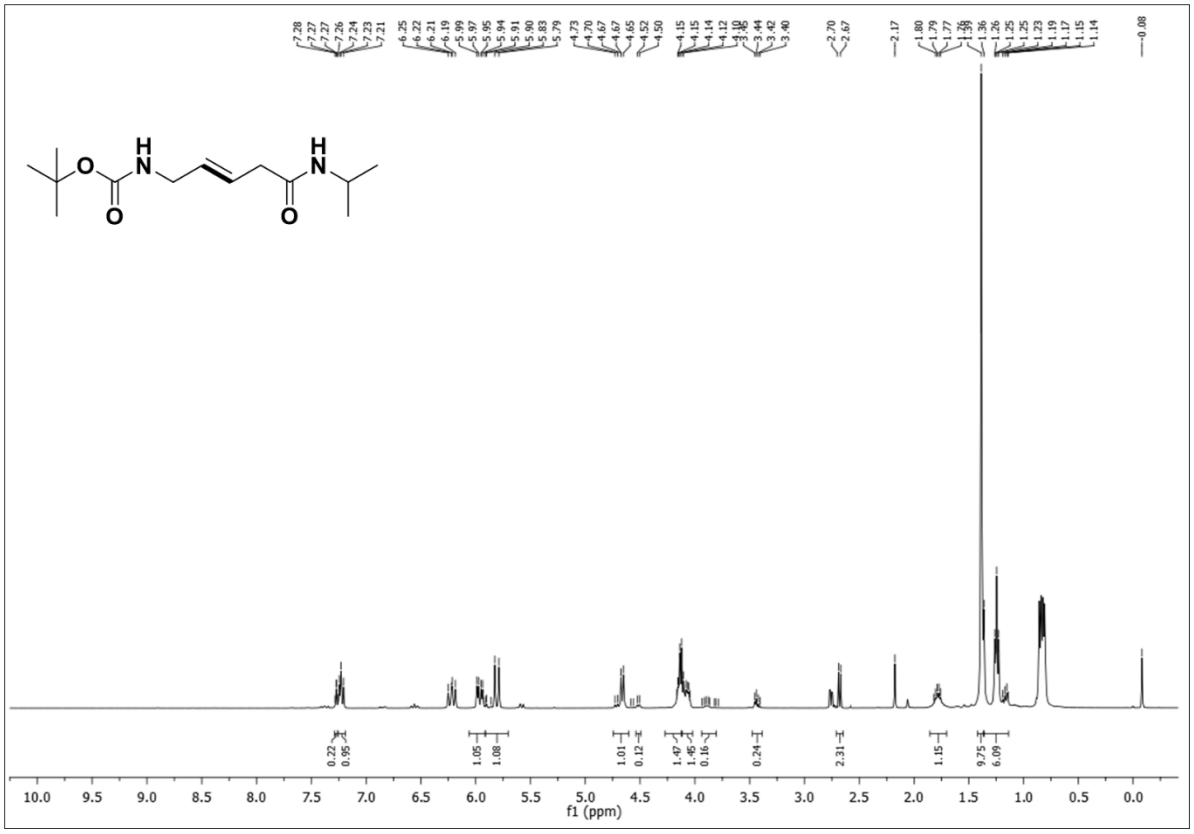


Figure S63: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*Propyl in $CDCl_3$

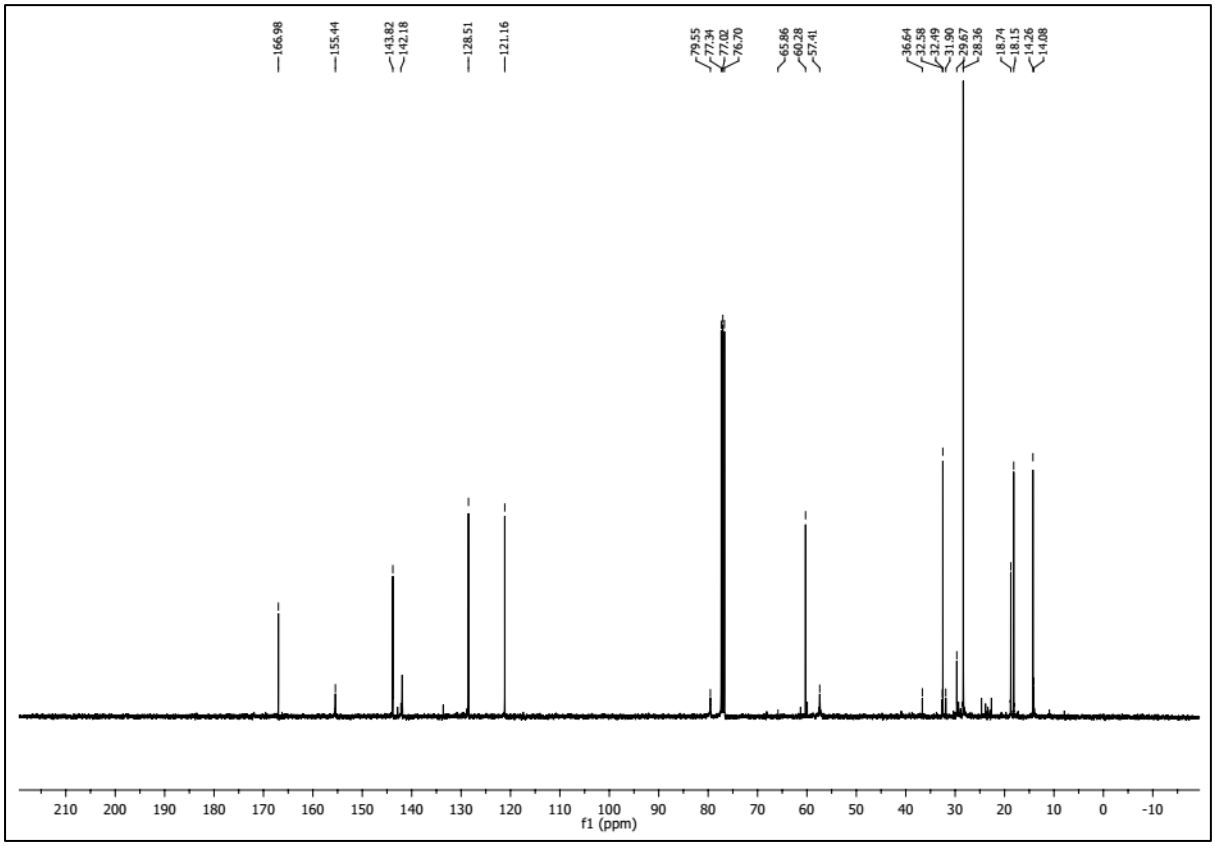


Figure S64: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*iso*Propyl in $CDCl_3$

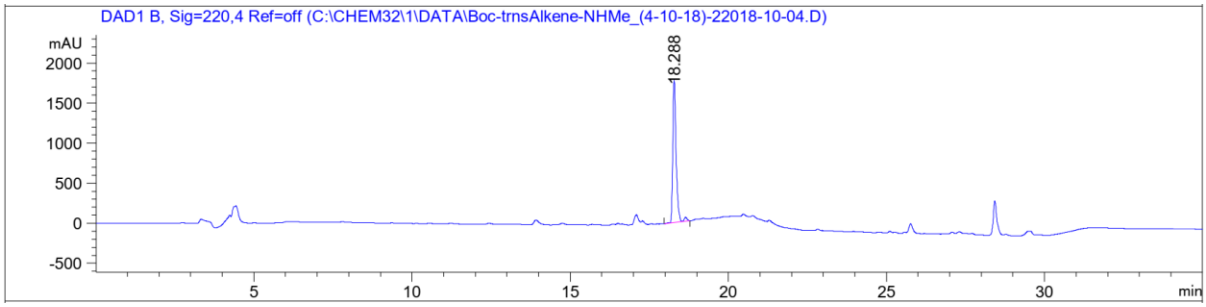


Figure S65: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NHMethyl

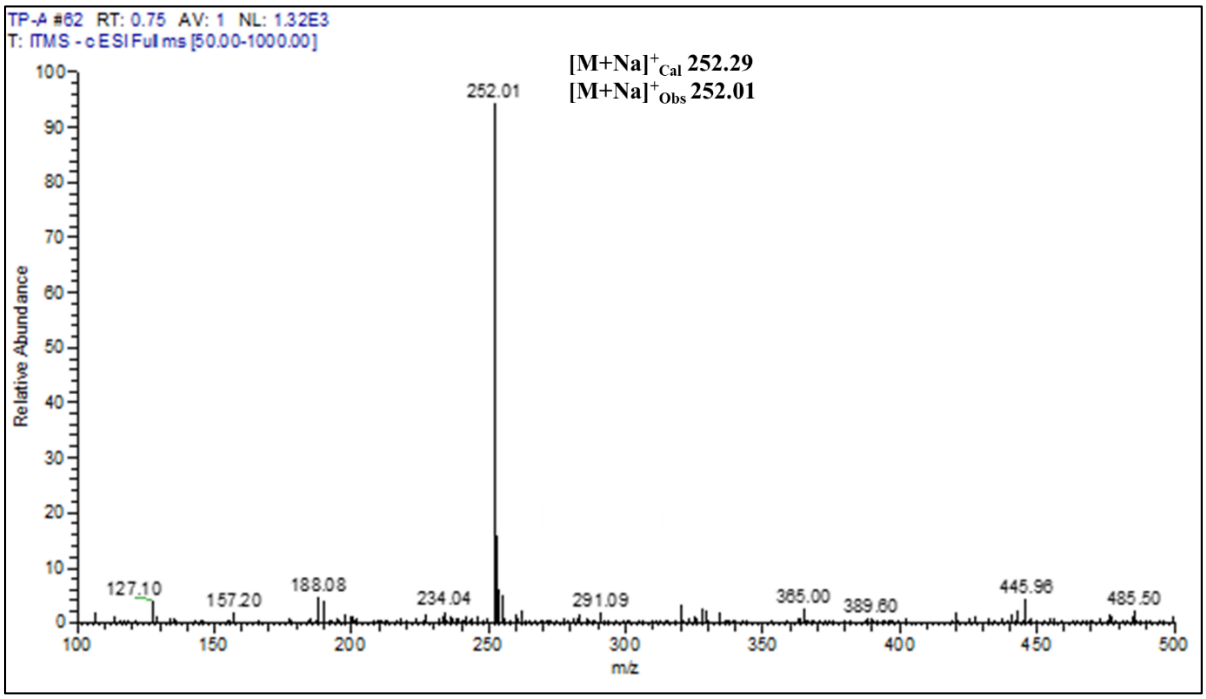


Figure S66: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NHMethyl

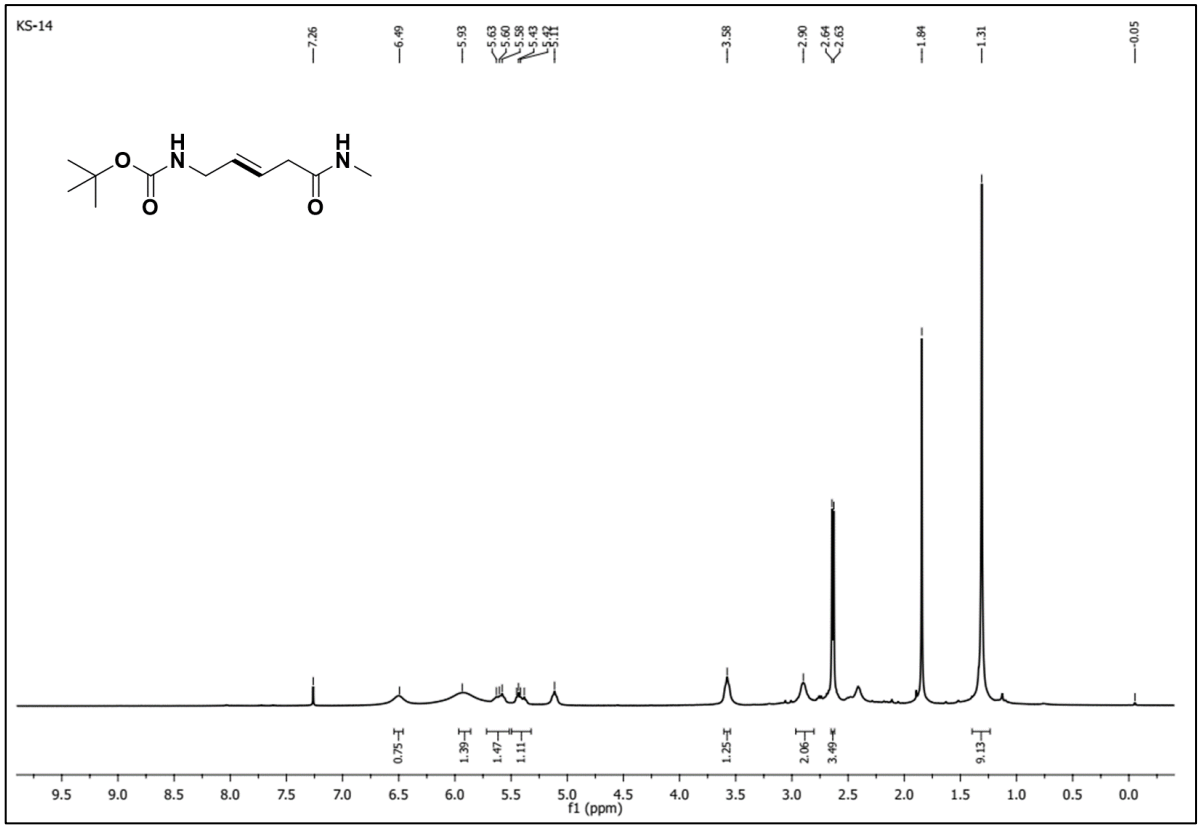


Figure S67: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NHMethyl in $CDCl_3$

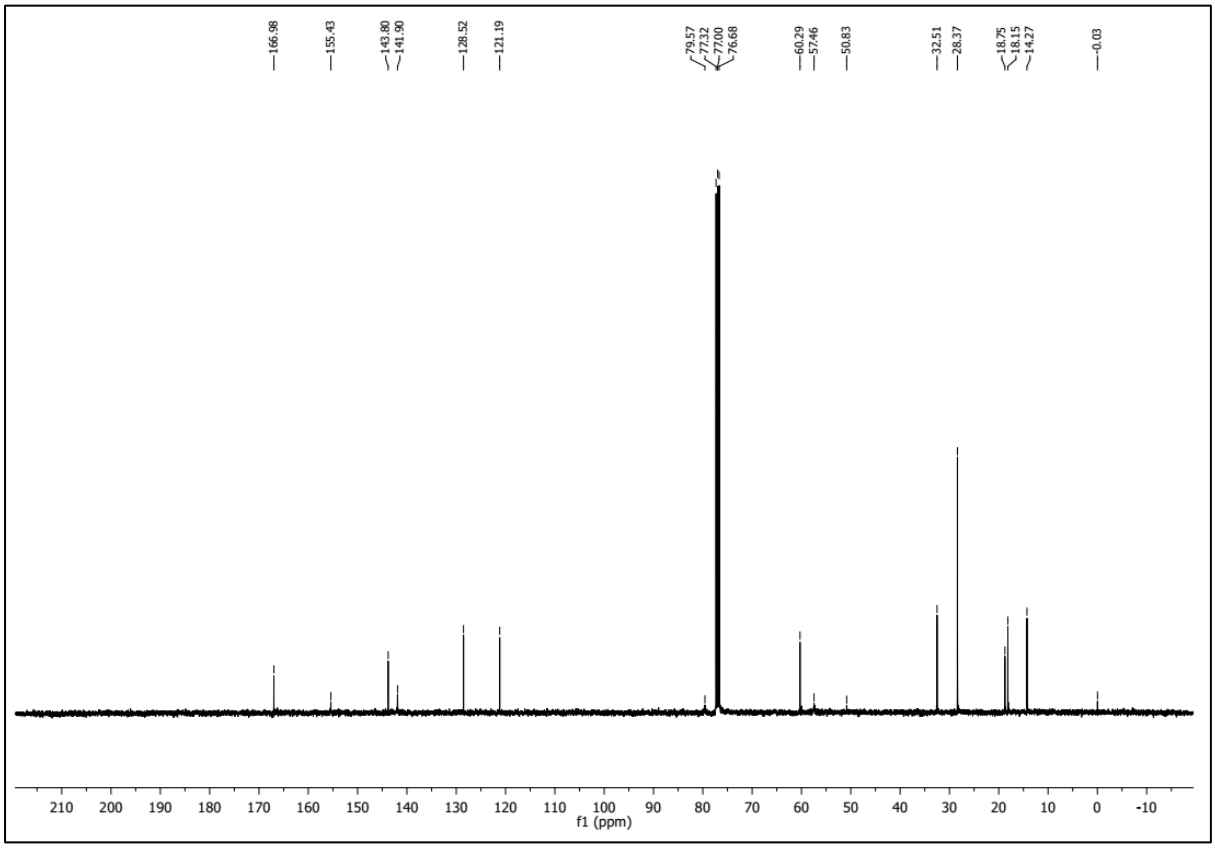


Figure S68: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NHMethyl in $CDCl_3$

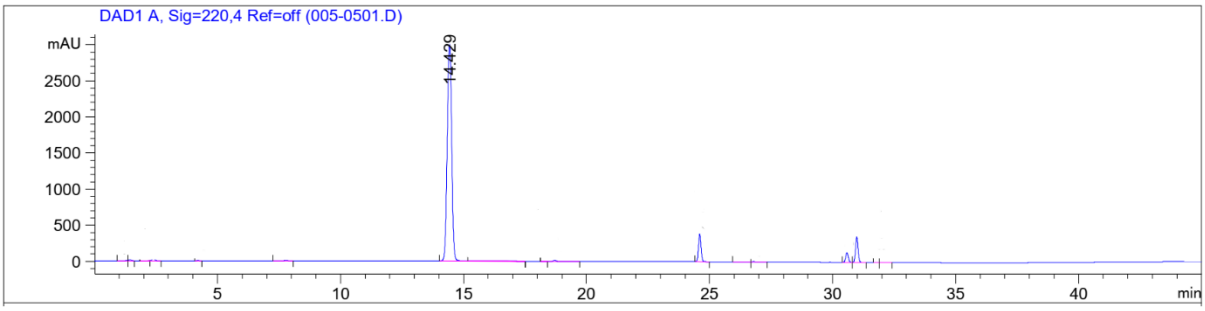


Figure S69: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NHEthyl

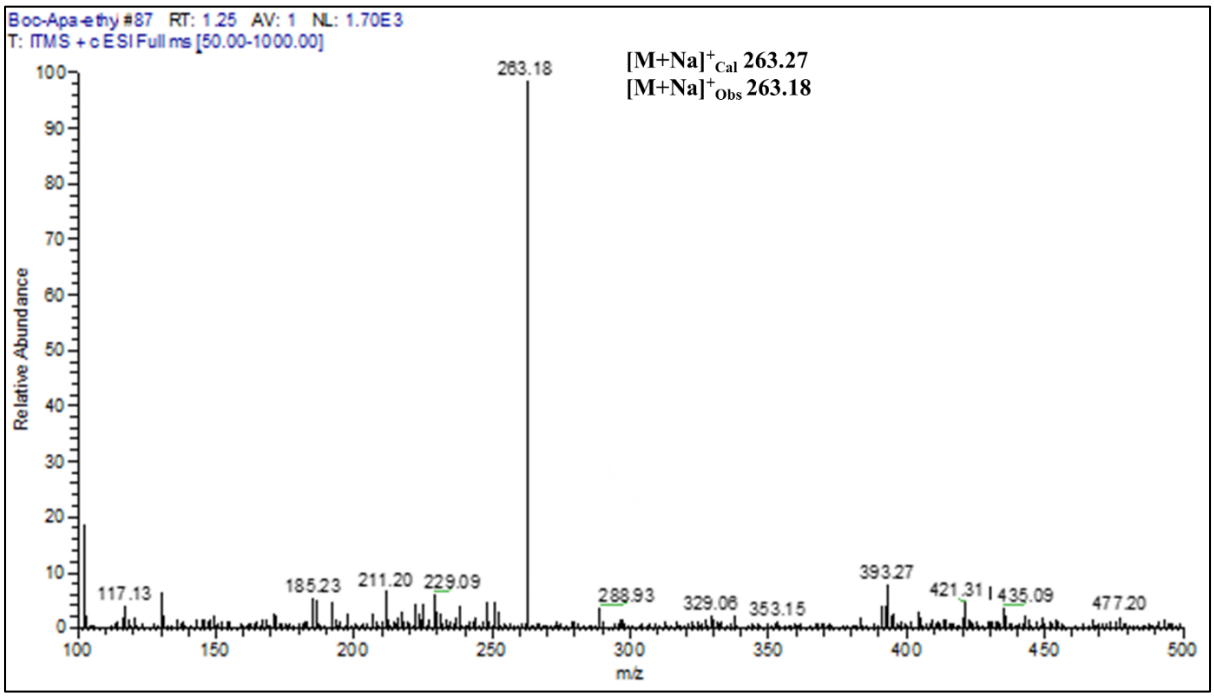


Figure S70: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NHEthyl

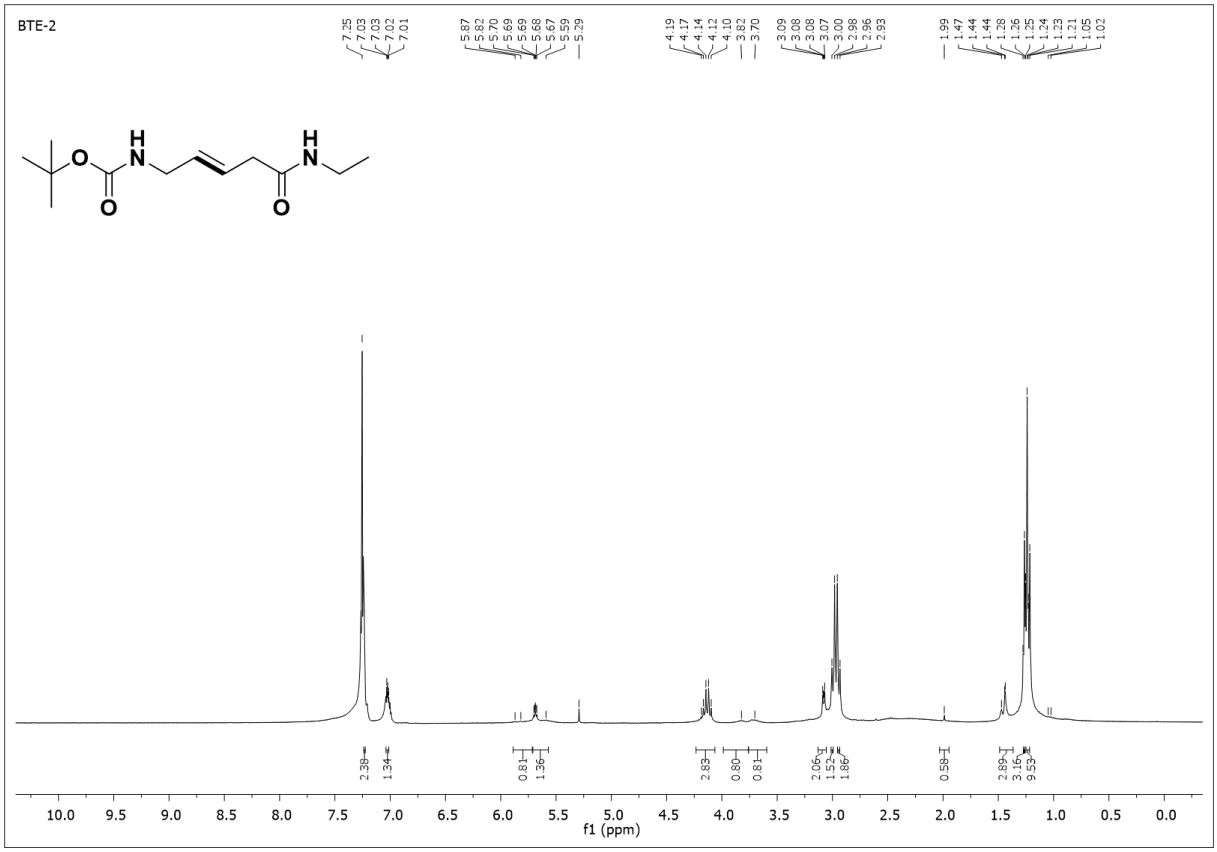


Figure S71: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NHEthyl in $CDCl_3$

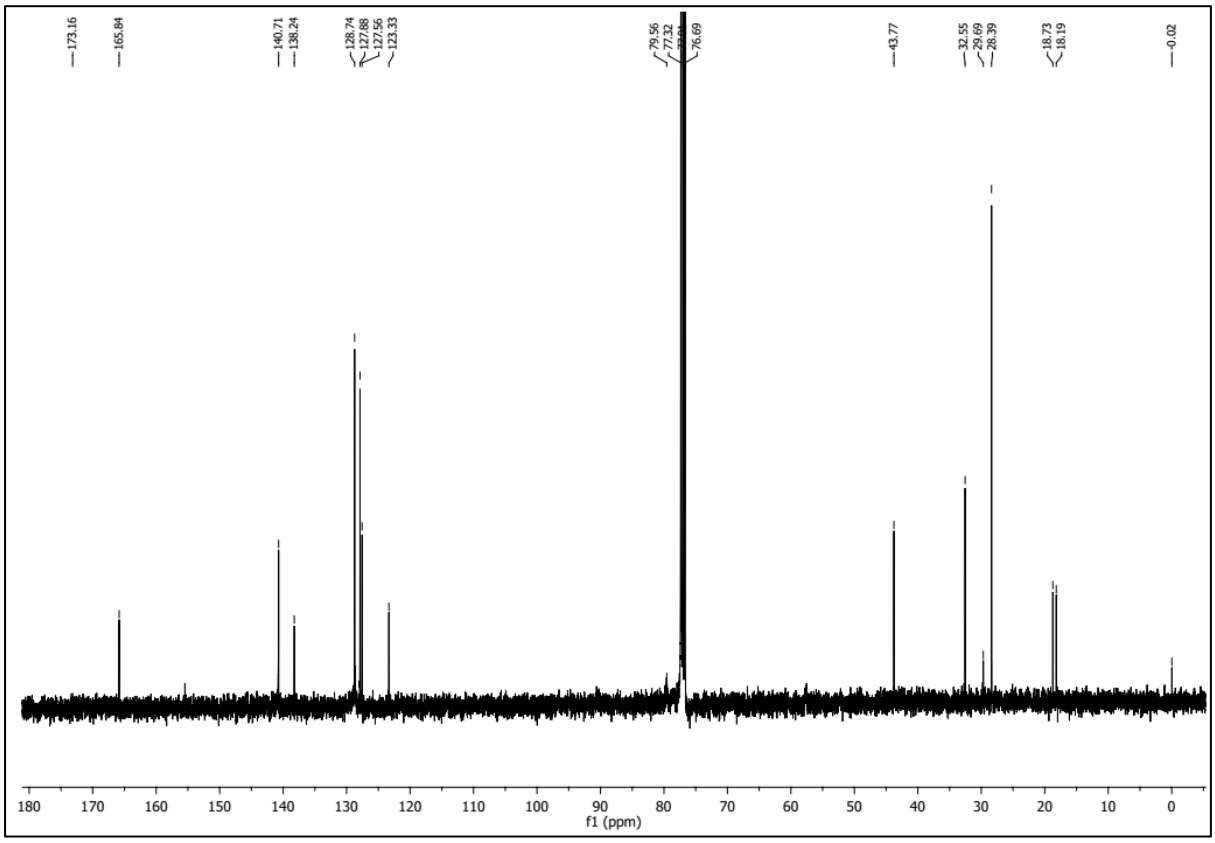


Figure S72: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NHEthyl in $CDCl_3$

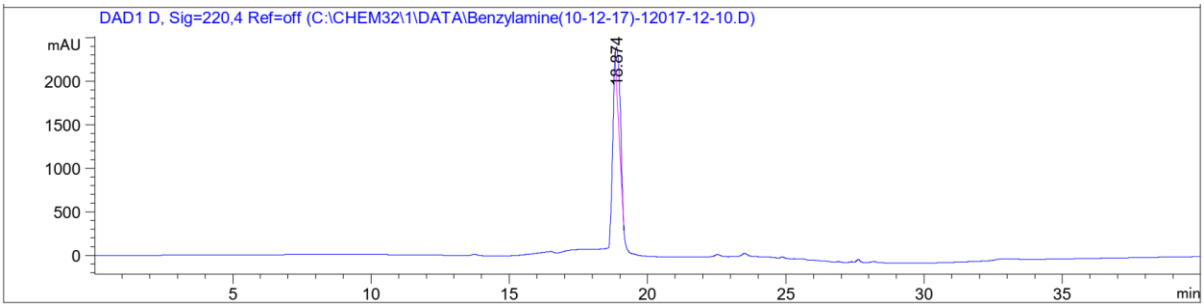


Figure S73: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NHbenzyl

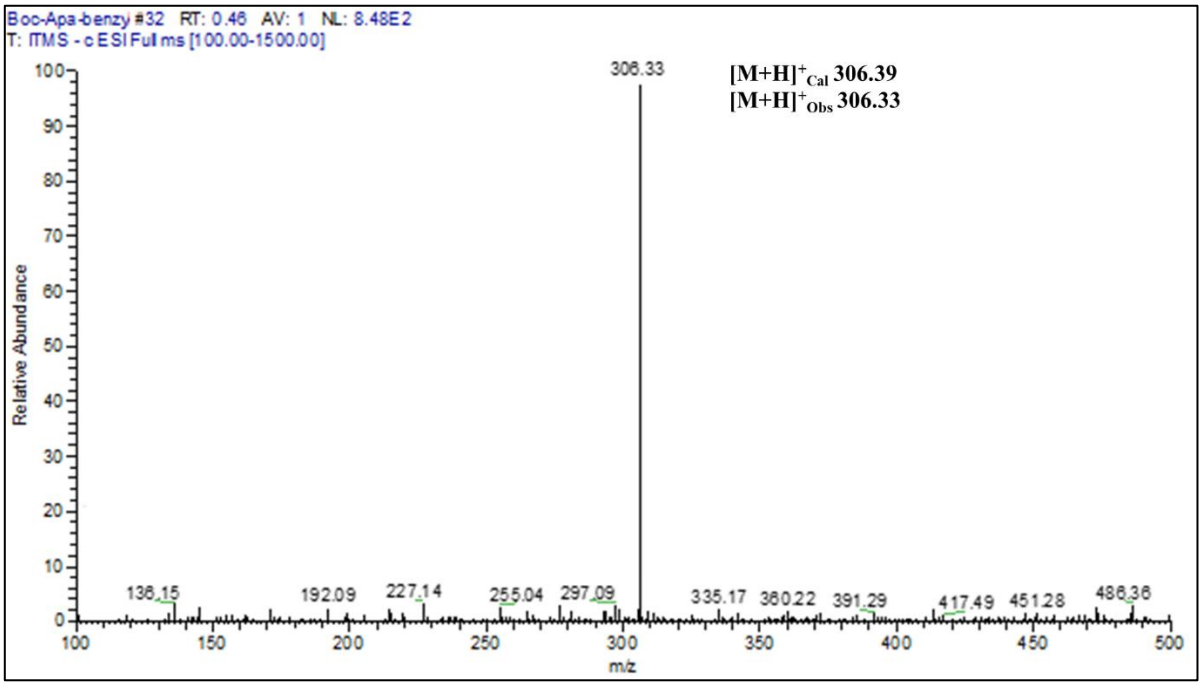


Figure S74: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NHbenzyl

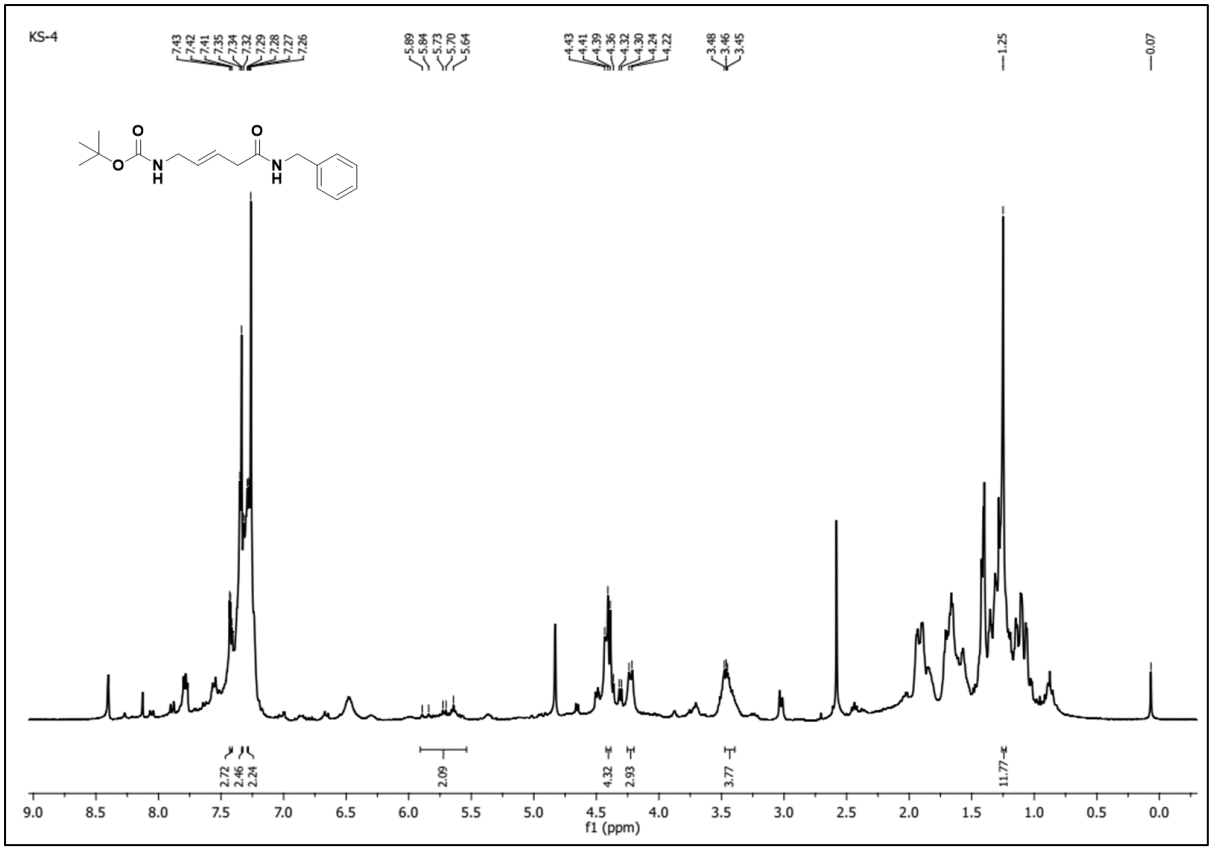


Figure S75: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NHbenzyl in $CDCl_3$

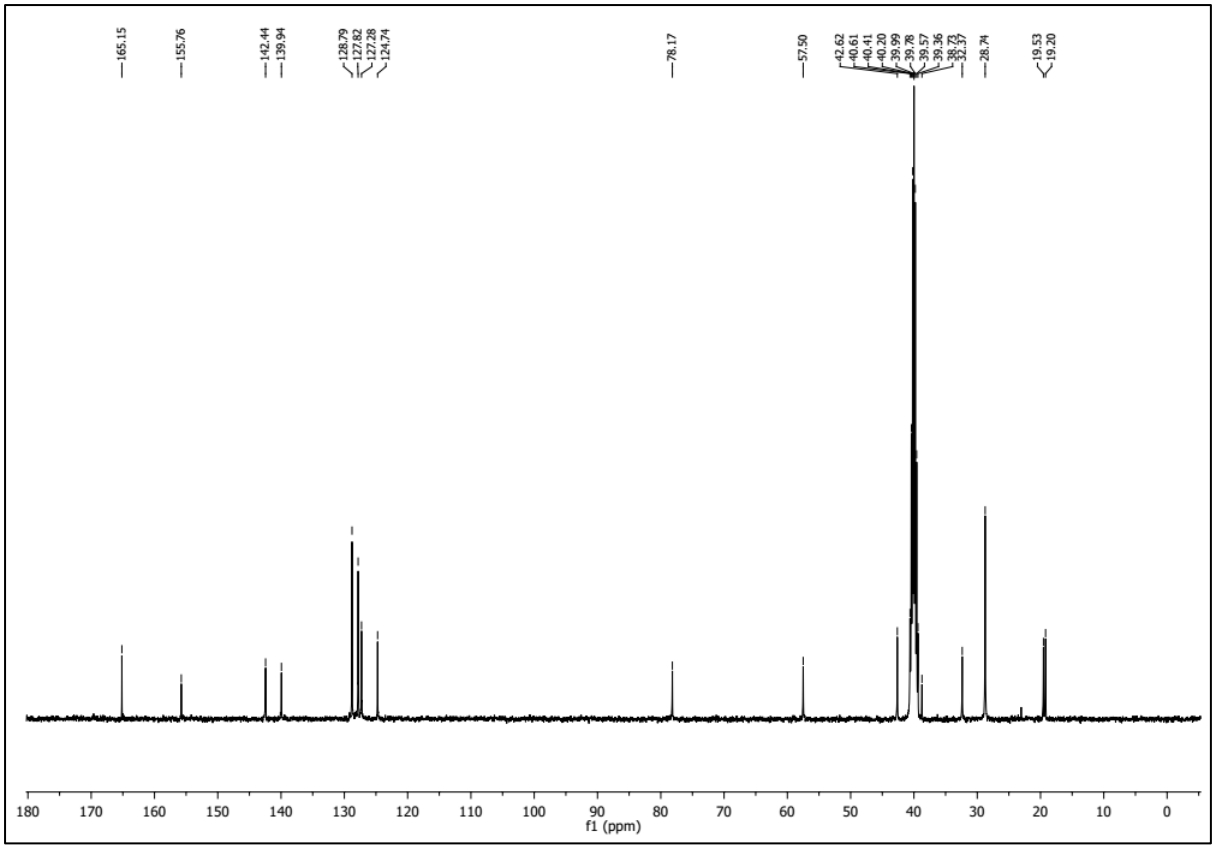


Figure S76: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NHbenzyl in DMSO-d_6

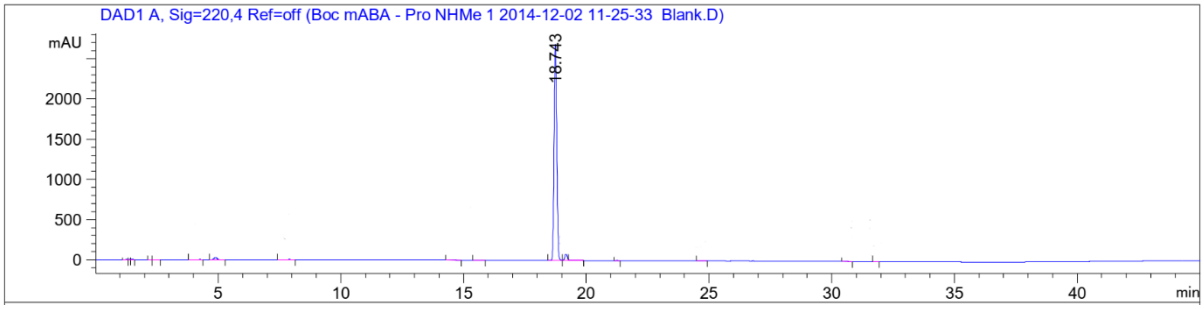


Figure S77: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NH*tert*butyl

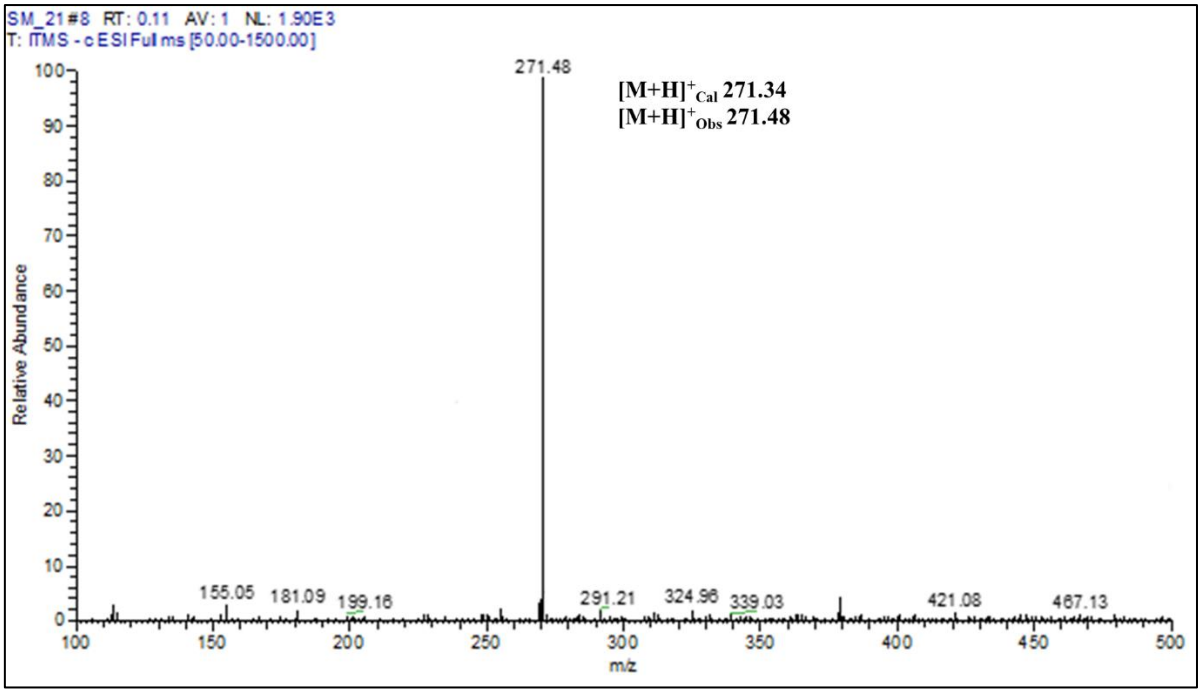


Figure S78: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NH*tert*butyl

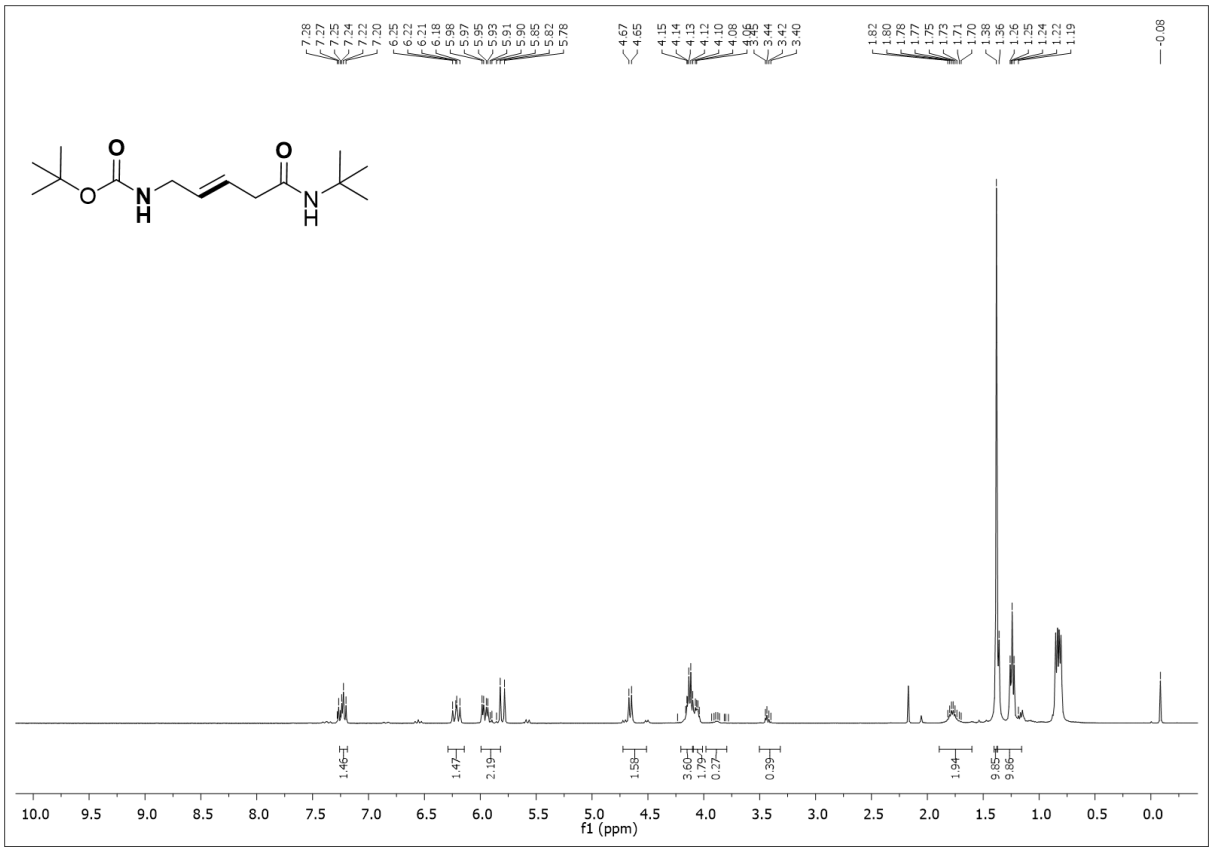


Figure S79: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*tert*butyl in $CDCl_3$

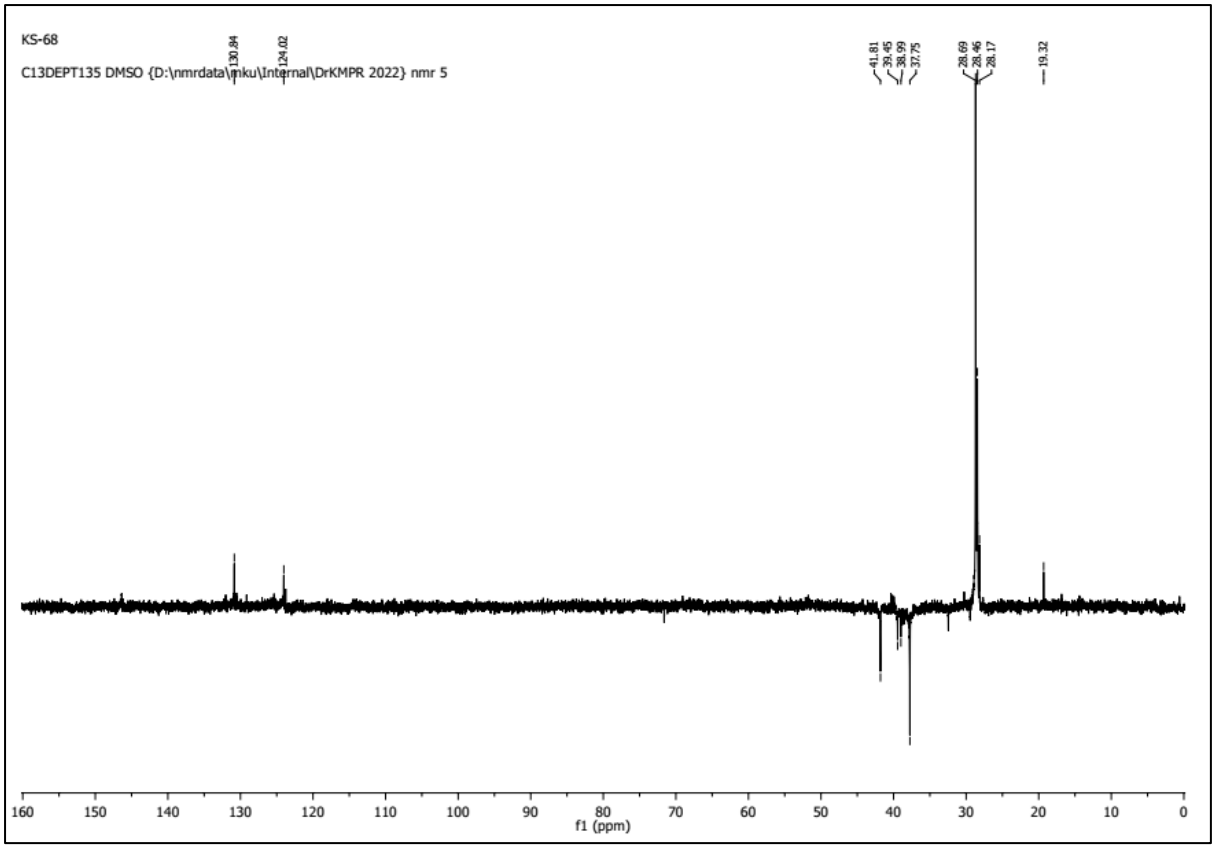


Figure S80: 300 MHz DEPT-135-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*tert*butyl in $CDCl_3$

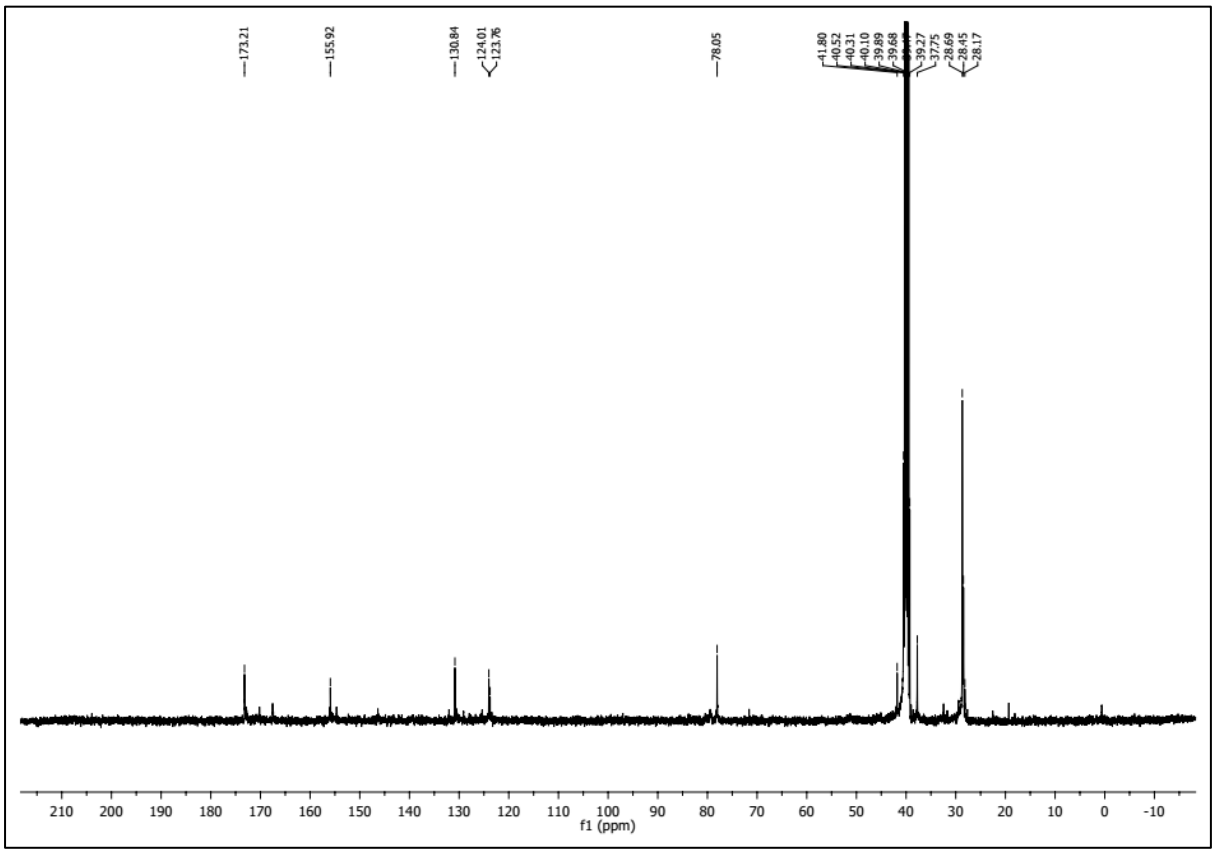


Figure S81: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*tert*butyl in DMSO-d_6

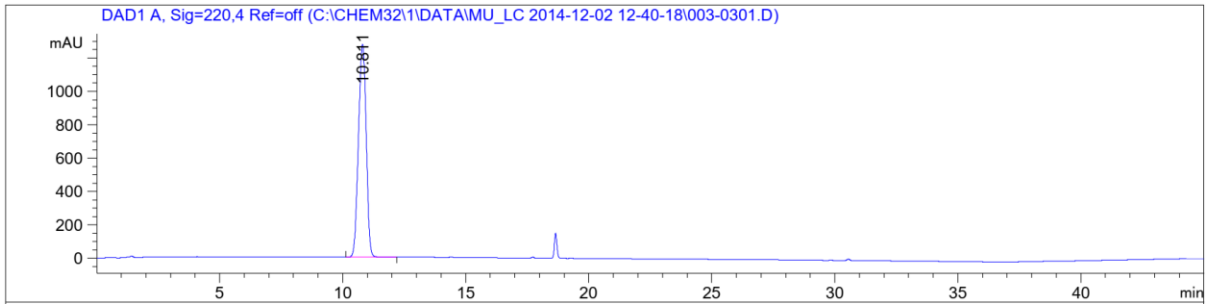


Figure S82: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NH*n*butyl

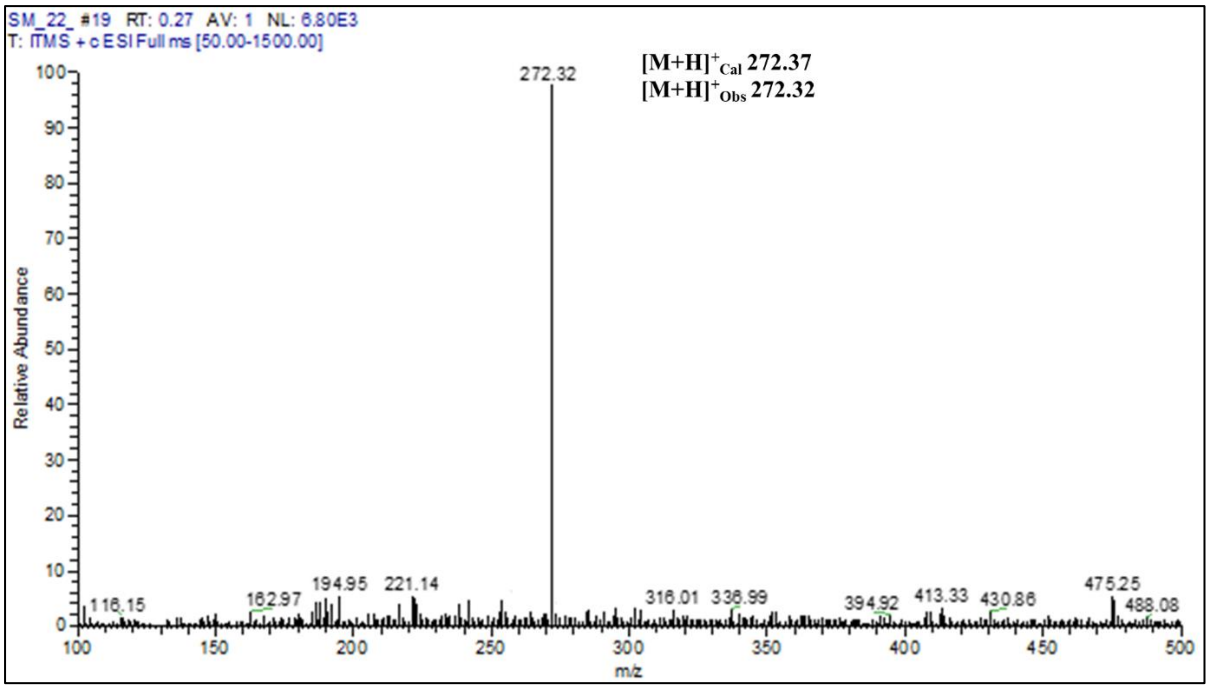


Figure S83: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NH*n*butyl

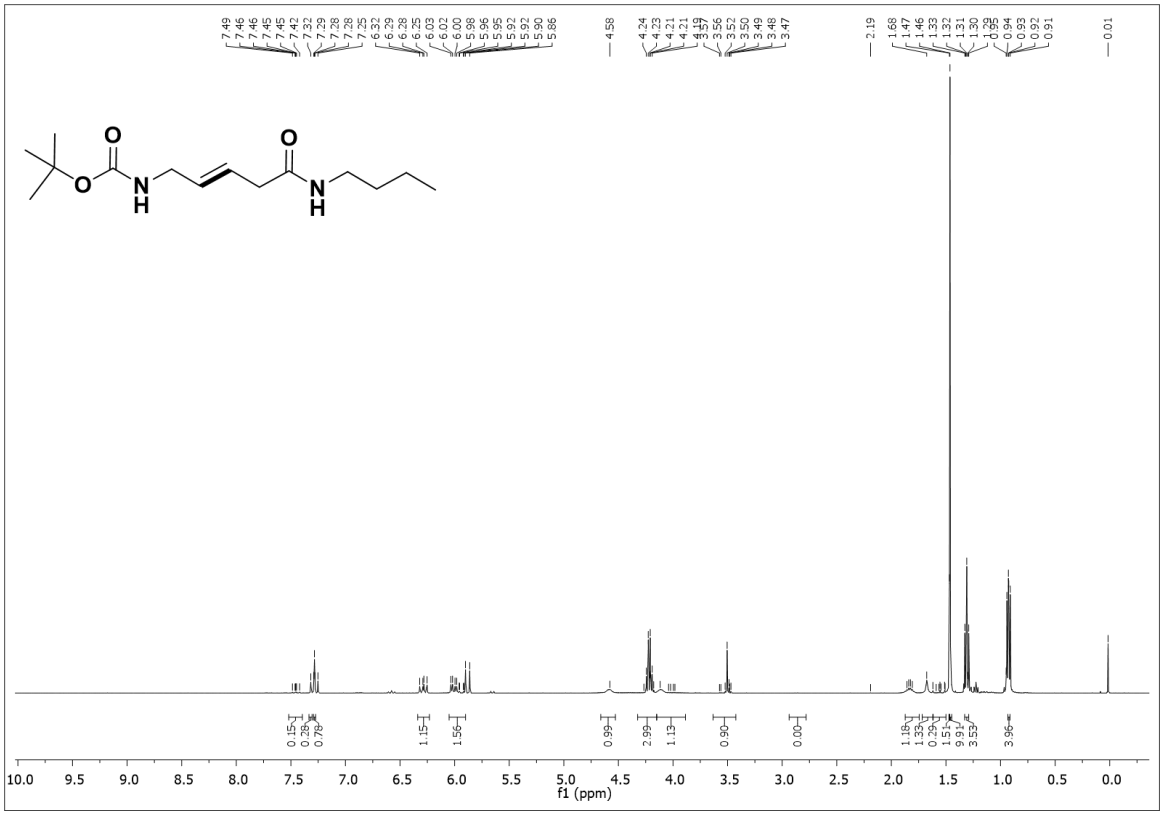


Figure S84: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*n*butyl in $CDCl_3$

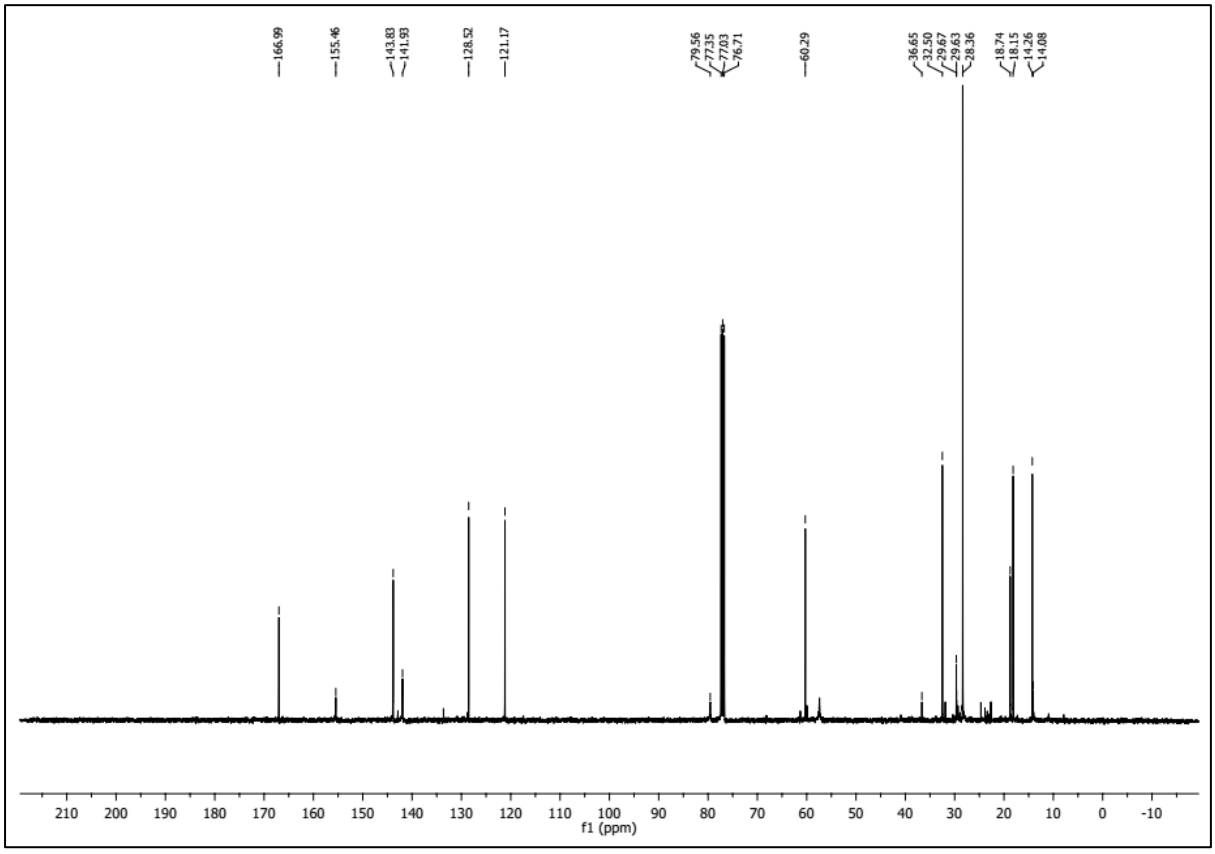


Figure S85: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*n*butyl in $CDCl_3$

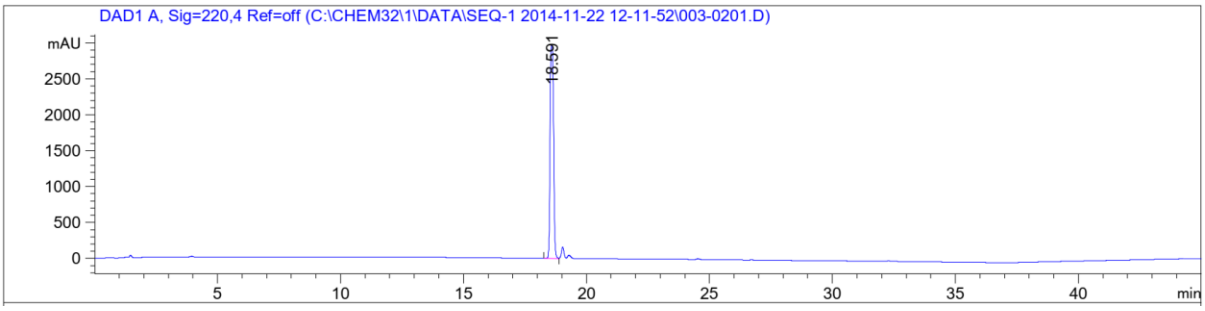


Figure S86: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NH*sec*butyl

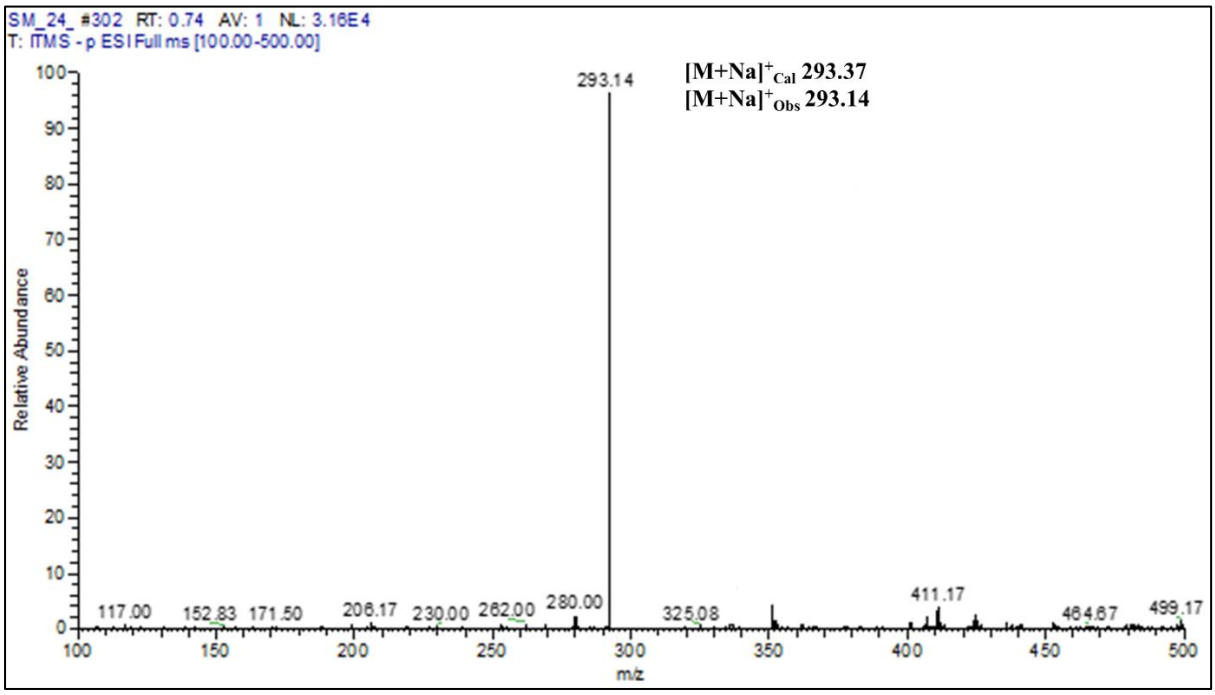


Figure S87: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NH*sec*butyl

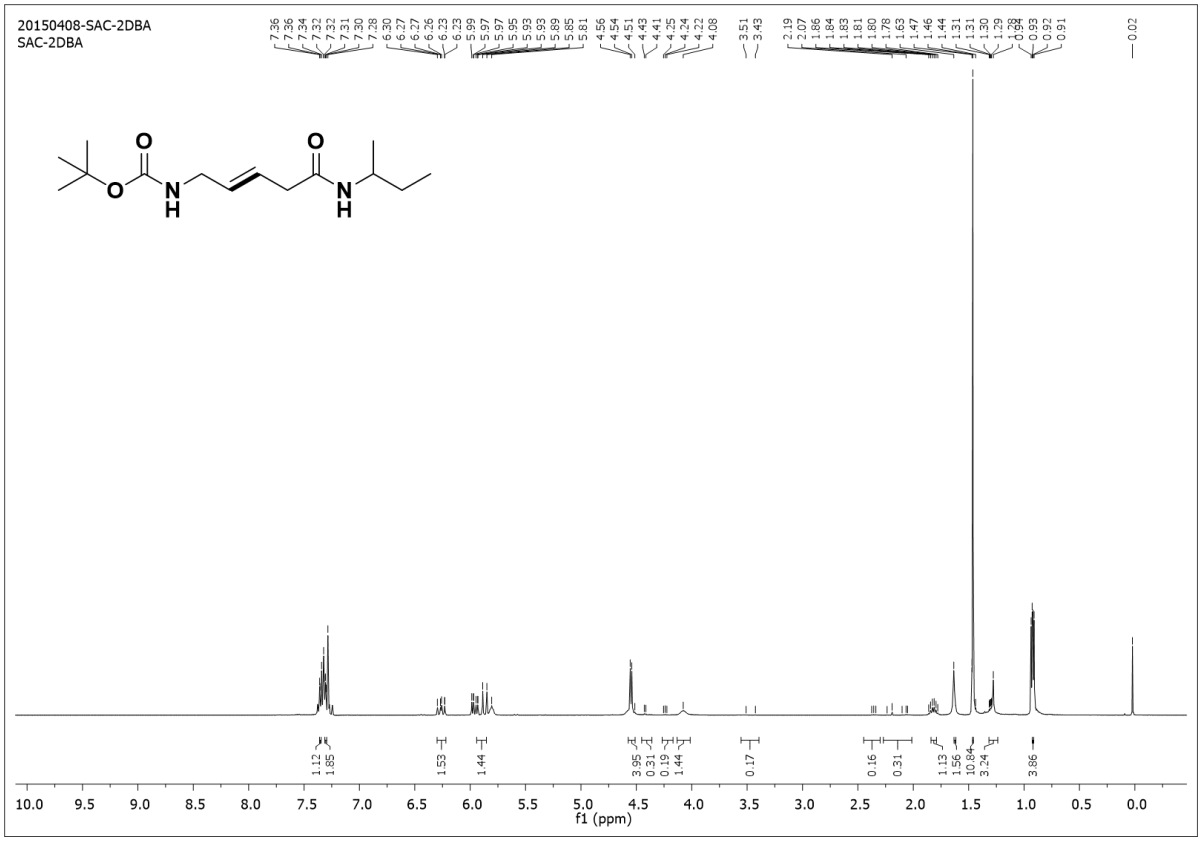


Figure S88: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*sec*butyl in $CDCl_3$

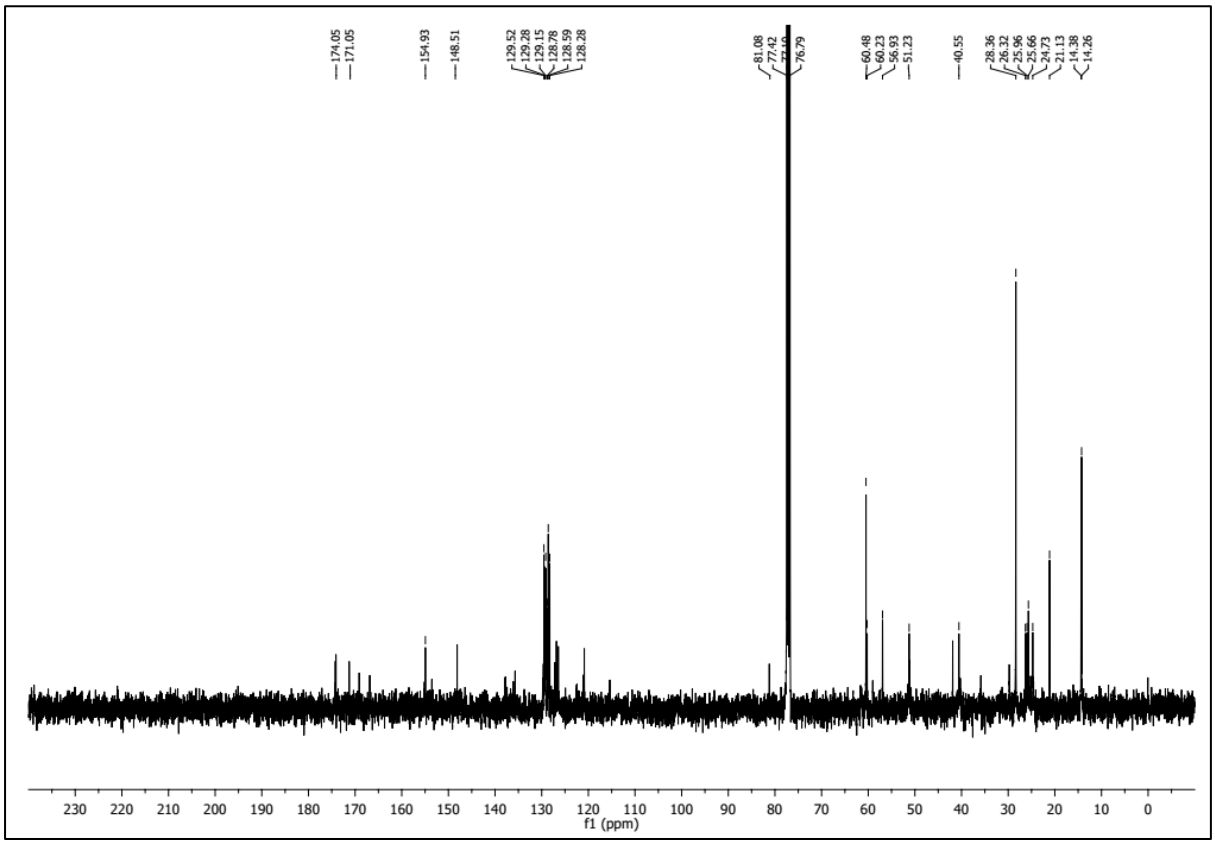


Figure S89: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NH*sec*butyl in $CDCl_3$

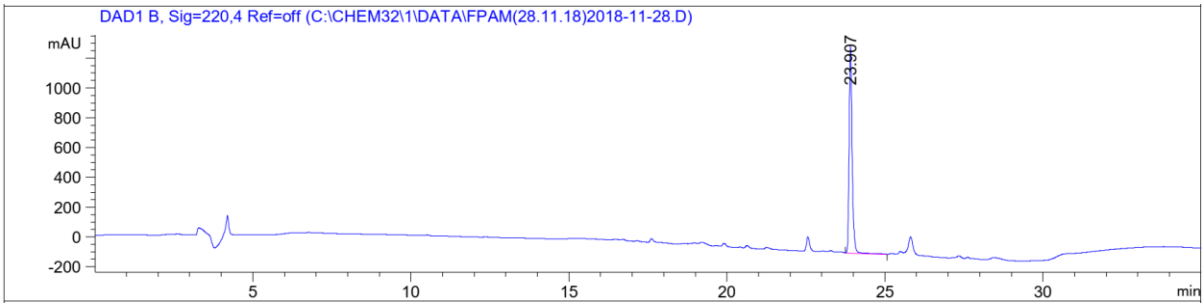


Figure S90: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-NDimethyl

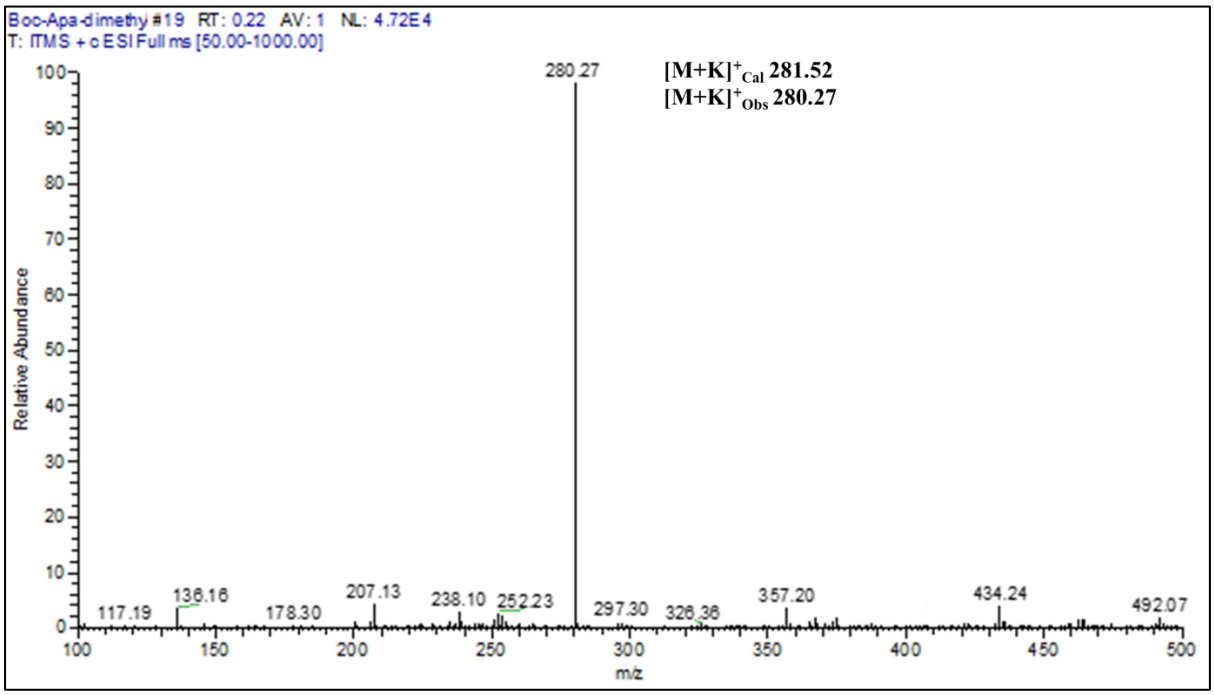


Figure S91: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-NDimethyl

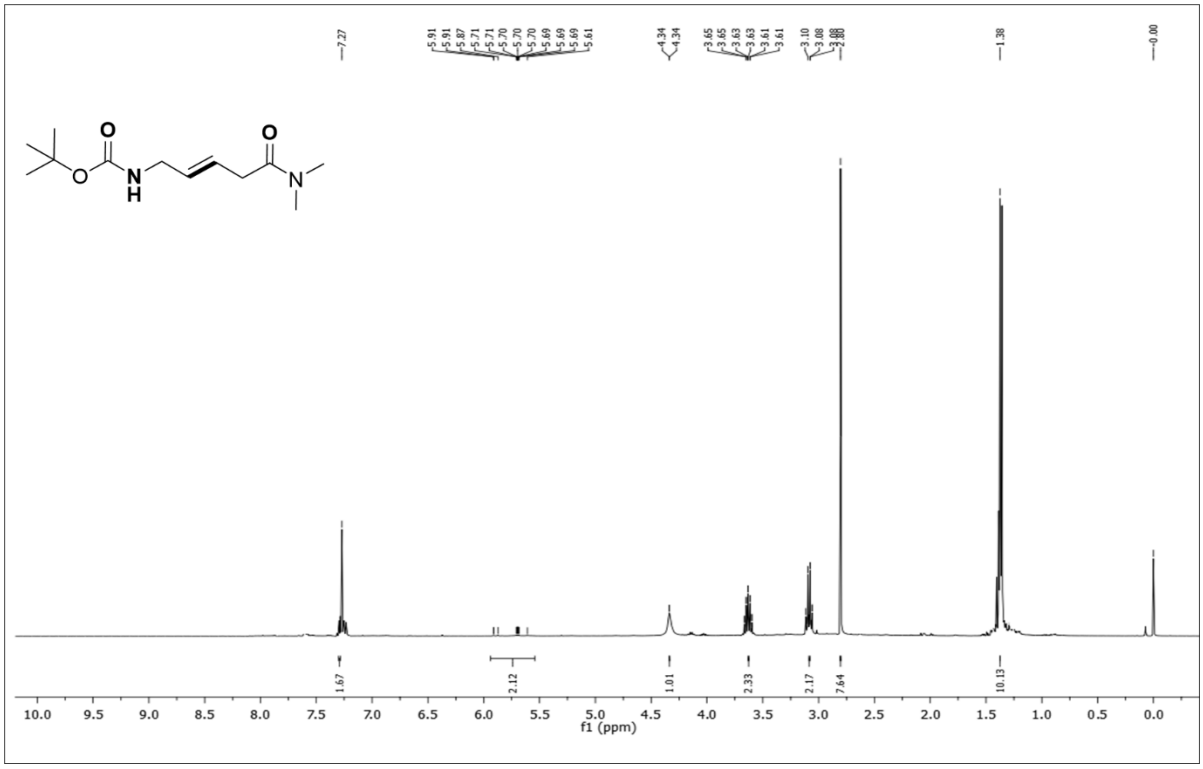


Figure S92: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-NDimethyl in $CDCl_3$

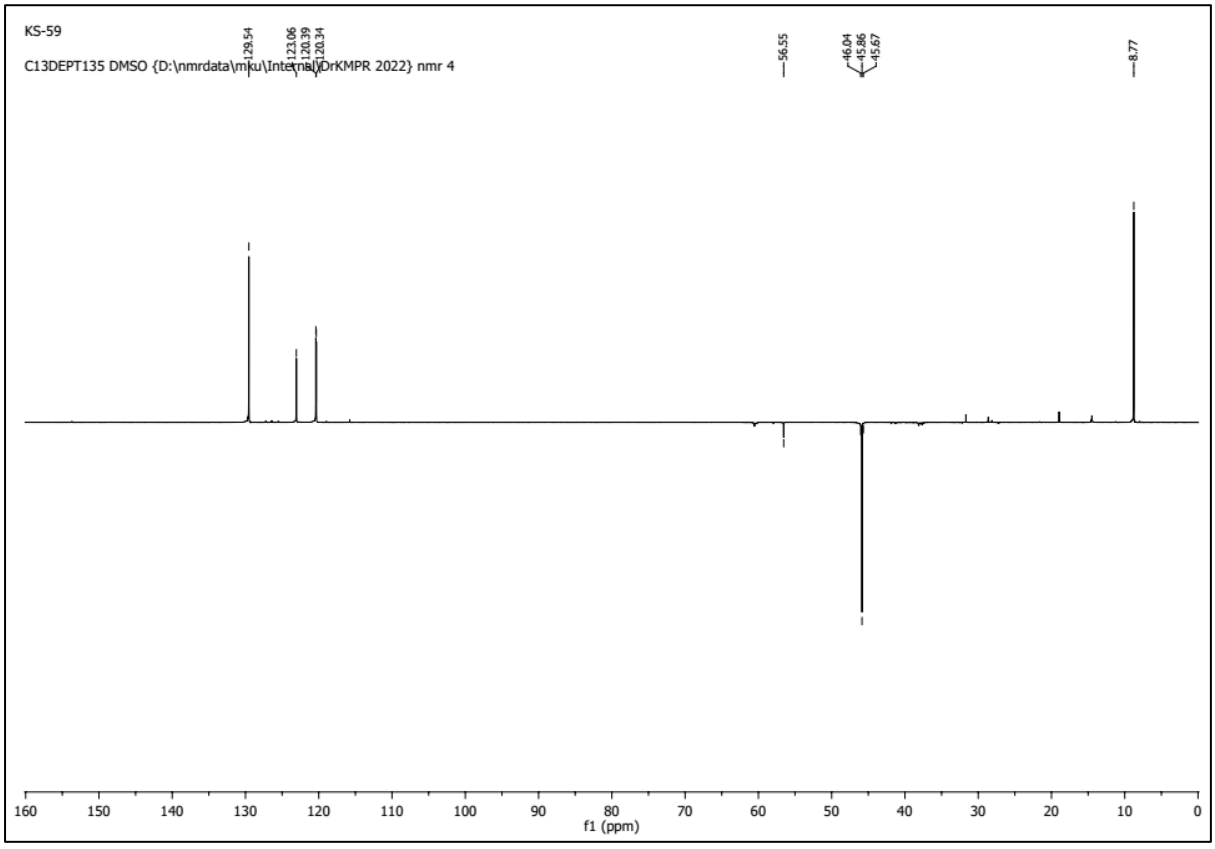


Figure S93: 300 MHz DEPT-135-NMR spectrum of *t*Boc-*trans*-δ-Apa-NDimethyl in $CDCl_3$

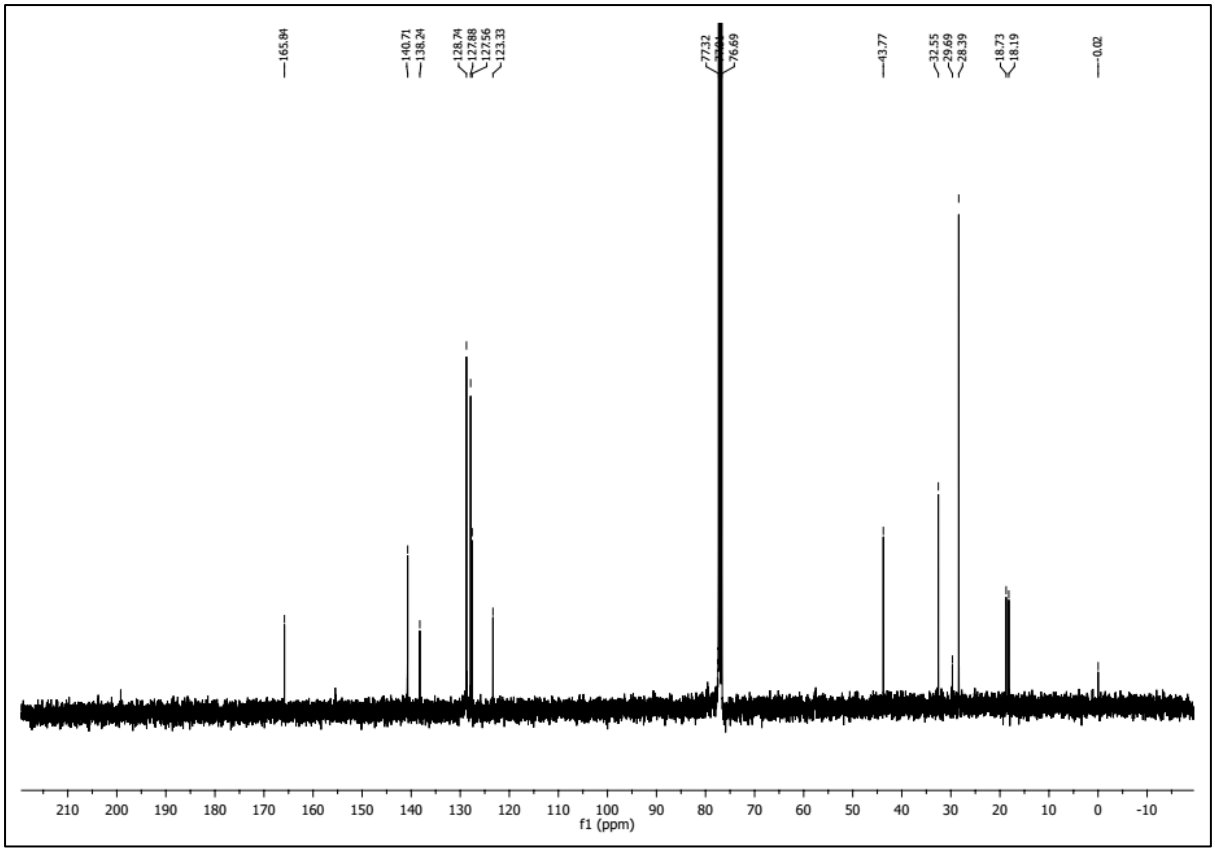


Figure S94: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-NDimethyl in $CDCl_3$

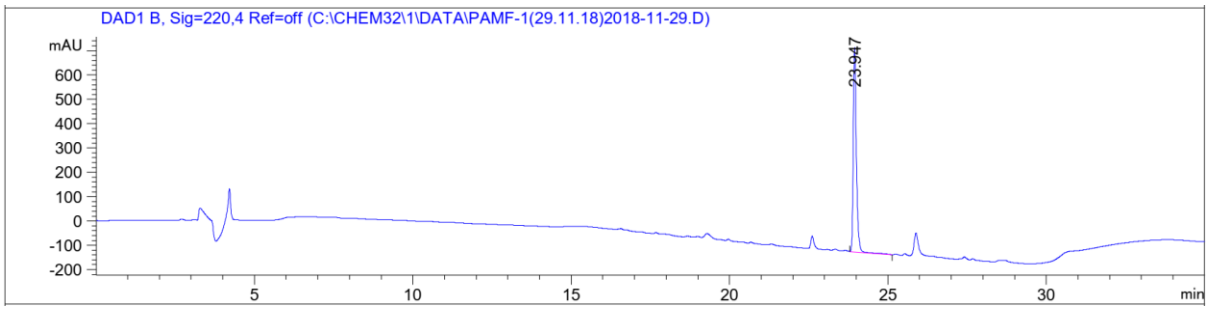


Figure S95: RP-HPLC Chromatogram of *iso*butyryl-*trans*-δ-Apa-NDimethyl

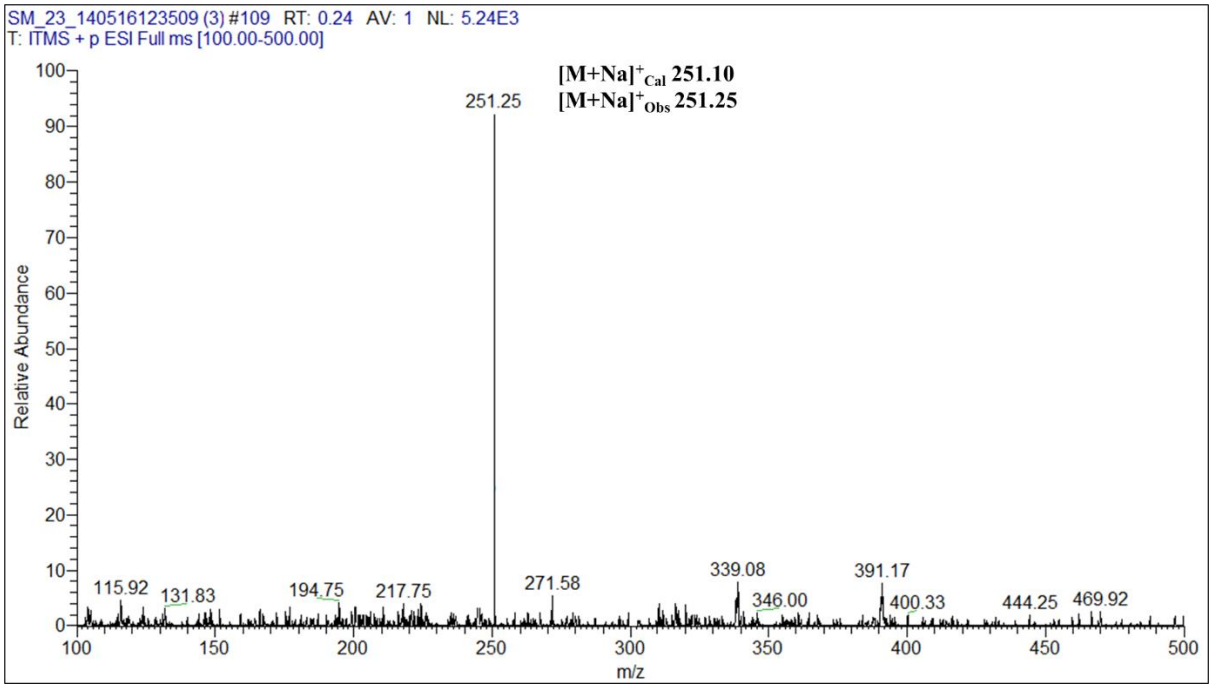


Figure S96: ESI-MS spectrum of *iso*butyryl-*trans*-δ-Apa-NDimethyl

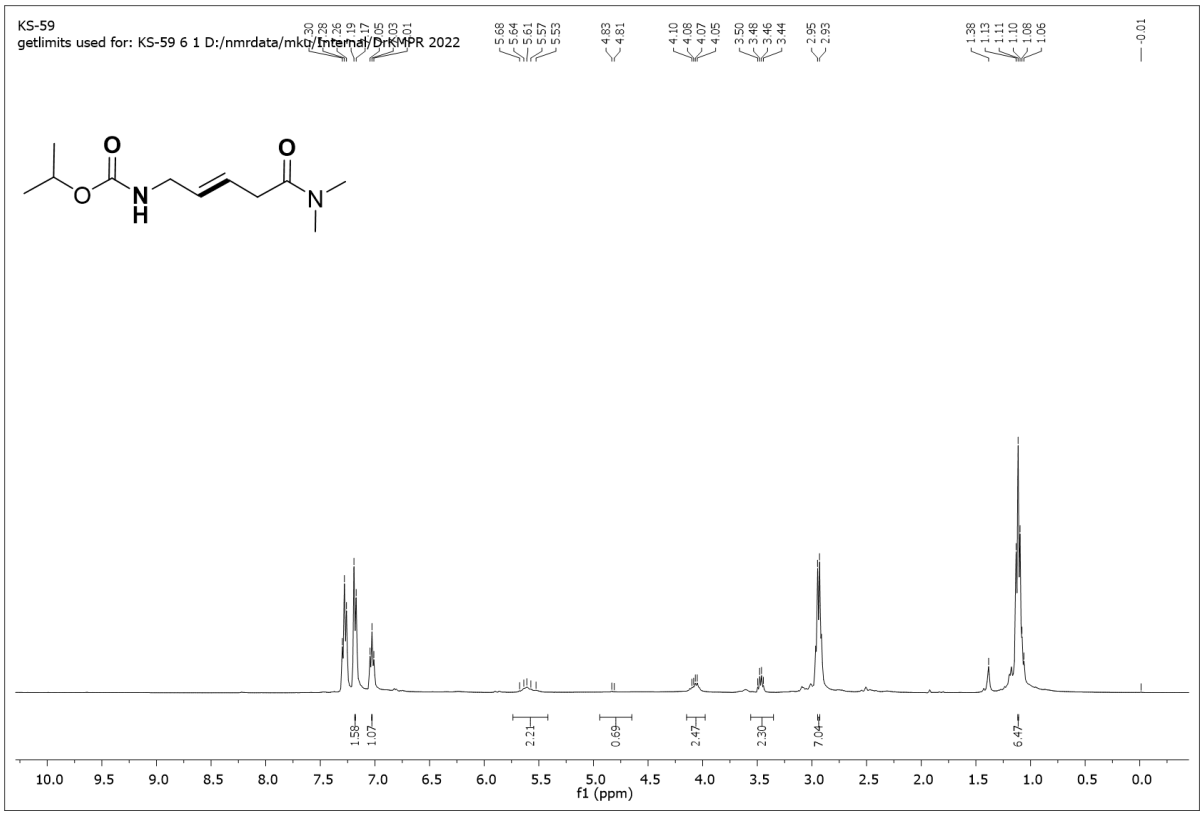


Figure S97: 300 MHz ^{1}H-NMR spectrum of *iso*butyryl-*trans*-δ-Apa-NDimethyl in $CDCl_3$

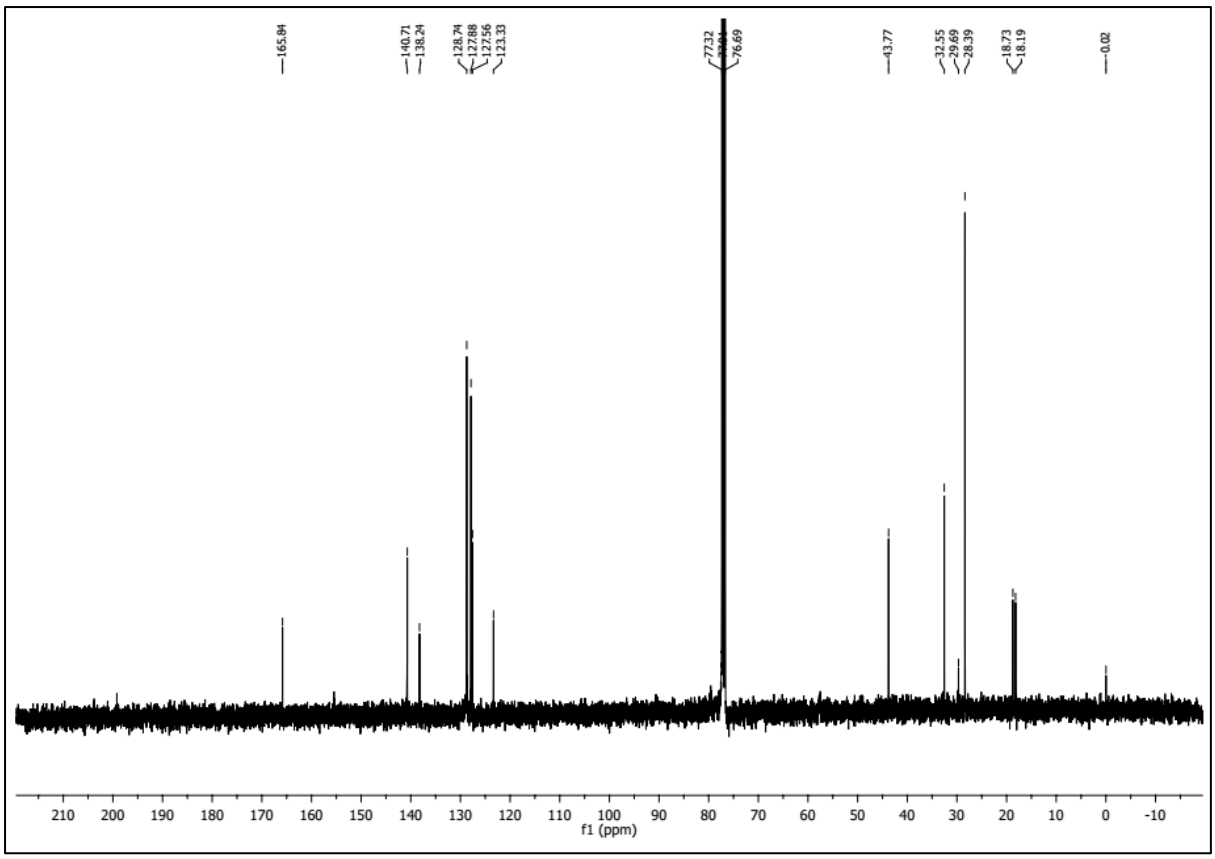


Figure S98: 75 MHz ^{13}C-NMR spectrum of *iso*butyryl-*trans*-δ-Apa-NDimethyl in $CDCl_3$

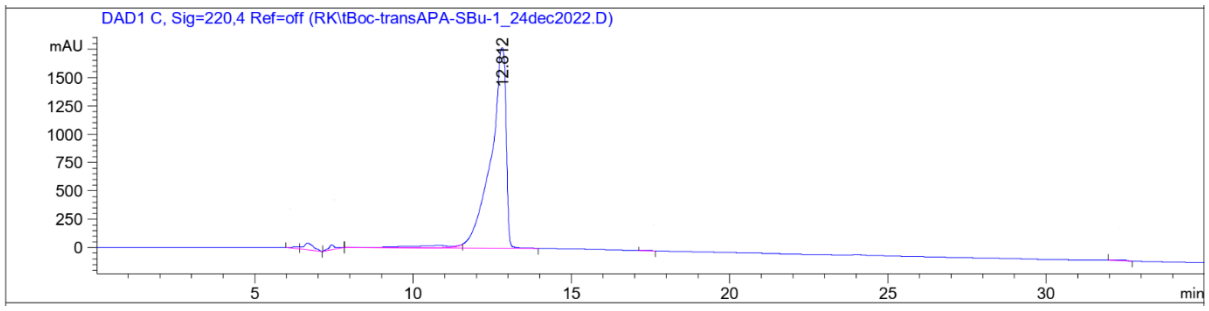


Figure S99: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-S*n*butyl

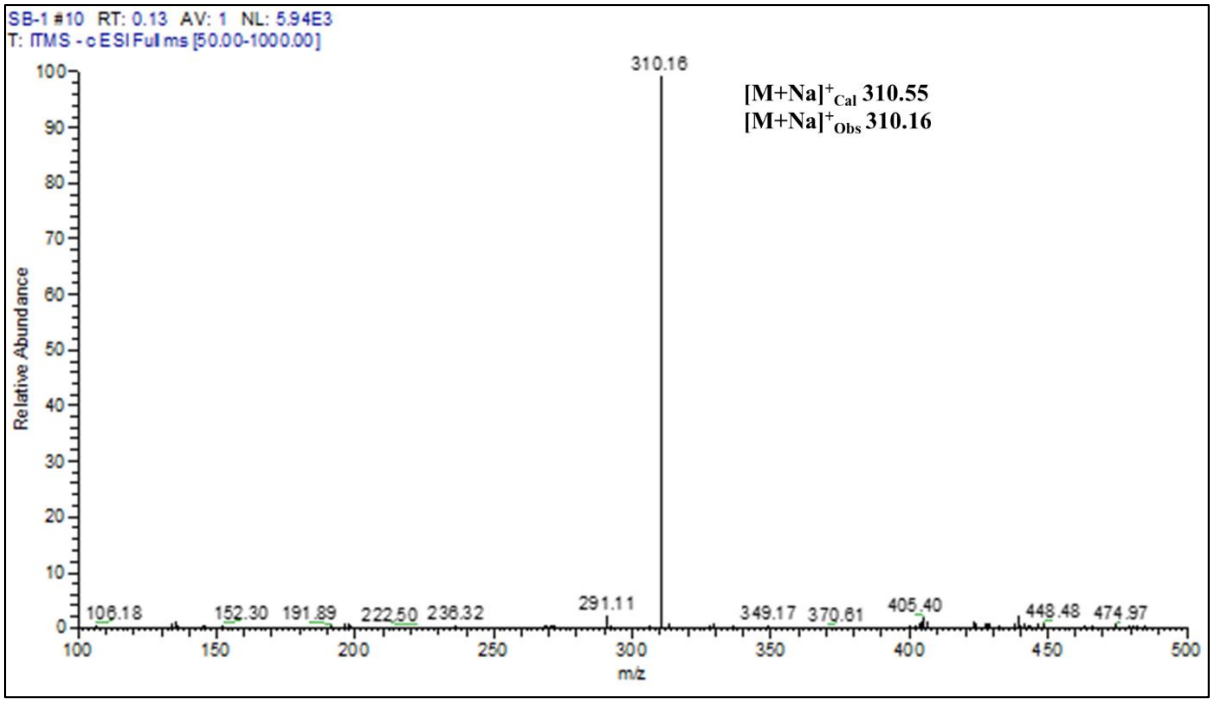


Figure S100: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-S*n*butyl

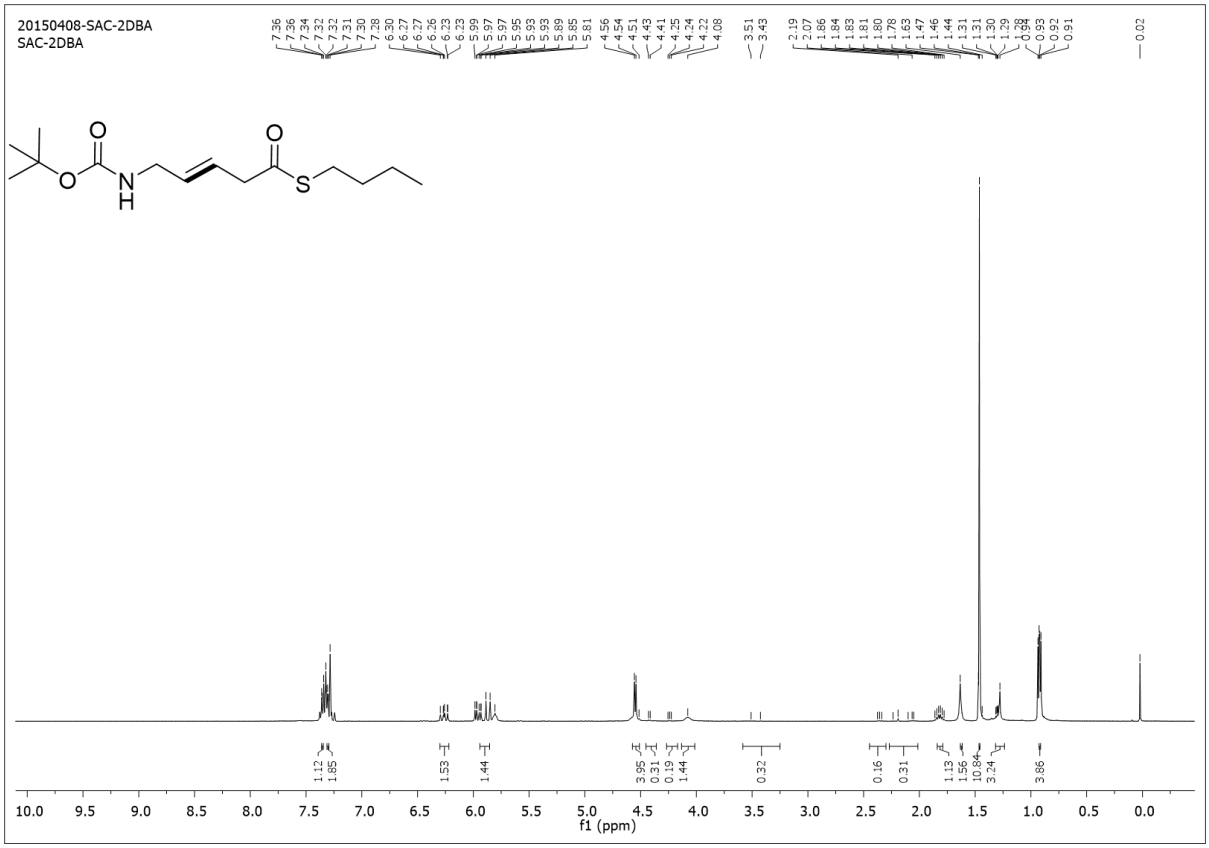


Figure S101: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-S*n*butyl in $CDCl_3$

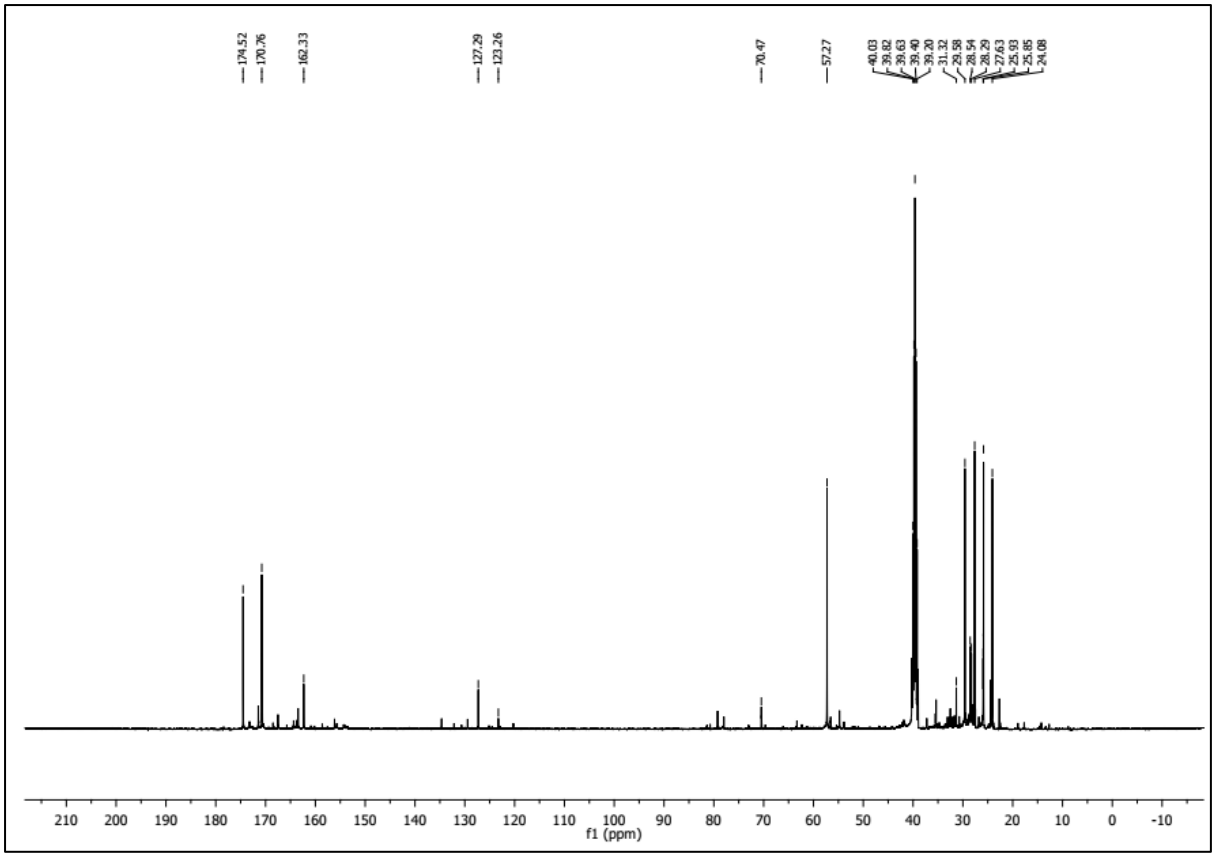


Figure S102: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-S*n*butyl in DMSO-d_6

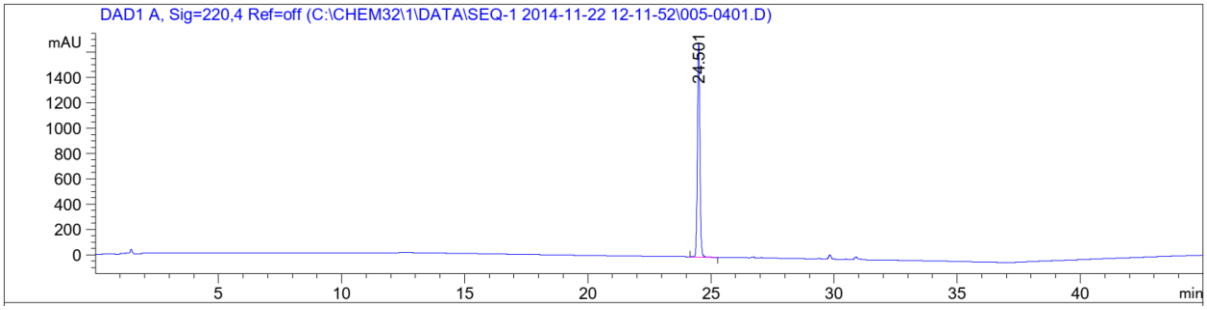


Figure S103: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-S*ert*butyl

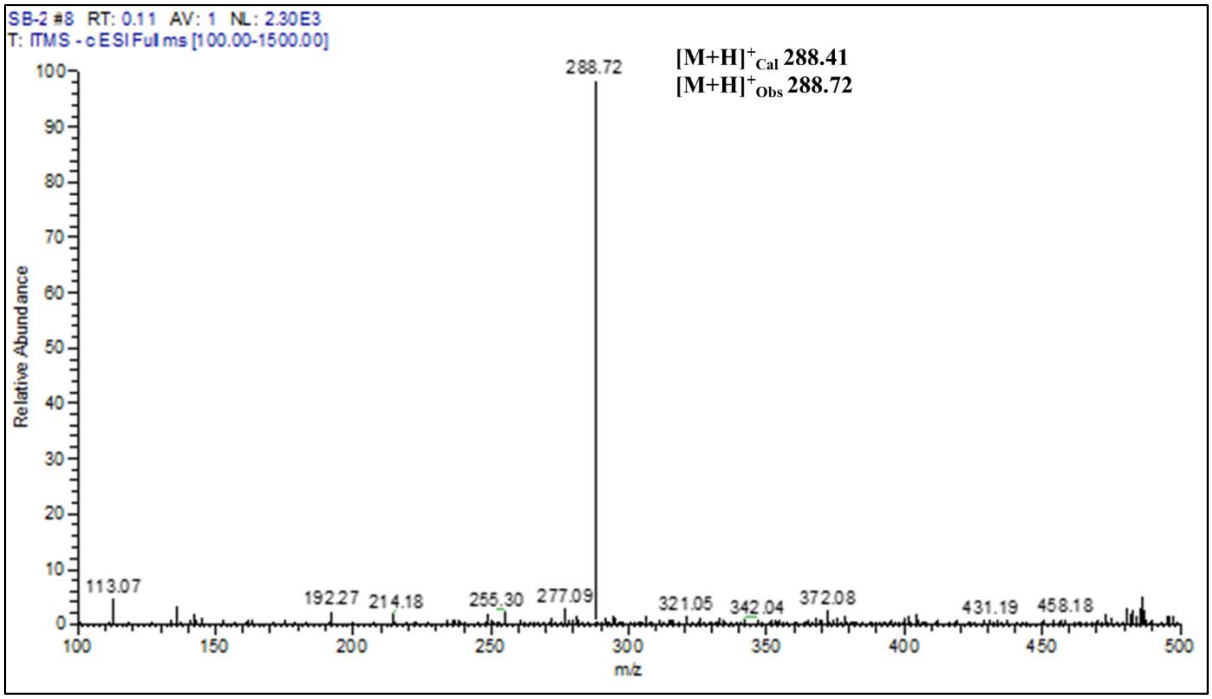


Figure S104: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-S*tert*butyl

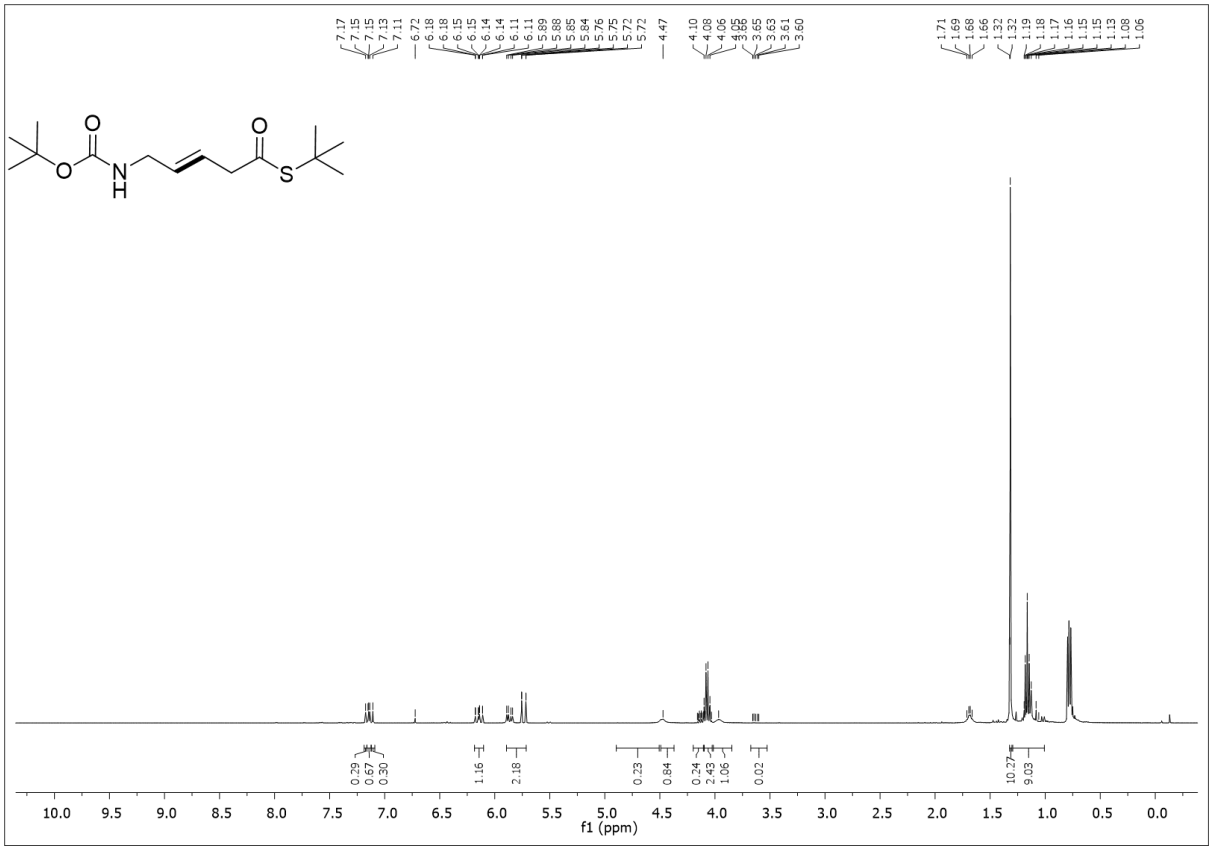


Figure S105: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-S*tert*butyl in $CDCl_3$

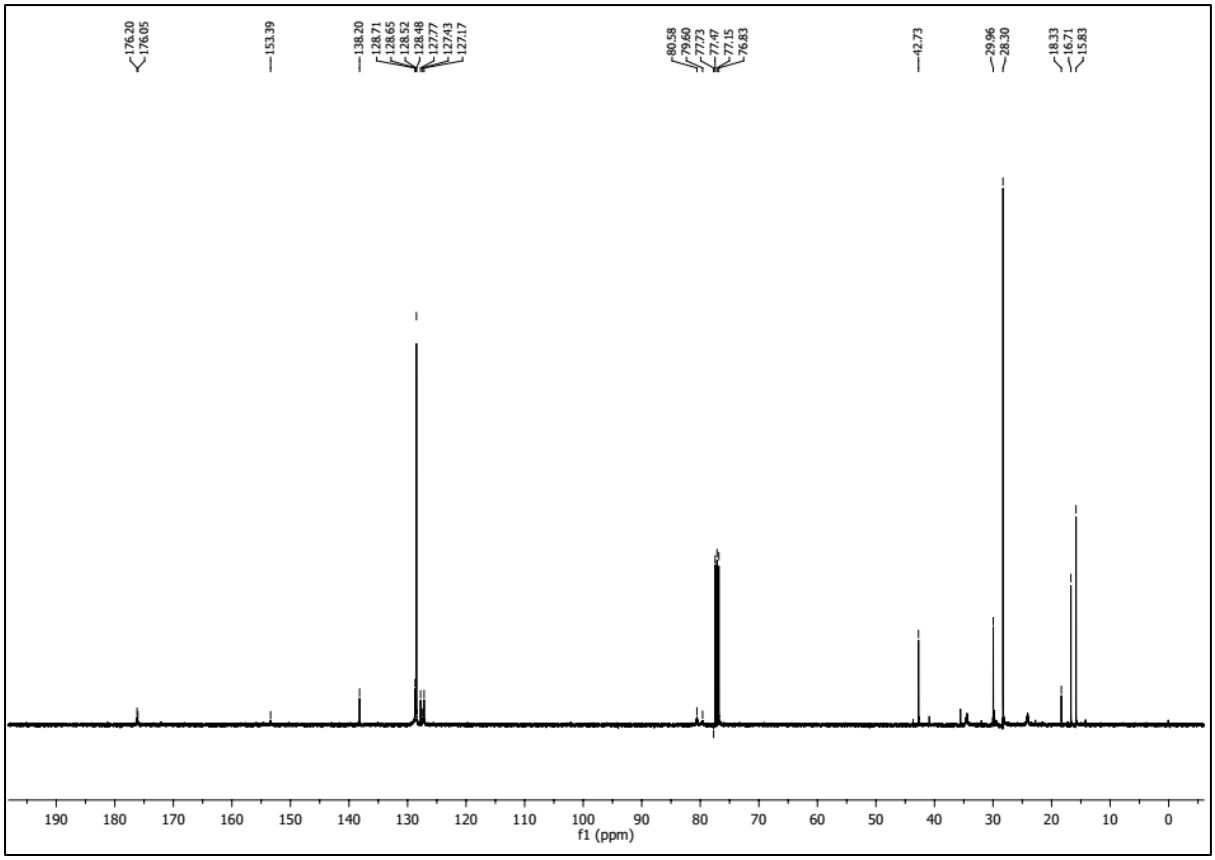


Figure S106: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-S*tert*butyl in $CDCl_3$

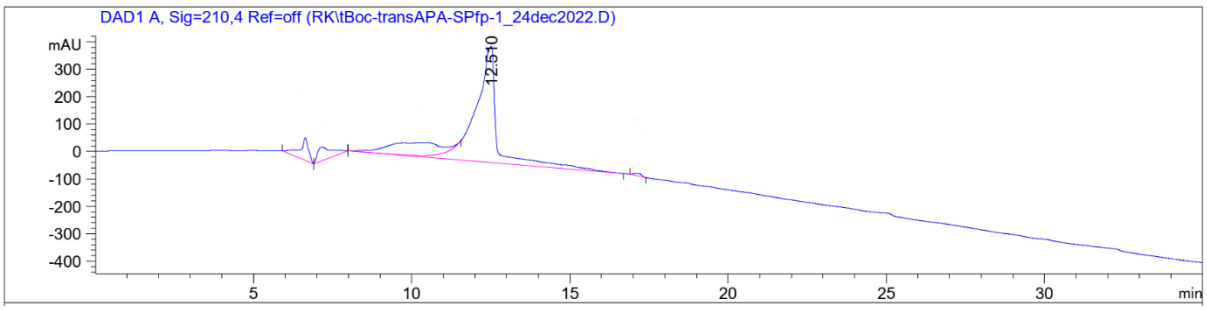


Figure S107: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-OPfp

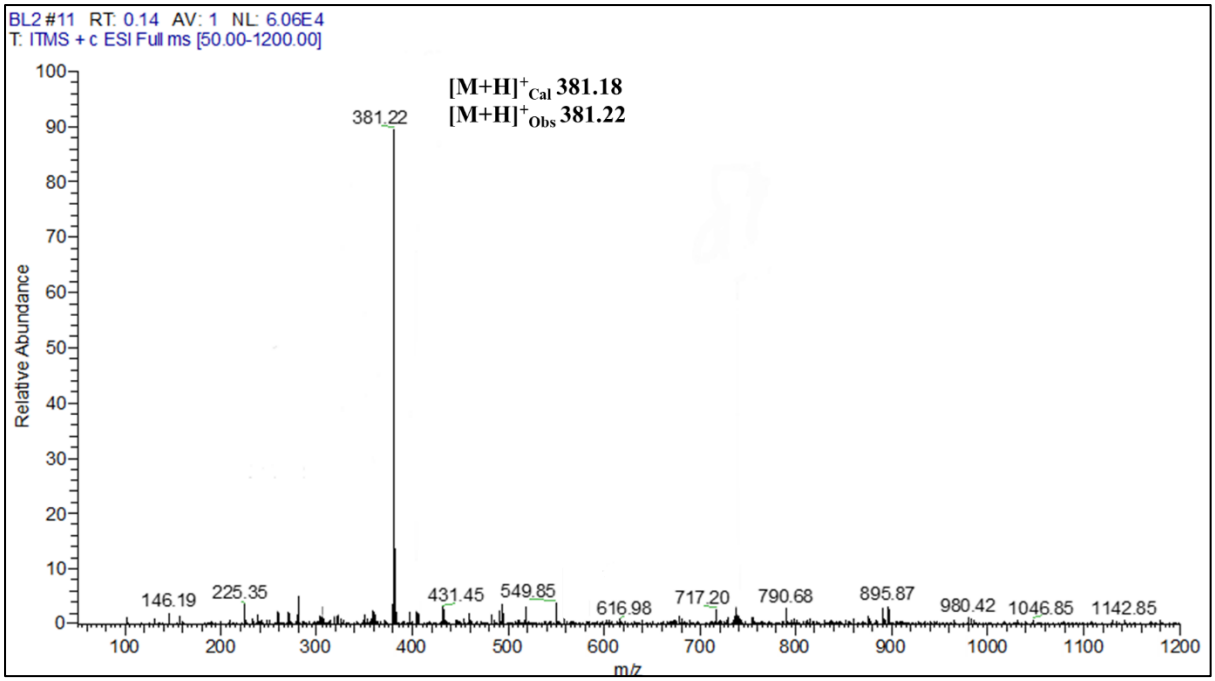


Figure S108: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-OPfp

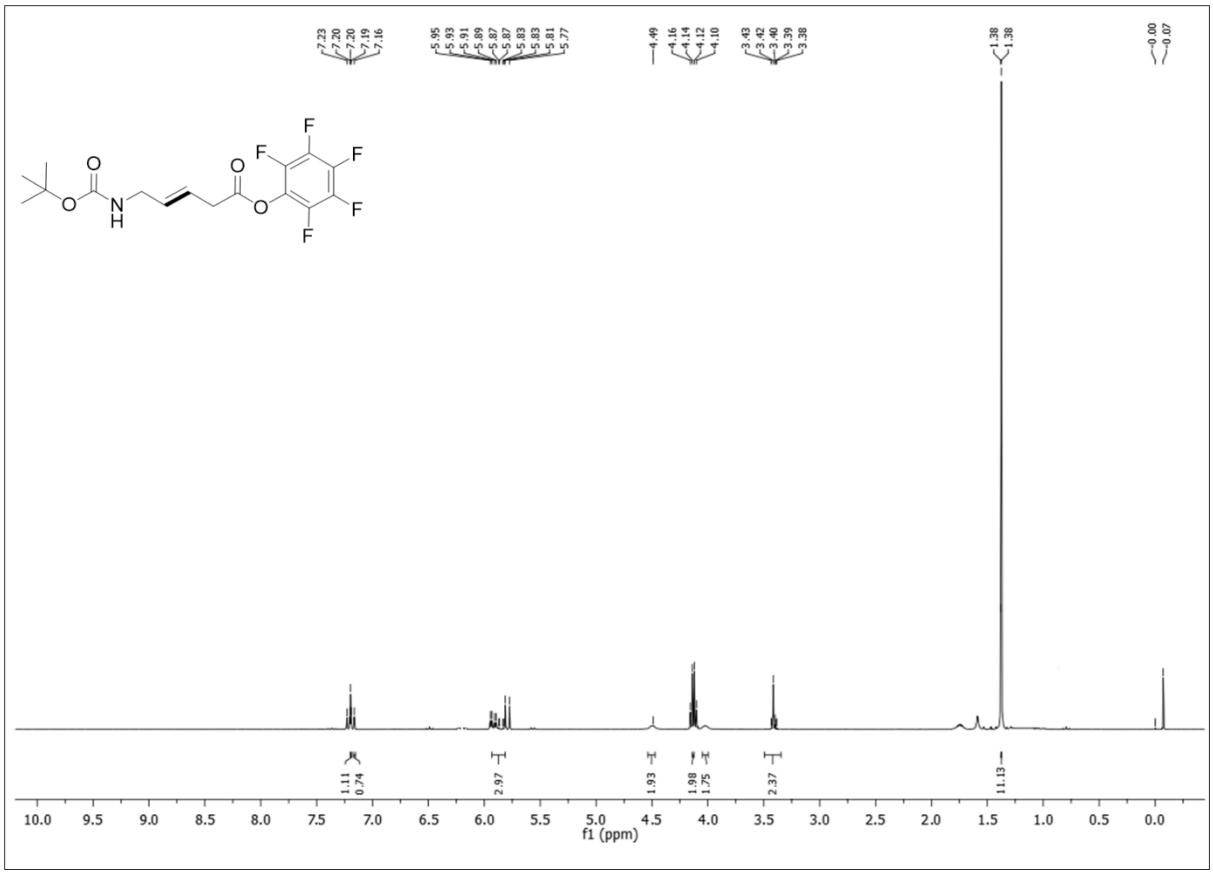


Figure S109: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-OPfp in $CDCl_3$

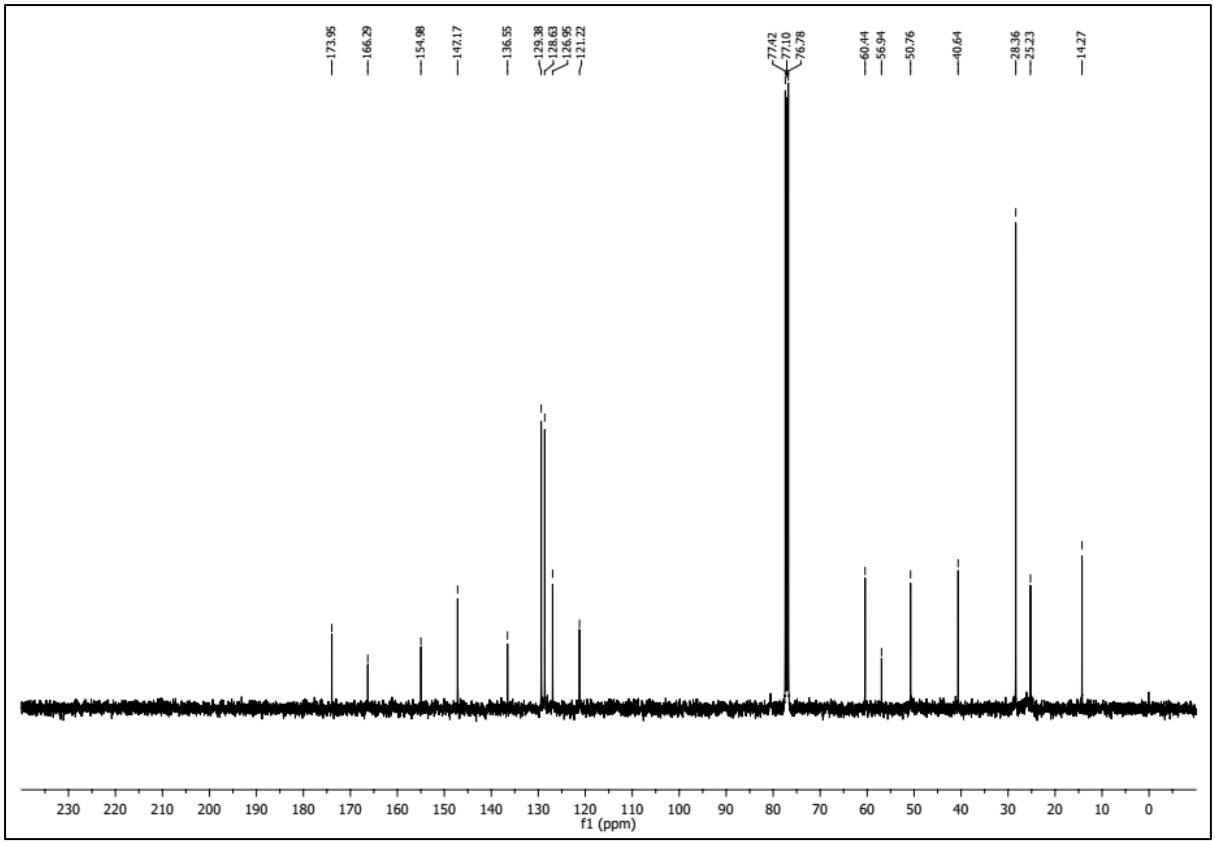


Figure S110: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-OPfp in $CDCl_3$

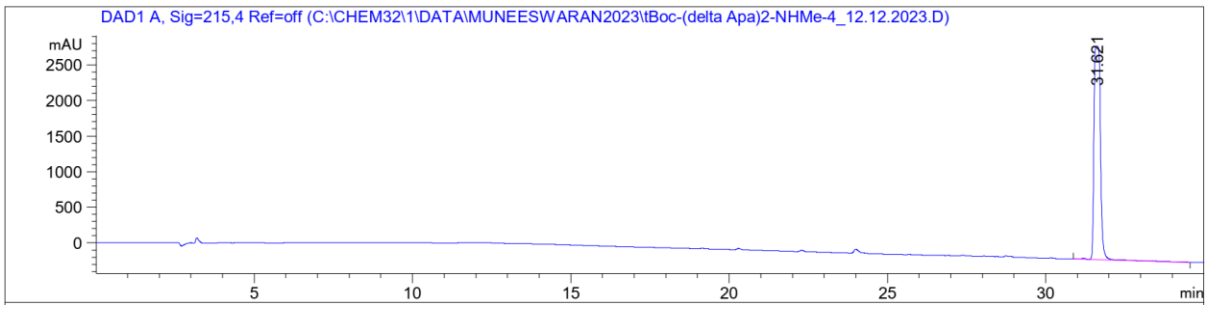


Figure S111: RP-HPLC Chromatogram of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe

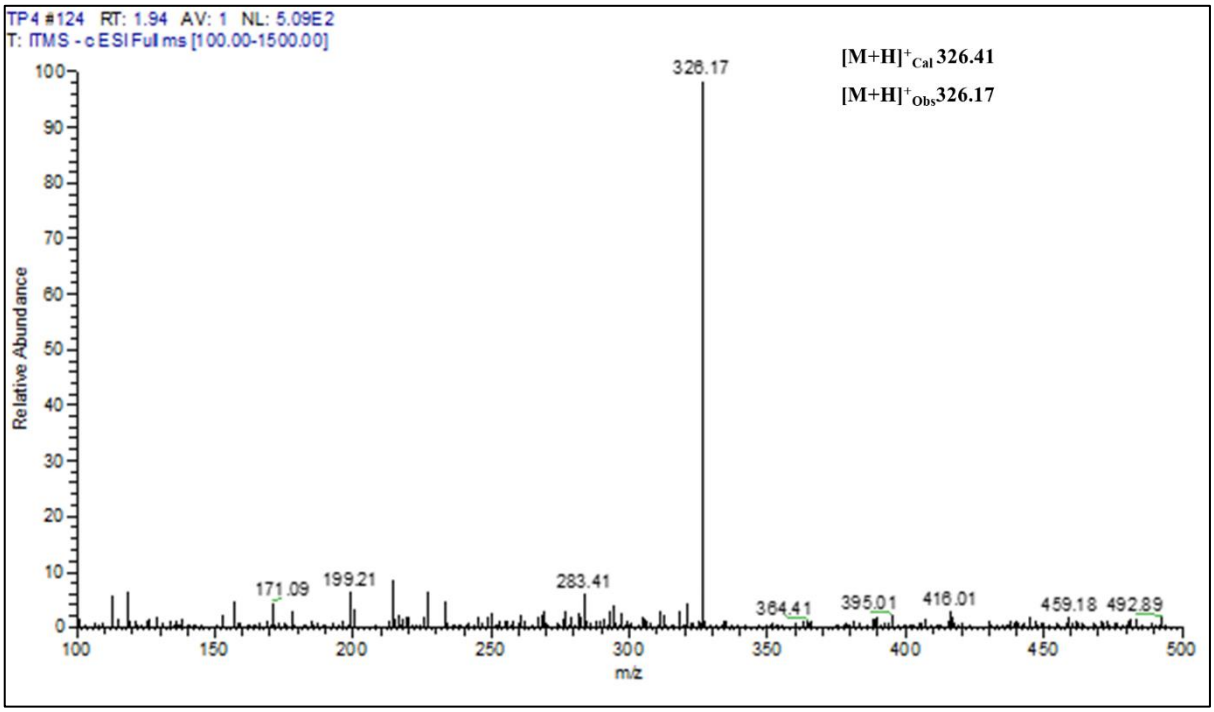


Figure S112: ESI-MS spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe

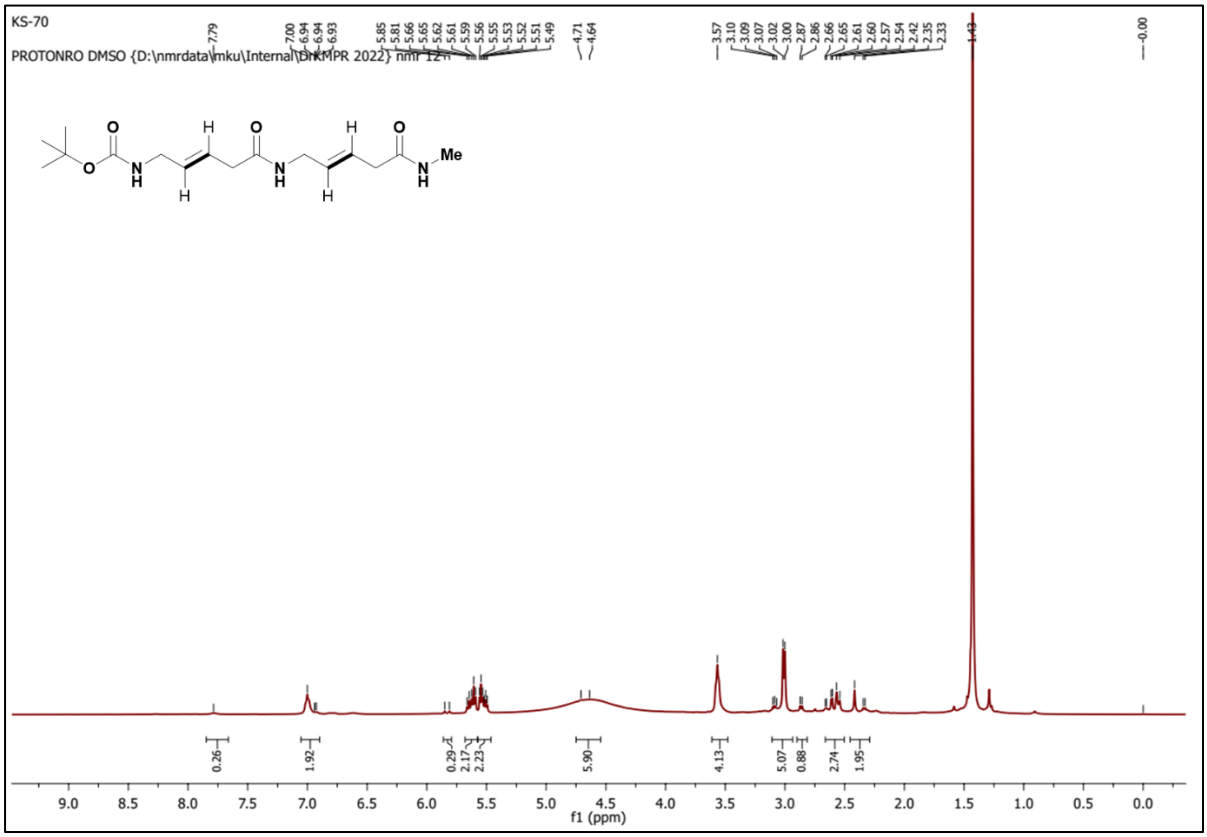


Figure S113: 300 MHz ^{1}H-NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe in DMSO-d_6

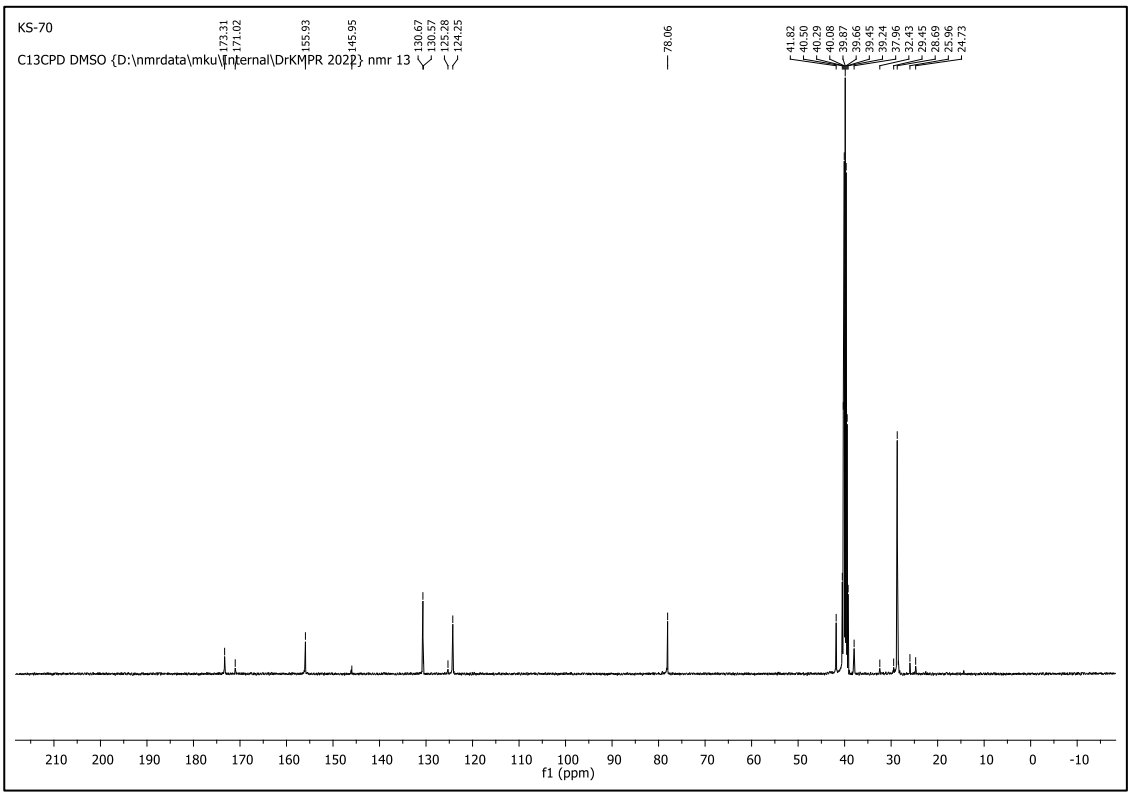


Figure S114: 75 MHz ^{13}C-NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe in DMSO-d_6

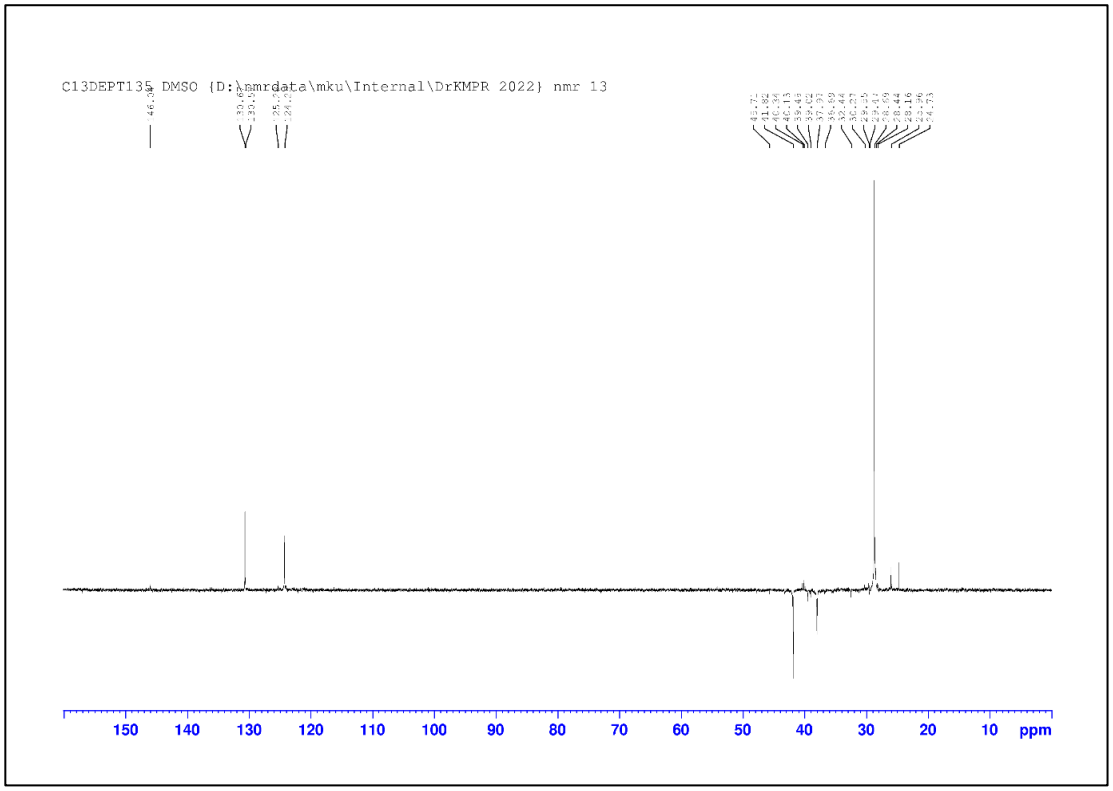


Figure S115: 300 MHz DEPT-135 NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe

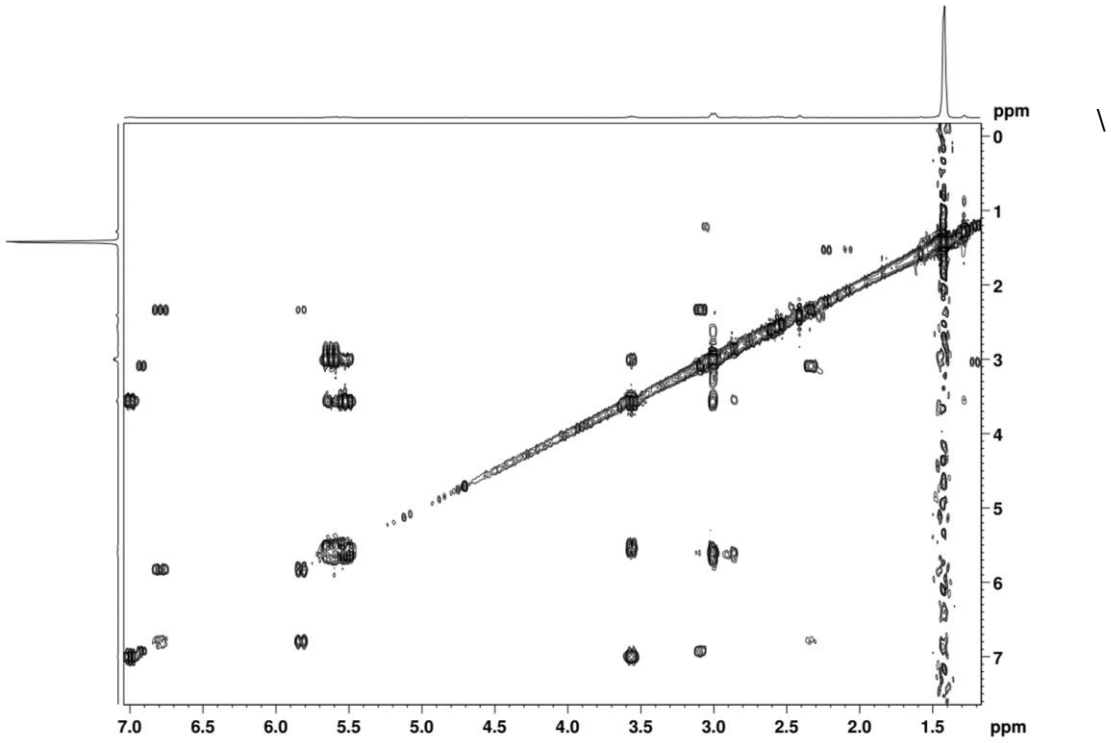


Figure S116: 300 MHz 2D-COSY NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe in DMSO-d_6

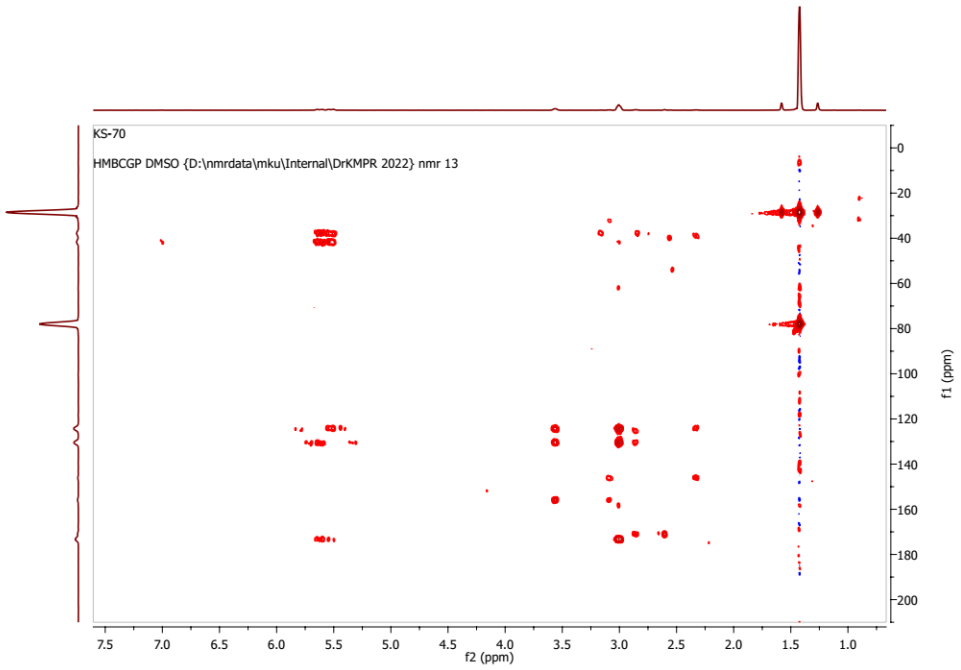


Figure S117: 300 MHz 2D-HMBC NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe in DMSO-d_6

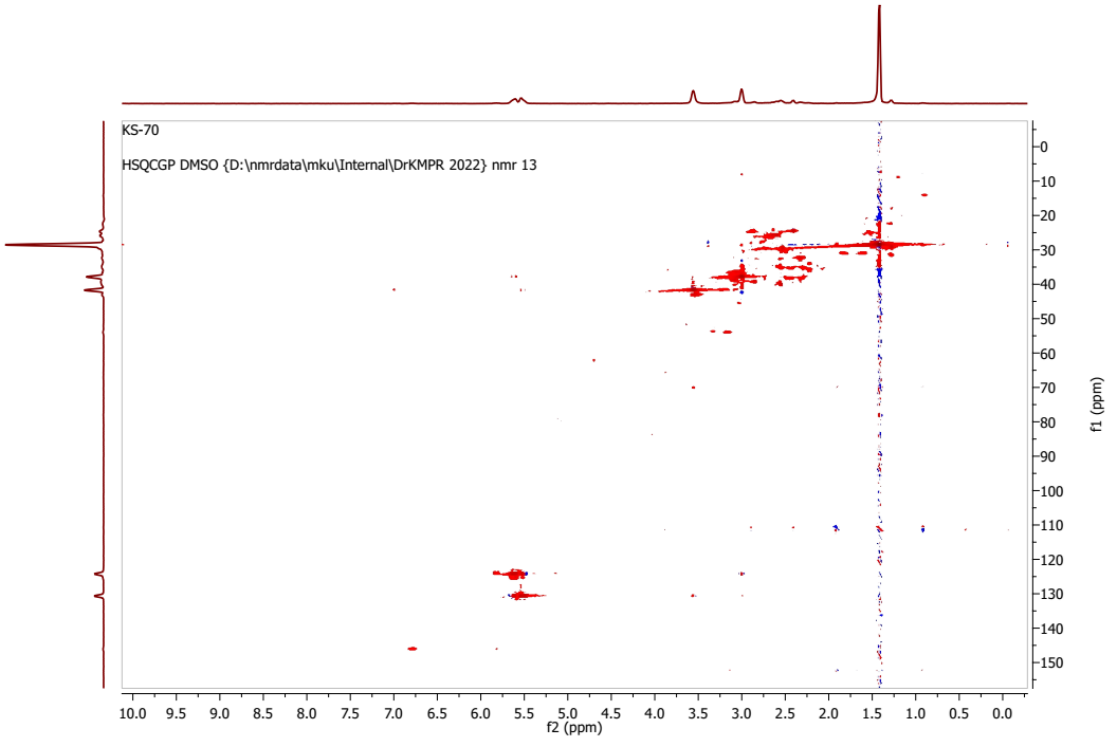


Figure S118: 300 MHz 2D-HSQC NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe in DMSO-d_6

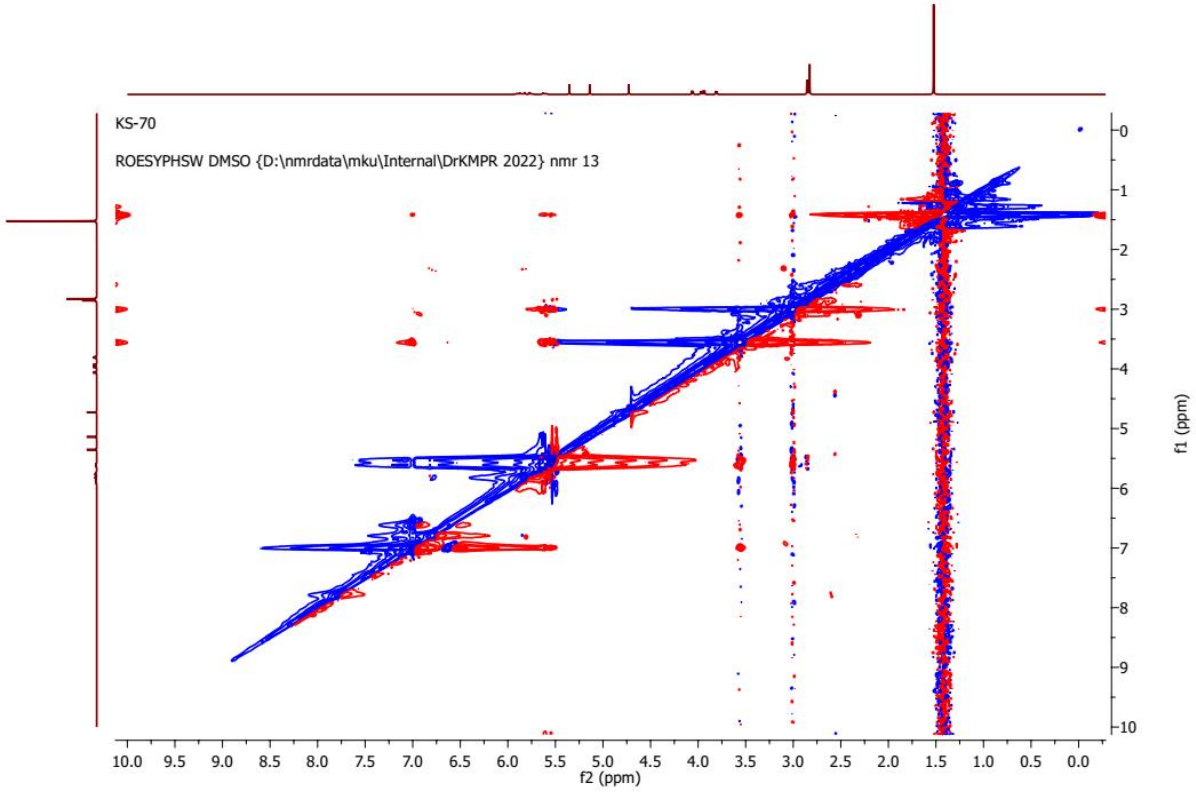


Figure S119: 300 MHz 2D-ROESY NMR spectrum of *t*Boc-*trans*-δ-Apa-*trans*-δ-Apa-NHMe in DMSO-d_6

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