Supporting Information

A concise synthetic approach toward Tamiflu (Oseltamivir phosphate): *Cis*-aziridine as the key synthon and RCM†

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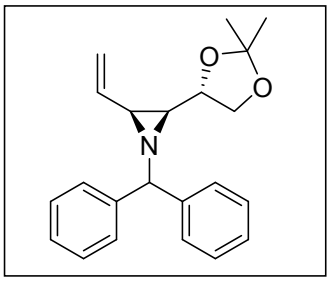
General experimental details

All chemicals and reagents required for the reactions were procured from Sigma-Aldrich with purity >98% and used without further purification. All reactions were monitored by TLC. TLC was performed on 0.25 mm E. Merck pre-coated silica gel plates ($60F_{254}$). Column chromatography was performed on silica gel, Merck grade 100–200 mesh size. The products were characterized using ^{1}H and ^{13}C-NMR spectra. NMR spectra were recorded on Bruker AC-200, AC-400 and AC-500 spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (J) are reported in Hz and refer to apparent peak multiplications. Mass spectra were taken on LC-MS (ESI) mass spectrometer and HRMS were scanned at CSIR-NCL, Pune.

(2*S*,3*S*)-1-Benzhydryl-2-((*S*)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-3-vinylaziridine (6):



To a stirred solution of *cis* aziridine 2-carboxylate **4**[1] (10 gm, 26.24 mmol) in dry DCM (100 mL) was added DIBAL-H (33.65 mL, 26.24 mmol, 1M solution in toluene) at -78 ^{o}C slowly over period of 15 min and the reaction mixture was stirred at same temperature for 20 min. Reaction was quenched by careful addition of pre-cooled MeOH (25 mL) and allowed to warm to 0 ^{o}C. Roche's salt (saturated solution of sodium potassium tartarate, 30 mL) was added and stirred for 0.5 h. The compound was

extracted with DCM (3 x 80 mL) and combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude aldehyde **5**, which was used as such for next reaction.

To a stirred solution of methyltriphenylphosphonium bromide (28.5 gm, 79.88 mmol) in dry toluene (90 mL) was added K^{t}OBu (7.54 gm, 66.57 mmol) portion wise and stirred at rt for 1 h. The crude aldehyde **5** (9.4 gm, 26.62 mmol) in dry THF (50 mL) was added dropwise to the reaction mixture and stirred at rt for 1.5 h. Reaction mixture was quenched by addition of saturated aq. solution of NH_4Cl and the compound was extracted with DCM (3 x 80 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford olefin **6** (5.71 gm, 65%) as a yellow syrup.

Rf: 0.7 (Pet ether: ethyl acetate, 80:20).

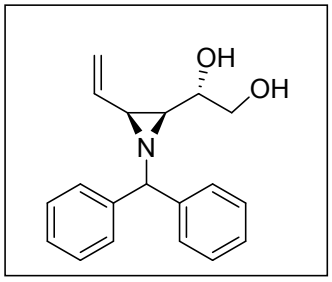
[α]Error!^{25} : +41.33 (*c* 1.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.42 - 7.12 (m, 10H), 5.91 - 5.74 (m, 1H), 5.43 - 5.22 (m, 2H), 3.80 - 3.59 (m, 3H), 2.85 (dd, *J* = 6, 8.0 Hz, 1H), 2.32 (t, *J* = 6 Hz, 3H), 1.87 (dd, *J* = 6, 8 Hz, 1H), 1.31 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 143.2, 142.5, 133.3, 128.4, 128.1, 128.0, 127.0, 126.8, 118.5, 109.1, 77.9, 68.1, 46.7, 45.9, 26.7, 25.3.

HRMS (ESI): Calculated- 336.1958, Observed-336.1957 $[M + H]^+$.

(*S*)-1-((2*S*,3*S*)-1-Benzhydryl-3-vinylaziridin-2-yl)ethane-1, 2-diol (7):



To a stirred, ice-cold solution of the aziridine acetonide **6** (6 gm 14.92 mmol) in anhydrous DCM (70 mL) under nitrogen atmosphere, was added TMSOTf (4.8 mL, 29.85 mmol) dropwise at 0 ^{o}C. The resulting solution was stirred at the same temperature for 2 h and the reaction mixture was quenched by addition of solid $NaHCO_3$. Water (50 mL) was added and the compound was extracted with DCM (3 X 50 mL). The combined organic layer was dried over anhydrous sodium

sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet.ether as an eluent to afford compound **7** (4.4 gm, 85%) as colourless syrup.

Rf: 0.3 (Pet ether: ethyl acetate, 50:50)

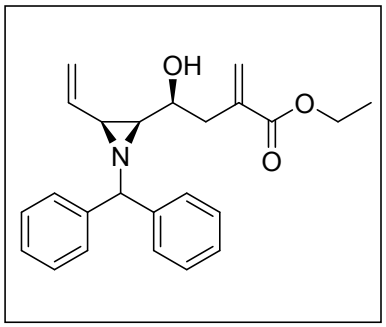
[α]Error!^{25} : +112.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.40 - 7.20 (m, 10H), 5.85-5.92 (m, 1H), 5.43 - 5.39 (m, 1H), 5.29 (dd, *J* = 1, 10 Hz, 1H), 3.73 (s, 1H), 3.52 - 3.47 (m, 1H), 3.27 (d, *J* = 10 Hz, 1H), 3.13 (dd, *J* = 5, 10 Hz, 1H), 2.38 - 2.35 (m, 1H), 2.16 (bs, 1H), 1.97 (dd, *J* = 5, 10 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 143.0, 142.2, 133.9, 128.6, 128.2, 128.1, 127.9, 127.1, 127.0, 118.8, 78.0, 69.8, 64.9, 46.3, 46.2.

HRMS (ESI): Calculated- 296.1645, Observed- 296.1643 $[M + H]^+$.

Ethyl-(*S*)-4-((2*S*,3*S*)-1-benzhydryl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (3b):



To the solution of diol **7** (3.3 gm, 11.18 mmol) in DCM (40 mL) was added sodium metaperiodate (5.4 gm, 22.37 mmol). The reaction mixture was stirred at rt for 1.5 h and completion of reaction was monitored by TLC. The reaction mass was quenched using ethylene glycol (0.01 mL), extracted with DCM (3 X 30 mL), washed with brine, dried over anhydrous sodium sulphate and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde **8** which was used as such for next reaction.

To the solution of crude aldehyde **8** (3.1 gm, 11.78 mmol) from above reaction in THF (40 mL) was added ethyl 2-(bromomethyl)acrylate (1.8 mL, 12.96 mmol), activated zinc powder (3 gm, 47.14 mmol) and saturated aq. solution of NH_4Cl (5 mL) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for additional 10 min. The reaction mixture was filtered through a simple filter paper and thoroughly washed with ethyl acetate (3 X 30 mL). Water was added to the filtrate and the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated

to give a crude residue that was purified by flash chromatography (pet.ether-ethyl acetate, 9:1) to afford **3a:3b** in 3:2 ratio (2.76 gm, 94%) as colourless syrup.

To the solution of **3a** (500 mg, 1.326 mmol) in toluene (10 mL) was added triphenyl phosphine (870 mg, 3.315 mmol), *p*-nitrobenzoic acid (560 mg, 3.315) and DEAD (0.6 mL, 3.315 mmol) at rt under nitrogen atmosphere. The reaction mixture was stirred at same temperature for 2.5 h and progress of reaction was monitored by TLC. To the reaction mass, water (20 mL) was added and the compound was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude product, which was as such subjected for next reaction.

The crude product (570 mg, 1.08 mmol) was dissolved in absolute ethanol (10 mL) and to the solution was added NaOEt (81 mg, 1.19 mmol) at -20 ^{o}C. The reaction mixture was stirred further for 0.5 h at same temperature. Drops of acetic acid were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (10 mL) and extracted with ethyl acetate (3 X 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 15% ethyl acetate in pet ether to provide the product **3b** (345 mg, 69% yield over two steps) as colourless syrup.

Ethyl 2-((*S*)-((2*S*,3*S*)-1-benzhydryl-3-vinylaziridin-2yl)- 4-hydroxy-2-methylenebutanoate (3b):

***Rf*:** 0.6 (Pet ether: ethyl acetate, 70:30).

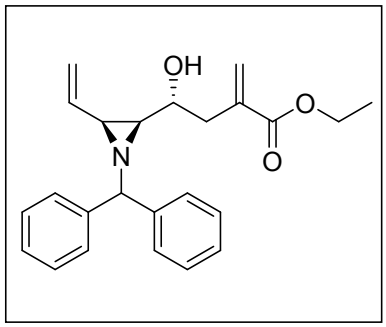
[α]Error!^{25} : +32.0 (*c* 1.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.41-7.21 (m, 10H), 6.16 (d, *J* = 1 Hz, 1H), 5.85-5.76 (m, 1H), 5.49 (s, 1H), 5.36 - 5.18 (m, 2H), 4.18 (q, *J* = 8 Hz, 2H), 3.77 (s, 1H), 3.65 - 3.60 (m, 1H), 2.36 - 2.29 (m, 2H), 2.24 - 2.19 (m, 1H), 1.92 (t, *J* = 8 Hz, 1H), 1.81 (bs, 1 H), 1.30 (t, *J* = 8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 166.7, 143.5, 142.3, 136.7, 134.2, 128.8, 128.2, 127.8, 127.7, 127.4, 127.1, 126.9, 118.8, 77.7, 67.6, 60.6, 49.6, 47.1, 37.8, 14.2.

HRMS (ESI): Calculated- 378.2064, Observed- 378.2065 $[M + H]^+$.

Ethyl (R)-4-((2S,3S)-1-benzhydryl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (3a):



[α]Error!^{25} : +13.33 (*c* 1.5, $CHCl_3$).

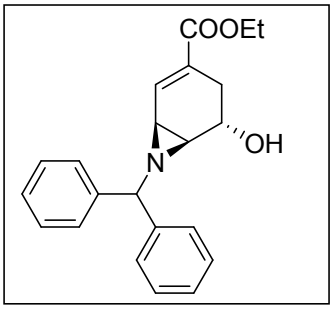
Rf: 0.5 (Pet ether: ethyl acetate, 70:30).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.42 - 7.16 (m, 10H), 6.11 (d, *J* = 2 Hz, 1H), 6.01 - 5.84 (m, 1H), 5.41 - 5.21 (m, 3H), 4.19 (q, *J* = 7 Hz, 2H)3.76 (s, 1 H), 3.64-3.54 (m, 1H), 2.92 (bs, 1H), 2.32 (t, *J* = 6 Hz, 1H), 2.22 – 2.10 (m, 2H), 1.93 (t, *J* = 6 Hz, 1H), 1.34 (t, *J* = 6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 167.9, 143.3, 142.6, 137.3, 134.4, 128.4, 128.2, 128.0, 127.6, 127.5, 127.0, 126.8, 118.2, 77.9, 69.0, 60.9, 49.1, 46.3, 37.6, 14.1.

HRMS (ESI): Calculated- 378.2064, Observed- 378.2065 $[M + H]^+$.

Ethyl (1*S*,5*S*,6*S*)-7-benzhydryl-5-hydroxy-7-azabicyclo-[4.1.0]hept-2-ene-3-carboxylate (9):



To the solution of the olefin compound **3b** (500 mg, 1.32 mmol) in dry DCM (400 mL) was added titanium tetraisopropoxide (0.23 mL, 0.079 mmol) and Grubbs' 2nd generation catalyst (45 mg, 0.05 mmol). The reaction mixture was refluxed for 12 h and the completion of the reaction was monitored with TLC. The reaction mixture was filtered through celite bed and thoroughly washed with DCM (3 X 50 mL). The solvent was evaporated under reduced pressure to furnish the crude product, which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford compound **9** (342 mg, 74%) as colourless syrup.

Rf: 0.3 (Pet ether: ethyl acetate, 70:30).

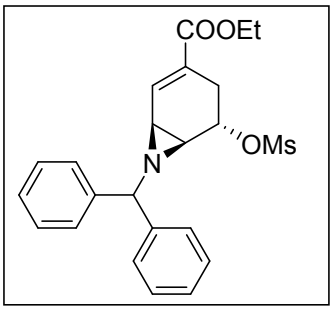
[α]Error!^{25} : - 128.75 (*c* 1.6, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.44-7.20 (m, 11H), 4.32-4.28 (m, 1H), 4.26-4.14 (m, 2H), 3.75 (s, 1H), 2.79 (d, *J* = 20 Hz, 1H), 2.52-2.47 (m, 1H), 2.38-2.36 (m, 1H), 2.20 (t, *J* = 5 Hz, 1H), 1.28 (t, *J* = 10 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 166.5, 143.0, 142.8, 136.4, 128.5, 128.4, 127.3, 127.2, 127.1, 76.5, 63.9, 60.6, 46.7, 35.8, 30.2, 14.3.

HRMS (ESI): Calculated- 350.1751, Observed- 350.1748 $[M + H]^+$.

Ethyl (1*S*,5*S*,6*S*)-7-benzhydryl-5-((methylsulfonyl)oxy)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (10)



To a solution of alcohol **9** (0.15 gm, 0.42 mmol) in DCM (3 mL) was added triethylamine (0.3 mL, 2.15 mmol) followed by mesyl chloride (0.04 mL, 0.47 mmol) and DMAP (cat.) at 0 ^oC. The reaction mixture was allowed to stir at room temperature for 2 h under nitrogen atmosphere. The completion of reaction was monitored by TLC and reaction mixture was poured in cold water. The compound was extracted with DCM (3 X 5 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford compound **10** (0.144 gm, 79%) as colourless syrup.

Rf: 0.4 (Pet ether: ethyl acetate, 70:30).

$[\alpha]_{Error!}^{25}$: - 4.44 (*c* 0.9, $CHCl_3$).

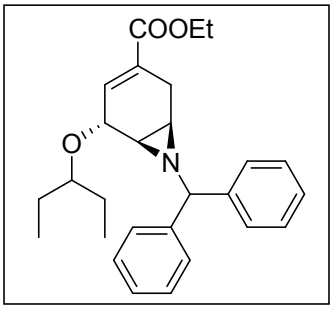
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.30-7.20 (s, 11H), 5.28-5.27 (m, 1H), 4.24-4.17 (m, 2H), 3.81 (s, 1H), 3.02 (d, *J* = 20 Hz, 1H,), 2.94 (s, 3H), 2.64-2.57 (m, 2H), 2.35 (t, *J* = 5Hz, 1H), 1.31 (t, *J* = 5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 165.9, 142.3, 139.3, 128.7, 128.5, 127.6, 127.3, 127.1,

126.9, 76.3, 73.4, 60.8, 44.2, 38.8, 36.1, 27.7, 14.3.

HRMS (ESI) Calculated- 428.1526, Observed- 428.1524 $[M + H]^+$.

Ethyl (1*R*,5*R*,6*R*)-7-benzhydryl-5-(pentan-3-yloxy)-7-azabicyclo[4.1.0]hept-3-ene-3-carboxylate (2):



Mesyl compound **10** (50 mg, 0.11 mmol) was dissolved in 3-pentanol (2 mL) and dry DCM (1 mL). To the reaction mixture was added $BF_3.Et_2O$ (0.083 mL, 0.58 mmol) dropwise and stirred at rt for 3 h. Then TEA (0.25 mL, 1.75 mmol) was added to the reaction mixture and stirred for 1 h at rt. Reaction mixture was concentrated over reduced pressure to remove low boiling impurities. To the remaining residue, water (3 mL) was added. The compound was extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude product, which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet ether as an eluent to afford compound **2** (39 mg, 80%) as a colourless syrup.

Rf: 0.4 (Pet ether: ethyl acetate, 70:30).

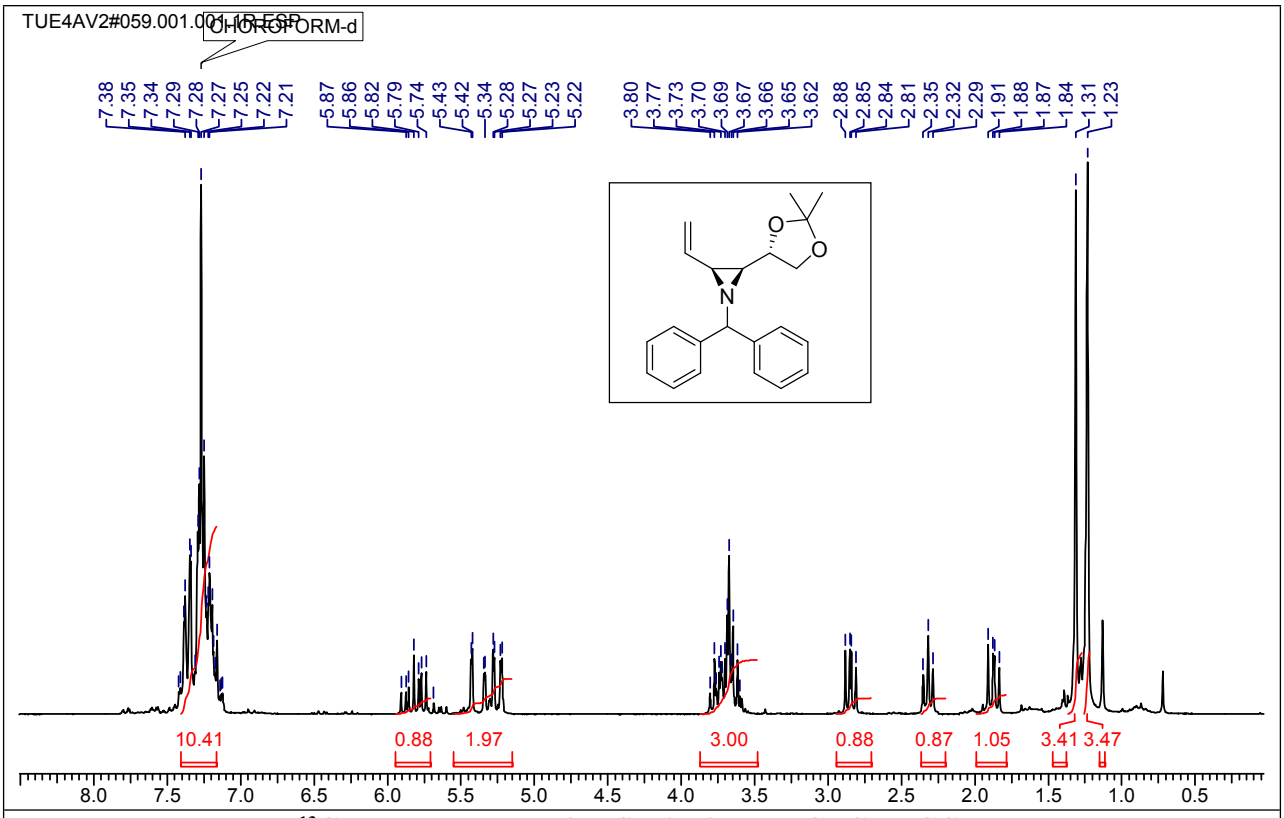
$[\alpha]_{Error!}^{25}$: - 4.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.40 - 7.20 (m, 10H), 6.78-6.76 (m, 1H), 4.26 - 4.16 (m, 2H), 4.05 (bs, 1H), 3.70 (s, 1H), 3.14-3.10 (m, 1H), 2.72 - 2.68 (m, 1H), 2.61 - 2.55 (m, 1H), 2.14 - 2.12 (m, 1H), 1.99-1.93 (m, 1H), 1.46 - 1.32 (m, 4H), 1.31 (t, *J* = 5 Hz, 3H), 0.86-0.80 (m, 6H).

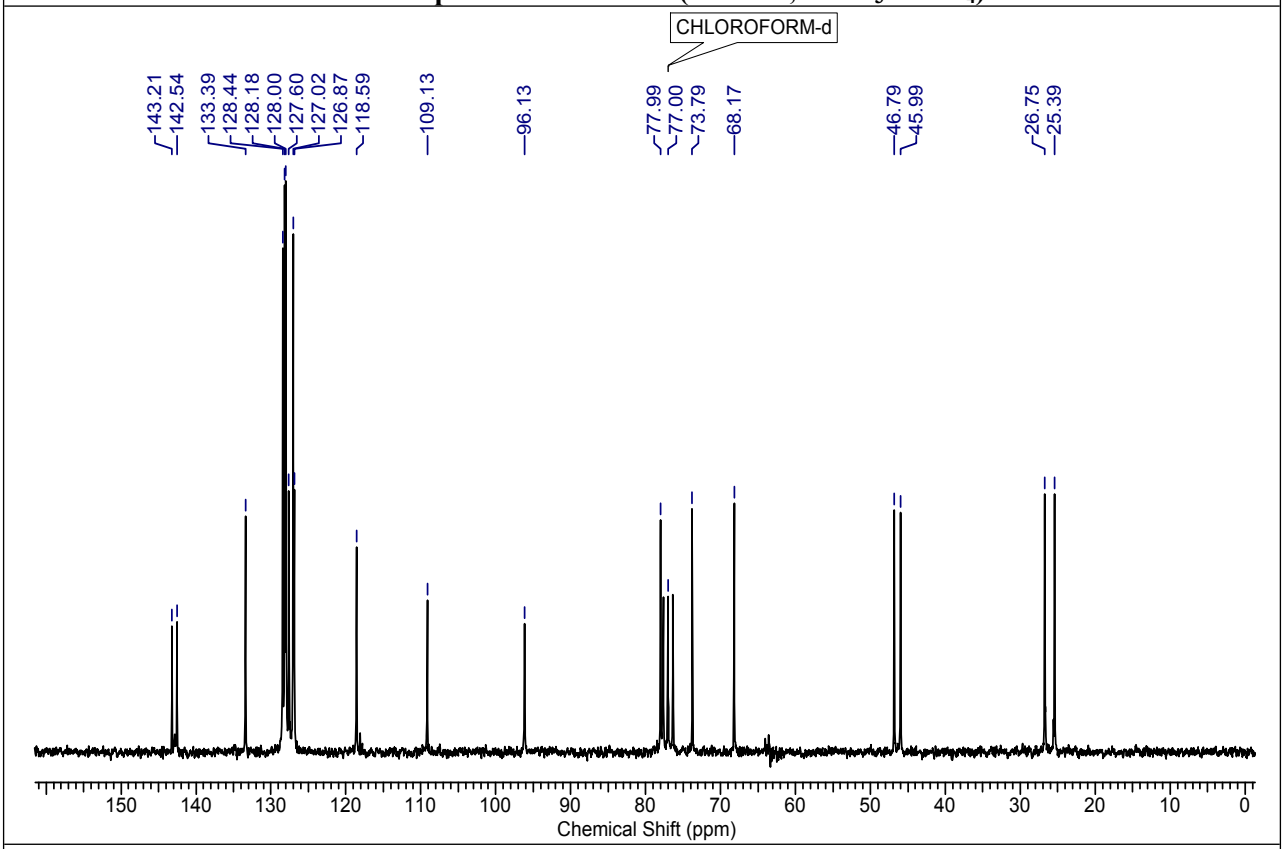
^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 166.9, 143.4, 143.0, 134.2, 128.3, 127.6, 127.2, 127.0, 82.1, 77.7, 69.8, 60.6, 39.8, 38.2, 26.5, 26.4, 14.3, 9.8, 9.7.

HRMS (ESI): Calculated- 420.2533, Observed- 420.2535 $[M + H]^+$.

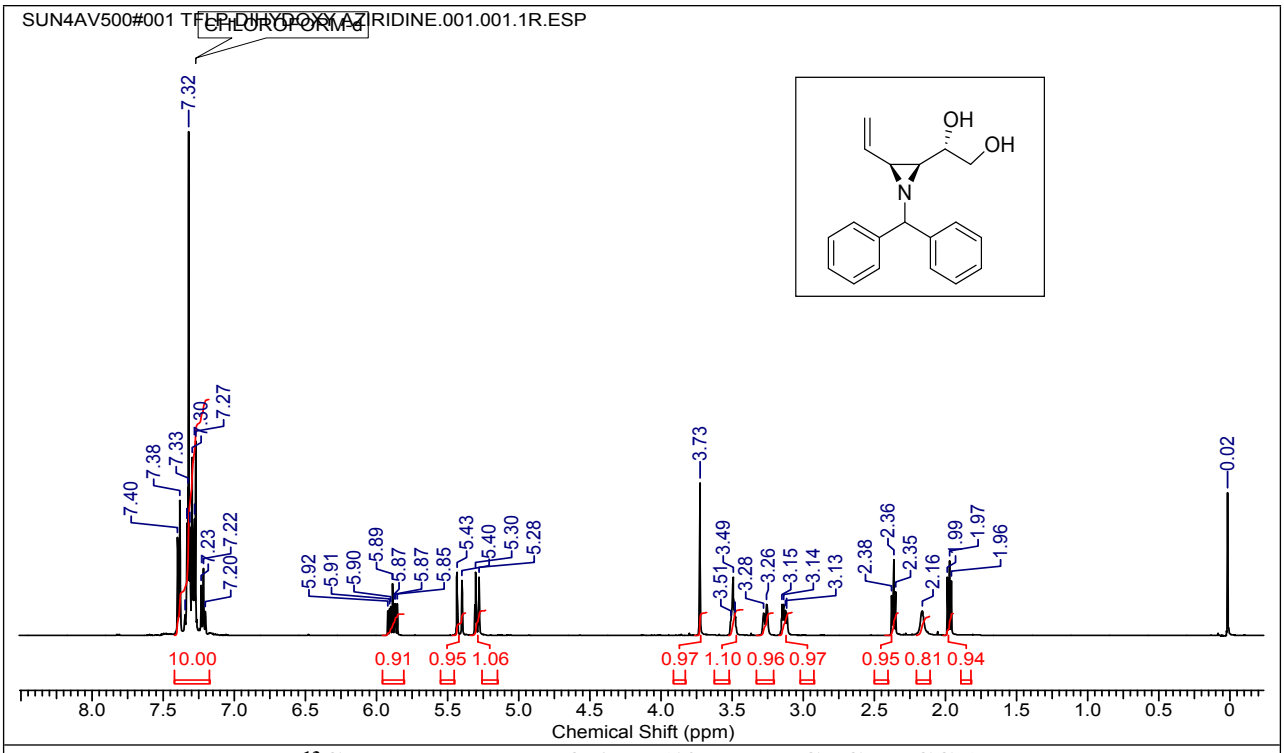
^{1}H NMR spectrum of olefin 6 (200 MHz, $CDCl_3$ + CCl_4)



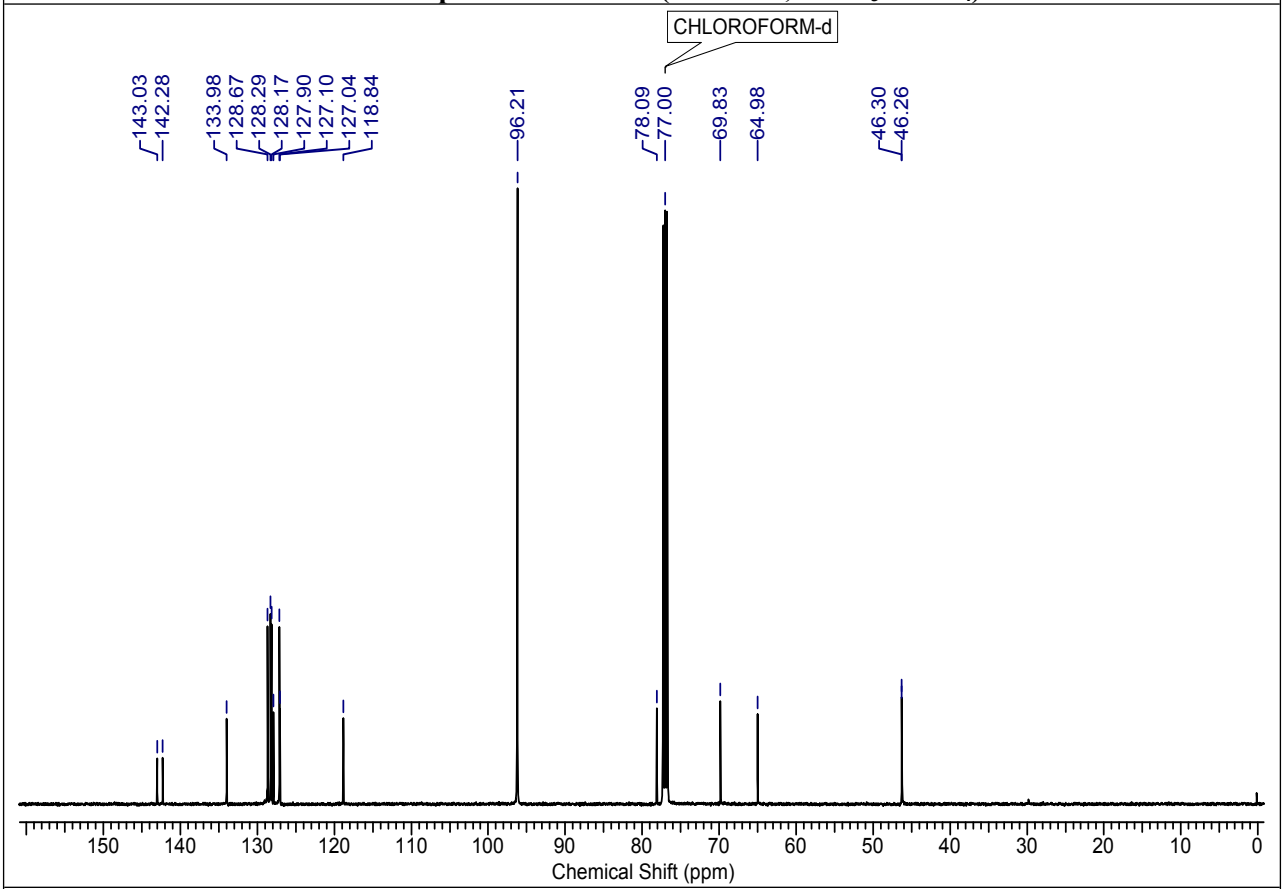
^{13}C NMR spectrum of olefin 6 (50 MHz, $CDCl_3$ + CCl_4)



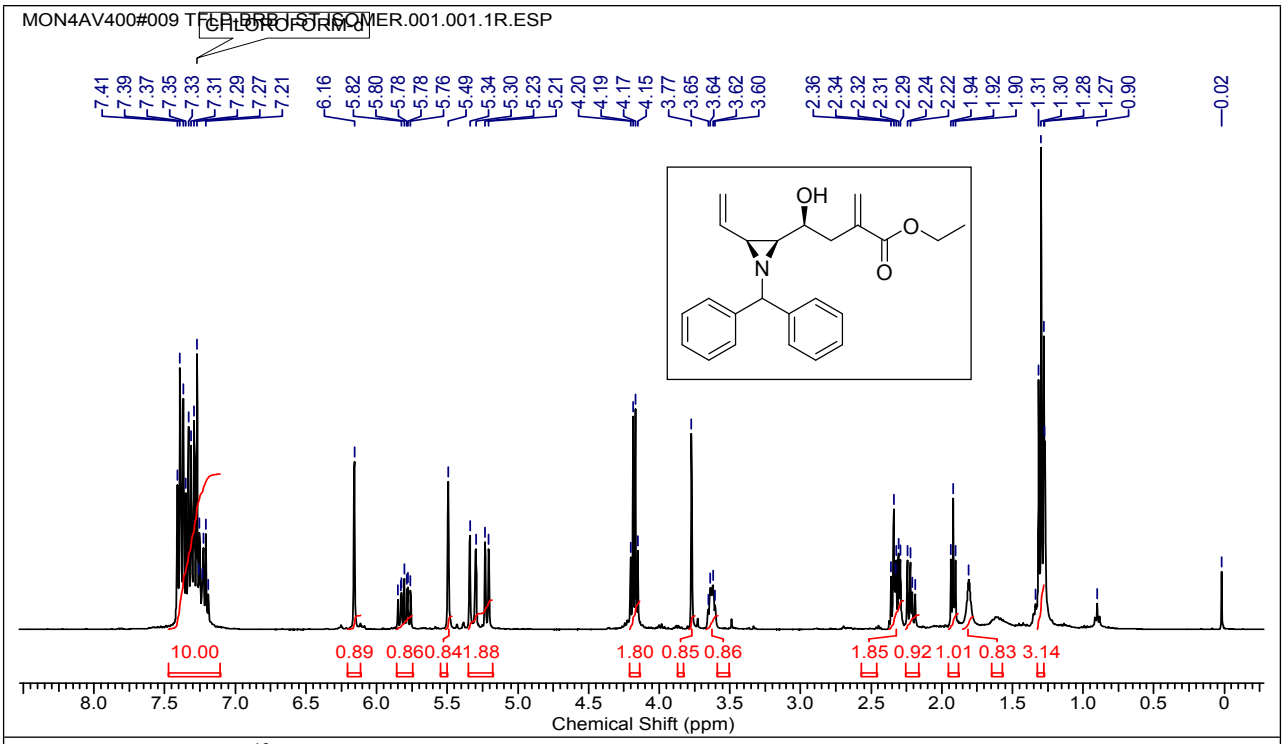
^{1}H NMR spectrum of diol 7 (500 MHz, $CDCl_3$ + CCl_4)



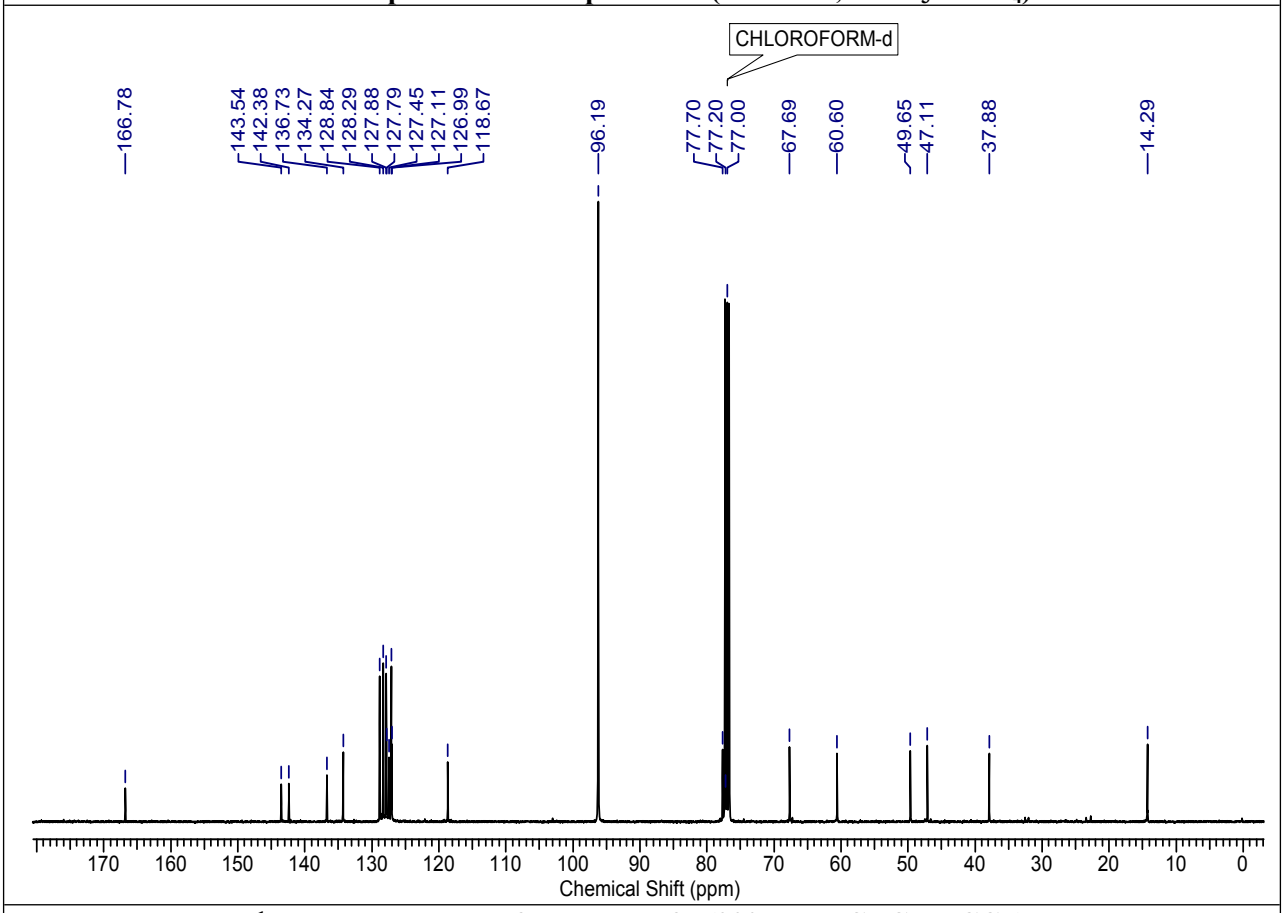
^{13}C NMR spectrum of diol 7 (125 MHz, $CDCl_3$ + CCl_4)



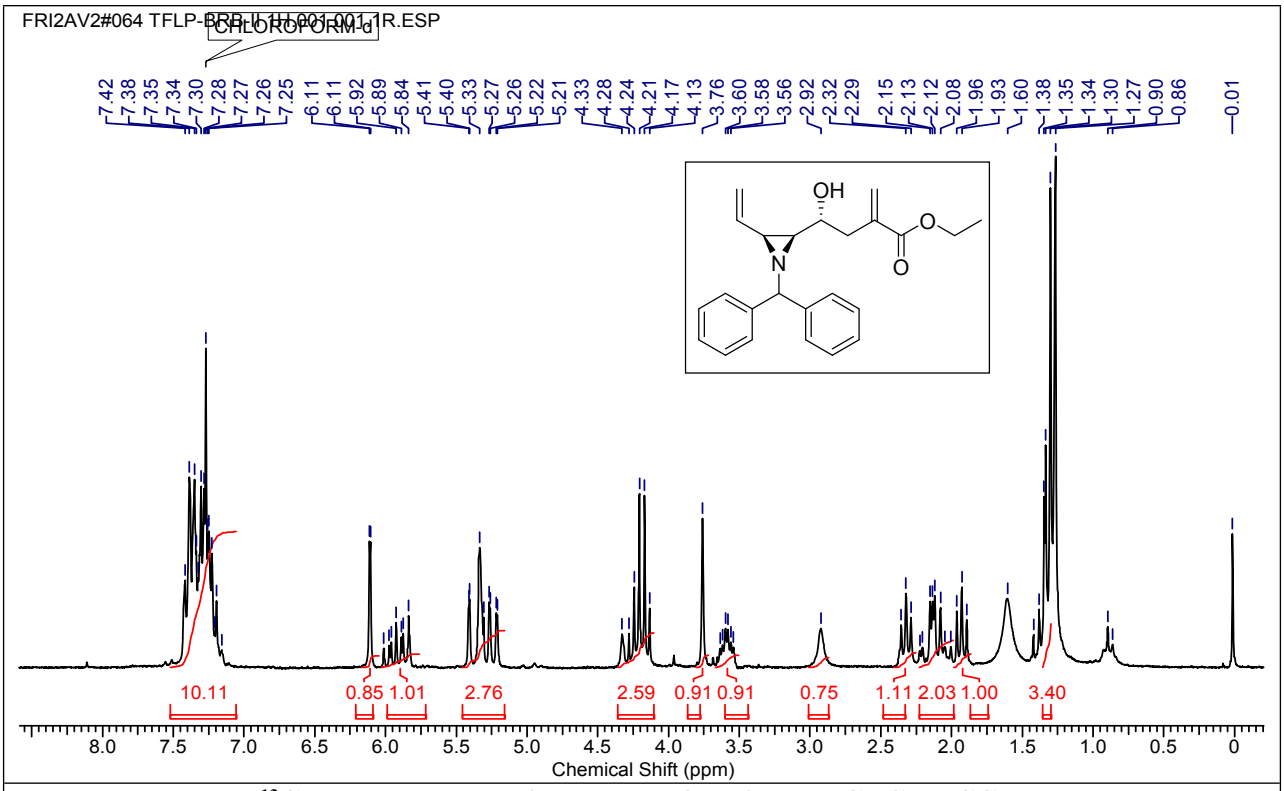
^{1}H NMR spectrum of compound 3b (400 MHz, $CDCl_3$ + CCl_4)



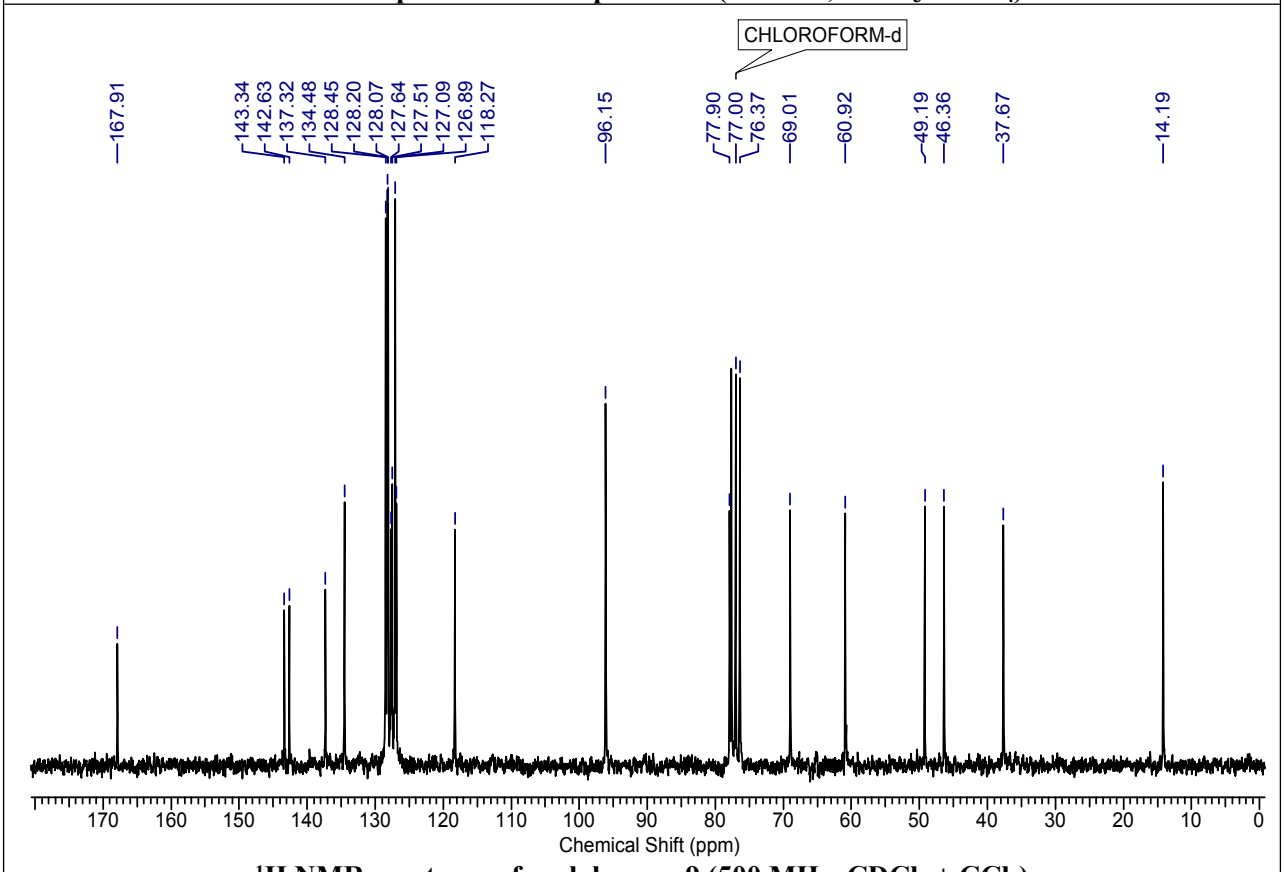
^{13}C NMR spectrum of compound 3b (100 MHz, $CDCl_3$ + CCl_4)



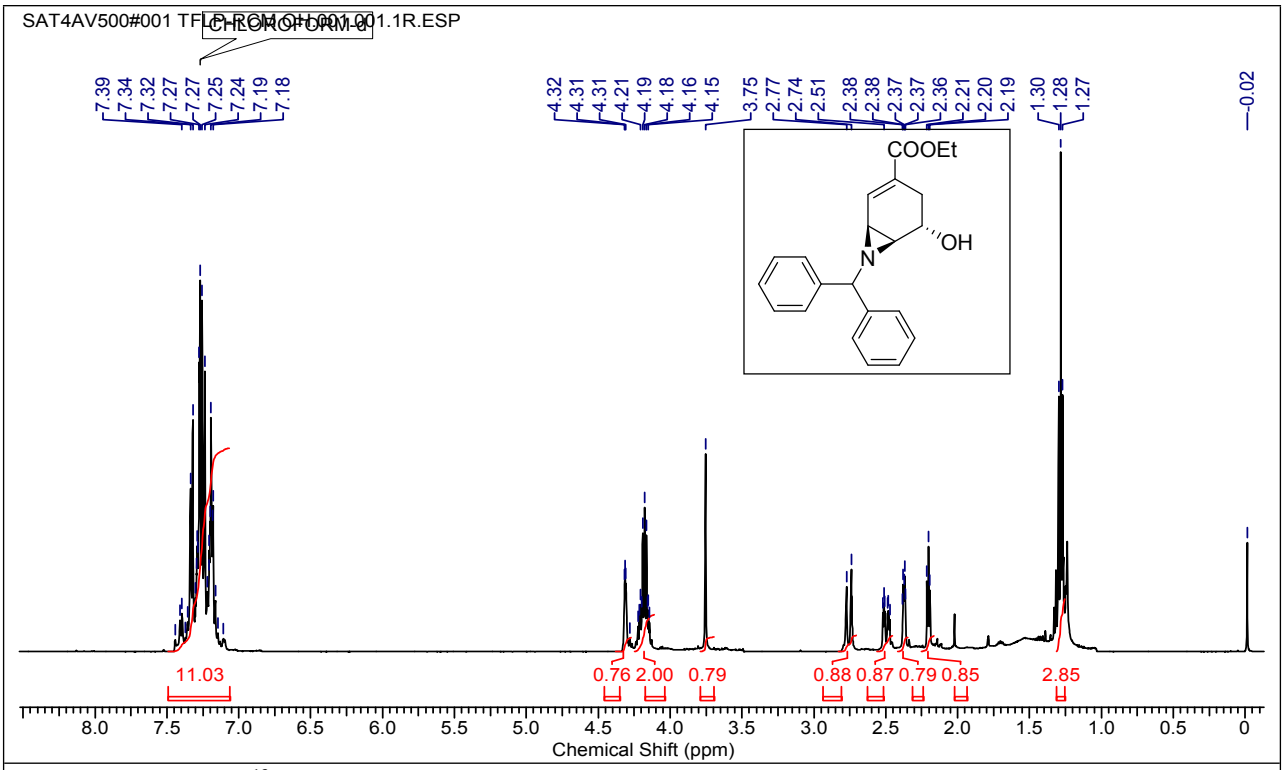
^{1}H NMR spectrum of compound 3a (200 MHz, $CDCl_3$ + CCl_4)



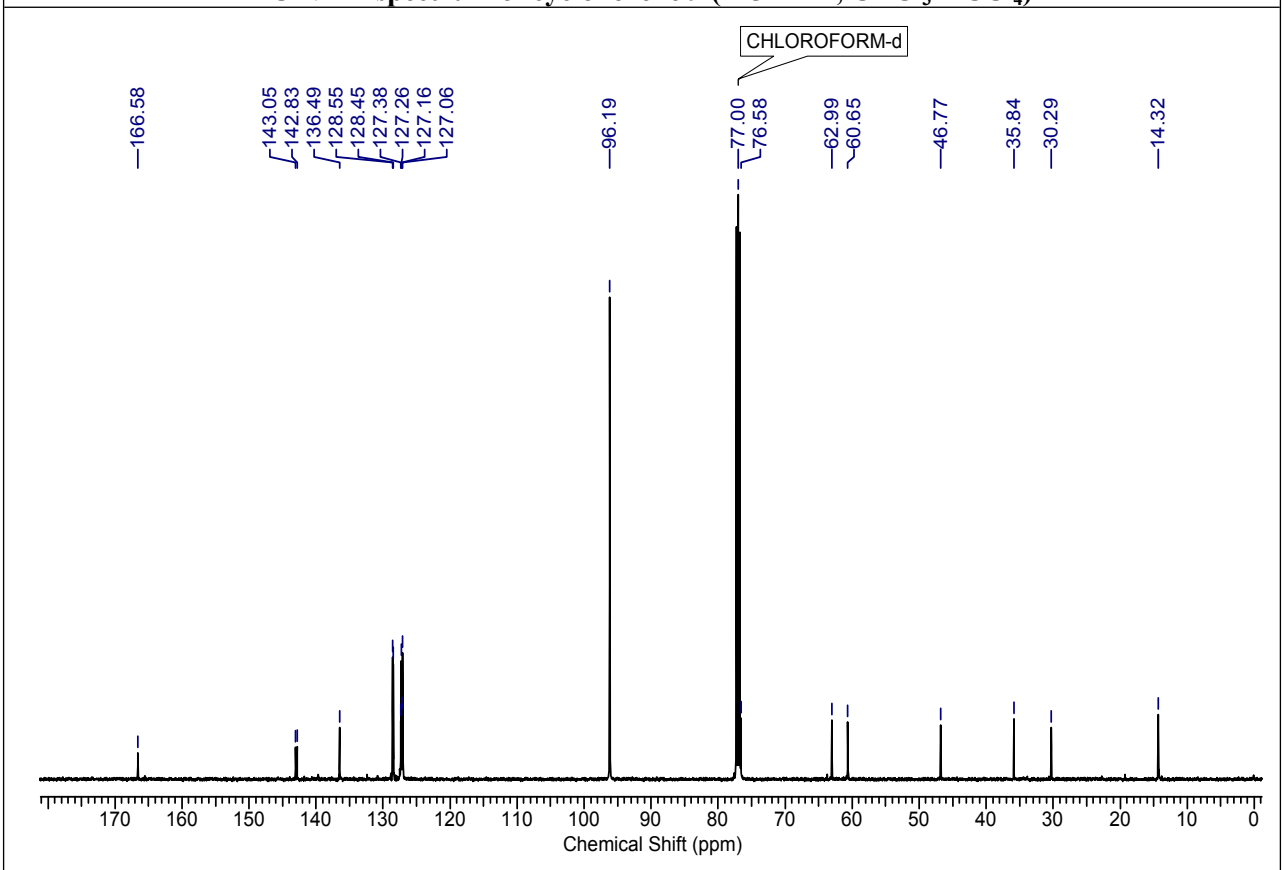
^{13}C NMR spectrum of compound 3a (50 MHz, $CDCl_3$ + CCl_4)



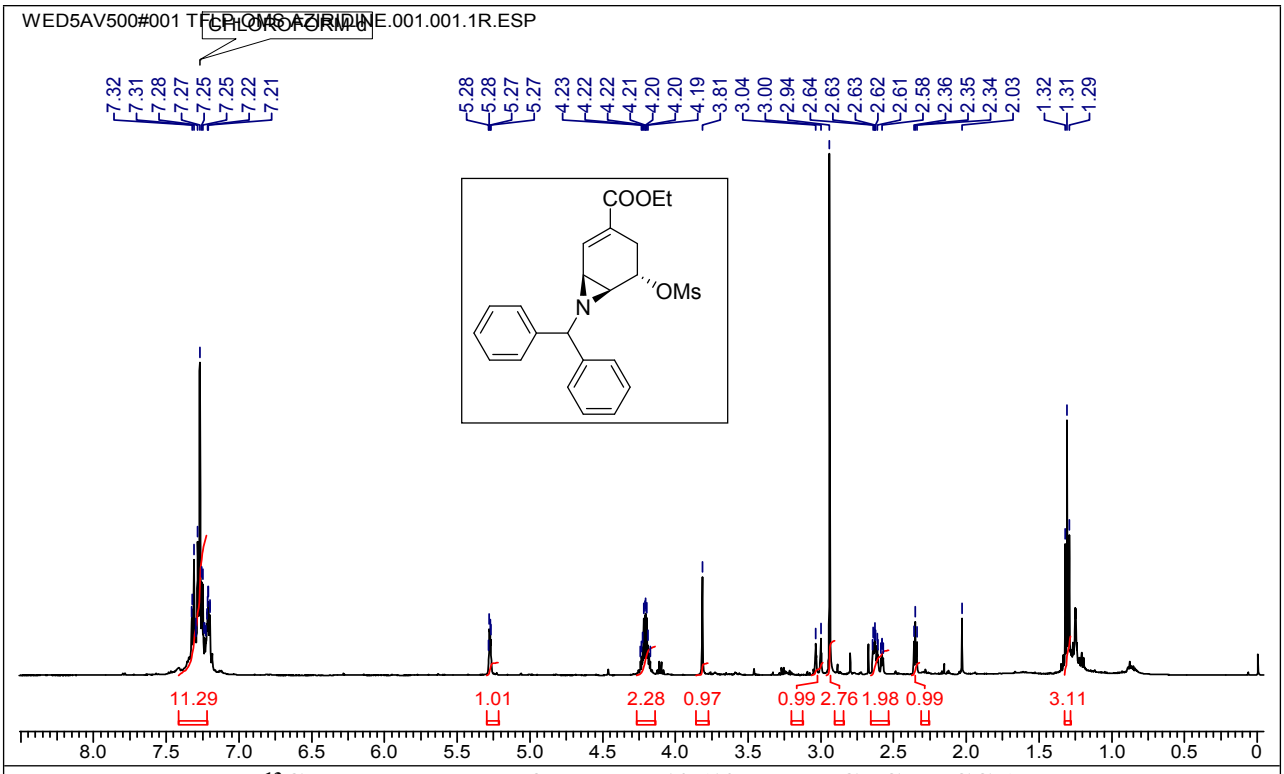
^{1}H NMR spectrum of cyclohexene 9 (500 MHz, $CDCl_3$ + CCl_4)



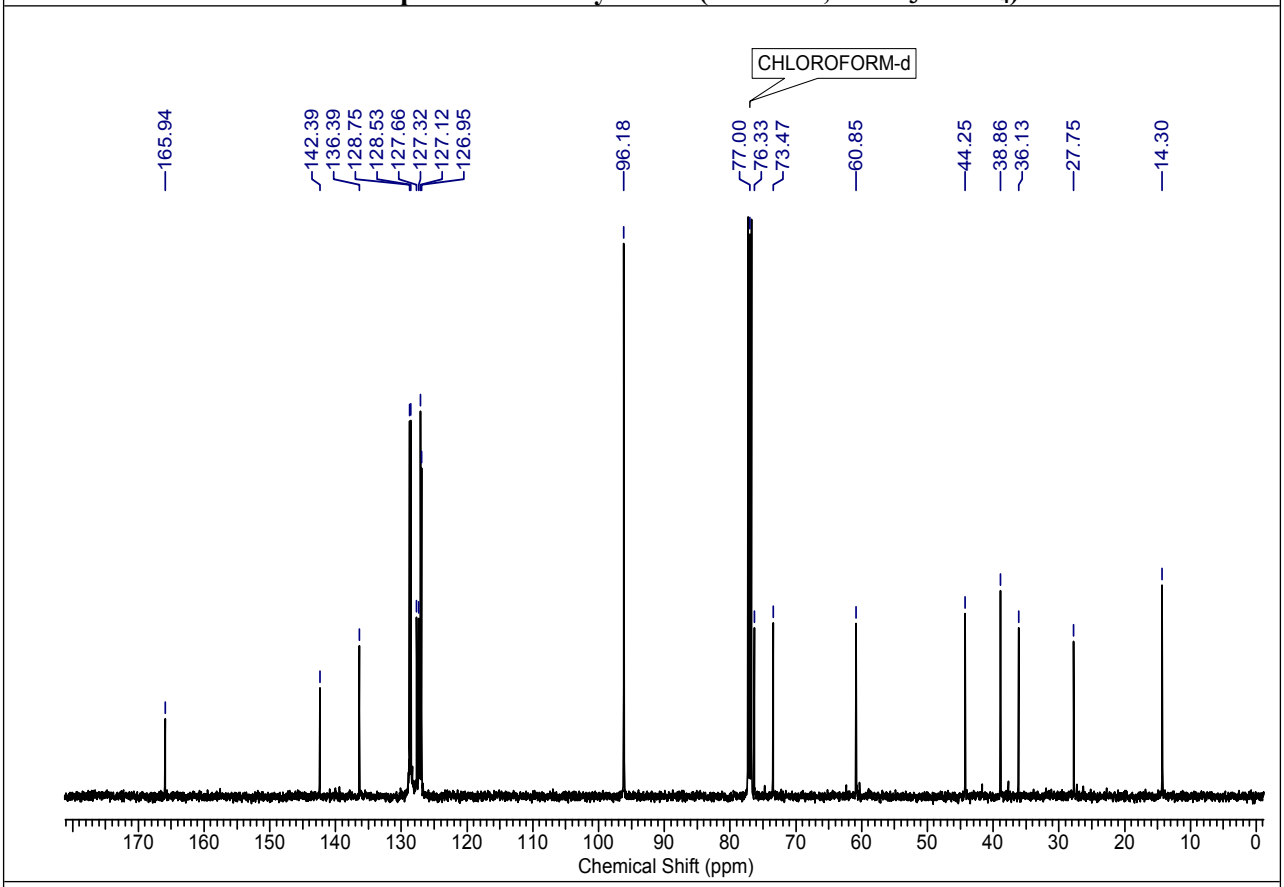
^{13}C NMR spectrum of cyclohexene 9 (125 MHz, $CDCl_3$ + CCl_4)



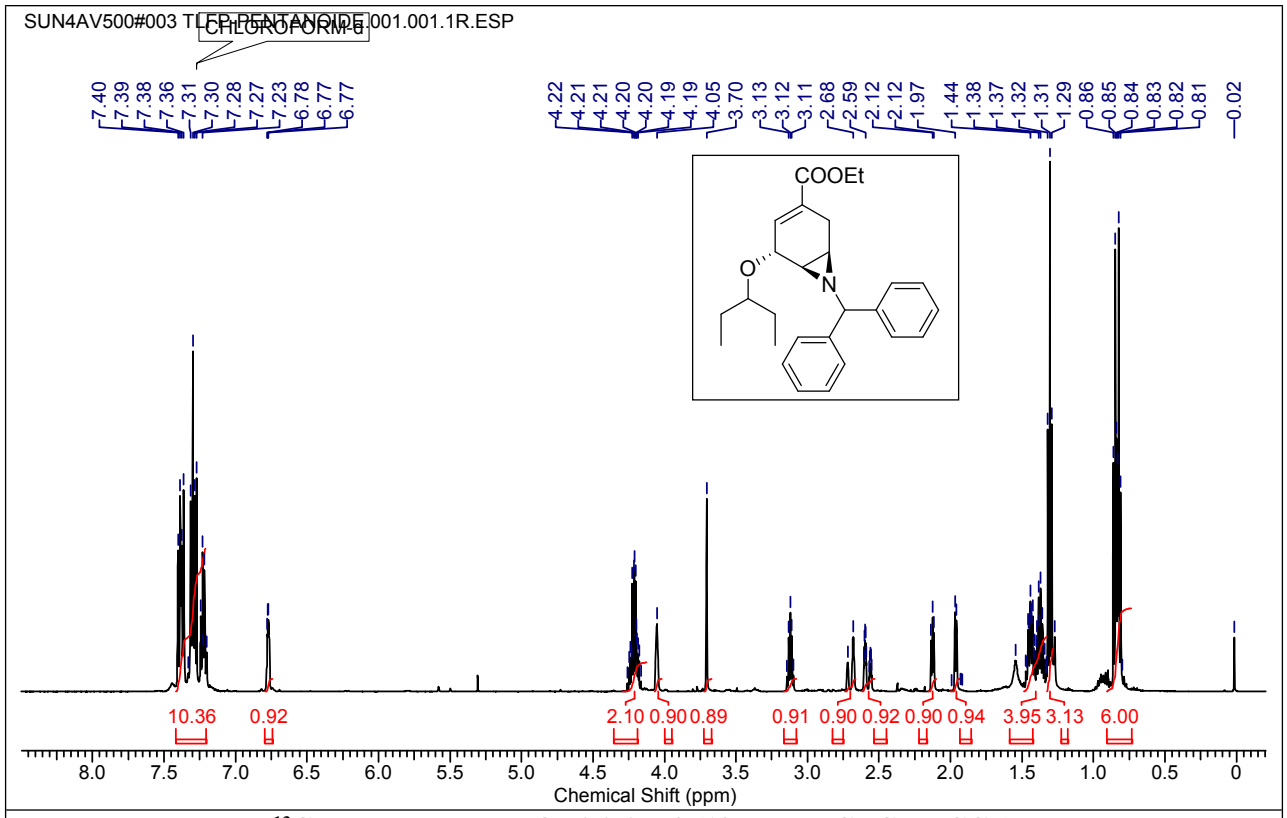
^{1}H NMR spectrum of mesylate 10 (500 MHz, $CDCl_3$ + CCl_4)



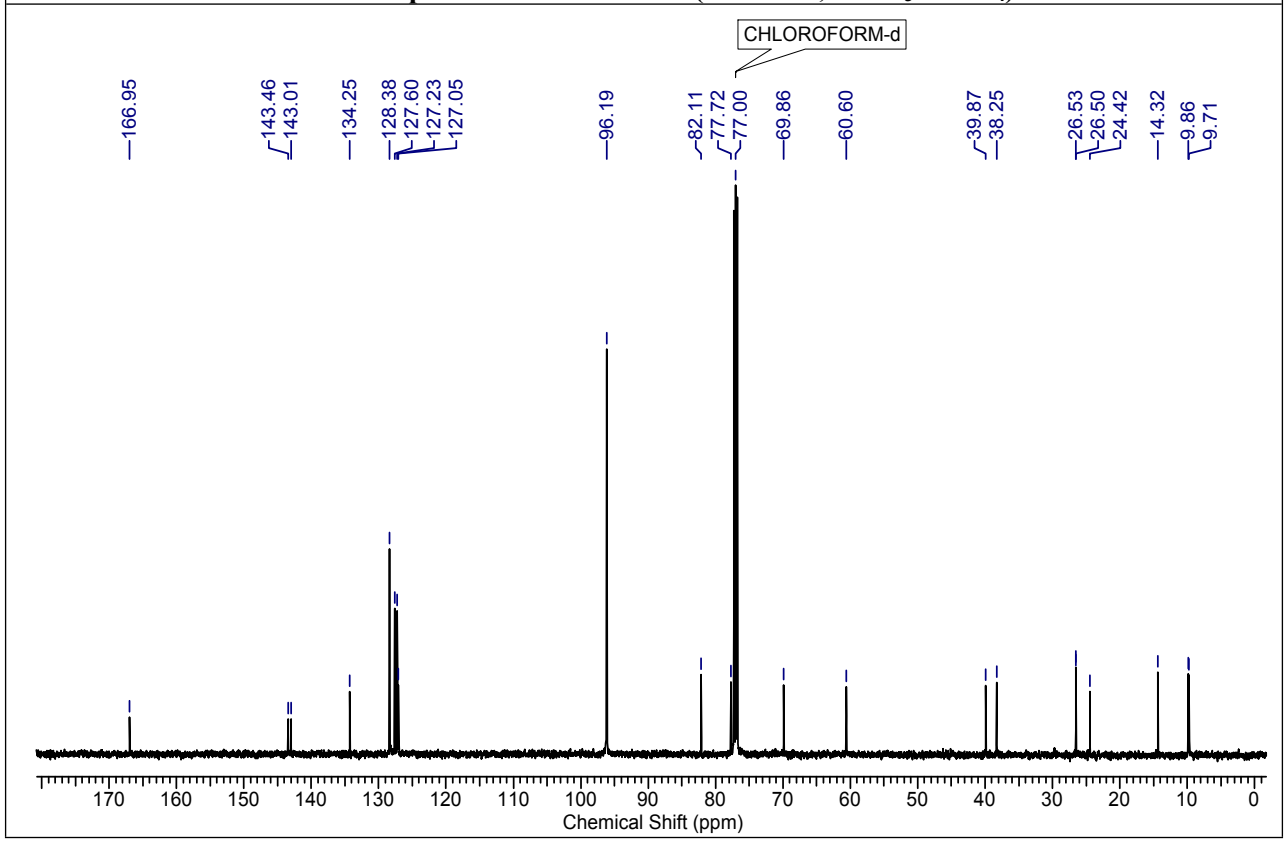
^{13}C NMR spectrum of mesylate 10 (125 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR spectrum of aziridine 2 (500 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR spectrum of aziridine 2 (125 MHz, $CDCl_3$ + CCl_4)



References:

1) A. L. Williams and J. N. Johnston, *J. Am. Chem. Soc.,* 2004, **126**, 1612.