Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Stereospecific Synthetic Approach Towards Tamiflu Using Ramberg-Backlund Reaction from Cysteine Hydrochloride

Subhash P. Chavan,[†]* Prakash N. Chavan,[†] and Rajesh G. Gonnade[‡]

[†] Organic Chemistry Division, and [‡] Center for Material Characterization CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, Maharashtra, INDIA, Tel +91-20-25902289, Fax: +91-20-25902629, E-mail: *sp.chavan@ncl.res.in*

Contents:

General information: All reagents and solvents were used as received from the manufacturer. HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 68B or on a Perkin-Elmer 1615 FT Infrared spectrophotometer. Chemical nomenclature was generated using ChemDraw Ultra 13.0. Melting points of solids were measured in Buchi melting point apparatus and are uncorrected. Optical rotation values were recorded on P-2000 polarimeter at 589 nm. ^{1}H (200 400 and 500 MHz) and ^{13}C (50 100 and 125 MHz) NMR spectra were recorded on Bruker and Bruker Advance 400 spectrometers, using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to chloroform, δ 7.27 (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra. The following abbreviations were used to explain the multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet. The reaction progress was monitored by the TLC analysis using thin layer plates precoated with silica gel 60 F_{254} (Merck) and visualized by fluorescence quenching or iodine or by charring after treatment with anisaldehyde and ninhydrin ethanolic solutions. Merck's flash silica gel (230-400 mesh) was used for column chromatography.

Experimental Section

(3a*R*,8a*S*)-1, 3-Dibenzylhexahydro-1*H*-thiepino-[3,4-*d*]-imidazol-2(3*H*)-one (8): To the compound **5**

1 (20 g, 57.14 mmol) strirred in THF (200 mL) was added zinc dust (111 g, 1.74 mol) and saturated aq solution of ammonium chloride (200 mL). The reaction mixture was refluxed for 6 h and progress of reaction was monitored by TLC. The reaction mixture was filtered through celite and washed with ethyl acetate (2 X 100 mL). The filtrate was washed with 10% HCl (100 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish thiol **7**.

The crude thiol **7** (20.00 g, 56.74 mmol) was stirred at room temperature in water (100 mL) for 4-5 h. The progress of reaction was monitored by TLC and the product was extracted with ethyl acetate (3 X 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue. The residue was purified by column chromatography over flash silica gel with 10% ethyl acetate in pet ether as the eluent to afford cyclic sulfide **8** (16.20 g, 81%) as a colourless liquid.

R_f: 0.6 (Pet ether: ethyl acetate, 70:30); ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.35 -7.25 (m, 10H), 4.76 (d, *J* = 16 Hz, 1H), 4.67 (d, *J* = 16 Hz, 1H), 4.22 (d, *J* = 16 Hz, 1H), 4.18 (d, *J* = 16 Hz, 1H), 3.27-3.22 (m, 2H), 2.97 (dd, *J* = 12.7, 3.6 Hz, 1H), 2.57 (ddd, *J* = 15.3, 8.2, 3.0 Hz, 1H), 2.58-2.54 (m, 1H), 2.26 (dd, *J* = 12.6, 10.0 Hz, 1H), 2.12-2.15 (m, 1H), 1.96-1.93 (m, , 1H), 1.78 – 1.71 (m, 1H), 1.43-1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4): δ 160.8, 137.0, 128.67, 128.63, 128.1, 128.0, 127.5, 127.2, 62.4, 58.8, 46.4, 45.9, 31.9, 29.8, 28.8, 28.1; IR ($CHCl_3$, cm^{-1}): νmax 3030, 1709, 1604, 1447, 1029; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{21}H_{24}N_2OSNa$:375.1502, found:375.1497, α]**Error!**^{25} : +37.6 (*c* 2.5, $CHCl_3$).

(3a*R*,8a*S*)-1,3-Dibenzylhexahydro-1*H*-thiepino[3,4-*d*]imidazol-2(3*H*)-one 5,5 dioxide (9): To a solution of sulfide **8** (10.00 g, 28.37 mmol) in THF: MeOH(1:1) was added oxone (52 g , 81.11 mmol) in water (100 mL). After stirring at room temperature for 4-5 h, the reaction mixture was filtered through celite and celite was washed thoroughly with methanol (3 X 60 mL). Filtrate was concentrated under reduced pressure and water (100 mL) was added to the residue. Compound was extracted with ethyl acetate (3 X 100 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude

residue. The residue was purified by column chromatography over silica gel with 30% ethyl acetate in pet ether as an eluent to afford sulfone **9** (9.16 g, 84%) as a white solid.

MP : 155-157 ^{o}C (recrystalized in ethyl acetate); R_f: 0.3 (Pet ether: ethyl acetate, 50:50); ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.42 - 7.22 (m, 10 H), 4.76 (d, *J*=16 Hz, 1H), 4.67 (d, *J* = 16 Hz, 1H), 4.22 (d, *J*=12 Hz, 1H), 4.15 (d, *J*=12 Hz, 1H), 3.60 - 3.22 (m, 3 H), 3.08 - 2.83 (m, 3H), 2.33 - 1.87 (m, 3 H), 1.50 - 1.33 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 160.2, 136.3, 135.9, 128.9, 128.8, 128.1, 127.9, 127.8, 127.7, 58.7, 58.4, 54.5, 53.4, 46.6, 46.0, 29.6, 18.7; IR ($CHCl_3$, cm^{-1}): νmax 2924, 1704, 1602, 1450, 1170; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{21}H_{24}N_2O_3SNa$: 407.1400, found: 407.1398; $[\alpha]^{25}_{\textbf{Error!}}$: +49.09 (*c* 1.1, $CHCl_3$).

(3a*S*,7a*S*)-1,3-Dibenzyl-3,3a,7,7a-tetrahydro-1*H*-benzo[*d*]imidazol-2(6*H*)-one (4): To a solution of sulfone **9** (3.00 g, 7.80 mmol) in CCl_4:*t*-BuOH (40 mL, 5:3) was added potassium hydroxide (660 mg, 11.71 mmol) and the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure and saturated solution of ammonium chloride was added to the residue. Compound was extracted with ethyl acetate (3 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain residue, which was purified by column chromatography over silica gel with 5% ethyl acetate in pet ether as an eluent to give olefin **4** (1.54 g, 62%) as a white solid.

MP: 75-77 ^{o}C (recrystalized in DCM); R_f: 0.5 (Pet ether: ethyl acetate, 80:20); ^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 7.39 - 7.23 (m, 10H), 5.74 (dd, *J* = 1.7, 9.9 Hz, 1H), 5.49 - 5.41 (m, 1H), 4.57 (d, *J* = 15 Hz, 1H), 4.50 (d, *J* = 15 Hz, 1H), 4.43 (d, *J* = 15 Hz, 1 H), 4.39 (d, *J* = 15 Hz, 1 H), 3.43 - 3.37 (m, 1 H), 3.01 - 2.93 (m, 1 H), 2.26 - 2.04 (m, 2H), 1.94 - 1.85 (m, 1 H), 1.52 - 1.41 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 164.0, 137.6, 137.2, 128.6, 128.5, 128.3, 127.5, 127.4, 127.3, 124.0, 59.0, 58.7, 47.4, 47.2, 25.2, 24.5; IR ($CHCl_3$, cm^{-1}): νmax 2925, 1704, 1629, 1495, 1238; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{21}H_{22}N_2ONa$: 341.1624, found: 341.1619; $[\alpha]^{25}_{\textbf{Error!}}$: +30.0 (*c* 0.4, $CHCl_3$).

Di-tert-butyl (1*S*,2*S*)-cyclohex-3ene-1,2-diylbis (benzylcarbamate) (10): To a cooled solution of olefin **4** (1.2 g, 3.77 mmol) in dry THF at 0 ^{o}C was added lithium aluminium hydride portionwise (715 mg, 18.84 mmol). The reaction mixture was stirred at room temperature for 30

min and was quenched by addition of 15% NaOH solution and ice pieces. Then anhydrous Na_2SO_4 was added to the reaction and stirred for 10 min. The resultant solution was filtered and the residue was washed with ethyl acetate (2 X 15 mL). The filterate was concentrated under reduced pressure. Crude compound was directly subjected for further reaction without purification.

The crude compound (1.15 g) was subjeted to hydrolysis by treatment with aq 1% HCl (10 mL) and $NH_2OH.HCl$ (3.5 g, excess) and heating at 80 ^oC for 1h. The reaction mixture was neutralised with solid $NaHCO_3$ and compound was extracted with DCM (3 X 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude diamine.

The crude diamine (1.1 g) without purification was chemically masked with neat $(Boc)_2O$ (1.93 mL, 11.30 mmol) and cat. DMAP (100 mg). The reaction mixture was stirred at room temperature for 3 h, water was added and the compound was extracted with DCM (3 X 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in pet ether as an eluent to afford dicabamate **10** (1.54 g, 67% over three steps) as a colourless syrup.

R_f: 0.7 (Pet ether: ethyl acetate, 80:20); ^1H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.48 - 7.04 (m, 10H), 5.93 - 5.31 (m, 2H), 5.26 - 3.27 (m, 6H), 2.40 - 1.74 (m, 4H), 1.59 - 1.22 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 156.2, 155.7, 140.6, 129.5, 128.8, 128.2, 128.0, 127.8, 126.5, 126.4, 126.2, 79.6, 79.5, 58.6, 58.0, 54.4, 53.2, 28.4, 28.3, 27.4, 25.7; IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 1695, 1603, 1365, 1165; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{30}H_{40}N_2O_4Na$: 515.2880, found: 515.2880; $[\alpha]^{25}$ **Error!** : +6.0 (*c* 2.0, $CHCl_3$).

Di-tert-butyl ((1*S*,2*S*)-cyclohex-3-ene-1,2-diyl) dicarbamate (11): To a solution of diboc compound **11** (300.00 mg, 0.58 mmol) in THF (5 mL) and ammonia (10 mL) at -78 ^oC was added sodium metal (428 mg, 18.75 mmol) portionwise and stirred at same temperature for 2 h. The reaction mixture was quenched with solid ammonium chloride and the reaction mass was brought to room temperature. Water (10 mL) was added to the residue and compound was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet ether as an eluent to afford compound **11** (173 mg, 91%) as a white solid.

MP : 135-137 ^oC (recrystalized in ethyl acetate) ; R_f: 0.4 (Pet ether: ethyl acetate, 70:30); ^1H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 5.81 - 5.70 (m, 1H), 5.48 (bd, J = 10 Hz, 1H), 5.04 (bd, J = 10 Hz, 1H), 4.74 (bd, J = 10 Hz, 1H), 4.15 - 4.03 (m, 1H), 3.48 (bd, J = 10 Hz, 1H), 2.34 - 1.93 (m, 4H), 1.44 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.5, 156.0, 129.5, 127.6, 79.5, 79.0, 53.2, 52.5, 28.6, 28.4, 24.8; IR ($CHCl_3$, cm^{-1}): ν_{max} 3360, 2923, 1675, 1600, 1463, 1166; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{16}H_{28}N_2O_4Na$: 335.1940, found:335.1942; $[\alpha]^{25}$**Error!** : +12.5 (c 0.8, $CHCl_3$).

Di-tert-butyl ((1*R*,2*R*,3*S*,6*S*)-7-oxabicyclo-[4.1.0]-heptane-2,3-diyl) dicarbamate (12): To a cooled (0 ^oC) and stirred solution of diboc olefin **11** (90 mg, 0.29 mmol) in DCM (2 mL) was added NaH_2PO_4 (315 mg, 2.01 mmol) followed by *m*-CPBA (355 mg, 2.01 mmol). Reaction mixture was stirred at 0 ^oC for 30 min and then allowed to stir at room temperature for 6 h. After completion of the reaction, saturated aq. solution of $Na_2S_2O_3$ (3 mL) was added and the reaction mixture was further stirred for 30 min. Water (3 mL) was added to the reaction mixture and it was extracted with ethyl acetate (3 X 5 mL). The combined organic layer was washed with saturated aq. solution of $NaHCO_3$ (3 mL) and dried over anhydrous Na_2SO_4, 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 epoxide **12** (92 mg, 97%) as a white solid.

MP: 135-137 ^oC (recrystalized in 100% DCM); R_f: 0.4 (Pet ether: ethyl acetate, 60:40); ^1H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 5.11 (bd, J = 10 Hz, 1H), 4.87 (bs, 1H), 3.87 - 3.75 (m, 1H), 3.52 (bd, J = 10 Hz, 1H), 3.27 (bs, 1H), 3.24 (bs, 1H), 2.11 - 1.88 (m, 2H), 1.81 (d, J = 10 Hz, 1H), 1.63-1.58 (m, 1H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.5, 155.9, 79.7, 79.2, 56.1, 53.9, 53.4, 49.7, 28.6, 28.47, 28.44, 22.7; IR ($CHCl_3$, cm^{-1}): ν_{max} 3359, 1681, 1519, 1168; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{16}H_{28}N_2O_5Na$: 351.1890, found: 351.1890; $[\alpha]^{25}$**Error!** : +27.27 (c 1.1, $CHCl_3$).

Di-tert-butyl (1*R*,2*R*,3*S*,6*S*)-7- oxabicyclo-[4.1.0]-heptane-2,3-diyldicarbamate (13): To a stirred solution of epoxide **12** (60 mg, 0.18 mmol) in methanol (1 mL) was added diphenyl diselenide (4 mg, 0.01 mmol) followed by sodium borohydride (8 mg, 0.21 mmol) and reaction mixture was stirred at rt for 2 h. After disappearance of starting material which was monitored by TLC, THF (1 mL) was added followed by H_2O_2 (0.38 mL, 30%, 3.65 mmol) and it was further stirred for 1 h. The reaction mixture was concentrated; water was added and extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, 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 allylic alcohol **13** (50 mg, 80%) as white solid.

MP: 121-123 ^oC (recrystalized in 100% DCM); R_f: 0.3 (Pet ether: ethyl acetate, 70:30); ^1H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 5.69-5.67 (m, 2H), 5.54 (bd, J = 7 Hz, 1H), 4.81 (bd, J = 8.5 Hz, 1H), 4.19 - 4.14 (m, 1H), 3.81 - 3.70 (m, 1H), 3.51 - 3.43 (m, 1H), 2.46 (dd, J = 5, 15Hz, 1H), 2.10 - 1.96 (m, 2H), 1.46 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 158.2, 156.8, 129.9, 124.8, 79.9, 73.6, 60.4, 48.8, 32.4, 28.4; IR ($CHCl_3$, cm^{-1}): νmax 3430, 1679, 1645, 1528, 1366, 1163; HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{16}H_{28}N_2O_5Na$: 351.1890, found: 351.1891; $[\alpha]_{\textbf{Error!}}^{25}$: -41.25 (*c* 3.2, $CHCl_3$).

Di-tert-butyl (1*R*,2*R*,3*S*,6*S*)-7-oxabicyclo-[4.1.0]heptane-2,3-diyldicarbamate

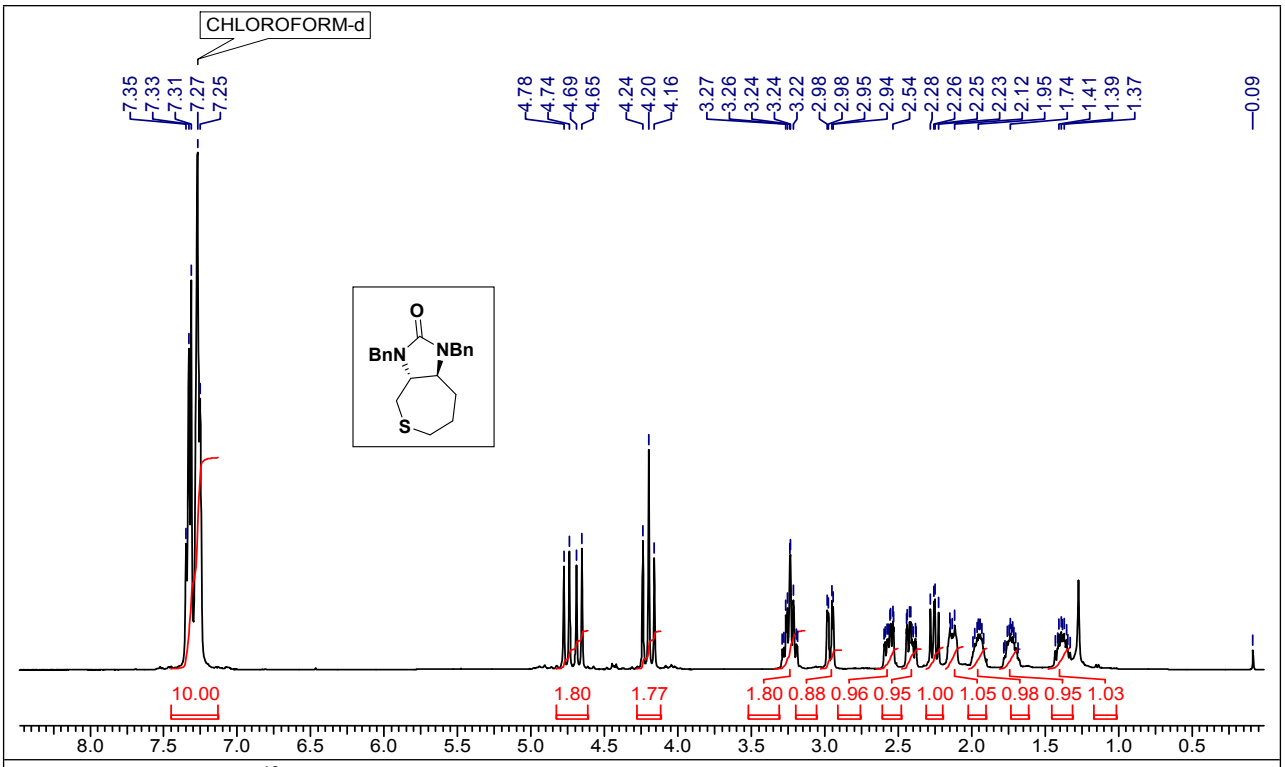
^{2} (3): To the solution of allylic alcohol **13** (25 mg, 0.07 mmol) in DCM (1 mL) was added $NaHCO_3$ (50 mg, 0.76 mmol) and Dess-Martin periodinate (85 mg, 0.22 mmol) at 0 ^oC. The reaction mixture was stirred for overnight at rt. After completion of reaction, water (3 mL) was added to the reaction mass and compound was extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet ether as an eluent to afford ketone **3** (22 mg, 90%) as semisolid mass.

R_f: 0.4 (Pet ether: ethyl acetate, 70:30); ^1H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.00 - 6.92 (m, 1H), 6.14 (dd, J = 10.1 Hz, 3.1 Hz, 1H), 5.98 (d, J = 7.3 Hz, 1H), 5.52 (d, J = 6.1 Hz, 1 H), 4.30 (dd, J = 13.1, 6.4 Hz, 1H), 3.97 - 3.81 (m, 1H), 3.00-2.94 (m, 1H), 2.50 - 2.24 (m, 1H), 1.48 (s,

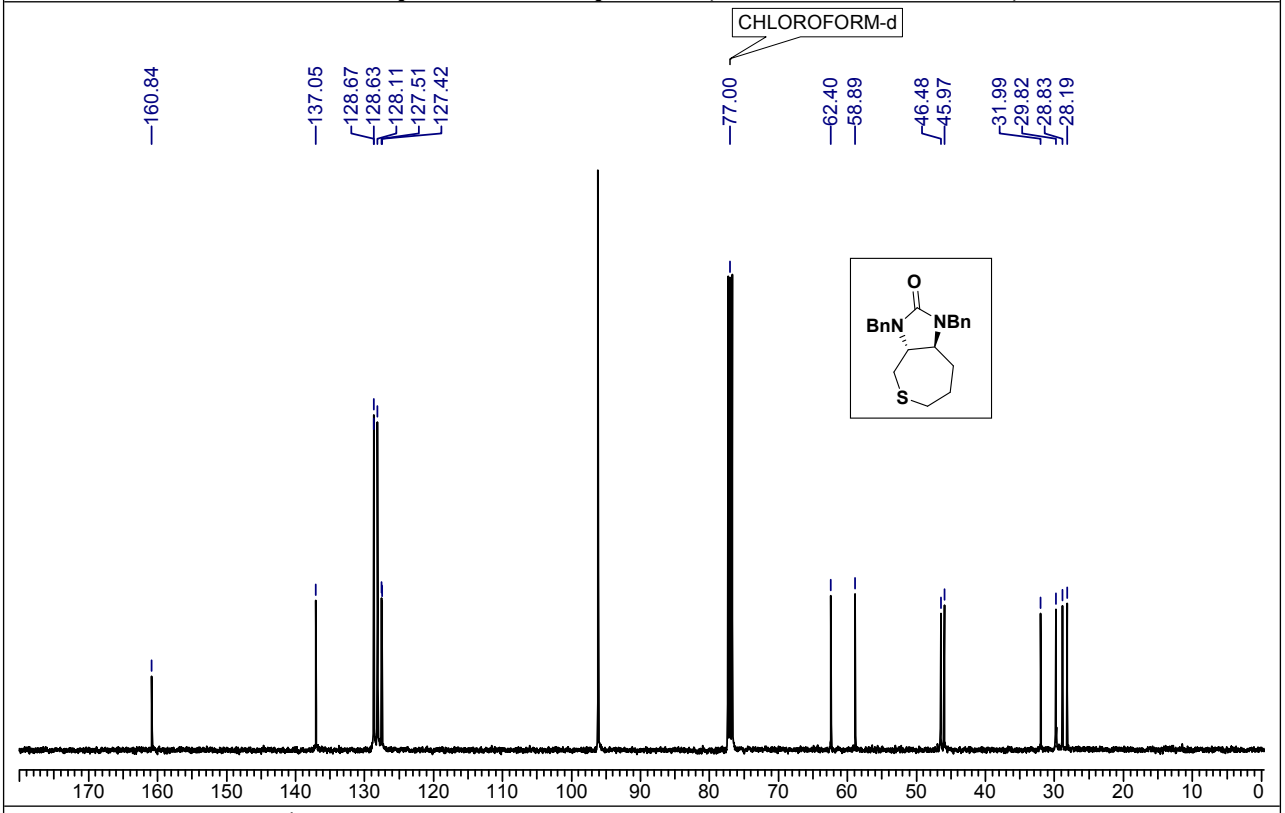
9H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 194.3, 157.7, 155.7, 148.4, 128.5, 80.4, 79.3, 60.5, 54.4, 34.6, 28.4, 28.3; IR ($CHCl_3$, cm^{-1}): ν_{max} 3411, 2926, 1695, 1514, 1173; HRMS (ESI) (m/z): $[M+Na]^+$ Calculated for $C_{16}H_{26}N_2O_5Na$ -349.1739, found: 349.1744; $[\alpha]^{25}_{\textbf{Error!}}$: -114.9 (*c* 0.5, $CHCl_3$), lit.[7c] -116.3 (*c* 0.945, $CHCl_3$).

Spectral Data

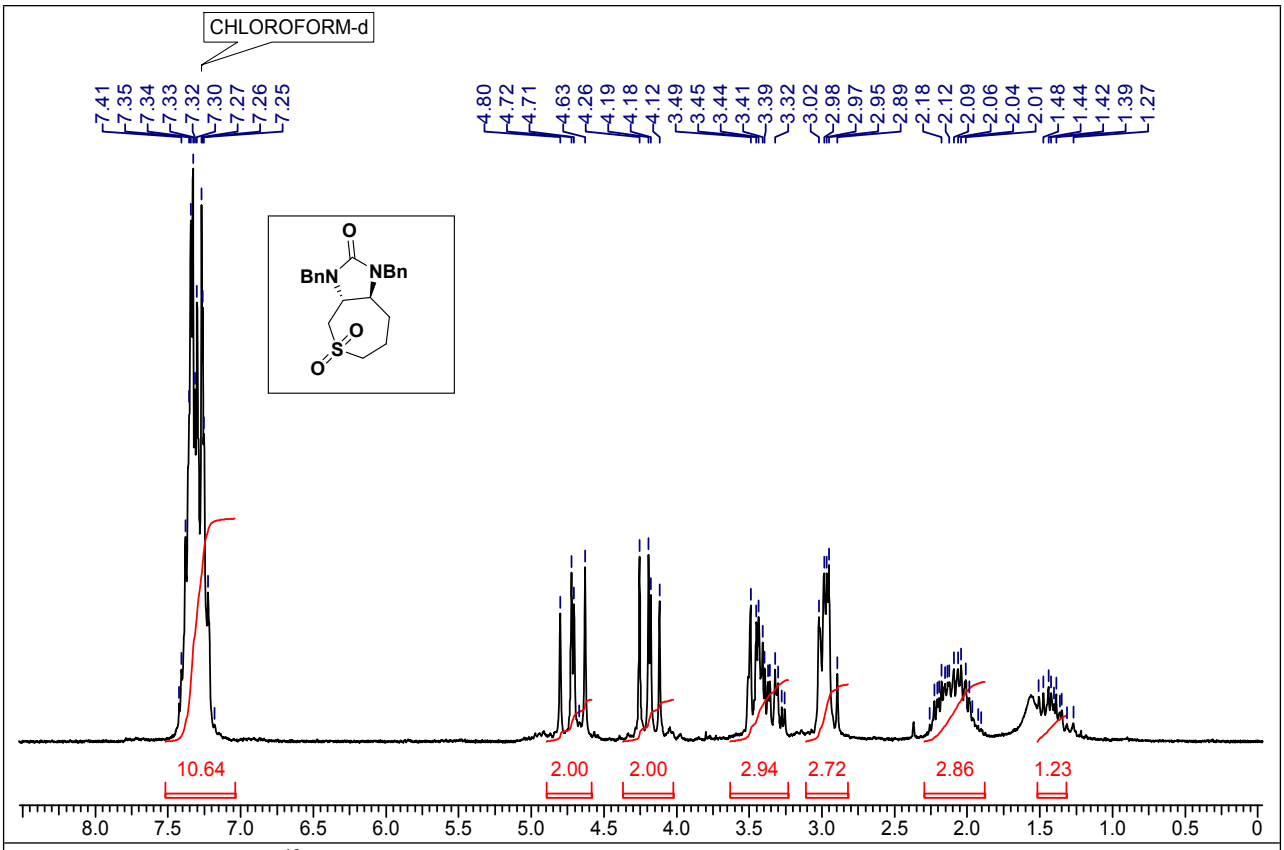
^{1}H NMR spectrum of cyclic sulfide 8 (400 MHz, $CDCl_3$ + CCl_4)



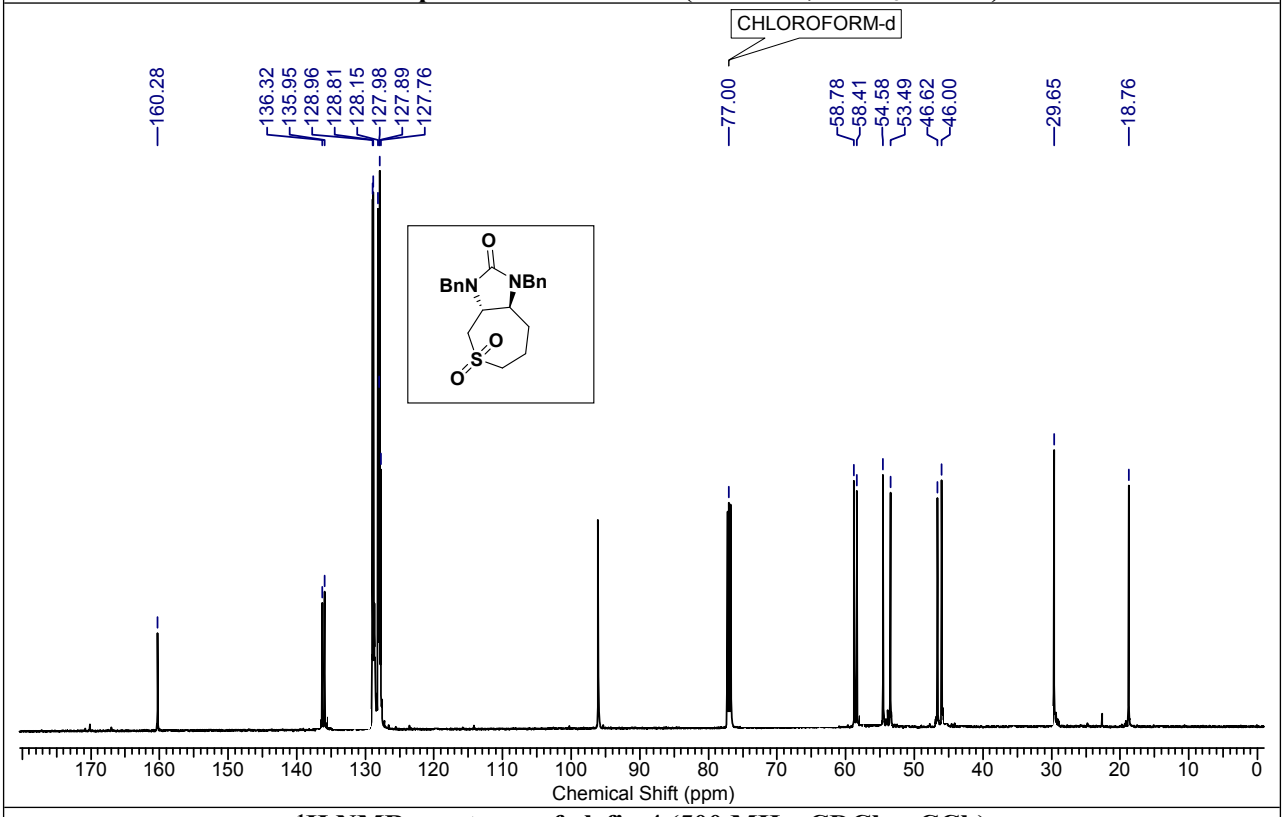
^{13}C NMR spectrum of compound 8 (100 MHz, $CDCl_3 + CCl_4$)



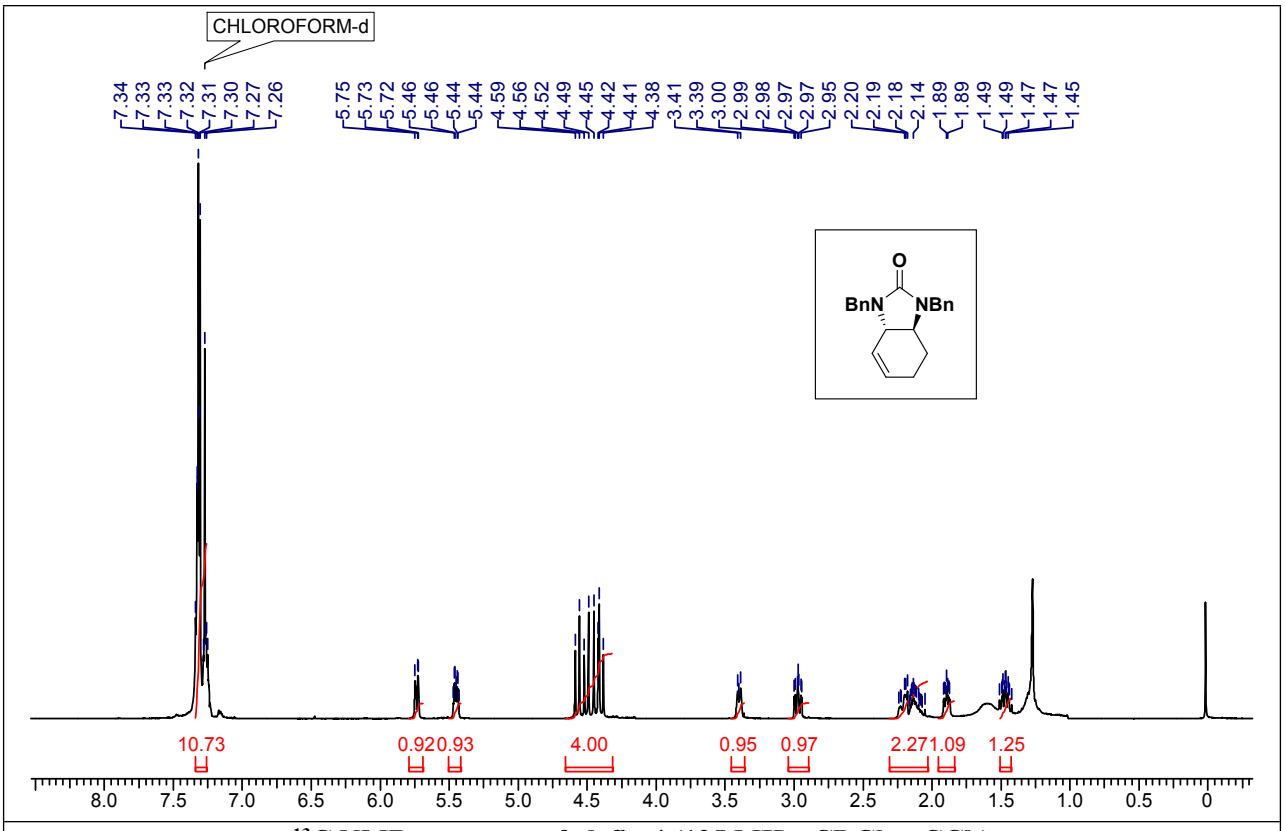
^{1}H NMR spectrum of sulfone 9 (200 MHz, $CDCl_3 + CCl_4$)



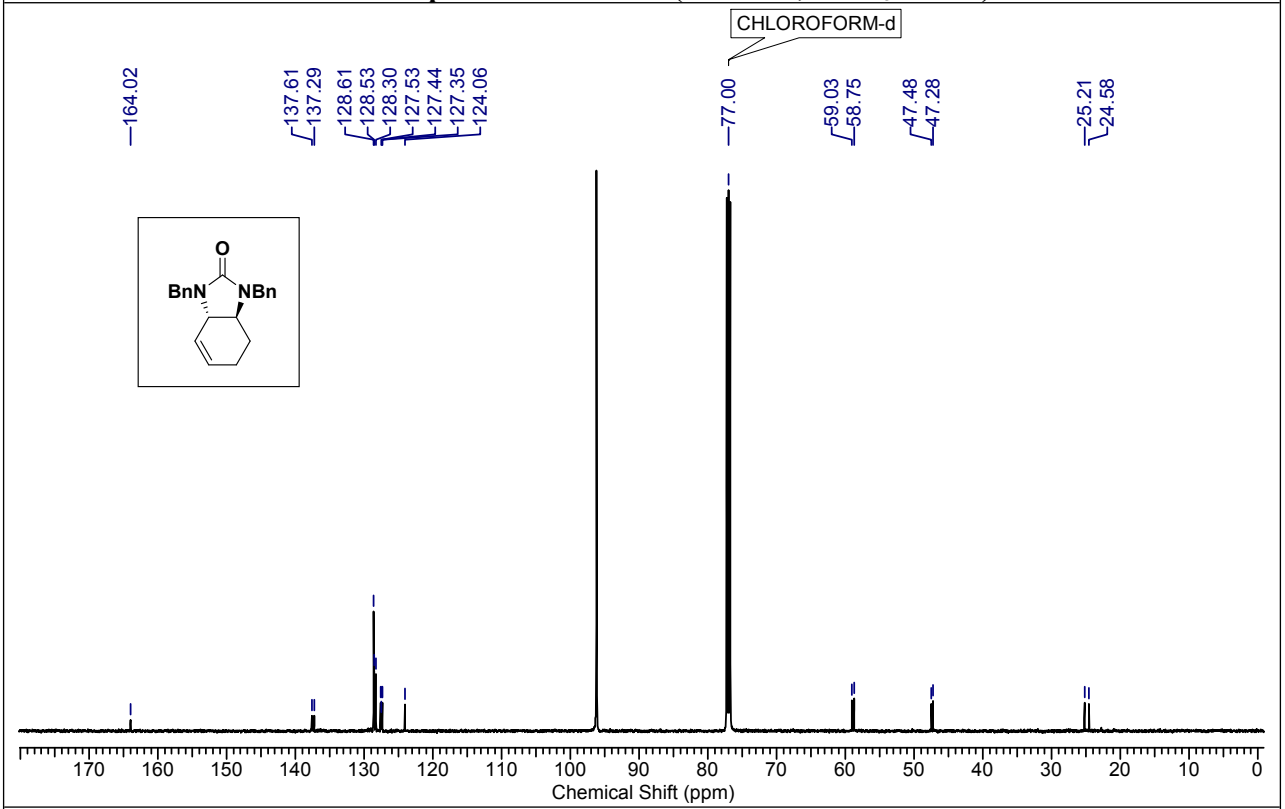
^{13}C NMR spectrum of sulfone 9 (125 MHz, $CDCl_3 + CCl_4$)



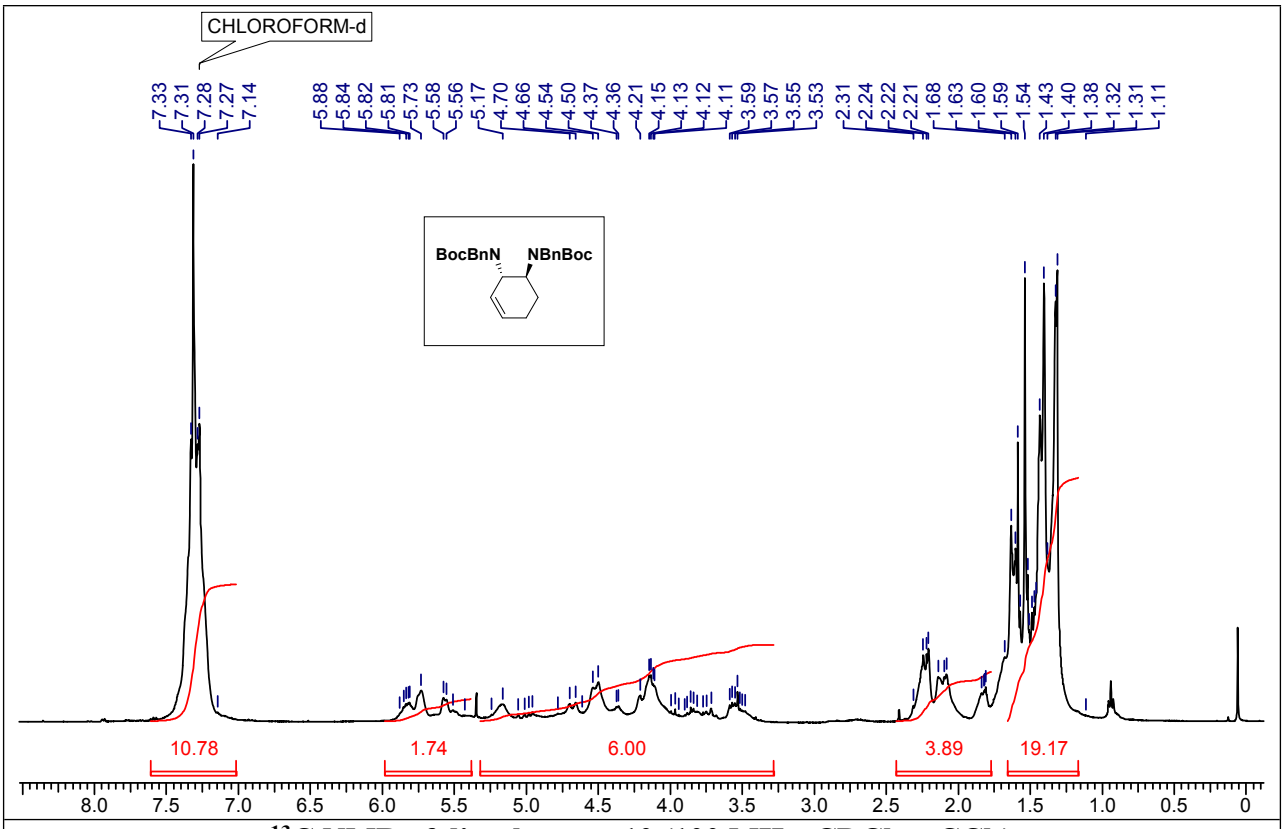
^{1}H NMR spectrum of olefin 4 (500 MHz, $CDCl_3 + CCl_4$)



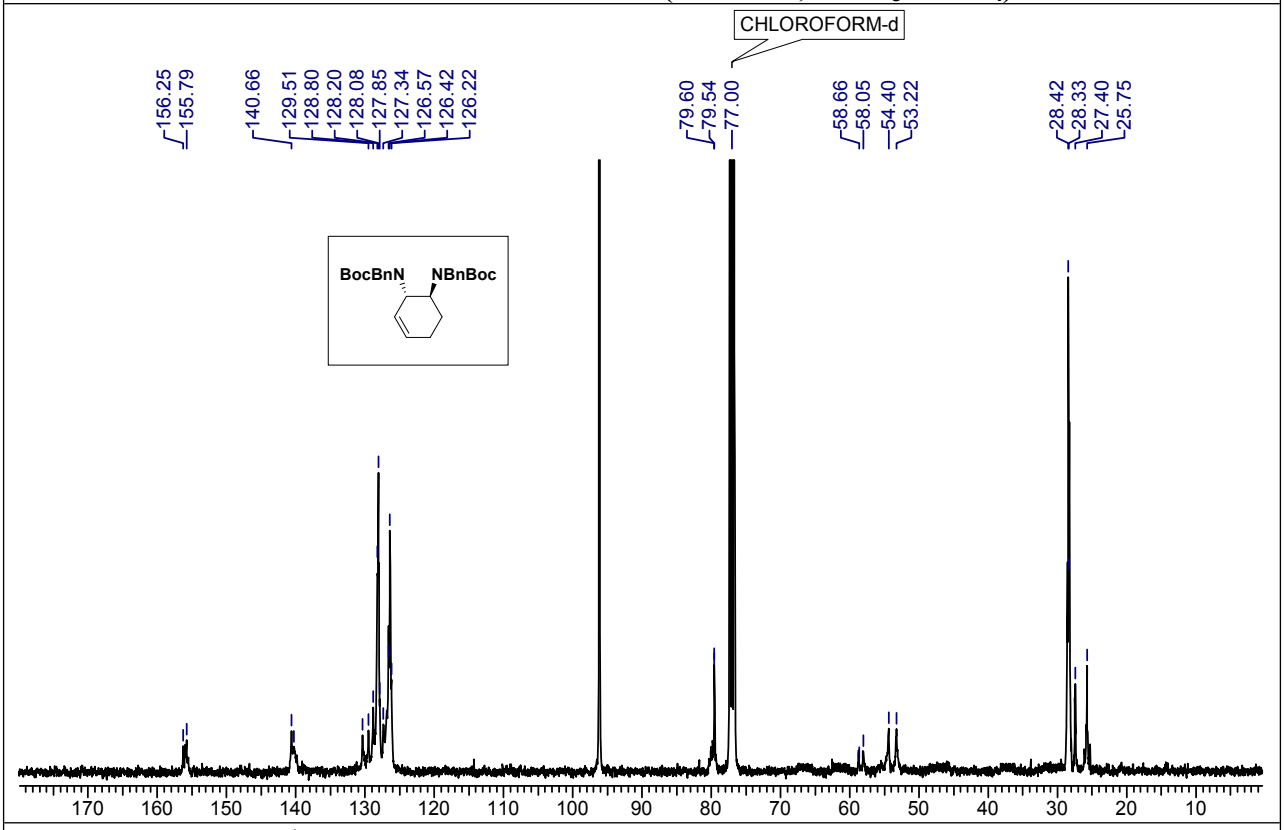
^{13}C NMR spectrum of olefin 4 (125 MHz, $CDCl_3$ + CCl_4)



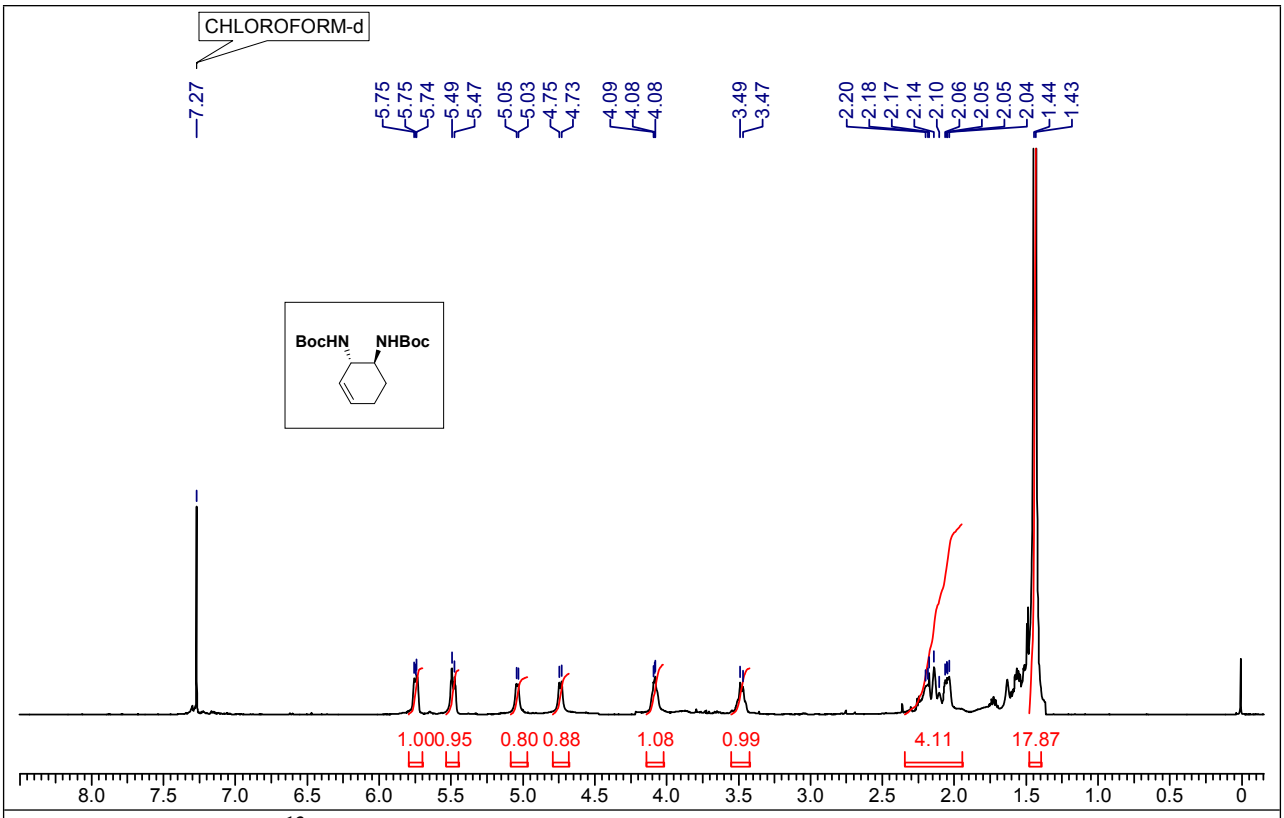
^{1}H NMR of dicarbamate 10 (400 MHz, $CDCl_3$ + CCl_4)



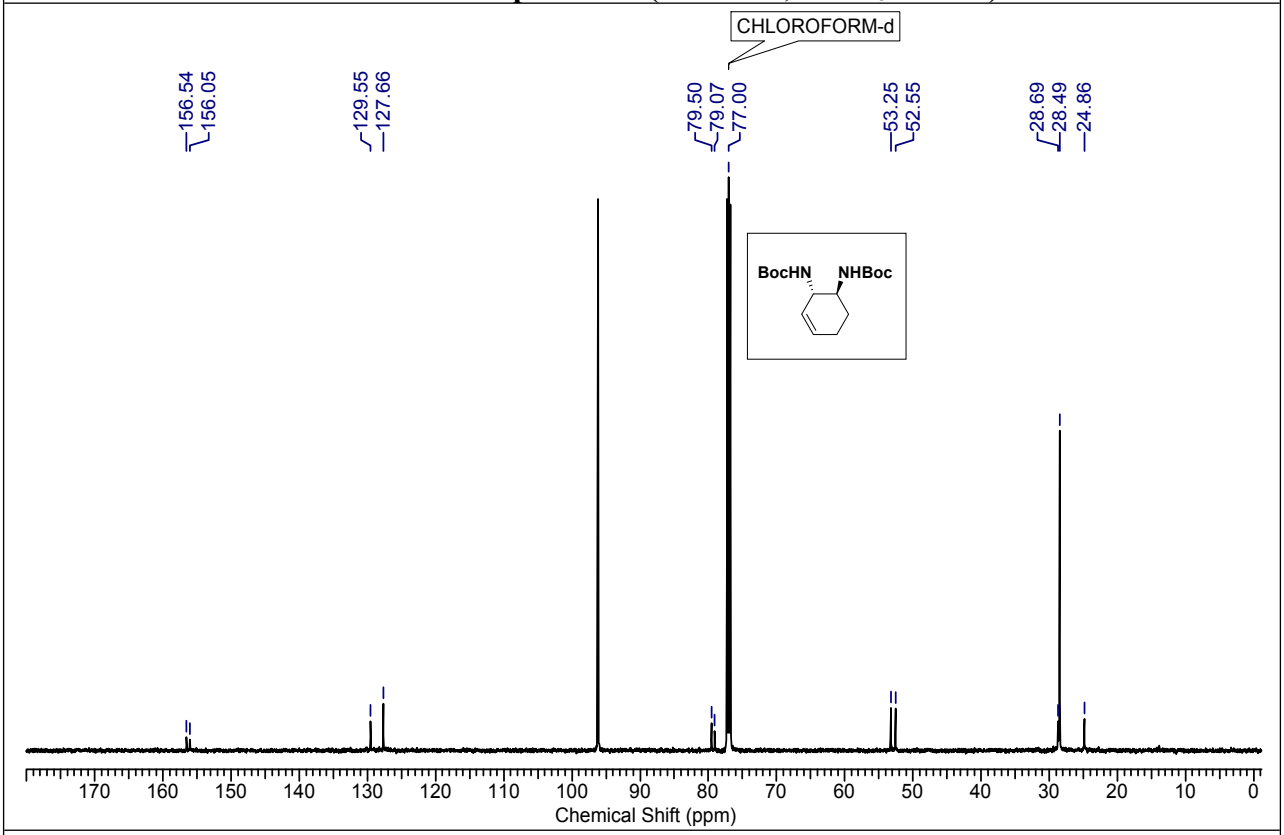
^{13}C NMR of dicarbamate 10 (100 MHz, $CDCl_3$ + CCl_4)



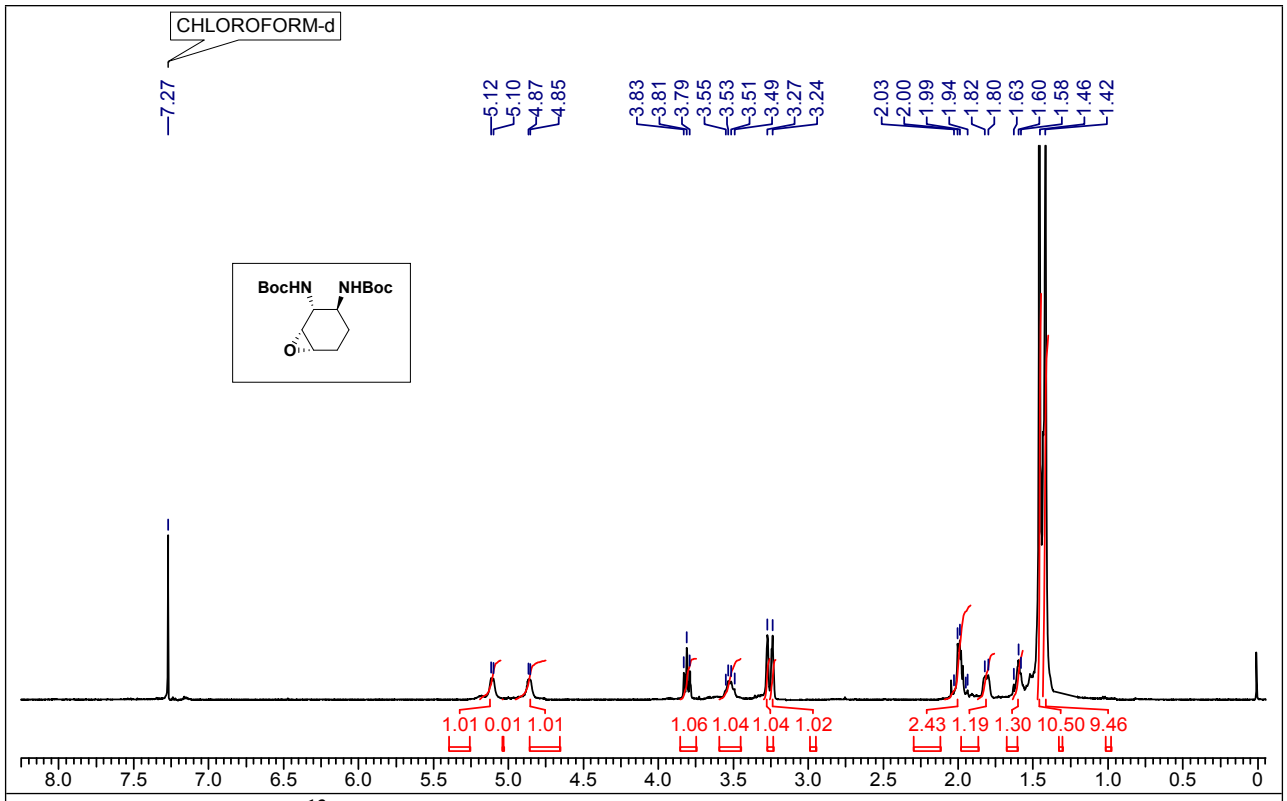
^{1}H NMR of compound 11 (500 MHz, $CDCl_3$ + CCl_4)



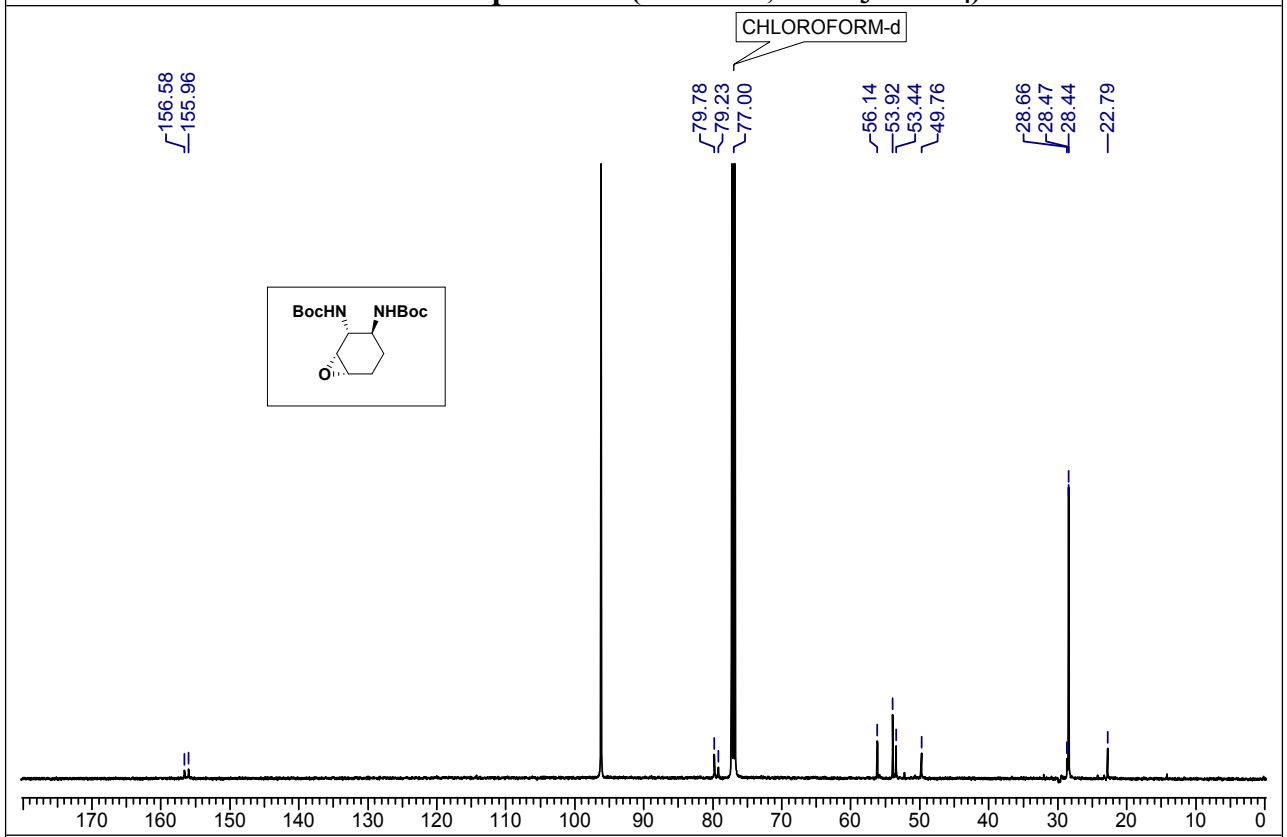
^{13}C NMR of compound 11 (125 MHz, $CDCl_3$ + CCl_4)



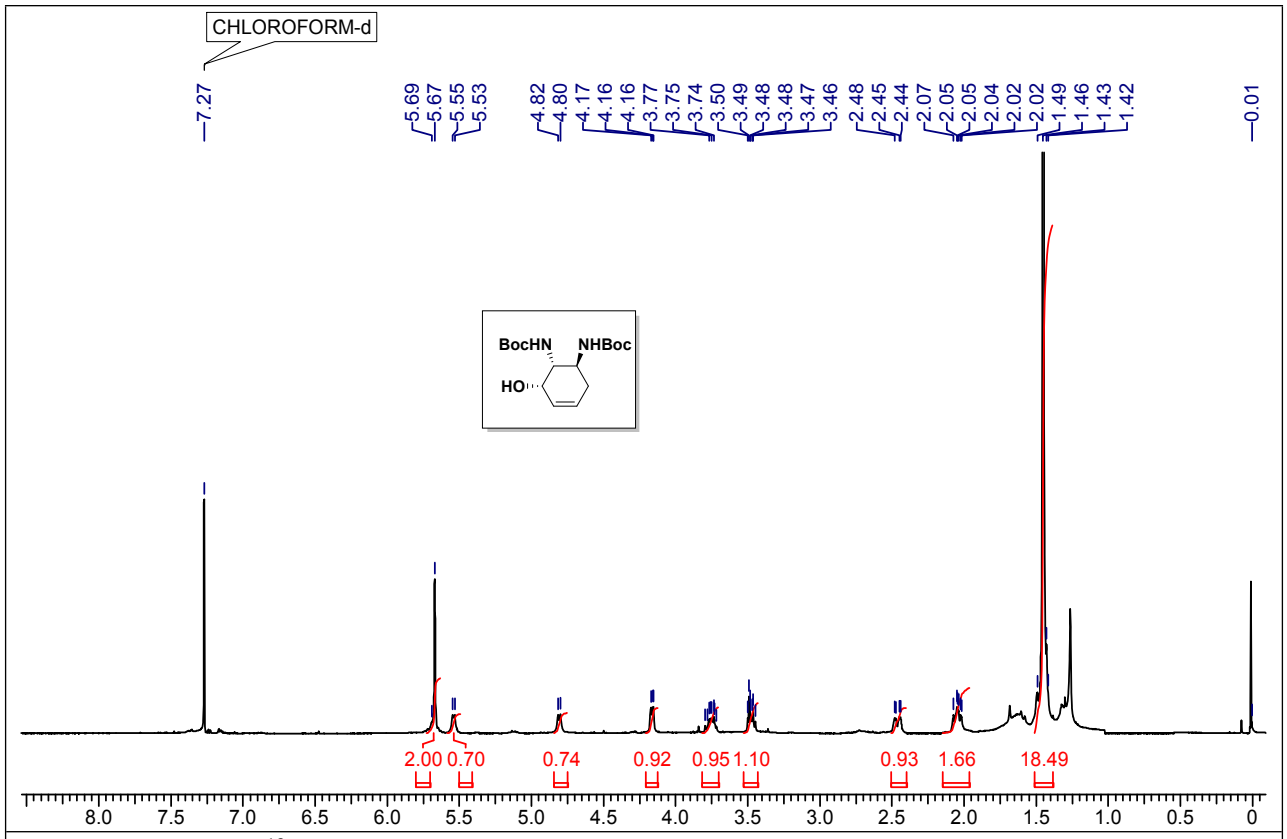
^{1}H NMR of epoxide 12 (500 MHz, $CDCl_3$ + CCl_4)



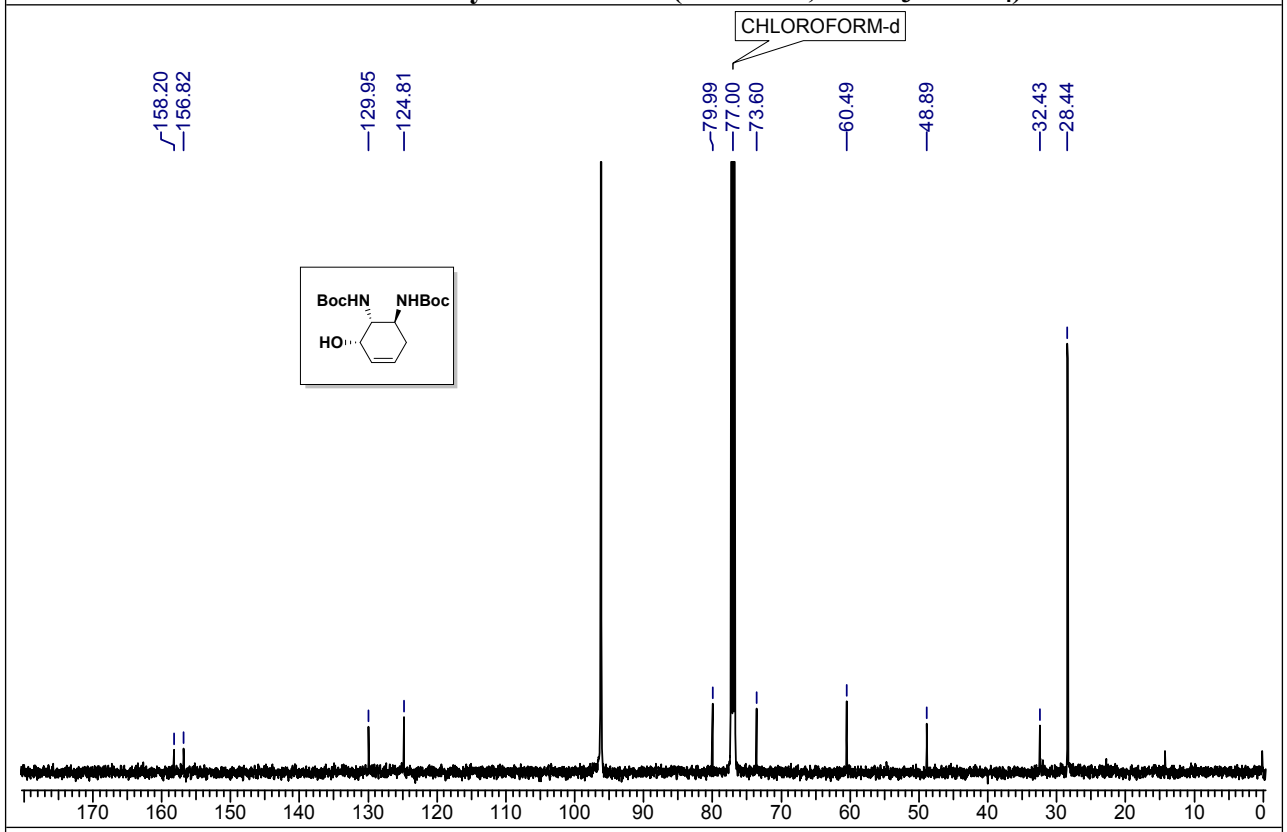
^{13}C NMR of epoxide 12 (125 MHz, $CDCl_3$ + CCl_4)



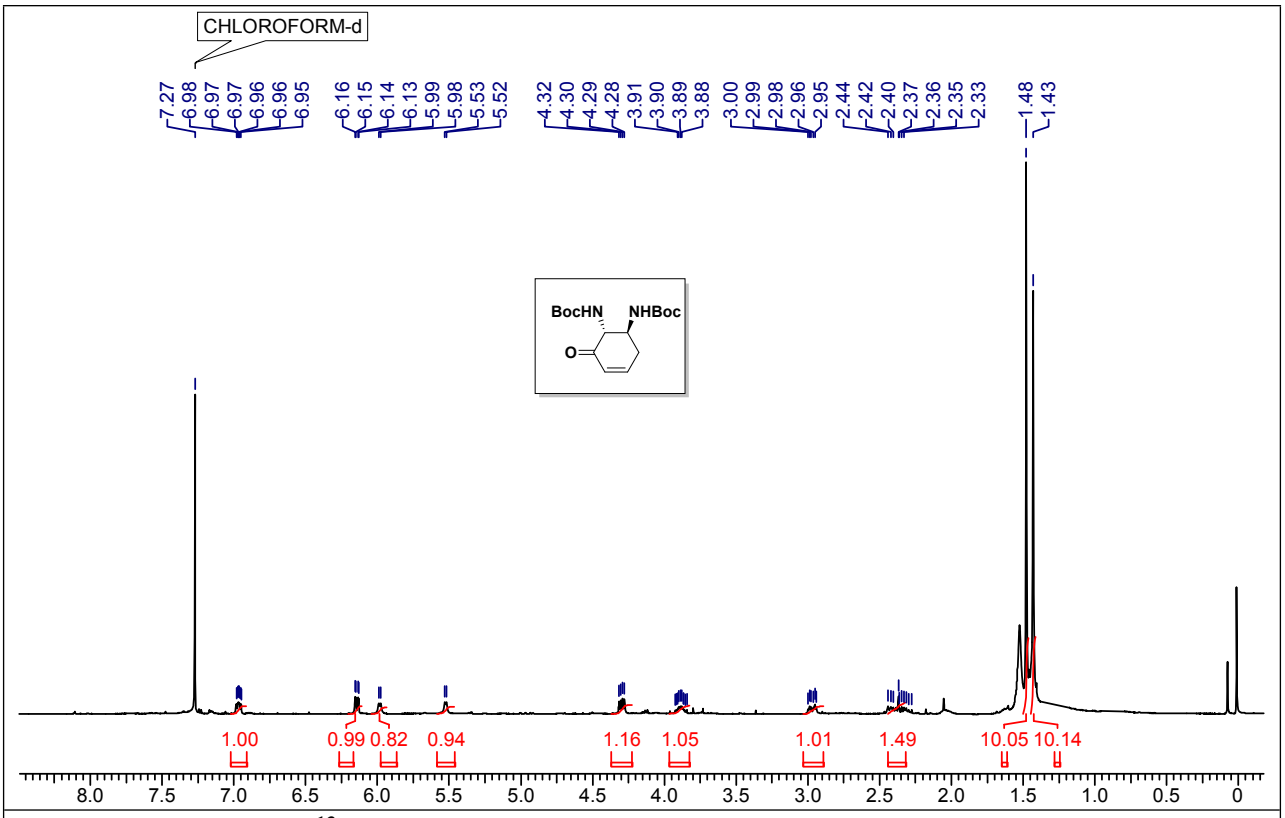
^{1}H NMR of allylic alcohol 13 (500 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of allylic alcohol 13 (125 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR of Ketone 3 (500 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of Ketone 3 (125 MHz, $CDCl_3$ + CCl_4)

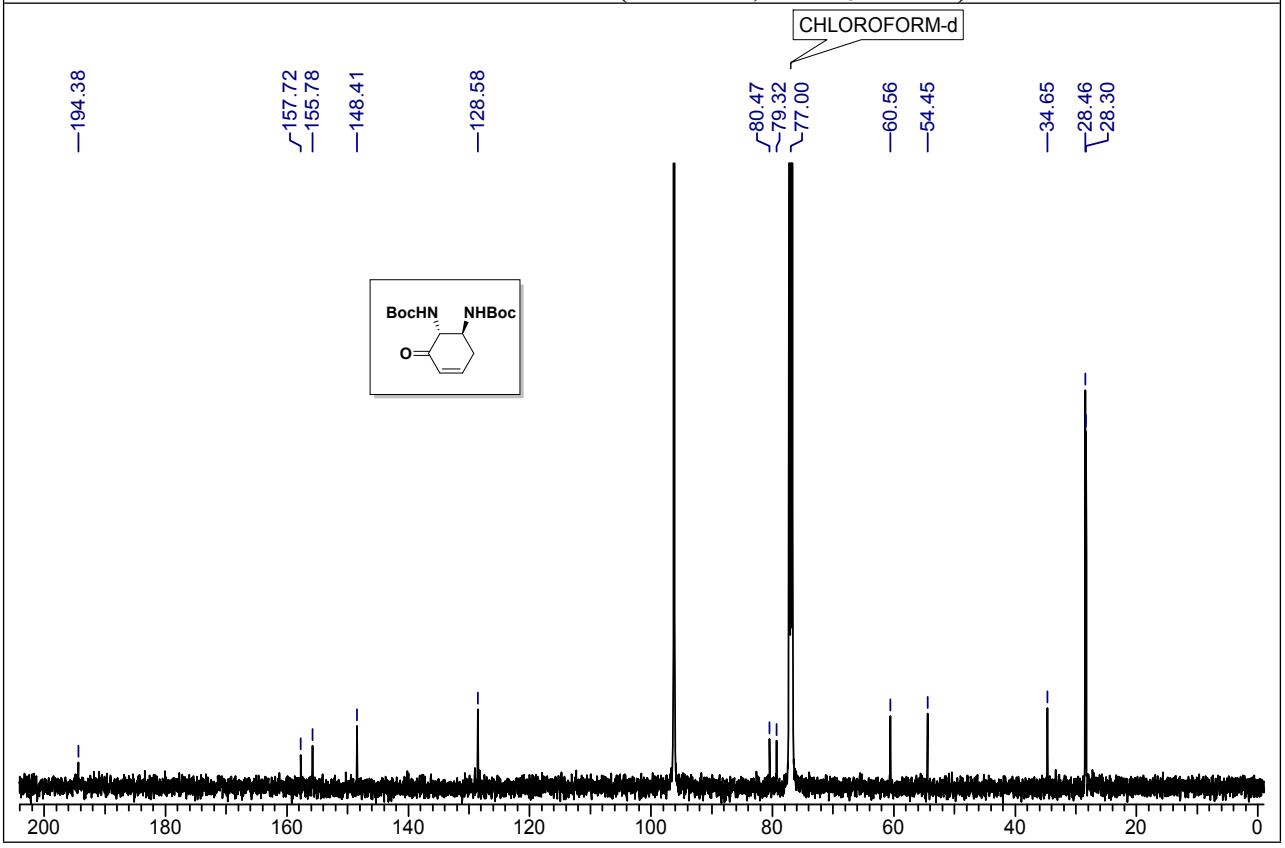
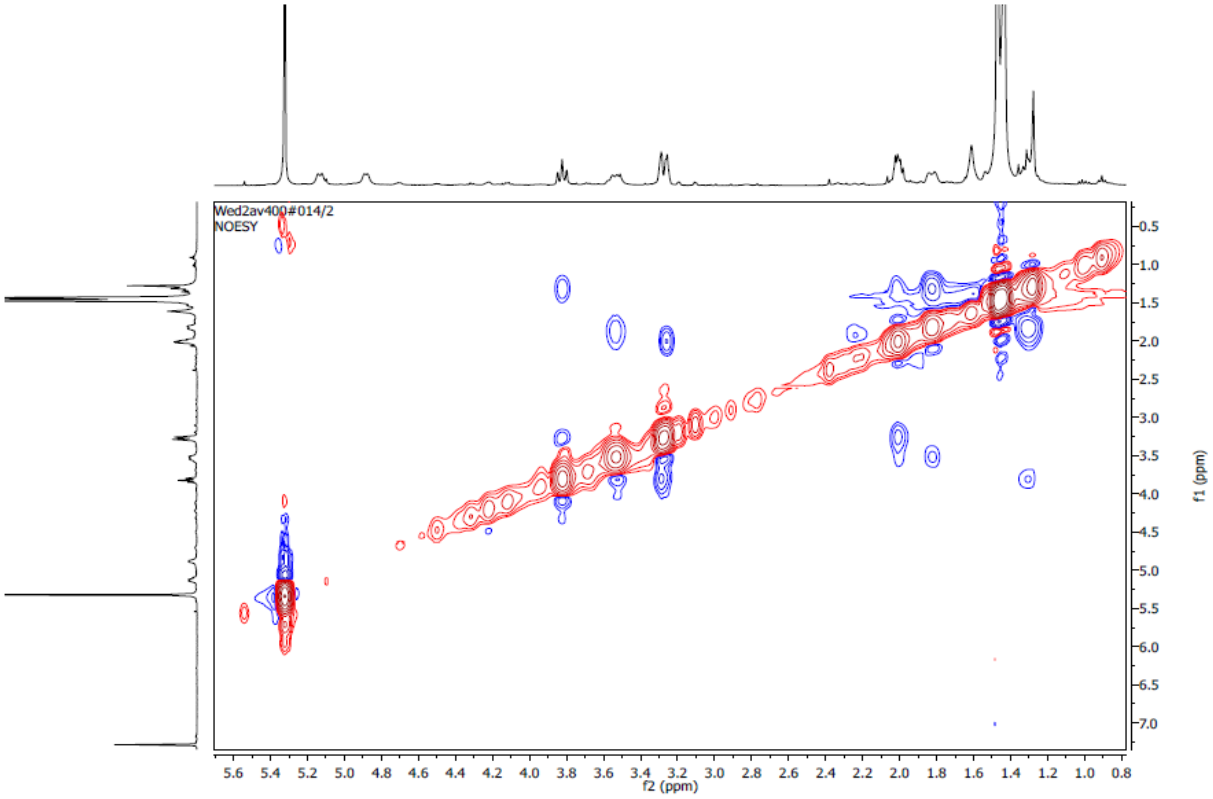
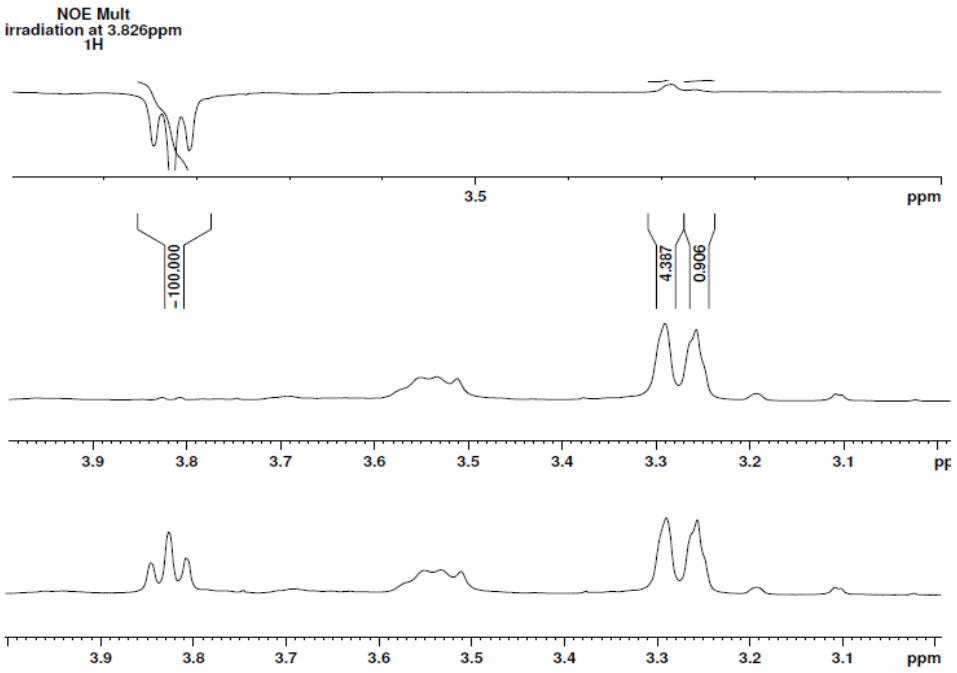
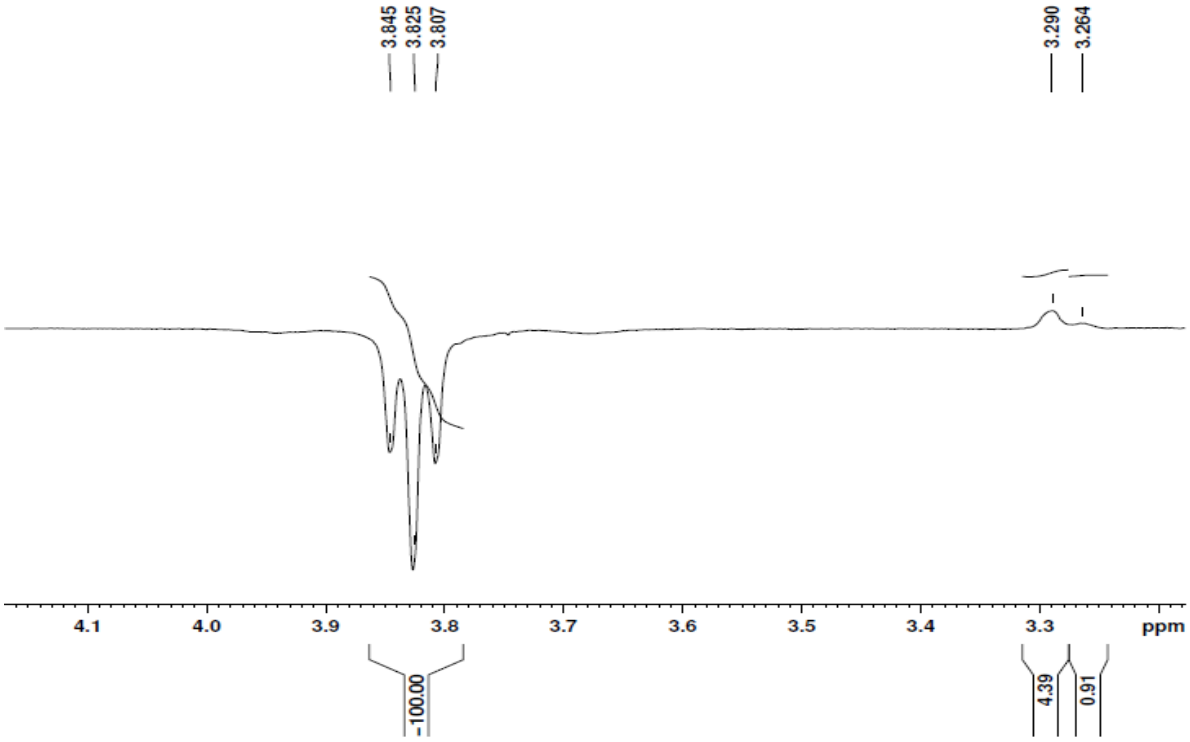
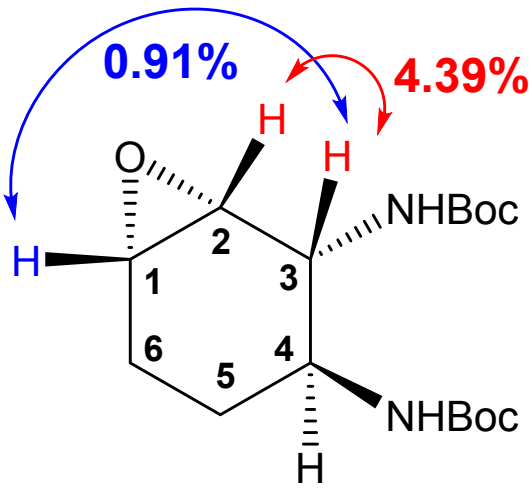


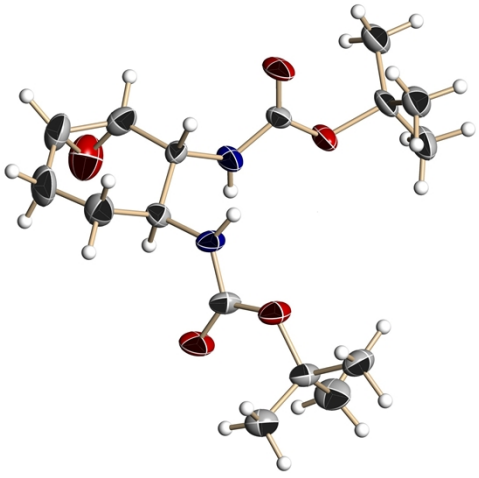
Fig NOESY and X-ray Single Crystal Analysis of epoxide **12** (ORTEP diagram; ellipsoids are drawn at 30 % probability)











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2. Y. Fukuta, T. Mita, N. Fukuda, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.,* 2006, **128**, 6312.