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Supporting Information

Enantio- and Diastereocontrolled conversion of chiral epoxide to *trans*-cyclopropane carboxylate: Application to the synthesis of Cascarillic acid, Grenadamide and L-(-)-CCG-II

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Experimental Section

General information

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al*.[1] Solvents used for chromatography were distilled at respective boiling points using known procedures. Progress of the reactions was monitored by TLC using precoated aluminium plates (Merck silica gel 60 F254). Column chromatographies were performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FTIR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX–500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (brs, broad; s, singlet; d, doublet; t, triplet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX-500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Büchi B-540 electrothermal melting point apparatus. Yields refer to chromatographically and spectroscopically pure compounds. Enantiomeric excess was determined using Mosher analysis.

(1*R*,2*R*)-2-Hexylcyclopropyl)methanol (7): To a stirred suspension of $LiAlH_4$ (765 mg, 20.17 mmol) in dry THF (100 mL) at -10 °C was added ester **3a** (5 g, 25.21 mmol) over 20 min under argon atmosphere. After stirring for 20 min, the reaction was quenched by adding 10% aqueous NaOH at 0 °C. The mixture was filtered with pad of celite, and washed with EtOAc. The organic layer was dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **7** (3.15 g, 80% yield) as a colorless syrupy liquid. $[\alpha]_D^{25}$: -22.24 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3350, 2854, 1466, 1216, 1033; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.26-0.41 (2H, m), 0.55-0.67 (1H, m), 0.76-0.91 (4H, m), 1.15-1.47 (10H, m), 1.70 (1H, brs), 3.44 (2H, dd, *J* = 1.9, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8, 14.0, 17.1, 21.0, 23.0, 29.0, 29.5, 31.8, 33.5, 67.0; MS (ESI): m/z 178.96 $(M+Na)^+$; Elemental analysis (%) calc. for ($C_{10}H_{20}O$): C, 76.86; H, 12.90 %; Found: C, 76.65; H, 12.72%.

(1*R*,2*R*)-Ethyl 2-heptylcyclopropanecarboxylate (3b): To a suspension of sodium hydride (4.25 g, 106.35 mmol, 60% in mineral oil) in toluene (100 ml) at 0 °C was added triethylphosphonoacetate (27.78 ml, 140.06 mmol) dropwise over 15 min. After stirring for 10 min, epoxide **1b** (5 g, 35.15 mmol) was added dropwise over 15 min, followed by heating at 80 °C for 8 h, then temperature increased to 110 °C and stirred for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (100 ml), and then washed with saturated aqueous ammonium chloride (100 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentration under reduced pressure. The crude material was purified by flash chromatography using petroleum ether/EtOAc (99:1) to give

cyclopropane **3b (**6.34 g, 85% yield) as a thick colorless oil. $[\alpha]_D^{25}$ -56.7 (*c* 1.0, $CHCl_3$); {lit.[2] $[\alpha]_D^{25}$ +56.9 (*c* 0.96, $CHCl_3$) for ***ent*-3b**}; IR (neat, cm^{-1}): ν_{max} 2933, 2855, 1730; ^1H NMR (400 MHz, $CDCl_3$): δ 0.31-0.36 (2H, m), 0.53-0.66 (1H, m), 0.76-0.8 (1H, m), 0.89 (3H, t, *J* 6.1 Hz,), 1.21-1.39 (15H, m), 4.10 (2H, q, *J* 7.2, 14.3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 13.9, 14.1, 18.7, 22.8, 29.3, 29.4, 29.5, 29.6, 31.9, 33.8, 60.6, 179.9.

3-((1*R*,2*R*)-2-Heptylcyclopropyl)propanoic acid (12): To the ester **11** (400 mg, 1.66 mmol) dissolved in MeOH (10 mL) and H_2O (6.67 mL) was added $LiOH.H_2O$ (208 mg, 4.98 mmol) and stirred at 0 °C to room temperature for 5 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified with (upto pH 5) with 1 M HCl and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na_2SO_4, concentrated and the crude product was purified by column chromatography eluting with petroleum ether/EtOAc (9:1) to give **12** (371 mg, 82% yield) as a pale yellow color syrupy liquid. $[\alpha]_D^{25}$ -13.99 (*c* 1.0, $CHCl_3$); {lit.[19d] $[\alpha]_D^{25}$ +13.5 (*c* 1, $CHCl_3$) for ***ent*-12**}; IR (neat, cm^{-1}): ν_{max} 3420, 2855, 1711, 1458, 1216, 759, 668. ^1H NMR (400 MHz, $CDCl_3$): δ 0.32-0.35 (2H, m), 0.54-0.59 (1H, m), 0.78-0.82 (1H, m), 0.89 (3H, t, *J* 6.1 Hz), 1.27-1.39 (12H, m), 1.53-1.68 (2H, m), 2.26-2.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 13.9, 14.1, 18.7, 22.8, 29.3, 29.6, 31.9, 33.8, 38.9, 179.9. MS (ESI): m/z 235.33 $(M+Na)^+$. Elemental analysis (%) calc. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39 %; Found**:** C, 73.70; H, 11.44%.

NMR Spectral data of 3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylpropanamide (13):

^1H NMR (400 MHz, $CDCl_3$): δ 0.13-0.18 (2H, m), 0.36-0.39 (2H, m), 0.78-0.82 (1H, m), 0.87 (3H, t, *J* 6.9 Hz), 0.9-1.40 (12H, m), 1.47-1.54 (2H, m), 2.18 (2H, t, J 7.6), 2.81 (2H, t, J 7.0), 3.51 (2H, q, J 7.0), 5.41 (1H, s, NH), 7.17-7.25 (3H, m, Ph), 7.27-7.28 (2H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 14.1, 18.2, 18.9, 22.7, 29.3, 29.5, 29.6, 30.3, 31.9, 34.1, 35.7, 36.9, 40.5, 126.5, 126.6, 128.7, 138.9, 172.9.

(2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate (18): To a mixture of triol **17** (4.00 g, 23.66 mmol), in dry CH_2Cl_2 (40.0 mL) was added dibutyltin oxide (0.292 mg, 0.2 mol %) followed by the addition of *p*-toluenesulfonyl chloride (4.94 g, 26.0 mmol) and Et_3N (3.62 mL, 26.0 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction (6 h) the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 100 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether:EtOAc (7:3) as eluent afforded monotosyl compound **18** (6.8 g, 89% yield) as a viscous liquid. $[\alpha]_D^{25}$ +15.4 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3503, 1729, 1493, 1359, 1189, 1175, 1096, 973, 758, 665; ^1H NMR (200 MHz, $CDCl_3$): δ 2.37 (3H, s), 2.83 (2H, brs), 3.77-3.82 (2H, m), 3.91-3.98 (1H, m), 4.55 (1H, d, *J* 6.1 Hz), 7.19-7.27 (7H, m), 7.67 (2H, d, *J* 8.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 70.4, 73.4, 73.5, 126.5, 127.8, 128.1, 128.5, 129.8, 132.2, 139.7, 145; Elemental analysis (%) calc. for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63; S, 9.95%; Found: C, 59.75; H, 5.49; S, 9.74%.

(*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (19): To a solution of compound **18** (1.0 g, 3.1 mmol) in methanol (10 mL) at 0 °C was added solid K_2CO_3 (0.857g, 6.2 mmol) in one portion and continued the stirring at 0 °C for 15 min. After consumption of starting material (15 min), solvent was evaporated under reduced pressure. Residue was diluted with water (5 mL), extracted with ethyl acetate (2 x 15 mL). Organic layer was washed with water, brine, dried over Na_2SO_4. Solvent was evaporated under reduced pressure to give crude epoxide, which was further purified by column chromatography using petroleum ether:EtOAc (8:2) as eluent to afford epoxide **19** (0.367 g, 79% yield) as a viscous liquid. $[\alpha]_D^{25}$ +7.89 (*c* 2.74, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3460, 3019, 2896, 1612, 1513, 1454, 1215, 1043, 755, 700, 668; ^1H NMR (200 MHz, $CDCl_3$): δ 2.71-2.79 (2H, m), 3.10-3.17 (1H, m), 4.36 (1H, d, *J* 5.7 Hz), 7.26-7.36 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.3, 56.0, 74.4, 126.2, 128.0, 128.4, 140; HRMS, (EI/DIP) for (M^+): calc. 150.06018, Found: 150.05492.

(1*R*,2*R*)-Ethyl 2-((*S*)-azido(phenyl)methyl)cyclopropanecarboxylate (15): To a solution of **20** (700 mg, 3.17 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonyl chloride (0.37 mL, 4.76 mmol), Et_3N (0.66 mL, 4.76) and DMAP (cat). After consumption of starting material (8 h), the reaction mixture was poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated to a yellow syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (20 mL) was added NaN_3 (824 mg, 12.88 mmol) and the reaction mixture stirred at 70 °C for 8 h. It was cooled and poured into water and extracted with Et_2O (4 x 20 mL). The organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel column using petroleum ether:EtOAc (9:1) as eluent gave **15 (**662 mg, 85% yield) as a pale yellow color liquid. IR (neat, cm^{-1}): ν_{max} 2924, 2892, 2097, 1726, 1615, 1463, 1372, 1181, 1074, 1029, 761; Elemental analysis (%) calc. for $C_{13}H_{15}N_3O_2$: C, 75.75; H, 12.71; N, 7.62%; Found: C, 75.87; H, 12.48; N, 7.91%

NMR Spectra: First diastereomer (Major, desired):

^1H NMR (500 MHz, $CDCl_3$): δ 0.89-0.94 (1H, m), 1.09-1.13(1H, m), 1.21 (3H, t, *J* 7.1), 1.64-1.68 (1H, m), 1.80-1.83 (1H, m), 4.13 (2H, q, *J* 7.0, 14.3 Hz), 4.28 (1H, d, *J* 6.6 Hz), 7.14-7.32 (5H, m). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 13.1, 14.2, 17.7, 25.9, 60.7, 66.3, 127.1, 128.6, 128.8, 138.2, 173.2.

Second diastereomer:

^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, t, *J* 7.2), 1.29-1.33(2H, m), 1.85-1.94 (1H, m), 4.02-4.10 (3H, m), 7.14-7.32 (5H, m); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 12.4, 14.2, 19.7, 26.5, 60.8, 67.3, 126.9, 128.6, 128.9, 138.2, 173.1.

Compound 15 was subjected to the ester hydrolysis to give the corresponding azido acid 21 following the method as described in the manuscript.

NMR Spectra of Compound 21:

Major diastereomer (desired):

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01-1.05 (1H, m), 1.19-1.23 (1H, m), 1.65-1.69 (1H, m), 1.82-1.85 (1H, m), 4.28 (1H, d, *J* 6.5 Hz), 7.33-7.43 (5H, m); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 13.9, 17.5, 26.9, 66.2, 126.9, 128.6, 128.9, 137.9, 179.6.

Second diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26-1.29 (2H, m), 1.37-1.40 (2H, m), 4.15 (1H, d, *J* 7.3 Hz), 7.33-7.43 (5H, m); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 13.1, 18.9, 27.6, 66.8, 126.9, 128.7, 128.9, 138.1, 179.5.

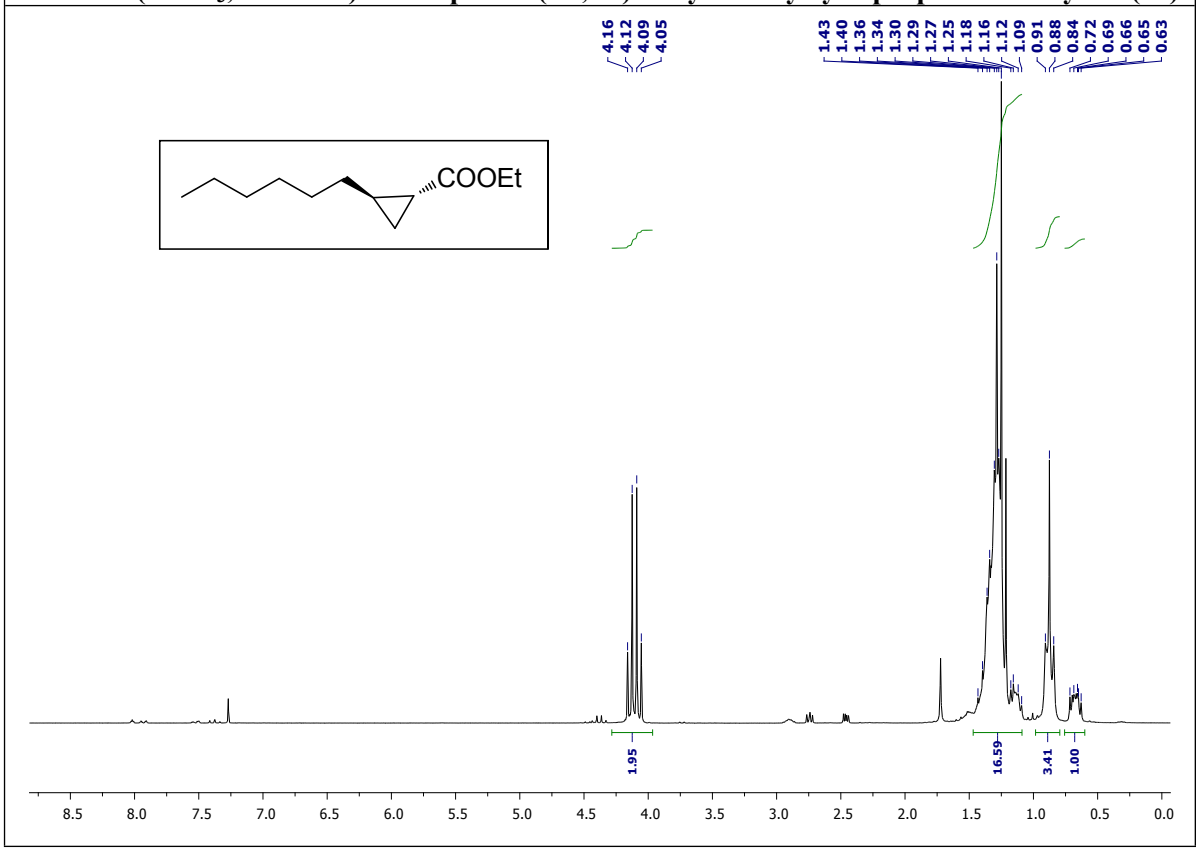
Please note that azido compound **15** was found to be a mixture of two diastereomers in the ratio (approx.) 6:4. The basic hydrolysis of the ester afforded the azido acid **21** as a mixture of diastereomers. Subsequent oxidation (**21** to **22**) followed by reduction of azido to amine led to the target compound CCG-II **14**. In the final step only, we were able to isolate the desired diastereomer of compound **14** by crystallization method. The physical and spectroscopic data of target CCG-II (**14**) were in full agreement with those reported.

References:

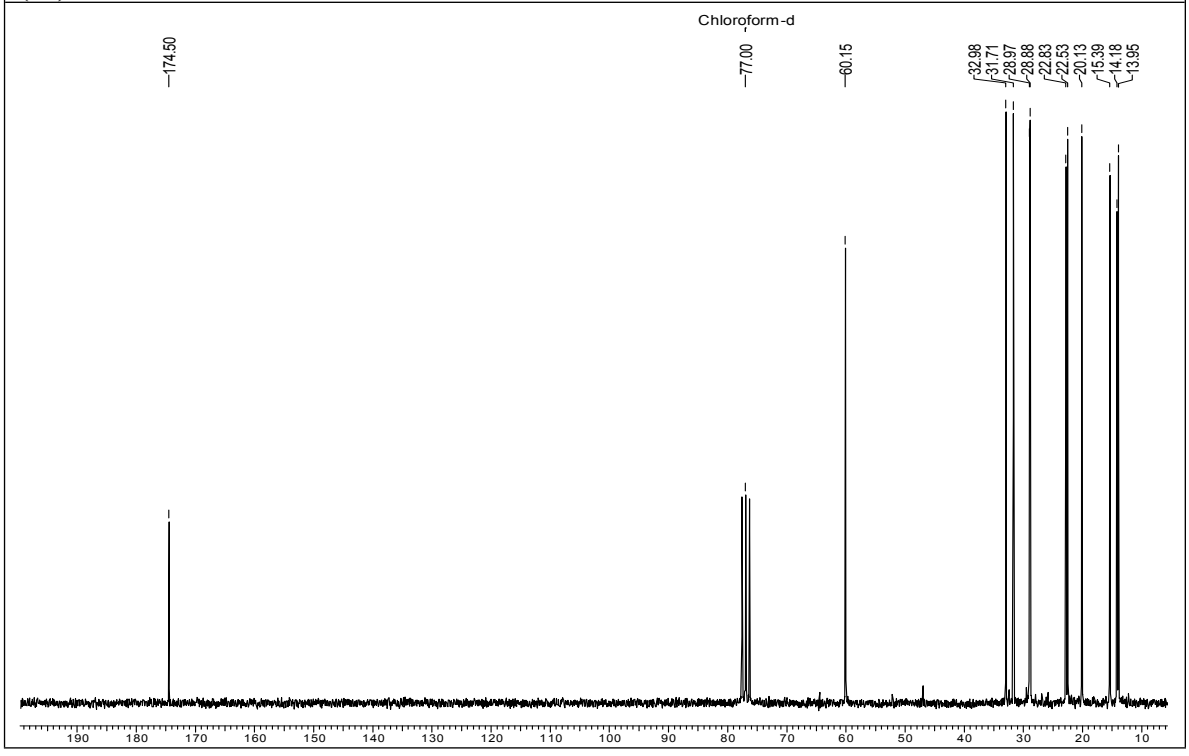
1. *Purification of Laboratory Chemicals* (Eds.: D. D. Perrin, W. L. F. Armarego), 2nd edition, Pergamon Press, Oxford, UK, **1988**.

2. T. Minuth, M. M. K. Boysen, *Synthesis* **2010**, 2799.

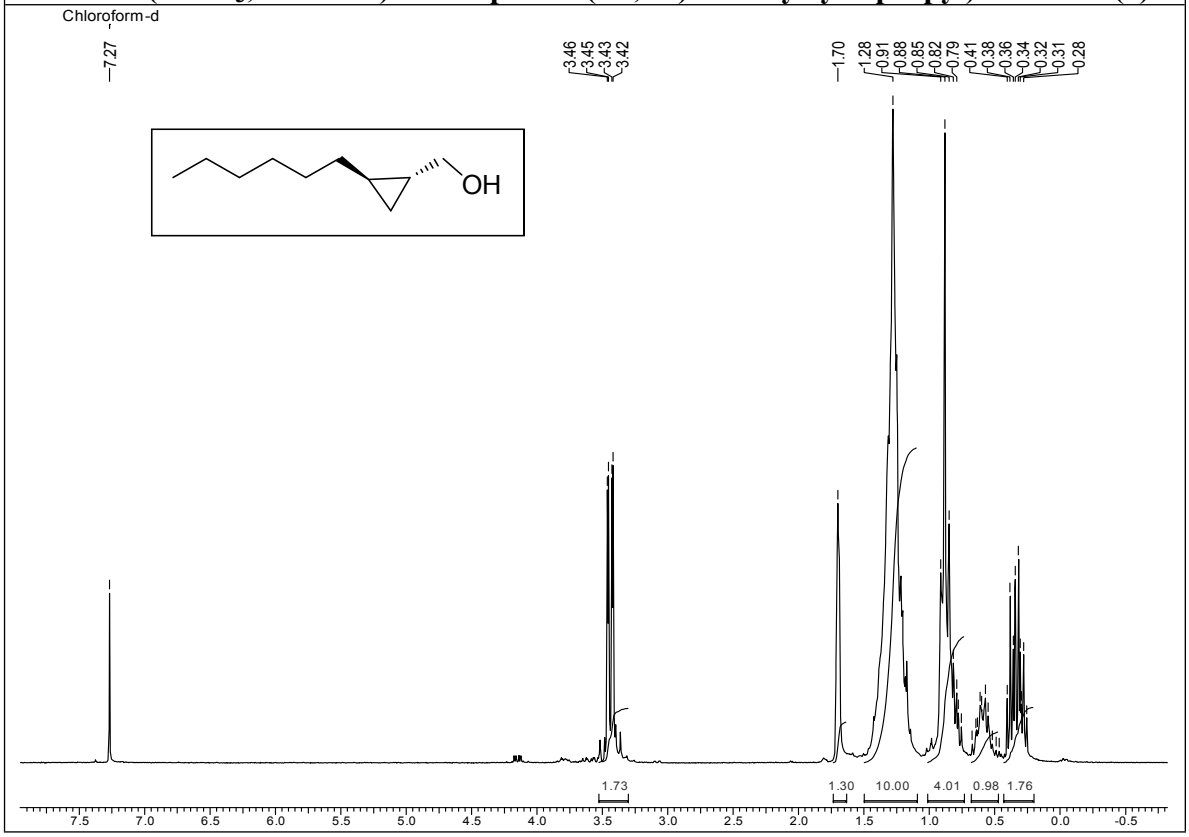
^{1}H NMR ($CDCl_3$, 400MHz) of compound (1*R*,2*R*)-Ethyl 2-hexylcyclopropanecarboxylate (3a)



^{13}C NMR ($CDCl_3$, 100MHz) of compound (1*R*,2*R*)-Ethyl 2-hexylcyclopropanecarboxylate (3a)



^{1}H NMR ($CDCl_3$, 400MHz) of compound (1*R*,2*R*)-2-Hexylcyclopropyl)methanol (7)



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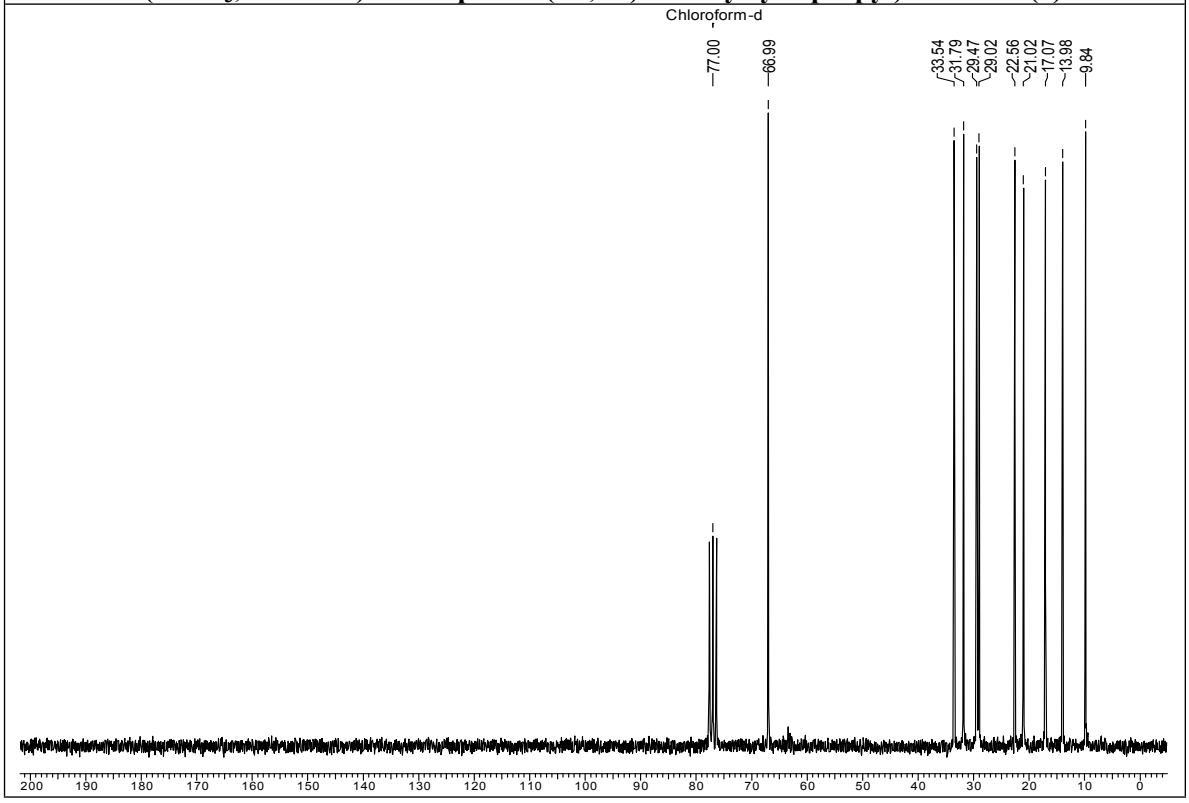
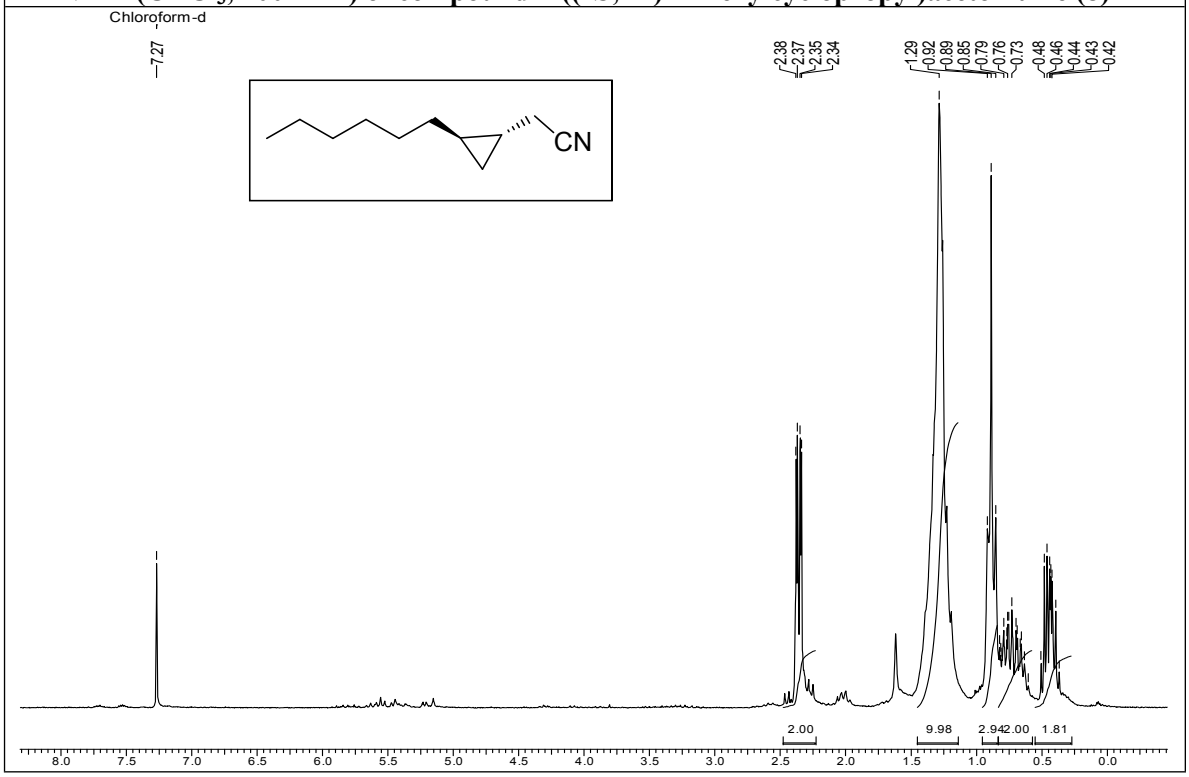
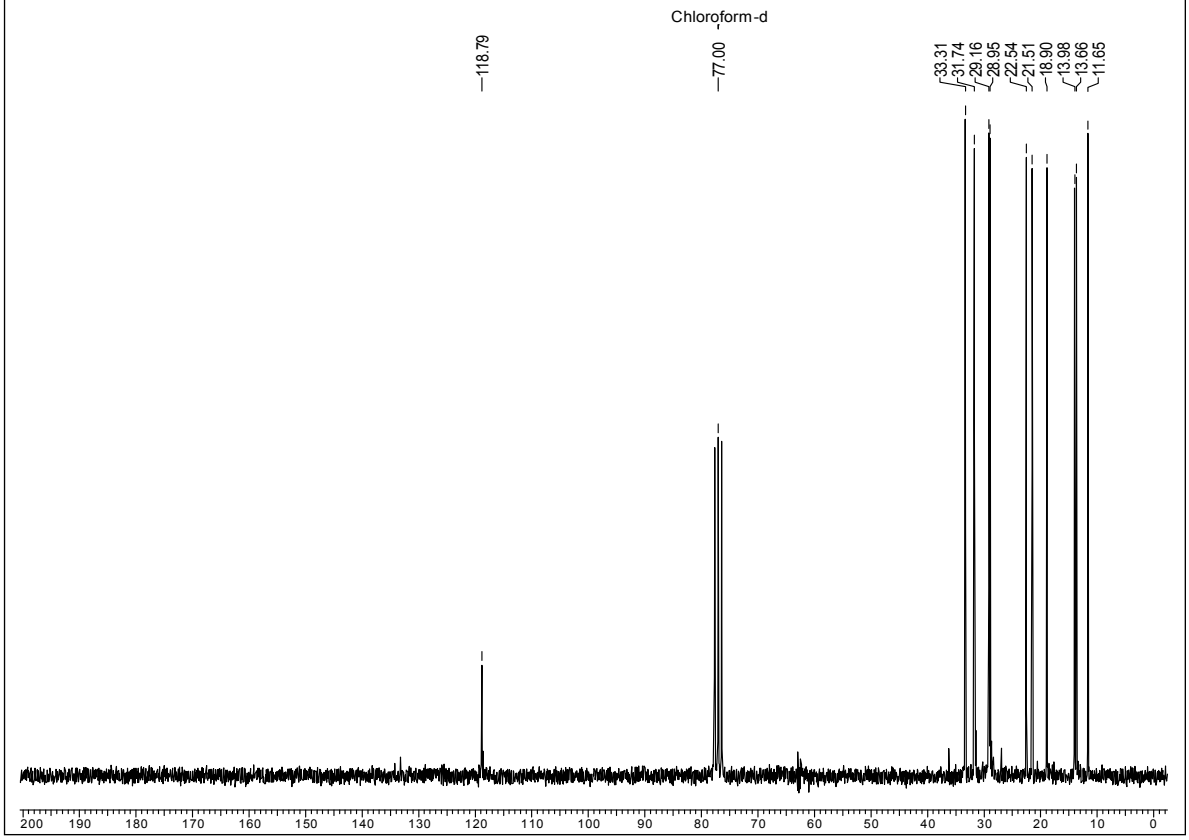


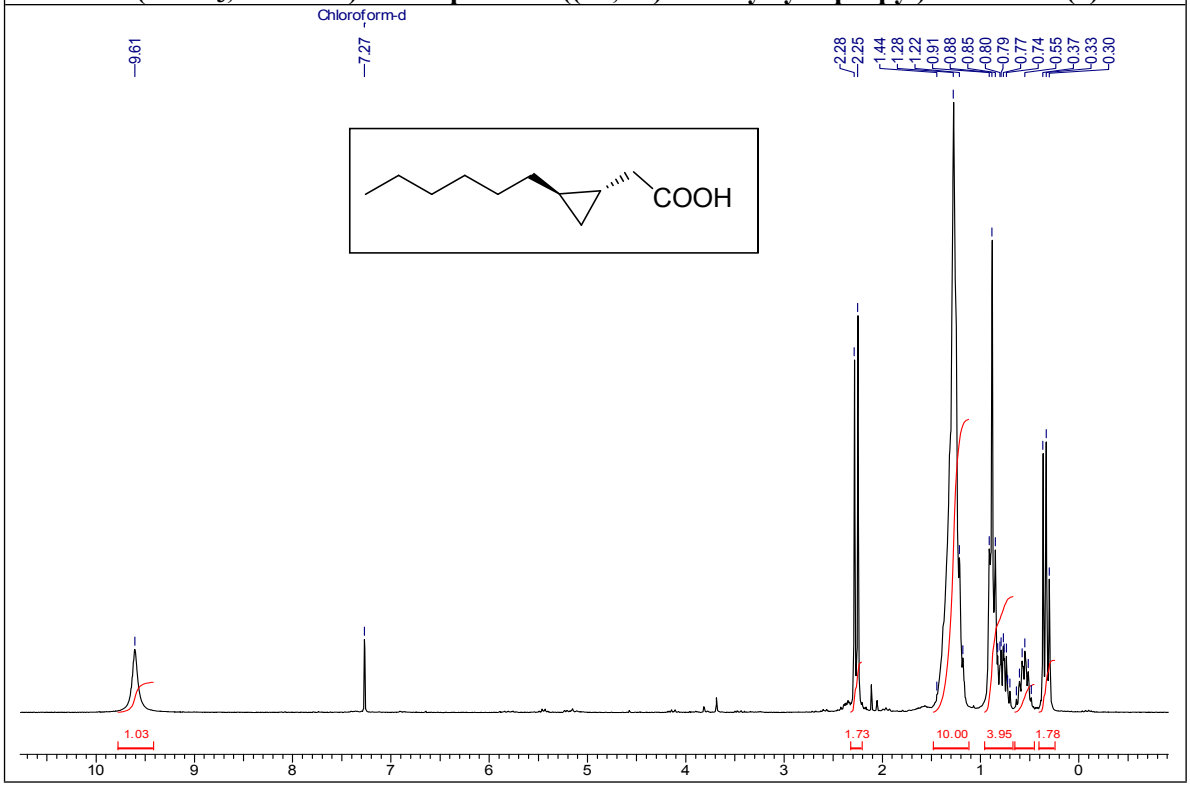
^{1}H NMR ($CDCl_3$, 200MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetonitrile (8)



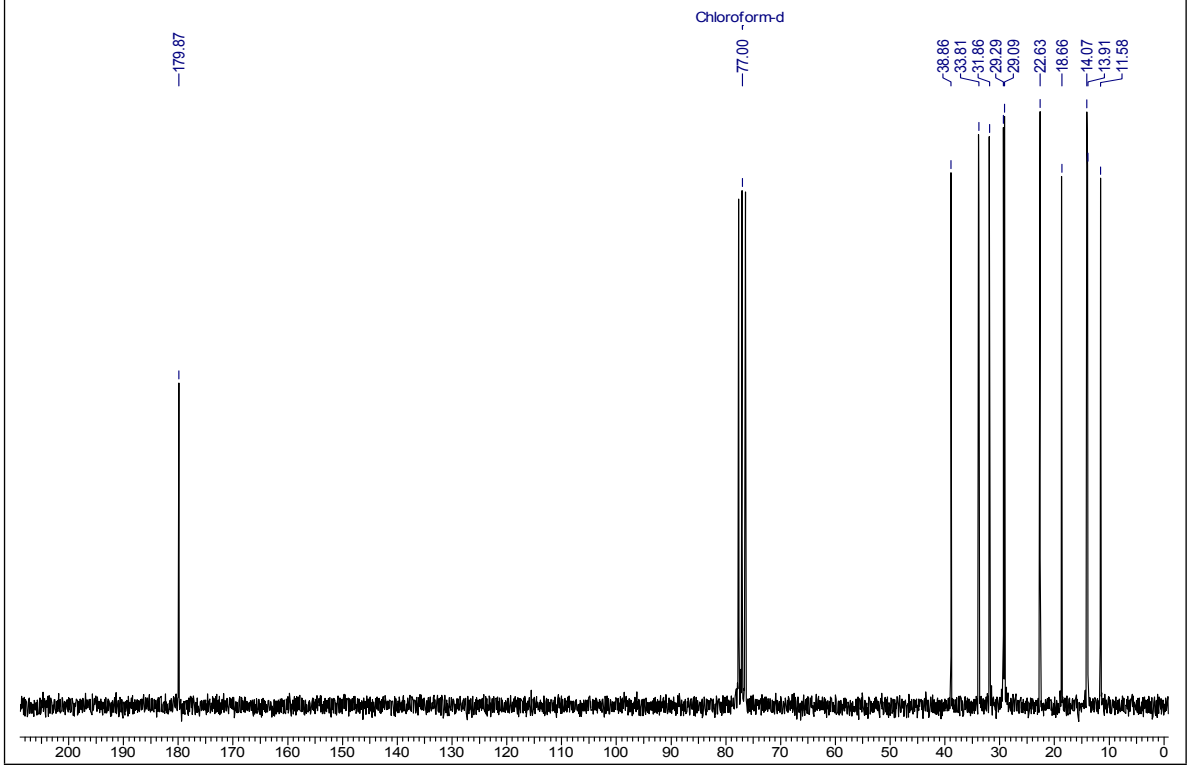
^{13}C NMR ($CDCl_3$, 50MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetonitrile (8)



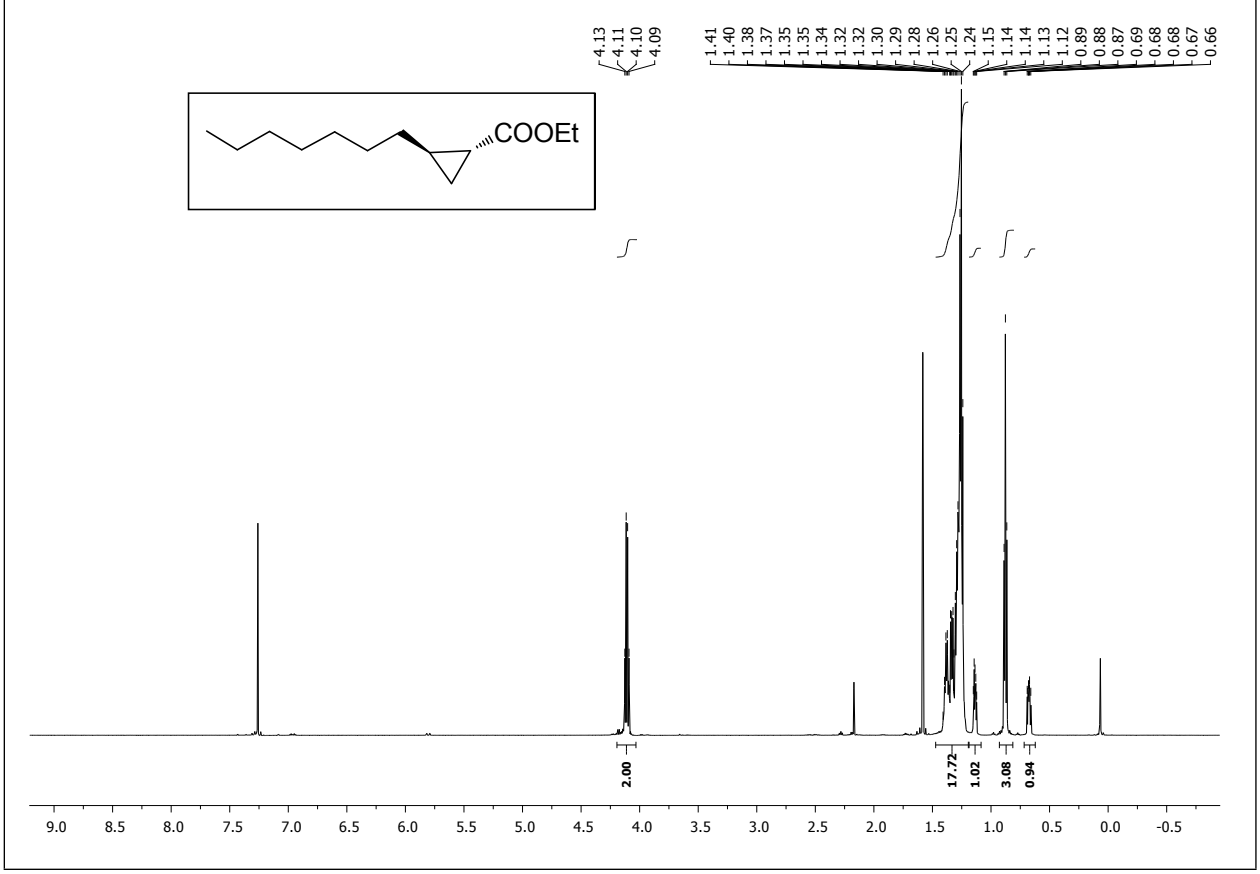
^{1}H NMR ($CDCl_3$, 400MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (9)



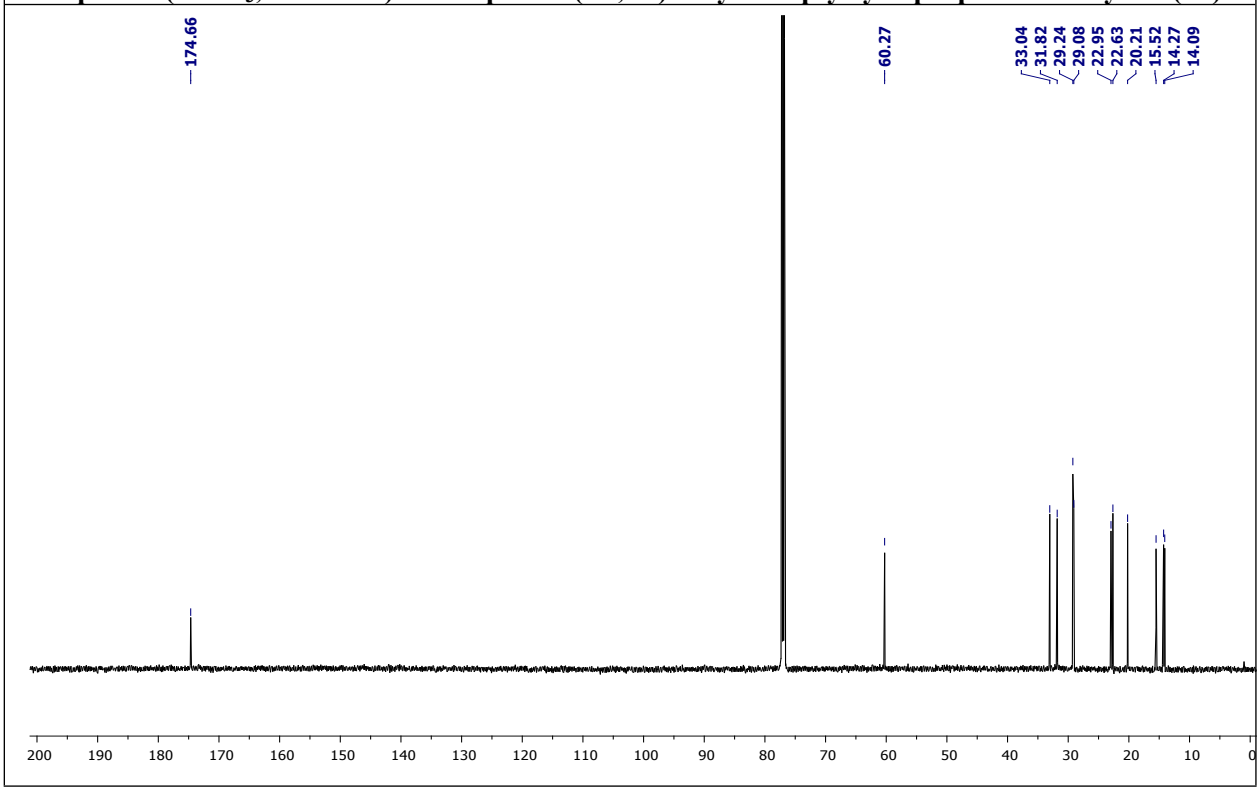
^{13}C NMR ($CDCl_3$, 100MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (9)



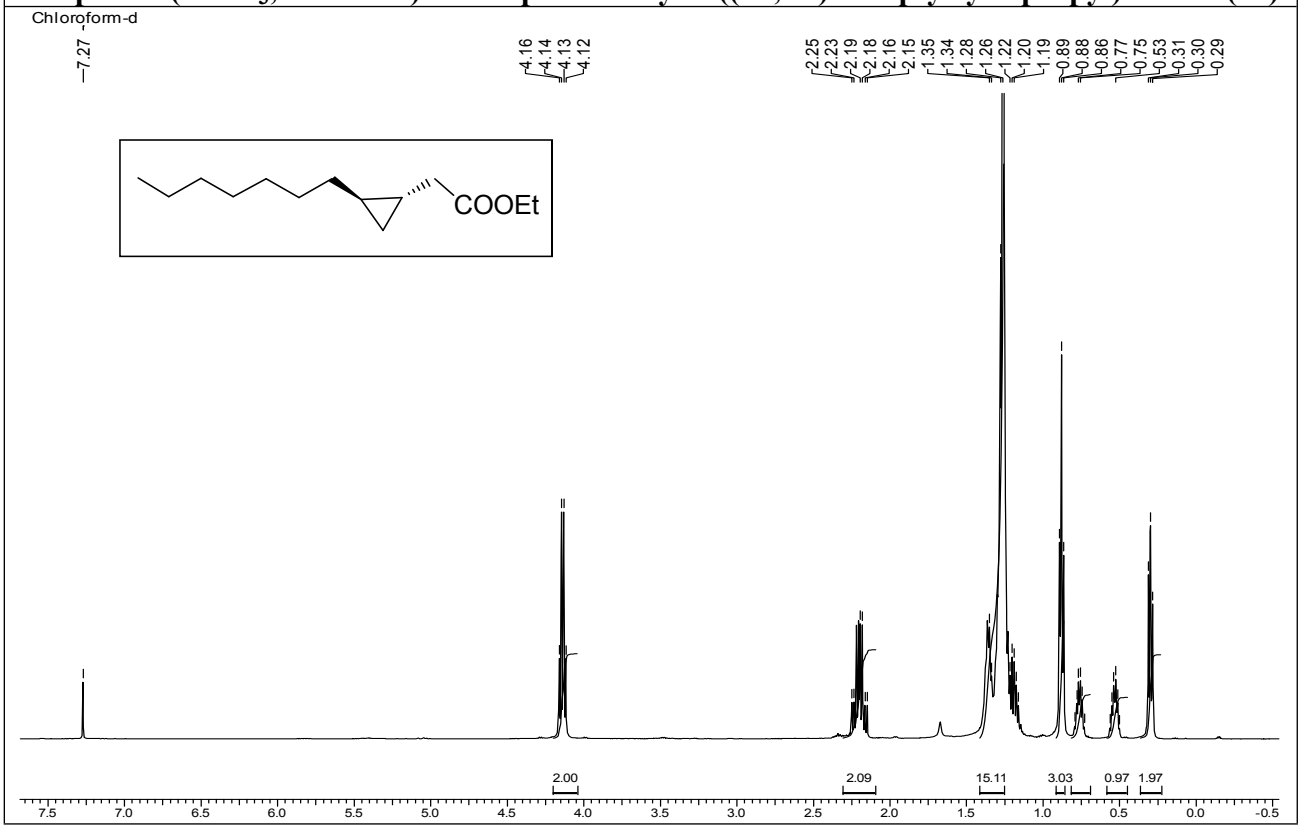
^{1}H spectra ($CDCl_3$, 500 MHz) of compound (1*R*,2*R*)-ethyl 2-heptylcyclopropanecarboxylate (3b)



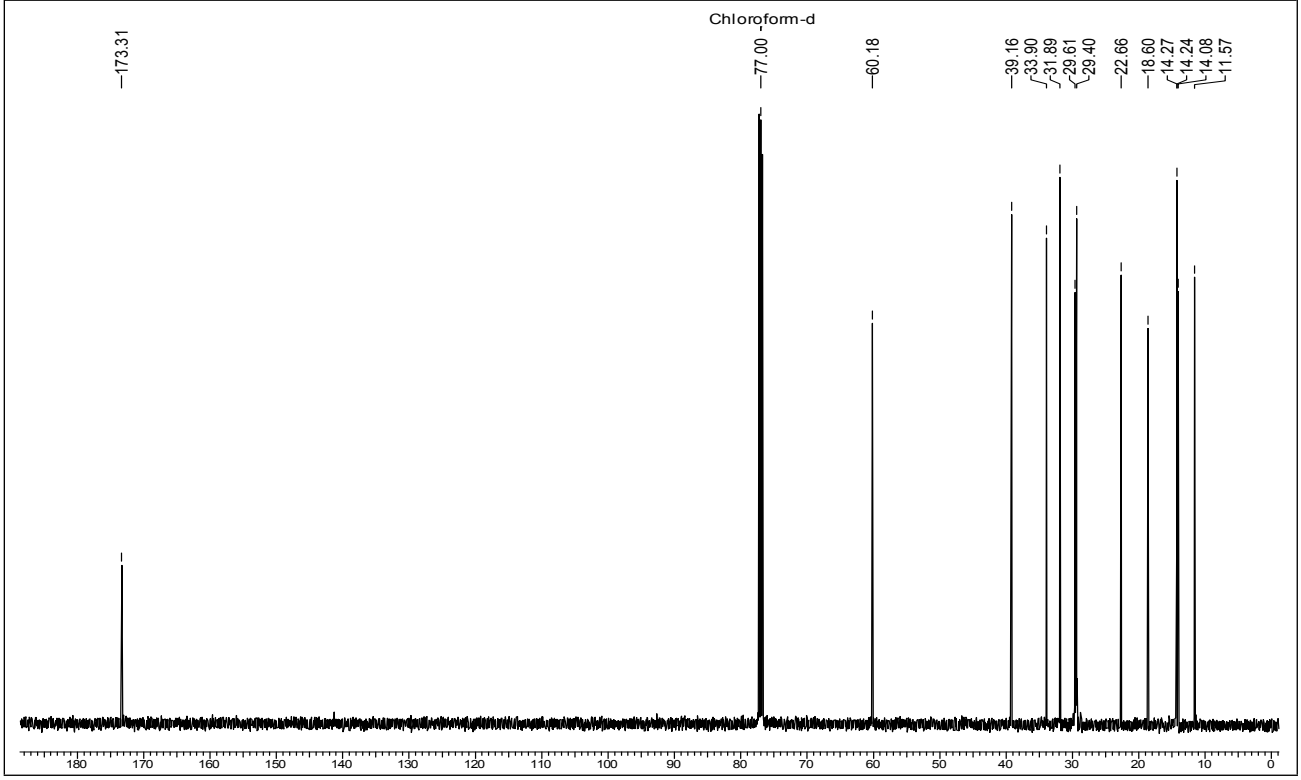
^{13}C spectra ($CDCl_3$, 100 MHz) of compound (1*R*,2*R*)-ethyl 2-heptylcyclopropanecarboxylate (3b)



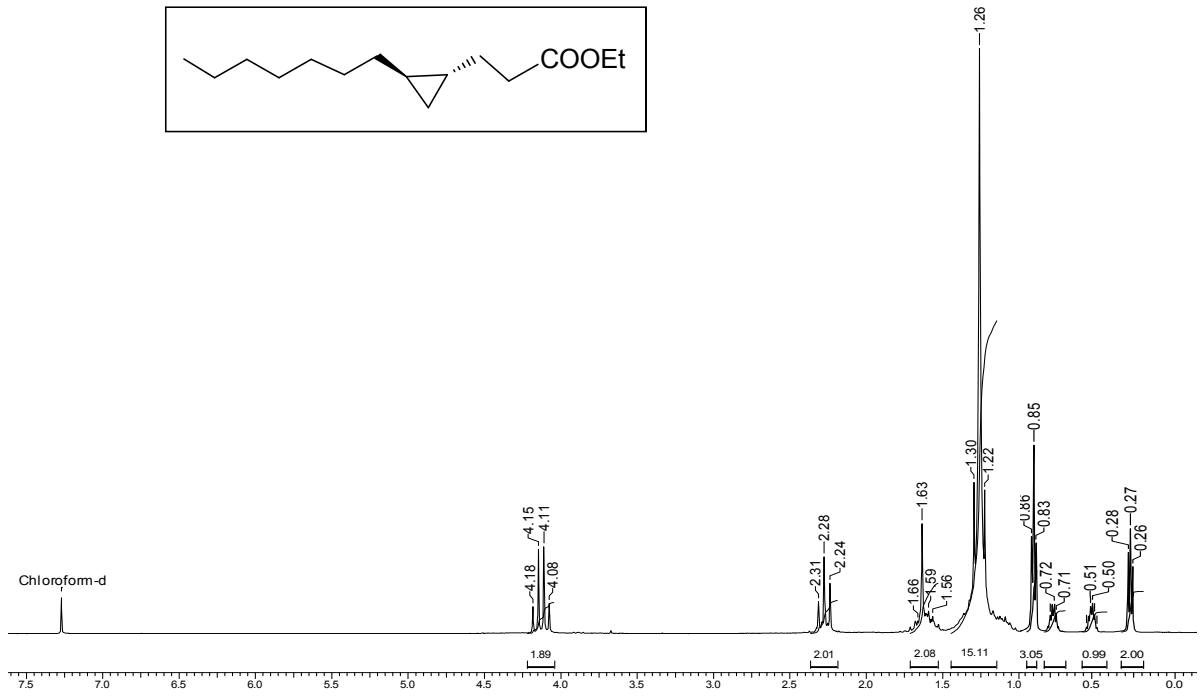
^{1}H spectra ($CDCl_3$, 500 MHz) of compound ethyl 2-((1*S*,2*R*)-2-heptylcyclopropyl)acetate (10)



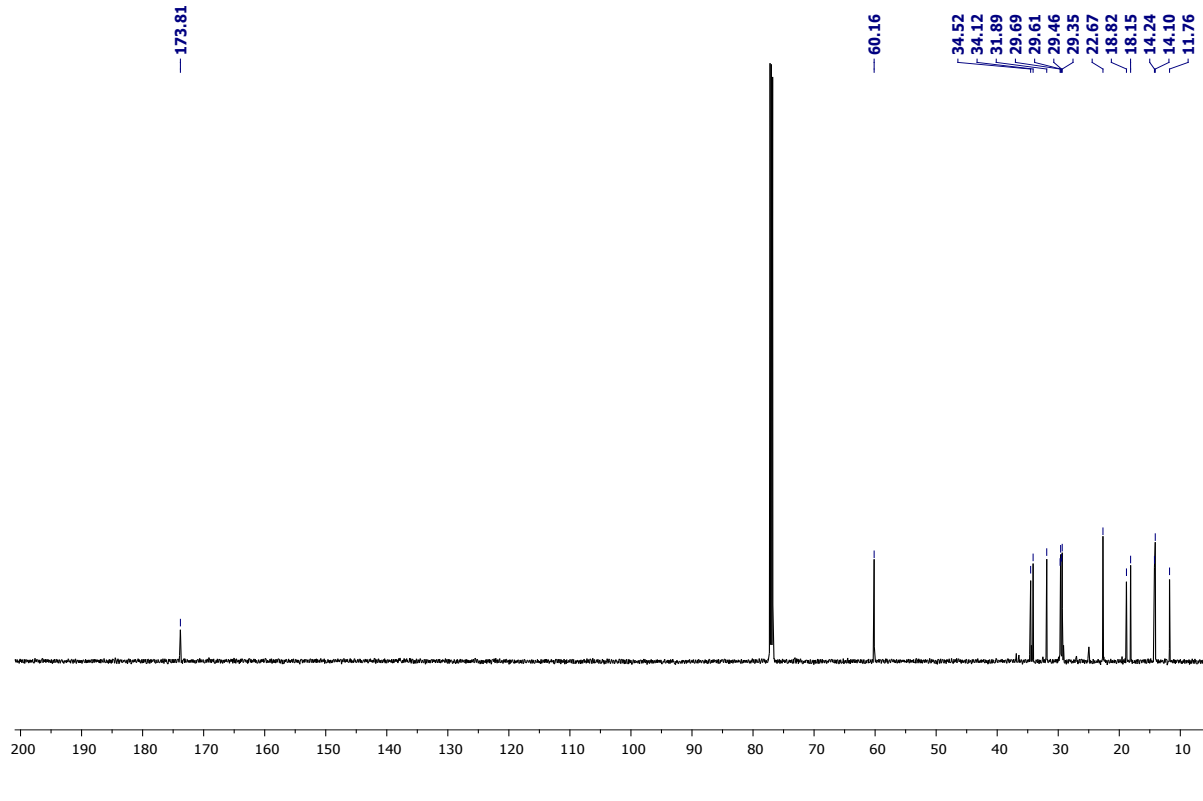
^{13}C spectra ($CDCl_3$, 125 MHz) of compound ethyl 2-((1*S*,2*R*)-2-heptylcyclopropyl)acetate



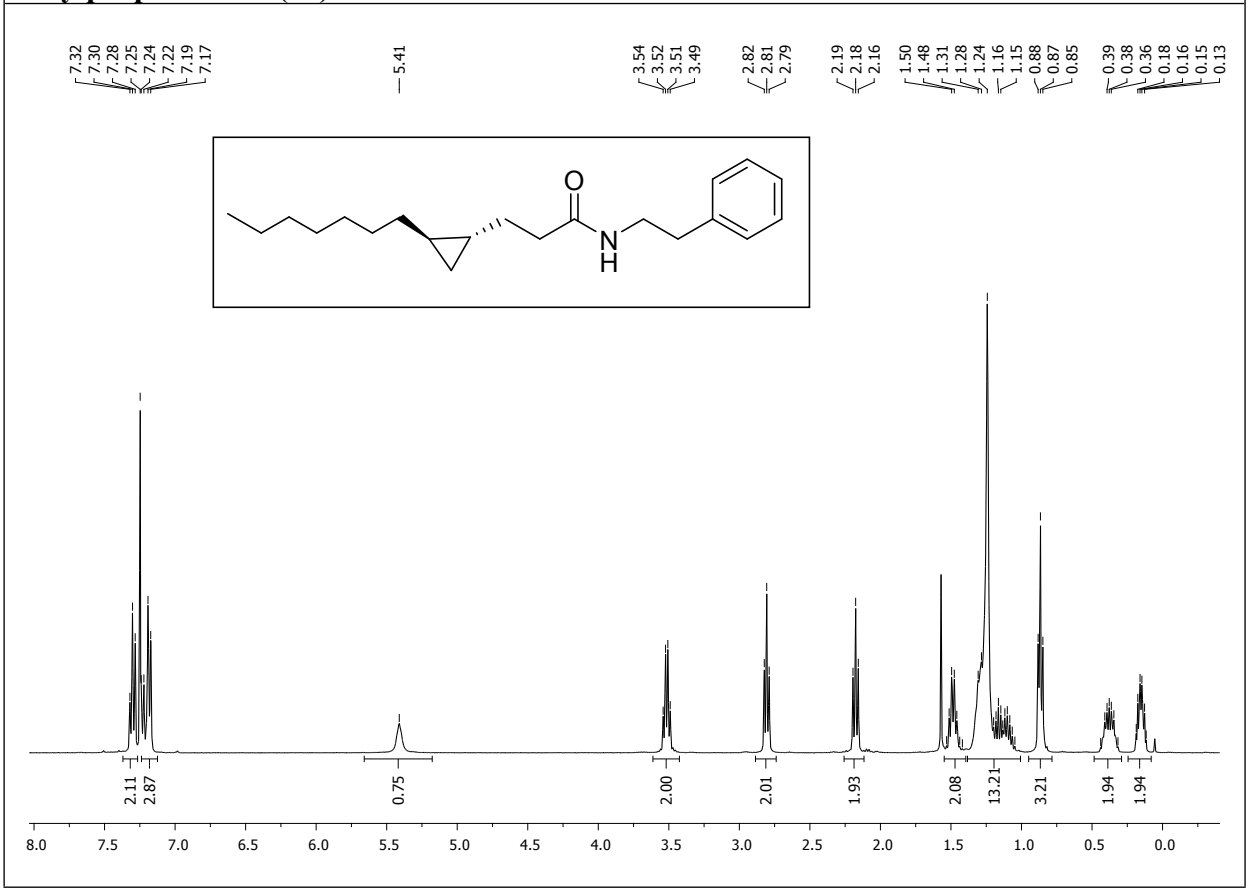
^{1}H spectra ($CDCl_3$, 400 MHz) of compound ethyl 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoate (11)



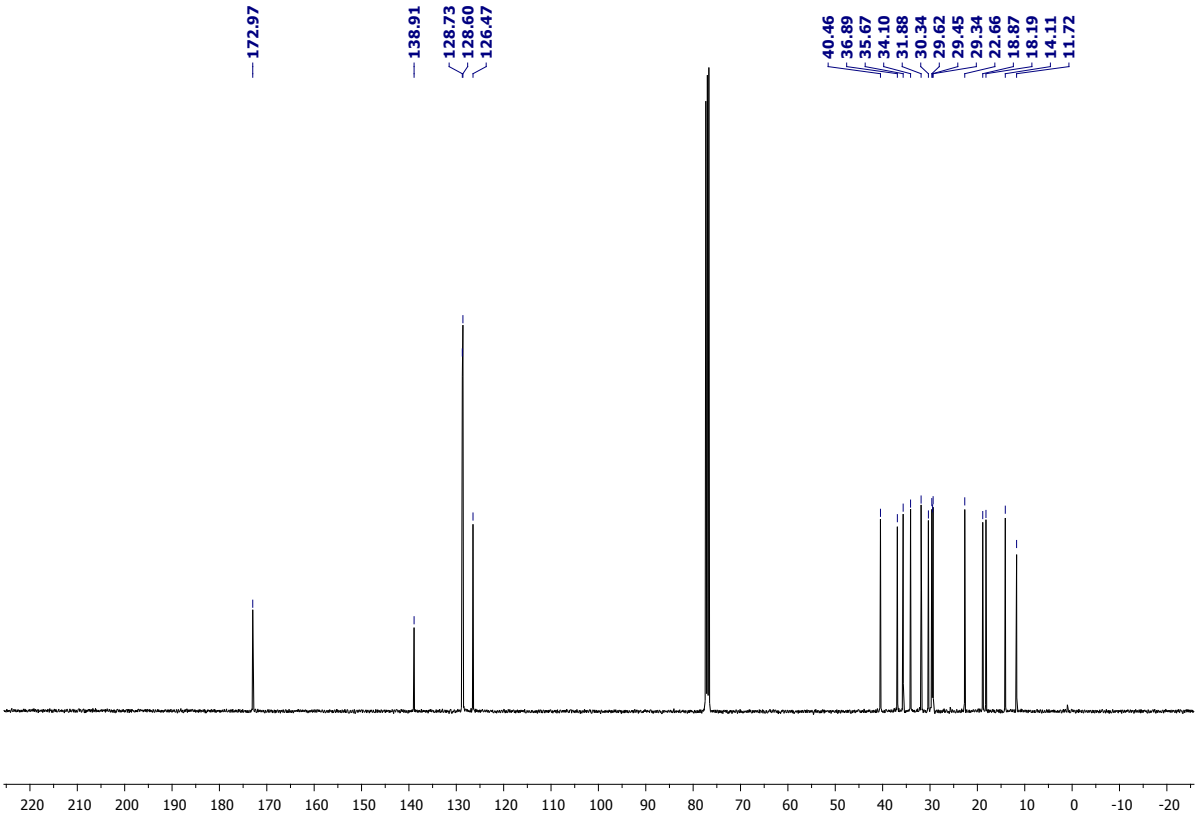
^{13}C spectra ($CDCl_3$, 100 MHz) of compound ethyl 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoate (11)



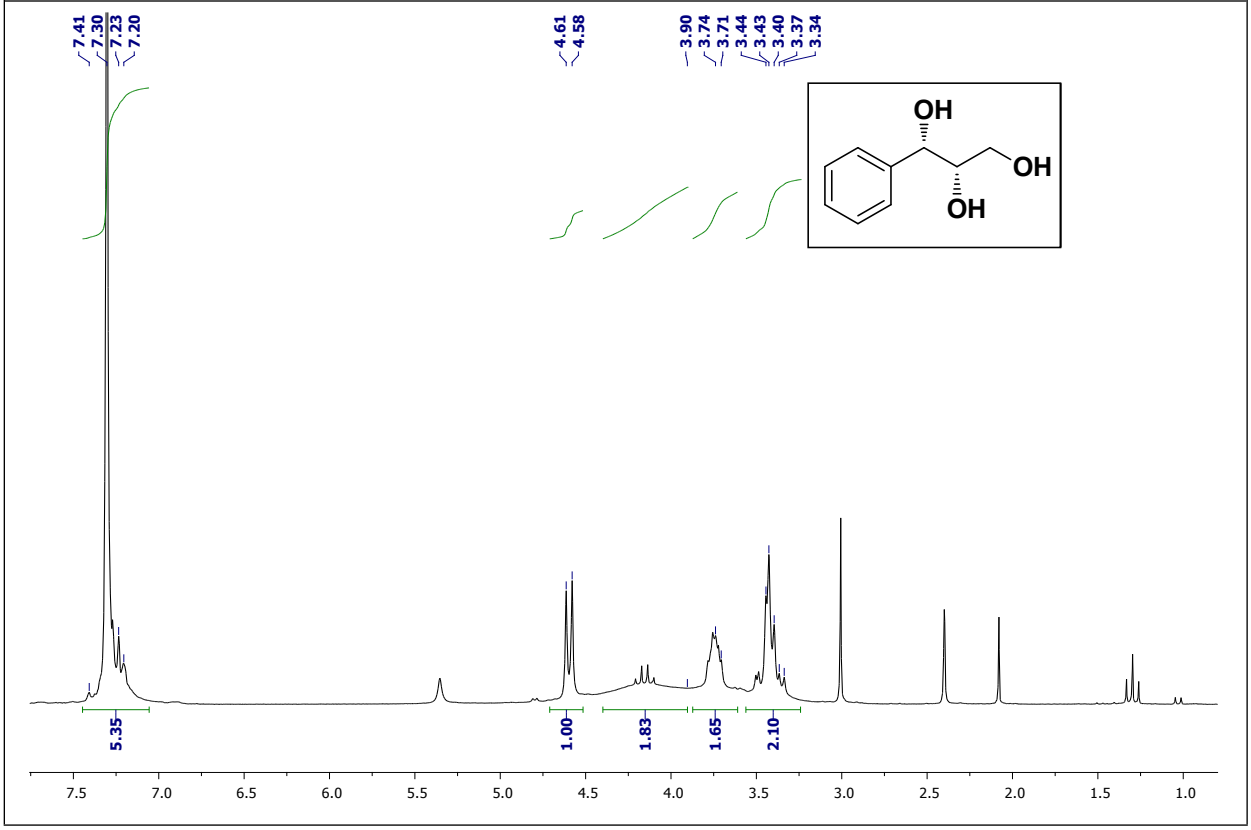
^{1}H spectra ($CDCl_3$, 400 MHz) of compound 3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylpropanamide (13)



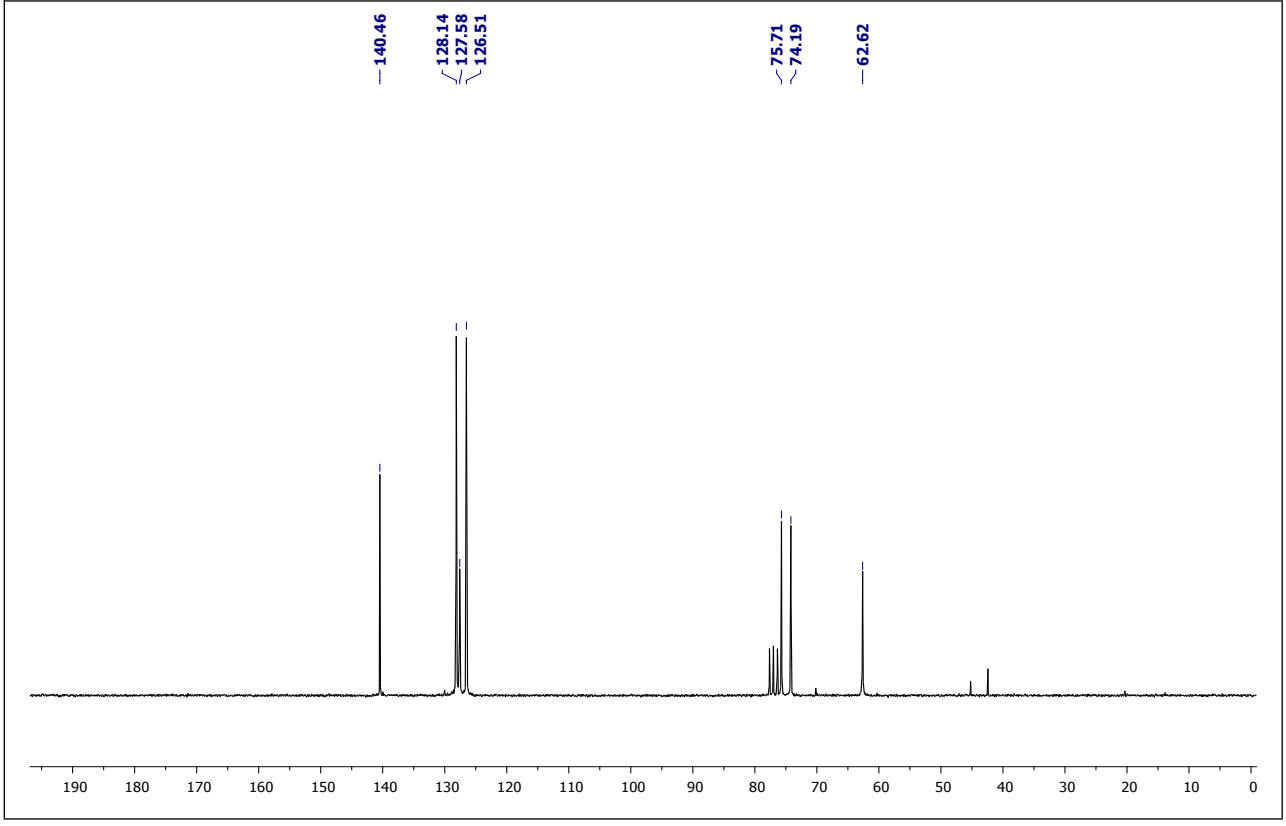
^{13}C spectra ($CDCl_3$, 100 MHz) of compound 3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylpropanamide (13)



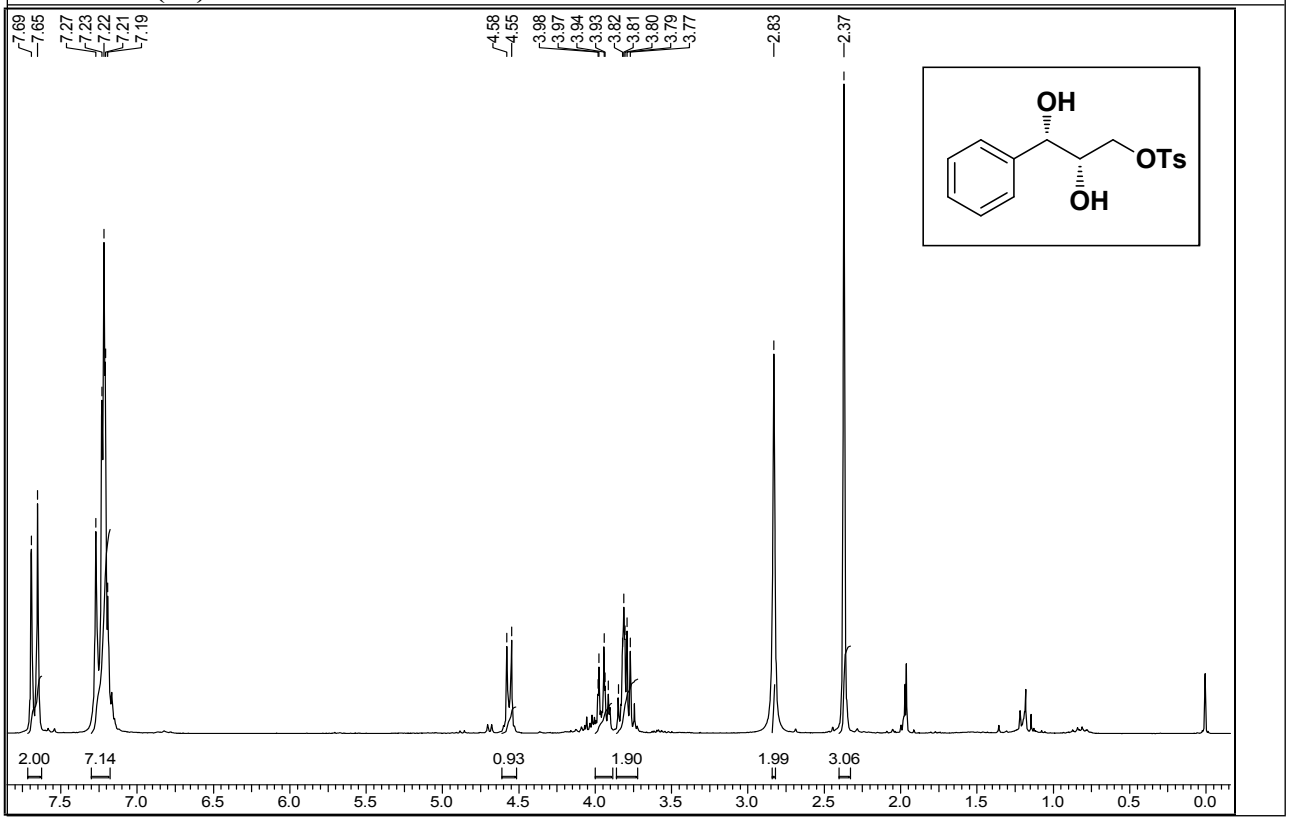
^{1}H NMR ($CDCl_3$, 400MHz) of (1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (17)



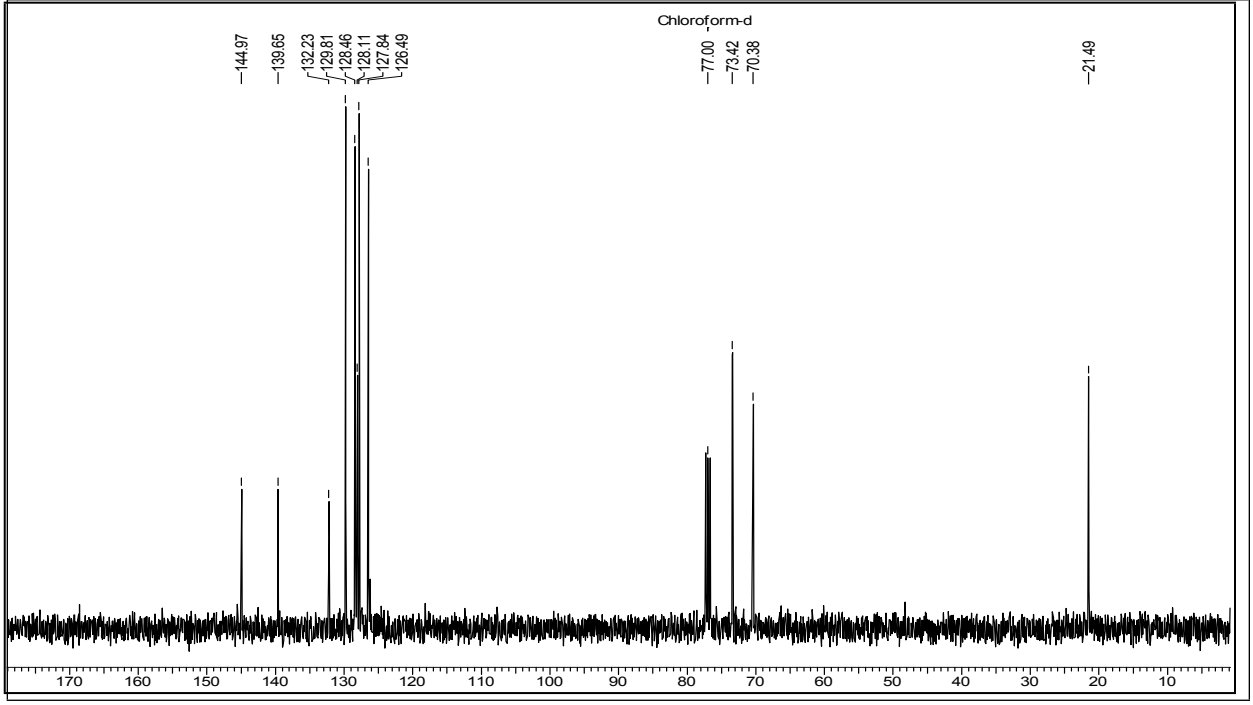
^{13}C NMR ($CDCl_3$, 100MHz) of (1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (17)



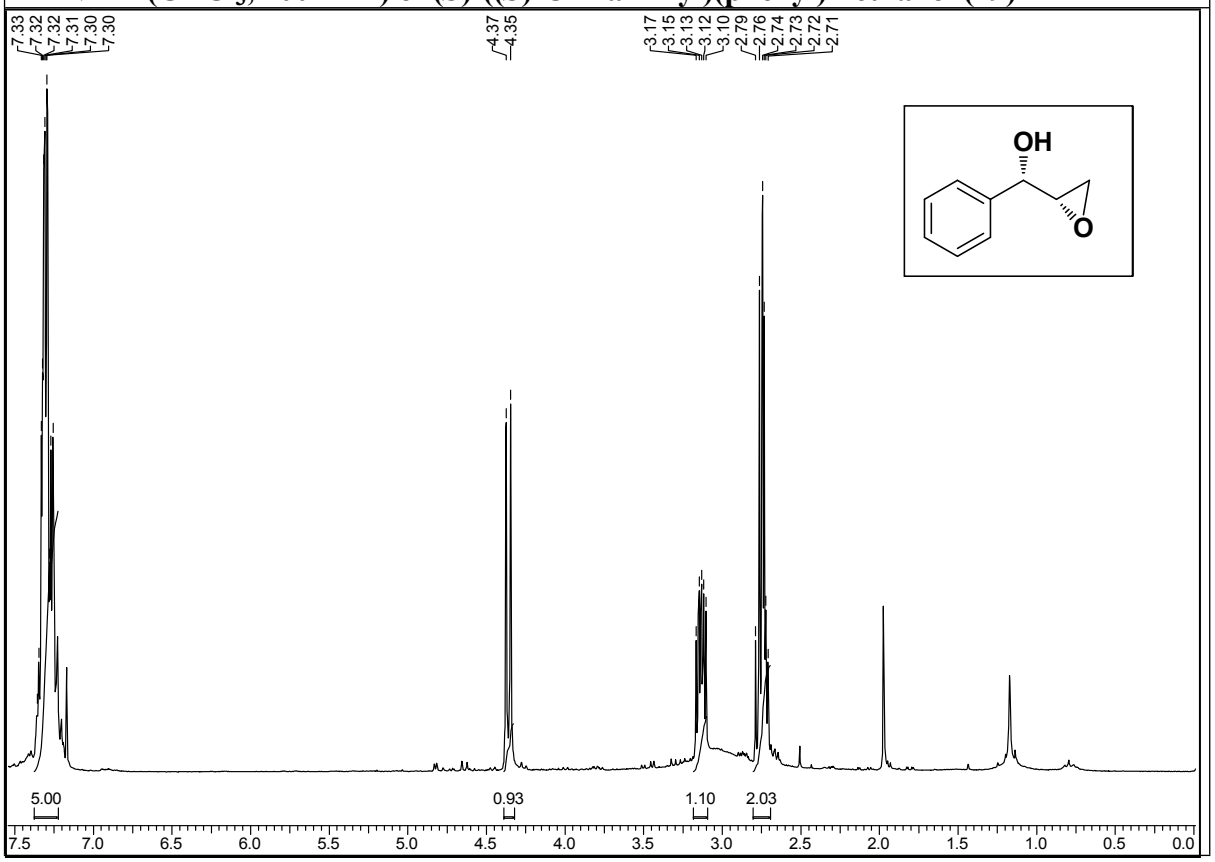
^{1}H NMR ($CDCl_3$, 200MHz) of (2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl-4-methylbenzen-sulfonate (18)



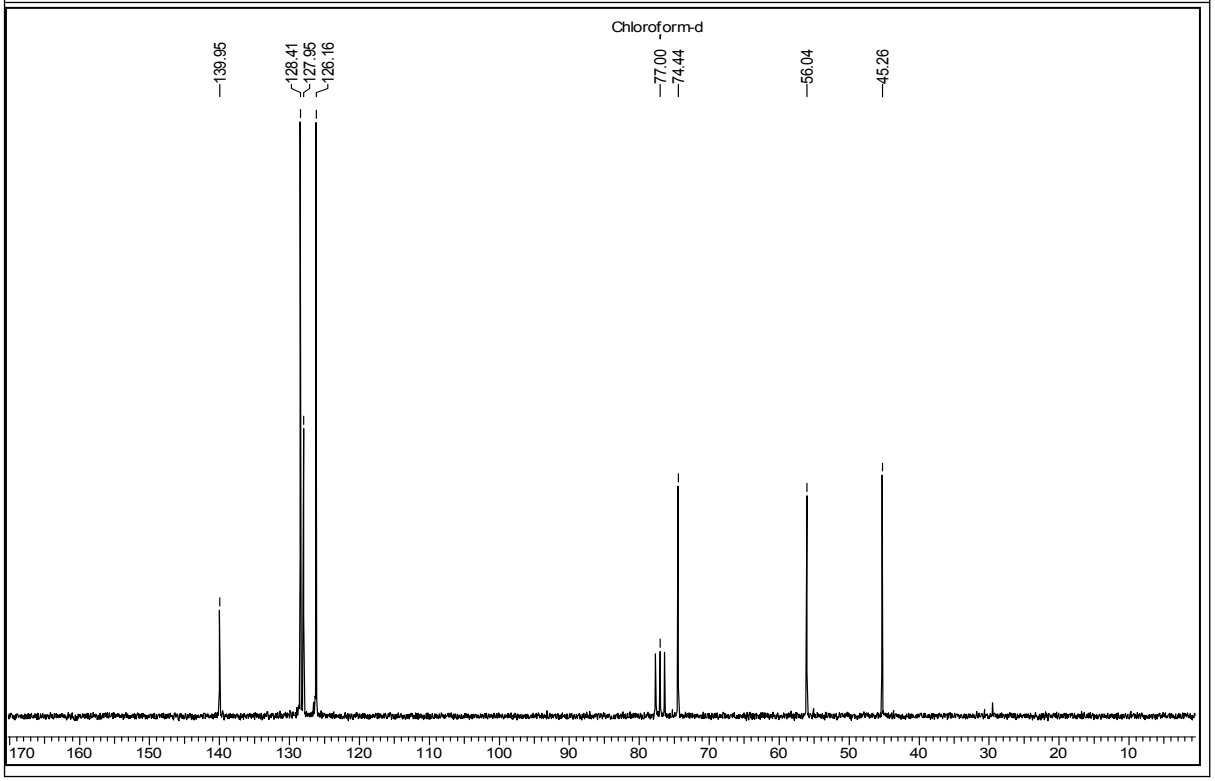
^{13}C NMR ($CDCl_3$, 50MHz) of (2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl 4-methylben-zenesulfonate (18)



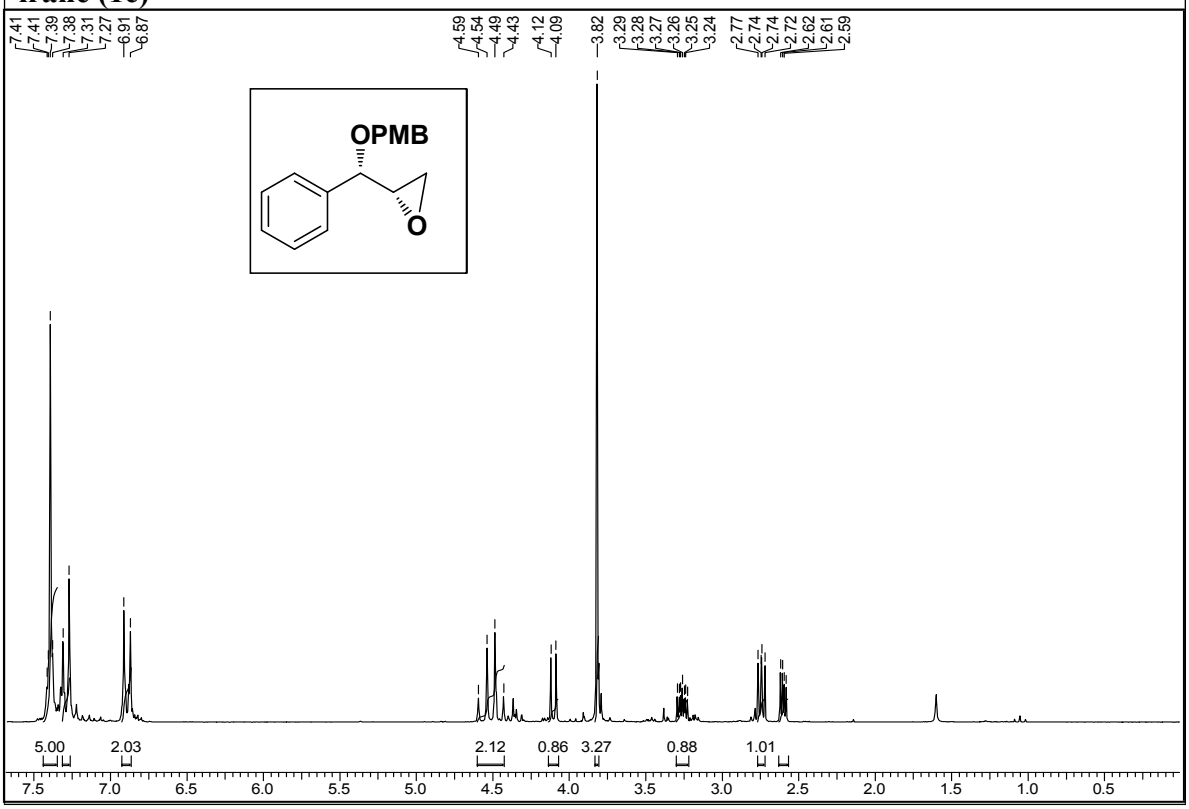
^{1}H NMR ($CDCl_3$, 200MHz) of (*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (19)



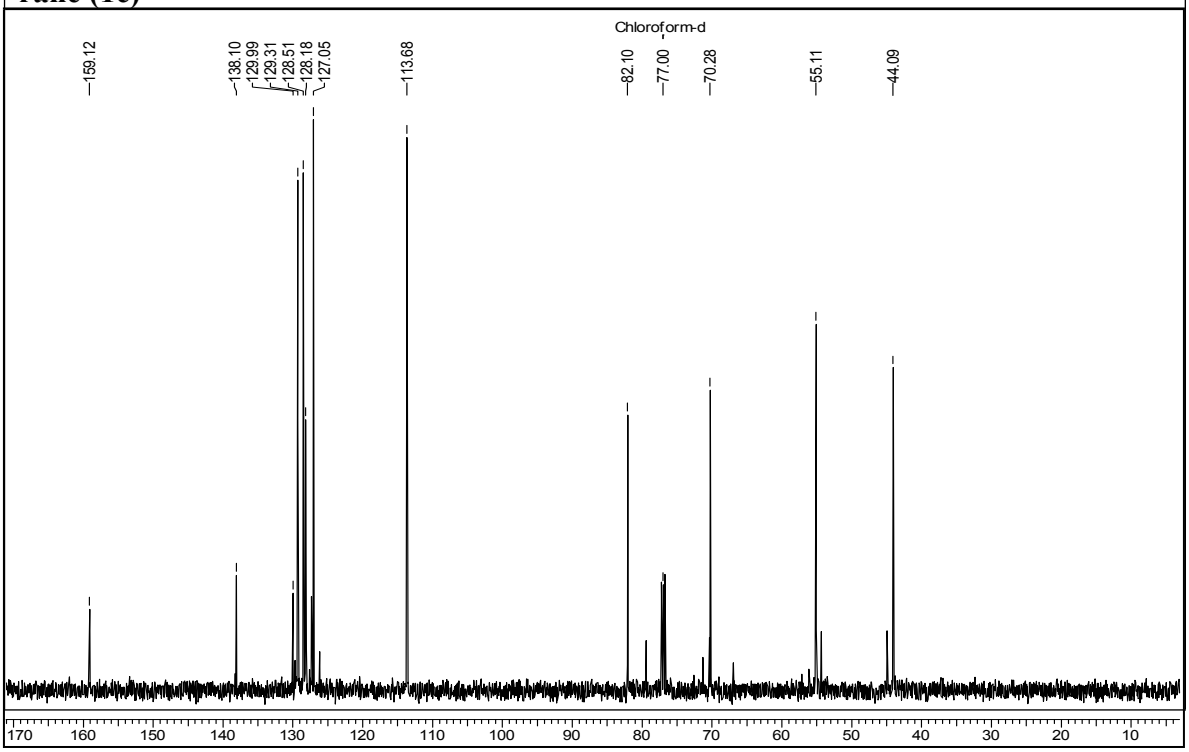
^{13}C NMR ($CDCl_3$, 50MHz) of (*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (19)



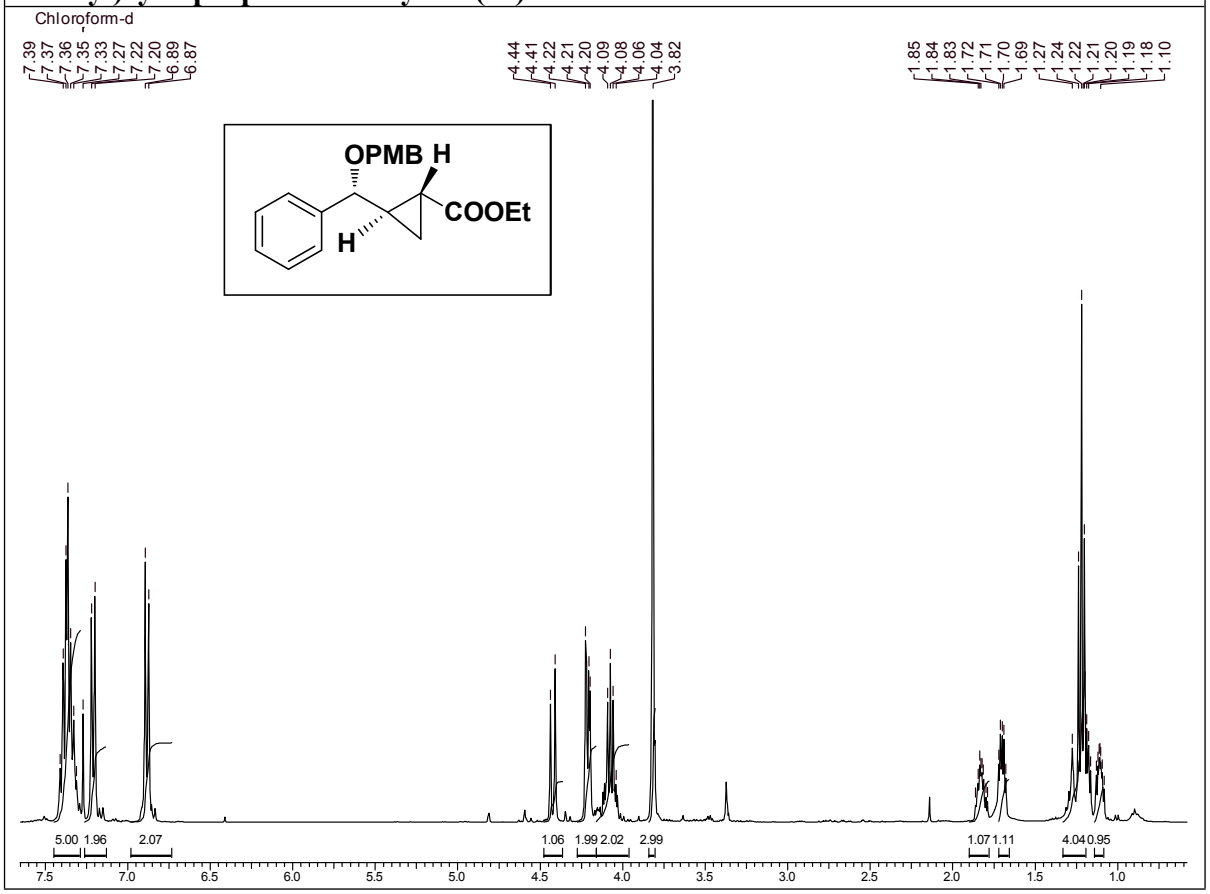
^{1}H NMR ($CDCl_3$, 400MHz) of (*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (1c)



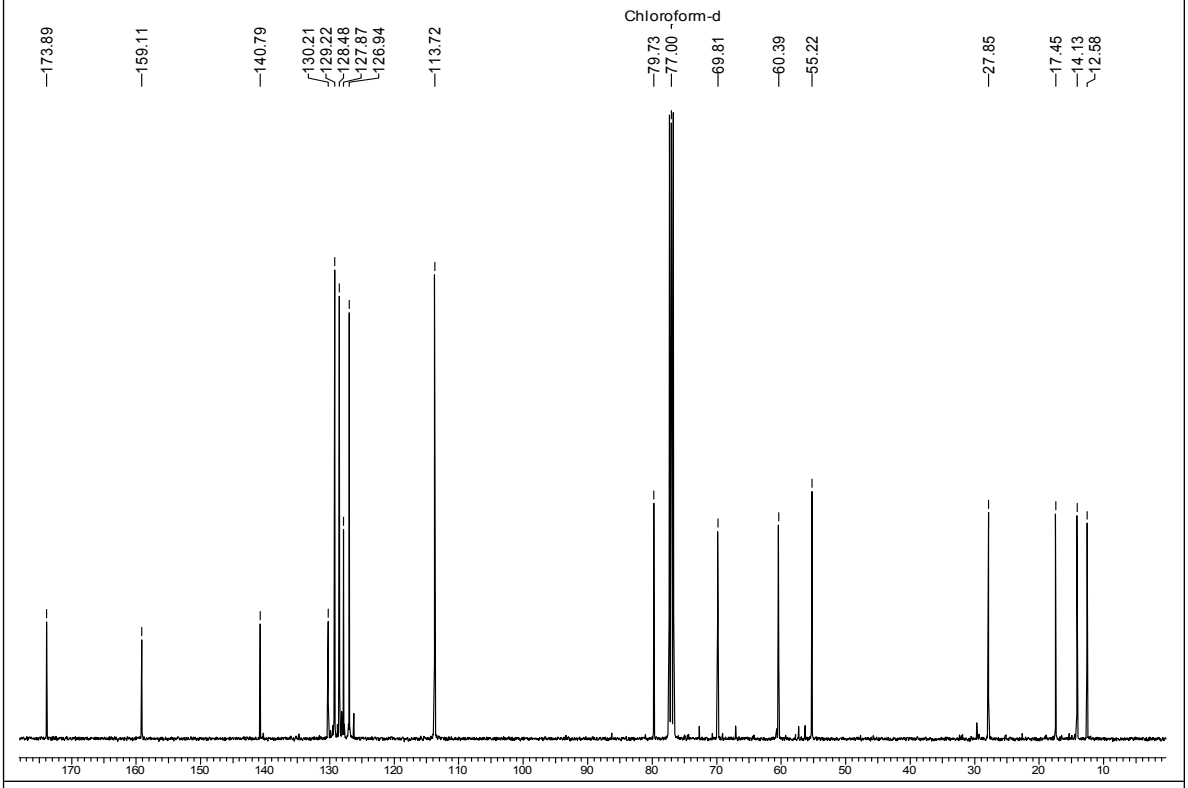
^{13}C NMR ($CDCl_3$, 100MHz) of (*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (1c)



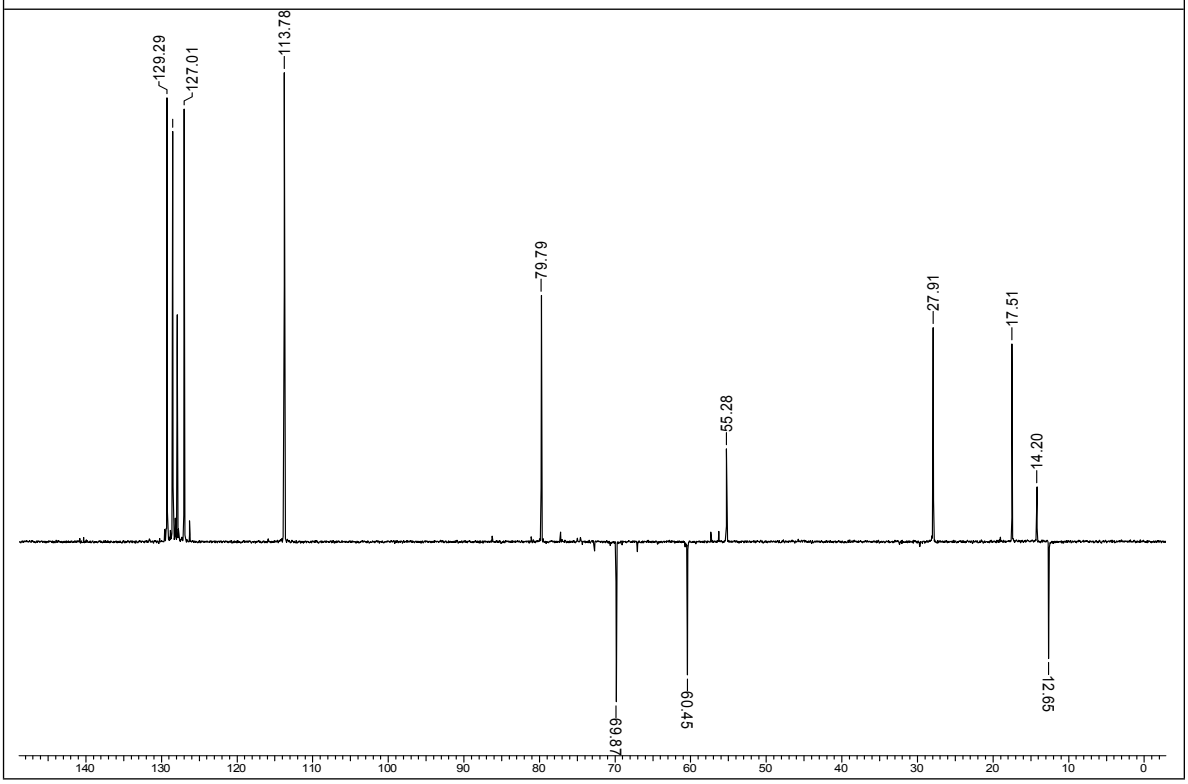
^{1}H NMR ($CDCl_3$, 400MHz) of (1*R*,2*R*)-Ethyl 2-((*R*)-(4-methoxybenzyloxy)(phenyl) methyl)cyclopropanecarboxylate (3c)



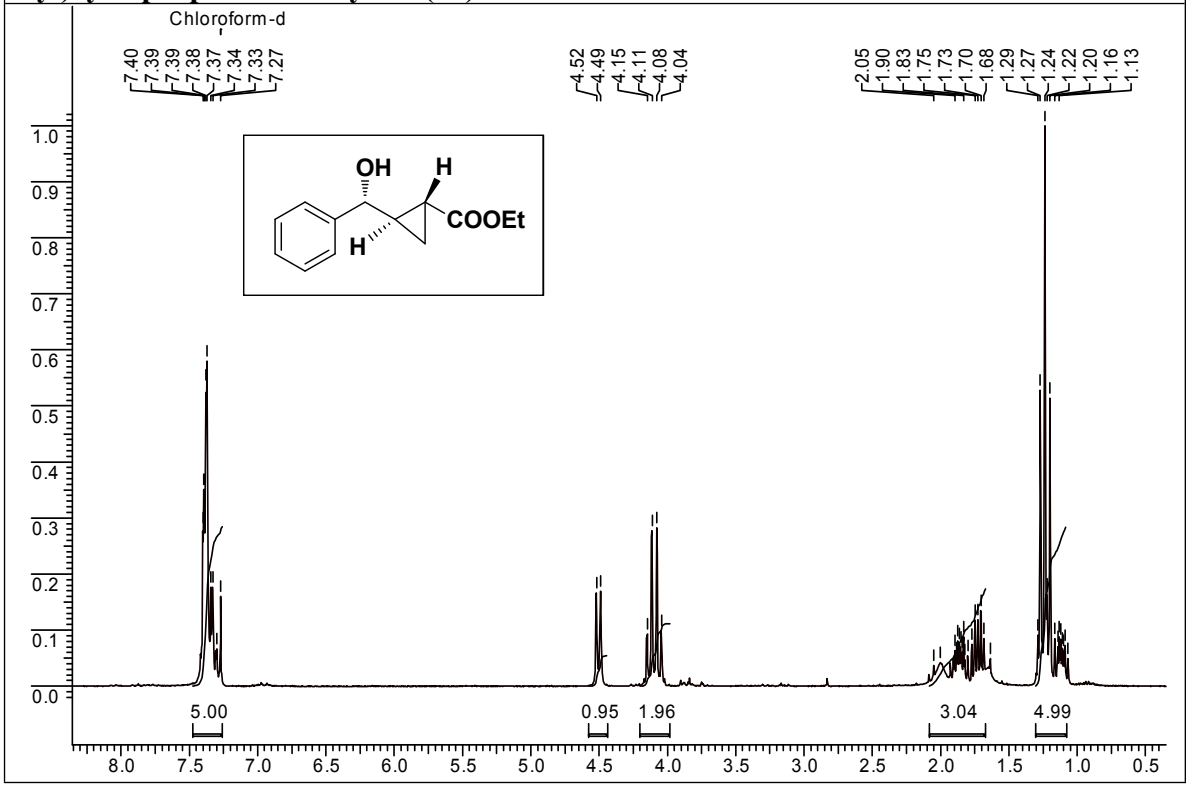
^{13}C NMR ($CDCl_3$, 100MHz) of (1*R*,2*R*)-Ethyl 2-((*R*)-(4-methoxybenzyloxy) (phenyl) methyl)cyclopropanecarboxylate (3c)



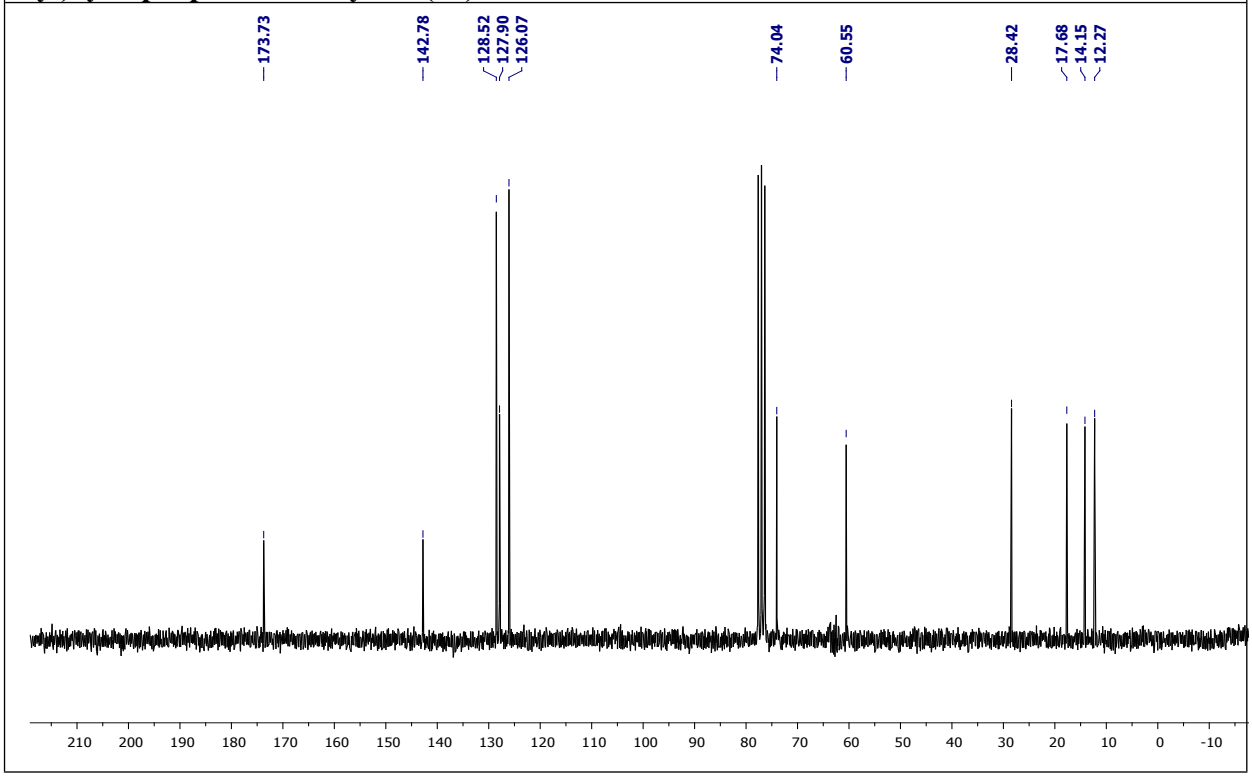
DEPT ($CDCl_3$, 100 MHz) spectrum (3c)



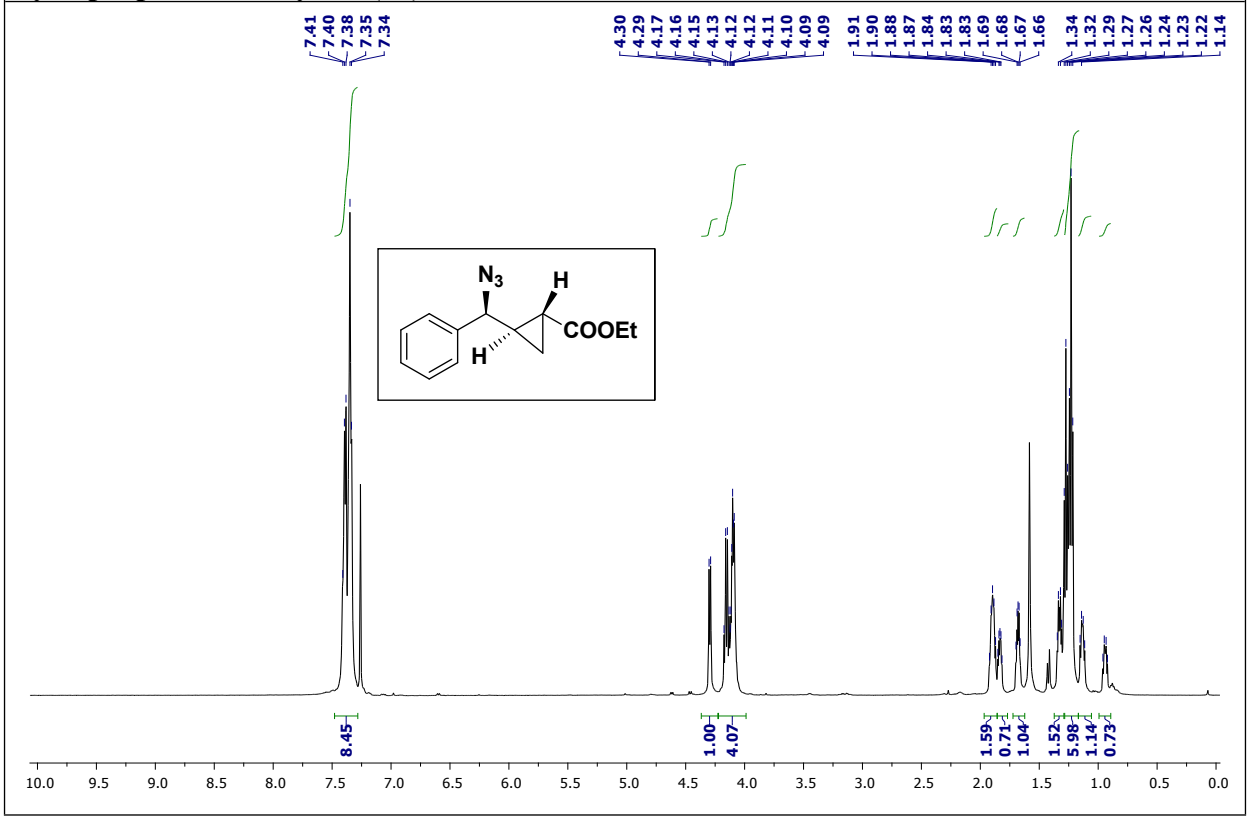
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*R*)-hydroxy(phenyl)methyl)cyclopropanecarboxylate (20)



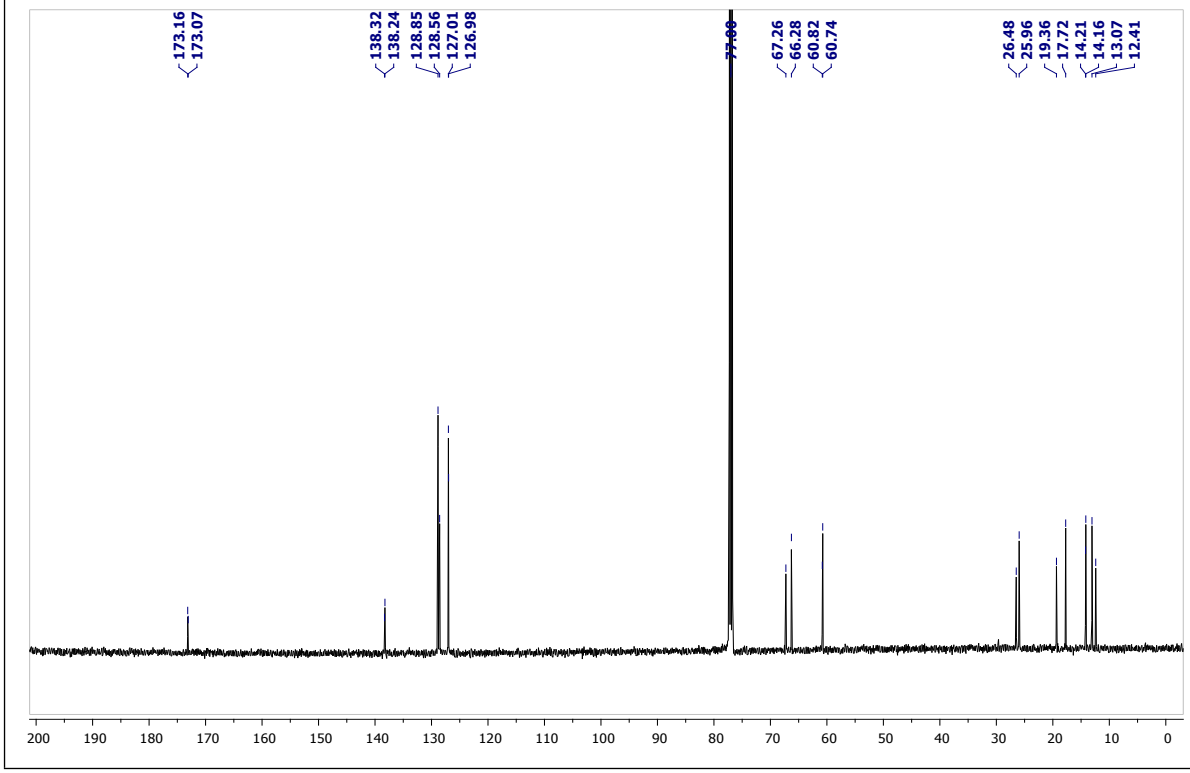
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*R*)-hydroxy(phenyl)methyl)cyclopropanecarboxylate (20)



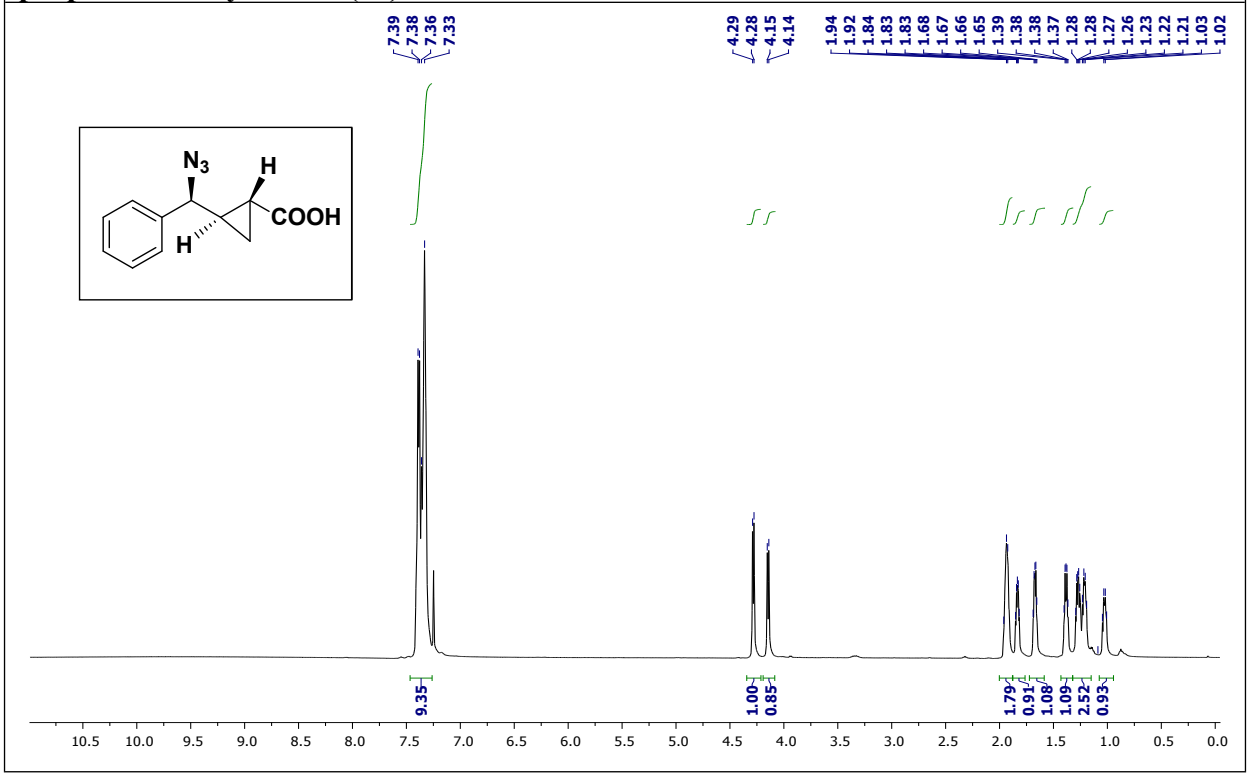
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*S*)-azido(phenyl)methyl) cyclopropanecarboxylate (15)



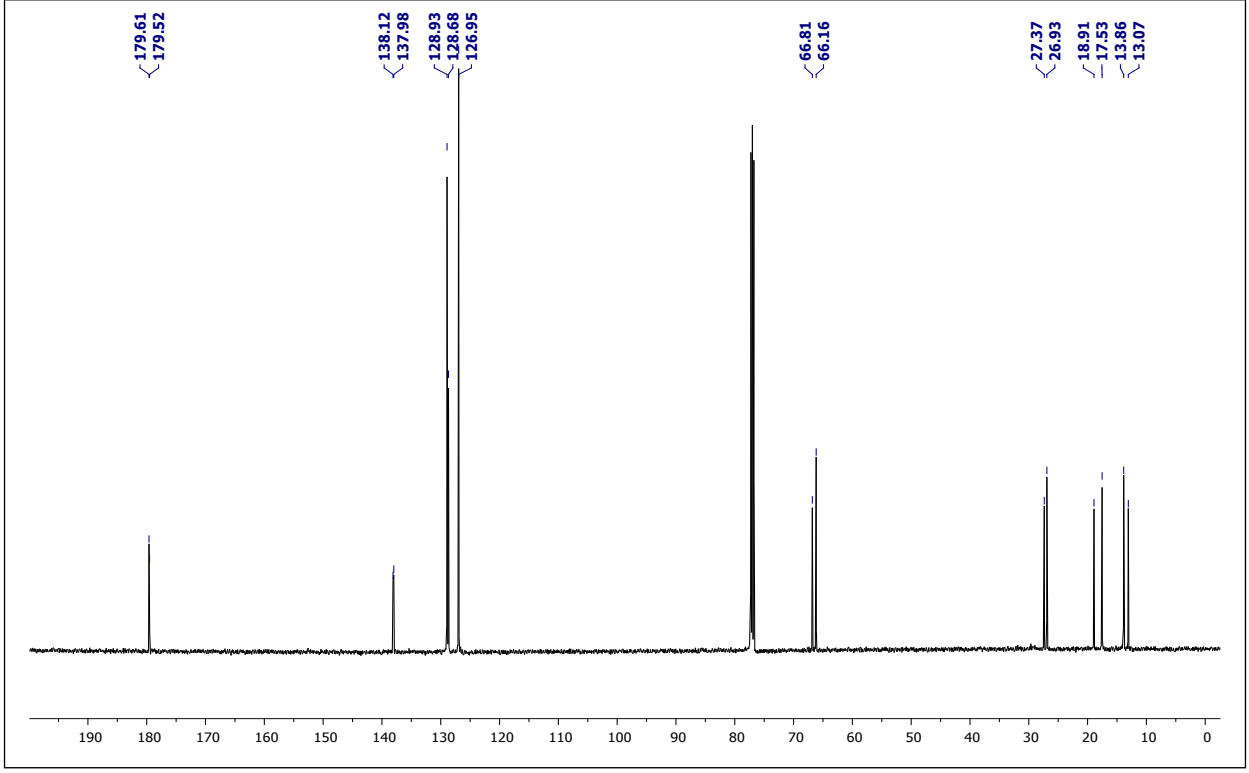
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*S*)-azido(phenyl)methyl) cyclopropanecarboxylate (15)



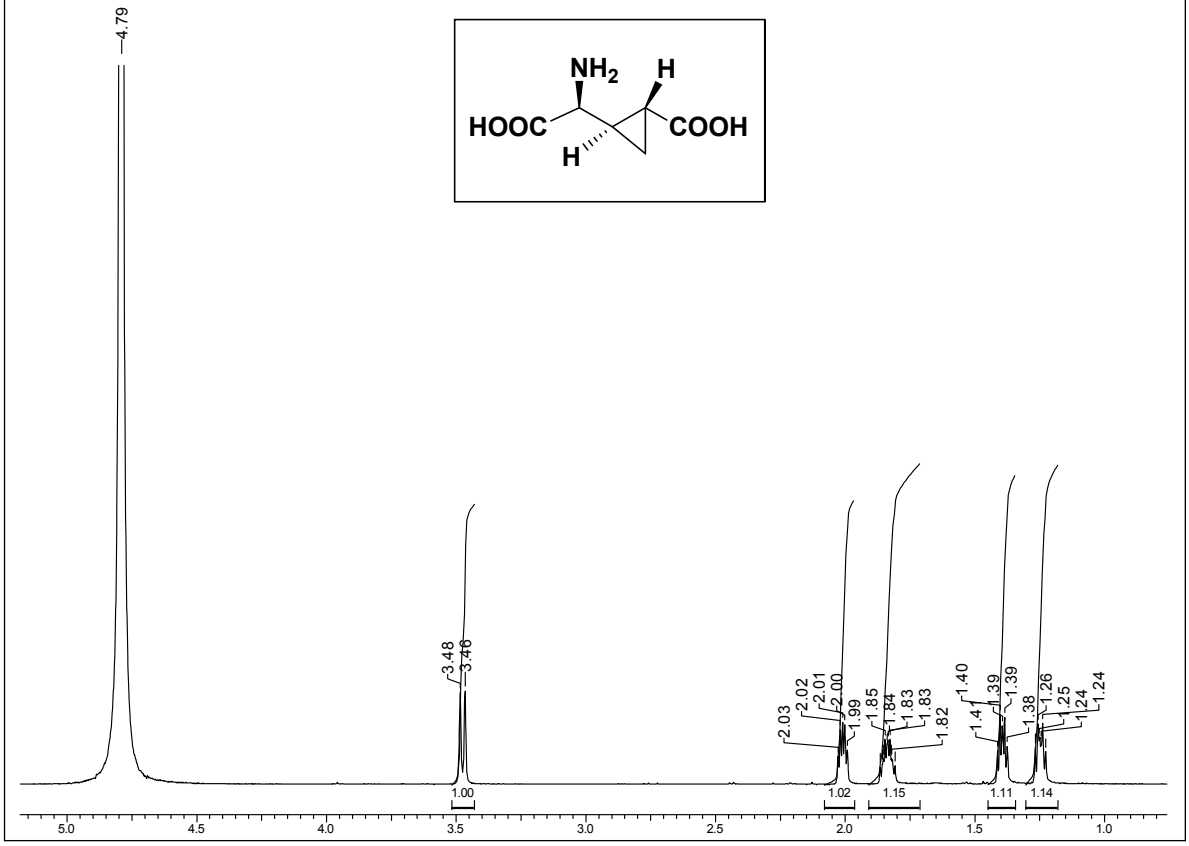
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (21)



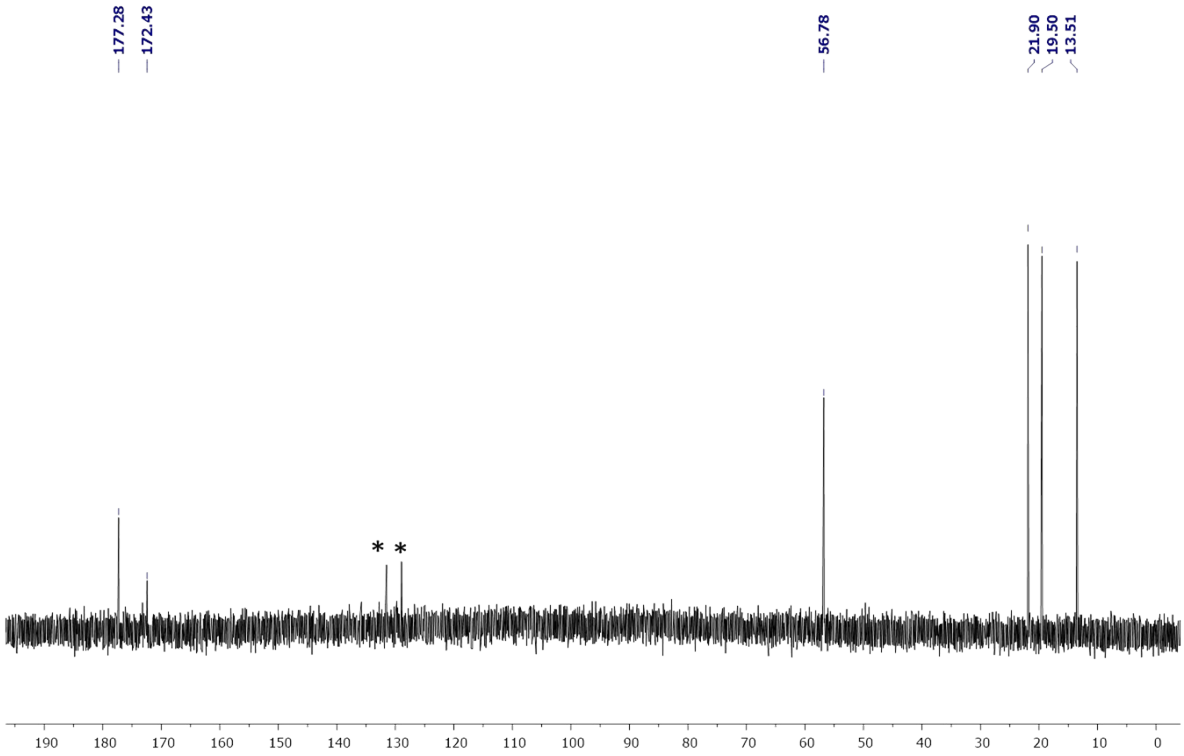
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (21)



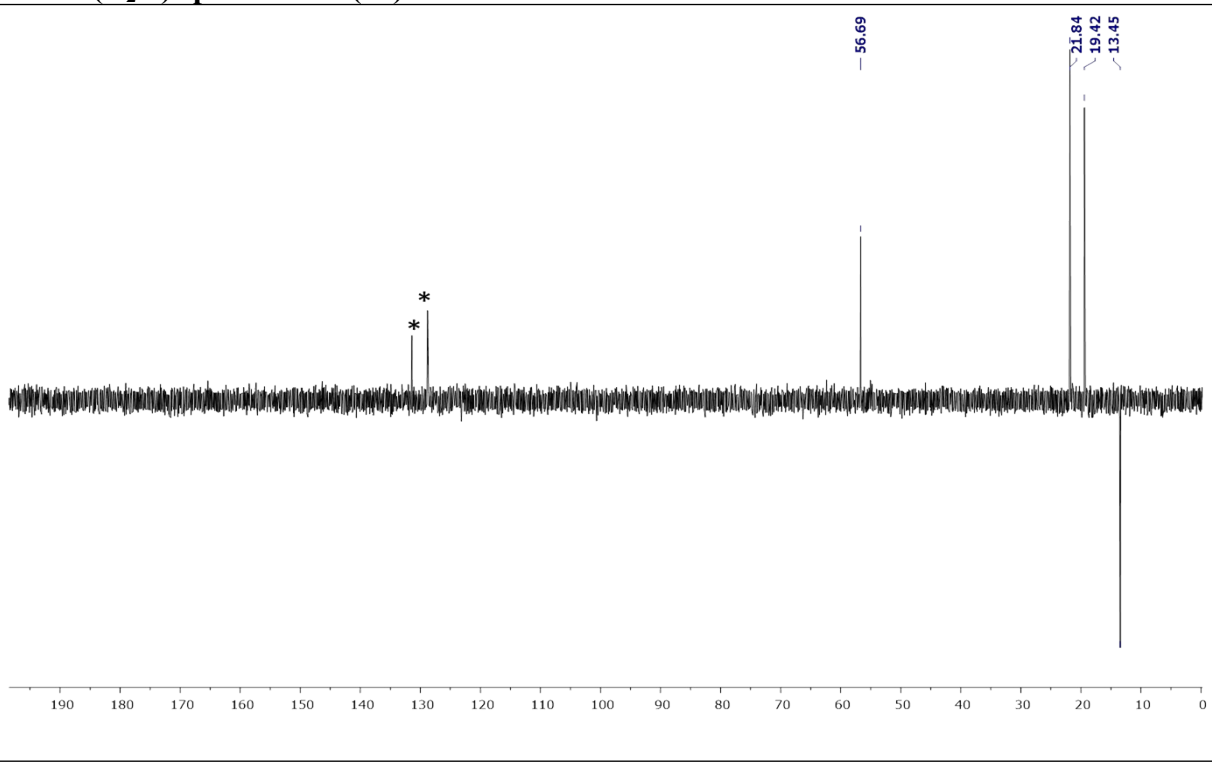
^{1}H NMR (D_2O, 500 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-amino(carboxy)methyl)cyclopropanecarboxylic acid (14)



^{13}C NMR (D_2O, 125 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-amino(carboxy)methyl)cyclopropanecarboxylic acid (14)



DEPT (D_2O) spectrum of (14)



* = unidentified impurities