Electronic Supplementary Material (ESI) for ChemComm.

Evidence for Heterolytic Cleavage of a Cyclic Oxonium Ylide: Implications for the Mechanism of the Stevens [1,2]-Shift

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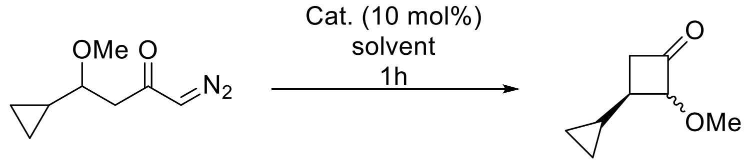
Supplementary Information

Contents

Table 1: Formation of the Cyclobutanone Derivatives via Endocyclic [1,2]-Stevens Rearrangement



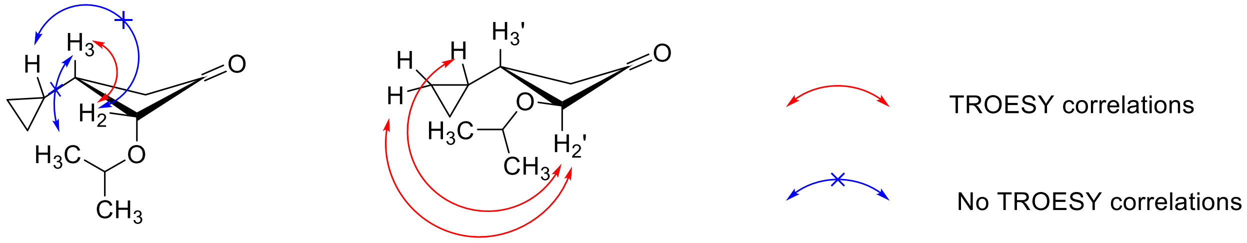
1c

6c
cis/trans mixture

Entry	Catalyst	Solvent	Temp (°C)	Yield% 6[a], (cis:trans)[b]
1	Cu(hfacac)$_2$	DCM	rt	60 (6:1)
2	Cu(hfacac)$_2$	DCM	-10	50[c] (6:1)
3	**Cu(hfacac)$_2$**	**DCM**	**reflux**	**80** (6:1)
4	Cu(tfacac)$_2$	DCM	reflux	72 (2:1)
5	Cu(acac)$_2$	DCM	reflux	65 (1:1)
6	Cu powder	DCM	reflux	NR
7	Cu powder (1 eq)	DCM	reflux	ND[d] (1:1)
8	$Rh_2(OAC)_4$	DCM	reflux	73 (2.2:1)
9	Cu(hfacac)$_2$	toluene	reflux	75[e] (2.5:1)
10	Cu(hfacac)$_2$	Benzene	reflux	80 (4:1)

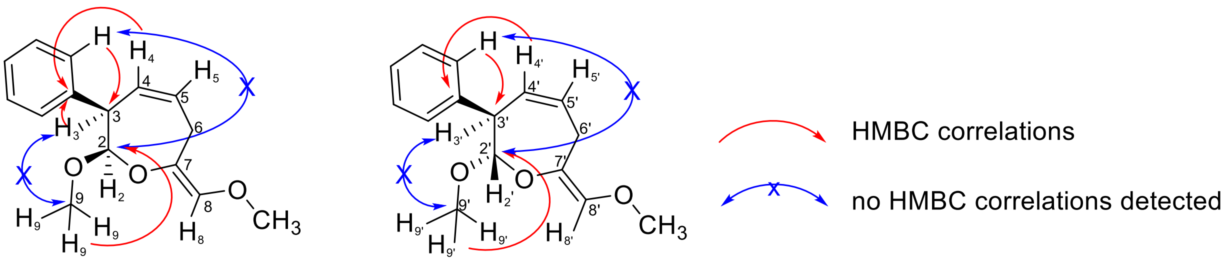
[a] Combined yield of both diastereomers. [b] Ratios were determined ^{1}H NMR analysis via integration of ether O–C–H resonances [c] 45% starting diazocarbonyl was recovered. [d] Reaction mixture was heated at reflux for 16h and a very messy crude mixture was obtained and the presence of cyclobutanones and starting material was confirmed by crude ^{1}H-NMR spectrum. [e] The cyclobutanones **6c** were not isolated as a pure mixture due to very complicated reaction mixture.

Scheme 4: TROESY Correlations of **6f**



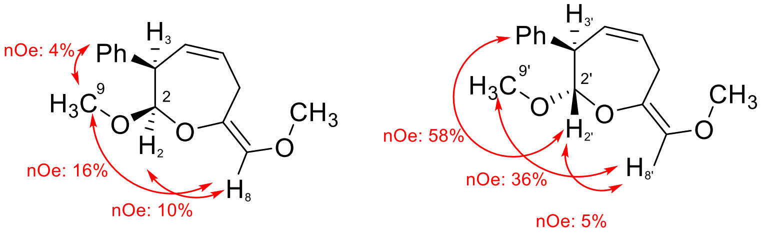
6f-cis **6f-trans**

Scheme 5: HMBC Correlations of **15a** and **16a**



15a **16a**

Scheme 6: nOe Correlations of **15a** and **16a**



15a **16a**

1. Experimental Section

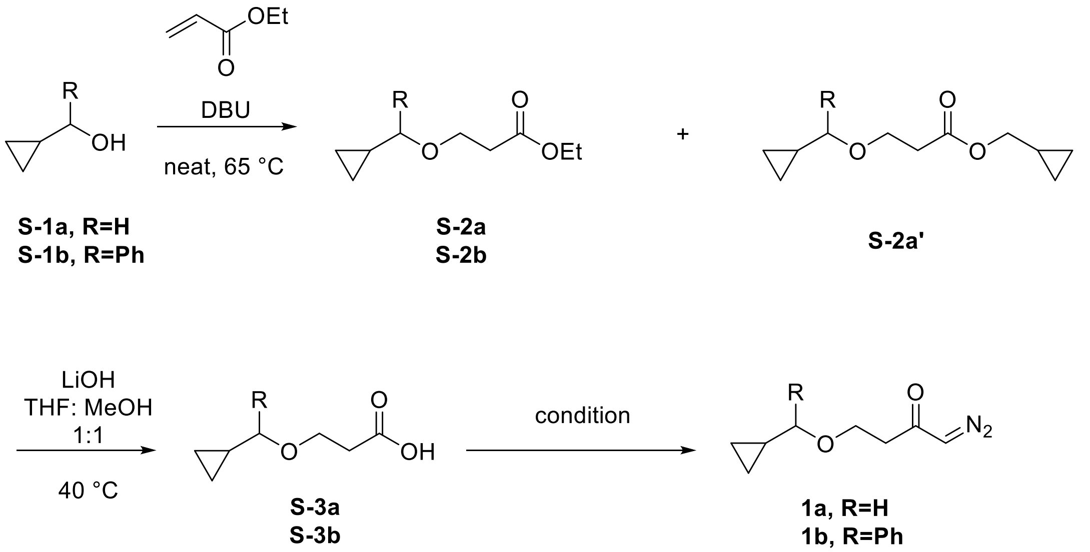
1.1 Materials and Methods

Reactions were carried out in flame or oven dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents and some reagents were distilled before use: methylene chloride, 1,2-

dichloroethane, diisopropylamine from calcium hydride, tetrahydrofuran and diethylether from sodium/benzophenone ketyl and benzene and toluene from sodium metal. Diazomethane was generated based on the Sigma-Aldrich protocol from Diazald®.[1] All other solvents and commercially available reagents were used without further purification. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel; the stains for TLC analysis were conducted with 2.5 % *p*-anisaldehyde in AcOH-H_2SO_4-EtOH (1:3:86) and further heating until development of color. Flash chromatography was performed on 230-400 mesh silica gel with the indicated eluents. Nuclear magnetic resonance (NMR) spectra were recorded in indicated deuterated solvents and are reported in ppm in the presence of TMS as internal standard and coupling constants (J) are reported in hertz (Hz). The spectra are referenced to residual solvent peaks: $CDCl_3$ (7.26 ppm, ^1H; 77.26 ppm, ^{13}C), CD_2Cl_2 (5.32 ppm, ^1H, 54.00 ppm, ^{13}C) as internal standards. Proton nuclear magnetic spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 500 and 125 MHz respectively Infrared (IR) spectra were recorded neat and reported in cm^{-1}. Mass spectra were recorded by using electron impact ionization (EI) or electrospray ionization (ESI) as specified in each case.

2. Procedures and Characterizations

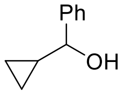
2.1 Preparation of Diazo Ketones 1a and 1b



condition:

1a: (1) $(COCl)_2$, DMF, CH_2Cl_2, -25 °C to rt (2) CH_2N_2, Et_2O, -78 °C to rt
1b: (1) ethylchloroformate, Et_3N, THF, -15 °C (2) CH_2N_2, Et_2O, -78 °C to rt

2.1.1 Preparation of alcohol S-1b

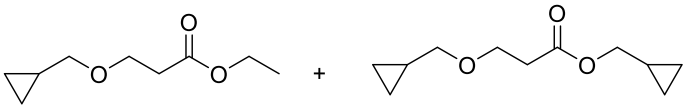


S-1b

Solid $LiAlH_4$ (0.31 g, 8.2 mmol) was added to dry THF (25 mL) and the suspension was cooled down to 0 °C. A solution of cyclopropyl phenyl ketone (0.95 mL, 6.8 mmol) in dry THF (5.0 mL) was added dropwise. The reaction was allowed to stir at 0 °C, with gradual warming to room temperature over 2h. The reaction mixture was cooled down again to 0 °C after completion and was quenched with a very slow addition of the saturated NH_4Cl to avoid severe gas evolution. The reaction mixture was filtered over Celite to separate the insoluble white precipitate and the filtrate was retained. The aqueous layer was extracted with Et_2O (3 × 5.0 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated under reduced pressure. No further purification was required and alcohol **S-1b** was obtained as a pale yellow oil (1.0 g, 98%); R_f 0.40 (30:70 EtOAc: hexane); IR (cast film) 3366, 3082, 3005, 1493, 1452, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.38-7.34 (m, 2H), 7.29 (ddd, *J* = 6.5, 1.4, 1.4 Hz, 1H), 4.01 (d, *J* = 8.3 Hz, 1H), 2.06 (br s, 1H), 1.22 (ddddd, *J* = 8.2, 8.2, 8.2, 5.0, 5.0 Hz, 1H), 0.64 (dddd, *J* = 8.8, 8.0, 5.6, 4.2 Hz, 1H), 0.56 (dddd, *J* = 10.0, 8.3, 5.6, 4.4 Hz, 1H), 0.50-0.45 (m, 1H), 0.40-0.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 128.3, 127.5, 126.0, 78.5, 19.2, 3.59, 2.83; HRMS (EI) calcd for $C_{10}H_{12}O$ $[M]^+$ 148.0888; found 148.0884.

2.1.2 General Procedure for Preparation of Esters S-2

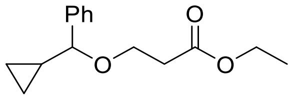
Ethyl acrylate (1.0 equiv.) was added to a flask containing corresponding alcohols **S-1** (3.5 equiv.) followed by the slow addition of DBU (1.0 equiv.) to the reaction mixture. The reaction was heated up to 65 °C overnight. The crude mixture was cooled to room temperature and was then directly loaded on a silica gel column and chromatographed eluting with mixture of EtOAc: hexane to isolate the desired product.



S-2a + **S-2a'**

column chromatography (30:70 EtOAc: hexane) was used to isolate inseparable esters **S-2a** and **S-2a'** in a 1:7 ratio. Pale yellow (0.57 mg, 57%), R_f 0.50 (30:70 EtOAc: hexane); IR (cast film) 3083, 3006, 2869, 1737, 1384, 1187, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.86 (d, *J* = 7.5 Hz, 2H), 3.66 (t, *J* = 6.5 Hz, 2H), 3.22 (d, *J* = 6.9 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 1.24-1.15 (m, 2H), 0.50-0.43 (m, 4H), 0.22-0.19 (m, 2H), 0.14-0.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 75.6, 69.1, 65.8, 35.1, 10.4, 9.7, 3.1, 2.9; HRMS (ESI) calcd for $C_{11}H_{19}O_3$ $[M+H]^+$ 198.1256; found 198.1254.

S-2a: observed peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.3 Hz, 2H), 3.73-3.70 (m, 2H), 3.22 (d, *J* = 7.0 Hz, 2H), 2.61-2.58 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.08-0.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 66.2, 65.7, 60.3, 15.0, 14.1.

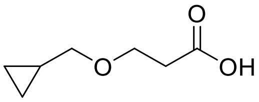


S-2b

S-2b: Following the general procedure employing alcohol **S-1b**, generated ester **S-2b** as the single isolated product. column chromatography (30:70 EtOAc: hexane) was used to isolate esters **S-2b** as a pale yellow oil (0.85 mg, 35%); R*f* 0.60 (30:70 EtOAc: hexane); IR (cast film) 3083, 3004, 2981, 2906, 2873, 1736, 1603, 1492, 1453, 1372, 1346, 1262, 1185, 1137, 1095, 1068 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.73 (d, *J* = 8.0 Hz, 1H), 3.66-3.62 (m, 2H), 2.63-2.59 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.24-1.15 (m, 1H), 0.68-0.54 (m, 1H), 0.53-0.42 (m, 2H), 0.33-0.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 142.0, 128.3, 127.5, 126.6, 86.1, 64.2, 60.4, 35.4, 17.7, 14.2, 4.1, 2.1; HRMS (EI) calcd for $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 271.1305; found 271.1302.

2.1.3 General Procedure for the Synthesis of Carboxylic Acids S-3

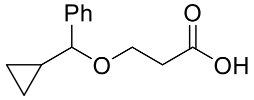
The corresponding ester **S-2** was dissolved in MeOH: THF (1:1, 0.25 M) and an aqueous solution of LiOH (2.0 M, 2.0 equiv.) was added dropwise. The reaction mixture was stirred overnight at 40 °C until the consumption of starting materials was confirmed by TLC. An equal volume of water was added to the reaction and the organic layer was separated. The aqueous layer was acidified with 1.0 M HCl to pH = 1 followed by extraction with Et_2O (3 x 5.0 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Acids **S-3** were obtained pure and were used for the next step without further purification.



S-3a

S-3a: light yellow oil (95%); IR (cast film) 3082, 3006, 2873, 1712, 1399, 1239, 1189, 1098, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20-8.40 (br s, 1H), 3.72 (t, *J* = 6.2 Hz, 2H), 3.30 (d, *J* = 7.0 Hz, 2H), 2.64 (t, *J* = 6.2

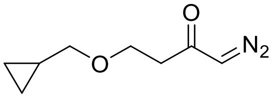
Hz, 2H), 1.11-1.02 (m, 1H), 0.55-0.47 (m, 2H), 0.23-0.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 75.7, 65.3, 34.8, 10.3, 2.9; HRMS (ESI) calcd for $C_7H_{11}O_3$ [M-H]$^-$ 143.0714; found 143.0713.



S-3b

S-3b: yellow oil (82%); IR (cast film) 3083, 3028, 3007, 2918, 2876, 1713, 1453, 1137 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H), 3.73 (d, J = 7.9 Hz, 1H), 3.67 (dt, J_{AB} = 16.2 Hz, J_{AX} = 6.5 Hz, 1H), 3.65 (dt, J_{AB} = 16.2 Hz, J_{AX} = 6.5 Hz, 1H), 2.68 (dt, J_{AB} = 16.7 Hz, J_{AX} = 6.4 Hz, 1H), 2.68 (dt, J_{AB} = 16.7 Hz, J_{AX} = 6.4 Hz, 1H), 1.20 (ddddd, J = 8.0, 8.0, 8.0, 5.2, 5.2, 1H), 0.69-0.63 (m, 1H), 0.53-0.46 (m, 2H), 0.34-0.29 (m, 1H), (the peak corresponding to the carboxylic acid proton did not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 141.6, 128.4, 127.7, 126.7, 86.5, 63.8, 35.0, 17.6, 4.2, 2.2; HRMS (EI) calcd for $C_{13}H_{16}O_3$ [M]$^+$ 220.1099; found 220.1097.

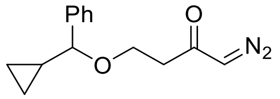
2.1.4 Preparation of Diazo Ketone 1a



1a

Oxalyl chloride (0.16 mL, 1.9 mmol) and catalytic amount of DMF (2 drops) was added to a solution of carboxylic acid **S-3a** (0.25 g, 1.6 mmol) in dichloromethane (11 mL) at -25 °C and the reaction was stirred for 1h then warmed to room temperature and stirred overnight. CH_2Cl_2 was removed under reduced pressure and the residue was immediately dissolved in Et_2O (10 mL). The acid chloride solution was added to a fresh solution of CH_2N_2 (~5 equivalents, prepared from Diazald®) in Et_2O via cannulae at -78 °C. The reaction was warmed gradually to room temperature overnight. Excess amount of diazomethane was quenched by dropwise addition of glacial acetic acid (1.0 mL) and the reaction mixture was washed with water. Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography, using a 50:50 mixture of hexane: EtOAc, aforeded diazo ketone **1a** in 55 % yield as a yellow oil (0.15 mg, 55%); R_f 0.40 (50:50 EtOAc: hexane); IR (cast film) 3082, 3005, 2866, 2104, 1639, 1359, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (br s, 1H), 3.71 (t, J = 6.5 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.58 (br s, 2H), 1.03 (ddddd, J = 6.8, 6.8, 6.8, 5.0, 5.0, 1H), 0.54-0.50 (m, 2H), 0.20-0.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 75.9, 66.0, 55.0, 41.4, 10.5, 3.0; HRMS (ESI) calcd for $C_8H_{13}N_2O_2$ $[M+H]^+$ 169.0972; found 169.0969.

2.1.5 Preparation of Diazo Ketone 1b

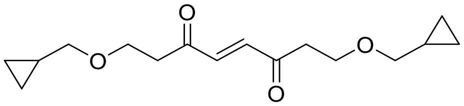


1b

To a solution of carboxylic acid **S-3b** (0.52 mg, 2.4 mmol) in dry THF (12 mL) was added Et_3N (0.36 mL, 2.6 mmol) followed by the addition of ethylchloroformate solution (0.25 mL, 2.6 mmol) in THF (2 mL) at -15 °C. The reaction was stirred for 1 h at -15 °C and an additional 3h of stirring at -5 °C. After the formation of white solid the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was immediately dissolved in Et_2O and transferred to an ethereal solution of CH_2N_2 (~5 equivalents, prepared from Diazald®) at -78 °C. The reaction mixture was stirred overnight with gradual warming to room temperature. The excess CH_2N_2 was quenched with glacial acetic acid (2.0 mL) and the reaction mixture was washed with water. The organic layer was separated and the aqueous phase was washed with Et_2O (2×5.0 mL). The organic layers were combined and dried over $MgSO_4$. The crude mixture was obtained after filtration and solvent removal by reduced pressure and was purified by column chromatography (30:70 EtOAc: hexane) to isolate diazo ketone **1b** as a yellow solid (0.31 mg, 53%); mp 38-40 °C R_f 0.20 (30:70 EtOAc: hexane); IR (cast film) 3085, 3005, 2869, 2103, 1639, 1453, 1360, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.39 (br s, 1H), 3.72 (d, *J* = 7.7 Hz, 1H), 3.68-3.60 (m, 2H), 2.59 (br s, 2H), 1.18 (ddddd, *J* = 8.0, 8.0, 8.0, 5.2, 5.2, 1H), 0.68-0.63 (m, 1H), 0.52-0.45 (m, 2H), 0.33-0.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 141.8, 128.4, 127.6, 126.7, 68.4, 64.5, 54.9, 41.6, 17.6, 4.2, 2.1; HRMS (ESI) calcd for $C_{14}H_{16}N_2NaO_2$ $[M+ Na]^+$ 267.1104; found 267.1096.

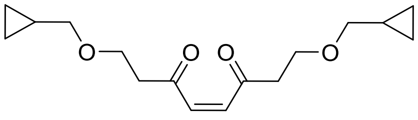
2.2 General Procedure for the Reaction of Diazo Ketones 1a and 1b with Cu(hfacac)$_2$:

To a refluxing solution of Cu(hfacac)$_2$ (10 mol%) in dichlrorethane (0.010 M) was added a solution of diazo ketone **1a/1b** (1.0 equiv.) in the same solvent (0.10 M) via syringe pump over 4h. Consumption of diazo ketone **1a/1b** was monitored by TLC and the reaction mixture was quenched by 10% aqueous solution of K_2CO_3. The organic layer was separated and the aqueous layer was washed with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the products were purified by flash chromatography.



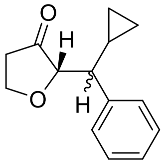
8a-isomer E

8a-isomer E: column chromatography (30:70 EtOAc: hexane) was used to isolate alkene **8a-isomer E** as a white solid (33 mg, 40%); mp 50-52 ˚C; R_f 0.37 (30:70 EtOAc: hexane); IR (cast film) 3081, 3004, 2899, 2820, 1675, 1407, 1388, 1351, 1110, 1059 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.94 (s, 2H), 3.79 (t, *J* = 6.5 Hz, 4H), 3.30 (d, *J* = 7.0 Hz, 4H), 2.95 (t, *J* = 6.5 Hz, 4H), 1.07-1.02 (m, 2H), 0.56-0.52 (m, 4H), 0.22-0.19 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.8, 136.7, 75.9, 65.1, 41.8, 10.5, 3.0; HRMS (ESI) calcd for $C_{16}H_{24}NaO_4$ [M+ Na]$^+$ 303.1567; found 303.1561.



8a-isomer Z

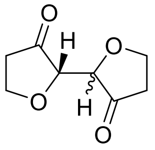
8a-isomer Z: column chromatography (30:70 EtOAc: hexane) was used to isolate alkene **8a-isomer Z** as a colorless oil (11 mg, 13%); R_f 0.26 (40:60 EtOAc: hexane); IR (cast film) 3005, 2867, 1696, 1608, 1393, 1255, 1143, 1097 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.38 (s, 2H), 3.76 (t, *J* = 6.4 Hz, 4H), 3.28 (d, *J* = 6.8 Hz, 4H), 2.85 (t, *J* = 6.5 Hz, 4H), 1.06 -1.03 (m, 2H), 0.56 - 0.52 (m, 4H), 0.22-0.19 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 201.5, 135.7, 76.8, 65.3, 42.8, 10.5, 3.0; HRMS (ESI) calcd for $C_{16}H_{24}NaO_4$ [M+ Na]$^+$ 303.1567; found 303.1566.



6b

6b: column chromatography (30:70 EtOAc: hexane) was used to isolate an inseparable mixture of diastereomers as a colorless oil (54 mg, 60%); R_f 0.51 (30:70 EtOAc: hexane); IR (cast film) 3079, 3063, 3028, 3001, 2925, 2888, 1755, 1602, 1495, 1453, 1430, 1402, 1360, 1155, 1142, 1093, 1042, 1019 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (m, 2H), 7.32-7.29 (m, 2H), 7.29-7.18 (m, 6H), 4.37-4.31 (m, 1H), 4.13 (d, *J* = 2.7 Hz, 1H), 4.05 (dd, *J* = 9.2, 7.4 Hz, 1H), 4.01-3.98 (m, 3H), 2.52-2.40 (m, 2H), 2.32 (dd, *J* = 10.6, 2.4 Hz, 1H), 2.26 (dddd, *J* = 18.0, 6.1, 6.1, 0.7 Hz, 1H), 2.17 (dd, *J* = 10.6, 2.6 Hz, 1H), 1.82 (dddd, *J* = 18.0, 9.3, 9.3, 0.4 Hz, 1H), 1.53-1.40 (m, 2H), 0.66 (dddd, *J* = 9.1, 8.0, 5.7, 4.6 Hz, 1H), 0.59-0.45 (m, 3H), 0.33 (dddd,

J = 9.4, 5.6, 4.6, 4.6 Hz, 1H), 0.28-0.24 (m, 1H), 0.15-0.08 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 216.2, 215.9, 142.6, 140.0, 129.3, 128.3, 128.1, 128.0, 126.8, 126.6, 83.7, 83.2, 65.1, 64.9, 52.8, 52.4, 37.7, 37.1, 14.2, 11.4, 6.1, 5.4, 5.2, 4.2; HRMS (EI) calcd for $C_{14}H_{16}O_2$ [M]$^+$ 216.1150; found 216.1149.



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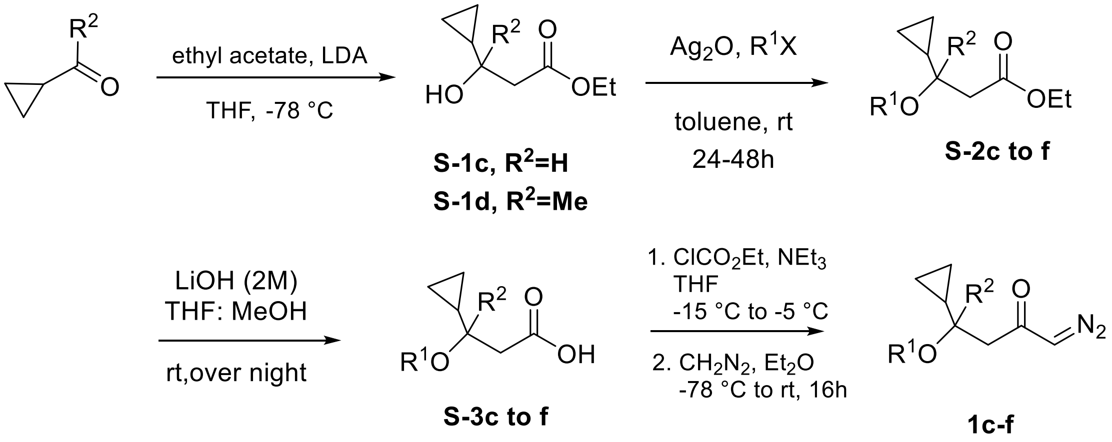
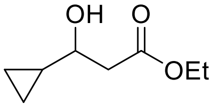
9: was isolated as two inseparable diastereomers; colorless oil (1.5 mg, 4.3%); R$_f$ 0.20 (30:70 EtOAc: hexane); IR (cast film) 3200, 2967, 2918, 1743, 1402, 1365, 1178, 1070, 1026 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 4.39-4.32 (m, 4H), 4.20-4.12 (m, 8H), 2.62-2.54 (m, 8H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 213.2, 212.5, 80.3, 79.3, 66.0, 65.7, 37.0, 36.8; HRMS (EI) calcd for $C_8H_{10}O_4$ [M]$^+$ 170.0579; found 170.0580.

2.3 General Procedure for Construction of Diazo Ketones 1c-f



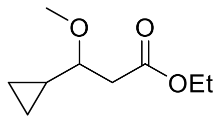
2.3.1 Preparation of alcohol 1c



S-1c

A flame dried round bottom flask was charged with diisopropylamine (3.3 mL, 24 mmol) in THF (80 mL) and was cooled to -78 °C. A solution of *n*-BuLi in hexane (2.5 M, 9.4 mL, 24 mmol) was added dropwise and the reaction was stirred for 15 min at -78 °C. Ethyl acetate (1.9 mL, 21 mmol) was added dropwise with an additional 45 min stirring at -78 °C. Then a solution of cyclopropanecarboxaldehyde (1.6 mL, 21 mmol) in THF (10 mL) was added to the reaction mixture. The reaction temperature was maintained at -78 °C over 2 h and the reaction completion was monitored with TLC. Then the reaction was warmed to room temperature followed by the addition of saturated ammonium chloride and the organic layer was separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The crude product was purified by flash chromatography (30:70 EtOAc: hexane) after concertation under reduced pressure and alcohol **S-1c** was isolated as a yellow oil.

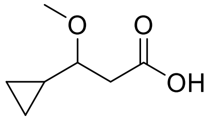
S-1c: (3.3 g, 97%); R_f 0.27 (30:70 EtOAc: hexane); IR (cast film) 3447, 3003, 2983, 1735, 1412, 1372, 1343, 1280, 1249, 1186, 1139, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.2 Hz, 2H), 3.32 (ddd, *J* = 8.4, 8.4, 3.1 Hz, 1H), 2.63 (dd, *J* = 16.0, 3.8 Hz, 1H), 2.57 (dd, *J* = 16.0, 8.4 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.94 (ddddd, *J* = 8.1, 8.1, 8.1, 4.9, 4.9, Hz, 1H), 0.57-0.47 (m, 2H), 0.40 (dddd, *J* = 4.5, 4.5, 4.5, 4.5 Hz, 1H), 0.22 (dddd, *J* = 4.5, 4.5, 4.5, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 72.7, 60.7, 41.4, 16.8, 14.2, 3.2, 2.2; HRMS (ESI) calcd for $C_8H_{14}NaO_3$ [M+ Na]$^+$ 181.0835; found 181.0836.



S-2c

To a stirred solution of alcohol **1-1c** (1.5 g, 9.5 mmol) in dry toluene (20 mL) was added anhydrous $CaSO_4$ (2.6 g, 19 mmol) and freshly prepared Ag_2O[2] (4.4 g, 19 mmol). The reaction mixture was cooled down to 0 °C and iodomethane (1.2 mL, 19 mmol) was added dropwise. The ice bath was removed and the flask was covered in aluminum foil. The reaction mixture was stirred for 3 h at room temperature. An additional aliquots of Ag_2O, $CaSO_4$ and MeI (the same amount as before) were added and the reaction progress was monitored by TLC. (Addition of excess Ag_2O, $CaSO_4$ and MeI may be required if the starting alcohol has not been consumed completely.) The reaction mixture was stirred overnight and was filtered through a Celite plug. The Celite was washed with ethyl acetate and the reaction mixture was concentrated under reduced pressure. The crude mixture was used in the next step without further purifications.

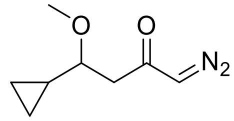
S-2c: yellow oil (1.7 g, quant.); R_f 0.29 (20:80 EtOAc: hexane); IR (cast film) 3082, 2982, 2937, 2824, 1738, 1394, 1279, 1250, 1138, 1111, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18-4.08 (m, 2H), 3.39 (s, 3H), 2.98 (ddd, *J* = 8.2, 8.2, 4.9 Hz, 1H), 2.61 (dd, *J* = 14.9, 8.1 Hz, 1H), 2.52 (dd, *J* = 14.9, 4.9 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.88-0.81 (m, 1H), 0.66-0.59 (m, 1H), 0.47-0.40 (m, 2H), 0.12-0.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 81.9, 60.3, 57.0, 40.9, 14.4, 14.2, 4.7, 0.6; HRMS (ESI) calcd for $C_9H_{17}O_3$ [M+ H]$^+$ 173.1172; found 173.1173.



S-3c

Ester **S-2c** (1.6 g, 9.5 mmol) was dissolved in MeOH:THF (1:1, 72 mL) and the aqueous solution of LiOH (2.0 M, 9.5 mL, 19 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature until complete consumption of starting materials. An equal volume of water was added to the reaction and the organic layer was separated. The aqueous layer was acidified with 1.0 M HCl to pH = 1 followed by extraction with Et_2O (3×10 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Acid **S-3c** was obtained as a pure mixture and was used for the next step without further purification.

S-3c: yellow oil (1.36 g, quant.); IR (cast film) 3083, 3006, 2983, 2828, 1711, 1408, 1286, 1218, 1190, 1107, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.00 (ddd, *J* = 8.8, 7.9, 5.0 Hz, 1H), 2.69 (dd, *J* = 15.2, 7.7 Hz, 1H), 2.66 (dd, *J* = 15.2, 4.7 Hz, 1H), 0.93-0.87 (m, 1H), 0.74-0.69 (m, 1H), 0.55-0.47 (m, 2H), 0.17-0.14 (m, 1H), (the peak corresponding to the carboxylic acid proton was not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 81.8, 57.0, 40.5, 14.2, 5.2, 0.6; HRMS (ESI) calcd for $C_7H_{11}O_3$ $[M-H]^-$ 143.0714; found 143.0714.

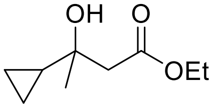


1c

To a solution of carboxylic acid **S-3c** (0.70 g, 4.9 mmol) in dry THF (25 mL) was added Et_3N (0.74 mL, 5.3 mmol) followed by the addition of a solution of ethylchloroformate (0.51 mL, 5.3 mmol) in THF (4.0 mL) at -15 °C. The reaction was stirred for 1 h at -15 °C and an additional 3h at -5 °C. After the formation of the white salt the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was immediately dissolved in Et_2O and transferred to an ethereal solution of CH_2N_2 (~5 equivalents, prepared from Diazald®) at -78 °C. The reaction mixture was stirred overnight by gradual warming to the room temperature. The excess CH_2N_2 was quenched with glacial acetic acid (1 mL) and the reaction mixture was washed with water. The organic layer was separated, combined and dried over $MgSO_4$ followed by filtration. The crude mixture was obtained after solvent removal and was purified by column chromatography (40:60 EtOAc: hexane) to isolate diazo ketone **1c.**

1c: yellow oil (0.53 g, 65%); R*f* 0.27 (50:50 EtOAc: hexane); IR (cast film) 3082, 3004, 2981, 2932, 2824, 2104, 1637, 1367, 1105, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 3.41 (s, 3H), 2.99 (ddd, *J* = 8.5, 8.5, 4.5 Hz, 1H), 2.55 (m, 2H), 0.89 (dddd, *J* = 13.5, 10.0, 7.9, 5.5 Hz, 1H), 0.70-0.64 (m, 1H), 0.49-0.43 (m, 2H), 0.14-0.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 82.2, 57.1, 55.4, 47.0, 14.6, 5.2, 0.6; HRMS (EI) calcd for $C_7H_9ON_2$ $[M-OCH_3]^+$ 137.0714; found 137.0715.

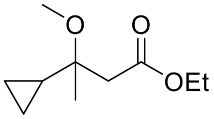
2.3.2 Preparation of Diazo Ketone 1d



S-1d

Alcohol **S-1d** was synthesized according to the procedure provided for **S-1c** using cyclopropylmethylketone as the starting material.

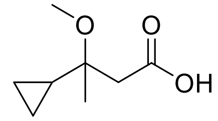
S-1d: yellow oil, (1.1 g, 68%); R*f* 0.35 (20:80 EtOAc: hexane); IR (cast film) 3512, 3087, 3004, 2980, 2935, 2907, 1713, 1464, 1395, 1372, 1330, 1218, 1200, 1140, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 3.34 (br s, 1H), 2.59 (d, *J* = 14.9 Hz, 1H), 2.53 (d, *J* = 14.9 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 3H), 0.94-0.88 (m, 1H), 0.47-0.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 69.1, 60.6, 46.1, 27.0, 20.8, 14.2, 0.7, 0.0; HRMS (ESI) calcd for $C_9H_{16}NaO_3$ $[M+ Na]^+$ 195.0992; found 195.0990.



S-2d

Compound **S-2d** was synthesized according to the procedure provided for **S-2c**.

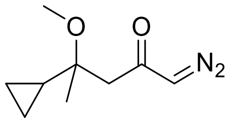
S-2d: Yellow oil (0.14g, 30%); R*f* 0.50 (20:80 EtOAc: hexane); IR (cast film) 3086, 2981, 2942, 2829, 1735, 1465, 1368, 1313, 1238, 1199, 1144, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.2 Hz, 2H), 3.28 (s, 3H), 2.55 (d, *J* = 13.2 Hz, 1H), 2.49 (d, *J* = 13.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 3H), 1.07-1.03 (m, 1H), 0.48-0.39 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 75.2, 60.2, 46.7, 44.4, 16.5, 18.5, 14.2, 1.3, 1.2; HRMS (ESI) calcd for $C_{10}H_{18}NaO_3$ $[M+ Na]^+$ 208.1148; found 209.1147.



S-3d

Carboxylic acid **S-3d** was prepared according to the procedure provided for **S-3c.**

S-3d: Colorless oil (62 mg, 52%); IR (cast film) 3086, 3010, 2984, 2944, 2831, 1732, 1709, 1465, 1436, 1409, 1386, 1314, 1239, 1201, 1150, 1095 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.41 (s, 3H), 2.61 (d, *J* = 15.2 Hz, 1H), 2.52 (d, *J* = 15.2 Hz, 1H), 1.04 (s, 3H), 1.02-0.97 (m, 1H), 0.65-0.47 (m, 3H), 0.20-0.13 (m, 1H), (the peak corresponding to the carboxylic acid proton was not observed); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.5, 76.7, 50.0, 45.5, 17.7, 17.4, 2.4, 0.7; HRMS (ESI) calcd for $C_8H_{13}O_3$ [M-H]$^-$ 157.0943; found 157.0870.

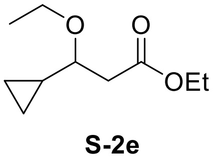


1d

Diazo ketone **1d** was prepared according to the procedure provided for **1c.**

1d: yellow oil, (21 mg, 34%); R$_f$ 0.49 (30:70 EtOAc: hexane); IR (cast film) 3271, 3086, 2979, 2944, 2829, 2102, 1634, 1465, 1429, 1356, 1163, 1093 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.49 (br s, 1H), 3.30 (s, 3H), 2.55-2.44 (br m, 2H), 1.03 (s, 3H), 1.00-0.95 (m, 1H), 0.55-0.42 (m, 3H), 0.22-0.14 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.2, 76.0, 55.9, 51.4, 49.7, 18.5, 18.4, 2.0, 0.9; HRMS (ESI) calcd for $C_9H_{15}N_2O_2$ [M+H]$^+$ 183.1128; found 183.1130.

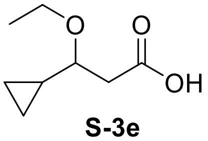
2.3.3 Preparation of Diazo Ketone 1e



S-2e

Compound **S-2e** was synthesized according to the procedure provided for compound **S-2c** using iodoethane as an alkyl halide. The reaction was stirred for 40 h and 60% of the starting alcohol was recovered.

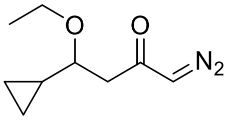
S-2e: yellow oil (230 mg, 39%); R$_f$ 0.47 (20:80 EtOAc: hexane); IR (cast film) 3082, 2978, 2932, 2873, 1738, 1463, 1445, 1430, 1390, 1372, 1317, 1279, 1189, 1139, 1096, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.18 (q, *J* = 7.1 Hz, 2H), 3.75 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.50 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.12 (ddd, *J* = 8.2, 8.2, 5.0 Hz, 1H), 2.66 (dd, *J* = 14.7, 8.1 Hz, 1H), 2.57 (dd, *J* = 14.7, 5.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H), 0.95-0.88 (m, 1H), 0.66-0.61 (m, 1H), 0.51-0.43 (m, 2H), 0.18-0.14 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.7, 80.3, 64.7, 60.3, 41.3, 15.5, 15.1, 14.2, 4.5, 1.0; HRMS (ESI) calcd for $C_{10}H_{19}O_3$ [M+ H]$^+$ 187.1329; found 187.1328.



S-3e

Compound **S-3e** was prepared according to the procedure provided for compound **S-3c.**

S-3e: yellow oil (180 mg, 92%); IR (cast film) 3082, 3006, 2977, 2931, 2897, 1712, 1429, 1406, 1293, 1206, 1140, 1122, 1096 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.85 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.54 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.10 (ddd, *J* = 8.4, 8.4, 4.9 Hz, 1H), 2.71 (dd, *J* = 15.4, 7.0 Hz, 1H), 2.67 (dd, *J* = 15.2, 4.8 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.92 (ddddd, *J* = 8.4, 8.4, 8.4, 5.2, 5.2 Hz 1H), 0.70 (dddd, , *J* = 8.9, 7.9, 5.7, 4.5, 1H), 0.56-0.51 (m, 1H), 0.50-0.45 (m, 1H), 0.17 (dddd, *J* = 9.5, 5.9, 4.8, 4.8, 1H), (the peak corresponding to the carboxylic acid proton was not observed); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.8, 80.1, 64.8, 40.7, 15.4, 14.7, 5.0, 0.9; HRMS (ESI) calcd for $C_8H_{13}O_3$ [M-H]$^-$ 157.0870; found 157.0871.

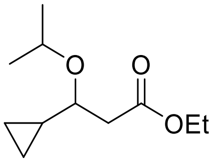


1e

Compound **1e** was prepared according to the procedure provided for compound **1c**.

1e: yellow oil (99 mg, 47%); R$_f$ 0.42 (40:60 EtOAc: hexane); IR (cast film) 3081, 3005, 2975, 2929, 2894, 2871, 21.03, 1638, 1361, 1092, 1053 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.40 (br s, 1H), 3.77 (dq, *J* = 6.9, 9.1 Hz, 1H), 3.45 (dq, *J* = 6.9, 9.1 Hz, 1H), 3.12 (ddd, *J* = 8.5, 8.5, 4.2 Hz, 1H), 2.69-2.55 (br s, 2H), 1.21 (t, *J* = 6.8 Hz, 3H), 0.87 (ddddd, *J* = 8.2, 8.2, 8.2, 5.0, 5.0 Hz 1H), 0.67-0.62 (m, 1H), 0.52-0.43 (m, 2H), 0.18-014 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.4, 80.5, 64.8, 55.3, 47.4, 15.6, 15.4, 4.9, 1.0; HRMS (EI) calcd for $C_9H_{15}N_2O_2$ [M+H]$^+$ 183.1128; found 183.1129.

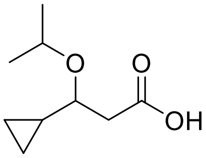
2.3.4 Preparation of Diazo Ketone 1f



S-2f

Ester **S-2f** was as synthesized according to the procedure provided for compound **S-2c** using isopropyl bromide as an alkyl halide.

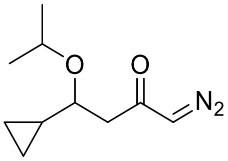
S-2f: yellow oil (1.9 g, 75%); R_f 0.63 (30:70 EtOAc: hexane); IR (cast film) 2974, 2934, 2902, 1738, 1466, 1369, 1340, 1311, 1278, 1188, 1140, 1063 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (sep, *J* = 6.0 Hz, 1H), 3.79 (ddd, *J* = 5.3, 7.9, 7.9 Hz, 1H), 2.61 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.54 (dd, *J* = 14.5, 5.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.94-0.81 (m, 1H), 0.63-0.57 (m, 1H), 0.51-0.45 (m, 1H), 0.43-0.38 (m, 1H), 0.20-0.16 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.7, 77.8, 69.7, 60.3, 41.7, 23.1, 22.3, 15.8, 14.2, 4.3, 1.5; HRMS (ESI) calcd for $C_{11}H_{20}NaO_3$ [M+ Na]$^+$ 223.1305; found 223.1304.



S-3f

Compound **S-3f** was prepared according to the procedure provided for compound **S-3c.**

S-3f: light yellow oil (1.6 g, 98%); IR (cast film) 3083, 3006, 2974, 2934, 1711, 1466, 1408, 1311, 1208, 1122, 1061, 1048 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.89 (sep, *J* = 6.3 Hz, 1H), 3.21 (ddd, *J* = 7.1, 7.1, 5.5 Hz, 1H), 2.67 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.64 (dd, *J* = 15.1, 5.2 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.94 (ddddd, *J* = 4.9, 4.9, 8.2, 8.2, 8.2 Hz, 1H), 0.65 (dddd, *J* = 9.0, 8.9, 5.8, 4.5 Hz, 1H), 0.52 (dddd, *J* = 8.6, 8.6, 5.7, 4.6 Hz, 1H), 0.44 (ddd, *J* = 9.6, 9.6, 5.1 Hz, 1H), 0.19 (dddd, *J* = 9.7, 4.9, 4.9, 4.9 Hz, 1H), (the peak corresponding to the carboxylic acid proton was not observed); ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.6, 77.5, 69.9, 41.2, 23.2, 22.0, 15.5, 4.6, 1.4; HRMS (ESI) calcd for $C_9H_{15}O_3$ [M-H]$^-$ 171.1027; found 171.1029.



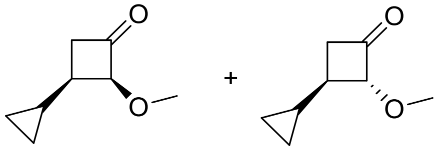
1f

Compound **1f** was prepared according to the procedure provided for compound **1c.**

1f: yellow oil (0.22 mg, 32%); R$_f$ 0.24 (30:70 EtOAc: hexane); IR (cast film) 3081, 3005, 2972, 2913, 2102, 1637, 1366, 1328, 1170, 1122, 1065 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.39 (br s, 1H), 3.80 (sep, *J* = 6.1 Hz, 1H), 3.24 (ddd, *J* = 8.1, 8.1, 4.8 Hz, 1H), 2.67-2.52 (m, 2H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.88 (ddddd, *J* = 5.1, 5.1, 8.2, 8.2, 8.2 Hz, 1H), 0.61 (dddd, *J* = 9.0, 8.1, 5.6, 4.4 Hz, 1H), 0.48 (dddd, *J* = 8.6, 8.6, 5.5, 4.6 Hz, 1H), 0.41 (ddd, *J* = 9.5, 9.5, 5.1 Hz, 1H), 0.19 (dddd, *J* = 9.7, 5.0, 5.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.5, 77.9, 69.8, 55.4, 47.8, 23.2, 22.2, 16.0, 4.5, 1.5; HRMS (ESI) calcd for $C_{10}H_{16}N_2NaO_2$ [M+ Na]$^+$ 219.1104; found 219.1098.

2.4 General procedure for Decomposition of Diazo Ketone 1c-f with Cu(hfacac)$_2$ to Generate Cyclobutanones 6c-f

To a refluxing solution of Cu catalyst (10 mol%) in CH$_2$Cl$_2$ (0.01M) was added the solution of diazo ketone **1c-f** (1 equiv.) in CH$_2$Cl$_2$ (0.1M) via syringe pump over 1 h. Consumption of staring diazo ketone was monitored by TLC and the reaction mixture was quenched by 10% solution of K$_2$CO$_3$. The organic layer was separated and the aqueous layer was washed with DCM (3×). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure and purified by flash chromatography.



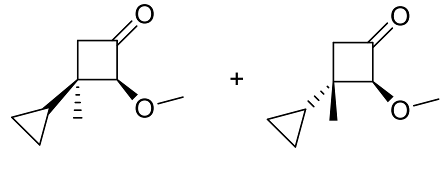
6c-cis **6c-trans**

6c-cis and **6c-trans** were isolated by flash chromatography (40:60 EtOAc: hexane) in 6:1 ratio (20 mg, 80%).

6c-cis: yellow oil; R$_f$ 0.60 (40:60 EtOAc: hexane); IR (cast film) 3081, 3003, 2952, 2834, 1787, 1436, 1268, 1214, 1344, 1214, 1165, 1145, 1020 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.46 (ddd, *J* = 8.8, 2.9, 2.9 Hz, 1H), 3.41 (s, 3H), 2.82 (ddd, *J* = 17.0, 2.9, 9.5 Hz, 1H), 2.31 (ddd, *J* = 17.0, 3.5, 2.7 Hz, 1H), 2.01 (dddd, *J* = 9.5, 9.5, 3.5 Hz, 1H), 0.73 (ddddd, *J* = 8.3, 8.3, 8.3, 5.0, 5.0 Hz, 1H), 0.58-0.53 (m, 1H), 0.42-0.36 (m, 1H), 0.13

(ddd, *J* = 9.5, 5.0, 5.0 Hz, 1H), 0.08 (ddd, *J* = 9.5, 5.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 89.6, 58.8, 44.6, 35.2, 9.7, 4.8, 2.1; HRMS (EI) calcd for $C_8H_{12}O_2$ $[M]^+$ 140.0837; found 140.0835.

6c-trans: yellow oil; R_f 0.65 (40:60 EtOAc: hexane); IR (cast film) 3082, 3004, 2953, 1786, 1437, 1267, 1267, 1192, 1166, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (ddd, *J* = 7.5, 2.6, 2.6 Hz, 1H), 3.46 (s, 3H), 2.69 (ddd, *J* = 16.8, 9.5, 2.6 Hz, 1H), 2.42 (ddd, *J* = 16.8, 9.5, 2.6 Hz, 1H), 2.01 (dddd, *J* = 9.5, 9.5, 7.5, 7.5 Hz, 1H), 1.03 (ddddd, *J* = 7.8, 7.8, 7.8, 5.0, 5.0, 5.0 Hz, 1H), 0.60-0.54 (m, 2H), 0.28-0.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 92.8, 58.0, 42.9, 36.6, 14.1, 3.6, 3.2; HRMS (EI) calcd for $C_8H_{12}O_2$ $[M]^+$ 140.0837; found 140.0835.

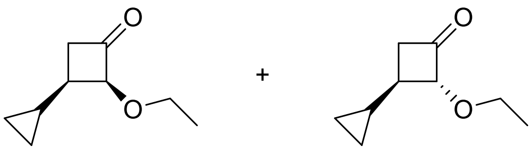


6d-cis **6d-trans**

Cyclobutanones **6d-cis** and **6d-trans** were isolated by flash chromatography (20:80 EtOAc: hexane) in 1.4:1 ratio (8.0 mg, 50%).

6d-cis: colorless oil; R_f 0.47 (20:80 EtOAc: hexane); IR (cast film) 3083, 3002, 2931, 1788, 1461, 1412, 1347, 1194, 1144, 1112, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (dd, *J* = 2.6, 2.6 Hz, 1H), 3.55 (s, 3H), 2.45 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.31 (dd, *J* = 16.8, 2.4 Hz, 1H), 1.43 (s, 3H), 0.97 (dddd, *J* = 8.4, 8.4, 5.5, 5.5 Hz, 1H), 0.50-0.43 (m, 1H), 0.49-0.43 (m, 1H), 0.29-0.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 95.0, 59.2, 48.1, 35.9, 26.0, 13.6, 0.7, 0.6; HRMS (EI) calcd for $C_9H_{13}O_2$ $[M\text{-}H]^+$ 14.0915; found 151.0916.

6d-trans: colorless oil; R_f 0.33 (20:80 EtOAc: hexane); IR (cast film) 3088, 3006, 2952, 2849, 1788, 1463, 1434, 1293, 1196 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (dd, *J* = 2.6, 2.6 Hz, 1H), 3.52 (s, 3H), 2.42 (dd, *J* = 16.3, 2.6 Hz, 1H), 2.14 (dd, *J* = 16.3, 2.6 Hz, 1H), 1.20 (dddd, *J* = 8.4, 8.4, 5.4, 5.4 Hz, 1H), 1.15 (s, 3H), 0.59-0.55 (m, 2H), 0.38-0.33 (m, 1H), 0.25-0.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 92.9, 59.0, 48.2, 36.1, 16.5, 19.0, 2.3, 1.7; HRMS (EI) calcd for $C_9H_{13}O_2$ $[M\text{-}H]^+$ 14.0915; found 151.0916.

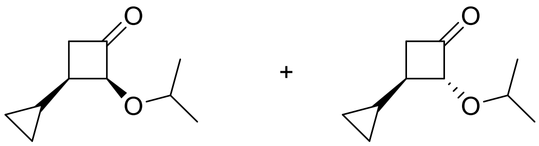


6e-cis **6e-trans**

6e-cis and **6e-trans** were isolated by flash chromatography (20:80 EtOAc: hexane) in 6:1 ratio (56 mg, 70%).

6e-cis: yellow oil; R_f 0.41 (20:80 EtOAc: hexane); IR (cast film) 3080, 3001, 2979, 2933, 2875, 1788, 1431, 1337, 1182, 1064 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 4.64 (ddd, *J* = 8.8, 2.7, 2.7 Hz, 1H), 3.69 (q, *J* = 7.0 Hz, 1H), 3.68 (q, *J* = 7.0 Hz, 1H), 2.90 (ddd, *J* = 17.1, 2.8, 9.7 Hz, 1H), 2.42 (ddd, *J* = 17.1, 3.1, 3.1, 1H), 2.10 (ddddd, *J* = 9.2, 9.2, 9.2, 3.6 Hz, 1H), 1.26 (t, *J* = 7.1, 3H), 0.86 (ddddd, *J* = 8.2, 8.2, 8.2, 5.2, 5.2 Hz, 1H), 0.69-0.54 (m, 1H), 0.53-0.47 (m, 1H), 0.25-0.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 88.3, 66.8, 44.5, 35.5, 15.1, 10.0, 4.9, 2.2; HRMS (EI) calcd for $C_9H_{14}O_2$ [M]+ 154.0994; found 154.0989.

6e-trans: yellow oil; R_f 0.50 (20:80 EtOAc: hexane); IR (cast film) 3080, 2979, 2929, 2874, 1786, 1444, 1398, 1334, 1212, 1177, 1122, 1052, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.33 (ddd, *J* = 7.7, 2.9, 2.9 Hz, 1H), 3.77 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.69 (dq, *J* = 9.3, 6.8 Hz, 1H), 2.73 (ddd, *J* = 17.0, 9.6, 2.7 Hz, 1H), 2.42 (ddd, *J* = 17.0, 9.5, 2.9 Hz, 1H), 2.08 (dddd, *J* = 9.7, 9.7, 7.2, 7.2 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (ddddd, *J* = 8.2, 8.2, 7.3, 5.0, 5.0 Hz, 1H), 0.63-0.58 (m, 2H), 0.34-0.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 91.7, 66.2, 42.7, 36.9, 15.3, 14.1, 3.6, 3.1; HRMS (EI) calcd for $C_9H_{14}O_2$ $[M]^+$ 154.0994; found 154.1002.



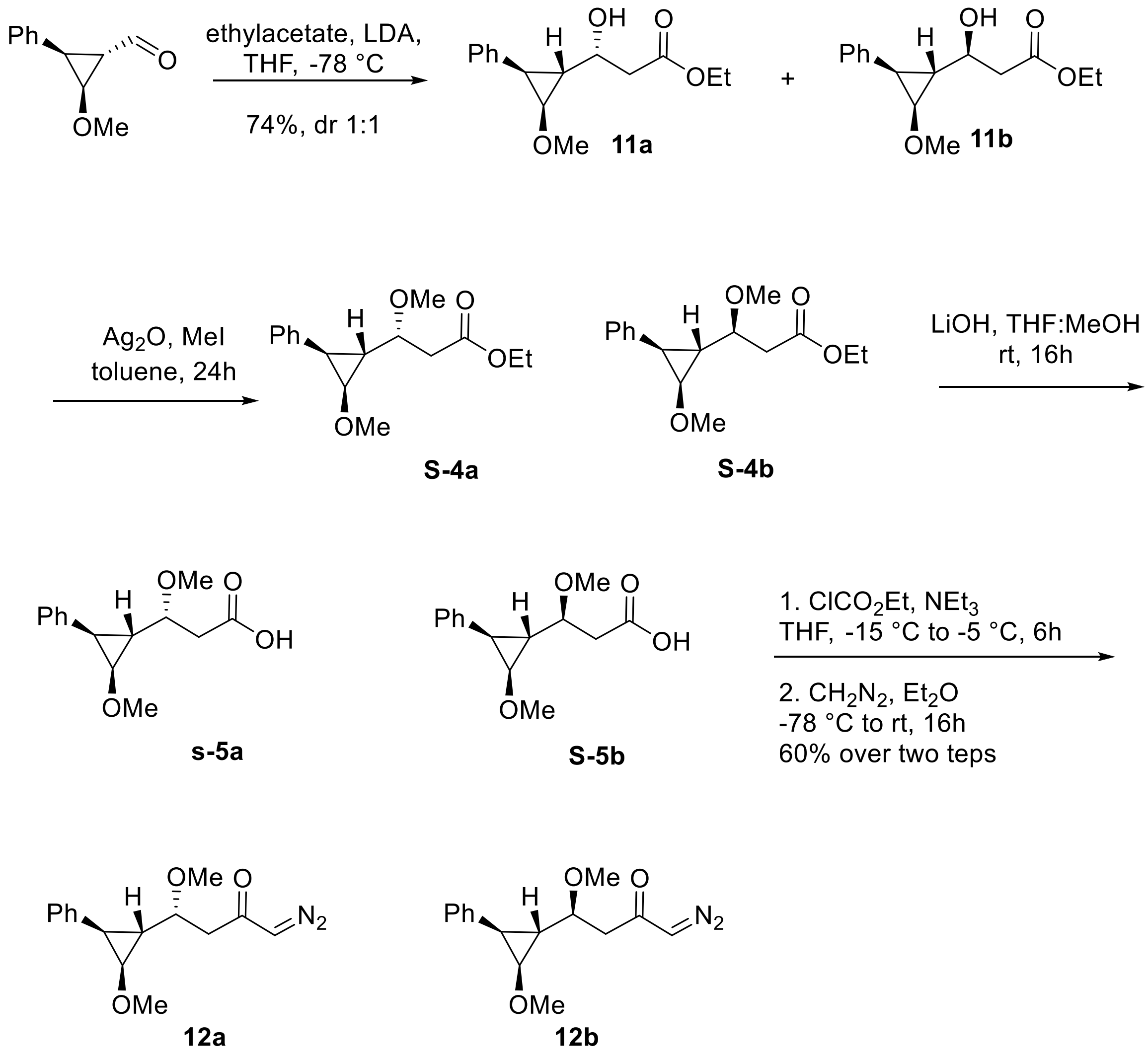
6f-cis **6f-trans**

6f-cis and **6f-trans** were isolated by flash chromatography (20:80 EtOAc: hexane) in 4.8:1 ration (0.12 g, 78%)

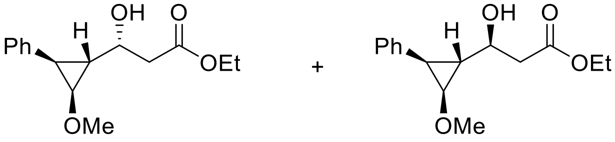
6f-cis: colorless oil; R_f 0.42 (20:80 E_2O: Pentane); IR (cast film) 3080, 2974, 2933, 2875, 1788, 1731, 1382, 1182, 1139, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.71 (ddd, *J* = 8.9, 2.7, 2.7 Hz, 1H), 3.77 (sep, *J* = 6.2 Hz, 1H), 2.90 (ddd, *J* = 17.1, 9.7, 2.9 Hz, 1H), 2.41 (ddd, *J* = 17.1, 3.5, 2.4 Hz, 1H), 2.10 (dddd, *J* = 8.9, 8.9, 8.9, 3.4 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 6H), 0.92-0.84 (m, 1H), 0.70-0.65 (m, 1H), 0.52-0.48 (m, 1H), 0.26-0.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 86.6, 72.6, 44.2, 35.8, 22.6, 21.8 10.2, 5.0, 2.2; HRMS (EI) calcd for $C_{10}H_{16}NaO_2$ $[M+Na]^+$ 191.1043; found 191.1038.

6f-trans: colorless oil; R_f 0.31 (20:80 E_2O: Pentane); IR (cast film) 3347, 3080, 2973, 2926, 2850, 1787, 1465, 1431, 1382, 1323, 1142, 1120, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.35 (ddd, *J* = 7.7, 2.6, 2.6 Hz, 1H), 3.84 (sep, *J* = 6.2 Hz, 1H), 2.90 (ddd, *J* = 17.0, 9.5, 2.5 Hz, 1H), 2.43 (ddd, *J* = 17.0, 9.7, 2.6 Hz, 1H), 2.05 (ddddd, *J* =9.8, 9.8, 9.8, 7.3, 7.3 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.13-1.07 (m, 1H), 0.62-0.57 (m, 2H), 0.35-0.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 90.1, 72.7, 42.4, 37.3, 22.5, 22.4, 13.9, 3.4, 2.9; HRMS (EI) calcd for $C_{10}H_{16}NaO_2$ $[M+Na]^+$ 191.1043; found 191.1038.

2.5 Procedure for the Formation of Esters 12a and 12b



A flame dried flask was charged with diisopropylamine (1.9 mL, 14 mmol) in THF (50 mL) and was cooled down to -78 °C. A solution of *n*-BuLi in hexane (2.5 M, 5.5 mL, 14 mmol) was added dropwise and the reaction was stirred for 15 min at – 78 °C. Ethyl acetate (1.2 mL, 13 mmol) was added dropwise with an additional 45 min stirring at -78 °C. Then a solution of 2-methoxy-3-phenyl carlopropanecarboxaldehyde[3] (2.2 g, 13 mmol) in THF (2.5 mL) was added to the reaction mixture. The reaction temperature was kept at -78 °C over 2 h and the reaction completion was monitored with TLC. Then the reaction was warmed to room temperature followed by the addition of saturated ammonium chloride (30 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The alcohols **11a** and **11b** were separated by flash chromatography (40:60 EtOAc: hexane) as two diastereomers in a 1:1 ratio (2.4 g, 74%).

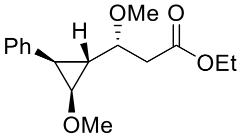


11a **11b**

11a: colorless oil; R_f 0.29 (40:60 EtOAc: hexane); IR (cast film) 3447, 3086, 3060, 3026, 2983, 2936, 2904, 2826, 1731, 1603, 1498, 1462, 1399, 1372, 1294, 1251, 1178, 1116, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 4.19 (dq, J_{AB} = 11.0 Hz, J_{AX} = 7.3 Hz, 1H), 4.15 (dq, J_{AB} = 11.0 Hz, J_{AX} = 7.3 Hz, 1H), 3.76 (dddd, J = 7.4, 7.4, 3.6, 3.6 Hz, 1H), 3.54 (dd, J = 6.8, 3.3 Hz, 1H), 3.21 (s, 3H), 3.14 (b, 1H), 2.68 (dd, J = 16.0, 3.9 Hz, 1H), 2.64 (dd, J = 16.0, 8.2 Hz, 1H), 2.06 (dd, J = 6.7, 6.7 Hz, 1H), 1.64 (ddd, J = 7.1, 7.1, 3.3 Hz, 1H), 1.27 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 136.7, 128.0 (2C), 125.9, 68.7, 63.6, 60.8, 58.2, 40.9, 31.4, 27.3, 14.1; HRMS (ESI) calcd for $C_{15}H_{20}NaO_4$ $[M+ Na]^+$ 287.1254; found 287.1255.

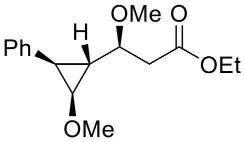
11b: light yellow oil; R_f 0.38 (40:60 EtOAc: hexane); IR (cast film) 3457, 3060, 2983, 2936, 2904, 2825, 1732, 1603, 1498, 1462, 1447, 1424, 1400, 1372, 1348, 1296, 1250, 1219, 1177, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 7.23-7.20 (m, 1H), 4.23-4.13 (m, 2H), 3.93 (ddd, J = 10.3, 7.8, 3.9 Hz, 1H), 3.46 (dd, J = 6.8, 3.3 Hz, 1H), 3.16 (s, 3H), 2.97 (d, J = 4.1 Hz, 1H), 2.72 (dd, J = 16.3, 3.9 Hz, 1H), 2.64 (dd, J = 16.3, 8.6 Hz, 1H), 2.20 (dd, J = 7.1, 7.1 Hz, 1H), 1.64 (ddd, J = 6.5, 6.5, 3.2 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 137.0, 128.0, 127.9, 125.8, 68.1, 63.1, 60.9, 58.1, 41.0, 31.4, 27.1, 14.1; HRMS (ESI) calcd for $C_{15}H_{20}NaO_4$ $[M+ Na]^+$ 287.1254; found 287.1255.

To a stirred solution of the corresponding alcohol **11** (1 equiv.) in dry toluene (0.50 M) was added anhydrous $CaSO_4$ (2 equiv.) and freshly prepared Ag_2O[2] (2 equiv.). The reaction mixture was cooled down to 0 °C and iodomethane (3 equiv.) was added dropwise. The ice bath was removed and the flask was covered in aluminum foil. The reaction mixture was stirred for 3 h at room temperature. Additional aliquots of Ag_2O, $CaSO_4$ and MeI (the same amount as before) were added and the reaction progress was monitored by TLC (Addition of excess Ag_2O, $CaSO_4$ and MeI may be required if the starting alcohol has not been consumed completely). The reaction mixture was stirred overnight and was filtered through Celite. The Celite was washed with ethyl acetate (2×) and the filtrate was concentrated under reduced pressure. The crude mixture was used in the next step without further purifications.



S-4a

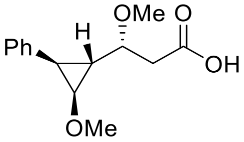
S-4a: Colorless oil (0.70 g, 92%); R_f 0.45 (50:50 EtOAc: hexane); IR (cast film) 3059, 2983, 2937, 2902, 2825, 1734, 1603, 1498, 1461, 1447, 1372, 1302, 1273, 1244, 1209, 1112, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 4.13 (dq, J_{AB} = 10.5 Hz, J_{AX} = 7.1 Hz, 1H), 4.09 (dq, J_{AB} = 10.5 Hz, J_{AX} = 7.1 Hz, 1H), 3.52 (dd, J = 6.7, 3.2 Hz, 1H), 3.51 (s, 3H), 3.39 (ddd, J = 7.9, 7.9, 5.3 Hz, 1H), 3.20 (s, 3H), 2.68 (dd, J = 14.9, 7.8 Hz, 1H), 2.56 (dd, J = 14.9, 5.4 Hz, 1H), 1.93 (dd, J = 6.6, 6.6 Hz, 1H), 1.63 (ddd, J = 6.7, 6.7, 3.4 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 136.6, 128.0, 127.9, 125.9, 78.4, 64.7, 60.6, 58.1, 57.4, 39.9, 29.8, 26.5, 14.1; HRMS (ESI) calcd for $C_{16}H_{22}NaO_4$ [M+ Na]$^+$ 301.1410; found 301.1407.



S-4b

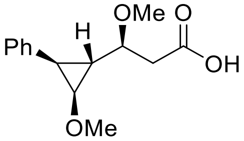
S-4b: Yellow oil (1.1 g, quant.); R_f 0.55 (40:60 EtOAc: hexane); IR (cast film) 3060, 2989, 2936, 2906, 2825, 1734, 1603, 1498, 1461, 1447, 1374, 1350, 1222, 1208, 1192, 1173, 1115, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 7.25-7.20 (m, 1H), 4.21 (dq, J_{AB} = 10.8 Hz, J_{AX} = 7.2 Hz, 1H), 4.17 (dq, J_{AB} = 10.8 Hz, J_{AX} = 7.3 Hz, 1H), 3.51 (ddd, J = 7.7, 7.7, 5.0 Hz, 1H), 3.40 (s, 3H), 3.38 (dd, J = 6.7, 3.4 Hz, 1H), 3.17 (s, 3H), 2.73 (dd, J = 15.2, 7.7 Hz, 1H), 2.64 (dd, J = 15.2, 5.3 Hz, 1H), 2.17 (dd, J = 6.9, 6.9 Hz, 1H), 1.62 (ddd, J = 7.7, 6.8, 3.3 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 136.7, 128.0, 127.9, 125.9, 78.1, 62.5, 60.6, 58.2, 57.3, 40.2, 29.8, 29.3, 14.2; HRMS (ESI) calcd for $C_{16}H_{22}NaO_4$ [M+ Na]$^+$ 301.1410; found 301.1412.

Corresponding ester **S-4** (1 equiv.) was dissolved in MeOH: THF (1:1, 0.26 M) and an aqueous solution of LiOH (2.0 M, 2.0 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature until the consumption of starting materials. An equal volume of water was added to the reaction and the organic layer was separated. The aqueous layer was acidified with 1.0 M HCl to pH = 1 followed by extraction with Et_2O (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The pure acid **S-5** was obtained and used in the next step without further purification



S-5a

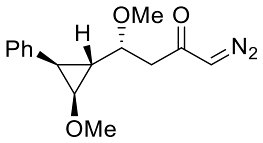
S-5a: yellow solid (0.63 g, quant.); mp: 68 - 70 °C; IR (cast film) 3087, 3060, 3026, 2987, 2937, 2826, 1730, 1710, 1603, 1498, 1447, 1424, 1348, 1224, 1178, 1111, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ7.34-7.21 (m, 5H), 3.54 (s, 3H), 3.41-3.37 (m, 1H), 3.40 (ddd, *J* = 4.9, 8.0, 8.0 Hz, 1H), 3.21 (s, 3H), 2.70 (dd, *J* = 15.5, 8.6 Hz, 1H), 2.63 (dd, *J* = 15.5, 4.3 Hz, 1H), 1.93 (dd, *J* = 6.6, 6.6 Hz, 1H), 1.64 (ddd, *J* = 8.0, 8.0, 3.3 Hz, 1H), (the peak corresponding to the carboxylic acid proton did not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 136.3, 128.1, 128.0, 126.0, 78.1, 68.8, 58.2, 57.4, 39.5, 29.5, 26.4; HRMS (ESI) calcd for $C_{14}H_{17}O_4$ [M-H]$^-$ 249.1132; found 249.1137.



S-5b

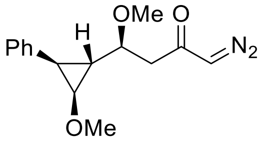
S-5b: white solid (0.50 mg, 54%); mp: 70-72 °C; IR (cast film) 3086, 3061, 3027, 2987, 2936, 2826, 1734, 1710, 1603, 1498, 1447, 1424, 1351, 1300, 1225, 1196, 1178, 1113, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H), 7.25-7.22 (m, 1H), 3.49-3.45 (m, 1H), 3.39 (s, 3H), 3.39 (dd, *J* = 6.7, 3.0 Hz, 1H), 3.19 (s, 3H), 2.81-2.72 (m, 2H), 2.19 (dd, *J* = 7.4, 7.4 Hz, 1H), 1.64 (ddd, *J* = 7.5, 3.1 Hz, 1H), (the peak corresponding to the carboxylic acid proton did not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 136.4, 128.1, 128.0, 126.0, 78.0, 62.4, 58.2, 57.3, 39.9, 29.7, 29.6; HRMS (ESI) calcd for $C_{14}H_{17}O_4$ [M- H]$^-$ 249.1132; found 249.1129.

To a solution of carboxylic acid **S-5** (1 equiv.) in dry THF (0.20 M) was added Et_3N (1.1 equiv.) followed by the addition of ethyl chloroformate solution (1.1 equiv.) in THF (1.2 M) at -15 °C. The reaction was stirred for 1 h at -15 °C and an additional 3 h stirring at -5 °C. After the formation of a white salt the reaction mixture, it was filtered and the filtrate was concentrated under reduced pressure. The residue was immediately dissolved in Et_2O and transferred to an ethereal solution of CH_2N_2 (~5 equivalents, prepared from Diazald®) at -78 °C. The reaction mixture was stirred overnight with gradual warming to the room temperature. The CH_2N_2 was quenched with excess glacial acetic acid and the reaction mixture was washed with water. The organic layer was separated and dried over $MgSO_4$ and filtered. The crude mixture was obtained after solvent removal and was purified by column chromatography to isolate diazo ketones **12** as a yellow oil.



12a

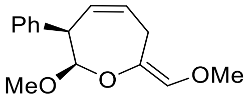
12a: yellow oil (0.19, 58%); R_f 0.17 (30:70 EtOAc: hexane); IR (cast film) 3088, 3026, 2984, 2936, 2825, 2102, 1635, 1603, 1498, 1424, 1447, 1353, 1228, 1179, 1151, 1105, 1032, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.11 (m, 5H), 5.28 (br s, 1H), 3.53 (ddd, *J* = 6.8, 6.8, 3.3 Hz, 1H), 3.51 (s, 3H), 3.41 (ddd, *J* = 8.2, 8.2, 4.9 Hz, 1H), 3.19 (s, 3H), 2.67-2.49 (br m, 2H), 1.89 (dd, *J* = 7.2, 7.2 Hz, 1H), 1.57 (ddd, *J* = 6.7, 6.7, 3.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 136.7, 128.0, 127.8, 125.9, 78.7, 65.2, 58.2, 57.5, 55.8, 45.9, 30.4, 26.5; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_3$ $[M+H]^+$ 275.1390; found 275.1385.



12b

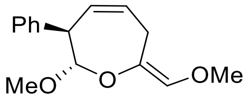
12b: yellow oil (80 mg, 73%); R_f 0.28 (40:60 EtOAc:hexane); IR (cast film) 3088, 2984, 2935, 2825, 2104, 1637, 1603, 1498, 1447, 1422, 1371, 1338, 1150, 1110, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 7.24-7.21 (m, 1H), 5.36 (br s, 1H), 3.50 (ddd, *J* = 7.6, 7.6, 4.4 Hz, 1H), 3.38 (s, 3H), 3.36 (ddd, *J* = 6.8, 6.8, 3.3 Hz, 1H), 3.16 (s, 3H), 2.70- 2.60 (br m, 2H), 2.16 (dd, *J* = 7.0, 7.0 Hz, 1H), 1.57 (ddd, *J* = 7.4, 7.4, 3.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 136.7, 128.1, 127.9, 126.0, 78.4, 62.5, 58.2, 57.4, 55.7, 46.2, 30.1, 29.7; HRMS (ESI) calcd for $C_{15}H_{18}N_2NaO_3$ $[M+Na]^+$ 297.1210; found 297.1204.

2.6 Procedure for the Treatment of Diazo Ketone 12a with Cu(hfacac)$_2$ to Generate Compounds 15a and 16a



15a

+



16a

To a solution of Cu(hfacac)$_2$ (18 mg, 0.036 mmol) in CH_2Cl_2 (3.6 mL, 0.010 M) at reflux was added a solution of diazo ketone **12a** (0.10 g, 0.36 mmol) in CH_2Cl_2 (3.6 mL, 0.10 M) via syringe pump over 2 h. Consumption of diazo ketone **12a** was monitored by TLC and the reaction mixture was quenched by 10% solution of aqueous K_2CO_3. The organic layer was separated and the aqueous layer was washed with DCM (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure and purified by flash chromatography. The obtained oxepines **15a** and **16a** were isolated in 1:1 ratio. (13 mg, 26%)

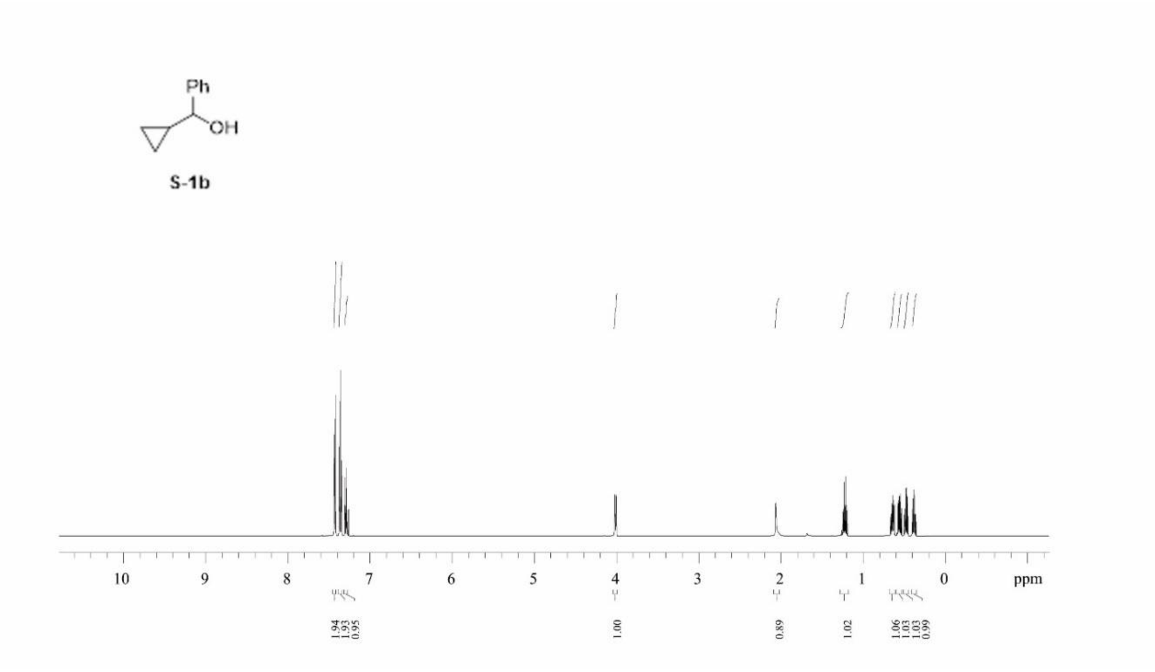
15a: colorless oil; R_f 0.59 (20:80 EtOAc: hexane); IR (cast film) 3060, 3026, 2993, 2931, 2898, 2833, 1689, 1655, 1602, 1492, 1543, 1417, 1361, 1349, 1246, 1221, 1154, 3311, 1110, 1072, 1036, 1003 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.31-7.28 (m, 4H), 7.25-7.22 (m, 1H), 6.06 (dd, *J* = 0.7, 0.7 Hz, 1H), 5.80 (dddd, *J* = 11.0, 5.4, 4.8, 2.4 Hz, 1H), 5.54 (dddd, *J* = 11.0, 4.0, 1.7, 0.6, 0.6 Hz, 1H), 4.84 (dd, *J* = 1.9, 0.6 Hz, 1H), 3.93 (dddd, *J* = 4.1, 4.1, 1.9, 1.9 Hz, 1H), 3.53 (s, 3H), 3.39 (s, 3H), 3.28 (ddddd, *J* = 17.5, 5.4, 1.8, 1.8, 0.7 Hz, 1H), 3.12 (ddddd, *J* = 17.5, 4.7, 2.2, 1.9, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 140.8, 138.3, 135.4, 129.7, 129.3, 128.0, 126.8, 126.7, 106.2, 59.8, 55.9, 50.7, 27.3; HRMS (ESI) calcd for $C_{15}H_{18}NaO_3$ [M+ Na]$^+$ 269.1148; found 269.1145.

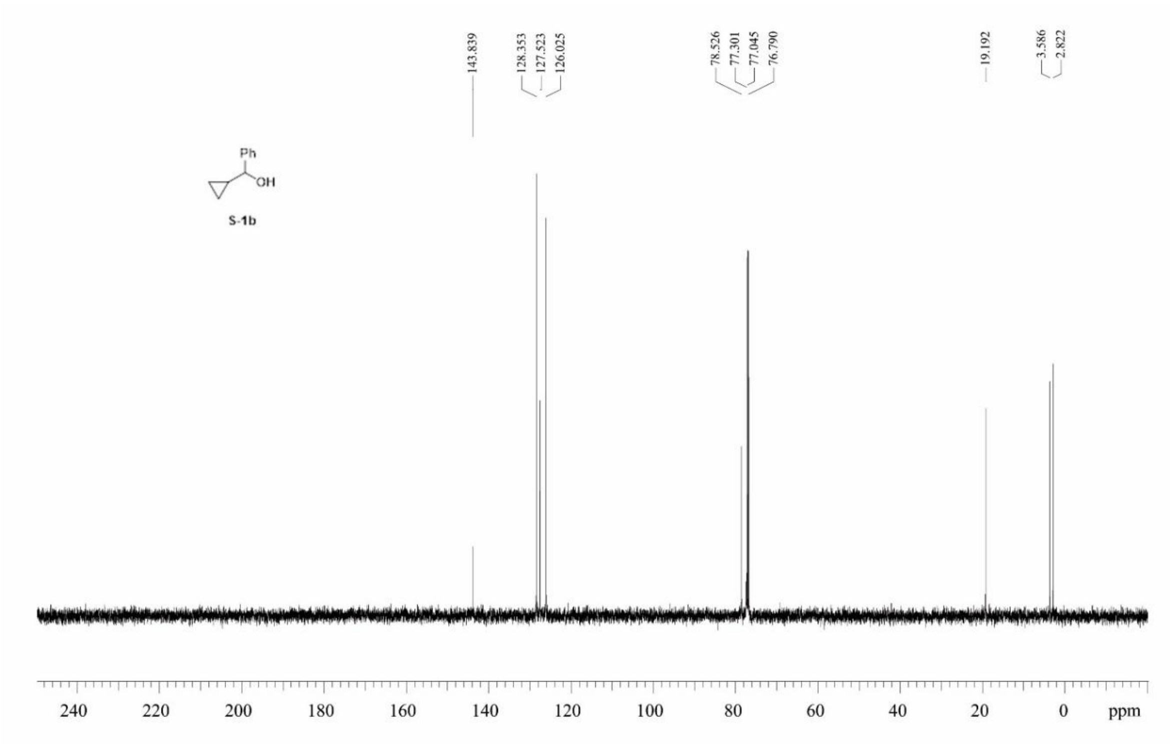
16a: colorless oil; R_f 0.55 (20:80 EtOAc: hexane); IR (cast film) 3085, 3061, 3028, 3001, 2931, 2834, 1696, 1654, 1599, 1494, 1453, 1357, 1251, 1211, 1170, 1130, 1035, 1009 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.32-7.29 (m, 2H), 7.25-7.22 (m, 3H), 6.05 (ddd, *J* = 2.1, 1.0, 0.5 Hz, 1H), 5.67 (ddddd, *J* = 11.1, 5.6, 3.7, 2.3, 0.5 Hz, 1H), 5.51 (dddd, *J* = 11.1, 4.5, 2.4, 1.6 Hz, 1H), 4.81 (d, *J* = 8.2 Hz, 1H), 3.92-3.88 (m, 1H), 3.57, (s, 3H), 3.34-3.29 (m, 1H), 3.31 (s, 3H), 3.07- 3.01 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 141.5, 137.6, 136.2, 129.9, 128.5, 128.3, 126.6, 126.5, 108.3, 59.8, 55.5, 50.1, 27.9; HRMS (ESI) calcd for $C_{15}H_{18}NaO_3$ [M+Na]$^+$ 269.1148; found 269.1145.

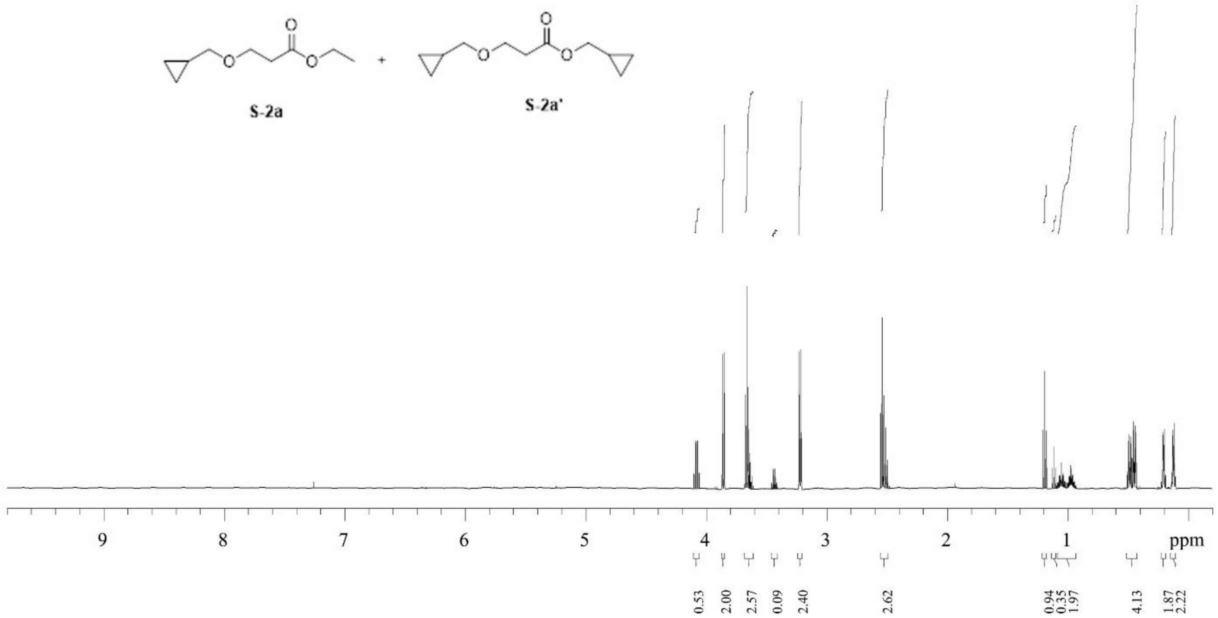
3. References

1. Diazald® and Diazomethane Generators, http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Bulletin/al_techbull_al180.pdf (accessed Sep 25, 2017).
2. A. Bouzide and G. Sauvé, *Tetrahedron Lett.* 1997, **38**, 5945–5948.
3. M. -H. Le Tadic-Biadatti and M. Newcomb, *J. Chem. Soc. Perkin Trans. 2*, 1996, **7**, 1467.

4. NMR Spectra







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O
O
+
O
O
O
S-2a
S-2a'
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8
7
6
5
4
3
2
1
ppm
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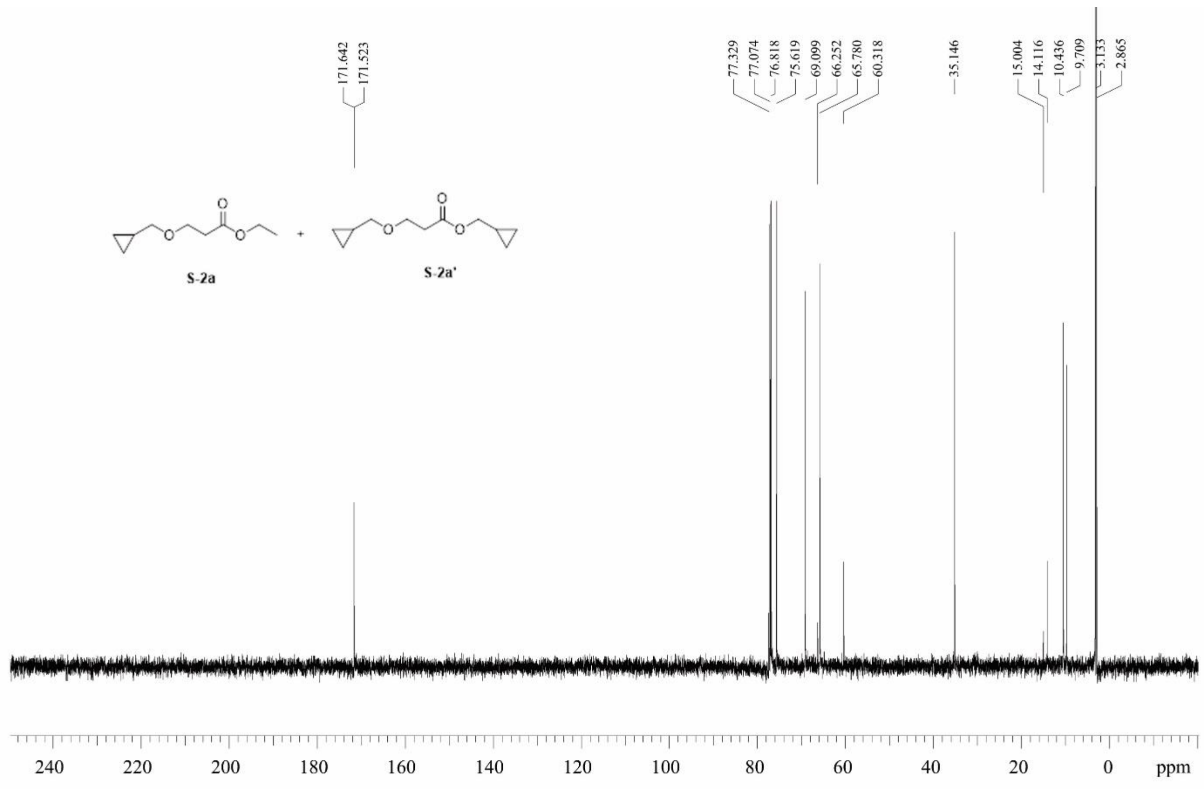
2.62
0.94
0.35
1.97
4.13
1.87
2.22



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75.619
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66.252
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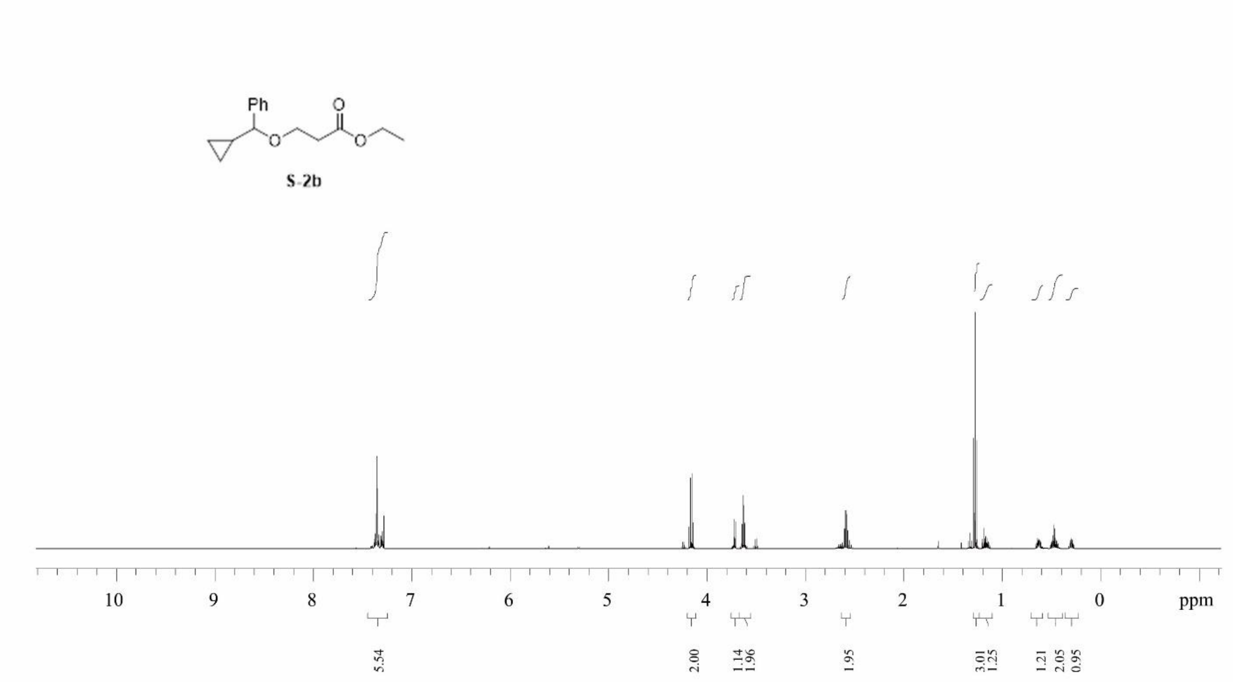
60.318
35.146
15.004
14.116
10.436
9.709
3.133
2.865
O
O
O
+
O
O
O
S-2a
S-2a'
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm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8
7
6
5
4
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3.01
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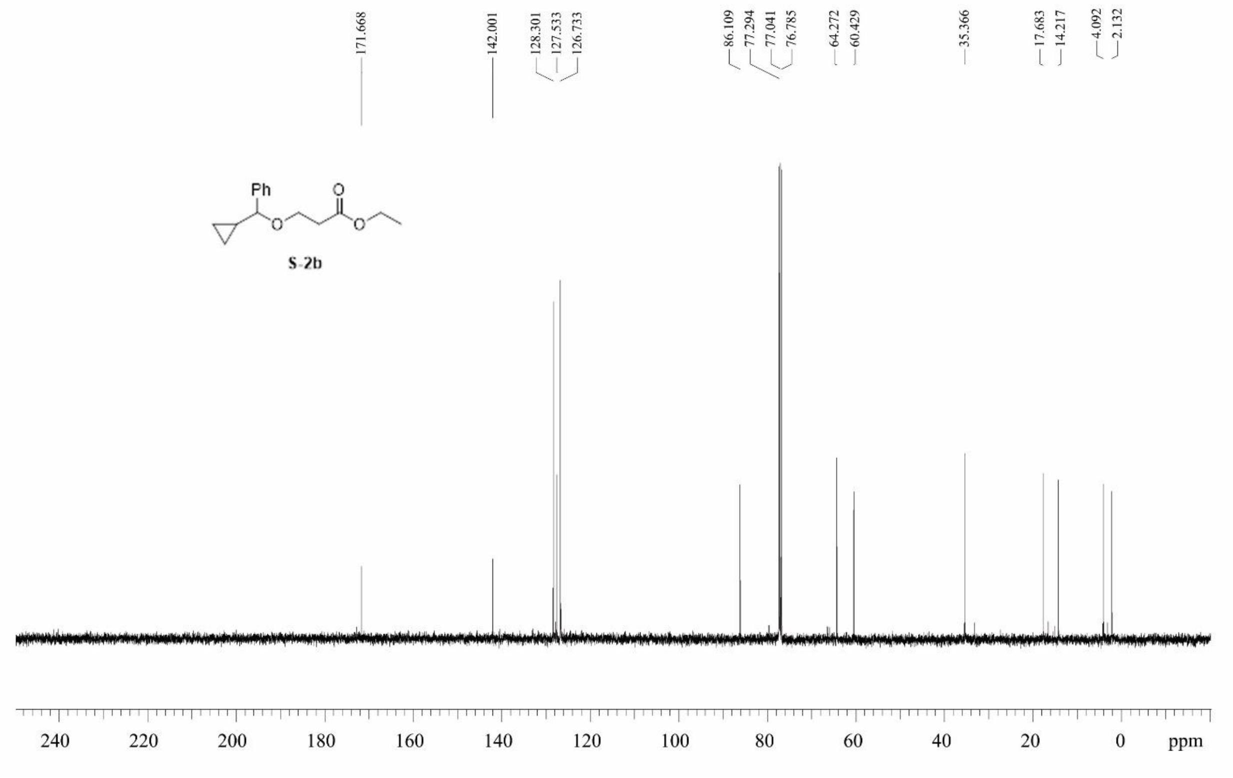
0.95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77.041
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17.683
14.217
4.092
2.132
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60
40
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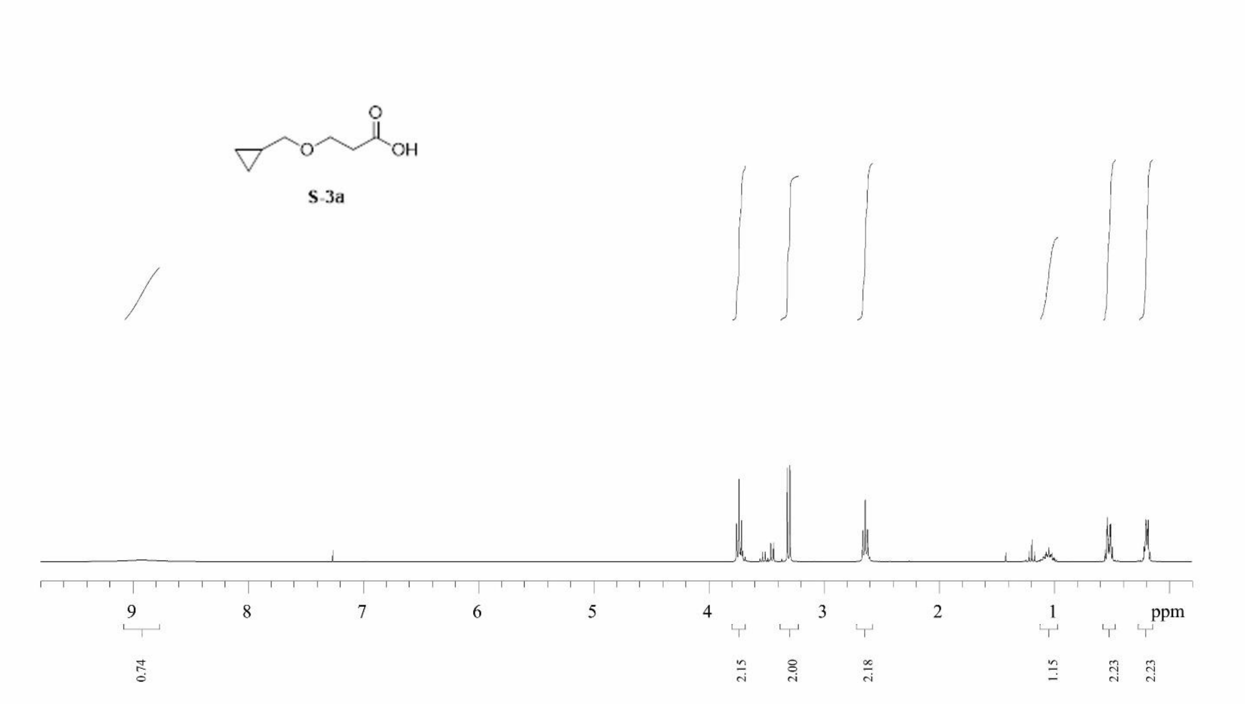
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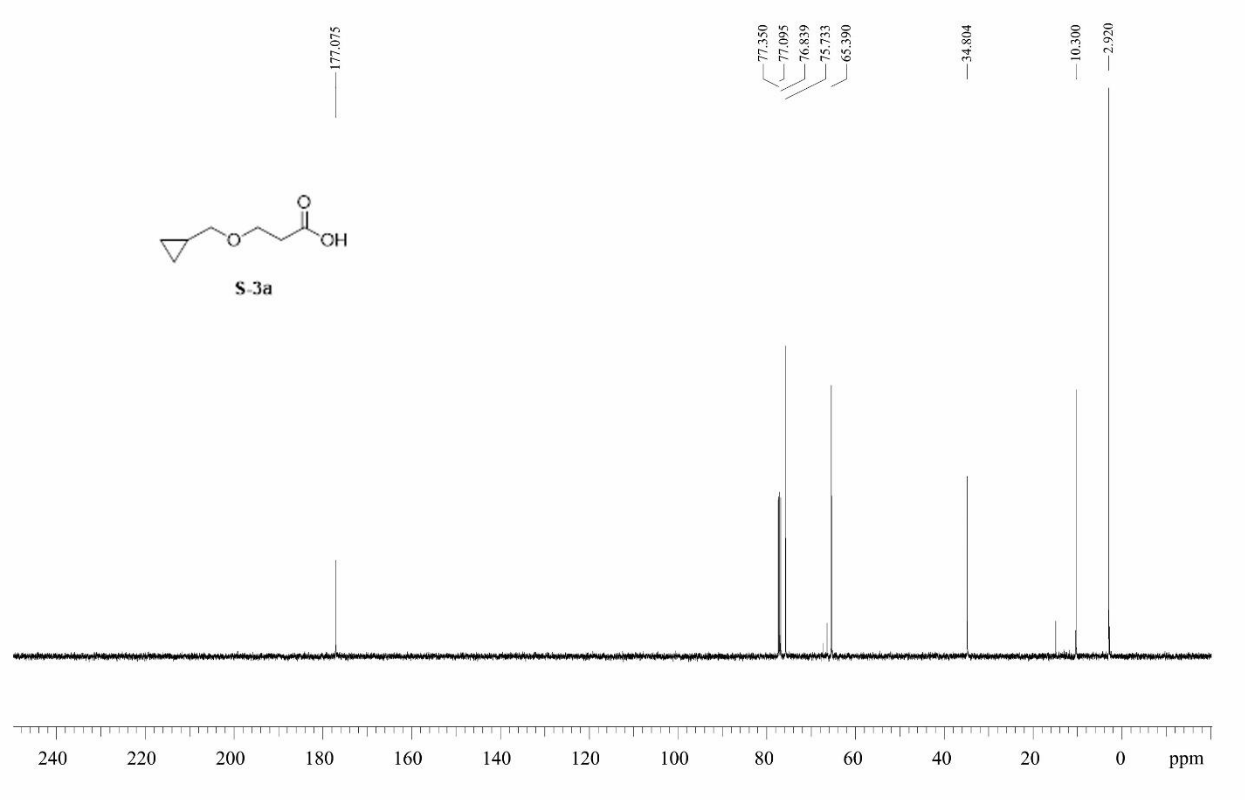
1.15
2.23
2.23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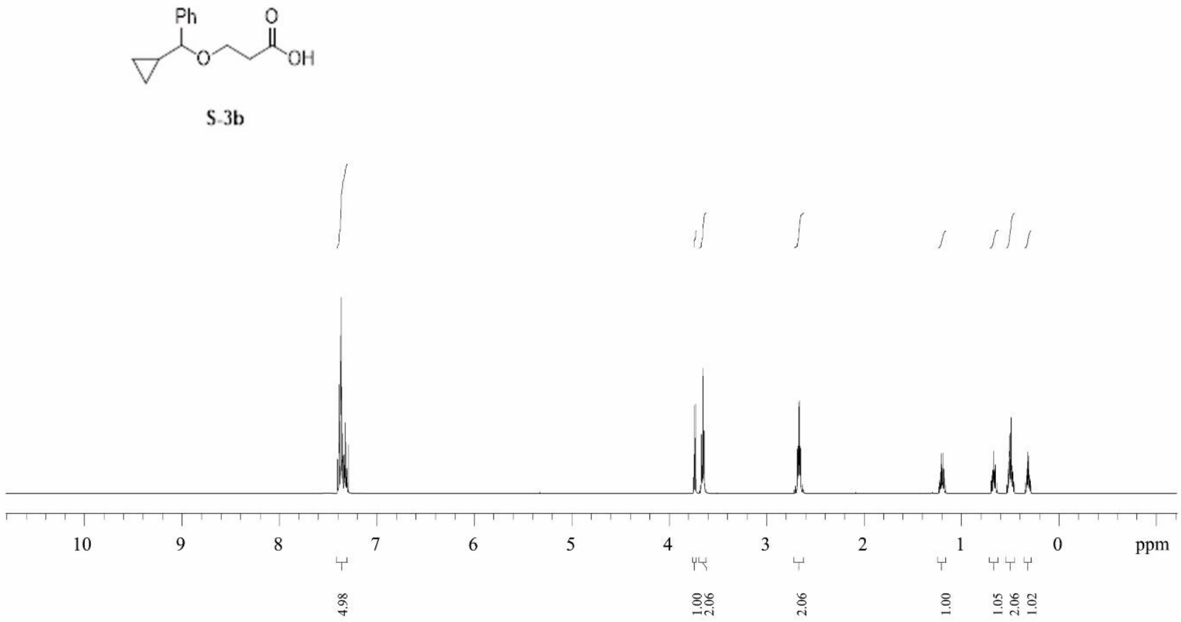
40
20
0
ppm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6
5
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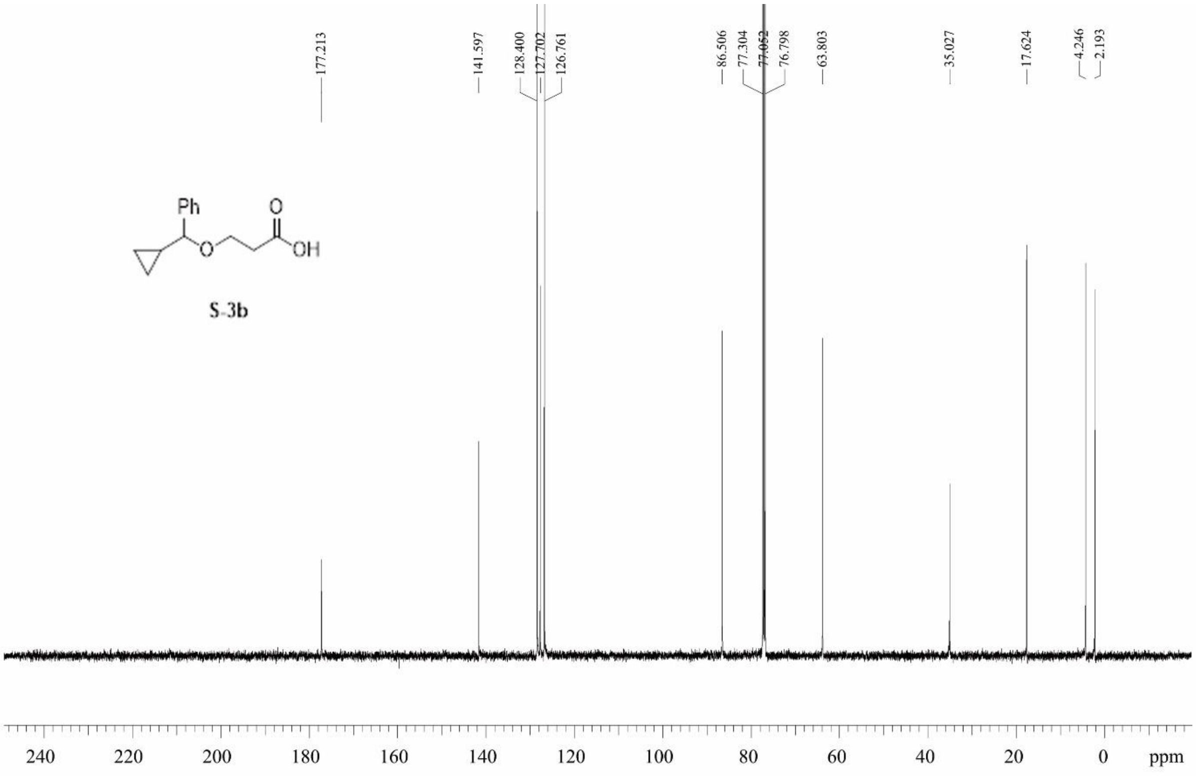
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2.193
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120
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40
20
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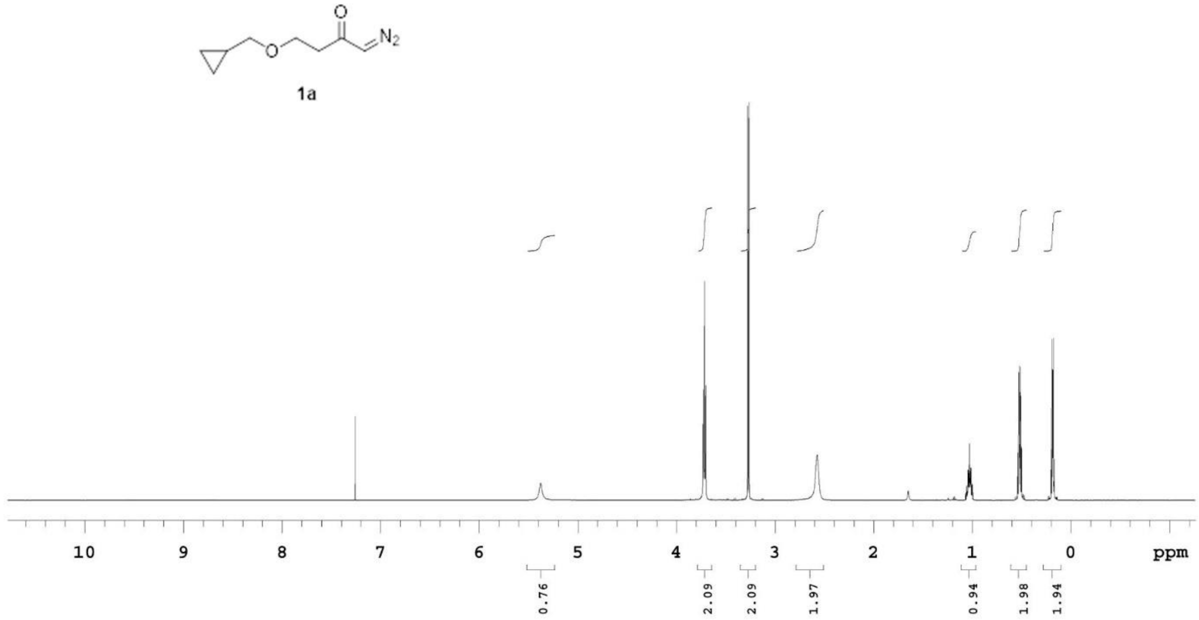
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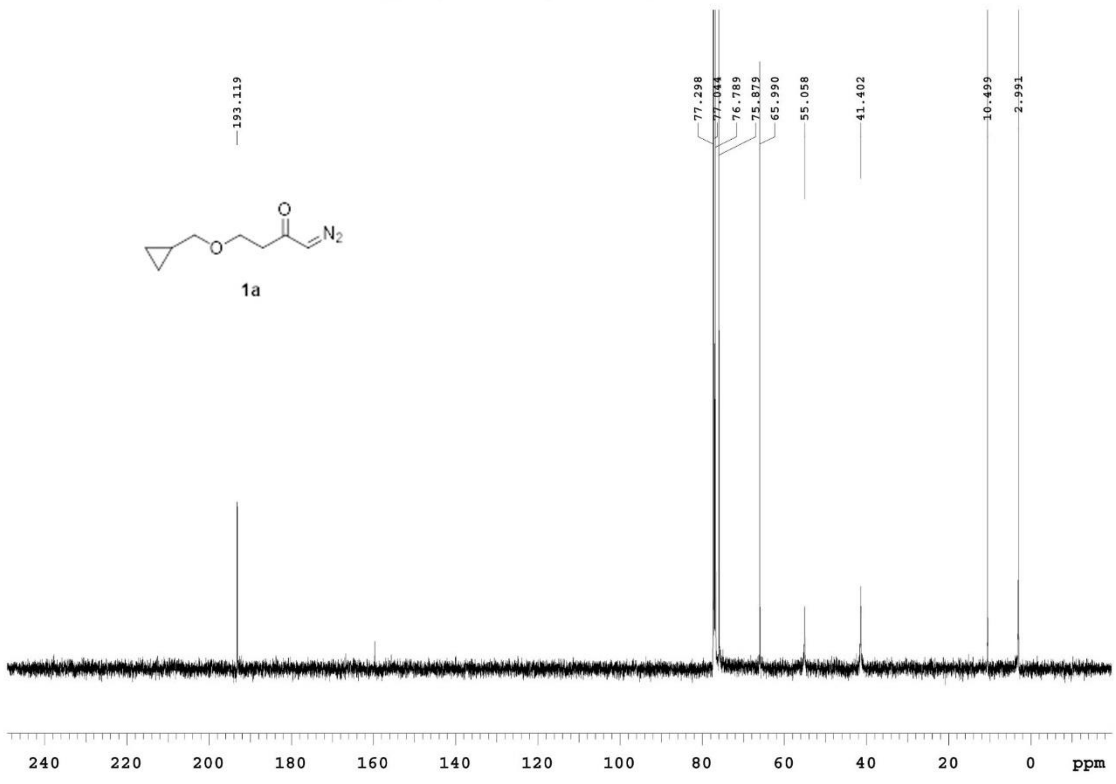
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41.402
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60
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20
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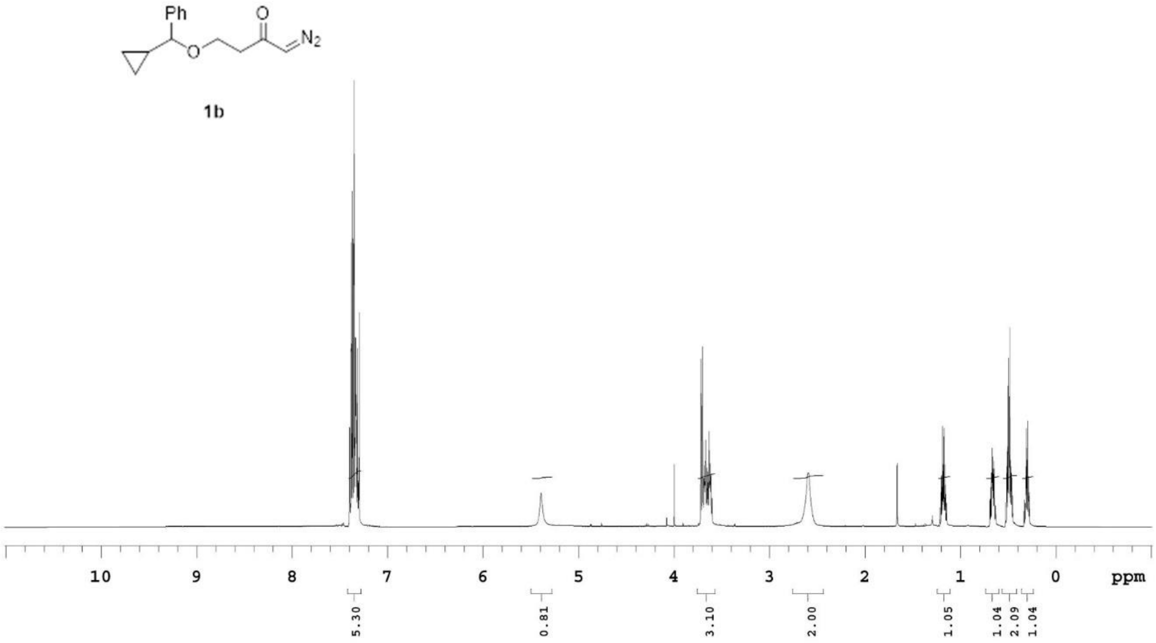

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7
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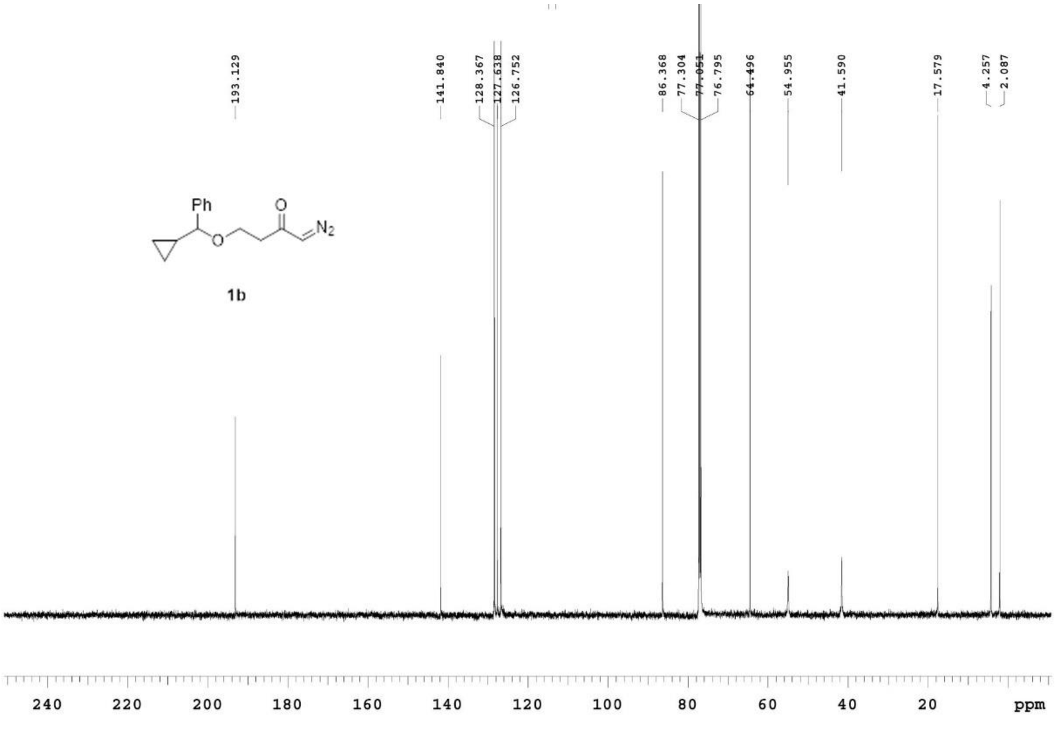
1.04



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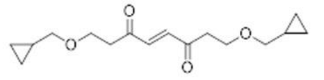
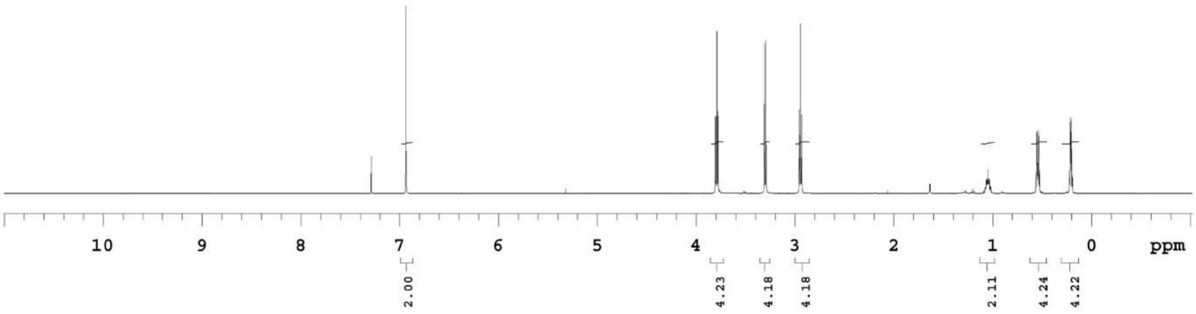
ppm



8a-isomer E



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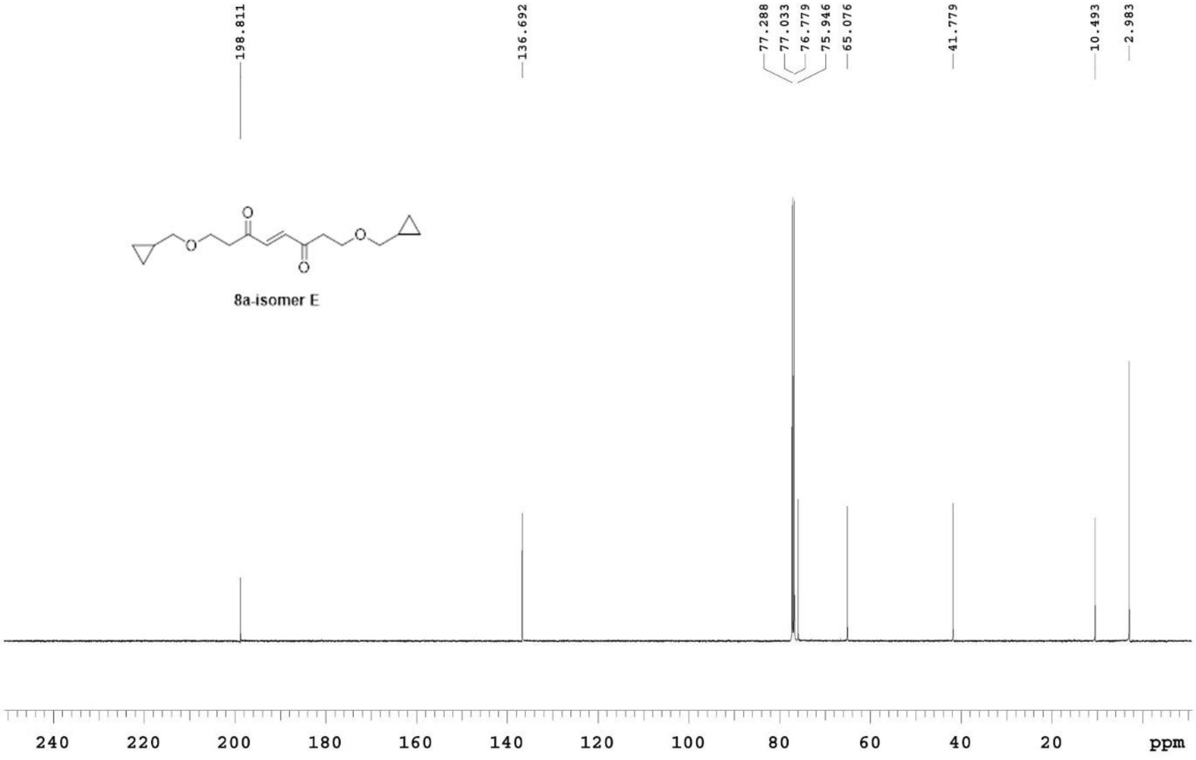
4.24
4.22



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41.779
10.493
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8a-isomer E
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200
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160
140
120
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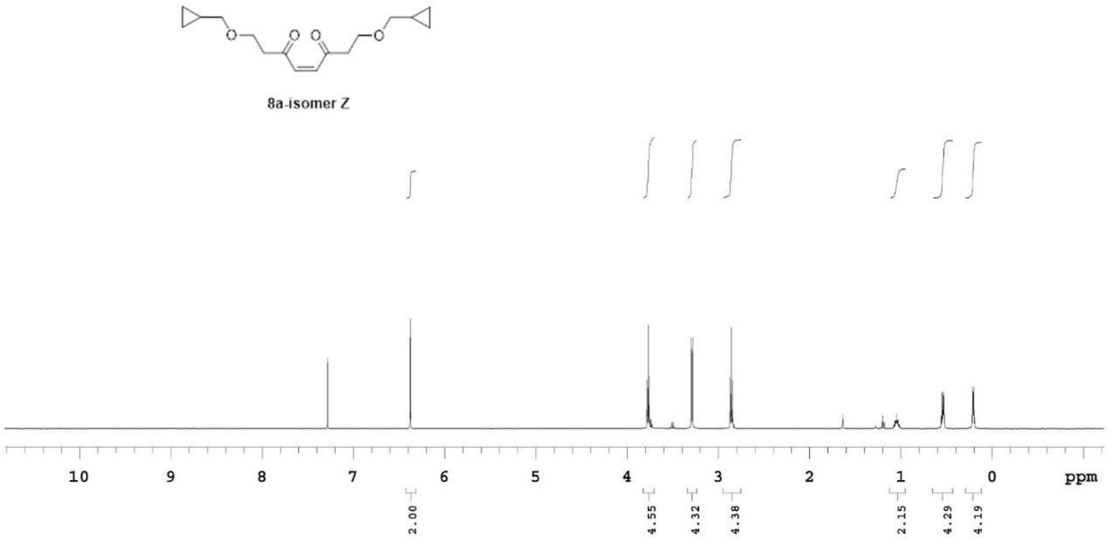
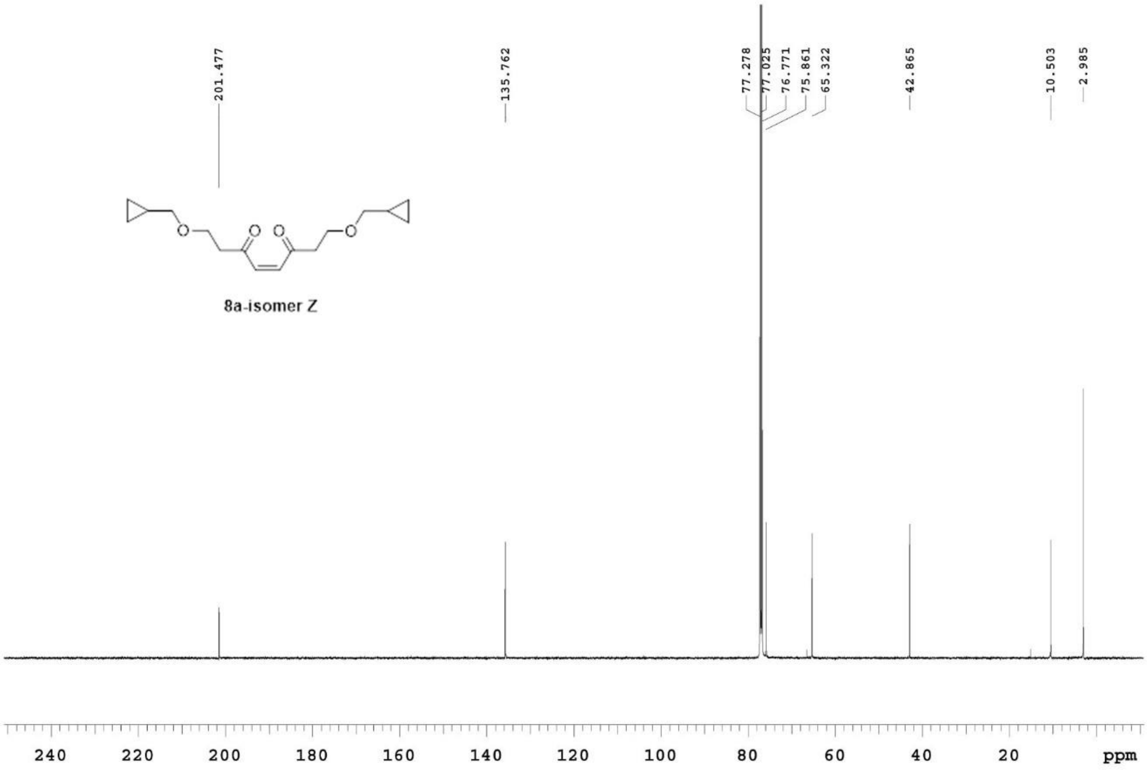
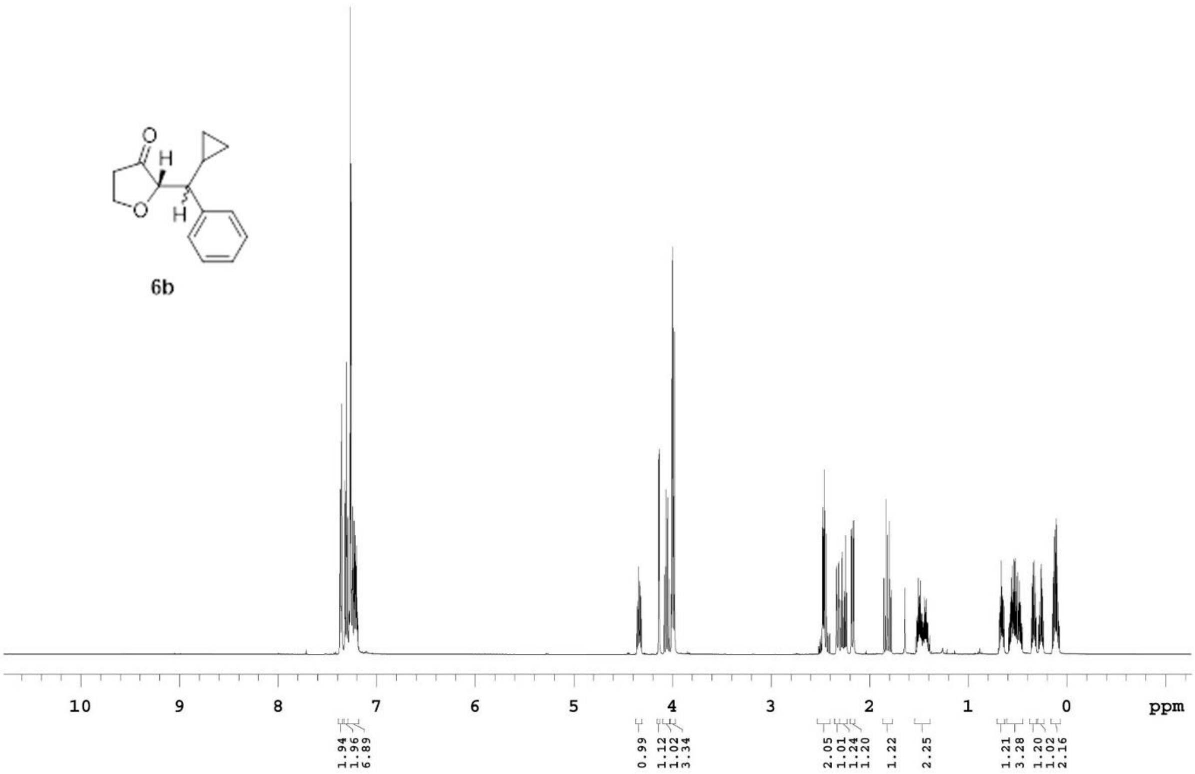
80
60
40
20
ppm


8a-isomer Z


8a-isomer Z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1.02
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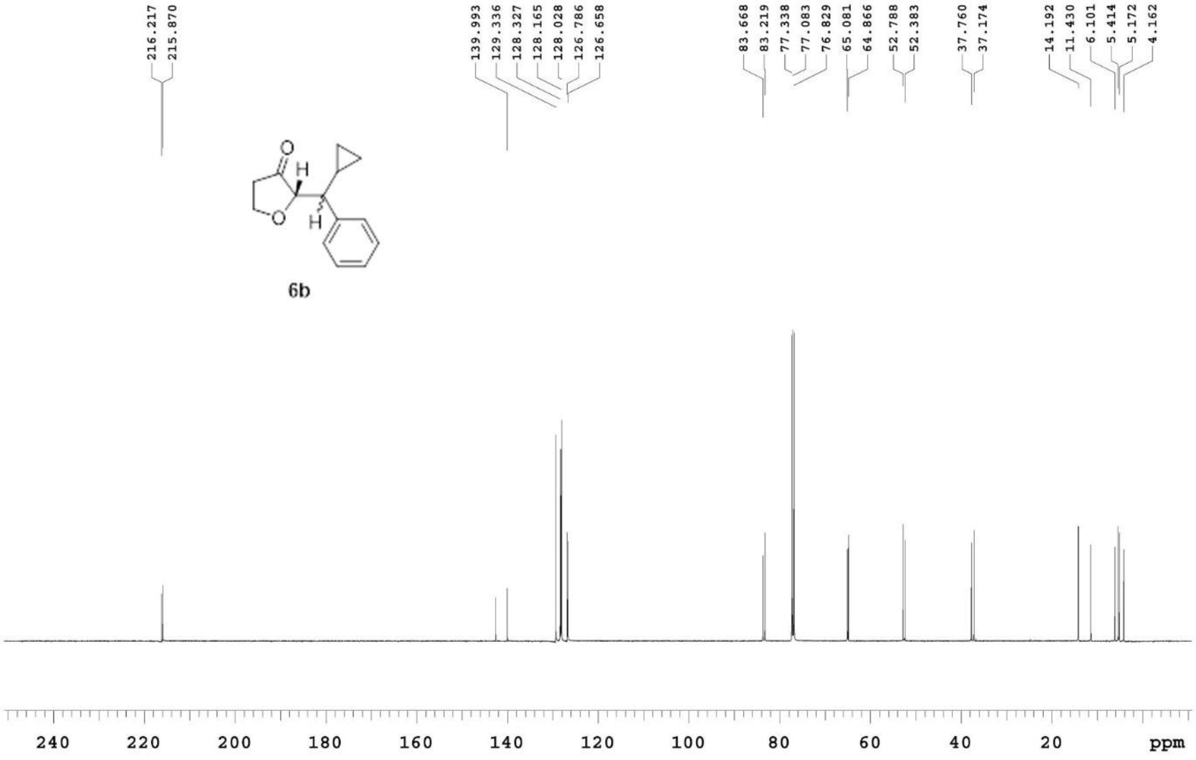
2.16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76.829
65.081
64.866
52.788
52.383
37.760
37.174
14.192
11.430
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80
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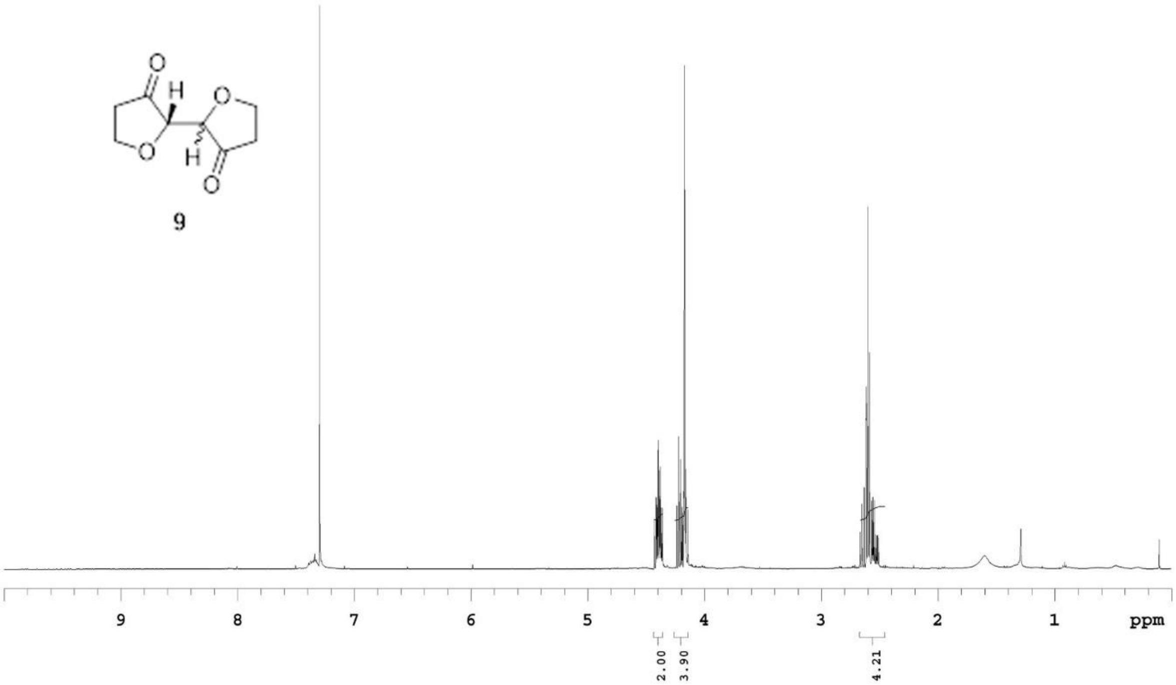
40
20
ppm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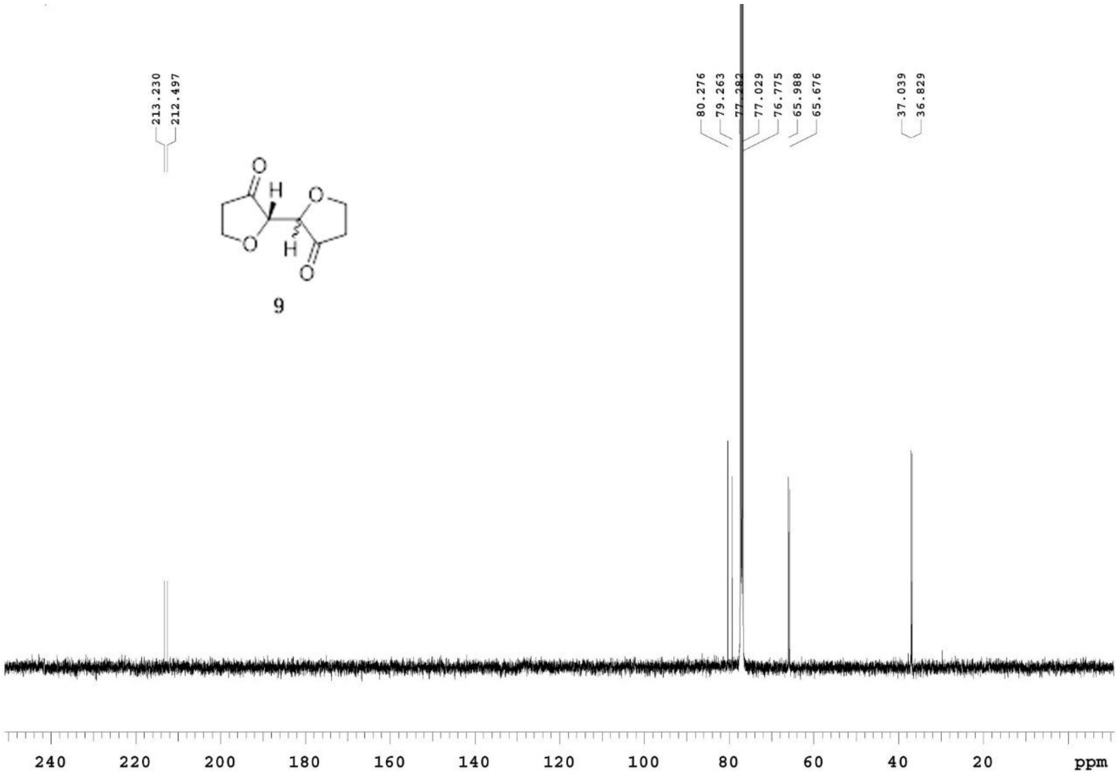
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140
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80
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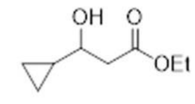
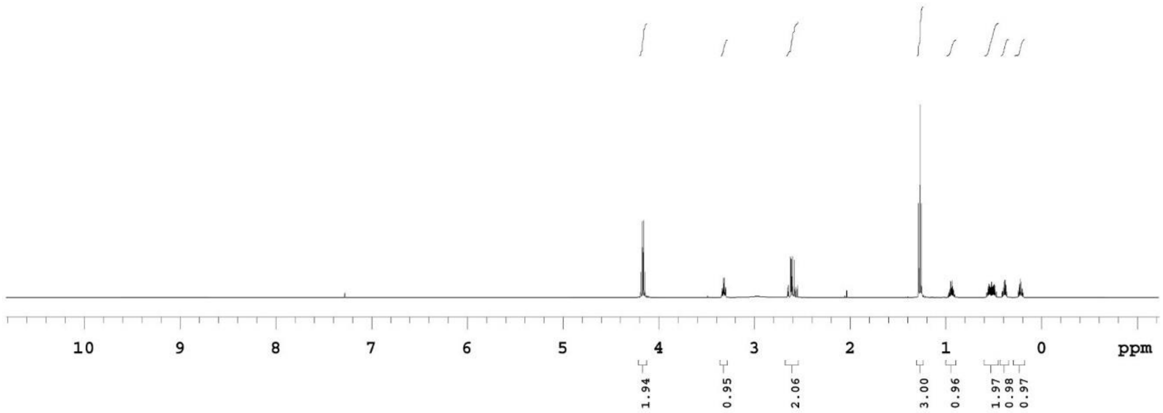
40
20
ppm



OH
O
OEt

S-1c



10
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8
7
6
5
4
3
2
1
0
ppm
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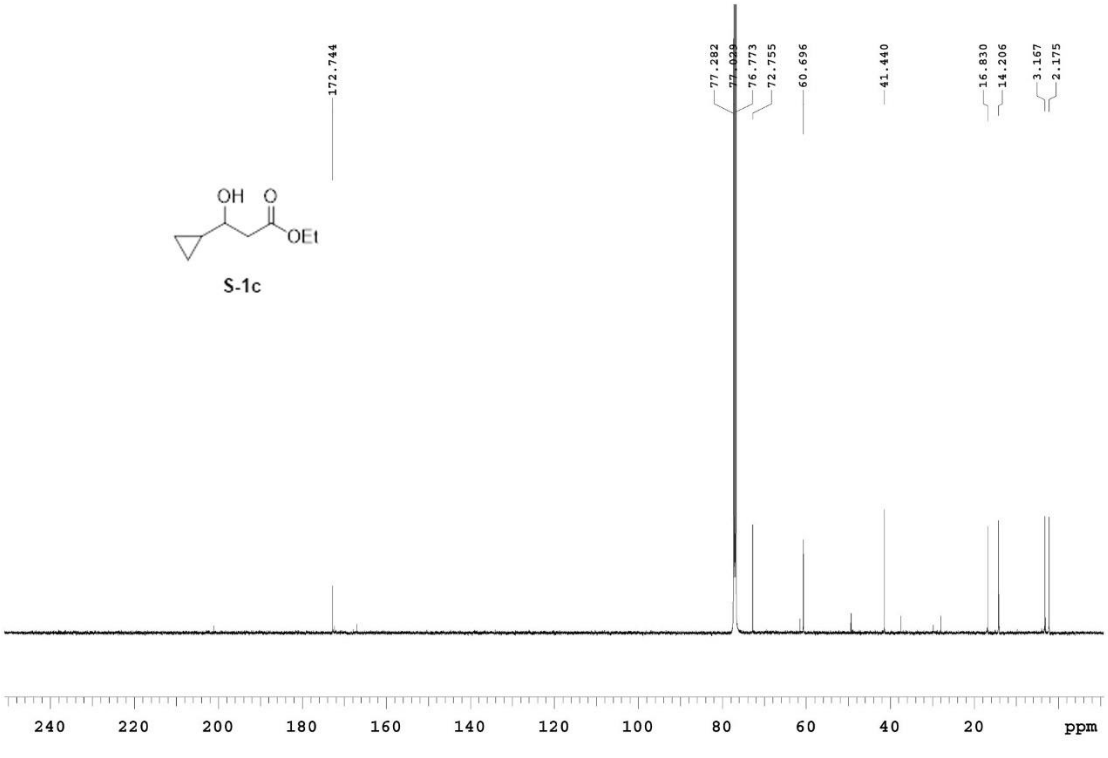
OH
O
OEt

S-1c



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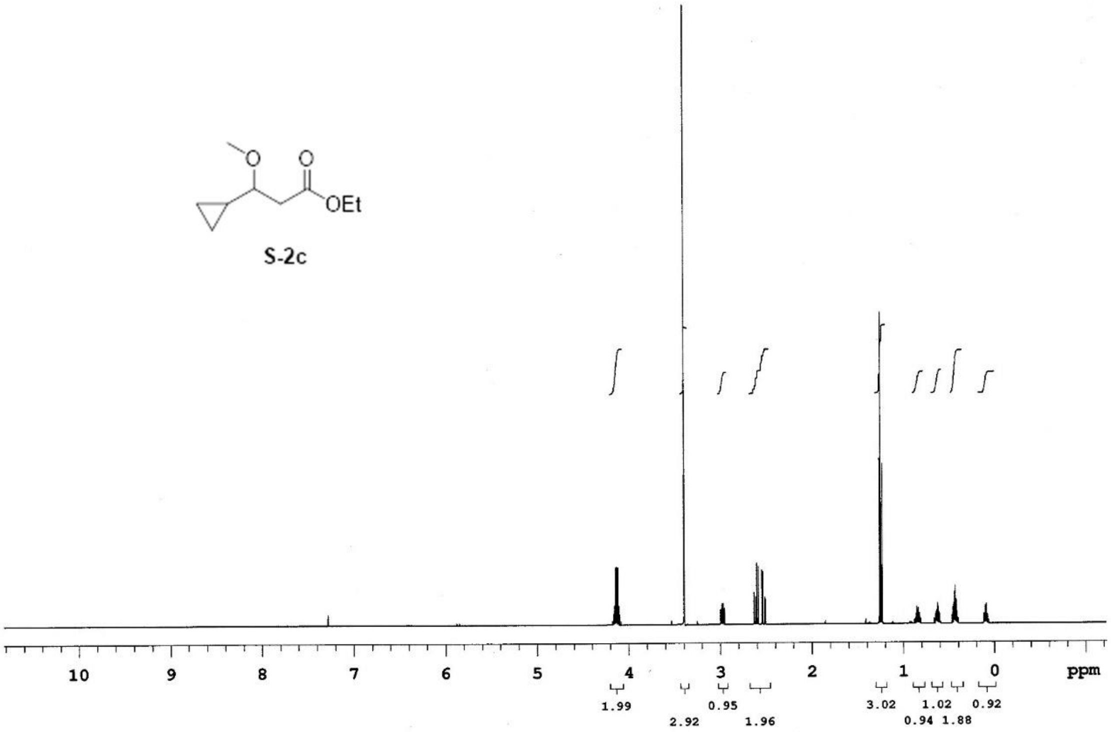
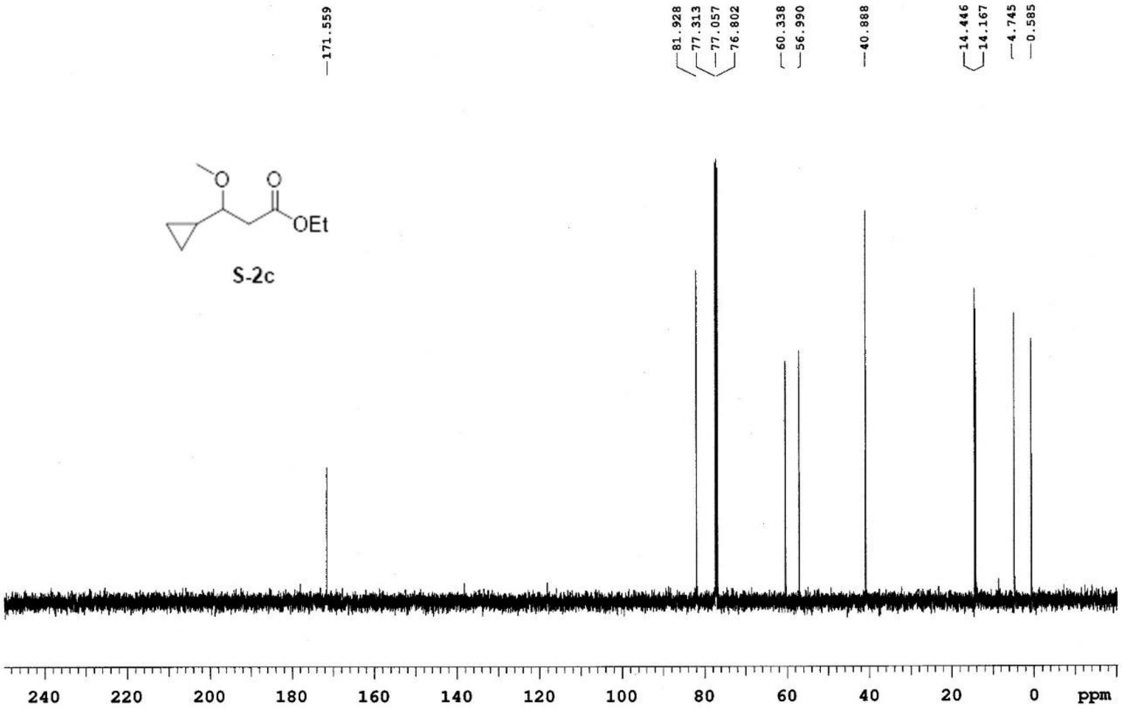
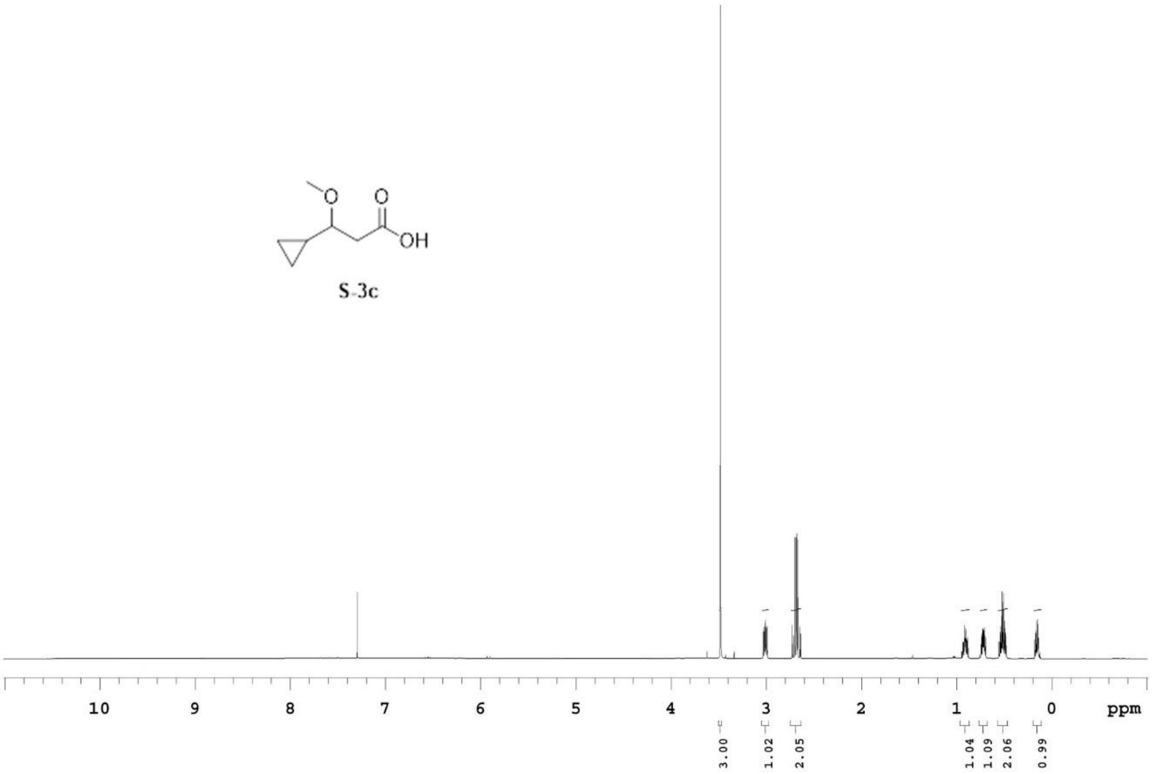
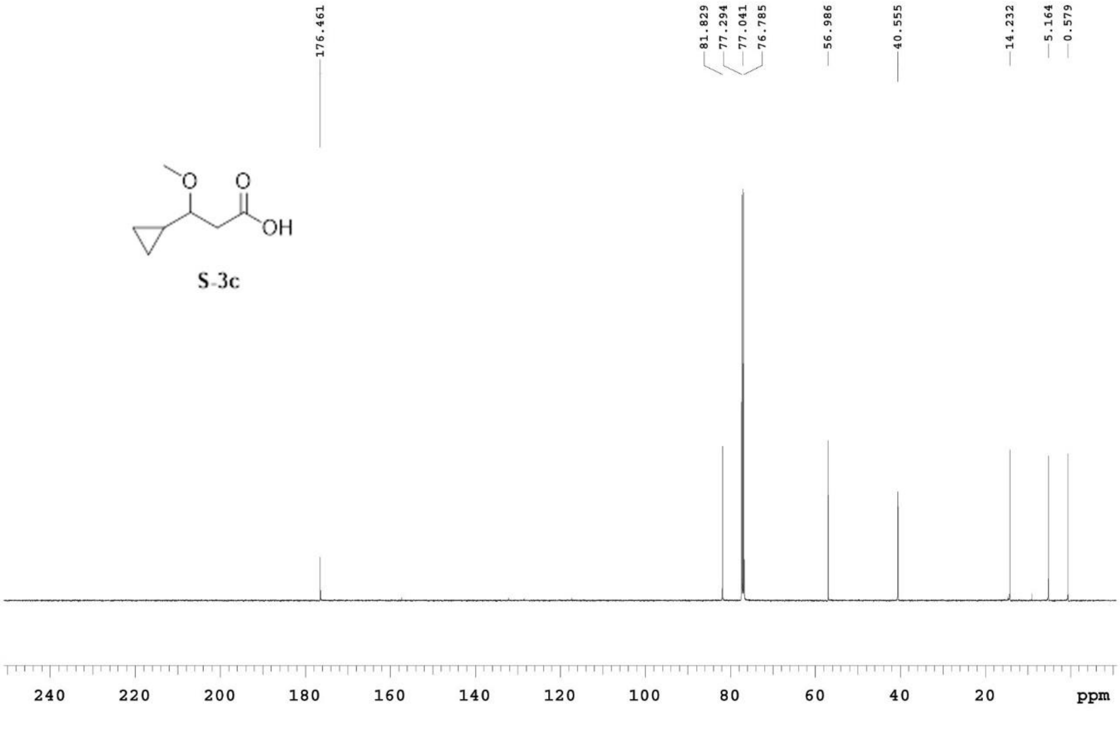
160
140
120
100
80
60
40
20
ppm


S-2c
OEt
1.99
2.92
0.95
1.96
3.02
0.94
1.02
1.88
0.92
10
9
8
7
6
5
4
3
2
1
0
ppm

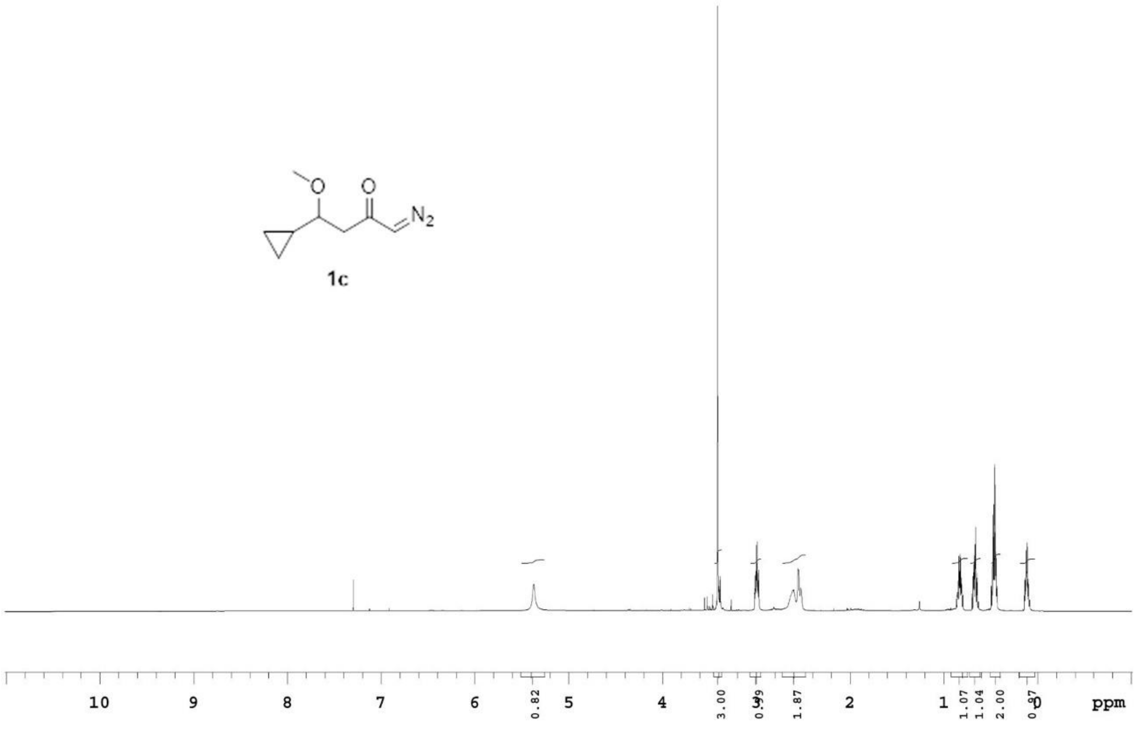

S-2c
171.559
81.928
77.313
77.057
76.802
60.338
56.990
40.888
14.446
14.167
4.745
0.585
OEt
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

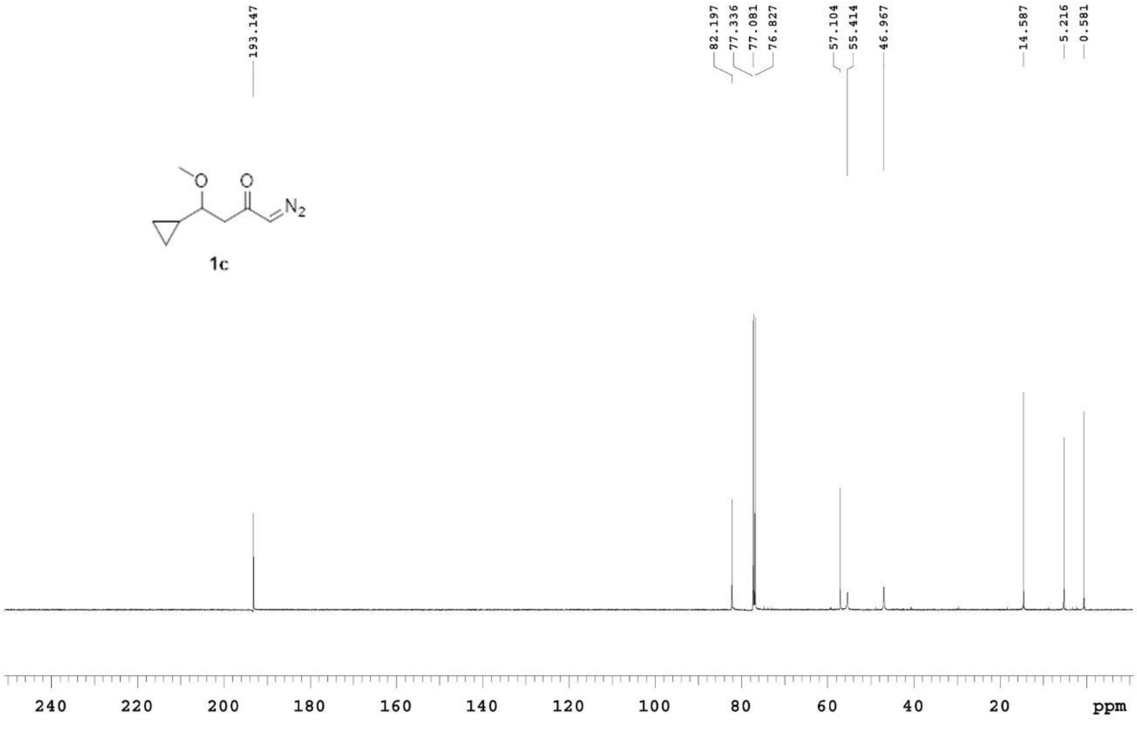


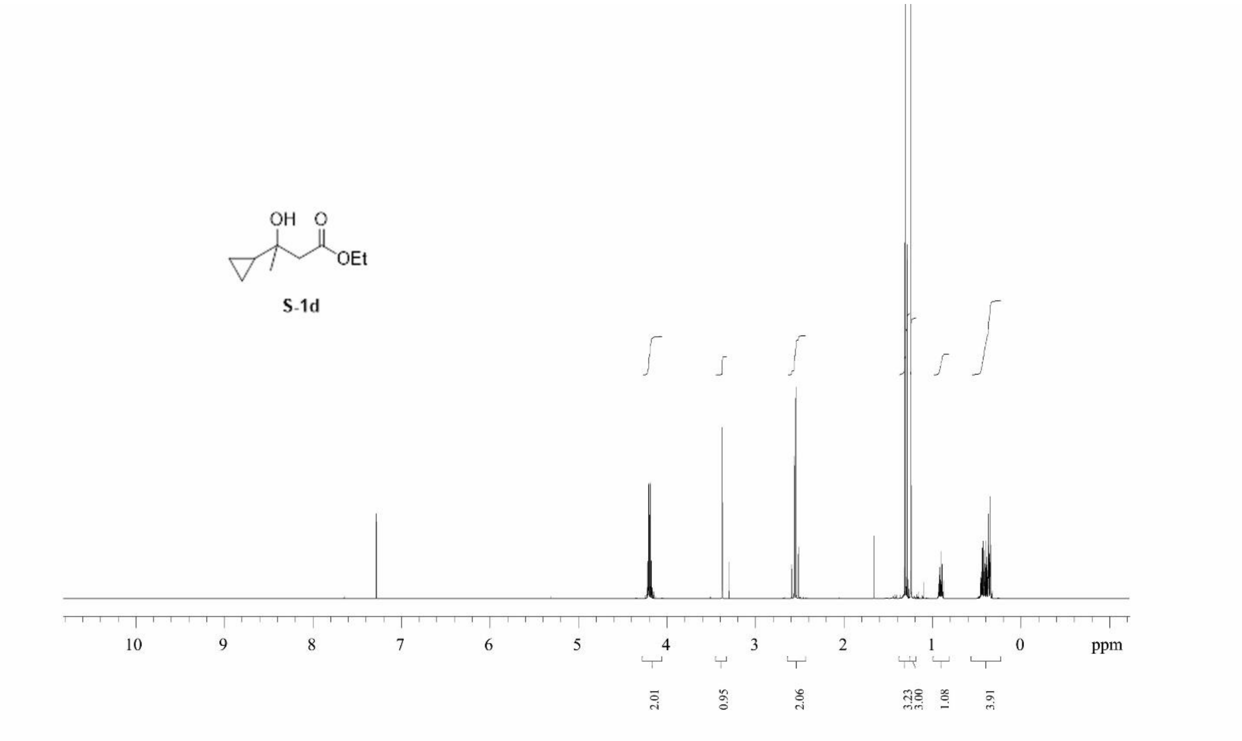
O
O
OH
S-3c
3.00
1.02
2.05
1.04
1.09
2.06
0.99
10
9
8
7
6
5
4
3
2
1
0
ppm

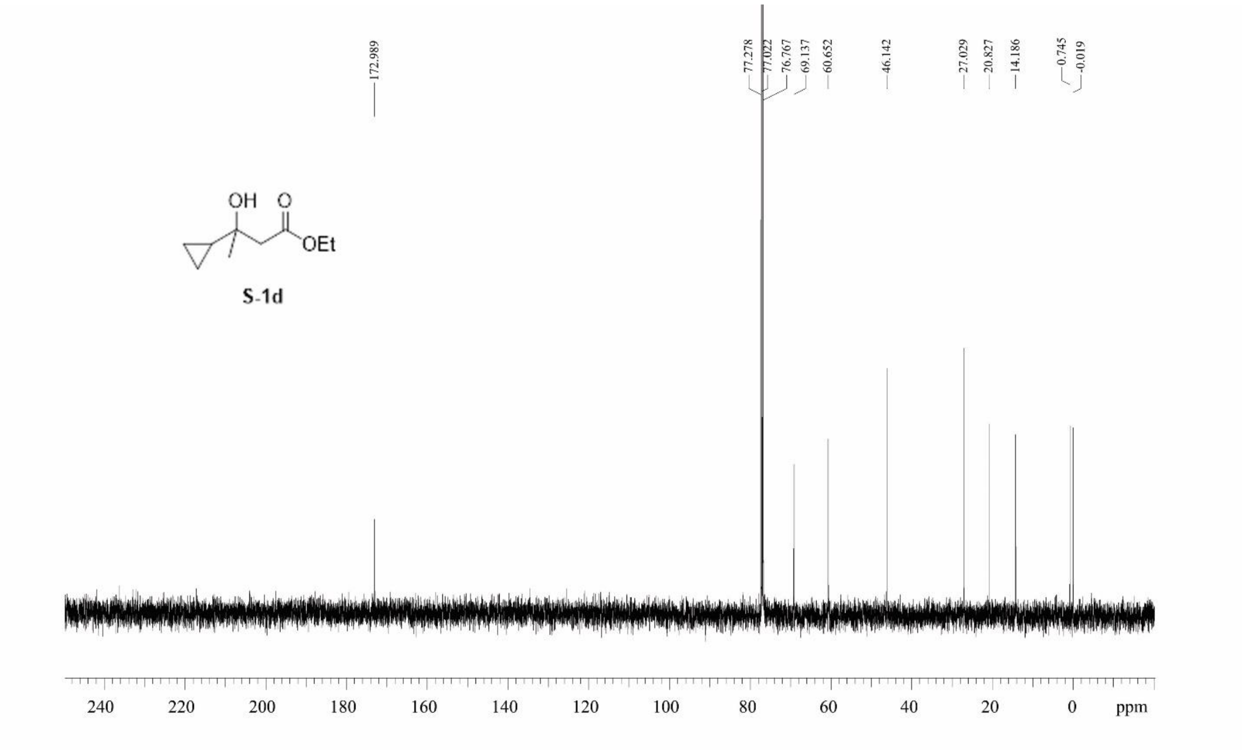


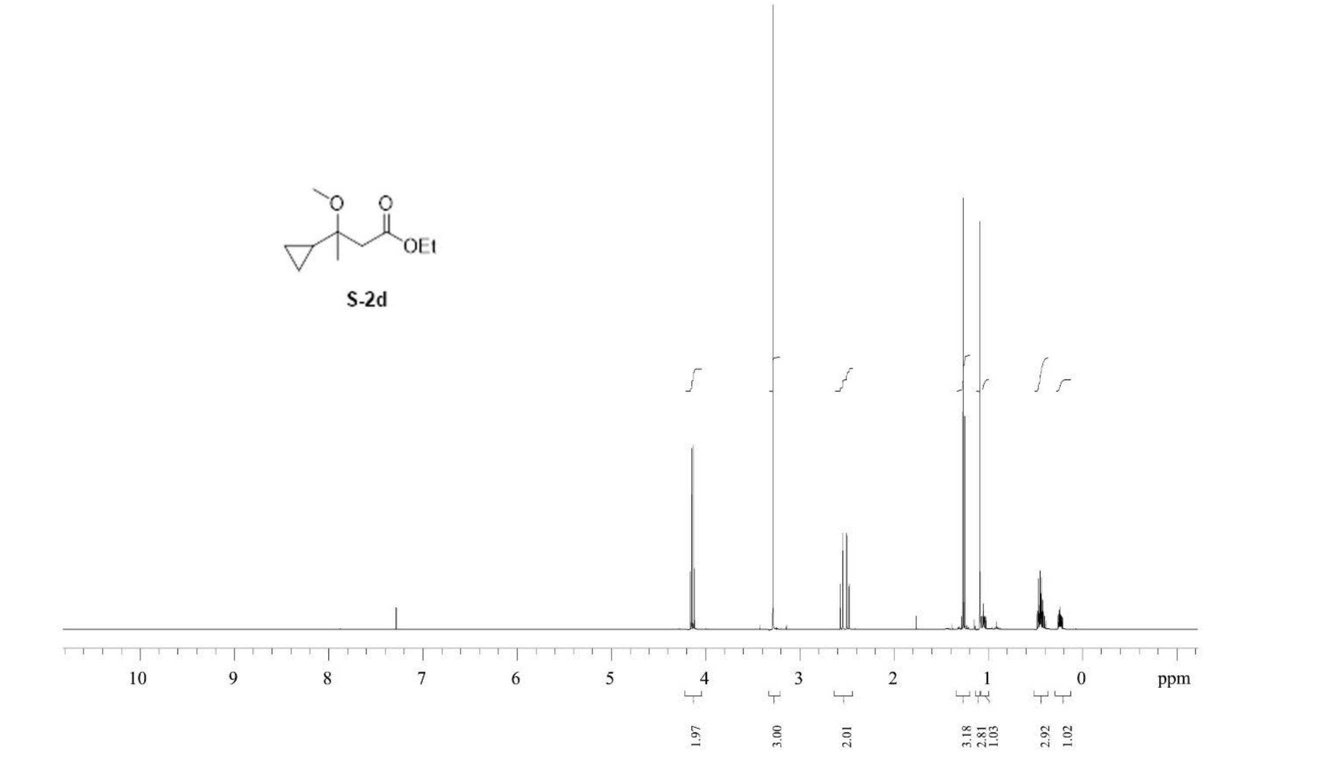
176.461
81.829
77.294
77.041
76.785
56.986
40.555
14.232
5.164
0.579
O
O
OH
S-3c
240
220
200
180
160
140
120
100
80
60
40
20
ppm

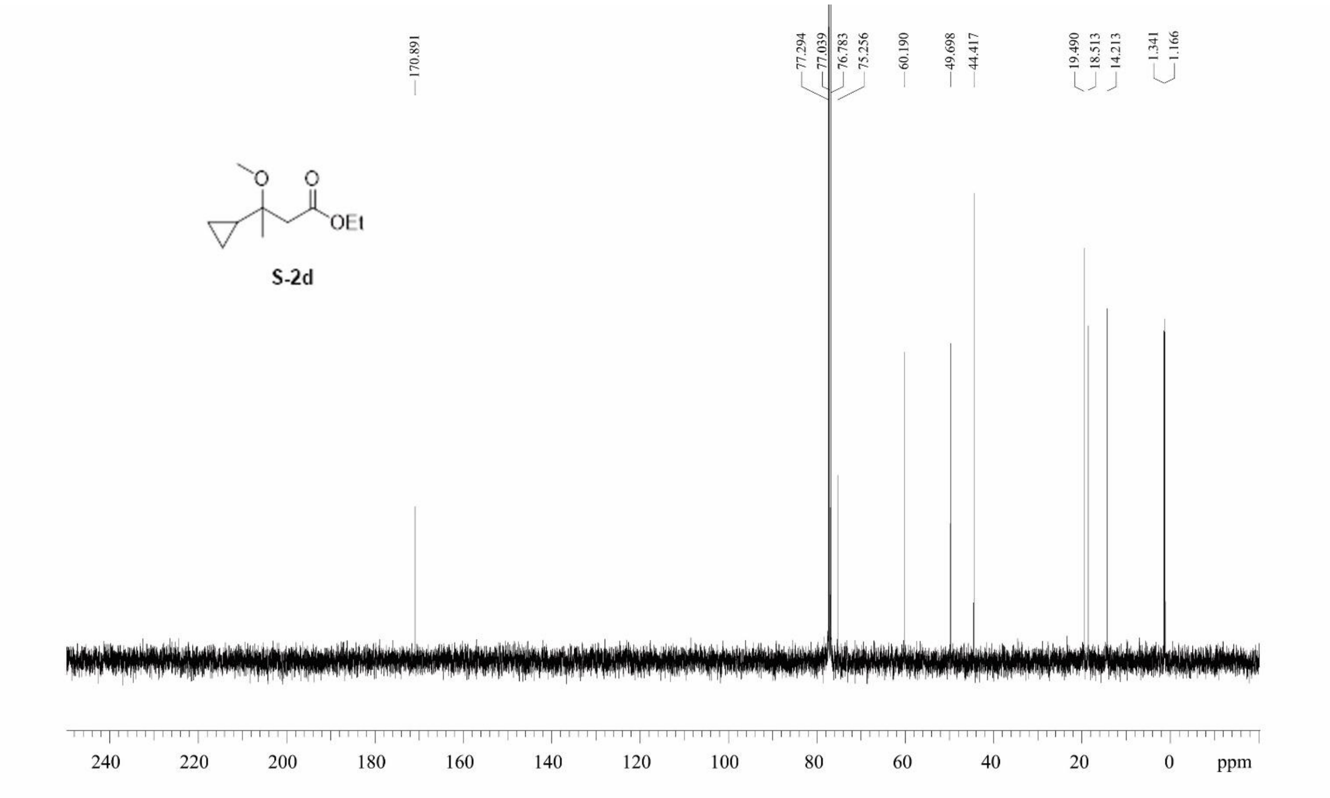

O
O
N2
1c
0.82
3.00
0.99
1.87
1.07
1.04
2.00
0.97
10
9
8
7
6
5
4
3
2
1
0
ppm

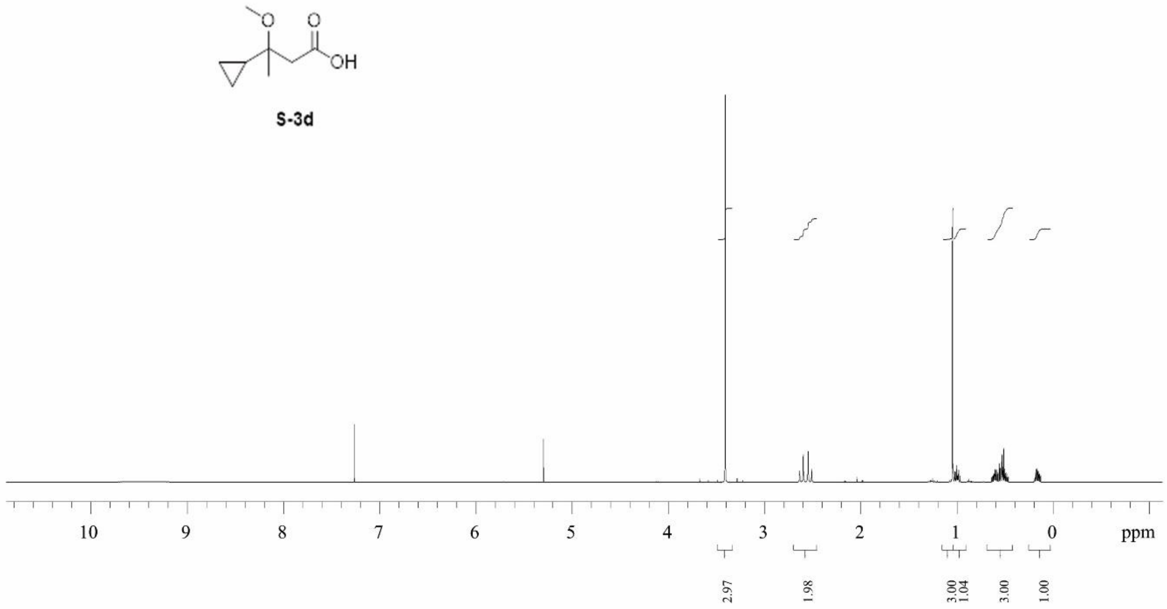

193.147
82.197
77.336
77.081
76.827
57.104
55.414
46.967
14.587
5.216
0.581
O
O
N2
1c
240
220
200
180
160
140
120
100
80
60
40
20
ppm

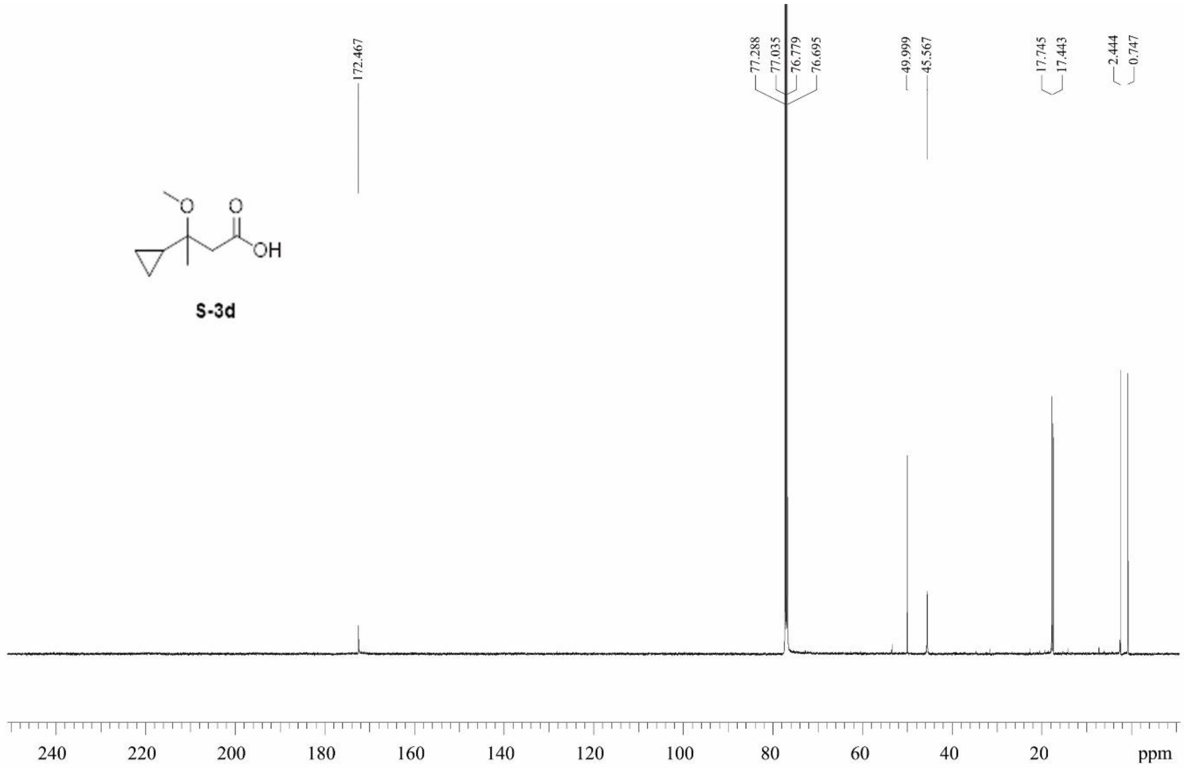

OH
O
OEt
S-1d
10
9
8
7
6
5
4
3
2
1
0
ppm
2.01
0.95
2.06
3.23
3.00
1.08
3.91

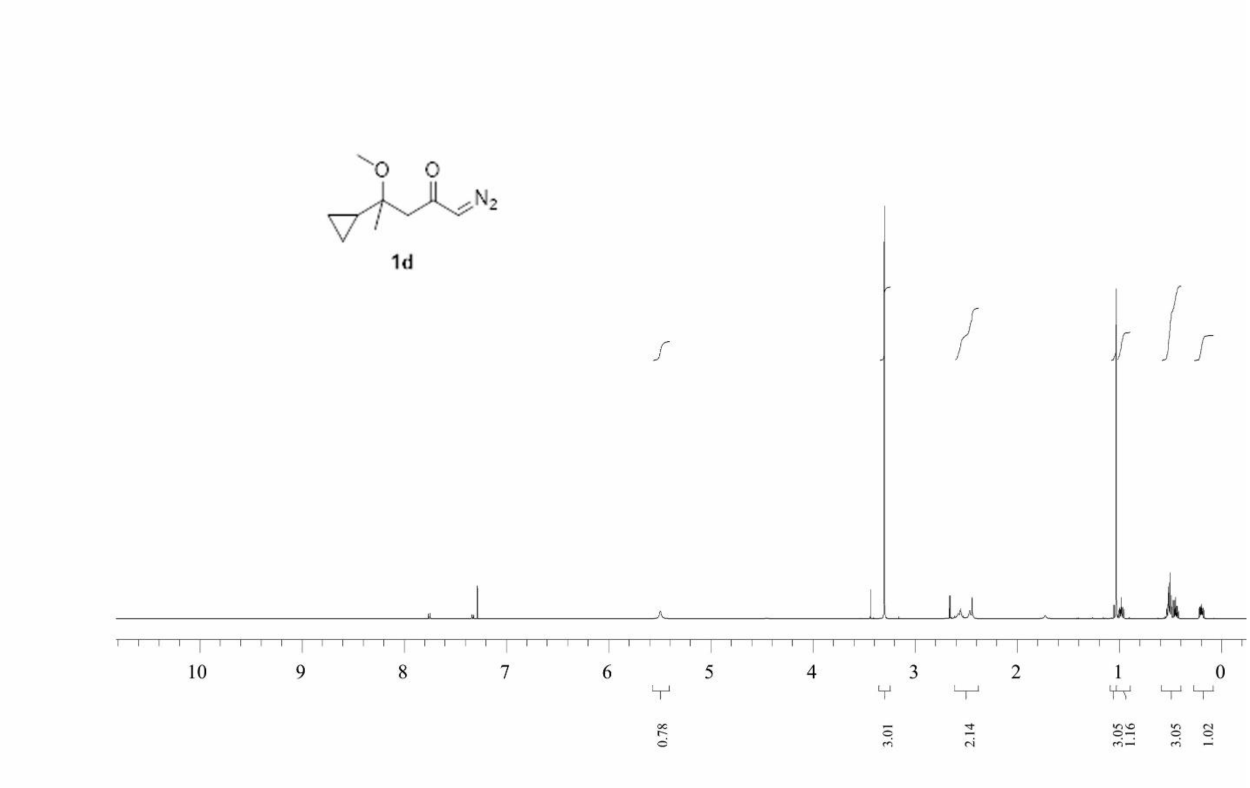

172.989
77.278
77.022
76.767
69.137
60.652
46.142
27.029
20.827
14.186
0.745
-0.019
OH
O
OEt
S-1d
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

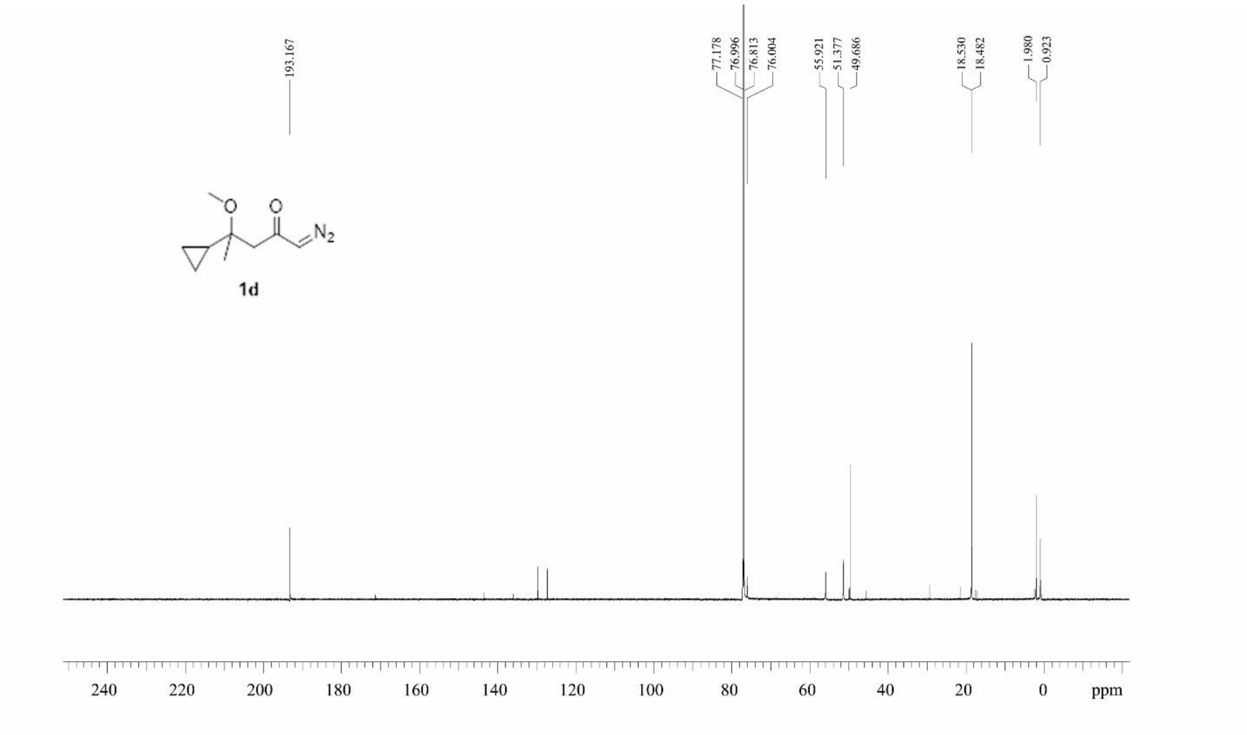

S-2d
OEt
10
9
8
7
6
5
4
3
2
1
0
ppm
1.97
3.00
2.01
3.18
2.81
1.03
2.92
1.02

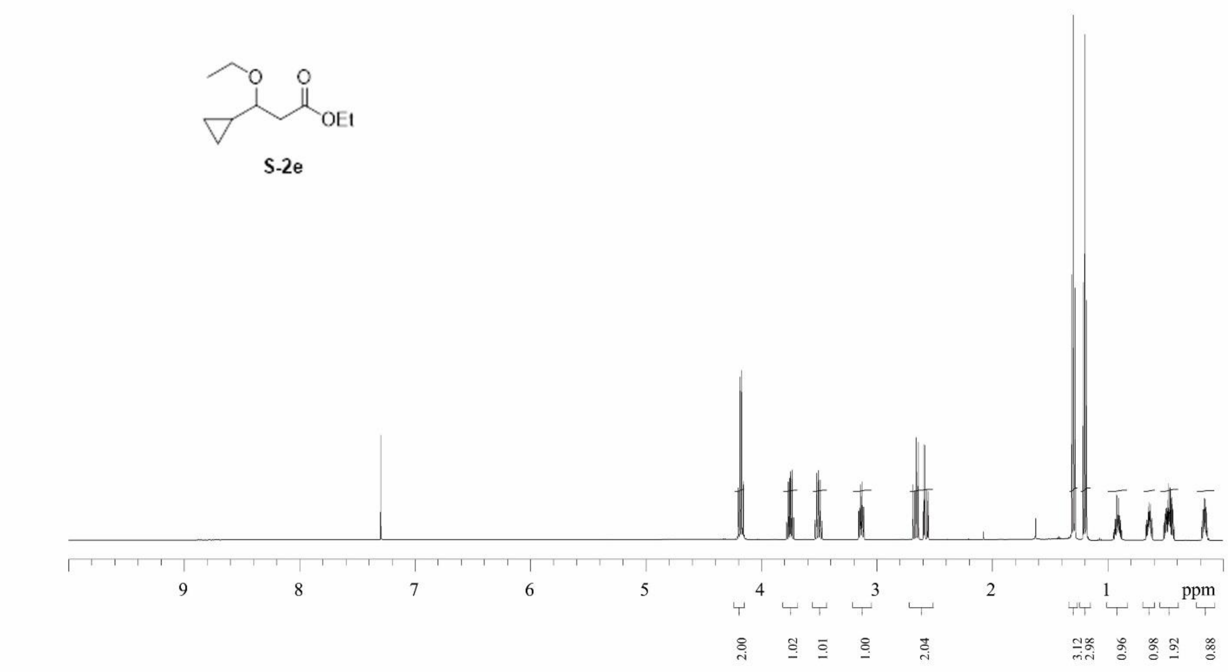

S-2d
170.891
77.294
77.039
76.783
75.256
60.190
49.698
44.417
19.490
18.513
14.213
1.341
1.166
OEt
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
OH
S-3d
10
9
8
7
6
5
4
3
2
1
0
ppm
2.97
1.98
3.00
1.04
3.00
1.00


172.467
77.288
77.035
76.779
76.695
49.999
45.567
17.745
17.443
2.444
0.747
O
OH
S-3d
240
220
200
180
160
140
120
100
80
60
40
20
ppm

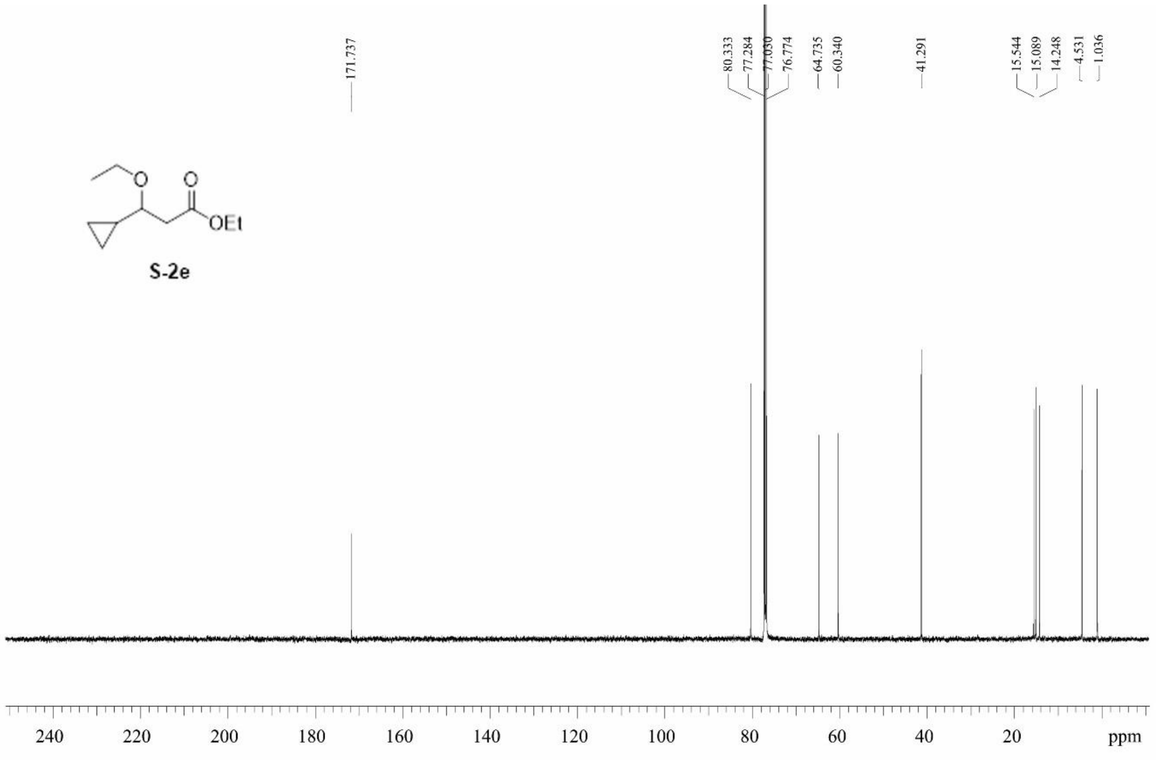

O
O
N2
1d
10
9
8
7
6
5
4
3
2
1
0
0.78
3.01
2.14
3.05
1.16
3.05
1.02


193.167
77.178
76.996
76.813
76.004
55.921
51.377
49.686
18.530
18.482
1.980
0.923
O
O
N2
1d
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm



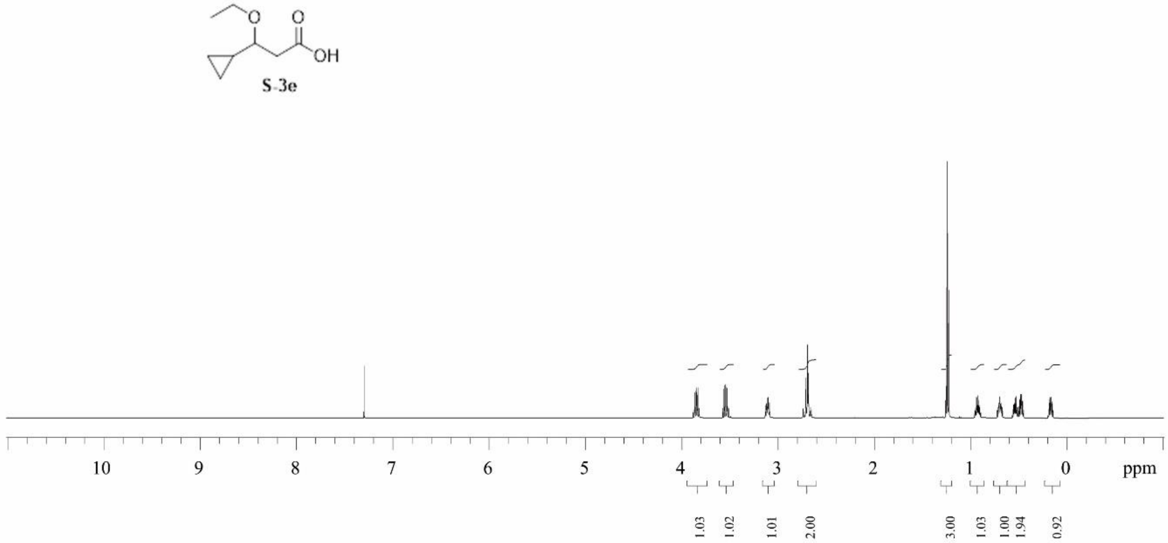
S-2e

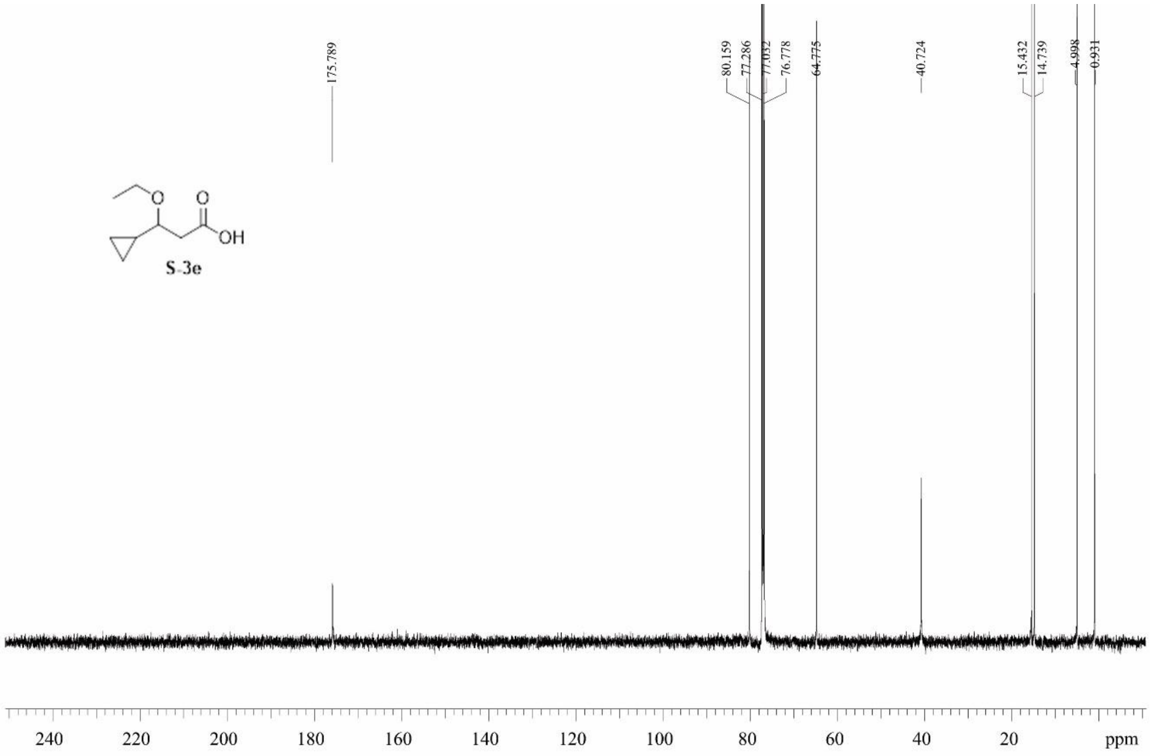
OEt
9
8
7
6
5
4
3
2
1
ppm
2.00
1.02
1.01
1.00
2.04
3.12
2.98
0.96
0.98
1.92
0.88

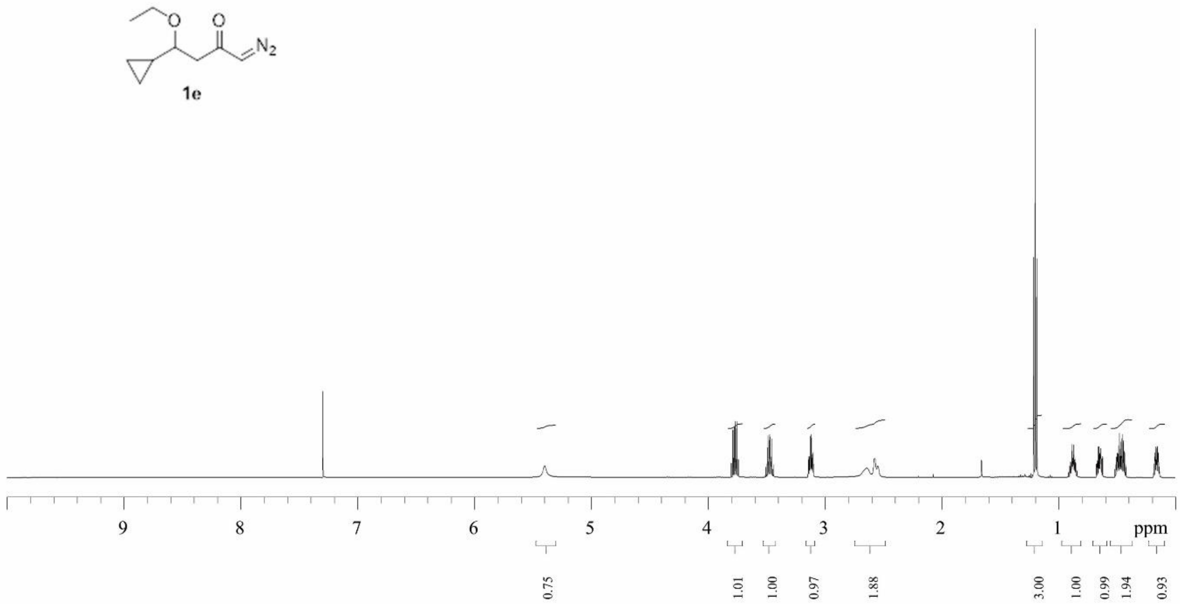


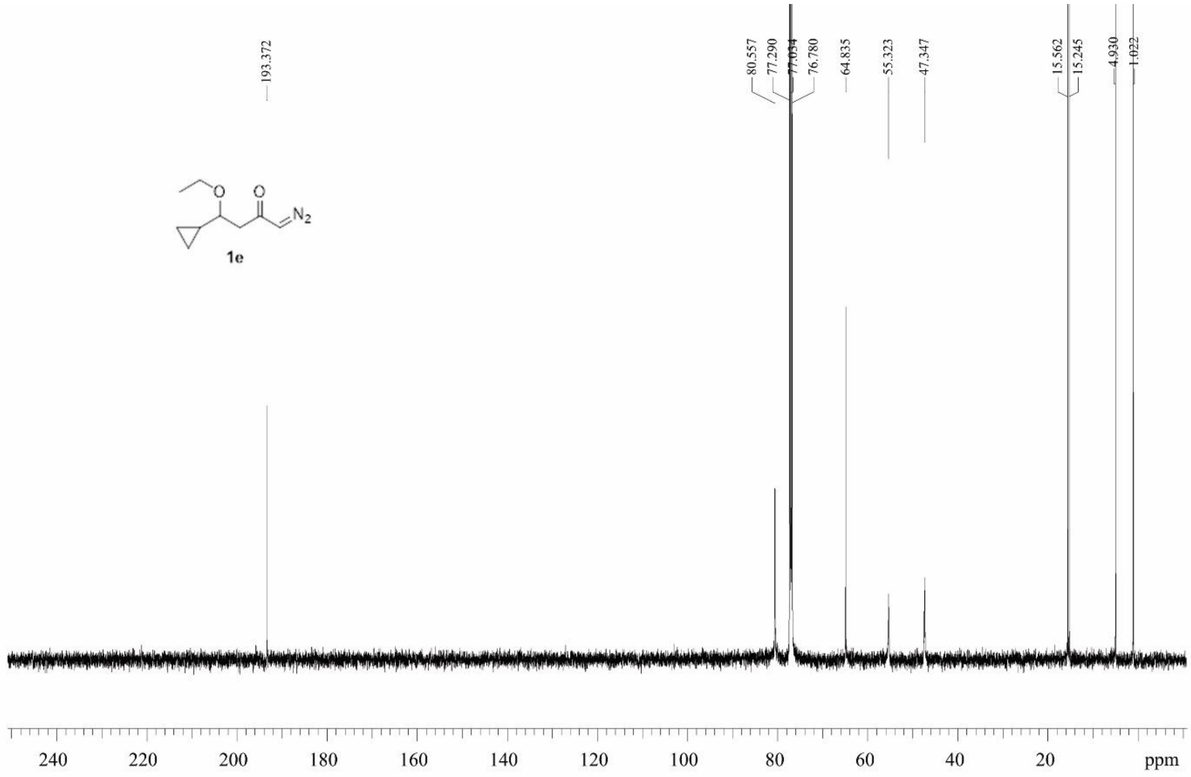
S-2e

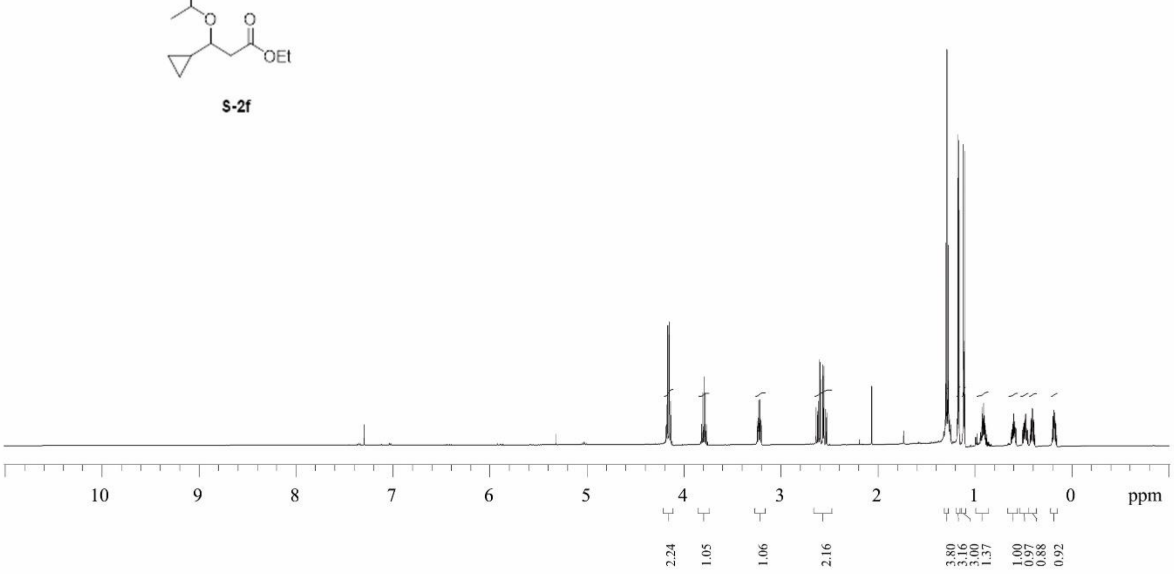
OEt
171.737
80.333
77.284
77.030
76.774
64.735
60.340
41.291
15.544
15.089
14.248
4.531
1.036
240
220
200
180
160
140
120
100
80
60
40
20
ppm

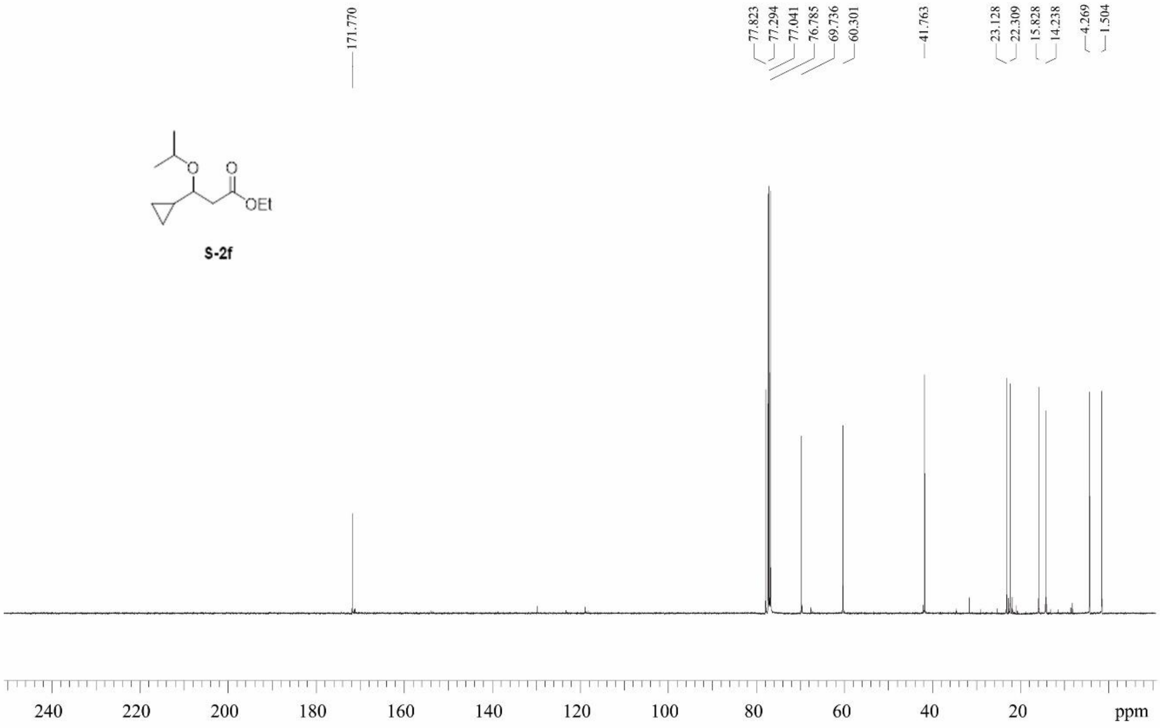

O
O
OH
S-3e
1.03
1.02
1.01
2.00
3.00
1.03
1.00
1.94
0.92
10
9
8
7
6
5
4
3
2
1
0
ppm

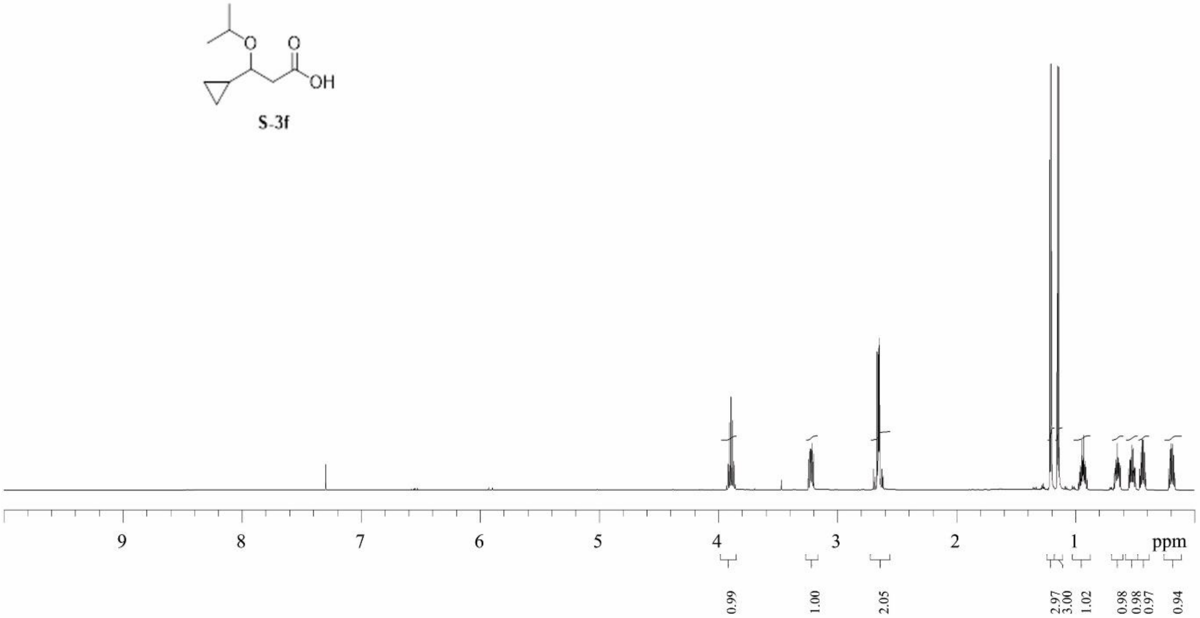

175.789
80.159
77.286
77.032
76.778
64.775
40.724
15.432
14.739
4.998
0.931
O
O
OH
S-3e
240
220
200
180
160
140
120
100
80
60
40
20
ppm

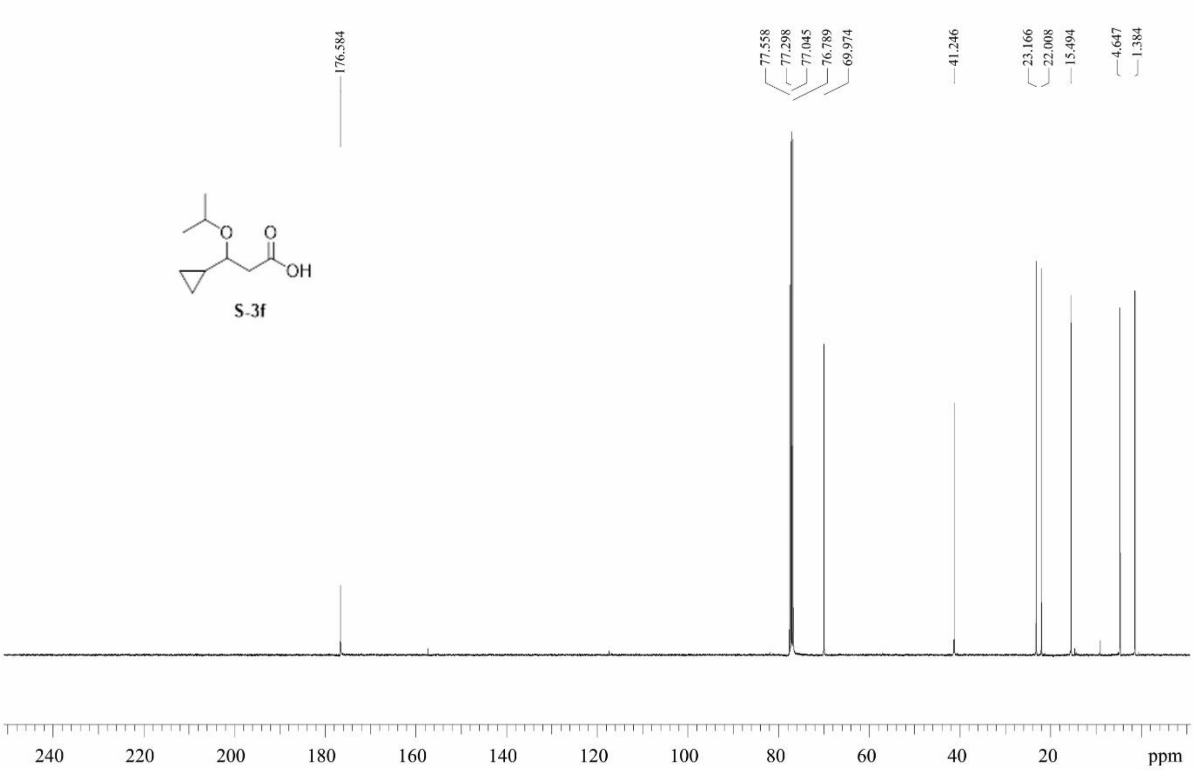

1e
9
8
7
6
5
4
3
2
1
ppm
0.75
1.01
1.00
0.97
1.88
3.00
1.00
0.99
1.94
0.93

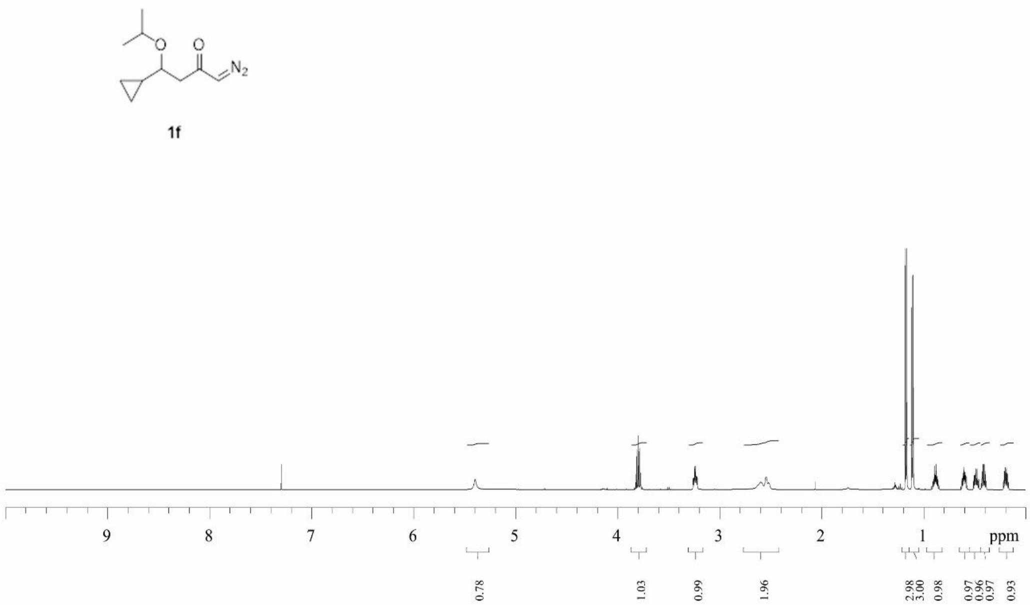

193.372
80.557
77.290
77.034
76.780
64.835
55.323
47.347
15.562
15.245
4.930
1.022
1e
240
220
200
180
160
140
120
100
80
60
40
20
ppm


OEt
S-2f
10
9
8
7
6
5
4
3
2
1
0
ppm
2.24
1.05
1.06
2.16
3.80
3.16
3.00
1.37
1.00
0.97
0.88
0.92


171.770
77.823
77.294
77.041
76.785
69.736
60.301
41.763
23.128
22.309
15.828
14.238
4.269
1.504
OEt
S-2f
240
220
200
180
160
140
120
100
80
60
40
20
ppm

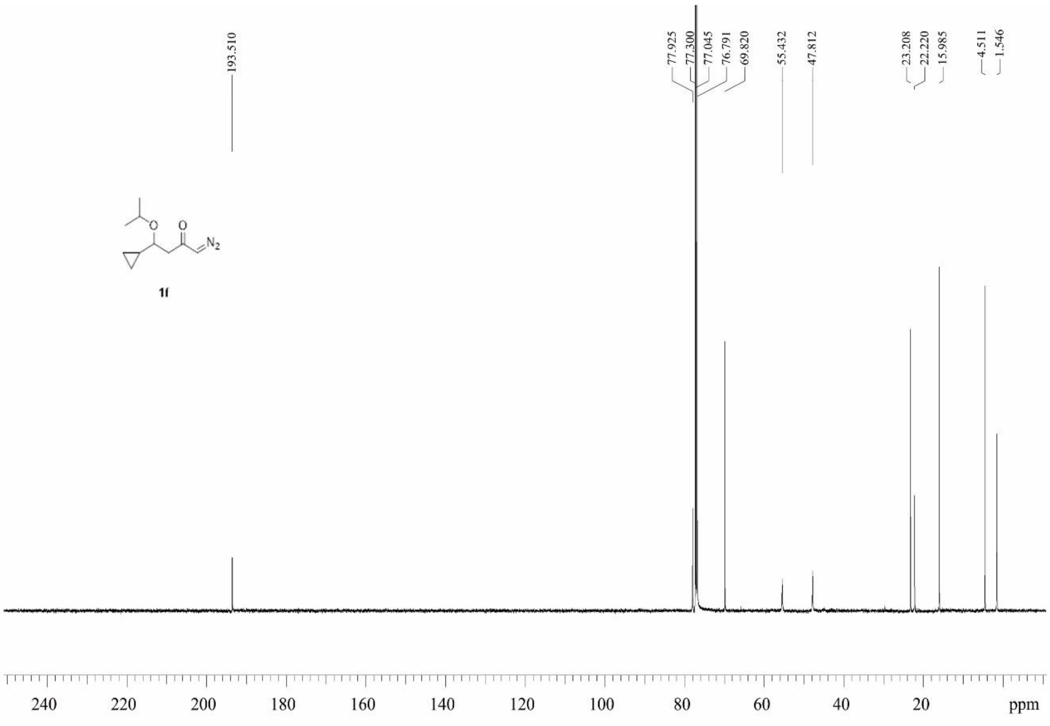

O
O
OH
S-3f
9
8
7
6
5
4
3
2
1
ppm
0.99
1.00
2.05
2.97
3.00
1.02
0.98
0.98
0.97
0.94


176.584
77.558
77.298
77.045
76.789
69.974
41.246
23.166
22.008
15.494
4.647
1.384
O
O
OH
S-3f
240
220
200
180
160
140
120
100
80
60
40
20
ppm



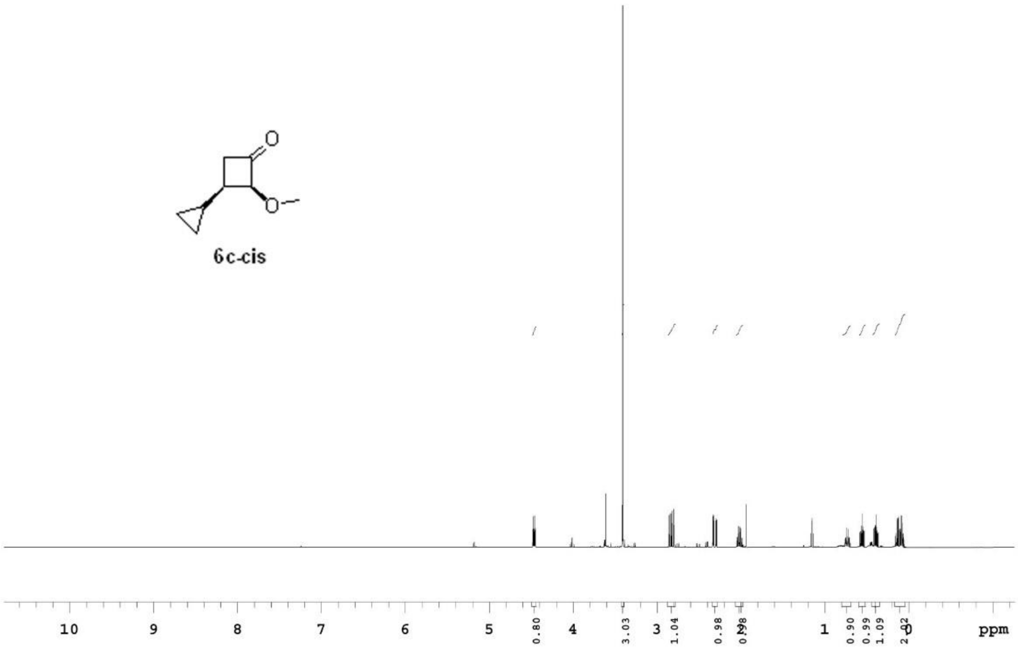
1f

9
8
7
6
5
4
3
2
1
ppm
0.78
1.03
0.99
1.96
2.98
3.00
0.98
0.97
0.96
0.97
0.93

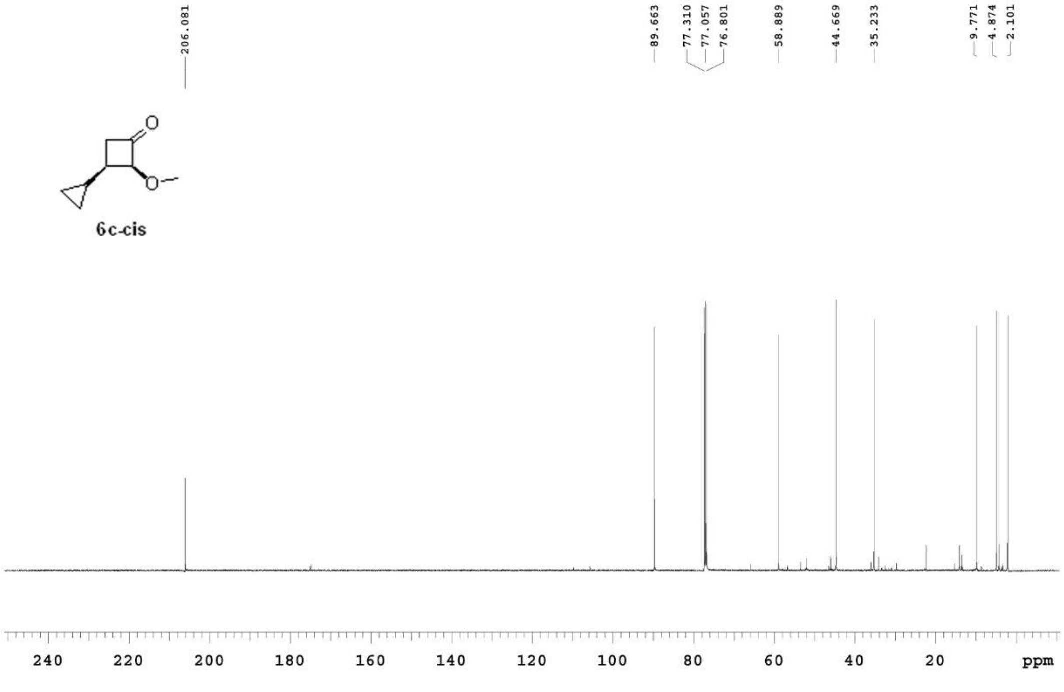


1f

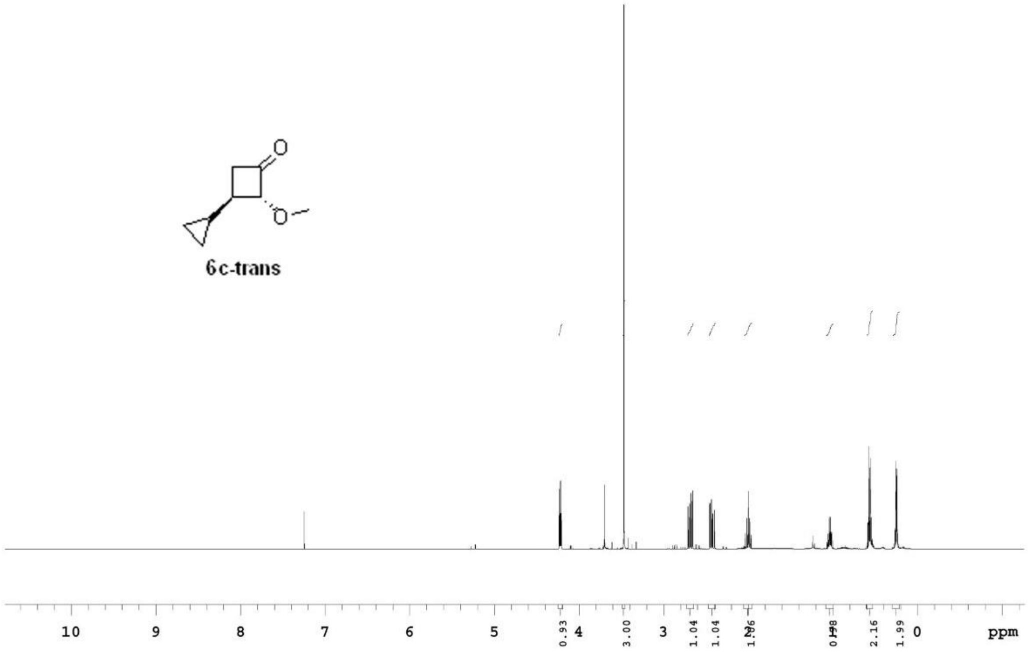
193.510
77.925
77.300
77.045
76.791
69.820
55.432
47.812
23.208
22.220
15.985
4.511
1.546
240
220
200
180
160
140
120
100
80
60
40
20
ppm

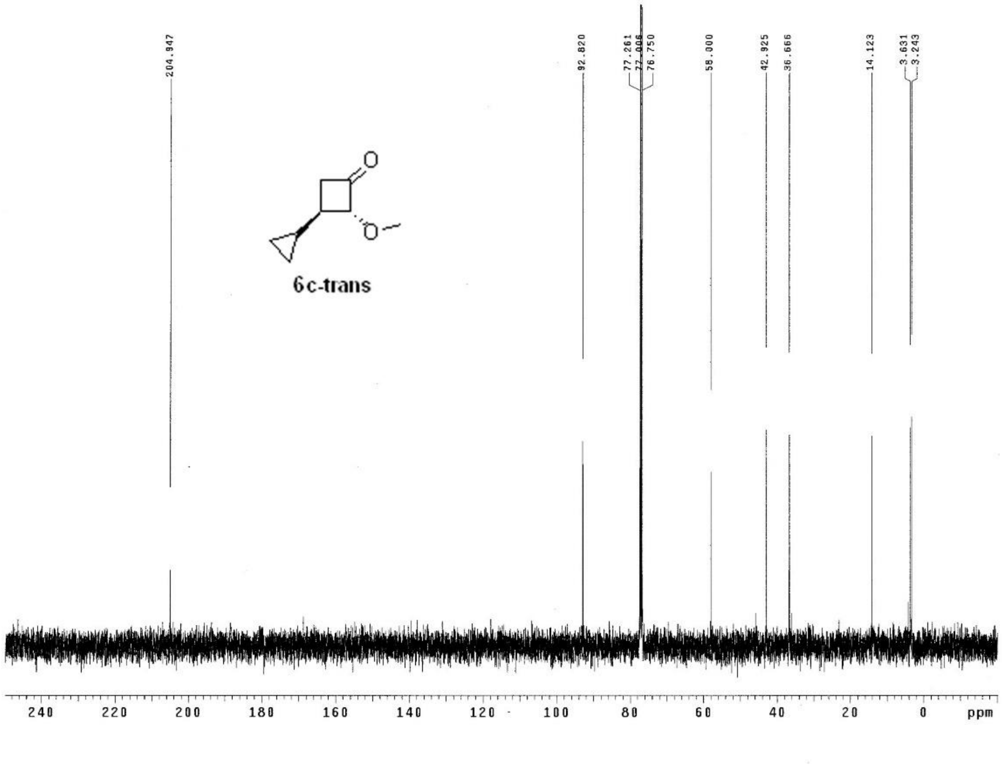


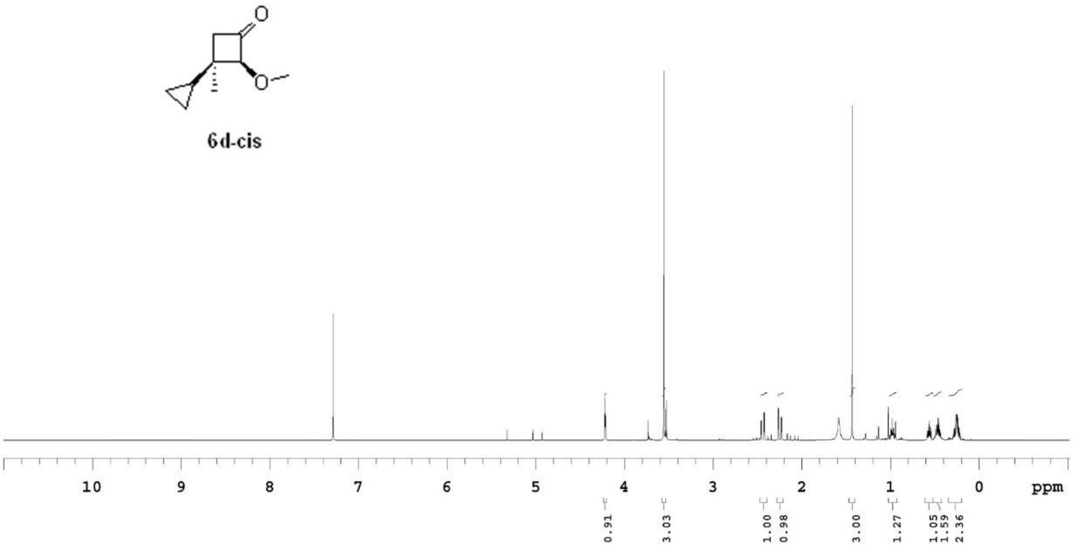
6c-cis
0.80
3.03
1.04
0.98
0.98
0.90
0.99
1.09
2.02
10
9
8
7
6
5
4
3
2
1
0
ppm

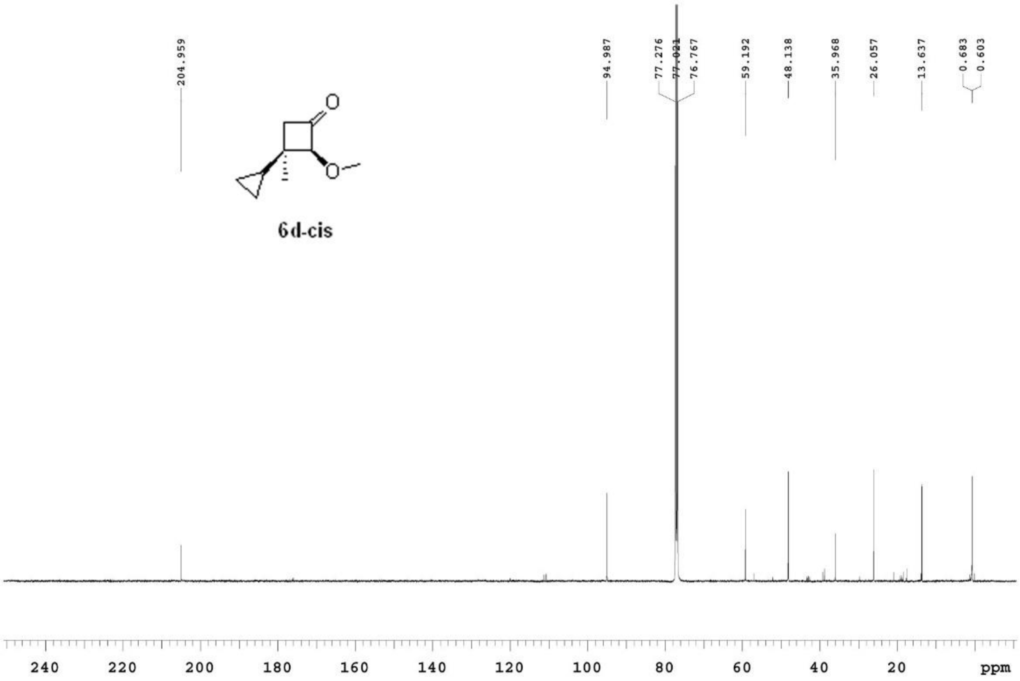


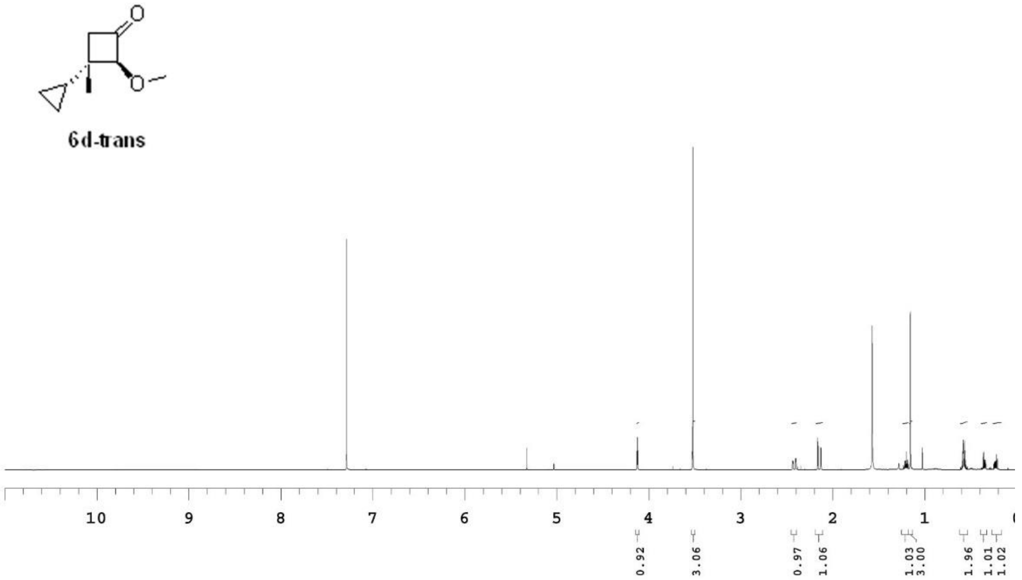
6c-cis
206.081
89.663
77.310
77.057
76.801
58.889
44.669
35.233
9.771
4.874
2.101
240
220
200
180
160
140
120
100
80
60
40
20
ppm

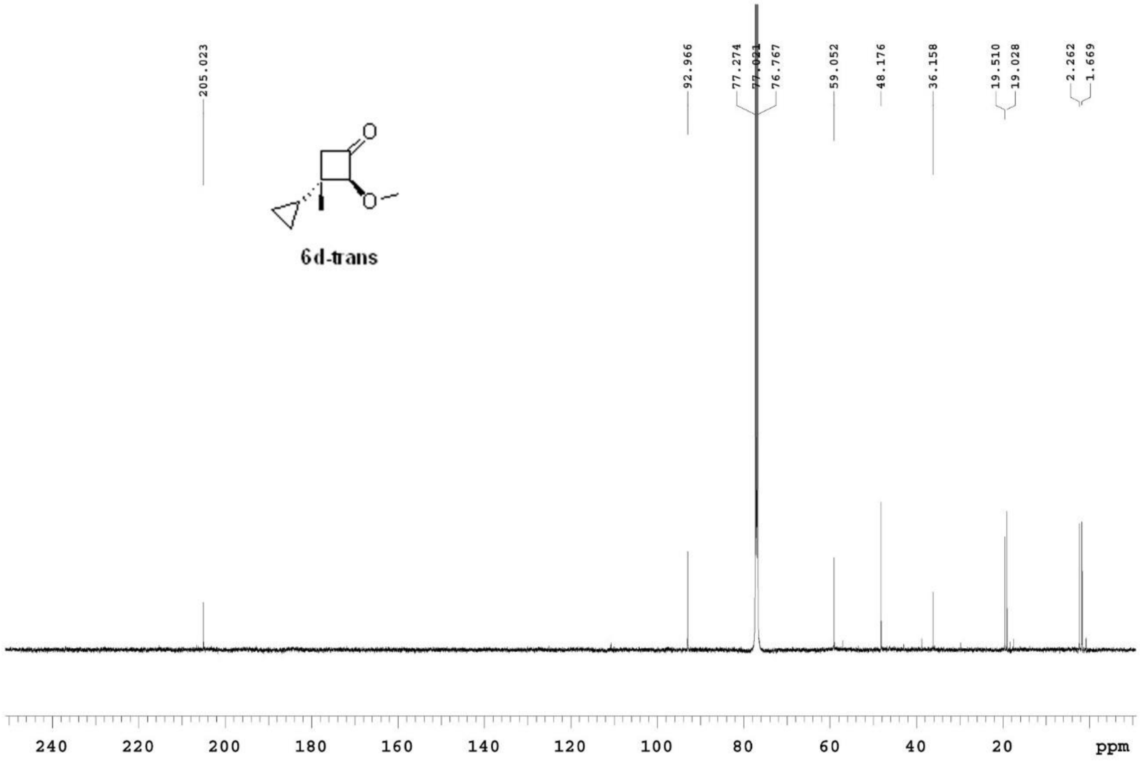

6c-trans
0.93
3.00
1.04
1.04
1.06
0.98
2.16
1.99
10
9
8
7
6
5
4
3
2
1
0
ppm

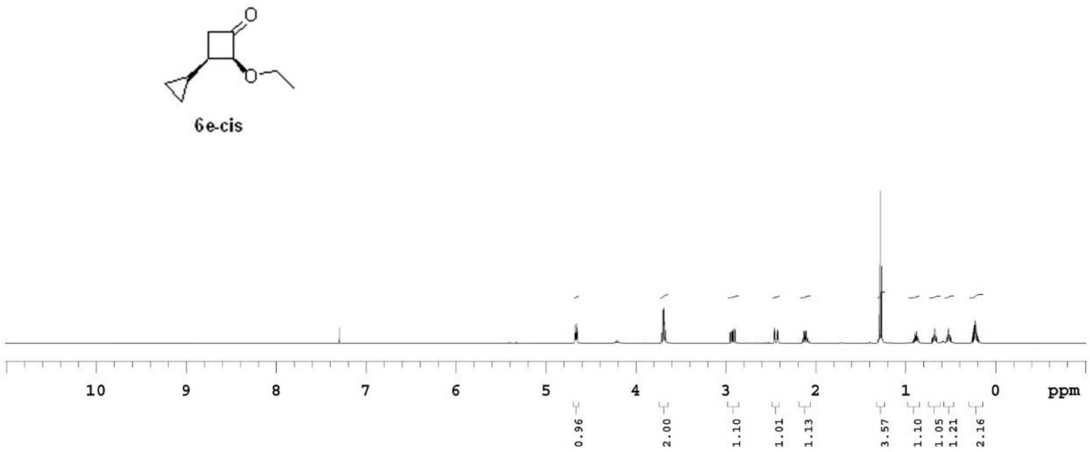

204.847
92.820
77.261
77.006
76.750
58.000
42.925
36.666
14.123
3.631
3.243
6c-trans
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

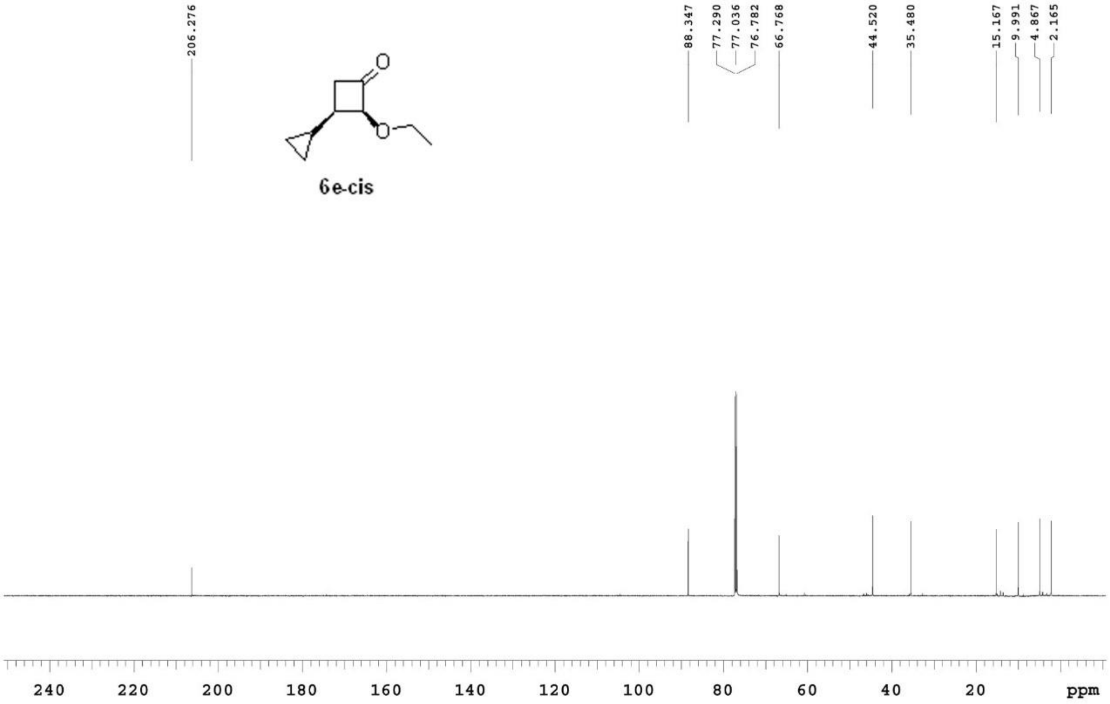

6d-cis
10
9
8
7
6
5
4
3
2
1
0
ppm
0.91
3.03
1.00
0.98
3.00
1.27
1.05
1.59
2.36

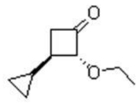

204.959
94.987
77.276
77.021
76.767
59.192
48.138
35.968
26.057
13.637
0.683
0.603
6d-cis
240
220
200
180
160
140
120
100
80
60
40
20
ppm


6d-trans

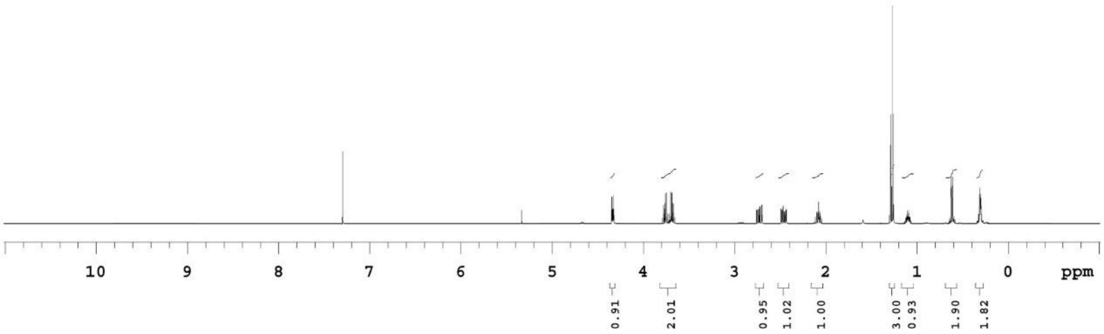

6d-trans

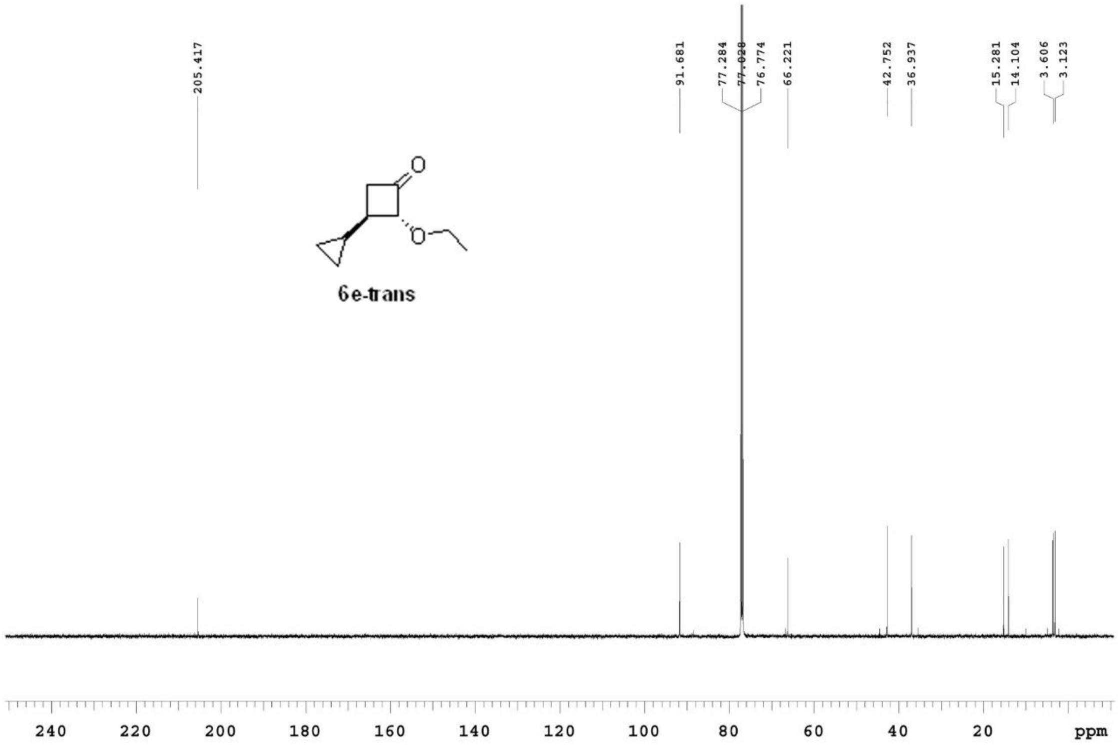

O
O
6e-cis
10
9
8
7
6
5
4
3
2
1
0
ppm
0.96
2.00
1.10
1.01
1.13
3.57
1.10
1.05
1.21
2.16

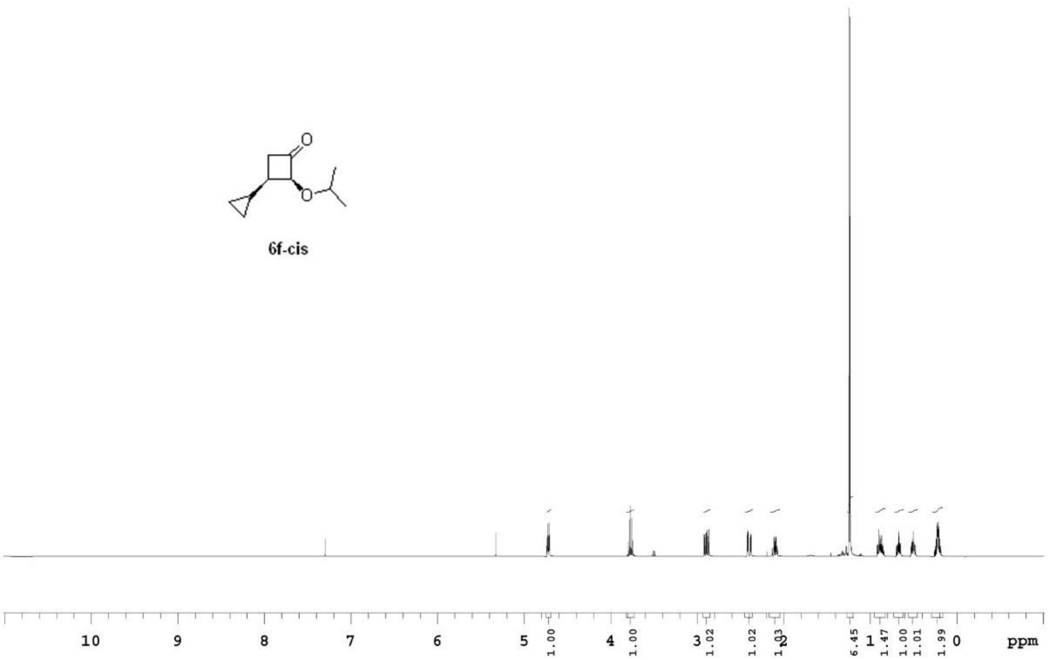

206.276
88.347
77.290
77.036
76.782
66.768
44.520
35.480
15.167
9.991
4.867
2.165
O
O
6e-cis
240
220
200
180
160
140
120
100
80
60
40
20
ppm



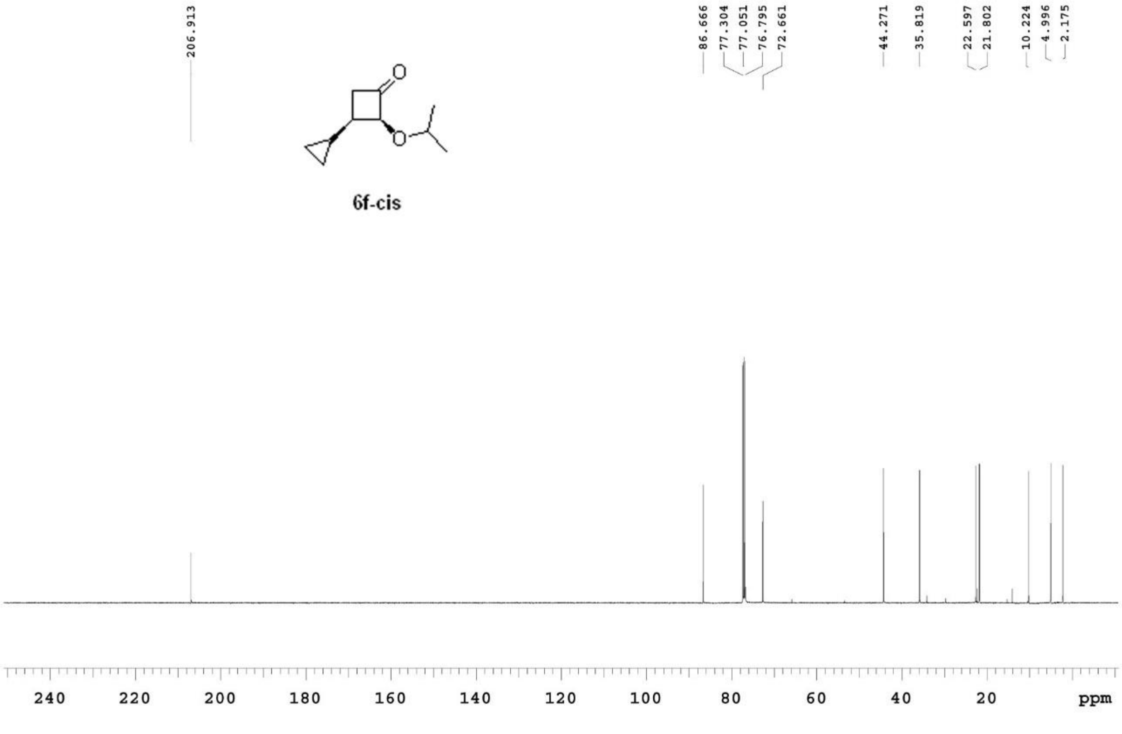
6e-trans


10
9
8
7
6
5
4
3
2
1
0
ppm
0.91
2.01
0.95
1.02
1.00
3.00
0.93
1.90
1.82

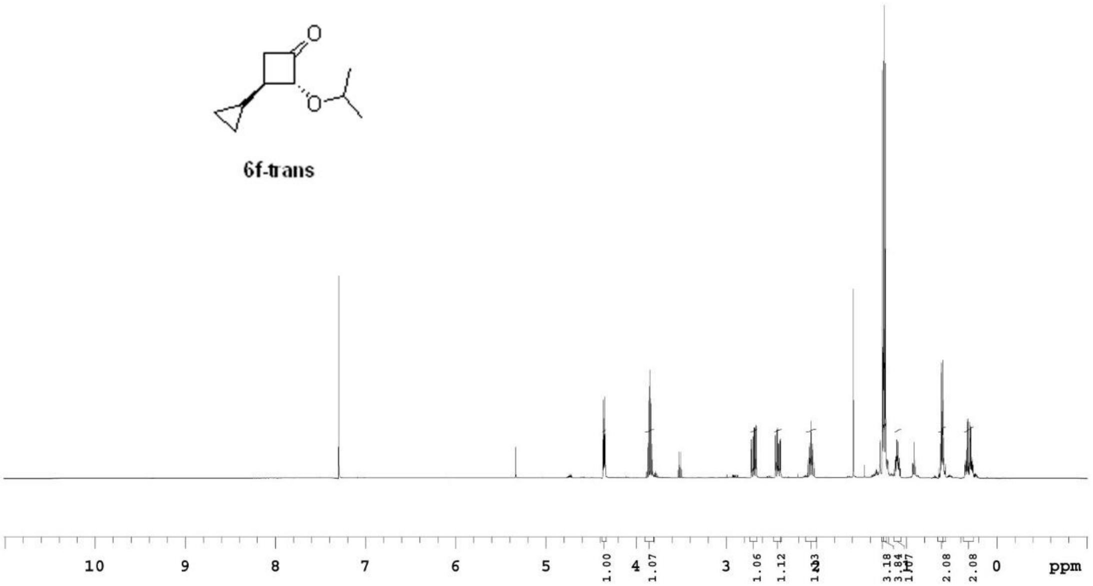

205.417
91.681
77.284
77.028
76.774
66.221
42.752
36.937
15.281
14.104
3.606
3.123
6e-trans
240
220
200
180
160
140
120
100
80
60
40
20
ppm

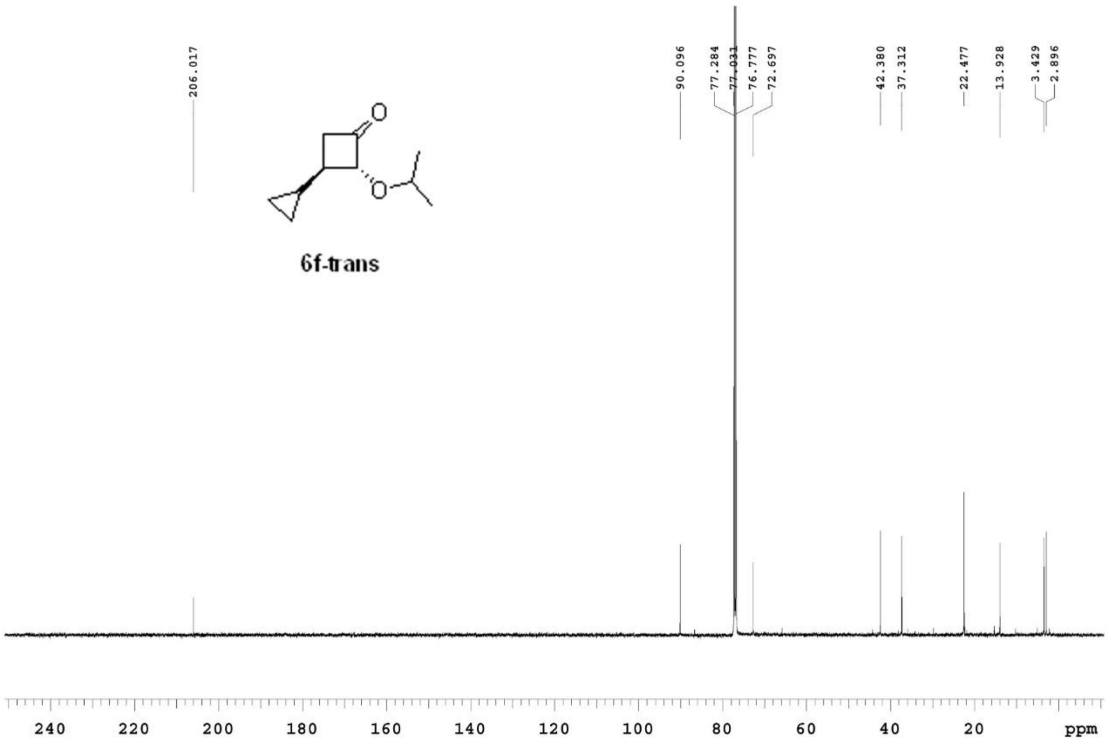

6f-cis

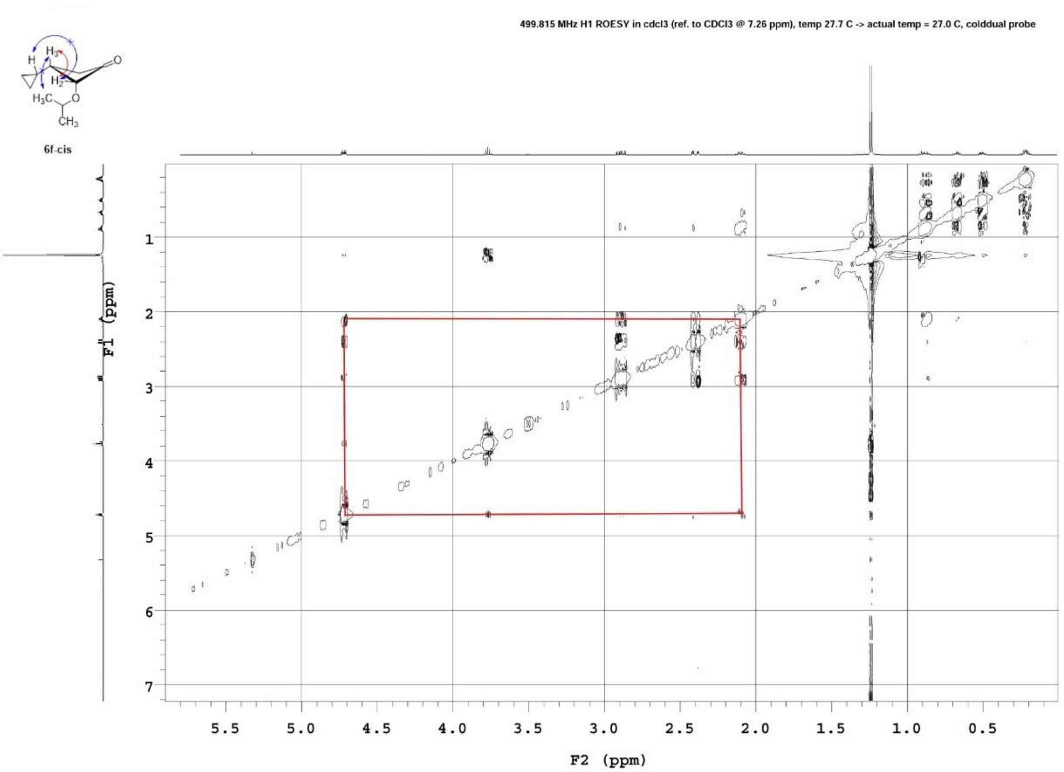
1.00
1.00
1.02
1.02
1.03
6.45
1.47
1.00
1.01
1.99
10
9
8
7
6
5
4
3
2
1
0
ppm


6f-cis

206.913
86.666
77.304
77.051
76.795
72.661
44.271
35.819
22.597
21.802
10.224
4.996
2.175
240
220
200
180
160
140
120
100
80
60
40
20
ppm

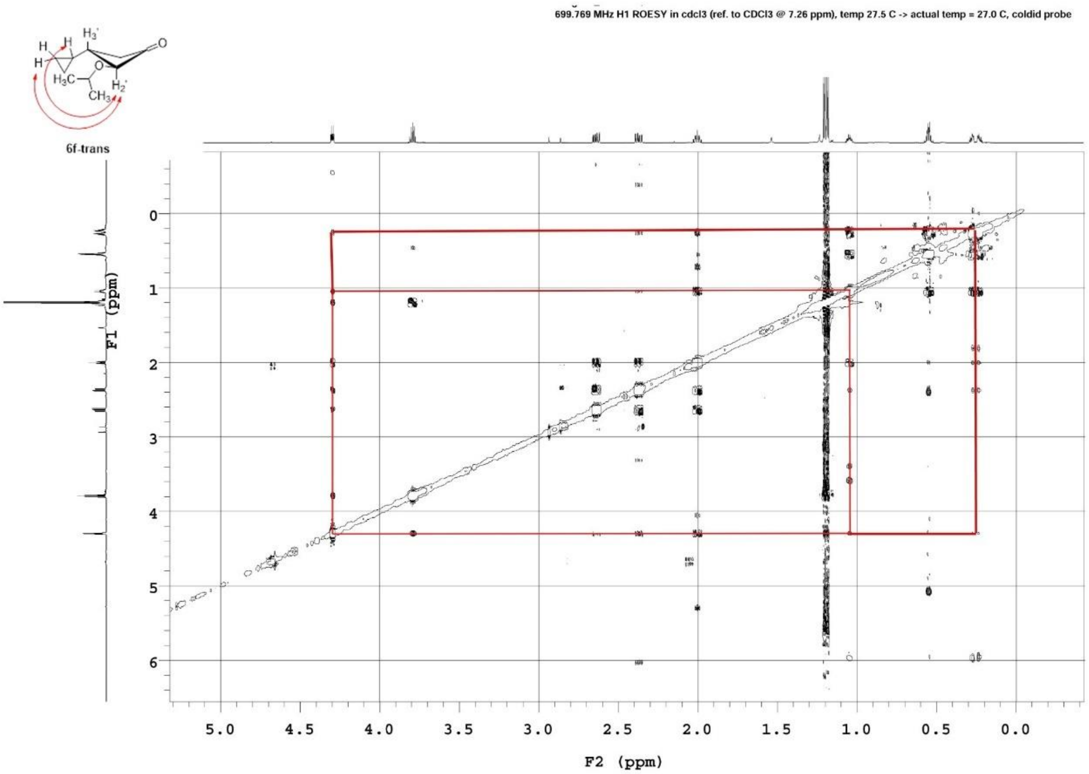

6f-trans


6f-trans



6f-cis

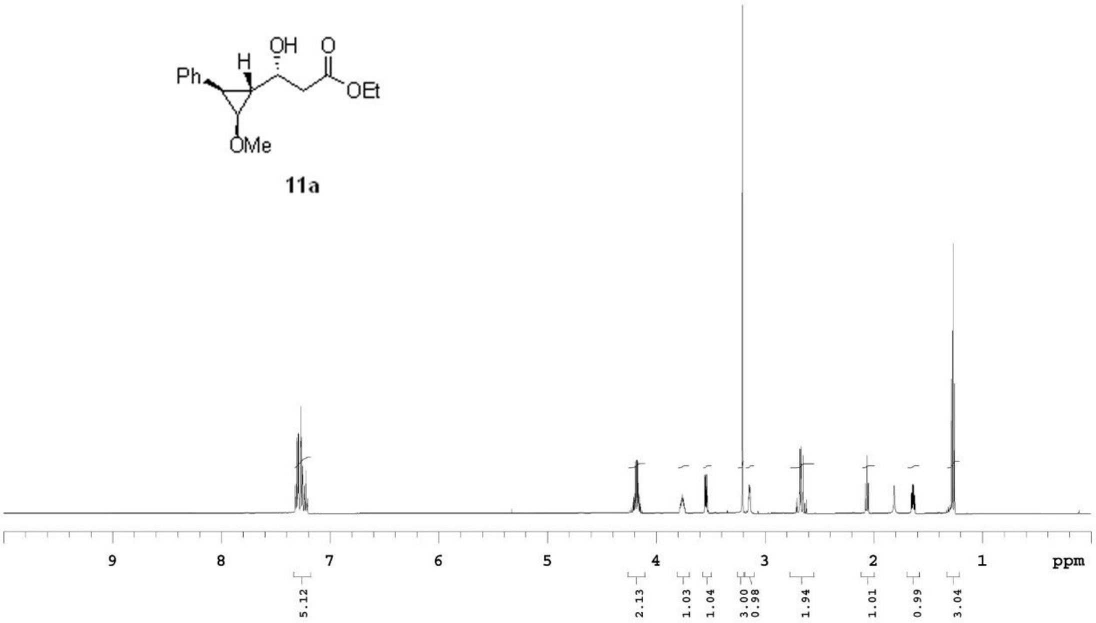
499.815 MHz H1 ROESY in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

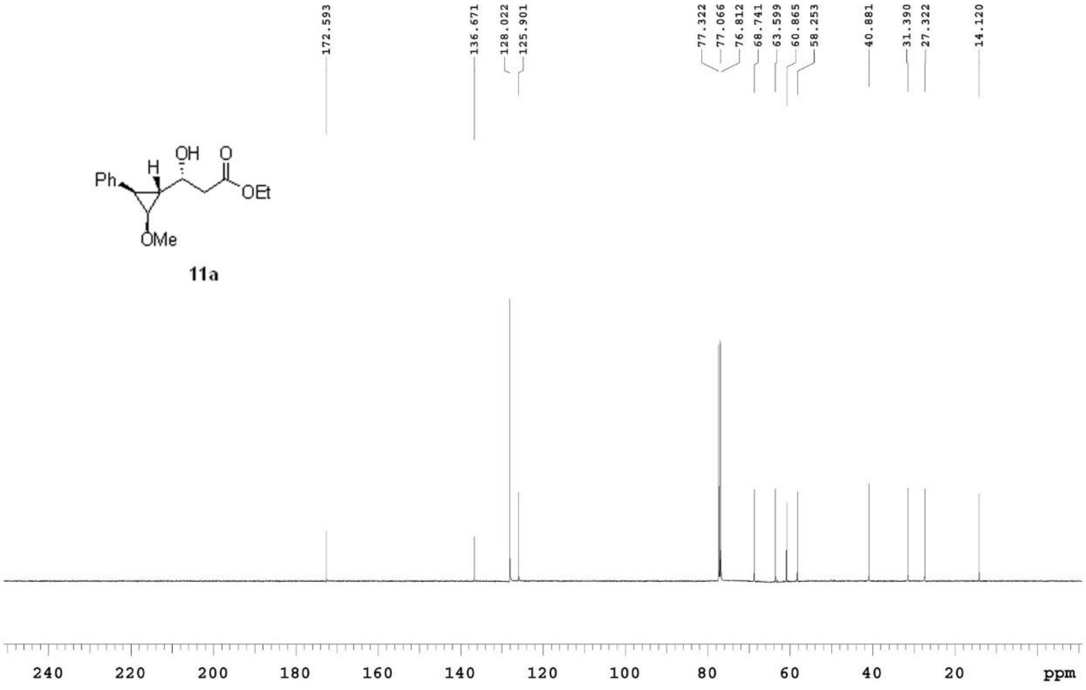


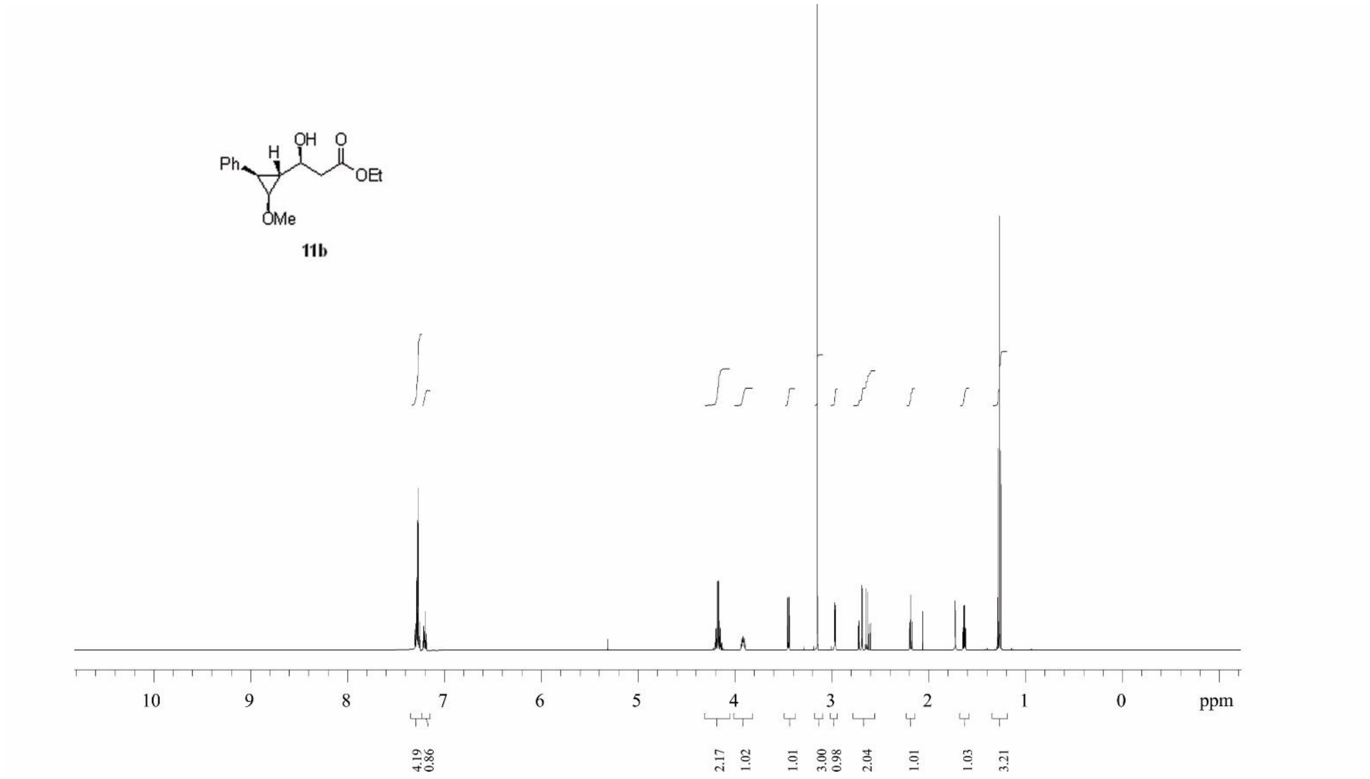
6f-trans

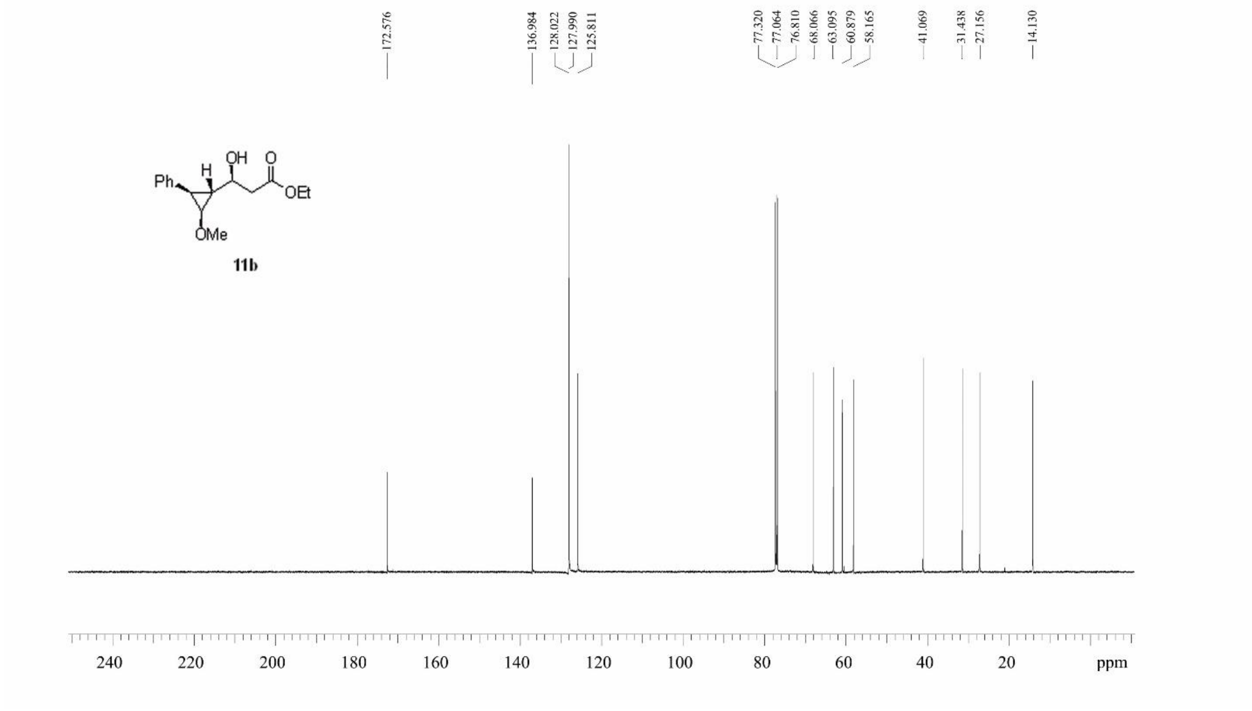
699.769 MHz H1 ROESY in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, coldid probe

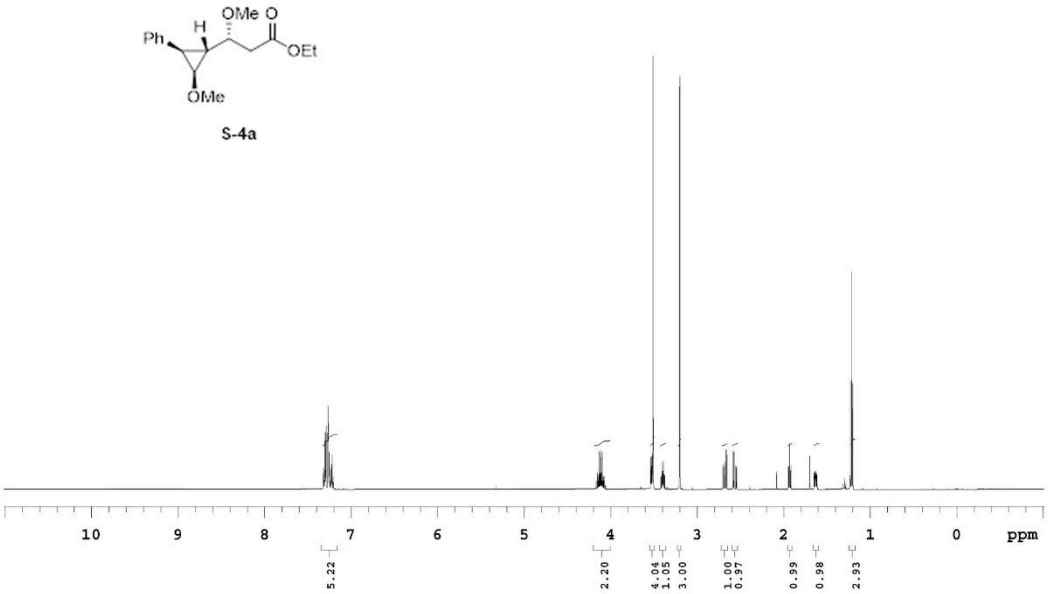
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Nargess_Hosseini/2015.02/2015.02.5.v7_SNH-03-194-F1-minor_loc37_20.05_H1_ROESY

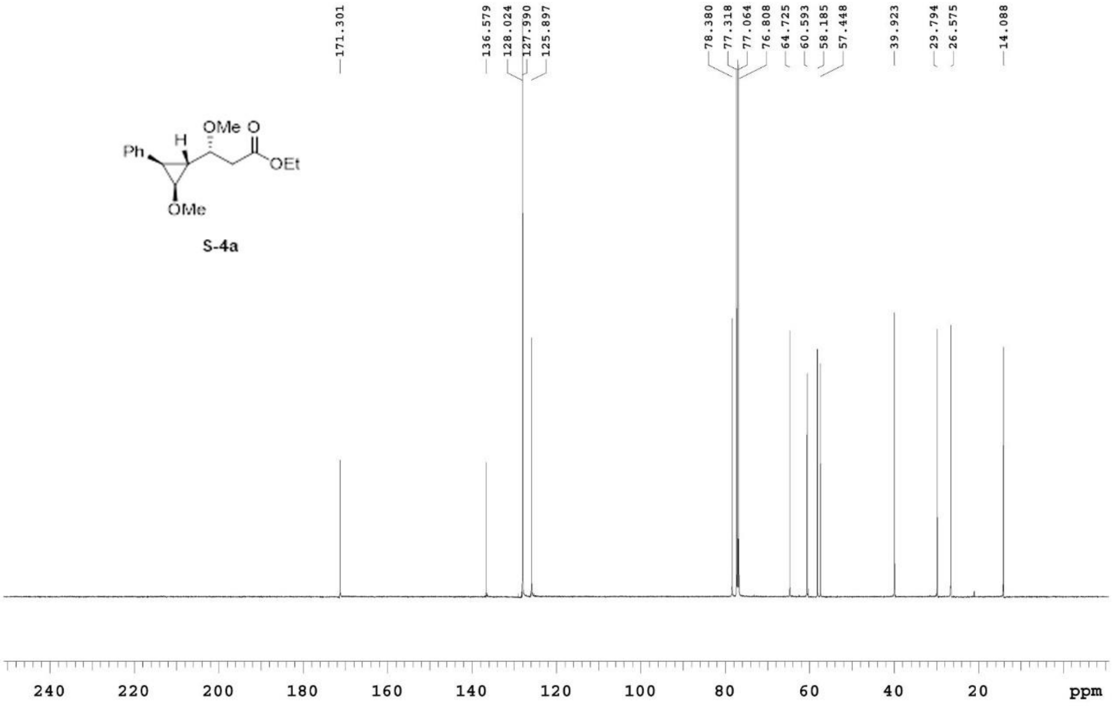

Ph
H
OH
O
OEt
OMe
11a
9
8
7
6
5
4
3
2
1
ppm
5.12
2.13
1.03
1.04
3.00
0.98
1.94
1.01
0.99
3.04

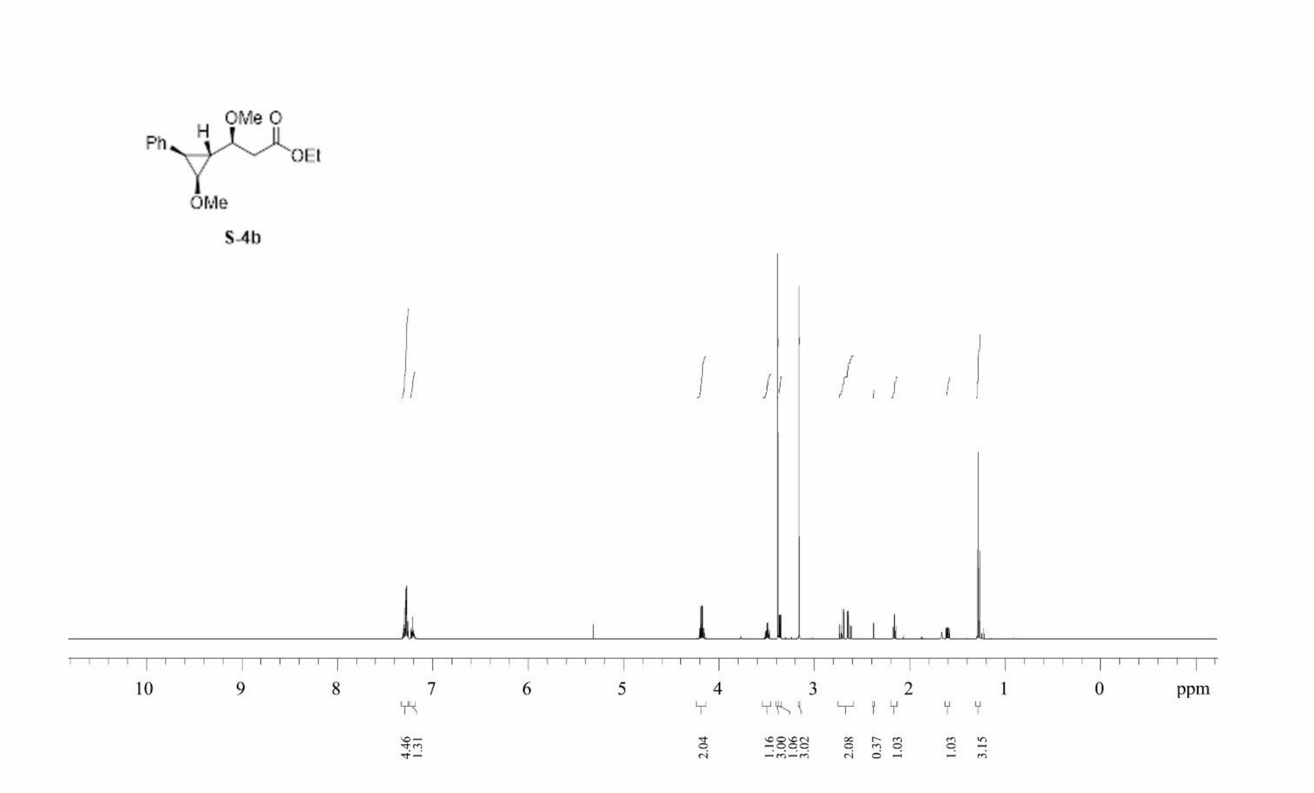

172.593
136.671
128.022
125.901
77.322
77.066
76.812
68.741
63.599
60.865
58.253
40.881
31.390
27.322
14.120
Ph
H
OH
O
OEt
OMe
11a
240
220
200
180
160
140
120
100
80
60
40
20
ppm

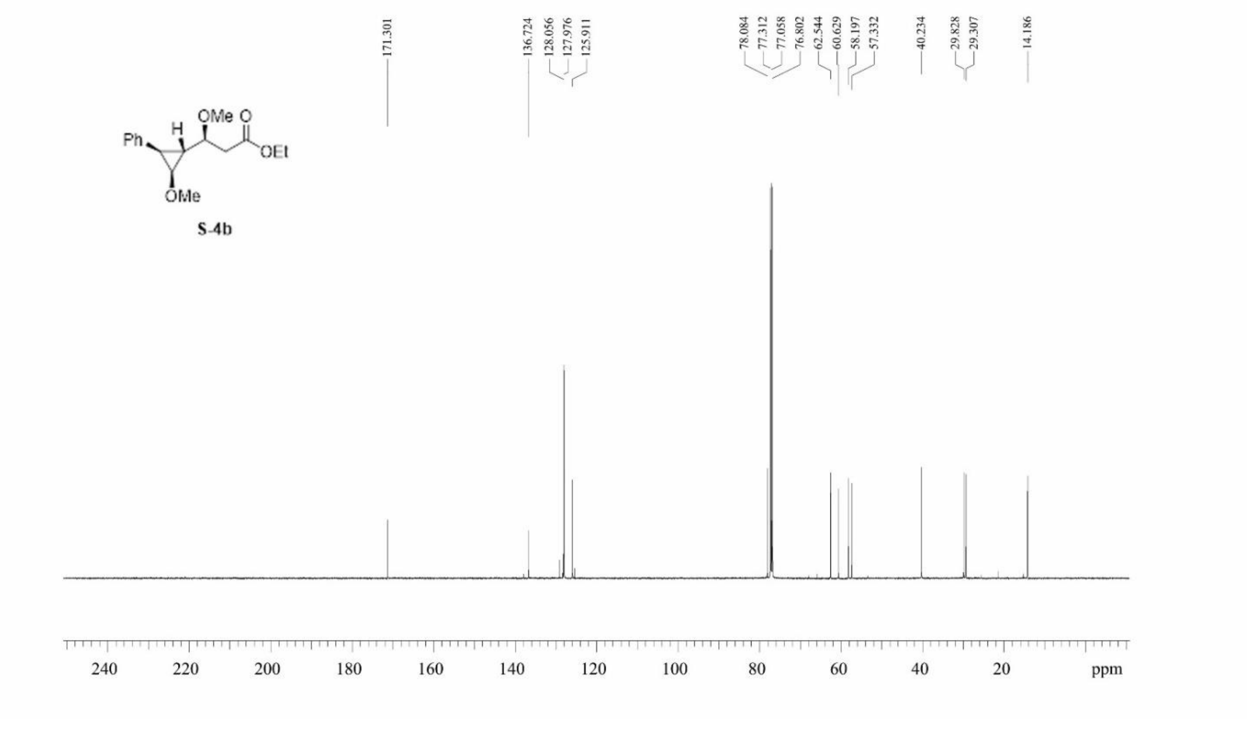

Ph
H
OH
O
OEt
OMe
11b
4.19
0.86
2.17
1.02
1.01
3.00
0.98
2.04
1.01
1.03
3.21
10
9
8
7
6
5
4
3
2
1
0
ppm

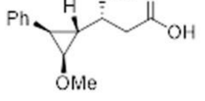

172.576
136.984
128.022
127.990
125.811
77.320
77.064
76.810
68.066
63.095
60.879
58.165
41.069
31.438
27.156
14.130
Ph
H
OH
O
OEt
OMe
11b
240
220
200
180
160
140
120
100
80
60
40
20
ppm


OMe
O
H
Ph
OEt
OMe
S-4a
10
9
8
7
6
5
4
3
2
1
0
ppm
5.22
2.20
4.04
1.05
3.00
1.00
0.97
0.99
0.98
2.93

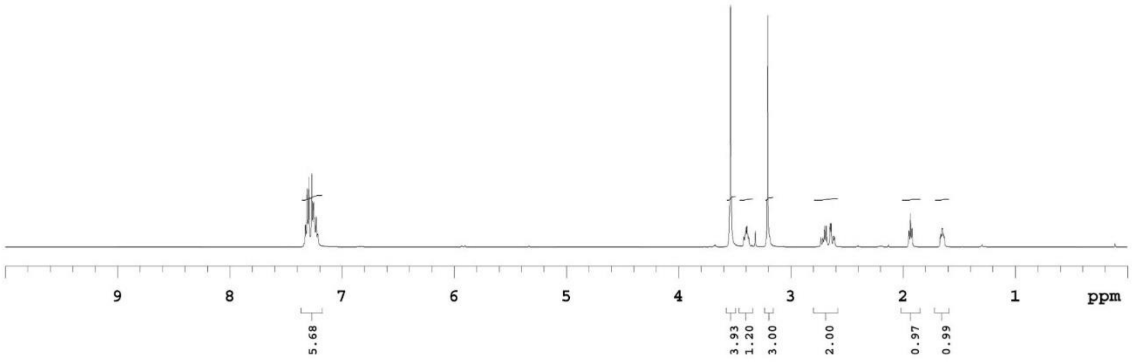

171.301
136.579
128.024
127.990
125.897
78.380
77.318
77.064
76.808
64.725
60.593
58.185
57.448
39.923
29.794
26.575
14.088
OMe
O
H
Ph
OEt
OMe
S-4a
240
220
200
180
160
140
120
100
80
60
40
20
ppm

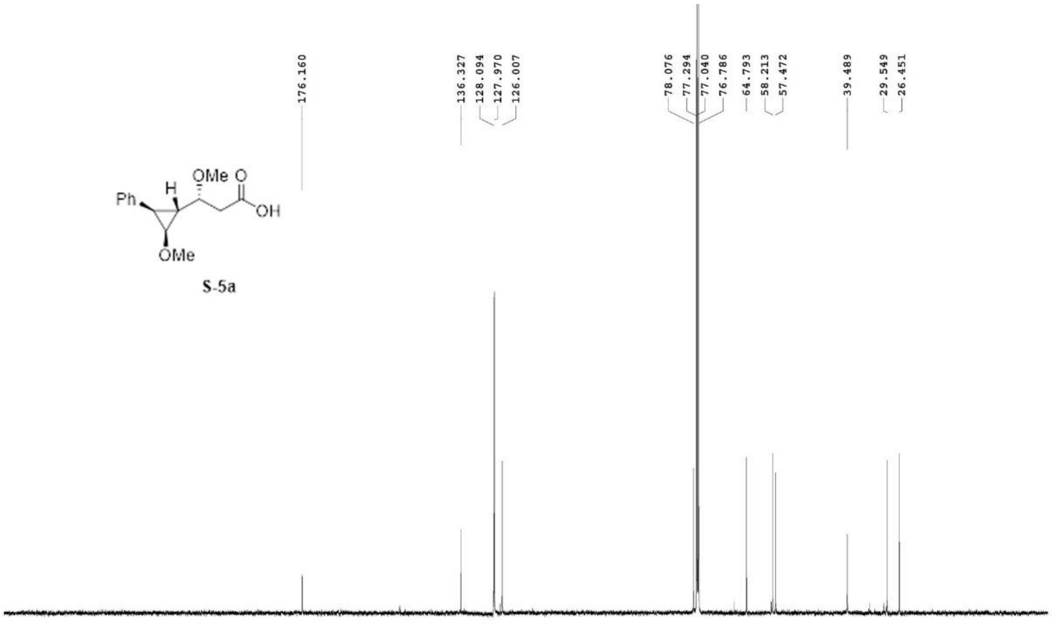

Ph
H
OMe
O
OEt
OMe
S-4b
10
9
8
7
6
5
4
3
2
1
0
ppm
4.46
1.31
2.04
1.16
3.00
1.06
3.02
2.08
0.37
1.03
1.03
3.15

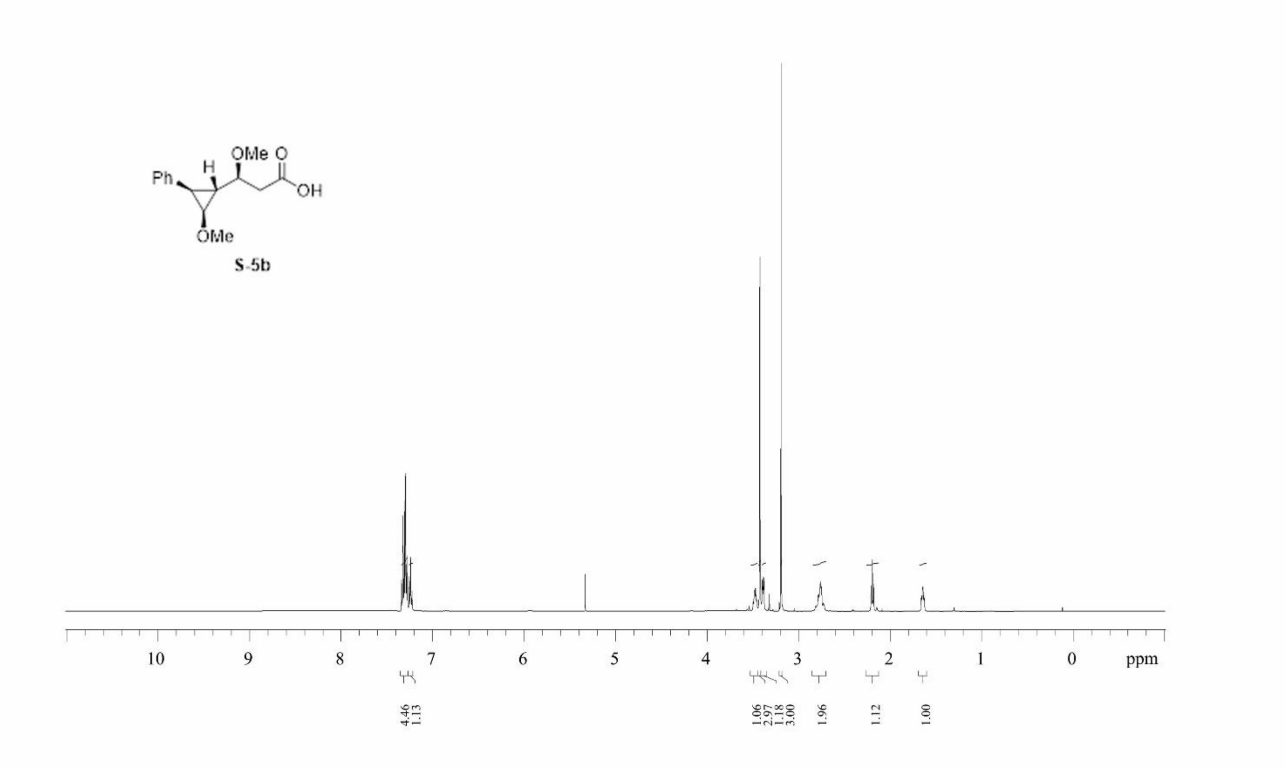

171.301
136.724
128.056
127.976
125.911
78.084
77.312
77.058
76.802
62.544
60.629
58.197
57.332
40.234
29.828
29.307
14.186
Ph
H
OMe
O
OEt
OMe
S-4b
240
220
200
180
160
140
120
100
80
60
40
20
ppm

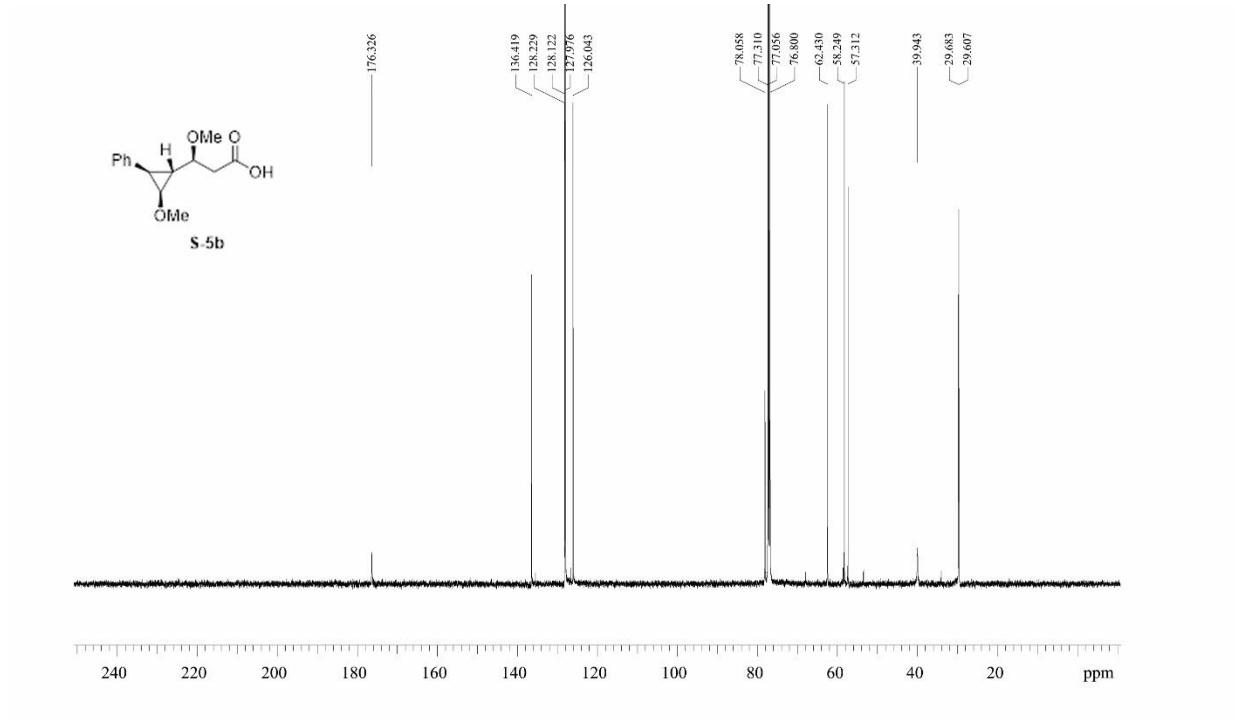


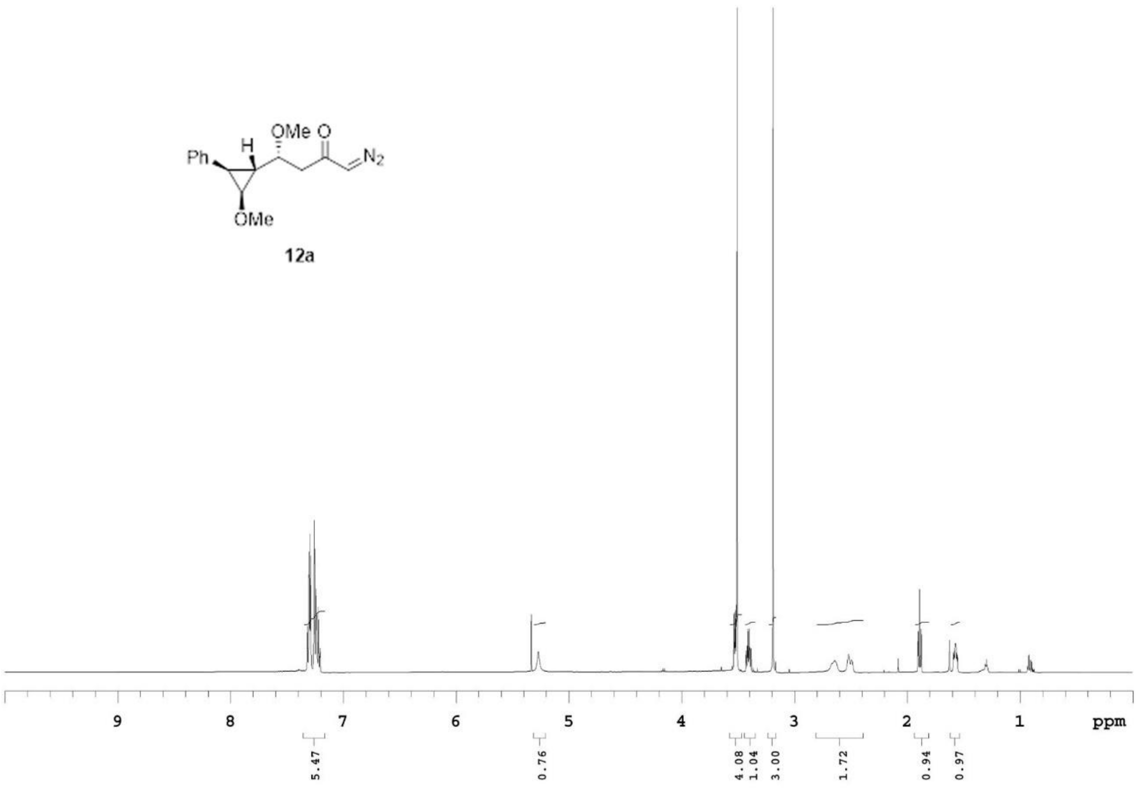
S-5a

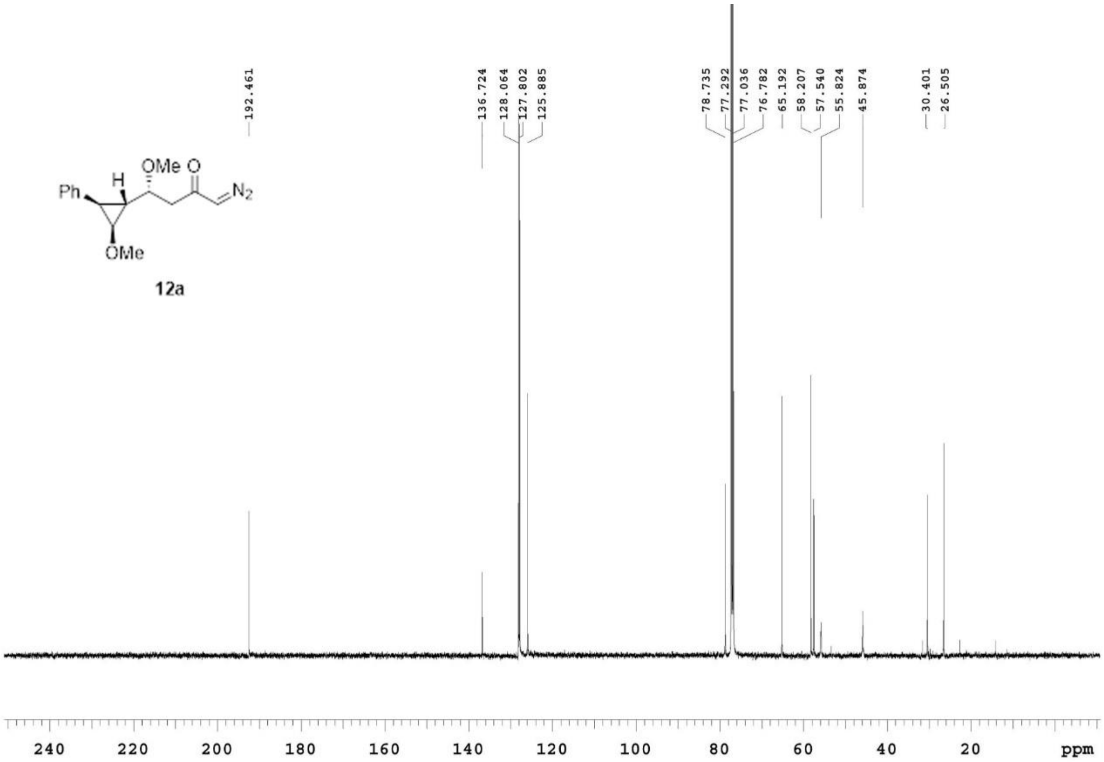

9
8
7
6
5
4
3
2
1
ppm
5.68
3.93
1.20
3.00
2.00
0.97
0.99

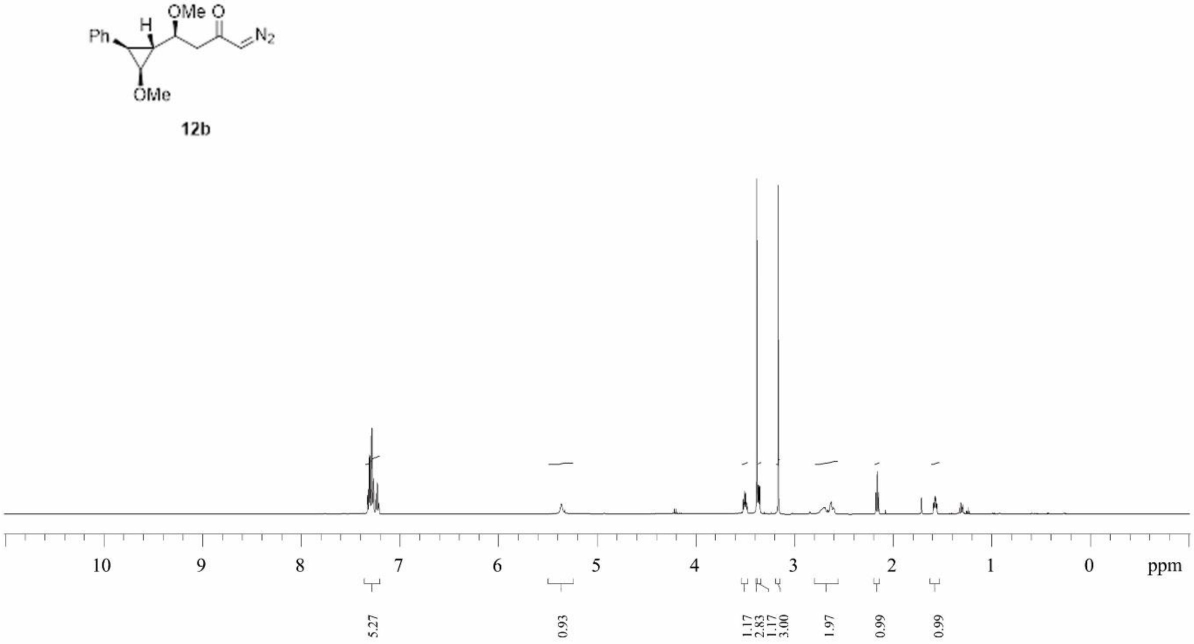

176.160
136.327
128.094
127.970
126.007
78.076
77.294
77.040
76.786
64.793
58.213
57.472
39.489
29.549
26.451
S-5a
240
220
200
180
160
140
120
100
80
60
40
20
ppm


OMe
O
Ph
H
OH
OMe
S-5b
10
9
8
7
6
5
4
3
2
1
0
ppm
4.46
1.13
1.06
2.97
1.18
3.00
1.96
1.12
1.00


176.326
136.419
128.229
128.122
127.976
126.043
78.058
77.310
77.056
76.800
62.430
58.249
57.312
39.943
29.683
29.607
OMe
O
Ph
H
OH
OMe
S-5b
240
220
200
180
160
140
120
100
80
60
40
20
ppm

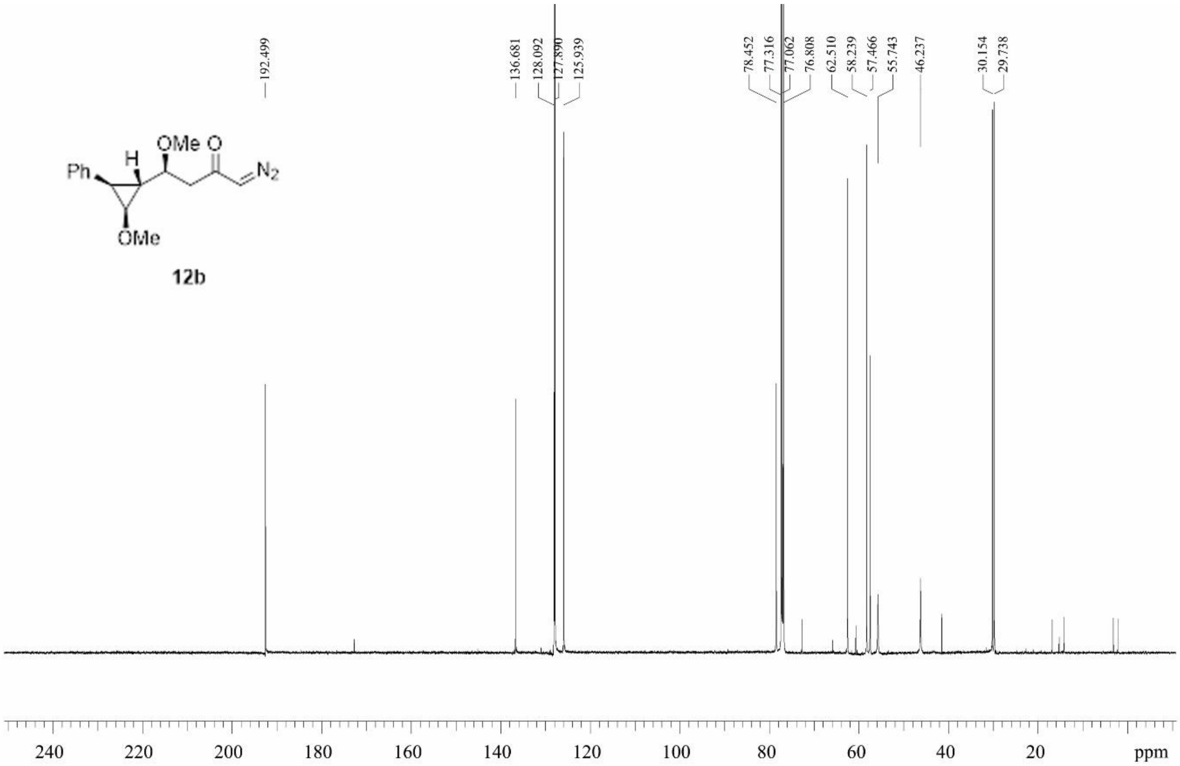

OMe
O
H
Ph
N2
OMe
12a
9
8
7
6
5
4
3
2
1
ppm
5.47
0.76
4.08
1.04
3.00
1.72
0.94
0.97


192.461
136.724
128.064
127.802
125.885
78.735
77.292
77.036
76.782
65.192
58.207
57.540
55.824
45.874
30.401
26.505
OMe
O
H
Ph
N2
OMe
12a
240
220
200
180
160
140
120
100
80
60
40
20
ppm



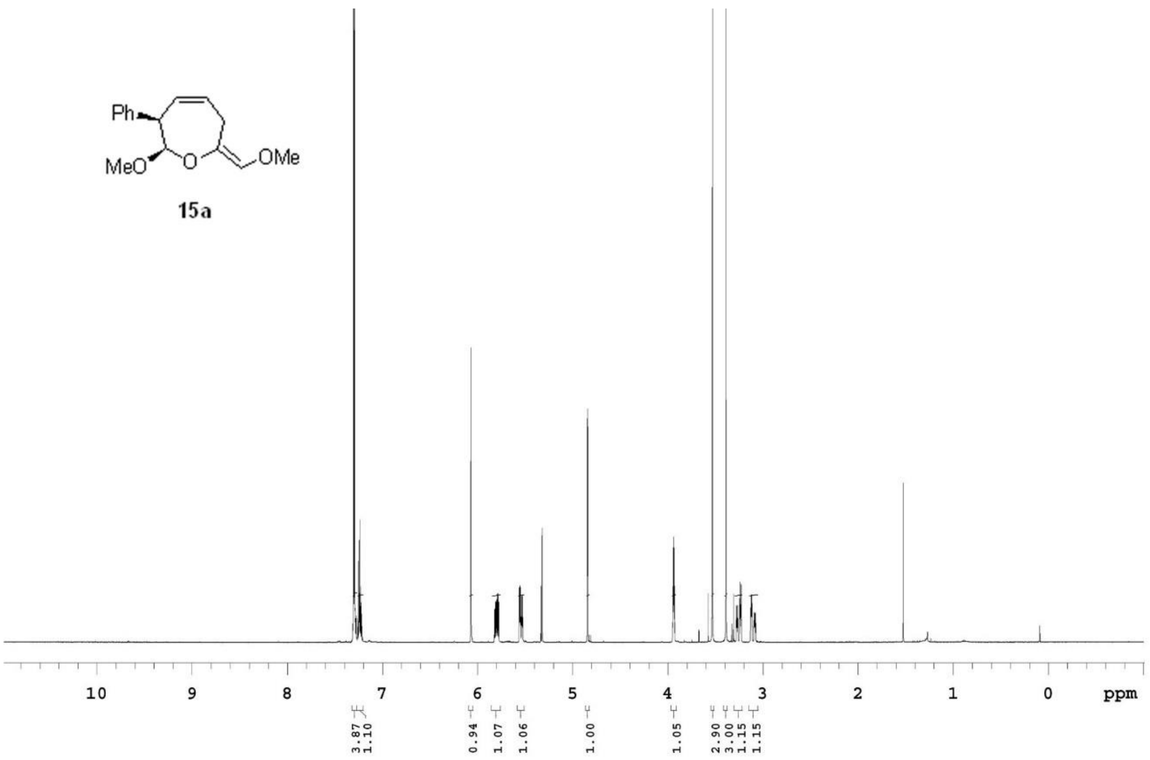
Ph
H
OMe
O
N2
OMe
10
9
8
7
6
5
4
3
2
1
0
ppm
5.27
0.93
1.17
2.83
1.17
3.00
1.97
0.99
0.99

12b

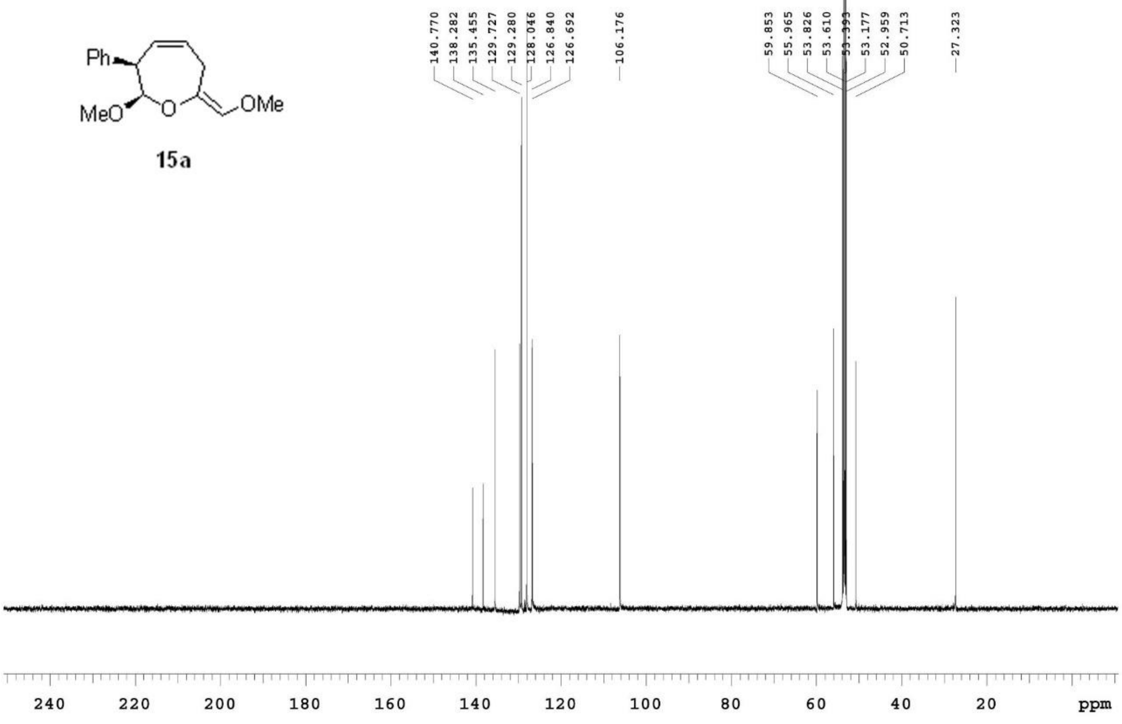


Ph
H
OMe
O
N2
OMe
192.499
136.681
128.092
127.890
125.939
78.452
77.316
77.062
76.808
62.510
58.239
57.466
55.743
46.237
30.154
29.738
240
220
200
180
160
140
120
100
80
60
40
20
ppm

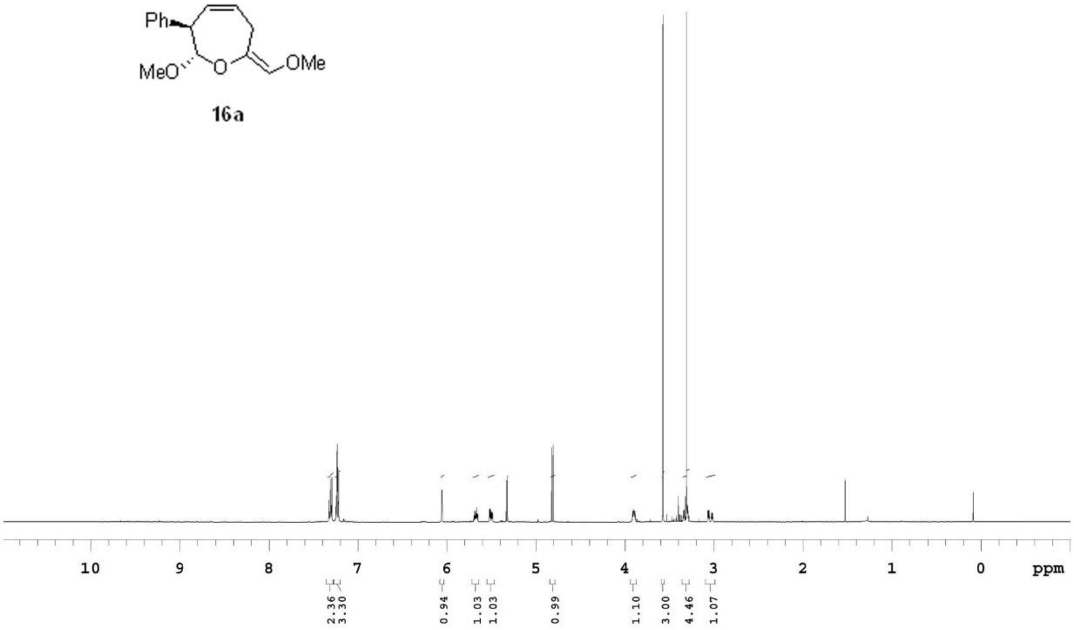
12b


Ph
MeO
O
OMe
10
9
8
7
6
5
4
3
2
1
0
ppm
3.87
1.10
0.94
1.07
1.06
1.00
1.05
2.90
3.00
1.15
1.15

15a

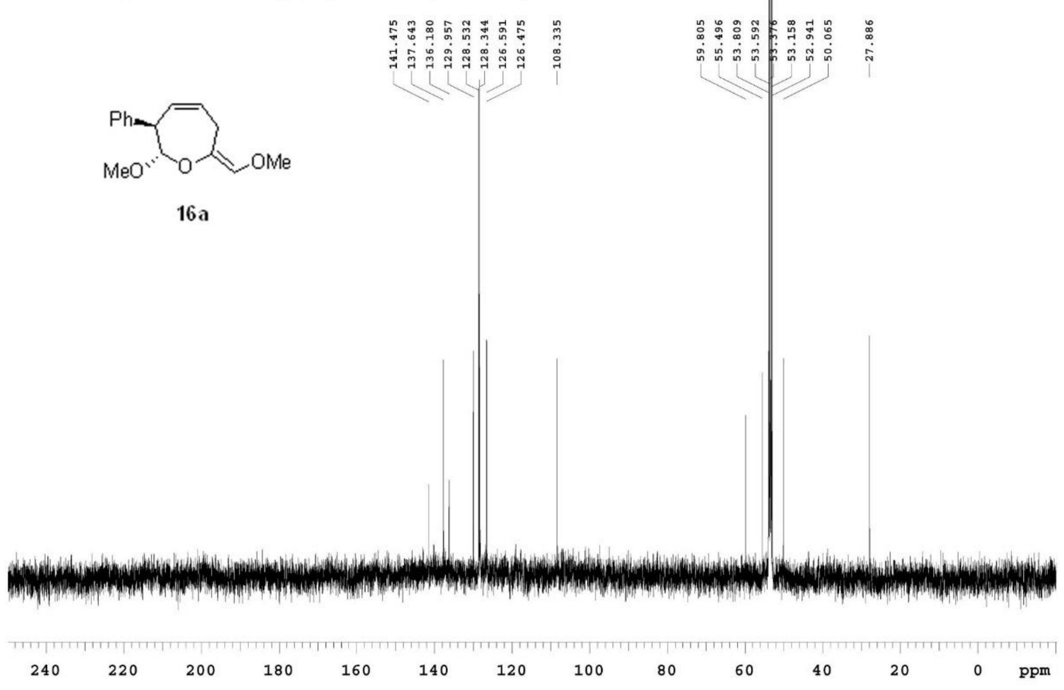

Ph
MeO
O
OMe
140.770
138.282
135.455
129.727
129.280
128.046
126.840
126.692
106.176
59.853
55.965
53.826
53.610
53.393
53.177
52.959
50.713
27.323
240
220
200
180
160
140
120
100
80
60
40
20
ppm

15a



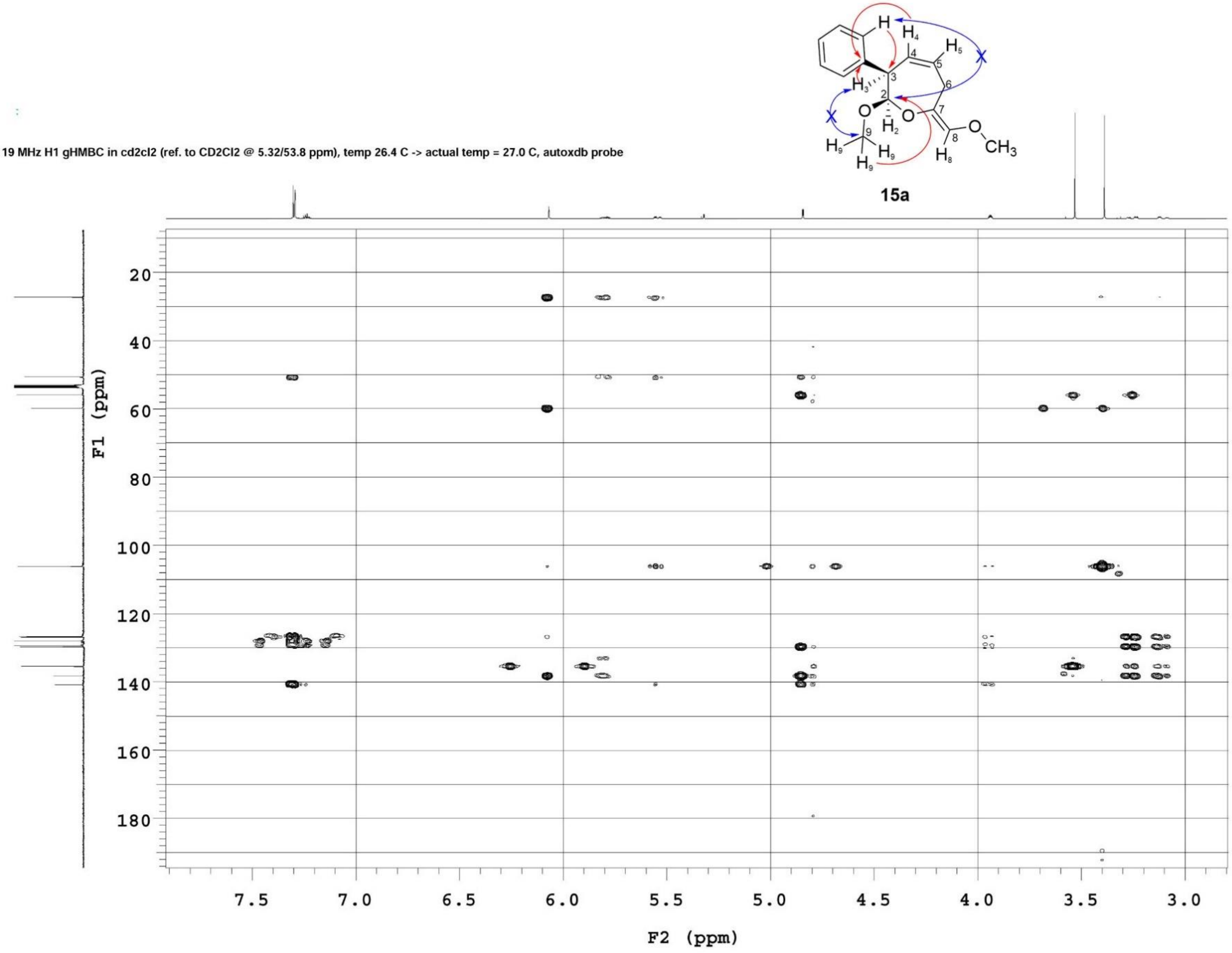
16a

125.266 MHz C13[H1] 1D in cd2cl2 (ref. to CD2Cl2 @ 53.8 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe



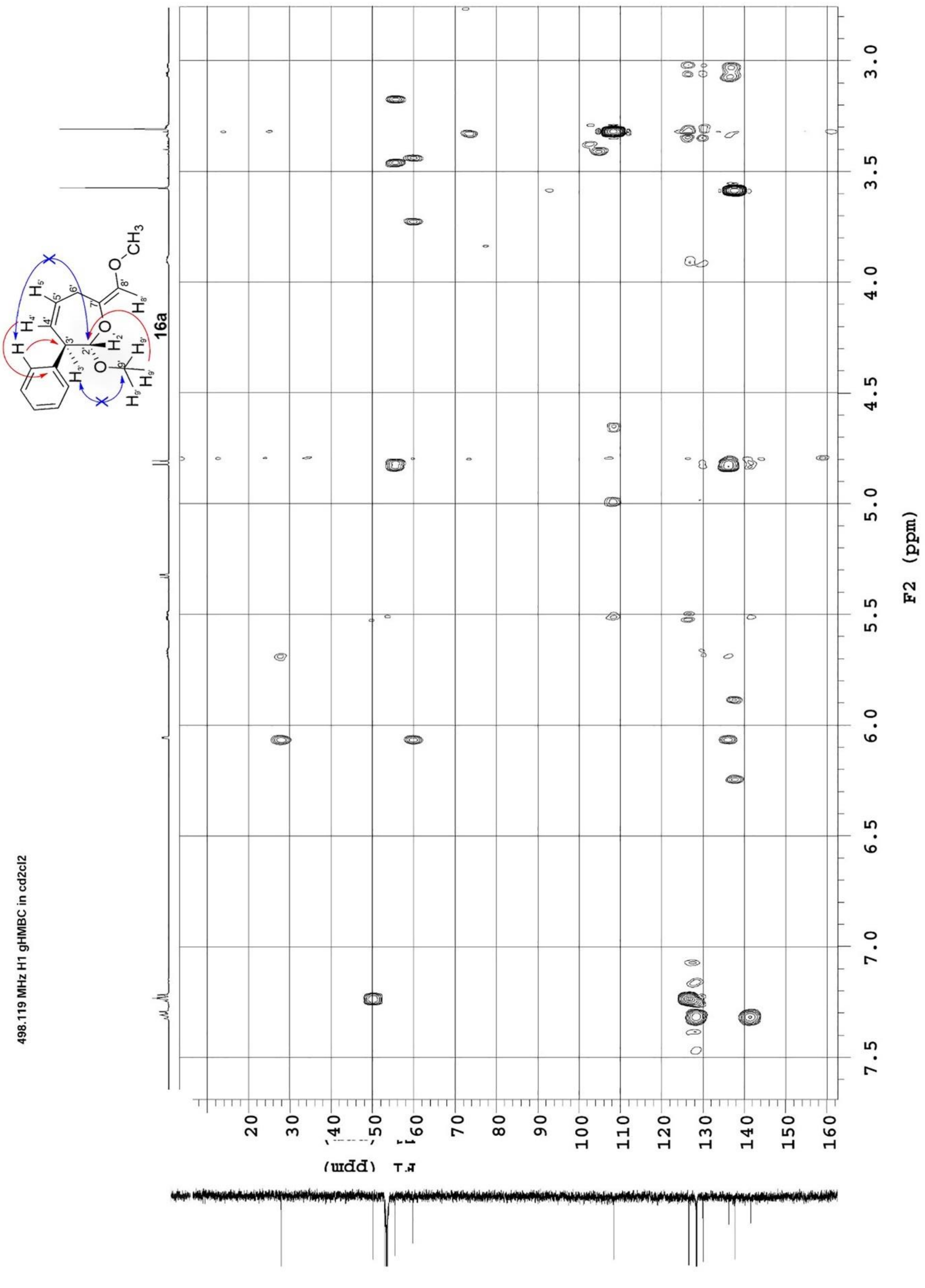
16a

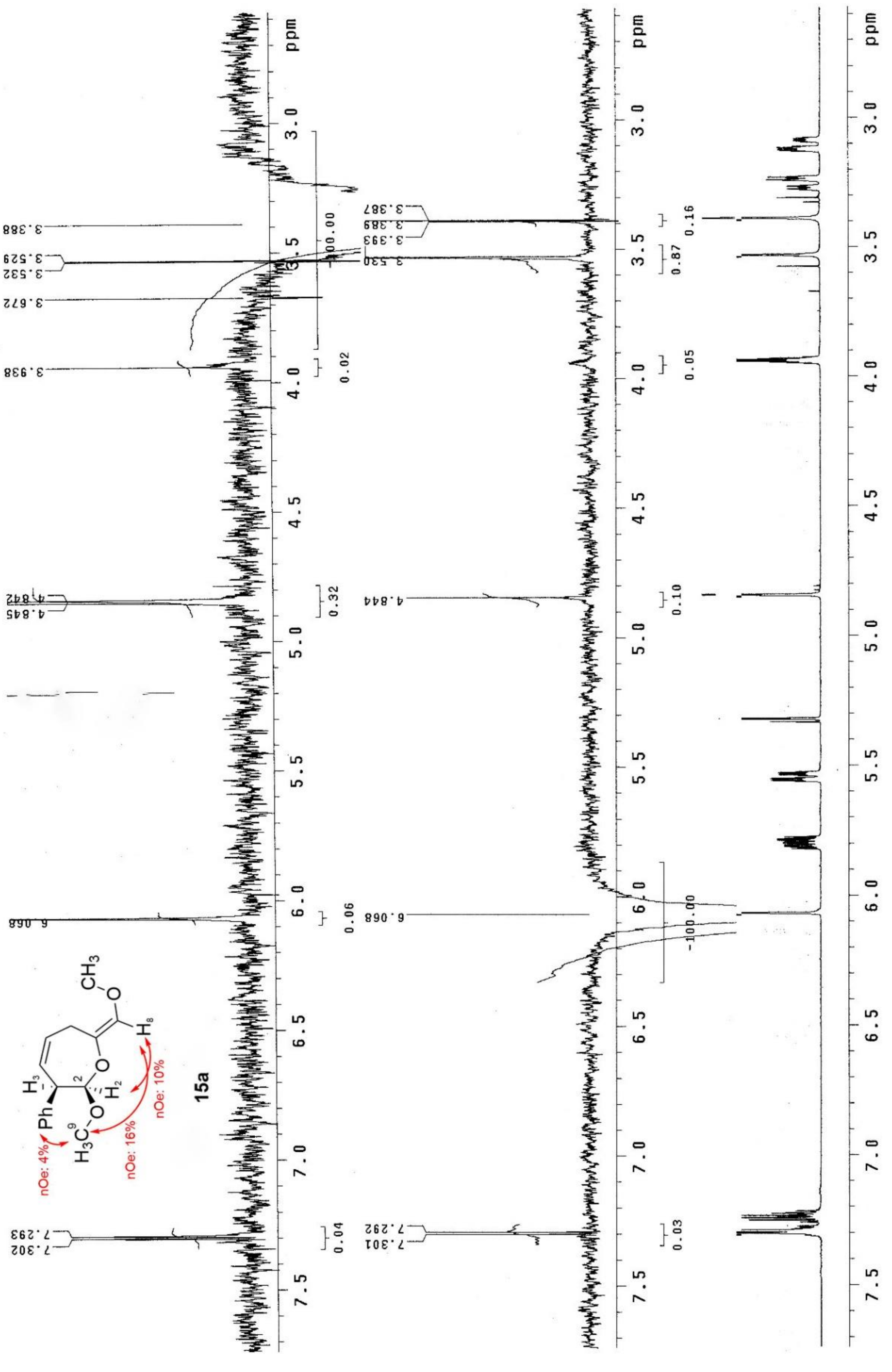
File: /mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Nargess/2014.03/2014.03.06._i5_SNH-06-074-F2-_C-NMR



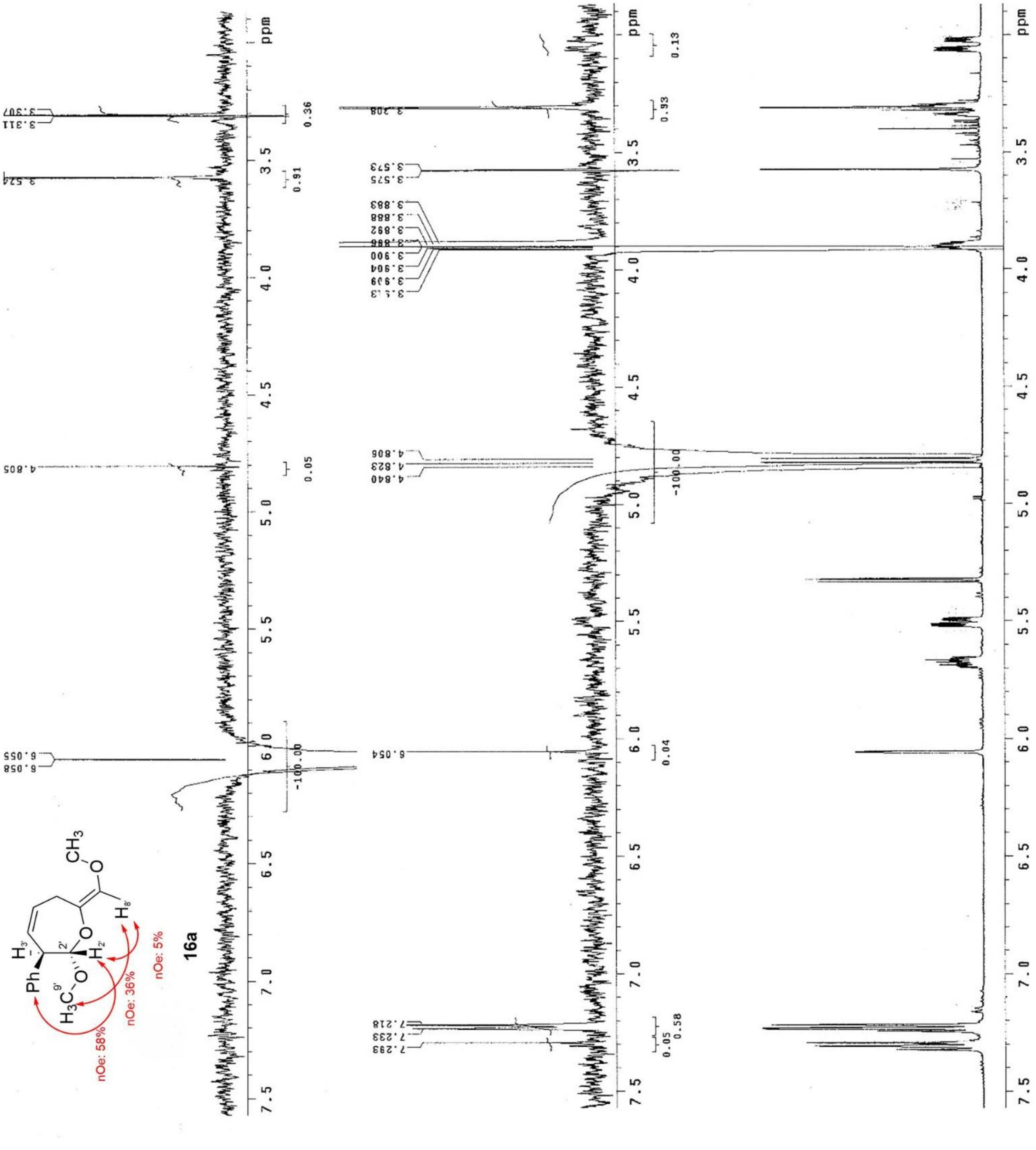
119 MHz H1 gHMBC in cd2cl2 (ref. to CD2Cl2 @ 5.32/53.8 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

15a


498.119 MHz H1 gHMBC in cd2cl2
16a
H3'
H4'
H5'
H8'
H9'
O
CH3
F2 (ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
F1 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160


ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.388
3.529
3.532
3.672
3.938
4.842
4.845
6.068
7.293
7.302
100.00
0.02
0.32
0.06
0.04
3.387
3.389
3.393
3.530
4.844
6.068
7.292
7.301
0.16
0.87
0.05
0.10
-100.00
0.03
CH3
O
H8
O
H2
2
H3
Ph
H3C
9
O
nOe: 4%
nOe: 16%
nOe: 10%

15a


nOe: 58%
nOe: 36%
nOe: 5%
Ph
H3'
2'
9'
H3C
O
H2'
O
H8'
O
CH3
3.307
3.311
3.574
4.805
6.055
6.058
0.36
0.91
0.05
-100.00
3.308
3.573
3.575
3.883
3.888
3.892
3.896
3.900
3.904
3.909
3.913
4.806
4.823
4.840
6.054
7.218
7.233
7.283
0.13
0.93
-100.00
0.04
0.05
0.58
ppm
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

16a

5. X-Ray Structure of S-5b