Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Total synthesis of (+)-Pentamethylsalvianolic acid C

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Electronic Supplementary Information

Experimental

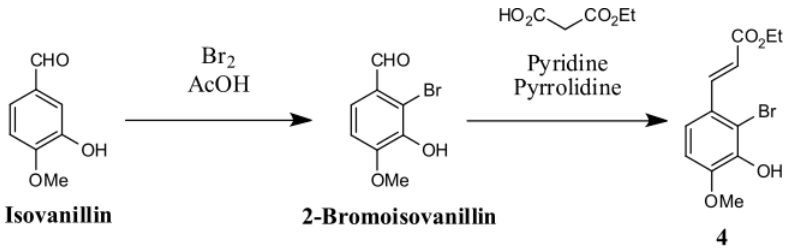
General methods

Unless otherwise noted, all materials obtained from commercial suppliers were used as received. Isovanillin and TBME were obtained from Merck. 3,4-Dimethoxybenzaldehyde was purchased from Acros Organics. 2-Chloroacetic acid, (1S)-(+)-10-camphorsulfonic acid and Amano lipase PS from *Burkholderia cepacia* were obtained from Sigma – Aldrich. Me_3SnOH was purchased from Strem chemicals. Pyridine and pyrrolidine were dried and distilled over KOH; MeOH was dried and distilled over $Mg(OMe)_2$; EtOAc was dried over K_2CO_3; $SOCl_2$ was freshly distilled before each use; K_2CO_3 was dried in an oven at 110^{o}C overnight and stored in a desiccator; Et_3N was dried and distilled over CaH_2 and stored over KOH; CH_2Cl_2 was dried and distilled over CaH_2; tetrachloroethylene (C_2Cl_4) was dried and distilled over CaH_2 under partial vacuum and 1,2-DCE was dried and distilled over CaH_2. Ethyl hydrogen malonate was prepared according to a procedure by Breslow *et al.*[1], (1*S*)-(+)-10-camphorsulfonyl chloride (**32**) was prepared from (1***S***)-(+)-10-camphorsulfonic acid according to procedure adapted from Smiles *et al.*[2], dimethyl (1-diazo-2-oxopropyl)phosphonate (BOH) was prepared from dimethyl (2-oxopropyl)phosphonate (AK Scientific) according to a procedure by Pietruszka *et al.*[3] Thin – layer chromatography was performed on aluminium-backed, SiO_2 gel TLC plates (60 F_{254}) obtained from Merck and were visualised with $KMnO_4$ dip ($KMnO_4$, K_2CO_3, NaOH, H_2O), 20% (w/w) phosphomolybdic acid in EtOH or UV (254 or 350 nm). Column Chromatography (CC), Flash Column Chromatography (FCC) and Vacuum – Liquid Chromatography (VLC) were performed with Davisil LC60A SiO_2 (40-63 µm) which was obtained from Grace Davison Discovery Sciences.

NMR spectra were obtained on the Bruker Avance III 300 MHz spectrometer where the residual solvent peaks from the deuterated solvents ($CDCl_3$ ^{1}H δ 7.27, ^{13}C δ 77.0; d_6-DMSO ^{1}H δ 2.50, ^{13}C δ 39.51) were used as the reference. HRMS spectra were recorded on either the Waters GCT Premier (HR-TOFMS) equipped with an Agilent 7890 GC or Agilent 6220 Accurate Mass LC-TOF system with Agilent 1200 Series HPLC (Monash University). FTIR spectra were obtained on a Perkin – Elmer Spectrum 100 spectrometer. Specific rotations ([α]) were measured on a Rudolph research analytical Autopol IV Polarimeter at the Sodium

D line (589 nm), in a 200 mm glass cell and are recorded in degrees (^{o}). Microwave reactions were performed in a CEM Discover Microwave reactor. Melting points were recorded on a Stuart SMP10 melting point apparatus and are uncorrected.

Ethyl (2*E*)-3(2-bromo-3-hydroxy-4-methoxyphenyl)prop-2-enoate 4[4]



To a stirred solution of isovanillin (38.04 g, 0.25 mol) in AcOH (175 mL) at room temperature was added a solution of Br_2 (42.35 g, 0.265 mol, 1.06 equiv) in AcOH (87 mL) dropwise over a period of 1 hour. The homogeneous solution turned red immediately and the brominated product began to precipitate within the first 5 to 10 minutes of Br_2 addition. Upon completion of the addition the resulting heterogeneous solution was stirred vigorously for an additional hour at room temperature. H_2O (50 mL) was then added and the cream coloured product was filtered off, washed with additional H_2O (50 mL) and allowed to air dry. The crude product was then recrystallised from aqueous EtOH (95%, 1250 mL) to obtain 39.7 g (69%) of **2-Bromoisovanillin** as white crystals.

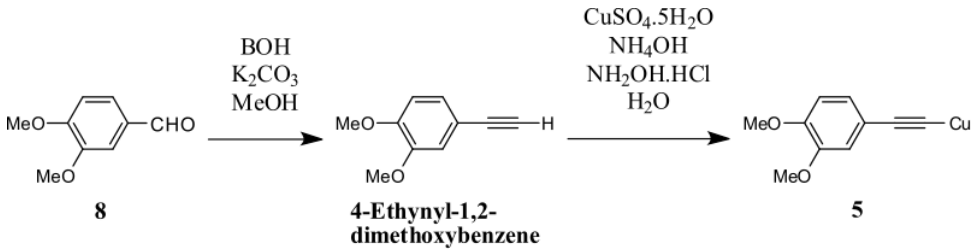
Mp = 202 – 205^{o}C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.93 (3H, s, OCH_3), 7.15 (1H, d, J = 8.4 Hz, ArH), 7.42 (1H, d, J = 8.4 Hz, ArH), 9.93 (1H, br s, OH), 10.11 (1H, s, CHO); ^{13}C NMR (75 MHz, d_6-DMSO) δ 59.45 (OCH_3), 110.37, 113.42, 121.97, 126.65, 144.01, 153.32, 190.78 (CHO); IR (KBr) 3202.79, 3019.97, 2979.42, 2942.76, 2894.70, 1663.40, 1588.30, 1563.45, 1494.07, 1460.27, 1429.51, 1277.13, 1236.33, 1205.90, 1170.06, 1130.80, 1022.26 cm^{-1}; HRMS (EI) calculated for $C_8H_7BrO_3$ $[M]^+$: 229.9579, found: 229.9607.

To a stirred solution of **2-bromoisovanillin** (11.55 g, 50 mmol) in freshly distilled pyridine (26 mL) was added ethyl hydrogen malonate (13.21 g, 100 mmol, 2 equiv) followed by anhydrous pyrrolidine (0.63 mL, 7.5 mmol, 15 mmol%). A reflux condenser was then attached followed by a $CaCl_2$ drying tube and the reaction mixture was heated to 100^{o}C. The moderately viscous solution was stirred vigorously at this temperature for 6 hours. The reaction mixture was then allowed to cool and the majority of the pyridine was evaporated. The oily residue was then treated with dilute aqueous HCl (2M, 120 mL) and EtOAc (200 mL). The layers were separated and the organic layer was washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered through a small pad (5 cm) of SiO_2 and evaporated. The

resulting pink solid was then recrystallised from hot EtOAc (130 mL) and dried *in vacuo* to yield 11.2 g (74%) of **4** as a light pink crystalline solid.

Mp. = 135 – 136°C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.25 (3H, t, J = 14.3, 7.1 Hz, **CH$_3$**CH$_2$), 3.87 (3H, s, OCH$_3$), 4.18 (2H, q, J = 21.4, 14.3, 7.1 Hz, CH$_3$**CH$_2$**), 6.50 (1H, d, J = 16 Hz, C=**CH**CO$_2$Et), 7.02 (1H, d, J = 8.7 Hz, ArH), 7.43 (1H, d, J = 8.7 Hz, ArH), 7.90 (1H, d, J = 15.8 Hz, Ar**CH=C**), 9.69 (1H, br s, OH); ^{13}C NMR (75 MHz, d_6-DMSO) δ 14.17 (**CH$_3$**CH$_2$), 56.22 (OCH$_3$), 60.05 (CH$_3$**CH$_2$**), 110.82, 112.92, 118.27, 118.78, 126.22, 142.66, 144.00, 149.82, 166.07 (**CO$_2$**Et); IR (KBr) 3379.80, 3000.79, 2984.60, 2966.86, 2941.57, 2873.44, 2842.73, 1698.21, 1631.66, 1591.38, 1490.29, 1467.14, 1453.32, 1443.39, 1276.45, 1257.79, 1190.11, 1172.10, 1139.40, 1029.15, 986.69, 972.88 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{13}BrO_4$ $[M]^+$: 299.9997, found: 299.9984.

Copper(I) (3,4-dimethoxyphenyl)ethyne 5[4]



A 1 L RBF was charged with 3,4-dimethoxybenzaldehyde (6.65 g, 40.0 mmol) followed by anhydrous K_2CO_3 (11.06 g, 80 mmol, 2 equiv) and an oval shaped magnetic stir bar. Freshly distilled MeOH (440 mL) was then added followed by a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (BOH, 9.22 g, 48 mmol, 1.2 equiv) in freshly distilled MeOH (4 mL) making [CHO] equal to 90 mM. The vessel was sealed with a rubber suba-seal and a needle was quickly placed in the seal to vent the N_2 gas evolved. Progress of the reaction was monitored via TLC (32% EtOAc/Hexane) and after 24 h of stirring at room temperature a maximum conversion of 88% to the acetylene was observed via GC/MS. The reaction mixture was then diluted with Et_2O (400 mL) and washed with dilute aqueous $NaHCO_3$ solution (400 mL, 5% (w/v)). The layers were separated and the aqueous layers were re-extracted with Et_2O (2 × 200 mL). The combined ethereal layers were then washed with brine (3 × 200 mL), dried over $MgSO_4$, filtered through a pad of Celite and evaporated. The yellow residue was then subjected to FCC (SiO_2, 10% EtOAc/Hexane) to obtain 5.1 g (79%) of **4-ethynyl-1,2-dimethoxybenzene** as white crystals.

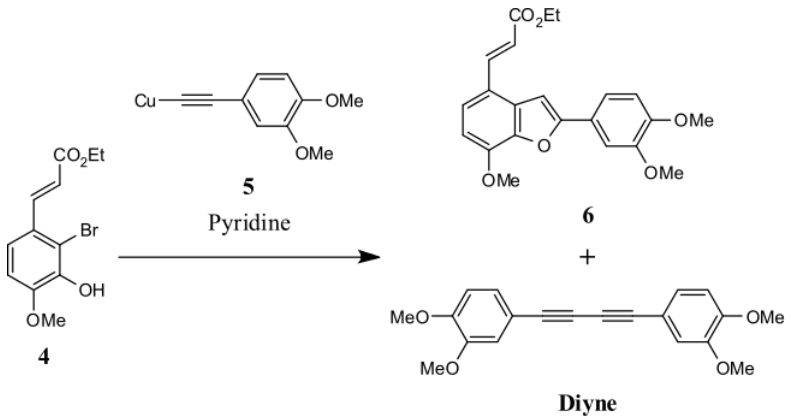
Mp. = 73 – 74°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (1H, s, CH), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.81 (1H, d, J = 8.3 Hz, ArH), 7.0 (1H, d, J = 1.9 Hz, ArH), 7.11 (1H, dd, J = 8.3, 1.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.80 (OCH_3), 55.81 (OCH_3), 75.61 (C≡**C**H), 83.71 (Ar**C**≡C), 110.88, 114.14, 114.65, 125.41, 148.52, 149.80; IR (KBr) 3259.03, 3250.87 (C≡C**H**), 2969.89, 2938.99, 2843.36, 1596.96, 1579.07, 1510.33, 1452.19, 1446.01, 1407.53, 1323.65, 1262.34, 1239.51, 1151.68, 1137.43, 1025.01 cm^{-1}; HRMS (EI) calculated for $C_{10}H_{10}O_2$ $[M]^+$: 162.0681, found: 162.0681.

In a 1 L conical flask, $CuSO_4.5H_2O$ (7.49 g, 30.0 mmol, 1 equiv) was dissolved in NH_4OH (30 mL, 28% (aq)) at room temperature and allowed to stir under a high flow of N_2 for 5 min. Deionised H_2O (120 mL) was added followed by $NH_2OH.HCl$ (5.59 g, 80.4 mmol,

2.68 equiv). The dark blue solution then turned light blue and a mild effervescence was observed. This is thought to be due to the oxidation state of the Cu species changing from 2^+ to 1^+. The light blue solution was cooled to 0^oC (ice/H_2O) and a solution of **4-ethynyl-1,2-dimethoxybenzene** (4.87 g, 30 mmol) in THF (27 mL) and absolute EtOH (27 mL) was added slowly. A bright yellow solid formed immediately and was filtered off. The yellow solid was washed with H_2O (5 × 50 mL), EtOH (5 × 50 mL) and Et_2O (5 × 50 mL) before being dried overnight (14 to 16 hours) at 65^oC in a vacuum oven (10 mmHg) to obtain 6.2 g (91%) of **5** as a dark yellow – orange solid. This cuprous acetylide is stable for over a year when stored in the refrigerator (3 – 5^oC) in a tightly sealed vial.

Mp. = 233 – 234^oC, IR (KBr) 2990.83, 2959.05, 2926.95, 2829.87, 1633.96, 1594.28, 1578.25, 1508.40, 1462.06, 1436.18, 1406.14, 1322.32, 1265.96, 1237.60, 1137.45, 1026.87 cm^{-1}.

Ethyl (2*E*)-3-[2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-4-yl]prop-2-enoate 6



A 500 mL, oven-dried, three-necked RBF was equipped with a reflux condenser topped with a gas inlet adapter, a rubber suba-seal, a glass stopper and a large, oval shaped magnetic stir bar. The whole apparatus was flame-dried (Bunsen burner) and allowed to cool under N_2. Freshly distilled pyridine (107 mL) was added and degassed with N_2 for 1 hour. **5** (4.49 g, 20 mmol, 1 equiv) was added and a viscous bright yellow suspension was obtained. In a separate, flame-dried 250 mL Schlenk flask a solution of **4** (6.02 g, 20 mmol) in freshly distilled, degassed pyridine (53 mL) was prepared under N_2 and transferred via cannula to the above suspension. The Schlenk flask and cannula were rinsed with additional distilled, degassed pyridine (5 mL) and the final reaction mixture was set to reflux at 130^{o}C with vigorous stirring for 20 hours. The dark brown solution was then allowed to cool to room temperature before the pyridine was evaporated. The resulting dark brown residue was then dissolved in $CHCl_3$ (230 mL) and deionised H_2O (80 mL) was added. The biphasic mixture was filtered through a Büchner funnel and the layers were separated. The aqueous layer was extracted again with $CHCl_3$ (2 × 200 mL) and the combined organic layers were washed with deionised H_2O (2 × 80 mL), dried over $MgSO_4$, filtered through Celite and evaporated to obtain 14.2 g of crude material.

With the crude product still highly contaminated with Cu salts and residues it was found best to conduct the purification over three steps. First the dark residue was subjected to FCC (SiO_2, 2:1 EtOAc/Hexane) on a short column to remove the black/brown band to provide 6.4 g of a mixture of **6** and the diyne by-product. This mixture was subjected to a second round of FCC (SiO_2, CH_2Cl_2 then EtOAc) where 0.8 g (12%) of diyne by-product was eluted

first with CH_2Cl_2 and 4.57 g of **6** eluted second with EtOAc. This sample of **6** was recrystallised from EtOAc to afford 2.9 g (51%) of pure **6**.

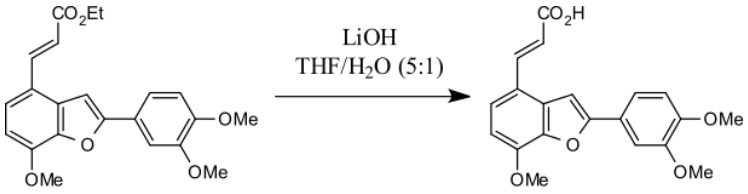
6

Mp. = 144 – 145°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 14.4, 7.2 Hz, **C**$\mathbf{H_3}$$CH_2$), 3.96 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 4.31 (2H, q, J = 21.4, 14.4, 7.2 Hz, **C**$\mathbf{H_2}$$CH_3$), 6.48 (1H, d, J = 16.0 Hz, C=**CH**CO_2Et), 6.81 (1H, d, J = 8.5 Hz, ArH), 6.96 (1H, d, J = 8.6 Hz, ArH), 7.20 (1H, s, ArH), 7.40 (2H, m, ArH), 7.53 (1H, dd, J = 8.5, 1.8 Hz, ArH), 7.94 (1H, d, J = 16.3 Hz, Ar**HC=C**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.28 (**C**$\mathbf{H_3}$$CH_2$), 55.79 ($OCH_3$), 55.95 (2 × OCH_3), 60.23 (**C**$\mathbf{H_2}$$CH_3$), 99.03, 106.35, 108.01, 111.10, 116.14, 118.23, 119.81, 122.63, 124.79, 130.36, 142.34, 143.51, 146.47, 149.06, 149.83, 157.21, 167.35 (**C**O_2Et); IR (KBr) 2984.83, 2932.52, 2906.20, 2837.30, 1700.61, 1614.74, 1578.29, 1516.78, 1506.08, 1464.76, 1406.47, 1260.50, 1217.54, 1173.39, 1141.17, 1097.68, 1046.61, 1024.89, 970.71; HRMS (EI) calculated for $C_{22}H_{22}O_6$ $[M]^+$ 382.1416, found 382.1418.

Diyne

Mp. = 187 – 188°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (6H, s, 2 × OCH_3), 3.91 (6H, s, 2 × OCH_3), 6.82 (2H, d, J = 8.4 Hz, 2 × ArH), 7.02 (2H, d, J = 2.0 Hz, 2 × ArH), 7.15 (2H, dd, J = 8.6, 2.0, Hz, 2 × ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.75 (4 × OCH_3), 77.68 (2 × ArC≡**C**), 81.37 (2 × Ar**C**≡C), 110.91 (2 × ArC), 113.74 (2 × ArC), 114.63 (2 × ArC), 126.01 (2 × ArC), 148.51 (2 × ArC), 150.15 (2 × Ar**C**OCH_3); IR (KBr) 2979.79, 2955.15, 2933.07, 2844.47, 2142.99 (C≡C), 1593.39, 1572.27, 1508.49, 1444.93, 1320.93, 1262.72, 1229.89, 1176.57, 1138.03, 1018.78 cm^{-1}; HRMS (EI) calculated for $C_{20}H_{18}O_4$ $[M]^+$: 322.1205, found: 322.1274.

(2*E*)-3-[2-(3,4-Dimethoxyphenyl)-7-methoxy-1-benzofuran-4-yl]prop-2-enoic acid 2

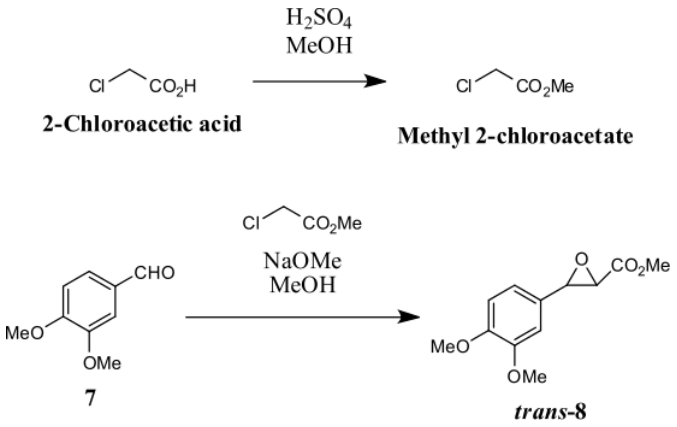


6 **2**

To a stirred solution of **6** (2.00 g, 5.23 mmol) in THF/H_2O (110 mL, 5:1) under N_2 was added an aqueous solution of LiOH (26.15 mL, 1 M (aq)). The biphasic mixture was then heated to 70°C and stirred at this temperature for 7 hours. Deionised H_2O (200 mL) and EtOAc (100 mL) were added and the layers were separated. The EtOAc layer was discarded and the pH of the aqueous phase was adjusted to 1 with dilute aqueous HCl (6 M). The free carboxylic acid then precipitated and was filtered off with a glass frit funnel, washed with Et_2O (2 × 100 mL) and dried *in vacuo* to liberate 1.5 g (83%) of **2** as a bright yellow solid. This product was sufficiently pure for the next step but could be recrystallised from a small volume of THF at room temperature.

Mp. = 250 – 251°C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.82 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 6.57 (1H, d, J = 16.1 Hz, C=C**H**CO_2H), 6.95 (1H, d, J = 8.5 Hz, ArH), 7.07 (1H, d, J = 8.1 Hz, ArH), 7.55 (3H, m, ArH), 7.79 (1H, s, ArH), 7.85 (1H, d, J = 16.1 Hz, Ar**H**C=C), 12.33 (1H, br s, CO_2**H**); ^{13}C NMR (75 MHz, d_6-DMSO) δ 55.56 (OCH_3), 55.75 (OCH_3), 56.00 (OCH_3), 99.88, 107.13, 108.53, 111.90, 117.26, 117.77, 119.48, 122.14, 125.13, 130.16, 141.54, 142.83, 146.19, 149.13, 149.86, 156.77, 168.04 (CO_2H); IR (KBr) 3434.77, 2999.44, 2967.28, 2939.72, 2840.48, 2590.53, 1665.44, 1609.03, 1516.72, 1499.59, 1405.67, 1283.58, 1258.88, 1183.40, 1140.84, 1102.83, 1026.77, 972.69 cm^{-1}; HRMS (ESI) calculated for $C_{20}H_{17}O_6$ $[M - H]^-$: 353.1025, found: 353.1029.

Methyl (2*E*)-3-(3,4-dimethoxyphenyl)oxirane-2-carboxylate *trans*-8



Methyl 2-chloroacetate

In a 2L three-neck RBF equipped with a 250 mL pressure equalising addition funnel, reflux condenser, glass stopper and large oval shaped magnetic stir bar, a solution of 2-chloroacetic acid (469.93 g, 5.0 mol) in AR grade MeOH (321.19 g, 10.0 mol, 2 equiv) was prepared. Concentrated H_2SO_4 (250.12 g, 2.6 mol, 50 mol%) was added quickly (within 5 min) via the addition funnel. An exothermic reaction is observed. After 30 min of stirring two separate layers were formed and the temperature of the reaction had returned to room temperature. The two layers were separated. The initial top layer (acidic, pH = 1) was washed with deionised H_2O (750 mL) and the layers were separated. The first and second bottom layers were then combined and washed with saturated aqueous $NaHCO_3$ (500 mL, 10% (w/v)), deionised H_2O (500 mL) and dried over $MgSO_4$. The crude product was then distilled over $MgSO_4$. The first fraction (5 – 10 mL) was discarded and the fraction boiling at 129 – 130^{o}C/760 mmHg was collected. The isolated yield of **methyl 2-chloroacetate** was 216.3 g (40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (3H, s, CO_2CH_3), 4.08 (2H, s, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.26 (CH_2), 52.44 ($CO_2\mathbf{C}H_3$), 167.34 ($\mathbf{C}O_2CH_3$); HRMS (EI) calculated for $C_3H_5ClO_2$ $[M]^+$: 107.9978 found: 107.9975

The apparatus, consisting of a 1L 3-neck RBF equipped with a mechanical stirrer, 250 mL pressure equalising addition funnel fitted with a rubber septum and a reflux condenser topped with an gas inlet adapter was assembled, flame dried under vacuum and cooled under N_2.

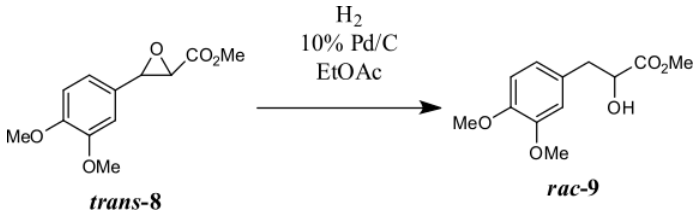
Freshly distilled MeOH (300 mL) was then added via cannula through the addition funnel. The stirrer was started and hexane-washed sodium metal (18.75 g, 0.81 mol, 2.7 equiv) was added in portions by removing and replacing the condenser. After approximately half of the Na was added, the rate of formation of NaOMe slowed. The stirrer speed was increased and the second half of Na was added at a faster rate. At this point the formation of NaOMe ceased and unreacted Na remained. The vessel was heated with a bunsen burner to reflux and maintained this temperature for 15 to 30 min until all Na had reacted. Once all Na had reacted the cloudy solution was allowed to cool to room temperature while the next reagents were prepared.

An oven dried 250 mL Schlenk flask was assembled with a rubber septum, flame dried and cooled under N_2. Ground 3,4-dimethozybenzaldehyde (49.86 g, 0.3 mol, 1 equiv) was added to the Schlenk flask followed by **methyl 2-chloroacetate** (87.97 g, 0.81 mol, 2.7 equiv). This flask was evacuated and purged with N_2 (3×) then swirled until a homogenous solution was achieved. The contents of this flask were then transferred via cannula to the addition funnel. The methanolic NaOMe solution was then cooled to -10^{o}C (ice/NaCl, -20^{o}C) and the yellow – orange solution in the addition funnel was added drop-wise over a period of 3 hours with vigorous stirring. During the addition a thick white precipitate formed and even stirring became difficult. The temperature of the ice bath was raised to -10^{o}C (reaction temperature 5^{o}C) and the reaction was stirred for a further 2 hours. The ice bath was then removed and the reaction mixture was allowed to warm to room temperature over 3 hours. During this time stirring became easier, the colour of the solution changed to yellow and a free flowing white precipitate formed. The crude mixture was then poured into a chilled solution of AcOH (15 mL) in deionised H_2O (585 mL) with additional deionised H_2O rinses. A white precipitate formed immediately, was filtered off and dried *in vacuo* yielding 59.28 g (83%) of an off white pasty solid. This crude solid was then dissolved in the minimum amount of EtOAc at room temperature and charcoal was added. The black suspension was stirred for 20 minutes at room temperature, dried over $MgSO_4$ and filtered. A sufficient amount of hexane was added to the filtrate to induce cloudiness and recrystallization was carried out. The recrystallisation was repeated three times for a total yield of 34.9 g (49%) where ***trans*-8** was obtained as white crystals.

Mp. = 60 – 62^{o}C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.73 (3H, s, CO_2CH_3), 3.75 (6H, s, 2 × OCH_3), 3.87 (1H, d, J = 1.9 Hz, *trans*-C**H**CO_2CH_3), 4.09 (1H, d, J = 1.9 Hz, *trans*-C**H**Ar),

6.90 (1H, s, ArH), 6.95 (2H, d, J = 0.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.32 (**CH**CO_2CH_3), 55.68 (OCH_3), 55.73 (OCH_3), 56.33 (CO_2**CH$_3$**), 57.84 (Ar**CH**), 107.91, 110.93, 118.70, 127.00, 149.51 (2 × Ar**CO**CH_3), 168.48 (**C**O_2CH_3); IR (KBr) 3007.27, 2952.81, 2843.58, 1726.20, 1610.76, 1595.57, 1520.52, 1452.98, 1437.99, 1413.59, 1307.46, 1267.75, 1242.14, 1224.48, 1155.11, 1141.17, 1025.15 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{14}O_5$ $[M]^+$: 238.0841, found: 238.0905

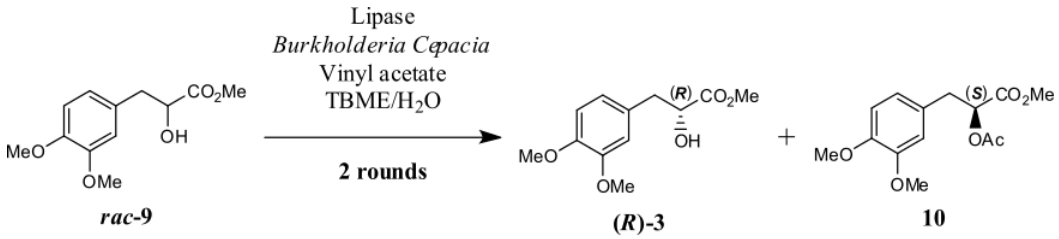
Methyl (2-*rac*)-3-(3,4-dimethoxyphenyl)-2-hydroxypropanoate *rac*-9



An oven dried 2-neck 250 mL RBF was assembled with a tubing adapter including Teflon tap, a second tubing adapter with Teflon tap attached to a balloon and a large oval shaped magnetic stir bar. ***trans*-8** (19.35 g, 81.22 mmol) was then added followed by anhydrous EtOAc (122 mL) and 10% Pd/C (1.35 g, 7% w/w per gram of ***trans*-8**). Both Quick-fit joins were then greased and the reaction vessel was evacuated and purged with H_2 (×3). The balloon was then filled with H_2 and the vessel was closed to maintain positive H_2 atmosphere. The black suspension was then vigorously stirred at room temperature for 8 hours. Progress of the reaction was monitored via TLC (32% EtOAc/Hexane + 1% Et_3N) and upon completion the H_2 was vented (fume-hood), the black suspension filtered through a pad of Celite with anhydrous EtOAc rinses (3×) and the combined filtrates were evaporated. The resulting crude light green to yellow oil was then purified via FCC (SiO_2, 10% Et_2O/CH_2Cl_2) to afford 16.7 g (85%) of ***rac*-9** as a white solid.

Mp. = 49 – 50°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69 (1H, d, J = 6.4 Hz, OH), 2.93 (1H, dd, J = 14.3, 6.8 Hz, **H**CH), 3.09 (1H, dd, J = 14.0, 4.4 Hz, HC**H**), 3.79 (3H, s, CO_2CH_3), 3.868 (3H, s, OCH_3), 3.875 (3H, s, OCH_3), 4.45 (1H, m, CH), 6.78 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.89, 52.17, 55.60, 55.64, 71.23, 110.99, 112.54, 121.30, 128.64, 147.80, 148.58, 174.34 (**CO_2**CH_3); IR (KBr) 3394.35, 3006.58, 2989.98, 2948.49, 2908.85, 2833.13, 1726.60, 1593.98, 1516.78, 1461.85, 1444.87, 1264.10, 1241.89, 1214.18, 1157.30, 1141.84, 1098.59, 1028.05 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{16}O_5$ $[M]^+$: 240.0998, found: 240.1012.

Methyl (2*R*)-3-(3,4-dimethoxyphenyl)-2-hydroxypropanoate (*R*)-3 and Methyl (2*S*)-2-(acetyloxy)-3-(3,4-dimethoxyphenyl)propanoate 10



This lipase mediated resolution was conducted in batches. A typical experiment would consist of two 10 mmol scale reactions run side-by-side. Upon completion they were filtered on the same sintered glass funnel, thereby combining the products from both reactions. Described below is a procedure for one of these batches.

To a 100 mL single neck RBF equipped with an oval shaped, Teflon coated magnetic stir bar was placed ground ***rac*-9** (2.40 g, 10 mmol) followed by TBME (25 mL) and deionised H_2O (250 µL). The resulting mixture was then stirred until homogenous and Amano lipase PS from *Burkholderia cepacia* (2.40 g, 1 wt equiv) was added followed by freshly distilled Vinyl acetate (9.4 mL, 10 equiv). A reflux condenser equipped with a gas inlet adapter was attached and the heterogeneous reaction mixture was placed under N_2, set to 50^{o}C (oil bath) and stirred vigorously (1000 rpm) at this temperature for 48 hours.

The two reaction mixtures were then cooled to room temperature and filtered through a pad of Celite/$MgSO_4$ on the same sintered glass funnel. The filter cake was rinsed with EtOAc (3×) and the combined filtrates were evaporated to afford an oily yellow residue. This mixture was analysed by ^{1}H NMR ($CDCl_3$) and the conversion to the acetylated product (**10**) was estimated to be 37%. This crude mixture was then separated by FCC (SiO_2, 0 – 10% Et_2O/CH_2Cl_2) to provide 3.17 g of (***R***)-enantiomer enriched **9** and 1.80 g of **10**. The (***R***)-enriched fraction of **9** was then dried under high vacuum (≤ 0.05 mmHg) to remove residual AcOH still present after FCC and resubjected to a second round of resolution.

To a 100 mL single neck RBF equipped with an oval shaped, Teflon coated magnetic stir bar was added (***R***)-enriched **9** (3.17 g, 13.19 mmol) followed by TBME (33 mL), deionised H_2O (330 µL) and freshly distilled Vinyl acetate (12.30 mL, 10 equiv). A reflux condenser

equipped with a gas inlet adapter was attached, and the heterogeneous reaction mixture was placed under N_2, set to 50°C (oil bath) and stirred vigorously (1000 rpm) at this temperature for 48 hours. The reaction mixture was then cooled to room temperature, filtered through a pad of Celite/$MgSO_4$ on a sintered glass funnel. The filter cake was rinsed with EtOAc (3×) and the combined filtrates were evaporated. The crude viscous yellow oil was then subjected to FCC (SiO_2, 0 – 10% Et_2O/CH_2Cl_2) to afford 2.26 g (94% based on a maximum yield of 50%) of (***R***)-**3** as a white crystalline solid and 0.85 g of **10** as a yellow oil bringing the total yield to 2.65 g (94% based on a maximum yield of 50%).

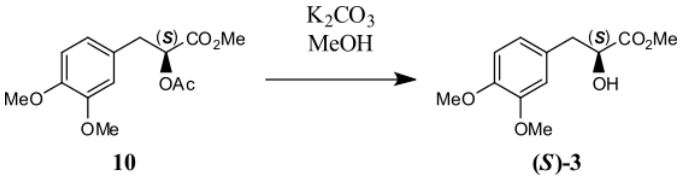
(*R*)-3

$[\alpha]_D^{24}$ + 9.1° (*c* 1.085 in CH_2Cl_2); Mp. = 64 – 65°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (1H, d, *J* = 6.2 Hz, OH), 2.93 (1H, dd, *J* = 13.9, 6.7 Hz, **H**CH), 3.09 (1H, dd, *J* = 14.1, 4.5 Hz, HC**H**), 3.79 (3H, s, CO_2CH_3), 3.868 (3H, s, OCH_3), 3.875 (3H, s, OCH_3), 4.45 (1H, m, CH), 6.79 (3H, m ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.90, 52.17, 55.60, 55.64, 71.23, 110.99, 112.54, 121.30, 128.64, 147.80, 148.58, 174.34 (**CO$_2$**CH_3); IR (KBr) 3393.52, 3006.56, 2990.09, 2948.48, 2929.96, 2908.76, 2833.15, 1726.38, 1593.95, 1516.83, 1461.85, 1444.96, 1421.62, 1264.09, 1242.03, 1214.53, 1157.38, 1141.87, 1098.66, 1028.03 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{16}O_5$ $[M]^+$: 240.0998, found: 240.1042.

10

$[\alpha]_D^{24}$ - 2.8° (*c* 0.726 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, s, $COCH_3$), 3.05 (2H, m, CH_2), 3.69 (3H, s, CO_2CH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.16 (1H, q, *J* = 13.0, 8.3, 4.7 Hz, CH), 6.74 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.45 (CO**CH$_3$**), 36.80, 52.13, 55.64, 55.65, 72.95, 110.94, 112.23, 121.22, 128.14, 147.88, 148.58, 170.01 (**CO**CH_3), 170.08 (**CO$_2$**CH_3); IR (neat, NaCl plates) 3001.58, 2955.31, 2938.67, 2837.52, 1747.50 (**CO**CH_3), 1608.74, 1592.04, 1517.42, 1464.78, 1454.62, 1441.09, 1374.96, 1263.88, 1238.64, 1158.83, 1142.94, 1074.81, 1028.43 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{18}O_6$ $[M]^+$: 282.1103, found: 282.1150.

Methyl (2*S*)-3-(3,4-dimethoxyphenyl)-2-hydroxypropanoate (*S*)-3



To a 100 mL single neck RBF equipped with an oval shaped, Teflon coated magnetic stir bar was added **10** (2.65 g, 9.37 mmol) followed by freshly distilled MeOH (23 mL). This mixture was stirred at room temperature until homogeneous and anhydrous K_2CO_3 (1.31 g, 9.48 mmol, 1.01 equiv) was added. The resulting suspension was stirred at room temperature for 30 min. The progress of the reaction was monitored via TLC (10% Et_2O/CH_2Cl_2) and upon completion the reaction mixture was evaporated. To the resulting yellow–green residue was added deionised H_2O (100 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (50 mL), dried over $MgSO_4$, filtered through a pad of SiO_2 on a sintered glass funnel and evaporated to afford 1.56 g (69%) of (***S***)-**3** as white crystals. This product was determined to be pure via ^{1}H NMR and GC/MS and did not require further purification.

$[\alpha]_D^{24}$ - 12.9^o (*c* 1.031 in CH_2Cl_2); Mp. = 65 – 66^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (1H, d, *J* = 6.2 Hz, OH), 2.93 (1H, dd, *J* = 14.2, 6.6 Hz, **H**CH), 3.09 (1H, dd, *J* = 14.2, 4.4 Hz, HC**H**), 3.79 (3H, s, CO_2CH_3), 3.868 (3H, s, OCH_3), 3.874 (3H, s, OCH_3), 4.45 (1H, m, CH), 6.78 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.86, 52.11, 55.56, 55.60, 71.21, 110.96, 112.51, 128.64, 147.75, 148.54, 174.30 (**CO$_2$**CH_3); IR (KBr) 3394.24, 3006.45, 2989.98, 2948.50, 2929.89, 2908.79, 2833.13, 1726.68, 1593.92, 1516.75, 1461.80, 1444.98, 1421.73, 1264.09, 1242.05, 1214.56, 1157.41, 1141.97, 1098.81, 1028.10 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{16}O_5$ $[M]^+$ 240.0998, found 240.0971.

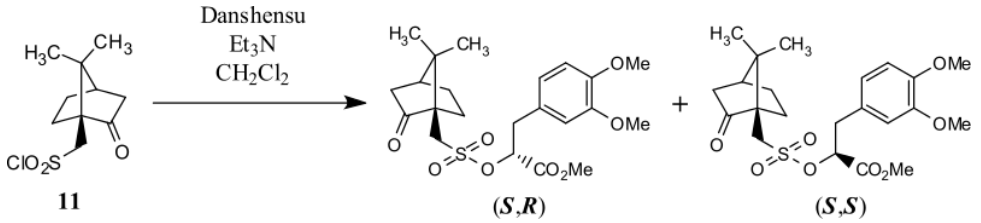
(1*S*)-(+)-10-Camphorsulfonyl chloride 11

(1*S*)-(+)-10-Camphorsulfonic acid **11**

To a 50 mL RBF was added (1S)-(+)-10-camphorsulfonic acid (5.0 g, 21.5 mmol) followed by freshly distilled $SOCl_2$ (10 mL, 137.1 mmol, 6.4 equiv) and 3 boiling chips. The flask was swirled, fitted with a reflux condenser and placed on a steam cone (110^{o}C). A vigorous evolution of SO_2 occurred and the sulfonic acid dissolved. The reaction mixture was then heated on the steam cone for 30 min and allowed to cool to room temperature. Excess $SOCl_2$ was evaporated on the pump through the condenser and the resulting oil was dried under high vacuum (≤ 0.20 mmHg) to form 5.23 g of an oily solid. This crude product was then recrystallised from petroleum ether (150 mL, Bp. = 40 – 60^{o}C) to afford 4.82 g (89%) of **11** as glistening white crystals.

$[\alpha]_D^{24}$ + 17.4^{o} (*c* 1.063 in CH_2Cl_2); Mp. = 62 – 65^{o}C (lit.[2] 67 – 68^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.50 (1H, sept, *J* = 25.7, 21.6, 16.5, 12.6, 9.3, 3.6 Hz, **H**CH), 1.78 (1H, sept, *J* = 27.8, 23.4, 18.5, 13.9, 9.3, 4.6 Hz, HC**H**), 2.00 (1H, d, *J* = 18.7 Hz, CH), 2.12 (2H, m, CH_2), 2.46 (2H, m, CH_2), 3.73 (1H, d, *J* = 14.5 Hz, **H**CH), 4.32 (1H, d, *J* = 14.5 Hz, HC**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.58, 19.68, 25.23, 26.81, 42.25, 42.73, 48.15, 59.64, 64.23, 212.72; IR (KBr) 2970.91, 2960.35, 2940.14, 2926.50, 2894.73, 1743.58, 1367.89, 1171.11, 1053.61 cm^{-1}.

Camphorsulfonic acid diastereomers 12[5]



To a 5 mL screw cap vial equipped with a small magnetic bar stirrer was added either (***R***) or (***S***)**-3** (50 µmol) followed by anhydrous CH_2Cl_2 (250 µL) and Et_3N (10.5 µL, 75 µmol, 1.5 equiv). The stirred reaction mixture was then cooled to 0°C (ice/H_2O) and **11** (13.8 mg, 55 µmol, 1.1 equiv) was added slowly. A white precipitate formed immediately (Et_3N.HCl) and the suspension was stirred at 0°C for 30 min then 30 min at room temperature. The reaction mixture was then quenched with cold (0°C) deionised H_2O (1 mL) and additional CH_2Cl_2 (4 mL) was added. The layers were separated and the combined organic layers were washed with dilute aqueous HCl (1 mL, 10%), saturated aqueous $NaHCO_3$ (1 mL, 10%), deionised H_2O (1 mL), dried over $MgSO_4$, filtered and evaporated. The resulting light yellow residue was then dried under high vacuum (≤ 0.2 mmHg) for an hour and analysed by ^1H NMR ($CDCl_3$).

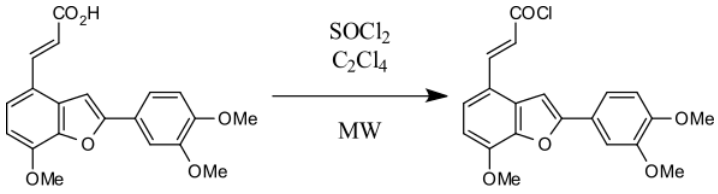
(***R***)**-3**

Diastereomer	(***R***, ***S***)	(***S***, ***S***)
δ R-CH_3 singlet (ppm)	0.79	0.75
Integral	100.02	4.01
ee (***R*****, %**)	96	

(***S***)**-3**

Diastereomer	(***R***, ***S***)	(***S***, ***S***)
δ R-CH_3 singlet (ppm)	0.75	0.79
Integral	3.96	99.98
ee (***S*****, %**)	96	

(2*E*)-3-[2-(3,4-dimethoxyphenyl)-7-methoxy-benzofuran-4-yl]prop-2-enoyl chloride 13



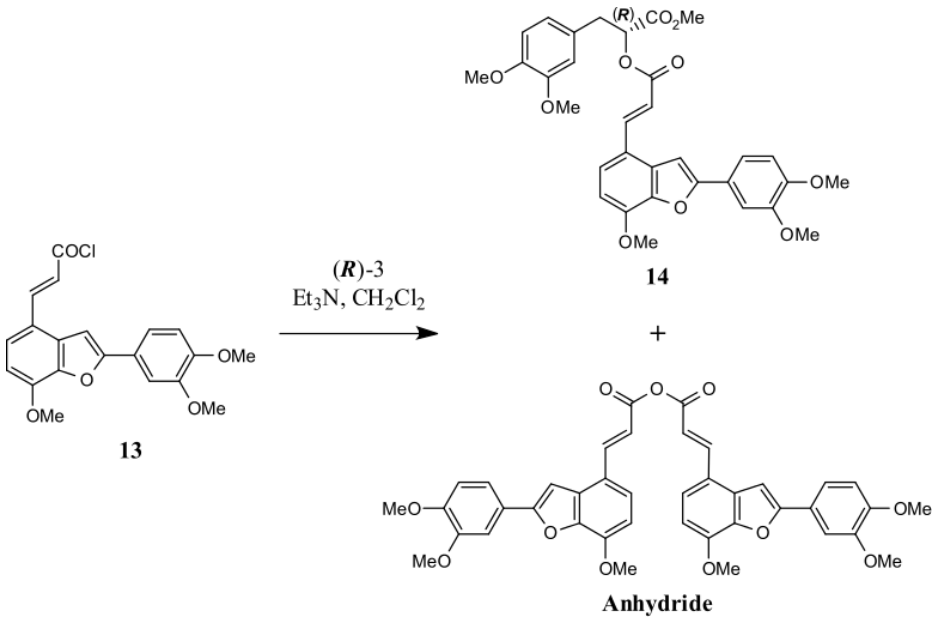
2 **13**

In a 35 mL CEM microwave vial equipped with a Teflon coated, oval shaped magnetic stir bar, **2** (500 mg, 1.41 mmol) was suspended in freshly distilled tetrachloroethylene (C_2Cl_4, 20 mL). Freshly distilled $SOCl_2$ (515 µL, 7.06 mmol, 5 equiv) was then added and the vessel was sealed with a Teflon cap. The reaction was briefly mixed by vortex to ensure an even distribution of reagents throughout the solvent. The vessel was then placed inside in the CEM Discover microwave and irradiated at 135°C (**see microwave conditions below**) with stirring for a hold time of 30 min. The vessel was cooled to 60°C and subjected to a second round of irradiation at 135°C for a hold time of 30 min. After two cycles of irradiation, the vial was vented while warm (40 to 50°C) and the contents were transferred to a 100 mL RBF and the volatiles were evaporated. The yellow residue was then suspended in C_2Cl_4 and enough CH_2Cl_2 was added to affect dissolution. The yellow solution was then evaporated and dried under high vacuum (≤ 0.2 mmHg) for 1 hour to afford 0.56 g (quantitative) of **13** as a yellow to orange, crystalline solid. This product was used immediately in the next step.

Microwave conditions

Temperature (°C)	135
Ramp time (min)	60
Hold time (min)	30
Pressure (PSI)	150
Power (W)	250
Power Max	On
Stirring	High

(2*R*)-3-(3,4-Dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yl (2*E*)-3-[2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-4-yl]prop-2-enoate 14



To a 100 mL RBF, which contained freshly prepared **13** (562 mg, 1.52 mmol, 2 equiv) and an oval shaped, Teflon coated magnetic stir bar was added (***R*)-3** (183 mg, 0.76 mmol, 1 equiv). Both reagents were then dissolved in anhydrous CH_2Cl_2 (25 mL) and the reaction vessel was equipped with a reflux condenser and a gas inlet adapter. The flask was then evacuated and purged with N_2 (3×) and anhydrous Et_3N (424 µL, 3.04 mmol, 4 equiv) was added. The intense red solution began to fume and the reaction mixture was heated to reflux (50 – 60^oC) and maintained at this temperature with vigorous stirring for 4 hours. The red-orange solution was then allowed to cool to room temperature and was placed in the fridge overnight to precipitate anhydride byproduct and $Et_3N.HCl$. The anhydride was filtered off (0.21 g, 20%) and the mother liquor evaporated to yield an orange-red residue. This residue was then subjected to VLC (SiO_2, 0 – 4% Et_2O/CH_2Cl_2) to yield **14** (311 mg, 71%) as an intense red to orange foam.

14

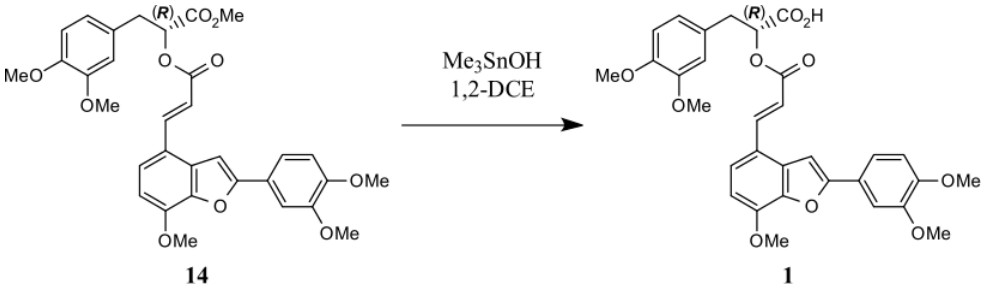
$[\alpha]_D^{24}$ + 43.1^o (*c* 1.005 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (2H, dd, *J* = 5.2, 2.0 Hz, CH_2), 3.78 (3H, s, CO_2Me), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 5.41 (1H, q, *J* = 13.1, 7.6, 5.5 Hz, CH), 6.50 (1H, d, *J* = 15.9 Hz, C=C**H**CO_2), 6.82 (4H, m, ArH), 6.97 (1H, d, *J* = 8.5 Hz, ArH), 7.17 (1H,

s, ArH), 7.39 (2H, m, ArH), 7.53 (1H, dd, *J* = 8.5, 2.1 Hz, ArH), 7.96 (1H, d, *J* = 16.3 Hz, ArC**H**=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.18 (CH_2), 52.37 (CO_2**C**H_3), 55.82 (OCH_3), 55.84 (OCH_3), 55.99 (OCH_3), 56.15 (OCH_3), 56.19 (OCH_3), 73.05 (CH), 99.18, 106.55, 108.22, 111.16, 111.26, 112.50, 114.87, 118.47, 119.70, 121.43, 122.72, 125.79, 128.38, 130.71, 143.68, 144.05, 146.93, 148.07, 148.79, 149.23, 150.06, 157.60, 166.66 (CO_2), 170.50 (**C**$O_2$$CH_3$); IR (KBr) 2999.40, 2951.62, 2935.35, 2835.91, 1751.76, 1709.19, 1611.52, 1578.20, 1515.84, 1463.31, 1440.49, 1293.66, 1255.09, 1218.13, 1142.02, 1097.99, 1025.42, 970.96 cm^{-1}; HRMS (ESI) calculated for $C_{32}H_{32}O_{10}Na$ $[M + Na]^+$: 599.1893, found: 599.1889.

Anhydride by-product

Mp. = 128 – 130^{o}C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.82 (6H, s, 2 × OCH_3), 3.88 (6H, s, 2 × OCH_3), 4.05 (6H, s, 2 × OCH_3), 6.86 (2H, d, *J* = 16.4 Hz, 2 × C=C**H**CO_2), 7.07 (4H, m, ArH), 7.56 (4H, m, ArH), 7.76 (4H, m, ArH), 7.92 (2H, s, ArH), 8.14 (2H, d, *J* = 16.4 Hz, 2 × ArC**H**=C); ^{13}C NMR (75 MHz, d_6-DMSO) δ 55.61 (2 × OCH_3), 55.79 (2 × OCH_3), 56.20 (2 × OCH_3), 100.11 (2 × ArC), 107.36 (2 × ArC), 108.56 (2 × ArC), 111.99 (2 × ArC), 114.66 (2 × ArC), 118.04 (2 × ArC), 118.89 (2 × ArC), 121.96 (2 × ArC), 127.18 (2 × ArC), 130.59 (2 × ArC), 142.84 (2 × ArC), 146.24 (2 × ArC), 147.22 (2 × ArC), 149.13 (2 × ArC), 150.02 (2 × ArC), 157.25 (2 × ArC), 163.50 (**C**O_2CO), 168.02 (CO**C**O_2); IR (KBr) 2998.89, 2934.95, 2836.34, 1757.53 (**CO$_2$**CO), 1705.68 (CO**CO$_2$**), 1610.27, 1576.95, 1514.60, 1501.74, 1462.73, 1441.38, 1405.07, 1292.65, 1277.39, 1253.25, 1217.72, 1180.48, 1165.61, 1140.33, 1098.63, 1074.75, 1024.92, 969.12 cm^{-1}; HRMS (ESI) calculated for $C_{40}H_{34}O_{11}Na$ $[M + Na]^+$ 713.1999, found 713.1989.

(2*R*)-3-(3,4-dimethoxyphenyl)-2-[[(2E)-3-[2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-4-yl]prop-2-enoyl]oxy]propanoic acid 1



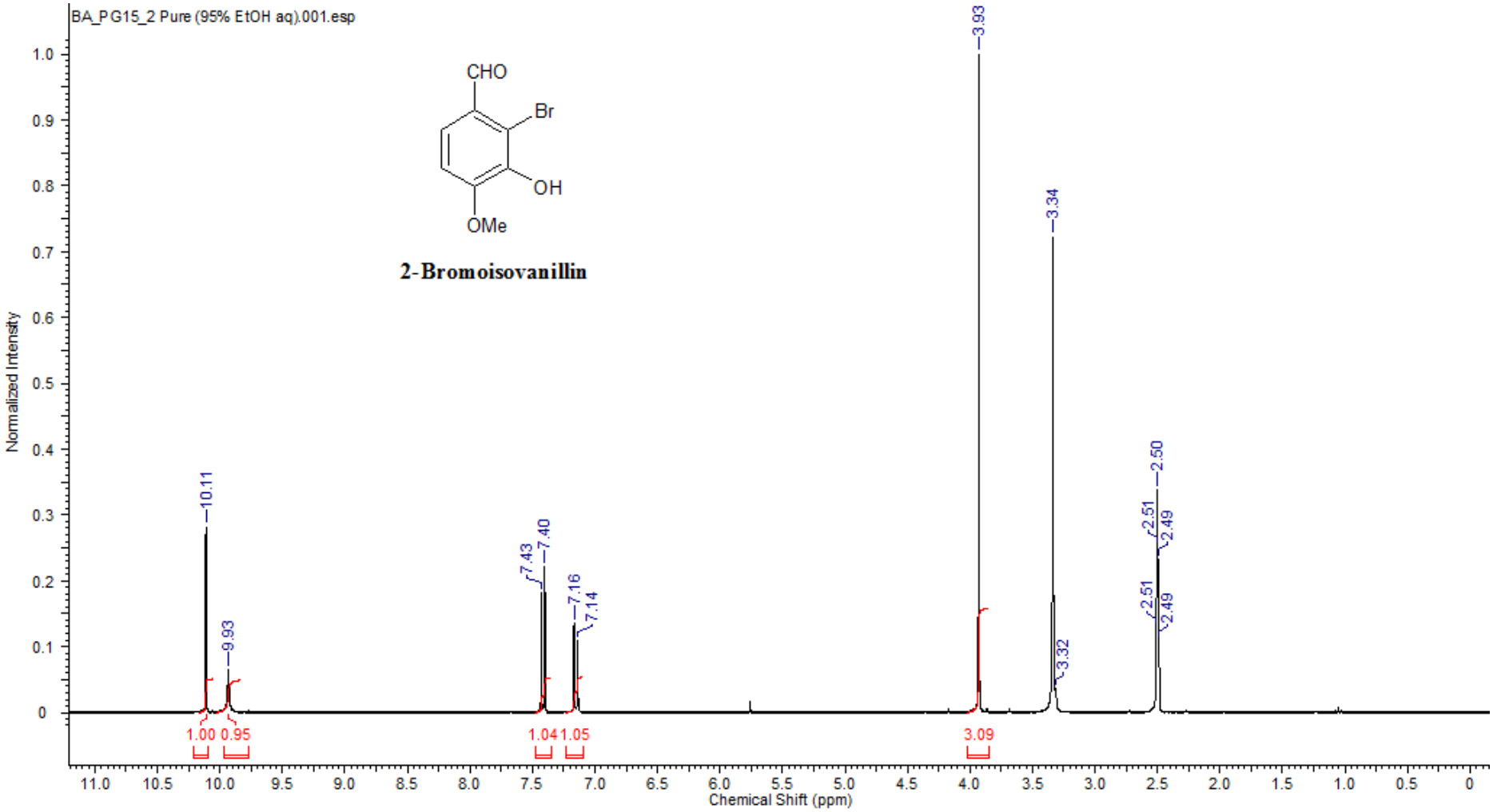
14 **1**

The apparatus consisting of a 3-neck 100 mL RBF, a rubber septum, reflux condenser with gas inlet adapter, glass stopper and a small Teflon coated magnetic stir bar was assembled, flame dried under vacuum and allowed cool under N_2. **14** (100 mg, 0.173 mmol) was then added to the vessel followed by freshly distilled 1,2-DCE (30 mL). A yellow solution was then obtained and Me_3SnOH (157 mg, 0.867 mmol, 5 equiv) was added. The reaction mixture was then heated to 80^{o}C and held at this temperature for 23 hours. Progress of the reaction was monitored by TLC (4% Et_2O/CH_2Cl_2) and upon completion the reaction mixture was allowed to cool to room temperature and the 1,2-DCE was evaporated. The resulting yellow residue was redissolved in EtOAc (100 mL) and transferred to a separatory funnel. The organic layer was washed with dilute aqueous HCl (2M, 3 × 50 mL), brine (50 mL) dried over $MgSO_4$, filtered through a pad of $MgSO_4$ and evaporated to yield a yellow-green residue. This residue was subjected to CC (SiO_2 deactivated with 0.5% AcOH, 10 – 20% Acetone/CH_2Cl_2 followed by 20% Acetone/CH_2Cl_2 + 0.5% AcOH) to provide **1** (91 mg, 93%) as a yellow foam. An analytically pure sample was generated by subjecting this sample to preparative-TLC (SiO_2, 10% Acetone/CH_2Cl_2 + 0.5% AcOH) and collecting the yellow band at R_f = 0.36 providing **1** (69 mg, 71%) as a light green solid.

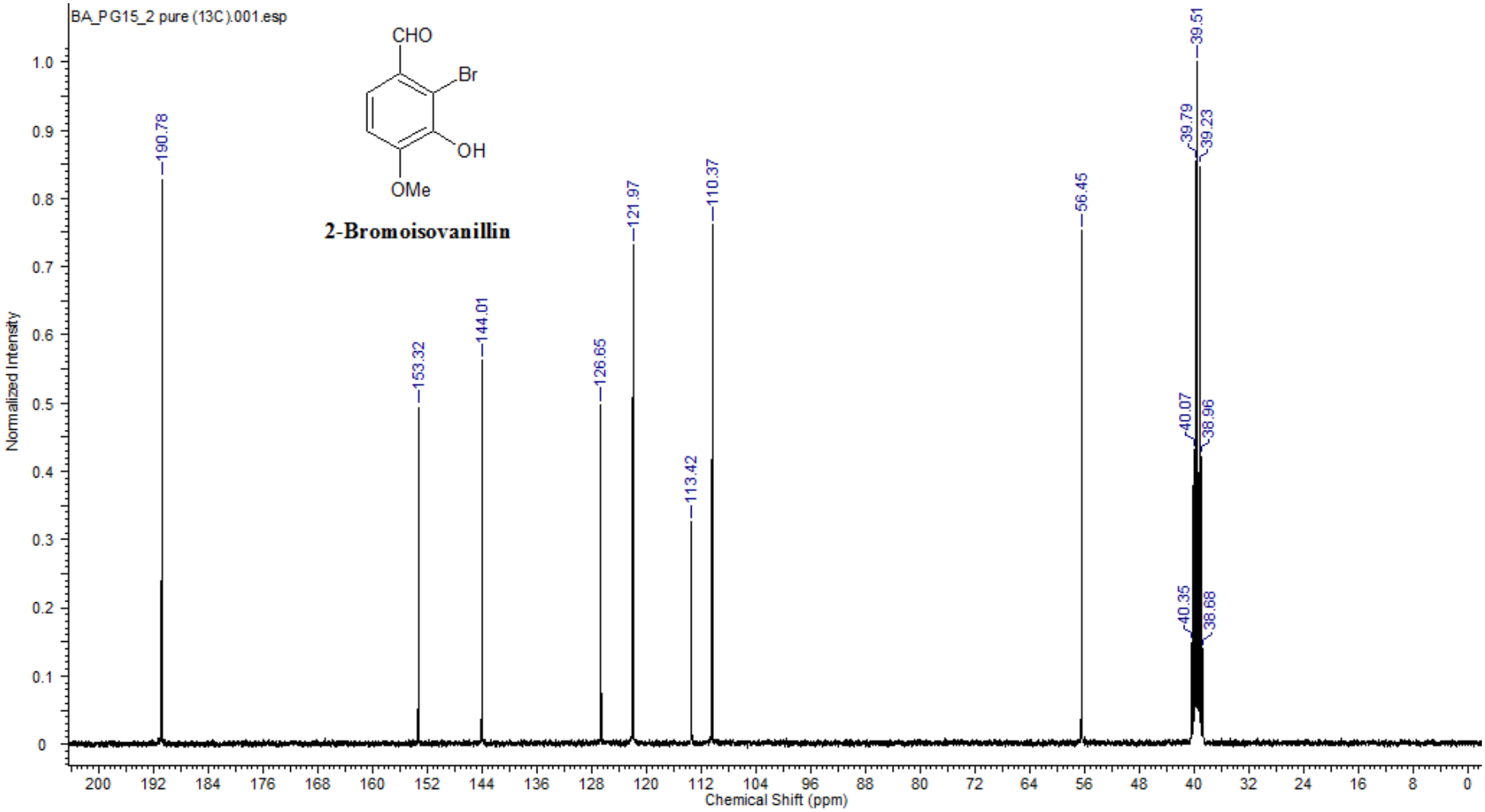
$[\alpha]_D^{22}$ + 0.7^o (*c* 1.060 in CH_2Cl_2); Mp. = 118 – 120^{o}C; ^{1}H NMR (500 MHz, d_6-DMSO) δ 3.01 (1H, dd, *J* = 13.8, 9.5 Hz, **H**CH), 3.18 (1H, dd, *J* = 14.6, 3.5 Hz, HC**H**), 3.68 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 5.10 (1H, dd, *J* = 9.5, 2.7 Hz, CH), 6.64 (1H, d, *J* = 15.9 Hz, C=C**H**CO_2H), 6.84 (2H, s, ArH), 6.99 (2H, d, *J* = 8.6 Hz, ArH), 7.09 (1H, d, *J* = 8.8 Hz, ArH), 7.58 (3H, m, ArH), 7.78 (1H, s, ArH), 7.85 (1H, d, *J* = 16.2 Hz, ArC**H**=C); ^{13}C NMR (75 MHz, d_6-DMSO) δ 36.80 (CH_2), 55.32 (OCH_3), 55.38 (OCH_3), 55.58 (OCH_3), 55.77 (OCH_3), 56.04 (OCH_3), 74.38 (CH),

99.86, 107.23, 108.56, 111.63, 111.95, 113.24, 116.23, 117.89, 119.26, 121.05, 122.08, 125.56, 130.11, 130.38, 141.97, 142.81, 146.38, 147.34, 148.34, 149.12, 149.89, 156.84, 166.06 (CH**C**CO_2), 171.14 (CO_2H); IR (KBr) 3435.48, 2923.65, 2851.76, 1702.70, 1614.45, 1515.73, 1463.76, 1404.95, 1255.32, 1158.28, 1141.06, 1097.82, 1024.86, 971.20 cm^{-1}; HRMS (ESI) calculated for $C_{31}H_{29}O_{10}$ $[M - H]^-$ 561.1761, found 561.1764

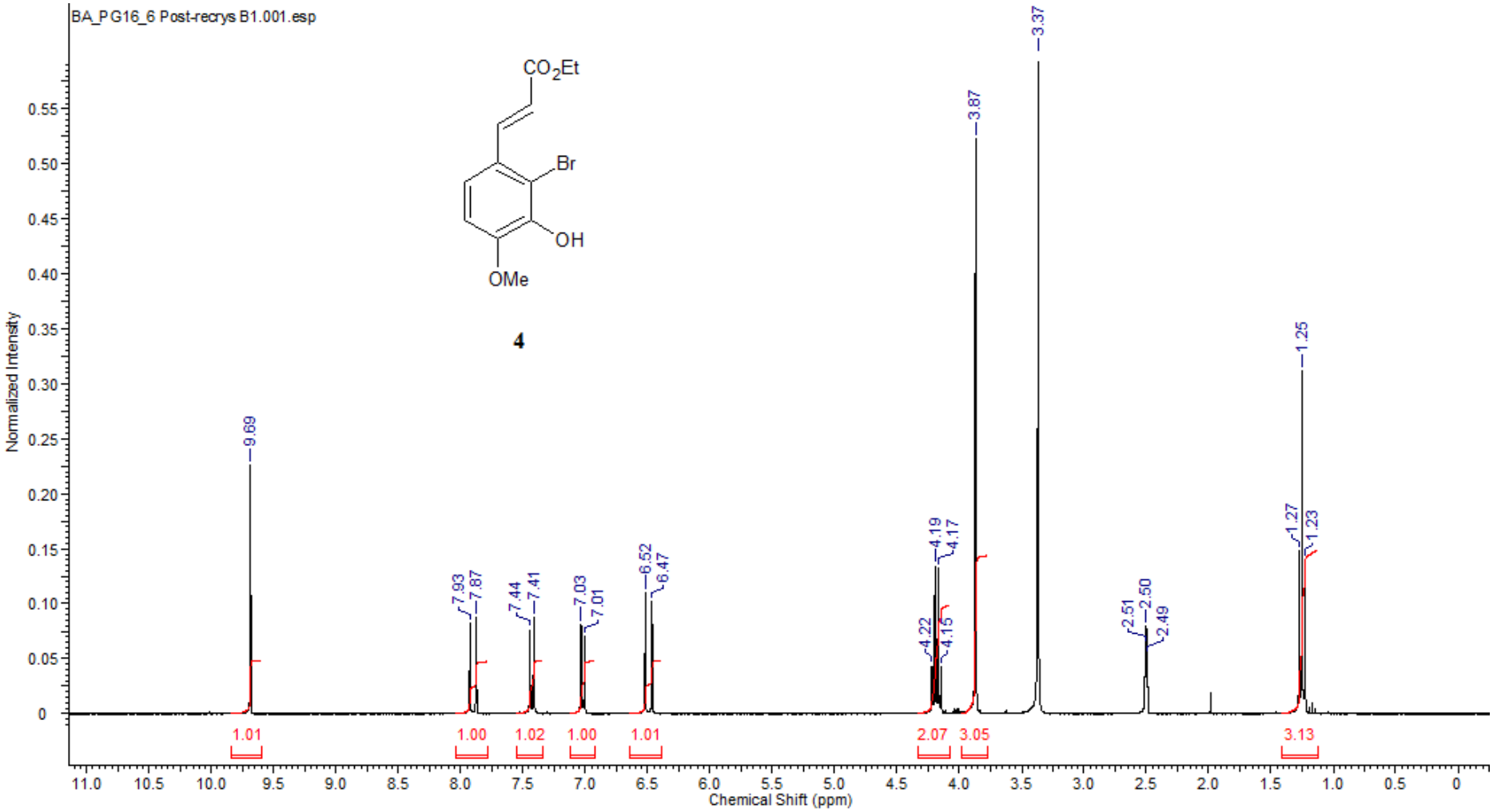
^{1}H NMR (300 MHz, d_6-DMSO)



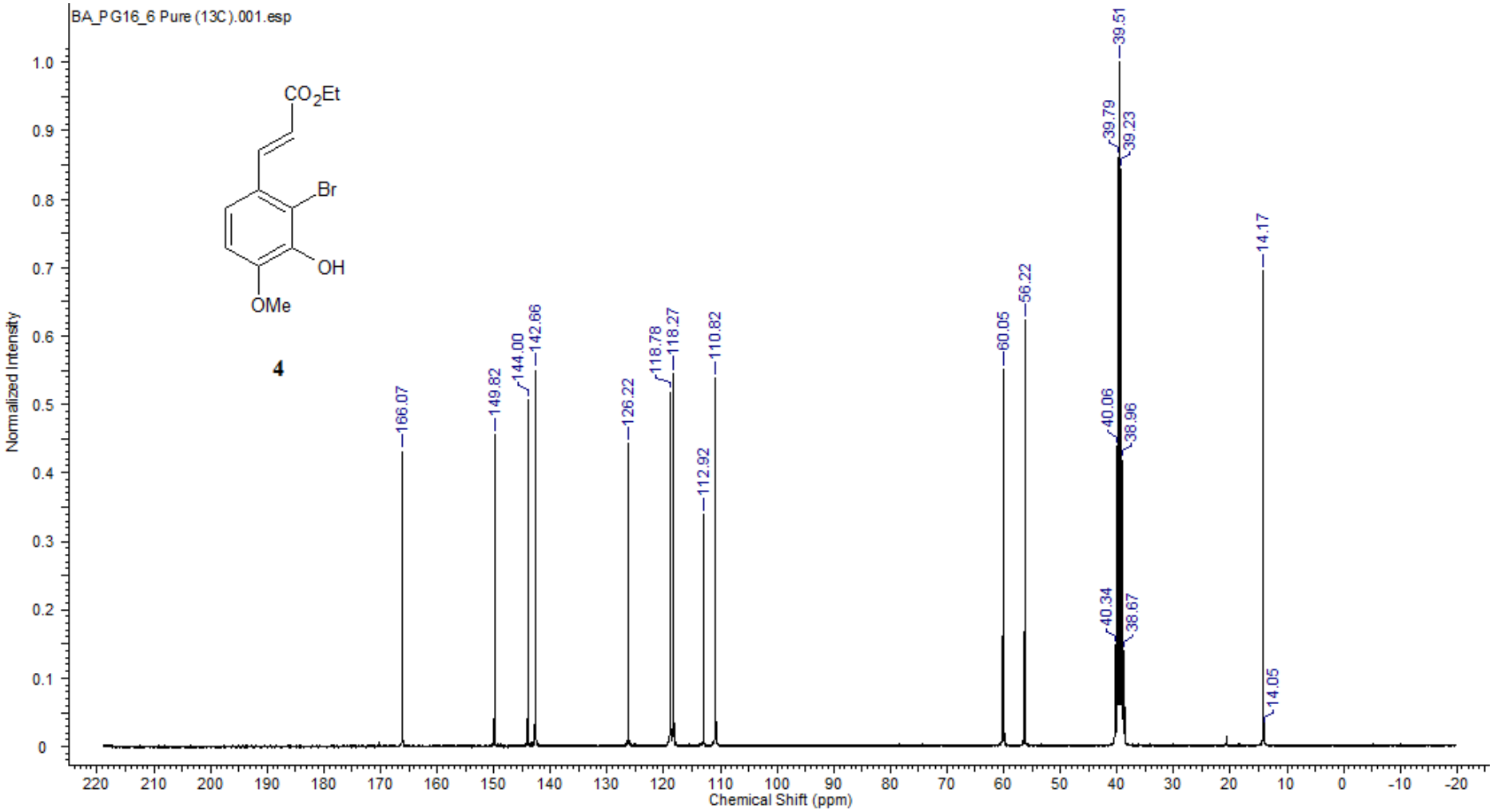
^{13}C NMR (75 MHz, d_6-DMSO)



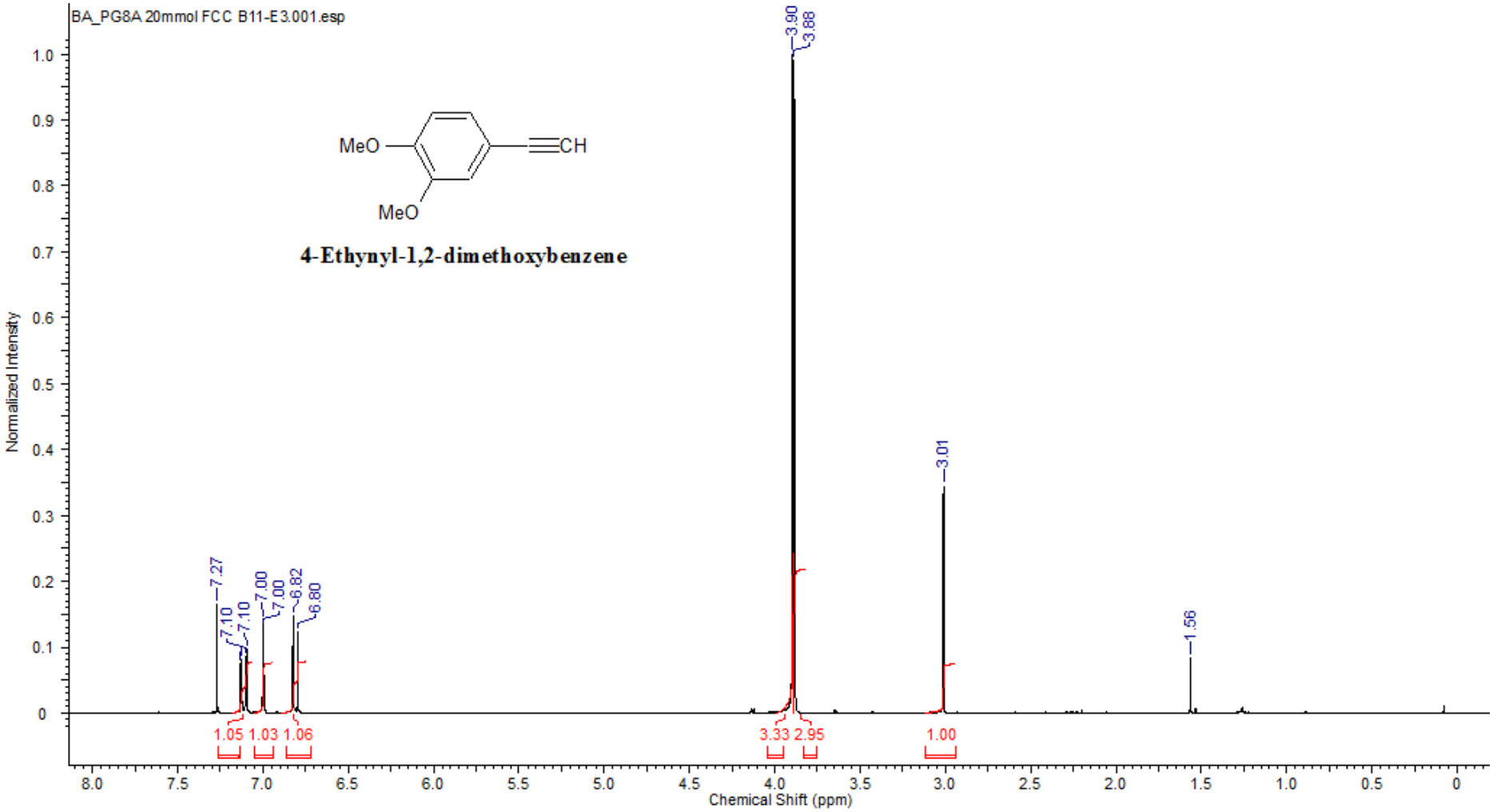
^{1}H NMR (300 MHz, d_6-DMSO)



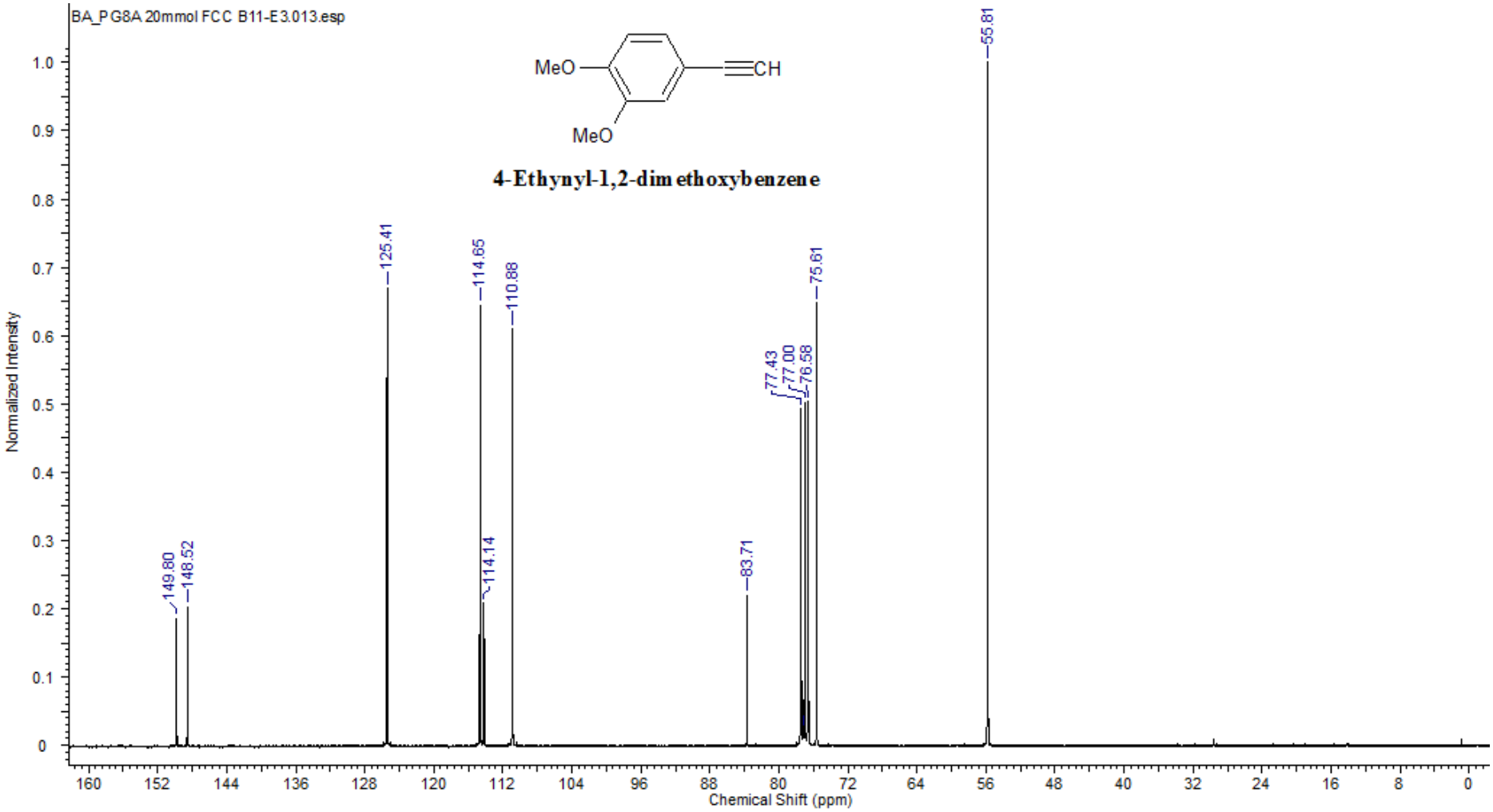
^{13}C NMR (75 MHz, d_6-DMSO)



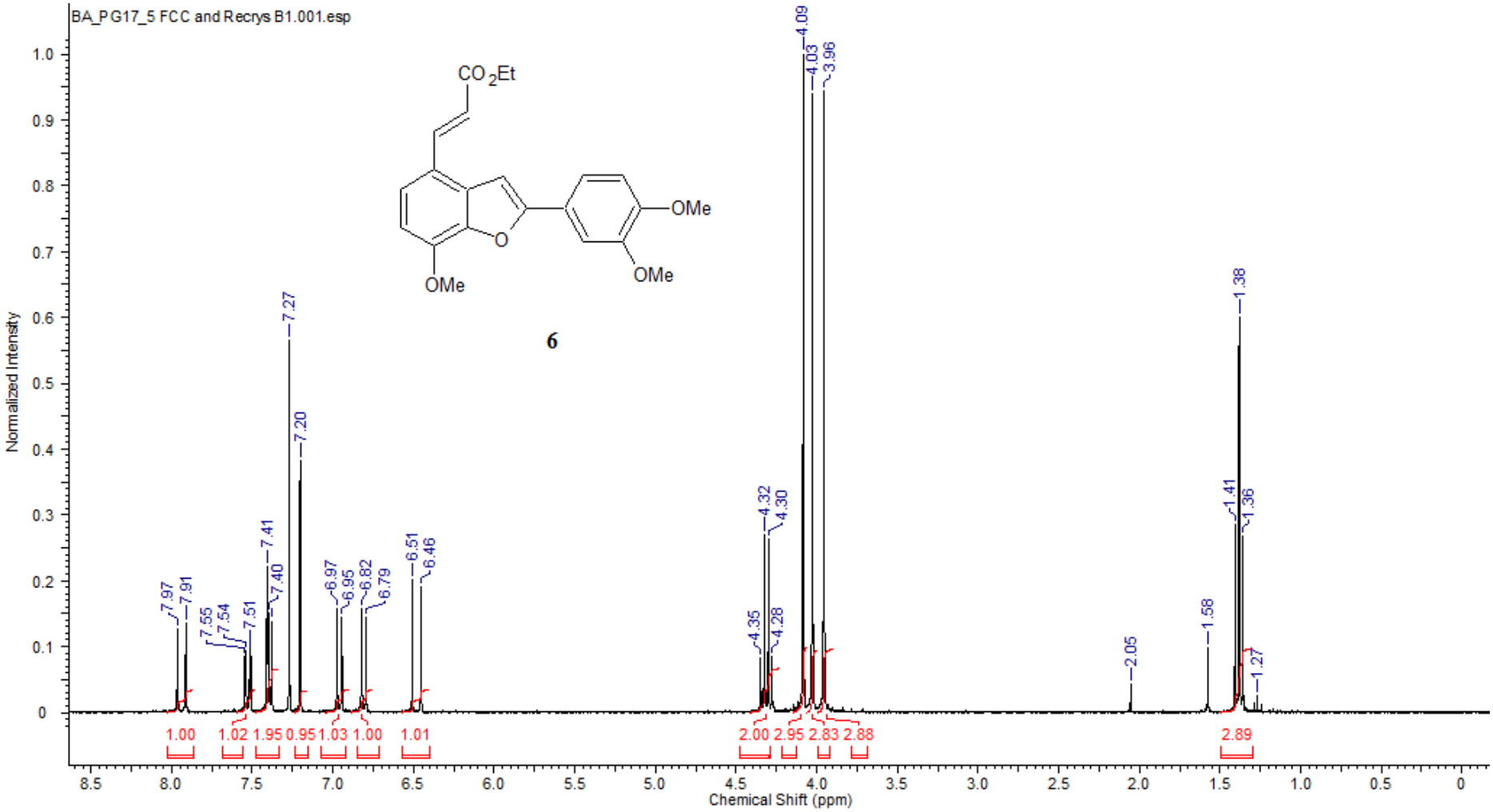
^{1}H NMR (300 MHz, $CDCl_3$)



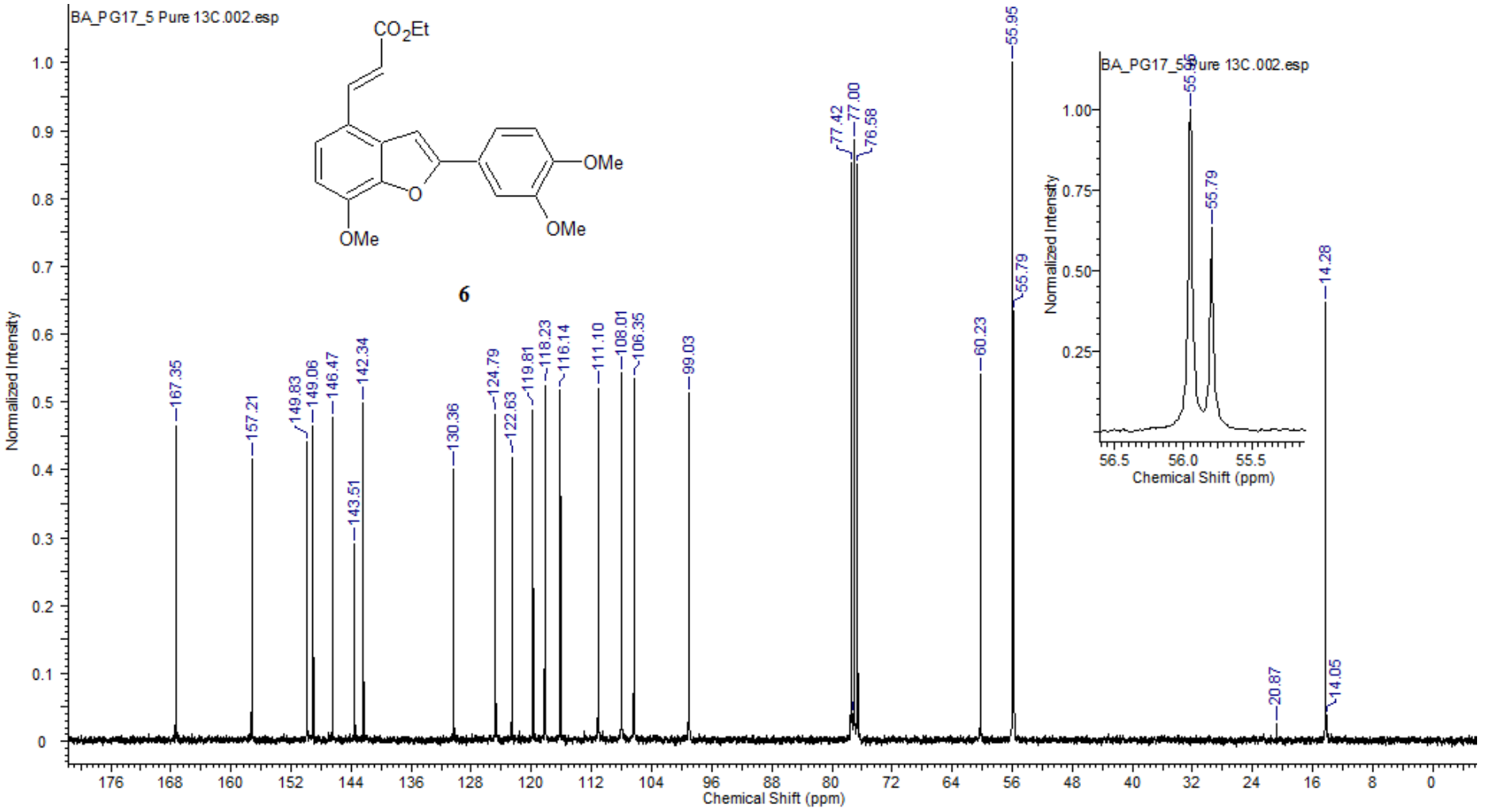
^{13}C NMR (75 MHz, $CDCl_3$)



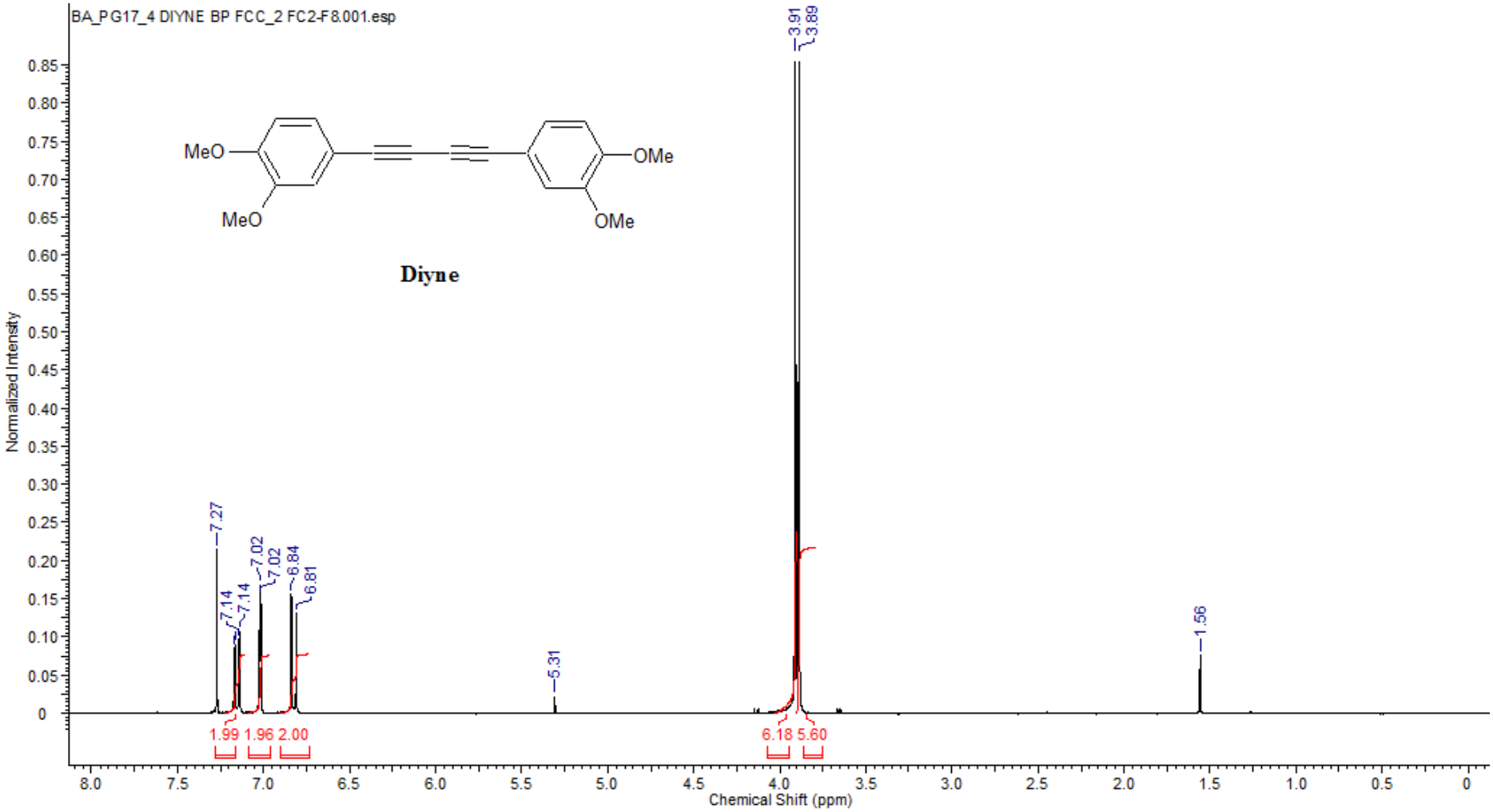
^{1}H NMR (300 MHz, $CDCl_3$)



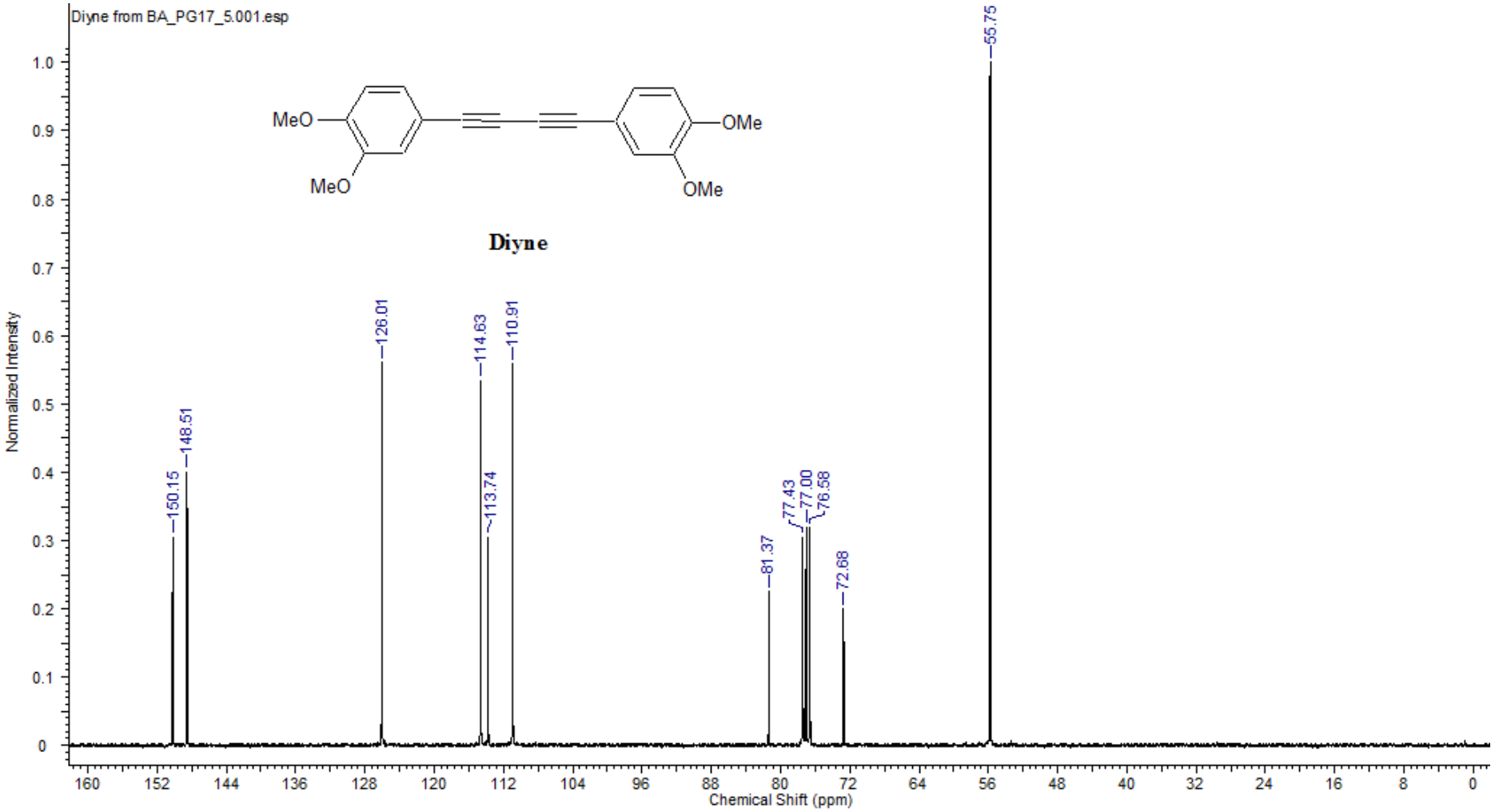
^{13}C NMR (75 MHz, $CDCl_3$)



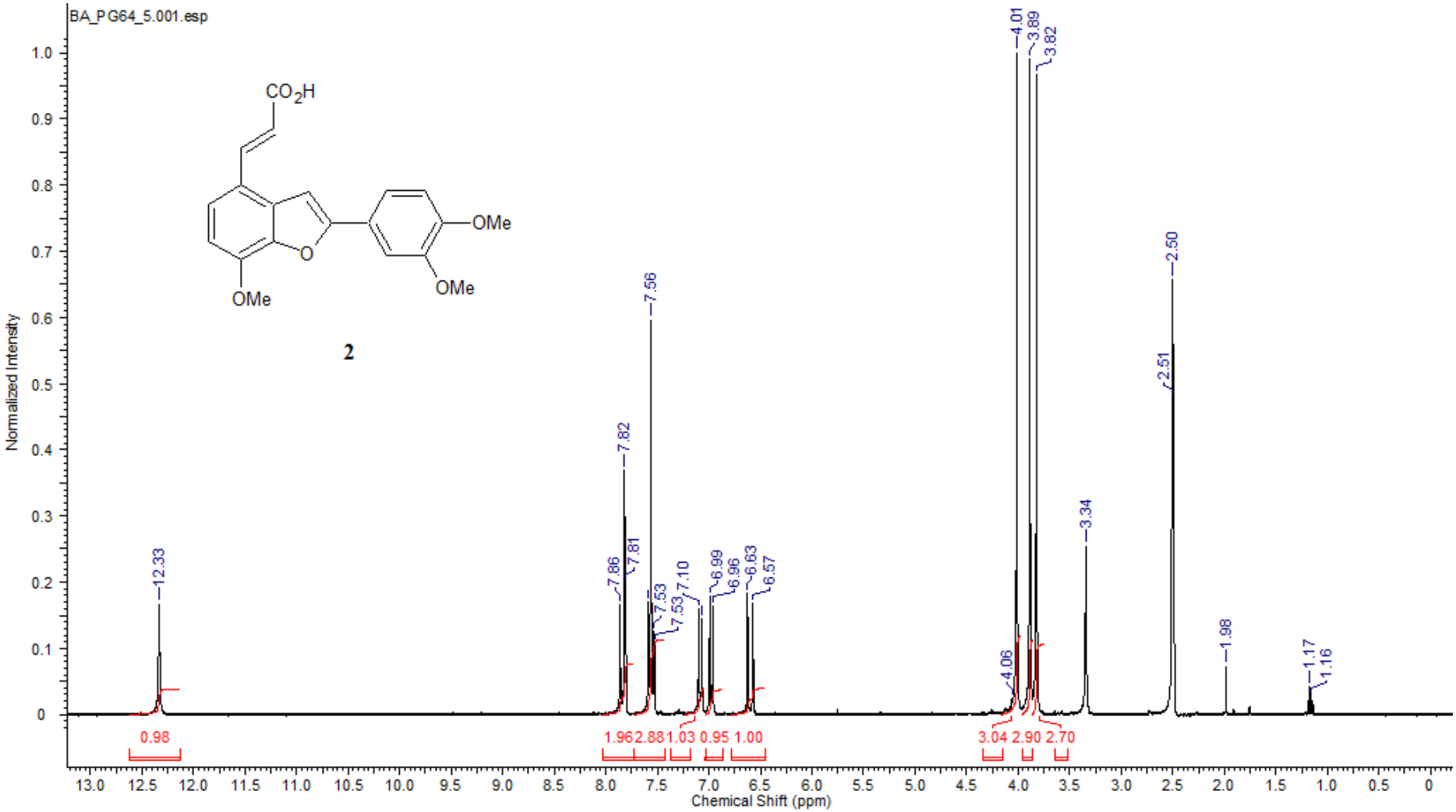
^{1}H NMR (300 MHz, $CDCl_3$)



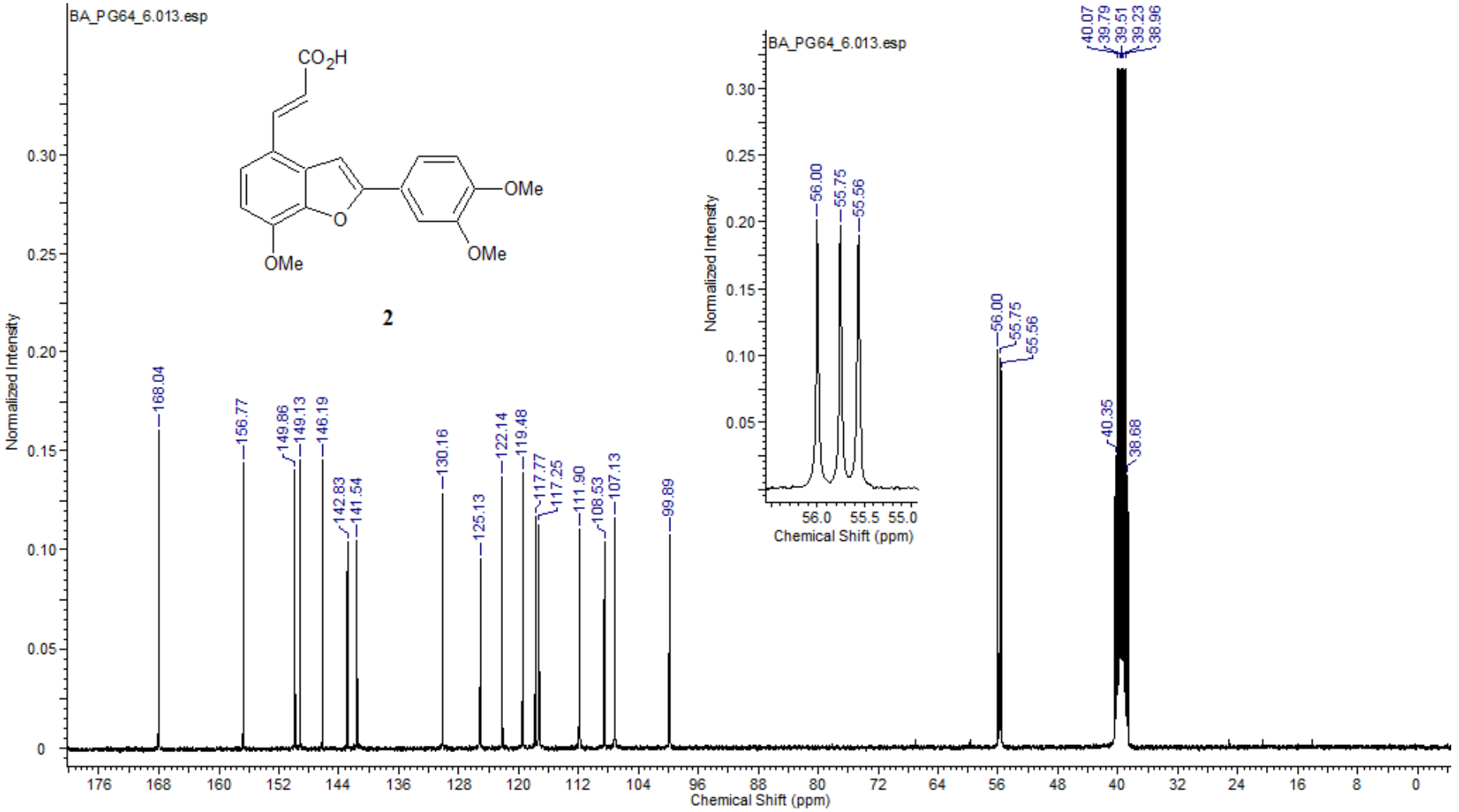
^{13}C NMR (75 MHz, $CDCl_3$)



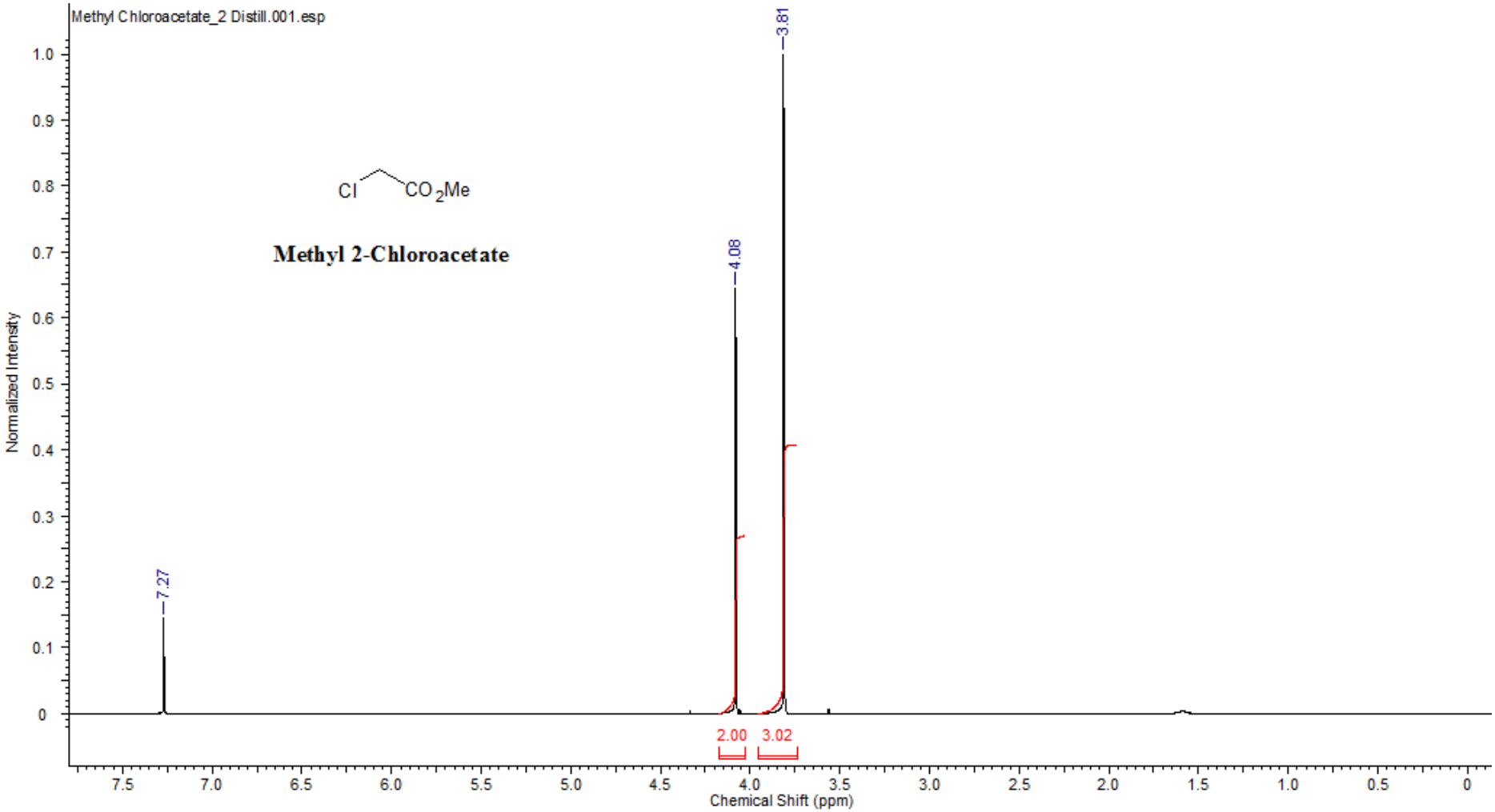
^{1}H NMR (300 MHz, d_6-DMSO)



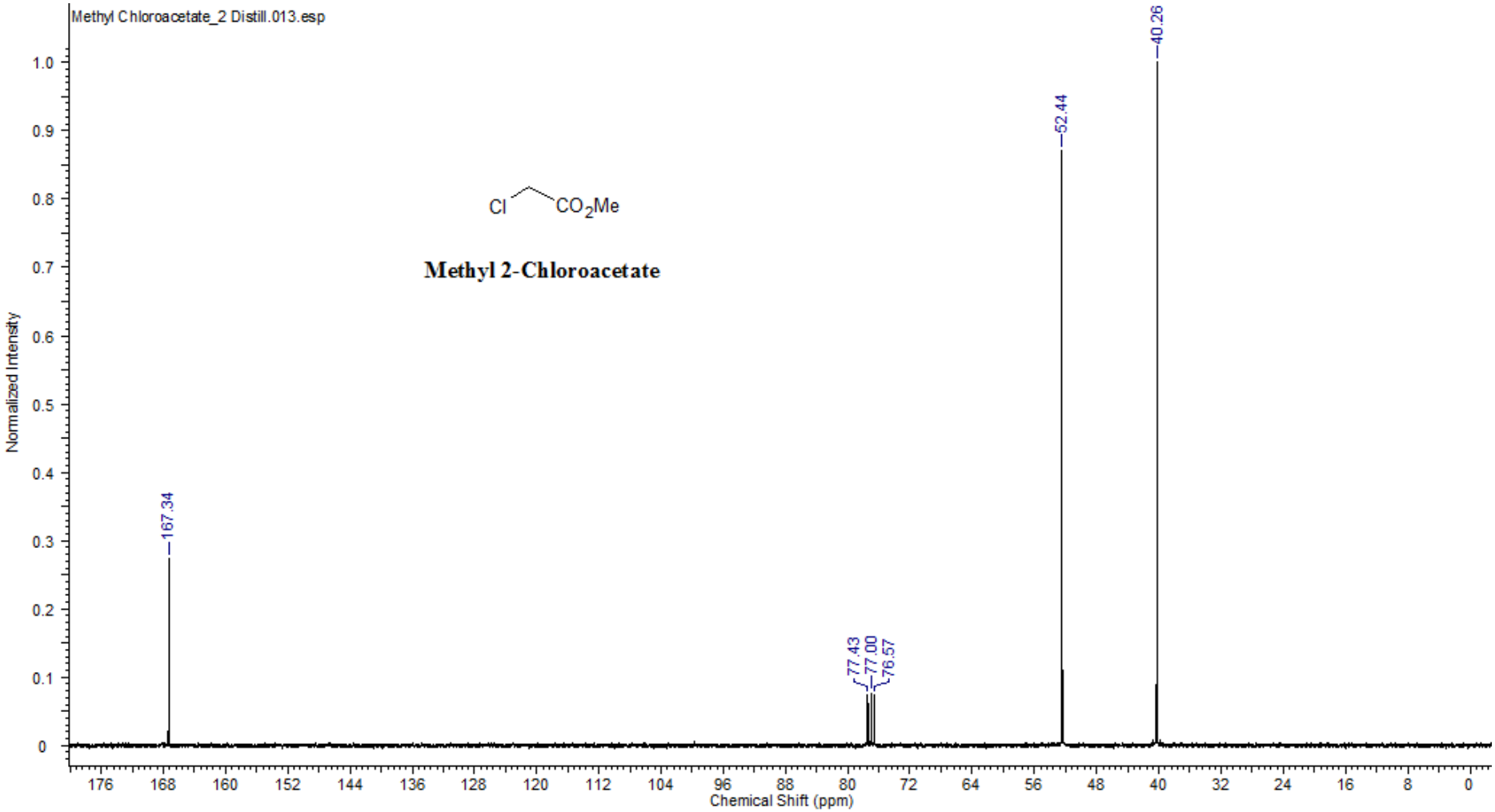
^{13}C NMR (75 MHz, d_6-DMSO)



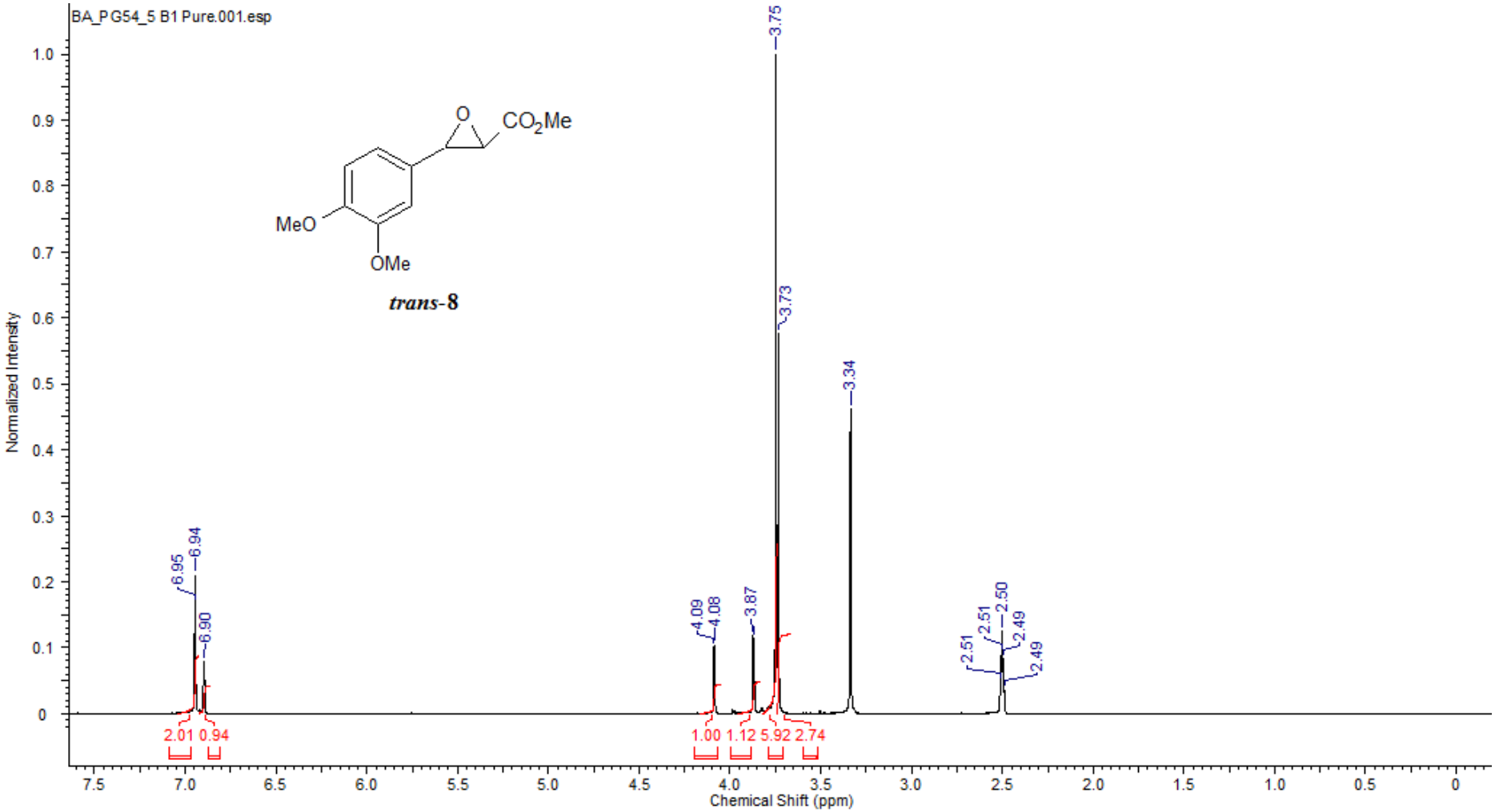
^{1}H NMR (300 MHz, $CDCl_3$)



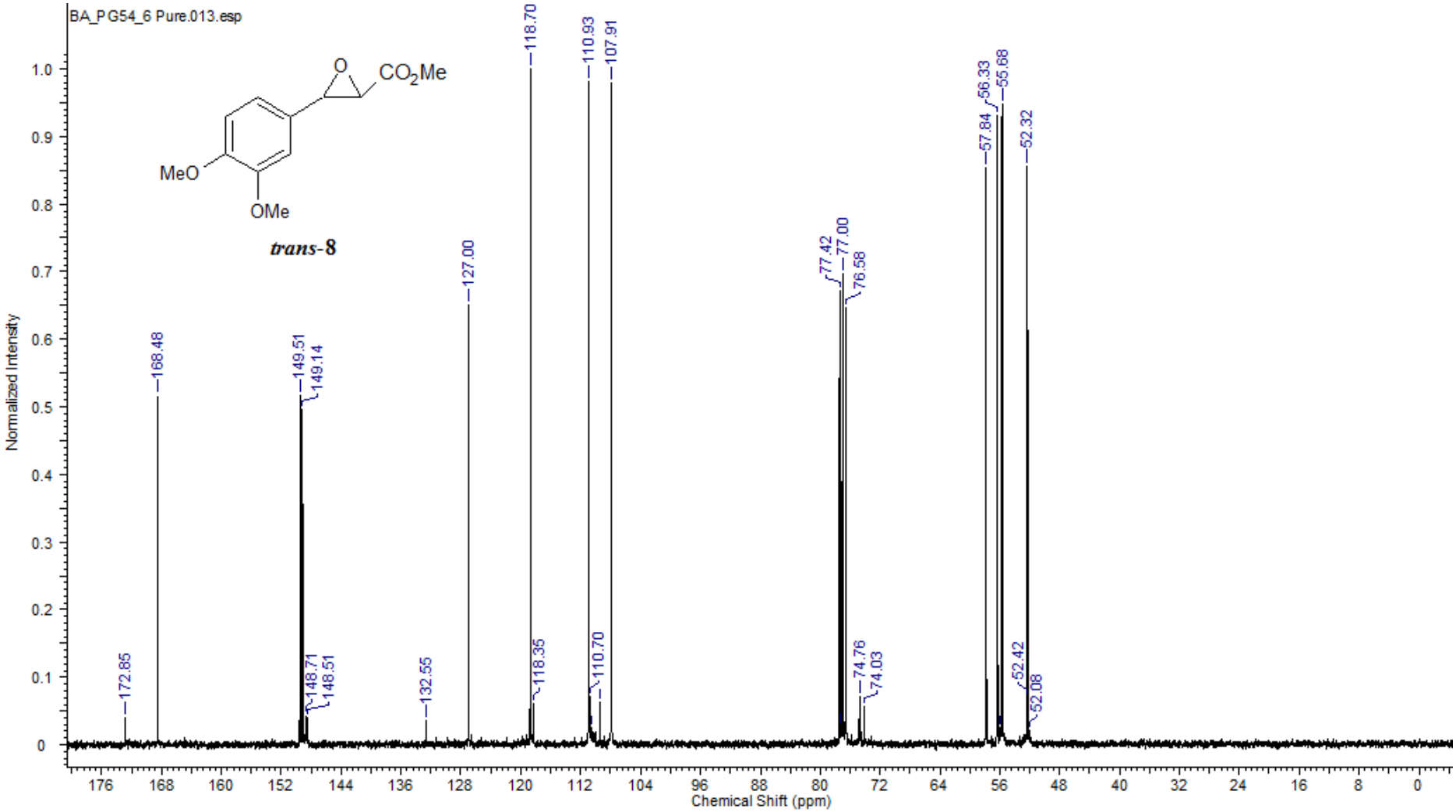
^{13}C NMR (75 MHz, $CDCl_3$)



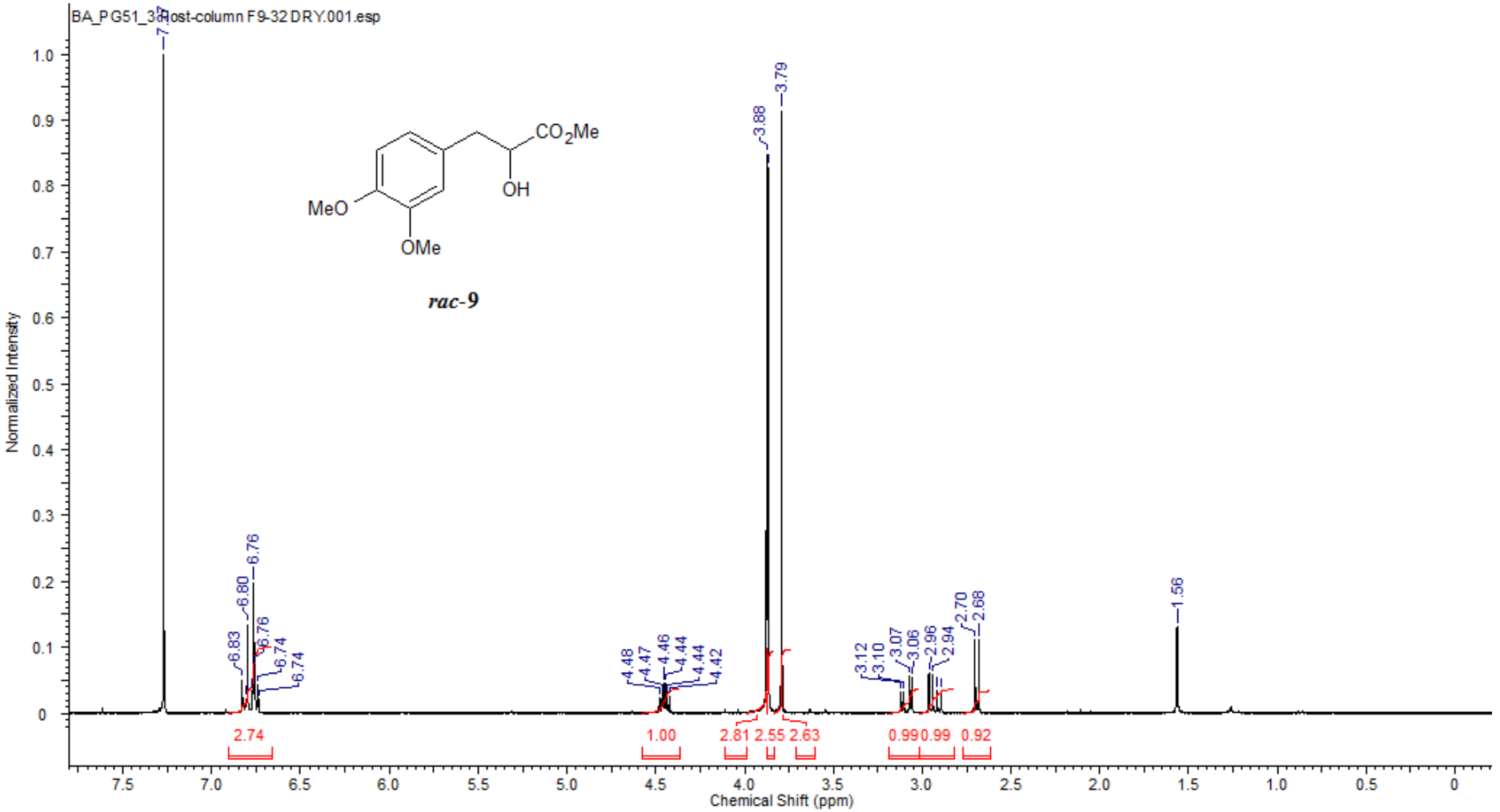
^{1}H NMR (300 MHz, d_6-DMSO)



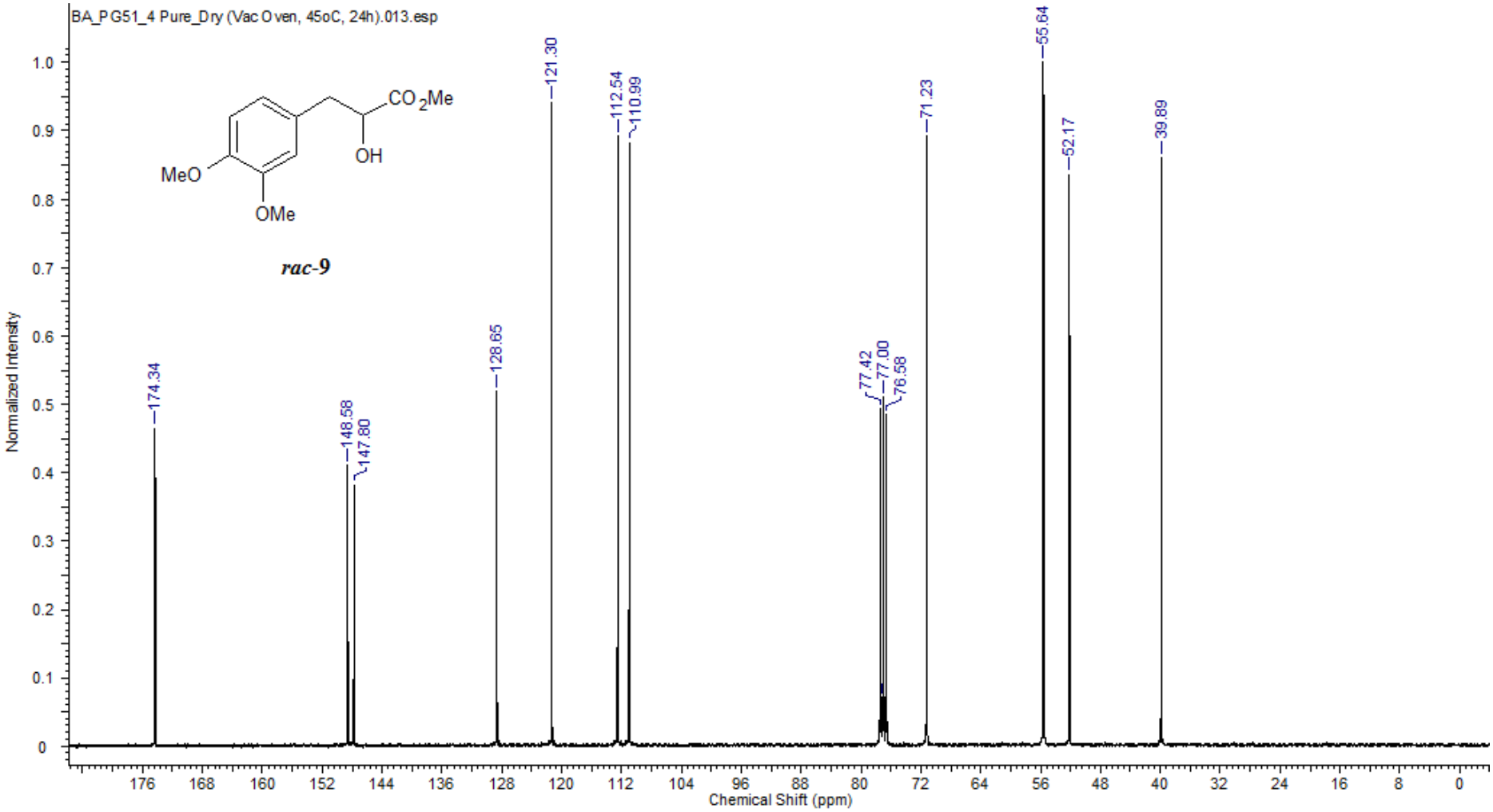
^{13}C NMR (75 MHz, $CDCl_3$)



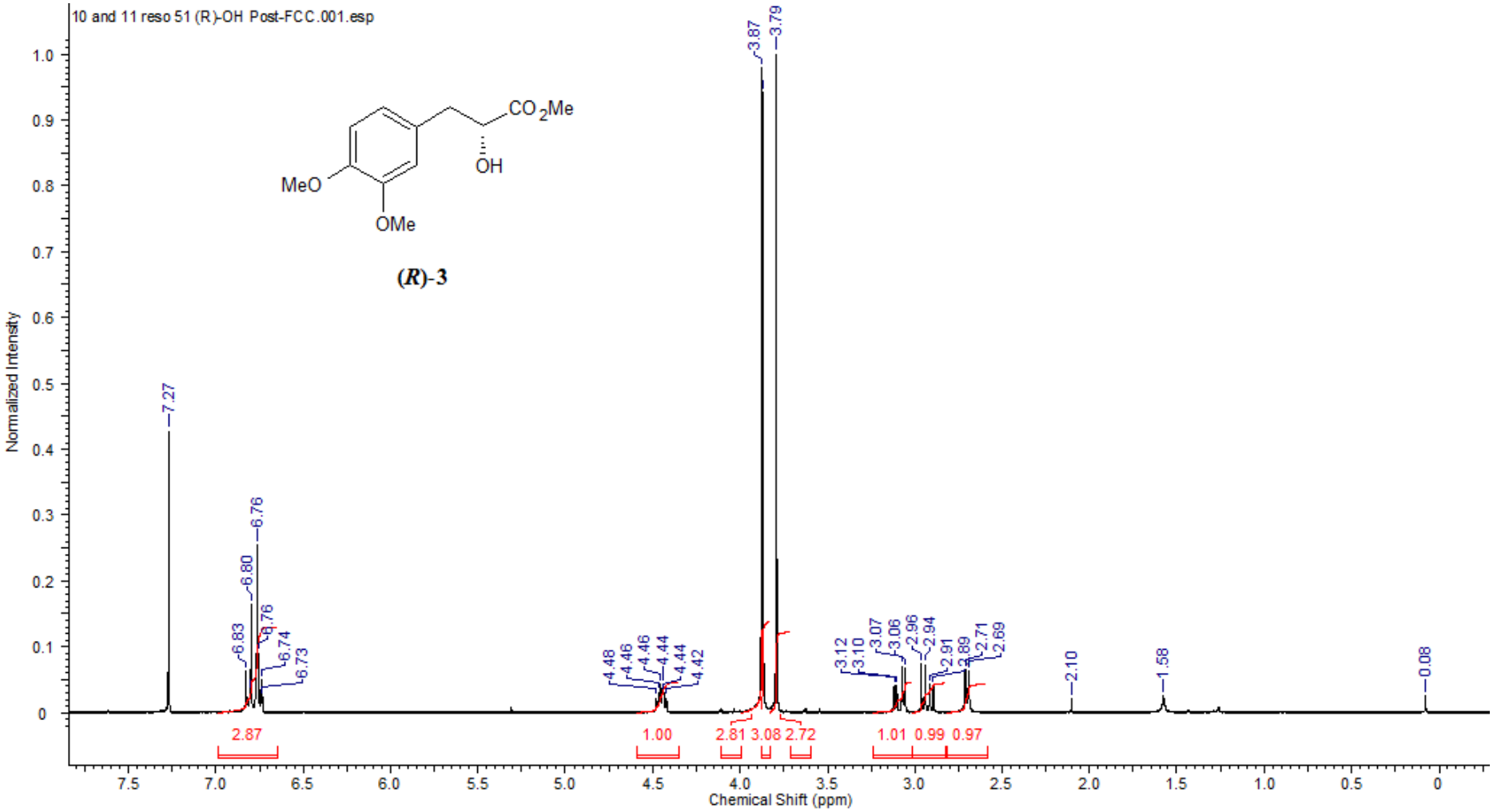
^{1}H NMR (300 MHz, $CDCl_3$)



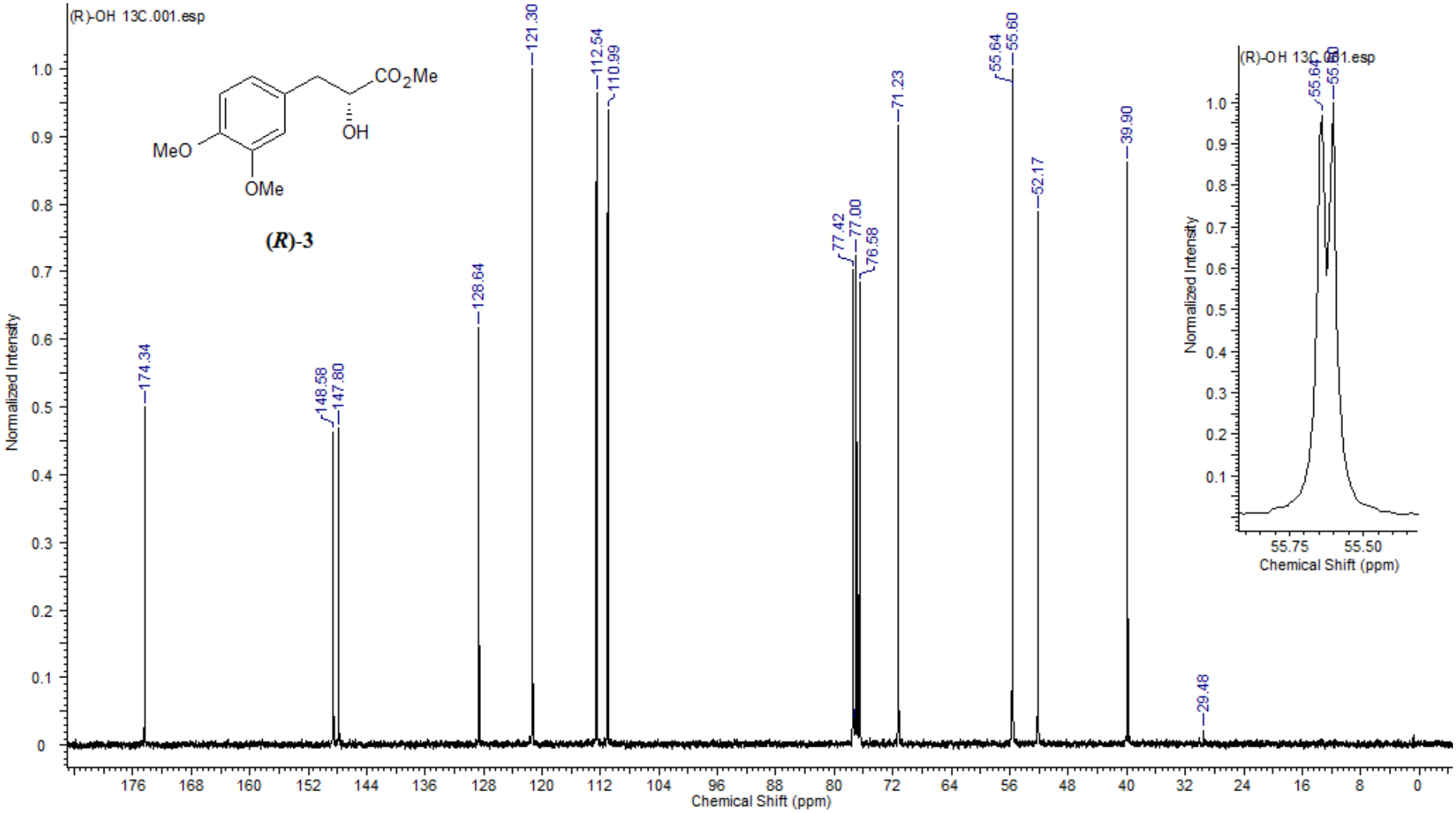
^{13}C NMR (75 MHz, $CDCl_3$)



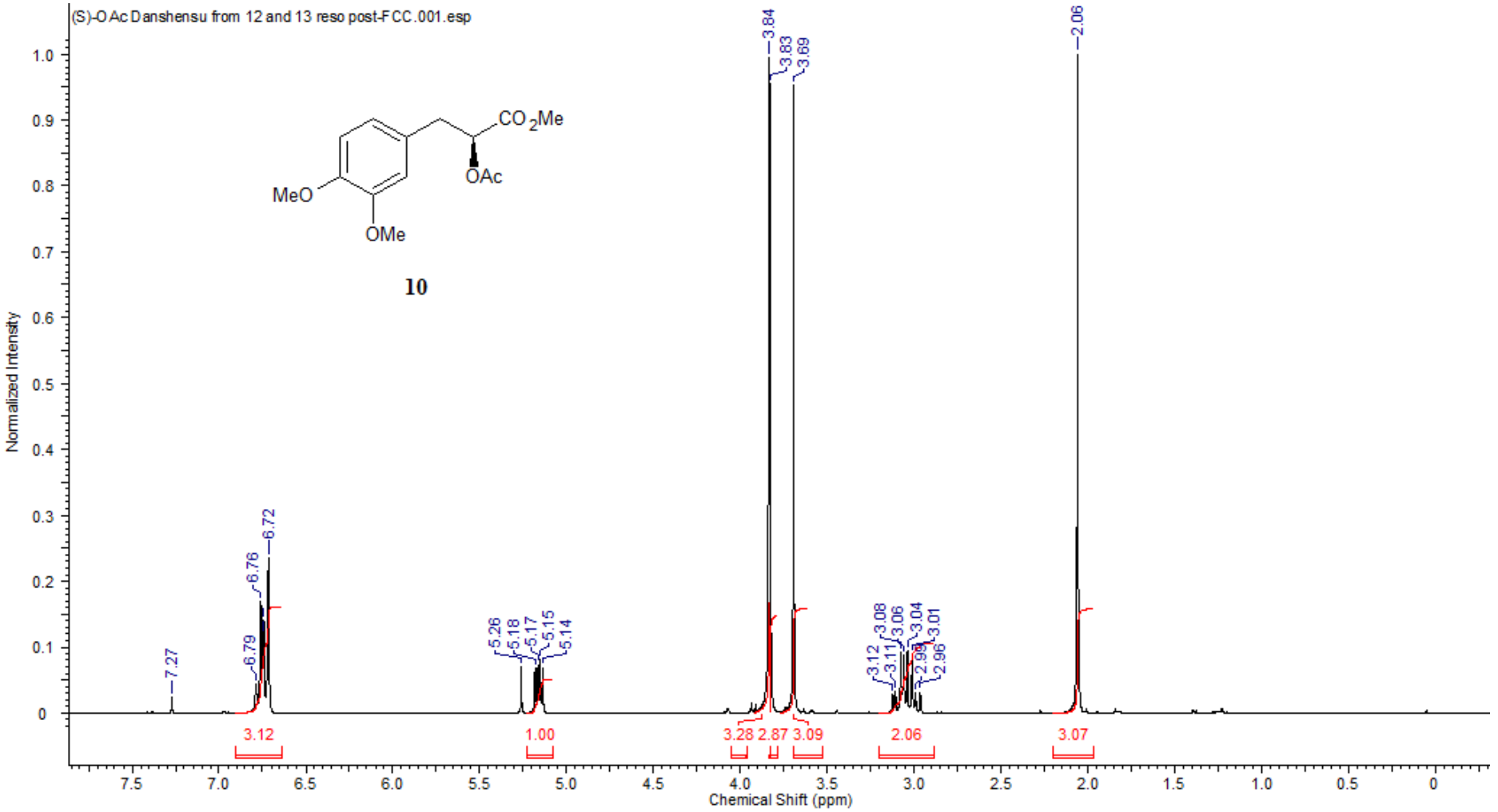
^{1}H NMR (300 MHz, $CDCl_3$)



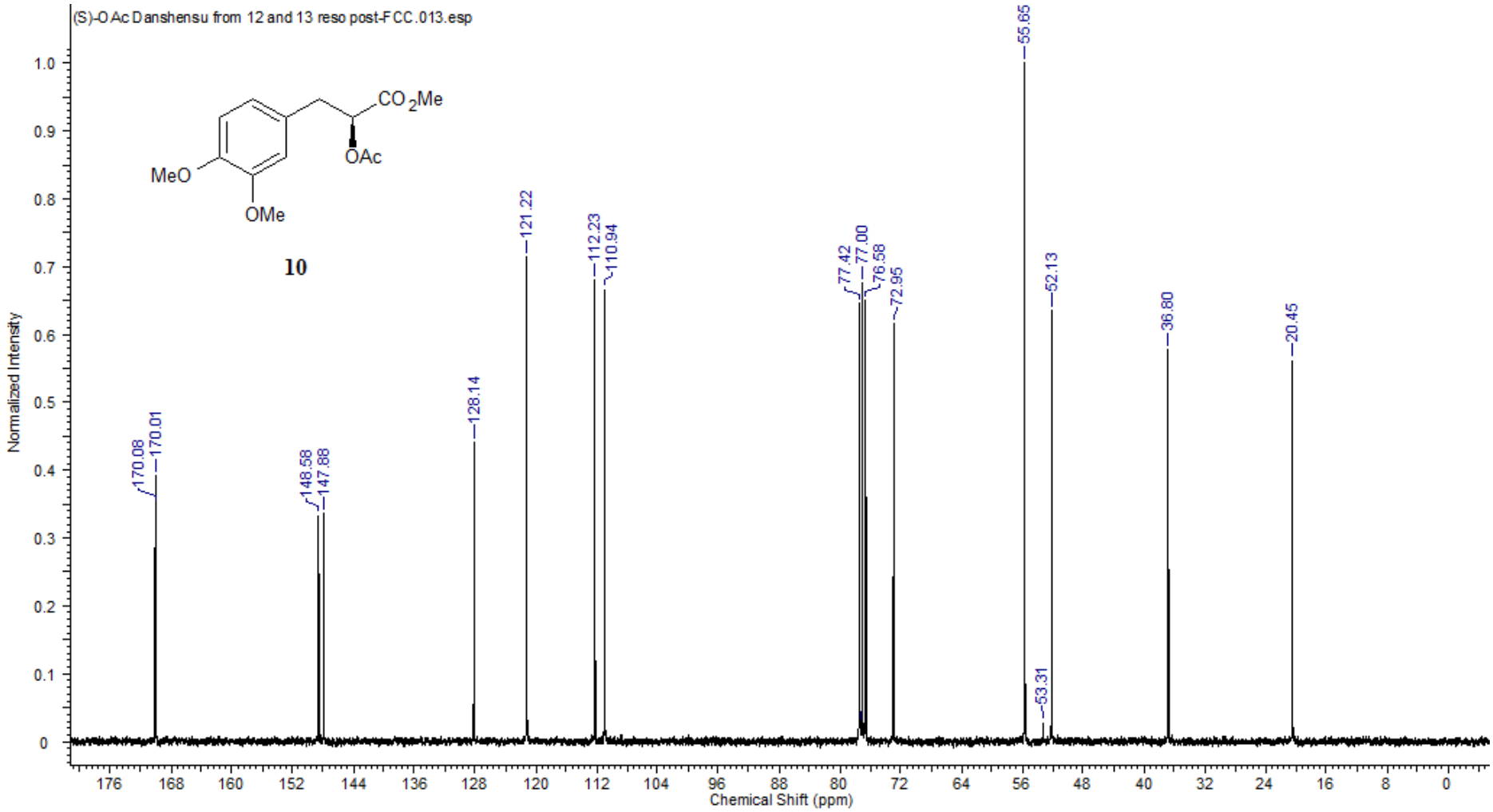
^{13}C NMR (75 MHz, $CDCl_3$)



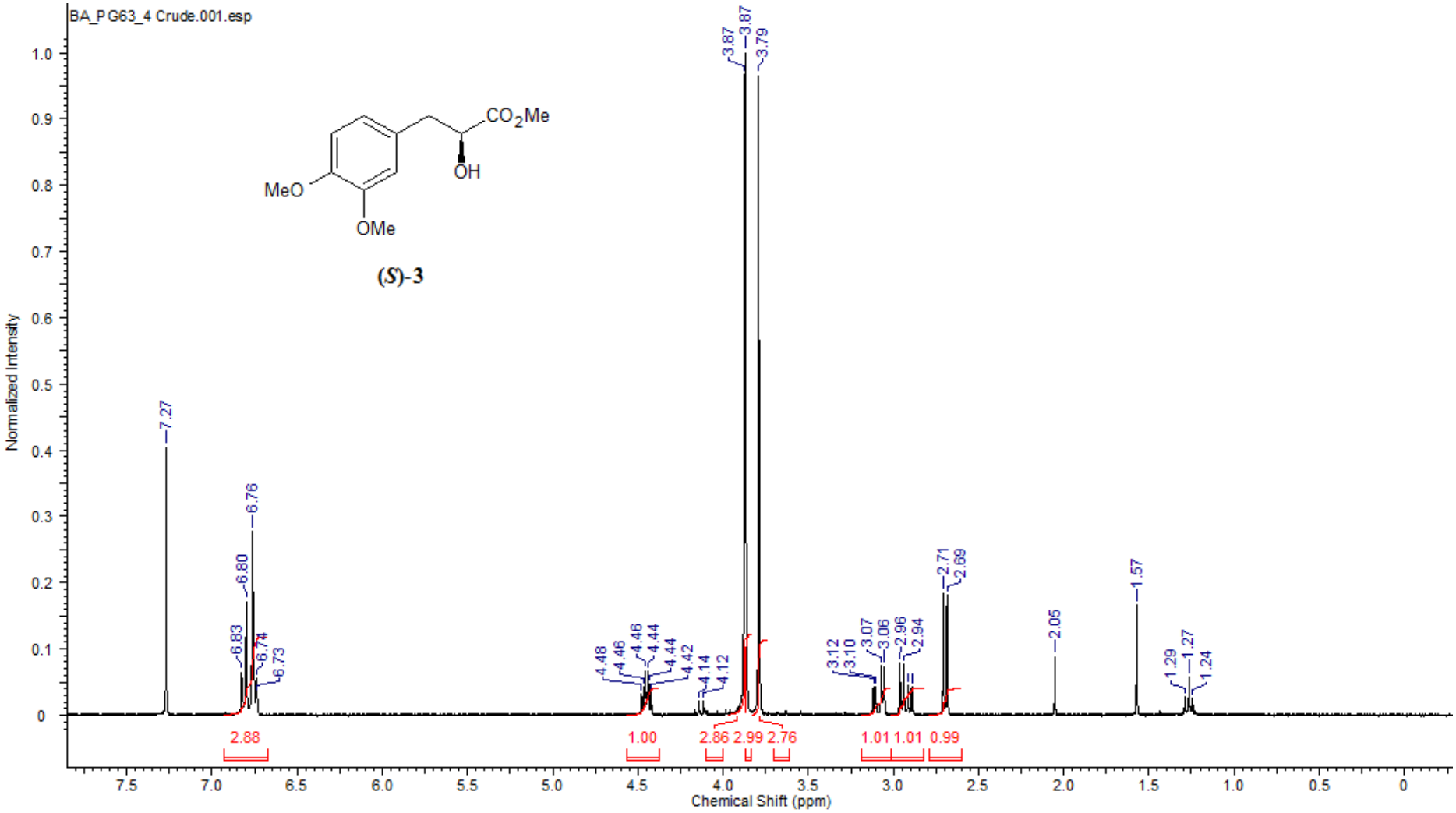
^{1}H NMR (300 MHz, $CDCl_3$)



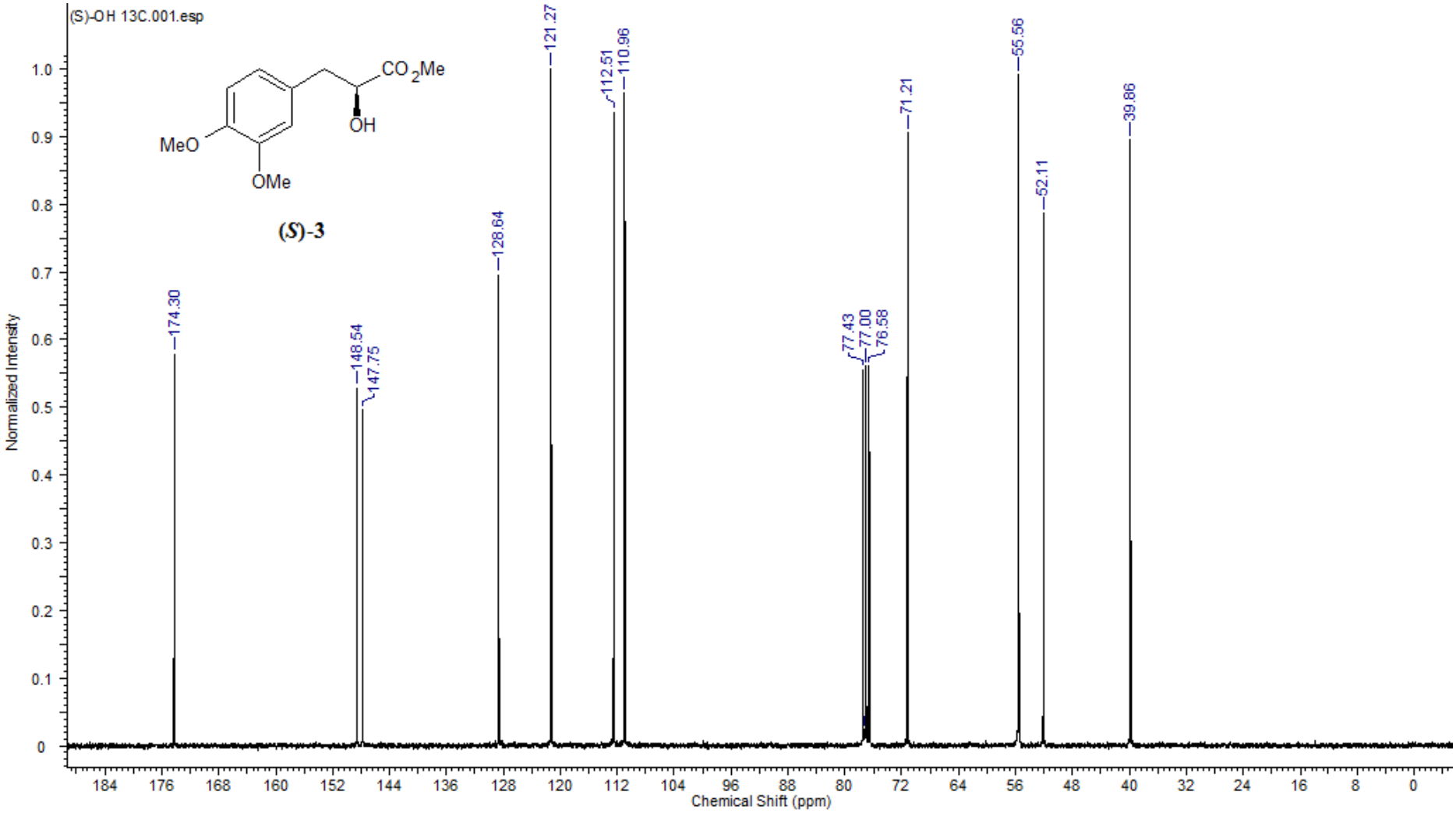
^{13}C NMR (75 MHz, $CDCl_3$)



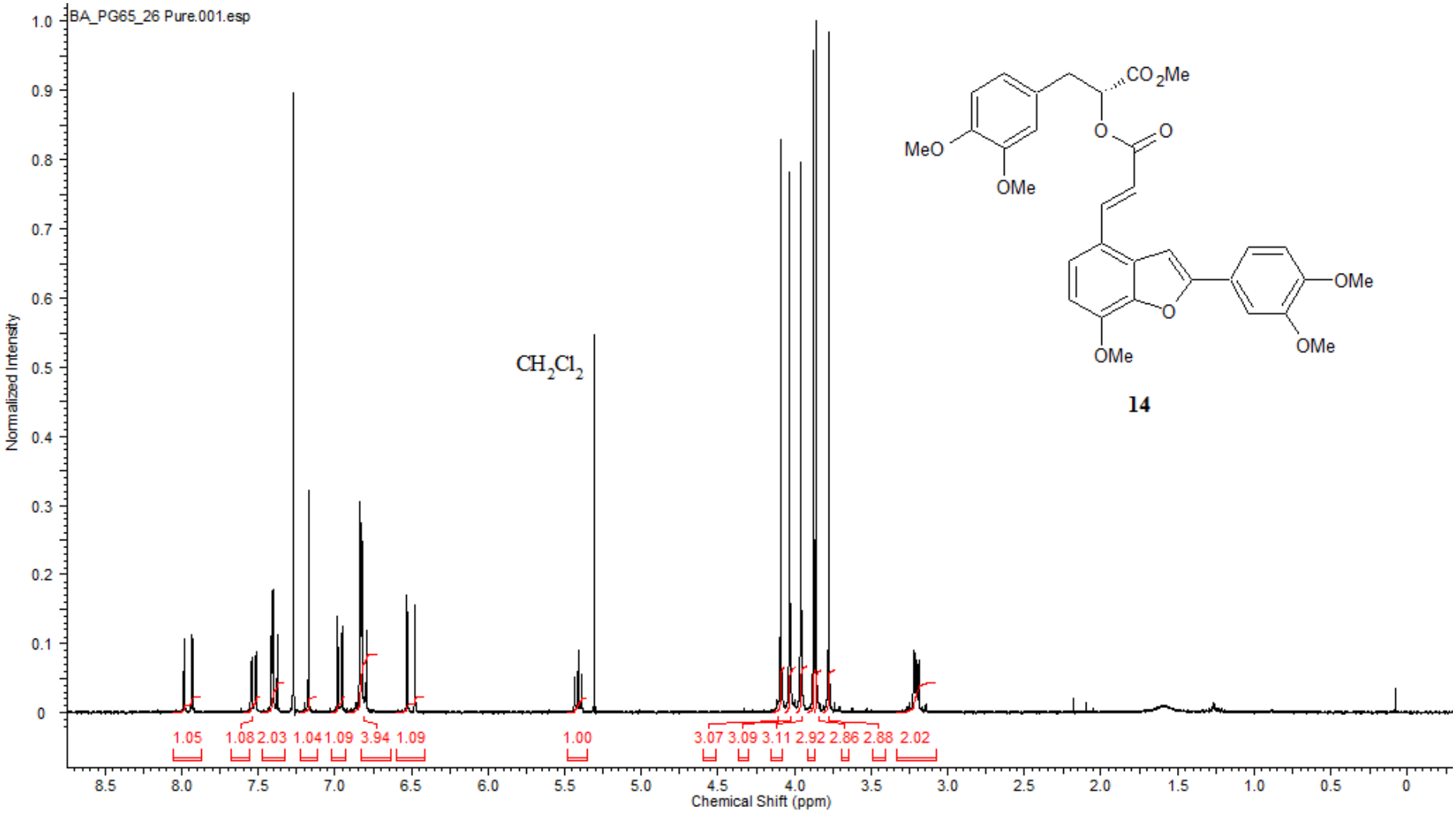
^{1}H NMR (300 MHz, $CDCl_3$)



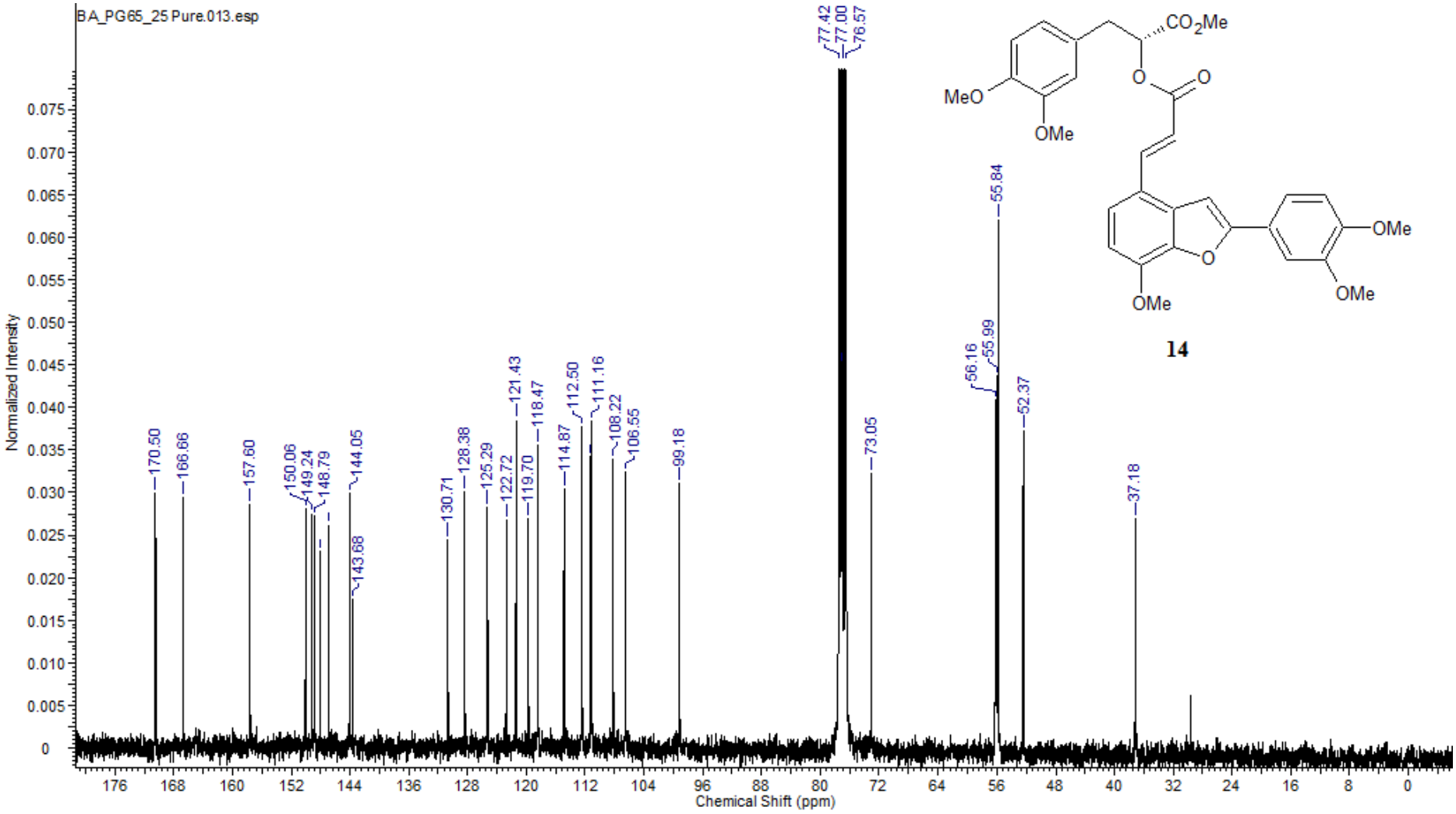
^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)

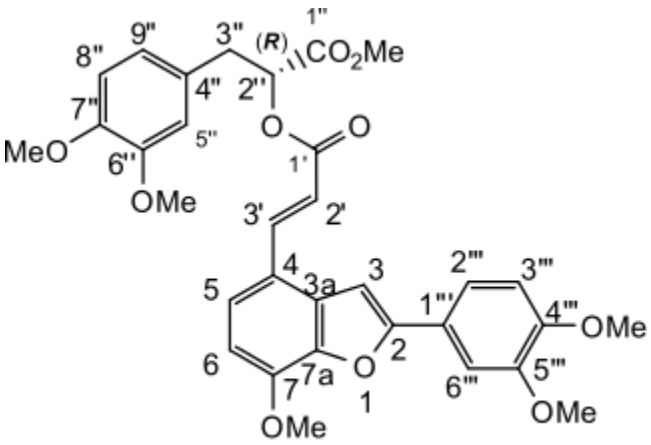


^{13}C NMR (75 MHz, $CDCl_3$)



Comparison table for (+)-Methyl pentamethylsalvianolate C (17)

Assignment (^{1}H)	*Natural* (90 MHz)[6] after methylation δ ppm (m, *J* in Hz)	*Synthetic* (300 MHz) δ ppm (m, *J* in Hz)
C2' - **H**	6.52 (d, 16)	6.50 (d, 15.9)
C3' - **H**	8.00 (d, 16)	7.96 (d, 16.3)
C2" - **H**	5.43 (t, 6)	5.41 (q, 13.1, 7.6, 5.5)
C3" - **H**	3.22 (d, 6)	3.21 (dd, 5.2, 2.0)
CO_2CH_3	3.80 (s)	3.78 (s)
	3.89 (s)	3.86 (s)
	3.90 (s)	3.88 (s)
5 × OCH_3	3.98 (s)	3.96 (s)
	4.05 (s)	4.03 (s)
	4.12 (s)	4.09 (s)
Ar - **H**	6.70 - 7.70	6.72 - 7.47



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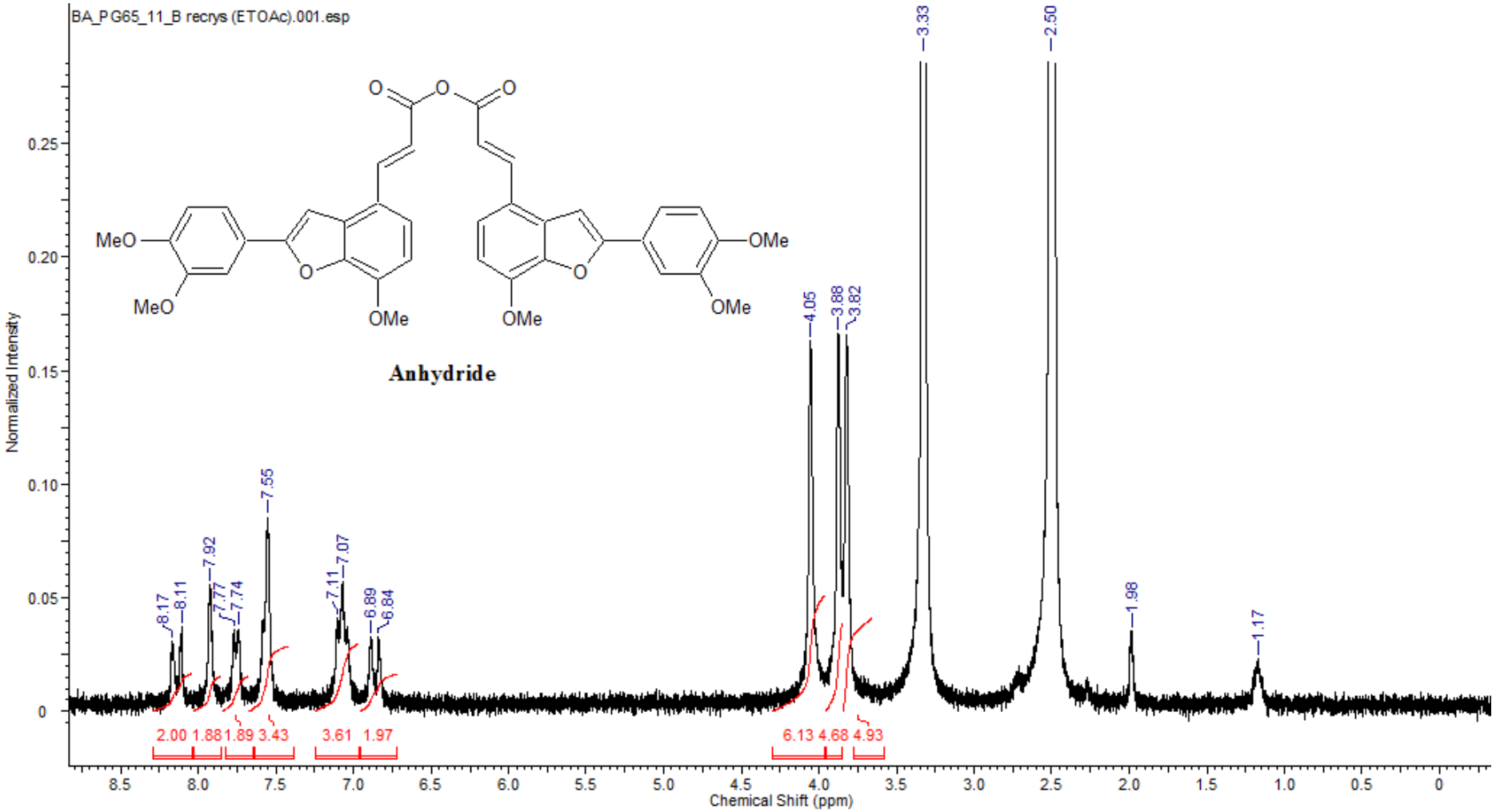
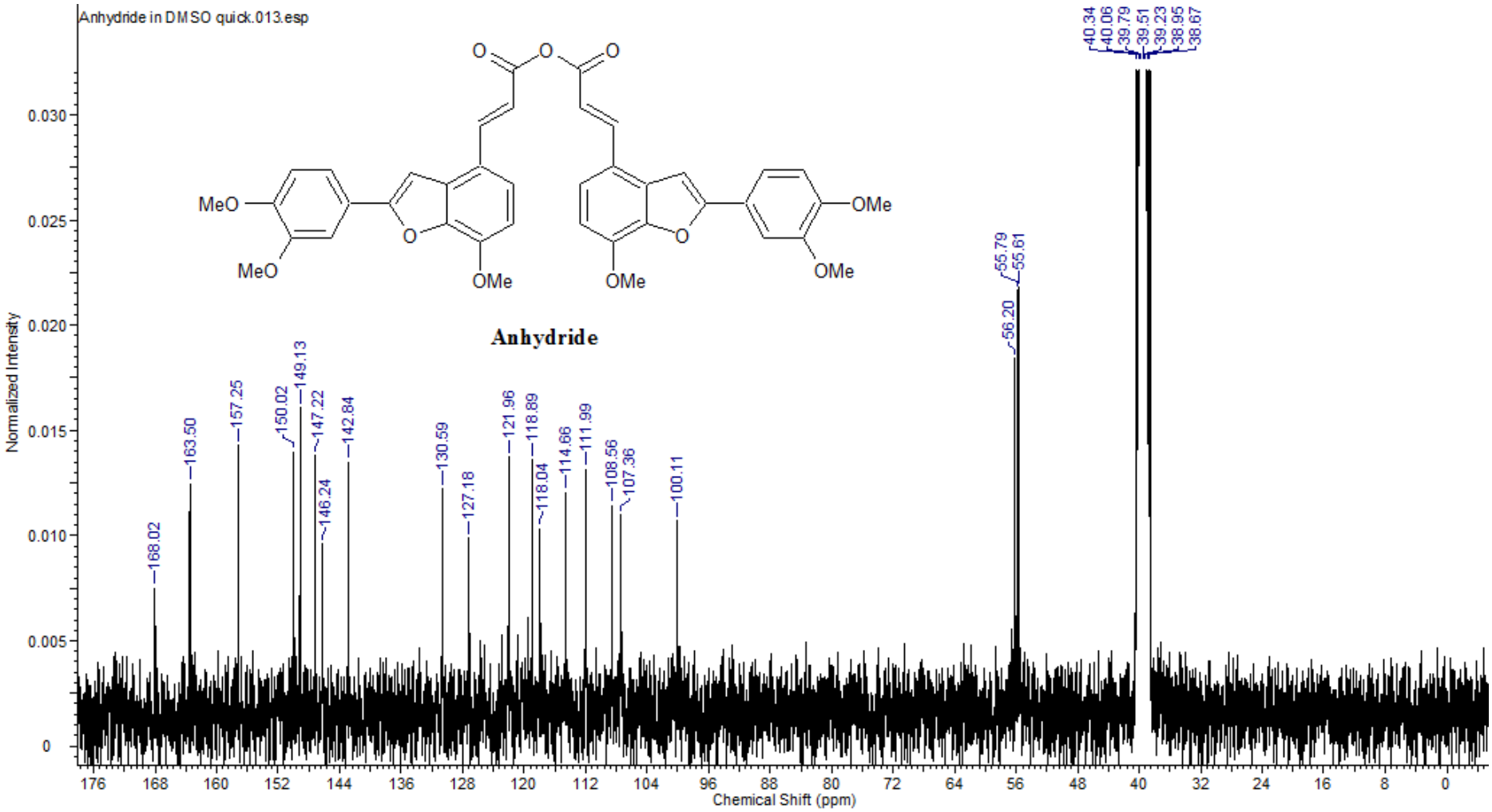
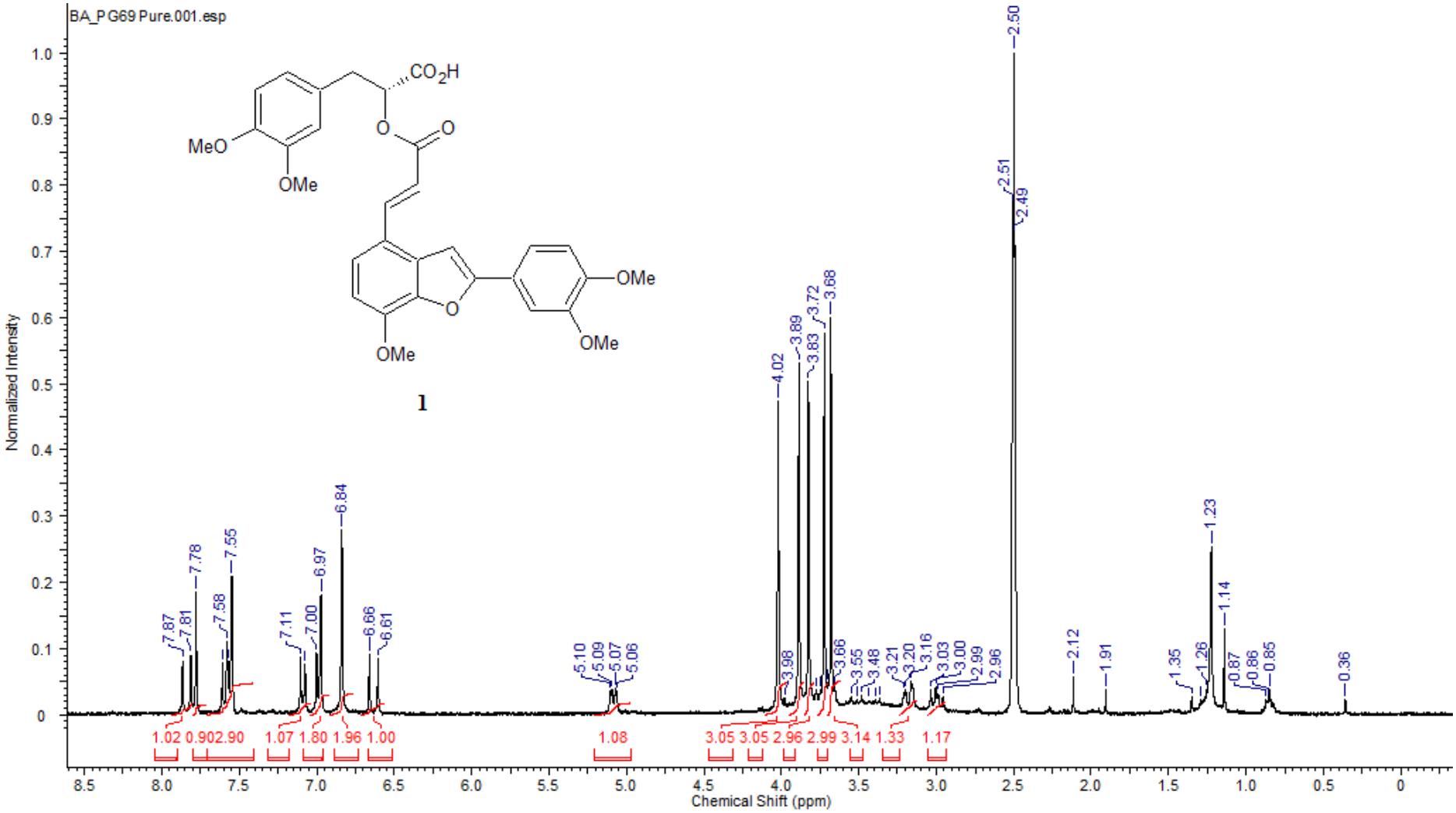
^{1}H NMR (300 MHz, d_6-DMSO)



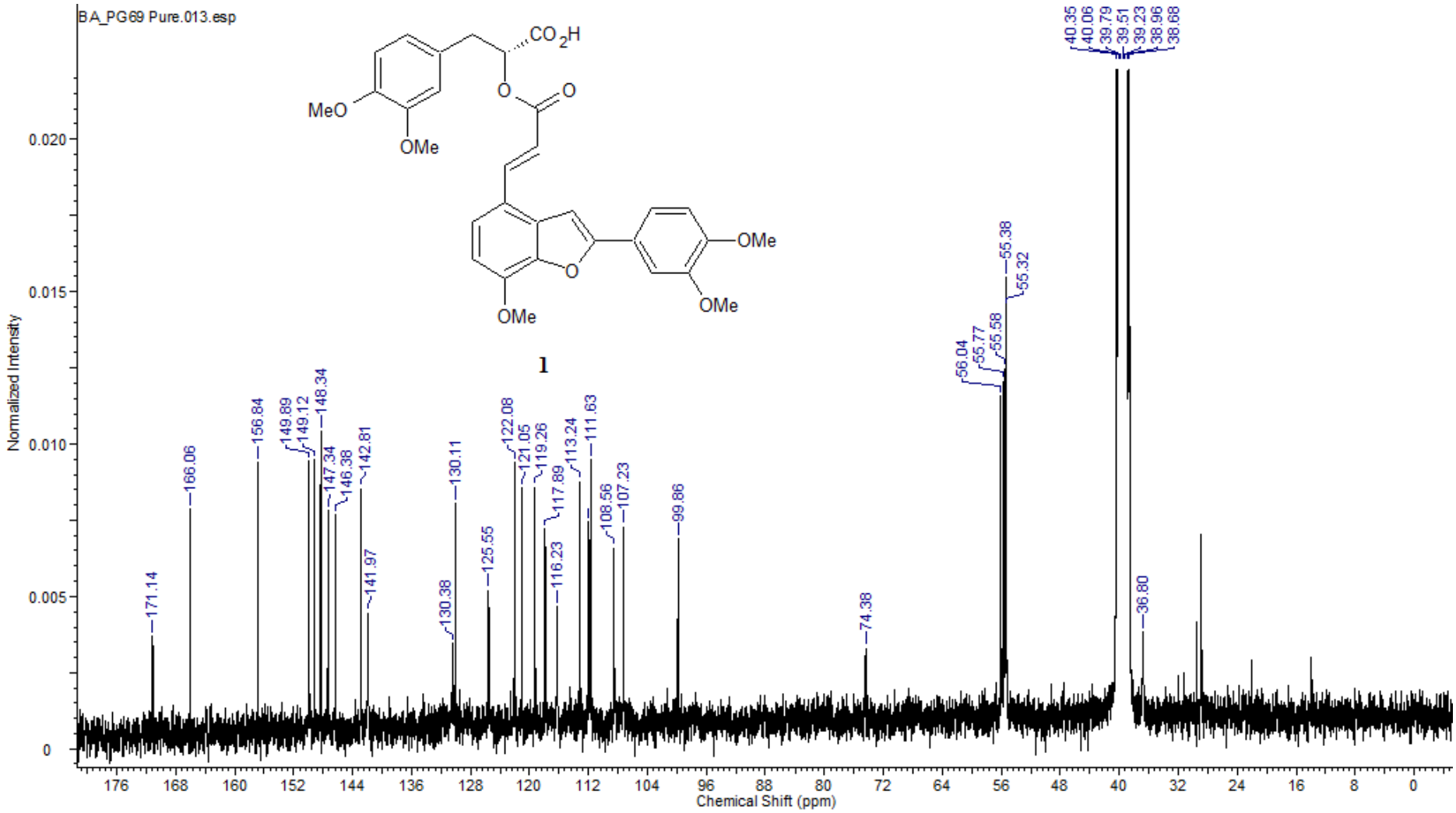
^{13}C NMR (75 MHz, d_6-DMSO)



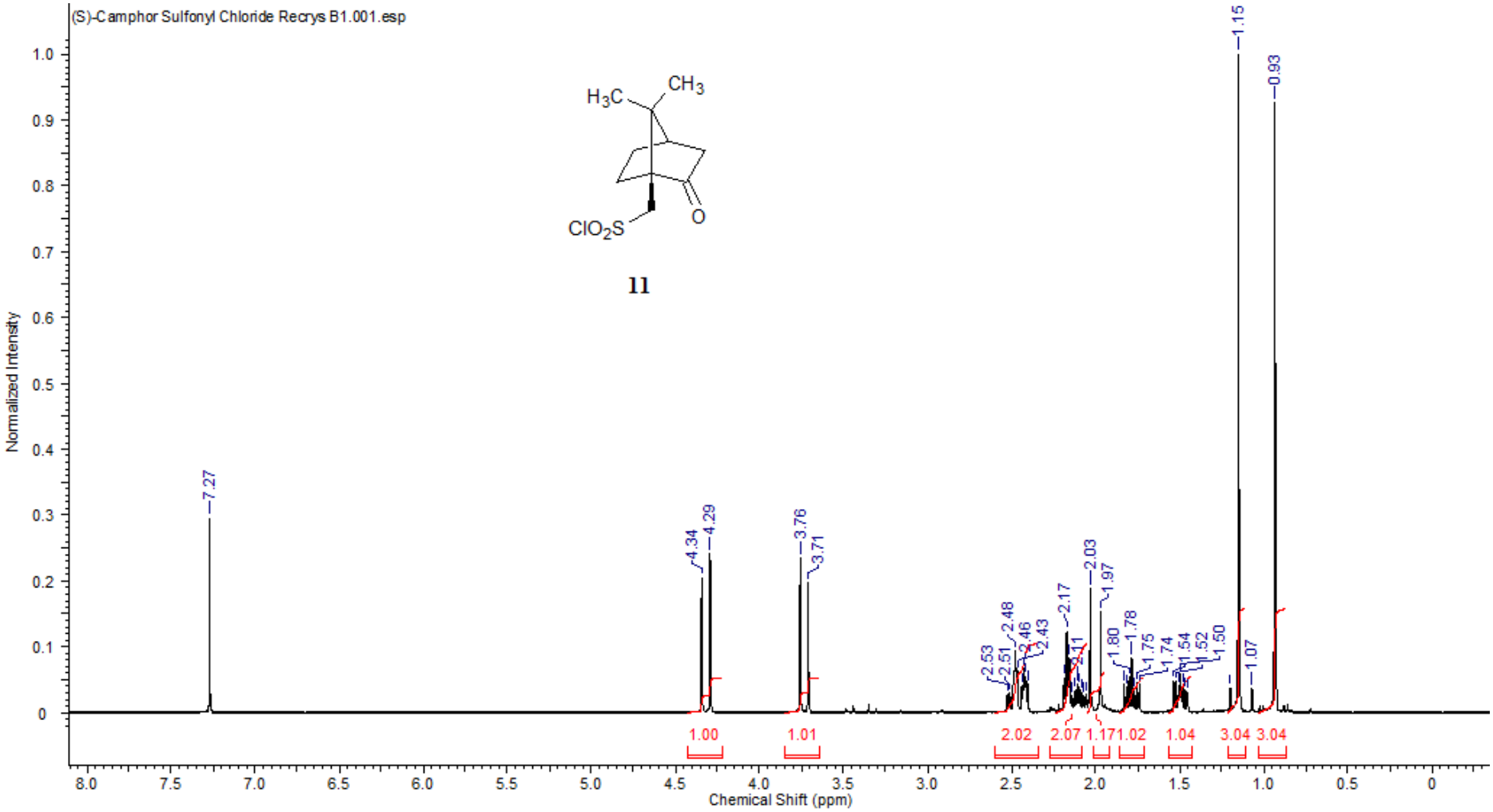
^{1}H NMR (300 MHz, d_6-DMSO)



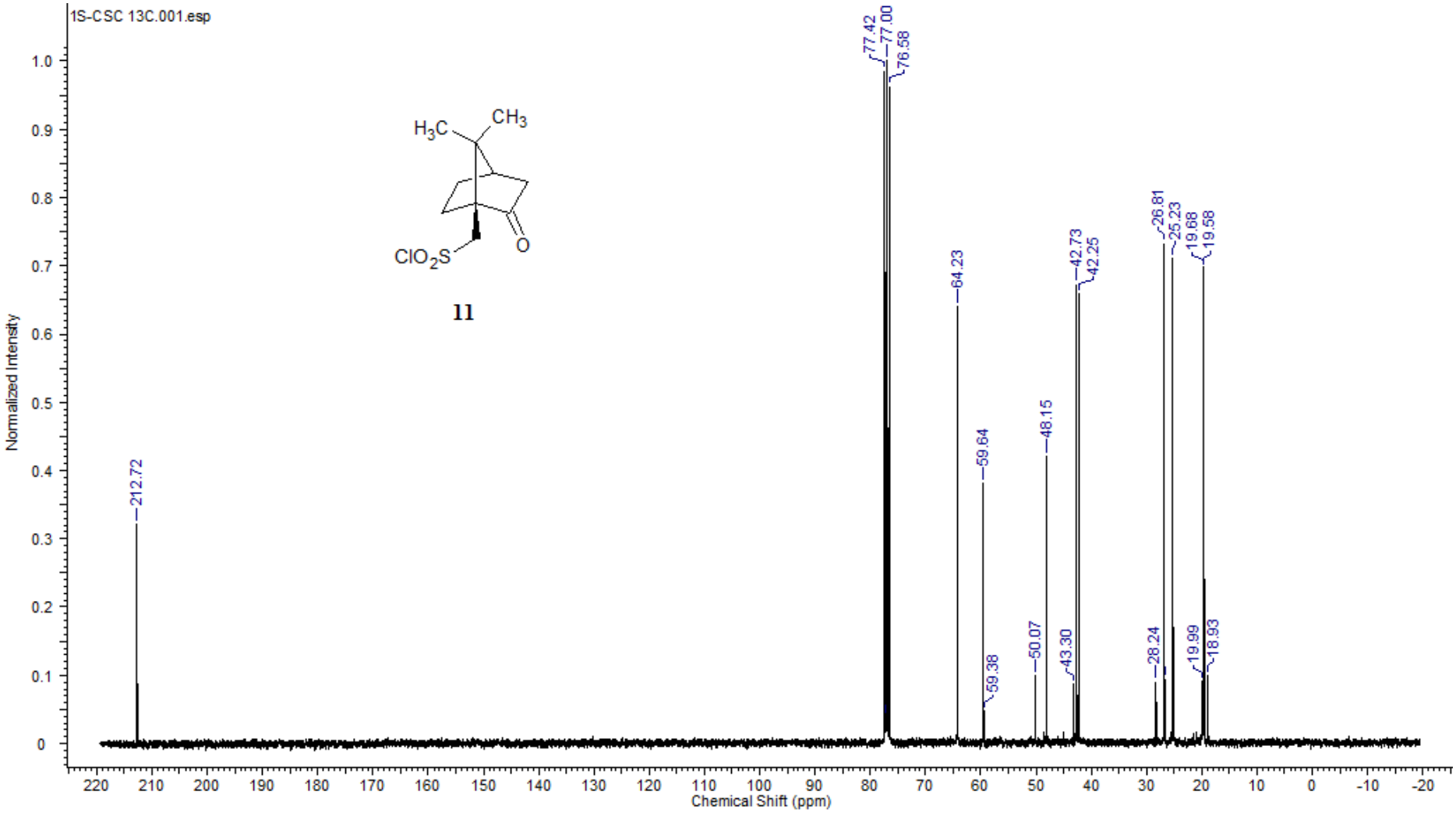
^{13}C NMR (75 MHz, d_6-DMSO)



^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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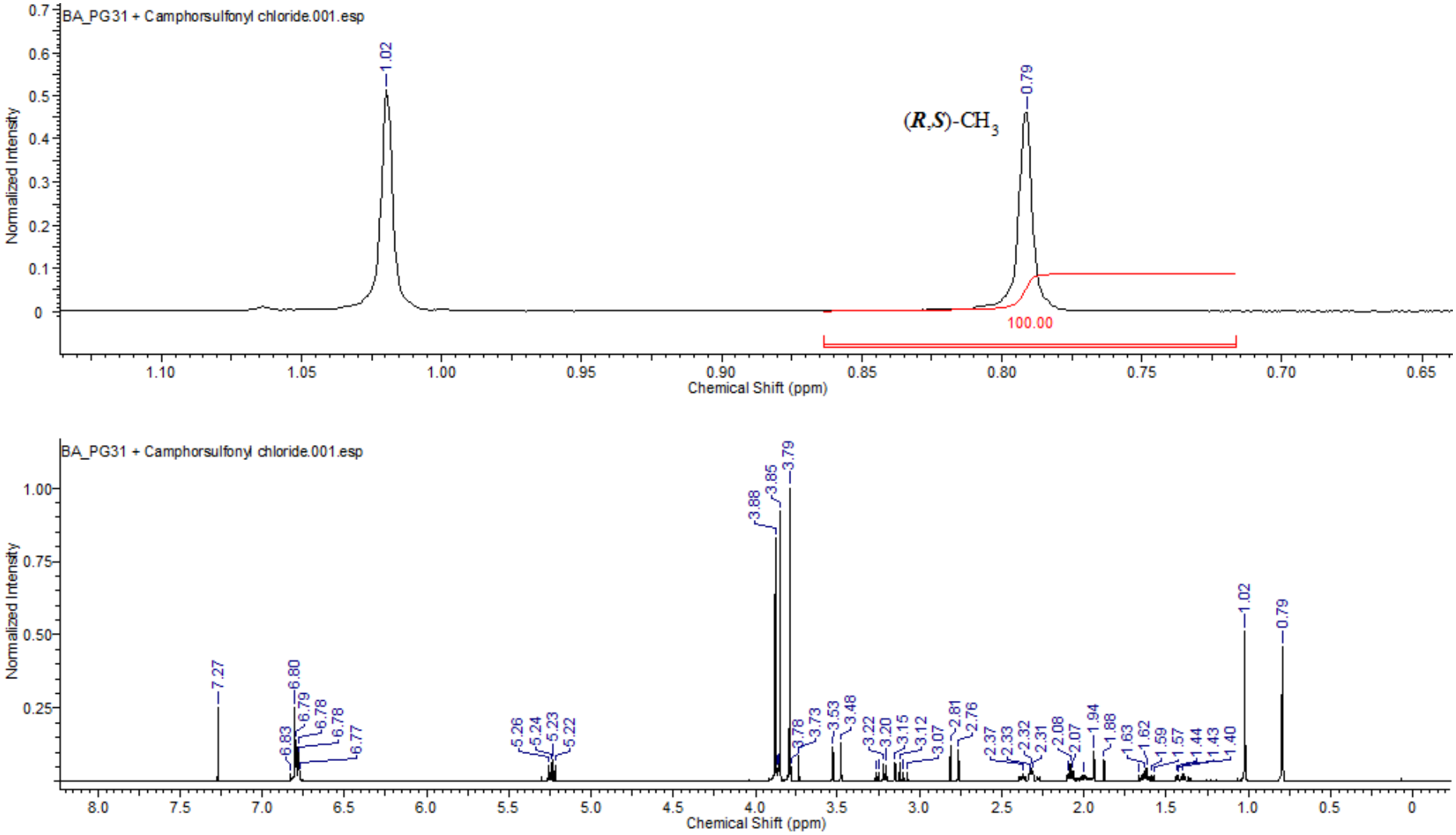
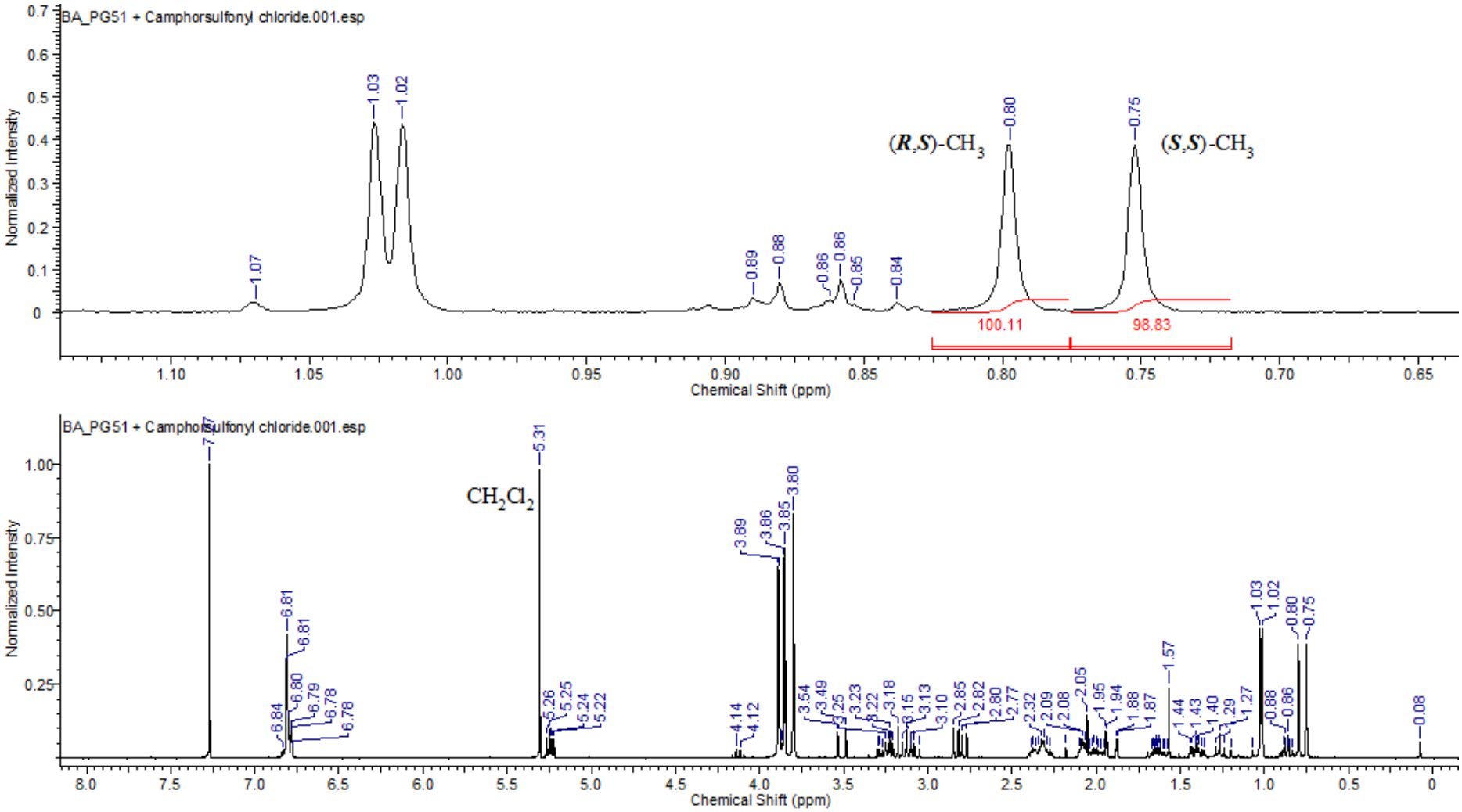
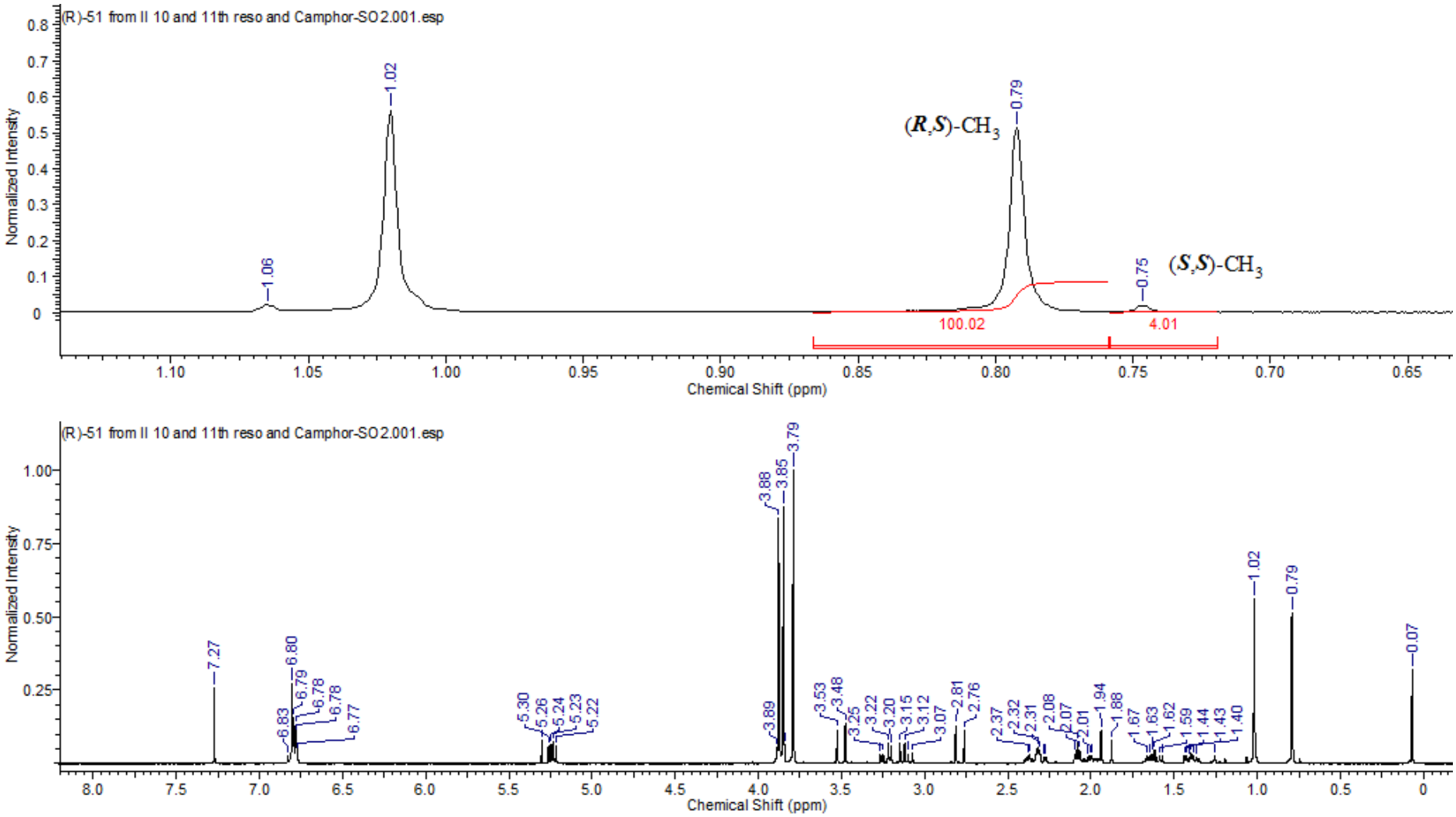
^{1}H NMR (300 MHz, $CDCl_3$) of standard (+)-Danshensu/11 sulfonate ester



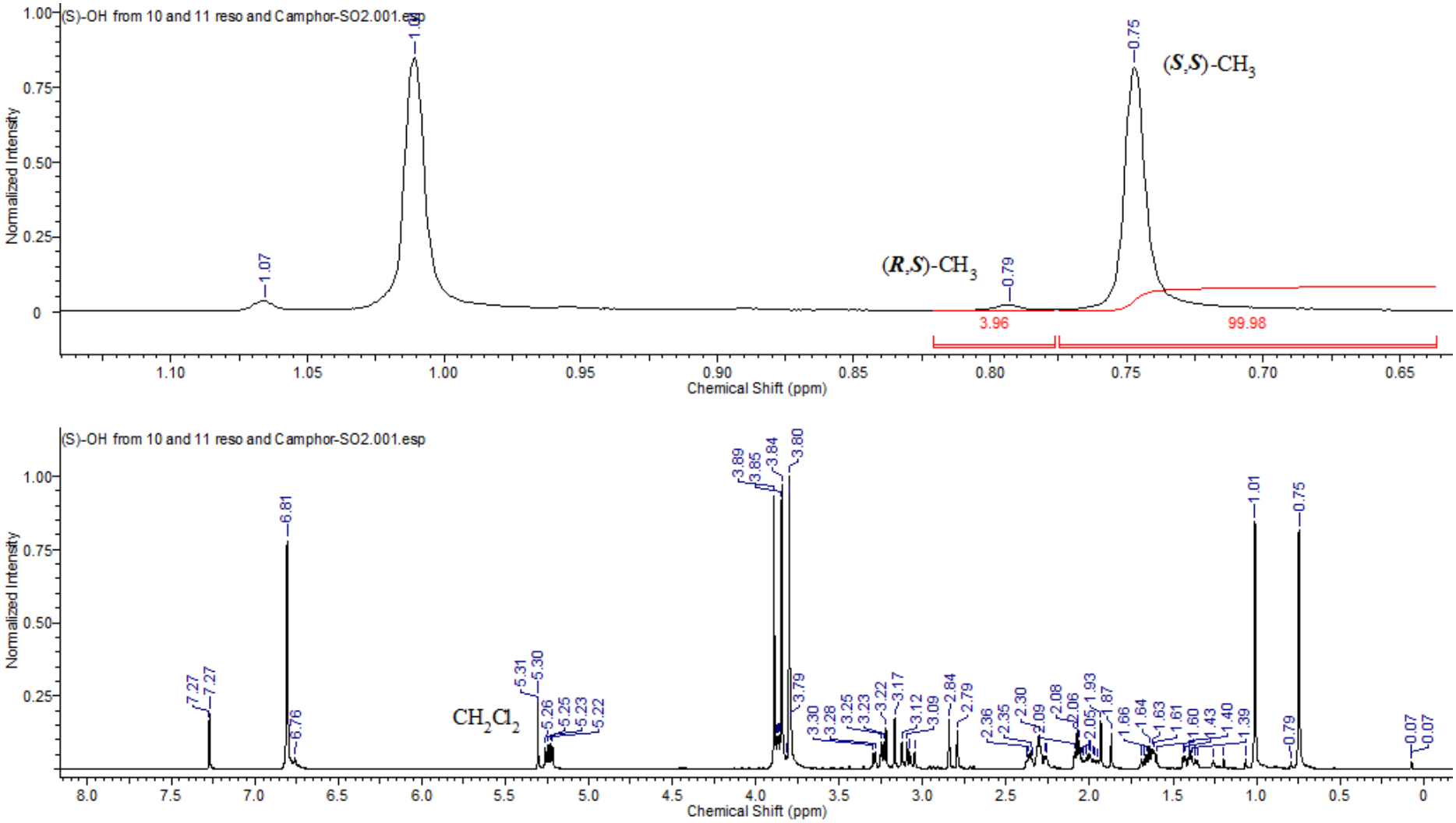
^{1}H NMR (300 MHz, $CDCl_3$) of *rac*-9/11 sulfonate ester



^{1}H NMR (300 MHz, $CDCl_3$) of (*R*)-3/11 sulfonate ester



^{1}H NMR (300 MHz, $CDCl_3$) of (*S*)-3/11 sulfonate ester



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2. Smiles S. and Hilditch T.P., *J. Chem. Soc., Trans.*, 1907, **91**, 519-528.
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