Synthesis of an Oxathiolane Drug Substance Intermediate Guided by Constraint Driven Innovation

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Supporting Information

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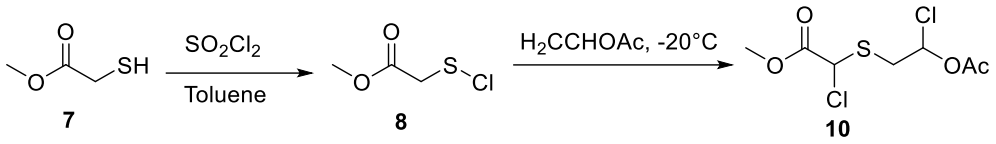
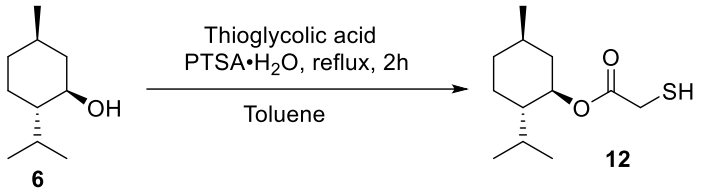
Experimental procedures:

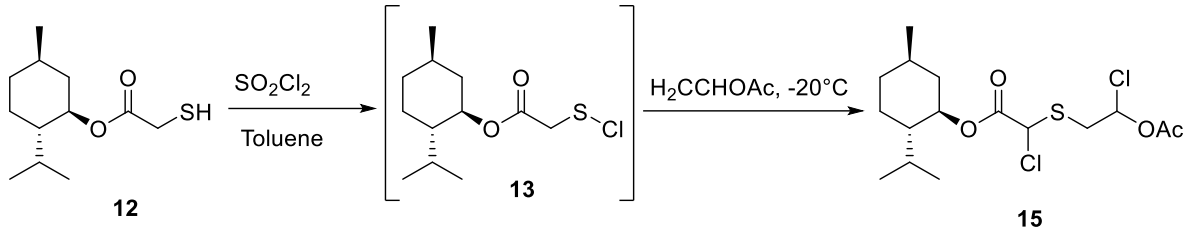


Methyl 2-((2-acetoxy-2-chloroethyl)thio)-2-chloroacetate (10), Screening Procedure: Methyl thioglycolate, **7** (50.0 mg, 42.0 µL, 1 eq) was added to an NMR tube in $CDCl_3$ (500 µL). The sample was cooled to -20 °C, and then sulfuryl chloride (136 mg, 79.9 µL, 2.1 eq) was quickly added and the NMR tube was capped and shaken. The NMR tube warmed to room temperature over the course of 1 hour. NMR showed formation of sulfenyl chloride **8**. ^{1}H NMR (600MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.59 (s, 2H); ^{13}C NMR (150MHz, $CDCl_3$): δ 169.8, 52.7, 41.2. The sulfenyl chloride solution was returned to -20 °C and the NMR cap was removed with slight release of pressure. Vinyl acetate (81.1 mg, 86.8 µL, 2 eq) was added within 5 seconds and the tube was capped and shaken. The reaction was kept at -20 °C for 2 hours. Mesitylene (18.9 mg, 21.8 µL, 0.333 equiv.) was added as external standard. NMR showed formation of dichloro compound **10.** ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of diastereomers): δ 6.56 (dd, *J* = 4.1, 7.8 Hz, 1H), 6.50 (dd, *J* = 5.1, 7.3 Hz, 1H), 5.43 (d, *J* = 12.7 Hz, 1H), 3.82 (d, *J* = 2.4 Hz, 3H), 3.49 - 3.29 (m, 2H), 2.12 (d, *J* = 1.10 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) (mixture of diastereomers): δ 168.2, 166.6, 81.3, 81.2, 60.6, 60.1, 53.8, 53.8, 37.5, 37.2, 20.7.



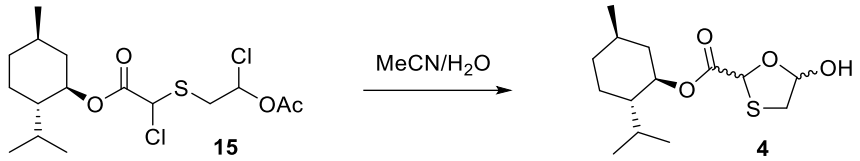
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-mercaptoacetate (12): L-Menthol, **6** (210g, 1.34 mol), thioglycolic acid (98.5 mL, 1.41 mmol) and PTSA•H_2O (5.11g, 26.9 mmol) were taken up in toluene (105 mL) and heated under reflux with azeotropic removal of water for 2h. The reaction mixture was cooled to room temperature, 1% NaOH (100 mL) was added and stirred for 5min. The organic layer was separated and concentrated under reduced pressure to afford compound **12** (304 g, 98%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.70 (dt, *J* = 4.4, 10.9 Hz, 1H), 3.22 (d, *J* = 8.4 Hz, 2H), 2.01 - 1.97 (m, 2H), 1.91-1.88 (m, 1H), 1.69 - 1.66 (m, 2H), 1.50-1.47 (m, 1H), 1.41 - 1.37

(m, 1H), 1.12 - 0.96 (m, 2H), 0.91 - 0.86 (m, 7H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.5, 77.3, 47.0, 40.6, 34.2, 31.4, 26.8, 26.2, 23.4, 22.0, 20.8, 16.3; MS: 272 $(M+ACN+H)^+$; Spectral data was compared with reported values and found to be identical.[1]

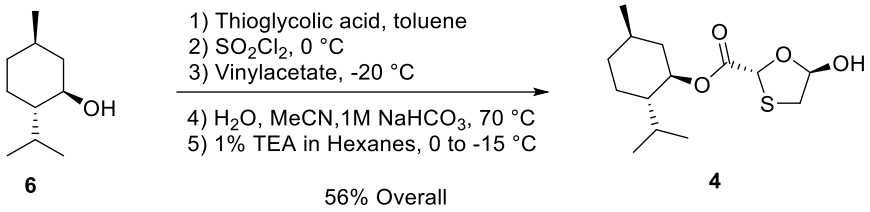


(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-((2-acetoxy-2-chloroethyl)thio)-2-chloroacetate (15): To a stirred solution of compound **12** (10 g, 43.4 mmol) in toluene (50 mL), sulfuryl chloride (7.72 mL, 95.5 mmol) was added drop wise for 10 min at -20 °C and stirred for 3 h. ^{1}H NMR showed formation of sulfenyl chloride **13**. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.79 (dt, *J* = 4.4, 10.9 Hz, 1H), 3.89 (s, 2H), 2.09 - 2.00 (m, 1H), 1.93 (dt, *J* = 2.8, 7.0 Hz, 1H), 1.77 - 1.64 (m, 2H), 1.56 - 1.38 (m, 2H), 1.18 - 1.01 (m, 2H), 0.95 - 0.84 (m, 7H), 0.80 - 0.73 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.4, 76.5, 46.9, 43.3, 40.7, 34.1, 31.4, 26.1, 23.2, 22.0, 20.7, 16.2. Then, vinyl acetate (8 mL, 86.8 mmol) was added drop wise for 10 min at -20 °C and stirred for another 3h. Then, the reaction mixture was quenched with 1M $NaHCO_3$ (100 mL) and organic layer was separated and extracted with toluene (50 mL). The combined organic fractions were dried over sodium sulfate and concentrated under reduced pressure. The crude compound was purified by column chromatography using 3% EtOAc in hexanes to afford desired compound **15** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of diastereomers): δ 6.59 - 6.52 (m, 1H), 5.41 - 5.36 (m, 1H), 4.74 (dt, *J* = 4.0, 11.0 Hz, 1H), 3.49 - 3.43 (m, 1H), 3.36 -3.31 (m, 1H), 2.14 (bs, 3H), 2.03 - 1.99 (m, 1H), 1.93 - 1.88 (m, 1H), 1.69 (d, *J* = 11.4 Hz, 2H), 1.49 - 1.43 (m, 2H), 1.08 - 1.01 (m, 2H), 0.92 - 0.86 (m, 7H), 0.77 - 0.75 (m, 3H); ^{13}C NMR (150MHz, $CDCl_3$) (mixture of diastereomers): δ 168.1, 168.1, 165.6, 165.5, 81.6, 81.5, 81.4, 81.3, 77.6, 77.5, 77.5, 61.7, 61.6, 61.0, 60.7, 47.0, 47.0, 46.9, 40.4, 40.3, 40.1, 37.6, 37.5, 37.5, 37.4, 34.0, 31.4, 31.4, 26.1, 26.1, 26.1, 23.3, 23.2, 21.9, 20.7, 20.7, 16.1; MS: 349 $(M-HCl)^+$; HRMS calculated for $C_{14}H_{20}O_4N$ $[M+H]^+$: 385.1007, found 385.1010.

General procedure for the cyclization:

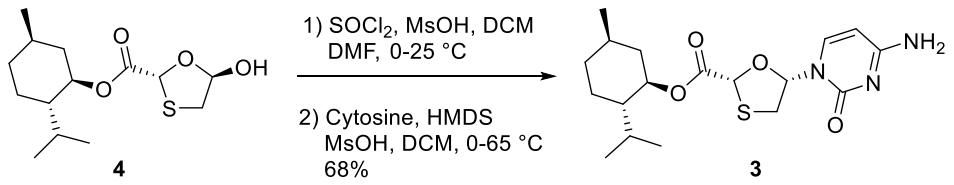


(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5-hydroxy-1,3-oxathiolane-2-carboxylate: To a stirred solution of compound **15** (1 eq) in acetonitrile (20 vol) and water (20 vol), additive (2 eq) was added and heated at the temperature as mentioned in Table 2 in manuscript. The reaction was monitored by TLC, and after consumption of starting material the reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic fraction was dried over sodium sulfate and concentrated under reduced pressure. The crude compound was purified by column chromatography or precipitated from hexanes to afford compound **4**.



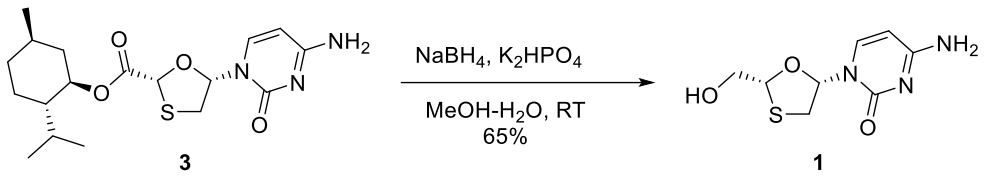
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,5*R*)-5-hydroxy-1,3-oxathiolane-2-carboxylate (4): L-Menthol, **6** (10.0 g, 64 mmol), PTSA·H_2O (243 mg, 1.3mmol), and thioglycolic acid (4.7 mL, 67.2 mmol) were taken up in toluene (50 mL) and heated at reflux with azeotropic removal of water for 2h. Then, the reaction mixture was cooled to 0 °C, sulfuryl chloride (11.4 mL, 141 mmol) was added in a rate of 0.76 mL/min over 15min using a syringe pump, and stirred for 1h at the same temperature. The mixture was then warmed to room temperature with continued stirring for 2h. The reaction mixture became yellow in color indicating formation of sulfenyl chloride **13**. The reaction mixture was cooled to -20 °C again, and vinyl acetate (11.8 mL, 128 mmol) was added at a rate of 0.786 mL/min over 15 min using a syringe pump. Stirring was continued for an additional 3h, and then the mixture was allowed to warm to 0 °C. The reaction was quenched using 1M $NaHCO_3$ (100 mL) and extracted with toluene (30 mL). It is important not to reach alkaline pH as base rapidly decomposes starting material and product. The combined organic fractions were dried over sodium sulfate and concentrated *in vacuo* to afford dichloro compound **15** (25.4 g) as a colorless oil. The crude compound **15** (25.4g) was taken up in ACN

(400 mL) and water (400 mL) and the reaction mixture was heated until the internal temperature reached 70 °C, typically over the course of 40 minutes. Once the temperature reached 70 °C, 1M $NaHCO_3$ (128 mL) was added over 2.5 h using a syringe pump at a flow rate of 0.85mL/min. Toluene (100mL) was added to the reaction mixture and the organic and aqueous layers were separated. The organic layer was dried over sodium sulfate and concentrated using a rotary evaporator and the residue was cooled to 0 °C. A solution of 1% triethylamine in hexanes (60 mL) was added dropwise over 30 min and stirred for an additional 2 h at the same temperature. Solid precipitation was observed. The suspension was stored in a freezer overnight. The solid was filtered using a Büchner Funnel, washed with cold hexanes (40 mL), and dried. Compound **4** was obtained as a white solid (10.41g, 56%,). HPLC purity 99.3%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.00 - 5.90 (m, 1H), 5.57 - 5.54 (m, 1H), 4.74 - 4.70 (m, 1H), 3.30 - 3.28 (m, 1H), 3.15-3.04 (m, 1H), 2.02 - 1.94 (m, 2H), 1.70 - 1.67 (m, 2 H), 1.50 - 1.41 (m, 2H), 1.06 - 0.98 (m, 2H), 0.93 - 0.86 (m, 7H), 0.77 - 0.75 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.4, 169.3, 103.2, 103.2, 101.1, 80.2, 80.2, 78.1, 76.0, 47.1, 47.0, 40.7, 40.4, 40.3, 38.5, 34.1, 34.1, 31.4, 31.4, 26.0, 23.3, 23.3, 23.2, 22.0, 22.0, 20.8, 20.7, 16.2, 16.1, 16.1. MS: 311 $(M+Na)^+$. Spectral data, HPLC data was compared with commercial sample purchased from combiblocks (catlog no AM2217) and found to be identical. (**Figure S1 & S2**). (Note: It was observed that Compound **4** epimerizes in NMR solvent)



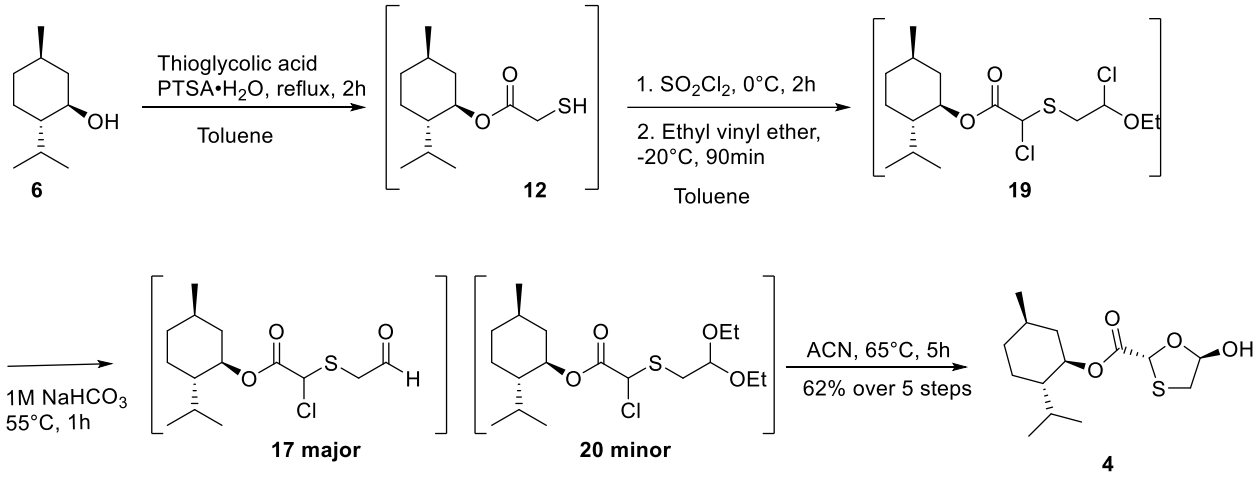
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,5*S*)-5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylate (3): (a) To a solution of compound **4** (1g, 3.47 mmol) in dichloromethane (10 mL), methanesulphonic acid (2.2 µL) and dimethylformamide (282 µL) were added and cooled to 0 °C. Then, thionyl chloride (264 µL) was added and the reaction mixture was stirred for 1h. (b) A suspension of cytosine (385 mg, 3.47mmol), methanesulphonic acid (2.2 µL) and hexamethyldisilazane (800 µL, 3.81mmol) was heated in toluene (2 mL) at reflux until a clear solution was obtained ~1h. The solution of silylcytosine was treated with triethylamine (483 µL). The solution of (a) was added to solution of (b) maintaining a gentle reflux, the resulting mixture was heated at reflux for 4 h. Then, to the reaction mixture triethylamine (240 µL) and

water (2 mL) were added and stirred for 1 h at room temperature followed by addition of hexanes (5 mL) which was added and then stirred overnight. Solid precipitated from solution. The solid was filtered, washed with water (5 mL) and isopropyl acetate (10 mL), and dried in *vacuo* to afford compound **3** as an off-white solid (0.9 g, 68%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (d, *J* = 7.3 Hz, 1H), 7.31 (brs., 1H), 7.27 (brs., 1H), 6.33 (t, *J* = 5.8 Hz, 1H), 5.82 - 5.71 (m, 1H), 5.67 (s, 1H), 4.66 (d, *J* = 4.2 Hz, 1H), 3.52 (dd, *J* = 4.9, 11.8 Hz, 1H), 3.11 (dd, *J* = 6.6, 11.9 Hz, 1H), 2.03 - 1.86 (m, 2H), 1.64 (d, *J* = 11.0 Hz, 2H), 1.47 (d, *J* = 3.3 Hz, 1H), 1.40 (brs., 1H), 1.03 (t, *J* = 11.6 Hz, 2H), 0.87 (dd, *J* = 6.9, 11.8 Hz, 7H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.6, 166.1, 155.1, 140.9, 94.8, 89.2, 77.8, 75.9, 46.8, 40.6, 35.7, 34.0, 31.3, 26.2, 23.3, 22.3, 21.0, 16.5. MS: 382 $(M+H)^+$. Spectral data was compared with reported values and found to be identical.[2]



4-Amino-1-((2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)pyrimidin-2(1*H*)-one (1): To a solution of compound **3** (0.5 g, 1.3 mmol) in methanol and water (3:2), K_2HPO_4 (680 mg, 3.9 mmol) in water (25 mL) was added at room temperature. After 15 min a solution of $NaBH_4$ (99 mg, 2.6 mmol) in water (1 mL) containing 25% w/w NaOH solution (10 µL) was added to the reaction mixture. Then the reaction mixture stirred for 5 h at the same temperature, monitoring the progress of the reaction by TLC (10% MeOH in DCM). After complete consumption of starting material, the reaction was quenched with HCl, adjusted to pH of 4 - 4.5, and washed with diethyl ether to remove the menthol. The aqueous layer pH was adjusted to 7-7.2 using 2 M NaOH solution, and the mixture was filtered and concentrated under the reduced pressure. The crude compound was purified by recrystallization using hexane: EtOAc: methanol (2:2:1) to afford lamivudine **1** (195 mg, 65%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 (d, *J* = 7.5 Hz, 1H), 6.28 (dd, *J* = 4.5, 5.2 Hz, 1H), 5.87 (d, *J* = 7.5 Hz, 1H), 5.26 (t, *J* = 3.9 Hz, 1H), 3.93 (dd, *J* = 3.5, 12.5 Hz, 1H), 3.86 (dd, *J* = 4.2, 12.5 Hz, 1H), 3.50 (dd, *J* = 5.4, 12.0 Hz, 1H), 3.12 (dd, *J* = 4.4, 11.9 Hz, 1H); ^{13}C NMR (150 MHz, Methanol-d_4) δ 166.3, 156.5, 141.4, 94.3, 87.4, 86.6, 62.6, 37.1; MS: 230 $(M+H)^+$. Spectral data was compared with reported values and found to be identical.[2]

HPLC (**Figure S3 & S4**) and chiral HPLC (**Figure S5 & S6**) of standard and synthesized were compared and found to be identical.



(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5-hydroxy-1,3-oxathiolane-2-carboxylate (4): A mixture of menthol **6** (5 g, 32 mmol), thioglycolic acid (2.3 mL, 34 mmol), PTSA·H_2O (120 mg, 0.64 mmol) in toluene (25 mL) was heated at reflux with azeotropic removal of water for 2h. The reaction mixture was cooled to 0 ˚C, and sulfuryl chloride (5.7 mL, 70 mmol) was added over the period of 10 min. The reaction was stirred for 2 h while allowing the reaction mixture to warm to room temperature. After this time, the mixture was cooled to -20 ˚C and ethyl vinyl ether (6.1 mL, 64 mmol) was added over the period of 10 min. The reaction mixture was stirred at same temperature for 90 min. Monitoring the reaction by NMR showed the formation of dichloro ether compound **19**. ^{1}H NMR (600MHz, $CDCl_3$) (mixture of diastereomers): δ 5.80 - 5.67 (m, 1H), 5.62 (d, *J* = 7.0 Hz, 1H), 4.78 - 4.68 (m, 1H), 4.04 - 3.91 (m, 1H), 3.66 - 3.52 (m, 1H), 3.50 - 3.30 (m, 1H), 3.22 (dd, *J* = 3.1, 14.7 Hz, 1H), 2.08 - 1.97 (m, 1H), 1.92 (dd, *J* = 2.1, 4.8 Hz, 1H), 1.69 (d, *J* = 12.3 Hz, 2H), 1.55 - 1.43 (m, 2H), 1.34 - 1.22 (m, 3H), 1.11 - 0.99 (m, 2H), 0.97 - 0.80 (m, 8H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150MHz ,$CDCl_3$) (mixture of diastereomers): δ 165.8, 165.8, 96.5, 96.2, 96.1, 67.0, 66.8, 62.8, 62.7, 61.4, 61.2, 47.0, 47.0, 46.9, 40.4, 40.3, 40.2, 40.2, 39.2, 39.1, 38.6, 38.5, 34.1, 31.4, 31.4, 31.4, 26.1, 26.0, 23.3, 23.3, 23.2, 22.0, 20.7, 20.7, 16.2, 16.1, 14.3, 14.3. The reaction mixture was quenched with 1M $NaHCO_3$ (50 mL) and heated at 50 ˚C for 1h. ^{1}H NMR showed formation of aldehyde **17** (major) and diethylacetal **20** (minor) mixture. Acetonitrile (50 mL) was added to the reaction mixture and heated at 65 ˚C for 5h. ^{1}HNMR showed formation of target compound **4**. The reaction mixture was cooled to room temperature, and the organic layer was separated and concentrated. The residue was cooled to 0 °C, a solution of 1%

triethylamine in hexanes (40 mL) was added dropwise over 30 min, and the mixture was stirred for an additional 2 h at the same temperature. Solid precipitation was observed. The suspension was stored in a freezer overnight. The solid was filtered using a Büchner Funnel, washed with cold hexanes (40 mL), and dried. Compound **4** was obtained as a white solid (5.7g, 62%). NMR purity 98%. Spectral data and purity were compared with the compound **4** from vinyl acetate route and found to be identical.

HPLC Analysis

HPLC analysis was accomplished using method described below

Mobile Phase A	15%: 2.5 mM Ammonium Formate in 18 MΩ Water, pH 4.12
Mobile Phase B	85%: Acetonitrile
Flowrate	1.5 mL/min
Column Compartment Temperature	10 ◦C
Column	Zorbax Eclipse XDB-C18 4.6 x 250 mm, 5 µm
Runtime	10 min
Injection Volume	10 µL
Monitored Wavelengths (nm)	210, 260

HPLC Chromatograms of compound 4

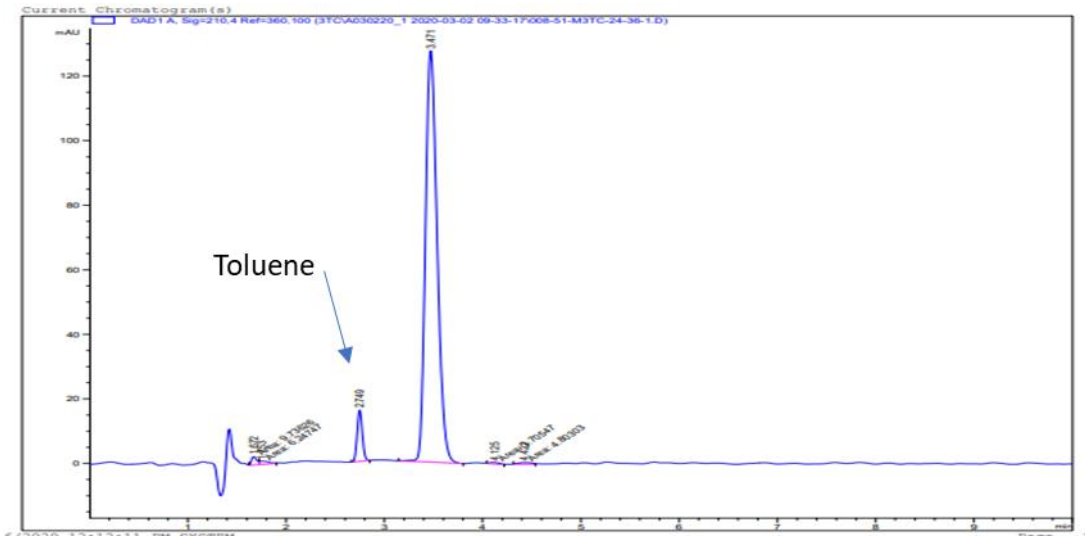


Figure S1. HPLC-DAD Chromatogram for Compound 4 (Synthesized from Vinyl Acetate)

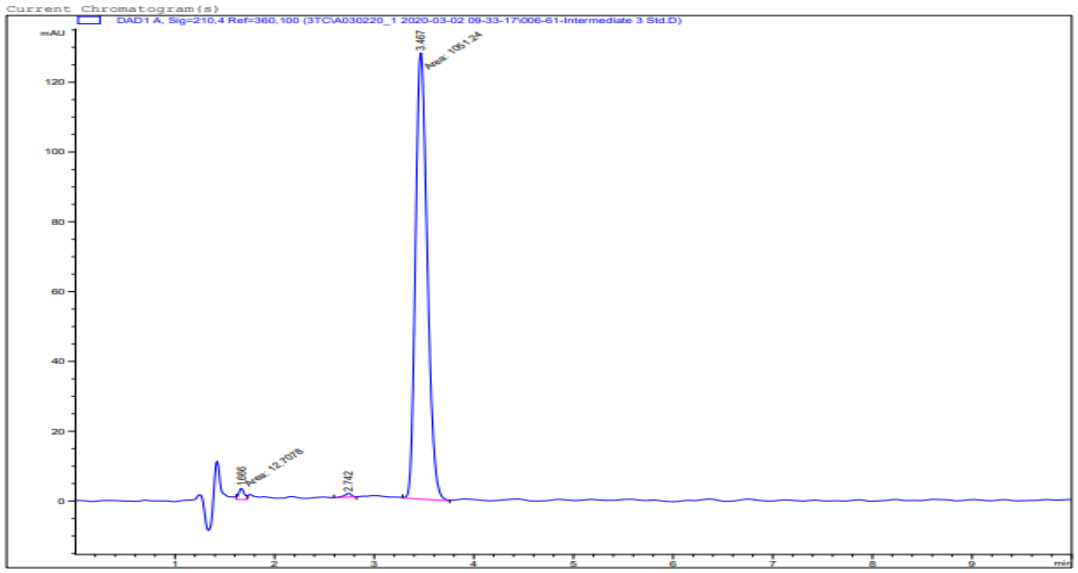


Figure S2. HPLC-DAD Chromatogram for Compound 4 (Commercial Sample)

HPLC Chromatograms of Lamivudine 1.

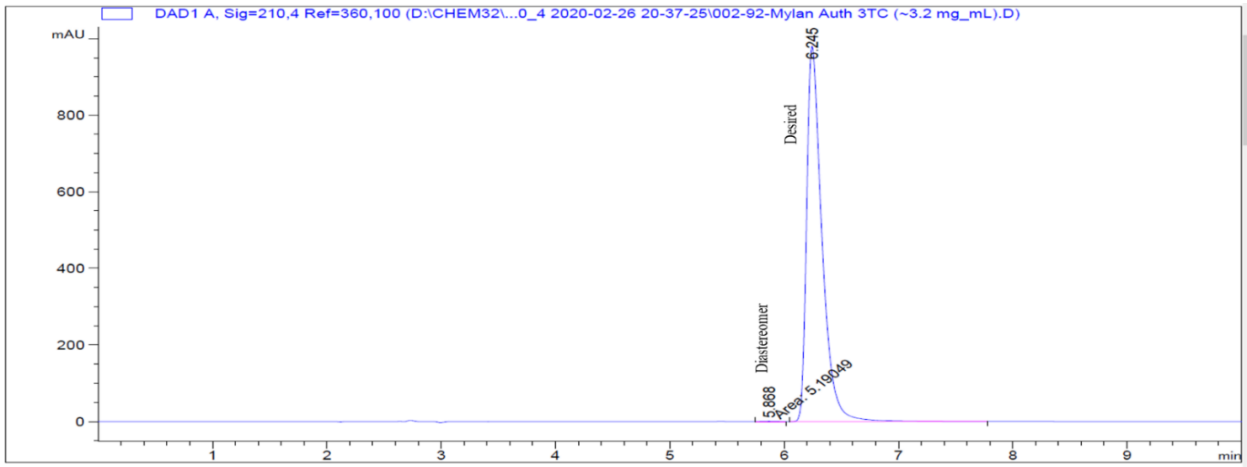


Figure S3. LC-DAD Chromatogram for Standard Lamivudine 1

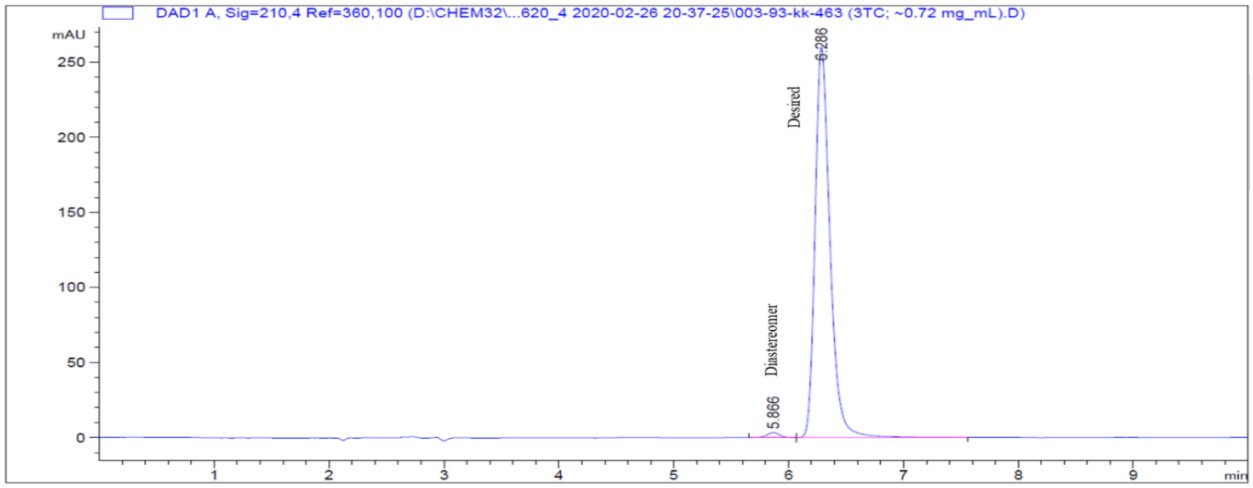


Figure S4. LC-DAD Chromatogram for Lamivudine 1 from Vinyl Acetate

HPLC Results:

ID	Area % @ 210 nm for desired peak	Area % @ 210 nm for diastereomer peak	Peak Area % for desired @ 260 nn
Lamivudine standard	99.94%	0.06%	99.803%
Lamivudine 1 synthesized	98.90%	1.10%	98.670%

Chiral Analysis

Chiral analysis was accomplished using the chiral SFC method described below.

Mobile Phase A	80%: CO_2
Mobile Phase B	20%: EtOH
Flowrate	2 mL/min
Column	ChiralPak IG 4.6 x 100 mm, 5 µm
Runtime	15 min
Injection Volume	10 µL
Monitored Wavelengths (nm)	210, 260

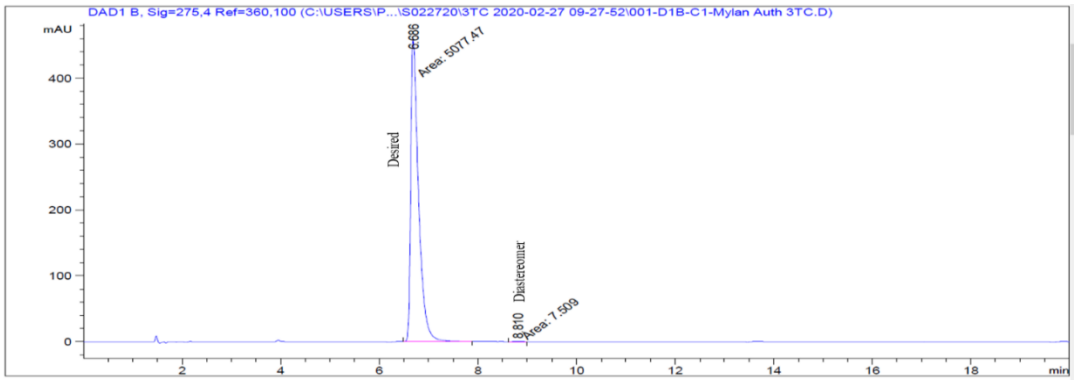


Figure S5. Chiral Chromatogram for Standard Lamivudine 1.

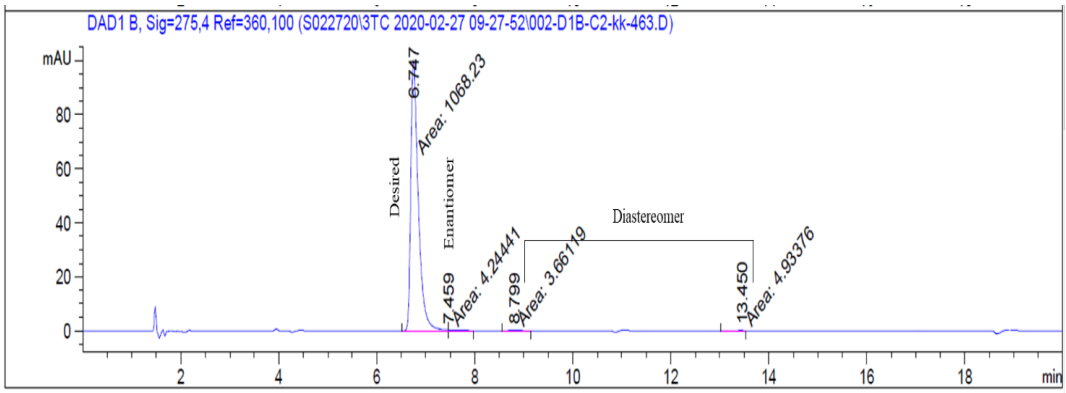


Figure S6. Chiral Chromatogram for Lamivudine 1 from Vinyl Acetate

SFC Results (Chiral)

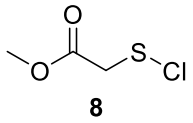
ID	Area % @ 210 nm for desired peak	Area % @ 210 nm for enantiomer peak	Area % @ 210 nm for diastereomer peak 1	Area % @ 210 nm for diastereomer peak 2
Lamivudine standard	99.96%	-	0.04%	-
Lamivudine 1 synthesized	98.84%	0.41%	0.31% %	0.43%

References:

1. Rozwadowska, M.D.; Sulima, A.; Gzella, A. Synthesis, crystal structure and oxidation of (R)-(+)-8,9-dimethoxy-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one. *Tetrahedron:Asymmetry*, **2002**, *13*, 2329-2333.

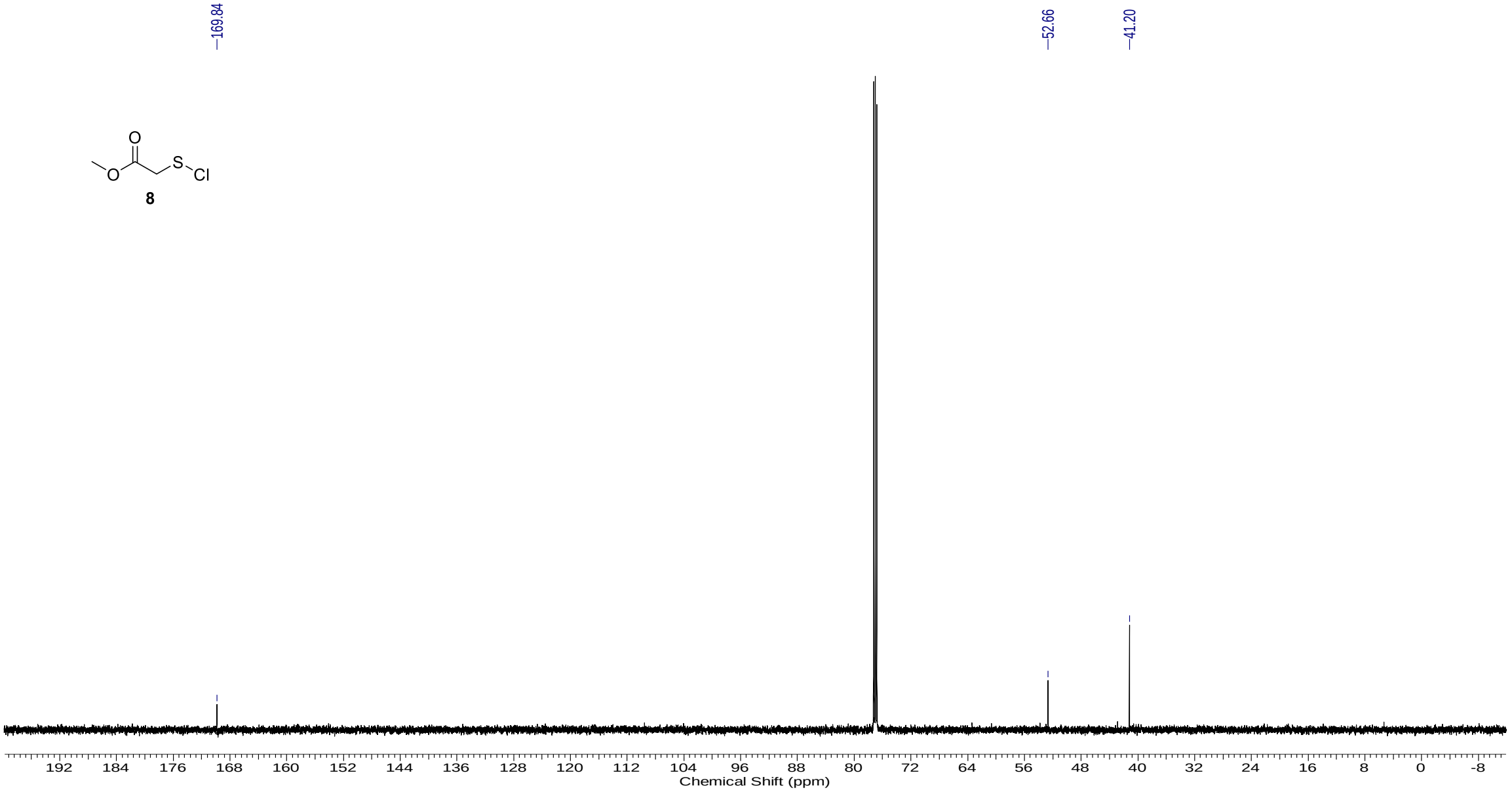
2. Goodyear, M.D.; Dwyer, P.O.; Hill, M.L.; Whitehead, A.J.; Hornby, R.; Hallet, P. Process for the Diastereoselective Synthesis of Nucleoside Analogues. US6051709, **2000**

^{1}H NMR (600 MHz, $CDCl_3$) of compound 8

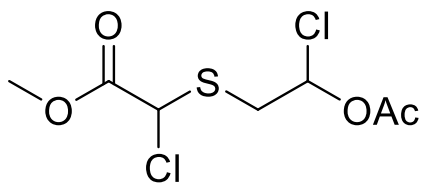


8

^{13}C NMR (150 MHz, $CDCl_3$) of compound 8

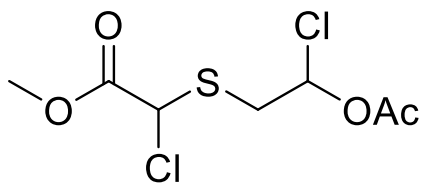


^{1}H NMR (600 MHz, $CDCl_3$) of compound 10



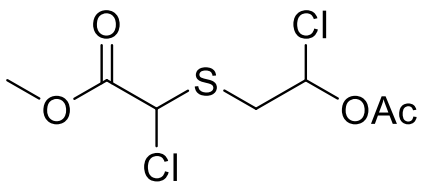
10

^{13}C NMR (150 MHz, $CDCl_3$) of compound 10



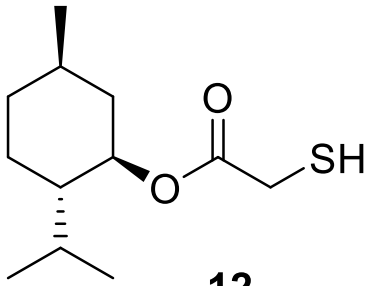
10

^{1}H NMR (Screening) (600 MHz, $CDCl_3$) of compound 10



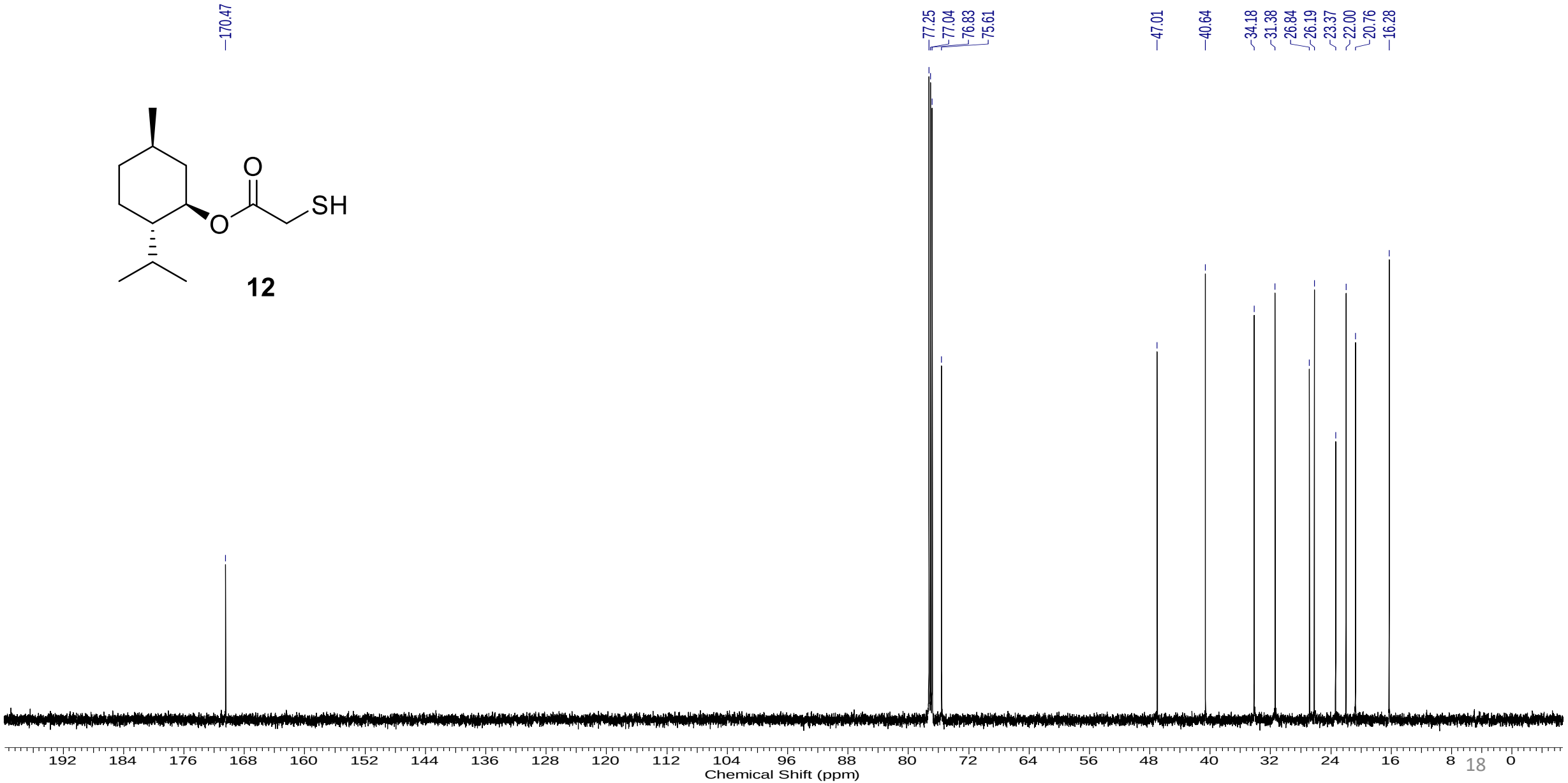
10

^{1}H NMR (600 MHz, $CDCl_3$) of compound 12

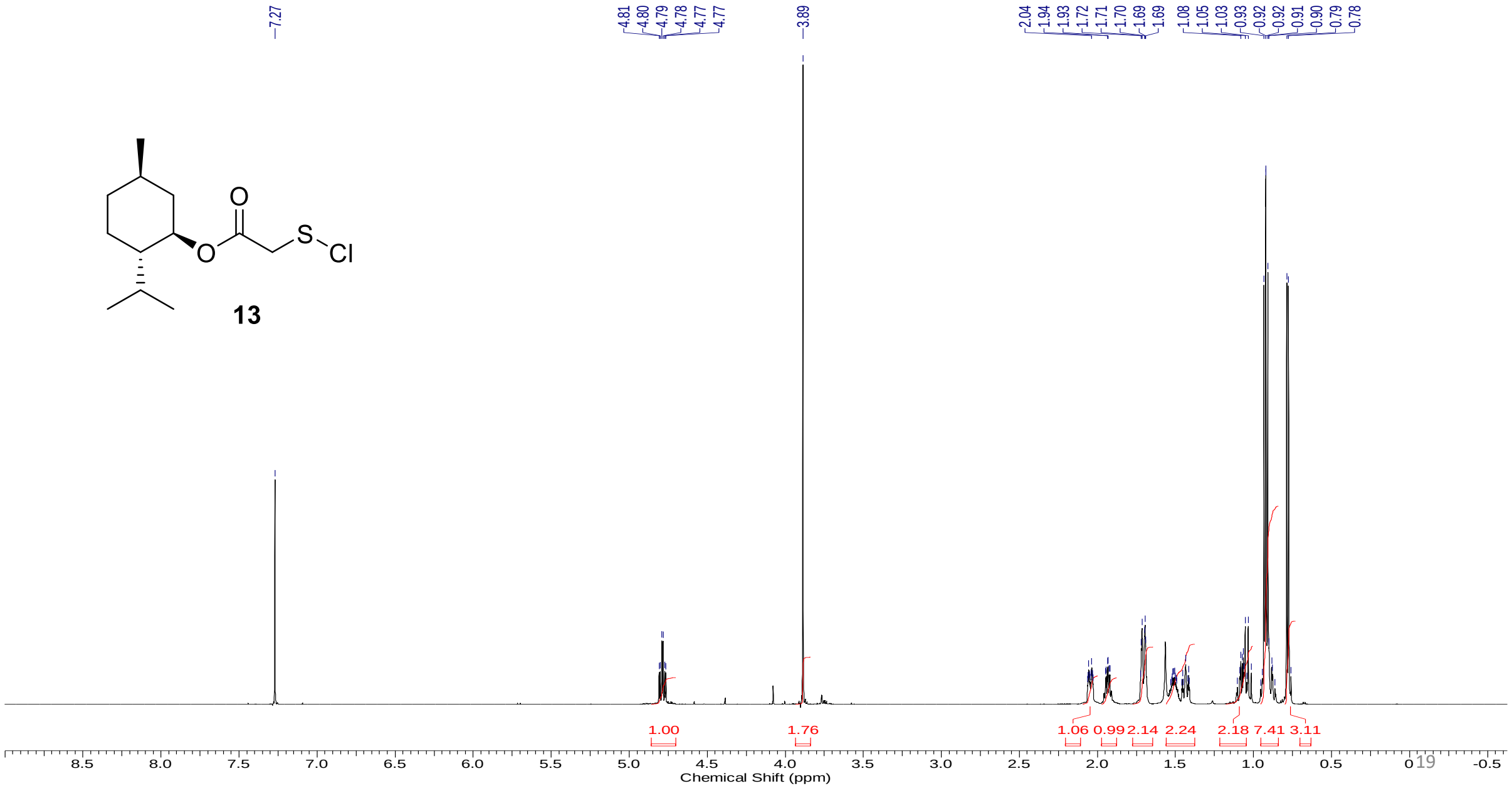


12

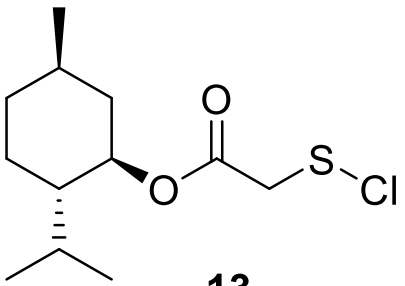
^{13}C NMR (150 MHz, $CDCl_3$) of compound 12



^{1}H NMR (600 MHz, $CDCl_3$) of compound 13

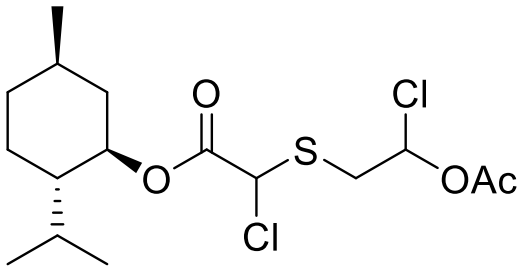


^{13}C NMR (150 MHz, $CDCl_3$) of compound 13



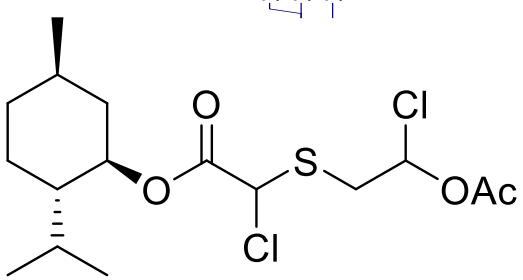
13

^{1}H NMR (600 MHz, $CDCl_3$) of compound 15



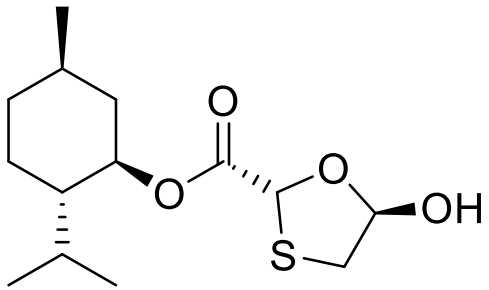
15

^{13}C NMR (150 MHz, $CDCl_3$) of compound 15



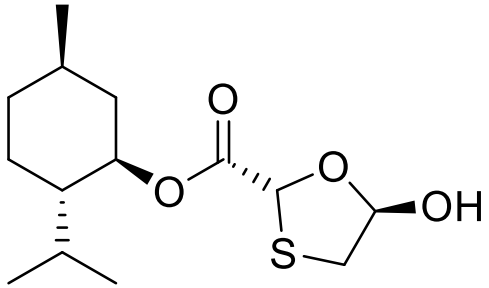
15

^{1}H NMR (600 MHz, $CDCl_3$) of compound 4



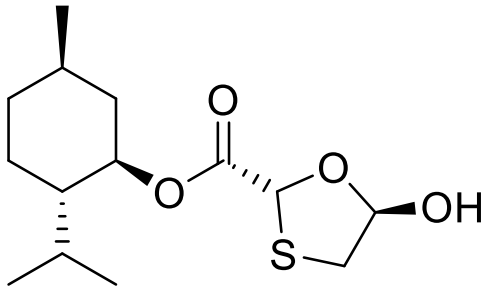
4

^{13}C NMR (150 MHz, $CDCl_3$) of compound 4



4

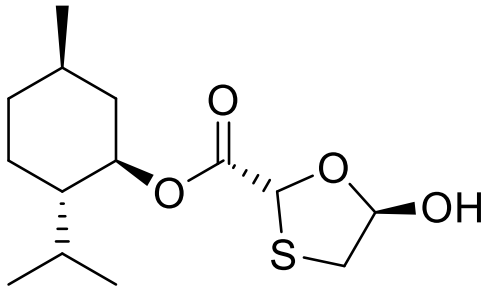
^{1}H NMR (600 MHz, $CDCl_3$) of compound 4 (Commercial)



4

(Commercial sample)

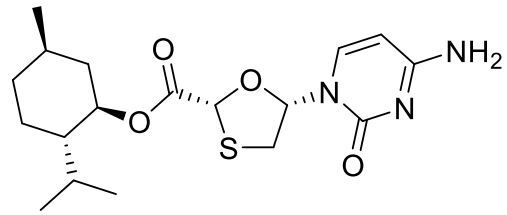
^{13}C NMR (150 MHz, $CDCl_3$) of compound 4 (Commercial)



4

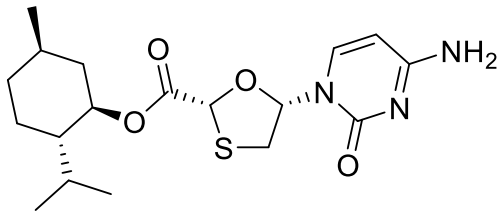
(Commercial sample)

^{1}H NMR (600 MHz, DMSO-d_6) of compound 3



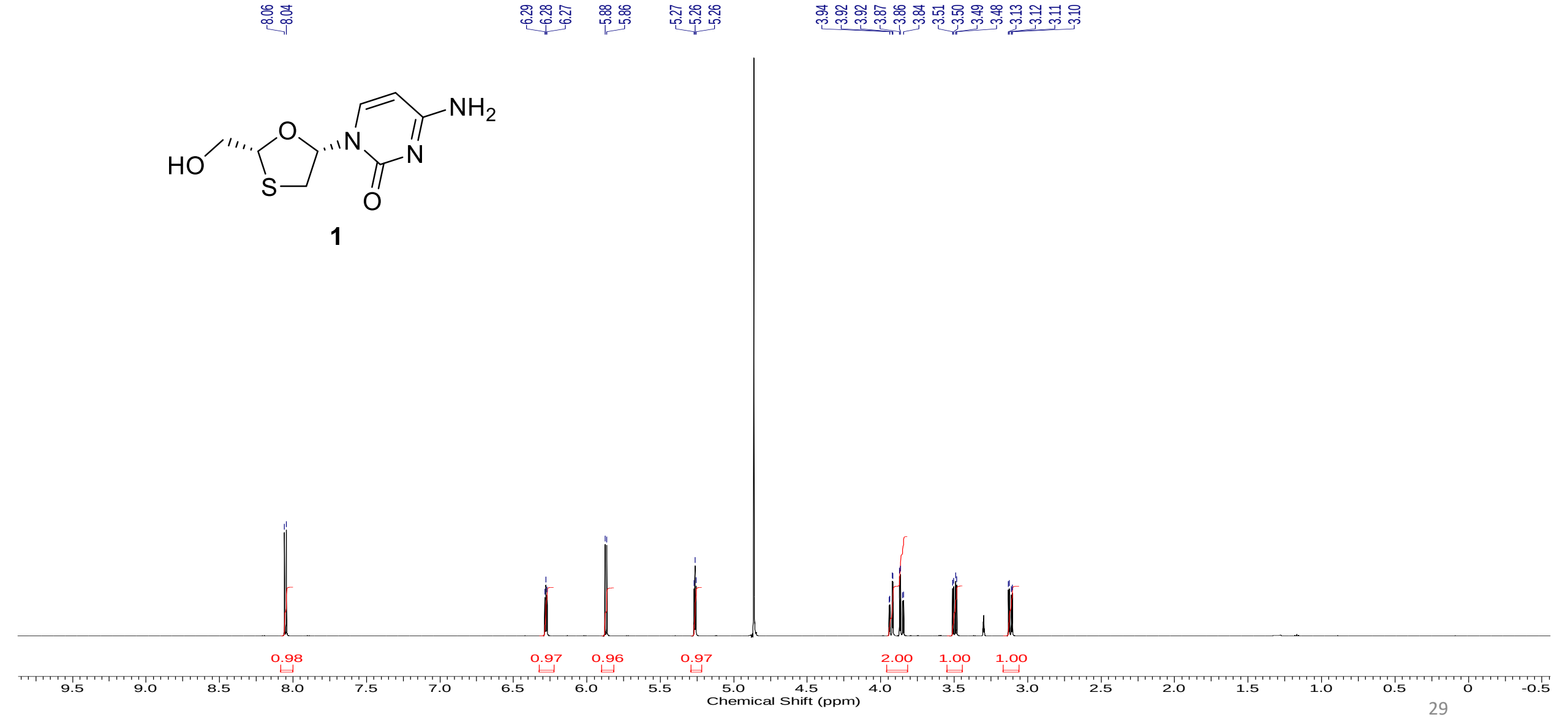
3

^{13}C NMR (150 MHz, DMSO-d_6) of compound 3

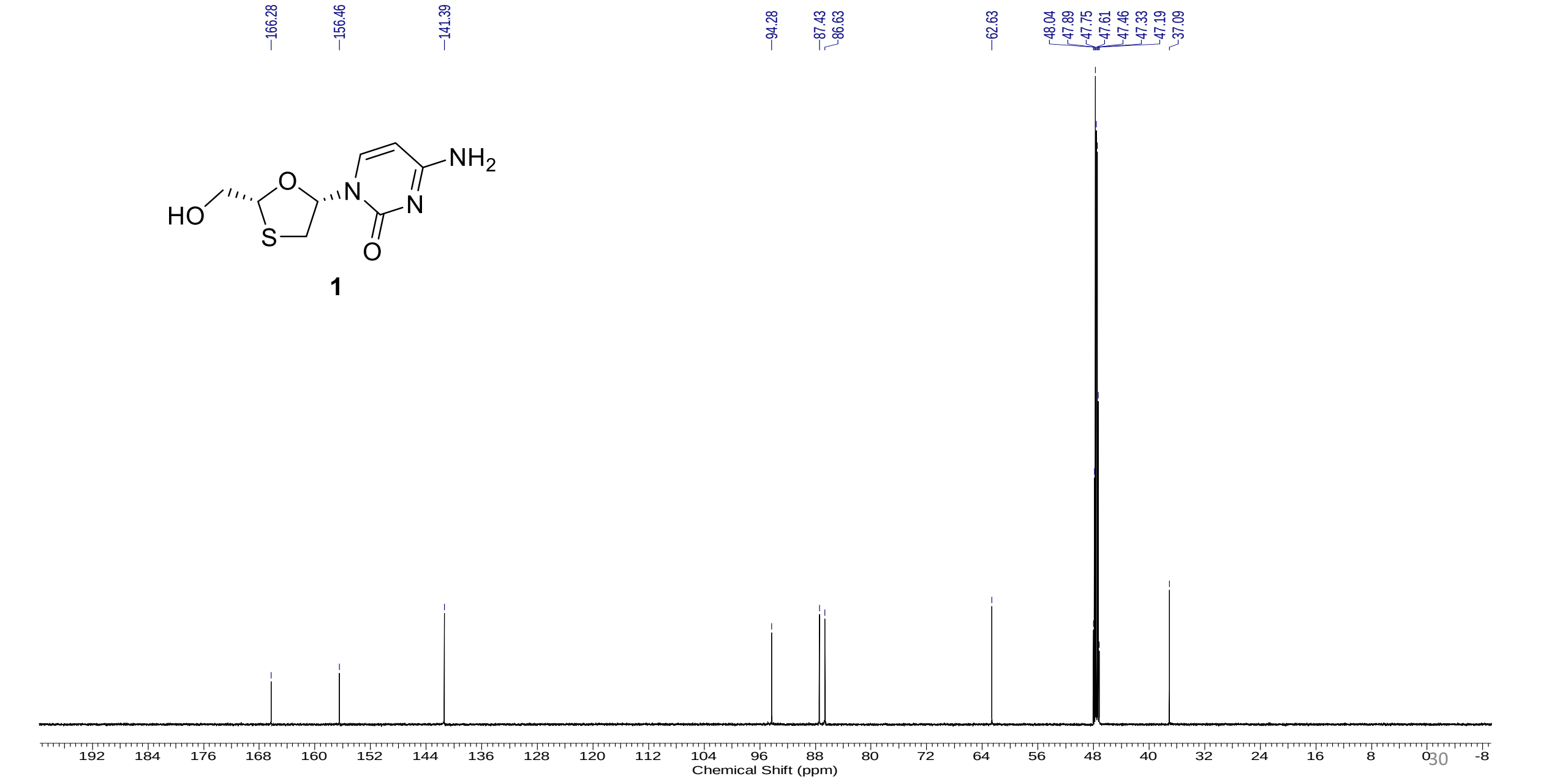


3

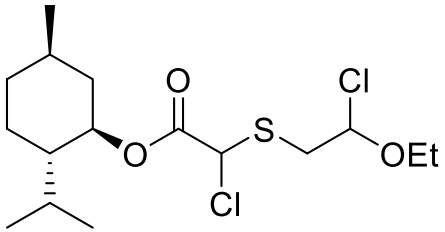
^{1}H NMR (600 MHz, CD_3OD) of compound 1



^{13}C NMR (150 MHz, CD_3OD) of compound 1

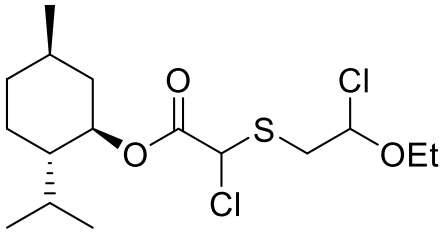


^{1}H NMR (600 MHz, $CDCl_3$) of compound 19



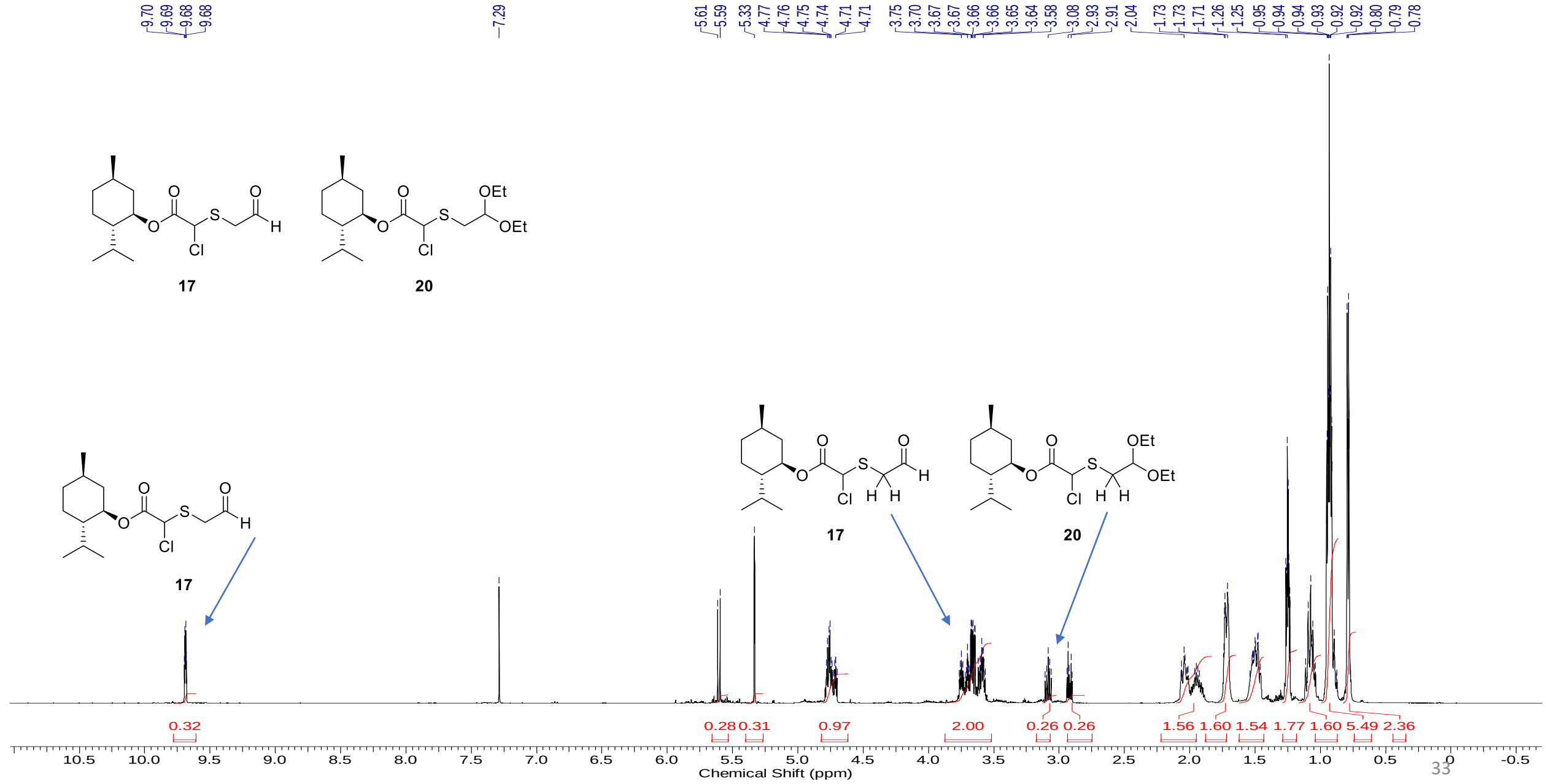
19

^{13}C NMR (150 MHz, $CDCl_3$) of compound 19

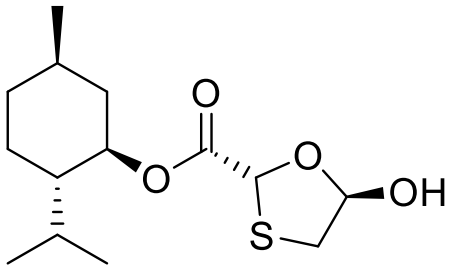


19

^{1}H NMR (600 MHz, $CDCl_3$) mixture of compounds 17 & 20

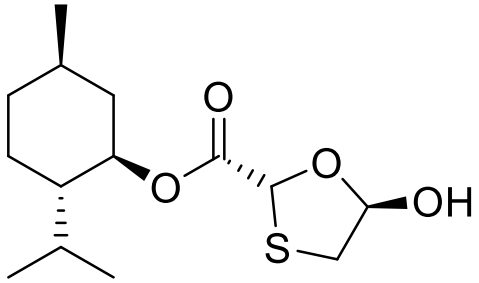


^{1}H NMR (600 MHz, $CDCl_3$) of compound 4 with mesitylene as standard (from Ethyl Vinyl Ether route)



4

^{1}H NMR (600 MHz, $CDCl_3$) of compound 4 with mesitylene as standard (from Vinyl Acetate route)



4