

Electronic Supplementary Informations

Exploiting enzymatic regioselectivity: a facile methodology for the synthesis of polyhydroxylated hybrid compounds

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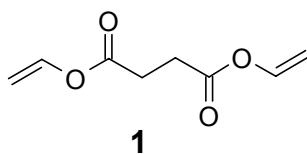
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Experimental Section

Materials and Methods

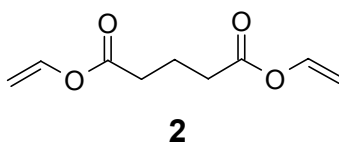
All chemicals were obtained from commercial sources (Aldrich) and used without further purification. All solvents were of reagent grade or HPLC grade. Novozym[®] 435 (immobilized lipase from *Candida antarctica*) was a gift from Novozymes Inc. Thin-Layer Chromatography (TLC) analysis were performed on precoated silica gel 60 F₂₅₄ plates (Merck) and treated with the molybdate reagent ((NH₄)₆MoO₂₄·4H₂O, 42 g; Ce(SO₄)₂, 2 g; H₂SO₄ concentrated 62 mL; made up to 1 L with deionized water) or KMnO₄ (0.5 g in 100 mL of NaOH 1M) or UV light (254 and 366 nm). Flash chromatography was performed using silica gel 60 (70 – 230 mesh, Merck). Molecular sieves (4Å, beads, 8-12 mesh) were preactivated at ca. 150 °C for 3 days. The ¹H NMR and ¹³C NMR spectra were recorded at the specified field strength and in the solvent indicated using standard pulse techniques on Bruker 300, 400, or 500 MHz and Varian Mercury 300 MHz spectrometers at ambient temperatures. Chemical shifts (δ) were expressed in parts per million (ppm) and were referenced to TMS or the residual solvent peak. Coupling constants (*J*) are quoted to the nearest 0.1 Hertz (Hz). Assignments of signals were made where possible, using COSY, DEPT, APT, HMQC and HMBC experiments where necessary. EI and FAB mass spectra were recorded at an ionizing voltage of 6 keV on a VG 70–70 EQ instrument.

Compound 1: divinyl succinate



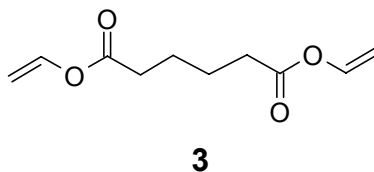
A solution of succinic acid (5.30 g, 44.92 mmol) and $\text{Hg}(\text{OAc})_2$ (350 mg) in vinyl acetate (42 mL) was stirred under nitrogen flow at r.t. and fuming H_2SO_4 (20 μL) was carefully added dropwise. The reaction mixture was then heated under reflux for 4 h. After cooling to r.t., $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (150 mg) was added portionwise and the mixture was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography [PetEt/EtOAc (95:5)] obtaining the pure compound **1** as a colorless oil (4.92 g, 65 %). **1**: $R_f = 0.55$ [PetEt/EtOAc (95:5)] (TLC detection by KMnO_4). ^1H NMR (300MHz, CDCl_3) δ : 2.74 (4H, s, CH_2) 4.57 (2H, dd, $J = 1.6, 6.0$ Hz, CH_2vin) 4.86-4.92 (2H, dd, $J = 1.6, 14.0$ Hz, CH_2vin) 7.21-7.28 (2H, dd, $J = 6.3, 14.0$ Hz, CHvin). EI^+ -MS (m/z) 170 $[\text{M}]^+$.

Compound 2: divinyl glutarate



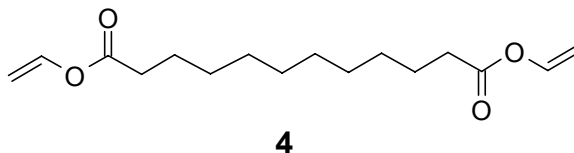
A solution of glutaric acid (20.00 g, 0.15 mol) and $\text{Hg}(\text{OAc})_2$ (1.21 g) in vinyl acetate (140 mL) was stirred under nitrogen flow at r.t. and fuming H_2SO_4 (100 μL) was carefully added dropwise. The reaction mixture was then heated under reflux for 4 h. After cooling to r.t., $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (440 mg) was added portionwise and the mixture was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography [PetEt/EtOAc (95:5)] obtaining the pure compound **2** (19.12 g, 69 %). **2**: $R_f = 0.56$ [PetEt/EtOAc (95:5)] (TLC detection by KMnO_4). ^1H NMR (300MHz, CDCl_3) δ : 2.06 (2H, t, $J = 7.4$ Hz, CH_2) 2.48 (4H, t, $J = 7.4$ Hz, CH_2) 4.55-4.58 (2H, dd, $J = 1.6, 6.3$ Hz, CH_2vin) 4.84-4.90 (2H, dd, $J = 1.6, 14.0$ Hz, CH_2vin) 7.22-7.29 (2H, dd, $J = 6.3, 14.0$ Hz, CHvin). EI^+ -MS (m/z) 184 $[\text{M}]^+$.

Compound 3: divinyl adipate



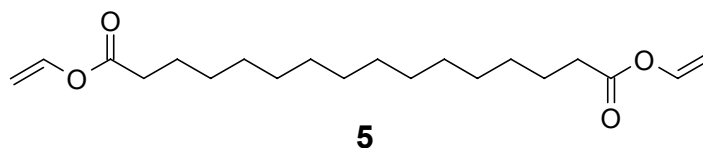
A solution of adipic acid (30.00 g, 0.20 mol) and $\text{Hg}(\text{OAc})_2$ (1.65 g) in vinyl acetate (150 mL) was stirred under nitrogen flow at r.t. and fuming H_2SO_4 (100 μL) was carefully added dropwise. The reaction mixture was then heated under reflux for 4 h. After cooling to r.t., $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (600 mg) was added portionwise and the mixture was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography [PetEt/EtOAc (95:5)] obtaining the pure compound **3** as a colorless oil (21.00 g, 52 %). **3**: $R_f = 0.18$ [PetEt (100 %)] (TLC detection by KMnO_4). ^1H NMR (500MHz, CDCl_3) δ : 1.60-1.82 (4H, m, CH_2) 2.37-2.46 (4H, m, CH_2) 4.55 (2H, dd, $J = 1.6, 6.3$ Hz, CH_2vin) 4.86 (2H, dd, $J = 1.5, 14.0$ Hz, CH_2vin) 7.25 (2H, dd, $J = 6.4, 14.0$ Hz, CHvin). EI^+ -MS (m/z) 198 $[\text{M}]^+$.

Compound 4: divinyl dodecanedioate



A solution of dodecanedioic acid (47.91 g, 0.21 mol) and $\text{Hg}(\text{OAc})_2$ (1.66 g) in vinyl acetate (193 mL) was stirred under nitrogen flow at r.t. and fuming H_2SO_4 (100 μL) was carefully added dropwise. The reaction mixture was then heated under reflux for 4 h. After cooling to r.t., $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (600 mg) was added portionwise and the mixture was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography [PetEt/EtOAc (98:2)] obtaining the pure compound **4** as a colorless oil (35.50 g, 60 %). **4**: $R_f = 0.27$ [PetEt (100 %)] (TLC detection by KMnO_4). ^1H NMR (500MHz, CD_3Cl) δ : 1.30 (12H, m, CH_2) 1.66 (4H, m, CH_2) 2.39 (4H, t, $J = 7.5$ Hz, CH_2) 4.57 (2H, dd, $J = 1.5, 6.5$ Hz, CH_2vin) 4.89 (2H, dd, $J = 1.5, 15.0$ Hz, CH_2vin) 7.30 (2H, dd, $J = 6.5, 15.0$ Hz, CHvin). ^{13}C NMR (75 MHz, CDCl_3) δ : 24.76, 29.20, 29.36, 29.50, 34.10, 97.59, 141.41, 171.01. EI^+ -MS (m/z) 282 $[\text{M}]^+$.

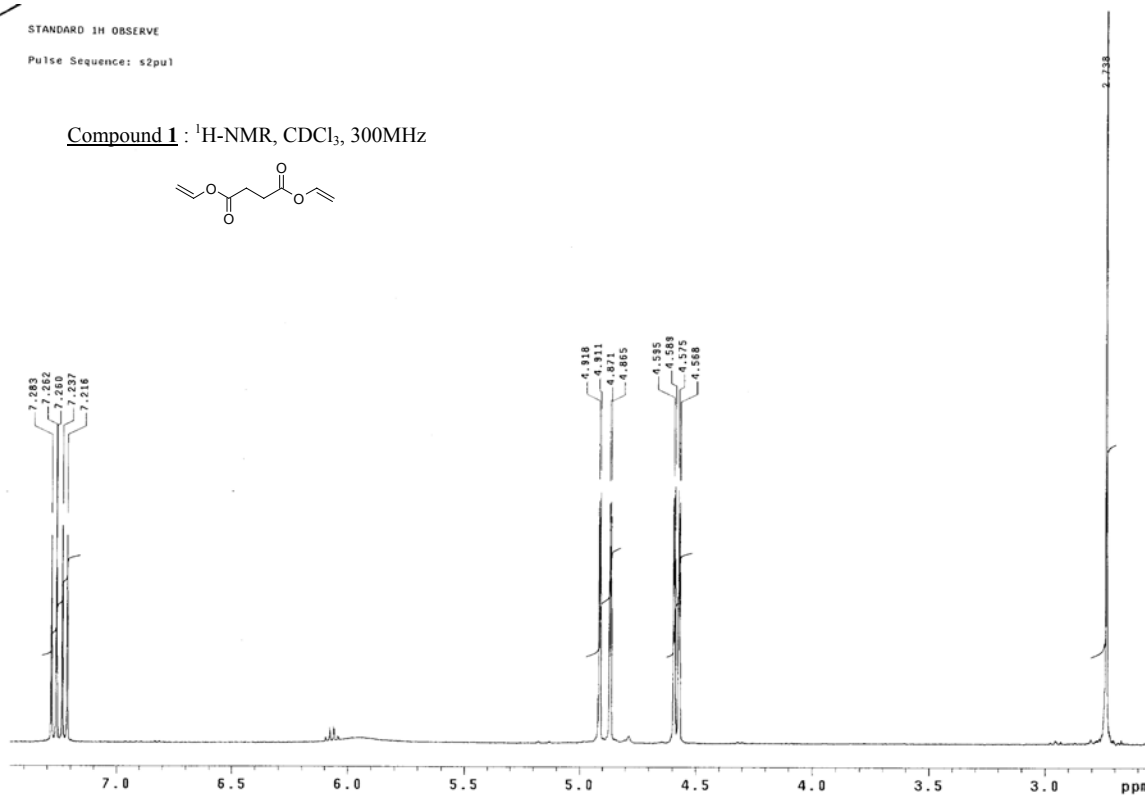
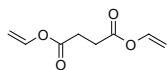
Compound 5: divinyl hexadecanedioate



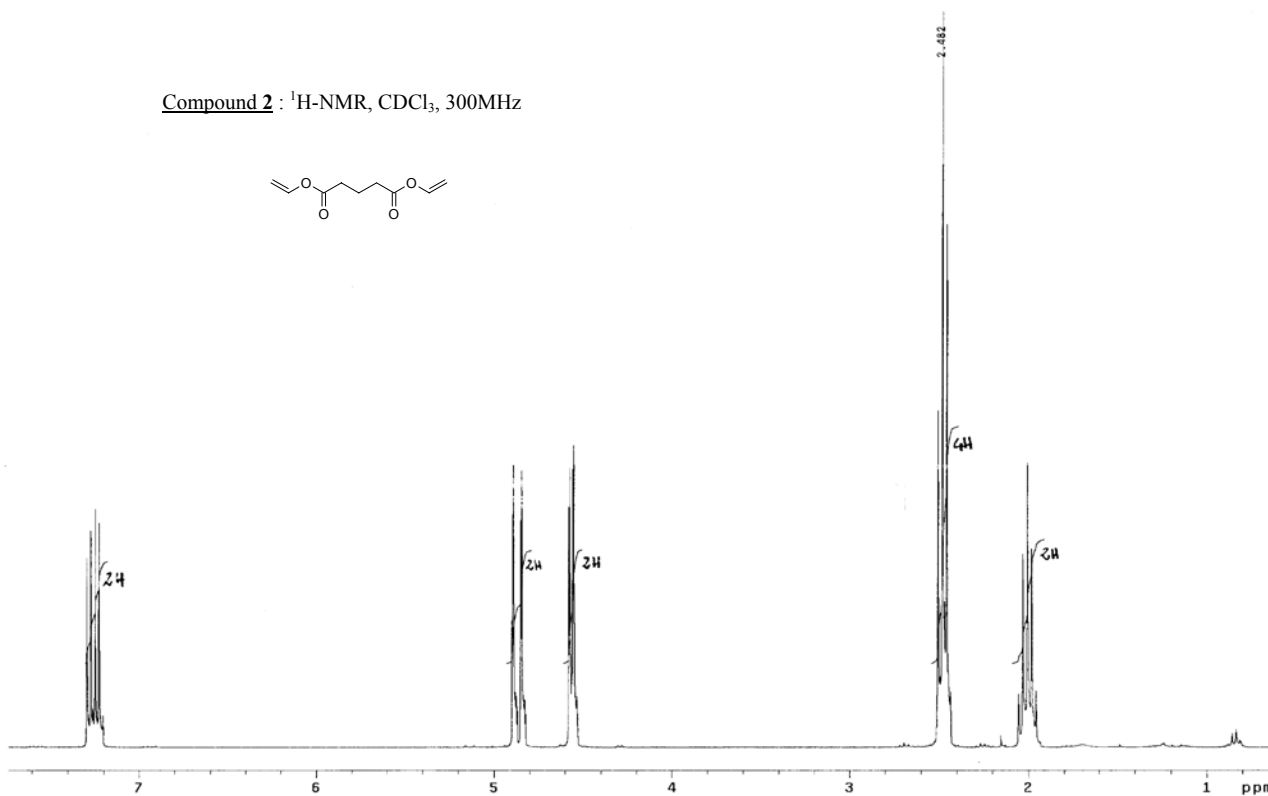
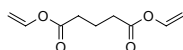
A solution of hexadecanedioic acid (5.00 g, 17.47 mmol) and $\text{Hg}(\text{OAc})_2$ (140 mg) in vinyl acetate (16 mL) was stirred under nitrogen flow at r.t. and fuming H_2SO_4 (10 μL) was carefully added dropwise. The reaction mixture was then heated under reflux for 4 h. After cooling to r.t., $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (50 mg) was added portionwise and the mixture was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography [PetEt/EtOAc (98:2)] obtaining the pure compound **5** as a colorless oil (3.76 g, 64 %). **5**: R_f = 0.48 [PetEt/EtOAc (98:2)] (TLC detection by KMnO_4). ^1H NMR (300MHz, CDCl_3) δ : 1.25 (20H, m, CH_2) 1.64 (4H, m, CH_2) 2.37 (4H, t, J = 7.7 Hz, CH_2) 4.54 (2H, dd, J = 1.6, 6.3 Hz, CH_2vin) 4.85 (2H, dd, J = 1.4, 14.0 Hz, CH_2vin) 7.27 (2H, dd, J = 6.3, 14.0 Hz, CHvin). ^{13}C NMR (75 MHz, CDCl_3) δ : 24.82, 29.26, 29.43, 29.63, 29.78, 29.82, 33.17, 97.63, 141.43, 171.11. EI^+ -MS (m/z) 338 [M] $^+$.

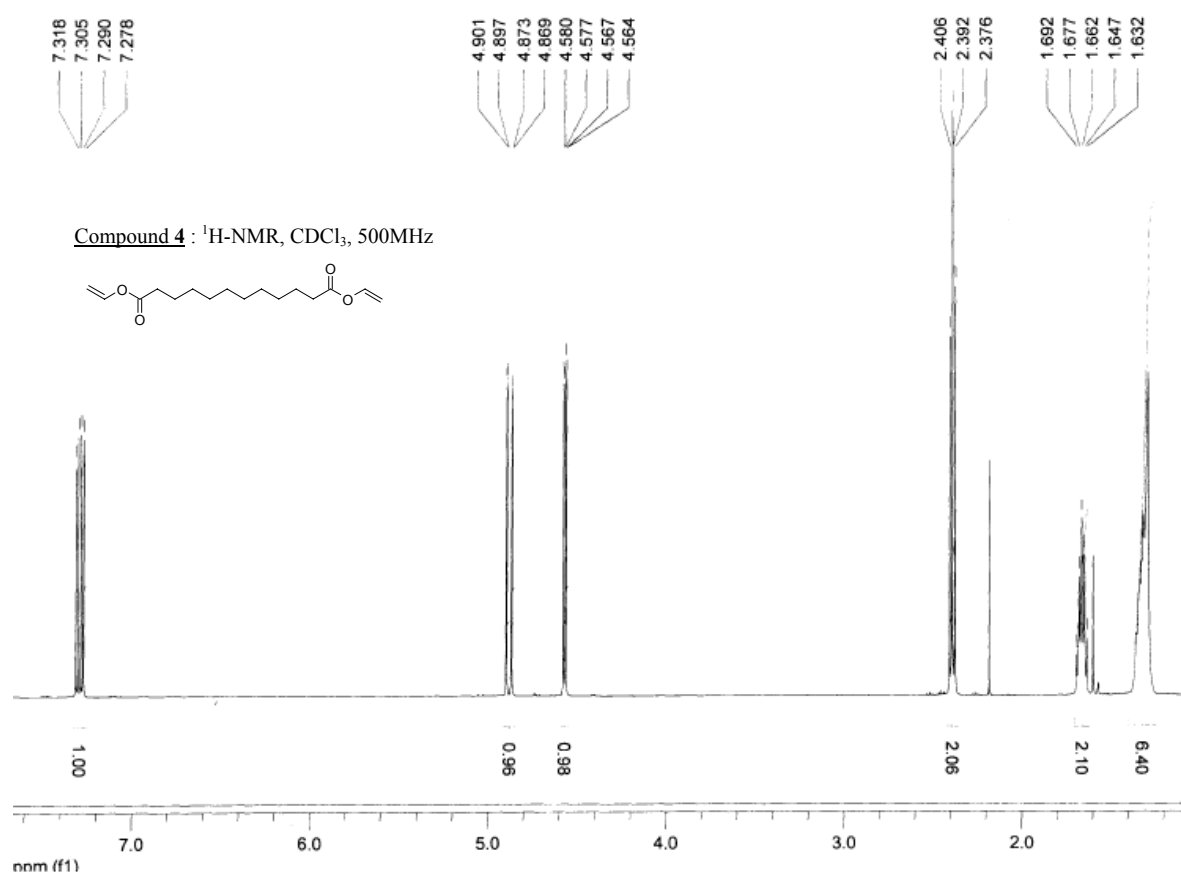
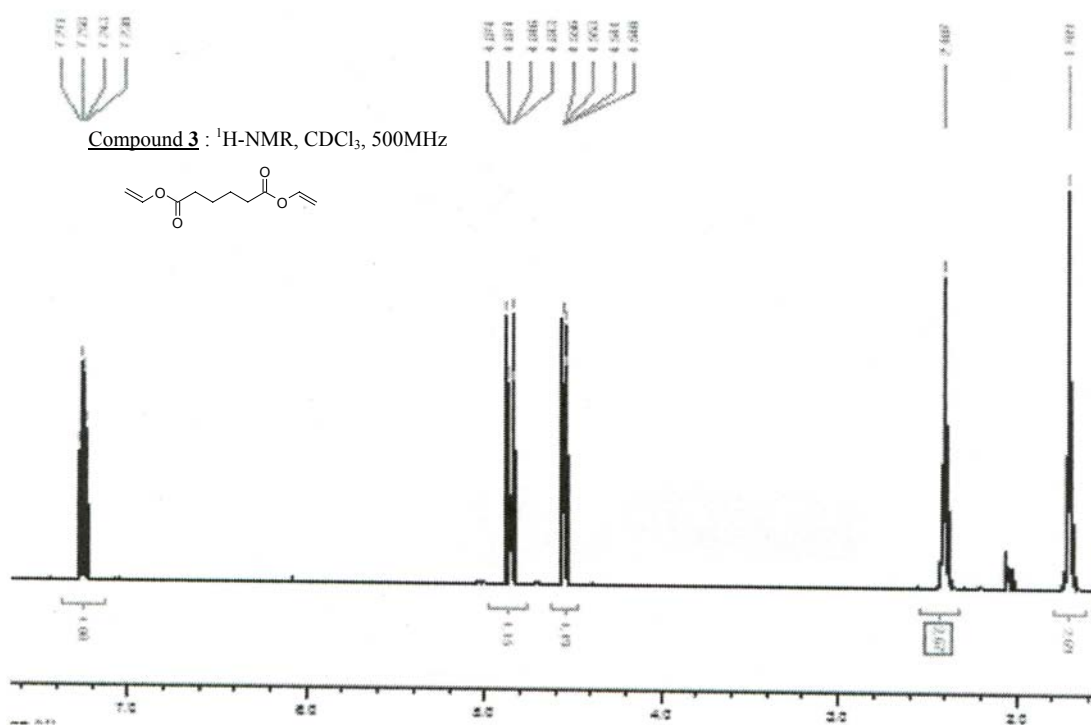
STANDARD 1H OBSERVE
Pulse Sequence: s2pu1

Compound 1 : ^1H -NMR, CDCl_3 , 300MHz



Compound 2 : ^1H -NMR, CDCl_3 , 300MHz



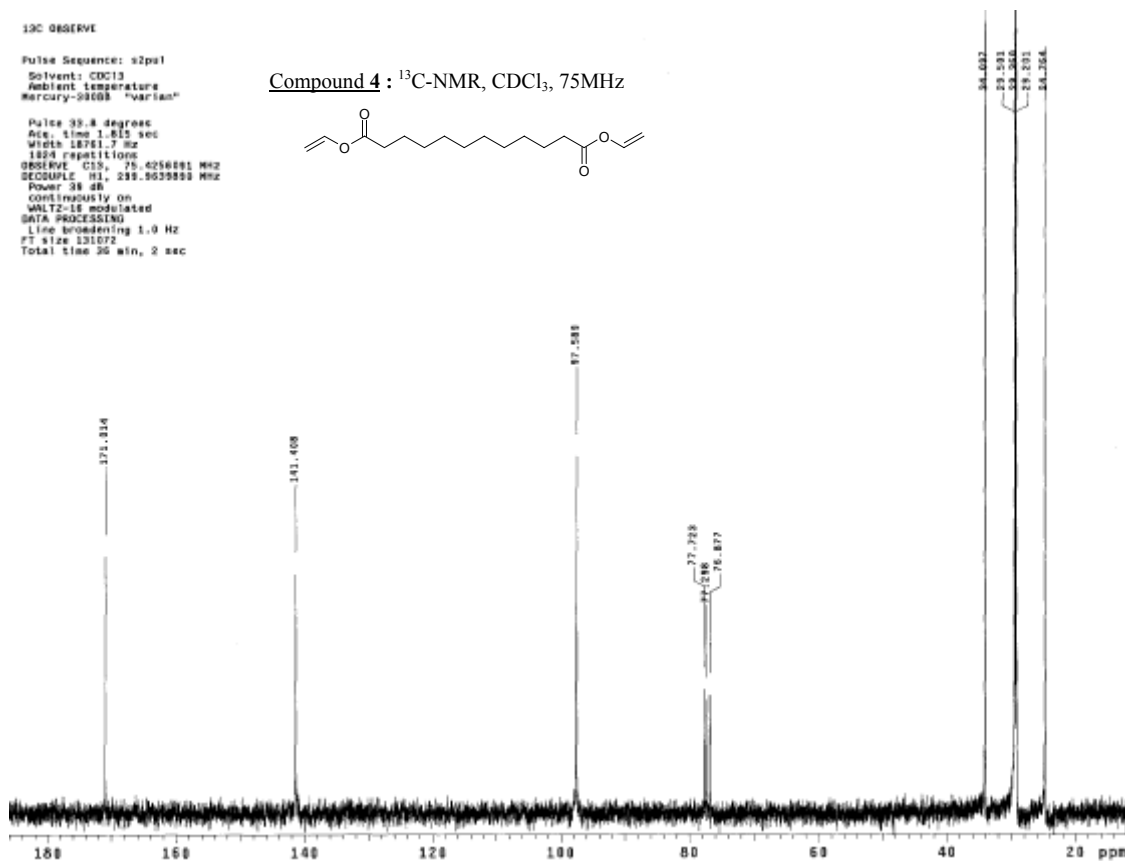
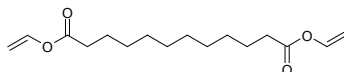


13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-2000B "Varian"

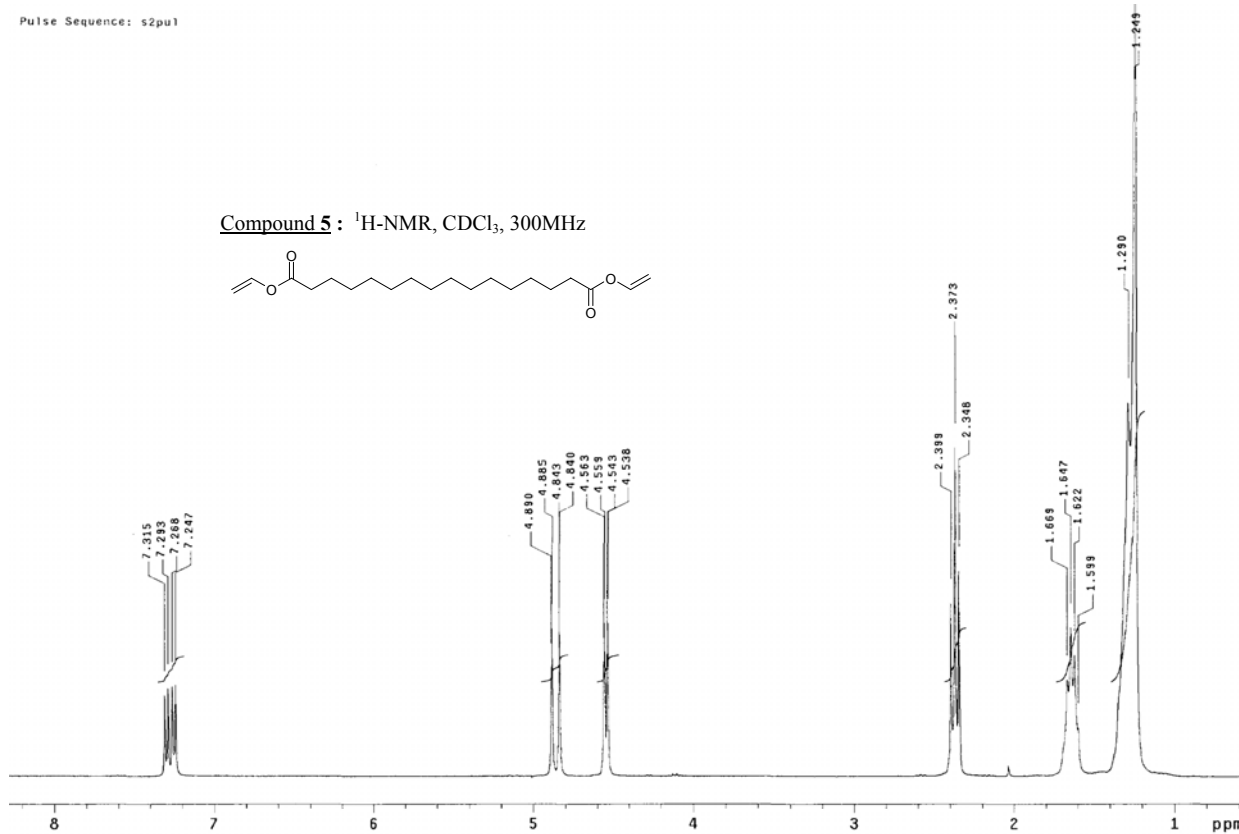
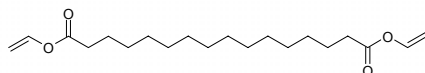
Pulse 35.8 degrees
Acq. time 1.815 sec
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1824 repetitions
OBSERVE C13, 75.6256081 MHz
DECOUPLE H1, 200.9635888 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 121072
Total time 36 min, 2 sec

Compound 4: ¹³C-NMR, CDCl₃, 75MHz

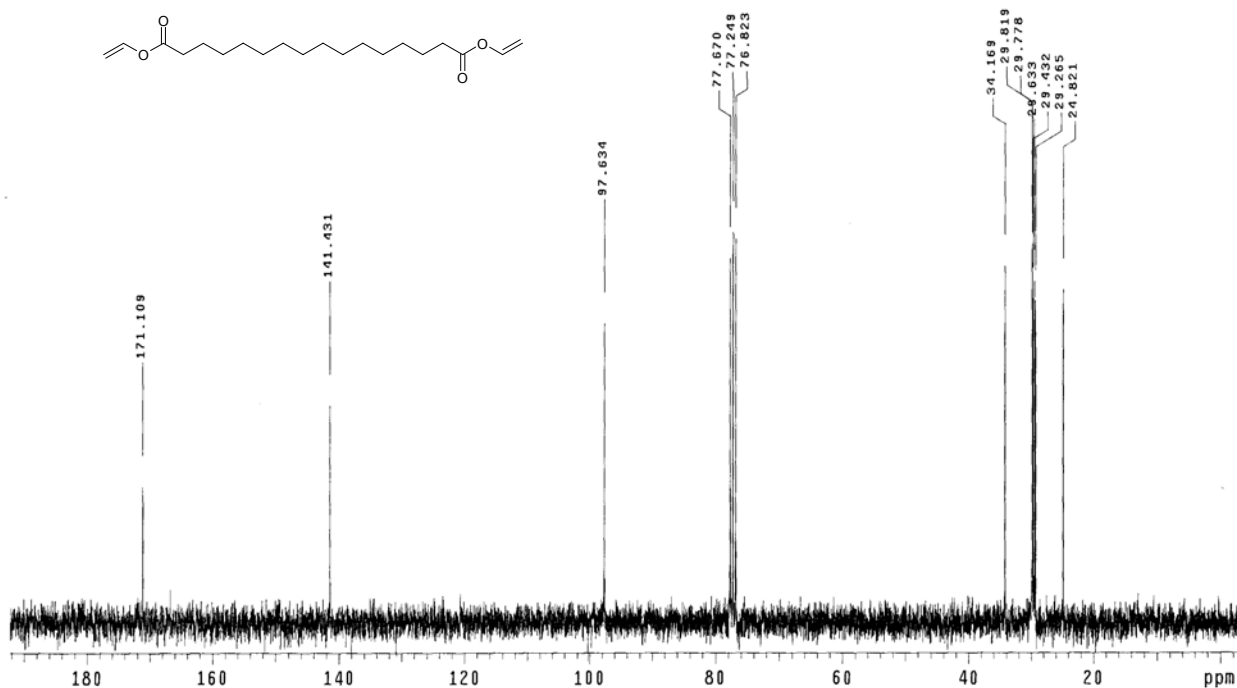


Pulse Sequence: s2pul

Compound 5: ¹H-NMR, CDCl₃, 300MHz



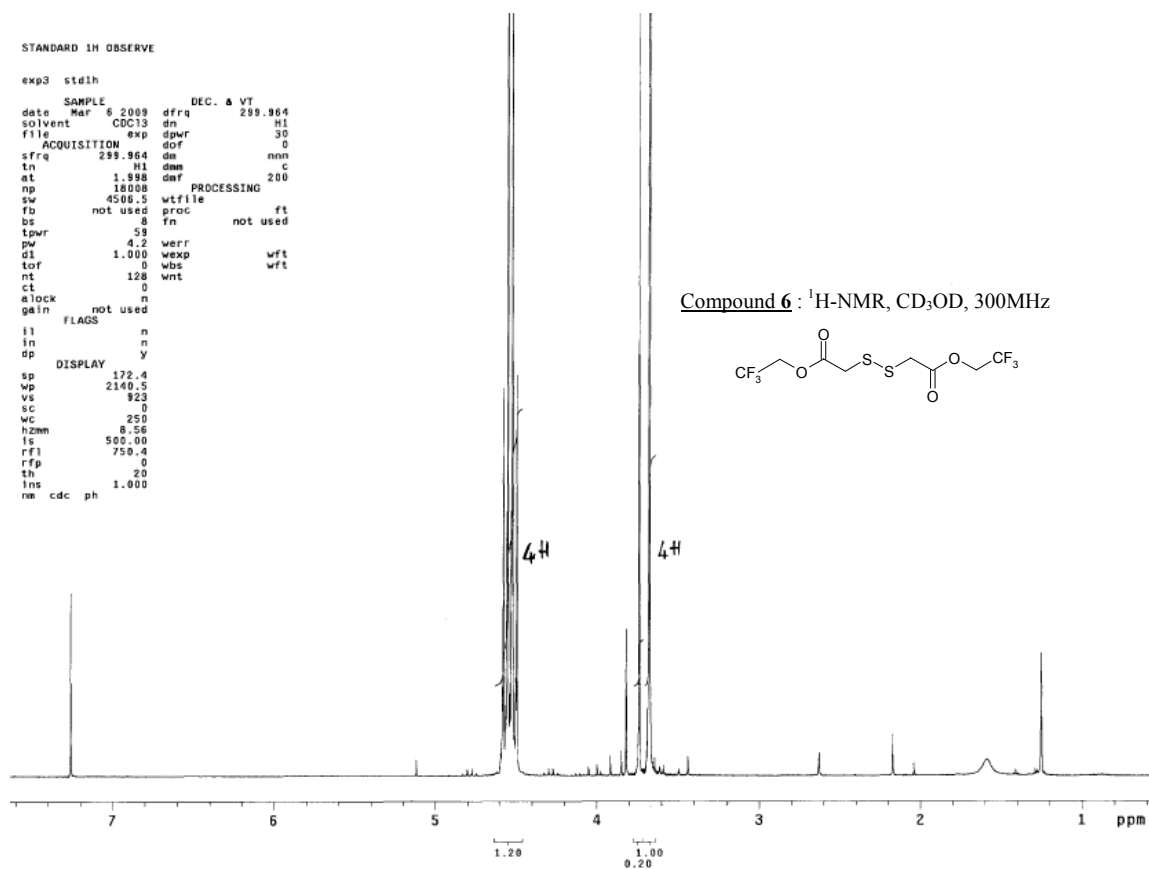
Compound 5: ^{13}C -NMR, CDCl_3 , 75MHz

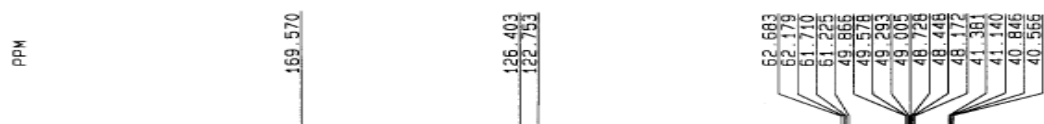


STANDARD 1H OBSERVE

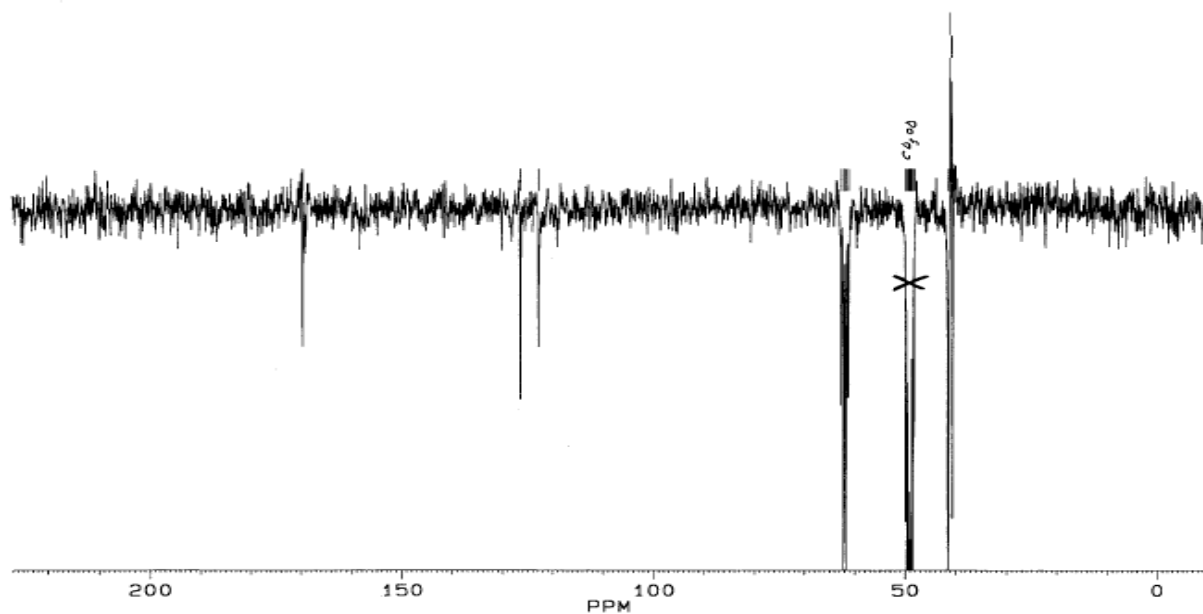
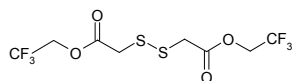
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tn H1 dm c
at 1.998 daf 200
np 18008 PROCESSING
sw 4566.5 wfile
fb not used proc ft
bs 8 fn not used
tpwr 59
pw 4.2 werr
d1 1.000 wexp wft
tof 0 wbs wft
nt 128 wnt
ct 0
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp 172.4
wp 2140.5
vs 923
sc 0
wc 250
h2mh 8.56
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rfp 0
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lms 1.000
nm cdc ph
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Compound 6: ^1H -NMR, CD_3OD , 300MHz

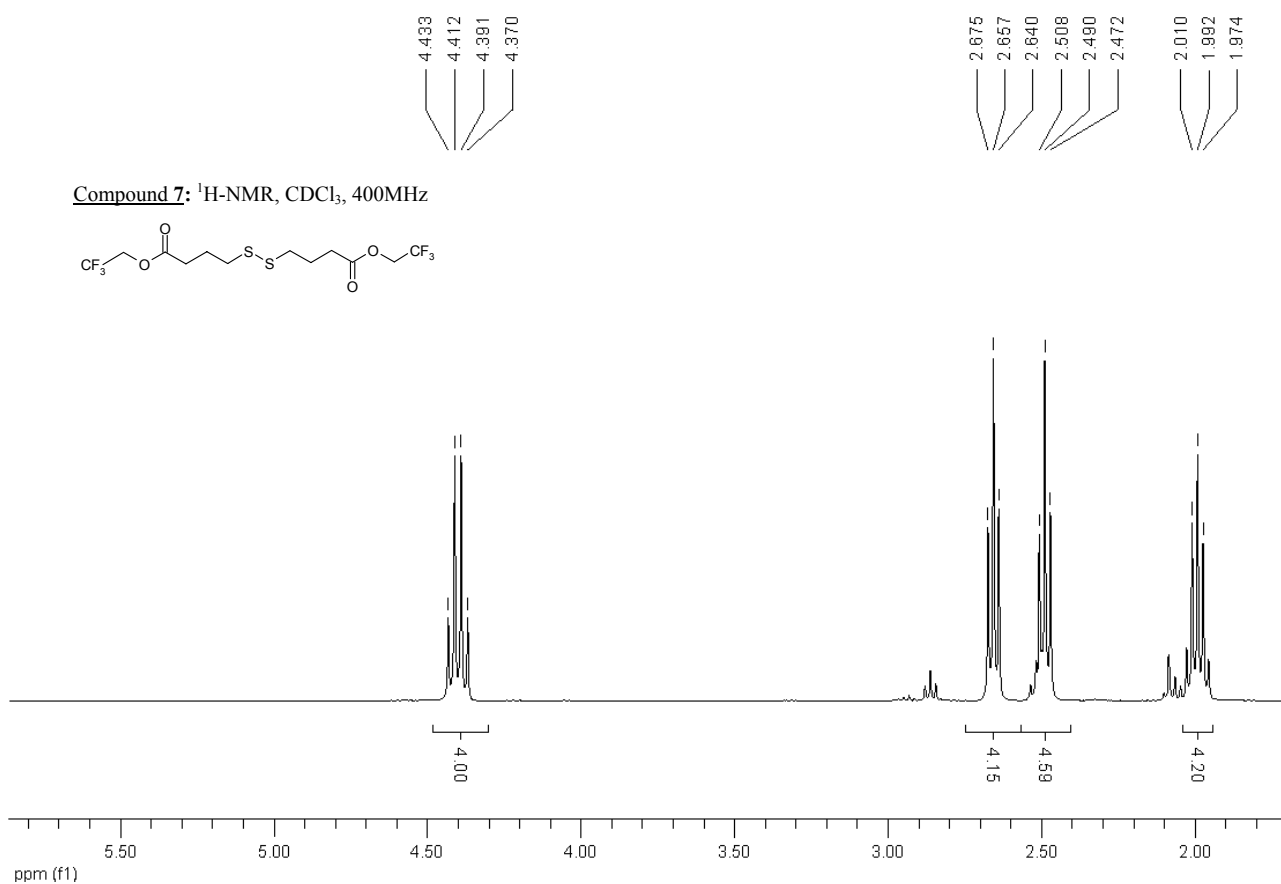
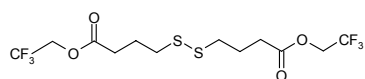




Compound 6 : ^{13}C -NMR (APT), CD_3OD , 75MHz

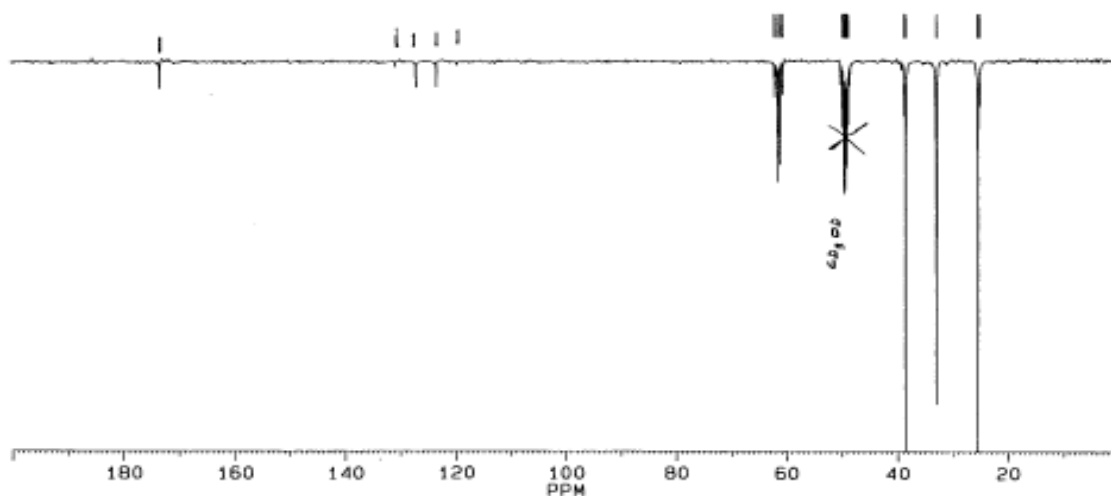
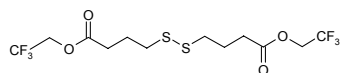


Compound 7: ^1H -NMR, CDCl_3 , 400MHz





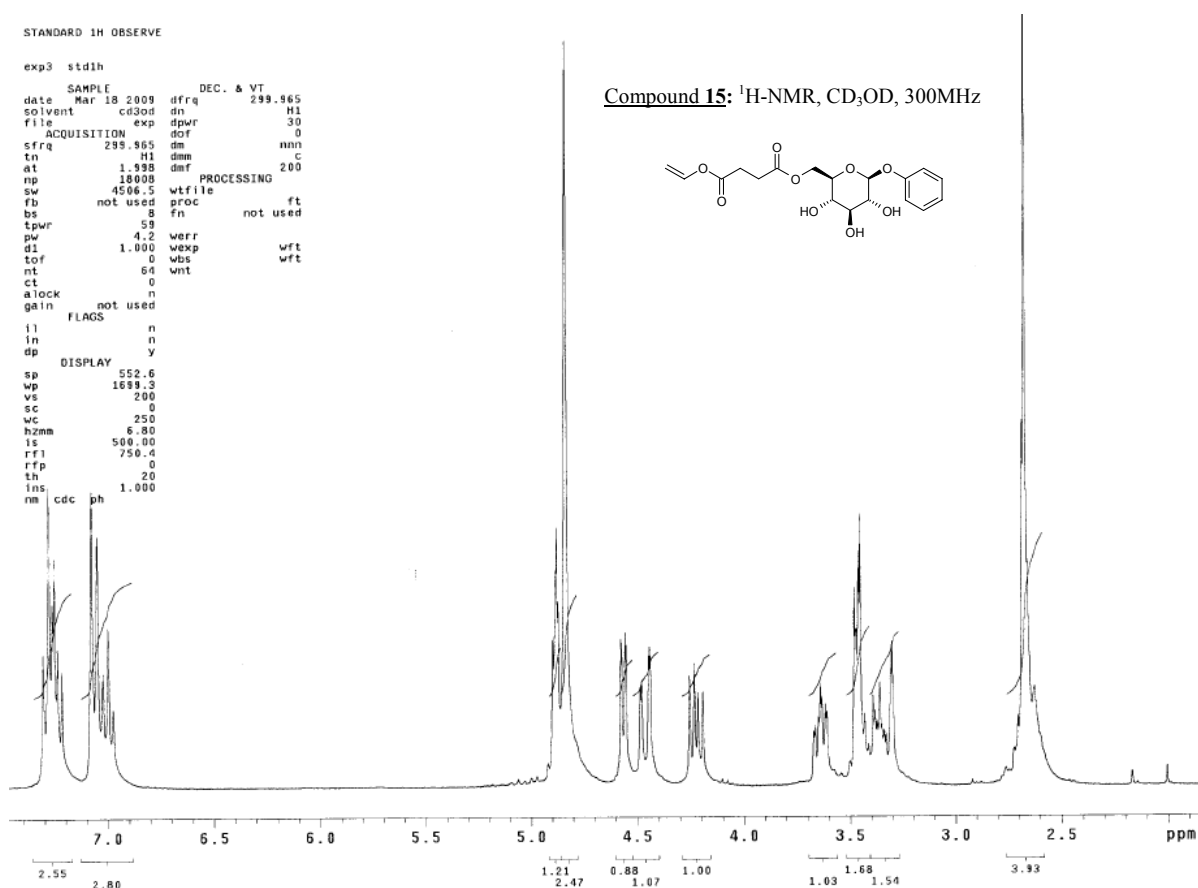
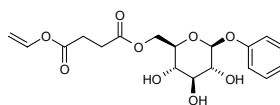
Compound 7: ^{13}C -NMR (APT), CD_3OD , 75MHz

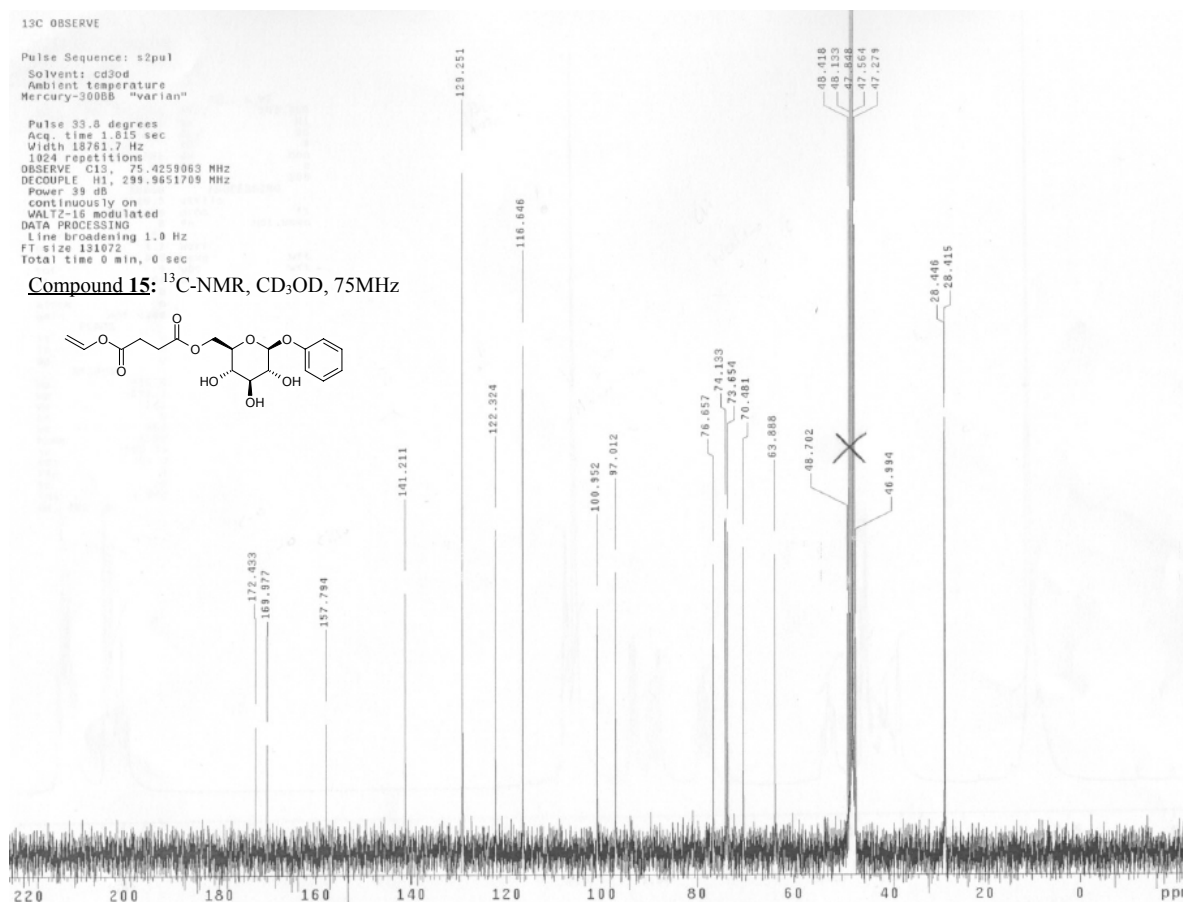
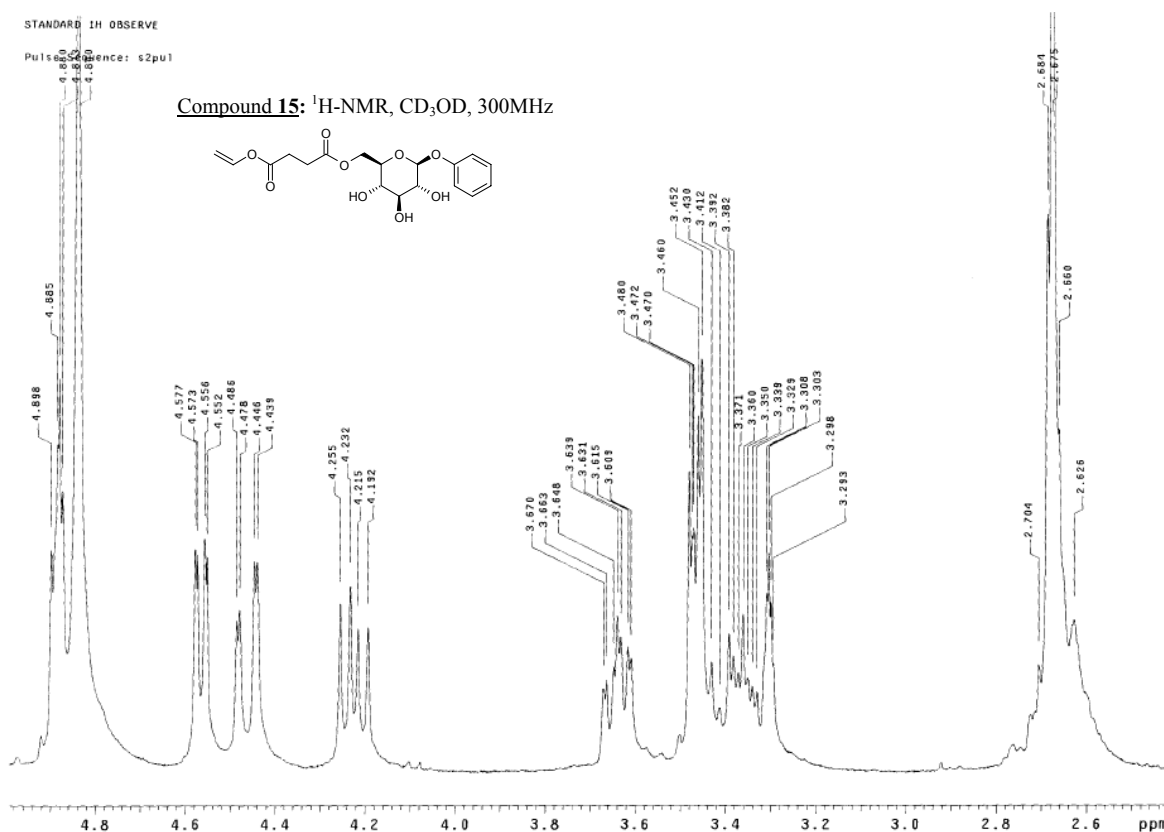


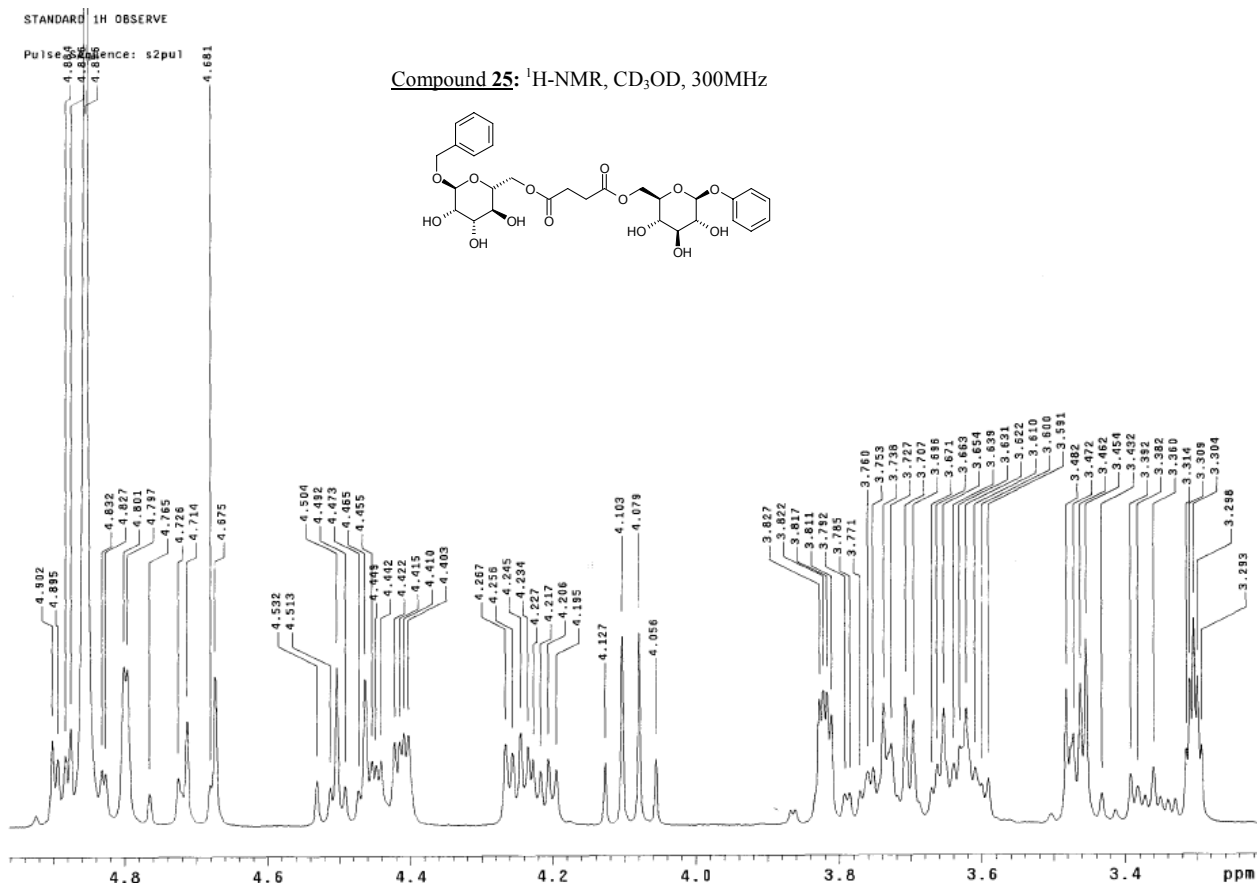
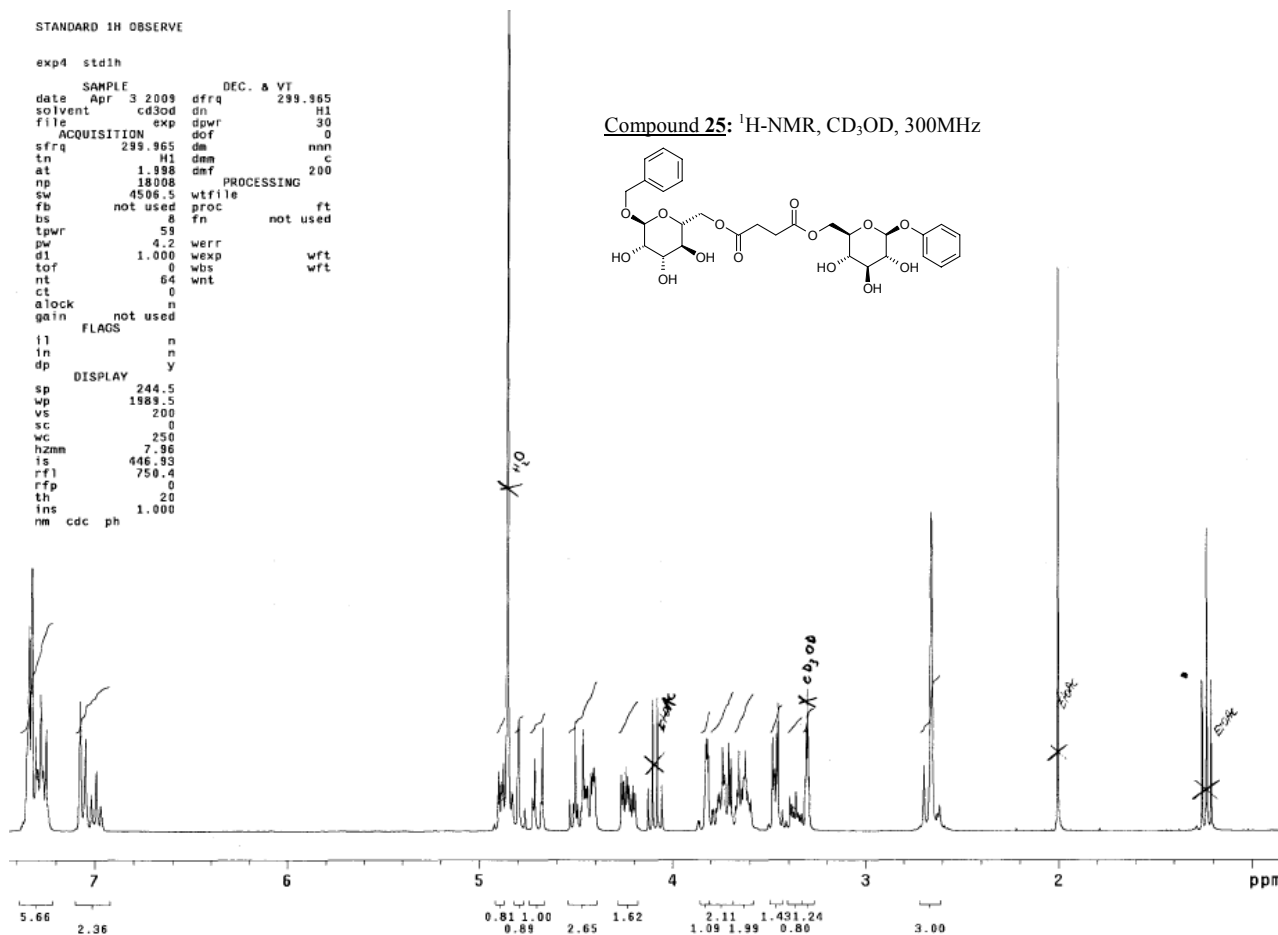
STANDARD 1H OBSERVE

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tn H1 dnm 200
at 1.998 dmf 200
np 18000
sw 4506.5 wtfile
fb not used proc ft
bs 8 fn not used
tpwr 59
pw 4.2 werr
d1 1.000 wexp wft
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gain not used
FLAGS
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in n
dp y
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wp 1699.3
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Compound 15: ^1H -NMR, CD_3OD , 300MHz





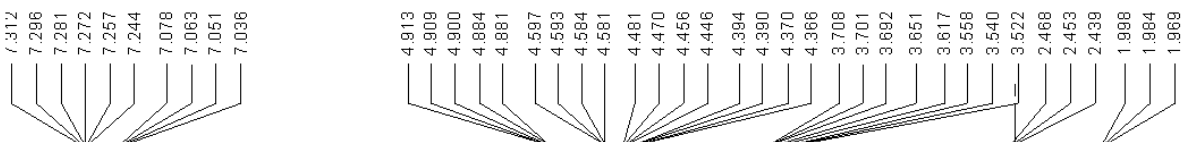
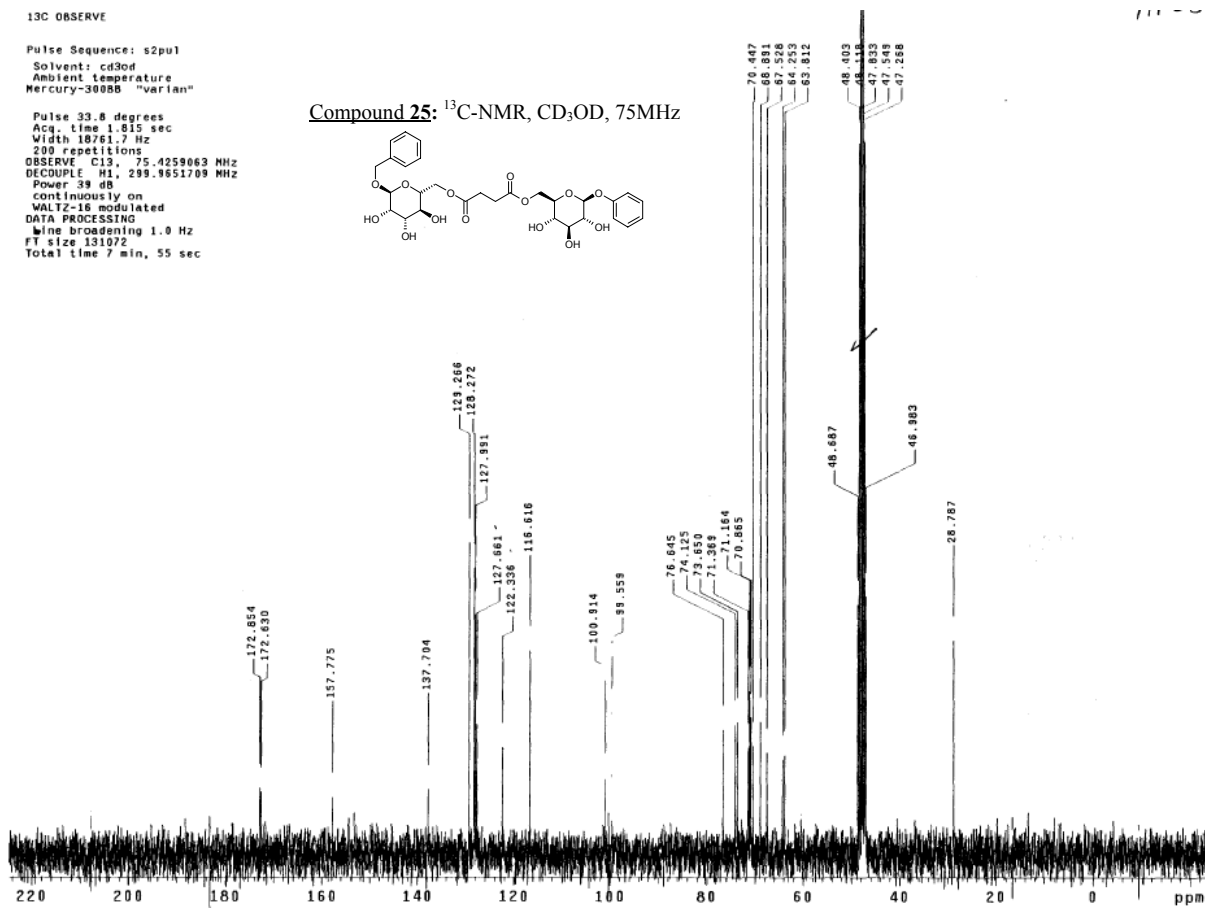
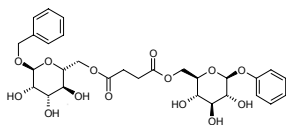


13C OBSERVE

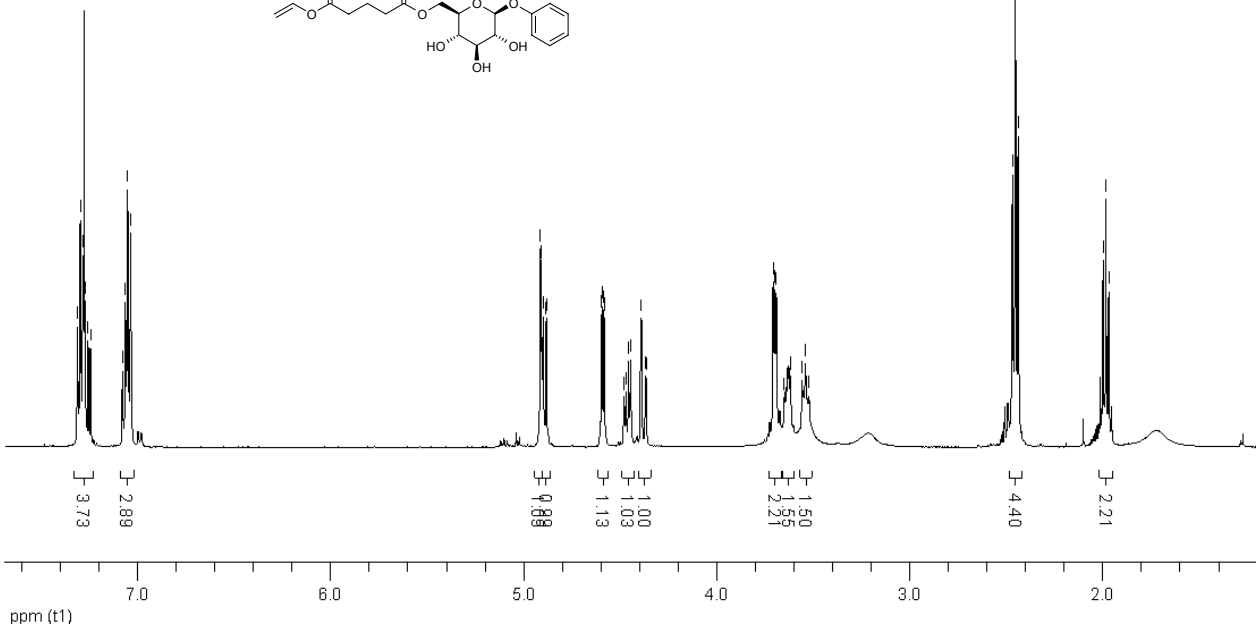
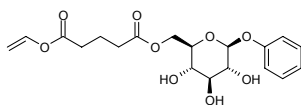
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Solvent: cd3od
Ambient temperature
Mercury-300SB "Varian"

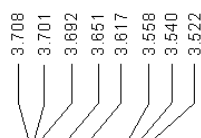
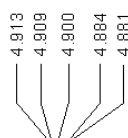
Pulse 33.8 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
200 repetitions
OBSERVE C13, 75.4259063 MHz
DECOUPLE H1, 299.9651709 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
line broadening 1.0 Hz
FT size 131072
Total time 7 min, 55 sec

Compound 25: ^{13}C -NMR, CD_3OD , 75MHz

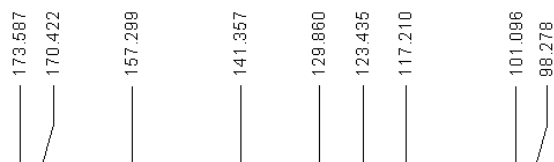
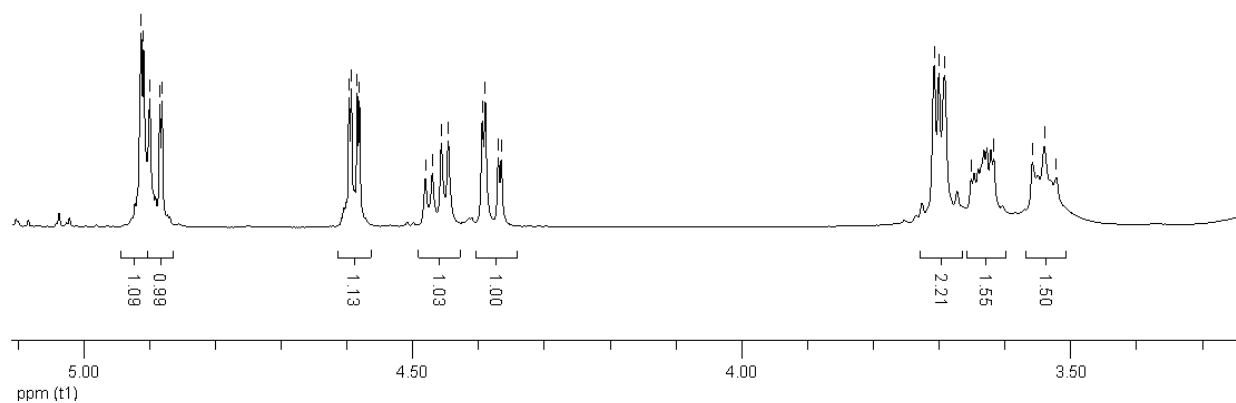
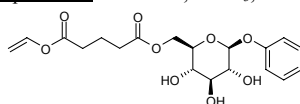


Compound 16: ^1H -NMR, CDCl_3 , 500MHz

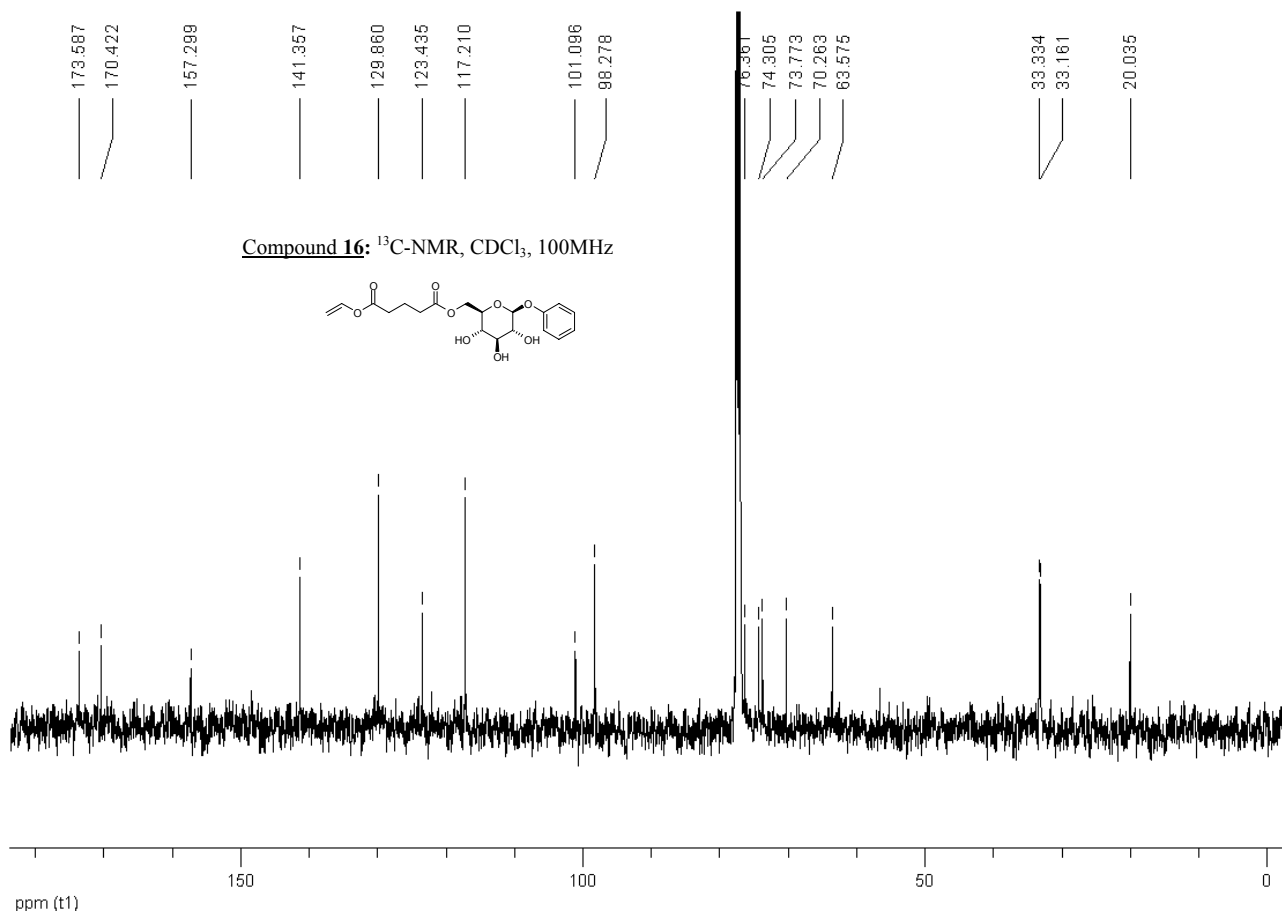
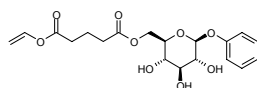


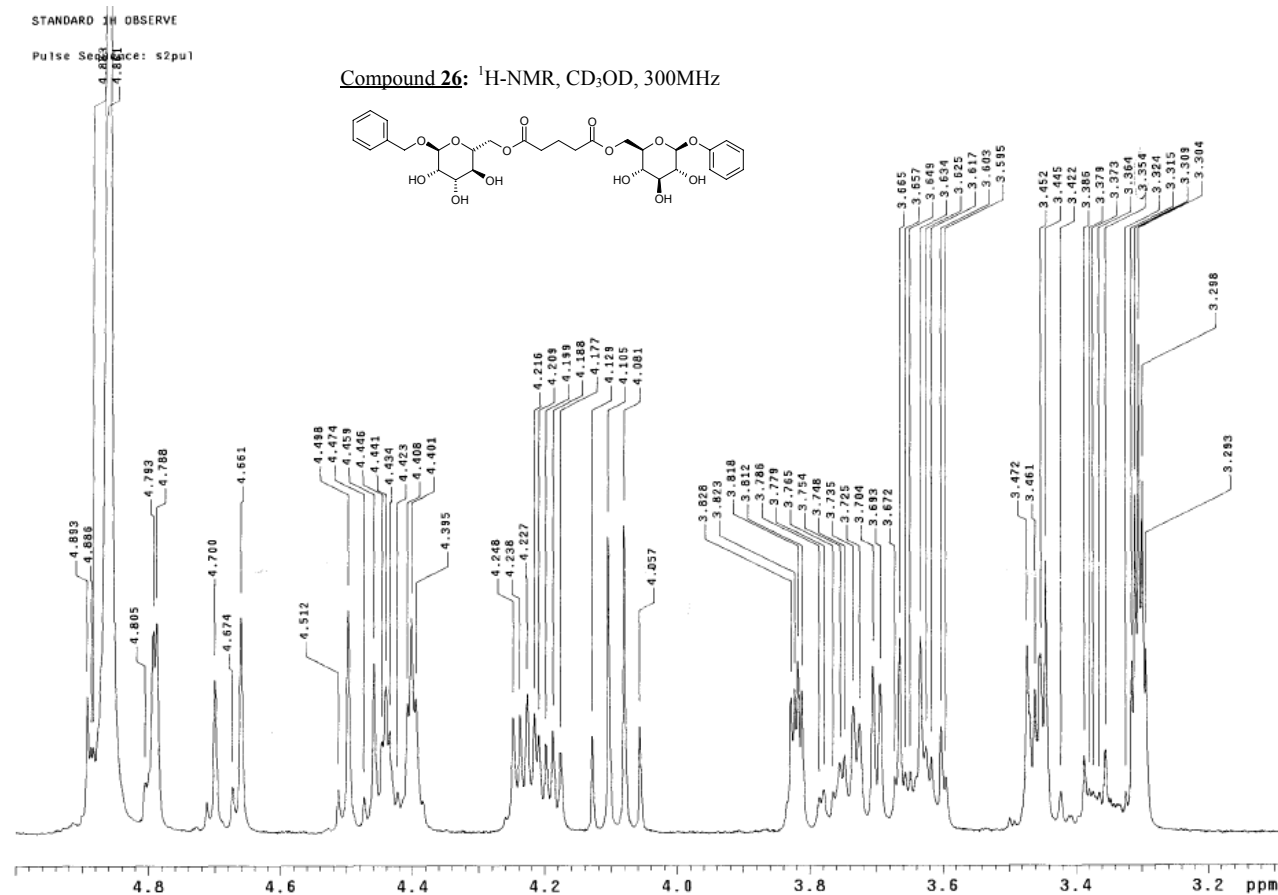
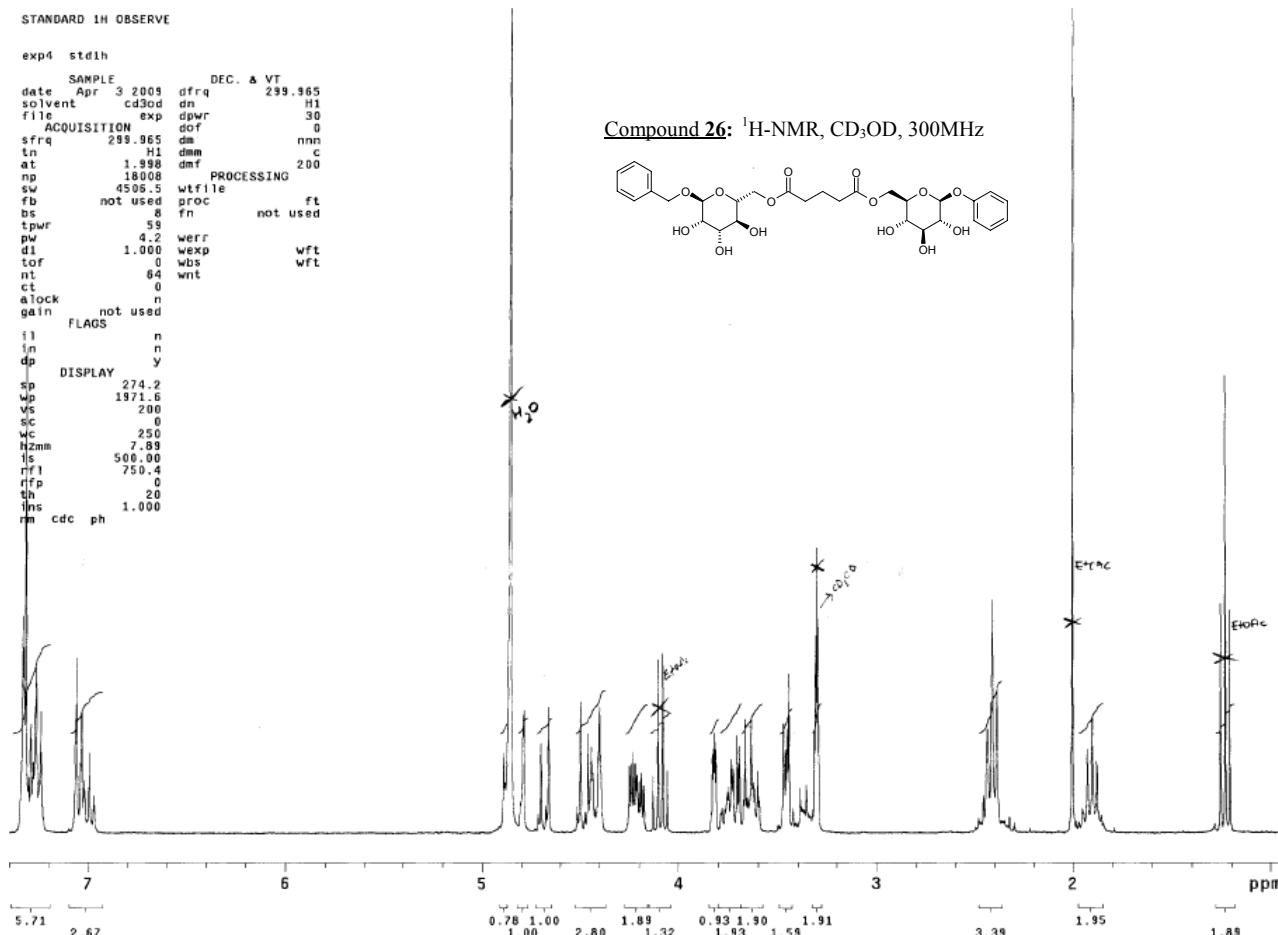


Compound 16: ^1H -NMR, CDCl_3 , 500MHz



Compound 16: ^{13}C -NMR, CDCl_3 , 100MHz



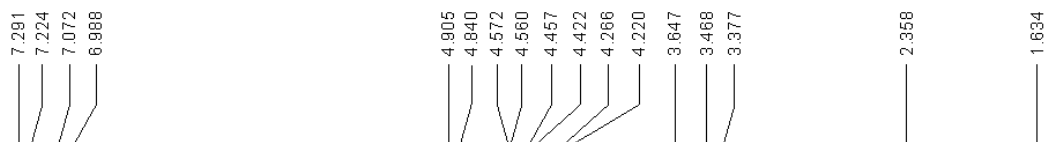
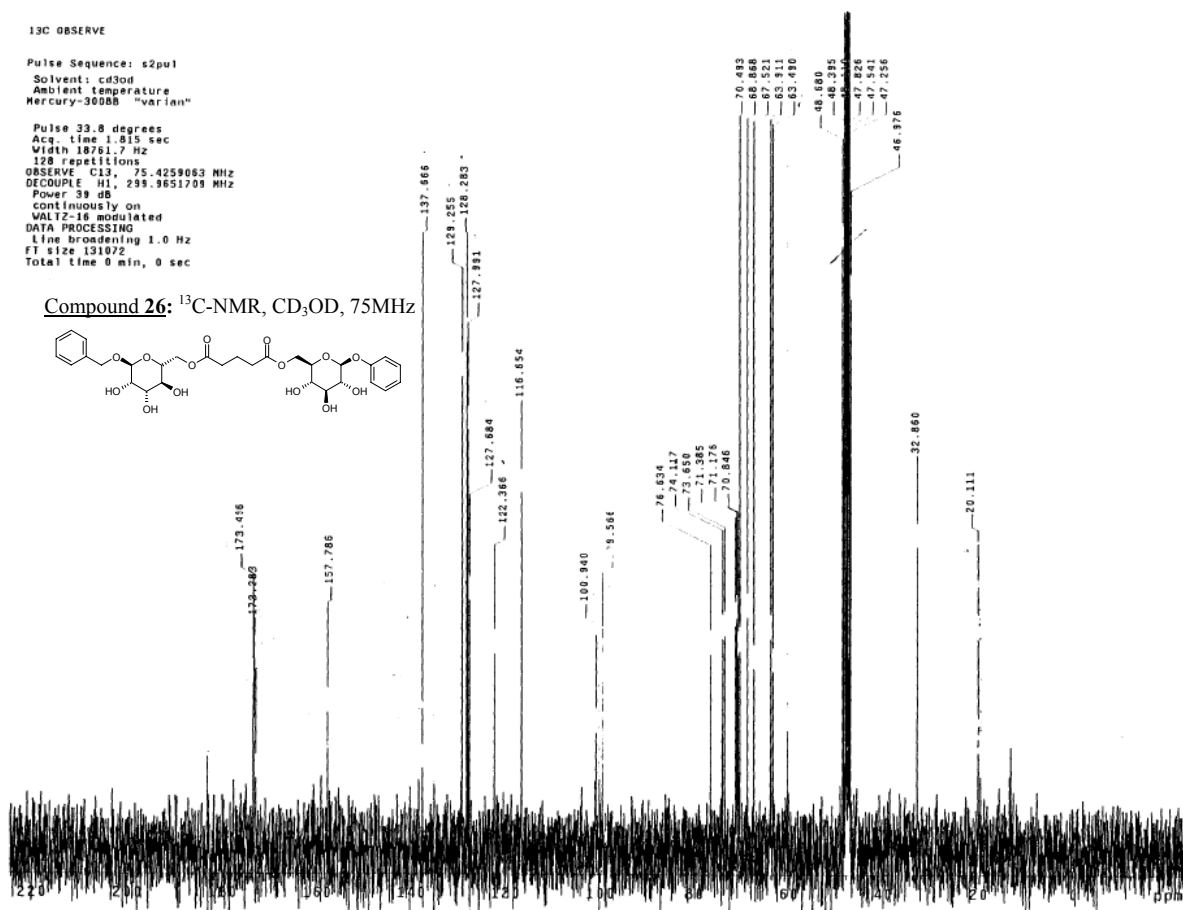
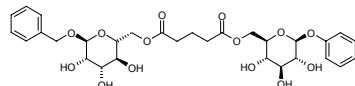


13C OBSERVE

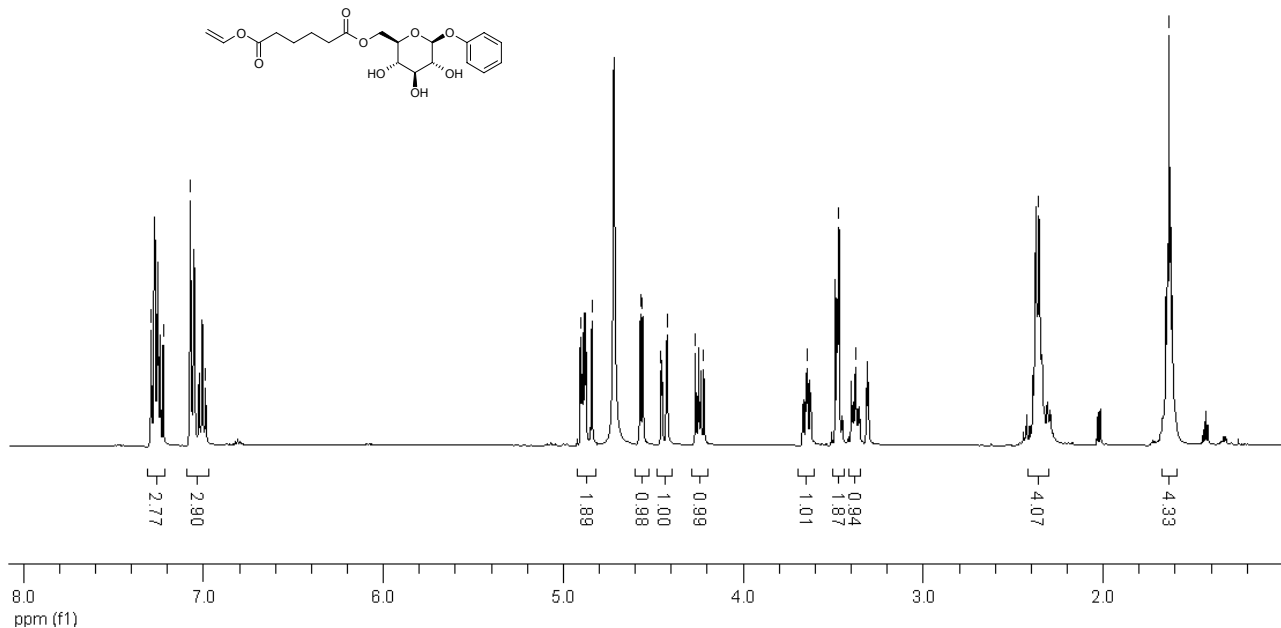
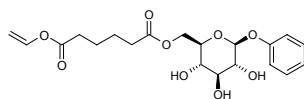
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Solvent: cd3od
Ambient temperature
Mercury-300DB "varian"

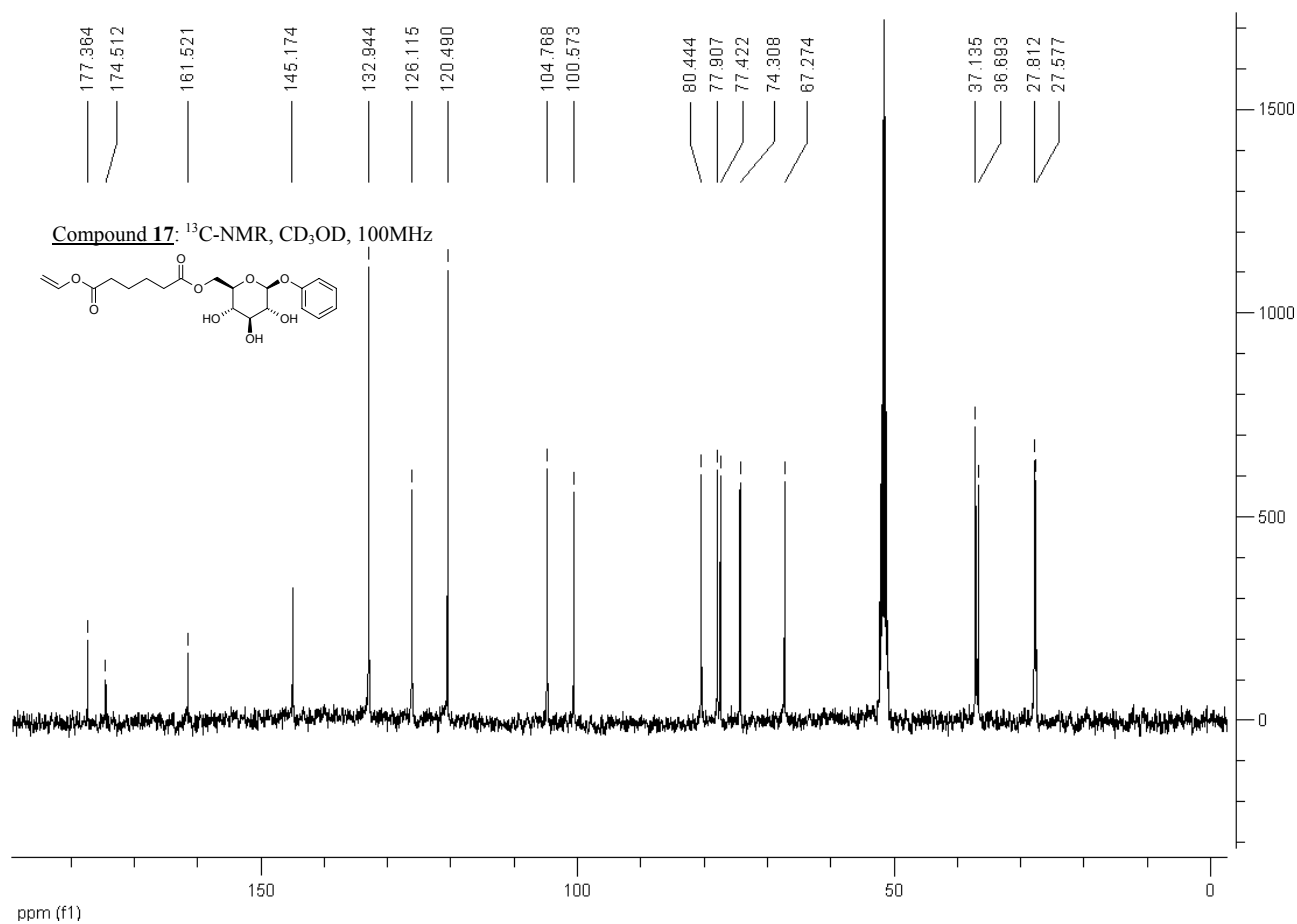
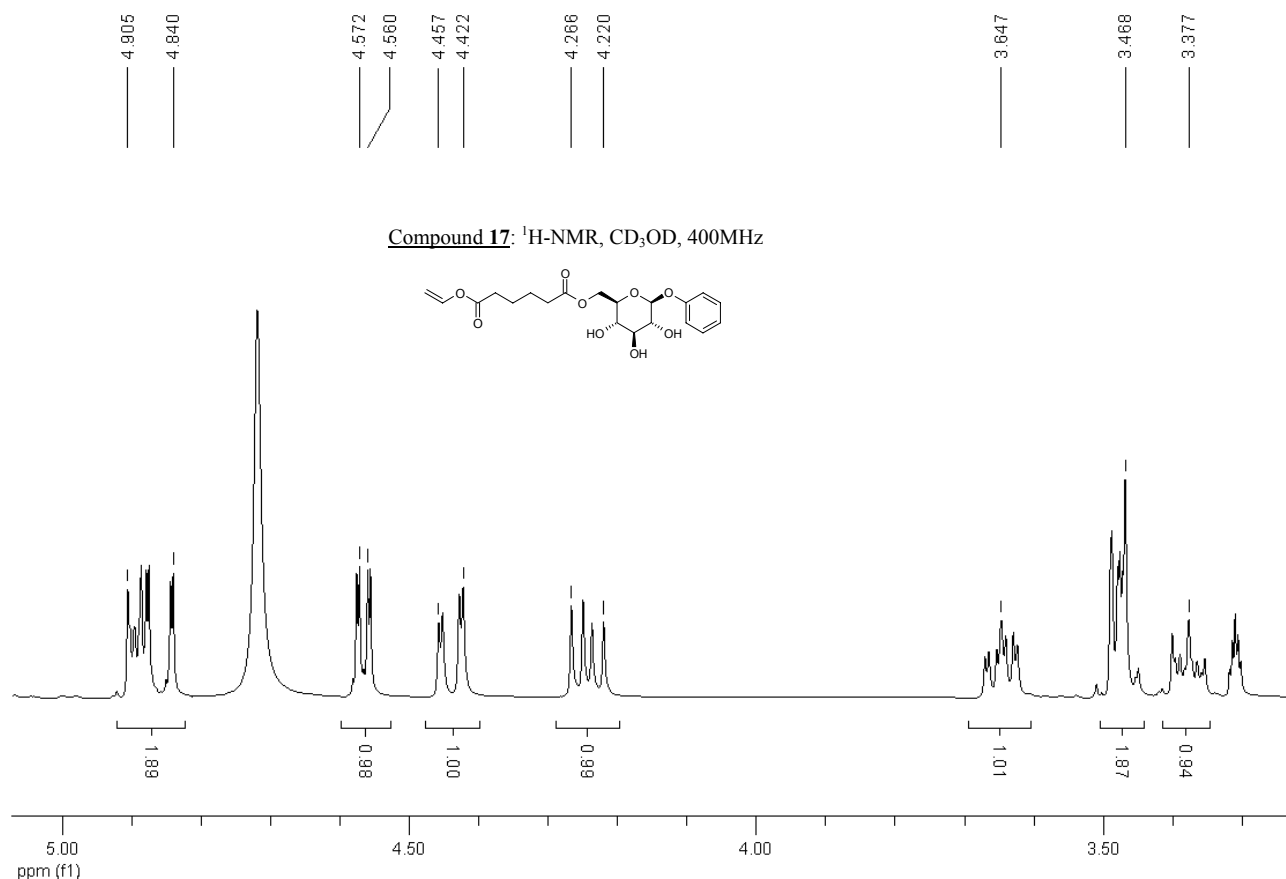
Pulse 33.8 degrees
Acq. time 1.515 sec
Width 18751.7 Hz
128 repetitions
OBSERVE C13, 75.4259063 MHz
DECOUPLE H1, 299.9651708 MHz
Power 39 dB
continuously on
VALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 0 min, 0 sec

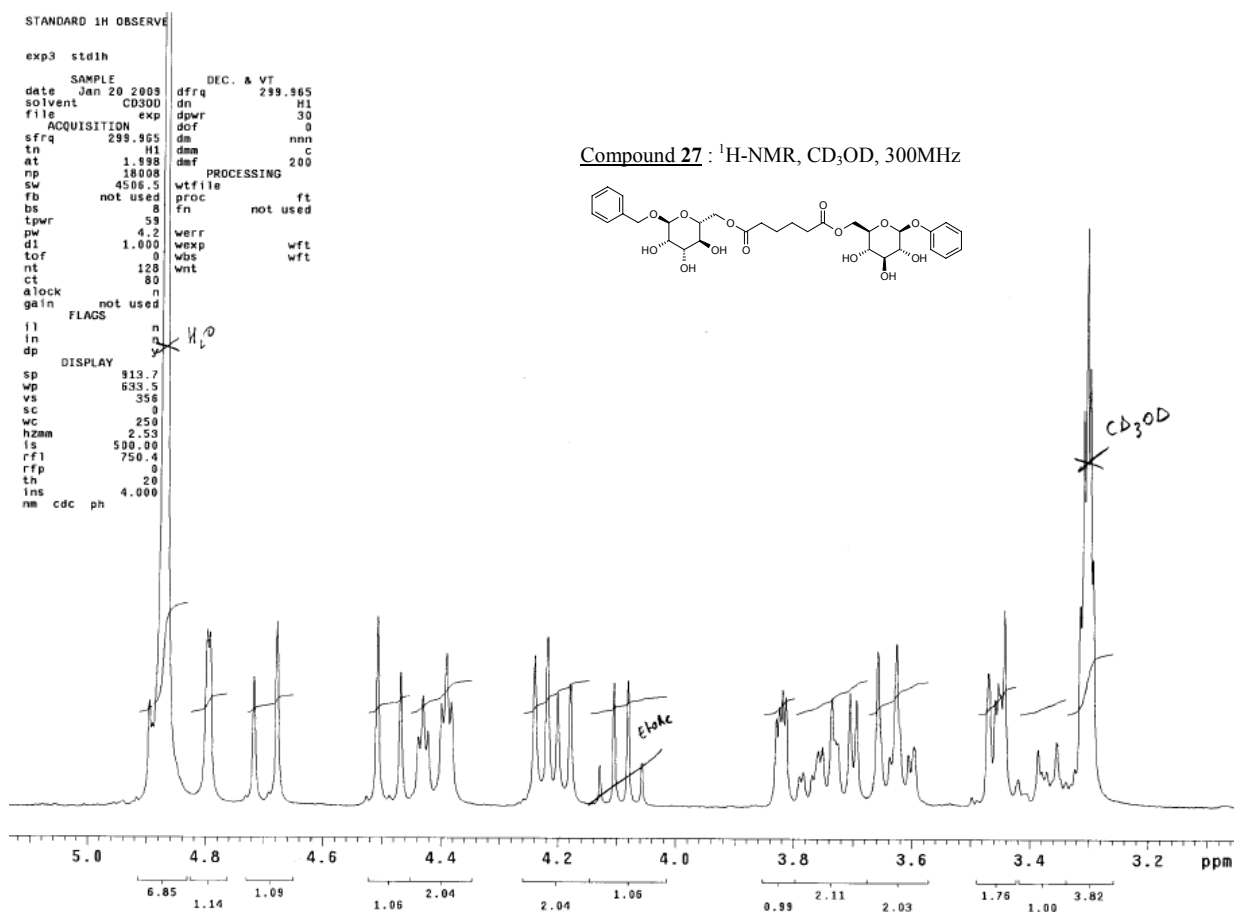
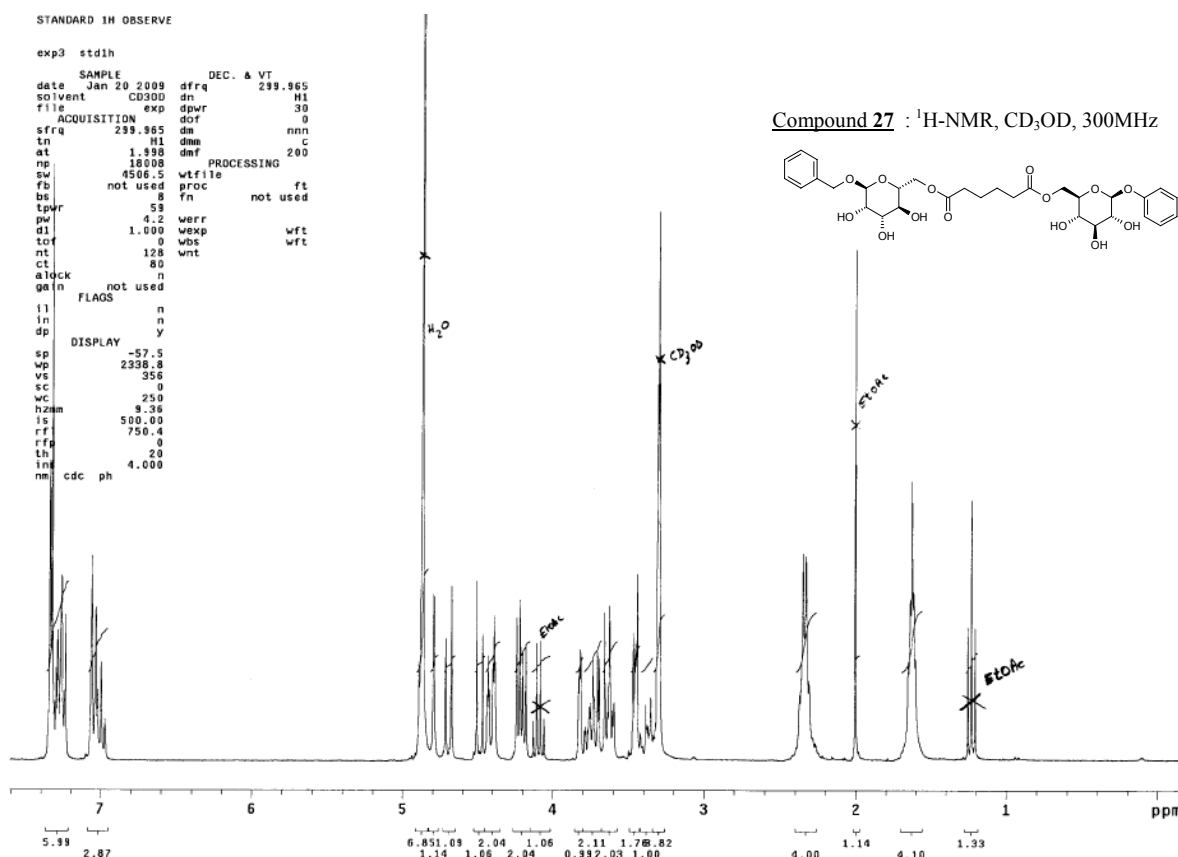
Compound 26: ¹³C-NMR, CD₃OD, 75MHz

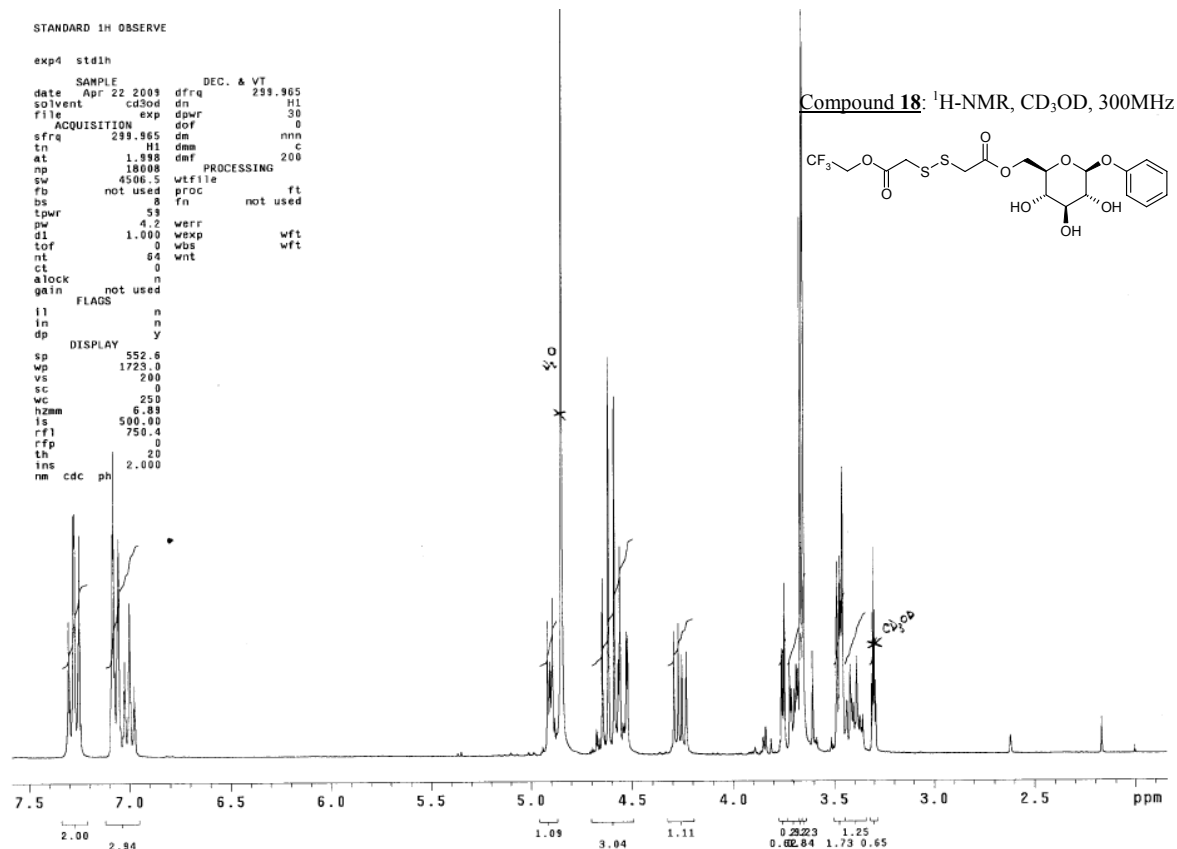
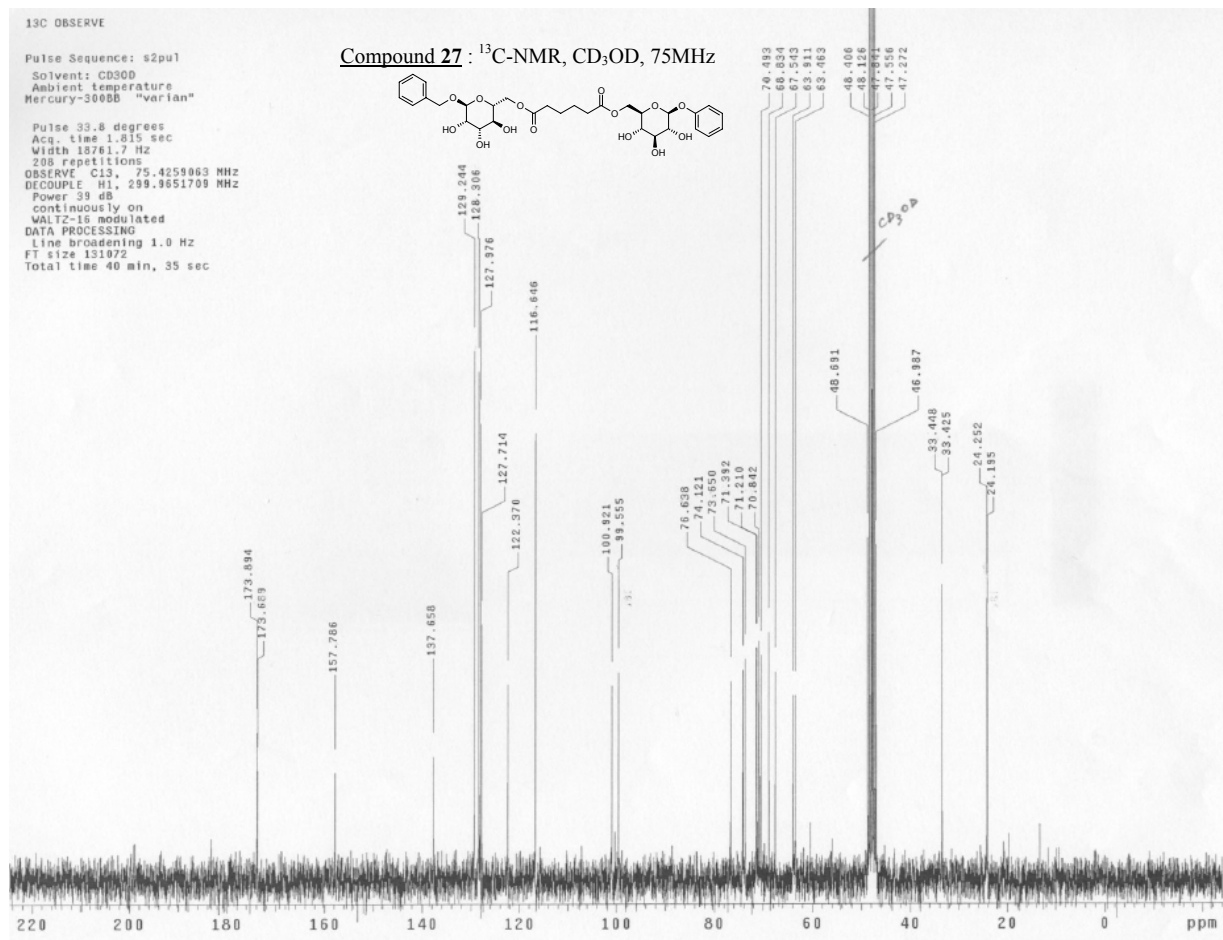


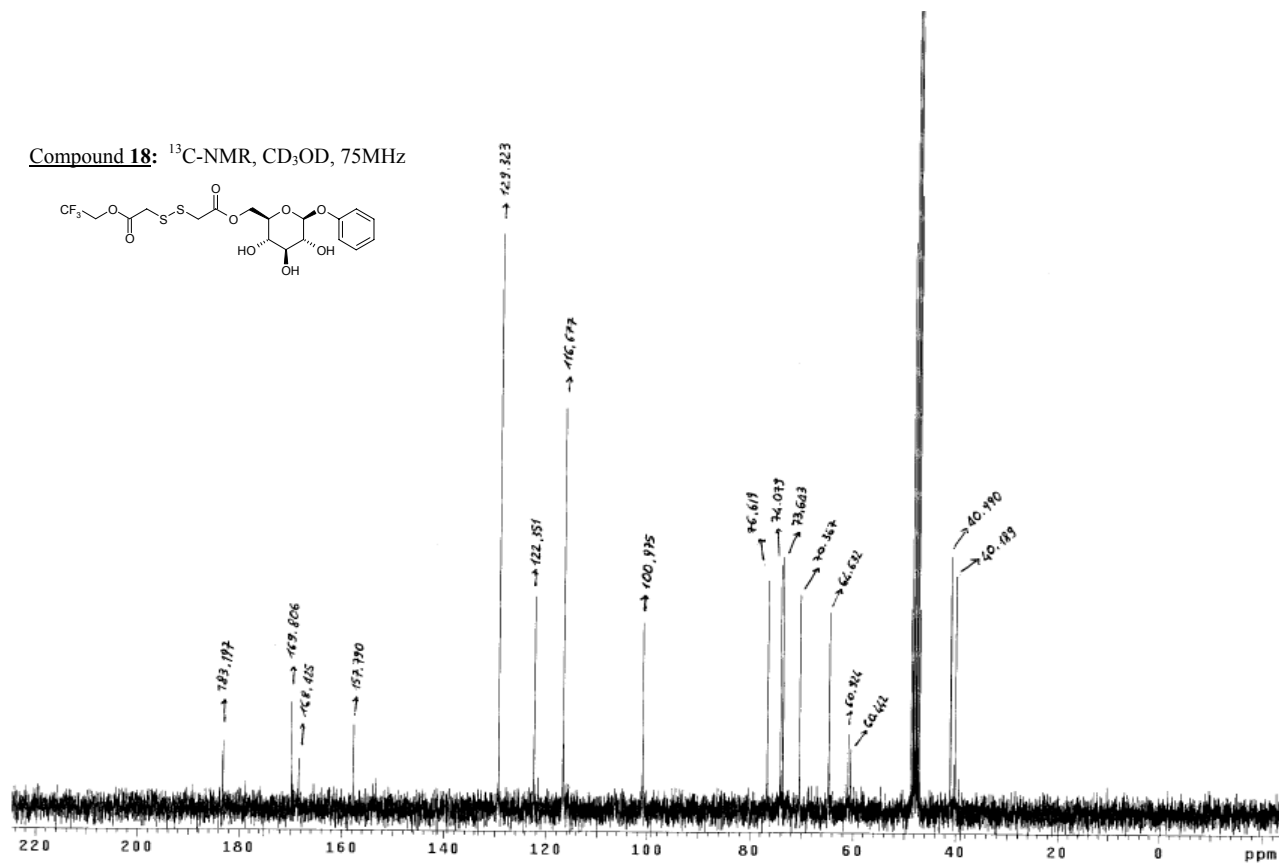
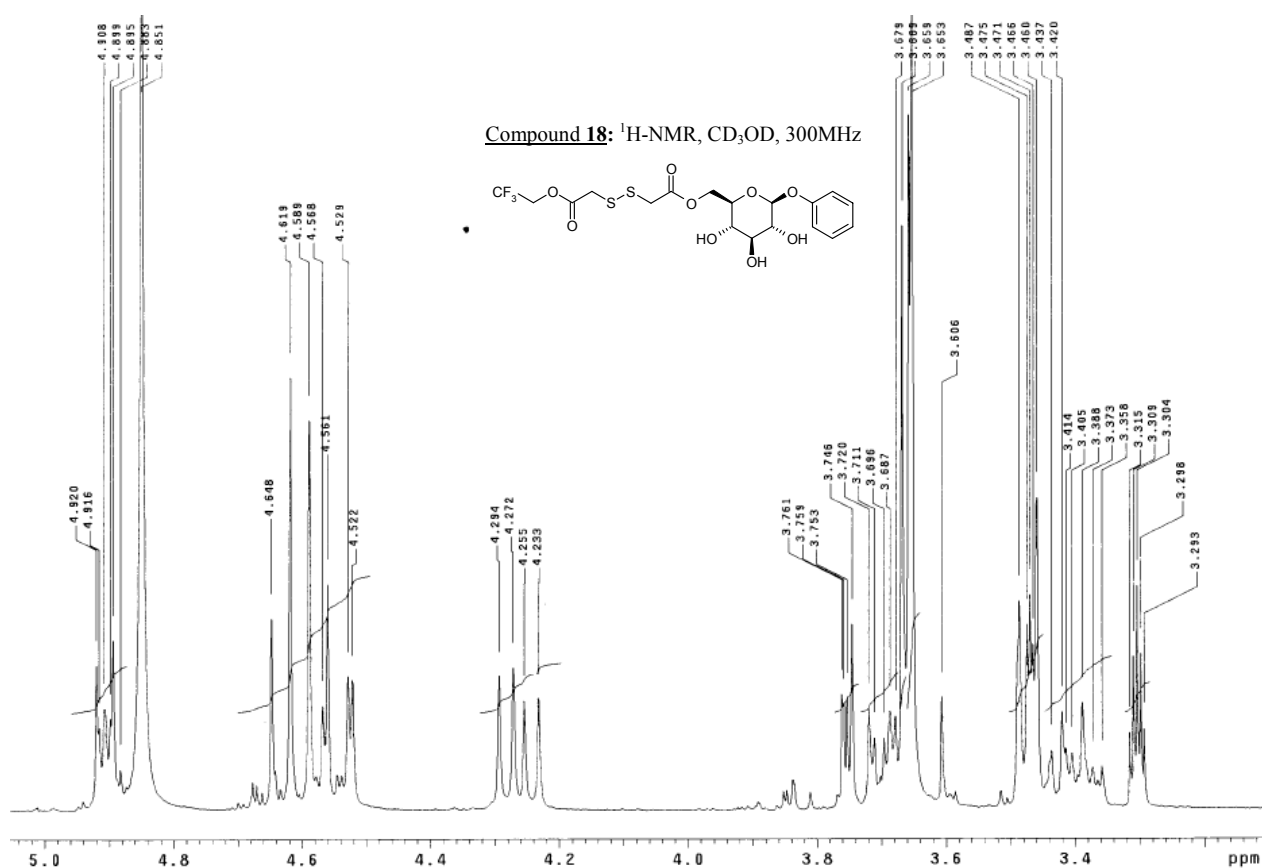
Compound 17: ¹H-NMR, CD₃OD, 400MHz

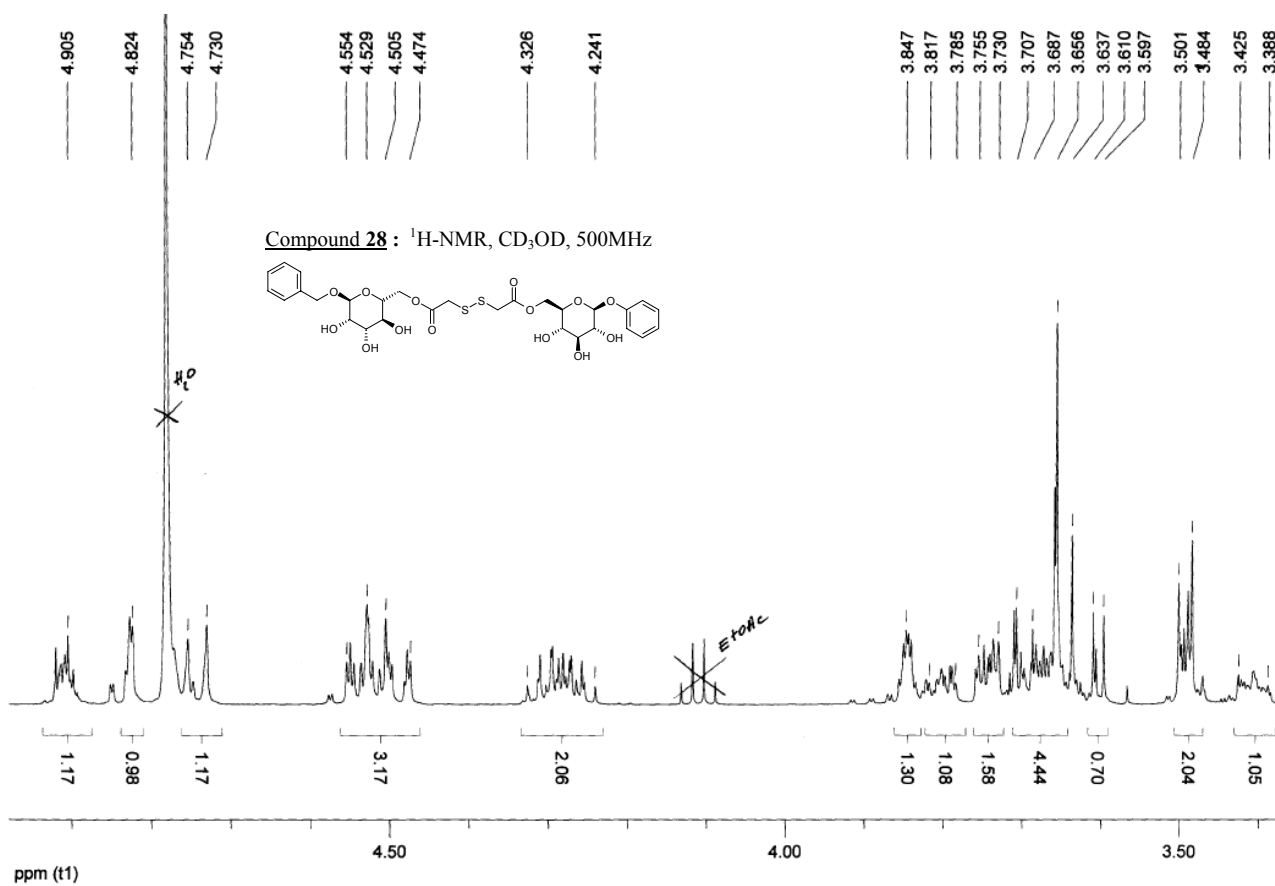
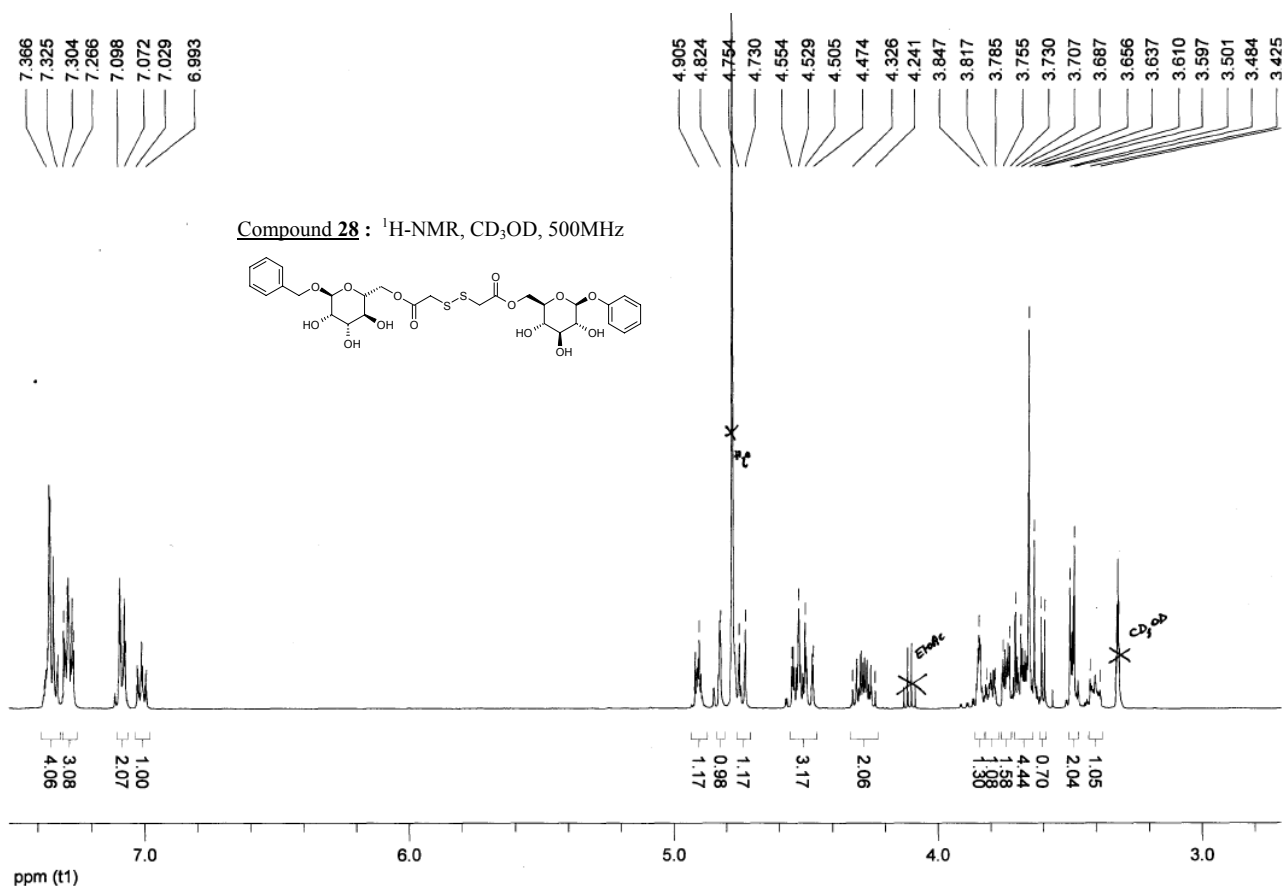


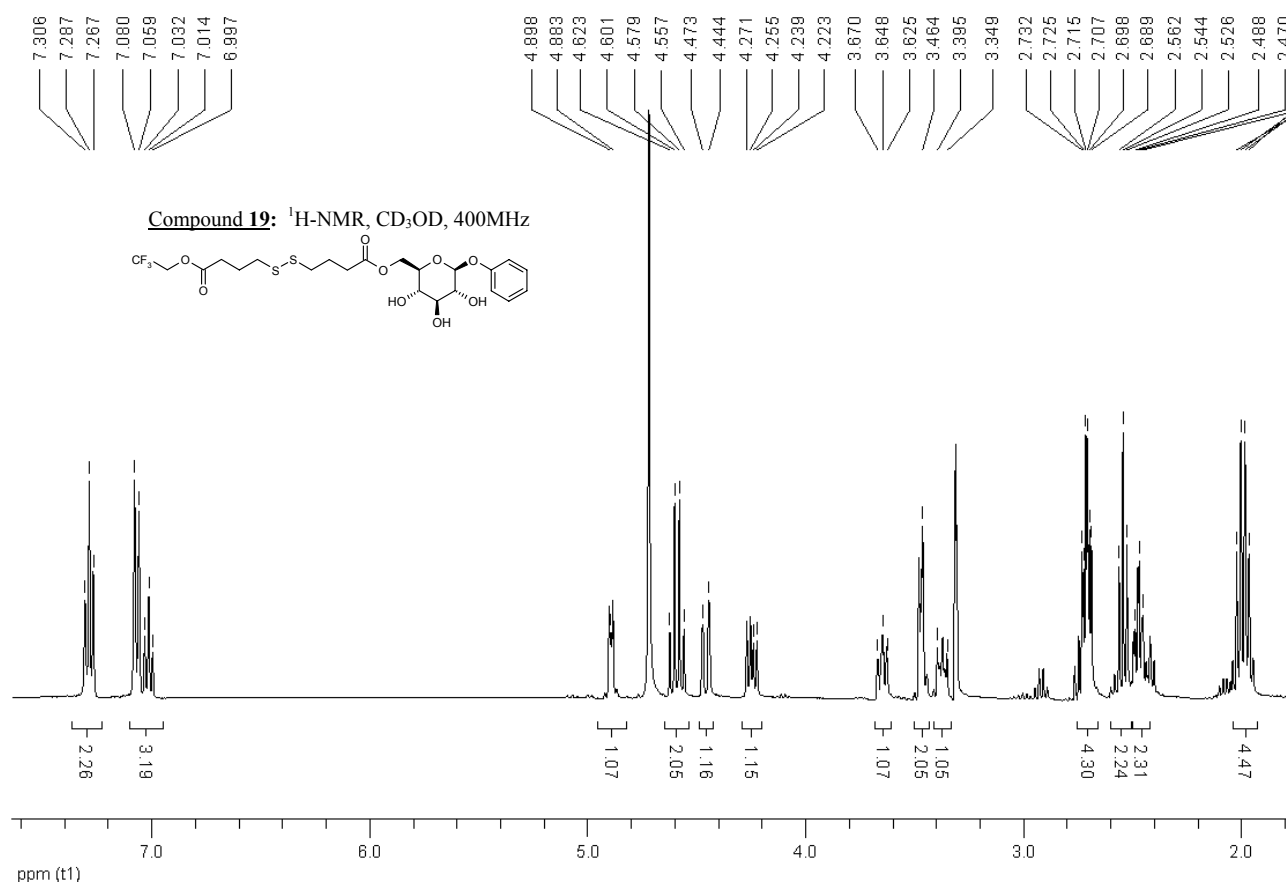
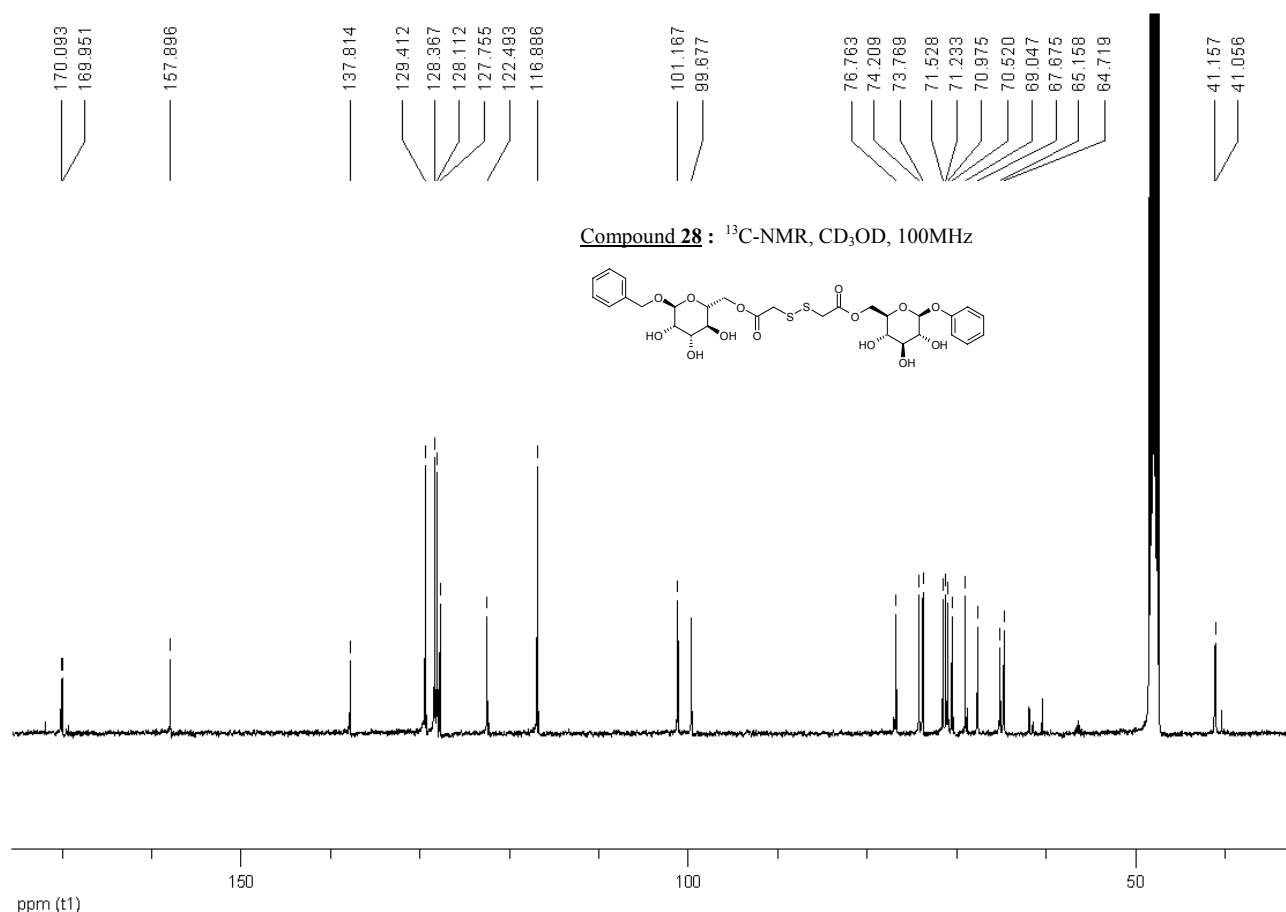


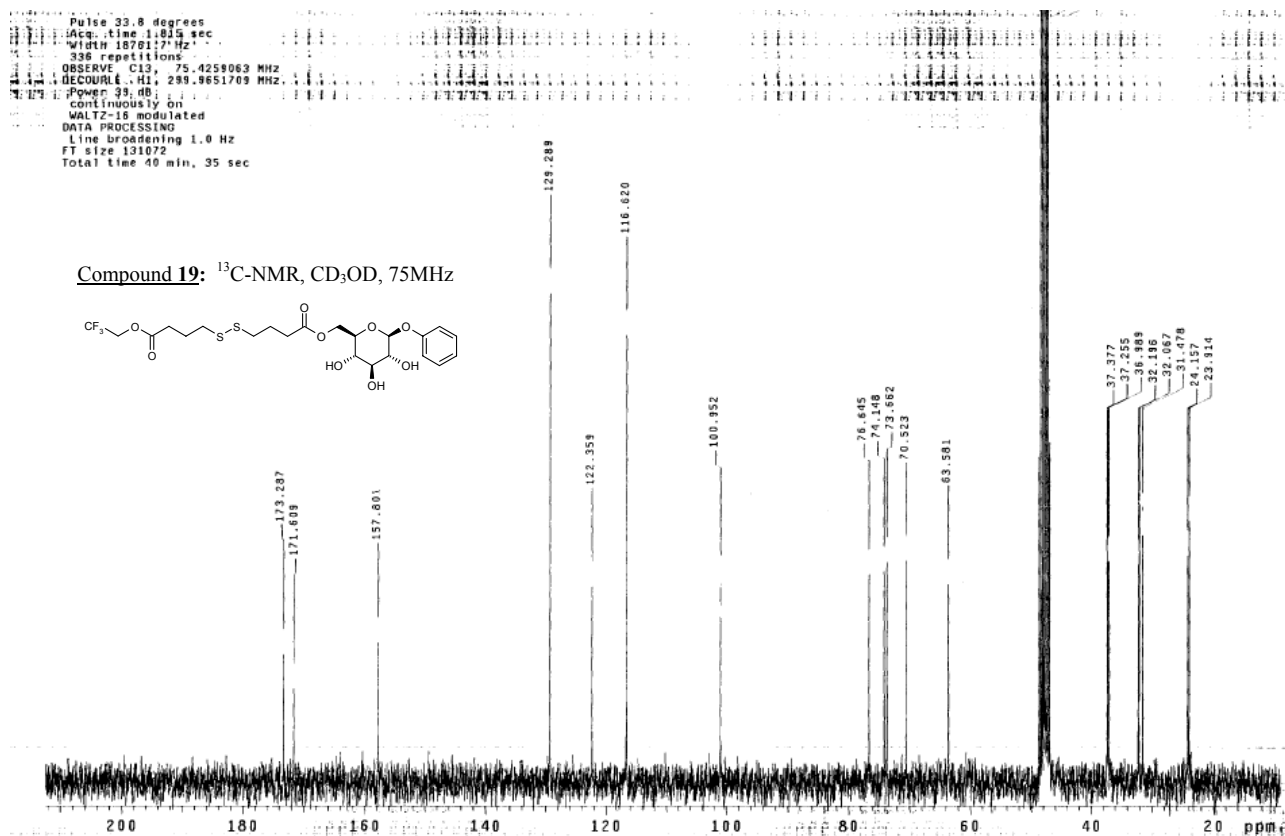
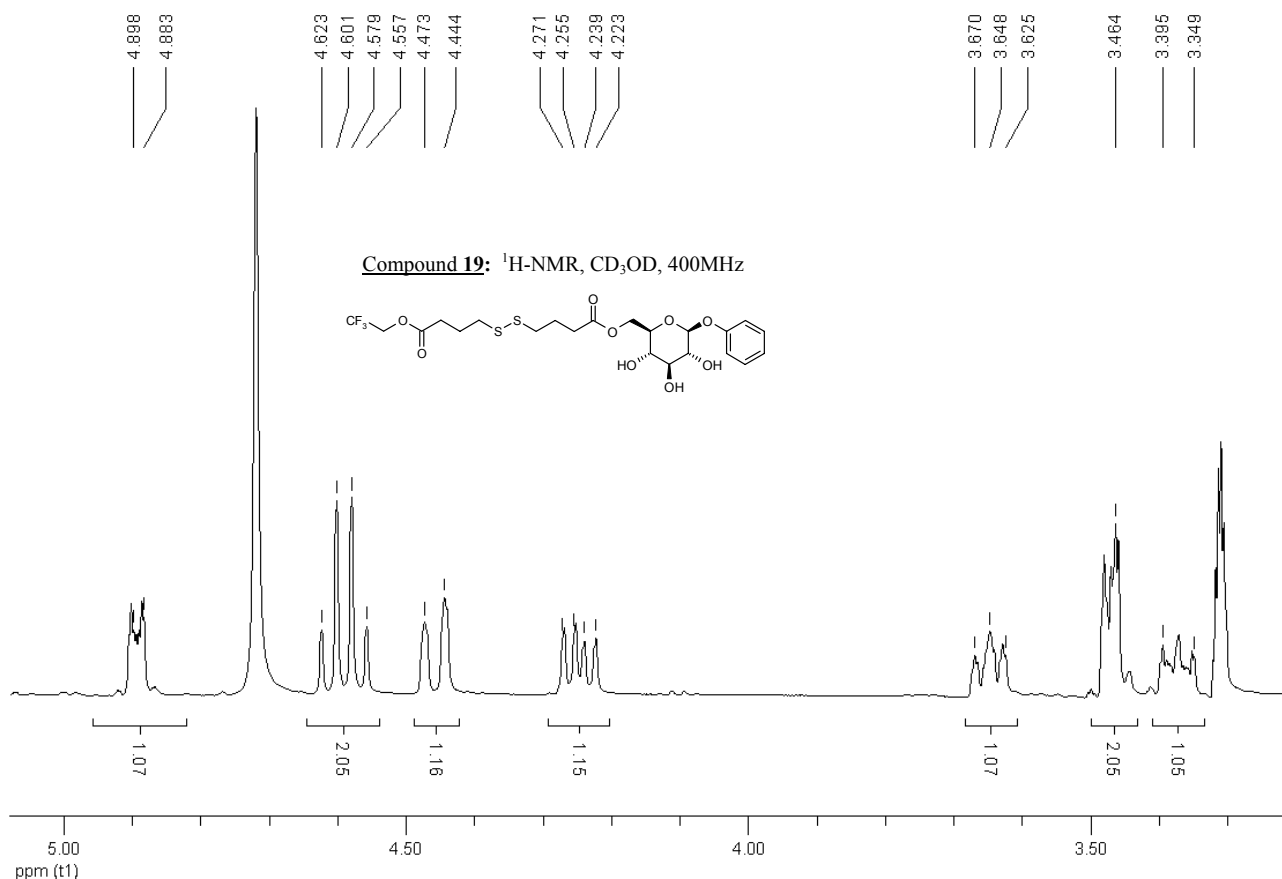


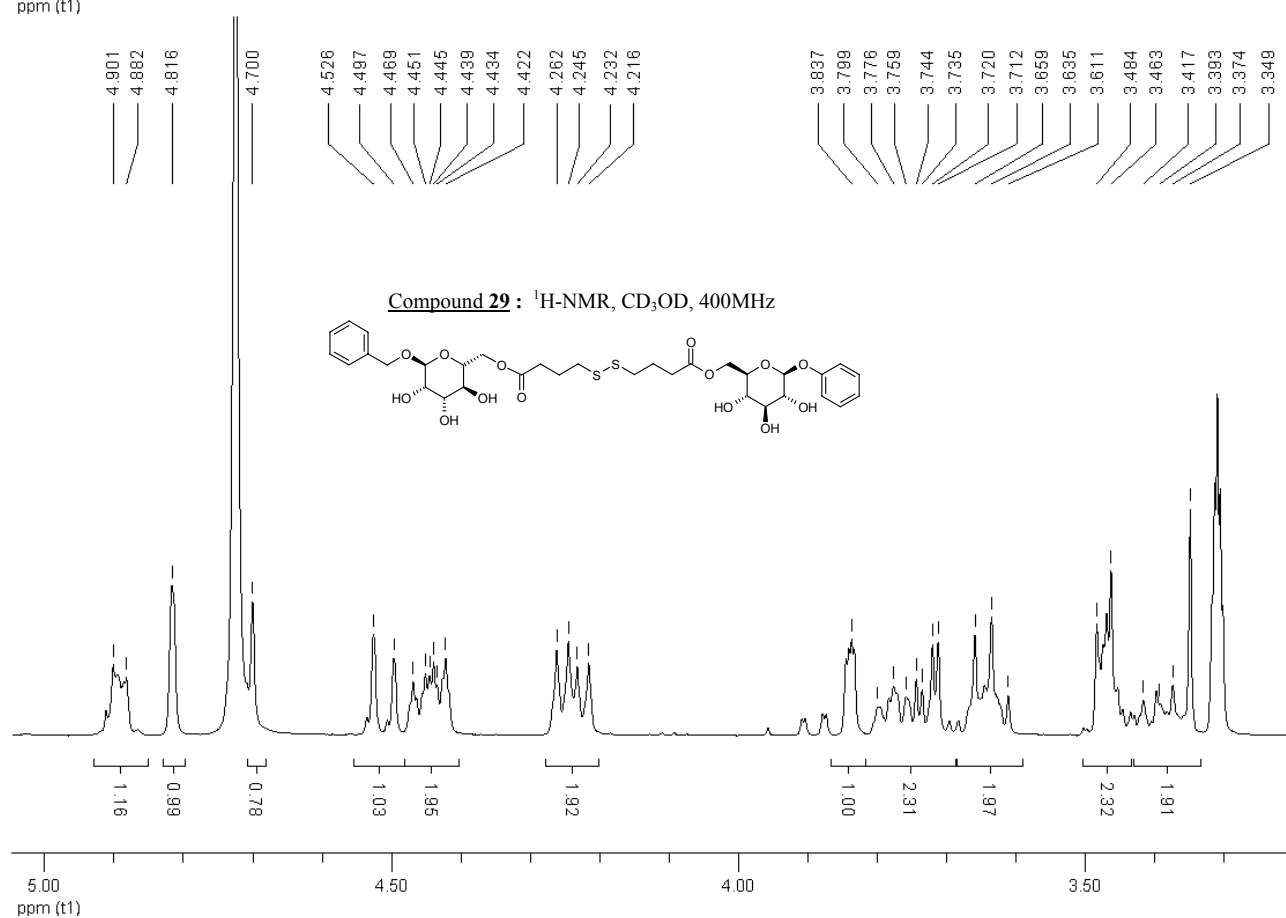
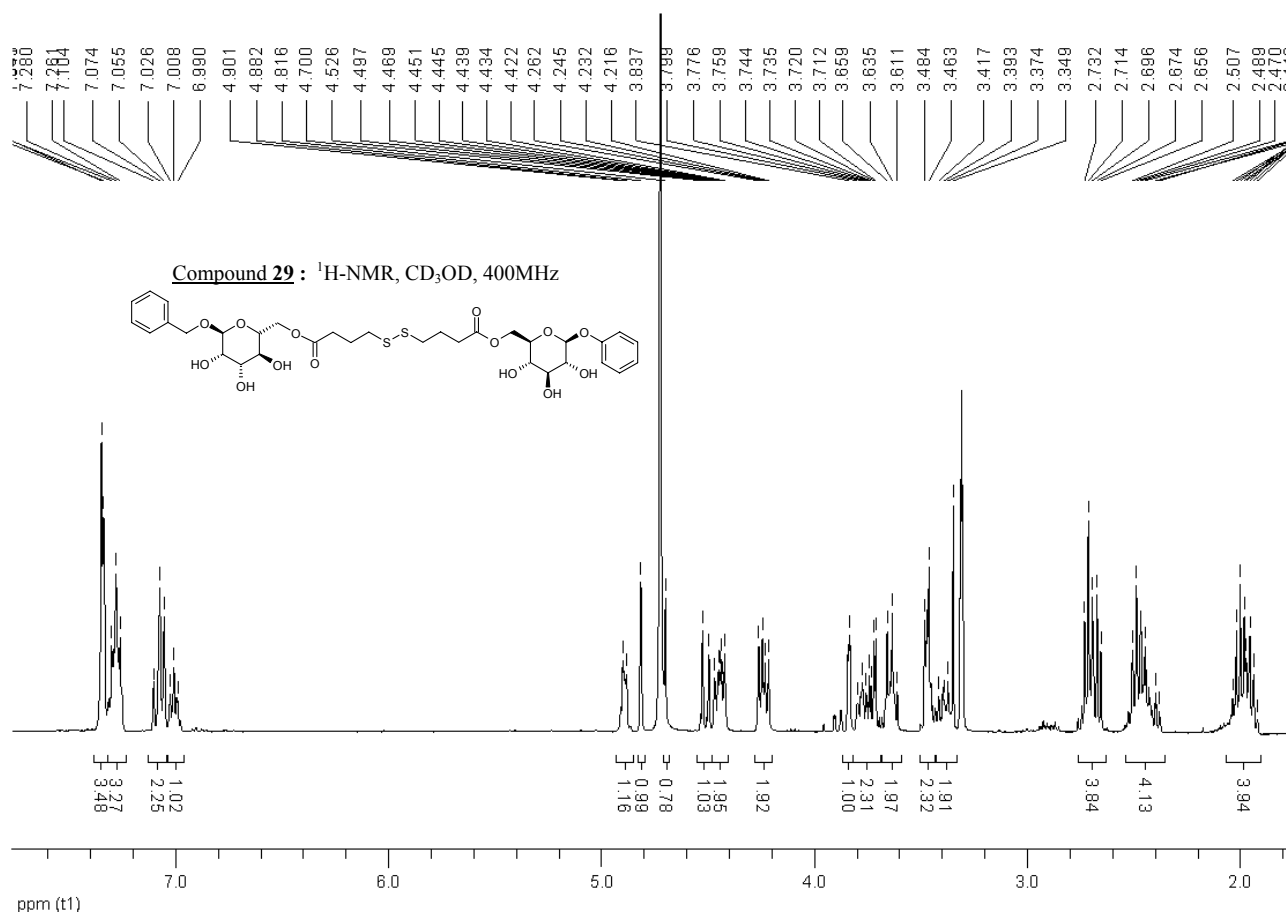




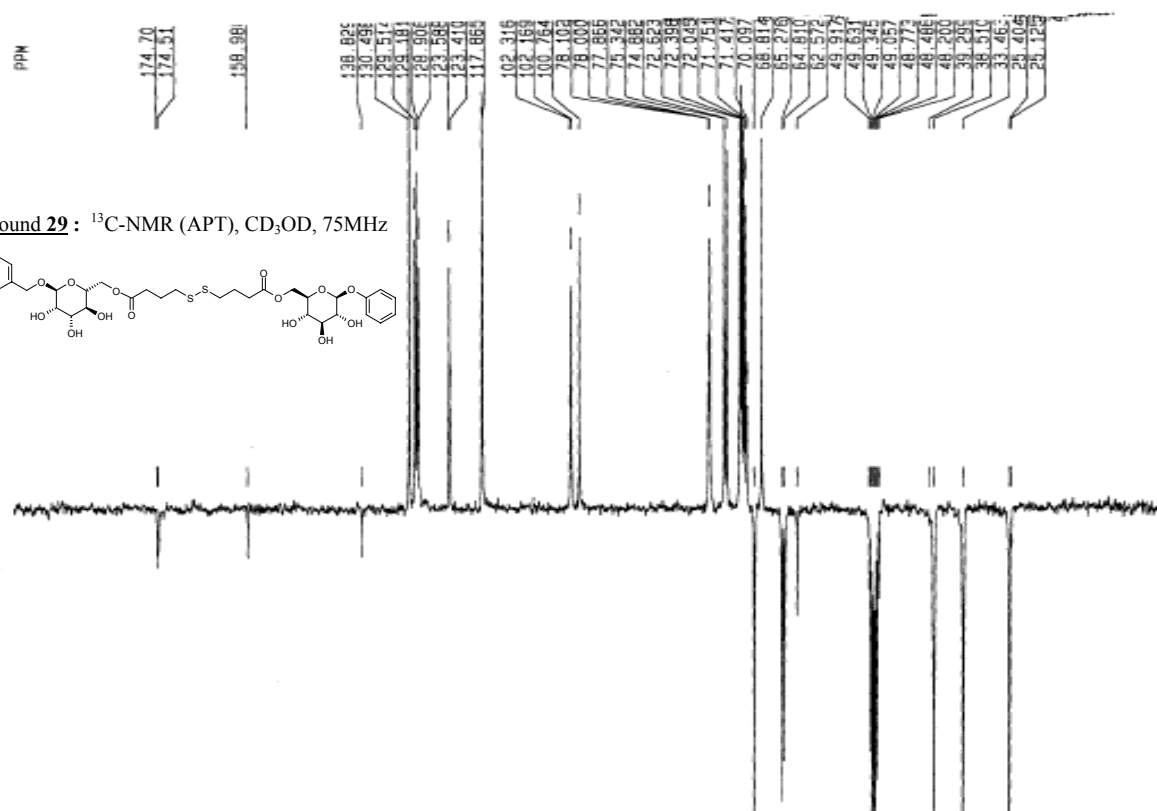
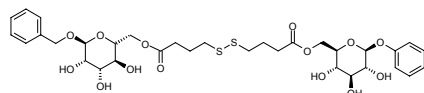




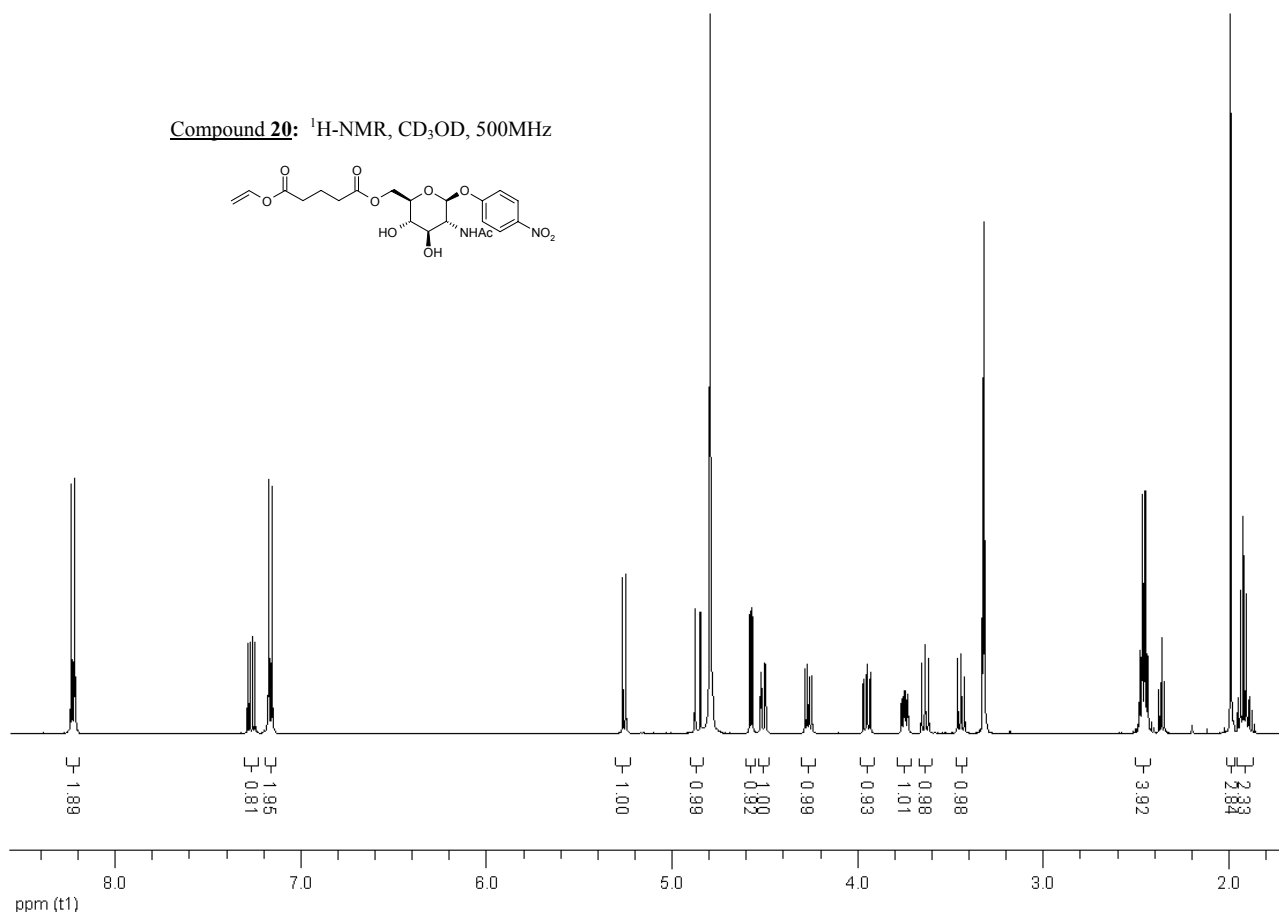
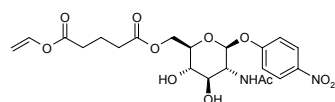


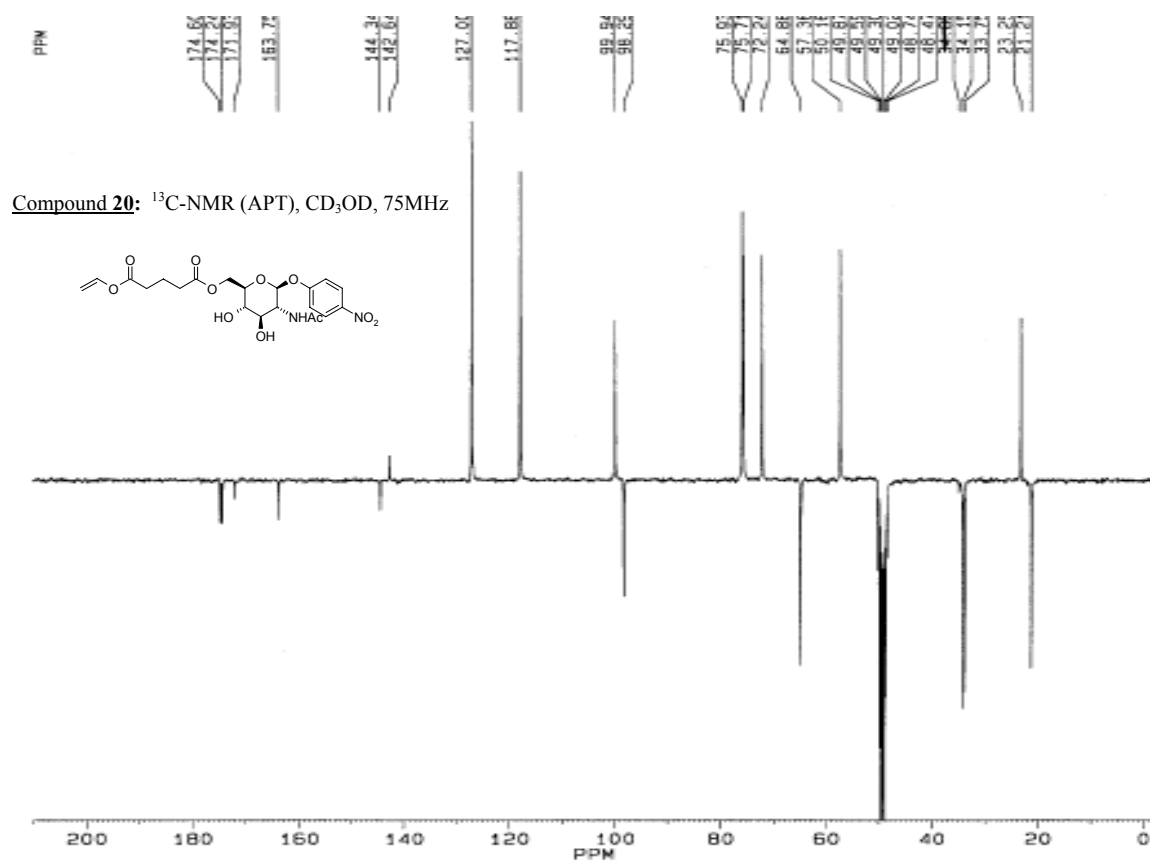
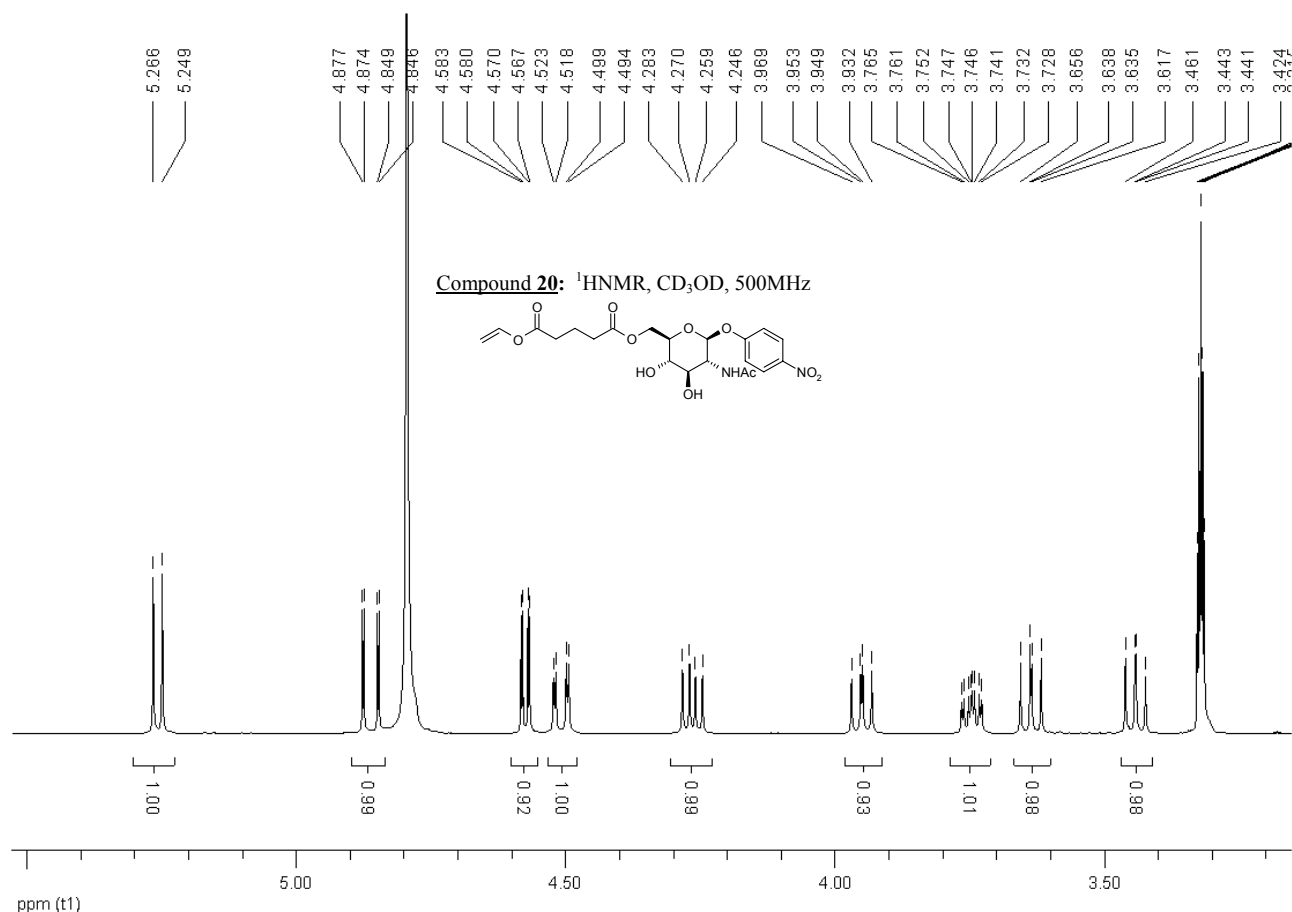


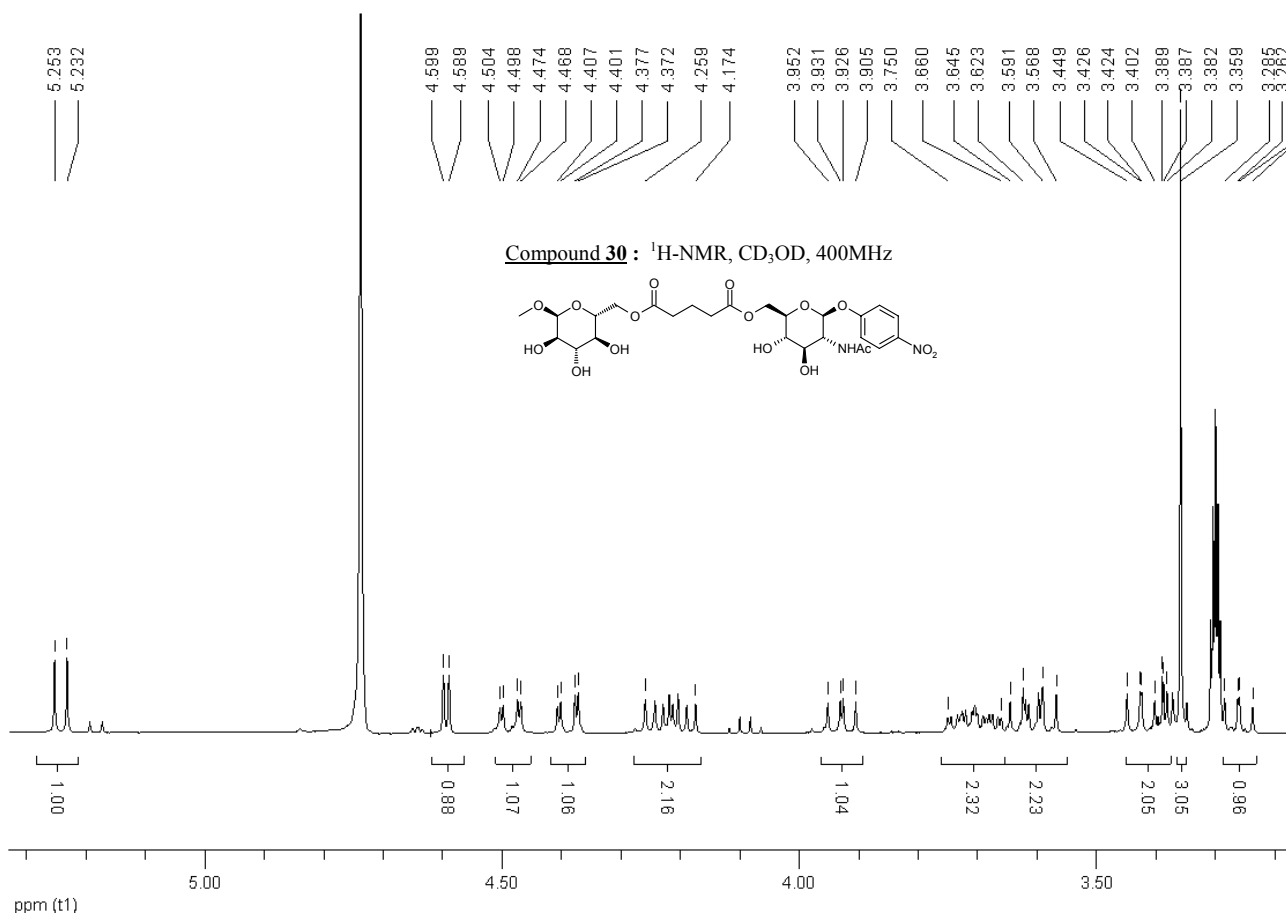
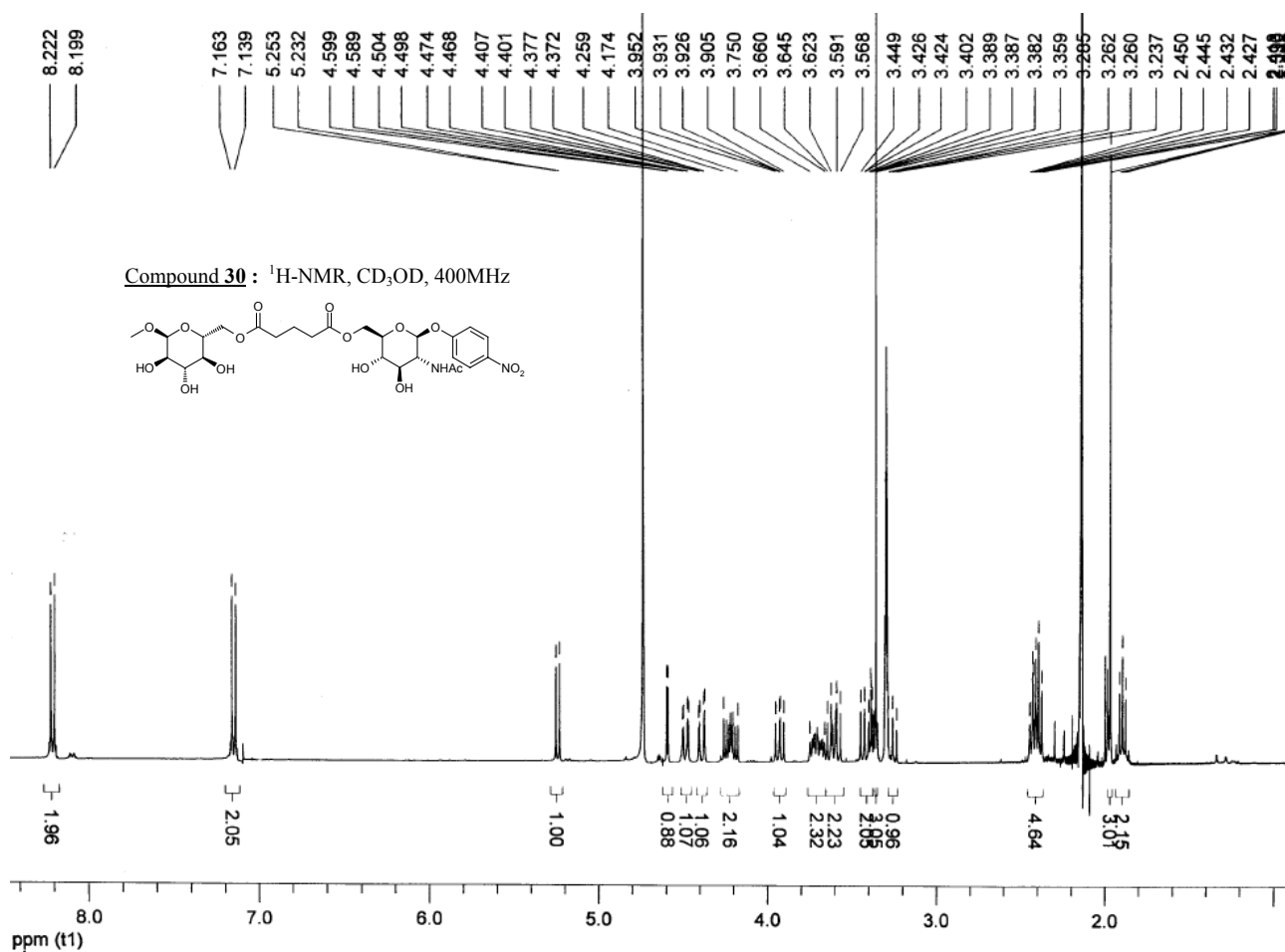
Compound 29 : ^{13}C -NMR (APT), CD_3OD , 75MHz

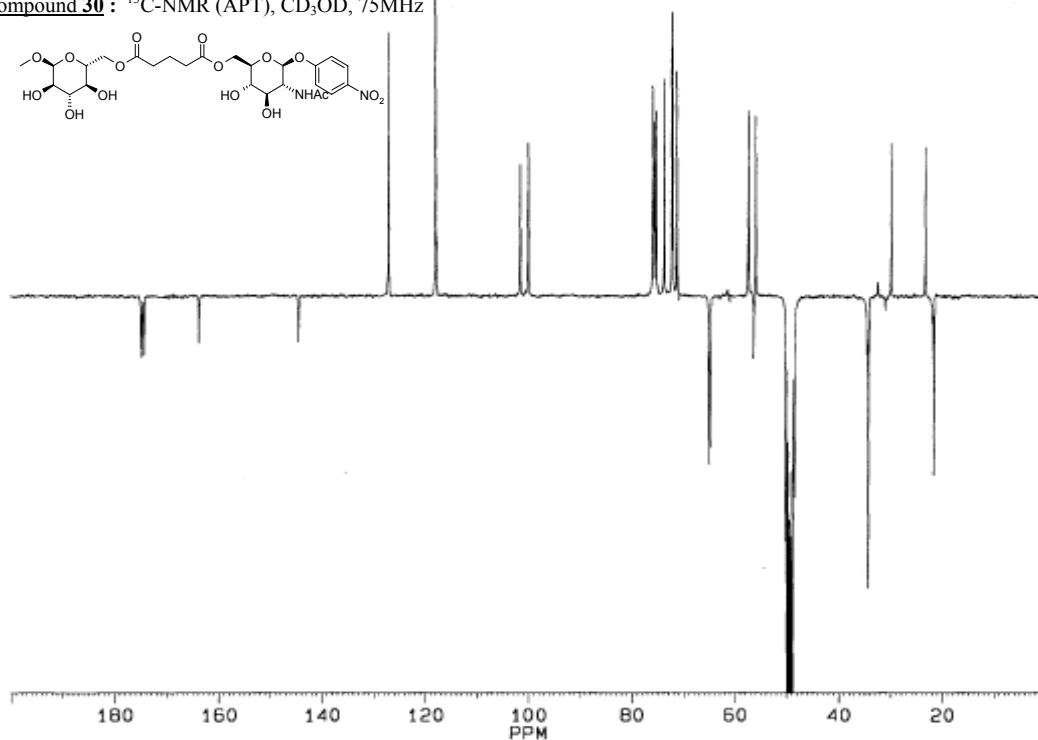
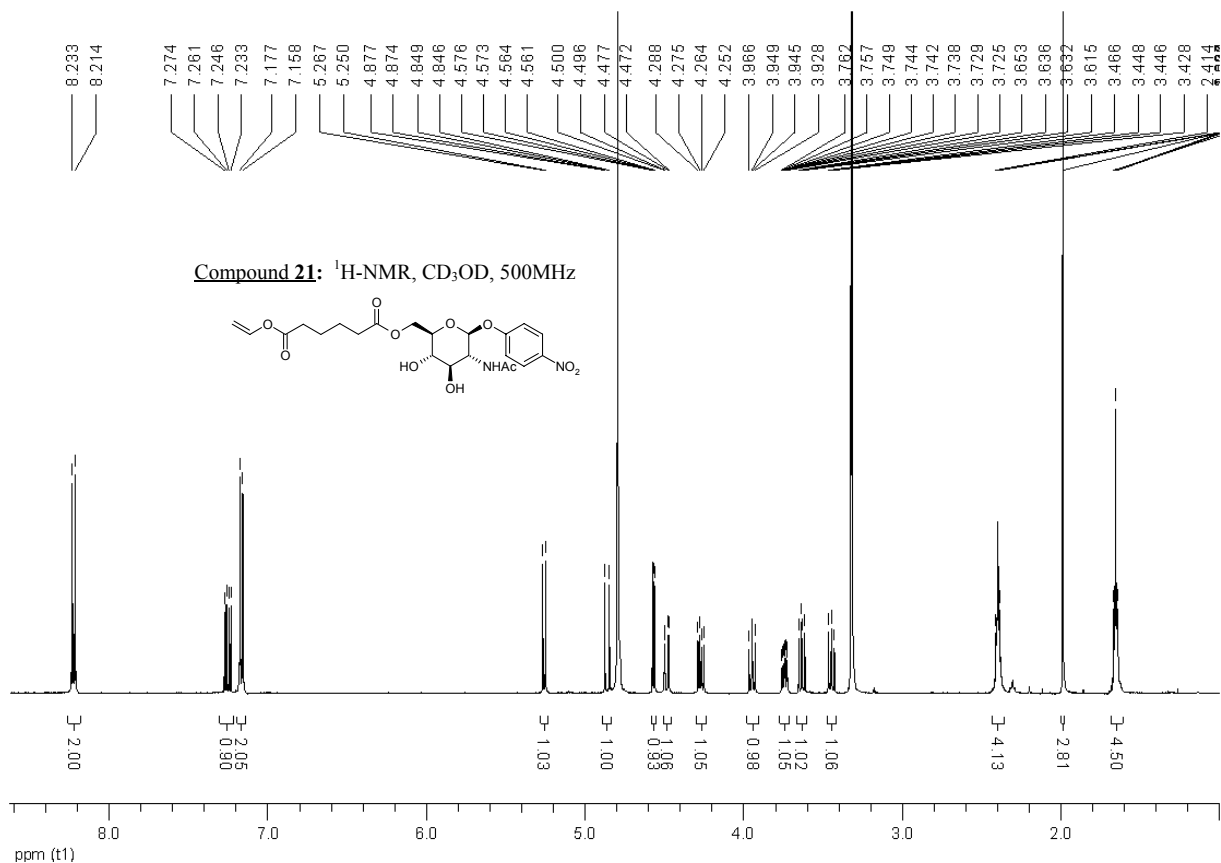


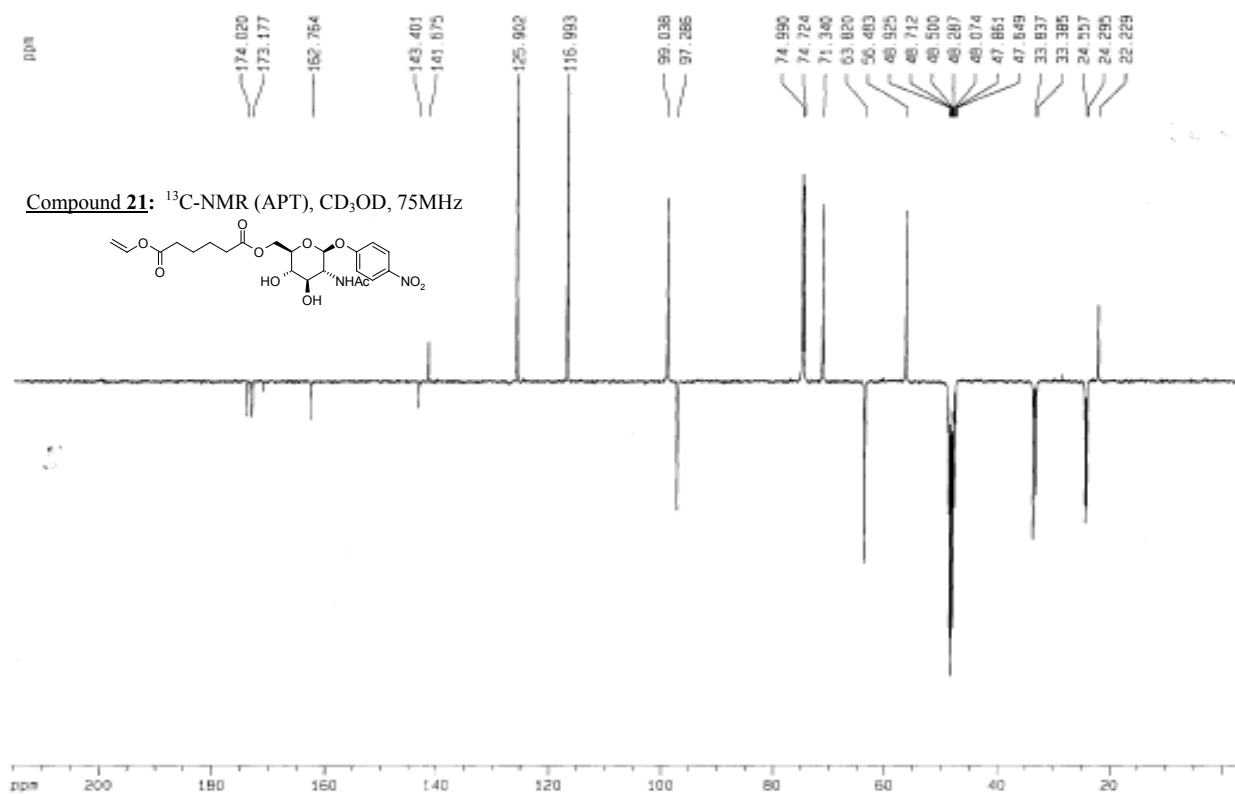
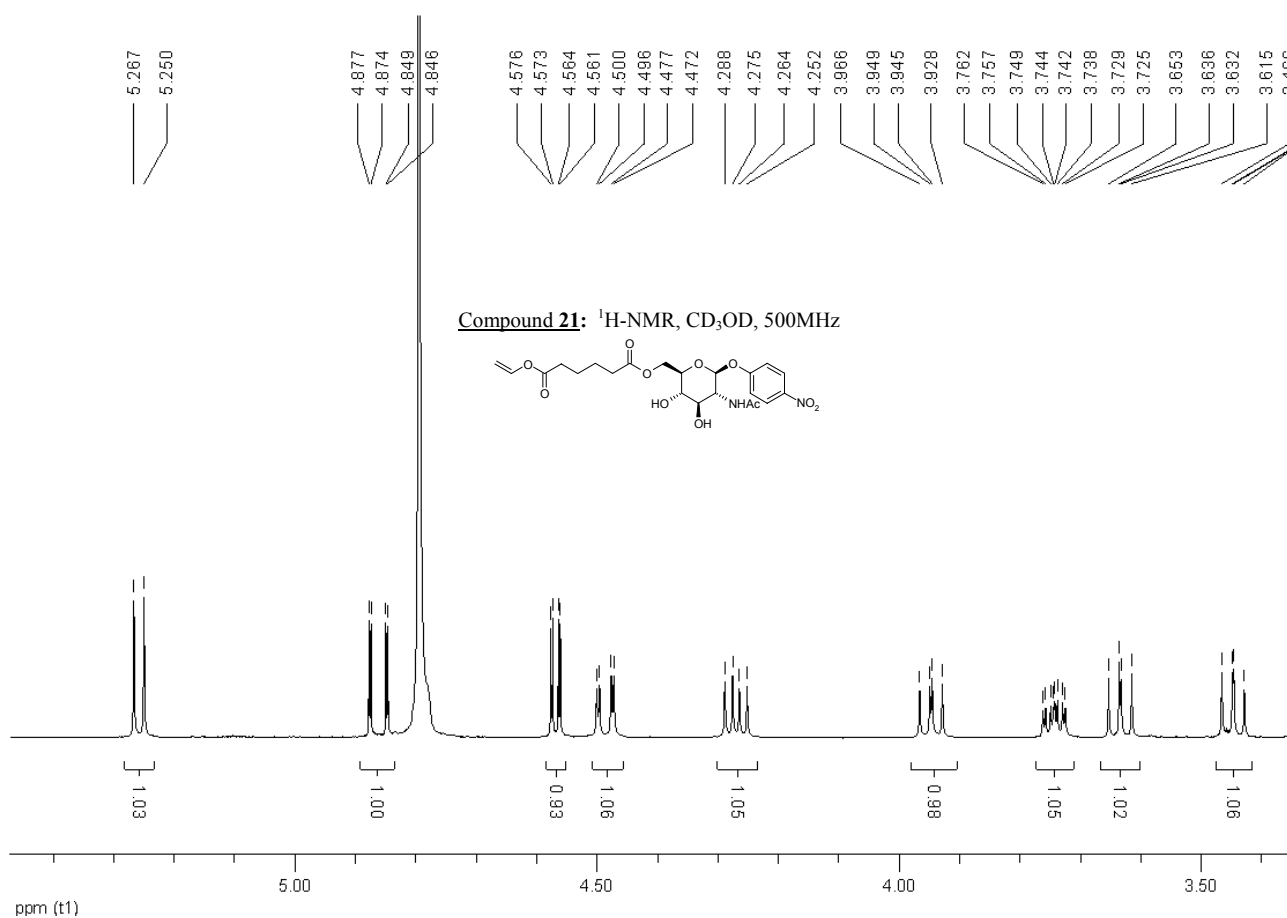
Compound 20: ^1H -NMR, CD_3OD , 500MHz



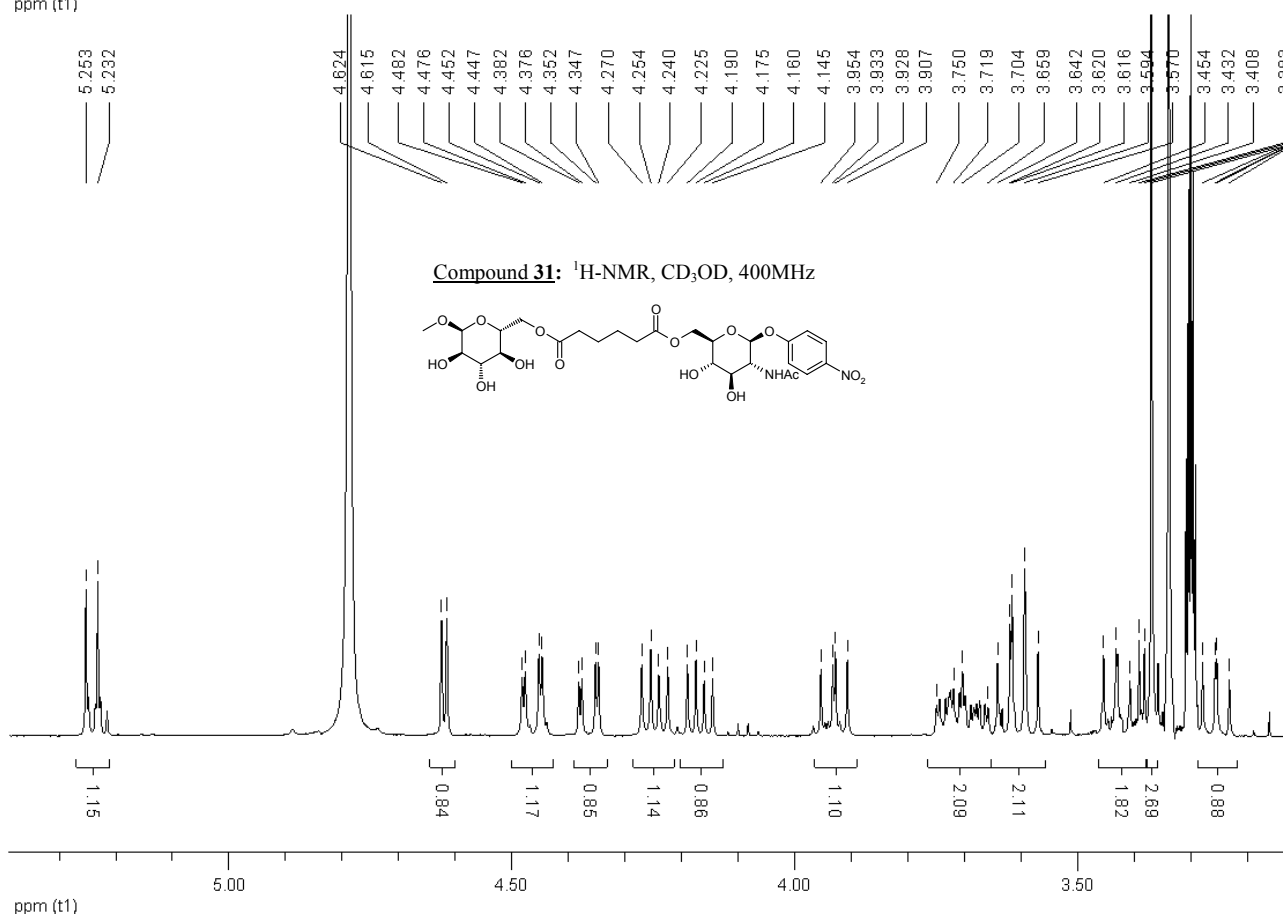
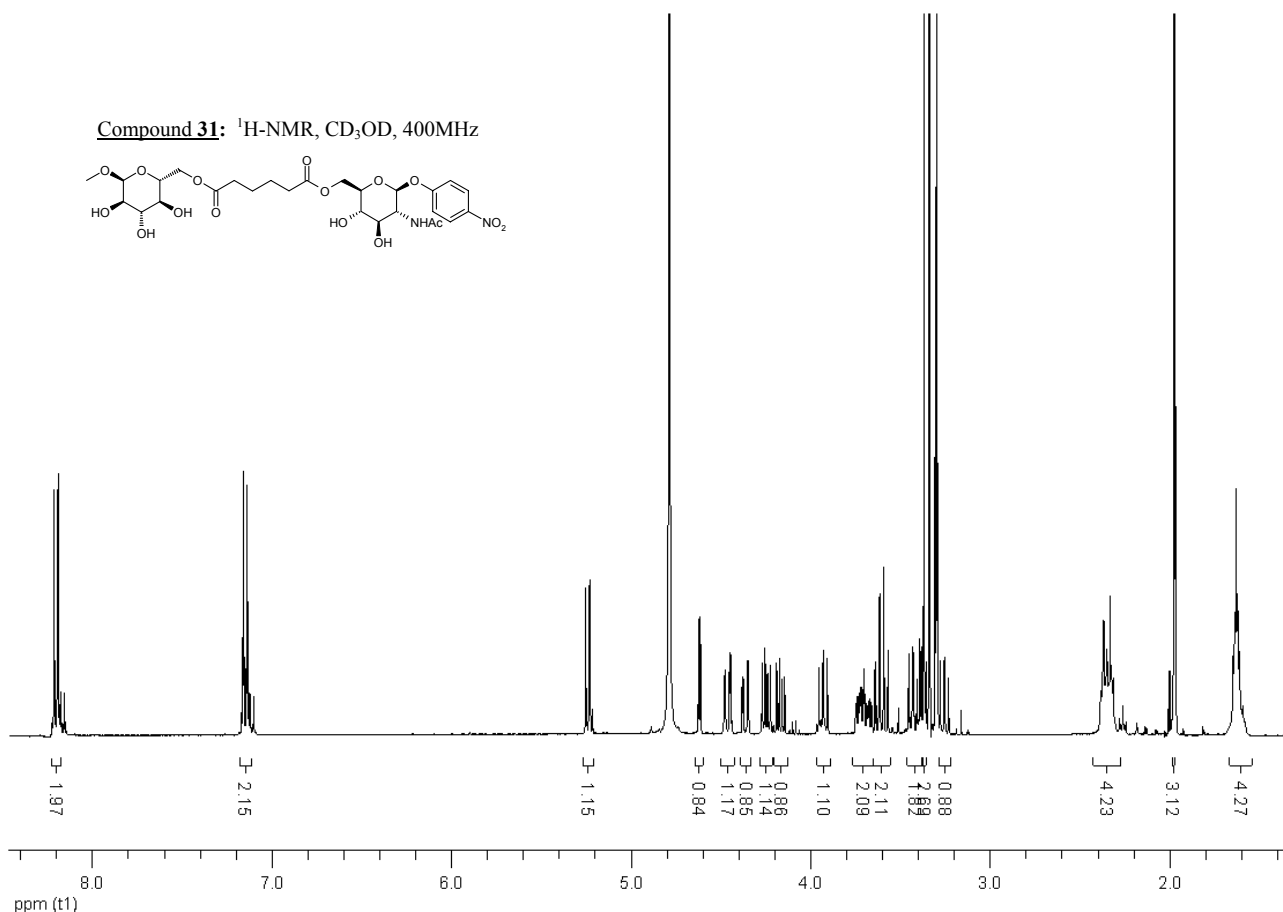
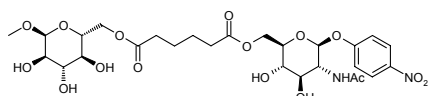


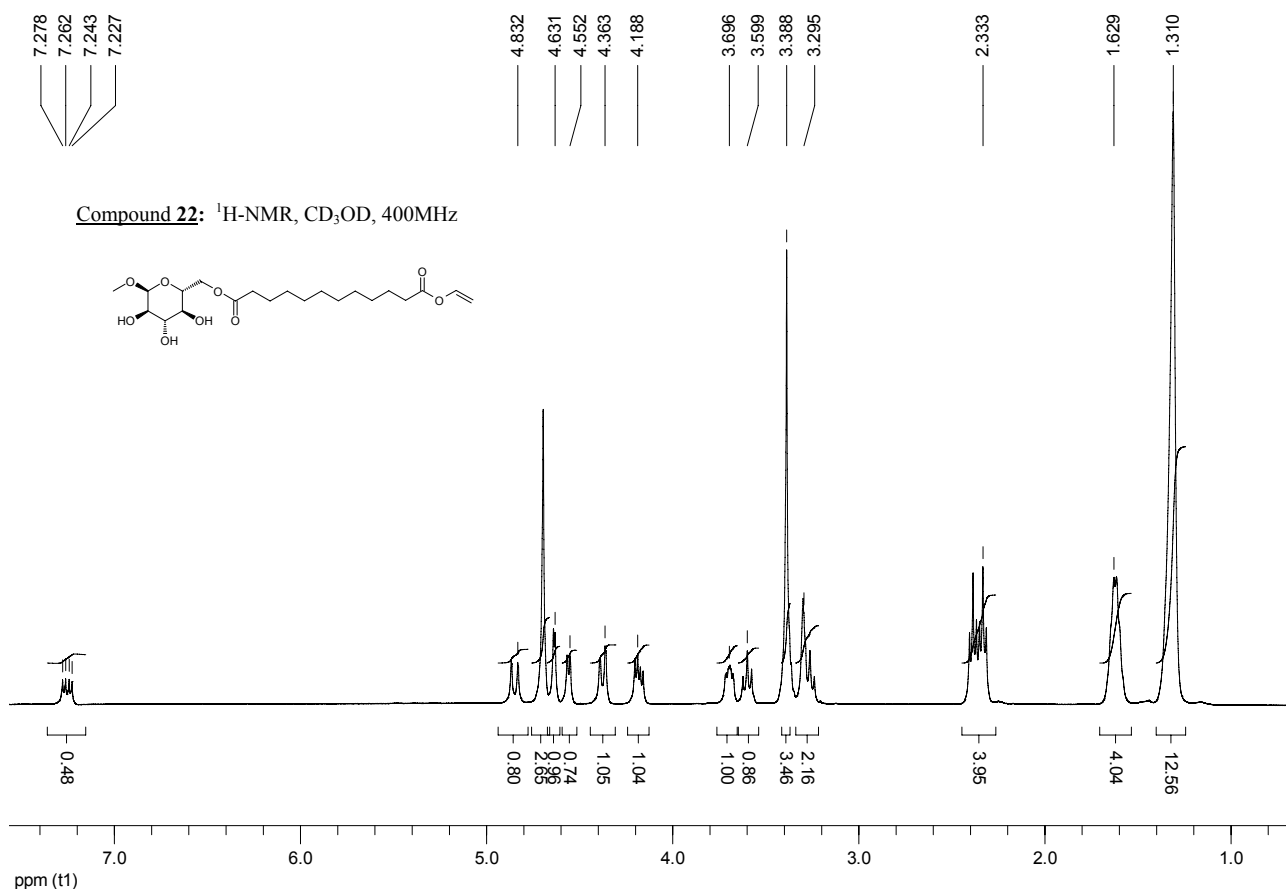
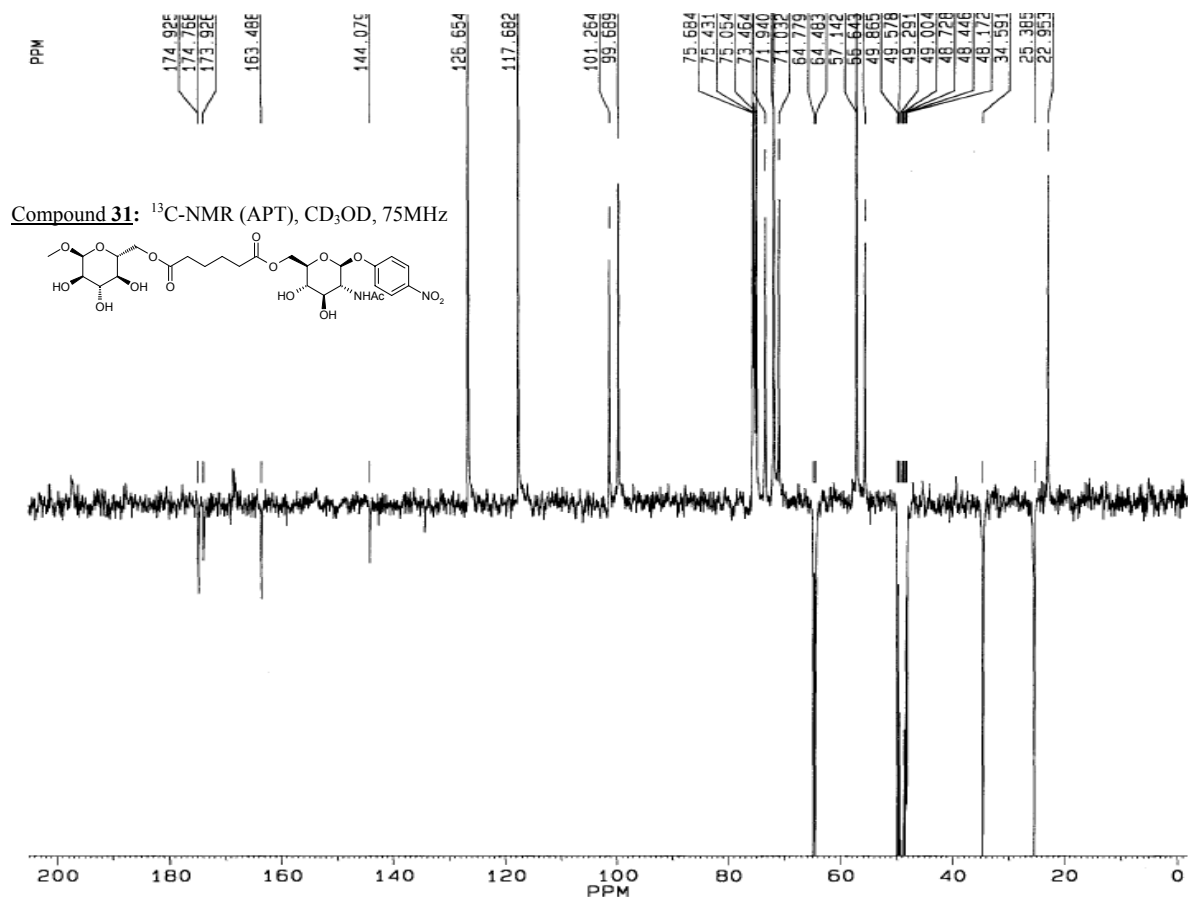


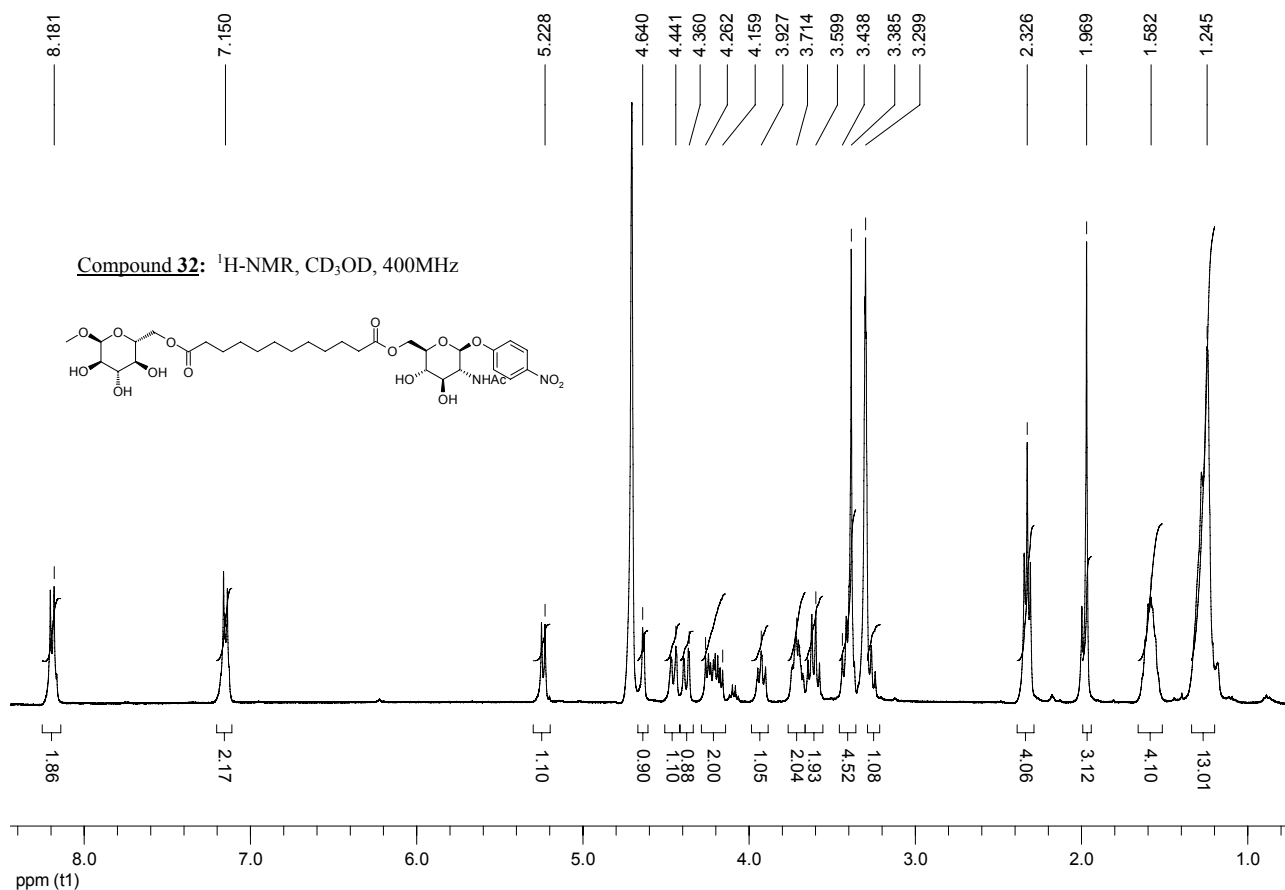
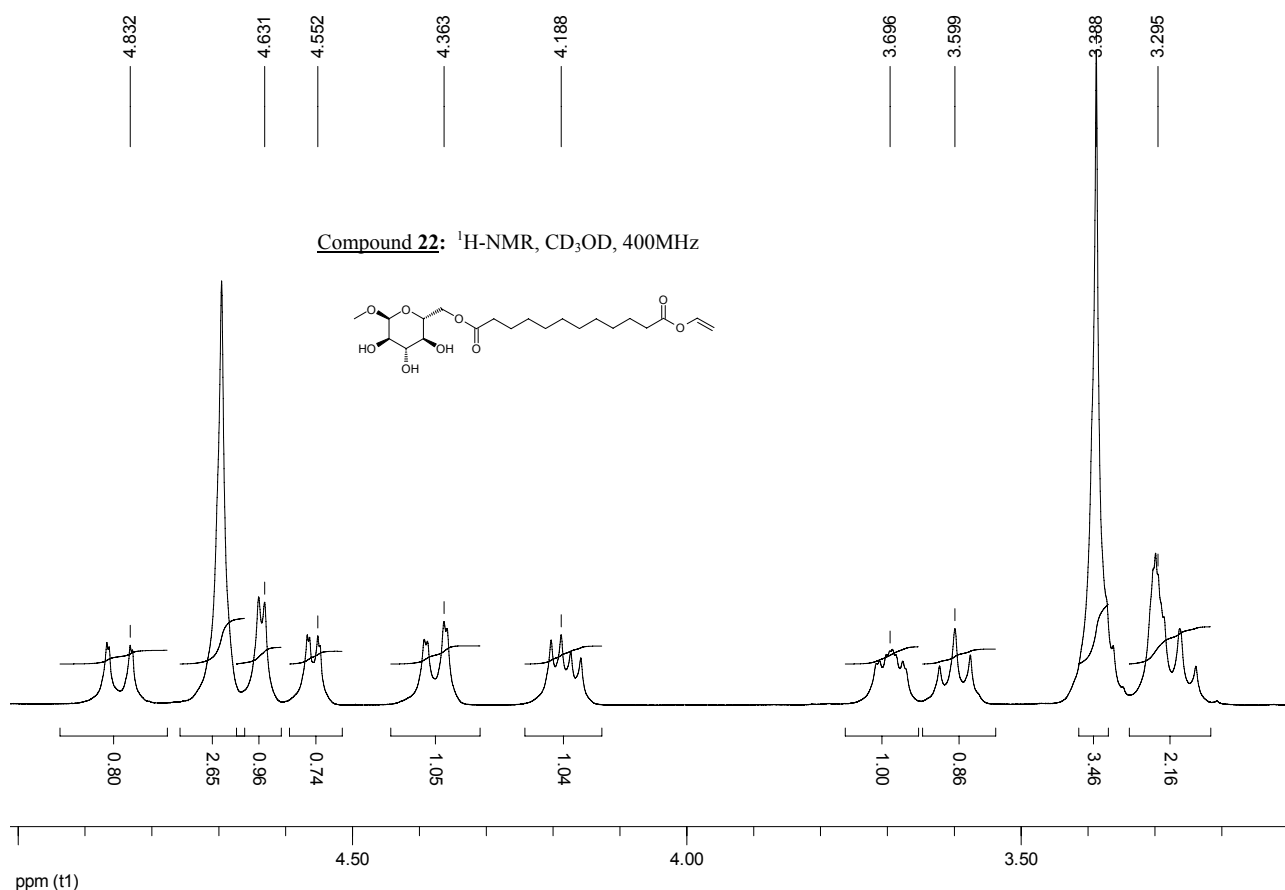
COC1OC(OC(=O)CCCC(=O)OC[C@H]2O[C@H](NC(=O)c3ccc([N+](=O)[O-])cc3)[C@H](O)[C@@H](O)[C@H]2O)[C@H](O)[C@@H](O)[C@H]1OC=CC(=O)OCCCCC(=O)O[C@@H]1O[C@H](OC(=O)c2ccc([N+](=O)[O-])cc2)[C@H](NC(=O)C)[C@@H](O)[C@H]1O

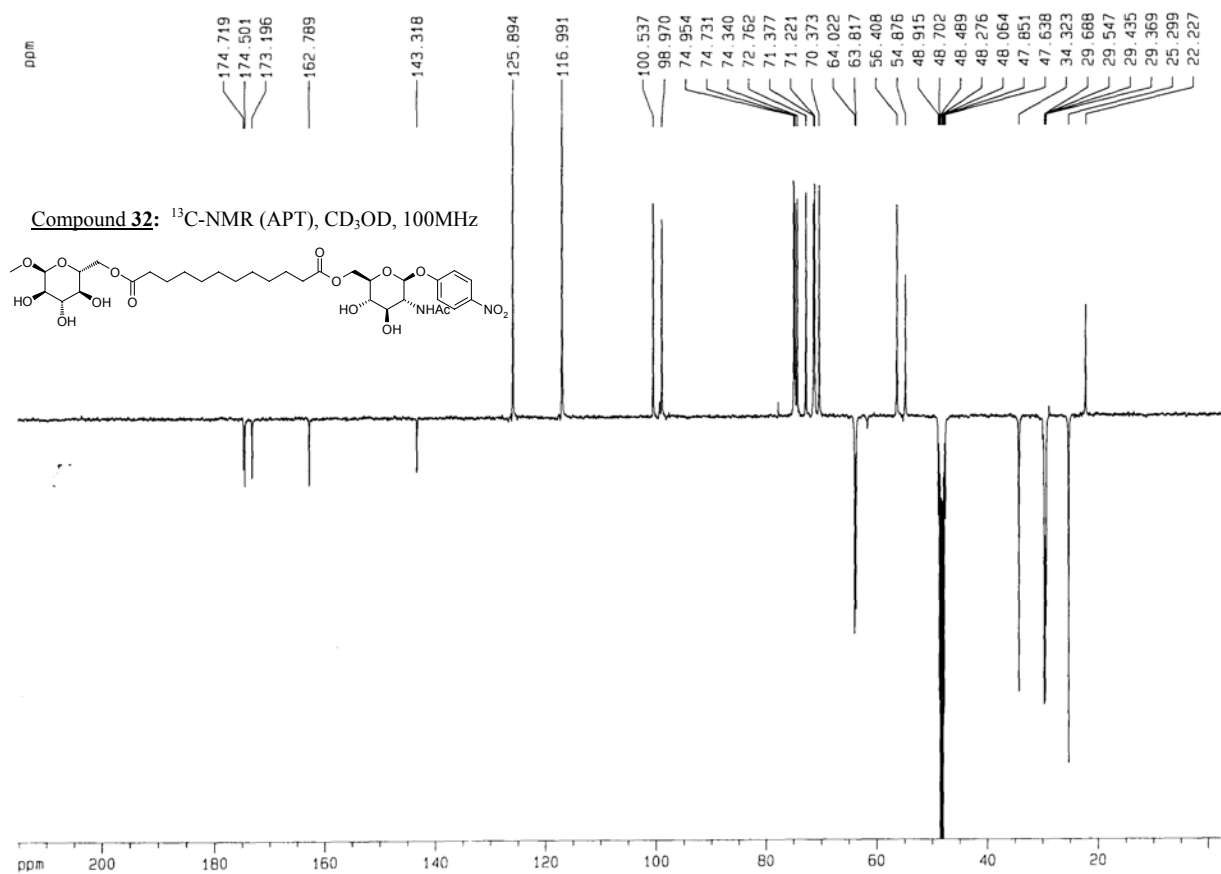
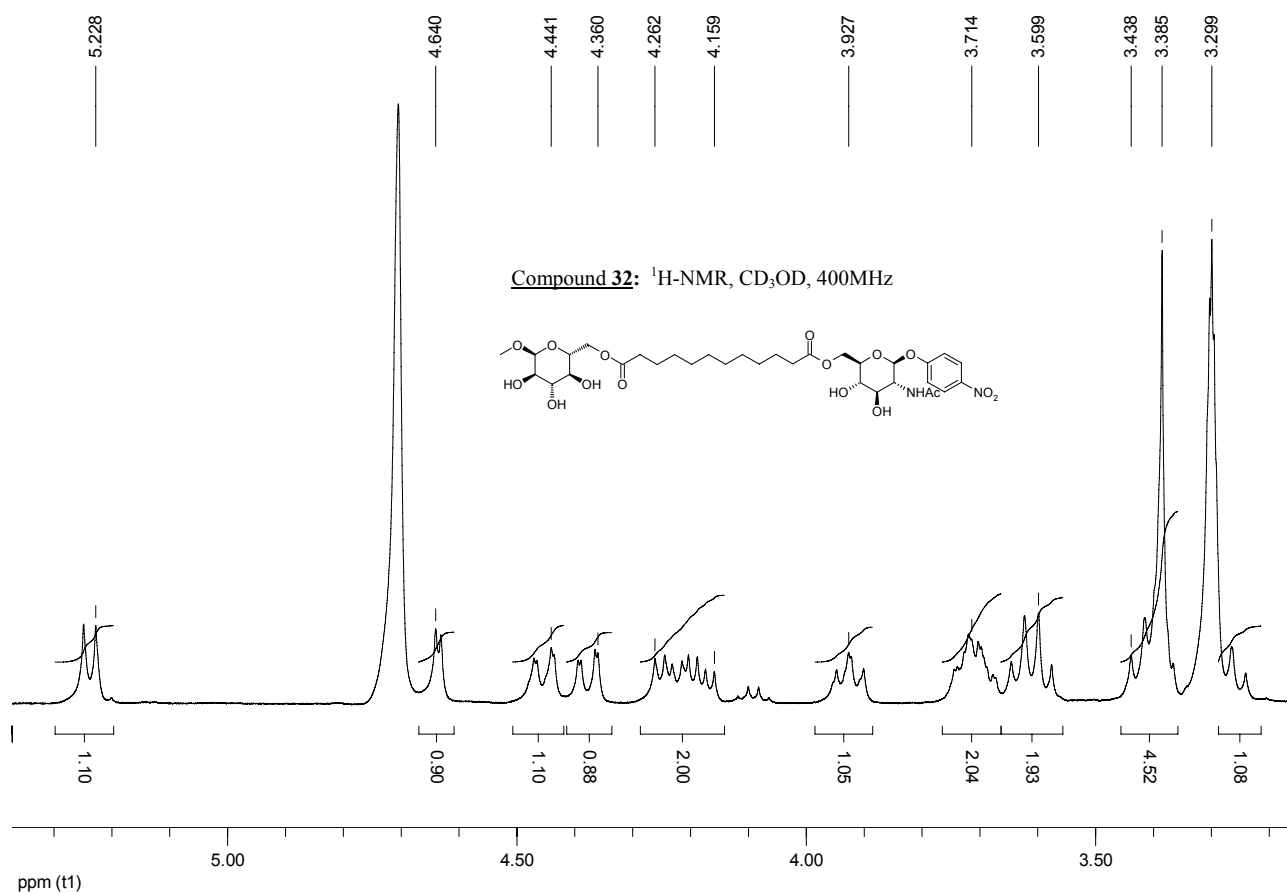


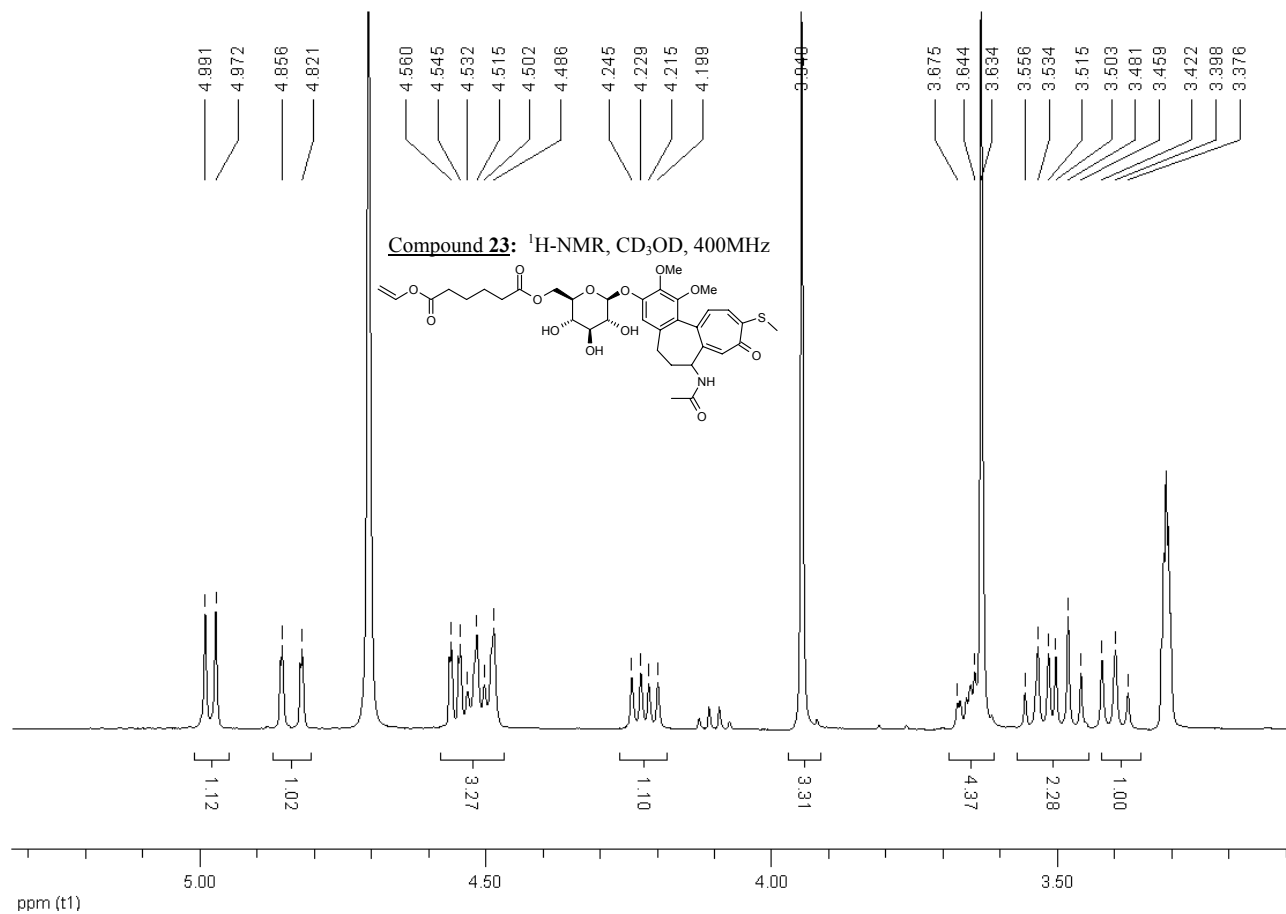
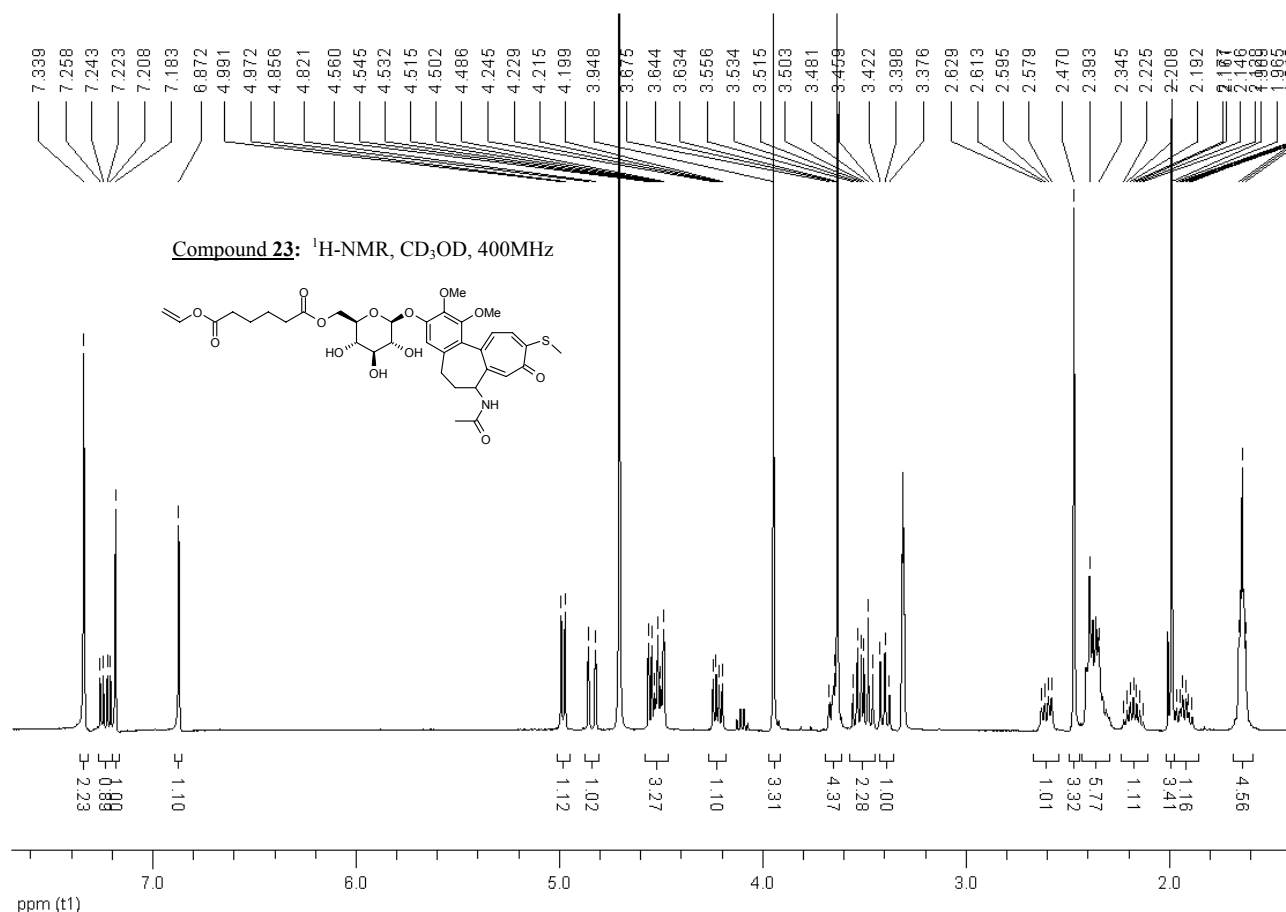
Compound 31: $^1\text{H-NMR}$, CD_3OD , 400MHz

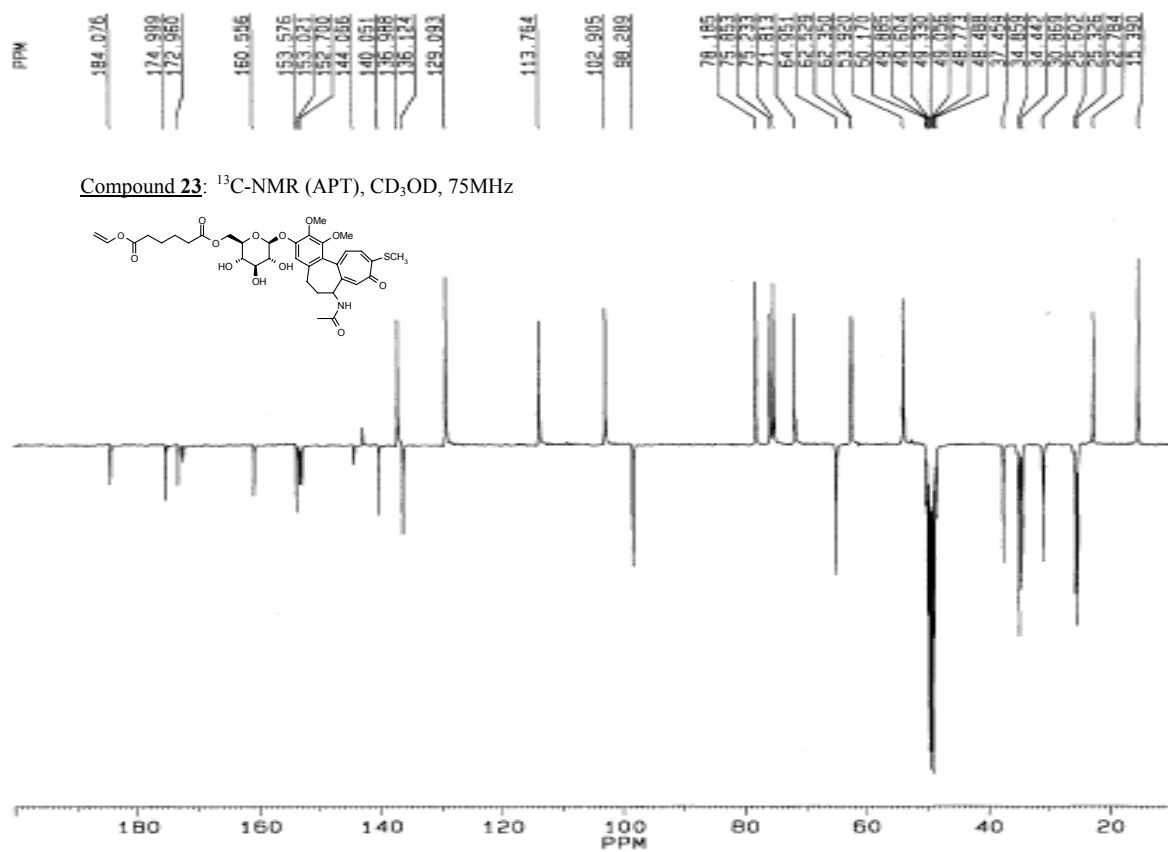


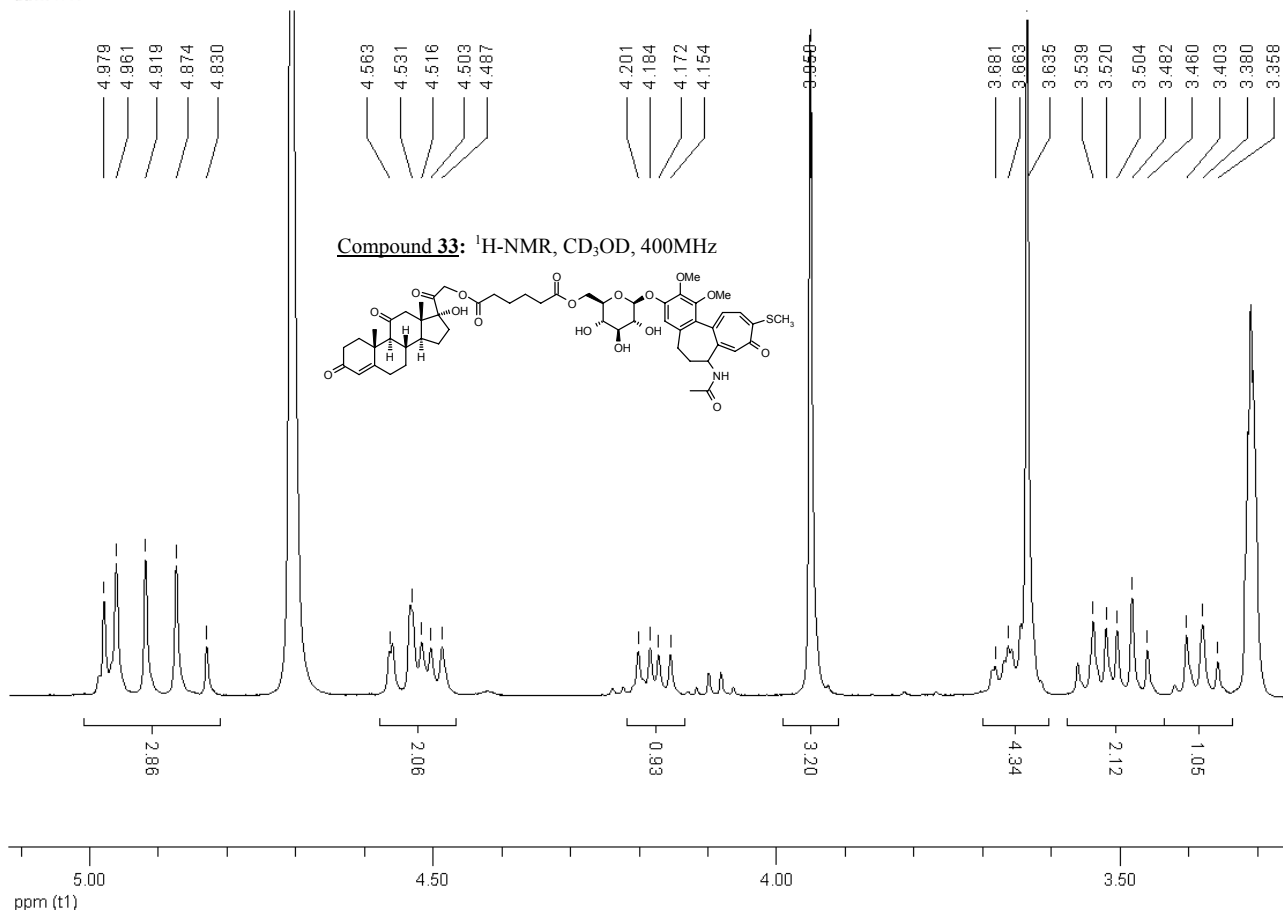
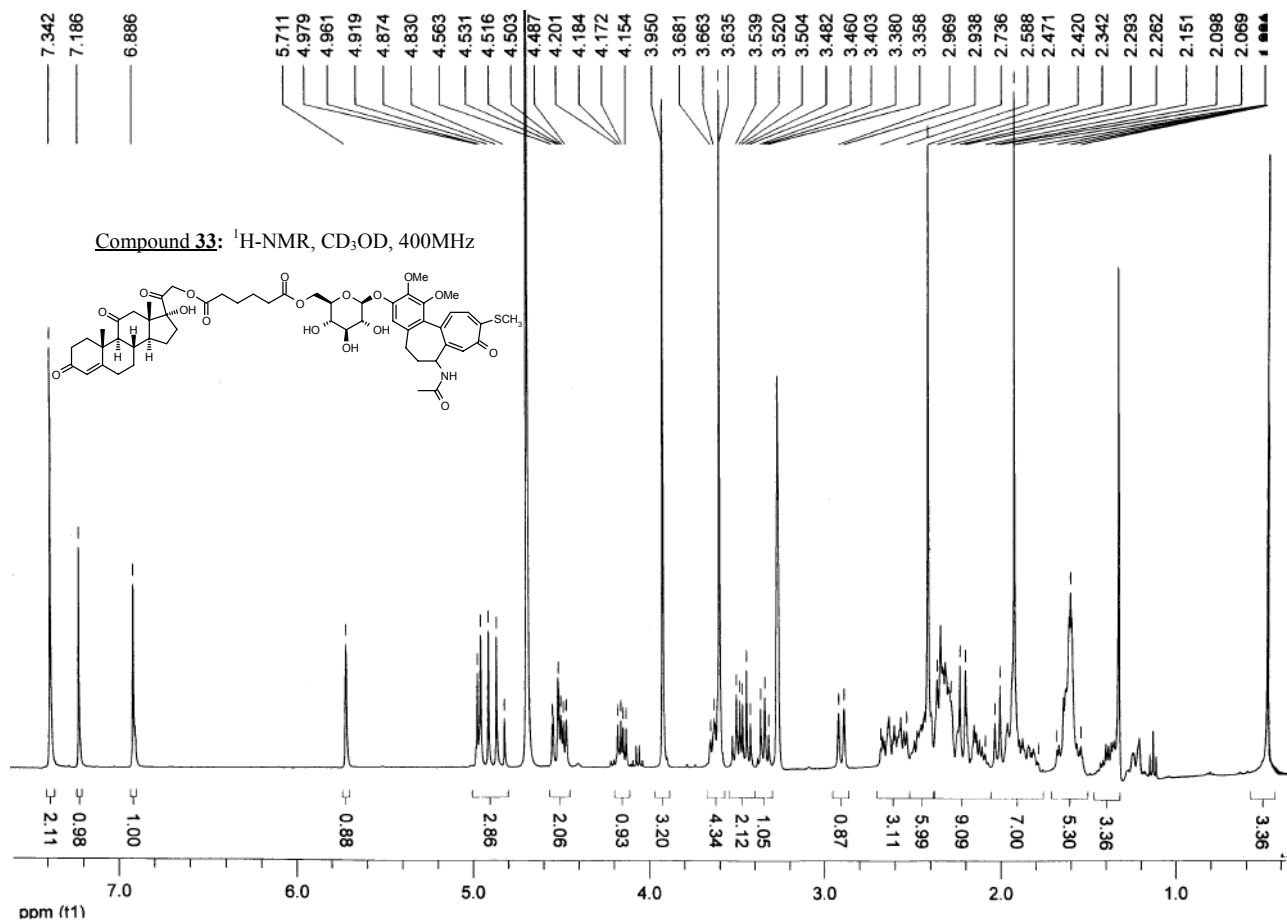


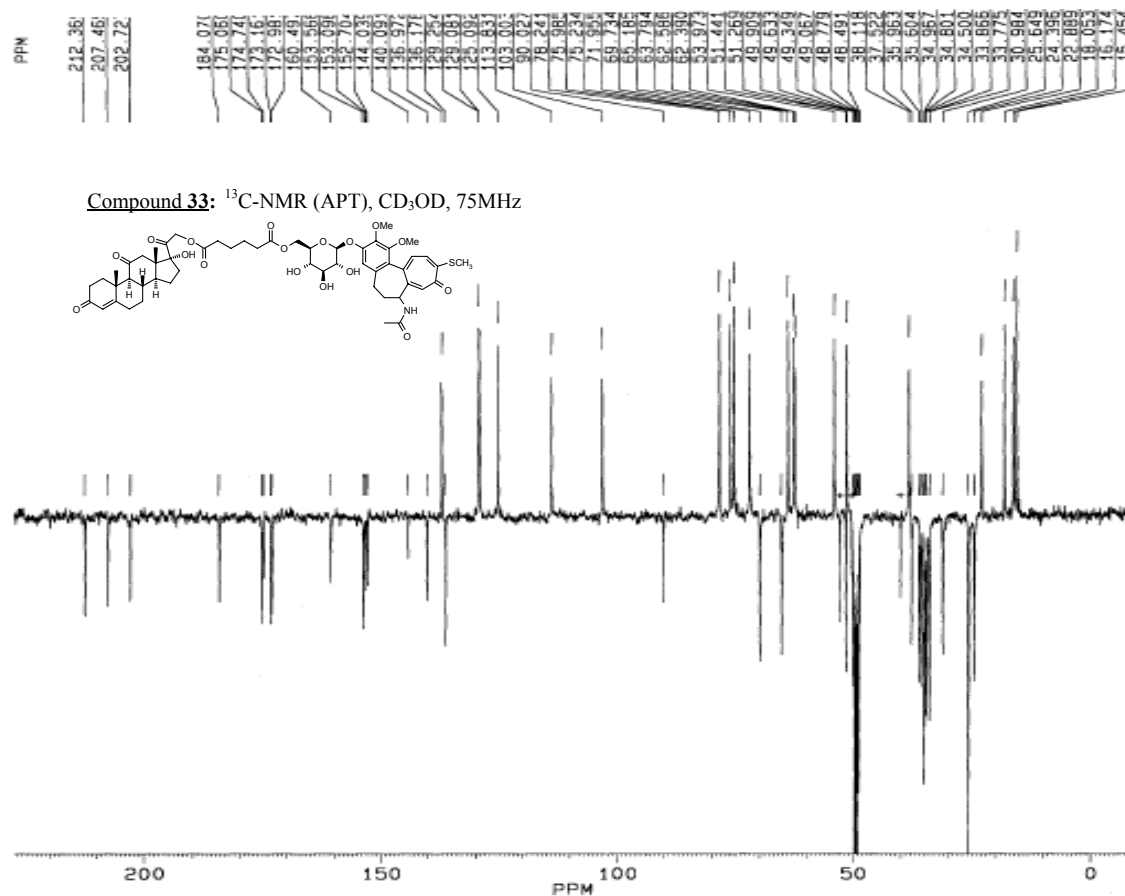
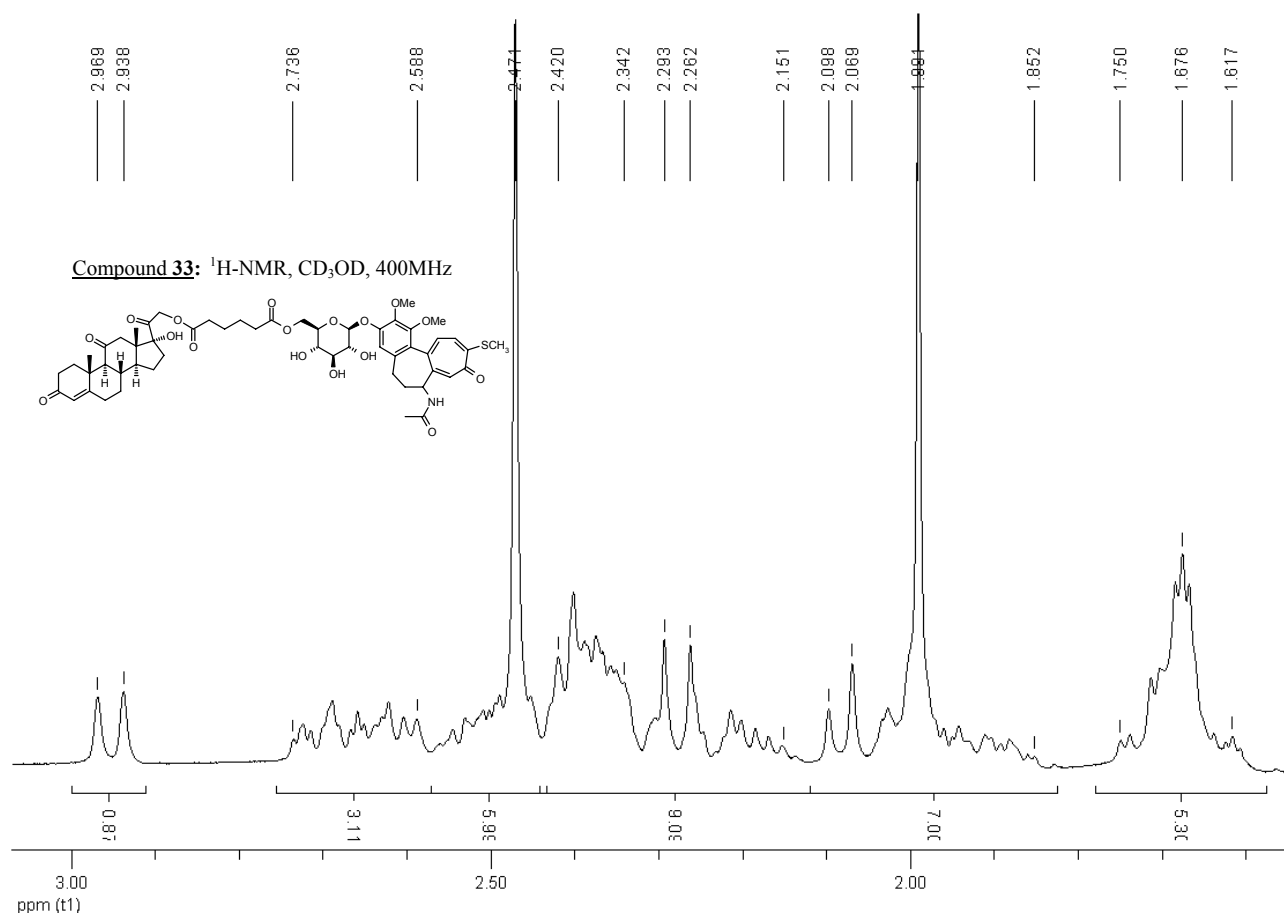




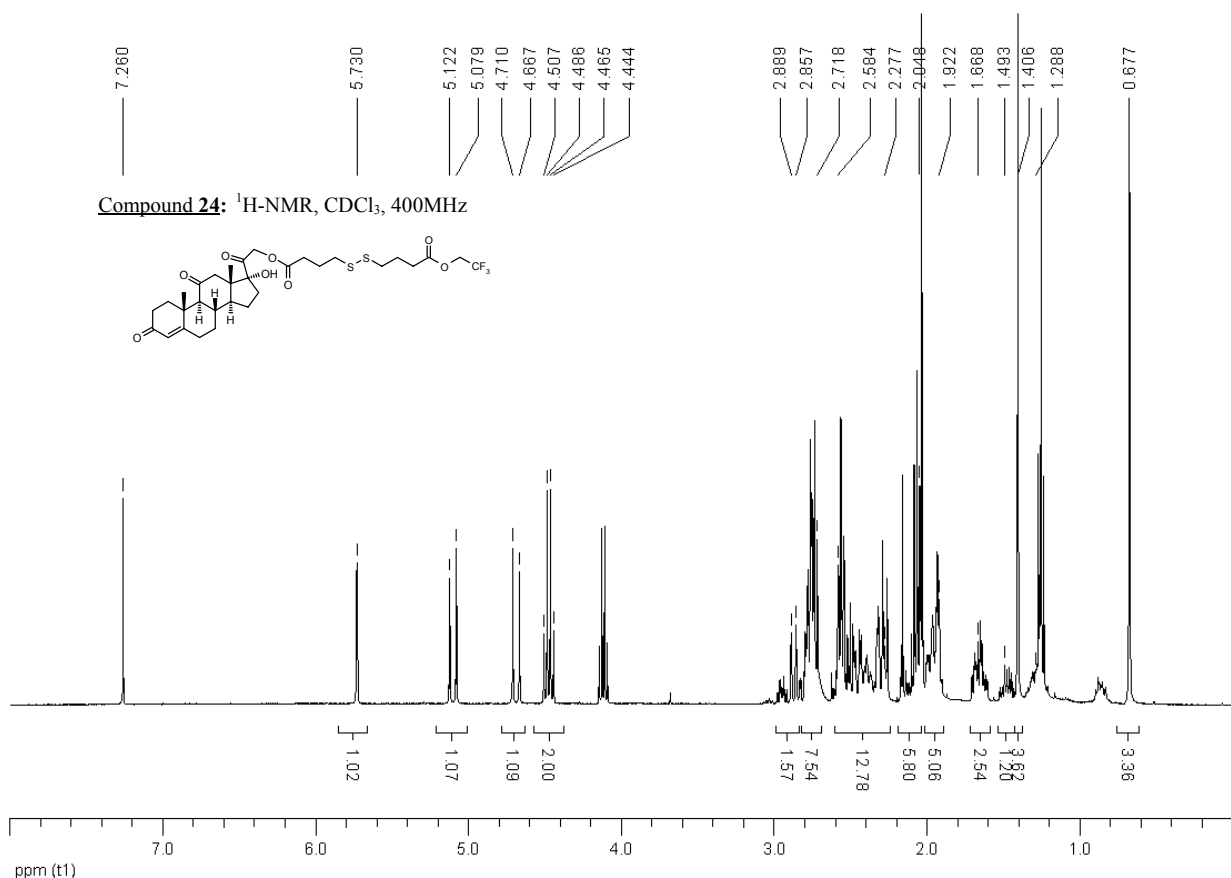
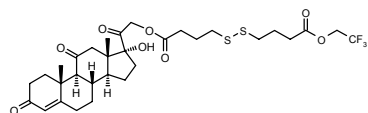








Compound 24: $^1\text{H-NMR}$, CDCl_3 , 400MHz



Compound 24: $^{13}\text{C-NMR}$, CDCl_3 , 125MHz

