

Rifamycin Biosynthetic Congeners: Isolation and Total Synthesis of Rifsaliniketal, and Total Synthesis of Salinisporamycin and Saliniketals A and B

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SUPPORTING INFORMATION

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1. General Experimental

Unless otherwise noted, commercially available materials were used without further purification.

Solvents used for moisture sensitive operations were tapped from a solvent purification system immediately before use. Reactions were performed under an atmosphere of nitrogen with magnetic stirring unless noted otherwise. Flash chromatography (FC) was performed using *E. Merck* silica gel 60 (240–400 mesh). Thin layer chromatography was performed using precoated plates purchased from *E. Merck* (silica gel 60 PF₂₅₄, 0.25 mm) that were visualized using a KMnO₄ or Ce (IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova-400*, *Varian Inova-500* or *Varian Inova-600* spectrometer at operating frequencies of 400/500/600 MHz (¹H NMR) or 100/125/150 MHz (¹³C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ 7.26 for ¹H NMR or δ 77.16 for proton decoupled ¹³C NMR), and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and br when the signal in question is broadened.

Infrared spectra were recorded on a *Perkin-Elmer* I1000 series FTIR with wavenumbers expressed in cm⁻¹ using samples prepared as thin films between salt plates. Electrospray ionization mass spectra (ESI-MS) were recorded on a Shimadzu 2010-LCMS. Optical rotations were measured at 20 °C on a Rudolph Research Analytical Autopol[®] IV polarimeter.

Procedures for the preparation of compounds **1b**, **15**, **14b**, **28-30**, **22-anti**, **23-anti**, **33**, **39-41**, and **42b-45b** along with compound characterizations and copies of NMR spectra can be found in the Supporting Information associated with: Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562-12563.

2. Isolation and Characterization of Rifsaliniketal

Collection and Phylogenetic Analysis

The marine-derived bacterium strain SNB-003, was isolated from sediment sample collected from Trinity Bay, Galveston, TX (29° 42.419'N, 94° 49.165' W). Bacterial spores were collected via stepwise centrifugation as follows: 2 g of sediment was dried over 24 h in an incubator at 35 °C and the resulting sediment added to 10 mL sH₂O containing 0.05% Tween 20. After a vigorous vortex for 10 min, the sediment was centrifuged at 18000 rpm for 25 min (4 °C) and the resulting spore pellet collected. The resuspended spore pellet (4 mL sH₂O) was plated on an acidified Gauze media, giving rise to individual colonies of SNB-003 after two weeks. Analysis of the 16S rRNA sequence of SNB-003 revealed 98% identity to *Salinospora arenicola*.

Cultivation and extraction: Bacterium SNB-003 was cultured in 120 Å~ 2.8 L Fernbach flasks each containing 1 L of a seawater based medium (10 g starch, 4 g yeast extract, 2 g peptone, 1 g CaCO₃, 40 mg

Fe₂(SO₄)₃·4H₂O, 100 mg KBr) and shaken at 200 rpm at 27 °C. After seven days of cultivation, sterilized XAD-7-HP resin (20 g/L) was added to adsorb the organic products, and the culture and resin were shaken at 200 rpm for 2 h. The resin was filtered through cheesecloth, washed with deionized water, and eluted with acetone. The acetone soluble fraction was dried *in vacuo* to yield 22.1g of extract.

Isolation of 9: The dried crude extract (22.1 g) was purified using solvent/solvent partitioning. The active methanol soluble portion (16.0 g) was further partitioned using EtOAc and H₂O (1:1 mixture). The ethyl acetate layer (2.2 g) was purified via reversed phase flash column chromatography, eluting with a step gradient of H₂O and MeOH (90:10 to 100:0) collecting 12 fractions. Fraction 12 (89.5 mg) was purified by reversed phase HPLC (Phenomenex Luna, Phenyl-Hexyl, 250 Å~10 mm, 2.5 ml/min, 5 µm, UV = 254 nm) using a gradient solvent system from 20% to 100% CH₃CN (+ 0.1% formic acid) over 20 min, collecting 11 fractions. Fraction 4 (8.7 mg) was further purified by reversed phase HPLC (Phenomenex Luna, Phenyl-Hexyl, 250 Å~10 mm, 2.5 ml/min, 5 µm, UV = 254 nm), a gradient solvent system was utilized (10% to 100% CH₃CN + 0.1% formic acid over 26 min) to give **9** (1.70 mg).

Rifsaliniketal (**9**)

Physical state: yellow solid

Optical Rotation: $[\alpha]_D^{20} = +30.4$ ($c = 0.5$, MeOH)

UV (MeOH) λ_{max} (log ϵ) 216 (3.80), 281 (3.71), 338 (3.73), 433 (3.44)

¹H NMR, ¹³C NMR, COSY, HMBC correlations: (table S1).

MS (ES): m/z 664.2 $[M + Na]^+$, 640.2 $[M - H]^-$

HR-ESIMS: m/z 642.2901 $[M + H]^+$ (C₃₄H₄₄NO₁₁, calculated 642.2908); 664.2713 $[M + Na]^+$ (C₃₄H₄₃NO₁₁Na, calculated 664.2728)

Conversion of 9 to 9a: To a solution of **9** (0.37 mg, 0.57 µmol) dissolved in dry MeOH (300 µL) was added TMSCHN₂ (0.6 µL). After stirring for 15 min, the reaction was stopped and the mixture was dried under nitrogen and was purified by reverse phase HPLC (Phenomenex Luna, C18, 150 mm Å~4.6 mm, 5 µm) isocratic conditions were utilized (58% CH₃CN + 0.1% formic acid over 15 min) followed by a gradient system from 58% to 100% CH₃CN + 0.1% formic acid over 8 min to give **9a** (0.20 mg, 53% yield). Rotamers were present in the sample in an approximate ratio of 0.6:0.4.

Rifsaliniketal methyl ester (**9a**)

¹H NMR (600 MHz, MeOH-*d*₄); signals of the major rotamer: δ 7.44 (s, 1H), 6.78 (dd, $J = 11.2$ Hz, 15.2 Hz, 1H), 6.48 (d, $J = 11.2$, 1H), 6.04 (dd, $J = 8.0$ Hz, 15.2 Hz, 1H), 4.21 (dd, $J = 6.7$ Hz, 3.4 Hz, 1H), 3.94 (d, $J = 10.5$ Hz, 1H), 3.87 (s, 3H), 3.79 (d, $J = 9.1$ Hz, 1H), 3.51 (dd, $J = 8.3$ Hz, 4.3 Hz, 1H), 2.43 (m, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.78-1.83 (m, 1H), 1.83-1.86 (m, 1H), 1.86-1.89 (m, 1H), 1.89-1.93 (m, 1H),

1.93-1.97 (m, 1H), 1.97-2.01(m, 1H), 2.01-2.05 (m, 1H), 1.39 (s, 3H), 1.01 (d, $J = 7.3$ Hz, 3H), 0.99 (d, $J = 7.3$ Hz, 3H), 0.89 (d, $J = 7.1$ Hz, 3H), 0.71 (d, $J = 6.9$ Hz, 3H)

MS (ES): m/z 678.3 $[M + Na]^+$, 654.2 $[M - H]^-$

Table S1. 1D and 2D NMR data of rifsaliniketal (**9**) in CD₃OD (600 MHz)

No.	δ_H , mult. (J in Hz)	δ_C	COSY	HMBC
1		^a		
2		141.1 qC ^b		3
3	7.66, s	117.5 CH ^b		2, 4, 10
4		183.8 qC ^b		3
5		117.5 qC ^b		12
6		162.6 qC ^b		12
7		^a		
8		^a		
9		^a		
10		128.6 qC ^b		3
11		^a		
12	2.16, s	7.9 CH ₃ ^b		5, 6
13		169.7 qC		15, 29
14		129.3 qC		16, 29
15	6.46, d (11.2)	138.0 CH	16, 29	13, 16, 17, 29
16	6.78, dd (11.2, 15.2)	127.3 CH	15, 17	14, 15, 18
17	6.02, dd (8.0, 15.2)	145.4 CH	16, 18	15, 18, 19, 30
18	2.42, ddq (9.1, 8.0, 6.9)	42.0 CH	17, 19, 30	16, 17, 19, 30
19	3.77, dd (9.1, 1.4)	75.5 CH	18, 20	17, 18, 20, 21, 30, 31
20	1.86-1.89, m	35.8 CH	19, 21, 31	21, 31
21	3.51, dd (8.3, 4.3)	77.9 CH	20, 22	19, 22
22	1.83-1.86, m	36.7 CH	21, 23, 32	21, 32
23	3.95, dd (10.6, 1.1)	74.7 CH	22, 24	21, 22, 32, 34
24	1.97-2.01, m	35.0 CH	23, 25, 34	
25	4.22, dd (6.7, 3.4)	81.3 CH	24, 26	23, 28
26a	1.89-1.93, m	24.6 CH ₂	25	24, 25, 27
26b	1.93-1.97, m			
27a	1.78-1.83, m	34.9 CH ₂		26
27b	2.01-2.05, m			
28		106.2 qC		25, 34
29	2.08, s	20.3 CH ₃	15	13, 14, 15
30	0.99, d (6.9)	16.7 CH ₃	18	17, 18, 19
31	1.01, d (7.2)	10.9 CH ₃	20	19, 20, 21
32	0.89, d (7.0)	10.1 CH ₃	22	21, 22, 23
33	1.39, s	24.0 CH ₃		27, 28
34	0.73, d (6.9)	12.6 CH ₃	24	23, 24, 25

^a Shifts not determined due to small amount of material. ^b Shifts determined from HMBC.

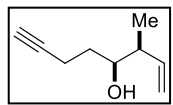
Table S2. ^1H and ^{13}C NMR for natural rifsaliniketal (600 MHz) and natural salinisporamycin (500 MHz) in CD_3OD

Rifsaliniketal			Salinisporamycin	
No.	δ_{H} , mult. (J in Hz)	δ_{C}	δ_{H} , mult. (J in Hz)	δ_{C}
1		^a		181.3
2		141.1 ^b		143.2
3	7.66, s	117.5 ^b	7.55, s	116.4
4		183.8 ^b		187.9
5		117.5 ^b	6.96, s	112.7
6		162.6 ^b		164.5
7		^a		117.8
8		^a		172.0
9		^a		106.6
10		128.6 ^b		132.5
11		^a	^c	^c
12	2.16, s	7.9 ^b	2.06	8.2
13		169.7		170.1
14		129.3		129.7
15	6.46, d (11.2)	138.0	6.46, d (11.3)	138.6
16	6.78, dd (11.2, 15.2)	127.3	6.79, dd (10.9, 15.0)	127.6
17	6.02, dd (8.0, 15.2)	145.4	6.03, dd (8.3, 15.0)	146.0
18	2.42, ddq (9.1, 8.0, 6.9)	42.0	2.43, m (8.3, 7.5)	42.4
19	3.77, dd (9.1, 1.4)	75.5	3.78, dd (9.8, 1.9)	75.8
20	1.86-1.89, m	35.8	1.83, m (6.8, 4.5, 1.9)	36.4
21	3.51, dd (8.3, 4.3)	77.9	3.50, dd (8.3, 4.5)	78.4
22	1.83-1.86, m	36.7	1.82, br dq (8.3, 6.8, 1.5)	37.1
23	3.95, dd (10.6, 1.1)	74.7	3.94, br d (10.5, 1.5)	75.2
24	1.97-2.01, m	35.0	1.97, br dq (10.5, 6.8, 3.8)	35.4
25	4.22, dd (6.7, 3.4)	81.3	4.20, br d (6.8, 3.8)	81.8
26a	1.89-1.93, m	24.6	1.93, m	24.1
26b	1.93-1.97, m		1.88, m	
27a	1.78-1.83, m	34.9	1.80, m	35.4
27b	2.01-2.05, m		2.01-2.05, m	
28		106.2		106.6
29	2.08, s	20.3	2.07, m (1.1)	20.7
30	0.99, d (6.9)	16.7	0.99, d (6.8)	17.1
31	1.01, d (7.2)	10.9	1.00, d (6.8)	11.3
32	0.89, d (7.0)	10.1	0.88, d (6.8)	10.5
33	1.39, s	24.0	1.39, s	24.4
34	0.73, d (6.9)	12.6	0.71, d (6.8)	13.0

^a Shifts not determined due to small amount of material. ^b Shifts determined from HMBC. ^c Carboxylate absent in salinisporamycin.

3. Experimental Procedures

(3*S*,4*S*)-3-Methyloct-1-en-7-yn-4-ol (**17**)



To a solution of pent-4-yn-1-ol (1.68 g, 20 mmol) in CH_2Cl_2 (160 mL) was added NaHCO_3 (3.36 g, 40 mmol) and Dess-Martin periodinane (17.68 g, 40 mmol) in one portion. The resulting mixture was allowed to stir for 2 h at RT. After removing the solvent, the residue was resolved in EtOAc (150 mL) and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) and saturated aqueous NaHCO_3 (50 mL) were added. After stirring for 3 h, the biphasic solution was separated. The aqueous phase was washed with ether (100 mL \times 2) and the combined organic layers were washed with brine (100 mL), dried over MgSO_4 , filtered, and concentrated in vacuum to provide the desired aldehyde as a colorless oil (~1.54 g, 94%, crude).

Potassium *tert*-butoxide (2.9 g, 26.0 mmol, 2.0 equiv) was heated at 80 °C under high vacuum overnight. Then, THF (10 mL) was added and the suspension was cooled to –78 °C. *Cis*-2-butene (3.3 mL) was then added via cannula, followed by *n*-BuLi (1.6 M in hexane, 17.0 mL, 2.1 equiv) dropwise to produce an orange suspension. After 10 min at –45 °C, the reaction mixture was cooled to –78 °C, followed by the dropwise addition (15 min) of a solution of (+)- Ipc_2BOMe (8.54 g, 27 mmol, 2.05 equiv) in THF (30 mL). After an additional 30 min at –78 °C, the colorless slurry was treated with $\text{BF}_3\cdot\text{OEt}_2$ (3.7 mL, 29 mmol, 2.1 equiv; added dropwise over 10 min), followed by a dropwise addition of a solution of the above-prepared pent-4-ynal (1.07 g, 13.0 mmol) in THF (5 mL and 5 mL rinse). After an additional 3 h at –78 °C, the pale yellow slurry was charged with 3N aq. NaOH (20 mL) and allowed to slowly warm to RT. During this time, H_2O_2 (30% aq., 6 mL) was added in 1 mL portions to control gas evolution and the resulting mixture was heated at reflux for 1 h. The biphasic solution was then cooled to ambient temperature and diluted with water (30 mL). The aqueous phase was then washed with ether (30 mL \times 2) and the combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated in vacuum. After FC (silica gel, 0 \rightarrow 10%, EtOAc/hexanes), homoallylic alcohol **17** (1.56 g, 11.3 mmol, 87% yield; >20:1 dr) was obtained.

Physical state: colorless oil.

TLC: R_f = 0.50 (3:1, hexanes/EtOAc)

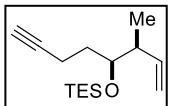
Optical Rotation: $[\alpha]_D^{20} = -22.3$ (c = 2.0, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 5.72-5.82 (m, 1H), 5.06-5.13 (m, 2H), 3.56-3.68 (m, 1H), 2.24-2.39 (m, 3H), 1.91 (t, J = 2.6 Hz, 1H), 1.70-1.80 (m, 1H), 1.48-1.62 (m, 2H), 1.04 (d, J = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 140.6, 115.9, 84.5, 73.7, 68.8, 43.8, 32.7, 15.5, 14.6

MS (ES) calculated for $\text{C}_9\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$ 139.1, found 139.1

Triethyl(((3*S*,4*S*)-3-methyloct-1-en-7-yn-4-yl)oxy)silane (**S1**)



To a solution of homoallylic alcohol **17** (1.38 g, 10 mmol) in CH₂Cl₂ (25 mL) was added triethylsilyl chloride (3.01 g, 20 mmol), imidazole (2.04 g, 30 mmol) and DMAP (610 mg, 5 mmol) at 0 °C. After stirring for 2 hours at RT, saturated aqueous NaHCO₃ (10 mL) was added. The biphasic solution was separated and the aqueous phase was washed with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. After FC (silica gel, 0→2%, EtOAc/hexanes), the desired silyl ether **S1** (2.4 g, 9.5 mmol, 95% yield) was obtained.

Physical state: colorless oil

TLC: *R_f* = 0.4 (20:1, hexanes/EtOAc)

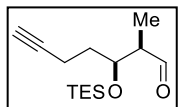
Optical rotation: $[\alpha]_D^{20} = -19.5$ (*c* = 1.0, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 5.76-5.83 (m, 1H), 4.90-5.06 (m, 2H), 3.62-3.67 (m, 1H), 2.15-2.35 (m, 3H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.50-1.70 (m, 2H), 0.95-0.97 (m, 9H), 0.61 (q, *J* = 8.0 Hz, 6H)

¹³C NMR (100 MHz, CDCl₃) δ 140.7, 114.6, 84.8, 74.8, 68.4, 43.2, 32.5, 15.4, 14.7, 7.2, 5.3

MS (ES) calculated for C₁₅H₂₉OSi [*M* + *H*]⁺ 253.2, found 253.2

(2*R*,3*S*)-2-Methyl-3-((triethylsilyl)oxy)hept-6-ynal (**13**)



To a solution of the above-prepared alkene **S1** (2.016 g, 8.0 mmol) in acetone/H₂O (40 mL, 10:1) was added OsO₄ (0.4 mmol, 4.0 mL, 0.1 M in *t*-BuOH) and NMO (1.84 g, 16.0 mmol) and the mixture was stirred for 2 hours at RT. After removal of the solvents *in vacuo*, the crude residue was dissolved in CH₂Cl₂ (40 mL), and Pb(OAc)₄ (5.316 g, 12 mmol, 1.5 eq) and pyridine (3.0 eq) were added at 0 °C. After stirring for overnight at RT, aq. CuSO₄ (20 mL) was added. The biphasic solution was then separated. The aqueous phase was washed with ethyl acetate (10 mL × 3) and the combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. After FC (silica gel, 0→10%, EtOAc/hexanes), the desired product **13** (1.73 g, 6.8 mmol, 85% yield) was obtained.

Physical state: pale yellow oil

TLC: *R_f* = 0.35 (2:1, hexanes/EtOAc)

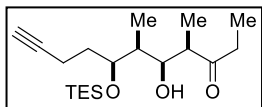
Optical rotation: $[\alpha]_D^{20} = -24.8$ (*c* = 1.0, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 9.81 (s, 1H), 4.26 (ddd, *J* = 7.5, 5.5, 3.8 Hz, 1H), 2.50 (qd, *J* = 7.0, 3.5 Hz, 1H), 2.24 (td, *J* = 7.1, 2.7 Hz, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.58-1.76 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 8.2 Hz, 6H)

¹³C NMR (100 MHz, CDCl₃) δ 204.9, 83.8, 70.9, 69.1, 51.4, 32.9, 14.9, 8.0, 6.9, 5.0

MS (ES) calculated for C₁₄H₂₇O₂Si [*M* + *H*]⁺ 255.2, found 255.2

(4*R*,5*S*,6*S*,7*S*)-5-Hydroxy-4, 6-dimethyl-7((triethylsilyl)oxy)undec-10-yn-3-one (18-*syn*)



TiCl₄ (1.0 M in CH₂Cl₂; 1.2 mL) and Bu₃N (185 mg, 1.4 mmol) were successively added to a stirred solution of 3-pentanone (134 mg, 1.0 mmol) in CH₂Cl₂ (2.0 mL)

at -78 °C under an Ar atmosphere. After 30 min, aldehyde **13** (305 mg, 1.2 mmol) was added to the mixture, which was stirred at -78 °C for 2 h. The reaction mixture was quenched with water (2 mL) and was extracted ether (5 mL × 3). The organic phase was washed with water, brine, dried with MgSO₄ and concentrated *in vacuo*. The obtained crude oil was purified by FC (silica gel, 0→10%, EtOAc/hexanes) to give the aldol product **18-*syn*** (192 mg, 53%).

Note: This experiment was repeated two times with yields varying between 43-53%. When two equivalents of titanium enolate were used, the yields varied between 37-46% yield. In all cases, the ratio of **18-*syn*** versus other diastereomers was > 10:1 (measured from crude NMR). Varying amounts (TLC) of compound **19** were observed during all of the above experiments. In one case, we obtained an analytically pure sample for characterization.

Characterization data for 18-*syn*:

Physical state: pale-yellow oil

TLC: *R_f* = 0.30 (5:1, hexanes/EtOAc)

Optical rotation: $[\alpha]_D^{20} = -24.2$ (*c* = 1.03 in CDCl₃)

¹H NMR (400 MHz, CDCl₃) δ 3.87-3.97 (m, 2H), 3.08 (br s, 1H), 2.82 (dq, *J* = 7.0, 7.0 Hz, 1H), 2.36-2.62 (m, 2H), 2.06-2.18 (m, 2H), 1.95 (br s, 1H), 1.63-1.76 (m, 2H), 1.50-1.58 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.62 (q, *J* = 7.9 Hz, 6H)

¹³C NMR (100 MHz, CDCl₃) δ 215.8, 83.5, 75.3, 74.5, 69.1, 49.2, 38.2, 35.4, 32.7, 15.1, 12.7, 7.9, 7.6, 7.1, 5.5

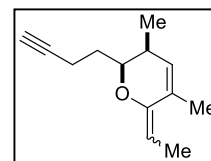
MS (ES) calculated for C₁₉H₃₆O₃SiNa [*M* + Na]⁺ 363.2, found 363.2

Characterization data for (2*S*,3*S*)-2-(But-3-yn-1-yl)-6-ethylidene-3,5-dimethyl-3,6-dihydro-2H-pyran (19**):**

Physical state: pale yellow oil

TLC: *R_f* = 0.80 (5:1, hexanes/EtOAc)

Optical rotation: $[\alpha]_D^{20} = -11.2$ (*c* = 0.25 in CH₂Cl₂)



¹H NMR (400 MHz, CDCl₃) δ 5.58 (d, *J* = 5.7 Hz, 1H), 4.69 (q, *J* = 6.9 Hz, 1H), 3.91 (dt, *J* = 10.1, 3.4 Hz, 1H), 2.26-2.50 (m, 2H), 2.17-2.25 (m, 1H), 1.94 (t, *J* = 2.8 Hz, 1H), 1.80-1.87 (m, 1H), 1.74 (s, 3H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.52-1.65 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H)

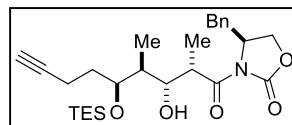
MS (ES) calculated for C₁₃H₁₈ONa [*M* + Na]⁺ 213.1, found 213.2

Aldol coupling of aldehyde **13 and oxazolidinone **20**:** TiCl₄ (1 M in CH₂Cl₂, 0.671 mL) was added dropwise to a solution of N-propionyl-4-benzyl-oxazolidinone **20** (142 mg, 0.61 mmol) in CH₂Cl₂ (3 mL) at 0 °C. After stirring for 5 min, (–)-sparteine (350 µL, 1.53 mmol) was added and stirring was continued for 20 min. A solution of aldehyde **13** (170 mg, 0.67 mmol) in CH₂Cl₂ (3 mL) was added and stirred for 1 h at 0 °C. The mixture was quenched with saturated aqueous NH₄Cl (10 mL) and CH₂Cl₂ (10 mL). The aqueous phase was extracted with EtOAc (10 mL × 3). The combined organic phase was dried over MgSO₄. After concentration *in vacuo*, the crude residue was purified by FC (silica gel, 0→10%, EtOAc/hexanes) to give compound **21-anti** (100 mg, 34%) and **21-syn** (120 mg, 39%).

Characterization data for (S)-4-Benzyl-3-((2S,3R,4S,5S)-3-hydroxy-2,4-dimethyl-5-((triethylsilyl)-oxy)non-8-ynoyl)oxazolidin-2-one (21-anti**):**

Physical state: pale yellow solid

TLC: *R_f* = 0.50 (3:1, hexanes/EtOAc)



Optical rotation: $[\alpha]_D^{20} = +35.5$ (*c* = 0.8 in CDCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.13-7.37 (m, 5H), 4.67 (dtd, *J* = 10.1, 7.5, 2.8 Hz, 1H), 4.34 (s, 1H), 4.13-4.25 (m, 2H), 3.98-4.05 (m, 2H), 3.86 (qd, *J* = 6.9, 2.4 Hz, 1H), 3.35 (dd, *J* = 13.3, 2.8 Hz, 1H), 2.75 (dd, *J* = 13.3, 10.1 Hz, 1H), 2.25-2.38 (m, 1H), 2.08-2.23 (m, 1H), 1.95 (br s, 1H), 1.80-1.87 (m, 1H), 1.65-1.76 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.85 (d, *J* = 6.0 Hz, 3H), 0.64 (q, *J* = 8.0 Hz, 6H)

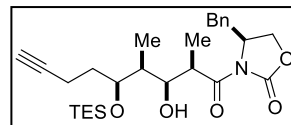
¹³C NMR (100 MHz, CDCl₃) δ 175.2, 153.5, 135.7, 129.6, 129.1, 127.5, 84.0, 75.6, 73.3, 69.1, 66.4, 56.1, 41.0, 39.9, 37.9, 30.8, 15.6, 12.5, 8.6, 7.0, 5.1

MS (ES) calculated for C₂₇H₄₂NO₅Si [*M* + *H*]⁺ 488.3, found 488.3

Characterization data for (S)-4-Benzyl-3-((2R,3S,4S,5S)-3-hydroxy-2,4-dimethyl-5-((triethylsilyl)-oxy)non-8-ynoyl)-oxazolidin-2-one (21-syn**):**

Physical state: pale yellow solid

TLC: *R_f* = 0.35 (3:1, hexanes:EtOAc)



Optical rotation: $[\alpha]_D^{20} = -27.8$ (*c* = 1.0 in CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 7.12-7.37 (m, 5H), 4.65 (ddt, *J* = 10.3, 6.8, 3.2 Hz, 1H), 3.93-4.23 (m, 5H), 3.32 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.19 (s, 1H), 2.66 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.10-2.23 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.74 (dt, *J* = 7.1, 7.0 Hz, 2H), 1.64-1.70 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.94 (d, *J* = 8.0 Hz, 3H), 0.63 (q, *J* = 7.9 Hz, 6H)

¹³C NMR (100 MHz, CDCl₃) δ 177.3, 153.0, 135.4, 129.5, 129.2, 127.6, 83.4, 74.9, 74.6, 69.2, 66.1, 55.5, 41.0, 38.4, 38.2, 32.7, 15.0, 13.5, 7.6, 7.1, 5.4

MS (ES) calculated for C₂₇H₄₂NO₅Si [*M* + *H*]⁺ 488.3, found 488.3

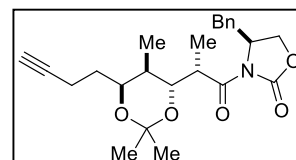
Acetonides **23-anti or **23-syn**:** PPTS (10 mol%) was added to a solution of aldol adduct **21-anti** or **21-syn** in EtOH (0.03 M) and stirred at room temperature until TLC analysis indicated the reaction was complete. After concentration *in vacuo*, the crude residue was dissolved in acetone/2,2-dimethoxypropane (4:1, 0.03 M) and PPTS (6 mol%) was added. This mixture was stirred at room temperature for 30 min; quenched by the addition of Et₃N (1 equiv.), then concentrated *in vacuo*. The crude was purified by FC (silica gel, 0→20%, EtOAc/hexanes) to give compound **23-anti** or **23-syn**.

Characterization data for (S)-4-benzyl-3-((S)-2-((4R,5R,6S)-6-(but-3-yn-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoyl)oxazolidin-2-one (23-anti**):**

Physical state: yellow solid

TLC: R_f = 0.55 (3:1, hexanes/EtOAc)

Optical rotation: $[\alpha]_D^{20}$ = 46.2 (c = 1.43 in CH₂Cl₂)



¹H NMR (400 MHz, CDCl₃) δ : 7.34-7.18 (m, 5H), 4.62 (dq, J = 6.4, 3.2, 1H), 4.18-4.11 (m, 2H), 4.04-3.98 (m, 1H), 3.92 (dt, J = 10.4, 3.2, 1H), 3.60 (dd, J = 7.2, 4.8, 1H), 3.33 (dd, J = 13.2, 3.2, 1H), 2.76 (dd, J = 13.2, 9.6, 1H), 2.34-2.17 (m, 2H), 1.93 (br s, 1H), 1.91-1.84 (m, 1H), 1.68-1.61 (m, 1H), 1.53-1.43 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.26 (d, J = 6.8, 3H), 0.89 (d, J = 6.8, 3H)

¹³C NMR (75 MHz, CDCl₃) δ 175.0, 153.4, 135.5, 129.7, 129.1, 127.5, **100.7**, 84.2, 75.4, 68.7, 68.0, 66.3, 56.1, 41.2, 38.0, 37.0, 30.0, **25.2**, **23.9**, 15.3, 12.3, 11.8; IR (film, cm⁻¹): 3290, 2936, 1781, 1698, 1382, 1210

MS (ES) calculated for C₂₄H₃₂NO₅ [$M + H$]⁺ 414.2; found 414.2

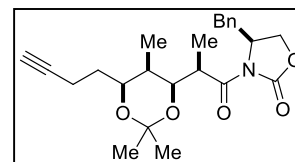
Note: The spectra of this acetonide are identical to the spectra of the acetonide of **22-anti** synthesized from **30** (Scheme 5B). [Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562-12563]

Characterization data for (S)-4-benzyl-3-((R)-2-((4S,5R,6S)-6-(but-3-yn-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoyl)oxazolidin-2-one (23-syn**):**

Physical state: yellow solid

TLC: R_f = 0.60 (3:1, hexanes/EtOAc)

Optical rotation: $[\alpha]_D^{20}$ = -20.2 (c = 0.85 in CH₂Cl₂)



¹H NMR (400 MHz, CDCl₃) δ 7.18-7.36 (m, 5H), 4.62-4.70 (m, 1H), 4.13-4.25 (m, 3H), 3.94-4.10 (m, 2H), 3.27 (dd, J = 13.3, 3.6 Hz, 1H), 2.71 (dd, J = 13.4, 9.6 Hz, 1H), 2.14-2.32 (m, 2H), 1.90 (br s, 1H), 1.69-1.80 (m, 1H), 1.40-1.53 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.25 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 13.2 Hz, 3H)

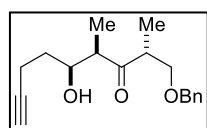
¹³C NMR (100 MHz, CDCl₃) δ 175.5, 152.9, 135.2, 129.6, 129.2, 127.6, **99.6**, 84.2, 75.2, 71.3, 68.6, 66.1, 55.4, 39.9, 38.4, 33.4, 31.8, **30.1**, **19.8**, 15.9, 15.0, 6.0

MS (ES) calculated for C₂₄H₃₂NO₅ [$M + H$]⁺ 414.2, found 414.3

Preparation of ethyl ketone 18-*syn* from 21-*syn*: To a stirred solution of *syn* aldol product **21-*syn*** (25 mg, 0.05 mmol) in CH₂Cl₂ (3 mL) at –78 °C was added EtMgBr (2 M in THF, 3.5 equiv, 0.175 mmol, 87.5 µL). After stirring at that temperature for 6 h, the reaction was quenched by the addition of water, followed by extraction with CH₂Cl₂, washing the organic phase with aqueous saturated NH₄Cl, and drying over MgSO₄. After removal of the solvent, the residue was purified by FC (silica gel, 2%→20%, EtOAc/hexanes) to yield ethyl ketone **18-*syn*** (4.7 mg, 33%) as a pale yellow oil. The spectra of this ethyl ketone are identical to the spectra of ethyl ketone **18-*syn*** synthesized from **13** (Scheme 3).

[¹H-NMR analysis of the crude mixture indicated that the remainder of the mass balance was primarily the diethyl carbinol from over-addition. We have not attempted to purify or characterize this byproduct].

(2*R*,4*R*,5*S*)-1-(Benzyloxy)-5-hydroxy-2,4-dimethylnon-8-yn-3-one (26)



To a solution of (+)-diisopinocampheylboron triflate (5.1 mmol) and *i*-Pr₂NEt (1.76 mL, 10.2 mmol) in CH₂Cl₂ (5 mL) at –78 °C was added dropwise a solution of ketone **25** (700 mg, 3.4 mmol) [prepared according to: Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295-3298] in CH₂Cl₂ (2 mL + 1 mL washing). The reaction was stirred at –78 °C for 15 min, then warmed to 0 °C and stirred for 2 h. The enolate solution was recooled to –78 °C and pent-4-ynal **24** (836 mg, 10.2 mmol) was added. The reaction was stirred at –78 °C for 3 h and placed in the freezer (–23 °C) for 16 h. The reaction was then warmed to 0 °C and quenched with excess MeOH (7 mL) and pH 7 phosphate buffer (7 mL). Hydrogen peroxide solution (30% aqueous, 3.5 mL, 31 mmol) was then added dropwise and the reaction stirred for 1 h, with warming to RT. The mixture was extracted with CH₂Cl₂ (10 mL × 4) and the combined organic fractions were washed with saturated aqueous NaHCO₃, dried (MgSO₄), filtered and concentrated *in vacuo* to remove residual solvent. The crude was purified by FC (silica gel, 0→10% EtOAc/hexanes) to give the aldol adduct **26** (813 mg, 83%).

Physical state: pale yellow oil

TLC: *R_f* = 0.30 (3:7, EtOAc/hexanes)

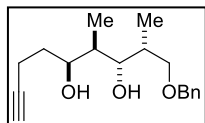
Optical rotation: [α]_D²⁰ = –16.2 (*c* = 1.0 in EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.20-7.38 (m, 5H), 4.45 (s, 2H), 4.14 (br d, *J* = 9.7 Hz, 1H), 3.64 (dd, *J* = 9.4, 8.4 Hz, 1H), 3.40-3.50 (m, 1H), 3.18 (dq, *J* = 9.6, 7.0, 4.6 Hz, 1H), 2.90 (br s, 1H), 2.68-2.78 (m, 1H), 2.18-2.37 (m, 2H), 1.91 (br s, 1H), 1.56-1.72 (m, 1H), 1.44-1.55 (dtd, *J* = 13.9, 7.8, 3.5 Hz, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 217.7, 137.4, 128.5, 127.9, 127.8, 84.0, 73.5, 73.3, 69.4, 68.5, 51.1, 44.8, 32.3, 15.2, 13.6, 9.0

MS (ES) calculated for C₁₈H₂₅O₃ [*M* + *H*]⁺, 289.2, found: 289.2

(1*S*,3*S*,4*R*,5*S*)-3-((*R*)-1-(Benzyloxy)propan-2-yl)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane (27)



To 5 mL of acetic acid at 0 °C was added portionwise NaBH₄ (293 mg, 7.7 mmol). After completion of gas evolution (about 10 min), the reaction was allowed to warm to RT and stirred for 1 h. To this solution was added a solution of β -hydroxy ketone **26** (373 mg in 2.5 mL acetic acid, 0.77 mmol). After 70 min, the reaction was concentrated *in vacuo*. The residue was poured into saturated aqueous NaHCO₃ (25mL, **caution!**). The aqueous layer was extracted with CH₂Cl₂ (30 mL \times 3) and the combined organic phase was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue (300 mg, 80%) was used as such in the next step (see general procedure for cycloisomerization of alkynediols).

General procedure for the cycloisomerization of alkynediols

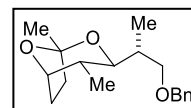
To a solution of alkynediol (**22-syn**, **22-anti**, **27**, or **31-syn**) in freshly distilled THF (0.1 M) was added Zeise's dimer ([Pt(CH₂CH₂)Cl₂]₂, 5 mol%) and the solution was stirred at room temperature for 5 min to 1.5 h. When the reaction was complete, it was quenched with 300 μ L of NEt₃ per mL of THF solvent. The mixture was concentrated *in vacuo* and purified by FC (silica gel, 0 \rightarrow 35%, EtOAc/hexanes) to give the compounds **32-35** with yields as reported in Table 1.

Characterization data for (1*S*,3*S*,4*R*,5*S*)-3-((*R*)-1-(Benzyloxy)propan-2-yl)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane (32**):**

Physical state: yellow oil (95% yield from crude **27**)

TLC: R_f = 0.25 (1:10, EtOAc/hexanes)

Optical rotation: $[\alpha]_D^{20}$ = -9.2 (c = 0.8 in CH₂Cl₂)



¹H NMR (500 MHz, CDCl₃) δ 7.24-7.34 (m, 5H), 4.49 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.15 (m, 1H), 3.67 (dd, J = 11.2, 4.8 Hz, 1H), 3.33 (br d, J = 11.5 Hz, 1H), 3.28 (dd, J = 11.2, 7.2 Hz, 1H), 2.13-1.74 (m, 6H), 1.46 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 138.9, 128.6, 127.4, 105.0, 80.1, 77.9, 73.7, 71.9, 35.2, 34.7, 33.9, 24.0, 24.0, 16.6, 13.5

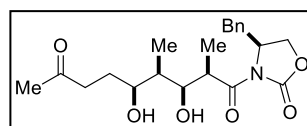
MS (ES) calculated for C₁₈H₂₆O₃Na [M + Na]⁺ 313.2, found 313.2

Characterization data for (2*R*,3*S*,4*R*,5*S*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-3,5-dihydroxy-2,4-dimethylnonane-1,8-dione (34**):**

Physical state: yellow solid (81% yield)

TLC: R_f = 0.18 (1:1, hexanes/EtOAc)

Optical rotation: $[\alpha]_D^{20}$ = +12.5 (c = 0.20 in CH₂Cl₂)



¹H NMR (400 MHz, CDCl₃) δ 7.13-7.35 (m, 5H), 4.65-4.75 (m, 1H), 3.98-4.25 (m, 4H), 3.78 (br d, *J* = 9.2 Hz, 1H), 3.26 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.00 (br d, *J* = 3.6 Hz, 1H), 2.74 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.5-2.70 (m, 2H), 2.16 (s, 3H), 1.70-1.82 (m, 1H), 1.53-1.62 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 210.0, 176.1, 153.6, 135.2, 129.6, 129.2, 127.7, 75.8, 74.0, 66.5, 55.4, 41.1, 40.9, 38.3, 30.3, 29.0, 12.1, 7.1

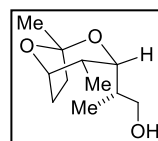
MS (ES) calculated for C₂₁H₃₀NO₆ [M + H]⁺ 392.2, found 392.2

Characterization data for (*S*)-2-((1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-propan-1-ol (35**):**

Physical state: colorless oil (94% yield)

TLC: *R_f* = 0.50 (1:2, hexanes/EtOAc)

Optical rotation: [α]_D²⁰ = -11.1 (*c* = 0.20 in CHCl₃)

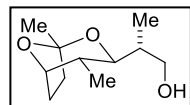


¹H NMR (400 MHz, CDCl₃) δ 4.00-4.06 (m, 1H), 3.56 (br dd, *J* = 8.7 Hz, 1H), 3.49 (br d, *J* = 10.2 Hz, 1H), 3.28 (br d, *J* = 10.1 Hz, 1H), 2.00-2.11 (m, 2H), 1.60-1.85 (m, 4H), 1.41 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 106.8, 84.1, 73.2, 62.1, 41.9, 39.9, 36.9, 29.6, 21.4, 15.2, 9.7

MS (ES) calculated for C₁₁H₂₀O₃Na [M + Na]⁺ 223.1, found 223.2

(*R*)-2-((1*S*,3*S*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)propan-1-ol (S2**)**



To a solution of benzyl ether **32** (65 mg, 0.22 mmol) in absolute EtOH (0.5 mL) was added Pd/C (5% by weight, 15 mg) in one portion. The slurry was degassed, purged with H₂ three times and stirred vigorously for 1 h at RT. The slurry was filtered through celite[®], eluting with EtOAc and concentrated *in vacuo* to give the title alcohol **S2** (43 mg, 96%) that was used without further purification. All spectral data matched those reported by Paterson [Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295-3298] and material obtained from LiBH₄ reduction of **33** as reported by us [Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562-12563].

Physical state: colorless oil

TLC: *R_f* = 0.20 (3:7, EtOAc/hexanes)

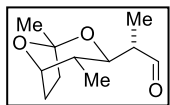
Optical rotation: [α]_D²⁰ = -20.7 (*c* = 1.0, CDCl₃)

¹H NMR (400 MHz, CDCl₃) δ 4.22 (dd, *J* = 6.9, 3.6 Hz, 1H), 3.72 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.68-3.61 (m, 2H), 2.42 (m, 1H), 2.07-1.76 (m, 6H), 1.46 (s, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 105.0, 80.1, 77.6, 67.6, 35.1, 34.5, 34.1, 24.0, 23.9, 12.6, 9.4

MS (ES) calculated for C₁₁H₂₁O₃ [M + H]⁺ 201.1, found 201.1

(S)-2-((1S,3R,4R,5S)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)propanal (38**)**



A slurry of Dess-Martin periodinane (865 mg, 2.04 mmol) and NaHCO₃ (344 mg, 4.1 mmol) in CH₂Cl₂ (6.5 mL) was stirred at ambient temperature for 20 min before being cooled to 0 °C. To the cold slurry was added the above-prepared alcohol **S2** (137 mg, 0.68 mmol) in CH₂Cl₂ (1 + 0.5 mL) dropwise. The reaction was warmed to RT and stirred for 20 min. The reaction was recooled to 0 °C and quenched by the addition of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (4 mL). The reaction was stirred for 1 h while warming to RT. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (5 mL × 4). The combined organic fractions were dried over Na₂SO₄, filtered and concentrated to dryness *in vacuo*. The resulting oil was purified by FC (silica gel, 5%→20%, EtOAc/hexanes) to give aldehyde **38** (129 mg, 95%).

Physical state: pale yellow oil

TLC: R_f = 0.37 (3:7, EtOAc/hexanes)

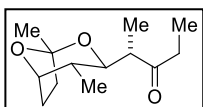
Optical rotation: $[\alpha]_D^{20} = -12.5$ ($c = 0.4$, CH₂Cl₂)

¹H NMR (500 MHz, CDCl₃) δ 9.66 (d, $J = 0.7$ Hz, 1H), 4.24 (dd, $J = 6.3, 3.3$ Hz, 1H), 3.98 (dd, $J = 10.5, 2.3$ Hz, 1H), 2.37 (qd, $J = 6.9, 2.4$ Hz, 1H), 2.07-1.75 (m, 5H), 1.40 (s, 3H), 1.14 (d, $J = 7.1$ Hz, 3H), 0.75 (d, $J = 7.0$ Hz, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 204.9, 105.3, 79.9, 74.1, 47.3, 34.4, 34.9, 24.0, 23.8, 12.7, 6.7

MS (ES) calculated for C₁₁H₁₈O₃Na $[M + Na]^+$ 221.1, found 221.1

(S)-2-((1S,3R,4R,5S)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)pentan-3-one (15**)**



To a solution of **38** (99 mg, 0.5 mmol) in THF (5 mL), Grignard reagent EtMgBr (0.5 mL, 3.0 M in ether) was added in one portion at 0 °C under an Ar atmosphere, which was stirred for an additional 0.5 h. It then was quenched with water (5 mL), and extracted with EtOAc (5 mL × 3). After concentration, the residue was dissolved in CH₂Cl₂ (5 mL), and a slurry of Dess-Martin periodinane (483 mg, 1.0 mmol) and NaHCO₃ (168 mg, 2.0 mmol) was added. The reaction was stirred for 60 min, and then quenched by the addition of saturated aqueous NaHCO₃ (2 mL) and saturated aqueous Na₂S₂O₃ (4 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (4 × 5 mL). The combined organic fractions were dried over Na₂SO₄, filtered and concentrated to dryness *in vacuo*. The resulting oil was purified by FC (silica gel, 5%→20%, EtOAc/hexanes) to give ethyl ketone **15** (103 mg, 91%, over two steps). All spectral data matched those of material obtained from **33** via the Weinreb route (bottom of Scheme 7) as reported by [Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562-12563].

Physical state: colorless oil

TLC: R_f = 0.60 (4:1, hexanes/EtOAc)

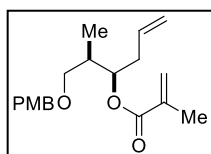
Optical rotation: $[\alpha]_D^{20} = -7.8$ ($c = 1.0$ in CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3) δ : 4.20 (dd, $J = 6.0, 3.6$, 1H), 3.84 (dd, $J = 10.4, 3.2$, 1H), 2.54-2.46 (m, 3H), 1.98-1.76 (m, 5H), 1.41 (s, 3H), 1.12 (d, $J = 7.2$, 3H), 1.02 (t, $J = 7.2$, 3H), 0.72 (d, $J = 7.2$, 3H)

^{13}C NMR (75 MHz, CDCl_3) δ 213.6, 105.2, 80.1, 75.6, 48.1, 34.8, 34.4, 33.9, 24.2, 24.0, 13.0, 9.5, 7.9

MS (ES) calculated for $\text{C}_{13}\text{H}_{23}\text{O}_3$ $[\text{M} + \text{H}]^+$ 227.2, found 227.1

(2R,3R)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-yl methacrylate (S3)



To a solution of methacrylic acid (69 μL , 0.8 mmol) and alcohol **41** (100 mg, 0.4 mmol, prepared according to: Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562-12563) in dry CH_2Cl_2 (10 mL) was added DCC (412 mg, 2.0 mmol) and DMAP (25 mg,

0.2 mmol) at 0 $^\circ\text{C}$ under a N_2 atmosphere. After stirring at 0 $^\circ\text{C}$ for 30 min, the solution was warmed to RT and stirred for 12 h, then poured into saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL \times 3) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by FC (silica gel, 0 \rightarrow 10%, EtOAc/hexanes) to give the title compound **S3** (114 mg, 90%).

Physical state: yellow oil

TLC: $R_f = 0.50$ (5:1, hexanes/EtOAc)

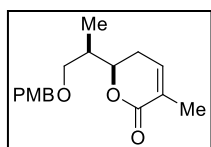
Optical rotation: $[\alpha]_D^{20} = +9.3$ ($c = 0.6$ in CDCl_3)

^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, $J = 6.8$ Hz, 2H), 6.86 (d, $J = 6.8$ Hz, 2H), 6.05 (br s, 1H), 5.73 (tdd, $J = 7.0, 7.1, 14.2$, 1H), 5.50 (br s, 1H), 5.23-5.13 (m, 1H), 5.05 (d, $J = 14.2$ Hz, 1H), 5.00 (d, $J = 7.0$ Hz, 1H), 4.38 (s, 2H), 3.79 (s, 3H), 3.31 (dd, $J = 7.0, 7.0$ Hz, 1H), 3.25 (dd, $J = 7.0, 7.0$ Hz, 1H), 2.26-2.47 (m, 2H), 1.98-2.11 (m, 1H), 1.90 (s, 3H), 0.96 (d, $J = 6.9$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 159.2, 136.8, 134.1, 130.6, 129.4, 125.2, 125.2, 117.7, 113.8, 73.7, 72.9, 72.2, 55.4, 36.6, 18.5, 11.6

MS (ES) calculated for $\text{C}_{19}\text{H}_{27}\text{O}_4$ $[\text{M} + \text{H}]^+$ 319.2, found 319.2

(R)-6-((R)-1-((4-Methoxybenzyl)oxy)propan-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-one (43a)



Grubbs' second generation catalyst (1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)-(dichlorophenylmethylene)(tricyclohexylphosphine) ruthenium, 28 mg, 0.033 mmol) was added to a solution of the above-prepared diene **S3** (0.33

mmol) in dry CH_2Cl_2 (120 mL). The reaction was refluxed for 14 h under N_2 . The solution was concentrated and purified by FC (silica gel, 0 \rightarrow 15%, EtOAc/hexanes) to give compound **43a** (62 mg, 64%) and recovered starting material (19 mg, 20%).

Physical state: brown oil

TLC: R_f = 0.20 (5:1, hexanes/EtOAc)

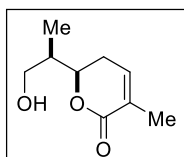
Optical rotation: $[\alpha]_D^{20} = +13.5$ ($c = 0.4$ in CDCl_3)

^1H NMR (400 MHz, CDCl_3) δ 7.22 (d, $J = 6.8$ Hz, 2H), 6.88 (d, $J = 6.8$ Hz, 2H), 6.57 (br d, $J = 5.0$ Hz, 1H), 4.51 (ddd, $J = 13.2, 4.0, 3.6$ Hz, 1H), 4.41 (d, $J = 11.2$, 1H), 4.37 (d, $J = 11.2$, 1H), 3.79 (s, 3H), 3.50 (dd, $J = 7.2, 9.2$ Hz, 1H), 3.40 (dd, $J = 5.2, 9.2$ Hz, 1H), 2.44 (m, 1H), 2.16 (m, 1H), 1.99 (m, 1H), 1.91 (s, 3H), 1.02 (d, $J = 7.2$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 159.4, 139.7, 130.5, 130.1, 129.5, 114.0, 82.10, 73.1, 71.5, 55.5, 37.7, 27.8, 17.2, 12.1

MS (ES) calculated for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$, 313.1, found 313.2

(S)-2-((R)-5-Methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)propanol (S4)



To a solution of **43a** (0.14 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (8 mL/0.4 mL) was added DDQ (38 mg, 0.17 mmol). After stirring at RT for 1 h, the solution was poured into saturated aqueous NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (3×10 mL), after which the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by FC (silica gel, 10%→35%, EtOAc/hexanes) to give the alcohol **S4**.

Physical state: pale yellow oil

TLC: R_f = 0.23 (1:1, hexanes/EtOAc)

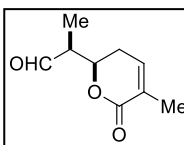
Optical rotation: $[\alpha]_D^{20} = +35.0$ ($c = 0.65$ in CDCl_3)

^1H NMR (400 MHz, CDCl_3) δ 6.62 (m, 1H), 4.57 (m, 1H), 3.73 (dd, $J = 10.8, 7.4$ Hz, 1H), 3.62 (dd, $J = 10.8, 5.3$ Hz, 1H), 2.48 (m, 1H), 2.05-2.24 (m, 2H), 1.87 (m, 1H), 1.85 (s, 3H), 1.01 (d, $J = 6.8$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 141.0, 128.1, 78.4, 64.8, 39.1, 27.4, 17.0, 11.3

MS (ES) calculated for $\text{C}_9\text{H}_{15}\text{O}_3$ $[\text{M} + \text{H}]^+$ 171.1, found: 171.1

(S)-2-((R)-5-Methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)propanal (14a)



To a solution of the above-prepared alcohol **S4** (80 mg, 0.234 mmol) in dry CH_2Cl_2 (10 mL) was added Dess-Martin reagent (198 mg, 0.47 mmol) and solid NaHCO_3 (79 mg, 0.94 mmol). The reaction was stirred for 30 min at RT, then poured into aqueous NaHCO_3 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL \times 3) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by FC (silica gel, 5%→25%, EtOAc/hexanes) to give compound **14a** (95%).

Physical state: colorless oil

TLC: R_f = 0.35 (1:1, hexanes/EtOAc)

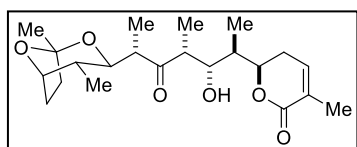
Optical rotation: $[\alpha]_D^{20} = -25.7$ ($c = 0.50$ in CDCl_3)

¹H NMR (500 MHz, CDCl₃) δ 9.79 (s, 1H), 6.64 (m, 1H), 4.78 (ddd, *J* = 12.0, 5.4, 4.4 Hz, 1H), 2.73 (m, 1H), 2.41 (m, 2H), 1.94 (s, 3H), 1.25 (d, *J* = 5.7 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 202.0, 165.4, 138.9, 128.6, 77.0, 49.7, 27.5, 17.1, 9.2

MS (ES) calculated for C₉H₁₃O₃ [*M* + *H*]⁺ 169.1, found 169.1

(*R*)-6-((2*R*,3*S*,4*R*,6*S*)-6-((1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabi-cyclo[3.2.1]octan-3-yl)-3-hydroxy-4-methyl-5-oxo-heptan-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-one (44a)



To a solution of ketone **15** (56.5 mg, 0.25 mmol) in dry THF (5 mL) at –78 °C was added a solution of lithium *bis*(trimethylsilyl)amide (1 M in THF, 0.3 mL, 0.3 mmol) dropwise. The resulting yellow solution was stirred at –

78 °C for 2 h and then a solution of aldehyde **14a** (58.8 mg, 0.35 mmol) in THF (1 mL) was added. After stirring at –78 °C for 2 h, the reaction was quenched by the addition of pH 7 phosphate buffer (6 mL). The aqueous layer was extracted with ether (10 mL × 3) and the combined organic phase was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude was purified by FC (silica gel, 5%→25%, EtOAc/hexanes) to give compound **44a** (69 mg, 70%).

Physical state: colorless oil

TLC: *R_f* = 0.20 (4:1, hexanes/EtOAc)

Optical rotation: [α]_D²⁰ = –14.2 (*c* = 0.27 in CH₂Cl₂)

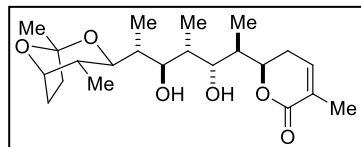
¹H NMR (400 MHz, CDCl₃) δ 6.60 (m, 1H), 4.96 (ddd, *J* = 13.4, 3.6, 1.7 Hz, 1H), 4.20 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.01 (d, *J* = 9.9 Hz, 1H), 3.82 (dd, *J* = 10.3, 3.1 Hz, 1H), 3.54 (d, *J* = 2.0 Hz, 1H), 3.03 (dq, *J* = 7.0, 1.5 Hz, 1H), 2.77 (dq, *J* = 7.0, 3.1 Hz, 1H), 2.44–2.54 (m, 1H), 2.00–2.10 (m, 1H), 1.86 (s, 3H), 1.50–2.00 (m, 6H), 1.42 (s, 3H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 218.6, 166.5, 139.7, 128.5, 105.5, 80.1, 76.6, 75.8, 69.8, 47.3, 43.4, 39.2, 34.8, 34.4, 28.1, 24.03, 24.00, 17.6, 13.1, 9.9, 8.9

IR (film): 326, 2937, 1778, 1693, 1386, 1211, 972 cm^{–1}

MS (ES) calculated for C₂₂H₃₅O₆ [*M* + *H*]⁺ 395.2, found 395.2

(*R*)-6-((2*R*,3*R*,4*R*,5*R*,6*R*)-6-((1*S*,3*S*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabi-cyclo[3.2.1]octan-3-yl)-3,5-dihydroxy-4-methylheptan-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-one (S5)



Tetramethylammonium triacetoxymethylborohydride (345 mg, 1.31 mmol) was added to CH₃CN/acetic acid (3 mL/3 mL), and the resulting solution was stirred for 30 min at RT and cooled to –20 °C before ketone **44a** (65 mg,

0.164 mmol) was added. After 48 h at –20 °C, the reaction was quenched by the addition of 20 mL of a

saturated aqueous solution of Rochelle's salt. The aqueous layer was then extracted with CH₂Cl₂ (20 mL × 3). The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by FC (silica gel, 10%→35%, EtOAc/hexanes) to give the *anti*-diol diol **S5** (56 mg, 86%, contaminated with ~5-10% of the *syn*-diol). We have not attempted to separate the diastereomers and data reported below are for the mixture.

Physical state: colorless oil

TLC: R_f = 0.15 (4:1, hexanes/EtOAc)

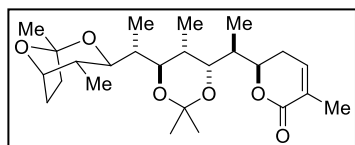
Optical rotation: $[\alpha]_D^{20} = -22.1$ ($c = 0.2$ in CDCl₃)

¹H NMR (600 MHz, CDCl₃) δ 6.62 (dt, $J = 6.5, 1.9$ Hz, 1H), 5.03-4.94 (m, 1H), 4.23 (dd, $J = 6.6, 3.3$ Hz, 1H), 4.13 (d, $J = 10.1$ Hz, 1H), 3.85-3.75 (m, 1H), 3.66-3.57 (m, 1H), 3.41 (s, 1H), 3.34 (d, $J = 5.8$ Hz, 1H), 2.54 (ddt, $J = 18.1, 13.4, 2.5$ Hz, 1H), 2.17 (s, 1H), 2.14-2.03 (m, 1H), 2.00-1.84 (m, 8H), 1.84-1.77 (m, 1H), 1.46 (s, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H), 0.92 (dd, $J = 8.5, 6.9$ Hz, 3H), 0.75 (d, $J = 6.9$ Hz, 3H)

¹³C NMR (150 MHz, CDCl₃) δ 166.7, 139.8, 128.4, 105.3, 80.3, 79.0, 76.8, 75.6, 70.1, 39.9, 35.6, 35.5, 34.6, 33.9, 28.1, 24.2, 24.1, 17.3, 13.0, 11.9, 10.6, 10.0

MS (ES) calculated for C₂₂H₃₆O₆Na $[M + Na]^+$ 419.2, found 419.2

(*R*)-6-((*S*)-1-((4*S*,5*R*,6*R*)-6-((*R*)-1-((1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxa-bicyclo[3.2.1]octan-3-yl)-ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-3-methyl-5,6-dihydro-2H-pyran-2-one (45a)



To a solution of *anti*-diol **S5** (20 mg, 0.05 mmol) in 2,2-dimethoxypropane/acetone (1.0 mL/1.0 mL) was added 2 mg PPTS. The mixture was stirred at room temperature for 30 min and concentrated *in vacuo*. The crude was purified by FC (silica gel, 2%→15%, EtOAc/hexanes) to give compound **45a** (19 mg, 87%).

Physical state: colorless oil

TLC: R_f = 0.75 (4:1, hexanes/EtOAc)

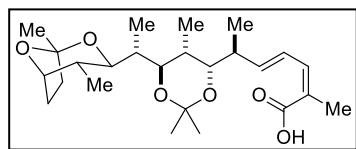
Optical rotation: $[\alpha]_D^{20} = -13.5$ ($c = 0.1$ in MeOH)

¹H NMR (400 MHz, CD₃OD) δ 6.60 (dd, $J = 6.2, 2.0$ Hz, 1H), 4.79 (m, 1H), 4.19 (m, 1H), 3.95 (dd, $J = 10.9, 3.6$ Hz, 1H), 3.73 (dd, $J = 10.6, 2.0$ Hz, 1H), 3.27 (m, 1H), 2.50 (m, 1H), 2.03 (m, 1H), 1.90 (s, 3H), 1.56-1.98 (m, 8H), 1.38 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 0.67 (d, $J = 6.9$ Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 166.5, 139.9, 128.4, 105.0, **100.8**, 80.5, 76.4, 75.1, 73.0, 68.7, 39.1, 36.8, 36.3, 34.4, 34.0, 29.9, 29.5, 27.8, **26.2**, **24.4**, 23.7, 17.3, 12.7, 9.0, 8.1

MS (ES) calculated for C₂₅H₄₁O₆ $[M + H]^+$ 437.3, found 437.3

(*S*,2*Z*,4*E*)-6-((4*S*,5*R*,6*R*)-6-((*R*)-1-((1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxa-bicyclo[3.2.1]octan-3-yl)-ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylhepta-2,4-dienoic acid (S6**; aka **79**)**



To a solution of acetone **45a** (19 mg, 0.0435 mmol) in THF (0.5 mL), was added LiHMDS (0.22 mL, 1.0 M in THF) in one portion at 0 °C. After stirring for 10 min at 0 °C, it was quenched with water (0.5 mL). The aqueous was extracted with EtOAc (1 mL × 3). The combined organic phase was dried over MgSO₄ and the solvent was removed *in vacuo*. The crude residue was purified by FC (silica gel, 10%→60%, EtOAc/hexanes) to give the title dienoic acid **S6** (aka **79** in scheme 16; 18 mg, 95%).

Physical state: pale yellow oil

TLC: R_f = 0.45 (1:1, hexanes/EtOAc)

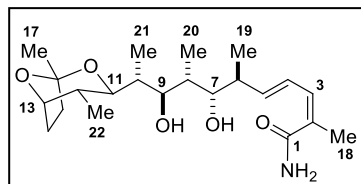
Optical rotation: $[\alpha]_D^{20} = -7.2$ (c = 0.10 in CD₃OD)

¹H NMR (400 MHz, CDCl₃) δ 7.21 (ddd, J = 15.3, 11.0, 2.4 Hz, 1H), 6.51 (d, J = 11.1 Hz, 1H), 6.00 (dd, J = 15.3, 7.0 Hz, 1H), 4.19 (m, 1H), 3.70 (br d, J = 10.5 Hz, 1H), 3.50 (m, 1H), 3.28 (dd, J = 9.1, 6.5 Hz, 1H), 2.41 (m, 1H), 1.95 (s, 3H), 1.56-1.98 (m, 7H), 1.40 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.66 (d, J = 6.6 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 172.6, 147.0, 143.7, 126.9, 122.7, 104.8, 100.4, 80.2, 74.6, 73.3, 72.8, 44.9, 38.8, 36.4, 34.1, 33.7, 25.6, 24.2, 24.0, 23.4, 20.5, 15.8, 12.8, 12.4, 7.9

MS (ES) calculated for C₂₅H₄₁O₆ [$M + H$]⁺ 437.3, found 437.3

(2*Z*,4*E*,6*S*,7*S*,8*R*,9*R*,10*R*)-10-((1*S*,3*S*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxa-bicyclo[3.2.1]octan-3-yl)-7,9-dihydroxy-2,6,8-trimethylundeca-2,4-dienamide (saliniketal A (1a**))**



To the solution of the above-prepared dienoic acid **S6** (aka **79**, 9.7 mg, 0.024 mmol) in THF (0.2 mL) was added HOBt (7.3 mg, 0.054 mmol) and EDC (10.4 mg, 0.054 mmol) followed by ammonia (0.5 M in 1,4-dioxane, 108 μ L, 0.054 mmol). After stirring the mixture at RT for 10 h, it was filtered over Celite. The Celite was washed twice with THF and the combined organic phase was concentrated *in vacuo*. The crude residue (compound **80** in scheme 16) was dissolved in MeOH (0.5 mL), followed by the addition of Dowex (5 mg). The mixture was stirred for 6 h, filtered and purified by FC (silica gel, 0→10%, MeOH/CH₂Cl₂) to give saliniketal A (**1a**, 8.4 mg, 90%). All spectral details match those reported by Fenical [Williams, P. G.; Asolkar, R. N.; Kondratyuk, T.; Pezzuto, J. M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 83-88] and Paterson [Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295-3298].

Physical state: white amorphous solid

TLC: R_f = 0.42 (1:10, MeOH/CH₂Cl₂)

Optical rotation: $[\alpha]_D^{20} = -7.2$ ($c = 0.10$ in CD_3OD)

^1H NMR (400 MHz, CD_3OD): δ 6.60 (dd, $J = 15.2, 11.1$ Hz, 1H), 6.18 (dd, $J = 11.2, 1.8$ Hz, 1H), 5.79 (dd, $J = 15.0, 8.3$ Hz, 1H), 4.24 (dd, $J = 6.4, 3.5$ Hz, 1H), 3.97 (br d, $J = 10.5$ Hz, 1H); 3.73 (dd, $J = 9.3, 1.8$ Hz, 1H); 3.53 (dd, $J = 8.6, 4.1$ Hz, 1H), 2.36 (br ddq, $J = 8.3, 8.3, 7.0$ Hz, 1H), 1.80-2.10 (m, 7H), 1.94 (br s, 3H), 1.40 (s, 3H), 1.02 (d, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 7.1$ Hz, 3H), 0.74 (d, $J = 7.1, 3\text{H}$)

^{13}C NMR (100 MHz, CD_3OD) δ 175.1, 142.0, 134.0, 131.4, 128.3, 106.6, 81.6, 78.1, 75.7, 74.9, 42.3, 37.1, 35.8, 35.2, 35.1, 24.9, 24.3, 21.0, 17.1, 12.8, 11.1, 10.3

MS (ES) calculated for $\text{C}_{22}\text{H}_{38}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 396.3, found 396.3

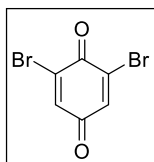
Table S3. Comparison of ^1H NMR for natural (500 MHz, CD_3OD) and synthetic saliniketal A (**1a**, 400 MHz, CD_3OD)

No.	Natural	Synthetic
[δ in ppm, multiplicity (J in Hz)]		
3	6.17, br d (11.1, 1.2)	6.18, d (11.2, 1.8)
4	6.60, dd (15.3, 11.1)	6.60, dd (15.2, 11.1)
5	5.78, dd (15.3, 8.4)	5.79, dd (15.0, 8.3)
6	2.35, m (9.3, 8.4, 6.8)	2.36, br ddq, (8.3, 8.3, 7.0)
7	3.71, dd (9.3, 1.8)	3.73, dd (9.3, 1.8)
8	1.88, m (7.4, 4.9, 1.8)	1.80-2.10, m (1H of 7H)
9	3.52, dd (8.3, 4.9)	3.53, dd (8.6, 4.1)
10	1.84, br dq (8.3, 7.2, 1.4)	1.80-2.10, m (1H of 7H)
11	3.97, br d (10.8, 1.4)	3.97, br d (10.5)
12	2.00, dqd (10.8, 7.3, 3.4)	1.80-2.10, m (1H of 7H)
13	4.23, br dd (6.3, 3.4)	4.24, dd (6.4, 3.5)
14a	1.94, m	1.80-2.10, m (1H of 7H)
14b	1.90, m	1.80-2.10, m (1H of 7H)
15	2.05, m	1.80-2.10, m (1H of 7H)
15b	1.80, m	1.80-2.10, m (1H of 7H)
17	1.39, s	1.40, (s)
18	1.94, d (1.2)	1.94, br s
19	0.96, d (6.8)	0.96, d (6.8)
20	1.02, d (7.3)	1.02, d (7.2)
21	0.89, d (7.2)	0.88, d (7.1)
22	0.76, d (7.3)	0.74, d (7.1)

Table S4. Comparison of ^{13}C NMR for natural (125 MHz, CD_3OD) and synthetic saliniketal A (**1a**, 100 MHz, CD_3OD)

No.	Natural (δ , ppm)	Synthetic (δ , ppm)
1	175.1	175.1
2	131.4	131.4
3	134.1	134.0
4	128.3	128.3
5	142.0	142.0
6	42.3	42.3
7	75.8	75.7
8	35.7	35.8
9	78.2	78.1
10	37.1	37.1
11	74.9	74.9
12	35.2	35.2
13	81.6	81.6
14a	24.9	24.9
15	35.1	35.1
16	106.4	106.6
17	24.2	24.3
18	20.9	21.0
19	17.1	17.1
20	11.1	11.1
21	10.2	10.3
22	12.8	12.8

2,6-Dibromocyclohexa-2,5-diene-1,4-dione (**47**)



This compound was prepared according to the literature [Omura, K. *Synthesis* **1998**, 8, 1145] with modifications. A solution of the 2,4,6-tribromophenol (2.65 g, 8 mmol) in AcOH (30 mL) was added dropwise over a period of 5 min to a stirred mixture of PbO_2 (3.82g, 16 mmol), 60% HClO_4 (10 mL) and AcOH (30 mL), and the resulting mixture was stirred for 10 min. The reaction mixture was worked up with water (20 mL), hexanes (20 mL) and Et_2O (20 mL). After extraction with hexanes and Et_2O (v/v 1:1, 20 mL \times 3). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (silica gel, 0 \rightarrow 15% EtOAc in hexanes) to give pure compound **47** (1.78 g, 85%). All spectral data matched those reported by: Omura, K. *Synthesis* **1998**, 8, 1145.

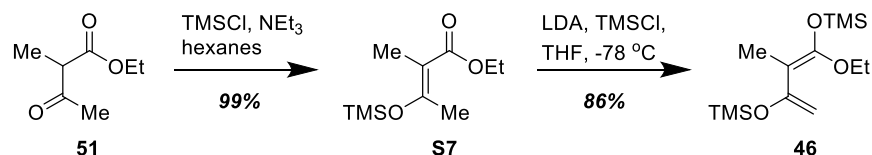
Physical state: red solid

TLC: R_f = 0.50 (1:4, EtOAc/hexanes)

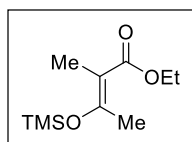
^1H NMR (600 MHz, CDCl_3) δ 7.33 (s, 2H)

^{13}C NMR (150 MHz, CDCl_3) δ 182.5, 172.5, 138.4, 135.8

MS (ES) calculated for $\text{C}_6\text{H}_3\text{Br}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 264.9, found 264.9



Ethyl (*E*)-2-methyl-3-((trimethylsilyl)oxy)but-2-enoate (**S7**)



The compounds **S7** and **46** were synthesized according to the literature: Langer, P.; Schneider, T.; Stoll, M. *Chem. Eur. J.* **2000**, 6, 3204. To a solution of ethyl 2-methyl-3-oxobutanoate **51** (1.44 g, 10.0 mmol) in hexanes (30 mL) was added NEt_3 (2.09 mL, 15.0 mmol) followed by TMSCl (1.26 mL, 15.0 mmol). After stirring for 24 h at ambient temperature, the white mixture was filtered over Celite[®] and washed with hexanes (20 mL \times 3). The combined organic phase was concentrated *in vacuo*. The crude residue **S7** (2.14 g, 99%) was used for the next step without further purification. All spectral data matched those reported by: Langer, P.; Schneider, T.; Stoll, M. *Chem. Eur. J.* **2000**, 6, 3204.

Physical state: slight yellow oil

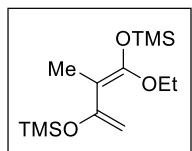
TLC: R_f = 0.25 (1:4, EtOAc/hexanes)

^1H NMR (600 MHz, CDCl_3) δ 4.15 (q, J = 7.2 Hz, 2H), 2.26 (q, J = 1.2 Hz, 3H), 1.76 (q, J = 1.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.24 (s, 9H)

^{13}C NMR (150 MHz, CDCl_3) δ 169.9, 161.3, 109.2, 59.8, 21.7, 14.5, 12.6, 1.0

MS (ES) calculated for $\text{C}_{10}\text{H}_{21}\text{O}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 217.1, found 217.1

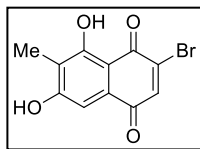
(*E*)-4-Ethoxy-2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxo-2,8-disilan-on-4-ene (**46**)



To a solution of diisopropylamine (1.54 mL, 10.89 mmol) in THF (30 mL) was added *n*-BuLi (2.5 M in hexanes, 4.75 mL, 11.88 mmol) at $-78\text{ }^\circ\text{C}$. After stirring for 10 min, the resulting solution was warmed to $0\text{ }^\circ\text{C}$ and stirred for an additional 15 minutes at that temperature; then it was cooled back to $-78\text{ }^\circ\text{C}$. A solution of the compound **S7** (2.14 g, 9.89 mmol) in THF (10 mL) was added dropwise over 10 minutes. After stirring for 15 minutes at $-78\text{ }^\circ\text{C}$, TMSCl (1.88 mL) was added in one portion and stirred for an additional 15 min. The resulting yellow mixture was warmed to RT over a 1 h period. After filtering over Celite[®] (wash with hexanes, 20 mL \times 3), the

combined organic phase was concentrated *in vacuo*. The crude residue (**46**) was used in the next step without further purification.

2-Bromo-6,8-dihydroxy-7-methylnaphthalene-1,4-dione (**53**)



To a solution of **47** (2.24 g, 8.50 mmol) in benzene (15 mL) was added compound **46** (crude residue prepared above) in benzene (20 mL) dropwise over 10 min under an Ar atmosphere. The resulting green solution was stirred for 4 h at RT and silica gel (5 g) was added. Then the mixture was stirred for 10 h at RT, followed by filtration over a plug of cotton. The filtrate was concentrated *in vacuo*, and the residue purified by FC (silica gel; 5%→20%, EtOAc/hexanes) to give pure compound **53** (1.73 g, 72%).

Physical state: red needle solid

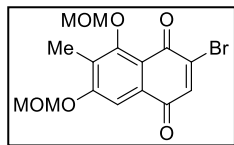
TLC: R_f = 0.3 (4:1, hexanes/EtOAc)

^1H NMR (400 MHz, CD_3OD) δ : 7.34 (s, 1H), 6.96 (s, 1H), 2.07 (s, 3H)

^{13}C NMR (100 MHz, CD_3OD) δ : 182.5, 180.7, 162.5, 162.3, 140.0, 139.8, 131.0, 119.8, 110.0, 108.1, 7.9

MS (ES) calculated for $\text{C}_{11}\text{H}_8\text{BrO}_4$ $[\text{M} + \text{H}]^+$ 283.0, found 283.0

2-Bromo-6,8-bis(methoxymethoxy)-7-methylnaphthalene-1,4-dione (**54**)



To a solution of compound **53** (1.73 g, 6.1 mmol) in dry CH_2Cl_2 (45 mL) was added MOMCl (1.39 mL, 18.3 mmol) and $i\text{Pr}_2\text{NEt}$ (4.25 mL, 24.4 mmol) under an Ar atmosphere. The resulting dark green solution was allowed to stir for 24 h at RT, followed by the addition of saturated aqueous NaHCO_3 (100 mL). The aqueous phase was extracted with EtOAc (50 mL \times 3) and the combined organic phase was dried over MgSO_4 and concentrated. The residue was purified by FC (silica gel; 0→15%, EtOAc/hexanes) to give pure compound **54** (1.73 g, 76%).

Physical state: dark red solid

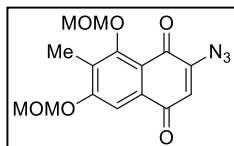
TLC: R_f = 0.50 (4:1, hexanes/EtOAc)

^1H NMR (400 MHz, CDCl_3) δ 7.57 (s, 1H), 7.41 (s, 1H), 5.34 (s, 2H), 5.09 (s, 2H), 3.63 (s, 3H), 3.49 (s, 3H), 2.30 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3): δ 182.2, 176.0, 160.6, 158.7, 142.4, 138.7, 132.7, 129.8, 117.2, 108.3, 102.0, 94.5, 58.1, 56.9, 10.5

MS (ES) calculated for $\text{C}_{15}\text{H}_{16}\text{BrO}_6$ $[\text{M} + \text{H}]^+$ 371.0, found 371.0

2-Azido-6,8-bis(methoxymethoxy)-7-methylnaphthalene-1,4-dione (**S8**)



To a solution of compound **54** (200 mg, 0.54 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}/\text{MeOH}$ (6 mL/0.6 mL/0.6 mL) was added NaN_3 (38 mg, 0.59 mmol). After stirring for 16 h at RT, the reaction was quenched by the addition of saturated aqueous NaHCO_3 . The aqueous

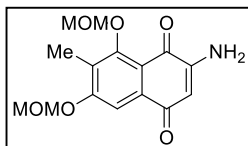
phase was extracted with EtOAc (5 mL \times 3) and the combined organic phase was dried over MgSO₄ and concentrated. The residue was used in next step without further purification.

Solid state: yellow solid

TLC: R_f = 0.35 (4:1, hexanes/EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.58 (s, 1H), 6.35 (s, 1H), 5.35 (s, 2H), 5.10 (s, 2H), 3.64 (s, 3H), 3.49 (s, 3H), 2.29 (s, 3H)

2-Amino-6,8-bis(methoxymethoxy)-7-methylnaphthalene-1,4-dione (**55**)



The above crude azide was dissolved in THF/H₂O (5 mL/0.5 mL) and PPh₃ (200 mg) was added. After stirring for 1 h at RT, aqueous workup followed by FC (silica gel; 0 \rightarrow 30%, EtOAc/hexanes) gave pure amine **55** (124 mg, 75%).

Solid state: yellow solid

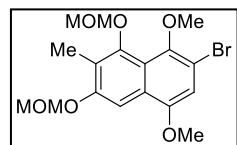
TLC: R_f = 0.25 (4:1, hexanes/EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.62 (s, 1H), 5.92 (s, 1H), 5.35 (s, 2H), 5.19 (br s, 2H), 5.05 (s, 2H), 3.66 (s, 3H), 3.52 (s, 3H), 2.30 (s, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 183.1, 179.6, 161.0, 158.0, 149.5, 134.9, 126.9, 116.7, 107.9, 103.4, 101.6, 94.4, 58.0, 56.8, 10.1

MS (ES) calculated for C₁₅H₁₈NO₆ [M + H]⁺ 308.1, found 308.1

7-Bromo-5,8-dimethoxy-1,3-bis(methoxymethoxy)-2-methylnaphthalene (**57**)



To a solution of bromide **54** (370 mg, 1.0 mmol) in ether (10 mL) was added Na₂S₂O₄ (1.39 g, 8 mmol) in H₂O (2 mL) at RT. After 30 min, water (10 mL) was added and the mixture was extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated. The residue was dissolved in DMF (10 mL) and NaH (120 mg, 3.0 mmol) was added under an Ar atmosphere. After the mixture was stirred for 15 min at RT, MeI (220 μ L, 4.0 mmol) was added and the mixture was stirred for 12 h at RT. Water (10 mL) and EtOAc (10 mL) were added. The crude was extracted with EtOAc (10 mL \times 3) and the combined organic phase was dried over MgSO₄ and concentrated. The residue was purified by FC (silica gel; 0 \rightarrow 15%, EtOAc/hexanes) to give pure bromide **57** (312 mg, 78%).

Physical state: pale yellow oil

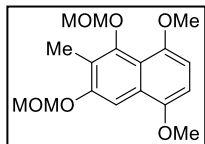
TLC: R_f = 0.55 (5:1, hexanes/EtOAc)

¹H NMR (500 MHz, CDCl₃) δ 7.57 (s, 1H), 6.86 (s, 1H), 5.35 (s, 2H), 5.06 (s, 2H), 3.94 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H), 3.54 (s, 3H), 2.43 (s, 3H)

¹³C NMR (125 MHz, CDCl₃): δ 154.4, 151.6, 150.8, 145.3, 126.7, 124.0, 119.0, 112.3, 108.2, 101.9, 100.4, 94.6, 61.8, 58.1, 56.6, 56.1, 10.7

MS (ES) calculated for C₁₇H₂₁BrO₆Na [M + Na]⁺ 423.0, found 423.0

5,8-Dimethoxy-1,3-bis(methoxymethoxy)-2-methylnaphthalene (**60**)



Method A: Trost Procedure [Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2485-2487]

To a solution of **57** (64 mg, 0.16 mmol) in dry THF (1.0 mL) was added *n*BuLi (70 μ L, 2.5 M in hexanes, 1.1 eq.) at -78 °C. After stirring in 30 minutes, magnesium bromide ethyl etherate (41 mg, 0.16 mmol) was added in one portion quickly under an Ar atmosphere. The resulting solution was transferred into the solution of azidomethylphenyl sulfide (29 mg, 0.176 mmol) in dry THF (0.3 mL) via a cannula at -78 °C. After 2 h, the reaction mixture was warmed to 0 °C and then quenched with saturated aqueous ammonium chloride (1 mL). The organic phase was dried over MgSO₄ and concentrated under vacuum. The resulting crude triazene **59** was dissolved in degassed THF and methanol (0.15 mL of each) and 50% aqueous potassium hydroxide solution (0.15 mL) was added slowly. After stirring for 6 h, saturated aq. NaHCO₃ (0.5 mL) and EtOAc (1 mL) were added. The aqueous phase was extracted with EtOAc (1 mL \times 3) and the combined organic phases were dried over MgSO₄ and concentrated under vacuum. The crude residue was purified by FC (silica gel, 0 \rightarrow 15%, EtOAc/hexanes) to yield compound **60** (32 mg, 62%) as a yellow oil. Before column purification, TLC indicated the presence of a more polar compound (presumably amine **56**). However, this compound was unstable and decomposed during further attempted purification.

Method B: From NH₄Cl quenching of intermediate **58a**

To a solution of dimethyl ether **57** (212 mg, 0.5 mmol) in THF (2 mL) was added *n*-BuLi (2.5 M in hexanes, 220 μ L) at -78 °C. After stirring for 30 min at that temperature, the solution quenched with saturated aqueous ammonium chloride (10 mL). After extraction with EtOAc, drying over MgSO₄, and concentration *in vacuo*, the residue was purified by FC (silica gel; 0 \rightarrow 10%, EtOAc/hexanes) to give pure compound **60** (116 mg, 72%).

Method C: From **67**

To a solution of **67** (100 mg, 0.203 mmol) in EtOAc (5 mL) was bubbled in H₂ gas over 45 min in the presence of Pd/C (10 mg, 10 wt. %). After filtration over a short pad of Celite[®], the solvent was removed *in vacuo*. The crude residue (~99 mg, without further purification) was dissolved in CH₂Cl₂ (2 mL), and ^tPr₂NEt (141 μ L, 0.813 mmol), followed by the addition of MOMCl (46 μ L, 0.61 mmol). The resulting reaction mixture was stirred for 4 hours at ambient temperature. Saturated aq. NaHCO₃ (5 mL) and CH₂Cl₂ (5 mL) were added to quench the reaction. The aqueous phase was washed with EtOAc (5 mL \times 3). The combined organic phase were dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue

was purified by flash column (silica gel, 0→20%, EtOAc/hexanes) to yield compound **60** (51 mg, 78% yield over 2 steps).

Physical state: yellow oil

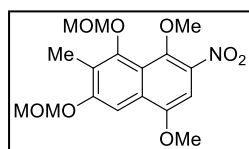
TLC: R_f = 0.5 (4:1, hexanes/EtOAc)

^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 9.1 Hz, 1H), 7.37 (s, 1H), 7.13 (d, J = 9.2 Hz, 1H), 5.34 (s, 2H), 5.11 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.66 (s, 3H), 3.52 (s, 3H), 2.32 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 152.1, 148.5, 142.3, 128.9, 128.2, 120.8, 118.4, 112.6, 100.0, 98.5, 94.5, 60.8, 57.8, 56.7, 56.3, 10.3

MS (ES) calculated for $\text{C}_{17}\text{H}_{23}\text{O}_6$ $[\text{M} + \text{H}]^+$ 323.2, found 323.2

5,8-Dimethoxy-1,3-bis(methoxymethoxy)-2-methyl-7-nitronaphthalene (**61**)



A mixture of $\text{Cu}(\text{NO}_3)_2 \cdot (\text{H}_2\text{O})_{2.5}$ (25 mg, 0.11 mmol) and CaCl_2 (25 mg) was dissolved in Ac_2O (1.0 mL) and stirred for 10 min at RT, then cooled to -40°C . A solution of **60** (32 mg, 0.1 mmol) in Ac_2O (0.2 mL) was added dropwise. After stirring for 1 h at -40°C , ether (1 mL) and water (1 mL) were added. The organic phase was concentrated *in vacuo*, and the crude residue was dried over MgSO_4 , and purified by FC (silica gel; 5%→20%, EtOAc/hexanes) to yield pure nitronaphthalene **61** (26 mg, 71%).

Physical state: yellow solid

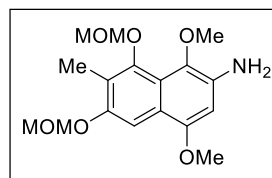
TLC: R_f = 0.4 (hexanes/EtOAc, 4:1)

^1H NMR (400 MHz, CDCl_3) δ 7.61 (s, 1H), 7.07 (s, 1H), 5.37 (s, 2H), 5.03 (s, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.61 (s, 3H), 3.53 (s, 3H), 2.41 (s, 3H)

^{13}C NMR (150 MHz, d_6 -DMSO) δ 153.7, 150.8, 150.2, 143.4, 125.3, 123.2, 121.8, 118.2, 105.9, 101.0, 99.9, 94.1, 61.2, 57.3, 56.1, 55.8, 10.3

MS (ES) calculated for $\text{C}_{17}\text{H}_{22}\text{NO}_8$ $[\text{M} + \text{H}]^+$ 368.1, found 368.1

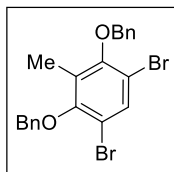
1,4-Dimethoxy-6,8-bis(methoxymethoxy)-7-methylnaphthalen-2-amine (**56**)



To a solution of **61** (9.2 mg, 25 μmol) in EtOAc (1 mL) was added Pd/C (10 wt. %, 5 mg) at ambient temperature. The reaction mixture was stirred for 30 minutes under H_2 atmosphere (during the process, the color of the solution changed from yellow to colorless). After filtering over a short pad of Celite[®], the solvent was

removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (100 μL) intermediately! (Note: the amine **56** was unstable in air and must be freshly prepared for next step.)

(((4,6-Dibromo-2-methyl-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (63)



Compound **63** was synthesized according to the literature: Nakata, M.; Wada, S.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, 58, 1801.

To a solution of 2-methylresorcinol (2.48 g, 20 mmol) in CH₂Cl₂ (200 mL) was added Br₂ (2.01 mL, 40 mmol) dropwise. After stirring for 2 h, the solvent was removed *in vacuo* and the crude 4,6-dibromo-2-methylbenzene-1,3-diol (5.54 g, 99%) was used directly for next step without further purification.

To a solution of 4,6-dibromo-2-methylbenzene-1,3-diol (2.0 g, 7.1 mmol) and potassium carbonate (2.26 g, 17.8 mmol) in acetone (20 mL), benzyl bromide (2.1 mL, 17.66 mmol) was added dropwise. The resulting mixture was stirred at 60 °C for 5 h and filtered with Celite[®]. The solvent was removed and the crude residue was purified by FC (silica gel; 0→3% EtOAc/hexanes) to yield **63** (3.04 g, 93%). All spectral details match those reported in: Nakata, M.; Wada, S.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, 58, 1801-1806.

Physical state: off-white solid

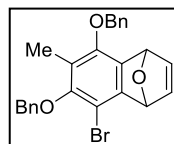
TLC: R_f = 0.35 (25:1, hexanes/EtOAc)

¹H NMR (600 MHz, CDCl₃) δ 7.71 (s, 1H), 7.54-7.50 (m, 4H), 7.44-7.37 (m, 6H), 4.94 (s, 4H), 2.23 (s, 3H)

¹³C NMR (150 MHz, CDCl₃) δ 154.4, 136.6, 133.5, 129.7, 128.7, 128.5, 128.4, 113.3, 74.8, 11.5

MS (ES) calculated for C₂₁H₁₉Br₂O₃ [M + H]⁺ 461.0; found 461.0

5,7-Bis(benzyloxy)-8-bromo-6-methyl-1,4-dihydro-1,4-epoxynaphthalene (64)



To a solution of ⁱPr₂NH (1.2 mL, 8.6 mmol) in THF (15 mL) was added *n*-BuLi (2.5 M in hexanes, 3.13 mL, 7.8 mmol) at -78 °C. After stirring for 10 min, the solution was warmed to 0 °C and stirred for an additional 15 min, then cooled back to -78 °C. To this solution was added a solution of compound **63** (3.0 g, 6.5 mmol) and furan (5 mL) in THF (30 mL) over a 1 h period. The resulting mixture was allowed to stir overnight. The reaction was quenched by the addition of pH 7 phosphate buffer (50 mL). The aqueous layer was extracted with ether (30 mL × 3) and the combined organic phase was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude was purified by FC (silica gel; 0→10%, EtOAc/hexanes) to give compound **64** (2.6 g, 89%). All spectral details match those reported in: Nakata, M.; Wada, S.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, 58, 1801-1806.

Physical state: yellow oil

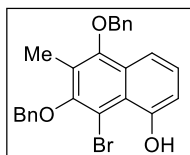
TLC: R_f = 0.70 (4:1 hexanes/EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 7.52 (m, 2H), 7.39 (m, 8H), 7.03 (dd, *J* = 5.6, 1.9 Hz, 1H), 6.73 (dd, *J* = 5.5, 1.8 Hz, 1H), 5.93 (br s, 1H), 5.78 (br s, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 4.88 (d, *J* = 12.2 Hz, 1H), 4.83 (d, *J* = 12.2 Hz, 1H), 2.15 (s, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 151.8, 150.6, 149.6, 143.2, 142.3, 137.1, 133.8, 129.0, 128.7, 128.5, 127.8, 123.2, 105.0, 83.4, 82.8, 75.2, 74.7, 11.4

MS (ES) calculated for C₂₅H₂₂BrO₃ [*M* + *H*]⁺ 449.1, found 449.1

5,7-Bis(benzyloxy)-8-bromo-6-methylnaphthalen-1-ol (**65a**)



To a solution of benzyne cycloadduct **64** (610 mg, 1.36 mmol) and 2,6-di-*t*-butylpyridine (1.89 mL, 8.54 mmol) in CH₂Cl₂ (14 mL) was added TMSOTf (1.29 mL, 7.12 mmol) at 0 °C. After stirring for 5 min at this temperature and 3 h at RT, TBAF (1.0 M in THF, 2.8 mL) was added at 0 °C. After stirring for an additional 15 min, the reaction was quenched with saturated aq. NaHCO₃ (15 mL), extracted with EtOAc (15 mL), dried with MgSO₄ and concentrated in vacuum to get the crude product (orange oil). The crude product was purified by FC (silica gel; 0→15%, EtOAc/hexanes) to yield pure **65a** (469 mg, 77%). The regiochemistry of the ring-opening isomerization was established via analysis of the NOESY spectrum of compound **65b** (see below).

Physical state: yellow solid

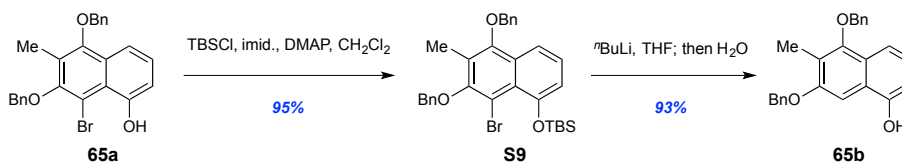
TLC: *R_f* = 0.5 (4:1, hexanes/EtOAc)

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.74 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48-7.55 (m, 4H), 7.30-7.47 (m, 7H), 7.04 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.95 (s, 4H), 2.37 (s, 3H)

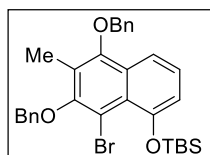
¹³C NMR (100 MHz, CDCl₃) δ 153.9, 153.0, 152.7, 136.8, 136.4, 128.6, 128.4, 128.1, 128.0, 127.9, 126.7, 124.2, 120.2, 114.7, 113.3, 105.5, 75.5, 74.6, 30.9, 11.2

MS (ES) calculated for C₂₅H₂₂BrO₃ [*M* + *H*]⁺ 449.1, found 449.1

Elucidation of the structure of compound **65a** via NOESY spectral analysis of derivative **65b**



((5,7-Bis(benzyloxy)-8-bromo-6-methylnaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane (**S9**)



A solution of **65a** (44.8 mg, 0.1 mmol), imidazole (13.6 mg, 0.2 mmol), DMAP (6.1 mg, 0.05 mmol), and TBSCl (30.1 mg, 0.2 mmol) in CH₂Cl₂ (0.5 mL) was stirred for 8 h followed by removal of the solvent *in vacuo*. The crude residue was purified by FC (silica gel; 0→5%, EtOAc/hexanes) to yield pure **S9** (53.4 mg, 95%).

Physical state: yellow solid

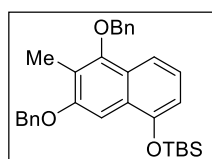
TLC: R_f = 0.75 (5:1, hexanes/EtOAc)

^1H NMR (600 MHz, CDCl_3) δ 7.90-7.80 (m, 1H), 7.66 (dt, J = 8.3, 1.7 Hz, 2H), 7.64-7.56 (m, 2H), 7.48-7.41 (m, 6H), 7.38-7.30 (m, 1H), 7.02 (dq, J = 7.5, 1.3 Hz, 1H), 5.07 (d, J = 2.2 Hz, 2H), 5.02 (d, J = 1.8 Hz, 2H), 2.43 (s, 3H), 1.10 (s, 9H), 0.48 (s, 6H)

^{13}C NMR (150 MHz, CDCl_3) δ 153.8, 153.1, 152.5, 137.2, 129.5, 128.7, 128.6, 128.3, 128.0, 125.7, 125.0, 124.3, 115.8, 115.4, 107.2, 75.6, 74.3, 26.6, 19.2, 11.3, -3.0

MS (ES) calculated for $\text{C}_{31}\text{H}_{36}\text{BrO}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 563.2, found 563.1

((5,7-Bis(benzyloxy)-6-methylnaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane (65b)



To a solution of **S9** (40 mg, 71.1 μmol) in THF (0.5 mL), was added $n\text{-BuLi}$ (2.5 M in hexanes, 31.3 μL , 78.3 μmol) dropwise. After stirring for 10 min, water (1.0 mL) and EtOAc (1.0 mL) were added, and the aqueous phase was extracted with EtOAc (1.0 mL \times 3). The combined organic phase was dried over MgSO_4 . After concentration, the crude residue was purified by FC (silica gel; 0 \rightarrow 5%, EtOAc/hexanes) to yield pure **65b** (53.4 mg, 93%).

Physical state: yellow solid

TLC: R_f = 0.65 (5:1, hexanes/EtOAc)

^1H NMR (600 MHz, CDCl_3) δ 7.69 (d, J = 8.4 Hz, 1H), 7.63-7.58 (m, 2H), 7.52 (dd, J = 7.5, 1.6 Hz, 2H), 7.49-7.38 (m, 6H), 7.38-7.33 (m, 1H), 7.21 (t, J = 8.4 Hz, 1H), 6.84 (dd, J = 7.5, 1.0 Hz, 1H), 5.23 (s, 2H), 5.02 (s, 2H), 2.41 (s, 3H), 1.12 (s, 9H), 0.29 (s, 6H)

^{13}C NMR (150 MHz, CDCl_3) δ 155.8, 153.3, 151.0, 137.7, 137.3, 128.7, 128.7, 128.2, 128.0, 127.9, 127.7, 127.3, 125.6, 123.6, 120.6, 115.1, 112.9, 97.9, 75.7, 70.0, 26.1, 18.5, 10.1, -4.1

MS (ES) calculated for $\text{C}_{31}\text{H}_{37}\text{BrO}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 485.3, found 485.3

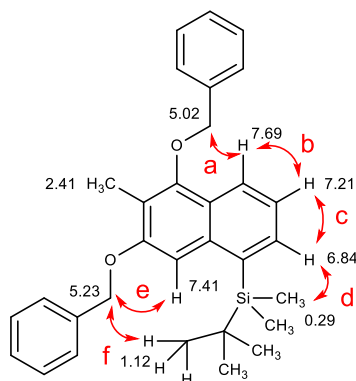


Figure S1. Structure of 65b with nOe effects indicated by red arrows

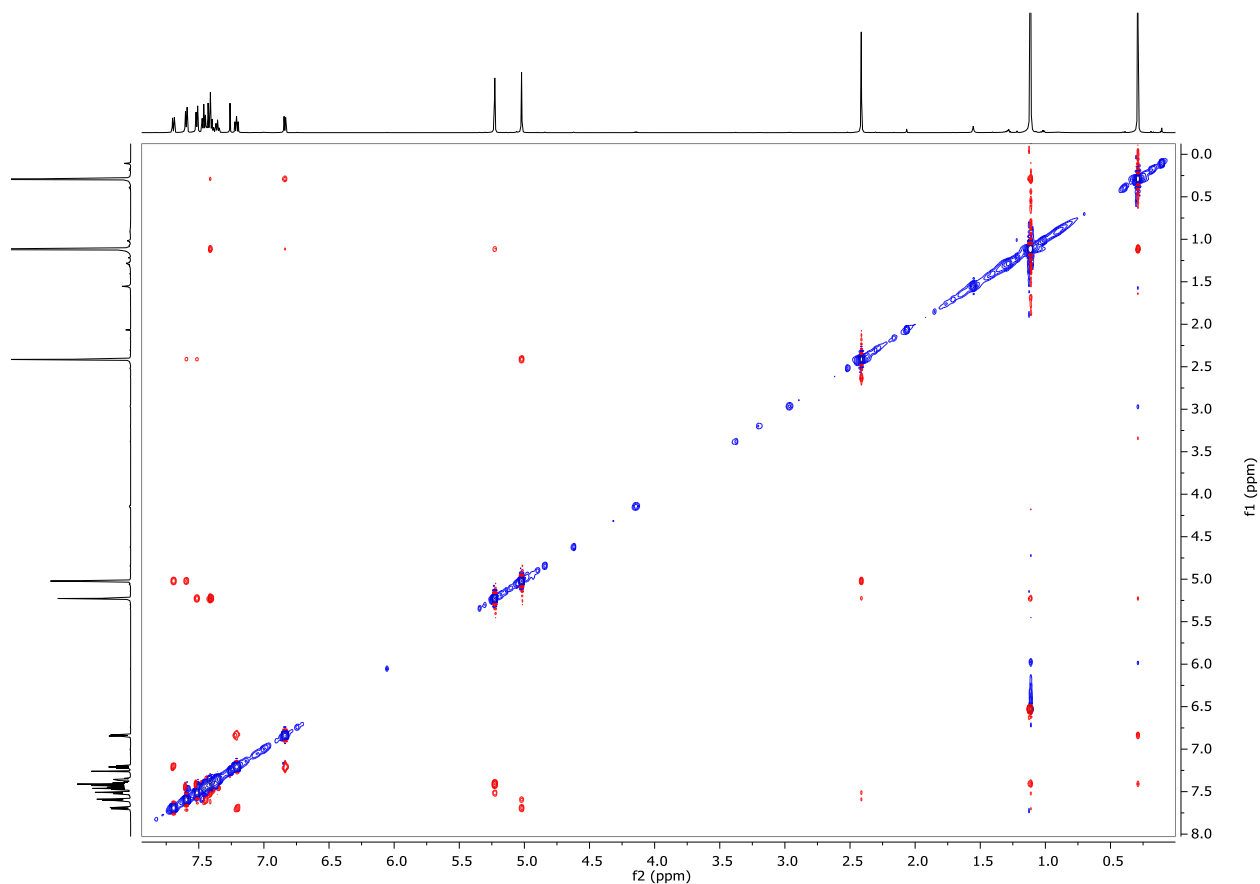
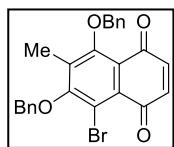


Figure S2. NOESY spectrum of compound 65b (600 MHz, CDCl₃)

5,7-Bis(benzyloxy)-8-bromo-6-methylnaphthalene-1,4-dione (66**)**



To a solution of compound **65** (76 mg, 0.17 mmol) in DMF (2.0 mL) was added salcomine (Co(salen), 7.6 mg). The resulting mixture was stirred under O₂ (1 atm) at 50 °C overnight.

The reaction was quenched with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by FC (silica gel; 10%→50%, EtOAc/hexanes) to give the pure naphthoquinone **66** (58 mg, 73%).

Physical state: yellow-red solid

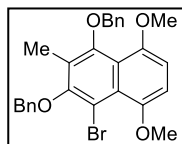
TLC: *R_f* = 0.3 (1:1, EtOAc/hexanes)

¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 10.5 Hz, 1H), 7.50 (m, 1H), 7.30-7.44 (m, 9H), 6.30 (d, *J* = 10.5 Hz, 1H), 4.98 (s, 2H), 4.87 (s, 2H), 2.24 (s, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 180.0, 178.3, 158.3, 155.8, 139.4, 135.7, 135.6, 135.2, 129.2, 129.0, 128.8, 128.4, 128.2, 127.0, 126.1, 118.7, 76.7, 75.0, 11.6

MS (ES) calculated for C₂₅H₂₀BrO₄ [M + H]⁺ 463.1, found 463.1

1,3-Bis(benzyloxy)-4-bromo-5, 8-dimethoxy-2-methylnaphthalene (67)



To a solution of naphthoquinone **66** (58 mg, 0.126 mmol) in ether (1.5 mL) and water (0.5 mL) was added $\text{Na}_2\text{S}_2\text{O}_4$ (175 mg, 1.0 mmol). The resulting mixture was stirred at RT for 15 min and then quenched with water, extracted with ether, dried over MgSO_4 and concentrated in vacuum. The crude product was dissolved in DMF (1 mL), followed by the addition of NaH (9.5 mg, 0.38 mmol) and MeI (50 μL , 0.91 mmol). The resulting mixture was stirred at RT overnight, and quenched with water. After extraction with EtOAc , and drying over MgSO_4 , the solvent was removed *in vacuo* to give a residue that was purified by FC (silica gel; 10% \rightarrow 40%, EtOAc /hexanes) to give product **67** (50 mg, 80 %).

Physical state: yellow oil

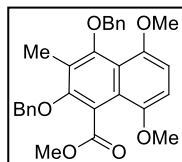
TLC: R_f = 0.65 (1:5, EtOAc /hexanes)

^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 9.3 Hz, 1H), 7.30-7.62 (m, 10H), 7.26 (d, J = 9.2 Hz, 1H), 5.01 (s, 2H), 4.93 (s, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 2.35 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 152.1, 148.6, 142.0, 137.2, 128.9, 128.6, 127.8, 127.3, 120.5, 118.4, 112.1, 100.0, 96.2, 70.0, 60.7, 57.9, 56.6, 10.3

MS (ES) calculated for $\text{C}_{27}\text{H}_{25}\text{BrO}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 515.1, found 515.1

Methyl-6,8-bis(benzyloxy)-7-methyl-1,4-dihydro-1,4-epoxynaphthalene-5-carboxylate (68)



To a solution of **67** (910 mg, 2.02 mmol) in THF (20 mL) was added $n\text{BuLi}$ (1.65 mL, 2.63 mmol, 1.6 M in THF) dropwise at -78°C . After stirring for 10 min at -78°C , ClCO_2Me (313 μL , 4.05 mmol) was added. The resulting orange solution was stirred at -78°C for 4 h and then slowly warmed to RT overnight. The reaction was quenched with water (20 mL), and the aqueous layer was extracted with EtOAc (20 mL \times 3). The combined organic layers were washed with brine, dried with MgSO_4 and concentrated in vacuum. The crude residue was purified by FC (silica gel, 0 \rightarrow 20%, EtOAc /hexanes) to yield the product **68** (828 mg, 95%).

Physical state: yellow oil

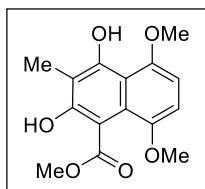
TLC: R_f = 0.3 (1:4, EtOAc /hexanes)

^1H NMR (400 MHz, CDCl_3) δ 7.80-7.72 (m, 1H), 7.50-7.22 (m, 10H), 7.12 (dd, J = 9.2, 1.5 Hz, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.66 (s, 3H), 2.36 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 169.7, 154.6, 154.2, 149.4, 142.1, 137.1, 128.7, 128.5, 128.3, 128.1, 125.8, 122.1, 121.0, 118.7, 118.1, 114.3, 76.7, 75.9, 61.2, 56.6, 52.2, 10.5

MS (ES) calculated for $\text{C}_{29}\text{H}_{29}\text{O}_6$ [$\text{M} + \text{H}$] $^+$ 473.2, found 473.2

Methyl 2,4-dihydroxy-5,8-dimethoxy-3-methyl-1-naphthoate (69)



To a solution of **68** (9.4 mg, 20 μ mol) in EtOAc (1 mL) was added Pd/C (10 wt. %, 5 mg) at ambient temperature. The reaction mixture was stirred for 2 hours under H₂ atmosphere. After filtering over a short pad of Celite[®], the solvent was removed *in vacuo*. The crude residue was purified by flash column (silica gel, 10 \rightarrow 40%, EtOAc/hexanes) to yield **69** (5.8 mg, 99% yield).

Physical state: off-white solid

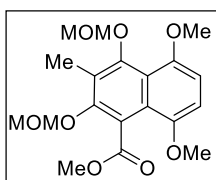
TLC: R_f = 0.3 (2:1, EtOAc/hexanes)

¹H NMR (600 MHz, CDCl₃) 9.31 (s, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.13 (d, J = 9.1 Hz, 1H), 5.50 (br s, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.74 (s, 3H), 2.25 (s, 3H)

¹³C NMR (150 MHz, CDCl₃) δ 172.6, 158.4, 153.5, 151.2, 142.4, 126.4, 118.2, 116.7, 111.5, 105.5, 99.4, 61.1, 56.5, 52.6, 8.4

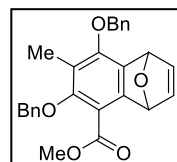
MS (ES) calculated for C₁₅H₁₇O₆ [M + H]⁺ 293.1, found 293.1

Methyl 5,8-dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-1-naphthoate (70) (Attempted)



To a solution of **69** (7.3 mg, 25 μ mol) in CH₂Cl₂ was added MOMCl (7.6 μ L, 100 μ mol) and *i*Pr₂NEt (13 μ L, 75 μ mol) under an Ar atmosphere. The resulting dark green solution was allowed to stir for a couple of hours at RT. TLC indicated complete decomposition during this process.

Methyl 6,8-bis(benzyloxy)-7-methyl-1,4-dihydro-1,4-epoxynaphthalene-5-carboxylate (72)



To a solution of **64** (1.34 g, 3.0 mmol) in THF (30 mL) was added *n*-BuLi (1.5 mL, 2.5 M in hexanes) dropwise over 5 min at -78 °C. After stirring for 15 min at -78 °C, methyl chloroformate (696 μ L, 9.0 mmol) was added in one portion. After stirring at -78 °C for an additional 2 h, the mixture was warmed to RT and water (20 mL) and ethyl acetate (20 mL) were added. The aqueous was extracted with ethyl acetate (3 \times 20 mL). The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by FC (silica gel; 5% \rightarrow 20% EtOAc/hexanes) to yield ester **72** (1.22 g, 95%).

Physical state: yellow oil

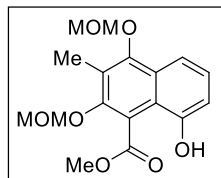
TLC: R_f = 0.31 (1:4, EtOAc/hexanes)

¹H NMR (400 MHz, CDCl₃) δ 7.51-7.27 (m, 10H), 7.05 (dd, J = 5.5, 1.9 Hz, 1H), 6.74 (dd, J = 5.5, 1.8 Hz, 1H), 6.09 (br s, 1H), 5.95 (br s, 1H), 5.21 (d, J = 11.8 Hz, 1H), 5.09 (d, J = 11.8 Hz, 1H), 4.95 (d, J = 10.6 Hz, 1H), 4.78 (d, J = 10.6 Hz, 1H), 3.86 (s, 3H), 2.14 (s, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 169.7, 154.6, 154.2, 149.4, 142.1, 137.1, 128.6, 128.5, 128.3, 128.1, 127.9, 125.8, 122.1, 120.9, 118.7, 118.0, 114.3, 76.7, 75.9, 61.2, 56.6, 52.2, 10.3

MS (ES) calculated for $C_{27}H_{25}O_5$ $[M + H]^+$ 429.2, found 429.2

Methyl 8-hydroxy-2,4-bis(methoxymethoxy)-3-methyl-1-naphthoate (75)



To a solution of **72** (610 mg, 1.42 mmol) and 2,6-di-*t*-butylpyridine (1.89 mL, 8.54 mmol) in CH_2Cl_2 (14 mL) was added TMSOTf (1.29 mL, 7.12 mmol) at 0 °C. The mixture was stirred for 5 min at 0 °C and 3 h at RT, followed by quenching with saturated aq. $NaHCO_3$ (20 mL), extraction with EtOAc (3 × 20 mL), drying over $MgSO_4$ and concentration *in vacuo*. The crude material (orange oil) thus obtained was used immediately in the next step. The crude residue was dissolved in EtOAc (14 mL) followed by the addition of Pd/C (50 mg, 10 wt%). The reaction mixture was stirred under H_2 (1 atm) for 2 h at RT and filtered through a pale of Celite®. After removal of the solvent, the crude product was dissolved in CH_2Cl_2 (14 mL), followed by the addition of *t*-Pr₂NEt (735 μL, 4.3 mmol, 3.0 equiv) and MOMCl (216 μL, 2.84 mmol, 2.0 equiv) at 0 °C. The resulting solution was stirred at RT overnight, quenched with water (10 mL), extracted with EtOAc (3 × 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude was purified by FC (silica gel; 0 → 50% EtOAc/hexanes) to yield *bis*-MOM ether **75** (172 mg, 36% for 3 steps) as a dark red oil. A less polar fraction contained primarily the *tris*-MOM ether **74** (97 mg, 18%). The latter could be partially deprotected to yield *bis*-MOM ether **75** as follows: To a solution of **74** (97 mg, 0.256 mmol) in CH_2Cl_2 (3 mL) was added BCl_3 (280 μL, 1.0 M solution in CH_2Cl_2) at -78 °C. The resulting solution was stirred for 1 h and quenched with sat. $NaHCO_3$ solution (3 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic phase were dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column (silica gel, 0 → 50% gradient of EtOAc/hexanes) to yield *bis*-MOM ether **75** (68 mg, 79%). The regiochemistry of the ring-opening isomerization was established via analysis of the NOESY spectrum of compound **74** (see below).

Characterization data for 74 (tris-MOM ether):

Physical state: yellow oil

TLC: R_f = 0.3 (1:1, EtOAc/hexanes)

1H NMR (600 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.4, 1.0 Hz, 1H), 7.35 (dd, J = 8.5, 7.7 Hz, 1H), 7.09 (dd, J = 7.7, 0.9 Hz, 1H), 5.24 (s, 2H), 5.12 (s, 2H), 5.09 (s, 2H), 3.96 (s, 3H), 3.66 (d, J = 0.4 Hz, 3H), 3.62 (s, 3H), 3.51 (d, J = 0.5 Hz, 3H), 2.45 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 153.5, 152.2, 152.0, 127.8, 126.0, 124.0, 121.9, 119.2, 116.1, 109.6, 101.2, 100.3, 95.3, 58.1, 57.8, 56.6, 52.3, 11.5

MS (ES) calculated for $C_{19}H_{27}O_8$ $[M + H]^+$ 381.2, found 381.2

Characterization data for 75 (bis-MOM ether):

Physical state: yellow oil

TLC: R_f = 0.2 (1:1, EtOAc/hexanes)

^1H NMR (600 MHz, CDCl_3) δ 7.61 (dd, J = 8.5, 0.9 Hz, 1H), 7.21 (dd, J = 8.5, 7.5 Hz, 1H), 6.79 (dd, J = 7.5, 1.0 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 3.92 (s, 3H), 3.66 (s, 3H), 3.62 (s, 3H), 2.44 (s, 3H)

^{13}C NMR (150 MHz, CDCl_3) δ 170.9, 153.5, 152.0, 150.0, 128.0, 126.0, 123.9, 120.7, 119.0, 115.0, 111.2, 101.1, 100.2, 58.1, 57.8, 52.9, 11.5

MS (ES) calculated for $\text{C}_{17}\text{H}_{21}\text{O}_7$ $[\text{M} + \text{H}]^+$ 337.1, found 337.1

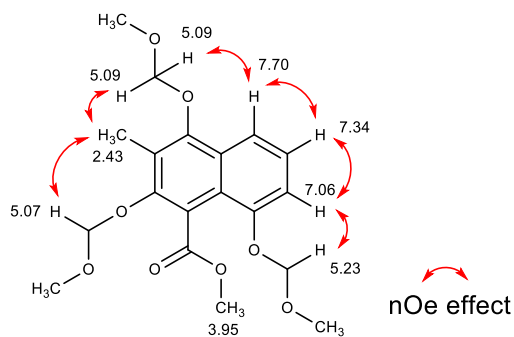


Figure S3. Structure of 74 with nOe effects indicated by red arrows

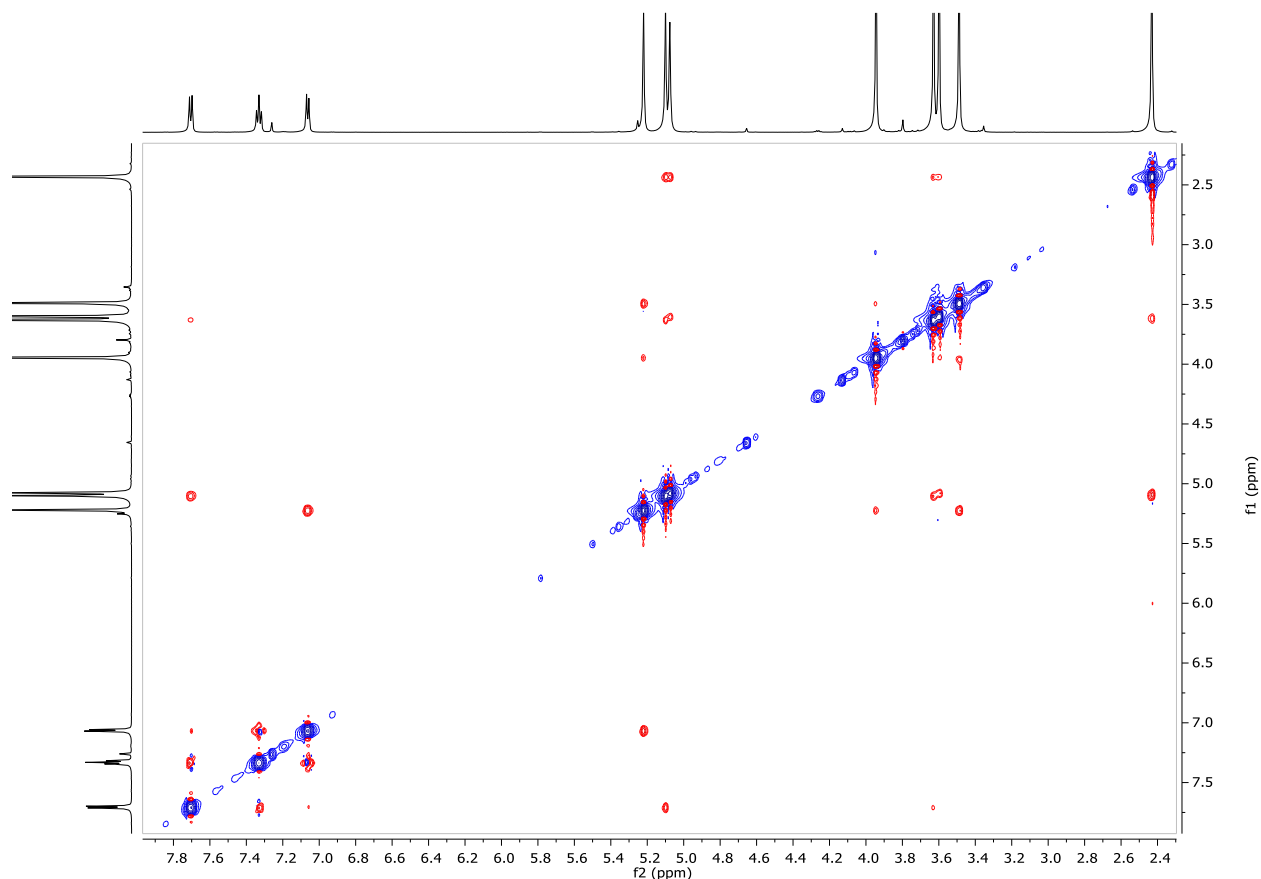
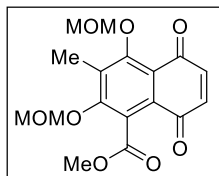


Figure S4. NOESY spectrum of compound 74 (600 MHz, CDCl_3)

Methyl 2,4-bis(methoxymethoxy)-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (**76**)



To a solution of **75** (76 mg, 0.226 mmol) in DMF (2.5 mL) was added salcomine catalyst (Co(salen) **71**, 7.6 mg, 0.1 equiv). The resulting mixture was stirred under O₂ (1 atm) at 50 °C overnight. The reaction was quenched with water (10 mL), extracted with EtOAc (10 mL), dried with MgSO₄ and concentrated *in vacuo*. The crude residue was purified by preparative TLC (1:1, EtOAc/hexanes) to yield pure naphthoquinone **76** (54 mg, 0.154 mmol, 68%).

Physical state: red solid

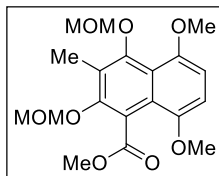
TLC: R_f = 0.3 (1:1, EtOAc/hexanes)

¹H NMR (600 MHz, CDCl₃): 7.82 (d, J = 10.5 Hz, 1H), 6.40 (d, J = 10.4 Hz, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 3.98 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 2.35 (s, 3H)

¹³C NMR (150 MHz, CDCl₃) δ 180.1, 177.5, 167.0, 156.4, 140.1, 136.1, 128.9, 127.7, 126.6, 125.2, 101.2, 101.0, 58.3, 58.0, 53.4, 12.1

MS (ES) calculated for C₁₇H₁₈O₈Na [M + Na]⁺ 373.1; found 373.1

Methyl 5,8-dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-1-naphthoate (**70**)



To a solution of **76** (57 mg, 0.163 mmol) in ether (1 mL) and water (0.2 mL) was added Na₂S₂O₄ (284 mg, 1.63 mmol). The resulting mixture was stirred at RT for 15 min and then quenched with water, extracted with ether, dried with MgSO₄ and concentrated *in vacuo*. The crude product was dissolved in DMF (1 mL), followed by the addition of NaH (60% in mineral, 20 mg, 3.0 equiv, 0.489 mmol) and MeI (41 μ L, 4.0 equiv, 0.652 mmol). The resulting mixture was stirred at RT overnight, quenched with water, extracted with EtOAc (10 mL), dried with MgSO₄ and concentrated *in vacuo*. The crude residue was purified by preparative TLC (2:3, EtOAc/hexanes) to yield the pure compound **70** (42 mg, 68%).

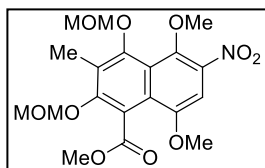
Physical state: yellow oil

TLC: R_f = 0.4 (2:3, EtOAc/hexanes)

¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 9.4 Hz, 1H), 7.25 (d, J = 9.4 Hz, 1H), 5.11 (s, 2H), 5.10 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.66 (s, 3H), 3.62 (s, 3H), 2.40 (s, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 169.5, 153.4, 152.6, 149.3, 141.8, 125.6, 122.4, 121.1, 118.8, 118.1, 114.3, 100.9, 100.1, 61.2, 57.9, 57.6, 56.4, 52.2, 11.1

MS (ES) calculated for C₁₉H₂₅O₈ [M + H]⁺ 381.2, found 381.2

Methyl 5,8-dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-6-nitro-1-naphthoate (77)

To a solution of **77** (42 mg, 0.1 mmol) in acetic anhydride (1.0 mL), $\text{Cu}(\text{NO}_3)_2 \cdot (\text{H}_2\text{O})_{2.5}$ (23.4 mg, 105 μmol , 1.05 equiv) and dry CaCl_2 (15 mg, 135 μmol , 1.35 equiv) were added in one portion. The mixture was stirred at RT for 15 min and cooled down to -40°C . Then a solution of **70** (38 mg, 0.1 mmol) in acetic anhydride (0.2 mL) was added dropwise. After stirring at -40°C for 1 h, ether (2.0 mL) and water (2.0 mL) were added to the mixture, which was allowed to warm to RT. The aqueous phase was extracted with EtOAc (3×2 mL). The combined organic phase was dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by FC (5% \rightarrow 25%, EtOAc/hexanes) to afford nitronaphthalene **77** (29.5 mg, 69%).

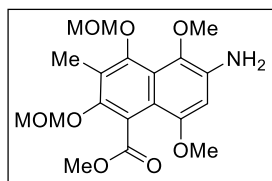
Physical state: orange solid

TLC: $R_f = 0.15$ (1:2, hexanes/EtOAc)

^1H NMR (500 MHz, CD_3COCD_3) δ 8.48 (s, 1H), 5.39 (s, 2H), 5.14 (s, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 3.91 (s, 3H), 3.64 (s, 3H), 3.51 (s, 3H), 2.32 (s, 3H)

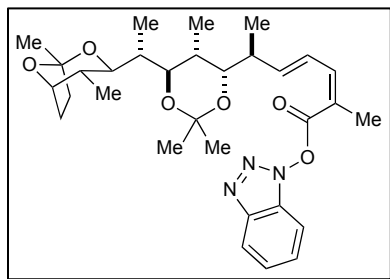
^{13}C NMR (125 MHz, CD_3COCD_3) δ 170.7, 155.2, 152.7, 148.9, 142.4, 129.2, 121.0, 118.5, 118.2, 113.1, 100.2, 98.5, 94.6, 60.1, 58.5, 57.2, 56.3, 55.6, 9.9

MS (ES) calculated for $\text{C}_{19}\text{H}_{24}\text{NO}_{10}$ $[\text{M} + \text{H}]^+$ 426.1, found 426.1

Methyl 6-amino-5,8-dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-1-naphthoate (78)

To a solution of **77** (10.6 mg, 25 μmol) in EtOAc (1 mL) was added Pd/C (10 wt. %, 5 mg) at ambient temperature. The reaction mixture was stirred for 45 minutes under H_2 atmosphere. After filtering with a short pad of Celite[®], the solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (100 μL)

intermediately! (Note: the amine **78** was unstable in air and must be freshly prepared for next step)

(S,2Z,4E)-1H-Benzo[d][1,2,3]triazol-1-yl 6-((4S,5R,6R)-6-((R)-1-((1S,3R,4R,5S)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylhepta-2,4-dienoate (81)

To a solution of dienoic acid **S6** (aka **79**; 1.0 mg, 2.3 μmol) and amine **55** (2.5 mg, 8.1 μmol) in CH_2Cl_2 (150 μL) was added HOBt (1.0 mg, 6.5 μmol), EDCI (1.0 mg, 6.4 μmol), and triethylamine (1 μL , 7.5 μmol). The mixture was stirred for 2 h at ambient temperature and concentrated under vacuum. The residue was purified by preparative TLC (hexanes/EtOAc, 4:1) to provide the title compound **81** (1.1 mg, 86%) as

a white solid and recovered amine **55** (2.0 mg, 80%).

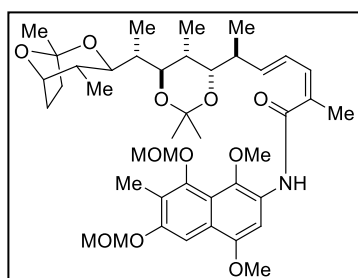
Physical state: white solid

TLC: R_f = 0.25 (4:1, hexanes/EtOAc)

^1H NMR (500 MHz, CDCl_3) δ 7.68 (dd, J = 12.0, 7.5 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.54-7.49 (m, 1H), 7.44-7.40 (m, 1H), 7.22 (dd, J = 15.3, 11.3 Hz, 1H), 6.87 (d, J = 10.2 Hz, 1H), 6.28 (dd, J = 10.8, 6.4 Hz, 1H), 5.36 (m, 1H), 5.13 (d, J = 5.9 Hz, 1H), 4.21 (q, J = 3.8, 3.1 Hz, 1H), 4.15 (dd, J = 6.4, 3.6 Hz, 1H), 3.72 (d, J = 10.8 Hz, 1H), 3.51 (dt, J = 10.4, 3.4 Hz, 1H), 3.29 (dd, J = 9.0, 6.4 Hz, 1H), 2.44 (m, 1H), 2.29 (d, J = 6.0 Hz, 1H), 2.25 (s, 3H), 2.23 (t, J = 7.7 Hz, 1H), 2.04 (s, 3H), 2.00-1.75 (m, 5H), 1.43 (s, 3H), 0.97 (d, J = 9.4 Hz, 3H), 0.87 (dd, J = 13.3, 6.5 Hz, 6H), 0.68 (d, J = 6.9 Hz, 3H)

MS (ES) calculated for $\text{C}_{31}\text{H}_{44}\text{N}_3\text{O}_6$ $[\text{M} + \text{H}]^+$ 554.3, found: 554.2

(*S*,2*Z*,4*E*)-*N*-(1,4-Dimethoxy-6,8-bis(methoxy-methoxy)-7-methyl-naphthalen-2-yl)-6-((4*S*,5*R*,6*R*)-6-((*R*)-1-((1*S*,3*R*,4*R*,5*S*)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylhepta-2,4-dienamide (84)



Method A: To a solution of dienolic acid **S6** (aka **79**; 5.4 mg, 12.4 μmol) in CH_2Cl_2 (100 μL) was added HOBt (3.34 mg, 24.7 μmol), EDCI (3.8 mg, 24.7 μmol), and triethyl amine (3.5 μL , 24.7 μmol). After stirring for 20 min at RT, the crude amine **56** (unstable; prepared immediately before use as described above; 8.5 mg, 24.7 μmol) in CH_2Cl_2 (100 μL) was added. The yellow solution was stirred for 6 h under Ar atmosphere. After removing the

solvent *in vacuo*, the crude residue was purified by preparative TLC (4:1, hexanes/EtOAc) to provide pure compound **84** (6.3 mg, 67%).

Method B: A mixture of CuI (0.25 mg, 10 mol%), the crude amide prepared from **S6** (aka **80**; see intermediate en route to saliniketal A, before acetone deprotection; 5.8 mg, 13.3 μmol), bromide **57** (6.4 mg, 15.6 μmol), K_3PO_4 (5.6 mg, 26.6 μmol), and *N,N'*-dimethylethylenediamine (0.5 μL) in toluene (150 μL) was stirred at 100 $^\circ\text{C}$ overnight. After removing the solvent *in vacuo*, the crude residue was purified by preparative TLC (4:1, hexanes/EtOAc) to yield pure compound **84** (5.7 mg, 57%).

Physical state: pale yellow foam

TLC: R_f = 0.45 (3:2, hexanes/EtOAc)

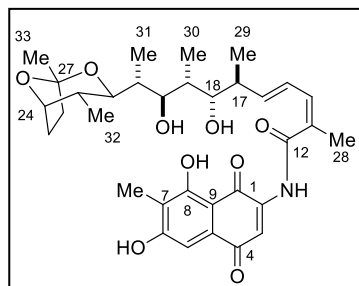
Optical rotation: $[\alpha]_D^{20} = +8.9$ (c = 0.05 in MeOH)

^1H NMR (600 MHz, CD_3OD) δ 7.67 (s, 1H), 7.05 (br t, J = 5.6 Hz, 1H), 6.86 (s, 1H), 6.37 (br d, J = 2.4 Hz, 1H), 5.84-5.81 (m, 1H), 5.37 (s, 2H), 5.03 (s, 2H), 4.23-4.20 (m, 1H), 3.98 (s, 3H), 3.80 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.68 (d, J = 7.8 Hz, 1H), 3.64 (s, 3H), 3.52-3.50 (m, 1H), 3.49 (s, 3H), 3.32 (s, 3H), 2.39 (s, 3H), 2.37-2.34 (m, 1H), 1.95 (s, 3H), 1.92-1.78 (m, 7H), 1.75-1.66 (m, 1H), 1.31 (d, J = 27.7 Hz, 3H), 1.26 (s, 3H), 1.08 – 0.79 (m, 9H), 0.68 (d, J = 6.9 Hz, 3H)

^{13}C NMR (150 MHz, CD_3OD) δ 173.8, 154.0, 151.1, 150.2, 143.7, 140.9, 132.7, 129.7, 126.1, 123.5, 121.7, 117.9, 109.7, 105.1, 104.8, 101.3, 99.8, 99.2, 93.8, 80.0, 74.0, 72.6, 72.3, 60.1, 56.4, 54.9, 38.4, 35.4, 35.1, 33.4, 24.1, 23.3, 22.4, 21.9, 19.0, 14.8, 10.8, 10.2, 9.0, 7.8

MS (ES) calculated for $\text{C}_{42}\text{H}_{62}\text{NO}_{11}$ $[\text{M} + \text{H}]^+$ 756.4, found: 756.4

(2Z,4E,6S,7S,8R,9R,10R)-N-(6,8-Dihydroxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-10-((1S,3S,4R,5S)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-7,9-dihydroxy-2,6,8-trimethylundeca-2,4-dienamide (Salinisporamycin, 2)



A solution of ceric ammonium nitrate (5.5 mg, 10 μmol) in 1:1 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (100 μL) was added to a 0 $^\circ\text{C}$ solution of **84** (2.5 mg, 10.0 μmol) in CH_3CN (200 μL) and H_2O (10 μL). The resulting solution was stirred at 0 $^\circ\text{C}$ for 15 min and then was poured into H_2O (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3×1 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo* to give a bright yellow oil. The

crude residue (**82**) was filtered over a short path of silica gel. The residue obtained after removal of the solvent was dissolved in $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$ (100 $\mu\text{L}/25$ $\mu\text{L}/10$ μL) and NaI (1.0 mg, 6.7 μmol) and HCl (3N aq., 10 μL) were added. The resulting mixture was stirred for 24 h at RT. Saturated aq. NaHCO_3 (150 μL) was added slowly to the reaction mixture followed by EtOAc (500 μL). The aqueous phase was extracted with EtOAc (3×0.5 mL). The combined organic phase was dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1, $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give salinisporamycin (**2**, 1.2 mg, 62%, 2 steps).

Physical state: off-white foam

TLC: R_f = 0.80 (4:1, $\text{CHCl}_3/\text{MeOH}$)

Optical rotation: $[\alpha]_D^{20} = +10.5$ ($c = 0.05$ in CD_3OD)

^1H NMR (600 MHz, CD_3OD) δ 7.57 (s, 1H), 6.95 (s, 1H), 6.79 (dd, $J = 15.0, 11.1$ Hz, 1H), 6.47 (br d, $J = 11.4$ Hz, 1H), 6.03 (dd, $J = 15.1, 7.9$ Hz, 1H), 4.20 (dd, $J = 6.7, 3.4$ Hz, 1H), 3.93 (dd, $J = 10.6, 1.7$ Hz, 1H), 3.78 (dd, $J = 9.1, 1.8$ Hz, 1H), 3.51 (dd, $J = 8.4, 4.3$ Hz, 1H), 2.43 (ddq, $J = 9.2, 7.6, 6.8$ Hz, 1H), 2.10 (d, $J = 1.4$ Hz, 3H), 2.05 (s, 3H), 1.75–2.06 (m, 7H), 1.39 (s, 3H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 0.71 (d, $J = 6.8$ Hz, 3H)

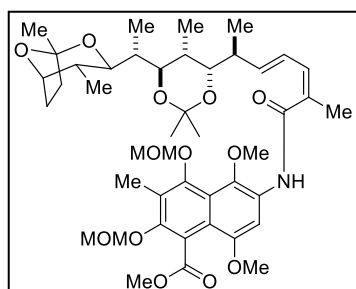
^{13}C NMR (125 MHz, CD_3OD) δ 187.8, 181.3, 171.9, 170.1, 164.5, 146.0, 143.2, 138.6, 132.6, 129.8, 127.6, 118.0, 116.4, 112.7, 106.7, 106.5, 81.8, 78.3, 75.8, 75.2, 42.4, 37.1, 36.4, 35.4, 35.4, 24.4, 24.1, 20.7, 17.1, 13.0, 11.3, 10.5, 8.2

MS (ES) calculated for $\text{C}_{33}\text{H}_{44}\text{NO}_9$ $[\text{M} + \text{H}]^+$ 598.3, found 598.3

Table S5. Comparison of ^1H and ^{13}C NMR for natural (500 and 125 MHz, CD_3OD) and synthetic salinisporamycin (**2**, 600 and 125 MHz, CD_3OD)

No.	Natural		Synthetic	
	δH , mult. (J in Hz)	δC	δH , mult. (J in Hz)	δC
1		181.3		181.3
2		143.2		143.2
3	7.55, s	116.4	7.57, s	116.4
4		187.9		187.8
5	6.96, s	112.7	6.95, s	112.7
6		164.5		164.5
7		117.8		118.0
8		172.0		171.9
9		106.6		106.7
10		132.5		132.6
11	2.06, s	8.2	2.05, s	8.2
12		170.1		170.1
13		129.7		129.8
14	6.46, br d (11.3)	138.6	6.47, dd (11.4, 1.6)	138.6
15	6.79, dd, (15.0, 10.9)	127.6	6.79, dd (15.0, 11.1)	127.6
16	6.03, dd, (15.0, 8.3)	146.0	6.03, dd (15.1, 7.9)	146.0
17	2.43, m, (8.3, 7.5)	42.4	2.43, ddq (9.2, 7.6, 6.8)	42.4
18	3.78, dd, (9.8, 1.9)	75.8	3.78, dd (9.1, 1.8)	75.8
19	1.83, m, (6.8, 4.5, 1.9)	36.4	1.75-2.06, m (1H of 7H)	36.4
20	3.50, dd, (8.3, 4.5)	78.4	3.51, dd (8.4, 4.3)	78.3
21	1.82, br dq (8.3, 6.8, 1.5)	37.1	1.75-2.06, m (1H of 7H)	37.1
22	3.94, br d (10.5, 1.5)	75.2	3.93, dd (10.6, 1.7)	75.2
23	1.97, br dq (10.5, 6.8, 3.8)	35.4	1.75-2.06, m (1H of 7H)	35.4
24	4.20, br d (6.8, 3.8)	81.8	4.20, dd (6.7, 3.4)	81.8
25a	1.93, m	24.1	1.75-2.06, m (1H of 7H)	24.1
25b	1.88, m		1.75-2.06, m (1H of 7H)	
26a	1.80, m	35.4	1.75-2.06, m (1H of 7H)	35.4
26b	2.01-2.05, m		1.75-2.06, m (1H of 7H)	
27		106.6		106.6
28	2.07, d (1.1)	20.7	2.10, d (1.4)	20.7
29	0.99, d (6.8)	17.1	0.99, d (6.8)	17.1
30	1.00, d (6.8)	11.3	1.01, d (7.0)	11.3
31	0.88, d (6.8)	10.5	0.89, d (6.9)	10.5
32	0.71, d (6.8)	13.0	0.71, d (6.8)	13.0
33	1.39, s	24.4	1.39, s	24.4

Methyl 6-((*S*,2*Z*,4*E*)-6-((4*S*,5*R*,6*R*)-6-((*R*)-1-((1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]-octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylhepta-2,4-dienamido)-5,8-dimethoxy-2,4-bis(methoxymethoxy)-3-methyl-1-naphthoate (85**)**



To a solution of dienamic acid **S6** (aka **79**; 5.4 mg, 12.4 μ mol) in CH_2Cl_2 (100 μ L) was added HOBt (3.34 mg, 24.7 μ mol), EDCI (3.8 mg, 24.7 μ mol), and triethyl amine (3.5 μ L, 24.7 μ mol). After stirring for 20 min at RT, a solution of the crude amine **78** (unstable; freshly prepared as described above before use; 0.25 M in CH_2Cl_2) in CH_2Cl_2 (100 μ L) was added. The yellow solution was stirred for 6 h under Ar atmosphere. After removing the

solvent *in vacuo*, the crude residue was purified by preparative TLC (4:1, hexanes/EtOAc) to yield pure compound **85** (6.3 mg, 67%).

Physical state: pale yellow foam

TLC: R_f = 0.30 (3:1, hexanes/EtOAc)

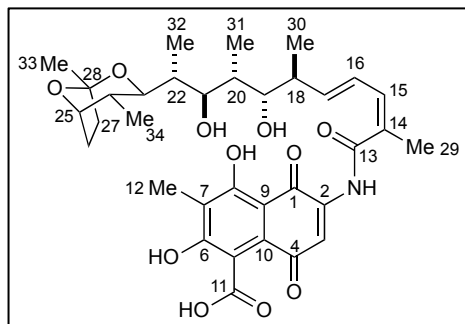
Optical rotation: $[\alpha]_D^{20}$ = +13.2 (c = 0.07 in EtOAc)

^1H NMR (500 MHz, CD_3OD) δ 7.43 (s, 1H), 6.59 (dd, J = 15.0, 11.1 Hz, 1H), 6.20 (dd, J = 11.4, 1.6 Hz, 1H), 5.82 (dd, J = 15.1, 7.9 Hz, 1H), 5.38 (s, 2H), 5.14 (s, 2H), 4.22 (m, 1H), 3.99 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 3.75-3.83 (m, 2H), 3.66 (s, 3H), 3.55 (s, 3H), 3.50-3.56 (m, 1H), 2.30-2.39 (m, 1H), 2.35 (s, 3H), 2.00 (s, 3H), 1.80-2.00 (m, 7H), 1.43 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 0.81-1.00 (m [3 \times d], 9H), 0.74 (d, J = 6.9 Hz, 3H)

^{13}C NMR (125 MHz, CD_3OD) δ 175.2, 172.4, 156.4, 153.7, 152.1, 150.0, 143.3, 142.3, 134.3, 130.2, 129.7, 128.2, 122.1, 119.7, 119.4, 113.7, 106.4, 101.4, 99.4, 95.6, 81.6, 78.0, 75.7, 74.9, 61.2, 58.9, 58.1, 57.1, 56.4, 55.3, 42.3, 37.1, 35.7, 35.2, 35.1, 24.9, 24.3, 24.2, 20.9, 17.0, 14.5, 12.8, 11.1, 10.5

MS (ES) calculated for $\text{C}_{44}\text{H}_{64}\text{NO}_{13}$ $[\text{M} + \text{H}]^+$ 814.4; found 814.4

6-((2*Z*,4*E*,6*S*,7*S*,8*R*,9*R*,10*R*)-10-((1*S*,3*S*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-7,9-dihydroxy-2,6,8-trimethylundeca-2,4-dienamido)-2,4-dihydroxy-3-methyl-5,8-dioxo-5,8-dihydro-naphthalene-1-carboxylic acid (Rifsaliniketal, **9)**



A solution of ceric ammonium nitrate (5.2 mg, 10 μ mol) in 1:1 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (100 μ L) was added to a 0 $^\circ\text{C}$ solution of **85** (2.3 mg, 3.2 μ mol) in CH_3CN (100 μ L) and H_2O (5 μ L). The resulting solution was stirred at 0 $^\circ\text{C}$ for 15 min and then was poured into H_2O (0.5 mL). The aq. phase was extracted with CH_2Cl_2 (3 \times 1 mL) and the combined organic extracts were dried (MgSO_4), filtered,

and concentrated *in vacuo*. The residue (**83**) was filtered over a short path of silica gel. The residue obtained after removal of the solvent was dissolved in THF/MeOH/H₂O (50 μ L/15 μ L/10 μ L) and NaI (1.0 mg, 6.7 μ mol) and aq. HCl (3N, 10 μ L) were added. The resulting mixture was stirred for 24 h at RT after which the solvent was removed and the residue dissolved in MeOH (70 μ L). An aq. LiOH solution (1.0 M, 20 μ L) was added and the mixture was stirred at 0 °C for overnight. Saturated aq. NaHCO₃ (150 μ L) was added, followed by extraction with EtOAc (3 \times 0.5 mL). The combined organic phase was dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by preparative TLC (5:1, CH₂Cl₂/MeOH) to give rifsaliniketal (**9**, 1.0 mg, 47%, 3 steps).

Physical state: yellow foam

TLC: R_f = 0.20 (EtOAc)

Optical rotation: $[\alpha]_D^{20}$ = +10.0 (c = 0.05 in acetone)

¹H NMR (600 MHz, CD₃OD) δ 7.66 (s, 1H), 6.78 (dd, J = 15.1, 11.1 Hz, 1H), 6.46 (dd, J = 11.4, 1.6 Hz, 1H), 6.02 (dd, J = 15.1, 7.9 Hz, 1H), 4.22 (dd, J = 6.7, 3.4 Hz, 1H), 3.95 (dd, J = 10.6, 1.7 Hz, 1H), 3.78 (dd, J = 9.1, 1.8 Hz, 1H), 3.51 (dd, J = 8.4, 2.9 Hz, 1H), 2.43 (ddq, J = 9.2, 7.6, 6.8 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 1.75-2.05 (m, 7H), 1.39 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H)

¹³C NMR (125 MHz, CD₃OD) δ 186.4, 184.0, 175.8, 169.9, 166.8, 162.8, 145.6, 141.3, 138.2, 129.5, 128.8, 127.5, 120.9, 117.6 (2), 106.9, 106.4, 81.5, 78.2, 75.6, 75.0, 42.3, 36.9, 36.0, 35.2, 35.1, 24.8, 24.1, 20.5, 16.9, 12.8, 11.1, 10.3, 8.0

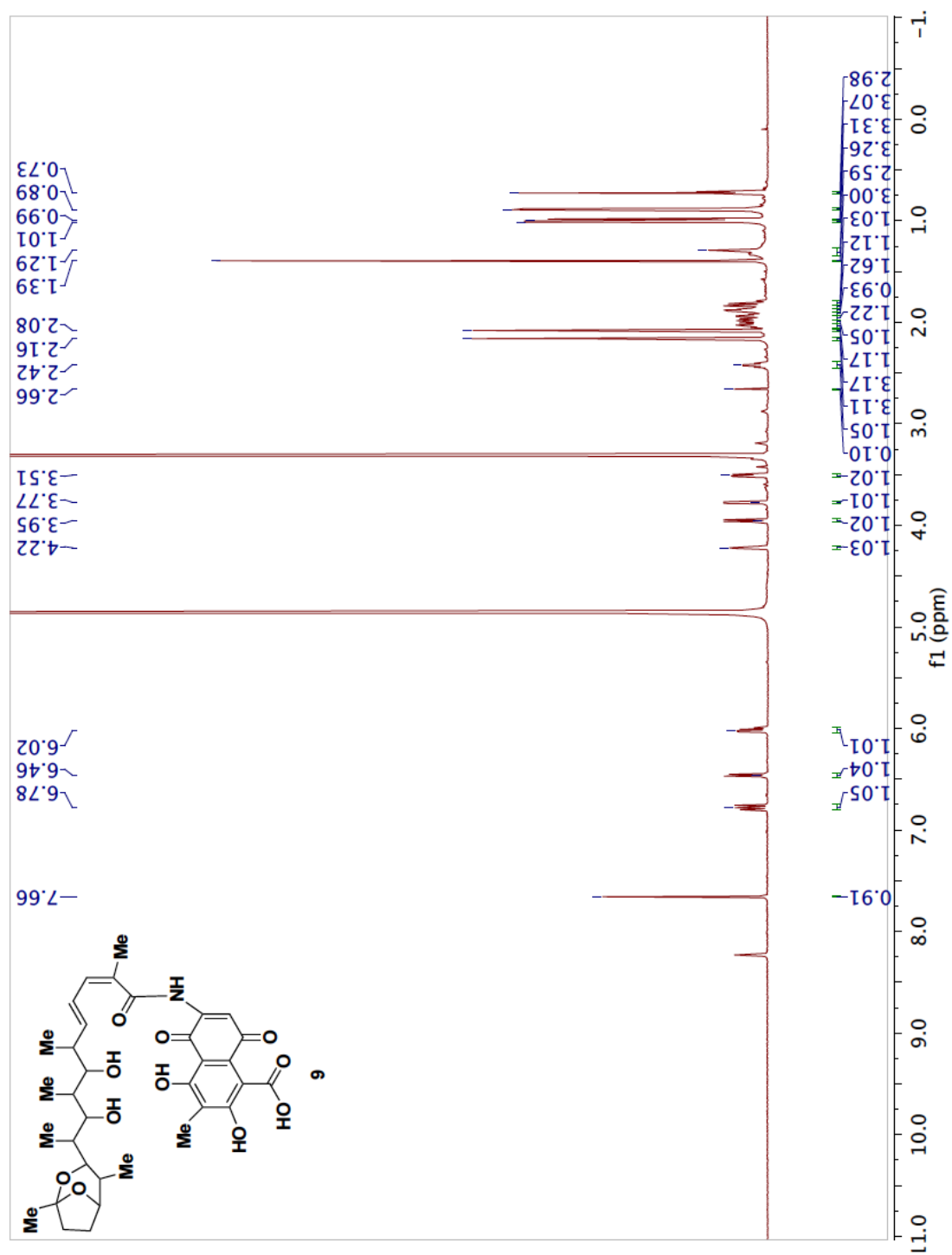
MS (ES) calculated for C₃₄H₄₄NO₁₁ $[M + H]^+$ 642.3; found 642.3

Table S6. Comparison of ^1H and ^{13}C NMR for natural (600 and 125 MHz, CD_3OD) and synthetic rifsaliniketal (**9**, 600 and 125 MHz, CD_3OD)

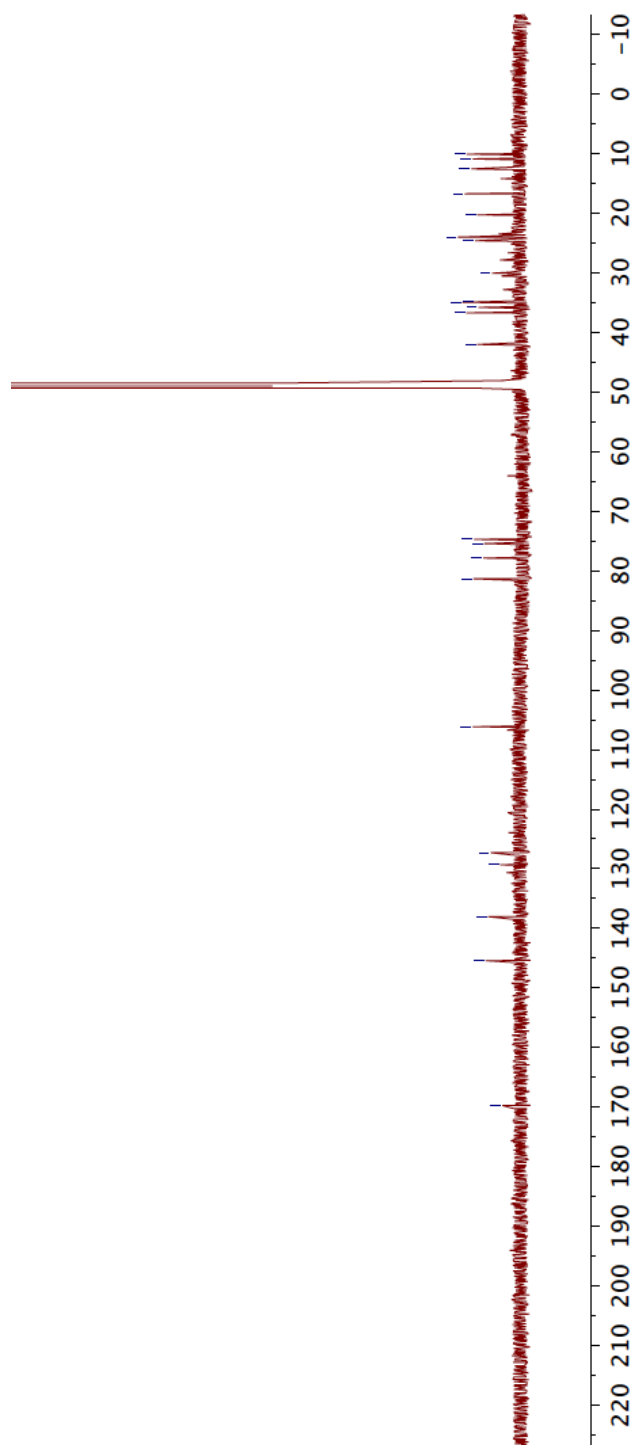
No.	Natural		Synthetic	
	δH , mult. (J in Hz)	δC	δH , mult. (J in Hz)	δC
1		^a		186.4
2		141.1 ^b		141.3
3	7.66, s	117.5 ^b	7.66, s	117.6
4		183.8 ^b		184.0
5		117.5 ^b		117.6
6		162.6 ^b		162.8
7		^a		120.9
8		^a		175.8
9		^a		106.9
10		128.6 ^b		128.8
11		^a		166.8
12	2.16, s	7.9 ^b	2.16, s	8.0
13		169.7		169.9
14		129.3		129.5
15	6.46, br d (11.2)	138.0	6.46, dd (11.4, 1.6)	138.2
16	6.78, dd (15.2, 11.2)	127.3	6.78, dd (15.1, 11.1)	127.5
17	6.02, dd (15.2, 8.0)	145.4	6.02, dd (15.1, 7.9)	145.6
18	2.42, ddq (9.1, 8.0, 6.9)	42.0	2.43, ddq (9.2, 7.6, 6.8)	42.3
19	3.77, dd (9.1, 1.4)	75.5	3.78, dd (9.1, 1.8)	75.6
20	1.86-1.89, m	35.8	1.75-2.05, m (1 of 7H)	36.0
21	3.51, dd (8.3, 4.3)	77.9	3.51, dd (8.4, 2.9)	78.2
22	1.83-1.89, m	36.7	1.75-2.05, m (1 of 7H)	36.9
23	3.95, dd (10.6, 1.1)	74.7	3.95, dd (10.6, 1.7)	75.0
24	1.97-2.01, m	35.0	1.75-2.05, m (1 of 7H)	35.2
25	4.22, dd (6.7, 3.4)	81.3	4.22, dd (6.7, 3.4)	81.5
26a	1.89-1.93, m	24.6	1.75-2.05, m (1 of 7H)	24.8
26b	1.93-1.97, m		1.75-2.05, m (1 of 7H)	
27a	1.78-1.83, m	34.9	1.75-2.05, m (1 of 7H)	35.1
27b	2.01-2.05, m		1.75-2.05, m (1 of 7H)	
28		106.2		106.4
29	2.08, s	20.3	2.08, s	20.5
30	0.99, d (6.9)	16.7	0.99, d (6.8)	16.9
31	1.01, d (7.2)	10.9	1.01, d (7.0)	11.1
32	0.89, d (7.0)	10.1	0.89, d (6.9)	10.3
33	1.39, s	24.0	1.39, s	24.1
34	0.73, d (6.9)	12.6	0.72, d (6.9)	12.8

^a Shifts not determined due to small amount of material. ^b Shifts determined from HMBC.

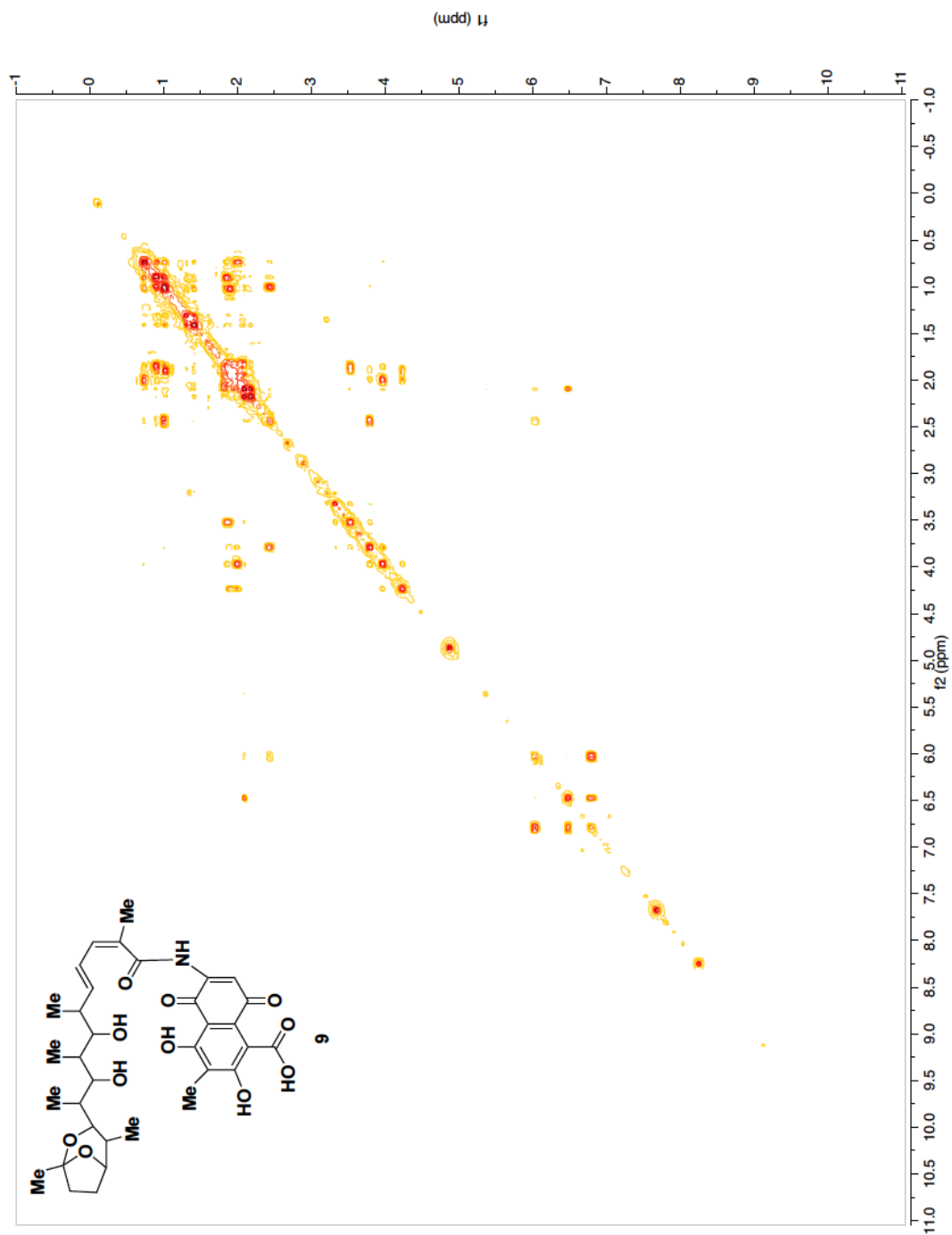
^1H NMR spectrum of isolated rifsaliniketal **9** in CD_3OD



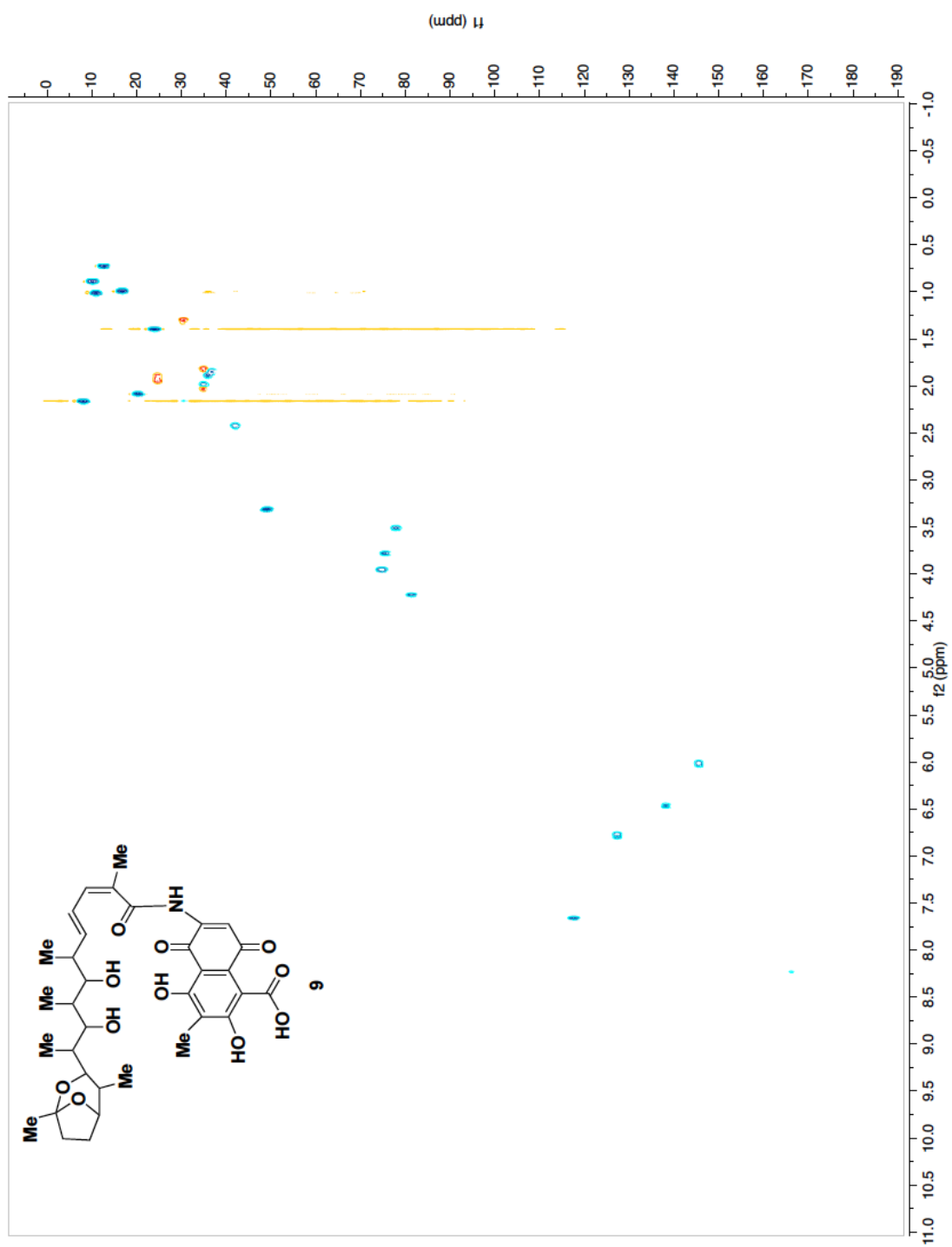
^{13}C NMR spectrum of isolated rifsaliniketal **9** in CD_3OD



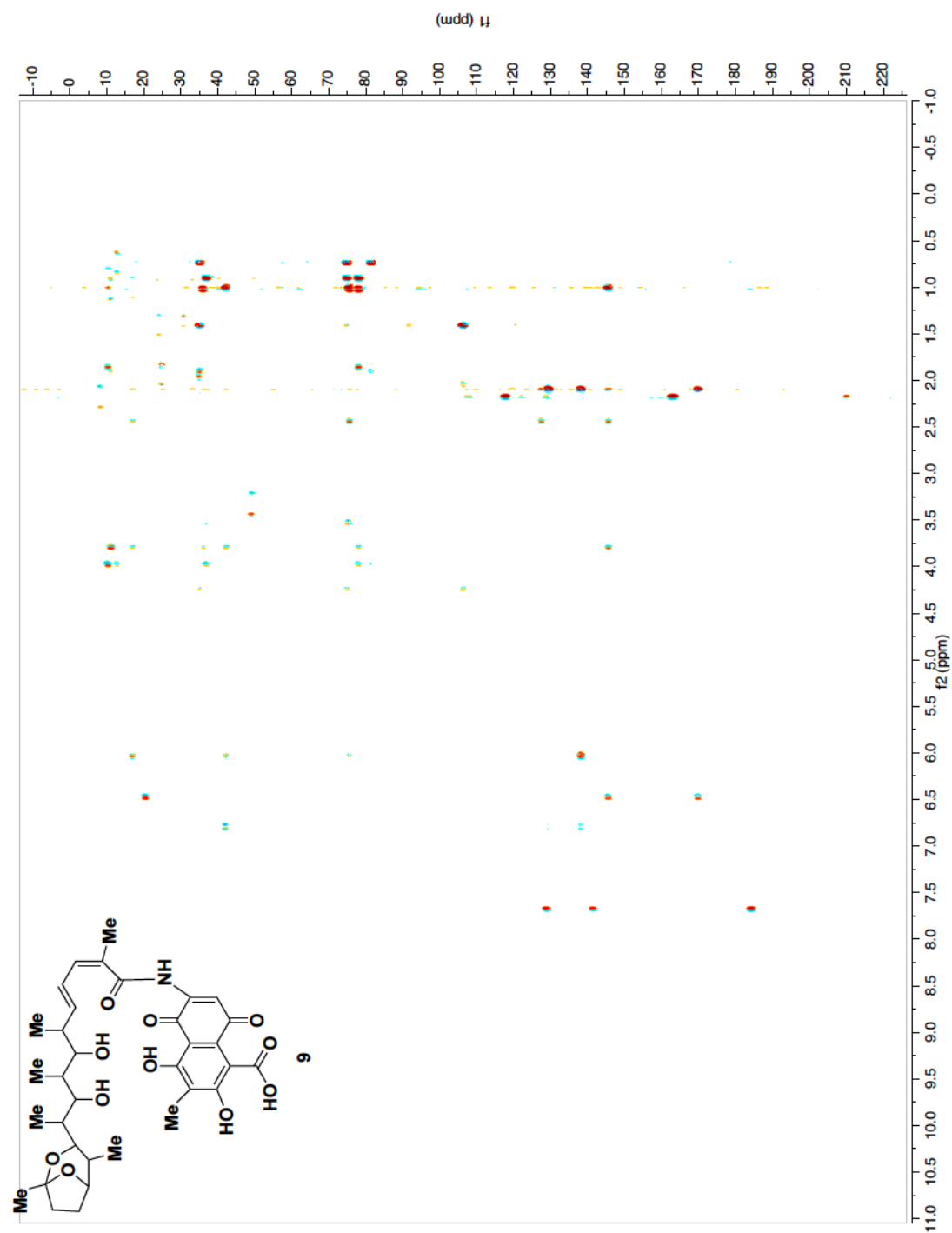
COSY spectrum of isolated rifsaliniketal **9** in CD₃OD



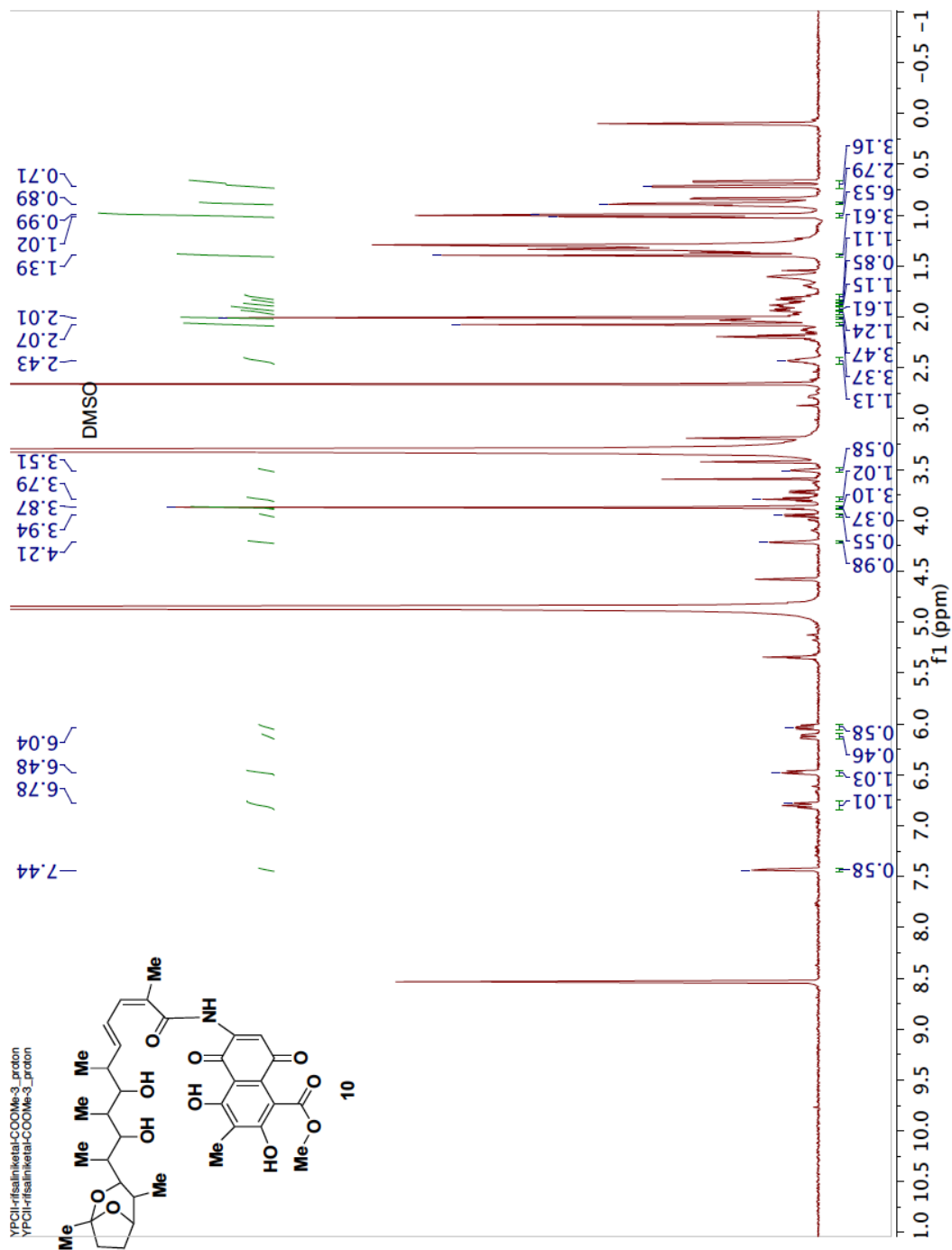
HSQC spectrum of isolated rifsaliniketal **9** in CD₃OD



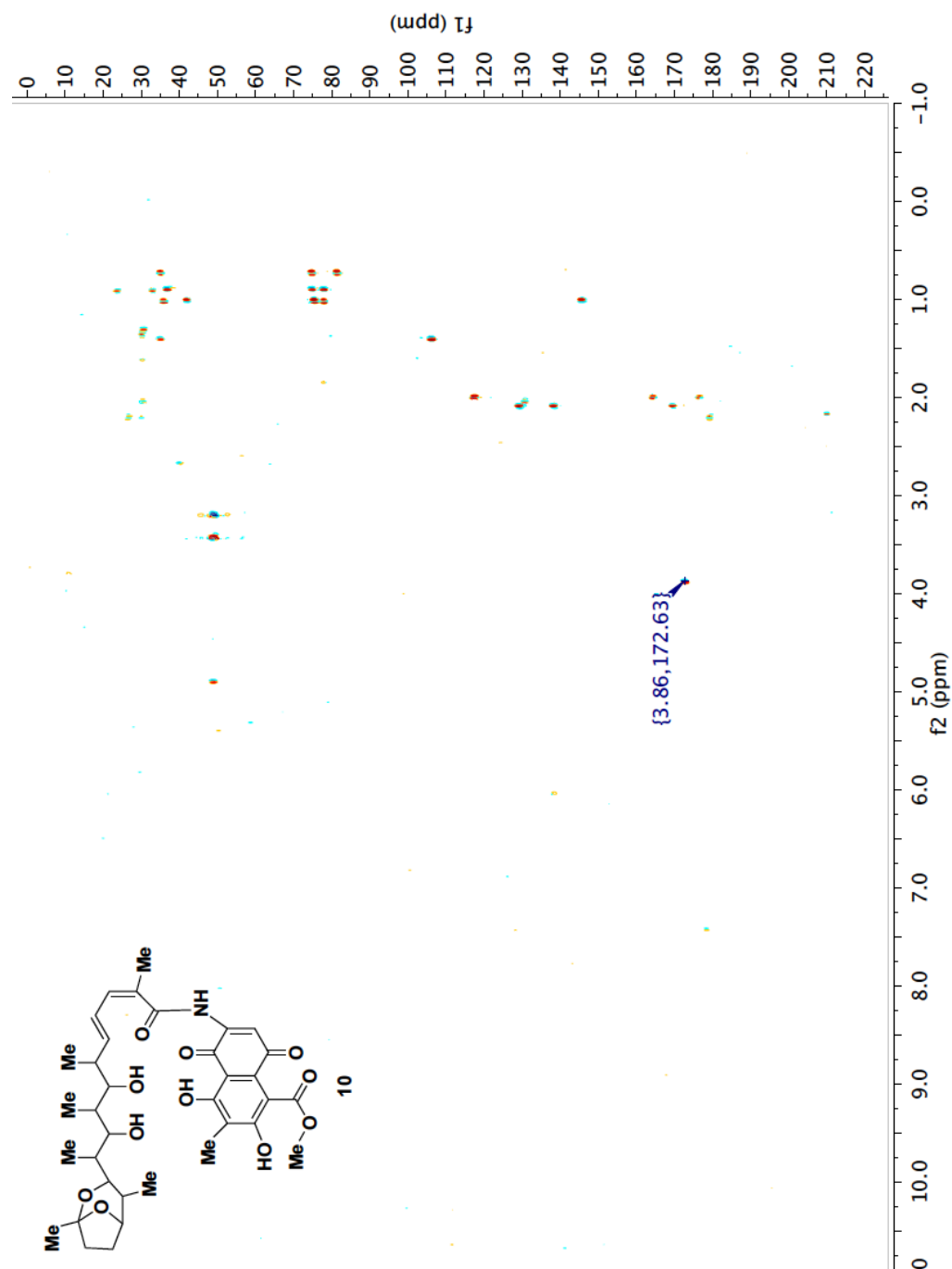
HMBC spectrum of isolated rifsaliniketal **9** in CD₃OD



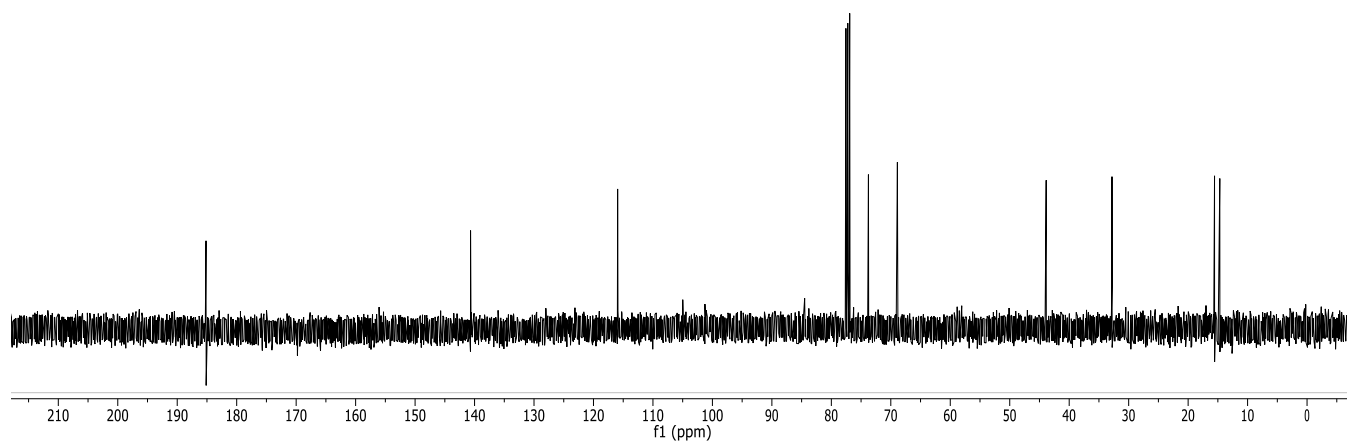
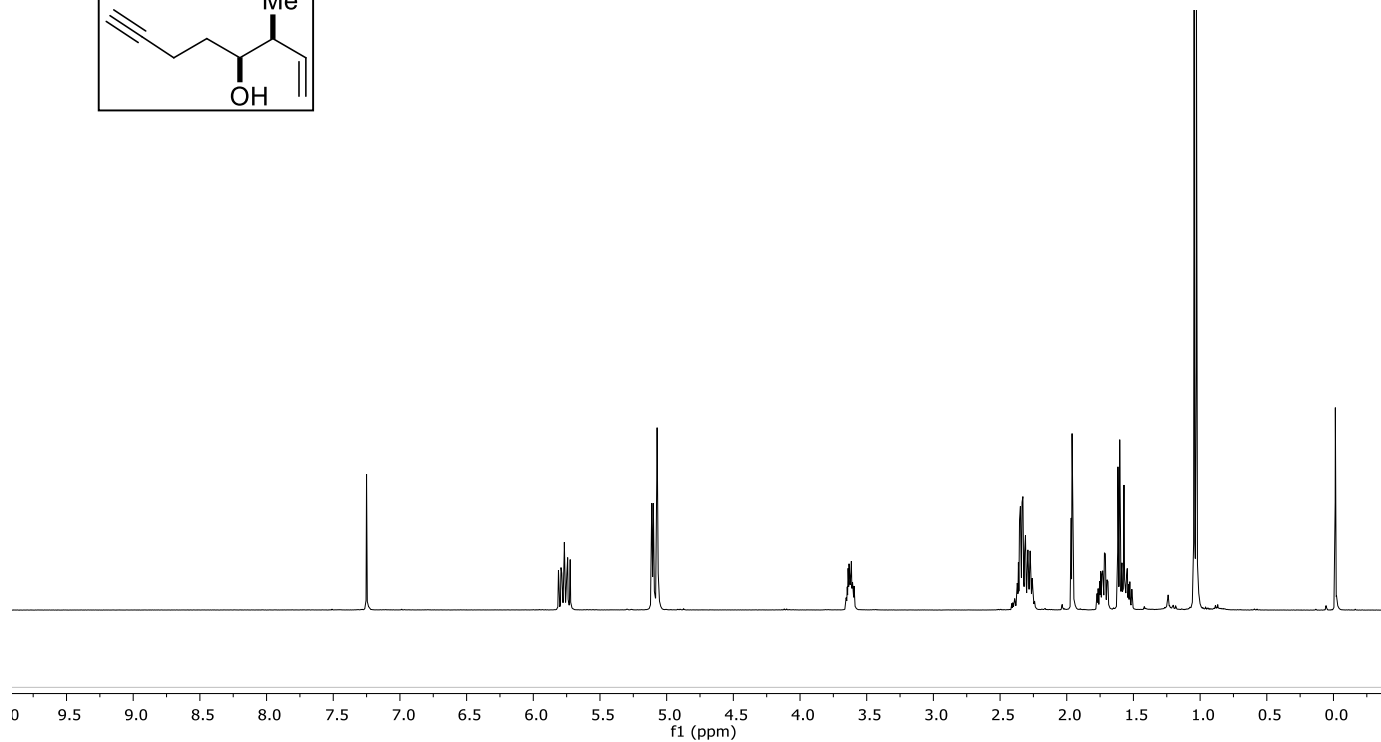
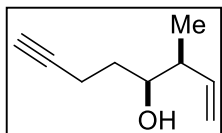
^1H spectrum of rifsaliniketal methyl ester **9a** in CD_3OD



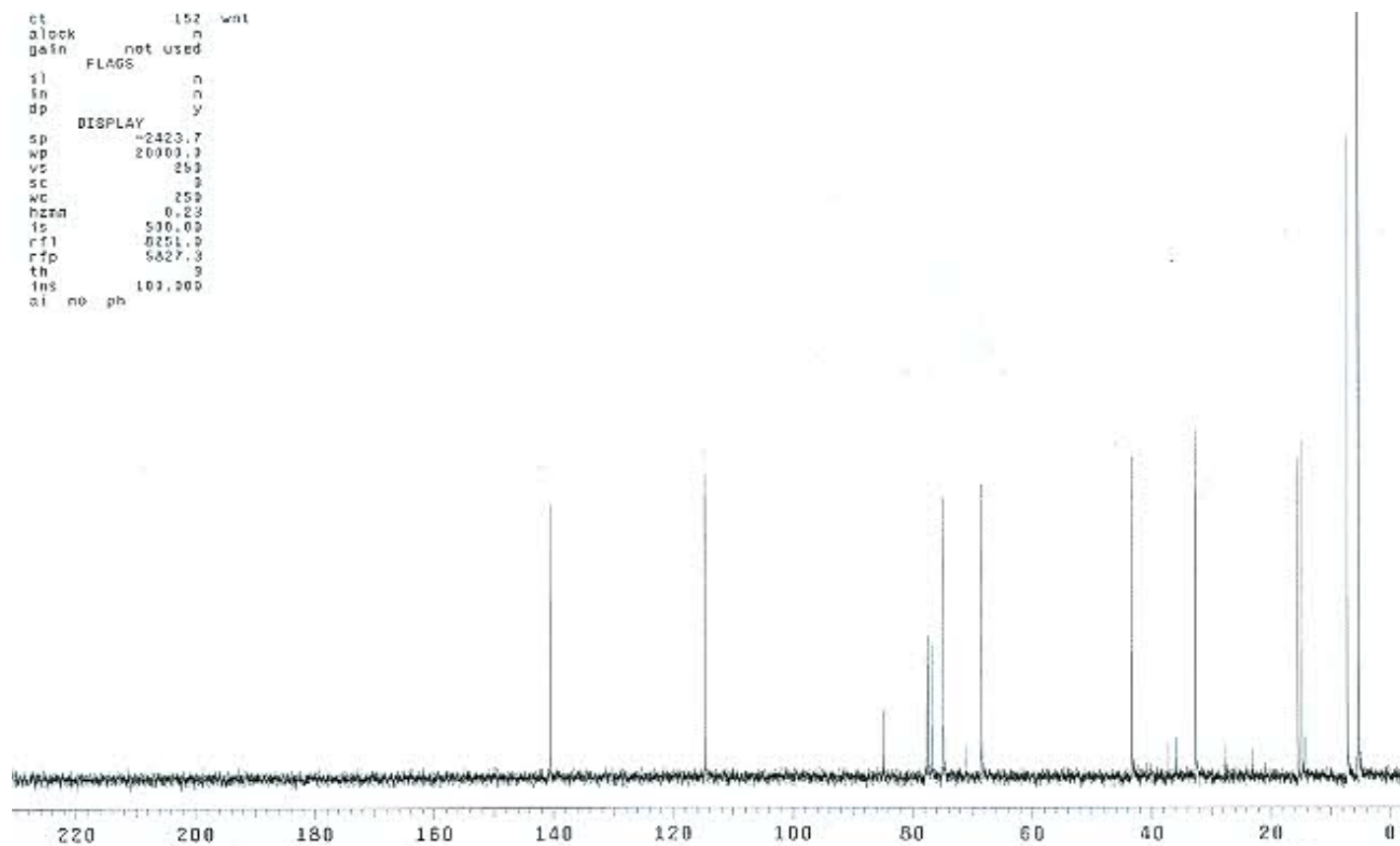
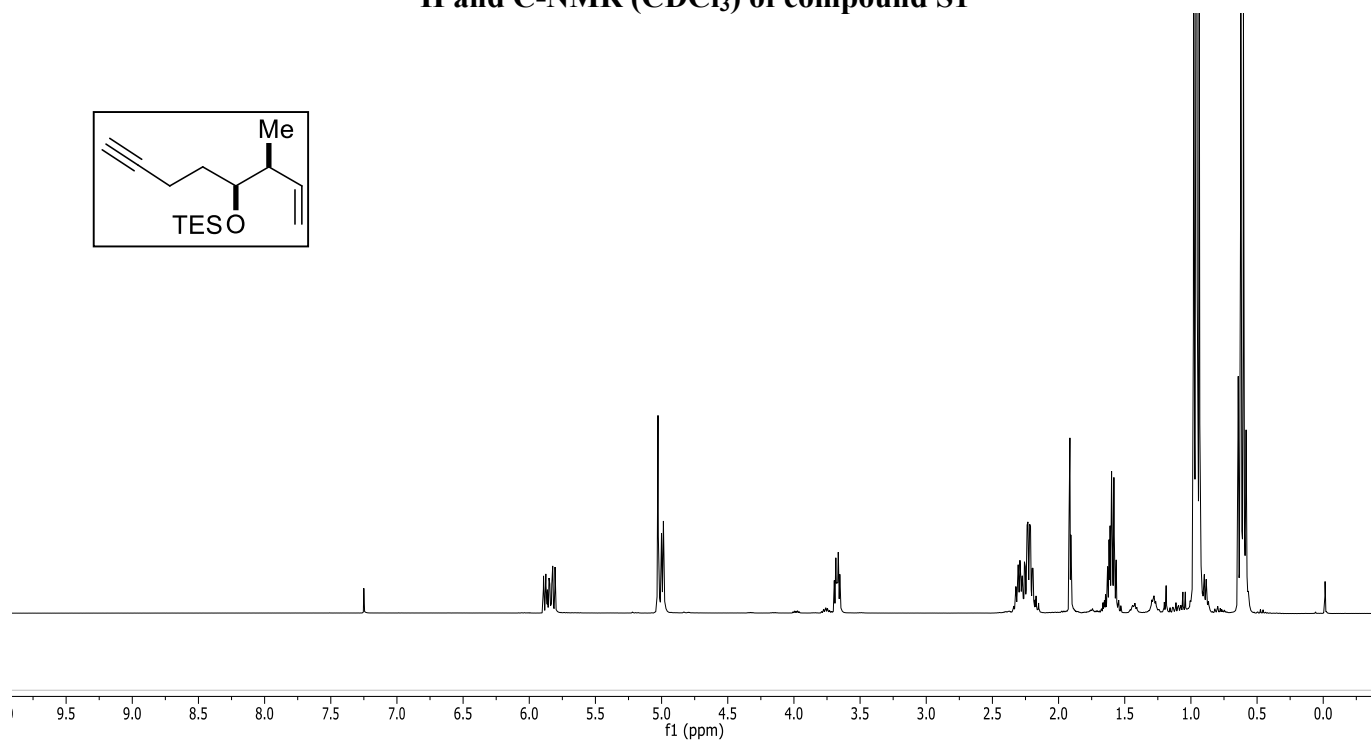
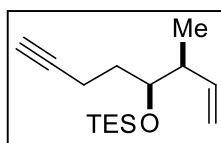
HMBC spectrum of rifsaliniketal methyl ester **9a** in CD₃OD



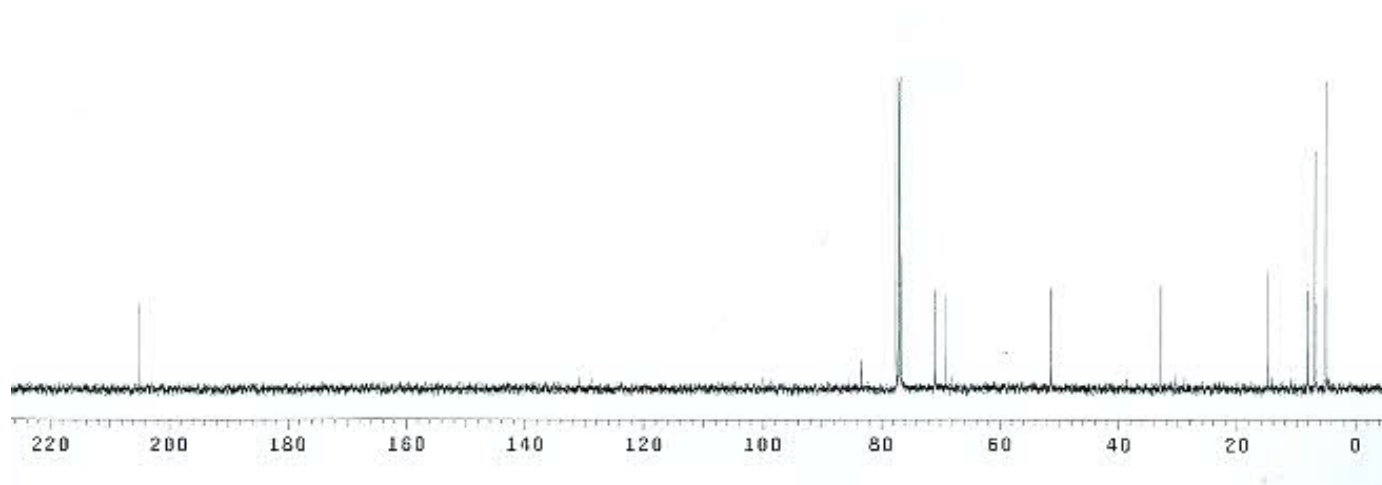
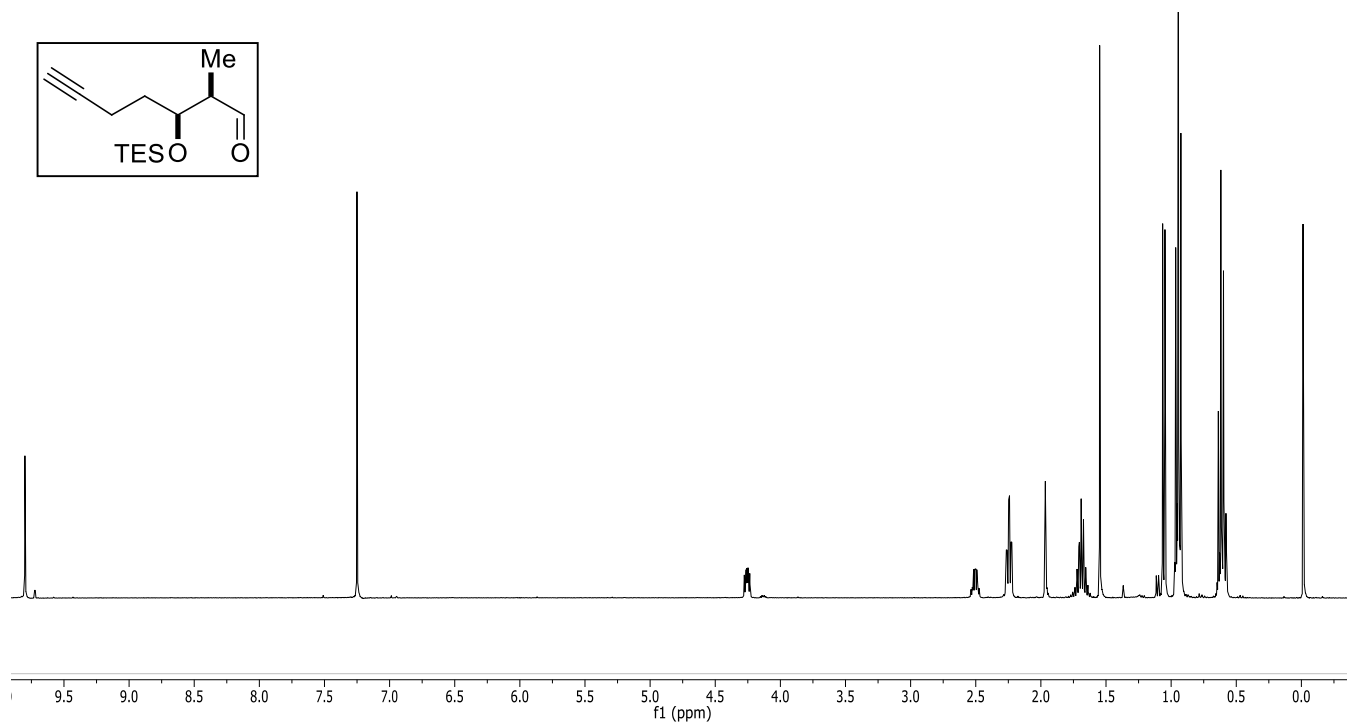
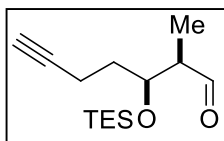
H and C-NMR (CDCl₃) of compound 17



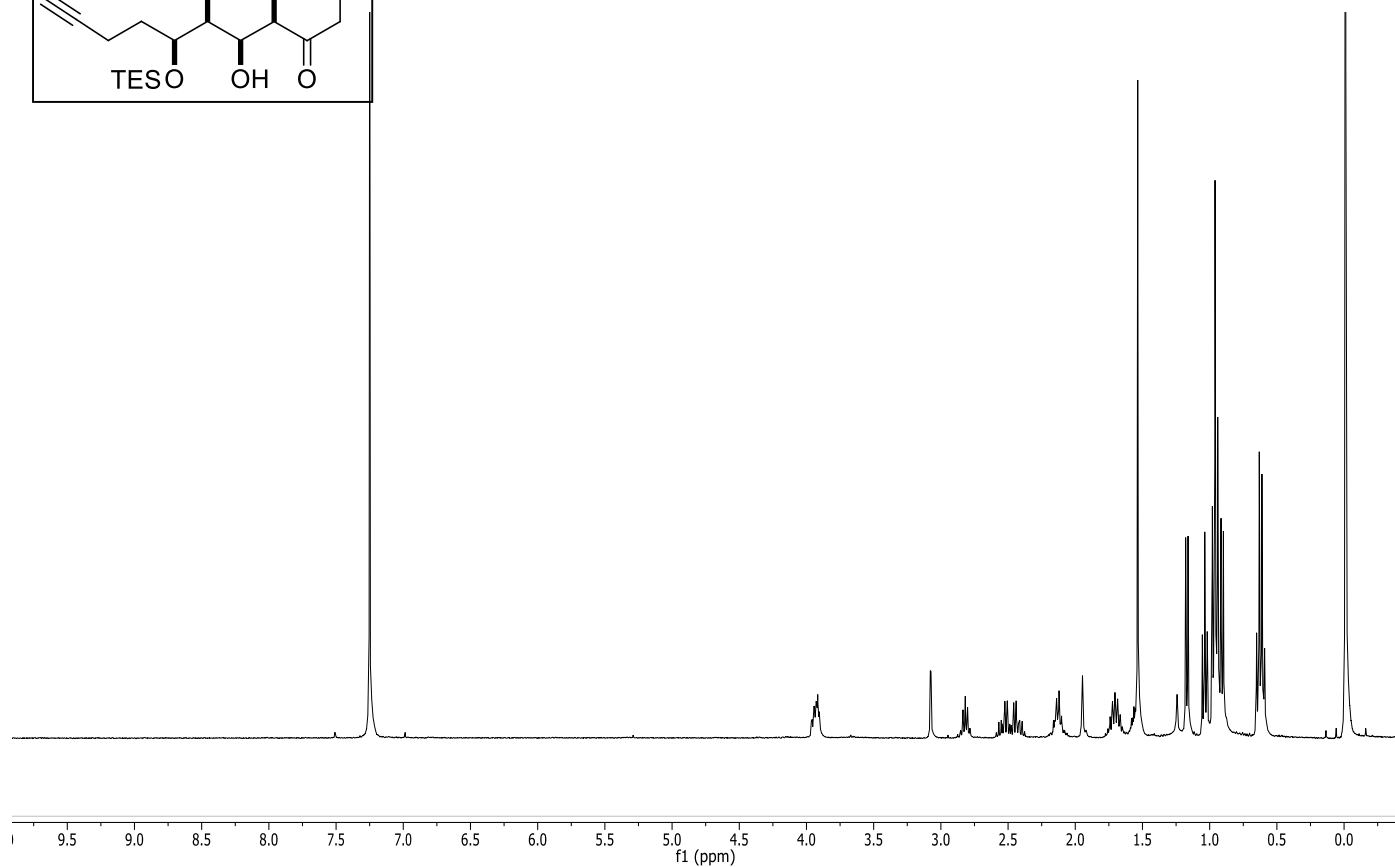
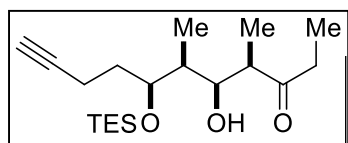
H and C-NMR (CDCl₃) of compound S1



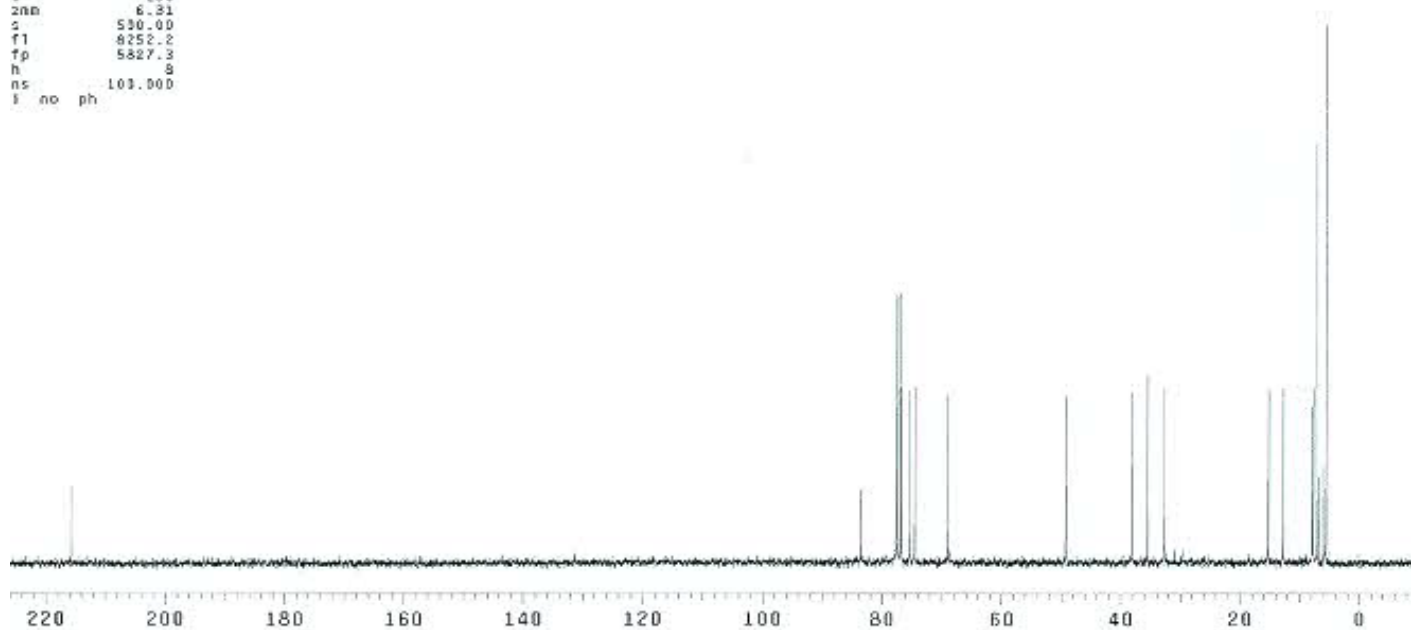
H and C-NMR (CDCl₃) of compound 13



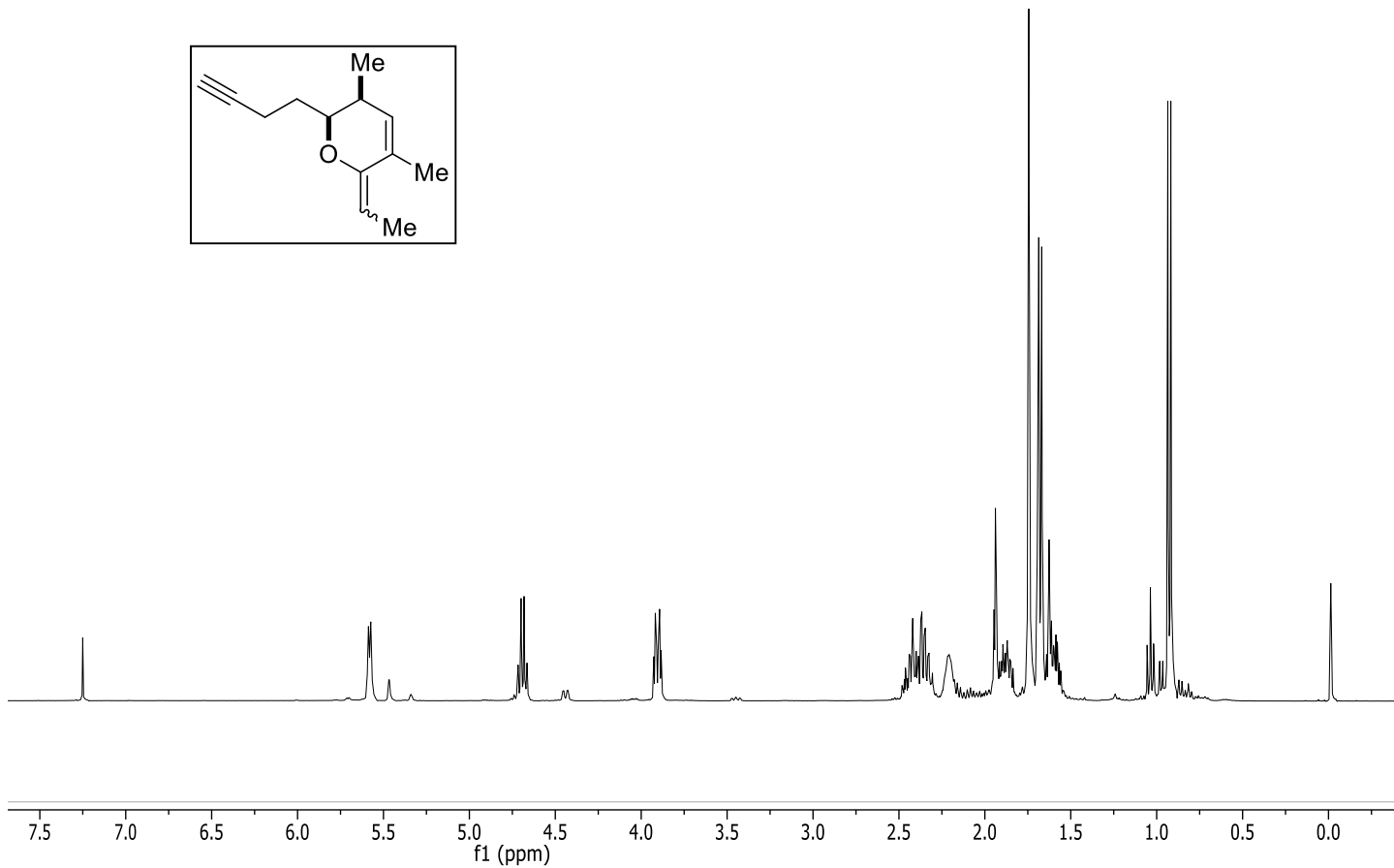
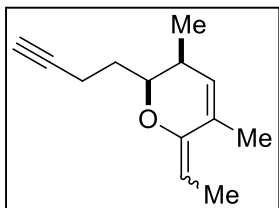
H and C-NMR (CDCl₃) of compound 18-*syn*



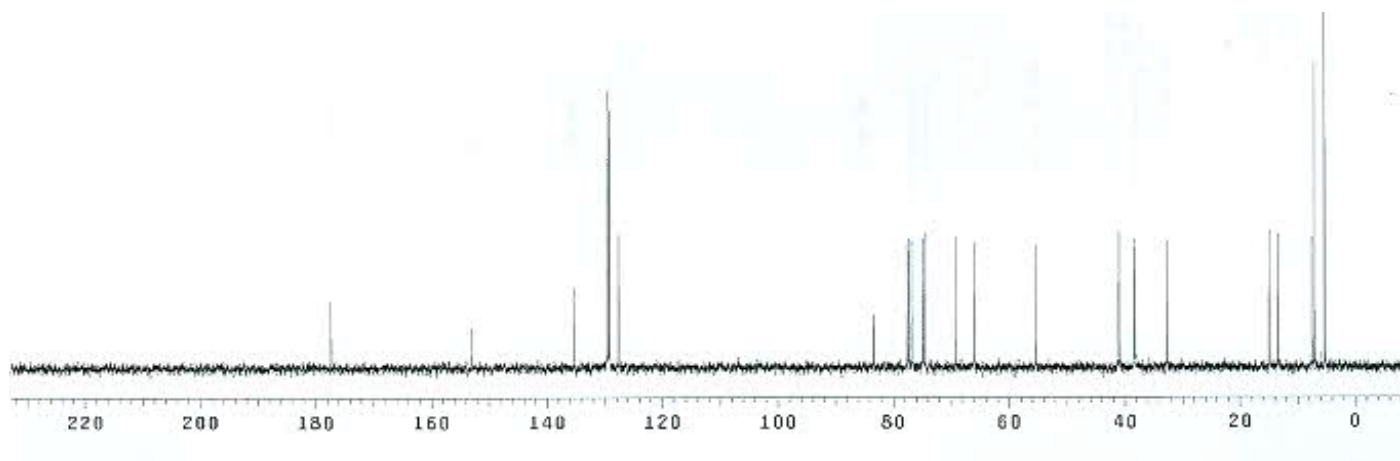
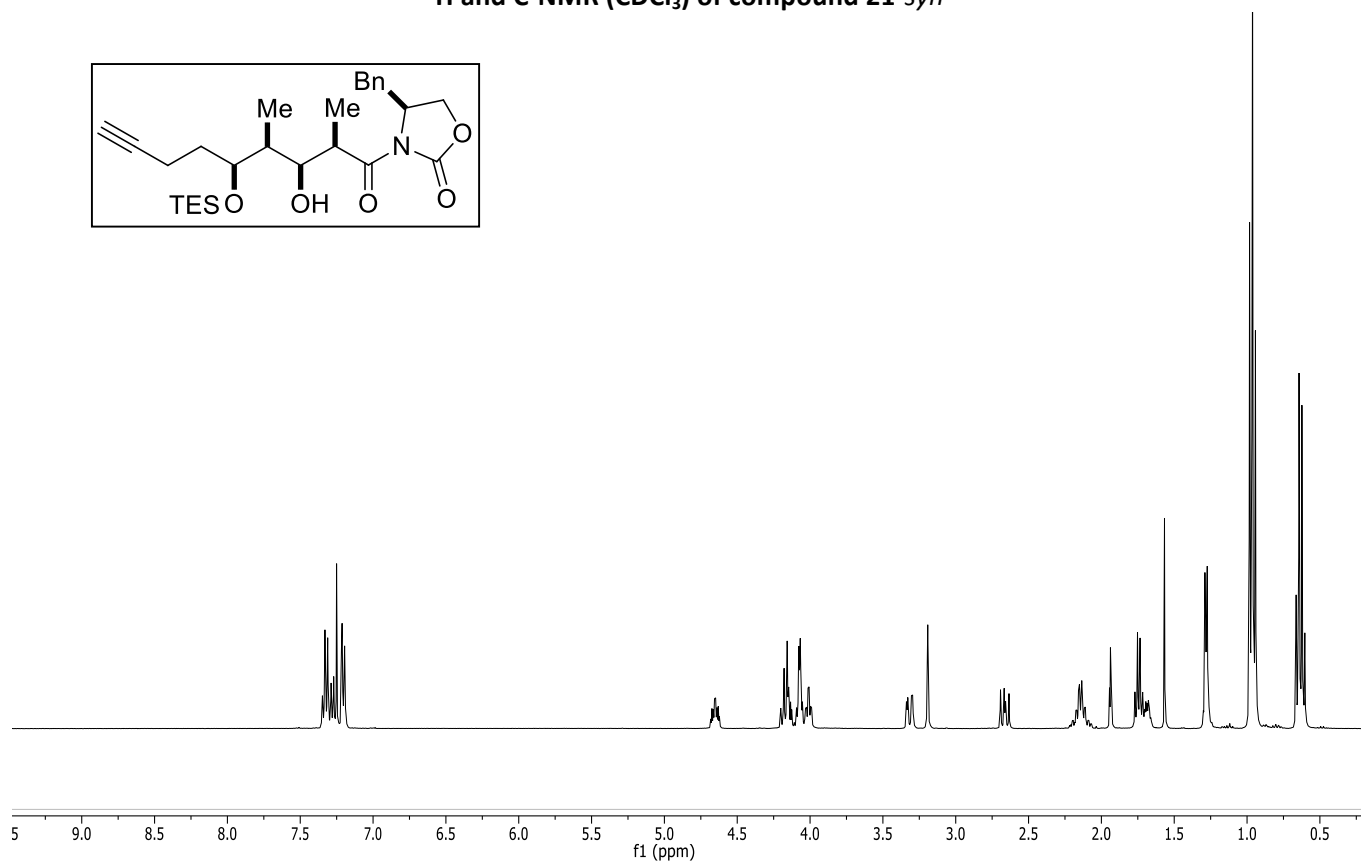
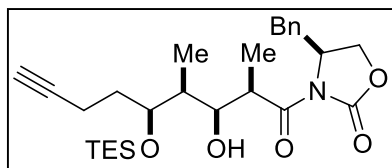
- 7.2
 c 0
 c 250
 2nm 6.31
 s 510.00
 f1 8252.2
 fp 5827.3
 h 8
 ns 101.000
 f no ph



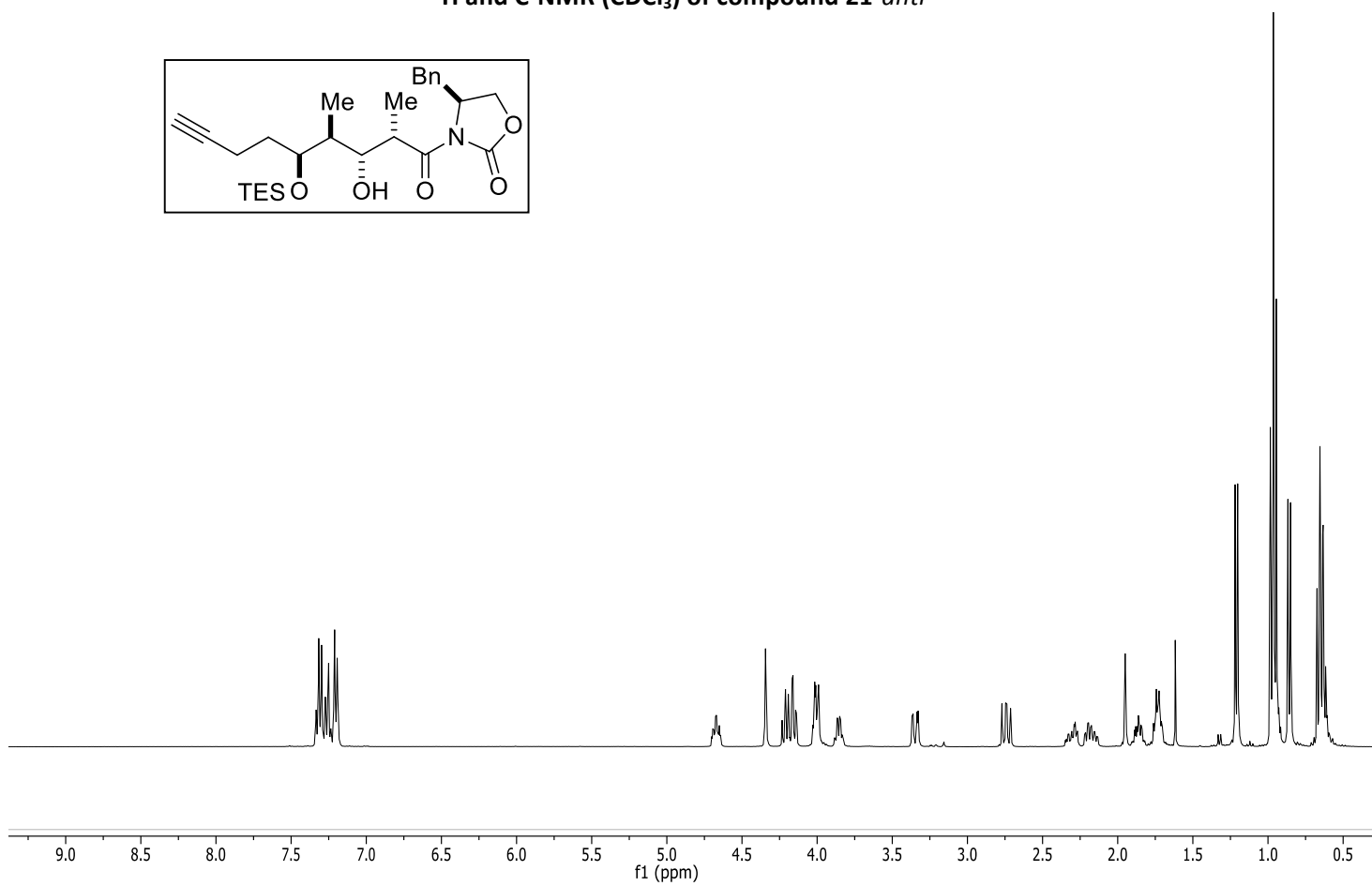
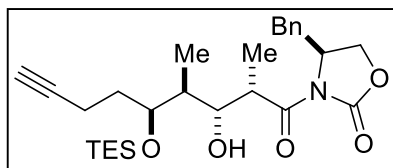
H- NMR (CDCl₃) of compound 19



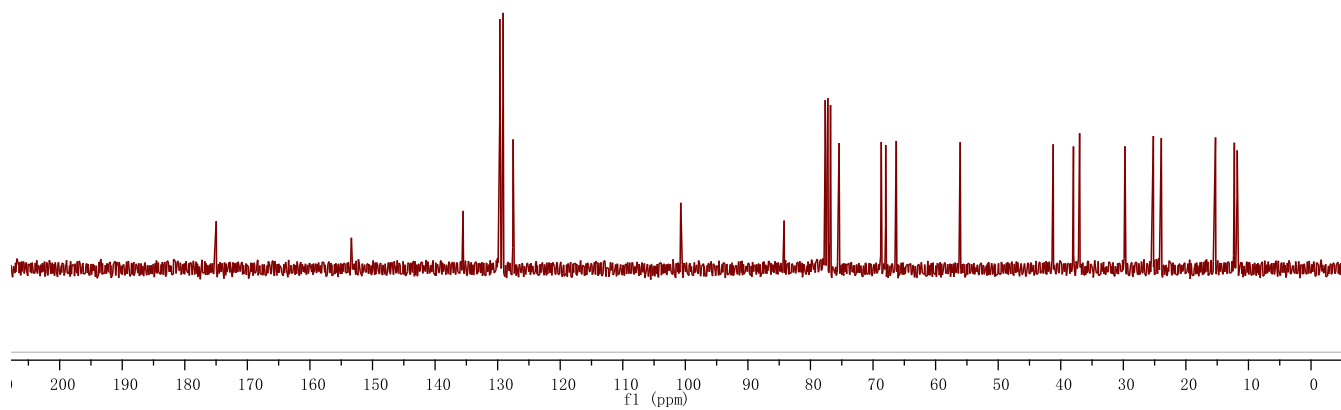
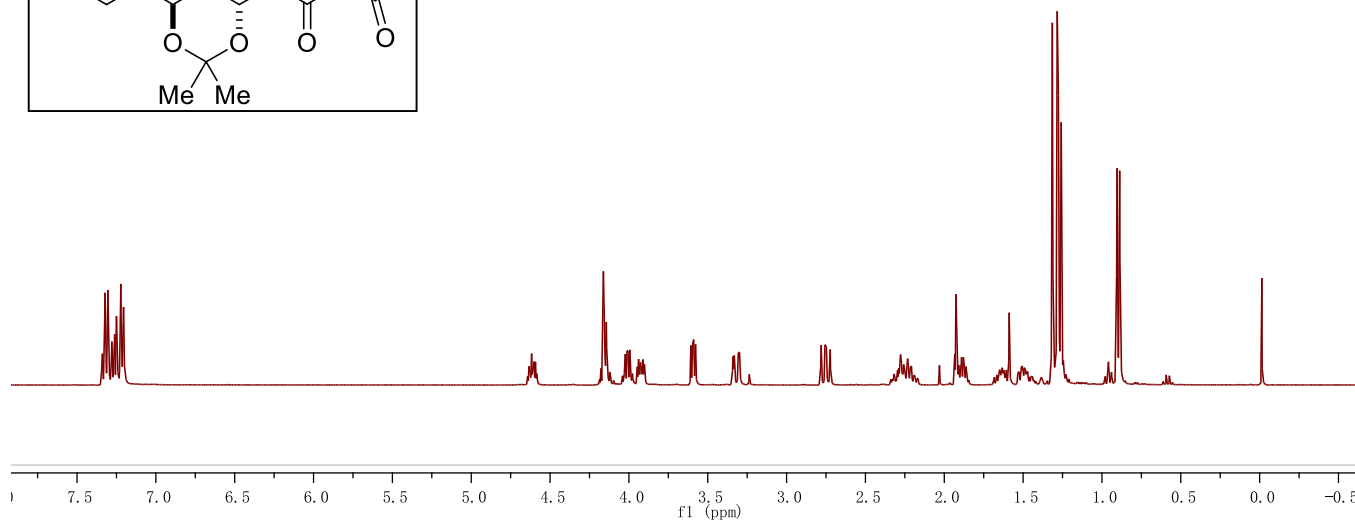
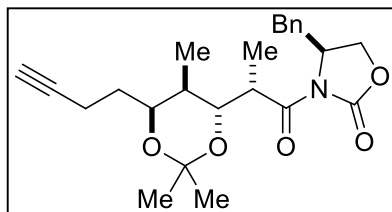
H and C-NMR (CDCl₃) of compound 21-*syn*



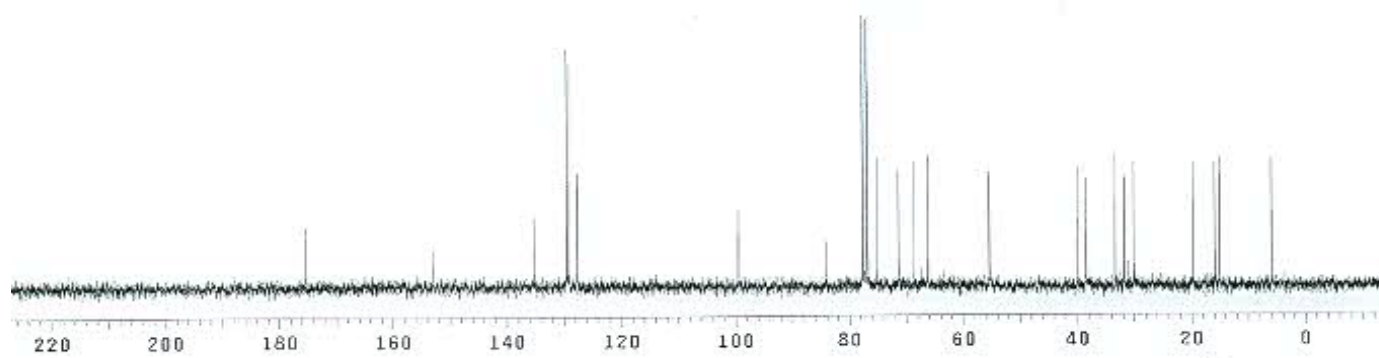
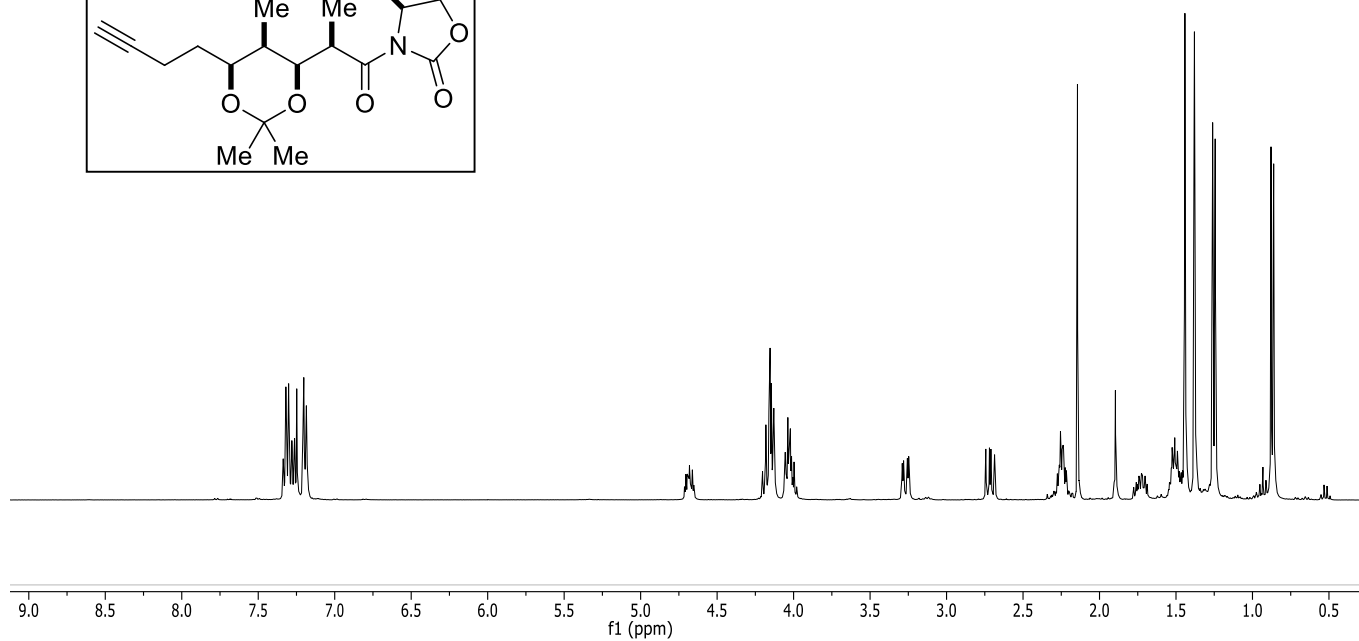
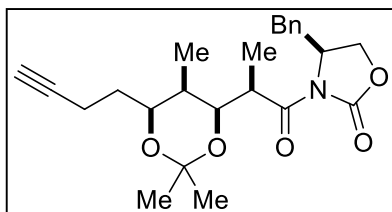
H and C-NMR (CDCl₃) of compound **21-anti**



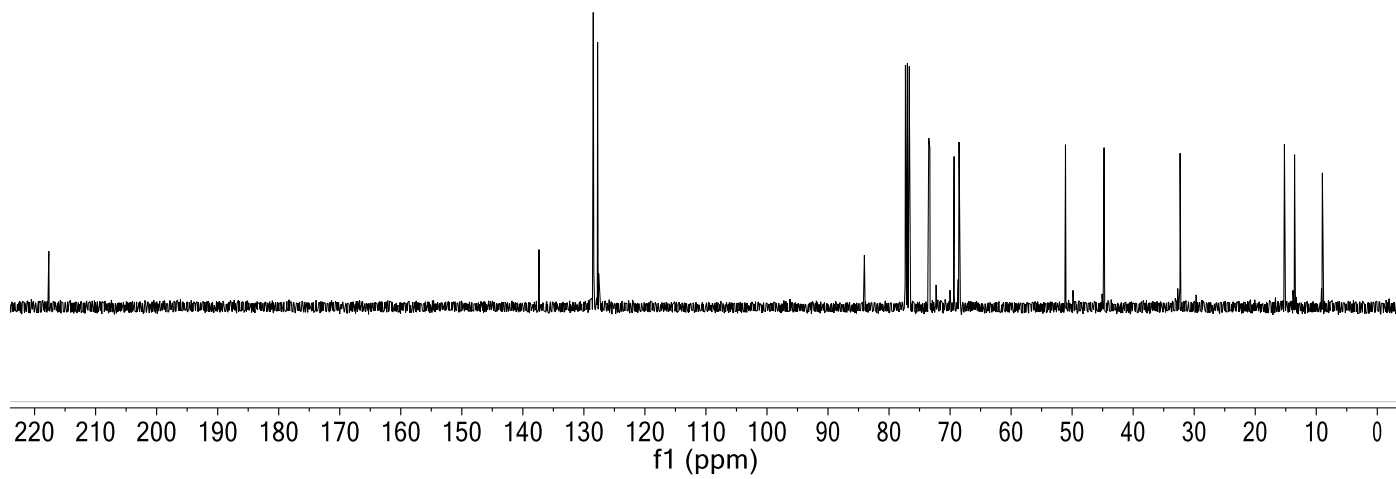
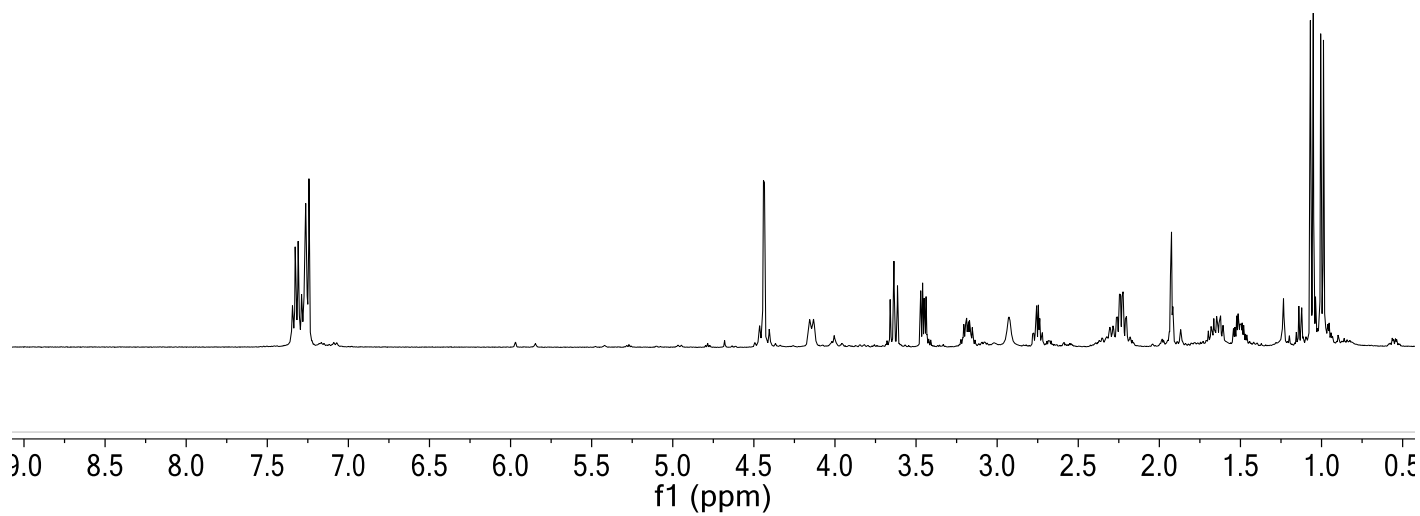
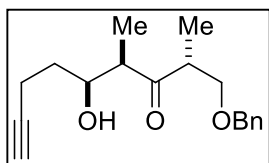
H and C-NMR (CDCl₃) of compound **23-anti**



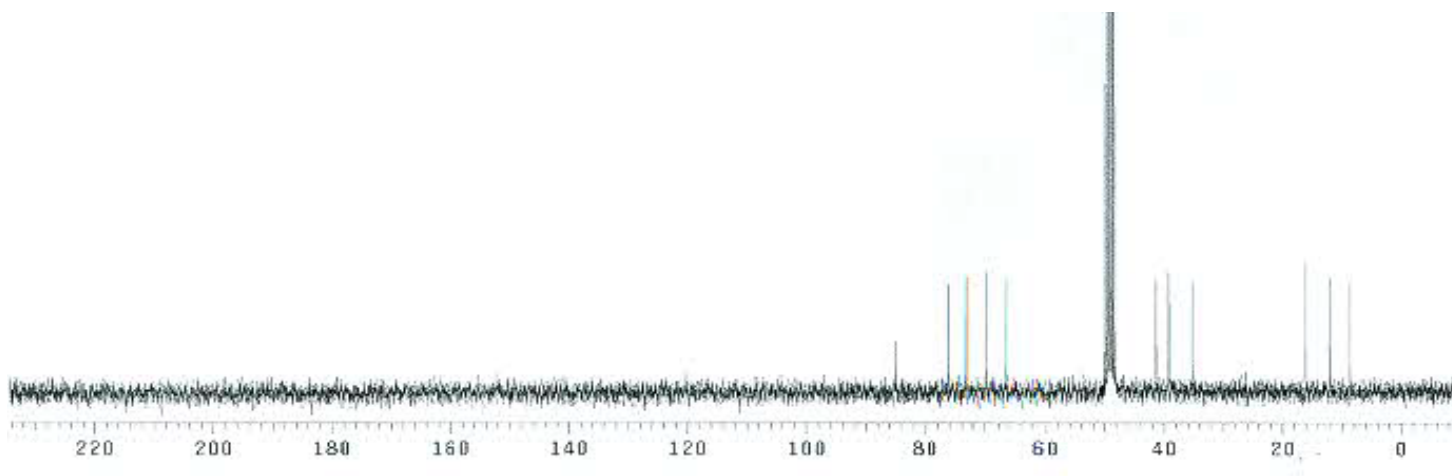
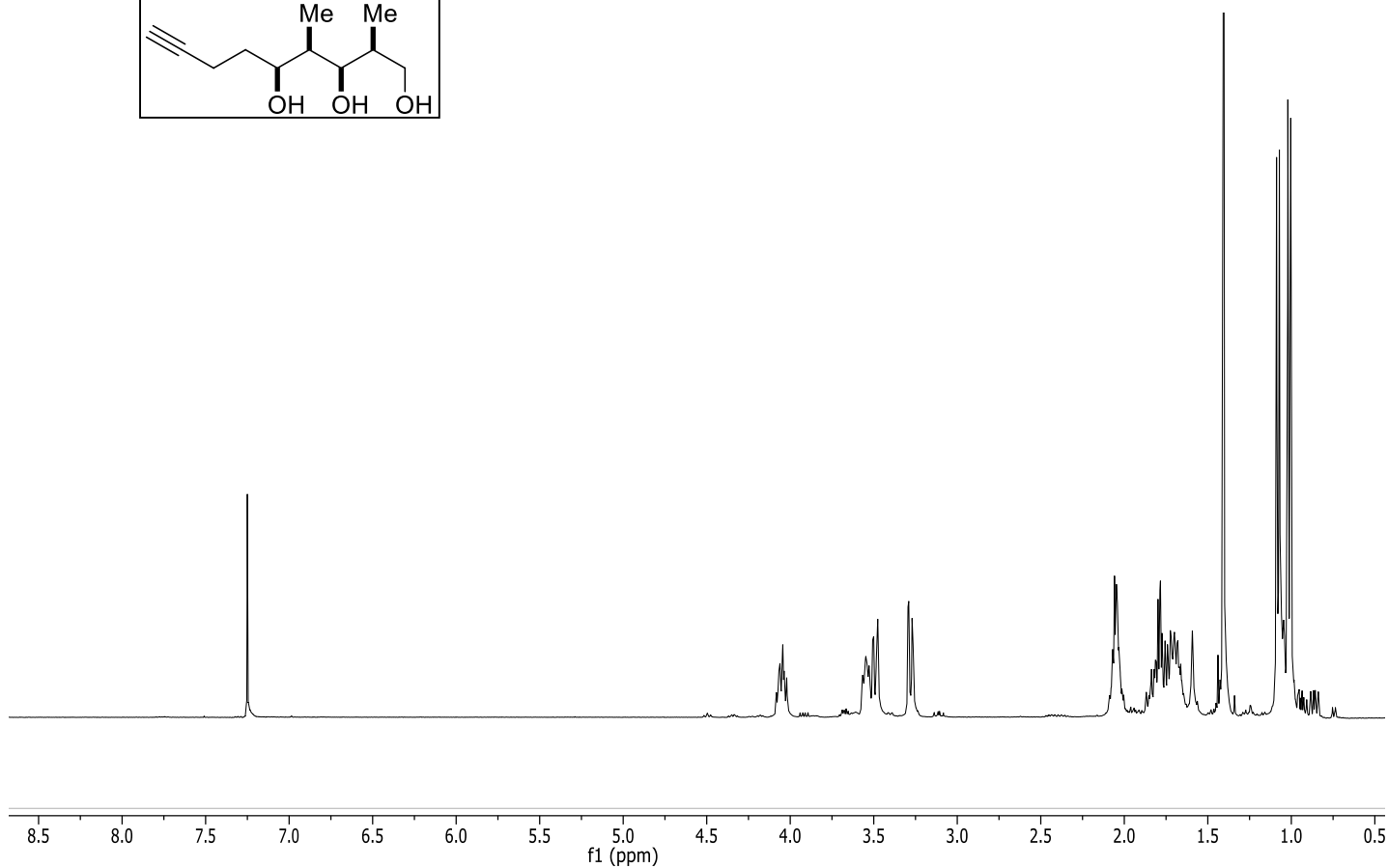
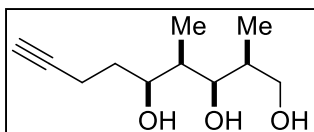
H and C-NMR (CDCl₃) of compound **23-syn**



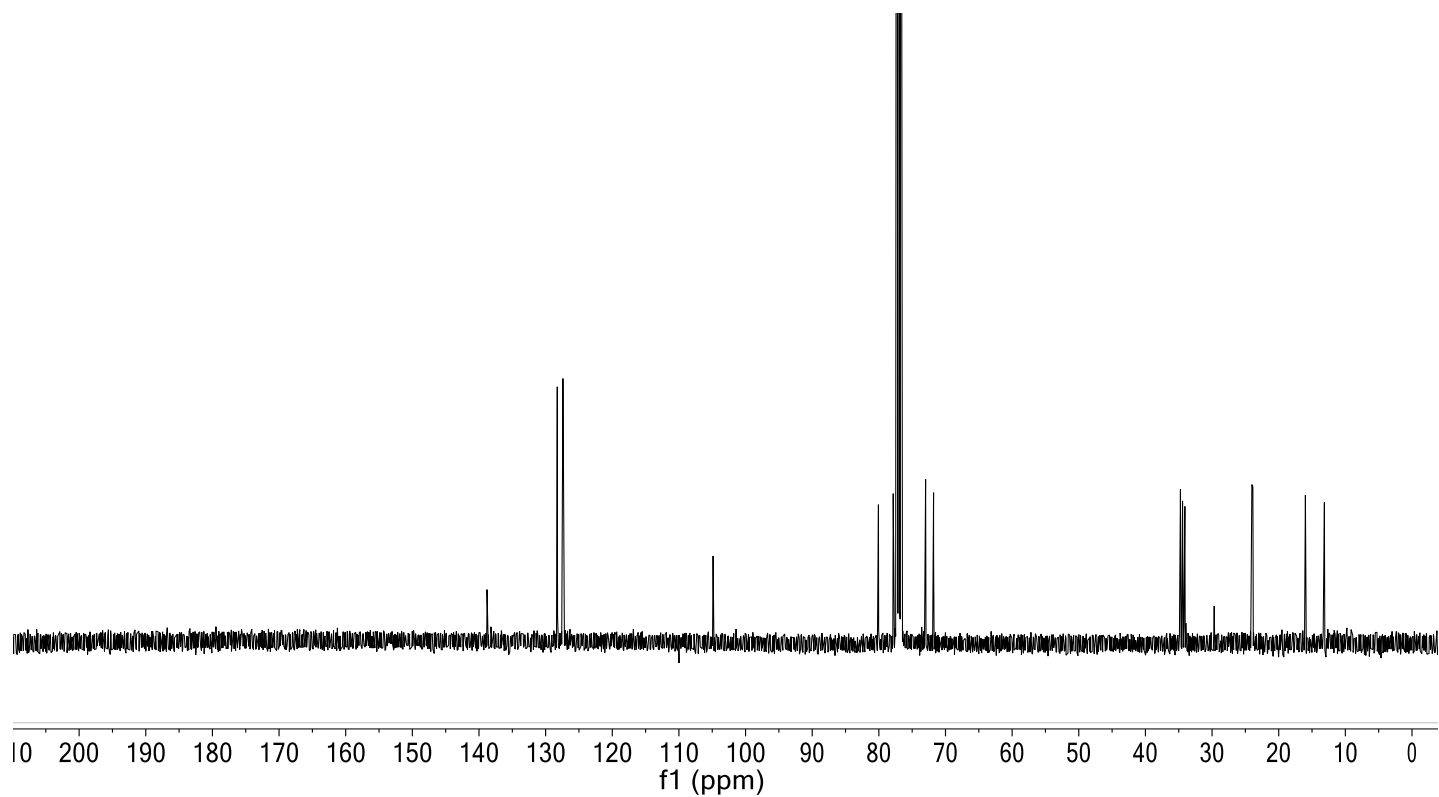
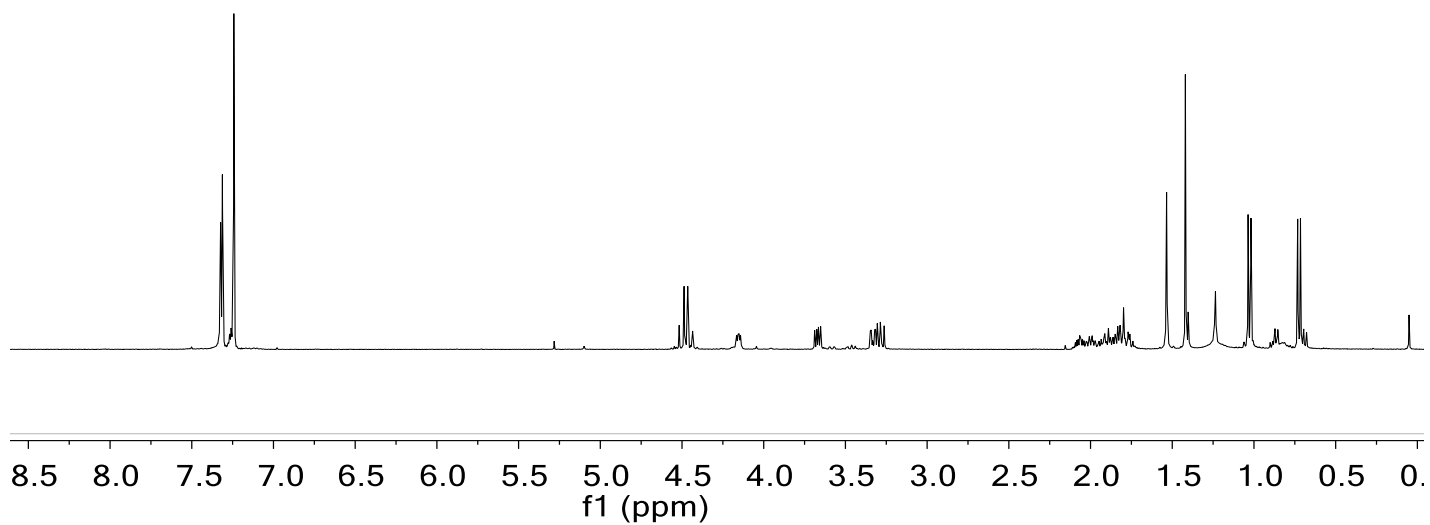
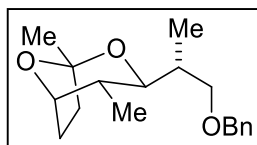
H and C-NMR (CDCl₃) of compound 26



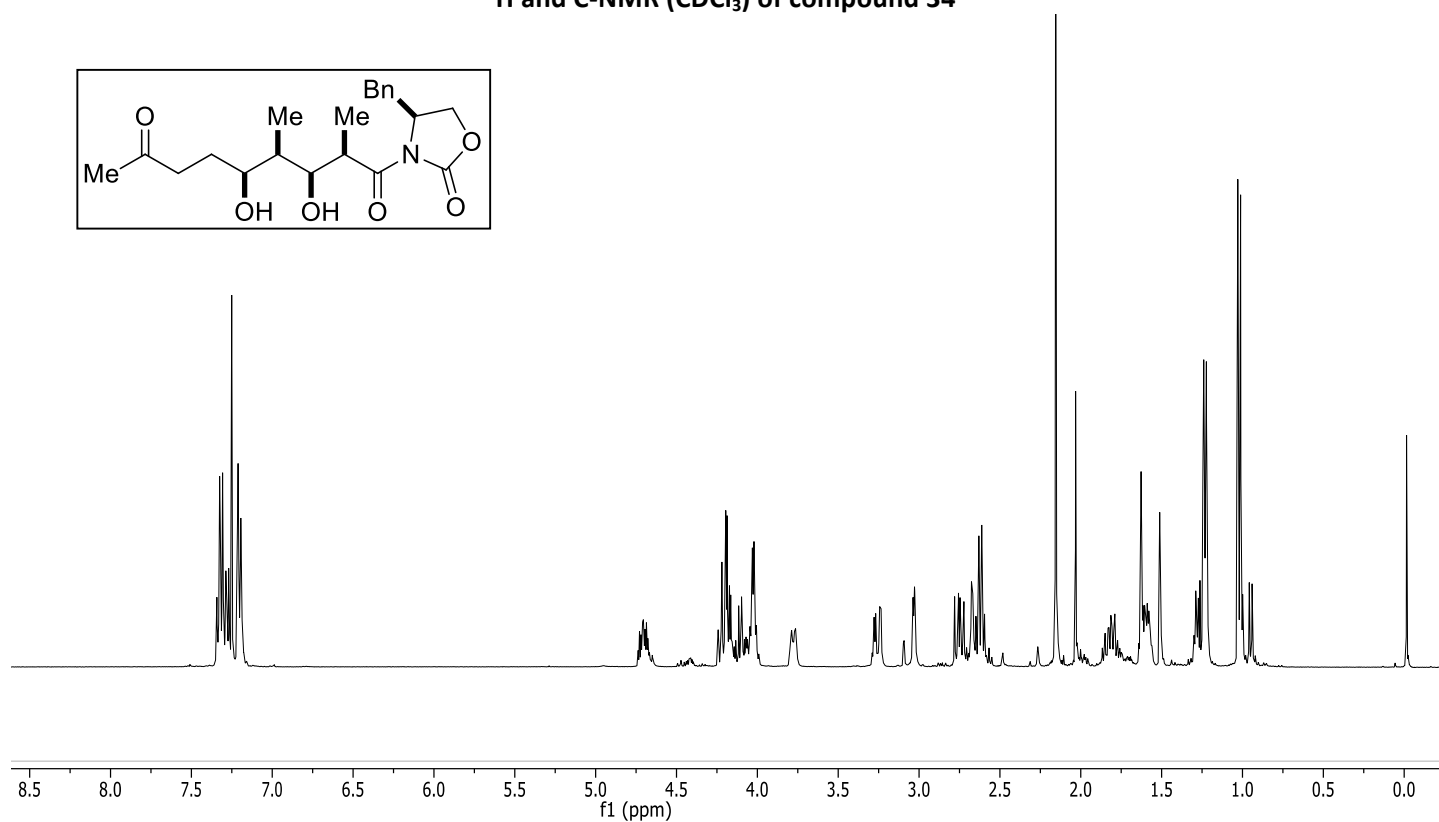
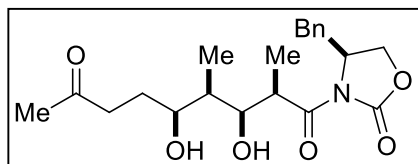
H-NMR (CDCl₃) and C-NMR (CD₃OD) of compound **31-syn**



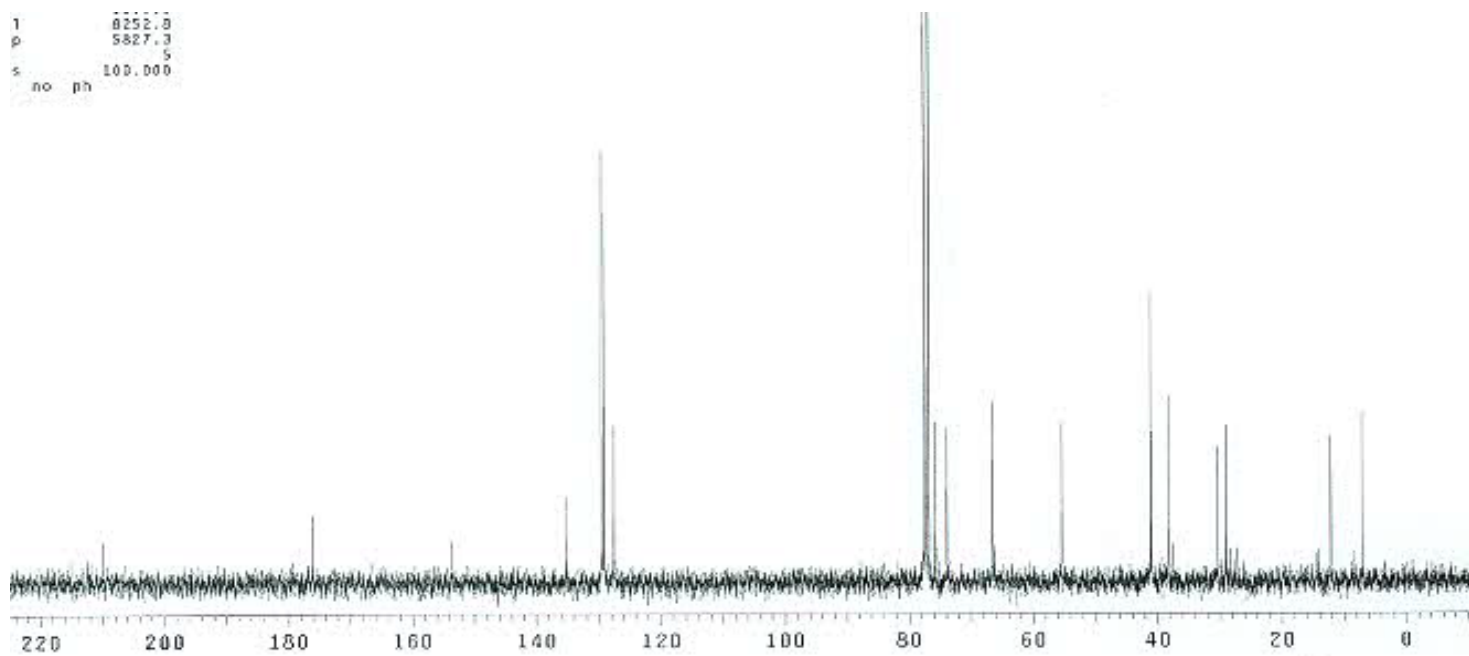
H and C-NMR (CDCl₃) of compound 32



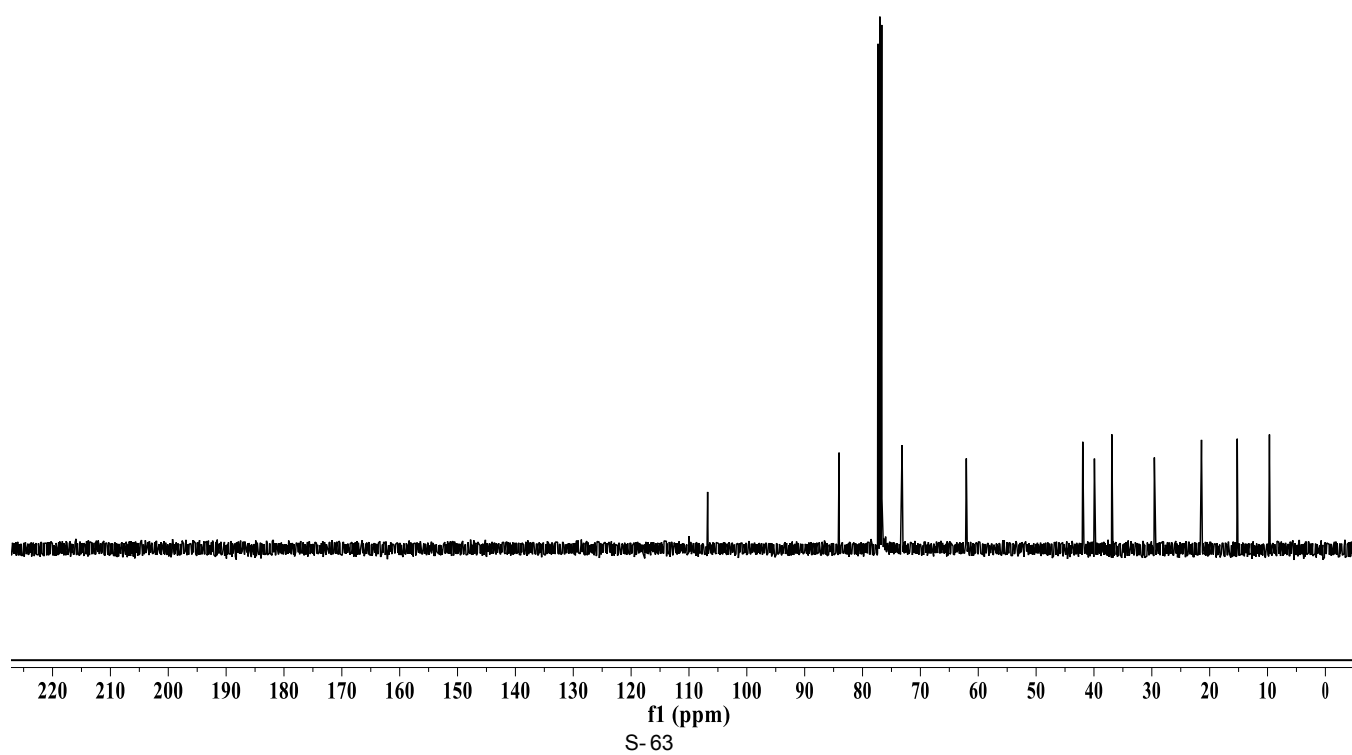
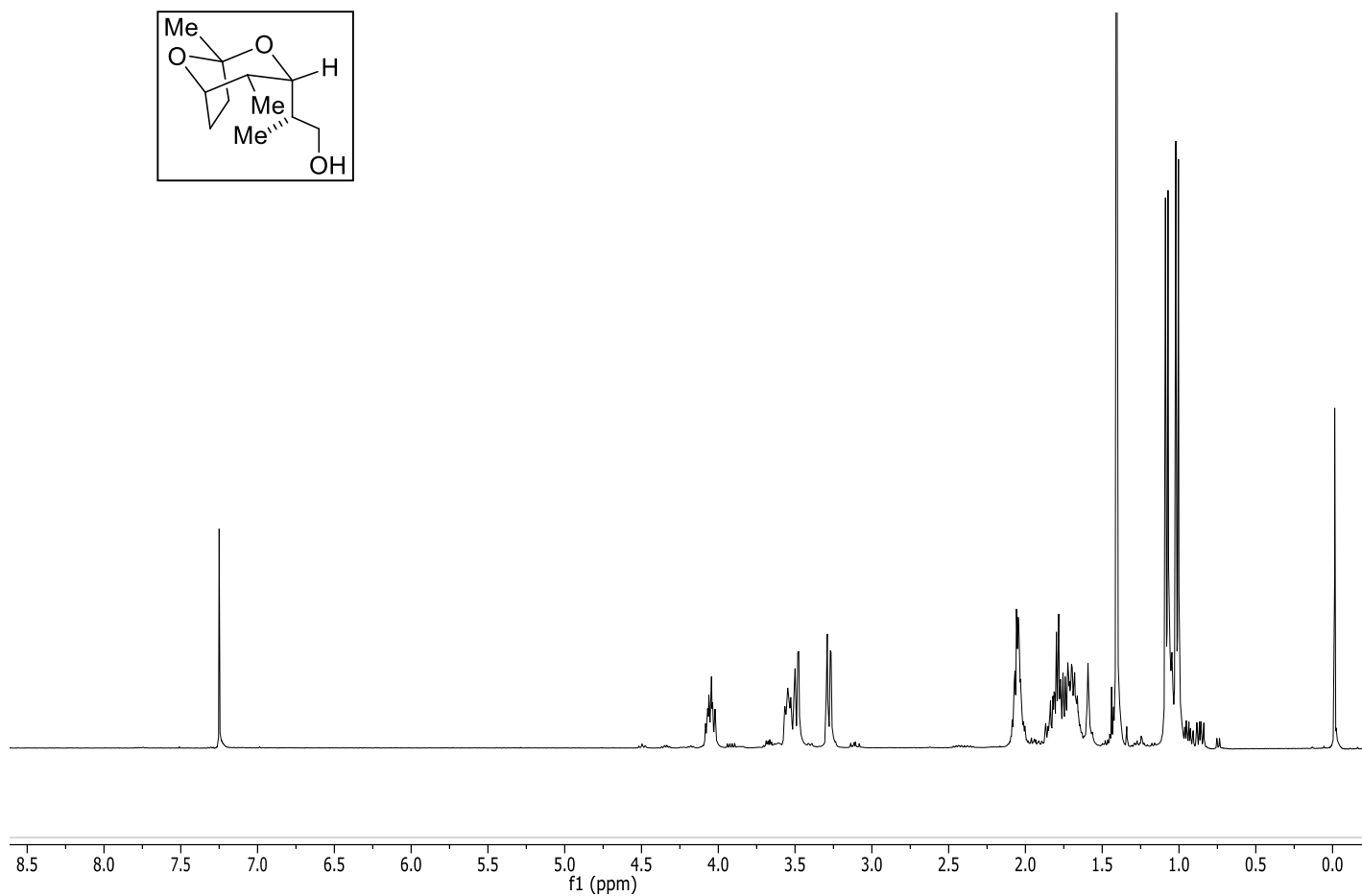
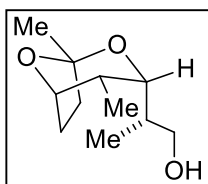
H and C-NMR (CDCl₃) of compound 34



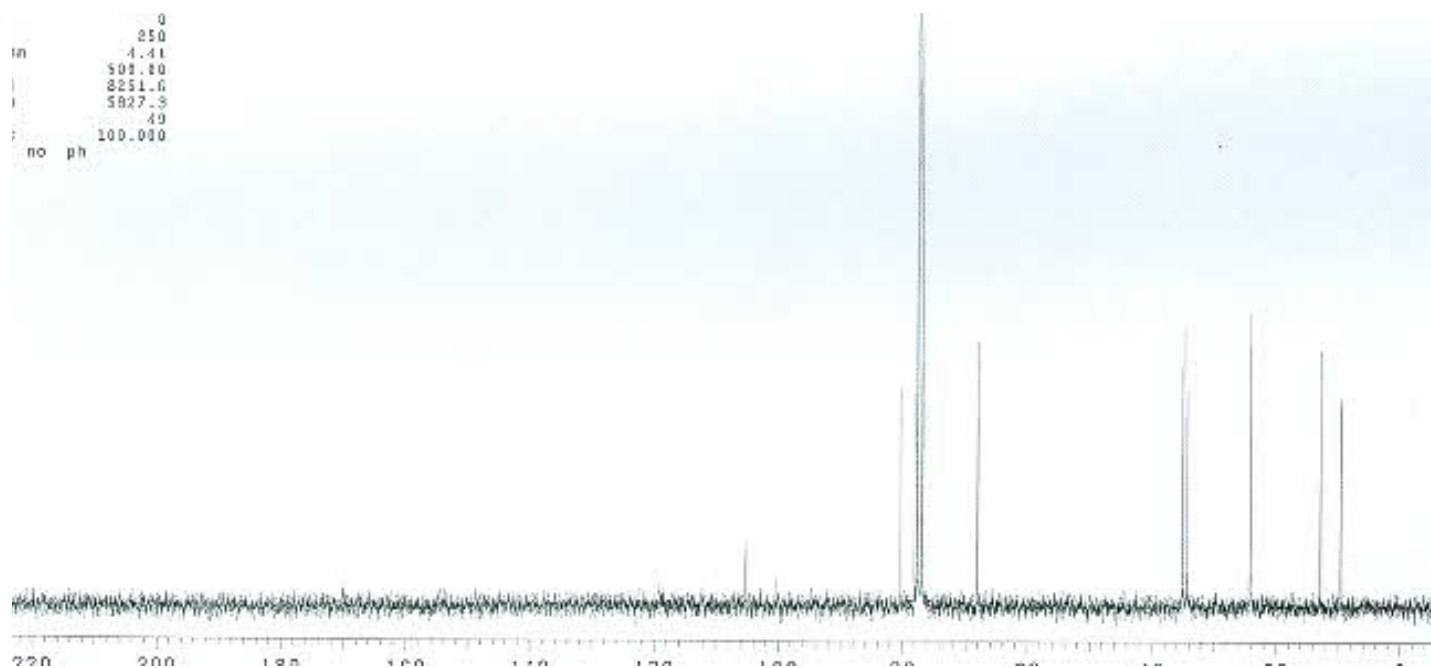
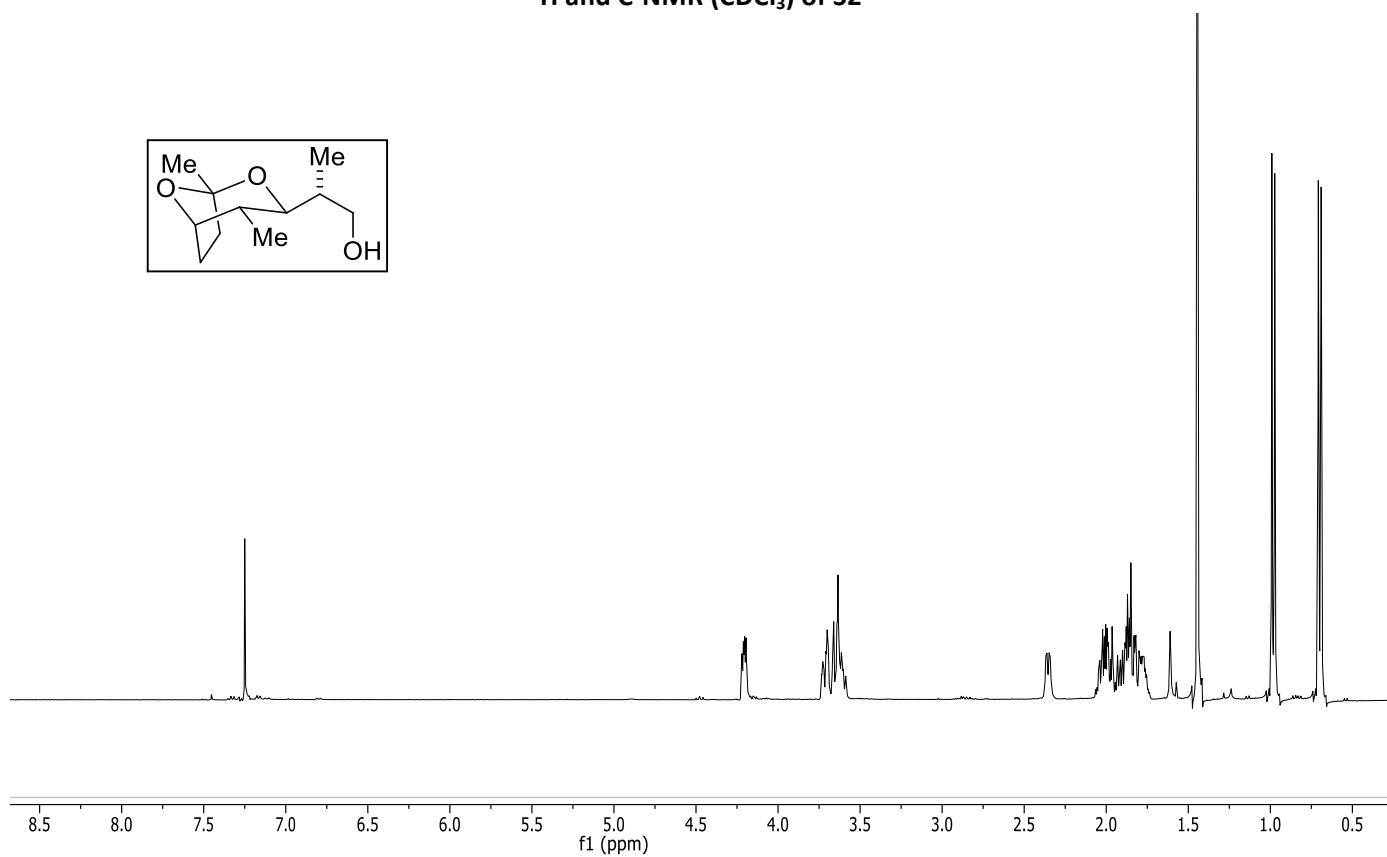
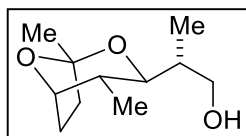
1 0252.0
p 5827.3
s 5
100.000
no ph



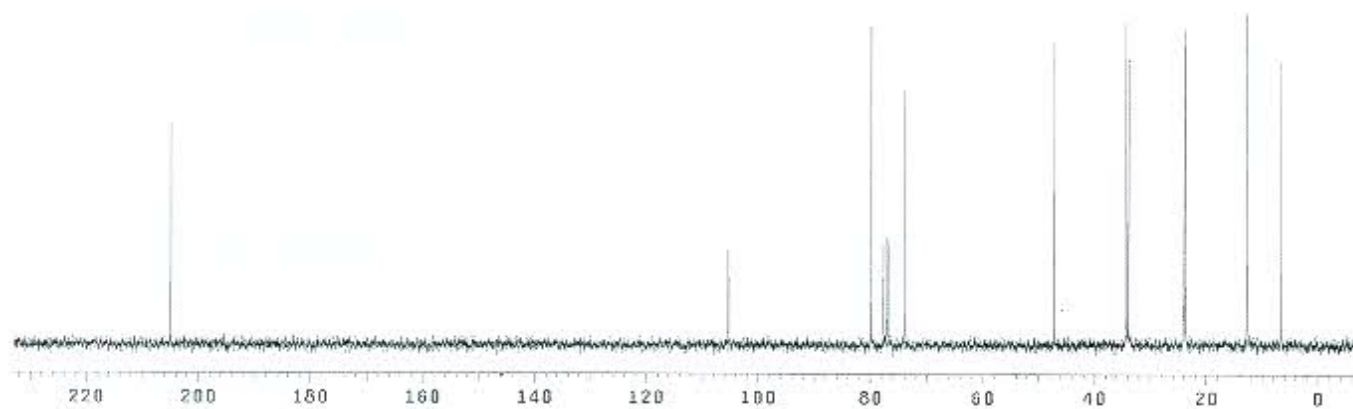
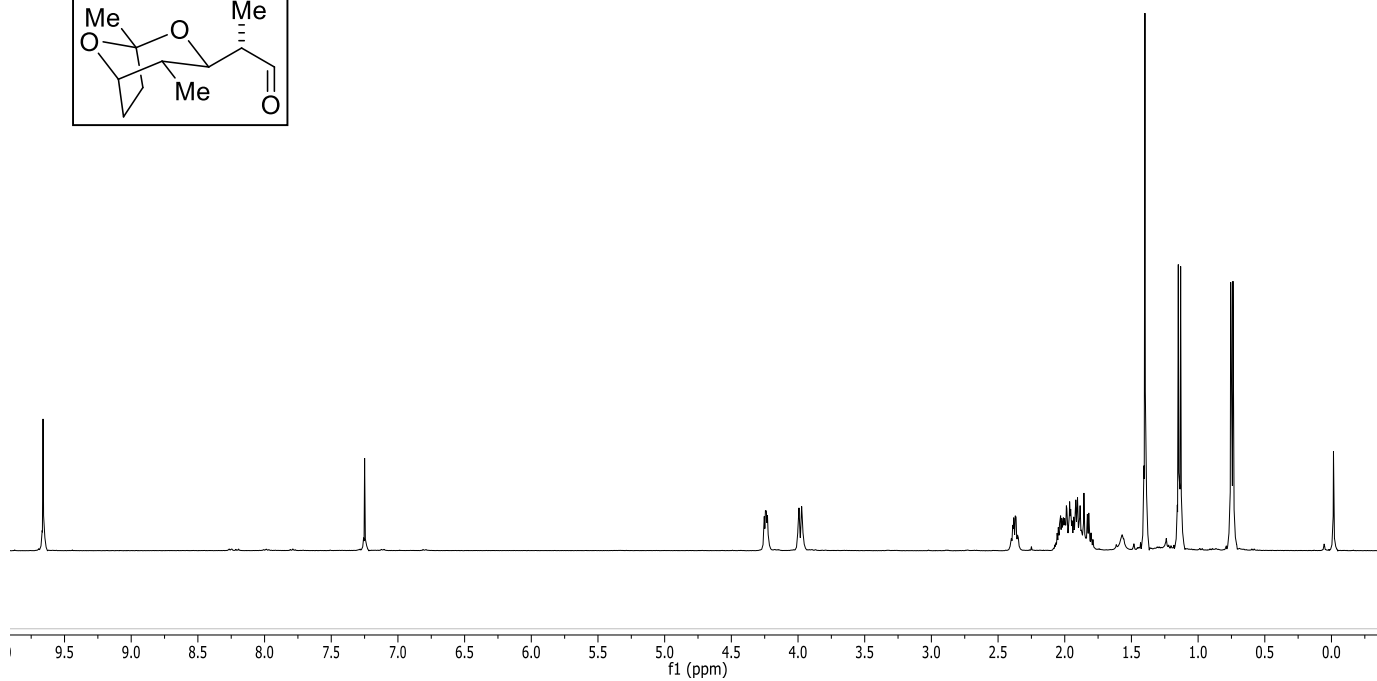
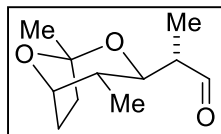
H and C-NMR (CDCl₃) of compound 35



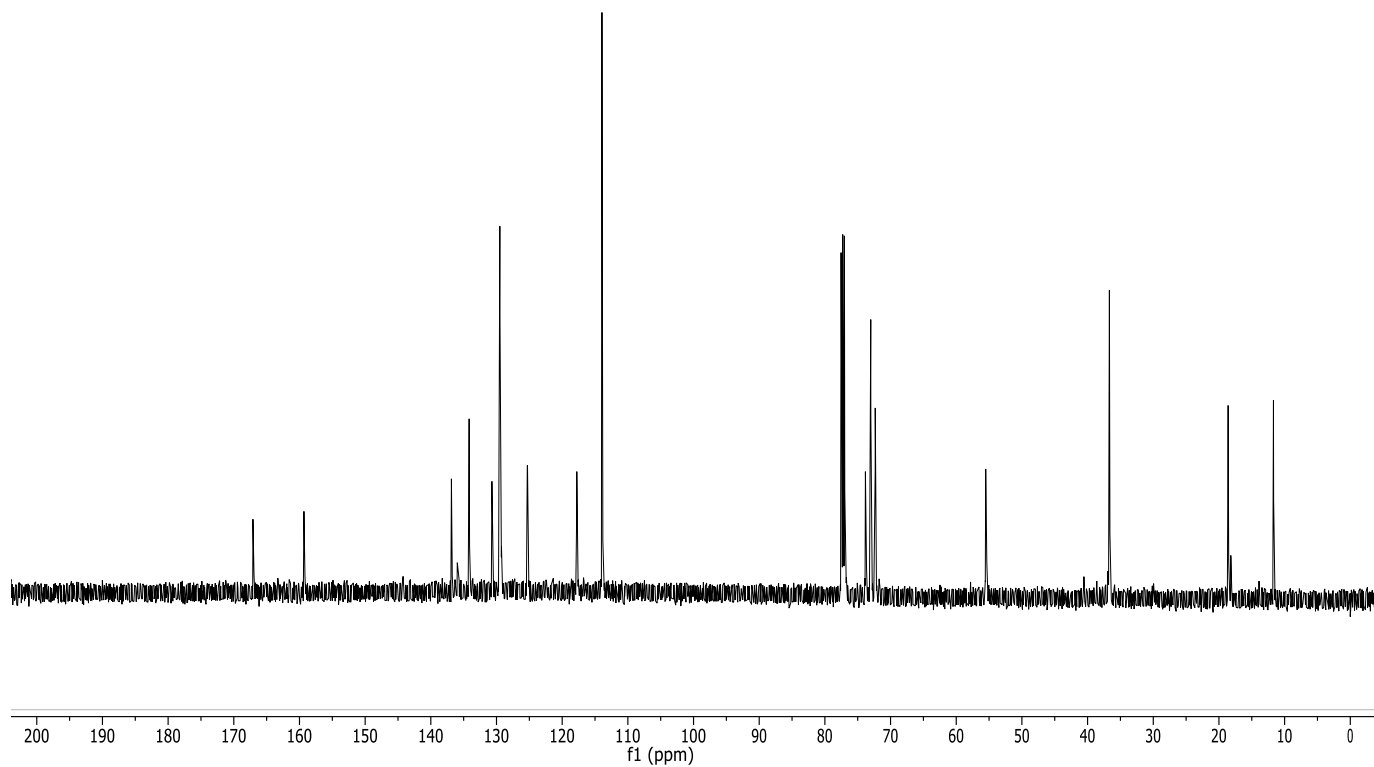
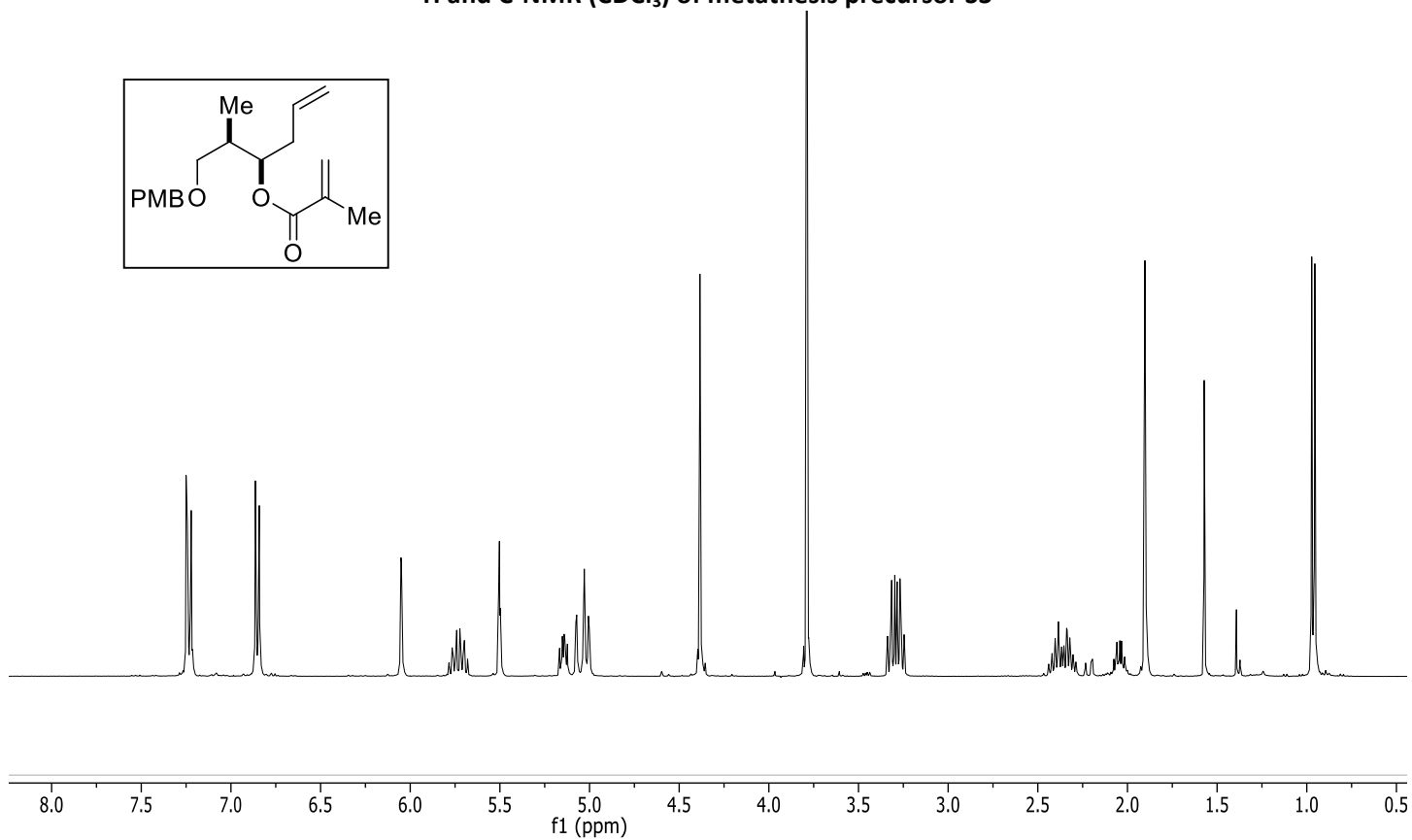
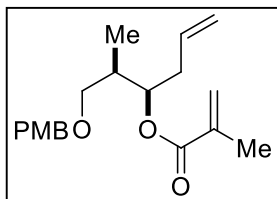
H and C-NMR (CDCl₃) of S2



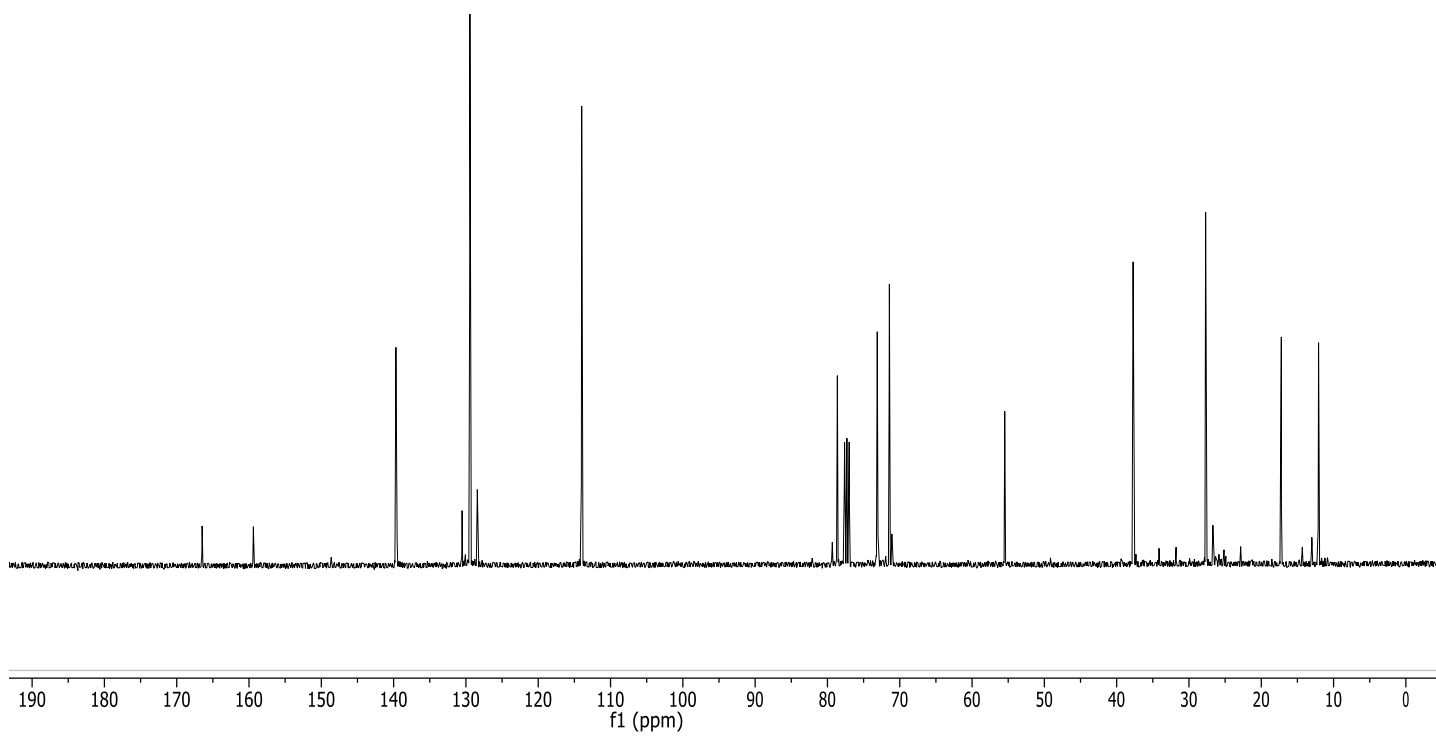
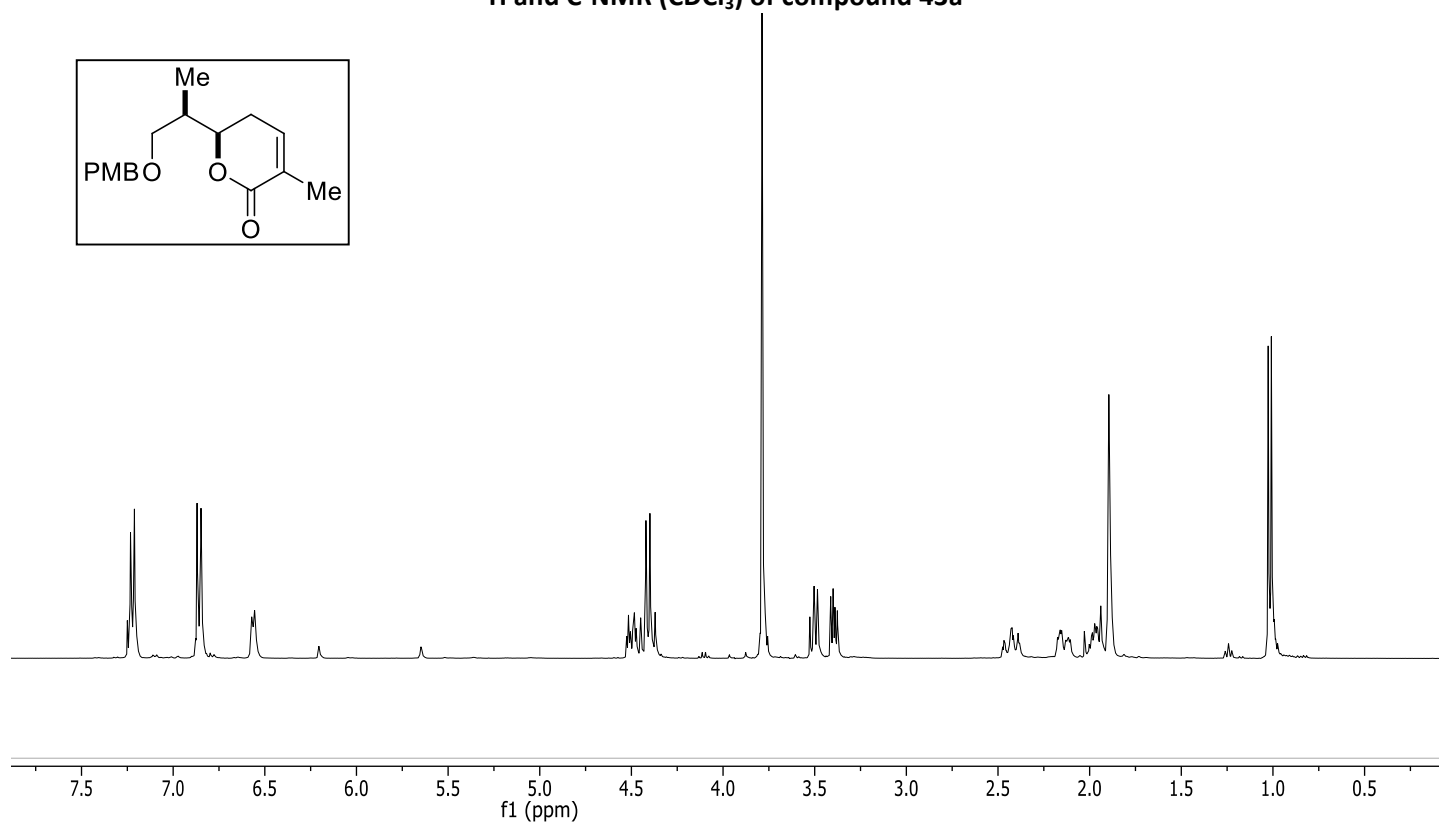
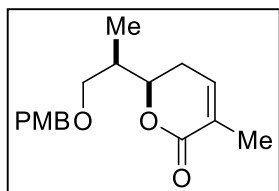
H and C-NMR (CDCl₃) of 38



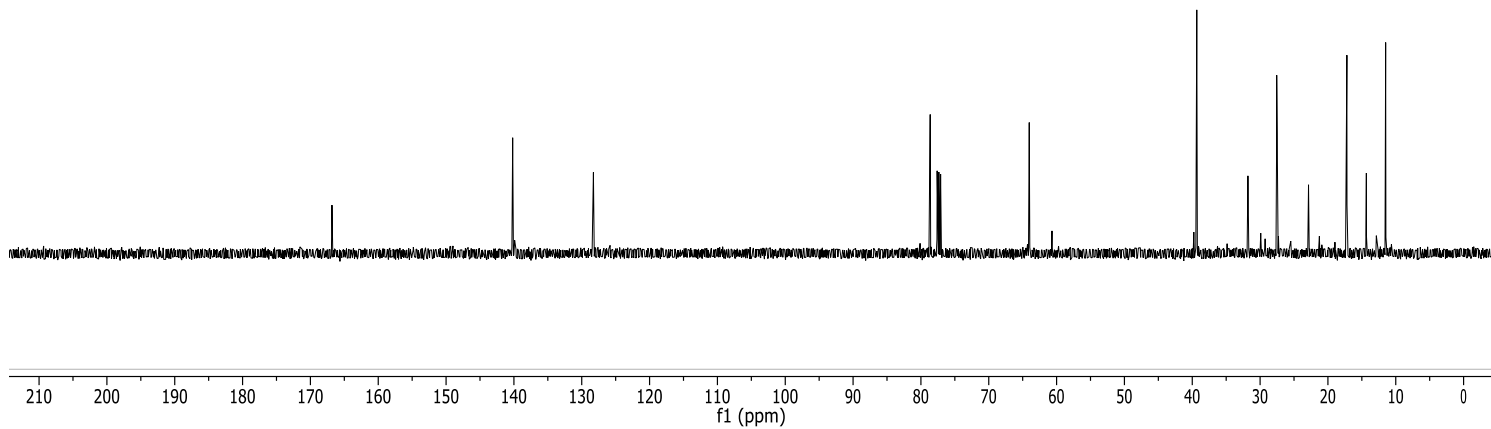
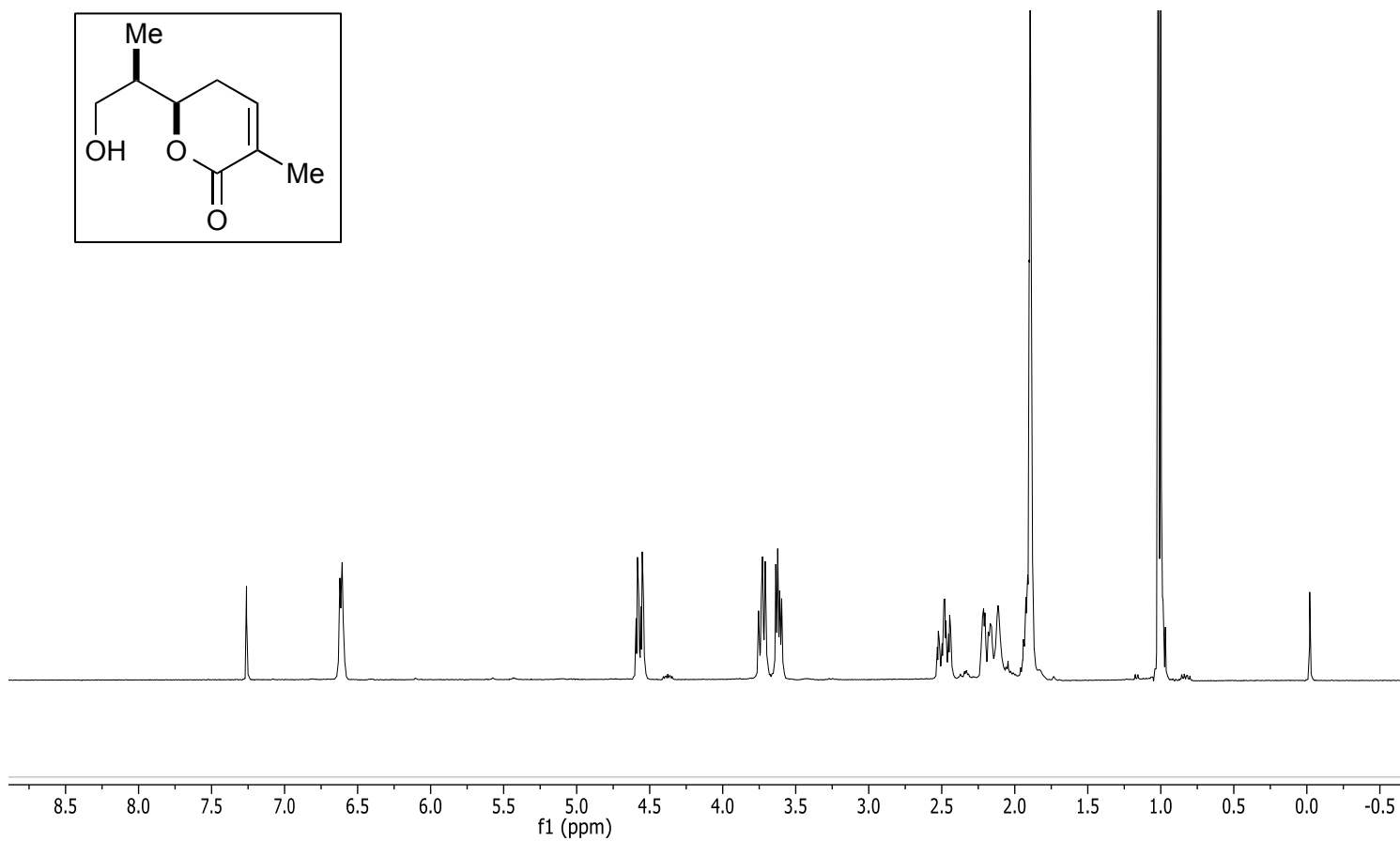
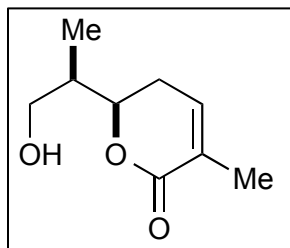
H and C-NMR (CDCl₃) of metathesis precursor S3



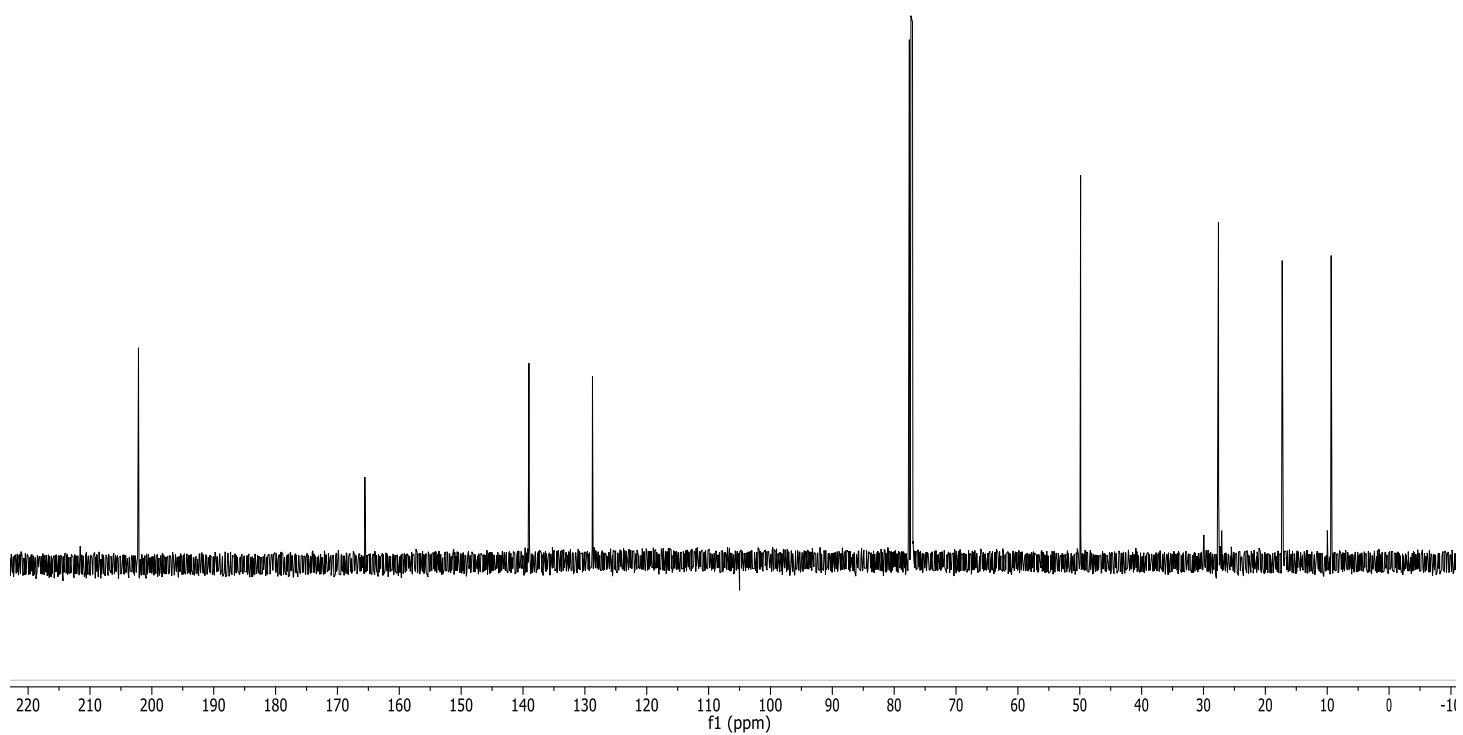
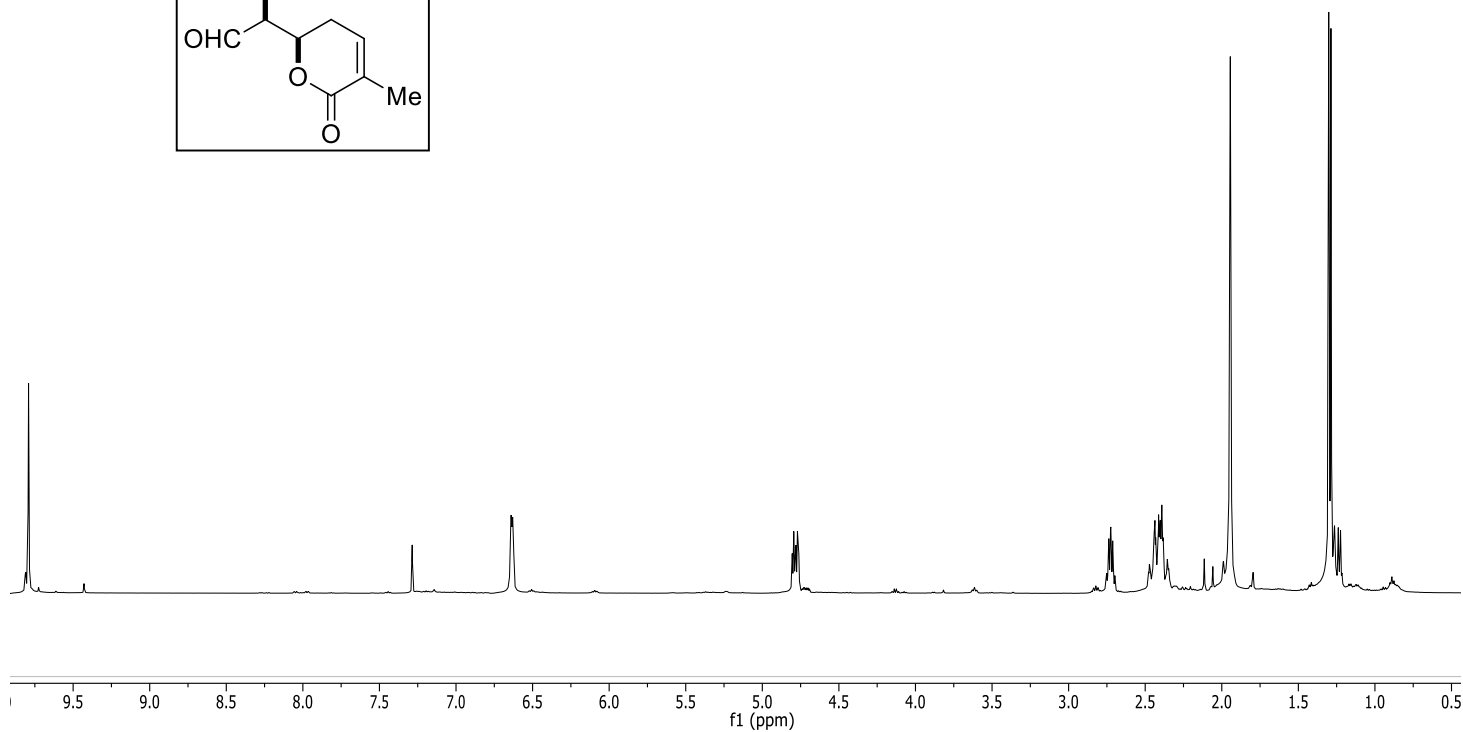
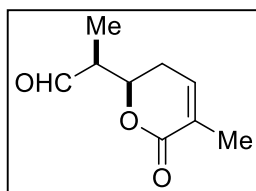
H and C-NMR (CDCl₃) of compound 43a



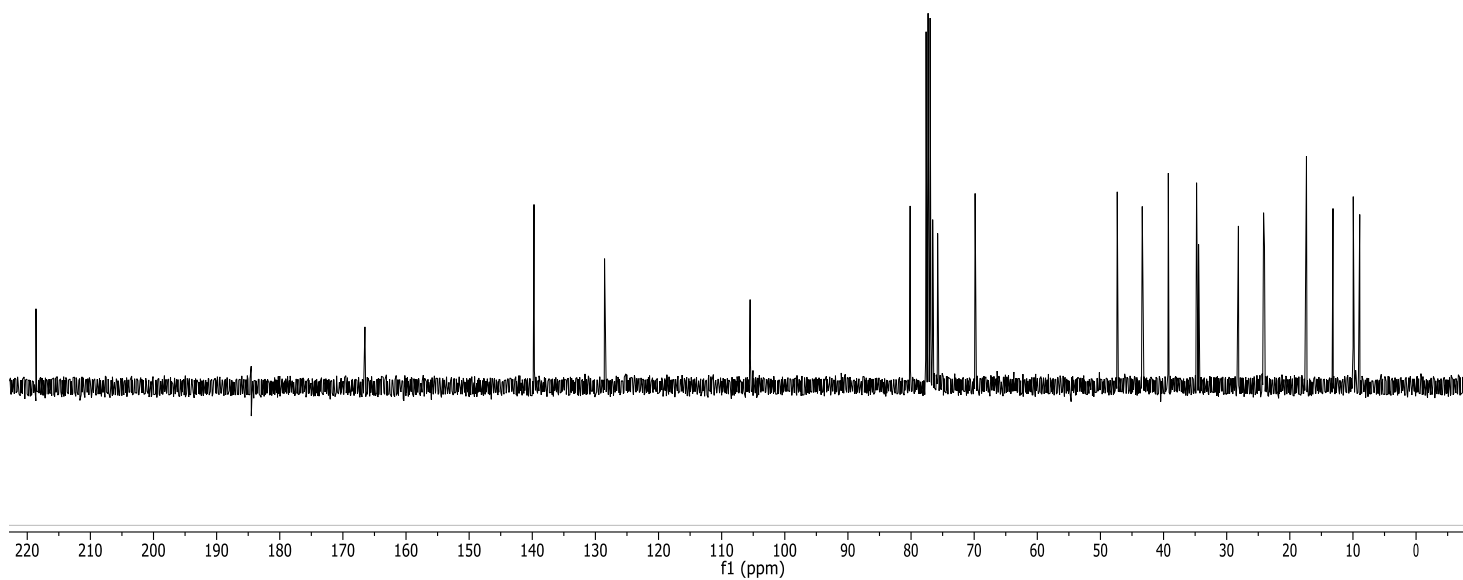
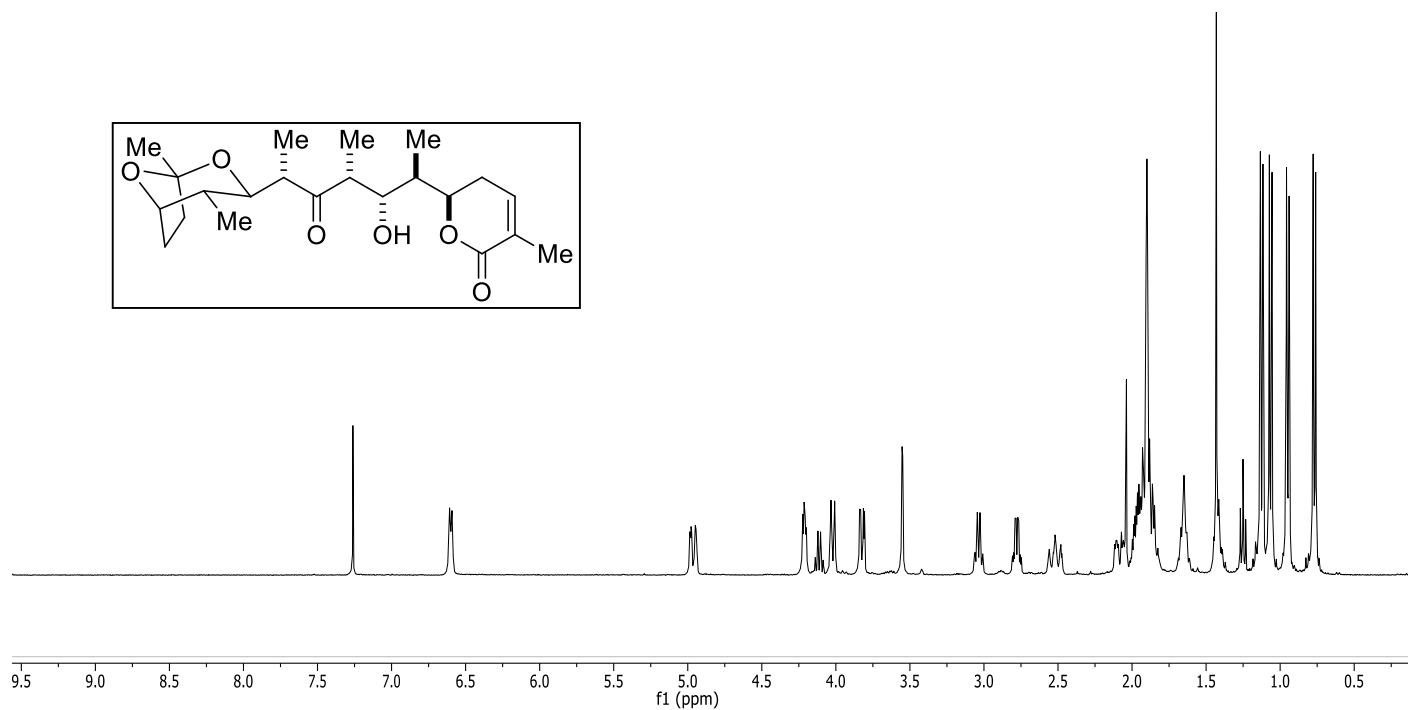
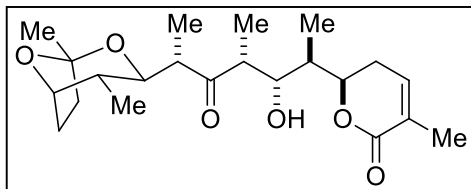
H and C-NMR (CDCl₃) of alcohol S4

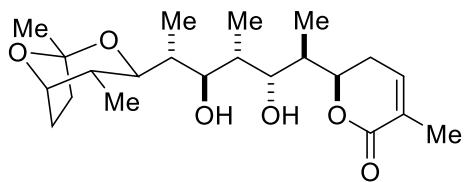


H and C-NMR (CDCl₃) of compound 14a

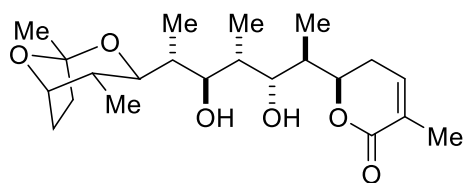
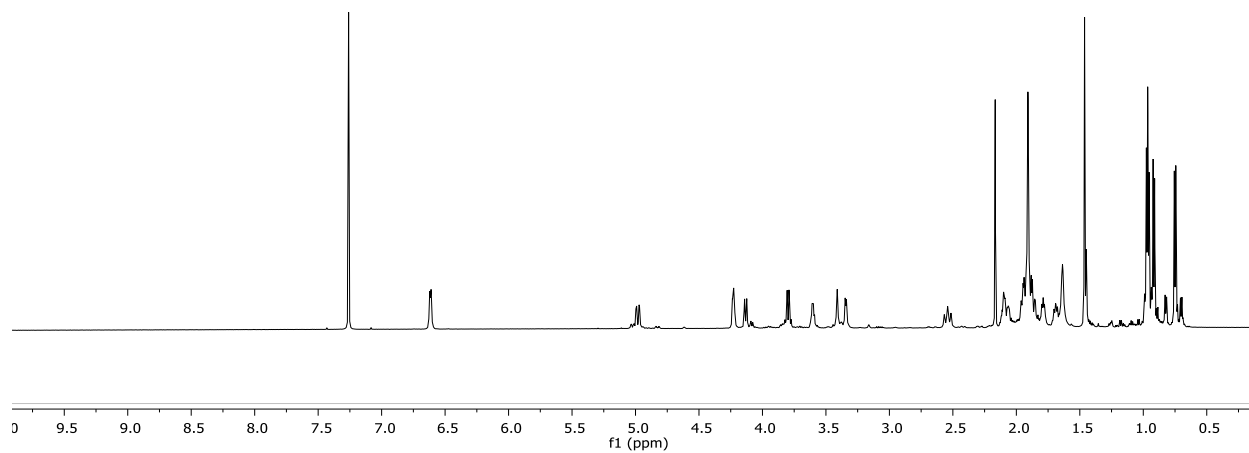


H and C-NMR (CDCl₃) of compound 44a

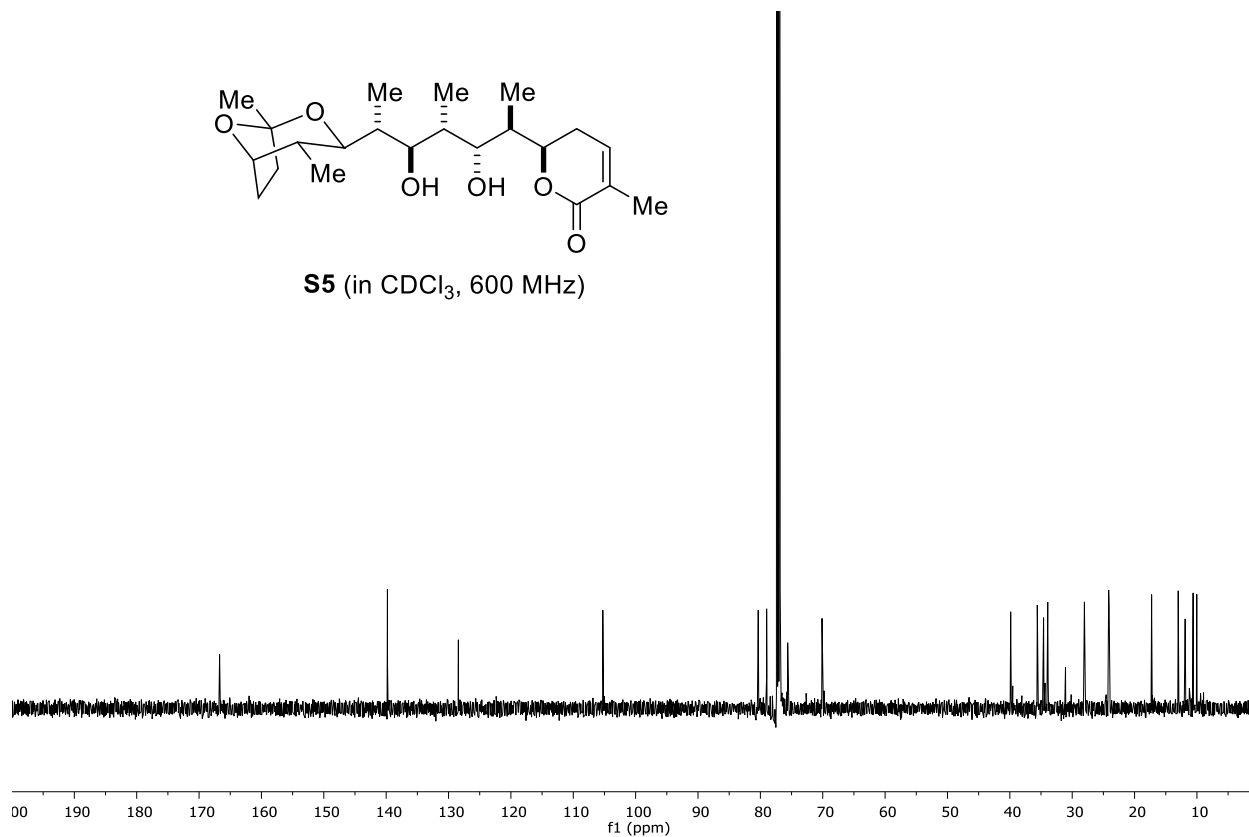




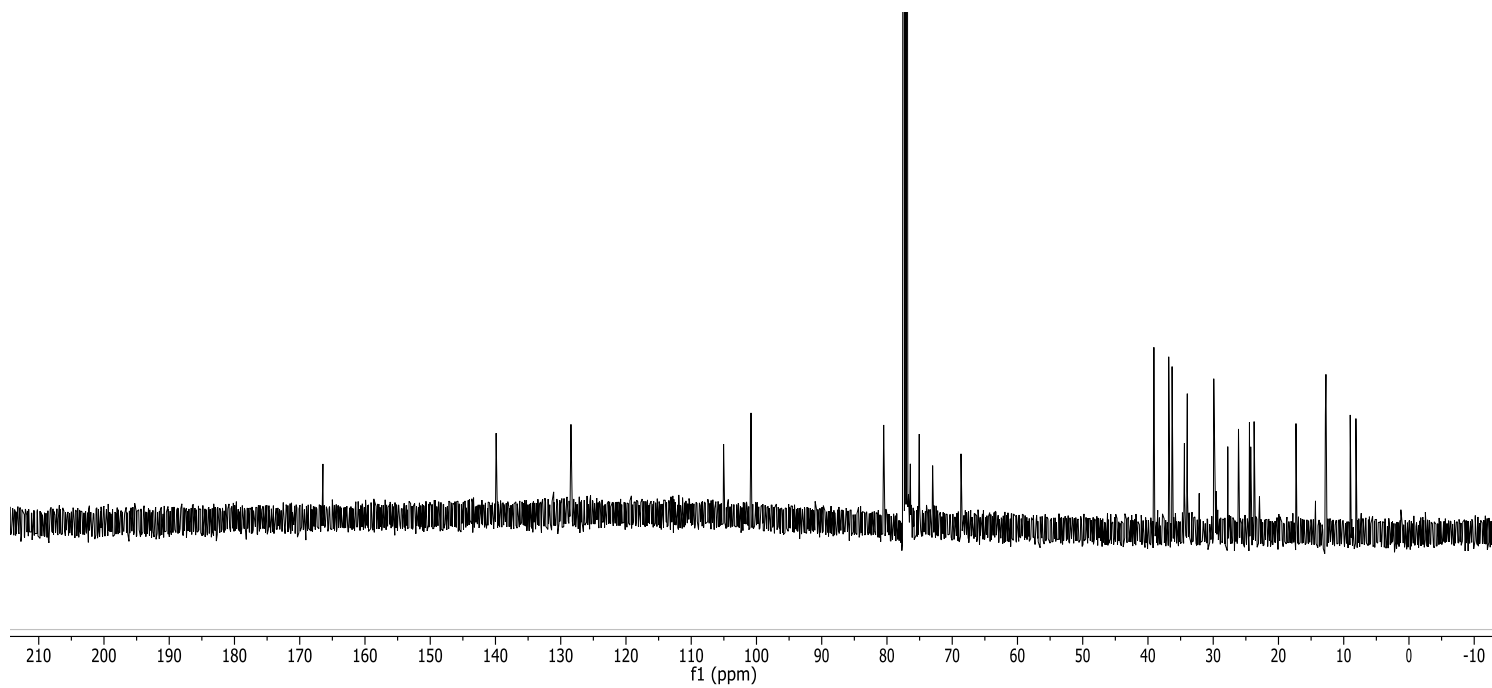
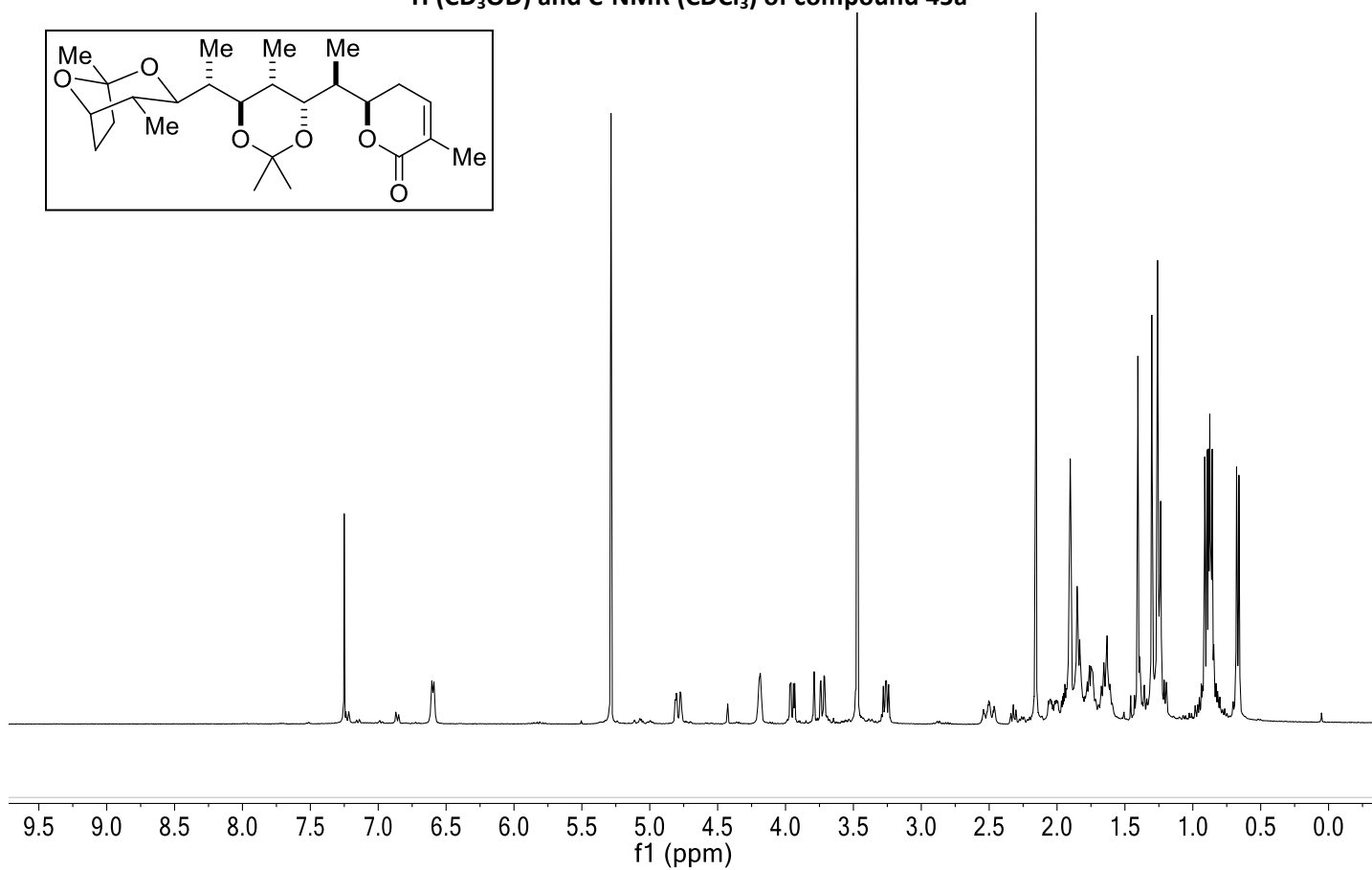
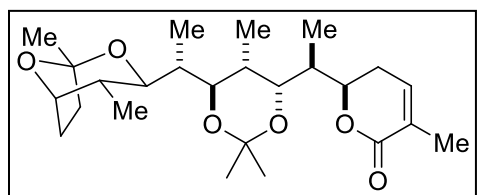
S5 (in CDCl₃, 600 MHz)



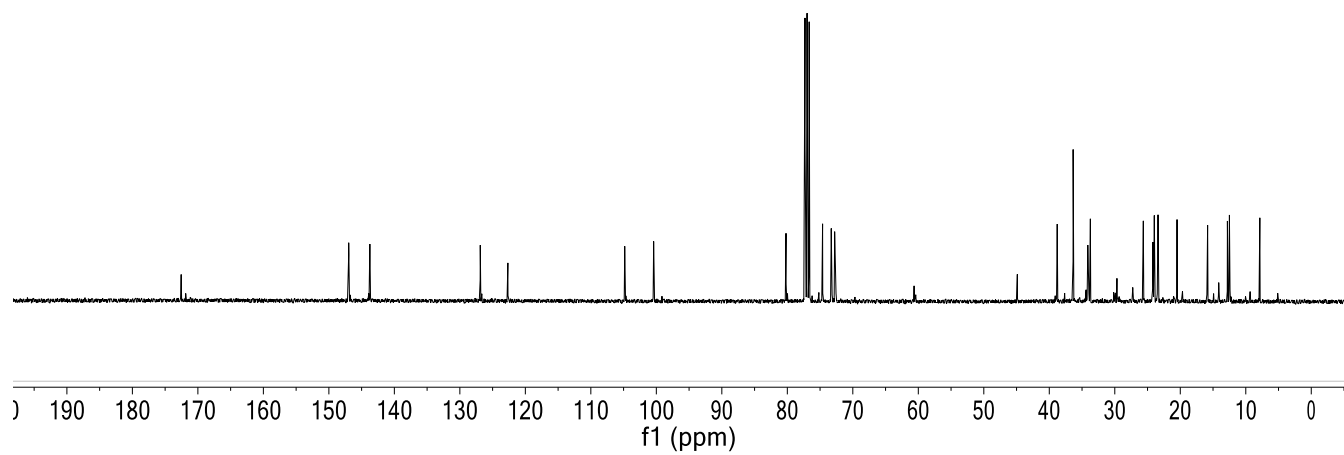
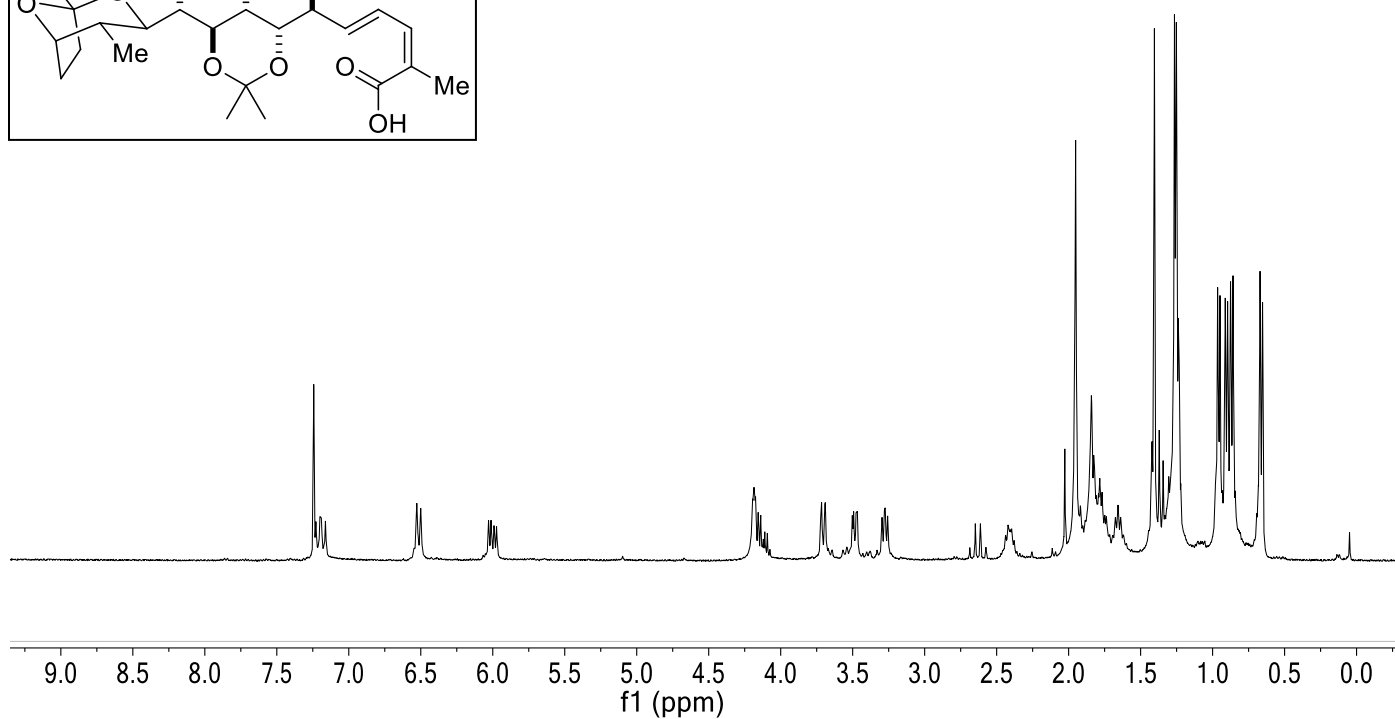
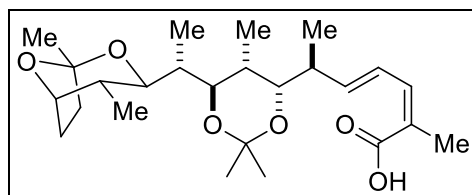
S5 (in CDCl₃, 600 MHz)

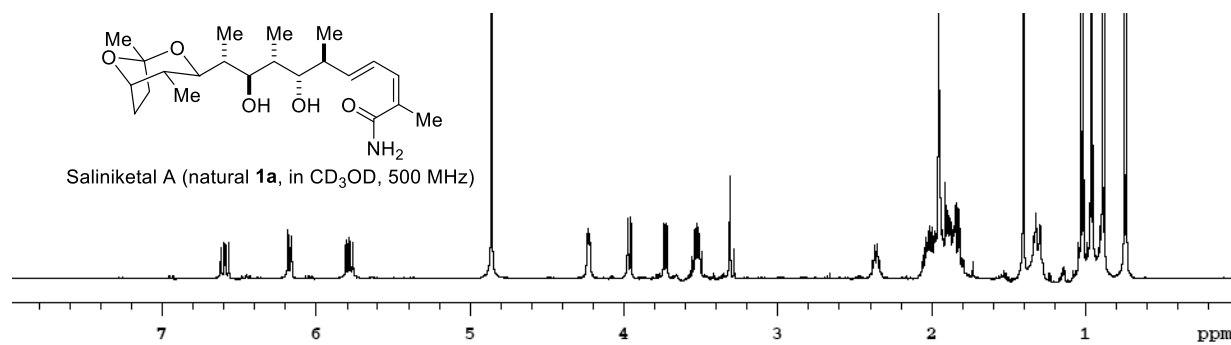
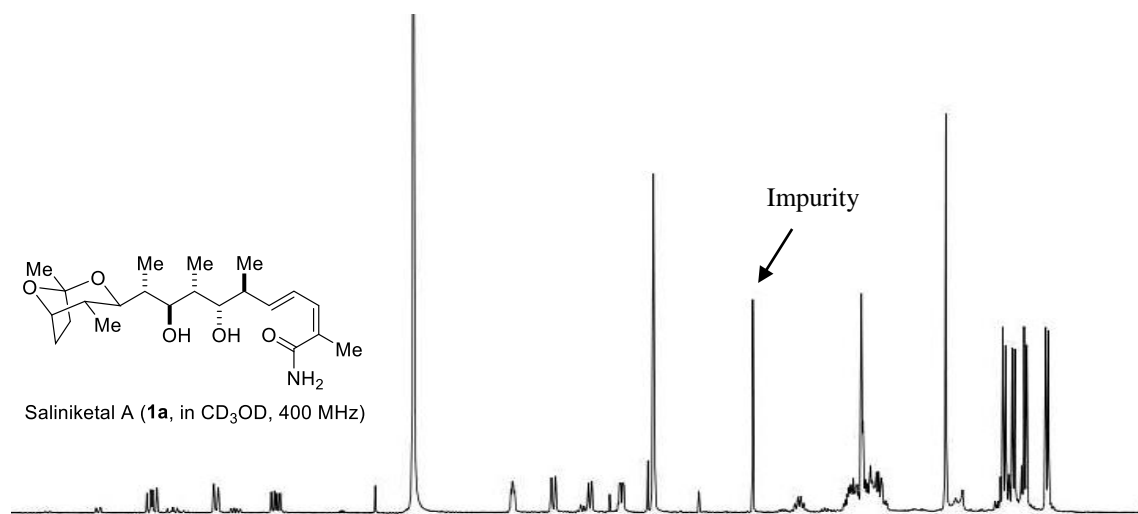
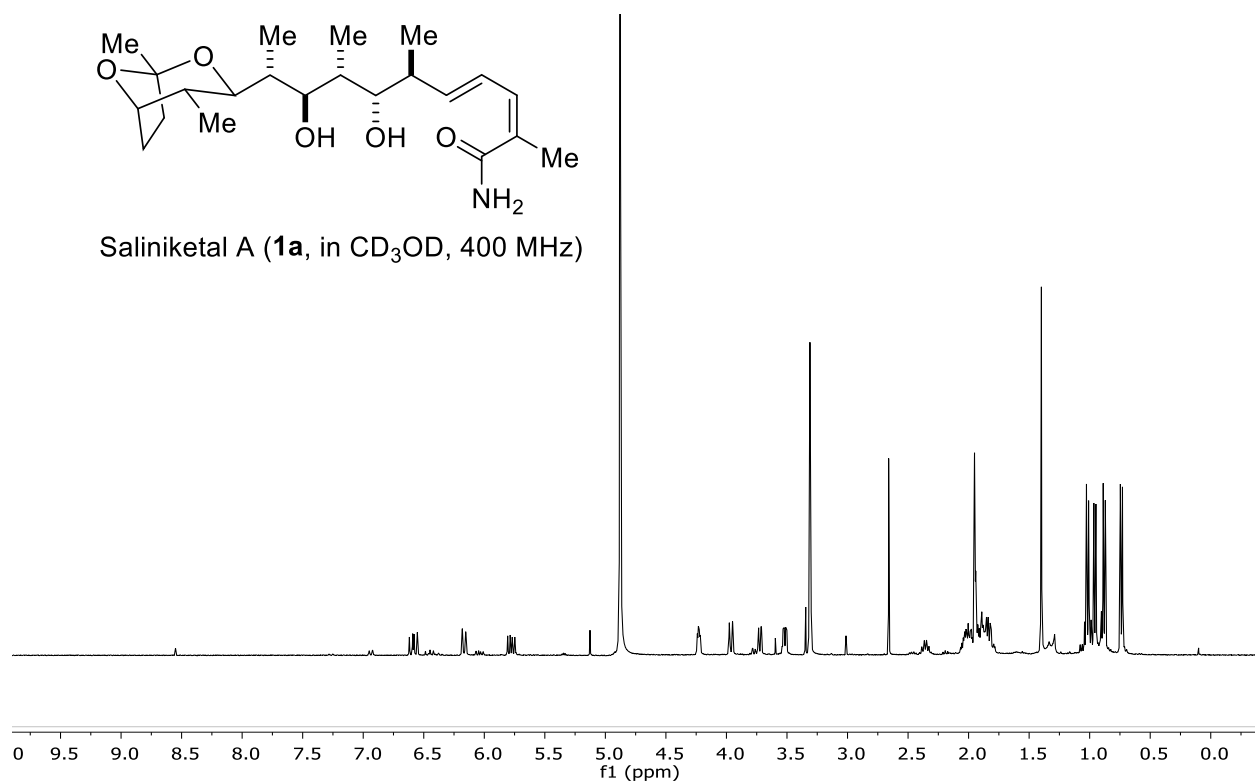


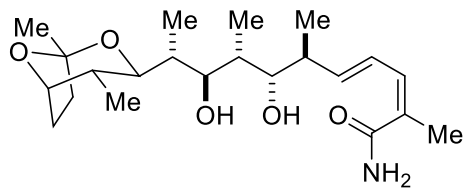
¹H (CD₃OD) and ¹³C-NMR (CDCl₃) of compound 45a



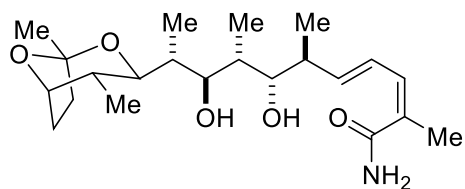
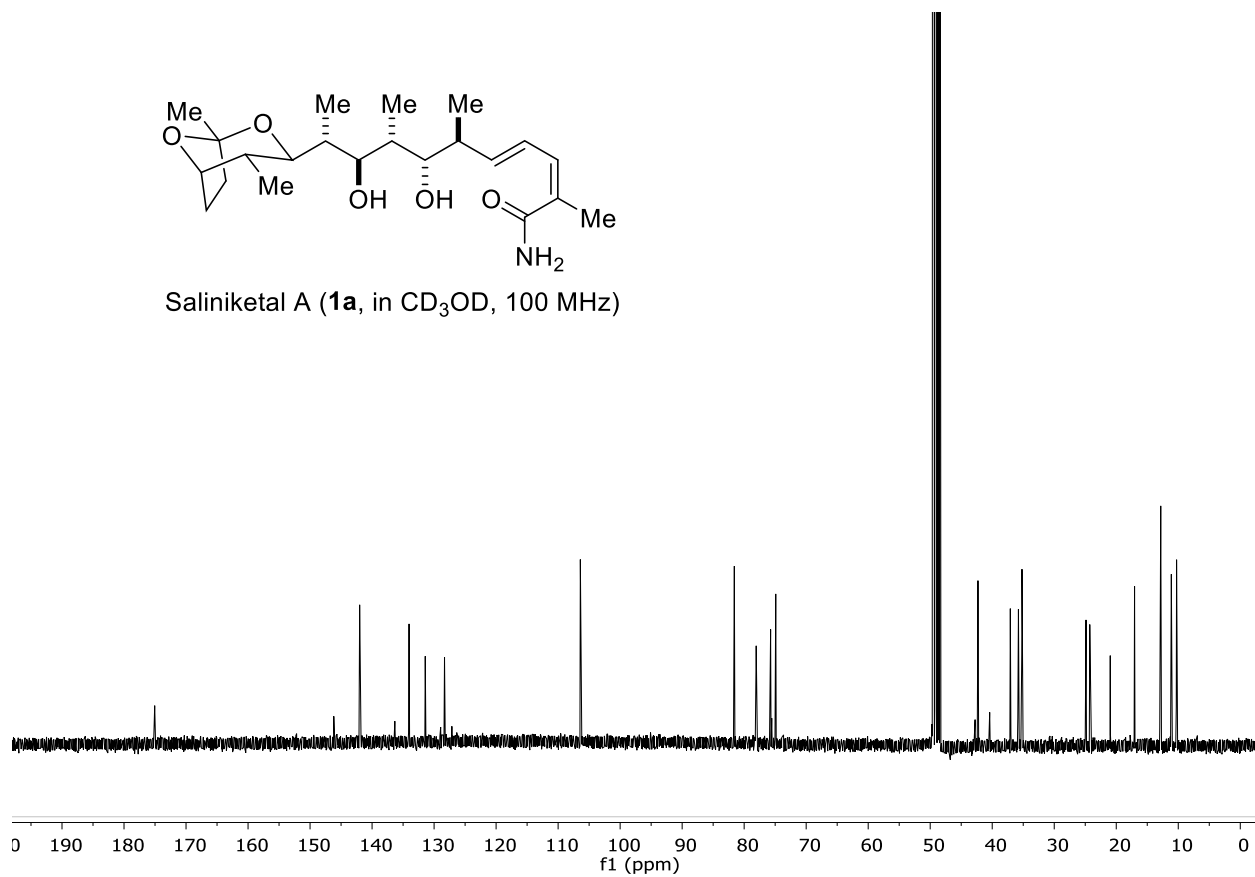
H and C-NMR (CDCl₃) of dienoic acid S6



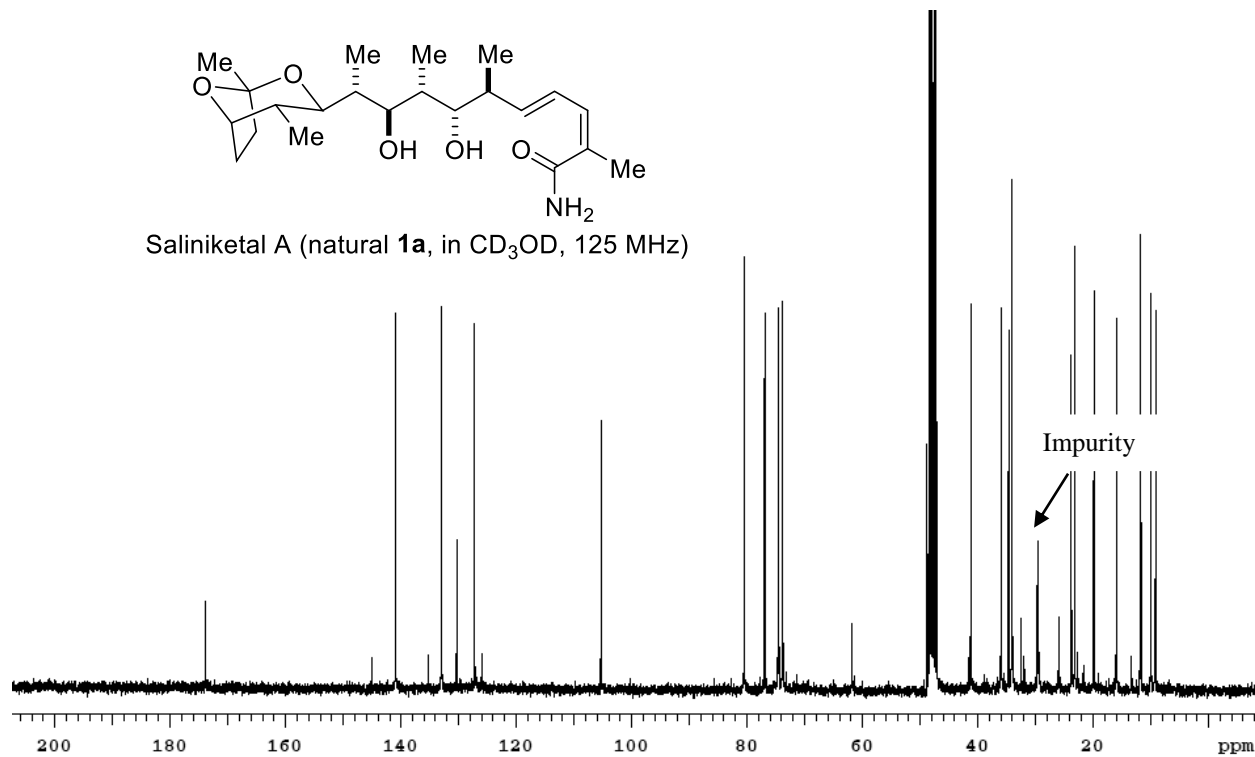




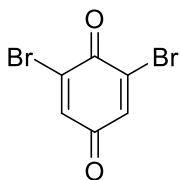
Saliniketal A (**1a**, in CD₃OD, 100 MHz)



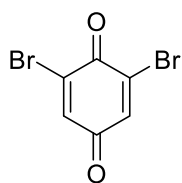
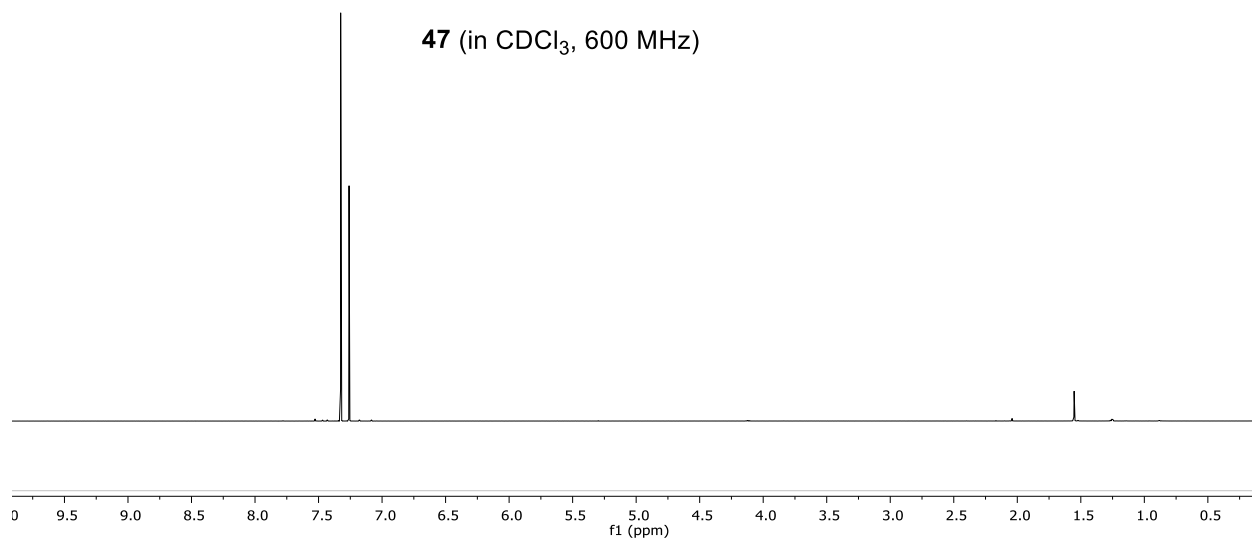
Saliniketal A (natural **1a**, in CD₃OD, 125 MHz)



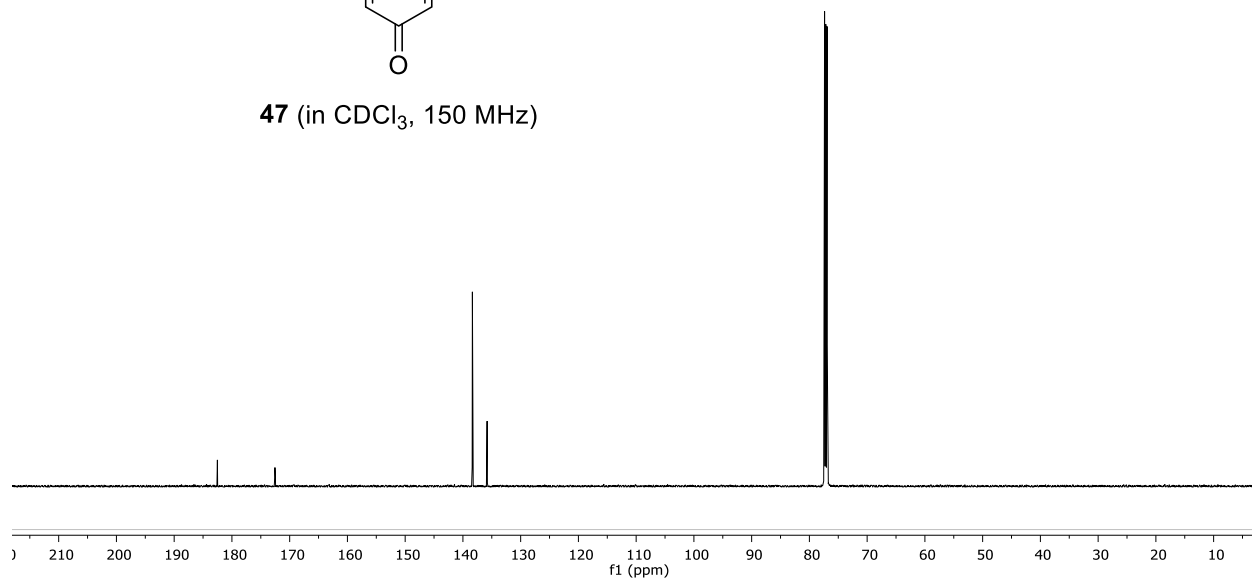
H and C-NMR (CDCl₃) of compound 47



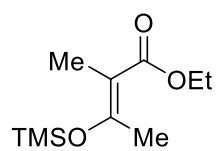
47 (in CDCl₃, 600 MHz)



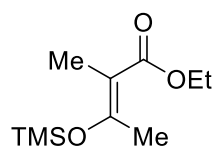
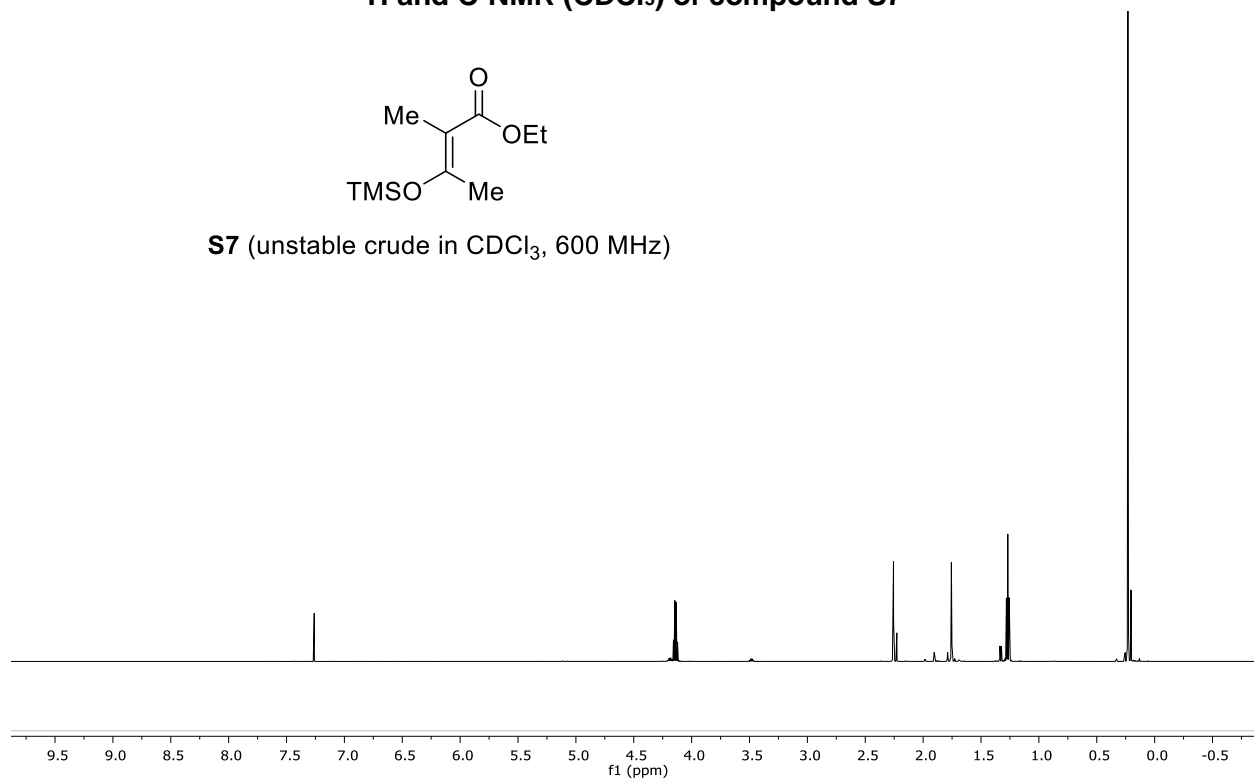
47 (in CDCl₃, 150 MHz)



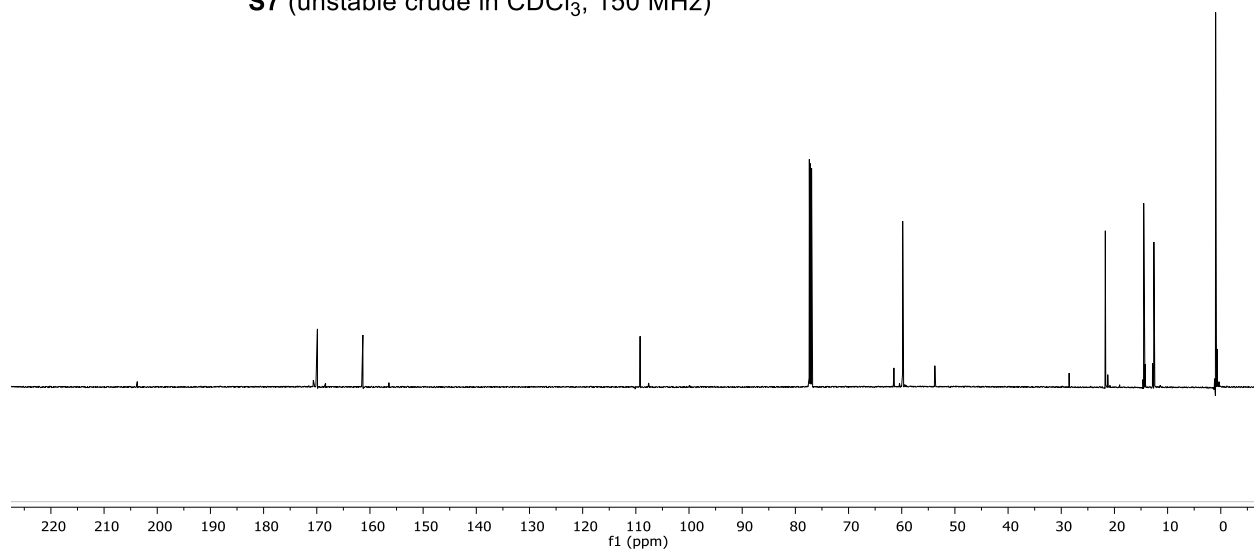
H and C-NMR (CDCl₃) of compound S7



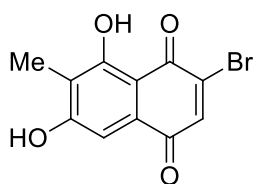
S7 (unstable crude in CDCl₃, 600 MHz)



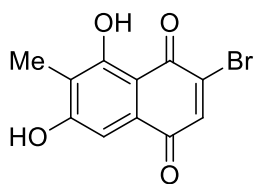
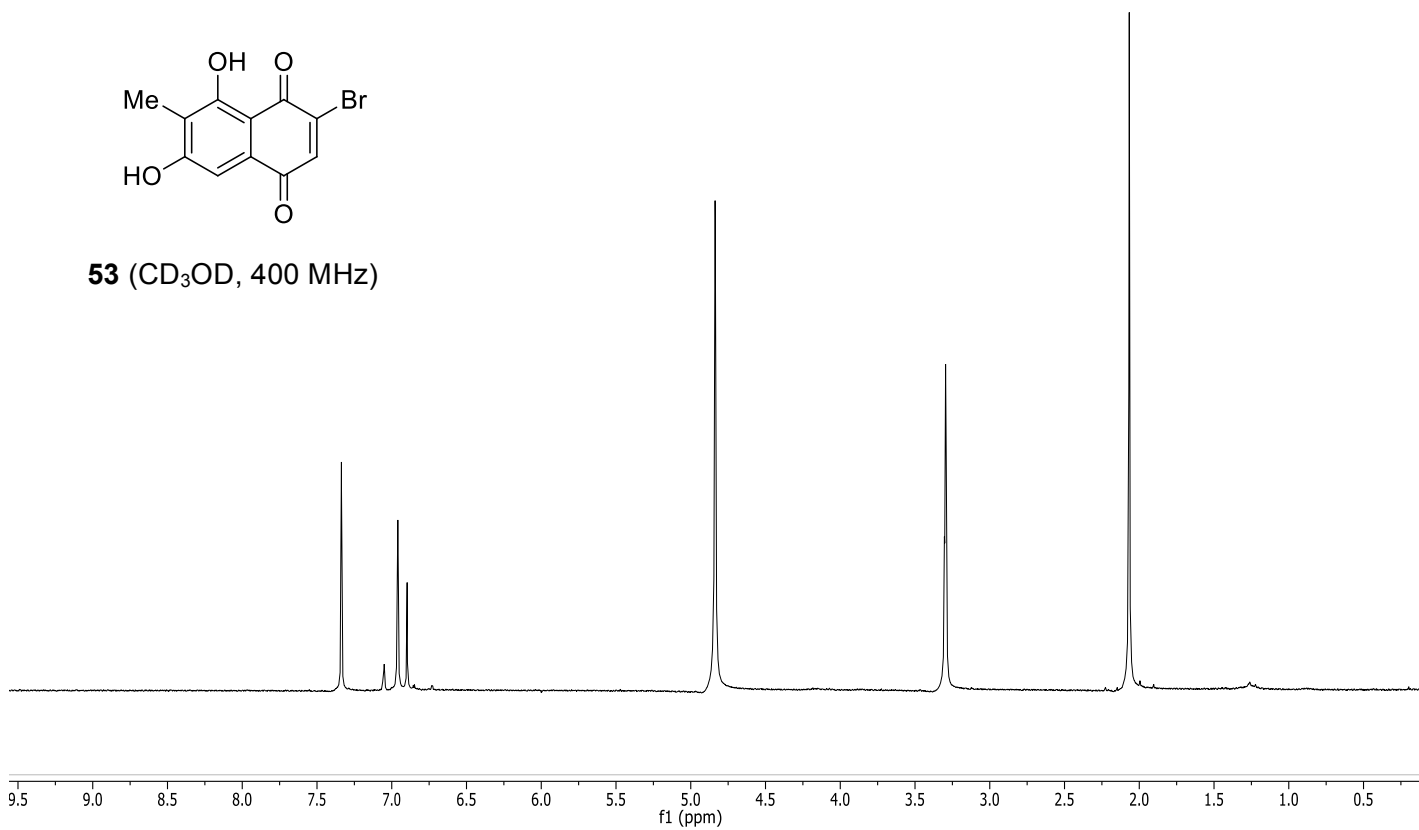
S7 (unstable crude in CDCl₃, 150 MHz)



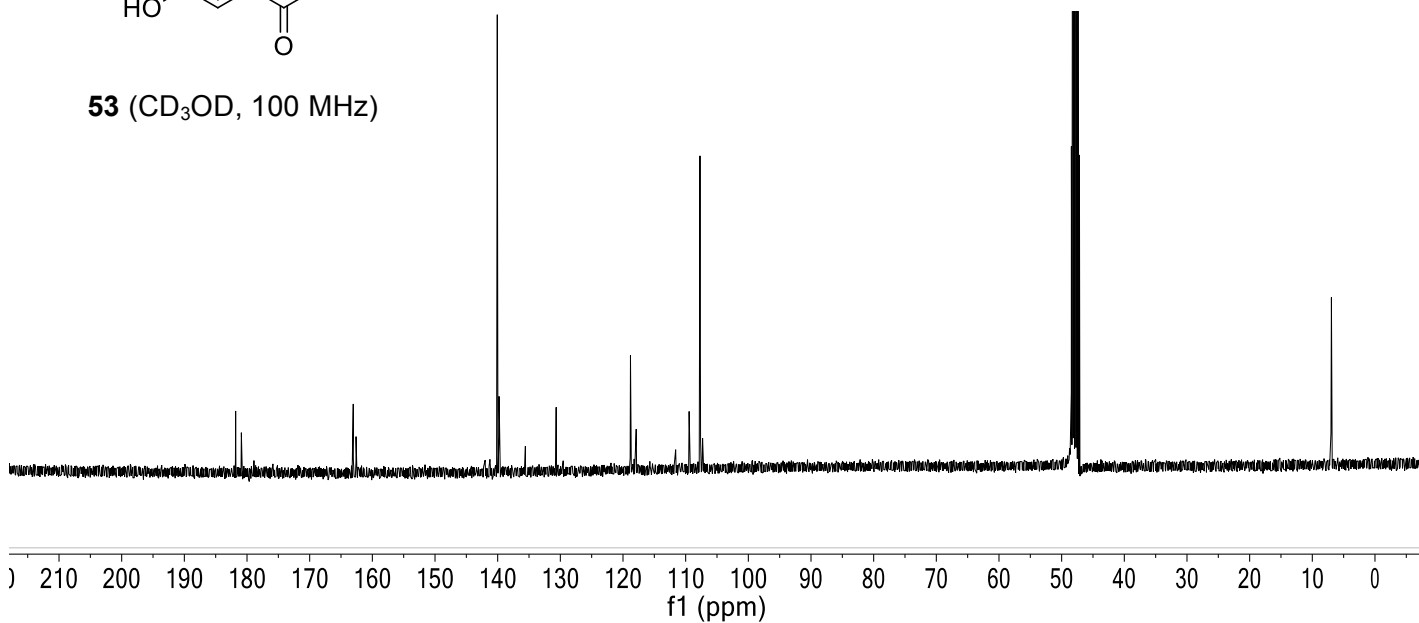
H and C-NMR (CD₃OD) of compound 53



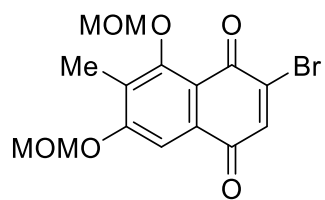
53 (CD₃OD, 400 MHz)



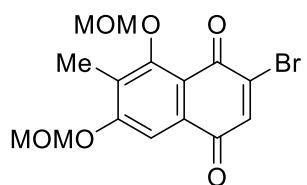
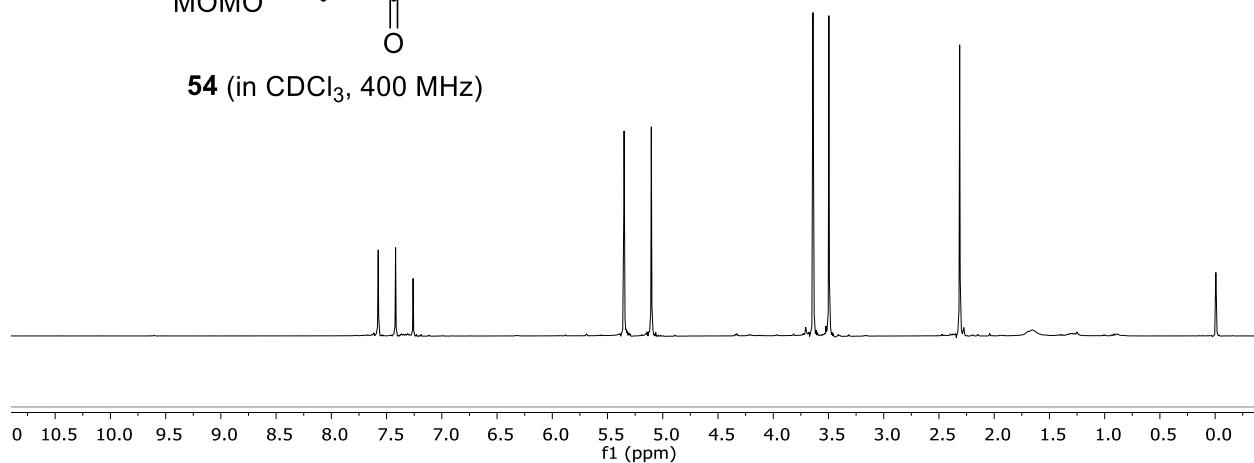
53 (CD₃OD, 100 MHz)



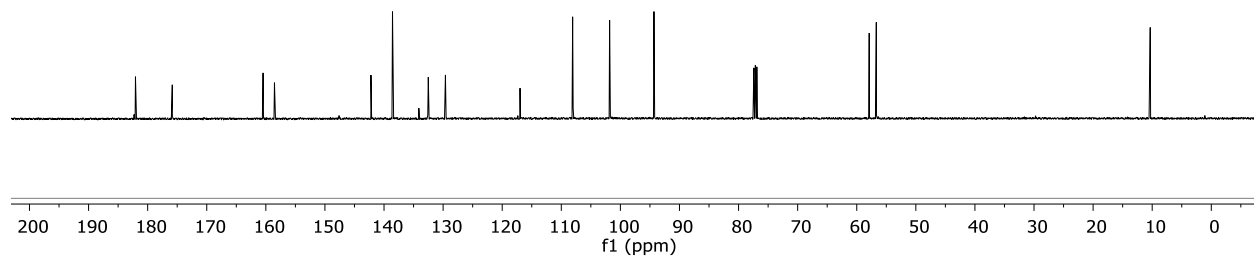
H and C-NMR (CDCl₃) of compound 54



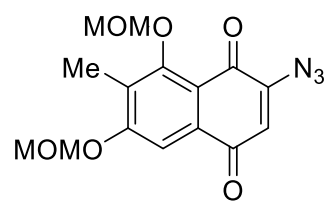
54 (in CDCl₃, 400 MHz)



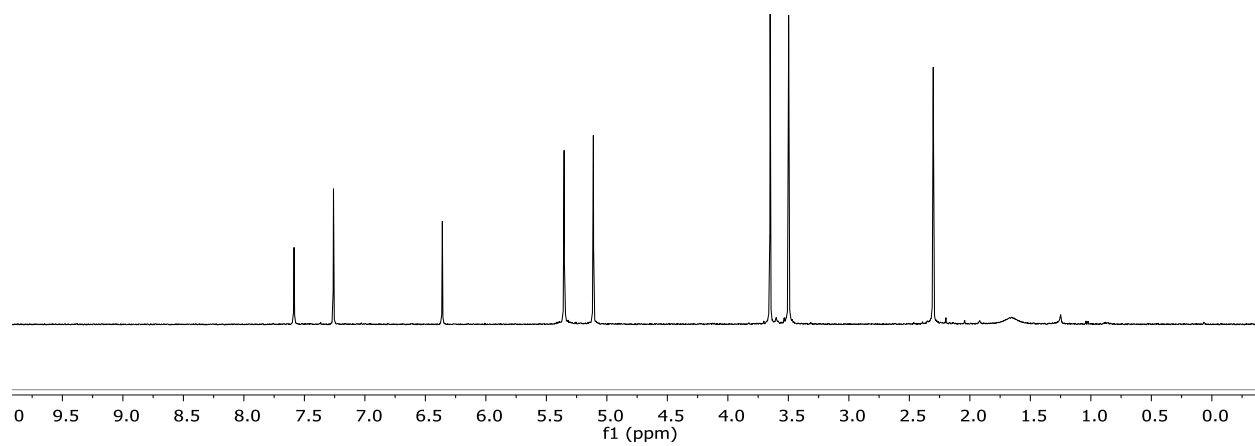
54 (in CDCl₃, 100 MHz)



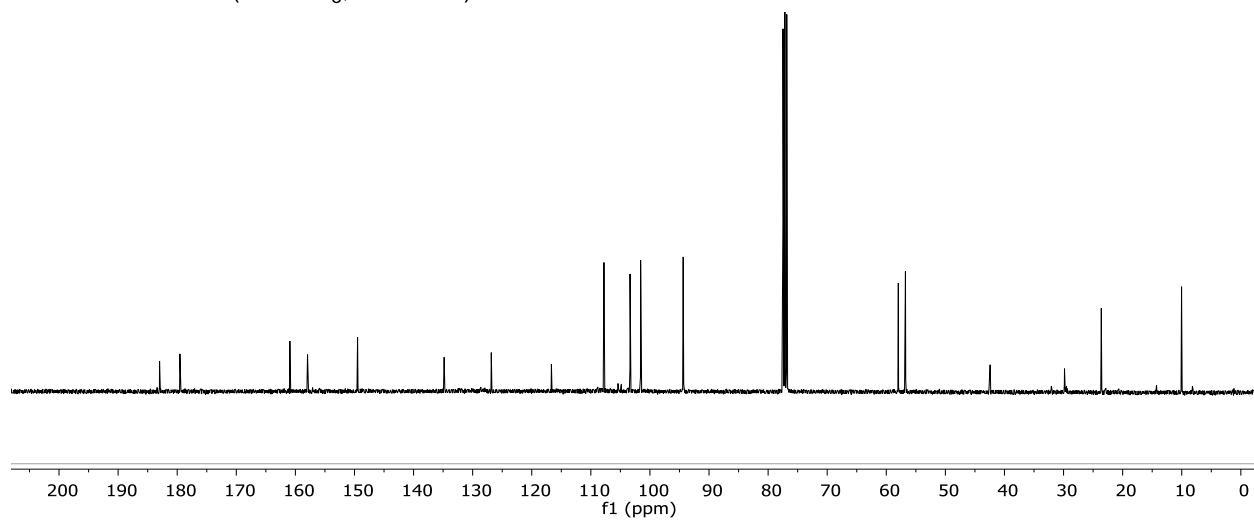
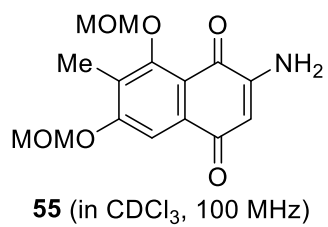
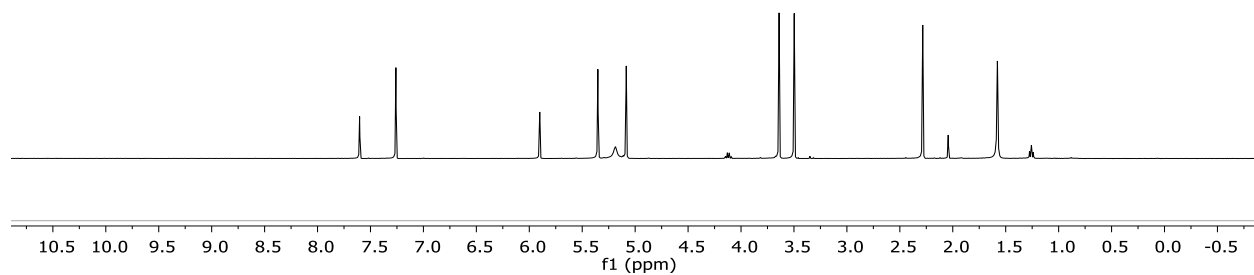
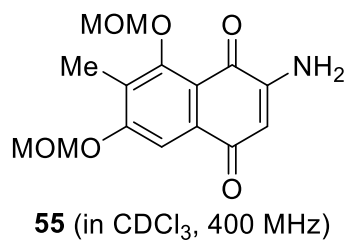
H-NMR (CDCl₃) of compound S8



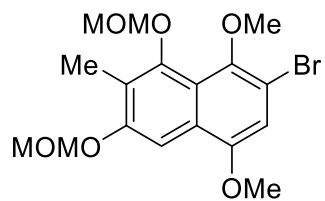
S8 (in CDCl₃, 400 MHz)



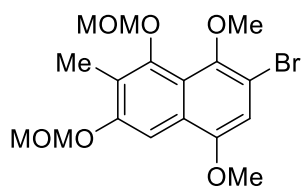
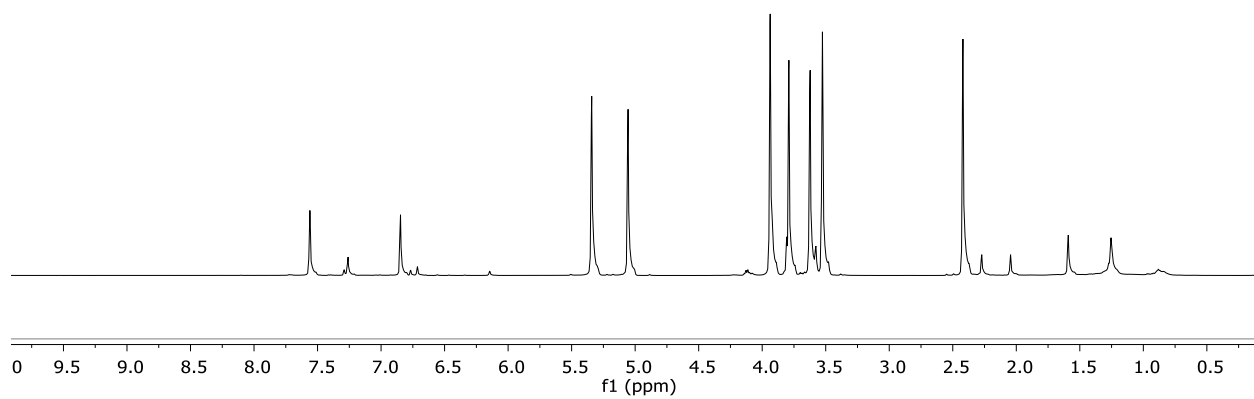
H and C-NMR (CDCl₃) of compound 55



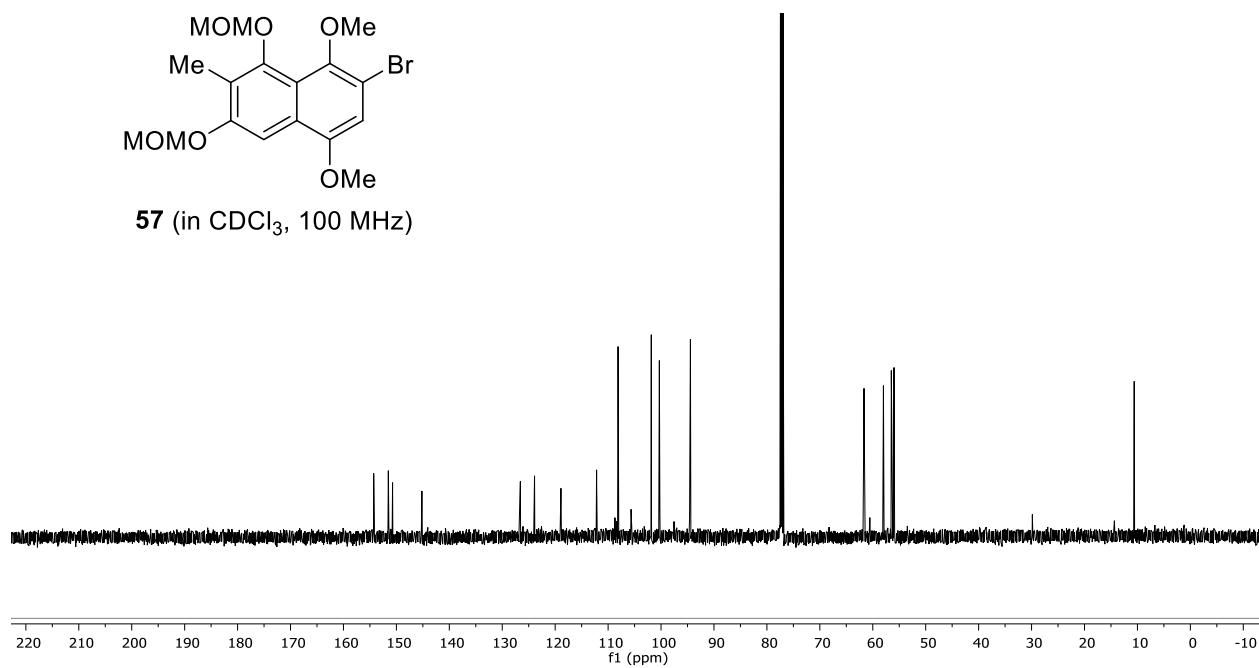
H and C-NMR (CDCl₃) of compound 57



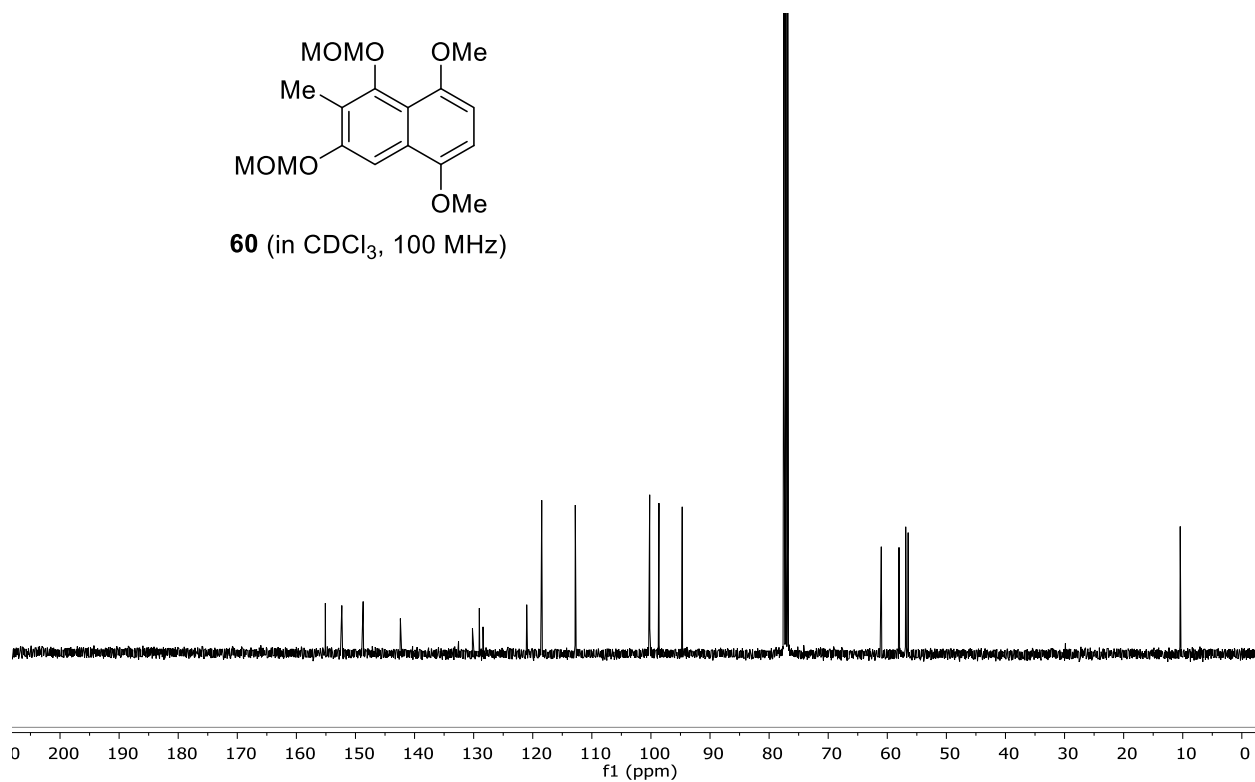
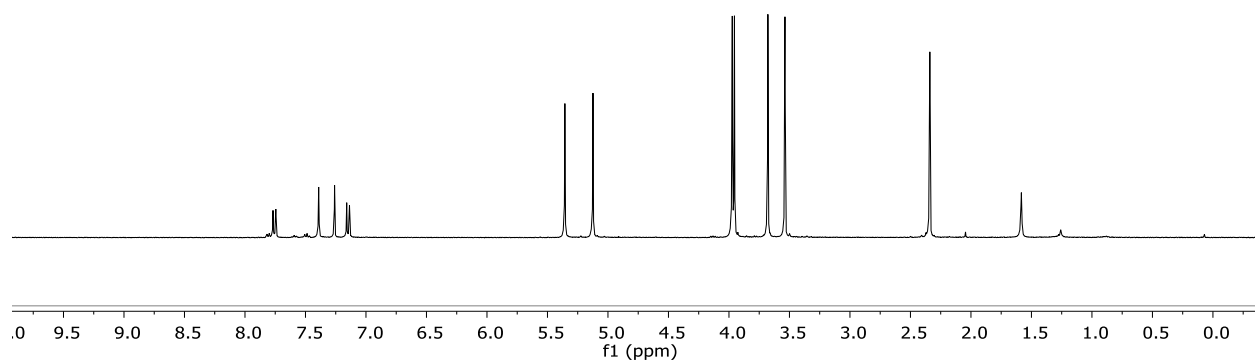
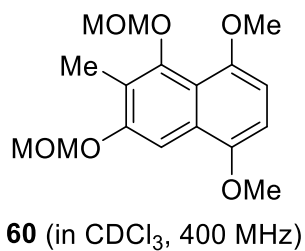
57 (in CDCl₃, 400 MHz)



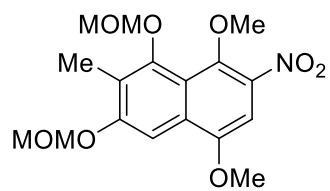
57 (in CDCl₃, 100 MHz)



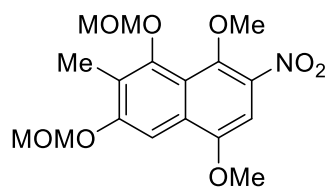
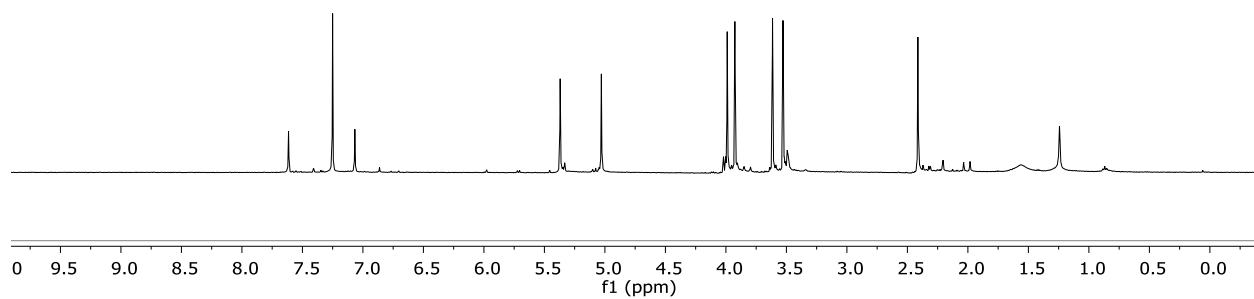
H and C-NMR (CDCl₃) of compound 60



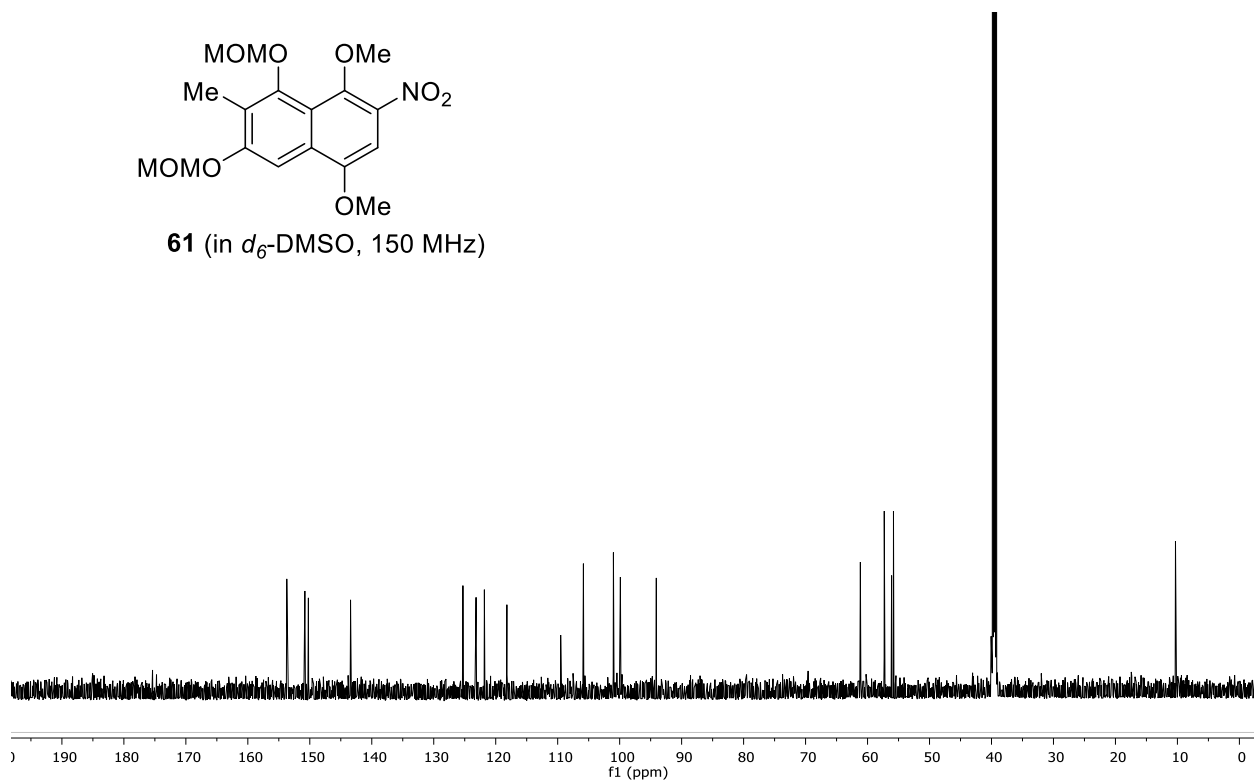
¹H (CDCl₃) and ¹³C (d₆-DMSO)-NMR of compound 61



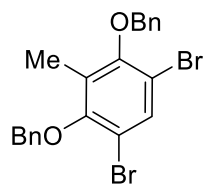
61 (in CDCl₃, 400 MHz)



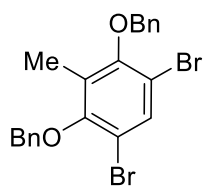
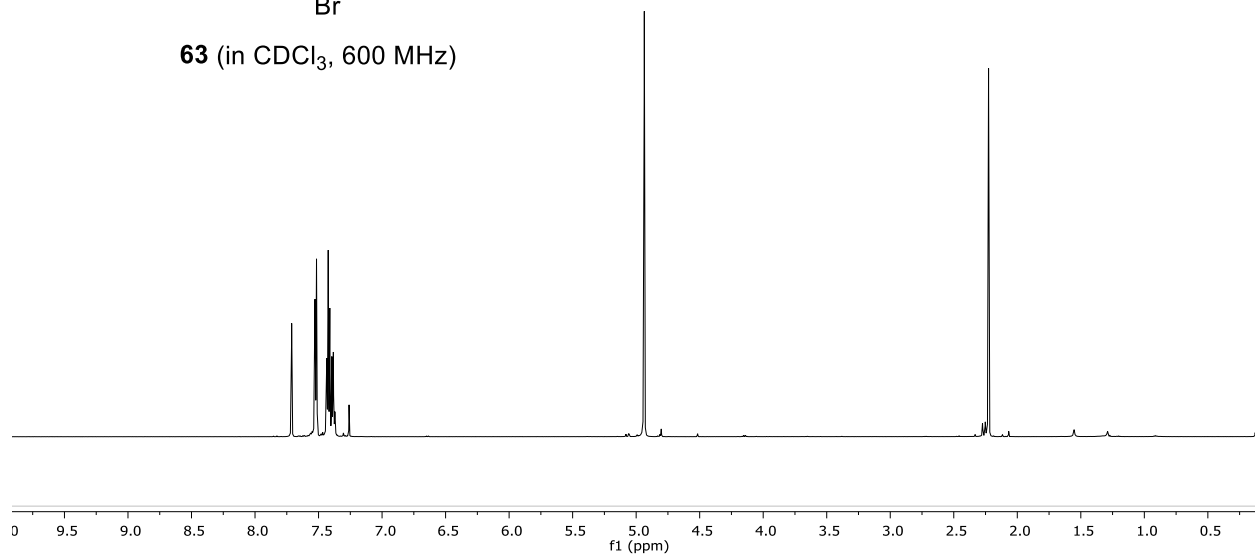
61 (in d₆-DMSO, 150 MHz)



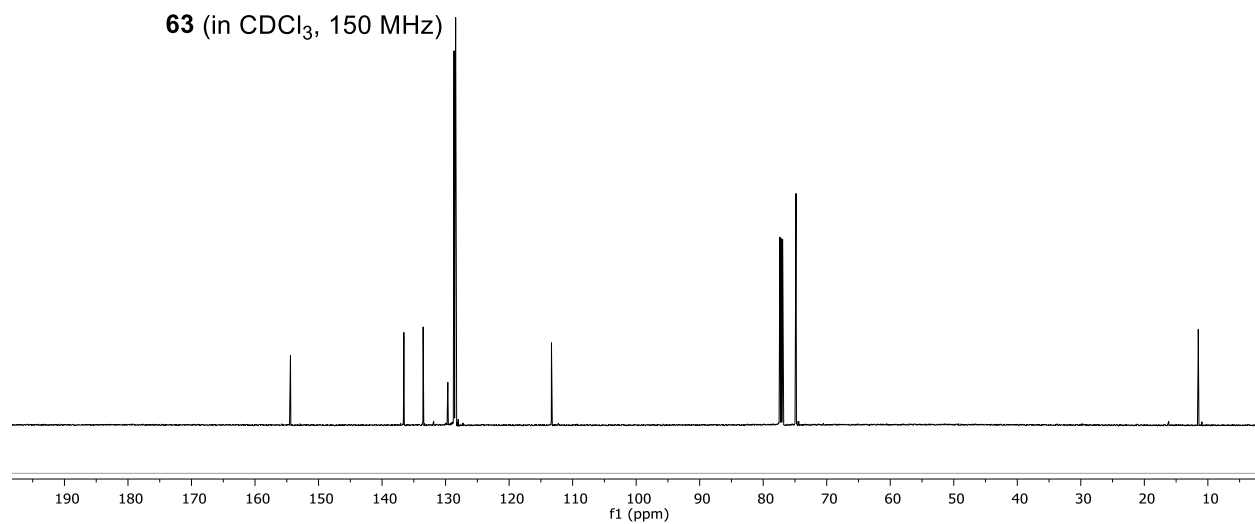
H and C-NMR (CDCl₃) of compound 63



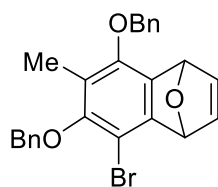
63 (in CDCl₃, 600 MHz)



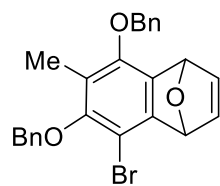
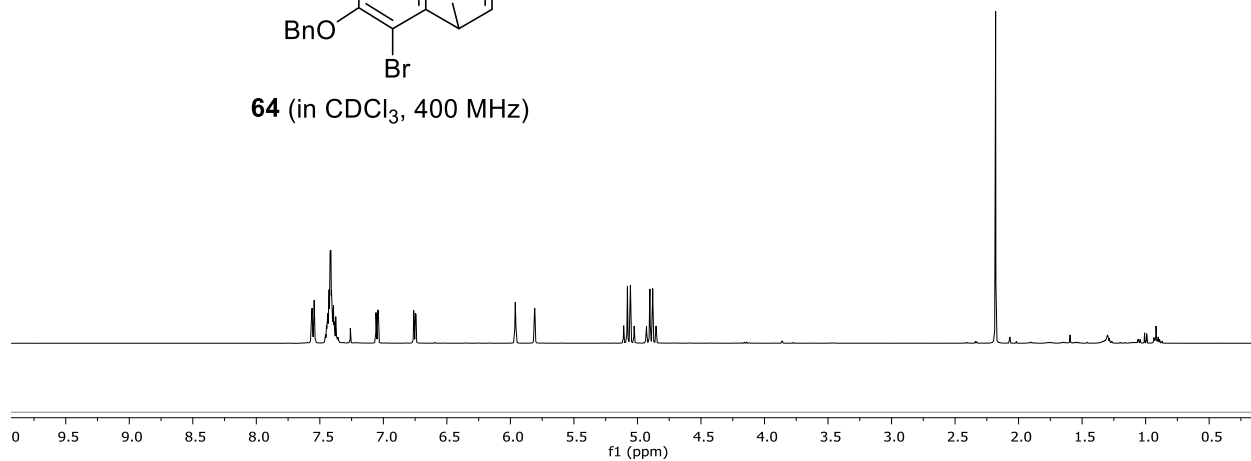
63 (in CDCl₃, 150 MHz)



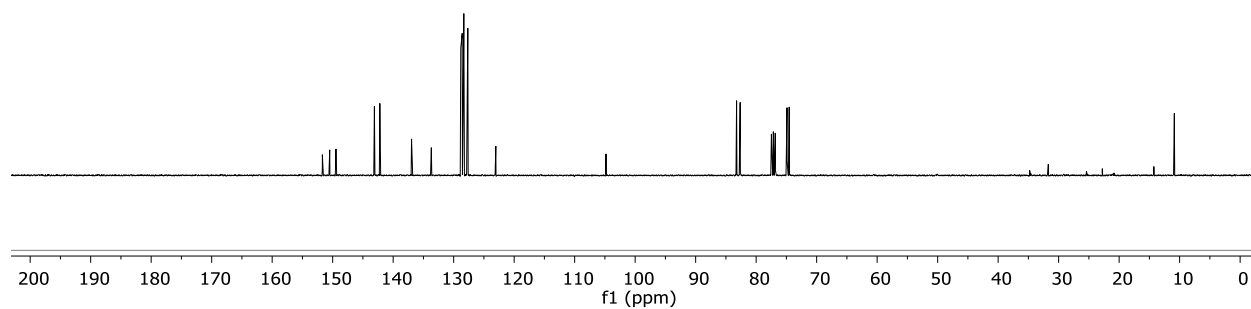
H and C-NMR (CDCl₃) of compound 64



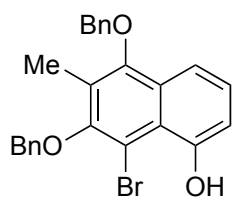
64 (in CDCl₃, 400 MHz)



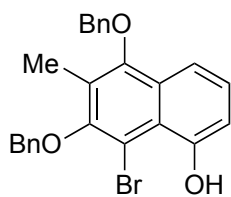
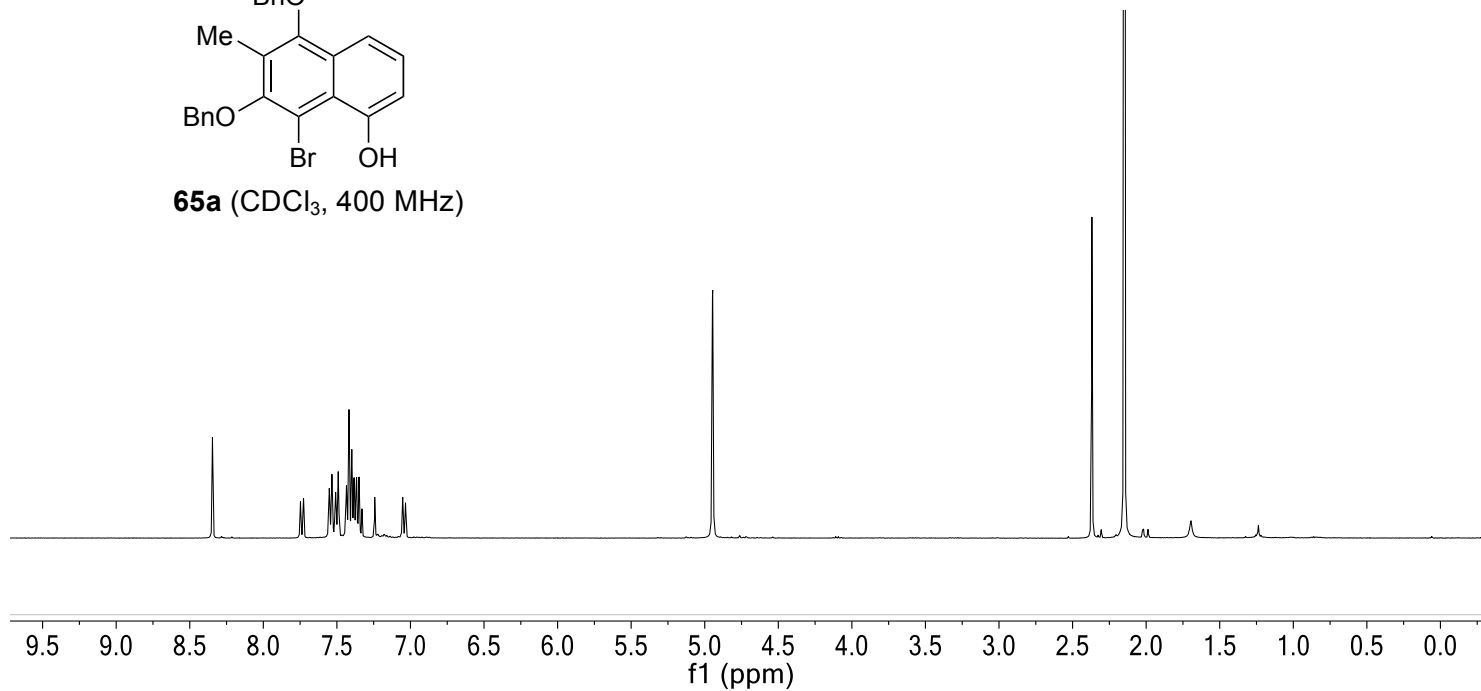
64 (in CDCl₃, 100 MHz)



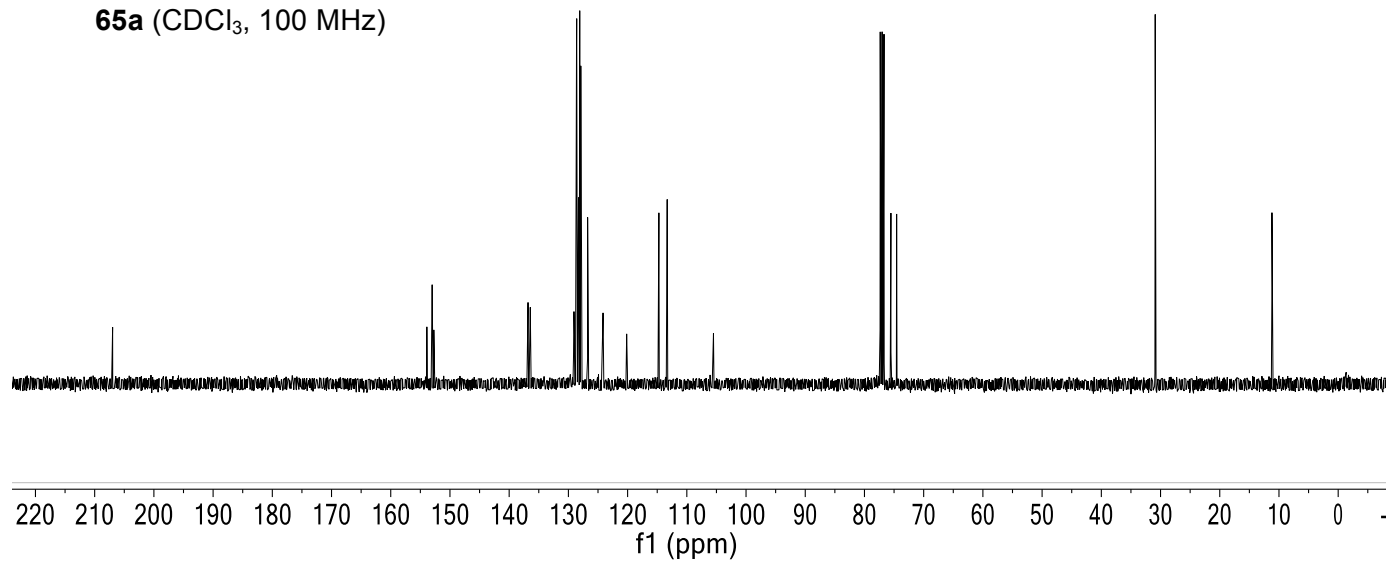
H and C-NMR (CDCl₃) of compound 65a



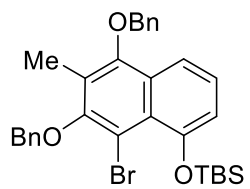
65a (CDCl₃, 400 MHz)



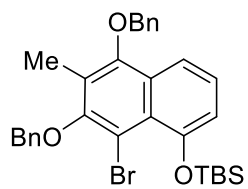
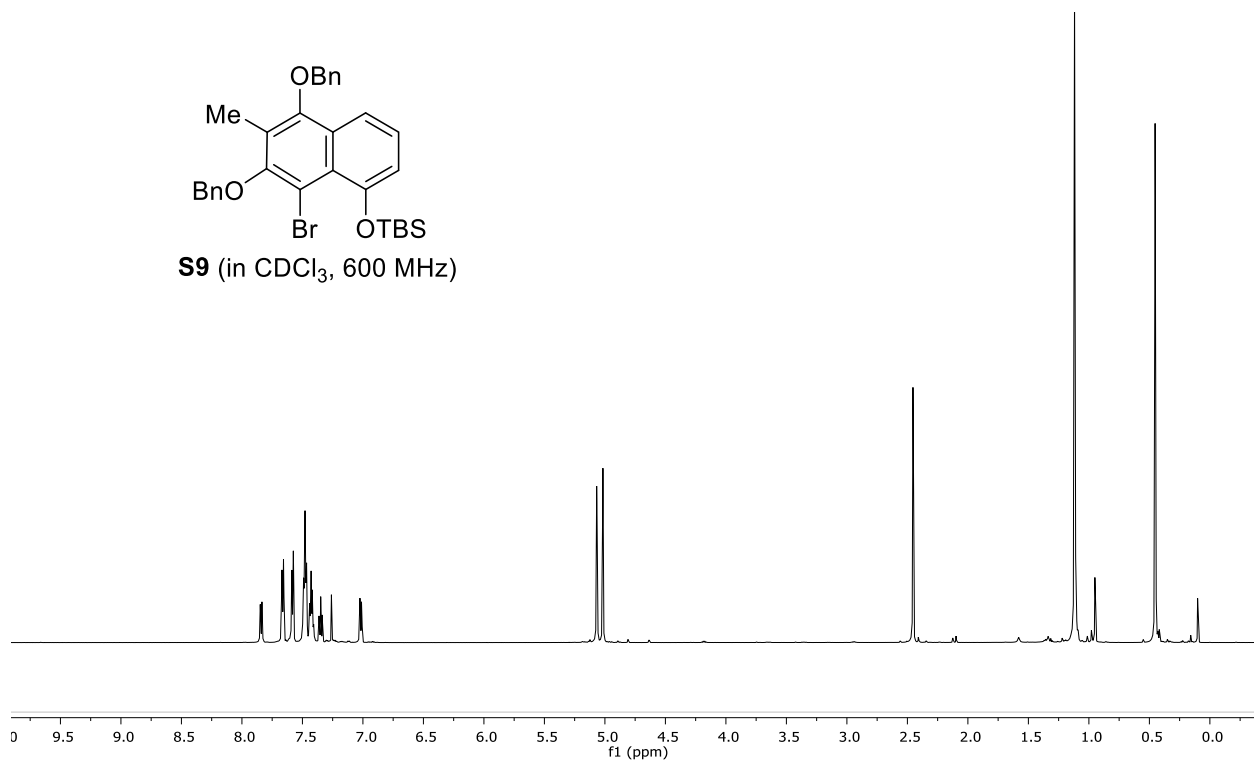
65a (CDCl₃, 100 MHz)



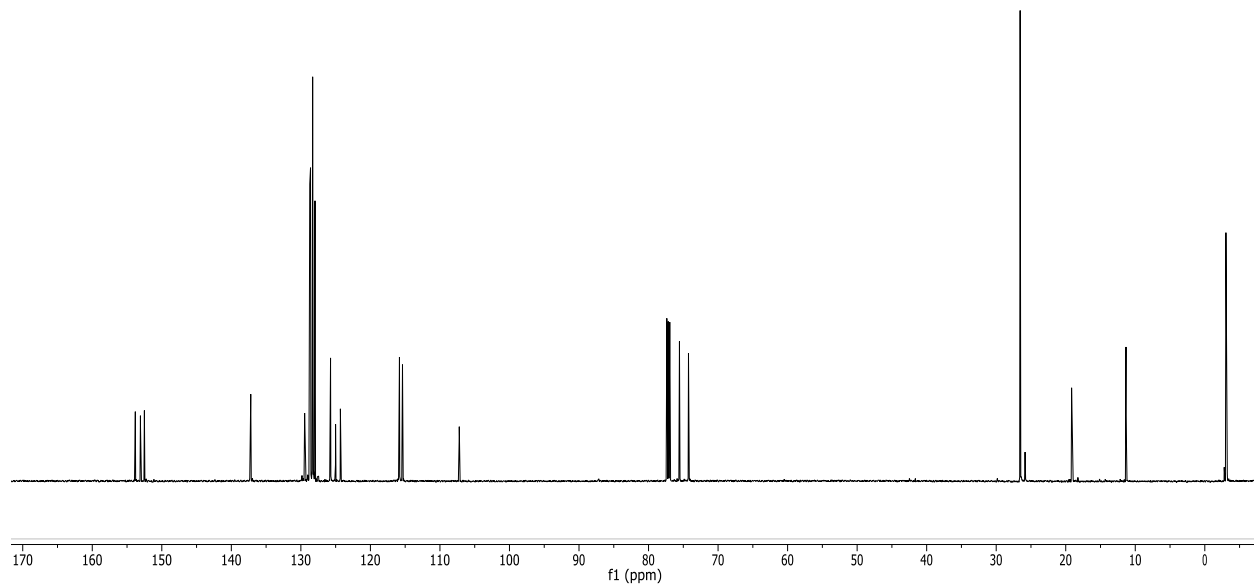
H and C-NMR (CDCl₃) of compound S9



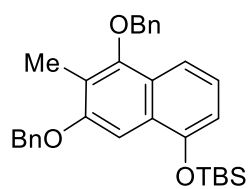
S9 (in CDCl₃, 600 MHz)



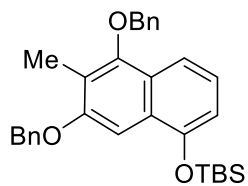
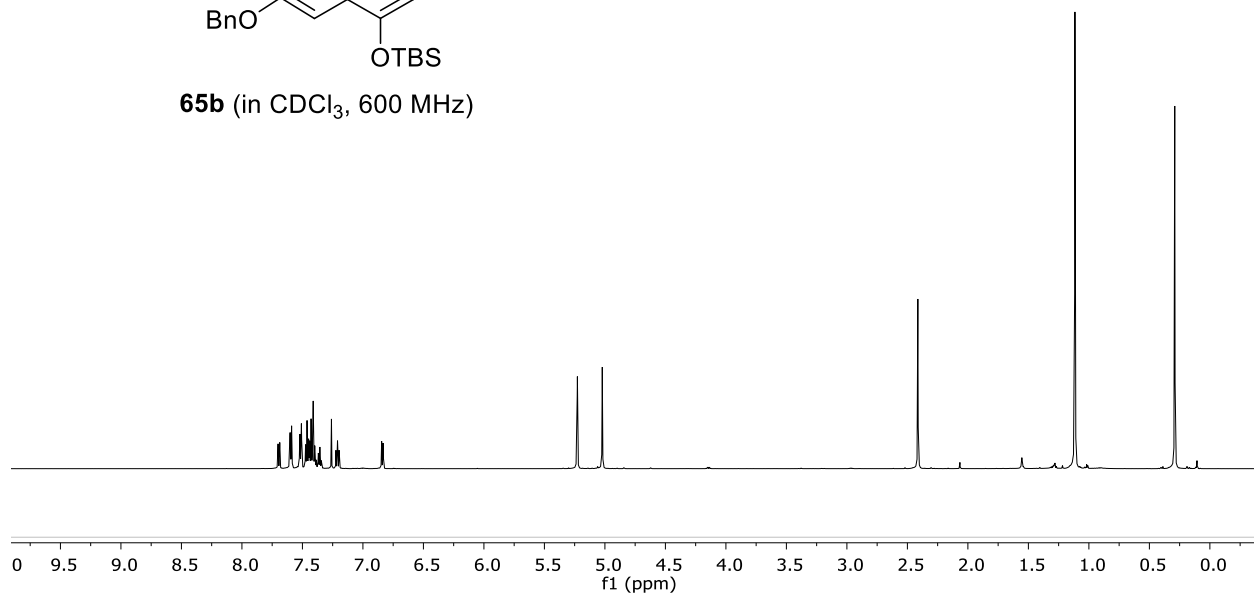
S9 (in CDCl₃, 150 MHz)



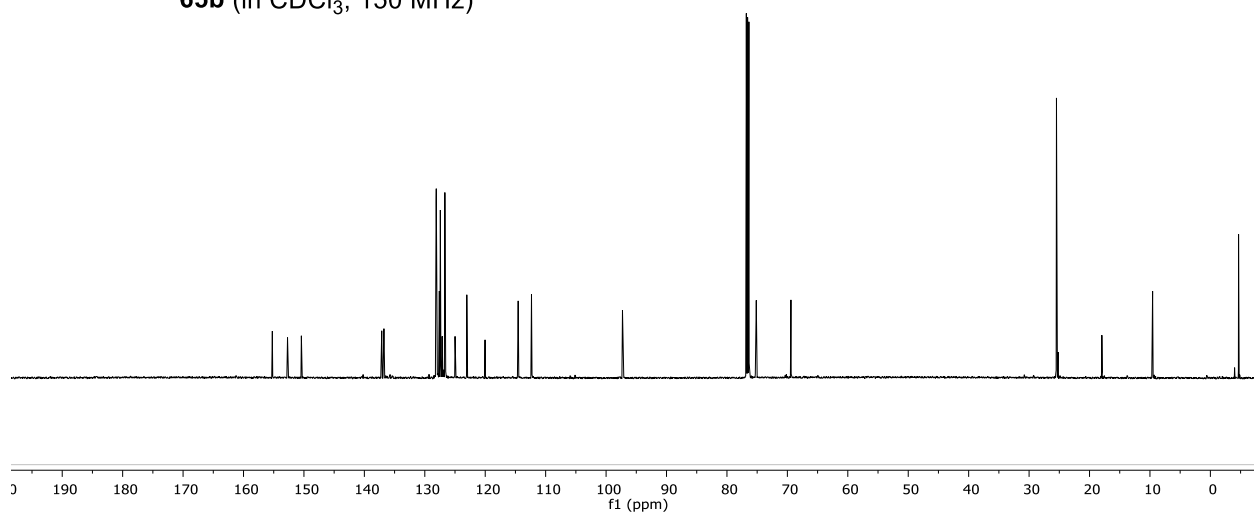
H and C-NMR (CDCl₃) of compound 65b



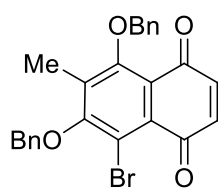
65b (in CDCl₃, 600 MHz)



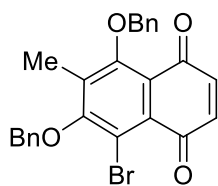
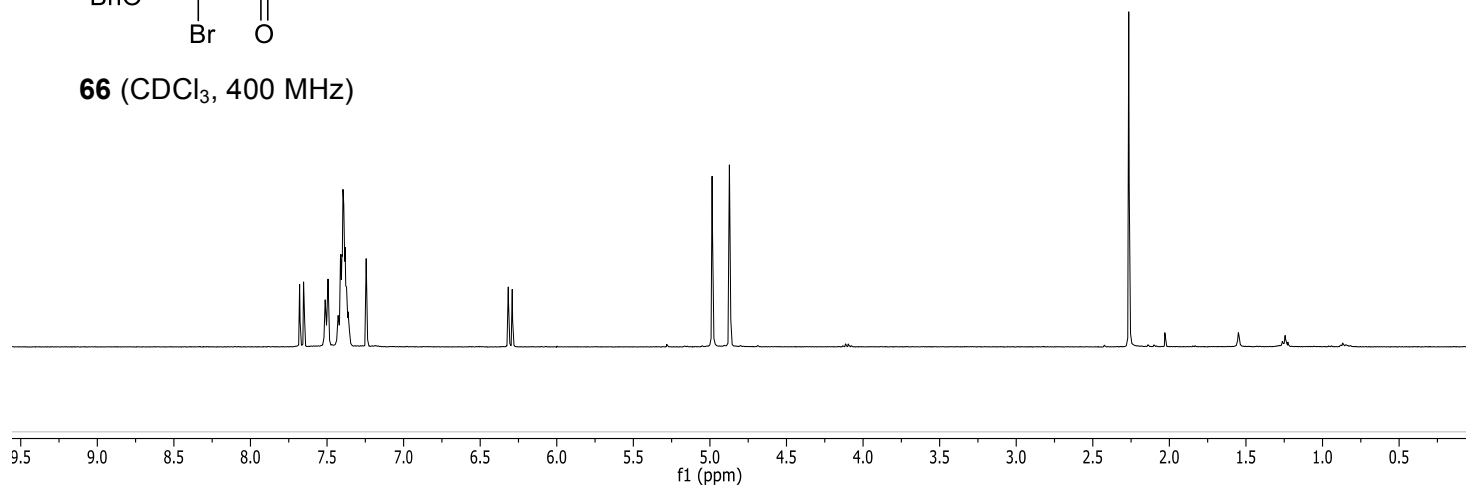
65b (in CDCl₃, 150 MHz)



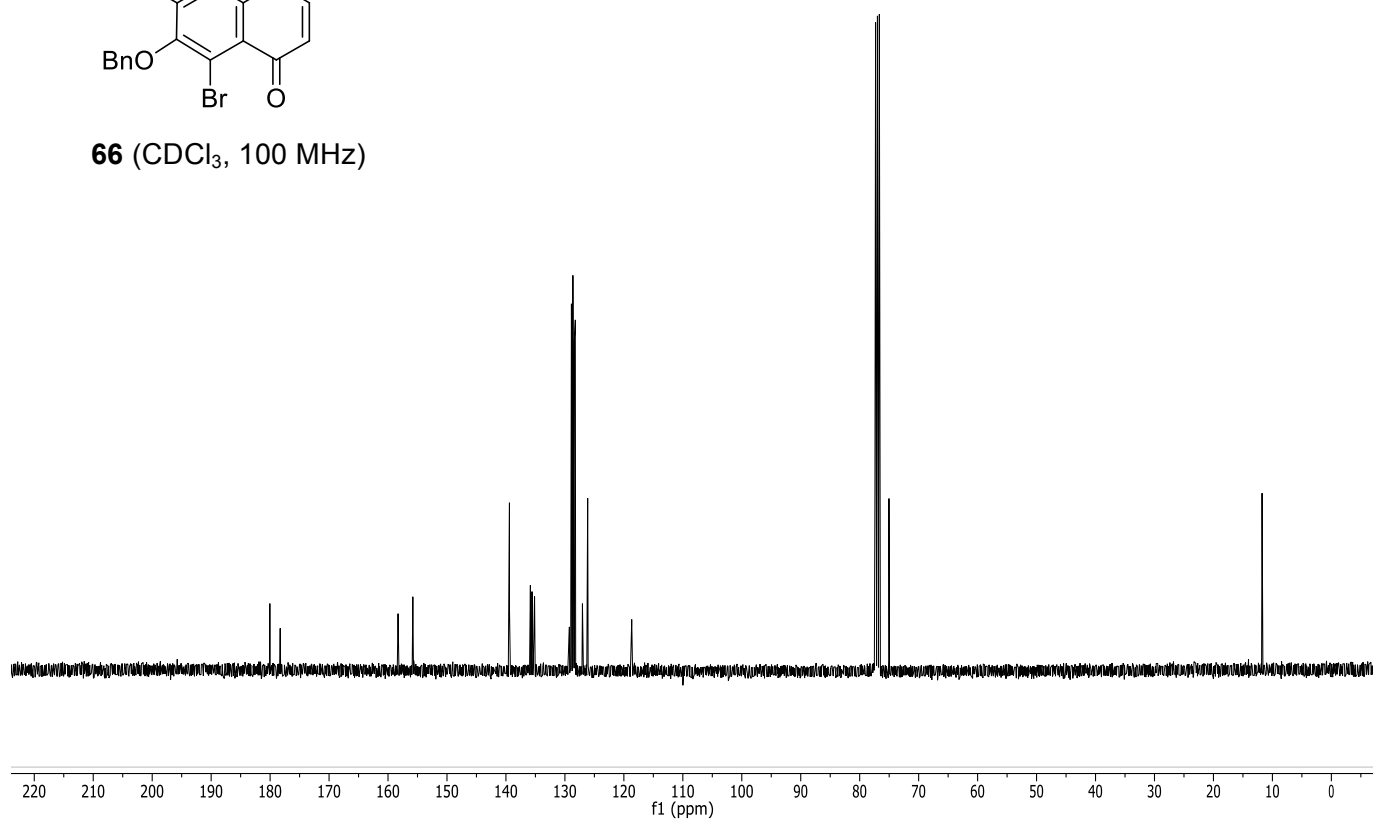
H and C-NMR (CDCl₃) of compound **66**

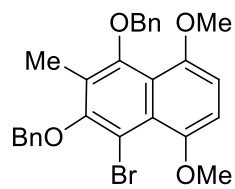


66 (CDCl₃, 400 MHz)



66 (CDCl₃, 100 MHz)



COC1=CC=C(C(=C2C(=C1)C(=C(C=C2)OCc3ccccc3)OC)c4ccccc4O)c5ccccc5

67 (CDCl₃, 100 MHz)

13C NMR spectrum (CDCl₃, 100 MHz) showing chemical shifts (ppm) on the x-axis (0 to 210 ppm). The spectrum displays several peaks, including a triplet for CDCl₃ at 77 ppm, a peak at 100 ppm, a peak at 125 ppm, a peak at 130 ppm, a peak at 155 ppm, and a peak at 160 ppm. There are also smaller peaks at 10, 20, and 30 ppm.

COc1cc(OC)c2cc(OC)c(C(=O)OC)c2cc1OC

68 (CDCl₃, 400 MHz)

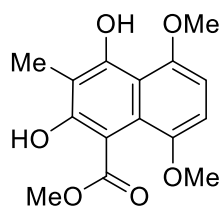
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

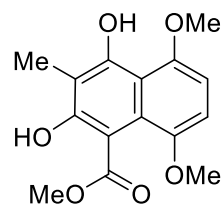
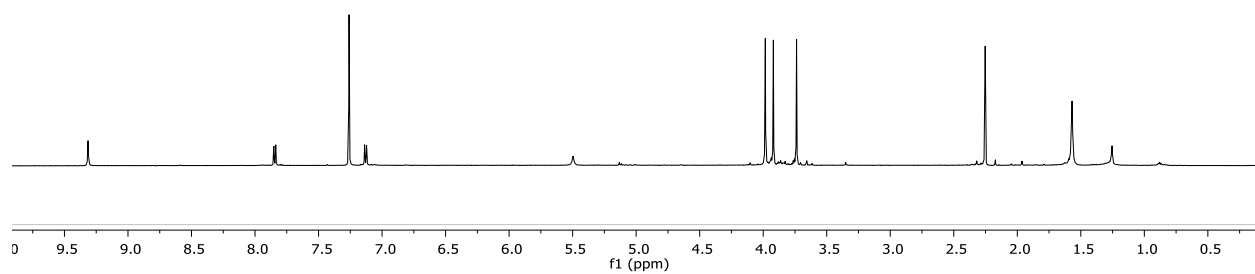
68 (CDCl₃, 100 MHz)

Chemical structure of **68** is shown above the spectrum. It is a naphthalene derivative with a methyl ester group (-COOMe) at position 1, a benzyl ether group (-OBn) at position 2, a methyl group (-Me) at position 3, a benzyl ether group (-OBn) at position 4, and methoxy groups (-OMe) at positions 5 and 8.

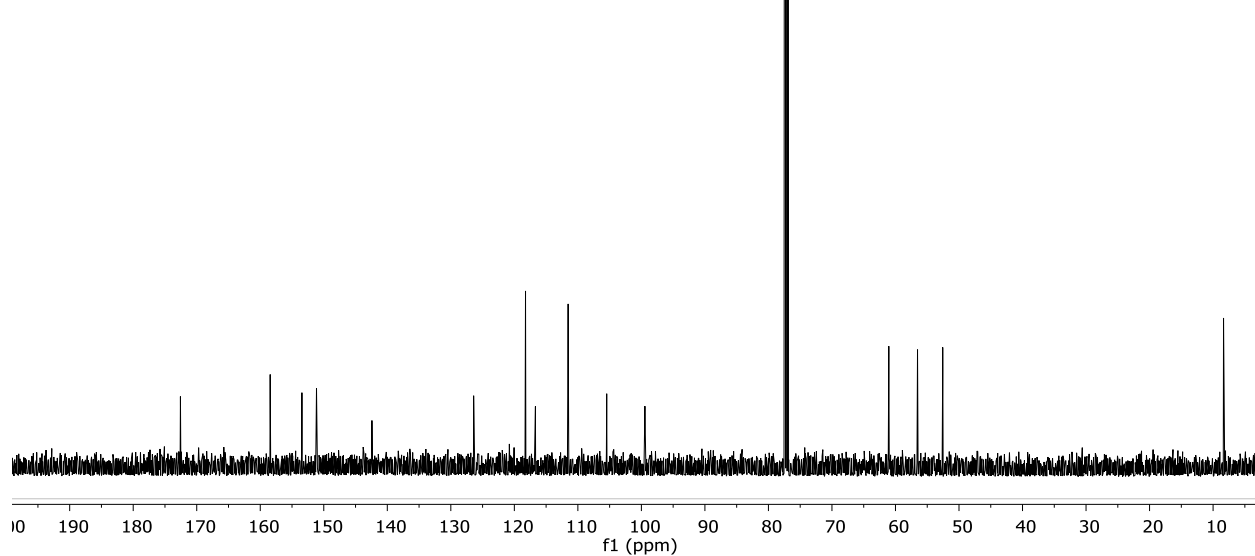
H and C-NMR (CDCl₃) of compound 69



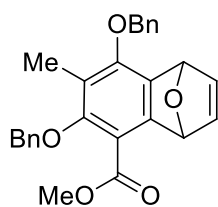
69 (600 MHz, in CDCl₃)



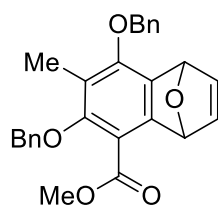
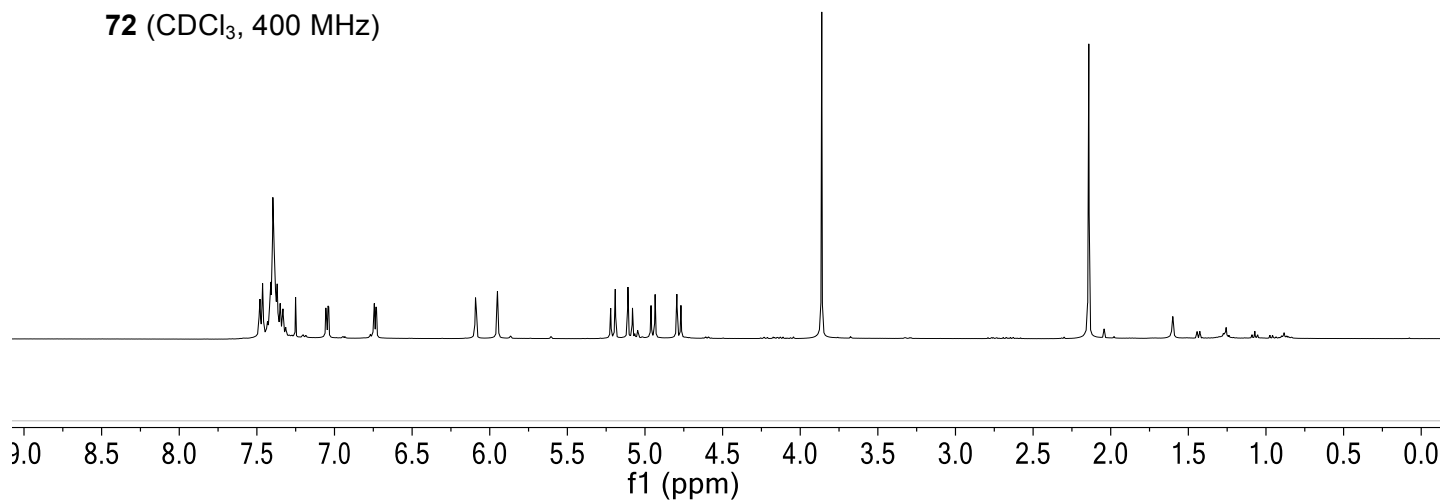
69 (150 MHz, in CDCl₃)



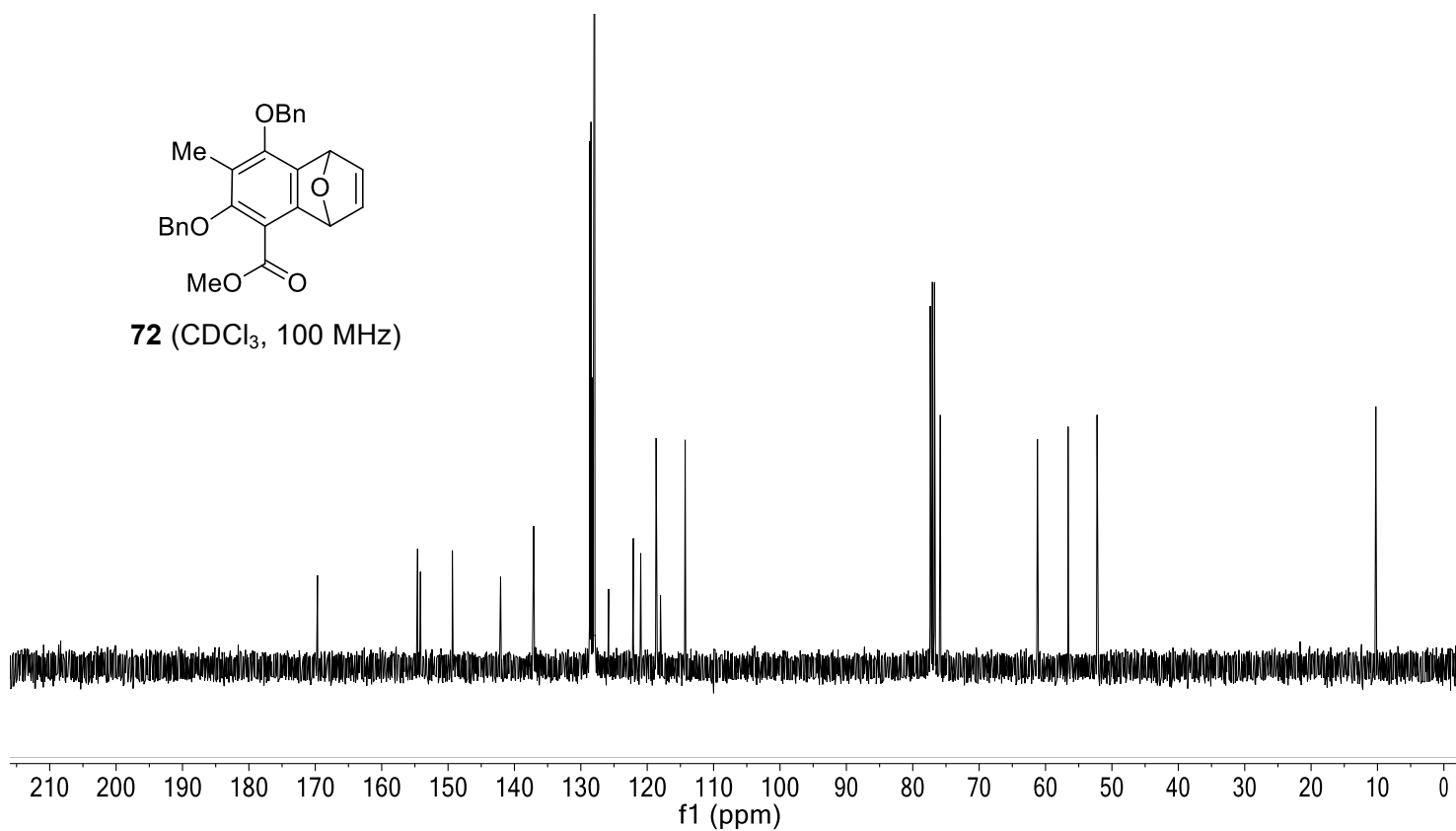
H and C-NMR (CDCl₃) of compound 72



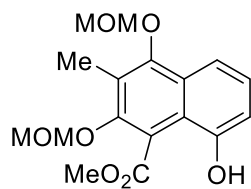
72 (CDCl₃, 400 MHz)



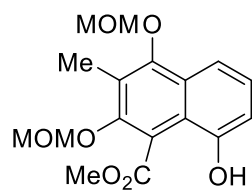
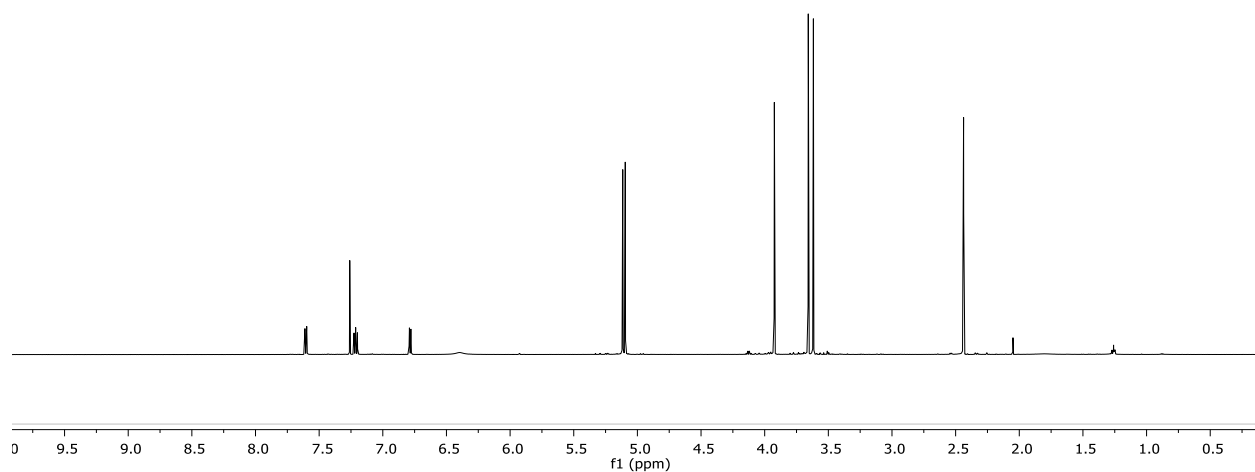
72 (CDCl₃, 100 MHz)



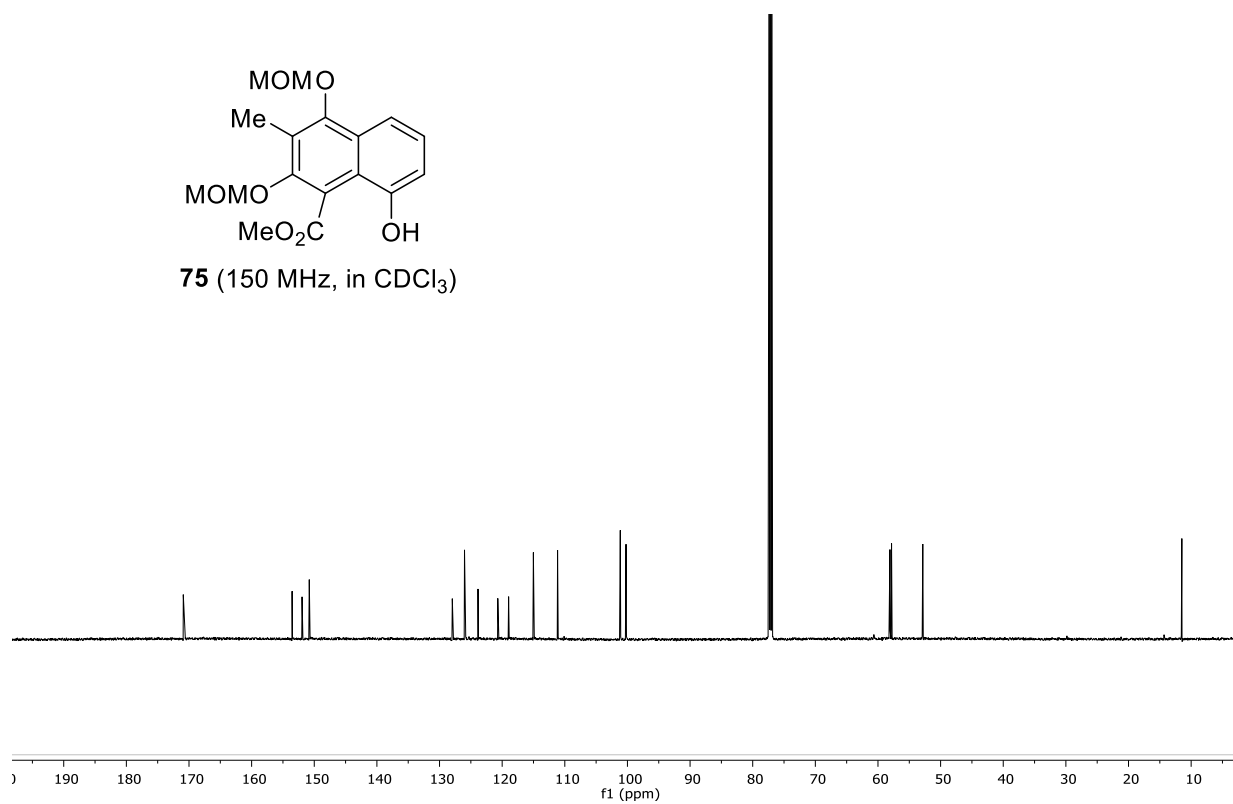
H and C-NMR (CDCl₃) of compound 75



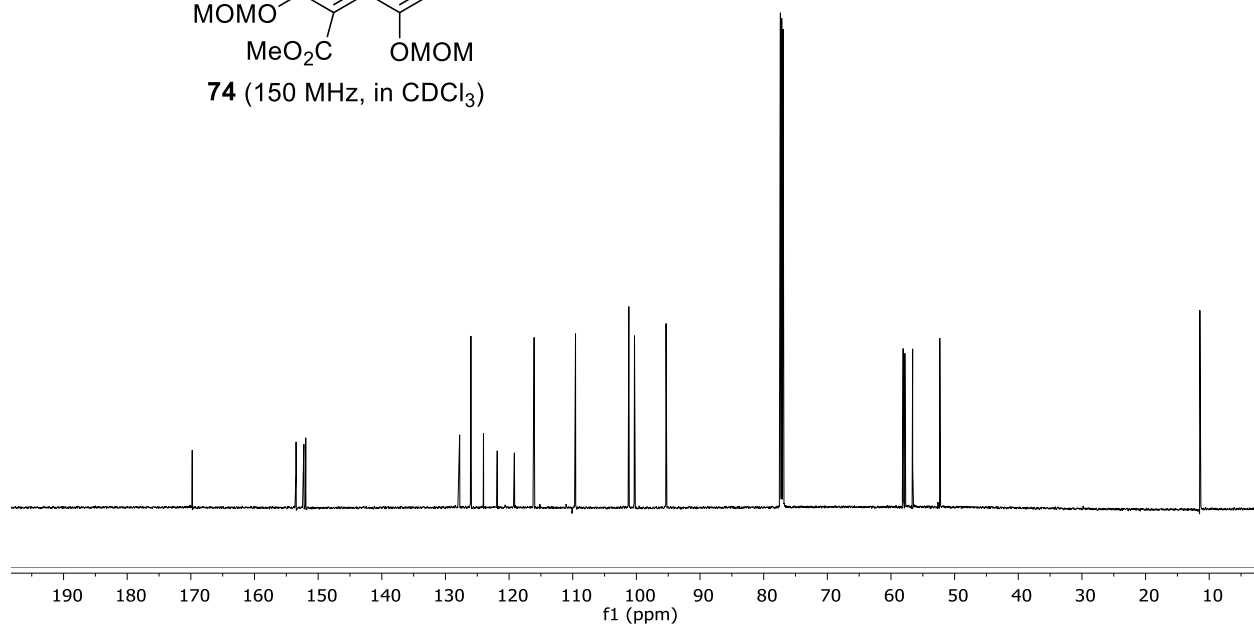
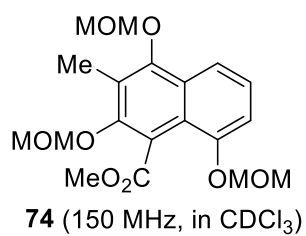
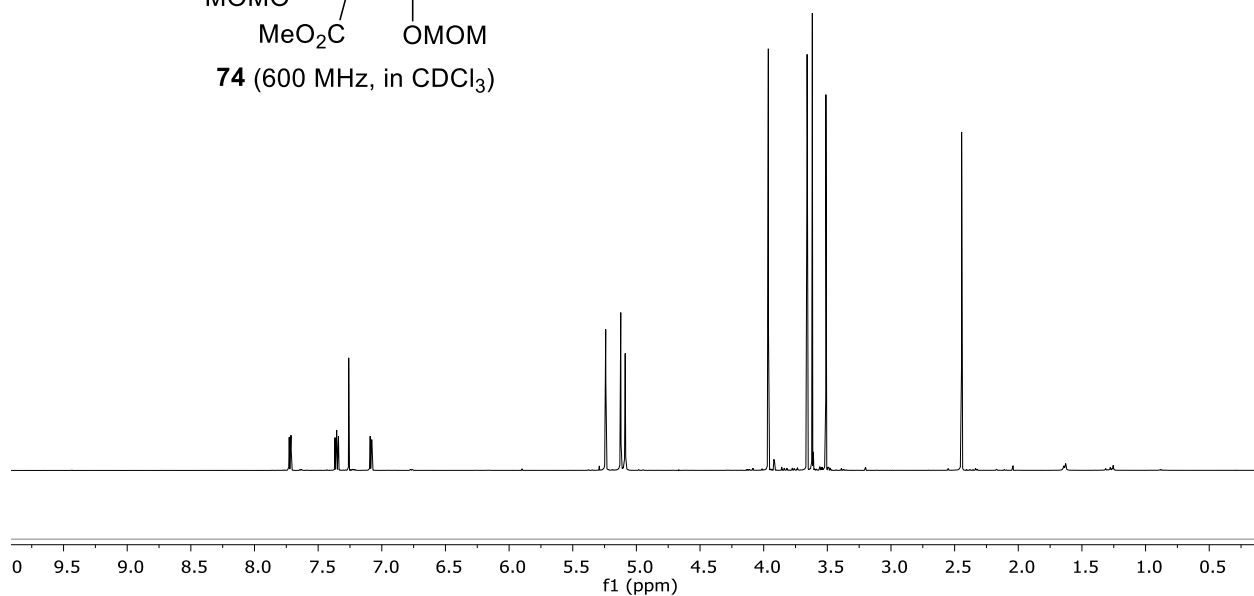
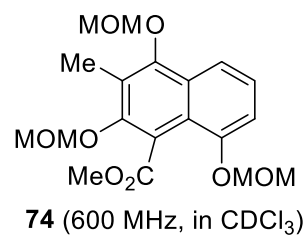
75 (600 MHz, in CDCl₃)



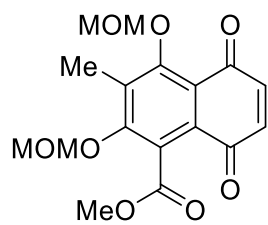
75 (150 MHz, in CDCl₃)



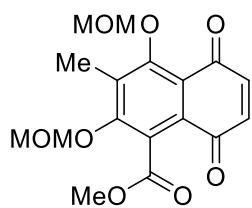
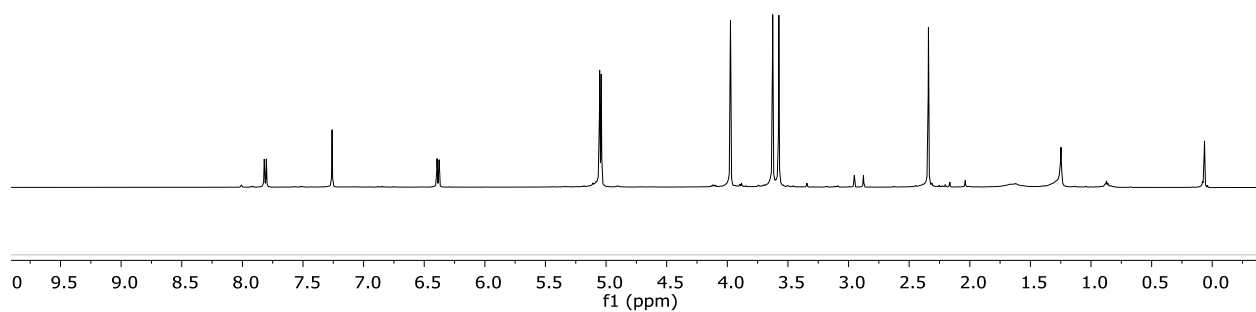
H and C-NMR (CDCl₃) of compound 74



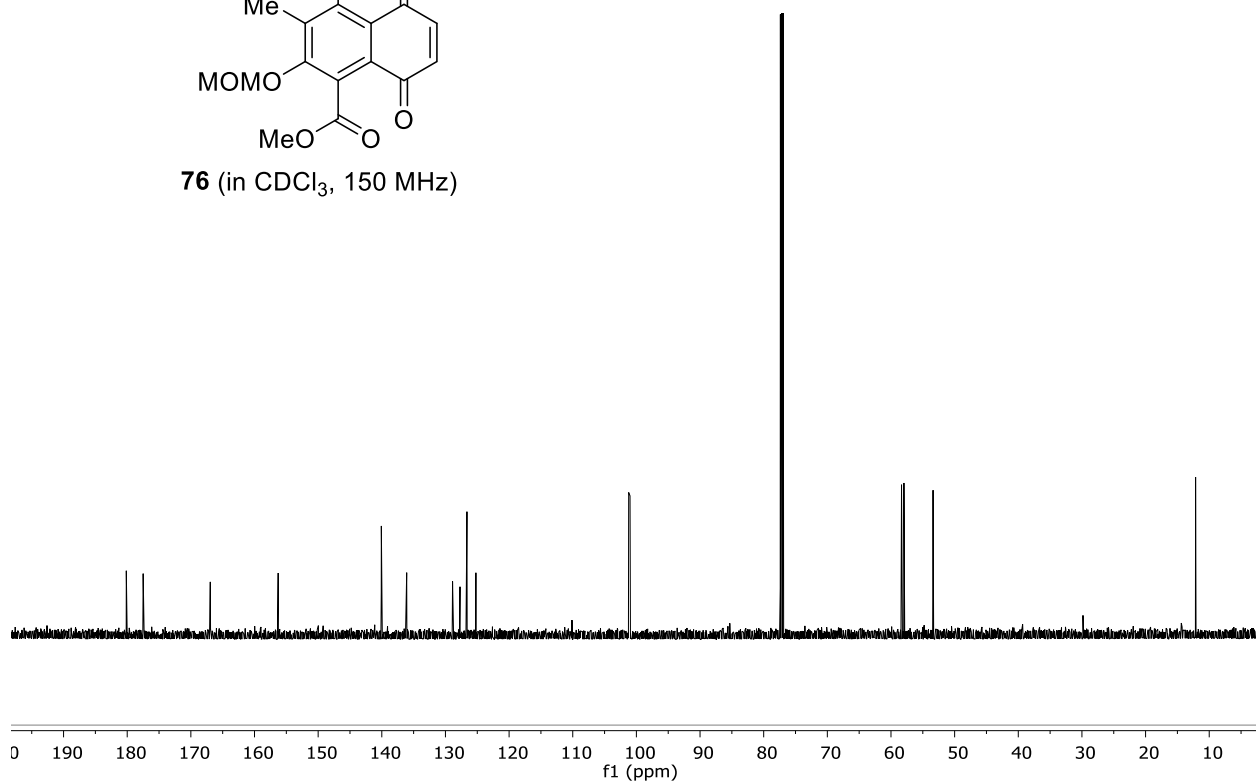
H and C-NMR (CDCl₃) of compound 76



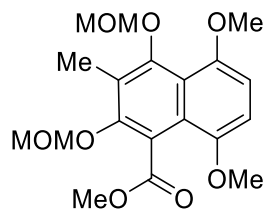
76 (in CDCl₃, 600 MHz)



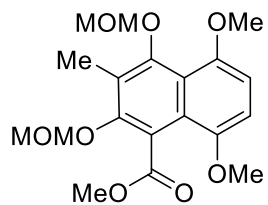
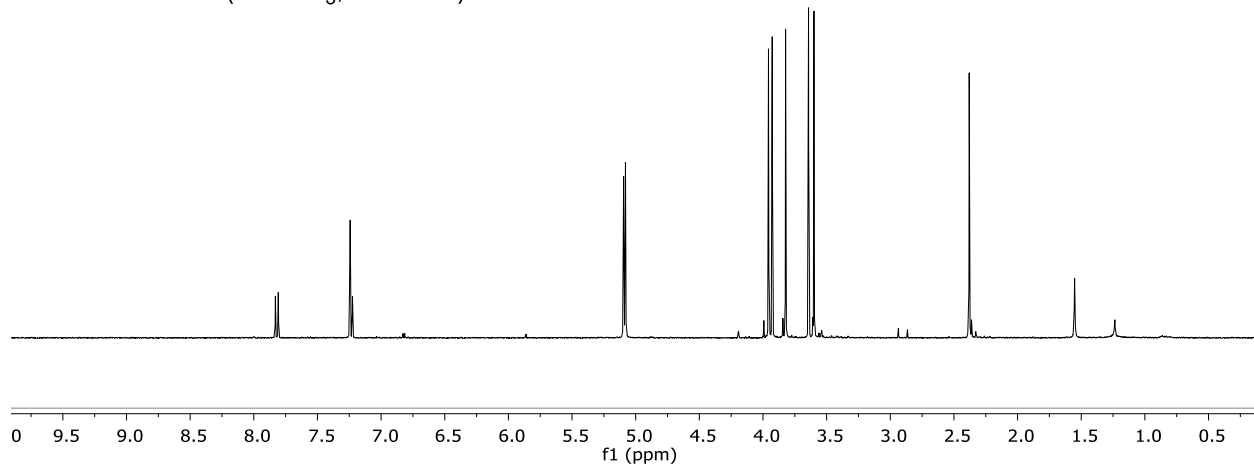
76 (in CDCl₃, 150 MHz)



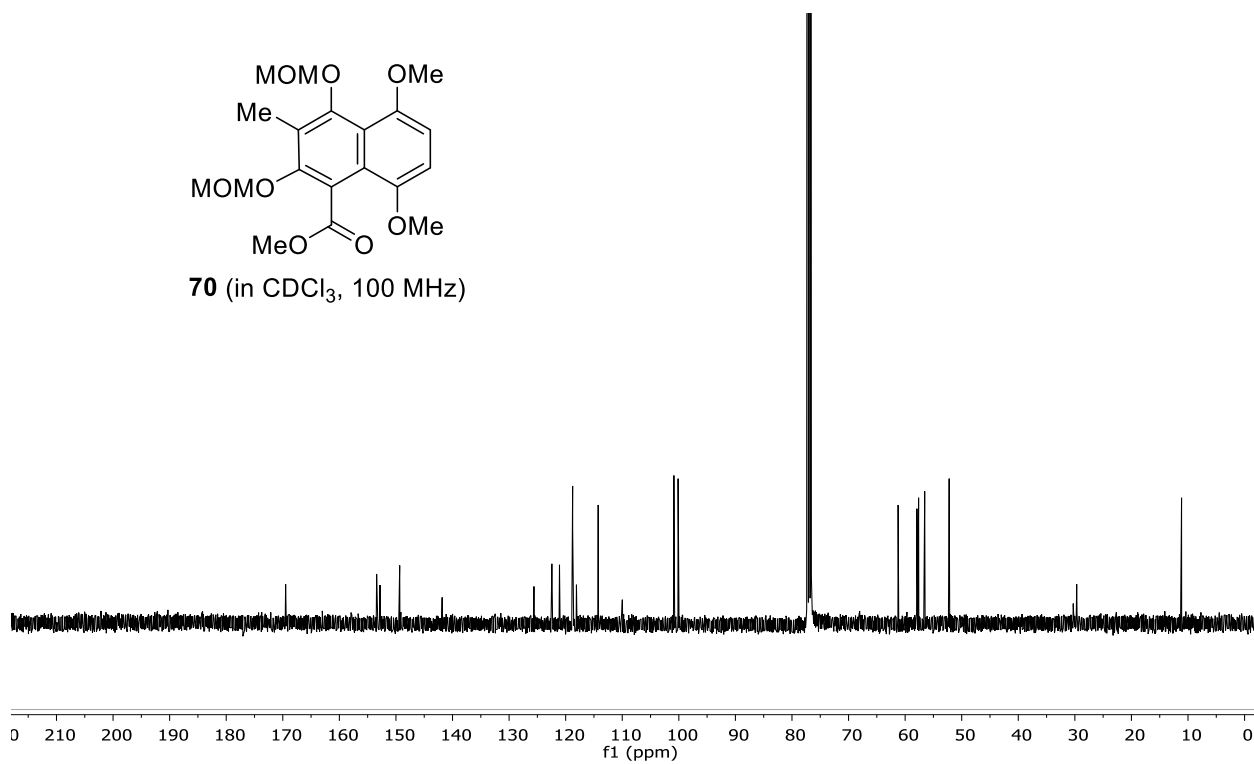
H and C-NMR (CDCl₃) of compound 70



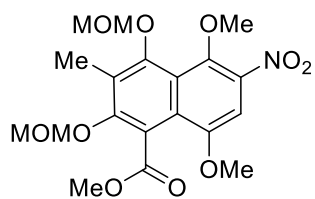
70 (in CDCl₃, 400 MHz)



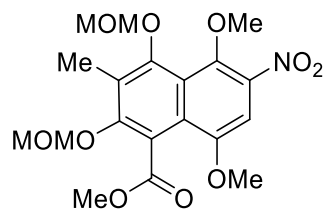
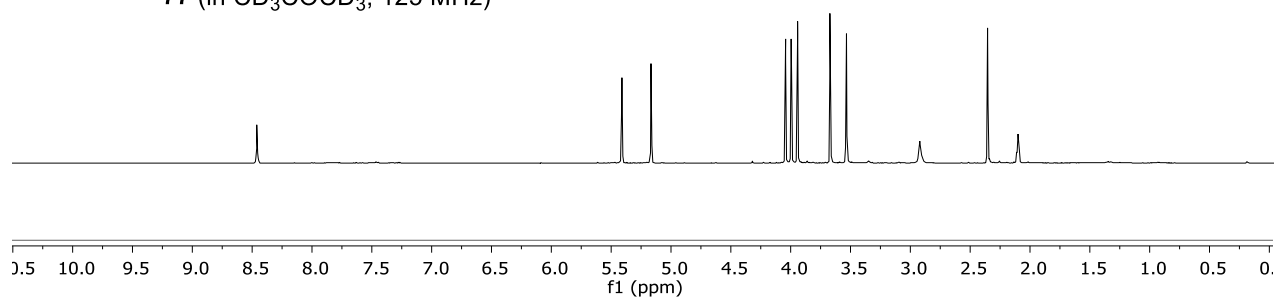
70 (in CDCl₃, 100 MHz)



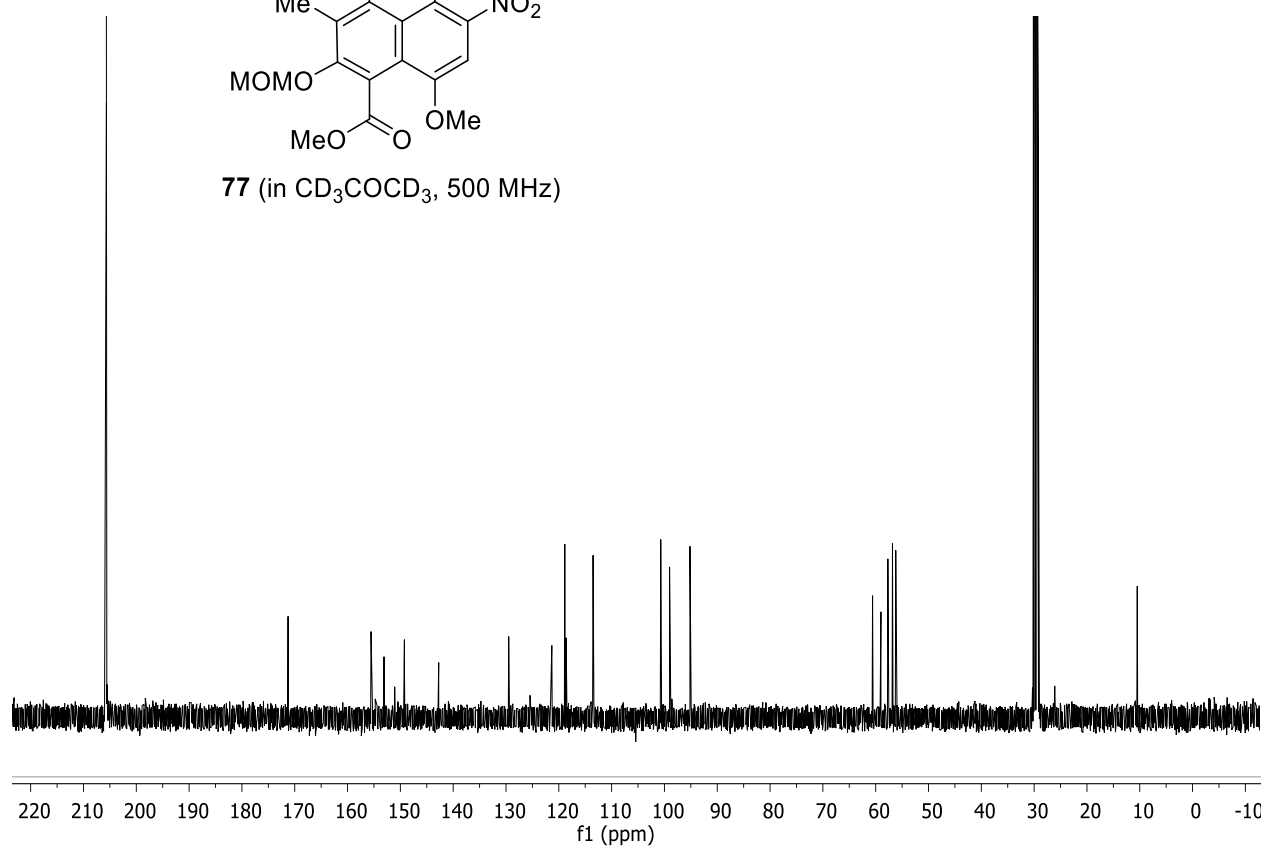
H and C-NMR (CD₃COCD₃) of compound 77



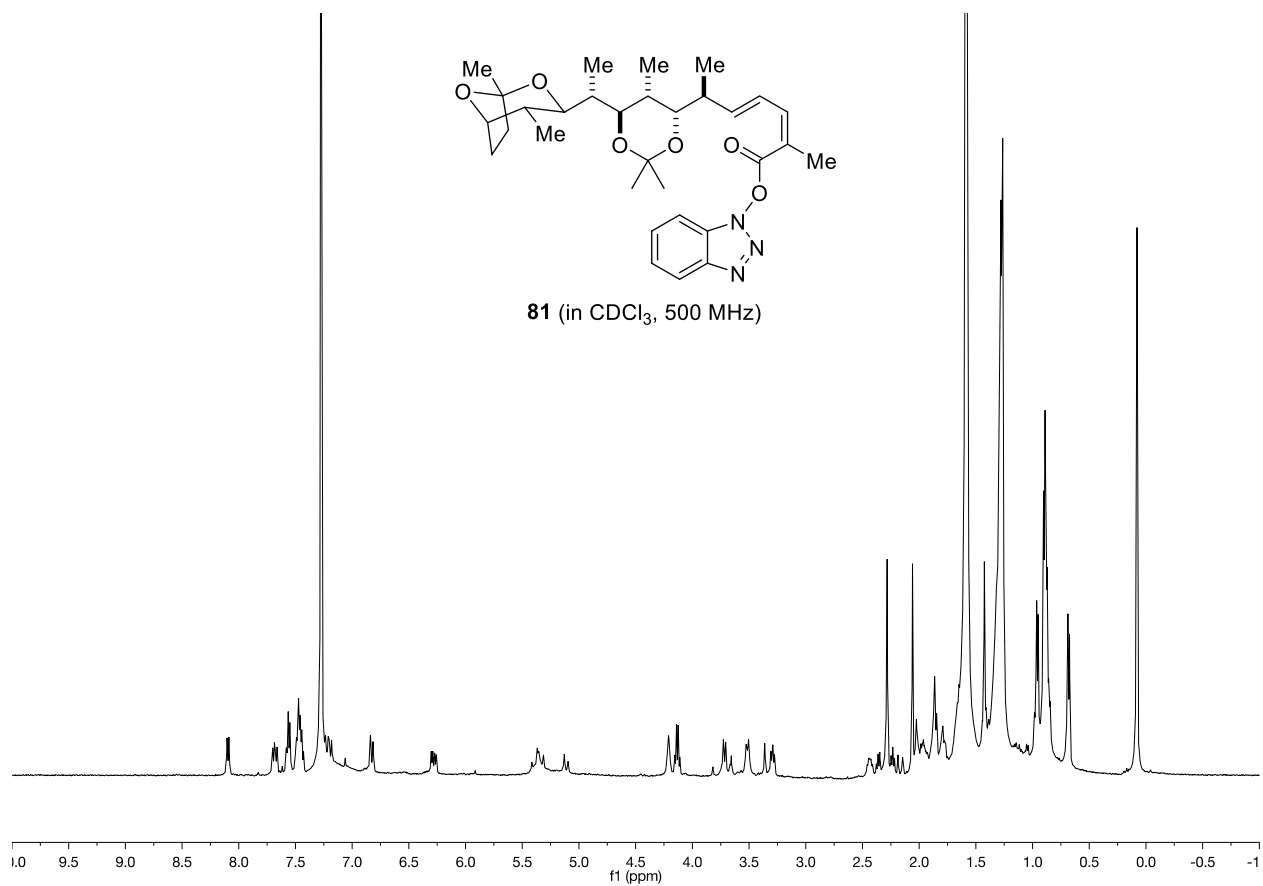
77 (in CD₃COCD₃, 125 MHz)



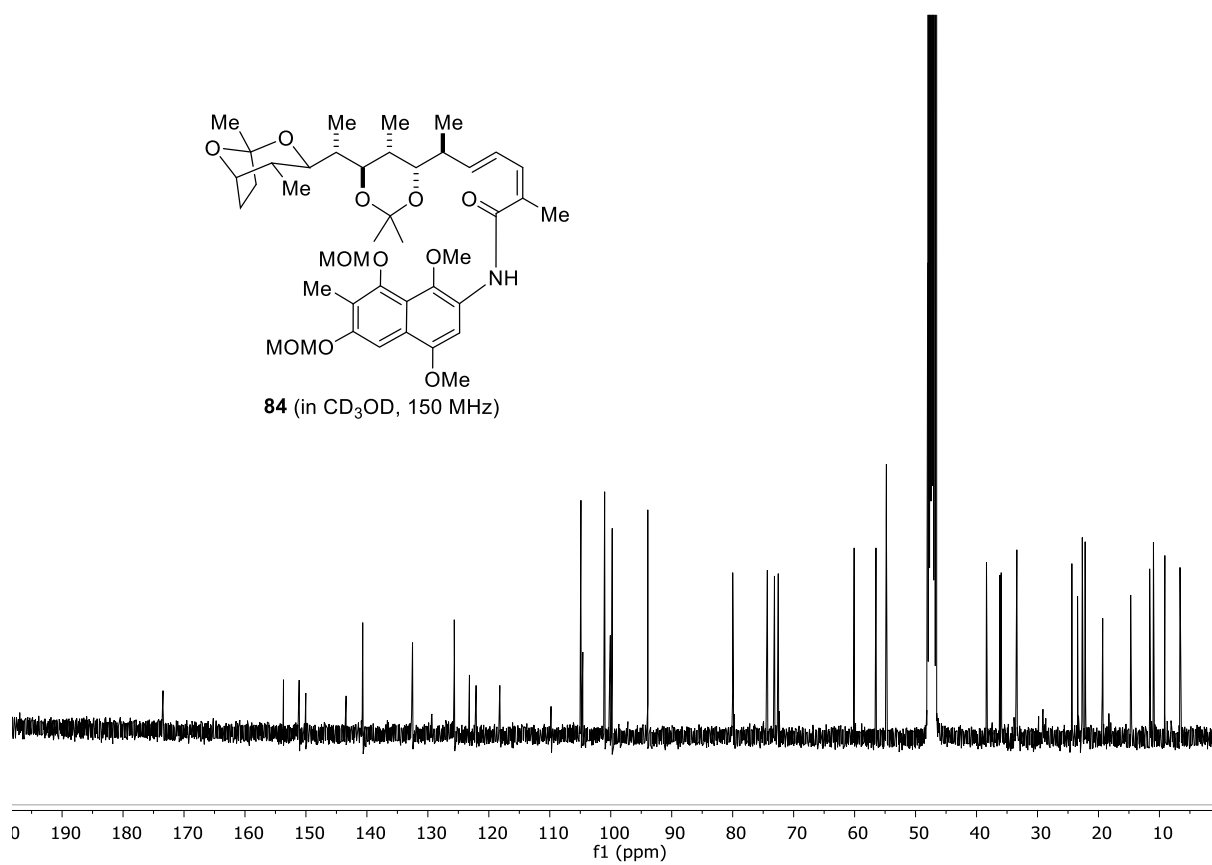
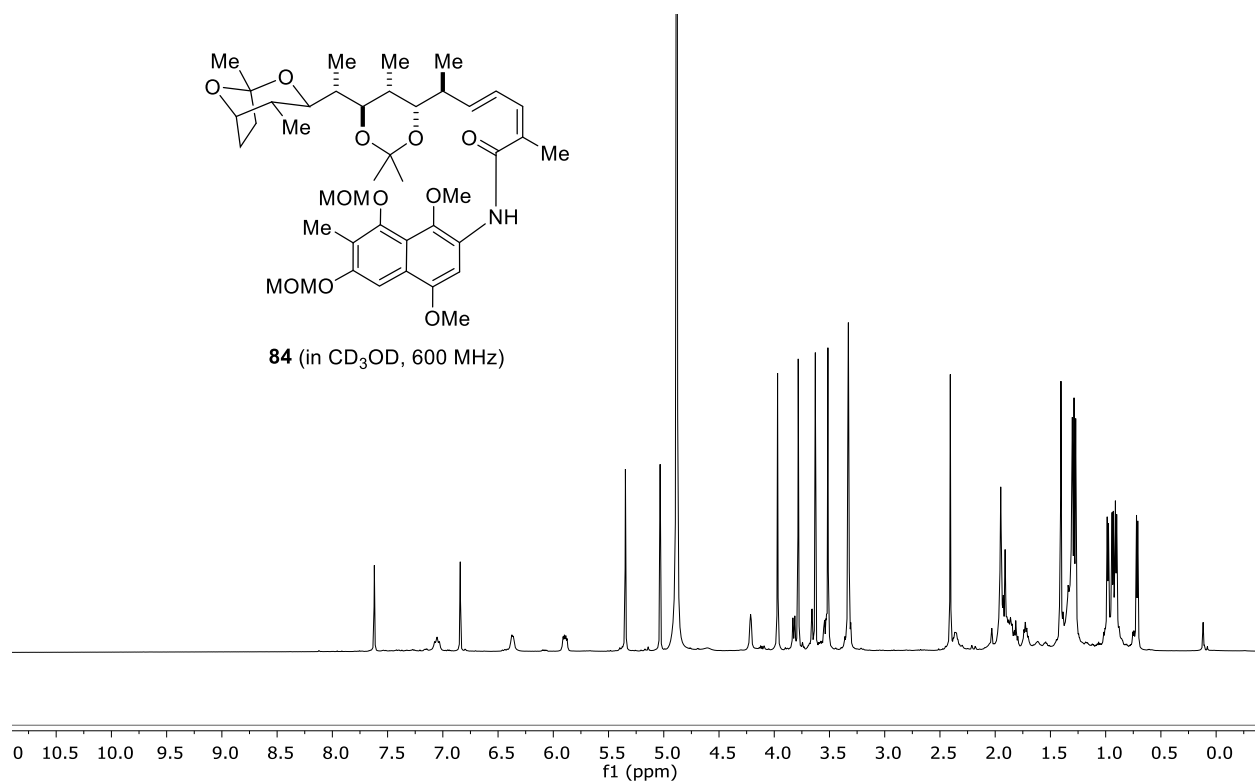
77 (in CD₃COCD₃, 500 MHz)



H-NMR (CDCl₃) of compound 81 (crude)

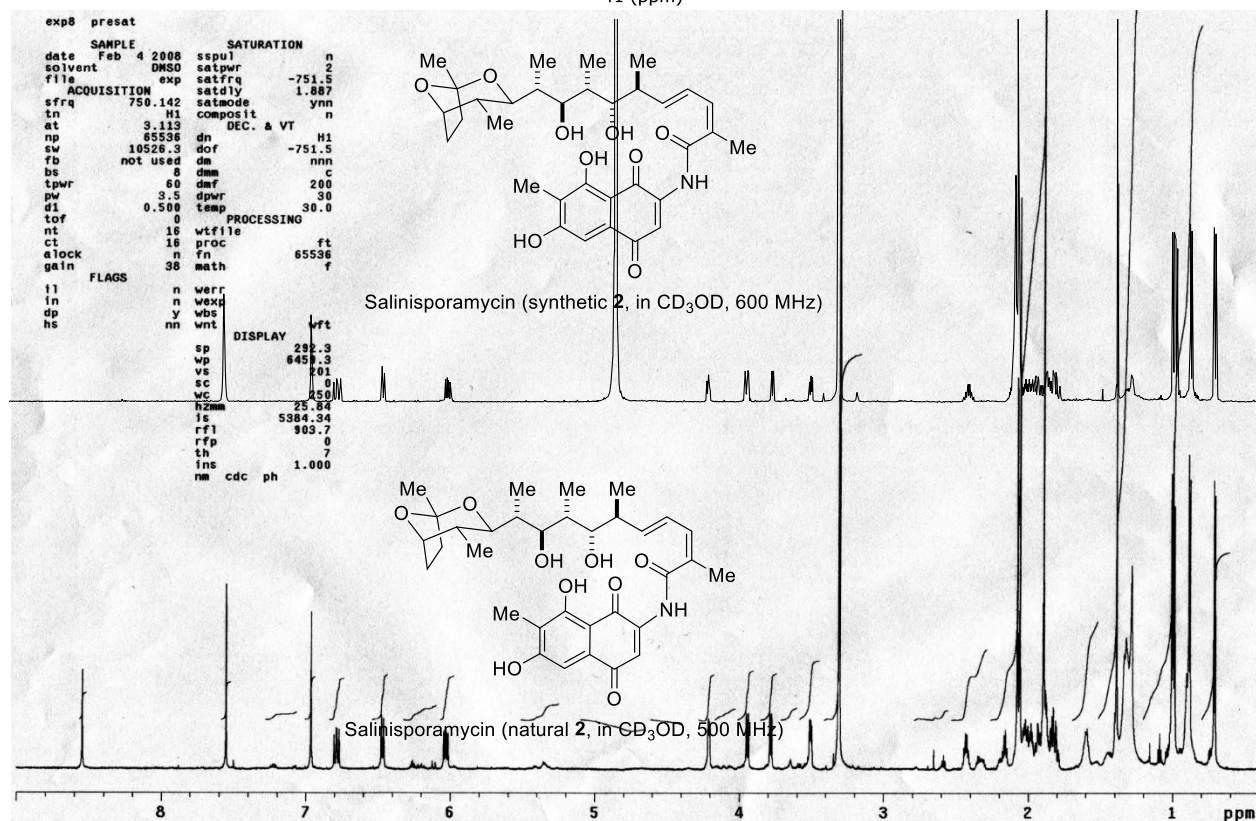


H and C-NMR (CD₃OD) of compound 84

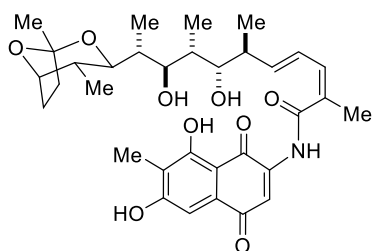


Salinisporamycin (synthetic **2**, in CD₃OD, 600 MHz)

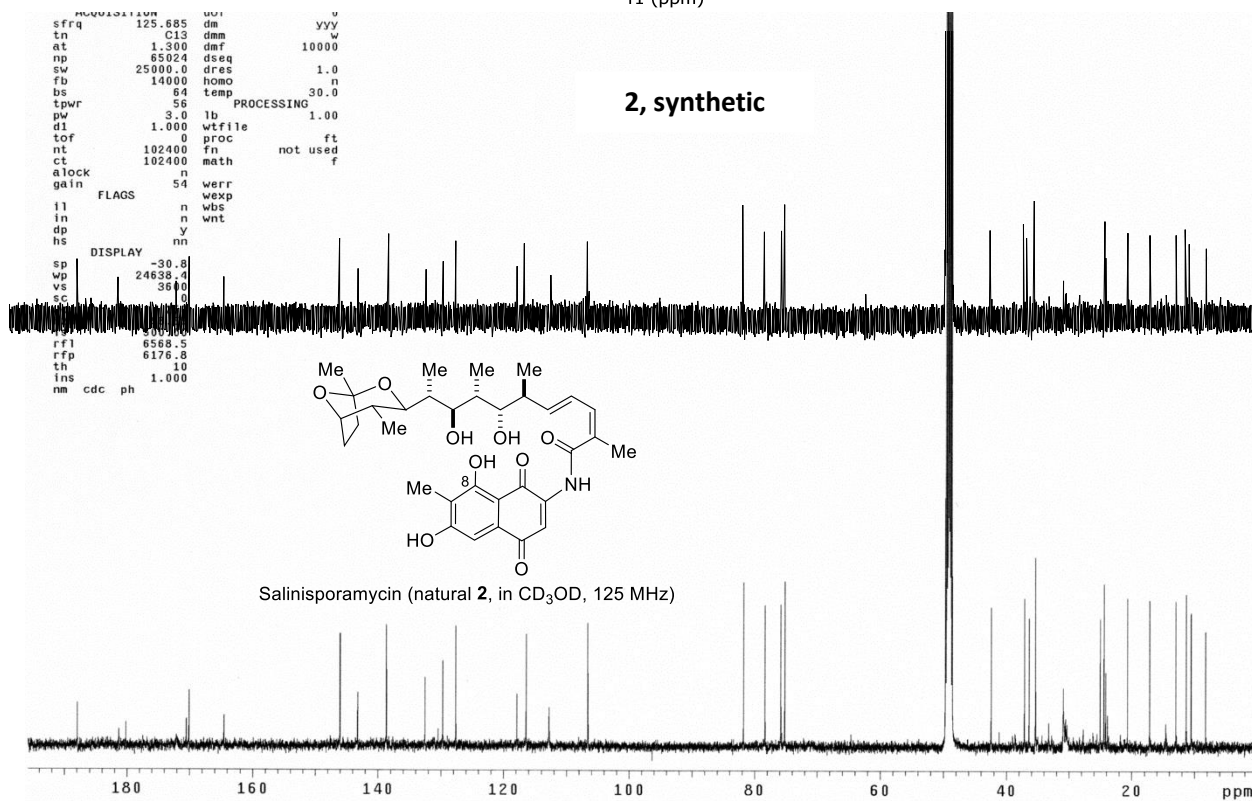
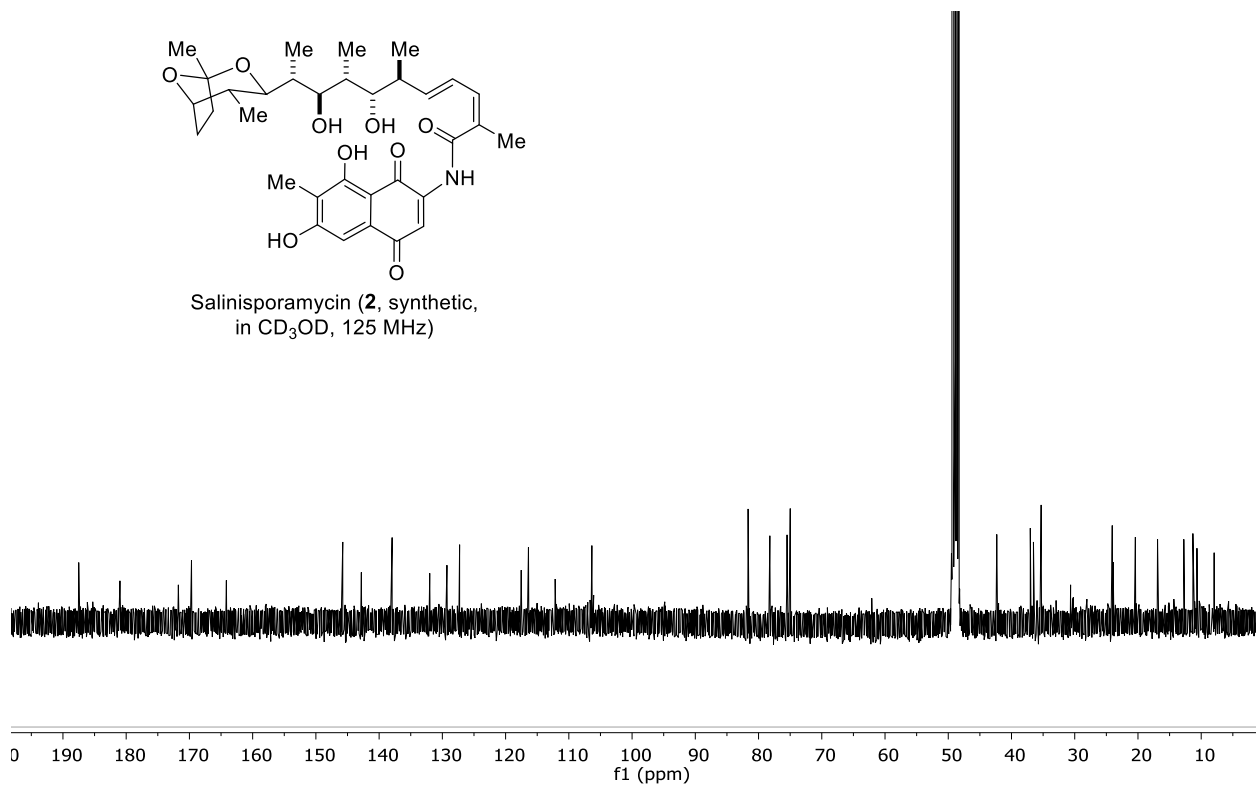
Chemical structure of Salinisporamycin (synthetic **2**) is shown above the spectrum. The structure features a complex polycyclic core with multiple methyl groups, hydroxyl groups, and a salicylic acid derivative moiety.



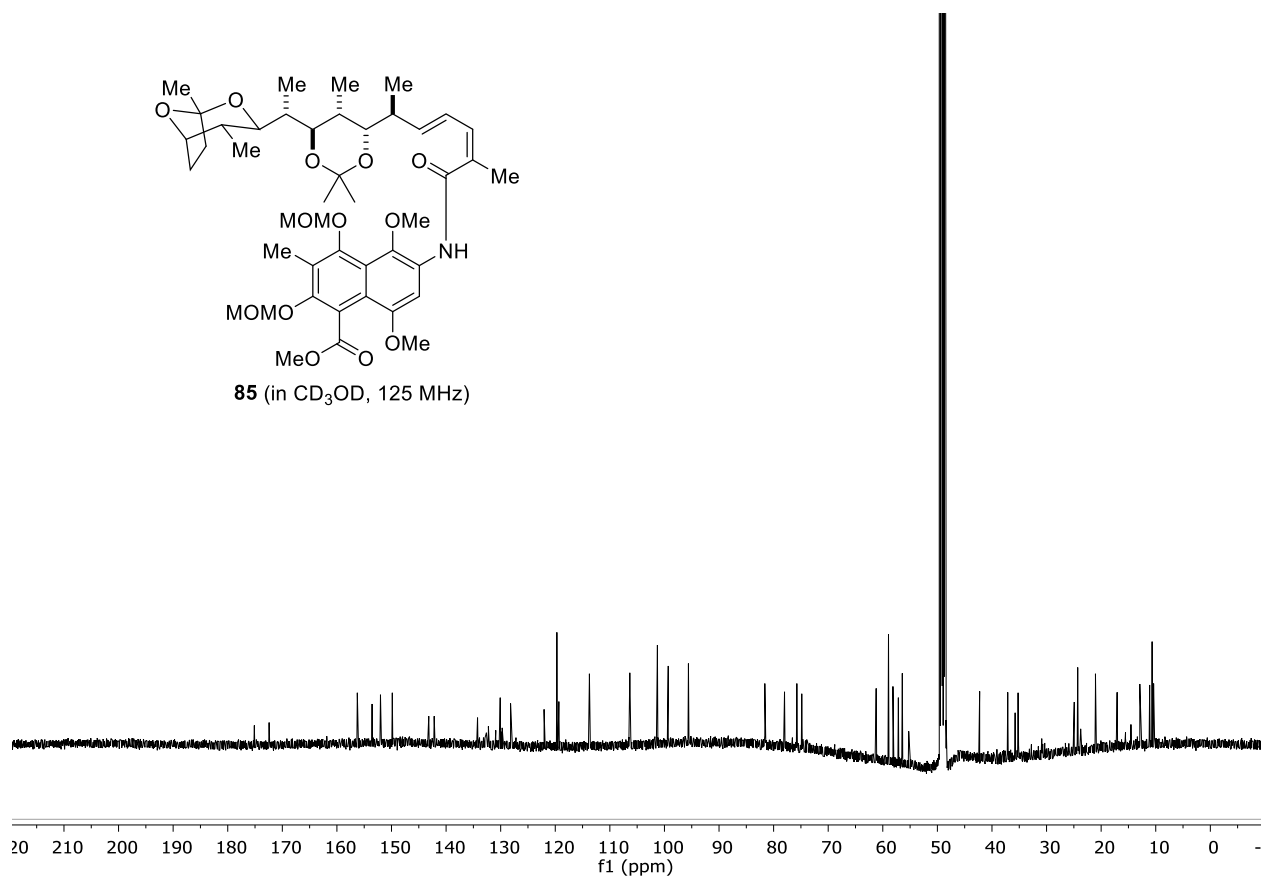
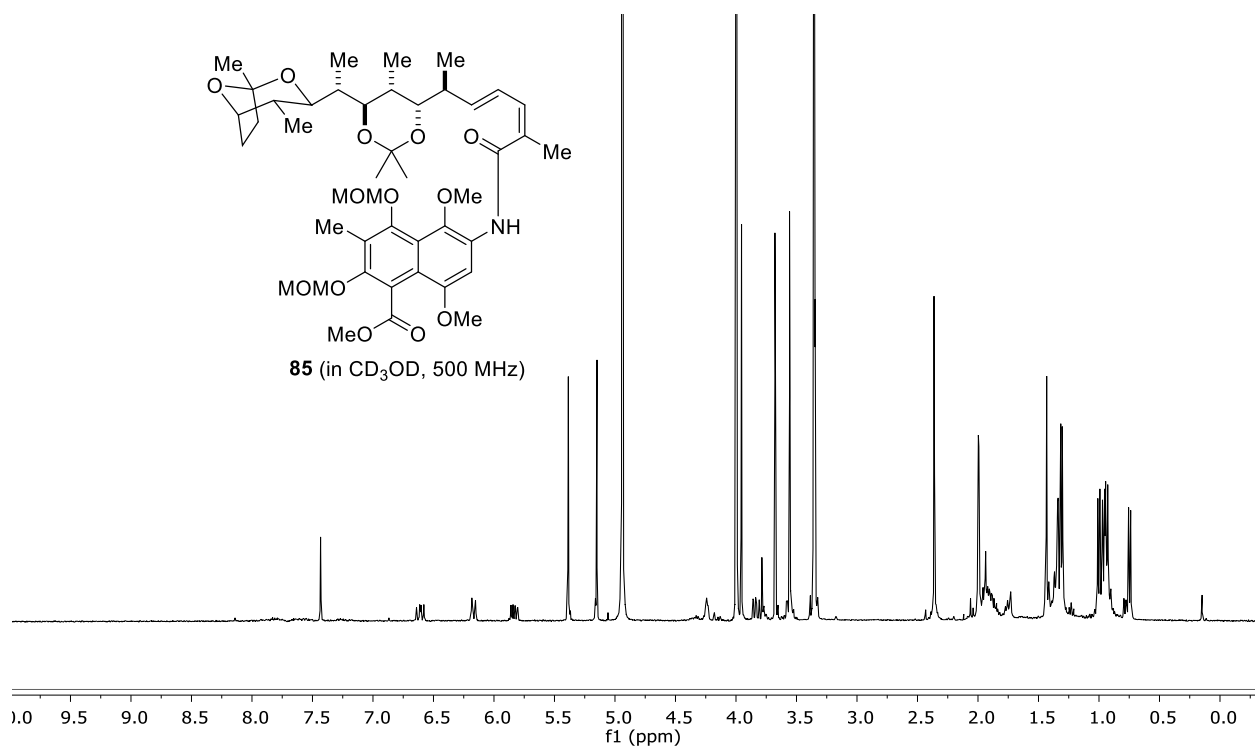
C-NMR (CD₃OD) of Salinisporamycin (2)



Salinisporamycin (2, synthetic,
in CD₃OD, 125 MHz)



H and C-NMR (CD₃OD) of compound 85



¹H and ¹³C-NMR (CD₃OD) of Rifsaliniketal (9)

