Supporting Information:

Total Synthesis of Aigialomycin D using a Ramberg-Bäcklund/RCM Strategy

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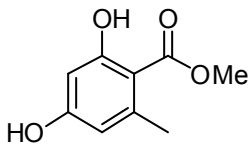
Supporting Information:

General experimental methods:

Unless otherwise stated, the following conditions apply. All reactions were performed under argon in oven-dried or flame-dried glassware using dry solvents and standard syringe techniques. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from the sodium benzophenone ketyl radical ion. Dichloromethane (CH_2Cl_2), triethylamine (NEt_3), and acetonitrile (MeCN) were distilled from calcium hydride. Toluene, hexanes and methanol (MeOH) were distilled from sodium. Diisopropylethylamine ($^iPr_2NEt$) and pyridine were distilled from sodium hydroxide. Acetone was distilled from potassium carbonate. Anhydrous dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were used as purchased without further purification. Sodium hydride (NaH) was obtained as a 60% suspension in mineral oil, washed three times with dry hexanes and dried under vacuum immediately prior to use. All other reagents were of commercial quality and distilled prior to use if necessary.

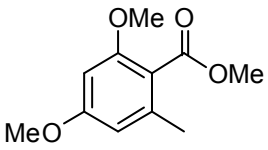
Reaction progress was monitored using aluminium backed thin layer chromatography (TLC) plates pre-coated with silica UV254 and visualised by UV radiation (254 nm) and developed with anisaldehyde dip. Purification of products via flash chromatography was conducted using a column filled with silica gel 60 (220–240 mesh) with solvent systems as indicated. MW-assisted reactions were carried out in a Milestone Microsynth reactor, monitored by a fibre optic temperature and pressure probe. ^1H and ^{13}C NMR spectra were recorded on either a 300 MHz (300 MHz for ^1H and 75 MHz for ^{13}C), or 500 MHz (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer. All chemical shifts (δ) were referenced to solvent peaks ($CDCl_3$: ^1H 7.26 ppm, ^{13}C 77.0 ppm; acetone-d_6: ^1H 2.05 ppm, ^{13}C 29.84 ppm; CD_3OD: ^1H 3.31 ppm, ^{13}C 49.00 ppm). Optical rotation was measured on a polarimeter operating at the sodium D-line.

Methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate, 7a)[14a]



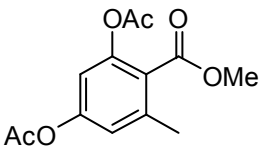
To a suspension of NaH (2.56 g of a 60% dispersion in mineral oil, 64 mmol, washed three times with dry hexanes) in THF (100 mL) at 0 °C was added methyl acetoacetate (5.0 g, 43 mmol) dropwise. The mixture was stirred for 1 h, warming to rt. The reaction was cooled to –78 °C and a 1.6 M solution of *n*-butyllithium in hexanes (25.6 mL, 41 mmol) was added dropwise over 2 h. The reaction was then stirred at rt for 12 h. The reaction mixture was then refluxed for a further 24 h. The cooled orange solution was acidified with 10% HCl to pH 1 and stirred at rt for 12 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 75 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified using flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) to provide methyl orsellinate (**7a**) as a white solid (1.56 g, 40%). R_f = 0.44 (2:1 hexanes:EtOAc). mp 141 – 142 °C. [lit.[29] mp 139 – 140 °C] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 6.23 (d, *J* = 2.5 Hz, 1H), 5.52 (s, 1H), 3.92 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 165.2, 160.3, 144.0, 111.4, 105.6, 101.2, 51.9, 24.3. Spectral data matched those reported in the literature.[14a]

Methyl 2,4-dimethoxy-6-methylbenzoate (7b)



A suspension of KOH (38 mg, 0.95 mmol) and methyl orsellinate (**7a**) (52 mg, 0.286 mmol) in THF (2 mL) was stirred at rt for 20 min, over which time a white precipitate formed. To the reaction was added MeI (100 μL, 0.309 mmol) and it was stirred for 12 h at rt. The reaction was quenched with 10% HCl (5 mL) and extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, filtered and reduced to give the title compound **7b** as a white solid. The crude product was purified using flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) giving a white solid (38 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 2.28 (s, 3H). Spectral data matched those reported in the literature.[30]

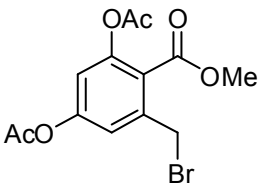
Methyl 2,4-bis(acetyloxy)-6-methylbenzoate (7c)



To a solution of methyl orsellinate (**7a**) (1.26 g, 6.90 mmol) in CH_2Cl_2 (17.5 mL) at rt were added NEt_3 (5.76 mL, 41.4 mmol) and acetic anhydride (2.60 mL, 27.6

[30] Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 2068-2076.

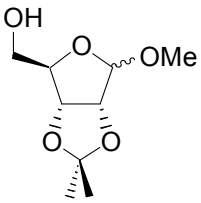
mmol). The reaction was stirred for 12 h at rt before being quenched with saturated aqueous $NaHCO_3$ solution (30 mL). The organic layer was separated, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified by passing it through a short silica column (gradient elution 5:1 to 2:1 hexanes/EtOAc) with a few drops of AcOH, yielding the title compound as a white solid (1.82 g, 98%). R_f = 0.31 (2:1 hexanes:EtOAc). mp 53 – 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 2.2 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 168.9, 168.6, 166.3, 151.7, 149.3, 139.8, 121.3, 114.2, 77.2, 52.2, 21.1, 20.8, 20.5. IR (neat): 3086, 2959, 1781, 1732, 1616, 1587, 1446, 1370, 1280, 1174, 1137, 1098, 1054, 1018, 953, 911 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{14}O_6Na^+$ $[M + Na]^+$ 289.0683, found 289.0685.



Methyl 2,4-bis(acetyloxy)-6-(bromomethyl)benzoate (4)

To a solution of **7c** (440 mg, 1.64 mmol) in CCl_4 (15 mL) were added NBS (180 mg, 1.01 mmol) and benzoyl peroxide (20 mg), and the reaction mixture was heated to reflux. After 3 h, another portion of NBS (180 mg, 1.01 mmol) and benzoyl peroxide (20 mg) was added to mixture and the reaction was heated to reflux for a further 3 h. After this time the reaction was cooled to rt, the solid succinimide filtered off, and the solvent removed under reduced pressure. The resulting orange oil was purified by flash column chromatography (silica, CH_2Cl_2) to yield the title compound **4** as a white solid (400 mg, 71%), and the corresponding dibromide as a white solid (81 mg, 12%). R_f = 0.46 (CH_2Cl_2). mp 62 – 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 2.2, 1H), 6.95 (d, *J* = 2.2, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 168.3, 165.2, 152.0, 149.8, 139.3, 123.0, 121.3, 117.0, 52.7, 29.7, 21.1, 20.7. IR (KBr): 3082, 2950, 1770, 1731, 1613, 1434, 1370, 1282, 1187, 1138, 1094, 1033, 1017, 907 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{13}O_6BrNa^+$ $[M + Na]^+$ 366.9793, found 366.9798.

Methyl 2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside[31]

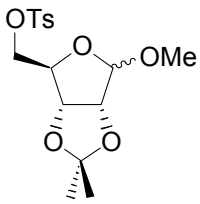


A solution of D-ribose (25 g, 167 mmol) in Me_2CO (95 mL), MeOH (95 mL) and conc. HCl (2.5 mL) was heated under reflux for 8 h. The reaction was poured into water (200 mL) and the organic solvents were removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organics were

[31] Lerner, L. M. *Carbohydr. Res.* **1977**, *53*, 177-185.

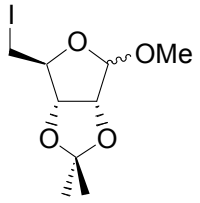
dried over $MgSO_4$, filtered and reduced, giving the title compound as a colourless oil (18.7 g, 55%), which was immediately reacted without further purification. R_f = 0.29 (2:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.84 (d, *J* = 5.9 Hz, 1H), 4.59 (d, *J* = 5.9 Hz, 1H), 4.44 (t, *J* = 2.6 Hz, 1H), 3.70 (dt, *J* = 12.6, 2.4 Hz, 1H), 3.62 (ddd, *J* = 12.6, 10.7, 3.4 Hz, 1H), 3.44 (s, 3H), 3.23 (dd, *J* = 10.7, 2.6 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H). Spectral data matched those reported in the literature. [32]

Methyl 5-(4-methylbenzenesulfonate)-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside



Crude methyl 2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (18.7 g, 97 mmol) was dissolved in dry pyridine (40 mL) and cooled to 0 °C. To this was added tosyl chloride (23.2 g, 122 mmol) and the reaction was allowed to warm to rt as it stirred for 15 h. The reaction mixture was cooled to 0 °C and was quenched by the addition of H_2O (100 mL), then extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with 5% H_2SO_4 (2 x 50 mL), 0.2 M KOH (3 x 50 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude solid was recrystallised from EtOH, yielding a white solid, collected over three crops (29.2 g, 84%). mp 80 – 81 °C (lit.[33] mp 80 – 84). R_f = 0.67 (2:1 hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.93 (s, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.53 (d, *J* = 5.9 Hz, 1H), 4.31 (t, *J* = 7.5 Hz, 1H), 4.01 (dd, *J* = 7.2, 1.5 Hz, 2H), 3.23 (s, 3H), 2.45 (s, 3H), 1.44 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 132.7, 129.9, 128.0, 112.7, 109.4, 84.8, 83.5, 81.3, 69.1, 55.0, 26.3, 24.8, 21.6. Spectral data matched those reported in the literature.[34]

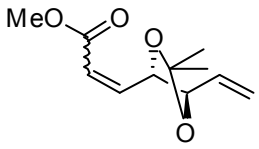
Methyl 5-deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (9)



To a solution of the tosylate (21.9 g, 61.2 mmol) in methyl ethyl ketone (200 mL) was added NaI (18.4 g, 122 mmol). The reaction was refluxed for 24 h before it was cooled to rt and the solvent removed. The crude yellow oil was dissolved in EtOAc and washed with H_2O (2 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and reduced to give the iodide as a yellow oil (19.0 g, 99%). R_f = 0.67 (2:1 hexanes:EtOAc). The ^{1}H NMR spectrum of the crude product confirmed its purity and it was used

[32] Kumar, G. D. K.; Baskaran, S. *J. Org. Chem.* **2005**, *70* 4520–4523.
[33] Bestwick, R. K.; Mokkapati, V. K.; Ferro, A. J. US, 1994; Vol. U.S. Patent 5366954.
[34] Kus, P. *Pol. J. Chem* **2002**, *76*, 543-550.

without further purification. $[\alpha]_D^{22}$ = –68.3 (*c* 1.00, $CHCl_3$) [lit.[31] –69.7 (*c* 2.55, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 4.44 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.37 (s, 3H), 3.29 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.16 (t, *J* = 10.0 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H). Spectral data matched those reported in the literature.[35]



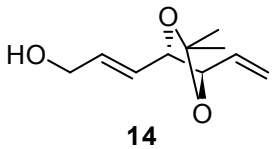
Methyl (2*Z*,4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hepta-2,6-dienoate [(*Z*)-11] and Methyl (2*E*,4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hepta-2,6-dienoate [(*E*)-11]

To iodide **9** (2.05 g, 6.52 mmol) in MeOH (30 mL) were added activated zinc (3.00 g, 45.9 mmol) and AcOH (100 μL) before the mixture was refluxed for 4 h. After this time another portion of zinc (1.50 g, 23.0 mmol) was added and the reaction refluxed for a further 4 h. Once TLC had confirmed the consumption of starting material, the reaction mixture was cooled and filtered through a wad of silica to remove the excess zinc metal and zinc salts. The filtrate was cooled to 0 °C and methyl (triphenylphosphoranylidene)acetate (2.62 g, 7.83 mmol) was added to the solution. The reaction was left to warm up over 12 h. The solvent was removed and the crude product partitioned between EtOAc (100 mL) and $NH_4Cl_{(aq)}$ (100 mL). The aqueous layer was extracted further with EtOAc (2 x 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting pale yellow oil was purified using flash column chromatography (silica,10:1 hexanes/EtOAc), yielding the α,β-unsaturated ester **11** as a colourless oil [1.06 g, 74% (*Z*/*E* = 4.7:1)]. A portion was subjected to flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) for the purposes of characterization to yield separated samples of (*Z*)-**11** and (*E*)- **11**. [(*Z*)-**11**]: $[\alpha]_D^{22}$ = +216.8 (*c* 1.00, $CHCl_3$). R_f = 0.59 (2:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 11.6, 7.5 Hz, 1H), 5.90 (dd, *J* = 11.6, 1.6 Hz, 1H), 5.68 (td, *J* = 7.3, 1.5 Hz, 1H), 5.66 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.28 (ddd, *J* = 17.1, 1.7, 1.3 Hz, 1H), 5.15 (ddd, *J* = 10.3, 1.9, 1.0 Hz, 1H), 4.87 (tt, *J* = 7.1, 0.9 Hz, 1H), 3.72 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 146.8, 134.0, 121.0, 117.9, 109.2, 79.7, 75.6, 51.5, 27.7, 25.1. IR (KBr): 2985, 2945, 1722, 1648, 1439, 1406, 1381, 1224, 1198, 1179, 1046, 1001, 927, 876, 825 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{16}O_4Na^+$ $[M + Na]^+$ 235.0946, found 235.0942. [(*E*)-**11**]: R_f = 0.51 (2:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 15.6 5.5 Hz, 1H), 6.08 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.69 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.37 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.27 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.78 (ddd, *J* =

[35] Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 611.

7.0, 5.6, 1.6 Hz, 1H), 4.71 (tt, *J* = 7.0, 0.9 Hz, 1H), 3.75 (s, 3H), 1.56 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 143.9, 133.4, 122.2, 119.3, 109.6, 79.8, 77.5, 51.7, 27.7, 25.4.

Attempted reduction of the α,β-unsaturated ester 11 with lithium aluminium hydride



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To a suspension of lithium aluminium hydride (27 mg, 0.70 mmol) in Et_2O (5 mL) at –78 °C was added a solution of α,β-unsaturated **11** (50 mg, 0.23 mmol) in Et_2O (2 mL). The reaction was stirred at –78 °C for 1.5 h before slowly warming to rt over 1.5 h. The reaction was quenched with wet Na_2SO_4. The aluminium salts were removed by filtration through a pad of Celite® with the aid of further Et_2O. The filtrate was concentrated to give a colourless oil which was purified by flash column chromatography (silica, 5:1 hexanes:EtOAc) yielding saturated ester **13** (7 mg, 14%) and an inseparable mixture of alcohols **14** (major) and **12** (minor) (~4.5:1, 28 mg, 63%). **13**: R_f = 0.56 (2:1 hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.1, 10.2, 7.7 Hz, 1H), 5.34 (dd, *J* = 17.2, 2.7 Hz, 1H), 5.27 (dd, *J* = 10.3, 2.5 Hz, 1H), 4.54 (t, *J* = 7.3 Hz, 1H), 4.15 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.68 (s, 3H), 2.58 – 2.24 (m, 2H), 1.74 (dd, *J* = 14.5, 8.1 Hz, 2H), 1.47 (s, 3H), 1.36 (s, 3H). **14**: R_f = 0.21 (2:1 hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 – 5.80 (m, 3H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.63 (m, 2H), 4.17 (d, *J* = 5.1 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H).

Attempted reduction of the α,β-unsaturated ester 11 with $NaBH_4$ in the absence and presence of metal catalysts

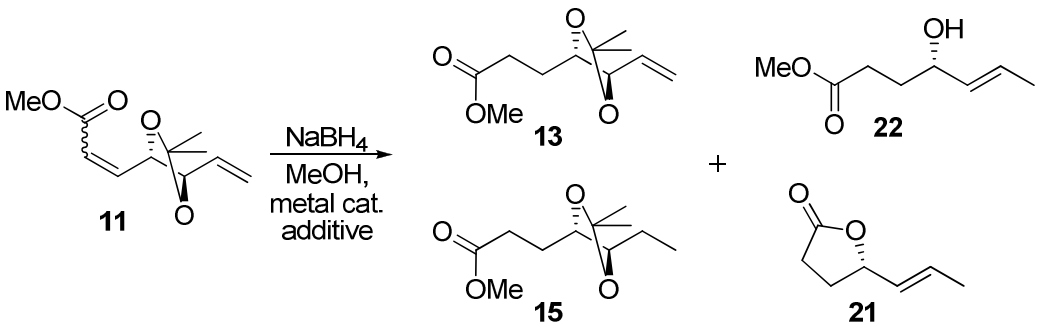


Table S–1. Metal-Catalyzed $NaBH_4$ Reduction of α,β-Unsaturated Ester **11**

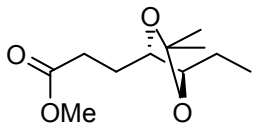
Entry	*Metal*	*Amount (equiv.)*	*Temp.*	*Other reagents/conditions*	*Yields*				
					11	**13**[a]	**15**[a]	**21**	**22**
1	none		0 °C		100%				
2	$NiCl_2$	0.5	0 °C				84%		
3	$CoCl_2$	0.2	rt				67%		
4	$CuCl_2$	0.75	0 °C	$NaBH_4$ added in portions	18%	32%	15%	17%	
5	$CuCl_2$	0.75	0 °C	$CuCl_2$ added in portions	24%	45%	8%	10%	3%
6	$CuCl_2$	0.75	0 °C	THF (1 mL)	37%	47%	9%		
7	$CuCl_2$	0.75	–78 °C		24%	24%	5%	10%	10%
8	CuCl	0.75	0 °C		47%	33%	5%		
9	CuCl	0.75	–78 °C	cyclohexene (4 eq.), NaOMe (0.75 eq.)	13%	71%	6%		
10	CuCl	0.75	–78 °C	cyclohexene (4 eq.)		96%			

Typical procedure: To a cooled solution of the olefin **11** and metal catalyst in MeOH was added $NaBH_4$ over several minutes. The reaction was kept cool for 1 h before warming to rt. *Entry 5* involved addition of the metal catalyst to a solution of olefin **11** already charged with $NaBH_4$.

[a] Yields of **13** and **15** were estimated from the ^1H NMR spectrum of the crude reaction mixture.

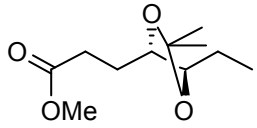
Attempted reduction of the α,β-unsaturated ester 11 with $NaBH_4$ (entry 1)

To a solution of α,β-unsaturated ester **11** (20 mg, 93 μmol) in MeOH (1 mL) at 0 °C was added $NaBH_4$ (18 mg, 0.467 mmol). The reaction was left to warm to rt with stirring over 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to a colourless oil (19 mg). ^{1}H NMR spectroscopy confirmed that starting material was recovered.



Reduction of the α,β-unsaturated ester 11 with $NiCl_2/NaBH_4$: Methyl 3-[(4*S*,5*R*)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate (15) (entry 2)

A solution of the α,β-unsaturated ester **11** (55 mg, 0.26 mmol) and $NiCl_2.6H_2O$ (30.5 mg, 0.129) in MeOH (4 mL) was cooled to –40 °C. To this solution was added $NaBH_4$ (49 mg, 1.29 mmol) in portions over 10 min. The solution slowly turned black. The reaction was stirred at –40 °C for a further 30 min before filtering the cold solution through a pad of Celite®. The filtrate was reduced to dryness and the residue was dissolved in CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give fully saturated ester **15** as a colourless oil (46 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (m, 2H), 3.67 (s, 3H), 2.54 (ddd, *J* = 16.4, 8.5, 7.0 Hz, 1H), 2.40 (ddd, *J* = 16.6, 8.4, 7.4 Hz, 1H), 1.73 (dd, *J* = 13.9, 7.4 Hz, 2H), 1.58 (dt, *J* = 13.7, 7.2 Hz, 1H), 1.48 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 107.6, 79.3, 76.8, 51.6, 30.6, 28.6, 26.0, 25.3, 22.5, 10.8. HRMS (ESI) calcd. for $C_{11}H_{20}O_3Na^+$ [M + Na]$^+$ 239.1259, found 239.1260.



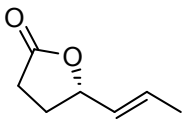
Reduction of the α,β-unsaturated ester 11 with $CoCl_2/NaBH_4$: Methyl 3-[(4S,5R)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate (15) (entry 3)

A solution of α,β-unsaturated ester **11** (55 mg, 0.257 mmol) and $CoCl_2.6H_2O$ (12 mg, 51 μmol) in MeOH (4 mL) was stirred at rt for 15 min. To this solution was added $NaBH_4$ (39 mg, 1.0 mmol). The reaction was stirred at rt for 30 min before quenching with water (5 mL) and extracting with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced. The crude residue was purified by flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) to give a colourless oil (37 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (m, 2H), 3.67 (s, 3H), 2.53 (ddd, J =

16.6, 8.6, 7.5 Hz, 1H), 2.40 (ddd, J = 16.6, 8.4, 7.2 Hz, 1H), 1.73 (dd, *J* = 14.7, 7.8 Hz, 2H), 1.58 (m, 1H), 1.47 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H). The ^{1}H NMR data closely matched those of the $NiCl_2$–catalysed reduction and so the product was assumed to be fully saturated ester **15**.

Attempted reduction of the α,β-unsaturated ester 11 with $CuCl_2$/$NaBH_4$ (entry 4)

To a solution of α,β-unsaturated ester **11** (50 mg, 0.234 mmol) in MeOH (4 mL) at 0 °C was added $CuCl_2$ (24 mg, 0.175 mmol). At this point, $NaBH_4$ (44 mg, 1.17 mmol) was added in portions over 5 min and the reaction allowed to warm to rt and stirred for 12 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a colourless oil. The crude product was purified using flash column chromatography (silica, 10:1 hexanes/EtOAc) returning **11** (9 mg, 18%) and affording an inseparable mixture of desired product **13** and compound **15** as a colourless oil (~2:1, 23 mg, 47%). R_f = 0.54 (2:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.34 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.26 (ddd, *J* = 10.3,1.6, 0.9 Hz, 1H), 4.54 (dd, *J* = 7.4, 6.4 Hz, 1H), 4.15 (ddd, *J* = 8.8, 6.2, 5.5 Hz, 1H), 4.02 (ddt, *J* = 10.6, 8.5, 5.6 Hz, 1H, minor), 3.67 (s, 3H), 2.58 – 2.45 (m, 1H), 2.40 (dtd, *J* = 14.1, 7.9, 6.3 Hz, 1H), 1.78 – 1.71 (m, 2H), 1.62 – 1.54 (m, 0.5H, minor), 1.54 – 1.46 (m, 0.5H, minor), 1.47 (s, 3H), 1.43 (s, 1.5H, minor), 1.36 (s, 3H), 1.33 (s, 1.5H, minor), 1.00 (t, *J* = 7.4 Hz, 1.5H, minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (minor), 173.6, 133.7, 118.6, 108.4, 107.6, (minor) 79.5, 79.4 (minor), 77.2, 76.9 (minor), 51.6, 51.6 (minor), 30.7, 30.6 (minor), 28.6 (minor), 28.2, 26.2, 26.0 (minor), 25.7, 25.4 (minor), 22.6 (minor), 10.8 (minor).

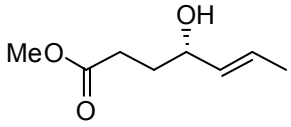


γ-*trans*-1-Propenyl-γ-butyrolactone (21): Lactone **21** was also isolated (5 mg, 17%). R_f = 0.30 (2:1 hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.52 (dddd, *J* = 15.3, 7.0, 3.1, 1.5 Hz, 1H), 4.89 (q, *J* = 7.2 Hz, 1H), 2.54 (m, 2H), 2.36 (dt, *J* = 13.6, 6.5 Hz, 1H), 1.98 (m, 1H), 1.78 – 1.72 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 130.1, 128.2, 80.7, 28.4, 28.4, 17.4. Spectral data matched those reported in the literature.[239]

Attempted reduction of the α,β-unsaturated ester 11 with $CuCl_2$/$NaBH_4$ (entry 5)

To a solution of α,β-unsaturated ester **11** (88.5 mg, 0.411 mmol) in MeOH (5 mL) was added $NaBH_4$ (78 mg, 2.06 mmol) in portions over 5 min at 0 °C. To this was added $CuCl_2$ (41.5 mg, 0.308 mmol) slowly over 5 min. The reaction was warmed to rt and stirred for 1 h. The solvent was removed and the residue

partitioned between saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were combined dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) returning **11** (21 mg, 24%), a mixture of compounds **13** and **15** (~5.6:1, 47 mg, 53%), lactone **21** (5 mg, 10%) and alcohol **22** (2 mg, 3%).



Methyl (4*S*,5*E*)-4-hydroxyhept-5-enoate (22): R_f = 0.28 (2:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.48 (dd, *J* = 15.3, 7.0 Hz, 1H), 4.10 (q, *J* = 6.3 Hz, 1H), 3.68 (s, 3H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.85 (dd, *J* = 13.5 , 7.2 Hz, 2H), 1.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.91, 130.52, 128.61, 81.10, 28.84, 28.82, 17.77.

Attempted reduction of the α,β-unsaturated ester 11 with $CuCl_2$/$NaBH_4$ (entry 6)

To a solution of α,β-unsaturated ester **11** (60 mg, 0.280 mmol) in 3:1 MeOH/THF (4 mL) at 0 °C was added $CuCl_2$ (28 mg, 0.210 mmol). At this point, $NaBH_4$ (53 mg, 1.40 mmol) was added in portions over 5 min and the reaction allowed to warm to rt and stirred for 12 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced to give a colourless oil. The crude product was purified using flash column chromatography (silica, gradient elution 10:1 to 3:1 hexanes/EtOAc) returning **11** (22 mg, 37%) and a mixture of compounds **13** and **15** (~5.2:1, 34 mg, 56%).

Attempted reduction of the α,β-unsaturated ester 11 with $CuCl_2$/$NaBH_4$ (entry 7)

To a solution of α,β-unsaturated ester **11** (65.5 mg, 0.306) and $CuCl_2$ (41 mg, 0.306 mmol) in MeOH (5 mL) at –78 °C was added $NaBH_4$ (58 mg, 1.53 mmol) in portions over 10 min. The solution turned from pale green to brown and a black precipitate began to form. The reaction was left at –78 °C for 15 min before warming to rt for 45 min. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 2:1 hexanes/EtOAc) returning **11** (16 mg, 24%), a mixture of compounds **13** and **15** (~4.8:1, 19 mg, 29%) lactone **21** (4 mg, 10%) and alcohol **22** (5 mg, 10%).

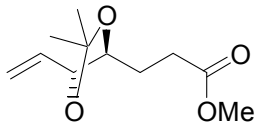
Attempted reduction of the α,β-unsaturated ester 11 with CuCl/$NaBH_4$ (entry 8)

To a solution of α,β-unsaturated ester **11** (58 mg, 0.271 mmol) and CuCl (20 mg, 0.203 mmol) in MeOH (4 mL) at 0 °C was added $NaBH_4$ (51 mg, 1.35 mmol) over 10 min. The reaction was warmed to rt and stirred for 4 h. A black precipitate slowly formed over the course of the reaction. The solvent was removed and the residue partitioned between saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were combined dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 2:1 hexanes/EtOAc) returning **11** (27 mg, 47%) and affording a mixture of compounds **13** and **15** (~6.6:1, 22 mg, 38%).

Attempted reduction of the α,β-unsaturated ester 11 with CuCl/$NaBH_4$ (entry 9)

To the α,β-unsaturated ester **11** (70 mg, 0.330 mmol), CuCl (24.5 mg, 0.248 mmol), cyclohexene (124 μL, 1.32 mmol) in MeOH (5 mL) was added NaOMe (13 mg, 0.25 mmol). The solution went from green to brown. TLC showed new products forming. The reaction mixture was cooled to –78 °C and $NaBH_4$ (62.4 mg, 1.65 mmol) was added. The resulting mixture was left to slowly warm to rt. The solvent was removed and the residue partitioned between saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were combined dried over $MgSO_4$, filtered and reduced to give a colourless oil which was purified using flash column chromatography (silica, gradient elution 10:1 to 2:1 hexanes/EtOAc) returning **11** (9 mg, 13%) and affording a mixture of compounds **13** and **15** (~11.8:1, 54 mg, 38%).

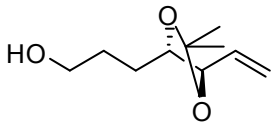
Methyl (4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hept-6-enoate (13) (entry 10)



To a solution of α,β-unsaturated ester **11** (519 mg, 2.45 mmol), CuCl (186 mg, 1.88 mmol) and cyclohexene (960 μL, 9.43 mmol) in MeOH (40 mL) at –78 °C was added $NaBH_4$ (446 mg, 11.8 mmol). The reaction was left at –78 °C for 1 h, during which time it turned from green to brown. While still cold, the solvent was removed on the rotary evaporator. The products were partitioned between saturated aqueous NH_4Cl solution (50 mL) and Et_2O (50 mL). The organic phase was separated and the aqueous layer was extracted with more Et_2O (4 x 20

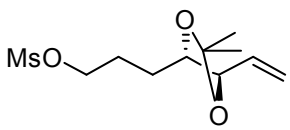
mL). The organic layers were combined, dried with $MgSO_4$, filtered and reduced to give a colourless oil (520 mg, 96%). The product was deemed sufficiently pure by ^{1}H NMR for use without further purification. R_f = 0.46 (2:1 hexanes:EtOAc). $[\alpha]_D^{22}$ = –31.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 1H), 5.34 (ddd, *J* = 17.1, 1.7, 1.1 Hz, 1H), 5.26 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.54 (dd, *J* = 7.5, 6.4 Hz, 1H), 4.16 (ddd, *J* = 8.8, 6.2, 5.4 Hz, 1H), 3.67 (s, 3H), 2.49 (ddd, *J* = 16.3, 8.3, 6.4 Hz, 1H), 2.40 (ddd, *J* = 16.4, 8.5, 7.4 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 133.7, 118.6, 108.4, 79.5, 77.2, 51.7, 30.7, 28.2, 26.2, 25.7. IR (KBr): 2987, 2935, 1736, 1645, 1440, 1371, 1255, 1217, 1162, 1067, 1011, 931, 871 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{18}O_4Na^+$ $[M + Na]^+$ 237.1103, found 237.1100.

(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)-hept-6-en-1-ol (12)



To a suspension of lithium aluminium hydride (115 mg, 3.03 mmol) in Et_2O (30 mL) at –10 °C was added methyl ester **13** (540 mg, 2.52 mmol) in Et_2O (15 mL). After 10 min, TLC analysis confirmed that all the starting material had been consumed. The reaction was quenched with wet Na_2SO_4,[36] filtered through a pad of Celite® and reduced to dryness to yield alcohol **12** as a colourless oil (458 mg, 97%). R_f = 0.20 (2:1 hexanes:EtOAc). $[\alpha]_D^{22}$ = –6.1 (*c* 1.00, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.31 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.24 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.52 (dd, *J* = 7.4, 6.7 Hz, 1H), 4.18 (ddd, *J* = 8.5, 6.2, 5.0 Hz, 1H), 3.68 (t, *J* = 5.8 Hz, 2H), 1.91 (s, 1H), 1.75 – 1.65 (complex m, 2H), 1.55 (m, 2H), 1.50 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 118.4, 108.3, 79.9, 78.2, 62.7, 29.8, 28.3, 27.5, 25.7. IR (KBr): 3435, 2934, 2874, 1644, 1429, 1380, 1248, 1217, 1165, 1047, 1018, 926, 872 cm^{-1}. HRMS (ESI) calcd. for $C_{10}H_{18}O_3Na^+$ $[M + Na]^+$ 209.1154, found 209.1152.

(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)-hept-6-en-1-methanesulfonate

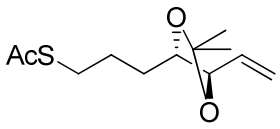


To a solution of alcohol **12** (213 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added NEt_3 (320 μL, 2.30 mmol), DMAP (14 mg, 0.115 mmol), and MsCl (134 μL, 1.70 mmol). The reaction was left to warm to rt and stir for 12 h. After this time, the reaction was deemed complete by TLC (colour change from purple to black with anisaldehyde dip). The solvent was removed and the crude product dissolved in EtOAc (20 mL), before

[36] Generated by adding water to sodium sulfate until a gelatinous solid formed.

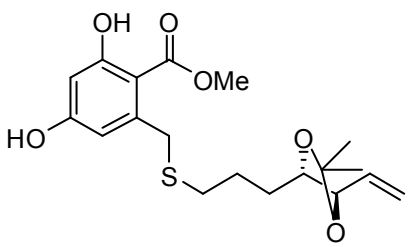
being washed with water (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting oil which was purified using flash column chromatography (silica, gradient elution 3:1 to 1:1 hexanes/EtOAc) yielding the title compound as a colourless oil (294 mg, 97%). R_f = 0.26 (2:1 hexanes:EtOAc). $[\alpha]_D^{22}$ = –14.3 (*c* 1.09, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.33 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.30 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.57 (dd, *J* = 7.5, 6.4 Hz, 1H), 4.30 (dt, *J* = 9.9, 6.3 Hz, 1H), 4.25 (ddd, *J* = 9.8, 7.0, 6.0 Hz, 1H), 4.19 (ddd, *J* = 9.0, 6.2, 4.7 Hz, 1H), 3.05 (s, 3H), 1.99 (tdd, *J* = 12.3, 9.2, 6.2 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.62 – 1.54 (complex m, 2H), 1.52 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 118.5, 108.3, 79.7, 77.7, 30.6, 29.6, 28.9, 28.2, 26.3, 25.6. IR (film): 2994, 2939, 1353, 1248, 1212, 1174, 926, 908, 733 cm^{-1}.

(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)-hept-6-en-1-thioacetate (8)



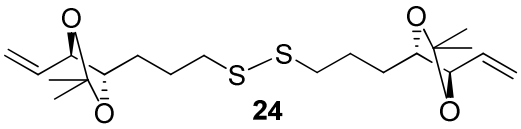
To a solution of the mesylate **23** (1.59 g, 6.02 mmol) in DMF (50 mL) at 0° C was added KSAc (824 mg, 7.23 mmol). The reaction was left to warm to rt and stirred for 12 h. The reaction was diluted with Et_2O (100 mL) and H_2O (100 mL). The organic layer was further washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) before drying with $MgSO_4$, filtering and concentrating to give a pale brown oil which was purified using flash column chromatography (silica, gradient elution 20:1 to 10:1 hexanes/EtOAc) yielding thioacetate **8** as a colourless oil (1.32 g, 90%). R_f = 0.56 (2:1 hexanes:EtOAc). $[\alpha]_D^{22}$ = –9.5 (*c* 1.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.1, 9.7, 7.8 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.24 (d, *J* = 10.3 Hz, 1H), 4.49 (t, *J* = 6.9 Hz, 1H), 4.13 (m, 1H), 2.95 – 2.83 (m, 2H), 2.32 (s, 3H), 1.80 – 1.68 (m, 1H), 1.66 – 1.50 (m, 2H), 1.49 – 1.41 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.8, 134.2, 118.5, 108.3, 79.7, 77.7, 30.6, 29.6, 28.9, 28.2, 26.3, 25.6. IR (film): 2986, 2916, 1692, 1455, 1428, 1379, 1369, 1244, 1216, 1134, 1134, 1048, 1012, 929, 871, 625 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{20}O_3SNa^+$ [M + Na]$^+$ 267.1031, found 267.1028.

Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-dihydroxybenzoate (16)



A solution of thioacetate **8** (340 mg, 1.39 mmol) and bromide **4** (485 mg, 1.41 mmol) in dry MeOH (25 mL) was degassed by bubbling dry argon through the solution for 10 min. After this time, K_2CO_3

(466 mg, 3.37 mmol) was added and the reaction was stirred at rt for 12 h. After TLC analysis confirmed the consumption of bromide **4**, the solvent was removed to dryness. The residue was dissolved in EtOAc (50 mL) and saturated aqueous NH_4Cl solution (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layers were combined, washed with brine (50 mL), dried with $MgSO_4$, filtered and reduced to dryness. The crude residue was purified using column chromatography (silica, gradient elution, 5:1 to 3:1 hexanes/EtOAc) to yield coupled product **16** as a colourless oil (447 mg, 86%). R_f = 0.33 (2:1 hexanes:EtOAc). $[\alpha]_D^{18}$ = –21.5 (*c* 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.67 (s, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.31 (s, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.31 (ddd, *J* = 17.1, 1.7, 1.1 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.50 (dd, *J* = 7.7, 6.4 Hz, 1H), 4.10 (ddd, *J* = 9.1, 6.1, 4.3 Hz, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.93 (s, 3H), 3.87 (d, *J* = 13.6 Hz, 1H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.76 – 1.66 (m, 1H), 1.65 – 1.50 (m, 2H), 1.49 (s, 3H), 1.50 – 1.40 (m, 1H), 1.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 165.7, 160.2, 143.9, 133.8, 118.7, 111.1, 108.4, 104.4, 102.5, 79.8, 77.7, 52.2, 37.0, 31.1, 29.5, 28.2, 25.8, 25.7. IR (KBr): 3272, 2988, 2951, 1655, 1621, 1588, 1441, 1381, 1326, 1259, 1210, 1162, 1109, 1031, 1003, 951, 851 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{26}O_6SNa^+$ $[M + Na]^+$ 405.1348, found 405.1345.



24

Disulfide **24** was isolated as a minor by-product (18 mg, 3%). R_f = 0.59 (2:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 17.2, 10.6, 7.8, 3.0 Hz, 2H), 5.31 (d, *J* = 17.1 Hz, 2H), 5.24 (dd, *J* = 10.3, 0.8 Hz, 2H), 4.50 (dd, *J* = 6.9, 7.8 Hz, 2H), 4.14 (ddt, *J* = 8.7, 6.1, 4.3 Hz, 2H), 2.70 (m, 2H), 2.56 (ddd, *J* = 14.4, 7.5, 3.7 Hz, 2H), 1.92 – 1.49 (m, 8H), 1.49 (s, 6H), 1.36 (s, 6H). HRMS (ESI) calcd. for $C_{20}H_{34}O_4S_2Na^+$ $[M + Na]^+$ 425.1796, found 425.1792.

Attempted hydrolysis of ester 16

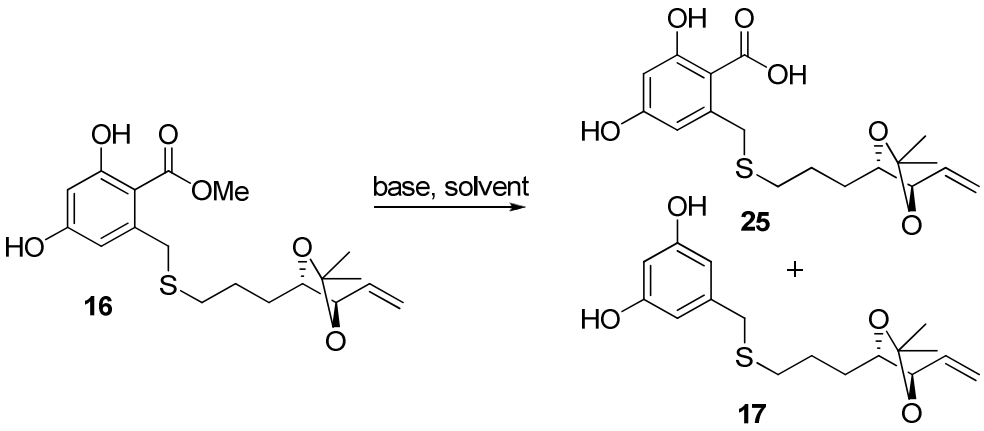
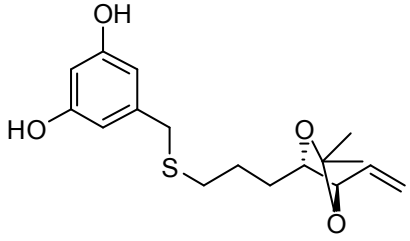


Table S–2. Summary of attempted hydrolyses of methyl ester **16**.

Entry	Reagent	Solvent	Reaction temperature	Reaction time (hr)	Yield 16	Yield 25	Yield 17
1	LiOH (4 eq)	1:1 THF/H_2O	50 °C	12	5 [a]	0	23 [a]
2	LiOH (4 eq)	2:1 MeOH/H_2O	50 °C	6	64 [b]	0	36 [b]
3	NaOH (4 eq)	2:1 MeOH/H_2O	50 °C	6	37 [b]	0	63 [b]
4	EtSH (5 eq), *n*-BuLi (4.5 eq)	THF	–10 °C to rt	2	100 [b]	0	0 [b]
5	EtSH (5 eq), NaH (4.5 eq)	DMF	–10 °C to rt	12	20 [b]	0	80 [b]
6	$Ba(OH)_2$ (3 eq)	EtOH	rt	18	decomposed		

[a] Isolated yield. [b] Relative yields are based on ratios in the ^{1}H NMR spectrum of the crude product mixture.

Attempted saponification of ester 16: 5-[({3-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]propyl}thio)methyl]benzene-1,3-diol (17) (entry 1)



A solution of methyl ester **16** (101 mg, 0.264 mmol) and LiOH (46 mg, 1.09 mmol) in 1:1 v/v THF/H_2O (4 mL) was heated to 50 °C for 12 h. The cooled solution was extracted with Et_2O (2 x 10 mL) and the organic fractions discarded. The aqueous layer was acidified to pH 1 with 10% HCl solution and further extracted with

Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and reduced to dryness. The crude residue was purified by flash column chromatography (silica, gradient chromatography, 10:1 to 1:1 hexanes/EtOAc), returning methyl ester **16** (5 mg, 5%) and affording decarboxylated compound **17** a colourless oil (22 mg, 26%). **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, *J* = 2.2 Hz, 2H), 6.23 (t, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.33 (s, 1H), 5.31 (ddd, *J* = 17.2, 1.7, 1.2 Hz, 1H), 5.24 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 4.49 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.10 (ddd, *J* = 8.7, 6.1, 4.5 Hz, 1H), 3.56 (s, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.78 – 1.65 (m, 1H), 1.64-1.50 (m, 2H), 1.49 (s, 3H), 1.48 – 1.42 (m, 1H), 1.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ δ 156.8, 141.4, 134.0, 118.7, 108.4, 108.4, 101.5, 79.8, 77.8, 35.8, 31.0, 29.5, 28.2, 25.7, 25.7. IR: 3339, 2987, 2930, 1603, 1454, 1373, 1340, 1218, 1156, 1003, 735 cm^{-1}. HRMS (ESI) calcd. for $C_{17}H_{24}O_4SNa^+$ $[M + Na]^+$ 347.1293, found 347.1288.

Attempted saponification of methyl ester 16 (entry 2)

A solution of methyl ester **16** (23 mg, 60.2 mmol) and LiOH (10 mg, 0.24 mmol) in 2:1 MeOH/H_2O (1.5 mL) was stirred at rt for 1 h. The reaction mixture was then heated at 50 °C for 8 h. The cooled solution reduced to dryness. The residue was partitioned between 10% HCl solution (10 mL) and EtOAc (10 mL). The aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~1.8:1 ratio of ester **16** to diol **17.**

Attempted saponification of methyl ester 16 (entry 3)

A solution of methyl ester **16** (23 mg, 60.2 mmol) and NaOH (13.5 mg, 0.24 mmol) in 2:1 MeOH/H_2O (1.5 mL) was stirred at rt for 1 h. The reaction mixture was then heated at 50 °C for 8 h. The cooled solution reduced to dryness. The residue was partitioned between 10% HCl solution (10 mL) and EtOAc (10 mL). The aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^{1}H NMR spectrum of the residue indicated the presence of a ~1:1.7 ratio of ester **16** to diol **17**.

Attempted saponification of methyl ester 16 (entry 4)

To a solution of methyl ester **16** (41 mg, 0.11 mmol) in EtOH (3.5 mL) was added $Ba(OH)_2$ (105 mg, 0.33 mmol) and the reaction mixture stirred at rt for 18 h. The solution turned a deep red colour. The reaction mixture was diluted with Et_2O (15 mL) and acidified with 10% HCl solution (15 mL). The organic phase was separated and the aqueous further extracted with Et_2O (10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated that the material had degraded.

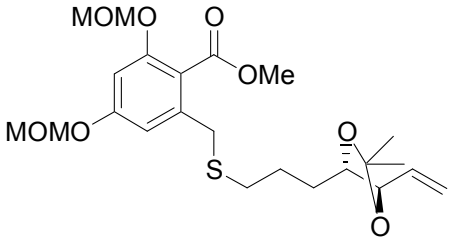
Attempted conversion of methyl ester 16 to acid 25 (entry 5)

To a solution of ethanethiol (49 μL, 0.65 mmol) in THF (2 mL) was added *n*-BuLi (370μL, 0.59 mmol) at –10 °C. The solution instantly went cloudy. The solution was warmed to rt for 5 min. The reaction mixture was cooled to –10 °C and a THF solution (2 mL) of methyl ester **16** (57 mg, 0.15 mmol) was added dropwise. After stirring at –10 °C for 30 min, the reaction mixture was warmed to rt for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated that starting material had been recovered.

Attempted conversion of methyl ester 16 to acid 25 (entry 6)

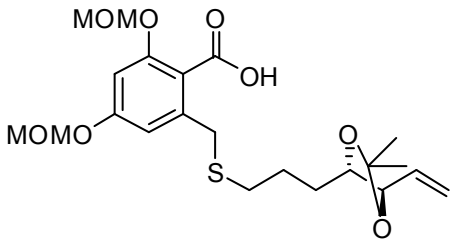
To a solution of ethanethiol (56 μL, 0.75 mmol) in DMF (2 mL) was added a 60% dispersion of NaH in mineral oil (27 mg, 0.67 mmol) at –10 °C. The solution was warmed to rt for 5 min. The reaction mixture was cooled to –10 °C and a DMF solution (2 mL) of methyl ester **16** (57 mg, 0.15 mmol) was added dropwise. After stirring at –10 °C for 30 min, the reaction mixture was warmed to rt for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and reduced to dryness. The ^1H NMR spectrum of the residue indicated the presence of a ~1:4 ratio of ester **16** to diol **17**.

Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-bis(methoxymethoxy)benzoate



To a solution of compound **16** (621 mg, 1.62 mmol) in DMF (6 mL) at 0 °C was added a 60% dispersion of NaH in mineral oil (163 mg, 4.06 mmol). The reaction was stirred at 0 °C for 20 min before the addition of MOMCl (370 μL, 4.89 mmol). The reaction mixture was left to warm to rt whilst stirring for 2 h. The reaction mixture was diluted with Et_2O (30 mL) and washed with saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer further extracted with Et_2O (2 x 15 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to give a colourless oil, which was purified using flash column chromatography (silica, gradient elution, 10:1 to 5:1 hexanes/EtOAc) affording the desired bis-MOM ether as a colourless oil (562 mg, 74%). R_f = 0.30 (2:1 hexanes:EtOAc). $[\alpha]_D^{18}$ = –30.3 (*c* 0.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 2.2 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.6, 1.1 Hz, 1H), 5.22 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 5.161 (s, 2H), 5.157 (s, 2H), 4.47 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.09 (ddd, *J* = 8.6, 6.1, 4.7 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 2.48 – 2.40 (m, 2H), 1.77 – 1.67 (m, 1H), 1.60 – 1.43 (m, 3H), 1.47 (s, 3H), 1.35 (s, H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 158.8, 156.0, 139.4, 134.3, 118.3, 110.6, 108.2, 102.5, 95.0, 94.3, 79.7, 77.8, 77.2 56.3, 56.2, 52.2, 34.0, 31.4, 29.5, 28.2, 25.8, 25.6. IR (neat): 2949, 2906, 1727, 1605, 1434, 1277, 1215, 1144, 1038, 1017, 928, 870 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{34}O_8SNa^+$ $[M + Na]^+$ 493.1872, found 493.1867.

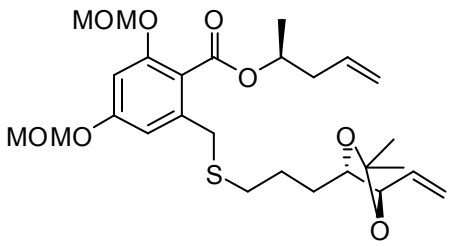
(6′*S*,7′*R*)-6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoic acid (18)



To a solution of the ester (455 mg, 0.968 mmol) in 2:1 MeOH/H_2O (15 mL) was added KOH (271 mg, 4.84 mmol) and the reaction mixture was heated to 90 °C for 48 h. After cooling to rt, the mixture was extracted with Et_2O (20 ml) and the organic layer discarded. The aqueous layer was acidified to pH 6 with an aqueous acetic acid solution (50%; v/v, 0.78 mL, 6.8 mmol) and extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with H_2O (4 x 20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the acid **18** as a

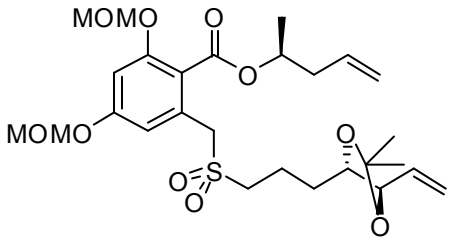
colourless oil (434 mg, 98%). $[\alpha]_D^{20} = -32.1$ (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 2.3 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.2, 7.8 Hz, 1H), 5.28 (ddd, *J* = 17.1, 1.6, 1.0 Hz, 1H), 5.22 (s, 2H), 5.22 (dd, *J* = 10.3, 1.6, 0.8 Hz, 1H), 5.18 (s, 2H), 4.47 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.12 (ddd, *J* = 8.4, 6.1, 4.6 Hz, 1H), 3.96 (d, *J* = 13.4 Hz, 1H), 3.92 (d, *J* = 13.4 Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.74 (m, 1H), 1.64 – 1.38 (m, 3H), 1.47 (s, 3H), 1.35 (s, 3H). IR (neat): 2908, 2845, 1604, 1586, 1462, 1377, 1277, 1216, 1151, 1028, 1020, 927, 744 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{32}O_8SNa^+$ $[M + Na]^+$ 479.1716, found 479.1720.

(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoate (3)



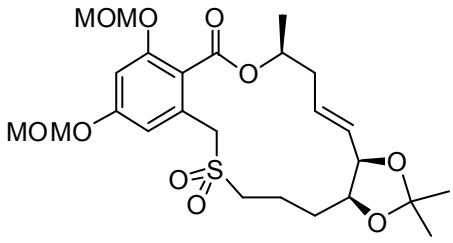
To a solution of alcohol **6** (147 μL, 1.43 mmol) and PPh_3 (624 mg, 2.38 mmol) in THF (20 mL) at 0 °C was added DIAD (463 μL, 2.38 mmol). The solution was stirred at 0 °C for 20 min during which time a white precipitate formed. After this time a solution of the acid **18** (434 mg, 0.952 mmol) in THF (15 mL) was added dropwise and the reaction was left to stir at rt for 2 days. To the crude reaction mixture was added a small amount of silica gel before removal of solvent. The silica gel was dry loaded onto a column and eluted (gradient elution 20:1 to 5:1 hexanes/EtOAc) to yield title compound **3** as a colourless oil (468 mg, 94%). R_f = 0.60 (2:1 hexanes:EtOAc). $[\alpha]_D^{18} = -34.9$ (*c* 0.18, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.78 (ddd, *J* = 17.9, 10.3, 7.8 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.15 (s, 2H), 5.14 (m, 2H), 5.13 – 5.07 (m, 2H), 4.46 (dd, *J* = 7.3, 6.6 Hz, 1H), 4.09 (ddd, *J* = 8.5, 6.0, 4.8 Hz, 1H), 3.73 (d, *J* = 13.7 Hz, 1H), 3.69 (d, *J* = 13.7 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.51 – 2.42 (m, 3H), 2.40 – 2.33 (m, 1H), 1.72 (m, 1H), 1.60 – 1.40 (m, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 158.6, 155.8, 139.0, 134.3, 133.8, 118.4, 118.3, 117.7, 110.4, 108.2, 102.3, 94.7, 94.3, 79.7, 77.8, 71.2, 56.2, 56.1, 40.2, 33.8, 31.6, 29.5, 28.2, 25.8, 25.6, 19.4. IR (neat): 2984, 2906, 2845, 1715, 1604, 1584, 1434, 1380, 1272, 1216, 1149, 1039, 1019, 926 cm^{-1}. HRMS (ESI) calcd. for $C_{27}H_{40}O_8SNa^+$ $[M + Na]^+$ 547.2342, found 547.2342.

(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1′′-methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoate 2′,2′-dioxide (2)



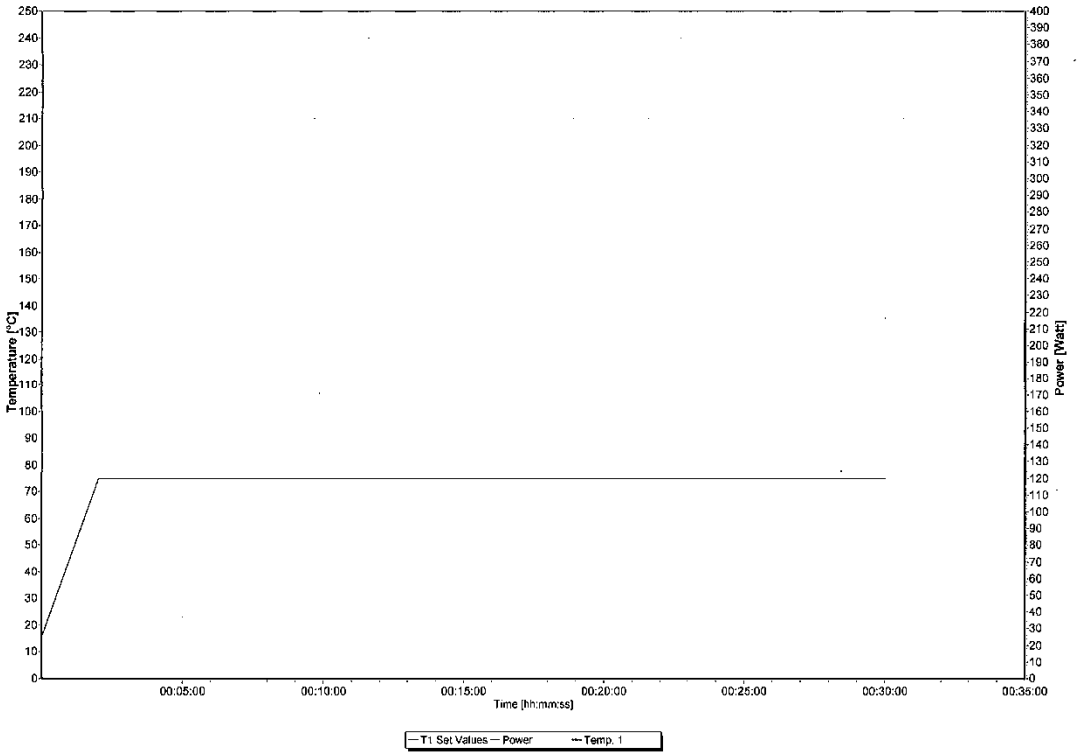
To a solution of thioether **3** (122 mg, 0.230 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 75% *m*-CPBA (115 mg, 0.501 mmol). The reaction was left to warm to rt whilst stirring for 2 h. The reaction was quenched with the addition of 20% aqueous Na_2SO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, filtered and reduced *in vacuo* to give a colourless oil. The product was purified by flash column chromatography (silica, gradient elution 3:1 to 2:1 hexanes/EtOAc) yielding the title compound **2** as a colourless oil (109 mg, 84%). R_f = 0.31 (2:1 hexanes:EtOAc). $[\alpha]_D^{22}$ = –11.0 (*c* 1.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.5, 1.1 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.18 (s, 2H), 5.17 – 5.14 (m, 3H), 5.11 (ddt, *J* = 9.0, 2.0, 1.1 Hz, 1H), 4.48 (dd, *J* = 7.5, 6.5 Hz, 1H), 4.38 (d, *J* = 14.1 Hz, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.02 (ddd, *J* = 13.9, 10.2, 5.7 Hz, 1H), 2.94 (ddd, *J* = 13.9, 10.1, 5.7 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.42 – 2.35 (m, 1H), 2.02 – 1.91 (m, 1H), 1.89 – 1.80 (m, 1H), 1.52 (tdd, *J* = 11.2, 7.0, 3.9 Hz, 2H), 1.45 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 159.0, 156.4, 134.0, 133.7, 128.5, 119.3, 118.6, 117.9, 112.2, 108.4, 104.2, 94.8, 94.3, 79.6, 77.6, 71.7, 56.7, 56.4, 56.3, 51.5, 40.2, 29.3, 28.1, 25.5, 19.5, 18.7. IR (neat): 1708, 1605, 1586, 1285, 1214, 1150, 1122, 1039, 1018, 914, 734. HRMS (ESI) calcd. for $C_{27}H_{40}O_{10}SNa^+$ $[M + Na]^+$ 579.2246, found 579.2240.

(5*S*,7*E*,9*R*,10*S*)-1,2-(3′,5′-Di-*O*-methoxymethyl)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)-pentadec-7-ene 14,14-dioxide (19)

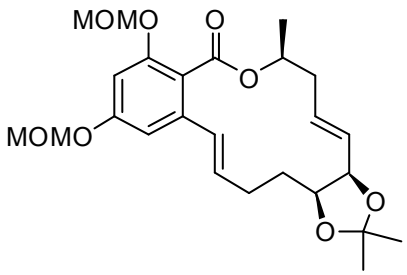


To a solution of the diene **2** (55 mg, 99 μmol) in CH_2Cl_2 (20 mL) in a 100 mL MW Teflon™ reactor vessel was added a catalytic amount of Grubbs' second generation catalyst (8.4 mg, 9.9 μmol). The vessel was flushed with argon before sealing with the cap. The vessel was placed in the MW carousel and the temperature/pressure probe inserted into the reaction vessel. The reaction mixture was irradiated for 30 min and heated to 75 °C (see temperature profile below). Once the reaction vessel had cooled to rt the cap was removed and the solution transferred to a round-bottom flask.

The solvent was removed to yield a brown oil. The crude product was purified on a silica column (gradient elution, 5:1 to 2:1 hexanes/EtOAc) yielding compound **19** as a colourless oil (45 mg, 86%). R_f = 0.14 (2:1 hexanes:EtOAc). $[\alpha]_D^{22}$ = –28.5 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 2.2 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 5.71 (ddd, *J* = 15.2, 9.3, 4.3 Hz, 1H), 5.55 (ddd, *J* = 15.4, 9.4, 1.4 Hz, 1H), 5.29 (m, 1H), 5.21 – 5.16 (m, 4H), 4.47 (d, *J* = 15.3 Hz, 1H), 4.43 (dd, *J* = 9.3, 5.8 Hz, 1H), 4.13 (d, *J* = 15.1 Hz, 1H), 4.11 (m, 1H), 3.47 (s, 3H), 3.47 (s, 3H), 2.83 (ddd, *J* = 14.6, 11.1, 5.3 Hz, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.41 (dd, *J* = 15.5, 9.8 Hz, 1H), 1.75 (m, 1H), 1.67 (m, 1H), 1.62 – 1.53 (m, 2H), 1.43 (s, 3H), 1.40 (d, *J* = 6.2 Hz, 3H), 1.32 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.1, 159.3, 156.6, 132.4, 129.0 (2), 118.6, 110.9, 107.9, 103.6, 94.6, 94.4, 76.3, 77.6, 72.3, 56.4, 56.4, 55.4, 51.1, 39.5, 28.3, 27.6, 25.5, 20.8, 18.5. IR (neat): 2982, 2903, 2829, 1708, 1604, 1585, 1277, 1215, 1149, 1122, 1017, 926, 737 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{36}O_{10}SNa^+$ $[M + Na]^+$ 551.1928, found 551.1927.

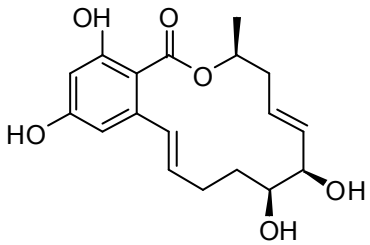


(5′*S*,6′*R*,10′*S*)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)-aigialomycin D (20)



To a solution of sulfone **19** (34 mg, 64.4 μmol) in ^{t}BuOH (250 μl) and CH_2Cl_2 (100 μL) was added powdered KOH (72 mg, 1.29 mmol) at rt. To the resulting suspension was added CCl_4 (250 μmol) dropwise over 2 min. The reaction was then heated to 35 °C for 30 min. After cooling to rt the solvent was removed to dryness and the residue partitioned between saturated aqueous NH_4Cl solution (5 mL) and EtOAc (5 mL). The aqueous layer was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced. The crude product was purified by flash column chromatography (silica, gradient elution 20:1 to 5:1 hexanes/EtOAc) to give the title compound **20** as a white solid (25 mg, 84%). R_f = 0.40 (2:1 hexanes:EtOAc). $[\alpha]_D^{19}$ = –118.6 (*c* 0.15, $CHCl_3$) [lit.[5c] –116.5 (*c* 0.13, $CHCl_3$) and lit.[5a] –120 (*c* 0.08, $CHCl_3$)] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 6.14 (ddd, *J* = 15.3, 9.6, 4.2 Hz, 1H), 5.74 (ddd, *J* = 15.3, 9.4, 3.5 Hz, 1H), 5.60 (ddd, *J* = 15.4, 9.7, 1.7 Hz, 1H), 5.34 (m, 1H), 5.20 – 5.12 (m, 4H), 4.57 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.19 (ddd, *J* = 11.6, 5.4, 3.1 Hz, 1H), 3.46 (s, 3H), 3.46 (s, 3H), 2.58 – 2.44 (m, 2H), 2.31 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H), 1.49 (m, 1H), 1.47 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 158.9, 155.1, 136.8, 132.3, 131.9, 129.3, 128.4, 117.9, 108.3, 104.8, 102.5, 94.5, 94.3, 80.1, 77.2, 71.6, 56.2, 56.1, 39.5, 29.0, 28.7, 28.6, 25.8, 21.1. IR (neat): 2984, 2897, 1722, 1601, 1579, 1263, 1218, 1148, 1052, 1018, 925 cm^{-1}. HRMS (ESI) calcd. for $C_{25}H_{34}O_8Na^+$ $[M + Na]^+$ 485.2151, found 485.2147.

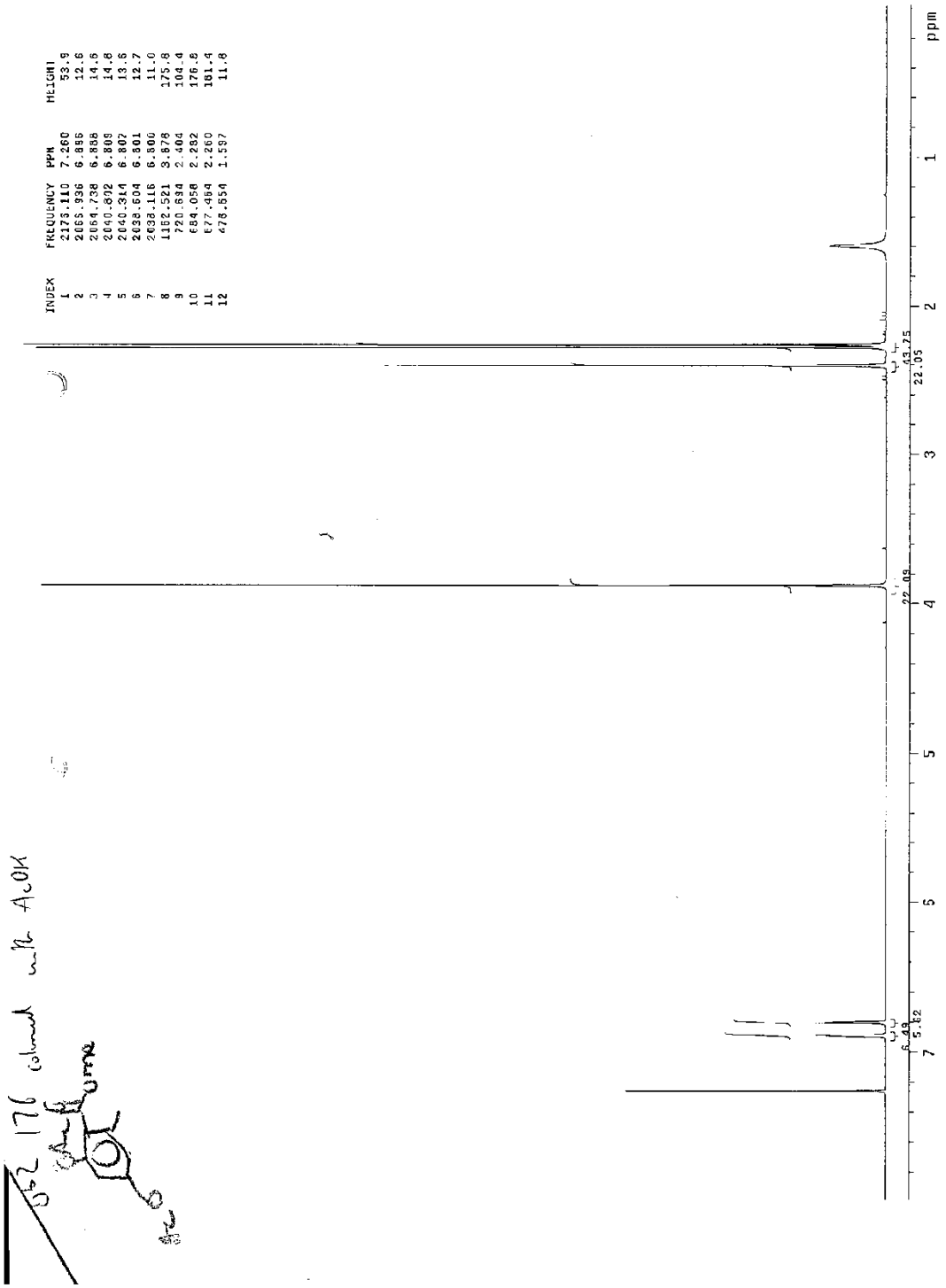
Aigialomycin D (1)



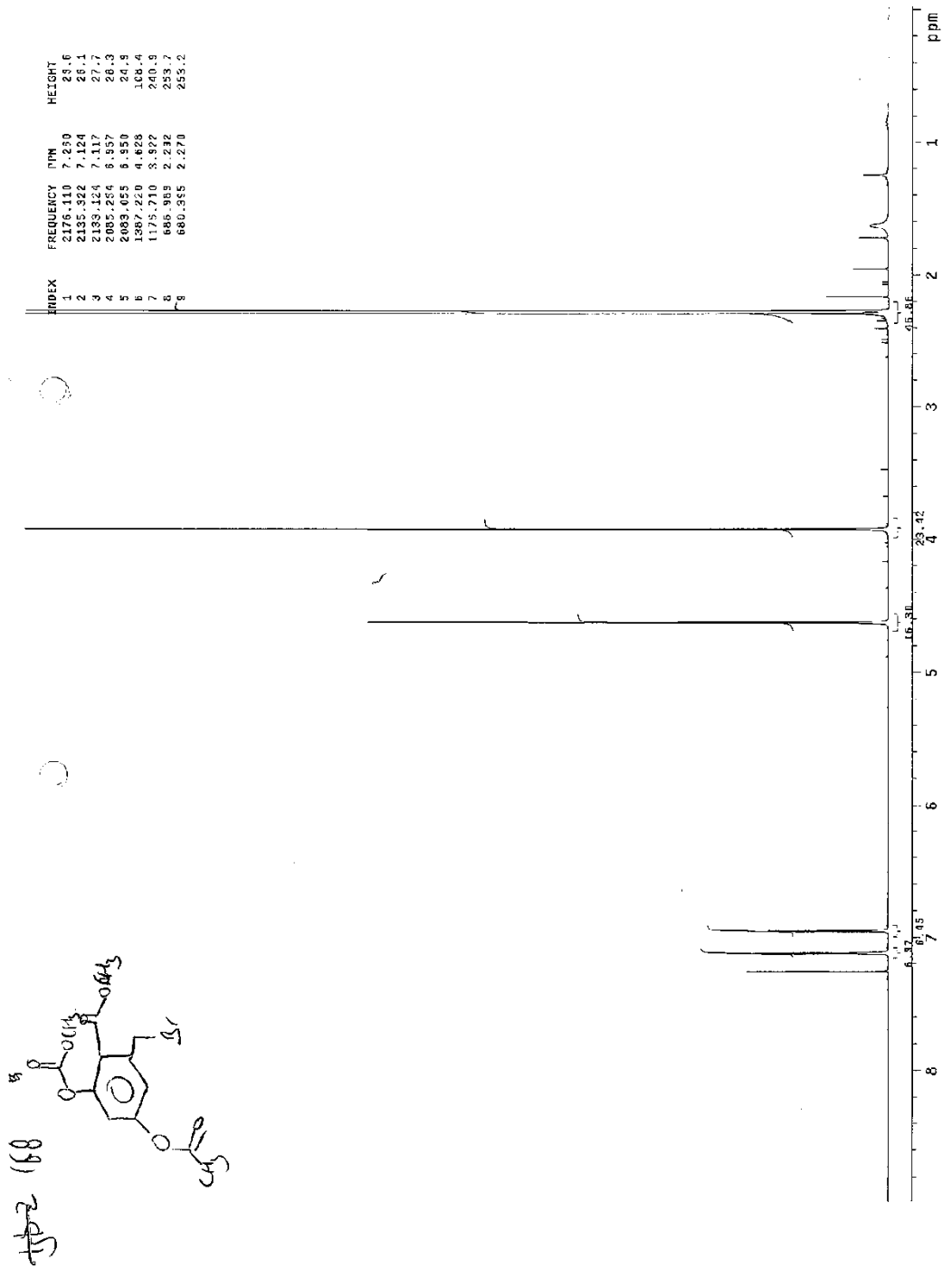
A solution of compound **20** (45 mg, 97.3 μmol) in 1:1 v/v MeOH/1M HCl (10 mL) was stirred at rt for 3 days. The reaction mixture was extracted with EtOAc (3 x 10 mL), washed with brine (5 ml), dried over $MgSO_4$, filtered and reduced to give aigialomycin D as a white solid (28 mg, 86%). R_f = 0.21 (5% MeOH/CH_2Cl_2). $[\alpha]_D^{19}$ = –25.1 (*c* 0.78, MeOH) [lit.[5b] –21.9 (*c* 0.35, MeOH)]. ^{1}H NMR (500 MHz, d_6-acetone) δ 11.66 (s, 1H), 9.25 (brs, 1H), 7.15 (d, *J* = 15.9 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.09 (ddd, *J* = 15.9, 5.7, 5.5 Hz, 1H), 5.88 (ddd, *J* = 15.6, 7.4, 1.6 Hz, 1H), 5.69 (ddd, *J* = 15.6, 5.2, 1.2 Hz, 1H), 5.44 (m, 1H), 4.35 (brd, *J* = 4.1 Hz, 1H), 3.82 (brs, 1H), 3.63 (m, 1H), 3.20 (brs, 1H), 2.57 (ddd, *J* = 14.6, 7.4, 3.1 Hz, 1H), 2.43 (m, 1H), 2.36 – 2.32 (m, 2H), 2.14 (m, 1H), 1.59 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125

MHz, d_6-acetone) δ 172.2, 165.8, 163.1, 144.3, 135.7, 133.6, 130.6, 125.4, 107.8, 104.4, 102.5, 76.5, 73.0, 73.0, 37.9, 28.5, 28.0, 19.1. IR (neat): 3338, 2979, 1644, 1608, 1448, 1312, 1259, 1167, 1110, 1018, 972 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{22}O_6Na^+$ $[M + Na]^+$ 357.1308, found 357.1314. Spectral data matched those reported in the literature.[1]

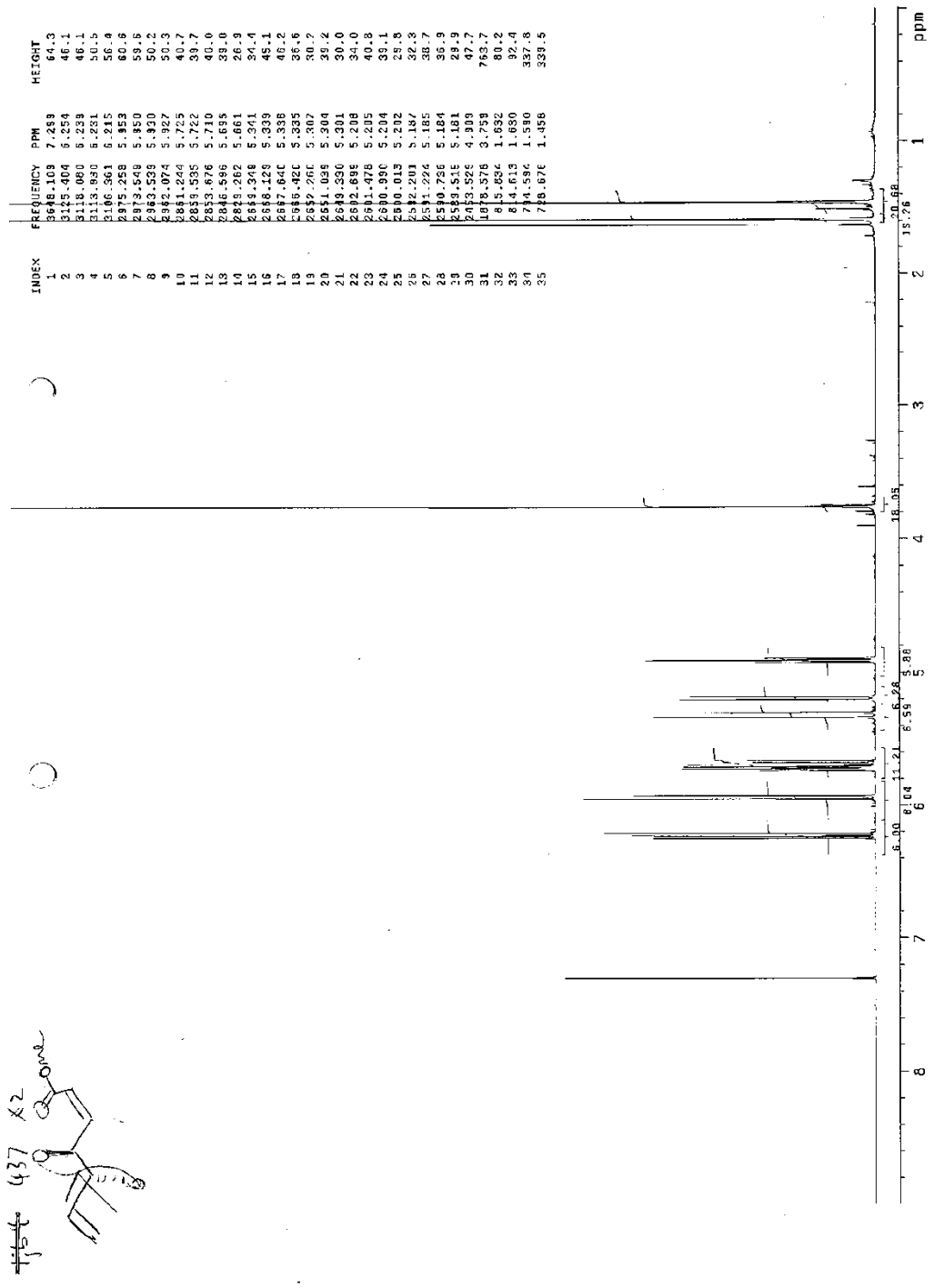
Supplementary Information: ^{1}H NMR spectrum of compound **7c** (300 MHz, $CDCl_3$)



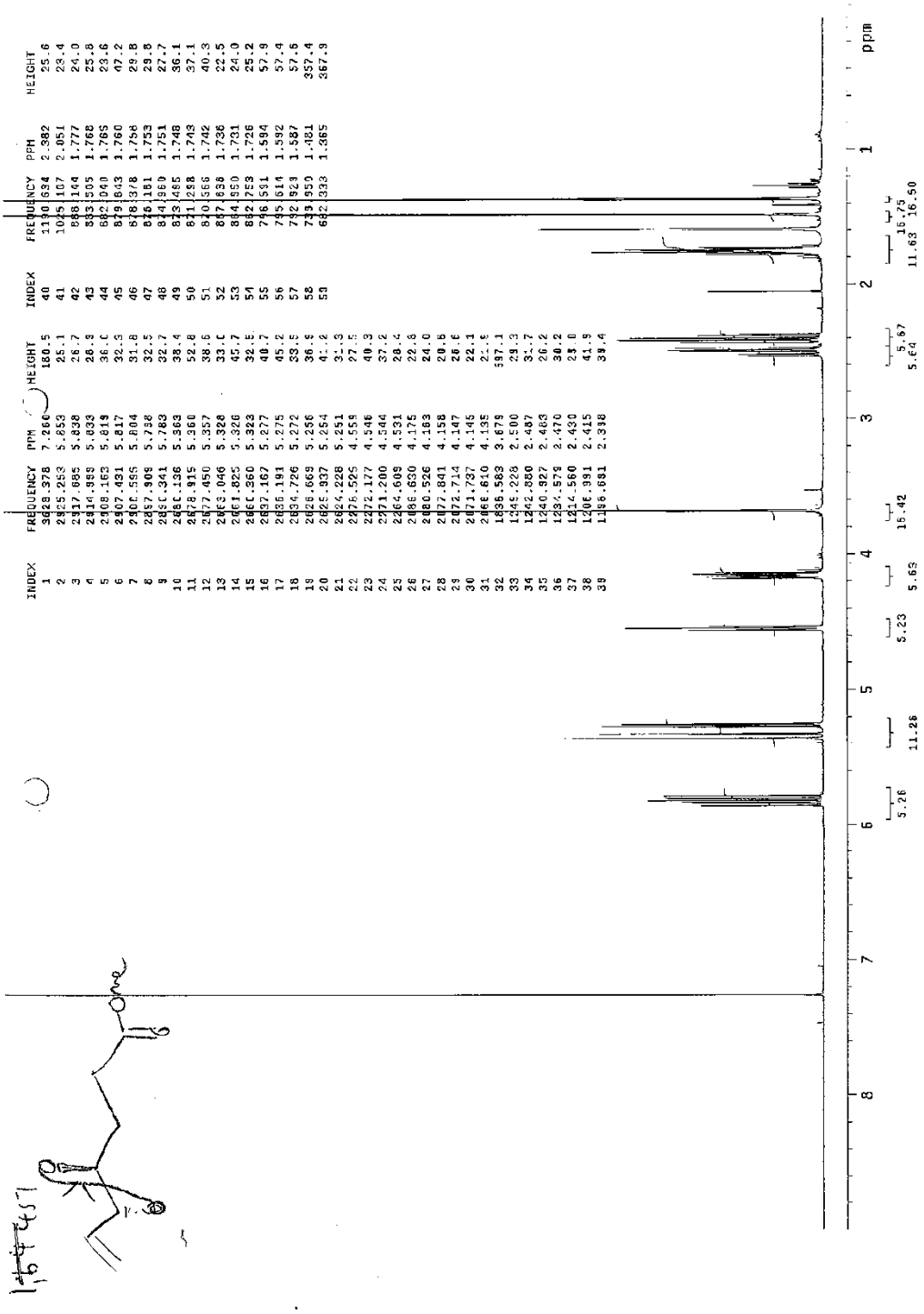
Supplementary Information: ^{1}H NMR spectrum of compound **4** (300 MHz, $CDCl_3$)



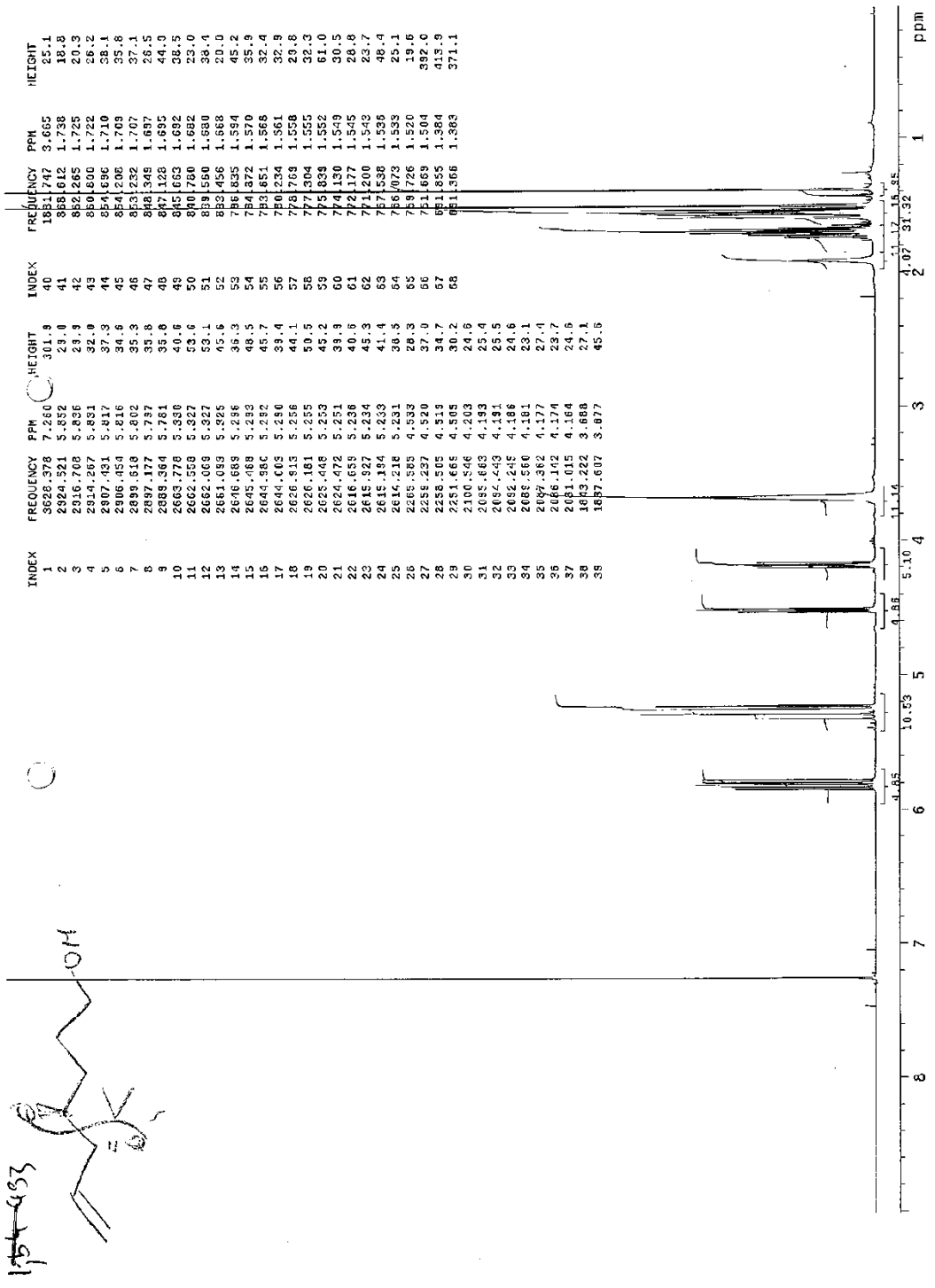
Supplementary Information: ^{1}H NMR spectrum of methyl (2*Z*,4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hepta-2,6-dienoate [(*Z*)-**11**] (500 MHz, $CDCl_3$)



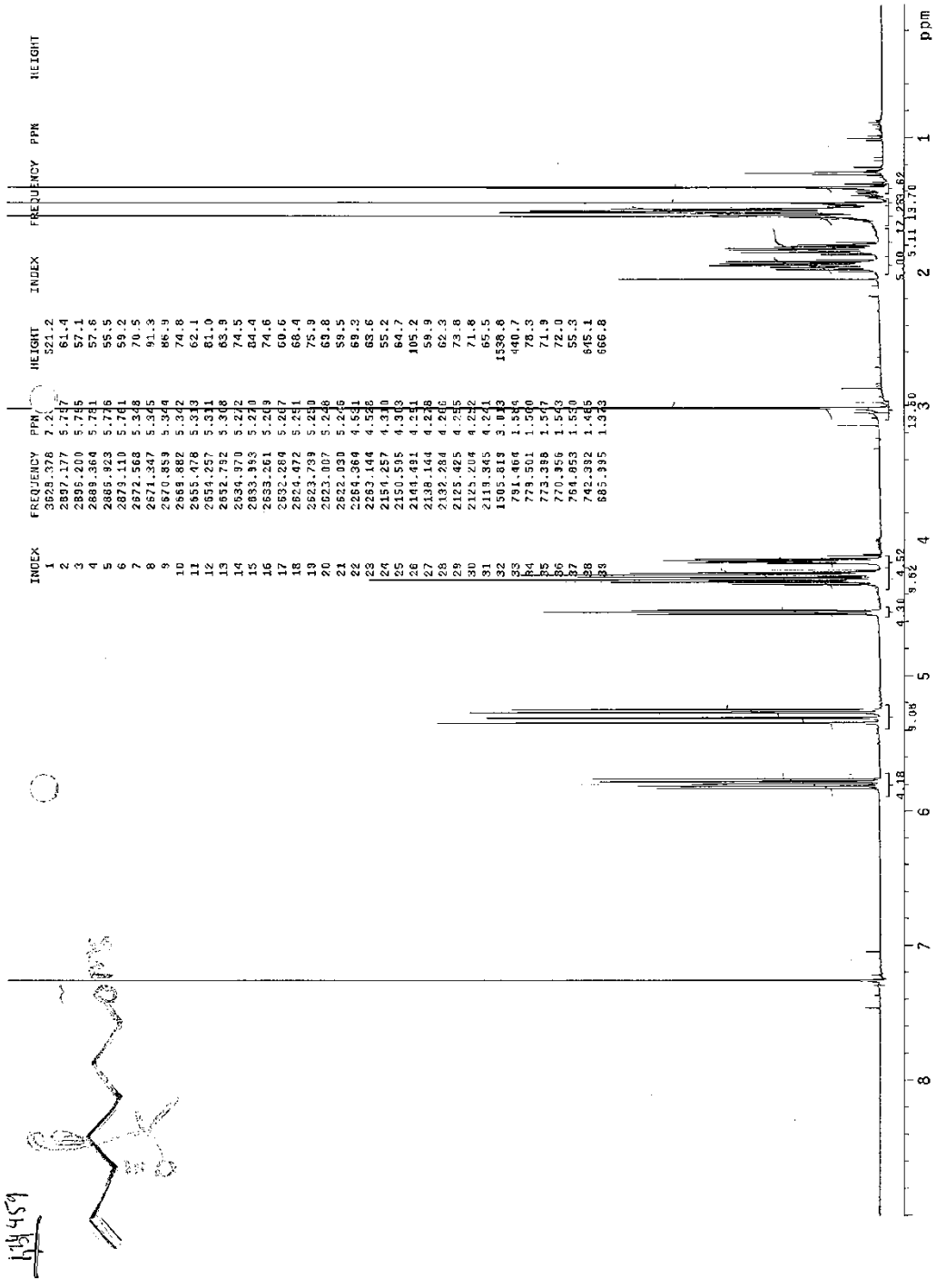
Supplementary Information: ^{1}H NMR spectrum of methyl (4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hept-6-enoate (**13**) (500 MHz, $CDCl_3$)



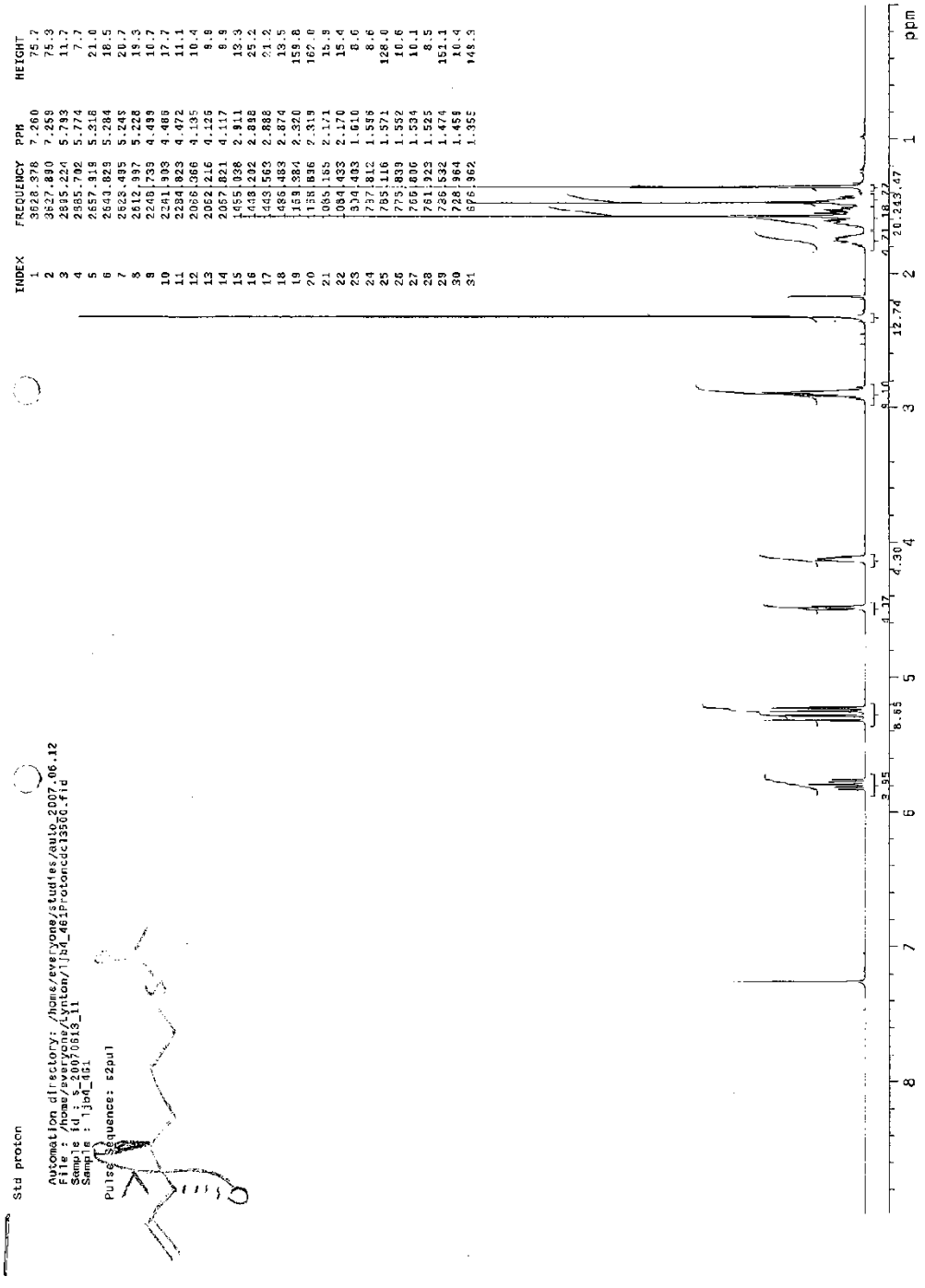
Supplementary Information: ^{1}H NMR spectrum of compound **12** (500 MHz, $CDCl_3$)



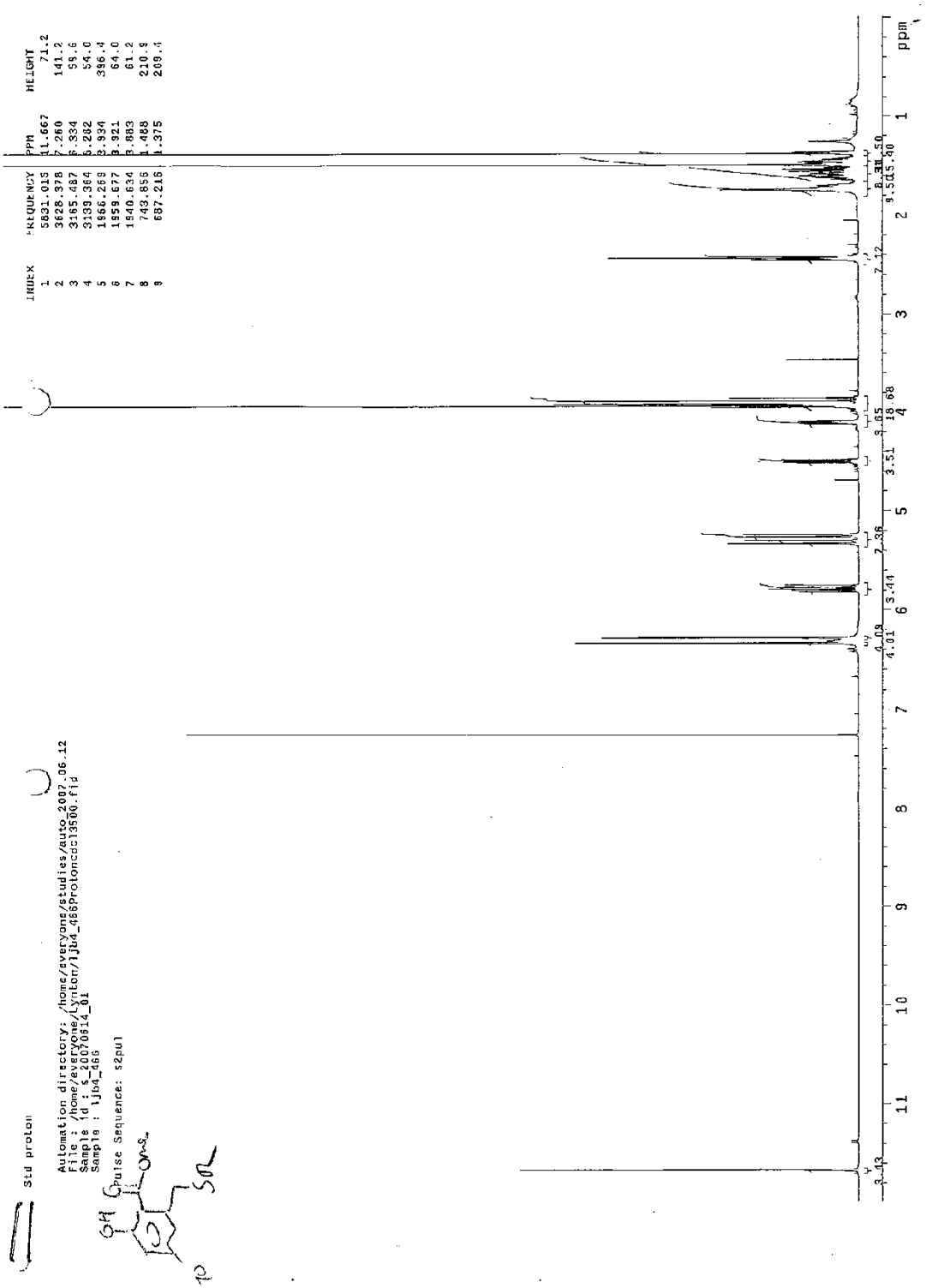
Supplementary Information: ^{1}H NMR spectrum of (4*S*,5*R*)-4,5-*O*-(1-methylethylidene)-hept-6-en-1-methanesulfonate (500 MHz, $CDCl_3$)



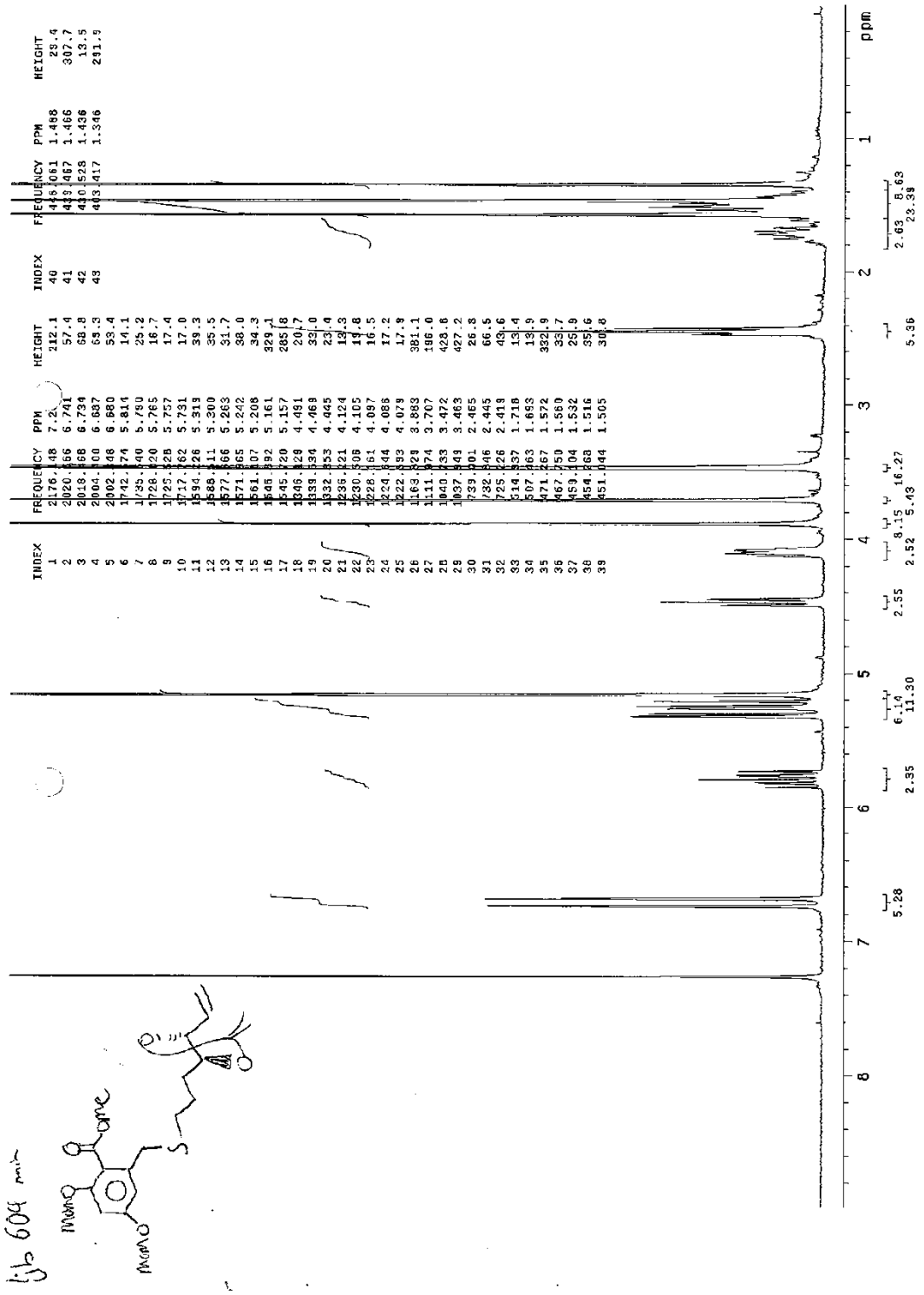
Supplementary Information: ^{1}H NMR spectrum of compound **8** (500 MHz, $CDCl_3$)



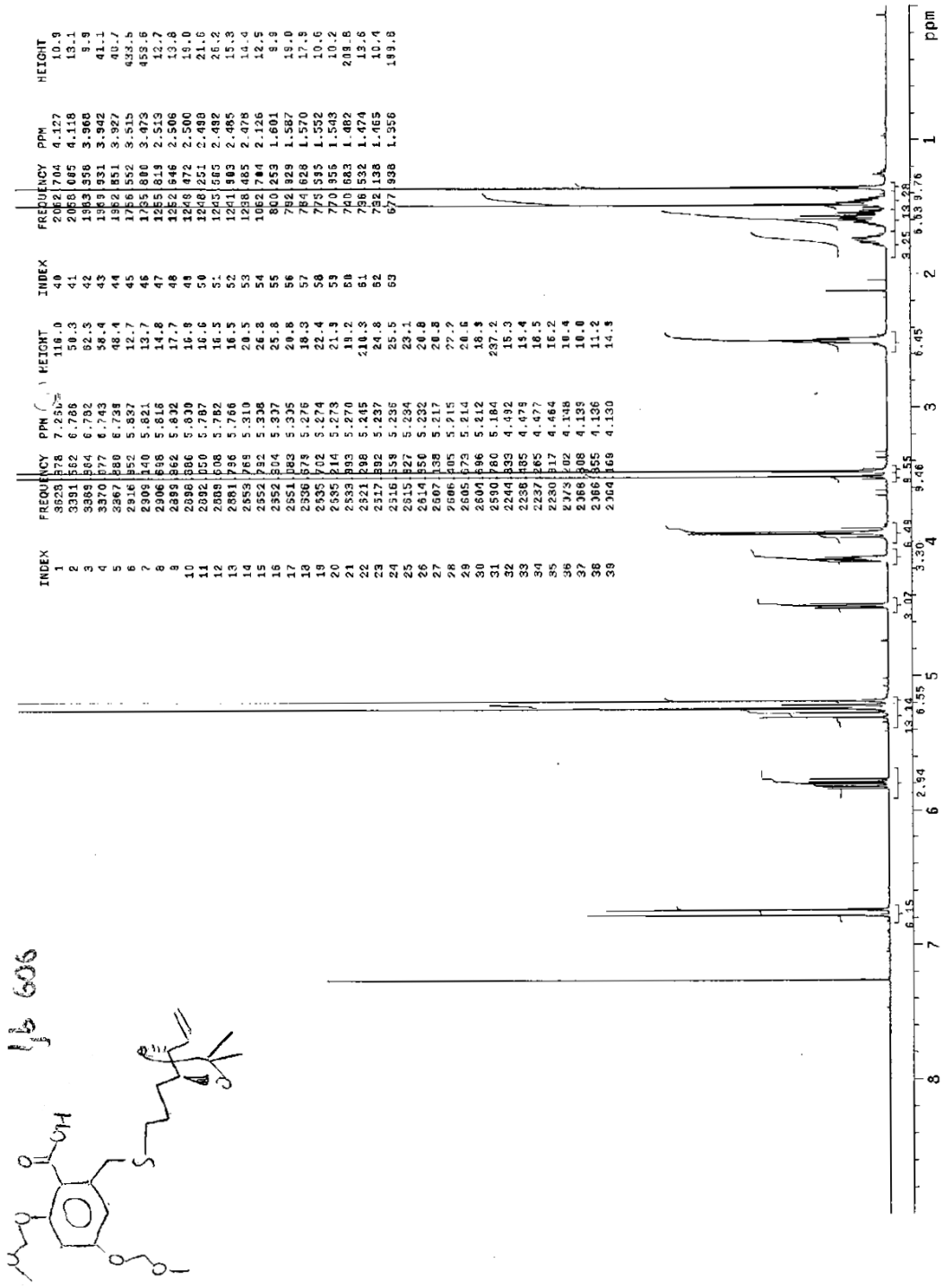
Supplementary Information: ^{1}H NMR spectrum of compound **16** (500 MHz, $CDCl_3$)



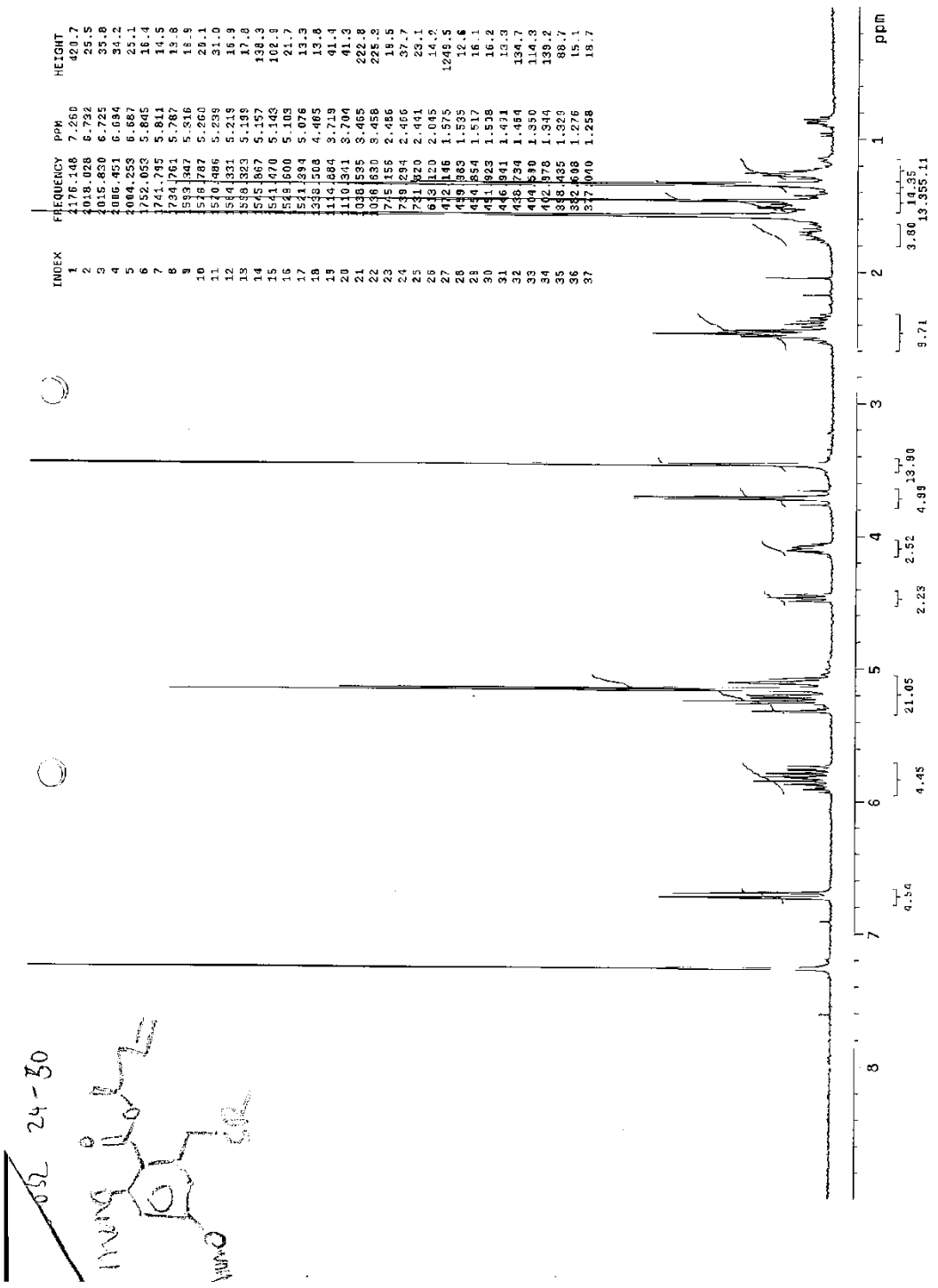
Supplementary Information: ^{1}H NMR spectrum of methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-bis(methoxymethoxy)benzoate ($CDCl_3$)



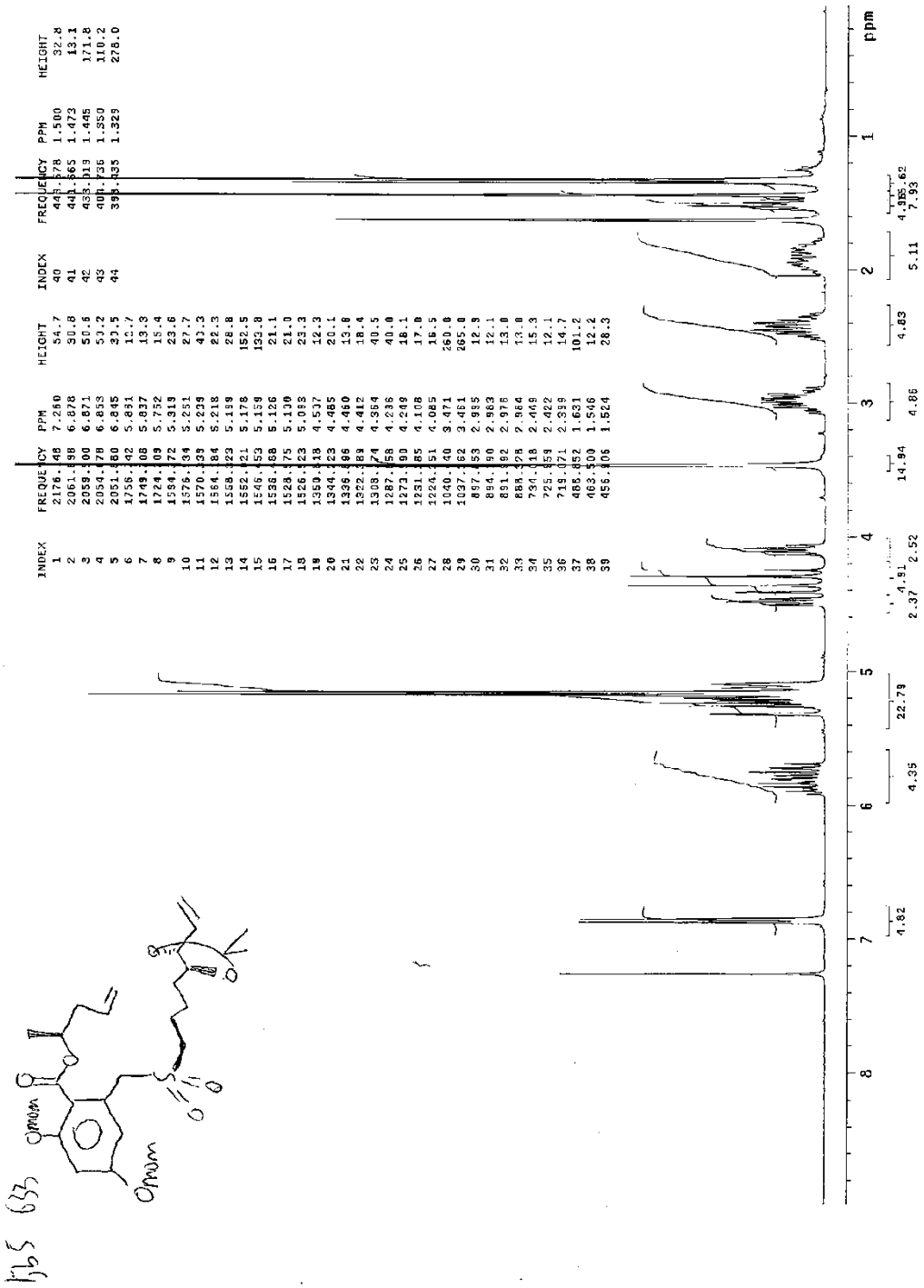
Supplementary Information: ^{1}H NMR spectrum of compound **18** (500 MHz, $CDCl_3$)



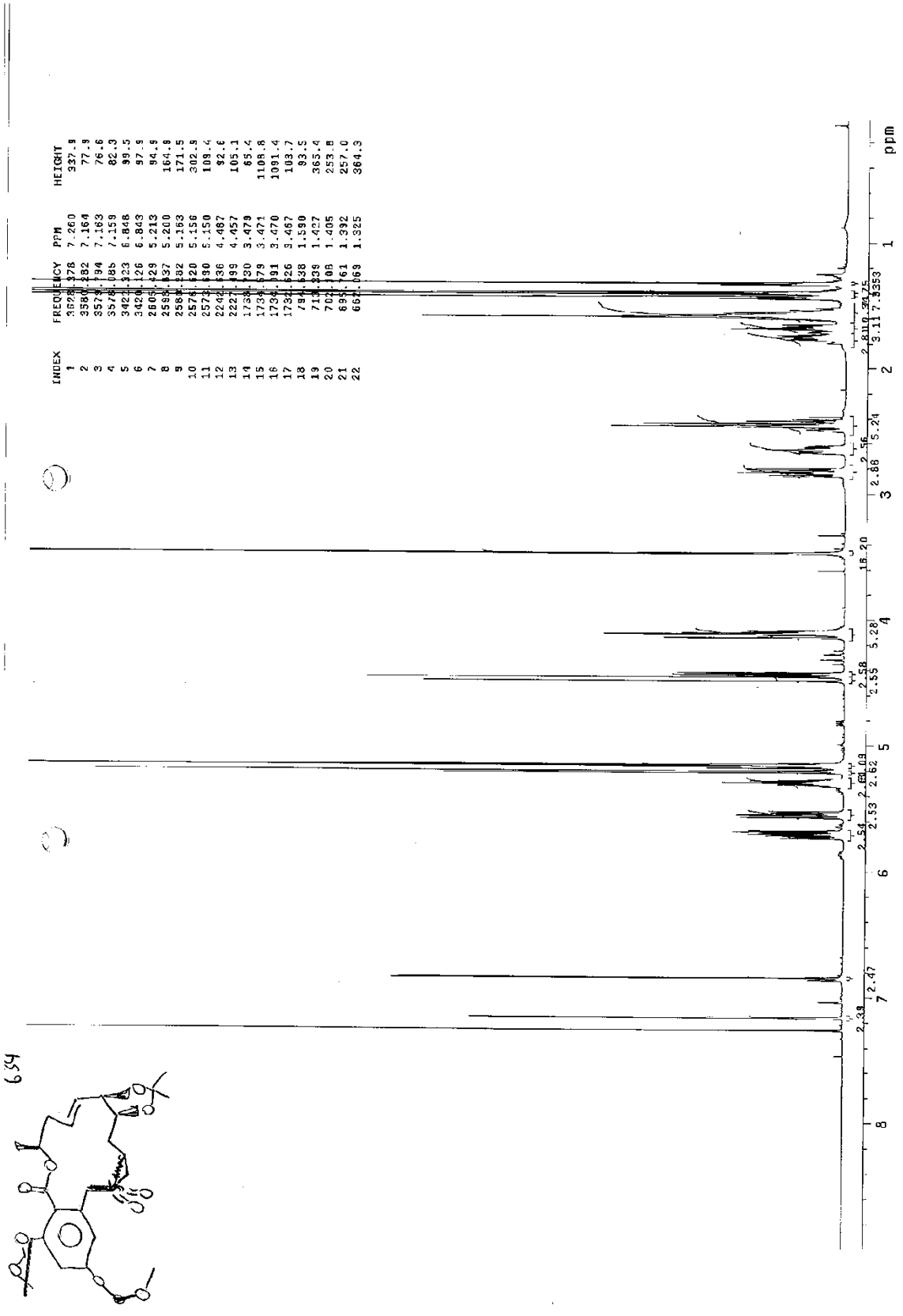
Supplementary Information: ^{1}H NMR spectrum of compound **3** (500 MHz, $CDCl_3$)



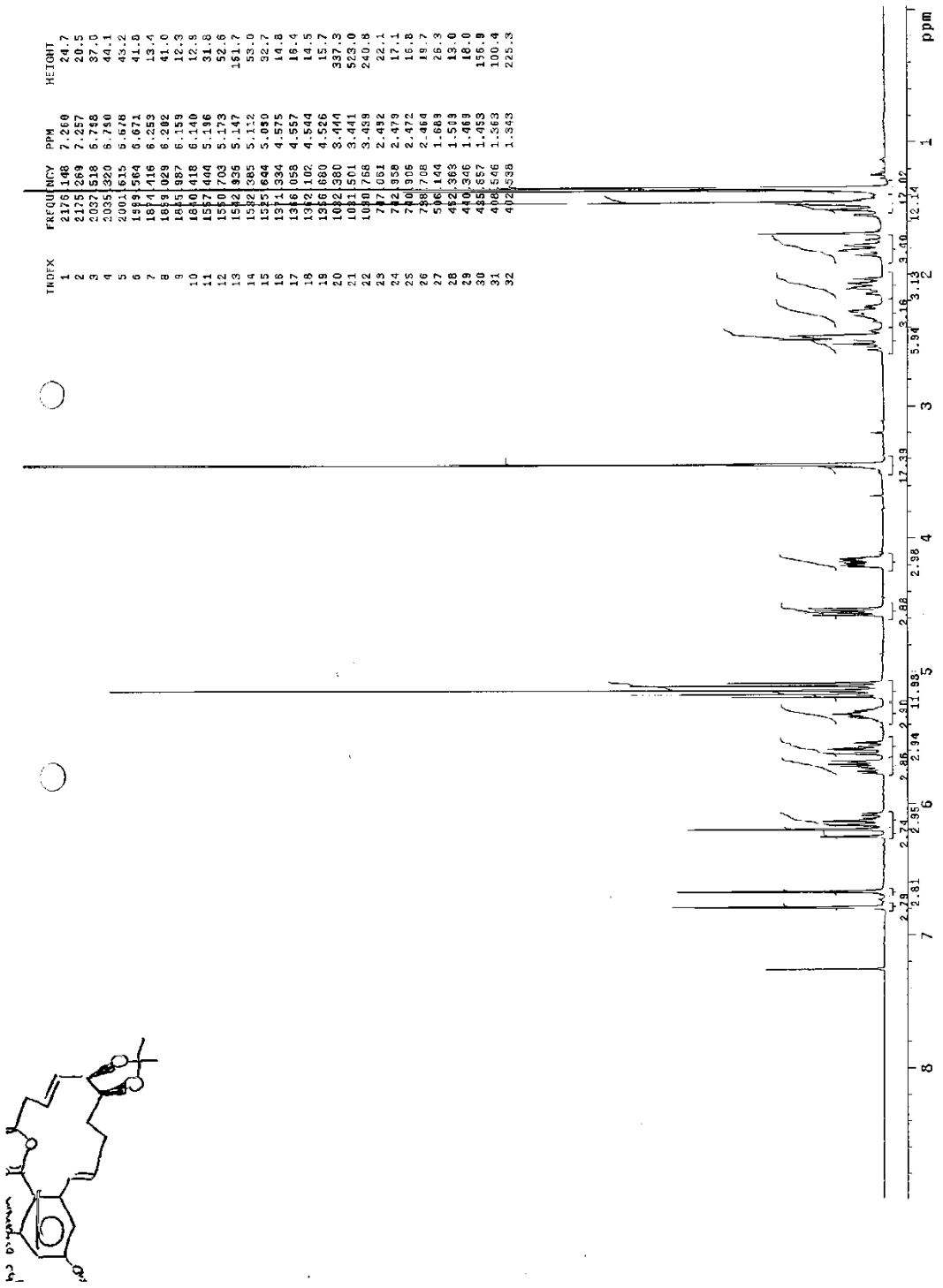
Supplementary Information: ^{1}H NMR spectrum of compound **2** (500 MHz, $CDCl_3$)



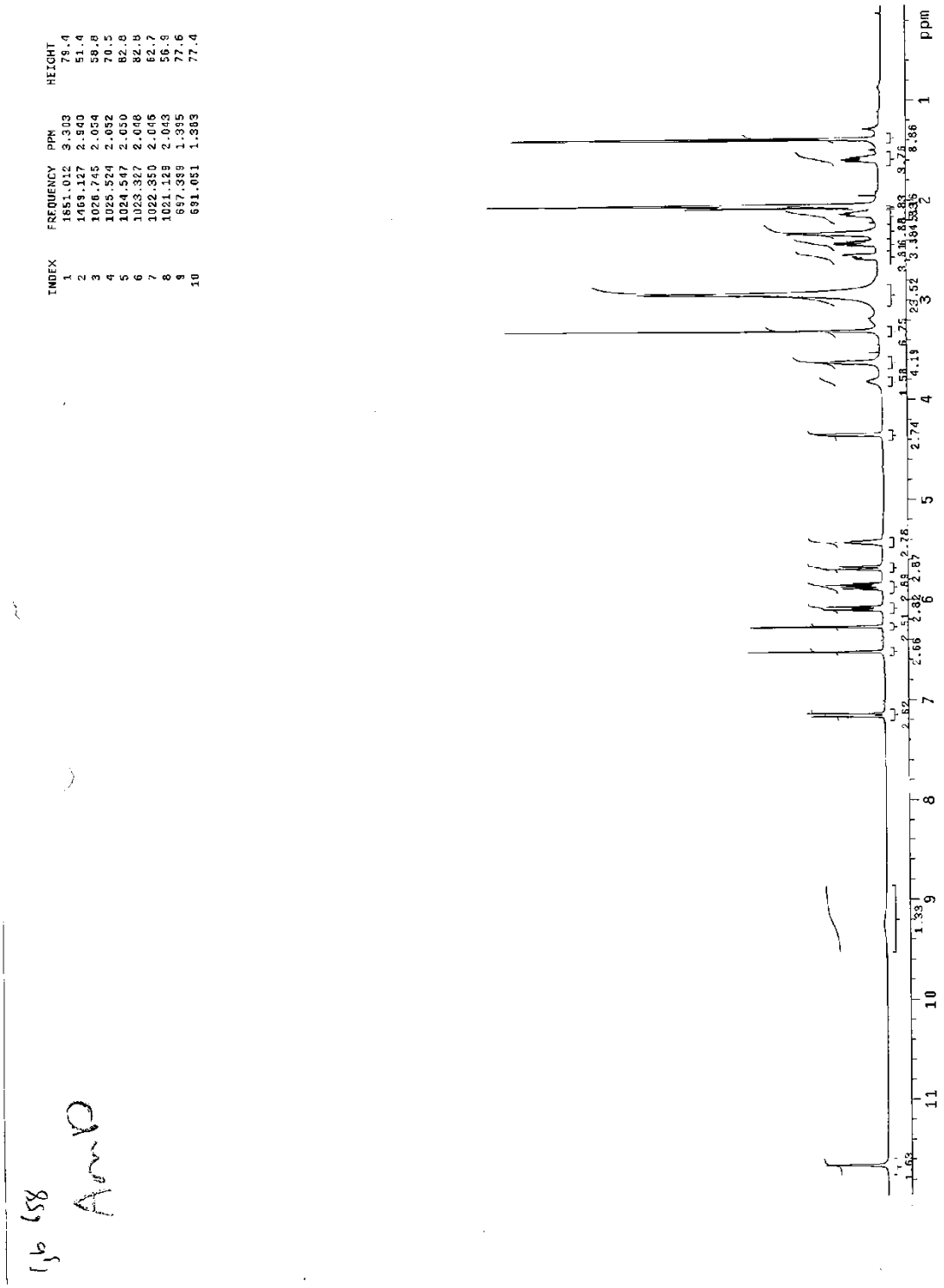
Supplementary Information: ^{1}H NMR spectrum of compound **19** (500 MHz, $CDCl_3$)



Supplementary Information: ^{1}H NMR spectrum of compound **20** (500 MHz, $CDCl_3$)



Supplementary Information: ^{1}H NMR spectrum of compound **1** (500 MHz, d_6-acetone)



Supplementary Information: ^{13}C NMR spectrum of compound **1** (500 MHz, d_6-acetone)