CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

Total Synthesis and Biological Activity of Neopeltolide and Analogues

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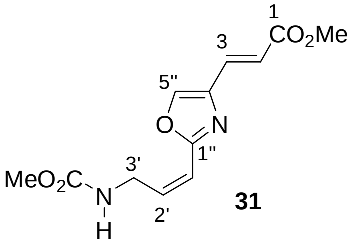
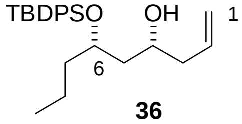
Remaining experimental details
^{1}H- and ^{13}C NMR spectra of important compounds

General. Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, dimethylformamide, methanol, ethyl acetate, benzene, and triethylamine were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under argon or nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used without purification. ^{1}H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K either in $CDCl_3$ or CD_3OD; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm), CD_3OD (δH 3.30, δC 49.0 ppm). Melting points: Büchi Melting Point B-540, uncorrected. HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Analytical LC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100-5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0-10-15-17-20 min with 20-80-80-99-99% acetonitrile, flow: 0.5 mL min^{-1}. Flash chromatography: J. T. Baker silica gel 43–60 mm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV254. Optical rotations: Perkin-Elmer Polarimeter 341, sodium D line (589 nm), *c* = g per 100 mL.



Methyl (2*E*)-3-(2-{(1Z)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)acrylate (31): To a solution of aldehyde **29** (67 mg, 0.32 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at ambient temperature was added (methoxycarbonylmethylene)triphenylphosphorane[1] (213.8 mg, 0.64 mmol, 2 equiv). The reaction mixture was stirred for 3 h, concentrated in vacuo and purified by flash column chromatography (CH_2Cl_2/MeOH, 98:2) to afford unsaturated ester **31** (78.3 mg, 92%) as a colorless solid; m.p. 117–118 °C. TLC (CH_2Cl_2/MeOH, 9:1): $R_f = 0.59$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.67$ (s, 3H, 4'-OCH_3), 3.71 (s, 3H, 1-OCH_3), 4.33–4.40 (m, 2H, 3'-H), 5.49 (br s, 1H, NH), 6.13–6.24 (m, 1H, 2'-H), 6.30 (d, $J = 11.9$ Hz, 1H, 1'-H), 6.63 (d, $J = 15.4$ Hz, 1H, 2-H), 7.48 (d, $J = 15.4$ Hz, 1H, 3-H), 7.72 (s, 1H, 5''-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 39.4$ (C-3'), 51.7 (OCH_3), 52.2 (OCH_3), 115.6 (C-1'), 120.0 (C-2), 132.1 (C-5''), 138.1 (C-4''), 138.5 (C-3), 139.0 (C-2'), 157.2 (CO_2CH_3), 160.7 (C-2''), 167.1 (C-1); HRMS (ESI): calcd for $C_{12}H_{14}NaN_2O_5$ $[M+Na]^+$: 289.07949, found 289.07953.



36

(4*R*,6*S*)-6-{[*tert*-Butyl(diphenyl)silyl]oxy}non-1-en-4-ol (36): To a cooled (–20 °C) solution of (*S*,*S*)-**6** (22.3 g, 40.4 mmol, 1.1 equiv) in CH_2Cl_2 (190 mL) was added aldehyde[2] **5** (13.0 g, 36.7 mmol, 1.0 equiv). The reaction mixture was then placed into a freezer (–10 °C) and maintained at that temperature for 24 h (without stirring). The reaction was quenched while cold with 1N HCl (100 mL) and EtOAc (100 mL) and the mixture was vigorously stirred at room temperature for 15 min. The obtained white precipitate of (*S*,*S*)-*N*,*N*'-bis-(4-bromobenzyl)-cyclohexane-1,2-diamine dihydrochloride was filtered, washed with Et_2O (3 × 50 mL) and dried in vacuo (recovered 18.6 g, 91% of (*S*,*S*)-diamine dihydrochloride). The filtrate layers were separated and the aqueous layer

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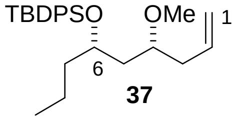
[1] a) R. W. Lang, H. J. Hansen, *Org. Synth.* **1984**, *62*, 202-209; *Org. Synth., Coll. Vol. 7*, **1990**, 232-236, b) T. M. Werkhoven, R. Van Nispen, J. Lugtenburg, *Eur. J. Org. Chem.* **1999**, 2909-2914.

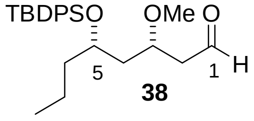
[2] V. V. Vintonyak, M. E. Maier, *Org. Lett.* **2008**, *10*, 1239-1242.

was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with H_2O (100 mL), saturated NaCl solution (100 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash chromatography (petroleum ether/EtOAc, 20:1? 10:1) to give homoallylic alcohol **36** (12.30 g, 85%) as a colorless oil. TLC (petroleum ether/EtOAc, 10:1): $R_f = 0.41$; $[\alpha]^{20}_D = +6.7$ (*c* 3.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.62$ (t, $J = 7.3$ Hz, 3H, 8-CH_3), 1.06 (s, 9H, $Si(C(CH_3)_3)$), 1.13–1.45 (m, 4H, 7-H, 8-H), 1.59–1.67 (m, 2H, 5-H), 2.08–2.21 (m, 2H, 3-H), 2.66 (d, $J = 3.0$ Hz, 1H, OH), 3.80–3.90 (m, 1H, 4-H), 3.93–4.02 (m, 1H, 6-H), 5.03–5.07 (m, 1H, 1-H), 5.08–5.10 (m, 1H, 1-H), 5.70–5.84 (m, 1H, 2-H), 7.35–7.47 (m, 6H, *m*CH, *p*CH ar Ph), 7.69–7.74 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$ (8-CH_3), 18.0 (C-8), 19.3 ($Si(\mathit{C}(CH_3)_3)$), 27.0 ($Si(C(\mathit{C}H_3)_3)$), 39.4 (C-7), 42.0 (C-3), 42.6 (C-5), 69.4 (C-4), 73.3 (C-6), 117.6 (C-1), 127.5, 127.6, 129.6, 129.7, 133.7, 134.4 (C of $SiPh_2$), 134.7 (C-2), 134.8, 135.9 (C of $SiPh_2$); HRMS (ESI): calcd for $C_{25}H_{36}NaO_2Si$ $[M+Na]^+$: 419.23768, found 419.23758.



37

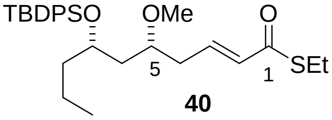
***tert*-Butyl{[(1*S*,3*R*)-3-methoxy-1-propylhex-5-enyl]oxy}diphenylsilane (37):** To a solution of alcohol **36** (8.51 g, 21.4 mmol) in CH_2Cl_2 (220 mL) in the dark at room temperature was added Me_3OBF_4 (11.1 g, 74.9 mmol) and proton sponge (22.9 g, 107 mmol). The mixture was allowed to stir for 48 h. After complete reaction (monitoring by TLC) H_2O was added (50 mL) and the mixture extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 1N HCI, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 40:1? 20:1) afforded methyl ether **37** (7.64 g, 87% yield) as a colorless oil. TLC (petroleum ether/EtOAc, 10:1): $R_f = 0.57$; $[\alpha]^{20}_D = -7.9$ (*c* 2.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.74$ (t, $J = 7.3$ Hz, 3H, 8-CH_3), 1.08 (s, 9H, $Si(C(CH_3)_3)$), 1.15–1.36 (m, 2H, 8-H), 1.37–1.60 (m, 3H, 7-H, 5-H), 1.74–1.82 (m, 1H, 5-H), 1.99–2.08 (m, 1H, 3-H), 2.10–2.19 (m, 1H, 3-H), 3.23 (s, 3H, OCH_3), 3.34–3.42 (m, 1H, 4-H), 3.81–3.89 (m, 1H, 6-H), 4.92–5.02 (m, 2H, 1-H), 5.64–5.77 (m, 1H, 2-H), 7.35–7.46 (m, 6H, *m*CH, *p*CH ar Ph), 7.68–7.74 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (8-CH_3), 17.9 (C-8), 19.4 ($Si(\mathit{C}(CH_3)_3)$), 27.1 ($Si(C(\mathit{C}H_3)_3)$), 37.6 (C-3), 39.1 (C-7), 40.1 (C-5), 56.0 (OCH_3), 70.6 (C-6), 77.2 (C-4), 116.8 (C-1), 127.4, 127.5, 129.4, 129.5, 134.4, 134.6 (C of $SiPh_2$), 134.7 (C-2), 135.9 (C of $SiPh_2$); HRMS (ESI): calcd for $C_{26}H_{38}NaO_2Si$ $[M+Na]^+$: 433.25333, found 433.25335.



38

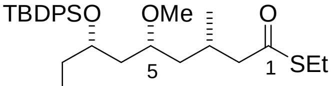
(3*S*,5*S*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-methoxyoctanal (38): To a solution of alkene **37** (6.50 g, 15.9 mmol) in a mixture of THF/*t*BuOH (200/40 mL) was added 4-methyl-morpholine-N-oxide (4.30 g, 31.8 mmol) and an aqueous solution of OsO_4 (10 mL of a 0.032M solution, 0.32 mmol, 2 mol%, prepared from $K_2OsO_4{\cdot}2H_2O$ (118 mg, 0.32 mmol)) at 0 ºC. After being stirred at room temperature for 20 h, 10% $Na_2S_2O_3$ solution (50 mL) was added to the mixture. After 30 min, the diol was extracted with EtOAc and the combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel followed by rinsing the pad with EtOAc. Removal of the solvent from the combined filtrate gave the crude diol. $NaIO_4$ (5.1 g, 24.0 mmol, 1.5 equiv) was added to a solution of crude diol in 90% MeOH (200 mL). After stirring at room temperature for 1 h, most of the methanol was removed in vacuo and the residue extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with water, saturated NaCl solution, dried over $MgSO_4$, and filtered. After concentration, the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1? 5:1) to give aldehyde **38** as a colorless oil (6.11 g, 93% for 2 steps).

TLC (petroleum ether/EtOAc, 10:1): *R*$_f$ = 0.37; $[\alpha]^{20}_D$ = –3.6 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.3 Hz, 3H, 7-CH_3), 1.05 (s, 9H, Si($C(CH_3)_3$)), 1.14–1.33 (m, 2H, 7-H), 1.38–1.60 (m, 3H, 6-H, 4-H), 1.86–1.94 (m, 1H, 4-H), 2.15–2.30 (m, 2H, 2-H), 3.21 (s, 3H, OCH_3), 3.72–3.82 (m, 2H, 3-H, 5-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.63–7.69 (m, 4H, *o*CH ar Ph), 9.54–9.57 (m, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (7-CH_3), 17.9 (C-7), 19.3 (Si(*C*(CH_3)$_3$)), 27.1 (Si(C(*C*H$_3$)$_3$)), 39.2 (C-6), 40.1 (C-4), 47.9 (C-2), 56.3 (OCH_3), 70.2 (C-5), 73.5 (C-3), 127.5, 127.6, 129.6, 129.7, 134.0, 134.3, 135.9, 135.9 (C of $SiPh_2$), 201.5 (C-1); HRMS (ESI): calcd for $C_{25}H_{36}NaO_3Si$ $[M+Na]^+$: 435.23259, found 435.23257.



40

***S*-Ethyl (2*E*,5*R*,7*S*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-5-methoxydec-2-enethioate (40):** A solution of aldehyde **38** (6.10 g, 14.8 mmol) and ylide[3] **39** (8.1 g, 22.2 mmol) in CH_2Cl_2 (250 mL) was heated at reflux for 10 h. The solution was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 40:1? 20:1) to afford the desired α,β-unsaturated thioester **40** as a colorless oil (6.71 g, 91%). TLC (petroleum ether/EtOAc, 10:1): *R*$_f$ = 0.51; $[\alpha]^{20}_D$ = –22.3 (*c* 3.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.3 Hz, 3H, 9-CH_3), 1.05 (s, 9H, Si($C(CH_3)_3$)), 1.14–1.33 (m, 5H, 9-H, SCH_2C*H*$_3$), 1.38–1.52 (m, 3H, 6-H, 8-H), 1.76–1.84 (m, 1H, 6-H), 1.99–2.08 (m, 1H, 4-H), 2.13–2.20 (m, 1H, 4-H), 2.93 (q, *J* = 14.7 Hz, 2H, SC*H*$_2$CH$_3$), 3.21 (s, 3H, OCH_3), 3.37–3.43 (m, 1H, 5-H), 3.75–3.80 (m, 1H, 7-H), 5.96 (d, *J* = 15.7 Hz, 1H, 2-H), 6.70–6.79 (m, 1H, 3-H), 7.34–7.46 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.70 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (9-CH_3), 14.8 (SCH_2*C*H$_3$), 18.0 (C-9), 19.3 (Si(*C*(CH_3)$_3$)), 23.0 (S*C*H$_2$CH$_3$), 27.1 (Si(C(*C*H$_3$)$_3$)), 36.2 (C-4), 39.2 (C-8), 40.3 (C-6), 56.3 (OCH_3), 70.3 (C-7), 76.5 (C-5), 127.4, 127.6, 129.5, 129.7 (C of $SiPh_2$), 130.5 (C-2), 134.1, 134.4, 135.9 (C of $SiPh_2$), 141.3 (C-3), 189.8 (C-1); HRMS (ESI): calcd for $C_{29}H_{42}NaO_3SSi$ $[M+Na]^+$: 521.25161, found 521.25170.



41

***S*-Ethyl (3*S*,5*R*,7*S*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-5-methoxy-3-methyldecanethioate (41):** CuBr·Me_2S (7.1 mg, 0.034 mmol, 3 mol%) and (*S*,*R*$_{Fe}$)-Josiphos **9** (26.0 mg, 0.04 mmol, 3.6 mol%) were dissolved in *t*BuOMe (10 mL) and stirred at room temperature for 30 min under nitrogen. The mixture was cooled to –75 °C and MeMgBr (3M solution in Et_2O, 465 µL, 1.4 mmol, 1.2 equiv) was added dropwise. After stirring for 10 min, a solution of unsaturated thioester **40** (572 mg, 1.15 mmol, 1 equiv) in *t*BuOMe (1.2 mL) was added via a syringe pump over 2 h. The reaction mixture was stirred at –75 °C for 12 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl solution was then added, the phases were separated and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 30:1? 20:1) to afford the desired 1,4-addition adduct **41** as a colorless oil (501 mg, 85%). TLC (petroleum ether/EtOAc, 10:1): *R*$_f$ = 0.57; $[\alpha]^{20}_D$ = –6.8 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.3 Hz, 3H, 9-CH_3), 0.86 (d, *J* = 6.6 Hz, 3H, 3-CH_3), 1.04 (s, 9H, Si($C(CH_3)_3$)), 1.14–1.31 (m, 7H, 4-H, 9-H, SCH_2C*H*$_3$), 1.34–1.53 (m, 3H, 6-H, 8-H), 1.72–1.81 (m, 1H, 6-H), 2.00–2.12 (m, 1H, 3-H), 2.13–2.21 (m, 1H, 2-H), 2.48 (dd, *J* = 14.4, 4.8 Hz, 1H, 2-H), 2.86 (q, *J* = 14.9 Hz, 2H, SC*H*$_2$CH$_3$), 3.16 (s, 3H, OCH_3), 3.24–3.30 (m, 1H, 5-H), 3.76–3.82 (m, 1H, 7-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.69 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (9-CH_3), 14.8 (SCH_2*C*H$_3$), 17.9 (C-9), 19.4 (Si(*C*(CH_3)$_3$)), 20.2 (3-CH_3), 23.2 (S*C*H$_2$CH$_3$),

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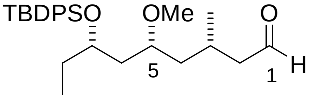
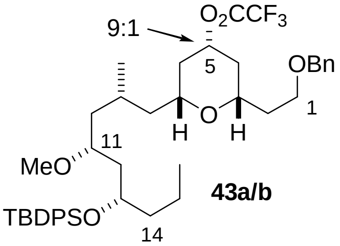
[3] G. E. Keck, E. P. Boden, S. A. Mabury, *J. Org. Chem.* **1985**, *50*, 709-710.

27.1 (Si(C(CH_3)$_3$)), 27.8 (C-3), 39.0 (C-8), 40.6 (C-6), 41.2 (C-4), 50.8 (C-2), 55.7 (OCH_3), 70.6 (C-7), 75.9 (C-5), 127.4, 127.5, 129.5, 129.5, 134.3, 134.6, 136.0 (C of $SiPh_2$), 199.0 (C-1); HRMS (ESI): calcd for $C_{30}H_{46}NaO_3SSi$ $[M+Na]^+$: 537.28291, found 537.28327.



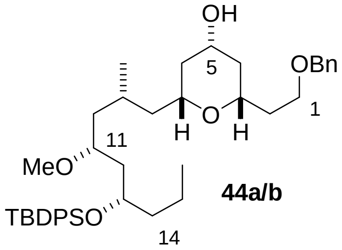
42

(3*S*,5*R*,7*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-5-methoxy-3-methyldecanal (42): To a stirred mixture of the thioester **41** (470 mg, 0.92 mmol) and Pd/C (47.0 mg, 10% wt) in CH_2Cl_2 (5 mL) was added Et_3SiH (438 µL, 2.76 mmol, 3 equiv) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 30 min. The catalyst was filtered off through a pad of celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 10:1? 5:1) to give the pure aldehyde **42** (397 mg, 95%) as a colorless oil. TLC (petroleum ether/EtOAc, 10:1): $R_f = 0.36$; $[\alpha]^{20}_D = -3.0$ (*c* 1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.73$ (t, $J = 7.3$ Hz, 3H, 9-CH_3), 0.87 (d, $J = 6.3$ Hz, 3H, 3-CH_3), 1.04 (s, 9H, Si(C(CH_3)$_3$)), 1.14–1.30 (m, 4H, 4-H, 9-H), 1.37–1.52 (m, 3H, 6-H, 8-H), 1.73–1.83 (m, 1H, 6-H), 1.98–2.09 (m, 2H, 2-H, 3-H), 2.25–2.32 (m, 1H, 2-H), 3.14 (s, 3H, OCH_3), 3.25–3.32 (m, 1H, 5-H), 3.76–3.81 (m, 1H, 7-H), 7.33–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.64–7.70 (m, 4H, *o*CH ar Ph), 9.61–9.64 (m, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (9-CH_3), 18.0 (C-9), 19.4 (Si(*C*(CH_3)$_3$)), 20.8 (3-CH_3), 24.7 (C-3), 27.1 (Si(C(CH_3)$_3$)), 39.2 (C-8), 40.3 (C-6), 41.1 (C-4), 50.5 (C-2), 55.4 (OCH_3), 70.6 (C-7), 75.7 (C-5), 127.4, 127.5, 129.5, 129.6, 134.3, 134.5, 136.0 (C of $SiPh_2$), 202.9 (C-1); HRMS (ESI): calcd for $C_{28}H_{42}NaO_3Si$ $[M+Na]^+$: 477.28009, found 477.27978.



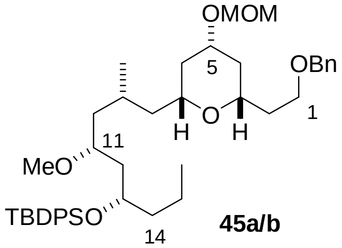
43a/b

Trifluoroacetate 43a/b (Prins cyclization): Trifluoroacetic acid (0.78 ml, 8.2 mmol, 10 equiv) was added to a solution of alcohol[2] **12** (220 mg, 1.07 mmol, 1.3 equiv) and aldehyde **42** (372 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) at –5 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at this temperature and then saturated aqueous $NaHCO_3$ solution (10 mL) was added dropwise. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, concentrated in vacuo and purified by column flash chromatography (petroleum ether/EtOAc, 15:1? 10:1) to afford trifluoroacetate **43a/b** (major/minor = 9:1) as a colorless oil (437 mg, 71%). TLC (petroleum ether/EtOAc, 4:1): $R_f = 0.75$; $[\alpha]^{20}_D = -2.7$ (*c* 3.8, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.65$ (t, $J = 7.3$ Hz, 3H, 16-H), 0.76 (d, $J = 6.8$ Hz, 3H, 9-CH_3), 0.98 (s, 9H, Si(C(CH_3)$_3$)), 1.03–1.54 (m, 12H, 14-H, 15-H, 6-H, 8-H, 2-H, 10-H), 1.64–1.82 (m, 3H, 12-H, 9-H), 1.84–2.00 (m, 2H, 4-H), 3.10 (s, 3H, OCH_3), 3.19–3.37 (m, 2H, 7-H, 3-H), 3.41–3.60 (m, 3H, 11-H, 1-H), 3.70–3.79 (m, 1H, 13-H), 4.40 (s, 2H, $PhCH_2O$), 4.96–5.07 (m, 1H, 5-H), 7.18–7.37 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.59–7.67 (m, 4H, *o*CH ar $SiPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (C-16), 17.9 (C-15), 19.4 (Si(*C*(CH_3)$_3$)), 19.9 (9-CH_3), 25.6 (C-9), 26.5, 27.1 (Si(C(CH_3)$_3$)), 36.1 (C-2), 36.7 (C-4), 37.3 (C-10), 39.0 (C-6), 40.9 (C-14), 42.3 (C-12), 42.9 (C-8), 55.7 (OCH_3), 66.4 (C-1), 70.6 (C-13), 71.9 (C-11), 72.5 (C-7), 73.1 (Ph*C*H_2O), 75.4 (C-5), 76.0 (C-3), 114.5 (q, $J = 286$ Hz, CF_3), 127.4, 127.4, 127.6, 127.6, 127.7, 128.4, 129.5, 129.6, 134.4, 134.5, 135.9, 138.3 (C of $SiPh_2$ and Ph of Bn), 156.9 (q, $J = 42$ Hz, $COCF_3$); HRMS (ESI): calcd for $C_{43}H_{59}F_3NaO_6Si$ $[M+Na]^+$: 779.39252, found 779.39261.



44a/b

Tetrahydropyran 44a/b: To a solution of trifluoracetate **43a/b** (360 mg, 0.476 mmol) in methanol (5 mL) were added K_2CO_3 (131 mg, 0.95 mmol) and water (0.2 ml). The reaction mixture was stirred at room temperature for 1 h, then diluted with water (5 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 3:1? 2:1) provided alcohol **44a/b** (290 mg, 92% yield) as a colorless oil. TLC (petroleum ether/EtOAc, 2:1): $R_f = 0.30$; $[\alpha]^{20}_D = -19.1$ (c 1.8, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): data for major isomer: $\delta = 0.65$ (t, $J = 7.3$ Hz, 3H, 16-H), 0.76 (d, $J = 6.6$ Hz, 3H, 9-CH_3), 0.98 (s, 9H, Si(C(CH_3)$_3$)), 1.02–1.54 (m, 12H, 14-H, 15-H, 6-H, 8-H, 2-H, 10-H), 1.62–1.80 (m, 5H, 12-H, 9-H, 4-H, 2-H), 1.83–1.89 (m, 1H, 4-H), 3.10 (s, 3H, OCH_3), 3.20–3.30 (m, 2H, 7-H, 11-H), 3.34–3.42 (m, 1H, 3-H), 3.47–3.58 (m, 2H, 1-H), 3.64–3.81 (m, 2H, 5-H, 13-H), 4.41 (s, 2H, $PhCH_2O$), 7.18–7.34 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.59–7.64 (m, 4H, *o*CH ar $SiPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (C-16), 17.8 (C-15), 19.4 (Si(*C*(CH_3)$_3$)), 19.9 (9-CH_3), 25.8 (C-9), 27.1 (Si(C(*C*H_3)$_3$)), 36.2 (C-2), 38.9 (C-10), 41.0 (C-4), 41.4 (C-6), 41.9 (C-14), 42.4 (C-12), 43.2 (C-8), 55.7 (OCH_3), 66.8 (C-1), 68.3 (C-13), 70.7 (C-5), 72.2 (C-11), 72.9 (C-7), 73.1 (Ph*C*H_2O), 76.1 (C-3), 127.4, 127.4, 127.5, 127.6, 128.3, 129.4, 129.4, 134.4, 134.6, 135.9, 135.9, 138.5 (C of $SiPh_2$ and Ph of Bn); HRMS (ESI): calcd for $C_{41}H_{60}NaO_5Si$ $[M+Na]^+$: 683.41022, found 683.41103.



45a/b

Methoxymethyl ether 45a/b: To a stirred, cooled (0 °C) solution of alcohol **44a/b** (278 mg, 0.44 mmol) in DMF (2 mL) were added *N*,*N*-diisopropylethylamine (0.68 mL, 4.0 mmol), chloromethylmethyl ether[4] (182 µL, 2.4 mmol), and tetrabutylammonium iodide (15 mg, 0.04 mmol). The reaction mixture was warmed to room temperature. After stirring for 4 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added followed by Et_2O (20 mL). After separation of the layers, the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with 1N HCl, saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 5:1) afforded MOM ether **45a/b** (304 mg, 98% yield) as a colorless oil. TLC (petroleum ether/EtOAc, 4:1): $R_f = 0.58$; $[\alpha]^{20}_D = -6.5$ (c 3.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): data for major isomer: $\delta = 0.65$ (t, $J = 7.3$ Hz, 3H, 16-H), 0.76 (d, $J = 6.6$ Hz, 3H, 9-CH_3), 0.99 (s, 9H, Si(C(CH_3)$_3$)), 1.03–1.55 (m, 11H, 14-H, 15-H, 6-H, 8-H, 2-H, 10-H), 1.64–1.94 (m, 6H, 12-H, 9-H, 4’-H, 2-H), 3.10 (s, 3H, CHOC*H*$_3$), 3.20–3.28 (m, 2H, 7-H, 11-H), 3.31 (s, 3H, CH_2OC*H*$_3$), 3.35–3.43 (m, 1H, 3-H), 3.46–3.59 (m, 2H, 1-H), 3.61–3.71 (m, 1H, 5-H), 3.73–3.81 (m, 1H, 13-H), 4.41 (s, 2H, $PhCH_2O$), 4.63 (s, 2H, C*H*$_2$OCH_3), 7.17–7.37 (m, 11H, *m*CH, *p*CH ar $SiPh_2$, Ph of Bn), 7.57–7.65 (m, 4H, *o*CH ar $SiPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (C-16), 17.8 (C-15), 19.4 (Si(*C*(CH_3)$_3$)), 19.9 (9-CH_3), 25.8 (C-9), 27.1 (Si(C(*C*H_3)$_3$)), 36.3 (C-2), 38.7 (C-4), 38.9 (C-10), 39.3 (C-6), 41.0 (C-

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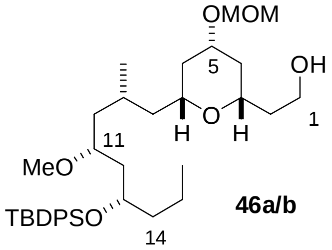
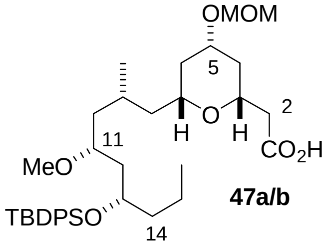
[4] M. Reggelin, S. Doerr, *Synlett* **2004**, 1117.

14), 42.5 (C-12), 43.3 (C-8), 55.2 (CH_2OCH_3), 55.8 (CHO*C*H_3), 66.8 (C-1), 70.7 (C-13), 72.3 (C-11), 72.9 (C-7), 73.1 (Ph*C*H_2O), 73.2 (C-5), 76.1 (C-3), 94.3 (*C*H_2OCH_3), 127.4, 127.4, 127.5, 127.6, 128.3, 129.4, 129.4, 134.4, 134.7, 135.9, 138.5 (C of $SiPh_2$ and Ph of Bn); HRMS (ESI): calcd for $C_{43}H_{64}NaO_6Si$ $[M+Na]^+$: 727.43644, found 727.43571.



46a/b

Primary alcohol 46a/b: A Parr hydrogenation vessel was charged with benzyl ether **45a/b** (195 mg, 0.276 mmol), Pd/C (20 mg), methanol (20 mL), attached to a hydrogen source and hydrogen was introduced into the reaction vessel until the pressure gauge indicated 2 atm. The pressure was carefully released to 1 atm by opening the stop valve. This procedure was repeated three times, and finally hydrogen was pressurized to 5 atm. The reaction mixture was vigorously shaken at room temperature for 10 h during which time the hydrogen cylinder was kept connected. After the stop valve was opened, excess hydrogen was carefully bled off, and the apparatus was disassembled. The catalyst was filtered off through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give the alcohol **46a/b** (158 mg, 93%) as a colorless oil. TLC (petroleum ether/EtOAc, 2:1): $R_f = 0.27$; $[\alpha]^{20}_D = +6.0$ (*c* 2.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): data for major isomer: $\delta = 0.70$ (t, $J = 7.3$ Hz, 3H, 16-H), 0.82 (d, $J = 6.6$ Hz, 3H, 9-CH_3), 1.04 (s, 9H, $Si(C(CH_3)_3)$), 1.06–1.60 (m, 11H, 14-H, 15-H, 6-H, 8-H, 2-H, 10-H), 1.65–1.80 (m, 4H, 12-H, 9-H, 2-H), 1.84–1.97 (m, 2H, 4-H), 2.58 (br s, 1H, OH), 3.14 (s, 3H, CHOC*H*$_3$), 3.26–3.40 (m, 5H, 7-H, 11-H, CH_2OC*H*$_3$), 3.46–3.55 (m, 1H, 3-H), 3.65–3.84 (m, 4H, 1-H, 5-H, 13-H), 4.69 (s, 2H, C*H*$_2OCH_3$), 7.31–7.43 (m, 6H, *m*CH, *p*CH ar $SiPh_2$), 7.64–7.70 (m, 4H, *o*CH ar $SiPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$ (C-16), 17.9 (C-15), 19.4 (Si(*C*$(CH_3)_3$)), 20.1 (9-CH_3), 25.8 (C-9), 27.1 (Si(C(*C*$H_3)_3$)), 37.9 (C-4), 38.6 (C-10), 39.0 (C-2), 39.0 (C-6), 40.8 (C-14), 42.4 (C-12), 43.0 (C-8), 55.3 (CH_2O*C*H_3), 55.5 (CHO*C*H_3), 61.3 (C-1), 70.7 (C-13), 72.9 (C-5), 73.6 (C-11), 75.7 (C-7), 75.9 (C-3), 94.4 (*C*H_2OCH_3), 127.4, 127.4, 129.4, 129.5, 134.4, 134.6, 135.9 (C of $SiPh_2$); HRMS (ESI): calcd for $C_{36}H_{58}NaO_6Si$ $[M+Na]^+$: 637.38949, found 637.38926.



47a/b

Acid 47a/b: a) Preparation of aldehyde: To a cooled (0 °C) solution of alcohol **46a/b** (155 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was added a solution of Dess-Martin periodinane[5] (15% wt, 0.83 mL, 0.4 mmol). After stirring for 0.5 h at 0 °C and for 2 h at room temperature, the reaction mixture was concentrated, loaded on a flash silica gel column, and eluted with petroleum ether/EtOAc, 4:1 to give 147 mg (96%) of the corresponding aldehyde, which was used directly in the next reaction. TLC (petroleum ether/EtOAc, 4:1): $R_f = 0.76$.

b) Preparation of acid 47a/b: The aldehyde obtained in the previous step (147 mg, 0.24 mmol) was dissolved in *t*BuOH (4 mL) and 2,3-dimethyl-2-butene (0.8 mL).[6] A solution of $NaClO_2$ (65

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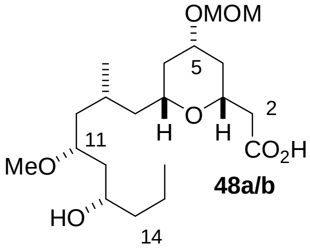
[5] R. K. Boeckman, Jr., P. Shao, J. J. Mullins, *Org. Synth.* **2000**, *77*, 141-152; *Org. Synth., Coll. Vol. 10*, **2004**, 696-702.

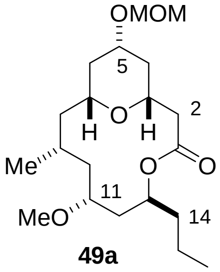
[6] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091-2096.

mg, 0.72 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (336 mg, 2.16 mmol) in water (3 mL) was added slowly at 0 °C. After stirring for 30 min at room temperature the mixture was diluted with water (5 mL), extracted with EtOAc (4 × 20 mL), washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1:0.01? 1:1:0.01) provided acid **47a/b** (151 mg, 98% yield) as a colorless oil. TLC (petroleum ether/EtOAc, 2:1): $R_f = 0.54$; $[\alpha]^{20}_D = -2.3$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): data for major isomer: δ = 0.70 (t, *J* = 7.3 Hz, 3H, 16-H), 0.80 (d, *J* = 6.6 Hz, 3H, 9-CH_3), 1.04 (s, 9H, $Si(C(CH_3)_3)$), 1.06–1.60 (m, 12H, 14-H, 15-H, 6-H, 8-H, 9-H, 10-H), 1.69–1.81 (m, 2H, 12-H), 1.85–1.93 (m, 1H, 4-H), 2.01–2.08 (m, 1H, 4-H), 2.42–2.62 (m, 2H, $\mathrm{C}\mathit{H}_2\mathrm{COOH}$), 3.15 (s, 3H, $\mathrm{CHOC}\mathit{H}_3$), 3.26–3.43 (m, 5H, 7-H, 11-H, $\mathrm{CH_2OC}\mathit{H}_3$), 3.66–3.84 (m, 3H, 3-H, 5-H, 13-H), 4.69 (s, 2H, $\mathrm{C}\mathit{H}_2\mathrm{OCH_3}$), 7.31–7.43 (m, 6H, *m*CH, *p*CH ar $SiPh_2$), 7.65–7.70 (m, 4H, *o*CH ar $SiPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (C-16), 17.9 (C-15), 19.4 ($\mathrm{Si(}\mathit{C}\mathrm{(CH_3)_3)}$), 20.1 (9-$CH_3$), 25.7 (C-9), 27.1 ($\mathrm{Si(C(}\mathit{C}\mathrm{H_3)_3)}$), 37.9 (C-4), 38.9 (C-10), 39.0 (C-6), 40.8 (C-14), 40.9 ($\mathit{C}\mathrm{H_2COOH}$), 42.3 (C-12), 42.9 (C-8), 55.3 ($\mathrm{CH_2O}\mathit{C}\mathrm{H_3}$), 55.7 ($\mathrm{CHO}\mathit{C}\mathrm{H_3}$), 70.7 (C-13), 71.9 (C-5), 72.7 (C-3), 73.7 (C-7), 76.0 (C-11), 94.5 ($\mathit{C}\mathrm{H_2OCH_3}$), 127.4, 127.5, 129.4, 129.5, 134.4, 134.6, 135.9 (C of $SiPh_2$), 174.5 ($\mathit{C}\mathrm{OOH}$); HRMS (ESI): calcd for $C_{36}H_{56}NaO_7Si$ $[M+Na]^+$: 651.36875, found 651.36884.



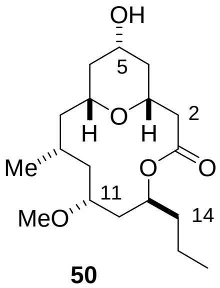
48a/b

Seco-acid 48a/b: To a solution of acid **47** (149 mg, 0.237 mmol) in THF (1 mL) was added $TBAF \cdot 3H_2O$ (450 mg, 1.44 mmol) at room temperature. The reaction mixture was stirred for 48 h. After addition of saturated NH_4Cl solution the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (10 ml), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc/HOAc, 1:1:0.01? 0:1:0.01) afforded seco-acid **48a/b** (92 mg, 99% yield) as a colorless oil. TLC (petroleum ether/EtOAc/HOAc, 2:1:0.01): $R_f = 0.2$; $[\alpha]^{20}_D = -18.8$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.94 (m, 6H, 16-H, 9-CH_3), 1.12–1.75 (m, 14H, 14-H, 15-H, 6-H, 8-H, 9-H, 10-H, 12-H), 1.86–1.94 (m, 1H, 4-H), 2.00–2.07 (m, 1H, 4-H), 2.42–2.60 (m, 2H, $\mathrm{C}\mathit{H}_2\mathrm{COOH}$), 3.31–3.47 (m, 8H, $\mathrm{CHOC}\mathit{H}_3$, 7-H, 11-H, $\mathrm{CH_2OC}\mathit{H}_3$), 3.68–3.83 (m, 3H, 3-H, 5-H, 13-H), 4.67 (s, 2H, $\mathrm{C}\mathit{H}_2\mathrm{OCH_3}$), 6.42 (br s, 2H, $\mathrm{O}\mathit{H}$, $\mathrm{COO}\mathit{H}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (C-16), 18.6 (C-15), 19.6 (9-CH_3), 26.3 (C-9), 38.0 (C-4), 38.8 (C-10), 39.7 (C-6), 40.8 (C-14), 40.9 ($\mathit{C}\mathrm{H_2COOH}$), 41.3 (C-12), 43.8 (C-8), 55.3 ($\mathrm{CH_2O}\mathit{C}\mathrm{H_3}$), 56.1 ($\mathrm{CHO}\mathit{C}\mathrm{H_3}$), 71.4 (C-5), 72.1 (C-13), 72.7 (C-11), 74.0 (C-7), 80.5 (C-3), 94.5 ($\mathit{C}\mathrm{H_2OCH_3}$), 174.4 ($\mathit{C}\mathrm{OOH}$); HRMS (ESI): calcd for $C_{20}H_{38}NaO_7$ $[M+Na]^+$: 413.25097, found 413.25110.



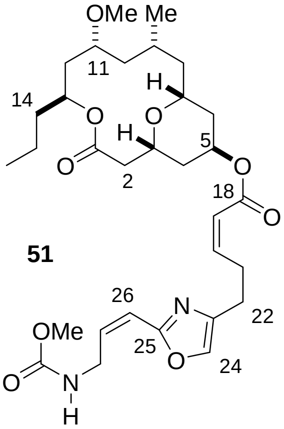
49a

Macrolactone 49a (11-*epi*): To an ice-cooled solution of seco-acid **48a/b** (85 mg, 0.21 mmol, 1.0 equiv) in THF (2.5 mL) was added Et_3N (177 µL, 1.26 mmol, 6.0 equiv) followed by 2,4,6-trichlorobenzoyl chloride (164 µL, 1.05 mmol, 5.0 equiv). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature, whereupon toluene (7.5 mL) was added. This solution was added over 8 h by syringe pump to a solution of DMAP (51 mg, 4.2 mmol, 20 equiv) in toluene (150 mL). Upon completion of the addition, stirring was maintained for an additional 2 h. The mixture was concentrated to dryness and filtered over silica gel (using petroleum ether/EtOAc 2:1 as eluant). The filtrate was concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc, 4:1) afforded lactone **49a** (69 mg, 85% yield) as a colorless oil and its 5-*epi* isomer **49b** (7.0 mg, 9% yield). TLC (petroleum ether/EtOAc, 2:1): R_f = 0.33; $[\alpha]^{20}_D$ = +10.8 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.84–0.90 (m, 6H, 15-CH_3, 9-CH_3), 1.07 (t, *J* = 11.7 Hz, 1H, 6-H), 1.14–1.50 (m, 8H, 6-H, 10-H, 12-H, 8-H, 14-H, 15-H), 1.56–1.64 (m, 1H, 14-H), 1.77–1.89 (m, 3H, 4-H, 8-H, 9-H), 1.96–2.01 (m, 1H, 4-H), 2.01–2.07 (m, 1H, 12-H), 2.31–2.38 (m, 1H, 2-H), 2.58–2.63 (m, 1H, 2-H), 3.18–3.25 (m, 1H, 7-H), 3.28–3.36 (m, 7H, 11-H, $CHOCH_3$, CH_2OCH_3), 3.63–3.73 (m, 2H, 3-H, 5-H), 4.65 (s, 2H, CH_2OCH_3), 4.86–4.94 (m, 1H, 13-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0 (C-16), 18.4 (C-15), 24.6 (9-CH_3), 28.9 (C-9), 37.2 (C-4), 37.9 (C-14), 38.1 (C-6), 39.3 (C-12), 40.2 (C-10), 42.6 (C-2), 44.2 (C-8), 55.2 (CH_2OCH_3), 56.1 ($CHOCH_3$), 71.3 (C-13), 71.5 (C-5), 72.7 (C-3), 76.7 (C-11), 77.0 (C-7), 94.4 (CH_2OCH_3), 170.2 (C-1); HRMS (ESI): calcd for $C_{20}H_{36}NaO_6$ $[M+Na]^+$: 395.24041, found 395.24036.



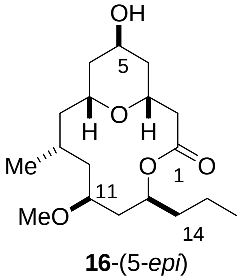
50

Hydroxylactone 50: To a cooled (0 °C) solution of MOM-ether **49a** (57.4 mg, 0.154 mmol) in MeOH (3 mL) was added concentrated HCl (100 µL). After stirring for 0.5 h at 0 °C and for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with EtOAc (4 × 20 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1? 1:1) provided alcohol **50** (48.6 mg, 96% yield) as a colorless oil. TLC (petroleum ether/EtOAc, 2:1): R_f = 0.24; $[\alpha]^{20}_D$ = +9.1 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_3OD): δ = 0.82–0.89 (m, 6H, 15-CH_3, 9-CH_3), 0.94–1.14 (m, 3H, 6-H, 8-H), 1.17–1.33 (m, 3H, 10-H, 9-H), 1.36–1.61 (m, 4H, 12-H, 14-H, 15-H), 1.69–1.86 (m, 3H, 14-H, 8-H, 4-H), 1.86–1.95 (m, 1H, 4H), 1.97–2.07 (m, 1H, 12-H), 2.16–2.24 (m, 1H, 2-H), 2.64–2.71 (m, 1H, 2-H), 3.23–3.35 (m, 5H, 7-H, 11-H, $CHOCH_3$), 3.61–3.72 (m, 2H, 3-H, 5-H), 4.83–4.93 (m, 1H, 13-H); ^{13}C NMR (150 MHz, CD_3OD): δ = 14.4 (C-16), 19.5 (C-15), 24.9 (9-CH_3), 30.5 (C-9), 38.1 (C-4), 39.1 (C-14), 41.3 (C-6), 41.6 (C-12), 42.9 (C-2), 43.5 (C-10), 45.4 (C-8), 56.5 ($CHOCH_3$), 68.4 (C-5), 72.3 (C-13), 72.9 (C-3), 78.2 (C-11), 78.5 (C-7), 172.5 (C-1); HRMS (ESI): calcd for $C_{18}H_{32}NaO_5$ $[M+Na]^+$: 351.21420, found 351.21413.



51

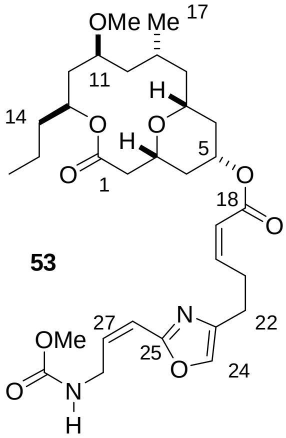
11-*epi*-neopeltolide (51): To a solution of alcohol **50** (7.6 mg, 0.023 mmol, 1 equiv), acid **23** (10.3 mg, 0.037 mmol, 1.6 equiv) and PPh_3 (10.5 mg, 0.040 mmol, 1.74 equiv) in absolute benzene (1 mL) was added diisopropyl azodicarboxylate (80 µL of a 0.5M solution in benzene, 0.040 mmol, 1.74 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (hexane/EtOAC, 2:1? 1:1? 1:2) to afford 11-*epi*-neopeltolide (**51**) (11.7 mg, 86%) as a colorless oil. TLC (petroleum ether/EtOAc, 1:1): R_f = 0.5; $[\alpha]^{20}_D$ = +19.4 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.88 (d, *J* = 6.8 Hz, 3H, 9-CH_3), 0.92 (t, *J* = 7.3 Hz, 3H, 16-H), 1.02–1.10 (m, 1H, 10-H), 1.20–1.42 (m, 5H, 8-H, 9-H, 15-H), 1.43–1.70 (m, 7H, 10-H, 4-H, 6-H, 14-H), 1.75–1.93 (m, 3H, 4-H, 14-H, 12-H), 2.06 (ddd, *J* = 14.1, 10.9, 3.0 Hz, 1H, 12-H), 2.21 (dd, *J* = 14.4, 11.1 Hz, 1H, 2-H), 2.66–2.73 (m, 3H, 2-H, 22-H), 2.96–3.04 (m, 2H, 21-H), 3.32–3.40 (m, 4H, 11-OCH_3, 7-H), 3.64 (s, 3H, 29-OCH_3), 3.75 (apt, *J* = 9.9 Hz, 1H, 11-H), 3.98–4.08 (m, 1H, 3-H), 4.29 (d, *J* = 5.1 Hz, 2H, 28-H), 4.90–4.98 (m, 1H, 13-H), 5.17–5.21 (m, 1H, 5-H), 5.85 (d, *J* = 11.4 Hz, 1H, 19-H), 5.98–6.07 (m, 1H, 27-H), 6.27 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.36 (dt, *J* = 11.5, 7.6 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.3 (C-16), 19.5 (C-15), 24.8 (C-17), 26.4 (C-22), 29.0 (C-21), 30.5 (C-9), 36.2 (C-4), 37.3 (C-6), 38.1 (C-14), 39.1 (C-10), 41.2 (C-12), 43.5 (C-2), 45.1 (C-8), 52.6 (29-OCH_3), 56.4 (11-OCH_3), 69.2 (C-5), 70.4 (C-3), 72.4 (C-13), 75.1 (C-7), 78.5 (C-11), 115.9 (C-26), 121.6 (C-19), 135.9 (C-24), 139.2 (C-27), 142.3 (C-23), 150.1 (C-20), 159.6 (C-29), 161.9 (C-25), 166.8 (C-18), 172.6 (C-1); HRMS (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+Na]^+$: 613.30955, found 613.30863.



16-(5-*epi*)

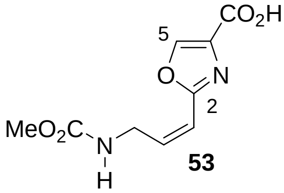
Deprotected macrolactone 16b (5-*epi*): To a cooled (0 °C) solution of MOM-ether **15b** (5-*epi*) (6.8 mg, 0.018 mmol) in MeOH (2 mL) was added concentrated HCl (70 µL). After stirring for 0.5 h at 0 °C and for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with EtOAc (4 × 10 mL), washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc/HOAc, 2:1? 1:1) provided alcohol **16b** (5-*epi*) (5.2 mg, 88% yield) as a colorless oil. TLC (petroleum ether/EtOAc, 1:1): R_f = 0.31; $[\alpha]^{20}_D$ = +7.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.94 (m, 6H, 15-CH_3, 9-CH_3), 1.11–1.22 (m, 3H, 6-H, 8-H), 1.23–1.44 (m, 6H, 10-H, 12-H, 8-H, 9-H), 1.45–1.80 (m, 6H, 10-H, 12-H, 14-H, 15-H, OH), 1.84–1.92 (m, 1H, 14-H), 1.92–2.02 (m, 2H, 4-H), 2.36 (dd, *J* = 12.1, 2.0 Hz, 1H, 2-H), 2.47 (dd, *J* = 12.1 Hz, 1H, 2-H), 3.00–3.07 (m, 1H, 11-H), 3.30 (s, 3H, $CHOCH_3$), 3.35–3.44 (m, 1H, 7-H), 3.55 (apt, *J* = 10.9 Hz, 1H, 3-H), 3.78–3.89 (m, 1H, 5-H), 5.04–5.12 (m, 1H, 13-H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 13.9 (C-16), 18.9 (C-15), 24.3 (9-CH_3), 24.4 (C-9), 36.9 (C-4), 39.3 (C-14), 39.7 (C-6), 40.8 (C-12), 42.0 (C-2), 42.4 (C-10), 45.1 (C-8), 56.9 (CHO*C*H_3), 67.9 (C-5), 72.8 (C-13), 74.1 (C-3), 74.8 (C-11), 76.9 (C-7), 172.7 (C-1); HRMS (ESI): calcd for $C_{18}H_{32}NaO_5$ $[M+Na]^+$: 351.21420, found 351.21429.



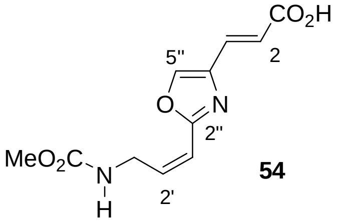
53

5-*epi*-neopeltolide (52): To a solution of alcohol **16b** (5-*epi*) (4.0 mg, 0.012 mmol, 1 equiv), acid **23** (5.4 mg, 0.019 mmol, 1.6 equiv) and PPh_3 (5.5 mg, 0.021 mmol, 1.75 equiv) in absolute benzene (0.7 mL) was added diisopropyl azodicarboxylate (42 µL of 0.5M solution in benzene, 0.021 mmol, 1.75 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (hexane/EtOAC, 2:1? 1:1? 1:2) to afford 5-*epi*-neopeltolide (**52**) (5.4 mg, 76%) as a colorless oil. TLC (petroleum ether/EtOAc, 1:1): R_f = 0.57; $[\alpha]^{20}_D$ = –3.3 (*c* 0.4, CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD): δ = 0.90–0.96 (m, 6H, 16-H, 9-CH_3), 1.11 (apt, *J* = 12.1 Hz, 1H, 10-H), 1.24–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.57 (m, 3H, 10-H, 4-H, 14-H), 1.57–1.93 (m, 8H, 6-H, 14-H, 4-H, 12-H), 2.28–2.37 (m, 2H, 2-H), 2.69 (t, *J* = 7.3 Hz, 2H, 22-H), 2.94–3.02 (m, 2H, 21-H), 3.12–3.20 (m, 1H, 11-H), 3.64 (s, 3H, 29-OCH_3), 3.71–3.81 (m, 1H, 7-H), 3.89–4.01 (m, 1H, 3-H), 4.29 (d, *J* = 4.6 Hz, 2H, 28-H), 4.95–5.03 (m, 1H, 13-H), 5.19–5.23 (m, 1H, 5-H), 5.82 (d, *J* = 11.6 Hz, 1H, 19-H), 5.99–6.07 (m, 1H, 27-H), 6.27 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.34 (dt, *J* = 11.6, 7.3 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.2 (C-16), 20.0 (C-15), 24.6 (C-17), 25.4 (C-9), 26.4 (C-22), 29.0 (C-21), 36.5 (C-4), 37.5 (C-6), 37.9 (C-14), 40.4 (C-12), 40.6, (C-10), 43.2 (C-2), 46.4 (C-8), 52.6 (29-OCH_3), 57.2 (11-OCH_3), 69.0 (C-5), 71.2 (C-3), 73.4 (C-13), 75.4 (C-7), 78.3 (C-11), 116.0 (C-26), 121.5 (C-19), 136.0 (C-24), 139.1 (C-27), 142.2 (C-23), 150.2 (C-20), 161.9 (C-29), 166.8 (C-18), 174.8 (C-1); HRMS (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+H]^+$: 591.32761, found 591.32815.



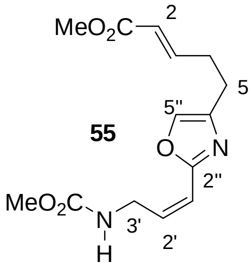
53

2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazole-4-carboxylic acid (53): A solution of ester **28** (21 mg, 0.08 mmol) in MeOH (1 mL) was treated with LiOH (1N solution in water, 0.8 mL, 0.8 mmol) at ambient temperature and the reaction mixture was stirred until TLC indicated complete consumption of the starting material (ca. 2 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.8 mL, 0.8 mmol). After the mixture was extracted with EtOAc (4 × 20 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford acid **53** (18 mg, 94%) as a slightly yellow solid; m.p. 153–155 °C. TLC (CH_2Cl_2/MeOH, 9:1): R_f = 0.2; ^1H NMR (400 MHz, CD_3OD): δ = 3.64 (s, 3H, OCH_3), 4.32 (d, *J* = 4.8 Hz, 2H, C*H_2*NH), 6.12–6.22 (m, 1H, HC=C*H*CH_2), 6.34 (d, *J* = 11.9 Hz, 1H, *H*C=CHCH_2), 8.47 (s, 1H, 5-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 40.9 (CH_2NH), 52.6 (OCH_3), 115.3 (H*C*=CHCH_2), 135.5 (C-4), 141.6 (HC=*C*HCH_2), 145.4 (C-5), 159.6 (CO_2CH_3), 162.4 (C-2), 164.0 (CO_2H); HRMS (ESI): calcd for $C_9H_{10}NaN_2O_5$ $[M+Na]^+$: 249.04819, found 249.04838.



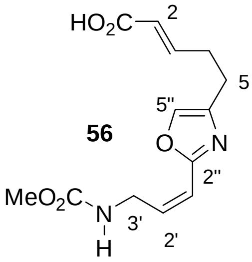
54

(2*E*)-3-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)acrylic acid (54): A solution of ester **31** (16.0 mg, 0.06 mmol) in THF (0.6 mL) was treated with LiOH (1N solution in water, 0.6 mL, 0.6 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 7 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.6 mL, 0.6 mmol). After the mixture was extracted with EtOAc (4 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH, 95:5? 9:1) afforded acid **54** (14.4 mg, 92% yield) as a colorless solid; m.p. 134–136 °C. TLC (CH_2Cl_2/MeOH, 9:1): $R_f = 0.30$; ^1H NMR (400 MHz, CD_3OD): $\delta = 3.65$ (s, 3H, OCH_3), 4.36 (d, $J = 4.3$ Hz, 2H, 3’-H), 6.10–6.18 (m, 1H, 2’-H), 6.32 (dt, $J = 11.9$, 2.0 Hz, 1H, 1’-H), 6.56 (d, $J = 15.4$ Hz, 1H, 2-H), 7.52 (d, $J = 15.4$ Hz, 1H, 3-H), 8.10 (s, 1H, 5’’-H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 41.1$ (C-3’), 52.6 (OCH_3), 115.4 (C-1’), 121.4 (C-2), 133.9 (C-5’’), 139.4 (C-4’’), 140.9 (C-3), 141.2 (C-2’), 159.7 (CO_2CH_3), 162.5 (C-2’’), 170.0 (C-1); HRMS (ESI): calcd for $C_{11}H_{12}NaN_2O_5$ $[M+Na]^+$: 275.06384, found 275.06377.



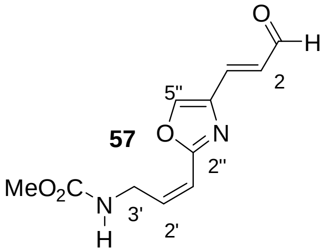
55

Methyl (2*E*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)pent-2-enoate (55): To a solution of aldehyde **22** (7 mg, 0.029 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at ambient temperature was added (methoxycarbonylmethylene)triphenylphosphorane[1] (19.4 mg, 0.058 mmol, 2 equiv). The reaction mixture was stirred for 2 h, concentrated in vacuo and purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford unsaturated ester **55** (7.9 mg, 93%) as a colorless oil. TLC (CH_2Cl_2/MeOH, 9:1): $R_f = 0.57$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.57$ (q, $J = 7.4$ Hz, 2H, 4-H), 2.70 (t, $J = 7.3$ Hz, 2H, 5-H), 3.67 (s, 3H, OCH_3), 3.71 (s, 3H, CCO_2CH_3), 4.30 (d, $J = 4.3$ Hz, 2H, 3’-H), 5.52 (br s, 1H, NH), 5.86 (d, $J = 15.7$ Hz, 1H, 2-H), 6.05–6.14 (m, 1H, 2’-H), 6.29 (d, $J = 11.6$ Hz, 1H, 1’-H), 6.97 (dt, $J = 15.7$, 6.8 Hz, 1H, 3-H), 7.35 (s, 1H, 5’’-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.8$ (C-5), 30.7 (C-4), 39.4 (C-3’), 51.5 (OCH_3), 52.2 (OCH_3), 116.6 (C-1’), 121.8 (C-2), 133.9 (C-5’’), 136.5 (C-4’’), 140.6 (C-2’), 147.8 (C-5’’), 157.2 (CO_2CH_3), 160.1 (C-2’’), 166.9 (C-1); HRMS (ESI): calcd for $C_{14}H_{18}NaN_2O_5$ $[M+Na]^+$: 317.11079, found 317.11064.



56

(2*E*)-5-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)pent-2-enoic acid (56): A solution of ester **55** (6.5 mg, 0.022 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.22 mL, 0.22 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 6 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.22 mL, 0.22 mmol). After the mixture was extracted with EtOAc (4 × 10 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH, 95:5? 9:1) afforded acid **56** (5.7 mg, 92% yield) as a white solid; m.p. 108–110 °C. TLC (CH_2Cl_2/MeOH, 9:1): $R_f = 0.38$; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (q, *J* = 7.2 Hz, 2H, 4-H), 2.72 (t, *J* = 7.1 Hz, 2H, 5-H), 3.67 (s, 3H, OCH_3), 4.26–4.34 (m, 2H, 3'-H), 5.51 (br s, 1H, NH), 5.87 (d, *J* = 15.7 Hz, 1H, 2-H), 6.05–6.14 (m, 1H, 2'-H), 6.29 (d, *J* = 11.9 Hz, 1H, 1'-H), 7.08 (dt, *J* = 15.5, 6.8 Hz, 1H, 3-H), 7.36 (s, 1H, 5''-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (C-5), 30.9 (C-4), 39.4 (C-3'), 52.2 (OCH_3), 116.5 (C-1'), 121.4 (C-2), 133.9 (C-5''), 136.5 (C-4''), 140.5 (C-2'), 150.1 (C-5''), 157.2 (CO_2CH_3), 160.1 (C-2''), 170.4 (C-1); HRMS (ESI): calcd for $C_{14}H_{18}NaN_2O_5$ $[M+Na]^+$: 303.09514, found 303.09516.

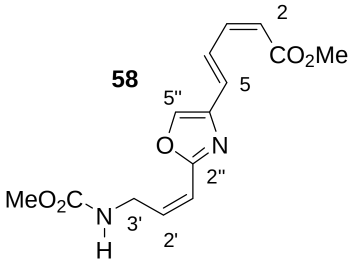


57

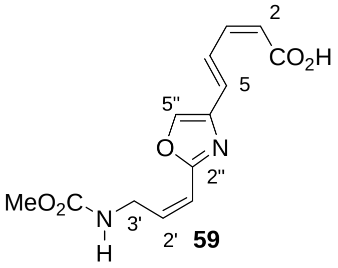
Methyl (2*Z*)-3-{4-[(1*E*)-3-oxoprop-1-enyl]-1,3-oxazol-2-yl}prop-2-enylcarbamate (57): a) Reduction to the allyl alcohol: To a solution of ester **31** (46 mg, 0.17 mmol) in CH_2Cl_2 (3 mL), at –80 °C, was added dropwise DIBAL-H (1M in hexanes, 0.43 mL, 0.43 mmol, 2.5 equiv). The reaction was stirred at –80 °C for 1 h, quenched with saturated aqueous NH_4Cl solution and warmed up to room temperature. It was then treated with saturated potassium and sodium tartrate (Rochelle salt)/EtOAc (20:20 mL) and the mixture was vigorously stirred for 10 min. After the layers were separated, the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (CH_2Cl_2/MeOH, 97:3? 95:5) afforded the corresponding alcohol (37.2 mg, 92% yield) which was subjected to Dess-Martin periodinane oxidation. TLC (CH_2Cl_2/MeOH, 9:1): $R_f = 0.38$.

b) Preparation of aldehyde 57: To a cooled (0 °C) solution of alcohol obtained in the previous step (37.2 mg, 0.16 mmol) in a mixture of CH_2Cl_2 (2 mL) and CH_3CN (0.8 mL) was added a solution of Dess-Martin periodinane (15% wt, 0.66 mL, 0.32 mmol), followed by addition of pyridine (26 µL, 0.32 mmol). After stirring for 10 min at 0 °C and for 1.5 h at room temperature, the reaction mixture was concentrated, loaded on a flash silica gel column, and eluted with petroleum ether/EtOAc, 4:1 to give 34 mg (93%) of aldehyde **57**, which was used directly in the next reaction. TLC (CH_2Cl_2/MeOH, 9:1): $R_f = 0.47$; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3H, OCH_3), 4.37 (dd, *J* = 5.9 Hz, 2H, 3'-H), 5.45 (br s, 1H, NH), 6.18–6.27 (m, 1H, 2'-H), 6.32 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.86 (dd, *J* = 15.5 Hz, 8.0 Hz, 1H, 2-H), 7.31 (d, *J* = 15.6 Hz, 1H, 3-H), 7.85 (s, 1H, 5''-H), 9.68 (d, *J* = 7.8 Hz, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (C-3'), 52.2 (OCH_3), 115.4 (C-1'), 125.9 (C-2), 130.3 (C-5''), 135.1 (C-4''), 139.1 (C-3), 139.3 (C-2'), 157.1 (CO_2CH_3), 161.0 (C-2''), 193.0 (C-1).

58



Methyl (2*Z*,4*E*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoate (58): A solution of 18-crown-6, freshly recrystallized from acetonitrile, (100 mg, 0.38 mmol, 6 equiv) and bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate[7] (**34**) (32 µL, 0.15 mmol, 2.4 equiv) in THF (2.0 mL) was cooled to –80 °C, and treated with KHMDS (0.5M solution in toluene, 260 µL, 0.13 mmol, 2.2 equiv). After 1 h, a solution of aldehyde **57** (15 mg, 0.063 mmol, 1 equiv) in THF (0.5 mL) was added over a period of 5 min. After 1 h, TLC indicated complete consumption of aldehyde. Now the reaction was quenched with saturated NH_4Cl and warmed to room temperature. After the mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH, 98:2) afforded ester **58** (12.6 mg, 68% yield) as a colorless oil. TLC (CH_2Cl_2/MeOH, 9:1): R_f = 0.65; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H, 4'-OCH_3), 3.75 (s, 3H, 1-OCH_3), 4.37 (dd, *J* = 5.9 Hz, 2H, 3'-H), 5.55 (br s, 1H, NH), 5.74 (d, *J* = 11.1 Hz, 1H, 2-H), 6.14–6.23 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.61–6.72 (m, 2H, 3-H, 5-H), 7.67 (s, 1H, 5''-H), 8.13 (dd, *J* = 15.4, 11.9 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.4 (C-3'), 51.3 (1-OCH_3), 52.2 (4'-OCH_3), 116.1 (C-1'), 118.2 (C-5), 127.0 (C-2), 128.5 (C-4), 136.4 (C-5''), 138.1 (C-4''), 139.7 (C-2'), 143.7 (C-3), 157.2 (C-4'), 160.4 (C-2''), 166.7 (C-1); HRMS (ESI): calcd for $C_{14}H_{16}NaN_2O_5$ $[M+Na]^+$: 315.09514, found 315.09542.



59

(2*Z*,4*E*)-5-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoic acid (59): A solution of ester **58** (11.2 mg, 0.038 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.5 mL, 0.5 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 8 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.5 mL, 0.5 mmol). After the mixture was extracted with EtOAc (4 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH, 95:5? 9:1) afforded acid **59** (9.8 mg, 93% yield) as a colorless solid; m.p. 158–160 °C. R_f = 0.47 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.64 (s, 3H, 4'-OCH_3), 4.36 (d, *J* = 5.8 Hz, 2H, 3'-H), 5.72 (d, *J* = 11.4 Hz, 1H, 2-H), 6.06–6.14 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.72–6.80 (m, 2H, 3-H, 5-H), 7.95 (s, 1H, 5''-H), 8.13 (dd, *J* = 15.4, 11.9 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 41.1 (C-3'), 52.6 (4'-OCH_3), 115.6 (C-1'), 119.9 (C-5), 128.1 (C-2), 129.3 (C-4), 138.9 (C-5''), 140.6 (C-2'), 141.0 (C-4''), 144.9 (C-3), 159.7 (C-4'), 162.3 (C-2''), 170.0 (C-1); HRMS (ESI): calcd for $C_{13}H_{14}NaN_2O_5$ $[M+Na]^+$: 301.07949, found 301.07988.

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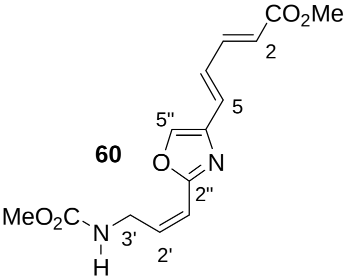
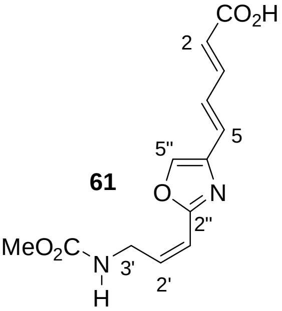
[7] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405-4408.



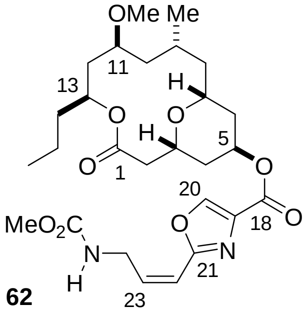
60

Methyl (2*E*,4*E*)-5-(2-{(1*Z*)-3-[(methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoate (60): To a solution of aldehyde **57** (14.2 mg, 0.06 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at ambient temperature was added (methoxycarbonylmethylene)triphenylphosphorane[1] (40.0 mg, 0.12 mmol, 2 equiv). The reaction mixture was stirred for 4 h, concentrated in vacuo and purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford unsaturated ester **60** (15.2 mg, 87%) as a colorless solid; m.p. 132–134 °C. R_f = 0.67 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H, 4'-OCH_3), 3.75 (s, 3H, 1-OCH_3), 4.35–4.42 (m, 2H, 3'-H), 5.47 (br s, 1H, NH), 6.02 (d, *J* = 15.4 Hz, 1H, 2-H), 6.12–6.20 (m, 1H, 2'-H), 6.30 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.69 (d, *J* = 15.2 Hz, 1H, 5-H), 7.04 (dd, *J* = 15.2, 11.6 Hz, 1H, 4-H), 7.38 (dd, *J* = 15.2, 11.5 Hz, 1H, 3-H) 7.62 (s, 1H, 5''-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (C-3'), 51.6 (1-OCH_3), 52.2 (4'-OCH_3), 115.9 (C-1'), 121.8 (C-5), 127.3 (C-4), 128.3 (C-2), 136.6 (C-5''), 138.3 (C-4''), 139.4 (C-2'), 143.9 (C-3), 157.2 (C-4'), 160.5 (C-2''), 167.4 (C-1); HRMS (ESI): calcd for $C_{14}H_{16}NaN_2O_5$ $[M+Na]^+$: 315.09514, found 315.09519.



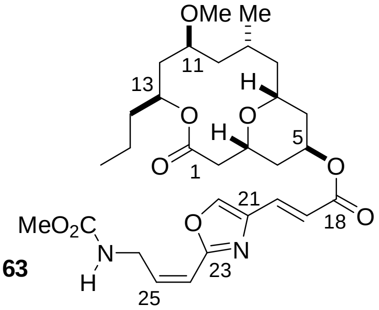
61

(2*E*,4*E*)-5-(2-{(1*Z*)-3-[(Methoxycarbonyl)amino]prop-1-enyl}-1,3-oxazol-4-yl)penta-2,4-dienoic acid (61): A solution of ester **60** (12.1 mg, 0.04 mmol) in THF (0.5 mL) was treated with LiOH (1N solution in water, 0.5 mL, 0.5 mmol) at ambient temperature and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (ca. 7 h). The reaction was cooled to 0 °C and neutralized with aqueous HCl (1N, 0.5 mL, 0.5 mmol). After the mixture was extracted with EtOAc (4 × 15 mL), the combined organic layers were washed with saturated NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH, 95:5? 9:1) afforded acid **61** (10.2 mg, 92% yield) as a colorless solid; m.p. 177–179 °C. R_f = 0.51 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.65 (s, 3H, 4'-OCH_3), 4.37 (d, *J* = 5.3 Hz, 2H, 3'-H), 6.01 (d, *J* = 15.4 Hz, 1H, 2-H), 6.07–6.15 (m, 1H, 2'-H), 6.31 (d, *J* = 11.9 Hz, 1H, 1'-H), 6.85 (d, *J* = 15.2 Hz, 1H, 5-H), 7.08 (dd, *J* = 15.2, 11.4 Hz, 1H, 4-H), 7.40 (dd, *J* = 15.0, 11.2 Hz, 1H, 3-H), 7.96 (s, 1H, 5''-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 41.1 (C-3'), 52.6 (4'-OCH_3), 115.5 (C-1'), 123.3 (C-5), 129.0 (C-4), 129.3 (C-2), 139.0 (C-5''), 140.7 (C-2'), 145.7 (C-3), 159.7 (C-4'), 162.3 (C-2''), 170.4 (C-1); HRMS (ESI): calcd for $C_{13}H_{14}NaN_2O_5$ $[M+Na]^+$: 279.09755, found 279.09812.



62

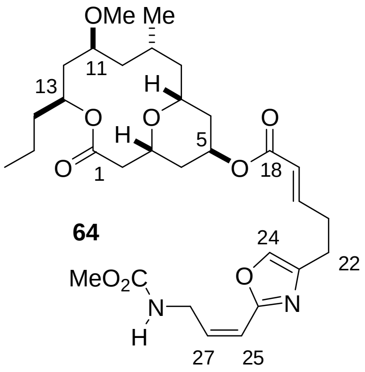
Neo-oxazole 62: To a solution of alcohol **16** (5.3 mg, 0.016 mmol, 1 equiv), acid **53** (7.7 mg, 0.032 mmol, 2.0 equiv) and PPh_3 (9.2 mg, 0.035 mmol, 2.2 equiv) in a mixture of absolute benzene (0.8 mL) and THF (1.5 mL), was added diisopropyl azodicarboxylate (70 µL, 0.5M solution in benzene, 0.035 mmol, 2.2 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (hexane/EtOAC, 2:1? 1.5:1? 1:1) to afford neopeltolide analogue **62** (7.5 mg, 88%) as a colorless oil. R_f = 0.58 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +28.8 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.6 Hz, 3H, 17-H), 1.08–1.16 (m, 1H, 10-H), 1.22–1.44 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.45–1.64 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.65–1.83 (m, 2H, 6-H, 14-H), 1.86–1.97 (m, 2H, 4-H, 12-H), 2.31 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.73 (dd, *J* = 14.7, 4.3 Hz, 1H, 2-H), 3.28 (s, 3H, 11-OCH_3), 3.59–3.75 (m, 5H, 7-H, 29-OCH_3, 11-H), 4.15–4.24 (m, 1H, 3-H), 4.34 (d, *J* = 4.8 Hz, 2H, 24-H), 5.14–5.22 (m, 1H, 13-H), 5.36–5.41 (m, 1H, 5-H), 6.15–6.23 (m, 1H, 23-H), 6.37 (dt, *J* = 11.9, 2.0 Hz, 1H, 22-H), 8.62 (s, 1H, 20-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 32.5 (C-9), 36.2 (C-4), 37.4 (C-6), 37.9 (C-14), 41.1 (C-12), 43.2 (C-2), 43.6 (C-10), 45.3 (C-8), 52.6 (25-OCH_3), 56.4 (11-OCH_3), 70.7 (C-5), 71.2 (C-3), 73.9 (C-13), 76.9 (C-7), 77.1 (C-11), 115.2 (C-22), 135.2 (C-20), 141.9 (C-23), 145.8 (C-19), 159.6 (C-25), 161.8 (C-21), 162.5 (C-18), 173.1 (C-1); HRMS (ESI): calcd for $C_{27}H_{40}NaN_2O_9$ $[M+Na]^+$: 559.26260, found 559.26265.



63

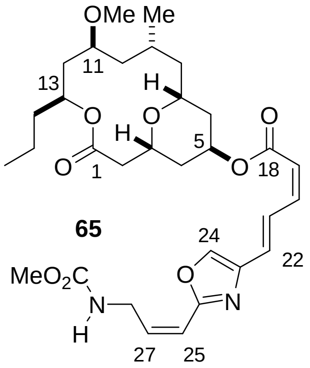
Neo-enoate 63: To a solution of alcohol **16** (4.1 mg, 0.0125 mmol, 1 equiv), acid **54** (5.6 mg, 0.02 mmol, 1.6 equiv) and PPh_3 (5.8 mg, 0.022 mmol, 1.76 equiv) in absolute benzene (0.7 mL) was added diisopropyl azodicarboxylate (44 µL, 0.5M solution in benzene, 0.022 mmol, 1.76 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAC, 2:1? 1:1? 1:2) to afford neopeltolide analogue **63** (5.6 mg, 76%) as a colorless oil. R_f = 0.57 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +20.5 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.6 Hz, 3H, 17-H), 1.07–1.14 (m, 1H, 10-H), 1.21–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.61 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.67–1.79 (m, 2H, 6-H, 14-H), 1.84–1.95 (m, 2H, 4-H, 12-H), 2.31 (dd, *J* = 14.7, 10.9 Hz, 1H, 2-H), 2.72 (dd, *J* = 14.7, 4.3 Hz, 1H, 2-H), 3.28 (s, 3H, 11-OCH_3), 3.62–3.74 (m, 5H, 7-H, 27-OCH_3, 11-H), 4.10–4.19 (m, 1H, 3-H), 4.38 (d, *J* = 4.6 Hz, 2H, 26-H), 5.14–5.22 (m, 1H, 13-H), 5.23–5.28 (m, 1H, 5-H), 6.11–6.19 (m, 1H, 25-H), 6.34 (dt, *J* = 11.9, 2.0 Hz, 1H, 24-H), 6.65 (d, *J* = 15.7 Hz, 1H, 19-H), 7.59 (d, *J* = 15.4 Hz, 1H, 20-H), 8.15 (s, 1H, 22-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 32.5 (C-9), 36.3 (C-4), 37.4 (C-6), 37.9 (C-14), 41.1 (C-12), 43.3 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (27-OCH_3), 56.4 (11-OCH_3), 69.8 (C-5), 71.3 (C-3), 74.0 (C-13), 77.1 (C-7), 77.1 (C-11), 115.3 (C-24), 121.0 (C-

19), 134.1 (C-22), 139.3 (C-25), 141.2 (C-20), 141.3 (C-21), 159.7 (C-27), 162.5 (C-23), 167.4 (C-18), 173.1 (C-1); HRMS (ESI): calcd for $C_{29}H_{42}NaN_2O_9$ $[M+Na]^+$: 585.27825, found 585.27827.



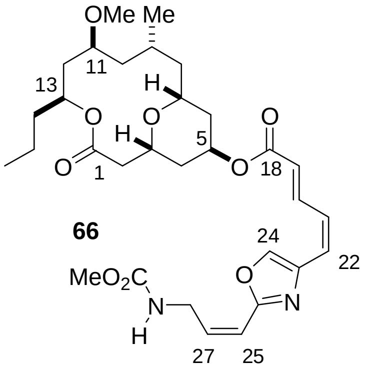
64

Neo-*trans* 64: To a solution of alcohol **16** (4.1 mg, 0.0125 mmol, 1 equiv), acid **56** (5.6 mg, 0.02 mmol, 1.6 equiv) and PPh_3 (5.8 mg, 0.022 mmol, 1.76 equiv) in absolute benzene (0.7 mL) was added diisopropyl azodicarboxylate (44 µL, 0.5M solution in benzene, 0.022 mmol, 1.76 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (hexane/EtOAC, 2:1? 1:1? 1:2) to afford 19-*trans* neopeltolide **64** (5.6 mg, 76%) as a colorless oil. R_f = 0.44 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +31.0 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.8 Hz, 3H, 17-H), 1.08–1.15 (m, 1H, 10-H), 1.23–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.62 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.64–1.76 (m, 2H, 6-H, 14-H), 1.78–1.93 (m, 2H, 4-H, 12-H), 2.28 (dd, *J* = 14.9, 11.1 Hz, 1H, 2-H), 2.60 (q, *J* = 7.2 Hz, 2H, 21-H), 2.66–2.77 (m, 3H, 2-H, 22-H), 3.27 (s, 3H, 11-OCH_3), 3.58 (apt, *J* = 10.0 Hz, 1H, 7-H), 3.62–3.72 (m, 4H, 29-OCH_3, 11-H), 4.03–4.12 (m, 1H, 3-H), 4.30 (d, *J* = 4.6 Hz, 2H, 28-H), 5.13–5.21 (m, 2H, 13-H, 5-H), 5.95 (d, *J* = 15.7 Hz, 1H, 19-H), 5.99–6.07 (m, 1H, 27-H), 6.28 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 7.03 (dt, *J* = 15.5, 6.8 Hz, 1H, 20-H), 7.65 (s, 1H, 24-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.1 (C-16), 20.0 (C-15), 25.5 (C-22), 26.0 (C-17), 31.8 (C-21), 32.6 (C-9), 36.2 (C-4), 37.4 (C-6), 38.0 (C-14), 41.1 (C-12), 43.2 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (29-OCH_3), 56.4 (11-OCH_3), 69.4 (C-5), 71.2 (C-3), 74.0 (C-13), 77.1 (C-7), 77.1 (C-11), 115.9 (C-26), 123.2 (C-19), 136.1 (C-24), 139.3 (C-27), 141.9 (C-23), 149.7 (C-20), 161.9 (C-25), 167.2 (C-18), 173.1 (C-1); HRMS (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+Na]^+$: 613.30955, found 613.31007.



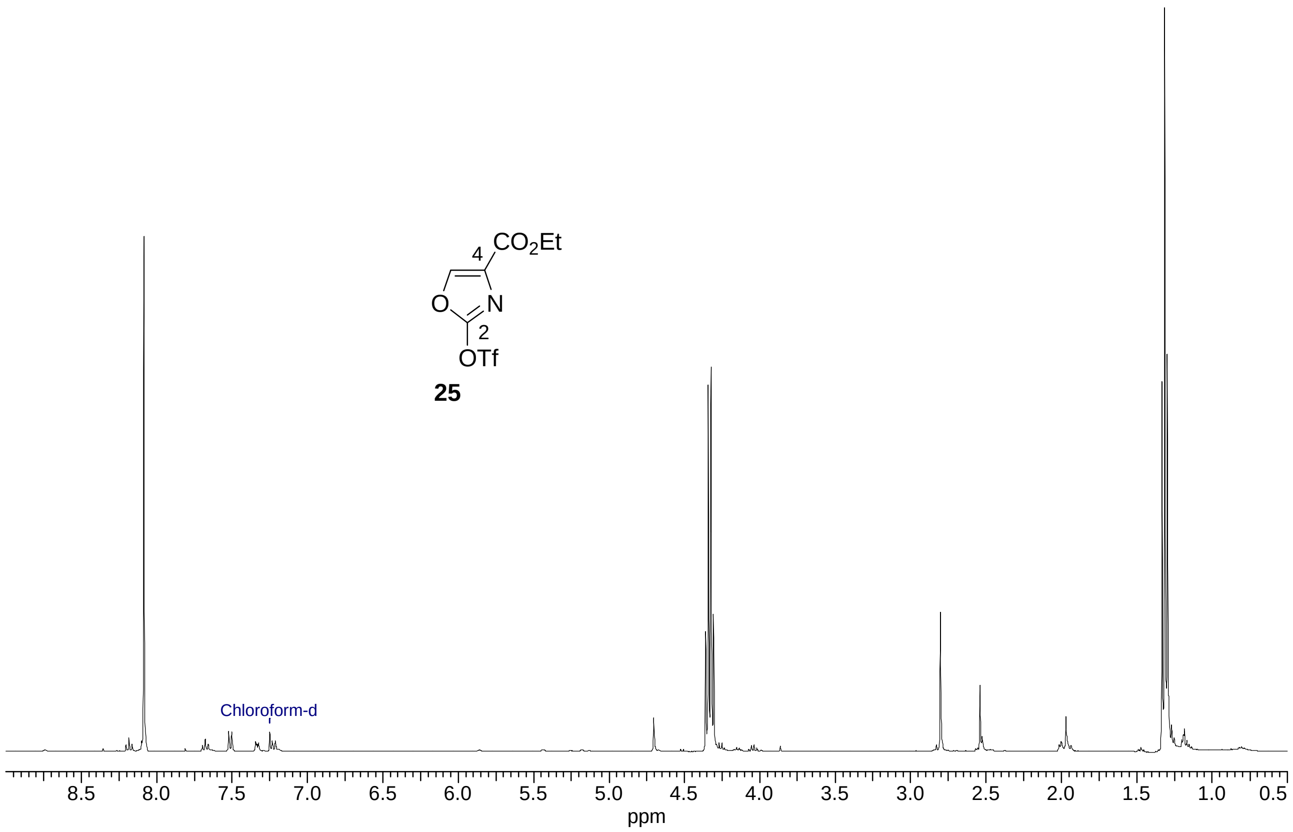
65

Neo-diene-*Z*,*E* 65: To a solution of alcohol **16** (4.6 mg, 0.014 mmol, 1 equiv), acid **59** (7.8 mg, 0.028 mmol, 2.0 equiv) and PPh_3 (8.1 mg, 0.031 mmol, 2.2 equiv) in a mixture of absolute benzene (1.0 mL) and THF (1.0 mL) was added diisopropyl azodicarboxylate (62 µL, 0.5M solution in benzene, 0.031 mmol, 2.2 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (hexane/EtOAC, 2:1? 1.5:1? 1:1) to afford neopeltolide analog **65** (7.0 mg, 85%) as a colorless oil. R_f = 0.61 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +30.5 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.92 (t, *J* = 7.3 Hz, 3H, 16-H), 0.97 (d, *J* = 6.8 Hz, 3H, 17-H), 1.08–1.15 (m, 1H, 10-H), 1.26–1.42 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.44–1.62 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.63–1.76 (m, 2H, 6-H, 14-H), 1.84–1.92 (m, 2H, 4-H, 12-H), 2.30 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.71 (dd, *J* = 14.8, 4.2 Hz, 1H, 2-H), 3.27 (s, 3H, 11-OCH_3), 3.56–3.72 (m, 5H, 7-H, 29-OCH_3, 11-H), 4.07–4.16 (m, 1H, 3-H), 4.36 (dd, *J* = 4.6 Hz, 2H, 28-H), 5.12–5.20 (m, 1H, 13-H), 5.21–5.25 (m, 1H, 5-H), 5.81 (d, *J* = 11.4 Hz, 1H, 19-H), 6.06–6.14 (m, 1H, 27-H), 6.32 (d, *J* = 11.9 Hz, 1H, 26-H), 6.77–6.87 (m, 2H, 20-H, 22-H), 7.98 (s, 1H, 24-H), 8.15 (dd, *J* = 15.5, 11.8 Hz, 1H, 21-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.1 (C-16), 20.0 (C-15), 25.9 (C-17), 32.5 (C-9), 36.3 (C-4), 37.4 (C-6), 37.9 (C-14), 41.0 (C-12), 43.2 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (29-OCH_3), 56.4 (11-OCH_3), 69.2 (C-5), 71.3 (C-3), 74.0 (C-13), 77.0 (C-7), 77.1 (C-11), 115.7 (C-26), 119.1 (C-22), 127.8 (C-19), 130.1 (C-24), 139.1 (C-27), 140.6 (C-23), 141.0 (C-21), 145.6 (C-20), 159.7 (C-29), 162.3 (C-25), 167.0 (C-18), 173.1 (C-1); HRMS (ESI): calcd for $C_{31}H_{44}NaN_2O_9$ $[M+Na]^+$: 611.29390, found 611.29403.

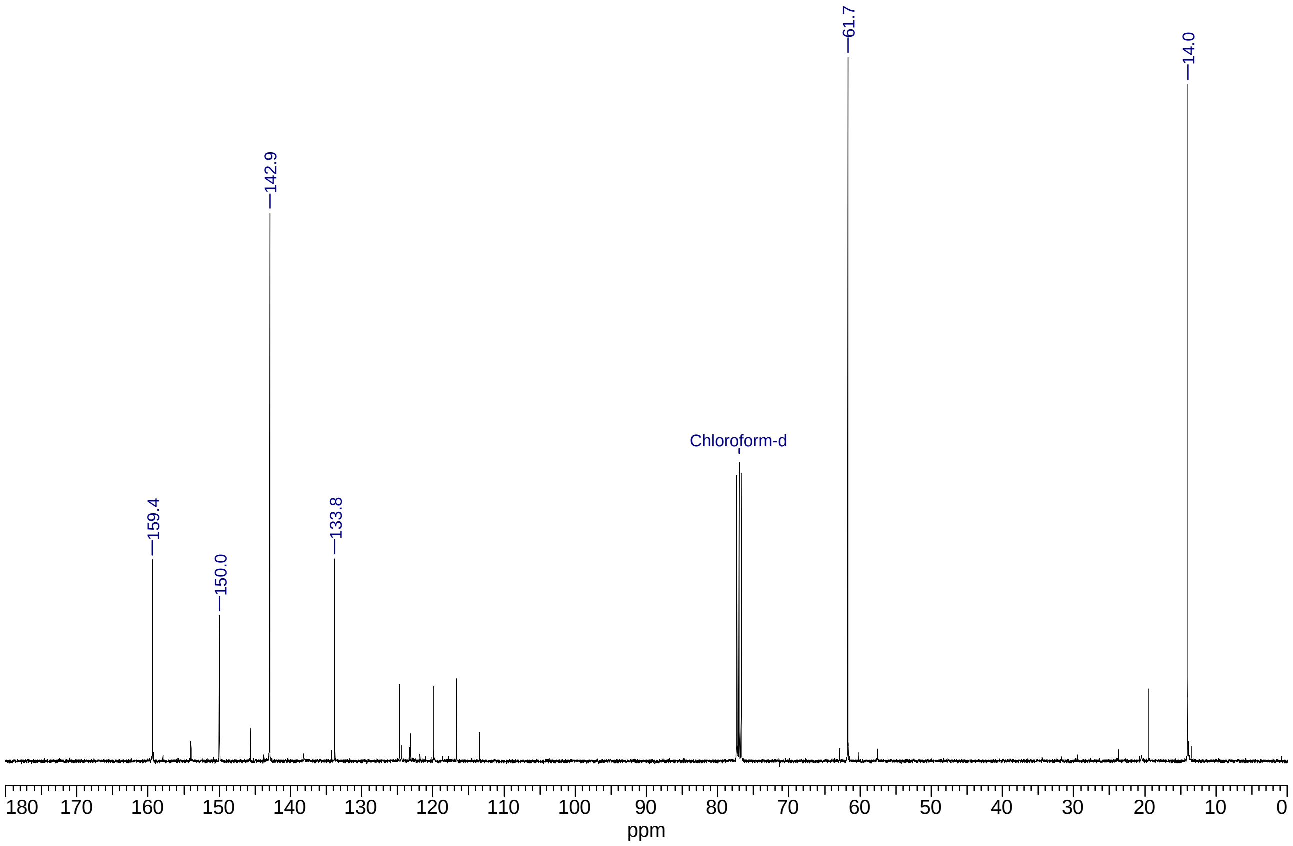


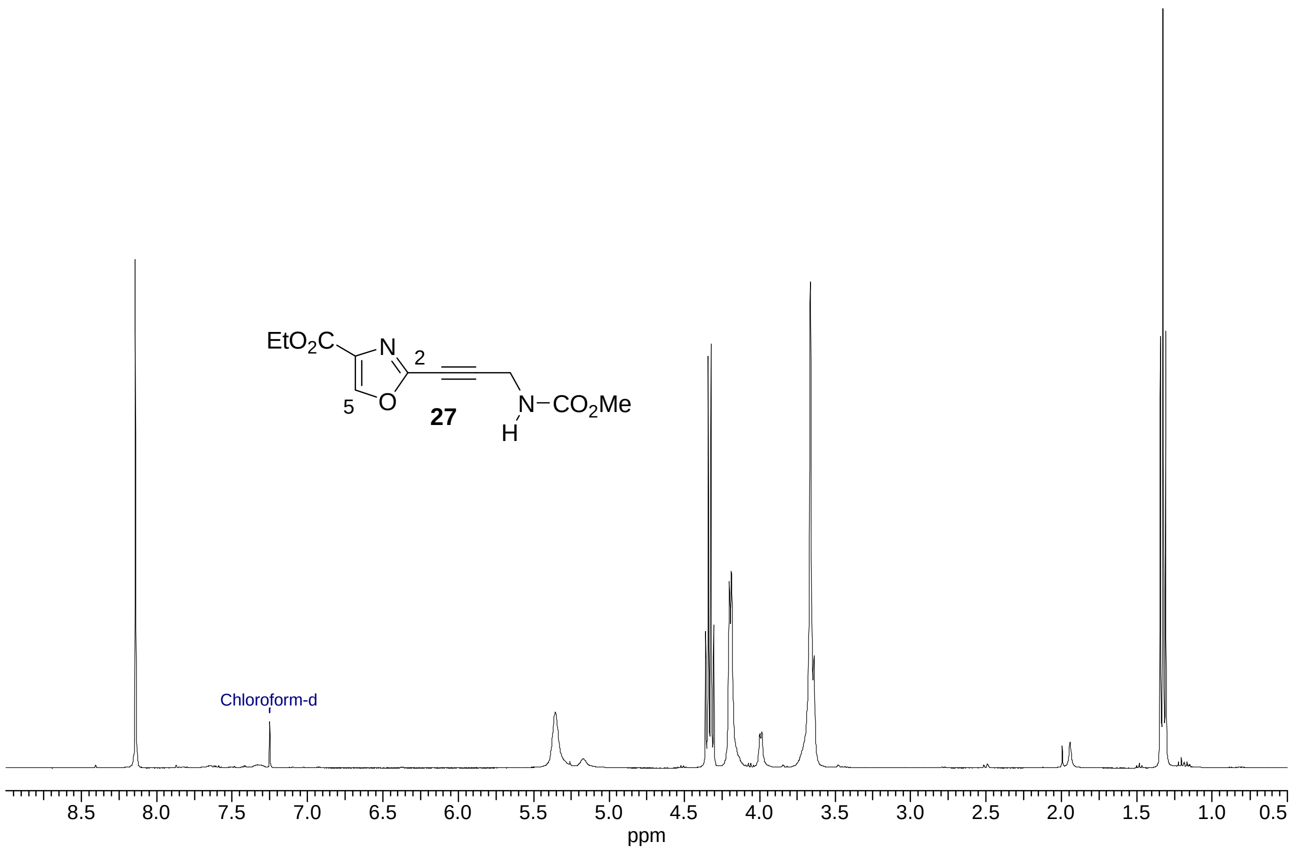
66

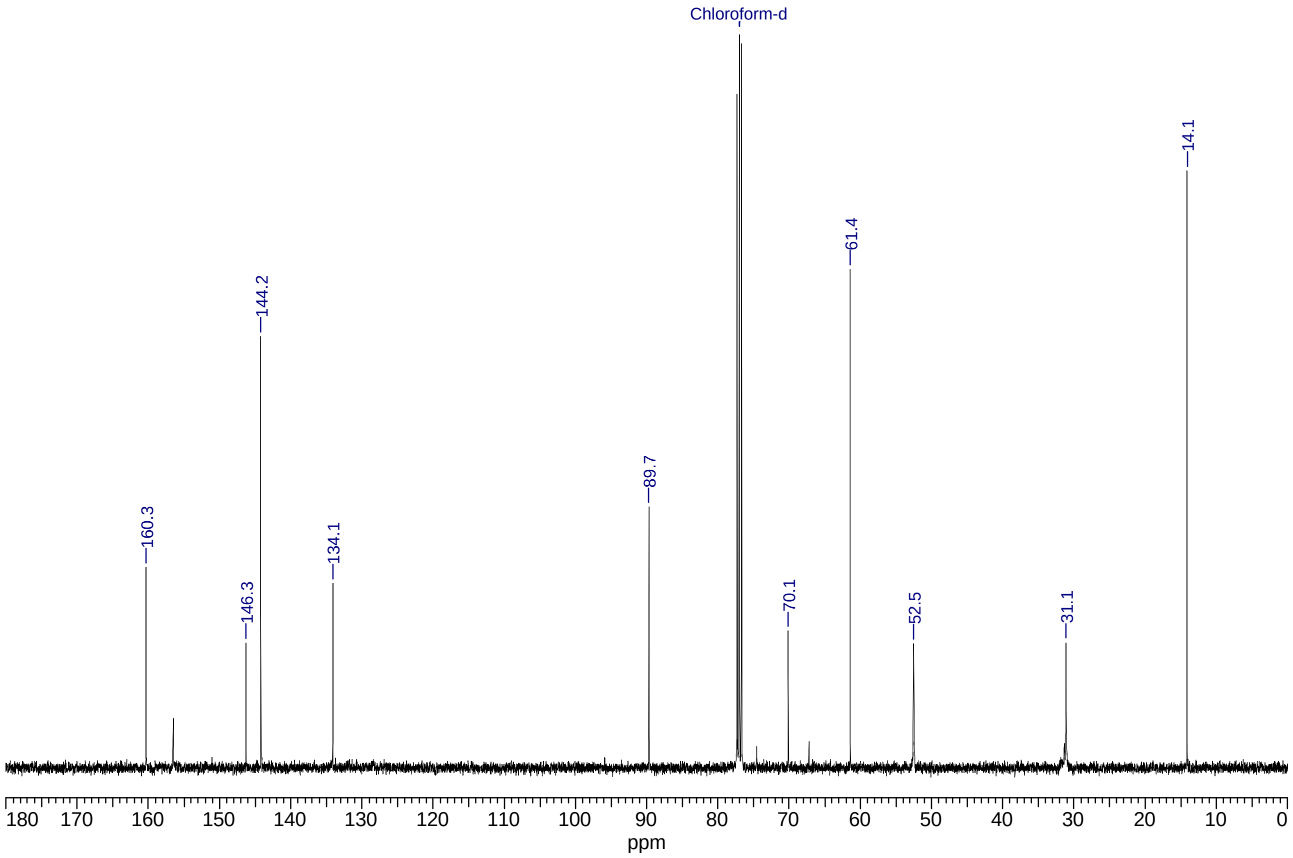
Neo-diene-*E*,*E* 66: To a solution of alcohol **16** (4.4 mg, 0.013 mmol, 1 equiv), acid **61** (7.2 mg, 0.026 mmol, 2.0 equiv) and PPh_3 (7.6 mg, 0.029 mmol, 2.2 equiv) in a mixture of absolute benzene (1.0 mL) and THF (1.0 mL) was added diisopropyl azodicarboxylate (58 µL, 0.5M solution in benzene, 0.029 mmol, 2.2 equiv). After stirring for 1 h at ambient temperature the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (hexane/EtOAC, 2:1? 1.5:1? 1:1) to afford neopeltolide analogue **66** (6.6 mg, 86%) as a colorless oil. R_f = 0.64 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +47.5 (*c* 0.6, CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD): δ = 0.93 (t, *J* = 7.3 Hz, 3H, 16-H), 0.99 (d, *J* = 6.6 Hz, 3H, 17-H), 1.08–1.17 (m, 1H, 10-H), 1.26–1.43 (m, 6H, 8-H, 9-H, 12-H, 15-H), 1.45–1.62 (m, 4H, 10-H, 4-H, 6-H, 14-H), 1.67–1.77 (m, 2H, 6-H, 14-H), 1.83–1.95 (m, 2H, 4-H, 12-H), 2.30 (dd, *J* = 14.8, 11.0 Hz, 1H, 2-H), 2.71 (dd, *J* = 14.9, 4.3 Hz, 1H, 2-H), 3.28 (s, 3H, 11-OCH_3), 3.59–3.72 (m, 5H, 7-H, 29-OCH_3, 11-H), 4.07–4.16 (m, 1H, 3-H), 4.38 (d, *J* = 4.6 Hz, 2H, 28-H), 5.14–5.24 (m, 2H, 13-H, 5-H), 6.07–6.16 (m, 2H, 19-H, 27-H), 6.31 (dt, *J* = 11.9, 2.0 Hz, 1H, 26-H), 6.91 (d, *J* = 15.2 Hz, 1H, 22-H), 7.11 (dd, *J* = 15.2, 11.4 Hz, 1H, 21-H), 7.46 (dd, *J* = 15.2, 11.1 Hz, 1H, 20-H), 7.97 (s, 1H, 24-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.1 (C-16), 20.0 (C-15), 26.0 (C-17), 32.5 (C-9), 36.3 (C-4), 37.4 (C-6), 38.0 (C-14), 41.1 (C-12), 43.3 (C-2), 43.5 (C-10), 45.3 (C-8), 52.6 (29-OCH_3), 56.4 (11-OCH_3), 69.6 (C-5), 71.2 (C-3), 74.0 (C-13), 77.0 (C-7), 77.1 (C-11), 115.5 (C-26), 122.9 (C-22), 129.2 (C-21), 129.5 (C-19), 139.2 (C-24), 140.7 (C-27), 140.7 (C-23), 145.8 (C-20), 159.7 (C-29), 162.3 (C-25), 167.8 (C-18), 173.1 (C-1); HRMS (ESI): calcd for $C_{31}H_{46}NaN_2O_9$ $[M+H]^+$: 589.31196, found 589.31195.

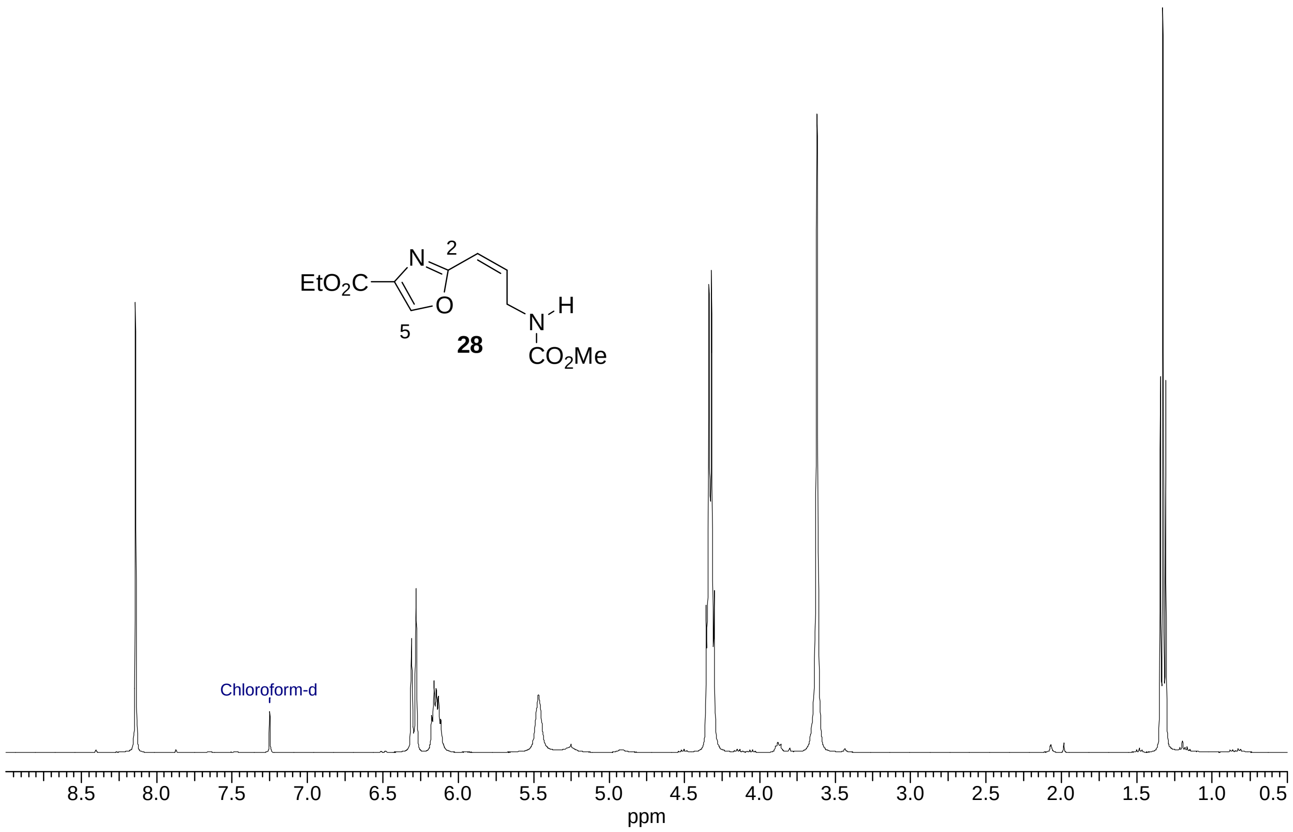

CO$_2$Et
4
O
N
2
OTf
Chloroform-d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

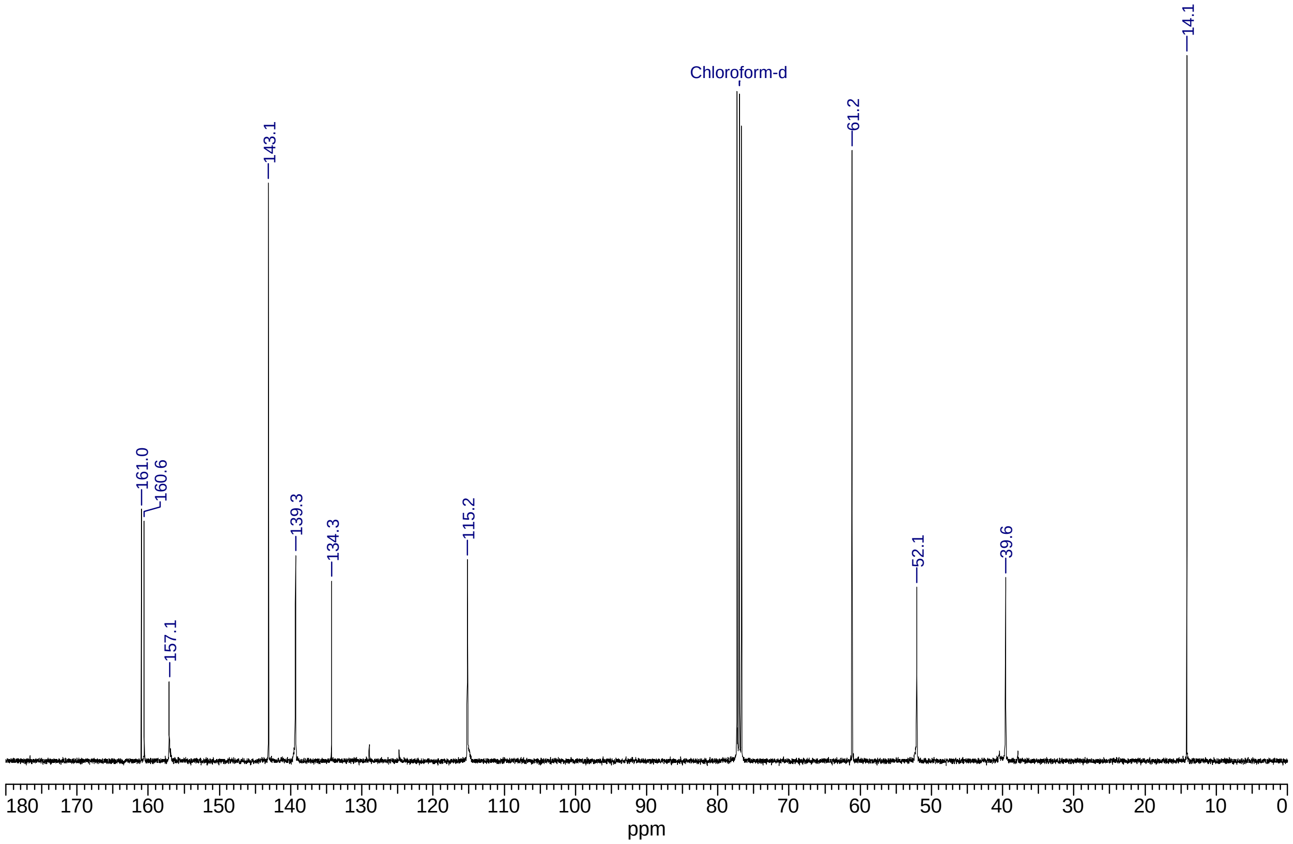
25

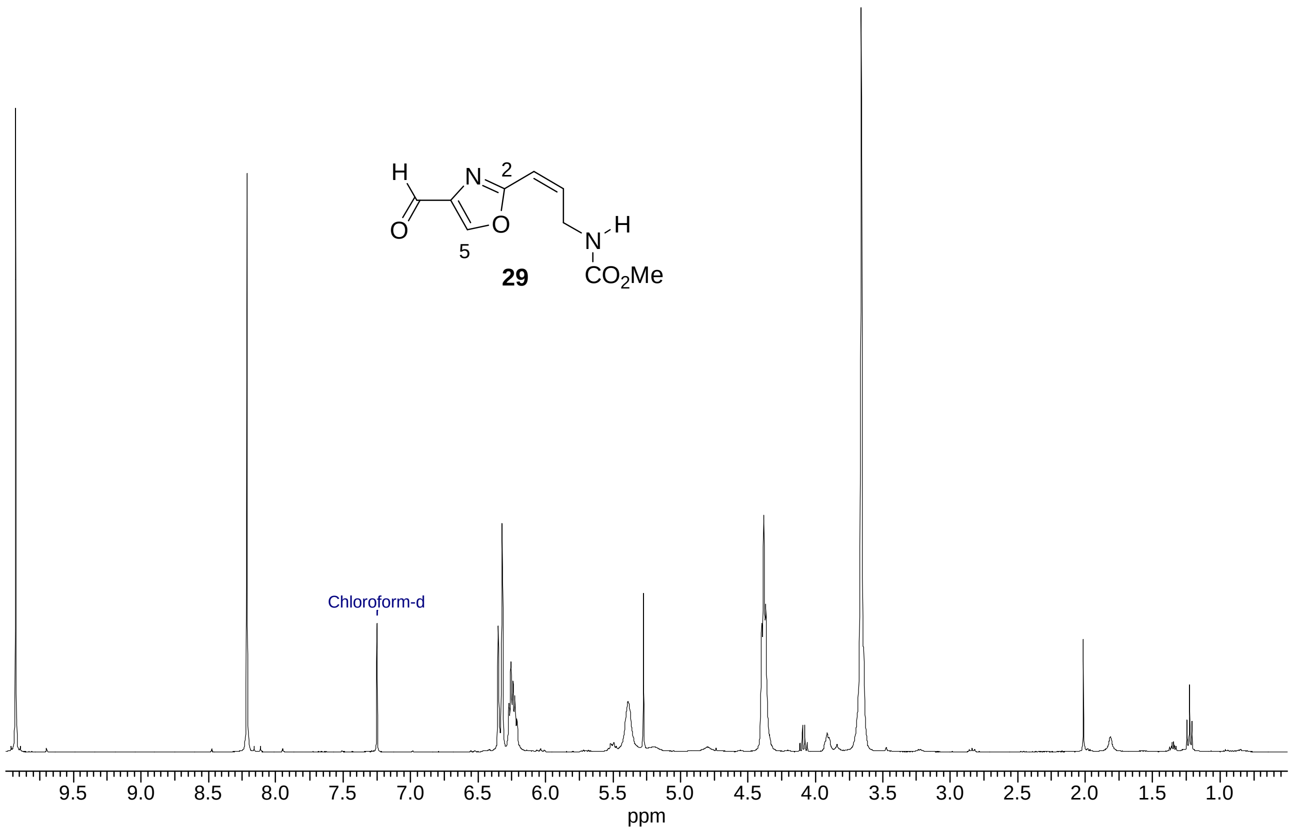

159.4
150.0
142.9
133.8
Chloroform-d
61.7
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

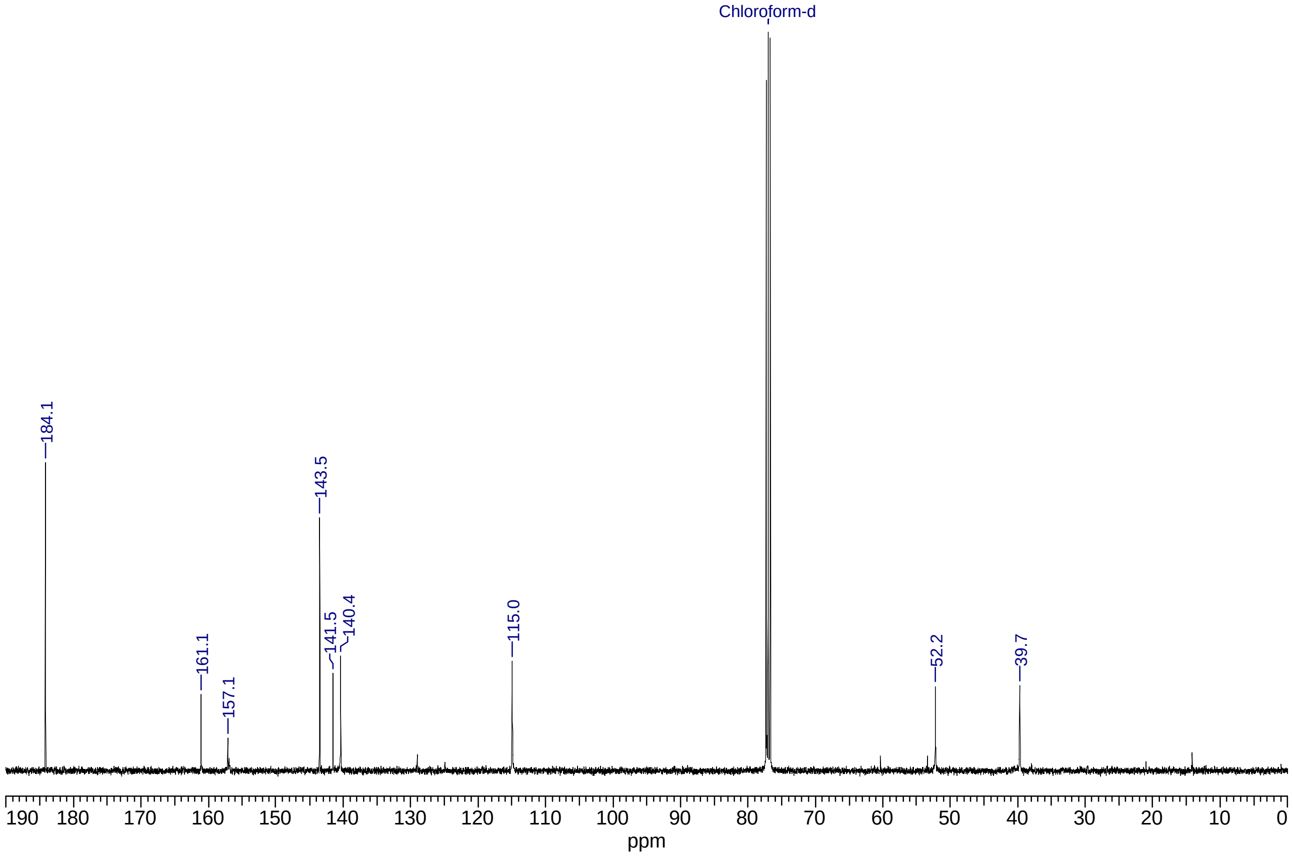

EtO2C
N
2
5
O
27
N−CO2Me
H
Chloroform-d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

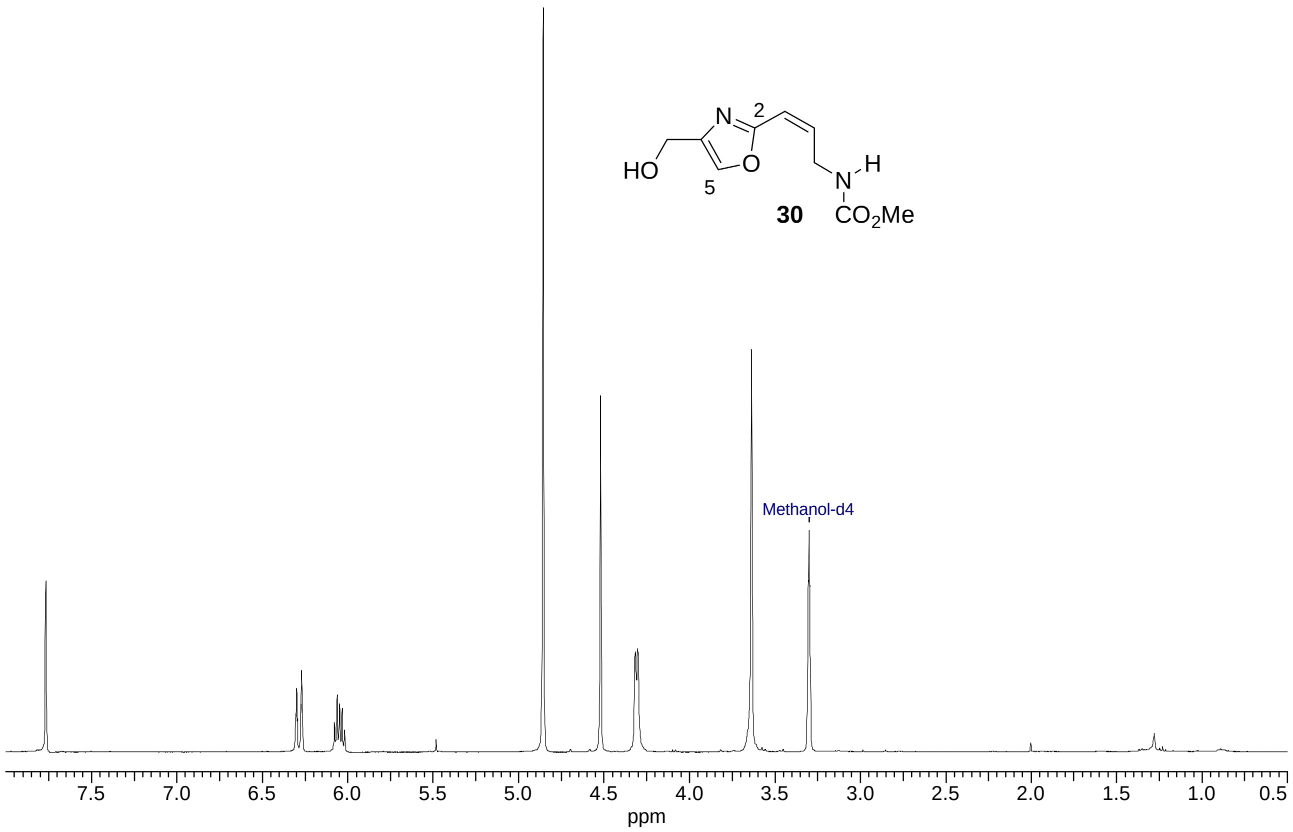

Chloroform-d
160.3
146.3
144.2
134.1
89.7
70.1
61.4
52.5
31.1
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

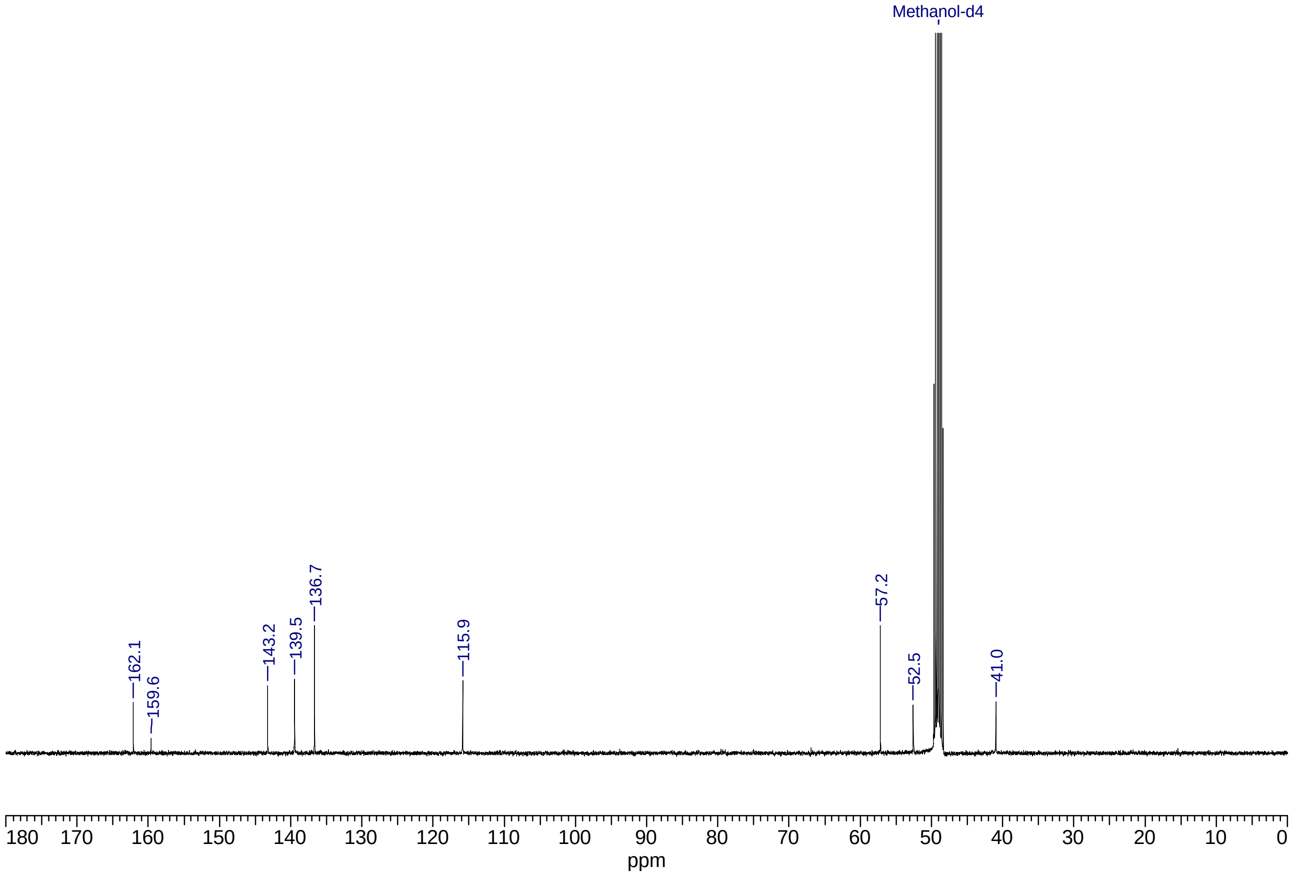

EtO$_2$C
N
2
O
5
28
N
H
CO$_2$Me
Chloroform-d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

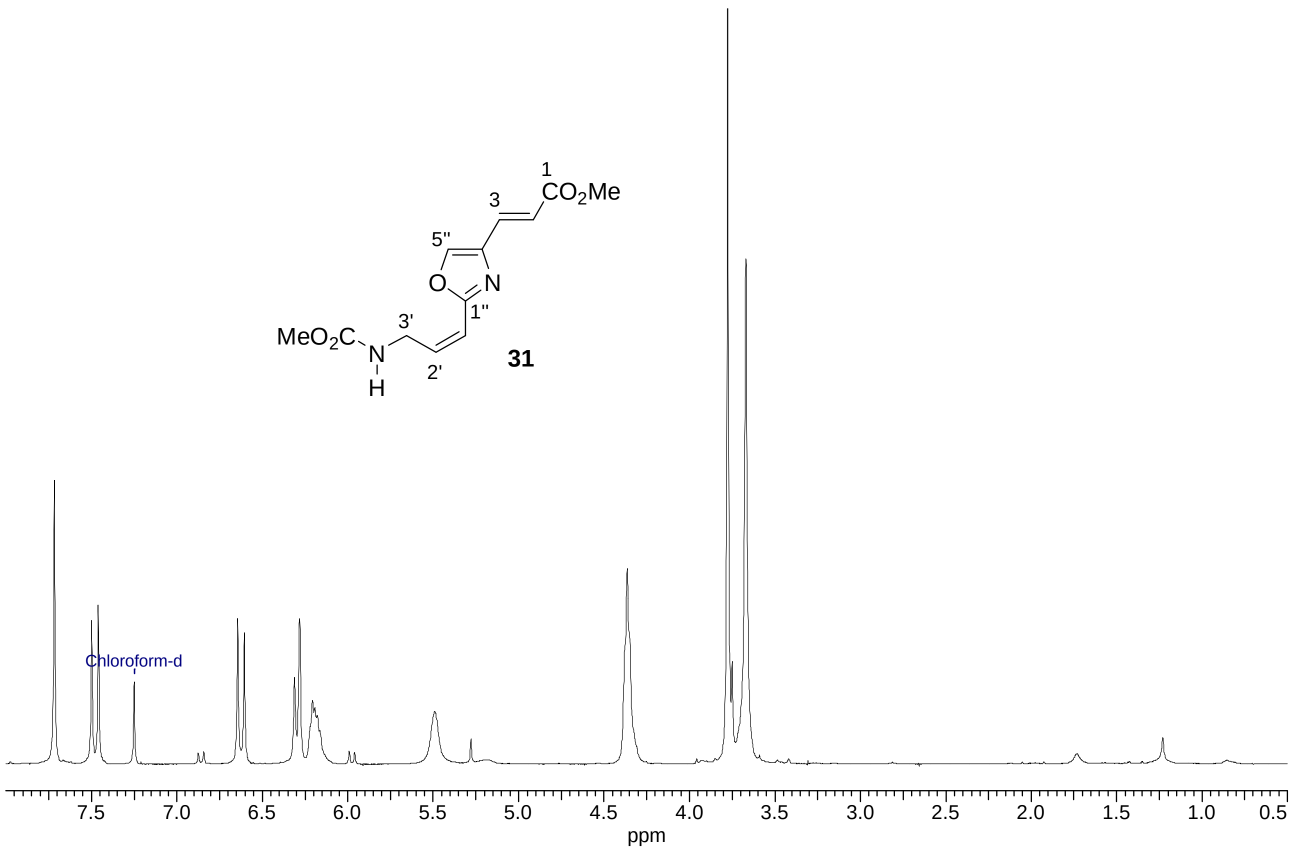

161.0
160.6
157.1
143.1
139.3
134.3
115.2
Chloroform-d
61.2
52.1
39.6
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

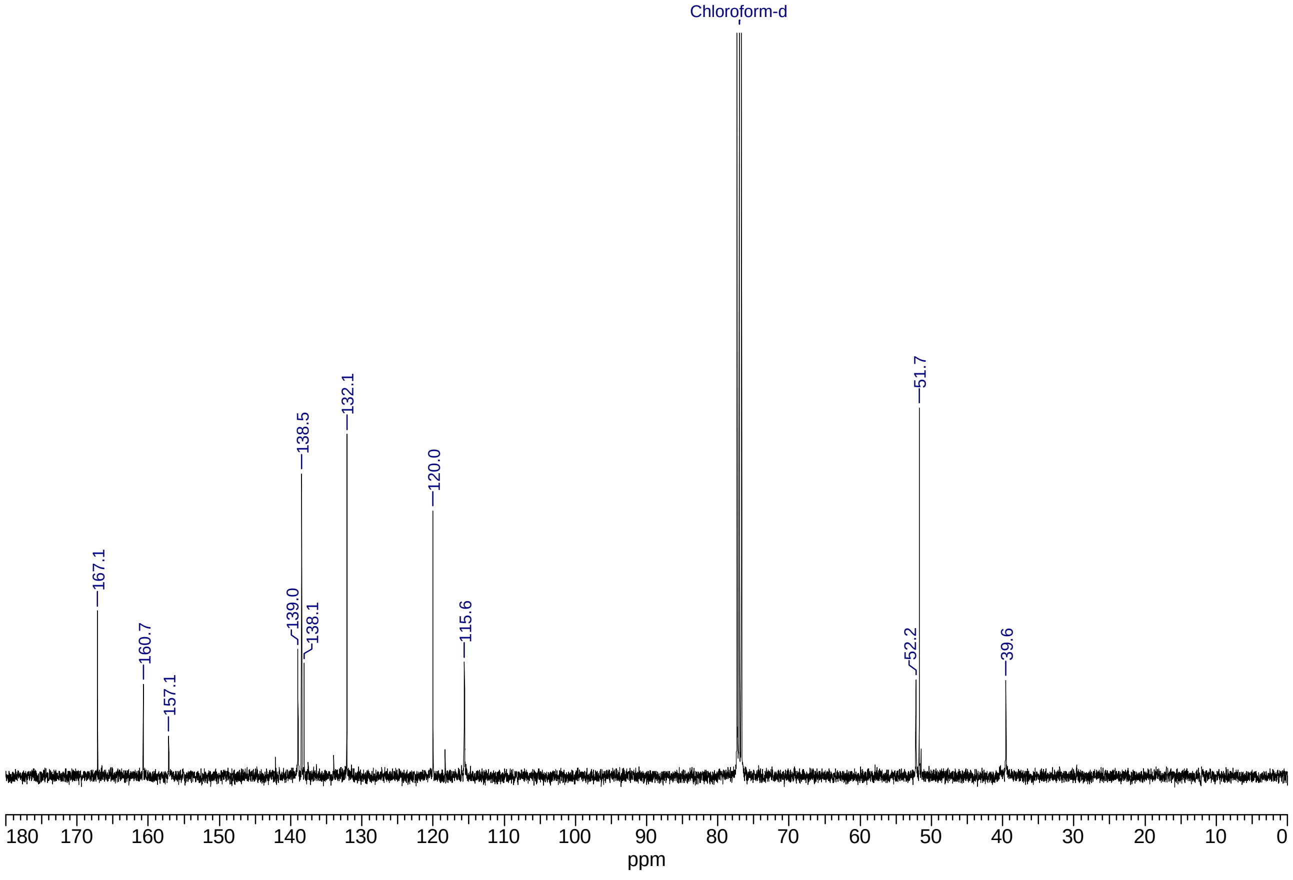

H
N
2
O
O
5
29
N
H
CO2Me
Chloroform-d
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

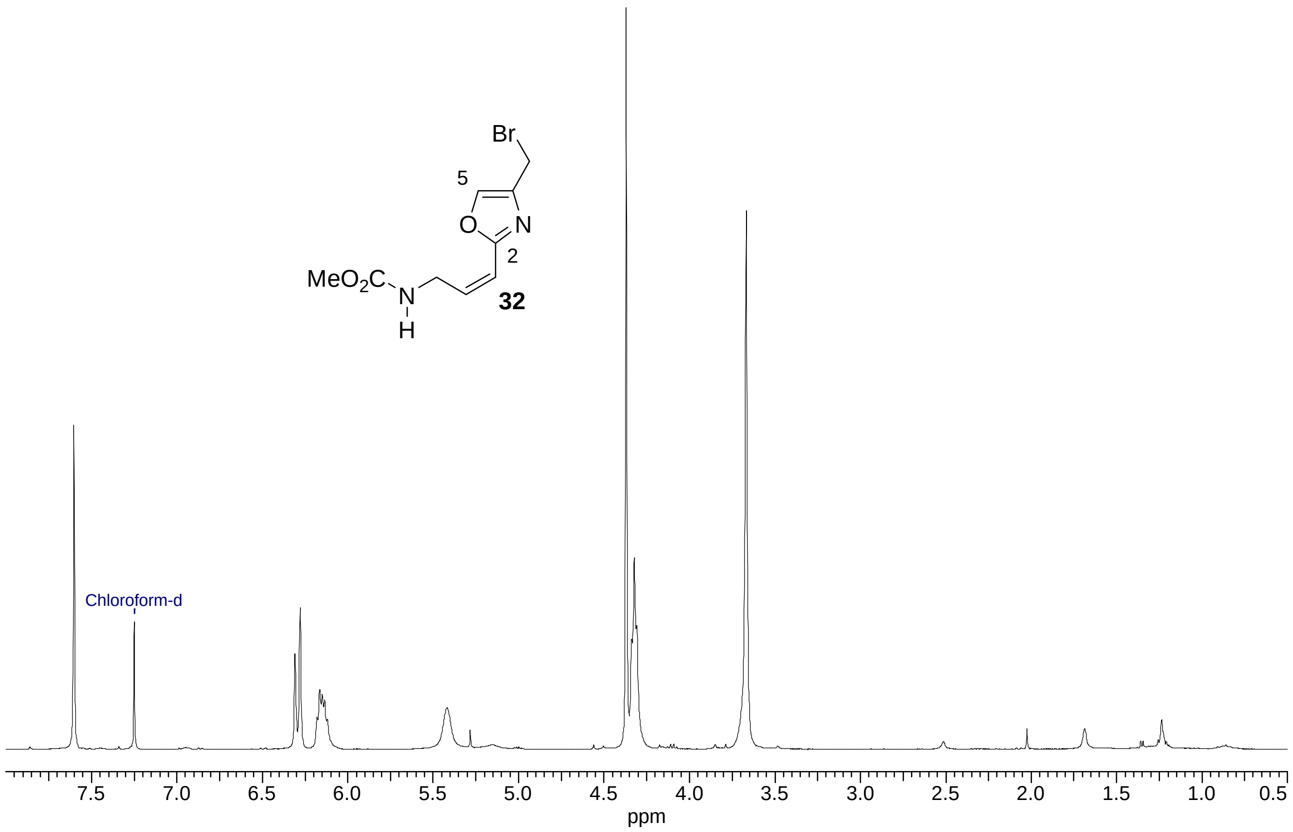

Chloroform-d
184.1
161.1
157.1
143.5
141.5
140.4
115.0
52.2
39.7
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

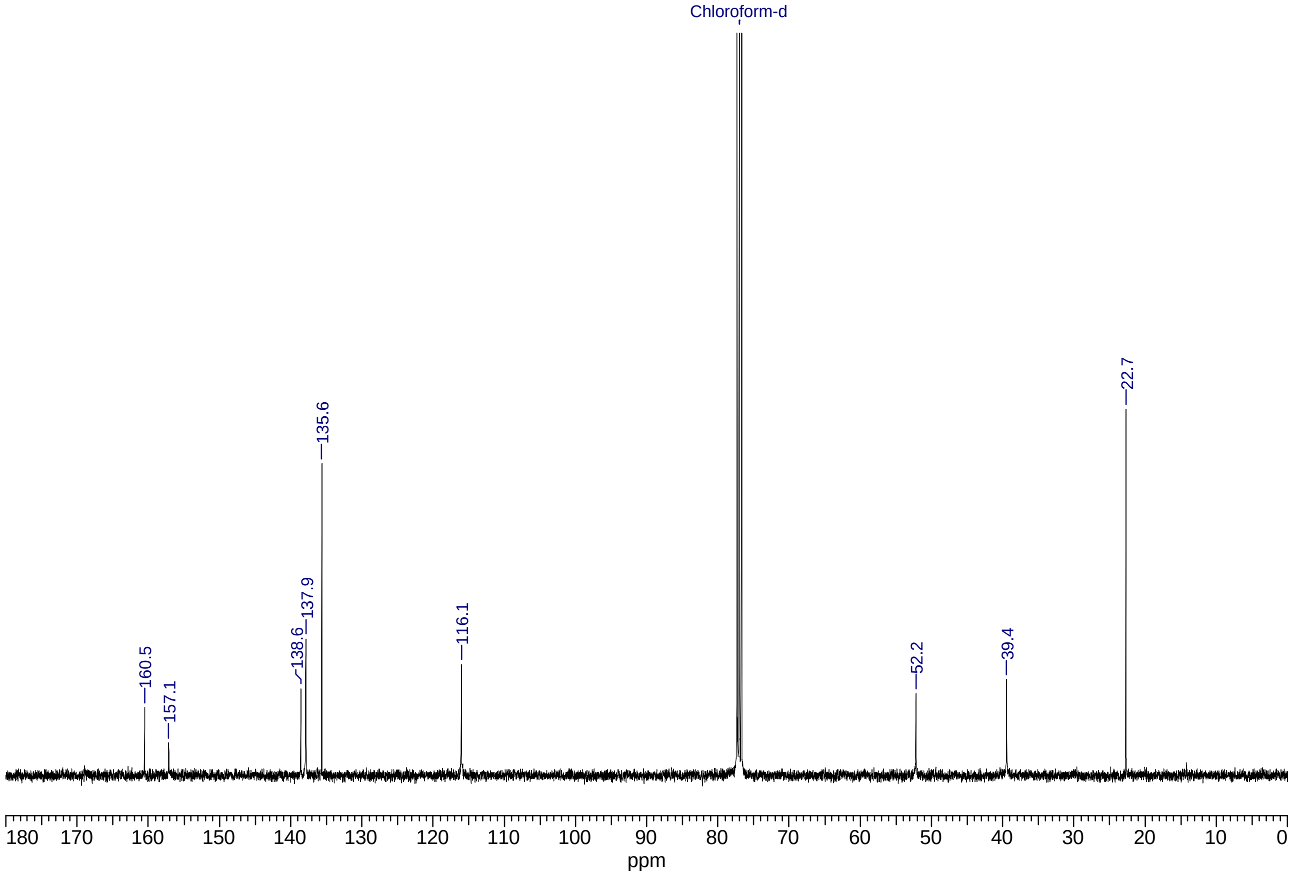

HO
N
2
O
5
N
H
30
CO_2Me
Methanol-d4
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

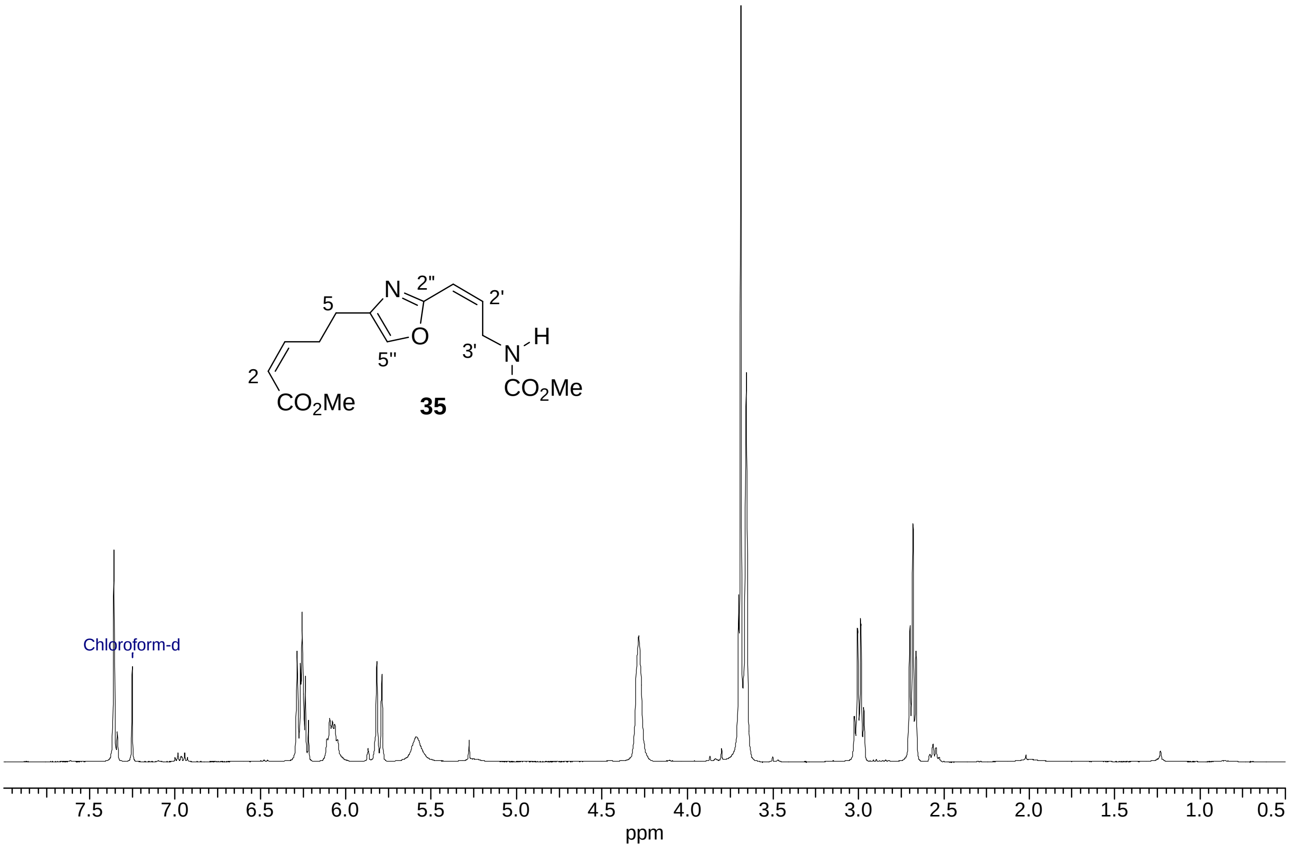

Methanol-d4
162.1
159.6
143.2
139.5
136.7
115.9
57.2
52.5
41.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


1
CO2Me
3
5''
O
N
1''
3'
MeO2C
N
H
2'
31
Chloroform-d
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
ppm

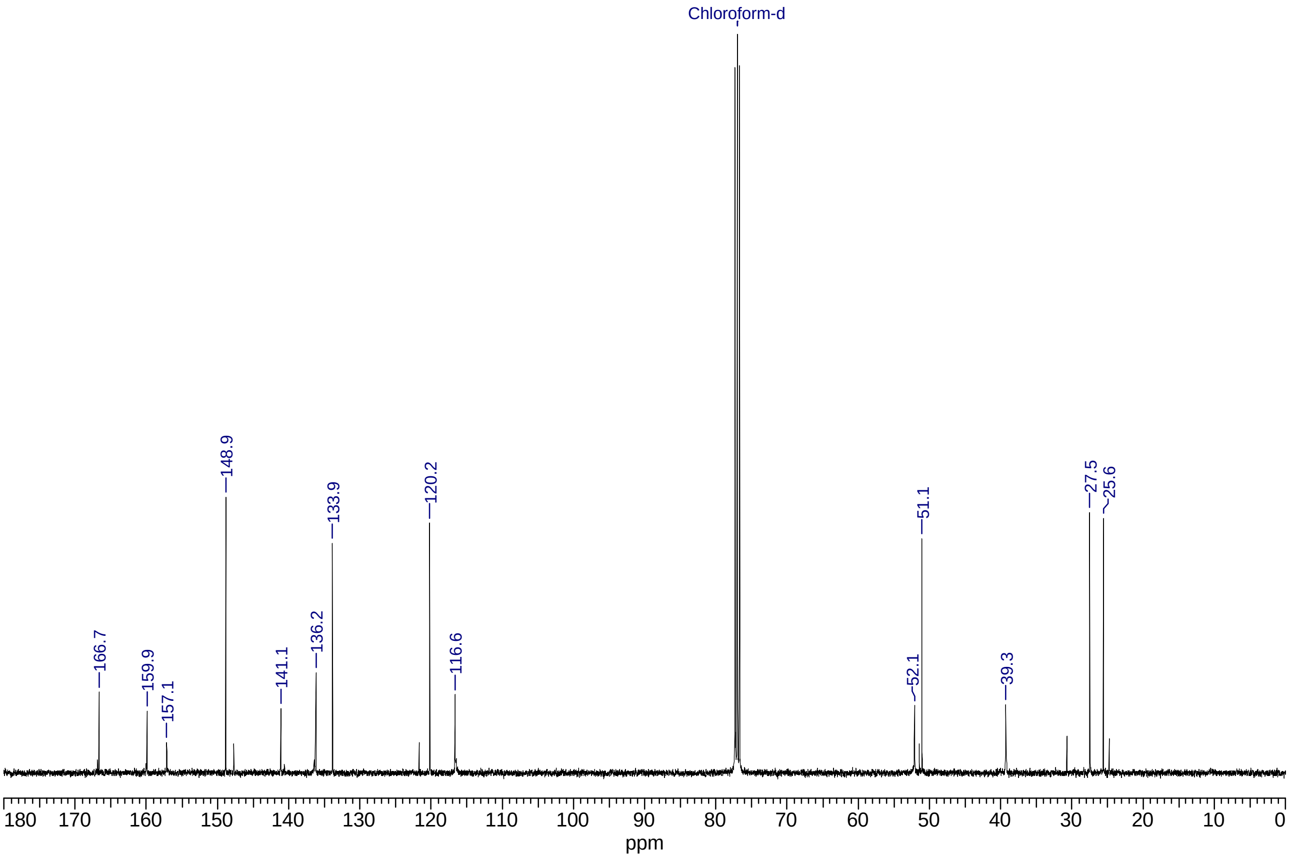

Chloroform-d
167.1
160.7
157.1
139.0
138.5
138.1
132.1
120.0
115.6
52.2
51.7
39.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


Br
5
O
N
2
MeO$_2$C
N
H
32
Chloroform-d
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
ppm

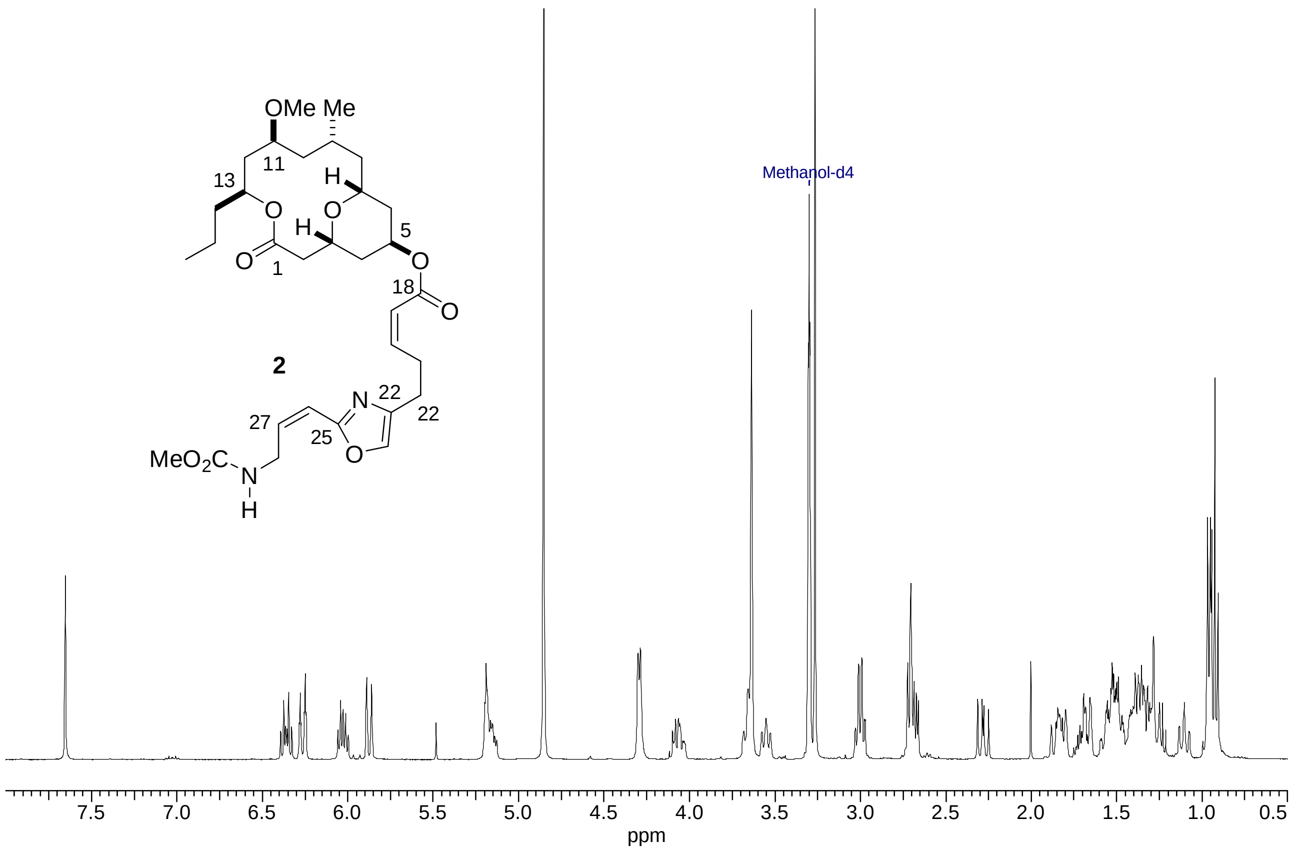

Chloroform-d
160.5
157.1
138.6
137.9
135.6
116.1
52.2
39.4
22.7
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

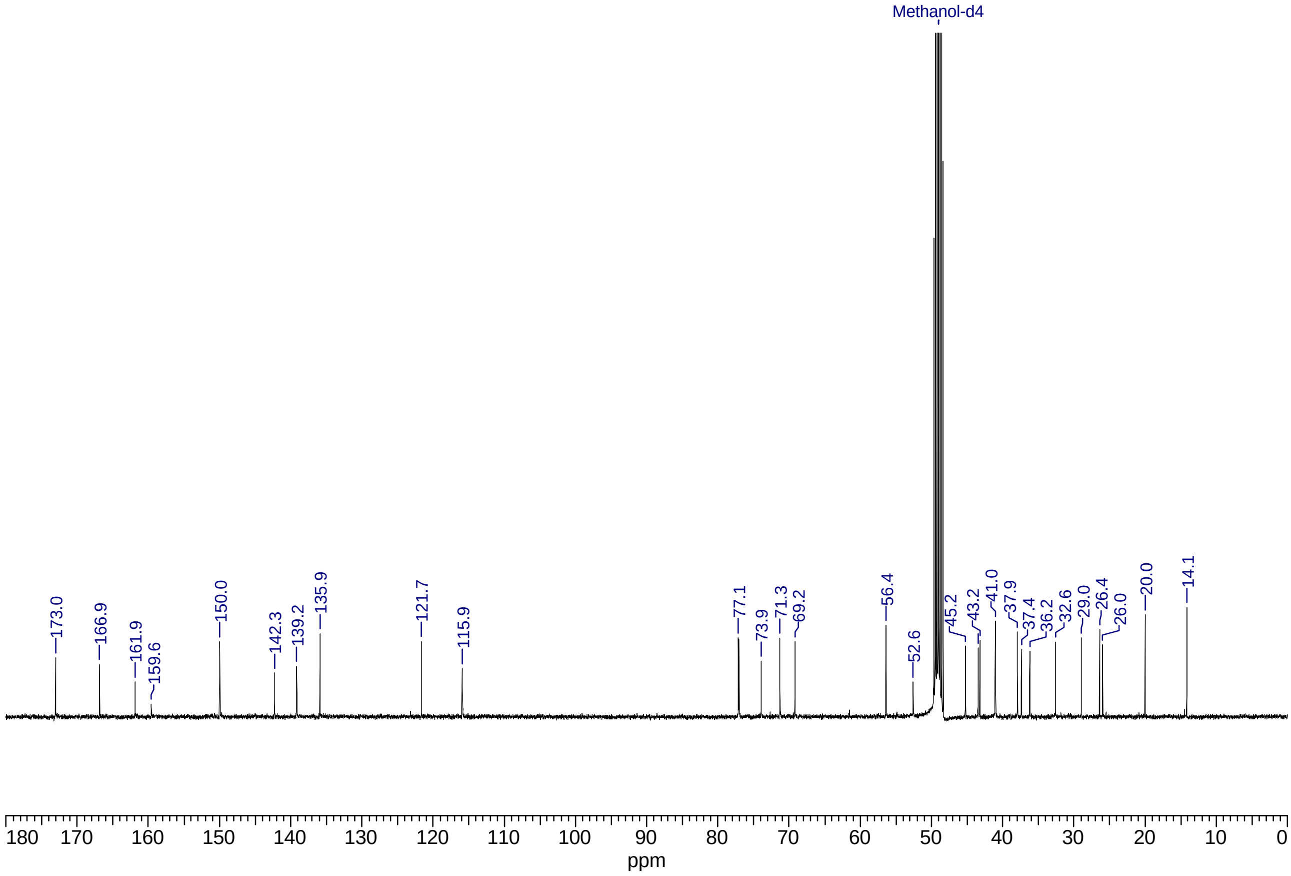


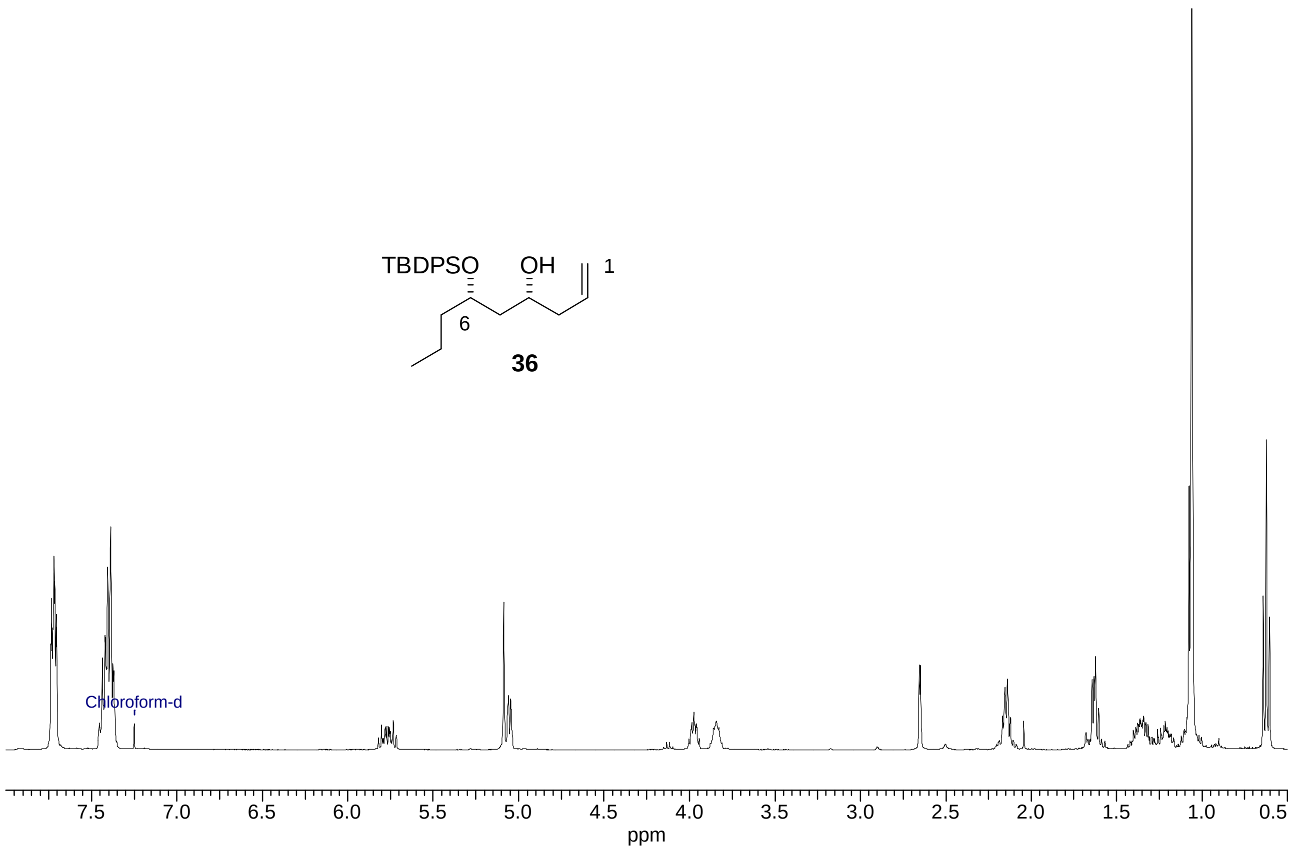
5
N
2"
2'
O
H
3'
N
5"
2
CO2Me
35
CO2Me
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



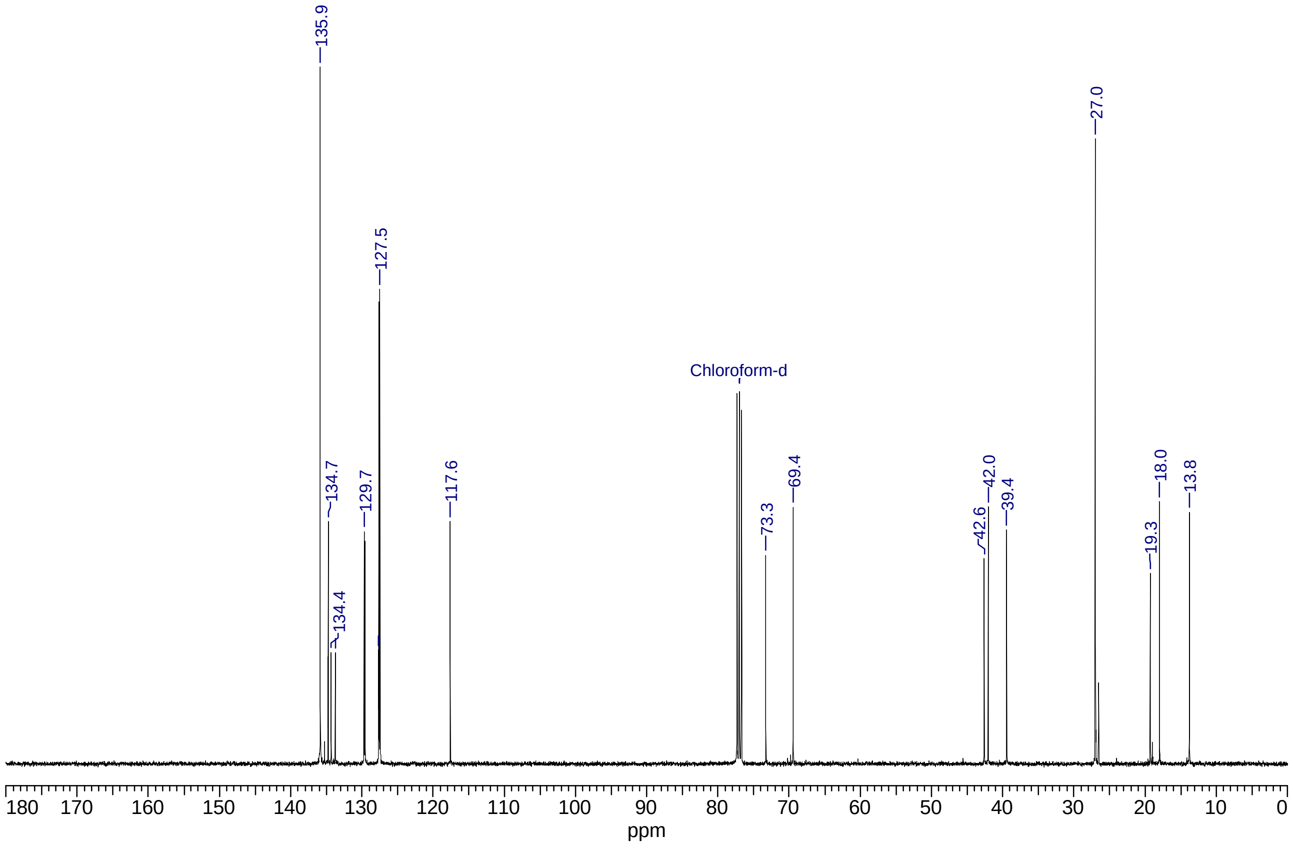
Chloroform-d
166.7
159.9
157.1
148.9
141.1
136.2
133.9
120.2
116.6
52.1
51.1
39.3
27.5
25.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

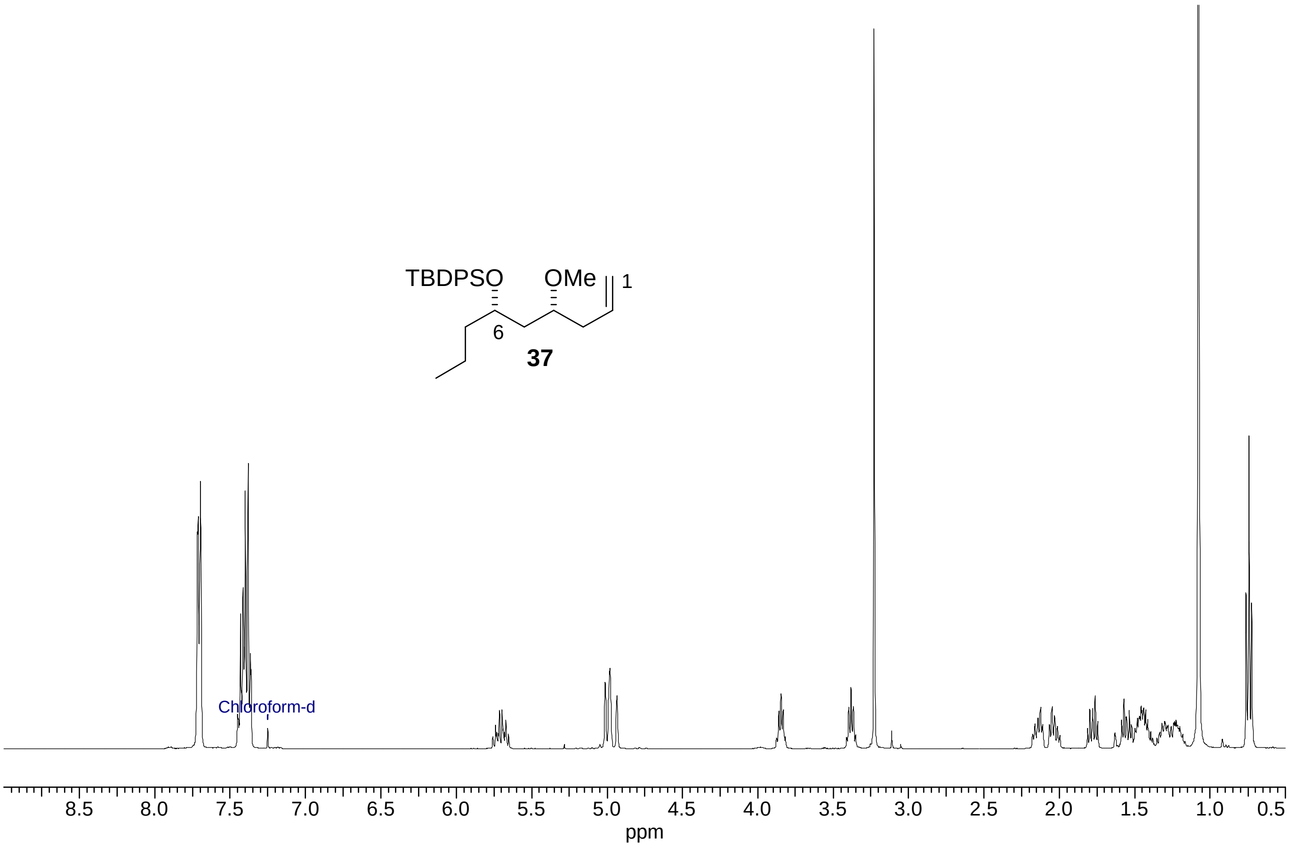

OMe Me
11
13
H
O
H
O
O
5
O
1
O
18
O
2
N
22
22
27
25
O
MeO2C
N
H
Methanol-d4
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

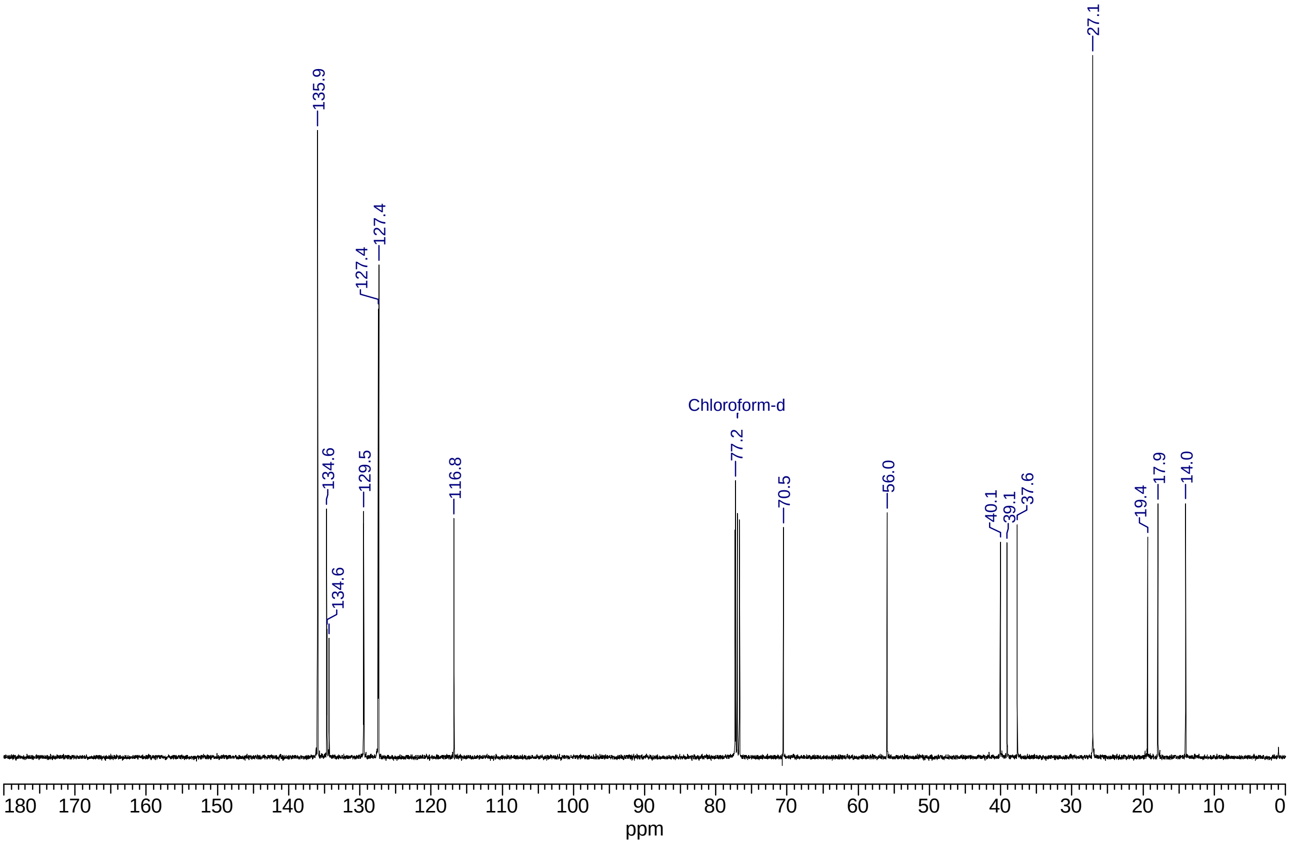

Methanol-d4
173.0
166.9
161.9
159.6
150.0
142.3
139.2
135.9
121.7
115.9
77.1
73.9
71.3
69.2
56.4
52.6
45.2
43.2
41.0
37.9
37.4
36.2
32.6
29.0
26.4
26.0
20.0
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

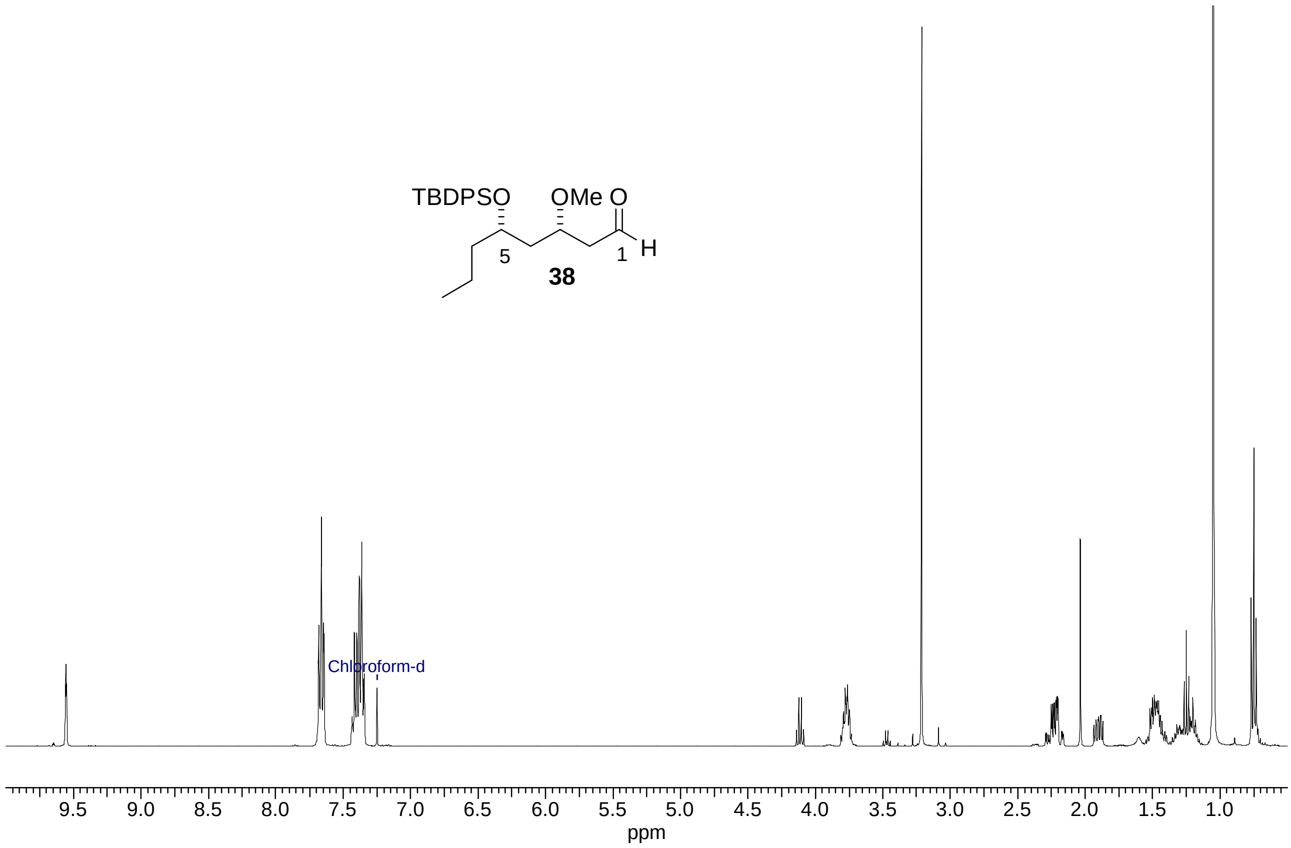

TBDPSO
OH
1
6
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

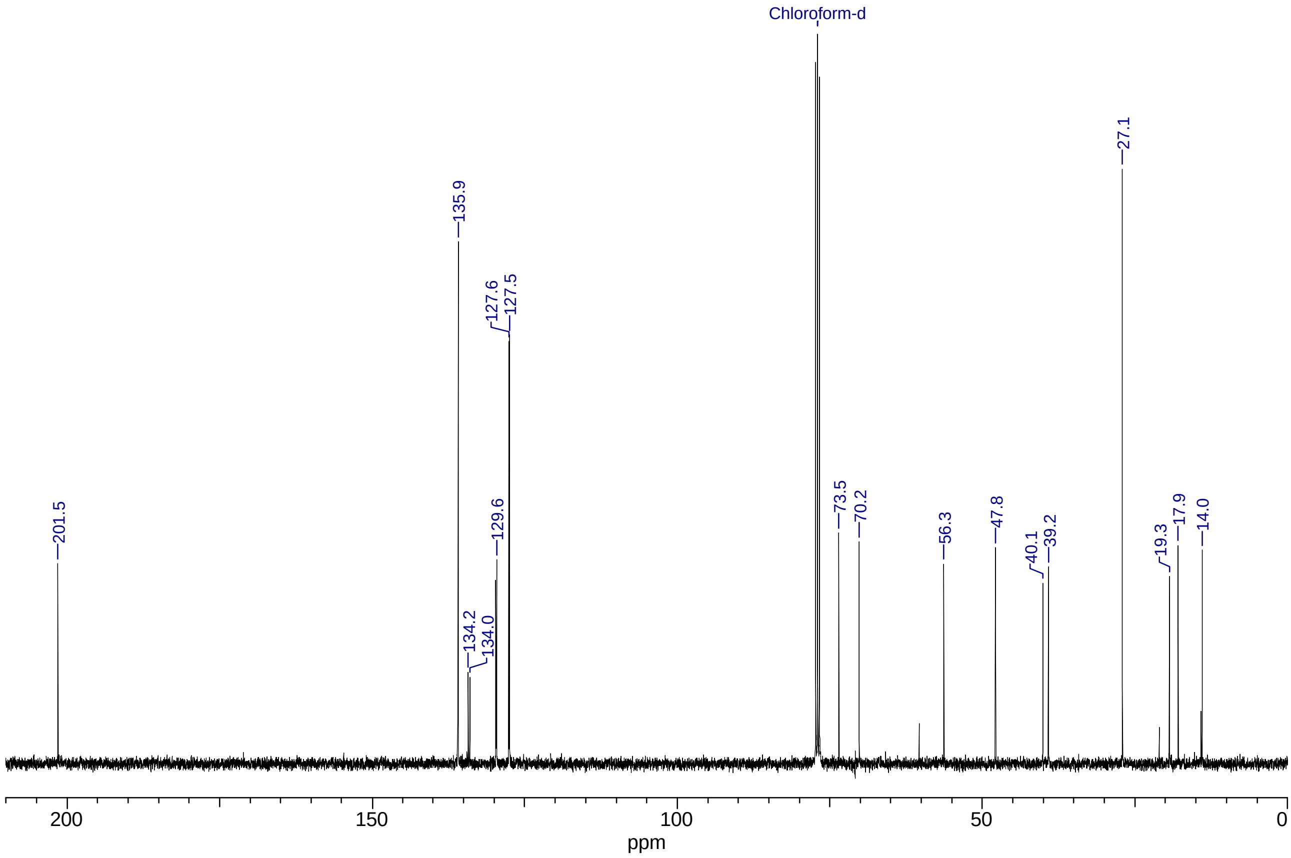
36


135.9
134.7
134.4
129.7
127.5
117.6
Chloroform-d
73.3
69.4
42.6
42.0
39.4
27.0
19.3
18.0
13.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


TBDPSO
OMe
1
6
37
Chloroform-d
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
ppm


135.9
134.6
134.6
129.5
127.4
127.4
116.8
Chloroform-d
77.2
70.5
56.0
40.1
39.1
37.6
27.1
19.4
17.9
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


TBDPSO
OMe
O
5
1
H
38
Chloroform-d
9.5
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
ppm


Chloroform-d
201.5
135.9
134.2
134.0
129.6
127.6
127.5
73.5
70.2
56.3
47.8
40.1
39.2
27.1
19.3
17.9
14.0
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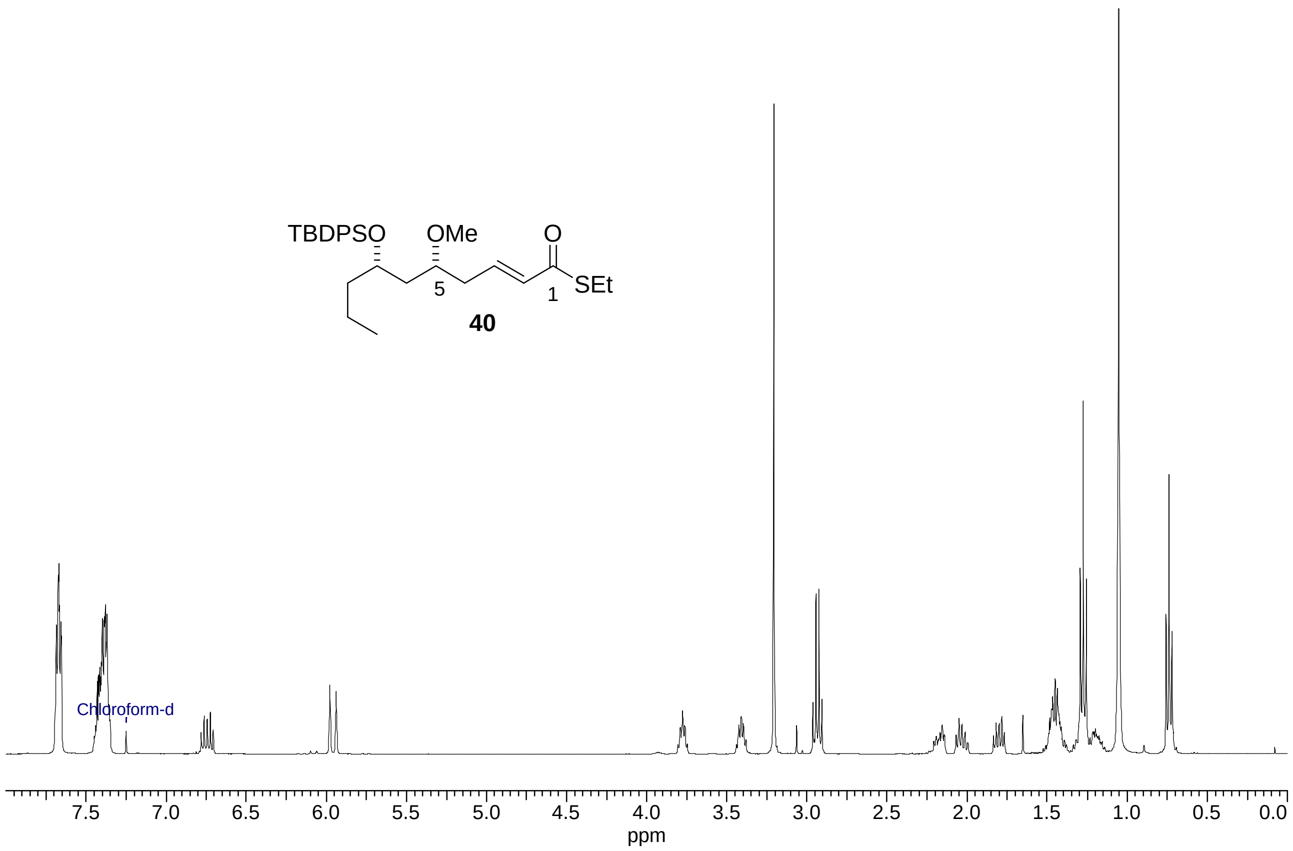
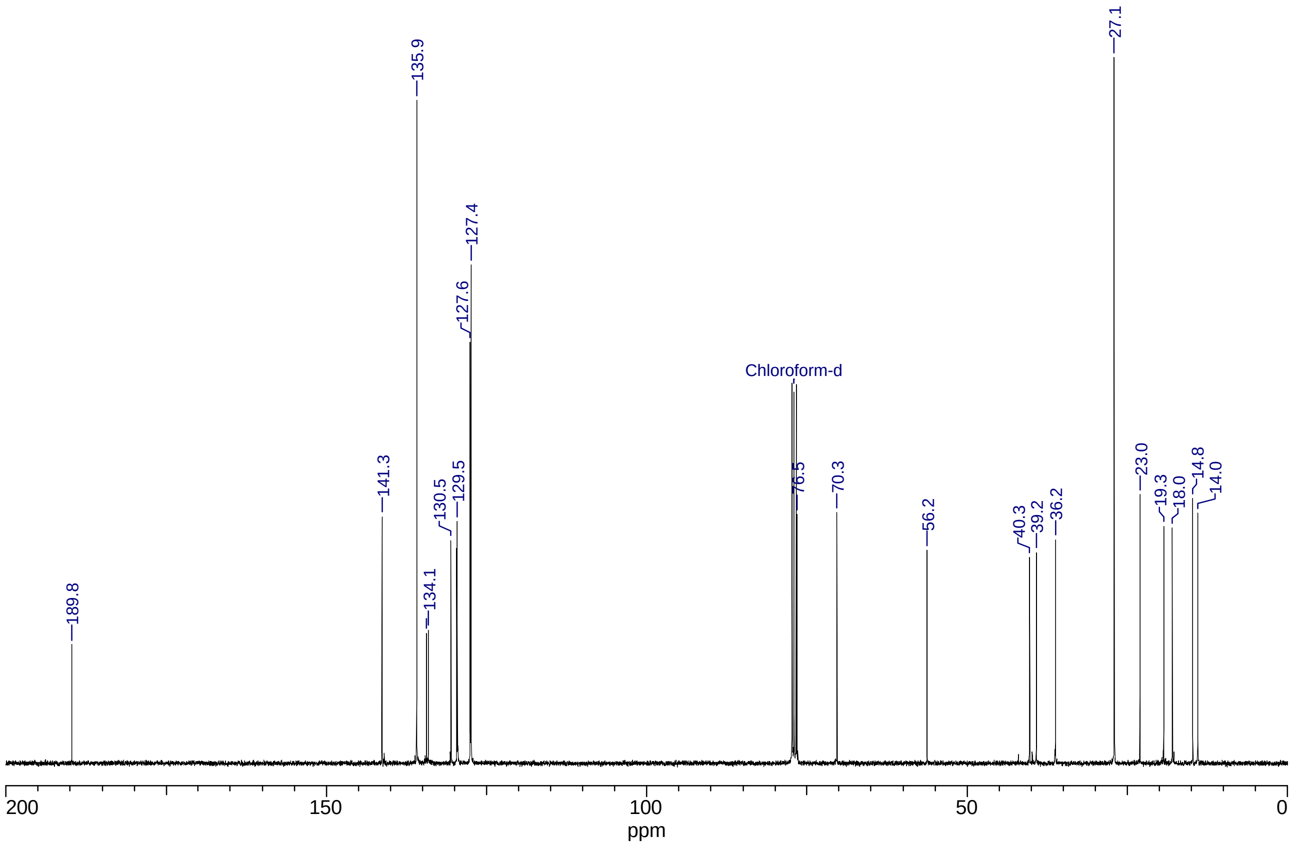
100
50
0
ppm

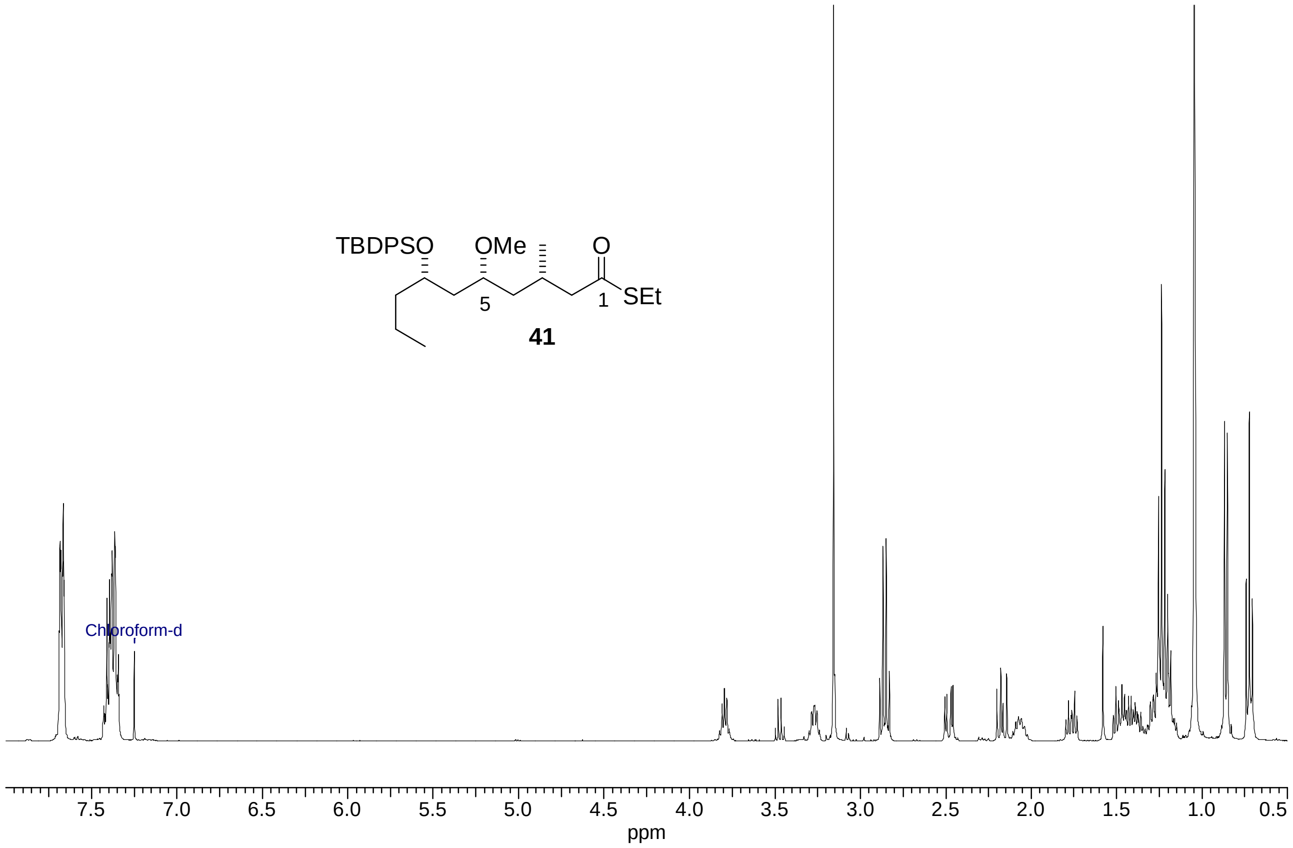


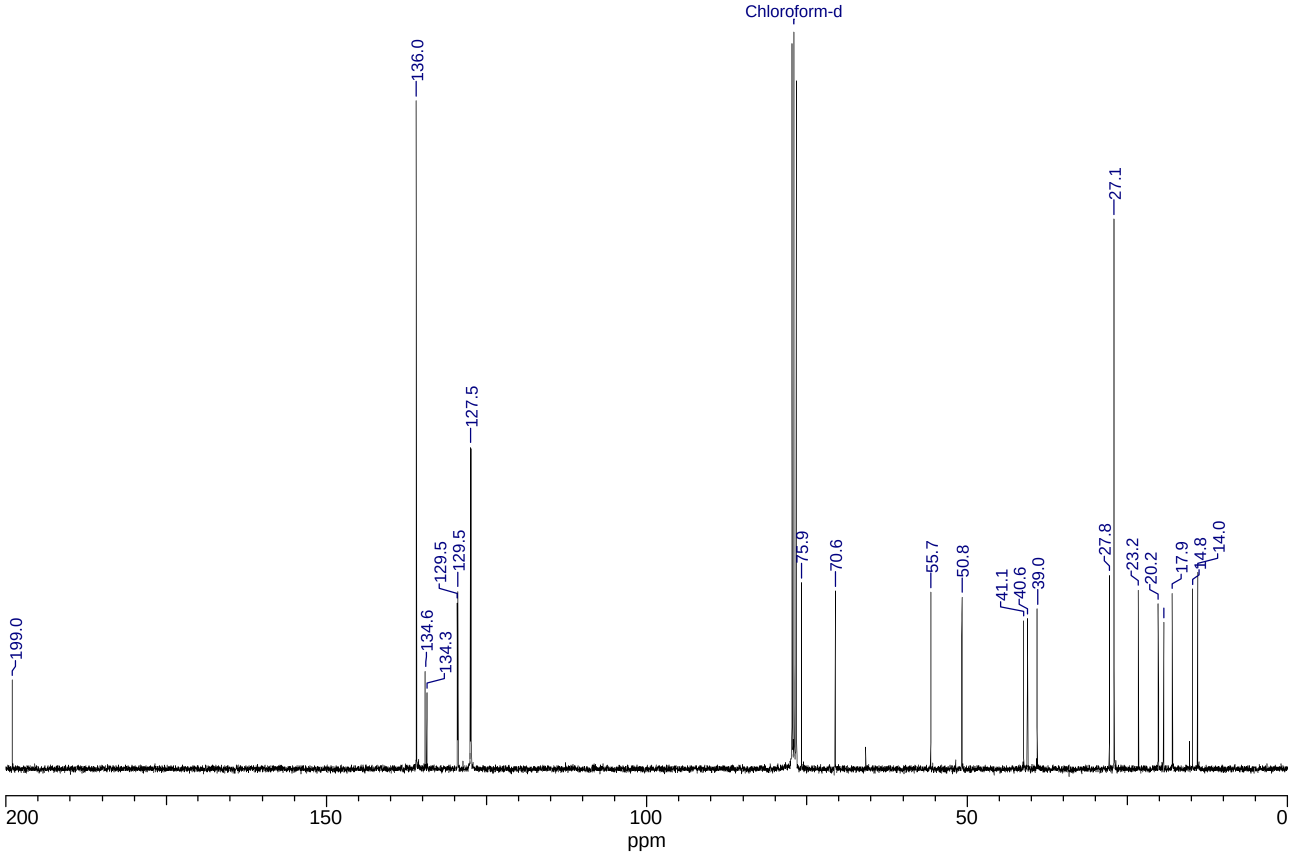
40

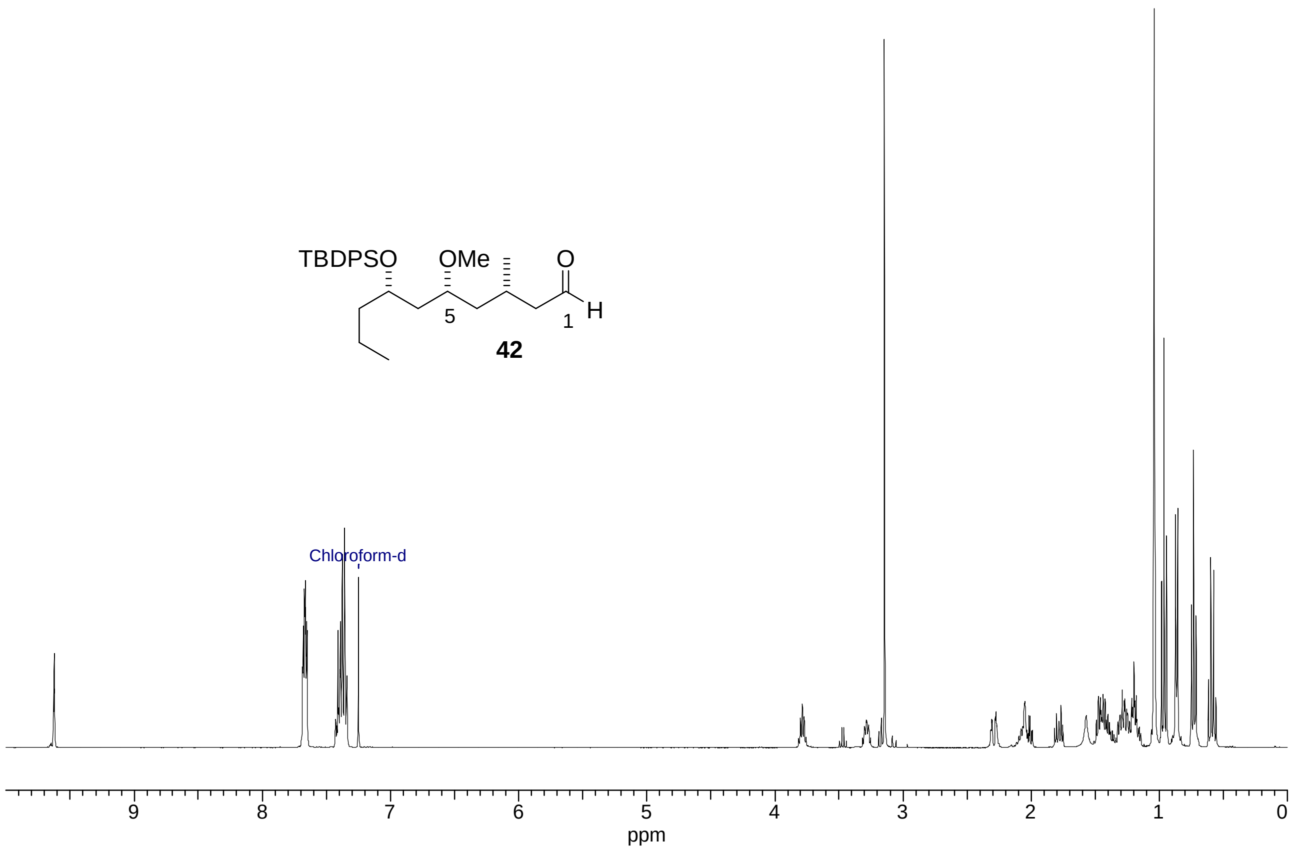
TBDPSO
OMe
O
SEt
5
1
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

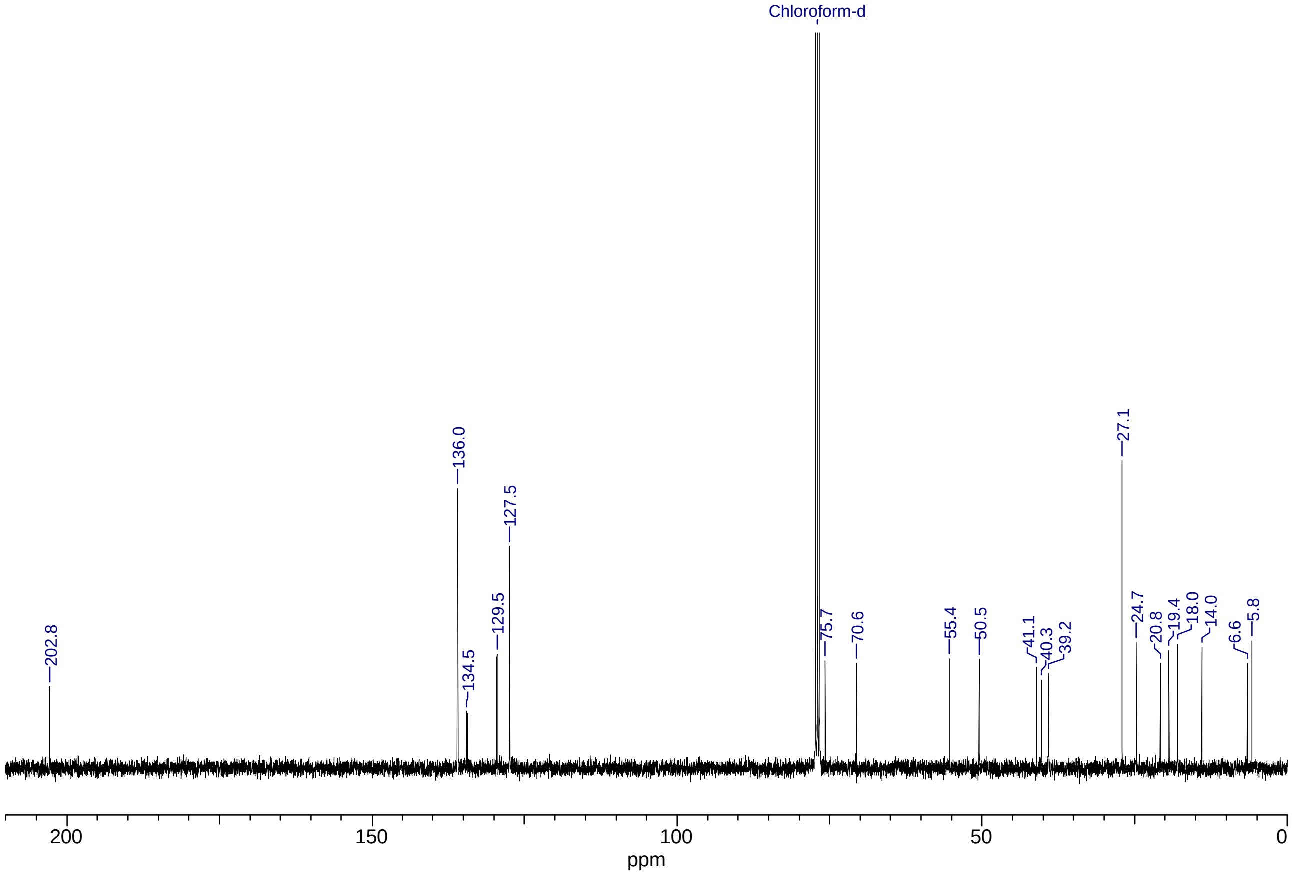


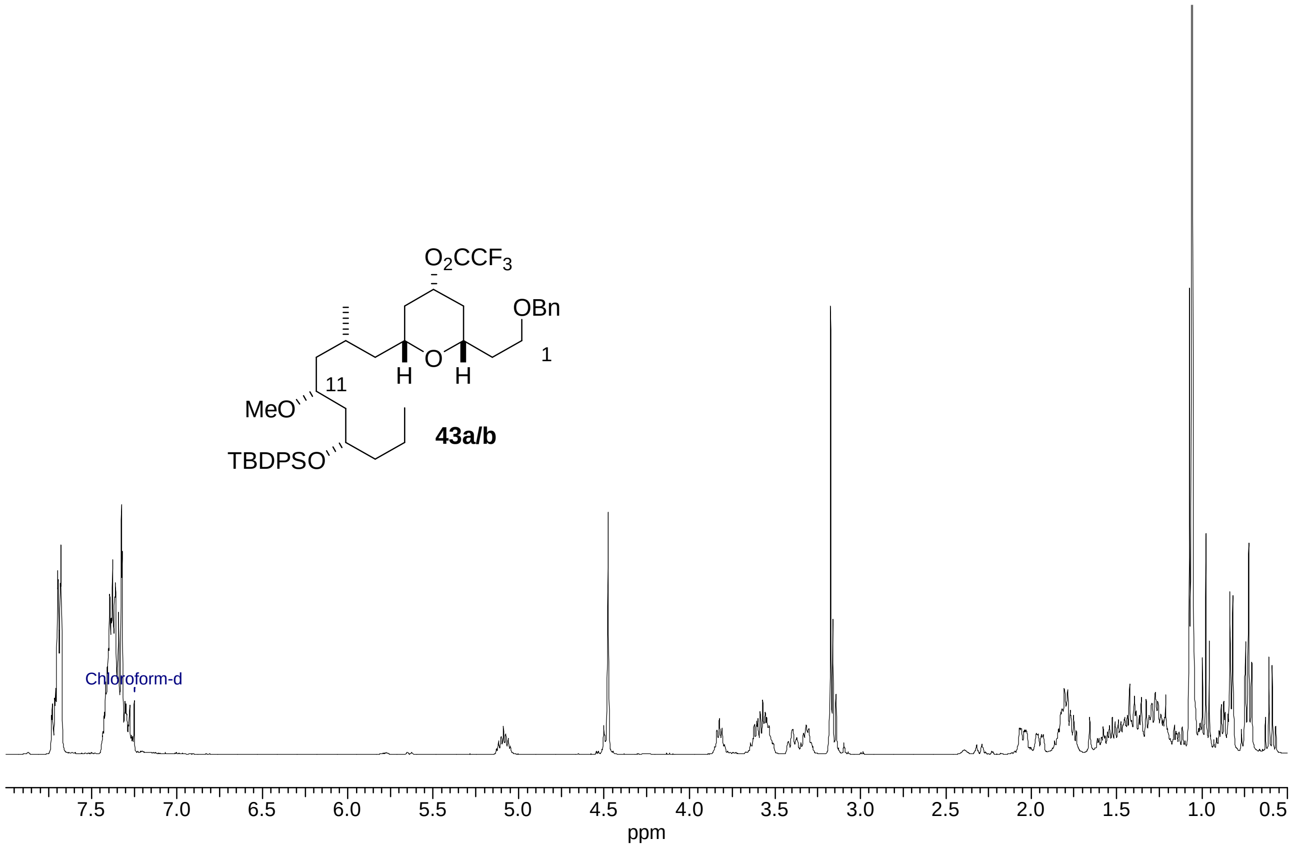
189.8
141.3
135.9
134.1
130.5
129.5
127.6
127.4
Chloroform-d
76.5
70.3
56.2
40.3
39.2
36.2
27.1
23.0
19.3
18.0
14.8
14.0
200
150
100
50
0
ppm


TBDPSO
OMe
O
5
1
SEt
41
Chloroform-d
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
ppm

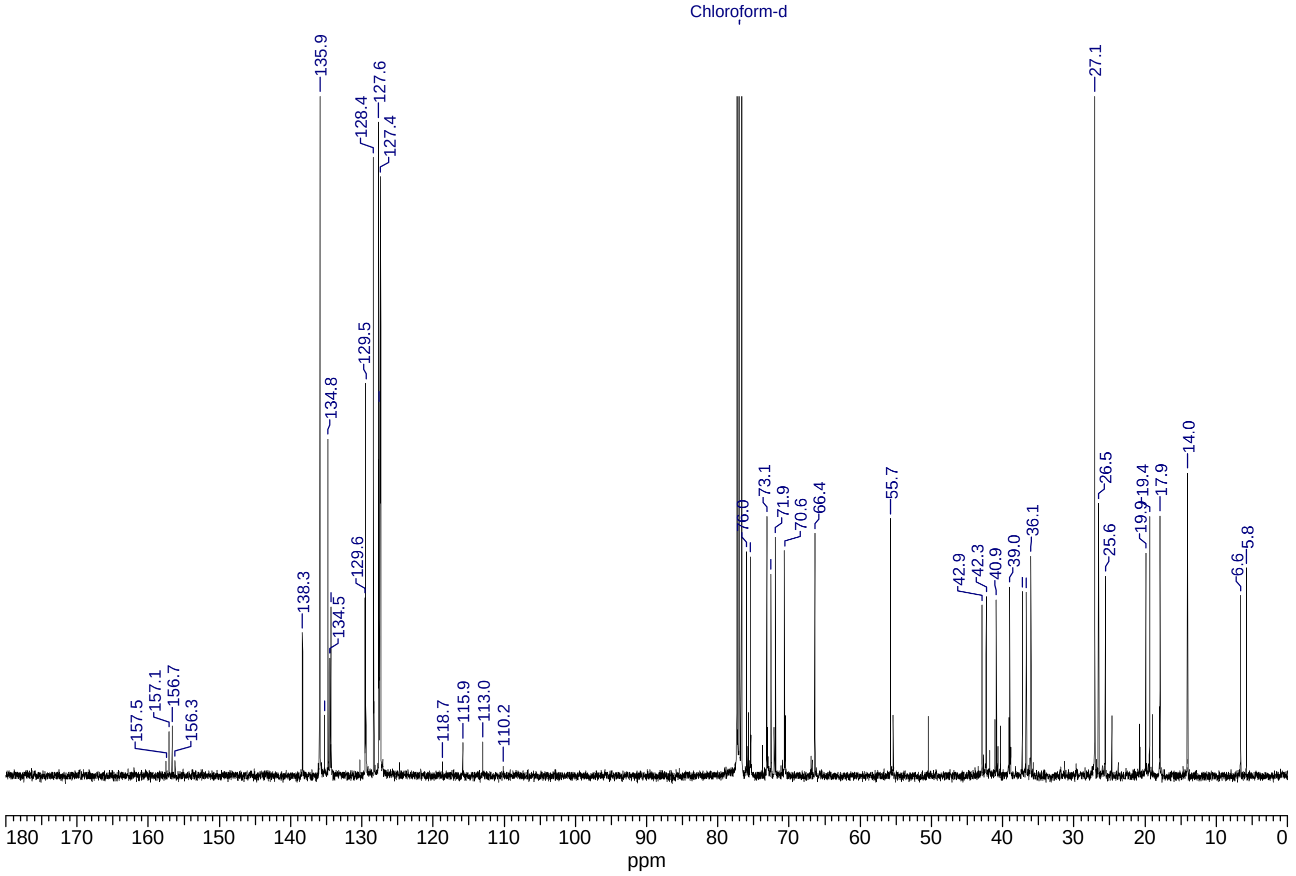

Chloroform-d
199.0
136.0
134.6
134.3
129.5
129.5
127.5
75.9
70.6
55.7
50.8
41.1
40.6
39.0
27.8
27.1
23.2
20.2
17.9
14.8
14.0
200
150
100
50
0
ppm

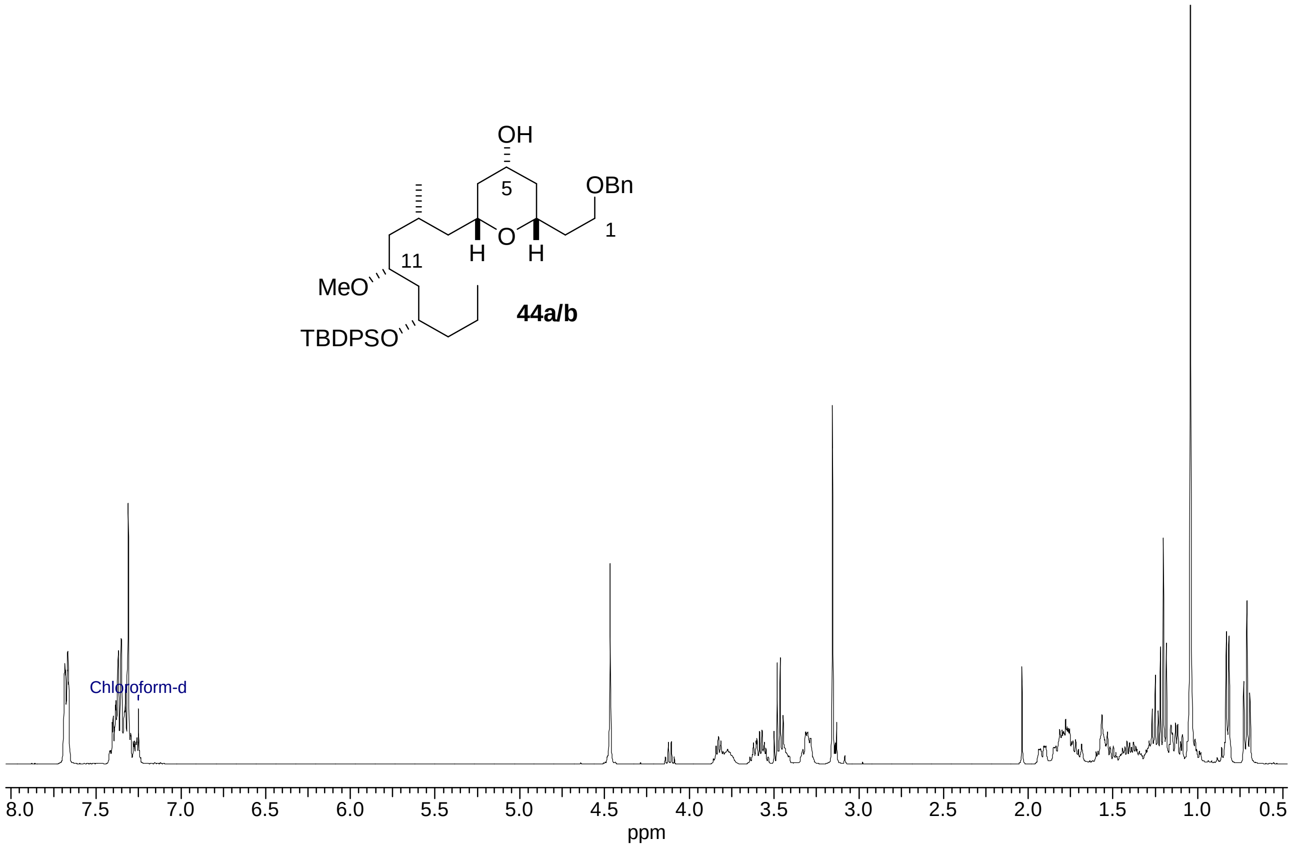

TBDPSO
OMe
O
H
5
1
42
Chloroform-d
9
8
7
6
5
4
3
2
1
0
ppm


Chloroform-d
202.8
136.0
134.5
129.5
127.5
75.7
70.6
55.4
50.5
41.1
40.3
39.2
27.1
24.7
20.8
19.4
18.0
14.0
6.6
5.8
200
150
100
50
0
ppm


O2CCF3
OBn
1
O
H
H
11
MeO
TBDPSO
Chloroform-d
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
ppm

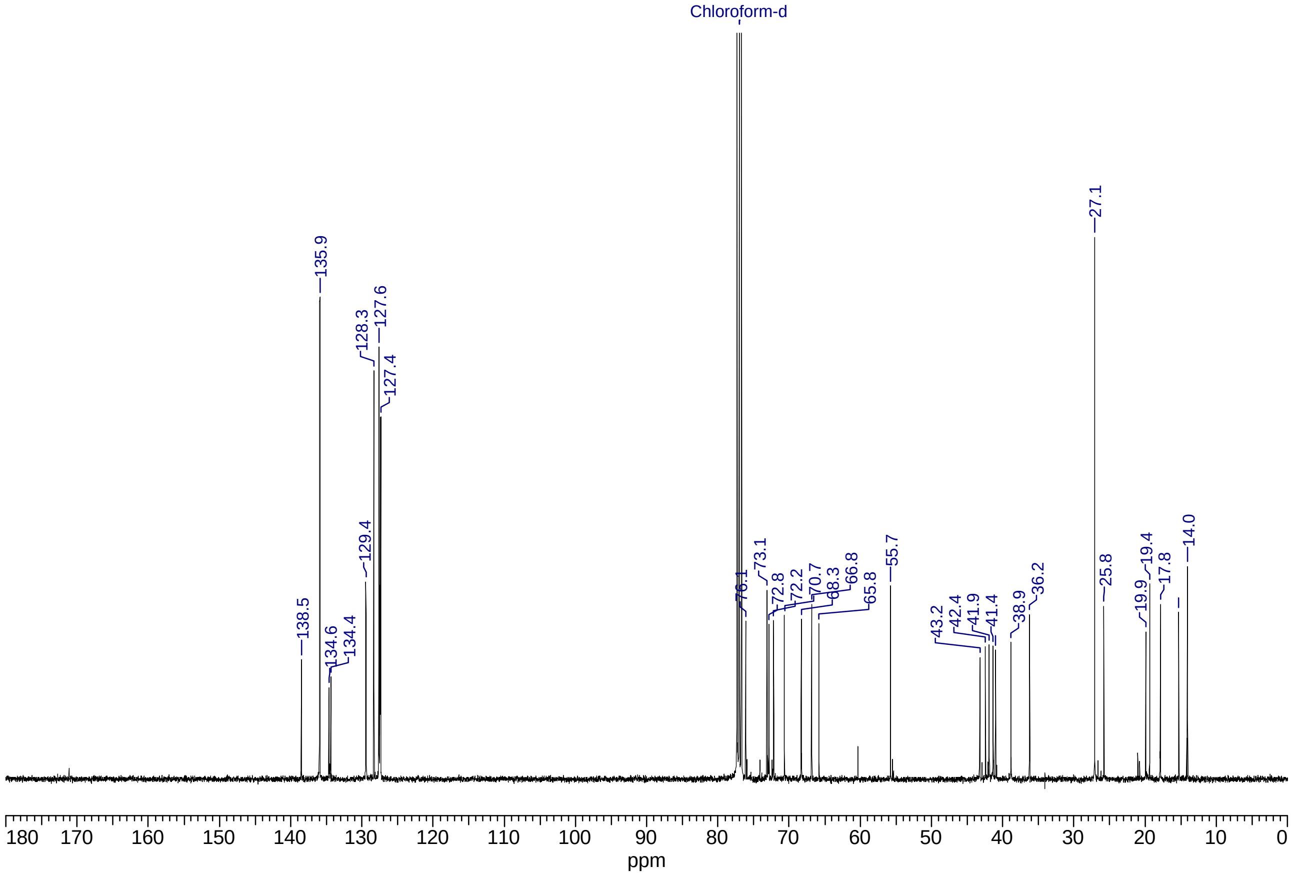
43a/b

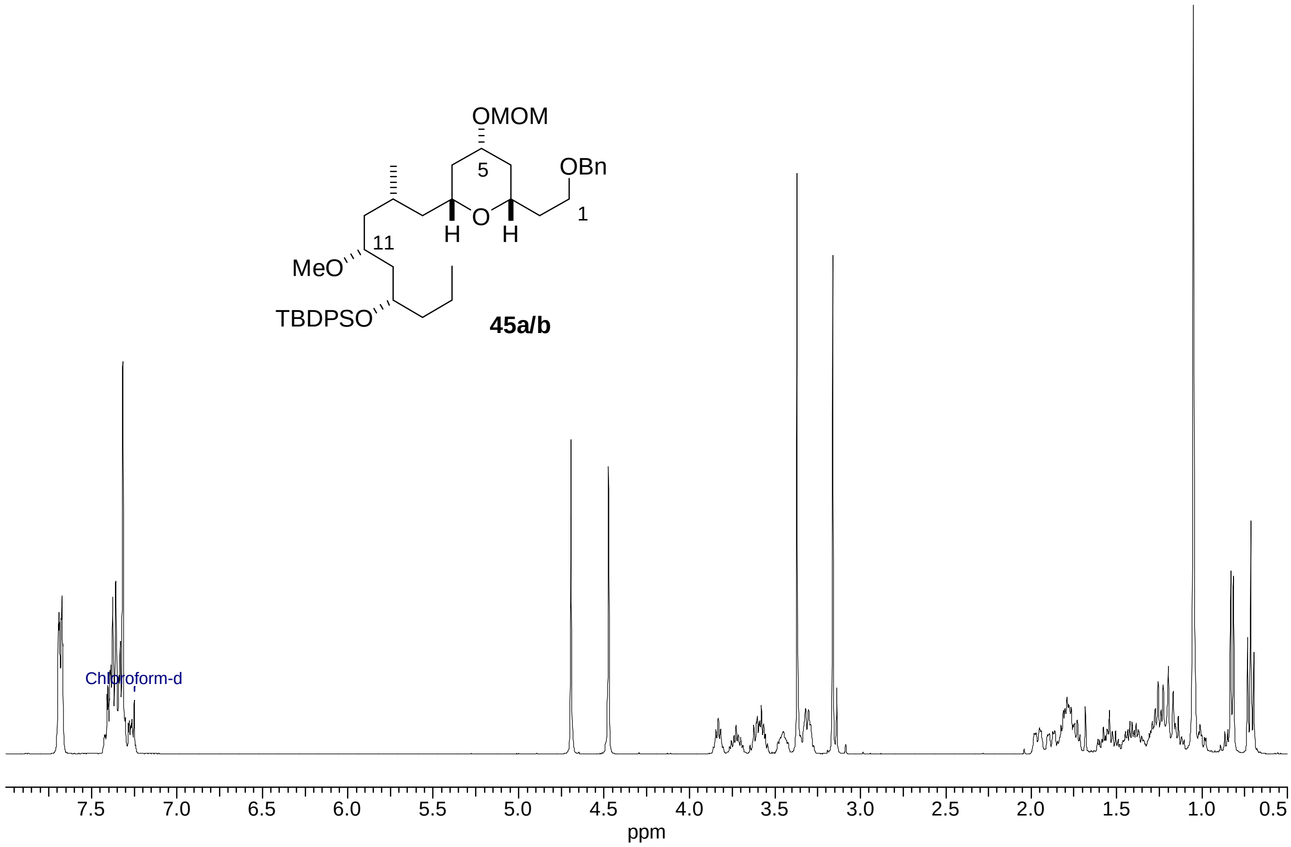

Chloroform-d
157.5
157.1
156.7
156.3
138.3
135.9
134.8
134.5
129.6
129.5
128.4
127.6
127.4
118.7
115.9
113.0
110.2
76.0
73.1
71.9
70.6
66.4
55.7
42.9
42.3
40.9
39.0
36.1
27.1
26.5
25.6
19.9
19.4
17.9
14.0
6.6
5.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OH
5
OBn
1
O
H
H
11
MeO
TBDPSO

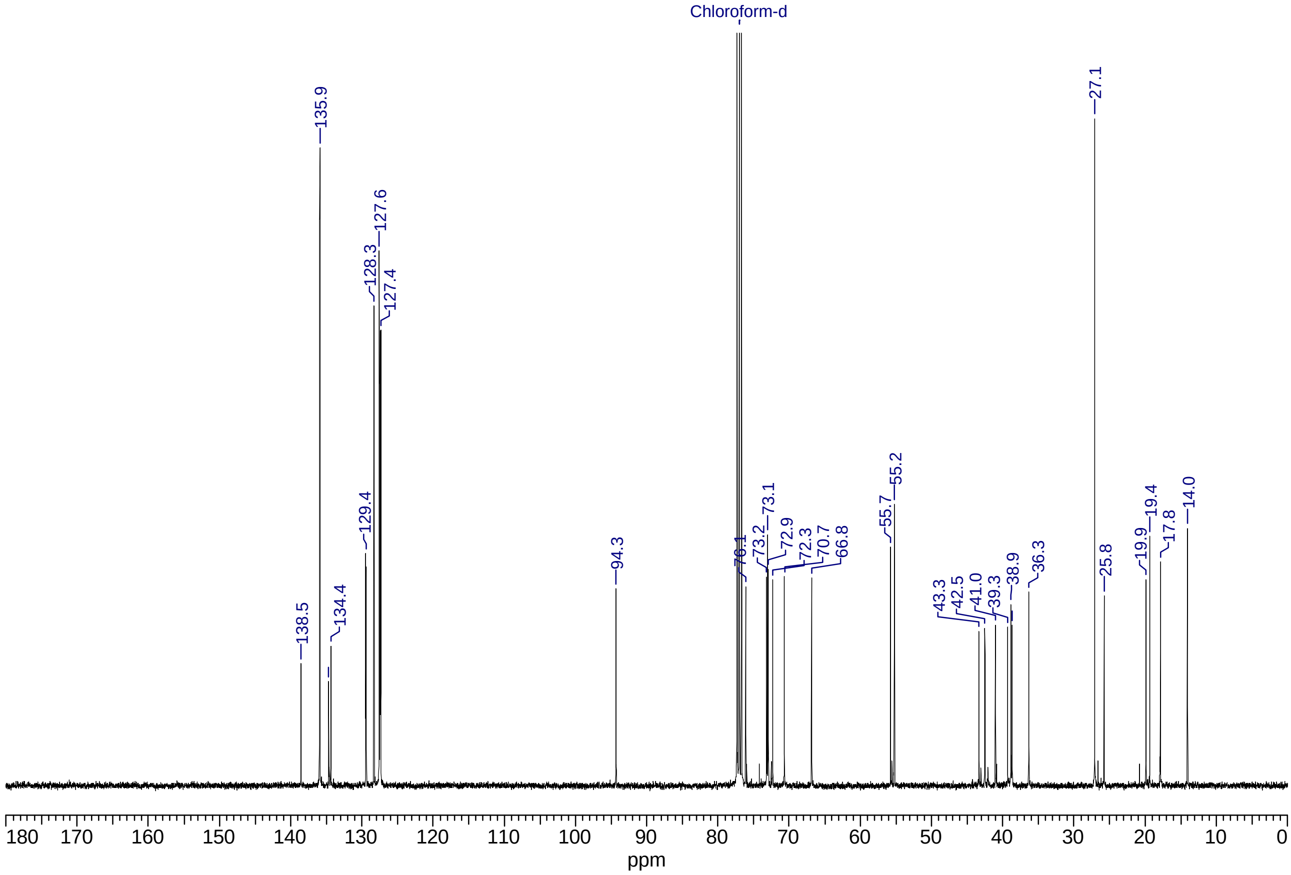
44a/b

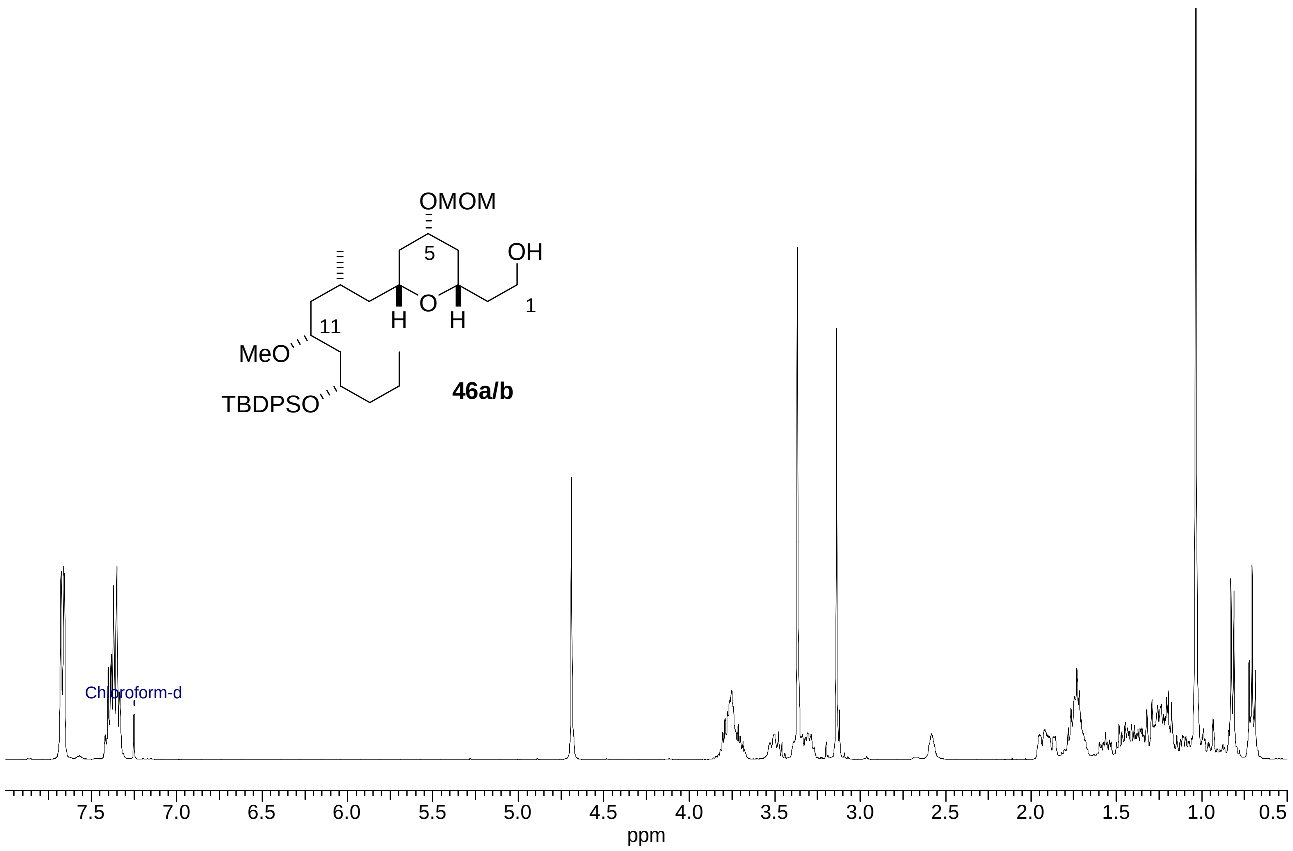
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
138.5
135.9
134.6
134.4
129.4
128.3
127.6
127.4
76.1
73.1
72.8
72.2
70.7
68.3
66.8
65.8
55.7
43.2
42.4
41.9
41.4
38.9
36.2
27.1
25.8
19.9
19.4
17.8
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

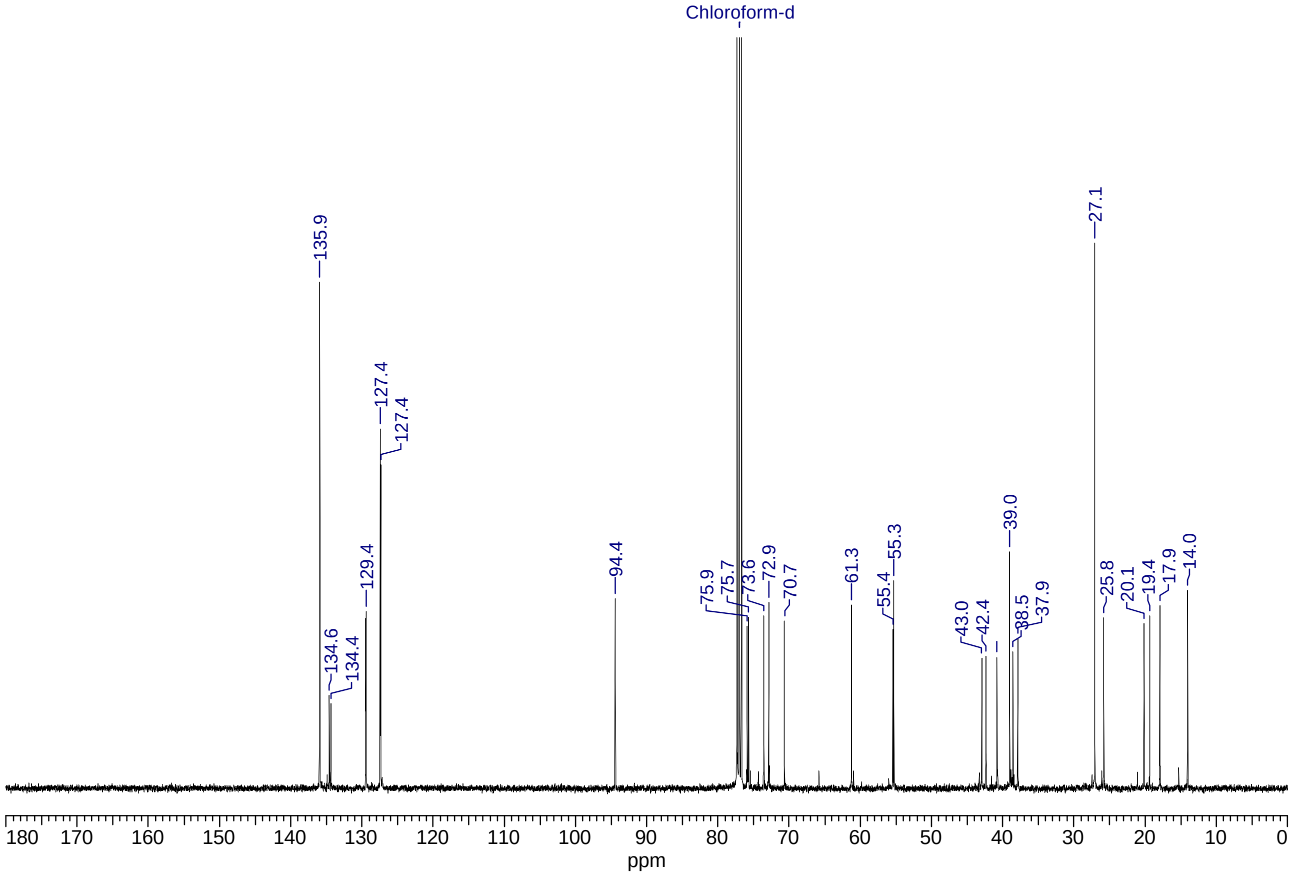

OMOM
5
OBn
1
O
H
H
11
MeO
TBDPSO
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

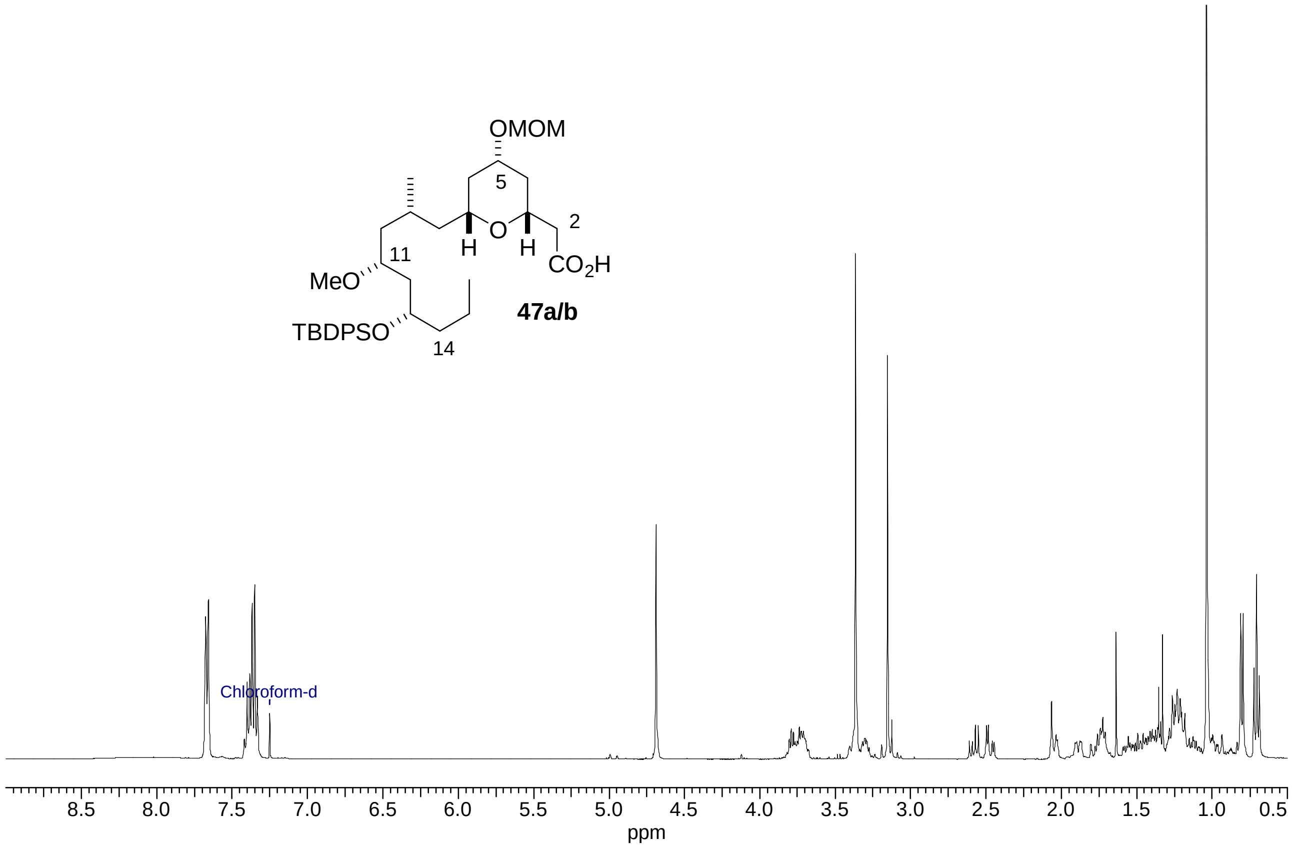
45a/b

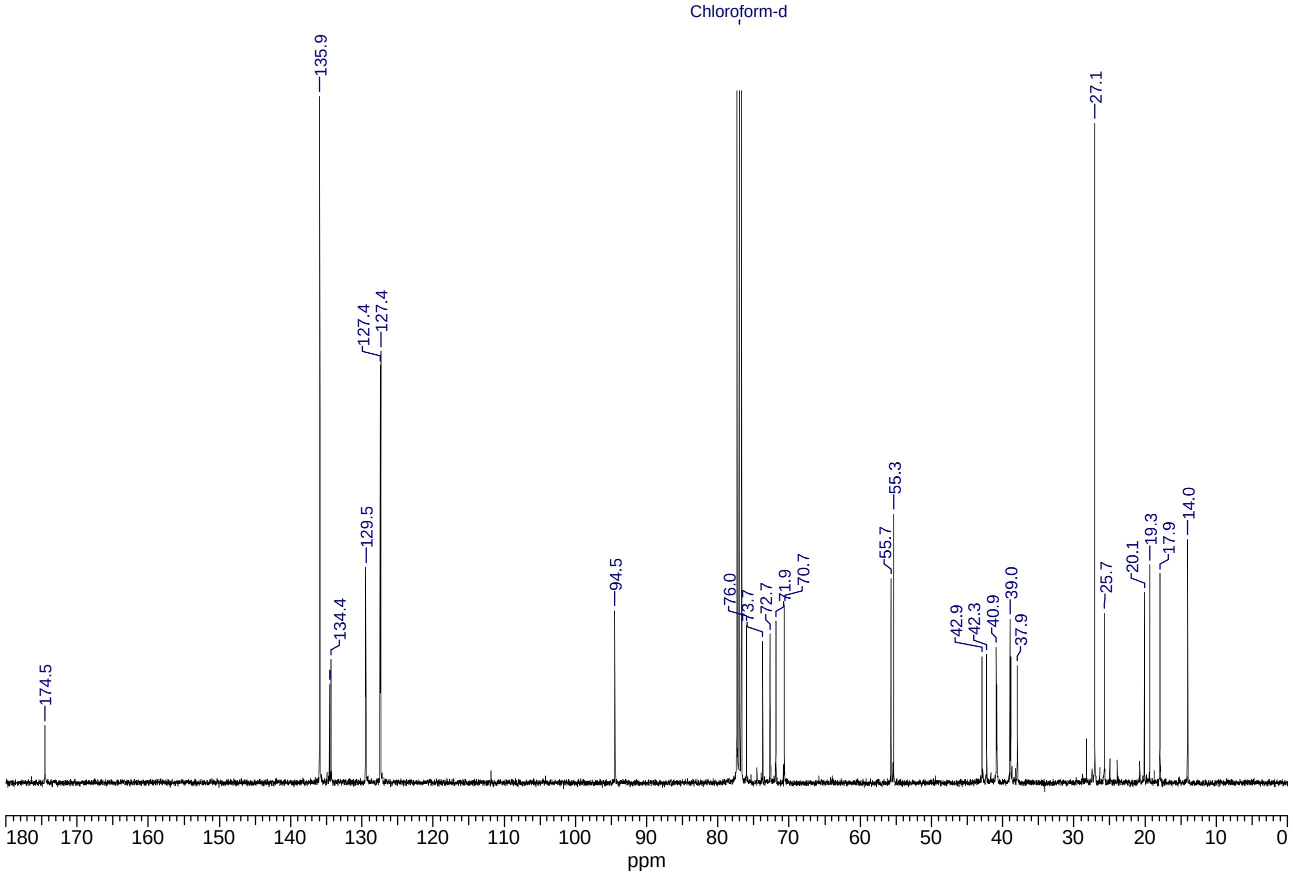

Chloroform-d
138.5
135.9
134.4
129.4
128.3
127.6
127.4
94.3
76.1
73.2
73.1
72.9
72.3
70.7
66.8
55.7
55.2
43.3
42.5
41.0
39.3
38.9
36.3
27.1
25.8
19.9
19.4
17.8
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

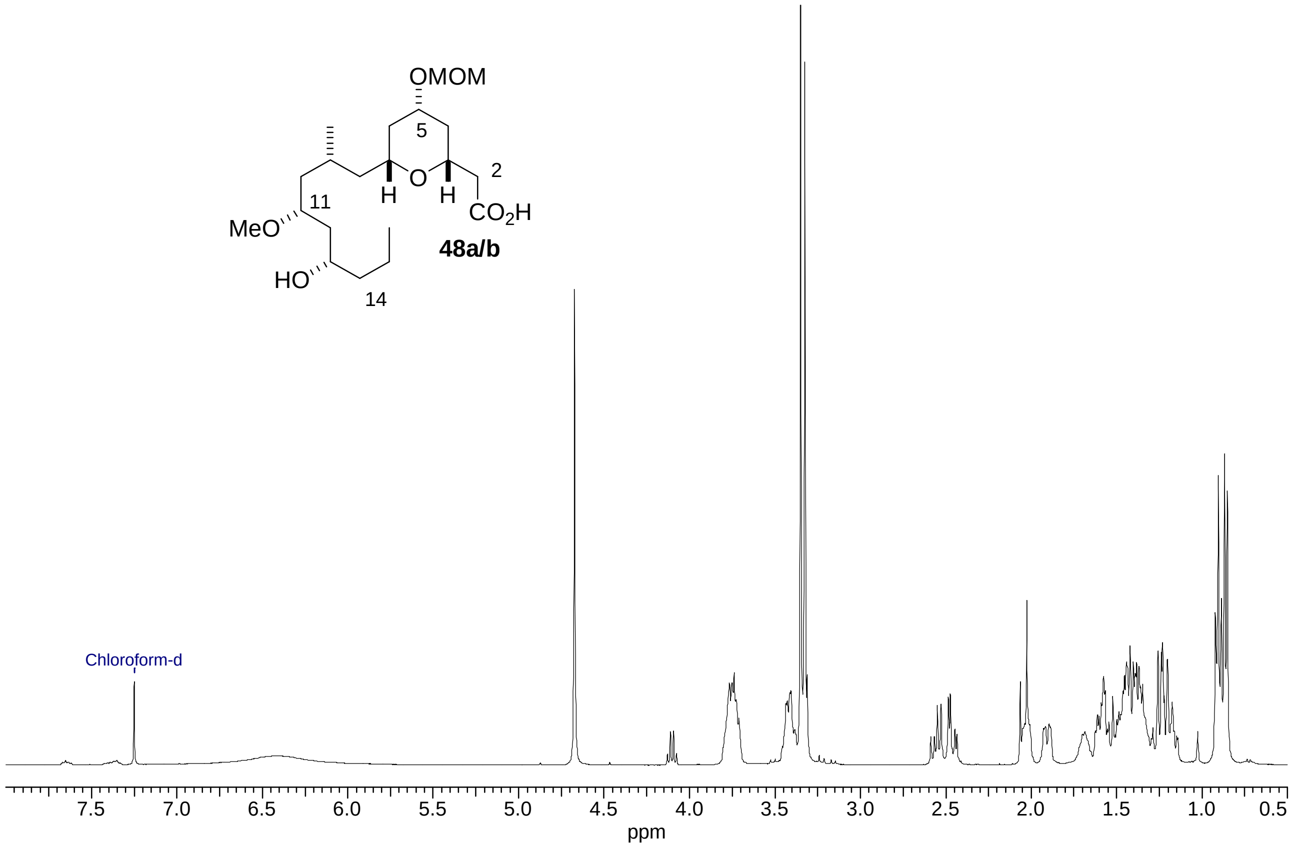

OMOM
5
OH
1
H
O
H
11
MeO
TBDPSO
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

46a/b

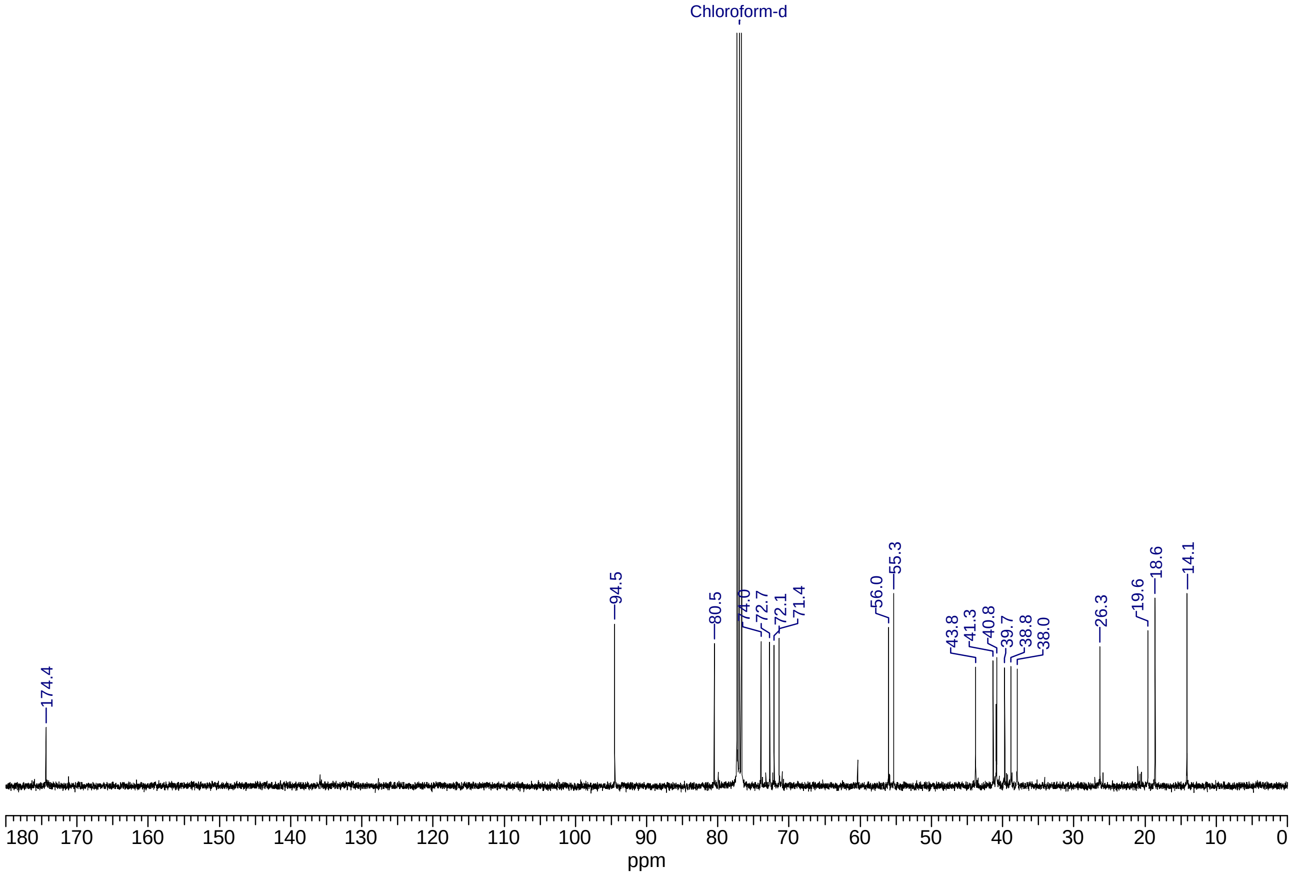

Chloroform-d
135.9
134.6
134.4
129.4
127.4
127.4
94.4
75.9
75.7
73.6
72.9
70.7
61.3
55.4
55.3
43.0
42.4
39.0
38.5
37.9
27.1
25.8
20.1
19.4
17.9
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OMOM
5
2
11
H
O
H
CO2H
MeO
TBDPSO
14
47a/b
Chloroform-d
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
ppm

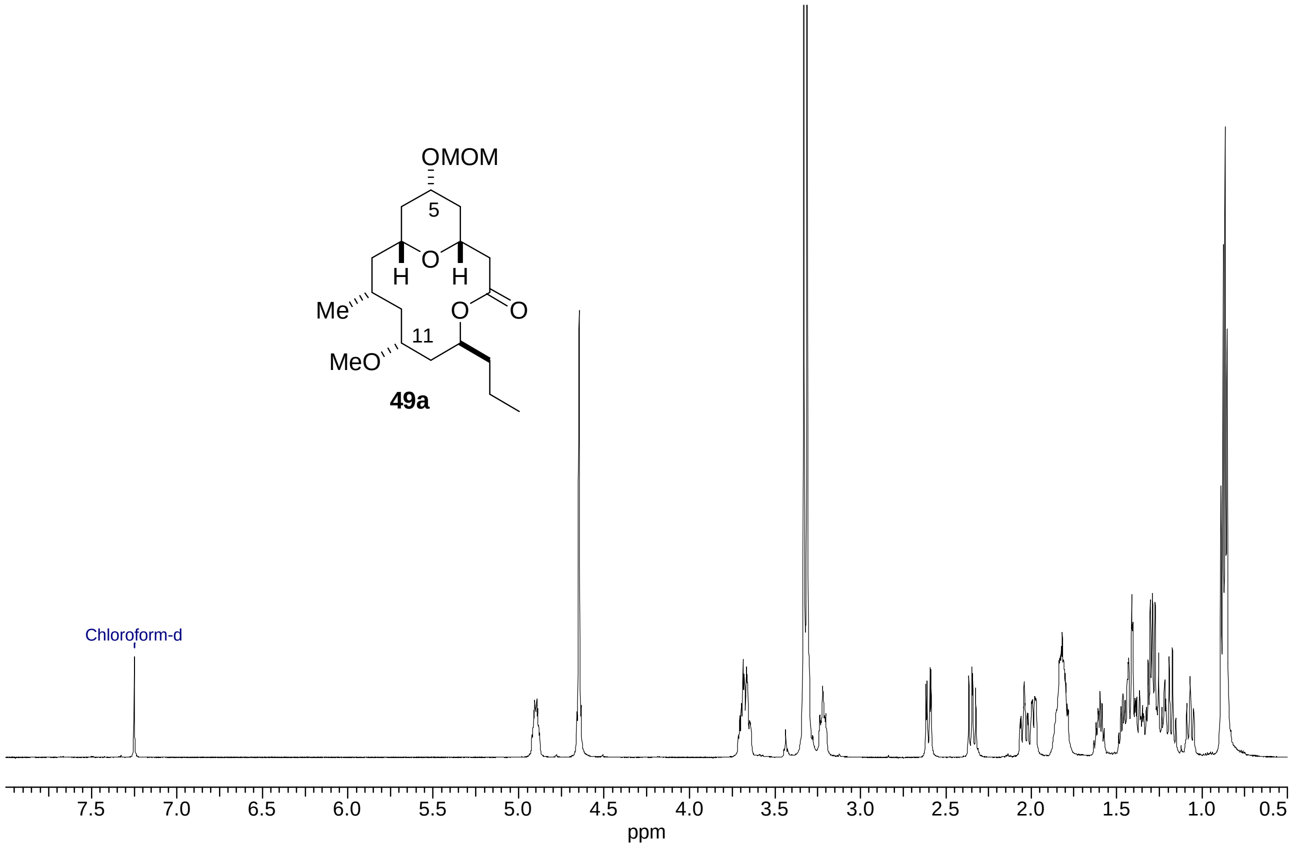

Chloroform-d
174.5
135.9
134.4
129.5
127.4
127.4
94.5
76.0
73.7
72.7
71.9
70.7
55.7
55.3
42.9
42.3
40.9
39.0
37.9
27.1
25.7
20.1
19.3
17.9
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


48a/b

OMOM
5
2
H
O
H
CO2H
11
MeO
HO
14
Chloroform-d
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
ppm

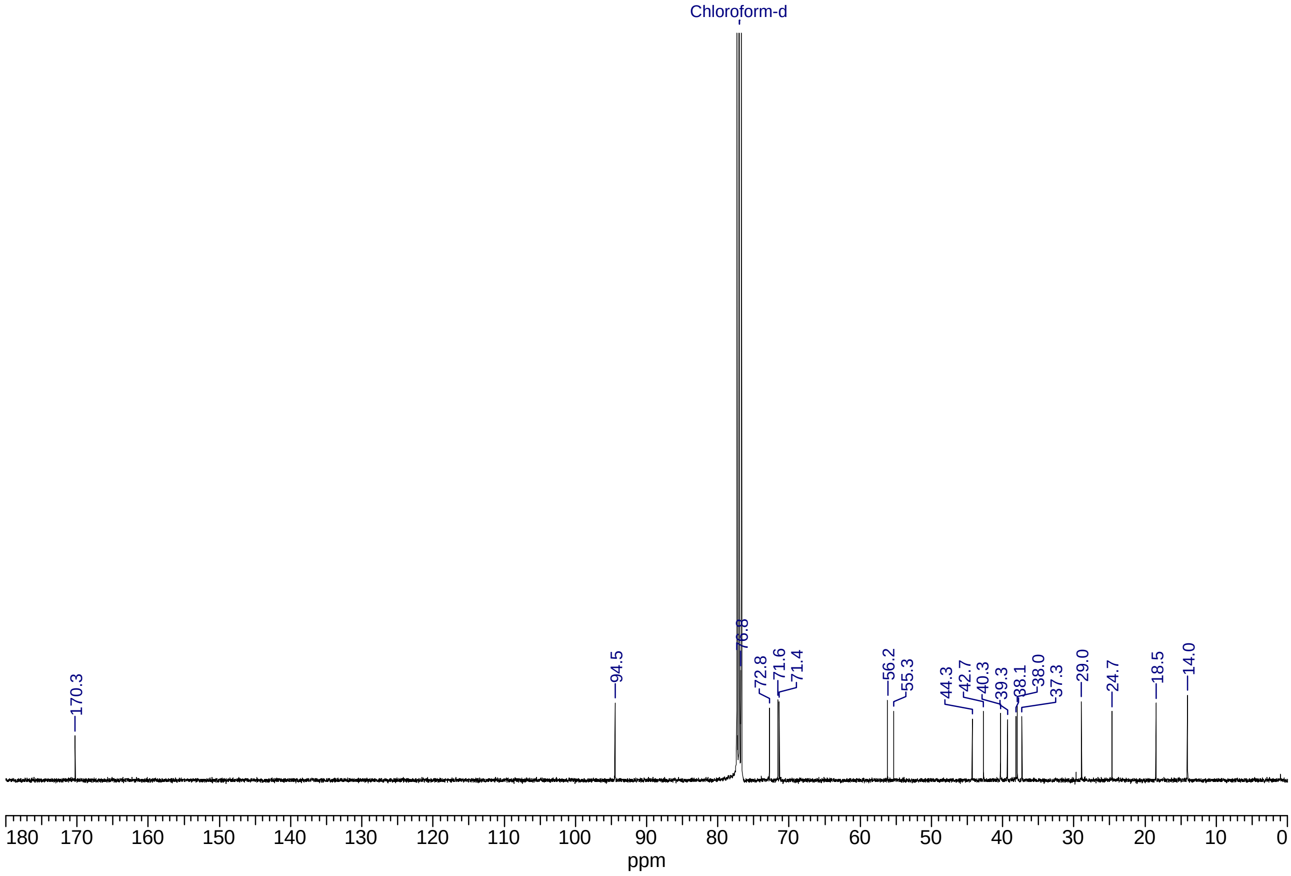


Chloroform-d
174.4
94.5
80.5
74.0
72.7
72.1
71.4
56.0
55.3
43.8
41.3
40.8
39.7
38.8
38.0
26.3
19.6
18.6
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

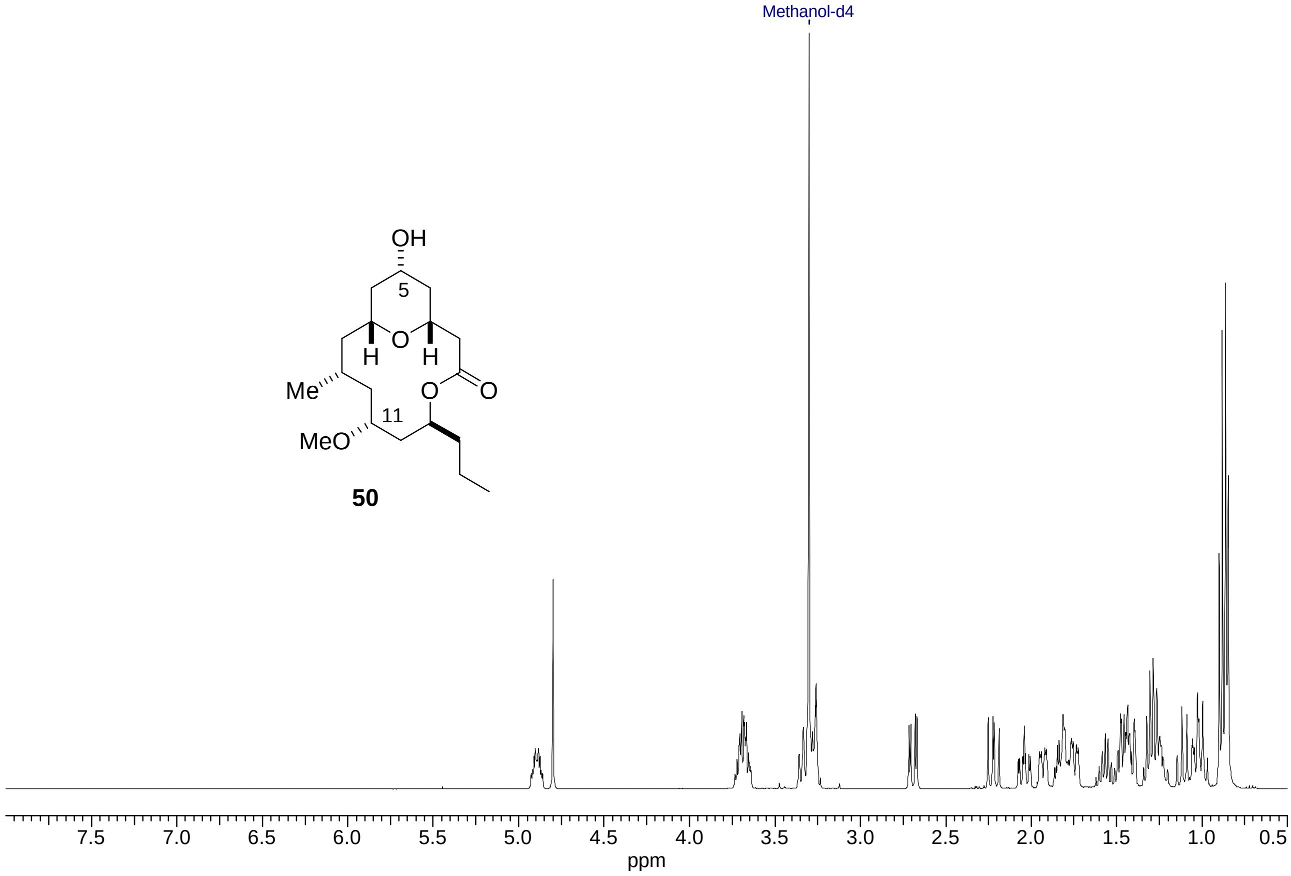


49a

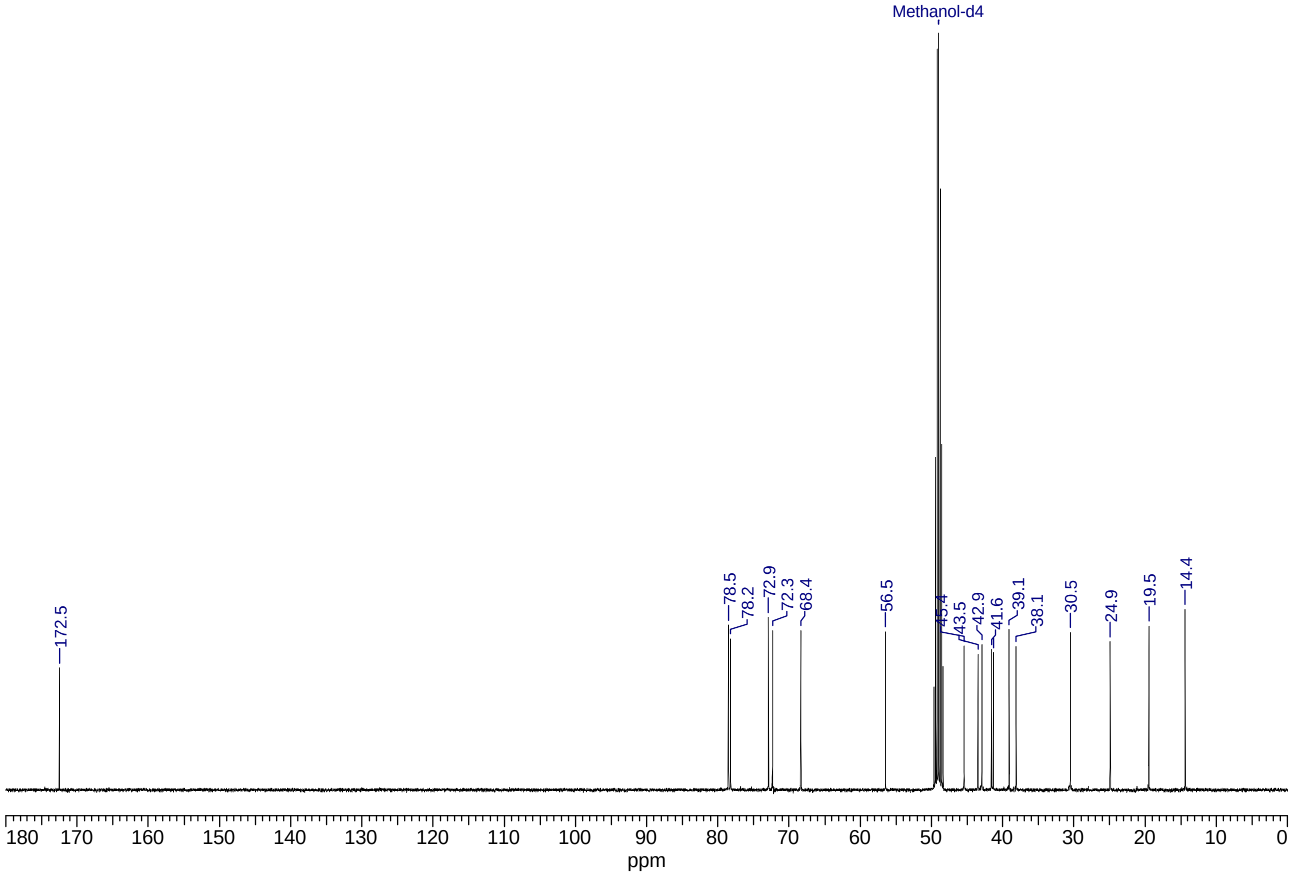
OMOM
5
H
O
H
Me
O
O
11
MeO
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

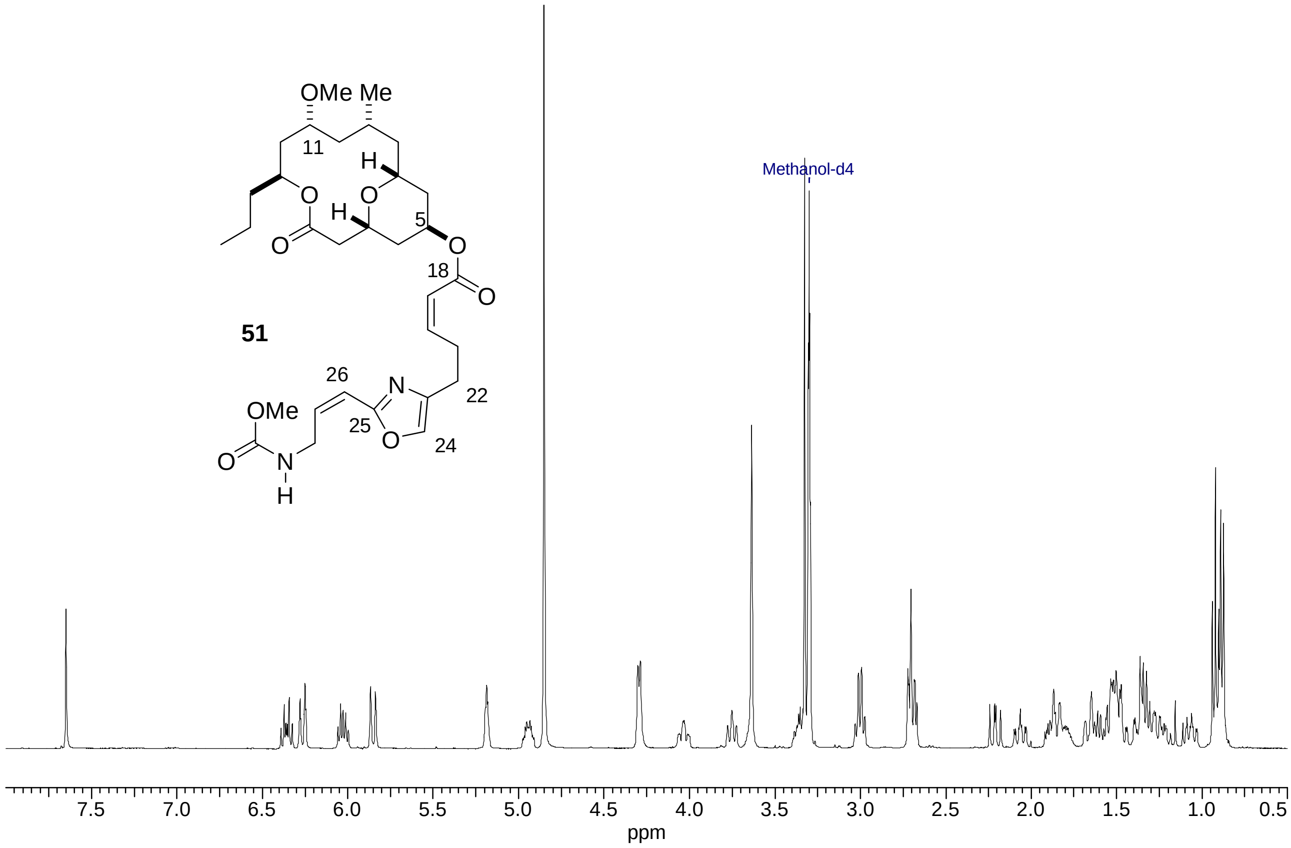


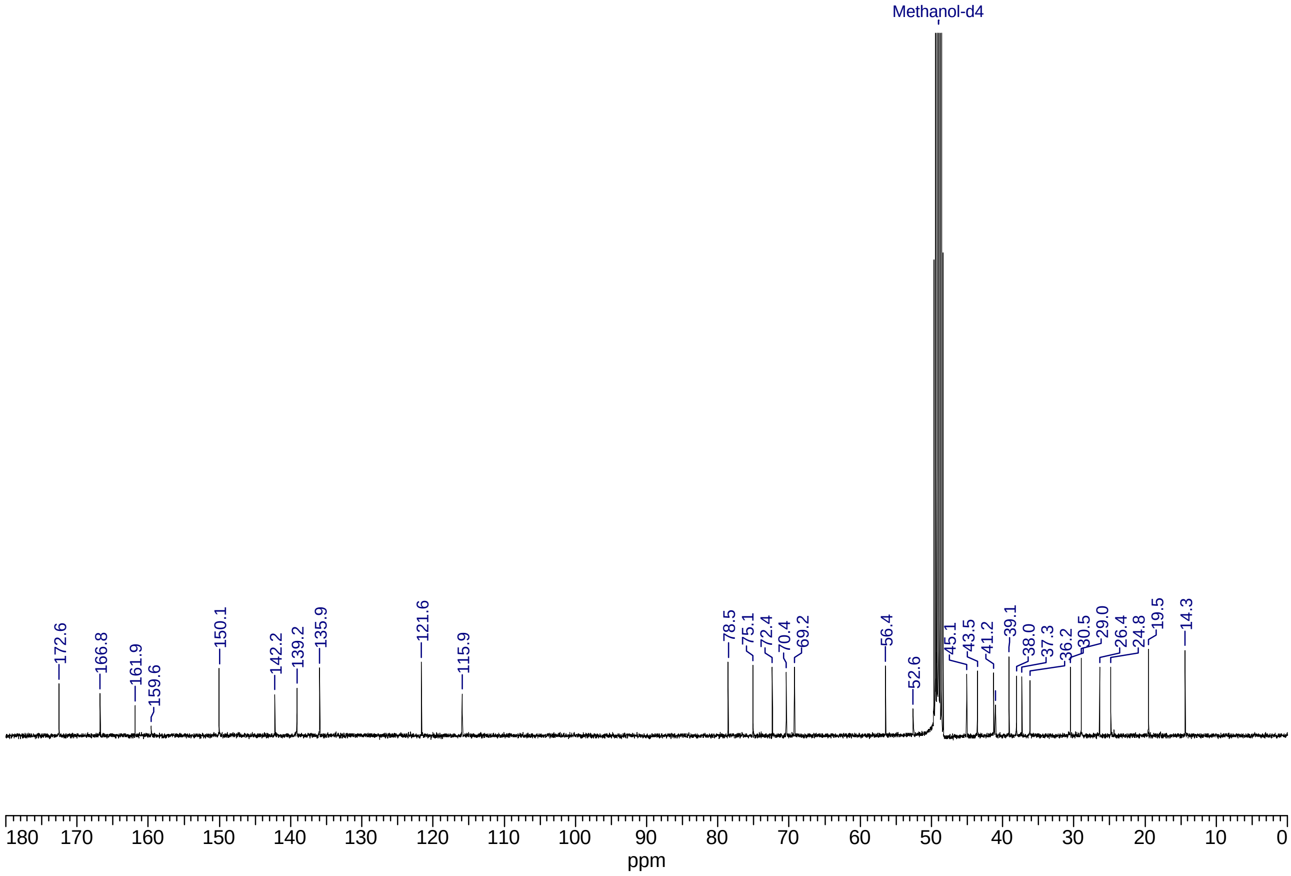
Chloroform-d
170.3
94.5
76.8
72.8
71.6
71.4
56.2
55.3
44.3
42.7
40.3
39.3
38.1
38.0
37.3
29.0
24.7
18.5
14.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

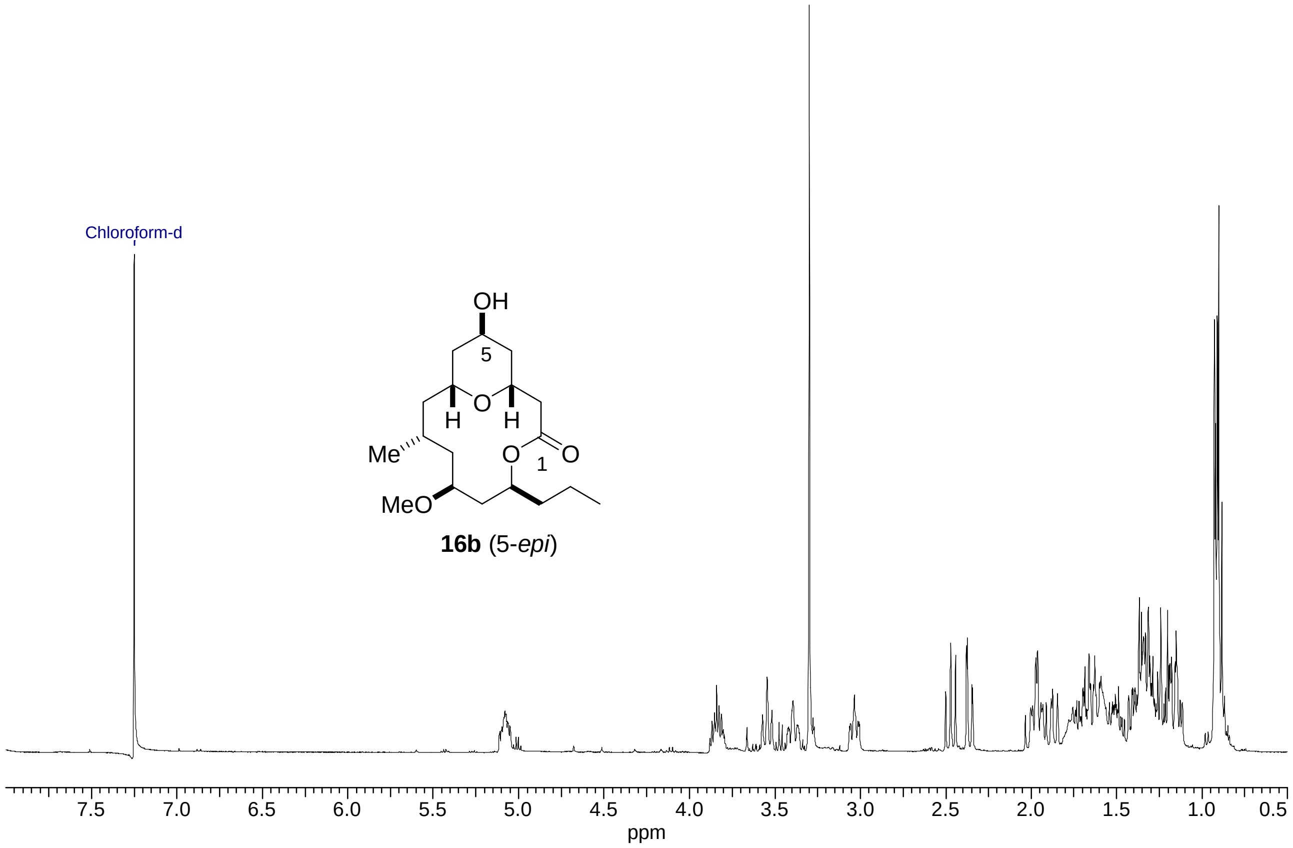

Methanol-d4
OH
5
O
H
H
Me
O
O
11
MeO
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

50


Methanol-d4
172.5
78.5
78.2
72.9
72.3
68.4
56.5
45.4
43.5
42.9
41.6
39.1
38.1
30.5
24.9
19.5
14.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

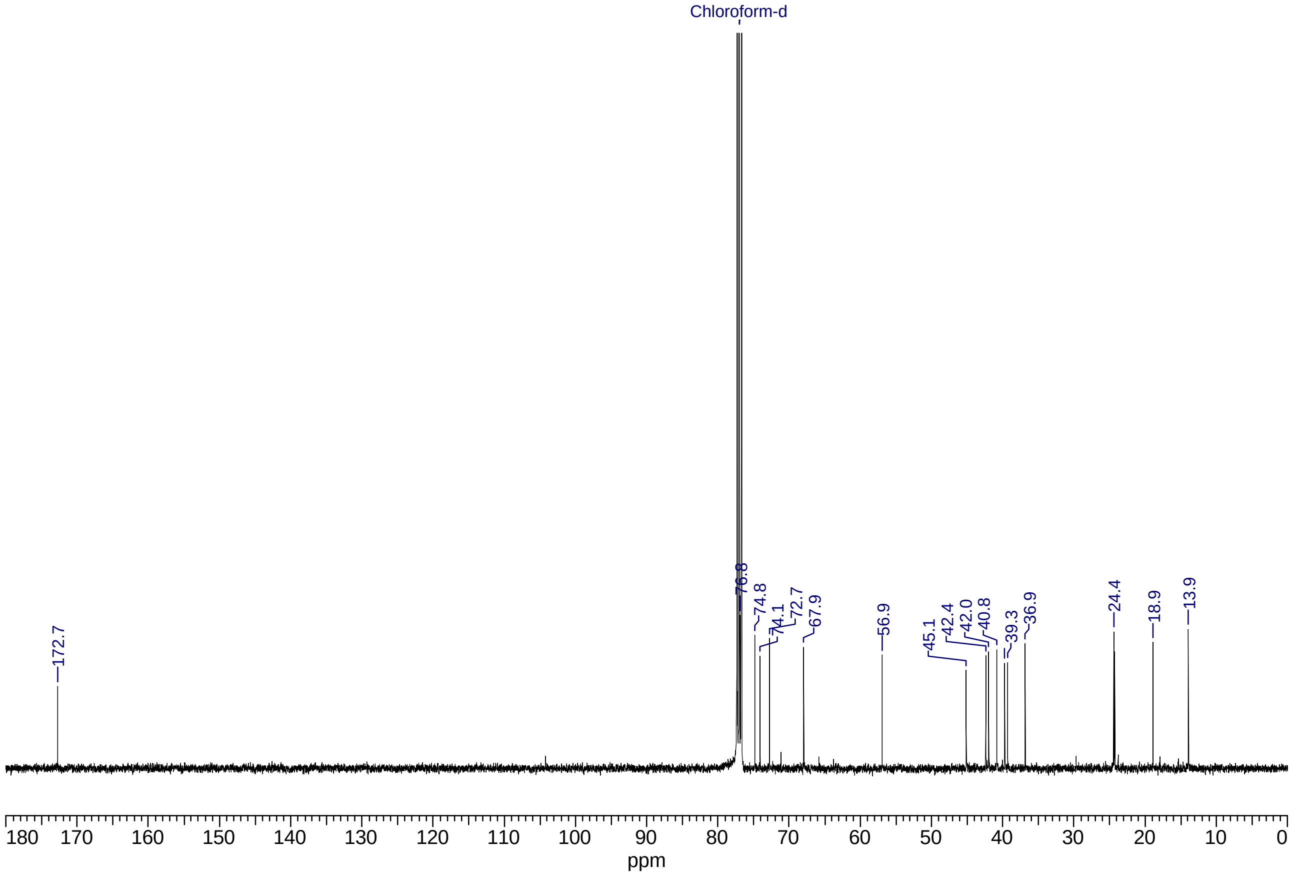

OMe
Me
11
H
O
H
5
O
O
18
O
51
26
N
22
OMe
25
O
24
O
N
H
Methanol-d4
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Methanol-d4
172.6
166.8
161.9
159.6
150.1
142.2
139.2
135.9
121.6
115.9
78.5
75.1
72.4
70.4
69.2
56.4
52.6
45.1
43.5
41.2
39.1
38.0
37.3
36.2
30.5
29.0
26.4
24.8
19.5
14.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

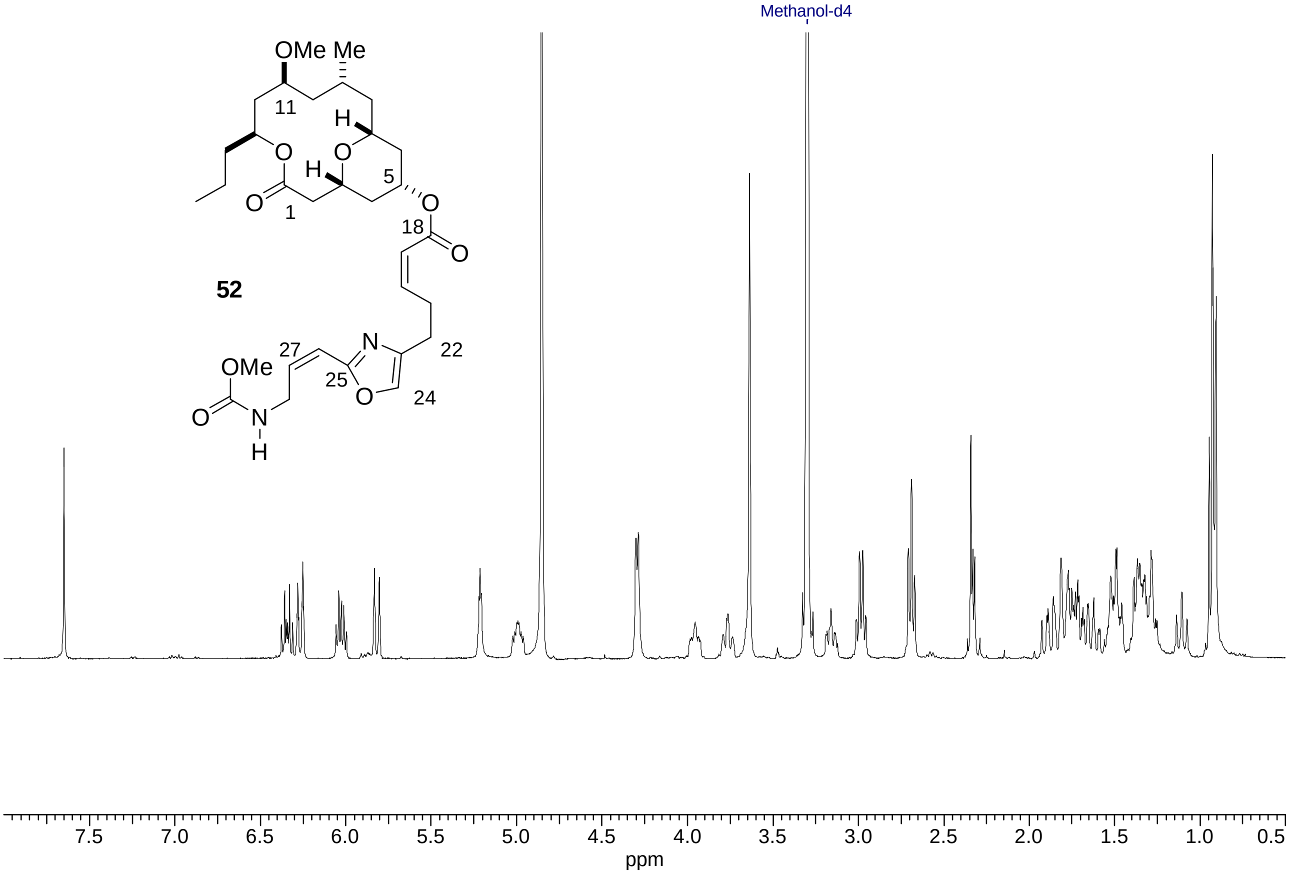


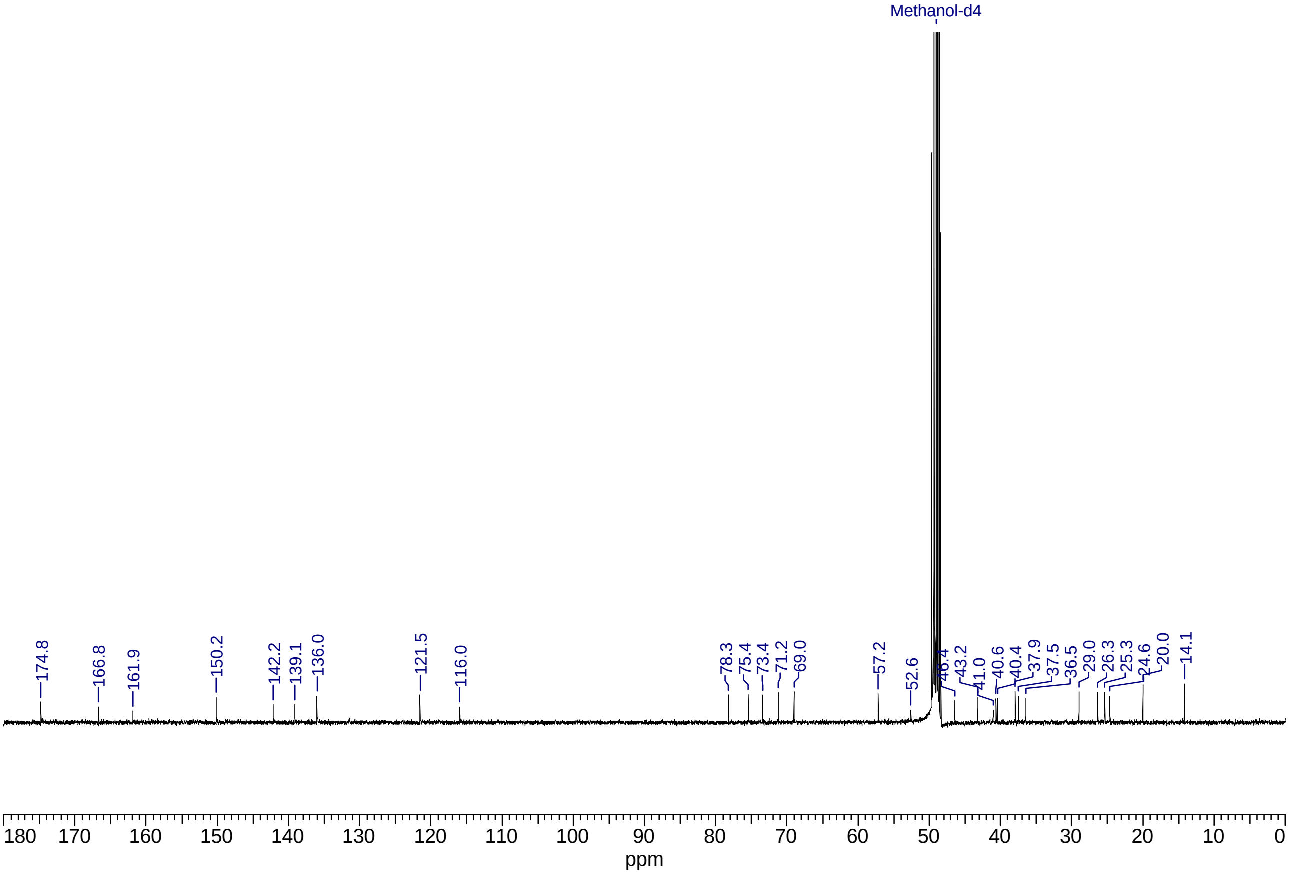
16b (5-*epi*)

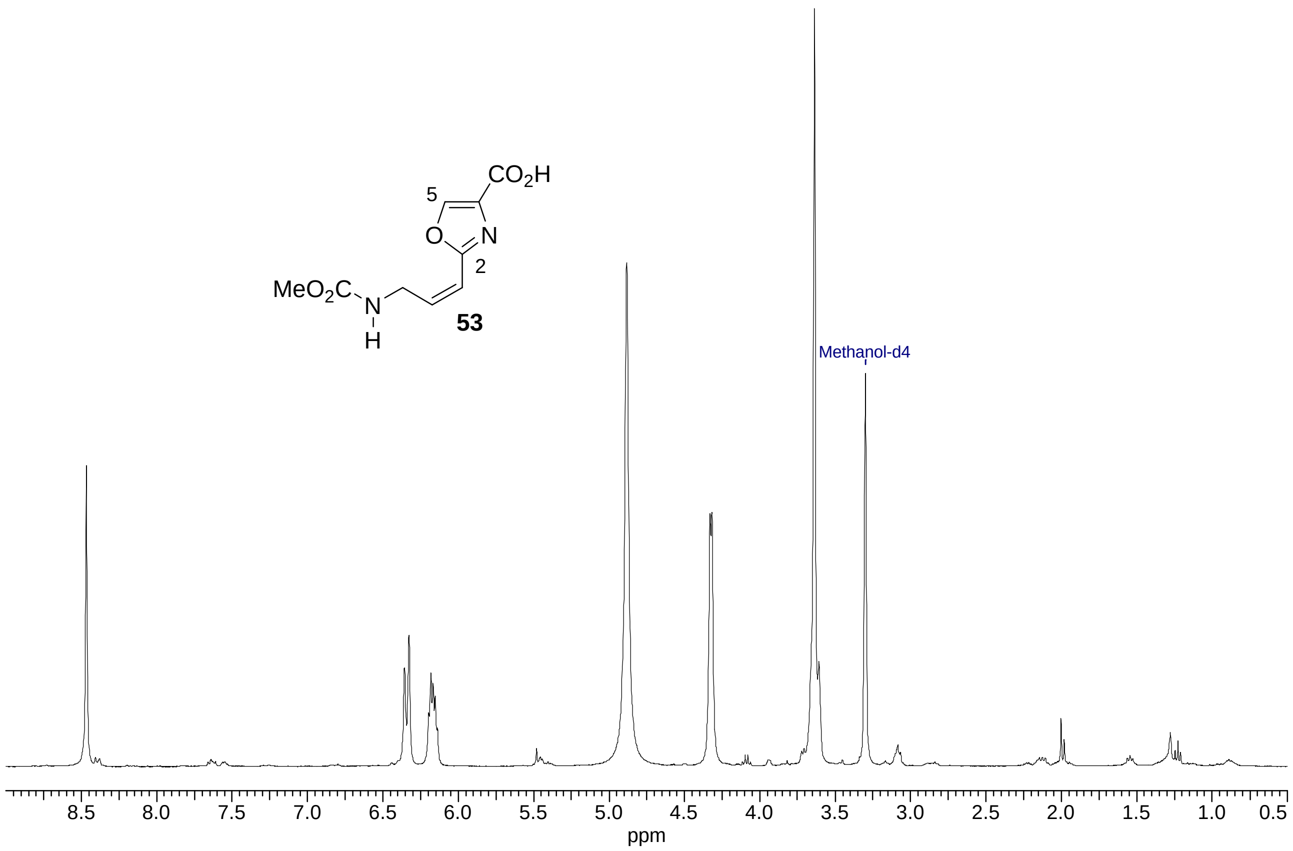
Chloroform-d
OH
5
O
H
H
Me
O
1
O
MeO
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



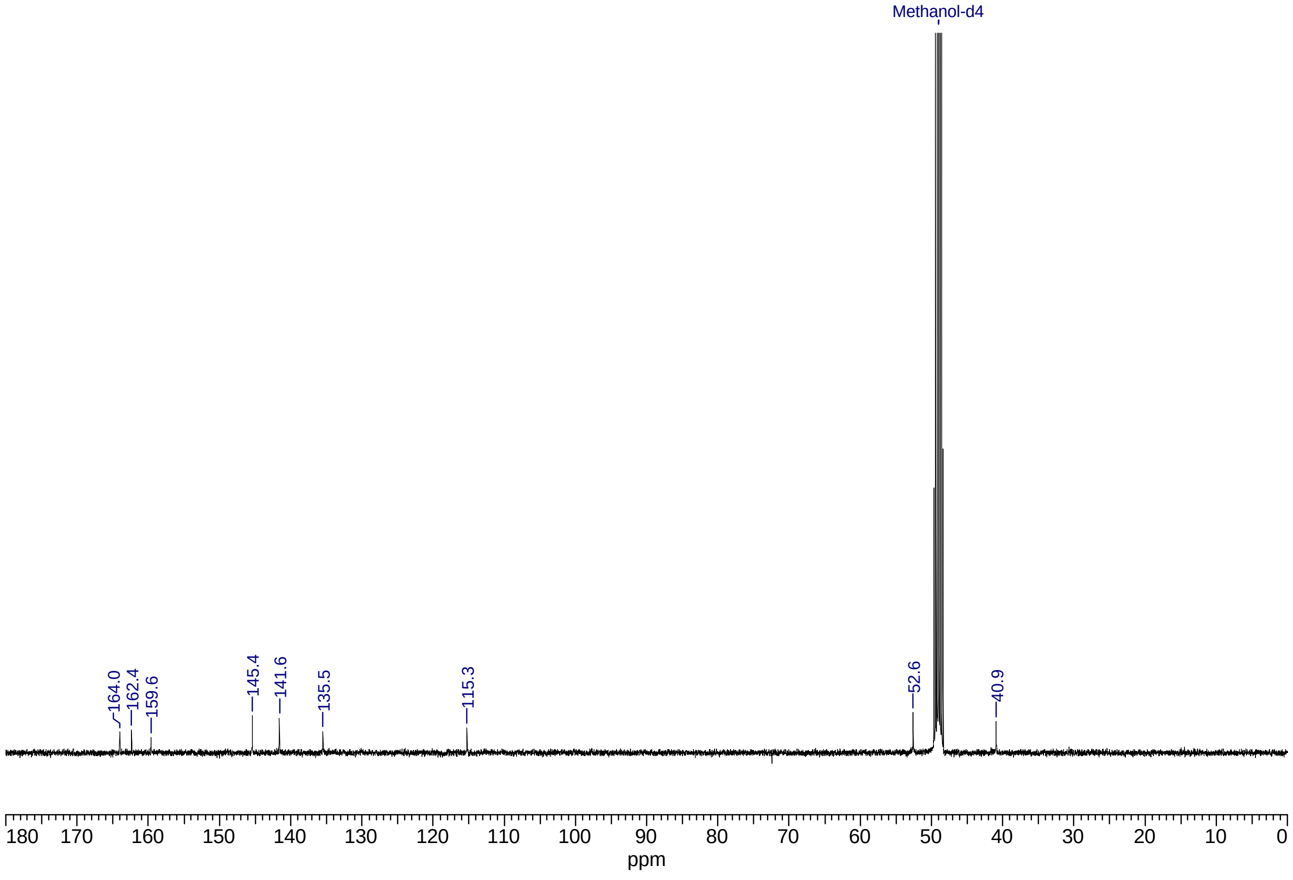
Chloroform-d
172.7
76.8
74.8
74.1
72.7
67.9
56.9
45.1
42.4
42.0
40.8
39.3
36.9
24.4
18.9
13.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

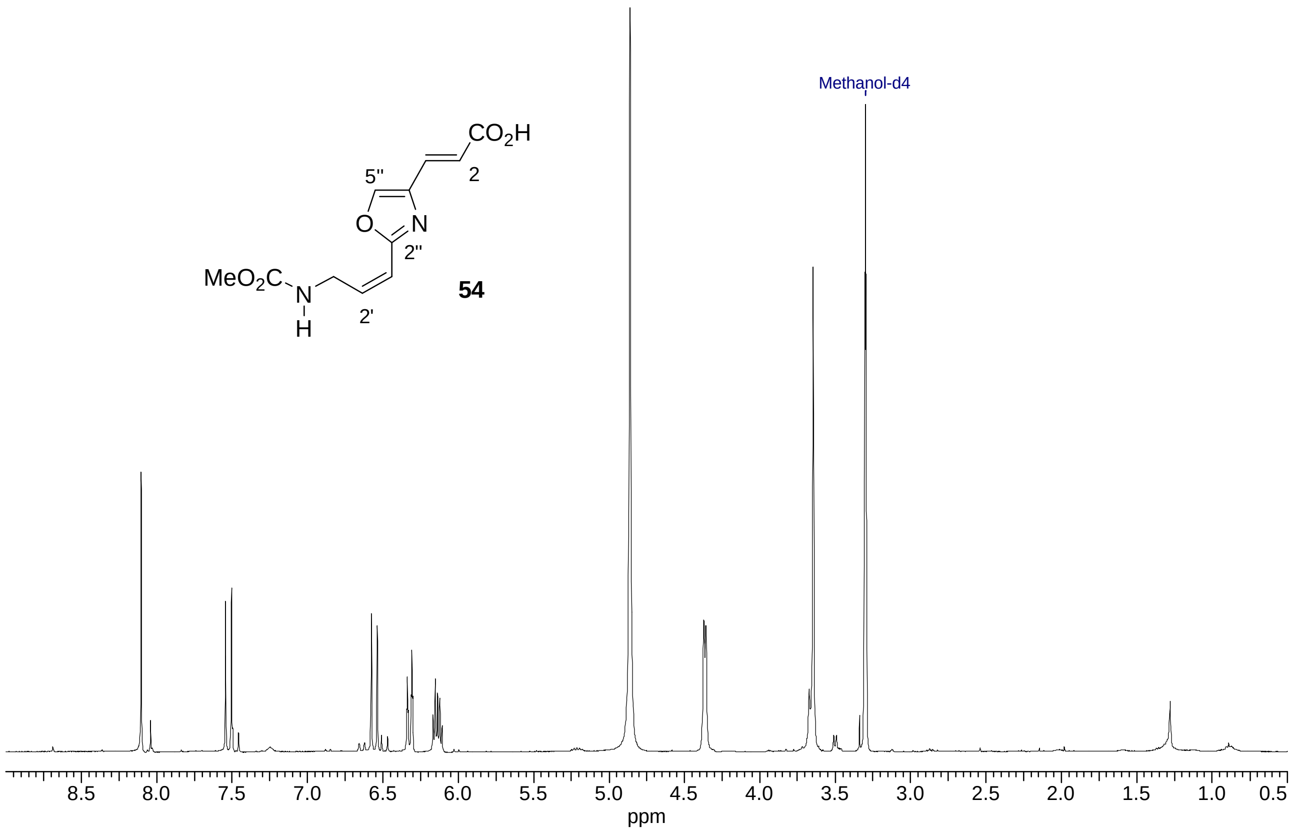

Methanol-d4
OMe Me
11
H
O
H
O
5
O
O
1
O
18
O
52
N
22
27
OMe
25
O
24
O
N
H
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Methanol-d4
174.8
166.8
161.9
150.2
142.2
139.1
136.0
121.5
116.0
78.3
75.4
73.4
71.2
69.0
57.2
52.6
46.4
43.2
41.0
40.6
40.4
37.9
37.5
36.5
29.0
26.3
25.3
24.6
20.0
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

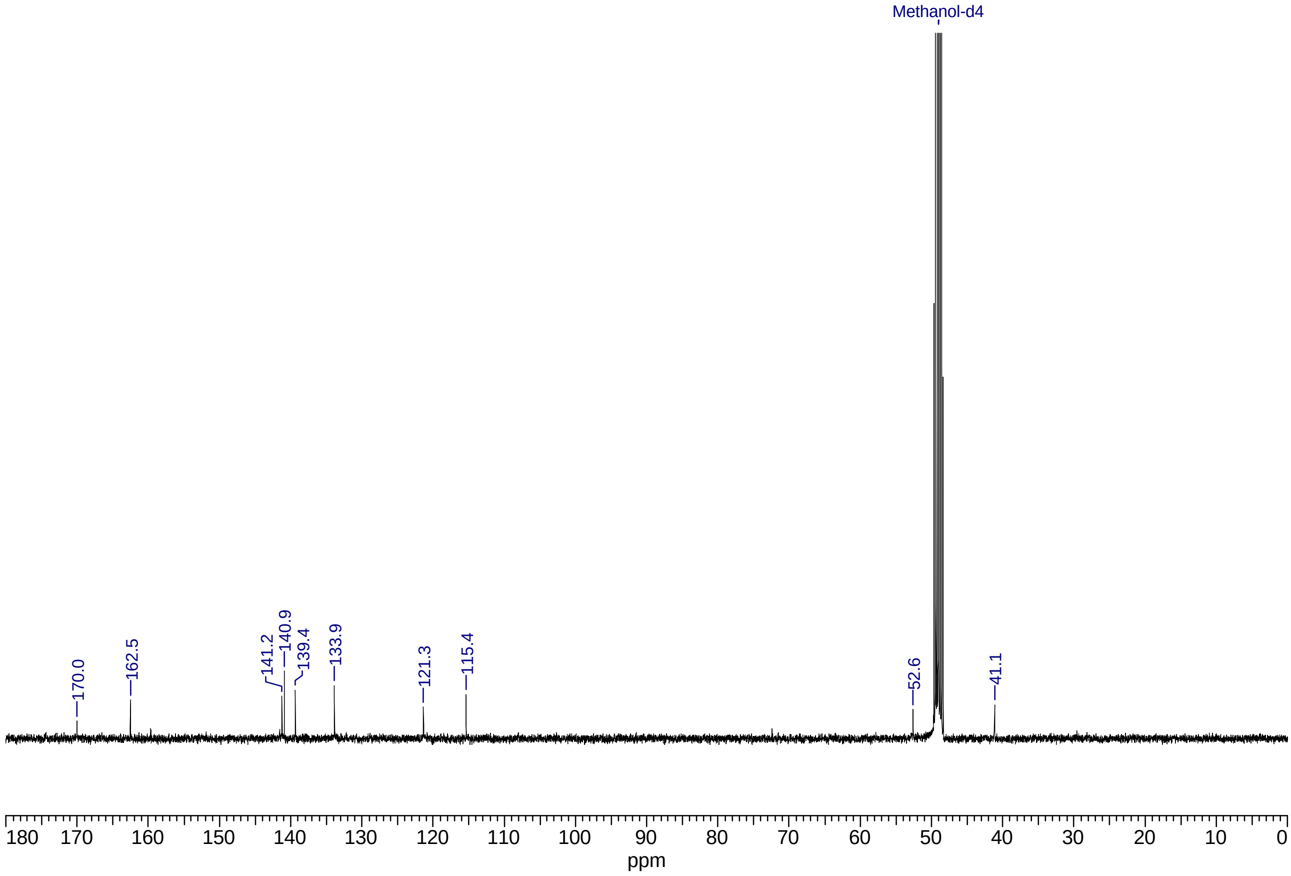

CO2H
5
O
N
2
MeO2C
N
H
Methanol-d4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

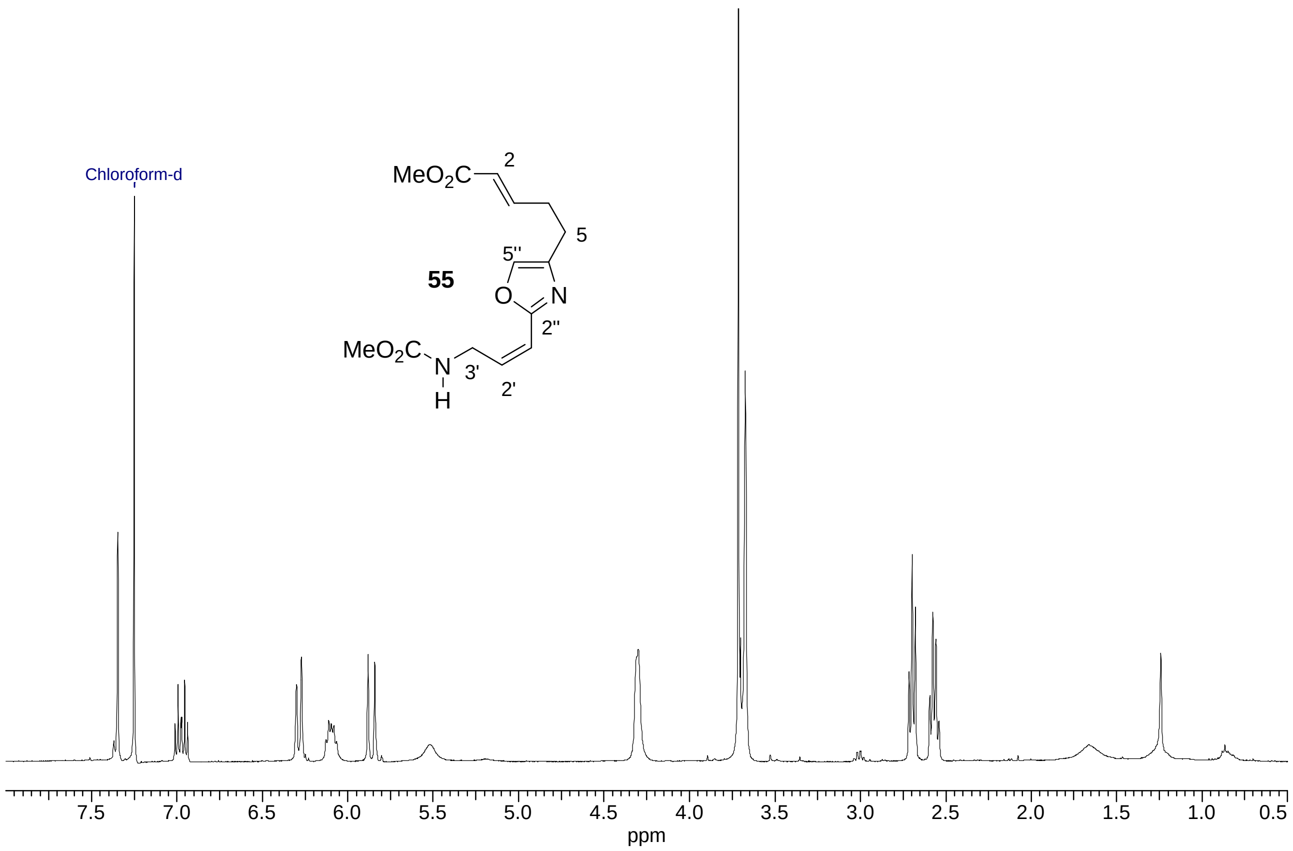
53

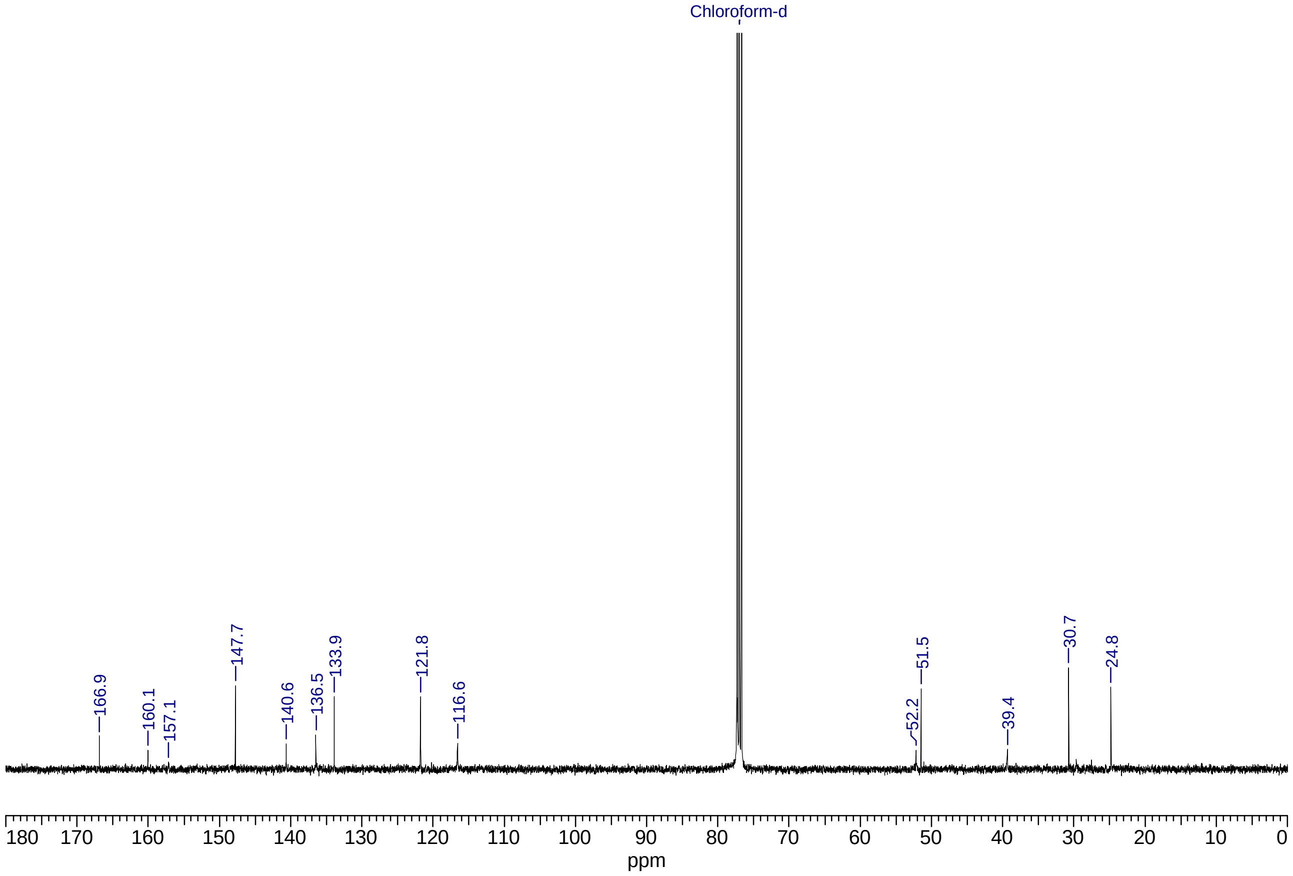

Methanol-d4
164.0
162.4
159.6
145.4
141.6
135.5
115.3
52.6
40.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

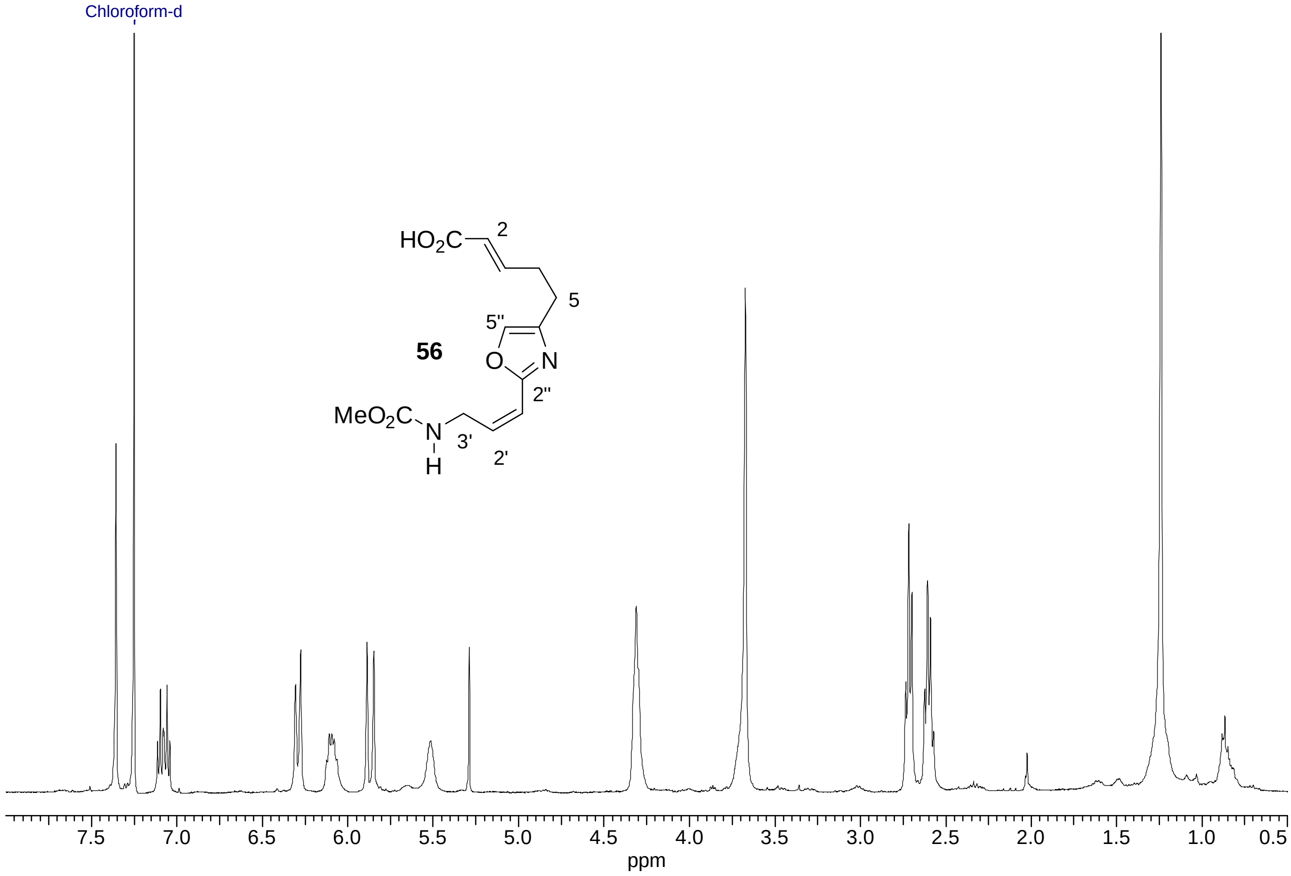

Methanol-d4
CO2H
2
5''
O
N
2''
MeO2C
N
H
2'
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

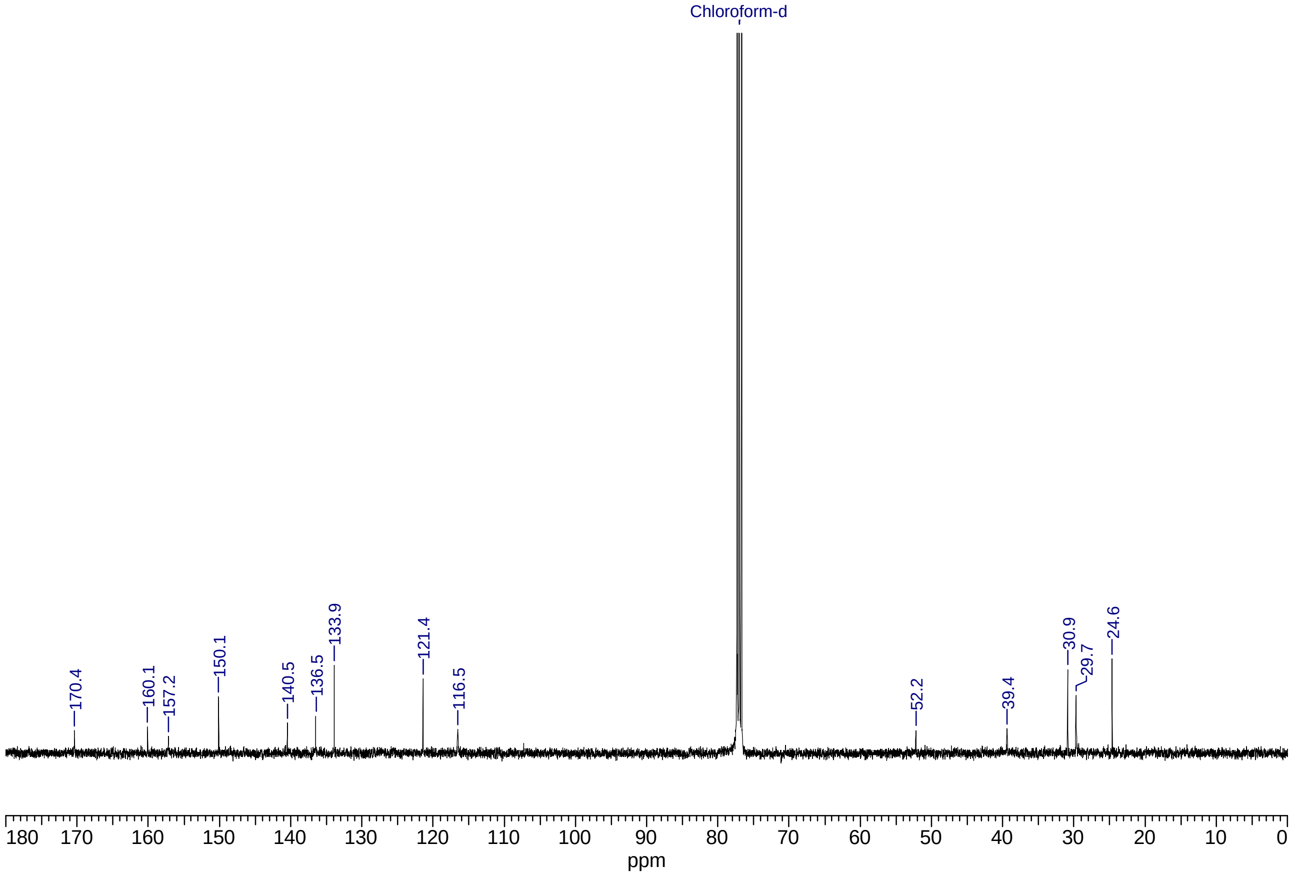
54

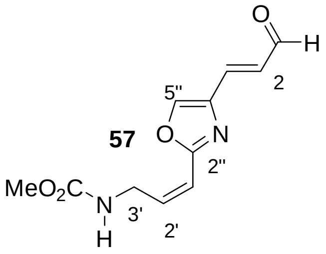

Methanol-d4
170.0
162.5
141.2
140.9
139.4
133.9
121.3
115.4
52.6
41.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


Chloroform-d
MeO$_2$C
2
5
5''
55
O
N
2''
MeO$_2$C
N
H
3'
2'
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
ppm

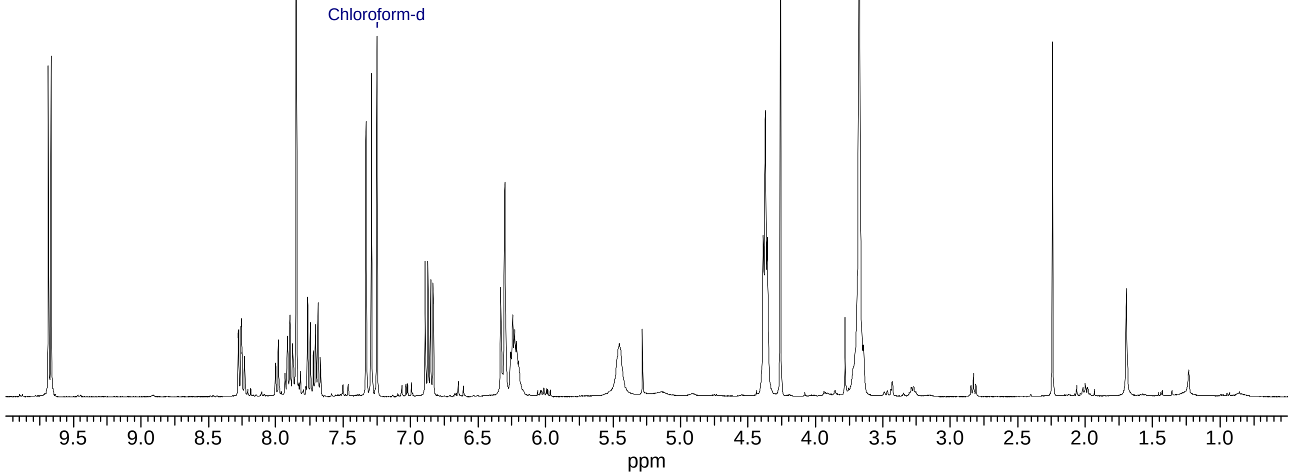

Chloroform-d
166.9
160.1
157.1
147.7
140.6
136.5
133.9
121.8
116.6
52.2
51.5
39.4
30.7
24.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

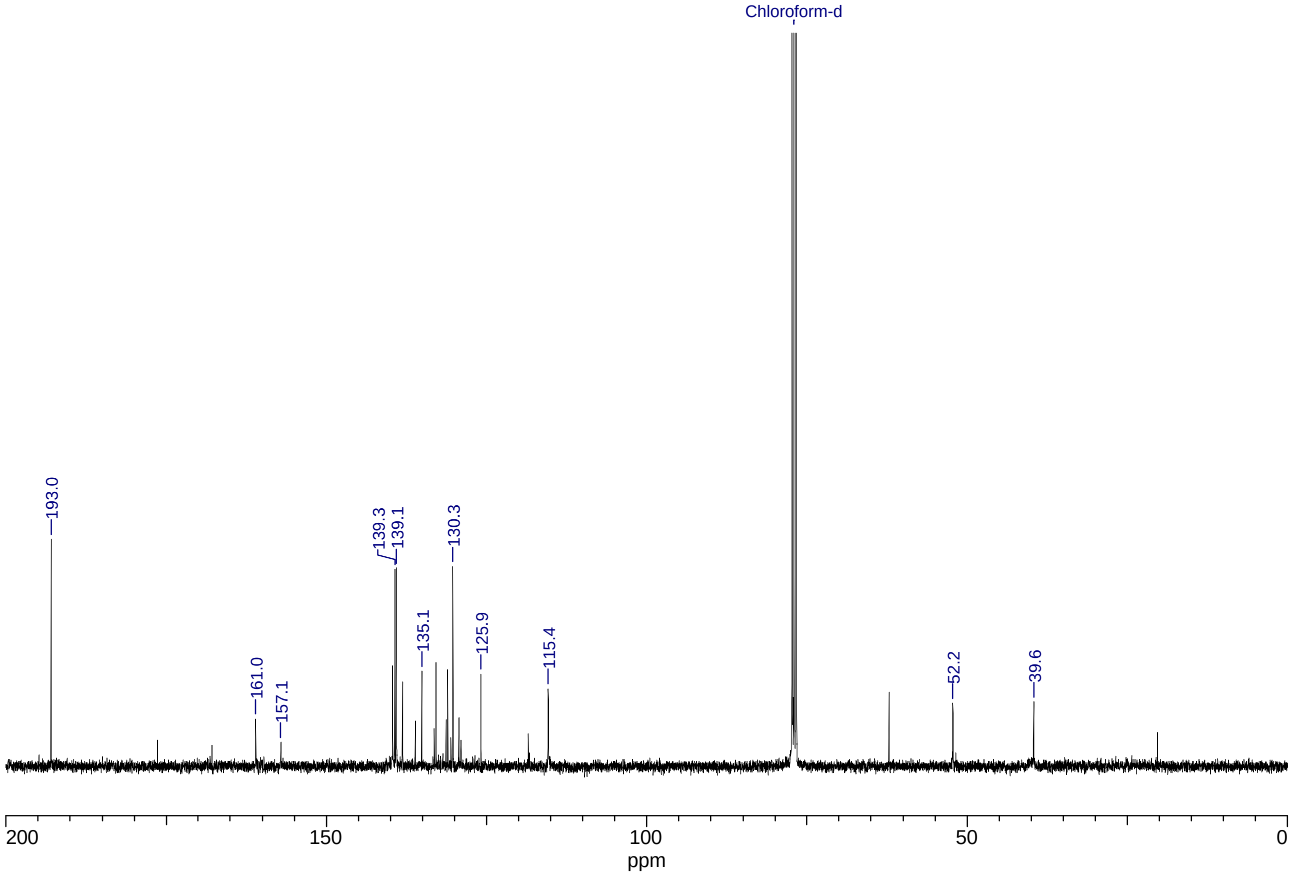

Chloroform-d
HO2C
2
5
5''
56
O
N
2''
MeO2C
N
H
3'
2'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
170.4
160.1
157.2
150.1
140.5
136.5
133.9
121.4
116.5
52.2
39.4
30.9
29.7
24.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

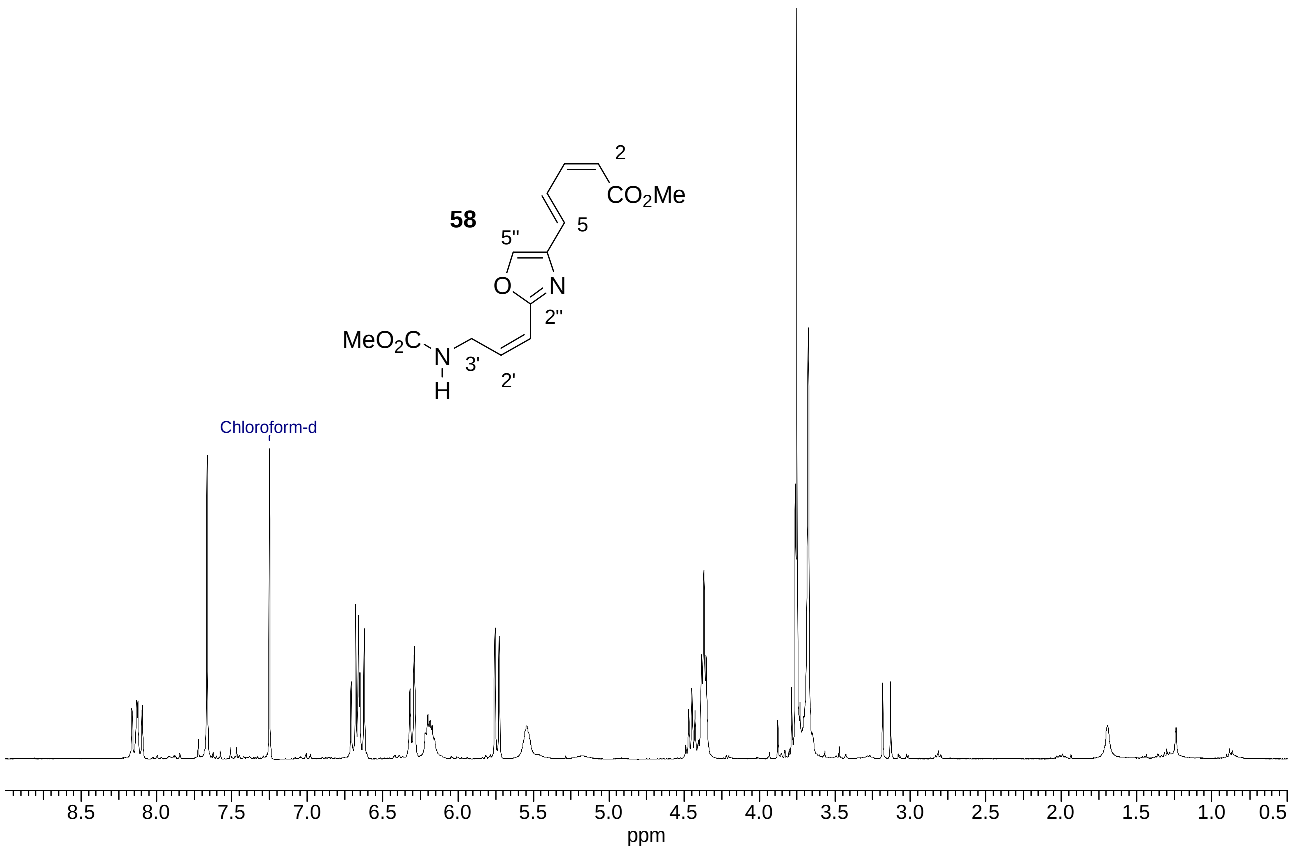

O
H
2
5''
O
N
2''
MeO$_2$C
N
H
3'
2'

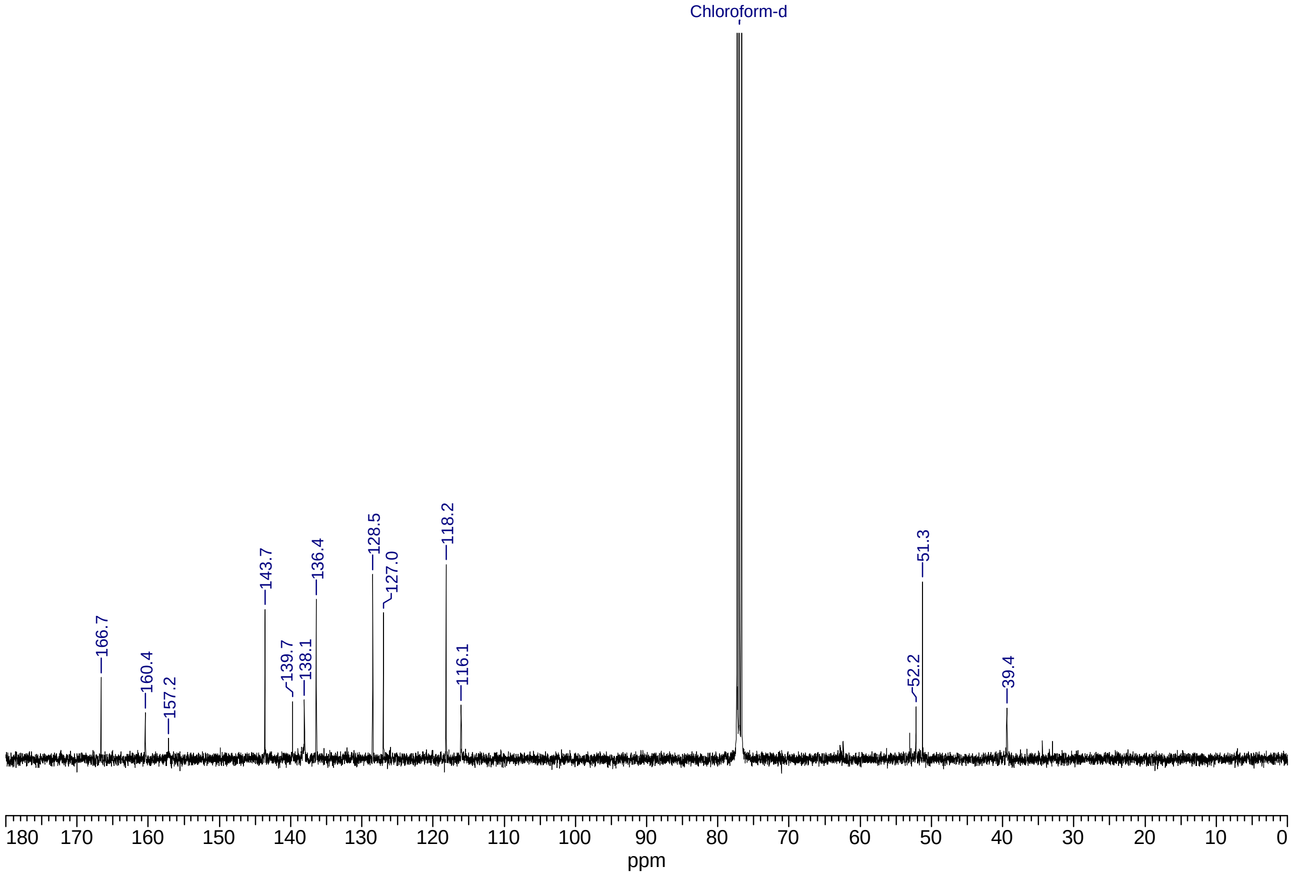
57

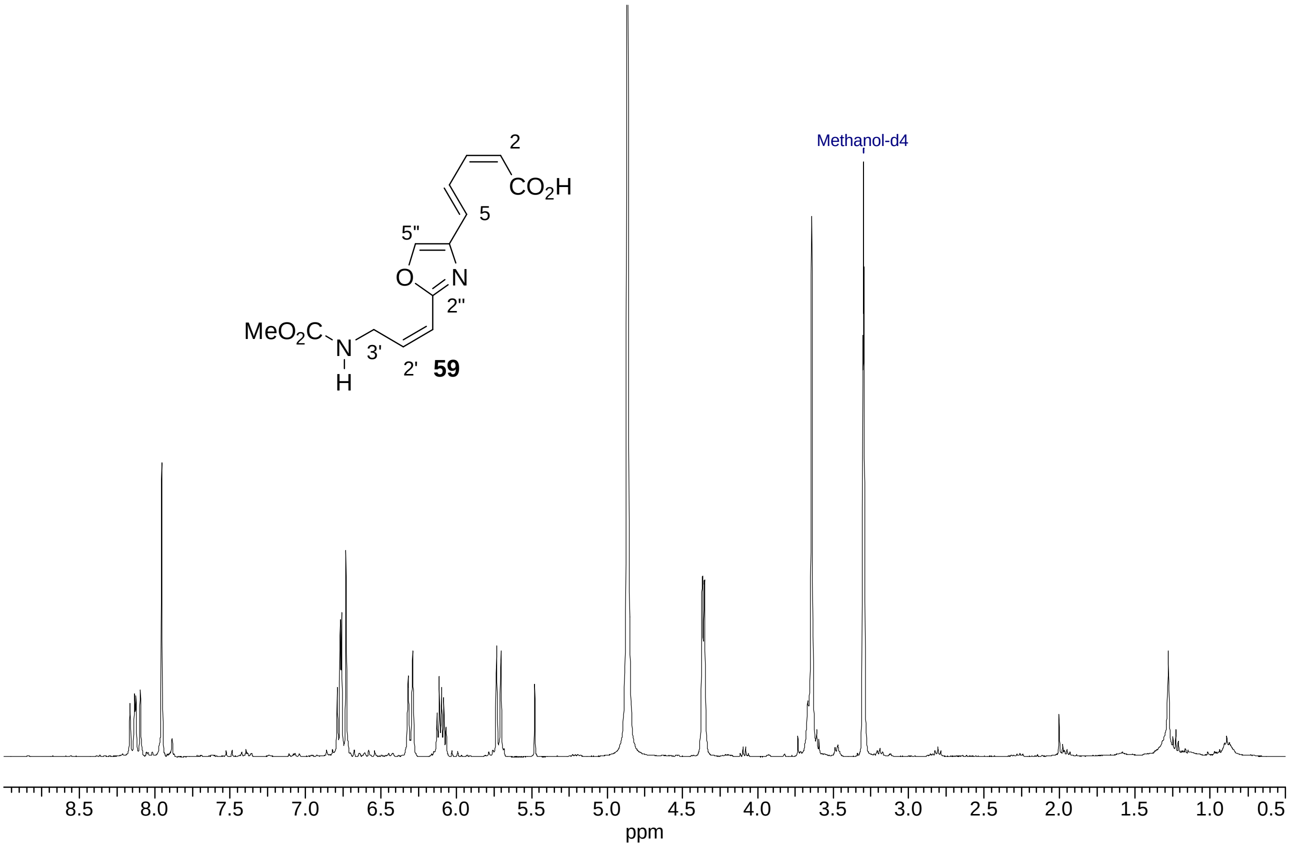

Chloroform-d
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
193.0
161.0
157.1
139.3
139.1
135.1
130.3
125.9
115.4
52.2
39.6
200
150
100
50
0
ppm

58

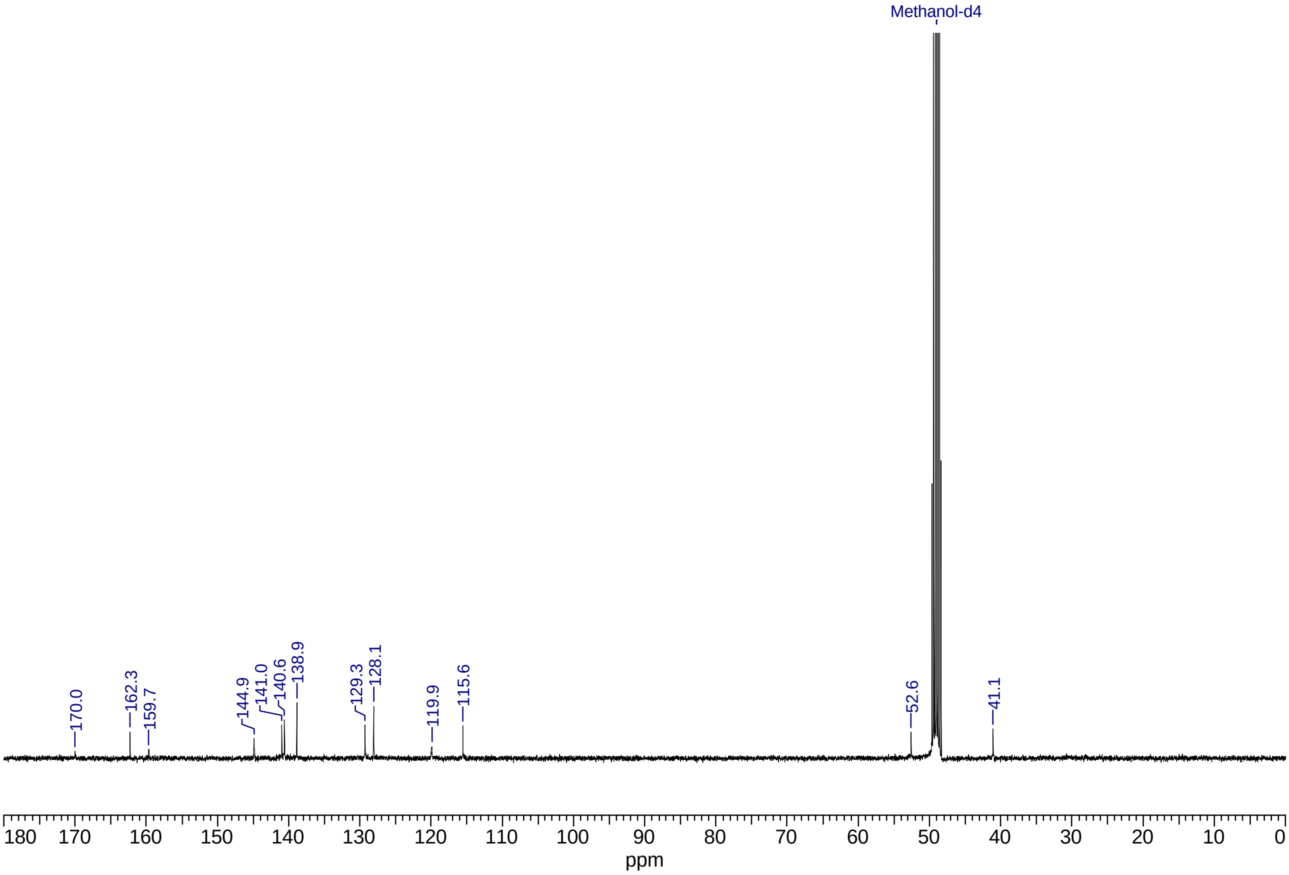

2
CO2Me
5
5''
O
N
2''
MeO2C
N
H
3'
2'
Chloroform-d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
166.7
160.4
157.2
143.7
139.7
138.1
136.4
128.5
127.0
118.2
116.1
52.2
51.3
39.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

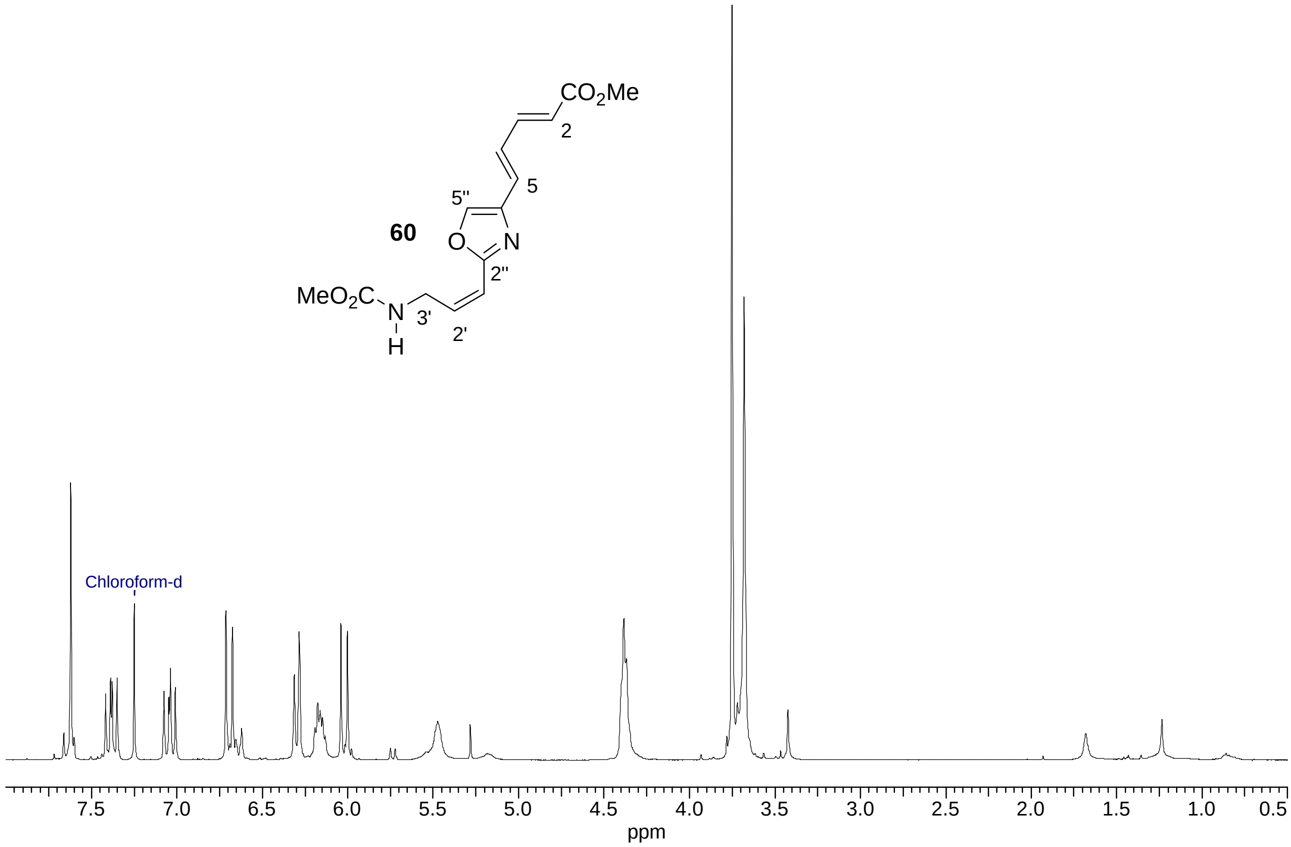


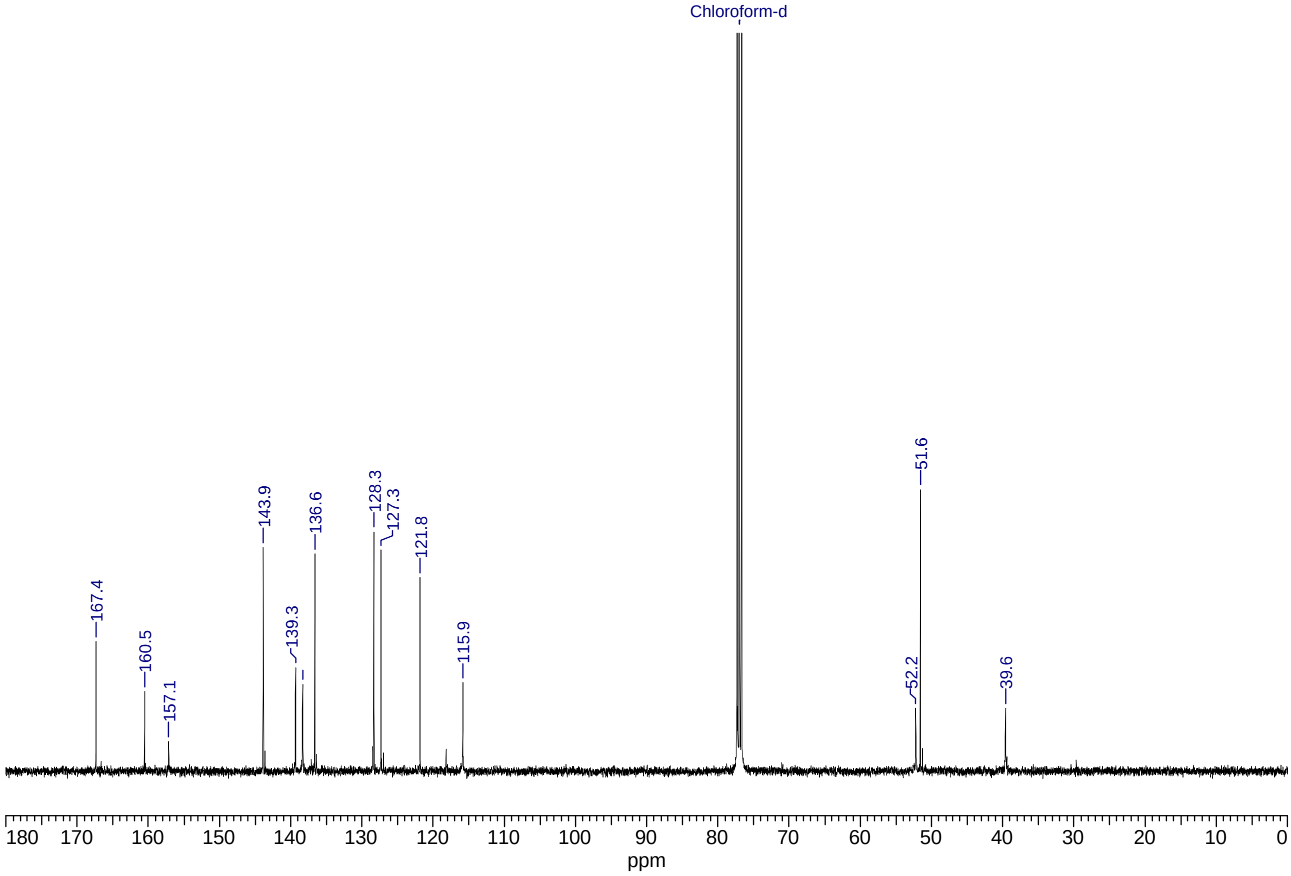
59

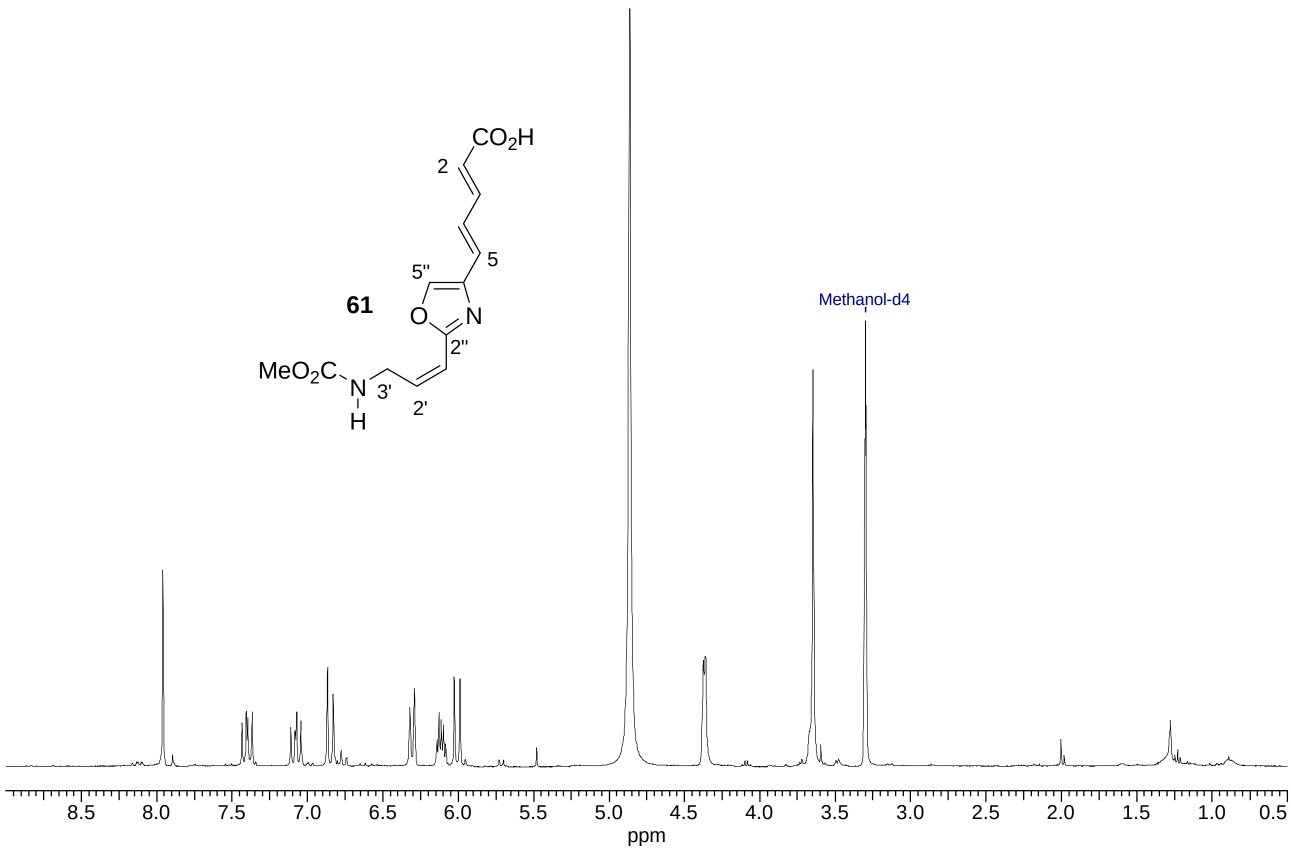
2
CO2H
5
5''
O
N
2''
MeO2C
N
H
3'
2'
Methanol-d4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

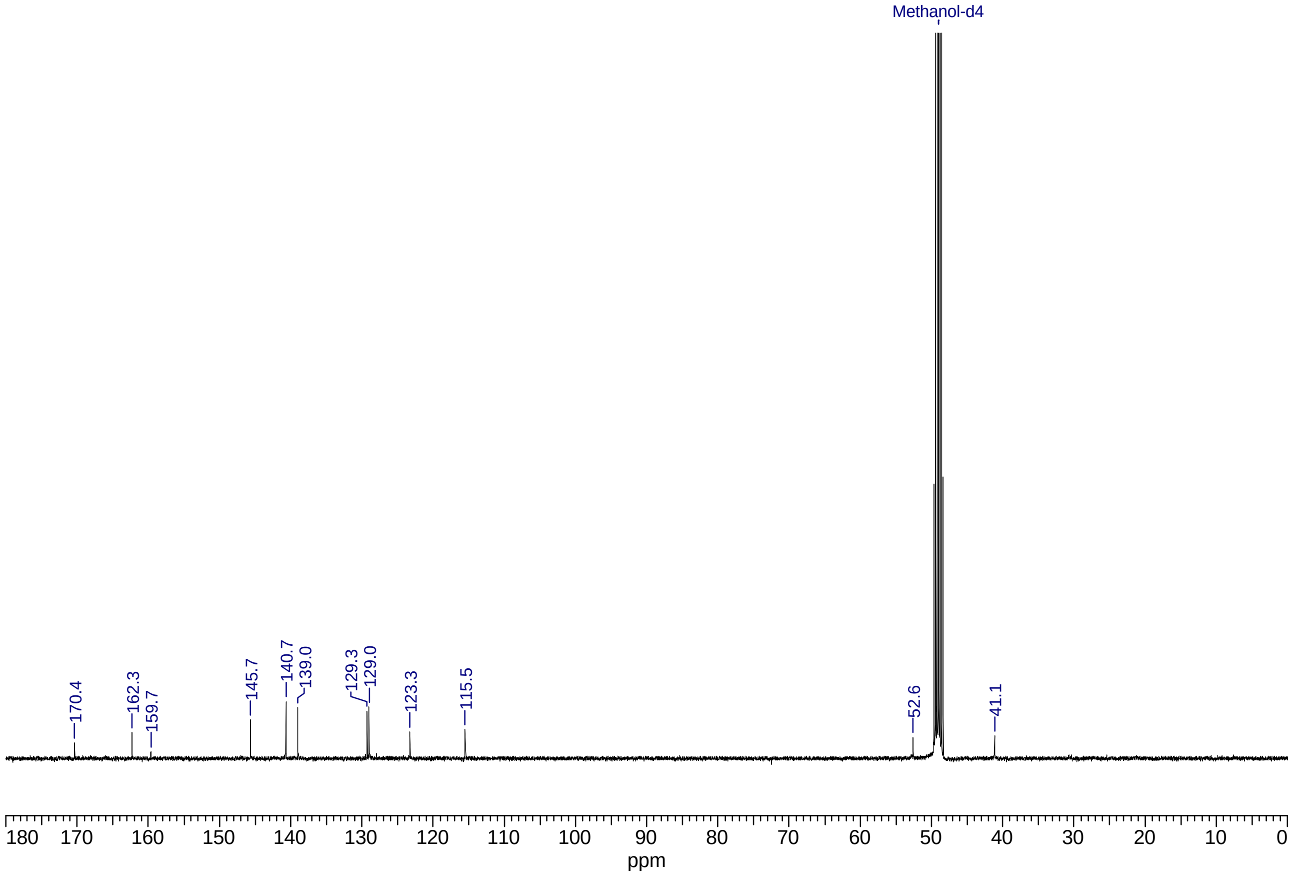


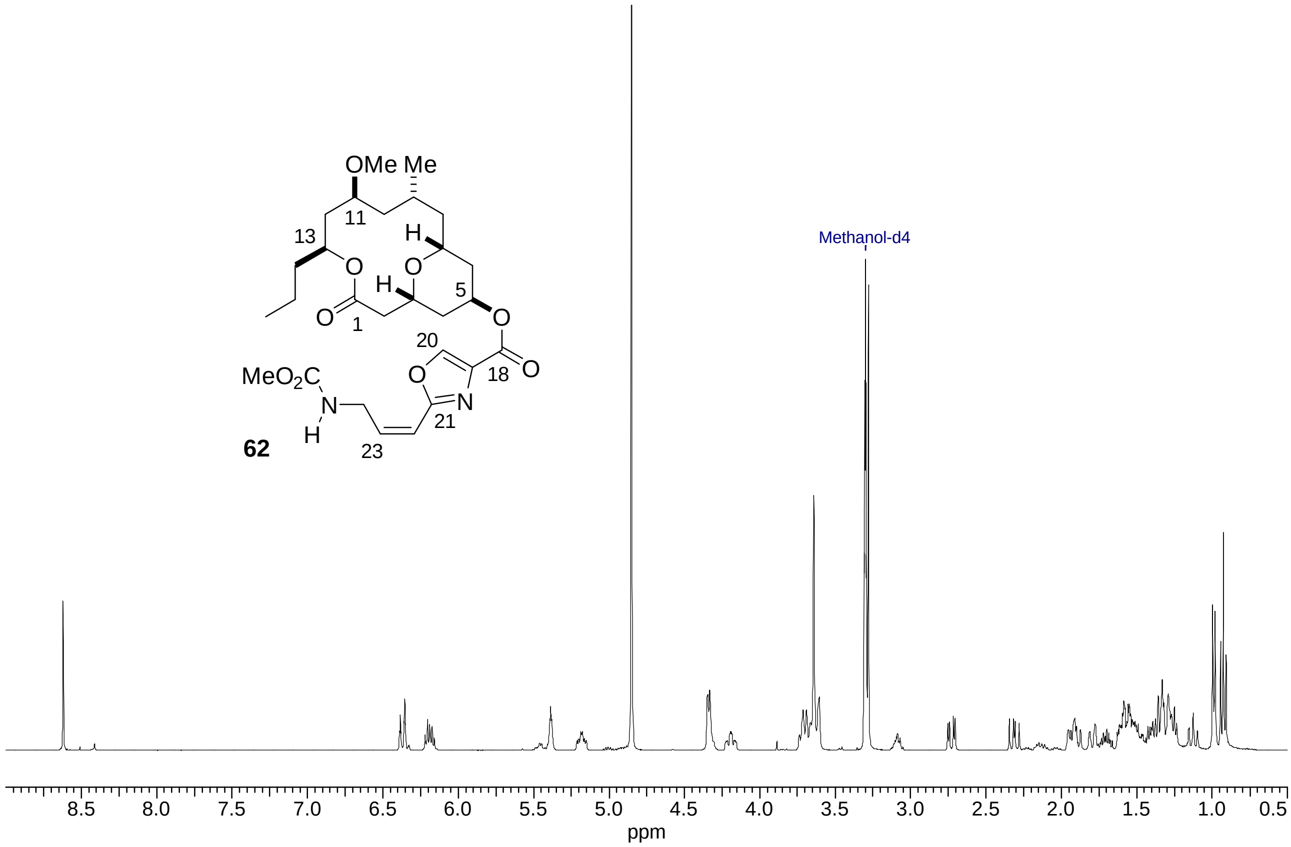
Methanol-d4
170.0
162.3
159.7
144.9
141.0
140.6
138.9
129.3
128.1
119.9
115.6
52.6
41.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


CO2Me
2
5
5''
60
O
N
2''
MeO2C
N
H
3'
2'
Chloroform-d
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
ppm

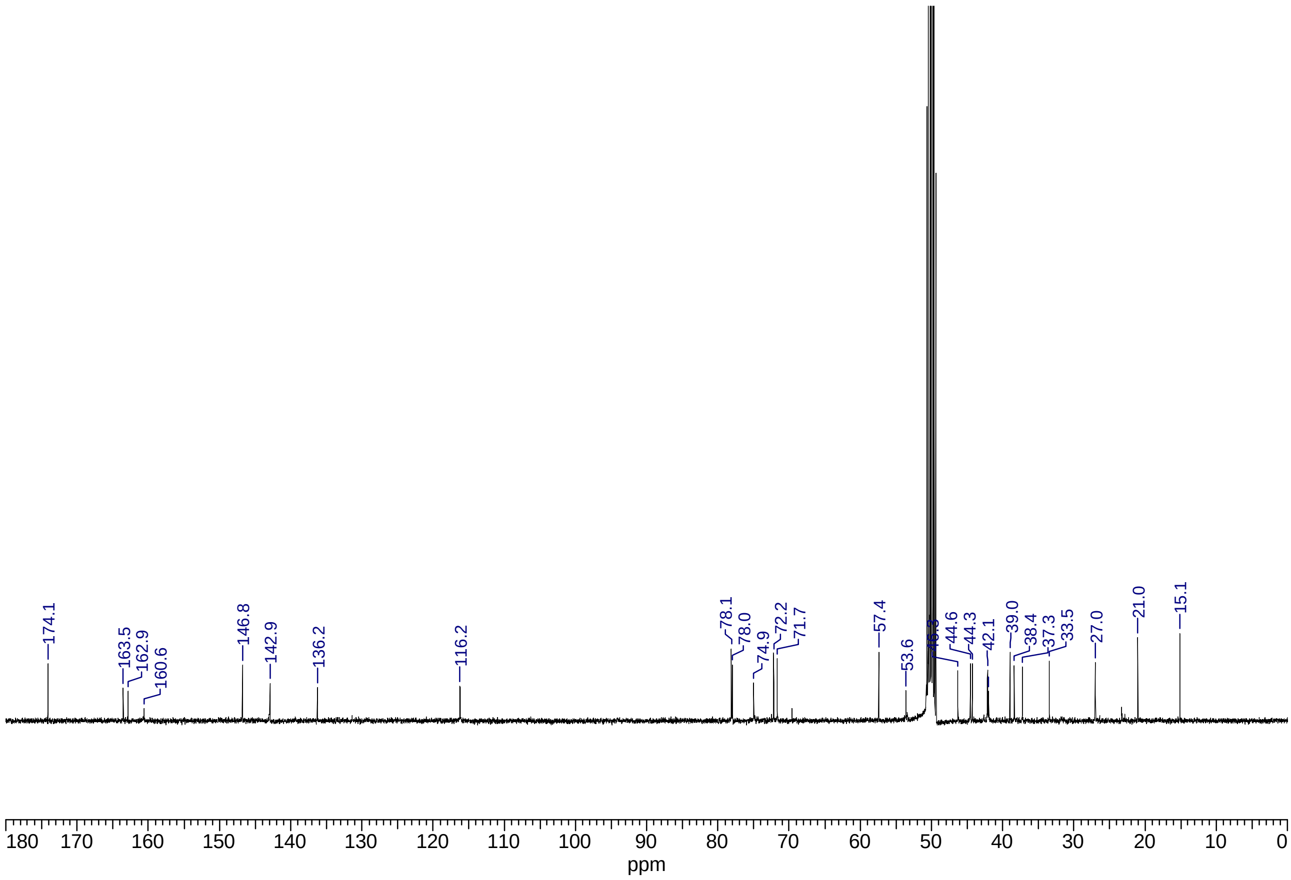

Chloroform-d
167.4
160.5
157.1
143.9
139.3
136.6
128.3
127.3
121.8
115.9
52.2
51.6
39.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

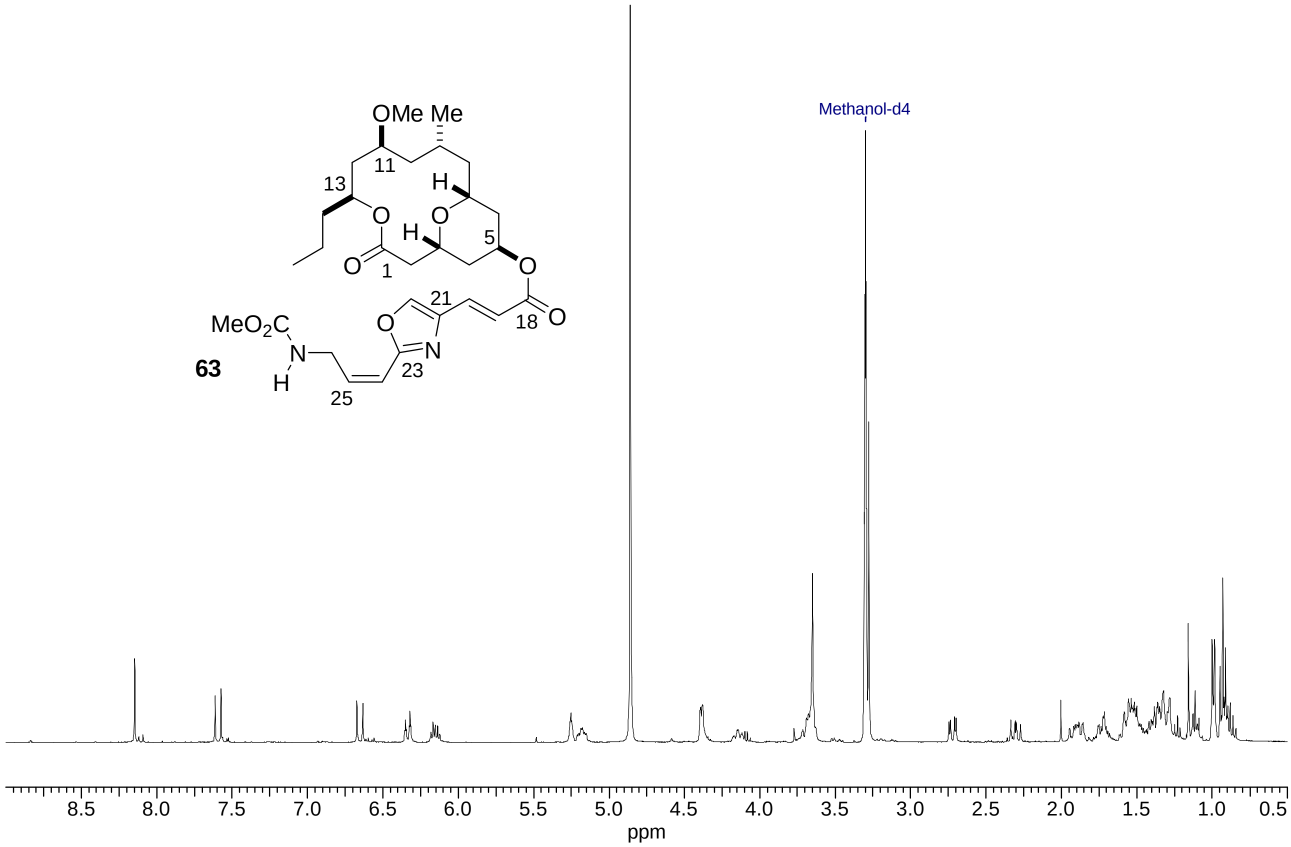

61
CO2H
2
5
5''
O
N
2''
MeO2C
N
H
3'
2'
Methanol-d4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

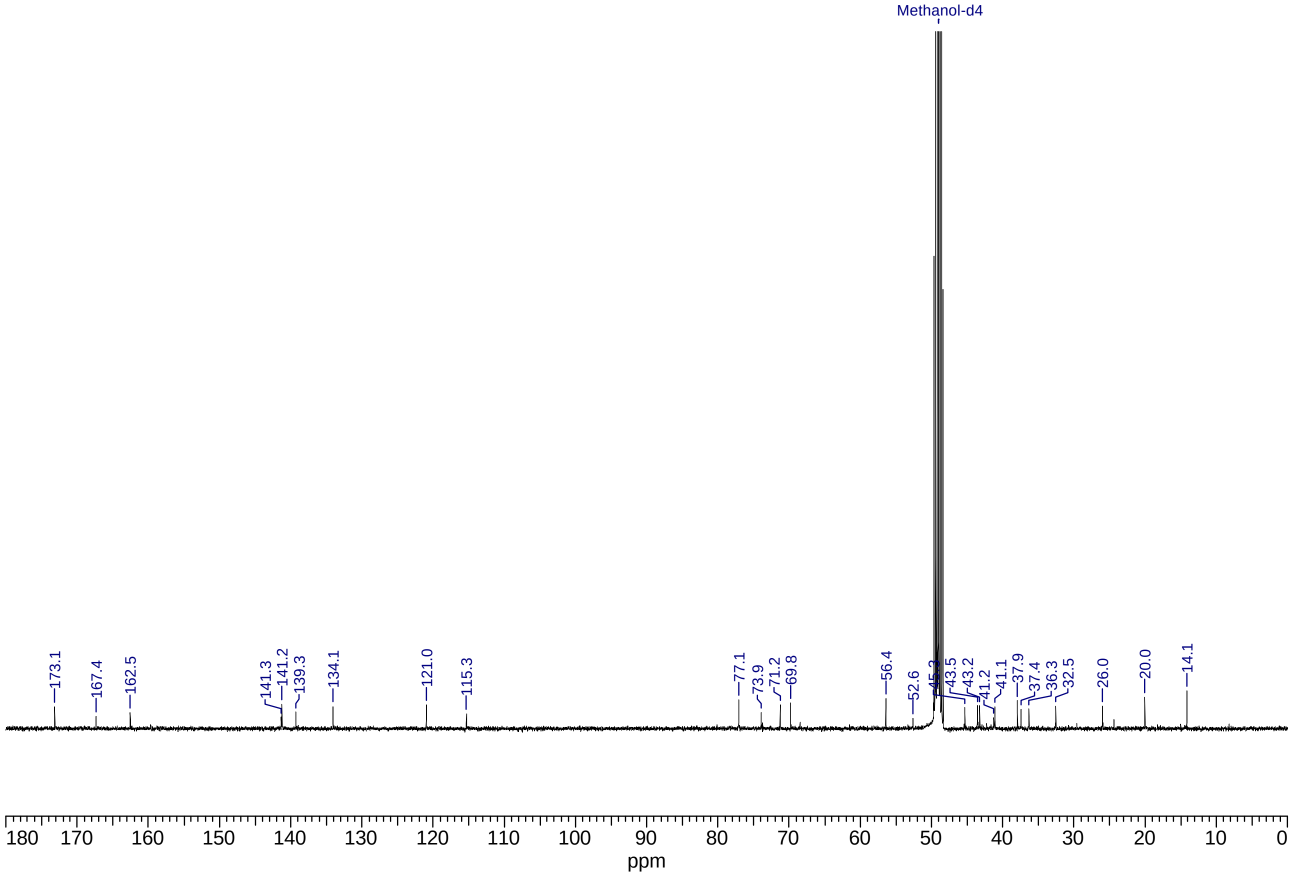

Methanol-d4
170.4
162.3
159.7
145.7
140.7
139.0
129.3
129.0
123.3
115.5
52.6
41.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

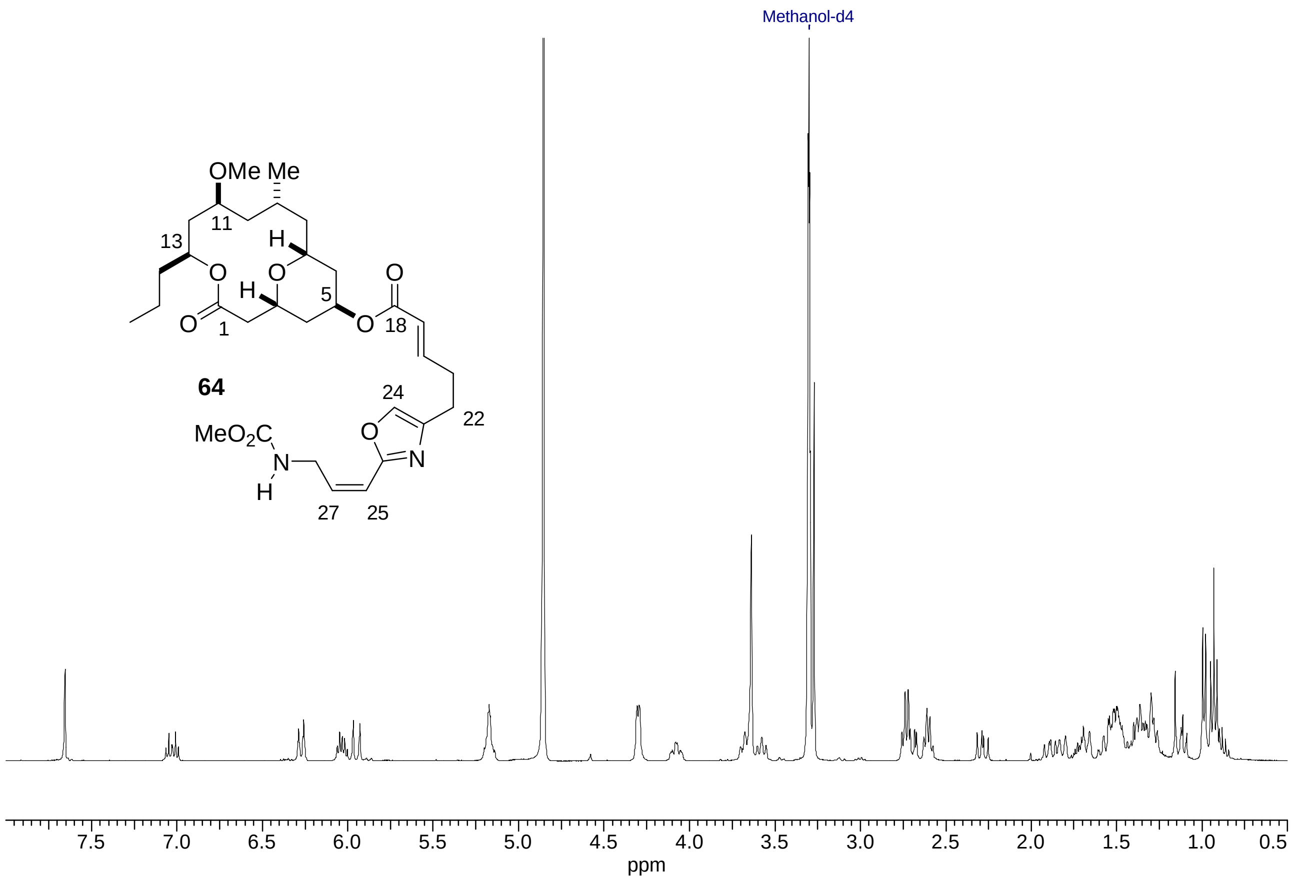

OMe
Me
11
13
H
O
O
H
5
O
1
O
20
18
O
MeO2C
O
N
N
21
H
23
Methanol-d4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

62

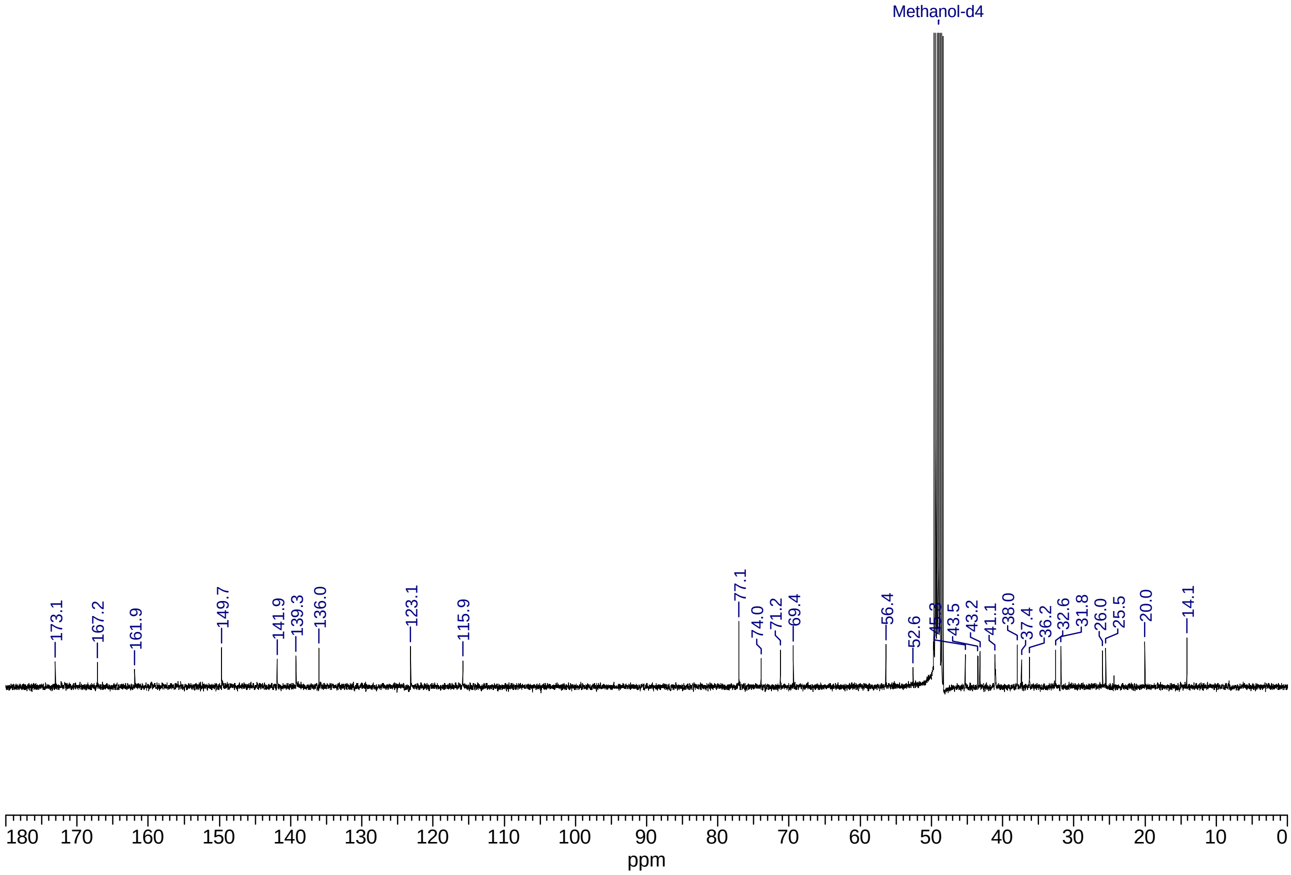

174.1
163.5
162.9
160.6
146.8
142.9
136.2
116.2
78.1
78.0
74.9
72.2
71.7
57.4
53.6
46.3
44.6
44.3
42.1
39.0
38.4
37.3
33.5
27.0
21.0
15.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

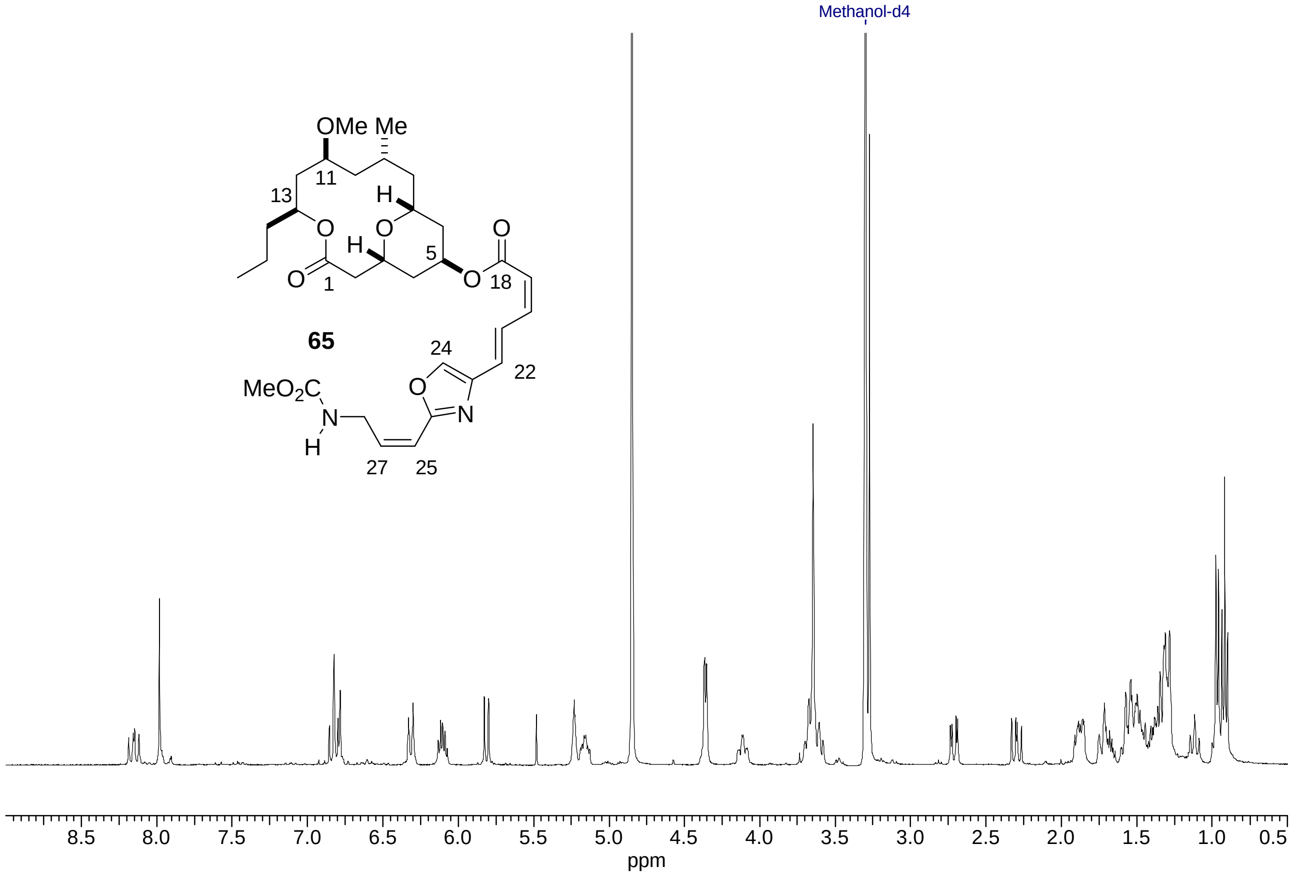

OMe
Me
11
13
H
O
O
H
5
O
1
O
21
18
O
MeO2C
N
H
O
N
23
25
63
Methanol-d4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Methanol-d4
173.1
167.4
162.5
141.3
141.2
139.3
134.1
121.0
115.3
77.1
73.9
71.2
69.8
56.4
52.6
45.3
43.5
43.2
41.2
41.1
37.9
37.4
36.3
32.5
26.0
20.0
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

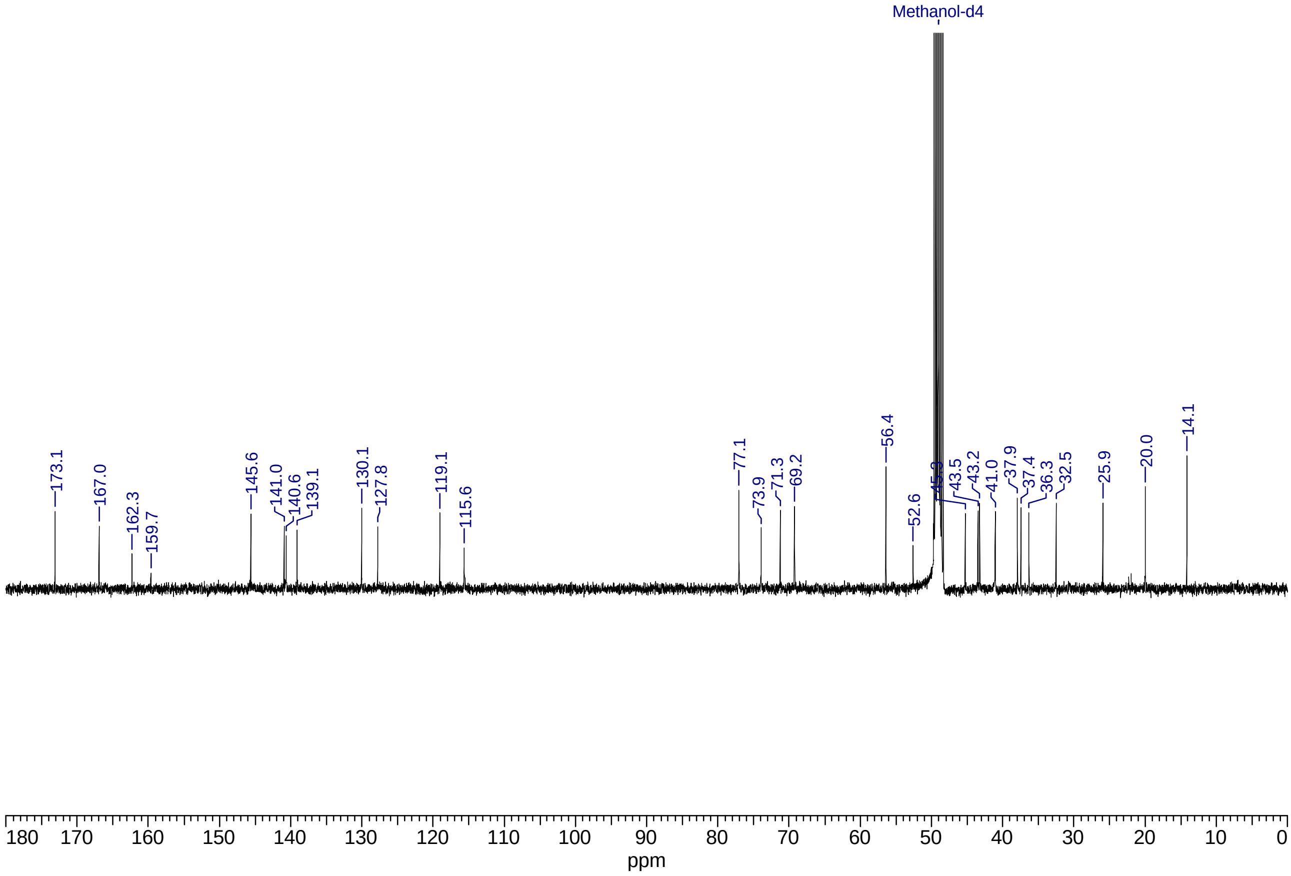

Methanol-d4
OMe
Me
11
13
H
O
O
H
5
O
O
1
O
18
O
24
22
MeO2C
N
H
O
N
27
25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

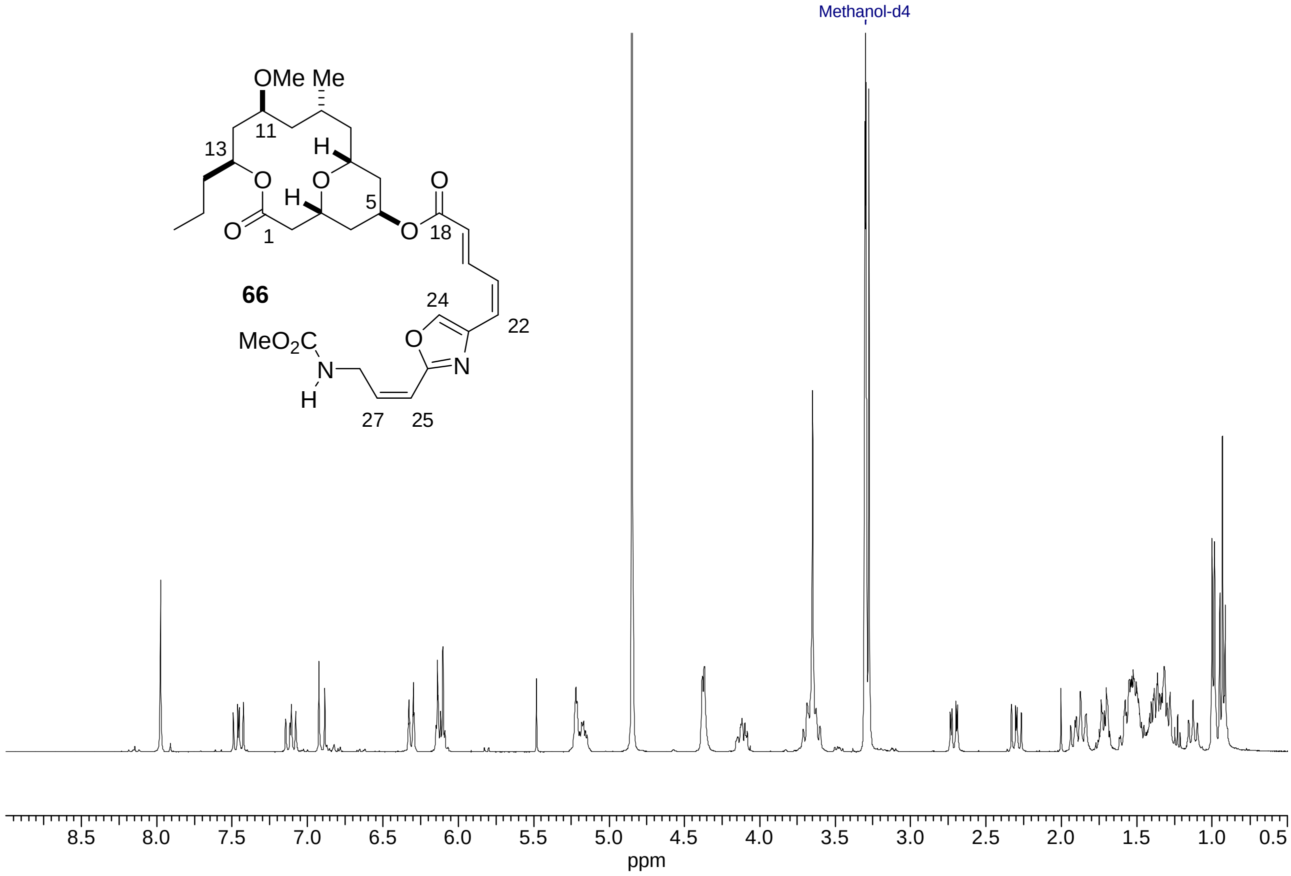
64

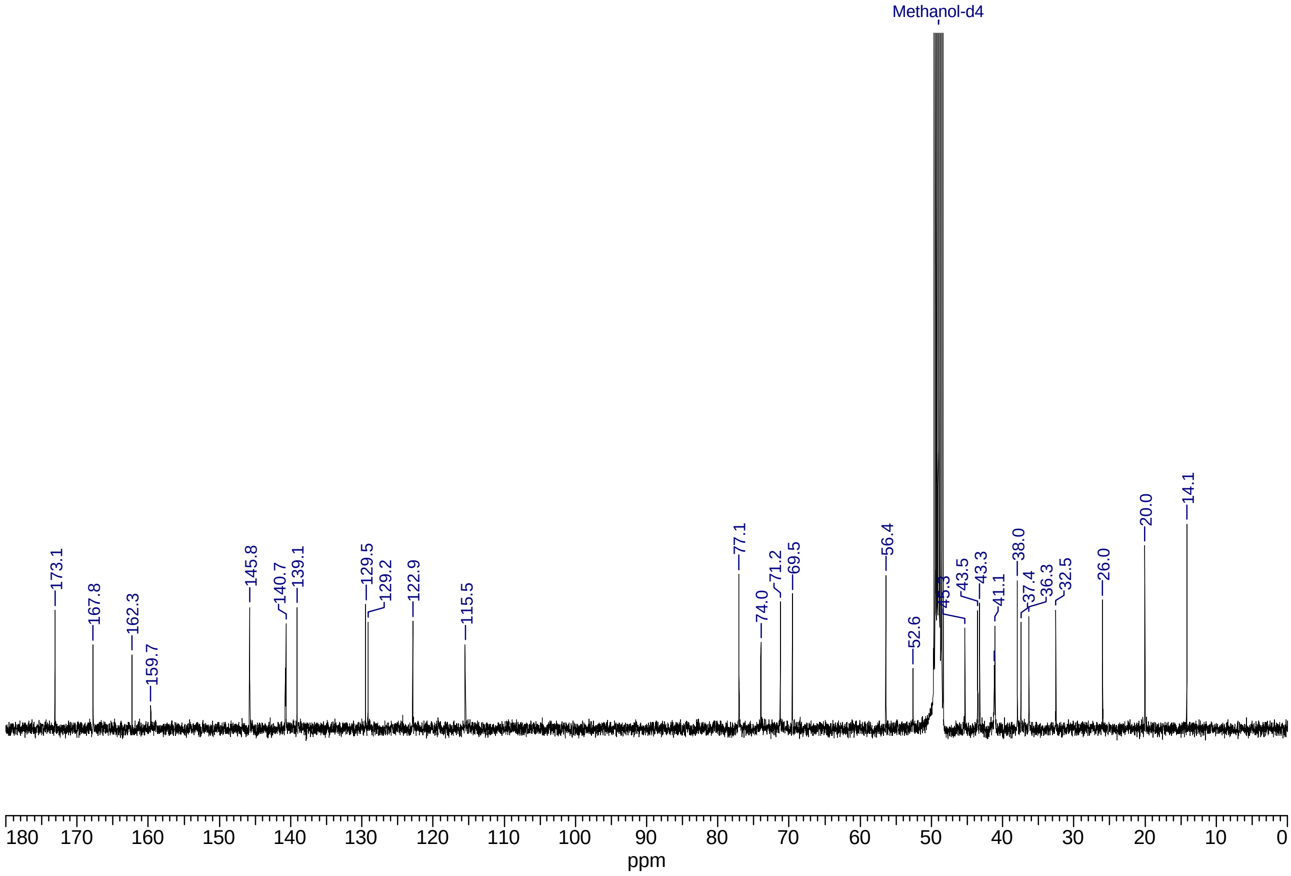

Methanol-d4
173.1
167.2
161.9
149.7
141.9
139.3
136.0
123.1
115.9
77.1
74.0
71.2
69.4
56.4
52.6
45.3
43.5
43.2
41.1
38.0
37.4
36.2
32.6
31.8
26.0
25.5
20.0
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


65

Methanol-d4
OMe
Me
11
13
H
O
O
H
5
O
O
O
1
18
24
22
MeO2C
N
H
O
N
27
25
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
ppm


Methanol-d4
173.1
167.0
162.3
159.7
145.6
141.0
140.6
139.1
130.1
127.8
119.1
115.6
77.1
73.9
71.3
69.2
56.4
52.6
45.3
43.5
43.2
41.0
37.9
37.4
36.3
32.5
25.9
20.0
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OMe
Me
11
13
H
O
O
H
O
5
O
O
1
O
18
66
24
22
MeO2C
N
H
O
N
27
25
Methanol-d4
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
ppm


Methanol-d4
173.1
167.8
162.3
159.7
145.8
140.7
139.1
129.5
129.2
122.9
115.5
77.1
74.0
71.2
69.5
56.4
52.6
45.3
43.5
43.3
41.1
38.0
37.4
36.3
32.5
26.0
20.0
14.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm