Bioinspired Total Synthesis and Human Proteasome Inhibitory Activity of (–)-Salinosporamide A, (–)-Homosalinosporamide A, and Derivatives Obtained via Organonucleophile Promoted Bis-Cyclizations

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Supporting Information

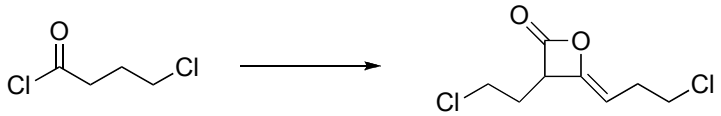
Supporting Information Available. General procedures and characterization data including ^{1}H and ^{13}C NMR spectra (for compounds **1a'**, **21e**, **44**, **45**, **61, 63**) and X-ray analysis (**61**, **1a'**). This material is available free of charge *via* the Internet at http://pubs.acs.org

Note: All procedures and characterization data associated with the synthesis of *rac*-cinnabaramide,[1] *rac*-salinosporamide,[1] (+)-salinosporamide,[2] and (+)-homosalinosporamide[2] have been published previously.

[1] See Supporting Information in: Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143.
[2] See Supporting Information in: Nguyen, H.; Ma, G.; Romo, D. *Chem. Comm.* **2010**, *46*, 4803.

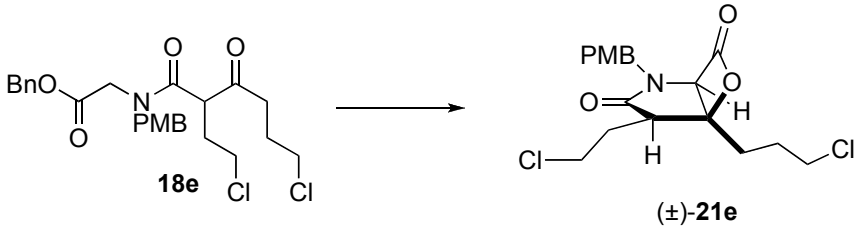
General Procedures:

All reactions were carried out under nitrogen atmosphere in oven-dried glassware. Dichloromethane, toluene and ethyl ether were purified by passage through activated molecular sieves. Methanol was distilled from magnesium turnings. Tetrahydrofuran was distilled from Na/benzophenone. Hünig's base and triethylamine were distilled from CaH_2 prior to use. All other commercially obtained reagents were used as received unless noted otherwise. *O*-Benzyl-*D*-serine was purchased from Chem-impex International. Flash column chromatography was performed using 60Å Silica Gel (Silicycle, 230-400 mesh) as a stationary phase. Diastereomeric ratios were determined by integration (^{1}H NMR, 500 MHz). Mass spectra were obtained at the Laboratory for Biological Mass Spectrometry (Texas A&M University). Thin layer chromatography (TLC) was performed using glass-backed silica gel 60_{F254} (Silicycle, 250 μm thickness).



SI-1 (±)-**12e**

Homoketene dimer, **(±)-12e:**To a solution of 4-chlorobutyrylchloride (**SI-1**) (5.64 mL, 0.05 mol) in Et_2O (50 mL) was added triethylamine (8.4 mL, 0.06 mol) via a syringe pump at 23 ºC for a period of 1 h. During addition of triethylamine, a salt precipitated as a white solid. After stirring for an additional 90 min, the reaction mixture was diluted with hexanes (75 mL), filtered through a pad of SiO_2 via a fritted funnel, and then the pad of SiO_2 was washed with 200 mL of 40% Et_2O/hexanes. The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (95:5 pentane/Et_2O) gave ketene dimer (±)-**12e** (2.25 g, 43 %) as a colorless oil. R_f = 0.29 (90% pentane/ether); IR (neat) 1874, 1726 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.20 (t, *J* = 7.0 Hz, 1H), 3.36 (t, *J* = 7.0 Hz, 1H), 2.98-3.01 (m, 2H), 2.92-2.96 (m, 1H), 2.86-2.90 (m, 1H), 2.09-2.21 (m, 2H), 1.30-1.45 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.7, 147.3, 98.2, 51.7, 44.1, 41.4, 30.4, 28.5; LRMS (EI) Calcd. for $C_{16}H_{28}O_2$ [M$^+$] 208, found 208. Satisfactory HRMS could not be obtained for this compound by MALDI or ESI.

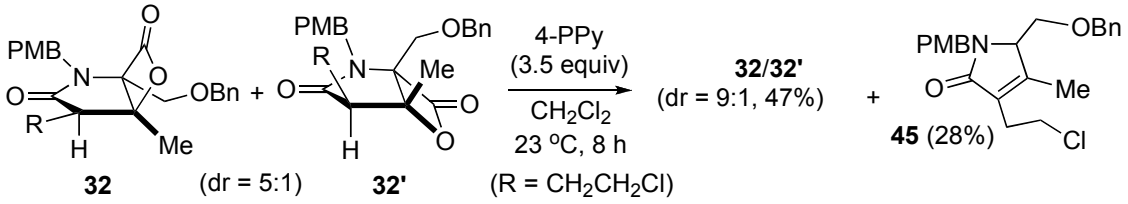


(±)-**21e**

β-lactone, (±)-21e: To a suspension of *N*-propyl-2-bromo pyridinium triflate (130 mg, 0.371 mmol) and 4-pyrrolidinopyridine (53 mg, 0.371 mmol) in CH_2Cl_2 (6 mL) was added Hünig's base (63 μL, 0.494 mmol) at 0 °C. After stirring for 10 min, a solution of the crude keto-acid from hydrogenolysis (100 mg, 0.247mmol) in CH_2Cl_2 (4 mL) was added via syringe pump over 1 h at 0 °C. The resulting suspension was

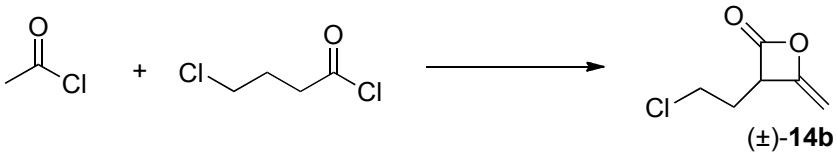
stirred for 2 h at 0 °C. The crude reaction mixture was diluted with Et_2O (70 mL) and washed with aqueous NH_4Cl solution and brine (30 mL of each). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (1:10 EtOAc/hexanes) to give a mixture of *β*-lactones **21e/21e'** (67 mg, 70%, dr 4:1) as a colorless oil. **(±)-21e** (major diastereomer): R_f = 0.66 (40% EtOAc/hexanes); IR (neat) 1832, 1702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 14.5 Hz, 2H), 6.90 (d, *J* = 14.5 Hz, 2H), 5.05 (d, *J* = 24.5 Hz, 1H), 4.45 (s, 1H), 4.02-4.10 (m, 1H), 4.06 (d, *J* = 24.5 Hz, 1H), 3.82 (s, 3H), 3.73-3.81 (m, 1H), 3.49-3.62 (m, 2H), 2.98 (t, *J* = 12 Hz, 1H), 2.26-2.40 (m, 1H), 2.05-2.24 (m, 3H), 1.84-1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 165.1, 159.6, 130.1(2C), 126.3, 114.4(2C), 81.4, 68.9, 53.3, 45.3, 43.8, 43.7, 42.4, 32.4, 29.0, 26.6; LRMS (ESI) Calcd. for $C_{18}H_{22}Cl_2NO_4$ [M+H] 386, found 386.

Cyclopropyl Ketoamide 44: R_f = 0.29 (95% DCM/EtOAc); IR (neat) 1759, 1697 cm^{-1}; (500 MHz, $CDCl_3$) δ 7.30-7.38 (m, 3H), 7.24-7.26 (m, 2H), 7.15 (d, *J* = 9Hz, 2H), 6.83 (d, *J* = 9Hz, 2H), 5.18 (d, *J* = 14.5 Hz, 1H), 4.46 (d, *J* = 12 Hz, 1H), 4.37 (d, *J* = 12 Hz, 1H), 4.08 (d, *J* = 14.5 Hz, 1H), 3.87 (t, *J* = 3.0 Hz, 1H), 3.79 (s, 3H), 3.74 (dd, *J* = 10, 3 Hz, 1H), 3.70 (dd, *J* = 10, 3 Hz, 1H), 1.76 (d, *J* = 9.5 Hz, 1H), 1.73 (d, *J* = 9.5 Hz, 1H), 1.64 (dd, *J* = 9.5, 5 Hz, 1H), 1.56(dd, *J* = 9.5, 5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 172.8, 159.5, 137.7, 129.9 (2C), 128.7 (2C), 128.2 (2C), 127.9 (2C), 114.4(2C), 73.5, 66.8, 65.2, 55.6, 44.0, 32.0, 21.7, 20.8; HRMS (ESI) Calcd. for $C_{22}H_{23}NO_4Li$ [M+Li] 372.1787, found 372.1786.



Decomposition of *β*-lactones 32/32' Leading to Unsaturated Lactam 45. To a mixture of *β*-lactones (16 mg, 0.036 mmol, dr 5:1) in 1.5 mL CH_2Cl_2 was added 4-pyrrolidinopyridine (18 mg, 0.126 mmol) at 23 °C. After 8 h, the reaction mixture was diluted with ether (25 mL) and washed with 20 % $CuSO_4$ solution (20 mL) to remove the majority of the 4-pyrrolidinopyridine and this was followed by washing with saturated NH_4Cl (20 mL), and then water (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (1:9 → 3:7 EtOAc/hexanes) to give a mixture of recovered β-lactones **32/32'** (7.5 mg, 47%, 9:1 dr) and unsaturated γ–lactam **45** (4.5 mg, 31%): R_f = 0.26 (95% DCM/EtOAc); IR (neat) 1682, 1513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.38 (m, 2H), 7.31-7.33 (m, 1H), 7.26-7.28 (m, 2H), 7.10 (d, *J* = 9Hz, 2H), 6.80 (d, *J* = 9Hz, 2H), 5.03 (d, *J* = 15 Hz, 1H), 4.45 (d, *J* = 12 Hz, 1H), 4.41 (d, *J* = 12 Hz, 1H), 4.17 (d, *J* = 15 Hz, 1H), 3.85 (t, *J* = 4.5,

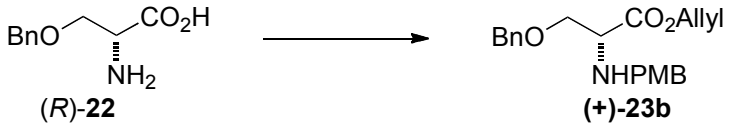
1H), 3.73-3.81 (m, 2H), 3.78 (s, 3H), 3.66 (dd, *J* = 10, 4 Hz, 1H), 3.53 (dd, *J* = 10, 5 Hz, 1H), 2.75-2.78 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 159.1, 151.2, 137.8, 130.2, 129.9, 129.6 (2C), 128.7 (2C), 128.2, 128.0 (2C), 114.2(2C), 73.6, 68.7, 63.0, 55.5, 44.1, 43.4, 27.9, 12.9; HRMS (ESI) Calcd. for $C_{23}H_{27}ClNO_3$ [M+H] 400.1679, found 400.1683.



(±)-**14b**

(Note: the following procedure is slightly modified from that previously reported[3])

Ketene heterodimerization leading to ketene dimer, (±)-14b. To a 2-neck 500 mL round bottom flask fitted with a condenser, acetyl chloride (11.0 mL, 0.156 mol), 4-chlorobutyrylchloride (14.7 mL, 0.130 mol), and Et_2O (200 mL) was added, followed by triethylamine (43.9 mL, 0.312 mol) via a syringe pump at 23 ºC for a period of 1 h. During addition of triethylamine, the triethylamine hydrochloride salt precipitated as a white solid. After stirring for an additional 1 h, the reaction mixture was diluted with hexanes (300 mL) and filtered through a pad of SiO_2 via a fritted funnel. The pad of SiO_2 was then washed with 300 mL (4:6 Et_2O/hexanes). The combined filtrates were concentrated under reduced pressure, and the residue was purified by flash chromatography (95/5 pentane/Et_2O) to afford heteroketene-dimer (±)-**14b** (2.3 g, 13 %) as a clear oil. R_f = 0.41 (9:1 pentane/Et_2O); IR (neat) 1860, 1694 cm^{-1}; ^{1}H NMR (300 MHz, benzene-d_6) δ 4.41 (dd, *J* = 2.1, 4.5 Hz, 1H), 3.80 (dd, *J* = 1.5, 4.5 1H), 3.35 (t, *J* = 7.8 Hz, 1H), 2.79-2.95 (m, 2H), 1.25-1.46 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 167.4, 152.6, 85.7, 51.7, 40.9, 29.9; LRMS (CI) Calcd. for $C_6H_8ClO_2$ [M+H] 147, found 147.



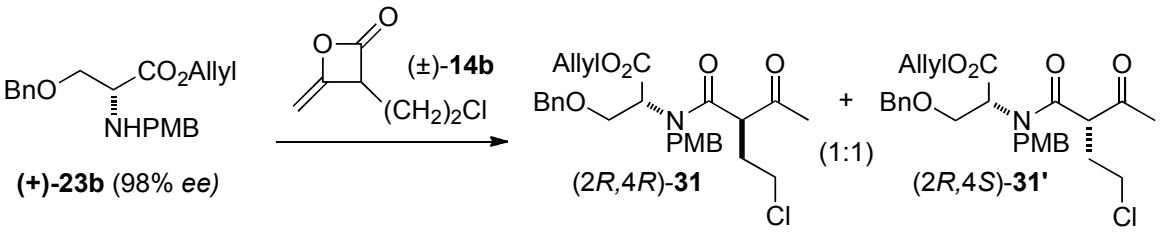
(*R*)-**22** **(+)-23b**

(*R*)-*O*-benzyl serine allyl ester, (+)-23b. To a suspension of *O*-benzyl-*D*-serine ((*R*)-**22**) (4.35 g, 22.3 mmol) in distilled MeOH (80 mL) was added triethylamine (3.76 mL, 26.8 mmol) and *p*-anisaldehyde (4.55 g, 33.4 mmol) at 23 ºC. The resulting suspension was stirred until the solution became homogeneous (~ 30 min). The solution was then cooled to 0 ºC, followed by addition of anhydrous $MgSO_4$ (13.4 g, 112 mmol). After 7 h, the $MgSO_4$ was filtered via fritted funnel and washed with MeOH (80 mL). The combined filtrate was cooled to 0 ºC for 15 min and then $NaBH_4$ (1.11 g, 29.4 mmol) was added portionwise. After stirring at 0 ºC for 2 h, the solidified reaction mixture was left in a freezer (~ –10 ºC) for 12 h. All volatiles were removed under reduced pressure and the remaining solid was

[3] Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9,* 2143.

resuspended in water (50 mL) and acidified to pH 3 with 2 N HCl. The precipitated white solid was filtered via a Büchner funnel, washed with ice-cold water (2 x 30 mL) and ice-cold Et_2O (2 x 30 mL), and dried under vacuum to give *O*-benzyl-*N*-PMB serine (6.80 g, 97 %) as a white solid.

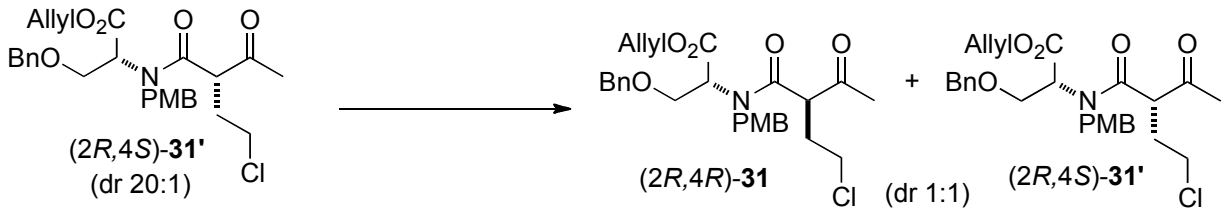
To *O*-benzyl-*N*-PMB serine (6.80 g, 21.6 mmol) and *p*-TsOH (4.93 g, 25.9 mmol) was added allyl alcohol (20 mL) and benzene (40 mL). The solution was stirred at reflux (~ 100 ºC) with a Dean-Stark apparatus until the calculated amount of water had been collected (~ 8 h). The resulting solution was concentrated, resuspended in 5% aqueous $NaHCO_3$ (120 mL), and extracted with EtOAc (500 mL). The pH was adjusted to 10.0 (until pH of aqueous solution maintained at 10 after extraction) with 2 M NaOH solution. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:6 EtOAc/hexanes) to give the desired allyl ester (+)-**23b** (6.30 g, 82%) as a yellow oil. R_f = 0.61 (33% EtOAc/hexanes); $[\alpha]^{23}_D$ = + 20.6 (*c* = 1.8, $CHCl_3$); IR (neat) 1738, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.35 (m, 7 H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.87-5.95 (m, 1 H), 5.22-5.35 (m, 2 H), 4.69 (dt, *J* = 1.2, 5.7 Hz, 2H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 3.89 (d, *J* = 12.6 Hz, 1H), 3.82 (s, 3H), 3.70-3.82 (m, 2H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.57 (t, *J* = 4.8 Hz, 1H), 2.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 158.9, 138.1, 132.2, 131.9, 129.8 (2C), 128.6 (2C), 127.9, 127.8(2C), 118.7, 114.0 (2C), 73.4, 71.3, 65.7, 60.6, 55.5, 51.6; HRMS (ESI) Calcd. for $C_{21}H_{26}NO_4$ [M+H] 356.1862, found 356.1858. Enantiomeric excess was determined to be 98% by chiral HPLC (CHIRALPAK IA, 250 x 4.6 mm (L x I.D.), solvent (isocratic) 95:5 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 230 nm). Retention times: (*S*)-serine derivative 15.97 min; (*R*)-serine derivative 22.34 min.



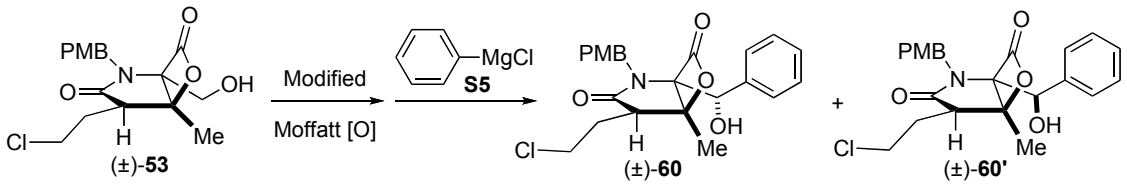
β-Ketoamide, 31/31'. To a 80 mL microwave vessel containing (*R*)-*O*-benzyl serine allyl ester (+)-**23b** (3.56 g, 0.01 mol, 1.0 equiv) was added ketene-dimer (±)-**14b** (1.61 g, 0.011 mmol, 1.1 equiv), 2-hydroxypyridine (1.05 g, 0.011 mmol, 1.1 equiv) and dichloroethane (35 mL). The reaction mixture was stirred at 23 ºC until the solution turned transparent. The reaction vessel was heated to 48 ºC and irradiated in the microwave at 100 W for 2 h (same scale reaction was repeated one more time). The reaction mixture was concentrated under reduced pressure, and the residue was purified by a short SiO_2 column (95:5 DCM/EtOAc) to afford a 1:1 mixture of diastereomeric keto amides **31/31'** (8.02 g, 80%) as a colorless oil. Two sequential separations by MPLC (SiO_2, 5:95 EtOAc/CH_2Cl_2) gave 2.30 g (46%) of (*R*,*R*)-**31** (30:1 dr). Data for (*R*,*R*)-**31** (45:1 dr, 98% ee): $[\alpha]^{23}_D$ = + 66.1 (*c* = 1.0, $CHCl_3$); IR (neat) 1739, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) for major rotamer δ 7.22-7.36 (m, 7H), 6.87 (d, *J* = 9 Hz, 2 H),

5.85-5.93 (m, 1H), 5.24-5.33 (m, 2H), 4.82 (d, *J* = 16.5 Hz, 1H), 4.66 (d, *J* = 16.5 Hz, 1H), 4.59-4.61 (m, 2H), 4.50 (dd, *J* = 4.0, 8.5 Hz, 1H), 4.47 (d, *J* = 12 Hz, 1H), 4.44 (d, *J* = 12 Hz, 1H), 4.08 (dd, *J* = 8.5, 10.0 Hz, 1H), 4.01 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.93 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.81 (s, 3H), 3.46-3.58 (m, 2H), 2.34-2.43 (m,1H), 2.17-2.24 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) for major rotamer δ 203.3, 169.9, 168.5, 164.9, 159.5, 137.8, 131.8, 128.9 (2C), 128.6 (2C), 128.0, 127.9 (2C), 119.1, 114.3 (2C), 73.9, 68.6, 66.3, 60.1, 55.5, 54.8, 52.6, 42.9, 32.1, 28.0; HRMS (ESI) Calcd. for $C_{27}H_{32}ClNO_6Li$ [M+Li] 508.2078, found 508.2073. Enantiomeric excess was determined by chiral HPLC (Chiralpak IA, 250 x 4.6 mm (L x I.D.), solvent (isocratic) 90:10 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 230 nm). Retention times: (*R*,*R*)-**31** 19.34 min; *ent*-**31**(*S*,*S*): 21.09 min.

For the bis-cyclization process and subsequent steps leading to (–)-salinosporamide A, see the Experimental Section of Article text.



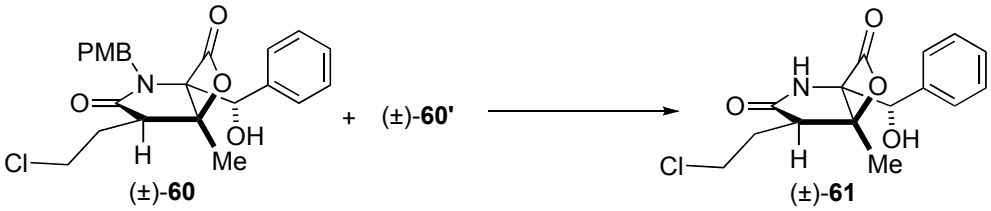
Epimerization of β-Ketoamide 31'. To a solution of ketoamide (*S*, *R*)-**31'** (0.30 g, 0.598 mmol, ~ 20:1 dr) in 10 mL of EtOAc/MeOH (4:1) was added TsOH (137 mg, 0.718 mmol) and the solution was heated to 45 ºC for 48 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (150 mL), H_2O (100 mL) was added and the pH of the aqueous layer was adjusted to ~10 using a 0.1 M NaOH solution. After extraction, the layers were separated and the organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver 0.295 g (98 %) of a 1:1 mixture of ketoamides **31**/**31'** which could be repurified by MPLC to increase material throughput of the desired diastereomer **31**. HPLC analysis of (*R*,*R*)-ketoamide **31** verified that epimerization only occurred at the β-ketoamide and not the α-amino acid position under these conditions.



***N*-PMB-phenyl salino A derivative, (±)-60.** Aldehyde was prepared according to the representative procedure for the modified Moffatt oxidation from alcohol (±)-**53** (80 mg, 0.218 mmol) in DMSO/toluene (1.2 mL/1.2 mL), and addition of EDCI (208 mg, 1.09 mmol), followed by dichloroacetic acid (10 μL,

0.109 mmol) at 23 °C for 5 h. The crude aldehyde was used in the subsequent step without further purification.

To a solution of aldehyde (0.109 mmol) in THF at -78 °C, phenyl Grignard (**S5**, 0.164 mmol) in THF was added slowly down the side of the flask. The reaction mixture was warmed to 0 °C for 10 min, quenched with NH_4Cl saturated solution, and diluted with ether (100 mL). The organic layer was then washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (95:5 → 85:15 EtOAc/hexanes) to provide a mixture of diasteomeric alcohols (±)-**60/60'** (22.5 mg, 48 %, dr = 3:1, 500 MHz ^{1}H NMR) as a colorless oil, which was carried directly to the next step without further purification.



***rac*-Phenyl salinosporamide A derivative, (±)-61.** Prepared according to the representative procedure for PMB deprotection using a diastereomeric mixture of alcohols (±)-**60/60'** (22 mg, 0.052 mmol, dr = 3:1) in *i*-PrOH (0.3 mL), an aqueous solution of CAN (285 mg, 0.52 mmol) in H_2O (0.1 mL) at 0 °C. The residue was purified by flash chromatography (5:95 to 15:85 EtOAc/CH_2Cl_2) to give β-lactone (±)-**61** (7.2 mg, 45 %, dr >19:1) as a white solid. Data matched that previously reported.[4] Data not previously reported: R_f = 0.48 (5:95 EtOAc/CH_2Cl_2); IR (neat) 3354, 1829, 1705 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{17}ClNO_4$ [M+H] 310.0848, found 310.0858. Crystals suitable for X-ray analysis were obtained by slow recrystallization from ~10% acetone/hexane at ambient temperature (23 °C).

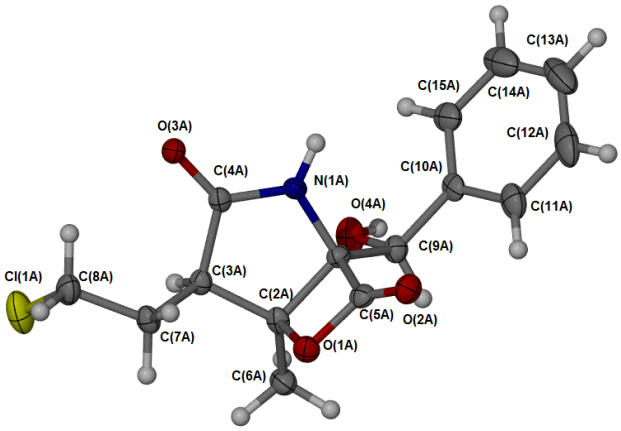
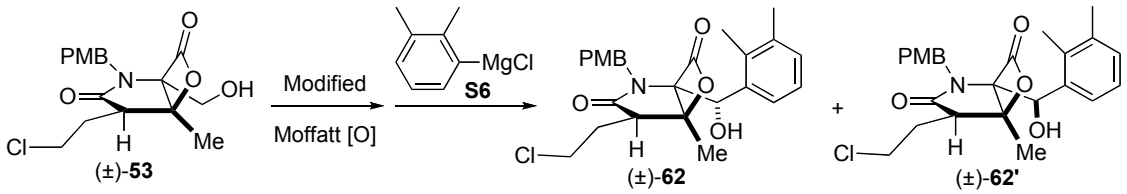


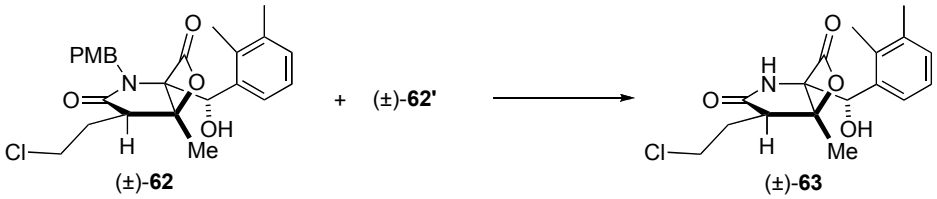
Figure 1. ORTEP plot of the X-ray structure of *rac*-phenyl salinosporamide A, (±)-**61**

[4] Nett, M.; Gulder, T. A. M.; Kale, A. J.; Hughes, C. C.; Moore, B. S. *J. Med. Chem.* **2009**, *52*, 6163–6167.



***N*-PMB-Dimethylphenylsalino A derivative, (±)-62.** Aldehyde was prepared according to the representative procedure for the modified Moffatt oxidation from alcohol (±)-**53** (80 mg, 0.218 mmol) in DMSO/toluene (1.2 mL/1.2 mL), and addition of EDCI (208 mg, 1.09 mmol), followed by dichloroacetic acid (10 μL, 0.109 mmol) at 23 ºC for 5 h. A portion of this crude aldehyde was used in the subsequent step without further purification.

To a solution of aldehyde (~0.109 mmol, ~ half of aldehyde prepared above) in THF at -78 ºC, Grignard reagent **S6** (0.164 mmol) in THF was added slowly down the side of the flask. The reaction mixture was then warmed up to 0 ºC for 10 min, quenched with NH_4Cl saturated solution, and diluted with ether (100 mL). The organic layer was then washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (95:5 → 85:15 EtOAc/hexanes) to provide a mixture of (±)-**62/**(±)-**62'** (22.0 mg, 44 %, dr = 3:1 according to 500 MHz ^{1}H NMR) as a colorless oil, which was carried directly to the next step without further purification.



***rac*-Dimethylphenylsalinosporamide A derivative, (±)-63.** Prepared according to the representative procedure for PMB deprotection using a mixture of alcohol (±)-**62/**(±)-**62'** (22.0 mg, 0.048 mmol, dr 3:1) in *i*-PrOH (0.3 mL) and an aqueous solution of CAN (263 mg, 0.48 mmol) in H_2O (0.1 mL) at 0 °C dropwise. The residue was purified by flash chromatography (5:95 → 15:85 EtOAc/CH_2Cl_2) to give dimethyl phenyl salino A derivative (±)-**63** (6.9 mg, 43 %, dr >19:1) as a white solid: R_f = 0.55 (4:6 EtOAc/Hexanes); IR (neat) 3350, 1825, 1702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5, 1H), 7.21-7-28 (m, 2H), 5.44 (s, 1H), 5.24 (d, *J* = 4.5 Hz, 1H), 3.98 (ddd, *J* = 5.0, 8.0, 11.0 Hz, 1H), 3.78 (ddd, *J* = 5.0, 7.0, 11.5 Hz, 1H), 2.91 (t, *J* = 7.0 Hz, 1H), 2.33 (s, 3H), 2.26-2.32 (m, 1H), 2.27 (s, 3H), 2.14-2.21 (m, 1H), 2.16 (d, *J* = 4.5 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ and C_3D_6O) δ 174.9, 167.6, 138.0, 135.9, 134.7, 131.3, 127.2, 124.8, 84.5, 78.8, 67.6, 45.3, 42.3, 28.2, 21.0, 19.1, 15.2; HRMS (ESI) Calcd. for $C_{17}H_{21}ClNO_4$[M+H] 338.1159, found 338.1152.

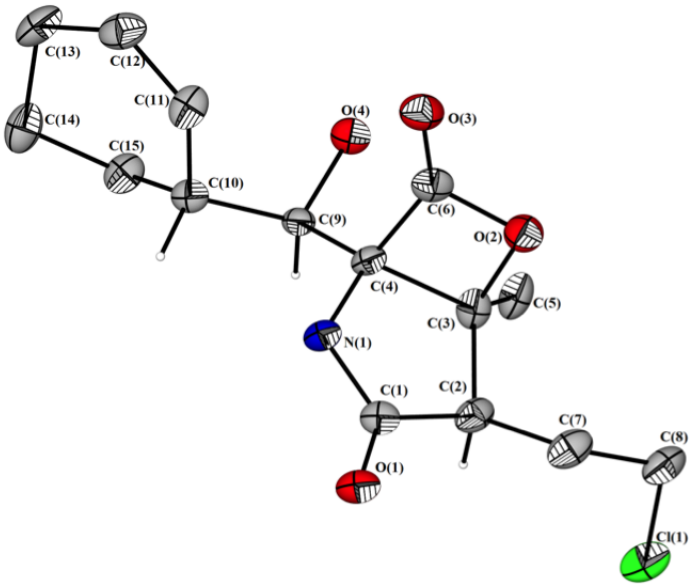
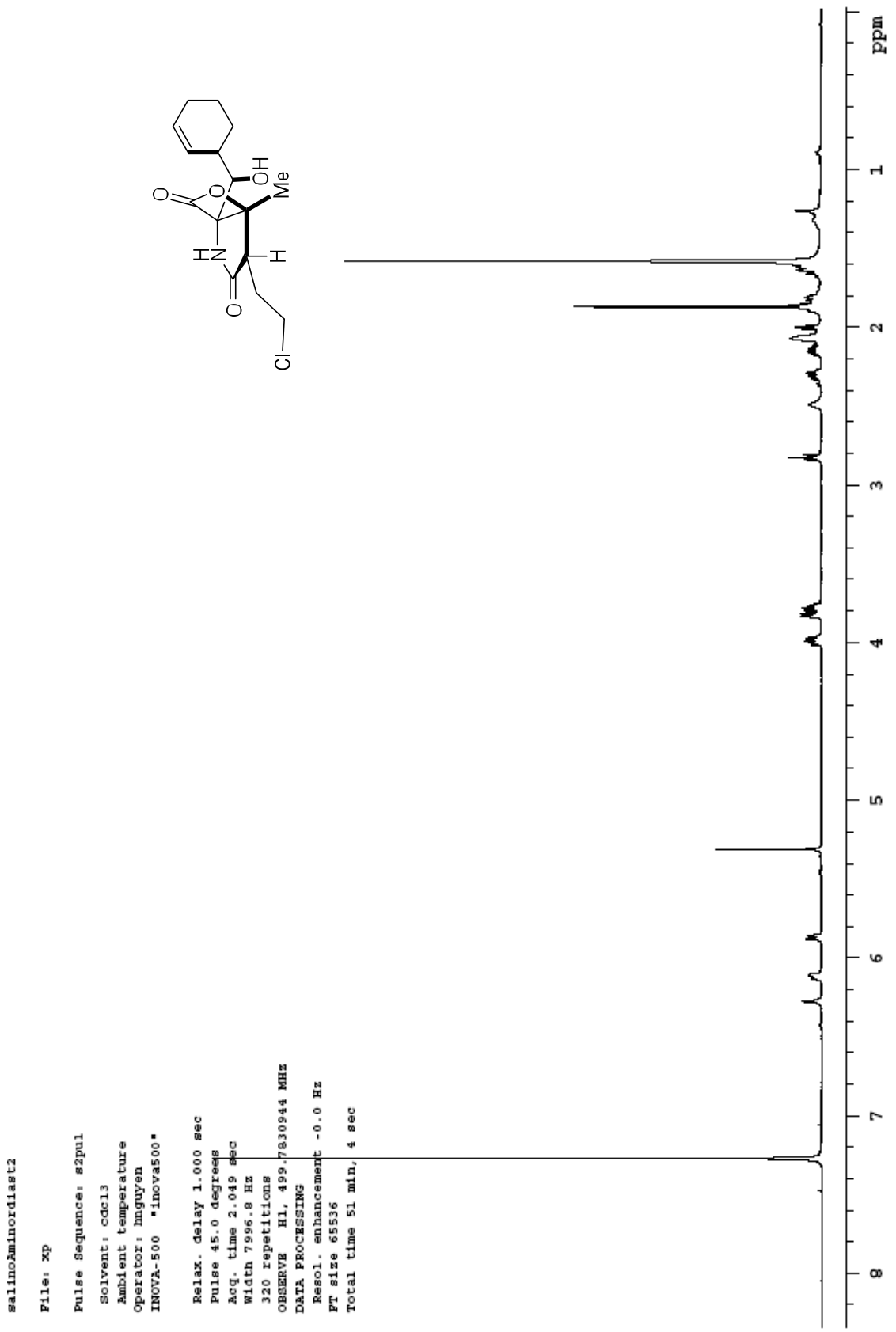
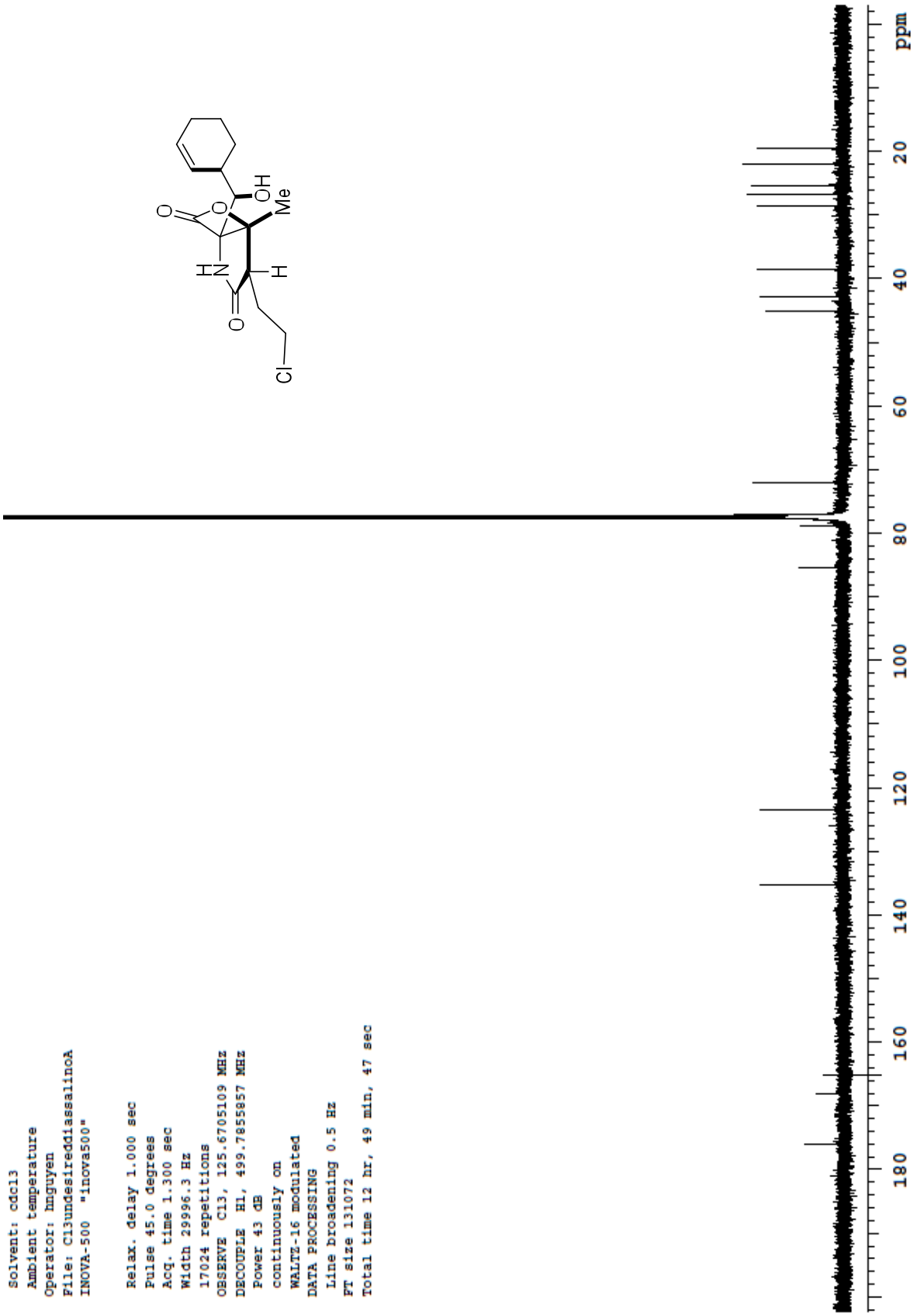


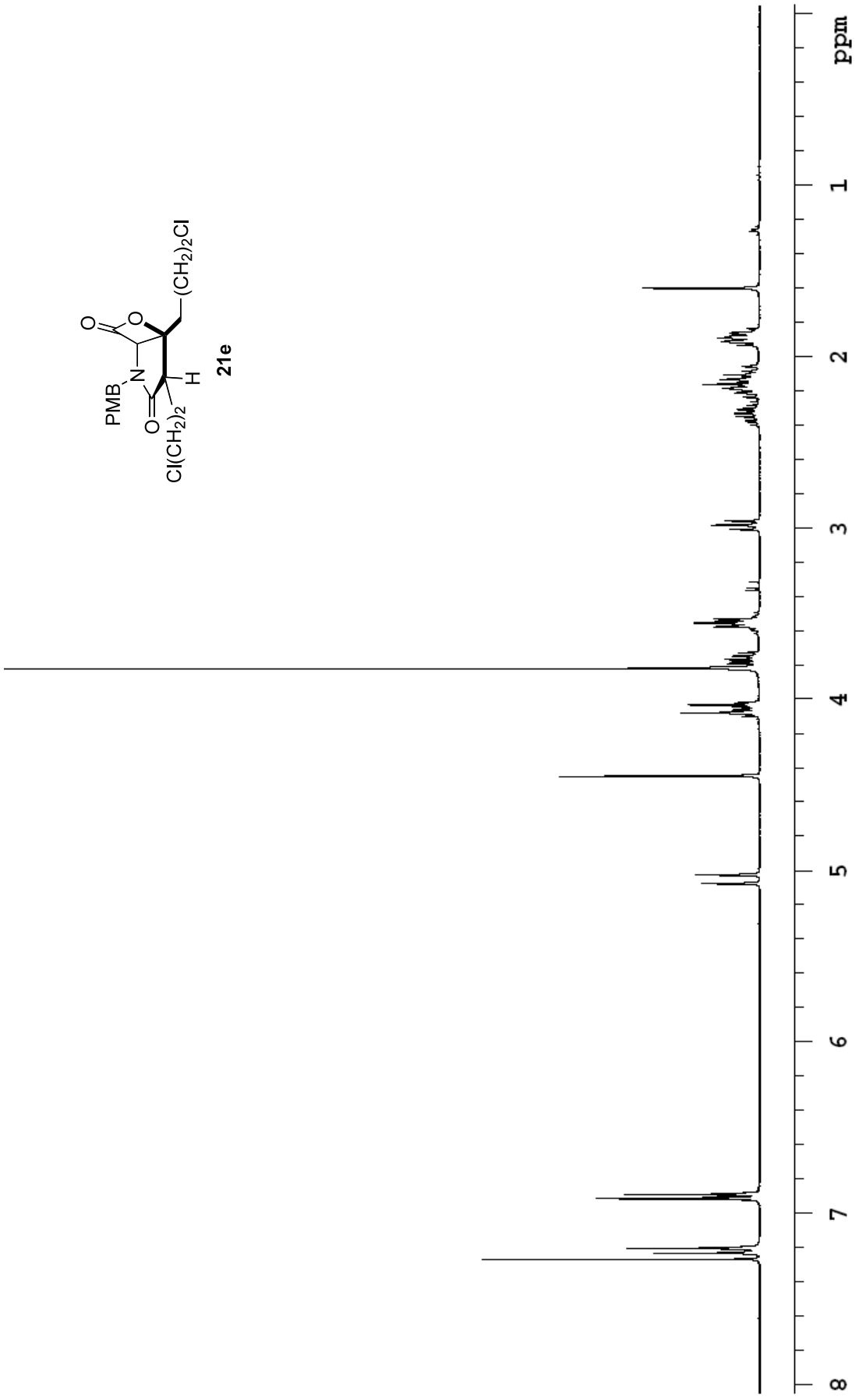
Figure 2. ORTEP plot of the X-ray structure of C5, C6-bis-*epi*-salinosporamide A (**1a'**)



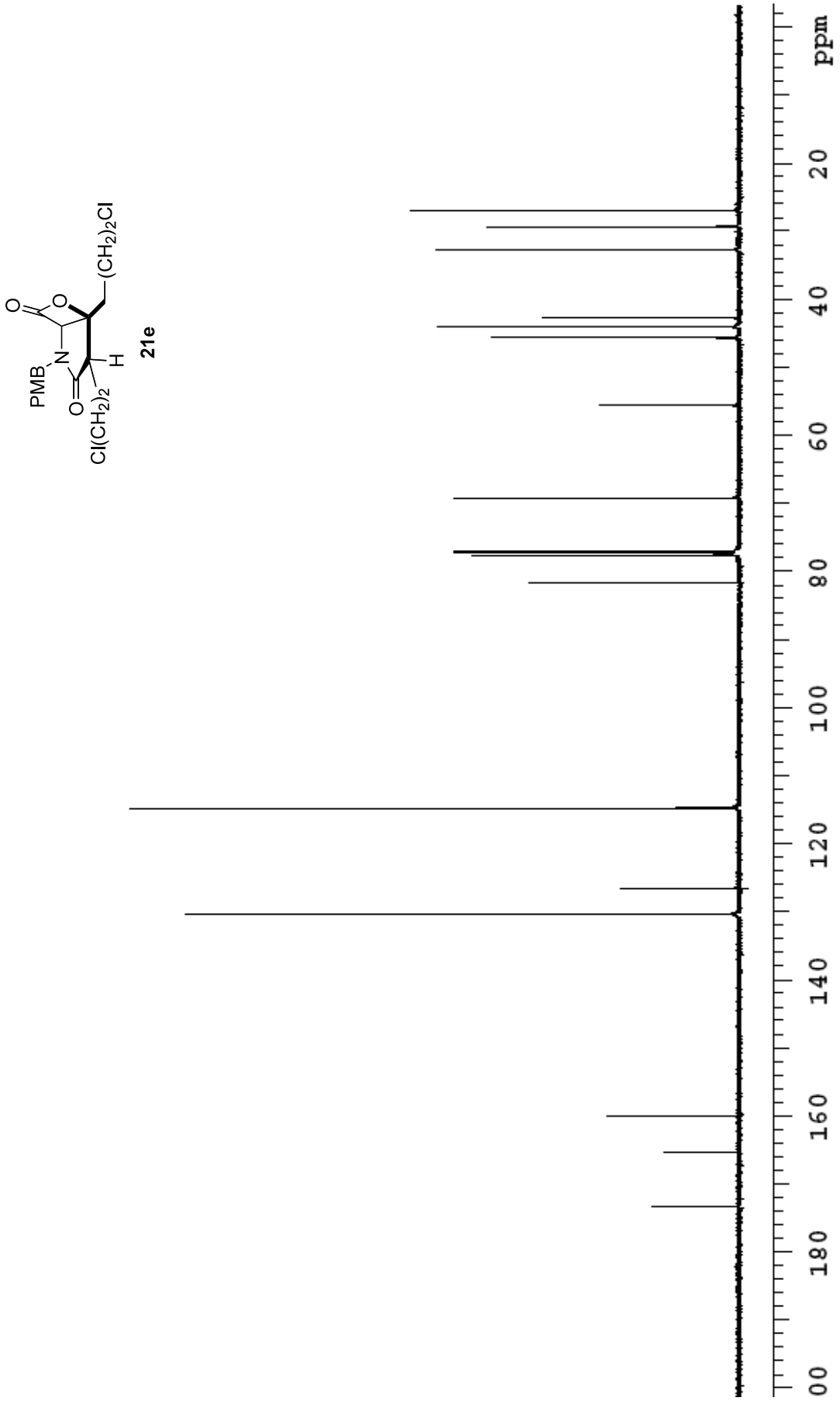
^{1}H NMR of β-lactone, (–)-**1a'** (500 MHz, $CDCl_3$)



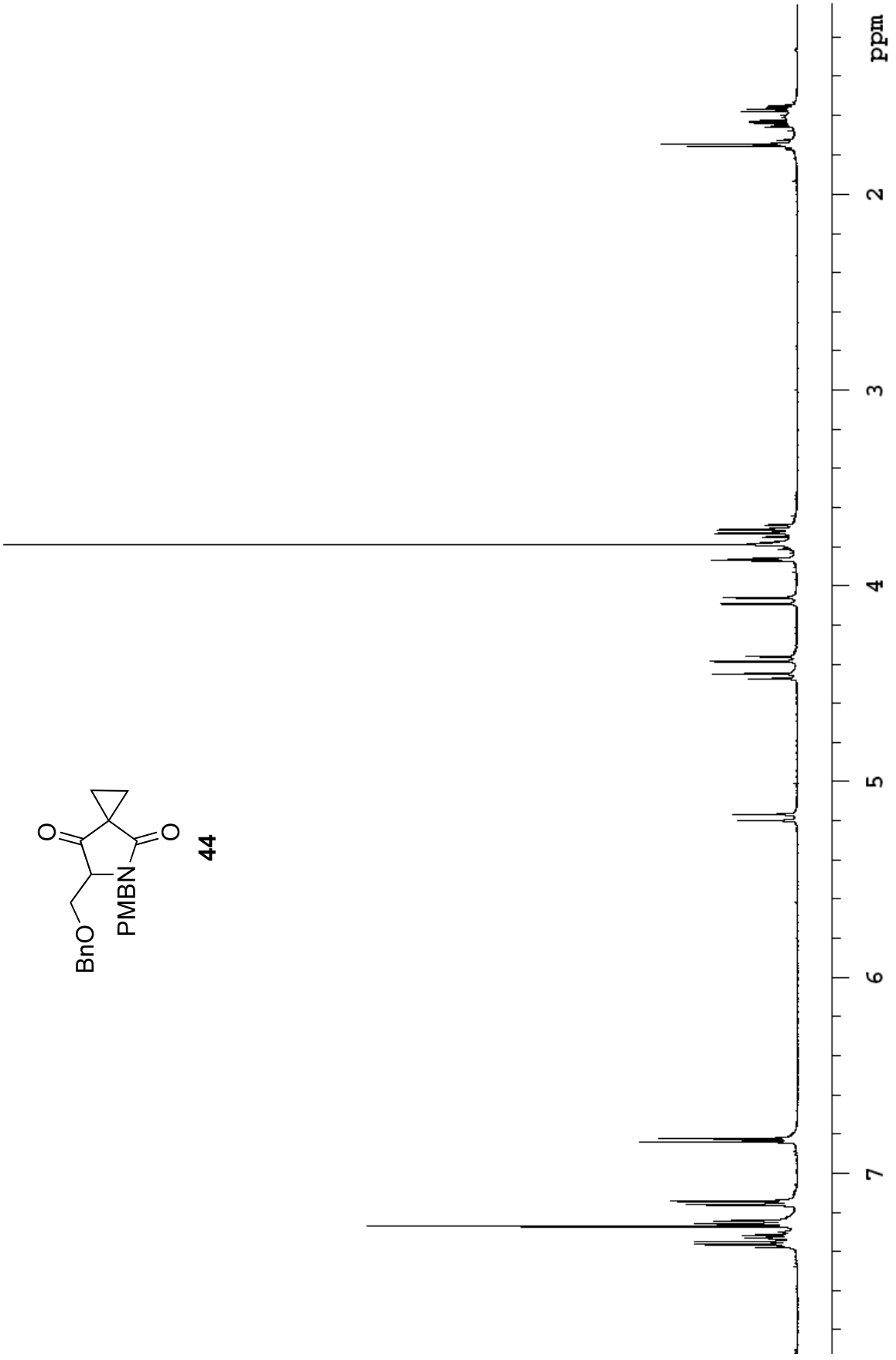
^{13}C NMR of β-lactone, C5, C6-bis-*epi*-salinosporamide A ((–)-**1a'**) (500 MHz, $CDCl_3$)



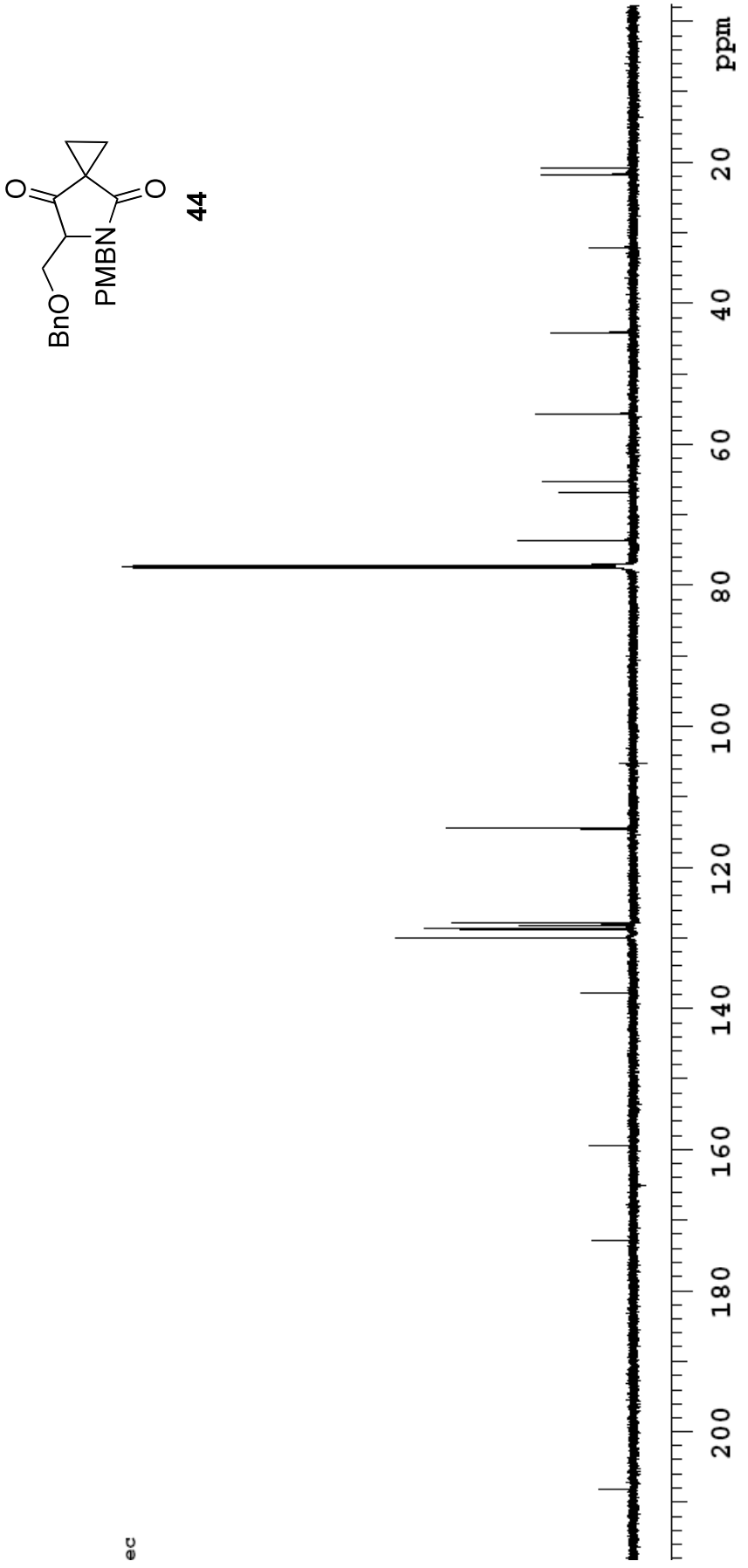
^{1}H NMR of β-lactone, (±)-**21e** (500 MHz, $CDCl_3$)



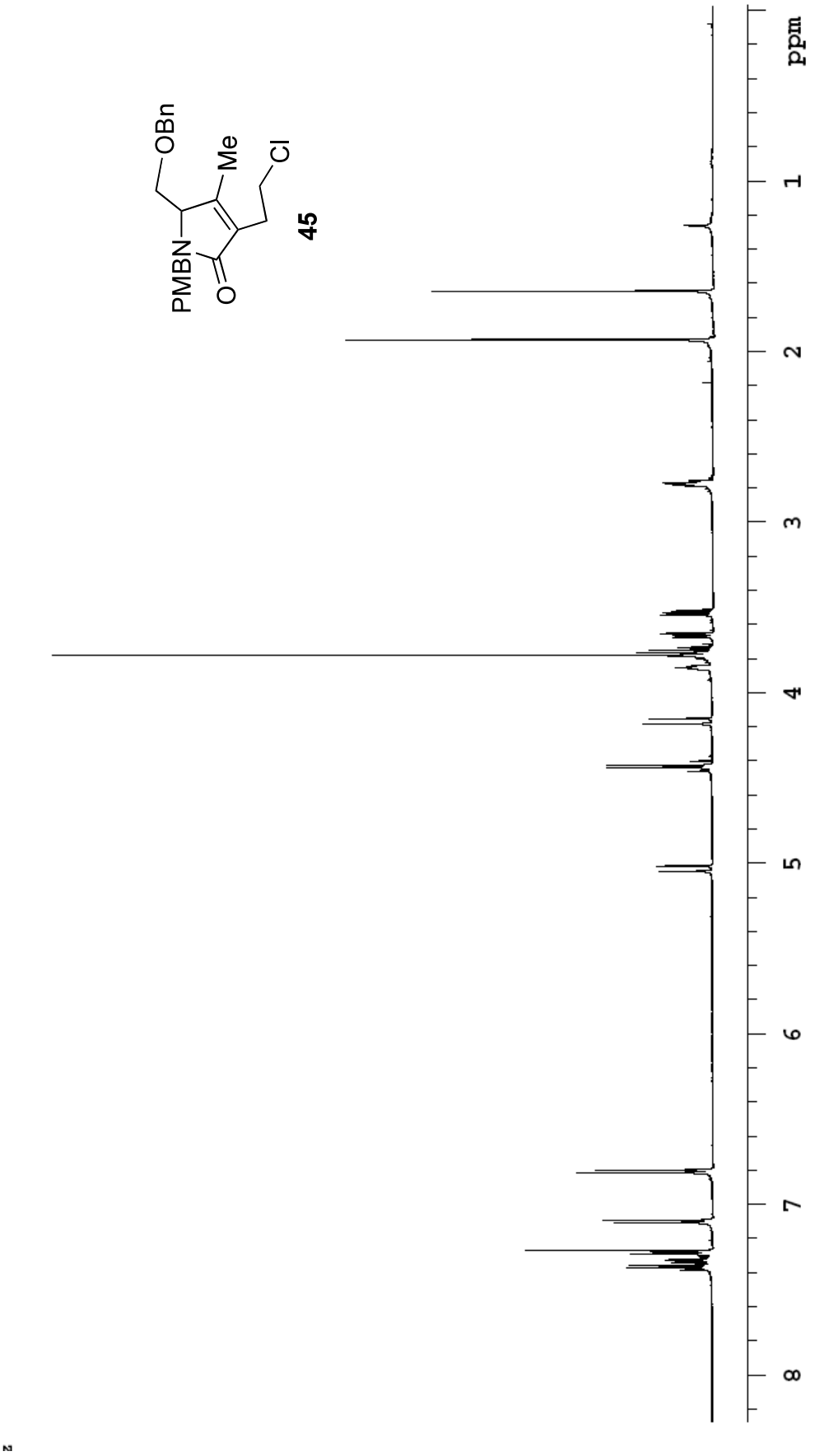
^{13}C NMR of β-lactone, (±)-**21e** (125 MHz, $CDCl_3$)



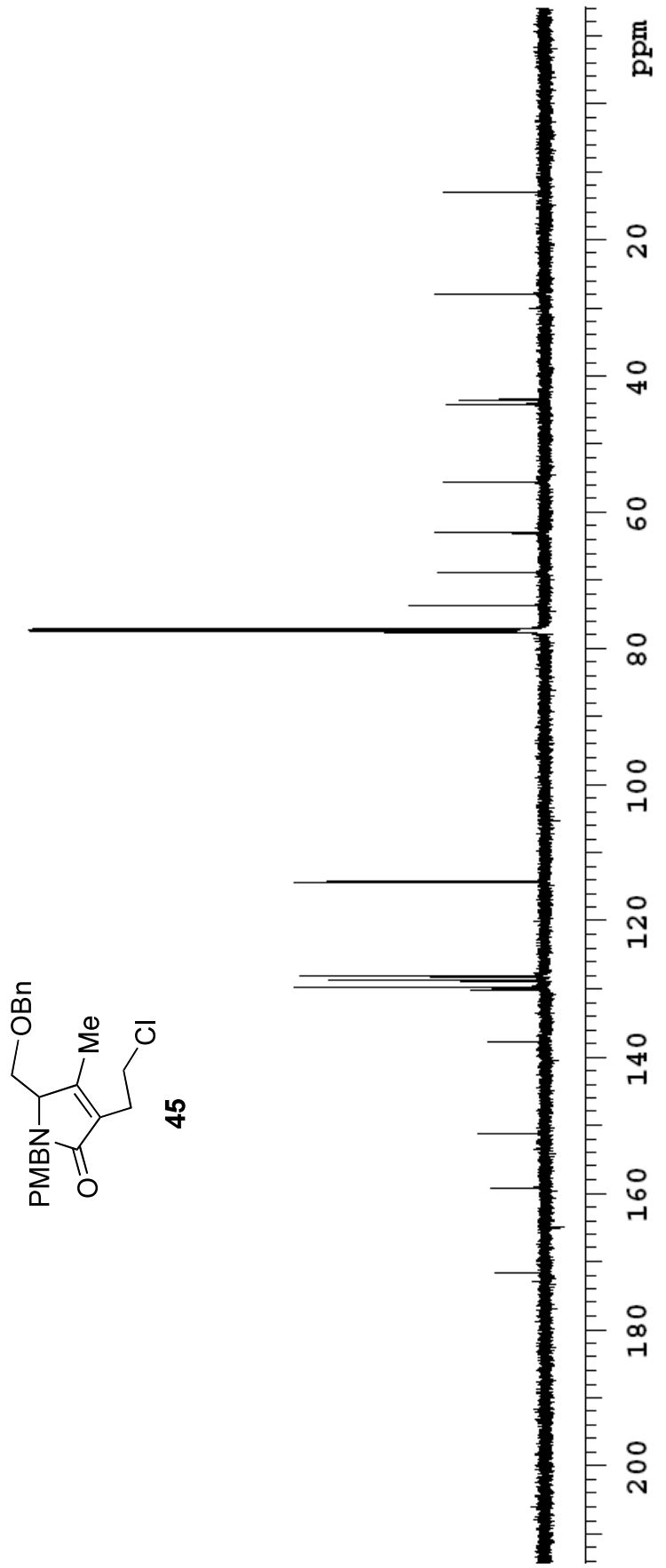
^{1}H NMR of Cyclopropyl Ketoamide **44** (500 MHz, $CDCl_3$)



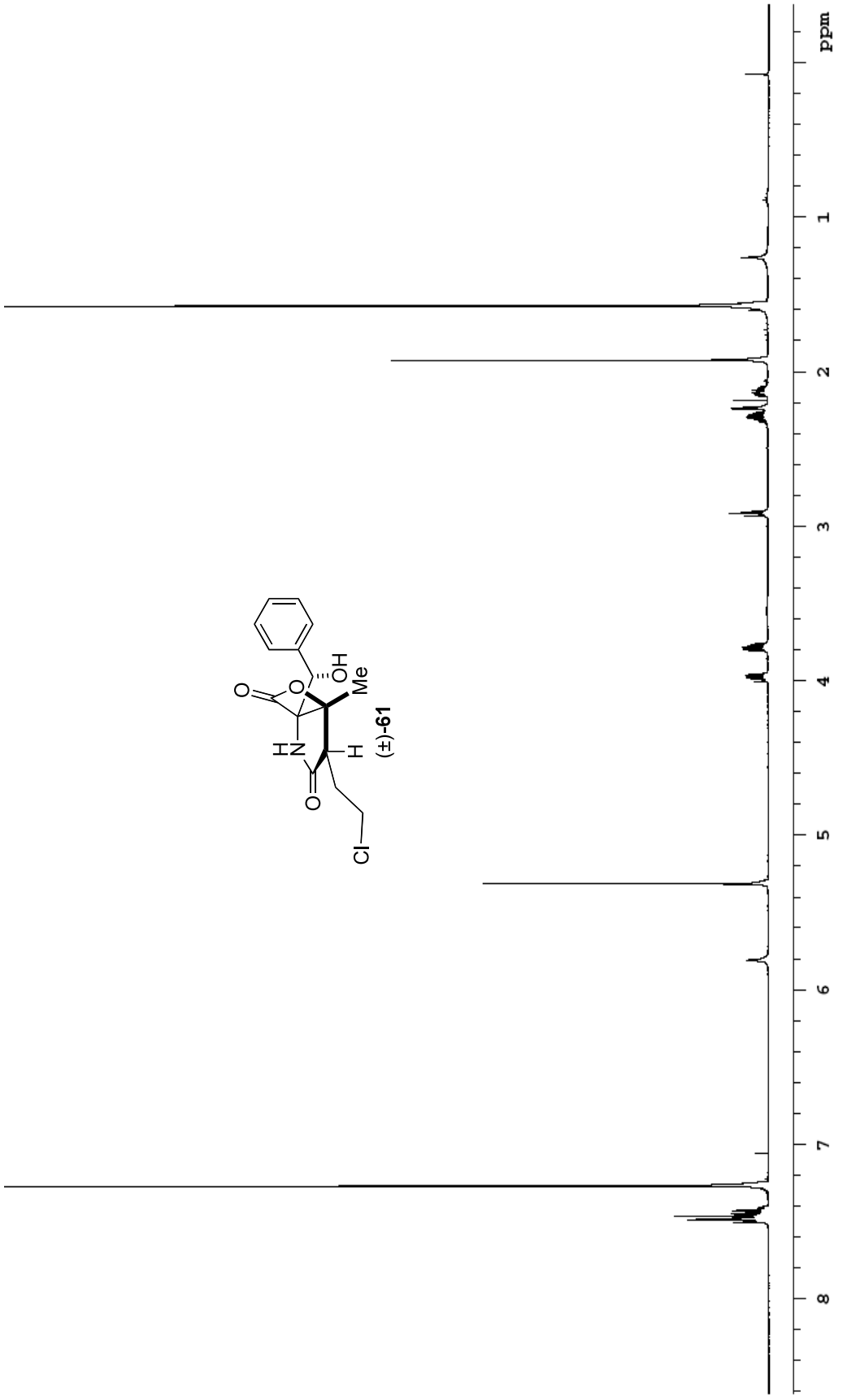
^{13}C NMR of Cyclopropyl Ketoamide **44** (125 MHz, $CDCl_3$)



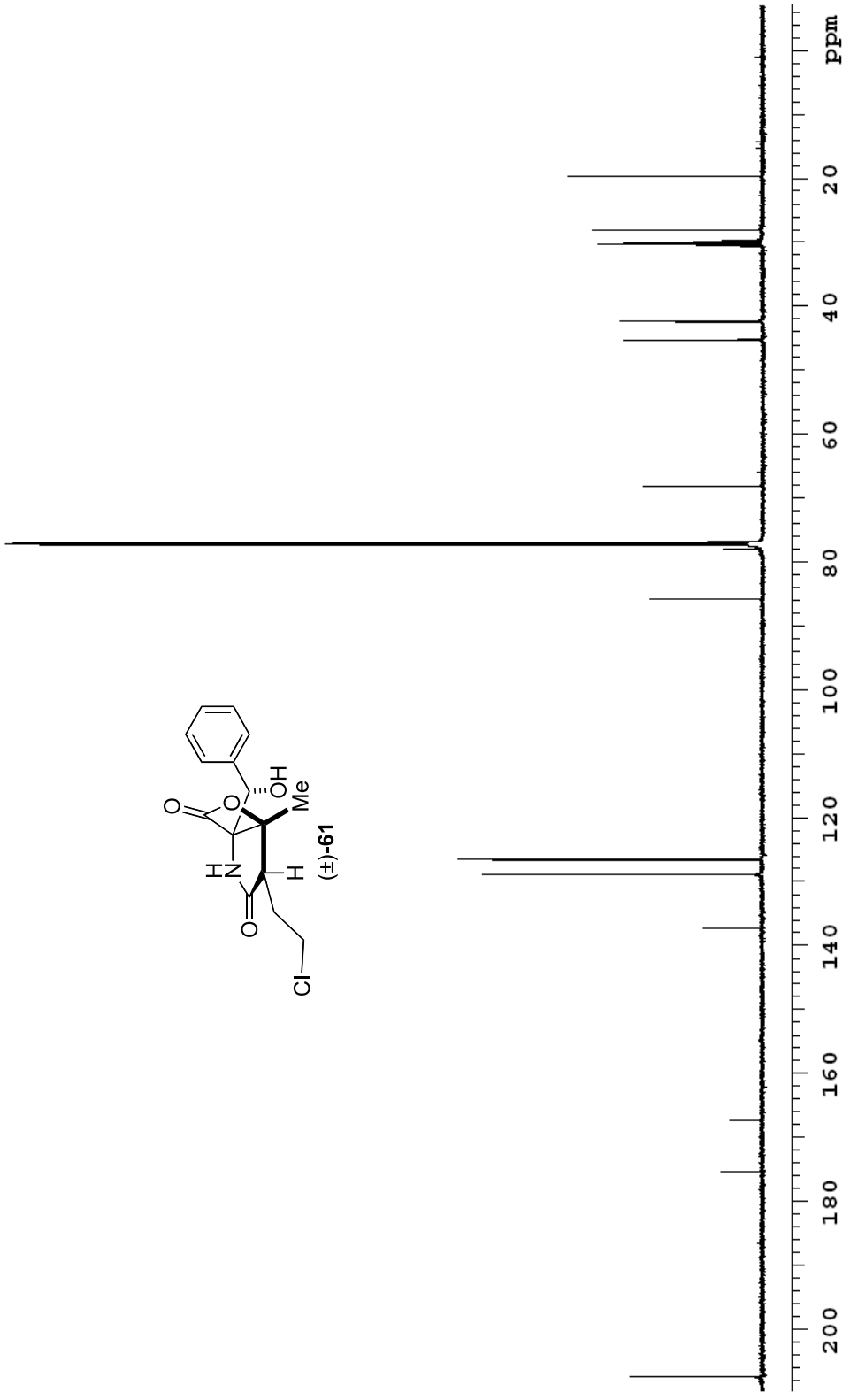
^{1}H NMR of γ-Lactam **45** (500 MHz, $CDCl_3$)



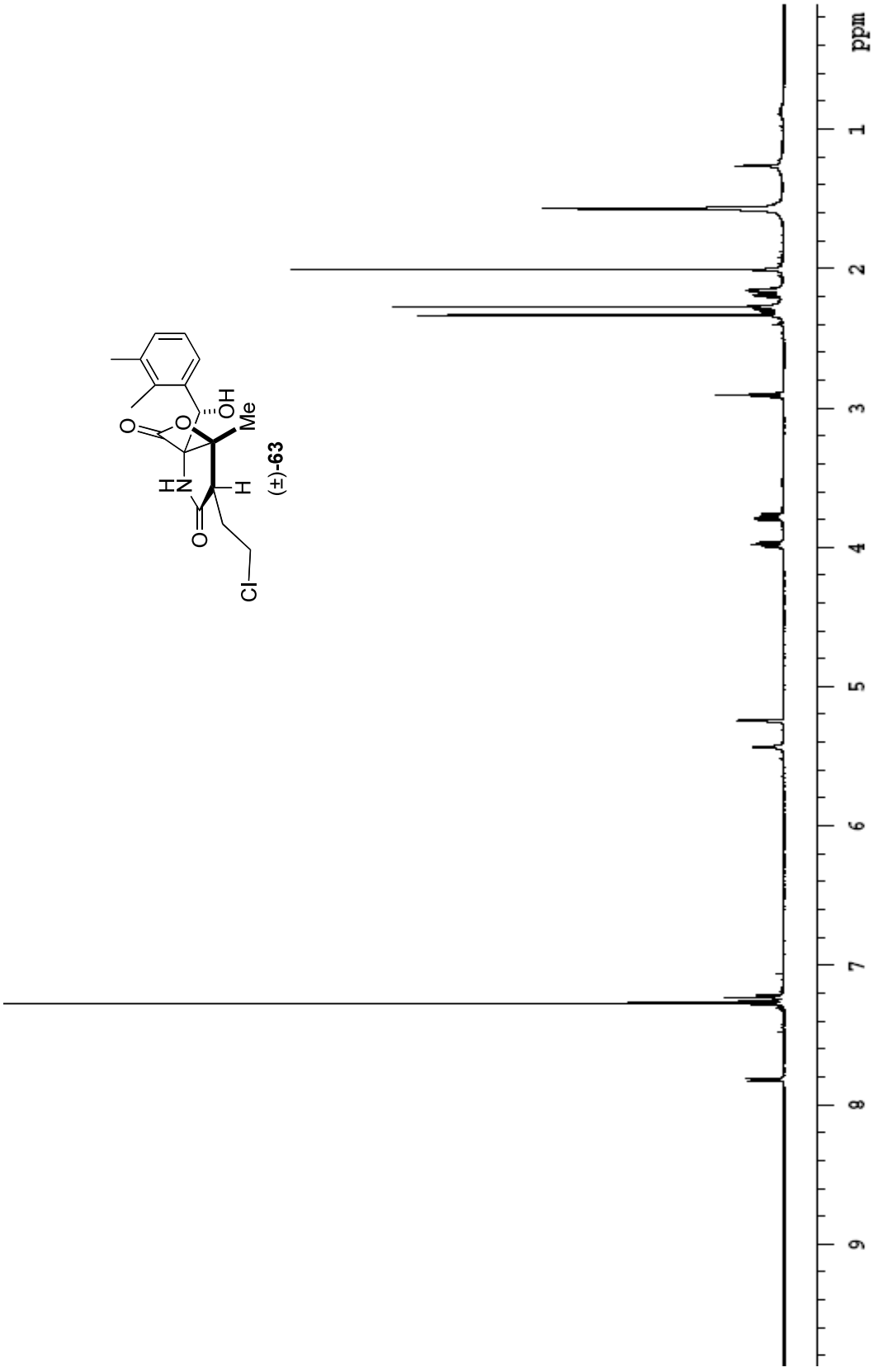
^{13}C NMR of γ-Lactam **45** (125 MHz, $CDCl_3$)



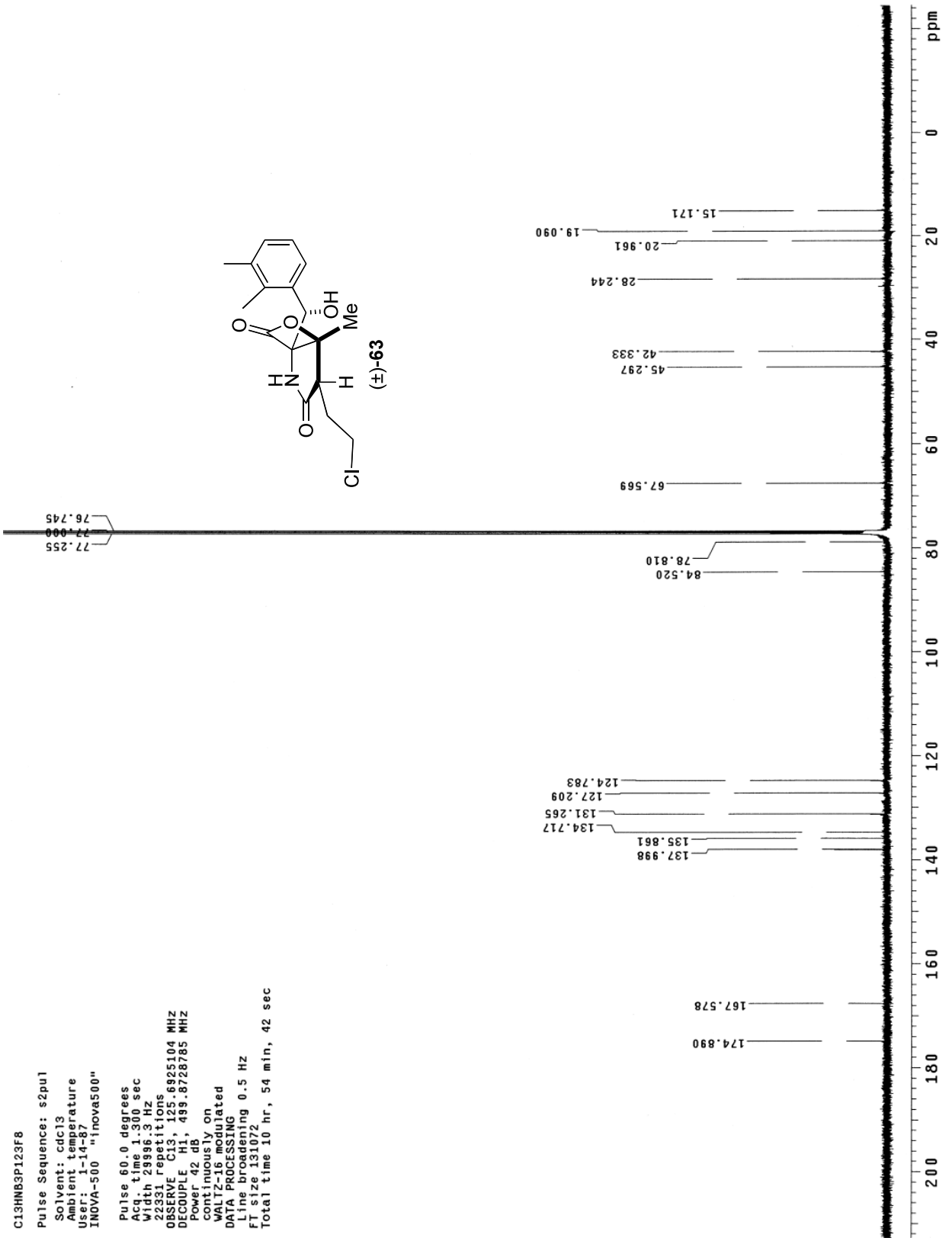
^{1}H NMR of (±)-salino A derivative, (±)-**61**(500 MHz, $CDCl_3$)



^{13}C NMR of (±)-salino A derivative, (±)-**61** (125 MHz, $CDCl_3$)



^{1}H NMR of (±)-salino A derivative, (±)-**63** (500 MHz, $CDCl_3$)



^{13}C NMR of (±)-salino A derivative, (±)-**63** (125 MHz, $CDCl_3$)