Electronic Supplementary Information

$A^{1,3}$-Strain Enabled Retention of Chirality During Bis-Cyclization of β-Ketoamides: Total Synthesis of (–)-Salinosporamide A and (–)-Homosalinosporamide A

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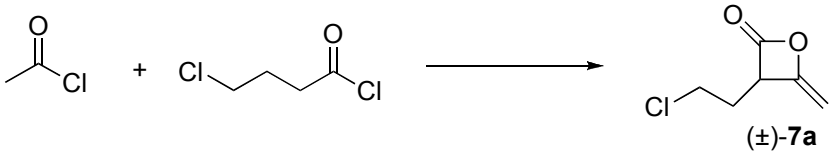
Electronic Supplementary Information Available. General procedures and characterization data including ^{1}H, ^{13}C NMR spectra (compounds **1a**, **3c**, **7c**, **12c, 9**, **10a**, **14**) and chiral HPLC traces (**9**, **10a**, **10c**, **3a**, **12c**), and X-ray analyses (**14**).

General Procedures:

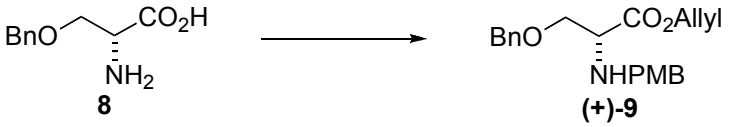
All reactions were carried out under nitrogen atmosphere in oven-dried glassware. Dichloromethane, toluene and ethyl ether were purified by passage through activated molecular sieves. Methanol was distilled from magnesium turnings. Tetrahydrofuran was distilled from Na/benzophenone. Hünig's base and 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). LC-MS analyses were done on C18 RP column using 0.1% formic acid with a CH_3CN/H_2O gradient. Thin layer chromatography (TLC) was performed using glass-backed silica gel 60_{F254} (Silicycle, 250 μm thickness).



(±)-**7a**

(Note: the following procedure is slightly modified from that previously reported[1])

Representative procedure for ketene-heterodimerization as described for ketene dimer, (±)-7a. 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 ketene-dimer (±)-**7a** (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.



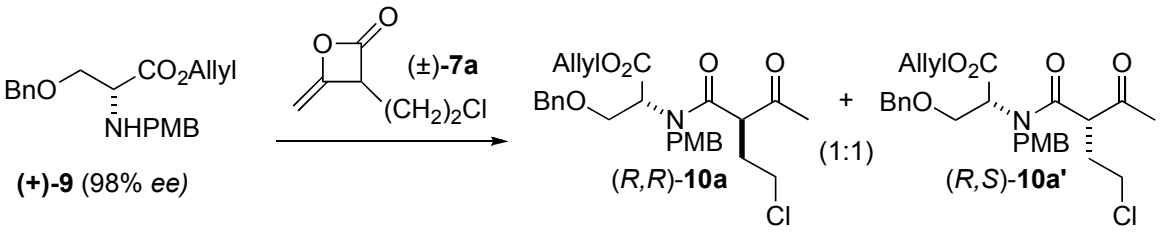
8 **(+)-9**

(*R*)-O-benzyl serine allyl ester, (+)-9. To a suspension of *O*-benzyl-*D*-serine (**8**) (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).

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

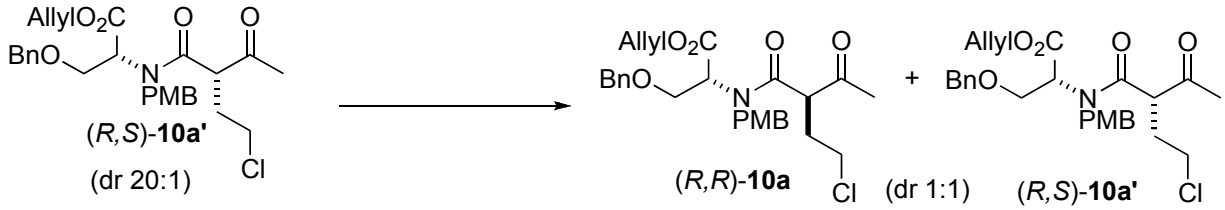
The solution was then cooled to 0 ºC, followed by addition of anhydrous $MgSO_4$ (13.4 g, 112 mmol). After 7 h, the $MgSO_4$ was filtered via fritted funnel and washed with MeOH (80 mL). The combined filtrate was cooled to 0 ºC for 15 min and then $NaBH_4$ (1.11 g, 29.4 mmol) was added portionwise. After 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 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 **9** (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.

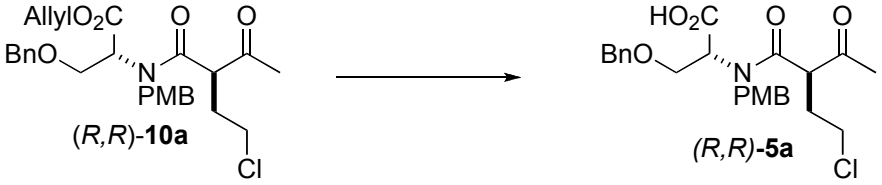


β-Ketoamide, 10a/10a'. To a 80 mL microwave vessel containing (*R*)-*O*-benzyl serine allyl ester (+)-**9** (3.56 g, 0.01 mol) was added ketene-dimer (±)-**7a** (1.61 g, 0.011 mmol), 2-hydroxypyridine (1.05 g, 0.011 mmol) and dichloroethane (35 mL). The reaction mixture was stirred at 23 ºC until the 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 **10a/10a'** (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 of (*R*,*R*)-**10a** (32:1 dr). Data for (*R*,*R*)-**10a** (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*)-**10a** 19.34 min; *ent*-**10a**(*S*,*S*): 21.09 min.

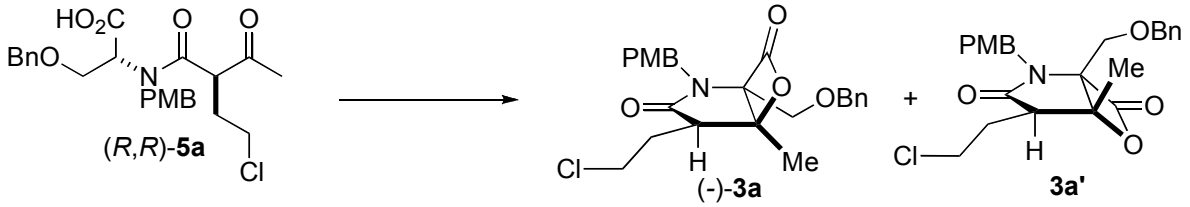


Epimerization of β-Ketoamide 10a'. To a solution of ketoamide (*S*, *R*)-**10a'** (0.30 g, 0.598 mmol, ~ 20:1 dr) in 10 mL of EtOAc/MeOH (4:1) was added TsOH (137 mg, 0.718 mmol) and the solution was heated to 45 ºC for 48 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (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 **10a**/**10a'** which could be repurified by MPLC to increase material throughput of the desired diastereomer **10a**. HPLC analysis of (*R*,*R*)-ketoamide **10a** verified that epimerization only occurred at the β-ketoamide and not the α-amino acid position under these conditions.



(*R*,*R*)-β-Ketoacid, 5a. To a solution of ketoamide (*R*,*R*)-**10a** (2.30 g, 4.55 mmol, ~ 32:1 dr) in THF (91.0 mL) at -5 ºC (ice and saturated NaCl solution) was added $Pd(PPh_3)_4$ (526 mg, 0.455 mmol), followed by

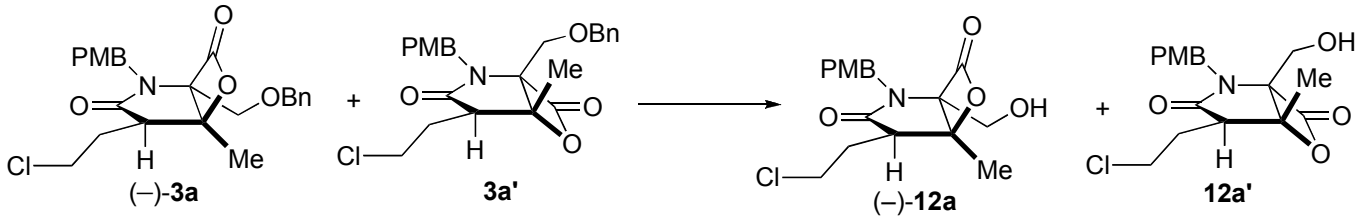
immediate addition of morpholine (0.475 ml, 5.46 mmol). The reaction mixture was stirred at -5 ºC for 70 min and diluted with ice cold Et_2O (800 mL). A 0.02 N HCl solution was added until the pH was measured to be ~3. The layers were separated and the organic layer was washed with brine (400 mL), dried over $MgSO_4$ and concentrated. The crude ketoacid (*R*,*R*)-**5a** (~ 32:1 dr according to 500 MHz ^{1}H NMR) was used in the subsequent step without further purification. (Note: longer reaction time led to epimerization).



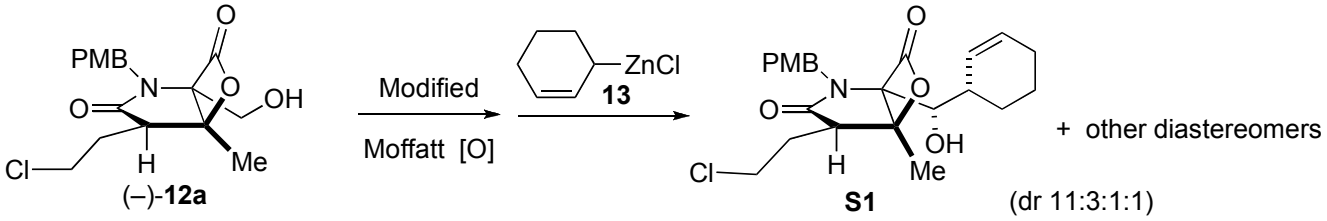
Benzyloxy-β-lactone, (–)-3a/3a': To a solution of 4-pyrrolidinopyridine (1.21g, 8.45 mmol) in toluene (46 mL) at –10 ºC was added MsCl (0.20 mL, 2.54 mmol). Immediately, a solution of freshly synthesized ketoacid (*R*,*R*)-**10a** (1.69 mmol) in toluene (12 mL) was added to the resulting suspension via syringe pump over 30 min. After 50 min, the reaction mixture was diluted with ice-cold Et_2O (400 mL) and washed with 20 % $CuSO_4$ solution (2 x 200 mL) to remove excess 4-pyrrolidinopyridine and then washed with water (2 x 200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Immediately, the residue was purified by flash chromatography (1:9 to 3:7 EtOAc/hexanes) to give a mixture of two co-eluting, inseparable *β*-lactones (–)-**3a**/**3a'** (260 mg, 35%, 7:1 dr, 500 MHz ^{1}H NMR) as a colorless oil and recovered ketoacid (36%, 2:1 dr). R_f = 0.36 (20% EtOAc/hexanes). Data for (–)-**3a:** IR (neat) 1830, 1703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.36 (m, 3H), 7.13-7.15 (m, 4H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 15.5 Hz, 1H), 4.31 (d, *J* = 15.5 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 4.01 (ddd, *J* = 5.0, 7.5, 12.5 Hz, 1H), 3.77-3.81 (m, 1H), 3.77 (s, 3H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 2.91 (t, *J* = 7.5 Hz, 1H), 2.31-2.38 (m, 1H), 2.10-2.16 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 166.1, 159.2, 136.4, 129.2(2C), 128.6, 128.5(2C), 128.2, 128.0(2C), 113.9(2C), 83.4, 79.3, 73.5, 61.6, 55.2, 45.0, 44.3, 42.5, 28.4, 19.2; LRMS (ESI) Calcd. for $C_{24}H_{27}ClNO_5$ [M+H] 444, found 444. Enantiomeric excess of (-)-**3a** was determined to be 92% by chiral HPLC (CHIRALPAK IA, 250 x 4.6 mm (L x I.D.), solvent (isocratic) 87:13 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 230 nm). Retention times: (–)-**3a**: 13.68 min; *ent*-**3a**: 16.12 min.

Benzyloxy-β-lactone, (–)-3a/3a' (gram scale synthesis). To a solution of 4-pyrrolidinopyridine (2.60 g, 18.2 mmol, 4.0 equiv) in toluene (84 mL) at -5 ºC (ice and saturated NaCl solution) was added MsCl (0.53 mL, 6.83 mmol, 1.5 equiv). Immediately, a solution of freshly prepared ketoacid (*R*,*R*)-**5a** (4.55 mmol) in toluene (25 mL) was added to the resulting suspension via syringe pump over 45 min and 5 mL of additional toluene were used to ensure complete transfer. After 3 h, the reaction mixture was diluted

with ice cold Et_2O (700 mL) and washed with 20% $CuSO_4$ solution (500 mL) to remove most of the 4-pyrrolidinopyridine, saturated NH_4Cl (500 mL), and then washed with water (2 x 500 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 two inseparable *β*-lactones (**–**)-**3a**/**3a'** (1.05 g, 52%, 5:1 dr, 500 MHz ^{1}H NMR) as a yellow oil and recovered ketoacid (10 %, 4:1 dr). R_f = 0.36 (20% EtOAc/hexanes). Enantiomeric excess of (**–**)-**3a** was determined to be 90%. The diasteromeric β-lactones were carried directly forward to the deprotection at which point they could be separated.



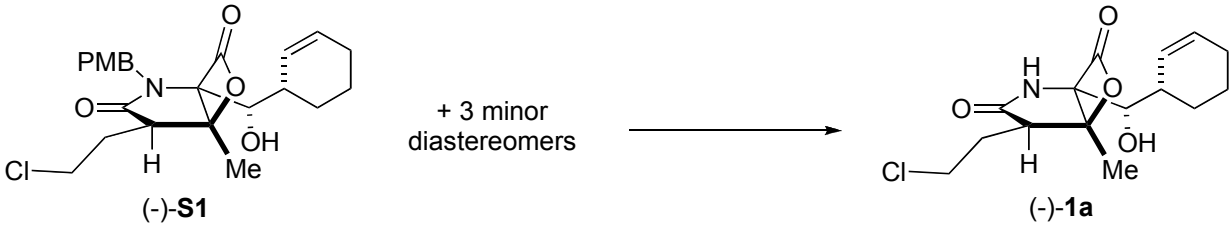
Representative procedure for debenzylation as described for hydroxy-β-lactone, (–)-12a/12a'. To a mixture of *β*-lactones (–)-**3a** and **3a'** (260 mg, 0.586 mmol, dr 7:1) in THF was added palladium on carbon (52 mg, 20 wt%). After evacuating twice by aspirator vacuum, and refilling with H_2, a balloon of H_2 was attached to the flask and the heterogenous solution was stirred vigorously at 23 °C for 12 h. The reaction mixture was then diluted with Et_2O, and dried over $MgSO_4$. The organics were filtered through a pad of Celite, concentrated, and purified by MPLC (SiO_2, 5:95 EtOAc/CH_2Cl_2) to give the desired alcohol (–)-**12a** in 75% yield (155 mg, dr >19:1, 92% ee) as a waxy solid. R_f = 0.29 (5:95 EtOAc/CH_2Cl_2); $[\lambda]^{23}_D$ = – 67.0 (*c* = 0.95, $CHCl_3$). Data for (–)-**12a**: IR (neat) 3449, 1831, 1687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.13 (d, *J* = 15.0 Hz, 1H), 4.06 (d, *J* = 15.5 Hz, 1H), 4.03 (ddd, *J* = 5.5, 7.5, 12.5 Hz, 1H), 3.92 (dd, *J* = 9.0, 13.5 Hz, 1H), 3.85 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.80 (s, 3H), 3.78-3.82 (m, 1H), 2.94 (t, *J* = 7.0 Hz, 1H), 2.32-2.38 (m, 1H), 2.01-2.18 (m, 1H), 1.77 (s, 3H), 0.86 (dd, *J* = 5.0, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.7, 159.6, 129.0(2C), 128.7, 114.7(2C), 83.6, 80.2, 55.3, 55.1, 44.9, 44.1, 42.4, 28.4, 19.1; LRMS (ESI) Calcd. for $C_{17}H_{21}ClNO_5$ [M+H] 354, found 354.



Representative procedure for *N*-PMB-salinosporamide A, S1. To a solution of alcohol (–)-**12a** (155 mg, 0.440 mmol, dr >19:1) in DMSO/toluene (2.2 mL/2.2 mL) was added EDCI (424 mg, 2.20 mmol), and dichloroacetic acid (18 μL, 0.22 mmol) at 23 °C. The reaction mixture was stirred for 5 h, and diluted with EtOAc (150 mL). The reaction mixture was acidified using 0.1 N HCl to pH 3. The organic layer

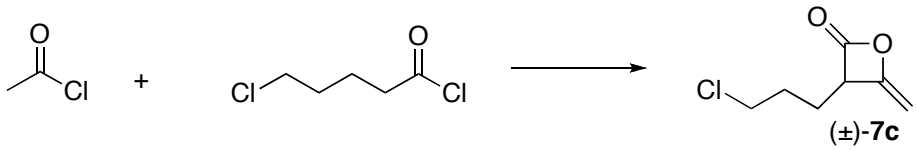
was then washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was used for the next step without further purification due to some instability of the resulting aldehyde to column chromatography. Based on ^{1}H NMR integration, the aldehyde was accompanied by ~15% of unreacted alcohol (–)-**12a**.

A solution of tri-*n*-butyl-2-cyclohexenyltin (490 mg, 1.32 mmol) in THF (2.0 mL) was treated with *n*-BuLi (2.5 M in hexanes, 512 μL, 1.28 mmol) at –78 °C. After 30 min, $ZnCl_2$ (0.5 M in THF, 2.62 mL, 1.41 mmol) was added and after an additional 30 min, a solution of the crude aldehyde in THF (1.5 mL) was slowly added to the freshly prepared zinc reagent **13**. The resulting mixture was stirred at –78 °C for 4 h, quenched with water and diluted with Et_2O (150 mL). Saturated NH_4Cl was added until a pH of 7 was achieved. The layers were separated and then the organic layer was washed with brine (100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (95:5 ⟶ 85:5 EtOAc/hexanes) to give a mixture of four inseparable diastereomers (100 mg, 62 %, dr = 11:3:1:1 according to 500 MHz ^{1}H NMR) as a colorless oil, which was carried directly to the next step without further purification. The major diastereomer (–)-**S1** was confirmed to possess the correct relative stereochemistry following subsequent conversion to salinosporamide A.

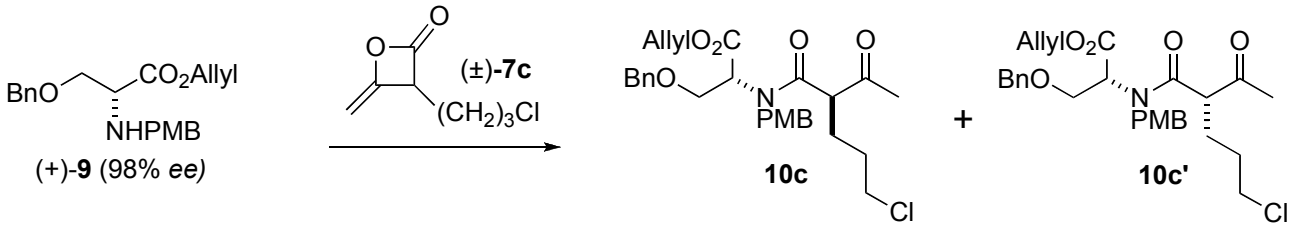


Representative procedure for PMB-deprotection as described for (–)-salinosporamide A, (–)-1a: To a methanolic solution (1.2 mL) containing the mixture of alcohol (–)-**S1** (100 mg, 0.23 mmol), along with other diastereomers from the previous step, was added an aqueous solution of CAN (1.26 g, 2.3 mmol) in H_2O (0.6 mL) at 0 °C dropwise. After stirring at 0 °C for 6 h, the reaction mixture was diluted with EtOAc (100 mL), washed with saturated solution of $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5:95 ⟶ 15:85 EtOAc/CH_2Cl_2) to give salinosporamide A (–)-**1a** (31 mg, 43 %) as a white solid (dr ~ 15:1, 500 MHz ^{1}H NMR). Further purification was accomplished by recrystallization involving slow evaporation from 95:5 CH_2Cl_2/acetone to provide (–)-**1a** (28 mg, 90 %, dr > 19:1): R_f = 0.50 (33 % EtOAc/hexanes); m.p. 152-156 °C, lit. 169-171 °C; $[\alpha]^{23}_D$ = – 71.3 (*c* = 0.39, MeOH); lit. $[\alpha]^{25}_D$ = – 72.9 (*c* = 0.55, MeOH); IR (neat) 3346, 1820, 1698 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-d_5) δ 10.69 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 6.45 (d, *J* = 10.0 Hz, 1H), 5.89-5.93 (m, 1H), 4.28 (t, *J* = 9.0 Hz, 1H), 4.16 (dt, *J* = 7.0, 11.0 Hz, 1H), 4.05 (dt, *J* = 7.0, 11.0 Hz, 1H), 3.21 (t, *J* = 7.0 Hz, 1H), 2.84-2.91 (m, 1H), 2.48-2.55 (m, 1H), 2.30-2.39 (m, 2H), 2.10 (s, 3H), 1.91-1.98 (m, 2H), 1.70-1.73 (m, 2H), 1.35-1.42 (m, 1H); ^{13}C NMR (125

MHz, pyridine-d_5) δ 176.9, 169.4, 129.1, 128.7, 86.3, 80.4, 71.0, 46.2, 43.3, 39.3, 29.0, 26.5, 25.4, 21.7, 20.0; HRMS (ESI) Calcd. for $C_{15}H_{21}ClNO_4$ [M+H] 314.1161, found 314.1162.



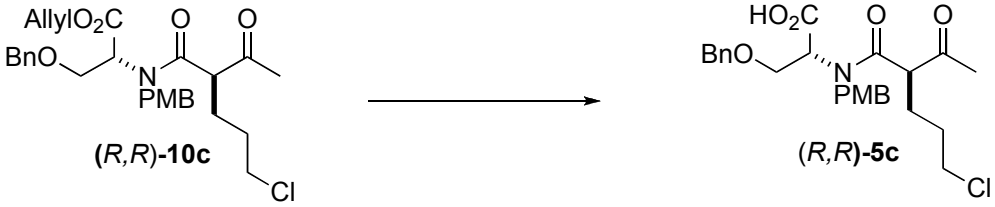
Ketene dimer, **(±)-7c:** To a solution of acetyl chloride (7.5 mL, 0.105 mol) and valerylchloride (10.4 mL, 0.081mol) in Et_2O (200 mL) was added triethylamine (29.6 mL, 0.211 mol) via a syringe pump at 0 ºC for a period of 1h. During addition of triethylamine, the triethylamine hydrochloride salt precipitated as a white solid. After stirring for an additional 10 min at 0 ºC, the reaction mixture was removed from the ice-bath and stirring was continued at 23 ºC for 45 min. The reaction mixture was diluted with hexanes (300 mL), filtered through a pad of SiO_2 via a fritted funnel, and then the pad of SiO_2 was washed with 300 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) to afford ketene-dimer (±)-**7c** (1.3 g, 10 %) as a clear oil. R_f = 0.51 (20% EtOAc/hexanes); IR (neat) 1860, 1694 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 4.43 (dd, *J* = 1.5, 4.5 Hz, 1H), 3.79 (dd, *J* = 1.5, 4.5 Hz, 1H), 2.98-3.01 (m, 1H), 2.80-2.83 (m, 2H), 1.25-1.36 (m, 1H), 1.16-1.24 (m, 3H); ^{13}C NMR (125 MHz, benzene-d_6) δ 168.2, 153.7, 85.6, 54.1, 44.1, 29.3, 24.8; LRMS (CI) Calcd. for $C_6H_{10}ClO_2$ [M+H] 161, found 161.



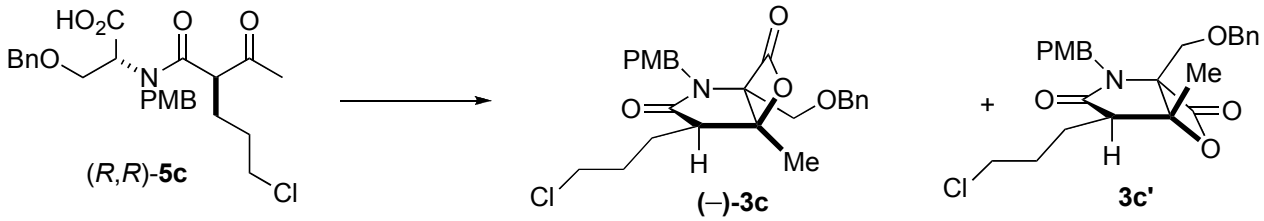
(*R*, *R*)-β-ketoamide, (–)-10c: To a 10 mL microwave vessel containing (*R*)-*O*-benzyl serine allyl ester (+)-**9** (356 mg, 1.00 mmol) was added ketene-dimer (±)-**7c** (177 mg, 1.1 mmol), 2-hydroxypyridine (105 mg, 1.1 mmol) and dichloroethane (3.5 mL). The reaction mixture was stirred at 23 ºC until the solution turned transparent. The reaction vessel was irradiated with microwave at 100 W for 2 h, maintaining the reaction temperature at 53 ºC (for optimal yields, the same scale reaction was repeated 3 times). The crude reaction mixtures were combined and concentrated by rotary evaporation, and the residue was purified by a short column (95:5 CH_2Cl_2/EtOAc) to afford a 1:1 mixture of diastereomeric keto amides **10c**/**10c'** (1.21g, 80%) as a colorless oil. MPLC separation (SiO_2, 5:95 EtOAc/CH_2Cl_2) gave 350 mg of (*R*,*R*)-**10c** (25:1 dr, 29%)**.** Enantiomeric excess was determined to be 94% ee by chiral HPLC (Chiralpak IA, 250 x 4.6 mm (L x I.D.), solvent (isocratic) 87:13 hexanes/2-propanol, flow rate 1.0 mL/min, wavelength λ = 230 nm). Retention times: (*R*, *R*)-**10c** 12.92 min; *ent*-**10c** (*S*, *S*) 16.52 min.

Data for **10c:** R_f = 0.74 (5:95 EtOAc/CH_2Cl_2); IR (neat) 1738, 1646, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) for major rotamer δ 7.21-7.35 (m, 7H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.85-5.93 (m, 1H), 5.24-

5.33 (m, 2H), 4.82 (d, *J* = 17.0 Hz, 1H), 4.66 (d, *J* = 17.0 Hz, 1H), 4.59-4.61 (m, 3H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.05 (dd, *J* = 8.0, 10.0 Hz, 1H), 3.98 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.81 (s, 3H), 3.53 (dd, *J* = 3.5, 8.0 Hz, 1H), 3.36-3.44 (m, 2H), 2.15 (s, 3H), 2.04-2.11 (m, 1H), 1.84-1.91 (m, 1H), 1.67-1.76 (m,1H), 1.53-1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) for major rotamer δ 204.5, 170.2, 168.5, 164.9, 159.4, 137.8, 131.8, 128.6(2C), 128.2(2C), 128.0, 127.8(2C), 119.1, 114.4(2C), 73.6, 68.5, 66.3, 60.1, 57.9, 55.5, 52.0, 44.5, 30.4, 27.3, 26.9; LRMS (ESI) Calcd. for $C_{28}H_{35}ClNO_6$ [M+H] 516, found 516.



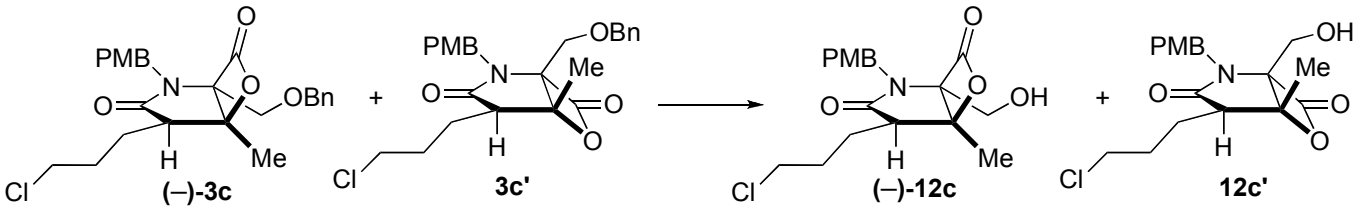
(*R*,*R*)-β-ketoacid, 5c: To a solution of ketoamide (*R*,*R*)-**10c** (350 mg, 0.678 mmol, 25:1 dr) in THF (13.6 mL) at -5 °C (ice and saturated NaCl solution), was added $Pd(PPh_3)_4$ (78 mg, 0.068 mmol) immediately followed by morpholine (0.071 mL, 0.814 mmol). The reaction mixture was stirred at -5 °C for 1 h and diluted with ice-cold Et_2O (500 mL). The organic layer was washed with 0.05 N HCl to pH 3 and brine, dried over $MgSO_4$, filtered and concentrated. The crude ketoacid (*R*,*R*)-**5c** (24:1 dr, 500 MHz ^{1}H NMR) was used in the subsequent step without further purification.



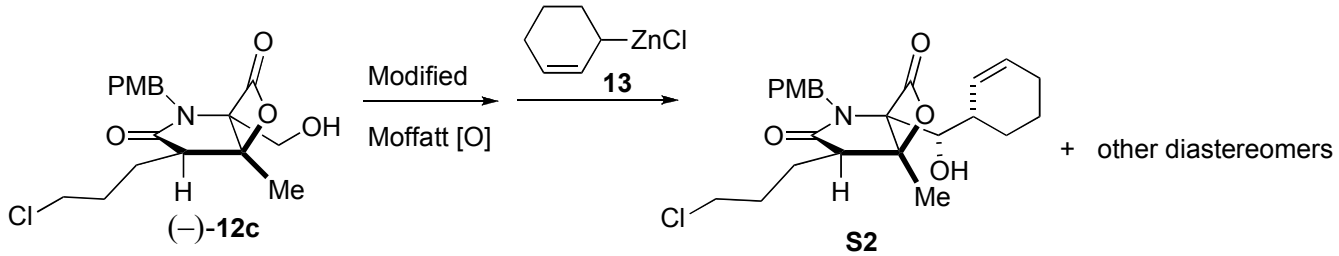
Benzyloxy-β-lactone, (–)-3c/3c': To a solution of 4-pyrrolidinopyridine (386 mg, 2.71 mmol) and TsCl (194 mg, 1.02 mmol) in toluene (16 mL) at -5 °C (ice and saturated NaCl solution), freshly synthesized ketoacid (*R*,*R*)-**5c** in toluene (7 mL) was added via syringe pump over a period of 30 min. The resulting suspension was stirred for 3.5 h. The reaction mixture was diluted with ice-cold Et_2O (400 mL) and washed with 20 % $CuSO_4$ solution (150 mL x 2) to remove excess 4-pyrrolidinopyridine and then washed with water (150 mL x 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes), which gave a mixture of two *β*-lactones **(–)-3c/3c'** (186 mg, 60 % for 2 steps, dr = 3.5:1 based on 500 MHz ^{1}H NMR).

(–)-3c: R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 1827, 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.62 (m, 3H), 7.13-7.16 (m, 4H), 6.79-6.81 (m, 2H), 4.72 (d, *J* = 15.5 Hz, 1H), 4.33 (d, *J* = 15.5 Hz, 1H), 4.14 (s, 2H), 3.77 (s, 3H), 3.74 (d, *J* = 11.0 Hz, 1H), 3.59 (d, *J* = 11.0 Hz, 1H), 3.58-3.64 (m, 2H), 2.54 (t, *J* = 7.0 Hz, 1H), 2.16-2.24 (m, 1H), 1.97-2.11 (m, 2H), 1.87-1.94 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 166.4, 159.3, 136.7, 129.5(2C), 128.9, 128.7(2C), 128.4, 128.2(2C), 114.1(2C),

83.8, 79.3, 73.7, 61.8, 55.5, 47.9, 44.8, 44.5, 30.6, 23.0, 19.9; HRMS (ESI) Calcd. for $C_{25}H_{28}ClNO_5Na$ [M+Na] 480.1554, found 480.1559.

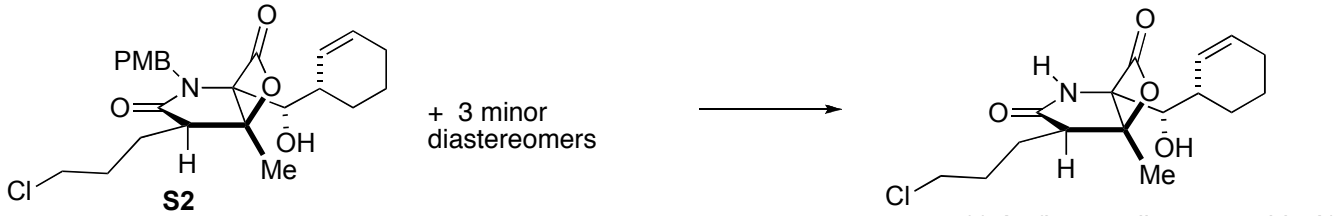


Hydroxy-β-lactone, (–)-**12c:** Prepared according to the representative procedure for debenzylation using the mixture of *β*-lactones (–)-**3c**/**3c'** (186 mg, 0.407 mmol, dr 3.5:1) and 20 wt% palladium on carbon (38 mg) in THF (10 mL) at 23 ºC for 12 h under H_2 atmosphere. Purification by flash chromatography (5:95 EtOAc/CH_2Cl_2) gave the desired alcohol (–)-**12c** (93 mg, 62%) in addition to the minor diastereomer **12c'** as a white solid. Enantiomeric excess of the major diastereomer (–)-**12c** was determined to be 82 % ee by chiral HPLC (Chiralcel OD, 250 x 4.6 mm (L x I.D.), solvent (isocratic) 87:13 hexanes/2-propanol, flow rate 1.0 mL/min, wavelength λ = 230 nm). Retention times: (–)-**12c** 19.72 min; *ent*-(–)-**12c'** 28.76 min. The enantiomeric purity of the desired alcohol could be improved by recrystallization (CH_2Cl_2/Et_2O), which removed the minor enantiomer since it had lower solubility and crystallized more readily leaving the major enantiomer in the mother liquor. One recrystallization led to enrichment to 89% ee for β-lactone (–)-**12c** (77 mg, 52 %): R_f = 0.26 (5% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.13 (d, *J* = 15.5 Hz, 1H), 4.07 (d, *J* = 15.5 Hz, 1H), 3.92 (dd, *J* = 9.0, 14.0 Hz, 1H), 3.86 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.81 (s, 3H), 3.61-3.64 (m, 2H), 2.56 (t, *J* = 7.0 Hz, 1H), 2.17-2.26 (m, 1H), 1.98-2.12 (m, 2H), 1.89-1.96 (m, 1H), 1.77 (s, 3H), 0.86 (dd, *J* = 4.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 167.0, 159.7, 129.2(2C), 129.1, 114.9(2C), 84.0, 80.3, 55.5, 55.3, 47.9, 44.7, 44.3, 30.5, 23.0, 19.8; HRMS (ESI) Calcd. for $C_{18}H_{23}ClNO_5$ [M+H] 368.1266, found 368.1265.



Hydroxy-β-lactone, S2: To alcohol (–)-**12c** (77 mg, 0.210 mmol), and EDCI (403 mg, 2.10 mmol), was added DMSO/toluene (1.5 mL/1.5 mL), followed by dichloroacetic acid (9 μL, 0.105 mmol). The reaction mixture was stirred at 23 ºC for 6h and diluted with Et_2O (150 mL). The organic layer was acidified to pH 3 with 0.1 N HCl, and washed with brine. The organics were then dried over $MgSO_4$, filtered, and concentrated. The residue was used for the next step without further purification due to some instability on SiO_2observed for the resulting aldehyde.

A solution of tri-*n*-butyl-2-cyclohexenyltin (234 mg, 0.630 mmol) in THF (1.5 mL) was treated with *n*-BuLi (2.05M in hexanes, 297 μL, 0.609 mmol) at –78 °C. After 30 min, $ZnCl_2$ (0.5 M in THF, 1.34 mL, 0.672 mmol) was added and after an additional 30 min, a solution of the crude aldehyde in THF (1.0 mL) was slowly added to the freshly prepared zinc reagent **13**. The resulting mixture was stirred at –78 °C for 5 h, quenched with water and diluted with EtOAc (150 mL). The organic layer was washed with saturated NH_4Cl until pH 7 and brine (100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (95:5 ⟶ 85:5 EtOAc/hexanes) to give a mixture of four diastereomers (58 mg, 61%, dr = 8:2:1:1 according to 500 MHz ^{1}H NMR) as a colorless oil with the desired diastereomer predominating. The mixture of diastereomers was carried directly to the next step without further purification.



(–)-**Homosalinosporamide A,** (–)-**14:** To a solution of alcohol **S2** (58 mg, 0.127 mmol in MeOH (0.9 mL), as a mixture with other diastereomers from the previous step, was added an aqueous solution of CAN (694 mg, 1.27 mmol) in H_2O (0.3 mL) at –10 °C dropwise. After stirring at -10 °C for 6 h, the reaction mixture was diluted with EtOAc (100 mL), washed with saturated solution of $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5:95 to 15:85 EtOAc/CH_2Cl_2) to give (–)-homosalinosporamide A (–)-**14** (17 mg, 41%) as a white solid (dr >19:1, 500 MHz ^{1}H NMR): R_f = 0.36 (40% EtOAc/hexanes); $[\alpha]^{23}_D$ = – 63.2 (c = 0.15, MeOH); IR (neat) 3360, 1821, 1697 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-d_5) δ 10.58 (s, 1H), 6.46 (d, *J* = 10.0 Hz, 1H), 5.89-5.93 (m, 1H), 4.28 (d, *J* = 9.0 Hz, 1H), 3.63 (dt, *J* = 2.0, 6.5 Hz, 2H), 2.93 (t, *J* = 7.0, 1H), 2.86-2.90 (m, 1H), 2.28-2.37 (m, 2H), 2.12-2.25 (m, 1H), 2.07 (s, 3H), 1.93-1.97 (m, 2H), 1.68-1.75 (m, 2H), 1.35-1.41 (m, 3H); ^{13}C NMR (125 MHz, C_3D_6O) δ 176.7, 169.1, 129.4, 128.8, 86.7, 79.8, 71.2, 48.2, 45.8, 39.4, 31.4, 26.6, 25.8, 23.3, 22.1, 20.4; HRMS (ESI) Calcd. for $C_{16}H_{23}ClNO_4$ [M+H] 328.1316, found 328.1315.

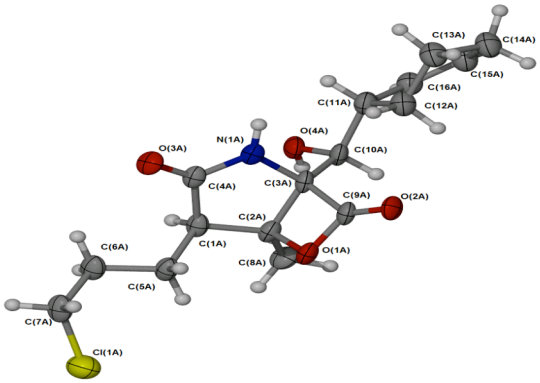
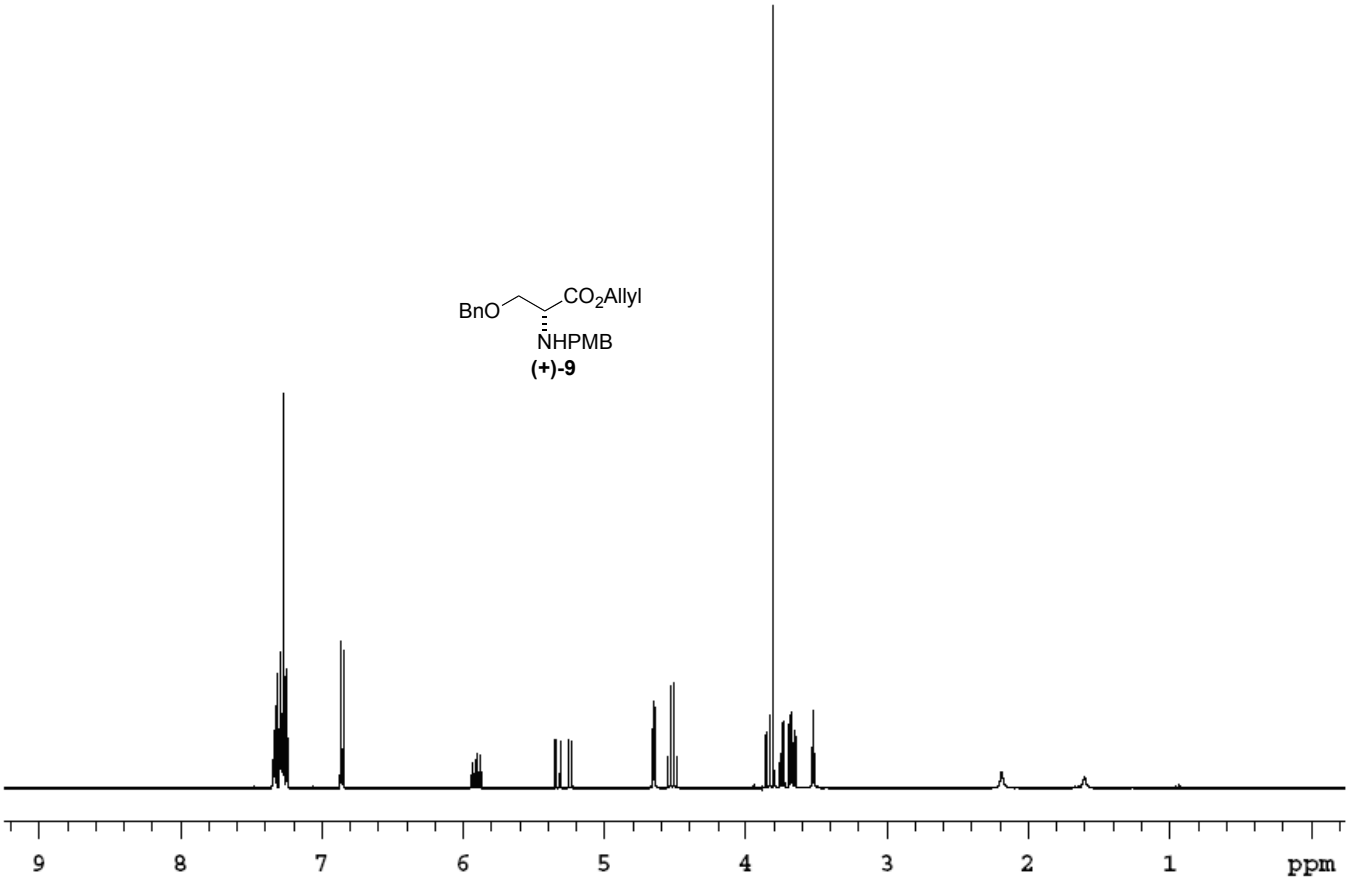
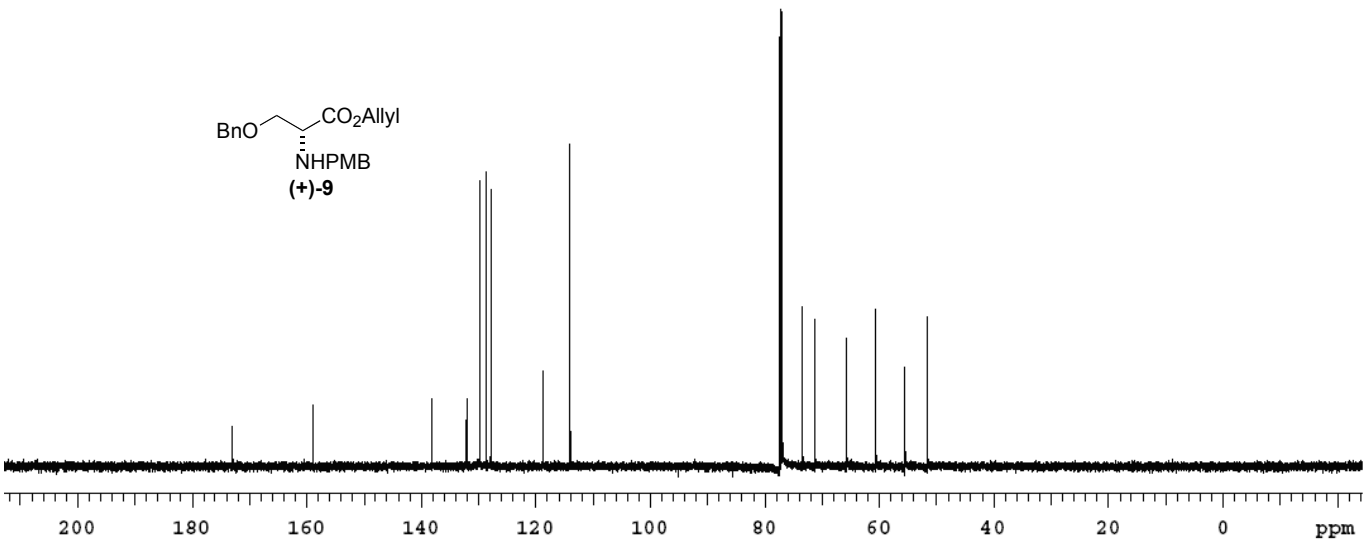


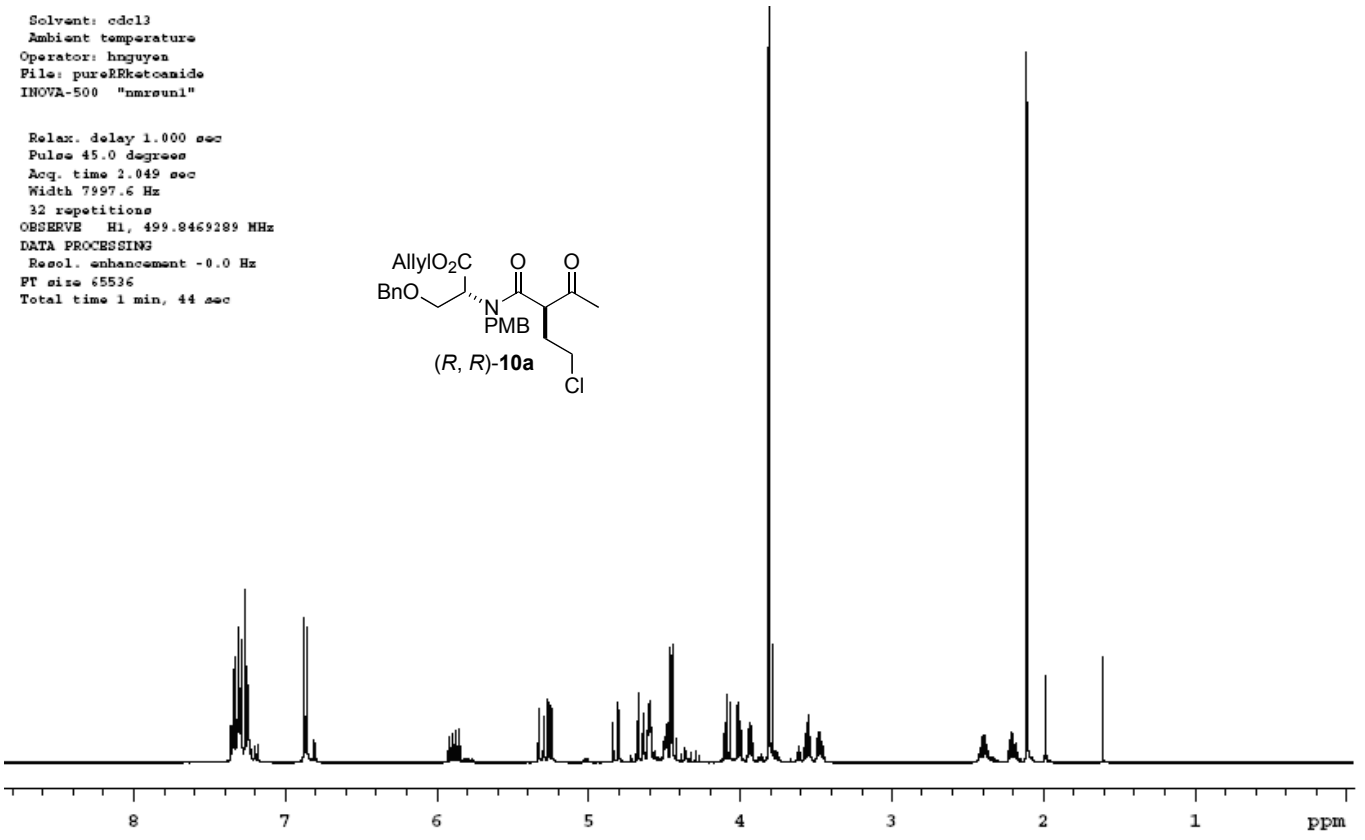
Figure 1. ORTEP plot of the X-ray structure of (–)-homosalinosporamide A, (–)- **14.**



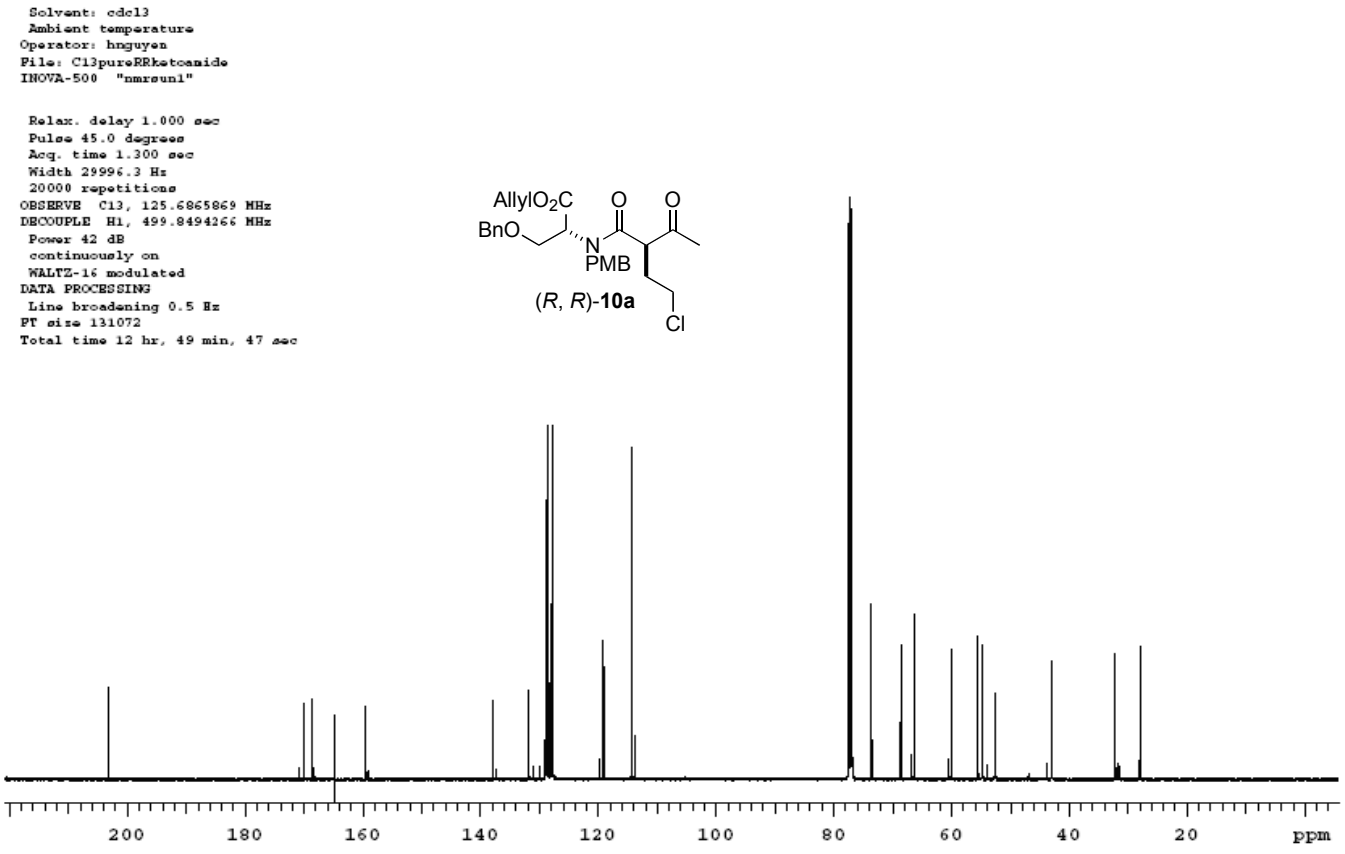
^{1}H NMR of (*R*)-O-benzyl serine allyl ester, (+)-**9** (500 MHz, $CDCl_3$)



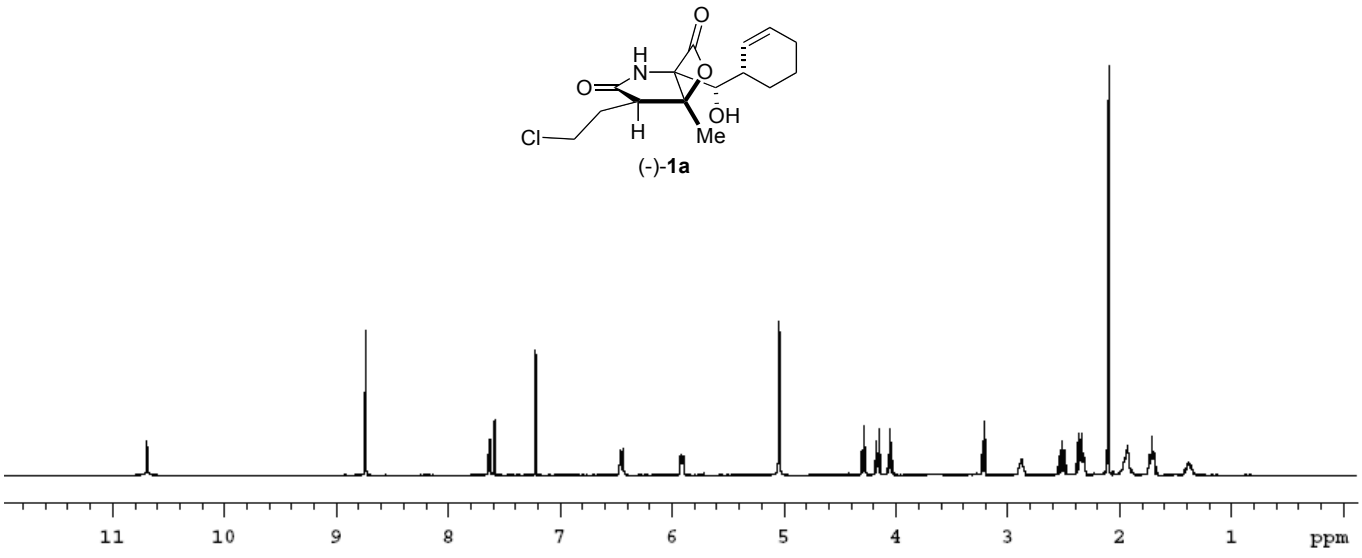
^{13}C NMR of (*R*)-O-benzyl serine allyl ester, (+)-**9** (125 MHz, $CDCl_3$)



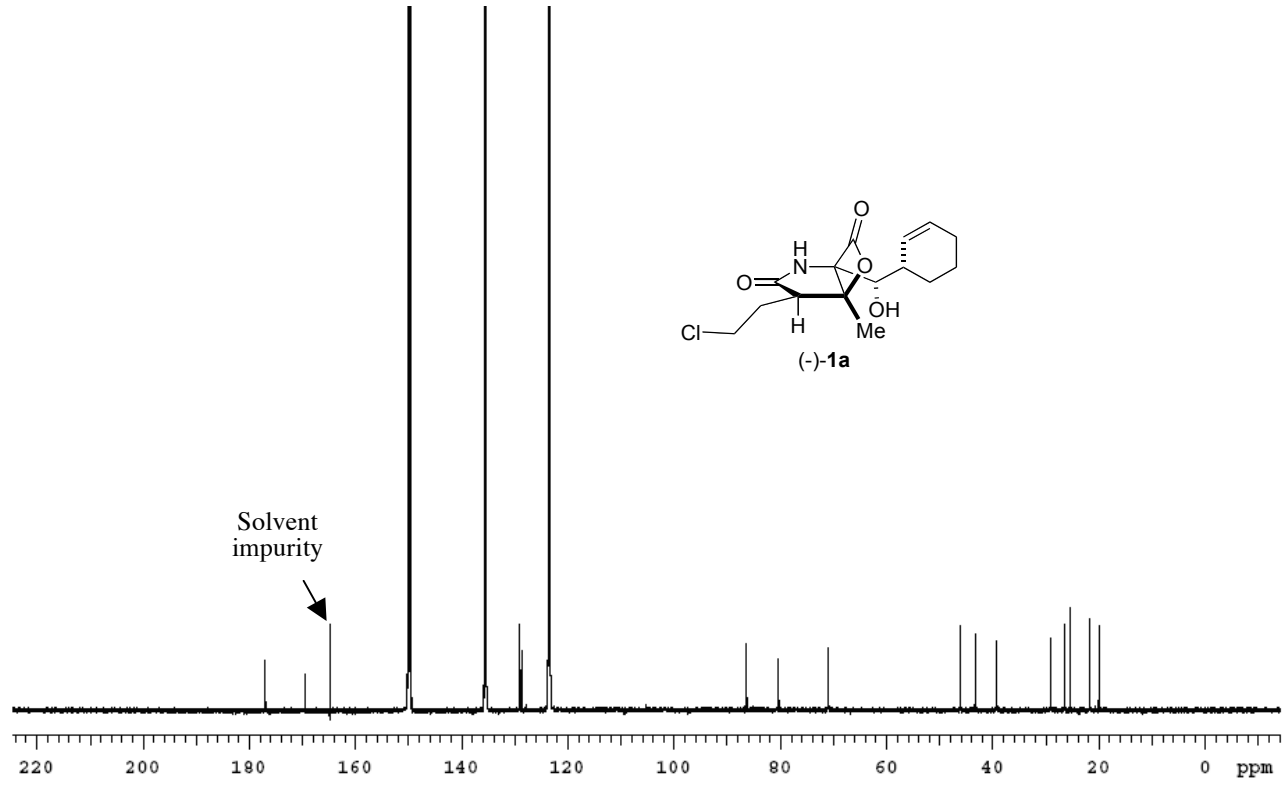
^{1}H NMR of (*R*,*R*)-β-ketoamide, (–)-**10a** (500 MHz, $CDCl_3$)



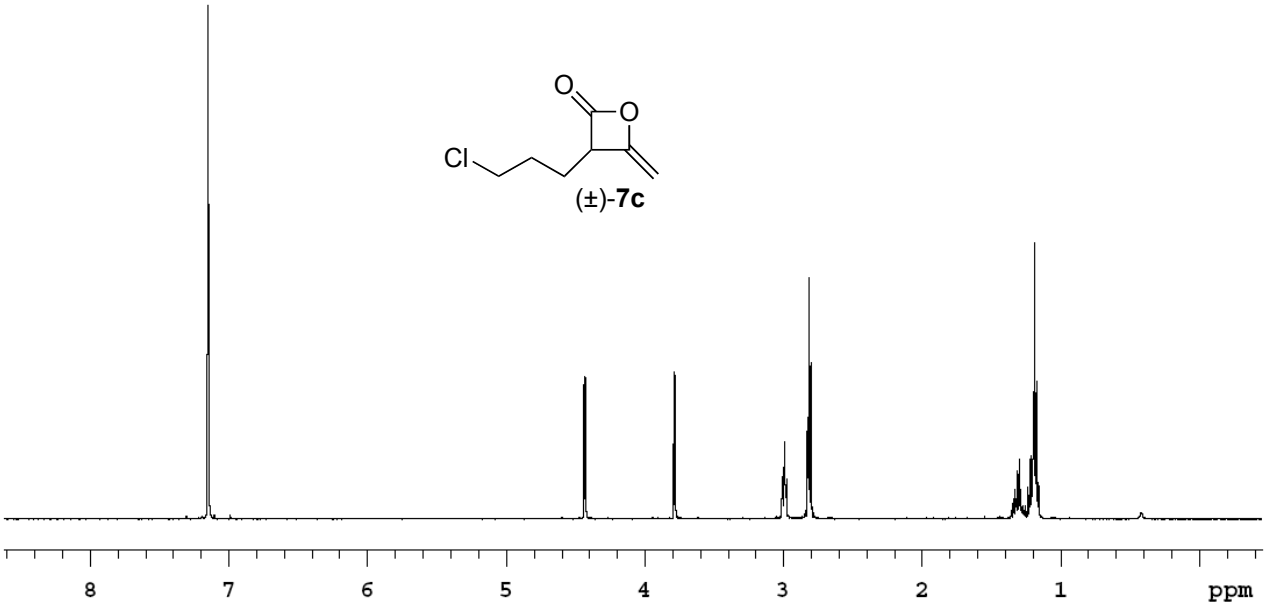
^{13}C NMR of (*R*,*R*)-β-ketoamide, **(–)-10a** (125 MHz, $CDCl_3$)



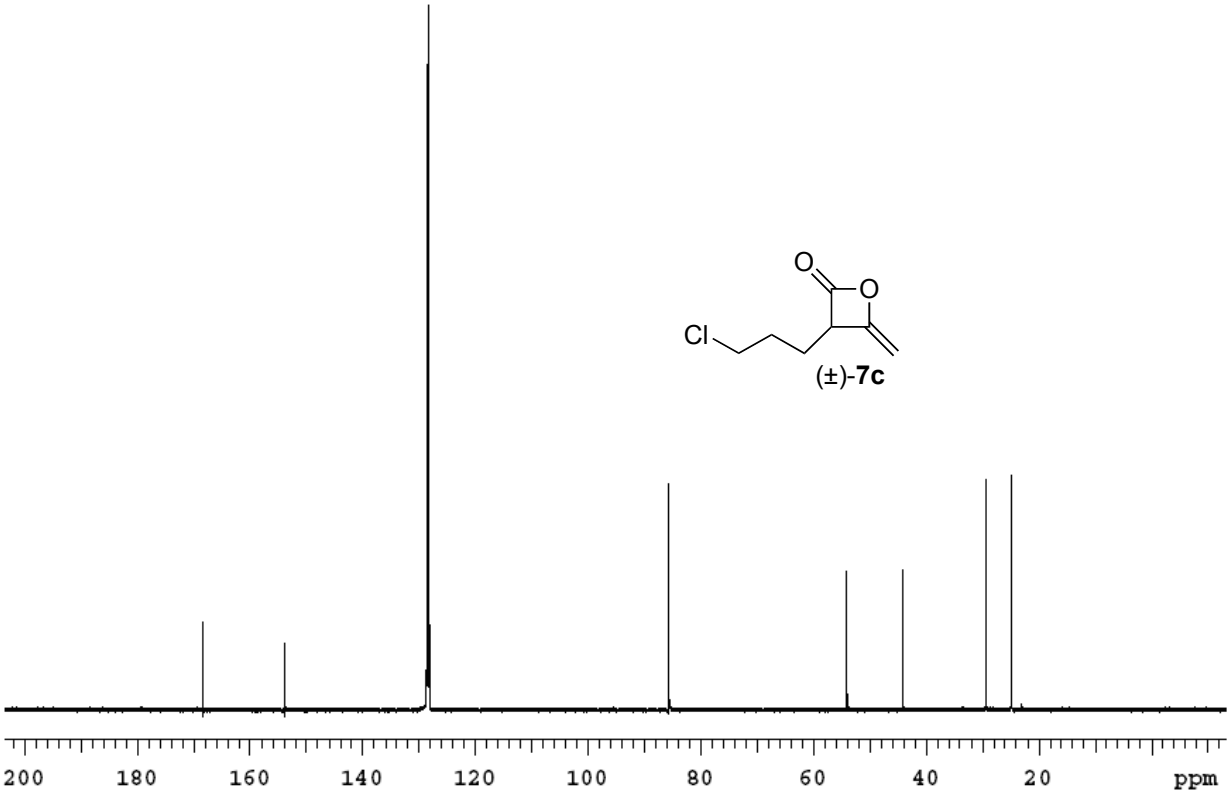
^{1}H NMR of (–)-salinosporamide A, (–)-**1a** (500 MHz, C_5D_5N)



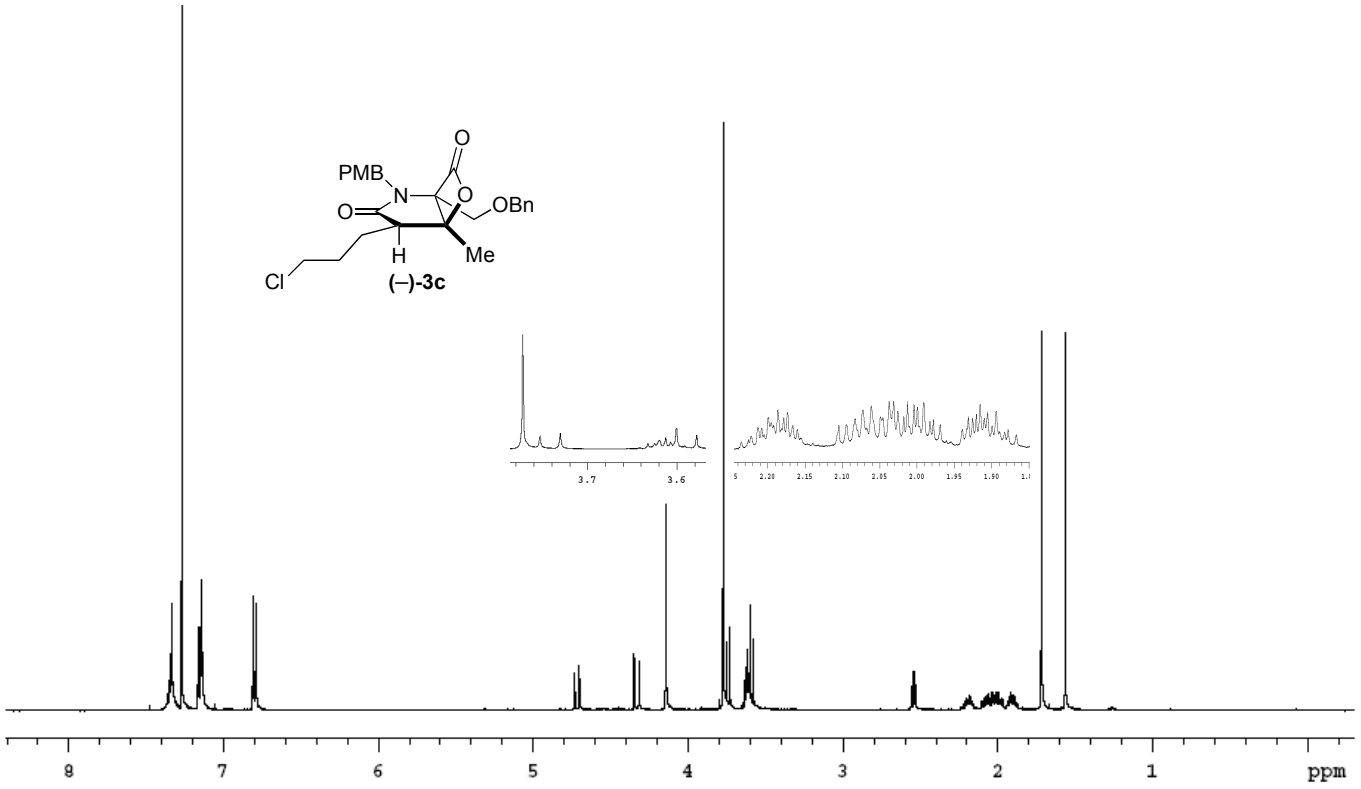
^{13}C NMR of (–)-salinosporamide A, (–)-**1a** (125 MHz, C_5D_5N)



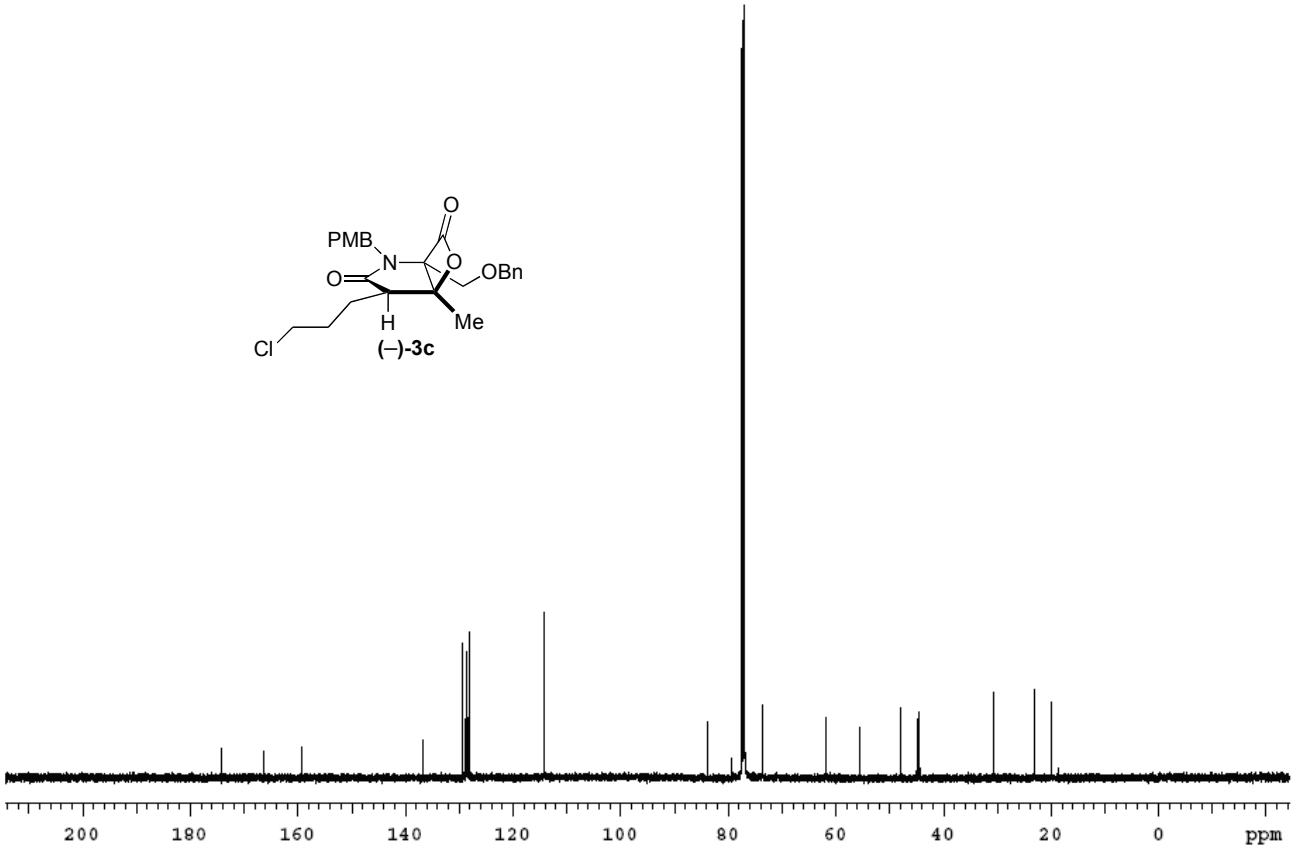
^{1}H NMR of ketene dimer, (±)-**7c** (500 MHz, benzene-d_6)



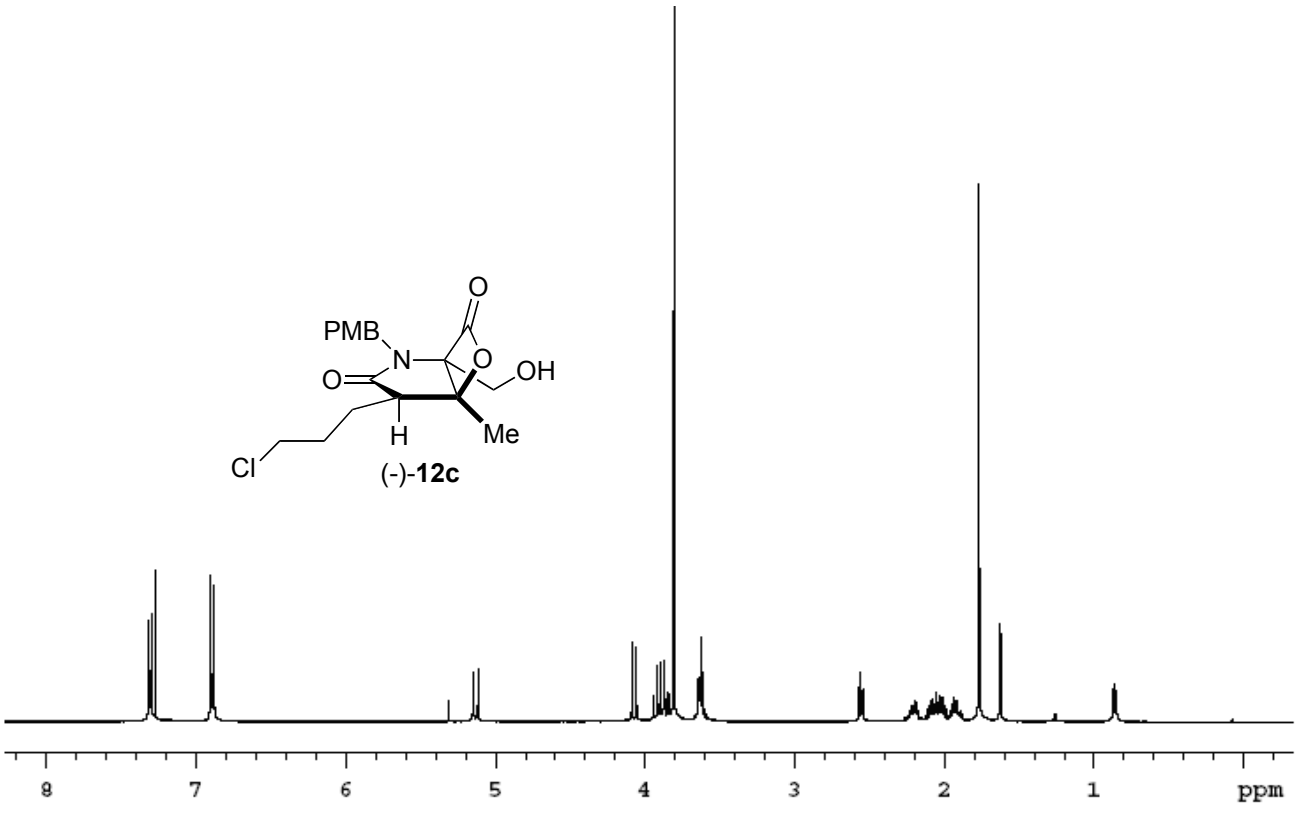
^{13}C NMR of ketene dimer, (±)-**7c** (125 MHz, benzene-d_6)



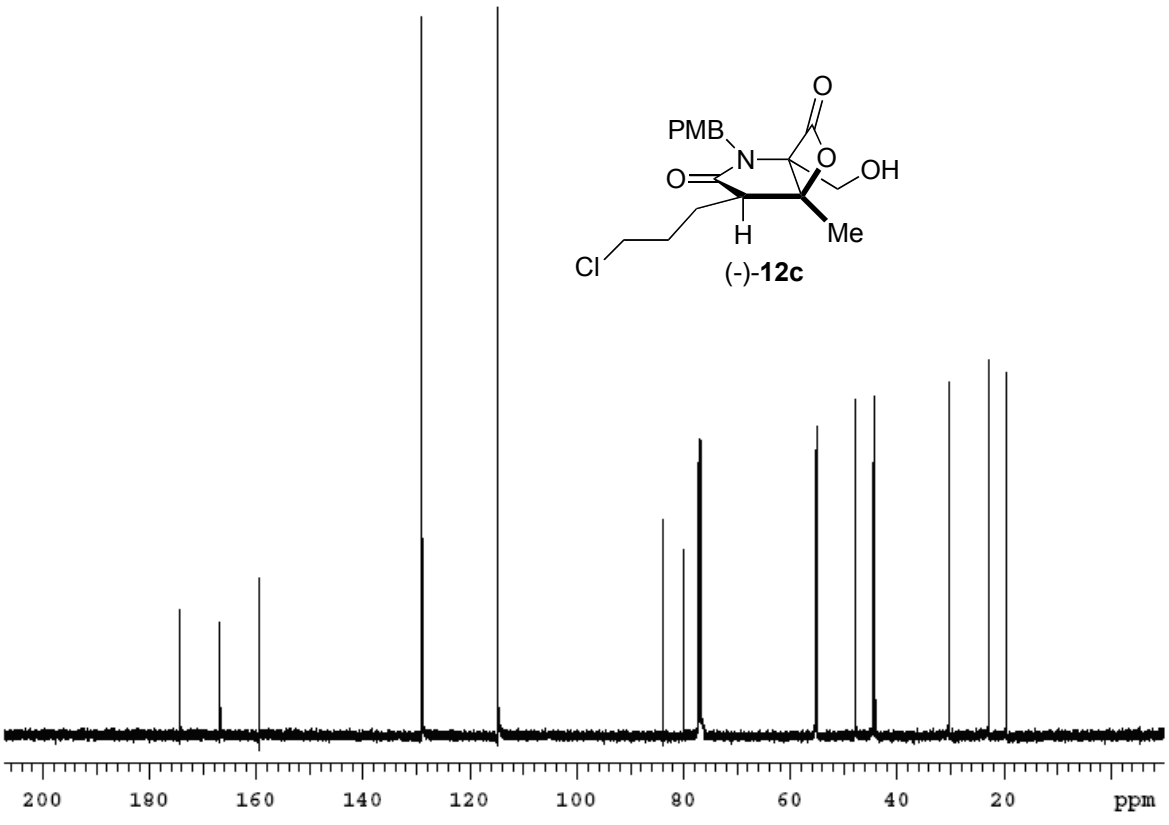
^{1}H NMR of OBn-β-lactone, (–)-**3c** (500 MHz, $CDCl_3$)



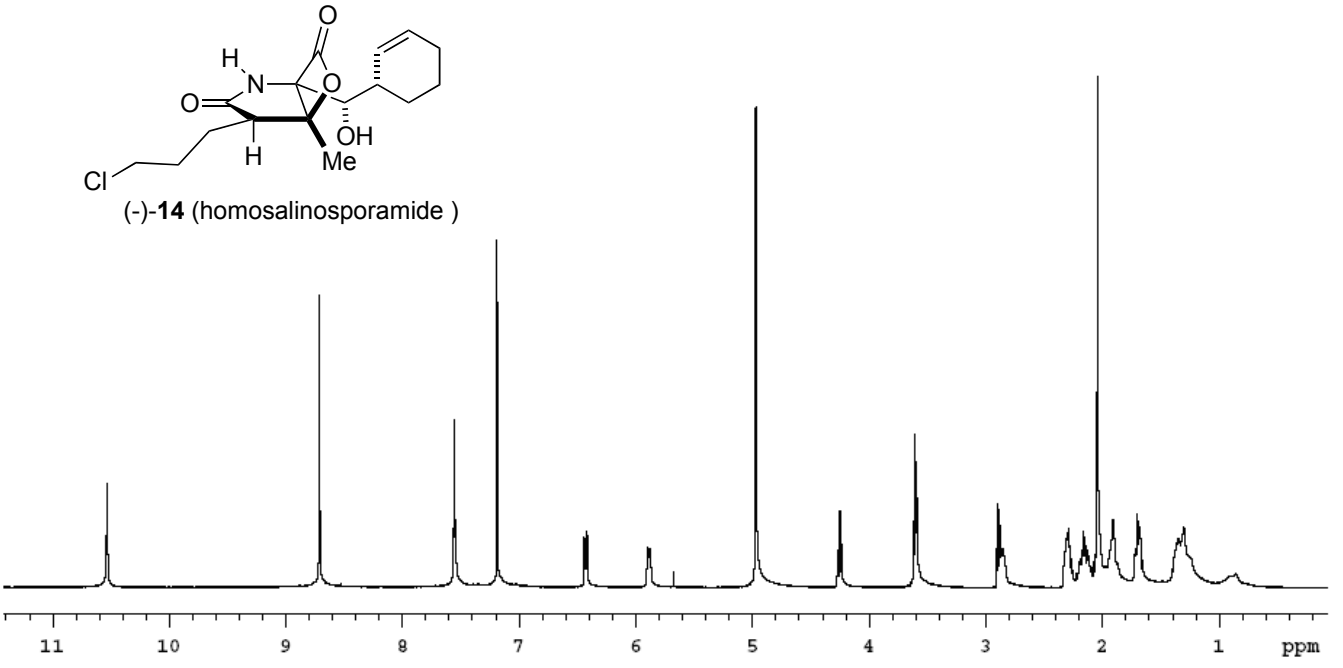
^{13}C NMR of OBn-β-lactone, (–)-**3c** (125 MHz, $CDCl_3$)



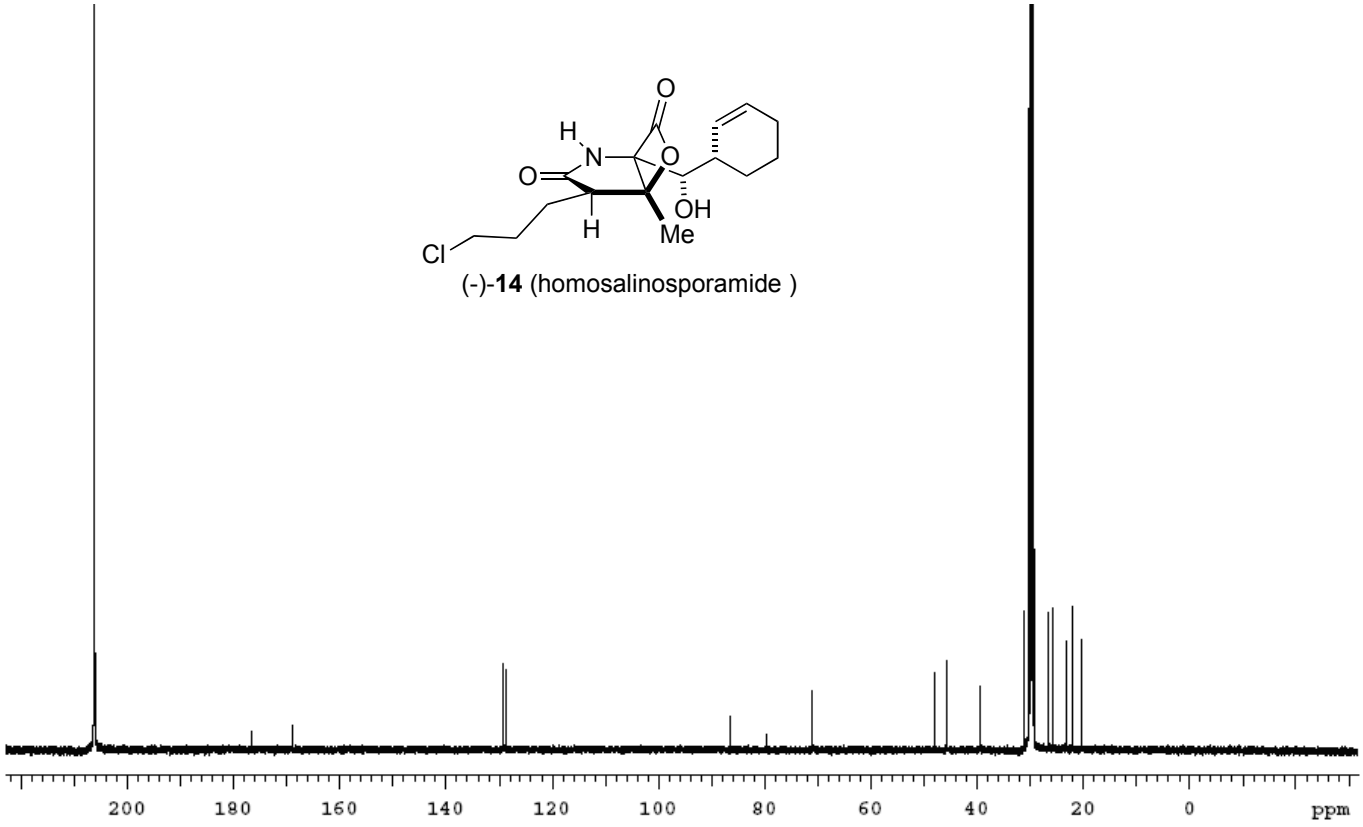
^{1}H NMR of OH-β-lactone, (–)-**12c** (500 MHz, $CDCl_3$)



^{13}C NMR of OH-β-lactone, (–)-**12c** (125 MHz, $CDCl_3$)

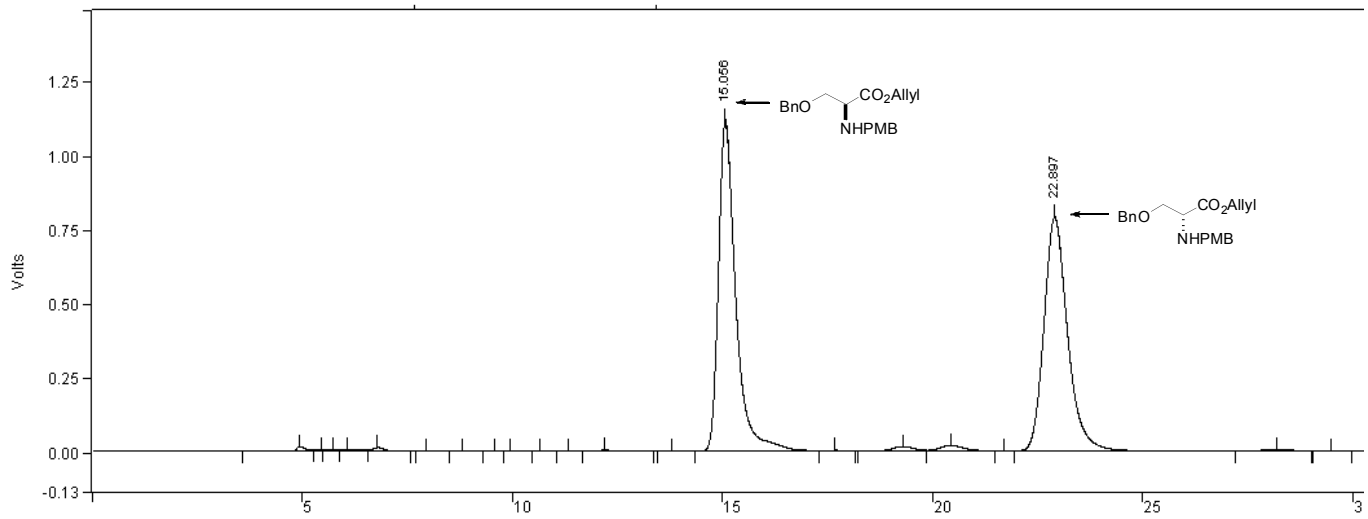


^{1}H NMR of (–)-homosalinosporamide A, (–)-**14** (500 MHz, C_5D_5N)



^{13}C NMR of (–)-homosalinosporamide A, (-)-**14** (125 MHz, C_3D_6O)

Determination of Optical Purity of (D)-Serine Derivative (+)-9 by HPLC (CHIRALPAK IA)



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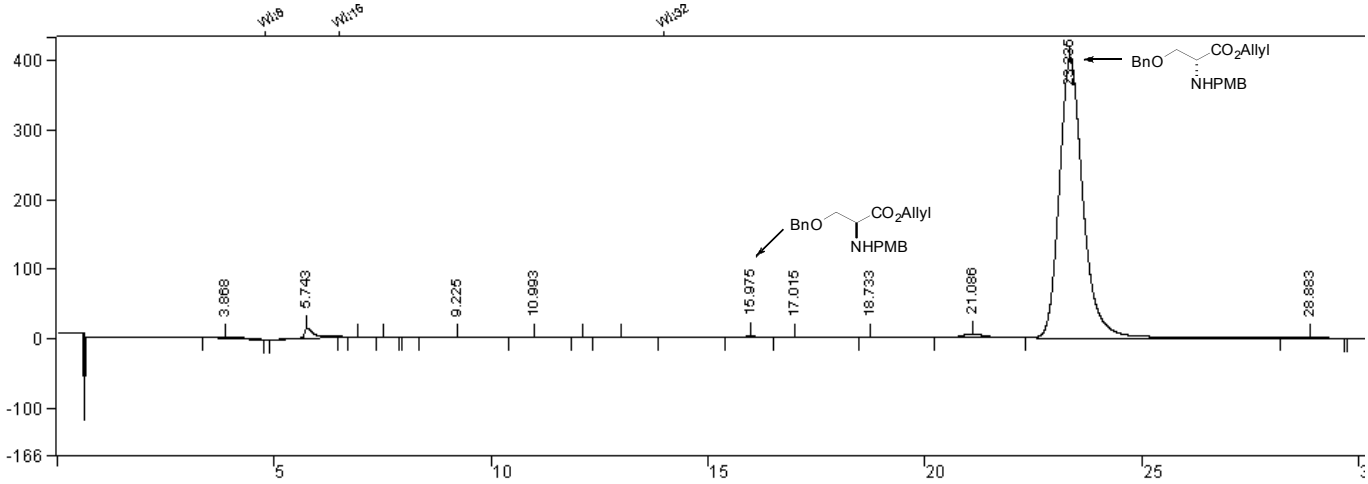
2		49.1037	22.897	0.000	31195020	VB	34.8	
	Totals:	100.0000		0.000	63528846			



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
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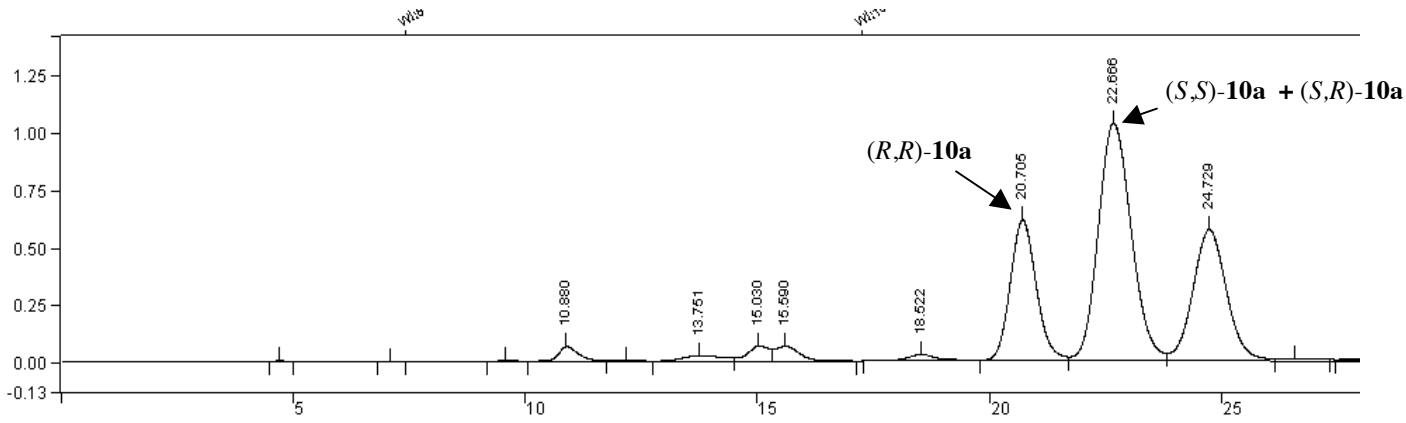
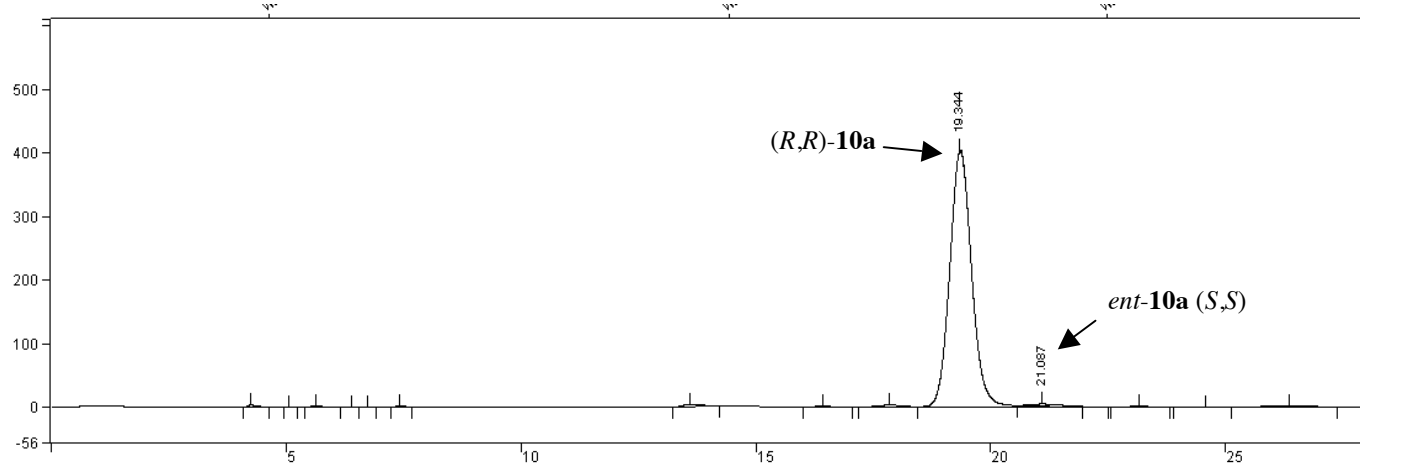
2		1.1642	5.743	0.000	193622	BB	14.5	
3		0.3121	9.225	0.000	51897	BV	55.7	
4		0.2912	10.993	0.000	48425	VP	15.1	
5		0.3036	15.975	0.000	50491	BV	26.4	
6		0.4087	17.015	0.000	67975	VV	52.6	
7		0.3253	18.733	0.000	54103	VV	49.4	
8		1.6436	21.086	0.000	273349	VV	29.8	
9		93.6909	23.335	0.000	15581641	VP	33.6	
10		0.3449	28.883	0.000	57363	TS	0.0	
11		0.6537	31.478	0.000	108708	PV	0.0	
12		0.4060	32.946	0.000	67527	VB	0.0	
	Totals:	100.0000		0.000	16630897			

Determination of Optical Purity of β-Ketoamide (*R*,*R*)-10a by HPLC (CHIRALPAK IA)

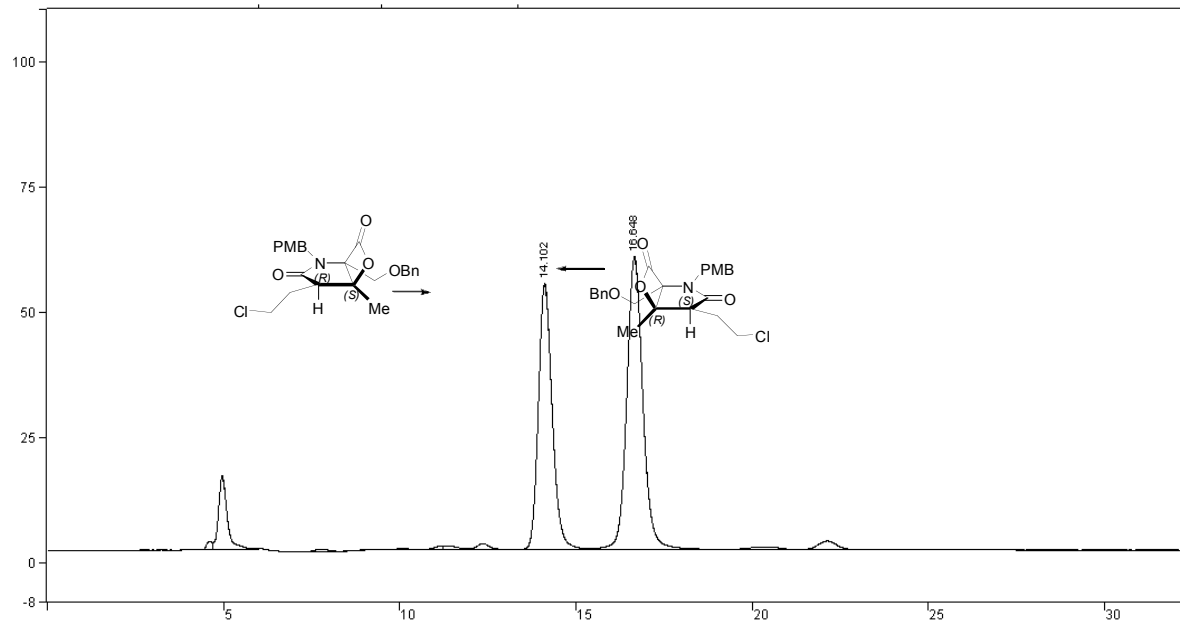


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.5248	10.880	0.000	1948910	VV	25.9	
2		1.1338	13.751	0.000	1449136	VV	0.0	
3		1.6503	15.030	0.000	2109397	VV	31.0	
4		1.8826	15.590	0.000	2406279	VB	50.5	
5		1.1183	18.522	0.000	1429367	BV	38.2	
6		18.9703	20.705	0.000	24246934	VV	35.9	
7		40.4567	22.666	0.000	51709932	VV	46.1	
8		24.7207	24.729	0.000	31596874	VV	46.0	
9		3.3943	30.161	0.000	4338403	TF	0.0	
10		1.7261	31.231	0.000	2206181	TF	0.0	
11		3.4222	33.213	0.000	4374092	VB	55.4	
	Totals:	100.0001		0.000	127815505			

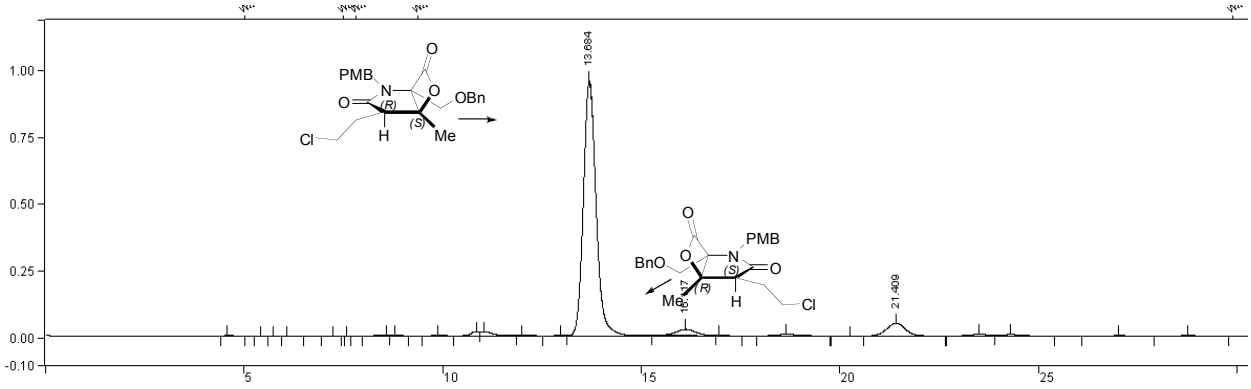


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		99.0706	19.344	0.000	13123981	VB	29.3	
2		0.9294	21.087	0.000	123121	TS	0.0	
	Totals:	100.0000		0.000	13247102			

Determination of Optical Purity of Bicyclic-β-Lactone (-)-3a by HPLC (CHIRALPAK IA)

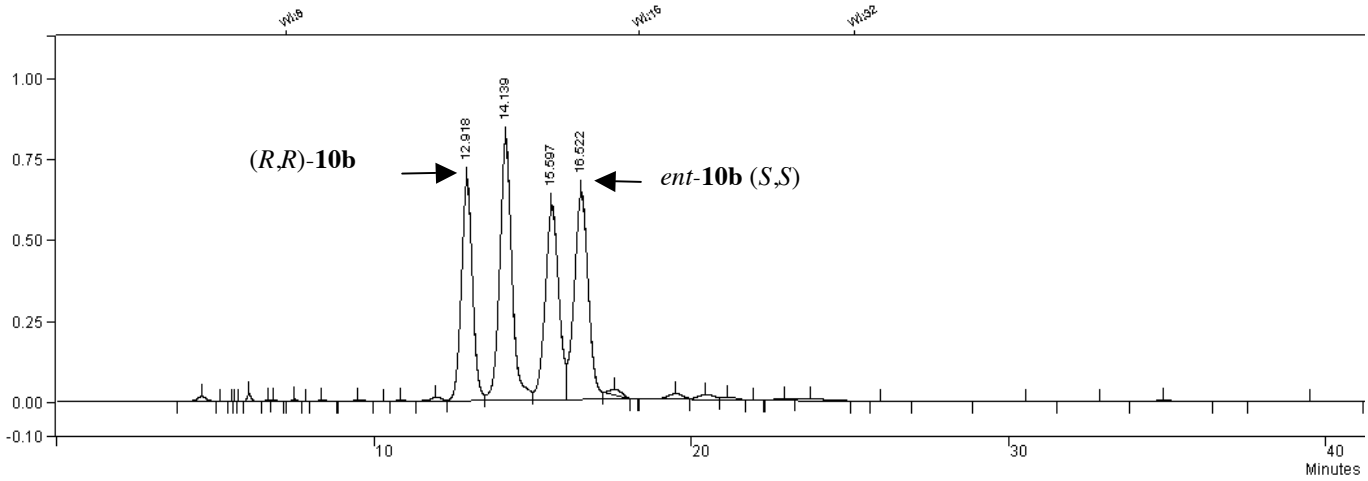


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		43.7507	14.102	0.000	1445281	BV	24.6	
2		56.2493	16.648	0.000	1858169	VB	28.2	
Totals:		100.0000		0.000	3303450			

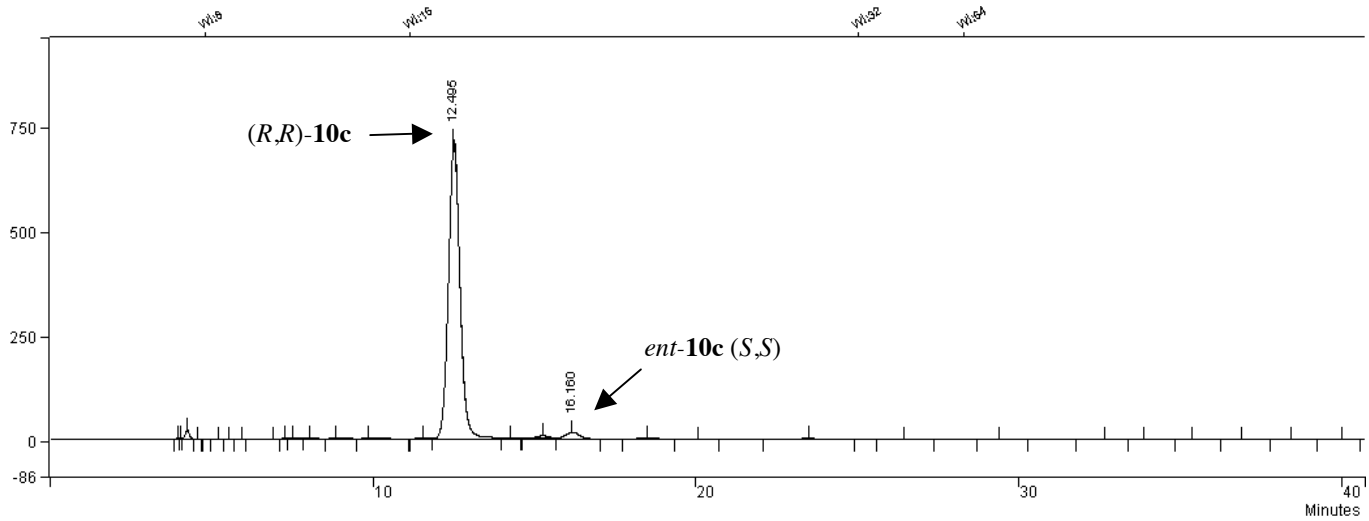


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		89.7037	13.684	0.000	21537478	VB	20.0	
2		3.6752	16.117	0.000	882407	TF	0.0	
3		6.6211	21.409	0.000	1589704	TF	0.0	
Totals:		100.0000		0.000	24009589			

Determination of Optical Purity of β-Ketoamide (*R*,*R*)-10c by HPLC (CHIRALPAK IA)

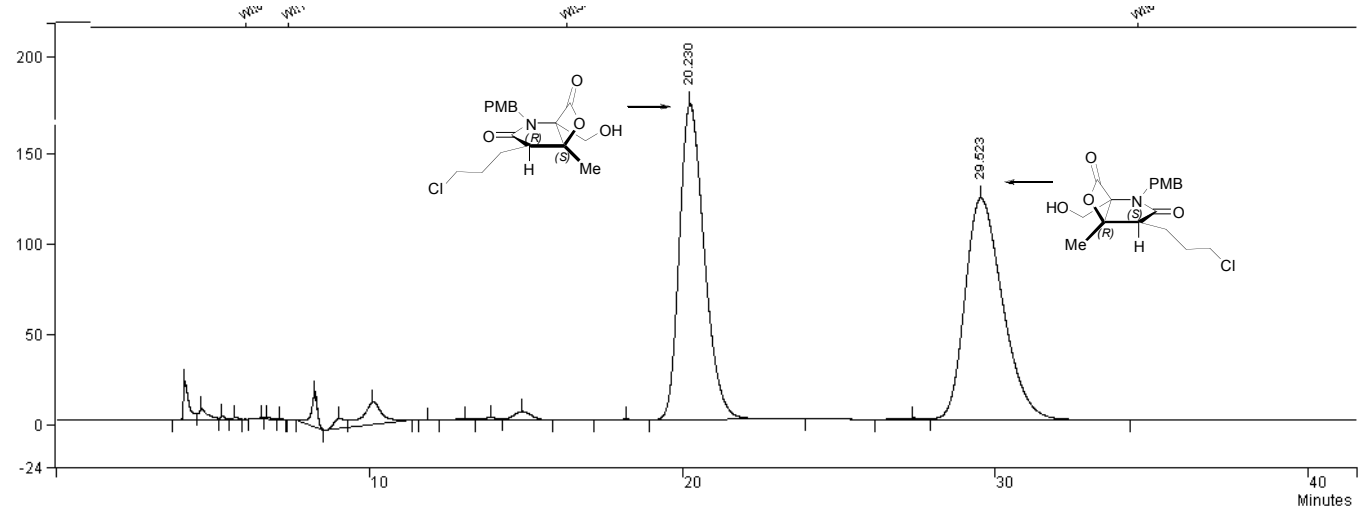


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		21.6266	12.918	0.000	16565099	VV	22.2	
2		28.2930	14.139	0.000	21671300	VV	23.2	
3		23.4216	15.597	0.000	17940036	VV	27.5	
4		26.6588	16.522	0.000	20419554	VB	28.2	
	Totals:	100.0000		0.000	76595989			

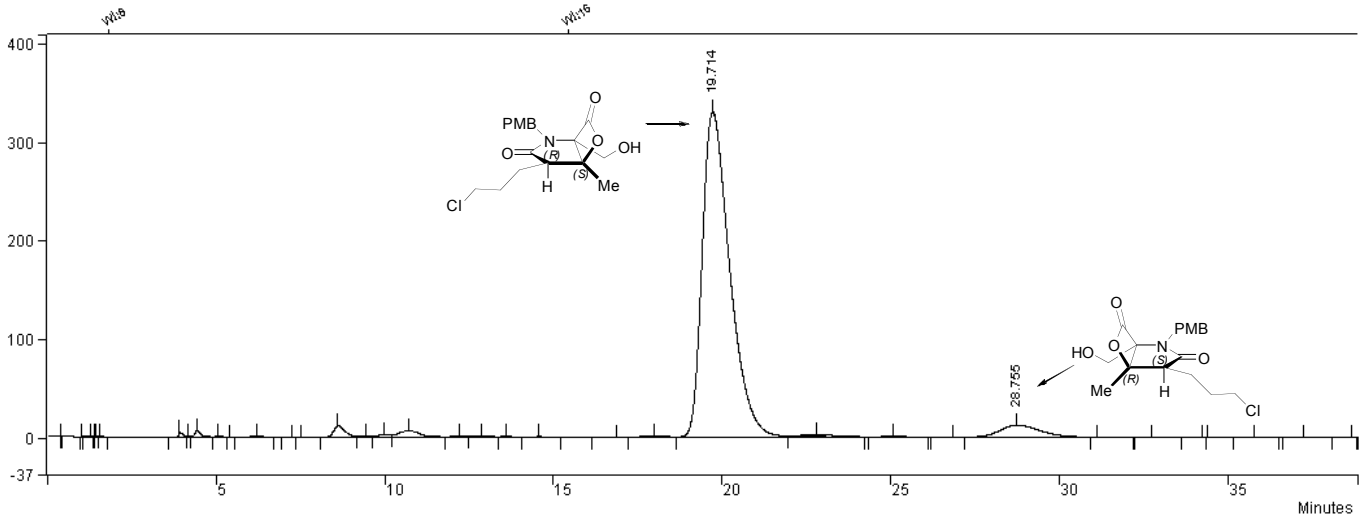


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		97.5160	12.495	0.000	17921656	VP	22.2	
2		2.4840	16.160	0.000	456514	TF	0.0	
	Totals:	100.0000		0.000	18378170			

Determination of Optical Purity of Bicyclic-β-Lactone (-)-12c by HPLC (CHIRALCEL OD)

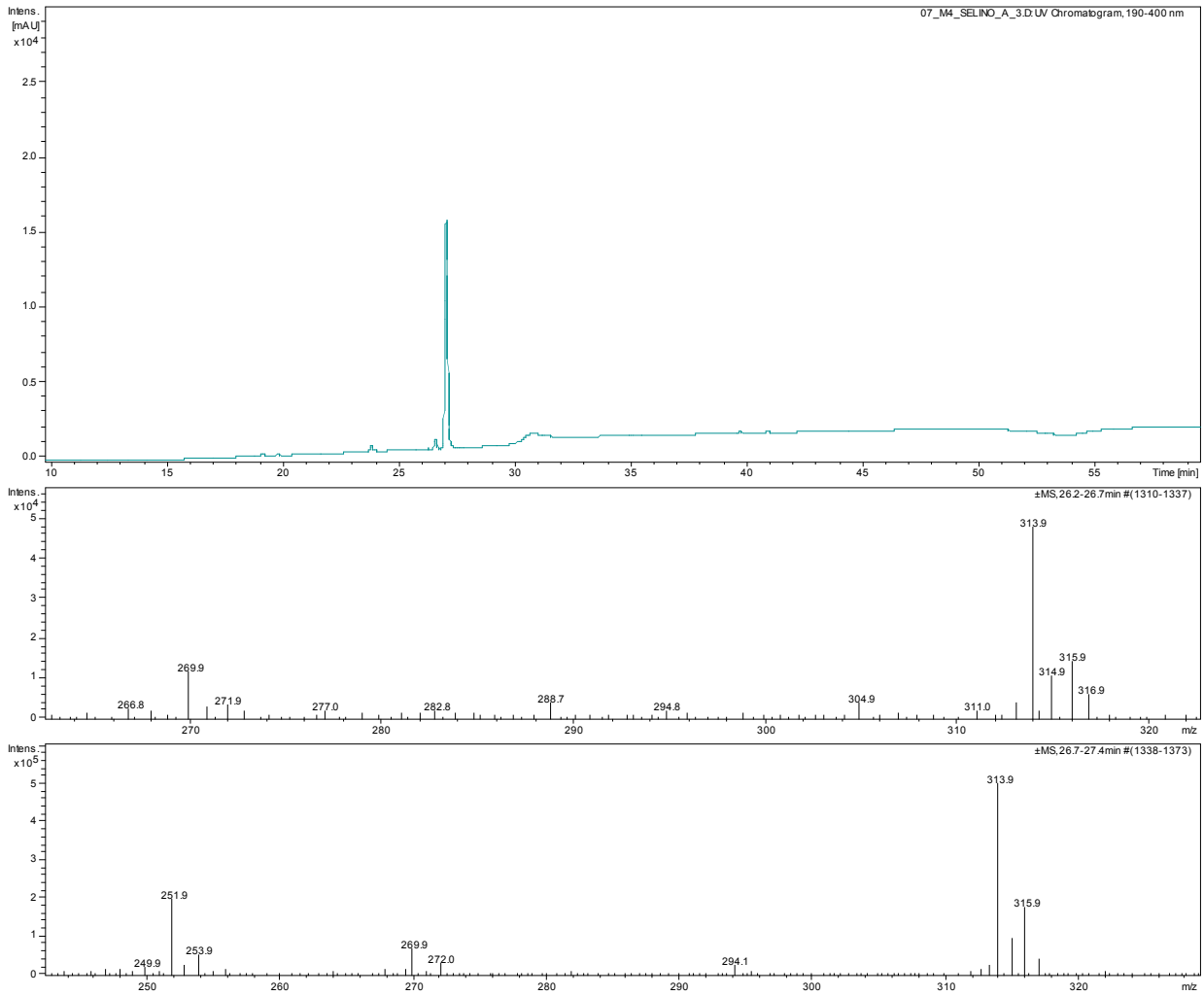


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		48.5806	20.230	0.000	9675606	PB	50.9	
2		51.4194	29.523	0.000	10240997	VB	76.8	
Totals:		100.0000		0.000	19916603			



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		94.9080	19.714	0.000	18868924	VP	51.6	
2		5.0920	28.755	0.000	1012350	TF	0.0	
Totals:		100.0000		0.000	19881274			

LC-MS Analysis of (–)-Salinosporamide A (**1a**)



LC-MS Analysis of (–)-Homosalinosporamide A (**14**)