A Stereoselective Synthesis of the Bromopyrrole Natural Product, (–)-Agelastatin A

Supplementary Material
(17 *pages*)

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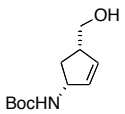
General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (ca. 15 Torr) by rotary evaporation. Dichloroethane (DCE), triethylamine, pyridine, and methanol were distilled from CaH_2 immediately prior to use. *tert*-Amyl alcohol was distilled from CaH_2 and stored in a Schlenk flask containing activated 4Å molecular sieves. Dichloromethane, tetrahydrofuran (THF), acetonitrile, and *N*,*N*–Dimethylformamide (DMF) were dried by passage under 12 psi N_2 through columns containing activated alumina. *N*,*N*–Dimethyl-acetamide (DMA) was dried over activated 4Å molecular sieves. Chlorosulfonyl isocyanate was obtained from Acros Chemicals, transferred via cannula to a Schlenk flask, and stored at –20 °C. Light magnesium oxide was flame-dried under reduced pressure (~1 Torr) prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle Ultra Pure Silica Gel Silia-P (40-63 μm). Compounds purified by chromatography on silica gel were typically applied to the adsorbent bed using the indicated solvent conditions with a minimum amount of added chloroform as needed for solubility. Thin layer chromatography was performed on EM Science silica gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with ethanolic anisaldehyde, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM) solution.

NMR spectra were acquired on a Varian Mercury-400 operating at 400 and 100 MHz or a Varian Inova-500 operating at 500 and 125 MHz for ^1H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C are reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded as thin films using NaCl salt plates on a Perkin-Elmer Paragon 500 FTIR spectrometer or a Thermo-Nicolet IR300 spectrometer and are reported in frequency of absorption. High-resolution mass spectra were obtained the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University.

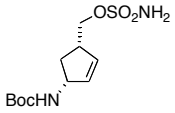
Experimental data for all reported compounds

To a solution of (1*R*,4*S*)-(-)-2-azabicyclo[2.2.1]hept-5-en-3-one (875 mg, 8.0 mmol) in 32 mL of CH_2Cl_2 was added sequentially Boc_2O (2.09 g, 9.6 mmol, 1.2 equiv) and DMAP (49 mg, 0.40 mmol, 0.05 equiv). The initially colorless solution was stirred for 16 h during which time the solution turned pale orange. All volatiles were then removed under reduced pressure to give an orange residue. Purification of this material by chromatography on silica (gradient elution 15→20% EtOAc/hexanes) afforded the desired imide **4a** as a white solid (1.64 g, 98%). TLC R_f = 0.30 (4:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.84 (dd, 1H, *J* = 2.0 Hz), 6.60 (ddd, 1H, *J* = 5.3, 3.0, 1.3 Hz), 4.91-4.89 (m, 1H, *J* = 1.9 Hz), 3.35-3.32 (m, 1H), 2.29 (dt, 1H, *J* = 8.5, 1.4 Hz), 2.10 (dt, 1H, *J* = 8.5, 1.3 Hz), 1.45 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.2, 150.2, 139.9, 138.0, 82.4, 62.3, 54.8, 54.2, 27.9 ppm; IR (thin film) ν 2974, 1751, 1707, 1456, 1332, 1307, 1152, 994, 855, 764 cm^{-1}.

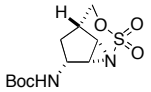


Solid $NaBH_4$ (412 mg, 10.9 mmol, 1.5 equiv) was added to a solution of imide **4a** (1.52 g, 7.26 mmol) in 60 mL of reagent grade MeOH. After 5 min, a second equivalent charge of $NaBH_4$ (412 mg, 10.9 mmol, 1.5 equiv) was added. The mixture stirred for 50 min and was then concentrated under reduced pressure to a volume of ~10 mL. The white suspension was diluted with 25 mL of EtOAc to which 25 mL of a 1:1 (v/v) mixture of saturated aqueous NH_4Cl and 10% aqueous HCl was slowly and cautiously added. The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was extracted with 4 x 15 mL of EtOAc. The combined organic fractions were rinsed successively with 15 mL of saturated aqueous $NaHCO_3$ and 15 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by chromatography on silica gel (35% EtOAc/hexanes) furnished the desired alcohol **5** as a white solid (1.47 g, 95%). TLC R_f = 0.36 (35% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz, 55 °C) δ 5.79 (dt, 1H, *J* = 5.6, 1.6 Hz), 5.76 (dt, 1H, *J* = 5.6, 1.6 Hz),

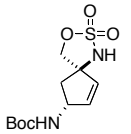
4.77 (br s, 1H), 4.71-4.62 (br m, 1H), 3.62 (dt, 1H, *J* = 10.6, 4.1 Hz), 3.55 (dt, 1H, *J* = 10.4, 5.5 Hz), 2.86-2.78 (m, 1H), 2.48 (dt, 1H, *J* = 13.7, 4.6 Hz), 1.77-1.71 (br m, 1H), 1.43 (s, 9H), 1.37 (dt, 1H, *J* = 13.6, 4.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 134.0, 133.9, 79.1, 64.9, 55.9, 46.8, 34.5, 28.4 ppm; IR (thin film) ν 3336, 3055, 2976, 2932, 1685, 1519, 1366, 1248, 1171, 1042, 746 cm^{-1}.



Formic acid (2.27 mL, 57.3 mmol, 2.5 equiv) was added dropwise to neat chlorosulfonyl isocyanate (5.25 mL, 57.3 mmol, 2.5 equiv) at 0 °C with rapid stirring. Vigorous gas evolution ensued during the addition process. Once the solution had solidified (~5 min), 15 mL of acetonitrile was added. The reaction was stirred for 1 h at 0 °C and then for 8 h at 25 °C. The reaction mixture was cooled to 0 °C and to this solution was added dropwise via cannula a solution of alcohol **5** (4.88 g, 22.9 mmol) and pyridine (4.9 mL, 57.3 mmol, 2.5 equiv) in 25 mL of DMA. The ice bath was removed and the solution was allowed to stir at 25 °C for 80 min. After this time, the contents were transferred to a separatory funnel containing 300 mL of H_2O. The organic phase was collected and the aqueous layer was extracted with 6 x 50 mL of a 4:1 (v/v) Et_2O/EtOAc solution. The combined organic fractions were washed successively with 1 x 30 mL of saturated aqueous $NaHCO_3$ and 1 x 30 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of this material was accomplished by chromatography on silica gel (35% EtOAc/hexanes) to afford sulfamate ester **6** as a tan solid (5.6 g, 83%). TLC R_f = 0.20 (35% EtOAc/hexanes); mp 89–91 °C; $[\alpha]^{23.7}_D$ –27.2° (*c* 3.0, MeOH); ^{1}H NMR (CD_3CN, 400 MHz, 75 °C) δ 5.81 (dd, 1H, *J* = 5.6, 1.6 Hz), 5.78 (dd, 1H, *J* = 6.0, 2.0 Hz), 5.54 (br s, 2H), 5.10 (br s, 1H), 4.68-4.58 (m, 1H), 4.09 (dd, 1H, *J* = 9.4, 6.2 Hz), 4.06 (dd, 1H, *J* = 9.6, 6.2 Hz), 3.04-2.96 (m, 1H), 2.50 (dt, 1H, *J* = 13.6, 8.4 Hz), 1.42 (s, 9H), 1.35 (dt, 1H, *J* = 13.6, 6.0 Hz) ppm; ^{13}C NMR (CD_3CN, 100 MHz, 75 °C) δ 156.7, 135.5, 133.9, 79.9, 74.2, 57.9, 45.4, 35.8, 29.1 ppm; IR (thin film) ν 3375, 2977, 1682, 1519, 1367, 1248, 1177, 1076, 976, 821 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{20}N_2O_5S$ 292.1093 found 315.0991 (MNa^+).

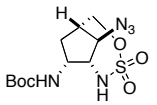


To a solution of sulfamate ester **6** (3.26 g, 11.15 mmol) in 75 mL of CH_2Cl_2 was added sequentially MgO (1.04 g, 25.6 mmol, 2.3 equiv), $Rh_2(esp)_2$ (4.6 mg, 6.06 μmol, .0006 equiv), and $PhI(OAc)_2$ (3.95 g, 12.26 mmol, 1.1 equiv). The resulting white suspension was stirred for 10 h and then filtered through a pad of Celite (25 x 50 mm). The flask and filter cake were rinsed with 150 mL of CH_2Cl_2, and the filtrate was concentrated under reduced pressure to afford a white solid. Purification of this material by chromatography on silica gel (70% EtOAc/hexanes) furnished the product aziridine **7** as a white solid (3.10 g, 95%). TLC R_f = 0.15 (60% EtOAc/hexanes); $[\alpha]^{23.7}_D$ +51.3° (*c* 3.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.85 (d, 1H, *J* = 8.8 Hz), 4.94 (dd, 1H, *J* = 3.4, 1.0 Hz), 4.84-4.74 (m, 1H), 4.28 (dd, 1H, *J* = 11.2, 2.4 Hz), 3.77 (t, 1H, *J* = 4.2 Hz), 3.50 (t, 1H, *J* = 4.2 Hz), 3.02 (dt, 1H, *J* = 14.8, 11.2 Hz), 2.63-2.56 (m, 1H), 1.74 (dt, 1H, *J* = 14.9, 2.7 Hz), 1.43 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 80.0, 76.0, 54.6, 51.3, 51.0, 38.9, 31.2, 28.3 ppm; IR (thin film) ν 3415, 2977, 1712, 1515, 1367, 1258, 1179, 970, 790 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{18}N_2O_5S$ 290.0936 found 313.0834 (MNa^+).

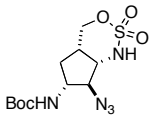


^{1}H NMR analysis of the unpurified reaction mixture from the Rh-catalyzed amination reaction revealed a small amount of the allylic C–H insertion product (≤ 1%), which was isolated by chromatography on silica gel. TLC R_f = 0.50 (50% EtOAc/hexanes); ^{1}H NMR (CD_3OD, 400 MHz) δ 6.86 (d, 1H, *J* = 6.8 Hz), 5.99 (dd, 1H, *J* = 5.6, 2.0 Hz), 5.90 (dd, 1H, *J* = 5.2, 2.0 Hz), 4.76-4.68 (m, 1H), 4.47 (d, 1H, *J* = 8.6 Hz), 4.44 (d, 1H, *J* = 8.6 Hz), 2.64 (dd, 1H, *J* = 14.4, 7.6 Hz), 1.86 (dd, 1H, *J* = 14.0, 5.2 Hz), 1.43 (s, 9H) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 157.8, 139.1, 133.6, 80.4, 80.2, 73.4, 56.4, 44.2, 28.7 ppm; IR (thin film) ν 3379, 3113, 2977, 1680, 1521, 1329, 1247, 1185,

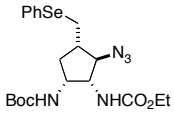
1162, 1077, 937, 780 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{18}N_2O_5S$ 290.0936 found 313.0834 (MNa^+).



Aziridine **7** (2.78 g, 9.55 mmol) was suspended in a solution of 38 mL of isopropanol and 38 mL of H_2O, and the mixture was vigorously stirred. Solid NaN_3 (684 mg, 10.5 mmol, 1.1 equiv) was then added in four equal portions at 30 min intervals. The reaction was stirred for 5 h during which time the initially white suspension turned to a yellow, homogenous solution. The reaction was quenched with 2 mL of saturated aqueous NH_4Cl, concentrated under reduced pressure to ~1/2 the original volume, and then poured into a separatory funnel containing 40 mL of saturated aqueous NaCl. The aqueous layer was extracted with 4 x 30 mL of EtOAc. The combined organic fractions were washed with 1 x 30 mL of saturated aqueous NaCl, dried over Mg_2SO_4, and concentrated under reduced pressure to a white foam. Purification of this material by chromatography on silica gel (gradient elution: 25%→40% EtOAc/hexanes) afforded the desired azide **8** as a white foam (2.27 g, 71%) and the regioisomeric product (see below) as a white solid (260 mg, 8%). TLC R_f = 0.45 (30% EtOAc/hexanes); mp 123–125 °C; $[\alpha]^{23.0}_D$ +45.7° (*c* 1.8, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 5.03 (br s, 1H), 4.94 (s, 1H), 4.79 (d, 1H, *J* = 4.8 Hz), 4.44 (dd, 1H, *J* = 12.2, 1.0 Hz), 4.42-4.34 (m, 1H), 4.04 (dd, 1H, *J* = 12.2, 2.6 Hz), 3.72 (d, 1H, *J* = 4.4 Hz), 2.59-2.49 (m, 2H), 1.54-1.44 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 155.3, 80.9, 72.5, 65.9, 58.0, 54.8, 44.2, 29.6, 28.3 ppm; IR (thin film) ν 3323, 2978, 2108, 1693, 1514, 1454, 1367, 1249, 1175, 1078, 948, 735 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{19}N_5O_5S$ 333.1107 found 356.1005 (MNa^+).



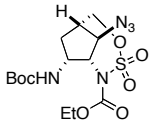
TLC R_f = 0.16 (30% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 6.69 (br s, 1H), 5.18 (d, 1H, *J* = 6.5 Hz), 4.90 (dd, 1H, *J* = 12.0, 3.0 Hz), 4.44 (dd, 1H, *J* = 12.0, 1.5 Hz), 4.05 (dd, 1H, *J* = 3.5, 1.0 Hz), 4.00 (dd, 1H, *J* = 9.0, 4.0 Hz), 3.57-3.49 (m, 1H), 2.52-2.39 (m, 1H), 2.14-2.05 (m, 2H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, 50 °C) δ 155.7, 81.3, 71.8, 70.7, 62.9, 58.1, 33.5, 29.6, 28.3 ppm; IR (thin film) ν 3384, 2979, 2106, 1685, 1520, 1368, 1256, 1184, 926, 786, 734 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{19}N_5O_5S$ 333.1107 found 356.1005 (MNa^+).



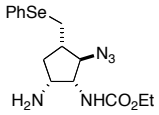
Diphenyldiselenide (609 mg, 1.95 mmol, 0.65 equiv) was added to a 50 mL Schlenk flask containing 10 mL of absolute EtOH that had been sparged with N_2 for 20 min. Under a positive flow of N_2, solid $NaBH_4$ (148 mg, 3.90 mmol, 1.3 equiv) was added portionwise over 5 min to the yellow suspension of Ph_2Se_2. Vigorous gas evolution was observed during the addition process. The EtOH mixture was stirred for an additional 5 min to give a colorless, homogeneous solution.

A 100 mL Schlenk flask containing azide **8** (1.00 g, 3 mmol) and DMAP (3.6 mg, 30 μmol, 0.01 equiv) was flushed with N_2 for 15 min prior to the addition of 12 mL of THF. To this solution was transferred dropwise $(EtOCO)_2O$ (485 μL, 3.3 mmol, 1.1 equiv). The contents stirred for 1 h during which time gentle gas evolution was observed. At the end of this time an aliquot was taken from the reaction for characterization purposes (see below). A freshly prepared 0.2 M ethanolic solution of NaSePh (10 mL, 1.95 mmol, 1.3 equiv, as described above) was then added dropwise via cannula. After stirring for 15 min, the reaction was quenched by the addition of 11 mL of 1% aqueous HCl and 35 mL of EtOAc. The biphasic solution was stirred vigorously for 15 min before being carefully poured into a separatory funnel containing 20 mL of saturated aqueous $NaHCO_3$. The organic layer was collected and the aqueous layer was extracted with 4 x 20 mL of EtOAc. The combined organics were washed with 1 x 20 mL of saturated NaCl, dried over Mg_2SO_4, and concentrated by under reduced pressure. Purification of the yellow material by chromatography on silica (gradient elution: 20%→30% EtOAc/hexanes) gave the desired selenide **10** as a white solid (1.34 g, 93%). TLC R_f = 0.45 (30% EtOAc/hexanes); mp 128–130 °C; $[\alpha]^{22.6}_D$ +18.0° (*c* 1.3, CH_2Cl_2); ^1H

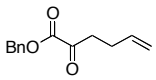
NMR ($CDCl_3$, 500 MHz, 50 °C) δ 7.56-7.52 (m, 2H), 7.32-7.28 (m, 3H), 5.12 (br s, 1H), 4.85 (br s, 1H), 4.21-4.11 (m, 2H), 4.00 (quint, 1H, *J* = 8.0 Hz), 3.90 (q, 1H, *J* = 8.2 Hz), 3.72 (br s, 1H), 3.23 (dd, 1H, *J* = 4.5 Hz), 2.99 (dd, 1H, *J* = 3.0 Hz), 2.37 (dt, 1H, *J* = 7.9 Hz), 2.10-2.00 (m, 1H), 1.60-1.53 (m, 1H), 1.47 (s, 9H), 1.28 (t, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, 55 °C) δ 156.7, 155.9, 132.7, 130.0, 129.3, 127.3, 80.1, 69.1, 61.3, 59.3, 50.2, 41.4, 35.2, 30.9, 28.3, 14.6 ppm; IR (thin film) ν 3356, 3054, 2978, 2918, 2105, 1694, 1550, 1336, 1261, 1171, 1053, 736 cm^{-1}; HRMS (ES^+) calcd for $C_{20}H_{29}N_5O_4Se$ 483.1385 found 506.1282 (MNa^+).



The intermediate *N*-acylated oxathiazepane **9** (white solid) has been isolated and characterized. TLC R_f = 0.40 (30% EtOAc/hexanes); mp 138–140 °C (dec); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.09 (d, 1H, *J* = 8.4 Hz), 4.95 (d, 1H, *J* = 9.2 Hz), 4.78 (d, 1H, *J* = 12.0 Hz), 4.76-4.66 (m, 1H), 4.42 (s, 1H), 4.39-4.31 (m, 3H), 2.70 (ddd, 1H, *J* = 14.4, 12.2, 8.4 Hz), 2.40 (ddd, 1H, *J* = 8.0, 1.6, 0.8 Hz), 1.57 (dd, 1H, *J* = 14.4, 3.6 Hz), 1.41 (s, 9H), 1.36 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 152.1, 79.7, 76.7, 68.7, 64.8, 63.8, 50.7, 42.5, 33.5, 28.0, 13.9 ppm; IR (thin film) ν 3442, 2980, 2105, 1741, 1709, 1505, 1390, 1277, 1169, 1022, 948, 733 cm^{-1}; HRMS (ES^+) calcd for $C_{14}H_{23}N_5O_7S$ 405.1318 found 428.1216 (MNa^+).

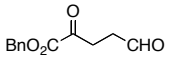


Selenide **10** (2.40 g, 4.96 mmol) was dissolved in 4.0 mL of CH_2Cl_2 and 4.0 mL of CF_3CO_2H. The reaction was stirred for 1 h, then poured into an Erlenmeyer flask containing 30 mL of CH_2Cl_2 and carefully quenched by the addition of 40 mL of saturated aqueous $NaHCO_3$. The biphasic mixture was stirred vigorously for 3 h while significant gas evolution was witnessed. The reaction mixture was transferred to a separatory funnel and the organic layer was collected. The following work-up was performed: 1) the aqueous layer was extracted with 4 x 20 mL of CH_2Cl_2, 2) the organic fractions were washed with 1 x 30 mL of saturated aqueous NaCl, 3) the brine layer was extracted with 1 x 20 mL of CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The product amine **10a** was isolated as a pale yellow oil and used without further purification. TLC R_f = 0.33 (5% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz, 55 °C) δ 7.54-7.48 (m, 2H), 7.29-7.21 (m, 3H), 5.45 (d, 1H, *J* = 6.8 Hz), 4.17 (dq, 1H, *J* = 10.6, 7.2 Hz), 4.14 (dq, 1H, *J* = 10.6, 7.2 Hz), 3.82 (q, 1H, *J* = 7.5 Hz), 3.53-3.44 (m, 2H), 3.20 (dd, 1H, *J* = 12.2, 5.0 Hz), 2.96 (dd, 1H, *J* = 12.2, 7.8 Hz), 2.33 (ddd, 1H, *J* = 13.8, 9.0, 7.0 Hz), 2.15-2.04 (m, 1H), 1.40 (s, 2H), 1.30-1.23 (m, 1H), 1.26 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 156.4, 132.7, 130.0, 129.2, 127.2, 70.1, 61.2, 59.9, 49.7, 41.5, 38.0, 32.1, 14.6 ppm; IR (thin film) ν 3319, 2929, 2100, 1698, 1534, 1261, 1059, 737 cm^{-1}.

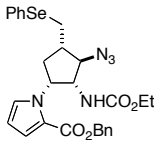


Magnesium turnings (1.00 g, 41.3 mmol, 1.05 equiv) were suspended in 40 mL of THF to which a drop (~25 μL) of $BrCH_2CH_2Br$ was added. The mixture was stirred for 10 min prior to the dropwise addition of neat 1-bromo-3-butene (4.0 mL, 39.4 mmol). The contents were stirred vigorously at 70 °C for 30 min and then cooled to 25 °C. With the aid of a cannula, the Grignard solution was added dropwise over a 30 min period to a –40 °C solution of dibenzyl oxalate (10.65 g, 39.4 mmol) in 145 mL of CH_2Cl_2. Once the addition was complete, the reaction mixture was allowed to warm over 1 h to –10 °C. The reaction stirred at this temperature for 1 h and was then quenched by the addition of 50 mL of saturated aqueous NH_4Cl. The contents were transferred to a separatory funnel and the organic layer was collected. The aqueous fraction was extracted with 3 x 50 mL of CH_2Cl_2. The combined organic fractions were washed with 1 x 30 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to a yellow oil. Purification of this material by rapid filtration through a small plug of silica gel (10% Et_2O/hexanes) furnished benzyl 2-oxohex-5-enoate as a pale yellow oil (4.8 g, 55%). TLC R_f = 0.40 (20% Et_2O/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.37 (m, 5H), 5.80 (ddt, 1H, *J* = 13.6, 8.4, 5.2 Hz), 5.28 (s, 2H), 5.05 (dq, 1H, *J* = 13.7, 1.3 Hz), 5.00 (dq, 1H, *J* = 8.1, 1.1 Hz), 2.95 (t, 2H, *J* = 5.8 Hz), 2.38 (qt, 2H, *J* = 5.6, 1.2 Hz)

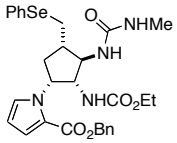
ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.4, 160.7, 136.0, 134.4, 128.8, 128.7, 128.6, 115.9, 67.9, 38.5, 26.9 ppm; IR (thin film) ν 3068, 3035, 2979, 2922, 1728, 1641, 1455, 1275, 1068, 915, 752, 698 cm^{-1}; HRMS (ES$^+$) calcd for $C_{13}H_{14}O_3$ 218.0943 found 241.0841 (MNa^+).



A 2-neck flask equipped with drying tube and a gas inlet was charged with benzyl 2-oxohex-5-enoate (2.6 g, 11.9 mmol) and 70 mL of CH_2Cl_2. The contents were cooled to –78 °C and a dilute stream of O_3 was bubbled through the solution until a blue color persisted. Ozone addition was ceased, the gas inlet was replaced with a N_2 bleed, and the reaction was sparged with N_2 until the blue color faded. Solid PPh_3 (3.12 g, 11.9 mmol, 1.0 equiv) was then added in a single portion, the dry ice bath was removed, and the reaction was allowed to warm slowly to 25 °C over a 1.5 h period. The resulting orange solution was transferred to a single neck flask and concentrated under reduced pressure. Purification of the orange residue was accomplished by chromatography on silica gel (40% EtOAc/hexanes) and afforded the desired aldehyde **13** as a yellow oil (1.9 g, 72%). Despite repeated attempts at purification, a ^{1}H NMR spectrum of the purified product shows numerous signals. This material likely exists in different hydrated forms, as further suggested by its chromatographic behavior. In general, the aldehyde should be used immediately following chromatography, although short-term storage (1–2 days) as a neat oil at –20 °C is possible. TLC R_f = 0.25 (40% EtOAc/hexanes, compound streaks on SiO_2); the ^{1}H NMR data reported is for reference: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.75 (s, 1H), 7.42-7.32 (m, 5H), 5.28 (s, 2H), 3.13 (q, 2H, *J* = 6.2 Hz), 2.81 (t, 2H, *J* = 6.2 Hz) ppm.

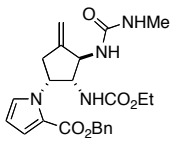


A flask containing amine **10a** (4.96 mmol) in 50 mL of DCE was charged with a 50 mL DCE solution of aldehyde **13** (1.36 g, 6.20 mmol, 1.25 equiv) and pyridinium *p*-toluenesulfonate (31 mg, 0.12 mmol, 0.025 equiv). The yellow mixture was stirred at 80–85 °C for 2 h during which time the solution turned orange. The contents of the reaction were then poured slowly into a separatory funnel containing 20 mL of saturated aqueous $NaHCO_3$. The organic phase was collected and the aqueous layer was extracted with 3 x 20 mL of CH_2Cl_2. The combined organic extracts were washed with 1 x 30 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to give an orange oil. Purification of this material by chromatography on silica gel (17% EtOAc/hexanes) afforded pyrrole **14** as a pale yellow oil (2.38 g, 85%). TLC R_f = 0.30 (20% EtOAc/hexanes); $[\alpha]^{23.8}_D$ +102.8° (*c* 3.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 7.58-7.54 (m, 2H), 7.44-7.24 (m, 8H), 7.07 (dd, 1H, *J* = 3.8, 1.8 Hz), 7.01 (t, 1H, *J* = 2.2 Hz), 6.21 (dd, 1H, *J* = 4.0, 2.8 Hz), 5.67 (q, 1H, *J* = 8.5 Hz), 5.31 (d, 1H, *J* = 12.4 Hz), 5.26 (d, 1H, *J* = 12.4 Hz), 4.65-4.35 (br m, 1H), 4.34 (q, 1H, *J* = 8.1 Hz), 3.95 (q, 2H, *J* = 7.1 Hz), 3.78 (br s, 1H), 3.30 (dd, 1H, *J* = 12.4, 4.0 Hz), 3.08 (dd, 1H, *J* = 12.6, 7.0 Hz), 2.52-2.40 (m, 1H), 2.21-2.05 (m, 2H), 1.10 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 160.8, 155.9, 136.1, 132.4, 129.6, 129.2, 128.4, 128.0, 127.8, 127.2, 126.5, 123.2, 119.3, 108.9, 86.6, 65.6, 60.9, 59.2, 55.7, 41.2, 34.1, 30.1, 14.4 ppm; IR (thin film) ν 3334, 3136, 3032, 2979, 2101, 1703, 1528, 1416, 1340, 1242, 1100, 1022, 737 cm^{-1}; HRMS (ES$^+$) calcd for $C_{27}H_{29}N_5O_4Se$ 567.1385 found 590.1282 (MNa^+).

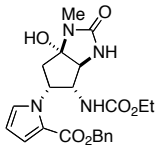


To a solution of pyrrole **14** (2.0 g, 3.52 mmol) in 32 mL of THF and 3.5 mL of H_2O was added 3.9 mL of a 1.0 M toluene solution of Me_3P (3.9 mmol, 1.1 equiv). The reaction stirred for 2 h, slowly turning opaque while evolving a gentle stream of gas. Methyl isocyanate (230 μL, 3.9 mmol, 1.1 equiv) was then added and the mixture was stirred for 1 h. After this time, all volatiles were removed under reduced pressure to give a yellow, oily suspension; this material was transferred to a separatory funnel with 20 mL of EtOAc and 30 mL of H_2O. The organic phase was collected and the aqueous fraction was extracted with 3 x 20 mL of EtOAc. The combined organic extracts were

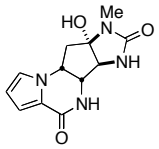
washed with 20 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to a pale yellow foam. Purification of this material by chromatography on silica gel (55% EtOAc/CH_2Cl_2) yielded the urea product **15** as a white foam (1.71 g, 81%). TLC R_f = 0.40 (60% EtOAc/CH_2Cl_2); mp 65–68 °C; $[\alpha]^{22.4}_D$ +117.0° (*c* 3.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (dd, 2H, *J* = 7.8, 1.8 Hz), 7.40-7.28 (m, 5H), 7.22-7.13 (m, 4H), 7.01 (dd, 1H, *J* = 4.0, 1.5 Hz), 6.14 (t, 1H, *J* = 3.3 Hz), 6.00-5.92 (m, 2H), 5.74 (s, 1H), 5.53 (d, 1H, *J* = 9.0 Hz), 5.28 (d, 1H, *J* = 12.5 Hz), 5.20 (d, 1H, *J* = 12.5 Hz), 4.27 (q, 1H, *J* = 9.0 Hz), 4.15 (q, 1H, *J* = 9.5 Hz), 3.87 (dq, 1H, *J* = 10.5, 7.2 Hz), 3.76 (dq, 1H, *J* = 10.5, 7.2 Hz), 3.38 (dd, 1H, *J* = 11.8, 3.8 Hz), 3.07 (dd, 1H, *J* = 12.0, 9.0 Hz), 2.68 (d, 3H, *J* = 5.0 Hz), 2.48 (quint, 1H, *J* = 6.5 Hz), 2.30-2.20 (m, 1H), 2.10 (q, 1H, *J* = 11.5 Hz), 1.02 (t, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 159.5, 156.8, 136.4, 132.1, 130.8, 129.0, 128.3, 127.8, 127.6, 126.8, 126.6, 122.9, 118.7, 108.4, 65.3, 60.6, 59.9, 59.2, 54.7, 42.5, 32.0, 30.6, 26.7, 14.3 ppm; IR (thin film) ν 3375, 3069, 2978, 2247, 1703, 1650, 1571, 1415, 1241, 1102, 1023, 909, 734 cm^{-1}; HRMS (ES$^+$) calcd for $C_{29}H_{34}N_4O_5Se$ 598.1694 found 621.1583 (MNa^+).



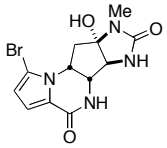
To an ice cold solution of urea **15** (1.66 g, 2.78 mmol) in 50 mL of DCE was added technical grade (70 wt.%) *meta*-chloroperbenzoic acid (1.03 g, 4.18 mmol, 1.5 equiv). The initially opaque mixture stirred for 30 min, slowly becoming a clear solution. Following this period, Et_3N (3.9 mL, 27.8 mmol, 10 equiv) was added and the reaction was heated to 80 °C for 2 h. After cooling to 25 °C, the resulting orange-red solution was poured into a separatory funnel containing 50 mL of 1 M aqueous NaOH. The organic phase was collected and the aqueous layer was extracted with 3 x 20 mL of CH_2Cl_2. The combined organic fractions were washed with 1 x 30 mL of saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to an orange residue. Purification by chromatography on silica gel (70% EtOAc/CH_2Cl_2) gave the desired alkene **16** as a pale yellow foam (1.10 g, 89%). TLC R_f = 0.25 (70% EtOAc/CH_2Cl_2); $[\alpha]^{22.6}_D$ +57.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz, 50 °C) δ 7.41-7.26 (m, 5H), 7.04 (t, 1H, *J* = 2.0 Hz), 6.98 (dd, 1H, *J* = 3.8, 1.8 Hz), 6.19 (t, 1H, *J* = 3.4 Hz), 5.89 (td, 1H, *J* = 7.2, 3.7 Hz), 5.21 (s, 2H), 5.18-5.15 (m, 2H, *J* = 2.4 Hz), 4.62-4.54 (m, 1H), 4.07 (dd, 1H, *J* = 9.6, 6.4 Hz), 3.90 (q, 2H, *J* = 6.6 Hz), 3.14-3.02 (m, 1H), 2.94-2.87 (m, 1H), 2.69 (s, 3H), 1.08 (t, 3H, *J* = 6.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C) δ 160.9, 159.4, 156.9, 145.9, 136.3, 128.4, 127.9, 127.7, 125.5, 123.6, 118.8, 109.8, 109.3, 65.3, 61.0, 60.2, 56.0, 54.5, 35.4, 26.9, 14.4 ppm; IR (thin film) ν 3340, 3065, 2981, 1704, 1643, 1562, 1416, 1241, 1101, 909, 737 cm^{-1}; HRMS (ES$^+$) calcd for $C_{23}H_{28}N_4O_5$ 440.2060 found 463.1949 (MNa^+).



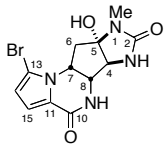
To a solution of alkene **16** (1.04 g, 2.36 mmol) in 45 mL of 1:1 THF/H_2O was added sequentially $NaIO_4$ (1.5 g, 7.05 mmol, 3.0 equiv) and a 4 wt.% aqueous solution of OsO_4 (375 μL, 59 μmol, 0.025 equiv). The reaction was stirred a 45 °C for 2 h then cooled to 25 °C and quenched by the addition of 4 mL of saturated aqueous $Na_2S_2O_3$. The mixture was stirred vigorously for 5 min before being transferred to a separatory funnel with 20 mL of EtOAc and 40 mL of saturated aqueous NaCl. The organic phase was collected and the aqueous layer was extracted with 5 x 15 mL of EtOAc. The combined organic extracts were dried over Mg_2SO_4 and concentrated under reduced pressure to an oily residue. Purification of this material by chromatography on silica (5% MeOH/CH_2Cl_2) yielded hemi-aminal **17** as a white foam (850 mg, 81%). TLC R_f = 0.25 (5% MeOH/CH_2Cl_2); mp 142–144 °C; $[\alpha]^{24.5}_D$ +87.4° (*c* 0.8, $CHCl_3$); ^{1}H NMR (CD_3CN, 400 MHz, 65 °C) δ 7.45-7.30 (m, 5H), 7.19 (dd, 1H, *J* = 2.6, 1.8 Hz), 6.96 (dd, 1H, *J* = 4.0, 1.6 Hz), 6.14 (dd, 1H, *J* = 4.0, 2.8 Hz), 5.56-5.48 (m, 2H), 5.43 (d, 1H, *J* = 8.4 Hz), 5.28 (d, 1H, *J* = 12.8 Hz), 5.24 (d, 1H, *J* = 12.8 Hz), 4.43 (s, 1H), 4.21 (ddd, 1H, *J* = 9.2, 5.6, 1.6 Hz), 3.92-3.80 (m, 2H), 3.67 (t, 1H, *J* = 2.0 Hz), 2.73 (s, 3H), 2.58-2.53 (m, 2H), 1.05 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C NMR (CD_3CN, 125 MHz, 65 °C) δ 162.0, 160.4, 157.2, 138.3, 129.8, 129.2, 129.1, 128.2, 124.2, 120.0, 109.4, 94.3, 68.2, 66.6, 61.9, 61.6, 58.0, 38.4, 24.7, 15.2 ppm; IR (thin film) ν 3331, 2980, 1697, 1467, 1416, 1379, 1245, 1102, 755 cm^{-1}; HRMS (ES$^+$) calcd for $C_{22}H_{26}N_4O_6$ 442.1852 found 465.1753 (MNa^+).



Hemi-aminal **17** (750 mg, 1.69 mmol) was suspended in 25 mL of *t*-amyl alcohol to which 25 mL of a warm *t*-amyl alcohol solution of KO^{t}Bu (570 mg, 5.08 mmol, 3.0 equiv) was added dropwise via cannula (note: warming the solution of KO^{t}Bu is needed to assist dissolution). The mixture was stirred at 45 °C for 45 min. During this time the suspension turned orange in color and became homogenous. The reaction was quenched by the addition of AcOH (310 μL, 5.41 mmol, 3.2 equiv) and concentrated under reduced pressure to an oily pink residue. Residual solvent was removed by heating this material to 40 °C under high vacuum (~1 Torr) for 8 h. Purification by chromatography on silica gel (gradient elution: 10→15% MeOH/CH_2Cl_2) afforded the desired lactam **18** as a white solid (345 mg, 77%). TLC R_f = 0.13 (10% MeOH/CH_2Cl_2); $[\alpha]^{26.2}_D$ –68.5° (*c* 0.8, MeOH) [literature values:[1] $[\alpha]^{20}_D$ –68.4° (*c* 0.4, MeOH); $[\alpha]^{20}_D$ –66.2° (*c* 0.21, MeOH)]; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.02 (dd, 1H, *J* = 2.4, 1.6 Hz), 6.88 (dd, 1H, *J* = 4.0, 1.2 Hz), 6.23 (dd, 1H, *J* = 3.8, 2.6 Hz), 4.65 (dt, 1H, *J* = 10.4, 6.0 Hz), 3.99 (dd, 1H, *J* = 5.3, 1.4 Hz), 3.80 (d, 1H, *J* = 1.2 Hz), 2.79 (s, 3H), 2.61 (dd, 1H, *J* = 13.2, 6.4 Hz), 2.27 (dd, 1H, *J* = 13.4, 10.2 Hz) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 162.1, 161.3, 125.7, 122.8, 115.4, 111.1, 95.8, 68.0, 62.8, 55.6, 41.6, 24.3 ppm; IR (thin film) ν 3274, 2924, 1671, 1632, 1553, 1379, 1298, 1070, 754 cm^{-1}; HRMS (ES$^+$) calcd for $C_{12}H_{14}N_4O_3$ 262.1066 found 285.0974 (MNa^+).



(–)-Agelastatin A was prepared according to a literature procedure.[2] To an ice cold solution of lactam **18** (275 mg, 1.05 mmol) in 36 mL of THF and 18 mL of MeOH was added *N*-bromosuccinimide (84 mg, 0.47 mmol, 0.45 equiv). Following the addition, the ice bath was removed and the reaction warmed slowly to 25 °C. After 2 h the reaction mixture was re-cooled to 0 °C and a second portion of *N*-bromosuccinimide (84 mg, 0.47 mmol, 0.45 equiv) was added. The ice bath was removed and the reaction was again allowed to warm to 25 °C and stirred for 2 h. The reaction was then concentrated under reduced pressure to a glassy residue. Purification of this material by chromatography on silica gel (gradient elution: 10→13% MeOH/CH_2Cl_2) furnished the natural product **19** as a white amorphous solid (270 mg, 75%). TLC R_f = 0.33 (12% MeOH/CH_2Cl_2); $[\alpha]^{23.3}_D$ –87.0° (*c* 1.1, MeOH) [literature value:[2] $[\alpha]^{20}_D$ –84.2° (*c* 1.0, MeOH)]; ^{1}H NMR (CD_3OD, 400 MHz) δ 6.90 (d, 1H, *J* = 4.0 Hz), 6.32 (d, 1H, *J* = 4.0 Hz), 4.59 (dt, 1H, *J* = 12.0, 6.0 Hz), 4.08 (d, 1H, *J* = 5.6 Hz), 3.87 (s, 1H), 2.80 (s, 3H), 2.64 (dd, 1H, *J* = 12.8, 6.4 Hz), 2.09 (dd, 1H, *J* = 12.8, 12.4 Hz) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 161.4, 161.1, 124.1, 116.0, 113.8, 107.3, 95.6, 67.4, 62.2, 54.4, 40.0, 24.2 ppm; IR (thin film) ν 3285, 2922, 1653, 1553, 1423, 1378, 1303, 1197, 1090, 747 cm^{-1}; HRMS (ES$^+$) calcd for $C_{12}H_{13}BrN_4O_3$ 340.0171 found 363.0058 (MNa^+).



	synthetic		***natural*** [3]	
position	**^{13}C NMR**	**^{1}H NMR**	**^{13}C NMR**	**^{1}H NMR**
N-Me	24.2	2.80 (s)	25.79	2.81 (s)
2	161.4	–	163.00	–
4	67.4	3.87 (br s)	68.98	3.89 (br s)
5	95.6	–	97.24	–
6a	40.0	2.64 (dd, *J* = 12.8, 6.4 Hz)	41.58	2.65 (dd, *J* = 12.9, 6.6 Hz)
6b		2.09 (dd, *J* = 12.8, 12.4 Hz)		2.10 (dd, *J* = 12.9, 12.3 Hz)
7	54.4	4.59 (dt, *J* = 12.0, 6.0 Hz)	55.96	4.60 (m, *J* = 12.3, 6.6, 5.4 Hz)
8	62.2	4.08 (d, *J* = 5.6 Hz)	63.76	4.09 (d, *J* = 5.4 Hz)
10	161.1	–	162.65	–
11	124.1	–	125.71	–
13	107.3	–	108.80	–
14	113.8	6.32 (d, *J* = 4.0 Hz)	115.37	6.33 (d, *J* = 4.2 Hz)
15	116.0	6.90 (d, *J* = 4.0 Hz)	117.59	6.92 (d, *J* = 4.2 Hz)

spectra recorded in CD_3OD

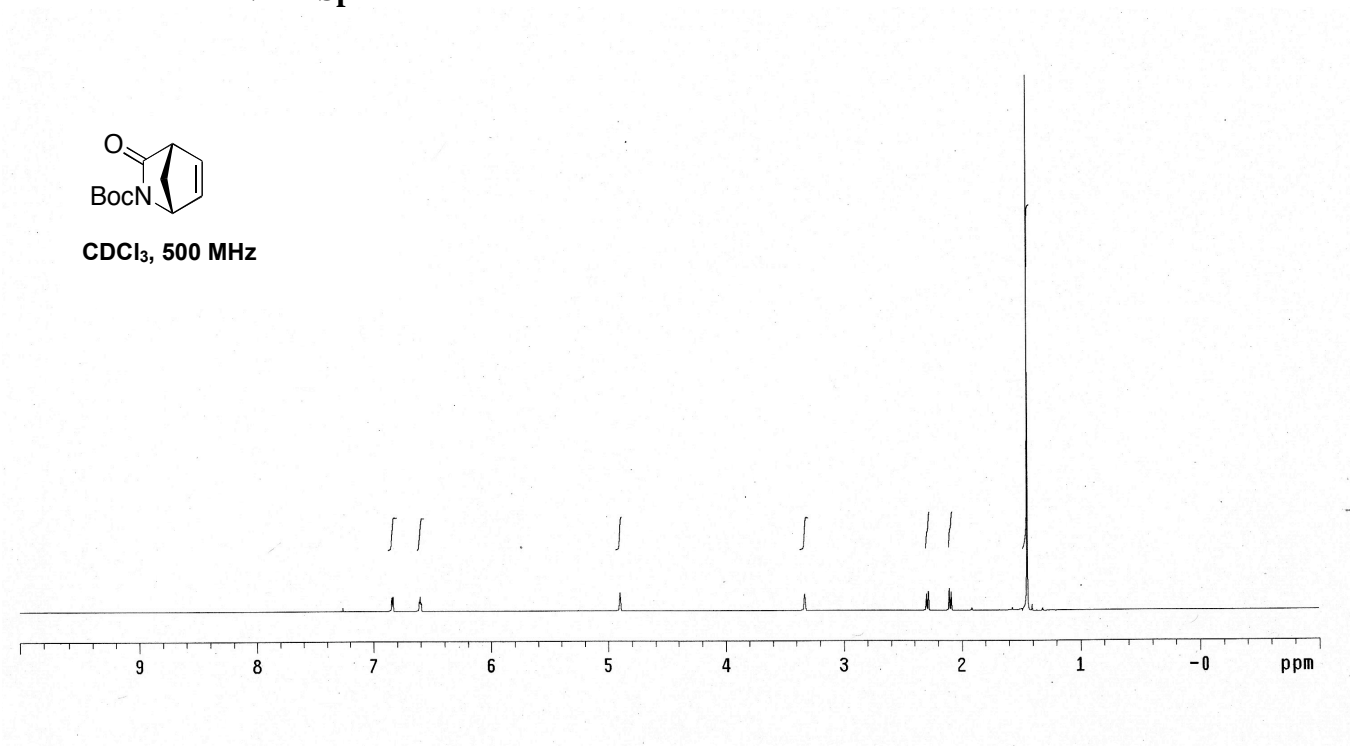
References

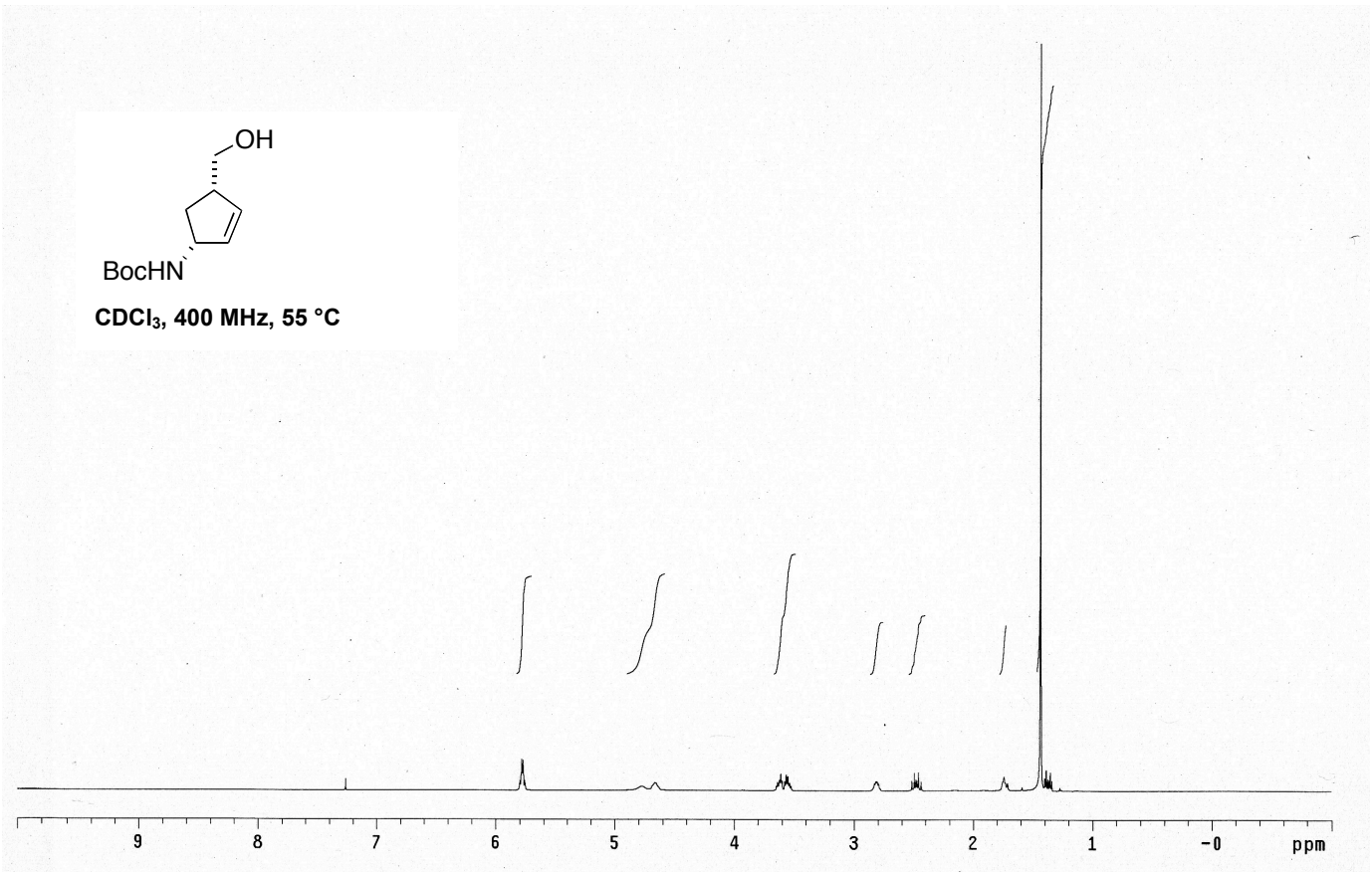
(1) (a) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem.* **2002**, *67*, 7096–7109. (b) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621–623.

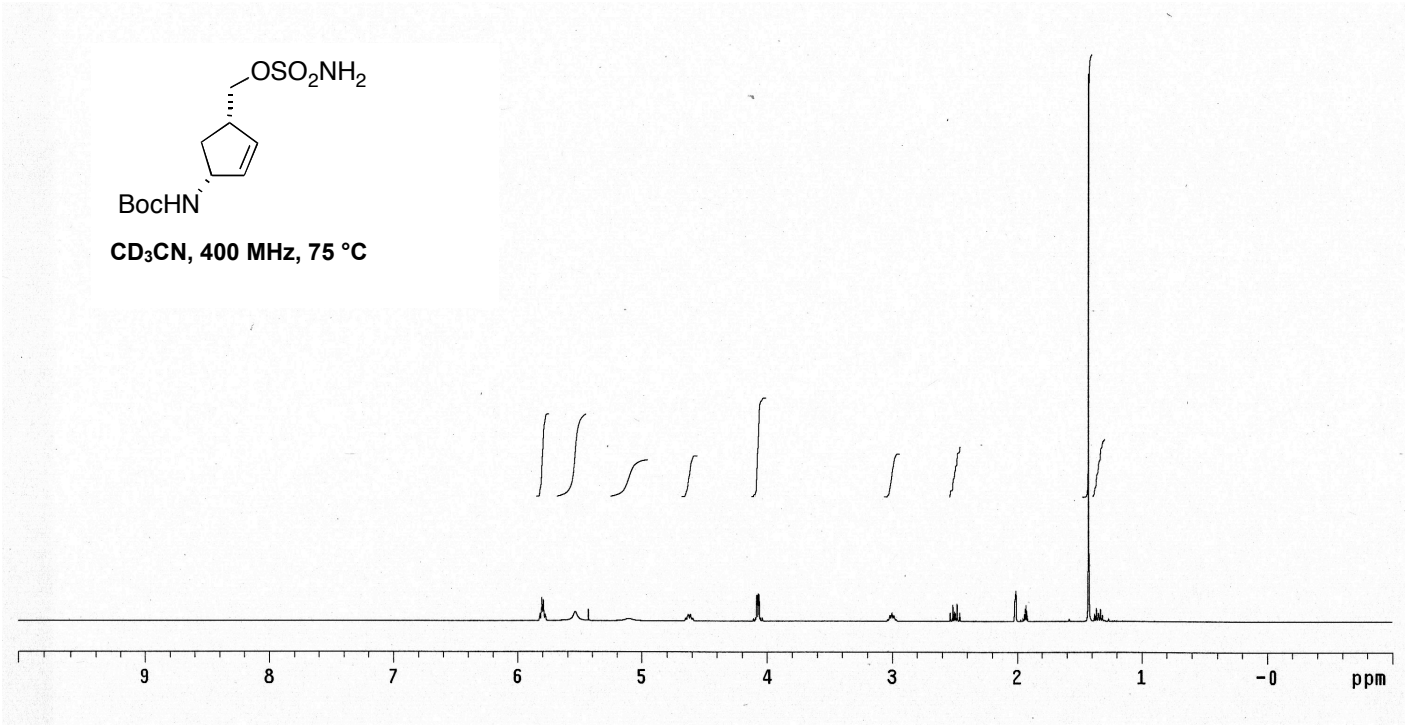
(2) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615–2618.

(3) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305–1306.

Recorded ^{1}H NMR Spectral Data



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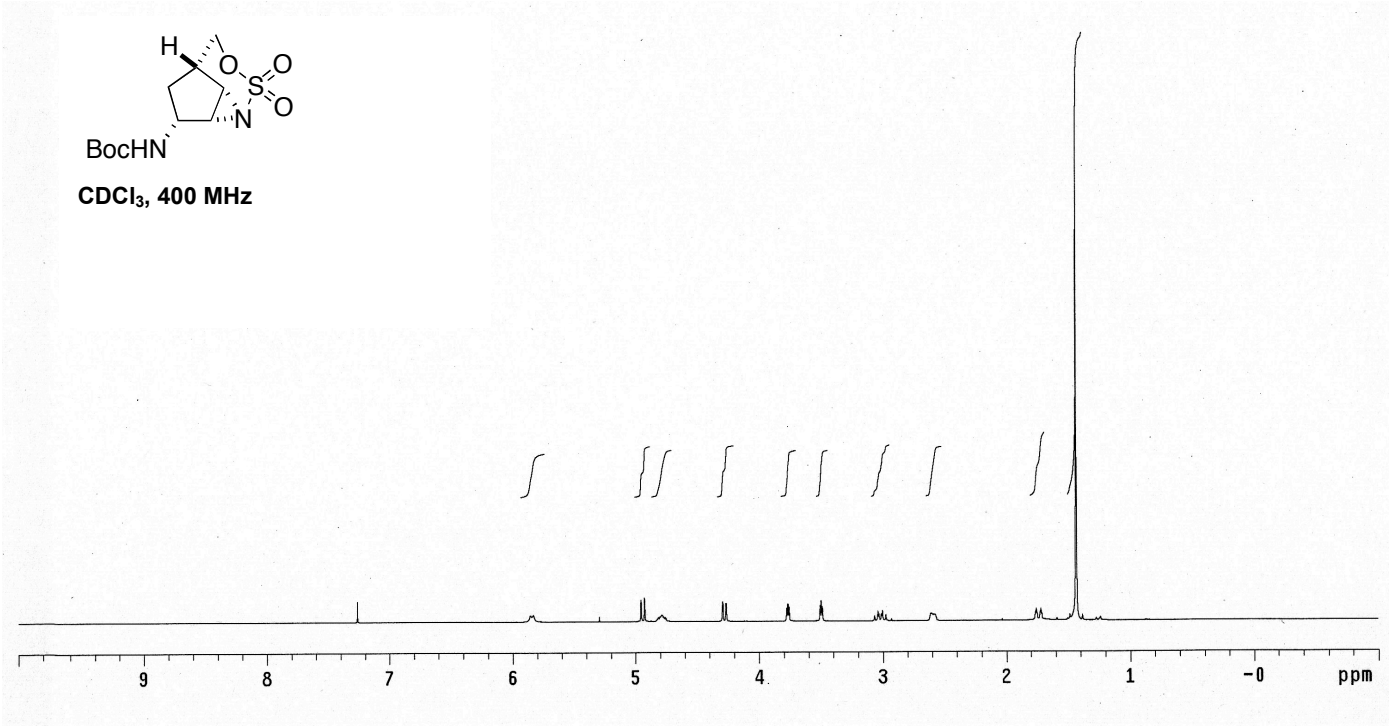
H
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S
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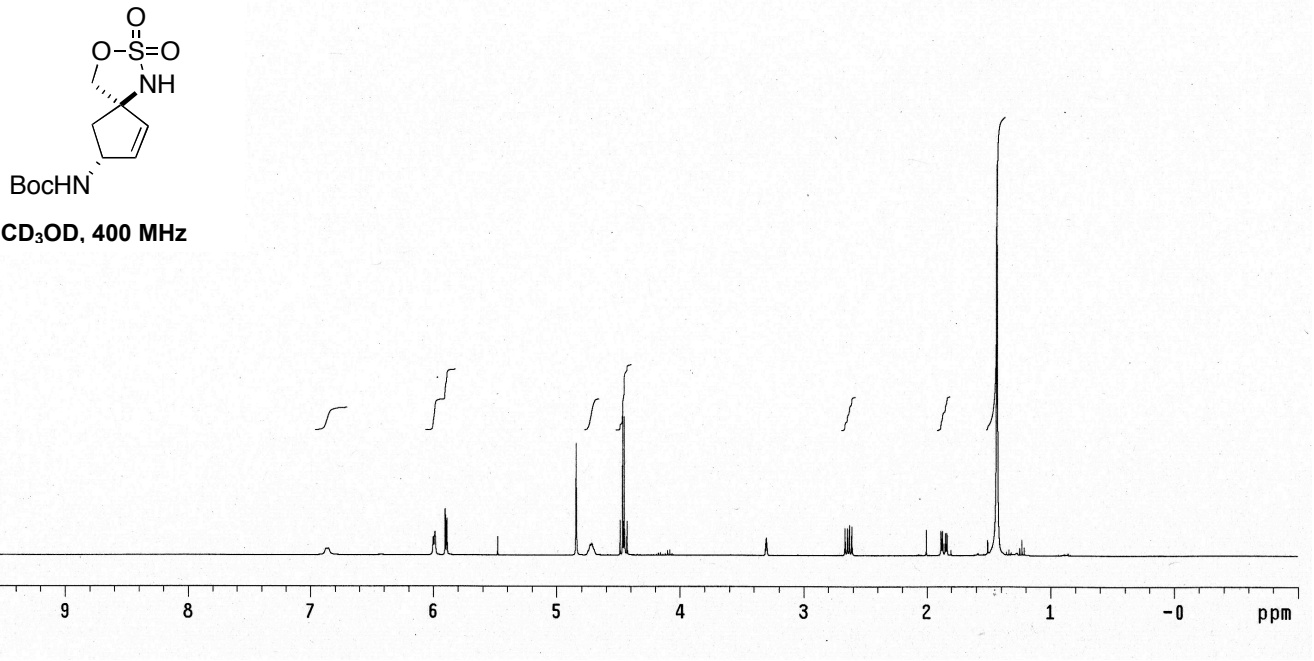
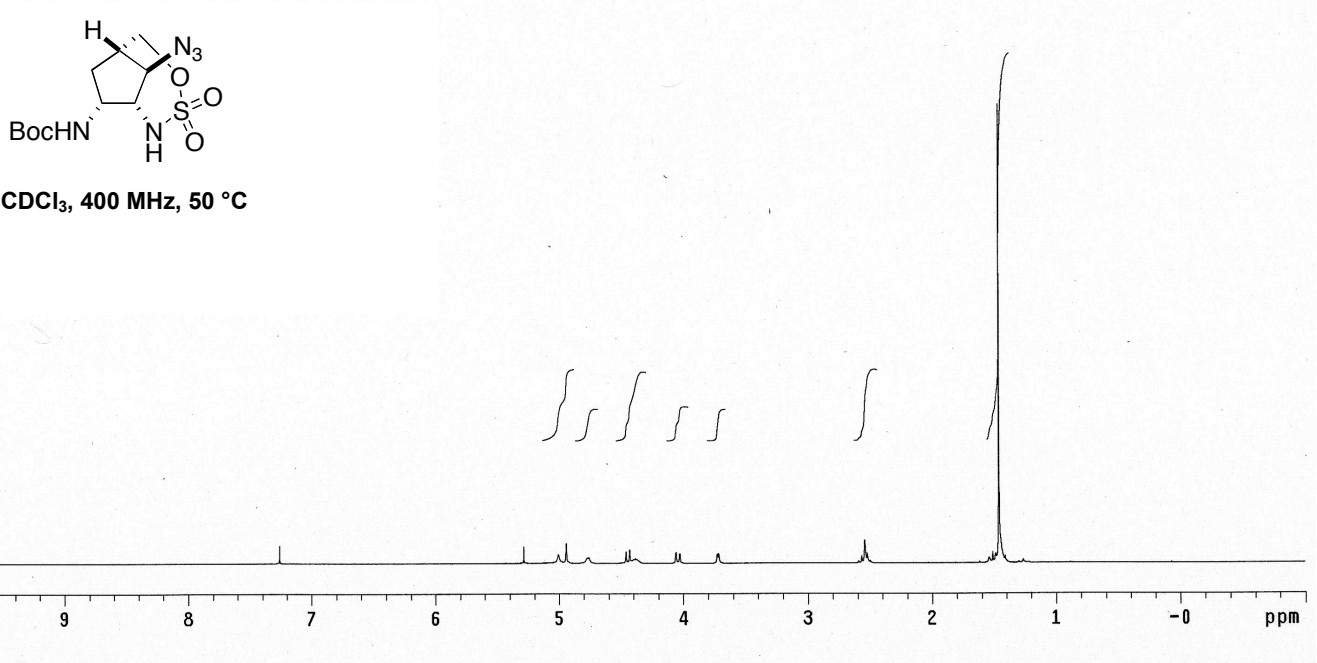
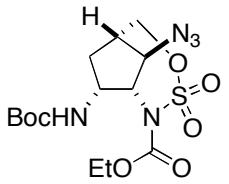


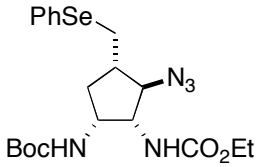
CD_3OD, 400 MHz



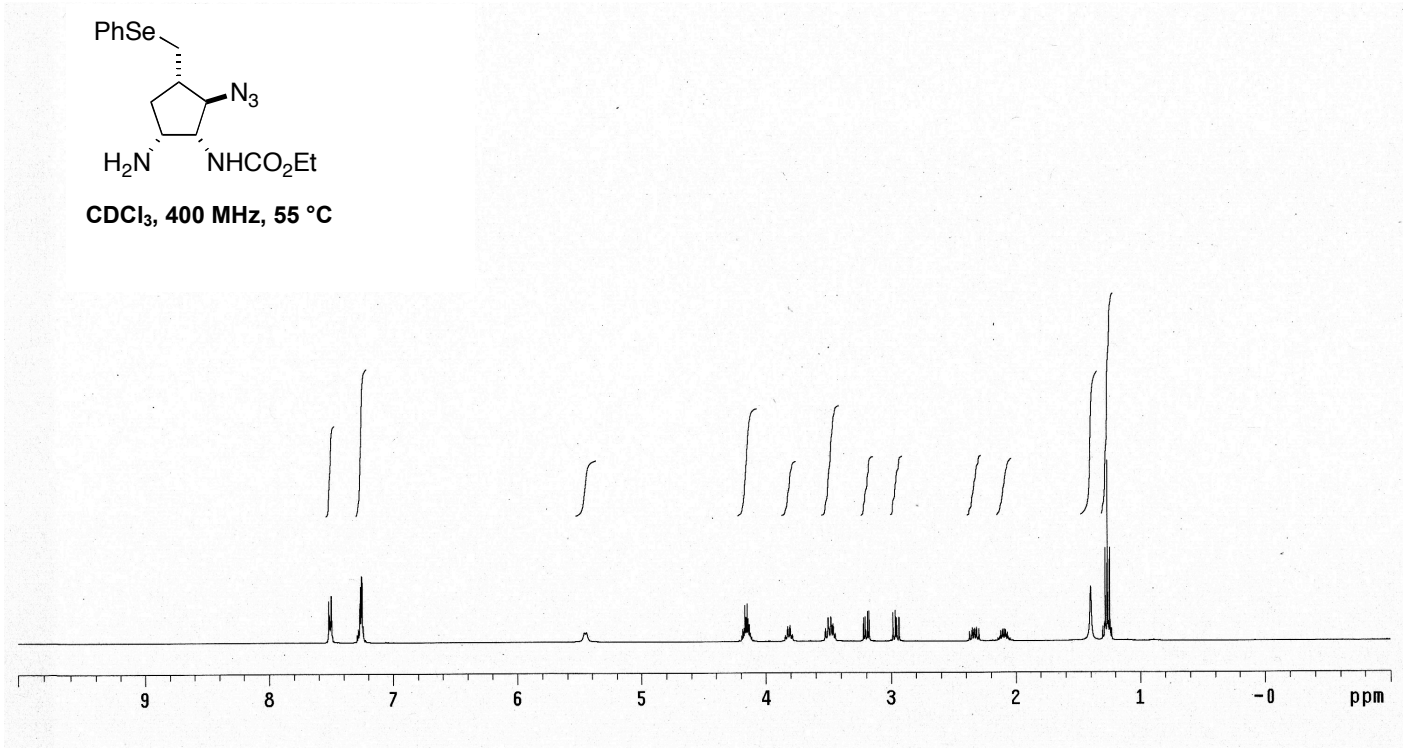
$CDCl_3$, 400 MHz, 50 °C

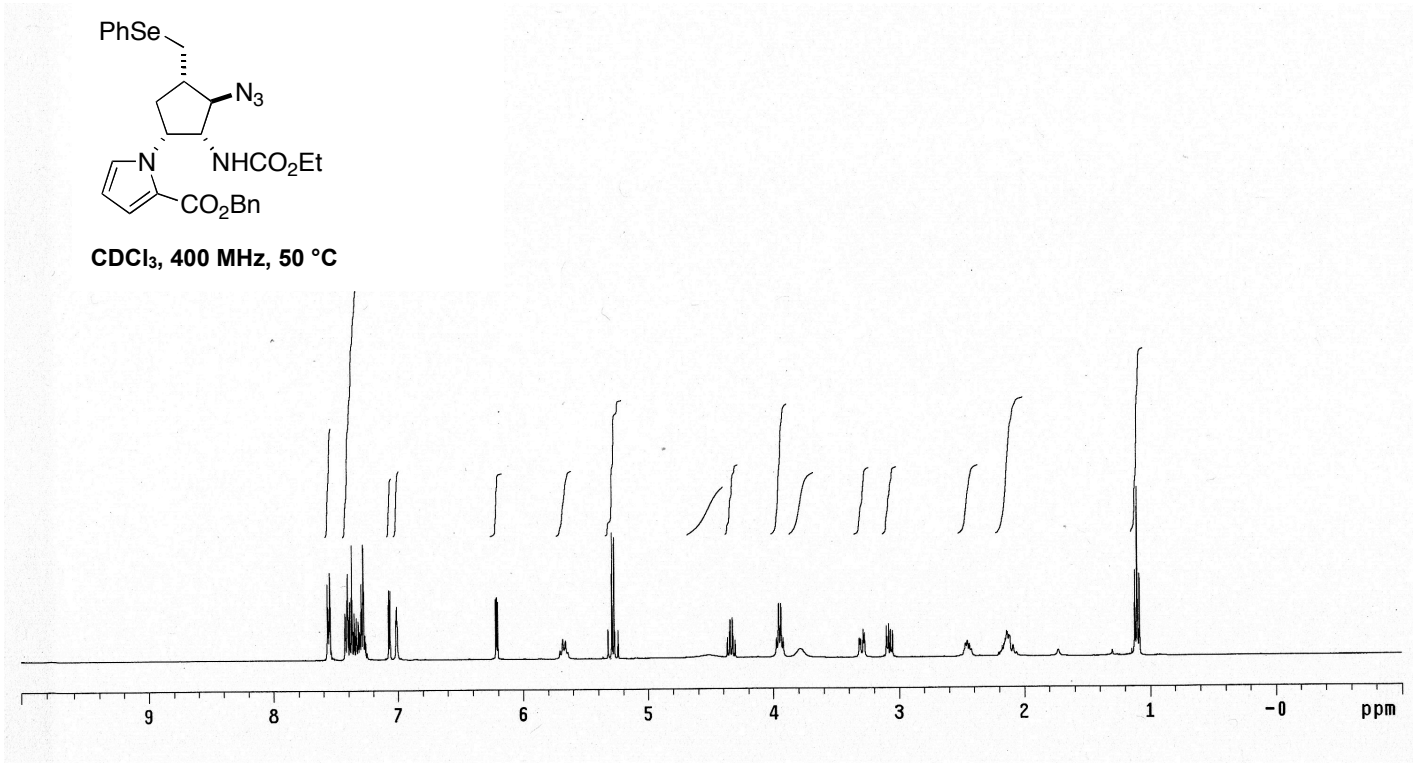


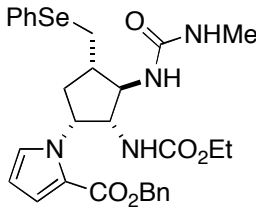
$CDCl_3$, 400 MHz



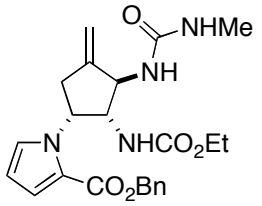
$CDCl_3$, 400 MHz


PhSe
N3
H2N
NHCO2Et
CDCl3, 400 MHz, 55 °C
9
8
7
6
5
4
3
2
1
-0
ppm

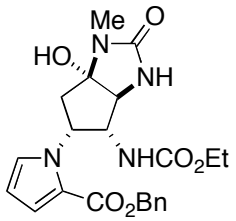

PhSe
N3
N
NHCO2Et
CO2Bn
CDCl3, 400 MHz, 50 °C
9
8
7
6
5
4
3
2
1
-0
ppm



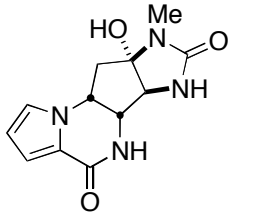
$CDCl_3$, 500 MHz



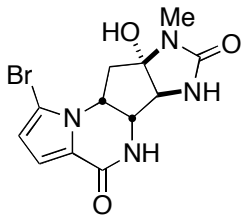
CD_3OD, 400 MHz, 50 °C



CD_3CN, 400 MHz, 65 °C



CD_3OH, 400 MHz



CD_3OH, 400 MHz

(–)-agelastatin A