The Total Synthesis of Caerulomycin C via the Halogen Dance Reaction

Supporting Info

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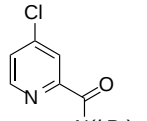
General: All moisture sensitive reactions were conducted under a nitrogen atmosphere in oven-dried glassware using solvents purified according to standard procedures.[1] ^{1}H NMR spectra were obtained at 500 MHz, ^{13}C NMR spectra at 125 MHz with ^{1}H decoupling (WALTZ) in chloroform-*d*, with chemical shifts reported in parts per million referenced to residual chloroform (δ = 7.24 for ^{1}H and 77.00 for ^{13}C). Infrared spectra were recorded as thin films on NaCl plates. Melting points are uncorrected.



20

4-Chloro-2-pyridine Carboxylic Acid *N*,*N*-Diisopropylamide (20). Picolinic acid (15 g, 0.12 mol, 1.0 equiv), sodium bromide (1.88 g, 0.018 mol, 0.15 equiv) and thionyl chloride (44 mL, 0.6 mol, 5.0 equiv) were brought to reflux in a 100 mL round bottom flask fitted with a condenser and a sodium hydroxide (100 mL of a 5 M aqueous solution) gas trap. After 14 hours, the reaction was cooled to room temperature, and the excess thionyl chloride was distilled under reduced pressure, leaving a solid residue in the still pot. The solids were dissolved in dichloromethane (100 ml) and cooled to 0 ˚C under a nitrogen atmosphere. Diisopropylamine (64 mL, 0.48 mol, 4 equiv) was added dropwise via addition funnel over a period of 1 hour, and the reaction was allowed to stir for an additional 30 minutes. The reaction was diluted with ethyl acetate, washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide 4-chloro-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**20**) (27.22 g, 93%) which was used without further purification. *Rf* 0.8 (ethyl acetate); IR: 2970, 1628, 1574, 1555 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, *J* = 6.6 Hz, 6H), 1.53 (d, *J* = 6.7 Hz, 6H), 3.53 (septet, *J* = 6.7 Hz, 1H), 3.79 (septet, *J* = 6.6 Hz, 1H), 7.28 (dd, *J* = 1.8, 5.4 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 8.44 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.36, 20.70, 46.18, 50.80, 122.58, 123.96, 145.01, 149.51, 157.69, 167.38; Anal. Calcd for $C_{12}H_{17}ClN_2O_2$: C, 59.87; H, 7.12; N, 11.64. Found: C, 59.92; H, 7.15; N, 11.69.

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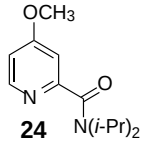
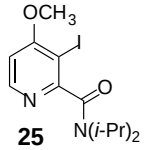
(1) Perrin, D. D. ; Armarego, W. L. F. *Purification of Laboratory Chemicals* Pergamon: Oxford, 1988.



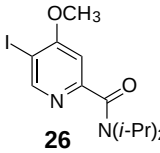
24

4-Methoxy-2-pyridine Carboxylic Acid *N*,*N*-Diisopropylamide (24). A solution of sodium methoxide was prepared by adding sodium metal (9.55 g, 0.42 mol, 5.0 equiv) to methanol (200 mL) and stirring until all the sodium was consumed. This solution was transferred via cannula to a 500 mL round bottom flask containing 4-chloro-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**20**) (20.0 g, 8.31 x 10^{-2} mol) under a nitrogen atmosphere. The reaction was brought to reflux for 18 hours, and then cooled. The reaction was diluted with ethyl acetate, washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) provided 4-methoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**24**) (17.54 g, 89%). *Rf* 0.4 (ethyl acetate); IR: 2968, 1629, 1599, 1562 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (d, *J* = 6.5 Hz, 6H), 1.53 (d, *J* = 6.7 Hz, 6H), 3.51 (septet, *J* = 6.7 Hz, 1H), 3.82 (septet, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 6.77 (dd, *J* = 2.4, 5.7 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 8.34 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.45, 20.71, 45.97, 50.61, 55.29, 107.40, 110.33, 149.87, 158.18, 166.31, 168.57; Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.88; H, 8.79; N, 11.87.



25

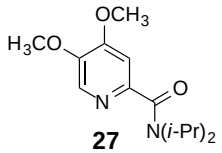
3-Iodo-4-methoxy-2-pyridine Carboxylic Acid *N*,*N*-Diisopropylamide (25). 4-Methoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**24**) (13 g, 5.5 x 10^{-2} mol, 1.0 equiv) was dissolved in THF (220 mL) under a nitrogen atmosphere. The solution was cooled to -78 ˚C, and then *n*-BuLi (41.8 mL, 1.58 M in hexanes, 6.6 x 10^{-2} mol, 1.2 equiv) was added dropwise via cannula over a period of 10 minutes. The red solution was allowed to stir at -78 ˚C for 1.5 hours. A solution of iodine (19.55 g, 7.7 x 10^{-2} mol, 1.4 equiv) in THF (50 mL) was added dropwise via cannula to the reaction mixture over a period of 10 minutes. The reaction was allowed to come to room temperature and diluted with 2:1 ethyl acetate:acetone. The organic layer was washed with 1 M $Na_2S_2O_3$, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The solids were dissolved in the minimum amount of hot ethyl acetate (approximately 400 mL), and then an equal amount of hexanes was added and the solution was allowed to cool overnight. Isolation of the crystals and recrystalization of the mother liquors provided 3-iodo-4-methoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**25**) (14.94 g, 75%, two crops). *Rf* 0.25 (ethyl acetate); IR: 2971, 1635, 1568, 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (bs, 6H), 1.58 (d, *J* = 6.7 Hz, 6H), 3.44 (septet, *J* = 6.7 Hz, 1H), 3.51 (septet, *J* = 6.7 Hz, 1H), 3.94 (s, 3H), 6.65 (d, *J* = 5.7 Hz, 1H), 8.33 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.21, 20.71, 46.01, 51.06, 56.46, 81.67, 105.72, 150.73, 161.22, 164.64, 167.83; Anal. Calcd for $C_{13}H_{19}IN_2O_2$: C, 43.11; H, 5.29; N, 7.73. Found: C, 43.32; H, 5.43; N, 7.75.



26

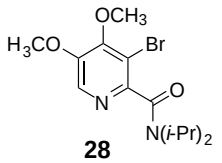
5-Iodo-4-methoxy-2-pyridine Carboxylic Acid *N*,*N*-Diisopropylamide (26). *n*-BuLi (52.4 mL, 1.58 M in hexanes, 8.28 x 10^{-2} mol, 3.2 equiv) was added to diisopropylamine (12.38 mL, 8.28 x 10^{-2} mol, 3.2 equiv) in THF (200 mL) at 0 ˚C. After stirring for 15 minutes, the solution was cooled to -78 ˚C and 3-iodo-4-methoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**25**) (10

g, 2.76 x 10^{-2} mol, 1.0 equiv) in THF (600 mL) was added dropwise via cannula to the LDA over a period of 1 hour. The solution was allowed to stir for 5 hours at -78 ˚C, then quenched with water and allowed to come to room temperature. The reaction was diluted with ethyl acetate, washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica gel, 2:1 hexanes:ethyl acetate) provided 5-iodo-4-methoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**26**) (8.80 g, 88%). *Rf* 0.9 (ethyl acetate); IR: 2973, 1627, 1568, 1435, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, *J* = 6.5 Hz, 6H), 1.52 (d, *J* = 6.7 Hz, 6H), 3.52 (septet, *J* = 6.7 Hz, 1H), 3.89 (septet, *J* = 6.5 Hz, 1H), 3.95 (s, 3H), 6.94 (s, 1H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.44, 20.75, 46.20, 50.81, 56.41, 105.76, 109.62, 156.26, 157.94, 164.86, 167.68; Anal. Calcd for $C_{13}H_{19}IN_2O_2$: C, 43.11; H, 5.29; N, 7.73. Found: C, 43.38; H, 5.01; N, 7.57.



27

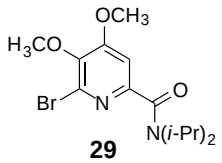
4,5-Dimethoxy-2-pyridine Carboxylic Acid *N*,*N*-Diisopropylamide (27). Sodium methoxide was prepared by treating sodium metal (920 mg, 4 x 10^{-2} mol, 2.0 equiv) with methanol (20 mL) until all the sodium was consumed, and then removing the excess methanol under reduced pressure. DMF (55 mL, freshly distilled from CaH_2) was then added via cannula to the solid sodium methoxide. 5-Iodo-4-methoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**26**) (6.0 g, 1.65 x 10^{-2} mol) and CuI (232 mg, 1.65 x 10^{-2} mol, 0.1 equiv) were added as solids while purging with nitrogen. The reaction was brought to reflux for 1 hour, and then cooled. The DMF was then removed by distillation at aspirator pressure, and the residue was dissolved in ethyl acetate, washed with 1 M NH_4OH, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) provided 4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**27**) (4.06 g, 92%). *Rf* 0.5 (ethyl acetate); IR: 2969, 1625, 1592, 1571, 1025 cm^{-1};^1H NMR ($CDCl_3$, 500 MHz) δ 1.16 (m, 6H), 1.51 (m, 6H), 3.59 (m, 1H), 3.90 (s, 3H), 3.93 (s, 3H), 4.03 (m, 1H), 7.05 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.49, 20.79, 46.07, 50.59, 55.94, 56.59, 105.86, 131.35, 145.63, 150.97, 155.45, 168.41; Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 62.84; H, 8.09; N, 10.55.



28

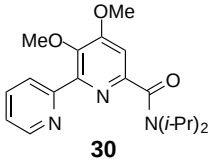
3-Bromo-4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (28). 4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide **27** (0.51g, 1.9 x 10^{-3} mol, 1 equiv) was dissolved in THF (50mL) under a nitrogen atmosphere. The solution was cooled to –78°C and then *n*-BuLi (1.14mL, 2.0M in hexanes, 2.3 x 10^{-3} mol, 1.2 equiv) was added by syringe and the solution was allowed to stir at –78°C for 2 h. Bromine (0.5mL, 9.8 x 10^{-3} mol, 5 equiv) was then added and the solution was stirred at –78°C for 15 minutes before being allowed to warm to room temperature over 2 h. Saturated aqueous sodium thiosulfate (10mL) was then added to quench the excess bromine. The reaction mixture was then diluted with ethyl acetate (50mL) and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, and dried over $MgSO_4$. The organics were filtered through a pad of celite and concentrated under reduced pressure. Purification by flash chromatograhy (SiO_2 deactivated with Et_3N, 2:1 hexanes/ethyl acetate) provided 0.55g (84%) 3-bromo-4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**28**) as a white solid. *Rf* 0.2 (1:1 hexanes/ethyl acetate). ^1H NMR ($CDCl_3$, 500MHz) δ 1.14 (d, *J*= 6.5Hz, 6H),

1.55 (d, *J*= 6.5Hz, 6H), 3.46 (septet, *J*= 6.5Hz, 1H), 3.50 (septet, *J*= 6.5Hz, 1H), 3.93 (s, 3H), 3.99 (s, 3H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 166.51, 153.03, 150.86, 148.72, 133.91, 111.01, 60.94, 56.99, 50.96, 45.97, 20.67, 20.22; IR (methylene chloride): 2972, 1642, 1301, 1025cm^{-1}; Anal. Calcd. for $C_{14}H_{21}BrN_2O_3$: C, 48.71; H, 6.13; N, 8.11. Found: C, 50.19; H, 6.33; N, 8.13.



29

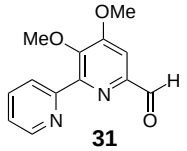
6-Bromo-4,5-dimethoxy-2-pyridine carboxylic acid *N,N*-diisopropylamide (29). LDA was prepared by adding *n*-BuLi (0.96mL, 2.0M, 1.2 equiv) by syringe to freshly distilled diisopropylamine (0.27mL, 1.2 equiv) in THF (25mL) at room temperature under a nitrogen atmosphere. After 10 minutes at room temperature, the base solution was cooled to –78°C. A THF solution (25mL) of 3-bromo-4,5-dimethoxy-2-pyridine carboxylic acid *N,N*-diisopropylamide **28** (0.55g, 1.60 x 10^{-3} mol, 1 equiv) was then added to the cold base solution dropwise by cannula over 30 minutes. The reaction mixture was stirred at –78°C for 1 h and then allowed to warm to –50°C. The cold bath temperature was held between –45°C and –50°C for 3 h. The reaction was then quenched with 1mL of methanol, diluted with ethyl acetate (50mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, and dried over $MgSO_4$. The organics were filtered through a pad of celite and concentrated under reduced pressure. Purification by flash chromatograhy (SiO_2 deactivated with Et_3N, 3:1 hexanes/ethyl acetate) provided 0.44g (80%) 6-bromo-4,5-dimethoxy-2-pyridine carboxylic acid *N,N*-diisopropylamide (**29**) as a pale yellow oil which solidifies upon standing to a white cake. *Rf* 0.6 (1:1 hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.18 (d, *J*= 7.0Hz, 6H), 1.48 (d, *J*= 6.5Hz, 6H), 3.50 (septet, *J*= 7.0Hz, 1H), 3.85 (s, 3H), 3.90 (s, 3H), 3.97 (septet, *J*= 6.5Hz, 1H), 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 166.74, 159.92, 152.50, 143.16, 135.60, 107.28, 60.70, 56.35, 50.91, 46.27, 20.65, 20.38; IR (methylene chloride): 2971, 1635, 1319, 1036cm^{-1}; Anal. Calcd. for $C_{14}H_{21}BrN_2O_3$: C, 48.71; H, 6.13; N, 8.11. Found: C, 48.94; H, 6.17; N, 8.14.



30

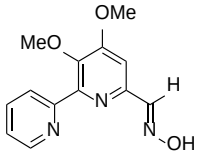
6-(2-pyridyl)-4,5-dimethoxy-2-pyridine carboxylic acid *N,N*-diisopropylamide (30). 2-Bromopyridine (21μL, 1.5 equiv) was added by syringe to a 10mL round bottom flask containing THF (5mL) under a nitrogen atmosphere. The solution was then cooled to –78°C and *t*-BuLi (250μL, 1.8M, 3.1 equiv) was added by syringe. The yellow solution was stirred at –78°C for 20 minutes, then a 5mL THF solution of anhydrous $ZnCl_2$ (63 mg, 4.6 x 10^{-4} mol, 3.2 equiv) was added quickly by cannula and the mixture was allowed to stir at room temperature for 90 minutes. Meanwhile, $Pd_2(dba)_3$ (3.3mg, 0.025 equiv) and PPh_3 (7.4mg, 0.2 equiv) were stirred in 5mL THF for 1 h at room temperature under a nitrogen atmosphere. A 25mL round bottom flask containing the 6-bromo-4,5-dimethoxy-2-pyridine carboxylic acid *N,N*-diisopropylamide (**29**) (0.050g, 1.45 x 10^{-4} mol, 1 equiv) was fitted with a condenser and purged with nitrogen. The pyridylzinc and palladium catalyst solutions were then added to the solution containing amide **29** by cannula, and the mixture was heated to reflux under a nitrogen atmosphere for 16 h. The reaction was quenched by adding EDTA (10mL, 0.1M) and the resulting mixture was then diluted with CH_2Cl_2 (10mL) and made basic with saturated aqueous sodium bicarbonate. The aqueous layer was extracted 3 times with 5mL portions of CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered through a pad of celite, and concentrated under reduced pressure. Purification by flash

chromatograhy (SiO_2 deactivated with Et_3N, 2:1 hexanes/ethyl acetate) followed by a second purification (SiO_2, 3:2 hexanes/ethyl acetate) provided **30** (41 mg, 80%) as a pale yellow solid. *Rf* 0.4 (1:1 hexanes/ethyl acetate). IR (chloroform): 2970, 1630, 1575, 1565, 1364, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 1.17 (d, *J*= 6.5Hz, 6H), 1.53 (d, *J*= 6.8Hz, 6H), 3.53 (septet, *J*= 6.8Hz, 1H), 3.81 (s, 3H), 3.96 (s, 3H), 4.21 (septet, *J*= 6.5Hz, 1H), 7.18 (s, 1H), 7.27 (m, 1H), 7.75 (m, 1H), 8.69 (m 1H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 168.23, 160.22, 156.47, 152.23, 149.74, 148.46, 144.54, 136.15, 124.37, 122.86, 107.19, 61.56, 56.07, 50.77, 46.22, 20.80, 20.53.



31

6-(2-pyridyl)-4,5-dimethoxy-2-formyl-pyridine (31). 6-(2-Pyridyl)-4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**30**) (139 mg, 3.8 x 10^{-4} mol, 1.0 equiv) was dissolved in THF (4 mL) under a nitrogen atmosphere and then cooled to -78 ˚C. Diisobutylaluminum hydride (568 µL, 1.0 M in hexanes, 5.7 x 10^{-4} mol, 1.5 equiv) was added dropwise via syringe. After 15 minutes, the cold bath was removed, and the reaction was allowed to come to room temperature going from a yellow to an orange solution. After 30 minutes at room temperature, the reaction was quenched with 1 M HCl and diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica gel, 10:1 ethyl acetate : triethylamine) provided 6-(2-pyridyl)-4,5-dimethoxy-2-formyl-pyridine (**31**) (63 mg, 68%). IR: 2941, 1707, 1577, 1366 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.83 (s, 3H), 4.02 (s, 3H), 7.34 (M, 1H), 7.59 (s, 1H), 7.81 (m, 2H), 8.80 (m, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.31, 61.49, 104.99, 123.38, 124.76, 136.43, 147.70, 149.53, 149.77, 151.52, 154.77, 159.91, 192.88; Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.97; H, 4.68; N, 11.24.



caerulomycin C

Caerulomycin C. 6-(2-Pyridyl)-4,5-dimethoxy-2-formyl-pyridine (**31**) (50 mg, 2.1 x 10^{-4} mol, 1.0 equiv), NH_2OH•HCl (356 mg, 5.1 x 10^{-3} mol, 25 equiv), pyridine (1 mL) and ethanol (absolute, 5 mL) were heated to 75 ˚C for 30 minutes. The contents were then transferred to a liquid-liquid continuous extractor along with 5 mL saturated $NaHCO_3$ and extracted with ethyl acetate for 48 hours. The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization from ethanol (4 mL) provided caerulomycin C (34 mg, 64%); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.73 (s, 3H), 3.96 (s, 3H), 7.41 (M, 1H), 7.46 (s, 1H), 7.66 (m, 1H), 7.88 (m, 1H), 8.01 (s, 1H), 8.65 (m, 2H), 11.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.00, 61.01, 103.50, 123.16, 123.98, 136.40, 143.84, 148.19, 148,50, 148,74, 150.99, 155.89, 159.42**;** Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.20; H, 4.98; N, 16.41. The spectral properties for **1** are in agreement with those reported in the literature.