**Supporting Information**

# Atypically modified carbapenem antibiotics display improved anti-mycobacterial activity in the absence of β-lactamase inhibitors.

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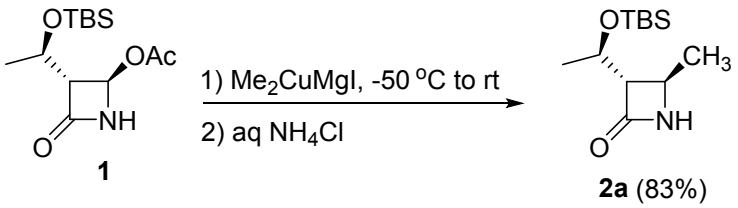
Supporting Information

Supporting Information Part 1: Procedures for the Synthesis of Atypical Carbapenems **10a**, **10b**, **13a**, and **13b**.



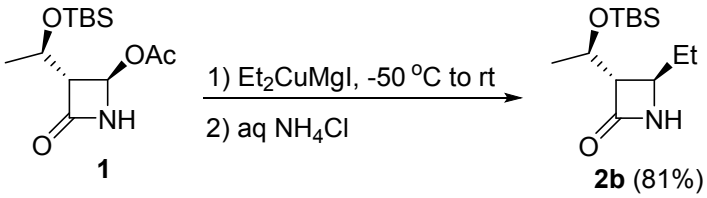

**2a**: A solution of methyl magnesium iodide was prepared as follows. To a stirred slurry of magnesium turnings (30.5 g, 1.26 mol, 1.5 eq) in anhydrous diethyl ether was added a small crystal of iodine, and then a solution of methyl iodide (118.6 g, 52 mL, 0.835 mol) in 50 mL of anhydrous diethyl ether dropwise at such a rate as to maintain a gentle reflux. Once complete, the reaction was allowed to stir under an inert atmosphere at room temperature overnight.

To a rapidly stirred (overhead stirrer) slurry of copper (I) iodide (79 g, 0.42 mol) in anhydrous THF (2 L) at room temperature was added dimethyl sulfide (25.8 g, 30.7 mL, 0.42 mol). This solution was allowed to stir under an inert atmosphere for 30 min, then chilled to -60 °C. To this rapidly stirred solution was added the ethereal solution of methyl magnesium iodide prepared above, at a rate so as to maintain the temperature below -40 °C. Then the temperature of the reaction mixture was allowed to rise to a temperature between -10 and 0 °C, and stirred at that temperature for 30 min. The solution was then again cooled to -60 °C and a solution of **1** (60 g, 0.208 mol) in 300 mL anhydrous THF was added slowly. The reaction was then allowed to warm to room temperature over the course of 90 min. The reaction was again chilled to 0 °C, and remaining organometallic quenched by slowly pouring the reaction into a rapidly stirred saturated aqueous solution of ammonium chloride (vigorously evolves methane and ammonia gas!, exothermic !). The THF was then removed *in vacuo*, water was added, and the product extracted with EtOAc. The combined EtOAc layers were washed with dilute aqueous ammonium hydroxide to remove copper. The organic layers were dried over $Na_2SO_4$, concentrated in vacuo, and the product purified by silica gel chromatography (increasing 2 to 40% EtOAc/$CH_2Cl_2$) to produce **2a** (42.2 g, 83% yield) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 1H), 5.29 (s, 1H), 4.19 (m, 1H), 3.83 (m, 1H), 2.69 (m, 1H), 1.3 (dd, J= 54 Hz, 3H), 0.86 (s, 9H), 0.067 (S, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 168.99, 65.74, 65.50, 47.88, 25.74, 25.59, 22.33, 20.59, 17.77, -4.34, -4.62, -4.75.

IR: 3415.79, 3229.86, 2959.39, 2929.27, 2893.85, 2857.09, 2708.17, 2249.20, 1754.52, 1471.48, 1462.92, 1446.72, 1378.34, 1347.43, 1333.39, 1299.97, 1254.06, 1187.16, 1143.14, 1096.71, 1037.92, 1005.93, 986.68, 956.49, 909.25, 835.17, 809.60, 766.45, 734.96, 661.74, 646.36.

HRMS: calcd $C_{12}H_{26}NO_2Si^+$ $[M + H]^+$ 244.1727, obs 244.1686



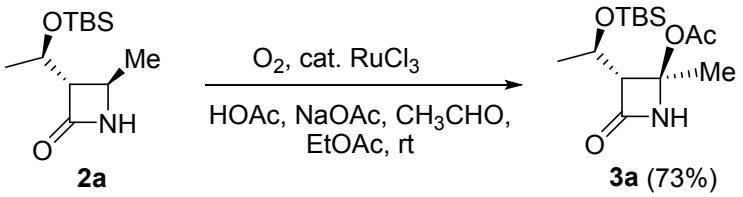

**2b**: compound **2b** was prepared as described above for **2a**, using ethyl iodide in place of methyl iodide and keeping the organocuprate reagent at -15 to -10 °C (instead of -10 to 0 °C). Purified yield of **2b** was 81%.

$^1$H NMR (400 MHz, $CDCl_3$): δ 5.32 (s, 1H), 2.5 (m, 1H), 2.14 (s, 1H), 1.87 (t, j= 3.2 Hz, 3H), 1.26 (q, j= 2.4 Hz, 2H), 0.92 (s, 9H), 0.094 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.20, 65.66, 63.92, 52.69, 27.98, 25.88, 22.75, 22.74, 17.94, 10.70, -4.26, -4.91.

IR: 3311.64, 2931.54, 2886.10, 2857.70, 2739.21, 2709.67, 1782.31, 1464.07, 1369.46, 1251.31, 1160.75, 1102.39, 1016.07, 990.17, 945.01, 885.89, 834.36, 812.53, 776.38, 752.23, 660.51.

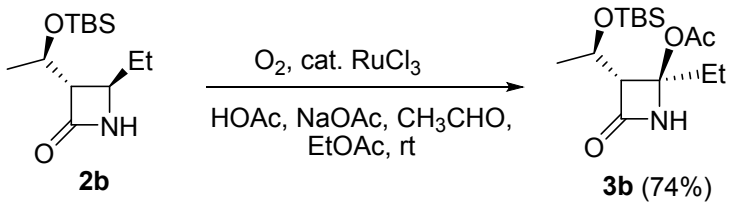
HRMS: calcd $C_{13}H_{28}NO_2Si^+$ $[M + H]^+$ 258.1884, obs 258.1843




**3a**: To a solution of **2a** (5.0 g, 20.5 mmol) in anhydrous ethyl acetate (205 mL) was added anhydrous sodium acetate (1.01 g, 12.3 mmol, 0.6 eq) and anhydrous acetic acid (10.25 mL, 10.8 g, 179 mmol, 8.7 eq). Commercial $RuCl_3$ was placed in a flask with a Teflon coated stir bar, put under high vacuum (0.1 mm Hg), and the flask heated with a Bunsen burner with external manual agitation until last traces of water were removed and the consistency was that of finely-divided free-flowing black powder (approximately 15 min). This dried $RuCl_3$ (0.3 g, 1.44 mmol, 0.07 eq) was allowed to cool to rt and then added to the reaction vessel. The flask was then sealed tightly with a wired septum and the flask placed under dynamic oxygen pressure (12 psi) using a pressurized needle through the septum and chilled in an external bath to 10-12 $^{o}$C. Freshly (twice) distilled acetaldehyde (11.8 g, 15 mL, 268 mmol, 13.4 eq) was then added using a chilled syringe. The reaction was then allowed to stir at 12 $^{o}$C while maintaining external pressure of oxygen and monitored by $^{1}$H NMR. Reaction completed in 1-2 h, and then was diluted with cold hexane and the hexane layer washed with ice cold brine until the pH of the aqueous layer reached 7 (approximately 7 to 10 washes). The organic layer was dried over $Na_2SO_4$ and evaporated *in vacuo* to afford **3a** (4.5 g, 73% crude yield) as a purple oil. This material was unstable toward further purification and was directly used in the next reaction.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.05 (S, 1H), 4.31 (m, 1H), 3.05 (d, J= 9.2 Hz, 1H), 2.04 (s, 3H), 1.82 (s, 3H), 1.33 (d, 6Hz, 3H), 0.86 (s, 9H), 0.067 (s, 6H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 170.22, 166.39, 88.61, 70.25, 68.75, 67.32, 64.69, 25.49, 21.90, 19.69, 17.64, 0.82, -3.98, -4.41.

IR: 3327.71, 2957.92, 2931.39, 2887.40, 2858.22, 2253.32, 1781.31, 1472.47, 1463.20, 1416.50, 1362.49, 1254.34, 1222.80, 1171.03, 1092.37, 1015.43, 963.78, 914.20, 835.01, 812.13, 778.15, 733.78, 647.79.

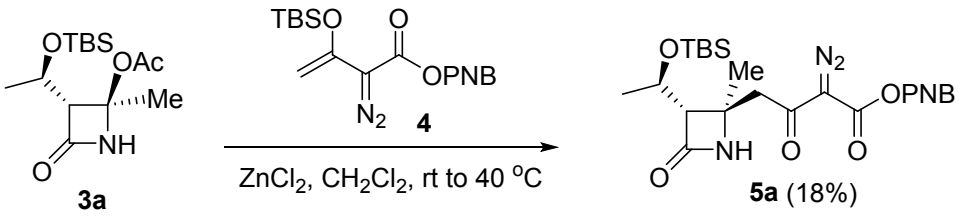



**3b**: To a solution of **2b** (10.0 g, 38.8 mmol) in anhydrous ethyl acetate (388 mL) was added anhydrous sodium acetate (1.8 g, 22 mmol, 0.6 eq) and anhydrous acetic acid (23.1 g, 22 mL, 384 mmol, 9.9 eq). Commercial $RuCl_3$ was placed in a flask with a Teflon coated stir bar, put under high vacuum (0.1 mm Hg), and the flask heated with a Bunsen burner with external manual agitation until last traces of water were removed and the consistency was that of finely-divided free-flowing black powder (approximately 15 min). This dried $RuCl_3$ (3.0 g, 14.5 mmol, 37 mol%) was allowed to cool to rt and then added to the reaction vessel. The flask was then sealed tightly with a wired septum and the flask placed under dynamic oxygen pressure (12 psi) using a pressurized needle through the septum and chilled in an external bath to 10-12 $^{o}$C. Freshly (twice) distilled acetaldehyde (23.6 g, 30 mL, 536 mmol, 13.8 eq) was then added using a chilled syringe. The reaction was then allowed to stir at 12 $^{o}$C while maintaining external pressure of oxygen and monitored by $^{1}$H NMR. Reaction completed in 1-2 h, and then was diluted with cold hexane and the hexane layer washed with ice cold brine until the pH of the aqueous layer reached 7 (approximately 7 to 10 washes). The organic layer was dried over $Na_2SO_4$ and evaporated *in vacuo* to afford **3b** (9.1 g, 74% crude yield) as a purple oil. This material was unstable toward further purification and was directly used in the next reaction.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ5.89 (s, 1H), 4.29 (m, 1H), 2.64 (q, J= 0.8 Hz, 2H), 1.27 (d, j= 3Hz, 3H), 1.05 (t, J= 3.2 Hz, 3H), 0.873 (s, 9H), 0.088 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$): 170.38, 166.22, 90.01, 66.10, 64.47, 28.77, 25.51, 22.21, 21.52, 17.72, 9.02, 0.84, -4.13, -4.76.

IR: 3092.33, 2963.11, 2927.92, 2895.10, 2853.16, 2282.96, 1754.39, 1710.67, 1463.12, 1444.34, 1381.09, 1369.22, 1348.24, 1332.02, 1300.65,1252.41, 1185.02, 1139.74, 1099.13, 1066.49, 1047.11, 961.20, 835.24, 807.11, 775.92, 739.17, 714.54, 662.98.

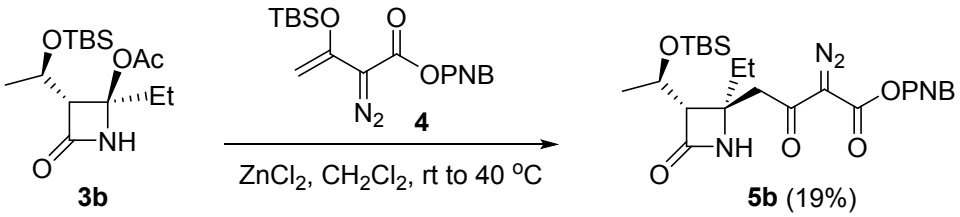



**5a**: To a solution of **3a** (3.0 g, 9.95 mmol) and TBS enol ether **4** (5.9 g, 15.6 mmol, 1.57 eq) in 25 mL dry $CH_2Cl_2$ was added a solution of $ZnCl_2$ in $Et_2O$ (7.3 mL, 1 M, 7.3 mmol, 0.7 eq) and the flask was heated to reflux. The reaction was monitored by $^1$HNMR, and once completed (30 min), the reaction was cooled to room temperature and diluted with EtOAc. The solution was washed with satd aq $NaHCO_3$ once and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried over $Na_2SO_4$ and then evaporated *in vacuo*. The crude material was purified by silica gel flash chromatography via gradient elution (2.5:97.5 EtOAc/ $CH_2Cl_2$ to 40/60 EtOAc/ $CH_2Cl_2$) to afford **5a** (0.92 g, 18% yield) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, J= 287 Hz, 8.4 Hz 4H), 6.38 (s, 1H), 5.35 (d, J= 14Hz, 2H), 4.27 (t, J= 2.8 Hz, 1H), 3.59 (dd, J= 292 Hz, 16.8 Hz, 2H), 2.85 (s, 1H), 1.538 (s, 3H), 1.40 (d, J=12, 3H), 1.33 (t, J= 13.6 Hz, 2 H), 0.085 (s, 9H), 0.866 (S, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$): 189.84, 167.09, 160.56, 147.85, 141.95, 128.66, 128.56, 123.88, 123.81, 66.80, 65.43, 65.21, 55.71, 49.90, 25.69, 25.33, 22.29, 21.15, 19.78, 17.76, -3.30, -4.82.

HRMS: calcd $C_{23}H_{33}N_4O_7Si^+$ $[M + H]^+$ 505.2113, obs 505.2836



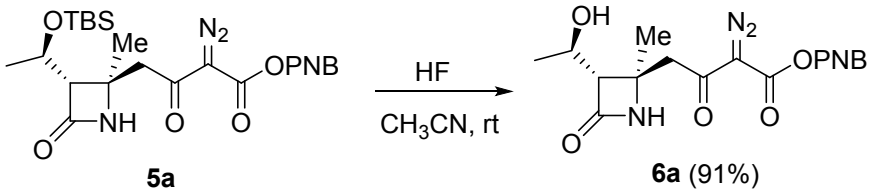

**5b**: To a solution of **3b** (12.3 g, 38.85 mmol) and TBS enol ether **4** (21.2g., 56.2 mmol, 1.45 eq) in 50 mL dry $CH_2Cl_2$ was added a solution of $ZnCl_2$ in $Et_2O$ (27 mL, 1 M, 27 mmol, 0.7 eq) and the flask was heated to reflux. The reaction was monitored by $^1$HNMR, and once completed (30 min), the reaction was cooled to room temperature and diluted with EtOAc. The solution was washed with satd aq $NaHCO_3$ once and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried over $Na_2SO_4$ and then evaporated *in vacuo*. The crude material was purified by silica gel flash chromatography via gradient elution (2.5:97.5 EtOAc/ $CH_2Cl_2$ to 40/60 EtOAc/ $CH_2Cl_2$) to afford **5b** (3.9 g, 19% yield) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J= 282 Hz, 20.4 Hz, 4 H), 6.21 (s, 1H), 5.36 (d, J= 36.8 Hz, 2 H), 4.29 (m, 1 H), 3.74 (dd, J = 343 Hz, 14.8 Hz, 2 H), 3.14 (d, J= 8.8 Hz, 1 H), 2.02 (q, J= 7.6 Hz, 1H), 1.90 (q, J = 7.6 Hz, 1 H), 1.34 (d, J= 36.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.932 (s, 9H), 0.138 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.20, 189.52, 168.88, 167.61, 160.90, 147.94, 141.85, 128.63, 123.95, 65.73, 61.61, 59.41, 52.50, 46.92, 27.89, 25.69, 22.64, 22.68, 17.82, 10.60, 8.05, 0.92, -3.33, -4.36.

IR: 3258.47, 2958.53, 2930.65, 2884.27, 2856.98, 2140.77, 1751.98, 1651.27, 1608.18, 1525.54, 1471.60, 1462.71, 1375.46, 1347.80, 1258.48, 1214.02, 1188.42, 1103.18, 1039.56, 987.42, 957.23, 896.93, 834.10, 811.33, 776.83, 739.51.

HRMS: calcd $C_{24}H_{34}N_4NaO_7Si^+$ $[M + Na]^+$ 541.2089, obs 541.2043



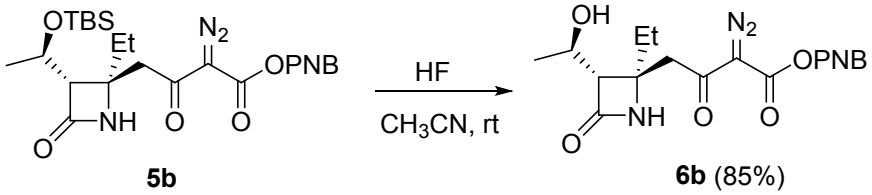

**5a** **6a** (91%)

**6a**: To a solution of **5a** (2g, 3.96 mmol) in 20 mL of acetonitrile, 2 mL of HF (48% aqueous) was added. The reaction was stirred at rt and monitored by thin layer chromatography and $^1$HNMR. If needed, additional HF was added to insure completion in 1-3 h. Once complete, the reaction was further diluted with 100 mL ethyl acetate, and finely ground $NaHCO_3$ was carefully added to the reaction (*caution* $CO_2$ evolution) to attain pH= 7. The reaction was filtered to remove the precipitated NaF, and evaporated *in vacuo* to afford **6a** (1.4 g, 91% yield) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, J= 280 Hz, 8.3 Hz, 4H), 5.34 (q, J=18.4 Hz, 13.2 Hz, 2H), 4.84 (s, 1H), 4.39 (m, 1H), 3.22 (d, J= 10` Hz, 1H), 2.7 (dd, J= 44.4, 18 Hz, 2H), 1.63 (s, 3H), 1.42 (d, J= 6.4 Hz, 3H), 0.89 (s, 1H), 0.085 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 190.53, 167.18, 160.14, 147.43, 141.86, 128.37, 123.50, 65.32, 63.51, 54.89, 49.67, 49.07, 48.64, 48.00 21.24, 20.29.

IR: 3362.70, 2969.02, 2143.11, 1722.43, 1648.53, 1522.75, 1347.90, 1306.60, 1216.14, 1127.81, 1025.25, 853.56, 739.51.




**5b** **6b** (85%)

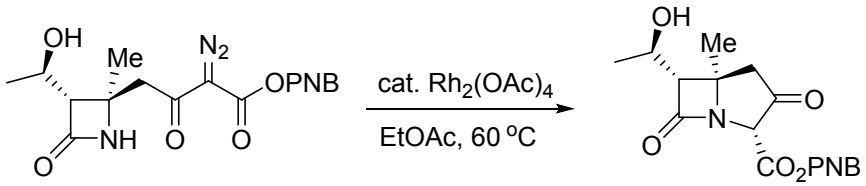
**6b**: To a solution of **5b** (6g, 11.6 mmol) in 40 mL of acetonitrile, 5 mL of HF (48% aqueous) was added. The reaction was stirred at rt and monitored by thin layer chromatography and $^1$HNMR. If needed, additional HF was added to insure completion in 1-3 h. Once complete, the reaction was further diluted with 200 mL ethyl acetate, and finely ground $NaHCO_3$ was carefully added to the reaction (*caution* $CO_2$ evolution) to attain pH= 7. The reaction was filtered to remove the precipitated NaF, and evaporated *in vacuo* to afford **6b** (4.0 g, 85% yield) as white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J= 289 Hz, 8.5 Hz, 4H), 5.35 (s, 2H), 4.23 (m, 1H), 3.35 (dd, J= 260 Hz, 18.4 Hz, 2 H), 2.05 (m, 1H), 1.88 (m, 1H), 1.35, (d, J= 4 Hz, 3H), 0.92 (t, J= 7 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 190.98, 167.27, 160.44, 147.99, 141.88, 128.82, 124.02, 66.76, 65.74, 63.57, 58.61, 46.13, 26.04, 21.85, 8.57.

IR: 3457.32, 2967.10, 2348.64, 2145.69, 1722.53, 1640.10, 1607.84, 1523.19, 1347.83, 1316.92, 1261.20, 1214.38, 1129.57, 1040.55, 1015.59, 853.38, 799.72, 738.72.

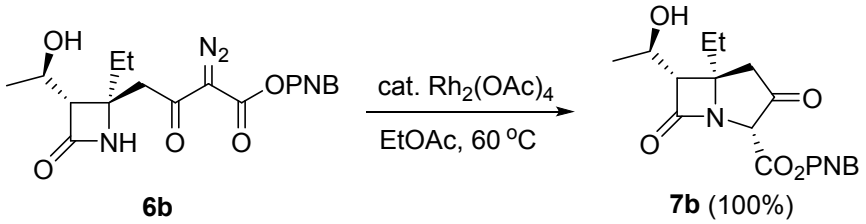
HRMS: calcd $C_{18}H_{20}N_4NaO_7^+$ $[M + Na]^+$ 427.1224, obs 427.1187




**6a** **7a** (100%)

To a solution of **6a** (1.3g, 3.33 mmol) in 50 mL dry EtOAc was added a catalytic amount of $Rh_2(OAc)_4$ (15 mg, 0.034 mmol, 0.01 eq). The reaction was warmed to 60 °C for 30 min while monitoring by $^{1}$HNMR. Once completed, the reaction was cooled to room temperature and the solvent was evaporated *in vacuo* to produce 1.21 g (100% crude yield) of **7a**. This material was unstable toward further purification and was used directly in the next step.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, J= 232 Hz, 8.4 Hz, 4H), 5.31 (q, J= 19.6 2H), 4.15 (q, J= 8 Hz, 1H), 3.68 (q, J= 10 Hz, 1H), 3.18 (d, J= 4Hz, 1H), 2.65 (dd, J= 40 Hz, 20 Hz, 1H)), 2.08 (s, 3H), 1.55 (dd, J= 30 Hz, 15 Hz, 3H), 1.45 (d, J= 15 Hz, 1H), 1.28 (m, 1H).

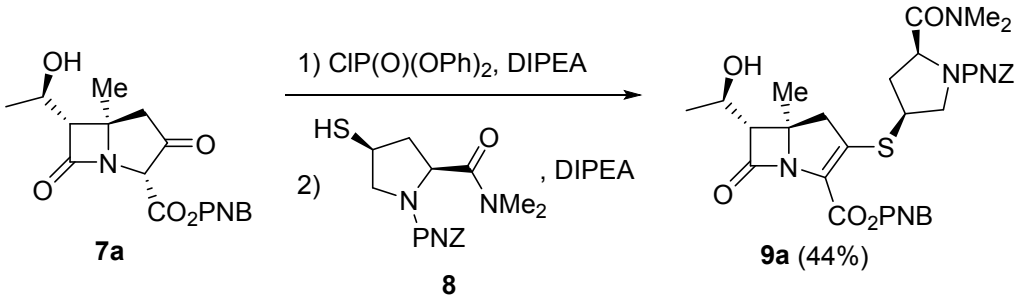



**6b** **7b** (100%)

**7b**: To a solution of **6b** (2.34 g, 5.79 mmol) in 100 mL dry EtOAc was added a catalytic amount of $Rh_2(OAc)_4$ (30 mg, 0.034 mmol, 0.01 eq). The reaction was warmed to 60 °C for 30 min while monitoring by $^1$HNMR. Once completed, the reaction was cooled to room temperature and the solvent was evaporated *in vacuo* to produce 2.18 g (100% crude yield) of **7b**. This material was unstable toward further purification and was used directly in the next step.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J= 272 Hz, 88 Hz, 4 H), 5.40 (dd, J= 38 Hz, 13.2 Hz, 2 H), 4.83 (s, 1H), 4.45 (m, 1H), 3.25 (d, J= 9.6 Hz, 1 H), 2.5 (dd, J= 158 Hz, 17.6 Hz, 2H), 1.95 (m, 2H), 1.49 (d, J= 3.5 Hz, 3H), 1.16 (dt, J=108 HZ, 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 189.62, 167.71, 161.00, 141.95, 128.73, 124.05, 65.55, 61.71, 52.60, 46.02, 27.46, 25.75, 22.68, 17.92, 10.70, 8.15, 1.02, -3.23, -4.26.




**7a** **8** **9a** (44%)

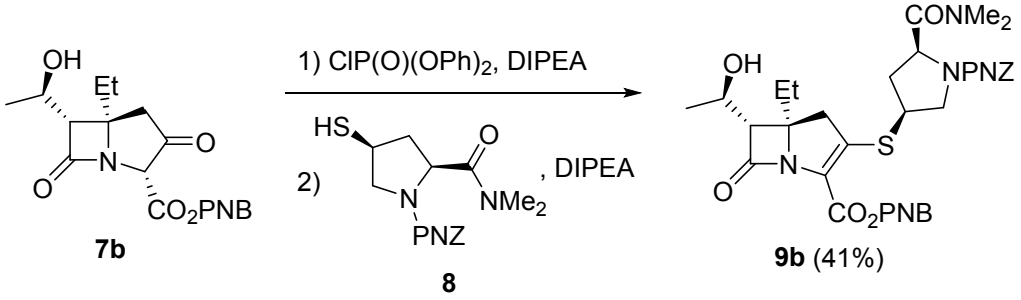
**9a**: A solution of **7a** (1.3g, 3.59 mmol) in 10 mL of dry $CH_3CN$ under inert atmosphere was cooled t0 -35 °C. Diphenyl phosphoryl chloride (0.96 g, 0.74 mL, 3.59 mmol, 1 eq) was then added to the flask, followed by a slow addition of N,N-diisopropylethylamine (0.46 g, 0.625 mL, 3.59 mmol, 1 eq), and the reaction was allowed to stir for 30 minutes, monitoring by tlc, to generate the intermediate enol phosphate, which was not isolated. Once the enol phosphate had formed, thiol **8** (1.27 g, 3.59 mmol, 1 eq) and an additional 1

eq of DIPEA (0.46 g, 0.625 mL, 3.59 mmol, 1 eq) were added. The reaction was then allowed to warm to room temperature over a course of 1 h, while monitoring by $^1$H NMR and TLC. Once completed, the reaction was diluted with EtOAc (200 mL) and successively washed with satd aq $NaHCO_3$ and satd aq $NH_4Cl$. The resultant EtOAc solution was then dried over $Na_2SO_4$, evaporated *in vacuo*, and further purified by column chromatography using an increasing gradient of MeOH/$CH_2Cl_2$ (0% to 10% in 1% increments) as eluent to afford **9a** (1.1 g, 44% yield) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J= 8.8 Hz, 2H), 7.67 (d, J= 8.4 Hz, 2H), 7.50 (dd, J= 28.8 Hz, 8.4 Hz, 2H), 5.54 (d, J= 13.6 Hz, 2H), 5.24 (m, 1H), 4.74, (m, 1H), 4.31 (m, 1H), 3.57 (m, 1H), 3.25 (dd, J= 56 Hz, 14.4 Hz, 2H), 3.09 (dd, J= 78 Hz, 4 Hz, 6H), 2.8 (m, 1H), 1.99 (m, 1H), 1.62 (d, J= 6 Hz, 3H), 1.45 (d, J= 6 Hz, 3H).

IR: 3429.25, 3114.77, 3080.51, 2970.22, 1773.76, 1708.32, 1648.96, 1606.81, 1520.54, 1429.55, 1403.63, 1375.21, 1345.86, 1287.63, 1208.91, 1173.33, 1149.68, 1111.84, 1046.69, 1014.02, 853.63, 853.63, 803.04, 778.75, 765.87, 736.85, 684.52.

HRMS: calcd $C_{32}H_{35}N_5NaO_{11}S^+$ $[M + Na]^+$ 720.1946, obs 720.1904




**9b**: A solution of **7b** (2.34 g, 6.22 mmol) in 30 mL of dry $CH_3CN$ under an inert atmosphere was cooled to -35 °C. Diphenyl phosphoryl chloride (1.67 g, 1.29 mL, 6.22 mmol, 1 eq) was then added to the flask, followed by a slow addition of N,N-diisopropylethylamine (0.804 g, 1.08 mL, 6.22 mmol, 1 eq), and the reaction was allowed to stir for 30 minutes, monitoring by TLC, to generate the intermediate enol phosphate, which was not isolated. Once the enol phosphate had formed, thiol **8** (2.20 g, 6.22 mmol, 1 eq) and an additional 1 eq of DIPEA (0.804 g, 1.08 mL, 6.22 mmol, 1 eq) were added. The reaction was then allowed to warm to room temperature over a course of 1 h, while monitoring by $^1$H NMR and TLC. Once completed, the reaction was diluted with EtOAc (400 mL) and successively washed with satd aq $NaHCO_3$ and satd aq $NH_4Cl$. The resultant EtOAc solution was then dried over $Na_2SO_4$, evaporated *in vacuo*,

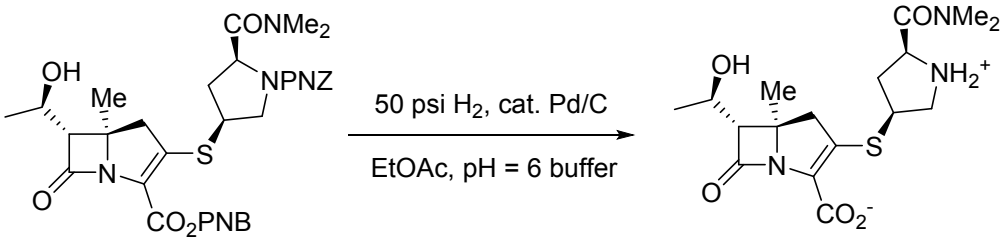
and further purified by column chromatography using an increasing gradient of MeOH/$CH_2Cl_2$ (0% to 10% in 1% increments) as eluent to afford **9b** (1.8 g, 41% yield) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.20 (m, 4H), 7.64 (d, J= 8.8 Hz, 2H), 7.47 (dd, J= 35 Hz, 8.8 Hz, 2 H), 5.52 (d, J= 14 Hz, 2H), 5.22 (m, 1H), 5.18 (dd, J= 77.2 Hz, 14 Hz, 2H), 4.15 (m, 1H), 3.65 (m, 1H), 3.55 (m, 1H), 3.26 (m, 2H), 3.09 (d, J= 78 Hz, 6H), 2.75 (m, 1H), 2.04 (m, 1H), 1.91 (m, 2H), 1.40 (d, J= 6 Hz, 3H), 0.99 (t, J= 7.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.86, 170.52, 160.54, 153.49, 153.02, 147.43, 146.01, 143.75, 143.06, 127.95, 124.34, 124.21, 123.66, 123.57, 69.04, 65.73, 65.13, 64.28, 64.17, 56.18, 55.85, 53.80, 52.90, 45.98, 41.44, 40.70, 37.14, 36.89, 36.06, 27.60, 22.67, 7.68, 0.91.

IR: 3412.08, 2917.18, 2282.69, 1770.98, 1708.50, 1650.00, 1606.39, 1520.45, 1403.11, 1345.69, 1281.09, 1206.45, 1147.09, 1110.40, 1036.35, 735.94.

HRMS: calcd $C_{33}H_{37}N_5NaO_{11}S^+$ $[M + Na]^+$ 734.2102, obs 734.2021




**9a** **10a** (46%)

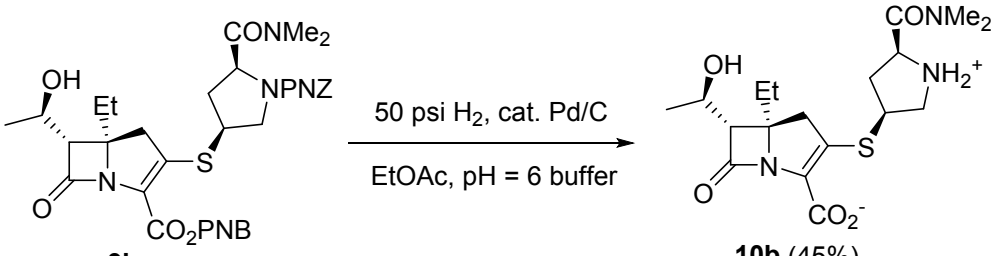
A two-phase solution of **9a** (0.55 g, 0.79 mmol) in 80 mL of EtOAc and 40 mL of pH 6 aqueous phosphate buffer solution (0.3 M) was placed in a 250 mL Parr hydrogenation vessel. This solution was degassed by bubbling argon through it for 5 min, then 10% Pd on carbon (0.55 g) was added. The vessel was connected to the Parr apparatus, further degassed by two successive evacuation-argon repressurization cycles, then evacuated once more and subjected to hydrogen pressure at 55 psi and shaken for 90 min at this pressure. The hydrogen gas was completely removed under vacuum, the vessel opened to air, the resultant solution was filtered through celite to remove the catalyst. The filtrate was placed in a separatory funnel and the aqueous (product) layer was separated. The aqueous layer was further washed with $Et_2O$ to remove traces

of EtOAc and remaining unionized organic material. Then the aqueous layer was further subjected to vacuum (rotary evaporator) to remove last traces of diethyl ether and to partially reduce the total volume. The aqueous layer was then placed on a column of Diaion CHP20P resin and eluted with increasing percentage of ethanol/water (0 to 40% in 5% increments). Tubes containing the product were identified by inspection of the UV of each fraction, those tubes displaying the carbapenem 296 nm absorption were combined, and the solvent was removed *in vacuo*. The remaining aqueous solution was transferred to a small vial, frozen, and lyophilized overnight to produce the purified carbapenem antibiotic **10a** (0.138 g, 46% yield) as white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 1H), 4.60 (t, J= 8.4 Hz, 1H), 4.33 (m, 1H), 3.98 (t, J= 6.4 Hz, 1H), 3.64 (q, J= 6.8 Hz, 1H), 3.36 (m, 2H), 3.09 (d, J= 47 Hz, 6H), 2.90 (d, J= 22 Hz, 2H), 1.87 (m, 1H), 1.55 (s, 3H), 1.34 (d, 66 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 178.0, 170.0, 168.5, 137.5, 129.7, 66.5, 66.4, 63.00, 60.5, 58.8, 52.0, 47.6, 41.7, 37.5, 36.5, 36.4, 22.0, 21.5.

HRMS: calcd $C_{17}H_{26}N_3O_5S^+$ $[M + H]^+$ 384.1588, obs 384.1545




**9b** **10b** (45%)

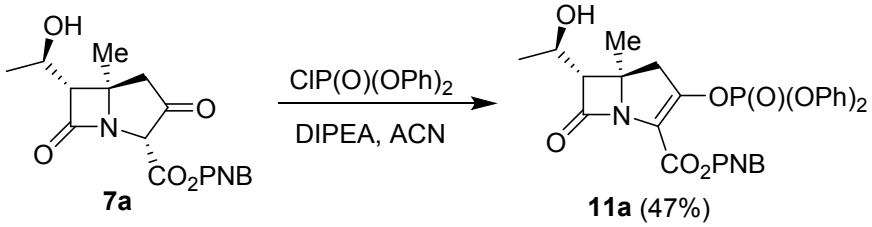
**10b**: A two-phase solution of **9b** (0.60 g, 0.84 mmol) in 30 mL of EtOAc and 30 mL of pH 6 aqueous phosphate buffer solution (0.3 M) was placed in a 250 mL Parr hydrogenation vessel. This solution was degassed by bubbling argon through it for 5 min, then 10% Pd on carbon (0.60 g) was added. The vessel was connected to the Parr apparatus, further degassed by two successive evacuation-argon repressurization cycles, then evacuated once more and subjected to hydrogen pressure at 55 psi and shaken for 90 min at this pressure. The hydrogen gas was completely removed under vacuum, the vessel opened to air, the resultant solution was filtered through celite to remove the catalyst. The filtrate was

placed in a separatory funnel and the aqueous (product) layer was separated. The aqueous layer was further washed with $Et_2O$ to remove traces of EtOAc and remaining unionized organic material. Then the aqueous layer was further subjected to vacuum (rotary evaporator) to remove last traces of diethyl ether and to partially reduce the total volume. The aqueous layer was then placed on a column of Diaion CHP20P resin and eluted with increasing percentage of ethanol/water (0 to 40% in 5% increments). Tubes containing the product were identified by inspection of the UV of each fraction, those tubes displaying the carbapenem 296 nm absorption were combined, and the solvent was removed *in vacuo*. The remaining aqueous solution was transferred to a small vial, frozen, and lyophilized overnight to produce the purified carbapenem antibiotic **10b** (0.15 g, 45% yield) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 4.58 (s, 1H), 3.43 (m, 2H), 3.29 (d, J=17.6 Hz, 2H), 3.02 (d, J= 4.4 Hz, 6H), 1.98 (m, 1H), 1.85 (m, 1H), 1.33 (d, J= 6.4 Hz, 3H), 0.97 (t, J= 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 182.09, 171.06, 170.79, 138.38, 134.87, 67.02, 66.44, 61.01, 54.74, 47.27, 43.88, 39.31, 38.53, 38.05, 29.90, 214.12, 18.83, 9.83.

HRMS: calcd $C_{18}H_{28}N_3O_5S^+$ $[M + H]^+$ 398.1744, obs 398.1708

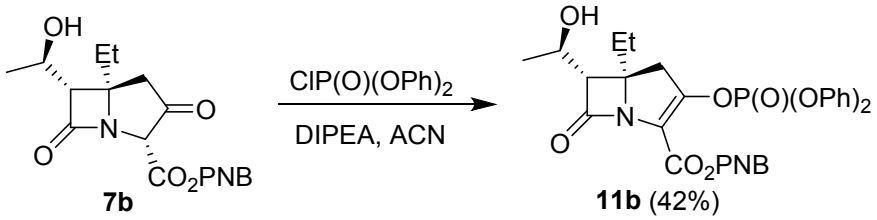



**11a**: Diphenyl phosphoryl chloride (0.89 g, 0.68 mL, 3.31 mmol, 1 eq) was added to a cold (-35 $^o$C) solution of **7a** (1.2 g, 3.31 mmol) in 10 mL of dry $CH_3CN$. Subsequently, diisopropylethylamine (0.43 g, 0.58 mL, 3.31 mmol, 1 eq) was added to the reaction dropwise over a period of 5 min. The reaction was allowed to warm to -20 $^o$C over a period of 30 min, while monitoring by TLC. Once completed, the reaction was diluted with EtOAc (100 mL), washed with aqueous $NH_4Cl$, dried over $Na_2SO_4$, and then evaporated *in vacuo*. The crude material was purified by silica gel flash chromatography via gradient elution (0.5/99.5 MeOH/$CH_2Cl_2$ to 6/94 MeOH/ $CH_2Cl_2$) to afford **11a** (0.92 g, 47% yield) as a white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, J= 236 Hz, 4 Hz, 4H), 7.30 (dd, J= 63 Hz, 6.8 Hz, 4 Hz, 10H), 5.36 (dd, J= 82 Hz, 14 Hz, 2 H), 4.25 (m, 1H), 3.15 (d, J= 173 Hz, 21 Hz, 2H), 3.16 (d, J= 10 Hz, 1H), 1.74 (d, J= 10 Hz, 1H), 1.58 (s, 3H), 1.43 (d, J= 18.4 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 176.42, 159.18, 152.42, 150.03, 147.62, 142.83, 129.93, 128.42, 126.03, 123.78, 120.17, 117.47, 68.58, 65.28, 64.68, 59.73, 45.18, 22.68, 21.63, 1.12.

IR: 3455.73, 1778.25, 1724.91, 1637.25, 1522.40, 1488.46, 1345.79, 1297.66, 1194.34, 1012.38, 971.78, 851.65, 773.25.




**7b** **11b** (42%)

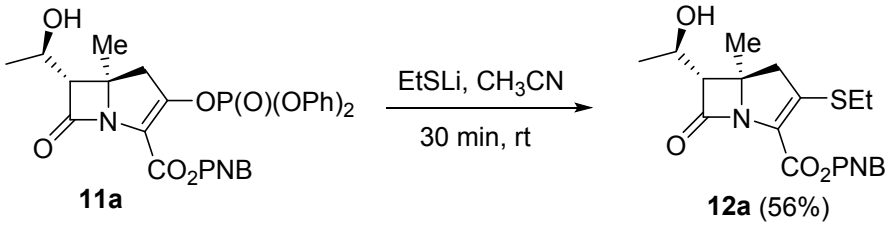
**11b**: Diphenyl phosphoryl chloride (1.67 g, 1.28 mL, 6.22 mmol, 1 eq) was added to a cold (-35 °C) solution of **7b** (2.34 g, 6.22 mmol) in 15 mL of dry $CH_3CN$. Subsequently, diisopropylethylamine (0.804 g, 1.08 mL, 6.22 mmol, 1 eq) was added to the reaction dropwise over a period of 5 min. The reaction was allowed to warm to -20 °C over a period of 30 min, while monitoring by TLC. Once completed, the reaction was diluted with EtOAc (150 mL), washed with aqueous $NH_4Cl$, dried over $Na_2SO_4$, and then evaporated *in vacuo*. The crude material was purified by silica gel flash chromatography via gradient elution (0.5/99.5 MeOH/$CH_2Cl_2$ to 6/94 MeOH/ $CH_2Cl_2$) to afford **11b** (1.6 g, 42% yield) as a white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J= 248 Hz, 5.2 Hz, 4 H), 7.28 (m, 5H), 5.32 (dd, J= 81.2 Hz, 4 Hz, 2H), 4.21 (m, 1H), 3.17 (d, J= 4 Hz, 1H), 3.17 (dd, J= 49.6 Hz, 4 Hz, 2H), 2.18 (s, 1H), 2.02 (m, 1 H), 1.84 (m, 1H), 1.30 (d, J= 6 Hz, 3H), 0.923 (t, J= 4 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 177.26, 158.85, 152.25, 152.19, 149.77, 147.49, 142.64, 129.98, 129.79, 129.52, 128.00, 126.12, 123.64, 119.93, 118.62, 118.51, 69.54, 65.16, 64.22, 62.95, 41.50, 27.74, 22.59, 7.36.

IR: 3330.57, 3076.23, 2973.44, 2252.61, 1762.98, 1639.31, 1590.35, 1522.95, 1489.09, 1457.42, 1385.69, 1347.37, 1296.95, 1186.99, 1163.02, 1106.84, 1072.32, 1046.82, 1025.78, 1012.10, 969.62, 912.30, 850.68, 776.44, 735.26, 689.20, 647.55.

HRMS: calcd $C_{30}H_{30}N_2O_{10}P^+$ $[M + H]^+$ 609.1633, obs 609.1583




**11a** **12a** (56%)

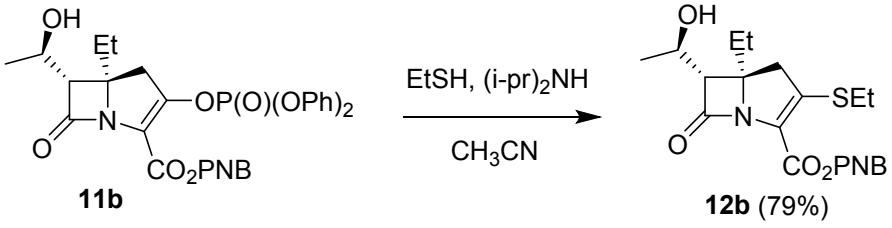
**12a**: *n*-BuLi (2.5 M in hexanes, 0.51 mL, 1.27 mmol, 1 eq) was added to a cold (-78 °C) solution of ethanethiol (0.197 g, 0.235 mL, 3.18 mmol, 2.5 eq) in anhyd THF (4 mL). This solution was allowed to stir for 15 min, and then transferred to a second flask containing a solution of **11a** (0.75 g, 1.26 mmol) in 10 mL of dry $CH_3CN$ at -30 °C. This reaction was allowed to warm to room temperature over a period of 30 min, then diluted with EtOAc (150 mL), and successively washed with saturated aq $NaHCO_3$ and saturated aq $NH_4Cl$. After drying over $Na_2SO_4$, the solvent was evaporated and the residue purified by flash chromatography on silica gel (EtOAc/$CH_2Cl_2$) to produce **12a** (0.29 g, 56% yield) as a white foam.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, J= 224 Hz, 8.4 Hz, 4H), 5.41 (dd, J= 128 Hz, 14 Hz, 2H), 4.30 (m, 1H), 3.11 (dd, J= 138 Hz, 17.6 Hz, 1H), 3.23 (d, J= 10Hz, 1H), 2.95 (d, J= 10 Hz), 3.9 (m, 2H), 1.69 (s, 3H), 1.45 (d, 6 Hz, 3H), 1.37 (t, 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 174.92, 160.99, 149.97, 147.48, 143.28, 128.00, 123.69, 121.68, 76.66, 67.79, 65.08, 64.98, 60.93, 48.57, 26.56, 22.64, 21.24, 14.81.

IR: 3418.95, 1764.33, 1696.54, 1606.15, 1520.10, 1378.46, 1331.14, 1290.03, 1212.07, 1150.74, 851.88, 736.74.

HRMS: calcd $C_{19}H_{22}N_2NaO_6S^+$ $[M + Na]^+$ 429.1091, obs 429.103




**11b** **12b** (79%)

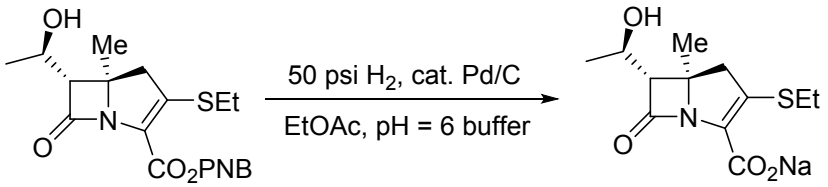
A cold (0 °C) solution of **11b** (180 mg, 0.30 mmol) and ethanethiol (28.0 mg, 33 µl, 0.45 mmol, 1.5 eq) in anhyd DMF (1.5 mL) was treated with diisopropylamine (39.5 mg, 55 µl, 0.39 mmol, 1.3 eq) and then allowed to stir at this temperature for 1.5 h. The reaction was then diluted with EtOAc (100 mL), and washed with saturated aq $NaHCO_3$ and with saturated aq $NH_4Cl$. After drying over $Na_2SO_4$, the solvent was removed *in vacuo*, and the residue purified by flash chromatography on silica gel using $MeOH/CH_2Cl_2$ as eluent to produce **12b** (0.10 g, 79% yield) as a white foam.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J= 224 Hz, 8.8 Hz, 4 H), 5.42 (dd, J= 122 Hz, 14 Hz, 2 H), 4.33 (m, 1H), 3.17 (m, 2H), 2.88 (m, 2H), 1.98 (m, 2H), 1.64 (m, 1 H), 1.44 (d, J= 64 Hz, 3H), 1.36 (t, J= 7.6 Hz, 3H), 1.03 (t, J= 7.6 Hz, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ 176.09, 160.80, 150.08, 147.36, 143.35, 127.88, 123.62, 122.66, 68.84, 64.88, 64.44, 64.11, 45.10, 27.65, 26.45, 22.65, 14.89, 7.71, 0.91.

IR: 3512.85, 3079.12, 2967.46, 2932.06, 1770.02, 1697.31, 1606.26, 1545.62, 1521.00, 1459.46, 1378.27, 1347.30, 1329.68, 1262.12, 1206.81, 1147.47, 1099.54, 1038.43, 848.90, 801.04, 737.00, 686.66.

HRMS: calcd $C_{20}H_{24}N_2NaO_6S^+$ $[M + Na]^+$ 443.1247, obs 443.1209




**12a** **13a** (9%)

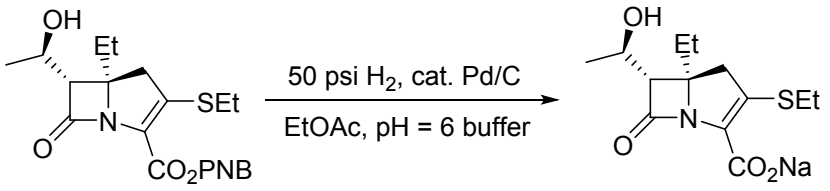
**13a**: A two-phase solution of **12a** (0.25 g, 0.62mmol) in 25 mL of EtOAc and 10 mL of pH 6 aqueous sodium phosphate buffer solution (0.3 M) was placed in a 250 mL Parr hydrogenation vessel. This solution was degassed by bubbling argon through it for 5 min, then 10% Pd on carbon (0.30 g) was added. The vessel was connected to the Parr apparatus, further degassed by two successive evacuation-argon repressurization cycles, then evacuated once more and subjected to hydrogen pressure at 55 psi and shaken for 90 min at this pressure. The hydrogen gas was completely removed under vacuum, the vessel opened to air, the resultant solution was filtered through celite to remove the catalyst. The filtrate was placed in a separatory funnel and the aqueous (product) layer was separated. The aqueous layer was

further washed with $Et_2O$ to remove traces of EtOAc and remaining unionized organic material. Then the aqueous layer was further subjected to vacuum (rotary evaporator) to remove last traces of diethyl ether and to partially reduce the total volume. The aqueous layer was then placed on a column of Diaion CHP20P resin and eluted with increasing percentage of ethanol/water (0 to 40% in 5% increments). Tubes containing the product were identified by inspection of the UV of each fraction, those tubes displaying the carbapenem 296 nm absorption were combined, and the solvent was removed *in vacuo*. The remaining aqueous solution was transferred to a small vial, frozen, and lyophilized overnight to produce the purified carbapenem antibiotic **13a** (0.016 g, 9% yield) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.33 (m, 1H), 3.14 (dd, J= 117 Hz, 6.8 Hz, 2H), 2.82 (m, 1H), 1.51 (s, 3H), 1.34 (d, J= 6 Hz, 3H), 1.28 (t, j= 7.6 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.14, 181.55, 154.21, 140.66, 78.60, 76.99, 73.72, 59.56, 38.47, 33.98, 32.43, 27.41, 9.83.

HRMS: calcd $C_{12}H_{17}NNaO_4S^+$ $[M + H]^+$ 294.0770, obs 294.0727




**12b** **13b** (14%)

**13b**: A two-phase solution of **12b** (0.185 g, 0.44mmol) in 20 mL of EtOAc and 20 mL of pH 6 aqueous sodium phosphate buffer solution (0.3 M) was placed in a 250 mL Parr hydrogenation vessel. This solution was degassed by bubbling argon through it for 5 min, then 10% Pd on carbon (0.26 g) was added. The vessel was connected to the Parr apparatus, further degassed by two successive evacuation-argon repressurization cycles, then evacuated once more and subjected to hydrogen pressure at 55 psi and shaken for 90 min at this pressure. The hydrogen gas was completely removed under vacuum, the vessel opened to air, the resultant solution was filtered through celite to remove the catalyst. The filtrate was placed in a separatory funnel and the aqueous (product) layer was separated. The aqueous layer was further washed with $Et_2O$ to remove traces of EtOAc and remaining unionized organic material. Then the aqueous layer was further subjected to vacuum (rotary evaporator) to remove last traces of diethyl ether and to partially reduce the total volume. The aqueous layer was then placed on a column of Diaion

CHP20P resin and eluted with increasing percentage of ethanol/water (0 to 40% in 5% increments). Tubes containing the product were identified by inspection of the UV of each fraction, those tubes displaying the carbapenem 296 nm absorption were combined, and the solvent was removed *in vacuo*. The remaining aqueous solution was transferred to a small vial, frozen, and lyophilized overnight to produce the purified carbapenem antibiotic **13b** (0.019 g, 14% yield) as white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 4.63 (s, 1H), 4.19 (m, 1H), 3.21 (d, 9.6Hz, 1H), 3.08 (dd, J= 54, 18 Hz, 2H), 2.73 (m, 2H), 1.82 (m, 2 H), 1.194 (m, 6H), 0.816 (t, 5.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 192.32, 181.42, 154.19, 142.01, 83.18, 56.42, 39.96, 38.45, 35.30, 34.17, 32.21, 19.85, 10.83.

HRMS: calcd $C_{13}H_{19}NNaO_4S^+$ $[M + H]^+$ 308.0927, obs 308.0889

## Table S1: Bacterial Strains

| Name | Genotype/Phenotype | Reference |
|---|---|---|
| **Strains** | | |
| *Mtb* | *M. tuberculosis* CDC1551 | 1 |
| *Mtb-lux* | *Mtb* CDC1551 expressing pMV306hsp+LuxG13 | 2 |
| *Mtb* CI 1 | *Mtb* clinical isolate 9532/03, Euroamerican lineage 2, Haarlem | 3 |
| *Mtb* CI 2 | *Mtb* clinical isolate 2191/99, Euroamerican lineage 13, Uganda | 3 |
| *Mtb* CI 3 | *Mtb* clinical isolate 1934/03, East Asian lineage 8, Beijing | 3 |
| *Mtb* CI 4 | *Mtb* clinical isolate 4850/03, Indo Oceanic lineage 5, EAI | 3 |
| *Mtb* CI 5 | *Mtb* clinical isolate 5468/02, West African 2 lineage 15, WA2 | 3 |
| *Mab* | *M. abscessus* 390S, smooth colony phenotype | 4 |
| *Mab-lux* | *M. abscessus* 390S expressing pMV306hsp+LuxG13 | 2 |
| *Mab* CI 1 | *Mab* clinical isolate | National Jewish Health |
| *Mab* CI 2 | *Mab* clinical isolate | National Jewish Health |
| *Mab* CI 3 | *Mab* clinical isolate | National Jewish Health |
| *Mab* CI 4 | *Mab* clinical isolate | National Jewish Health |
| *Mab* CI 5 | *Mab* clinical isolate | National Jewish Health |

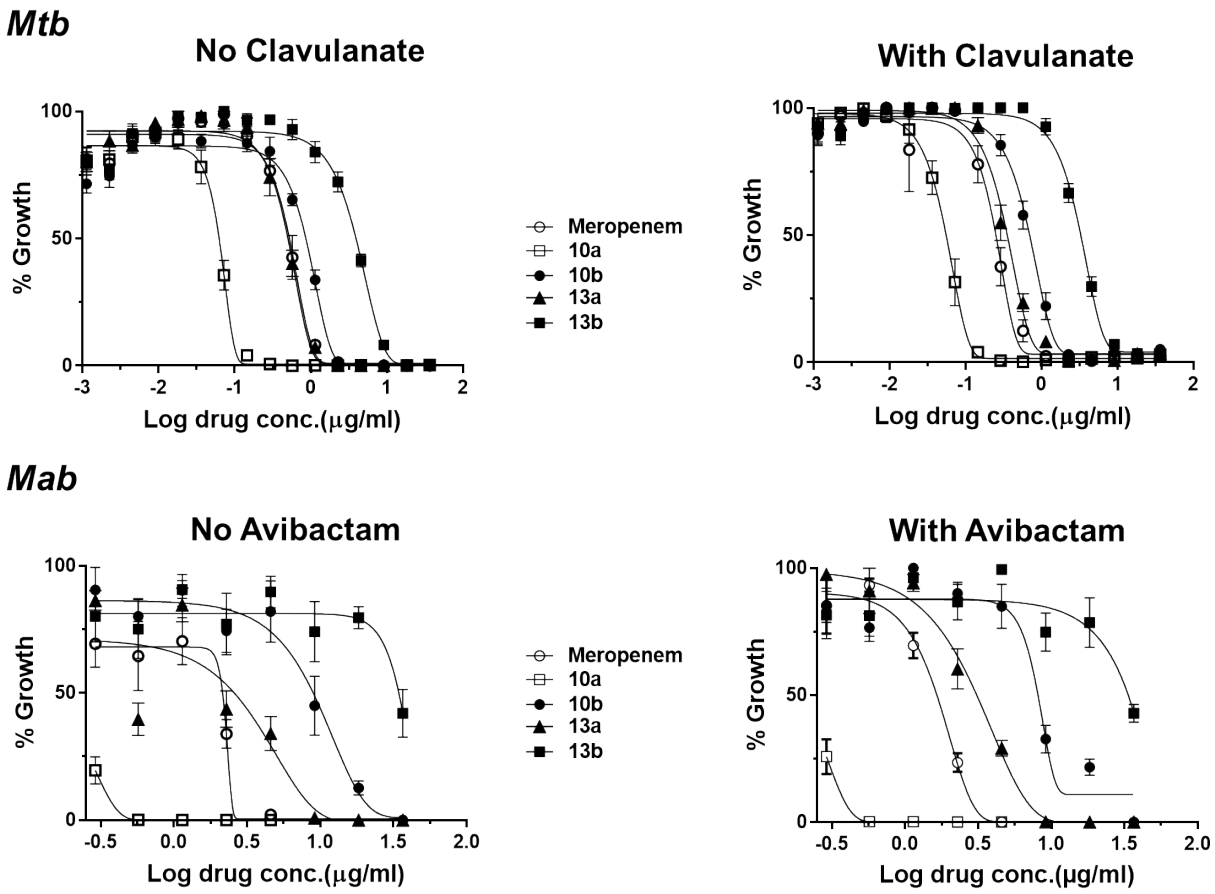



**Figure S1** : Dose response curves for C5-substituted carbapenems against *Mtb* (top panel) and *Mab* (bottom panel) with and without β-lactam inhibitors (5 μg/ml). Data is an average of three independent experiments each with two technical replicates with SEM error bars

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