Supporting Information

Dimeric and trimeric derivatives of the azinomycin B chromophore show enhanced DNA binding

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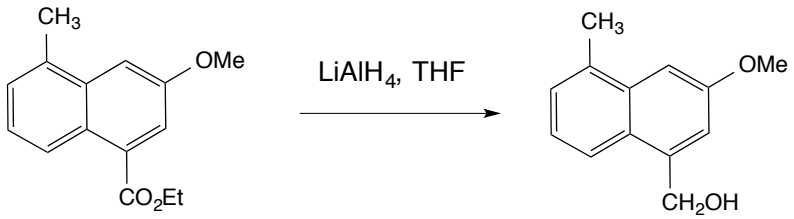
General Information

Distilled water was used in all of the experiments. Organic extracts were dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator at aspirator pressure (20-30 mmHg). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 MHz and 100 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (d) from Me_4Si.



4

Ethyl 3-methoxy-5-methyl-1-naphthoate (1g, 4.10 mmol) was dissolved in THF (20 mL, 0.2M) and the solution was cooled to 0 °C. Then, $LiAlH_4$ (171 mg, 4.5 mmol, 1.1 eq) was added slowly, and the solution was allowed to warm to room temperature. After completion of the reaction as monitored by TLC (1:1 Hexane: EtOAc), the mixture was quenched with deionized water/1M HCl (3:1) and extracted with EtOAc. Purification by flash column chromatography (silica gel, 1:1 Hexane/EtOAc) afforded **4** as a white solid (798 mg, 96%).

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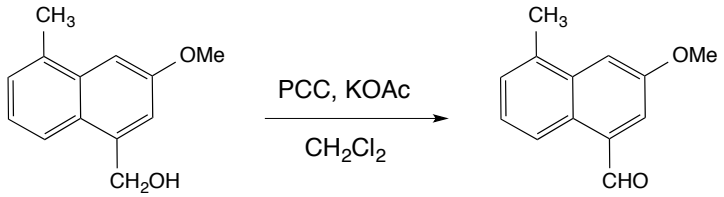
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 7.36-7.3 (m, 3H), 7.22 (d, J = 2.2 Hz, 1H), 5.15 (s, 2H), 3.98 (s, 3H), 2.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 138.7, 134.3, 133.6, 127.3, 126.6, 123.6, 121.5, 117.1, 102.7, 63.5, 55.3

IR: 3321.6 cm^{-1} (broad), 2921.7, 1620.2, 1601.9.

mp.:133.6-134.0 °C

HRMS–ESI (m/z): calculated for $C_{13}H_{14}NaO_2$: 225.0891; found 225.0857 (M+Na)



4 **5**

Pyridinium chlorochromate (1.2 g, 5.4 mmol, 1.1 eq) and potassium acetate (533 mg, 5.4 mmol, 1.1 eq) were added to a solution of alcohol **4** (1 g, 4.94 mmol) in DCM (10 mL). The reaction mixture was stirred at room temperature until completion as determined by TLC (10:1 Hex: EtOAc; R_f: 0.35). The crude residue was filtered through a plug of celite, and further purification by flash column chromatography (10:1 Hex/EtOAc) afforded aldehyde **5** as a pale yellow solid (937 mg, 4.7 mmol, 95%).

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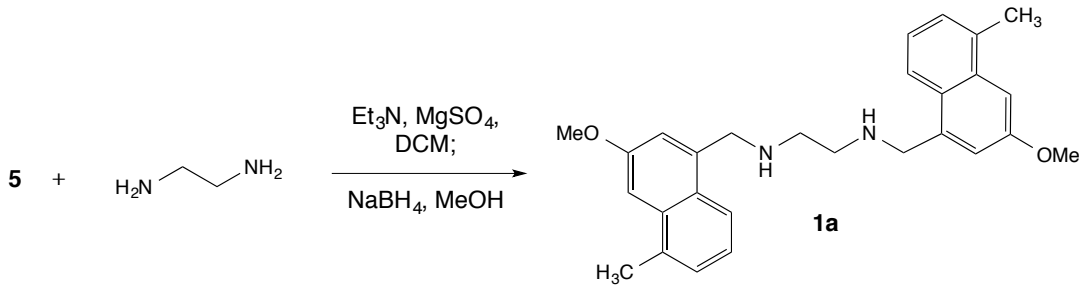
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.90 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.42-7.34 (m, 3H), 3.94 (s, 3H), 2.62 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 156.4, 134.5, 133.3, 133.1, 128.2, 126.6, 126.4, 126.1, 122.5, 110.0, 55.6, 20.1

IR: 2965.1 cm^{-1}, 2841.1, 2755.5, 1684.9, 1616.6, 1596.5.

mp.:81.8-84.5 °C

HRMS–ESI (m/z): calculated for $C_{13}H_{12}NaO_2$: 223.0735; found 223.0771 $(M+Na)^+$



In dry DCM (5 mL, 0.3M), aldehyde **5** (300 mg, 1.5 mmol), triethylamine (0.2 mL, 1.5 mmol, 1eq), magnesium sulfate (144 mg, 1.2 mmol, 0.8 eq), ethylenediamine (0.05 mL, 0.75 mmol, 0.5 eq) were stirred for 3 hours under argon. The solvent was then removed *in vacuo* and the flask was charged with dry MeOH (7.5 mL). $NaBH_4$ (142 mg, 7.5 mmol, 5 eq) was added in five portions and the reaction mixture was stirred for 20 hours. MeOH was removed *in vacuo* and then the crude mixture was diluted with DCM. The suspension was washed with 1M HCl (10 mL) and the aqueous extract was washed with DCM (10 mL) 3 times. Then, the aqueous layer was basified to pH 10-11 with 1M NaOH and was extracted with DCM (3 x 10 mL). The organic layer was dried over anhydrous $NaSO_4$, filtered, and the solvent was removed *in vacuo* to afford compound **1a** as a white solid (209 mg, 0.98 mmol, 65%).

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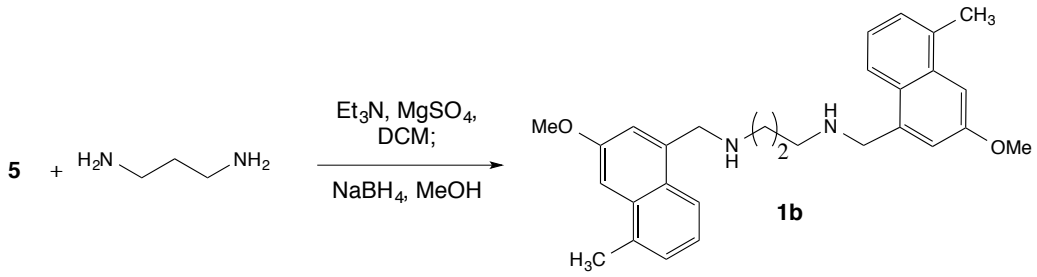
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 2H), 7.32-7.20 (m, 4H), 7.17 (d, J = 2.1 Hz, 4H), 4.19 (s, 4H), 3.95 (s, 6H), 2.91 (s, 4H), 2.66 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.0, 134.3, 133.5, 127.2, 127.1, 123.4, 121.7, 118.0, 102.2, 55.2, 51.2, 48.8, 20.0

IR: 3290.3 cm^{-1} (sharp), 2919.8, 2831.6, 1619.8, 1599.6.

mp.:144.5-145.8 °C (dec.)

HRMS–ESI (m/z): calculated for $C_{28}H_{32}N_2O_2$: 428.2464; found $(M+H)^+$ 428.2457



In dry DCM (5 mL, 0.3M), compound **5** (300 mg, 1.5 mmol), triethylamine (0.2 mL, 1.5 mmol, 1eq), magnesium sulfate (144 mg, 1.2 mmol, 0.8eq), 1,3-propanediamine (0.06 mL, 0.75 mmol 0.5 eq) were stirred for 3 hours under argon. Next, the solvent was removed in vacuo and the flask was charged with dry MeOH (3.4 mL). $NaBH_4$ (142 mg, 7.5 mmol, 5 eq) was added in five portions and the reaction mixture was stirred for 20 hours. MeOH was removed *in vacuo* and then the crude mixture was diluted with DCM. The suspension was washed with 1M HCl (10 mL) and the aqueous extract was washed with DCM (10 mL) 3 times. Then, the aqueous layer was basified to pH 10-11 with 1M NaOH and was extracted with DCM (3 x 10 mL). The organic layer was dried over anhydrous $NaSO_4$, filtered, and the solvent was removed *in vacuo* to afford compound **1b** as a yellow oil (198 mg, 0.9 mmol, 60%).

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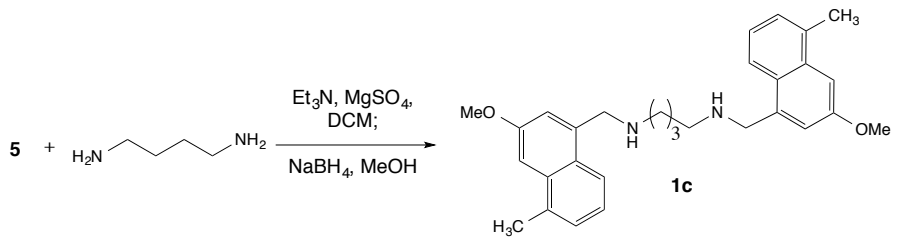
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.35-7.28 (m, 4H), 7.21 (d, *J* = 12.2, 4H), 4.22 (s, 4H), 3.97 (s, 6H), 2.84 (t, *J* = 6.5, 4H), 2.70 (s, 6H), 1.81 (t, *J* = 6.6 Hz, 2H), 1.65 (broad s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.6, 134.4, 133.5, 127.2, 127.1, 123.3, 121.7, 117.9, 102.0, 55.2, 51.7, 48.4, 30.4, 20.1

IR: 3288.5 cm^{-1} (broad), 2937.7, 2827.9, 1622.1, 1602.2.

HRMS–ESI (m/z): calculated for $C_{29}H_{34}N_2O_2$: 443.2699; found $(M+H)^+$ 443.2660



In dry DCM (5mL, 0.3M), compound **5** (300 mg, 1.5 mmol), triethylamine (0.2 mL, 1.5 mmol, 1eq), magnesium sulfate (144 mg, 1.2 mmol, 0.8eq), 1,4-butanediamine (0.08 mL, 0.75 mmol 0.5 eq) were stirred for 3 hours under argon. Next, the solvent was removed *in vacuo* and the flask was charged with dry MeOH (3.4 mL). $NaBH_4$ (142 mg, 7.5 mmol, 5 eq) was added in five portions and the reaction mixture was stirred for 20 hours. MeOH was removed *in vacuo* and then the crude mixture was diluted with DCM. The suspension was washed with 1M HCl (10 mL) and the aqueous extract was washed with DCM (10 mL) 3 times. Then, the aqueous layer was basified to pH 10-11 with 1M NaOH and was extracted with DCM (3 x 10 mL). The organic layer was dried over anhydrous $NaSO_4$, filtered, and the solvent was removed *in vacuo,* which afforded compound **1c** as a light brown oil (216 mg, 0.95 mmol, 63%).

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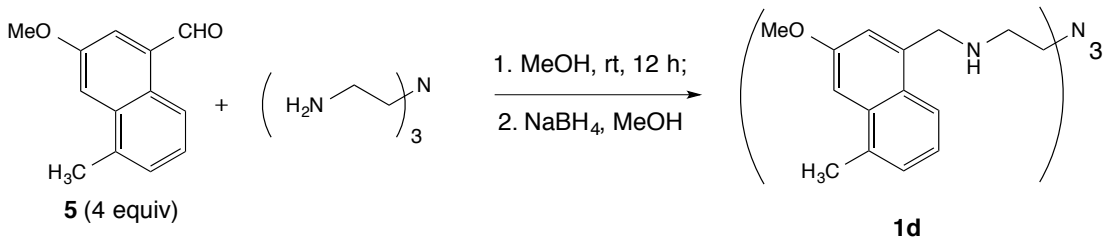
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.32-7.28 (m, 4H), 7.20 (d, *J* = 11.7 Hz, 4H), 4.22 (s, 4H), 3.97 (s, 6H), 2.77 (s, 4H), 2.69 (s, 6H), 1.63 (s, 4H), 1.44 (broad s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.6, 134.4, 133.6, 127.3, 127.0, 123.4, 121.7, 117.9, 102, 55.2, 51.6, 49.8, 28.0, 20.0

IR: 3293.0 cm^{-1} (broad), 2930.4, 2815.2, 1620.8, 1601.6.

HRMS–ESI (m/z): calculated for $C_{30}H_{36}N_2O_2$: 457.2855; found $(M+H)^+$ 457.2888



In dry MeOH (0.5 mL) compound **5** (68 mg, 0.34 mmol) and *N,N*-bis(2-aminoethyl)-1,2-ethanediamine (16 mg, 0.11 mmol) were stirred for 18 hours under argon. Next, $NaBH_4$ (38 mg, 1.0 mmol) was added in five portions and the reaction mixture was stirred for 2 hours. MeOH was removed *in vacuo* and then the crude mixture was diluted with DCM. The suspension was washed with 1M HCl (10 mL) and the aqueous extract was washed with DCM (10 mL) 3 times. Then, the aqueous layer was basified to pH 10-11 with 1M NaOH and was extracted with DCM (3 x 10 mL). The organic layer was dried over anhydrous $NaSO_4$, filtered, and the solvent was removed *in vacuo.* Purification by column chromatography gave **1d** as a viscous yellow oil (40 mg, 0.057 mmol, 52%).

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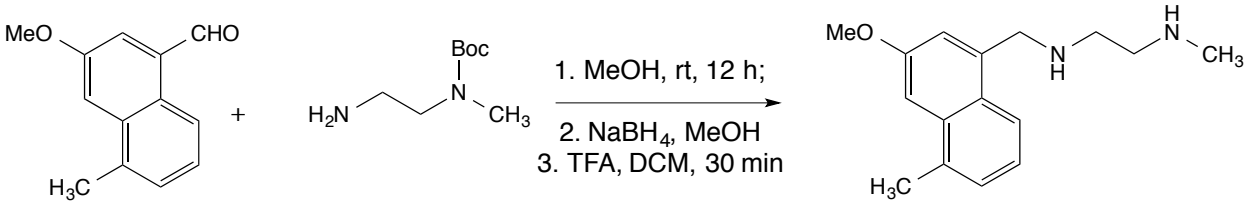
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.4 Hz, 3H); 7.24 (d, *J*=8.0 Hz, 3H); 7.12 (m, 6H); 7.04 (s, 3H), 4.01 (s, 6H); 3.83 (s, 9H); 2.71 (m, 6H); 2.62 (m, 6H); 2.55 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 134.2, 133.6, 127.1, 126.9, 123.4, 121.3, 118.5, 102.5, 55.1, 53.4, 49.8, 46.9, 19.6.

IR: 3315.5 cm^{-1} (broad), 2925.4, 2855.3, 1623.2, 1602.6.

HRMS–ESI (m/z): calculated for $C_{45}H_{55}N_4O_3$: 699.4274; found 699.4331$(M+H)^+$



In dry MeOH (0.5 mL) compound **5** (68 mg, 0.34 mmol) and *N*-Boc,*N*-methyl-1,2-ethanediamine (59 mg, 0.34 mmol) were stirred for 18 hours under argon. Next, $NaBH_4$ (38 mg, 1.0 mmol) was added in five portions and the reaction mixture was stirred for 2 hours. MeOH was removed *in vacuo* and then the crude mixture was diluted with DCM. The suspension was washed with saturated NH_4Cl (3 x 10 mL) and the organic layer was concentrated *in* vacuo. The crude material was dissolved in DCM (3 mL) and TFA (3 mL) was added. The mixture was stirred for 30 minutes at room temperature and then concentrated *in vacuo*. Purification by column chromatography (5% → 20% MeOH/$CHCl_3$, 1% NH_4OH) gave **2a** as a light yellow oil (60 mg, 0.232 mmol, 68%).

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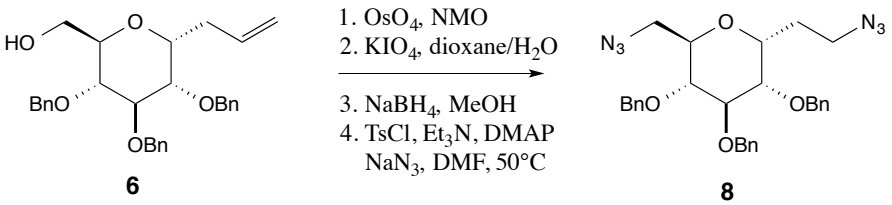
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=7.6 Hz, 1H); 7.27 (m, 4H); 4.38 (s, 2H); 3.91 (s, 3H); 3.15 (s, 4H); 2.63 (s, 3H); 2.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 138.3, 137.5, 130.9, 130.8, 127.4, 125.0, 123.0, 106.7, 58.3, 53.4, 47.6, 36.1, 22.5.

IR: 3291.6 cm^{-1} (broad), 2936.7, 2823.8, 1621.2, 1602.1.

HRMS–ESI (m/z): calculated for $C_{16}H_{23}N_2O$: 259.1810; found 259.1810 $(M+H)^+$



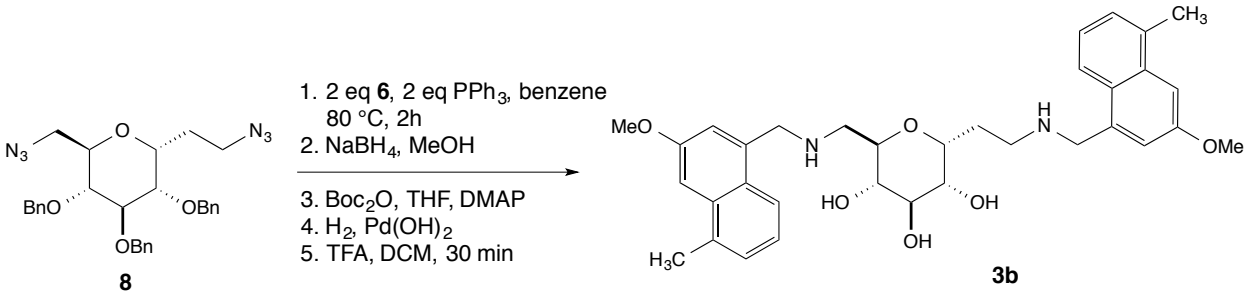
6 **8**

Compound **6** (202 mg, 0.43 mmol) was dissolved in 8:1 acetone: 50% aqueous NMO (9.0 mL) and OsO_4 (0.136 mL, 0.022 mmol, 4% solution in water) and the mxture was stirred at room temperature for two hours. Solid Na_2SO_3 (100 mg) was added and the mixture was diluted with water (20 mL) and stirred overnight. The mixture was concentrated *in vacuo* and extracted with ethyl acetate (3 x 10 mL). The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude diol was dissolved in 1:1 dioxane/pH 6.75 phosphate butter (10 mL) and KIO_4 (690 mg, 3 mmol) was added; the mixture was stirred for 5 hours at room temperature. Ethyl acetate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde was dissolved in methanol (5.0 mL) and solid $NaBH_4$ (100 mg, 2.7 mmol) was added in four portions. After stirring for one hour at room temperature, the mixture was concentrated *in vacuo*. Ethyl actetate (10 mL) and 1N HCl solution (10 mL) was added and the layers were separated. The aqueous layer was further extracted with ethyl acetate (10 mL) and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude diol alcohol was filtered through a pad of silica gel with 1:1 hexanes ethyl acetate (50 mL) and the solution was concentrated *in vacuo*. The diol was dissolved in CH_2Cl_2 (1.7 mL) and Et_3N (0.24 mL, 1.72 mmol) and DMAP (10 mg) was added. Then TsCl (190 mg, 1 mmol, 2.2 eq) was added and the mixture was stirred for one hour at room temperature. Ether (10 mL) and saturated $NaHCO_3$ solution (10 mL) was added and the layers were separated. The aqueous layer was further extracted with ether (3 x 10 mL) and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude di-tosylate was dissolved in DMF (1.6 mL) and sodium azide (195 mg, 3 mmol) was added. The mixture was heat to 50 °C and stirred at this temperature for 48 hours. Upon cooling to room temperature, the mixture was diluted with ether (20 mL) and saturated $NaHCO_3$ solution (20 mL) and the layers were separated. The aqueous layer was further extracted with ether (3 x 10 mL) and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (5:1 Hexanes:Ethyl Acetate) gave **8** as a colorless oil (135 mg, 0.26 mmol, 60%) .

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 13H); 7.31 (m, 2H); 4.99 (d, *J*=10.9, 1H); 4.94 (d, *J*=11.0 Hz, 1H); 4.84 (d, *J*=10.9 Hz, 1H); 4.76 (d, *J*=11.5 Hz, 1H); 4.68 (d, *J*=11.6 Hz, 1H); 4.63 (d, *J*=11.0 Hz, 1H); 4.21 (m, 1H); 3.80 (m, 2H); 3.67 (m, 1H); 3.48 (m, 3H); 3.34 (m, 2H); 2.30 (q, *J*=7.12 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 81.8, 79.4, 78.5, 75.3, 75.0, 73.2, 71.5, 71.3, 51.7, 47.9, 24.8.

HRMS–ESI (m/z): calculated for $C_{29}H_{32}N_6NaO_4$: 551.2383; found $(M+Na)^+$ 551.2433



Compound **8** (40 mg, 0.075 mmol) was dissolved in benzene (0.5 mL) and triphenylphosphine (40 mg, 0.15 mmol, 2 eq) and **6** (30 mg, 0.15 mmol, 2 eq) was added. The mixture was heated to 80°C and stirred at this temperature for two hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The crude material was take up in MeOH (1 mL) and $NaBH_4$ (37 mg, 1 mmol) was added portionwise. The mixture was allowed to stir overnight and was then concentrated *in vacuo.* The crude material was taken up in EtOAc (10 mL) and was washed with 1N HCl solution (3 x 5mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was take up in CH_3CN (1.2 mL) and Boc_2O (49 mg, 0.225 mmol, 3 eq) and DMAP (40 mg, 0.3 mmol, 4 eq) were added. The mixture was stirred overnight at room temperature and was then concentrated *in vacuo.* The crude material was flushed through a plug of silica gel with 1:1 hexanes:ethyl acetate and the eluent was concentrated. The resulting clear oil was taken up in EtOH (1.5 mL) and palladium hydroxide (4 mg) was added, and the mixture was stirred under an atmosphere of hydrogen for 18 hours. The solution was then filtered through plug of celite with excess ethyl acetate and the eluent was concentrated *in vacuo.* The crude material was dissolved in a 1:1 mixture of CH_2Cl_2/TFA and DMS (0.2 mL) was added. The solution was stirred at room temperature for 30 minutes and then concentrated *in vacuo*. Purification of the residue by flash chromatography (EtOAc → 20% MeOH/EtOAc, 1% NH_4OH) gave **3b** as a viscous yellow oil (19.4 mg, 45% overall).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H); 7.31 (m, 6H); 7.15 (d, *J*=11.8 Hz, 2H); 4.40 (d, *J*= 5.32 Hz, 2H); 4.19 (d, *J*=6.3 Hz, 2H); 4.09 (m, 2H); 3.88 (s, 3H); 3.87 (s, 3H); 3.74 (m, 2H); 3.65 (m, 1H); 3.58 (t, *J*=7.9 Hz, 1H); 3.25 (m, 3H); 3.16 (m, 2H); 3.00 (t, *J*=9.3 Hz, 1H); 2.60 (s, 3H); 2.58 (s, 3H); 2.15 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 156.6, 134.2, 133.7, 133.6, 127.2, 126.9, 126.8, 126.5, 123.8, 123.4, 120.8, 120.5, 119.8, 118.5, 103.5, 102.2, 73.4, 73.0, 72.2, 71.6, 70.9, 54.3, 49.5, 46.1, 22.7, 20.6, 18.6, 18.5.

IR: 3319.2 cm^{-1} (broad), 2923.8, 1623.8, 1603.5.

HRMS–ESI (m/z): calculated for $C_{34}H_{43}N_2NaO_6$: 575.3121; found $(M+Na)^+$ 575.3082