Concise, Asymmetric, Stereocontrolled Total Synthesis of Stephacidins A, B and Notoamide B

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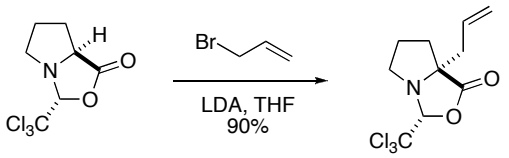
Supporting Information

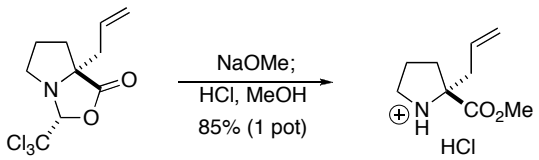
GENERAL METHODS: All reactions were performed in single-neck round bottom flasks fitted with rubber septa under positive pressure of argon, unless otherwise noted. Organic solutions were concentrated under reduced pressure by rotary evaporation below 40 ^{O}C at 20 Torr. Analytical and preparative thin-layer chromatography (TLC) was performed using glass plates pre-coated with a 0.25-mm layer of silica gel impregnated with a fluorescent indicator (254 nm). Reaction progress was followed by TLC analysis and visualized by UV light and/or submersion in standard TLC stains ($KMnO_4$, Vanillin, Anisaldehyde, etc.) followed by heating on a hot plate (~200^{O}C, 15 s). Flash silica gel chromatography was conducted as described by Still and coworkers using 60 Å, standard grade silica gel purchased from Sorbtech. ^{1}H and ^{13}C NMR spectra were obtained using Varian 300 MHz, 400 MHz or 500 MHz spectrometers. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual $CDCl_3$ δ 7.27 ppm for proton spectra and relative to $CDCl_3$ at δ 77.23 ppm for carbon spectra, unless otherwise noted. IR spectra were recorded on a Perkin-Elmer 1600 FTIR as thin films in CH_2Cl_2. Mass spectra were obtained using a Fisons VG Autospec spectrometer. Flash column chromatography was performed with silica gel grade 60 (230-400 mesh). All materials were obtained from commercially available sources and used without further purification. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene (PhMe), benzene (PhH), *N*,*N*-dimethylforamide (DMF), acetonitrile (CH_3CN), triethylamine (Et_3N), *N*,*N*-diisopropylamine and methanol (MeOH) were all purified using a LabContour solvent purification system. Sodium hydride (NaH) was dispersed in petroleum ether,

stirred for 15 min, filtered through a sintered glass funnel and washed with an additional aliquot of Pet. Et_2O before use.



12 **13**

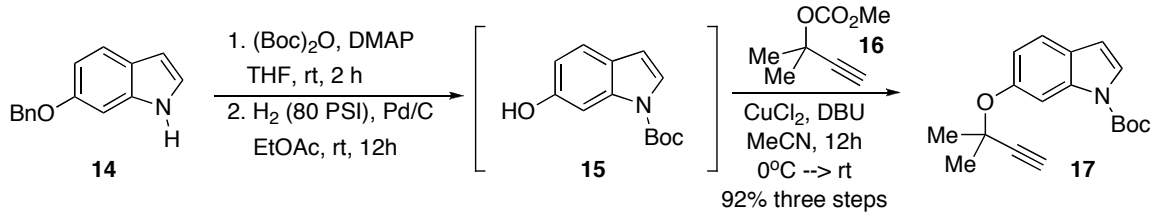
(3*R*,7a*R*)-7a-allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (13). To a flame-dried 500-mL round-bottomed flask, *N*,*N*-diisopropylamine (10 mL, 71 mmol) is added to tetrahydrofuran (THF, 140 mL). The reaction vessel is cooled to -78^{O}C in a CO_2/isopropanol bath before *n*-butyllithium in hexane (Aldrich, 1.6M, 46 mL, 74 mmol) is added via syringe. The reaction mixture is stirred for an additional 30 min at -78^{O}C under argon. In a separate 250-mL round-bottomed flask, commercially available (3*R*,7*aS*)-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (**12**, AK Scientific, 12.2 g, 49.9 mmol) is dissolved in THF (100 mL). This solution is cooled to 0^{O}C and stirred for 10 min. A cannula is used to deliver the ethereal solution to the LDA solution at -78^{O}C under argon over 5 min. The resulting solution is stirred for an additional 20 min at -78^{O}C before the addition of commercially available allyl bromide (Alfa Aesar, 7.8 mL, 90 mmol) via syringe in a single portion. The reaction mixture is slowly allowed to warm to -40^{O}C, where it is maintained for an additional 2-3 h. Progress of the alkylation can be monitored by TLC developing plates in 1:7 EtOAc:hexanes (product R_f=0.56; starting material R_f = 0.39). The reaction mixture is then poured into a 1-L separatory funnel filled with 300 mL of water. The aqueous solution is extracted with chloroform (3 x 300 mL). The combined organic extracts are dried over Na_2SO_4 and concentrated *in vacuo* to afford the allyl lactone **13** (10.7 g, 75%) as an orange oil, which is generally used without purification. Analytically pure material for spectral analysis was generated using PTLC (1:7 EtOAc:hexane) to afford **13** as a light yellow oil, which displayed excellent correlation to the previously reported data. $[\alpha]_D$ = +34.0 (*c* 2, C_6H_6), lit.[1] $[\alpha]_D$ = +33 (*c* 2, C_6H_6).



13 **11**

[1] Wang, H.; Germanas, J. P. *Synlett* **1999**, 33-36.

(*R*)-methyl 2-allylpyrrolidine-2-carboxylate hydrochloride (11). A 500-mL three-neck round-bottomed flask equipped with a magnetic stirbar, a reflux condenser with an argon inlet is fitted on the center neck, a 125-mL pressure-equalizing additional funnel with rubber septum is fitted on the left neck, and a rubber septum fitted on the right neck of the flask. The rubber septum is removed and the flask is charged with allyl lactone **13** (8.19 g, 28.8 mmol) and MeOH (100 mL). Small chunks of Na^0 (Aldrich, 400 mg, 17.4 mmol) are slowly added over 30 min by removal of the rubber septum from the right neck of the flask and the reaction mixture is stirred for an additional 30 min once no more of the starting material is observed by TLC (1:5 EtOAc:hexanes). The reaction vessel is cooled in an ice/water bath and the pressure-equalizing addition funnel is charged with commercially available AcCl (Aldrich, 40 mL, 563 mmol), which is added dropwise into the reaction mixture over 1 h. The funnel is removed and replaced with a rubber septum and an argon inlet and the resulting milky brown solution is heated to reflux until no more of the intermediate *N*-formyl ester remains by TLC (1:1 EtOAc:hexanes, *N*-formyl ester R_f = 0.25; **11** R_f = 0.00). The volatile organics are removed under reduced pressure and the resulting oily solid is diluted with CH_2Cl_2 (50 mL). The precipitated NaCl is removed via filtration through a Büchner funnel. The filtrate is concentrated under reduced pressure and the process of dilution with CH_2Cl_2/filtration is repeated two additional times to afford a brown oil. Purification of the crude hydrochloride salt is achieved using flash silica gel chromatography eluting with a gradient of 95:5→90:10 CH_2Cl_2:MeOH to afford the amine salt **11** (5.0 g, 85%) as an oil, which crystallizes upon standing under reduced pressure. Spectral correlation was identical to the previously reported data/. However, we performed our NMR experiments in $CDCl_3$ vs. D_2O.[1] $[\alpha]_D$ = +74.0 (*c* 2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-2.25 (m, 3H), 2.30-2.50 (m, 1H), 2.71-3.07 (m, 2H), 3.33-3.76 (m, 2H), 3.85 (s, 3H), 5.20-5.33 (m, 2H), 5.72-5.99 (m, 1H), 8.06 (br. s, 1H).

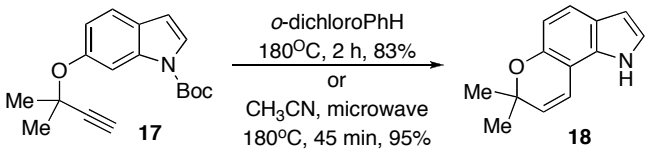


***tert*-Butyl 6-(2-methylbut-3-yn-2-yloxy)-1*H*-indole-1-carboxylate (17)**. To a 500 mL round bottom flask, commercially available 6-benzyloxyindole (**14**, 3B Medical Systems, 4.47 g, 20.0 mmol) was dissolved in THF (200 mL). Commercially available $(Boc)_2O$ (Fluka, 4.74 g, 21.7 mmol) and DMAP (Aldrich, 237 mg, 1.94 mmol) are added sequentially to the reaction flask. The reaction mixture was

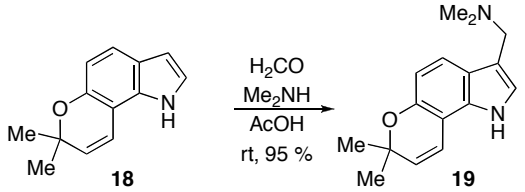
stirred until no more starting material remained by TLC (1:9 EtOAc:hexane, product R_f = 0.75; **14** R_f = 0.3, 2h). The volatile organics were removed under reduced pressure and the crude oily product is used without further purification.

The crude *N*-Boc indole was diluted with EtOAc (100 mL) and transferred to a high-pressure hydrogenation vessel. Commercially available 10% Pd/C (604 mg) is added in a single portion and the vessel was sealed. 80 PSI of H_2 is introduced and the reaction vessel is evacuated. This process is repeated twice more. The vessel is then placed under 80 PSI of H_2 pressure and stirred at rt overnight. TLC analysis of the reaction mixture after 10 h showed no more starting material remained (1:9 EtOAc:hexane, **15** R_f = 0.2; starting material R_f = 0.75). The remaining H_2 gas is evacuated and the palladium catalyst is removed via filtration through a pad of Celite®. The filtrate of low boiling organics is removed *in vacuo* to afford intermediate **15** as an aoil, which is used without further purification.

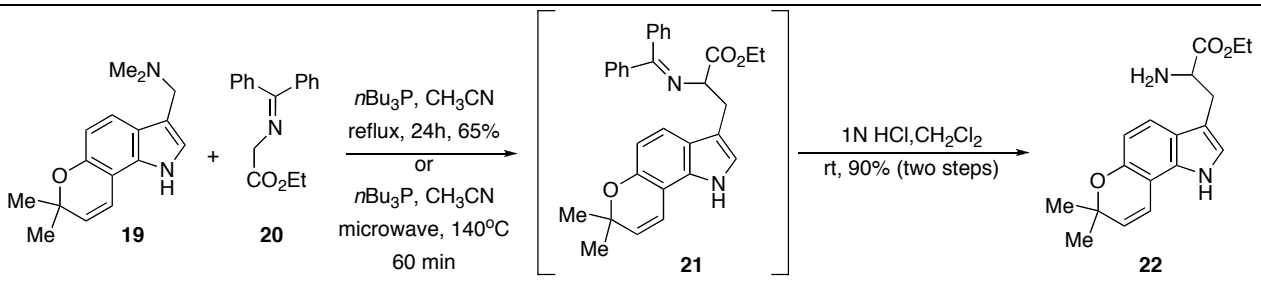
The crude phenol **15** was dissolved in CH_3CN (40 mL) and cooled to 0^oC. Commercially available $CuCl_2•2H_2O$ (Aldrich, 3.1 mg, 0.018 mmol) is then added followed methyl 2-methylbut-3-yn-2-yl carbonate (**16**, 8.50 g, 60.0 mmol). The reaction mixture is stirred for 15 min before the addition of commercially available DBU (Aldrich, 3.3 mL, 22.1 mmol) via syringe. The reaction mixture remains at 0^oC and was stirred until the starting phenol **15** is consumed by TLC (1:9 EtOAc: hexane, ~3h). The volatile organics are removed under reduced pressure and the resulting oil is diluted with EtOAc (150 mL). The organic solution is washed sequentially with 1N HCl (50 mL), water (50 mL) and brine (50 mL). The organic layer is dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting brown oil is purified by flash silica gel chromatography (1:10 EtOAc:hexanes) to afford the desired aryl ether **17** (5.51 g, 92 % over three steps) as a colorless oil**.** IR (Thin Film) 3305, 2984, 2252, 1727, 1534, 1474, 908, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.69 (s, 6H), 2.57 (s, 1H), 6.52 (dd, *J* = 3.6, 0.6 Hz, 1H), 7.12 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 3.9 Hz, 1H), 8.01 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.99, 135.50, 126.75, 125.86, 120.71, 118.63, 117.56, 109.50, 107.25, 86.51, 83.75, 73.98, 73.25, 29.86, 28.46; HMRS-FAB: $[M+H]^+$ calcd for $C_{18}H_{21}NO_3$, 300.1594; found, 300.1601.



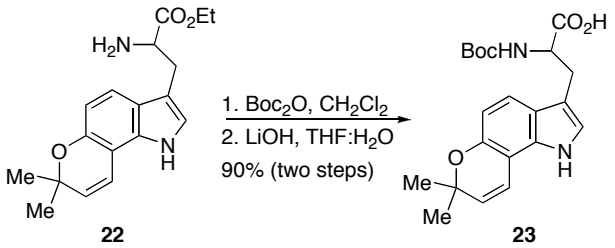
7,7-Dimethyl-1,7-dihydropyrano[2,3-g]indole (18). Using a CEM Discovery Microwave Reactor, the aryl ether **17** (5.51 g, 18.3 mmol) is dissolved in CH_3CN (210 mL) in an Erlenmeyer flask. 70-mL aliquots are removed from the flask and placed in a CEM 80-mL reaction vessel containing a stir bar. The reaction vessel is placed in the microwave cavity, sealed and heated at 180^{O}C for 20 min at 300W of power. This process is repeated until all of the aryl ether **17** had been cycled through the microwave (3 runs). The combined reaction mixtures are concentrated under reduced pressure and the resulting brown oil is purified by flash silica gel chromatography (1:9 EtOAc:hexanes) to afford the desired pyranoindole **18** (3.44 g, 95 %) as a light yellow oil. IR (Thin Film) 3480, 3423, 2978, 1642, 1489, 909, 732, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 6H), 5.67 (d, *J*= 9.8 Hz, 1H), 6.47 (dd, *J*= 3.2, 3.0 Hz, 1H), 6.57 (d, *J* = 9.7 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 3.1, 3.0 Hz, 1H), 7.32 (d, *J*= 8.4 Hz, 1H), 8.05 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.88, 132.49, 129.73, 123.15, 122.72, 121.08, 117.19, 111.04, 105.18, 103.37, 75.93, 27.76; HRMS-FAB: $[M+H]^+$ calcd for $C_{13}H_{13}NO$, 200.1070; found, 200.1069.



(7,7-Dimethyl-1,7-dihydropyrano[2,3-g]indol3-yl)-*N,N*-dimethylmethanamine (19). To a 100 mL round bottom flask, aqueous formaldehyde (37 %, 0.80 mL, 9.86 mmol) was diluted with glacial AcOH (30 mL). Aqueous dimethylamine (40 %, 4.2 mL, 37.3 mmol) was then added followed by the indole **18** (1.74 g, 8.73 mmol). The reaction was stirred at rt until the disappearance of the starting indole **18** by TLC (1:9 EtOAc:hexane, ~2 h). The reaction mixture was then diluted with 2N NaOH to raise the pH > 10. The aqueous solution was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and the volatile organics removed under reduced pressured to afford the desired gramine **19** (2.13, 95%) as a golden foam, which was used without further purification. IR (Thin Film) 3478, 2978, 2777, 1641, 1436, 731, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 6H), 2.29 (s, 6H), 3.58 (s, 2H), 5.59 (d, *J* = 13.0 Hz, 1H), 6.49 (d, *J* = 9.7 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.92 (br. s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 8.49 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.67, 132.97, 129.75, 122.40, 119.71, 117.61, 117.21, 114.25, 110.76, 105.14, 75.89, 54.85, 45.64, 27.66; HRMS-FAB: $[M+H]^+$ calcd for $C_{16}H_{20}N_2O$, 257.1648; found, 257.1644.

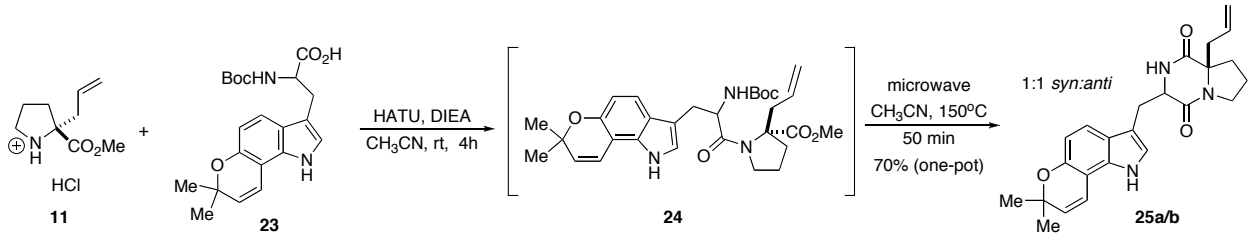


Tryptophan Derivative 22. To a 250-mL Erlenmeyer flask, gramine **19** (2.12 g, 8.27 mmol) is suspended in CH_3CN (120 mL). Commercially available glycine **20** (Aldrich, 2.22 g, 8.27 mmol) and tributylphosphine (Aldrich, 0.5 mL, 2.0 mmol) are added to the reaction mixture. 60-mL aliquots are removed from the flask and placed in a CEM 80-mL reaction vessel containing a stirbar. The reaction vessel is placed in the microwave cavity, sealed and heated at 140^{O}C for 60 min at 300W of power. This process is repeated until all of solution in the Erlenmeyer flask had been cycled through the microwave (~2 runs). The combined reaction mixtures are concentrated under reduced pressure and the resulting brown oil containing **21** is used without purification. Dilution of the crude reaction mixture in THF (50 mL) followed by addition of 1N HCl (25 mL, 25 mmol) results in a reddish-orange solution. The acidic solution is stirred for an additional 30 min before removal of the volatile organics under reduced pressure. The resulting oil is diluted with water and basified by the addition of saturated aqueous $NaHCO_3$ to raise the pH >8. The basic solution is then extracted with CH_2Cl_2 (3 x 75 mL) and the combined organics are dried over Na_2SO_4. The drying agent is removed via filtration and the filtrate concentrated *in vacuo*. The resulting oil is purified by flash silica gel chromatography first eluting 1:1 EtOAc:hexanes to remove the benzophenone by-product then 95:5 CH_2Cl_2:MeOH to afford the amine **22** (2.34 g, 90%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.44 (s, 6H), 1.56 (br s. 2H), 2.97 (dd, J = 14.4, 7.8 Hz, 1H), 3.23 (dd, J = 4.1, 0.6 Hz, 1H), 3.79 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 5.64 (d, J = 9.9 Hz, 1H), 6.54 (d, J = 9.9 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 8.23 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.19, 152.91, 132.88, 129.81, 121.99, 119.87, 117.55, 117.42, 114.13, 111.01, 105.01, 75.77, 64.21, 54.85, 35.44, 27.66 (2x), 15.10; HRMS-FAB: $[M+H]^+$ calcd for $C_{18}H_{22}N_2O_3$, 315.1703; found, 315.1719.



Carboxylic Acid 23. The amine **22** (2.33 g, 7.44 mmol) is dissolved in CH_2Cl_2 (75 mL) to give a homogenous solution at rt. Commercially available $(Boc_2)O$ (1.71 g, 8.20 mmol) is added followed by 0.5N NaOH (16 mL). The reaction mixture is stirred until no more of the starting amine remained by TLC (95:5 CH_2Cl_2:MeOH, ~2 h). The reaction mixture is then concentrated under reduced pressure and the resulting oil used without further purification.

The crude oil from the *N*-Boc protection is diluted with THF (60 mL) and water (30 mL). Commercially available LiOH (Aldrich, 1.56 g, 37.2 mmol) is added and the reaction mixture is stirred at rt for 4 h. The volatile organics are then removed under reduced pressure and the resulting solid is suspended in water. 1N $KHSO_4$ is slowly added to the rapidly stirred solution to lower the pH to ~2. The cloudy aqueous solution is extracted with EtOAc (3 x 75 mL) and the combined extracts are dried over Na_2SO_4. The drying agent is removed via filtration and the filtrate is concentrated to afford the desired crude acid **23** (2.57 g, 90%) as a foam, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) 1.42 (s, 9H), 1.46 (s, 6H), 3.26 (m, 2H), 4.61-4.65 (m, 1H), 5.10 (d, J = 8.4 Hz, 1H), 5.63 (d, J = 9.6 Hz, 1H), 6.57 (d, J = 9.6 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 7.30 (d, J = 8.4 Hz, 1H), 8.34 (br. s, 1H), 10.2-10.6 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.21, 153.01, 151.89, 131.88, 129.77, 122.11, 119.72, 117.62, 117.32, 114.09, 110.96, 105.11, 86.75, 75.87, 54.85, 35.44, 29.11 (3x), 27.66 (2x); HRMS-ESI; calcd for $C_{21}H_{26}N_2O_5$, 387.1914; found, 387.1921.



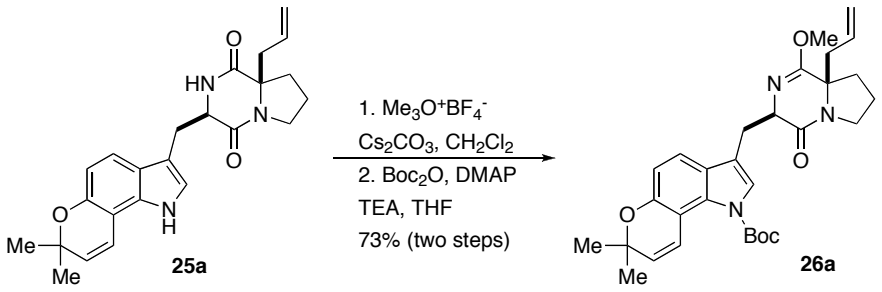
(3*R*,8a*R*,*E*)-8a-allyl-3-((7,7-dimethyl-1,7-dihydropyrano[2,3-*g*]indol-3-yl)methyl)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (25a) and (3*S*,8a*R*,*E*)-8a-allyl-3-((7,7-dimethyl-1,7-dihydropyrano[2,3-*g*]indol-3-yl)methyl)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (25b). To a 250-mL round bottom flask, the amine salt **11** (1.51 g, 7.33 mmol) and carboxylic acid **23** (2.57 g, 6.70

mmol) were dissolved in CH_3CN (120 mL). Commercially available *N*,*N*-diisopropylethylamine (Aldrich, 3.00 mL, 16.8 mmol) and HATU (2.84 g, 7.40 mmol) were sequentially added. The reaction mixture was stirred at rt until no more of the starting amine was observed by TLC (95:5 EtOAc:hexanes for starting amine; 2:1 EtOAc:hexanes for amide product).

Once complete, the reaction mixture is divided into aliquots of 60 mL. Each aliquot was placed into a 80-mL reaction vessel for the CEM microwave reactor. Heating of the crude reaction mixture in the CEM microwave reactor at 150^{O}C for 50 min at 300 W results in cleavage of the *N*-Boc protecting group and cyclization to afford crude **25a/b** based on TLC (EtOAc, **25a:** R_f = 0.1; **25b:** R_f = 0.21). Once all the aliquots have been processed through the microwave reactor, the aliquots are combined and concentrated under reduced pressure. The resulting crude oil is diluted with EtOAc (150 mL) and washed sequentially with 1N $KHSO_4$ (50 mL), water (50 mL) and brine (50 mL). The organic solution is dried using Na_2SO_4, filtered to remove the insolubles and the filtrate is concentrated under reduced pressure. The resulting oil is purified via flash silica gel chromatography (EtOAc → 95:5 EtOAc:MeOH) to afford first the *anti* diketopiperazine **25b** (0.86 g, 32%) as a foam followed by the *syn* diketopiperazine **25a** (1.03 g, 38%) as a foam.

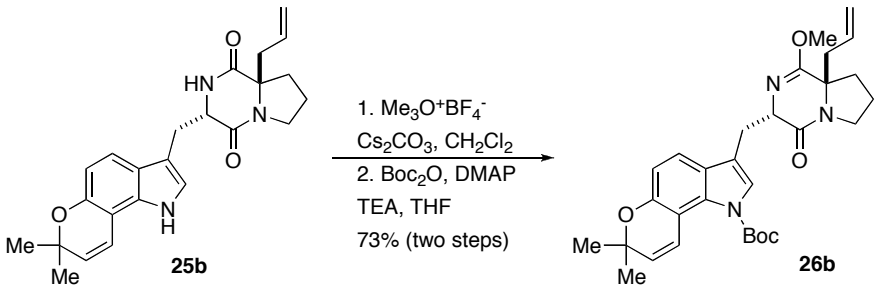
25a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6H), 1.98-2.07 (m, 3H), 2.18-2.29 (m, 1H), 2.41-2.44 (m, 1H), 2.62-2.65 (m, 1H), 2.93-2.99 (m, 1H), 3.47-3.50 (m, 2H), 4.08-4.15 (m, 3H), 5.20-5.31 (m, 2H), 5.58-5.67 (m, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.81 (br. s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.82 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.31, 170.42, 151.92, 149.24, 137.92, 133.31, 128.61, 124.11, 124.01, 122.32, 120.17, 118.71, 113.93, 110.81, 75.97, 53.39, 52.44, 47.33, 35.87, 34.22, 29.99, 29.67, 26.4, 26.2; HRMS-FAB: $[M+H]^+$ calcd for $C_{24}H_{27}N_3O_3$, 406.2125; found, 406.2131.

25b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.44 (s, 3H), 1.80-2.20 (m, 2H), 2.44-2.65 (m, 2H), 2.85 (dd, *J* = 15.0, 10.8, 1H), 3.48-3.65 (m, 2H), 3.79-3.89 (m, 1H), 4.03 (s, 2H), 4.35 (dd, *J* = 10.2, 4.8 Hz, 1H), 5.15-5.26 (m, 2H), 5.45-5.60 (m, 2H), 5.89 (br. s, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 7.21 (d, *J* = 9.6 Hz, 1H), 8.90 (br. s, 1H); HRMS-FAB: $[M+H]^+$ calcd for $C_{24}H_{27}N_3O_3$, 406.2125; found, 406.2130.

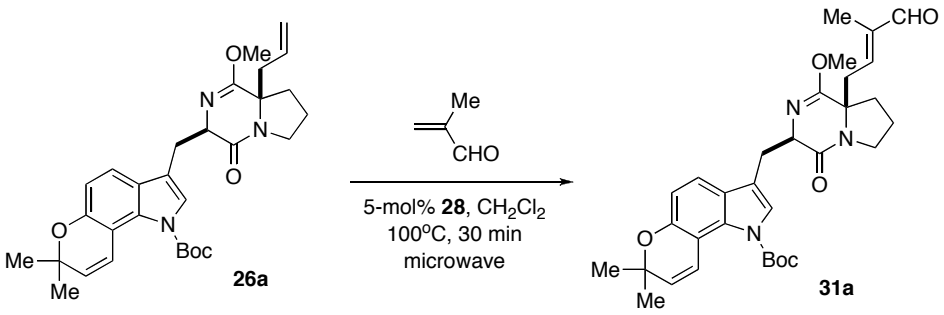


***tert*-Butyl 3-(((3*R*,8a*R*)-8a-allyl-1-methoxy-4-oxo-3,4,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-7,7-dimethylpyrano[2,3-*g*]indole-1(7*H*)-carboxylate (26a)**. The DKP **25a** (1.03 g, 3.00 mmol) is dissolved in CH_2Cl_2 (60 mL) and stirred at rt. Commercially available Cs_2CO_3 (Alfa Aesar, 14.6 g, 45 mmol) is added in a single portion. Commercially available $Me_3O^+ \bullet BF_4^-$ (2.22 g, 15 mmol) is ground into a fine powder and added to the reaction mixture in a single portion. The reaction continued stirring at rt until no more starting material remained by TLC (EtOAc, ~6 h). The reaction is poured into water (50 mL) and the organic layer removed. The aqueous solution is further extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic extracts are dried over Na_2SO_4. The drying agent is removed by filtration through a sintered glass funnel and the volatile organics are removed *in vacuo* to afford an oil, which was used without further purification.

The crude lactim ether was dissolved in CH_2Cl_2 (30 mL) and stirred at rt. Commercially available DMAP (Aldrich, 367 g, 3.00 mmol) and Et_3N (0.52 mL, 3.0 mmol) were added sequentially to the reaction mixture followed by commercially available $(Boc)_2O$ (1.87 g, 9.00 mmol). The reaction mixture is stirred until no more of the unprotected indole was observed by TLC (2:1 EtOAc:hexanes, ~2 h). The reaction mixture is concentrated *in vacuo* and the crude reaction mixture is purified by flash silica gel chromatography (2:1 EtOAc:hexanes) to afford the desired protected compound **26a** (1.12 g, 73 %) as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6H), 1.59 (s, 9H), 1.80-2.20 (m, 4H), 2.90 (dd, J = 14.4, 9.3 Hz, 1H), 3.26-3.36 (m, 2H), 3.65 (s, 3H), 3.91-3.94 (br. m, 2H), 3.98-4.04 (m, 1H), 4.34 (dd, J = 9.0, 3.9 Hz, 1H), 5.15-5.21 (m 2H), 5.45-5.57 (d, J = 9.9 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 9.9 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.39 (s, 1H); HRMS-FAB: calcd for $C_{30}H_{37}N_3O_5$, 520.2806; found, 520.2804.

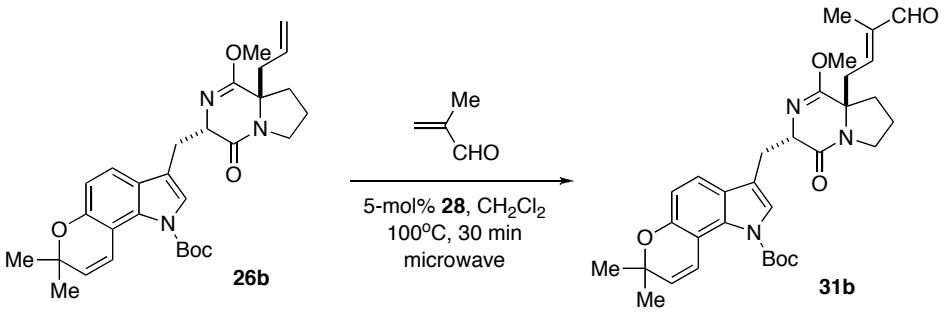


***tert*-Butyl 3-(((3*S*,8a*R*)-8a-allyl-1-methoxy-4-oxo-3,4,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-7,7-dimethylpyrano[2,3-*g*]indole-1(7*H*)-carboxylate (26b)**. The procedure outlined for the conversion of **25a** to **25b** was followed using **25b** (860 mg, 2.12 mmol) to afford **26b** (782 mg, 71 %), which was purified by flash silica gel chromatography (2:1 EtOAc:hexanes) to afford **26b** as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.46 (s, 3H), 1.59 (s, 9H), 1.70-2.00 (m, 3H), 2.25-2.40 (m, 3H), 3.09 (dd, *J* = 14.4, 6.9 Hz, 1H), 3.30-3.36 (m, 2H), 3.62 (s, 3H), 3.65-3.75 (m, 1H), 4.23 (dd, *J* = 6.3, 6.6 Hz, 1H), 5.20-5.27 (m, 2H), 5.50-5.60 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 9.9 Hz, 1H), 7.26 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H); HRMS-FAB: calcd for $C_{30}H_{37}N_3O_5$, 520.2806; found, 520.2811.

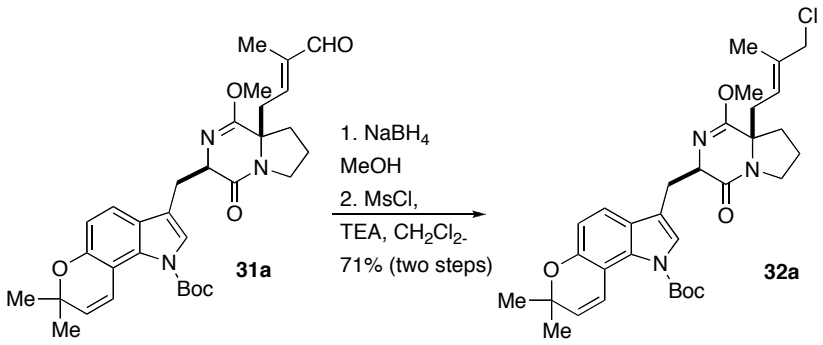


***tert*-Butyl 3-(((3*R*,8a*R*)-8a-((*E*)-4-carboxaldehyde-3-methylbut-2-enyl)-1-methoxy-4-oxo-3,4,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-7,7-dimethylpyrano[2,3-*g*]indole-1(7*H*)-carboxylate (31a)**. To a 25-mL round-bottomed flask, the allyl lactim ether **26a** (250 mg, 0.48 mmol) is dissolved in CH_2Cl_2 (5 mL). Commercially available methacrolein (Aldrich, 0.5 mL, 6.0 mmol) is added in a single portion via syringe. The reaction mixture is stirred for 5 min then transferred to a CEM 10-mL microwave tube. Commercially available Hoveyda-Grubbs 2nd Generation catalyst (**28**, 15 mg, 0.02 mmol) is added to the microwave tube in a single portion. The microwave tube is capped and irradiated using a CEM Discovery unit for 30 min at 100^{O}C at 200 W of power. Following cooling, the tube is removed and the contents are transferred to a 25-mL round-bottomed flask and the volatile organics are

removed under reduced pressure. The remaining residue is purified by flash silica gel chromatography eluting 2:1 EtOAc:hexanes to afford the starting allyl **26a** first (25 mg, 10%) followed by the desired aldehyde **31a** (196 mg, 73%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6H), 1.56 (s, 3H), 1.59 (s, 9H), 1.80-2.20 (m, 3H), 2.90 (dd, *J* = 14.4, 9.3 Hz, 1H), 3.26-3.36 (m, 2H), 3.65 (s, 3H), 3.91-3.94 (br. m, 2H), 3.98-4.04 (m, 1H), 4.34 (dd, *J* = 9.0, 3.9 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 6.42 (t, *J* = 6.7 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 9.9 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 9.07 (s, 1H); HRMS-FAB: $[M+H]^+$ calcd for $C_{32}H_{39}N_3O_6$, 562.2912; found, 562.2911.



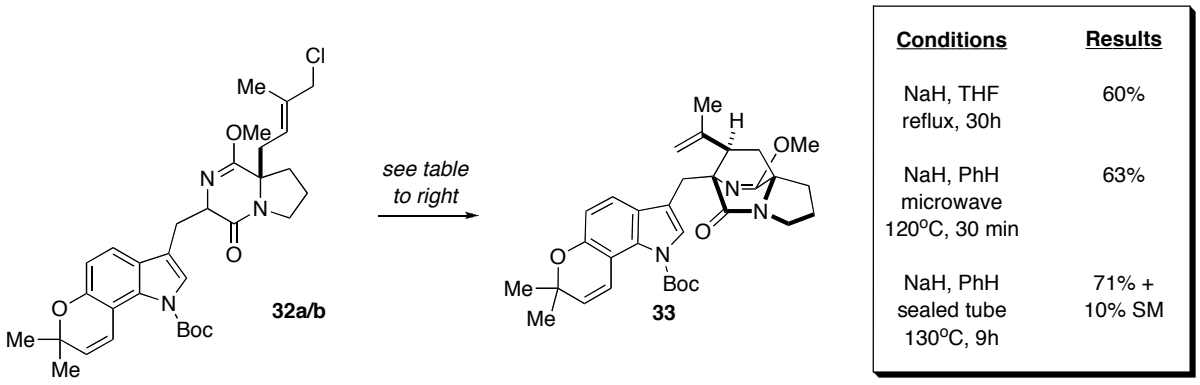
***tert*-Butyl 3-(((3*S*,8a*R*)-8a-((*E*)-4-carboxaldehyde-3-methylbut-2-enyl)-1-methoxy-4-oxo-3,4,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-7,7-dimethylpyrano[2,3-*g*]indole-1(7*H*)-carboxylate (31b)**. To a 25-mL round-bottomed flask, the allyl lactim ether **26b** (250 mg, mmol) is dissolved in CH_2Cl_2 (5 mL). Commercially available methacrolein (Aldrich, 0.5 mL, 6.0 mmol) is added in a single portion via syringe. The reaction mixture is stirred for 5 min then transferred to a CEM 10-mL microwave tube. Commercially available Hoveyda-Grubbs 2nd Generation catalyst (**28**, 15 mg, 0.02 mmol) is added to the microwave tube in a single portion. The microwave tube is capped and irradiated using a CEM Discovery unit for 30 min at 100^{O}C at 200 W of power. Following cooling, the tube is removed and the contents are transferred to a 25-mL round-bottomed flask and the volatile organics are removed under reduced pressure. The remaining residue is purified by flash silica gel chromatography eluting 2:1 EtOAc:hexanes to afford the starting allyl **26b** first (25 mg, 10 %) followed by the desired aldehyde **31b** (193 mg, 71 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.46 (s, 3H), 1.57 (s, 3H), 1.59 (s, 9H), 1.70-2.00 (m, 3H), 2.25-2.40 (m, 3H), 3.09 (dd, *J* = 14.4, 6.9 Hz, 1H), 3.30-3.36 (m, 2H), 3.62 (s, 3H), 3.65-3.75 (m, 1H), 3.92 (s, 2H), 4.23 (dd, *J* = 6.3, 6.6 Hz, 1H), 5.27 (t, *J* = 6.9 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 6.31 (t, *J* = 6.5 Hz, 1H) 6.76 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 9.9 Hz, 1H), 7.26 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 9.10 (s, 1H); HRMS-FAB: $[M+H]^+$ calcd for $C_{32}H_{39}N_3O_6$, 562.2912; found, 562.2917.



***tert*-butyl 3-(((3*R*,8a*R*)-8a-((*E*)-4-chloro-3-methylbut-2-enyl)-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-7,7-dimethylpyrano[2,3-*g*]indole-1(7*H*)-carboxylate (32a)**. To a 25-mL round-bottomed flask, the aldehyde **31a** (164 mg, 0.29 mmol) is dissolved in MeOH (5 mL) then cooled in an ice/water bath. $NaBH_4$ (Acros, 28 mg, 0.90 mmol) is then added in a single portion and the reaction mixture is stirred at $0^{O}C$ for an additional 5 min. The cooling bath is then removed and the reaction is allowed to warm to rt. The reaction is monitored by TLC (3:1 EtOAc:hexanes) for the disappearance of the starting aldehyde (~1 h). The reaction is quenched by the addition of aqueous saturated $NaHCO_3$ (5 mL). The aqueous solution is extracted with EtOAc (3 x 10 mL) and the combined organic extracts are dried over Na_2SO_4. Following removal of the drying agent, the filtrate is concentrated *in vacuo* and the resulting crude alcohol is used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6H), 1.56 (s, 3H), 1.59 (s, 9H), 1.80-2.20 (m, 9H), 2.90 (dd, *J* = 14.4, 9.3 Hz, 1H), 3.26-3.36 (m, 2H), 3.65 (s, 3H), 3.91-3.94 (br. m, 2H), 3.98-4.04 (m, 1H), 4.34 (dd, *J* = 9.0, 3.9 Hz, 1H), 5.15 (t, *J* = 7.5 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 9.9 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H).

To a 25-mL round-bottomed flask, triethylamine (100 μL, 0.60 mmol) is added to the crude alcohol in CH_2Cl_2 (10 mL). The reaction mixture is cooled in an ice/water bath for 10 min before the addition of commercially available methanesulfonyl chloride (Aldrich, 45 μL, 0.60 mmol) via a syringe in a single portion. The reaction mixture is allowed to slowly warm to rt with stirring and is monitored by TLC (5:1 EtOAc:hexanes) for the disappearance of the starting alcohol (R_f = 0.25, ~10 h). Once the reaction is finished, the volatile organics are removed and the resulting oil was purified by flash silica gel chromatography eluting 5:1 EtOAc:hexanes to afford the desired allyl chloride **32a** (120 mg, 71%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.71 (s, 9H), 1.75 (s, 3H), 1.78-2.10 (m, 4H), 2.22 (m, 1H), 2.38 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.61 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.87 (dd, *J* = 14.1, 10.8 Hz, 1H), 3.45-3.51 (m, 2H), 4.06 (s, 3H), 4.21 (dt, *J* = 11.1, 3.0 Hz, 1H), 5.2-5.58 (br. t, 1H), 5.61 (d, *J* = 9.9 Hz, 1H), 5.74 (br. d, *J* = 3 Hz, 1H), 6.83 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.99 (dd, *J* = 9.9, 0.6 Hz, 1H), 7.31

(d, J = 8.4 Hz, 1H), 7.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.99, 167.65, 156.88, 152.45, 148.91, 137.62, 132.91, 127.04, 124.62, 123.87, 122.01, 120.54, 119.76, 113.39, 111.32, 86.01, 75.67, 61.01, 58.17, 57.97, 51.21, 41.55, 37.11, 34.01, 28.67 (3x), 28.56, 27.7, 27.3, 24.5, 19.21; HRMS-FAB: $[M+H]^+$ calcd for $C_{32}H_{40}N_3O_5Cl$, 582.2729; found, 582.2731.

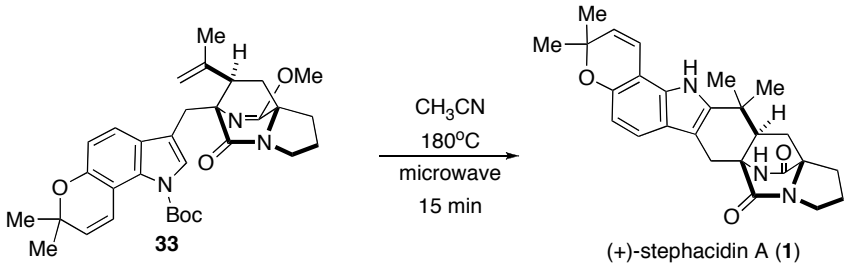


Conditions	Results
NaH, THF reflux, 30h	60%
NaH, PhH microwave 120°C, 30 min	63%
NaH, PhH sealed tube 130°C, 9h	71% + 10% SM

S_N2' Cyclization of 32a/b (33). To a 25-mL round-bottomed flask, the allyl chloride **32a/b** (100 mg, 0.17 mmol) is dissolved in PhH (10 mL) and transferred to a 42-mL sealed tube. Commercially available NaH (60% dispersion, Aldrich, 140 mg, 3.5mmol) is suspended in petroleum ether (5 mL) and stirred at rt for 20 min. The cloudy solution is filtered through a sinter glass funnel and the remaining NaH is added to the sealed tube. The reaction vessel is tightly sealed and placed in an oil bath and heated to 130°C for 9h. The progress of the reaction is occasionally monitored by TLC (5:1 EtOAc:hexanes) for the disappearance of the starting allyl chloride **32a**. Once the reaction is complete, the reaction is cooled to 0°C in an ice/water bath and slowly quenched by the addition of water (1 mL). Once no more NaH is visibly suspended in solution, the reaction mixture is poured into an additional quantity of water (8 mL) and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 10 ml) and the combined organic extracts are dried over Na_2SO_4, filtered to remove the drying agent and concentrated under reduced pressure. The crude product is purified by flash silica gel chromatography eluting 2:1 EtOAc:hexanes to afford the bridged bicycle **33** (65 mg, 71%) as an oil in addition to recovered **32a** (10 mg, 10%).

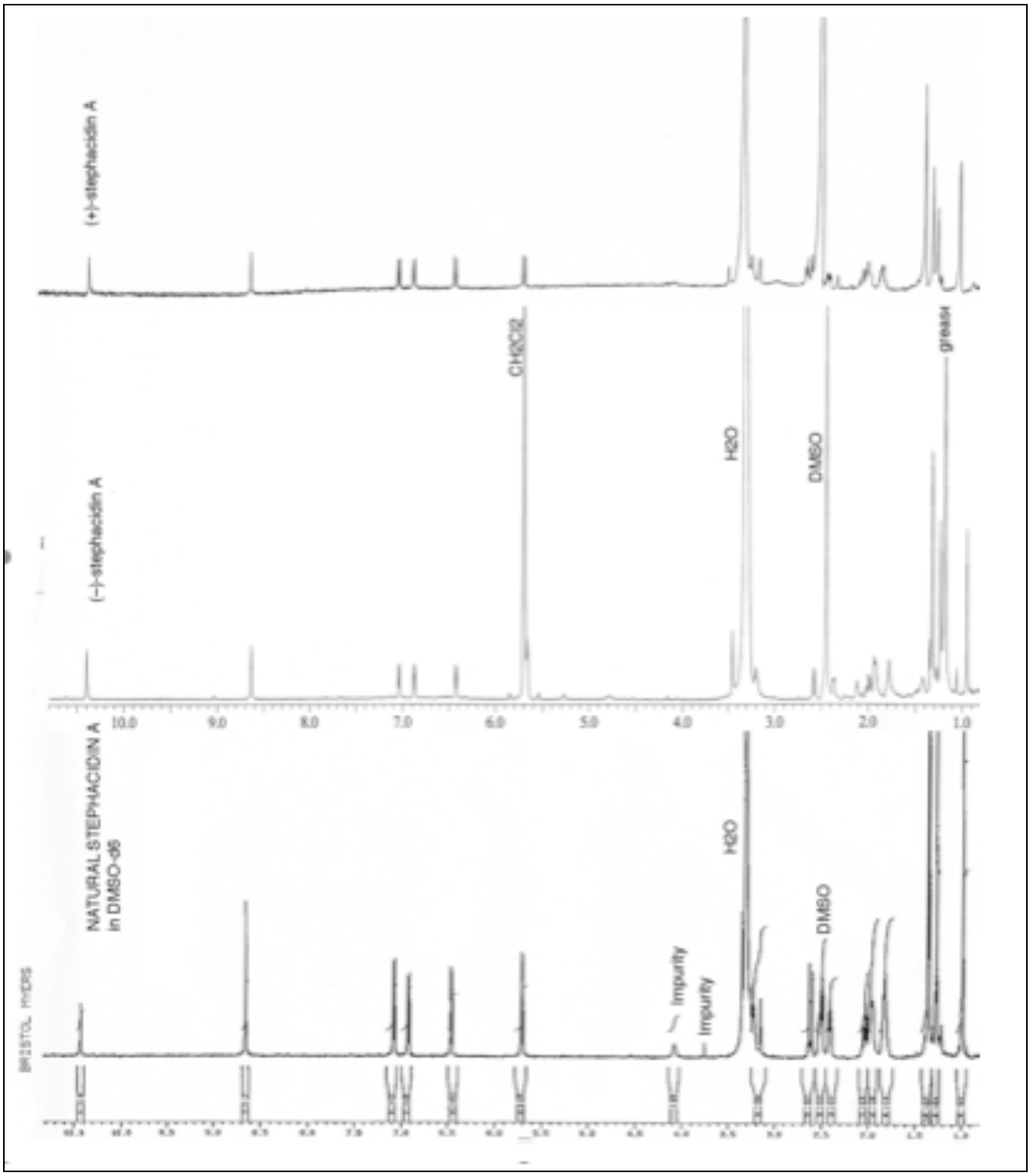
The same procedure detailed above was employed for allyl chloride **32b** and afforded the desired bridged bicycle **33** in 70% yield in addition to recovered **32b** (8 mg, 8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 3H), 1.50 (s, 3H), 1.63 (s, 9H), 1.69 (s, 3H), 1.82-1.88 (m, 1H), 1.91-1.99 (m, 2H), 2.02-2.07 (m, 1H), 2.52 (dd, J = 10.5, 5.5 Hz, 1H), 2.60 (dt, J = 12.5, 5.5 Hz, 1H), 3.11 (d, J = 15.0 Hz, 1H), 3.40

(d, *J* = 15.0 Hz, 1H), 3.44-3.48 (m, 1H), 3.55-3.60 (m, 1H), 3.68 (s, 3H), 4.76 (s, 1H), 4.88 (s, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 10.0 Hz, 1H), 7.54 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 171.8, 151.3, 150.4, 144.4, 132.0, 127.9, 126.8, 126.4, 122.3, 122.1, 117.2, 115.4, 112.9, 109.5, 83.1, 74.9, 69.3, 64.1, 54.7, 48.7, 43.6, 37.8, 29.2, 28.4, 27.5, 27.3, 27.0, 25.0, 19.7. HRMS-FAB: $[M+H]^+$ calcd for $C_{32}H_{39}N_3O_5$, 546.2962; found, 546.2961.



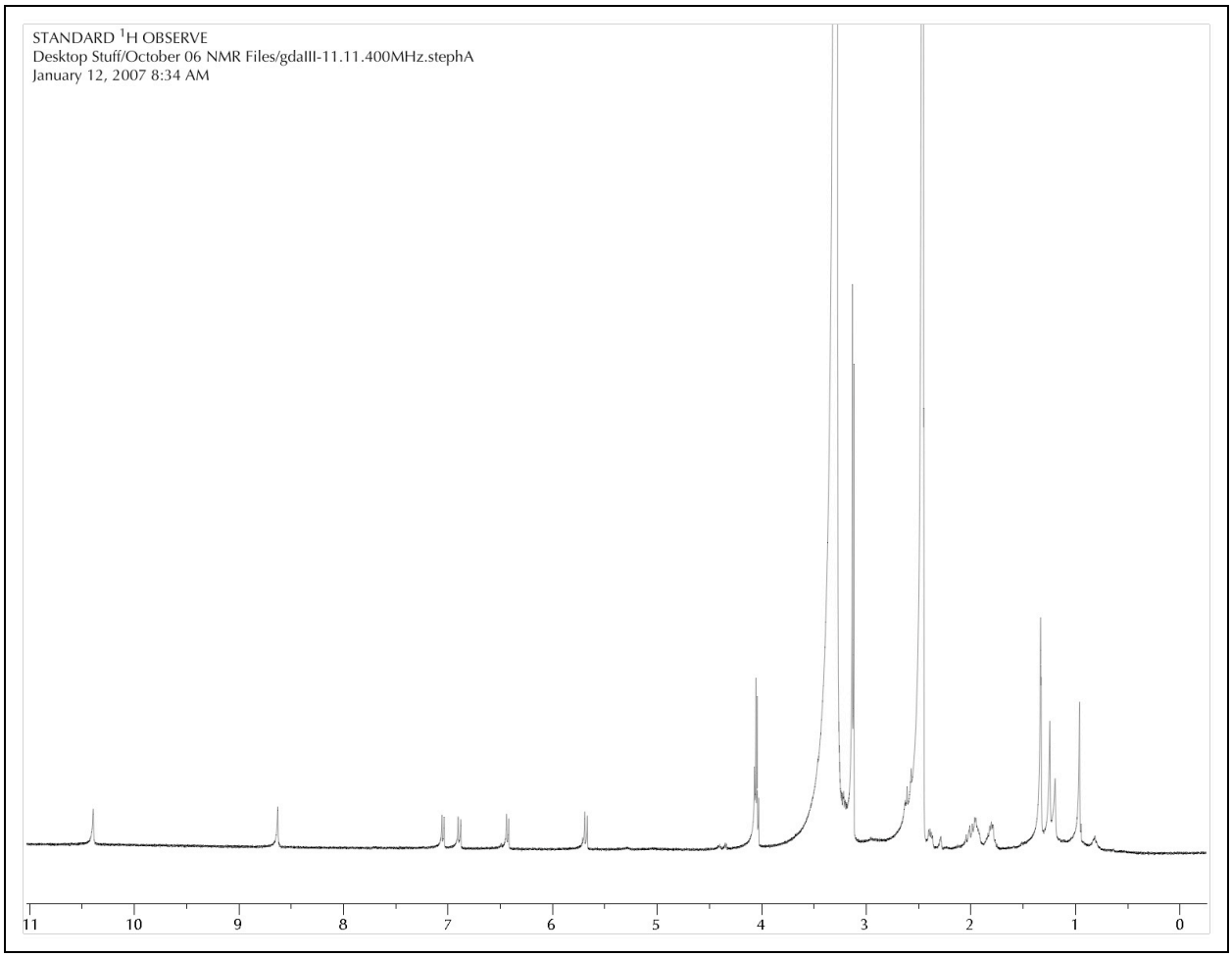
(-)-Stephacidin A (1). To a 10-mL round-bottomed flask, the bridged bicycle **33** (15 mg, 0.027 mmol) is dissolved in CH_3CN (1 mL). Commercially available $Pd(TFA)_2$ (50 mg, 0.15 mmol) is added in a single portion and the reaction mixture is stirred at rt and monitored by TLC (2:1 EtOAc:hexanes) for the consumption of the starting olefin **33** (~30 min). Once no more of the starting olefin is visible by TLC, the reaction mixture is diluted with EtOH (1 mL) and cooled to 0^{O}C in an ice/water bath. $NaBH_4$ (Acros, 10 mg, 0.33 mmol) is added slowly over 10 min to quench the intermediate alkyl-palladium species during which excessive gas evolution is observed and palladium crashes out of solution as Pd black. The reaction is stirred for an additional 30 min before concentration *in vacuo*. The crude product is dissolved in EtOAc (5 mL) and filtered through a plug of Celite® to remove any residual Pd black. The filtrate is washed with 0.1N HCl (2 x 2.5 mL) and the combined aqueous extracts are back extracted with EtOAc (2 x 5 mL). The combined organic extracts are dried over Na_2SO_4 and the volatile organics are removed under reduced pressure. The crude heptacycle is dissolved in CH_3CN (1 mL) and heated in a 10-mL CEM microwave tube at 180^{O}C for 15 min. The volatile organics are removed under reduced pressure to afford (-)-stephacidin A (**1**, 7 mg, 58%) as white flaky powder that displayed spectral (^{1}H NMR and HRMS) and physical properties to those reported in the literature. ^{1}H NMR (400 MHz, DMSO) δ 0.96 (s, 3H), 1.19 (s, 3H), 1.25 (s, 3H), 1.33 (s 3H), 1.77-1.87 (m, 2H), 1.90-1.99 (m, 2H), 2.01 (dd, *J* = 13.9, 10.1 Hz, 1H), 2.39 (dd, *J* = 9.8, 5.0 Hz, 1H), 2.48 (m, 1H, underneath DMSO peak), 2.59 (d, *J* = 15.5 Hz, 1H), 3.20-3.29 (m, 3H), 5.65 (d, *J* = 9.8 Hz, 1H), 6.43 (d, *J* = 8.3 Hz, 1H), 6. 87 (d, *J* = 9.8 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 8.62 (s, 1H),10.39 (s, 1H); HRMS-FAB: $[M+H]^+$ calcd for $C_{26}H_{29}N_3O_3$, 432.2287; found, 432.2282.

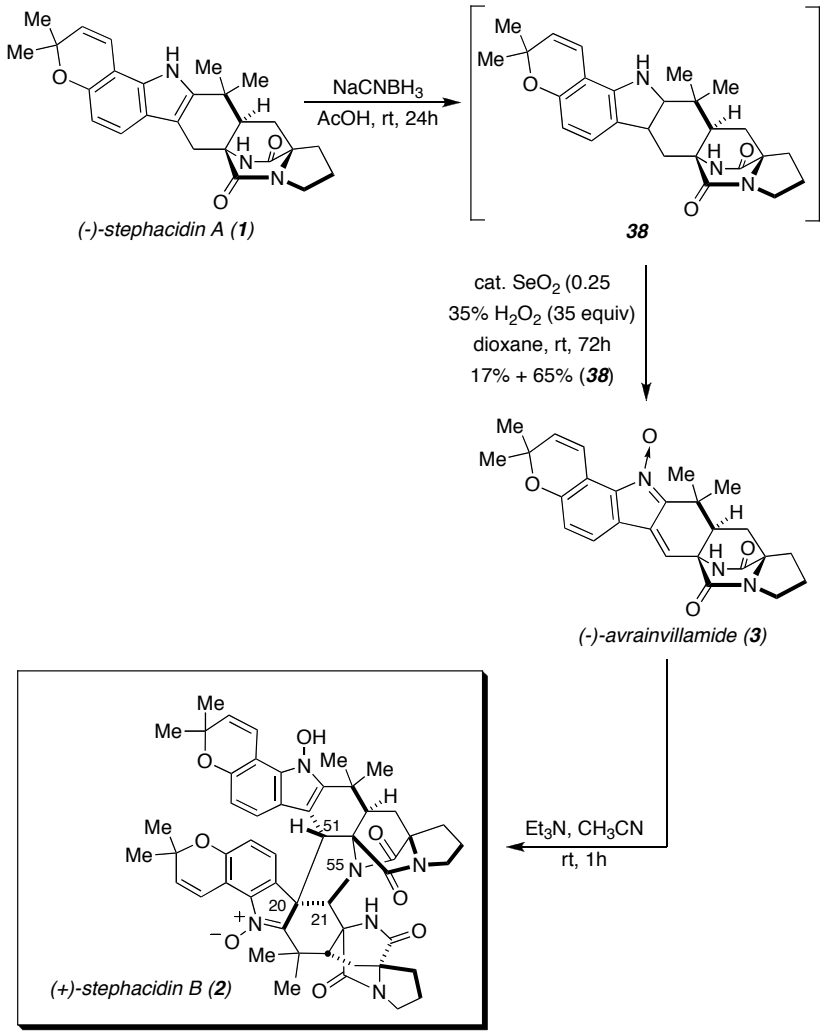
Published ^{1}H NMR Spectra of Stephacidin A by the Baran Group in d_6-DMSO[2]



[2]Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678-8693.

^{1}H NMR of synthetic (-)-Stephacidin A (400 MHz, d_6-DMSO)

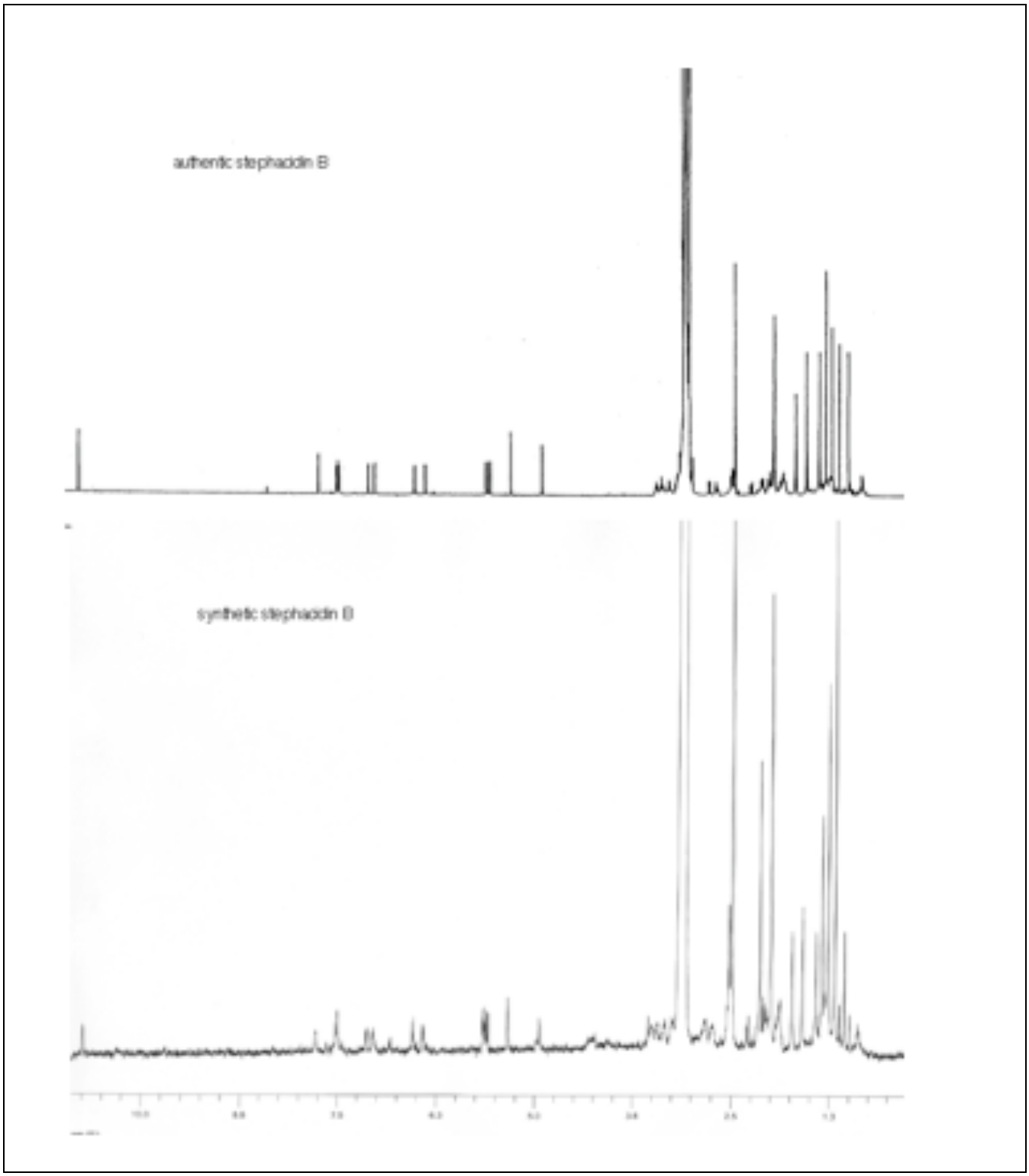




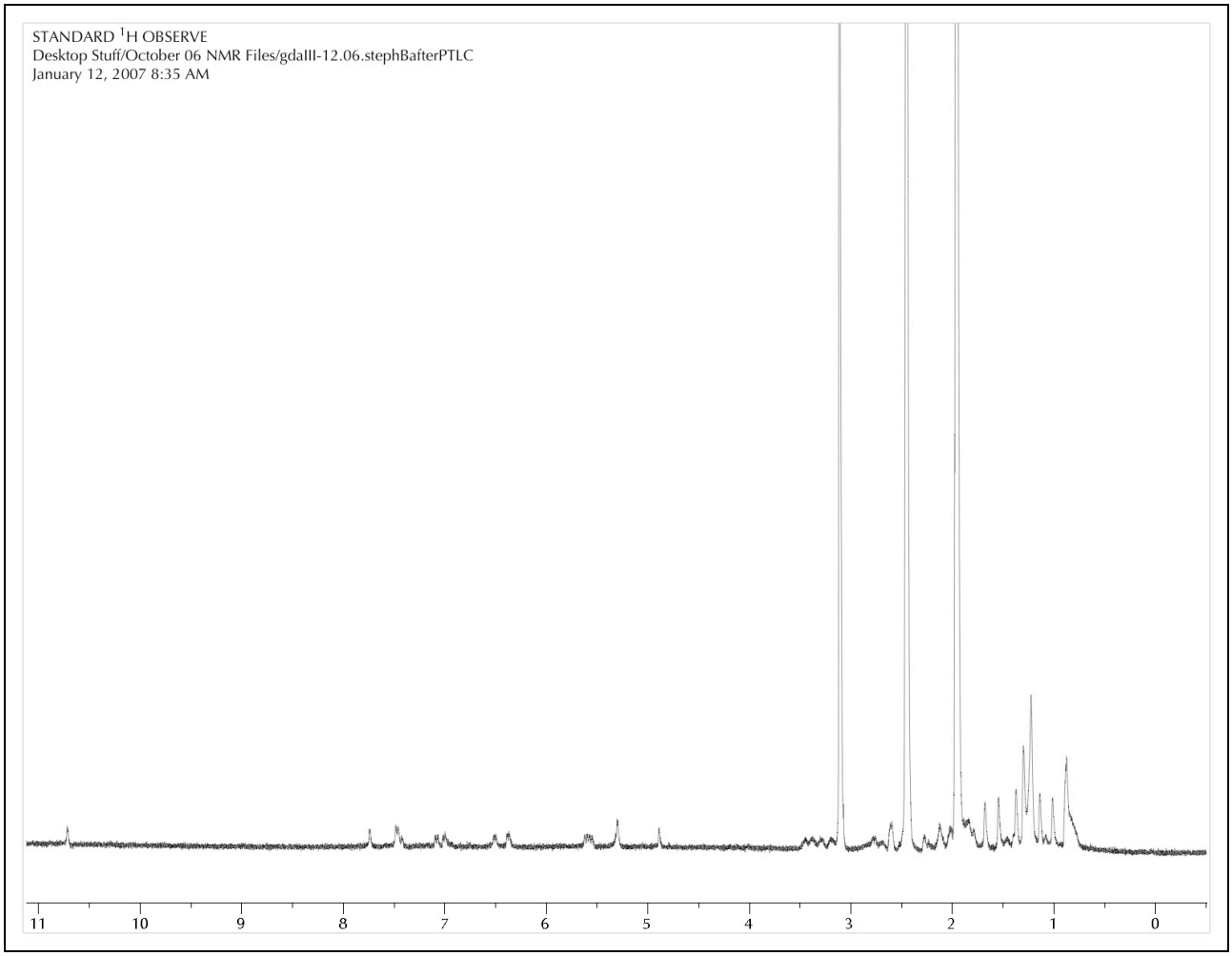
(+)-Stephacidin B (2). The previously reported procedure developed by Baran for the oxidation of stephacidin A (**1**) to avrainvillamide (**3**) was followed using 7 mg of **1** to afford 1 mg of **3** (17%). The totally synthetic avrainvillamide (**3**) was dimerized to (+)-stephacidin B (**2**) using the procedure developed by Myers' laboratory in ~100% yield by NMR analysis.

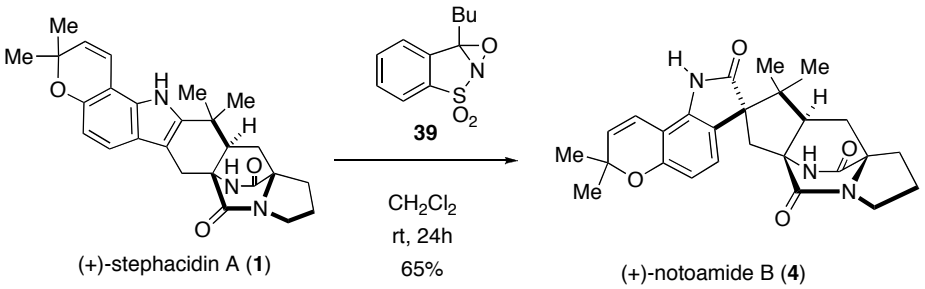
Spectral Data for (+)-Stephacidin B (**2**): ^{1}H NMR (400 MHz, CD_3CN:DMSO 1:1) δ 1.01 (s, 3H), 1.14 (s, 3H), 1.23 (s, 3H), 1.27-1.32 (br. s, 6H), 1.37 (s, 3H), 1.55 (s, 3H), 1.68 (s, 3H), 1.91-1.76 (m, 4H), 2.00-2.15 (br. m, 4H), 2.28 (m, 1H), 2.52 (br. m, 2H), 2.71 (br. m, 1H), 2.77 (br. m, 1H), 3.15-3.24 (br. m, 2H), 3.34-3.44 (br. m, 2H), 3.46-3.49 (m, 1H), 4.90 (s, 1H), 5.31 (s, 1H), 5.57 (d, J = 10.1 Hz, 1H), 5.62 (d, J= 10.3 Hz, 1H), 6.38 (d, J = 9.3 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 10.6 Hz, 1H), 7.08 (d, J = 10.5 Hz, 1H), 7.44 (d, J = 9.2 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.74 (s, 1H), 10.72 (s, 1H); HRMS-FAB: $[M+H]^+$ calcd for $C_{52}H_{54}N_6O_8$, 891.4076; found, 891.4071.

Published ^{1}H NMR Spectra of Stephacidin B by the Baran Group in d_6-DMSO:CD_3CN[2]



^{1}H NMR Spectrum of synthetic (+)-Stephacidin B (400 MHz, d_6-DMSO:CD_3CN)



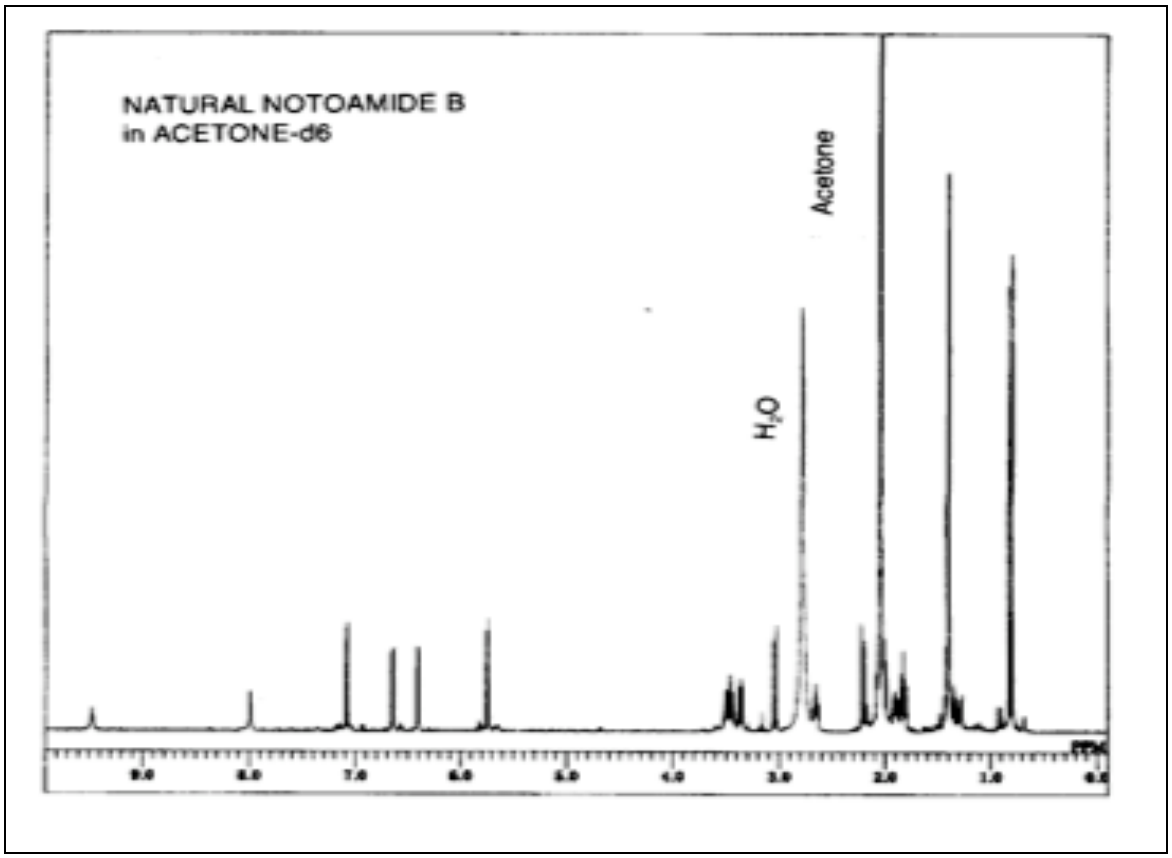


(+)-stephacidin A (**1**) (+)-notoamide B (**4**)

(+)-Notoamide B (4). To a 5-mL round bottomed flask, (+)-Stephacidin A (**1**, 3 mg, 0.007 mmol) was suspended in CH_2Cl_2 (1 mL). The oxaziridine **39** (30 mg, 0.125 mmol) was added in a single portion and the reaction mixture was stirred at rt for 24 h during, which time the solution slowly becomes clear. The

reaction is then quenched by the addition of saturated aqueous $Na_2S_2O_3$ (2 mL) and the organic layer is separated from the aqueous. The aqueous layer is extracted twice more with CH_2Cl_2 (2 x 2 mL) and the combined extracts are dried over Na_2SO_4. Removal of the drying agent and the volatile organics under reduced pressure gives the crude product, which is purified by PTLC eluting 95:5 CH_2Cl_2:MeOH to afford (+)-notoamide B (2 mg, 65%). The product displayed good spectral correlation to the reported data, but with opposite sign of rotation: $[\alpha]_D$ = +114˚ (*c* 0.05, MeOH); lit: $[\alpha]_D$ = -118˚ (*c* 0.064 , MeOH). ^{1}H NMR (400 MHz, d_6-Acetone) δ 0.79 (s, 3H), 0.82 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 1.76-2.06 (m, 5H, underneath acetone peak), 2.23 (d, *J*= 14.1 Hz, 1H), 2.60-2.67 (m, 1, underneath water peak), 3.02 (d, *J* = 14.2 Hz, 1H), 3.37 (dd, *J* = 10.1, 8.4 Hz, 1H), 3.40-3.59 (m, 2H), 5.78 (d, *J* = 9.5 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 9.5 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 8.00 (br. s, 1H), 9.45 (br. s, 1H); HRMS-FAB: $[M+H]^+$ calcd for $C_{26}H_{29}N_3O_4$, 448.2231; found, 448.2237.

Published ^{1}H NMR Spectrum of Notoamide B by the Tsukamoto Group in d_6-Acetone[3]



[3]Kato, H.; Yoshida, T.; Tokue, T.; Nojiri, Y.; Hirota, H.; Ohta, T.; Williams, R. M.; Tsukamoto, S. *Angew. Chem. Int. Ed*. **2006**, *46*, 2254-2256.

^{1}H NMR Spectrum of synthetic (+)-Notoamide B in d_6-Acetone