



Supporting Information

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Short, Enantioselective Synthesis of Stephacidin A

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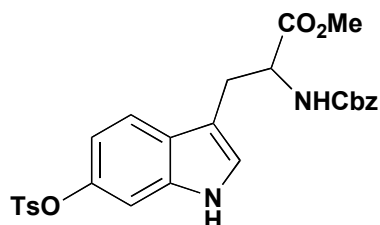
General Procedures. All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), toluene, benzene, acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), methanol (MeOH), *N,N*-dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Crystalline palladium acetate ($\text{Pd}(\text{OAc})_2$) was prepared from palladium sponge following the procedure of Wilkinson *et al.*¹ Diazomethane was prepared according to Aldrich Technical Bulletin No. 180. Tris(dibenzylideneacetone)dipalladium(0) chloroform complex ($\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$) was prepared according to the procedure of Ukai *et al.*² Chloromethyl methyl ether (MOMCl) was dried by distillation over calcium hydride. Sodium chlorite (NaClO_2) was recrystallized from water. Iron(III) acetylacetonate ($\text{Fe}(\text{acac})_3$) was recrystallized from EtOH. The Burgess reagent was prepared according to the procedure of Burgess *et al.*³ Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde or phosphomolybdic acid or basic aqueous potassium permanganate (KMnO_4) and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). Optical rotation measurements were recorded on a Perkin Elmer Model 341 polarimeter using a 10 cm cell. NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b =

¹ T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, G. Wilkinson, *J. Chem. Soc.* **1965**, 3632 – 3640.

² T. Ukai, H. Kawazawa, Y. Ishii, J. J. Bonnett, J. A. Ibers. *Organomet. Chem.* **1974**, 65, 253 – 266.

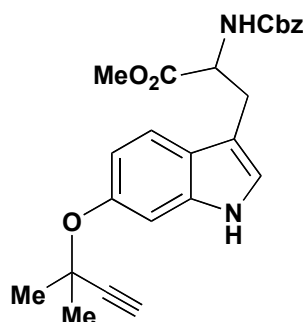
³ E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, *J. Org. Chem.* **1973**, 26 – 31.

broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.



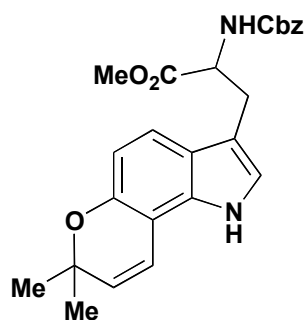
Tryptophan derivative 8: Compound **5** (100 mg, 360 μ mol) was dissolved in THF (3.6 mL, 0.1 M) and cooled to -78°C . After 5 min at -78°C , lithium triethylborohydride (4.0 mL from a 1 M solution in THF, 0.40 mmol, 1.1 equiv) was added over 30 sec. After 10 min of stirring, saturated aqueous NH_4Cl (5 mL) was added at -78°C . The reaction was

allowed to warm to ambient temperature and water (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (10 mL). The organic layers were combined and washed with brine (15 mL), dried over anhydrous MgSO_4 , and concentrated *in vacuo*. To the resultant crude clear oil was added compound **6** (156 mg, 0.40 mmol, 1.1 equiv), diazabicyclo-[2.2.2]-octane (DABCO, 120 mg, 1.1 mmol, 3.0 equiv), and tetrabutylammonium iodide (406 mg, 1.1 mmol, 3.0 equiv). The mixture was azeotropically dried using benzene. The reaction flask was evacuated under high vacuum and backfilled with N_2 . DMF (1.2 mL) was added to the reaction flask followed by $\text{Pd}(\text{OAc})_2$ (4.0 mg, 17 μ mol, 0.05 equiv). The reaction flask was placed in an oil bath preheated to 85°C . After 4 hr the reaction was removed from the heat and water (5 mL) was added. The reaction was extracted with EtOAc (5×10 mL) and the organic portions were washed with brine (15 mL), dried over anhydrous MgSO_4 , and concentrated *in vacuo* to give a crude orange foam. This material was purified by flash column chromatography (silica gel, 1:6 \rightarrow 1:1 EtOAc:hexanes) to yield 141 mg (75%) of compound **8**: white foam; $R_f = 0.38$ (silica gel, 1:1 EtOAc:hexanes); IR (neat) ν_{max} 3406, 1707, 1598, 1508, 1457, 1364, 1213, 1177, 1089, 950, 841, 814, 733, 551 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.27 (s, 1 H), 7.63 (d, $J = 8.0$ Hz, 2 H), 7.28 (m, 5 H), 7.21 (d, $J = 7.2$ Hz, 2 H), 7.06 (s, 1 H), 6.91 (s, 1 H), 6.49 (d, $J = 8.5$, 1 H), 5.26 (d, $J = 7.8$ Hz, 1 H), 5.05 (d, $J = 12$ Hz, 1 H), 5.00 (d, $J = 12$ Hz, 1 H), 4.63 – 4.60 (m, 1 H), 3.57 (s, 3 H), 3.21 – 3.12 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.4, 155.9, 145.6, 145.4, 136.3, 135.7, 132.6, 129.8 (2 C), 128.7 (3 C), 128.4 (2 C), 128.2 (2 C), 126.5, 124.6, 119.0, 114.3, 110.0, 105.8, 67.1, 54.6, 52.5, 28.0, 21.8; HRMS (ESI-TOF) calcd for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_7\text{S}$ [$\text{M}+\text{H}^+$] 523.1533; found 523.1536.



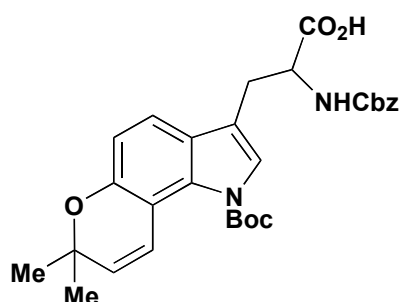
Tryptophan derivative 10: Tryptophan derivative **8** (120 mg, 0.23 mmol) was dissolved in 1:1 CH₂Cl₂:CH₃CN (2.3 mL total volume, 0.1 M) and 4-DMAP (0.3 mg, 2.3 μmol, 0.01 equiv) followed by di-*tert*-butyl dicarbonate (Boc₂O, 50 mg, 0.23 mmol, 1.0 equiv) were added. After 30 min, the reaction was concentrated *in vacuo* and purified by flash column chromatography (silica gel, 1:6 → 1:3 EtOAc:hexanes) to afford 140 mg (95%) of the Boc protected tryptophan. The

Boc protected tryptophan (4.343 g, 6.98 mmol) so prepared was dissolved in methanol (70 mL, 0.1 M) and cooled to 0 °C. Mg turnings (1.697 g, 69.8 mmol, 10 equiv) were added to the reaction solution and the ice bath was removed. After 2.5 hr, the reaction was poured through a cotton plug and EtOAc (100 mL) was used to rinse the plug. The reaction mixture was washed with 1 M aqueous HCl (100 mL) upon which a white gel formed in the separatory funnel which dissolved upon vigorous shaking. The layers were separated and the aqueous portion was extracted with EtOAc (2 × 50 mL). Organic layers were combined and washed with brine (100 mL), dried over anhydrous MgSO₄ and concentrated *in vacuo* to produce a yellow foam. The free phenol was dissolved in CH₃CN (70 mL, 0.1 M). 1,1-dimethylprop-2-ynyl methyl carbonate (2.97g, 20.9 mmol, 3.0 equiv) and CuCl₂ (0.9 mg, 6.98 μmol, 0.001 equiv) were added to the reaction mixture and the solution was cooled to 0 °C. After 5 min at 0 °C, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.18g, 20.9 mmol, 3.0 equiv) was added dropwise over 10 min. Color change was observed from a light yellow color through red to brown-green clear color. After 24 hr, the reaction was diluted with EtOAc (50 mL) and 1 M aqueous HCl (100 mL) was added at 0 °C. The layers were separated and the aqueous portion was extracted with EtOAc (2 × 50 mL). Organics were combined and washed with brine (100 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica gel, 1:6 EtOAc:hexanes) to give compound **10** (2.81 g, 75% over two steps): white foam; R_f = 0.51 (silica gel, 1:1 EtOAc: hexanes); IR (neat) ν_{max} 2985, 1725, 1477, 1438, 1380, 1254, 1212, 1155, 1084, 956, 818, 768, 698, 682, 565; ¹H NMR (500 MHz, CDCl₃) δ 7.97 (s, 1 H), 7.34 (m, 6 H), 7.09 (d, *J* = 8.5 Hz, 1 H), 5.43 (d, *J* = 7.9 Hz, 1 H), 5.14 (d, *J* = 12, 1 H), 5.09 (d, *J* = 12, 1 H), 4.74 – 4.69 (m, 1 H), 3.69 (s, 3 H), 3.26 – 3.16 (m, 2 H), 2.56 (s, 1 H), 1.67 (s, 6 H), 1.66 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 155.9, 153.3, 149.7, 136.4, 135.7, 128.7 (2 C), 128.4, 128.3 (2 C), 126.5, 124.0, 118.7, 118.4, 114.8, 109.4, 86.4, 83.9, 74.1, 73.2, 67.2, 54.3, 54.7, 29.9 (2 C), 28.4 (3 C), 28.0; HRMS (ESI-TOF) calcd. for C₃₀H₃₅N₂O₇ [M + H⁺] 535.2444; found 535.2428.



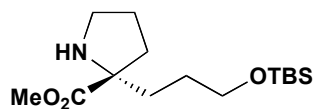
Tryptophan derivative 11: Tryptophan derivative **10** (2.81 g, 5.26 mmol) was dissolved in degassed acetic acid (281 mL, 1 mL / 1 mg) and placed in a 120 °C preheated oil bath. After 80 min, reaction was removed from the heating bath and evaporated *in vacuo*. The crude oil was purified by flash column chromatography (silica gel, 20:1 → 80:1 CH₂Cl₂:hexanes, then 100% CH₂Cl₂, then 99:1 → 95:5 CH₂Cl₂:Et₂O) furnishing 1.51 g of tryptophan derivative **11**

was along with 350 mg of its indole *N*-Boc analogue (79 % total).



Tryptophan derivative 12: Tryptophan derivative **11** (310 mg, 0.713 mmol) was dissolved in 1:1 CH₂Cl₂:CH₃CN (7 mL total volume). 4-DMAP (0.9 mg, 7.13 μmol, 0.01 equiv) was added followed by the dropwise addition of di-*tert*-butyl dicarbonate (156 mg, 0.713 mmol, 1.0 equiv) in CH₂Cl₂ (0.5 mL). After 30 min of stirring at ambient temperature, the reaction was concentrated *in vacuo*. The resultant

brown-orange oil was purified by flash column chromatography (silica gel, 1:3 → 2:1 Et₂O:hexanes) to yield 293 mg (77%) of the indole *N*-Boc compound. The indole *N*-Boc compound so prepared (534 mg, 1.00 mmol) was dissolved in 1:1 THF:water (10 mL total volume) and the reaction was cooled to 0 °C. LiOH (360 mg, 15.0 mmol, 15.0 equiv) was added to the reaction and stirred for 3 hr. The reaction was acidified to pH 2 with concentrated H₂SO₄, extracted with EtOAc (3 × 15 mL), washed with brine (20 mL), dried over anhydrous MgSO₄ and concentrated *in vacuo* furnishing 520 mg (100%) tryptophan derivative **12**. Data given for methyl ester of **12**: White needles; m.p. 109 – 111 °C (1:99 CH₂Cl₂:Et₂O); *R*_f = 0.63 (silica gel, EtOAc:hexanes 1:2); IR (neat): ν_{max} = 3344, 2975, 2359, 1371, 1508, 1370, 1352, 1275, 1216, 1154, 1119, 1087, 1056, 812, 768 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.38 – 7.29 (m, 5 H), 7.23 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 10.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 5.61 (d, *J* = 10.0, 1 H), 5.35 (d, *J* = 8.0 Hz, 1 H, D₂O exchangeable), 5.13 (d, *J* = 12.0 Hz, 1 H), 5.10 (d, *J* = 12.0 Hz, 1 H), 4.70 (dd, *J* = 13.5, 6.0 Hz, 1 H), 3.69 (s, 3 H), 3.23 – 3.11 (m, 2 H), 1.61 (s, 9 H), 1.48 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃): δ = 172.2, 155.8, 152.0, 149.9, 136.4, 132.4, 128.7 (2 C), 128.4 (2 C), 128.2 (2 C), 127.0, 125.9, 125.1, 121.9, 119.1, 115.1, 113.8, 110.0, 83.9, 75.0, 67.2, 54.2, 52.6, 28.3 (3 C), 27.4, 27.3; HRMS calcd for C₃₀H₃₄N₂O₇Na⁺ [*M* + Na⁺]: 557.2264; found: 557.2252.



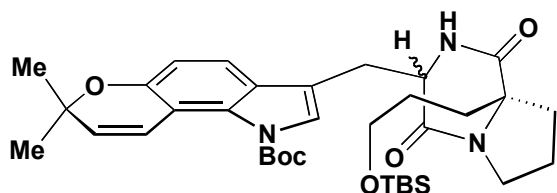
Proline derivative 13. To a solution of (*R*)-2-allylproline hydrochloride^{4,5}

(1.00 g, 4.80 mmol) in 1:1 MeOH:benzene (20 mL total volume) at 0 °C was added dropwise a solution of diazomethane in ether until the yellow color persisted. The mixture was stirred for 30 min. Unreacted diazomethane was quenched by the dropwise addition of glacial acetic acid until the yellow color disappeared. The mixture was concentrated *in vacuo* and suspended in a solution of saturated aqueous NaHCO₃ (30 mL) which was cooled to 0 °C. To this mixture was added benzyl chloroformate (1.6 g, 9.72 mmol, 2.0 equiv) dropwise with vigorous stirring. The reaction mixture was then gradually allowed to attain ambient temperature by removing the ice bath and then stirred at 50 °C for 4 hr. The product mixture was extracted with EtOAc (3 × 30 mL), washed with brine (30 mL), dried with anhydrous MgSO₄, concentrated *in vacuo*, and purified by flash column chromatography (silica gel; 1:6 EtOAc:hexanes). To remove any traces of benzyl alcohol the product obtained was subjected to heating to 110 °C under high vacuum to afford 1.10 g (74%) of *N*-Cbz-(*R*)-allylproline methyl ester. To a solution of this ester (1.0 g, 3.29 mmol) in anhydrous THF (11 mL) was added 9-BBN (13 mL from a 0.5 *M* in THF, 6.59 mmol, 2.0 equiv). The mixture was stirred for 9 hr at room temperature. It was subjected to oxidative workup by adding 3 *M* aqueous NaOH (30 mL) immediately followed by careful and dropwise addition of 35% aqueous H₂O₂ (30 mL) with vigorous stirring. The reaction mixture was stirred for 1 hr and then extracted with EtOAc (3 × 40 mL), washed with brine (40 mL), dried with anhydrous MgSO₄, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 1:4 EtOAc:hexanes) furnishing 0.84 g (79%) of the primary alcohol. To a solution of this alcohol (630 mg, 1.96 mmol) in CH₂Cl₂ (10 mL) at room temperature, was added imidazole (160 mg, 2.35 mmol, 1.2 equiv) and the solution was stirred for 5 min. TBSCl (325 mg, 2.15 mmol, 1.1 equiv) was then added and the mixture stirred for 30 min. The solution was concentrated *in vacuo* and purified by flash column chromatography (silica gel, 1:2 EtOAc:hexanes) furnishing 0.82 g (96%) of the protected alcohol. To a flask containing the *O*-TBS and *N*-Cbz protected proline derivative (700 mg, 1.60 mmol) was added 0.2 % (w/w) 10% Pd/C. The flask was flushed with nitrogen gas and MeOH (20 mL) was added. The flask was evacuated using low vacuum and flushed with hydrogen. Hydrogen gas from a balloon was then bubbled through the suspension until the reaction deemed complete as determined by TLC. The suspension was filtered through Celite[®] using CH₂Cl₂. The filtrate was concentrated *in vacuo* and the resulting residue was pass through a short pad of silica gel furnishing 480 mg (100%) of proline derivative **13**: colorless oil; *R*_f = 0.22 (silica gel, ether); [α]_D = − 9.3 (*c* = 1.8, CHCl₃); IR (neat) *v*_{max} = 2952, 1730, 1462, 1253, 1197, 1095, 1004, 834, 774, 625, 459, 448, 418 cm^{−1}; ¹H

⁴ D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390 – 5398.

⁵ M. G. Hinds, J. H., Welsh, D. M. Bernnand, J. Fisher, M. J. Glennie, N. G. J. Richards, D. L. Turner, J. A. Robinson, *J. Med. Chem.* **1991**, *34*, 1777 – 1789.

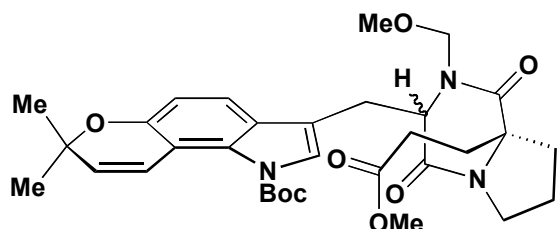
exchangeable), 5.10 (s, 2 H), 4.90 (dd, $J = 15.1, 8.1$ Hz, 1 H), 3.87 – 3.81 (m, 1 H), 3.63 (s, 3 H), 3.53 – 3.48 (m, 1 H), 3.46 – 3.40 (m, 1 H), 3.14 (dd, $J = 16.9, 7.6$ Hz, 1 H), 3.05 (dd, $J = 14.5, 7.9$ Hz, 1 H), 2.96 (dd, $J = 14.4, 6.1$ Hz, 1 H), 2.08 – 1.88 (m, 6 H), 1.79 – 1.71 (m, 1 H), 1.60 (s, 9 H), 1.49 (s, 3 H), 1.47 (s, 3 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 173.9, 169.6, 155.7, 151.7, 149.7, 136.2, 132.1, 128.4 (2 C), 128.0, 127.7 (2 C), 126.7, 125.6, 124.9, 121.6, 119.0, 115.4, 113.6, 109.8, 83.5, 74.7, 68.9, 66.7, 62.8, 52.1, 48.9, 35.1, 30.2, 29.7, 28.9, 28.0, (3 C), 27.3, 27.0, 26.8, 25.9 (3 C), 23.6, 18.2, – 5.35 (2 C); HRMS (ESI-TOF) calcd. for $\text{C}_{44}\text{H}_{62}\text{N}_3\text{O}_9\text{Si}$ $[\text{M} + \text{H}^+]$ 804.4250; found 804.4251. Both diastereomers could be carried forward to hexacycle **17** using identical procedures; however, only data for compounds derived from the major diastereomer are presented.



Diketopiperazine 15. To a solution of amide **14** (608 mg, 756 μmol , major diastereomer) in CH_2Cl_2 (15 mL, 0.05 M) were added Et_3SiH (4.83 mL, 30.2 mmol, 40 equiv), Et_3N (211 μL , 1.51 mmol, 2.0 equiv), and $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (157 mg, 151 μmol , 0.2 equiv) at room temperature. The

reaction vessel was sealed with a plastic stopper and Parafilm M[®]. The reaction mixture was stirred vigorously for 4 hr, rapidly turning from a purple solution to a black suspension. Upon completion of the reaction, the reaction mixture was diluted with EtOAc and passed through a tightly packed anhydrous MgSO_4 -on-Celite[®] column filter. The filtrate was passed through a second column filter (only Celite[®]) to remove any remaining palladium. The resultant yellow filtrate was concentrated *in vacuo*. The residue was dissolved MeOH (20 mL) and heated at vigorous reflux for 30 min to cleave the intermediate silyl carbamate. The solution was evaporated *in vacuo* and the residue was suspended in toluene (20 mL). The suspension was heated at reflux for 2 hr during which dissolution occurred. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; 1:2 \rightarrow 2:3 EtOAc:hexanes) furnishing 256 mg (53%) of diketopiperazine **15**: white foam; $R_f = 0.43$ (silica gel, 1:1 EtOAc:hexanes); $[\alpha]_D = -29.4$ ($c = 0.81$, CH_2Cl_2); IR (neat) $\nu_{\text{max}} = 2931, 1735, 1655, 1395, 1358, 1277, 1256, 1156, 982, 835, 772, 735$ cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (s, 1 H), 7.26 (d, $J = 8.4$ Hz, 1 H), 7.01 (d, $J = 9.9$ Hz, 1 H), 6.83 (d, $J = 8.4$ Hz, 1 H), 5.69 (bs, 1 H, D_2O exchangeable), 5.63 (d, $J = 9.9$ Hz, 1 H), 4.31 (dd, $J = 10.8, 2.9$ Hz, 1 H), 3.86 – 3.77 (m, 1 H), 3.68 (dd, $J = 15.0, 2.3$ Hz, 1 H), 3.54 (t, $J = 5.8$ Hz, 2 H), 3.53 – 3.45 (m, 1 H), 2.75 (dd, $J = 14.8, 11.0$ Hz, 1 H), 2.15 (t, $J = 7.2$ Hz, 2 H), 2.00 – 1.89 (m, 2 H), 1.84 – 1.71 (m, 2 H), 1.64 (s, 9 H), 1.48 (s, 6 H), 0.83 (s, 9 H), – 0.01 (s, 3 H), – 0.02 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 164.8, 152.2, 149.5, 132.7, 127.1, 125.3, 124.6, 121.5, 118.8, 114.9, 113.9, 110.2, 84.1,

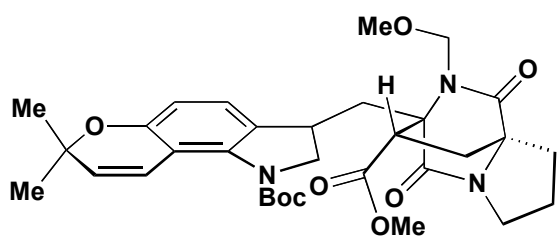
77.2, 74.9, 67.9, 62.1, 53.7, 45.0, 33.6, 33.3, 28.1 (3 C), 27.6, 27.2, 27.1, 25.8 (3 C), 20.5, 18.2, – 5.4 (2 C); HRMS (ESI-TOF) calcd. for $C_{44}H_{62}N_3O_9Si$ [$M + H^+$] 638.3620; found 638.3623.



Diketopiperazine 16. To a solution of diketopiperazine **15** (220 mg, 345 μ mol, major diastereomer) in DMF (3.45 mL, 0.1 M) at 0 °C was added NaH (17 mg, 414 μ mol, 1.2 equiv). The suspension was stirred vigorously for 30 min before MOMCl (29 μ L, 379 μ mol, 1.1 equiv) was injected into the orange suspension. The reaction was allowed to stir

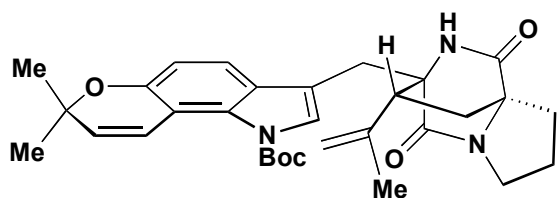
for 1 hr during which the color changed from orange to yellow. The cooling bath was removed and the reaction was immediately quenched by the addition of saturated aqueous NH_4Cl (5 mL). The resulting suspension was diluted with water (5 mL) and EtOAc (10 mL). The mixture was poured into a separatory funnel and the layers were separated. The aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel; 1:4 \rightarrow 1:2 EtOAc:hexanes) furnishing 153 mg (65%) of the *N*-(methoxy)methyl analogue of **15**: white foam; R_f = 0.44 (silica gel; 1:2 EtOAc:hexanes); $[\alpha]_D = +10.0$ ($c = 0.59$, CH_2Cl_2); IR (neat) ν_{max} 2929, 1741, 1657, 1431, 1393, 1276, 1257, 1156, 1090, 983, 835, 774 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, $J = 8.4$ Hz, 1 H), 7.09 (s, 1 H), 6.95 (d, $J = 9.9$ Hz, 1 H), 6.80 (d, $J = 8.4$ Hz, 1 H), 5.59 (d, $J = 9.9$ Hz, 1 H), 5.23 (d, $J = 10.2$ Hz, 1 H), 4.65 (d, $J = 10.2$ Hz, 1 H), 4.47 (bs, 1 H), 3.68 – 3.47 (m, 4 H), 3.42 (s, 3 H), 3.26 (dd, $J = 15.4, 4.6$ Hz, 1 H), 3.21 – 3.14 (m, 1 H), 1.88 – 1.82 (m, 1 H), 1.82 – 1.75 (m, 1 H), 1.70 – 1.63 (m, 2 H), 1.59 (s, 9 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.45 – 1.36 (m, 2 H), 1.27 – 1.20 (m, 1 H), 1.09 (dd, $J = 22.2, 10.2$ Hz, 1 H), 0.84 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 164.2, 151.7, 149.6, 131.8, 126.8, 125.6 (2 C), 121.6, 119.7, 114.2, 113.5, 109.6, 83.6, 75.4, 74.8, 67.4, 62.1, 58.5, 57.3, 43.9, 34.6, 34.0, 28.0 (3 C), 27.3, 27.2, 26.9, 26.0, 25.8 (3 C), 19.5, 18.2, – 5.4 (2 C); HRMS (ESI-TOF) calcd. for $C_{44}H_{61}N_3O_9SiNa^+$ [$M + Na^+$] 704.3701; found 704.3686. To a solution of *N*-(methoxy)methyl tryptophan derivative **15** (146 mg, 214 μ L) in THF (4.3 mL, 0.05 M) was added tetrabutylammonium fluoride (TBAF, 642 μ L of a 1 M wet solution in THF, 3.0 equiv). Once desilylation was complete (approximately 1 hr), the reaction was diluted with EtOAc (10 mL), saturated aqueous NH_4Cl (5 mL), water (5 mL), and was poured into a separatory funnel. The layers were separated and the aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 (4.3 mL, 0.05 M, wet CH_2Cl_2) and the Dess–Martin periodinane (DMP, 136 mg, 321 μ mol, 1.5

equiv) was added. The reaction vessel was left open to the ambient atmosphere. The reaction was stirred vigorously for 2 hr during which the reaction produced a white cloudy precipitate. Once complete, the reaction mixture was diluted with EtOAc (15 mL). The contents of the reaction vessel were poured into a separatory funnel and washed with 1:1 water:saturated aqueous NaHCO₃ (4 × 10 mL). The aqueous portions were combined and extracted with EtOAc (15 mL). The organic portions were combined, washed with brine (15 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. The crude residue was dissolved in THF (4.3 mL, 0.05 M) and 2-methyl-2-butene (453 µL, 4.28 mmol, 20 equiv) was added. NaH₂PO₄•H₂O (89 mg, 642 µmol, 3.0 equiv) was dissolved in water (214 µL) and added *via* pipette to the vigorously stirring THF solution. NaClO₂ (54 mg, 599 µmol, 2.8 equiv) was dissolved in water (214 µL) and added *via* pipette dropwise over 30 sec to the vigorously stirring biphasic mixture. The reaction turned an intense yellow color soon after addition of the oxidant. The reaction was stirred vigorously for 20 min after which it was diluted with EtOAc (10 mL), saturated aqueous NH₄Cl (5 mL), and water (5 mL), and was poured into a separatory funnel. The layers were separated and the aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with brine (10 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. The crude residue was dissolved in MeOH (approximately 5 mL) and treated with an ethereal solution of diazomethane (1 mL portions) until the starting material had been consumed. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel; 1:1 → 2:1 EtOAc:hexanes) furnishing 88 mg (69%) of diketopiperazine **16**.



Hexacycle 17. (Note: The THF used in this reaction, including the portions used for preparing LDA and Fe(acac)₃, was purified by distillation over excess sodium metal and benzophenone in a still. The THF was collected minutes prior to use and always transferred *via* dry, oxygen-free syringes. LDA was prepared by standard methods with care taken to exclude oxygen. The Fe(acac)₃ was dissolved in benzene and dried azeotropically prior to dissolution in THF.) To a solution of diketopiperazine **16** (84 mg, 141 µL) in dry THF (3.3 mL, 0.05 M) at –78 °C was added LDA (618 µL from a 0.5 M solution in THF, 310 µmol, 2.2 equiv) over 3 sec. The reaction immediately turned yellow. The bis-enolate was allowed to form for 5 min after addition after which Fe(acac)₃ (1.54 mL from a 0.2 M solution in THF, 310 µmol, 2.2 equiv) was added dropwise into the reaction mixture at –78 °C over 20 sec. The reaction immediately turned dark green-brown and was allowed to stir for 15 min at –78 °C. The cooling bath was removed and the reaction was allowed to stir without the cooling bath for an additional 45 min. The reaction was quenched by diluting it to twice its original volume with EtOAc and passing it

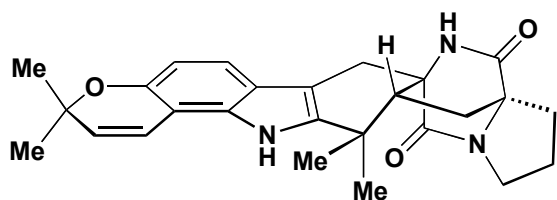
through a short pad of silica gel with EtOAc. To the resultant orange filtrate was added 1 *M* aqueous HCl (10 mL). The layers were separated and the aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with brine (10 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 1:2 → 3:1 EtOAc:hexanes) furnishing 34 mg (41%) of hexacycle **17** along with recovered **16** (12.6 mg, 15%). Hexacycle **17**: white foam; *R*_f = 0.53 (silica gel, EtOAc:hexanes 4:1); [α]_D = − 5.8 (*c* = 0.24, CH₂Cl₂); IR (neat): ν_{max} = 2928, 1737, 1697, 1370, 1276, 1156, 1085, 982, 813, 735 cm^{−1}; ¹H NMR (400 MHz, CDCl₃): δ = 7.45 (s, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 6.96 (d, *J* = 9.9 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 5.60 (d, *J* = 9.9 Hz, 1 H), 4.84 (d, *J* = 10.6 Hz, 1 H), 4.63 (d, *J* = 10.6 Hz, 1 H), 3.70 – 3.56 (m, 2 H), 3.53 (s, 3 H), 3.50 – 3.44 (m, 3 H), 3.17 (s, 3 H), 2.85 – 2.78 (m, 1 H), 2.28 (dd, *J* = 13.3, 10.4 Hz, 1 H), 2.13 (dd, *J* = 13.3, 4.8 Hz, 1 H), 2.09 – 1.99 (m, 2 H), 1.92 – 1.85 (m, 1 H), 1.61 (s, 9 H), 1.48 (s, 3 H), 1.47 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ = 173.8, 171.9, 165.9, 151.8, 149.9, 131.6, 126.7, 126.5, 126.1, 121.8, 118.9, 114.1, 113.5, 109.7, 83.9, 74.9, 73.3, 67.3, 65.9, 65.6, 56.5, 52.4, 44.4, 29.7, 29.6, 28.1 (3 C), 27.3, 26.9, 23.1, 21.9; HRMS (ESI-TOF) calcd for C₃₂H₃₉N₃O₈Na⁺ [*M* + Na⁺]: 616.2629; found: 616.2639. Stereochemistry confirmed using ROESY. Peak assignments made using HMBC, HMQC and COESY analysis.



Olefin 18. To a solution of hexacycle **17** (34 mg, 57.2 μ mol) in CH₂Cl₂ at 0 °C was added *B*-bromocatecholborane (430 μ L from a 0.2 *M* solution in CH₂Cl₂, 1.5 equiv). The reaction was allowed to stir until the starting material had been consumed, approximately 1.5 hr. The reaction vessel

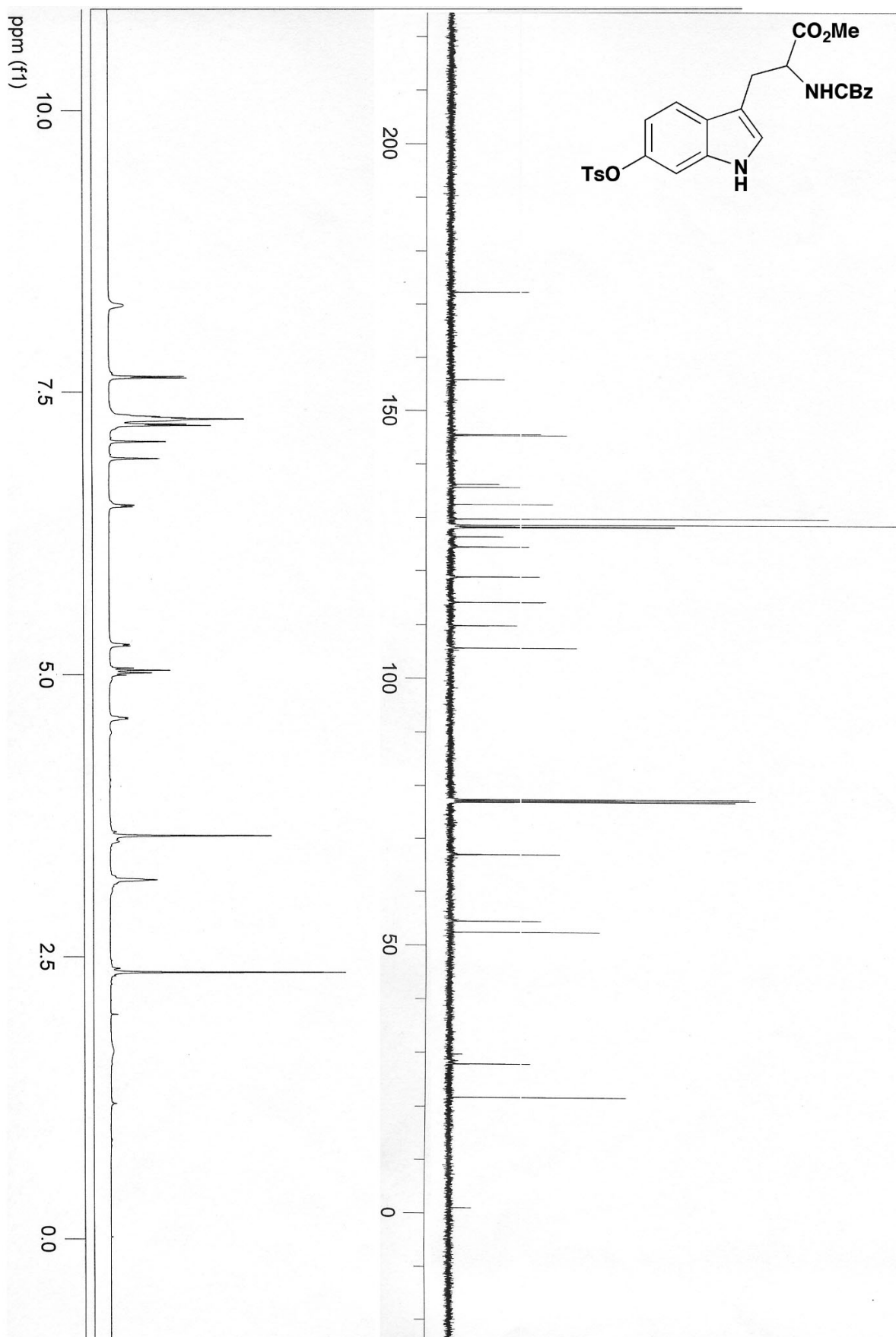
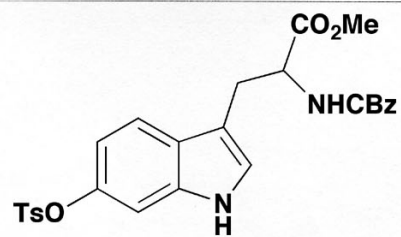
was opened and the reaction mixture was diluted with EtOAc (5 mL). 2 *M* aqueous NaOH (10 mL) was added and the reaction mixture was stirred vigorously for 15 min. The mixture was poured into a separatory funnel and the layers were separated. The organic portion was washed repeatedly with 2 *M* aqueous NaOH (4 \times 10 mL). The aqueous portions were combined and extracted with EtOAc (10 mL). The organic portions were combined, washed with brine (10 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by PTLC (silica gel, EtOAc) furnishing 21 mg (63 %) of de(methoxy)methyl hexacycle **17**. To a solution of de(methoxy)methyl hexacycle **17** (21 mg, 36.1 μ mol) in toluene (722 μ L, 0.05 *M*) at ambient temperature was added MeMgBr [155 μ L, 1.4 *M* solution (3:1 toluene:THF) 216 μ mol, 6 equiv]. The solution immediately turned yellow and gas evolution was observed. The reaction was allowed to stir until starting material had been consumed, approximately 1 hr. The reaction was quenched by the dropwise addition of 1 mL saturated aqueous NH₄Cl (1 mL). The

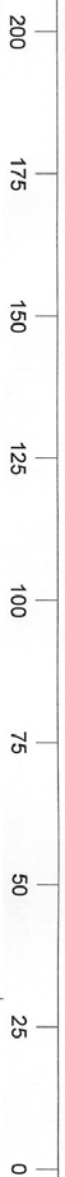
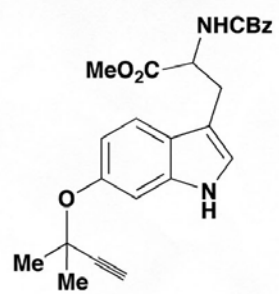
reaction mixture was diluted with water (10 mL) and EtOAc (10 mL). The biphasic mixture was poured into a separatory funnel and the layers were separated. The aqueous portion was extracted with EtOAc (10 mL). The organic portions were combined, washed with brine (10 mL), dried over anhydrous MgSO_4 , and concentrated *in vacuo*. The crude residue was dissolved in benzene (approximately 0.5 mL) and treated with the Burgess reagent (17 mg, 72.2 μmol , 2.0 equiv). The solution was sealed with a plastic stopper and Parafilm M[®]. The reaction vessel was immersed in an oil bath preheated to 50 °C for 30 min. The reaction vessel was then removed from the bath and TLC was used to determine the extent of reaction. Once complete, the solvent was evaporation *in vacuo* and the residue was purified by PTLC (silica gel, 4:1 EtOAc:hexanes) furnishing 17 mg (88%) of olefin **18**: white foam, $R_f = 0.61$ (silica gel; 4:1 EtOAc:hexanes); $[\alpha]_D = -8.8$ ($c = 0.57$, MeOH); IR (neat) ν_{max} 3391, 2975, 1687, 1371, 1276, 1155, 982, 814 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (s, 1 H), 7.31 (d, $J = 8.4$ Hz, 1 H), 6.99 (d, $J = 9.9$ Hz, 1 H), 6.84 (d, $J = 8.4$ Hz, 1 H), 5.79 (bs, 1 H, D_2O exchangeable), 5.62 (d, $J = 9.9$ Hz, 1 H), 5.00 (bs, 2 H), 3.62 – 3.55 (m, 1 H), 3.54 – 3.49 (m, 1 H), 3.50 (d, $J = 15.2$ Hz, 1 H), 2.98 (dd, $J = 10.4, 5.6$ Hz, 1 H), 2.94 (d, $J = 15.4$ Hz, 1 H), 2.73 – 2.67 (m, 1 H), 2.26 (dd, $J = 13.4, 10.4$ Hz, 1 H), 2.04 – 1.93 (m, 2 H), 1.80 – 1.74 (m, 2 H), 1.74 (s, 3 H), 1.63 (s, 9 H), 1.48 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.7, 168.4, 152.1, 149.6, 143.3, 132.1, 127.1, 126.8, 126.2, 121.5, 118.5, 116.1, 114.1, 113.1, 110.1, 84.0, 74.9, 66.5, 63.4, 52.3, 44.2, 36.7, 29.1, 28.1 (3 C), 27.2, 27.1, 24.4, 23.6, 19.3; HRMS (ESI-TOF) calcd for $\text{C}_{32}\text{H}_{39}\text{N}_3\text{O}_8\text{Na}^+$ [$M + \text{Na}^+$]: 532.2806; found: 532.2788.

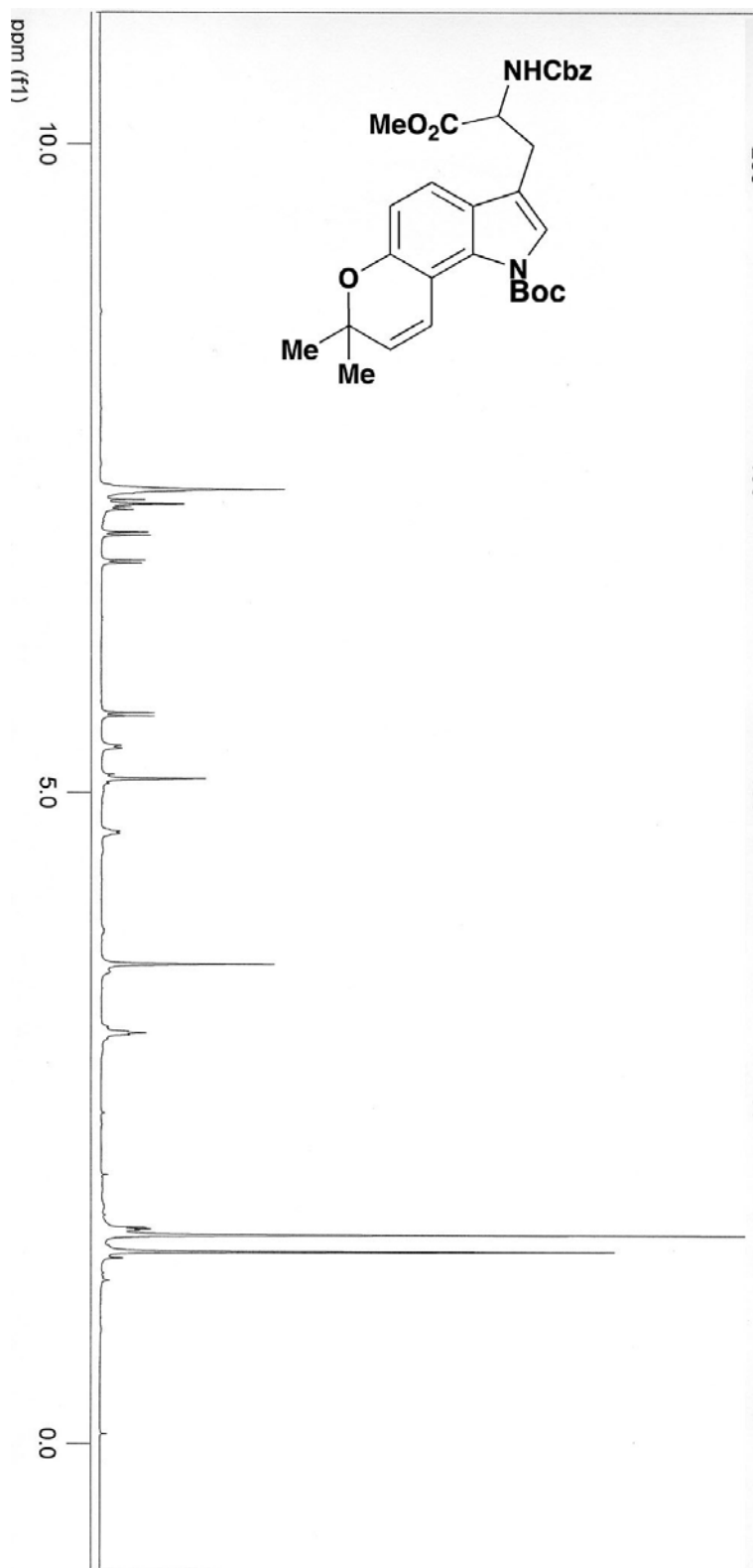
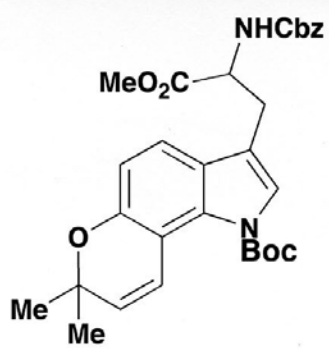
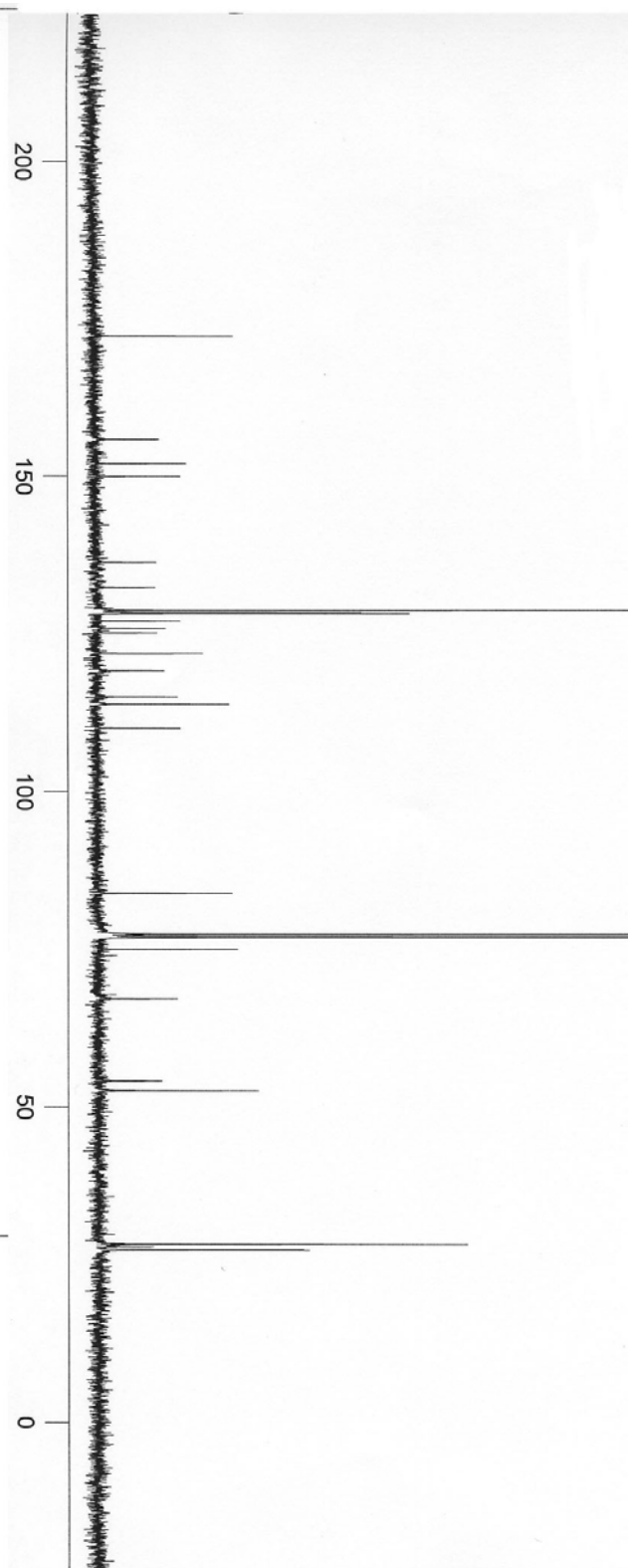


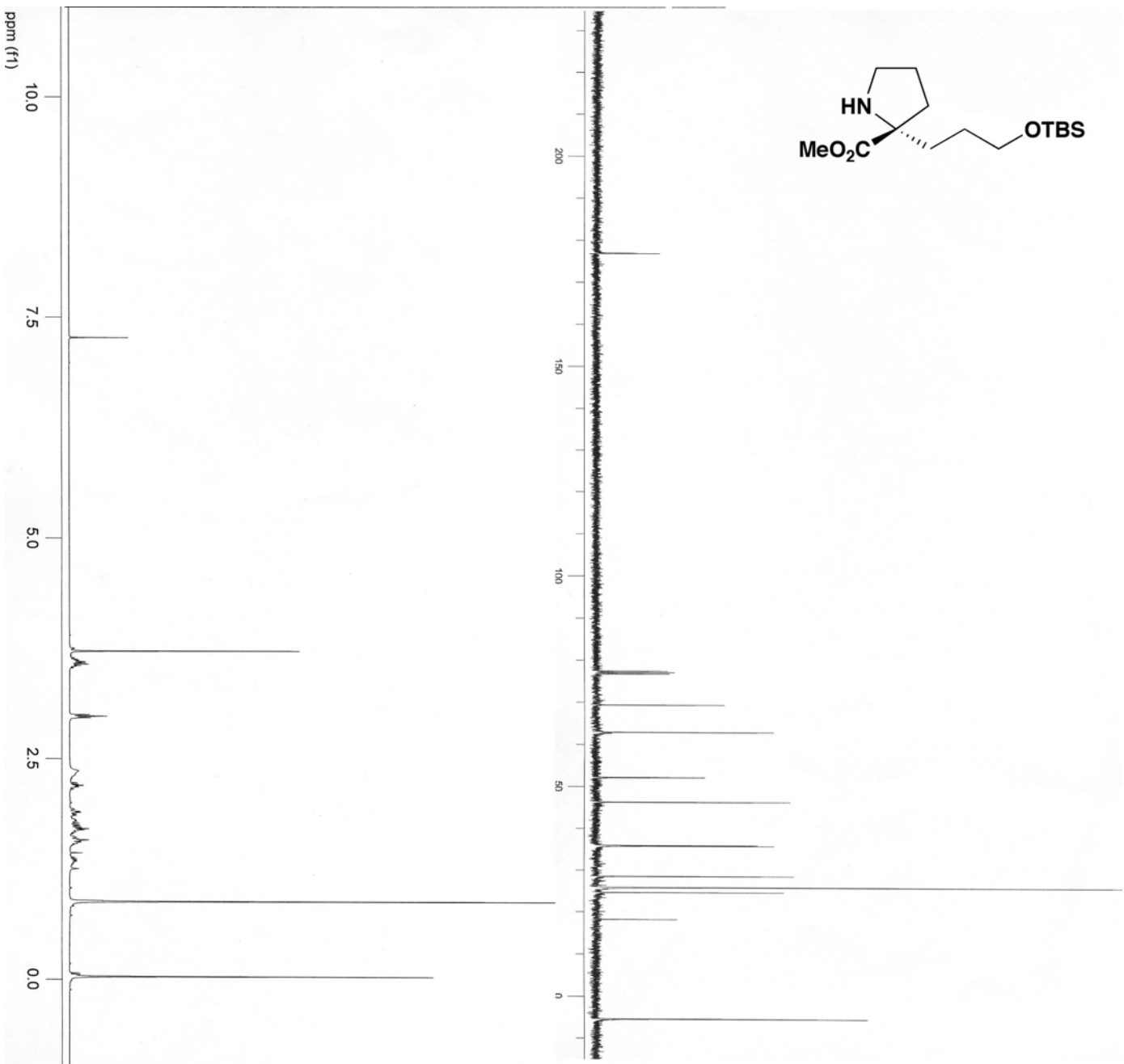
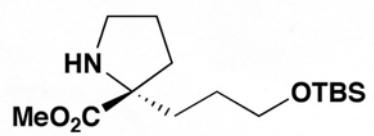
Stephacidin A (1): Olefin **18** (5 mg, 9.4 μmol) was transferred to a new round bottom flask. Any solvent was removed first by exposure to a stream of dry nitrogen followed by exposure to high vacuum. The reaction vessel

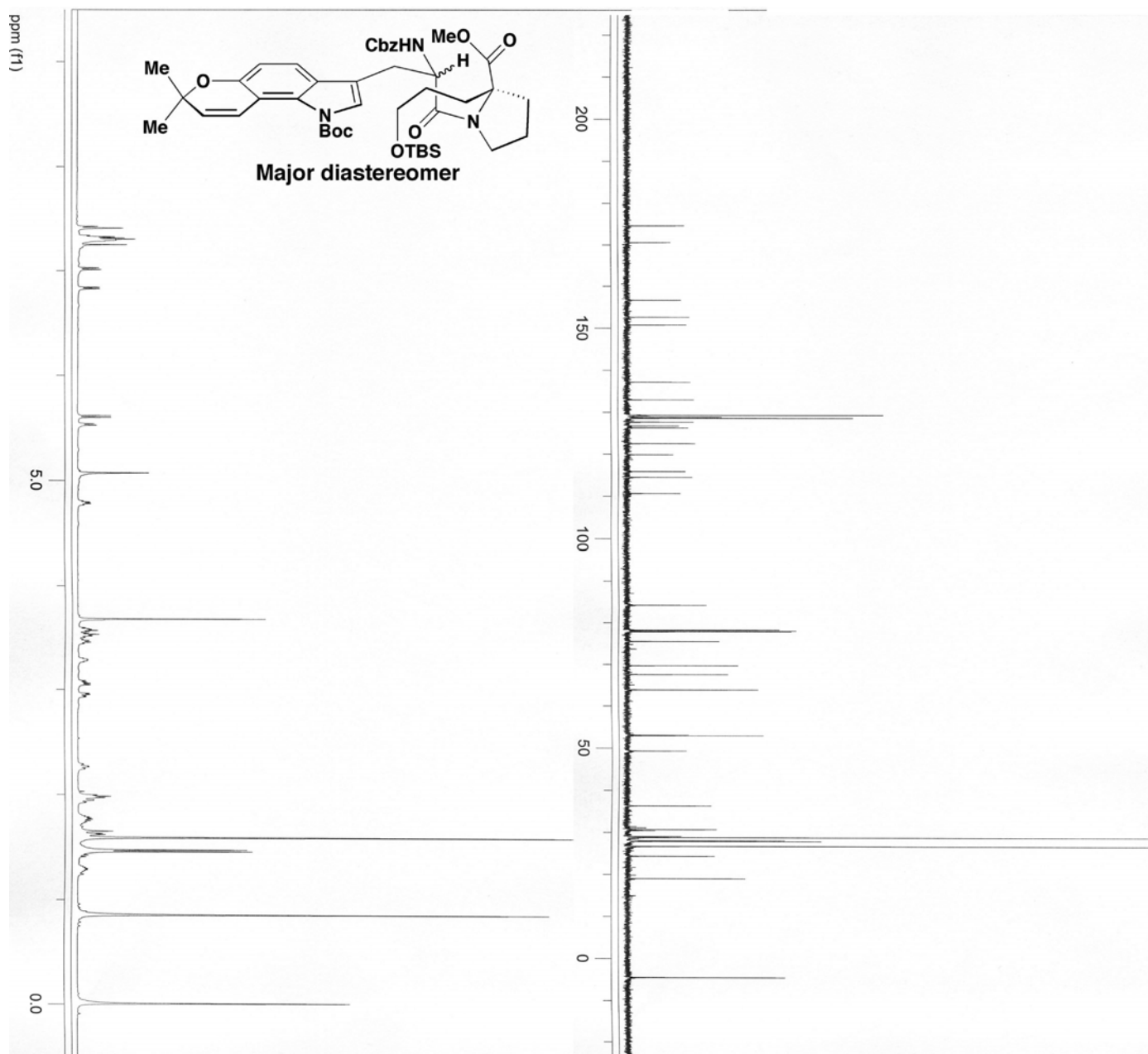
was sealed and attached to a source of dry nitrogen. The reaction vessel was immersed in an oil bath preheated to 200 °C and removed after 1 h of heating. Once at room temperature, the residue was dissolved in CH_2Cl_2 and purified by PTLC (silica gel; 4:1 EtOAc:hexanes) furnishing 1.8 mg (45%) of stephacidin A (**1**) along with recovered **19** (0.4 mg). Synthetic stephacidin A displayed identical spectroscopic properties to that reported for natural stephacidin A (^1H NMR in two solvents, ^1H -H COESY, HRMS; DMSO- d_6 spectra attached).



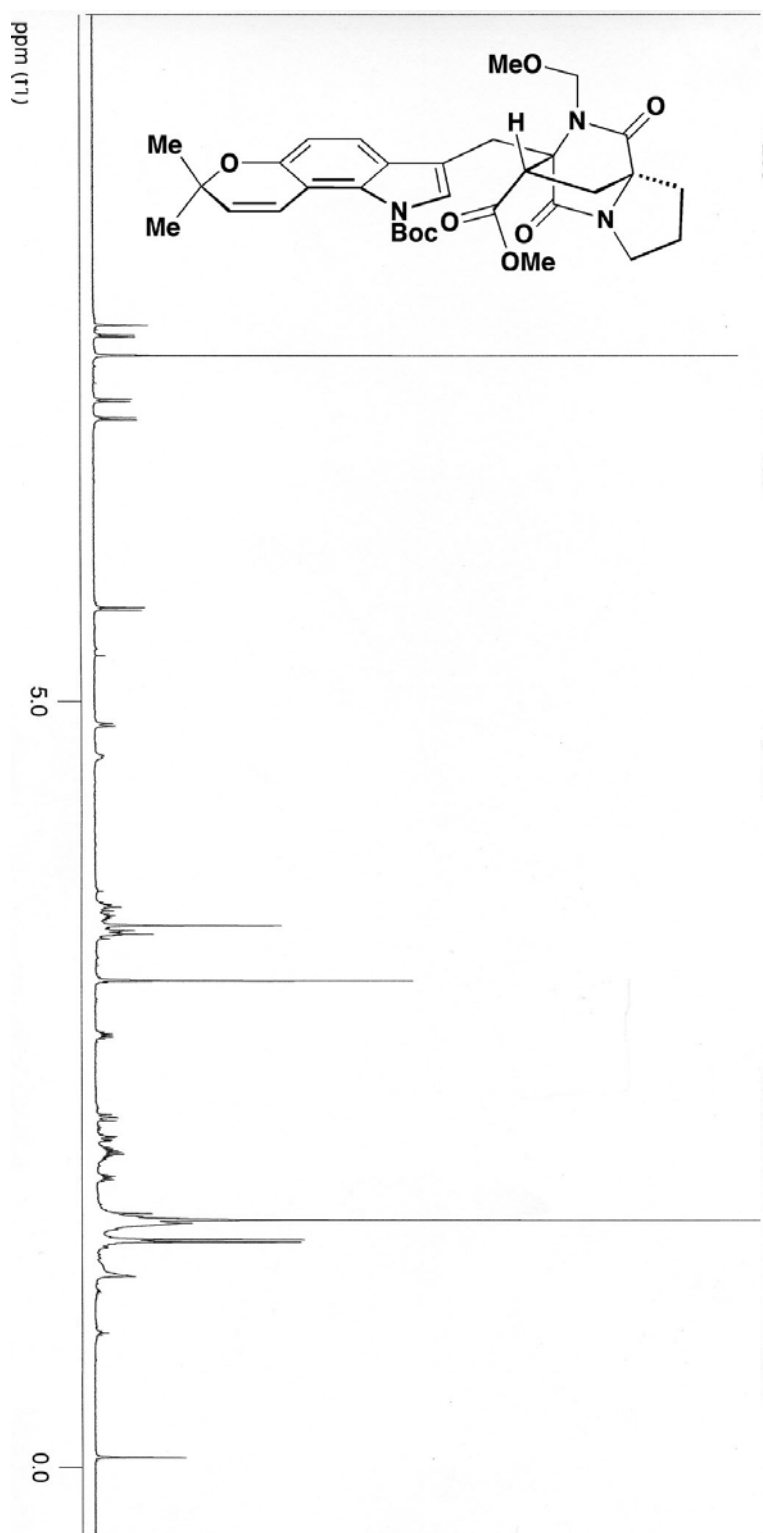
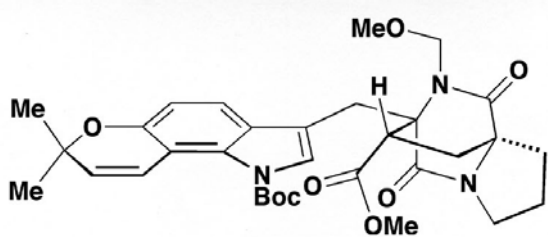
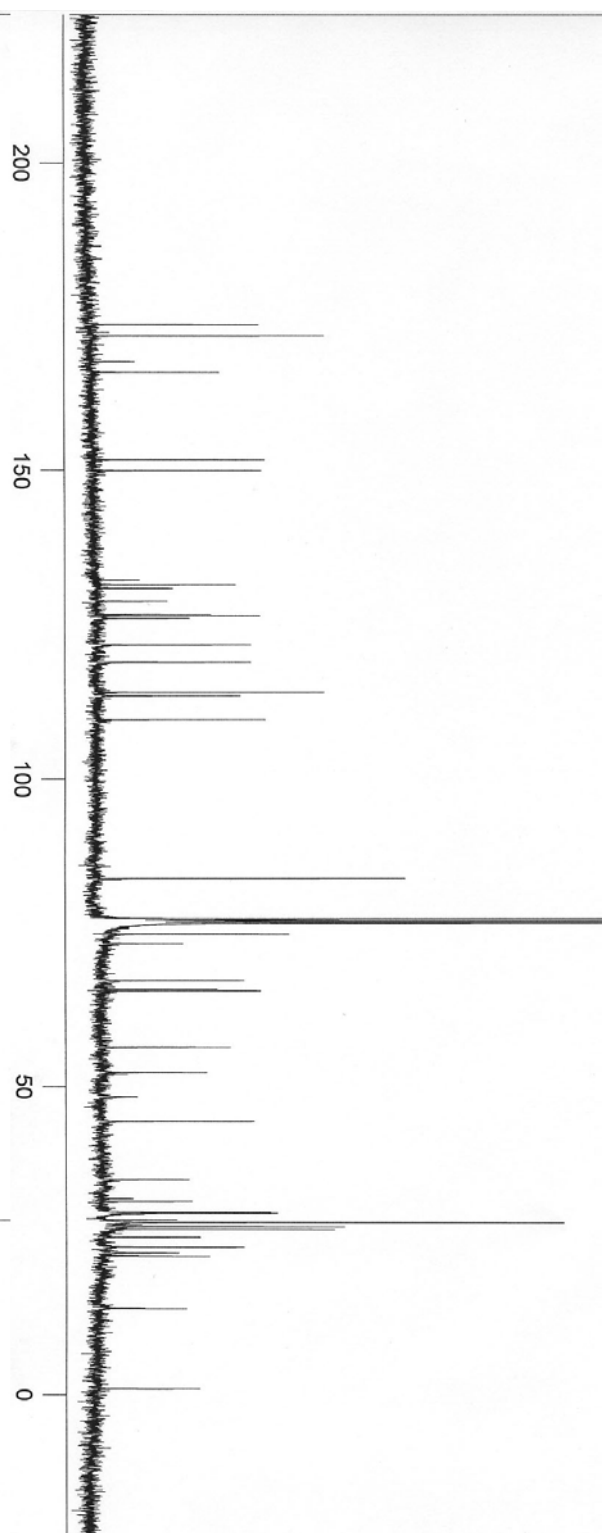


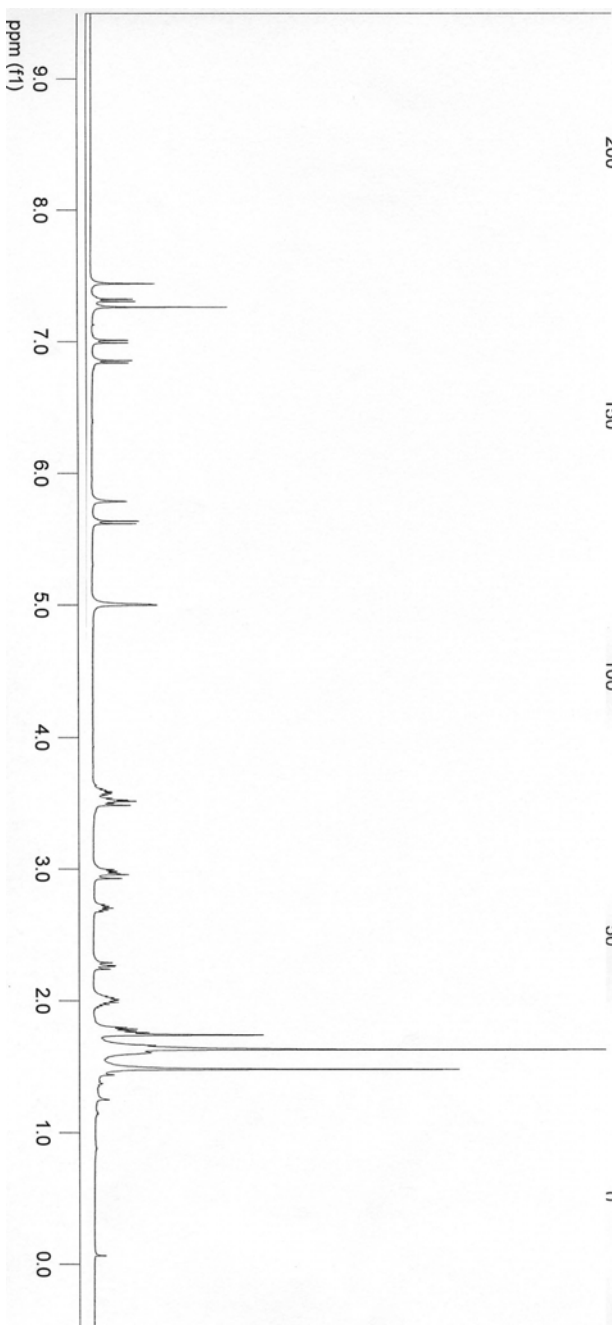
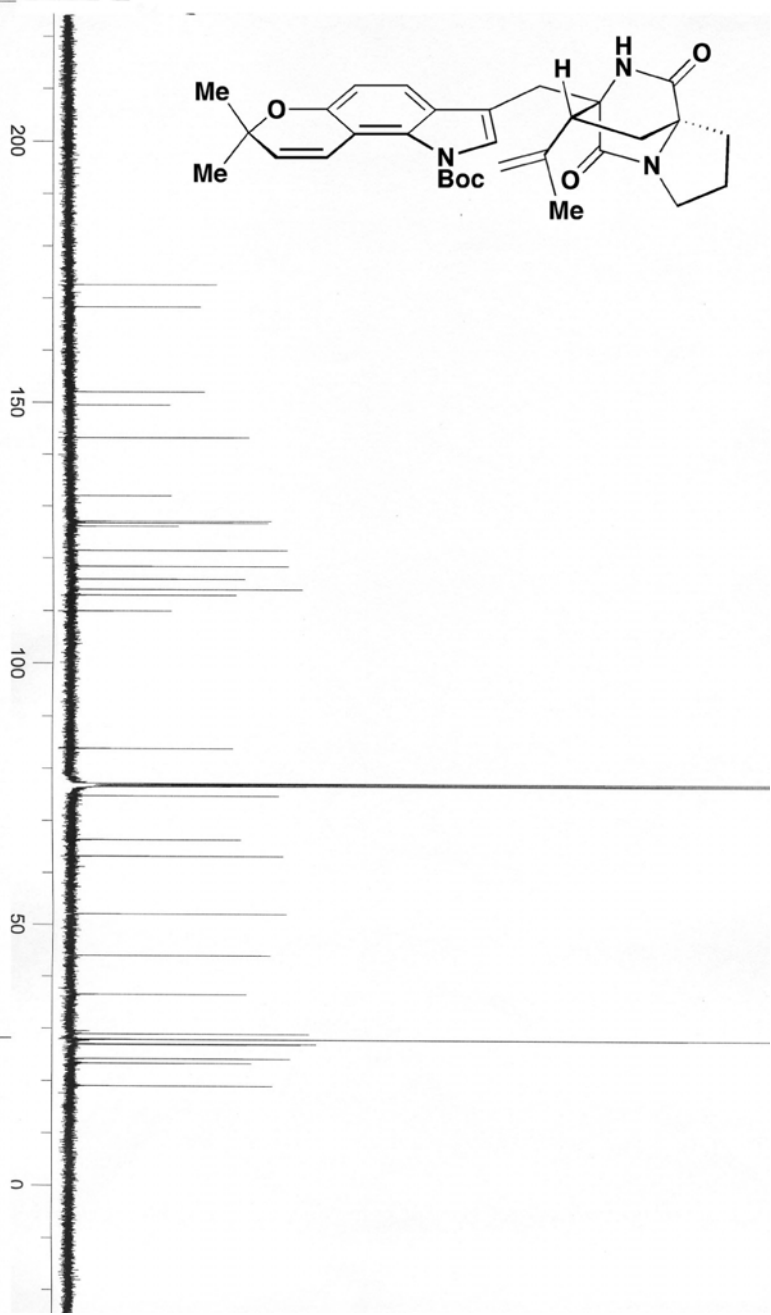
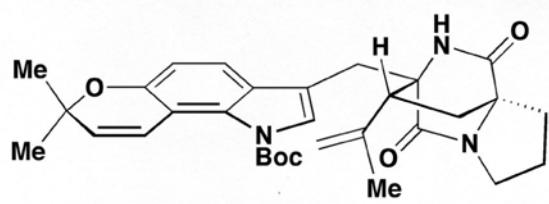












The figure displays two ^1H NMR spectra side-by-side, comparing natural and synthetic Stephacidin A. Both spectra are recorded in $\text{DMSO}-d_6$ and feature a chemical shift scale from 1.0 to 10.5 ppm.

Left Spectrum: NATURAL STEPHACIDIN A in $\text{DMSO}-d_6$

- 10.5 ppm:** Aromatic proton (1H, s).
- 8.5 ppm:** Aromatic proton (1H, s).
- 7.0-7.5 ppm:** Aromatic protons (2H, m).
- 6.5 ppm:** Aromatic proton (1H, s).
- 5.5 ppm:** Aromatic proton (1H, s).
- 4.0 ppm:** Impurity (1H, s).
- 3.5 ppm:** H_2O (1H, s).
- 2.5-3.0 ppm:** DMSO (1H, s).
- 1.0-2.0 ppm:** Aliphatic protons (10H, m).

Right Spectrum: SYNTHETIC STEPHACIDIN A in $\text{DMSO}-d_6$

- 10.5 ppm:** Aromatic proton (1H, s).
- 8.5 ppm:** Aromatic proton (1H, s).
- 7.0-7.5 ppm:** Aromatic protons (2H, m).
- 6.5 ppm:** Aromatic proton (1H, s).
- 5.5 ppm:** Aromatic proton (1H, s).
- 4.0 ppm:** CH_2Cl_2 (1H, s).
- 3.5 ppm:** H_2O (1H, s).
- 2.5-3.0 ppm:** DMSO (1H, s).
- 1.0-2.0 ppm:** Aliphatic protons (10H, m).
- 0.5 ppm:** grease (1H, s).