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# Asymmetric Total Synthesis of (+)-Merobatzelladine B\*\*

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Experimental procedures, characterization data for new compounds, and copies of NMR spectra.

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General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium and tri-(2-furyl)phosphine were purchased from Strem Chemical Co. and used without further purification. Tricyclohexylphosphonium tetrafluoroborate was purchased from Acros Chemical Co. and used without further purification. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. POCl<sub>3</sub> was purified by distillation under  $N_2$  prior to use. (*Z*)-1-bromobut-1-ene, <sup>1</sup> *tert*-butyl 2-allylpyrrolidine-1-carboxylate, <sup>2</sup> and (*E*)-1-bromodec-1-ene <sup>3</sup> were prepared according to published procedures. Toluene, THF, methylene chloride and diethyl ether were purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by either <sup>1</sup>H NMR or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by <sup>1</sup>H NMR.

#### **Experimental Procedures and Compound Characterization Data**

(±)-2-Allyl-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide (11). A round bottomed flask equipped with a stirbar was charged with tert-butyl 2-allylpyrrolidine-1-carboxylate (465 mg, 2.2 mmol) and methylene chloride (2.2 mL). The resulting solution was cooled to 0  $^{\circ}$ C and trifluoroacetic acid (2.2 mL, 28.7 mmol) was added. The solution was gradually warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (ca. 30 min). The reaction mixture was diluted with water, basified with NH<sub>4</sub>OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in methylene chloride (11 mL) and 4-methoxyphenyl isocyanate (285 μL, 2.2 mmol) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel to afford 300 mg (53%) of the title compound as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.29 (d, J = 9.5 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 6.07 (s, 1 H), 5.82 (ddt, J = 17.0, 10.0, 7.5 Hz, 1 H), 5.13-5.07 (m, 2 H), 4.07-4.04 (m, 1 H), 3.78 (s, 3 H), 3.45-3.42 (m, 2 H), 2.60-2.55 (m, 1 H), 2.22-2.16 (m, 1 H), 2.04-1.93 (m, 3 H), 1.83-1.79 (m, 1 H);  $^{13}$ C NMR (125) MHz, CDCl<sub>3</sub>) δ 155.6, 154.3, 135.2, 132.2, 121.7, 117.4, 114.1, 57.2, 55.5, 46.3, 38.7, 29.5, 23.8; IR (film) 3306, 1639 cm<sup>-1</sup>. MS (ESI) 261.1599 (261.1598 calcd for  $C_{15}H_{20}N_2O_2$ ,  $M + H^+$ ).

#### $(\pm)$ -(3R\*,4aR\*)-2-(4-Methoxyphenyl)-3-(4-methylbenzyl)hexahydropyrrolo[1,2-

*c*]pyrimidin-1(2*H*)-one (12a). A flame-dried Schlenk tube was cooled under a stream of N<sub>2</sub> and charged with Pd<sub>2</sub>(dba)<sub>3</sub> (6.4 mg, 0.007 mmol), PCy<sub>3</sub>•HBF<sub>4</sub> (10.3 mg, 0.028 mmol) and NaO<sup>t</sup>Bu (50 mg, 0.52 mmol). The flask was purged with N<sub>2</sub>, then a solution of 11 (83 mg, 0.35 mmol) in

toluene (3.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. 4-Bromotoluene (89 µL, 0.52 mmol) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH<sub>4</sub>Cl (3 mL) and ethyl acetate (3 mL) were added. The organic layer was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (10 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Analysis of the crude material by <sup>1</sup>H NMR revealed the product had been formed as a 14:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 78 mg (70%) of the title compound as a pale yellow oil with 14:1 dr. Data are for the major isomer. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (d, J = 9.0 Hz, 2 H), 7.06 (d, J = 8.0 Hz, 2 H), 6.92–6.90 (m, 4 H), 3.96 (dt, J =11.5, 4.5 Hz, 1 H), 3.82 (s, 3 H), 3.82–3.76 (m, 1 H), 3.60 (dt, J = 11.5, 7.5 Hz, 1 H), 3.55–3.51 (m, 1 H), 3.02 (dd, J = 13.8, 3.8 Hz, 1 H), 2.64 (dd, J = 13.5, 11.0 Hz, 1 H), 2.30 (s, 3 H), 2.13(dt, J = 12.0, 5.5 Hz, 1 H), 2.05-1.95 (m, 2 H), 1.88-1.82 (m, 1 H), 1.54 (dt, J = 12.5, 2.5 Hz, 1 Hz)H) 1.50–1.44 (m, 1 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 157.5, 154.4, 135.9, 135.5, 134.8, 130.1, 129.2, 128.8, 114.2, 60.4, 55.4, 52.5, 46.1, 38.1, 33.8, 29.5, 23.4, 20.9; IR (film) 1640 cm<sup>-1</sup>. MS (ESI) 351.2071 (351.2071 calcd for  $C_{22}H_{26}N_2O_2$ ,  $M + H^+$ ).

## $(\pm)$ - $(E,3R^*,4aR^*)$ -2-(4-Methoxyphenyl)-3-(undec-2-en-1-yl)hexahydropyrrolo[1,2-

clpyrimidin-1(2*H*)-one (12b). A flame-dried Schlenk tube was cooled under a stream of N<sub>2</sub> and charged with Pd<sub>2</sub>(dba)<sub>3</sub> (6.4 mg, 0.007 mmol), PCy<sub>3</sub>•HBF<sub>4</sub> (10.3 mg, 0.028 mmol) and NaO'Bu (67 mg, 0.70 mmol). The flask was purged with N<sub>2</sub>, then a solution of 11 (83 mg, 0.35 mmol) in toluene (3.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. A solution of (*E*)-1-bromodec-1-ene (153 mg, 0.70 mmol) in toluene (1 mL) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH<sub>4</sub>Cl (3 mL) and ethyl acetate (3 mL) were added. The organic layer was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (10 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated

*in vacuo*. Analysis of the crude material by  $^{1}$ H NMR revealed the product had been formed as a 18:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 98 mg (77%) of the title compound as a pale yellow oil with 18:1 dr. Data are for the major isomer.  $^{1}$ H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.13 (d, J = 9.0 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 5.42 (dt, J = 15.5, 7.5 Hz, 1 H), 5.16 (dt, J = 15.0, 7.0 Hz, 1 H), 3.79 (s, 3 H), 3.76–3.73 (m, 1 H), 3.68–3.62 (m, 1 H), 3.58 (dt, J = 11.5, 7.5 Hz, 1 H), 3.50–3.46 (m, 1 H), 2.39 (dt, J = 13.5, 5.0 Hz, 1 H), 2.24 (ddt, J = 13.0, 2.0, 1.5 Hz, 1 H), 2.20-2.11 (m, 2 H), 2.00–1.91 (m, 3 H), 1.85–1.78 (m, 1 H), 1.62 (dt, J = 12.3, 5.0 Hz, 1 H), 1.49 (ddt, J = 12.0, 10.0, 7.5 Hz, 1 H), 1.30–1.23 (m, 12 H), 0.87 (t, J = 7.0 Hz, 3 H);  $^{13}$ C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  157.5, 154.4, 135.7, 134.2, 129.3, 125.4, 114.1, 58.7, 55.4, 52.5, 46.0, 35.9, 33.9, 32.5, 31.8, 30.3, 29.4, 29.2, 29.1, 23.4, 22.6, 14.1 (one carbon signal is absent due to incidental equivalence); IR (film) 1640 cm<sup>-1</sup>. MS (ESI) 399.3009 (399.3006 calcd for C<sub>25</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>, M + H<sup>+</sup>).

(+)-( $S_S$ )-2-Methyl-*N*-(pent-4-en-1-ylidene)propane-2-sulfinamide (16). This compound was prepared according to a published procedure by Ellman.<sup>4</sup> A flame-dried flask was cooled under a stream of N<sub>2</sub> and charged with pent-4-enal (1.38 mL, 14 mmol) and THF (40 mL). Titanium ethoxide (4.2 mL, 20 mmol) was added and the reaction mixture was stirred at rt for 5 min. (S)-tert-butanesulfinamide (1.21 g, 10 mmol) was added in one portion and the mixture was stirred overnight (ca. 14 h) at rt. The reaction mixture was poured into brine (40 mL) and stirred for 10 min. Ethyl acetate (20 mL) was added, the mixture was filtered through celite and the celite was washed with ethyl acetate (100 mL). The mixture was transferred to a separatory funnel, brine (20 mL) was added, and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 1.62 g (87%) of the title compound as a colorless oil: [ $\alpha$ ]<sup>23</sup><sub>D</sub> +244.8 (c 5.5, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.08 (t, J = 4.5 Hz, 1 H), 5.84 (ddt, J = 17.0, 10.0, 4.5 Hz, 1 H), 5.08 (dd, J = 17.0, 1.5 Hz, 1 H), 5.02 (dd, J = 10.0, 1.5 Hz, 1 H), 2.63 (td, J = 7.5, 4.0 Hz, 2 H), 2.40 (q, J = 7.0 Hz, 2 H), 1.19 (s, 9 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  168.8, 136.7,

115.8, 56.5, 35.2, 29.3, 22.3; IR (film) 1621 cm $^{-1}$ . MS (ESI) 188.1101 (188.1104 calcd for  $C_9H_{17}NOS$ ,  $M + H^+$ ).

(+)- $(S_5,5S)$ -2-Methyl-N-(7-oxododec-1-en-5-yl)propane-2-sulfinamide (17). This compound was prepared via a modification of a published procedure by Davis.<sup>5</sup> A flame-dried flask was cooled under a stream of N<sub>2</sub>, charged with diethyl ether (80 mL), and cooled to -78 °C. Solid KHMDS (5.6 g, 28.0 mmol) was added and the reaction mixture was stirred for 5 min at -78 °C. Heptan-2-one (3.43 mL, 24.0 mmol) was slowly added to the reaction flask and the mixture was stirred at -78 °C for 1 h. A solution of 16 (1.50 g, 8.0 mmol) in diethyl ether (10 mL) was added to the reaction flask and stirred at -78 °C for 2 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) at -78 °C and gradually warmed to rt. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with water (1 x 10 mL) and then the combined aqueous layers were extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 1.95 g (81%) of the title compound as a pale yellow oil:  $[\alpha]^{23}_D + 47.8$  (c 3.2, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.77 (ddt, J = 16.8, 10.0, 6.8 Hz, 1 H), 5.04–4.96 (m, 2 H), 4.07 (d, J= 9.2 Hz, 1 H), 3.53 (oct, J = 4.8 Hz, 1 H), 2.90 (dd, J = 17.6, 5.6 Hz, 1 H), 2.77 (dd, J = 17.6, 4.4 Hz, 1 H), 2.39 (t, J = 7.6 Hz, 2 H), 2.24–2.02 (m, 2 H), 1.78–1.67 (m, 1 H), 1.60–1.50 (m, 3 H), 1.38–1.18 (m, 4 H), 1.22 (s, 9 H), 0.88 (t, J = 7.0 Hz, 3 H);  $^{13}$ C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ 210.8, 137.7, 115.2, 55.8, 53.2, 48.0, 43.8, 34.7, 31.2, 30.4, 23.1, 22.6, 22.4, 13.9; IR (film) 3216, 1708 cm<sup>-1</sup>. MS (ESI) 302.2155 (302.2148 calcd for  $C_{16}H_{31}NO_2S$ ,  $M + H^+$ ).

(+)-( $S_5$ ,5S,7S)-N-(7-Hydroxydodec-1-en-5-yl)-2-methylpropane-2-sulfinamide (18). A flame-dried flask was cooled under a stream of  $N_2$  and charged with 17 (322 mg, 1.1 mmol) and THF

(11 mL). The reaction flask was cooled to 0 °C, CeCl<sub>3</sub>•7H<sub>2</sub>O (831 mg, 2.2 mmol) was added, and the mixture was stirred for 5 min. NaBH<sub>4</sub> (600 mg, 15.9 mmol) was added in a single portion and the resulting solution was stirred until the starting material had been consumed as judged by ESI<sup>+</sup> MS analysis (ca. 2 h). The reaction mixture was slowly quenched with water (3 mL) and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Analysis of the crude material by <sup>1</sup>H NMR revealed the product had been formed as a 3:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 204 mg (63%) of the title compound as a colorless oil with >20:1 dr:  $[\alpha]_{D}^{23}$  +55.1 (*c* 2.1, CH<sub>2</sub>Cl<sub>2</sub>). H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.79 (ddt, J = 17.3, 10.3, 6.8 Hz, 1 H), 5.03–4.95 (m, 2 H), 3.79 (m, 1 H), 3.65 (d, J = 8.0 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.36 (d, J = 4.5 Hz, 1 H), 2.21–2.04 (m, 2 H), 1.80 (ddd, J = 14.5, 10.5, 4.0 Hz, 1 H), 1.64–1.21 (m, 11 H), 1.23 (s, 9 H), 0.87 (t, J = 7.0 Hz, 3 H);  $^{13}$ C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  138.0, 115.0, 67.8, 55.8, 53.9, 42.6, 37.8, 36.3, 31.9, 30.3, 25.5, 22.7, 22.6, 14.0; IR (film) 3243 cm<sup>-1</sup>. MS (ESI) 304.2314 (304.2305 calcd for C<sub>16</sub>H<sub>33</sub>NO<sub>2</sub>S, M + H<sup>+</sup>).

(+)-( $S_8$ ,5S,7S)-N-[7-(Benzyloxy)dodec-1-en-5-yl]-2-methylpropane-2-sulfinamide (S1). A flame-dried flask was cooled under a stream of  $N_2$  and charged with 18 (345 mg, 1.1 mmol) and THF (11 mL). The reaction was cooled to 0 °C and NaH (65 mg, 1.6 mmol, 60% suspension in mineral oil) was added. The reaction flask was stirred for 5 min at 0 °C and then benzyl bromide (190  $\mu$ L, 1.6 mmol) was added and the resulting mixture was stirred overnight at rt. The reaction was quenched with water (10 mL) and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 428 mg (96%) of the title compound as a colorless oil. The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Regis Tech. (R,R) WHELK-O1, 0.46 cm x 25 cm, 5% *i*PrOH/hexanes, 1.0 mL/min,  $\lambda$  = 254 nm, RT = 8.57 and 11.82 min).  $[\alpha]^{23}_{D}$  +63.4 (c 2.1, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500

MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.24 (m, 5 H) 5.79 (ddt, J = 17.5, 11.5, 6.5 Hz, 1 H), 5.04–4.96 (m, 2 H), 4.60 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H), 4.13 (d, J = 6.0 Hz, 1 H), 3.76–3.69 (m, 1 H), 3.54-3.47 (m, 1 H), 2.18–2.03 (m, 2 H), 1.84 (ddd, J = 15.0, 9.5, 3.0 Hz, 1 H), 1.76–1.51 (m, 5 H), 1.35–1.24 (m, 6 H), 1.07 (s, 9 H), 0.89 (t, J = 6.8 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  138.5, 138.2, 128.3, 128.1, 127.6, 114.9, 76.9, 71.0, 55.4, 53.9, 39.1, 35.4, 33.0, 32.0, 30.0, 24.8, 22.7, 22.6, 14.0; IR (film) 3257 cm<sup>-1</sup>. MS (ESI) 394.2777 (394.2774 calcd for C<sub>23</sub>H<sub>39</sub>NO<sub>2</sub>S, M + H<sup>+</sup>).

$$\begin{array}{c} \text{Bn.} \\ \text{O} \\ \text{HN} \end{array} \begin{array}{c} \text{Boc} \\ \text{C}_4 \text{H}_9 \end{array}$$

(+)-(5S,7S)-tert-Butyl 7-(benzyloxy)dodec-1-en-5-ylcarbamate 19. A flame-dried flask was cooled under a stream of N<sub>2</sub> and charged with (S1) (426 mg, 1.1 mmol) and methanol (5.5 mL). A solution of anhydrous hydrochloric acid (1.1 mL, 4.4 mmol, 4 M in dioxane) was added and the mixture was stirred at rt for 1 h, at which time TLC analysis indicated that the starting material had been completely consumed. The reaction mixture was diluted with water (5 mL) and  $CH_2Cl_2$  (5 mL), basified with  $NH_4OH$  to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The crude product was dissolved in THF (11 mL), solid di-tert-butyldicarbonate (264 mg, 1.2 mmol) was added and the reaction mixture was stirred at rt for 3 h. 1 M NaOH (5 mL) was added and the resulting biphasic mixture was stirred overnight at rt. The mixture was transferred to a separatory funnel, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 401 mg (95%) of the title compound as a colorless oil:  $[\alpha]^{23}$ <sub>D</sub> +31.8 (c 1.5, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.41–7.32 (m, 4 H), 7.30–7.26 (m, 1 H), 5.81 (ddt, J =17.0, 10.0, 7.5 Hz, 1 H), 5.01 (dd, J = 17.3, 1.8 Hz, 1 H), 4.95 (d, J = 10.0 Hz, 1 H), 4.79 (d, J = 10.0 Hz, 1 H), 4.70 (d, J = 10.0 Hz, 1 H), 4.7 14.0 Hz, 1 H), 4.55 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H), 3.84–3.76 (m, 1 H), 3.60– 3.52 (m, 1 H), 2.18–2.02 (m, 2 H), 1.74–1.47 (m, 6 H), 1.44 (s, 9 H), 1.37–1.24 (m, 6 H), 0.90 (t, J = 7.3 Hz, 3 H; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  155.5, 138.6, 138.3, 128.3, 128.1, 127.5, 114.6, 78.6, 76.3, 71.3, 47.9, 39.2, 34.8, 33.8, 32.0, 30.4, 28.4, 24.7, 22.6, 14.0; IR (film) 3347, 1702 cm<sup>-1</sup>. MS (ESI) 390.3004 (390.3003 calcd for  $C_{24}H_{39}NO_3$ ,  $M + H^+$ ).

(+)-(E,2S,2'S,5R)-tert-Butyl 2-[2'-(benzyloxy)heptyl]-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate (20). A flame-dried Schlenk flask was cooled under a stream of N<sub>2</sub> and charged with Pd<sub>2</sub>(dba)<sub>3</sub> (18.3 mg, 0.02 mmol), tri-(2-furyl)phosphine (18.6 mg, 0.08 mmol) and NaO<sup>t</sup>Bu (200 mg, 2.08 mmol). The flask was purged with N<sub>2</sub>, then a solution of 19 (406 mg, 1.04 mmol) in distilled xylenes (5.2 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. (E)-(2-bromovinyl)trimethylsilane (319 μL, 2.08 mmol) was added and the flask was heated to 140 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH<sub>4</sub>Cl (5 mL) and ethyl acetate (5 mL) were added. The mixture was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (20 mL). The mixture was transferred to a separatory funnel, water was added (10 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 347 mg (68%) of the title compound as a pale brown oil. This compound was found to exist as a mixture of rotamers as judged by <sup>1</sup>H and <sup>13</sup>C NMR analysis; data are for the mixture.  $[\alpha]^{23}_D + 14.5$  (c 0.7,  $CH_2Cl_2$ ). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.38–7.26 (m, 5 H), 6.00–5.91 (m, 1 H), 5.69 (d, J =18.5 Hz, 1 H), 4.57–4.42 (m, 2 H), 3.99–3.60 (m, 2 H), 3.58–3.24 (m, 1 H), 2.59–2.52 (m, 1 H), 2.37-2.18 (m, 1 H), 2.02-1.81 (m, 3 H), 1.78-1.63 (m, 2 H), 1.59-1.23 (m, 9 H), 1.46 (s, 9 H), 0.90 (t, J = 7.3 Hz, 3 H), 0.04 (s, 9 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  154.5, 143.1, 138.9, 133.1, 128.3, 127.8, 127.5, 127.4, 79.0, 78.1, 70.7, 57.5, 57.1, 41.7, 40.8, 34.0, 32.0, 30.2, 28.6, 28.4, 24.8, 22.6, 14.1, 0.0, -1.0, -1.2, -1.4; IR (film) 1693 cm<sup>-1</sup>. MS (ESI) 488.3553 (488.3554 calcd for  $C_{29}H_{49}NO_3Si$ ,  $M + H^+$ ).

#### (+)-(2R,2'S,5S)-2-Allyl-5-[2'-(benzyloxy)heptyl]-N-(4-methoxybenzyl)pyrrolidine-1-

carboxamide (21). A round bottomed flask equipped with a stirbar was charged with 20 (397) mg, 0.81 mmol) and methylene chloride (1.6 mL). The resulting solution was cooled to 0 °C and trifluoroacetic acid (1.6 mL, 20.9 mmol) was added. The solution was gradually warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (ca. 15 min). The reaction mixture was diluted with water, basified with NH<sub>4</sub>OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in methylene chloride (8 mL) and 4methoxybenzyl isocyanate (159 µL, 0.97 mmol) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel to afford 282 mg (72%) of the title compound as a colorless oil:  $\left[\alpha\right]^{23}$ <sub>D</sub> +52.7 (c 4.3,  $CH_2Cl_2$ ). <sup>1</sup>H NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.31–7.24 (m, 3 H), 7.22–7.18 (m, 2 H), 6.97 (d, J = 9.0Hz, 2 H), 6.73 (d, J = 9.0 Hz, 2 H), 5.96–5.88 (m, 1 H), 5.78 (ddt, J = 17.8, 10.3, 7.5 Hz, 1 H), 5.07 (dd, J = 17.5, 2.0 Hz, 1 H), 5.03 (dd, J = 11.5, 2.0 Hz, 1 H), 4.49 (d, J = 11.5 Hz, 1 H), 4.20(d, J = 11.5 Hz, 1 H), 4.13 (dd, J = 14.5, 5.5 Hz, 1 H), 4.10-4.05 (m, 1 H), 4.02 (dd, J = 14.5, 5.5 Hz, 1 H)5.5 Hz, 1 H), 3.94–3.88 (m, 1 H), 3.76 (s, 3 H), 3.68–3.62 (m, 1 H), 2.64–2.57 (m, 1 H), 2.27– 2.20 (m, 1 H), 2.05–1.89 (m, 2 H), 1.76–1.55 (m, 5 H), 1.56–1.42 (m, 1 H), 1.34–1.22 (m, 6 H), 0.89 (t, J = 7.0 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  158.3, 158.3, 138.2, 135.3, 132.5, 128.7, 128.3, 127.4, 126.8, 116.8, 113.5, 75.8, 67.4, 57.9, 55.1, 54.9, 43.6, 40.5, 40.3, 32.2, 31.8, 31.8, 28.7, 24.6, 22.5, 13.9; IR (film) 3361, 1642 cm<sup>-1</sup>. MS (ESI) 479.3271 (479.3268 calcd for  $C_{30}H_{42}N_2O_3, M + H^+$ ).

$$C_4H_9 \xrightarrow{\text{OBn}} H$$

$$O \xrightarrow{\text{N}} H$$

$$C_2H_5$$

### (+)-(Z,2'S,3R,4aR,7S)-7-[2'-(Benzyloxy)heptyl]-2-(4-methoxybenzyl)-3-(pent-2-en-1-

yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (22). A flame-dried Schlenk tube was cooled under a stream of N<sub>2</sub> and charged with Pd<sub>2</sub>(dba)<sub>3</sub> (8.0 mg, 0.009 mmol), PCy<sub>3</sub>•HBF<sub>4</sub> (12.9 mg, 0.04 mmol) and NaO'Bu (56 mg, 0.58 mmol). The flask was purged with N<sub>2</sub>, then a solution of 21 (138 mg, 0.29 mmol) in toluene (1.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. A solution of (Z)-1-bromobut-1-ene (78.3 mg, 0.58 mmol) in toluene (1 mL) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH<sub>4</sub>Cl (2 mL) and ethyl acetate (2 mL) were added. The mixture was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (10 mL). The mixture was transferred to a separatory funnel, water was added (5 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 139 mg (91%) of the title compound as a pale yellow oil:  $\left[\alpha\right]^{23}$ <sub>D</sub> +35.3 (c 2.7, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.29 (m, 3 H), 7.28–7.23 (m, 2 H), 7.17 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 5.51–5.42 (m, 1 H), 5.22–5.12 (m, 2 H), 4.55 (d, J = 11.4 Hz, 1 H), 4.49 (d, J = 11.4 Hz, 1 H), 4.02 (d, J = 15.2 Hz, 1 H), 4.01-3.94 (m, 1 H), 3.77 (s, 3 H), 3.60-3.48 (m, 2 H), 3.24–3.16 (m, 1 H), 2.46–2.38 (m, 1 H), 2.26 (dd, J = 13.2, 3.6 Hz, 1 H), 2.19– 2.10 (m, 1 H), 2.05-1.81 (m, 6 H), 1.65-1.20 (m, 11 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (t, J = 6.8 (m, 1 H), 0.94 (m, 1 H),Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 158.5, 154.6, 139.0, 134.4, 131.3, 128.7, 128.2, 127.7, 127.3, 124.4, 113.7, 78.9, 70.9, 56.8, 55.1, 53.6, 52.2, 47.3, 39.0, 34.1, 32.0, 31.3, 31.0, 30.9, 29.7, 24.7, 22.6, 20.8, 14.0, 14.0; IR (film) 1631 cm<sup>-1</sup>. MS (ESI) 533.3737 (533.3738 calcd for  $C_{34}H_{48}N_2O_3, M + H^+$ ).

### (+)-(Z,2'S,3R,4aR,7S)-7-[2'-(Benzyloxy)heptyl]-2-(4-methoxybenzyl)-3-(pent-2-en-1-

yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-iminium tetrafluoroborate (23). A flame-dried flask was cooled under a stream of N<sub>2</sub> and charged with 22 (86 mg, 0.16 mmol) and toluene (1.6 mL). Freshly distilled POCl<sub>3</sub> (1.6 mL, 17.2 mmol) was added, and the reaction mixture was refluxed overnight (ca. 14 h). The reaction mixture was cooled to rt and concentrated in vacuo. The crude product was dissolved in acetonitrile (1.6 mL) and a solution of ammonia (6.4 mL, 2 M in ethanol) was added. The mixture was stirred at rt until the starting material had been consumed as judged by ESI<sup>+</sup> MS analysis (ca. 15 min). The reaction mixture was concentrated and dissolved in methylene chloride (5 mL). Water (5 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with saturated aqueous NaBF<sub>4</sub> (3 x 10 mL). The combined aqueous layers were extracted with methylene chloride (3 x 10 mL). The combined organics layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 88 mg (89%) of the title compound as a pale brown oil:  $[\alpha]^{23}_{D}$  +59.9 (c 3.6, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.30–7.21 (m, 5 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 5.99 (s, 2 H), 5.62-5.51 (m, 1 H), 5.20-5.12 (m, 1 H), 4.63(d, J = 17.0 Hz, 1 H), 4.58 (d, J = 17.5 Hz, 1 H), 4.57 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H)1 H), 4.09–4.06 (m, 1 H), 3.80 (s, 3 H), 3.68–3.62 (m, 1 H), 3.61–3.52 (m, 2 H), 2.56–2.44 (m, 1 H), 2.36–2.20 (m, 2 H), 2.19–2.08 (m, 2 H), 2.02–1.93 (m, 4 H), 1.78–1.56 (m, 4 H), 1.43–1.20 (m, 7 H), 0.95 (t, J = 7.5 Hz, 3 H) 0.87 (t, J = 7.0 Hz, 3 H);  $^{13}$ C NMR (125 MHz, CDCl<sub>3</sub>) 8 159.5, 151.5, 137.7, 136.2, 128.4, 128.2, 127.8, 127.4, 125.8, 122.3, 114.7, 77.2, 71.4, 57.6, 55.9, 55.3, 55.3, 52.6, 51.2, 38.3, 32.5, 32.0, 31.8, 31.2, 29.8, 29.5, 24.9, 22.5, 20.9, 13.9; IR (film) 3366, 3252, 1592 cm<sup>-1</sup>, MS (ESI) 532,3908 (532,3898 calcd for C<sub>34</sub>H<sub>49</sub>N<sub>3</sub>O<sub>2</sub>, M<sup>+</sup>).

(+)-Merobatzelladine B (5). A glass vial equipped with a magnetic stirbar was charged with 23 (43 mg, 0.07 mmol), Pd/C (43 mg), and methanol (3 mL). The glass vial was placed in a stainless steel bomb equipped with a regulator. The vessel was pressurized to 45 psig with H<sub>2</sub> and stirred overnight (ca. 14 h) at rt under a hydrogen atmosphere (45 psig). Complete consumption of starting material was confirmed with ESI<sup>+</sup> MS analysis. The mixture was filtered through a plug of celite and washed with methanol (20 mL). The crude product was transferred to a round-bottomed flask and concentrated in vacuo. The Mitsunobu reaction was carried out based on a published procedure by Nagasawa. 6 The crude product was dissolved in toluene (3.5 mL) and PPh<sub>3</sub> (22 mg, 0.08 mmol) was added. The reaction flask was cooled to 0 °C and DIAD (16.3 µL, 0.083 mmol) was added. The reaction mixture was stirred at 0 °C until the starting material had been consumed as judged by ESI<sup>+</sup> MS analysis (ca. 1 h). The reaction was quenched with a drop of water and concentrated in vacuo. The material was purified by flash chromatography on silica (EtOAc, 2:98 MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 10:90 MeOH:CH<sub>2</sub>Cl<sub>2</sub>) to provide N-pmethoxybenzyl merobatzealladine B in ca 70% purity (the remaining impurities were not identified). The PMB deprotection was carried out using the procedure of Gin, with slight modifications.7 This material was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (6 mL, 78 mmol) was added. The reaction mixture was refluxed overnight (ca. 15 h). The crude material was concentrated in vacuo and then purified by flash chromatography on silica gel to afford 11.9 mg (41%) of the title compound as a pale brown oil. Spectroscopic properties are identical to those reported for the natural product.  $^{8}$  [ $\alpha$ ]<sup>23</sup><sub>D</sub>+40.1 (c 0.7, MeOH) [lit.  $^{8}$  [ $\alpha$ ]<sup>25</sup><sub>D</sub>+27 (c0.15, MeOH)].  $^{1}$ H NMR (700 MHz, CD<sub>3</sub>OD)  $\delta$  3.78–3.71 (m, 2 H), 3.52–3.48 (m, 1 H), 3.42 (dtd, J = 11.6, 6.3, 3.2 Hz, 1 H), 2.28-2.21 (m, 3 H), 2.17 (ddd, J = 13.3, 4.6, 1.8 Hz, 1 H), 1.62-1.22 (m, 20 H), 0.93–0.88 (m, 6 H); <sup>13</sup>C NMR (175 MHz, CD<sub>3</sub>OD) δ 150.6, 57.5, 53.5, 51.6, 50.2, 36.2, 35.9, 34.8, 32.8, 32.7, 31.9, 31.2, 30.8, 26.8, 25.9, 23.6, 23.6, 14.3, 14.3; IR (film) 3188, 3107, 1679 cm<sup>-1</sup>. MS (ESI) 306.2909 (306.2904 calcd for C<sub>19</sub>H<sub>36</sub>N<sub>3</sub>, M<sup>+</sup>).

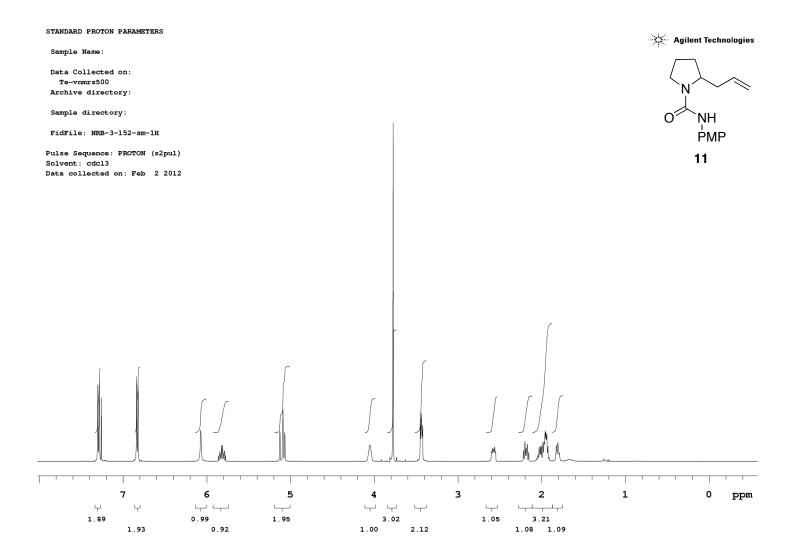
#### Assignment of Stereochemistry of 12a-b

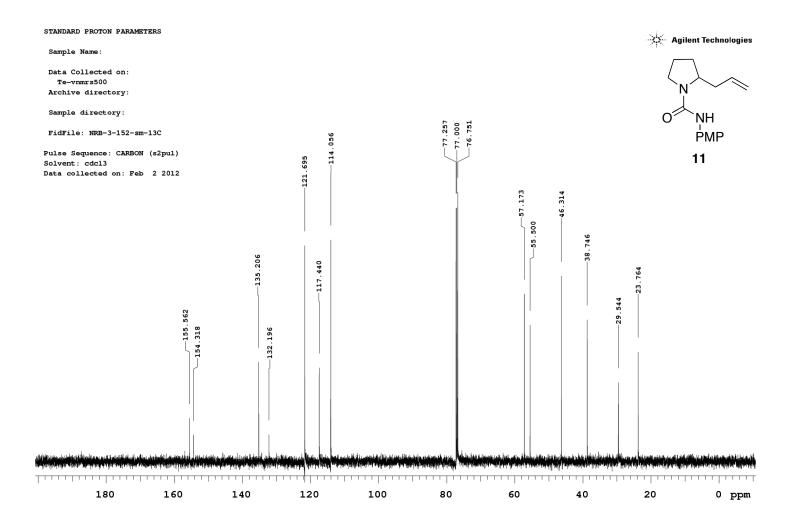
The relative stereochemistry of compound **12a** was assigned on the basis of observed <sup>1</sup>H NMR nOe experiments. Significant nOe relationships are shown below.

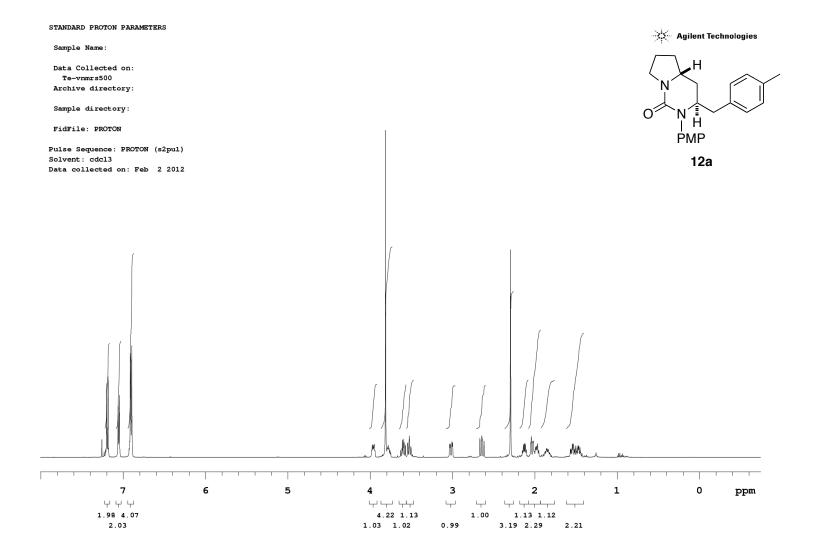
The relative stereochemistry of compound **12b** was assigned on the basis of observed <sup>1</sup>H NMR nOe experiments. Significant nOe relationships are shown below.

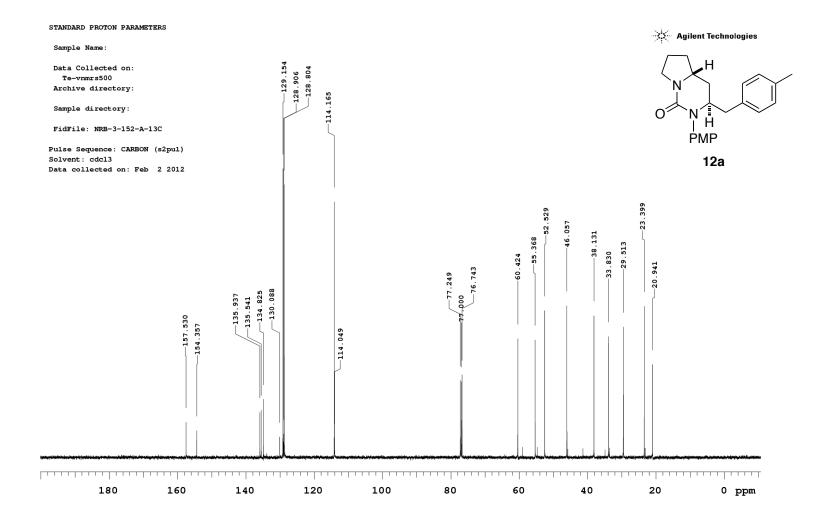
#### References

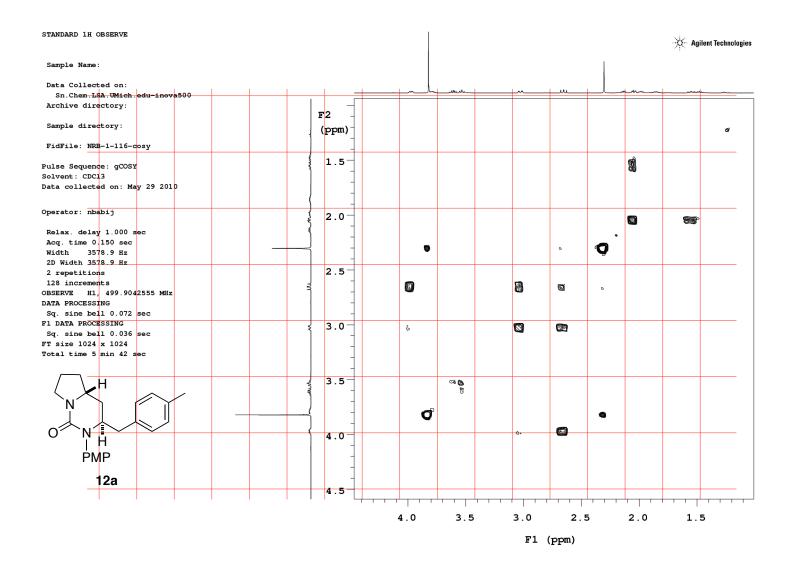
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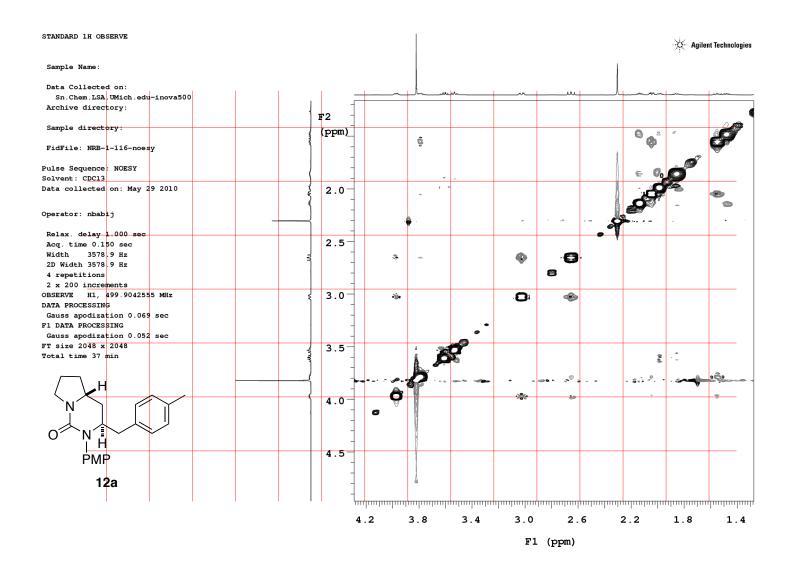


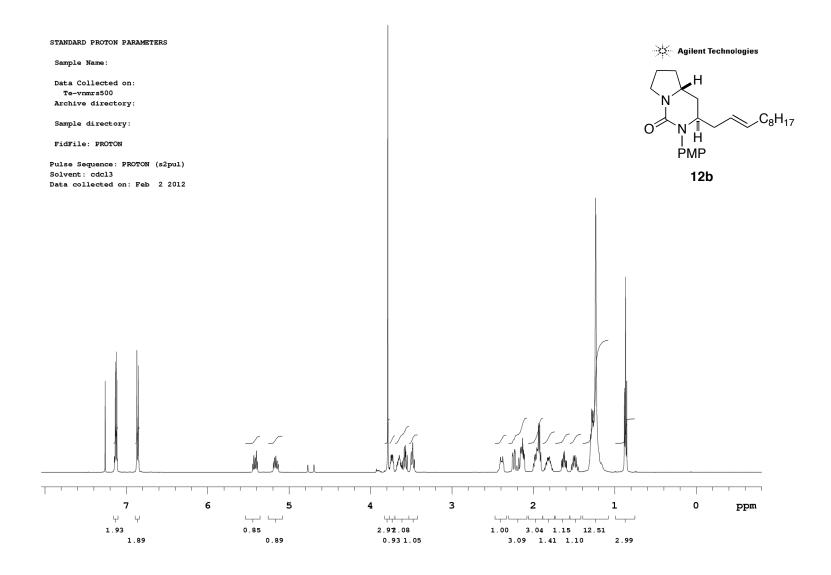


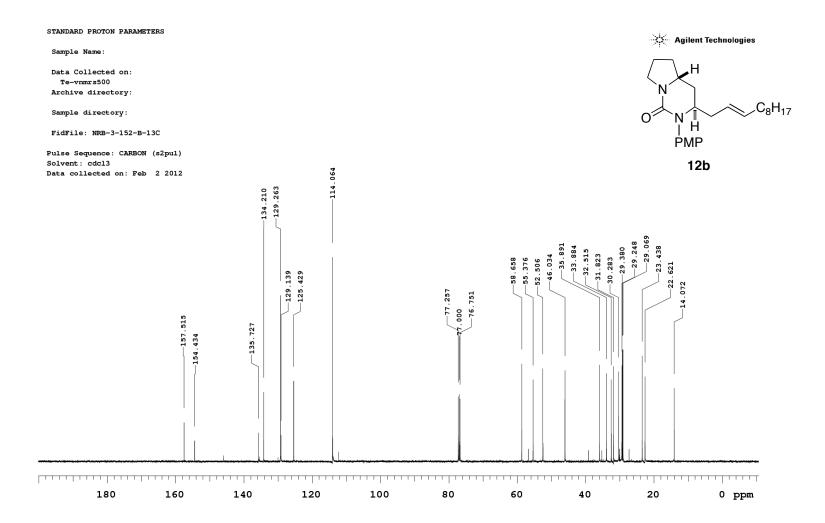


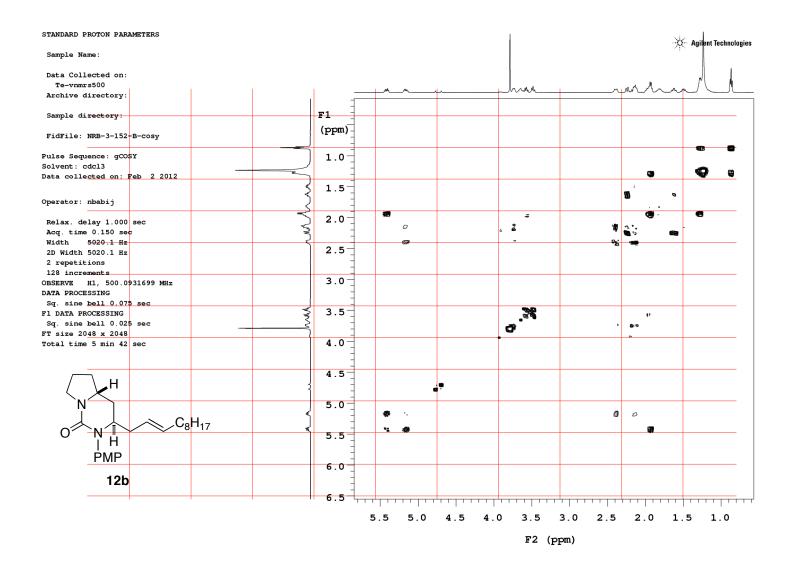


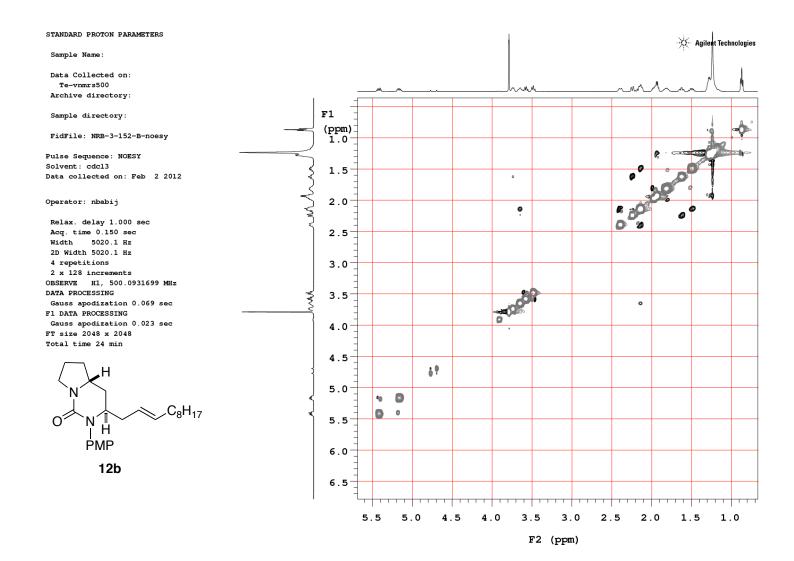


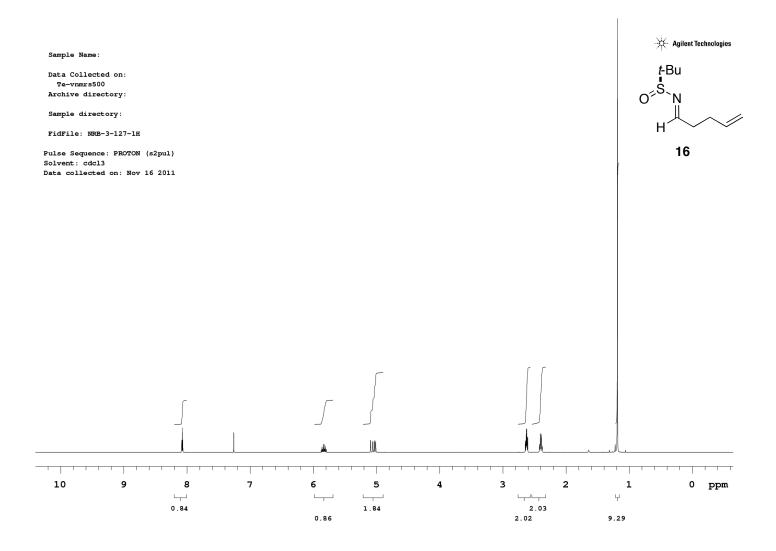


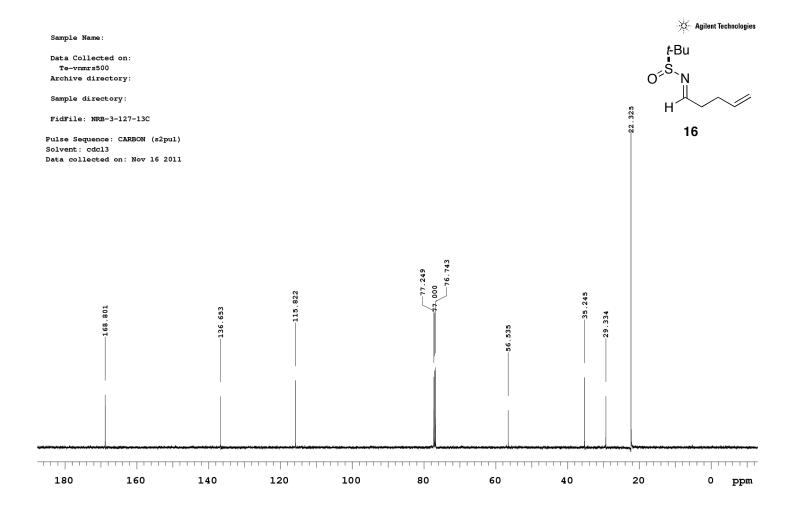


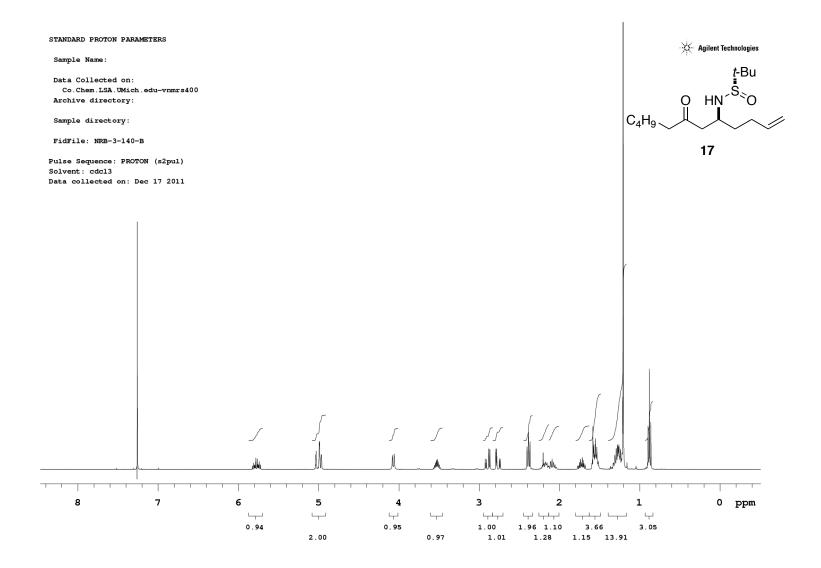


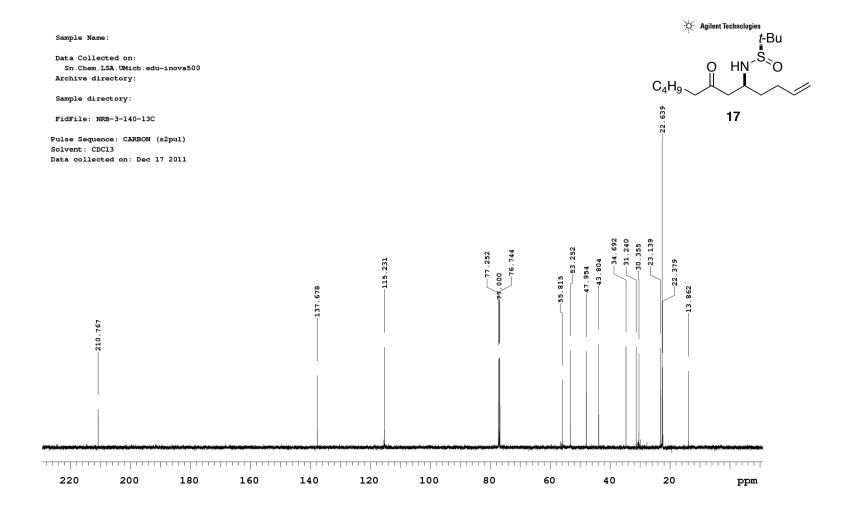


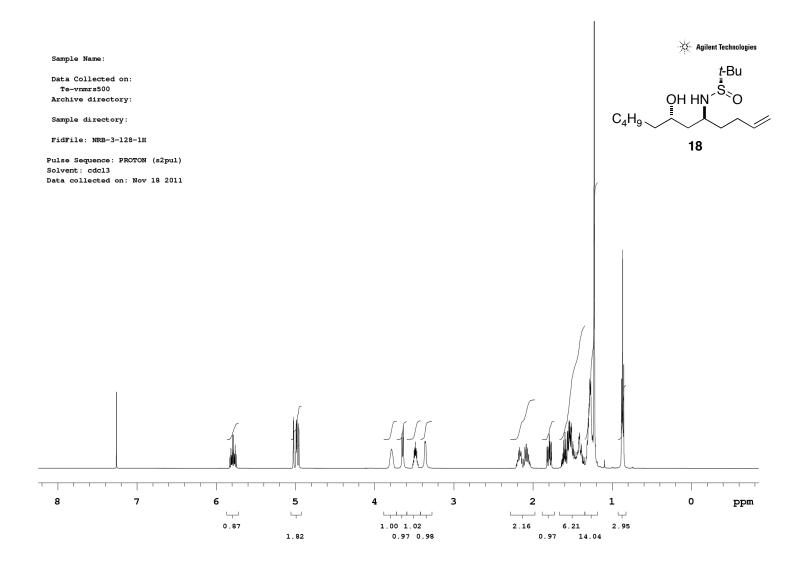


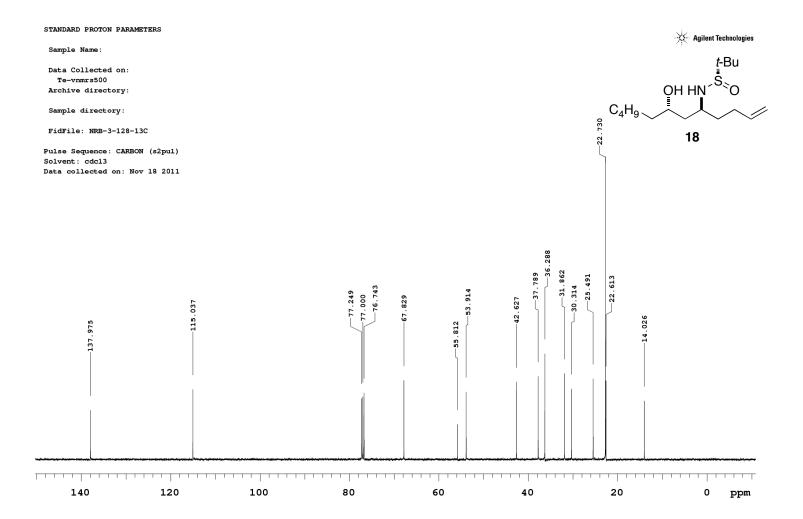


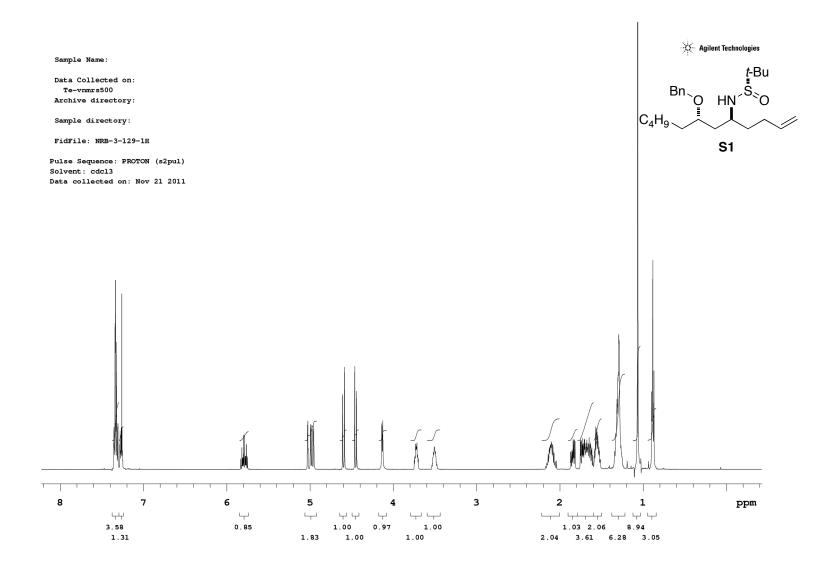


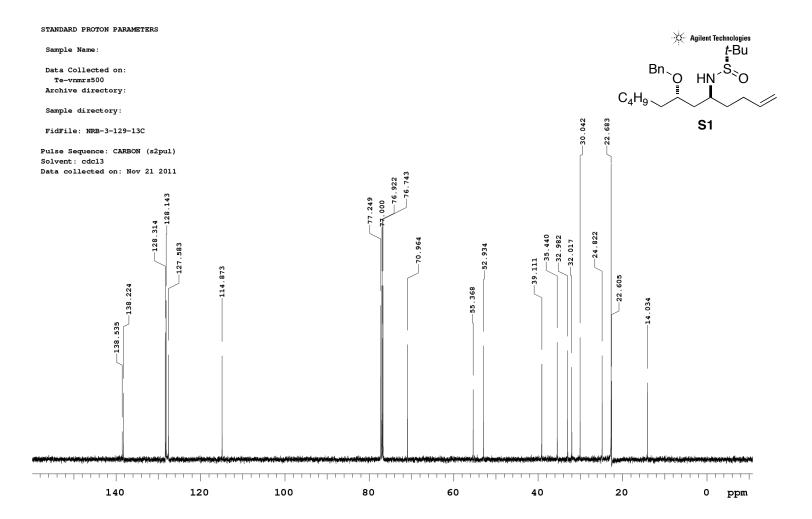






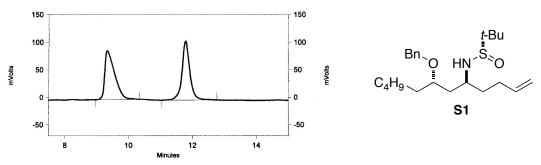






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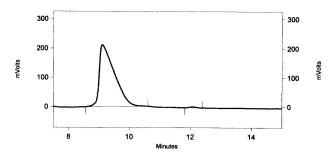
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Results

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SPD-10Avp Ch2-254nm

Results

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