

**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

# Synthesis of Macrocyclic Lactam via a Novel Ring Expansion Reaction: Construction of the Cripowellin Skeleton

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## Supporting Information

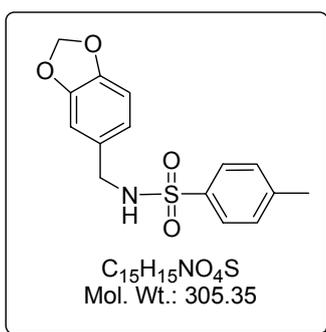
Experimental procedures and characterization data for the preparation of compounds  
**15-25, 10, 11, 19, 9.**

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were obtained using a Varian Gemini-300 (300 MHz for <sup>1</sup>H, and 75 MHz for <sup>13</sup>C), or a Varian Inova-500 (500 MHz for <sup>1</sup>H, and 125 MHz for <sup>13</sup>C) spectrometer. Chemical shifts are reported relative to tetramethylsilane peak ( $\delta$  0.00) or solvent peak ( $\delta$  7.27 for CDCl<sub>3</sub> in <sup>1</sup>H NMR,  $\delta$  77.2 for CDCl<sub>3</sub> in <sup>13</sup>C NMR). Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. IR spectra were obtained using a Thermo-Nicolet Avartar-330 IR spectrometer with a single-bounce ATR (Ge crystal) accessory (Smart MIRacle). High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS. THF and ethyl ether were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from calcium hydride. DME was distilled over LAH. *N,N*-dimethylformamide (DMF) was dried over 4 Å molecular sieves. HMPA was dried by vacuum distilling over LAH. The Stryker's reagent [(Ph<sub>3</sub>PCuH)<sub>6</sub>] was either synthesized following the literature procedure<sup>1</sup> or purchased from Fluka. All other chemicals were used as received otherwise specified.

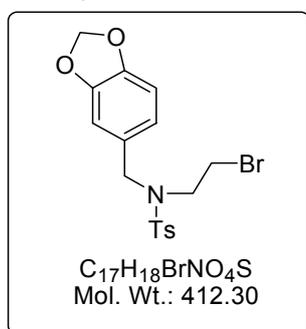
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<sup>1</sup> Chiu, P.; Li, Z.; Fung, K. C. M. *Tetrahedron Lett.* **2003**, *44*, 455.

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***N*-Piperonyl-*p*-toluenesulfonylamide (15)<sup>2</sup>:** A solution of *p*-toluene sulfonyl chloride (26.7 g, 140 mmol) in  $CH_2Cl_2$  (40 ml) was slowly added to a solution of piperonyl amine (15.1 g, 100 mmol) and triethylamine (34.0 ml, 250 mmol) in dry  $CH_2Cl_2$  (250 mL) at room temperature. The resulting solution was stirred at room temperature for 2.5 h. To the mixture was added aqueous 10% HCl, and then it was extracted with  $CH_2Cl_2$  (3 × 100 ml). The combined organic layers were dried over  $MgSO_4$ . After filtration, the filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 2:1) to provide **15** (25.2 g, 83%): <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.67 (m, 3H), 5.93 (s, 2H), 4.47 (br, s, 1H), 4.03 (s, 2H), 2.44 (s, 3H); <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ) δ 148.11, 147.51, 143.72, 137.08, 130.20, 129.92, 127.37, 121.53, 108.65, 108.42, 101.33, 47.34, 21.71.

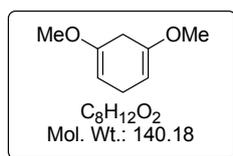


***N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide (16):** Sulfonamide **15** (319 mg, 1.04 mmol) was dissolved in DMSO (10mL). To the solution were added potassium carbonate (722 mg, 5.23 mmol) and dibromoethane (180 μL, 2.09 mmol). The resulting suspension was stirred at

<sup>2</sup> Known and commercially available compound: Shozo, Y. *Nippon Kagaku Zasshi* **1968**, *89*, 1099.

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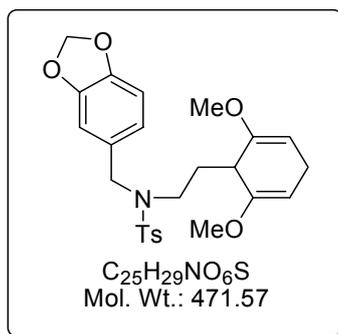
room temperature overnight. The reaction was quenched by adding H<sub>2</sub>O (10 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried over MgSO<sub>4</sub> and filtered. The filtrate was concentrated in vacuo to give a crude product as a white solid. Flash column chromatography of the crude product on silica gel (Hex:EtOAc = 2:1) provided the product **16** (392 mg, 91%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.81 (s, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 5.97 (s, 2H), 4.22 (s, 2H), 3.39 (t, *J* = 8.4 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 2H), 2.45 (s, 3H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 148.25, 147.72, 143.89, 136.24, 130.02, 129.76, 127.22, 121.93, 108.83, 108.33, 101.35, 53.20, 49.69, 29.29, 21.63; IR (film) 2905, 1490, 1446, 1338, 1244, 1158, 1091, 1038, 930 cm<sup>-1</sup>. Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>BrNO<sub>4</sub>S: C, 49.52; H, 4.40; N, 3.40; S, 7.78. Found: C, 49.57; H, 4.50; N, 3.38; S, 7.96.



**1,5-Dimethoxy-cyclohexa-1,4-diene (17)<sup>3</sup>:** 1,3-Dimethoxybenzene (6.47 mL, 50 mmol) was dissolved in dry THF (25 mL) and ethanol (4.61 mL, 100 mmol). While cooling the reaction flask by dry ice/acetone bath, ~250 mL of liquid ammonia was condensed by blowing ammonia gas through a needle into the solution. After adding lithium metal chunks (1.22 g, 200 mmol) to the solution, the flask was capped with a rubber septum. The resulting deep blue solution was stirred for 1.5 h at -78 °C. The reaction was quenched by adding ethanol until the mixture turned white and became cloudy. After allowing NH<sub>3</sub> to slowly evaporate, a saturated aqueous NH<sub>4</sub>Cl solution (30 mL) was added. The aqueous layer was extracted with ether (3 × 100 mL). The combined ether layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. Simple distillation of the crude product provided **17** (6.0 g, 86%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.66 (t, *J* = 3.3 Hz, 2H), 3.57 (s, 6H), 2.84 (m, 2H), 2.80 (m, 2H); LR-MS (*m/e*): 140 (M<sup>+</sup>, 65), 125 (18), 109 (100), 97(20), 77(16), 65(15), 39(12).

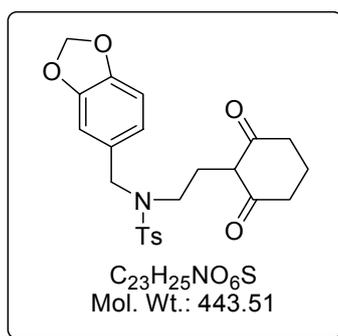
<sup>3</sup> Arisawa, M.; Ramesh, N. G.; Nakajima, M.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 59.

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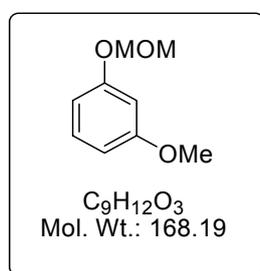


***N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-[2-(2,6-dimethoxycyclohexa-2,5-dienyl)ethyl]-4-methylbenzenesulfonamide (18):** A solution of 1,5-dimethoxy-1,4-cyclohexadiene (**17**) (160 mg, 1.14 mmol) in dry THF (4 mL) was added to a solution of *t*-BuLi (1.7 M in *n*-pentane, 0.89 mL, 1.5 mmol) at  $-78\text{ }^{\circ}\text{C}$  under inert atmosphere. The resulting solution was allowed to stir at  $-78\text{ }^{\circ}\text{C}$  for 1 h. After adding freshly distilled HMPA (320  $\mu\text{L}$ , 1.9 mmol) to the solution via a syringe, the resulting yellow-orange solution was allowed to stir for an additional 10 min. Bromide **16** (314 mg, 0.762 mmol) in THF (2 mL) was added at  $-78\text{ }^{\circ}\text{C}$ . The solution turned to yellow immediately. After stirring for 40 min at  $-78\text{ }^{\circ}\text{C}$ , the reaction was quenched by adding saturated  $\text{NH}_4\text{Cl}$  (5 mL) at  $-78\text{ }^{\circ}\text{C}$ , and the mixture was allowed to warm to room temperature. It was diluted with brine and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and filtered. Concentration of the filtrate under vacuo afforded the crude product as a yellow oil. Purification of the crude product by flash column chromatography on silica gel (Hex:EtOAc = 3:1) provided **18** (240 mg, 67%):  $^1\text{NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.0$  Hz, 2H), 7.29 (d,  $J = 8.0$  Hz, 2H), 6.81 (s, 1H), 6.718 (s, 1H) 6.717 (s, 1H), 5.94 (s, 2H), 4.62 (t,  $J = 4.0$  Hz, 2H), 4.21 (s, 2H), 3.46 (s, 6H), 2.97 (m, 2H), 2.80 (m, 1H), 2.69 (dt,  $J = 6.90$  and 3.6 Hz, 2H), 2.43 (s, 3H), 1.71 (dt,  $J = 13.5$  and 4.2 Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 153.07, 147.95, 147.29, 143.10, 137.96, 130.28, 129.72, 127.32, 122.23, 109.32, 108.08, 101.19, 92.05, 54.38, 50.52, 42.93, 38.74, 26.02, 24.46, 21.69. IR (film) 2954, 2897, 1687, 1489, 1388, 1245, 1204, 1161, 1151, 1104, 1038, 937, 805, 787  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{25}\text{H}_{29}\text{NO}_6\text{S}$ : C, 63.67; H, 6.20; N, 2.97; S, 6.80. Found: C, 63.65; H, 6.24; N, 2.83; S, 6.69.

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***N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-[2-(2,6-dioxocyclohexyl)ethyl]-4-methylbenzenesulfonamide (10):** To a solution of *N*-benzo[1,3]dioxol-5-ylmethyl-*N*-[2-(2,6-dimethoxy-cyclohexa-2,5-dienyl)ethyl]-4-methyl-benzenesulfonamide (**18**) (75 mg, 0.16 mmol) in THF (3 mL) were added 10% HCl (1 mL). The resulting solution was stirred at room temperature for 1 h. The reaction was quenched by adding saturated  $NH_4Cl$  solution (6 mL), and the mixture was extracted with ether (3 x 15 mL). The combined ether extracts were washed with brine and dried over  $MgSO_4$ . After filtration, the filtrate was concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 1:2) to yield dione **10** (68 mg, 96%). Since the dione is unstable under ambient conditions, it was freshly prepared each time and subjected to the next reaction in a day:  $^1H$  NMR (300 MHz,  $CDCl_3$ ) (enol form)  $\delta$  8.28 (br s, 1H), 7.71 (d,  $J = 8.4$  Hz, 2H), 7.35 (d,  $J = 8.4$  Hz, 2H), 6.78 (d,  $J = 1.5$  Hz, 1H), 6.70 (d,  $J = 7.8$  Hz, 1H), 6.62 (dd,  $J = 7.8, 1.5$  Hz, 1H), 5.93 (s, 2H), 4.08 (s, 2H), 2.97 (t,  $J = 6.3$  Hz, 2H), 2.54 (t,  $J = 6.3$  Hz, 2H), 2.45 (s, 3H), 2.43 (br t, 2H), 2.07 (br t, 2H), 1.82 (pent,  $J = 6.3$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ) (ketone form) 204.26, 148.04, 147.57, 144.34, 133.85, 130.12, 129.86, 127.76, 122.58, 109.40, 108.28, 101.29, 64.11, 54.68, 47.96, 40.00, 23.07, 21.77, 20.62. IR (film) 2917, 1711, 1491, 1446, 1386, 1335, 1245, 1157, 1096, 1038, 929, 813, 743, 659  $cm^{-1}$ .

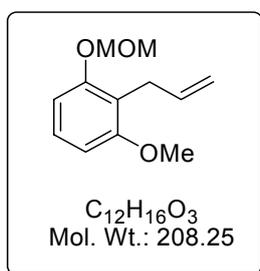


**Methoxy-3-methoxymethoxy-benzene (20)**<sup>4</sup>: To a solution of 3-methoxyphenol (6.70 g, 54.7 mmol) in  $CH_3CN$  (250 mL) was added under nitrogen at 0

<sup>4</sup> Pave, G.; Leger, J.-M.; Jarry, C.; Viaud-Massuard, M.-C.; Guillaumet, G. *J. Org. Chem.* **2003**, *68*, 1401.

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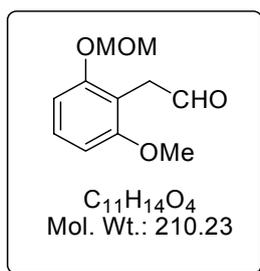
$^{\circ}\text{C}$  dry  $\text{K}_2\text{CO}_3$  (22.0 g, 159 mmol). After 15 min, 18-crown-6 ether (2.03 g, 14.8 mmol) and MOMCl (6.81 mL, 89.7 mmol) were added. The mixture was stirred for 26 h at room temperature and filtered. The filtrate was evaporated under reduced pressure and purified by flash chromatography on silica gel (Hex:EtOAc = 3:1) to provide **20** (8.55 g, 93%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.18 (t,  $J = 8.0$  Hz, 1H), 6.64 (dd,  $J = 8.0, 2.0$  Hz, 1H), 6.61 (t,  $J = 2.0$  Hz, 1H), 6.57 (dd,  $J = 8.0, 2.5$  Hz, 1H); 5.16 (s, 2H), 3.79 (s, 3H), 3.48 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 160.96, 158.64, 130.09, 108.57, 107.67, 102.81, 94.64, 56.19, 55.46.



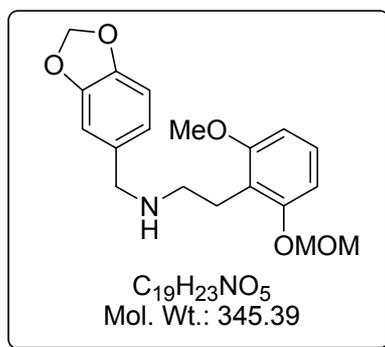
**2-Allyl-1-methoxy-3-methoxymethoxy-benzene**<sup>5</sup>: To a solution of 1-methoxy-3-methoxymethoxy-benzene (**20**) (550 mg, 3.27 mmol) in ether (10 mL) was added *n*-BuLi (2.5 M in hexanes, 1.7 mL, 4.3 mmol) under nitrogen atmosphere at room temperature. After additional stirring for 1.5 h at room temperature, allyl bromide (340  $\mu\text{L}$ , 3.9 mmol) was added to the solution via a syringe. After 30 min, the reaction was quenched by adding  $\text{H}_2\text{O}$  (10 mL) and the mixture was extracted with ether ( $3 \times 20$  mL). The combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 9:1) to provide 2-Allyl-1-methoxy-3-methoxymethoxy-benzene (500 mg, 73%) as a colorless oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 (t,  $J = 8.0$  Hz, 1H), 6.73 (d,  $J = 8.0$  Hz, 1H), 6.58 (d,  $J = 8.5$  Hz, 1H), 5.96 (dddd,  $J = 16.5, 10.5, 6.0, 6.0$  Hz, 1H); 5.18 (s, 2H), 4.97 (dd,  $J = 17.0, 2.0$  Hz, 1H), 4.93 (dd,  $J = 10.0, 1.5$  Hz, 1H), 3.81 (s, 3H), 3.46 (s, 3H), 3.44 (d,  $J = 6.0$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 158.52, 155.93, 137.02, 127.34, 117.67, 114.25, 107.27, 104.85, 94.65, 56.21, 55.99, 27.60.

<sup>5</sup> Ortho-lithiation and alkylation of the *O*-MOM- and *O*-benzylresorcinol is described in the literature. See Simas, A. B. C.; Coelho, A.; Costa, P. R. R. *Synthesis* **1999**, 1017.

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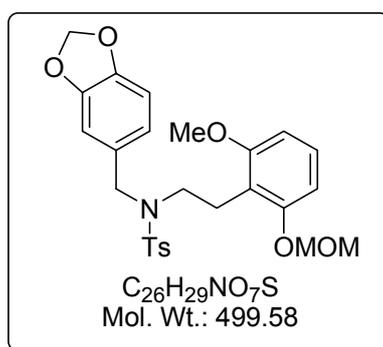
**(2-Methoxy-6-methoxymethoxy-phenyl)-acetaldehyde (21):** Ozone was bubbled through a solution of 2-allyl-1-methoxy-3-methoxymethoxybenzene (1.05 g, 5.04 mmol) in  $CH_2Cl_2/MeOH$  (1:1, 10 mL) at  $-78\text{ }^\circ\text{C}$  and the reaction progress was monitored by TLC. When the starting material spot was disappeared by TLC analysis, the bubbling was immediately stopped and the reaction was quenched by adding excess dimethyl sulfide (5 mL). The mixture was allowed to warm to ambient temperature and stirred for 3-5 h. After the resulting solution was concentrated in vacuo, the residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 6:1) to yield aldehyde **21** (911 mg, 86%) as a colorless oil:  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  9.62 (t,  $J = 2.0$  Hz, 1H), 7.22 (t,  $J = 8.5$  Hz, 1H), 6.79 (d,  $J = 8.5$  Hz, 1H), 6.62 (d,  $J = 8.5$  Hz, 1H), 5.18 (s, 2H), 3.81 (s, 3H), 3.72 (d,  $J = 2.0$  Hz, 2H), 3.44 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ) 200.85, 158.73, 156.39, 128.95, 110.63, 107.01, 104.59, 94.64, 56.35, 55.92, 38.58. IR (film) 2917, 1723, 1596, 1473, 1254, 1154, 1107, 1072, 1001  $cm^{-1}$ .



**Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methoxy-6-methoxymethoxy-phenyl)-ethyl]amine (22):** To a solution of aldehyde (800 mg, 3.80 mmol) and piperonyl amine (575 mg, 3.80 mmol) in MeOH (10 mL) was added  $NaBH_4$  (288 mg; 7.60 mmol) and the pH of the solution was adjusted to 4-5 by adding acetic acid. The reaction mixture was stirred at room temperature for 30 min. The major solvent was removed by rotary evaporation. The residue was dissolved in EtOAc and it was washed with saturated  $Na_2CO_3$ . The organic layer was washed with water, brine, and dried over  $Na_2SO_4$ . After filtration, the filtrate was concentrated under reduced pressure and the residue was

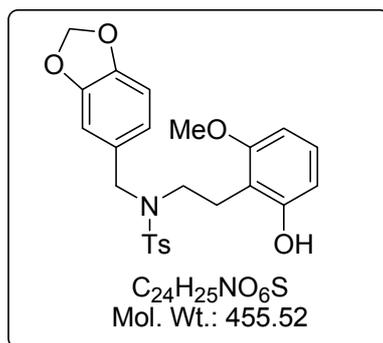
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purified by flash column chromatography (Hex/EtOAc (1:2) + 10% MeOH) to give a yellow oil (958 mg, 73%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (t,  $J = 8.5$  Hz, 1H), 6.83 (s, 1H), 6.75 (d,  $J = 8.5$  Hz, 1H), 6.73 (d,  $J = 8.5$  Hz, 2H), 6.56 (d,  $J = 8.5$  Hz, 1H), 5.92 (s, 2H), 5.17 (s, 2H), 3.80 (s, 3H), 3.74 (s, 2H), 3.43 (s, 3H), 2.92 (t,  $J = 8.0$  Hz, 2H), 2.80 (t,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  127.38, 121.45, 108.97, 108.18, 107.03, 104.63, 101.01, 94.60, 56.22, 55.84, 53.52, 48.48, 23.82; IR (film) 3734, 2898, 1594, 1489, 1471, 1440, 1250, 1113, 1067, 1038, 1014  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{19}\text{H}_{23}\text{NO}_5$ : C, 66.07; H, 6.71; N, 4.06. Found: C, 66.24; H, 6.43; N, 4.34.

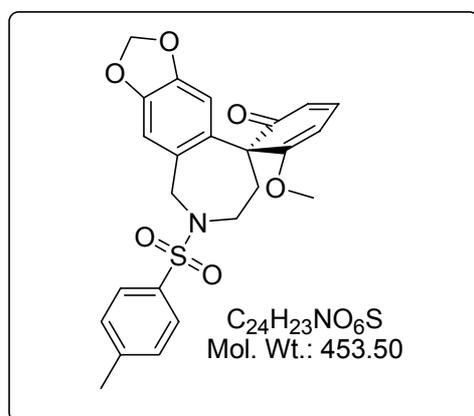


***N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-[2-(2-methoxy-6-methoxymethoxy-phenyl)-ethyl]-4-methylbenzenesulfonamide (23):** To a solution of amine **22** (500 mg, 1.45 mmol) and pyridine (487 mg, 5.79 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) was added tosyl chloride (275 mg, 1.45 mmol) at 0 °C. The mixture was stirred for 12 h at 0 °C. After quenching the reaction by adding 10% HCl solution (10 mL), the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  three times. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and evaporated. Flash chromatography of the residue (Hex/EtOAc from 3/1 to 2/1) afforded the desired product (486 mg, 67%) as a white solid;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 8.0$  Hz, 2H), 7.27 (d,  $J = 8.0$  Hz, 2H), 7.06 (t,  $J = 8.5$  Hz, 1H), 6.89 (s, 1H), 6.80 (d,  $J = 8.5$  Hz, 1H), 6.73 (d,  $J = 7.5$  Hz, 1H), 6.65 (d,  $J = 8.5$  Hz, 1H), 6.47 (d,  $J = 8.0$  Hz, 1H), 5.93 (s, 2H), 5.10 (s, 2H), 4.36 (s, 2H), 3.73 (s, 3H), 3.41 (s, 3H), 3.24 (t,  $J = 8.0$  Hz, 2H), 2.74 (t,  $J = 8.0$  Hz, 2H), 2.41 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.53, 156.14, 147.90, 147.26, 143.02, 138.03, 130.55, 129.65, 127.68, 127.37, 122.24, 115.57, 109.36, 108.08, 106.75, 104.36, 101.16, 94.41, 56.14, 55.62, 50.71, 45.57, 21.64, 21.56; IR (film) 2962, 2920, 1595, 1489, 1473, 1326, 1259, 1245, 1156, 1134, 1114, 1077, 1038, 1018, 928, 806  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{26}\text{H}_{29}\text{NO}_7\text{S}$ : C, 62.51; H, 5.85; N, 2.80. Found: C, 61.69; H, 5.98; N, 2.48.

**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.



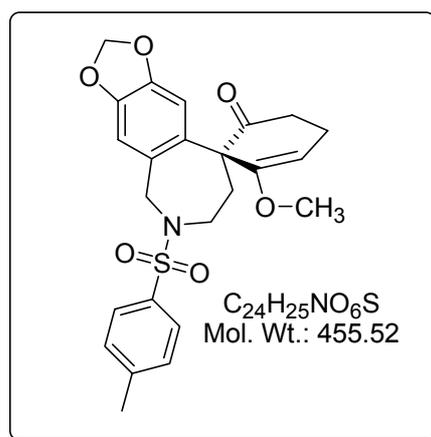
***N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-[2-(2-hydroxy-6-methoxy-phenyl)ethyl]-4-methyl-benzenesulfonamide (11):** To a stirred solution of MOM ether **23** (300 mg, 0.60 mmol) in *i*-PrOH (5 mL) was added TsOH (11 mg, 0.060 mmol). The solution was heated at 65 °C overnight while stirring. After cooling the reaction mixture, a few drops of triethylamine was added. The resulting mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (Hex/EtOAc from 2:1 to 1:2) to give **11** as a yellow gum (227 mg, 83%):  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.74 (d,  $J = 8.0$  Hz, 2H), 7.31 (d,  $J = 8.0$  Hz, 2H), 6.99 (t,  $J = 8.0$  Hz, 1H), 6.69 (d,  $J = 1.5$  Hz, 1H), 6.66 (d,  $J = 8.00$  Hz, 1H), 6.63 (dd,  $J = 8.0, 1.5$  Hz, 1H), 6.47 (d,  $J = 8.5$  Hz, 1H), 6.29 (d,  $J = 8.0$  Hz, 1H), 5.93 (s, 2H), 5.81 (s, 1H), 4.19 (s, 2H), 3.63 (s, 3H), 3.15 (t,  $J = 7.5$  Hz, 2H), 2.78 (t,  $J = 7.5$  Hz, 2H), 2.43 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  158.49, 155.48, 147.92, 147.41, 143.63, 136.11, 129.94, 129.90, 127.82, 127.59, 122.36, 112.57, 109.37, 109.08, 107.95, 102.59, 101.19, 55.48, 52.61, 46.38, 23.30, 21.71; IR (film) 3448, 3056, 2938, 1597, 1490, 1470, 1445, 1328, 1265, 1244, 1154, 1106, 1039, 930, 813  $cm^{-1}$ . Anal. Calcd for  $C_{24}H_{25}NO_6S$ : C, 63.28; H, 5.53; N, 3.07; S, 7.04. Found. C, 63.22; H, 5.56; N, 2.96; S, 7.17.



**5',6',7',8'-Tetrahydro-6'-(*p*-toluenesulfonyl)-spiro[6-methoxy-cyclohexa-3,5-dien-1,9'-[9H-1,3]dioxolo[4,5-*h*][2]benzazepin]-2-one (24):** To a stirred solution

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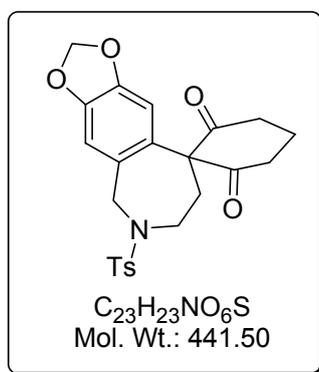
of methoxyphenol **11** (80 mg, 0.18 mmol) in  $\text{CF}_3\text{CH}_2\text{OH}$  (3 mL) was added a solution of PIFA (76 mg, 0.18 mmol) in  $\text{CF}_3\text{CH}_2\text{OH}$  (2 mL) in one portion at 0 °C under nitrogen atmosphere. After stirring for 1~2 min, the solution was concentrated and the residue was flash column chromatographed [Hex/EtOAc (from 2:1 to 1:2)] to give the cyclized dienone **24** as a yellow solid (48 mg, 58%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d,  $J$  = 8.5 Hz, 2H), 7.26 (d,  $J$  = 8.5 Hz, 2H), 7.16 (dd,  $J$  = 7.5, 10.0 Hz, 1H), 6.57 (s, 1H), 6.21 (s, 1H), 5.89 (d,  $J$  = 1.5 Hz, 1H), 5.86 (d,  $J$  = 1.5 Hz, 1H), 5.74 (d,  $J$  = 10.0 Hz, 1H), 5.39 (d,  $J$  = 7.5 Hz, 1H), 4.76 (d,  $J$  = 15.0 Hz, 1H), 4.52 (d,  $J$  = 15.0 Hz, 1H), 3.70-3.58 (m, 1H), 3.64 (s, 3H), 2.42 (m, 1H), 2.40 (s, 3H), 2.26 (m, 1H), 2.16 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  201.84, 173.48, 147.69, 146.73, 144.35, 143.32, 136.56, 131.63, 129.76, 129.68, 127.44, 117.25, 111.39, 109.13, 101.55, 92.46, 62.53, 56.32, 48.72, 42.96, 33.63, 21.68; IR (film) 2920, 1661, 1622, 1544, 1505, 1489, 1337, 1239, 1158, 1091, 1039, 919, 801  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  476.1148 (476.1144 calculated for  $\text{C}_{24}\text{H}_{23}\text{NO}_6\text{SNa}$  [ $\text{M} + \text{Na}^+$ ]).



**5',6',7',8'-Tetrahydro-6'-(*p*-toluenesulfonyl)-spiro[6-methoxy-cyclohex-5-en-1,9'-[9H-1,3]dioxolo[4,5-h][2]benzazepin]-2-one (**25**):** Stryker's reagent (179 mg, 0.092 mmol) was transferred into an oven-dried 1 mL round bottomed flask in a dry box. The flask was capped with a septum, and then removed from the dry-box. After adding dry toluene (0.5 mL) to the flask via a syringe through the septum, the resulting dark-red Stryker's reagent solution was transferred to a solution of dienone **24** (83.0 mg, 0.183 mmol) in dry toluene (1 mL) through a cannula under inert atmosphere. The progress of the reaction was monitored by TLC. The reaction was complete in 30 min as judged by TLC. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography [Hex/EtOAc (from 2:1 to 1:1)] to give ketone **25** as a white solid (68 mg, 81%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (d,  $J$  = 8.0

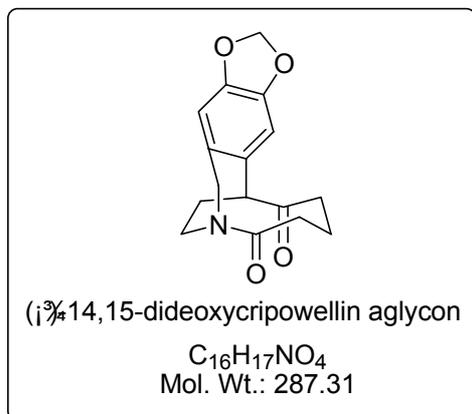
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

Hz, 2H), 7.27 (d,  $J = 8.0$  Hz, 2H), 6.76 (s, 1H), 6.55 (s, 1H), 5.92 (s, 2H), 5.01 (dd,  $J = 5.0, 2.5$  Hz, 1H), 4.50 (d,  $J = 14.0$  Hz, 1H), 4.36 (d,  $J = 14.0$  Hz, 1H), 3.80 (dd,  $J = 13.5, 7.5$  Hz, 1H), 3.52 (s, 3H), 3.25 (dd,  $J = 12.8, 9.3$  Hz, 1H), 2.62 (ddd,  $J = 13.0, 11.0, 8.0$  Hz, 1H), 2.52 (dd,  $J = 15.5, 8.5$  Hz, 1H), 2.43 (m, 1H), 2.41 (s, 3H), 2.32 (m, 1H), 2.23 (ddd,  $J = 12.5, 5.5, 3.0$  Hz, 1H), 1.98 (dd,  $J = 6.5, 15.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  207.63, 158.30, 147.94, 146.95, 143.29, 136.75, 131.80, 129.75, 128.05, 127.50, 111.68, 110.21, 101.58, 95.21, 60.84, 55.33, 48.58, 44.25, 35.14, 30.87, 21.69, 21.64. IR (film) 2919, 1711, 1662, 1505, 1485, 1336, 1240, 1158, 1092, 1043, 914  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{24}\text{H}_{25}\text{NO}_6\text{S}$ : C, 63.28; H, 5.53; N, 3.07; S, 7.04. Found. C, 63.77; H, 6.28; N, 2.96; S, 7.04.



**5',6',7',8'-Tetrahydro-6'-(*p*-toluenesulfonyl)-spiro[cyclohexane-1,9']-[9H-1,3]dioxolo[4,5-*h*][2]benzazepin]-2,6-dione (19):** To a solution of **25** (30 mg, 0.066 mmol) in THF (1.5 ml) was added aqueous 3N-HCl (1 mL). While stirring the reaction mixture at room temperature, the progress of the reaction was followed by TLC. After 1 h, the reaction was complete as judged by TLC. The mixture was diluted with water and extracted with  $\text{CH}_2\text{Cl}_2$  three times. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Hex/EtOAc = 2:1) to give a white solid (21 mg, 72%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (d,  $J = 8.0$  Hz, 2H), 7.24 (d,  $J = 8.0$  Hz, 2H), 6.68 (s, 1H), 6.32 (s, 1H), 5.96 (s, 2H), 4.25 (s, 2H), 3.62 (t,  $J = 5.8$  Hz, 2H), 2.73 (ddd,  $J = 16.5, 6.0, 6.0$  Hz, 2H), 2.57 (ddd,  $J = 16.5, 7.5, 6.5$  Hz, 2H), 2.40 (s, 3H), 2.18 (t,  $J = 6.0$  Hz, 2H), 2.03 (dt,  $J = 14.5, 7.5, 7.5$  Hz, 1H), 1.88 (dt,  $J = 14.5, 7.0, 7.0$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  208.13, 147.81, 147.25, 143.42, 136.62, 130.67, 129.94, 129.75, 127.36, 111.96, 109.64, 101.92, 73.37, 49.90, 44.27, 38.57, 29.54, 21.67, 16.83, ; IR (neat) 2919, 1727, 1696, 1508, 1489, 1335, 1240, 1158, 1091, 1039, 926  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_6\text{S}$ : C, 62.57; H, 5.25; N, 3.17; S, 7.26. Found. C, 62.64; H, 5.22; N, 2.95; S, 7.26.

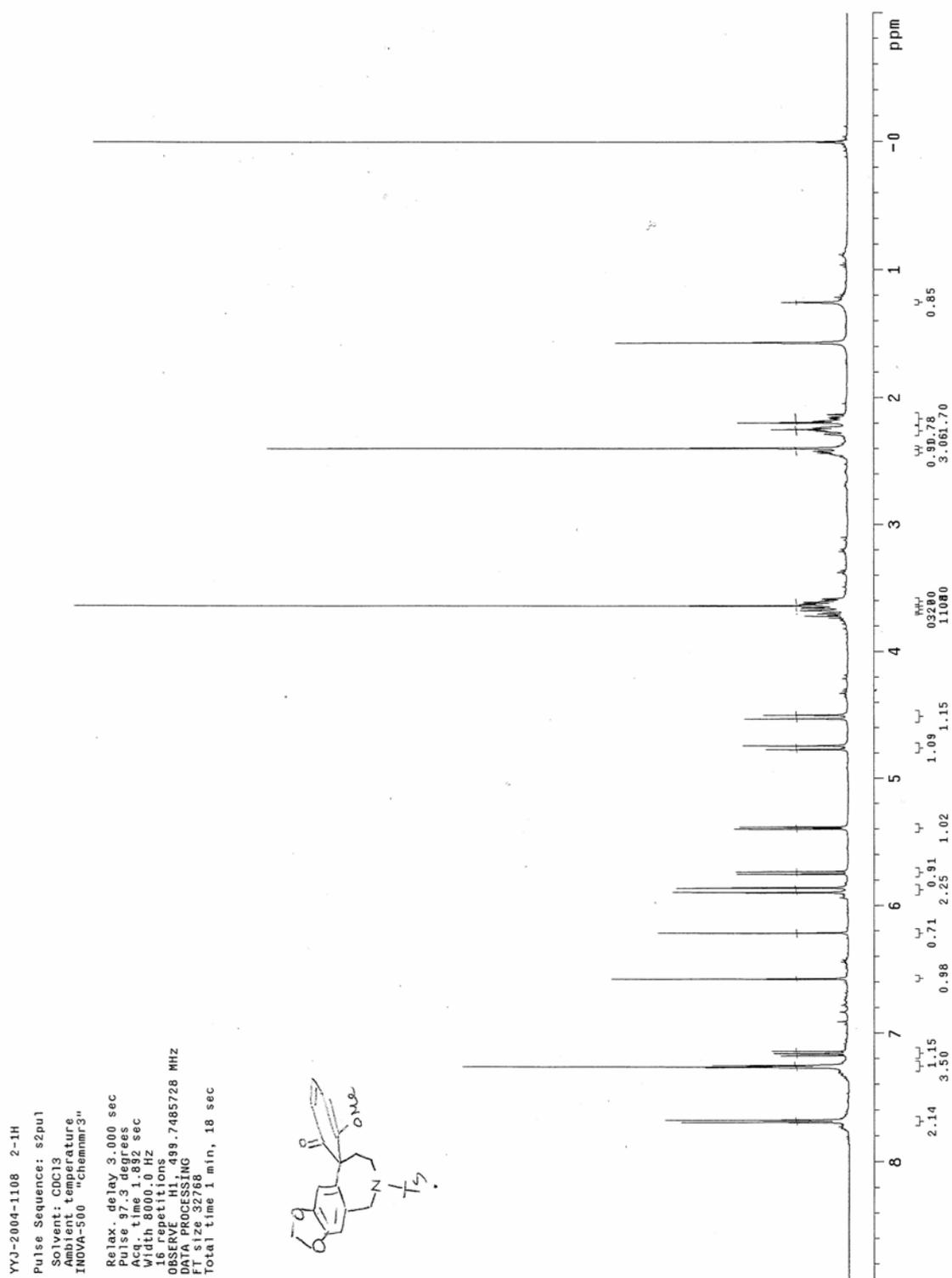
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.



**(±)-5H-6,12-Ethano-1,3-dioxolo[4,5-k][2]benzazecine-7,11(8H,12H)-dione [(±)-14,15-dideoxycripowellin aglycon] (9):** To a solution of dione **19** (15 mg, 0.034 mmol) in 1 mL of dry DME was added a solution of sodium naphthalenide [sodium (5 mg, 0.217 mmol) + naphthalene (27 mg, 0.211 mmol) in DME (1 mL)] at  $-78\text{ }^{\circ}\text{C}$  under inert atmosphere. The green color of the sodium naphthalenide solution disappeared immediately during the addition. The resulting yellow solution was stirred for 5 min, warmed to room temperature, and the reaction was quenched by adding water. It was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The resulting crude product was purified by flash column chromatography on silica gel [Hex/EtOAc (1:2) + 10% MeOH] to give **9** as a white solid (5 mg, 51%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.75 (s, 1H, Ar-*H*), 6.48 (s, 1H, Ar-*H*), 5.96 (m, 2H,  $\text{OCH}_2\text{O}$ ), 5.33 (d,  $J = 15.5$  Hz, 1H,  $\text{ArCH}_a\text{H}_b\text{N}$ ), 3.89 (ddd,  $J = 14.5, 6.5, 6.5$  Hz, 1H,  $\text{CH}_2\text{CH}_a\text{H}_b\text{N}$ ), 3.87 (d,  $J = 15.5$  Hz, 1H,  $\text{ArCH}_a\text{H}_b\text{N}$ ), 3.54 (m, 1H, ArCHCO), 3.34 (ddd,  $J = 14.5, 8.5, 3.5$  Hz, 1H,  $\text{CH}_2\text{CH}_a\text{H}_b\text{N}$ ), 2.92 (ddd,  $J = 15.0, 6.5, 3.5$  Hz, 1H,  $\text{CH}_a\text{H}_b\text{CH}_2\text{N}$ ), 2.67 (m, 1H,  $\text{COCH}_a\text{H}_b\text{CH}_2$ ), 2.39 (dddd,  $J = 15.0, 7.5, 7.5, \text{ and } 2.5$  Hz, 1H,  $\text{COCH}_a\text{H}_b\text{CH}_2$ ), 2.35 (m, 1H,  $\text{NCOCH}_a\text{H}_b$ ), 2.22 (br m, 1H,  $\text{NCOCH}_a\text{H}_b$ ), 2.16 (br m, 3H,  $\text{CH}_2\text{CH}_2\text{CH}_2$  and  $\text{COCH}_a\text{H}_b\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  213.80, 173.54, 147.13, 146.83, 130.25 (br), 130.01 (br), 111.52, 109.47, 101.48, 57.00, 49.73 (br), 45.69 (br), 35.49 (br), 32.98, 29.40 (br), 25.47 (br); IR (film) 2924, 1696, 1635, 1504, 1487, 1356, 1231, 1037, 911,  $730\text{ cm}^{-1}$ . HRMS (ESI)  $m/z$  310.1067 (310.1055 calculated for  $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{Na}$  [ $\text{M} + \text{Na}^+$ ])

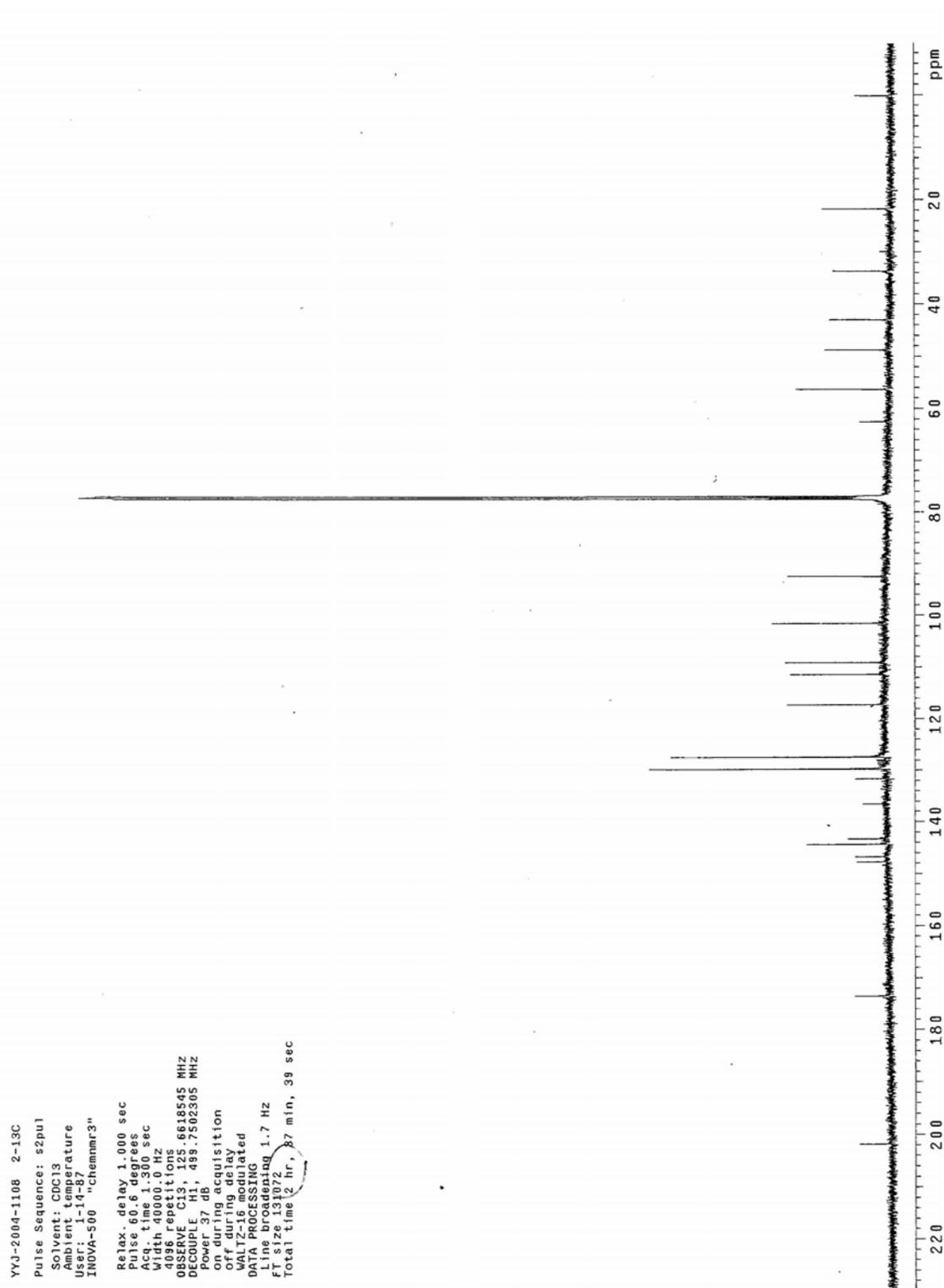
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

<sup>1</sup>H-NMR of 24



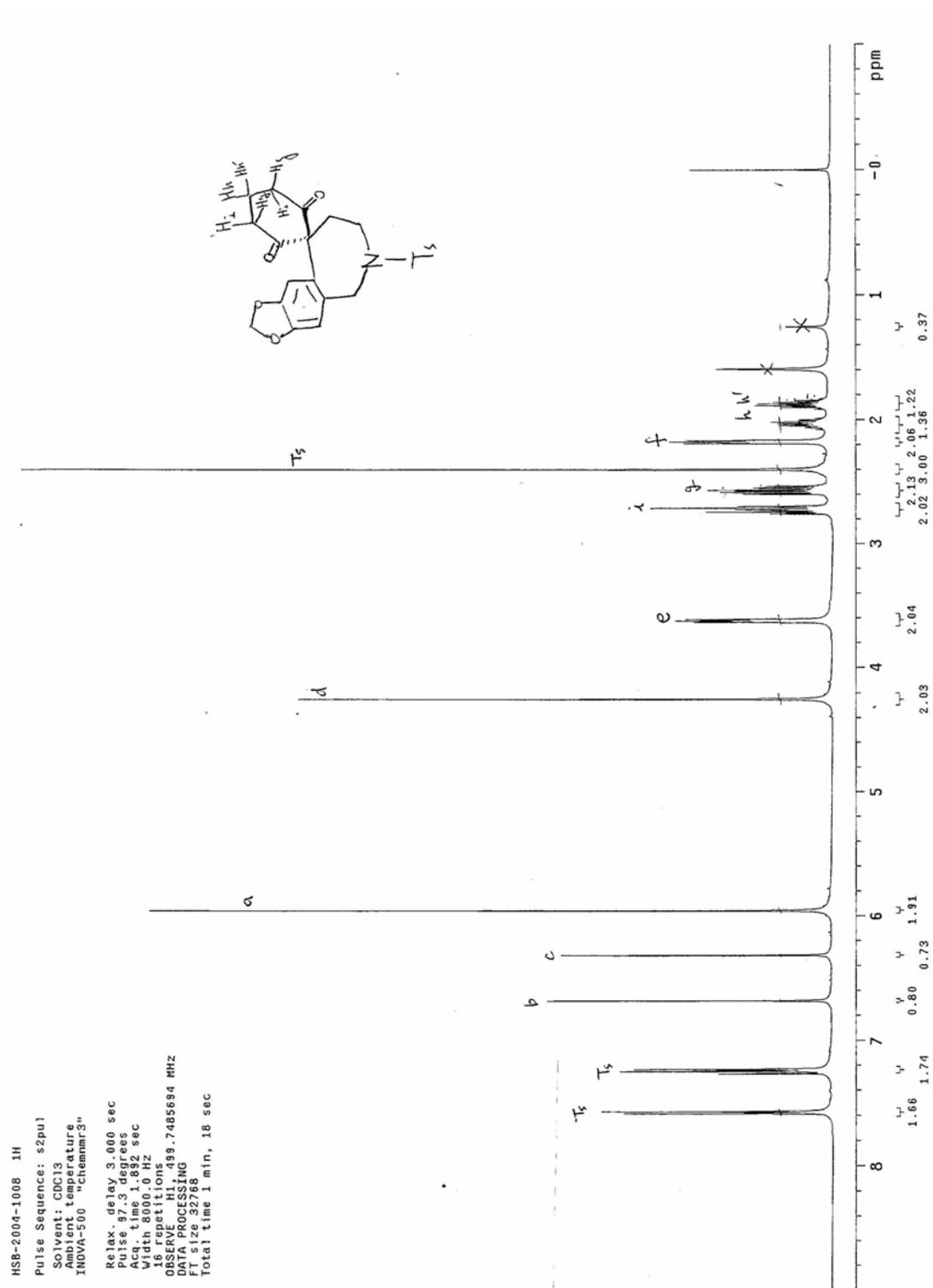
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### $^{13}\text{C}$ -NMR of 24



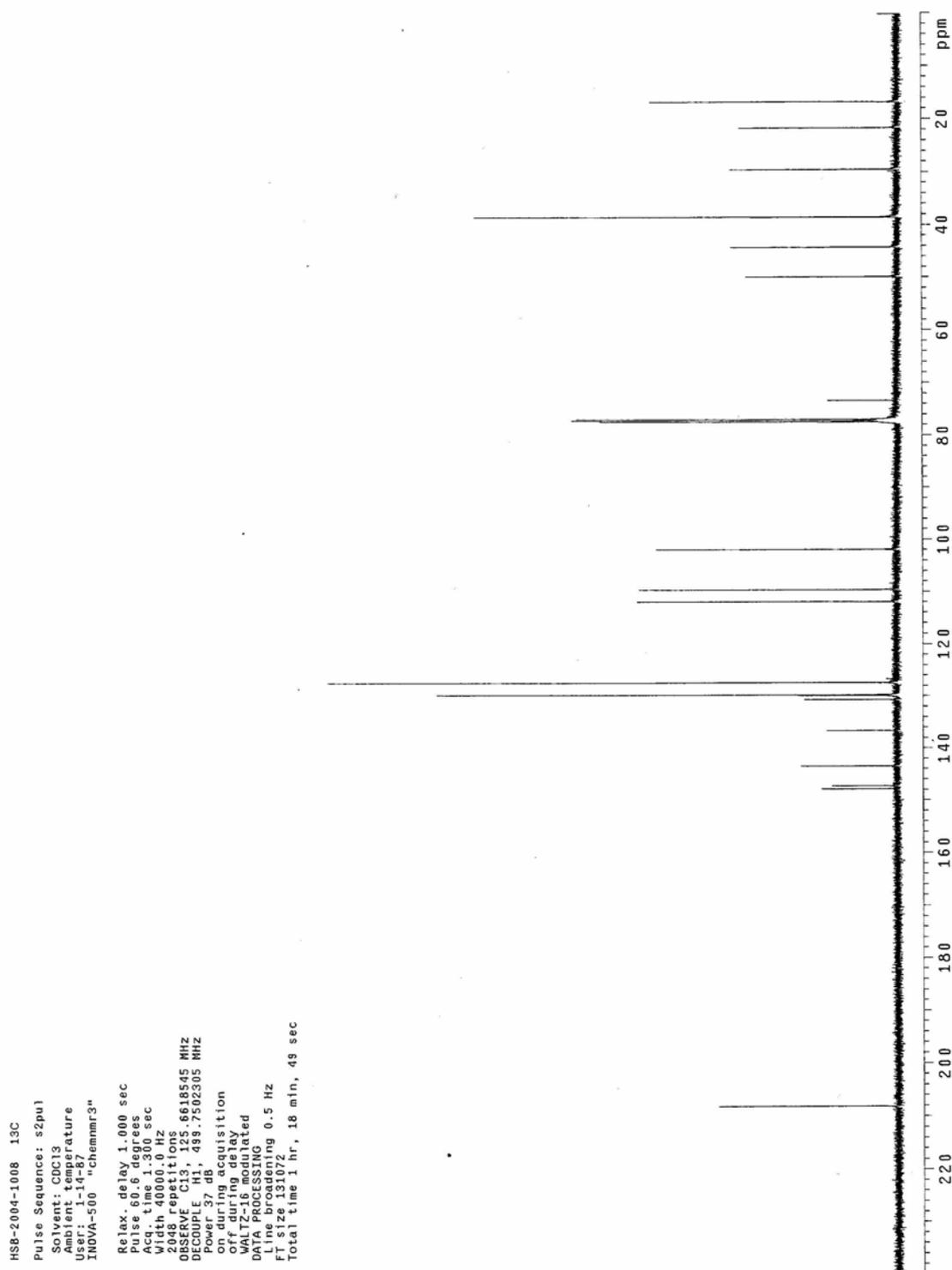
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<sup>1</sup>H-NMR of **19**



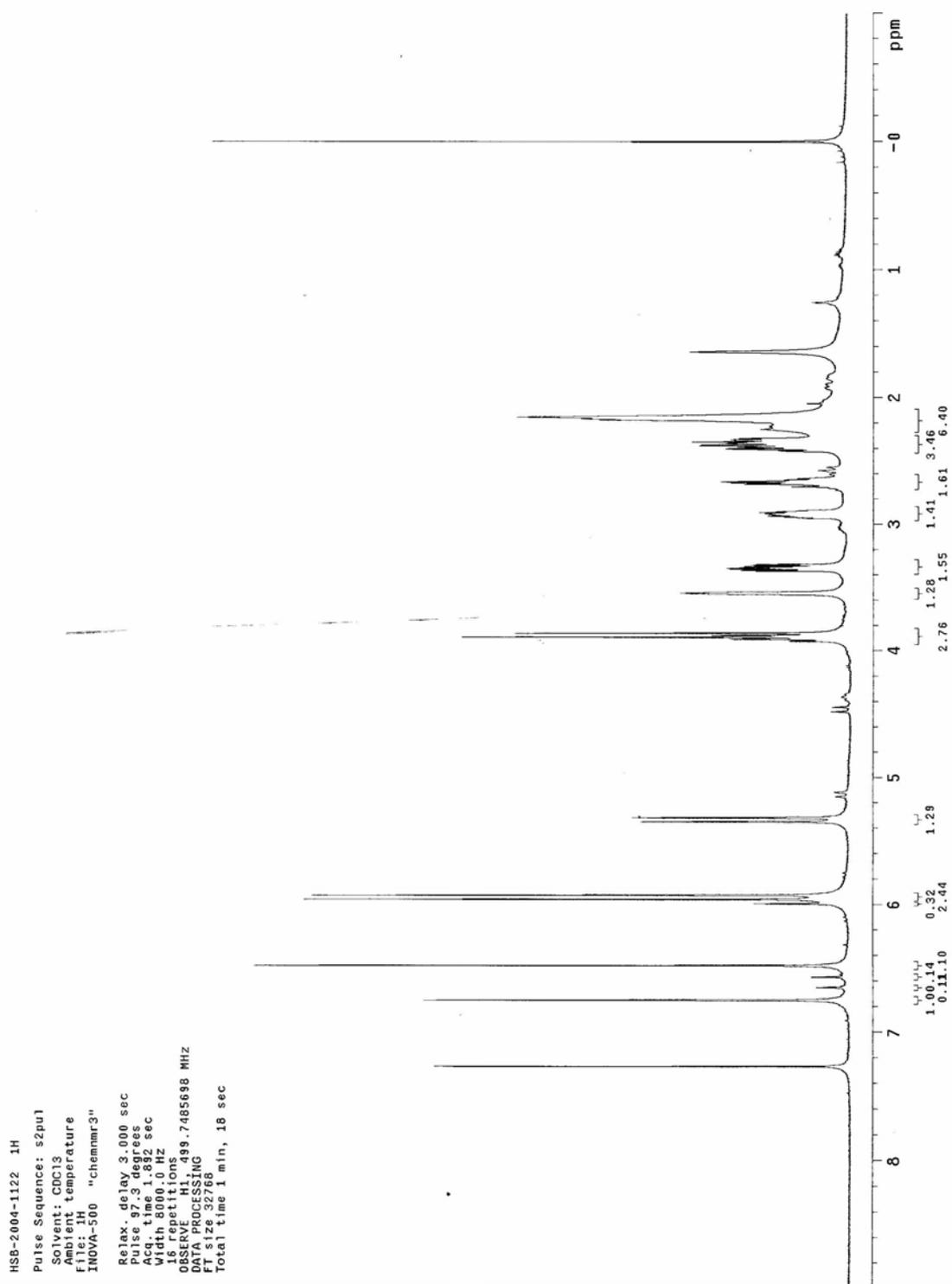
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

### $^{13}\text{C}$ -NMR of 19



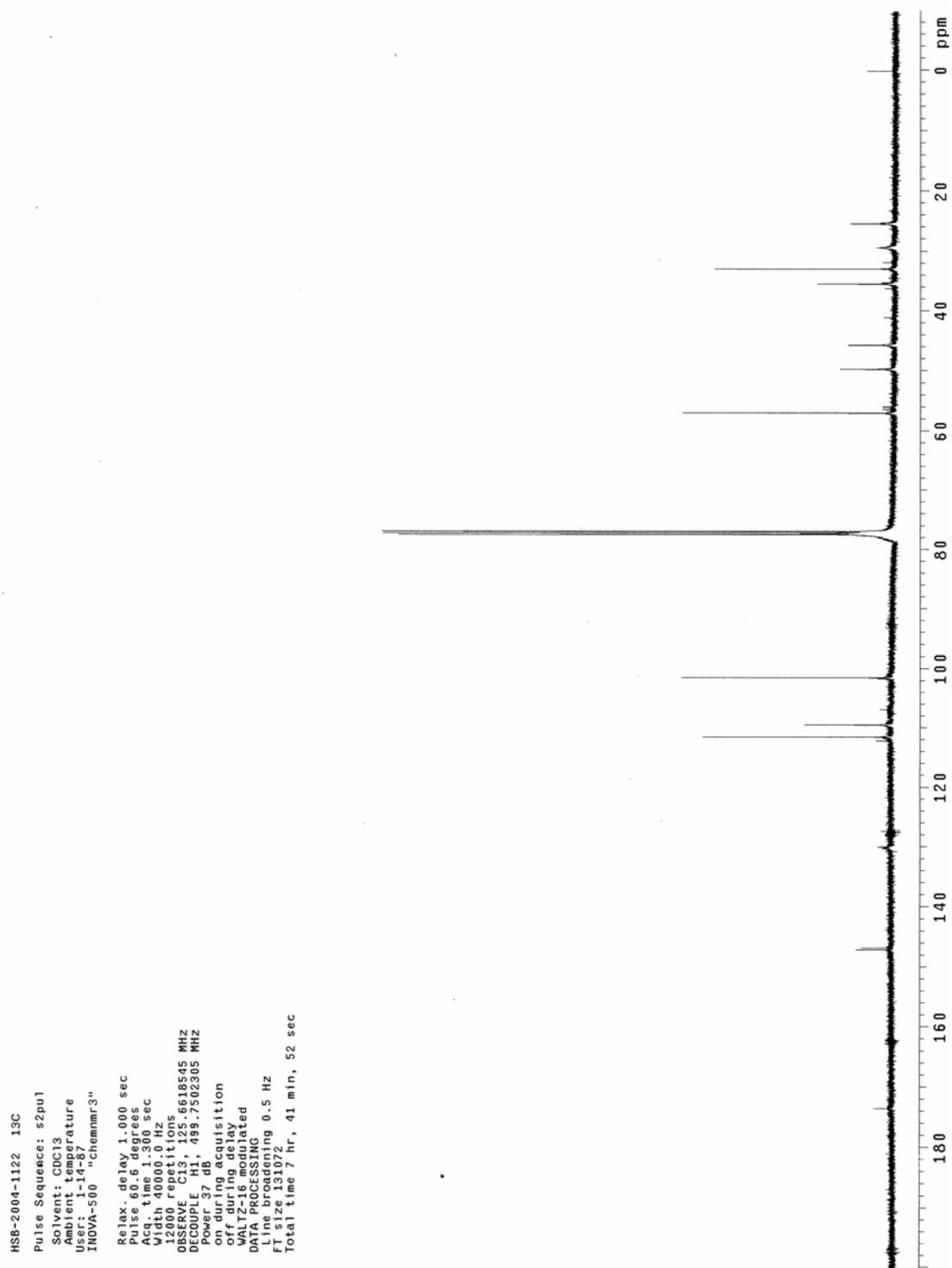
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

<sup>1</sup>H-NMR of 14,15-dideoxycripowellin (**9**)



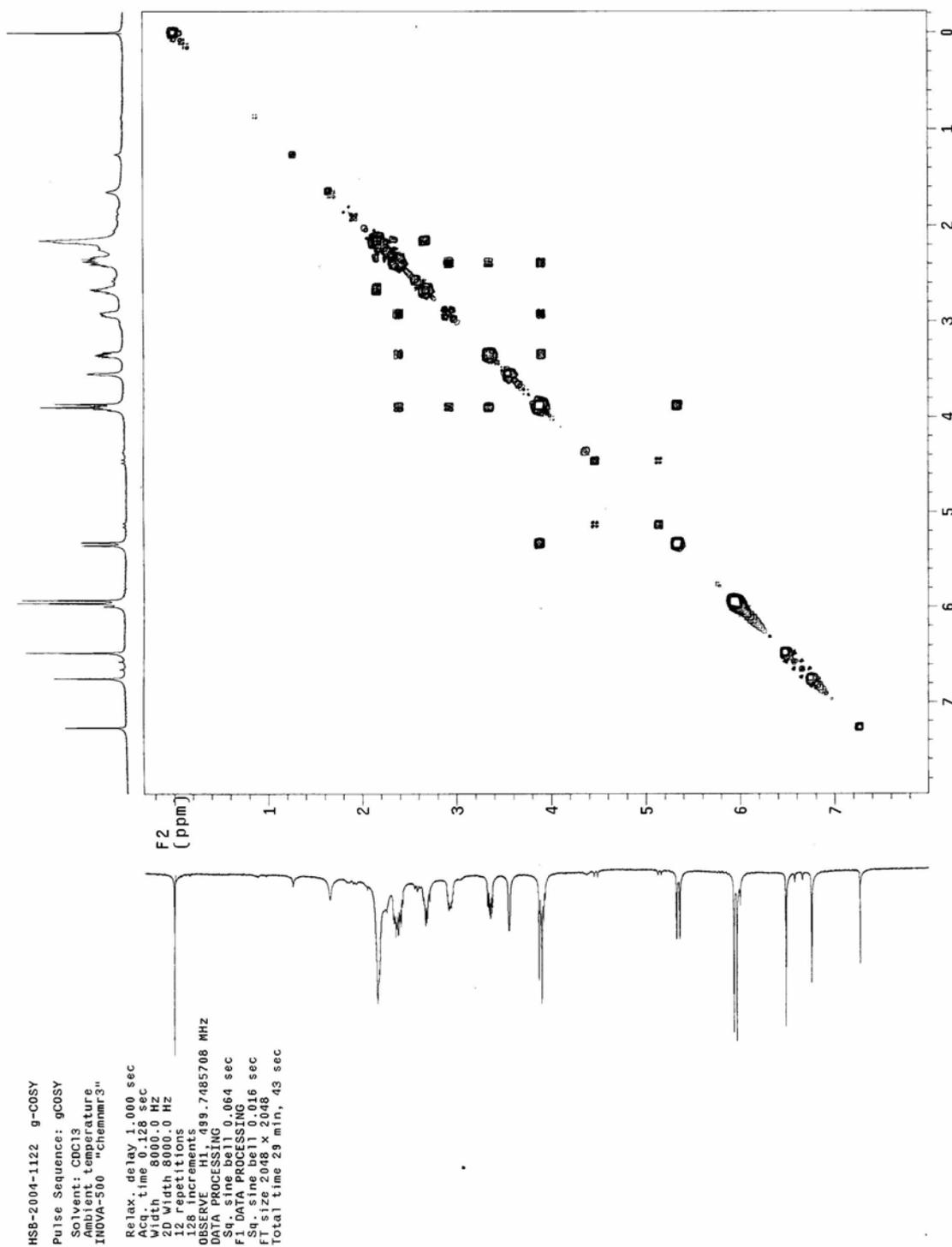
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

<sup>13</sup>C-NMR of 14,15-dideoxycripowellin (**9**)



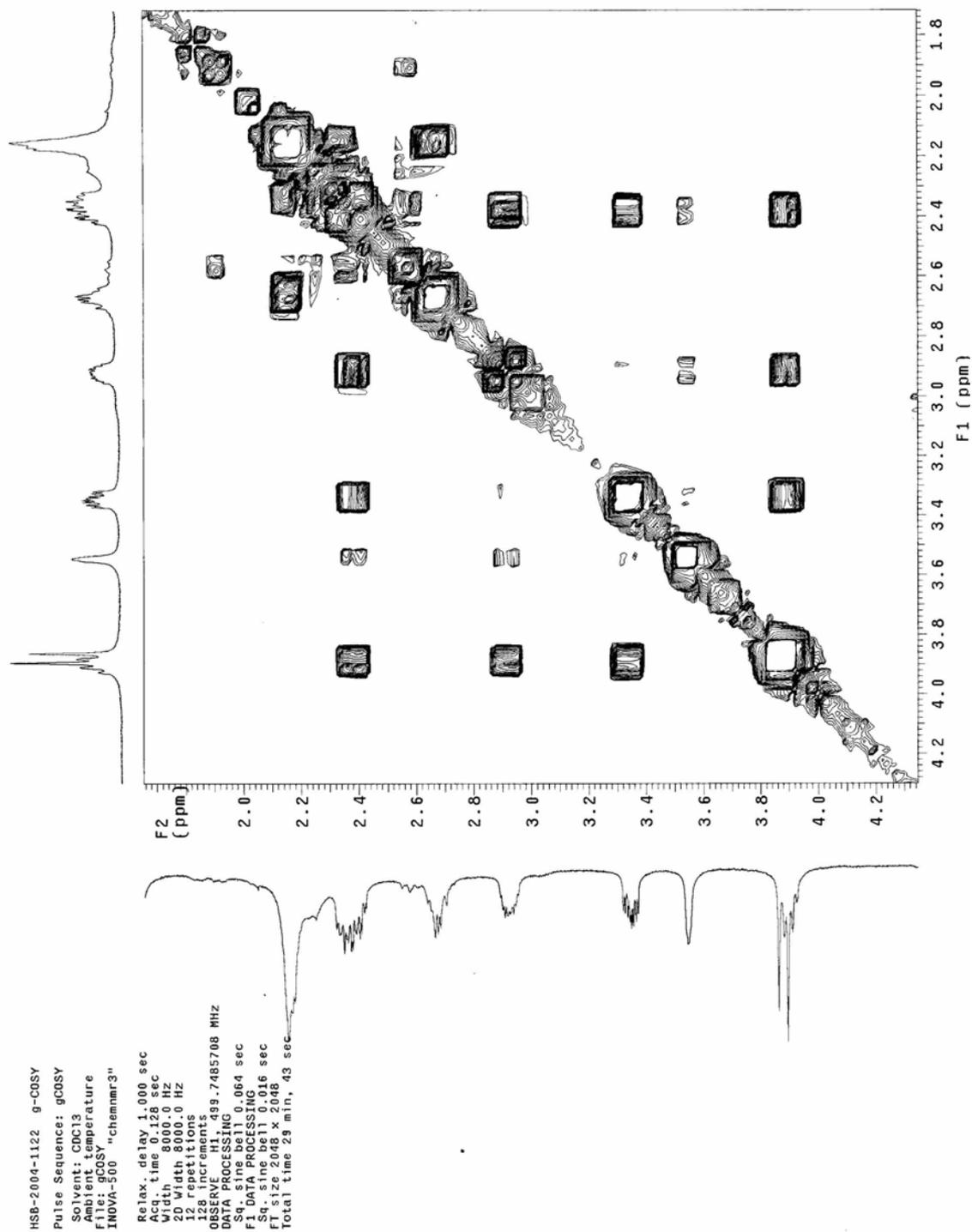
**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

## 2D-COSY NMR of 14,15-dideoxycripowellin (9)



**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

### 2D-COSY NMR of 14,15-dideoxycripowellin (9) (expansion)



**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

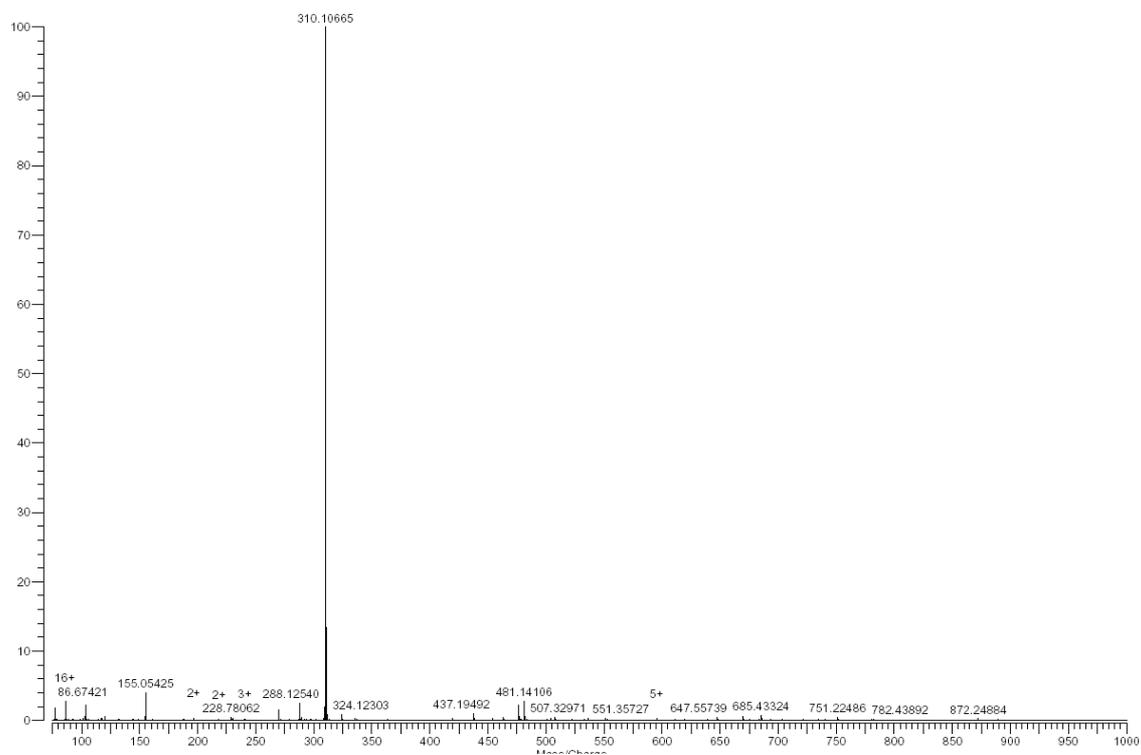
## HRMS of 14,15-dideoxycripowellin (9)

IonSpec HiResESI

File: Moon\_02\_ESI1trans Sample Tracking No. SUHBO  
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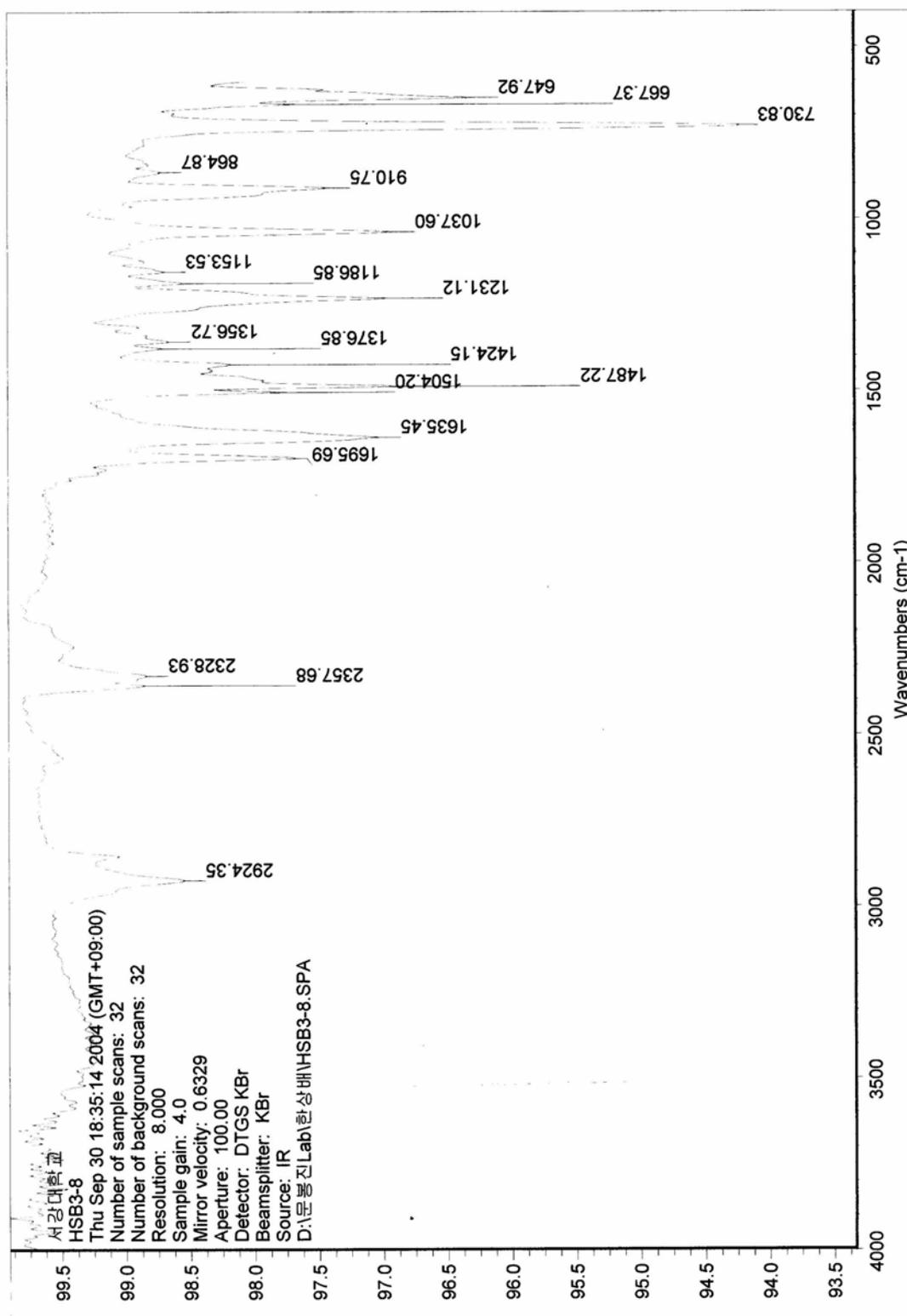
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**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

IR spectrum of 14,15-dideoxycripowellin (9)



**Supporting Information:** Synthesis of Macrocyclic Lactam via Novel Ring Expansion Reaction; Construction of the Cripowellin Skeleton; Moon, Han, Yoon, and Kwon, December 3, 2004.

## 2D-HMBC NMR of 14,15-dideoxycripowellin (**9**)

