

**Organic Letters**

SUPPORTING INFORMATION

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**“A Five-Step Synthesis of (*S*)-Macrostomine from (*S*)-Nicotine”**

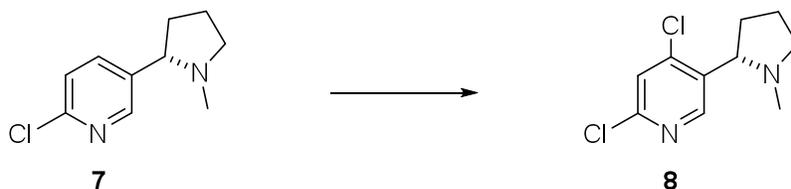
- I. General Information
- II. Experimental procedures for **1, 8, 10, 11, 12**.
- III. Characterization data,  $^1\text{H}$  and  $^{13}\text{C}$  NMR for **1, 10, 11**.
- IV. Comparison data for (*S*)-Macrostomine

Total pages of supporting information: (17).

## I. General Information.

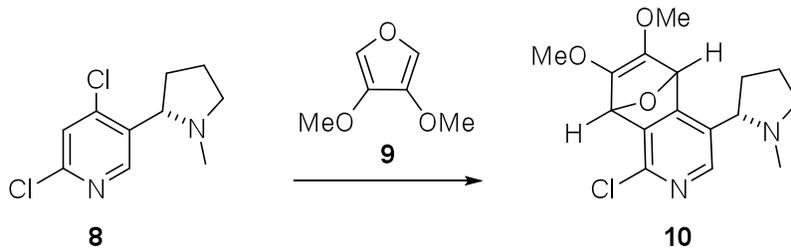
All reactions were performed in oven and flame-dried glassware under argon atmosphere and stirred magnetically. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use. *n*-Butyllithium was titrated against diphenylacetic acid according to the procedure of Kofron and Baclawski.<sup>1</sup> Other reagents and solvents from commercial sources were stored under argon and used directly. Radial preparative layer chromatography (Radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. NMR spectra were obtained using a (300 MHz) or (400 MHz) spectrometer. Chemical shifts are in  $\delta$  units (ppm) with TMS (0.0 ppm) used as an internal standard for <sup>1</sup>H NMR spectra and the CDCl<sub>3</sub> absorption of 77.23 for <sup>13</sup>C NMR.

## II. Experimental Procedures.



### (S)-4,6-Dichloronicotine (**8**).<sup>2</sup> Improved procedure.

Neat (*S*)-6-chloronicotine (**7**) (714 mg, 3.63 mmol) was added dropwise to a solution of *n*-BuLi 1.7 mL, 2.19 M in hexanes, 3.63 mmol) in THF (5 mL) at -78 °C. After 1 h, a solution of C<sub>2</sub>Cl<sub>6</sub> (946 mg, 3.99 mmol, 1.1 equiv) in THF (2 mL) over 4Å molecular sieves was added to the mixture at -78 °C. After 10 min at -78 °C, the reaction was quenched with 20 mL of saturated aqueous NaHCO<sub>3</sub>, and the mixture was allowed to warm to rt. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 15 mL). The combined organic layers were dried over K<sub>2</sub>CO<sub>3</sub>, filtered through Celite, and concentrated under reduced pressure to afford the crude product. Purification by radial PLC (SiO<sub>2</sub>, 1% TEA/1% EtOAc/hexanes) afforded 773 mg (92%) of **8** as a colorless oil.  $[\alpha]_D^{27}$  -182 (*c* 0.55, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.55 (s, 1H), 7.30 (s, 1H), 3.54 (t, *J* = 7.6 Hz, 1H), 3.23 (dt, *J* = 1.6, 8.4 Hz, 1H), 2.42-2.30 (m, 2H), 2.22 (s, 3H), 1.94-1.76 (m, 2H), 1.58-1.47 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 150.0, 149.9, 145.3, 136.5, 124.2, 65.1, 57.0, 40.9, 33.7, 23.0; IR (neat) 2955, 2778, 1556, 1450, 1357, 1215, 1108, 876 cm<sup>-1</sup>.



**(S)-1-Chloro-5,8-dihydro-6,7-dimethoxy-5,8-epoxy-4-(1-methylpyrrolidin-2-yl)isoquinoline (10).**

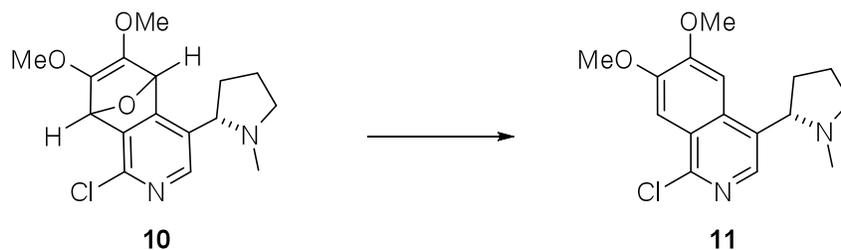
Freshly distilled (*S*)-4,6-dichloronicotine (**8**) (233 mg, 1.01 mmol) was dissolved in 1 mL of dry THF (over 4Å sieves) and stirred at rt. After 1 h, the solution was transferred by syringe to a flame dried flask, cooled to -78 °C, and *n*-BuLi (520 μL, 2.33 M in hexanes, 1.21 mmol, 1.2 equiv) was added dropwise. After stirring the mixture at -78 °C for 3 h, 3,4-dimethoxyfuran (1.08 g, 8.47 mmol, 8.4 equiv) was added dropwise, and the mixture was allowed to warm to rt. The reaction was stirred at rt for 15 h and then quenched with 2 mL of saturated aqueous NaHCO<sub>3</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x15 mL). The combined organic layers were dried over K<sub>2</sub>CO<sub>3</sub>, filtered through Celite, and concentrated under reduced pressure to afford the crude product. Purification by radial PLC (SiO<sub>2</sub>, 1% TEA/20% EtOAc/hexanes) afforded 178 mg (55%) of **10** (1:1 mixture of diastereomers) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.04 (s, 1H), 8.02 (s, 1H), 5.93 (s, 1H), 5.81 (s, 1H), 5.51 (s, 1H), 5.48 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.11-3.26 (m, 4H), 2.18-2.34 (m, 4H), 2.17 (s, 3H), 2.12 (s, 3H), 1.7-2.02 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 22.7, 23.1, 35.3, 35.4, 40.5, 40.7, 57.0, 57.1, 58.8, 59.1 (2C overlap), 59.3, 67.3, 67.6, 79.9 (2C overlap), 80.1, 80.8, 131.7, 132.0, 140.2, 140.3, 143.7, 143.8, 144.7, 144.9, 145.8, 146.0, 148.6, 148.9, 161.0, 161.1; IR (neat) 3052, 2944, 2846, 2782, 2304, 1685, 1585, 1457, 1423, 1321, 1265 cm<sup>-1</sup>; HRMS calcd for C<sub>16</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>3</sub>

(M+H)<sup>+</sup>

323.1157,

found

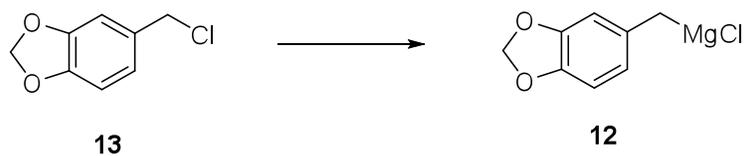
323.1156.



**(S)-1-Chloro-6,7-dimethoxy-4-(1-methylpyrrolidin-2-yl)isoquinoline (11).**

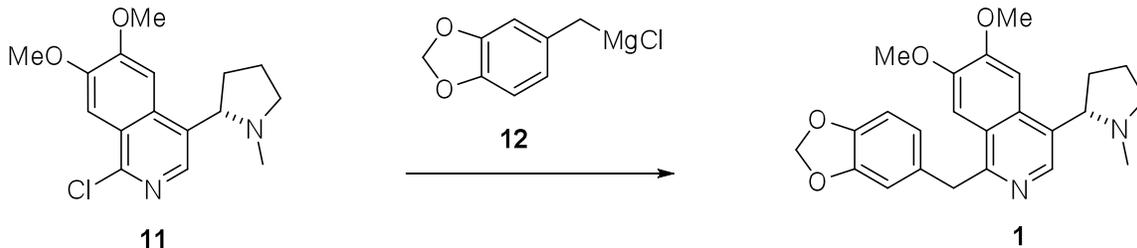
Magnesium powder (89 mg, 3.66 mmol, 10.0 equiv) was dried at 120 °C on a sand bath for 2 h while stirring under vacuum. After 2 h, the metal was allowed to cool to rt and 3 mL of THF was added under an argon atmosphere. The mixture was cooled to -78 °C and neat TiCl<sub>4</sub> (0.20 mL, 1.83 mmol, 5.0 equiv) was added dropwise. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After stirring for 20 h, a fine black suspension was obtained. The mixture was cooled to -78 °C and treated with a solution of **10** (118 mg, 0.366 mmol, 1.0 equiv) in dry THF (2 mL). After 30 min at -78 °C, the mixture was allowed to warm to rt. The mixture was stirred for 21 h at rt, then quenched by pouring it into an ice cold aqueous solution of saturated K<sub>2</sub>CO<sub>3</sub> (15 mL). After stirring for 30 min at rt, the mixture was extracted with Et<sub>2</sub>O (2 x 15 mL) and CH<sub>2</sub>Cl<sub>2</sub> (1 x 15 mL). The combined organic layers were dried over anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered through Celite, and concentrated under reduced pressure to obtain the crude product. Purification by radial PLC (SiO<sub>2</sub>, 1% TEA/20% EtOAc/hexanes) afforded 78 mg (70%) of **11** as a pale yellow oil.  $[\alpha]_D^{27}$  -128 (*c* 0.67, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.21 (s, 1H), 7.78 (s, 1H), 7.56 (s, 1H), 4.06 (s, 3H), 4.03 (s, 3H), 3.54 (t, *J* = 8.0 Hz, 1H), 3.30 (t, *J* = 8.0 Hz, 1H), 2.29-2.42 (m, 2H), 2.24 (s, 3H), 1.85-2.08 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 23.3, 33.5, 40.9, 56.3 (2C overlap), 57.4, 67.7, 103.1, 105.1, 122.7, 131.0, 133.2, 139.8, 148.8,

150.7, 152.8; IR (neat) 2967, 2834, 2776, 1508, 1263, 1147  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{16}\text{H}_{19}\text{ClN}_2\text{O}_2$  (M+H)<sup>+</sup> 307.1208, found 307.1208.



**(Benzo[d][1,3]dioxol-5-ylmethyl)magnesium chloride (12).**

A suspension of magnesium powder (3.6 g, 146.5 mmol) in THF (5 mL) was treated dropwise with 1,2-dibromoethane (381  $\mu$ L, 4.397 mmol) at rt under an argon atmosphere. After 1 h, the solvent was removed with a syringe, and the residue in the reaction flask was washed with 5 mL of THF (2x), and then fresh THF (5 mL) was added. The mixture was treated with a solution of piperonyl chloride<sup>3</sup> (**13**) (5 g of the crude material, 29.31 mmol) in THF (5 mL) at rt, added dropwise over a period of 4 h with stirring. The brownish suspension obtained contained the Grignard reagent **12** and was left standing overnight to allow the excess magnesium to settle. The solution of reagent **12** was kept under argon at rt and was titrated prior to use employing a literature procedure.<sup>4</sup>

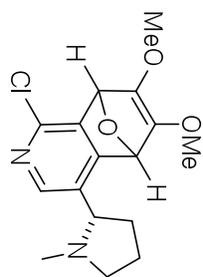


### (S)-Macrostomine (**1**).

A solution of **11** (20 mg, 0.0652 mmol, 1.0 equiv) and Ni(acac)<sub>2</sub> (6.8 mg, 0.0261, 40 mol %) in dry THF (2 mL) at rt was treated dropwise with piperonylmagnesium chloride (**12**) (450  $\mu$ L, 0.44 M in THF, 3.0 equiv). The mixture was stirred at rt for 4 days and then quenched with 2 mL of saturated aqueous NaHCO<sub>3</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 15 mL). The combined organic layers were dried over K<sub>2</sub>CO<sub>3</sub>, filtered through Celite, and concentrated under reduced pressure to afford the crude product. Purification by radial PLC (SiO<sub>2</sub>, 1% TEA/30% EtOAc/hexanes) afforded 16.7 mg (63%) of amorphous **1**.  $[\alpha]_D^{26}$  -54 (*c* 0.72, CHCl<sub>3</sub>); lit.<sup>5</sup>  $[\alpha]_D^{25}$  -51  $\pm$  3 (*c* 0.892, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  8.80 (s, 1H), 7.88 (s, 1H), 7.32 (s, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.22 (s, 2H), 4.56 (s, 2H), 3.51 (s, 3H), 3.43 (s, 3H), 3.38 (t, *J* = 8.0 Hz, 1H), 3.08 (t, *J* = 8.0 Hz, 1H), 2.13 (s, 3H), 2.01-2.10 (m, 2H), 1.75-1.98 (m, 2H), 1.53-1.63 (m, 1H). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.40 (s, 1H), 7.79 (s, 1H), 7.32 (s, 1H), 6.68-6.80 (m, 3H), 5.86 (s, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 3.89 (s, 3H), 3.54 (t, *J* = 8.0 Hz, 1H), 3.31 (t, *J* = 8.0 Hz, 1H), 2.28-2.42 (m, 2H), 2.25 (s, 3H), 1.86-2.11 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  23.3, 33.4, 41.0, 42.6, 56.0, 56.1, 57.5, 68.3, 101.0, 103.2, 104.9, 108.3, 109.2, 121.6, 123.1, 129.6, 132.0, 133.9, 140.3, 146.1, 148.0, 149.4, 151.7, 157.0; IR (neat) 3376, 2938, 2834, 2775, 1619, 1562, 1511, 1486, 1419, 1245, 1205, 1176, 1039 cm<sup>-1</sup>; HRMS calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> (M+H)<sup>+</sup> 407.1965, found 407.1974.

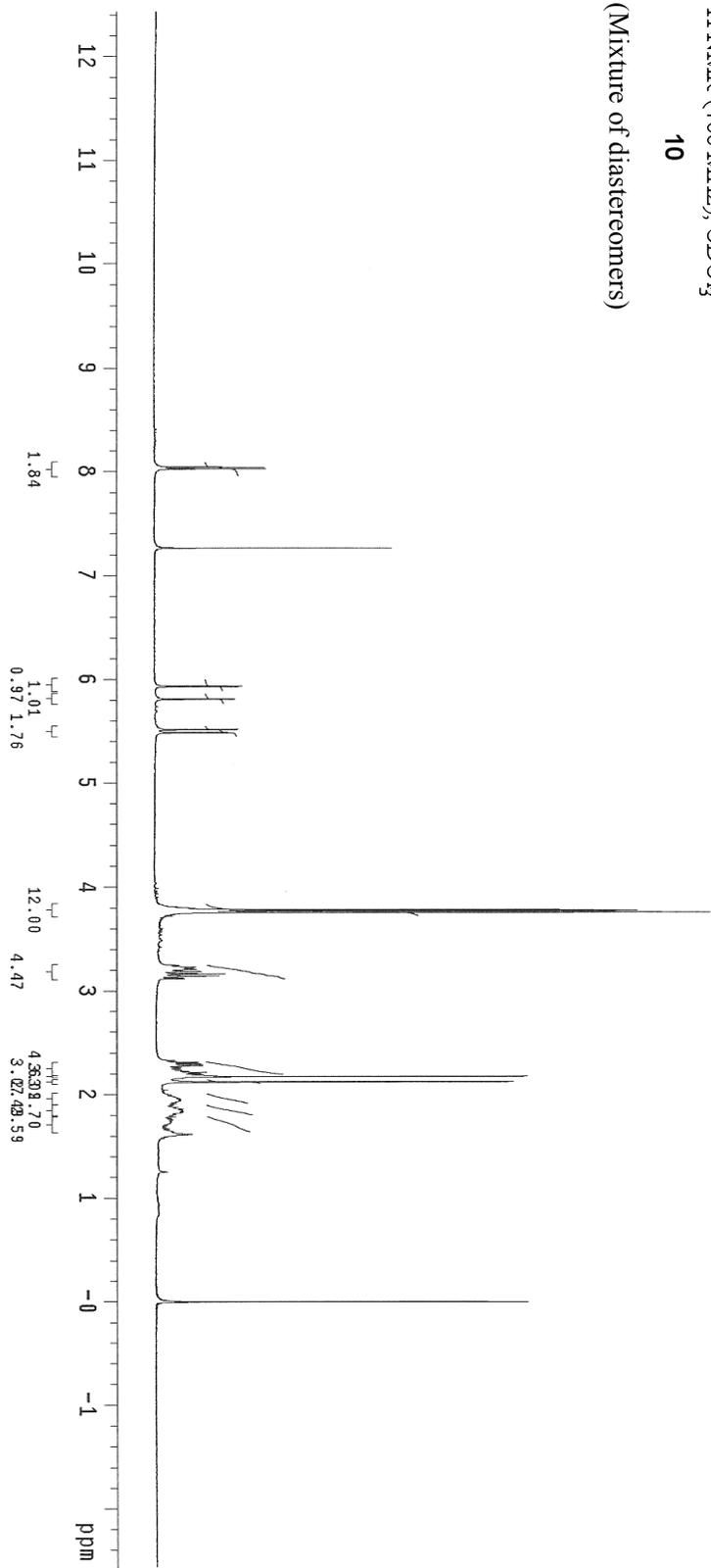


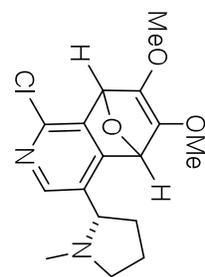
### III. Characterization data



$^1\text{H NMR}$  (400 MHz),  $\text{CDCl}_3$   
**10**

(Mixture of diastereomers)

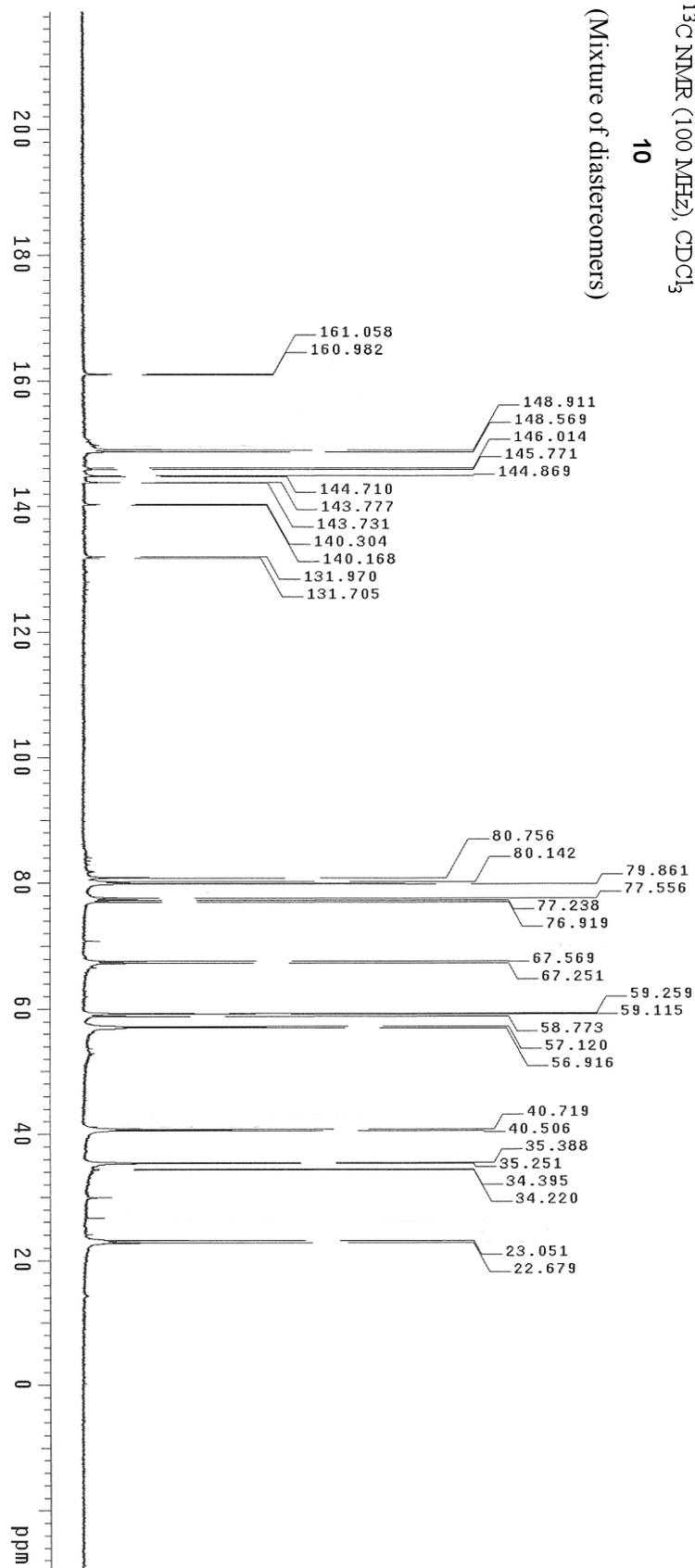


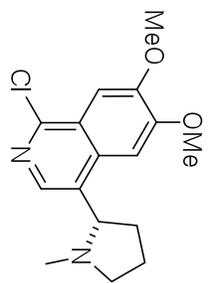


**10**

$^{13}\text{C}$  NMR (100 MHz),  $\text{CDCl}_3$

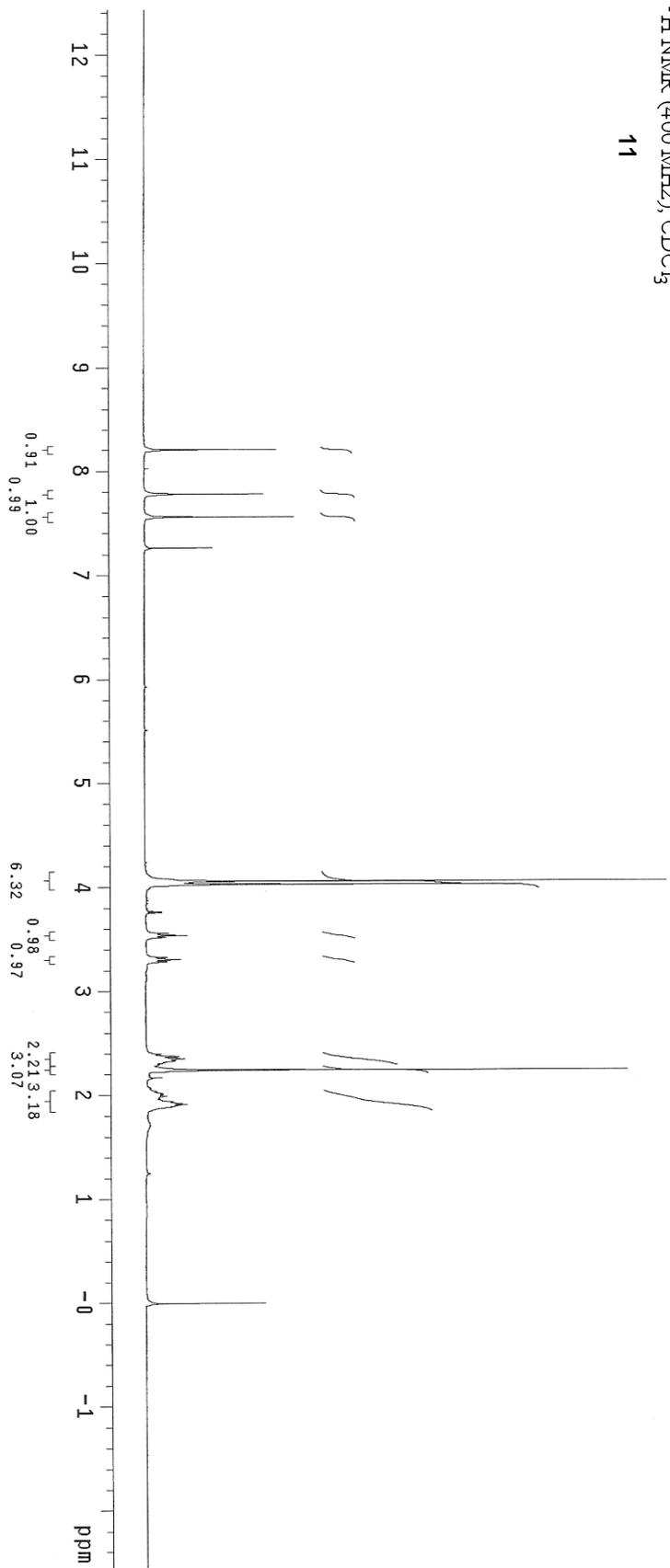
(Mixture of diastereomers)

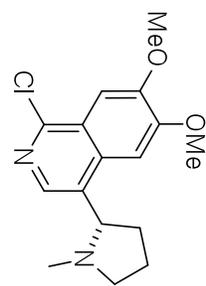




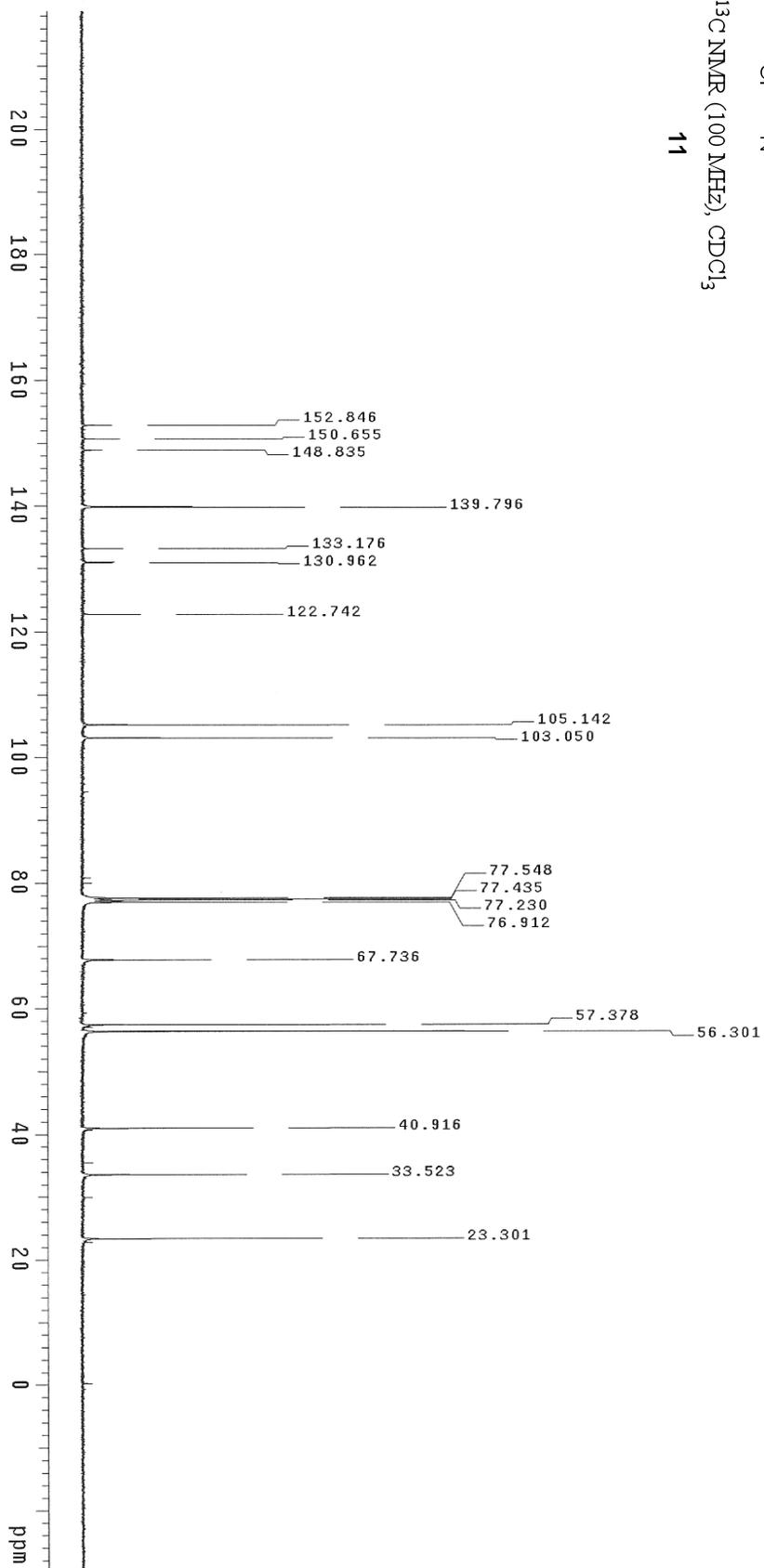
$^1\text{H NMR}$  (400 MHz),  $\text{CDCl}_3$

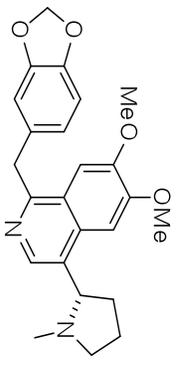
11



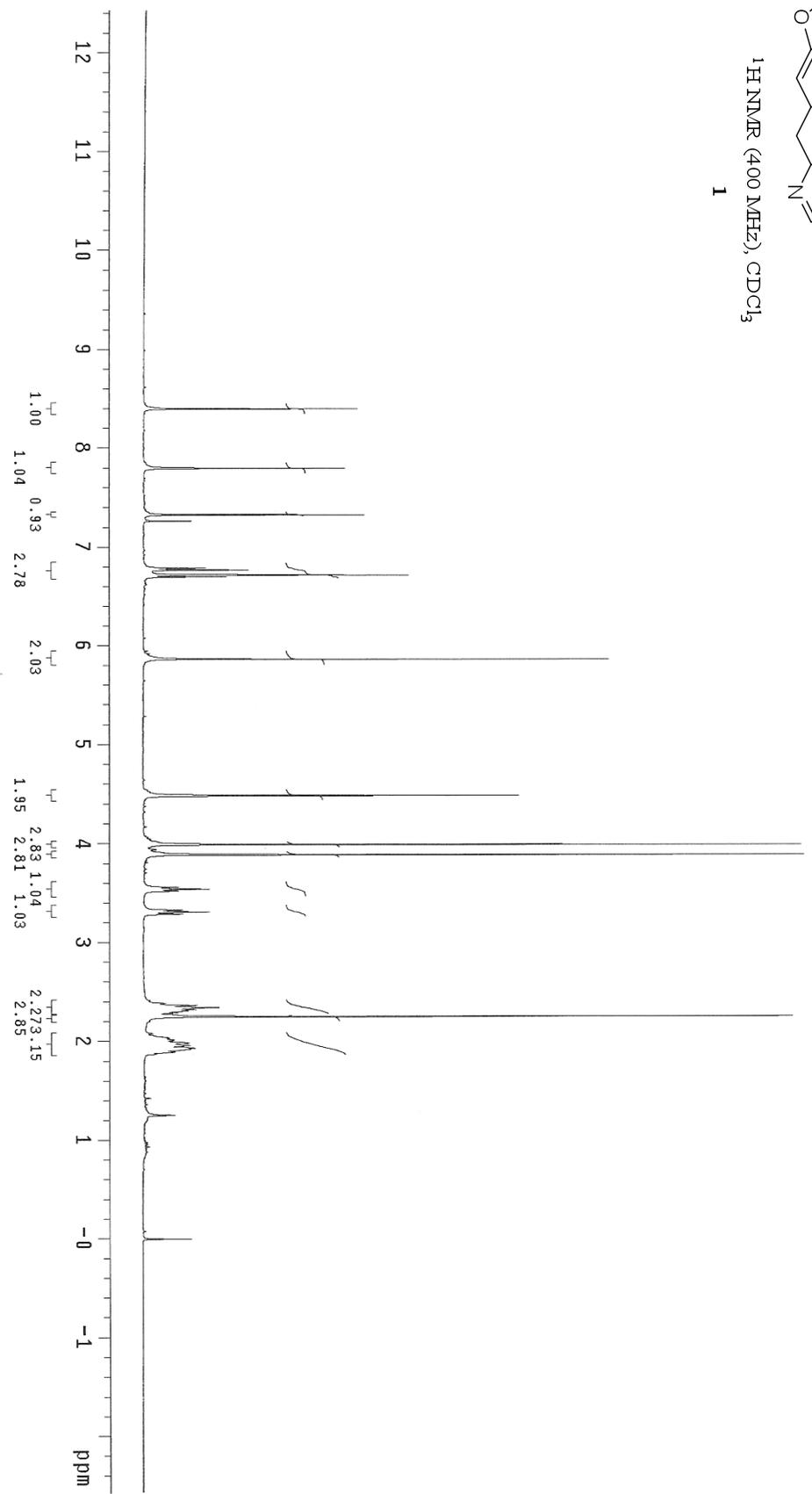


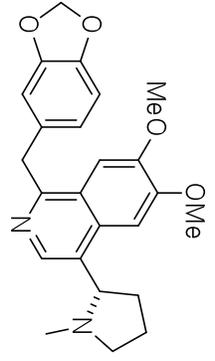
$^{13}\text{C}$  NMR (100 MHz),  $\text{CDCl}_3$   
11



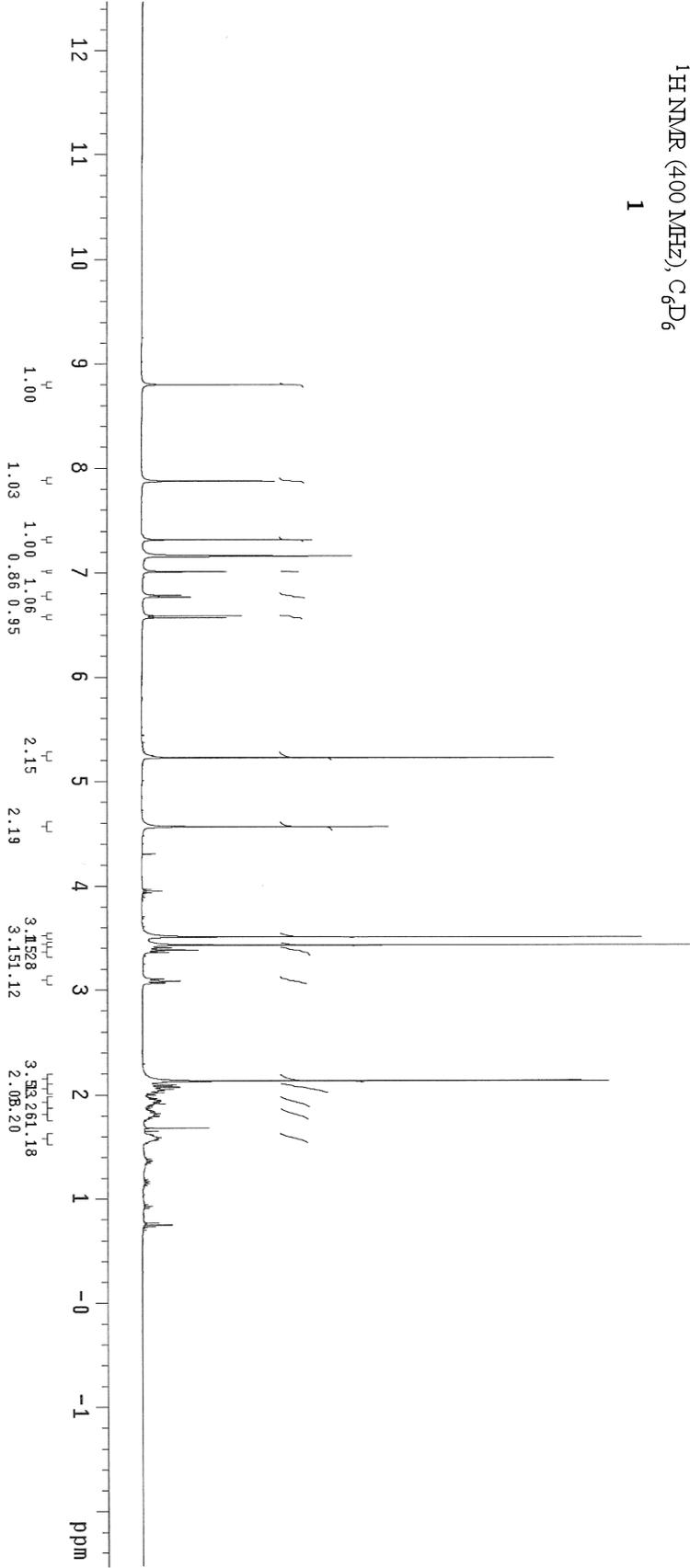


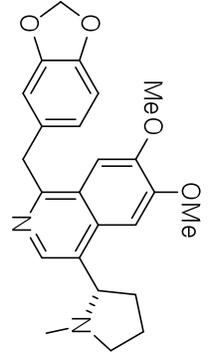
<sup>1</sup>H NMR (400 MHz), CDCl<sub>3</sub>  
**1**





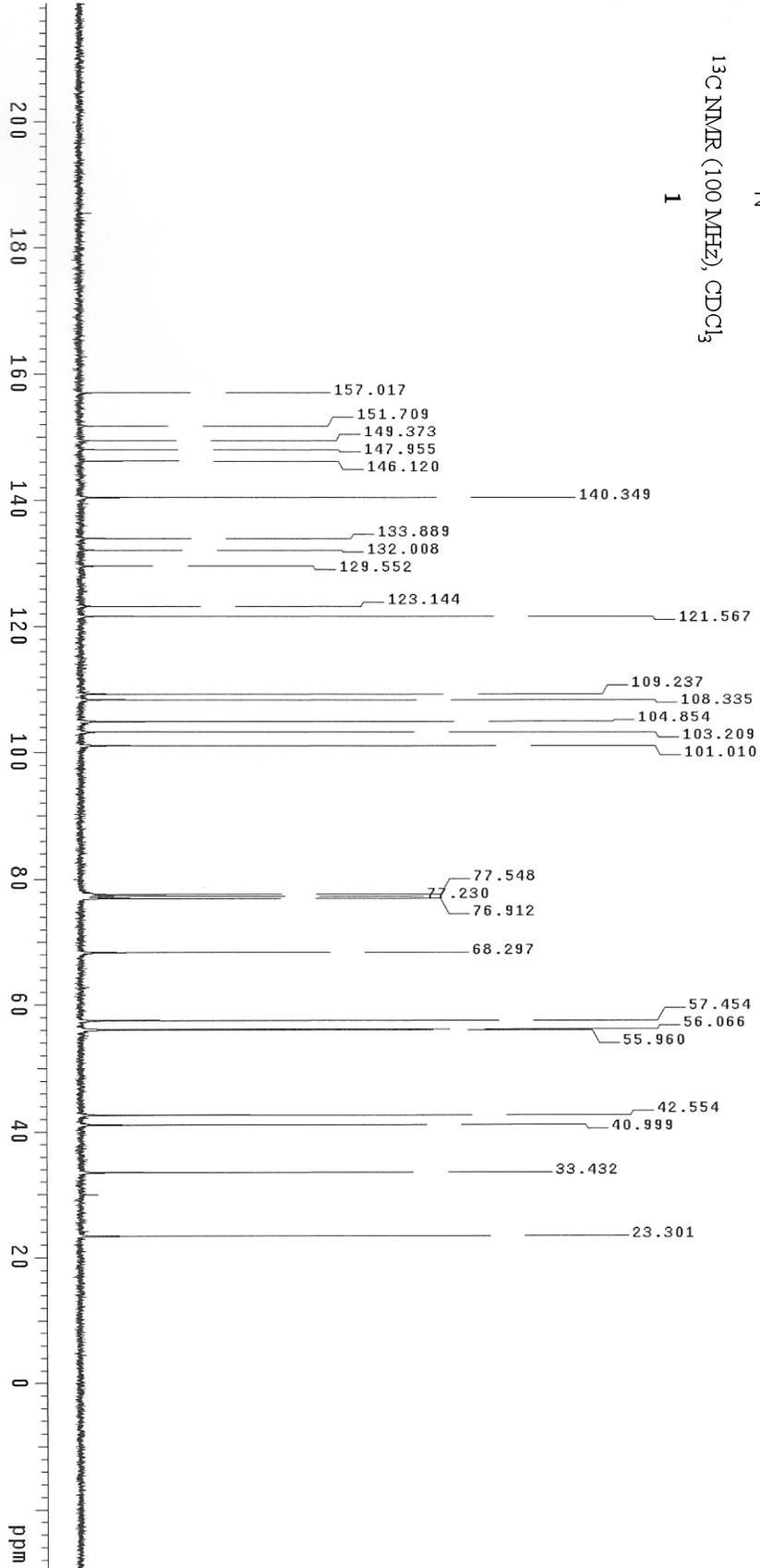
$^1\text{H NMR}$  (400 MHz),  $\text{C}_6\text{D}_6$   
**1**





$^{13}\text{C}$  NMR (100 MHz),  $\text{CDCl}_3$

**1**



**IV. Comparison Data for (S)-Macrostomine.**

<b>Literature:</b>	<b>Our Synthetic (S)-Macrostomine:</b>
<b><sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 60 MHz)<sup>5</sup></b>	<b><sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz)</b>
8.72 (1H, s)	8.80 (1H, s)
7.87 (1H, s)	7.88 (1H, s)
7.35 (1H, s)	7.32 (1H, s)
6.97 (1H, d, <i>J</i> = 1.0 Hz)	7.01 (1H, d, <i>J</i> = 2.0 Hz)
6.80 (1H, q, <i>J</i> = 8.0, 1.0 Hz)	6.78 (1H, dd, <i>J</i> = 8.0, 1.2 Hz)
6.55 (1H, d, <i>J</i> = 8.0 Hz)	6.58 (1H, d, <i>J</i> = 8.0 Hz)
5.30 (2H, s)	5.22 (2H, s)
4.55 (2H, s)	4.56 (2H, s)
3.55 (3H, s)	3.51 (3H, s)
3.47 (3H, s)	3.43 (3H, s)
3.0-3.6 (3H, m)	3.38 (1H, t, <i>J</i> = 8.0 Hz)
	3.08 (1H, t, <i>J</i> = 8.0 Hz)
2.13 (3H, s)	2.13 (3H, s)
1.5-2.2 (4H, m)	2.01-2.10 (2H, m)
	1.75-1.98 (2H, m)
	1.53-1.63 (1H, m)

Literature:	Our Synthetic ( <i>S</i> )-Macrostomine:
<sup>1</sup> H NMR (CDCl <sub>3</sub> , 250 MHz) <sup>6</sup>	<sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz)
8.40 (1H, s)	8.40 (1H, s)
7.80 (1H, s)	7.79 (1H, s)
7.32 (1H, s)	7.32 (1H, s)
6.68-6.82 (3H, m)	6.68-6.80 (3H, m)
5.87 (2H, s)	5.87 (2H, s)
4.48 (2H, s)	4.48 (2H, s)
4.02 (3H, s)	3.99 (3H, s)
3.89 (3H, s)	3.89 (3H, s)
3.48-3.62 (1H, m)	3.53 (1H, t, <i>J</i> = 8.0 Hz)
3.26-3.38 (1H, m)	3.31 (1H, t, <i>J</i> = 8.0 Hz)
2.18-2.46 (2H, m)	2.28-2.42 (2H, m)
2.25 (3H, s)	2.25 (3H, s)
1.81-2.15 (3H, m)	1.86-2.11 (3H, m)
<b>Specific rotation</b> <sup>5</sup>	
[α] <sub>D</sub> <sup>25</sup> -51 ± 3 ( <i>c</i> 0.892, CHCl <sub>3</sub> )	[α] <sub>D</sub> <sup>26</sup> -54 ( <i>c</i> 0.72, CHCl <sub>3</sub> )

<sup>1</sup> Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879-1880.

<sup>2</sup> Wagner, F. F.; Comins, D. L. *Eur. J. Org. Chem.* **2006**, *16*, 3562-3565.

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<sup>3</sup> Piperonyl chloride was prepared from piperonyl alcohol according to: Porcal, W.; Merlino, A.; Boiani, M.; Gerpe, A.; Gonzalez, M.; Cerecetto, H. *Org. Process Res. Dev.* **2008**, *12*, 156-162.

<sup>4</sup> Lin, H. S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503-2506.

<sup>5</sup> Mnatsakanyan, V. A.; Preininger, V.; Simanek, V.; Klasek, A.; Dolejs, L.; Santavy, F. *Tetrahedron Lett.* **1974**, *10*, 851-852.

<sup>6</sup> Brunner, H.; Kurzinger, A.; Mahboobi, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim)*. **1988**, *321*, 73-76.