

# Supporting Information

## Asymmetric Total Synthesis of (-)-Cebulactam A1

Shouliang Yang,<sup>†</sup> Yumeng Xi,<sup>†</sup> Jiahua Chen,<sup>\*,†</sup> Zhen Yang<sup>\*,†,‡</sup>

<sup>†</sup> Key Laboratory of Bioorganic Chemistry and Molecular Engineering, Ministry of Education and Beijing National Laboratory for Molecular Science, College of Chemistry, Peking University, Beijing 100871, China

<sup>‡</sup> Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China

E-mail: jhchen@pku.edu.cn  
zyang@pku.edu.cn

Tel: +86 10 6275 9105; fax: +86 10 6275 9105

**Table of Contents:**

<b>General Information</b> -----	S3
<b>Experimental Data for SmI<sub>2</sub>-mediated Reformatsky Reactions</b> -----	S4
<b>Comparison of NMR spectra with natural products</b> -----	S7
<b>NMR Spectra</b> -----	S9

## General Information

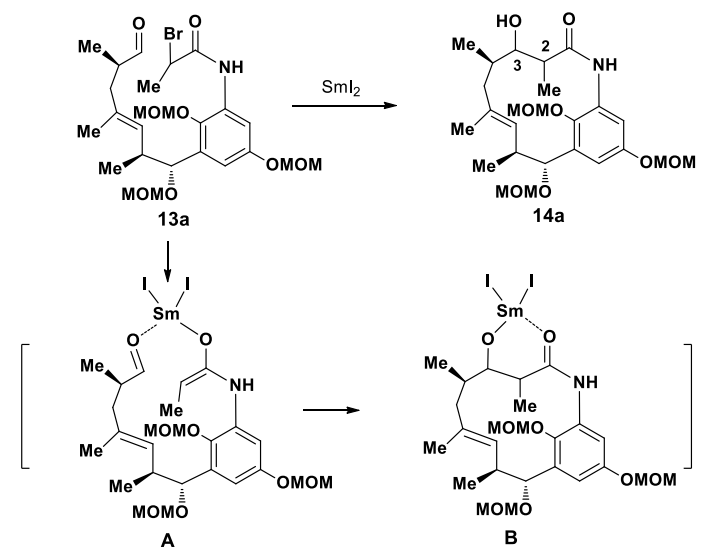
Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere using Schlenk techniques. Solvent purification was conducted according to *Purification of Laboratory Chemicals* (Peerrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Compound **6** was synthesized from L-Phenylglycinol according to literature.<sup>1</sup> Compound **7** was synthesized from 2-hydroxy-5-methoxybenzaldehyde according to literature.<sup>2</sup> All other reagents were purchased from commercial sources and used as received. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR) homogeneous materials. Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by Yantai Chemicals (China) using UV light as visualizing agent and iodine as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200-300 mesh) supplied by Tsingtao Haiyang Chemicals (China).

NMR spectra were recorded on Bruker Ascend 500, Ascend 400 instruments. TMS was used as internal standard for <sup>1</sup>H NMR (0 ppm), solvent signal was used as reference for <sup>13</sup>C NMR (CDCl<sub>3</sub> = δ 77.0 ppm, d<sub>6</sub>-DMSO = δ 39.5 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, br = broad, dd = double doublet, m = multiplet. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 330 FT-IR spectrometer. Mass spectra were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Ultra Performance Liquid Chromatograph (UPLC) was performed on a UPLC SQD (Waters Technology) equipment.

1. Nicolaou, K. C.; Guduru, R.; Sun, Y. P.; Banerji, B.; Chen, David Y.-K. *Angew. Chem. Int. Ed.* **2007**, *46*, 5896.
2. Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587.

**Investigation of SmI<sub>2</sub>-mediated Reformatsky reaction.** With **13** in hand, we proceeded to evaluate its performance in the SmI<sub>2</sub>-mediated intramolecular Reformatsky reaction. The treatment of **13** with SmI<sub>2</sub> in THF under the optimized conditions<sup>1</sup> at a concentration of 0.005M under refluxing conditions gave the desired product **14** in 84% yield as a couple of diastereoisomers. Then detailed investigation of the key reaction was conducted with **13a**, the key intermediate in our previous synthesis<sup>1</sup>, in hoping that we could further get insight into this key reaction. Treatment of **13a** under the typical condition gave the desired product **14a** as a mixture of two pairs of diastereoisomers at the C2 and C3 carbon centers in a ratio of 3.9:1:4.0:3.3 based on UPLC analysis (see SI). We then investigated the concentration effect<sup>2</sup> on the outcome of the annulation by carrying out the reaction at a substrate concentration of 0.017 M. At this concentration, compound **14a** was obtained in 82% yield, indicating that the reductive annulation reaction was independent of the substrate concentration.

A variety of different solvents were tested to evaluate their effect on the outcome of the reductive annulation. The use of benzene<sup>2</sup> as a solvent gave the desired product **14** in approximately 50% yield, whereas the use of protic solvents<sup>3</sup> such as MeOH and *n*-BuOH, did not give any of the desired product. Based on these results, it was proposed that the reaction was proceeding via a samarium enolate intermediate<sup>4</sup> which would effectively mediate the ring contraction<sup>5</sup> reaction to afford the annulated products (Table 1).



entry	reaction conditions	concentration	yield <sup>a</sup>	ratio of the products <sup>b</sup>
1	THF, reflux, 2 h	0.017 M	82%	4.6 : 1 : 4.0 : 3.3
2	THF, reflux, 2 h	0.005 M	84%	3.9 : 1 : 4.0 : 3.3
3	PhH, reflux, 2 h	0.005 M	ca.50%	3.4 : 1 : 13.4 : 8.6
4	MeOH, reflux, 2 h	0.005 M	no desired product	
5	<i>n</i> BuOH, reflux, 2 h	0.005 M	no desired product	

<sup>a</sup>isolated yield; <sup>b</sup>ratio of the diastereoisomers was determined by UPLC.

**Table 1.** SmI<sub>2</sub>-mediated Reformatsky reaction

## Experimental Data for SmI<sub>2</sub>-mediated Reformatsky Reaction

**Entry 1:** To a solution of SmI<sub>2</sub> (1.8 mL, 0.1 M in THF, 0.18 mmol) was added **13a** (17.4 mg, 0.031 mmol) in dry THF (0.2 mL), and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH<sub>4</sub>Cl (3 mL) at room temperature, and the mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (10 mL), and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:1) to give product **14a** (12.2 mg, 82%) as a mixture of four diastereoisomers. R<sub>f</sub> = 0.28, 0.30, 0.50, 0.60 (hexane/ethyl acetate = 1:2). The ratio of four diastereoisomers was determined by UPLC: 4.6/1.0/4.0/3.3.

**Entry 2** To a solution of SmI<sub>2</sub> (60 mL, 0.1 M in THF, 6.0 mmol) in anhydrous THF (130 mL) was slowly added **13a** (0.55 g, 0.98 mmol) in (5 mL) under refluxing conditions in a dropwise manner, the reaction mixture was then stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH<sub>4</sub>Cl (50 mL) at room temperature, and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:2) to give product **14a** (0.397 g, 84%) as a mixture of diastereoisomers. R<sub>f</sub> = 0.28, 0.30, 0.50, 0.60 (hexane/ethyl acetate = 1:2). The ratio of four diastereoisomers was determined by UPLC: 3.9/1.0/4.0/3.3.

**Entry 3:** Benzene (3 mL) was degassed by bubbling N<sub>2</sub> for 0.5 h, followed by addition of a solution of SmI<sub>2</sub> (0.9 mL, 0.1 M in THF, 0.09 mmol). To this solution was a solution of **13a** (8.7 mg, 0.0155 mmol) in dry benzene (0.2 mL) at refluxing conditions in a dropwise manner, and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (3 mL) at room temperature, and the resultant mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (10 mL), and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:1) to give product **14a** (4.0 mg, 53%) as a mixture of four diastereoisomers. R<sub>f</sub> = 0.28, 0.30, 0.50, 0.60 (hexane/ethyl acetate = 1:2). The ratio of four diastereoisomers was determined by UPLC: 3.4/1.0/13.4/8.6.

**Entry 4:** MeOH (3 mL) was degassed with N<sub>2</sub> for 0.5 h, followed by addition of a solution of SmI<sub>2</sub> (1 mL, 0.1 M in THF, 0.10 mmol). To this solution was added a solution of **13a** (10 mg, 0.018 mmol) in dry MeOH (0.2 mL) under refluxing conditions in a dropwise manner, and the reaction mixture was then stirred at the same temperature for 2 h. The reaction was quenched by addition of a

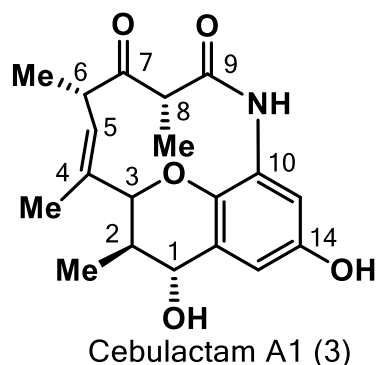
saturated solution of NH<sub>4</sub>Cl (3 mL), and the resultant mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (10 mL), and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuum, and no desired product was detected on UPLC.

**Entry 5:** *n*BuOH (3.2 mL) was degassed with N<sub>2</sub> for 0.5 h, followed by addition of a solution of SmI<sub>2</sub> (1 mL, 0.1 M in THF, 0.10 mmol). To this solution was added a solution of **13a** (9 mg, 0.016 mmol) in dry *n*BuOH (0.2 mL) under refluxing conditions in a dropwise manner, and reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated solution of NH<sub>4</sub>Cl (3 mL), and the resultant mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (10 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuum, and no desired product was detected on UPLC.

### Reference:

- 1: Yang, S.-L.; Xi, Y.-M.; Zhu, R.; Wang, L.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2013**, *15*, 812.
- 2: Tamiya, H.; Goto, K.; Matsuda, F. *Org. Lett.* **2004**, *6*, 545.
- 3: Kunishima, M.; Tanaka, S.; Kono, K.; Hioki, K.; Tani, S. *Tetrahedron Lett.* **1995**, *36*, 3707.
- 4: (a) Chopade, P. R.; Prasad, E.; Flowers, II, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 44; (b) Kleiner, G.; Tarnopolsky, A.; Hoz, S. *Org. Lett.* **2005**, *7*, 4197.
- 5: Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556.
- 6: Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371.

## Comparison of NMR spectra with natural products (NMR spectroscopic data of Cebulactam A1 in acetone-d<sub>6</sub>)



Note: the numbering was according to the original isolation paper.

### <sup>1</sup>H NMR Comparison:

Position	$\delta_{\text{H}}$ of Cebulactam A1 (Synthesized, 400 MHz, $\delta$ in ppm, $J$ in Hz,)	$\delta_{\text{H}}$ of Cebulactam A1 (Natural, 400 MHz, $\delta$ in ppm, $J$ in Hz)
1	4.38 (d, $J = 10.1$ )	4.38 (dd, $J = 10.0, 6.4$ ) <sup>a</sup>
2	1.82 (m)	1.82 m
Me-2	1.19 (d, $J = 6.6$ )	1.20 (d, $J = 6.4$ )
3	4.27 (d, $J = 8.5$ )	4.27 (d, $J = 8.5$ )
Me-4	1.86 (s)	1.87 (d, $J = 1.6$ )
5	4.98 (d, $J = 9.8$ )	5.00 (dd, $J = 10.0, 1.0$ )
6	3.19 (m)	3.19 m
Me-6	1.00 (d, $J = 6.3$ )	1.01 (d, $J = 6.8$ )
8	3.43 (q, $J = 6.8$ )	3.42 (q, $J = 6.8$ )
Me-8	1.21 (d, $J = 6.8$ )	1.22 (d, $J = 6.8$ )
13	7.02 (d, $J = 2.8$ )	7.02 (d, $J = 2.8$ )
15	6.65 (d, $J = 2.8$ )	6.65 (d, $J = 2.8$ )
NH	7.88 (br)	7.91 br

Ref. a: Addition of a drop of D<sub>2</sub>O could change dd peak into d (10.5)

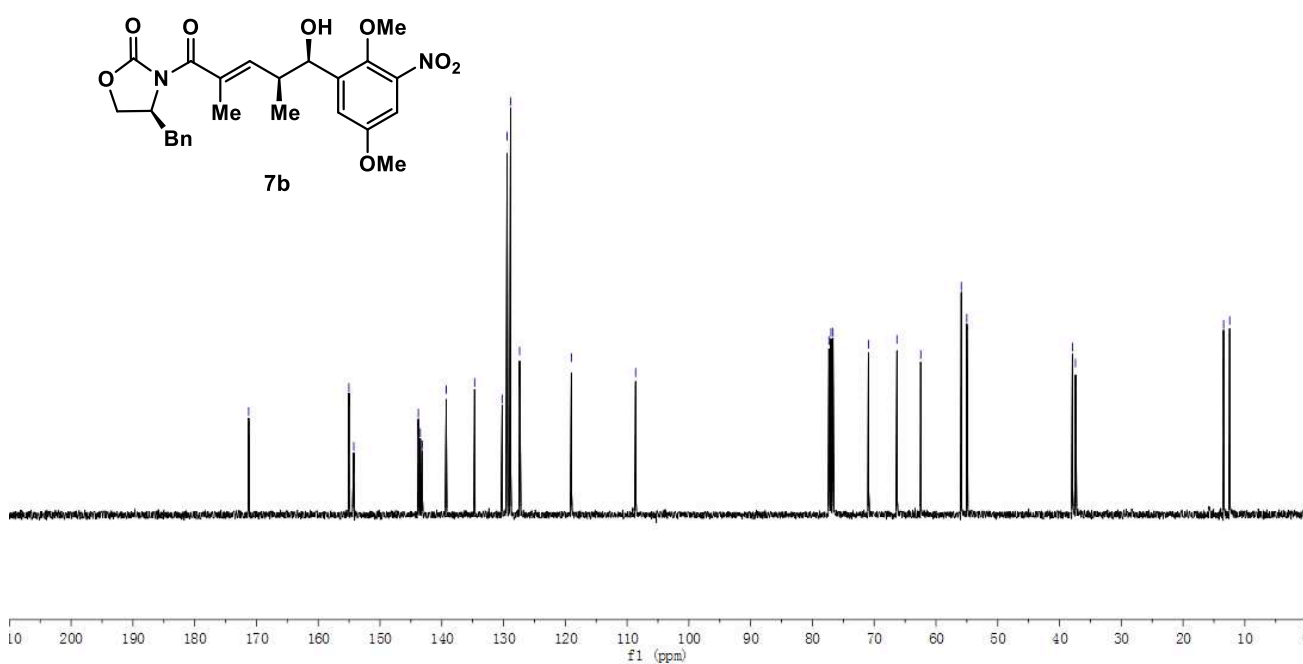
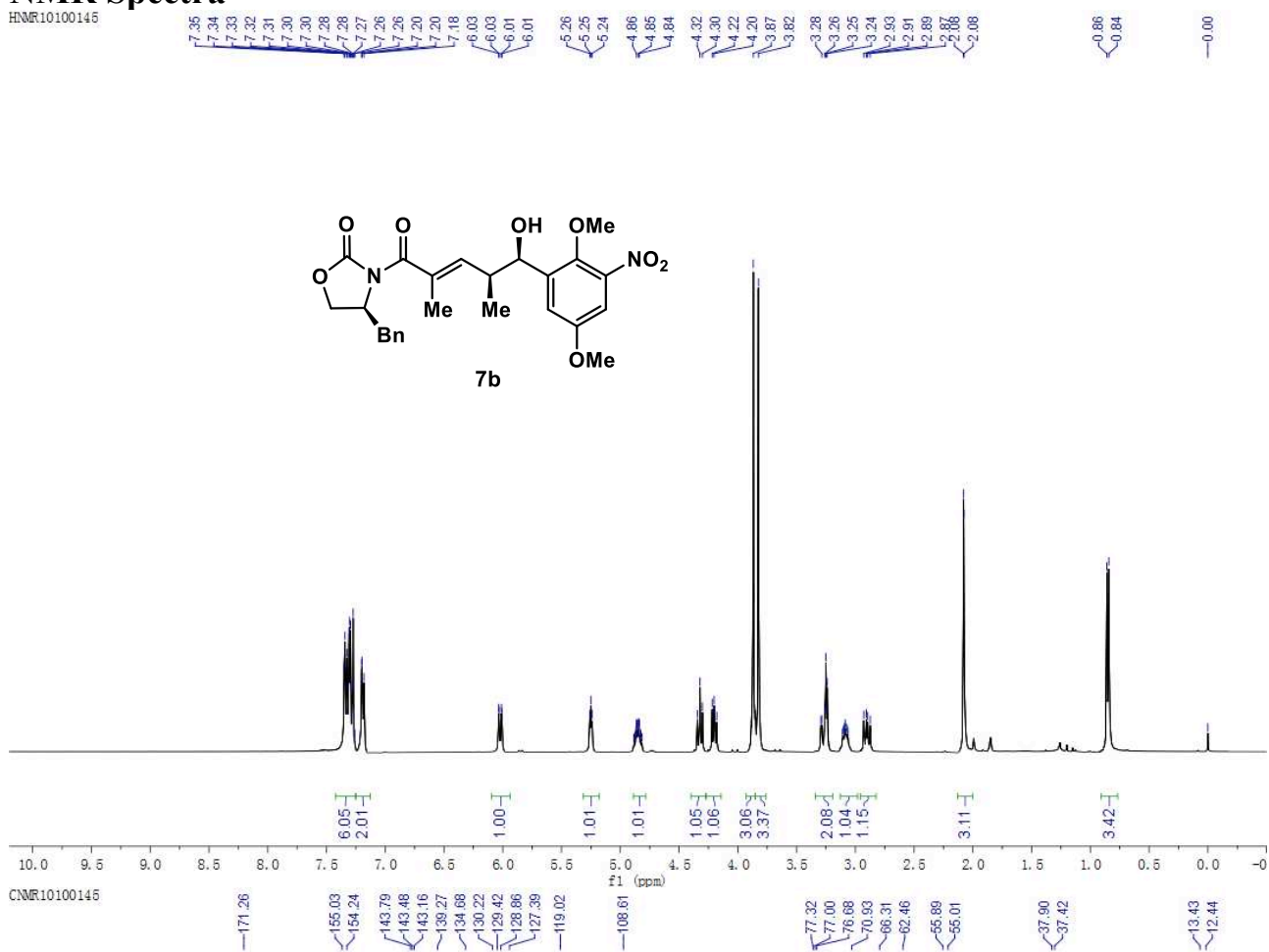
### <sup>13</sup>C NMR Comparison:

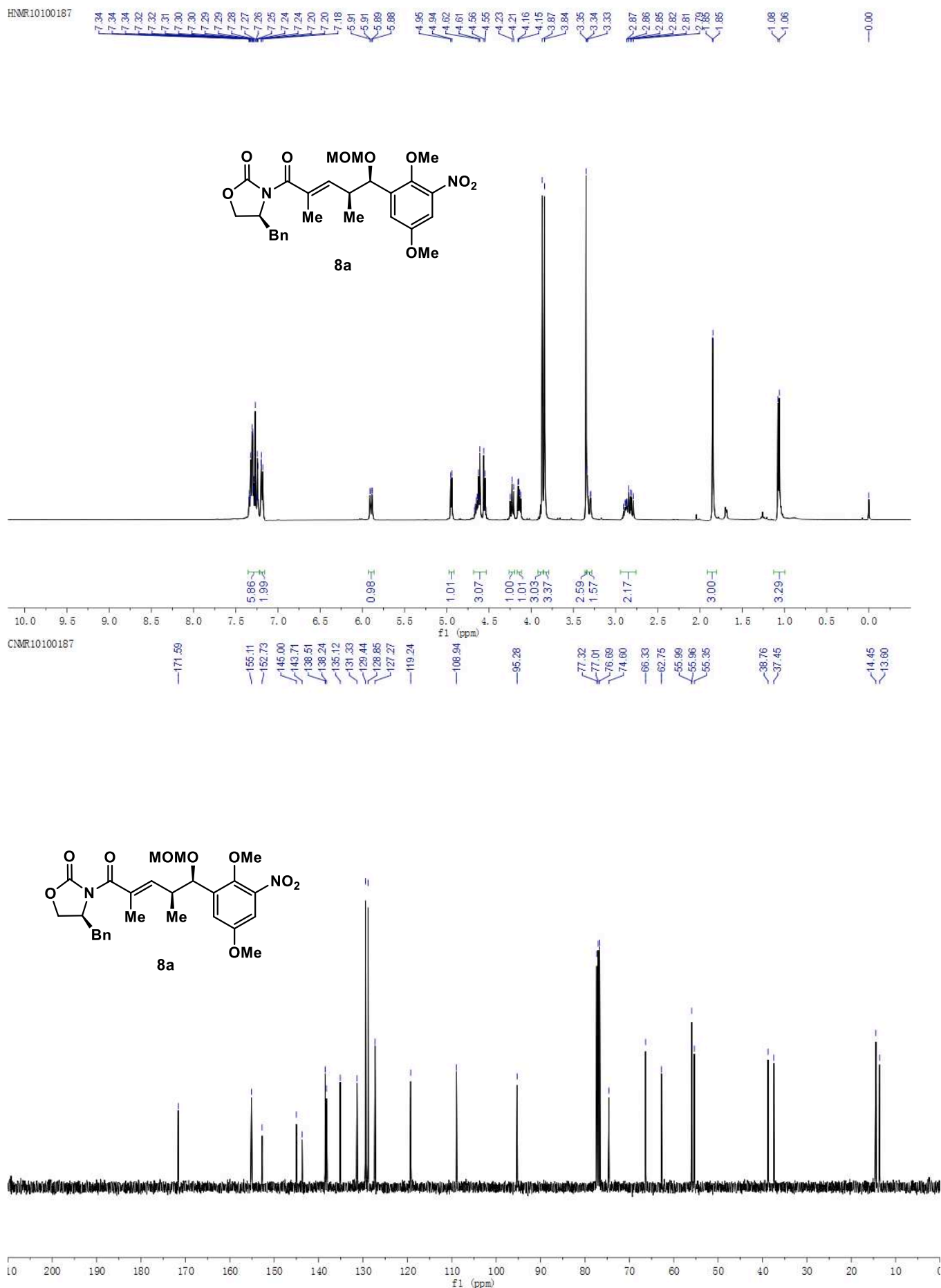
Position	$\delta_c$ of Cebulactam A1 (in ppm, literature, 100 MHz)	$\delta_c$ of Cebulactam A1 (in ppm, Synthesized, 100 MHz)	$\delta_c$ of Cebulactam A1 (in ppm, Synthesized, 125 MHz)	$\delta_c$ difference between synthesized (in ppm, 100 MHz) and literature (in ppm, 100 MHz)
1	70.9	70.5	70.5	-0.4
2	42.4	41.9	41.9	-0.5
Me-2	16.7	16.2	16.2	-0.5
3	87.4	86.9	87.0	-0.5
4	140.5	140.0	140.0	-0.5
Me-4	19.3	18.8	18.8	-0.5
5	124.7	124.3	124.3	-0.4
6	46.2	45.6	45.6	-0.6
Me-6	17.8	17.3	17.3	-0.5
7	207.1	206.5	206.5	-0.6
8	48.2	47.8	47.8	-0.4
Me-8	16.6	16.1	16.1	-0.5
9	173.9	173.4	173.4	-0.5
10	131.0	130.5	130.5	-0.5
11	142.7	142.3	142.3	-0.4
12	140.9	140.4	140.4	-0.5
13	111.1	110.6	110.6	-0.5
14	154.4	153.9	153.9	-0.5
15	114.0	113.6	113.6	-0.4

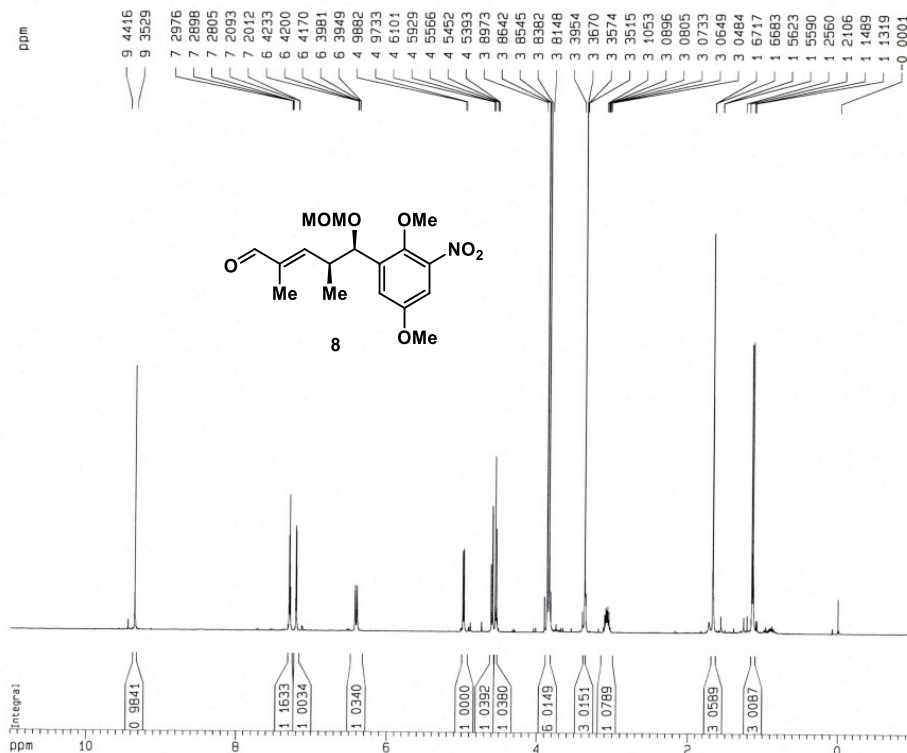


## NMR Spectra

HNMR10100145





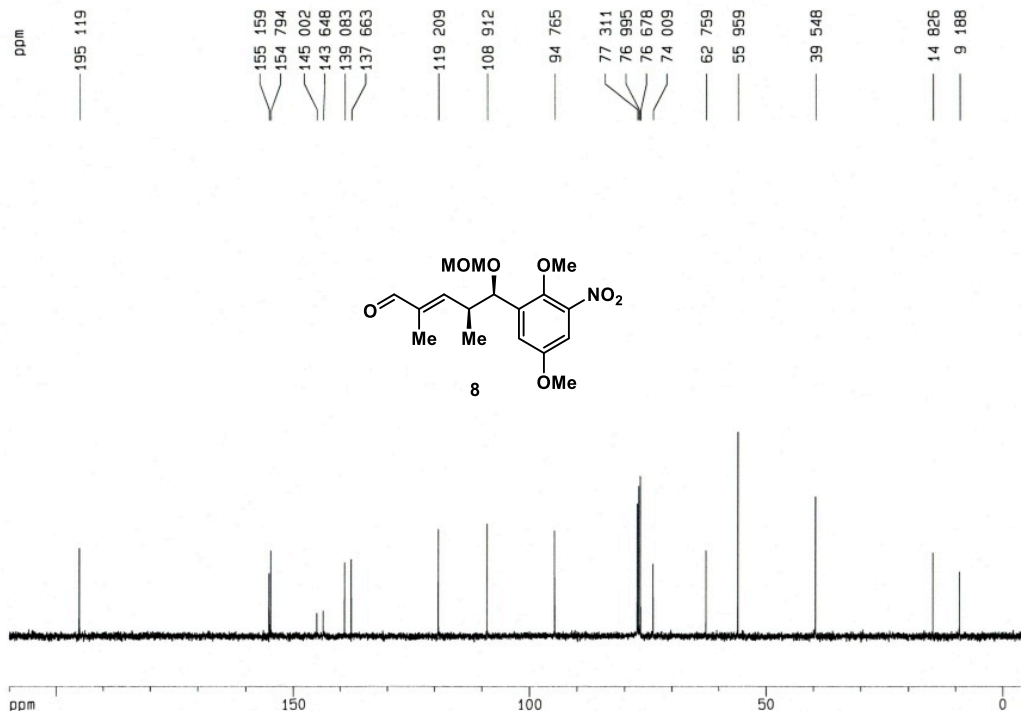


Current Data Parameters  
 NAME HNMR10090009  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20100901  
 Time 16 04  
 INSTRUM ARX400  
 PROBHD 5 mm Multinu  
 PULPROG zg  
 TD 32768  
 SOLVENT CDC13  
 NS 16  
 DS 0  
 SWH 8064 516 Hz  
 FIDRES 0 246110 Hz  
 AQ 2 0316660 sec  
 RG 360  
 DW 62 000 usec  
 DE 88 57 usec  
 TE 300 0 K  
 D1 1 50000000 sec  
 P1 3 00 usec  
 DE 88 57 usec  
 SF01 400 1318844 MHz  
 NUCLEUS 1H

F2 - Processing parameters  
 SI 16384  
 SF 400 1300012 MHz  
 WDW no  
 SSB 0  
 LB 0 00 Hz  
 GB 0  
 PC 4 00

1D NMR plot parameters  
 CX 20 00 cm  
 F1P 11 000 ppm  
 F1 4401 43 Hz  
 F2P -1 000 ppm  
 F2 -400 13 Hz  
 PPMCM 0 60000 ppm/cm  
 HZCM 240 07800 Hz/cm

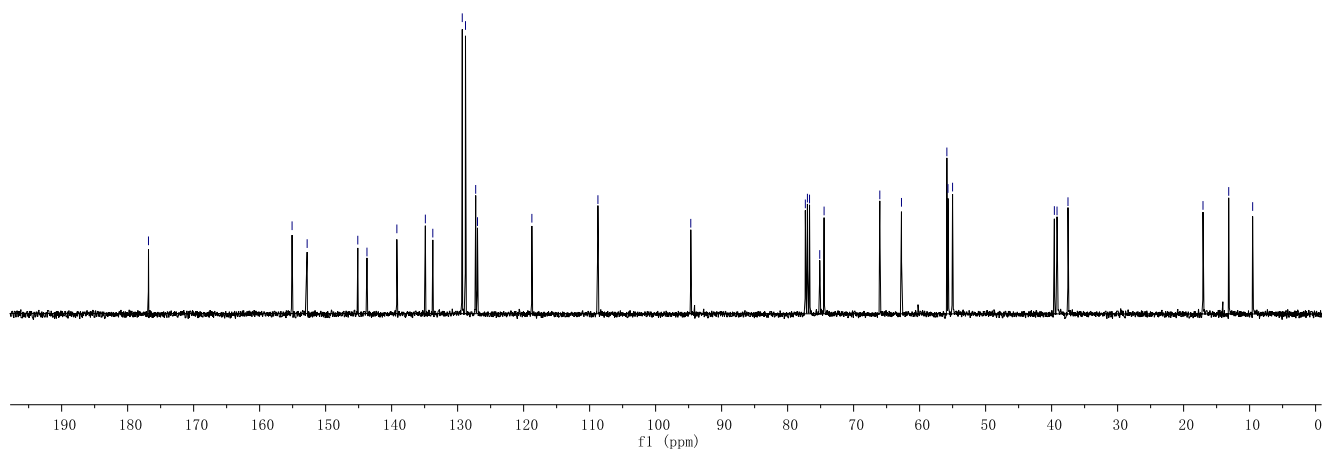
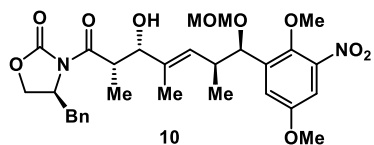
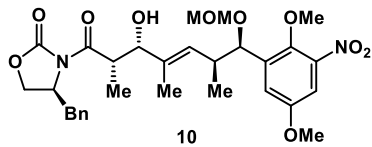
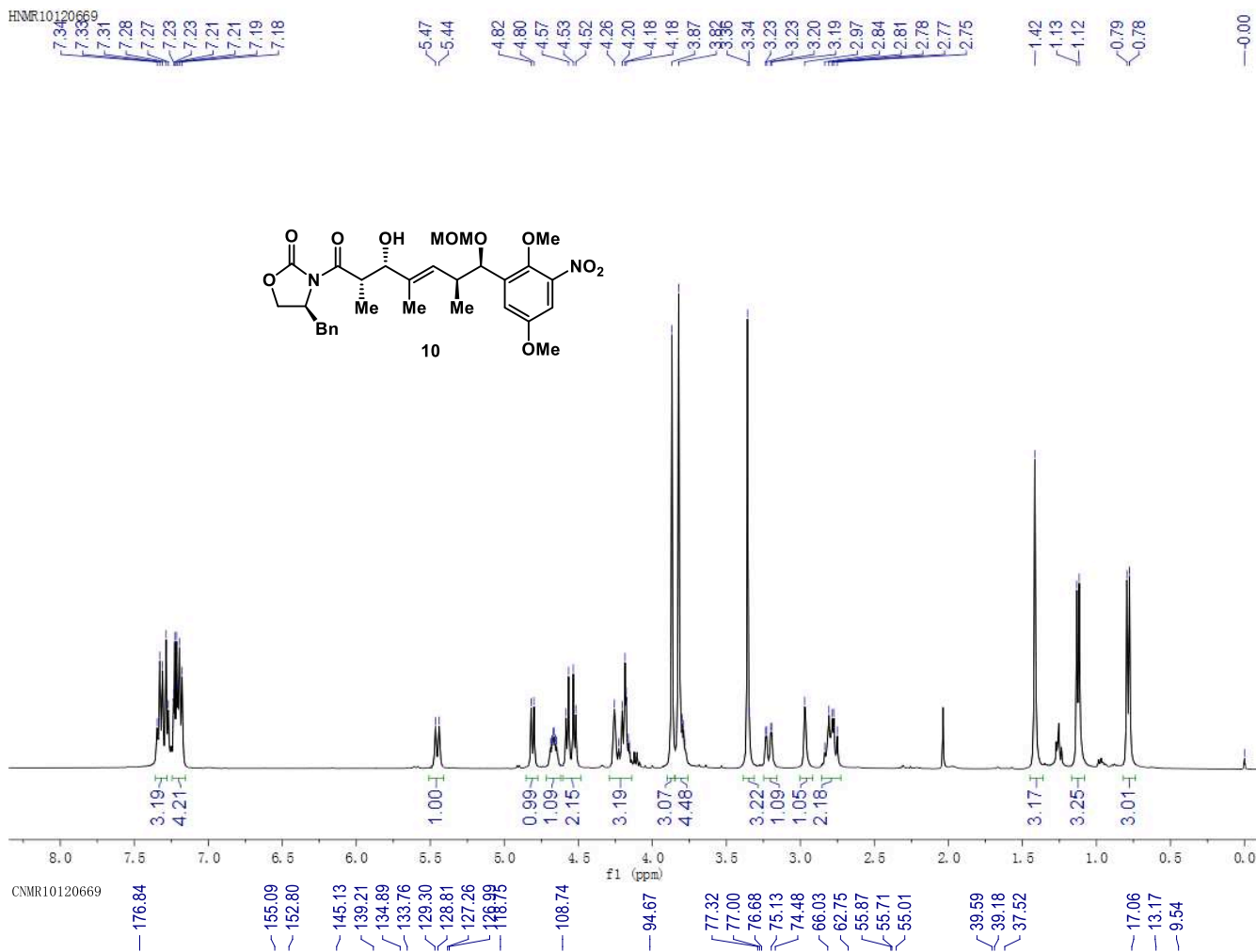


Current Data Parameters  
 NAME CNMR10090009  
 EXPNO 1  
 PROCNO 1

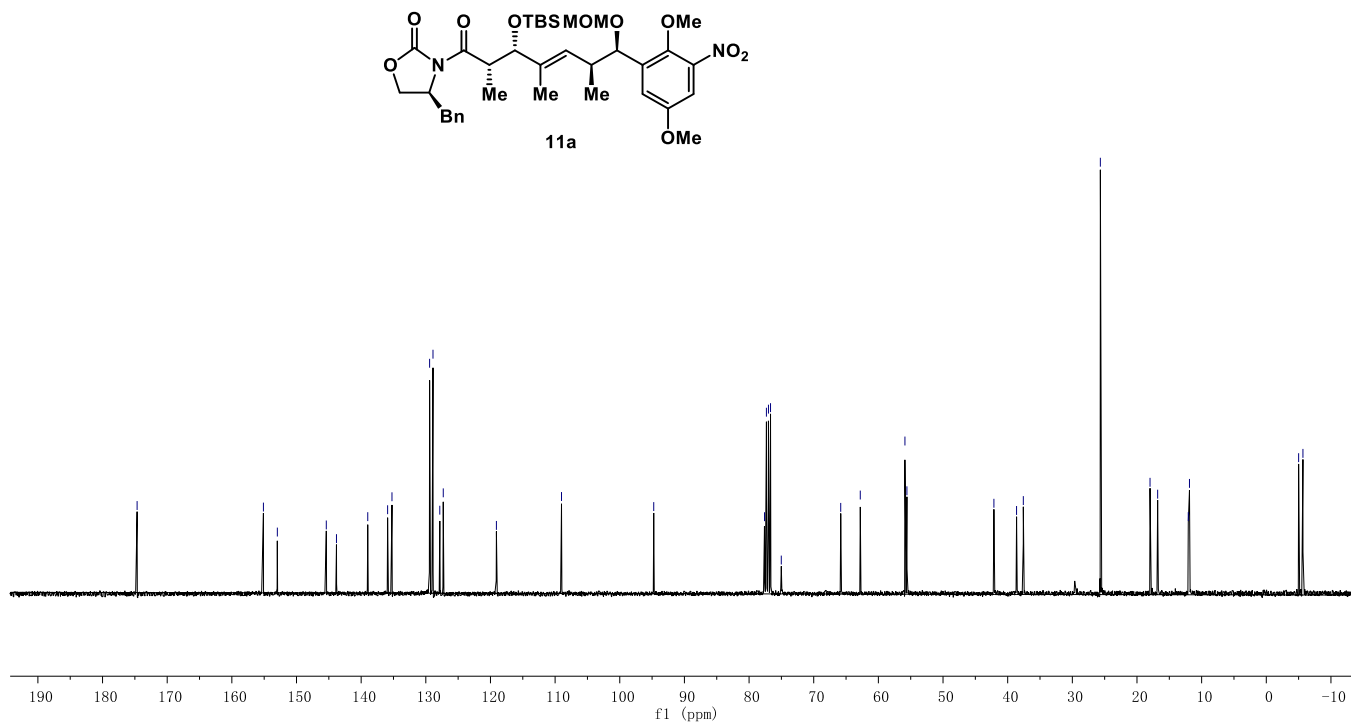
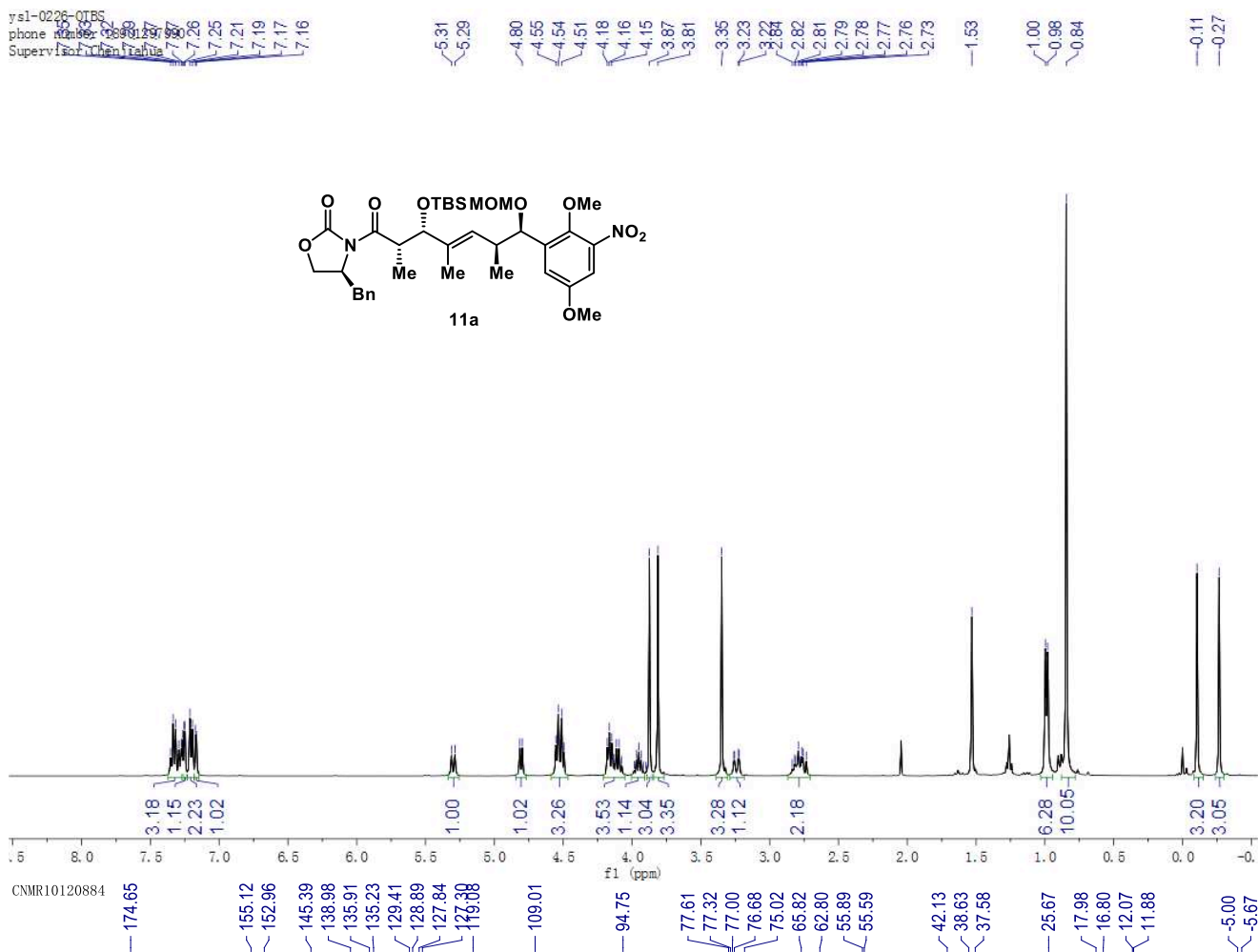
F2 Acquisition Parameters  
 Date\_ 20100901  
 Time 16 09  
 INSTRUM ARX400  
 PROBHD 5 mm Multinu  
 PULPROG zgdc  
 TD 32768  
 SOLVENT CDC13  
 NS 177  
 DS 2  
 SWH 26315 789 Hz  
 FIDRES 0 803094 Hz  
 AQ 0 6226420 sec  
 RG 8192  
 DW 19 000 usec  
 DE 27 14 usec  
 TE 300 0 K  
 D12 0 00002000 sec  
 DL5 22 20 dB  
 CPDPRG waltz16  
 P31 100 00 usec  
 D1 2 00000000 sec  
 P1 3 00 usec  
 DE 27 14 usec  
 SF01 100 6233680 MHz  
 NUCLEUS 13C  
 D11 0 03000000 sec

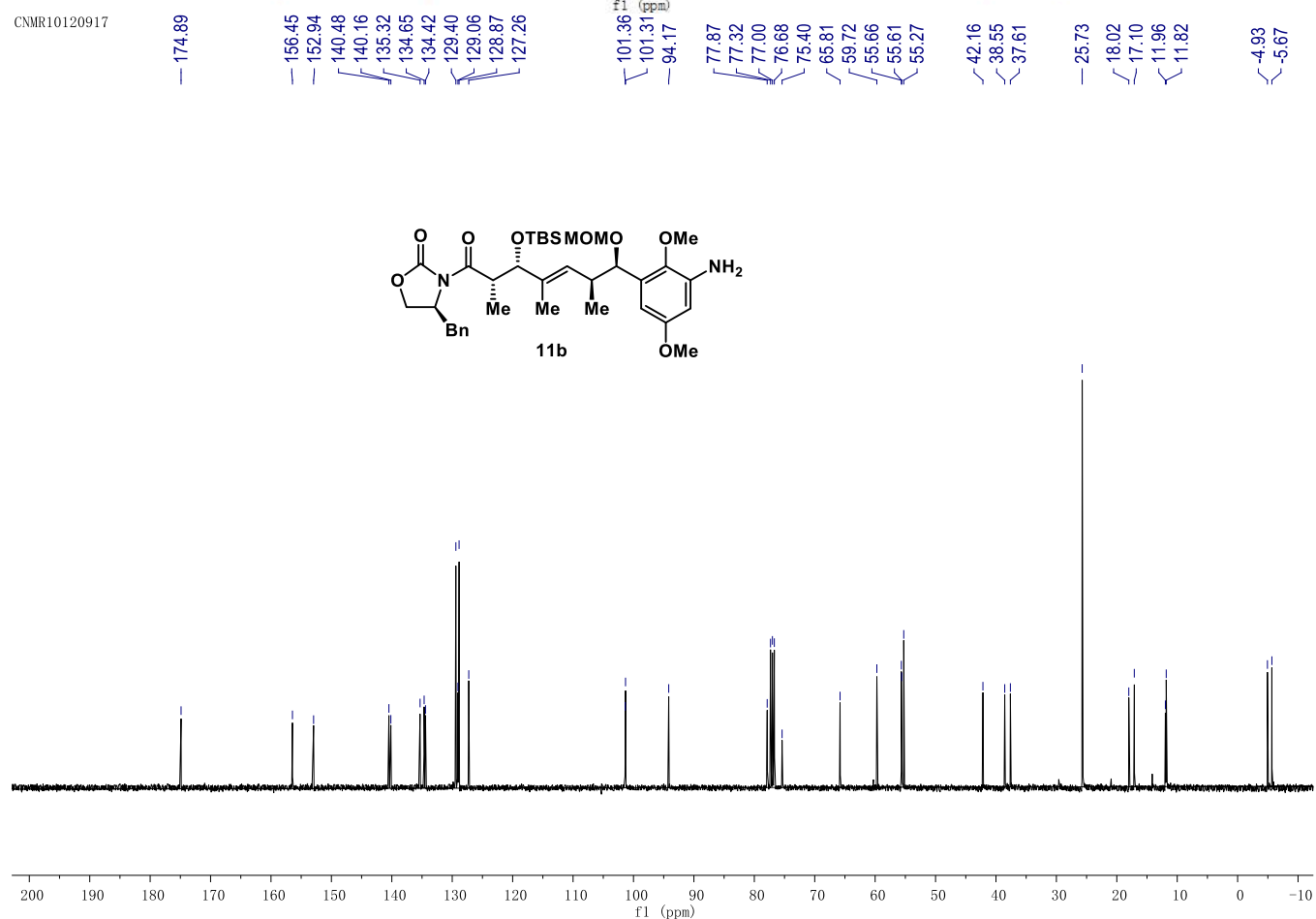
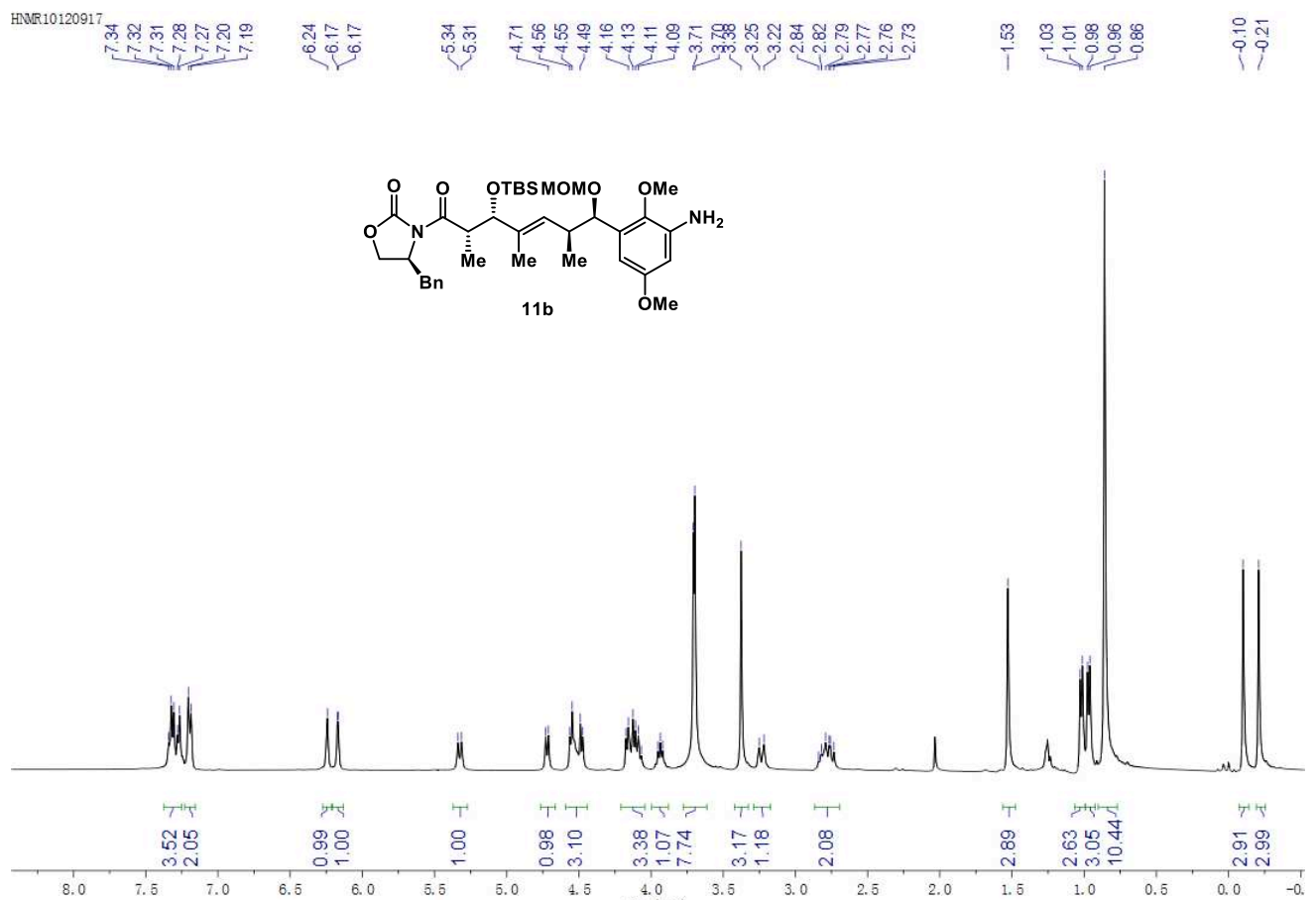
F2 - Processing parameters  
 SI 16384  
 SF 100 6127746 MHz  
 WDW EM  
 SSB 0  
 LB 0 50 Hz  
 GB 0  
 PC 1 00

1D NMR plot parameters  
 CX 20 00 cm  
 F1P 210 000 ppm  
 F1 21128 68 Hz  
 F2P -5 000 ppm  
 F2 -503 06 Hz  
 PPMCM 10 75000 ppm/cm  
 HZCM 1081 58740 Hz/cm

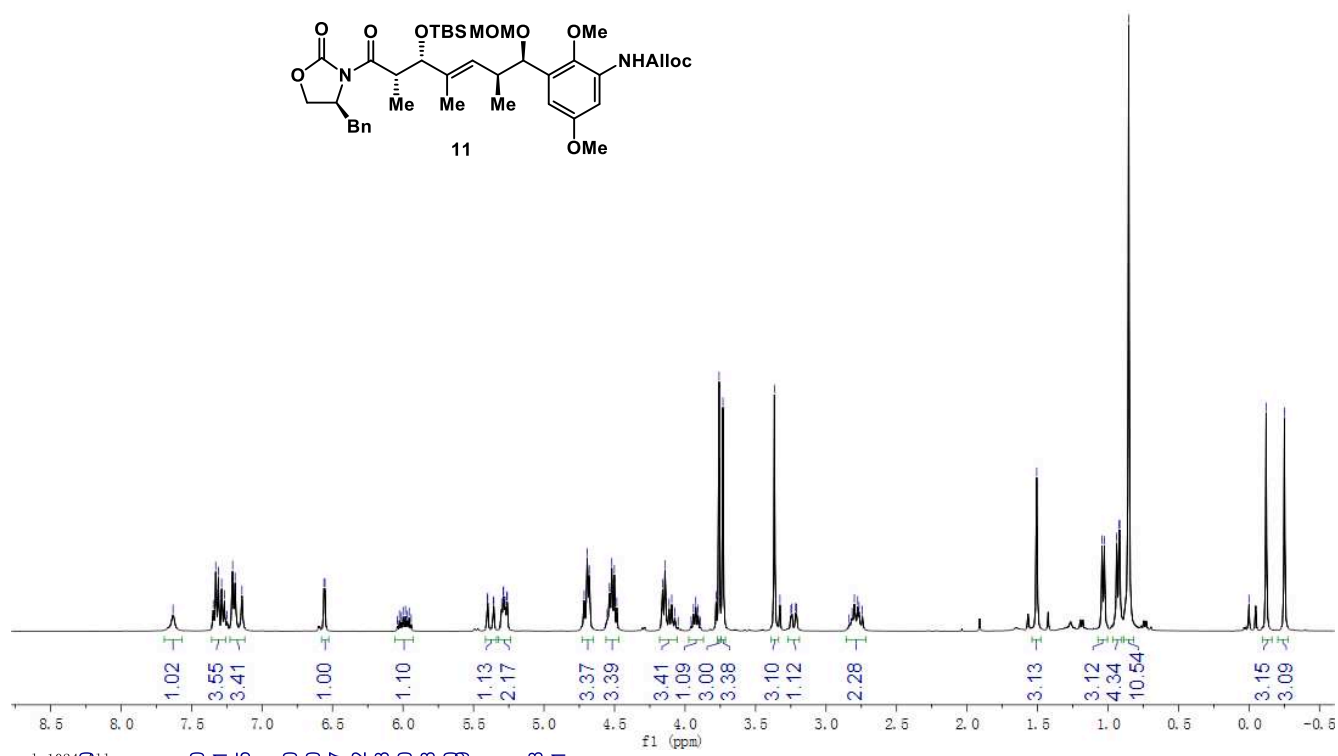
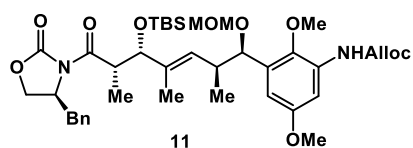


ys1-0226-OTB  
 phone number: 03981291990  
 Supervisor: Chen Tafuu



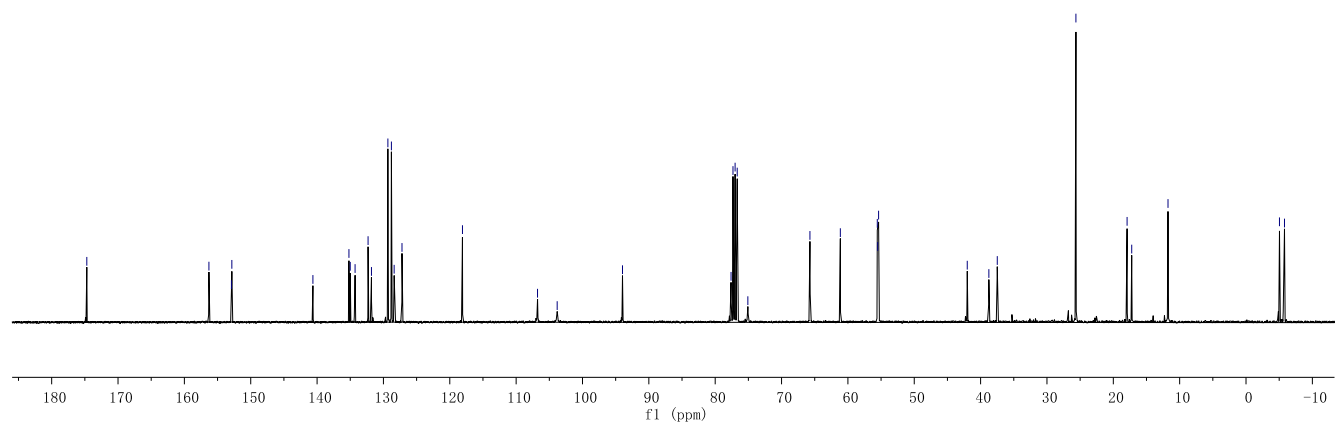
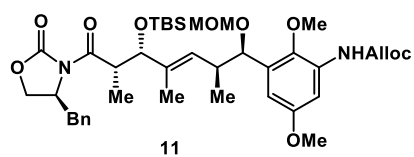


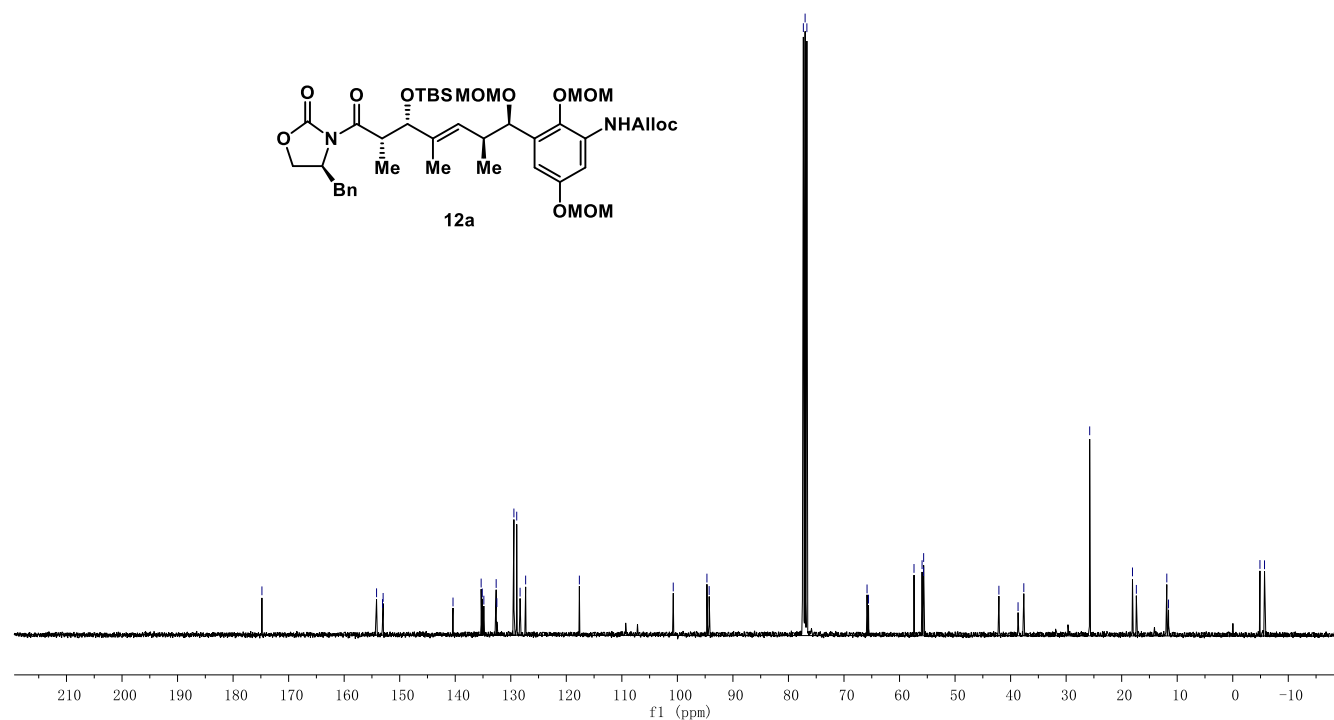
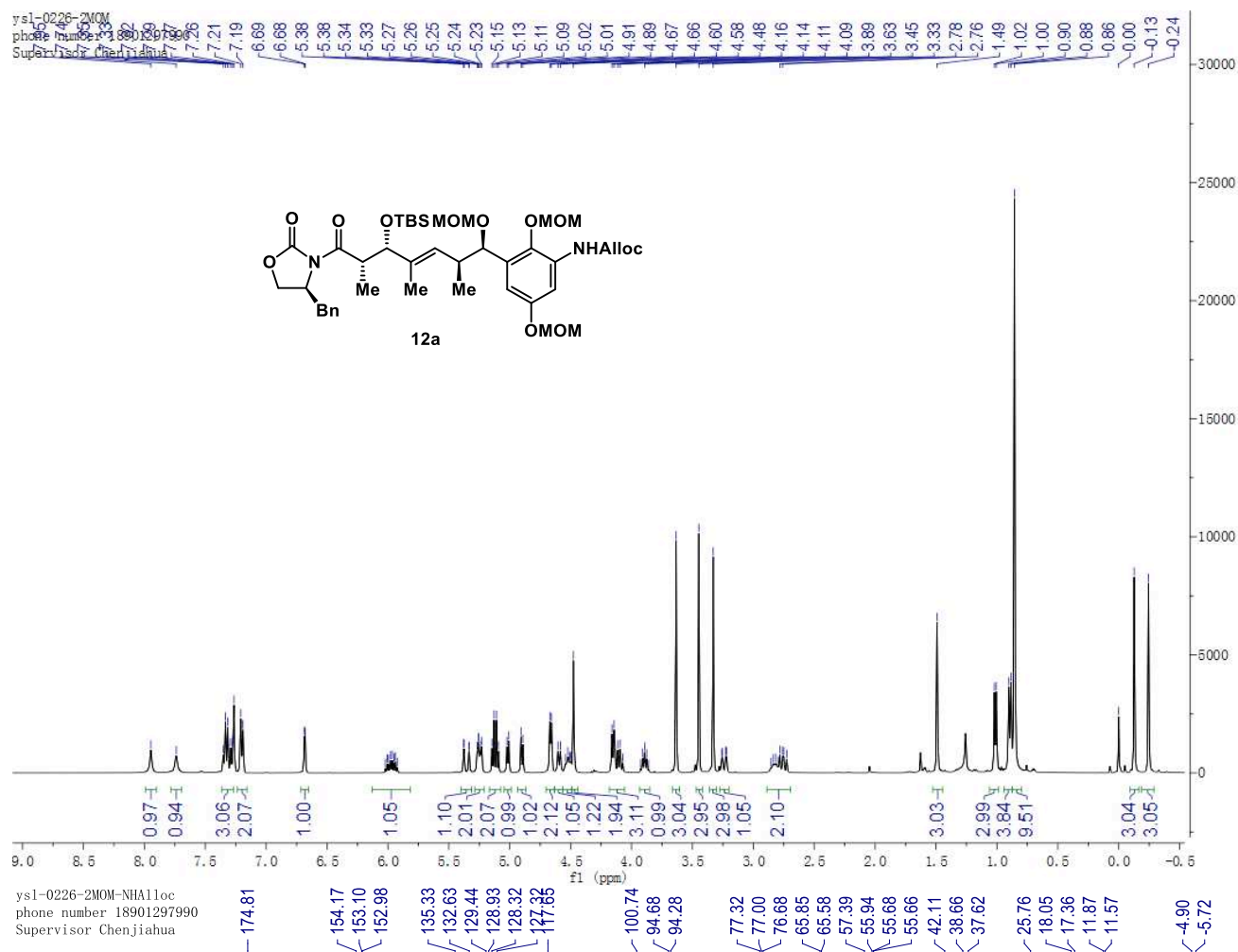
ys1-1024-11loc  
1890129740  
Chenjiahan  
7.310  
7.27  
7.21  
7.19  
7.14  
6.56  
6.55  
5.40  
5.36  
5.36  
5.30  
5.29  
5.29  
5.28  
5.26  
5.26  
4.72  
4.69  
4.68  
4.54  
4.52  
4.50  
4.48  
4.16  
4.14  
4.11  
4.09  
3.94  
3.92  
3.91  
3.78  
3.76  
3.73  
3.37  
3.33  
3.25  
3.24  
3.22  
3.21  
2.80  
2.78  
2.77  
1.51  
1.04  
1.03  
0.94  
0.92  
0.92  
0.85  
0.00  
-0.12



ys1-1024-11loc  
1890129740  
Chenjiahan

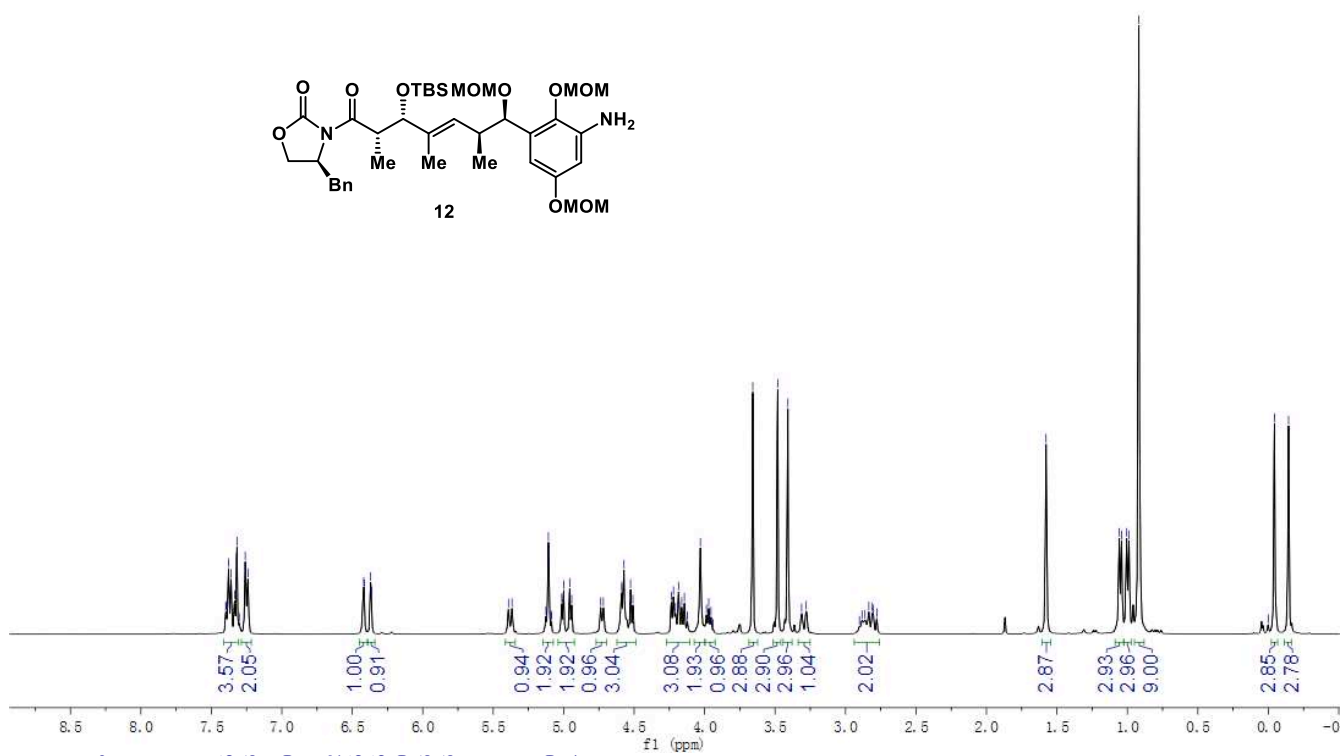
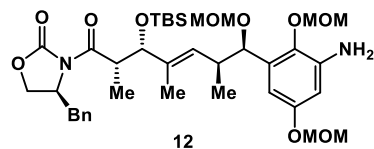
7.770  
156.30  
152.91  
152.85  
135.20  
135.00  
134.27  
132.32  
129.33  
128.80  
128.38  
118.09  
106.78  
103.81  
93.97  
77.61  
77.32  
77.00  
76.68  
75.08  
65.72  
61.14  
55.57  
55.51  
55.37  
42.01  
38.76  
37.49  
25.64  
17.92  
17.23  
11.76  
-5.04  
-5.80





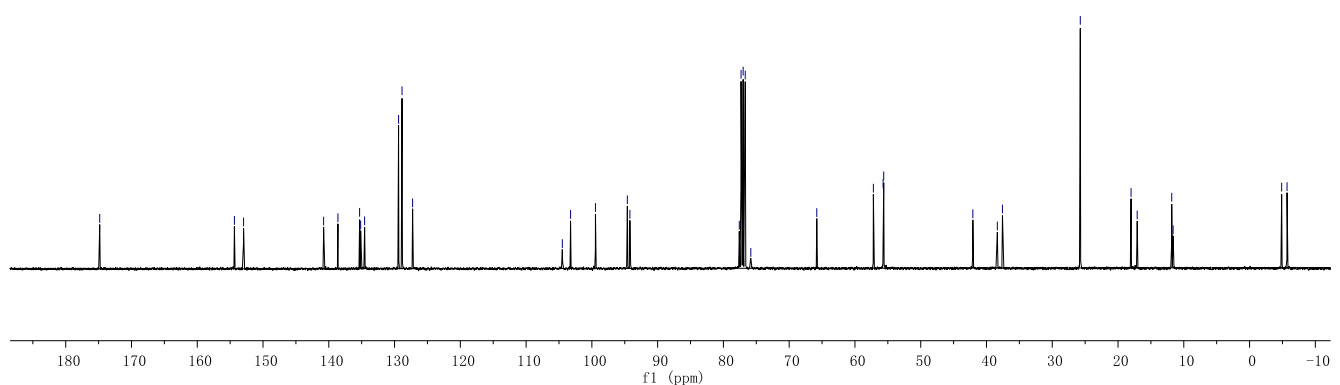
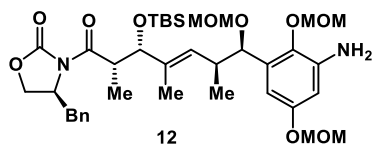


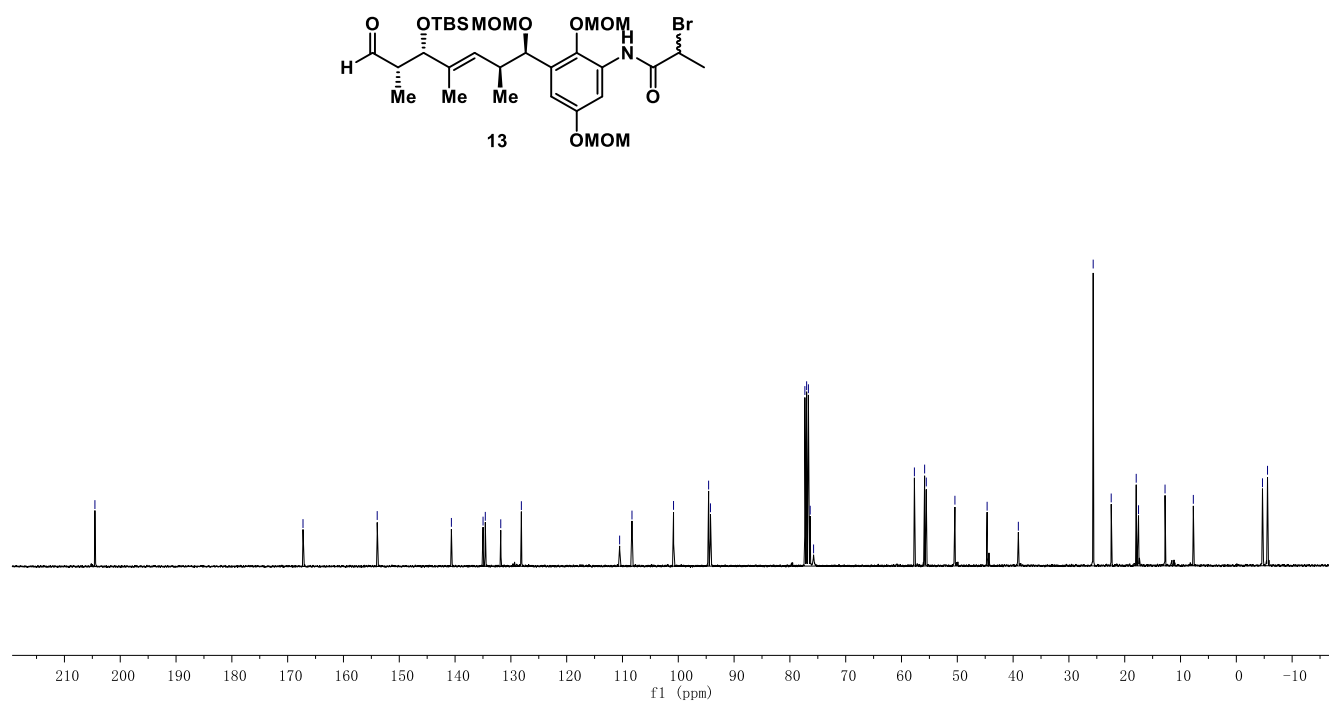
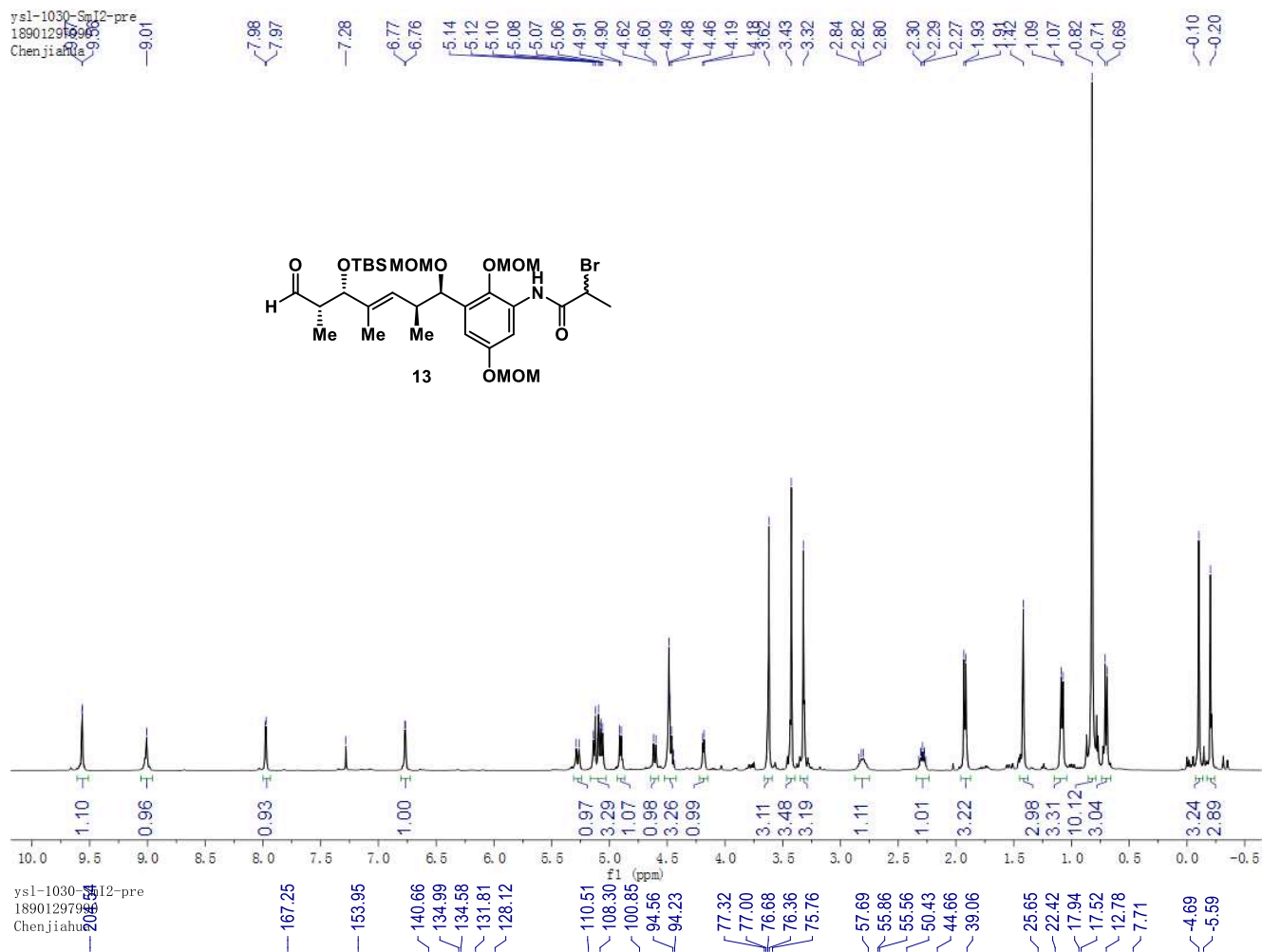
Chemical shift (ppm): 7.36, 7.35, 7.32, 7.26, 7.24, 6.42, 6.42, 6.37, 6.36, 6.36, 5.39, 5.37, 5.13, 5.11, 5.10, 5.01, 5.00, 4.96, 4.94, 4.74, 4.72, 4.59, 4.57, 4.53, 4.51, 4.24, 4.22, 4.21, 4.18, 4.16, 4.14, 4.03, 3.99, 3.97, 3.95, 3.66, 3.48, 3.41, 3.31, 3.28, 2.88, 2.86, 2.83, 2.81, 2.80, 2.78, 1.58, 1.06, 1.04, 1.00, 0.99, 0.92, 0.14



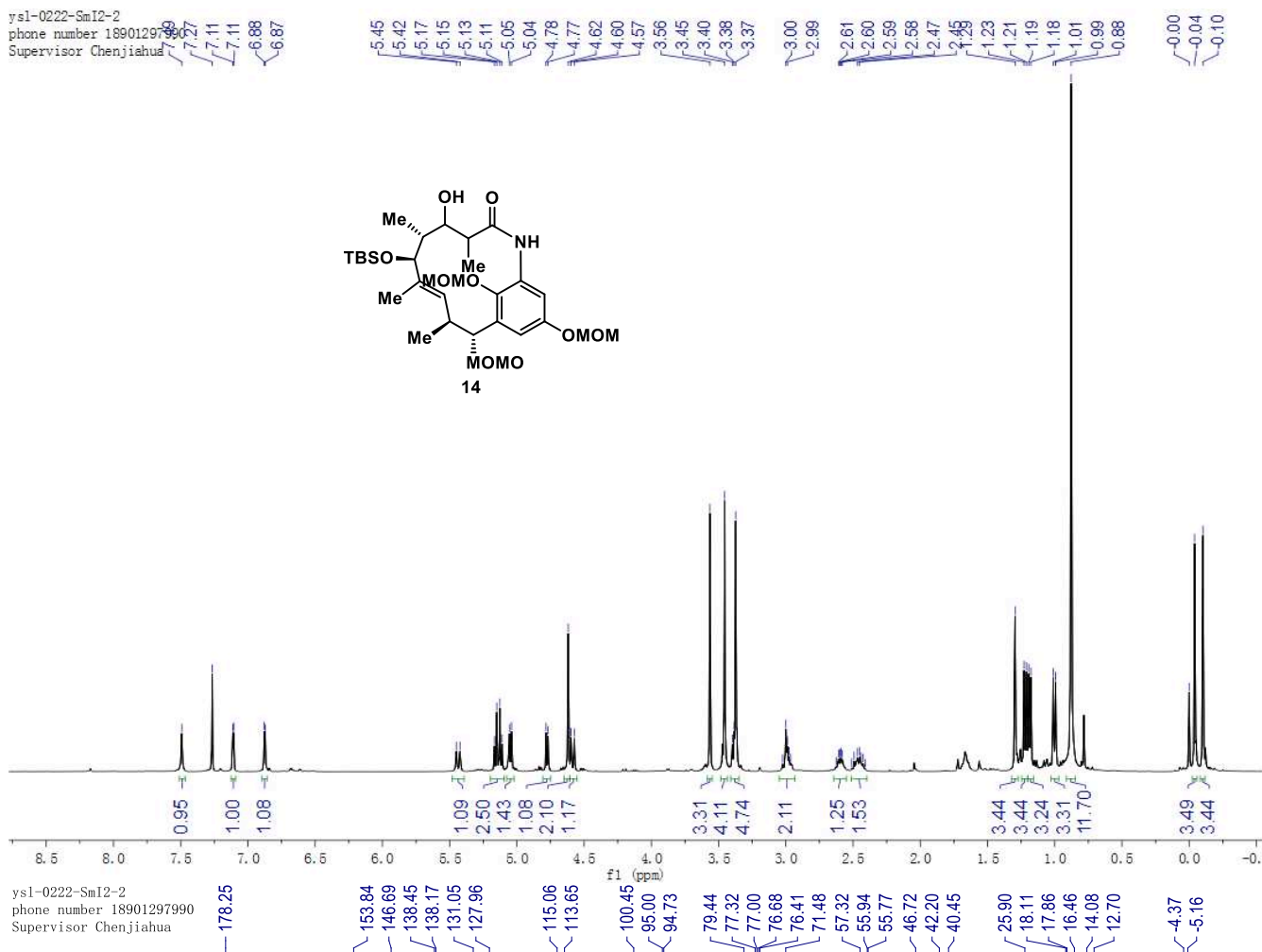
ys1-1029-209-NH2  
 18901297999  
 Chenjiahua

Chemical shift (ppm): 154.35, 152.96, 140.79, 138.61, 135.32, 135.15, 134.55, 129.39, 128.86, 127.26, 104.49, 103.24, 99.45, 94.61, 94.22, 77.59, 77.32, 77.00, 76.68, 75.84, 65.80, 57.20, 55.72, 55.65, 55.62, 42.07, 38.35, 37.57, 25.74, 18.02, 17.08, 11.83, 11.62, 4.88, 5.70

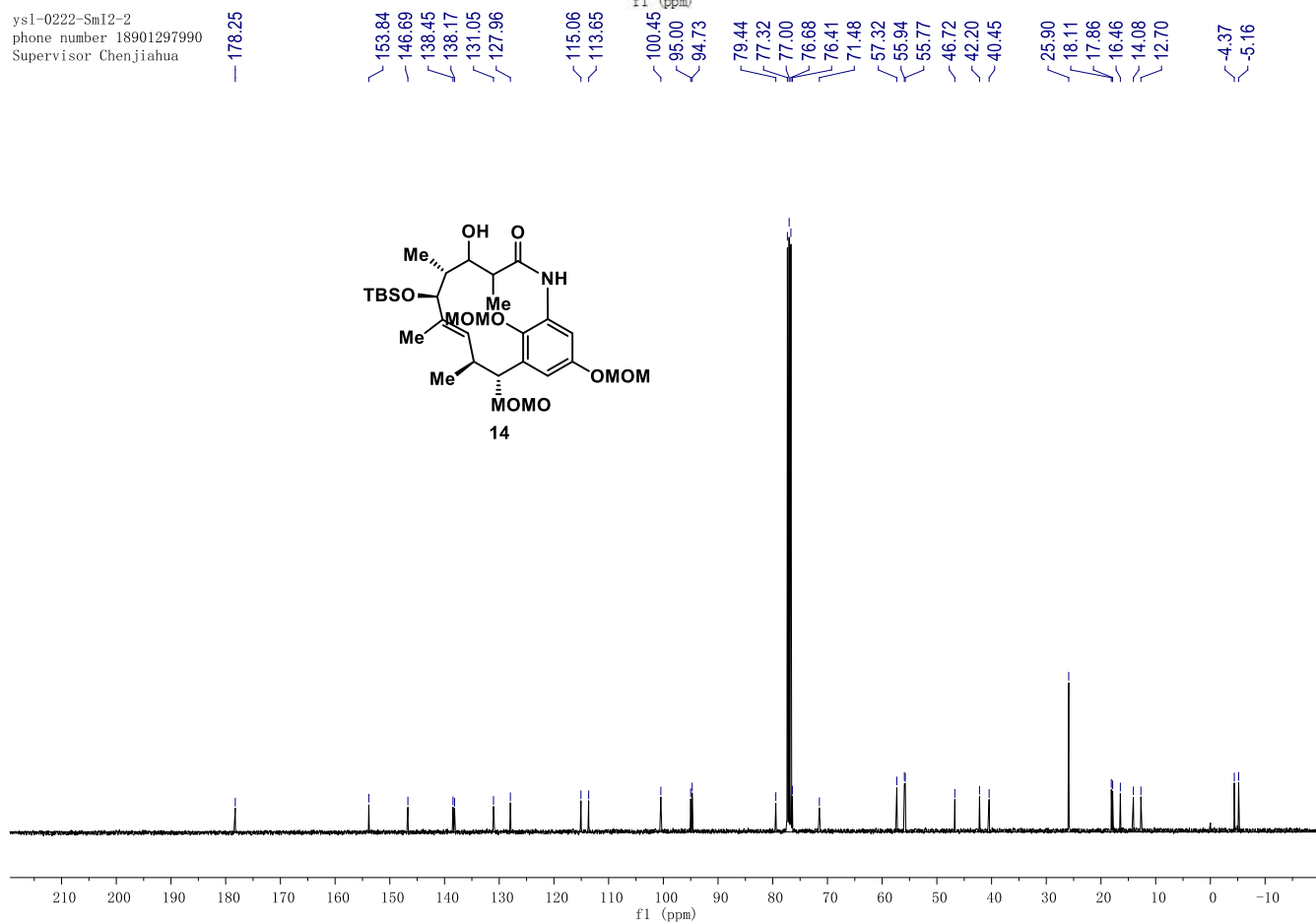




ysl-0222-SmI2-2  
 phone number 18901297990  
 Supervisor Chenjiahua



ysl-0222-SmI2-2  
 phone number 18901297990  
 Supervisor Chenjiahua



ysl-0222-IBX-2  
 phone number 18901297990  
 Supervisor Chenjiahua

7.26  
 7.17  
 7.17  
 6.83  
 6.83

5.69  
 5.66  
 5.15  
 5.14  
 5.09  
 5.08  
 4.98  
 4.97  
 4.89  
 4.88  
 4.61  
 4.59

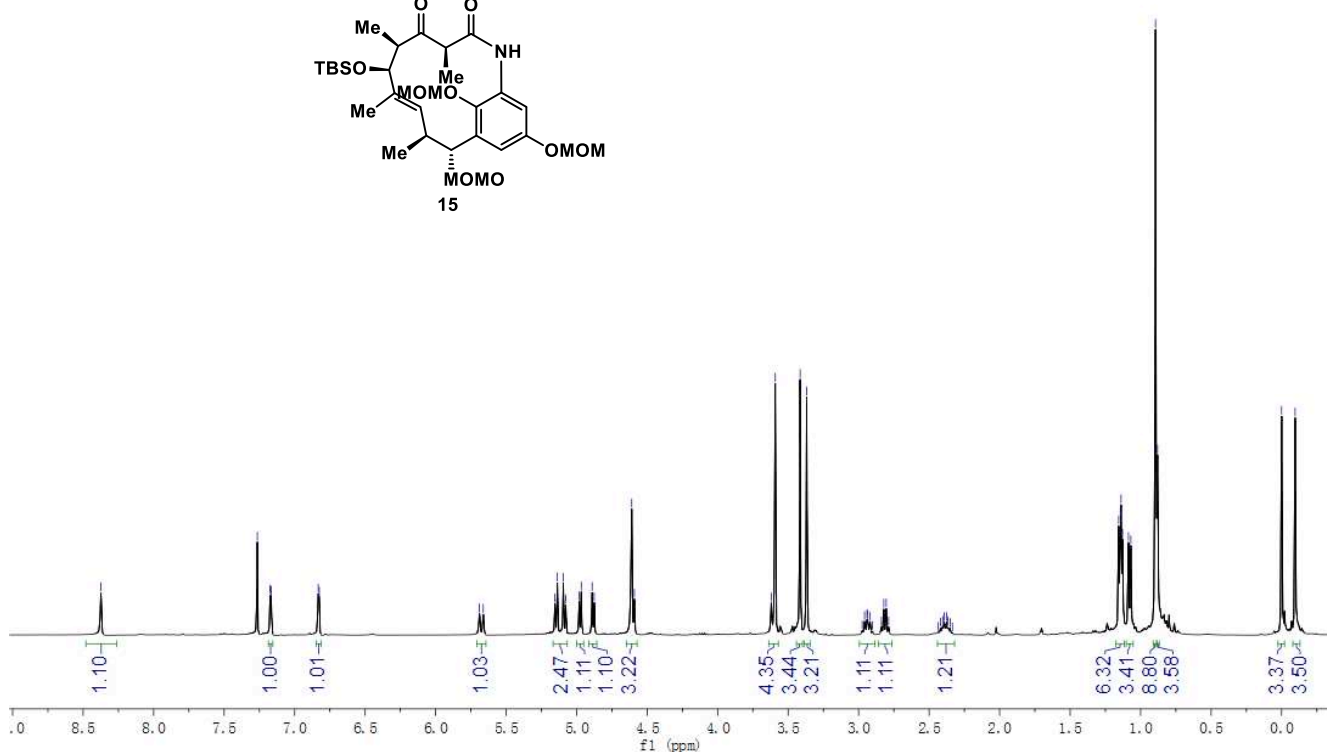
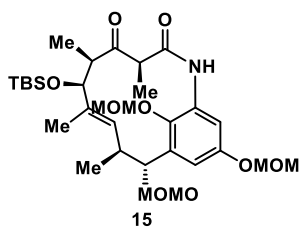
3.62  
 3.59  
 3.41  
 3.37

2.94  
 2.82  
 2.80

2.42  
 2.40  
 2.39  
 2.38  
 2.37  
 2.16

1.14  
 1.14  
 1.13  
 1.09  
 1.07  
 0.89  
 0.88

0.00  
 0.10



ysl-0222-IBX-2  
 phone number 18901297990  
 Supervisor Chenjiahua

174.79

153.86

146.94

138.54

136.65

131.61

128.66

116.49

114.75

100.38

95.09

94.55

77.32

77.00

76.68

76.33

57.34

55.86

55.81

53.74

51.35

42.17

25.84

18.09

18.02

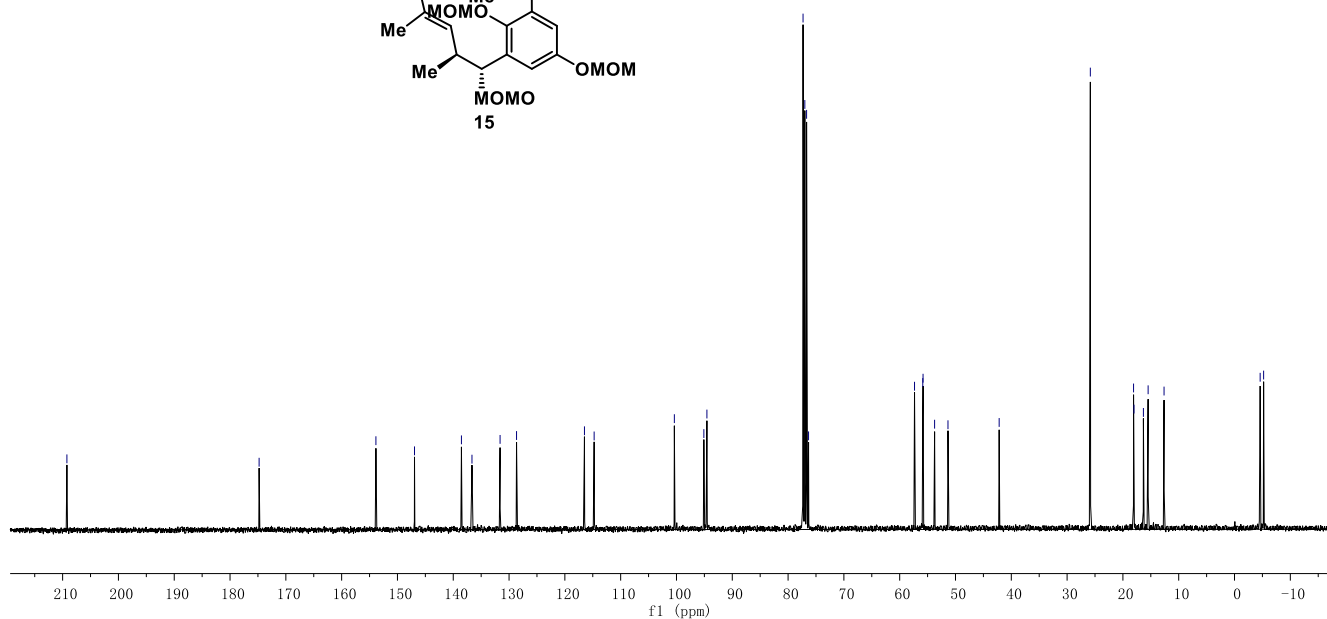
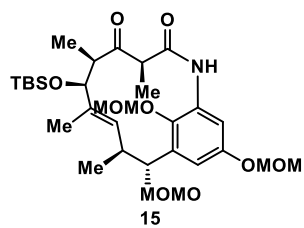
16.33

15.48

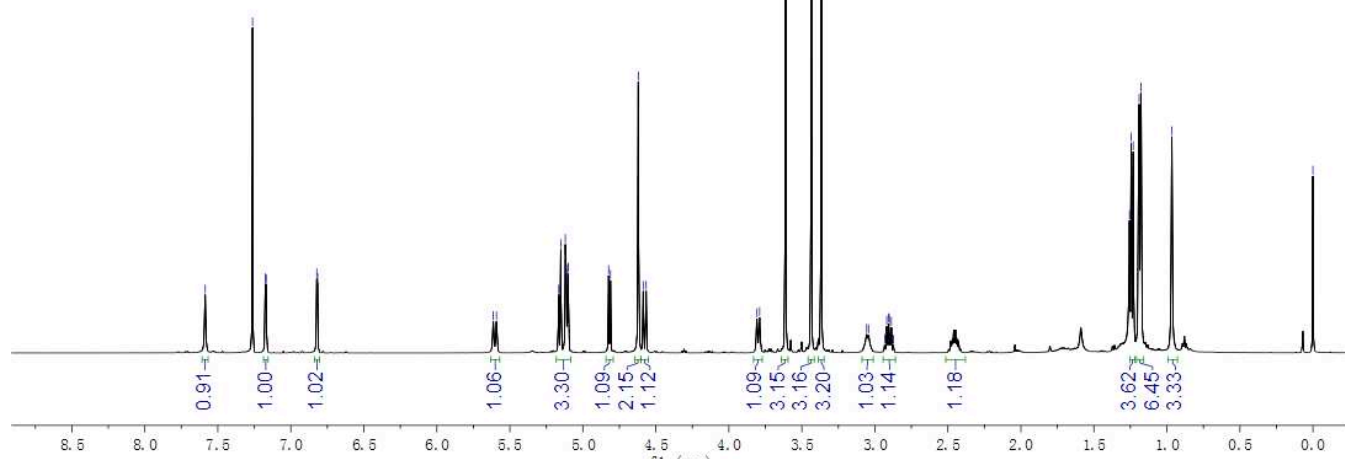
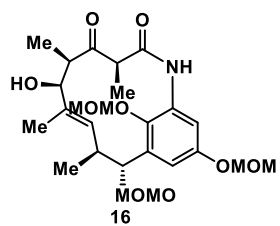
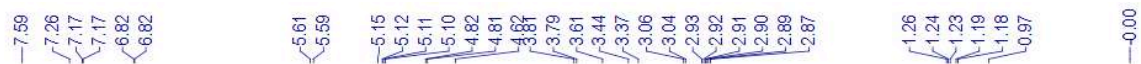
12.63

4.60

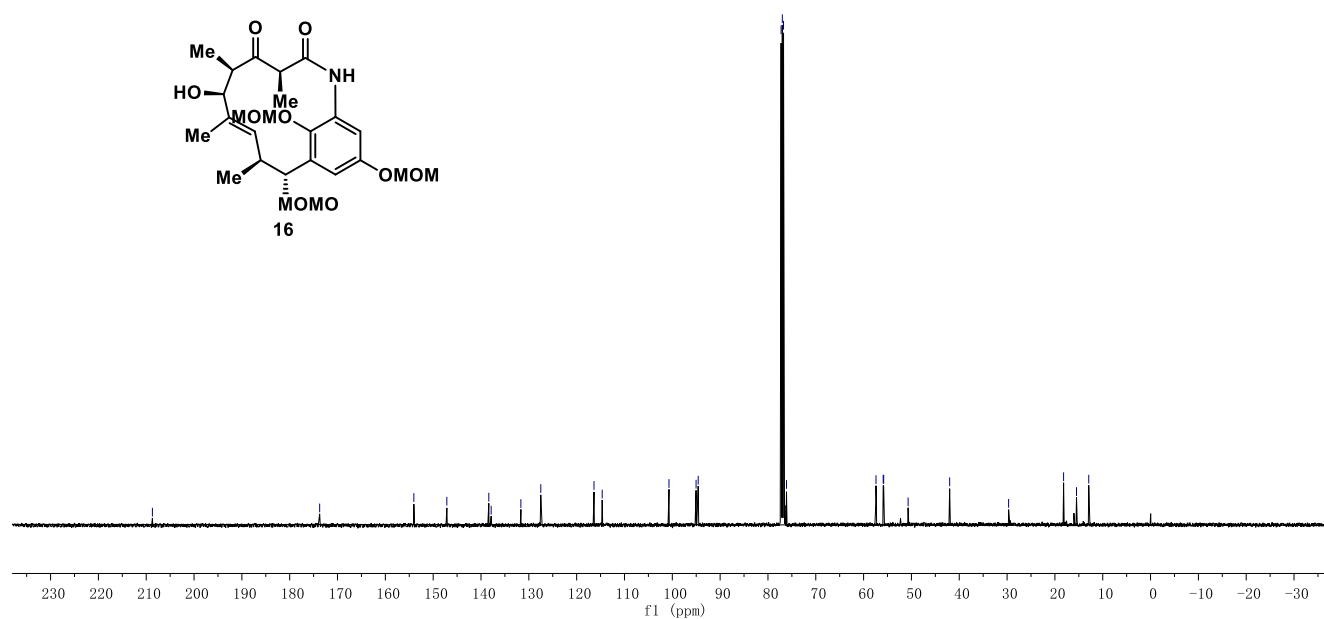
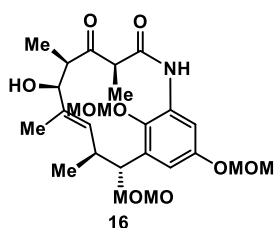
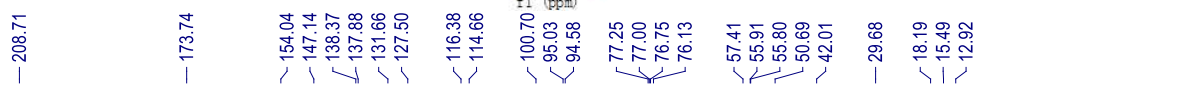
5.22



NMR13030308

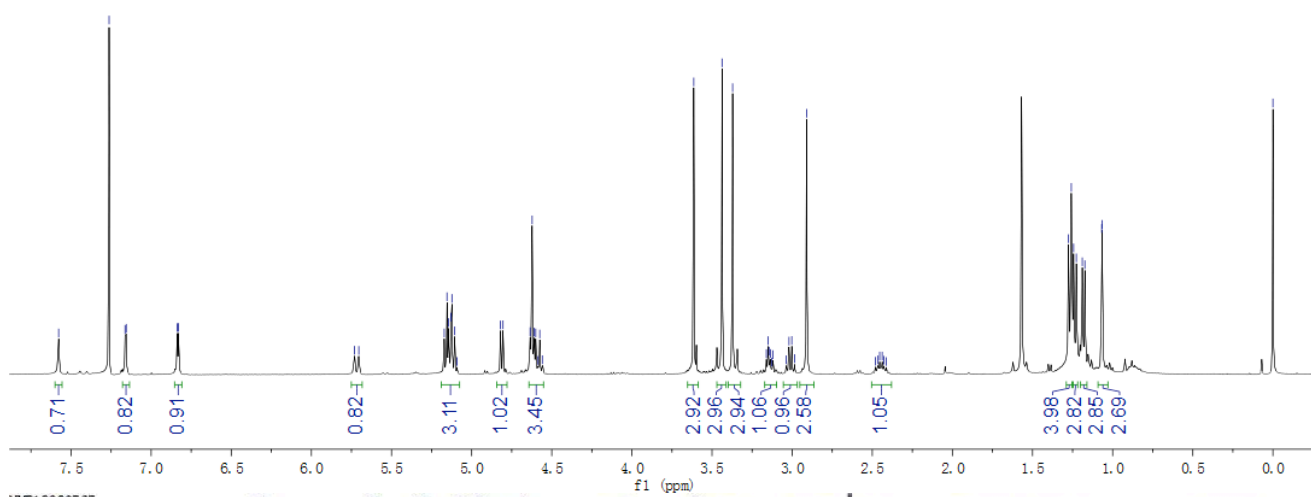
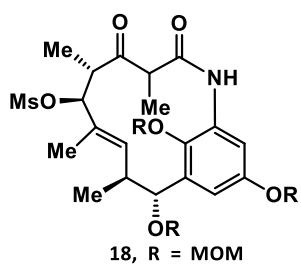


NMR13030308



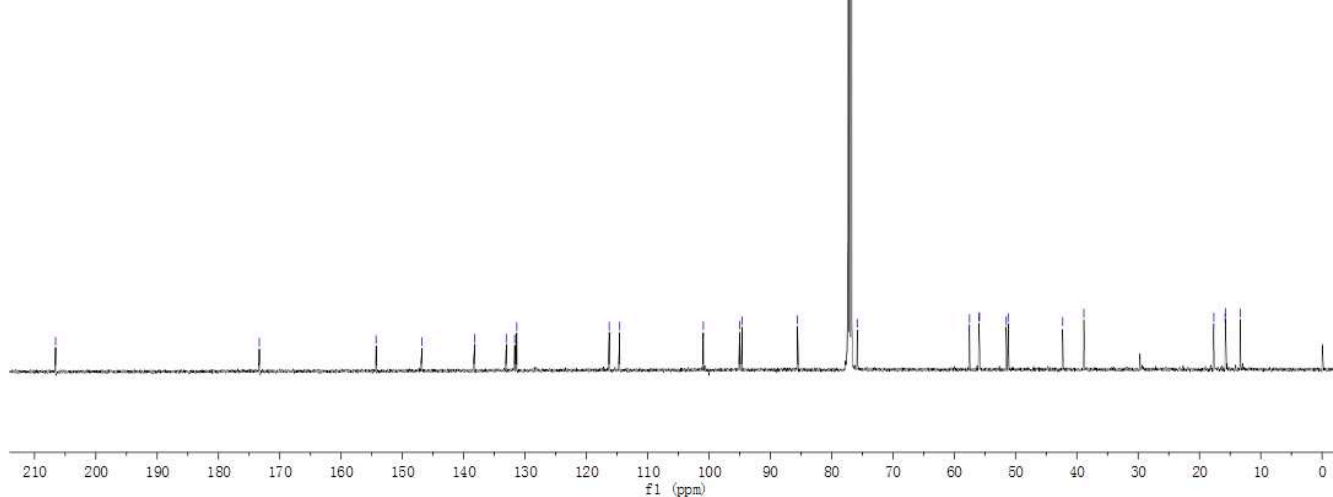
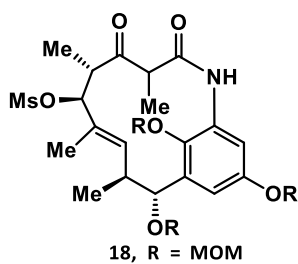
ysl-0916-OMs-pure  
 phone number: 13909127988  
 Supervisor: Chenjiahua

5.731 6.704 5.154 5.144 5.129 5.123 5.106 4.820 4.804 4.635 4.622 4.610 3.614 3.437 3.371 3.150 3.144 3.136 3.020 3.002 2.980 2.960 2.464 2.454 2.438 2.428 2.412 1.276 1.258 1.244 1.227 1.190 1.173 1.068 1.066 -0.000



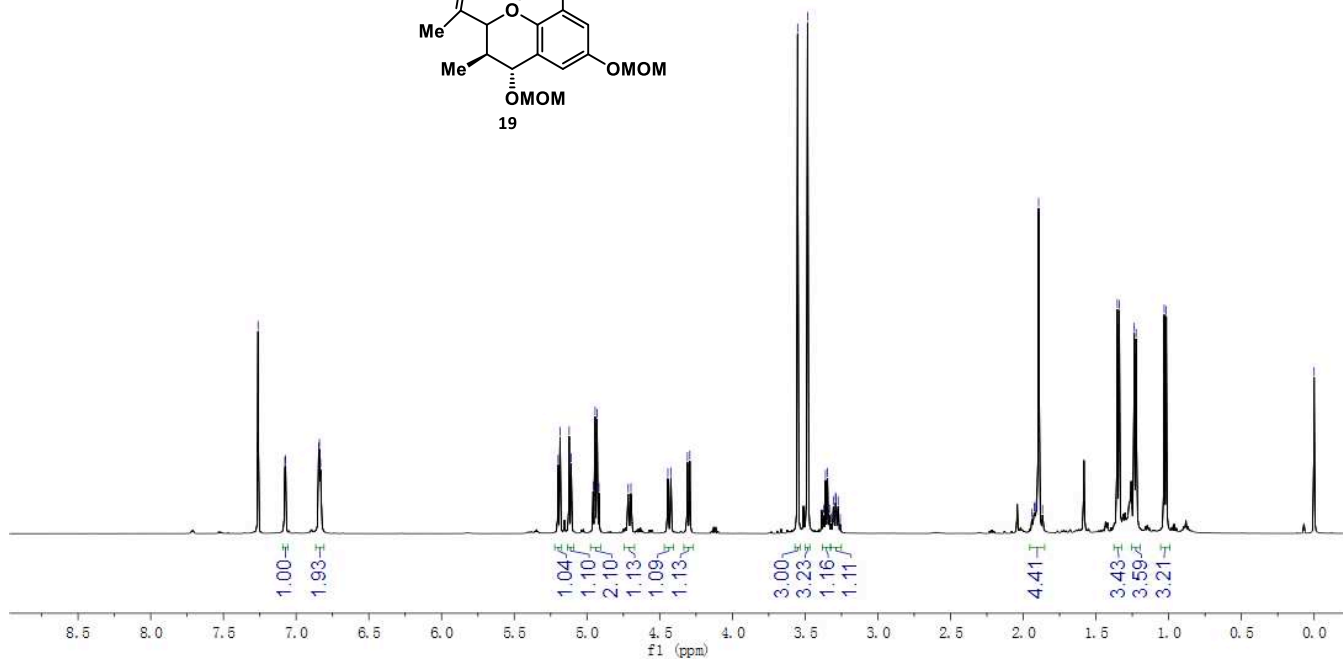
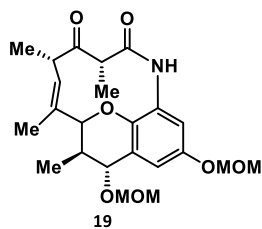
NMR13690767

206.5690767 173.340 154.293 146.796 138.210 133.059 131.681 131.347 116.271 114.564 100.919 95.014 84.590 85.552 77.254 77.000 76.746 75.822 57.501 55.958 55.882 51.516 51.205 42.315 38.880 17.659 15.812 15.772 13.362



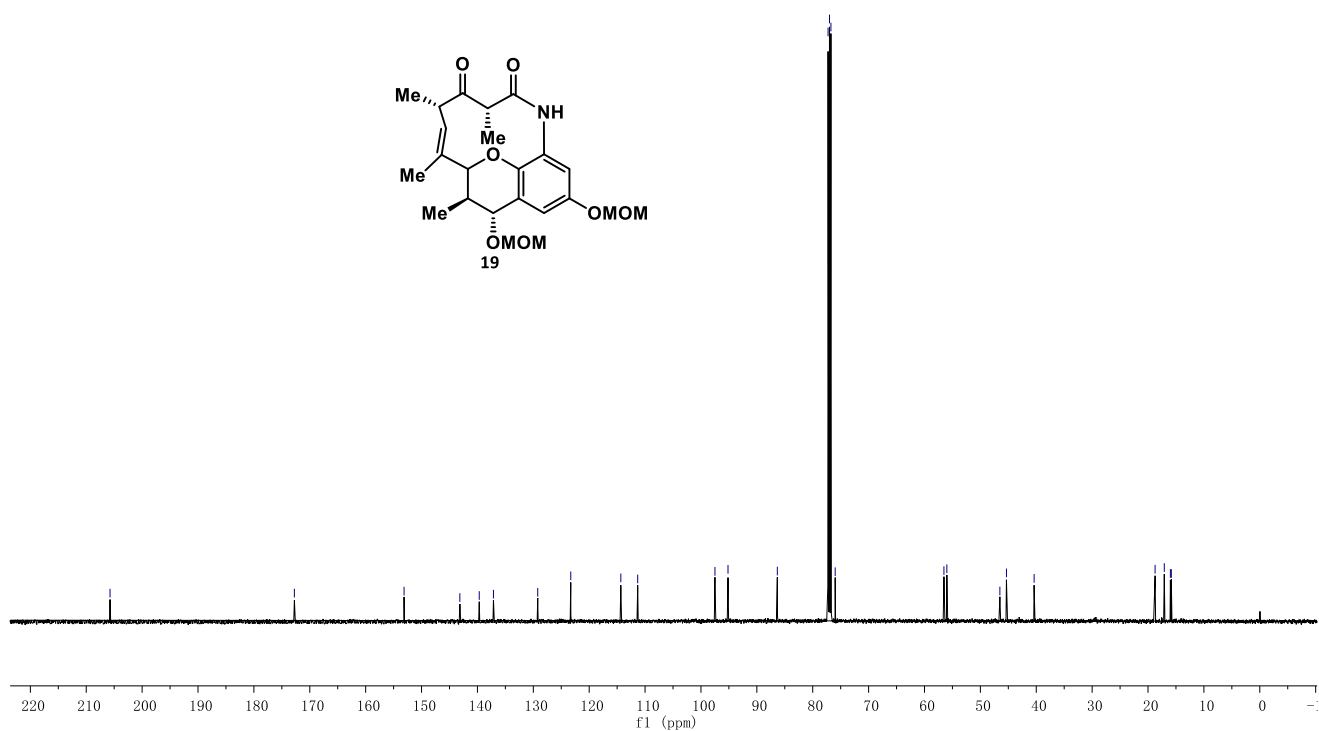
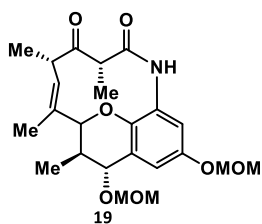
NMR13030329

7.26, 7.08, 7.07, 6.85, 6.84, 6.83, 5.20, 5.19, 5.12, 5.11, 4.96, 4.94, 4.93, 4.92, 4.72, 4.70, 4.44, 4.42, 4.31, 4.29, 3.55, 3.48, 3.36, 3.35, 3.31, 3.29, 3.29, 3.27, 1.92, 1.92, 1.91, 1.89, 1.87, 1.35, 1.34, 1.24, 1.22, 1.03, 1.02, -0.00

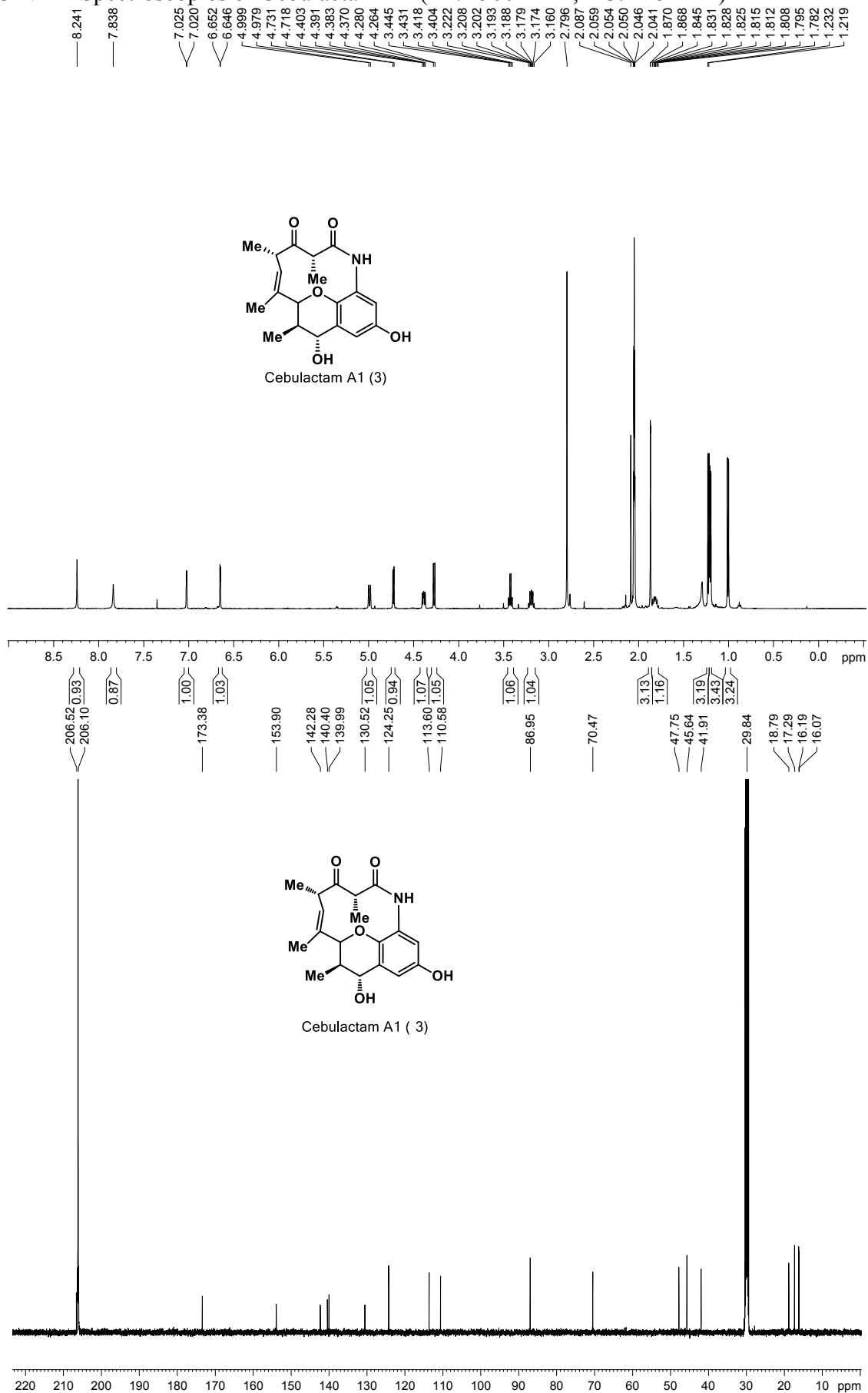


NMR13030329

205.74, 172.75, 153.13, 143.14, 139.68, 137.13, 129.21, 123.30, 114.34, 111.32, 97.50, 95.16, 86.34, 77.25, 77.00, 76.75, 75.98, 56.52, 56.00, 46.51, 45.33, 40.38, 18.73, 17.09, 16.00, 15.83



$^1\text{H}$  &  $^{13}\text{C}$  NMR Spectroscopies of Cebulactam A1 ( $^1\text{H}$ : 500 MHz;  $^{13}\text{C}$ : 125MHz)





$^1\text{H}$  &  $^{13}\text{C}$  NMR Spectroscopies of Cebulactam A1 ( $^1\text{H}$ :400 MHz;  $^{13}\text{C}$ :100MHz)

