**SUPPORTING INFORMATION**

# Total Synthesis of the Potent Marine-Derived Elastase Inhibitor Lyngbyastatin 7 and in Vitro Biological Evaluation in Model Systems for Pulmonary Diseases

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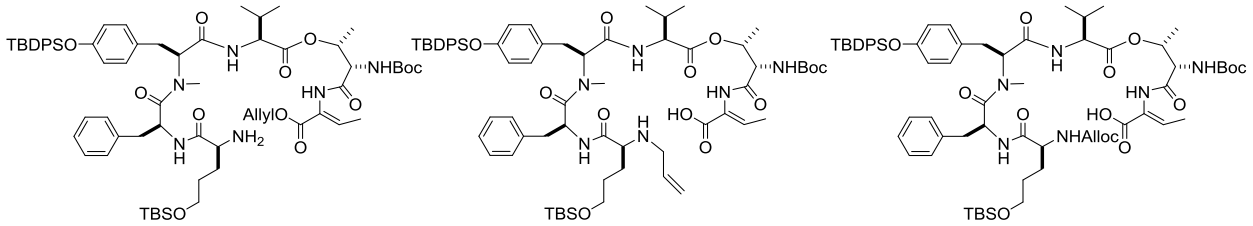



**Figure S1.** Proposed structures of the side products generated in the deprotection of the linear macrocyclization precursor **5**. When using morpholine, *N*-methylaniline, dimedone as allyl group scavengers, upon treating with $Pd(PPh_3)_4$ for 2 h we detected molecular ion peaks 1299.8 and 1233.8 as major peaks by ESI-LRMS (positive mode). Peak 1299.8 was considered as a side product of which the Alloc group was still attached ($[M+Na]^+$ 1276.7+23=1299.7). Peak 1233.8 was suspected as the compound with allyl group still attached or a decarboxylative rearrangement side product ($[M+H]^+$ 1232.7+1=1233.7).

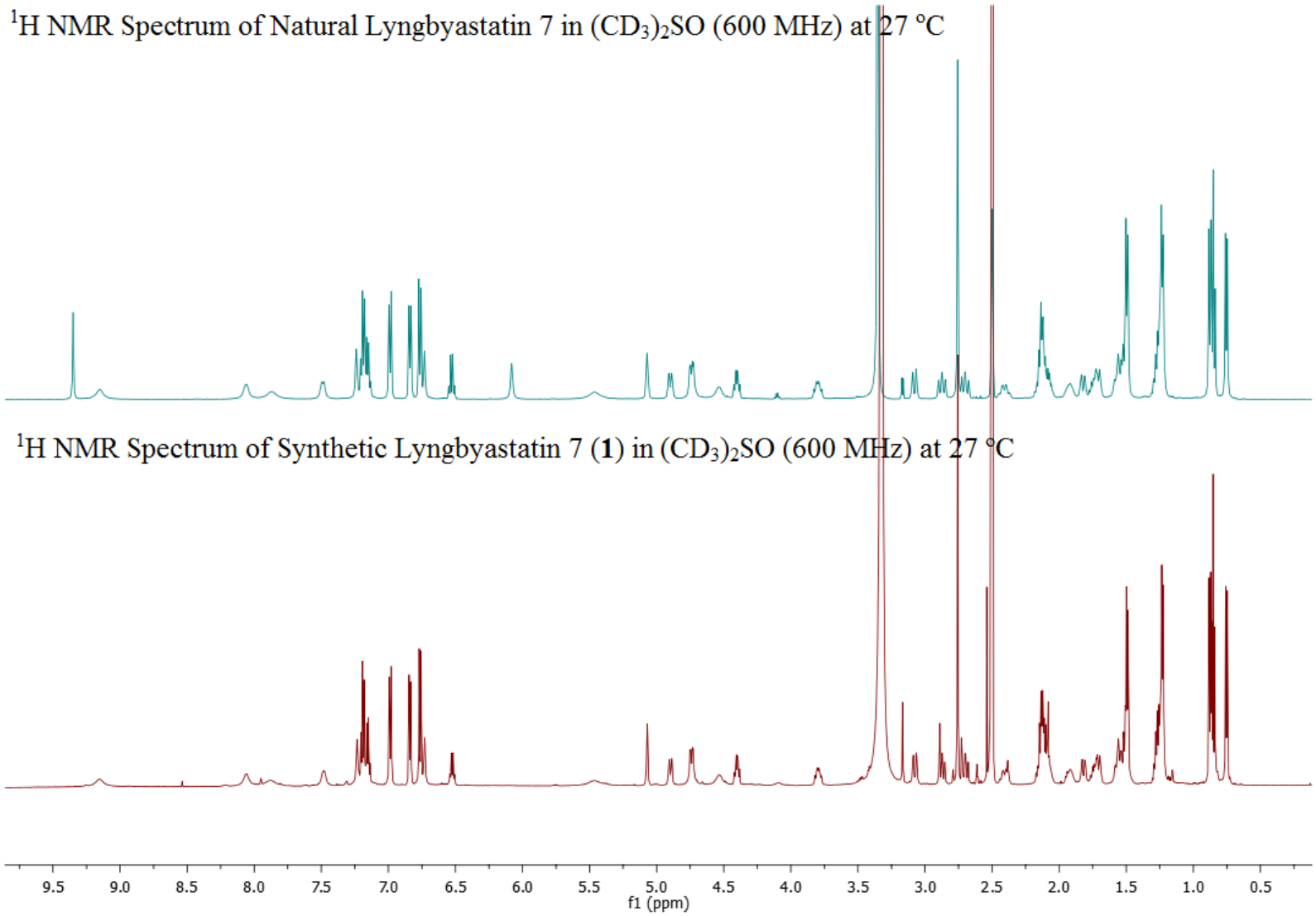



**Figure S2.** Comparison of $^1$H NMR spectrum of natural lyngbyastatin 7 and synthetic lyngbyastatin 7 (**1**).

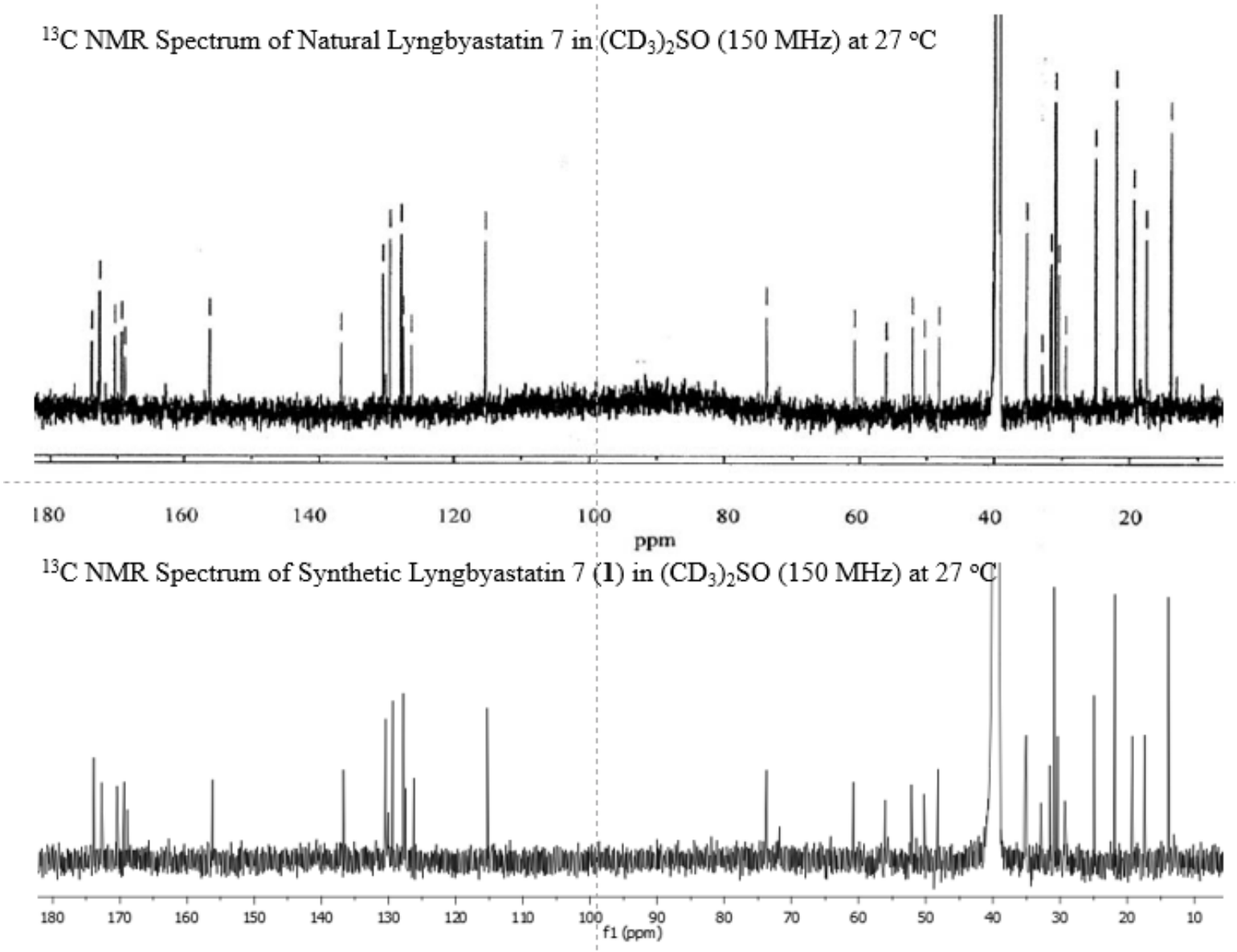



**Figure S3.** Comparison of $^{13}C$ NMR spectrum of natural lyngbyastatin 7 and synthetic lyngbyastatin 7 (**1**).

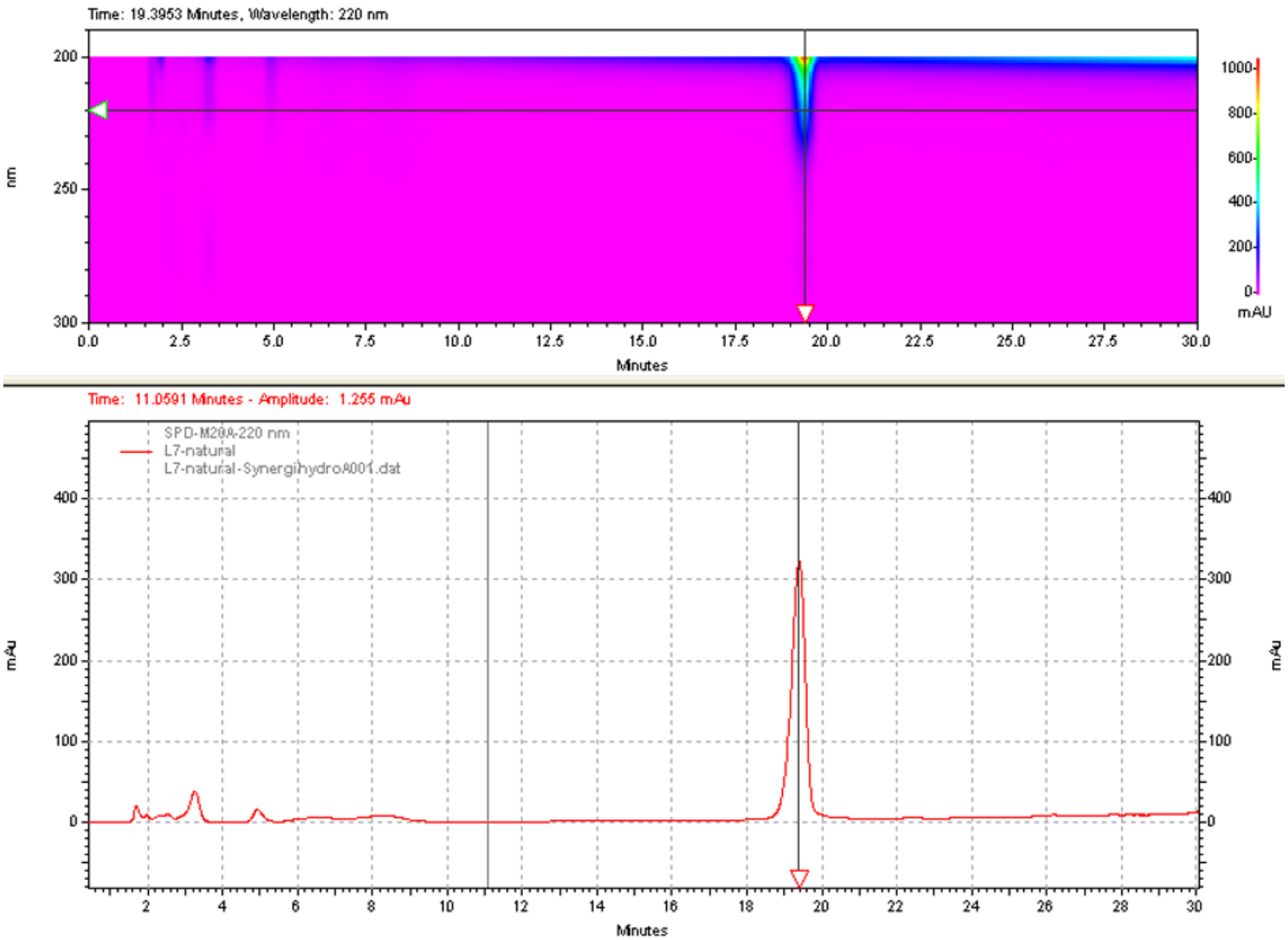



**Figure S4.** HPLC profile of natural lyngbyastatin 7 (column, Phenomenex Synergi 4 μ Hydro-RP 80 Å column 250 × 4.68 mm, 4 μm; flow rate, 1.0 mL/min; elution method, $H_2O$/MeOH=50/50–20/80 linear gradient (0.0–36.0 min), $H_2O$/MeOH=0/100 isocratic (36.0–46.0 min)). Retention time = 19.40 min.

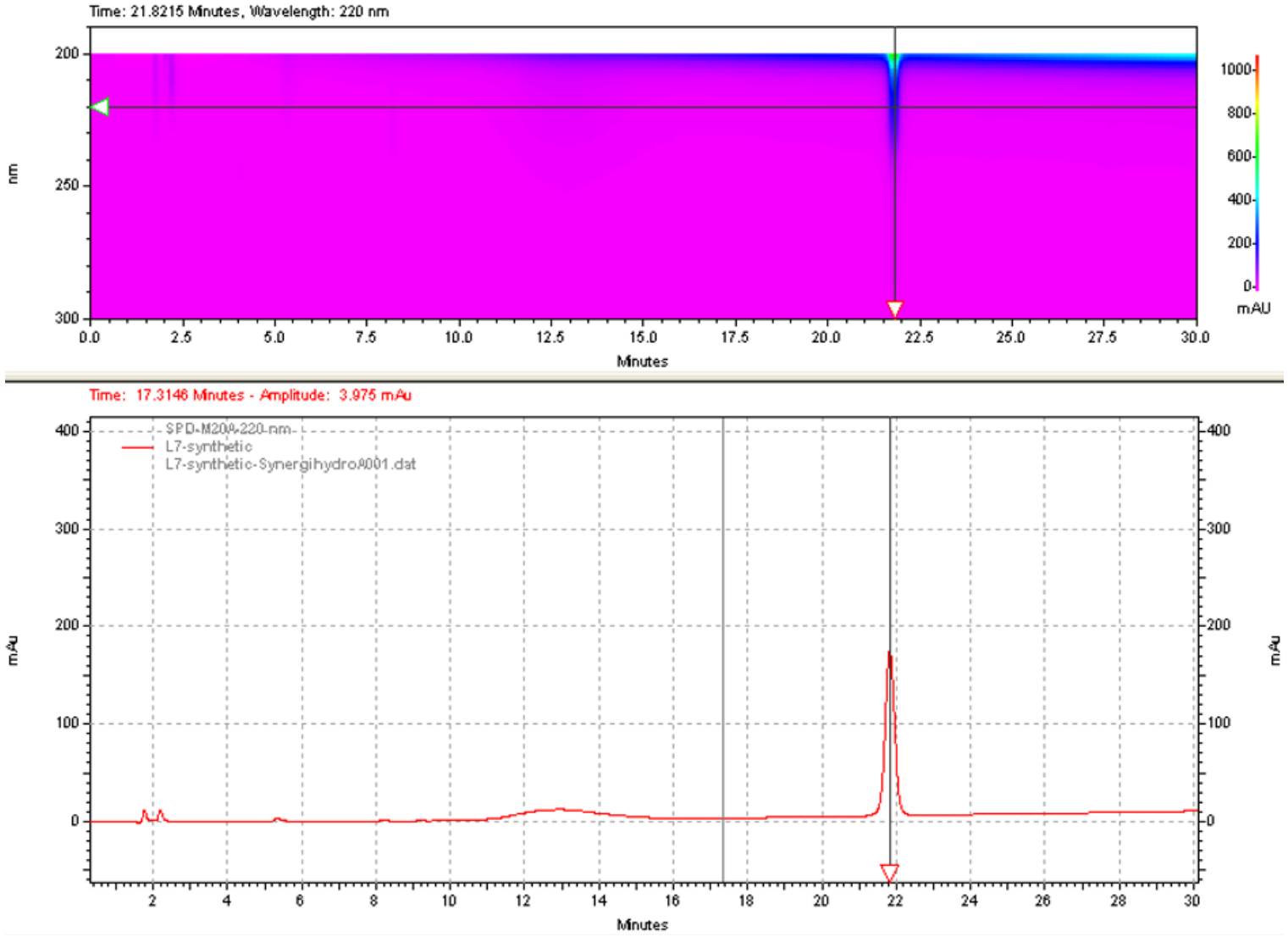



**Figure S5.** HPLC profile of synthetic lyngbyastatin 7 (**1**) (column, Phenomenex Synergi 4 μ Hydro-RP 80 Å column 250 × 4.68 mm, 4 μm; flow rate, 1.0 mL/min; elution method, $H_2O$/MeOH=50/50–20/80 linear gradient (0.0–36.0 min), $H_2O$/MeOH=0/100 isocratic (36.0–46.0 min)). Retention time = 21.82 min.

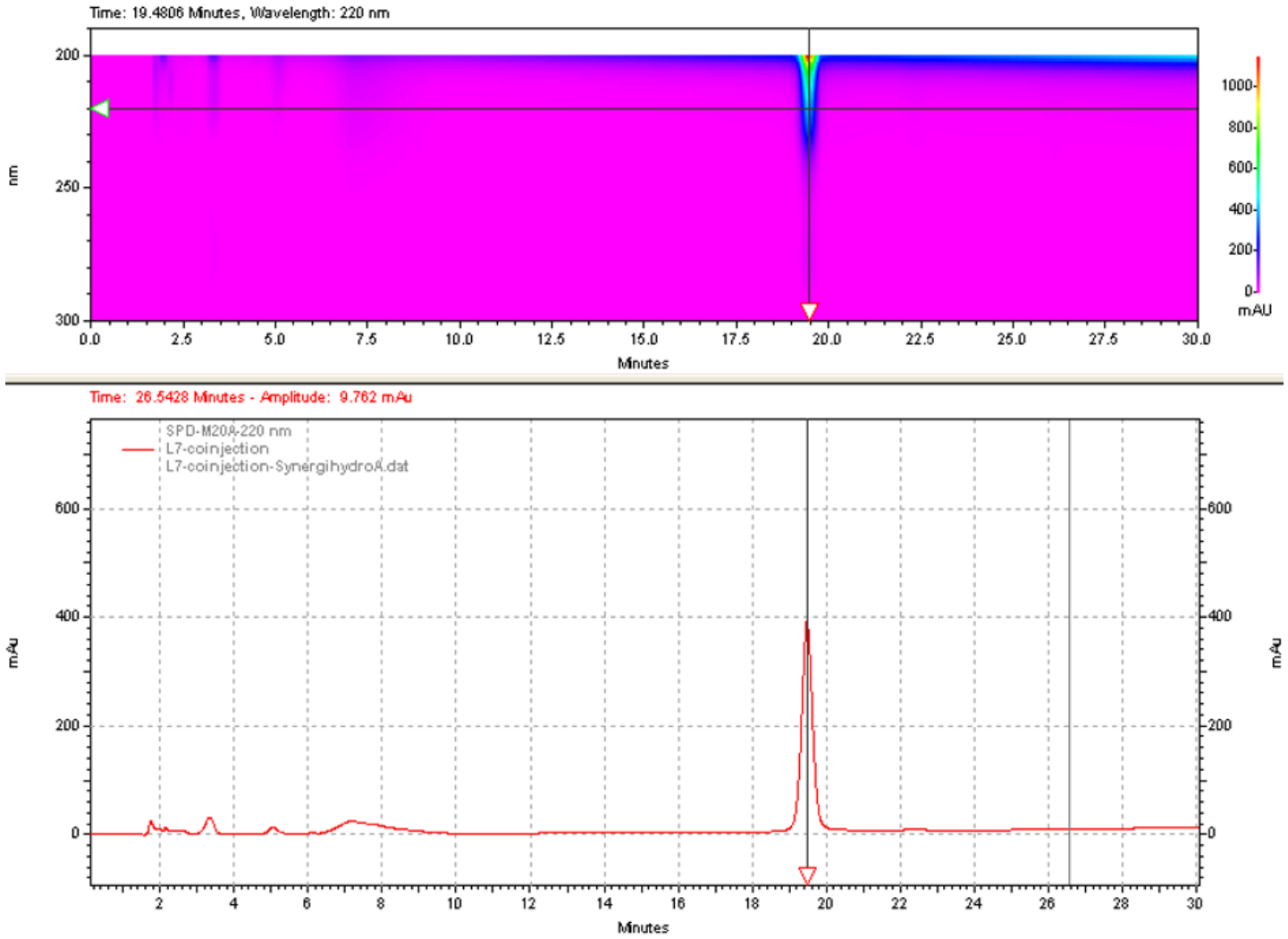



**Figure S6.** HPLC profile of coinjection of natural lyngbyastatin 7 and synthetic lyngbyastatin 7 (**1**) (column, Phenomenex Synergi 4 μ Hydro-RP 80 Å column 250 × 4.68 mm, 4 μm; flow rate, 1.0 mL/min; elution method, $H_2O$/MeOH=50/50–20/80 linear gradient (0.0–36.0 min), $H_2O$/MeOH=0/100 isocratic (36.0–46.0 min)). Retention time = 19.48 min.

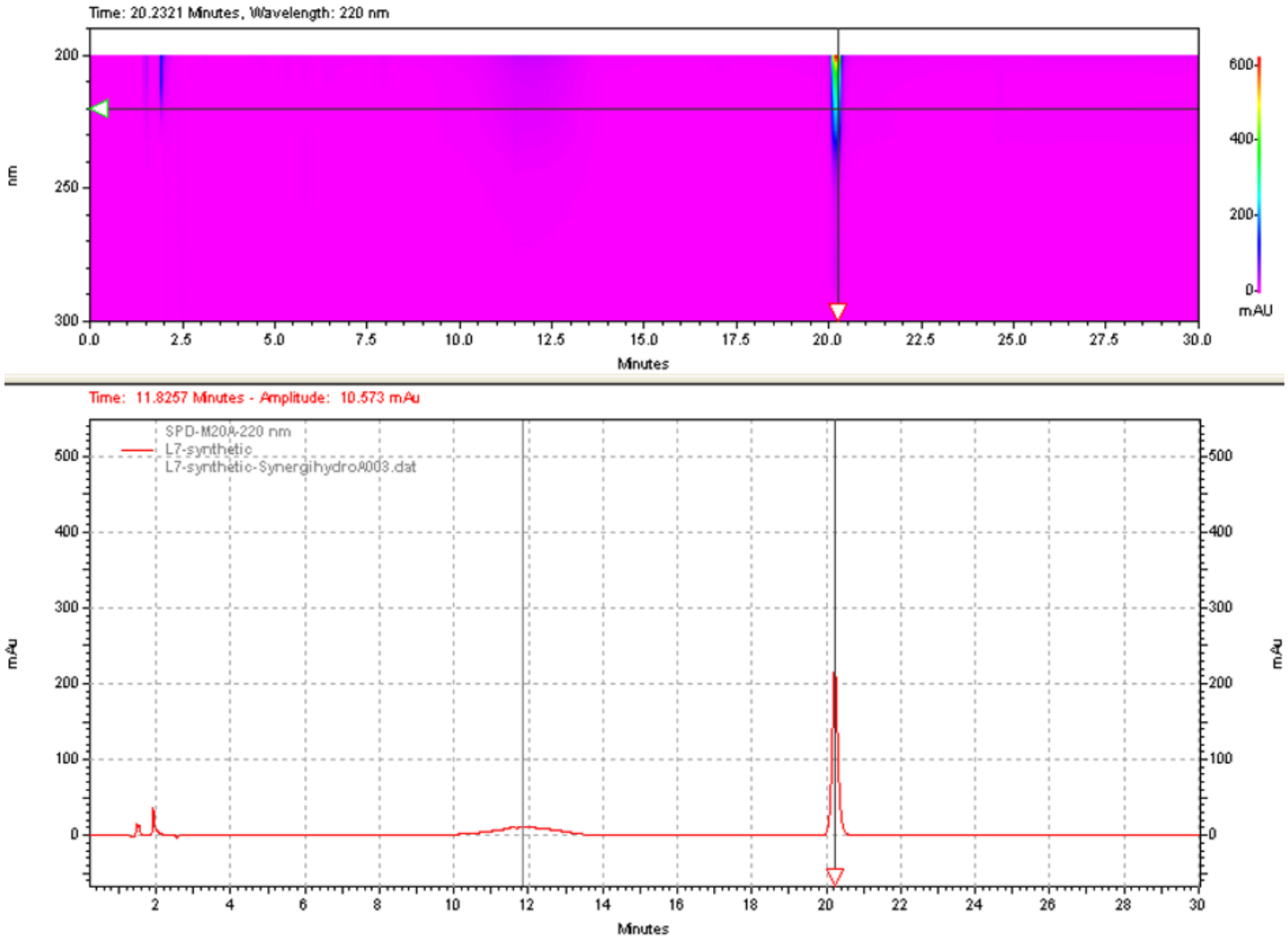
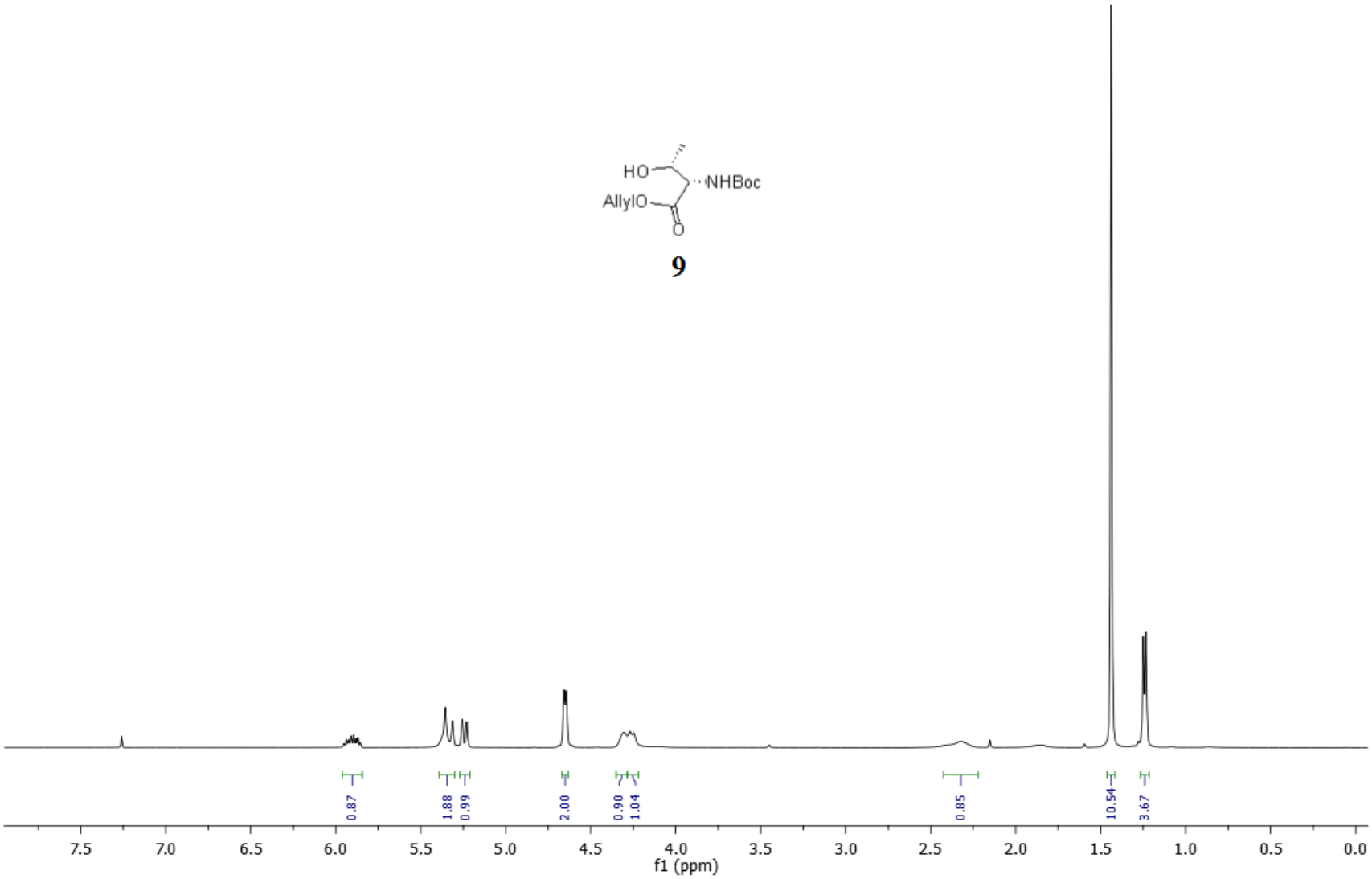


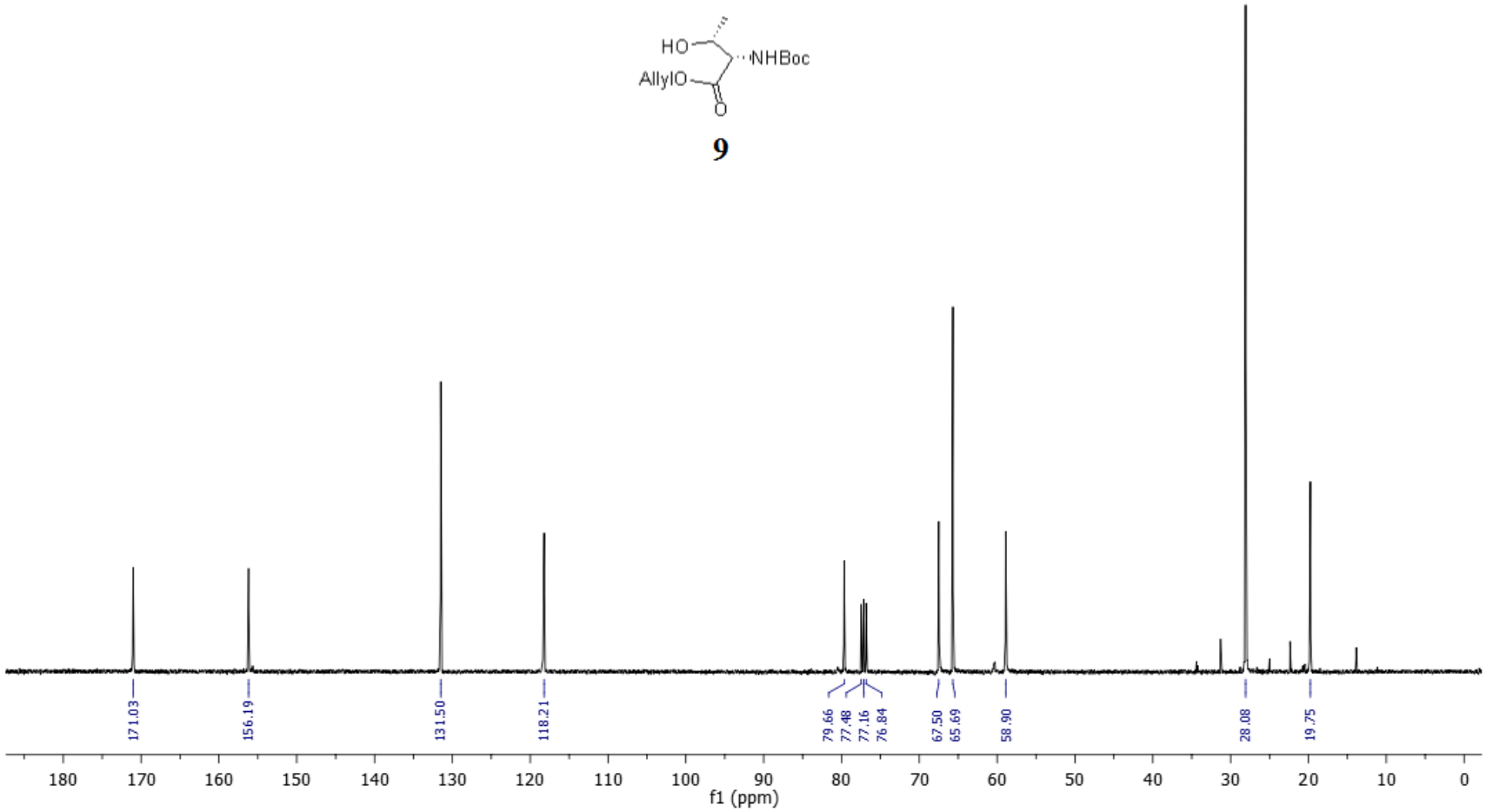

**Figure S7.** HPLC profile of synthetic lyngbyastatin 7 (**1**) (column, Phenomenex Synergi 4 μ Hydro-RP 80 Å column 250 × 4.68 mm, 4 μm; flow rate, 1.0 mL/min; elution method, $H_2O$/MeCN=80/20–50/50 linear gradient (0.0–30.0 min), $H_2O$/MeCN=50/50–0/100 linear gradient (30.0–45.0 min), $H_2O$/MeCN =0/100 isocratic (45.0–55.0 min)). Retention time = 20.21 min.

$^{1}$H NMR Spectrum of **9** in $CDCl_3$ (400 MHz) at 25 °C




**9**

$^{13}C$ NMR Spectrum of **9** in $CDCl_3$ (100 MHz) at 25 °C

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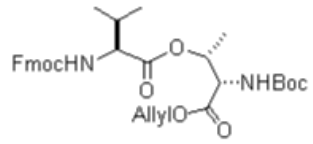
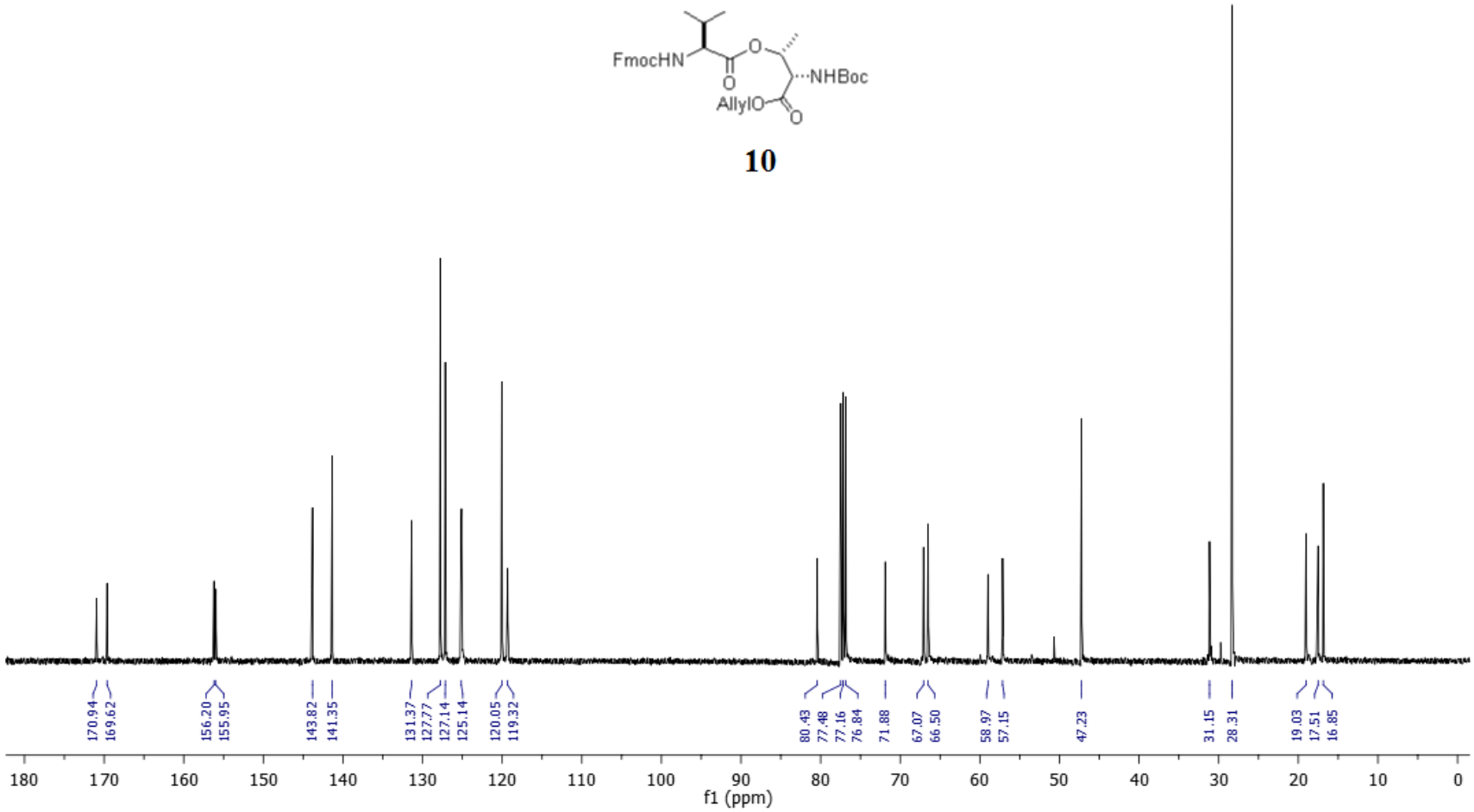
$^{1}$H NMR Spectrum of **10** in $CDCl_3$ (400 MHz) at 25 °C




**10**

$^{13}C$ NMR Spectrum of **10** in $CDCl_3$ (100 MHz) at 25 °C

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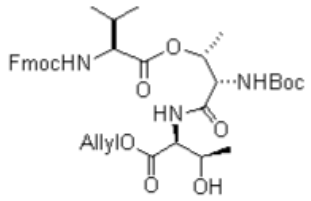
$^{1}$H NMR Spectrum of **11** in $CDCl_3$ (400 MHz) at 25 °C

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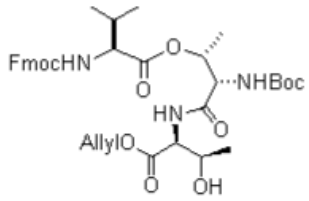
$^{13}$C NMR Spectrum of **11** in $CDCl_3$ (100 MHz) at 25 °C

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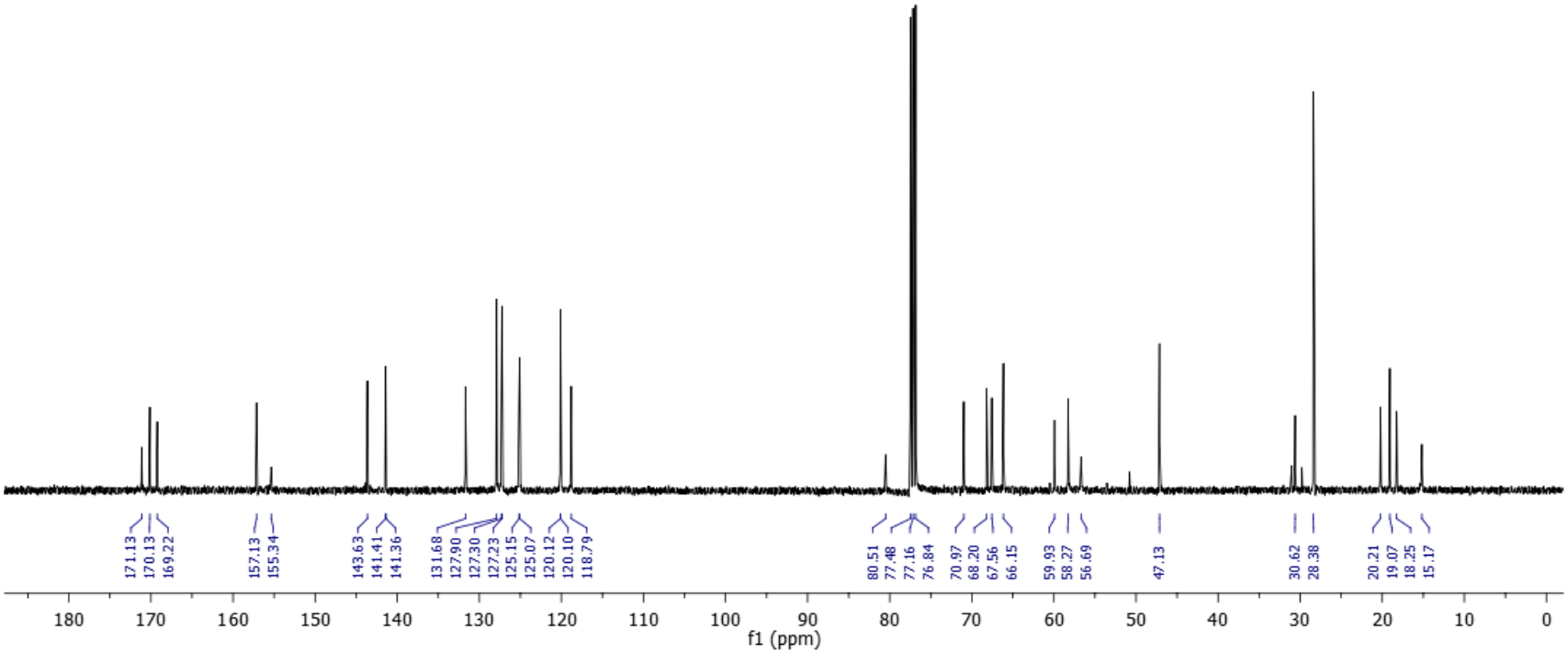
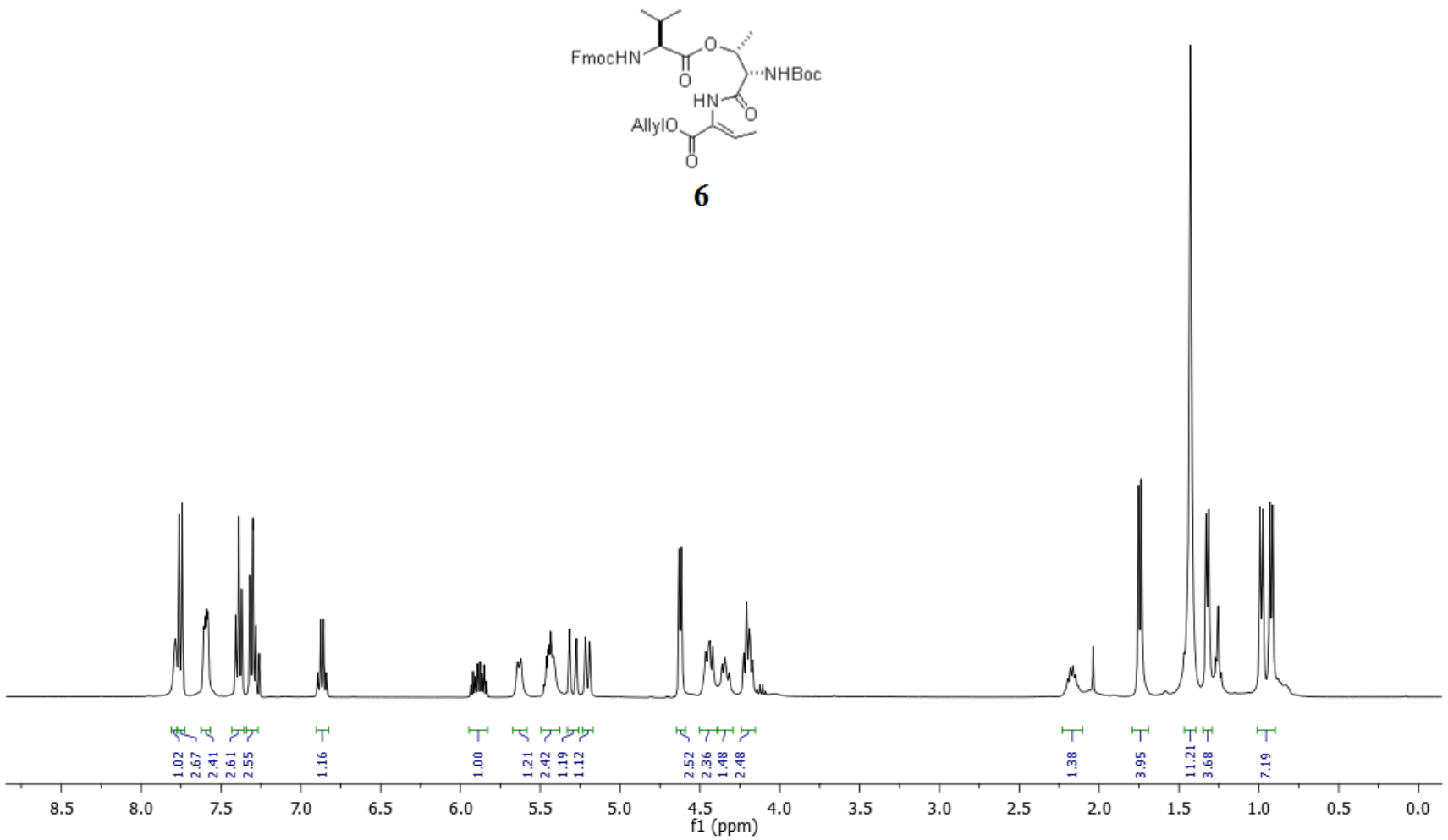
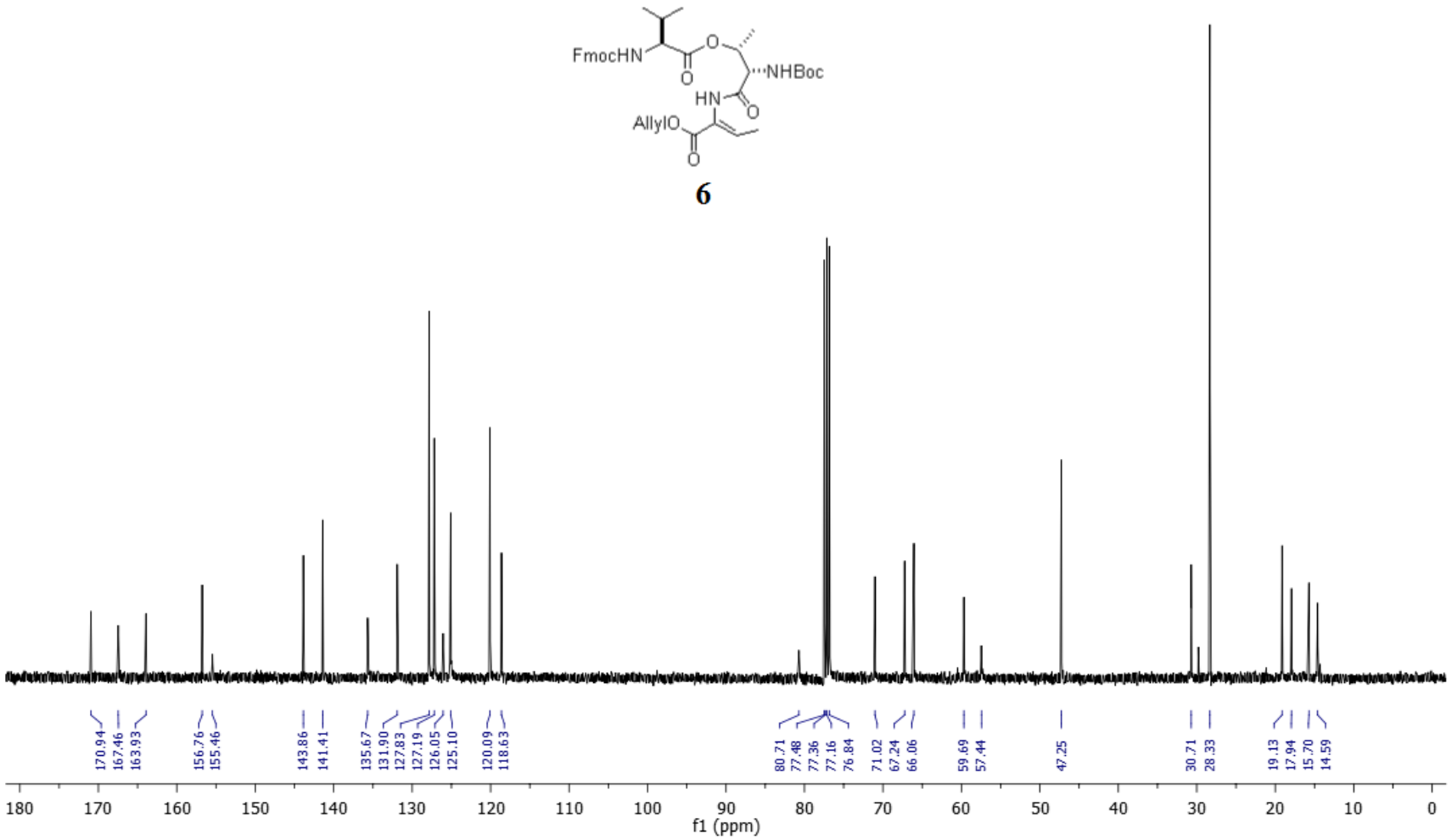


$^{1}$H NMR Spectrum of **6** in $CDCl_3$ (400 MHz) at 25 °C




**6**

$^{13}$C NMR Spectrum of **6** in $CDCl_3$ (100 MHz) at 25 °C

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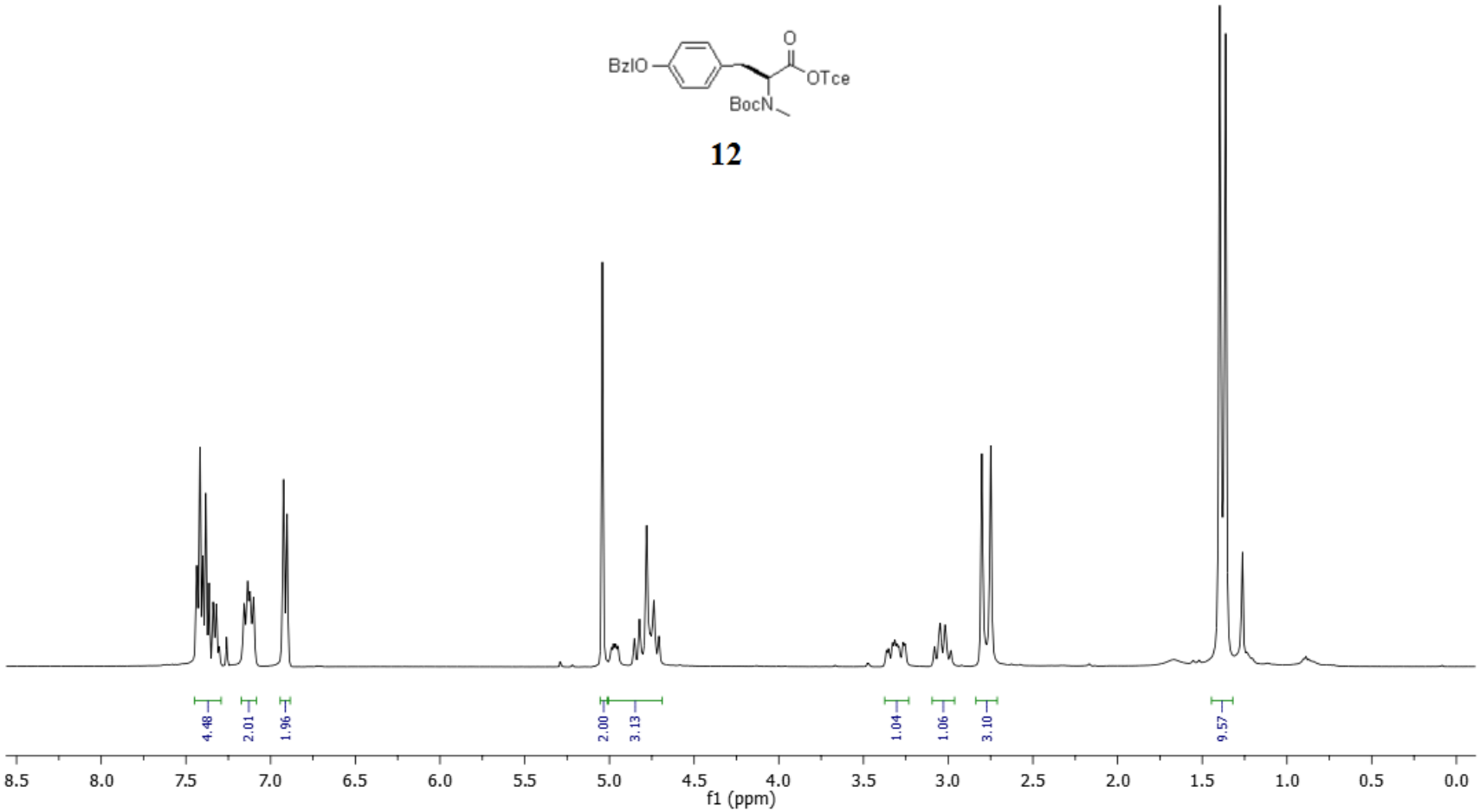
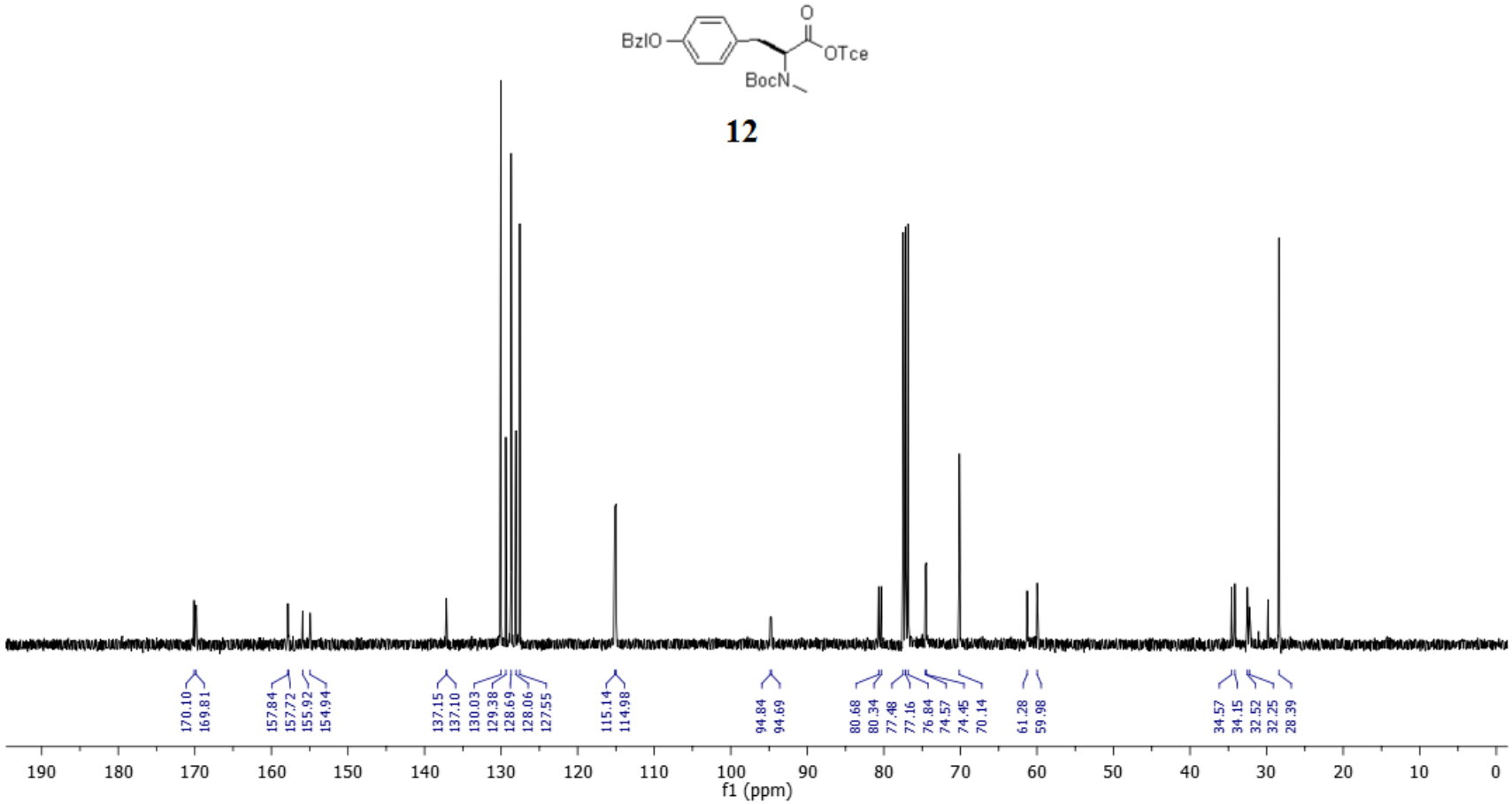
$^{1}$H NMR Spectrum of **12** in $CDCl_3$ (400 MHz) at 25 °C




**12**

$^{13}$C NMR Spectrum of **12** in $CDCl_3$ (100 MHz) at 25 °C

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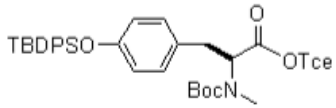
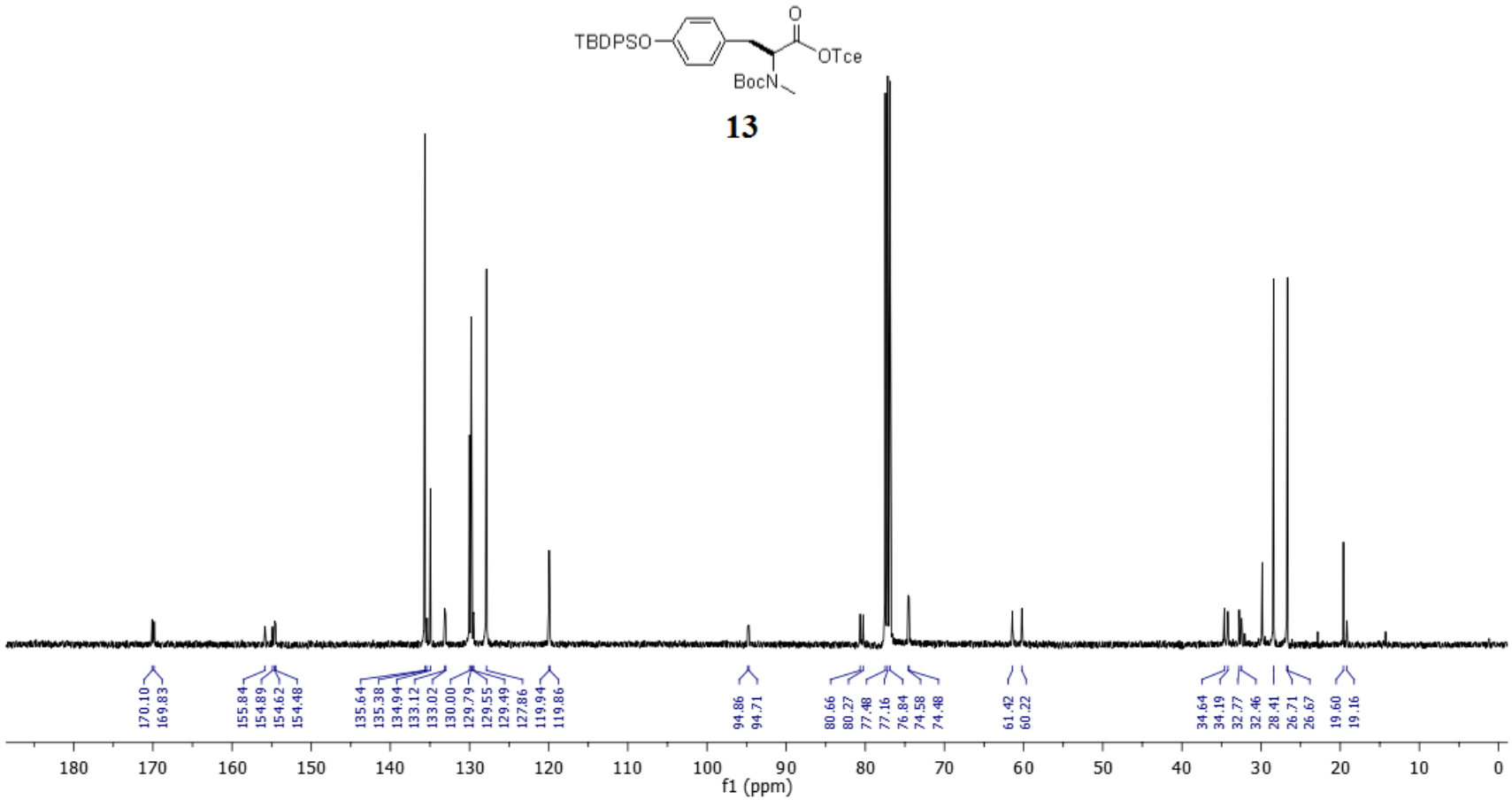
$^{1}$H NMR Spectrum of **13** in $CDCl_3$ (400 MHz) at 25 °C

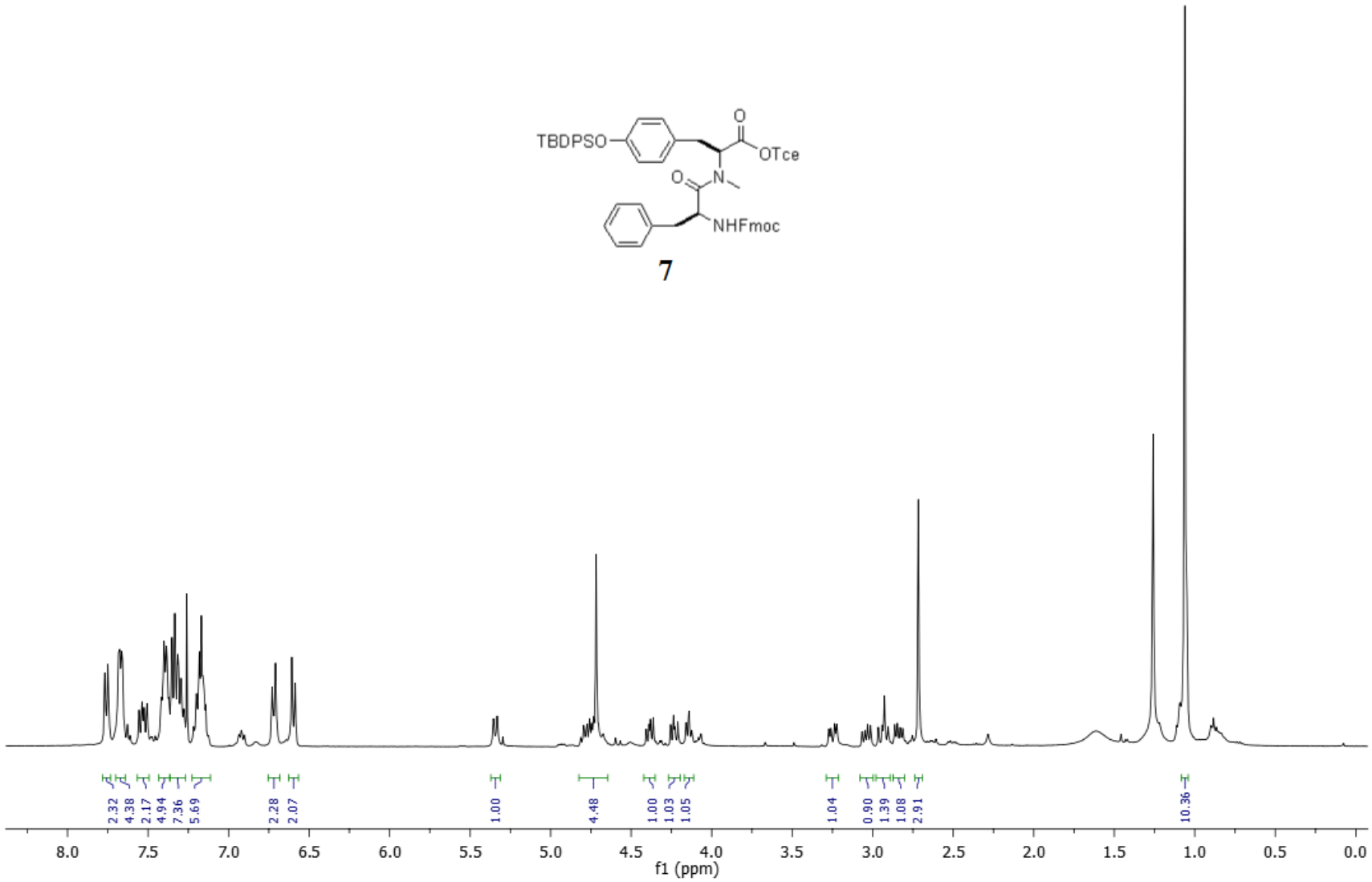



**13**

$^{13}C$ NMR Spectrum of **13** in $CDCl_3$ (100 MHz) at 25 °C

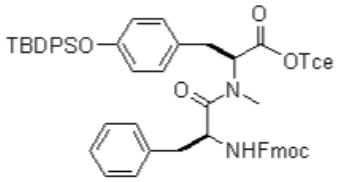


$^{1}$H NMR Spectrum of **7** in $CDCl_3$ (400 MHz) at 25 °C




**7**

$^{13}$C NMR Spectrum of **7** in $CDCl_3$ (100 MHz) at 25 °C

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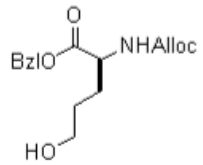
$^{1}$H NMR Spectrum of **14** in $CDCl_3$ (400 MHz) at 25 °C

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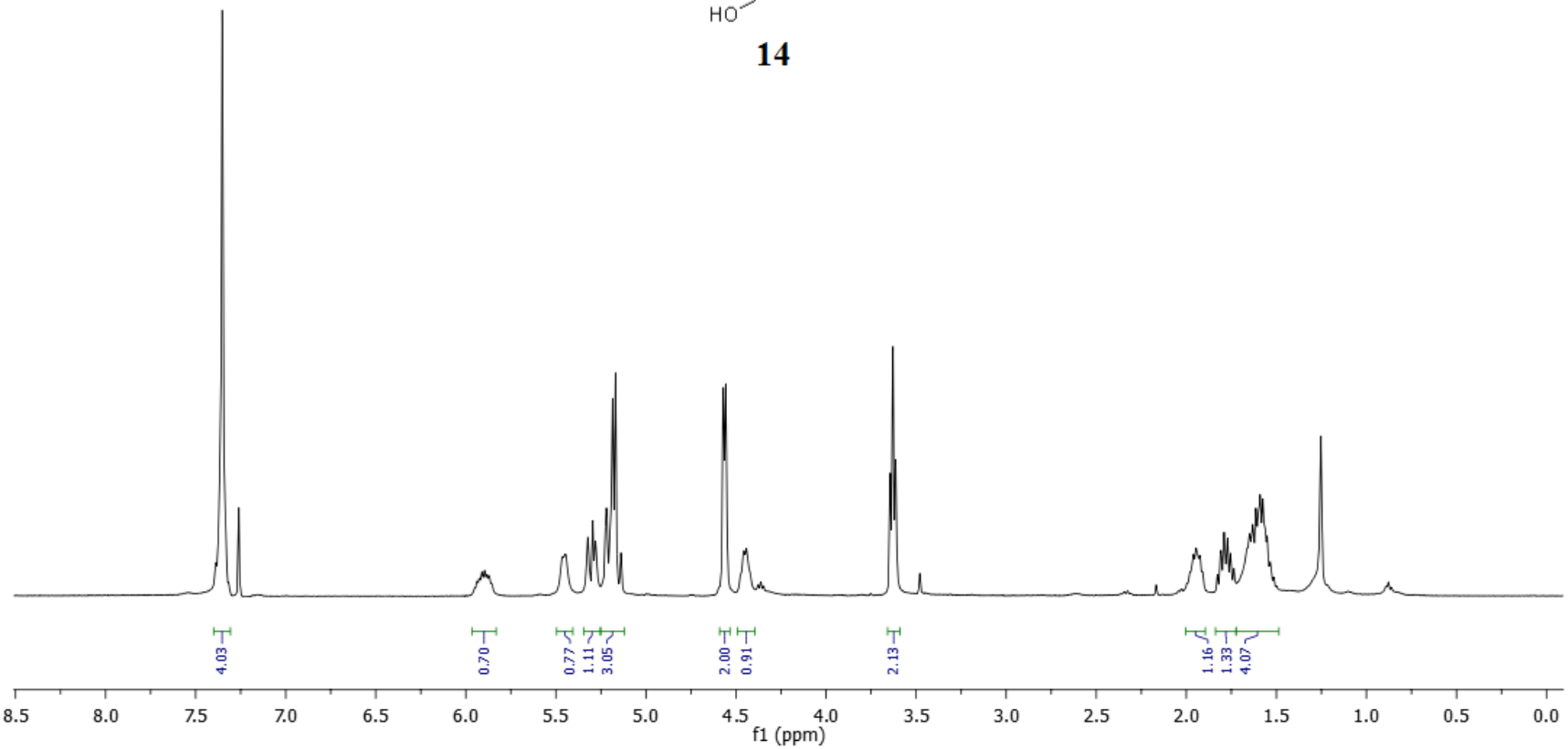
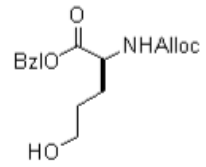


$^{13}C$ NMR Spectrum of **14** in $CDCl_3$ (100 MHz) at 25 °C

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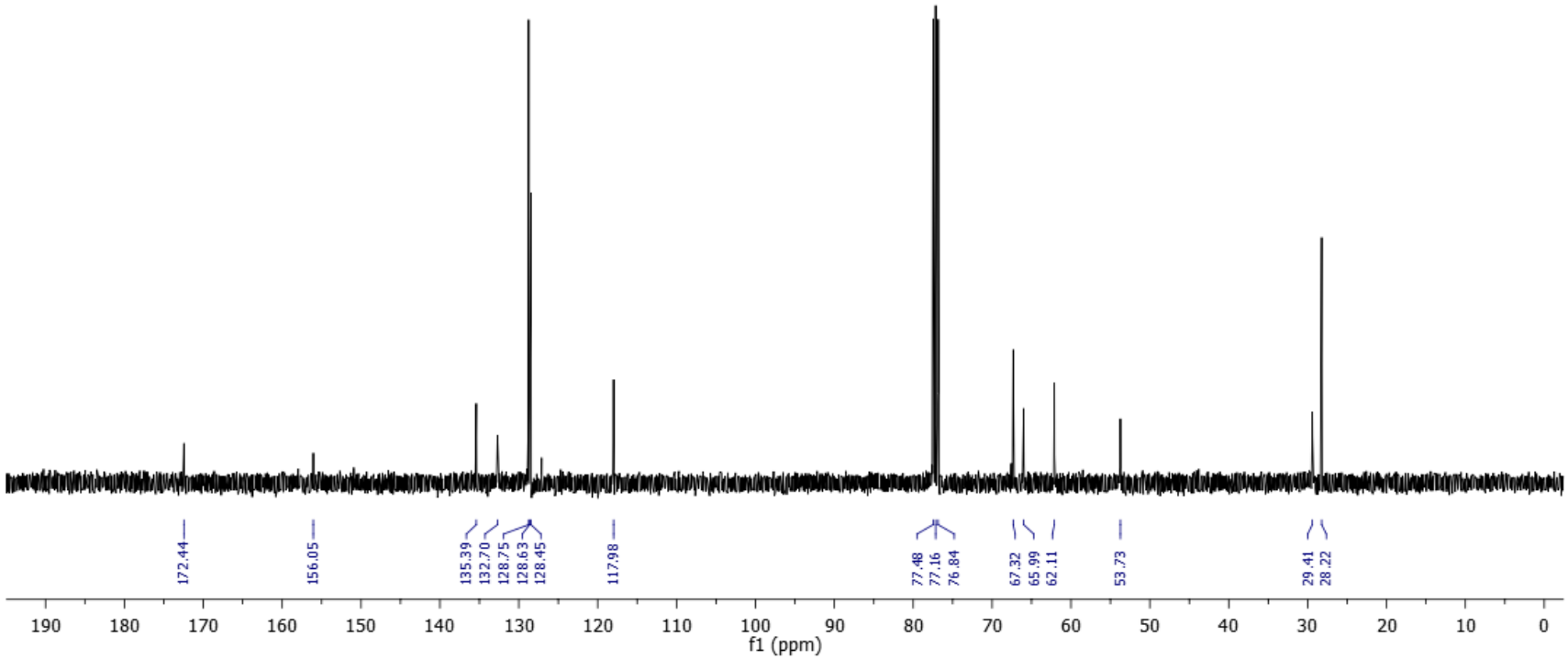
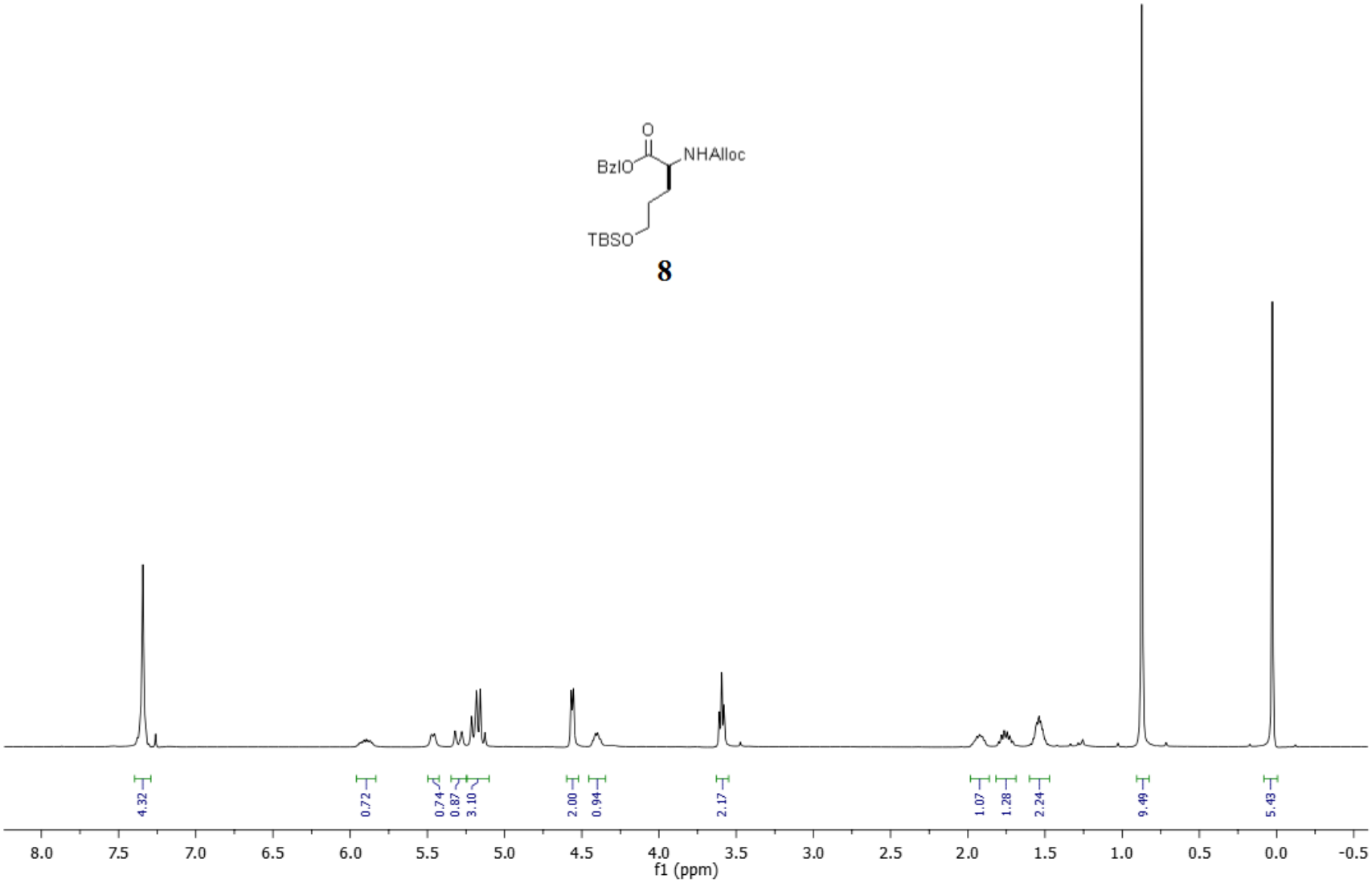
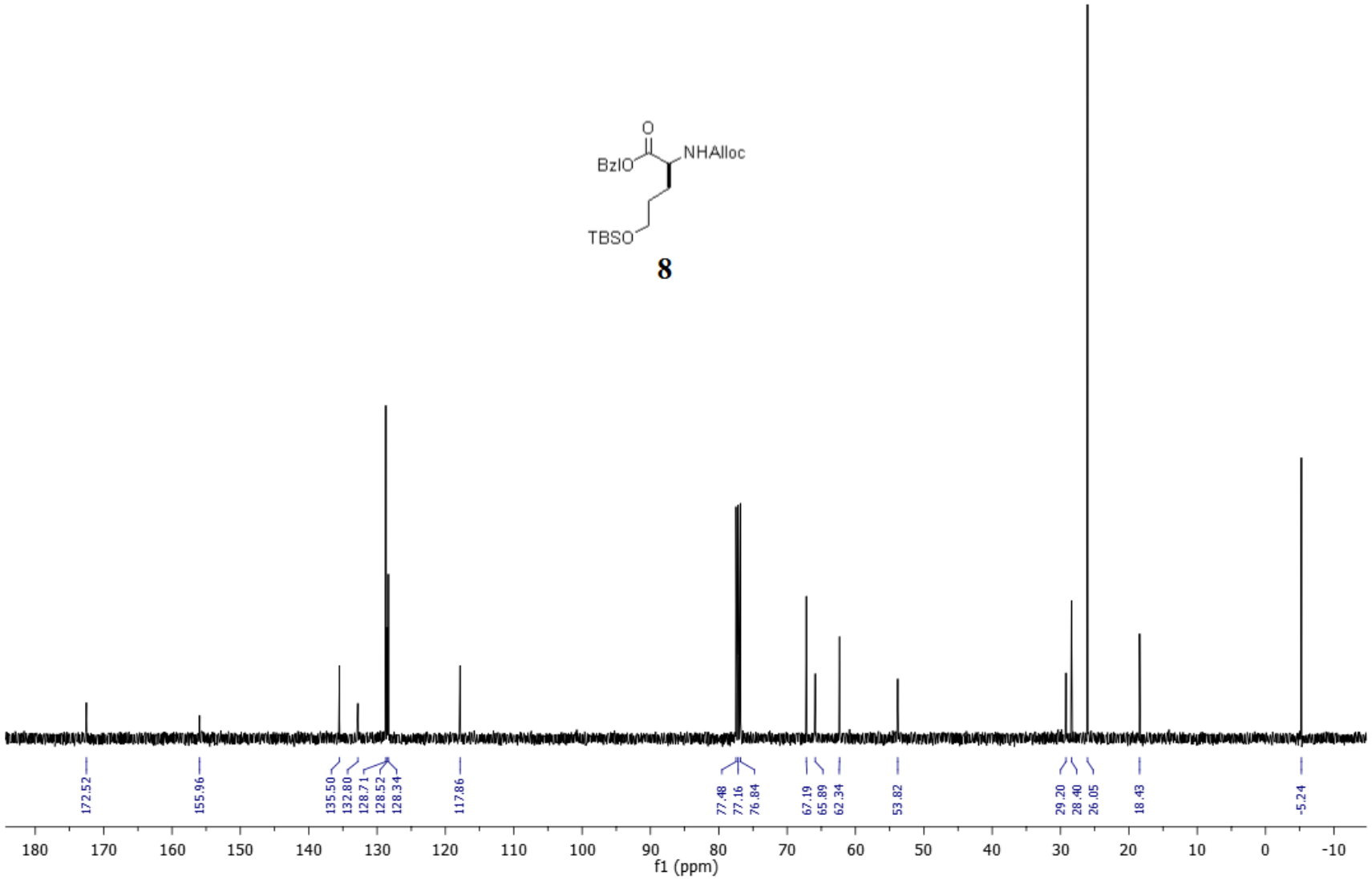


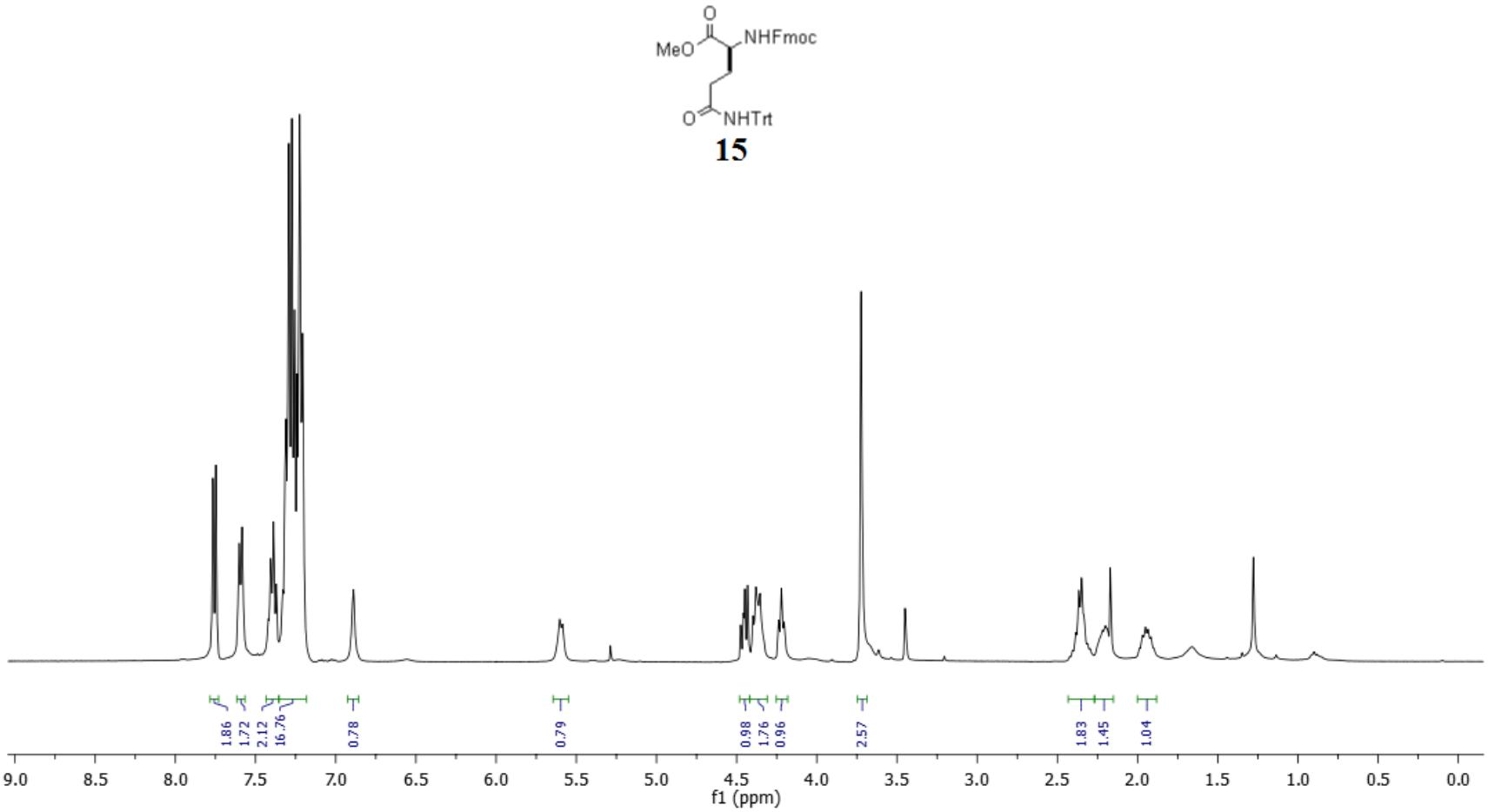
$^{1}$H NMR Spectrum of **8** in $CDCl_3$ (400 MHz) at 25 °C



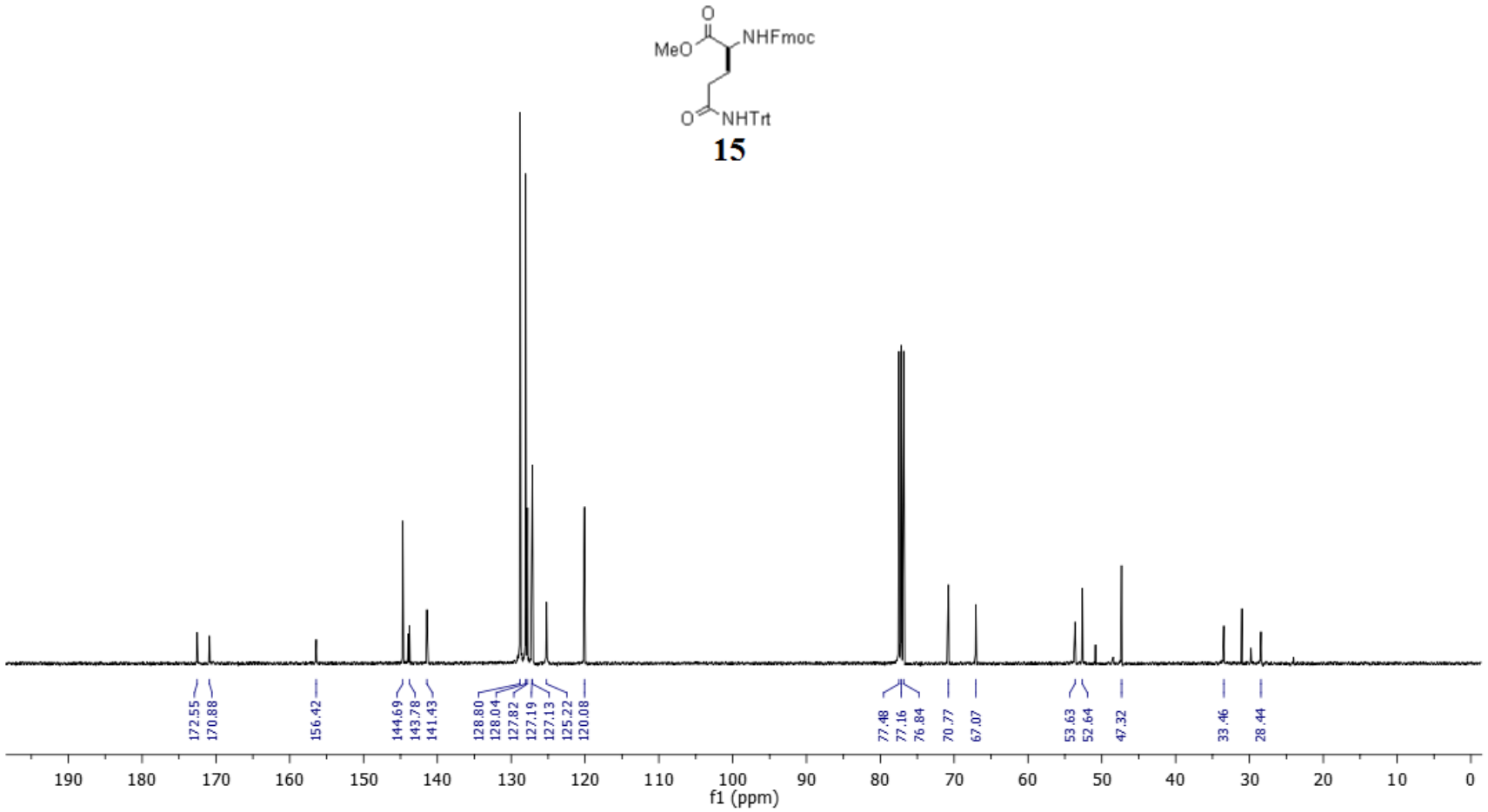
$^{13}C$ NMR Spectrum of **8** in $CDCl_3$ (100 MHz) at 25 °C



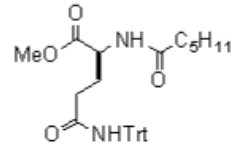
$^{1}$H NMR Spectrum of **15** in $CDCl_3$ (400 MHz) at 25 °C



$^{13}C$ NMR Spectrum of **15** in $CDCl_3$ (100 MHz) at 25 °C

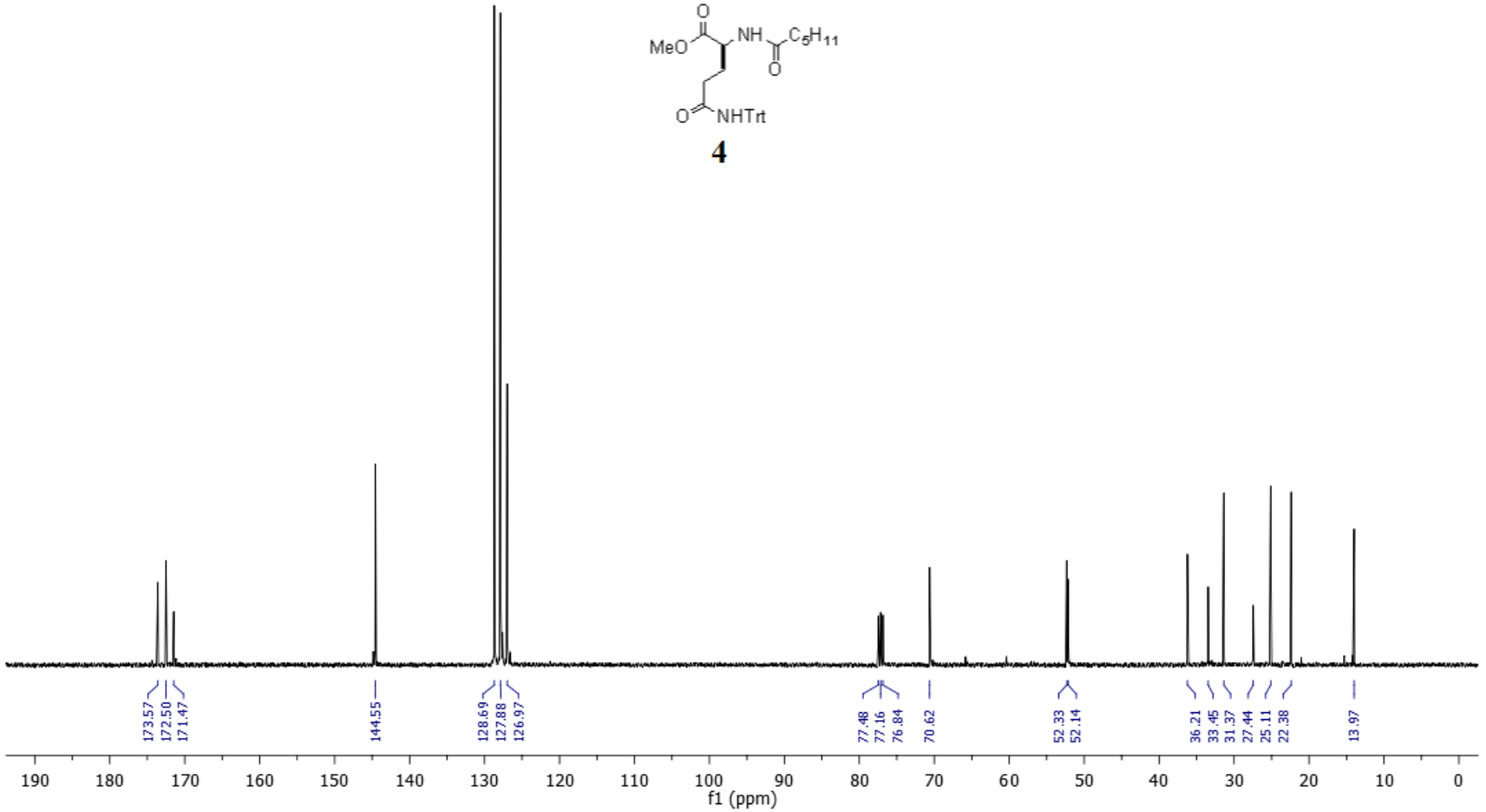


$^{1}$H NMR Spectrum of **4** in $(CD_3)_2SO$ (400 MHz) at 25 °C

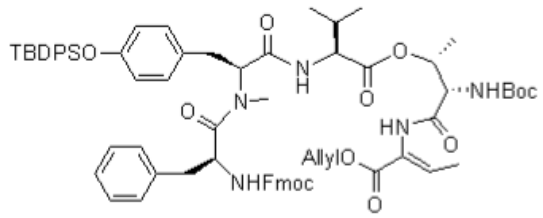



**4**

$^{13}C$ NMR Spectrum of **4** in $CDCl_3$ (100 MHz) at 25 °C

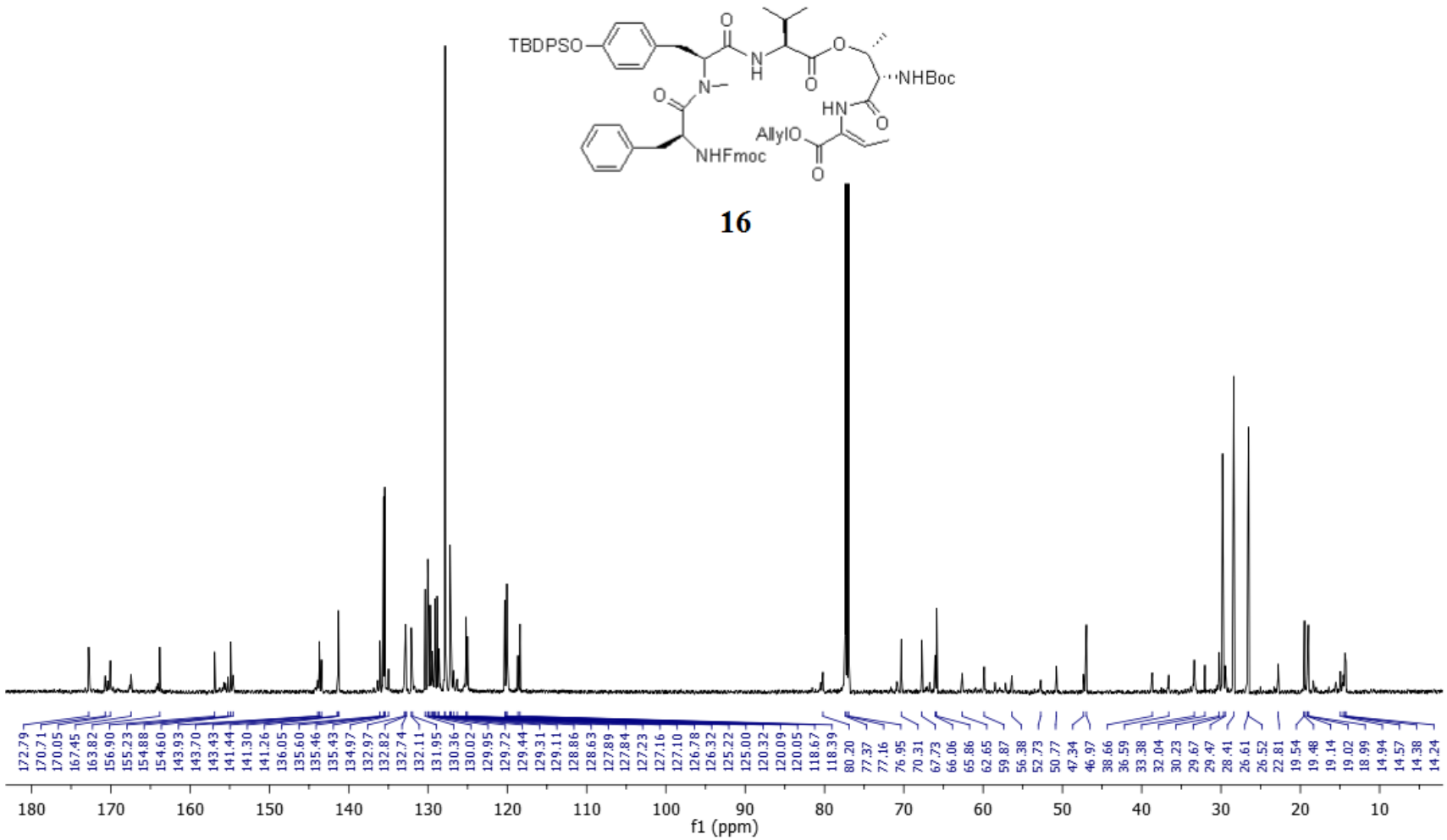


$^{1}$H NMR Spectrum of **16** in $CDCl_3$ (600 MHz) at 27 °C



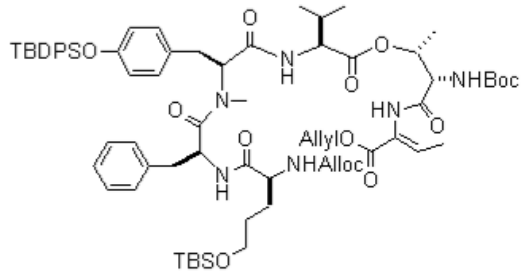

**16**

$^{13}$C NMR Spectrum of **16** in $CDCl_3$ (150 MHz) at 27 °C



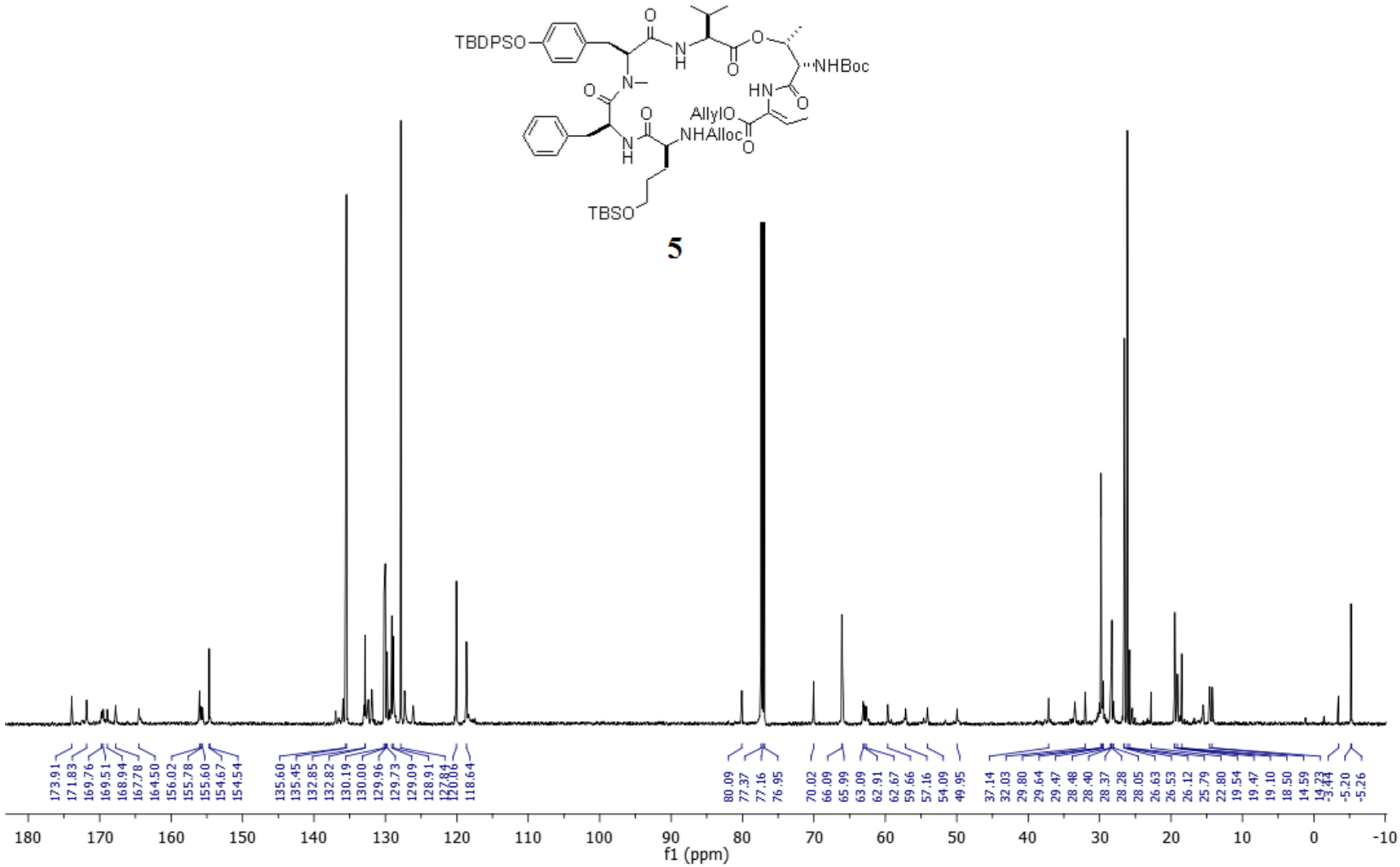

**16**

$^{1}$H NMR Spectrum of **5** in $CDCl_3$ (600 MHz) at 25 °C

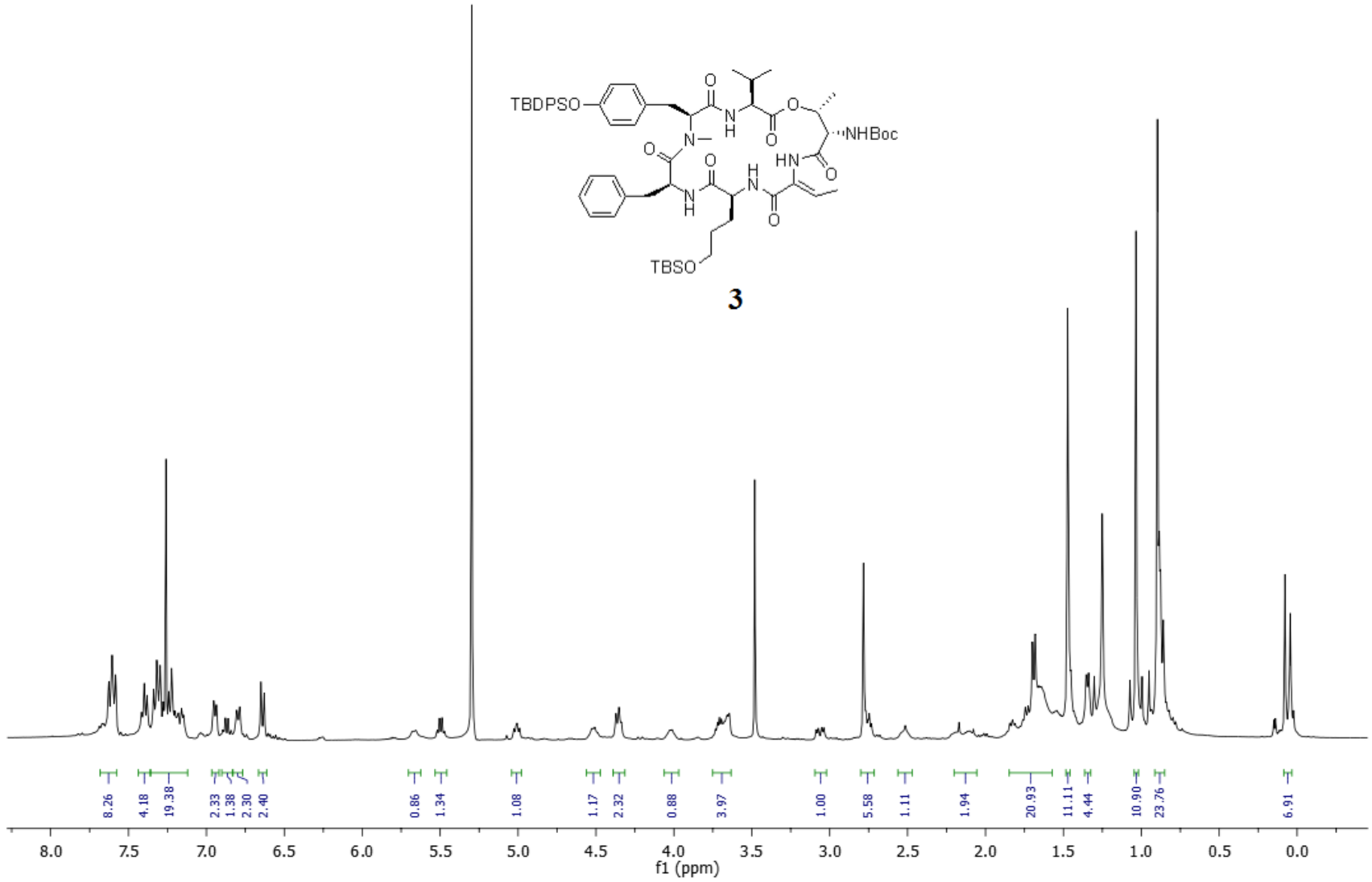



**5**

$^{13}C$ NMR Spectrum of **5** in $CDCl_3$ (150 MHz) at 27 °C

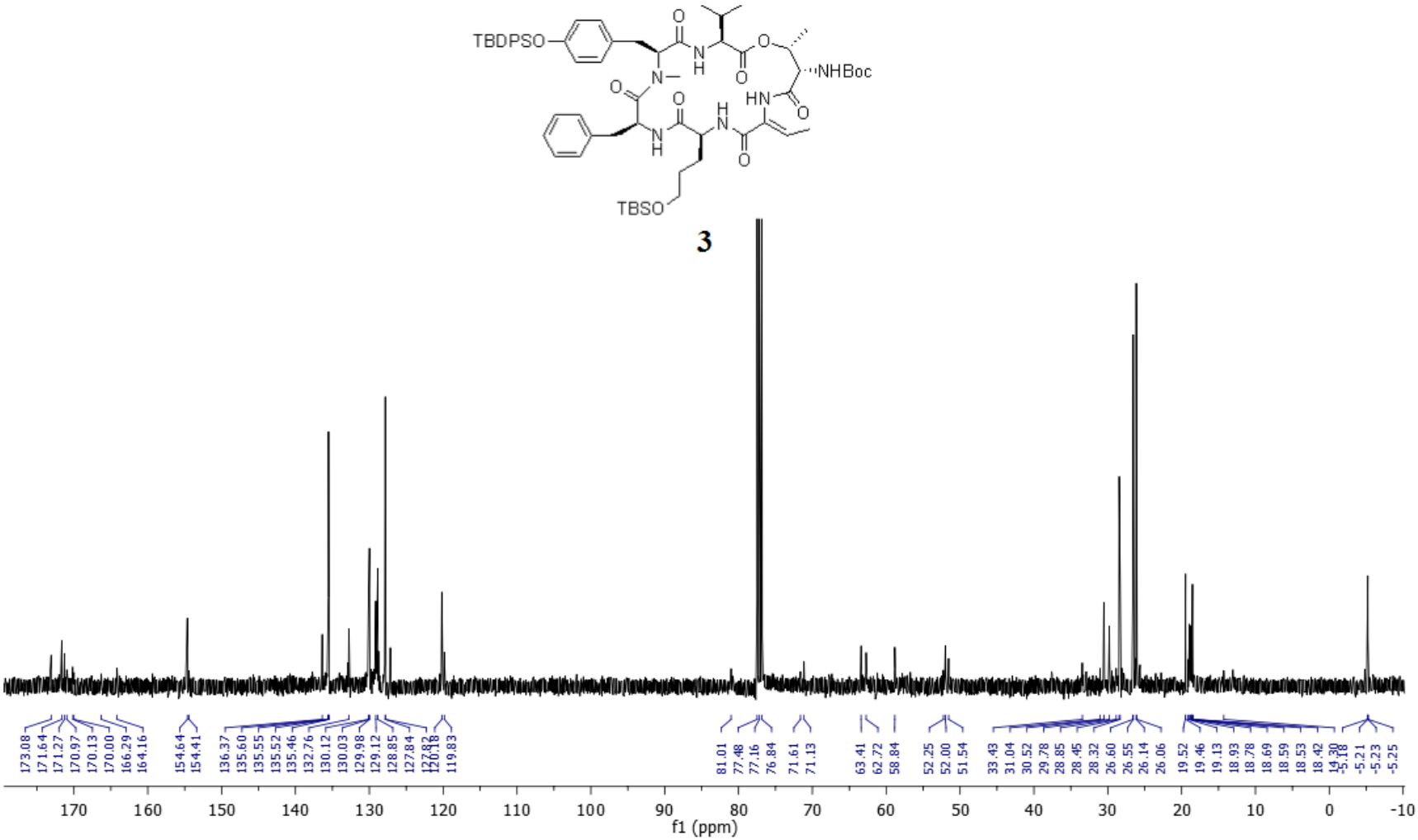


$^{1}$H NMR Spectrum of **3** in $CDCl_3$ (400 MHz) at 25 °C

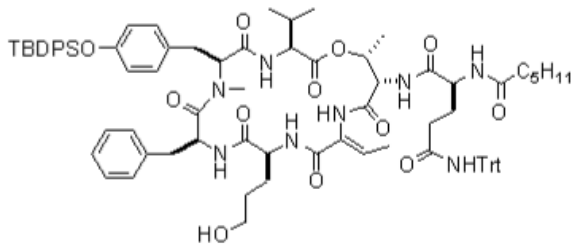



**3**

$^{13}$C NMR Spectrum of **3** in $CDCl_3$ (100 MHz) at 25 °C

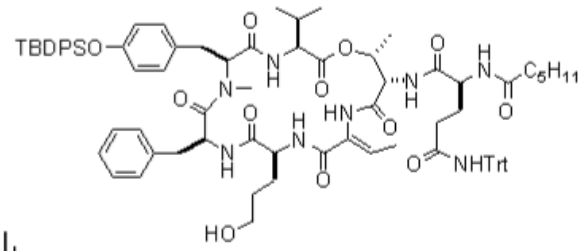


$^{1}$H NMR Spectrum of **17** in $(CD_3)_2SO$ (600 MHz) at 27 °C



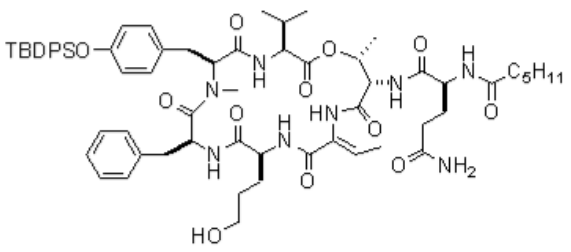

**17**

$^{13}$C NMR Spectrum of **17** in $(CD_3)2SO$ (150 MHz) at 25 °C



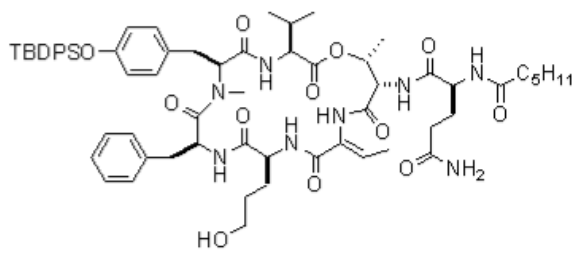

**17**

$^{1}$H NMR Spectrum of **2** in $(CD_3)2SO$ (600 MHz) at 25 °C



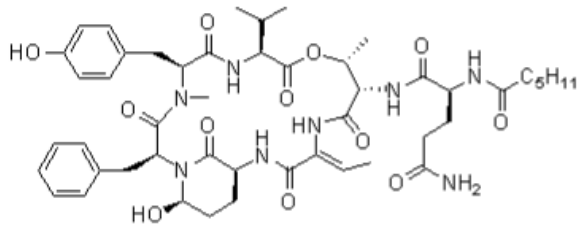

**2**

$^{13}$C NMR Spectrum of **2** in $(CD_3)2SO$ (150 MHz) at 25 °C



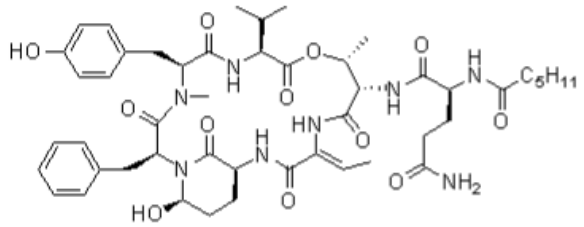

**2**

$^{1}$H NMR Spectrum of Lyngbyastatin 7 (**1**) in $(CD_3)_2SO$ (600 MHz) at 27 °C



**1**

$^{13}$C NMR Spectrum of Lyngbyastatin 7 (**1**) in $(CD_3)_2SO$ (150 MHz) at 27 °C



**1**