Total synthesis and biological evaluation of apratoxin E and its C30 epimer: configurational reassignment of the natural product

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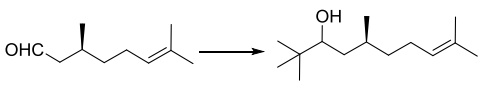
1. General

All reactions were carried out in oven- or flame-dried glassware. All commercial reagents were used without further purification unless otherwise noted. Anhydrous CH_2Cl_2 (DCM), THF, Et_2O, DMF, CH_3CN, toluene and methanol were obtained by Solvent Purification System (PS-MD-5, Innovation Technology, USA). Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254) with UV light, visualized phosphomolybdic acid/ethanol solution. Flash column chromatography was performed with silica gel (200-300 meshes) with the indicated solvent system and preparative thin layer chromatography was performed on silica gel F254 glass plates (layer thick 400 - 500 mm). Yields refer to chromatographically and spectroscopically pure compounds. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz, Bruker Avance II 600, Bruker Avance III 600 MHz, or Agilent VNMR 600 MHz spectrometer as indicated in the data list. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal residual $CDCl_3$ at 7.26 ppm, CD_3CN at 1.94 ppm and benzene-d_6 at 7.16 ppm. Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.0 ppm. The abbreviations s, d, dd, ddd, dddd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, doublet of doublet of doublets, doublet of doublet of doublet of doublets, triplet, quartet, broad and multiplet, respectively. Optical rotation was measured on an AUTOPOL V (Na D line) or Perkin-Elmer 341 polarimeter using a microcell of 1 dm path length. High resolution mass spectra (HRMS) were obtained using a Q TOF mass spectrometer or Agilent LC-TOF mass spectrometer equipped with an APCI/ESI multimode ion source detector.

2. Experimental Procedures

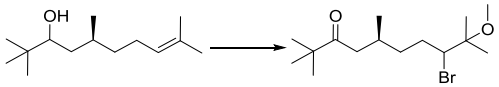
(5*S*)-2,2,5,9-Tetramethyldec-8-en-3-ol (7)



(-)-Citronellal **7**

To a solution of (-)-citronellal (5.00 g, 32.4 mmol) in anhydrous THF (100 mL) at -78 °C was added *t*-BuLi (30.0 mL, 39.0 mmol, 1.3 M in THF) drop-wise under nitrogen. The mixture was stirred at the same temperature for 2 h and quenched with saturated NH_4Cl. After concentrated under reduced pressure to remove the solvent, the residue was diluted with ethyl acetate (200 mL), washed with saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/100) to afford 6.53 g of **7** as colorless oil, yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 5.13–5.09 (m, 1H), 3.30 (d, J = 10.4 Hz， 1H), 2.09–1.86 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.55-1.00 (m, 5H), 0.97-0.86 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of diastereromers) δ 131.29, 131.25, 125.04, 124.99, 77.8, 77.4, 50.9, 39.4, 39.0, 38.6, 35.8, 35.0, 34.9, 31.0, 29.9, 29.4, 25.85, 25.81, 25.78, 25.5, 21.1, 19.0, 17.8.

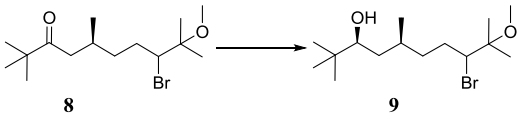
(5*S*)-8-Bromo-9-methoxy-2,2,5,9-tetramethyldecan-3-one (8)



7 8

To a solution of compound **7** (5.00 g, 23.5 mmol) in methanol (90 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (DDH, 13.50 g, 47.2 mmol) and stirred overnight at room temperature. Then the reaction mixture was quenched with 10% $NaHSO_3$. After concentrated under reduced pressure to remove the solvent, the residue was diluted with ethyl acetate (200 mL), washed with water and saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/150) to afford 6.20 g of **8** as light yellow oil, yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 3.96–3.89 (m, 1H), 3.22 (s, 3H), 2.40 (dd, J = 6.7, 1.3 Hz, 2H), 2.14–2.05 (m, 1H), 1.94 (dddd, J = 12.2, 7.6, 5.5, 2.6 Hz, 1H), 1.75–1.66 (m, 1H), 1.57–1.45 (m, 1H), 1.40–1.34 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.13 (s, 9H), 0.90–0.87 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of diastereomers): δ 215.5, 209.1, 77.04, 76.98, 64.8, 64.1, 53.0, 52.1, 51.6, 49.84, 49.77, 44.6, 44.4, 43.5, 36.2, 35.9, 35.4, 33.4, 33.3, 31.11, 31.05, 30.6, 29.9, 28.5, 28.2, 26.4, 23.7, 21.6, 21.5, 20.6, 19.6, 17.5, 17.1; ESI-MS: 343.1, 345.1 $[M+Na]^+$; HRMS (ESI–TOF) calcd for $[C_{15}H_{29}BrO_2 + Na]^+$ 343.1243, found 343.1242.

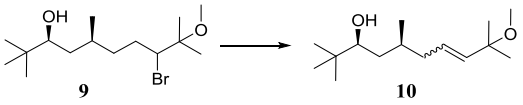
(3*S*,5*S*)-8-Bromo-9-methoxy-2,2,5,9-tetramethyldecan-3-ol (9)



8 **9**

To a solution of (*R*)-CBS (1.30 g, 4.7 mmol, 0.5 eq.) in toluene (30 mL) was added BH_3-Me_2S (1.7 mL, 28.0 mmol, 3.0 eq.) and stirred at 40 °C in an oil bath for 30 min. Then compound **8** (3.00 g, 9.3 mmol) dissolved in toluene (20 mL) was added to the reaction mixture dropwisely. The resultant mixture was stirred at the same temperature for 8 h and quenched with methanol. After concentrated under reduced pressure to remove the solvent, the residue was diluted with ethyl acetate (200 mL), washed with 10% $NaHCO_3$ and saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/10) to afford 2.87 g of **9** as colorless oil, yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 4.00–3.93 (m, 1H), 3.35–3.29 (m, 1H), 3.232 and 3.227 (both s, total 3H), 2.04–1.89 (m, 1H), 1.79– 1.63 (m, 3H), 1.62–1.53 (m, 1H), 1.46–1.36 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H), 0.96–0.89 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 77.8, 65.3, 49.8, 39.1, 35.1, 34.9, 30.7, 30.1, 25.8, 23.7, 21.51, 21.48. ESI-MS: 345.1, 347.1 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{15}H_{31}BrO_2 +H]^+$ 323.1580, found 323.1584.

(3*S*,5*S*)-9-Methoxy-2,2,5,9-tetramethyldec-7-en-3-ol (10)

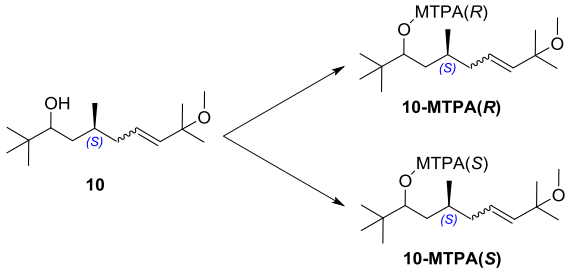


9 **10**

To a solution of compound **9** (3.00 g, 9.3 mmol) in 1,4-dioxane (25 mL) was added KOH (1.57 g, 28.0 mmol) and stirred at 125 °C in an oil bath for 12 h . After concentrated under reduced pressure to remove the solvent, the residue was diluted with ethyl acetate (200 mL), washed with 10% HCl and saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/8) to afford 2.12 g of **10** as colorless oil, yield 94%. $[\alpha]_D^{25}$ = -38.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (ddd, *J* = 15.7, 7.3, 6.4 Hz, 1H), 5.40 (d, *J* = 15.8 Hz, 1H), 3.29 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.13 (s, 3H), 2.22–2.17 (m, 1H), 1.88–1.81 (m, 1H), 1.79–1.71 (m, 1H), 1.43–1.36 (m, 2H), 1.23 (s, 6H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 128.5, 77.7, 76.9,

75.0, 50.4, 38.5, 38.4, 35.1, 30.2, 26.1, 26.0, 25.7, 21.1; ESI-MS:265.3[M+Na]$^+$; HRMS (ESI–TOF) calcd for [$C_{15}H_{30}O_2$ +Na] $^+$ 265.2138, found 265.2138.

Synthesis of (*R*)- and (*S*)-Mosher's esters of 10.

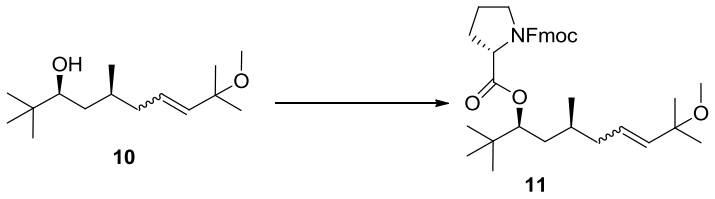


To a suspension of (*R*)-(+)-Mosher's acid or (*S*)-(-)-Mosher's acid (9.5 μL, 0.06 mmol) in 1.0 mL of anhydrous benzene under nitrogen was added 2,4,6-trichlorobenzoyl chloride (9.1 μL, 0.06 mmol) followed by DIPEA (10.5 μL, 0.06 mmol). After stirred for 5 min, a solution of **10** (5.0 mg, 0.02 mmol) in 100 μL of benzene and DMAP (5.0 mg, 0.04 mmol) were added in one portion. The mixture was stirred overnight and concentrated in *vacuo*. The resultant oil was purified by PTLC with ethyl acetate/petroleum ether (1/8) to afford the corresponding (*R*)- or (*S*)-Mosher's esters. **10-MTPA (*R*)**, 9.1 mg, yield 96%; **10-MTPA (*S*)**, 9.0 mg, yield 95%.

10-MTPA (*R*): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6103–7.5902 (m, 2H), 7.4038–7.3900 (m, 3H), 5.4821–5.3029 (m, 2H), 5.0508 (dd, *J* = 8.2, 3.5 Hz, 1H), 3.5604 (s, 2.8H), 3.5301 (s, 0.24H), 3.1390 (s, 0.2H), 3.1240 (s, 2.75 H), 2.2841–2.2265 (m, 1 H), 1.8588–1.7904 (m, 1 H), 1.5016–1.4625 (m, 2H), 1.3943–1.3316 (m, 1H), 1.2546 and 1.2372 (both s, total 6H), 0.8739 (s, 9H), 0.8361 (dd, *J* = 6.6 Hz, 3H); ESI-MS: 459.2 [M+H]$^+$, 481.0 [M+Na]$^+$.

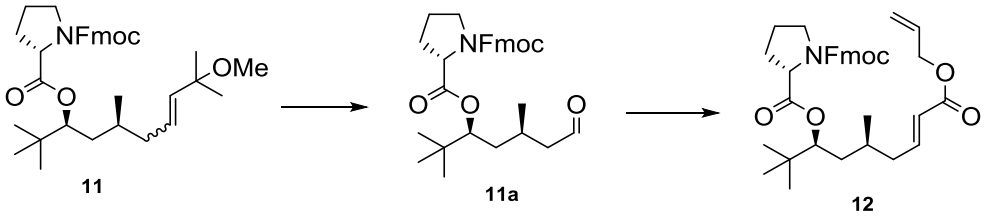
10-MTPA (*S*): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6019–7.5811 (m, 2H), 7.4164–7.4016 (m, 3H), 5.4959–5.3961 (m, 2H), 5.0345 (dd, *J* = 8.5, 3.6 Hz, 1H), 3.5331 (s, 3H), 3.1396 (s, 3H), 2.2676–2.2114 (m, 1 H), 1.8609–1.7926 (m, 1 H), 1.4538–1.4129 (m, 2H), 1.3732–1.3327 (m, 1H), 1.2510 (s, 6H), 0.8770 (s, 9H), 0.7956 (dd, *J* = 6.6 Hz, 3H); ESI-MS: 459.2 [M+H]$^+$, 481.0 [M+Na]$^+$.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*)-9-methoxy-2,2,5,9-tetramethyldec-7-en-3-yl) (*S*)-pyrrolidine-1,2-dicarboxylate (11)



To a suspension of N-Fmoc-*L*-proline (4.06 g, 12.0 mmol) in 100 mL of anhydrous benzene under nitrogen was added 2,4,6-trichlorobenzoyl chloride (2.49 mL, 16.4 mmol) followed by DIPEA (2.67 mL, 16.4 mmol). The solution was stirred for 20 min, then added a solution of **10** (2.65 g, 10.9 mmol) in 10 mL of benzene and DMAP (2.67 g, 21.9 mmol) in one portion. The mixture was stirred overnight and concentrated in vacuo to about 20 mL, then diluted with ethyl acetate, washed with water, 10% $KHSO_4$ solution and saturate brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/8) to afford 5.70 g of **11** as white foam, yield 93%. R_f = 0.41 (PE:EA = 4:1); $[\alpha]_D^{25}$ = -41.3 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 2H), 7.65–7.60 (m, 1.5H), 7.57–7.55 (m, 0.5H), 7.40 (t, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.1 Hz, 2H), 5.52–5.32 (m, 2H), 4.92–4.84 (m, 1H), 4.54–4.38 (m, 2H), 4.35–4.24 (m, 1H), 4.19–4.14 (m, 1H), 3.71–3.64 (m, 1H), 3.61–3.51 (m, 1H), 3.10 and 3.04 (both s, total 3H), 2.39–2.22 (m, 1.5H), 2.17–2.05 (m, 1.5H), 2.02–1.92 (m, 2H), 1.86–1.79 (m, 1.1H), 1.76–1.66 (m, 0.9H), 1.44–1.36 (m, 2H), 1.20 (s, 3H), 1.16 and 1.15 (both s, total 3H), 0.91–0.83 (m, 10.5H), 0.67–0.61 (m, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 154.8, 154.5, 144.1, 141.4, 137.5, 137.0, 128.5, 127.8, 127.1, 125.4, 125.3, 120.1, 80.0, 79.7, 75.0, 74.9, 67.8, 67.5, 59.7, 59.5, 50.4, 47.4, 47.1, 46.5, 38.3, 38.1, 36.6, 34.9, 31.4, 30.2, 29.6, 29.4, 26.0, 24.5, 23.5, 21.0, 20.6; HR MS (ESI–TOF) calcd for $[C_{35}H_{47}NO_5 + Na]^+$ 584.3346, found 584.3362.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*,*E*)-9-(allyloxy)-2,2,5-trimethyl-9-oxonon-7-en-3-yl) (*S*)-pyrrolidine-1,2-dicarboxylate (12)

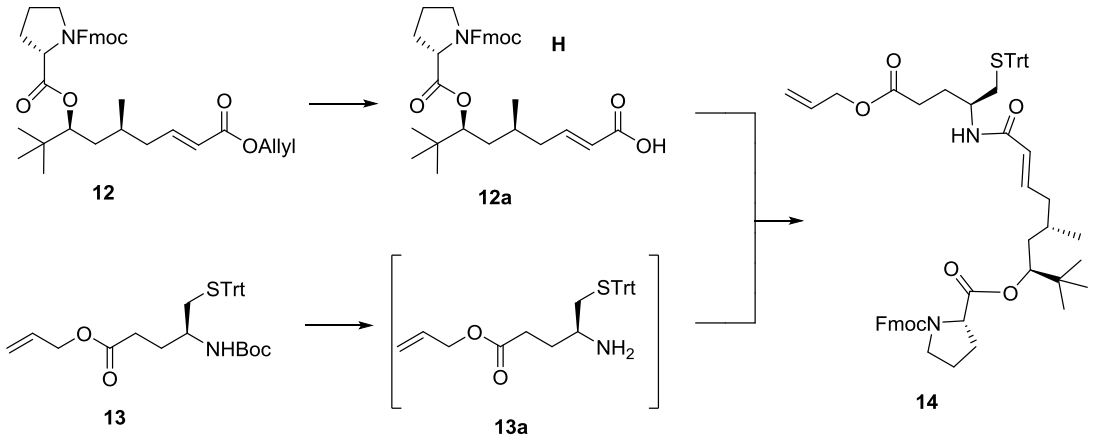


To a solution of compound **11** (5.14 g, 9.2 mmol) in 200 mL of dichloromethane at -78 °C was bubbled ozone till the solution turned blue. The ozone generator was turned off and oxygen was allowed to bubble in order to expel the redundant ozone. Then dimethylsulfide (5 mL) was added and the resultant solution was stirred overnight at room temperature. After drying over Na_2SO_4, filtered and concentrated in *vacuo*, the resultant oil was purified by chromatography with ethyl acetate/petroleum ether (1/80) quickly to afford the corresponding aldehyde **11a** as colorless liquid, which was used directly in the next step.

To a solution of allyl *P*,*P*-diethylphosphonoacetate (2.13 mL, 10.1 mmol, 1.2 eq.) in anhydrous THF (50 ml) at 0 °C was added NaH (403.2 mg, 10.1 mmol, 1.2 eq.) and stirred for 30 min. Then a solution of **11a** in anhydrous THF (10ml) was added dropwisely and stirred for another 1 h. The reaction mixture was quenched with 10 mL saturated NH_4Cl, concentrated in *vacuo* to remove the solvent, diluted with ethyl acetate, washed with 10% $KHSO_4$ and saturated brine, dried over $NaSO_4$, filtered and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/25 to 1/5) to afford 4.41 g of **12** as colorless oil, yield 84% for two steps. R_f = 0.44 (PE:EA = 4:1); $[\alpha]_D^{25}$ = -61.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 2H), 7.64 and 7.56 (both d, *J* = 7.4 Hz, total 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.97 and 6.85 (both ddd, *J* = 15.3, 8.7, 6.3 Hz, total 1H), 5.99–5.79 (m, 2H), 5.33–5.15 (m, 2H), 4.89–4.83 (m, 1H), 4.59 and 4.55 (both d, *J* = 5.6 Hz, total 2H), 4.52–4.41 (m, 2H), 4.35 and 4.27 (both m, total 1H) , 4.22–4.12 (m, 1H), 3.71–3.63 (m, 1H), 3.62–3.49 (m, 1H), 2.48–2.42 (m, 1H), 2.38–2.30 (m, 1H), 2.28–2.20 (m, 1H), 2.09–1.93 (m, 4H), 1.56–1.46 (m, 1H), 1.46–1.36 (m, 1H), 0.93 and 0.71 (both d, *J* = 6.7 Hz, total 3H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 166.3, 156.1, 154.8, 154.5, 148.6, 147.6, 144.3, 144.2, 143.9, 141.4, 132.6, 132.5, 127.9, 127.8, 127.2, 127.1, 125.5, 125.3, 123.0, 122.6, 120.1, 118.2, 118.0, 79.6,

79.2, 67.8, 67.5, 65.0, 64.9, 59.7, 59.5, 47.4, 47.1, 46.5, 37.8, 37.6, 36.7, 34.8, 31.5, 30.2, 29.2, 28.0, 26.0, 24.6, 23.5, 21.0, 20.6; HRMS (ESI–TOF) calcd for $[C_{35}H_{43}NO_6 + H]^+$ 574.3163, found 574.3158.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*,*E*)-9-(((*S*)-5-(allyloxy)-5-oxo-1-(tritylthio)pentan-2-yl)amino)-2,2,5-trimethyl-9-oxonon-7-en-3-yl)(*S*)-pyrrolidine-1,2-dicarboxylate (14)

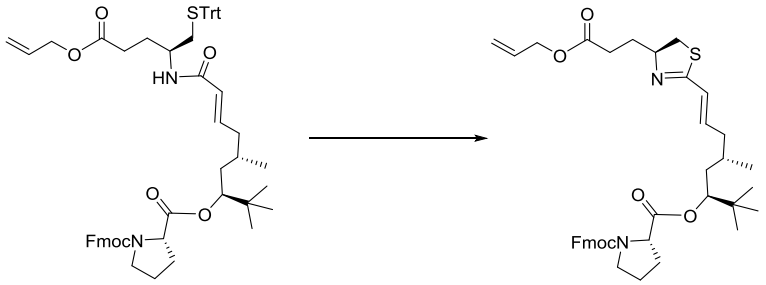


To a solution of compound **12** (3.82 g, 6.66 mmol) in anhydrous THF (22 mL) was added $Pd(PPh_3)_4$ (1.54 g, 1.33 mmol), N-methylaniline (2.04 mL, 16.65 mmol) and stirred at room temperature for 2 h. The solution was concentrated in *vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 10% $KHSO_4$ and saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo.* The resultant oil was purified by chromatography ethyl acetate/petroleum ether (1/3) to give 3.27 g of **12a** as white solid, yield 92%. R_f = 0.2 (PE:EA=4:1); $[\alpha]_D^{25}$ = -11.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.64–7.55 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.05 (ddd, *J* = 15.2, 8.6, 6.4 Hz, 0.6H), 6.90 (ddd, *J* = 15.3, 8.4, 6.9 Hz, 0.3H), 5.85 (d, *J* = 15.6 Hz, 0.6H), 5.78 (d, *J* = 15.6 Hz, 0.3H), 4.89 (d, *J* = 10.7 Hz, 0.6H), 4.86–4.82 (m, 0.3H), 4.52–4.47 (m, 0.6H), 4.46–4.40 (m, 1.4H), 4.37–4.31 (m, 0.6H), 4.26 (t, *J* = 7.2 Hz, 0.6H), 4.22–4.09 (m, 0.8H), 3.70–3.62 (m, 1H), 3.61–3.47 (m, 1H), 2.50–2.46 (m, 0.6H), 2.38–2.20 (m, 1.4H), 2.14–1.91 (m, 4H), 1.79–1.69 (m, 1H), 1.59–1.49 (m, 1H), 1.42–1.39 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 2H), 0.88 (s, 9H), 0.71 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 169.2, 154.9, 149.1, 148.0, 144.0, 143.9, 143.7, 141.3, 127.7, 127.1, 125.3, 123.1, 112.7, 119.9, 79.5, 79.1, 67.7, 59.5, 47.2, 47.0, 46.4, 37.5, 36.5, 34.7,

31.3, 30.0, 29.1, 25.9, 24.4, 23.4, 20.8; HR MS (ESI–TOF) calcd for $[C_{32}H_{39}NO_6 +H]^+$ 534.2850, found 534.2840.

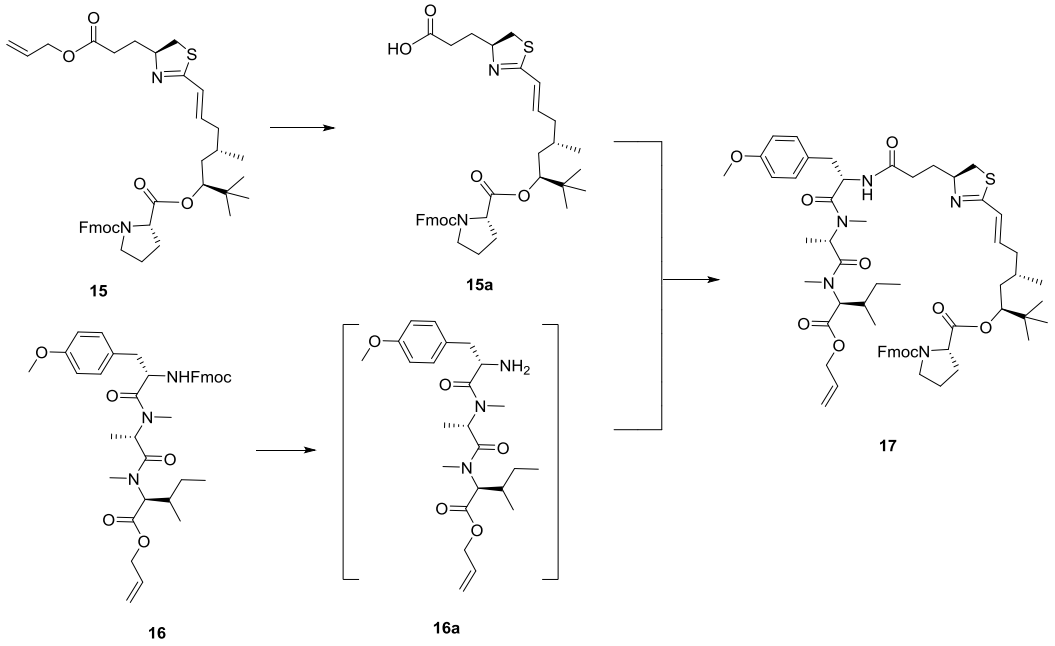
To a solution of compound **13** (107.2 mg, 0.2 mmol) in anhydrous dichloromethane (2 mL) was added with 2,6-lutidine (138 μL, 1.2 mmol, 6.0 eq) and TMSOTf (109 μL,0.6 mmol) at 0 °C. The resultant solution was stirred for 2h at room temperature and quenched with water, diluted with ethyl acetate and washed with 10% $NaHCO_3$ solution and brine. After filtration, the solution was concentrated in *vacuo* to dryness to afford **13a**. Then **13a** was dissolved in anhydrous dichloromethane (5 mL) and a solution of compound **12a** (106.7 mg, 0.2 mmol) in dichloromethane (1 mL), HATU (144.1 mg, 0.30 mmol) and DIPEA (105μL, 0.60 mmol) were added. The resultant solution was stirred overnight at room temperature and diluted with dichloromethane (20 mL), washed with 5% $KHSO_4$ and brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The resultant oil was purified by chromatography eluting with ethyl acetate/petroleum ether (1/4) to afford 116.2 mg of **14** as colorless oil, yield 61%. R_f = 0.29（PE:EA=2:1）; $[\alpha]_D^{25}$ = -40.4 (c 1.0, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.82–7.77 (m, 2H), 7.69–7.62 (m, 1.8H), 7.59 (dd, *J* = 7.6 Hz, 0.2H), 7.45–7.21 (m, 19H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.38–6.26 (m, 1.6H), 6.21 (d, *J* = 7.6 Hz, 0.4H), 6.00–5.88 (m, 1H), 5.33 (dd, *J* = 1.2, 17.6 Hz, 1H), 5.24 (dd, *J* = 2.4, 10.4 Hz, 1H), 4.94–4.87 (m, 1H), 4.77 (ddd, *J* = 7.6, 14.8, 15.0 Hz, 1H), 4.67–4.59 (m, 2H), 4.58–4.48 (m, 1.5H), 4.47–4.34 (m, 1.5H), 4.31–4.20 (m, 1H), 3.72–3.63 (m, 1H), 3.63–3.51 (m, 1H), 2.66–2.53 (m, 1H), 2.49–2.41 (m, 1H), 2.37–2.15 (m, 2H), 2.14–1.95 (m, 3H), 1.85 (s, 3H), 1.84–1.79 (m, 3H), 1.77–1.65 (m, 1H), 1.60–1.43 (m, 2H), 1.36–1.26 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 2.2H), 0.88 (s, 9H), 0.78 (d, *J* = 6.4 Hz, 0.8H); ^{13}C NMR(125 MHz, $CDCl_3$): δ 172.7, 168.8, 167.2, 154.7, 144.6, 144.2, 144.0, 143.8, 141.3, 139.8, 135.0, 134.6, 132.4, 131.4, 130.1, 129.6, 128.0, 127.7, 127.1, 126.8, 125.2, 120.0, 118.1, 80.0, 77.3, 67.8, 67.4, 67.0, 65.4, 59.6, 47.3, 47.0, 46.4, 37.3, 37.1, 36.3, 34.8, 34.7, 34.5, 31.3, 30.1, 29.6, 29.5, 25.9, 24.4, 23.4, 21.7, 12.9; ESI-MS 947.5$[M+H]^+$, 969.4$[M+Na]^+$; HRMS (ESI–TOF) calcd for $[C_{59}H_{67}N_2O_7S+Na]^+$ 947.4663, found 947.4659.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*,*E*)-8-((*S*)-4-(3-(allyloxy)-3-oxopropyl)-4,5-dihydrothiazol-2-yl)-2,2,5-trimethyloct-7-en-3-yl)(*S*)-pyrrolidine-1,2-dicarboxylate (15)



To a solution of triphenylphosphine oxide (500.9 mg, 1.8 mmol) in anhydrous dichloromethane (5 mL) at 0 °C was added trifluoromethanesulfonic anhydride (151.4 μL, 0.9 mmol) and the mixture was stirred for 15 min under nitrogen atmosphere. Then a solution of compound **14** (280.0 mg, 0.3 mmol) in dichloromethane (1 mL) was added. The resultant solution was stirred for another 30 min at 0 °C and quenched with saturated $NaHCO_3$ solution, and extracted with dichloromethane. The combined organic phase was washed with saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography eluting with ethyl acetate /petroleum ether (1/3) to afford 160.9 mg of **15** as white powder, yield 79%. R_f = 0.20 (PE:EA = 3:1); $[\alpha]_D^{25}$ = -43.5 (c 1.0, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 1.6H), 7.56 (d, *J* = 7.0 Hz, 0.4H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 6.28 (d, *J* = 10.6 Hz, 1H), 6.18–6.10 and 5.96–5.86 (both m, total 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 4.90–4.84 (m, 1H), 4.58 (d, *J* = 4.8 Hz, 2H), 4.52–4.40 (m, 3H), 4.38–4.36 and 4.29–4.26 (both m, total 1H), 4.20–4.13 (m, 1H), 3.74–3.63 (m, 1H), 3.60–3.54 (m, 1H), 3.37–3.30 (m, 0.4H), 3.24–3.19 (m, 0.6H), 2.92–2.81 (m, 0.4H), 2.80–2.70 (m, 0.6H), 2.58–2.46 (m, 2H), 2.36–2.22 (m, 1H), 2.15–1.86 (m, 6H), 1.72 (brm, 1H), 1.55–1.46 (m, 1H), 1.42–1.33 (m, 2H), 1.28–1.18 (m, 1H), 0.88 (brs, 11H), 0.70 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ: 173.0, 172.6, 166.7, 154.7, 144.4, 144.1, 143.0, 141.3, 132.2, 127.7, 127.6, 127.1, 127.0, 126.4, 125.3, 125.2, 119.2, 118.2, 79.6, 79.1, 76.0, 75.9, 67.5, 65.2, 59.5, 59.3, 47.3, 46.5, 38.6, 38.3, 37.1, 37.0, 36.7, 34.7, 31.5, 30.3, 30.1, 29.3, 28.7, 25.9, 24.5, 23.3, 20.9, 20.6; ESI MS: 687.6 $[M+H]^+$, 709.2 $[M+Na]^+$; HRMS (ESI–TOF) calcd for $[C_{40}H_{50}N_2O_6S+Na]^+$ 709.3287, found 709.3291.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*,*E*)-8-((*S*)-4-((5*S*,8*S*,11*S*)-11-((*S*)-sec-butyl)-5-(4-methoxybenzyl)-7,8,10-trimethyl-3,6,9,12-tetraoxo-13-oxa-4,7,10-triazahexadec-15-en-1-yl)-4,5-dihydrothiazol-2-yl)-2,2,5-trimethyloct-7-en-3-yl)(*S*)-pyrrolidine-1,2-dicarboxylate(17)

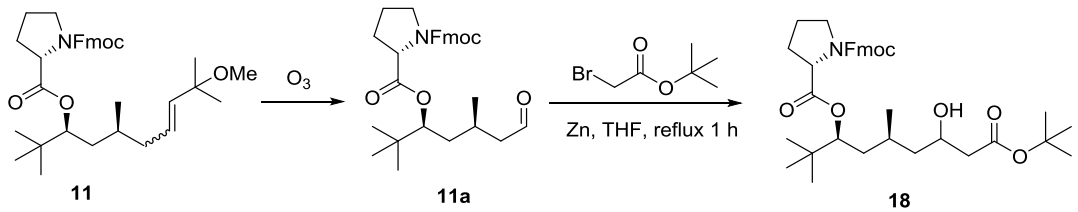


The procedure of preparation of **15a** was the same as **12a**. The crude product was purified by chromatography eluting with dichloromethane/methanol (30/1) to afford **15a** as white solid, yield 81%. R_f = 0.4 (DCM:MeOH = 15:1); $[\alpha]_D^{25}$ = -82.8 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 1.6H), 7.56 (d, *J* = 7.2 Hz, 0.4H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 2H), 6.40–6.17 (m, 2H), 4.90–4.84 (m, 1H), 4.54–4.48 (m, 1H), 4.46–4.36 (m, 2.5H), 4.29–4.26 (m, 0.7H), 4.20–4.13 (m, 0.8H), 3.74–3.65 (m, 1H), 3.60–3.54 (m, 1H), 3.37–3.30 (m, 0.4H), 3.23–3.18 (m, 0.6H), 3.18–2.90 (m, 0.4H), 2.74–2.72 (m, 0.6H), 2.64–2.48 (m, 2.6H), 2.40–2.22 (m, 1.4H), 2.14–1.83 (m, 6H), 1.72 (brm, 1H), 1.57–1.50 (m, 1H), 1.44–1.25 (m, 2H), 0.89 (s, 11H), 0.69 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 172.6, 169.5, 168.7, 154.7, 154.4, 146.3, 144.5, 144.1, 144.0, 143.7, 141.4, 127.7, 127.6, 127.0, 126.0, 125.3, 119.9, 79.6, 79.0, 75.4, 75.2, 67.8, 67.6, 59.5, 59.3, 47.2, 47.0, 46.5, 38.7, 38.3, 37.3, 37.2, 36.7, 34.7, 32.5, 32.3, 31.3, 30.0, 29.8, 29.7, 29.4, 28.6, 25.9, 24.4, 23.3, 21.0, 20.6; ESI MS: 647.6 $[M+H]^+$; HRMS (ESI–TOF) calcd for $[C_{37}H_{46}N_2O_6S+H]^+$ 647.3155, found 647.3145.

To a solution of tripeptide **16** (310.6 mg, 0.46 mmol) in acetonitrile (2.5 mL) was added diethylamine (2.5 mL) and stirred for 20 min at room temperature. The reaction mixture was

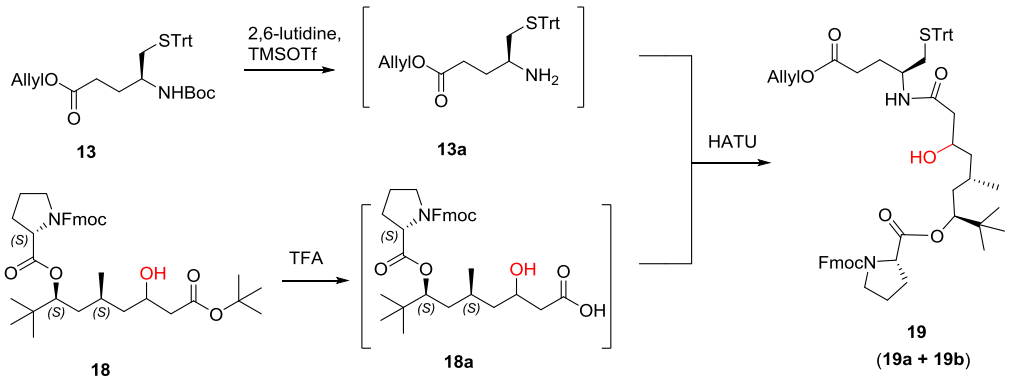
concentrated in *vacuo* to dryness and the resultant oil was dissolved in dry dichloromethane (10 mL), to which **15a** (300.0 mg, 0.46 mmol), HATU (262.4 mg, 0.69 mmol)and DIPEA (241.0 μL, 1.38 mmol) were added at 0 °C. The resultant solution was stirred overnight under nitrogen atmosphere at room temperature and quenched with NH_4Cl, washed with 10% $KHSO_4$, 10% $NaHCO_3$ and saturated brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography eluting with dichloromethane/methanol (100/1) to afford 446.8 mg of **17** as white solid, yield 90%. R_f = 0.5 (DCM:MeOH = 30:1); $[\alpha]_D^{25}$ = -84.3 (c 1.0, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 1.5H), 7.56 (d, *J* = 7.3 Hz, 0.5H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 0.2H), 6.45 (d, *J* = 8.4 Hz, 0.3H), 6.34–6.30 (m, 1H), 6.21–6.12 (m, 0.4H), 5.94–5.84 (m, 0.6H), 5.55–5.46 (m, 0.1H), 5.42–5.36 (m, 0.9H), 5.32–5.28 (m, 1H), 5.24–5.15 (m, 2H), 5.14–5.05 (m, 0.1H), 4.99–4.80 (m, 1.9H), 4.64–4.55 (m, 1.7H), 4.54–4.50 (m, 0.3H), 4.47–4.35 (m, 2H), 4.29–4.26 (m, 0.8H), 4.20–4.17 (m, 1.2H), 3.77 (s, 0.6H), 3.75 (s, 2.4H), 3.77–3.64 (m, 1H), 3.60–3.54 (m, 1H), 3.05–2.97 (m, 3.8H), 2.91–2.88 (m, 0.2H), 2.85–2.78 (m, 1.5H), 2.75 (s, 2H), 2.71 (s, 1H), 2.67–2.61 (m, 0.5H), 2.52–2.45 (m, 0.4H), 2.42–2.20 (m, 2.6H), 2.10–1.89 (m, 6H), 1.84–1.62 (m, 4H), 1.55–1.47 (m, 1H), 1.42–1.37 (m, 1.5H), 1.28–1.22 (m, 7.5H), 1.01–0.92 (m, 5H), 0.88 (s, 9H), 0.87–0.78 (m, 4H), 0.69 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 172.0, 171.9, 171.5, 170.7, 158.6, 154.7, 154.3, 144.2, 144.1, 144.0, 141.3, 131.7, 130.4, 127.7, 127.6, 127.0, 125.3, 125.2, 119.9, 118.7, 113.9, 79.6, 79.1, 67.8, 67.6, 65.4, 60.5, 59.5, 59.3, 55.2, 50.3, 49.7, 47.2, 47.0, 46.5, 38.6, 38.1, 37.7, 37.1, 37.0, 36.7, 34.7, 33.6, 33.3, 31.3, 30.9, 30.5, 30.1, 29.7, 29.5, 28.7, 25.9, 25.0, 24.4, 23.4, 20.9, 20.6, 15.8, 14.3, 11.6, 10.6; ESI MS: 1098.4 $[M+Na]^+$; HRMS (ESI–TOF) calcd for $[C_{37}H_{46}N_2O_6S+Na]^+$ 1098.5602, found 1098.5651.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*)-9-(*tert*-butoxy)-7-hydroxy-2,2,5-trimethyl-9-oxononan-3-yl) (2*S*)-pyrrolidine-1,2-dicarboxylate (18)



The preparation of **11a** was the same as that described in the preparation of **12**. To a solution of compound **11a**（1.00 g, 2.03 mmol）and *tert*-butyl bromoacetate (2.13 mL,10.2 mmol, 5.0 eq.) in anhydrous THF (50 mL) was added activated zinc powder (2.65 g, 40.6 mmol, 20.0 eq.) and refluxed for 1 h under nitrogen atmosphere. After cooling to room temperature, the solution was quenched with saturated NH_4Cl, diluted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography eluting with petroleum ether/ethyl acetate (5/1) to afford 1.20 g of **18** as white solid, yield 97%. $[\alpha]_D^{20}$ = -50.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.67–7.54 (m, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.0 Hz, 2H), 4.93–4.82 (m, 1H), 4.57–4.14 (m, 4H), 4.06 and 3.96 (both m, total 1H), 3.71–3.66 (m, 1H), 3.60–3.47 (m, 1H), 3.37–3.26 (m, 1H), 2.47–2.19 (m, 3H), 2.08–1.94 (m, 3H), 1.84–1.69 (m, 2H), 1.67–1.53 (m, 2H), 1.47–1.34 (m, 10H), 0.98 and 0.78 (both d, *J* = 6.2 Hz, total 3H), 0.88 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.0, 171.9, 171.8, 171.0, 153.3, 153.7, 143.5, 143.4, 143.3, 143.1, 140.7, 140.6, 127.1, 127.0, 126.4, 124.7, 124.6, 119.3, 80.6, 80.1, 79.6, 78.9, 77.9, 67.1, 67.0, 66.2, 65.9, 65.4, 59.0, 58.9, 58.8, 46.6, 46.3, 45.9, 45.8, 44.1, 42.0, 41.8, 41.6, 41.4, 37.3, 36.8, 34.1, 30.7, 29.4, 29.3, 27.5, 27.4, 26.6, 25.9, 25.4, 25.3, 24.5, 23.8, 22.7, 21.2, 20.8, 19.9; HRMS (ESI–TOF) calcd for $[C_{36}H_{49}NO_7+Na]^+$ 630.3401, found 630.3400.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*)-9-(((*S*)-5-(allyloxy)-5-oxo-1-(tritylthio)pentan-2-yl)amino)-7-hydroxy-2,2,5-trimethyl-9-oxononan-3-yl)(2*S*)-pyrrolidine-1,2-dicarboxylate (19)



To a solution of compound **13** (481.5 mg, 0.91 mmol) in anhydrous dichloromethane (10 mL) was added with 2,6-lutidine (629 μL, 5.46 mmol) and TMSOTf (494 μL, 2.73 mmol) at 0 °C. The

resultant solution was stirred for 2h at room temperature and quenched with water, diluted with ethyl acetate and washed with 10% $NaHCO_3$ solution and brine. After filtration, the solution was concentrated in *vacuo* to dryness to afford **13a**.

In another 25 mL two necked round bottle, compound **18** (500.0 mg, 0.82 mmol) was dissolved in anhydrous dichloromethane (4 mL) and 1 mL of trifluoroacetic acid was added. The result solution was stirred at room temperature for 10 min and concentrated in *vacuo* to dryness to afford **18a**.

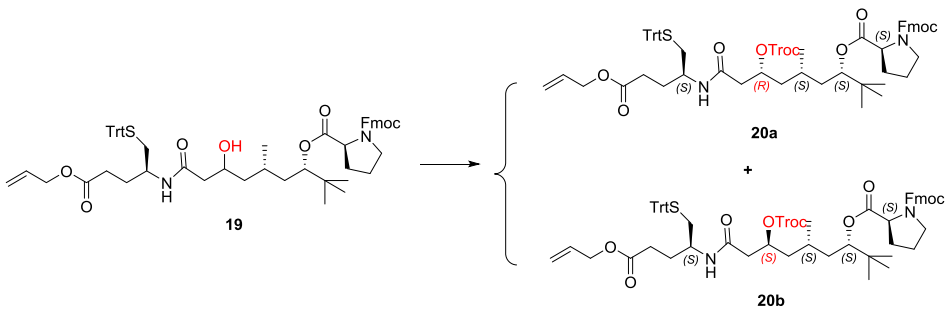
The newly prepared **13a** was dissolved in anhydrous dichloromethane (20 mL) and transformed to the bottle containing **18a**. Then HATU (467.7 mg, 1.23 mmol) and DIPEA (430 μL, 2.46 mmol) was added. The solution was stirred overnight at room temperature and diluted with dichloromethane (20 mL), washed with 10% $KHSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography eluting with petroleum ether/ ethyl acetate (2/1) to afford 573.7 mg of **19** as white solid, yield 72%. 20 mg compound **19** was further purified by preparative TLC to afford 8.2 mg of **19a** (*R*) and 7.9 mg of **19b** (*S*).{by comparing their NMRs with known data[2]. }

19a (*R*): R_f = 0.32 (PE:EA=2:1, twice), $[\alpha]_D^{20}$ = -45.6 (*c* 0.24, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.75 (m, 2H), 7.64−7.53 (m, 2H), 7.41−7.38 (m, 4H), 7.35−7.33 (m, 4H), 7.30−7.28 (m, 4H), 7.24−7.20 (m, 5H), 7.17−7.14 (m, 2H), 6.75 (d, *J* = 9.0 Hz, 0.51H), 6.16 (d, *J* = 8.7 Hz, 0.13H), 5.93−5.76 (m, 1H), 5.30−5.17 (m, 2H), 4.87 (d, *J* = 10.3 Hz, 0.66H), 4.80 (d, *J* =10.2 Hz, 0.2H), 4.63–4.57 (m, 0.2H), 4.53−4.45 (m, 1.8H), 4.44−4.41 (m, 1H), 4.36−4.31 (m, 1H), 4.28−4.19 (m, 2H), 4.03–3.95(m, 1H), 3.93−3.86 (m, 1H), 3.66–3.55 (m, 1H), 3.50−3.40 (m, 1H), 2.39−2.16 (m, 3H), 2.13−2.07 (m, 3H), 1.99−1.84 (m, 2H), 1.62−1.37 (m, 6H), 1.21−1.07 (m, 2H), 1.04–0.98 (m, 1H), 0.96 (d, *J* = 6.1 Hz, 2.2H), 0.87 (s, 9H), 0.77 (d, *J* = 6.1 Hz, 0.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.2, 173.0, 172.5, 171.8, 171.2, 155.0, 144.6, 144.0, 143.7, 141.3, 132.2, 129.6, 128.0, 127.9, 127.7, 127.2, 127.1, 126.8, 126.7, 125.14, 125.11, 119.99, 119.96, 118.3, 118.2, 79.1, 67.6, 66.8, 66.6, 65.2, 65.1, 60.4, 59.4, 48.0, 47.1, 46.4, 42.3, 41.2 , 37.0, 36.5, 34.9, 34.5, 31.2, 30.8, 29.9, 29.7, 29.5, 29.2, 26.0, 25.9, 24.1, 23.2, 21.5, 20.1, 14.2; ESI MS: 965.4$[M+H]^+$, 987.4 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{59}H_{68}NO_8S +Na]^+$ 987.4589, found 987.4628.

19b(*S*): R_f = 0.29 (PE:EA=2:1, twice), $[\alpha]_D^{20}$ = -31.0 (*c* 0.24, CH_2Cl_2), {literature[2] $[\alpha]_D^{20}$ = -31.2 (c 0.24, CH_2Cl_2) }; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.64−7.52 (m, 2H), 7.42−7.33 (m, 8H), 7.32−7.21 (m, 9H), 7.20−7.15 (m, 2H), 6.69 (d, *J* = 8.8 Hz, 0.66H), 6.07 (d, *J* = 8.7 Hz, 0.13H), 5.94−5.72 (m, 1H), 5.31−5.12 (m, 2H), 4.89 (d, *J* = 11.3 Hz, 0.79H), 4.79 (d, *J* =10.2 Hz, 0.2H), 4.53−4.44 (m, 2H), 4.40−4.27 (m, 2H), 4.23−4.17 (m, 1H), 4.01 (br m, 1H), 3.95−3.86 (m, 1H), 3.79 (br, 1H), 3.66−3.61 (m, 1H), 3.57−3.44 (m, 1H), 2.40−2.15 (m, 6H), 2.10−2.06 (m, 3H), 2.01−1.90 (m, 2H), 1.86−1.75 (m, 1H), 1.71−1.60 (m, 3H), 1.55−1.41 (m, 2H), 1.39−1.30 (m, 1H), 1.04–1.01 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 2.6H), 0.88 (s, 9H), 0.77 (d, *J* = 6.5 Hz, 0.4H); ESI MS: 965.4$[M+H]^+$, 987.4 $[M+Na]^+$.

19 (mixture)： $[\alpha]_D^{20}$ = -37.1 (*c* 0.24, CH_2Cl_2).

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*)-9-(((*S*)-5-(allyloxy)-5-oxo-1-(tritylthio)pentan-2-yl)amino)-2,2,5-trimethyl-9-oxo-7-(((2,2,2-trichloroethoxy)carbonyl)oxy)nonan-3-yl) (2*S*)-pyrrolidine-1,2-dicarboxylate (20)

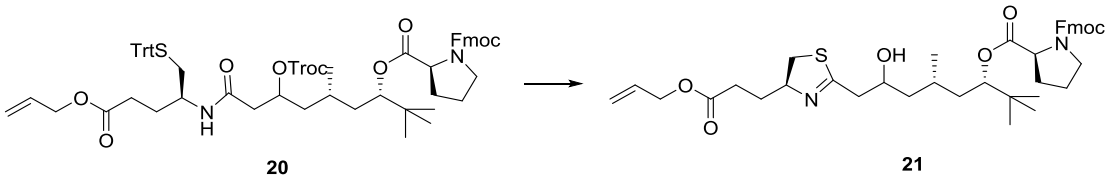


To a solution of compound **19** (mixture, 300.0 mg, 0.31 mmol) in anhydrous dichloromethane (2 mL) was added pyridine (250 μL, 3.1 mmol) and stirred for 10 min at 0 °C. Then TrocCl (213 μL, 1.55 mmol) and DMAP (37.9 mg, 0.31 mmol) were added. The reaction solution was stirred for another 1 h at the same temperature and quenched with saturated NH_4Cl. The result solution was extracted with ethyl acetate (5 mL×3). The combined organic phase was washed with saturated $NaHCO_3$, 5% $KHSO_4$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography eluting with petroleum ether/ethyl acetate (4/1) to afford 165.5 mg of **20a (*R*)** and 154.5 mg of **20b (*S*)** both as white solid, total yield 90%.{by comparing their NMRs with known data[2]. }

20a (*R*): $[\alpha]_D^{20}$ = -25.5 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.74 (m, 2H), 7.64–7.57 (m, 2H), 7.41–7.38 (m, 3H), 7.34–7.29 (m, 7H), 7.25–7.21 (m, 6H), 7.19–7.15 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 0.8H), 5.84–5.74 (m, 1H), 5.54 (d, *J* = 8.6 Hz, 0.2H), 5.36–5.27 (m, 1H), 5.21 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.15 (dd, *J* = 10.5, 0.8 Hz, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.84–4.72 (m, 2H), 4.68–4.62 (m, 1H), 4.56–4.51 (m, 1H), 4.48–4.36 (m, 3H), 4.31–4.11 (m, 3H), 3.94–3.83 (m, 1H), 3.69–3.60 (m, 1H), 3.51–3.44 (m, 1H), 2.44 (t, *J* = 5.8 Hz, 1H), 2.27 (d, *J* = 5.8 Hz, 1H), 2.15–2.02 (m, 3H), 1.91 (d, *J* = 9.7 Hz, 4H), 1.59–1.53 (m, 2H), 1.49–1.40 (m, 2H), 1.36–1.28 (m, 2H), 0.89–0.81 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 172.7, 171.7, 169.3, 155.0, 153.3, 144.9, 144.1, 143.8, 141.5, 141.4, 132.4, 129.8, 128.1, 128.0, 127.9, 127.4, 127.2, 126.8, 125.4, 125.3, 120.1, 118.3, 94.7, 78.7, 76.7, 76.1, 67.8, 66.8, 65.2, 59.6, 48.4, 47.3, 46.4, 40.8, 39.9, 37.8, 36.6, 35.0, 30.9, 30.0, 29.8, 29.5, 26.2, 26.0, 25.5, 24.2, 20.8; ESI MS: 1161.4 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{62}H_{69}Cl_3N_2O_{10}S + Na]^+$ 1161.3631, found 1161.3634.

20b (*S*): $[\alpha]_D^{20}$ = -44.1 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.77−7.74 (m, 2H), 7.66 (d, *J* = 7.4 Hz, 0.5H), 7.59 (d, *J* = 7.4 Hz, 1.5H), 7.41−7.36 (m, 7H), 7.33−7.17 (m, 12H), 6.09 (d, *J* = 8.3 Hz, 0.6H), 5.92−5.80 (m, 1H), 5.57 (d, *J* = 8.3 Hz, 0.4H), 5.29−5.18 (m, 2.8H), 4.84−4.81 (m, 1.2H), 4.77 (d, *J* = 12.0 Hz, 0.6H), 4.60 (d, *J* = 12.0 Hz, 0.4H), 4.54−4.43 (m, 4H), 4.40−4.30 (m, 1.4H), 4.26−4.18 (m, 1.6H), 3.92−3.82 (m, 1H), 3.65−3.60 (m, 1H), 3.57−3.45 (m, 1H), 2.56−2.54 (m, 4H), 2.20−2.13 (m, 3H), 2.00−1.85 (m, 3H), 1.75−1.60 (m, 2H), 1.52−1.34 (m, 3H), 0.97 (d, *J* = 6.5 Hz, 2H), 0.87 (s, 4H), 0.85 (s, 5H), 0.80 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 172.7, 172.6, 172.3, 168.7, 168.3, 154.8, 154.4, 153.52, 153.46, 144.9, 144.6, 144.5, 144.2, 144.1, 143.9, 143.7, 141.3, 141.2, 132.2, 132.1, 129.6, 127.99, 127.96, 127.72, 127.69, 127.3, 127.1, 126.84, 126.78, 125.4, 125.3, 125.1, 119.96, 119.94, 118.3, 118.2, 94.74, 94.71, 79.5, 79.1, 76.7, 76.6, 75.3, 74.7, 67.8, 67.5, 66.8, 66.7, 65.2, 65.1, 60.4, 59.7, 59.4, 48.4, 47.3, 47.0, 46.4, 41.5, 41.0, 39.8, 39.5, 38.0, 37.6, 36.4, 36.3, 35.0, 34.9, 34.7, 31.9, 31.3, 30.8, 30.0, 29.7, 29.1, 25.95, 25.86, 25.83, 24.3, 23.4, 22.7, 21.0, 20.7, 20.6, 14.2, 14.1; ESI MS: 1161.4 $[M+Na]^+$.

1-((9H-fluoren-9-yl)methyl)2-((3*S*,5*S*)-8-((*S*)-4-(3-(allyloxy)-3-oxopropyl)-4,5-dihydrothiazol-2-yl)-7-hydroxy-2,2,5-trimethyloctan-3-yl)(2*S*)-pyrrolidine-1,2-dicarboxylate (21)



To a solution of triphenylphosphine oxide (223.3 mg, 0.8 mmol) in anhydrous dichloromethane (1 mL) was added Tf_2O (68 μL, 0.4 mmol) at 0 °C and stirred for 10 min at the same temperature. Then compound **20** (mixture, 114.0 mg, 0.1 mmol) dissolved in THF (0.5 mL) was added and stirred for another 30 min and quenched by 6 mL of saturated $NaHCO_3$ at 0 °C. The resultant solution was extracted with ethyl acetate (10 mL×4). The combined organic phase was washed with brine (10 mL) and concentrated in *vacuo.* The residue was not purified and used for the next step immediately.

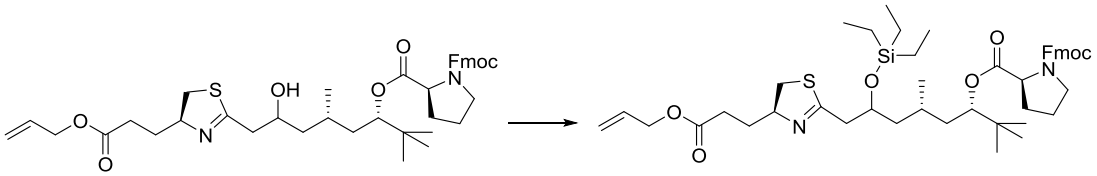
To a solution of the intermediate prepared above in THF (4 mL) was added activated zinc powder (100 mg) and ammonium acetate aqueous solution (1 mL, 1M). The result mixture was stirred vigorously for 1 h at room temperature. Then to the reaction solution was added ethyl acetate (5 mL) and brine (5 mL). The organic phase was separated and the water phase was extracted with ethyl acetate (5 mL×3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo.* The residue was purified by chromatography eluting with petroleum ether/ethyl acetate (4/3) to afford 52.8 mg of **21** as colorless oil, yield 75% over two steps.

Note: All the solutions and solvents used during the experiment should be pre-cooled in an ice bath and the operation should be as quick as possible otherwise the yield of the product would be quite low due to the elimination of hydroxy. Besides, the mixture cannot be separated by PTLC.

$[\alpha]_D^{20}$ = -69.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.5 Hz, 2H), 7.65–7.62 (m, 1.6 H), 7.56 (d, *J* = 7.3 Hz, 0.4H), 7.40 (t, *J* = 7.2, 7.2 Hz, 2H), 7.33−7.29 (m, 2H), 5.91 (ddd, *J* = 16.2, 10.9, 5.7 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.89–4.83 (m, 1H), 4.58 (d, *J* = 5.5 Hz, 2H), 4.53–4.44 (m, 1H), 4.42−4.37 (m, 2H), 4.28−4.15 (m, 2H), 4.05–

3.93 (m, 1H), 3.74−3.63 (m, 1H), 3.60−3.54 (m, 1H), 3.35 (dd, *J* = 10.8, 8.8 Hz, 0.4H), 3.24 (dd, *J* = 10.8, 8.8 Hz, 0.6H), 2.92 (dd, *J* = 10.7, 8.7 Hz, 0.4H), 2.71 (dd, *J* = 10.7, 8.7 Hz, 0.6H), 2.59−2.33 (m, 4H), 2.30−2.24 (m, 1H), 2.15−1.95 (m, 4H), 1.90 (dd, *J* = 14.6, 7.3 Hz, 1H), 1.67−1.61 (m, 1H), 1.58−1.41 (m, 3H), 1.33–1.25 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 2H), 0.88 (s, 9H), 0.78 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.01, 172.96, 172.7, 172.5, 170.8, 170.4, 154.9, 154.5, 144.3, 144.2, 143.9, 141.42, 141.37, 132.2, 127.84, 127.78, 127.17, 127.14, 125.5, 125.4, 125.3, 80.3, 79.4, 76.3, 76.0, 68.0, 67.9, 67.7, 66.0, 65.4, 65.3, 59.7, 59.5, 47.4, 47.1, 46.6, 42.5, 42.4, 40.6, 40.4, 38.21, 38.16, 37.9, 37.7, 34.82, 34.79, 31.7, 31.4, 30.5, 30.2, 27.6, 26.6, 26.1, 24.5, 23.5, 21.8, 21.5, 15.4; HRMS (ESI–TOF) calcd for $[C_{40}H_{52}N_2O_7S + Na]^+$ 727.3387, found 727.3399.

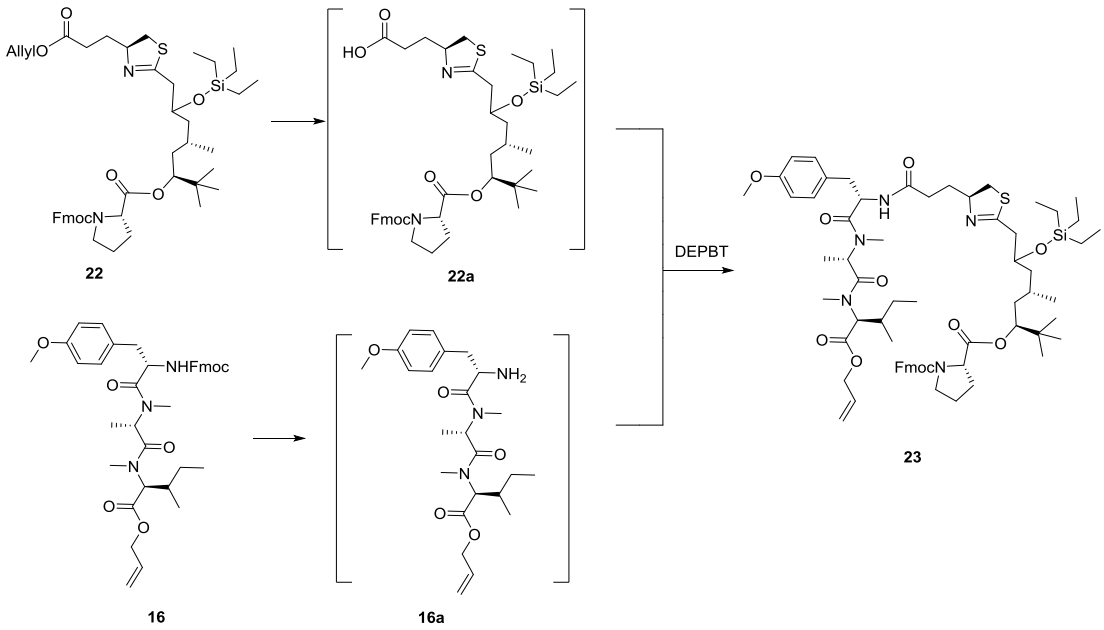
1-((9H-fluoren-9-yl)methyl)2-((3*S*,5*R*)-8-((*S*)-4-(3-(allyloxy)-3-oxopropyl)-4,5-dihydrothiazol-2-yl)-2,2,5-trimethyl-7-((triethylsilyl)oxy)octan-3-yl)(2*S*)-pyrrolidine-1,2-dicarboxylate (22)



To a solution of **21** (150.6 mg, 0.214 mmol) in anhydrous dichloromethane (2 mL) was added 2,6-lutidin (50 μL, 0.427 mmol) and stirred at -78 °C for 10 min. Then TESOTf (73 μL, 0.321 mmol) was added and stirred for another 20 min at the same temperature. After quenched with saturated NH_4Cl, the reaction mixture was extracted with diethyl ether (10 mL×3). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by chromatography eluting with petroleum ether/ethyl acetate (3/1) to afford 138.1 mg of **22** as colorless oil, yield 79%. $[\alpha]_D^{20}$ = -62.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN) δ: 7.82 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.43–7.40 (m, 2H), 7.36–7.30 (m, 2H), 5.98–5.85 (m, 1H), 5.32–5.26 (m, 1H), 5.21–5.17 (m, 1H), 4.81–4.75 (m, 1H), 4.55–4.51 (m, 2H), 4.46–4.37 (m, 1H), 4.26–4.23 (m, 2H), 4.11–3.97 (m, 3H), 3.56–3.38 (m, 2H), 3.31 (dd, *J* = 10.9, 8.5 Hz, 0.3H), 3.08 (dd, *J* = 10.9, 8.5 Hz, 0.7H), 2.85 (dd, *J* = 10.9, 8.7 Hz, 0.3H), 2.61–2.56 (m, 1.7H), 2.53–2.19 (m, 4H), 1.90–1.79 (m, 2H), 1.76–1.62 (m, 2H), 1.47–1.31 (m, 3H), 1.30–1.22 (m, 1H), 1.18–1.04 (m, 1H), 0.95–0.82 (m, 21H), 0.71 (d,

J = 6.4 Hz, 1H), 0.59–0.49 (m, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ: 173.6, 173.5, 168.3, 167.9, 155.4, 155.0, 145.4, 145.2, 145.0, 144.9, 142.2, 142.1, 133.8, 128.7, 128.14, 128.12, 126.4, 126.3, 126.1, 121.0, 80.6, 79.8, 77.4,77.3, 70.6, 70.4, 68.0, 65.5, 60.6, 60.2, 48.3, 48.0, 47.8, 47.3, 45.3, 43.7, 42.5, 39.2, 39.0, 38.9, 35.4, 35.2, 32.4, 32.3, 31.9, 31.24, 30.20, 30.8, 28.1, 27.2, 26.2, 25.2, 24.1, 21.4, 21.3, 7.3, 5.84, 5.79; ESI-MS:819.4$[M+H]^+$, HRMS (ESI–TOF) calcd for $[C_{46}H_{66}N_2O_7SSi + Na]^+$ 841.4252, found 841.4258.

1-((9H-fluoren-9-yl)methyl)2-((3*S*,5*R*)-8-((S)-4-((5*S*,8*S*,11*S*)-11-((S)-sec-butyl)-5-(4-methoxybenzyl)-7,8,10-trimethyl-3,6,9,12-tetraoxo-13-oxa-4,7,10-triazahexadec-15-en-1-yl)-4,5-dihydrothiazol-2-yl)-2,2,5-trimethyl-7-((triethylsilyl)oxy)octan-3-yl) (2S)-pyrrolidine-1,2-dicarboxylate (23)



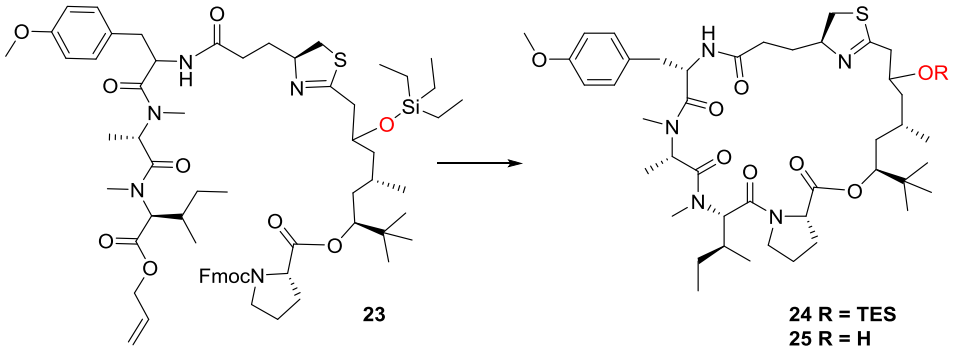
The procedure of the preparation of **22a** was the same as **12a**. The crude product was purified by chromatography eluting with dichloromethane/methanol (20/1) to afford 40.5 mg of **22a** as colourless oil, yield 85%.

To a solution of tripeptide **16** (35.0 mg, 0.052 mmol) in acetonitrile (1 mL) was added diethylamine (0.5 mL) and stirred for 20 min at room temperature. The reaction mixture was concentrated in *vacuo* and azeotroped with toluene and dichloromethane twice, respectively. Then the residue was

dried in *vacuo* to afford **16a**, which was used in the next coupling reaction without further purification.

To a solution of **16a** in anhydrous THF (3 mL) was added the newly prepared **22a**, DEPBT (15.6 mg, 0.052 mmol) and DIPEA (14.0 μL， 0.080 mmol). The resultant mixture was stirred overnight at room temperature under nitrogen atmosphere and concentrated in *vacuo*. The residue was purified by chromatography eluting with dichloromethane/methanol (20/1) to afford 41.3 mg of **23** as white solid, yield 66%. $[\alpha]_D^{20}$ = -79.2 (*c* 0.12, MeOH); ^{1}H NMR (400 MHz, CD_3CN) δ: 7.84–7.81 (m, 2H), 7.68–7.61 (m, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.96–5.87 (m, 1H), 5.35–5.24 (m, 2H), 5.21 (dd, *J* = 10.6, 0.9 Hz, 1H), 5.05–4.98 (m, 1H), 4.78–4.72 (m, 2H), 4.60–4.55 (m, 2H), 4.45–4.37 (m, 1H), 4.33–4.24 (m, 2H), 4.20–4.08 (m, 3H), 4.07–4.02 (m, 1H), 3.73 (s, 3H), 3.52–3.41 (m, 2H), 3.28–3.18 (m, 1H), 2.93 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.88 and 2.87 (both s, total 3H), 2.85–2.80 (m, 1H), 2.77–2.71 (m, 2H), 2.59–2.57 (m, 2H), 2.55–2.51 (m, 1H), 2.29–2.12 (m, 5H), 1.79–1.65 (m, 3H), 1.61–1.51 (m, 2H), 1.46 (d, *J* = 6.8 Hz, 1H), 1.41–1.30 (m, 4H), 1.14–1.08 (m, 3H), 0.94–0.76 (m, 28H), 0.70 (d, *J* = 6.3 Hz, 1H), 0.61–0.50 (m, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ: 172.7, 172.14, 172.08, 172.0, 170.8, 158.7, 154.8, 154.5, 144.7, 144.3, 144.2, 143.9, 141.4, 131.9, 130.5, 127.84, 127.77, 127.1, 126.5, 125.4, 125.3, 120.1, 118.8, 114.0, 79.7, 79.2, 76.0, 75.8, 67.9, 67.7, 65.5, 64.0, 63.9, 60.6, 59.7, 59.4, 55.3, 50.4, 49.8, 47.4, 47.2, 46.6, 38.7, 38.3, 37.9, 37.3, 37.1, 36.8, 34.8, 33.8, 33.7, 33.4, 31.5, 31.1, 30.7, 30.2, 29.8, 29.6, 28.8, 26.1, 25.2, 24.6, 23.5, 22.8, 21.1, 20.7, 16.28, 16.24, 14.46, 14.42, 10.7; ESI-MS: 1208.6$[M+H]^+$, HRMS (ESI–TOF) calcd for $[C_{67}H_{97}N_5O_{11}SSi + Na]^+$ 1230.6567, found 1230.6639.

(30*S*)-Apratoxin E (2)



23

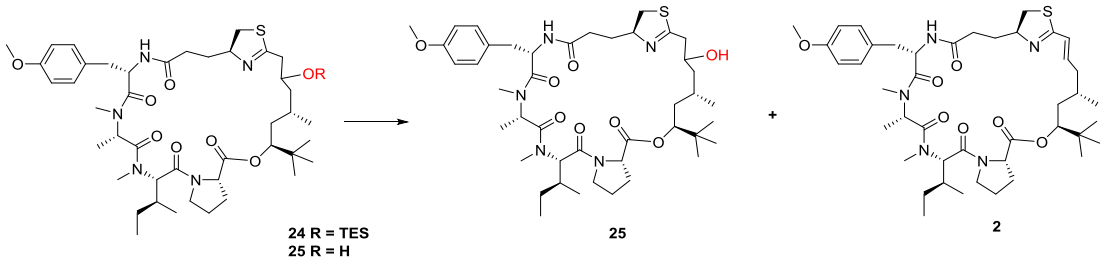
24 R = TES
25 R = H

To a solution of compound **23** (30.0 mg, 0.025 mmol) in anhydrous THF (1 mL) was added $Pd[P(Ph)_3]_4$ (13.7 mg, 0.012 mmol) and *N*-methyl aniline (8.0 μL, 0.060 mmol). The reaction mixture was stirred for 2 h at room temperature and concentrated in *vacuo*. The residue was purified by chromatography eluting with dimethylchloride/MeOH (10/1) to afford the intermediate of acid without further purification.

To a solution of the newly prepared acid in acetonitrile (1 mL) was added diethylamine (0.5 mL). The result solution was stirred for 20 min at room temperature under nitrogen atmosphere and concentrated in *vacuo* and azeotroped with toluene and dichloromethane two times, respectively. Then the residue was dried in *vacuo* to dryness which was used in the next coupling reaction without further purification.

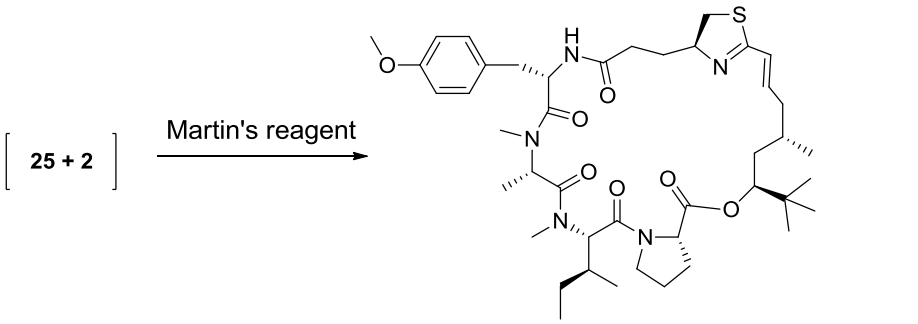
The residue was dissolved in anhydrous DMF (20 mL), then DEPBT (36.8 mg, 0.123 mmol) and DIPEA (72 μL, 0.41 mmol) was added at 0 °C. The resultant solution was stirred for 24 h at room temperature under nitrogen atmosphere and concentrated in *vacuo*. The residue was purified by chromatography eluting with dichloromethane/methanol (10/1) to afford 15.1 mg of a mixture of **24** and **25**.

24: ESI-MS: 928.5$[M+H]^+$, 951.4$[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{49}H_{81}N_5O_8SSi +H]^+$ 928.5648, found 928.678.



To a mixture of **24** and **25** in THF (1 mL) was added HF-pyridine complex (0.2 mL) and stirred for 30 min at room temperature. The LC-MS showed that compound **25** and the title compound **2** were both existed. Then the reaction mixture was quenched with saturated NH_4Cl, diluted with ethyl acetate, washed with 5% $KHSO_4$, 10% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*.

25: ESI-MS: 814.6[M+H]$^+$, 836.6[M+Na]$^+$, HRMS (ESI–TOF) calcd for [$C_{43}H_{67}N_5O_8S$ +H] $^+$ 814.4783, found 814.4812.

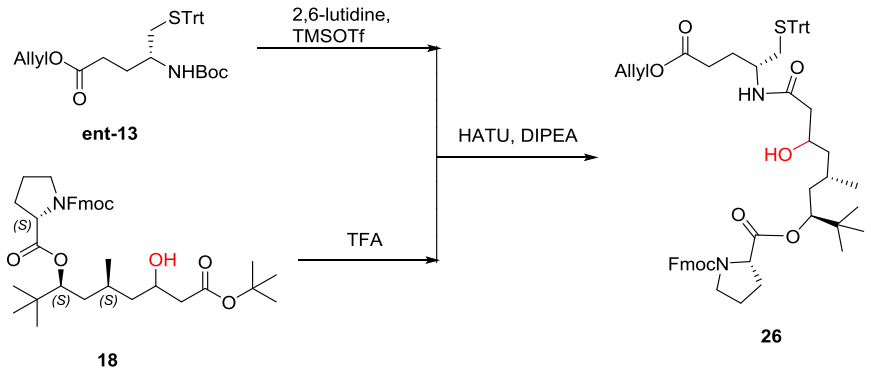


Originally Proposed Apratoxin E (2)

To the mixture above (containing **25** and **2**) in anhydrous dichloromethane (500 μL) was added Martin's reagent (20.0 mg) and stirred for 30 min under nitrogen atmosphere. When the LC-MS showed the reaction was completed, the reaction mixture was concentrated in *vacuo* and purified by PTLC (DCM : MeOH = 10 : 1) to afford the crude product 5.6 mg. Then the crude product was taken a further purification by semipreparative reversed-phase HPLC (Phenomenex Ultracarb, ODS 250 mm × 10 mm, 5 μm, 3.0 mL/min, UV detection at 200/220 nm) using an isocratic system of 80% aqueous MeCN for 30 min, 80−100% MeCN for 30−40 min, and 100% MeCN for 40−60 min to afford 3.6 mg of apratoxin E (**2**), yield 18% for 5 steps (from **23**). t_R = 33.7 min; $[\alpha]_D^{20}$ = -163.4 (*c* 0.106, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) (Data includes two conformers with ratio of 3:2) δ 7.15 (d, *J* = 8.6 Hz, 0.8H), 7.13 (d, *J* = 8.6 Hz, 1.2H), 6.81 (d, *J*= 8.6 Hz, 1.2H), 6.79 (d, *J*= 8.6 Hz, 0.8H), 6.60 (d, *J*= 15.7 Hz, 0.6H), 6.46-6.36 (m, 1.4H), 6.14 (d, *J* = 8.2 Hz, 0.6H), 5.84 (d, *J* = 9.8 Hz, 0.4H), 5.24 (d, *J* = 11.2 Hz, 0.6H), 5.22 (ddd, *J* = 15.0, 10.8 and 4.8 Hz, 0.4H), 5.16 (ddd, *J* = 10.6, 10.2 and 4.8 Hz, 0.6H), 4.97 (dd, *J* = 12.1, 1.40 Hz, 0.4H), 4.92 (dd, *J* = 11.7, 2.7 Hz, 0.6H), 4.89 (d, *J* = 11.4 Hz, 0.4H), 4.65 (q, *J* = 6.6 Hz, 0.6H), 4.41-4.35 (m, 1H), 4.33 (dd, *J* = 8.4 and 5.5 Hz, 0.6H), 4.22 (dd, *J* = 7.4 and 7.4 Hz, 0.4H), 4.15 – 4.11 (m, 0.4H), 4.08 – 4.04 (m, 0.6H), 3.78 (s, 1.2H), 3.77 (s, 1.8H), 3.70 - 3.66 (m, 0.4H), 3.65 – 3.61 (m, 0.6H), 3.32 (dd, *J* = 10.8 and 8.2 Hz, 0.6H), 3.30 (dd, *J* = 14.0 and 7.5 Hz, 0.4H), 3.29 (q, *J* = 6.9 Hz, 0.4H), 3.10 (dd, *J* = 13.2 and 11.0 Hz, 0.4H), 3.05 (dd, *J* = 12.8 and 10.5 Hz, 0.6H), 2.98 (s, 2H), 2.93(dd, *J* = 12.6, 5.0 Hz, 0.6 H), 2.92 (dd, *J* = 12.6, 4.2 Hz, 1H), 2.84 (s, 1H), 2.81 (s, 1H), 2.78 (dd, *J* = 13.0, 4.5 Hz, 0.4H), 2.62 (s, 2H), 2.65-2.59 (m, 0.4 H), 2.51-2.44(m, 1H), 2.43 - 2.40 (m, 0.6H), 2.36 – 2.31 (m, 0.4H), 2.28-2.24 (m, 3H), 2.05-1.94 (m, 5.6H), 1.72-1.69 (m, 1H), 1.64 (m, 0.4H), 1.57

(m, 0.4H), 1.56 (m, 0.6H), 1.45 (m, 0.6H), 1.32 (m, 0.4H), 1.29 (m, 0.4H), 1.25 (m, 0.6H), 1.23 (d, *J* = 6.7 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 1.8H), 1.03 (d, *J* = 6.6 Hz, 1.2H), 1.00 (t, *J* = 7.4, 1H), 0.96 (m, 0.4H), 0.94 (d, *J* = 6.6 Hz, 1.2H), 0.93 (d, *J* = 6.6 Hz, 1.8H), 0.88 and 0.87 (both s, total 9H), 0.83 (t, *J* = 7.4, 2H), 0.55 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (Data includes two conformers with ratio of 3:2) δ: 172.6, 172.1, 171.3, 171.0, 170.3, 170.1, 169.9, 169.7, 166.3, 166.2, 158.5, 158.4, 144.5, 130.3, 130.2, 129.4, 128.4, 126.4, 126.2, 113.9, 113.7, 77.4, 76.1, 60.4, 59.2, 58.9, 56.9, 57.6, 55.1, 53.9, 50.4, 49.6, 47.4, 39.6, 38.1, 37.5, 37.1, 36.5, 35.0, 34.6, 33.9, 33.4, 32.8, 31.7, 30.7, 30.2, 29.6, 29.5, 29.4, 29.2, 28.6, 25.9, 25.8, 25.7, 25.3, 25.0, 47.2, 20.3, 14.8, 13.9, 13.8, 13.7, 9.9, 9.8; HRMS (ESI–TOF) calcd for $[C_{43}H_{65}N_5O_7S+H]^+$ 796.4677, found 796.4680.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*S*)-9-(((*R*)-5-(allyloxy)-5-oxo-1-(tritylthio)pentan-2-yl)amino)-7-hydroxy-2,2,5-trimethyl-9-oxononan-3-yl)(2*S*)-pyrrolidine-1,2-dicarboxylate (26)



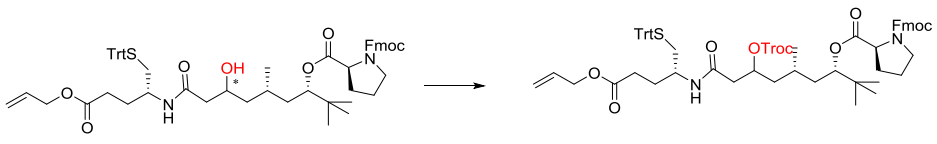
The procedure was the same as the preparation of **19**. The mixture was separated by chromatography eluting with petroleum ether/ ethyl acetate (4/1~1/1) to afford **26a** and **26b** both as white solid, yield 44% and 38%, respectively, total yield 82%.

26a: R_f = 0.57 (PE:EA=2:1, twice); $[\alpha]_D^{20}$ = -25.8 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.75–7.74 (m, 2H), 7.63−7.55 (m, 2H), 7.40−7.34 (m, 8H), 7.30−7.21 (m, 9H), 7.18−7.14 (m, 2H), 6.68 (d, *J* = 8.2 Hz, 0.5H), 6.21 (d, *J* = 8.3 Hz, 0.11H), 5.92−5.76 (m, 1H), 5.29−5.17 (m, 2H), 4.88−4.82 (m, 0.84H), 4.63−4.59 (m, 0.13H), 4.52 (d, *J* = 5.3 Hz, 0.55H), 4.48 (d, *J* = 5.4 Hz, 1.44H), 4.39−4.24 (m, 2H), 4.18−4.11 (m, 1H), 4.09–3.98(m, 1H), 3.92−3.80 (m, 1H), 3.67–3.53 (m, 1H), 3.51−3.37 (m, 1H), 2.38−2.24 (m, 3H), 2.22−2.04 (m, 5H), 2.00−1.86

(m, 2H), 1.61−1.50 (m, 3H), 1.47−1.37 (m, 2H), 1.35–1.30 (m, 1H), 0.95 (d, *J* = 5.0 Hz, 2.3H), 0.88 and 0.86 (both s, total 9H), 0.68 (d, *J* = 4.5 Hz, 0.7H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ: 173.3, 172.9, 172.74, 172.65, 172.6, 172.0, 155.1, 154.6, 144.7, 144.0, 143.9, 141.4, 132.3, 129.7, 128.07, 128.02, 127.8, 127.7, 127.3, 126.9, 126.8, 125.34, 125.30, 125.2, 120.13, 120.07, 118.4, 118.3, 80.3, 79.4, 67.7, 67.6, 66.94, 66.86, 65.3, 65.2, 60.5, 59.6, 59.3, 48.4, 48.3, 47.5, 47.3, 47.1, 46.5, 42.5, 42.3, 41.6, 41.3 , 37.9, 37.1, 36.7, 36.6, 35.0, 34.6, 31.2, 31.0, 30.1, 29.8, 29.1, 26.4, 26.2, 26.1, 24.3, 23.3, 21.6, 21.5, 21.2, 14.3, 14.2; ESI MS: 965.4$[M+H]^+$, 987.4 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{59}H_{68}NO_8S +Na]^+$ 987.4589, found 987.4628.

26b: R_f = 0.37 (PE:EA=2:1, twice); $[\alpha]_D^{20}$ = -23.2 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ: 7.73 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 0.22H), 7.56 (d, *J* = 7.1 Hz, 1.68H), 7.41−7.34 (m, 8H), 7.30−7.21 (m, 9H), 7.18−7.14 (m, 2H), 6.39 (d, *J* = 8.9 Hz, 0.62H), 6.04 (d, *J* = 8.7 Hz, 0.07H), 5.91−5.78 (m, 1H), 5.35−5.16 (m, 2H), 4.89 (d, *J* = 11.2 Hz, 0.71H), 4.80 (d, *J* =9.1 Hz, 0.2H), 4.52−4.46 (m, 2H), 4.35−4.33 (m, 2H), 4.21−4.15 (m, 1H), 3.97 (br m, 1H), 3.92−3.83 (m, 1H), 3.62−3.54 (m, 1H), 3.46−3.40 (m, 1H), 2.31−2.19 (m, 5H), 2.15−2.11 (m, 2H), 2.07−1.91 (m, 2H), 1.88−1.74 (m, 1H), 1.71−1.61 (m, 3H), 1.58−1.41 (m, 2H), 1.37−1.31 (m, 1H), 1.05–1.02 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 2.5H), 0.87 (s, 9H), 0.77 (d, *J* = 6.5 Hz, 0.5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ: 173.6, 173.0, 172.8, 172.4, 171.9, 171.7, 155.2, 154.4, 144.8, 144.04, 144.0, 141.42, 141.39, 132.34, 132.28, 129.7, 128.2, 128.08, 128.02, 127.8, 127.3, 127.2, 126.9, 126.8, 125.5, 125.34, 125.26, 125.2, 120.06, 120.04, 118.4, 118.2, 80.2, 78.8, 67.9, 67.6, 66.8, 66.5, 65.4, 65.2, 59.6, 48.1, 47.3, 47.1, 46.6, 44.8, 43.0, 42.6, 38.0, 37.2, 36.8, 34.8, 34.6, 32.1, 31.4, 30.9, 30.0, 29.8, 29.5, 29.4, 27.4, 26.1, 25.7, 25.3, 24.5, 23.5, 22.8, 21.0, 20.7, 14.2; ESI MS: 965.4 $[M+H]^+$, 987.4 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{59}H_{68}NO_8S +Na]^+$ 987.4589, found 987.4628.

1-((9H-fluoren-9-yl)methyl)2-((3*S*,5*S*)-9-(((*R*)-5-(allyloxy)-5-oxo-1-(tritylthio)pentan-2-yl)amino)-2,2,5-trimethyl-9-oxo-7-(((2,2,2-trichloroethoxy)carbonyl)oxy)nonan-3-yl) (2*S*)-pyrrolidine-1,2-dicarboxylate (27)



26a or 26b

27a from 26a

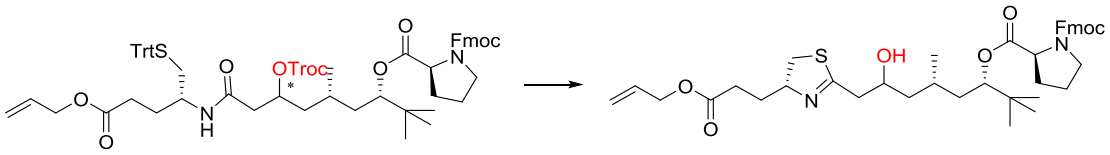
27b from 26b

The procedure was the same as the preparation of **20**.

27a: Yield 80%; $[\alpha]_D^{20}$ = -35.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.75–7.73 (m, 2H), 7.69–7.54 (m, 2H), 7.40–7.36 (m, 3H), 7.32–7.26 (m, 7H), 7.24–7.18 (m, 5H), 7.15–7.12 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 0.6H), 5.97–5.80 (m, 1H), 5.69 (d, *J* = 6.5 Hz, 0.03H), 5.32–5.28 (m, 1H), 5.23–5.17 (m, 1H), 4.90 (d, *J* = 11.3 Hz, 0.8H), 4.77 (d, *J* = 11.3 Hz, 1.2H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.52–4.48 (m, 2H), 4.44–4.27 (m, 2H), 4.24–4.09 (m, 2H), 3.89–3.71 (m, 1H), 3.64–3.59 (m, 1H), 3.56–3.40 (m, 1H), 2.52–2.29 (m, 3H), 2.27–2.04 (m, 5H), 1.98–1.88 (m, 3H), 1.77–1.70 (m, 2H), 1.67–1.53 (m, 2H), 1.49–1.39 (m, 2H), 1.36–1.19 (m, 3H), 1.03–0.74 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 172.7, 171.7, 169.3, 155.0, 153.3, 144.9, 144.1, 143.8, 141.5, 141.4, 132.4, 129.8, 128.1, 128.0, 127.9, 127.4, 127.2, 126.8, 125.4, 125.3, 120.1, 118.3, 94.7, 78.7, 76.7, 76.1, 67.8, 66.8, 65.2, 59.6, 48.4, 47.3, 46.4, 40.8, 39.9, 37.8, 36.6, 35.0, 30.9, 30.0, 29.8, 29.5, 26.2, 26.0, 25.5, 24.2, 20.8; ESI MS: 1139.4[M+H] $^+$, 1161.3[M+Na] $^+$, HR-MS (ESI–TOF) calcd for [$C_{62}H_{69}Cl_3N_2O_{10}S$ +Na] $^+$ 1161.3631, found 1161.3634.

27b: Yield 75%; $[\alpha]_D^{20}$ = -27.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ: 7.77−7.72 (m, 2H), 7.66 (d, *J* = 7.6 Hz, 0.38H), 7.58 (d, *J* = 7.4 Hz, 1.62H), 7.39−7.35 (m, 7H), 7.33−7.16 (m, 12H), 6.01 (d, *J* = 8.7 Hz, 0.34H), 5.92−5.81 (m, 1H), 5.52 (d, *J* = 8.6 Hz, 0.24H), 5.30−5.18 (m, 2.6H), 4.84−4.81 (m, 1.2H), 4.78–4.58 (m, 1H), 4.52−4.46 (m, 3H), 4.44−4.29 (m, 2H), 4.25−4.09 (m, 2H), 3.92−3.84 (m, 1H), 3.66−3.59 (m, 1H), 3.57−3.45 (m, 1H), 2.46−2.27 (m, 4H), 2.19−2.10 (m, 3H), 1.99−1.89 (m, 3H), 1.73−1.57 (m, 2H), 1.52−1.36 (m, 3H), 0.97 (d, *J* = 6.3 Hz, 2H), 0.86 and 0.85 (both s, total 9H), 0.79 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 172.8, 172.5, 168.9, 168.5, 154.9, 154.5, 153.61, 153.55, 144.7, 144.3, 144.2, 144.0, 143.9, 141.44, 141.35, 132.3, 129.7, 128.10, 128.08, 127.9, 127.8, 127.2, 127.0, 126.9, 125.4, 125.3, 120.1, 118.5, 94.8, 79.7, 79.4, 76.8, 75.6, 75.0, 68.0, 67.6, 66.9, 65.3, 59.9, 59.6, 48.4, 47.4, 46.5, 41.7, 40.0, 37.7, 36.5, 35.0, 30.9, 30.2, 29.8, 29.3, 26.2, 26.0, 24.5, 23.5, 20.8; ESI MS: 1139.4 [M+H] $^+$, 1161.4 [M+Na] $^+$, HRMS (ESI–TOF) calcd for [$C_{62}H_{69}Cl_3N_2O_{10}S$ +Na] $^+$ 1161.3631, found 1161.3634.

1-((9H-fluoren-9-yl)methyl)2-((3*S*,5*S*)-8-((*R*)-4-(3-(allyloxy)-3-oxopropyl)-4,5-dihydrothiazol-2-yl)-7-hydroxy-2,2,5-trimethyloctan-3-yl)(2*S*)-pyrrolidine-1,2-dicarboxylate (28)



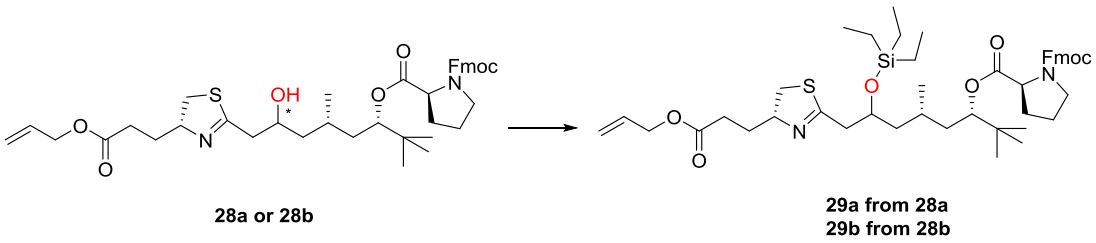
The procedure was the same as the preparation of **21**.

28a: $[\alpha]_D^{20}$ = -33.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.65–7.56 (m, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 5.96–5.86 (m, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.90–4.83 (m, 1H), 4.58 (d, *J* = 5.1 Hz, 2H), 4.52−4.44 (m, 1H), 4.42−4.32 (m, 3H), 4.28−4.23 (m, 1H), 4.21−4.14 (m, 1H), 4.06–3.94 (m, 1H), 3.74−3.63 (m, 1H), 3.60−3.53 (m, 1H), 3.37 (t, *J* = 9.7 Hz, 0.24H), 3.16 (t, *J* = 9.8 Hz, 0.49H), 2.90 (t, *J* = 9.2 Hz, 0.18H), 2.70–2.58 (m, 1H), 2.54−2.47 (m, 2H), 2.40−2.21 (m, 2H), 2.15−1.93 (m, 4H), 1.89–1.84 (m, 1H), 1.68−1.42 (m, 4H), 1.39−1.30 (m, 2H), 0.97 (d, *J* = 6.3 Hz, 2H), 0.88 (s, 9H), 0.79 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 173.01, 172.97, 172.7, 172.5, 170.6, 170.2, 154.9, 154.4, 144.7, 144.3, 144.2, 143.9, 141.41, 141.31, 132.3, 129.7, 128.0, 127.83, 127.77, 1227.20, 127.16, 127.12, 125.5, 125.4, 125.3, 120.07, 120.01, 118.4, 80.3, 79.4, 76.2, 76.0, 67.9, 67.7, 65.4, 65.3, 59.7, 59.5, 47.4, 47.1, 46.6, 42.5, 42.4, 40.6, 40.4, 38.3, 38.2, 37.9, 37.7, 34.8, 31.6, 31.4, 30.5, 30.2, 29.8, 27.5, 26.4, 26.1, 24.5, 23.6, 21.8, 21.4; ESI MS: 705.4[M+H]$^+$, 727.3 [M+Na]$^+$, HR-MS (ESI–TOF) calcd for [$C_{40}H_{52}N_2O_7S$ +Na] $^+$ 727.3387, found 727.3399.

28b: Yield 76%. $[\alpha]_D^{20}$ = -22.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ: 7.76 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 6.4 Hz, 1.7 H), 7.57 (d, *J* = 7.3 Hz, 0.3H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.3 (t, *J* = 7.2 Hz, 2H), 5.95–5.85 (m, 1H), 5.30 (d, *J* = 17.3 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.90 and 4.84 (both d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 5.1 Hz, 2H), 4.45−4.19 (m, 5H), 4.03–3.91 (m, 1H), 3.70−3.62 (m, 1H), 3.58−3.45 (m, 1H), 3.35 and 3.27 (both t, *J* = 9.8 Hz, total 1H), 2.93–2.81 (m, 1H), 2.56−2.48 (m, 4H), 2.33−2.18 (m, 1H), 2.08−1.91 (m, 5H), 1.86–1.80 (m,

1H), 1.73−1.57 (m, 3H), 1.44−1.28 (m, 2H), 0.97 (d, *J* = 6.3 Hz, 2H), 0.88 (s, 9H), 0.79 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 173.1, 173.0, 172.9, 172.5, 169.5, 155.1, 154.5, 144.4, 144.3, 144.1, 144.0, 141.44, 141.35, 132.4, 127.76, 127.74, 127.2, 125.6, 125.5, 125.4, 120.0, 118.4, 79.8, 78.8, 76.3, 75.9, 67.9, 67.8, 67.4, 66.9, 65.4, 65.3, 59.72, 59.68, 47.4, 47.1, 46.6, 42.9, 42.5, 42.2, 38.0, 38.16, 37.7, 34.9, 34.8, 31.6, 31.3, 30.4, 30.0, 29.8, 26.12, 26.06, 25.4, 24.6, 23.4, 20.7; ESI MS: 705.4 $[M+H]^+$, 727.3 $[M+Na]^+$, HR-MS (ESI–TOF) calcd for $[C_{40}H_{52}N_2O_7S + Na]^+$ 727.3387, found 727.3399.

1-((9*H*-Fluoren-9-yl)methyl)2-((3*S*,5*R*)-8-((*R*)-4-(3-(allyloxy)-3-oxopropyl)-4,5-dihydrothiazol-2-yl)-2,2,5-trimethyl-7-((triethylsilyl)oxy)octan-3-yl)(2*S*)-pyrrolidine-1,2-dicarboxylate (29)

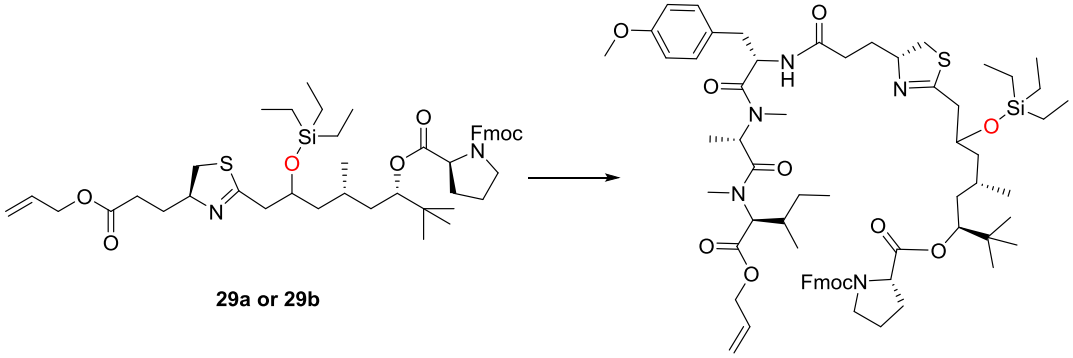


The procedure was the same as the preparation of **22**.

29a: Yield 80%. $[\alpha]_D^{20}$ = -52.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN, mixture of rotamers) δ: 7.83 (d, *J* = 7.3 Hz, 2H), 7.65 (dd, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.44–7.40 (m, 2H), 7.36–7.31 (m, 2H), 5.97–5.87 (m, 1H), 5.33–5.26 (m, 1H), 5.21–5.18 (m, 1H), 4.81–4.76 (m, 1H), 4.54–4.50 (m, 2H), 4.46–4.37 (m, 1H), 4.26–4.21(m, 2H), 4.16–4.02 (m, 2.4H), 3.93–3.85 (m, 0.6H), 3.56–3.40 (m, 2H), 3.31 (dd, *J* = 10.8, 8.6 Hz, 0.3H), 3.03 (dd, *J* = 10.8, 8.5 Hz, 0.7H), 2.83 (dd, *J* = 10.5, 9.6 Hz, 0.2H), 2.61–2.48 (m, 1.7H), 2.47–2.23 (m, 4H), 2.16–2.11 (m, 1H), 1.86–1.81 (m, 1H), 1.74–1.64 (m, 2H), 1.45–1.32 (m, 3H), 1.30–1.24 (m, 1H), 1.17–1.09 (m, 1H), 0.91–0.84 (m, 21H), 0.71 (d, *J* = 6.4 Hz, 1H), 0.53 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, CD_3CN, mixture of rotamers): δ 173.6, 173.5, 168.5, 168.1, 167.3, 155.4, 155.0, 145.4, 145.2, 145.0, 144.8, 142.2, 142.1, 133.8, 128.7, 128.1, 126.4, 126.2, 121.0, 80.6, 79.7, 77.4, 70.5, 70.4, 68.1, 68.0, 65.5, 60.5, 60.2, 48.3, 47.9, 47.8, 47.3, 45.3, 45.2, 42.6, 42.4, 39.1, 38.8, 35.4, 35.2, 32.4, 32.3, 31.8, 31.3, 30.8, 28.1, 27.1, 26.2, 25.2, 24.0, 21.29, 21.25, 7.3, 5.8; ESI-MS:819.4 $[M+H]^+$, 841.4 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{46}H_{66}N_2O_7SSi + Na]^+$ 841.4252, found 841.4258.

29b: Yield 83%. $[\alpha]_D^{20}$ = -30.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN, mixture of rotamers) δ: 7.83 (d, *J* = 7.2 Hz, 2H), 7.68–7.61 (m, 2H), 7.44–7.40 (m, 2H), 7.35–7.32 (m, 2H), 5.97–5.87 (m, 1H), 5.31–5.27 (m, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 4.73 (d, *J* = 8.9 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H), 4.44–4.38 (m, 1H), 4.33–4.25(m, 3H), 4.20–4.05 (m, 2H), 3.52–3.39 (m, 2H), 3.35–3.27 (m, 1H), 2.90–2.83 (m, 1H), 2.57–2.44 (m, 4H), 2.37–2.20 (m, 1H), 2.13–1.97 (m, 1H), 1.87–1.80 (m, 1H), 1.56–1.45 (m, 3H), 1.42–1.30 (m, 2H), 1.26–1.13 (m, 2H), 0.94–0.83 (m, 21H), 0.77 (d, *J* = 5.6 Hz, 1H), 0.61–0.52 (m, 6H); ^{13}C NMR (125 MHz, CD_3CN, mixture of rotamers): δ 173.6, 173.3, 168.3, 167.5, 167.3, 155.4, 155.0, 145.3, 145.23, 145.17, 144.8, 142.2, 142.1, 133.8, 128.7, 128.1, 126.4, 126.1, 121.0, 81.1, 80.6, 77.2, 69.9, 69.7, 68.0, 67.9, 65.5, 60.8, 60.3, 48.2, 48.0, 47.8, 47.2, 44.9, 43.8, 43.6, 39.3, 38.9, 35.6, 32.2, 31.8, 31.6, 31.1, 30.7, 30.5, 27.8, 27.3, 26.1, 25.1, 24.1, 21.6, 21.3, 7.3, 5.8; ESI-MS: 819.4 $[M+H]^+$, 841.4 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{46}H_{66}N_2O_7SSi + Na]^+$ 841.4252, found 841.4258.

1-((9H-fluoren-9-yl)methyl)2-((3S,5R)-8-((R)-4-((5S,8S,11S)-11-((S)-sec-butyl)-5-(4-methoxybenzyl)-7,8,10-trimethyl-3,6,9,12-tetraoxo-13-oxa-4,7,10-triazahexadec-15-en-1-yl)-4,5-dihydrothiazol-2-yl)-2,2,5-trimethyl-7-((triethylsilyl)oxy)octan-3-yl)(2S)-pyrrolidine-1,2-dicarboxylate (30)



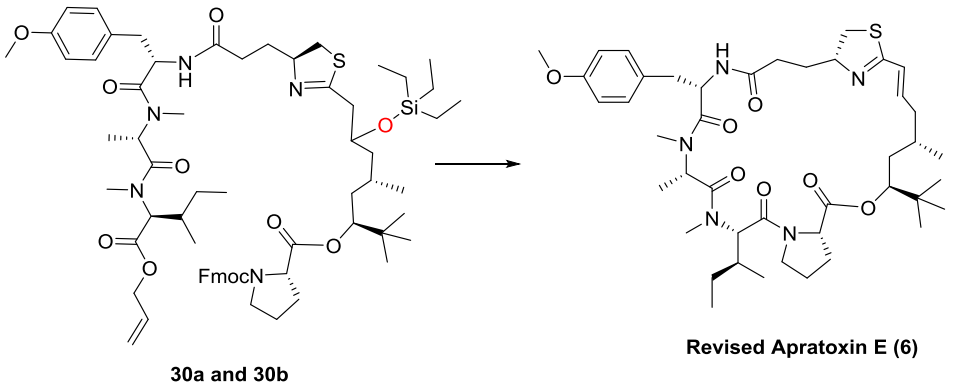
The procedure was the same as the preparation of **23** from **22**.

30a: Yield 46%. $[\alpha]_D^{20}$ = -92.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN, mixture of rotamers) δ: 7.83–7.81 (m, 2H), 7.67–7.62 (m, 2H), 7.43–7.39 (m, 2H), 7.36–7.30 (m, 2H), 7.15–7.13 (m, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.95–5.88 (m, 1H), 5.32–5.25 (m, 2H), 5.21 (d, *J* = 11.7 Hz, 1H), 5.03–4.98 (m, 1H), 4.80–4.75 (m, 2H), 4.59–4.53 (m, 2H), 4.46–4.43 (m, 1H), 4.40–4.37 (m, 1H),

4.35–4.30 (m, 1H), 4.28–4.25 (m, 1H), 4.21–4.15 (m, 1H), 4.12–4.08 (m, 1H), 3.73 (s, 3H), 3.53–3.43 (m, 2H), 3.28–3.18 (m, 1H), 3.03–2.92 (m, 2H), 2.884 and 2.878 (both s, total 3H), 2.85–2.80 (m, 1H), 2.75–2.71 (m, 2H), 2.60 and 2.57 (both s, total 3H), 2.33–2.24 (m, 2H), 1.85–1.76 (m, 2H), 1.73–1.64 (m, 2H), 1.61–1.50 (m, 2H), 1.45–1.39 (m, 2H), 1.34–1.22 (m, 8H), 1.16–1.02 (m, 5H), 0.94–0.79 (m, 24H), 0.69 (d, *J* = 6.4 Hz, 1H), 0.61–0.51 (m, 4H); ^{13}C NMR (125 MHz, CD_3CN, mixture of rotamers): δ 173.7, 173.5, 172.7, 172.5, 172.1, 171.2, 159.4, 155.4, 155.1, 145.4, 145.2, 145.1, 142.15, 142.11, 133.2, 131.4, 130.1, 128.8, 128.1, 126.3, 126.0, 121.0, 114.6, 79.7, 77.6, 77.4, 70.6, 70.4, 68.2, 68.0, 67.9, 65.9, 61.5, 60.5, 60.2, 55.8, 51.5, 50.7, 48.2, 47.9, 47.3, 47.2, 45.4, 45.2, 43.5, 42.6, 42.4, 39.0, 38.8, 38.0, 37.8, 35.3, 35.2, 34.0, 33.8, 31.9, 31.8, 31.5, 31.0, 30.8, 30.3, 30.2, 27.9, 27.1, 26.2, 26.1, 25.6, 25.2, 24.1, 23.3, 21.3, 16.0, 14.5, 11.8, 10.6, 7.31, 7.27, 5.79, 5.75; ESI-MS: 1208.6 $[M+H]^+$, 1231.6 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{67}H_{97}N_5O_{11}SSi + Na]^+$ 1230.6567, found 1230.6639.

30b: Yield 55%. $[\alpha]_D^{20}$ = -65.0 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN, mixture of rotamers) δ: 7.84–7.81 (m, 2H), 7.66–7.64 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 5.96–5.87 (m, 1H), 5.33–5.26 (m, 2H), 5.21 (d, *J* = 10.5 Hz, 1H), 5.05–4.99 (m, 1H), 4.78–4.72 (m, 2H), 4.61–4.51 (m, 2H), 4.46–4.36 (m, 1H), 4.33–4.25 (m, 2H), 4.22–4.05 (m, 3H), 3.72 (s, 3H), 3.52–3.39 (m, 2H), 3.30–3.21 (m, 1H), 2.94 (dd, *J* = 13.1, 6.3 Hz, 1H), 2.890 and 2.886 (both s, total 3H), 2.85–2.71 (m, 3H), 2.61–2.55 (m, 4H), 2.32–2.27 (m, 2H), 1.92–1.86 (m, 2H), 1.79–1.65 (m, 2H), 1.59–1.47 (m, 3H), 1.42–1.28 (m, 3H), 1.24–1.18 (m, 2H), 1.16–1.09 (m, 3H), 0.94–0.79 (m, 28H), 0.76 (d, *J* = 5.5 Hz, 1H), 0.61–0.52 (m, 6H); ^{13}C NMR (125 MHz, CD_3CN, mixture of rotamers): δ 173.3, 173.2, 172.6, 172.4, 172.1, 171.3, 159.5, 155.3, 155.0, 145.3, 145.1, 144.6, 142.13, 142.07, 133.4, 133.0, 132.66, 132.62, 131.4, 130.0, 129.64, 128.7, 128.1, 126.4, 126.1, 121.0, 114.6, 81.0, 80.6, 77.3, 69.9, 68.1, 67.9, 65.9, 61.5, 60.8, 60.3, 55.8, 51.4, 50.8, 48.1, 48.0, 47.8, 47.2, 44.9, 44.8, 43.7, 43.6, 39.32, 39.28, 38.90, 38.86, 38.0, 35.6, 33.81, 33.77, 33.71, 31.8, 31.7, 31.6, 31.5, 31.0, 30.7, 30.3, 27.6, 27.4, 26.1, 25.6, 25.1, 24.0, 21.6, 21.5, 16.0, 14.5, 10.6, 7.30, 5.74; ESI-MS: 1208.6 $[M+H]^+$, 1231.6 $[M+Na]^+$, HRMS (ESI–TOF) calcd for $[C_{67}H_{97}N_5O_{11}SSi + Na]^+$ 1230.6567, found 1230.6639.

(30*R*)-Apratoxin E (6)



The procedure was the same as the preparation of **2** from **23**. Crude yield 15% over 5 steps (from **30**). Compound **6** (4 mg, t_R 35.8 min) was purified using same method as compound **2**. $[\alpha]_D^{20}$−68 (*c* 0.182, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) (Data includes two conformers with ratio of 3:2) δ 7.16 (d, *J* = 8.7 Hz, 1.2H), 7.14 (d, *J* = 8.8 Hz, 0.8H), 6.82 (d, *J*= 9.0 Hz, 0.8H), 6.80 (d, *J*= 8.8 Hz, 1.2H), 6.54 (d, *J*= 15.8 Hz, 0.4H), 6.40-6.48 (m, 1.6H), 6.16 (d, *J* = 8.1 Hz, 0.4H), 5.89 (d, *J* = 9.6 Hz, 0.6H), 5.25 (d, *J* = 11.4 Hz, 0.6H), 5.20 (ddd, *J* = 11.0, 9.8 and 4.8 Hz, 0.6H), 5.07 (ddd, *J* = 9.0, 6.5 and 6.0 Hz, 0.4H), 4.99 (dd, *J* = 12.5, 1.90 Hz, 0.6H), 4.92 (dd, *J* = 11.5, 2.60 Hz, 0.4H), 4.87 (d, *J* = 11.3 Hz, 0.4H), 4.68 (m, 0.4H), 4.62 (q, *J* = 6.7 Hz, 0.4H), 4.31-4.38 (m, 1H), 4.20 (dd, *J* = 7.7 and 7.7 Hz, 0.6H), 4.17 (m, 0.6H), 4.07 (m, 0.4H), 3.78 (s, 1.8H), 3.77 (s, 1.2H), 3.68 (m, 0.6H), 3.65 (m, 0.4H), 3.42 (dd, *J* = −10.5 and 7.6 Hz, 0.4H), 3.31 (dd, *J* = −10.7 and 7.6 Hz, 0.6H), 3.28 (q, *J* = 6.7 Hz, 0.6H), 3.06 (dd, *J* = −12.0 and 9.0 Hz, 0.4H), 3.05 (dd, *J* = −12.2 and 11.0 Hz, 0.6H), 3.03 (s, 1.2H), 2.70-2.84 (m, 6.2H), 2.63 (s, 1.2H), 2.57, (ddd, *J* = −13.0, 8.0 and 4.3 Hz, 0.6H), 2.53 (m, 0.4H), 2.49 (m, 0.6H), 2.43 (m, 0.4H), 2.40 (m, 0.6H), 2.37 (m, 0.4H), 2.12-2.28 (m, 2H), 2.02-2.08 (m, 1H), 1.83-1.98 (m, 3.4H), 1.63-1.74 (m, 2.4H), 1.57 (m, 0.6H), 1.56 (m, 0.6H), 1.35 (m, 0.4H), 1.29 (m, 0.6H), 1.27 (m, 0.4H), 1.25 (m, 0.6H), 1.24 (dd, *J* = 6.7 and 6.7 Hz, 1.8H), 1.11 (d, *J* = 6.6 Hz, 1.2H), 1.10 (d, *J* = 6.6 Hz, 1.8H), 1.03 (t, *J* = 7.3, 1.8H), 0.97 (m, 0.4H), 0.95 (d, *J* = 6.6 Hz, 1.8H), 0.94 (d, *J* = 6.6 Hz, 1.2H), 0.88 (s, 3.6H), 0.87 (s, 5.4H), 0.85 (t, *J* = 7.2, 1.2H), 0.49 (d, *J* = 6.6 Hz, 1.2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 171.9, 171.8, 171.4, 171.3, 170.6, 170.2, 170.1, 170.0, 169.8, 166.4 166.2 158.7, 158.6, 144.2, 143.5, 130.5, 130.3, 128.6, 128.3, 126.5, 126.2, 114.1, 113.9, 77.6, 77.3, 75.9, 75.3, 60.5, 59.4, 58.9, 58.0, 56.7, 55.3, 55.2, 53.6, 51.4, 49.6, 47.4, 47.3, 39.7, 38.4, 37.9, 37.7, 37.6, 37.4, 37.3, 37.2, 36.6, 35.0, 34.8, 34.2, 33.4, 33.3, 32.5, 31.5, 31.0, 30.9, 30.0, 29.8, 29.5, 29.4, 29.2, 28.7, 3×26.1,

3×26.0, 25.7, 25.6, 25.3, 25.1, 20.6, 20.3, 14.6, 14.2, 13.9, 13.8, 10.11, 10.07. HRESIMS *m*/*z* [M + H]$^+$ 796.4648 (calcd for $C_{43}H_{66}N_5O_7S$ 796.4677).

Cell culture

HCT116 cells were maintained in DMEM medium supplemented with 10% FBS under a humidified environment with 5% CO_2 at 37°C.

Antiproliferative activity test using MTT assay

HCT116 (10000) cells were seeded in 96-well plates. Cells were treated with a series of concentrations of apratoxin E (**2**) or 30-*epi*-apratoxin E (**6**) dissolved in EtOH, 24 h postseeding. Cells were incubated for an additional 48 h before the addition of the MTT reagent. Cell viability was measured according to the manufacturer's instructions (Promega). Treatments were done in triplicate. Nonlinear regression analysis was carried out using GraphPad Prism software for IC_{50} value calculations.

3. Supplementary References

(1) Zou, B.; Wei, J.; Cai, G.; Ma, D. *Organic Letters* **2003**, *5*, 3503-3506.

(2) Chen, Q. Y.; Liu, Y.; Cai, W.; Luesch, H. *Journal of Medicinal Chemistry* **2014**, 3011-3029.

4. Figures

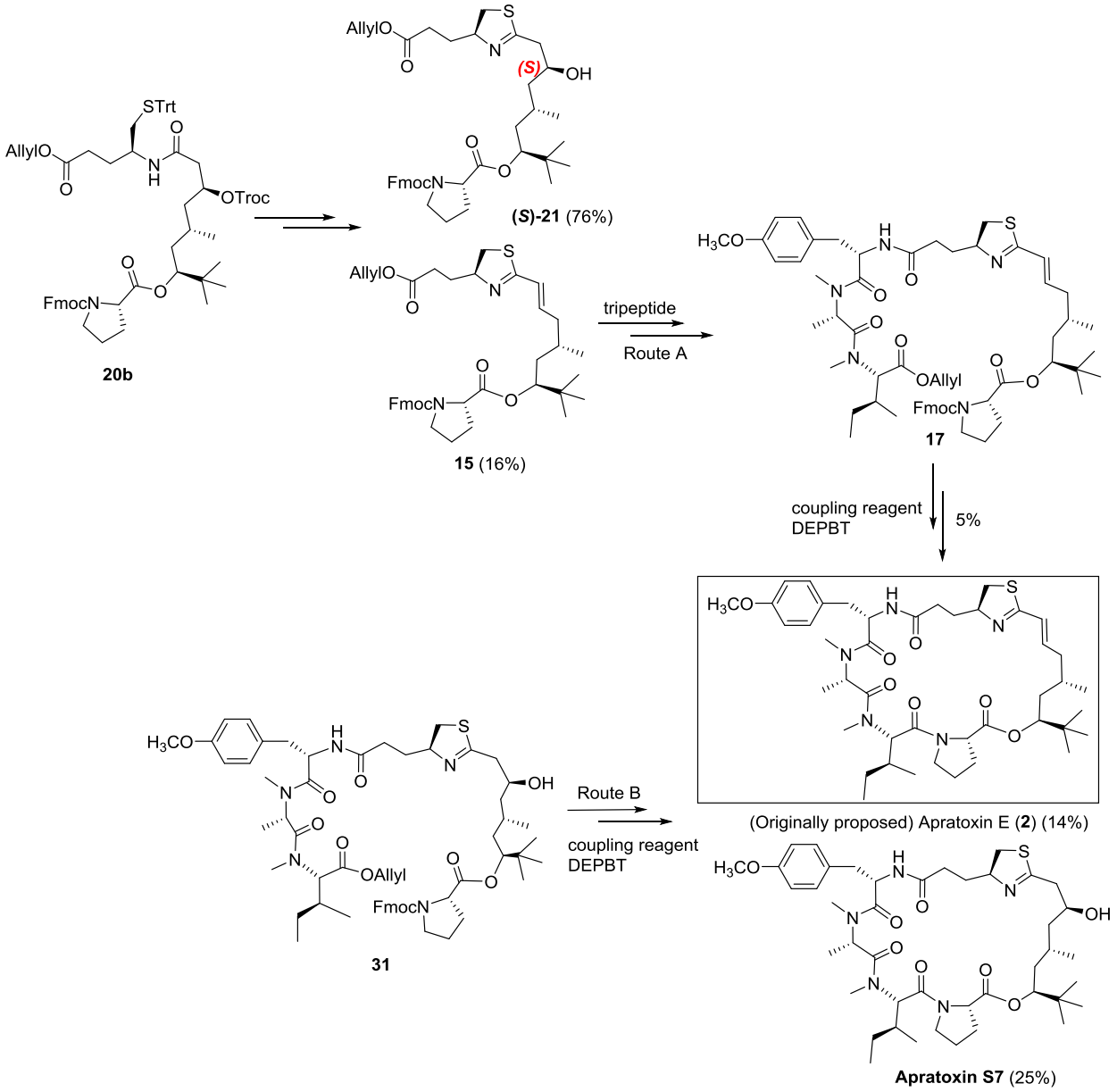


Figure S1 The side product apratoxin E (proposed) from the synthesis of apratoxin S7.

The originally proposed apratoxin E was obtained from the synthesis of apratoxin S7 through two strategies. First strategy: the minor dehydration product from the reaction of thiazoline ring formation was used as a starting material for the preparation of apratoxin E (originally proposed) with a yield of 5%. Second strategy: 14% apratoxin E (originally proposed) was obtained during the step of macrocyclization (The detailed procedures are the same as the synthesis of apratoxin S7. Please refer to Chen, et al. *J. Med. Chem.* **2014**, 57, 3011-3029).

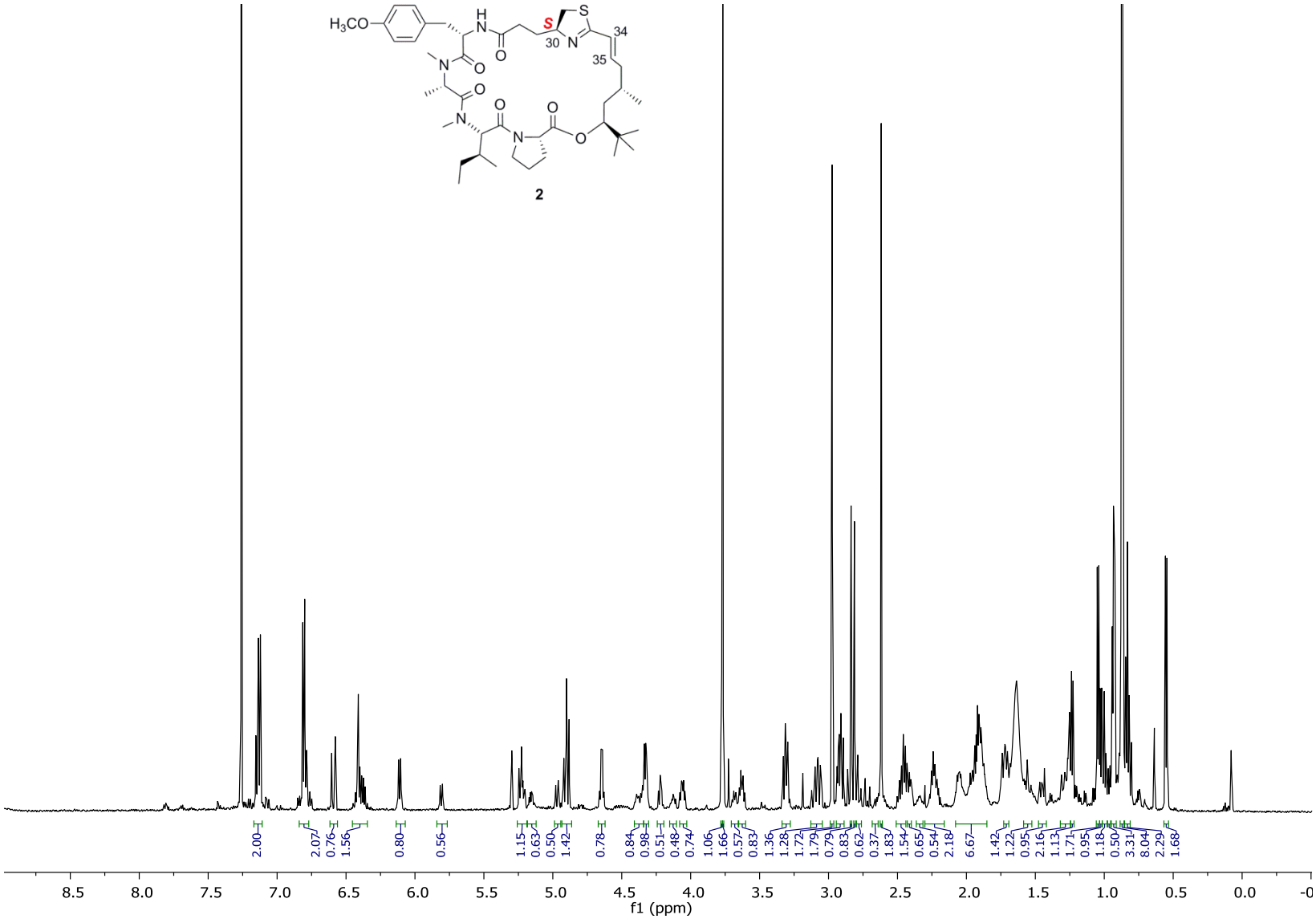


Figure S2 ^{1}H NMR spectrum of dehydration product from the synthesis of apratoxin S7.

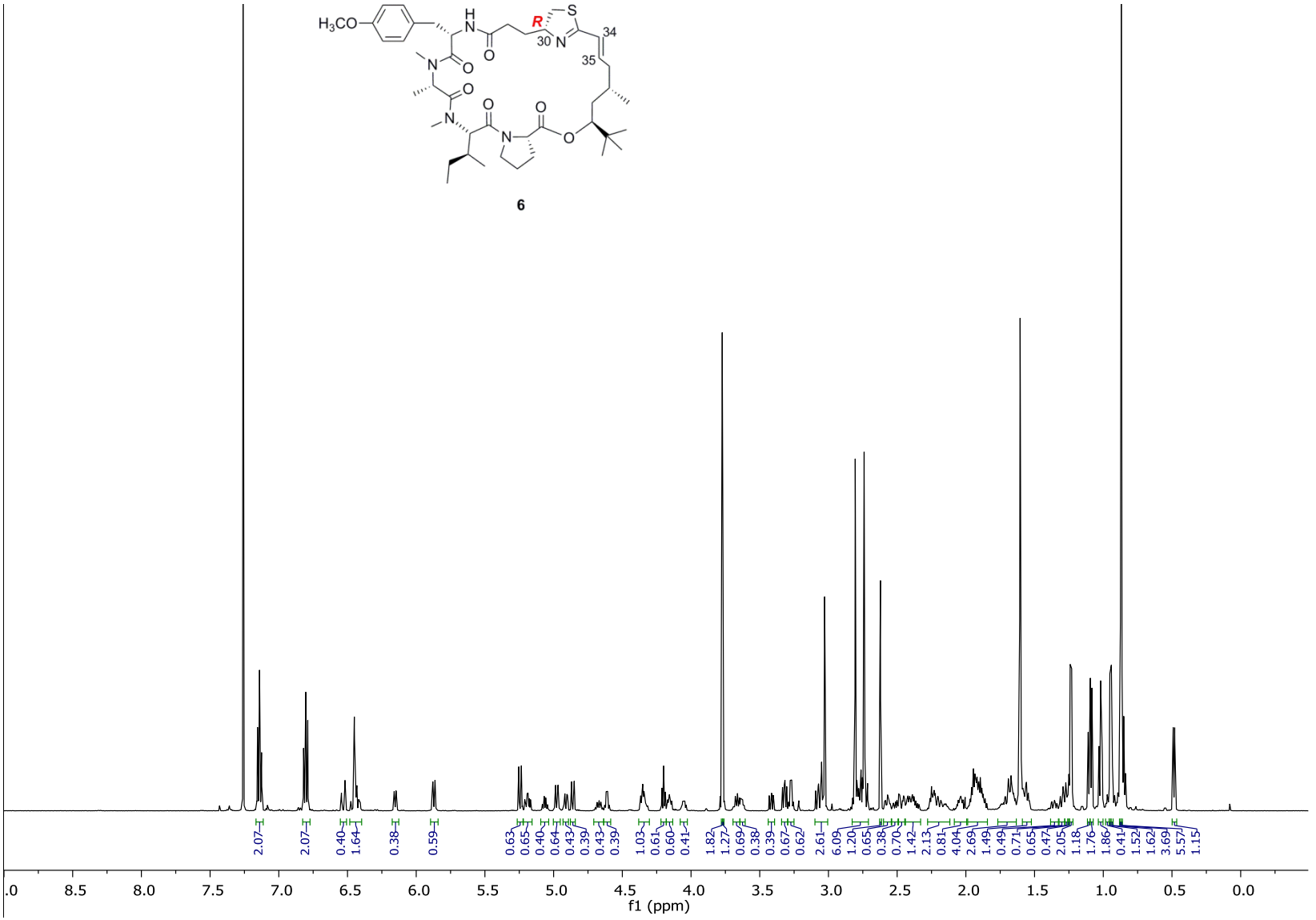


Figure S3 ^{1}H NMR spectrum of (30*R*)-apratoxin E (**6**) in $CDCl_3$ (600 MHz).

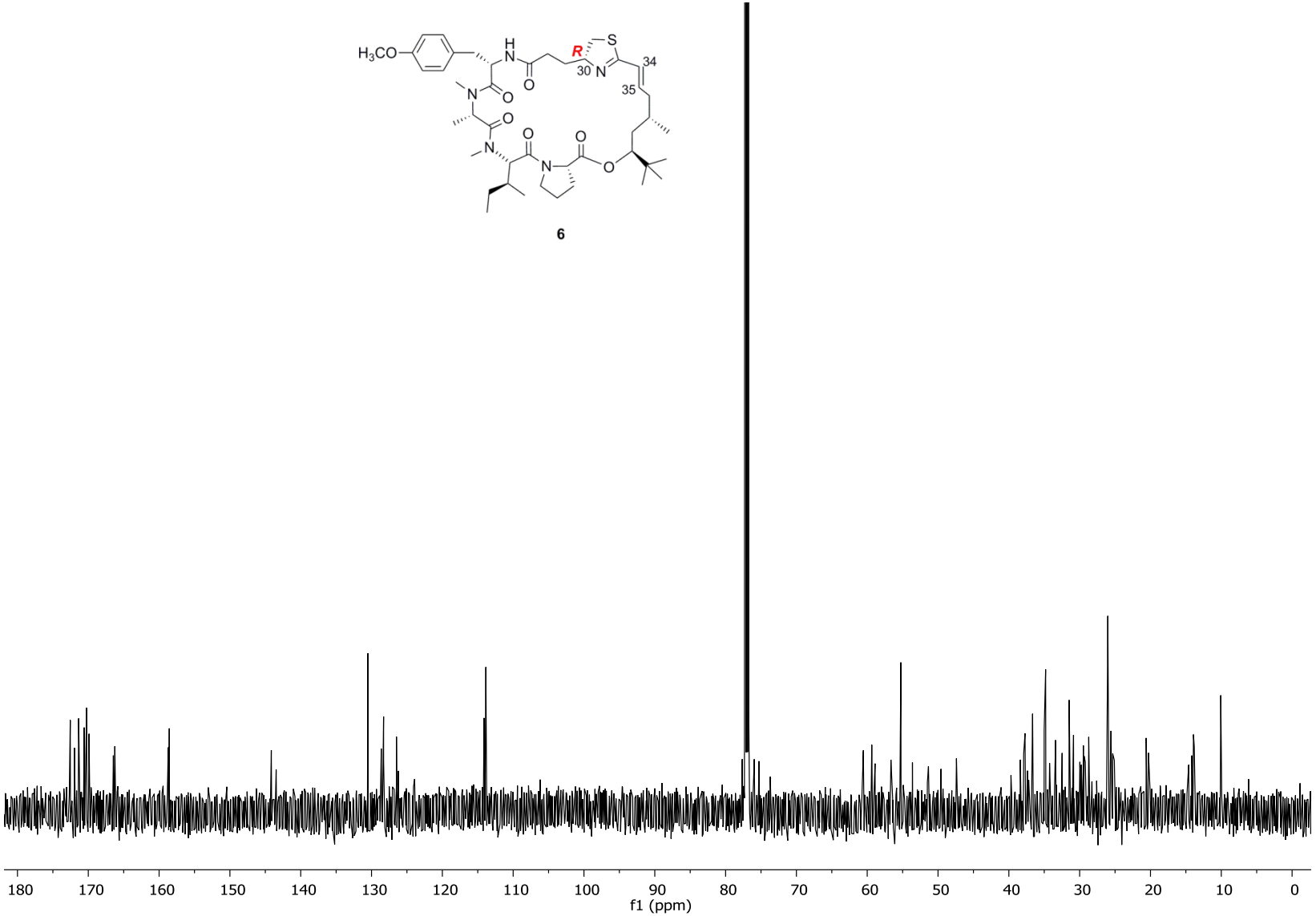


Figure S4 ^{13}C NMR spectrum of (30*R*)-apratoxin E (**6**) in $CDCl_3$ (150 MHz).

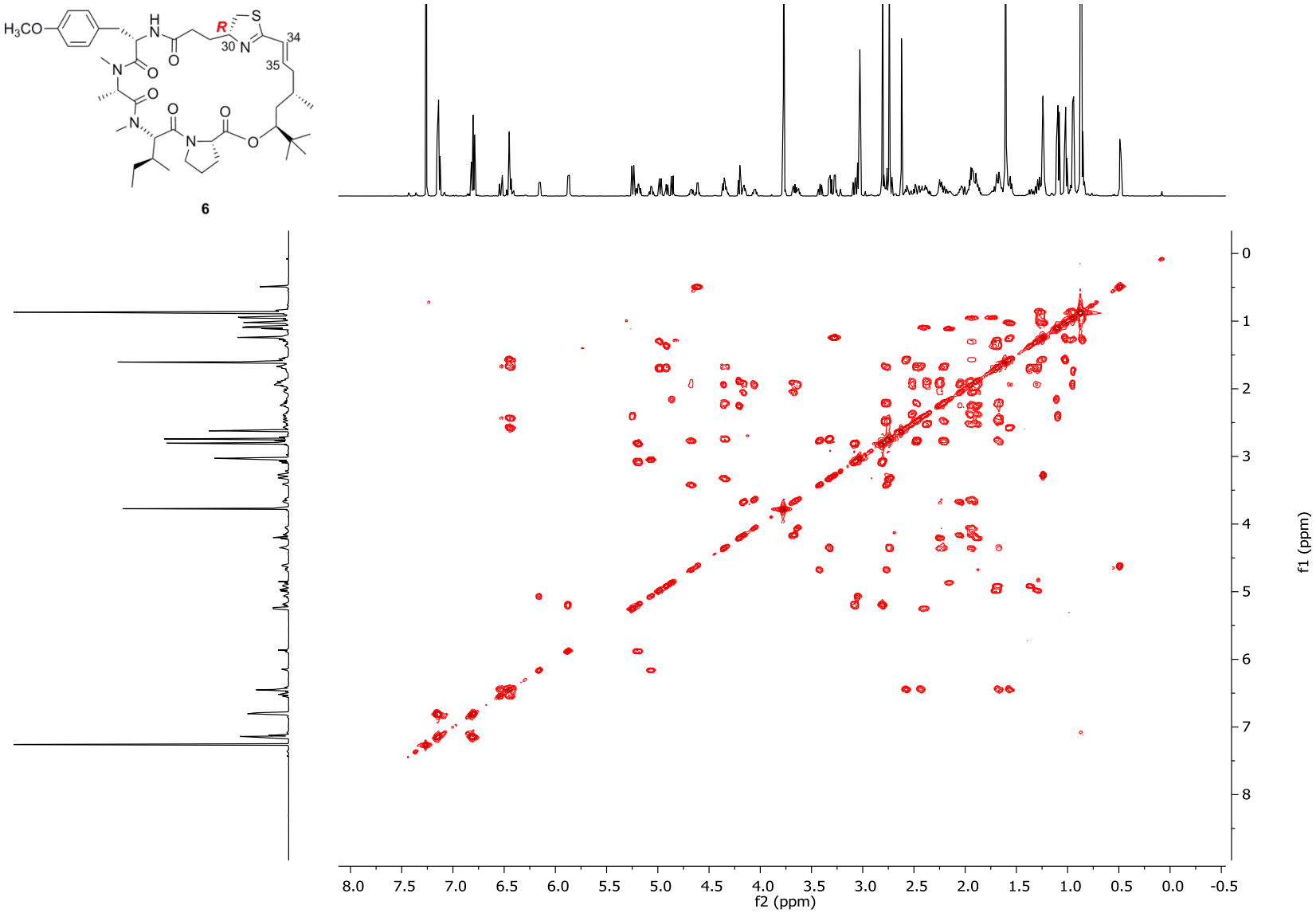


Figure S5 COSY spectrum of (30*R*)-apratoxin E (**6**) in $CDCl_3$.

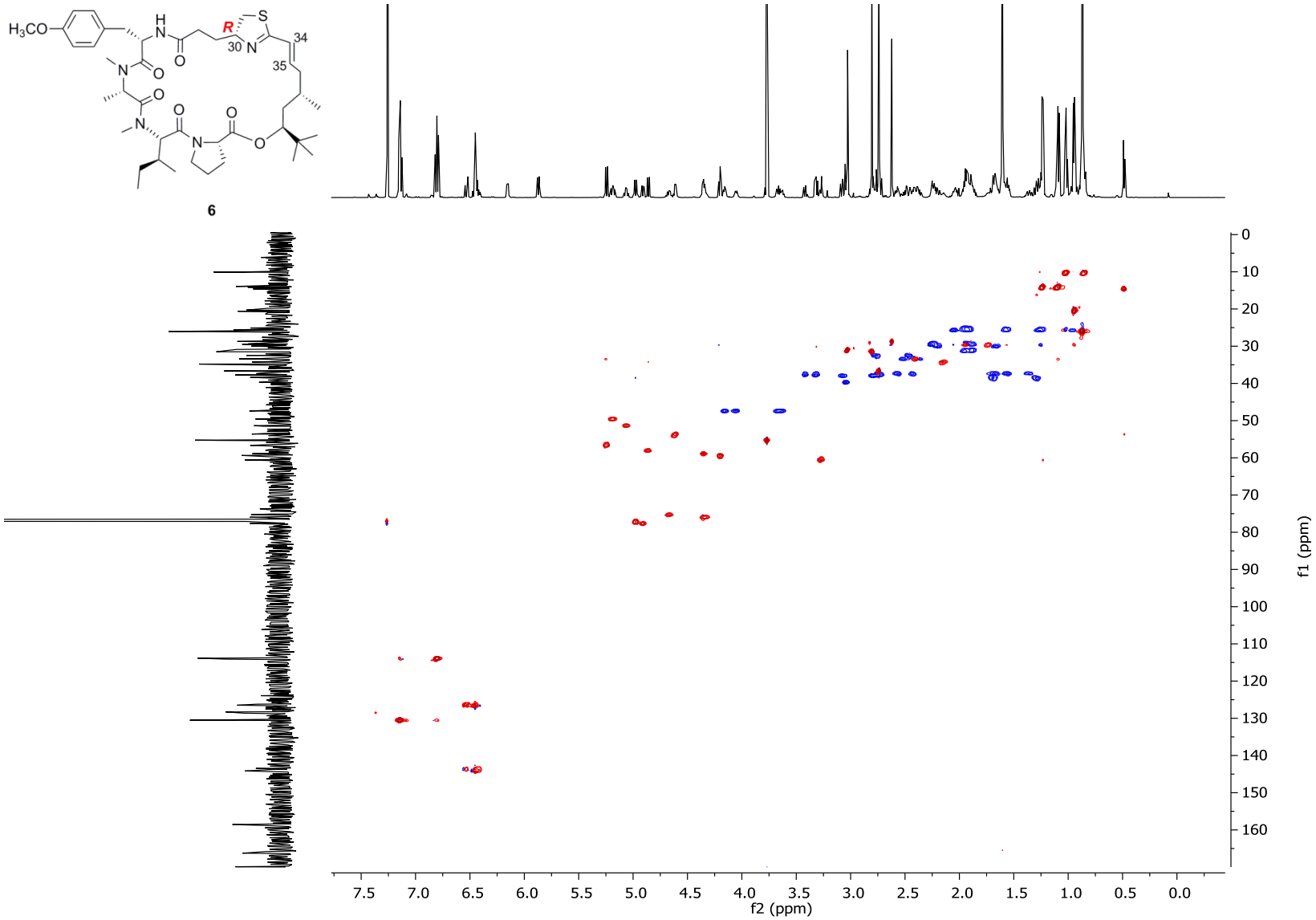


Figure S6 HSQC spectrum of (30*R*)-apratoxin E (**6**) in $CDCl_3$.

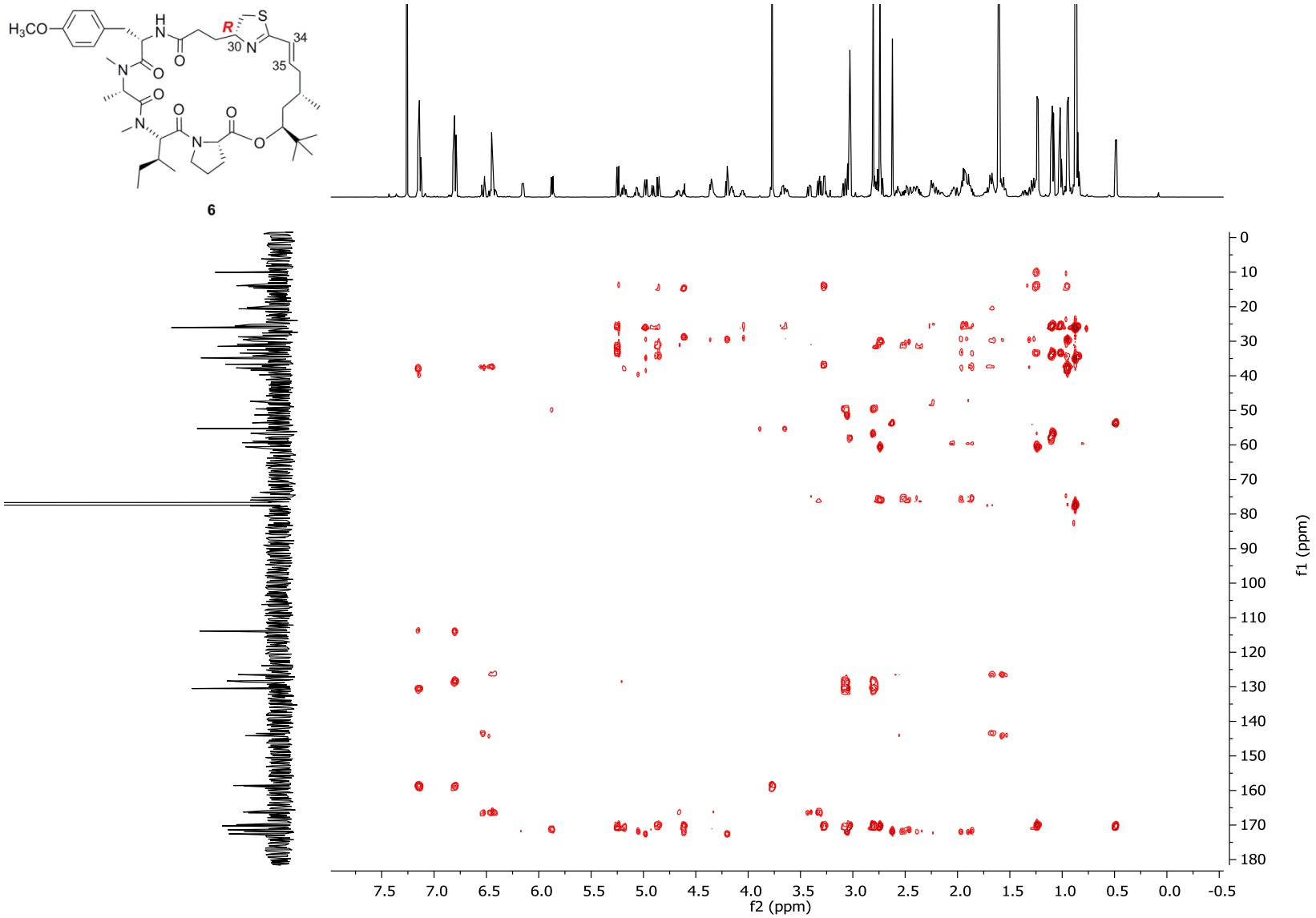


Figure S7 HMBC spectrum of (30*R*)-apratoxin E (**6**) in $CDCl_3$.

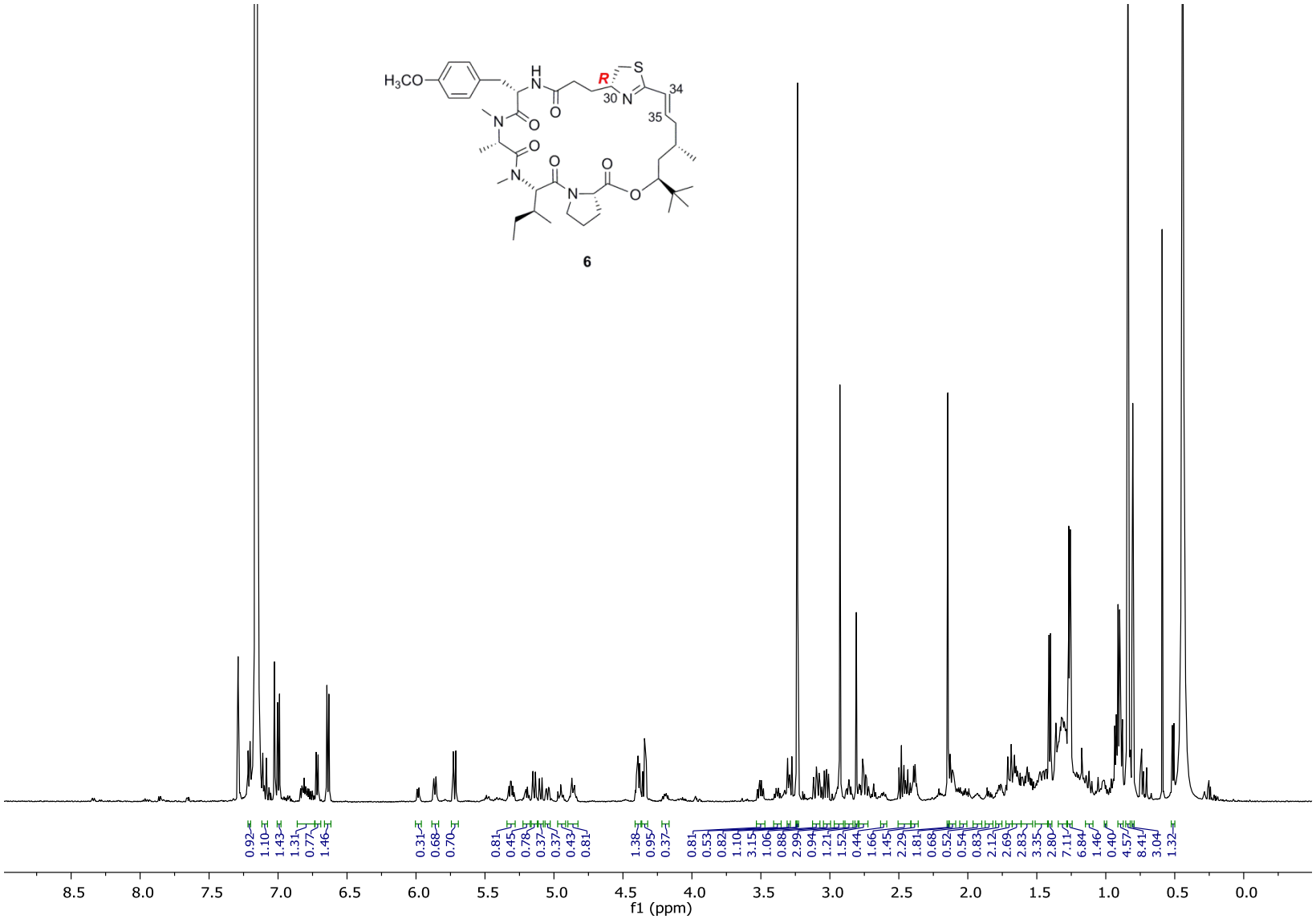


Figure S8 ^{1}H NMR spectrum of (30*R*)-apratoxin E (**6**) in C_6D_6 (600 MHz)

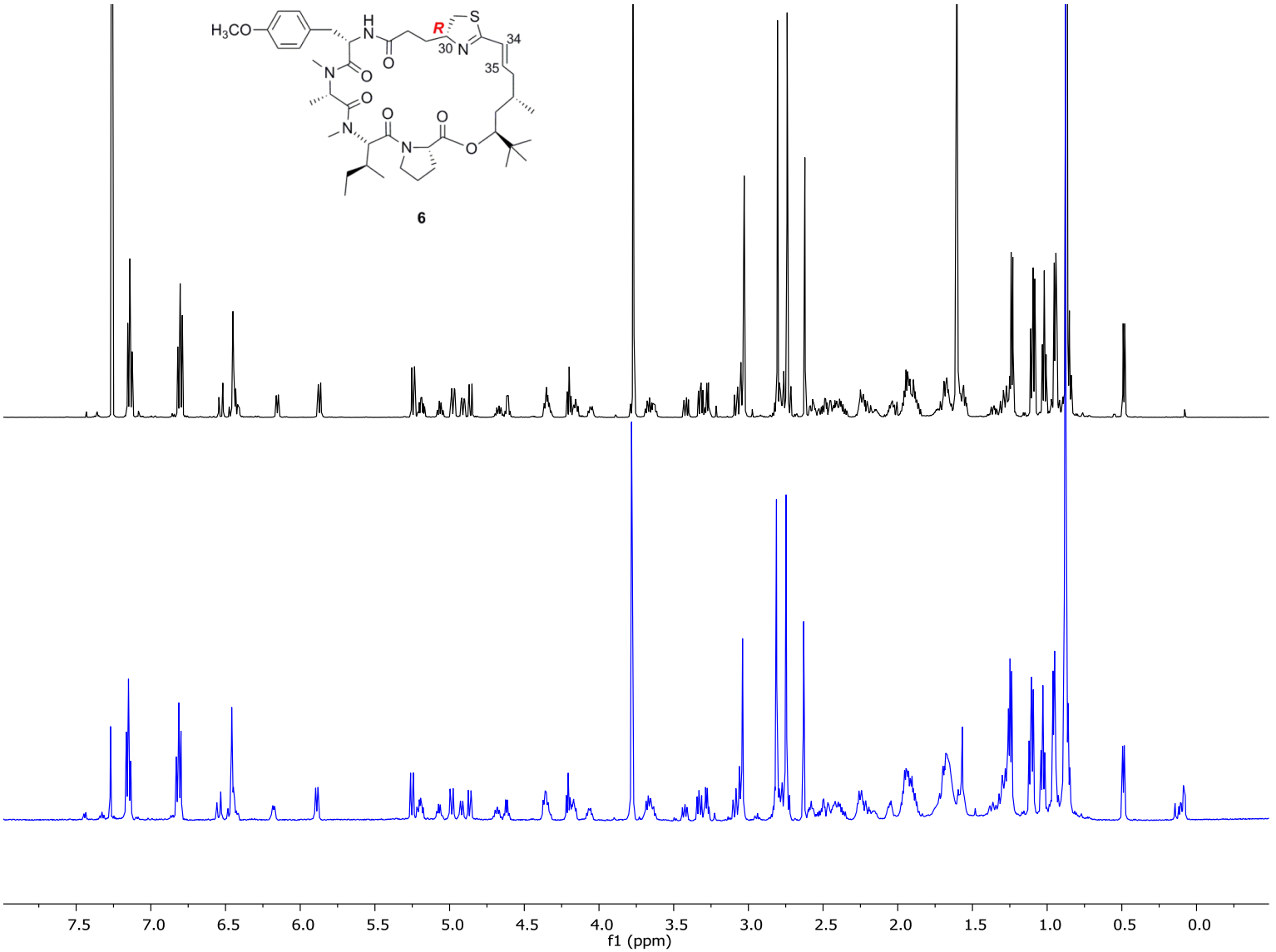


Figure S9 ^{1}H NMR spectrum of (30*R*)-apratoxin E (**6**, top) and natural apratoxin E (bottom) in $CDCl_3$ (600 MHz)

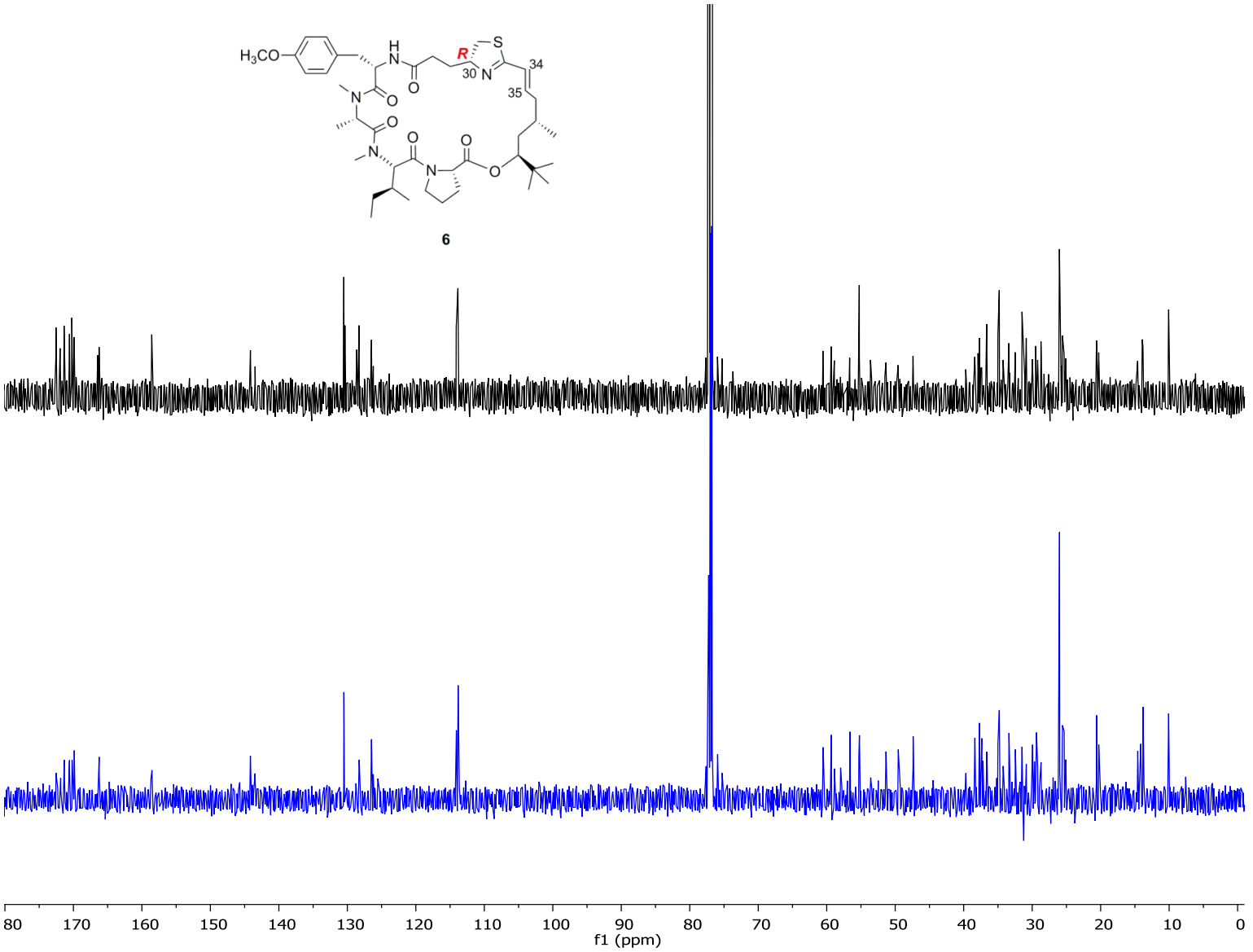


Figure S10 ^{13}C NMR spectrum of (30*R*)-apratoxin E (**6**, top) and natural apratoxin E (bottom) in $CDCl_3$ (150 MHz).

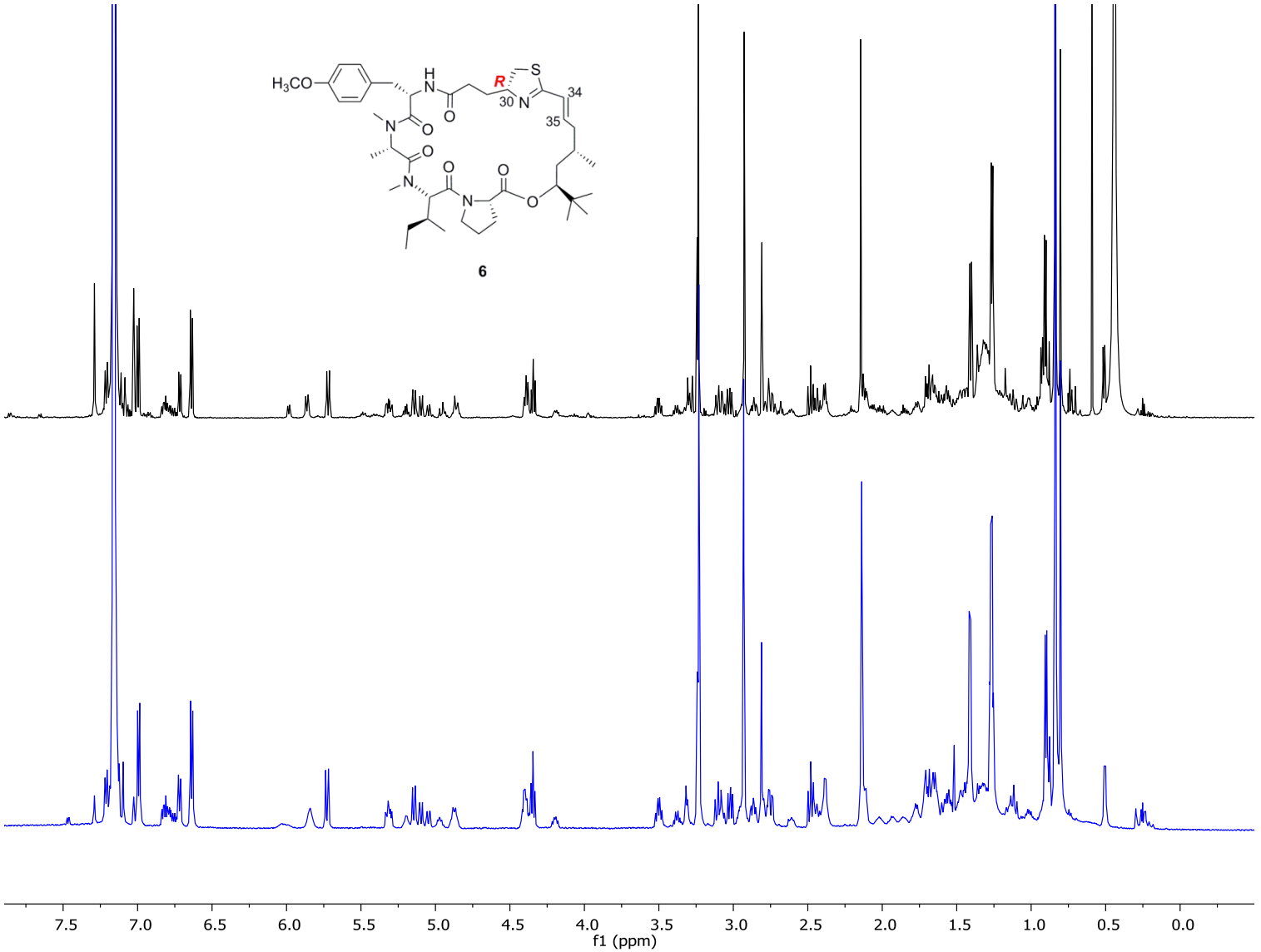


Figure S11 ^{1}H NMR spectrum of (30*R*)-apratoxin E (**6**, top) and natural apratoxin E (bottom) in C_6D_6 (600 MHz).

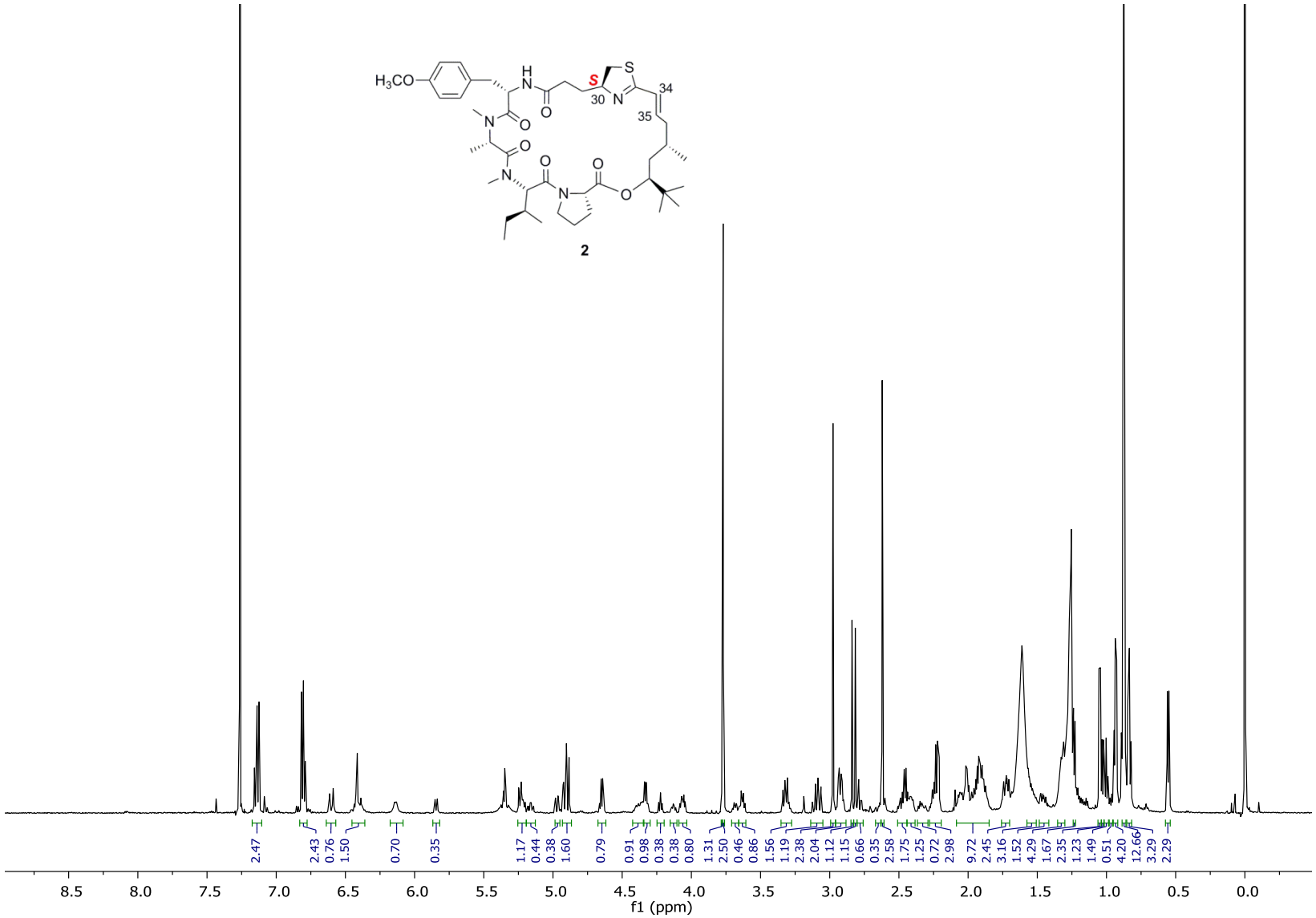


Figure S12 ^{1}H NMR spectrum of (30*S*)-apratoxin E (**2**) in $CDCl_3$ (600 MHz)

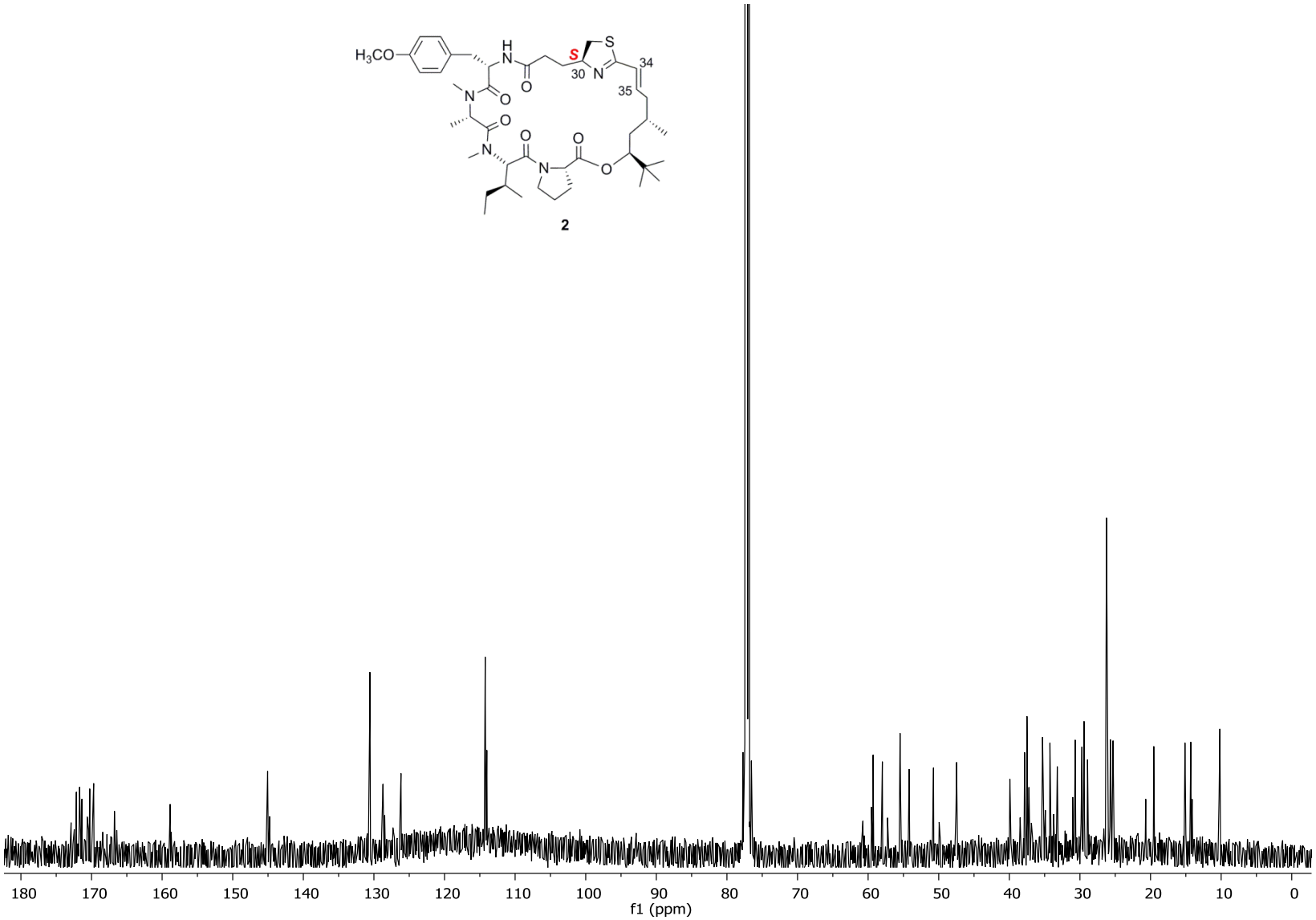


Figure S13 ^{13}C NMR spectrum of (30*S*)-apratoxin E (**2**) in $CDCl_3$ (150 MHz)

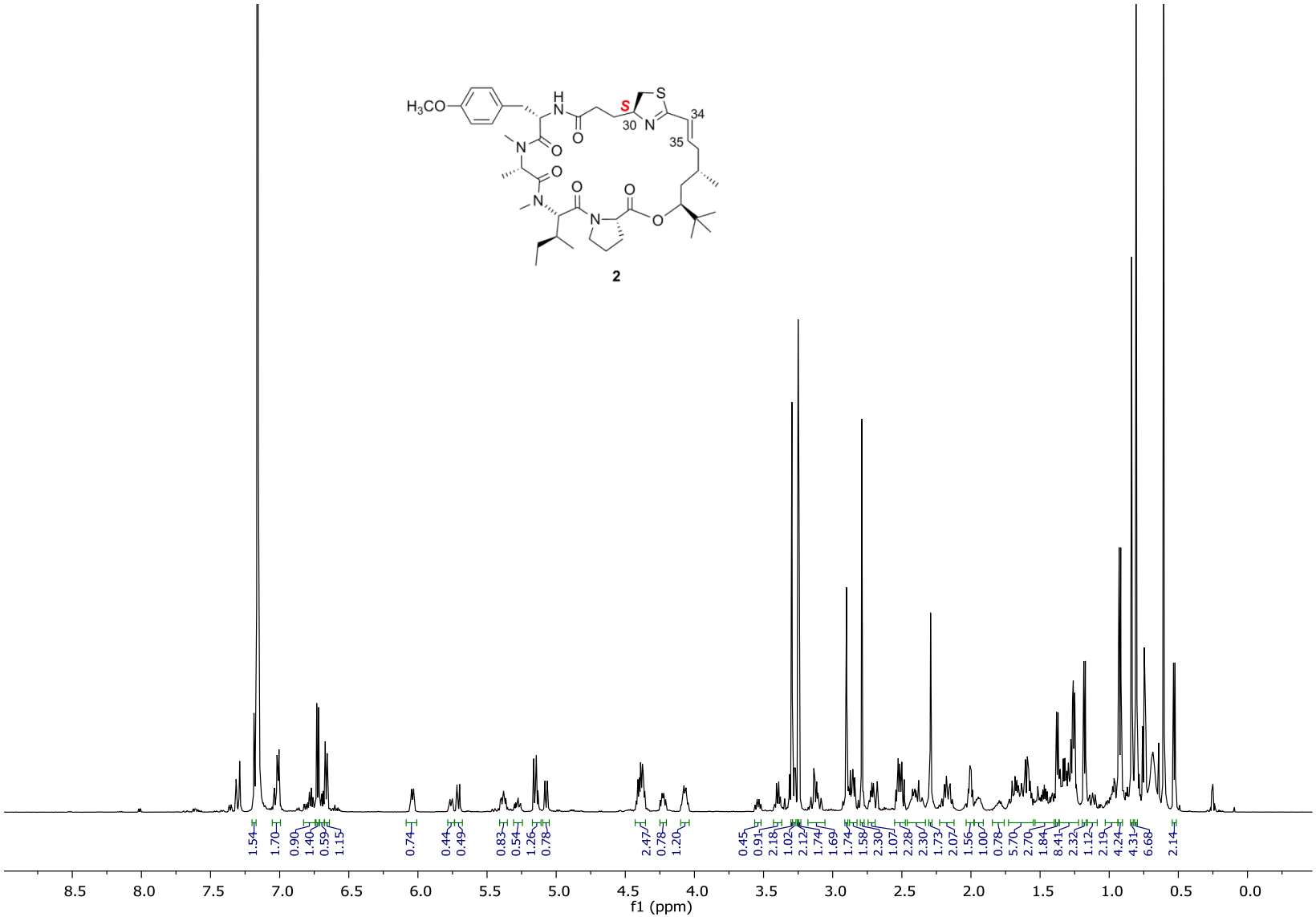


Figure S14 ^{1}H NMR spectrum of (30*S*)-apratoxin E (**2**) in C_6D_6 (600 MHz)

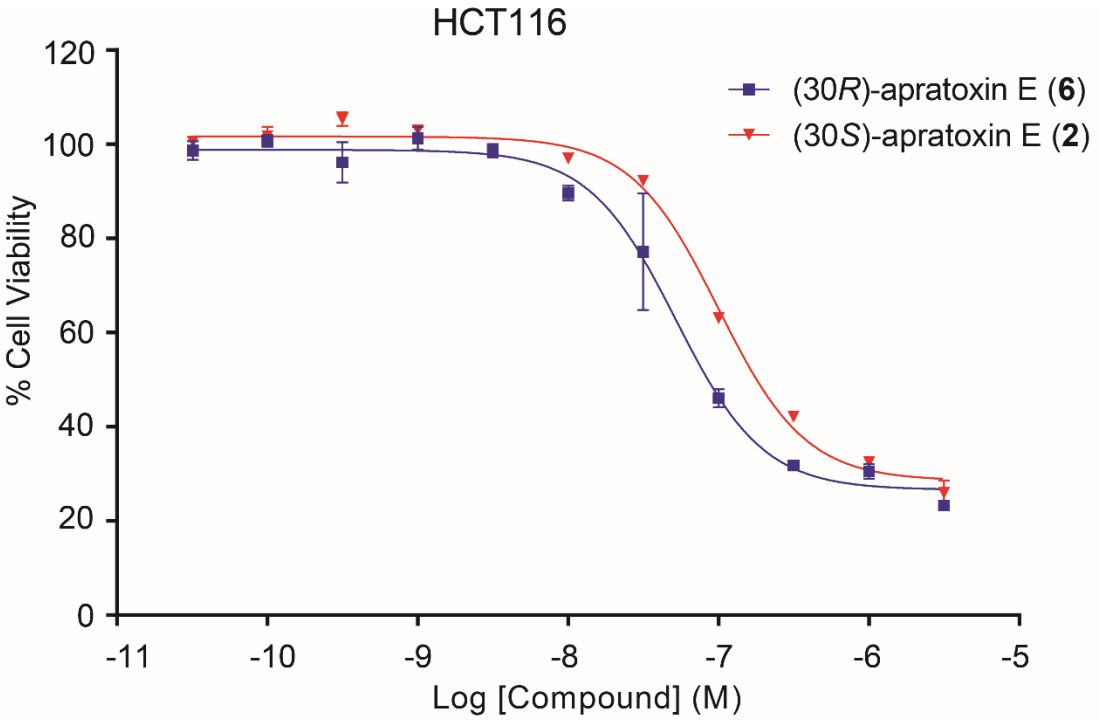
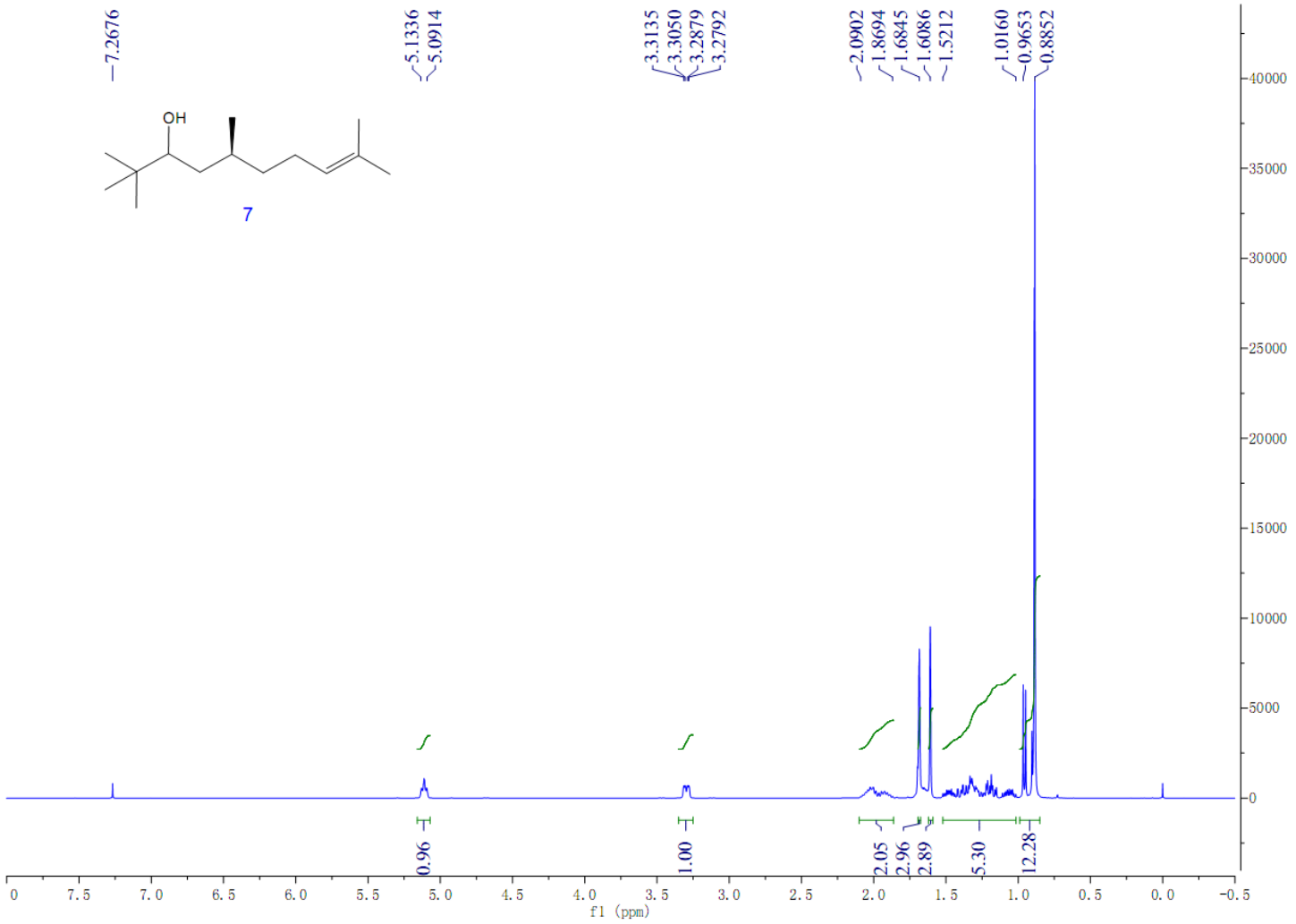
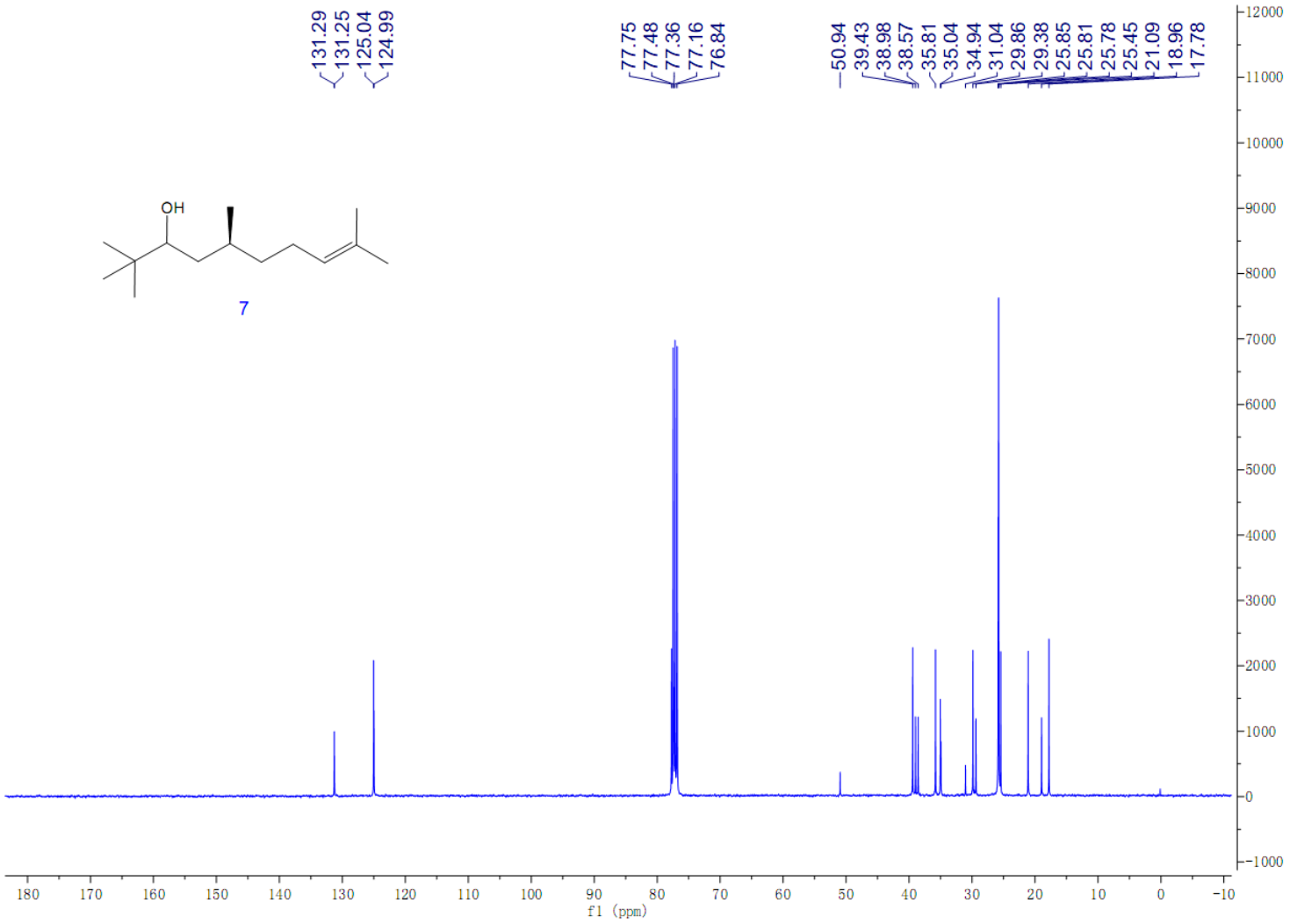


Figure S15 antiproliferative activity of (30*R*)-apratoxin E (**6**) and (30*S*)-apratoxin E (**2**) in HCT116 cells.

Figure S16 NMRs of all intermediates

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125.04
124.99
77.75
77.48
77.36
77.16
76.84
50.94
39.43
38.98
38.57
35.81
35.04
34.94
31.04
29.86
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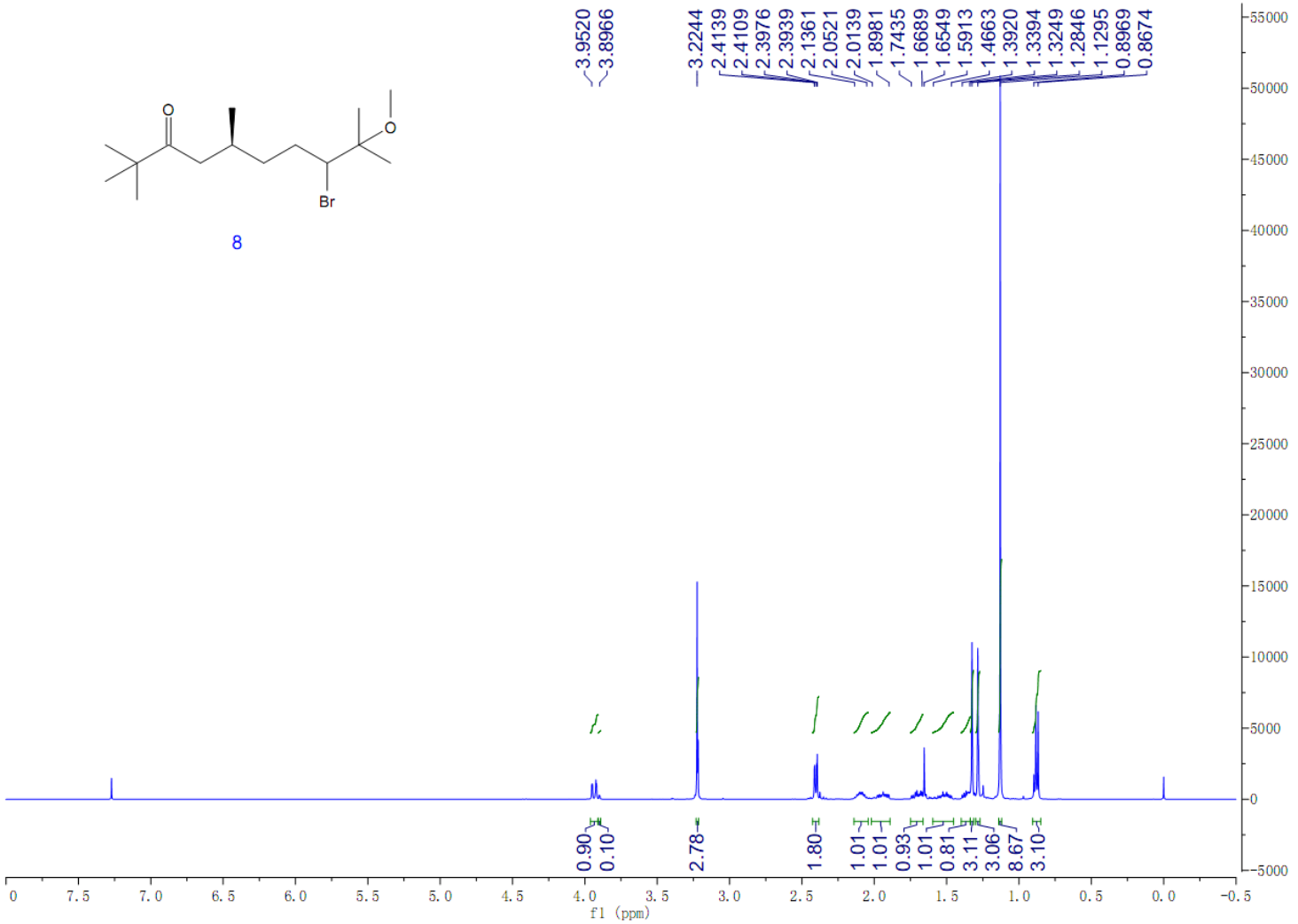
25.85
25.81
25.78
25.45
21.09
18.96
17.78
OH
7
f1 (ppm)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O
Br
8
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3.8966
3.2244
2.4139
2.4109
2.3976
2.3939
2.1361
2.0521
2.0139
1.8981
1.7435
1.6689
1.6549
1.5913
1.4663
1.3920
1.3394
1.3249
1.2846
1.1295
0.8969
0.8674
0.90
0.10
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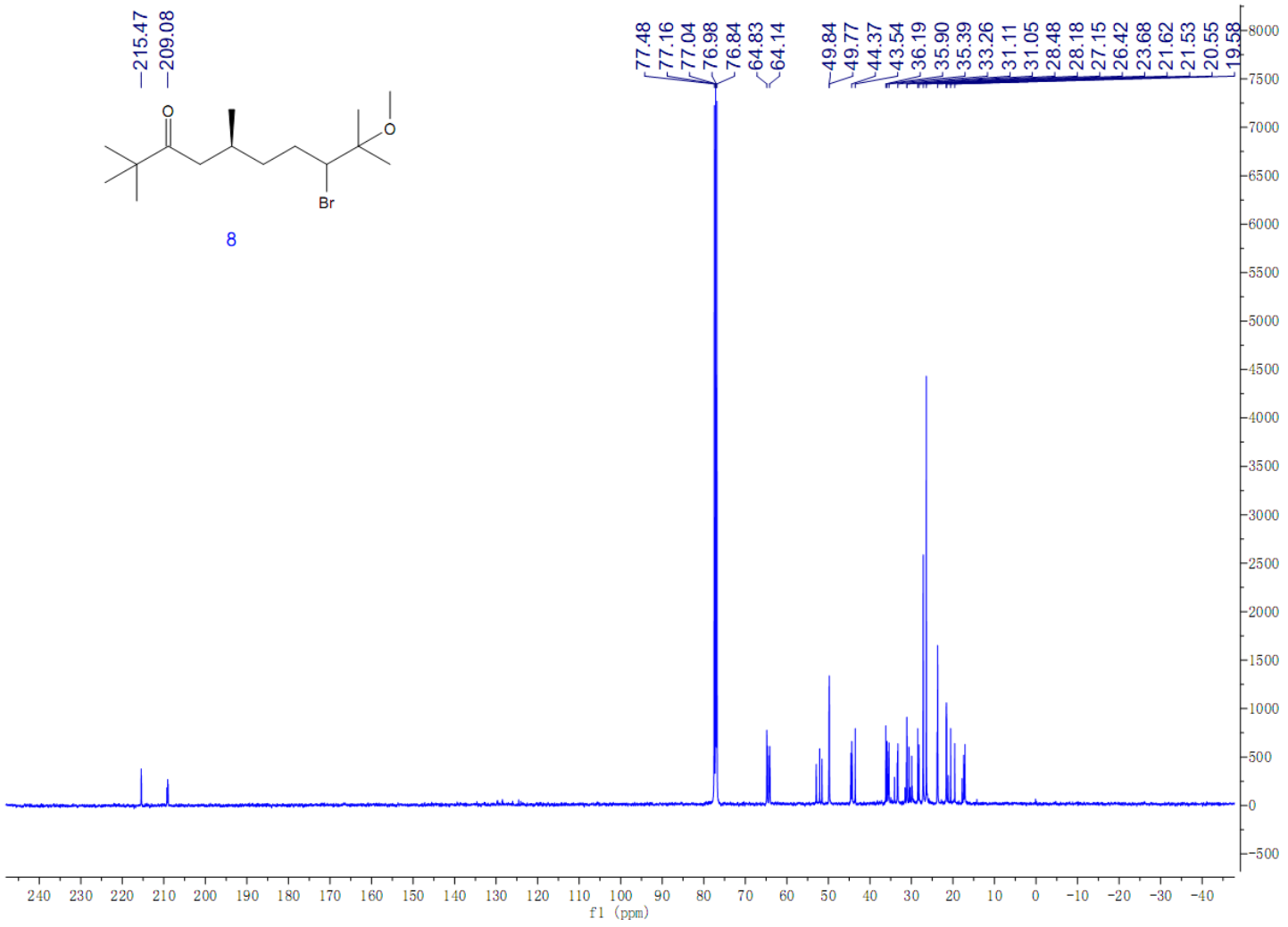
1.80
1.01
1.01
0.93
1.01
0.81
3.11
3.06
8.67
3.10
f1 (ppm)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209.08
O
O
Br
8
77.48
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76.98
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49.84
49.77
44.37
43.54
36.19
35.90
35.39
33.26
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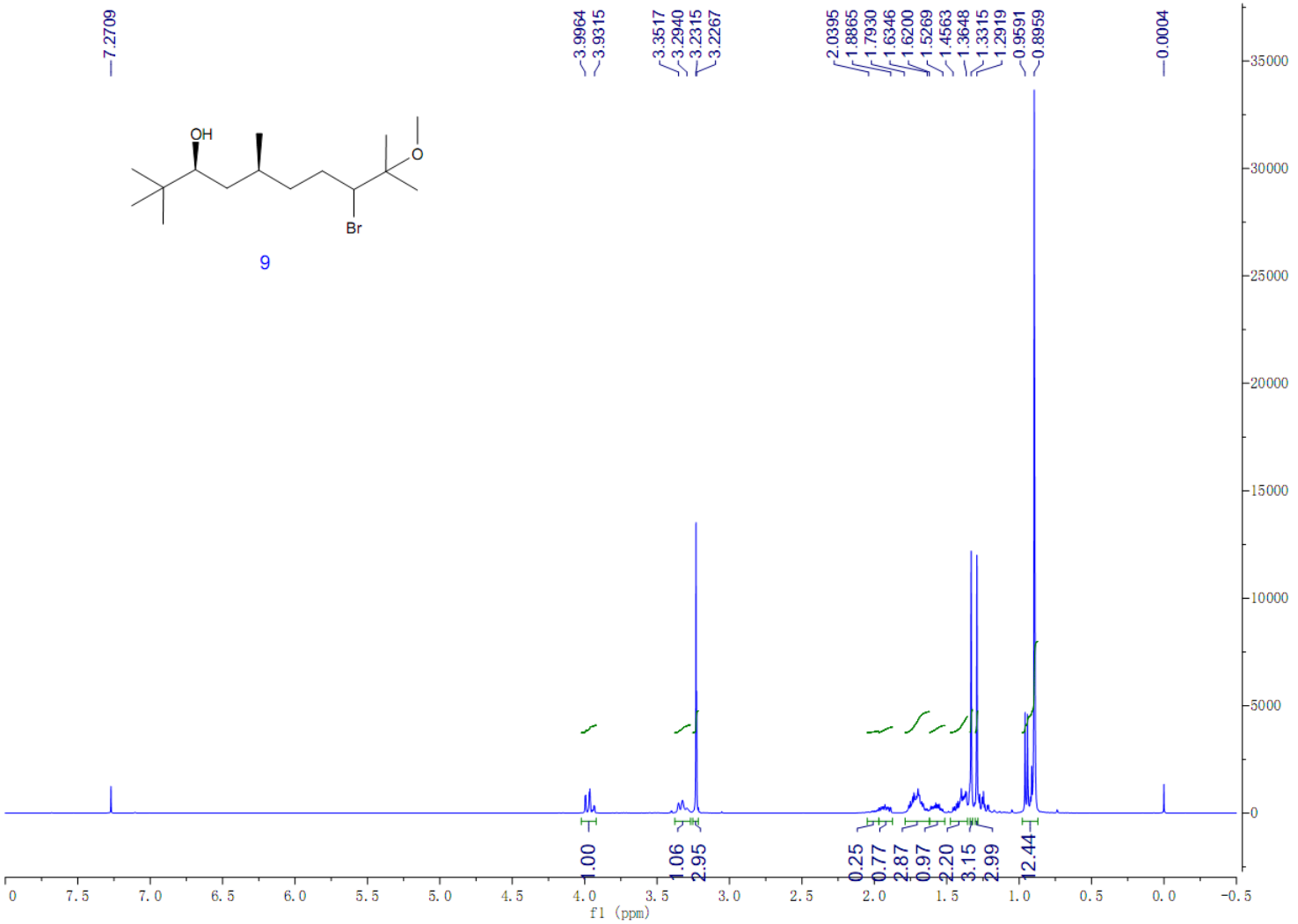
28.18
27.15
26.42
23.68
21.62
21.53
20.55
19.58
f1 (ppm)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3.2940
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3.2267
2.0395
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1.7930
1.6346
1.6200
1.5269
1.4563
1.3648
1.3315
1.2919
0.9591
0.8959
0.0004
OH
O
Br
9
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1.06
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0.97
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3.15
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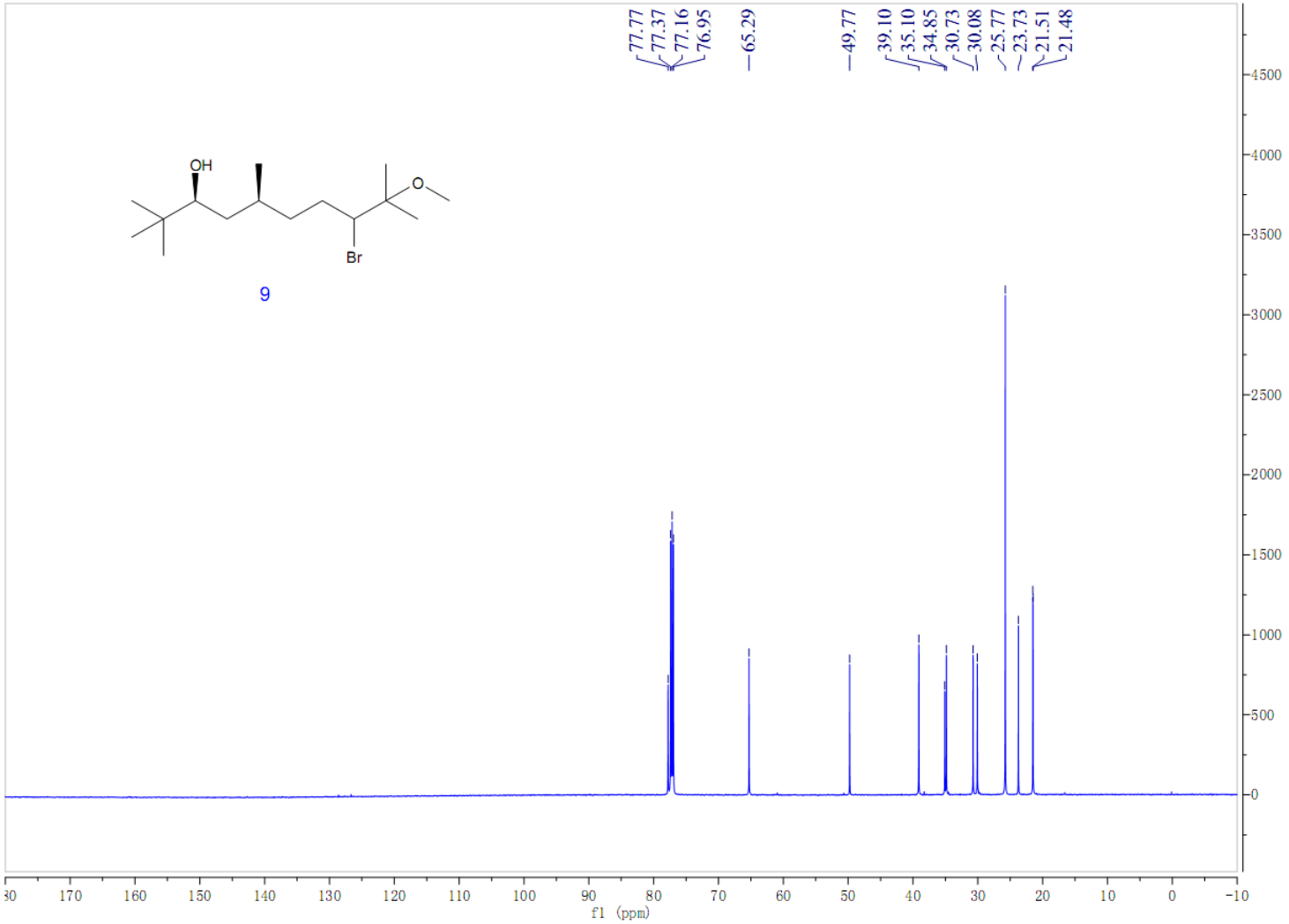
f1 (ppm)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35.10
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23.73
21.51
21.48
OH
O
Br
9
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3500
3000
2500
2000
1500
1000
500
0
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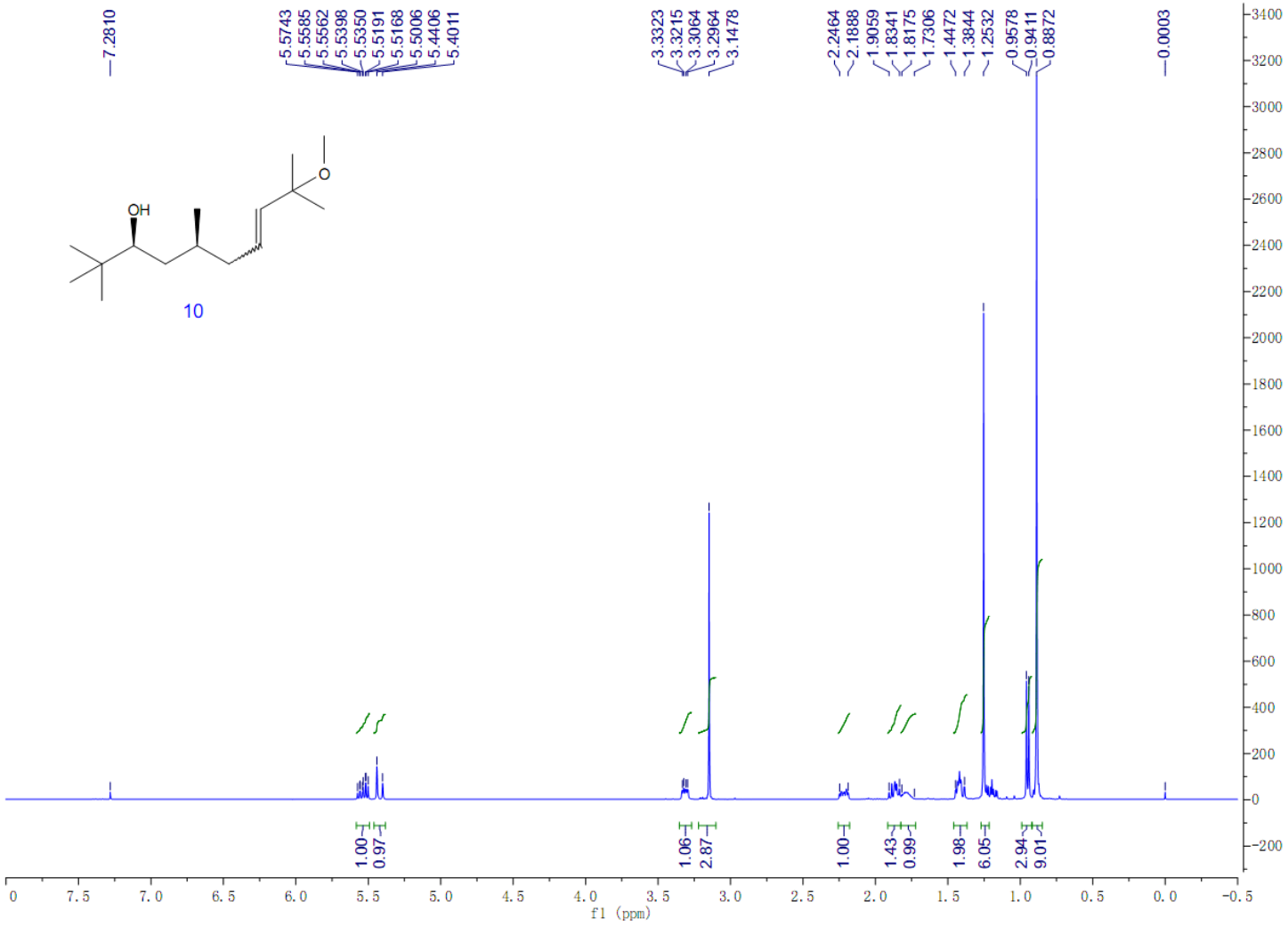
f1 (ppm)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3.3215
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3.1478
2.2464
2.1888
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1.8341
1.8175
1.7306
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O
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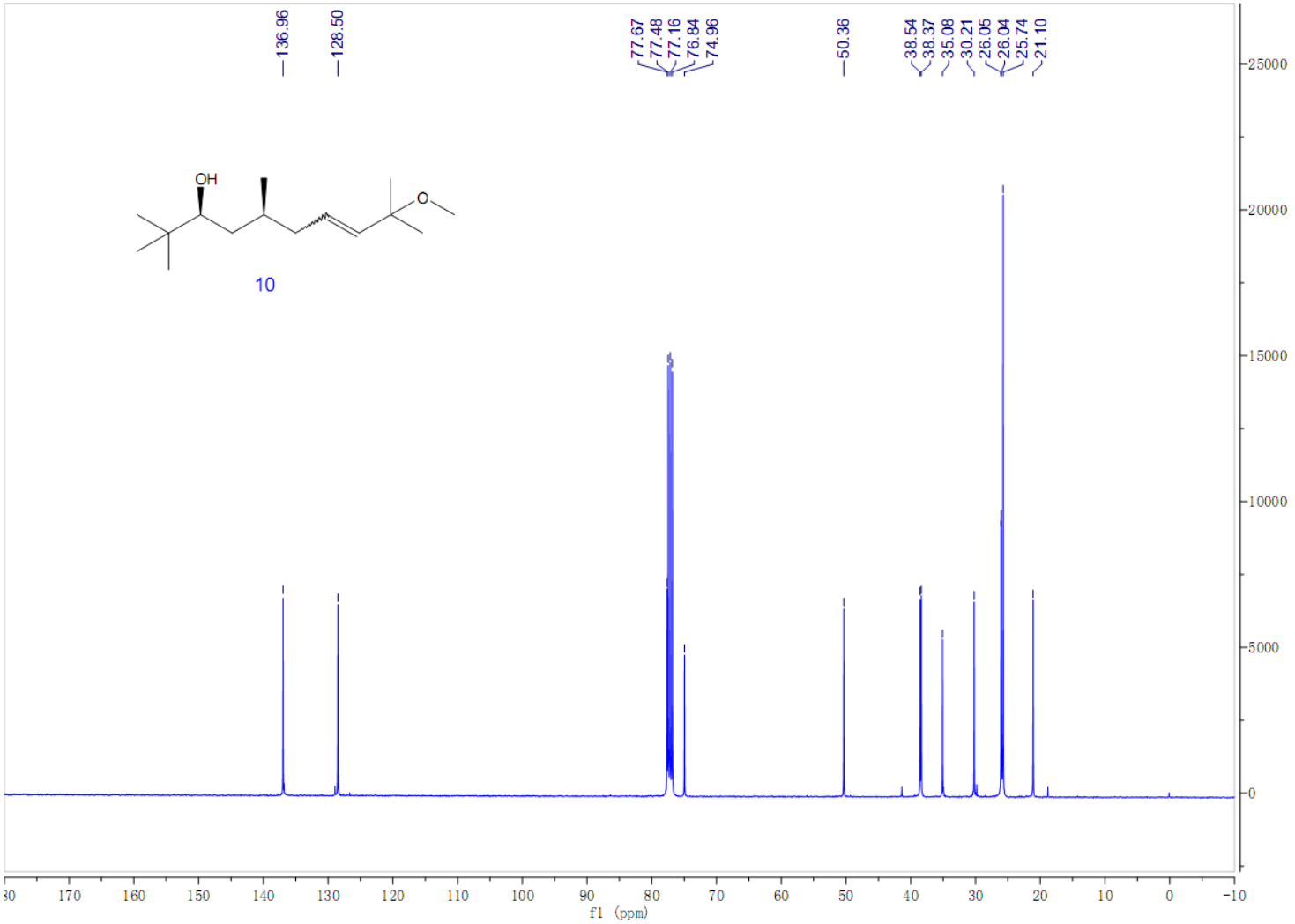
9.01
f1 (ppm)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76.84
74.96
50.36
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38.37
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26.04
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5000
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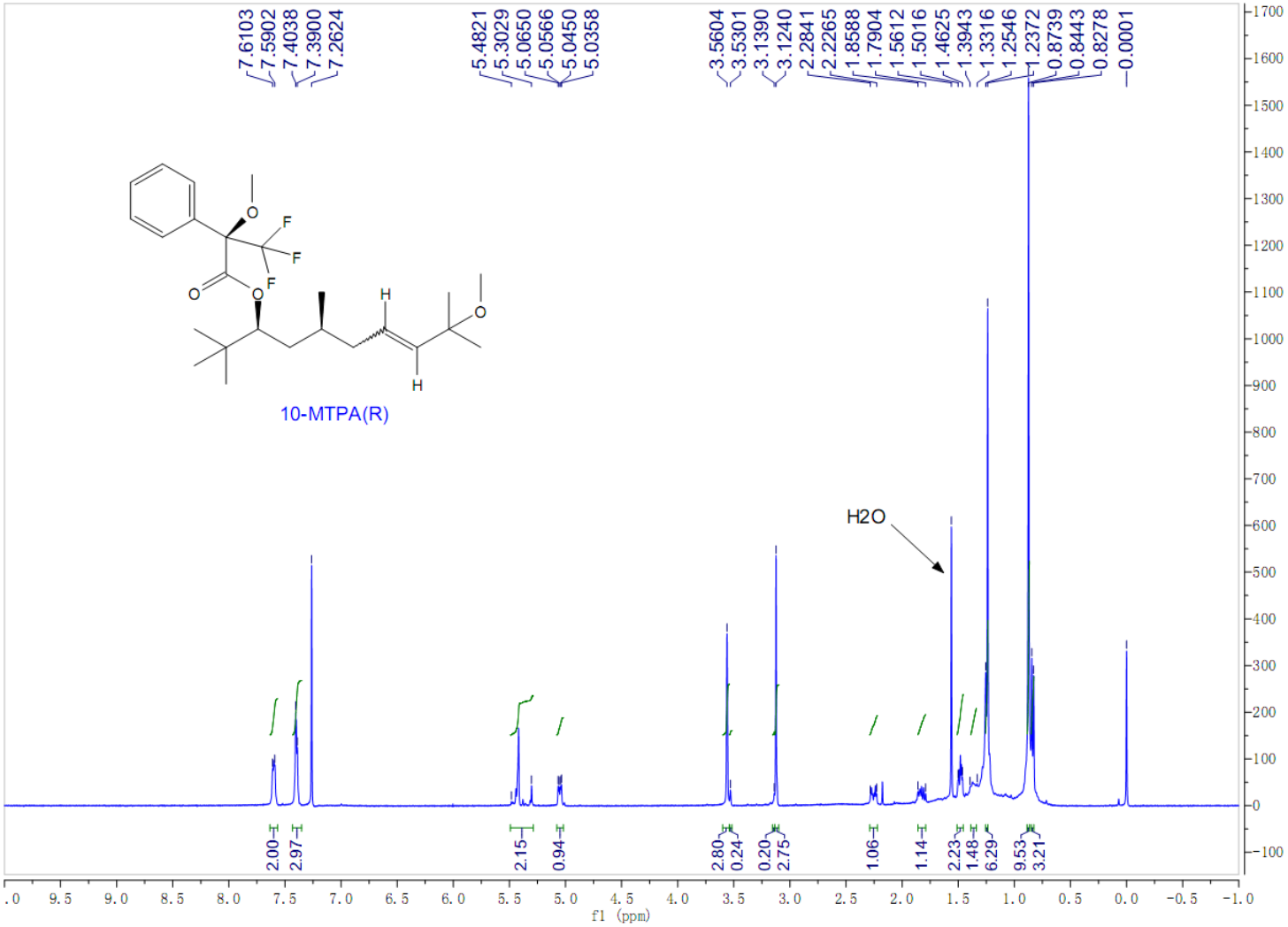
f1 (ppm)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3.5604
3.5301
3.1390
3.1240
2.2841
2.2265
1.8588
1.7904
1.5612
1.5016
1.4625
1.3943
1.3316
1.2546
1.2372
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O
F
F
F
O
O
H
O
H
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H2O
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2.15
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1.14
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6.29
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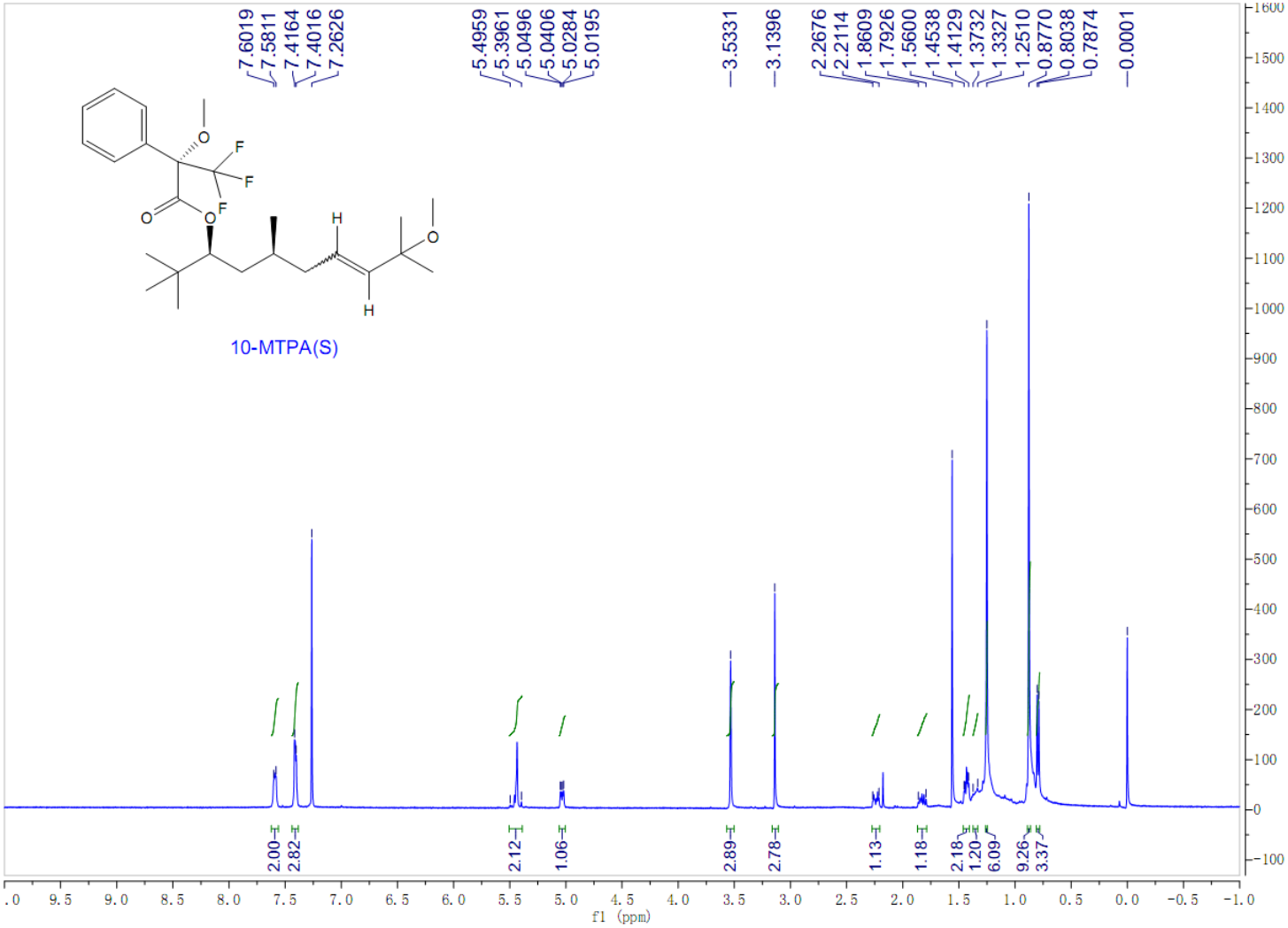
3.21
f1 (ppm)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3.5331
3.1396
2.2676
2.2114
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1.7926
1.5600
1.4538
1.4129
1.3732
1.3327
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0.0001
10-MTPA(S)
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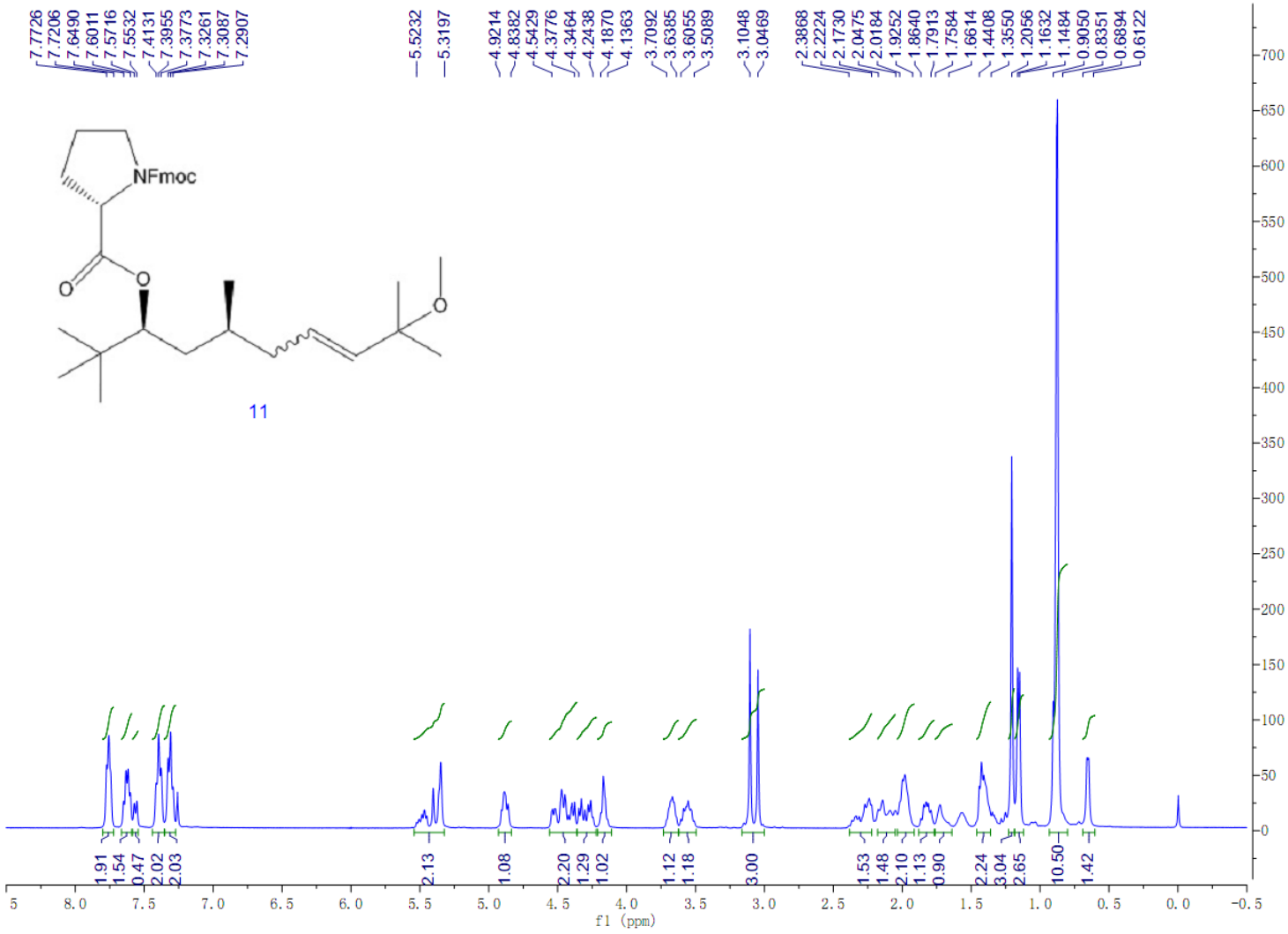
f1 (ppm)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4.5429
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0.8351
0.6894
0.6122
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O
O
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1.54
0.47
2.02
2.03
2.13
1.08
2.20
1.29
1.02
1.12
1.18
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2.10
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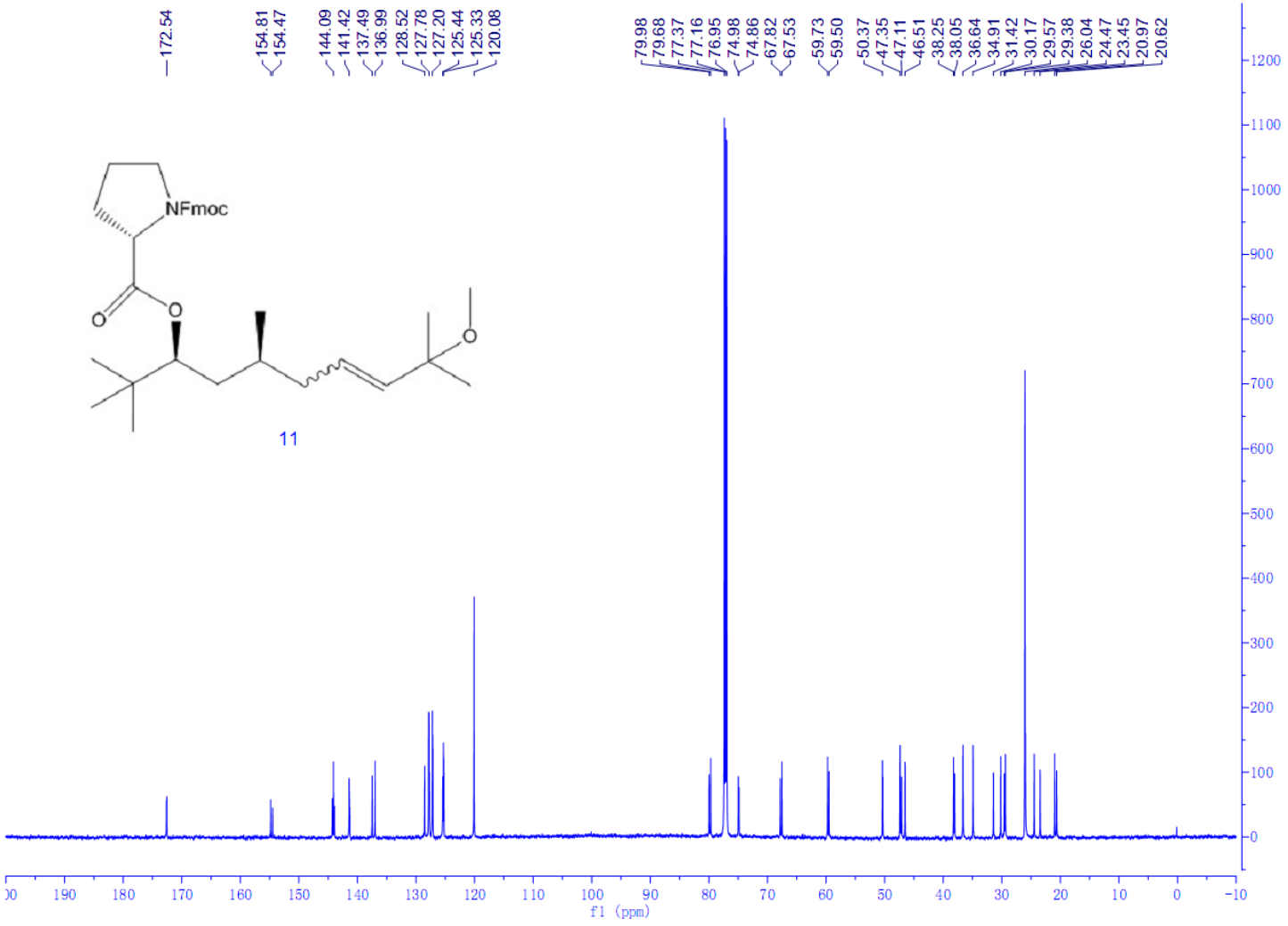
1.42
f1 (ppm)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79.98
79.68
77.37
77.16
76.95
74.98
74.86
67.82
67.53
59.73
59.50
50.37
47.35
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38.25
38.05
36.64
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31.42
30.17
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O
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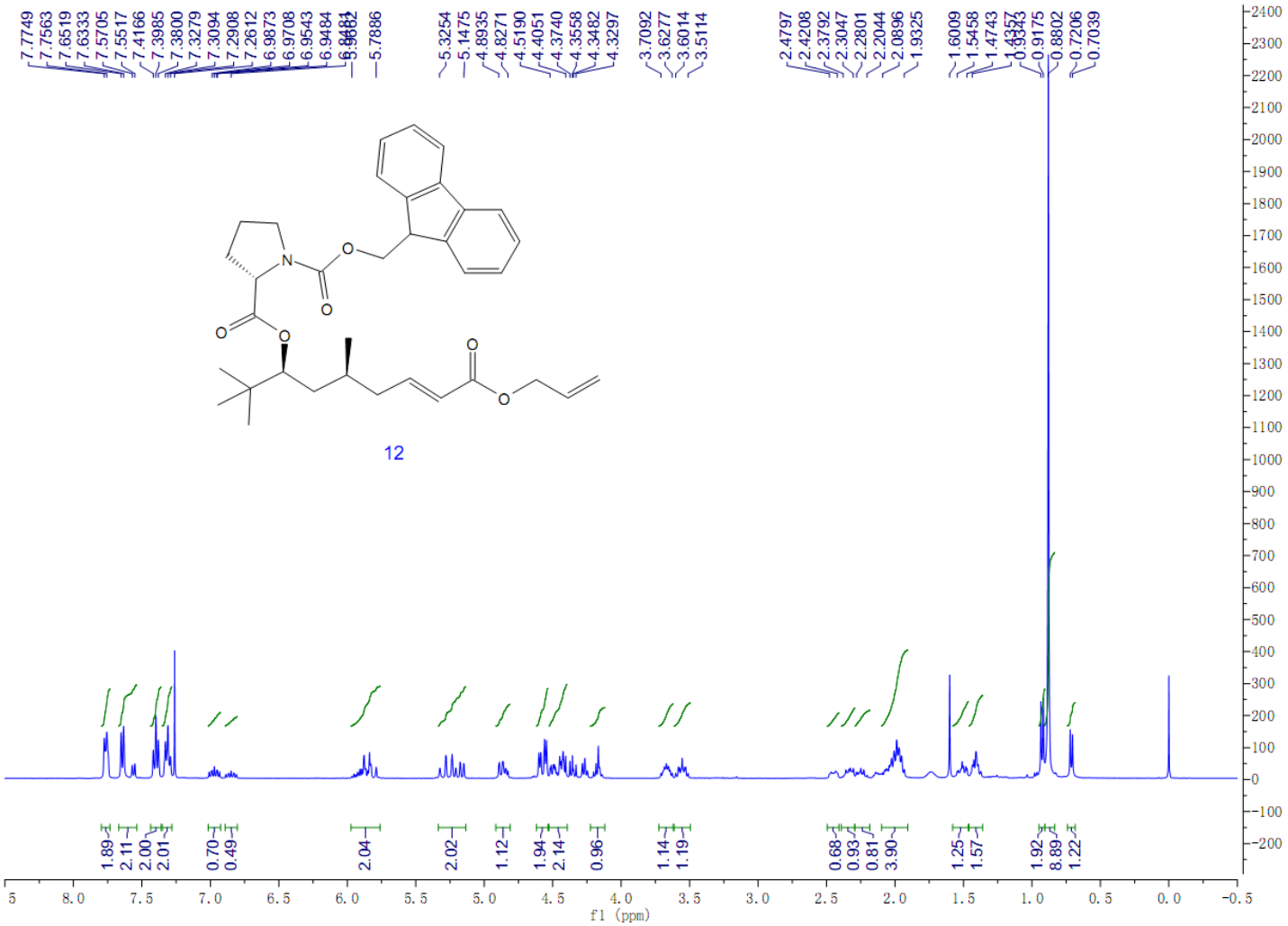
f1 (ppm)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2.02
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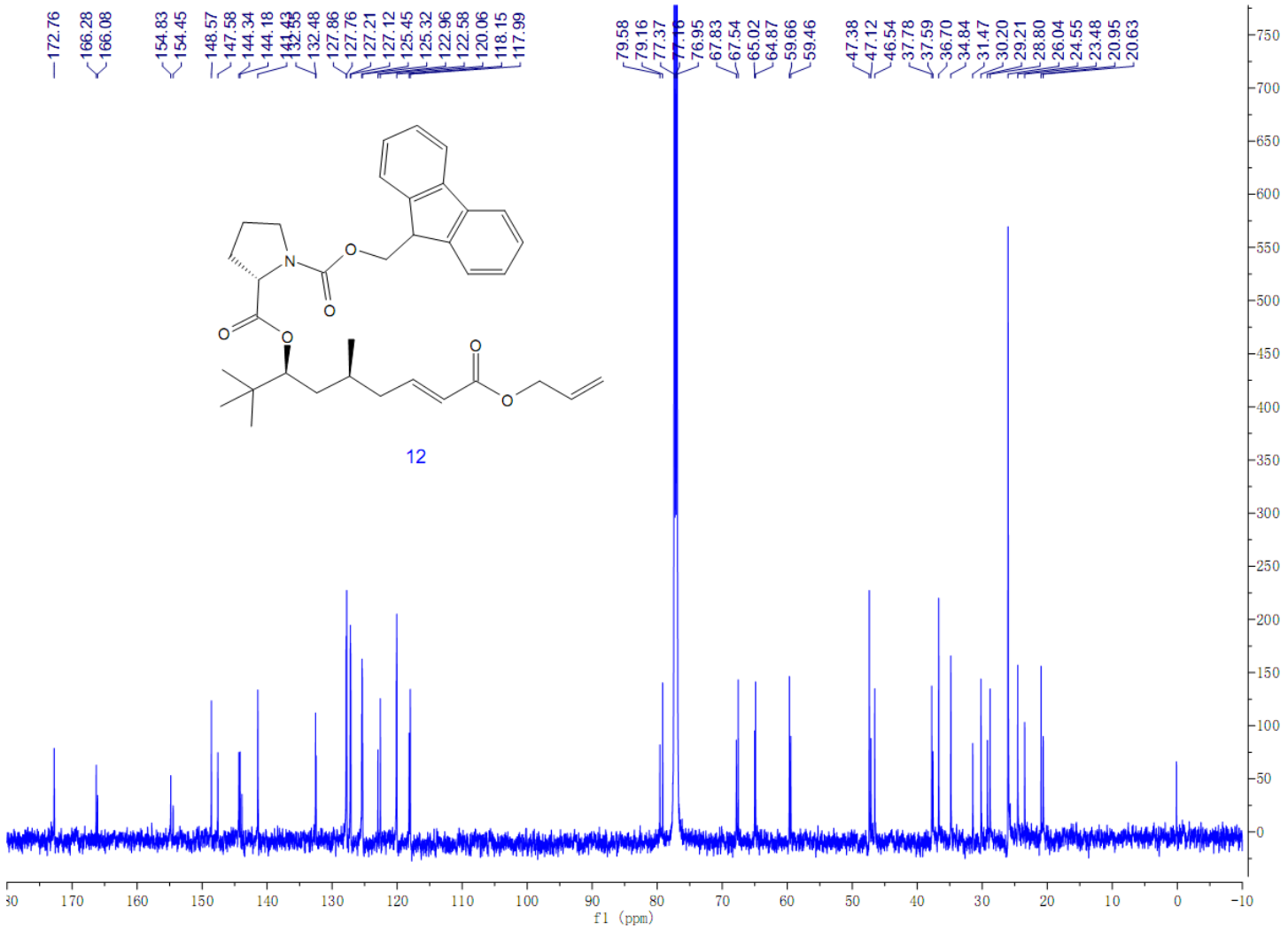
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125.32
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122.58
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76.95
67.83
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65.02
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47.12
46.54
37.78
37.59
36.70
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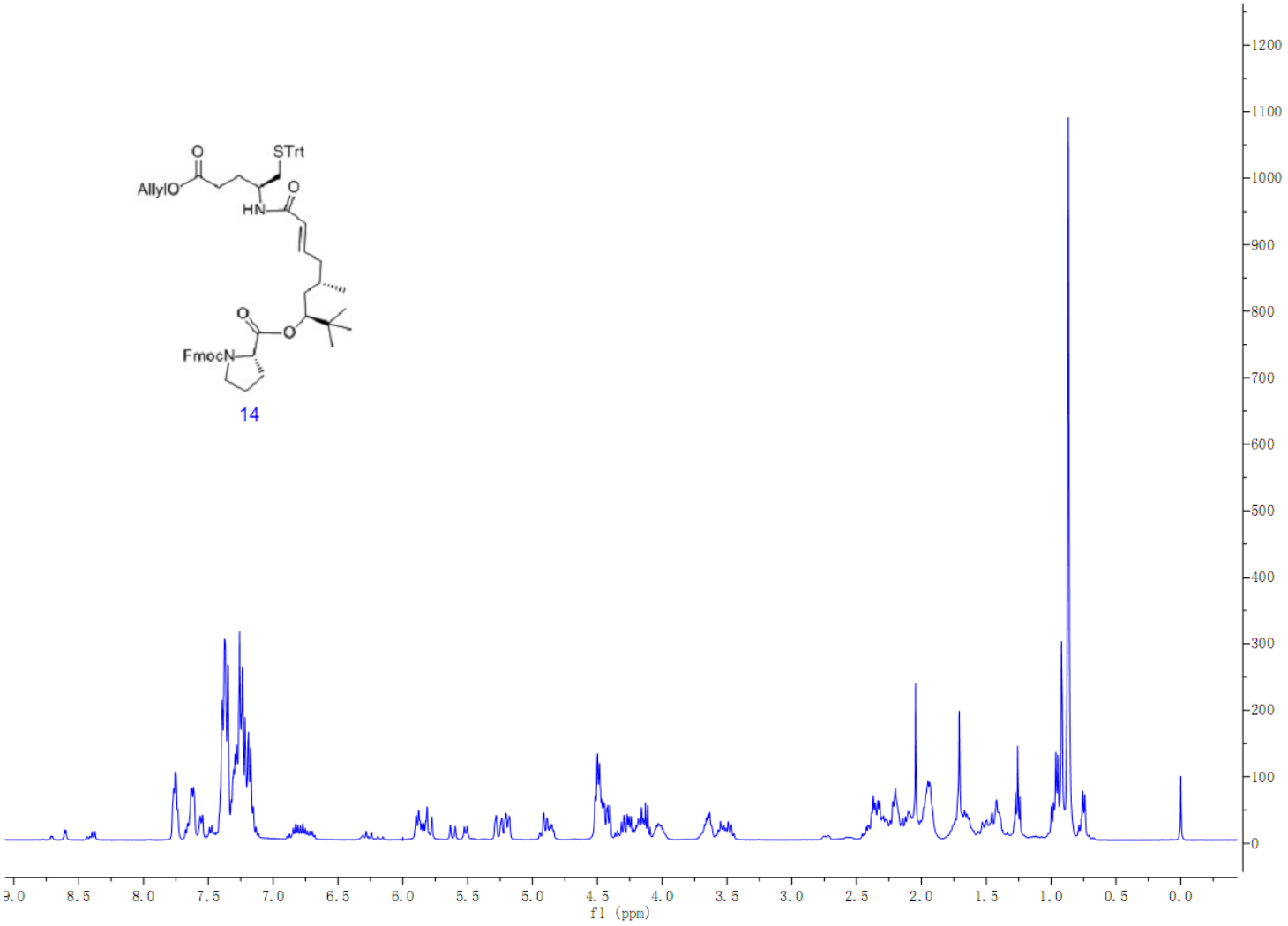
20.63
12
f1 (ppm)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STrt
HN
O
O
O
FmocN
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1200
1100
1000
900
800
700
600
500
400
300
200
100
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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3.5
3.0
2.5
2.0
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1.0
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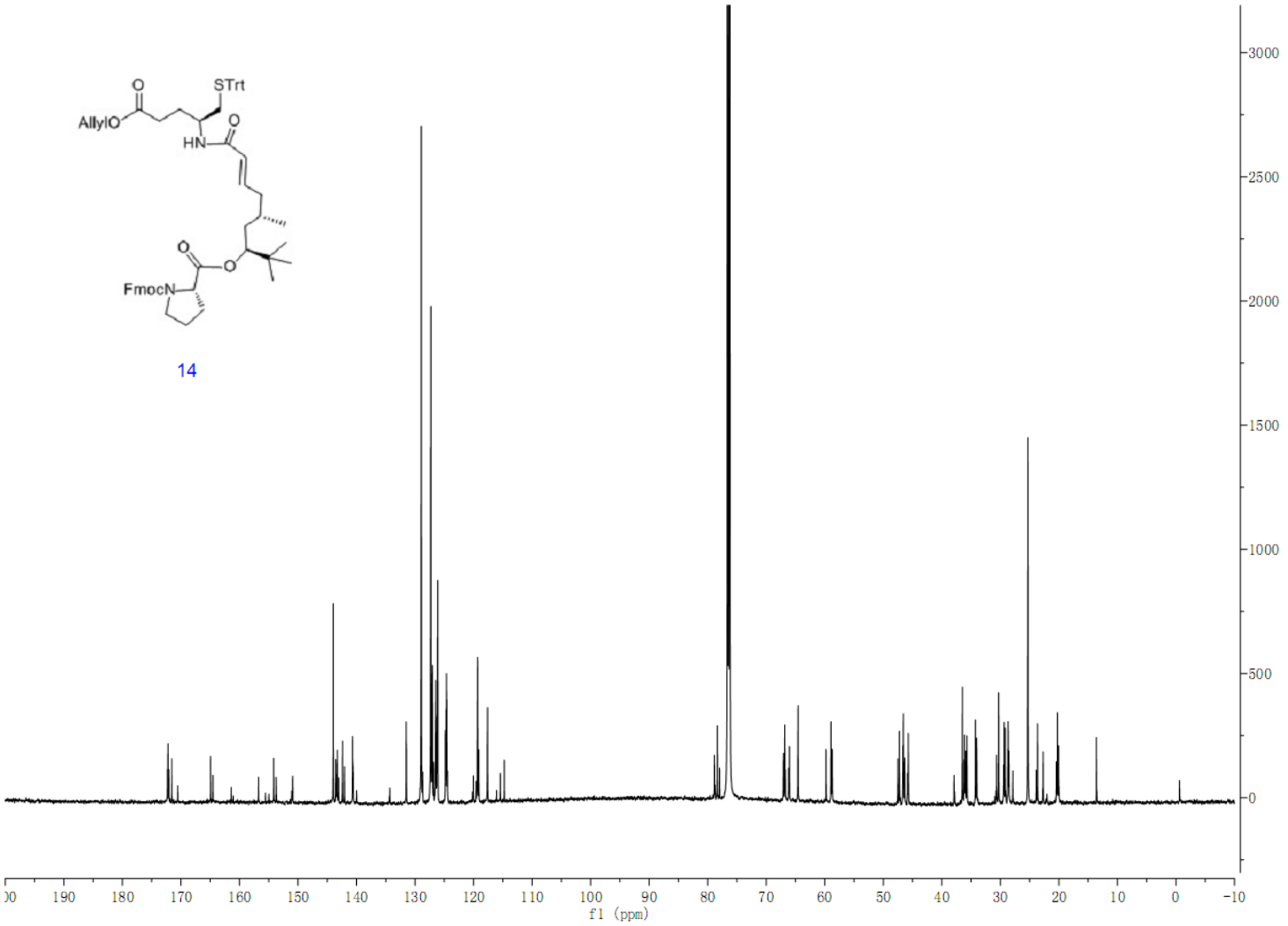
0.0
f1 (ppm)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FmocN
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1500
1000
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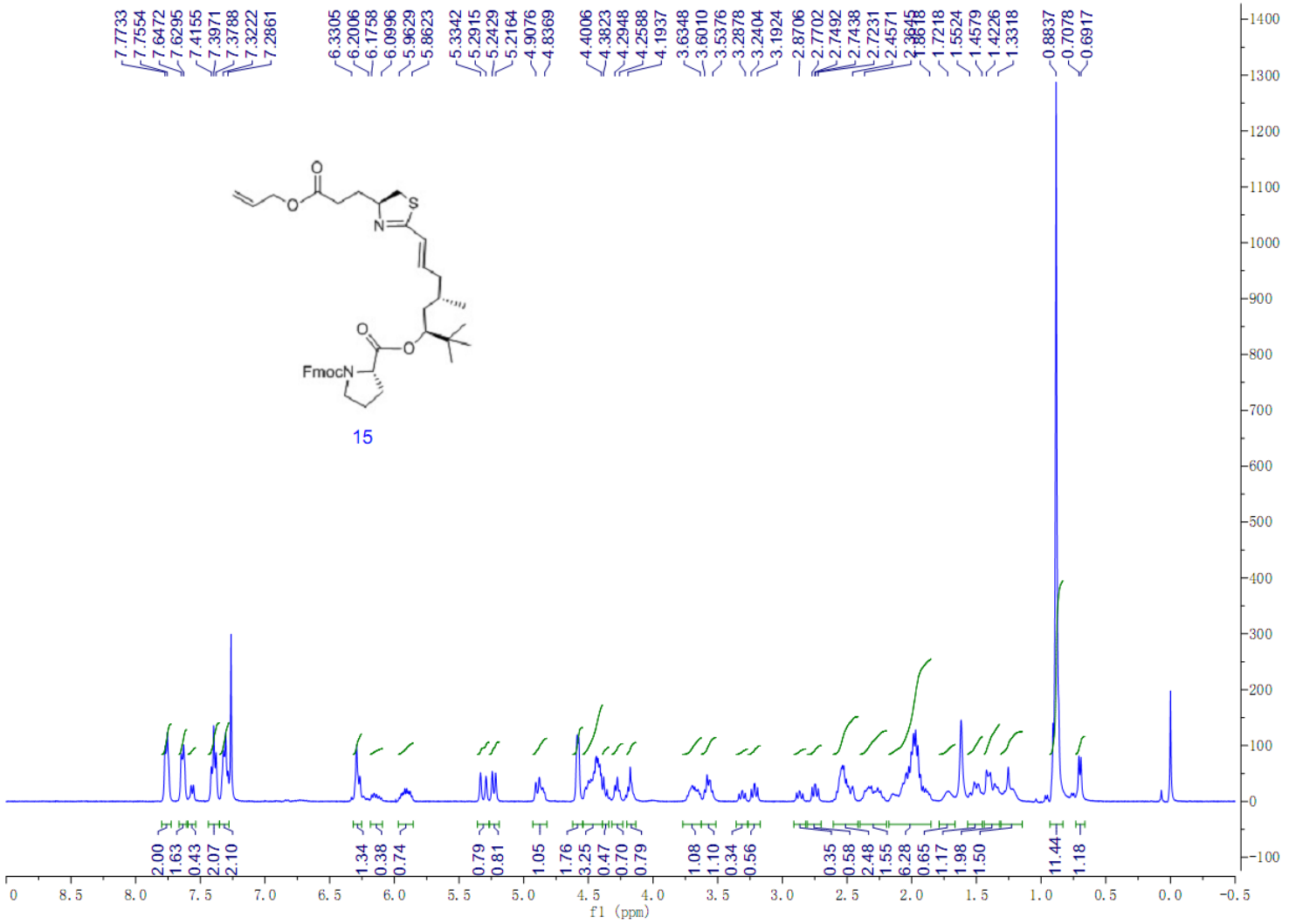
40
30
20
10
0
-10
f1 (ppm)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5.8623
5.3342
5.2915
5.2429
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3.1924
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2.7492
2.7438
2.7231
2.4571
1.7218
1.5524
1.4579
1.4226
1.3318
0.8837
0.7078
0.6917
O
O
S
N
O
O
FmocN
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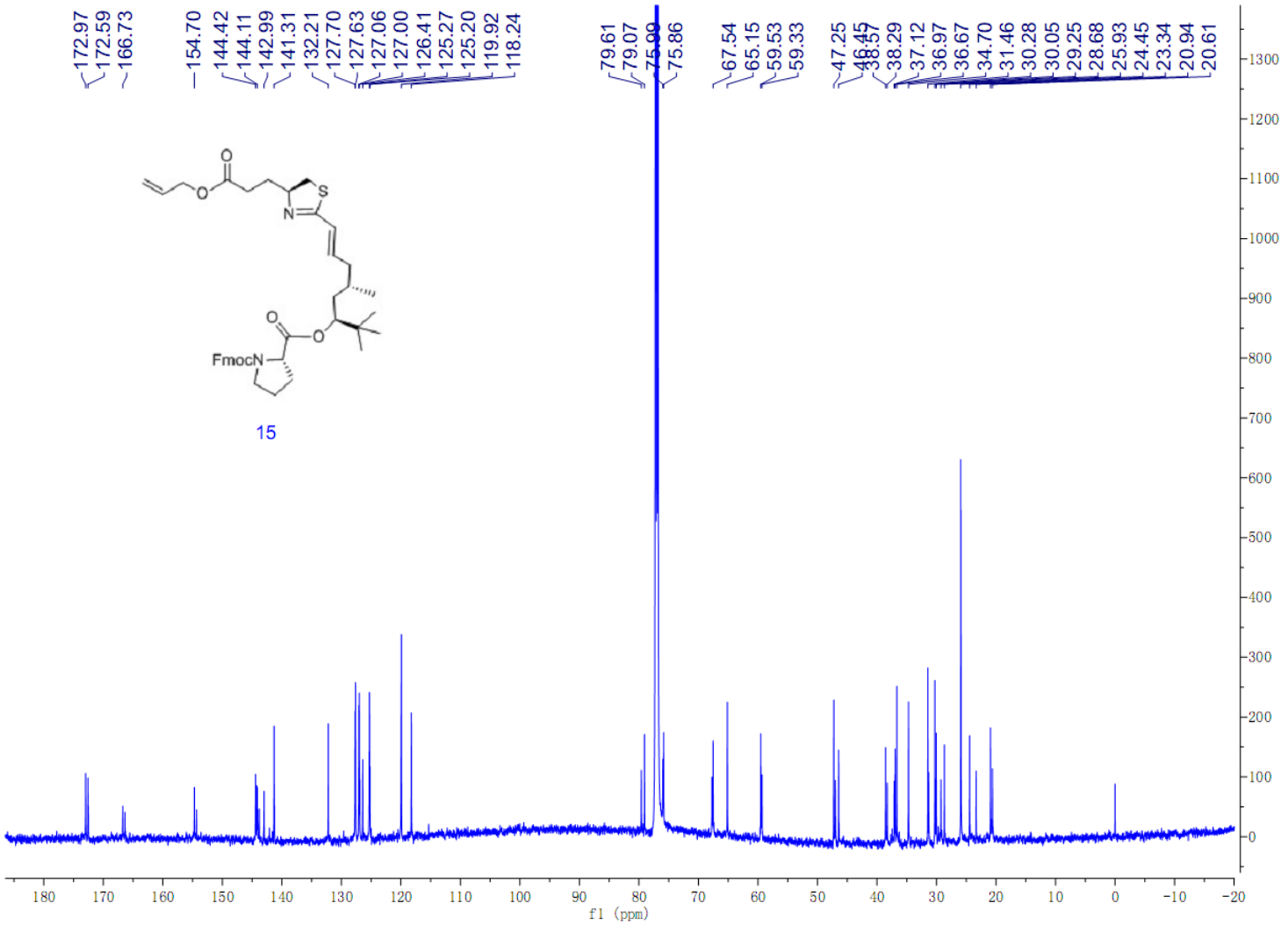
0.43
2.07
2.10
1.34
0.38
0.74
0.79
0.81
1.05
1.76
3.25
0.47
0.70
0.79
1.08
1.10
0.34
0.56
0.35
0.58
2.48
1.55
6.28
0.65
1.17
1.98
1.50
11.44
1.18
f1 (ppm)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127.06
127.00
126.41
125.27
125.20
119.92
118.24
79.61
79.07
75.99
75.86
67.54
65.15
59.53
59.33
47.25
46.45
38.57
38.29
37.12
36.97
36.67
34.70
31.46
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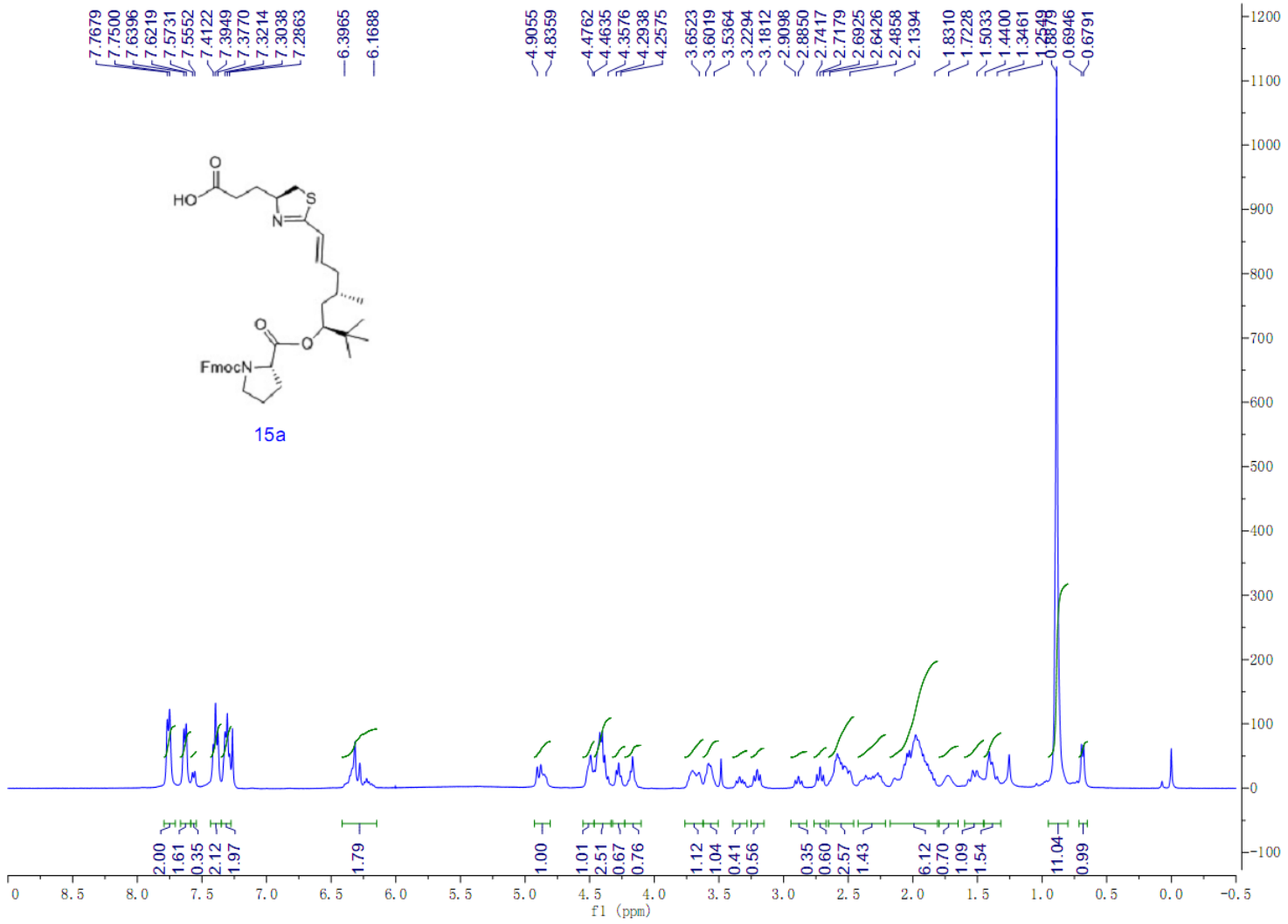
29.25
28.68
25.93
24.45
23.34
20.94
20.61
FmocN
15
f1 (ppm)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7.3038
7.2863
6.3965
6.1688
4.9055
4.8359
4.4762
4.4635
4.3576
4.2938
4.2575
3.6523
3.6019
3.5364
3.2294
3.1812
2.9098
2.8850
2.7417
2.7179
2.6925
2.6426
2.4858
2.1394
1.8310
1.7228
1.5033
1.4400
1.3461
0.8879
0.6946
0.6791
HO
O
S
N
O
O
FmocN
15a
2.00
1.61
0.35
2.12
1.97
1.79
1.00
1.01
2.51
0.67
0.76
1.12
1.04
0.41
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6.12
0.70
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1.54
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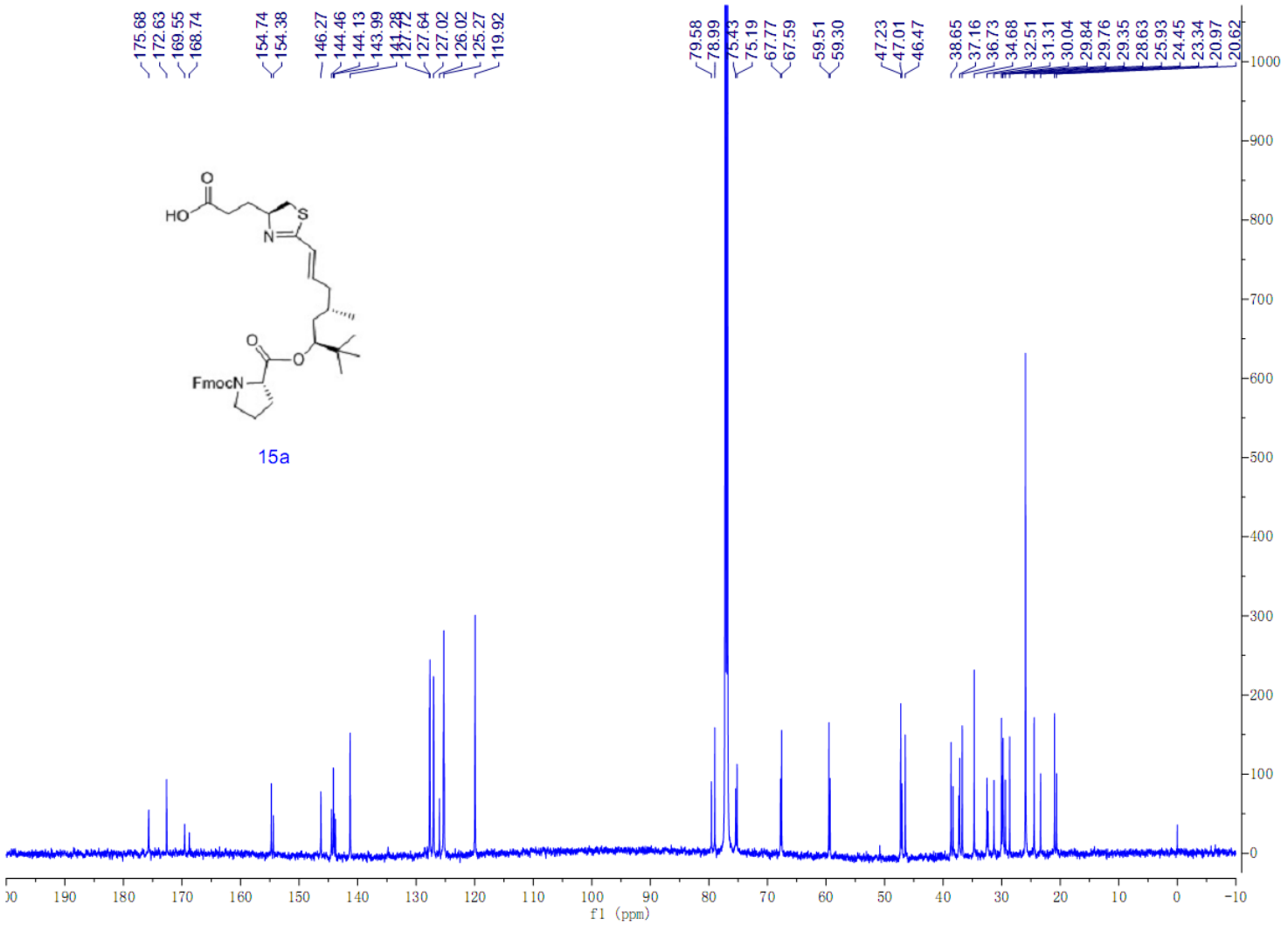
0.99
f1 (ppm)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127.02
126.02
125.27
119.92
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78.99
75.43
75.19
67.77
67.59
59.51
59.30
47.23
47.01
46.47
38.65
37.16
36.73
34.68
32.51
31.31
30.04
29.84
29.76
29.35
28.63
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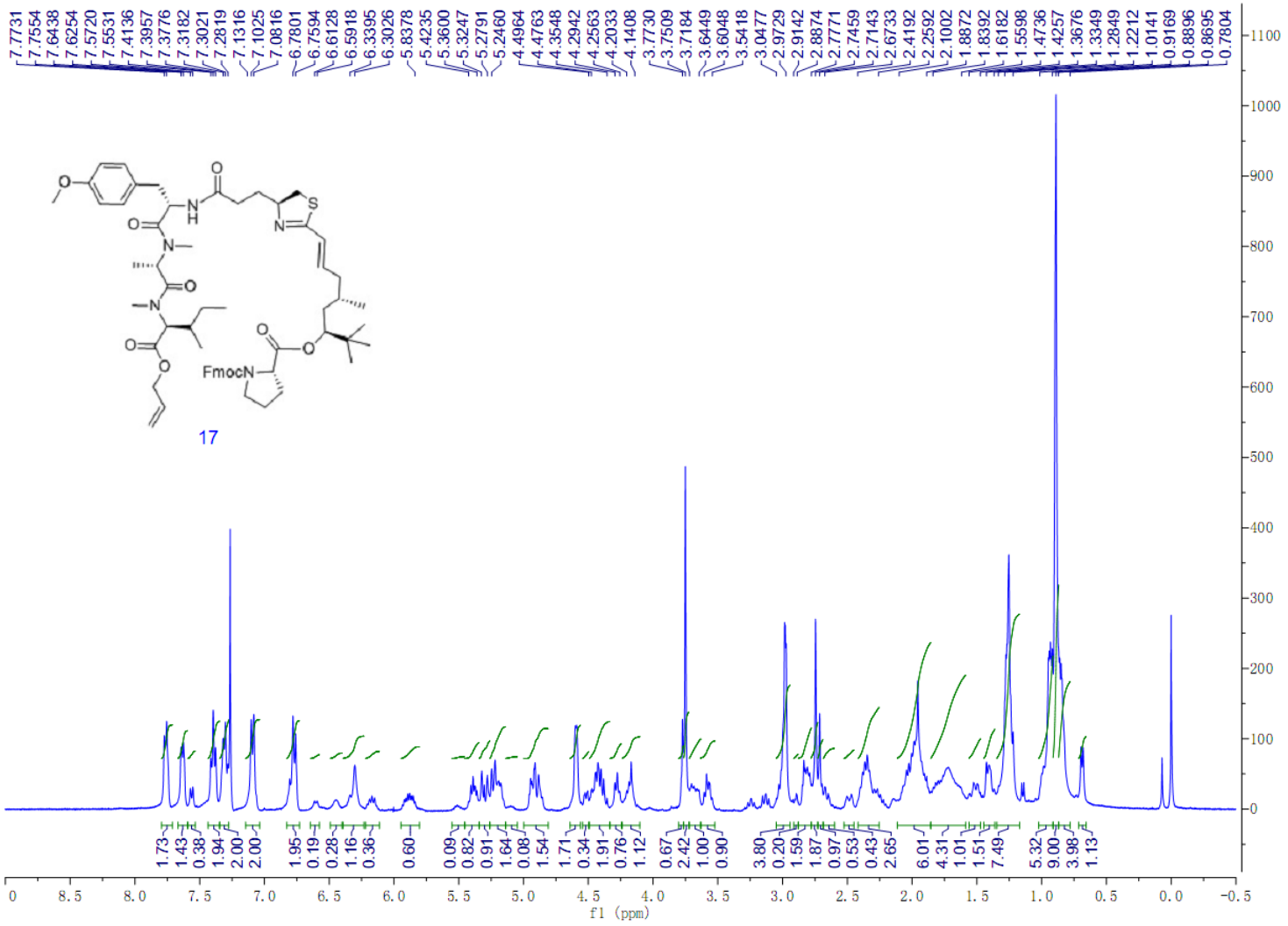
23.34
20.97
20.62
HO
O
S
N
O
O
FmocN
15a
f1 (ppm)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7.3776
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7.2819
7.1316
7.1025
7.0816
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6.7594
6.6128
6.5918
6.3395
6.3026
5.8378
5.4235
5.3600
5.3247
5.2791
5.2460
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4.4763
4.3548
4.2942
4.2563
4.2033
4.1408
3.7730
3.7509
3.7184
3.6449
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3.5418
3.0477
2.9729
2.9142
2.8874
2.7771
2.7459
2.7143
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1.5598
1.4736
1.4257
1.3676
1.3349
1.2849
1.2212
1.0141
0.9169
0.8896
0.8695
0.7804
FmocN
17
1.73
1.43
0.38
1.94
2.00
2.00
1.95
0.19
0.28
1.16
0.36
0.60
0.09
0.82
0.91
1.64
0.08
1.54
1.71
0.34
1.91
0.76
1.12
0.67
2.42
1.00
0.90
3.80
0.20
1.59
1.87
0.97
0.53
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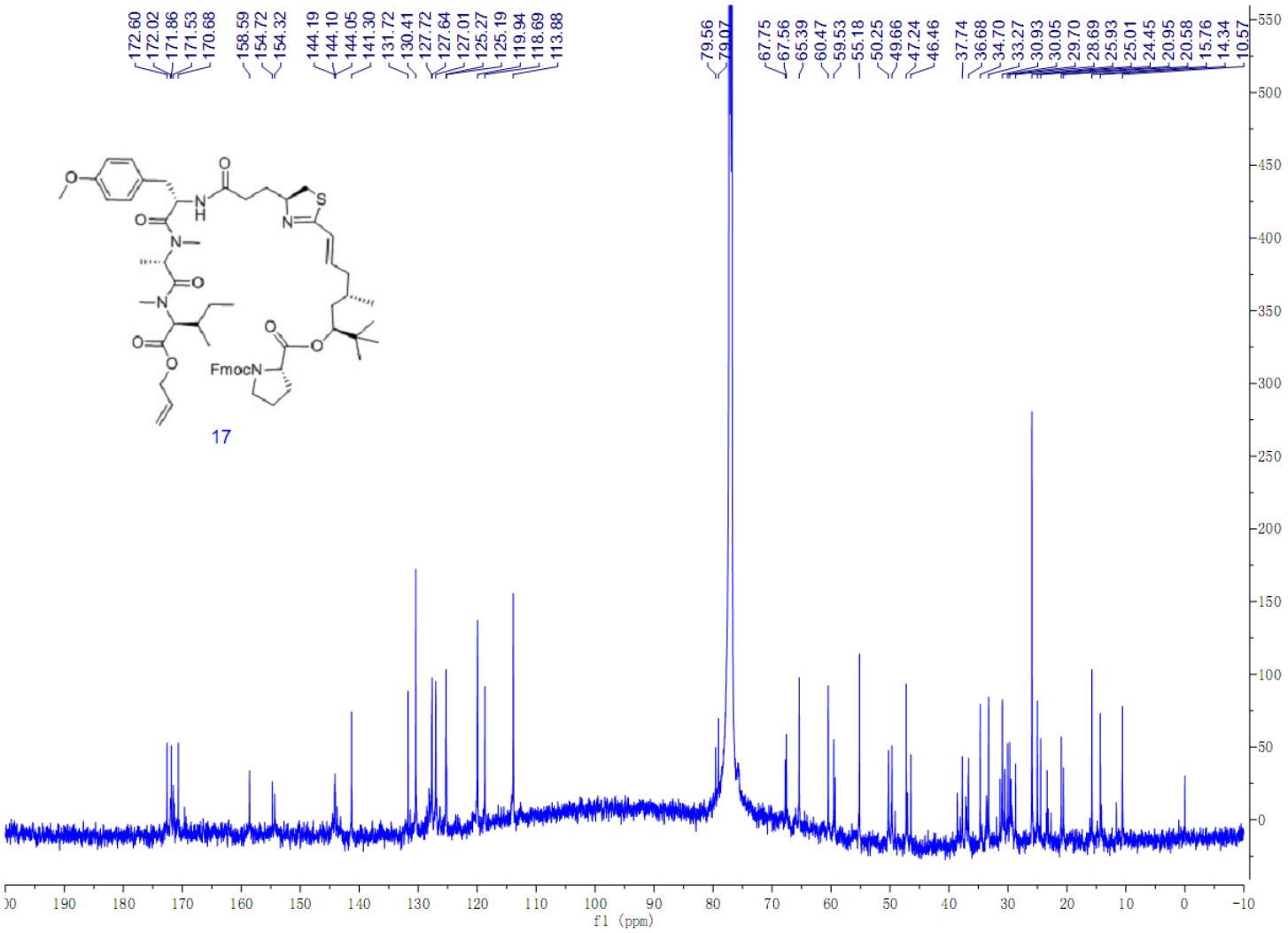
1.51
7.49
5.32
9.00
3.98
1.13
f1 (ppm)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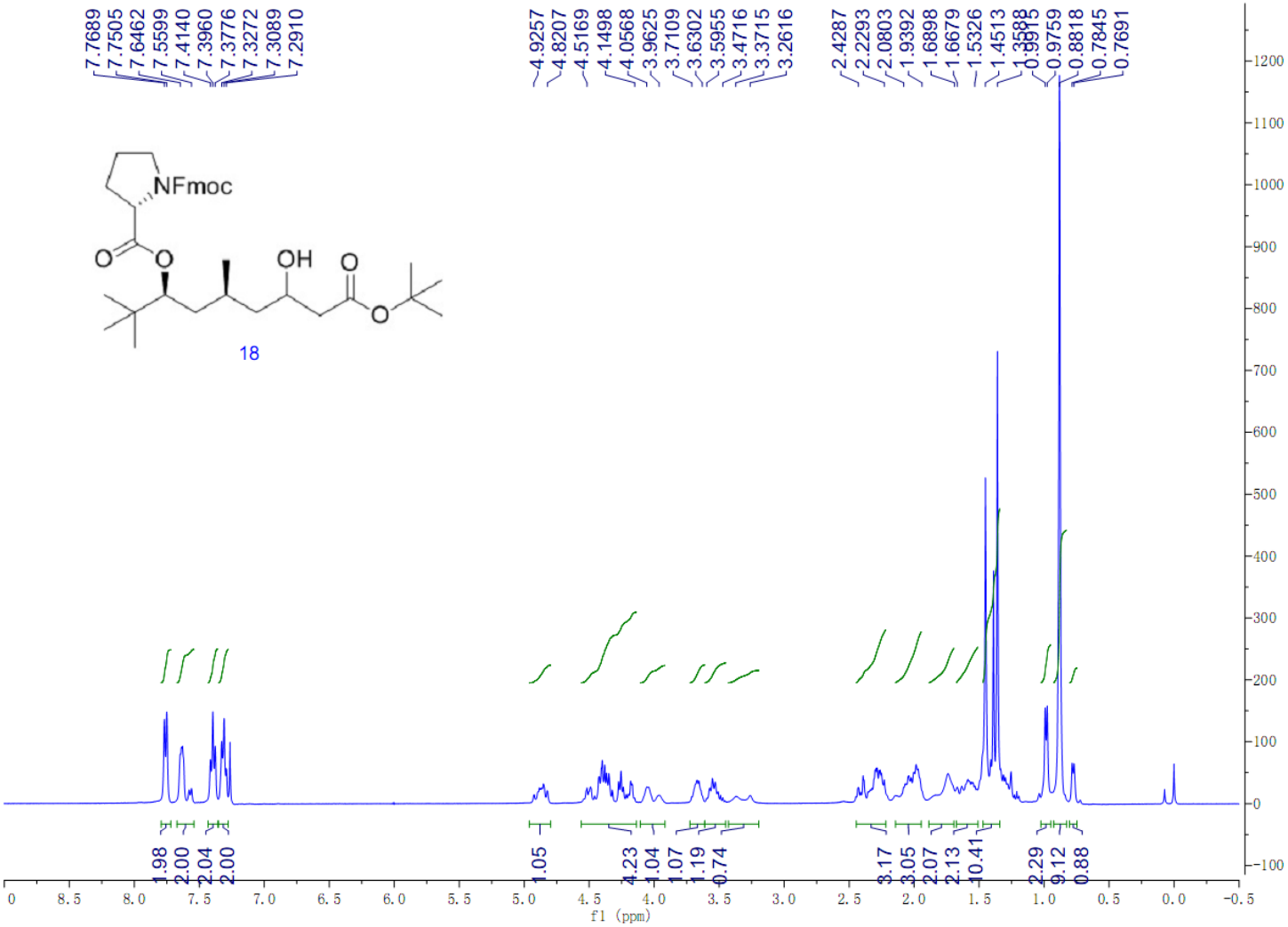
144.10
144.05
141.30
131.72
130.41
127.72
127.64
127.01
125.27
125.19
119.94
118.69
113.88
79.56
79.07
67.75
67.56
65.39
60.47
59.53
55.18
50.25
49.66
47.24
46.46
37.74
36.68
34.70
33.27
30.93
30.05
29.70
28.69
25.93
25.01
24.45
20.95
20.58
15.76
14.34
10.57
FmocN
17
f1 (ppm)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7.3776
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7.2910
4.9257
4.8207
4.5169
4.1498
4.0568
3.9625
3.7109
3.6302
3.5955
3.4716
3.3715
3.2616
2.4287
2.2293
2.0803
1.9392
1.6898
1.6679
1.5326
1.4513
1.3588
0.9759
0.8818
0.7845
0.7691
NFmoc
O
O
OH
O
O
18
1.98
2.00
2.04
2.00
1.05
4.23
1.04
1.07
1.19
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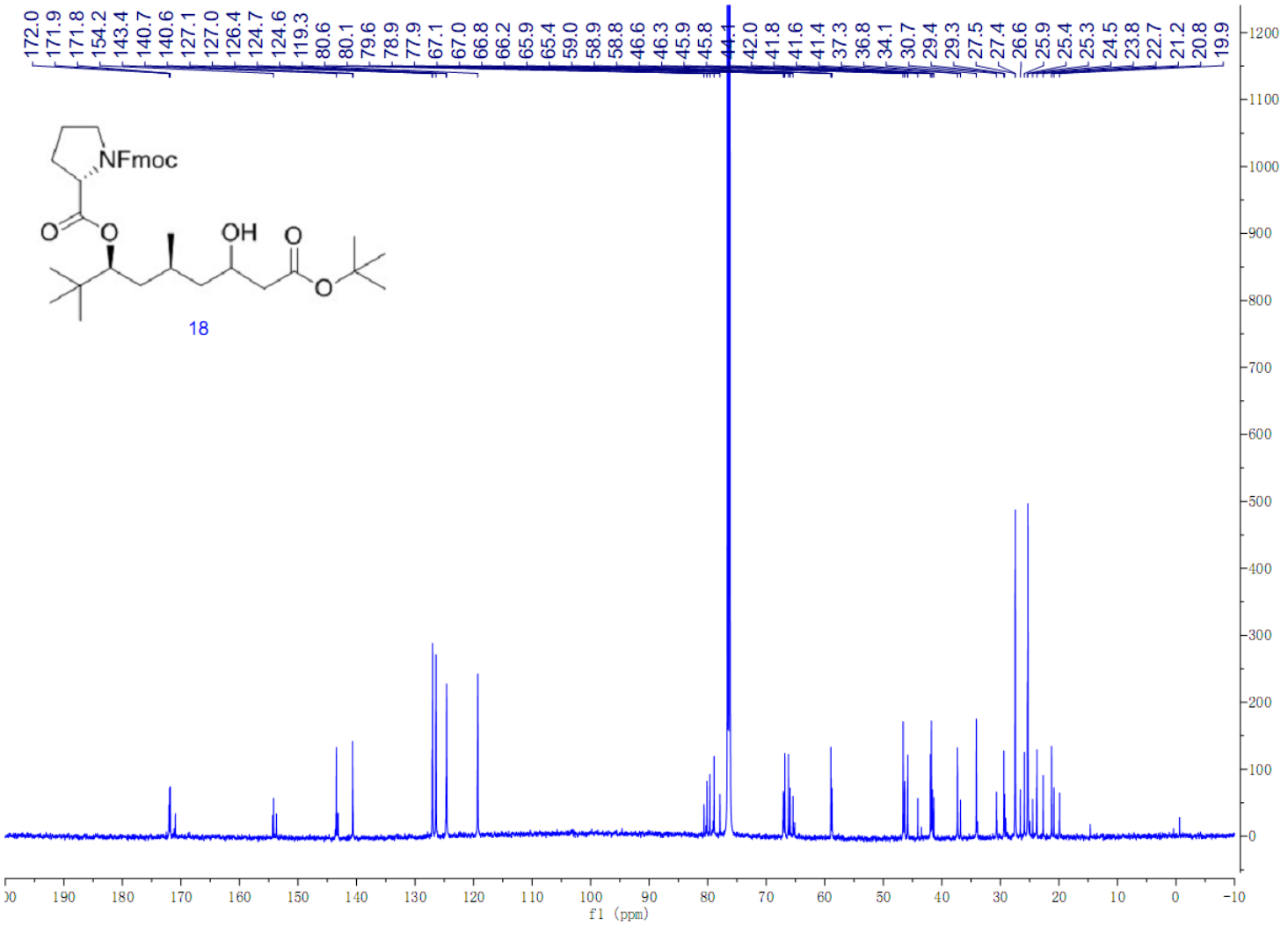
3.17
3.05
2.07
2.13
10.41
2.29
9.12
0.88
f1 (ppm)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154.2
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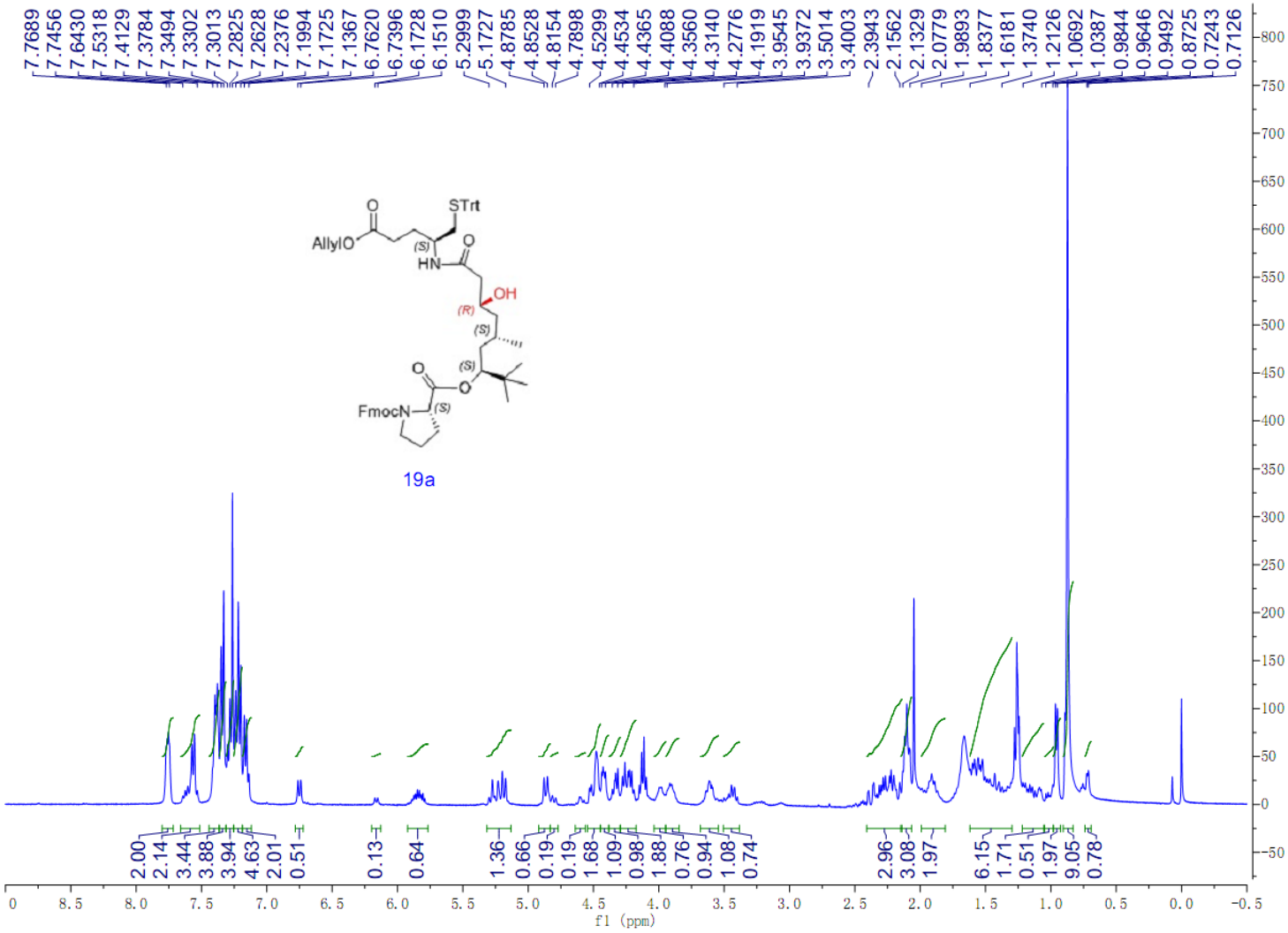
140.7
140.6
127.1
127.0
126.4
124.7
124.6
119.3
80.6
80.1
79.6
78.9
77.9
67.1
67.0
66.8
66.2
65.9
65.4
59.0
58.9
58.8
46.6
46.3
45.9
45.8
44.1
42.0
41.8
41.6
41.4
37.3
36.8
34.1
30.7
29.4
29.3
27.5
27.4
26.6
25.9
25.4
25.3
24.5
23.8
22.7
21.2
20.8
19.9
NFmoc
O
O
OH
O
O
18
f1 (ppm)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7.2376
7.1994
7.1725
7.1367
7.0620
6.7396
6.1728
6.1510
5.2999
5.1727
4.8785
4.8528
4.8154
4.7898
4.5299
4.4534
4.4365
4.4088
4.3560
4.3140
4.2776
4.1919
3.9545
3.9372
3.5014
3.4003
2.3943
2.1562
2.1329
2.0779
1.9893
1.8377
1.6181
1.3740
1.2126
1.0692
1.0387
0.9844
0.9646
0.9492
0.8725
0.7243
0.7126
AllylO
O
STrt
(S)
HN
O
OH
(R)
(S)
(S)
O
O
FmocN
(S)
19a
2.00
2.14
3.44
3.88
3.94
4.63
2.01
0.51
0.13
0.64
1.36
0.66
0.19
0.19
1.68
1.09
0.98
1.88
0.76
0.94
1.08
0.74
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3.08
1.97
6.15
1.71
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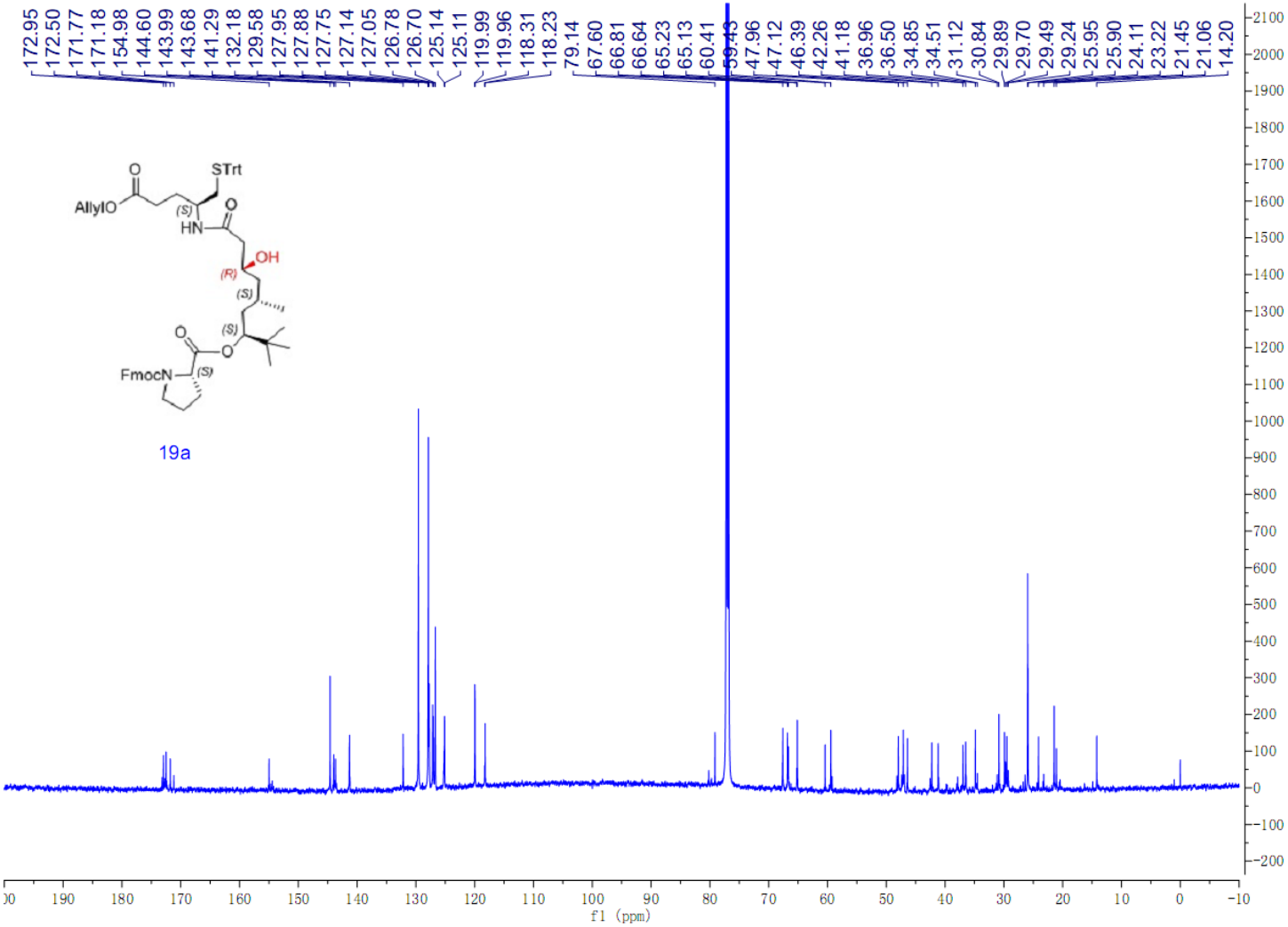
1.97
9.05
0.78
f1 (ppm)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143.99
143.68
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132.18
129.58
127.95
127.88
127.75
127.14
127.05
126.78
126.70
125.14
125.11
119.99
119.96
118.31
118.23
79.14
67.60
66.81
66.64
65.23
65.13
60.41
59.43
47.96
47.12
46.39
42.26
41.18
36.96
36.50
34.85
34.51
31.12
30.84
29.89
29.70
29.49
29.24
25.95
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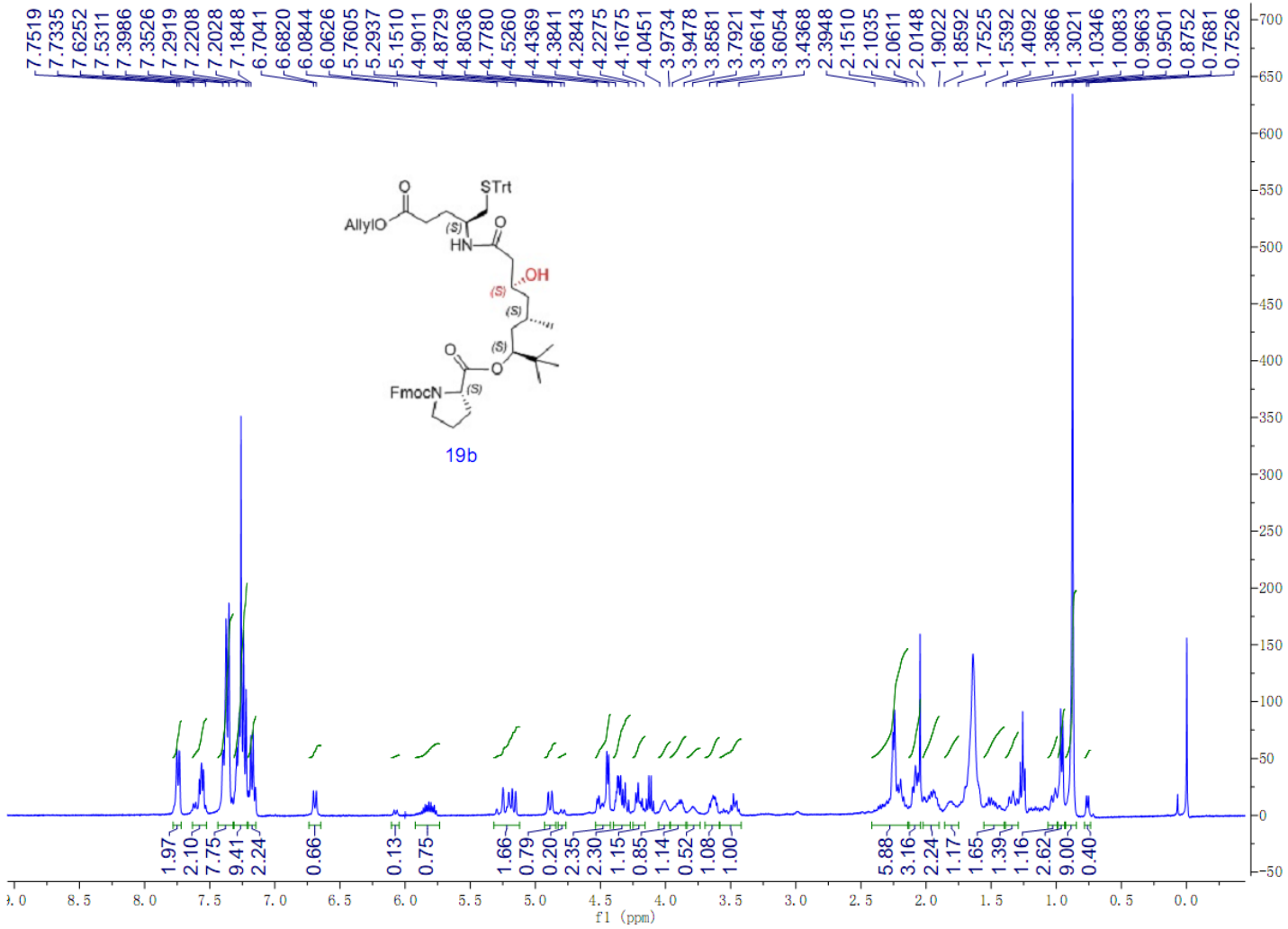
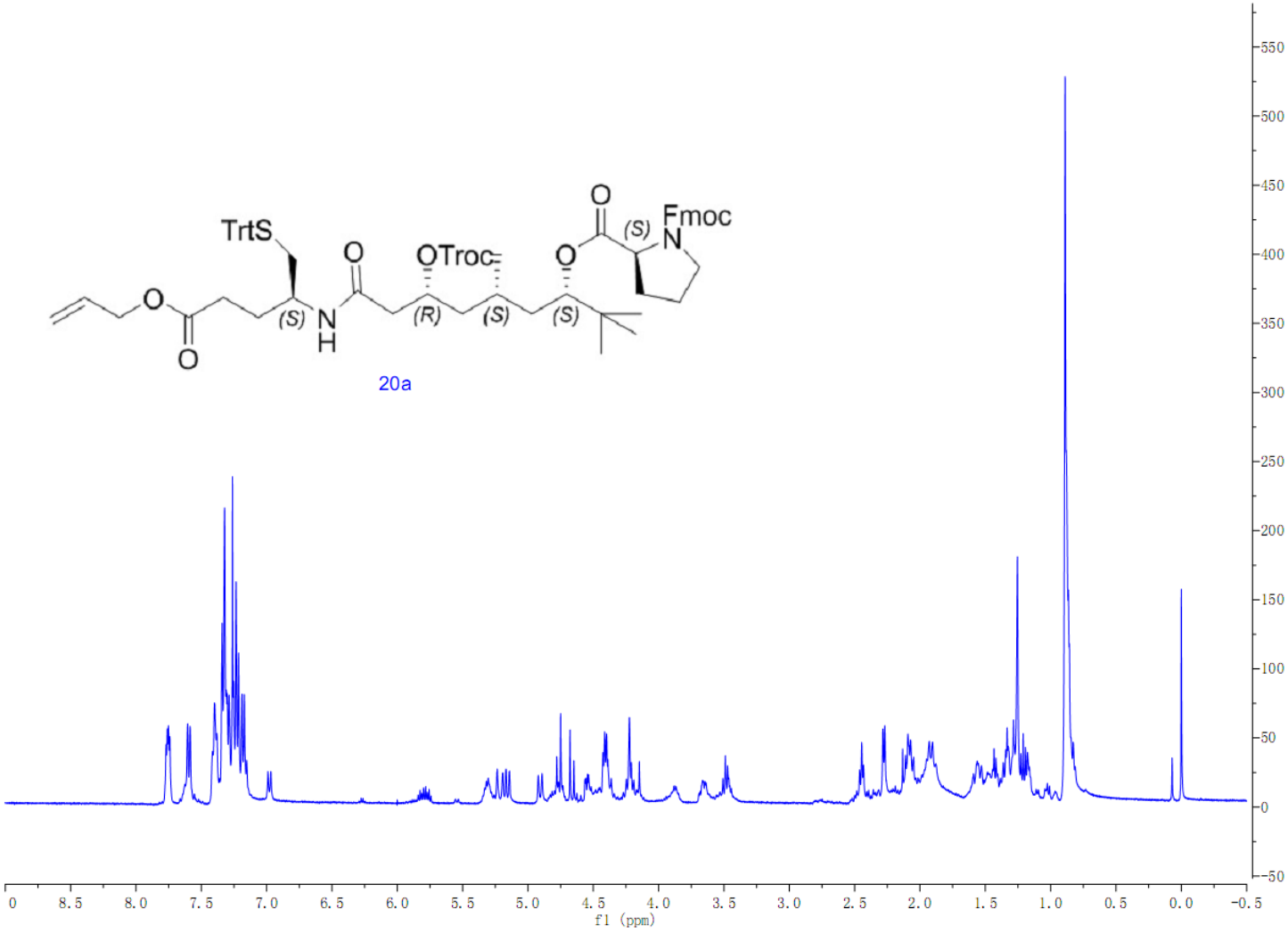
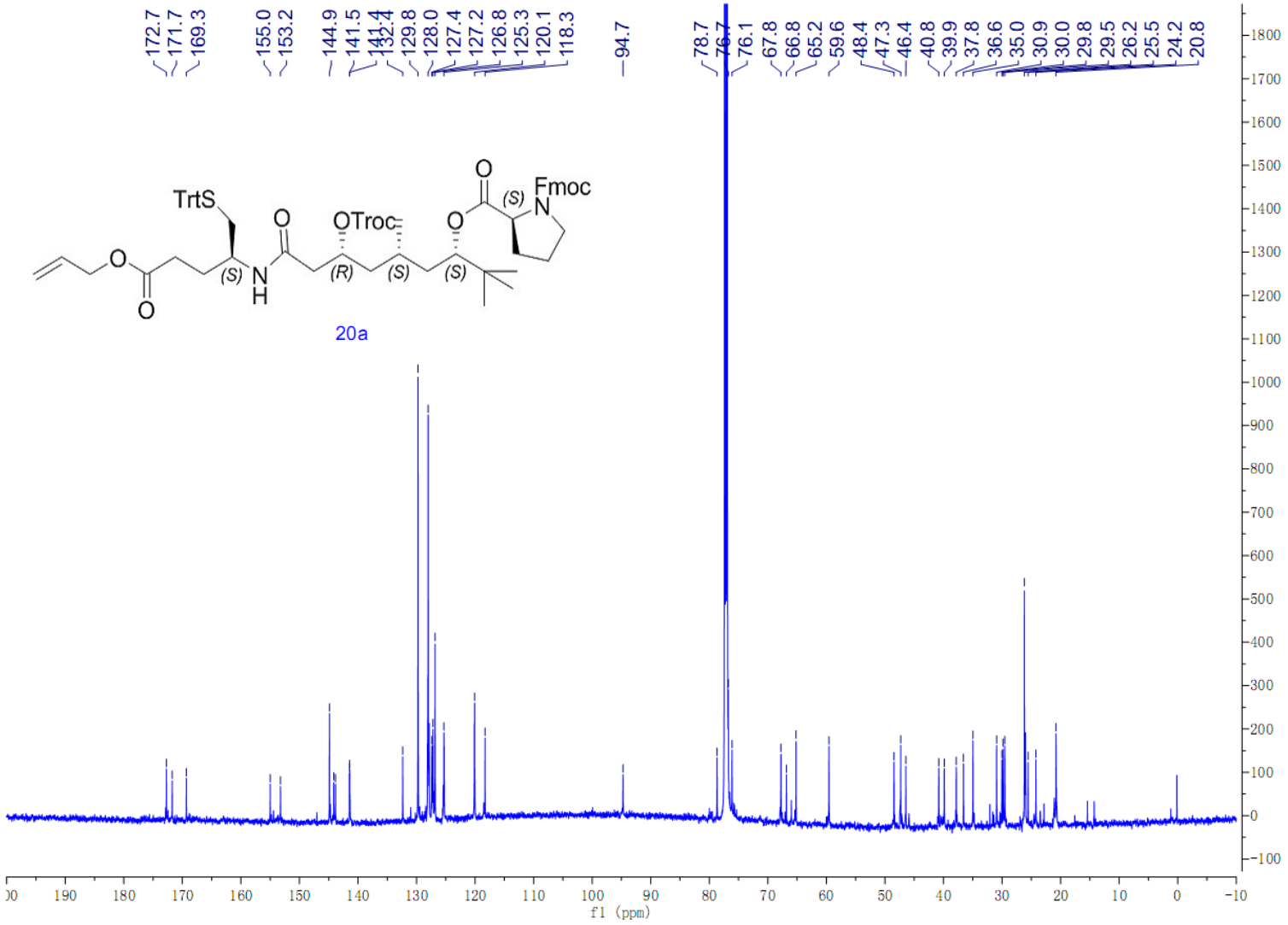
21.45
21.06
14.20
AllylO
STrt
HN
OH
FmocN
19a
f1 (ppm)


19b
f1 (ppm)


TrtS
O
OTroc
O
O
(S)
Fmoc
N
O
O
(S)
N
H
(R)
(S)
(S)
20a
550
500
450
400
350
300
250
200
150
100
50
0
-50
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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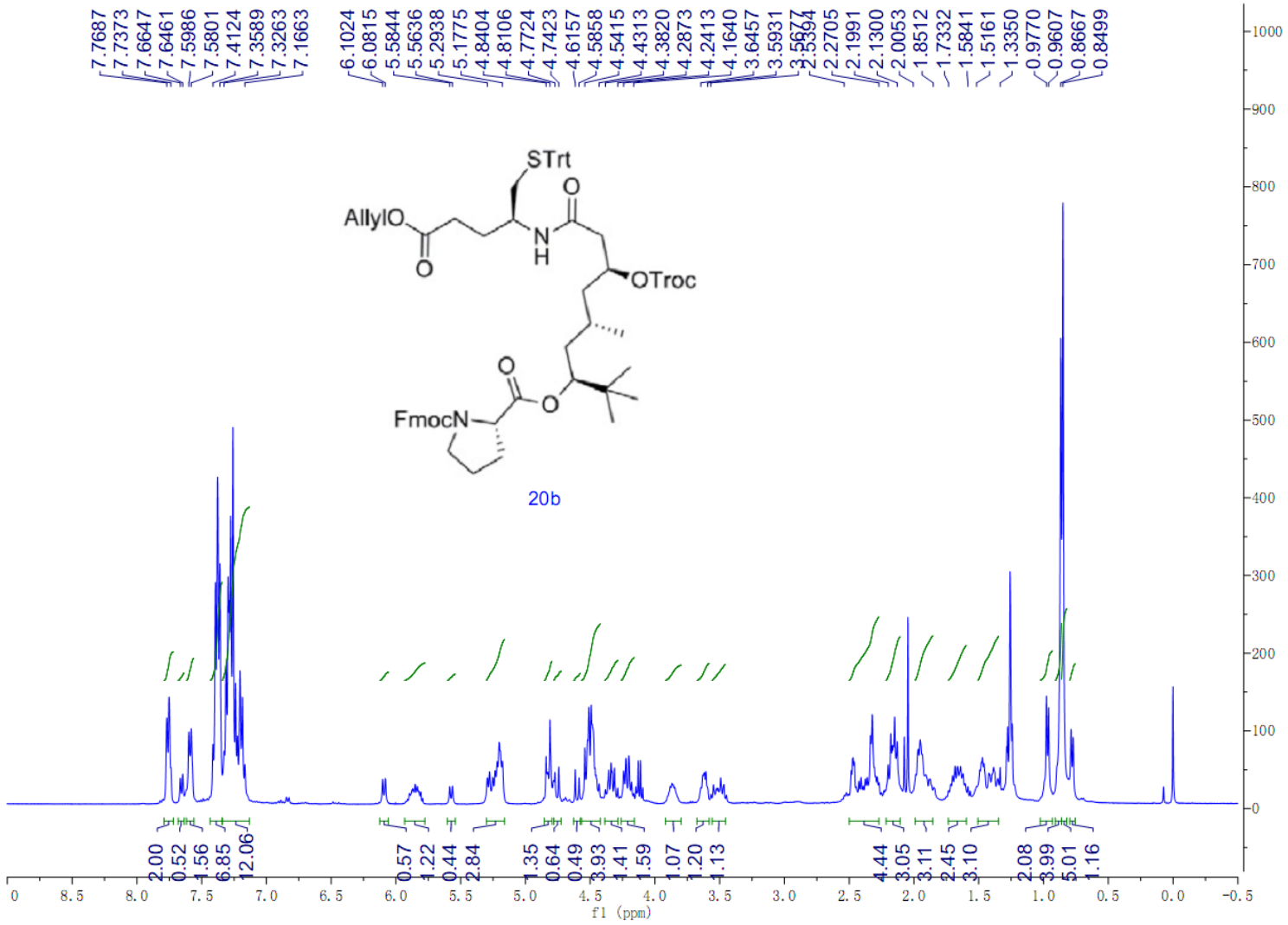
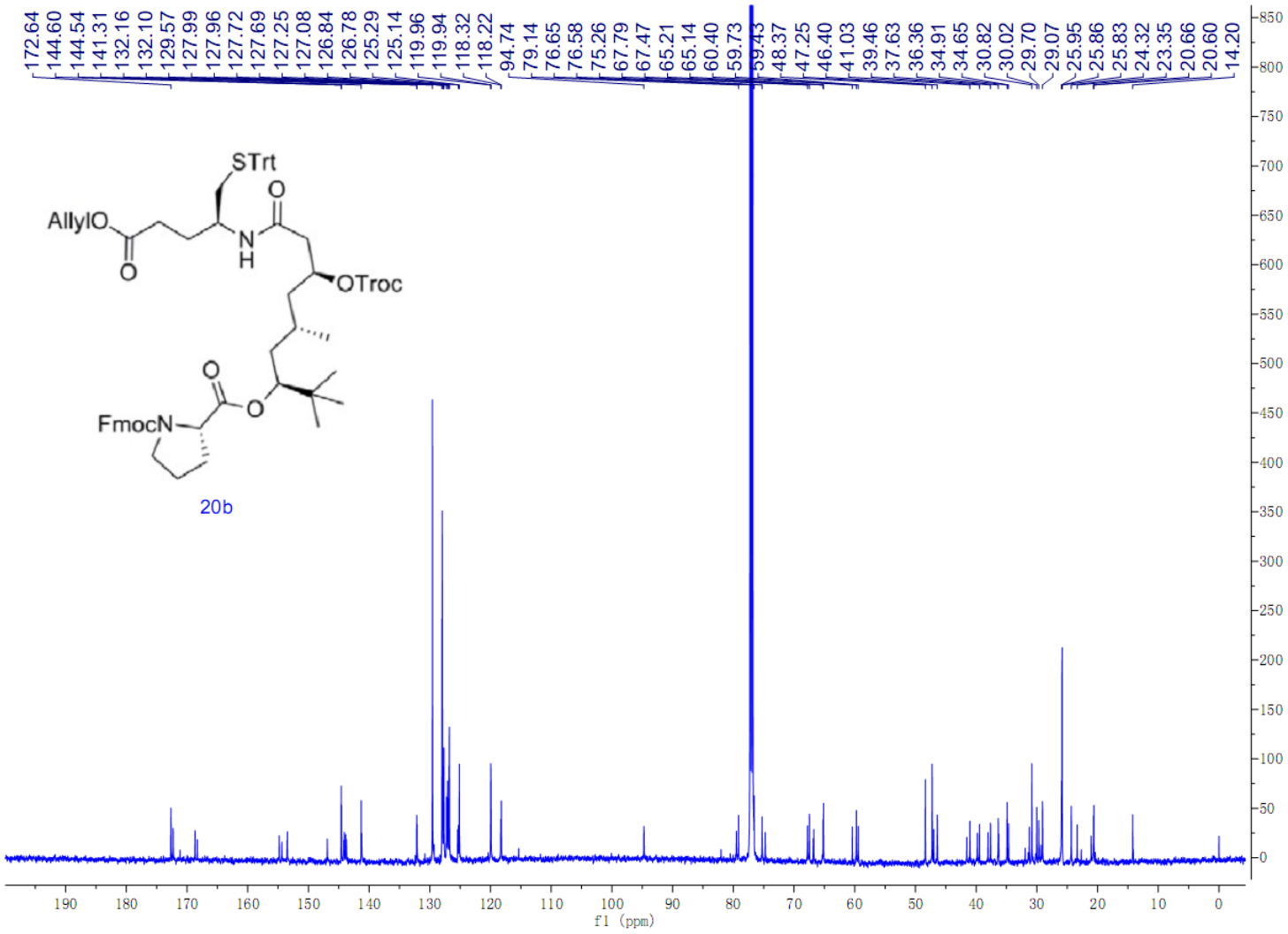
127.4
127.2
126.8
125.3
120.1
118.3
94.7
78.7
76.7
76.1
67.8
66.8
65.2
59.6
48.4
47.3
46.4
40.8
39.9
37.8
36.6
35.0
30.9
30.0
29.8
29.5
26.2
25.5
24.2
20.8
TrtS
OTroc
Fmoc
(S)
(R)
(S)
(S)
(S)
20a
f1 (ppm)


STrt
AllylO
O
N
H
OTroc
FmocN
20b
f1 (ppm)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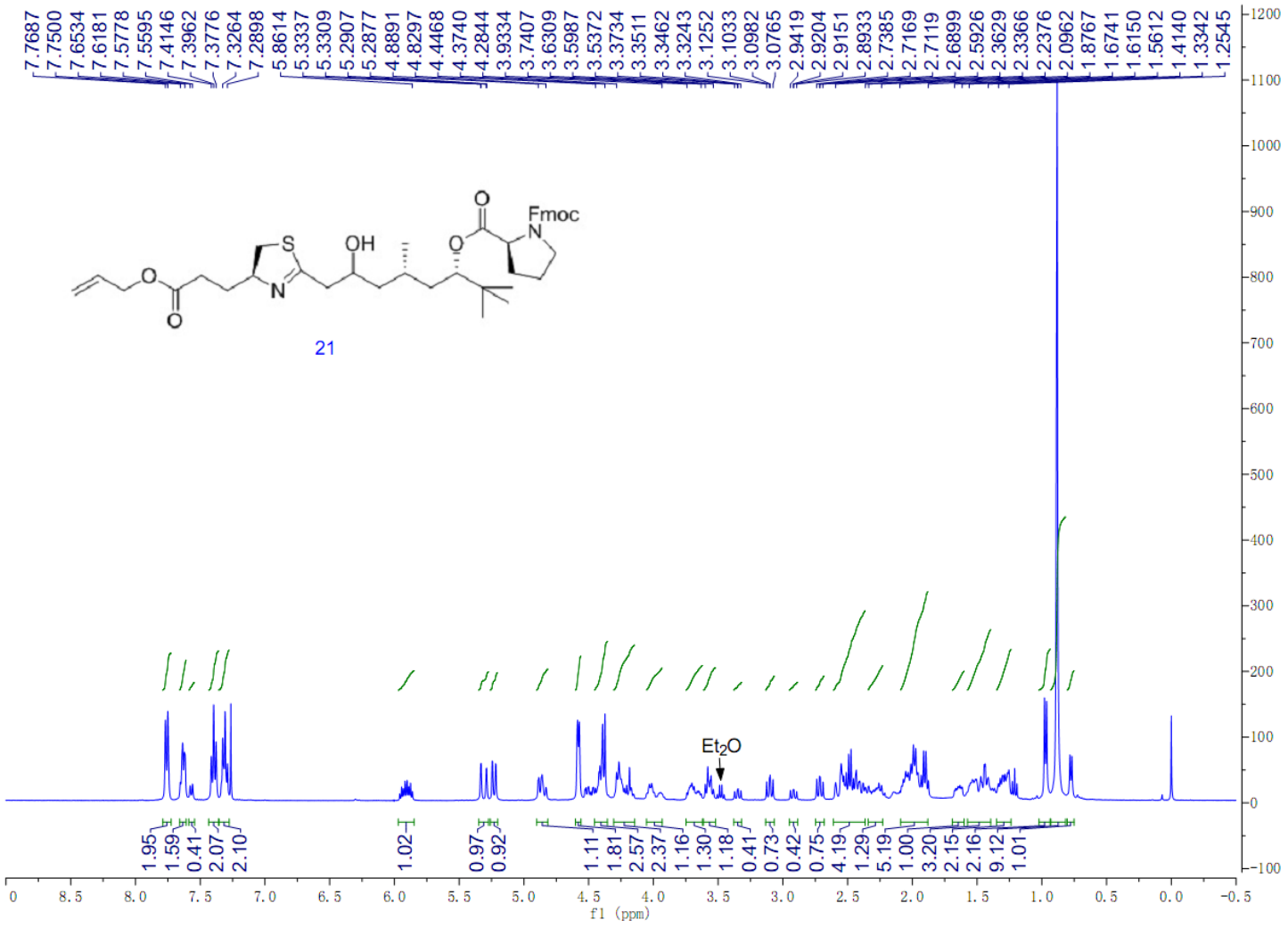
132.10
129.57
127.99
127.96
127.72
127.69
127.25
127.08
126.84
126.78
125.29
125.14
119.96
119.94
118.32
118.22
94.74
79.14
76.65
76.58
75.26
67.79
67.47
65.21
65.14
60.40
59.73
59.43
48.37
47.25
46.40
41.03
39.46
37.63
36.36
34.91
34.65
30.82
30.02
29.70
29.07
25.95
25.86
25.83
24.32
23.35
20.66
20.60
14.20
STrt
AllylO
O
N
H
O
OTroc
O
O
FmocN
O
20b
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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5.3337
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5.2907
5.2877
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4.3740
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3.5372
3.3734
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3.3462
3.3243
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3.1033
3.0982
3.0765
2.9419
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2.7169
2.7119
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1.3342
1.2545
Fmoc
OH
S
N
O
21
Et2O
1.95
1.59
0.41
2.07
2.10
1.02
0.97
0.92
1.11
1.81
2.57
2.37
1.16
1.30
1.18
0.41
0.73
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0.75
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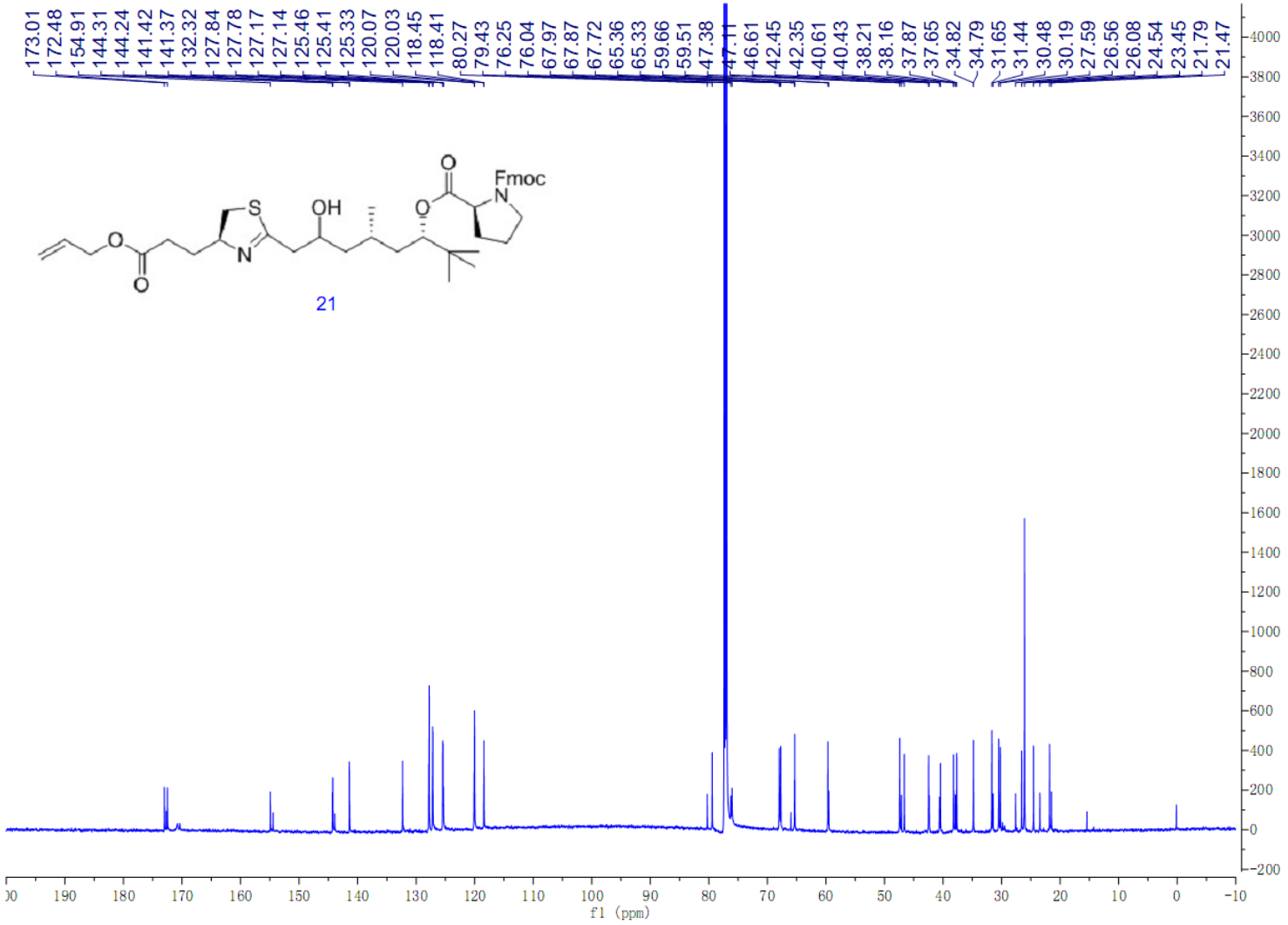
1.29
5.19
1.00
3.20
2.15
2.16
9.12
1.01
f1 (ppm)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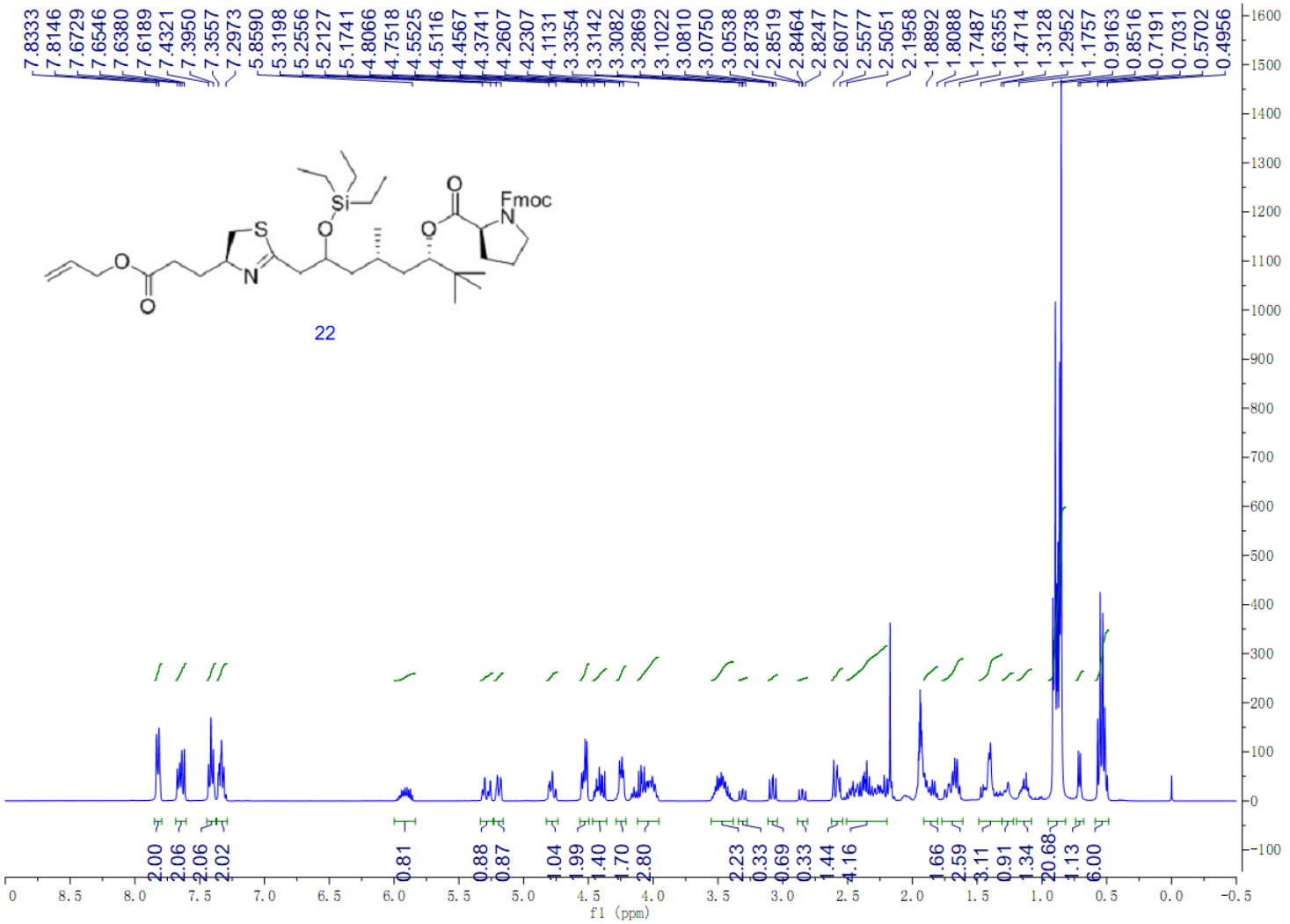
127.17
127.14
125.46
125.41
125.33
120.07
120.03
118.45
118.41
80.27
79.43
76.25
76.04
67.97
67.87
67.72
65.36
65.33
59.66
59.51
47.38
47.11
46.61
42.45
42.35
40.61
40.43
38.21
38.16
37.87
37.65
34.82
34.79
31.65
31.44
30.48
30.19
27.59
26.56
26.08
24.54
23.45
21.79
21.47
Fmoc
OH
S
N
O
21
f1 (ppm)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5.2127
5.1741
4.8066
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4.5525
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4.4567
4.3741
4.2607
4.2307
4.1131
3.3354
3.3142
3.3082
3.2869
3.1022
3.0810
3.0750
3.0538
2.8738
2.8519
2.8464
2.8247
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2.5051
2.1958
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1.8088
1.7487
1.6355
1.4714
1.3128
1.2952
1.1757
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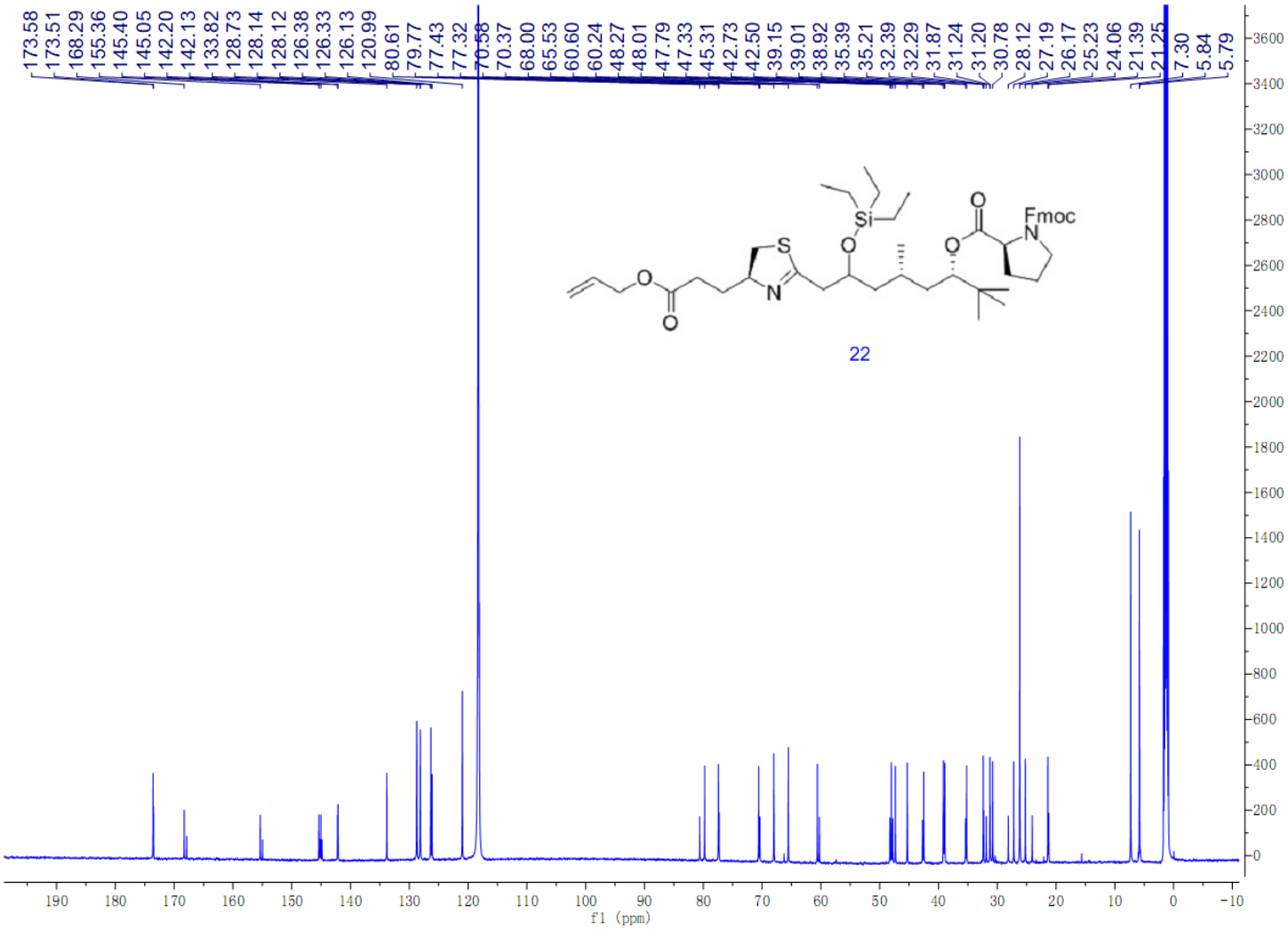
0.8516
0.7191
0.7031
0.5702
0.4956
Si
O
S
N
O
O
O
O
Fmoc
N
22
2.00
2.06
2.06
2.02
0.81
0.88
0.87
1.04
1.99
1.40
1.70
2.80
2.23
0.33
0.69
0.33
1.44
4.16
1.66
2.59
3.11
0.91
1.34
20.68
1.13
6.00
f1 (ppm)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142.13
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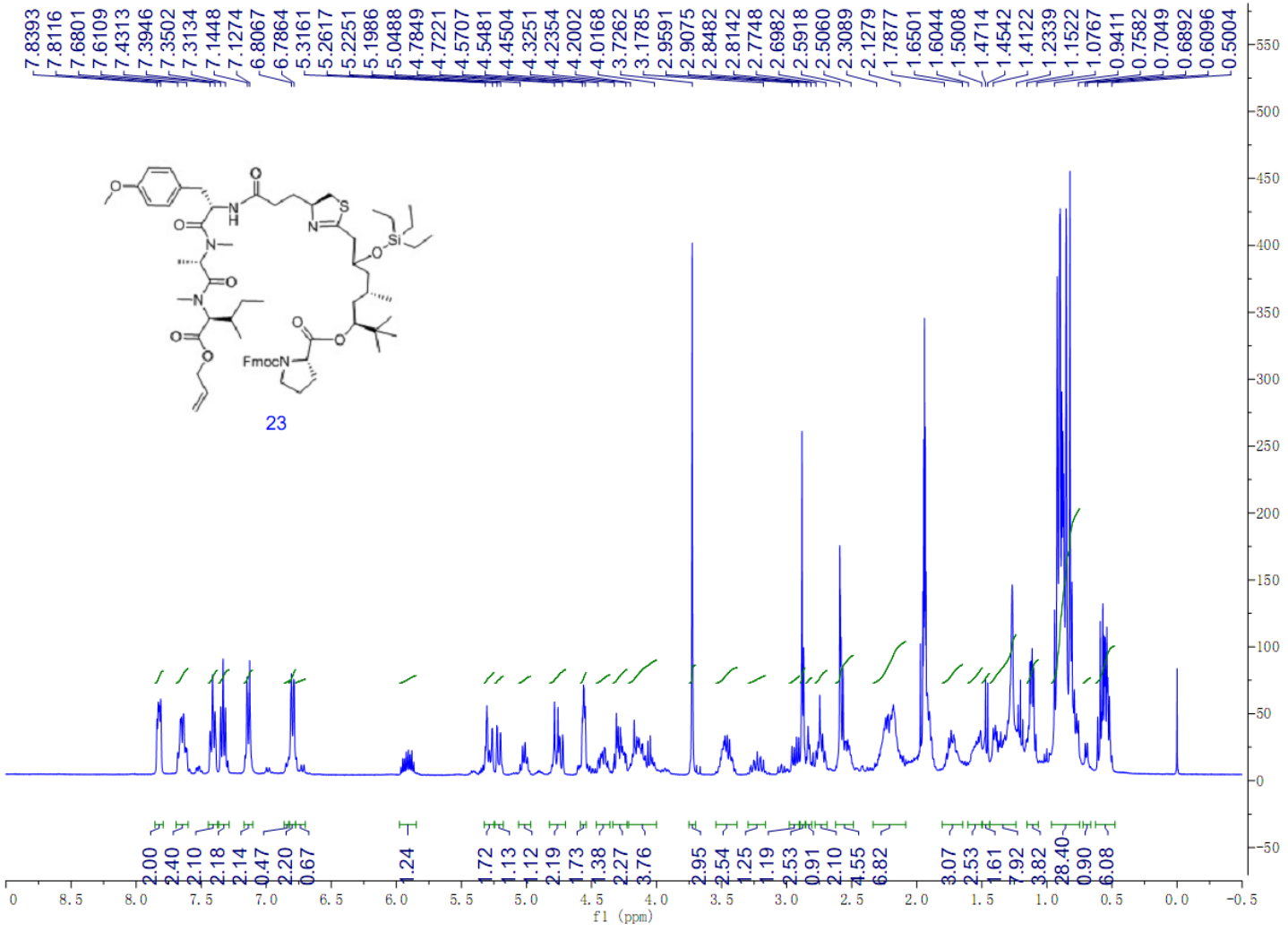
128.14
128.12
126.38
126.33
126.13
120.99
80.61
79.77
77.43
77.32
70.58
70.37
68.00
65.53
60.60
60.24
48.27
48.01
47.79
47.33
45.31
42.73
42.50
39.15
39.01
38.92
35.39
35.21
32.39
32.29
31.87
31.24
31.20
30.78
28.12
27.19
26.17
25.23
24.06
21.39
21.25
7.30
5.84
5.79
Fmoc
22
f1 (ppm)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6.7864
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5.2617
5.2251
5.1986
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4.7221
4.5707
4.5481
4.4504
4.3251
4.2354
4.2002
4.0168
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3.1785
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2.9075
2.8482
2.8142
2.7748
2.6982
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1.4542
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0.6892
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2.18
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2.27
3.76
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1.25
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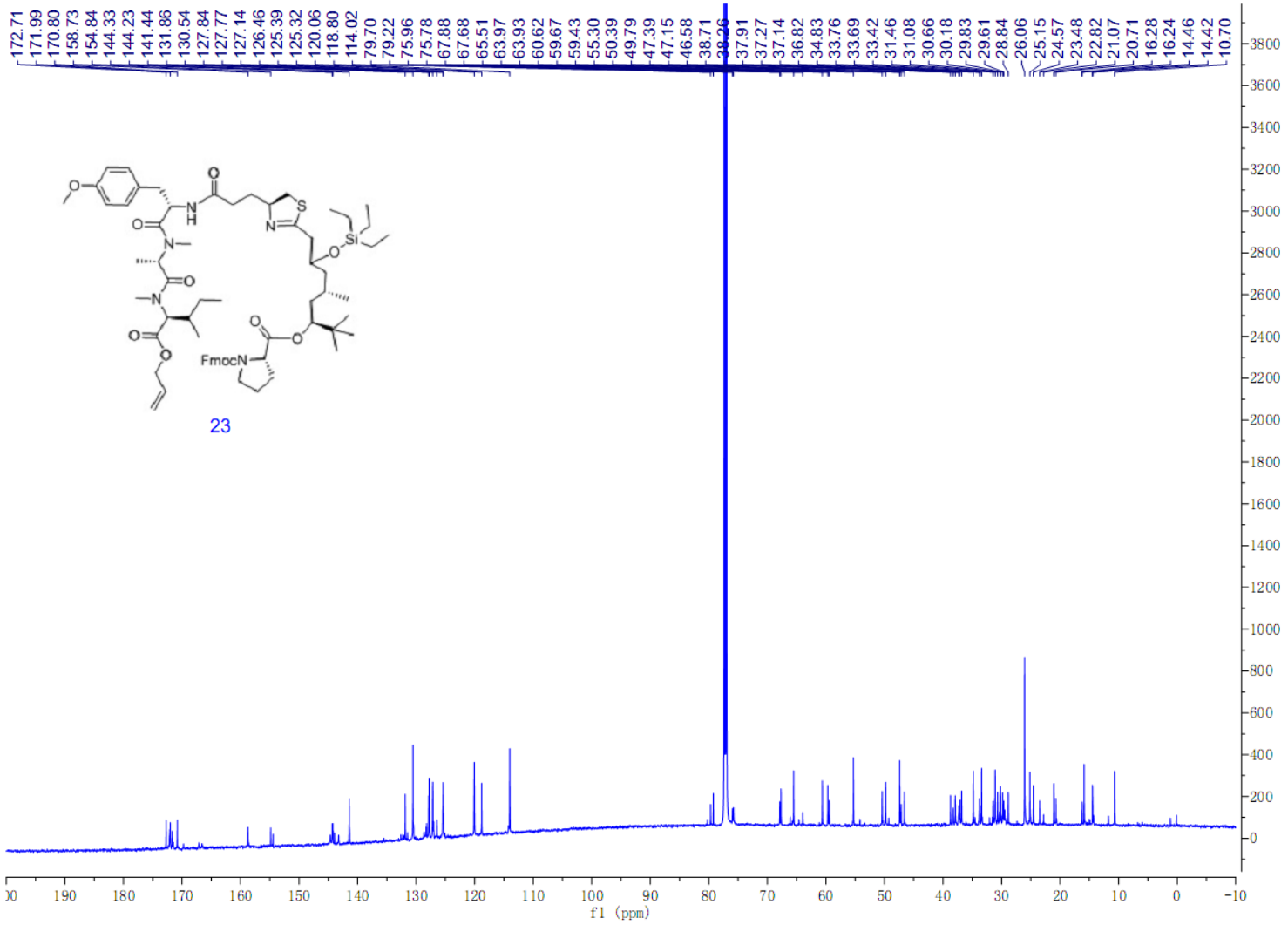
f1 (ppm)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125.39
125.32
120.06
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75.78
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67.68
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33.76
33.69
33.42
31.46
31.08
30.66
30.18
29.83
29.61
28.84
26.06
25.15
24.57
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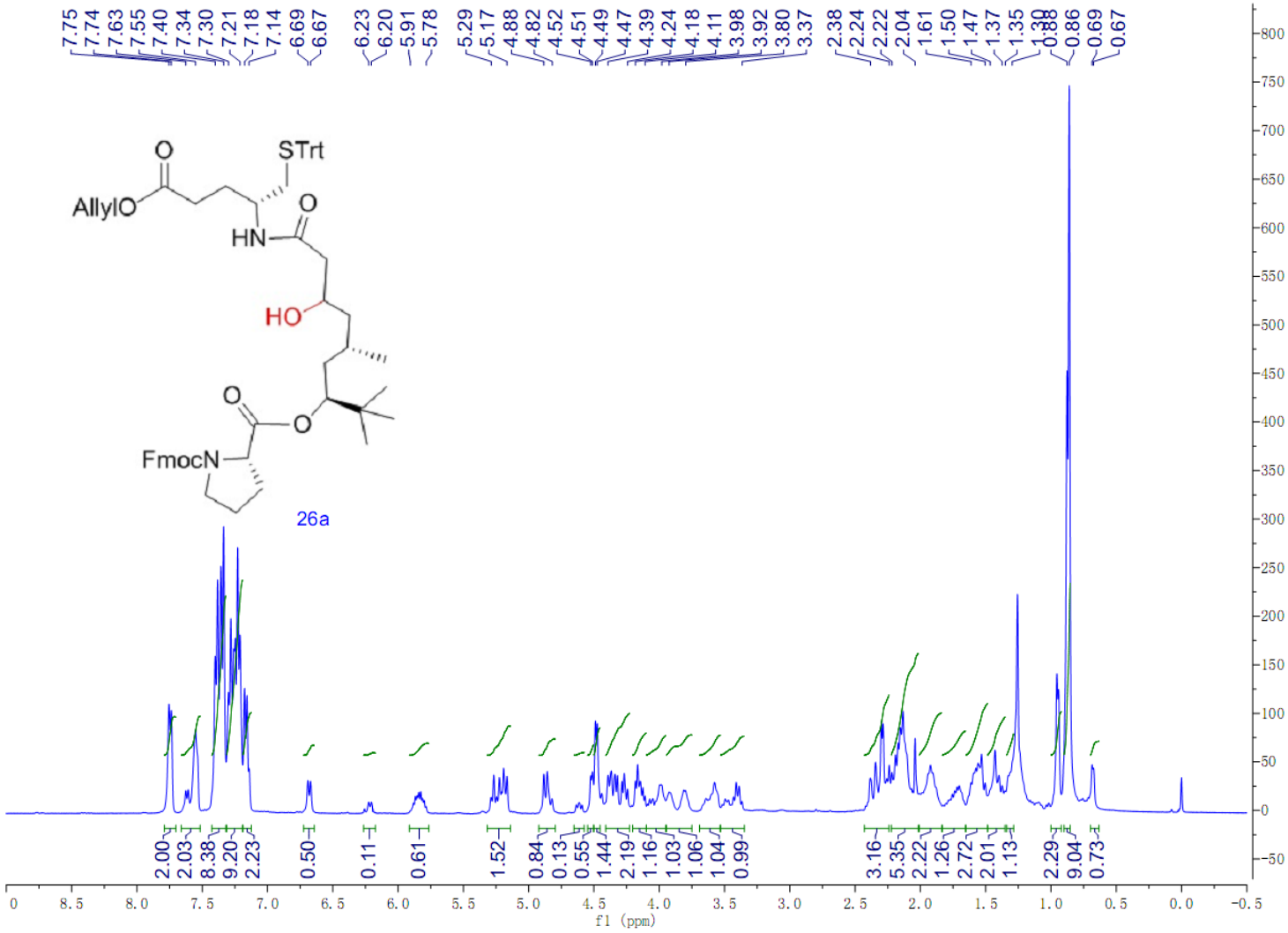
23
f1 (ppm)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5.78
5.29
5.17
4.88
4.82
4.52
4.51
4.49
4.47
4.39
4.24
4.18
4.11
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3.92
3.80
3.37
2.38
2.24
2.22
2.04
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1.50
1.47
1.37
1.35
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0.69
0.67
O
STrt
AllylO
O
HN
HO
O
O
FmocN
26a
2.00
2.03
8.38
9.20
2.23
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0.11
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0.13
0.55
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1.16
1.03
1.06
1.04
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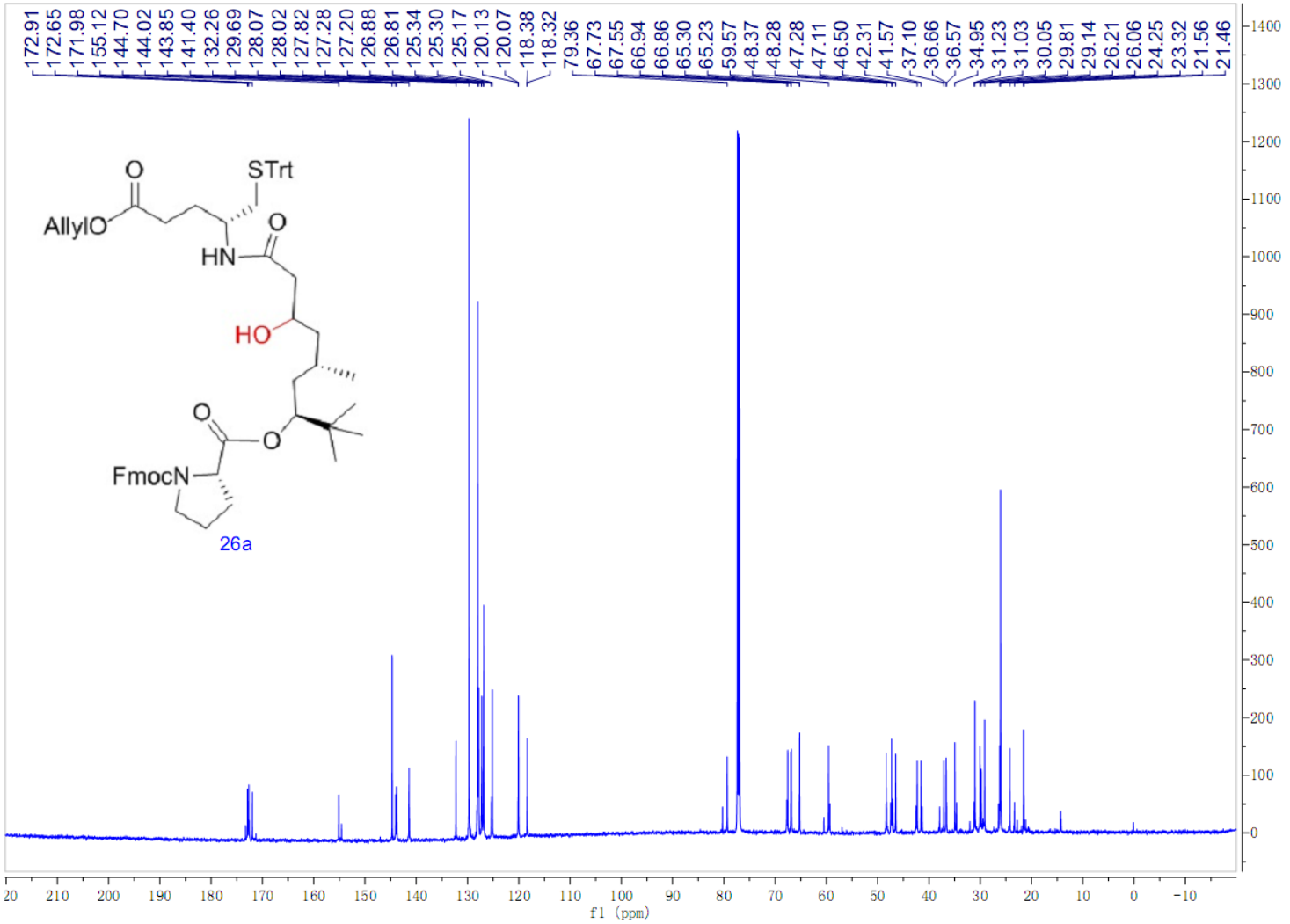
f1 (ppm)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127.20
126.88
126.81
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125.30
125.17
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120.07
118.38
118.32
79.36
67.73
67.55
66.94
66.86
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48.28
47.28
47.11
46.50
42.31
41.57
37.10
36.66
36.57
34.95
31.23
31.03
30.05
29.81
29.14
26.21
26.06
24.25
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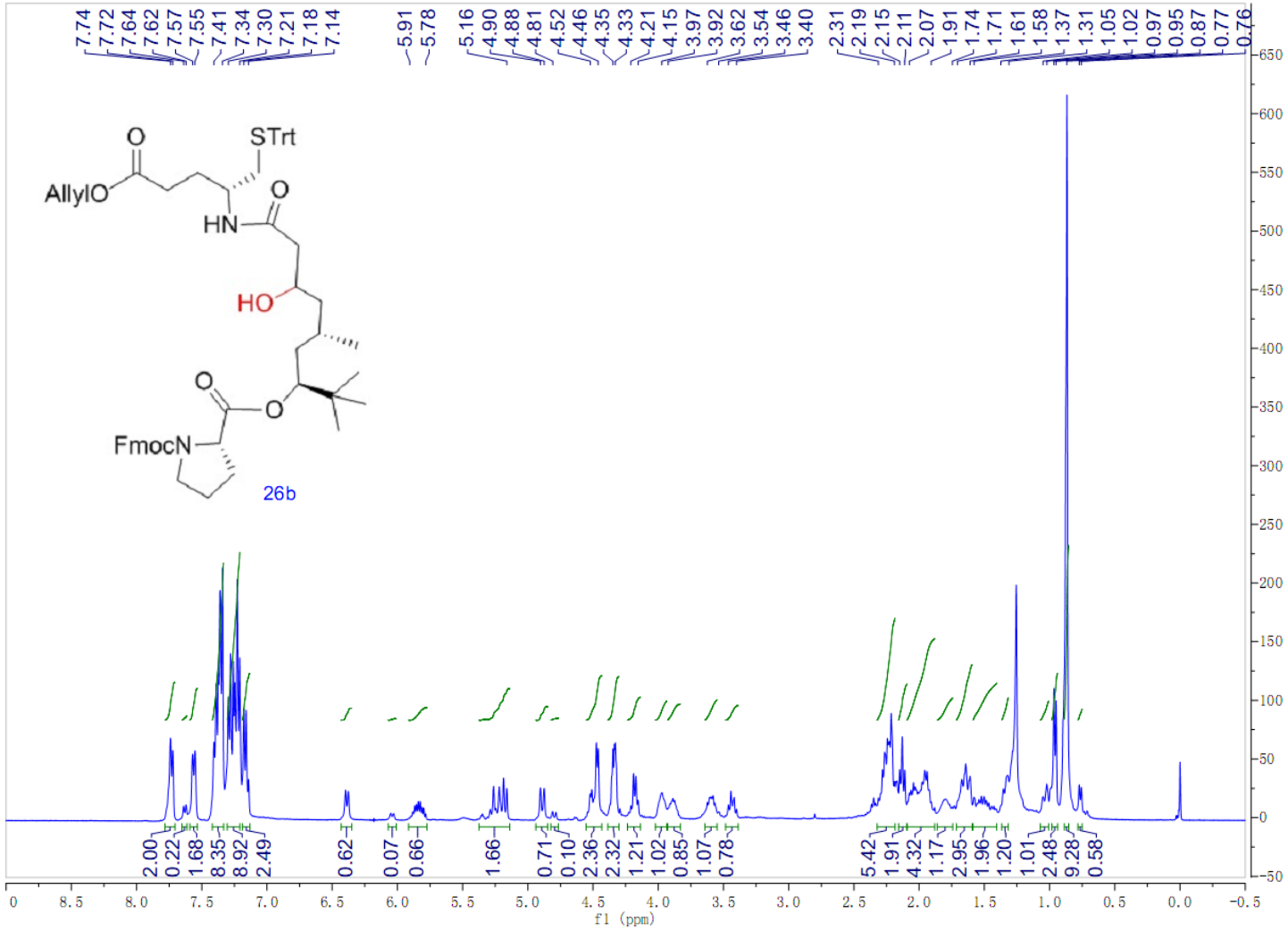
O
STrt
AllylO
O
HN
HO
O
O
FmocN
26a
f1 (ppm)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7.34
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7.21
7.18
7.14
5.91
5.78
5.16
4.90
4.88
4.81
4.52
4.46
4.35
4.33
4.21
4.15
3.97
3.92
3.62
3.54
3.46
3.40
2.31
2.19
2.15
2.11
2.07
1.91
1.74
1.71
1.61
1.58
1.37
1.31
1.05
1.02
0.97
0.95
0.87
0.77
0.76
O
STrt
AllylO
O
HN
HO
O
O
FmocN
26b
2.00
0.22
1.68
8.35
8.92
2.49
0.62
0.07
0.66
1.66
0.71
0.10
2.36
2.32
1.21
1.02
0.85
1.07
0.78
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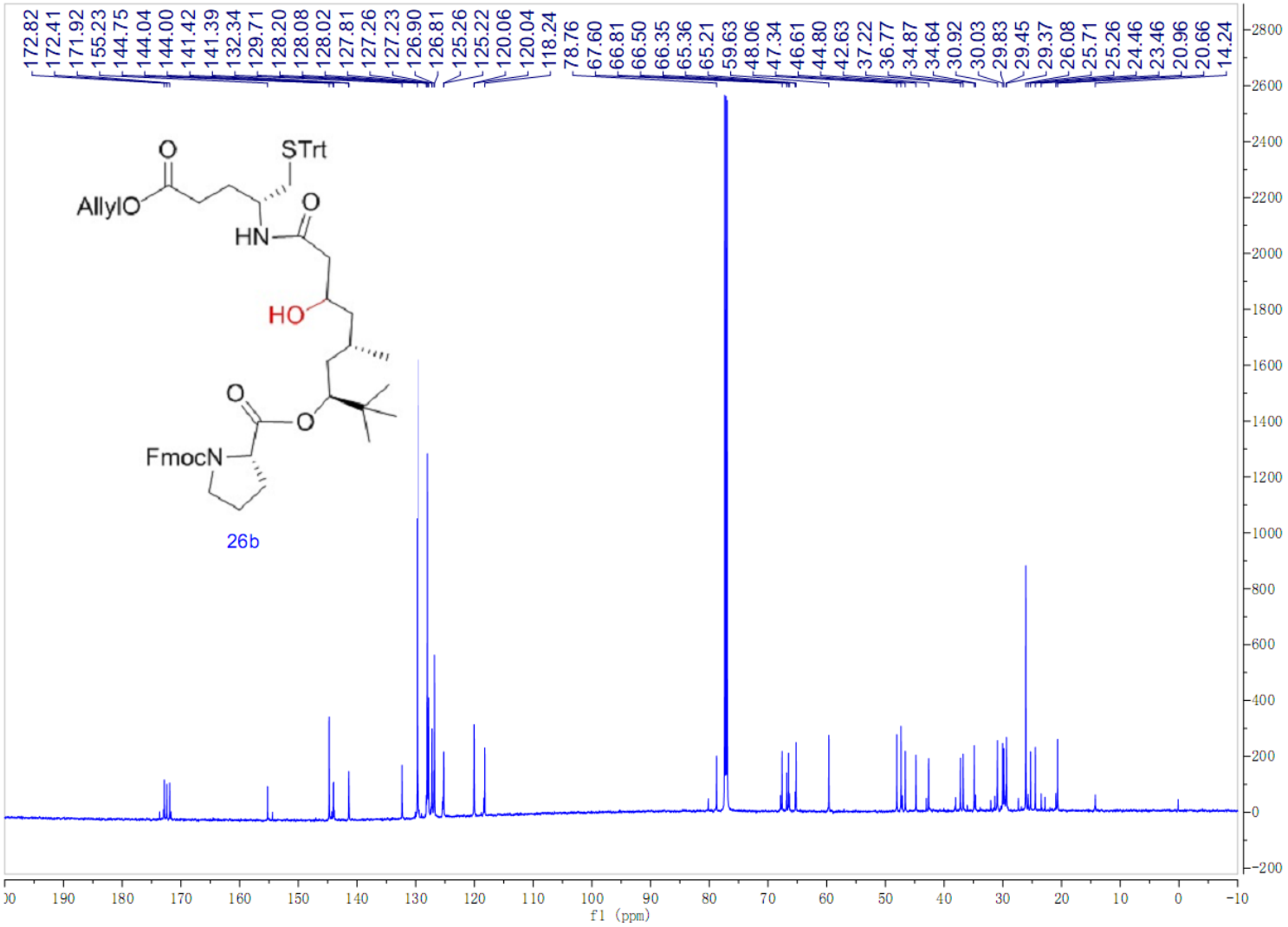
0.58
f1 (ppm)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128.08
128.02
127.81
127.26
127.23
126.90
126.81
125.26
125.22
120.06
120.04
118.24
78.76
67.60
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66.50
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65.36
65.21
59.63
48.06
47.34
46.61
44.80
42.63
37.22
36.77
34.87
34.64
30.92
30.03
29.83
29.45
29.37
26.08
25.71
25.26
24.46
23.46
20.96
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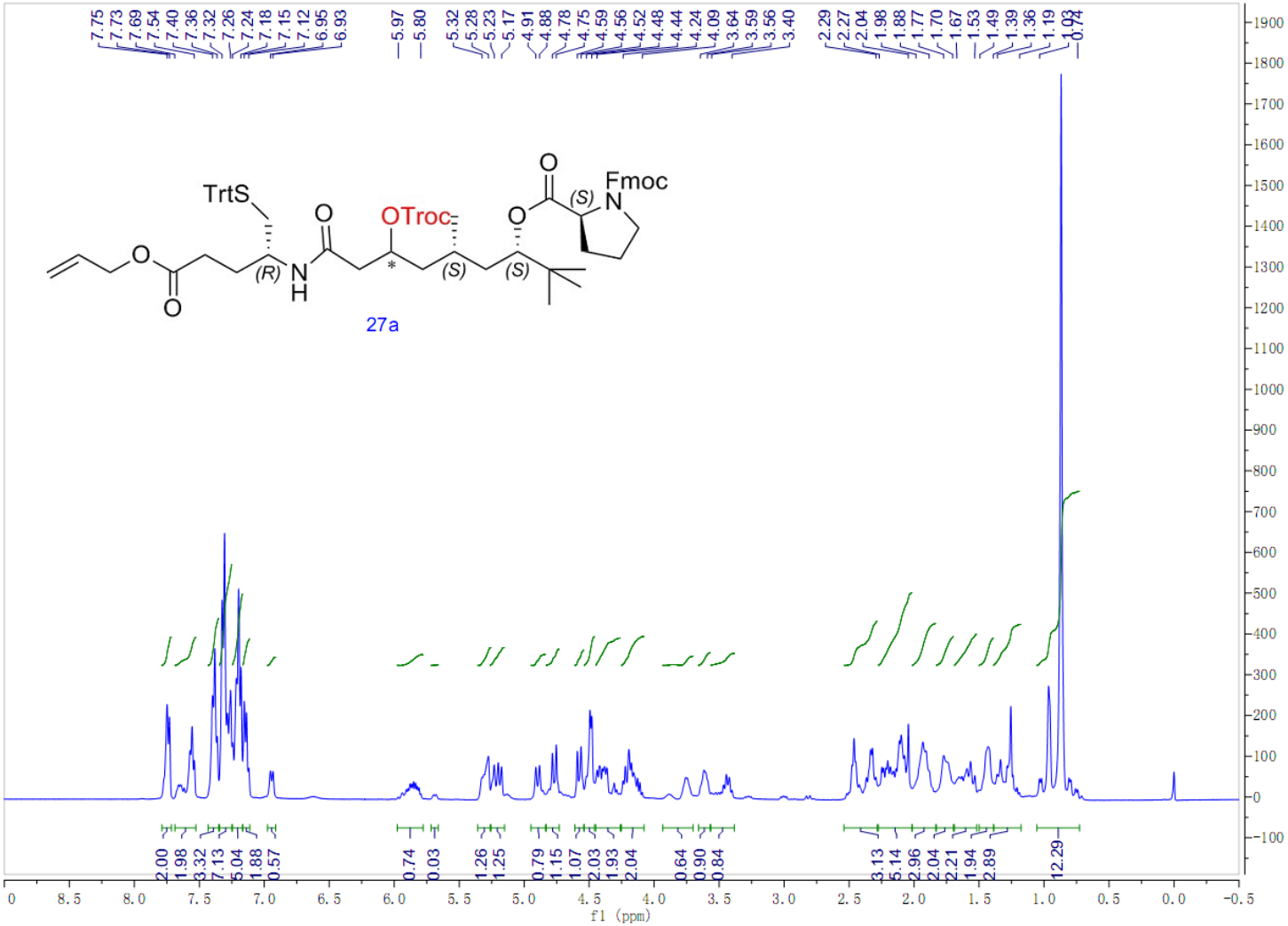
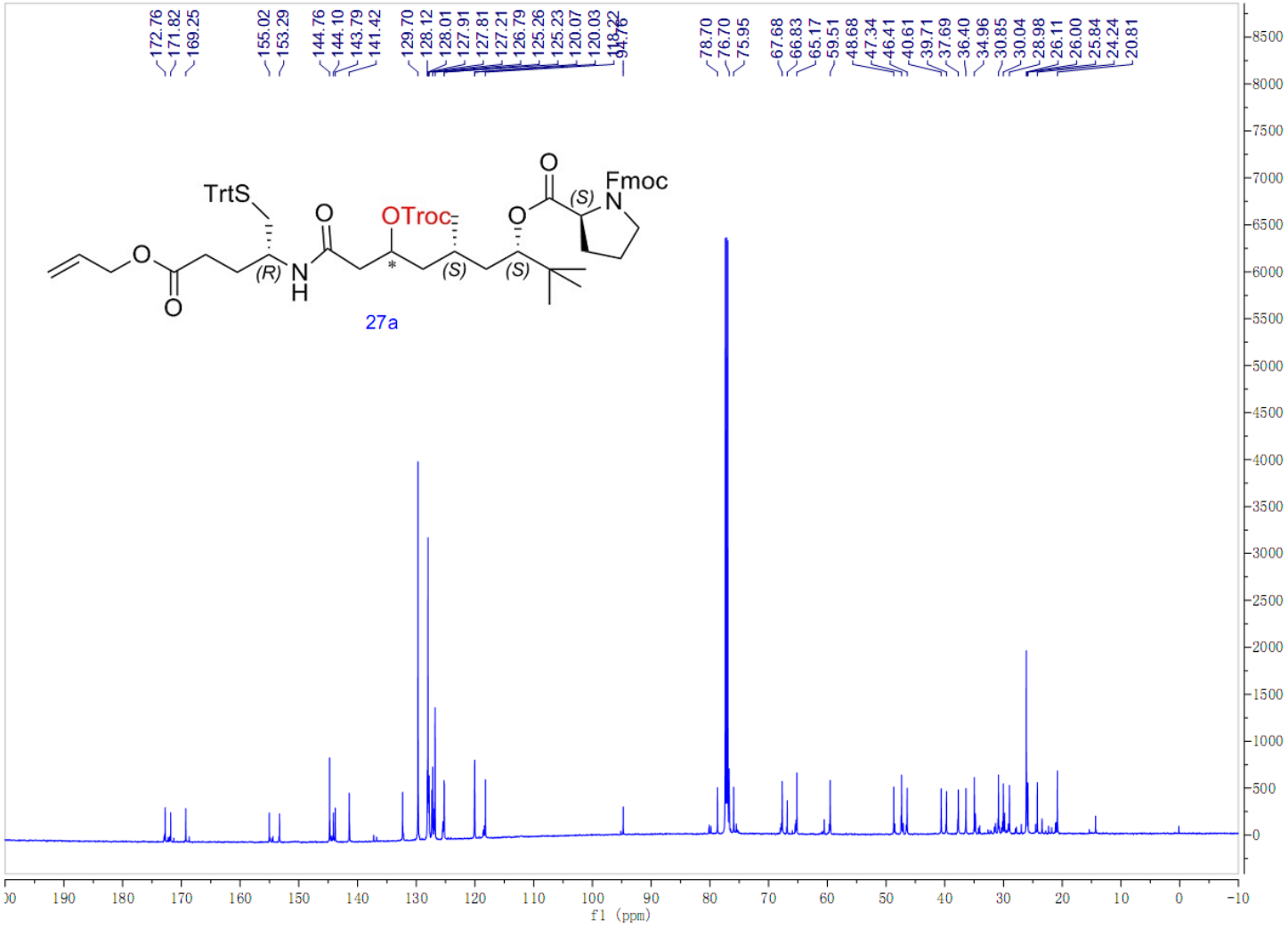
O
STrt
AllylO
O
HN
HO
O
O
FmocN
26b
f1 (ppm)


TrtS
OTroc
Fmoc
(R)
(S)
(S)
(S)
27a
f1 (ppm)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125.23
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120.03
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94.76
78.70
76.70
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59.51
48.68
47.34
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37.69
36.40
34.96
30.85
30.04
28.98
26.11
26.00
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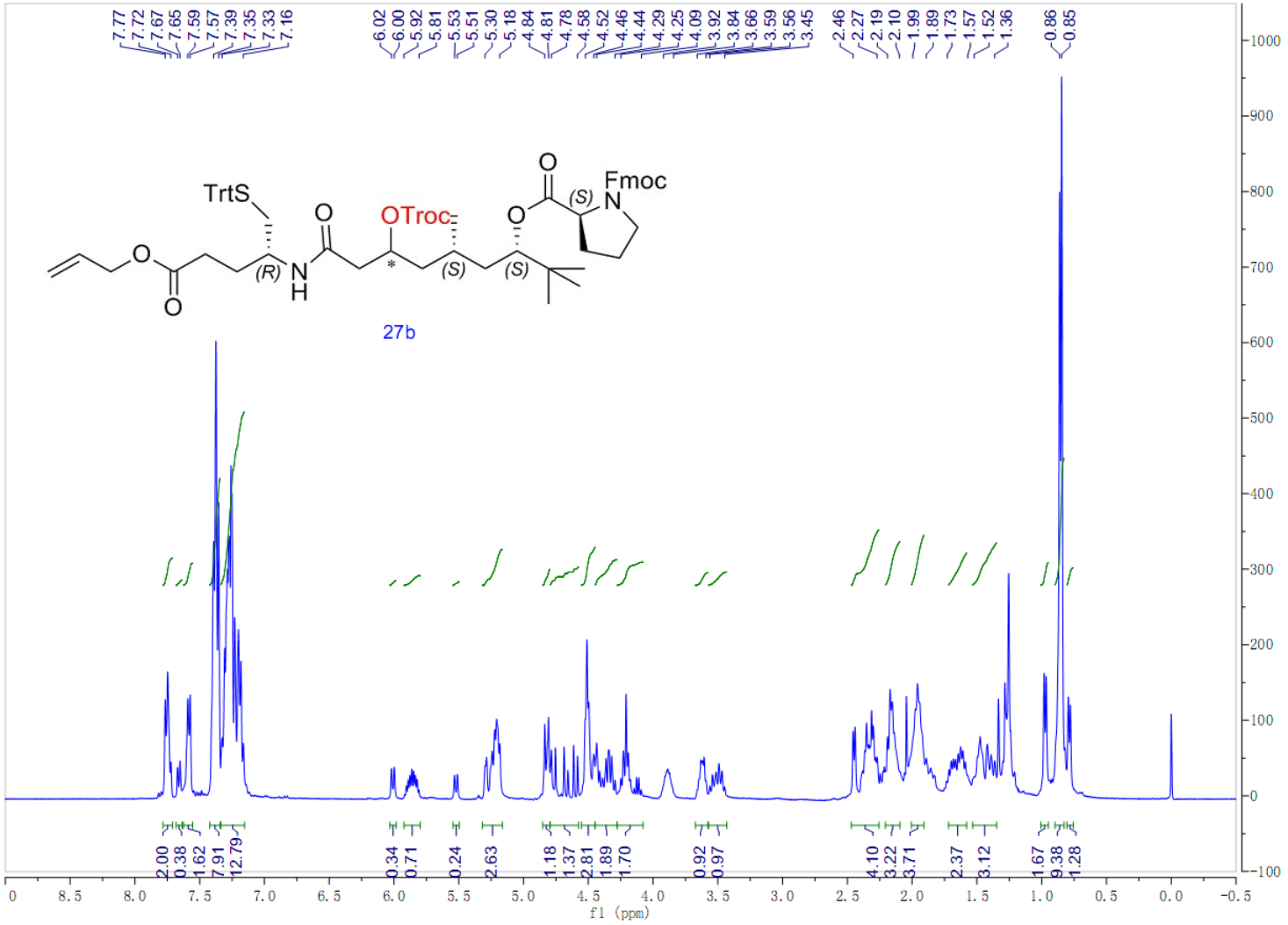
20.81
TrtS
OTroc
Fmoc
(R)
(S)
(S)
(S)
27a
f1 (ppm)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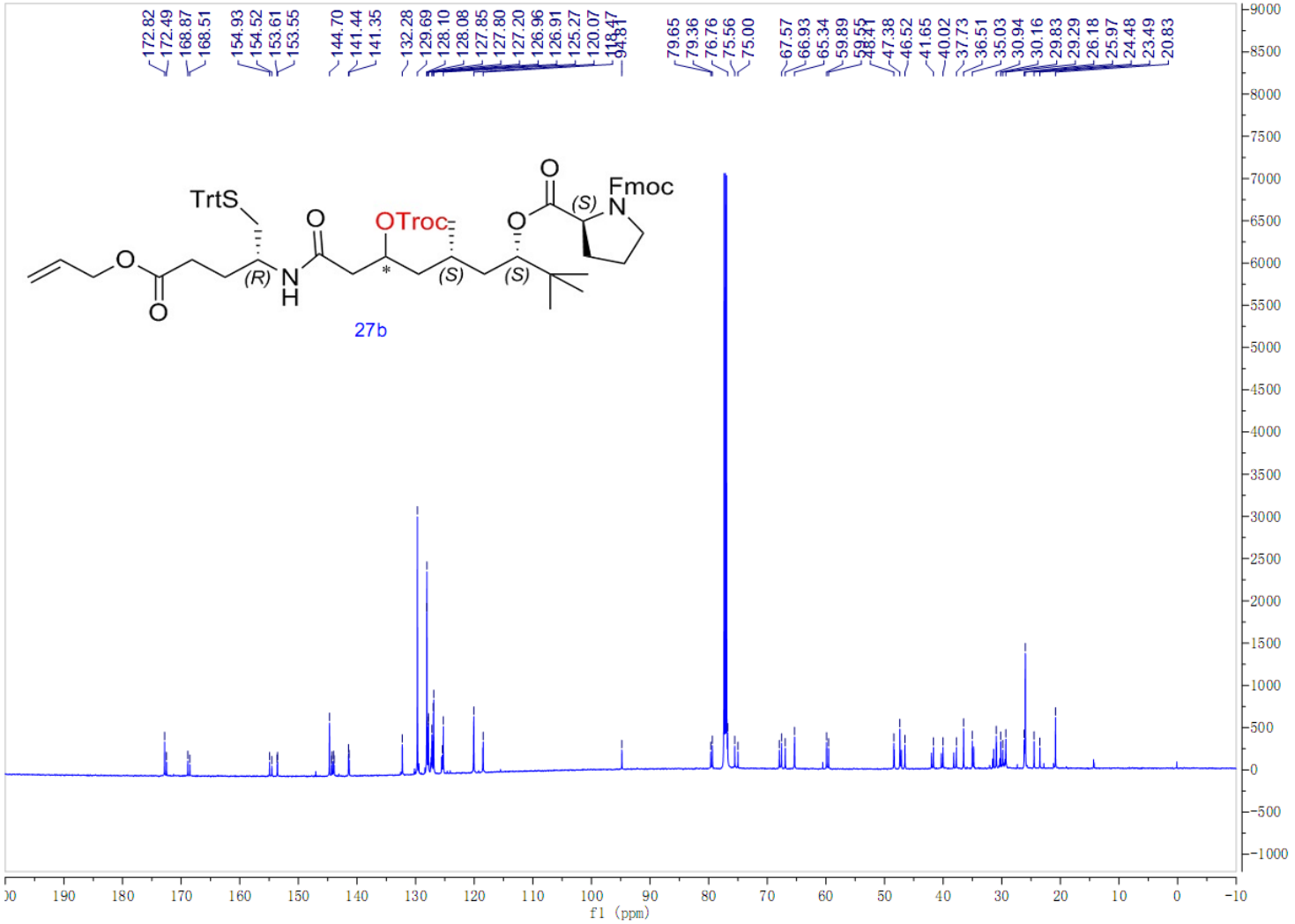
OTroc
Fmoc
(R)
(S)
(S)
(S)
27b
f1 (ppm)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128.10
128.08
127.85
127.80
127.20
126.96
126.91
125.27
120.07
79.65
79.36
76.76
75.56
75.00
67.57
66.93
65.34
59.89
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29.29
26.18
25.97
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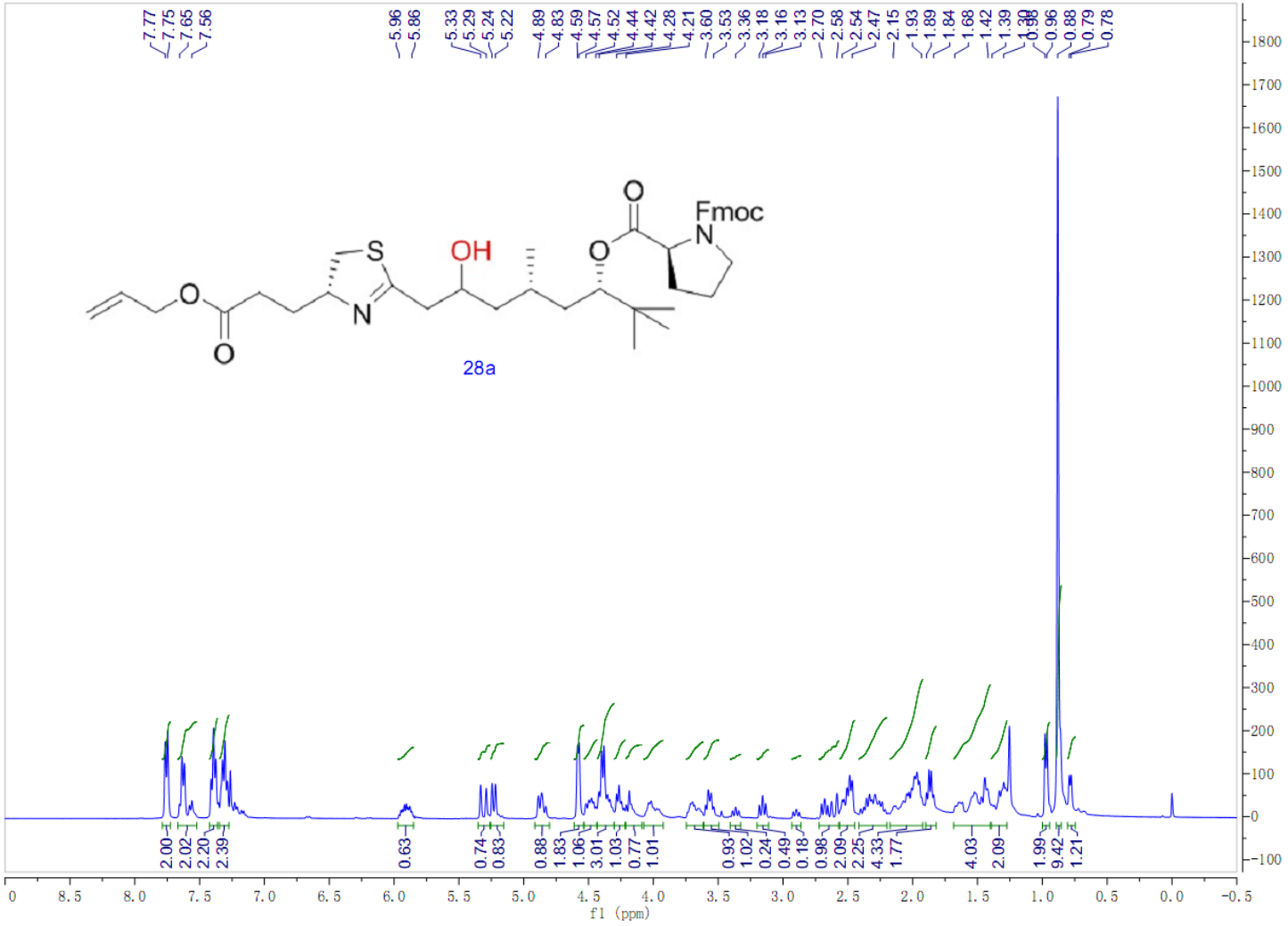
TrtS
OTroc
Fmoc
(R)
(S)
(S)
(S)
27b
f1 (ppm)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4.59
4.57
4.52
4.44
4.42
4.28
4.21
3.60
3.53
3.36
3.18
3.16
3.13
2.70
2.58
2.54
2.47
2.15
1.93
1.89
1.84
1.68
1.42
1.39
0.96
0.88
0.79
0.78
Fmoc
N
O
S
OH
N
O
O
O
28a
2.00
2.02
2.20
2.39
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0.74
0.83
0.88
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1.06
3.01
1.03
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1.01
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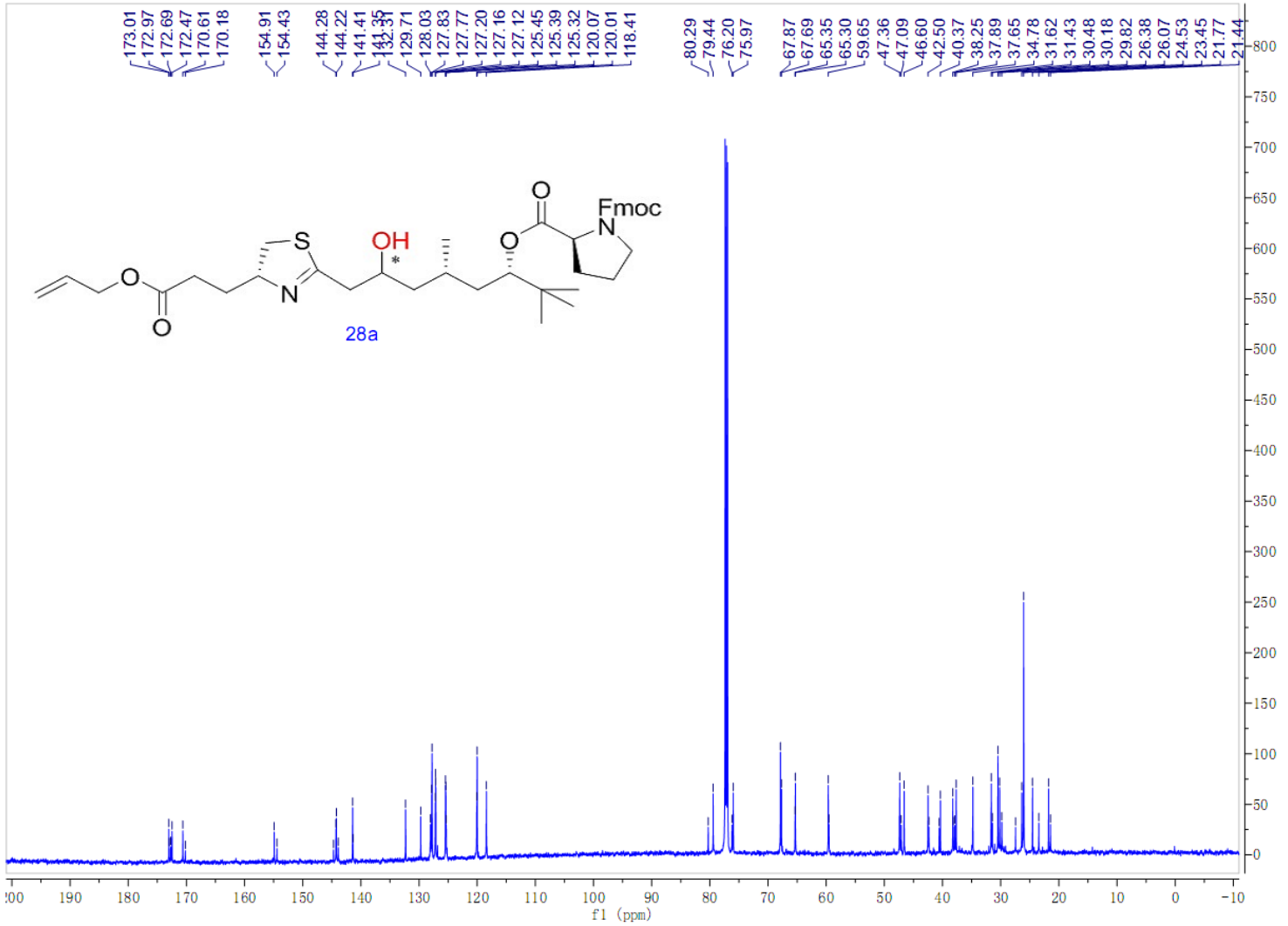
f1 (ppm)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125.39
125.32
120.07
120.01
118.41
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75.97
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38.25
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37.65
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31.62
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30.48
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26.07
24.53
23.45
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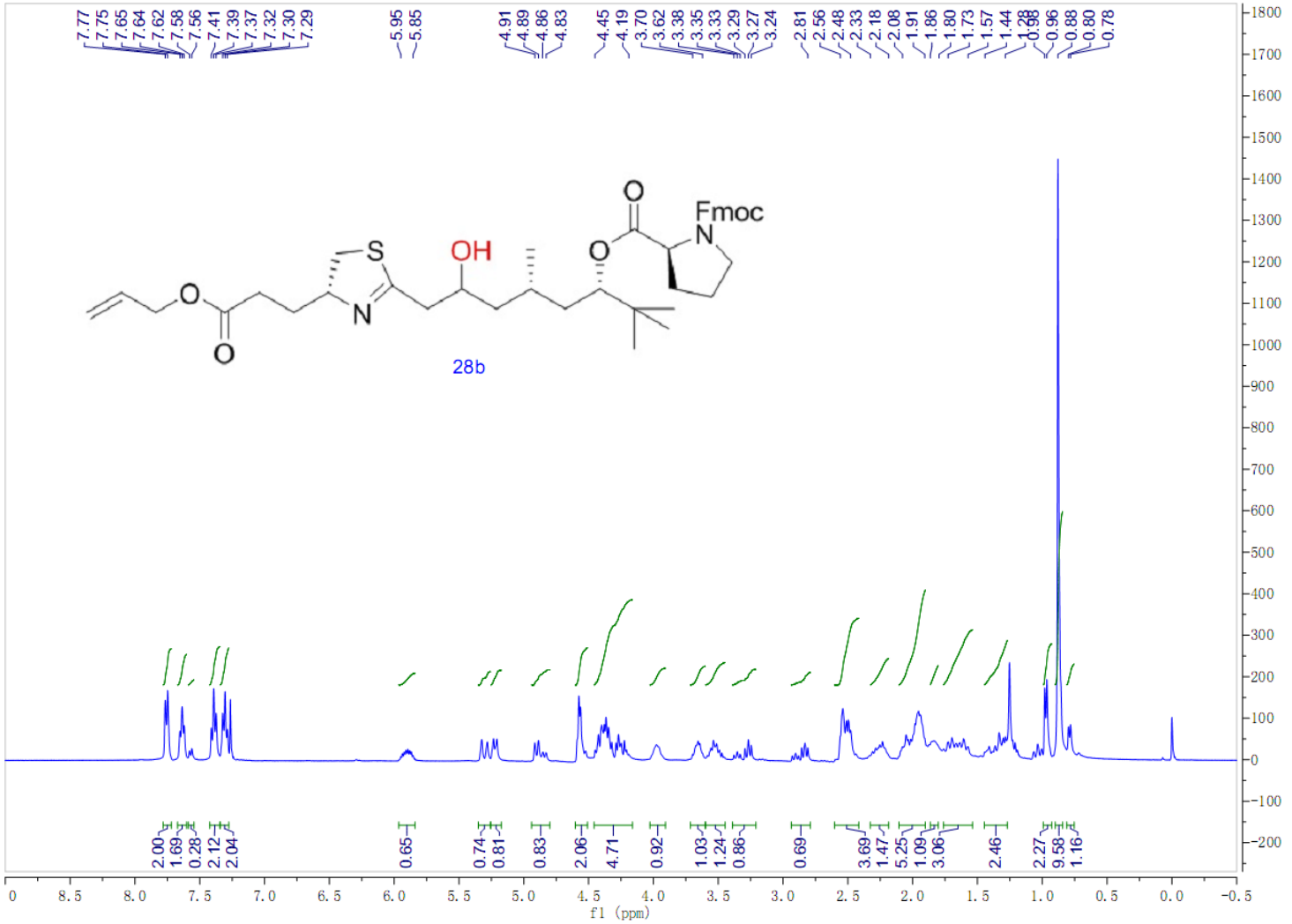
21.44
Fmoc
OH
28a
f1 (ppm)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7.32
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5.85
4.91
4.89
4.86
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3.35
3.33
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2.18
2.08
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1.86
1.80
1.73
1.57
1.44
0.96
0.88
0.80
0.78
O
Fmoc
N
S
OH
O
O
N
O
28b
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0.81
0.83
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0.92
1.03
1.24
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3.06
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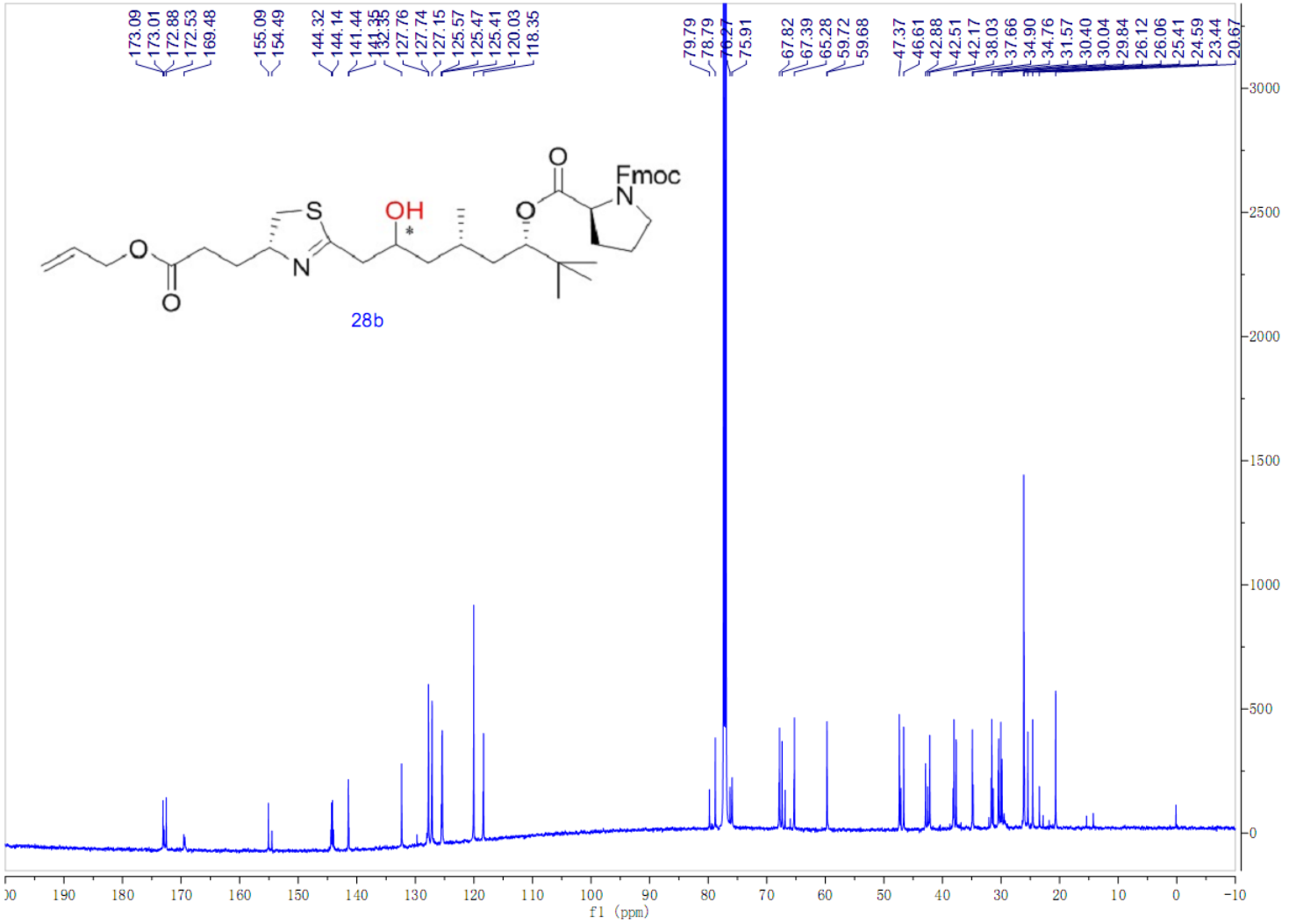
9.58
1.16
f1 (ppm)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125.47
125.41
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67.39
65.28
59.72
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46.61
42.88
42.51
42.17
38.03
37.66
34.90
34.76
31.57
30.40
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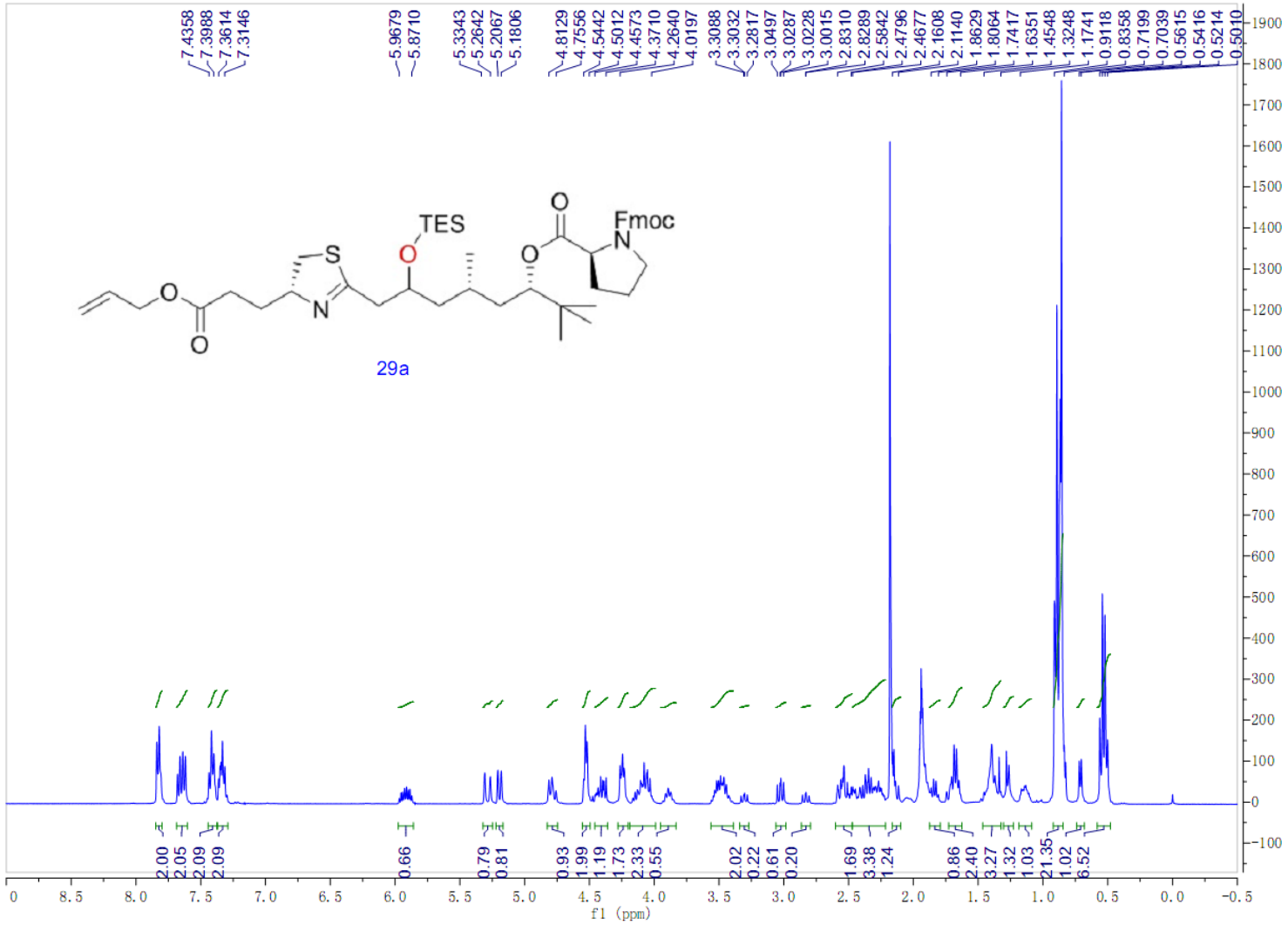
26.06
25.41
24.59
23.44
20.67
Fmoc
OH
28b
f1 (ppm)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3.3032
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Fmoc
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2.09
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2.02
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0.20
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3.27
1.32
1.03
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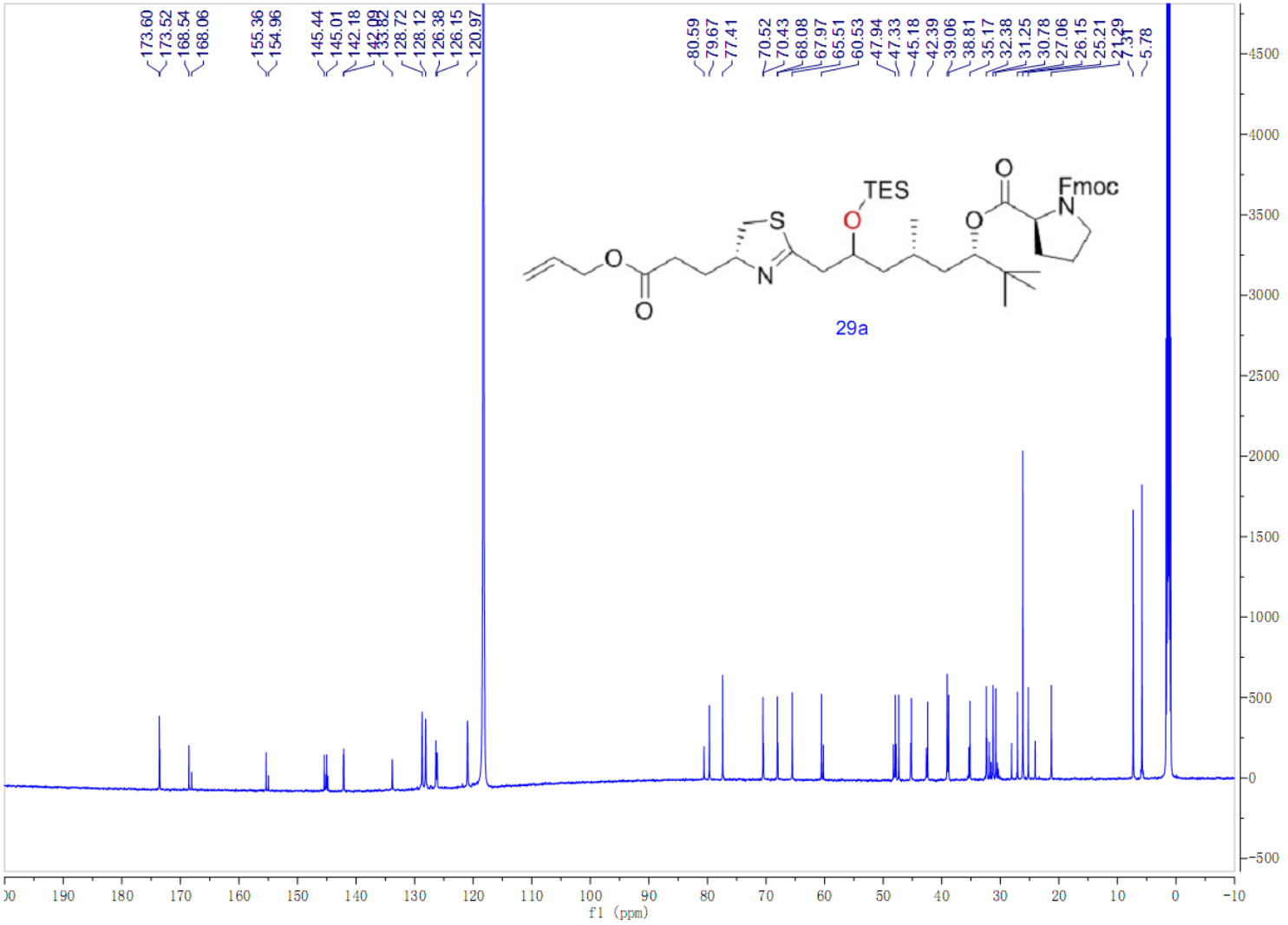
1.02
6.52
f1 (ppm)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80.59
79.67
77.41
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70.43
68.08
67.97
65.51
60.53
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47.33
45.18
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39.06
38.81
35.17
32.38
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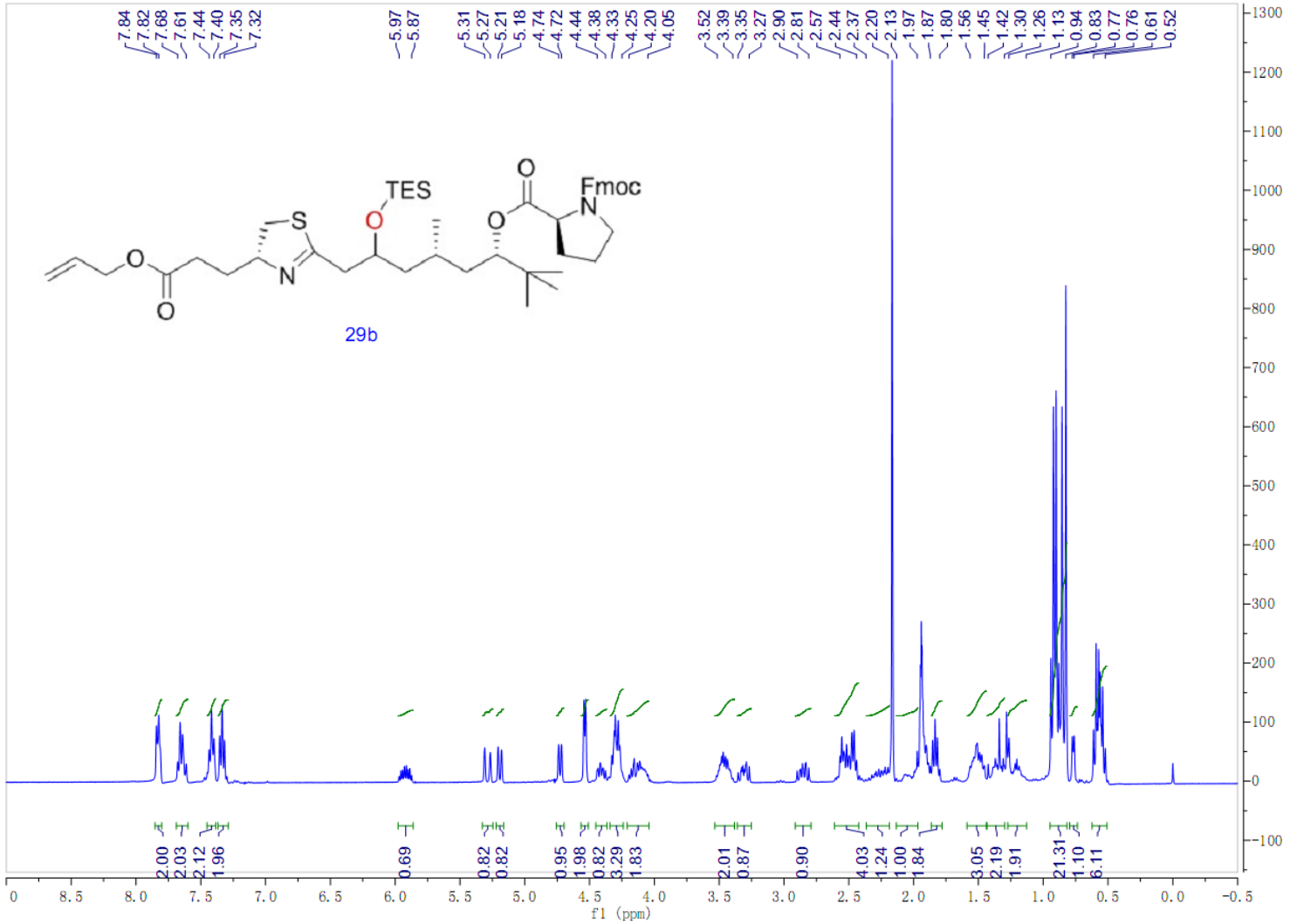
27.06
26.15
25.21
21.29
7.31
5.78
TES
Fmoc
29a
f1 (ppm)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5.18
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4.44
4.38
4.33
4.25
4.20
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3.52
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3.27
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1.45
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1.26
1.13
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0.83
0.77
0.76
0.61
0.52
TES
Fmoc
O
S
N
O
O
O
O
O
N
29b
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2.03
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0.95
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2.19
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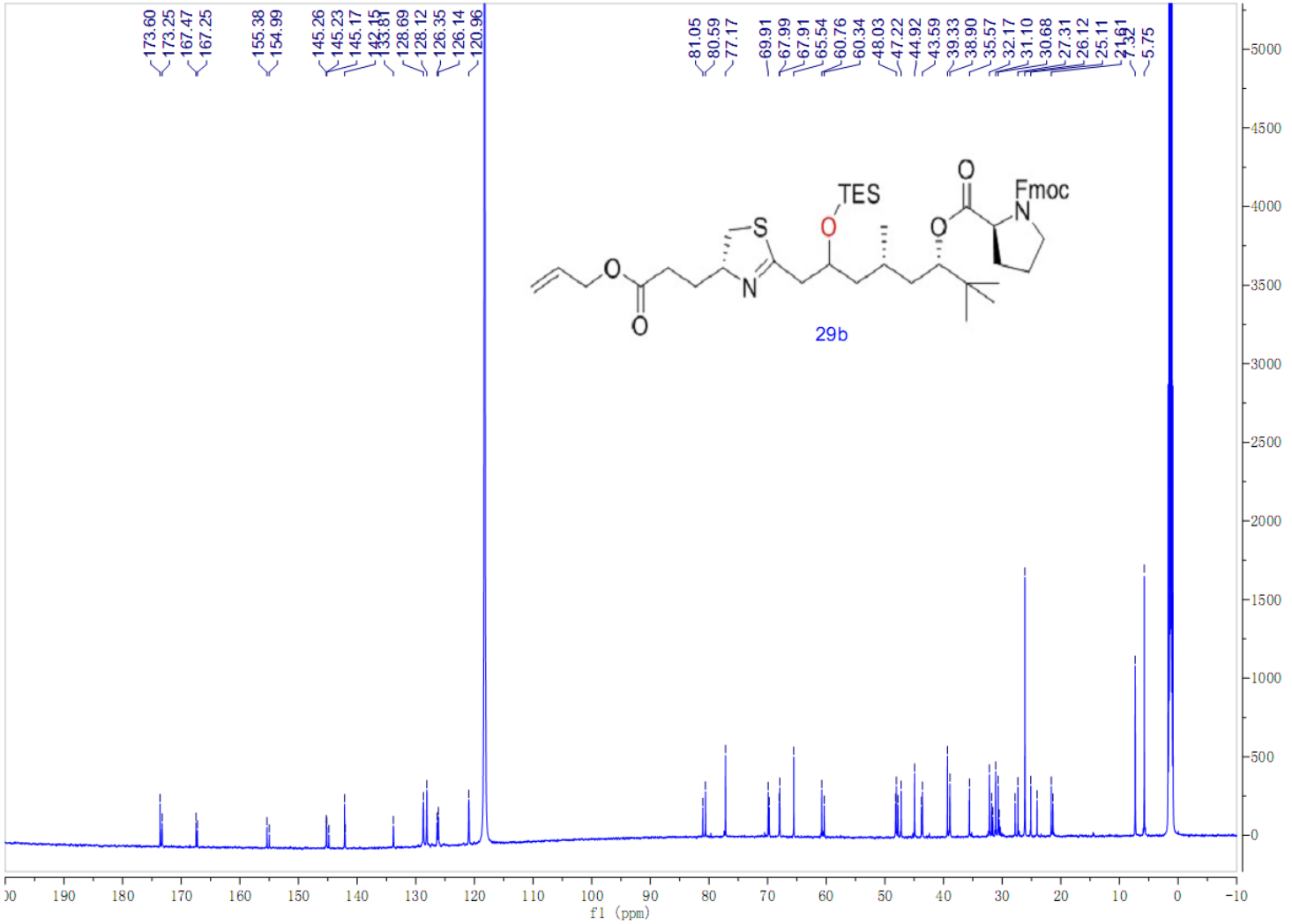
21.31
1.10
6.11
f1 (ppm)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80.59
77.17
69.91
67.99
67.91
65.54
60.76
60.34
48.03
47.22
44.92
43.59
39.33
38.90
35.57
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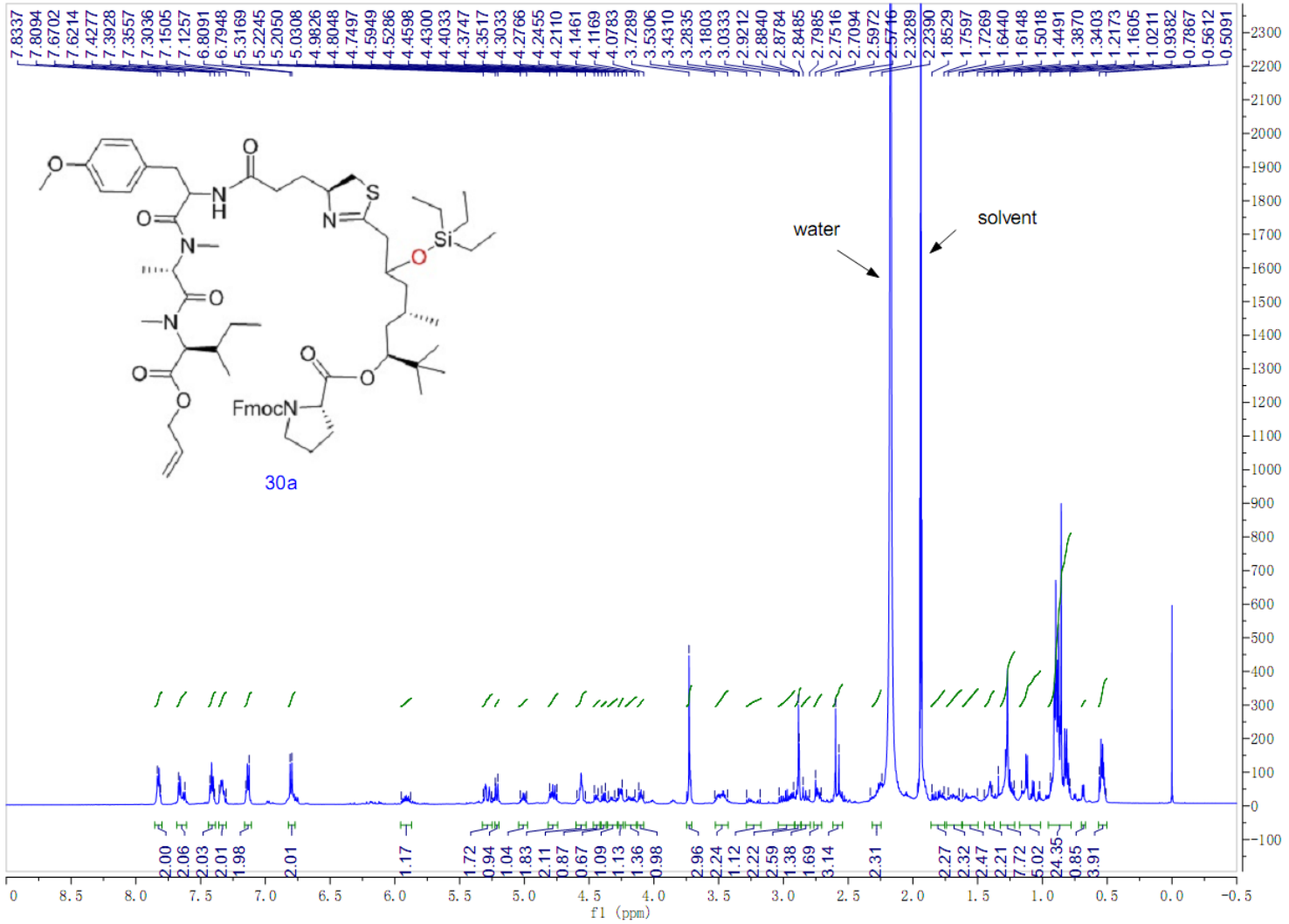
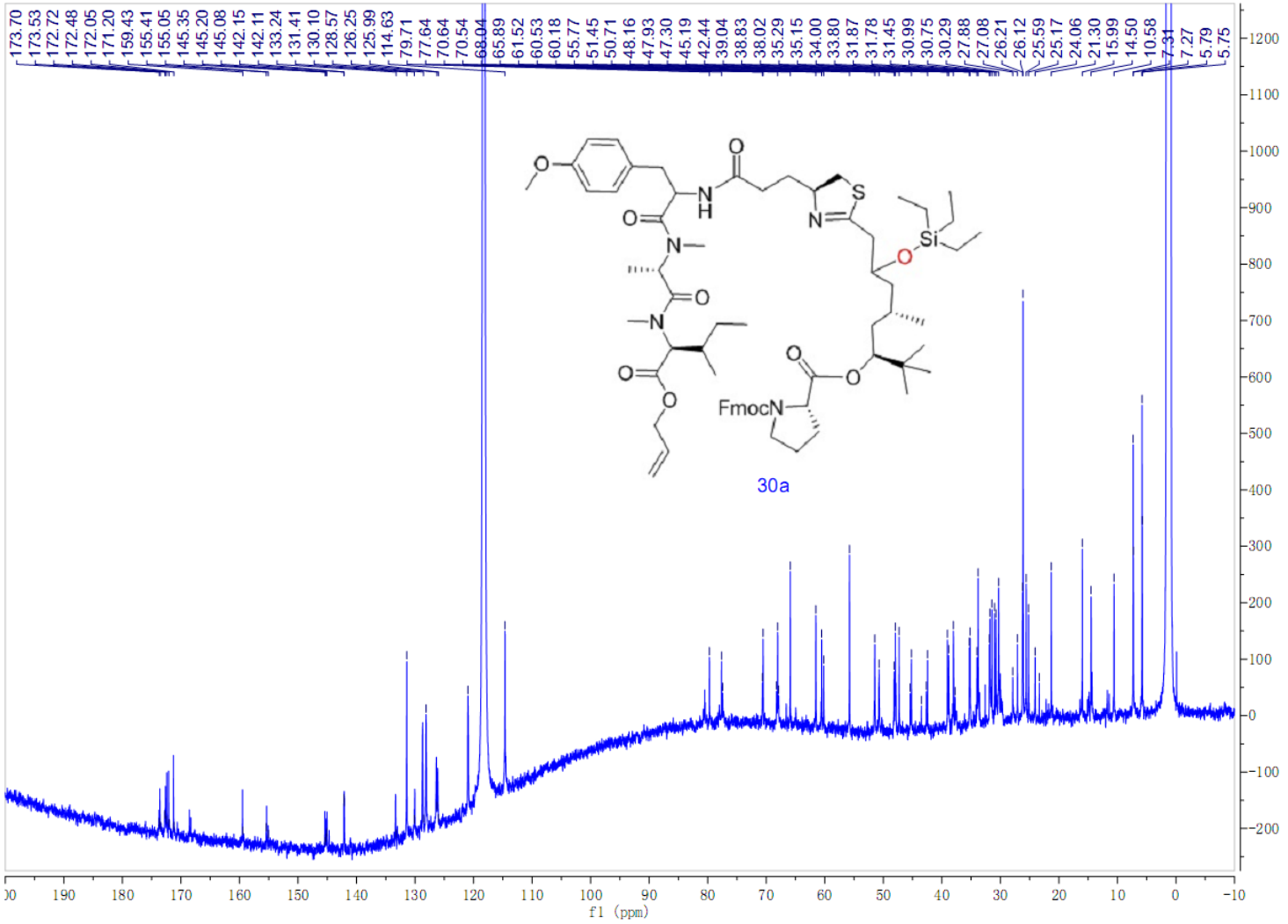
30.68
27.31
26.12
25.11
5.75
TES
Fmoc
29b
f1 (ppm)


water
solvent
FmocN
30a
f1 (ppm)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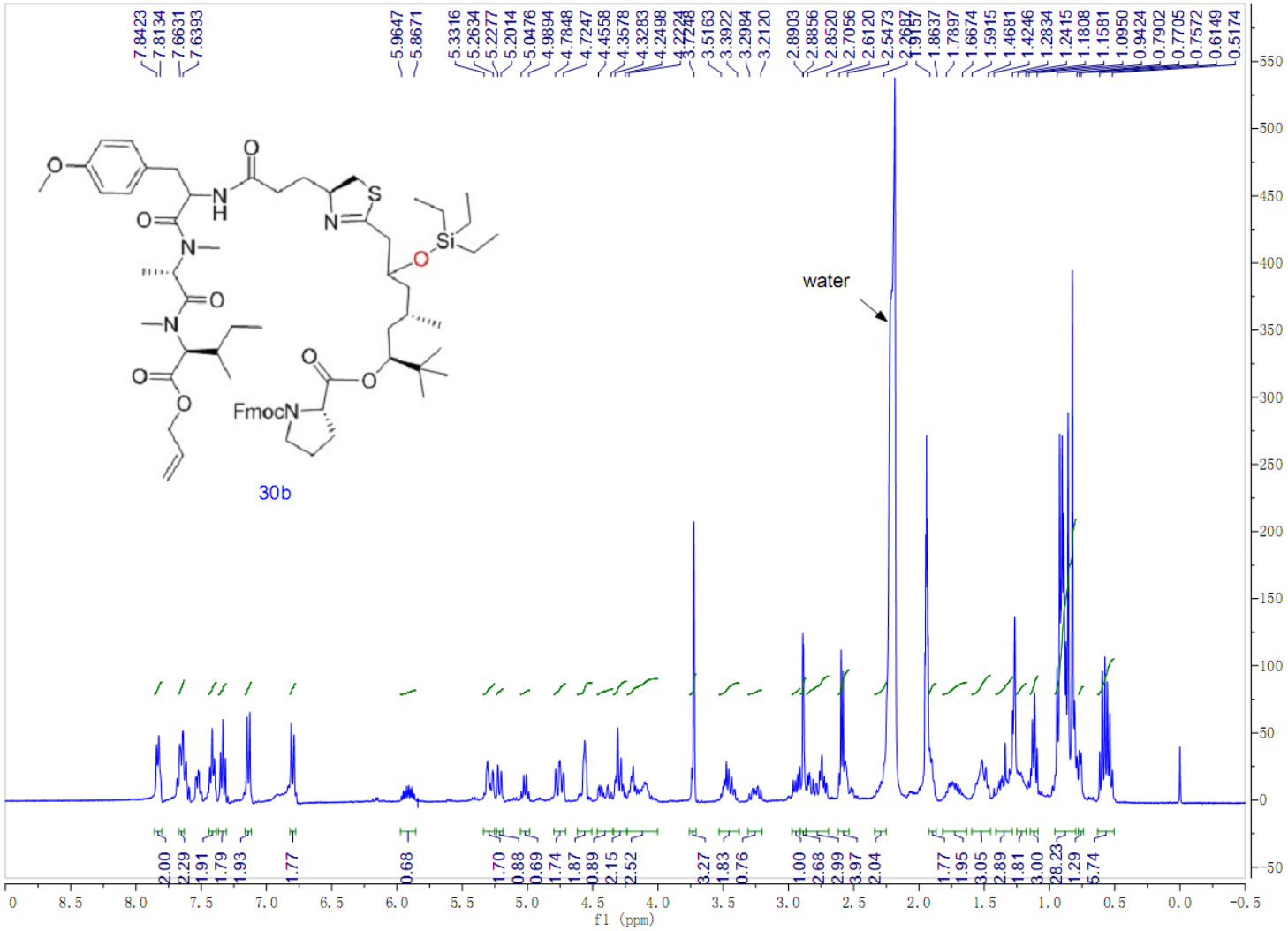
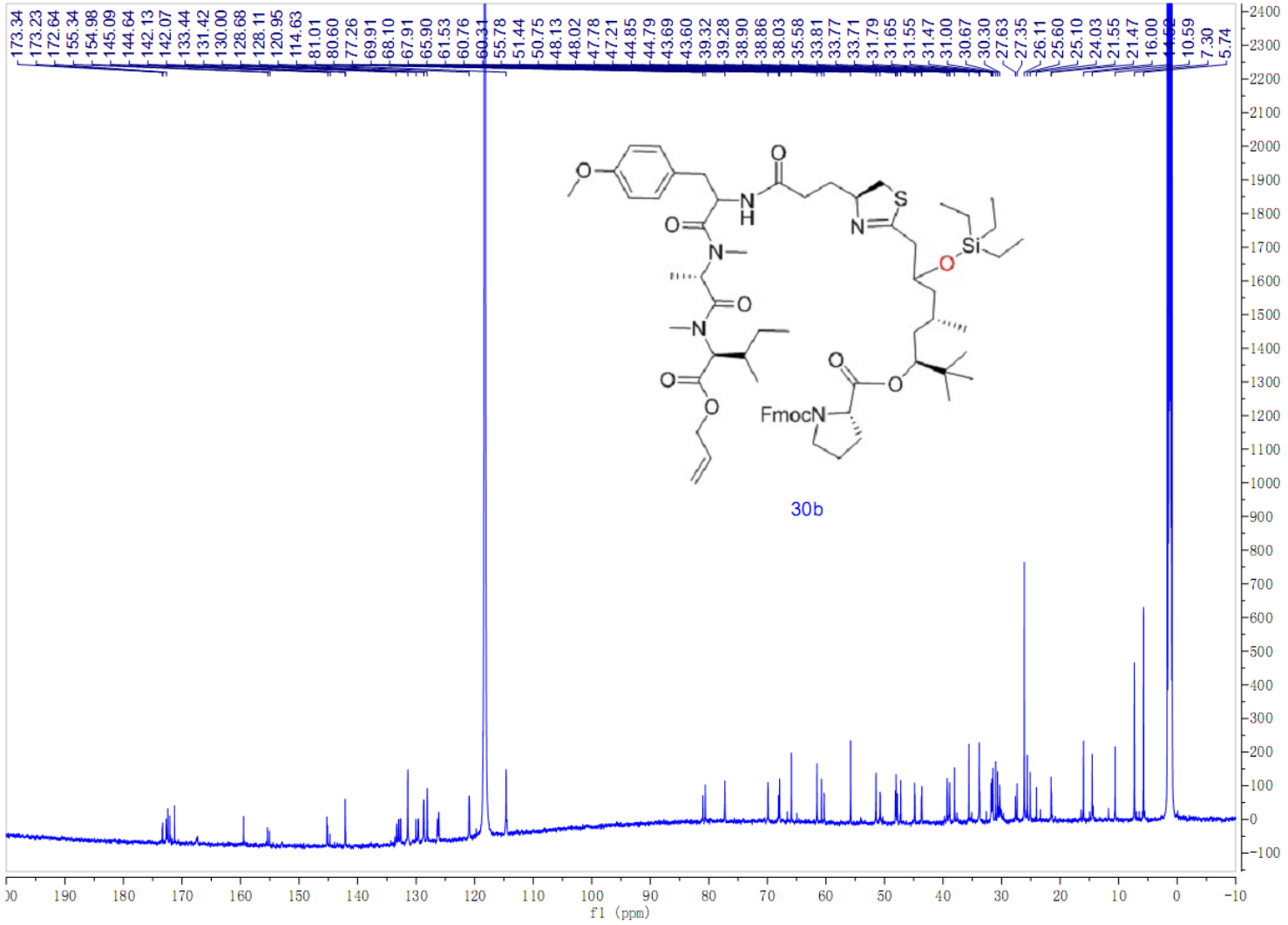
173.53
172.72
172.48
172.05
171.20
159.43
155.41
155.05
145.35
145.20
145.08
142.15
142.11
133.24
131.41
130.10
128.57
126.25
125.99
114.63
79.71
77.64
70.64
70.54
68.04
65.89
61.52
60.53
60.18
55.77
51.45
50.71
48.16
47.93
47.30
45.19
42.44
39.04
38.83
38.02
35.29
35.15
34.00
33.80
31.87
31.78
31.45
30.99
30.75
30.29
27.88
27.08
26.21
26.12
25.59
25.17
24.06
21.30
15.99
14.50
10.58
7.31
7.27
5.79
5.75
FmocN
30a
f1 (ppm)


water
30b
FmocN
f1 (ppm)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173.23
172.64
155.34
154.98
145.09
144.64
142.13
142.07
133.44
131.42
130.00
128.68
128.11
120.95
114.63
81.01
80.60
77.26
69.91
68.10
67.91
65.90
61.53
60.76
60.31
55.78
51.44
50.75
48.13
48.02
47.78
47.21
44.85
44.79
43.69
43.60
39.32
39.28
38.90
38.86
38.03
35.58
33.81
33.77
33.71
31.79
31.65
31.55
31.47
31.00
30.67
30.30
27.63
27.35
26.11
25.60
25.10
24.03
21.55
21.47
16.00
14.59
10.59
7.30
5.74
FmocN
30b
f1 (ppm)