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Electronic Supplementary Information

Concise total synthesis of opioids

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Table of Contents

I. Summary of the Syntheses of Morphine Alkaloids

Table S1 Summary of the syntheses of morphine alkaloids

Principle author	Year	Target	Steps	Overall yield	Publication
Gates	1952	(−)-Morphine	31	0.06%	*J. Am. Chem. Soc*. **1952**, *74*, 1109; *J. Am. Chem. Soc*. **1956**, *78*, 1380.
Ginsberg	1954	*rac*-Dihydrothebainone	21	8.9%	*J. Chem. Soc.* **1954**, 3052.
Grewe	1967	*rac*-Dihydrothebainone	9	0.81%	*Chem. Ber. Recl.* **1967**, *100*, 1550; *Chem. Ber. Recl.* **1967**, *100*, 1.
Rice	1980	*rac*-Dihydrocodeinone	14	29.7%	*J. Org. Chem.* **1980**, *45*, 3135.
Evans	1982	*rac*-*O*-Me-thebainone A	12	16.7%	*Tetrahedron Lett.* **1982**, *23*, 285.
White	1983	(−)-Codeine	8	1.8%	*Tetrahedron* **1983**, *39*, 2393.
Rapoport	1983	*rac*-Codeine	26	1.2%	*J. Org. Chem.* **1983**, *48*, 227.
Fuchs	1987	*rac*-Codeine	23	1.3%	*J. Org. Chem.* **1987**, *52*, 473.
Tius	1992	*rac*-Thebainone-A	24	1.1%	*J. Am. Chem. Soc.* **1992**, *114*, 5959.
Parker	1992	*rac-Dihydrocodeineone*	11	1.1%	*J. Am. Chem. Soc.* **1992***, 114,* 9688; *J. Org. Chem.* **2006***, 71,* 449.
Overman	1993	(−) and (+)-Dihydrocodeinone	14	1.9%	*J. Am. Chem. Soc.* **1993**, *115*, 11028.
Mulzer	1998	(−)-Dihydrocodeinone	15	9.1%	*J. Org. Chem.* **1998**, *63*, 5908.
White	1999	*ent*-Morphine	28	3.0%	*J. Org. Chem.* **1999**, *64*, 7871.
Cheng	2000	*rac*-Desoxycodeine-D	15	13.26%	*Tetrahedron Lett.* **2000**, *41*, 915.

Principle author	**Year**	**Target**	**Steps**	**Overall yield**	**Publication**
Ogasawara	2000	*rac*-3,4-Dimethoxy-6-morphinanone	29	0.25%	*Org. Lett.* **2000**, *2*, 2785.
Ogasawara	2001	(−)-Dihydrocodeinone ethylene ketal	21	1.5%	*Chem. Commun.* **2001**, 1094.
Taber	2002	(−)-Morphine	27	0.51%	*J. Am. Chem. Soc.* **2002**, *124*, 12416.
Trost	2002	(−)-Codeine	15	6.8%	*J. Am. Chem. Soc.* **2002**,*124,* 14542; *J. Am. Chem. Soc.* **2005,** *127*, 14785.
Fukuyama	2006	*rac*-Morphine	25	6.7%	*Org. Lett.* **2006**, *8*, 5311.
Hudlicky	2007	*ent*-Codeine	15	0.23%	*Synlett* **2007**, 2859.
Iorga/Guillou	2008	*rac*-Codeine	17	0.64%	*Chem. Eur. J.* **2008**, *14*, 6606.
Chida	2008	*rac*-Dihydroisocodeine	24	3.8%	*Tetrahedron. Lett.* **2008**, *49*, 358.
Hudlicky	2009	(+)- and (−)-codeine	18	0.19%	*Tetrahedron* **2009**, *65*, 9862.
Magnus	2009	*rac*-Codeine	13	20.1%	*J. Am. Chem. Soc.* **2009**, *131*, 16045.
Stork	2009	*rac*-Codeine	22	2.0%	*J. Am. Chem. Soc.* **2009**, *131*, 11402.
Fukuyama	2010	(−)-Morphine	18	4.8%	*Chem. Asian. J.* **2010**, *5*, 2192.
Metz	2011	*rac*-Codeine	20	2.8%	*Angew. Chem., Int. Ed.* **2011**, *50*, 3892.
Fukuyama	2014	(−)-Oxycodone	21	2.4%	*Org. Lett.* **2014**, *16*, 6244.
Hudlicky	2014	*ent*-Hydromorphone	12	4.8%	*Angew. Chem., Int. Ed.* **2014**, *53*, 4355.
Opatz	2014	(−)-Thebaine	18	18%	*Org. Lett.* **2014**, *16*, 5282.
Zhang	2015	*rac*-Codeine	14	3.6%	*Chem. Eur. J.* **2015**, *21*, 16379.
Smith	2016	*rac*-Morphine	10	6.6%	*Angew. Chem., Int. Ed.* **2016**, *55*, 14306.
Opatz	2018	(−)-Thebaine	21	2.4%	*Angew. Chem., Int. Ed.* **2018***, 57,* 11055.

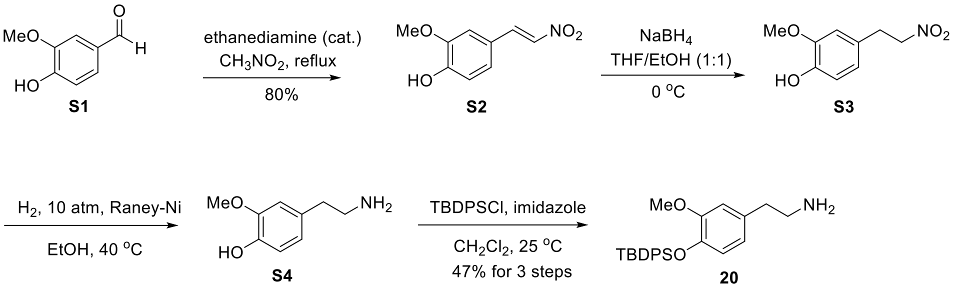
Principle author	**Year**	**Target**	**Steps**	**Overall yield**	**Publication**
Chen	2018	*rac*-Oxycodone	13	0.9%	*Chem. Commun.* **2018**, *54,* 13018.
Tu	2019	(−)-Codeine	15	1.6%	*Nat. Commun.* **2019**, *10,* 2507.
Optaz	2019	(−)-Oxycodone	18	3.4%	*Org. Lett.* **2019**, *21,* 1828.
Hudlicky	2019	(+)-Oxycodone	18	1.8%	*J. Am. Chem. Soc.* **2019**, *141,* 10883.
Ellman	2019	(−)-Naltrexone	17	1.7%	*Chem. Sci.* **2019**, *10,* 535.
Metz	2020	*rac*-Thebainone A	22	2.6%	*Org. Lett.* **2020**, *22,* 3145.
Dong	2021	(−)-Thebainone A	13	4.7%	*Angew. Chem., Int. Ed.* **2021**, *60,* 13057.
Qin/Zhong	2021	(−)-Codeine	15	13%	*CCS Chem.* **2021**, *3,* 1376.
		(−)-Oxycodone	17	11%	
		(−)-Naloxone	21	5.9%	
Qin/Zhong (**This work**)	2022	(−)-Codeine	12	34%	
		(−)-Oxycodone	14	20%	
		(−)-Naloxone	15	16%	

II. Experimental Procedures

1. General information

All reactions that require anhydrous conditions were performed in flame-dried glassware under argon atmosphere and all reagents were purchased from commercial suppliers without further purification. Solvent purification was conducted according to Purification of Laboratory Chemicals 8th edn (Armarego, W. L. F., Elsevier: Oxford, 2017). Reactions were monitored by thin layer chromatography (TLC, 0.2 mm, HSGF254) supplied by Yantai Chemicals (China). Visualization was accomplished with UV light, exposure to iodine, stained with ethanolic solution of phosphomolybdic acid or basic solution of $KMnO_4$. The products were purified by flash column chromatography on silica gel (200 – 300 meshes) from Anhui Liangchen Silicon Material Company (China). ^1H NMR and ^{13}C NMR spectra were recorded on Varian INOVA-400/54, Agilent DD2-600/54 and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, td = triple doublet, dt = double triplet, dd = double doublet, ddd = double double doublet, m = multiplet, and coupling constants (J) were reported in Hertz (Hz). Photochemical reactions were conducted using a Kessil H150-BLUE LED purchased from Amazon. Melting points (m.p.) were obtained with digital micro melting point apparatus (Beijing Focus Instrument Co., Ltd.). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent LC-MSD TOF ESI mass spectrometers. Optical rotation was obtained from Rudolph Research Analytical Autopol VI automatic polarimeter. LC-MS analyses were performed on HP Agilent 6420 Triple Quad LC/MS. Chiral HPLC analyses were performed on HP Agilent 1260 apparatus. Manipulations of all the controlled substances according to *Narcotics and Psychotropic Drugs Regulations* in China were conducted in an authorized laboratory at National Engineering Research Center for the Emergence Drugs, Beijing Institute of Pharmacology and Toxicology. Therefore, although the whole synthetic route is readily scalable, all compounds possessing the morphinan core were prepared in small scales due to the *Narcotics and Psychotropic Drugs Regulations* in China.

2. Synthesis of compound 20



(1) Synthesis of compound S2

The known compound ***S2*** *was prepared according to the literature method.*[1] To a solution of compound **S1** (220.0 g, 1.446 mol, 1.0 equiv.) in CH_3NO_2 (800 mL) was added ethanediamine (1.1 mL) with stirring. The resulting solution was refluxed for 2 hours. Upon cooling to room temperature, the precipitate was collected by filtration, washed with MeOH/H_2O mixture (1:1, 200 mL × 3), EtOH (200 mL × 2) and dried under vacuum to give compound **S2** as a yellow crystalline solid (225.8 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 13.2 Hz, 1H), 7.52 (d, J = 13.2 Hz, 1H), 7.14 (dd, J = 8.0, 2.0 Hz, 1H), 7.03 – 6.95 (m, 2H), 6.04 (s, 1H), 3.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.0, 139.5, 135.0, 124.9, 122.4, 115.3, 110.1, 56.1.

IR (neat): ν_{max} = 3470, 3116, 1603, 1485, 1475, 1291, 1212, 1020, 816.

(2) Synthesis of compound 20

To a mixed solution of compound **S2** (40.0 g, 0.205 mol, 1.0 equiv.) in THF/EtOH (1:1 v/v, 480 mL) at 0 °C was added $NaBH_4$ (15.5 g, 0.410 mol, 2.0 equiv.) in small portions with vigorously stirring. After the reaction was complete as monitored by TLC, it was quenched with AcOH/H_2O (1:4 v/v, 250 mL), and the resulting mixture was subjected to evaporation under reduced pressure to remove the solvent. The residue was extracted with EtOAc (300 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was filtered through a short pad of silica gel (eluted with petroleum ether/ethyl acetate = 3:1, v/v), and concentrated *in vacuo* to afford the crude compound **S3** as a yellow oil, which was directly used in the next step without further purification.

A mixture of the above crude compound **S3** and Raney-Ni (wet, ca. 4.0 g) in EtOH (400 mL) was stirred under 10 atm of H_2 at 40 °C until the reaction was complete as monitored by TLC. Then the mixture was diluted with MeOH (300 mL) and heated to 70 °C. After the precipitate was dissolved, the mixture was filtered through a pad of Celite immediately. The filtrate was concentrated *in vacuo* to a total batch volume of 100 mL, at which point a large amount of solid was precipitated. After cooling to room temperature, the precipitate was collected by filtration and dried under vacuum to give the crude compound **S4** as a pale brown solid, which was directly used in the next step without further purification.

The above crude compound **S4** and imidazole (15.4 g, 0.226 mol, 1.1 equiv.) were dissolved in anhydrous CH_2Cl_2 (200 mL). After being stirred at 25 °C for 10 minutes, TBDPSCl (35.4 mL, 0.136 mol, 0.66 equiv.) was added. The reaction was stirred for 5 hours before being quenched with saturated NH_4Cl solution (200 mL). The resulting mixture was filtered through a short pad of Celite, and the layers of the filtrate were separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with brine (100 mL × 1), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH = 20:1, v/v, containing 0.5% ammonia) to afford compound **20** as a light brown oil (39.0 g, 47% for three steps).

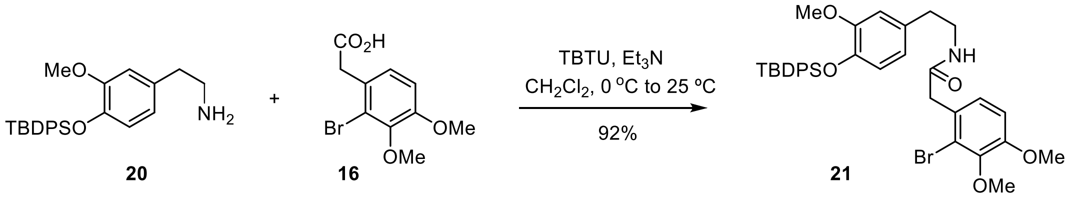
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.66 (m, 4H), 7.43 – 7.30 (m, 6H), 6.64 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 8.0, 2.0 Hz, 1H), 3.56 (s, 3H), 2.88 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 6.8 Hz, 2H), 1.11 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 143.4, 135.4, 133.7, 133.0, 129.5, 127.4, 120.7, 120.0, 113.0, 55.4, 43.6, 39.7, 26.7, 19.7.

IR (neat): ν_{max} = 3053, 2933, 2858, 1587, 1513, 1264.

HRMS (m/z): $[M + H]^+$ calculated for $C_{25}H_{32}NO_2Si^+$, 406.2197; found, 406.2190.

3. Synthesis of compound 21



Under argon, to a flame-dried flask was added acid **16** (40.0 g, 0.145 mol, 1.0 equiv.), amine **20** (64.9 g, 0.160 mol, 1.1 equiv.), TBTU (55.9 g, 0.174 mol, 1.2 equiv.) and anhydrous CH_2Cl_2 (400 mL). The resulting mixture was cooled to 0 °C, to which Et_3N (50.5 mL, 0.363 mol, 2.5

equiv.) was added. Then the reaction was warmed to 25 °C and stirred overnight before it was quenched by the addition of saturated NH_4Cl solution (400 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (500 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (400 mL) and washed sequentially with 0.1 M HCl (150 mL × 2), saturated $NaHCO_3$ solution (500 mL × 2), water (200 mL × 1) and brine (200 mL × 1). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/acetone = 4:1, v/v) to afford compound **21** as a white foam (88.4 g, 92%).

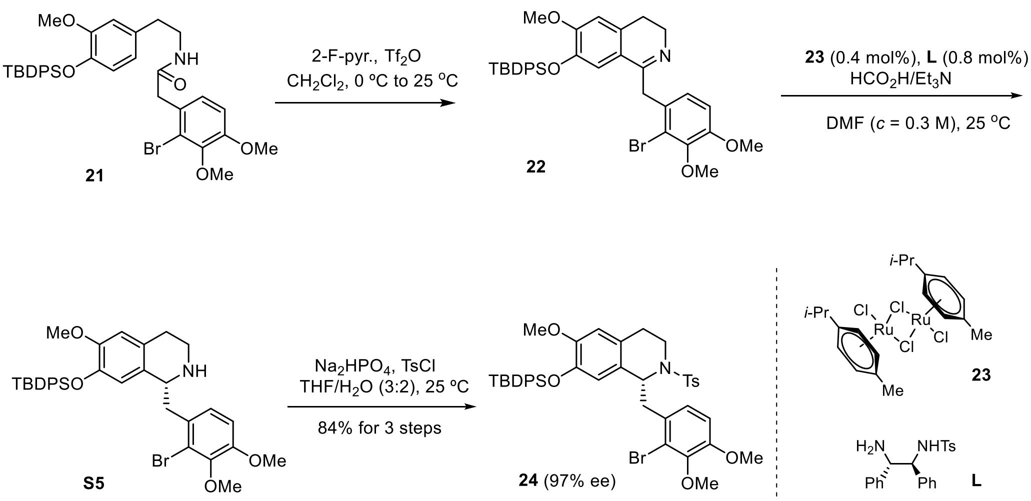
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.68 (m, 4H), 7.41 – 7.32 (m, 6H) , 6.92 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 2.0 Hz, 1H), 6.31 (dd, J = 8.0, 2.0 Hz, 1H), 5.38 (t, J = 5.6 Hz, 1H), 3.821 (s, 3H, overlapped), 3.817 (s, 3H, overlapped), 3.59 (s, 2H), 3.51 (s, 3H), 3.39 (q, J = 6.0 Hz, 2H), 2.60 (t, J = 7.2 Hz, 2H), 1.10 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.8, 152.8, 150.5, 146.8, 143.6, 135.3, 133.6, 131.8, 129.6, 127.6, 127.4, 126.3, 120.7, 120.5, 120.0, 112.7, 111.5, 60.4, 56.0, 55.3, 43.6, 40.7, 35.1, 26.6, 19.7.

IR (neat): 3311, 3052, 2934, 2858, 1663, 1512, 1486, 1265, 1034, 733, 701.

HRMS (m/z): $[M + H]^+$ calculated for $C_{35}H_{41}{}^{79}BrNO_5Si^+$, 662.1932; found, 662.1930; $C_{35}H_{41}{}^{81}BrNO_5Si^+$, 664.1911; found, 664.1922.

4. Synthesis of compound 24



Under argon, to a solution of compound **21** (30.0 g, 45.27 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (300 mL) was sequentially added 2-fluoropyridine (7.8 mL, 90.54 mmol, 2.0 equiv.) and Tf_2O (9.4 mL, 54.32 mmol, 1.2 equiv.) at 0 ºC. The reaction was then stirred at 25 ºC. After the starting material **21** was completely consumed, the reaction was cooled to 0 ºC and quenched with saturated NH_4Cl solution (300 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (300 mL × 3). The combined organic layers were washed with brine (150 mL × 1), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude compound **22** was used in the next reaction without purification.

Under argon, the above crude **22** was dissolved in anhydrous degassed DMF (140 mL) and stirred at 25 ºC. To another flame-dried round-bottom flask equipped with a stir bar was added catalyst **23** (111 mg, 0.181 mmol, 0.004 equiv.) and ligand **L** (133 mg, 0.362 mmol, 0.008 equiv.). The flask was evacuated and backfilled with argon three times followed by the addition of anhydrous degassed DMF (10 mL). After stirring at 25 ºC for 30 minutes, the mixture was added to the above-mentioned solution of **22** in DMF via syringe. The resulting mixture was stirred at 25 ºC for 10 min and cooled to 0 ºC, whereupon $HCOOH/Et_3N$ (5:2 complex) (14.2 mL, 99.6 mmol, 2.2 equiv.) was added. After being stirred at 25 ºC for 17 h, TLC analysis indicated that the reaction was complete. Then the mixture was cooled to 0 ºC and saturated $NaHCO_3$ solution was added to adjust pH = 9. The layers were separated, and the aqueous layer was extracted with EtOAc (300 mL × 3). The combined organic layers were washed with water (300 mL × 1), brine (300 mL × 1), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude compound **S5**, which was used directly in the next reaction without purification.

To a solution of the above crude compound **S5** in THF/H_2O (300 mL, v/v = 3:2), disodium phosphate dodecahydrate (48.64 g, 135.8 mmol, 3.0 equiv.) and tosyl chloride (8.630 g, 45.27 mmol, 1.0 equiv.) was sequentially added at 25 ºC. After being stirred at the same temperature for 1 h, the mixture was extracted with EtOAc (200 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether/acetone = 7:1, v/v) to afford compound **24** as a white foam (30.5 g, 84% for three steps, 97% ee).

Optical rotation: $[\alpha]_D^{25} = -117.9$ ($c = 0.8$, $CHCl_3$).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.74 – 7.71 (m, 4H), 7.47 – 7.29 (m, 8H), 6.96 (d, J = 8.0 Hz, 2H), 6.72 – 6.68 (m, 2H), 6.51 (s, 1H), 6.33 (s, 1H), 4.90 (q, J = 4.8 Hz, 1H), 3.89 – 3.86 (m, 1H, overlapped), 3.84 (s, 3H), 3.82 (s, 3H), 3.58 (s, 3H), 3.50 – 3.42 (m, 1H), 2.83 – 2.73 (m, 2H), 2.57 – 2.48 (m, 1H), 2.42 – 2.37 (m, 1H), 2.31 (s, 3H), 1.13 (s, 9H).

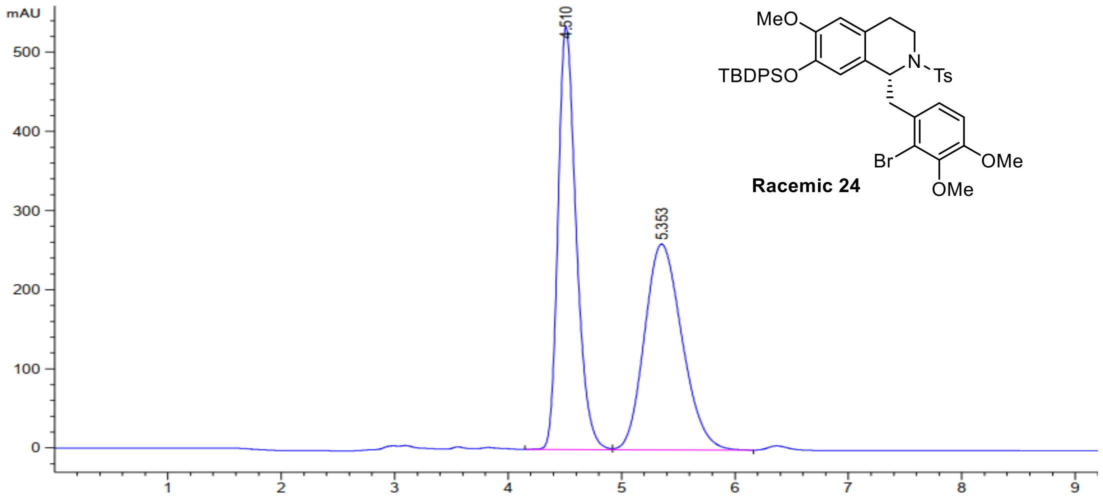
^{13}C NMR (100 MHz, CDCl$_3$): δ 152.2, 149.5, 143.3, 142.6, 137.6, 135.5, 135.4, 133.4, 133.3, 130.0, 129.74, 129.71, 129.0, 127.7, 127.6, 126.8, 126.5, 125.6, 118.5, 112.2, 110.6, 60.4, 55.8, 55.53, 55.46, 42.6, 38.6, 26.7, 26.2, 21.4, 19.7.

IR (neat): 2933, 1513, 1487, 1448, 1261, 1155, 1113, 1033, 701.

HRMS (m/z): $[M + H]^+$ calculated for $C_{42}H_{47}{}^{79}BrNO_6SSi^+$, 800.2071; found, 800.2066; $C_{26}H_{37}{}^{81}BrNO_6Si^+$, 802.2051; found, 802.2050.

HPLC for measuring ee value of compound 24

Racemic 24



Run information:

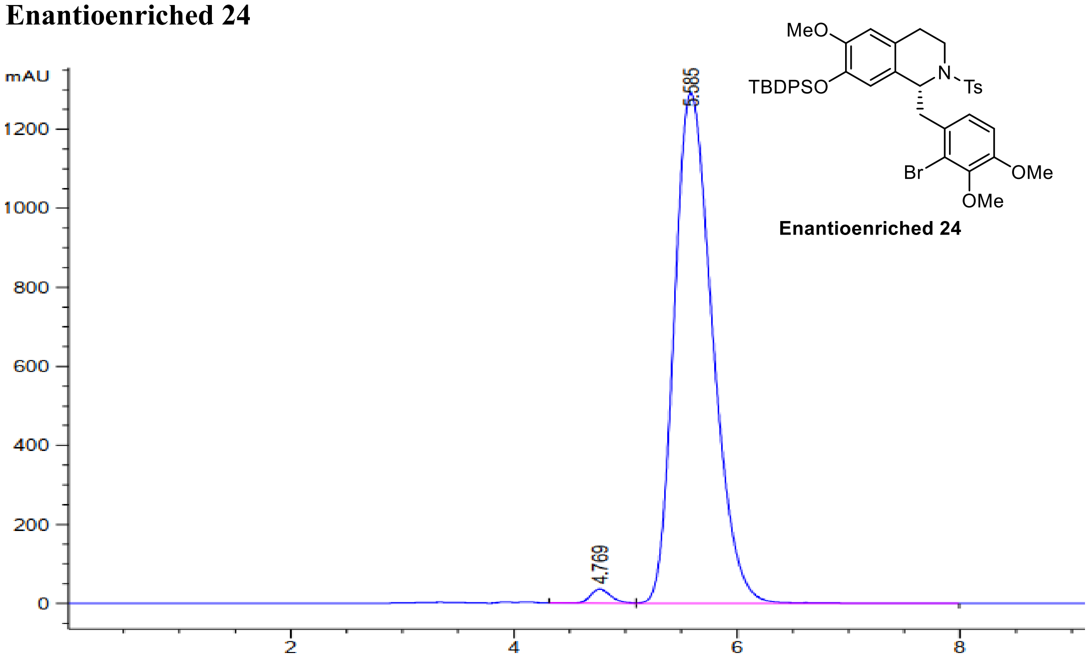
Column: DAICEL CHIRALCEL AD-H, 4.6 × 250 mm, 5 μm;

Solvent: Hexane: *i*-PrOH = 70:30, flow: 1.0 mL/min, 25 ºC.

Peak information (wavelength: 254 nm): $t_{\text{isomer-1}}$ = 4.510 min，$t_{\text{isomer-2}}$ = 5.353 min.

Peak(#)	*t* (min)	Width (min)	Area (mAU*s)	Height (mAU)	Ratio (%)
1	4.510	0.1702	5963.0181	534.2270	49.9126
2	5.353	0.3584	5983.9116	260.1107	50.0874

Enantioenriched 24



Run information:

Column: DAICEL CHIRALCEL AD-H, 4.6 × 250 mm, 5 μm;

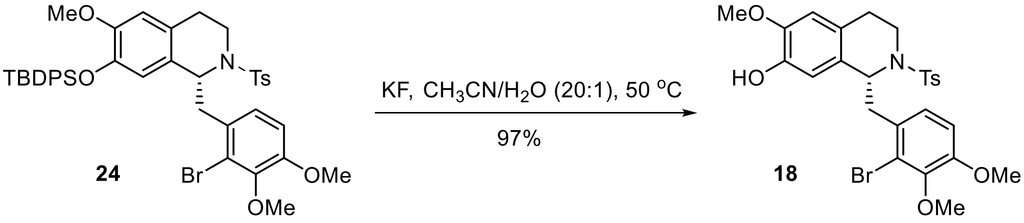
Solvent: Hexane: *i*-PrOH = 70:30, flow: 1.0 mL/min, 25 ºC.

Peak information (wavelength: 254 nm): t_{major} = 5.585 min， t_{minor} = 4.769 min.

Peak(#)	*t* (min)	Width (min)	Area (mAU*s)	Height (mAU)	Ratio (%)
1	4.769	0.1945	452.2409	35.7803	1.4510
2	5.585	0.3694	3.0715e4	1291.5951	98.5490

The ee value was determined as 97%.

5. Synthesis of compound 18



To a solution of compound **24** (30.00 g, 37.46 mmol, 1.0 equiv.) in CH_3CN/H_2O (630 mL, v/v =20:1) was added KF (4.353 g, 74.92 mmol, 2.0 equiv.) at 25 ºC. The reaction was then heated to 50 ºC and stirred for 3 hours. Then the mixture was evaporated under reduced pressure to remove CH_3CN. The residue was diluted with water and extracted with CH_2Cl_2 (500 mL ×

3). The combined organic layers were washed with brine (200 mL × 2), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by silica gel flash chromatography (petroleum ether/acetone = 4:1, v/v) gave compound **18** as a white foam (20.4 g, 97%).

Optical rotation: $[\alpha]_D^{25} = –96.9$ (c = 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 4.8 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.45 (s, 1H), 5.48 (s, 1H), 5.13 – 5.10 (m, 1H), 3.94 – 3.87 (m, 1H), 3.86 (s, 3H), 3.82 (s, 6H), 3.61 – 3.54 (m, 1H), 3.16 (dd, J = 14.0, 4.8 Hz, 1H), 3.04 (dd, J = 14.0, 10.0 Hz, 1H), 2.79 – 2.70 (m, 1H), 2.57 – 2.51 (m, 1H), 2.32 (s, 3H).

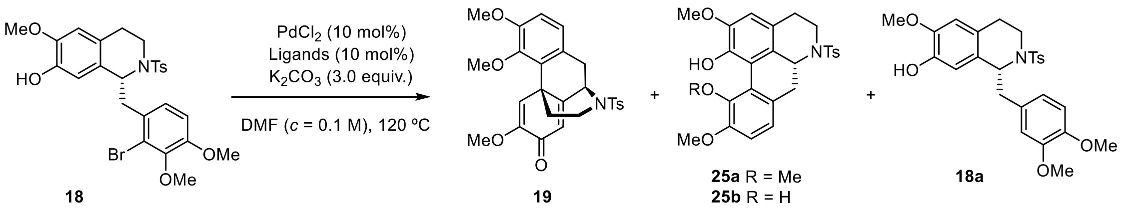
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 146.3, 145.6, 143.8, 142.8, 137.2, 130.0, 129.1, 128.6, 127.0, 126.5, 124.6, 120.8, 112.7, 110.8, 110.6, 60.4, 55.90, 55.85, 55.80, 42.8, 39.0, 26.7, 21.4.

IR (neat): 3428, 1512, 1487, 1449, 1265, 1149, 1031.

HRMS (m/z): $[M + H]^+$ calculated for $C_{26}H_{29}{}^{79}BrNO_6S^+$, 562.0893; found, 562.0893; $C_{33}H_{35}{}^{81}BrNO_7S^+$, 564.0873; found, 564.0873.

6. Optimization of the dearomatization arene coupling reaction

Table S2 Screening of the ligands[a]

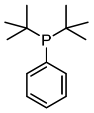


Entry	Ligand	Reaction Time	Conv.	Yield of 19	Yield of 25a, 25b	Yield of 18a
1	**L1**	3 h	57%	32%	7%, 9%	trace
2	**L2**	3 h	42%	14%	8%, 11%	trace
3	**L3**	3 h	62%	8%	22%, 24%	trace
4	**L4**	3 h	100%	48%	13%, 17%	16%
5	**L5**	3 h	54%	10%	7%, 11%	12%

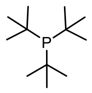
6	**L6**	3 h	40%	7%	trace, 8%	trace
7	**L7**	3 h	36%	8%	6%, 11%	trace
8	**L8**	3 h	45%	11%	12%, 16%	trace
9	**L9**	3 h	100%	57%	12%, 21%	trace
10	**L14**	3 h	87%	trace	36%, 43%	trace
11	**L15**	3 h	12%	trace	trace, trace	trace
12	**L16**	3 h	55%	trace	18%, 22%	11%
13	**L17**	3 h	45%	trace	6%, 8%	trace
14	**L18**	3 h	37%	trace	trace, 12%	trace
15	**L19**	3 h	< 10%	trace	trace, trace	trace
16	**L20**	3 h	< 10%	trace	trace, trace	trace
17	**L21**	3 h	< 10%	trace	trace, trace	trace
18	**L22**	3 h	< 10%	trace	trace, trace	trace
19	**L23**	3 h	< 10%	trace	trace, trace	trace
20	**L24**	3 h	< 10%	trace	trace, trace	trace

[a]Reactions were conducted on 0.2 mmol scale unless otherwise stated. Yields were determined according to the isolated material.

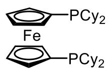
Ligands used in Table S2



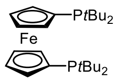
L1



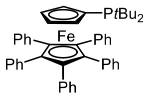
L2



L3



L4



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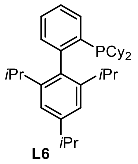
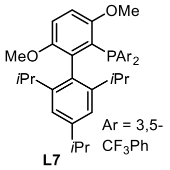
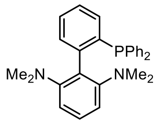


L6



L7



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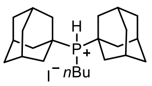

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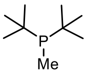

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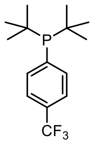

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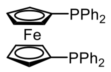

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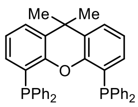
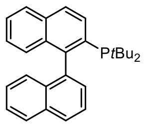
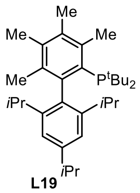


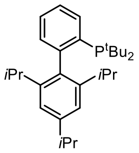
L17



L18



L19



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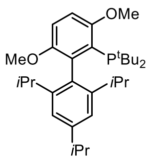

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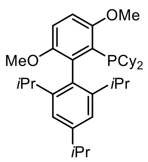

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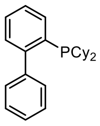
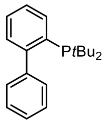
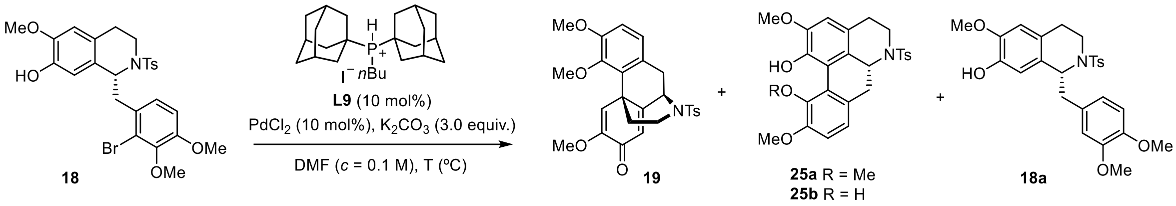


L23



L24

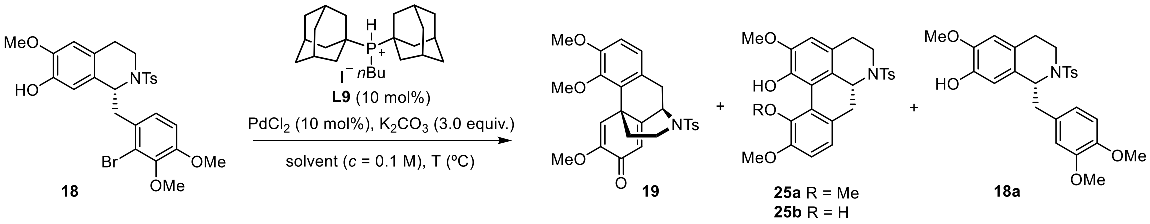
Table S3 Screening of Reaction Temperature[a]



Entry	T (ºC)	Reaction Time	Conv.	Yield of 19	Yield of 25a, 25b	Yield of 18a[b]
1	100	18 h	80%	11%	14%, 29%	trace
2	120	3 h	100%	57%	12%, 21%	trace
3	145	1 h	100%	67%	11%, 16%	trace

[a]Reactions were conducted on 0.2 mmol scale unless otherwise stated. Yields were determined according to the isolated material.

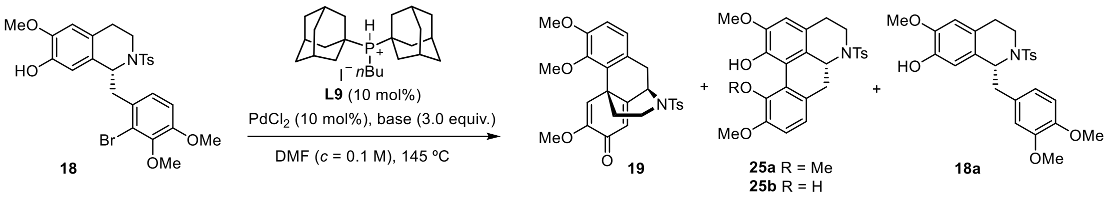
Table S4 Screening of solvents[a]



Entry	Solvent	T (ºC)	Reaction Time	Conv.	Yield of 19	Yield of 25a, 25b	Yield of 18a
1	DME	85	16 h	15%	trace	trace, N.D.	trace
2	PhMe	110	16 h	50%	19%	18%, N.D.	trace
3	dimethylbezene	145	16 h	100%	55%	40%, N.D.	trace
4	PhOMe	145	16 h	100%	62%	23%, N.D.	trace
5	DMF	145	1 h	100%	67%	11%, 16%	trace
6	THF	80	16 h	< 10%	trace	N.D.	N.D.
7	dioxane	80	16 h	< 10%	trace	N.D.	N.D.

[a]Reactions were conducted on 0.2 mmol scale unless otherwise stated. Yields were determined according to the isolated material. N.D.: not detected.

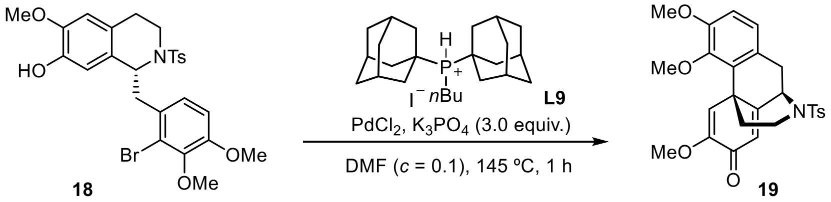
Table S5 Screening of bases[a]



Entry	Base	Reaction Time	Conv.	Yield of 19	Yield of 25a, 25b	Yield of 18a
1	K_2CO_3	1 h	100%	67%	11%, 16%	trace
2	Cs_2CO_3	3 h	100%	<10%	18%, 29%	trace
3	*t*-BuOK	3 h	100%	28%	22%, 7%	24%
4	KH	3 h	100%	30%	13%, 11%	41%
5	KOH	3 h	100%	25%	21%, 26%	trace
6	K_3PO_4	1 h	100%	72%	12%, 11%	trace

[a]Reactions were conducted on 0.2 mmol scale unless otherwise stated. Yields were determined according to the isolated material.

Table S6 Screening of the loadings of $PdCl_2$ and ligands[a]

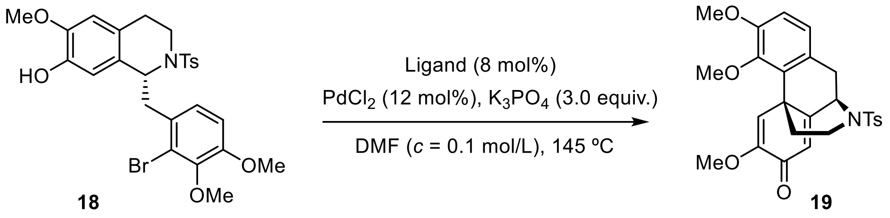


Entry[a]	Equiv. of $PdCl_2$ (mol%)	Equiv. of L3 (mol%)	Conv.	Yield of 19
1	10	10	100%	72%
2	10	15	100%	76%
3	10	20	100%	77%
4	10	30	100%	78%
5	10	40	100%	78%
6	10	50	100%	78%
7	8	12	100%	76%

8	8	16	100%	76%
9	8	24	100%	76%
10	5	15	100%	71%
11	5	10	100%	67%
12	2.5	7.5	100%	51%
13	2.5	5	100%	46%

[a] Reactions were conducted on 0.4 mmol scale unless otherwise stated. Yields were determined according to the isolated material.

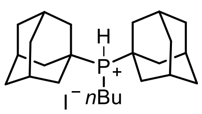
Table S7 Screening of ligands[a]



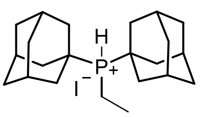
Entry	Ligands	Reaction Time	Conv.	Yield of 19[b]
1	**L9**	1 h	100%	76%
2	**L10**	1 h	100%	69%
3	**L11**	1 h	100%	80%
4	**L12**	1 h	100%	65%
5	**L13**	1 h	100%	75%
6	**L25**	6 h	50%	trace
7	**L26**	4 h	100%	< 10%
8	**L27**	4 h	76%	21%

[a] Reactions were conducted on 0.2mmol scale unless otherwise stated. Yields were determined according to the isolated material.

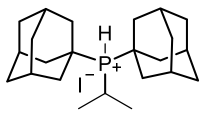
Ligands used in Table S7



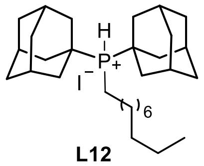
L9



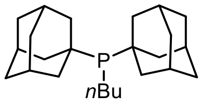
L10



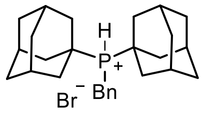
L11



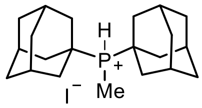
L12



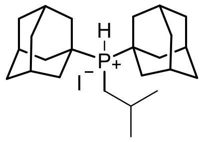
L13



L25



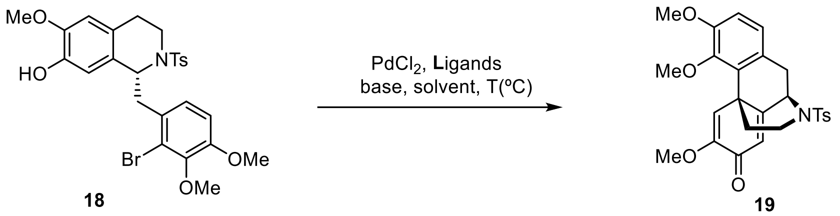
L26



L27

7. Synthesis of compound 19

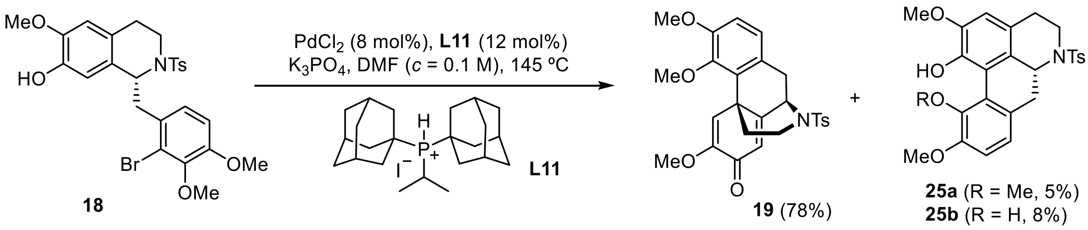
(1). General Procedure



18 **19**

To a flamed-dried Schlenk flask equipped with a stir bar was added compound **18**, $PdCl_2$, ligand and K_3PO_4. The flask was evacuated and backfilled with argon three times, followed by the addition of anhydrous degassed solvent. Then the flask was placed in a preheated oil-bath and stirred. After the reaction was stirred for the given time shown in the above tables, the mixture was subjected to evaporation under reduced pressure to remove the solvent. The residue was diluted with EtOAc and water with stirring. Then the mixture was filtered through a pad of Celite. The layers of the filtrate were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography to deliver compound **19**, along with the corresponding byproducts.

(2). Scale-up synthesis of compound 19 using the optimized conditions



18 **19** (78%) **25a** (R = Me, 5%) **25b** (R = H, 8%)

To a flamed-dried Schlenk flask equipped with a stir bar was added compound **18** (20.0 g, 35.56 mmol, 1.0 equiv.), $PdCl_2$ (504.5 mg, 2.845 mmol, 0.08 equiv.), ligand **L11** (2.016 g, 4.272 mmol, 0.12 equiv.) and K_3PO_4 (22.64 g, 106.7 mmol, 3.0 equiv.). The flask was evacuated and backfilled with argon three times, followed by the addition of anhydrous degassed DMF (474 mL, *c* = 0.075 mol/L). Then the flask was placed in a preheated 145 °C oil-bath and stirred for 2 hours. After the TLC analysis indicated the complete consumption of **18**, the mixture was subjected to evaporation under reduced pressure to remove the solvent. The residue was diluted with EtOAc (300 mL) and water (300 mL) with stirring. Then the mixture was filtered through a pad of Celite. The layers of the filtrate were separated, and the aqueous layer was extracted with EtOAc (200 mL × 3). The combined organic layers were washed with water (200 mL × 1), brine (200 mL × 1), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography (petroleum ether/dichloromethane/acetone = 15:15:1, v/v) to deliver compound **19** as an off-white foam (13.4 g, 78%), along with two byproducts **25a** (a white foam, 856 mg, 5%) and **25b** (a white solid, 1.33 g, 8%).

Characterization Data for 19:

Optical rotation: $[\alpha]_D^{25} = +4.5$ ($c = 0.4$, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 4.4 Hz, 2H), 7.64 (d, J = 1.2Hz, 2H), 7.15 (s, 1H), 6.83 – 6.76 (m, 2H), 6.21 (s, 1H), 4.95 – 4.93 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.72 – 3.67 (m, 1H), 3.29 – 3.16 (m, 2H), 3.02 – 2.95 (m , 1H), 2.39 (s, 3H), 2.22 – 2.17 (m, 1H), 1.39 – 1.31 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 157.7, 152.0, 151.2, 147.2, 143.7, 137.0, 130.1, 129.8, 127.7, 126.9, 123.9, 122.3, 119.8, 112.2, 60.8, 55.8, 54.9, 54.7, 43.5, 40.1, 38.8, 21.5.

IR (neat): 2936, 1674, 1649, 1616, 1483, 1280, 1213, 1159.

HRMS (m/z): $[M + H]^+$ calculated for $C_{26}H_{28}NO_6S^+$, 482.1632; found, 482.1636.

Characterization Data for 25a:

Optical rotation: $[\alpha]_D^{25} = -250$ ($c = 1.2$, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.58 (s, 1H), 4.56 (dd, J = 13.2, 3.6 Hz, 1H), 4.00 (dt, J = 13.6, 3.6 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.28 – 3.18 (m, 1H), 2.97 (dd, J = 13.6, 4.0 Hz, 1H), 2.80 (t, J = 13.2 Hz, 1H), 2.52 – 2.46 (m, 2H), 2.38 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ 151.9, 149.1, 143.8, 143.2, 143.1, 138.1, 130.5, 129.7, 126.8, 125.8, 125.6, 125.0, 123.6, 119.8, 111.6, 111.3, 62.2, 56.0, 53.1, 40.4, 37.5, 28.6, 21.4.

IR (neat): 3181, 2939, 2837, 1464, 1231, 1156, 730.

HRMS (m/z): $[M + H]^+$ calculated for $C_{26}H_{28}NO_6S^+$, 482.1632; found, 482.1636.

Characterization Data for 25b:

Optical rotation: $[\alpha]_D^{25} = -351.1$ (c = 0.7, DMSO).

^{1}H NMR (400 MHz, CD$_3$SOCD$_3$): δ 9.80 (brs, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 4.24 (dd, J = 12.4, 4.0 Hz, 1H), 3.95 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.21 (m, 1H), 2.87 – 2.72 (m, 2H), 2.51 – 2.43 (m, 1H, overlapped), 2.32 (s, 3H), 2.23 – 2.11 (m, 1H).

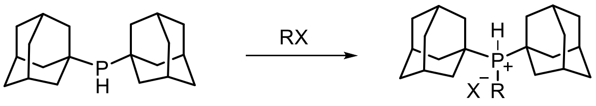
^{13}C NMR (100 MHz, CD$_3$SOCD$_3$): δ 148.3, 148.1, 143.3, 142.1, 141.3, 137.5, 130.1, 129.5, 126.6, 125.0, 123.9, 120.5, 120.4, 119.6, 111.4, 111.1, 55.9, 558, 53.1, 40.4, 38.0, 27.4, 20.9.

IR (neat): 3302, 2939, 1598, 1439, 1272, 1239, 1153, 728.

HRMS (m/z): $[M + H]^+$ calculated for $C_{25}H_{28}NO_6S^+$, 468.1475; found, 468.1476.

8. Synthesis of ligands L9–L12 and L25–L27

*Ligands **L9–L12, L25–L27** were prepared according to a literature method.*[2] *The general procedures are shown as follows:*



S6

L9 R = $CH_2CH_2CH_2CH_3$, X = I
L10 R = CH_2CH_3, X = I
L11 R = $CH(CH_3)_2$, X = I
L12 R = $CH_2(CH_2)_7CH_2CH_3$, X = I
L25 R = Bn, X = Br
L26 R = Me, X = I
L27 R = $CH_2CH(CH_3)_2$, X = I

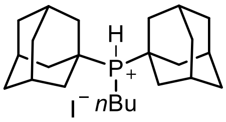
Table S8 Reaction conditions for preparation of the phosphonium salts

Entry	Alkyl Halide	Equiv. of Alkyl Halide	Solvent	T (ºC)	Reaction Time	Product	Yield
1	$CH_3CH_2CH_2CH_2I$	1.5	*n*-Bu_2O	130	8 h	**L9**	90%
2	CH_3CH_2I	5	neat	100	48 h	**L10**	71%
3	$(CH_3)_2CHI$	5	neat	100	48 h	**L11**	72%
4	$CH_3(CH_2)_8CH_2I$	3	*n*-Bu_2O	100	22 h	**L12**	56%
5	BnBr	5	neat	25	1 h	**L25**	81%
6	MeI	3	*n*-Bu_2O	25	46 h	**L26**	86%
7	$(CH_3)_2CHCH_2I$	5	neat	100	5 h	**L27**	34%

General procedure for the synthesis of phosphonium salts L9–L12 and L25–L27.

Method A**:** To a flamed-dried round bottom flask equipped with a stir bar was added di(1-adamantyl)phosphine (1.0 equiv.). The flask was evacuated and backfilled with argon three times, followed by addition of di-*n*-butyl ether and alkyl halide (1.5–3.0 equiv.). The reaction was stirred at the temperature shown in Table **S8**, and the desired product was precipitated gradually. After being stirred for the given time (see Table **S8**), the mixture was diluted with di-*n*-butyl ether at room temperature. The precipitate was collected by filtration and dried under vacuum to give the product, which was directly used without further purification.

Method B**:** To a flamed-dried round bottom flask or a sealed tube equipped with a stir bar was added di(1-adamantyl)phosphine (1.0 equiv.). The flask was evacuated and backfilled with argon three times, followed by the addition with alkyl halide (5.0 equiv.). The reaction was stirred at the temperature shown in Table **S8**, and the desired product was precipitated gradually. After being stirred for the given time (see Table **S8**), the mixture was diluted with di-*n*-butyl ether at room temperature. The precipitate was collected by filtration and dried under vacuum to give the product, which was directly used without further purification.



L9

Di(1-adamantyl)-*n*-butylphosphonium iodide (L9): Following the general procedure (***Method A***), the alkylation of **S6** (1.00 g, 3.31 mmol, 1.0 equiv.) with *n*-butyl iodide (0.57 mL, 4.97 mmol, 1.5 equiv.) in *n*-butyl ether (22 mL) proceeded for 8 h to provide the product **L9** (1.45 g, 90%) as a white solid.

M.p. = 245 – 249 °C.

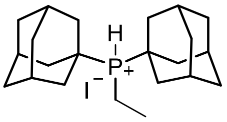
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (dt, $J_{H,P}$ = 472.4, $J_{H,H}$ = 3.6 Hz, 1H), 2.32 – 1.74 (m, 34H), 1.59 – 1.48 (m, 2H), 0.98 (t, $J_{H,H}$ = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 38.0 (d, $J_{C,P}$ =2.5 Hz), 37.6 (d, 32.6 Hz), 35.6 (d, $J_{C,P}$ = 1.3 Hz), 28.3 (d, $J_{C,P}$ = 5.6 Hz), 27.4 (d, $J_{C,P}$ = 9.3 Hz), 24.4 (d, $J_{C,P}$ = 12.2 Hz), 13.3, 11.7 (d, $J_{C,P}$ = 39.3 Hz).

^{31}P NMR (CDCl$_3$): δ 19.9.

HRMS (ESI): m/z calcd. for $C_{24}H_{40}P^{+}$ $[M]^{+}$ 359.2862; found 359.2860.

IR (neat): 2905, 2852, 2257, 1450, 728, 697 cm^{-1}



L10

Di(1-adamantyl)ethylphosphonium iodide (L10): Following the general procedure (***Method B***), the alkylation of **S6** (5.00 g, 16.5 mmol, 1.0 equiv.) with ethyliodide (6.6 mL, 82.5 mmol, 5.0 equiv.) in a sealed tube at 100 °C proceeded for 48 h to provide the product **L10** (5.37 g, 71%) as a white solid.

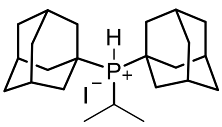
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.54 (dt, $J_{H,P}$ = 468.8, 3.6 Hz, 1H), 2.34 – 1.69 (m, 32H), 1.54 (dt, $J_{H,H}$ = 18.0, 7.6 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 38.0 (d, $J_{C,P}$ = 2.6 Hz), 37.8 (d, $J_{C,P}$ = 32.4 Hz), 35.5 (d, $J_{C,P}$ = 1.4 Hz), 27.4 (d, $J_{C,P}$ = 9.2 Hz), 11.0 (d, $J_{C,P}$ = 6.3 Hz), 6.2 (d, $J_{C,P}$ = 41.0 Hz).

^{31}P NMR (CDCl$_3$): δ 25.2.

IR (neat): 2900, 2850, 2262, 1450, 732.

HRMS (ESI): m/z calcd. for $C_{22}H_{36}P^{+}$ $[M]^{+}$ 331.2549; found 321.2545.



L11

Di(1-adamantyl)isopropylphosphonium iodide (L11): Following the general procedure (***Method B***), the alkylation of **S6** (5.00 g, 16.5 mmol, 1.0 equiv.) with 2-iodopropane (8.2 mL, 82.5 mmol, 5.0 equiv.) in a sealed tube at 100 °C proceeded for 48 h to provide the product **L11** (5.61 g, 72%) as a white solid.

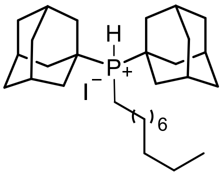
^{1}H NMR (400 MHz, CDCl$_3$): 7.71 (d, $J_{H,P}$ = 466 Hz, 1H,), 3.07–2.96 (m, 1H), 2.34 (m, 12H), 2.13 (m, 6H), 1.87–1.78 (m, 12H), 1.65 (dd, $J_{H,H}$ = 16.0 Hz, 8.0 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): (100 MHz, CDCl$_3$) δ 40.3 (d, $J_{C,P}$ = 29.0 Hz), 38.9 (d, $J_{C,P}$ = 3.0 Hz), 35.6 (d, $J_{C,P}$ = 2.0 Hz), 27.6 (d, $J_{C,P}$ = 9.0 Hz), 20.2 (d, $J_{C,P}$ = 35.0 Hz), 20.2 (d, $J_{C,P}$ = 3.4 Hz).

^{31}P NMR (CDCl$_3$): δ 24.3.

IR (neat): ν_{max} = 2905, 2850, 1452, 1266, 727, 698.

HRMS (ESI): m/z calcd. for $C_{23}H_{38}P^+$ $[M]^+$ 345.2706; found 345.2701.



L12

Di(1-adamantyl)-decylphosphonium iodide (L12): Following the general procedure (***Method A***), the alkylation of **S6** (3.00 g, 9.92 mmol, 1.0 equiv.) with 1-iodododecane (6.35 mL, 29.8 mmol, 3.0 equiv.) in *n*-butyl ether (66 mL) at 100 °C proceeded for 22 h to provide the product **L12** (3.17 g, 56%) as a white solid.

M.p. = 122 – 125 °C.

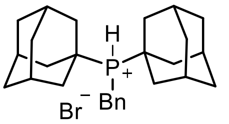
^{1}H NMR (600 MHz, CDCl$_3$): δ 7.90 (d, $J_{H,P}$ = 473.4 Hz, 1H), 2.38 – 1.76 (m, 34H), 1.53 – 1.18 (m, 14H), 0.87 (t, $J_{H,H}$ = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 38.0 (d, $J_{C,P}$ =2.5 Hz), 37.6 (d, $J_{C,P}$ = 32.4 Hz), 35.6 (d, $J_{C,P}$ = 1.0 Hz), 31.8, 31.3 (d, $J_{C,P}$ = 12.2 Hz), 29.4, 29.3, 29.2, 28.7, 27.4 (d, $J_{C,P}$ = 9.3 Hz), 26.4 (d, $J_{C,P}$ = 5.6 Hz), 22.6, 14.1, 12.0 (d, $J_{C,P}$ = 39.1 Hz).

^{31}P NMR (CDCl$_3$): δ 19.7.

IR (neat): 2907, 2851, 2250, 1451, 730.

HRMS (ESI): m/z calcd. for C30H52P+ $[M]^+$ 443.3801; found 443.3796.



L25

Di(1-adamantyl)-benzylphosphonium bromide (L25): Following the general procedure (***Method B***), the alkylation of **S6** (1.00 g, 3.31 mmol, 1.0 equiv.) with benzyl bromide (2.00 mL, 16.6 mmol, 5 equiv.) proceeded at 25 °C for 1 h to provide the product **L25** (1.27 g, 81%) as white solid.

M.p. = 260 – 265 °C.

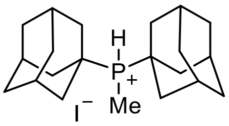
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dt, $J_{H, P}$ = 479.6, $J_{H, H}$ = 6.0 Hz, 1H), 7.63 (d, $J_{H, H}$ = 7.6 Hz, 2H), 7.36 (t, $J_{H, H}$ = 7.6 Hz, 2H), 7.28 (d, $J_{H, H}$ = 6.8 Hz, 1H), 3.74 (dd, $J_{H, H}$ = 13.2, 6.0 Hz, 2H), 2.36 – 1.65 (m, 30H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.4 (d, $J_{C, P}$ = 7.6 Hz), 130.1 (d, $J_{C, P}$ = 5.8 Hz), 129.5 (d, $J_{C, P}$ = 1.1 Hz), 128.2 (d, $J_{C, P}$ = 2.1 Hz), 38.3 (d, $J_{C, P}$ = 30.6 Hz), 38.2 (d, $J_{C, P}$ = 2.8 Hz), 35.5 (d, $J_{C, P}$ = 1.2 Hz), 27.5 (d, $J_{C, P}$ = 9.3 Hz), 19.6 (d, $J_{C, P}$ = 37.3 Hz).

^{31}P NMR ($CDCl_3$) δ 22.5.

IR (neat): 2903, 2852, 2248, 1495,1450, 1266, 727, 698 cm^{-1}.

HRMS (ESI): m/z calcd. for $C_{27}H_{38}P^+$ $[M]^+$ 393.2706; found 393.2701.



L26

Di(1-adamantyl)methylphosphonium iodide (L26): Following the general procedure (***Method A***), the alkylation of **S6** (3.00 g, 9.92 mmol, 1.0 equiv.) with methyl iodide (1.85 mL, 29.8 mmol, 3.0 equiv.) in *n*-butyl ether (66 mL) proceeded for 46 h to provide the product **L26** (3.8 g, 86%) as a white solid.

M.p. = 253 – 257 °C.

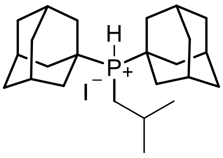
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, $J_{H, P}$ = 475.2 Hz, 1H), 2.44 – 1.48 (m, 33H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 37.9 (d, $J_{C,P}$ = 2.3 Hz), 36.1 (d, $J_{C,P}$ = 35.6 Hz), 35.5 (d, $J_{C,P}$ = 1.4 Hz), 27.3 (d, $J_{C,P}$ =9.6 Hz), –3.8 (d, $J_{C,P}$ = 46.6 Hz)

^{31}P NMR (CDCl$_3$): δ 19.2

IR (neat): 2905, 2850, 1452, 1266, 727, 698.

HRMS (ESI): m/z calcd. for $C_{21}H_{34}P^+$ $[M]^+$317.2393; found 317.2390.



L27

Di(1-adamantyl)-isobutylphosphonium iodide (L27): Following the general procedure (***Method B***), the alkylation of **S6** (1.00 g, 3.31 mmol, 1.0 equiv.) with isobutyl iodide (1.9 mL, 16.6 mmol, 5.0 equiv) in *n*-butyl ether (22 mL) proceeded for 5 h to provide the product **L27** (5.47 g, 34%) as white solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.99 (dt, $J_{H,P}$ = 472.0, $J_{H,H}$ = 4.4 Hz, 1H), 2.28 – 1.73 (m, 33H), 1.21 (d, $J_{H,H}$ = 6.4 Hz, 6H).

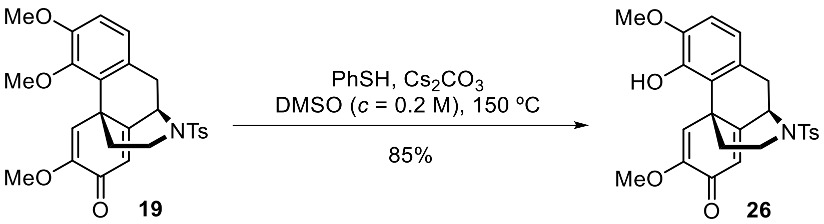
^{13}C NMR (100 MHz, CDCl$_3$): δ 37.7 (d, $J_{C,P}$ = 2.6 Hz), 37.4 (d, $J_{C,P}$ = 33.2 Hz), 35.6 (d, $J_{C,P}$ = 1.2 Hz), 27.4 (d, $J_{C,P}$ = 9.2 Hz), 26.9 (d, $J_{C,P}$ = 5.0 Hz), 24.1 (d, $J_{C,P}$ = 7.9 Hz), 20.0 (d, $J_{C,P}$ = 37.4 Hz).

^{31}P NMR (CDCl$_3$): δ 12.5

IR (neat): 2906, 2853, 2270, 1451, 730.

HRMS (ESI): m/z calcd. for C24H40P+ $[M]^+$ 359.2862; found 359.2860.

9. Synthesis of compound 26



To a flamed-dried Schlenk flask equipped with a stir bar was added compound **19** (20.00 g, 41.6 mmol, 1.0 equiv.) and Cs_2CO_3 (20.4 g, 62.4 mmol, 1.5 equiv.). The flask was evacuated and backfilled with argon three times, followed by the addition of anhydrous degassed DMSO

(200 mL, *c* = 0.2 mol/L) and PhSH (5.74 mL, 56.2 mmol, 1.35 equiv.). Then the flask was placed in a preheated 150 ºC oil-bath. After stirring at 150 ºC for 1.5 hours, TLC analysis indicated that the starting material **19** was completely consumed. The reaction was cooled to room temperature and quenched with water. The layers were separated, and the aqueous layer was extracted with EtOAc (300 mL × 5). The combined organic layers were sequentially washed with water (300 mL × 2), brine (300 mL × 1), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Subjection of the resulting residue to silica gel flash chromatography (petroleum ether/dichloromethane/acetone = 15:15:1 to 10:10:1, v/v) yielded compound **26** as a white foam (16.54 g, 85%).

Optical rotation: $[\alpha]_D^{25} = +13.8$ (c = 1.44, $CHCl_3$).

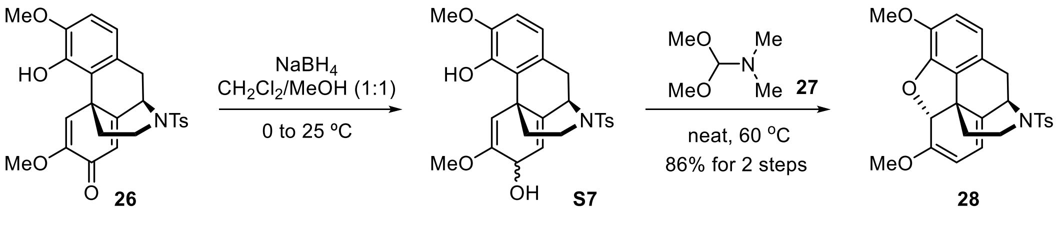
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, J = 8.2 Hz, 2H), 7.43 (s, 1H), 7.28 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.23 (s, 1H), 6.19 (s, 1H), 4.94 (d, J = 3.6 Hz, 1H), 3.87 (s, 3H), 3.74 – 3.71 (m, 1H, overlapped), 3.69 (s, 3H), 3.28 – 3.17 (m, 2H), 3.01 (td, J = 13.2, 3.2 Hz, 1H), 2.39 (s, 3H), 2.37 – 2.34 (m, 1H, overlapped), 1.29 (td, J = 12.8, 4.8 Hz, 1H).

^{13}C NMR (150 MHz, CDCl$_3$): δ 180.7, 157.6, 151.3, 145.6, 143.7, 143.3, 137.1, 129.8, 128.0, 126.9, 122.4, 122.2, 119.5, 119.4, 109.9, 56.2, 54.8, 54.7, 43.2, 40.3, 38.7, 37.5, 21.5.

IR (neat): 3350, 2929, 1670, 1640, 1484, 1219, 1158, 1054.

HRMS (m/z): $[M + H]^+$ calculated for $C_{25}H_{26}NO_6S^+$, 468.1475; found, 468.1477.

10. Synthesis of compound 28



To a solution of compound **26** (15.75 g, 33.69 mmol, 1.0 equiv.) in CH_2Cl_2/MeOH (v/v = 1:1, 300 mL) was slowly added $NaBH_4$ (2.55 g, 67.38 mmol, 2.0 equiv.) at 0 ºC. Then the reaction was warmed to 25 ºC with stirring. After 30 minutes, TLC analysis indicated the complete consumption of **26**. The reaction was cooled to 0 ºC again and quenched by addition of water (150 mL). The resulting mixture was evaporated under reduced pressure to remove the volatiles. The residue was extracted with CH_2Cl_2 (150 mL × 3). The combined organic layers were washed with brine (150 mL × 1), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude compound **S7**, which was directly used in the next step.

Under argon, to a round-bottom flask equipped with a stir bar was added compound **S7** and *N*,*N*-dimethylformamide dimethyl acetal (75 mL). The reaction was stirred at 60 °C for 2 hours, before it was evaporated under reduced pressure to remove the volatiles. The resulting residue was purified by silica gel flash chromatography (petroleum ether/ethyl acetate = 5:1 to 3.5:1, v/v) to afford compound **28** as a white foam (13.08 g, 86% for two steps).

Optical rotation: $[\alpha]_D^{25} = -117.8$ ($c = 0.72$, $CHCl_3$).

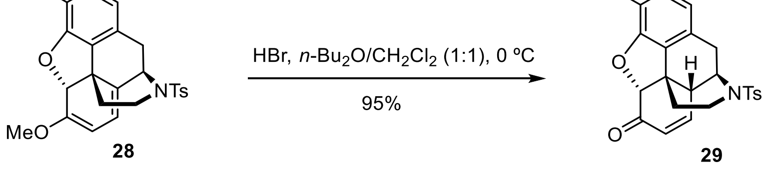
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.64 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.60 (d, J = 6.4 Hz, 1H), 5.19 (s, 1H), 4.98 (dd, J = 13.6, 6.4 Hz, 2H), 3.82 (s, 3H), 3.74 (dd, J = 12.0, 5.2 Hz, 1H), 3.59 (s, 3H), 3.26 (td, J = 13.2, 3.6 Hz, 1H), 3.00 (dd, J = 18.2, 6.8 Hz, 1H), 2.89 (d, J = 18.0 Hz, 1H), 2.44 (s, 3H), 1.95 (td, J = 12.8, 5.4 Hz, 1H), 1.74 – 1.70 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 144.8, 143.4, 143.1, 137.3, 132.1, 129.7, 129.0, 127.4, 126.1, 119.5, 113.2, 112.5, 95.4, 88.6, 56.4, 55.0, 54.4, 45.9, 38.9, 37.1, 36.0, 21.6.

IR (neat): 2922, 1603, 1502, 1234, 1155, 725.

HRMS (m/z): $[M + H]^+$ calculated for $C_{25}H_{26}NO_5S^+$, 452.1526; found, 452.1519.

11. Synthesis of compound 29



Under argon, to a round-bottom flask was sequentially added compound **28** (50.0 mg, 0.111 mmol, 1.0 equiv.), *n*-butyl ether (2.0 mL) and CH_2Cl_2 (2.0 mL). The mixture was cooled to 0 °C and HBr (11 M in H_2O, 2 μL, 0.0222 mmol, 0.2 equiv.) was added. After being stirred at 0 °C for 15 hours, TLC indicated the complete consumption of compound **28**. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 4). The combined organic layers were dried over

$MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (petroleum ether/dichloromethane/ethyl acetate = 15:15:1 to 10:10:1, v/v) to afford compound **29** as a white foam (46 mg, 95%).

Optical rotation: $[\alpha]_D^{25} = -149.0$ (c = 0.52, $CHCl_3$).

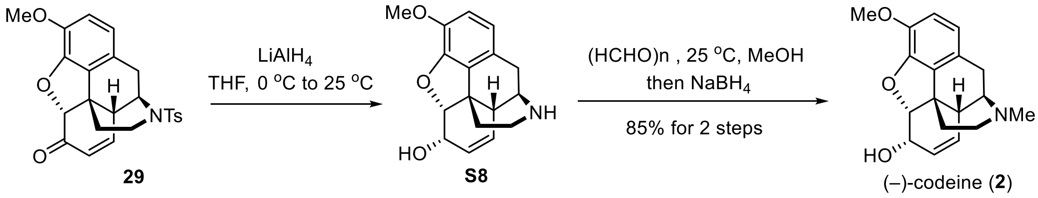
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.66 (d, J = 4.4 Hz, 1H), 6.58 (dd, J = 10.4, 2.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.10 (dd, J = 10.4, 3.2 Hz, 1H), 4.75 (s, 1H), 4.65 (s, 1H), 3.83 (s, 3H), 3.82–3.77 (m, 1H, overlapped), 3.09 – 3.08 (m, 1H), 2.94 – 2.87 (m, 1H), 2.73 – 2.61 (m, 2H), 2.45 (s, 3H), 1.98 (td, J = 12.4, 5.2 Hz, 1H), 1.91 – 1,87 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 193.6, 146.5, 144.9, 143.7, 142.9, 137.3, 133.3, 130.0, 127.6, 127.0, 124.2, 120.4, 115.3, 87.6, 56.8, 52.4, 43.4, 40.8, 39.3, 33.4, 28.1, 21.6.

IR (neat): 2923, 2852, 1676, 1505, 1442, 1278, 1158.

HRMS (m/z): $[M + H]^+$ calculated for $C_{24}H_{24}NO_5S^+$, 438.1370; found, 438.1362.

12. Synthesis of (–)-codeine (2)



Under argon, to a solution of compound **29** (10.0 mg, 0.0229 mmol, 1.0 equiv.) in anhydrous THF (10 mL) at 0 °C was slowly added $LiAlH_4$ (1 M in THF, 115 μL, 0.115 mmol, 5.0 equiv.). The reaction was then warmed to 25 °C. After being stirred for 10 hours, the reaction was cooled to 0 °C and quenched with isopropanol (15 μL). The mixture was sequentially treated with water (5 μL), 15% aqueous NaOH (5 μL) and water (15 μL). The resulting suspension was allowed to warm to 25 °C and stirred for additional 30 min. The mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2/MeOH (10:1, v/v, 1 mL × 5). The filtrate was concentrated *in vacuo* to give the crude compound **S8**, which was directly used in the next step.

To a solution of the above compound **S8** in MeOH (1.0 mL) was added paraformaldehyde (10.4 mg, 0.115 mmol, 5.0 equiv.). The reaction was stirred for 2 hours at 25 °C. Then $NaBH_4$

(5.3 mg, 0.14 mmol, 6.0 equiv.) was added at 0 ºC. The reaction was warmed to 25 ºC with stirring. After the TLC analysis showed the reaction was complete, saturated NH_4Cl solution was added. The resulting mixture was diluted with CH_2Cl_2 (1 mL). Then 15% aqueous NaOH solution was added to adjust the pH = 10. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography (dichloromethane/methanol = 20:1 to 8:1, v/v) to afford (–)-codeine (**2**) as a white solid (5.8 mg, 85% for two steps).

Optical rotation: $[\alpha]_D^{25} = -131.0$ (c = 0.2, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 5.71 (d, J = 9.6 Hz, 1H), 5.29 (dt, J = 10.0, 2.8 Hz, 1H), 4.89 (dd, J = 6.4, 0.8 Hz, 1H), 4.19 – 4.16 (m, 1H), 3.84 (s, 1 H), 3.35 (dd, J = 6.0, 3.4 Hz, 1H), 3.05 (d, J = 18.4 Hz, 1H), 2.91 (brs, 1H), 2.69 – 2.67 (m, 1H), 2.60 (dd, J = 12.0, 4.0 Hz, 1H), 2.44 (s, 3H), 2.40 (td, J = 12.4, 3.6 Hz, 1H), 2.30 (dd, J = 18.4, 6.0 Hz, 1H), 2.07 (td, J = 12.4, 4.8 Hz, 1H), 1.90 – 1.85 (m, 1H).

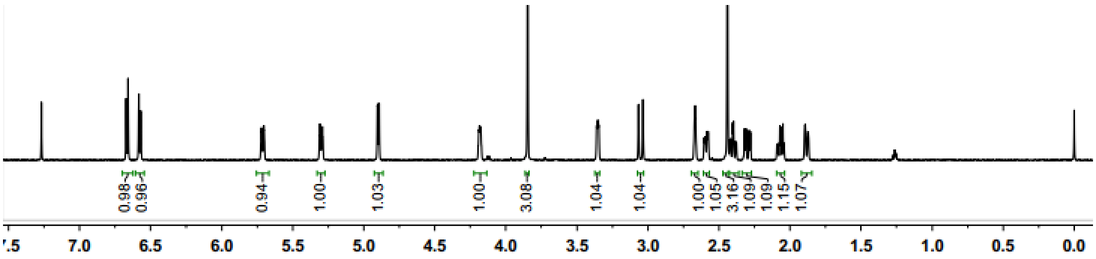
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 142.2, 133.4, 131.0, 128.2, 127.1, 119.5, 112.8, 91.3, 66.4, 58.9, 56.3, 46.4, 43.1, 42.9, 40.7, 35.7, 20.4.

IR (neat): 3370, 2929, 2843, 1635, 1502, 1452, 1274, 1265, 1205, 1120, 1054, 731. **HRMS (m/z):** $[M + H]^+$ calculated for $C_{18}H_{22}NO_3^+$, 300.1594; found, 300.1587.

Table S9 Comparison of ^{1}H NMR spectral data of (–)-codeine

A: Tu's report[3]	B: Our synthetic one	Erro (A-B)
δ (ppm, 600 MHz, $CDCl_3$)	δ (ppm, 400 MHz, $CDCl_3$)	$\Delta\delta/ppm$
6.66 (d, J = 8.2 Hz, 1H)	6.66 (d, J = 8.0 Hz, 1H)	0.00
6.57 (d, J = 8.2 Hz, 1H)	6.57 (d, J = 8.0 Hz, 1H)	0.00
5.71 (d, J = 9.9 Hz, 1H)	5.71 (d, J = 9.6 Hz, 1H)	0.00
5.30 (d, J = 9.9 Hz, 1H)	5.29 (dt, J = 10.0, 2.8 Hz, 1H)	0.01
4.90 (dd, J = 6.5, 0.9 Hz, 1H)	4.89 (dd, J = 6.4, 0.8 Hz, 1H)	0.01
4.22 – 4.13 (m, 1H)	4.19 – 4.16 (m, 1H)	0.03
3.85 (s, 3H)	3.84 (s, 1 H)	0.01
3.35 (dd, J = 5.9, 3.1 Hz, 1H)	3.35 (dd, J = 6.0, 3.4 Hz, 1H)	0.00
3.05 (d, J = 18.6 Hz, 1H)	3.05 (d, J = 18.4 Hz, 1H)	0.00
2.70 – 2.65 (m, 1H)	2.69 – 2.67 (m, 1H)	0.01
2.59 (dd, J = 12.2, 4.3 Hz, 1H)	2.60 (dd, J = 12.0, 4.0 Hz, 1H)	–0.01
2.44 (s, 3H)	2.44 (s, 3H)	0.00
2.40 (td, J = 12.3, 3.5 Hz, 1H)	2.40 (td, J = 12.4, 3.6 Hz, 1H)	0.00
2.30 (td, J = 18.6, 6.2 Hz, 1H)	2.30 (dd, J = 18.4, 6.0 Hz, 1H)	0.00
2.07 (td, J = 12.4, 4.9 Hz, 1H)	2.07 (td, J = 12.4, 4.8 Hz, 1H)	0.00
1.88 (dd, J = 12.6, 1.3 Hz, 1H)	1.90 – 1.85 (m, 1H)	–0.01
–	2.91(brs, 1H) (-OH)	–

^{1}H NMR of Tu's synthetic codeine



^{1}H NMR of our synthetic codeine

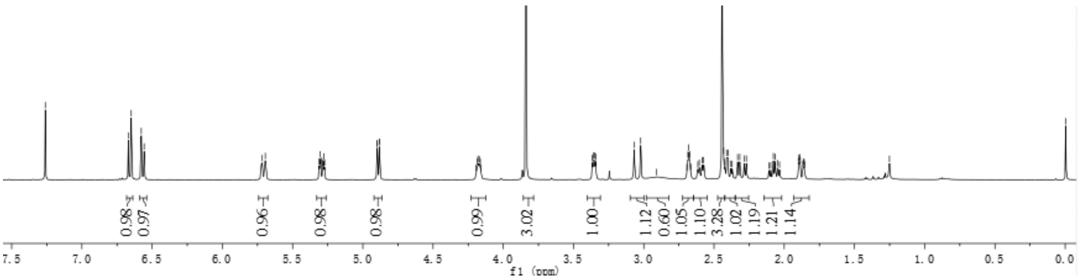
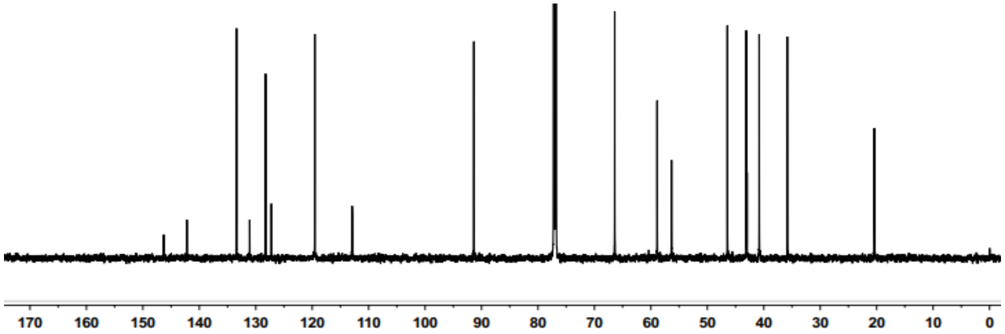


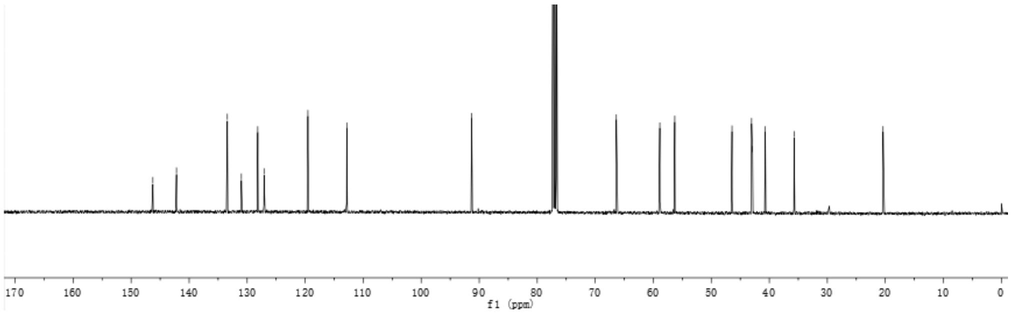
Table S10 Comparison of ^{13}C NMR spectral data of (–)-codeine

A: Tu's report[3]	B: Our synthetic one	Erro (A-B)
δ (ppm, 150 MHz, $CDCl_3$)	δ (ppm, 100 MHz, $CDCl_3$)	$\Delta\delta$/ppm
146.3	146.3	0.0
142.2	142.2	0.0
133.4	133.4	0.0
131.1	131.0	0.1
128.3	128.2	0.1
127.3	127.1	0.2
119.5	119.5	0.0
112.9	112.8	0.1
91.4	91.3	0.1
66.4	66.4	0.0
58.9	58.9	0.0
56.5	56.3	0.2
46.5	46.4	0.1
43.1	43.1	0.0
43.0	42.9	0.1
40.8	40.7	0.1
35.8	35.7	0.1
20.4	20.4	0.0

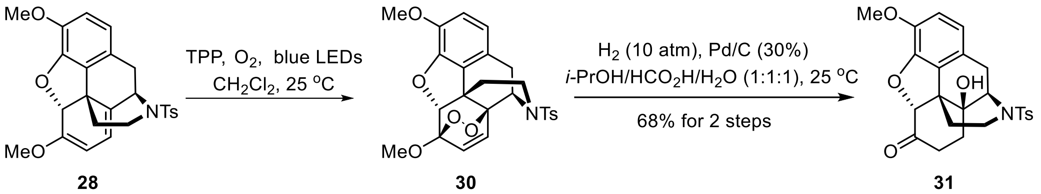
^{13}C NMR of Tu's synthetic codeine



^{13}C NMR of our synthetic codeine



13. Synthesis of compound 31



To a solution of compound **28** (50.0 mg, 0.111 mmol, 1.0 equiv.) in dichloromethane (2 mL) was added tetraphenylporphyrine (14.0 mg, 0.0222 mmol, 0.2 equiv.). The reaction mixture was bubbled with O_2 and irradiated with blue LED (40 w, Kessil®) at 25 °C, during which additional CH_2Cl_2 was added to minimize the solvent loss. After 1 hour, TLC indicated that the starting material **28** was completely consumed. The reaction mixture was diluted with dichloromethane (2 mL) and degassed with argon for 30 min (additional CH_2Cl_2 was added during the degassing). Next, to the above dark purple solution was added the mixture of isopropanol/formic acid/water (v/v/v = 1:1:1, 1.5 mL) and palladium (10% on carbon, 15 mg, 30% of weight). The reaction was then stirred for 24 h under H_2 (10 atm.) at 25 °C, after which it was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified through silica gel chromatography (petroleum ether/acetone = 3:1, v/v) to give the desired product **31** as a pale-yellow foam (34.3 mg, 68% yield for 2 steps).

Optical rotation: $[\alpha]_D^{25} = -188.1$ (c = 0.84, $CHCl_3$).

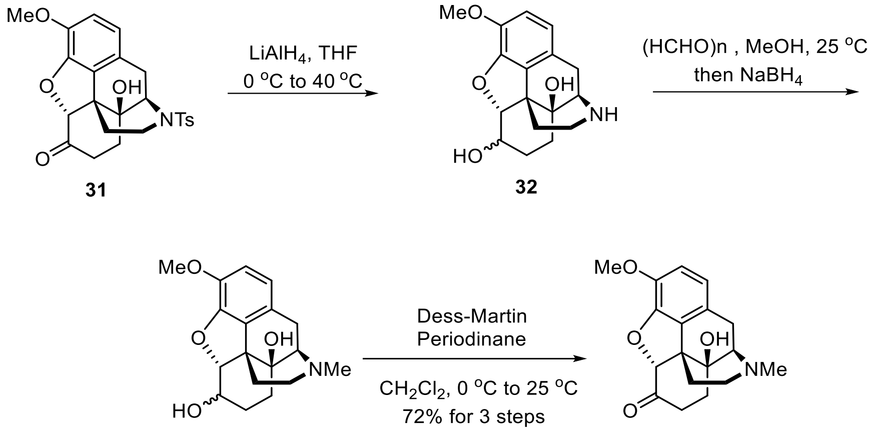
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.0 Hz, 1H), 4.65 (s, 1H), 4.22 (d, J = 6.0 Hz, 1H), 3.87 (s, 3H), 3.74 (dd, J = 12.8, 4.8 Hz, 1H), 3.23 (s, 1H), 3.03 (td, J = 14.4, 5.2 Hz, 1H), 2.81 (dd, J = 18.8, 6.0 Hz, 1H), 2.72 (td, J = 12.8, 3.6 Hz, 1H), 2.57 (d, J = 18.4 Hz, 1H), 2.48 – 2.40 (m, 1H, overlapped), 2.46 (s, 3H), 2.29 (dt, J = 14.4, 2.8 Hz, 1H), 1.95 – 1.90 (m, 1H), 1.69 – 1.54 (m, 2H, overlapped with the peak of H_2O).

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 145.1, 144.1, 143.4, 136.4, 130.1, 128.2, 127.2, 123.2, 119.7, 115.3, 89.9, 70.4, 58.7, 56.8, 50.3, 38.6, 35.9, 31.1, 29.4, 29.2, 21.6.

IR (neat): 3492, 2929, 1726, 1504, 1440, 1278, 1157, 1048, 753.

HRMS (m/z): $[M + H]^+$ calculated for $C_{24}H_{26}NO_6S^+$, 456.1475; found, 456.1481.

14. Synthesis of (–)-oxycodone (3)



Under argon, to a solution of compound **31** (25.0 mg, 0.0549 mmol, 1.0 equiv.) in anhydrous THF (2.0 mL) at 0 °C was slowly added $LiAlH_4$ (1 M in THF, 0.28 mL, 0.28 mmol, 5.0 equiv.). The reaction was then stirred at 40 °C for 24 hours, and TLC analysis indicated the complete consumption of the starting material **31**. The reaction was cooled to 0 °C and quenched with isopropanol (35 μL), followed by the sequential treatment with water (15 μL), 15% aqueous NaOH (15 μL) and water (45 μL). The resulting suspension was allowed to warm to 25 °C and stirred for additional 30 min. The mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2/MeOH (10:1, v/v, 1 mL × 5). The filtrate was concentrated *in vacuo* to give the crude compound **32**, which was used in the next step without purification.

To a solution of the above compound **32** in MeOH (2.0 mL) was added paraformaldehyde (30.0 mg, 0.329 mmol, 6.0 equiv.). The reaction was stirred for 2 hours at 25 °C. Then $NaBH_4$ (16.6 mg, 0.439 mmol, 8.0 equiv.) was added at 0 °C. The reaction was warmed to 25 °C with stirring. After the TLC analysis showed the reaction was complete, saturated NH_4Cl solution was added. The resulting mixture was diluted with CH_2Cl_2 (2.0 mL) and 15% aqueous NaOH solution was added to adjust the pH = 10. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude compound **S9**, which was directly used in the next step without purification.

To a solution of the above compound **S9** in CH_2Cl_2 (2.5 mL) was added Dess-Martin Periodinane (70.0 mg, 0.165 mmol, 3.0 equiv.) at 0 °C. Then the reaction was warmed to 25 °C with stirring. After 1 hour, TLC analysis showed the reaction was complete. The mixture was cooled to 0 ºC. Saturated $Na_2S_2O_3$ and $NaHCO_3$ solution was sequentially added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified through silica gel chromatography (dichloromethane/methane = 20:1, v/v) to give the desired product (–)-oxycodone (**3**) as a white solid. (12.5 mg, 72% yield for 3 steps).

M.p.: 204 – 206 ºC.

Optical rotation: $[\alpha]_D^{25} = -205$ ($c = 0.28$, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 4.65 (s, 1H), 3.89 (s, 3H), 3.15 (d, J = 18.8 Hz, 1H), 3.01 (td, J = 14.4, 4.8 Hz 1H), 2.86 (d, J = 5.8 Hz, 1H), 2.55 (d, J = 18.4, 5.6 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.40 (s, 3H), 2.30 (dt, J = 14.4, 3.2 Hz, 1H), 2.19 – 2.12 (m, 1H), 1.87 (ddd, J = 13.2, 4.8, 2.8 Hz, 1H), 1.66 – 1.53 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 144.9, 142.9, 129.3, 124.9, 119.4, 114.8, 90.3, 70.3, 64.5, 56.8, 50.2, 45.2, 42.7, 36.1, 31.4, 30.5, 21.9.

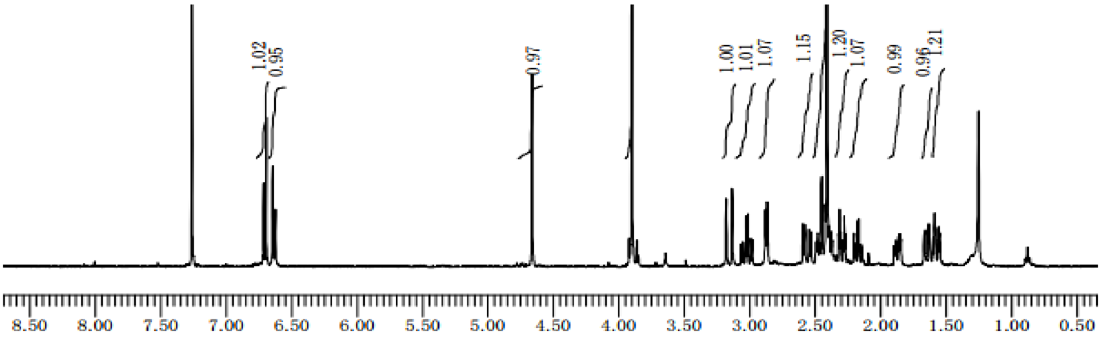
IR (neat): 3380, 2926, 1724, 1610, 1502, 1438, 1272, 1112, 1039, 941.

HRMS (m/z): $[M + H]^+$ calculated for $C_{18}H_{22}NO_4^+$, 316.1543; found, 316.1524.

Table S11 Comparison of ^{1}H NMR spectral data of (–)-oxycodone

A: Fukuyama's report[4]	B: Our synthetic one	Erro (A-B)
δ (ppm, 400 MHz, $CDCl_3$)	*δ* (ppm, 400 MHz, $CDCl_3$)	Δ*δ/ppm*
6.70 (d, *J* = 8.1 Hz, 1H)	6.70 (d, *J* = 8.0 Hz, 1H)	0.00
6.63 (d, *J* = 8.1 Hz, 1H)	6.62 (d, *J* = 8.4 Hz, 1H)	0.01
4.66 (s, 1H)	4.65 (s, 1H)	0.01
3.90 (s, 3H)	3.89 (s, 3H)	0.01
3.16 (d, *J* = 18.6 Hz, 1H)	3.15 (d, *J* = 18.8 Hz, 1H)	0.01
3.02 (ddd, *J* = 14.4, 14.3, 5.1 Hz 1H)	3.01 (td, *J* = 14.4, 4.8 Hz 1H)	0.01
2.88 (d, *J* = 5.8 Hz, 1H)	2.86 (d, *J* = 5.8 Hz, 1H)	0.02
2.57 (dd, *J* = 18.6, 5.8 Hz, 1H)	2.55 (d, *J* = 18.4, 5.6 Hz, 1H)	0.02
2.50 – 2.34 (m, 2H)	2.47 – 2.36 (m, 2H)	–
2.41 (s, 3H)	2.40 (s, 3H)	0.01
2.30 (ddd, *J* = 13.8, 5.1, 3.1 Hz, 1H)	2.30 (dt, *J* = 14.4, 3.2 Hz, 1H)	0.00
2.22 – 2.13 (m, 1H)	2.19 – 2.12 (m, 1H)	–
1.87 (ddd, *J* = 13.2, 5.2, 3.2 Hz, 1H)	1.87 (ddd, *J* = 13.2, 4.8, 2.8 Hz, 1H)	0.00
1.64 (ddd, *J* = 14.3, 13.8, 3.23 Hz, 1H)	1.66 – 1.53 (m, 2H)	–
1.60 – 1.54 (m, 1H)	overlapped	–

^{1}H NMR of Fukuyama's synthetic oxycodone



^{1}H NMR of our synthetic oxycodone

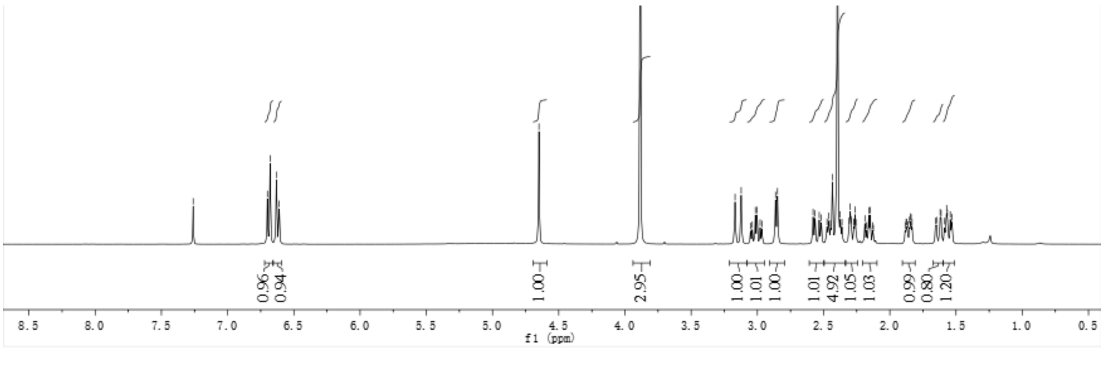
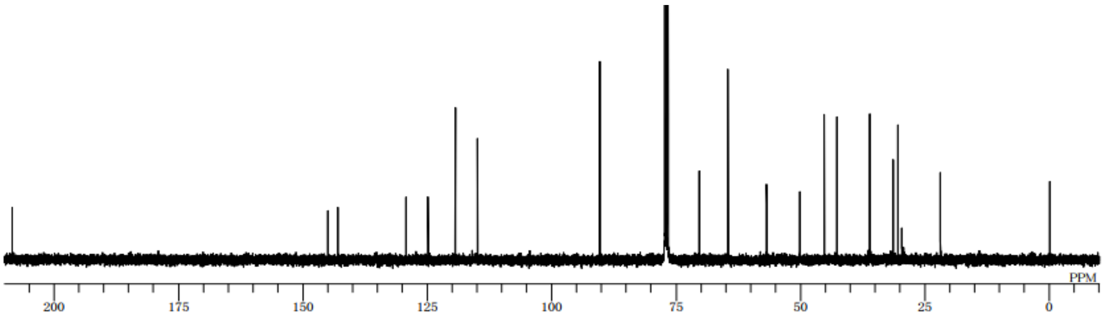


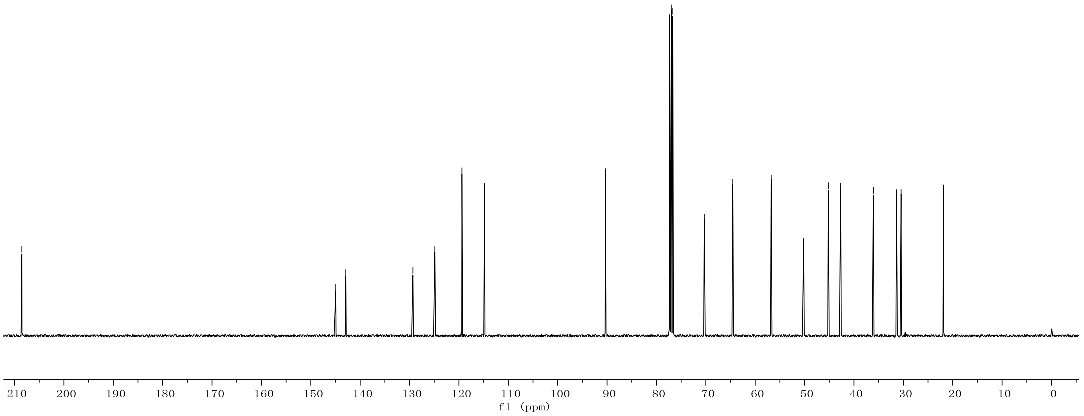
Table S12 Comparison of ^{13}C NMR spectral data of (–)-oxycodone

A: Fukuyama's report[4]	B: Our synthetic one	Erro (A-B)
δ (ppm, 100 MHz, $CDCl_3$)	δ (ppm, 100 MHz, $CDCl_3$)	$\Delta\delta/ppm$
208.7	208.5	0.2
145.2	144.9	0.3
143.1	142.9	0.2
129.5	129.3	0.2
125.0	124.9	0.1
119.6	119.4	0.2
115.1	114.8	0.3
90.5	90.3	0.2
70.5	70.3	0.2
64.8	64.5	0.3
57.0	56.8	0.2
50.4	50.2	0.2
45.4	45.2	0.2
42.9	42.7	0.2
36.3	36.1	0.2
31.6	31.4	0.2
30.7	30.5	0.2
22.1	21.9	0.2

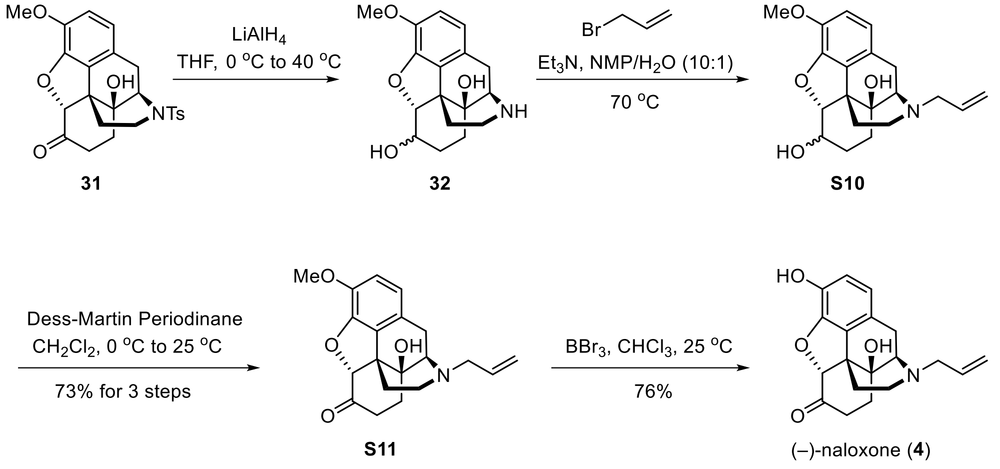
^{13}C NMR of Fukuyama's synthetic oxycodone



^{13}C NMR of our synthetic oxycodone



15. Synthesis of (–)-naloxone (4)



(1) Synthesis of compound S11

Under argon, to a solution of compound **31** (25.0 mg, 0.0549 mmol, 1.0 equiv.) in anhydrous THF (2.0 mL) at 0 °C was slowly added $LiAlH_4$ (1 M in THF, 0.28 mL, 0.28 mmol, 5.0 equiv.). The reaction was then stirred at 40 °C for 24 hours, and TLC analysis indicated the complete consumption of the starting material **31**. The reaction was cooled to 0 °C and quenched with isopropanol (35 μL), followed by the sequential treatment with water (15 μL), 15% aqueous NaOH (15 μL) and water (45 μL). The resulting suspension was allowed to warm to 25 °C and stirred for additional 30 min. The mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2/MeOH (10:1, v/v, 1 mL × 5). The filtrate was concentrated *in vacuo* to give the crude compound **32**, which was directly used in the next step without purification.

Under argon, to a mixed solution of the above compound **32** in NMP/H_2O (10:1 v/v, 0.55 mL) was added Et_3N (15 μL, 0.11 mmol, 2.0 equiv.) at 25 °C, followed by the dropwise addition of allyl bromide (7.0 μL, 0.082 mmol, 1.5 equiv.) with stirring. The mixture was then stirring at 70 °C for 1 hour and TLC analysis indicated that the reaction was complete. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (2 mL) and washed with saturated $NaHCO_3$ solution (1 mL × 3). The combined aqueous layers were extracted with CH_2Cl_2 (3 mL × 1), and all the organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude compound **S10** without further purification.

To a solution of the above crude compound **S10** in anhydrous CH_2Cl_2 (1.0 mL) was added Dess-Martin Periodinane (70.0 mg, 0.165 mmol, 3.0 equiv.) at 0 °C. Then the reaction was warmed to 25 °C with stirring. After 1 hour, TLC analysis showed the reaction was complete. The mixture was cooled to 0 °C. Saturated $Na_2S_2O_3$ and $NaHCO_3$ solution was sequentially added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified through silica gel chromatography (dichloromethane/methane = 20:1, v/v) to give the desired product **S11** as a colorless oil (13.7 mg, 73% for 3 steps).

Optical rotation: $[\alpha]_D^{25} = -190.0$ (c = 0.36, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ. 6.70 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 14.4 Hz, 1H), 5.86 – 5.76 (m, 1H), 5.24 – 5.16 (m, 2H), 4.66 (s, 1H), 3.89 (s, 3H), 3.16 – 3.14 (m, 2H), 3.11 – 2.97 (m, 3H), 2.60 – 2.54 (m, 2H), 2.42 – 2.33 (m, 1H), 2.32 – 2.26 (m, 1H), 2.13 (td, J = 12.0, 4.0 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.66 – 1.55 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 145.0, 143.0, 135.1, 129.4, 124.8, 119.4, 118.1, 114.8, 90.3, 70.2, 62.2, 57.6, 56.8, 50.7, 43.3, 36.1, 31.4, 30.5, 22.7.

IR (neat): 3386, 2925, 1725, 1607, 1503, 1440, 1276, 1112, 1047, 940.

HRMS (m/z): $[M + H]^+$ calculated for $C_{20}H_{24}NO_4^+$, 342.1700; found, 342.1700.

(2) Synthesis of (–)-naloxone (4)

Under argon, compound **S11** (10.0 mg, 0.0293 mmol, 1.0 equiv.) was dissolved in anhydrous $CHCl_3$ (0.5 mL), and a solution of BBr_3 (1 M in CH_2Cl_2, 176 μL，0.176 mmol，6.0 equiv.) in anhydrous $CHCl_3$ (0.5 mL) was dropwise added at 25 °C with stirring. After 4 hours, TLC indicated the complete consumption of compound **S11**. The reaction was poured into ice water, basified with ammonia solution (the pH = 10 was achieved) and diluted with brine. The resulting mixture was extracted with $CHCl_3$ (2 mL × 10). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified through silica gel chromatography (dichloromethane/methane = 20:1, v/v) to give the desired product (–)-naloxone (**4**) as a white solid (7.3 mg, 76%).

M.p.: 176–177 °C.

Optical rotation: $[\alpha]_D^{25} = -195.0$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.87 – 5.77

(m, 1H), 5.25 – 5.17 (m, 2H), 4.70 (s, 1H), 3.17 – 3.15 (m, 2H), 3.11 – 2.99 (m, 3H), 2.62 – 2.53 (m, 2H), 2.40 (td, *J* = 12.4, 5.2 Hz, 1H), 2.31 (dt, *J* = 14.4, 3.2 Hz, 1H), 2.17 (td, *J* = 12.0, 3.6 Hz, 1H), 1.87 (ddd, *J* = 13.6, 5.2, 2.8 Hz, 1H), 1.67–1.55 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 209.7, 143.5, 138.8, 135.1, 128.9, 124.2, 119.9, 118.1, 117.8, 90.5, 70.4, 62.2, 57.6, 50.9, 43.3, 36.1, 31.2, 30.5, 22.7.

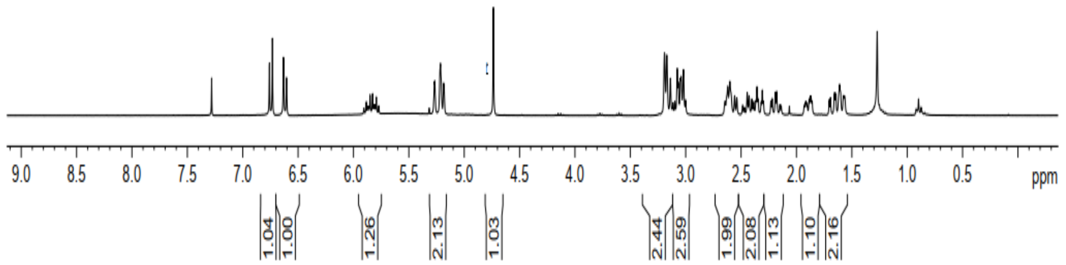
IR (neat): 3362, 2925, 1721, 1616, 1503, 1315, 1280, 1111, 1055, 940.

HRMS (m/z): [M + H]$^+$ calculated for $C_{19}H_{22}NO_4^+$, 328.1543; found, 328.1543.

Table S13 Comparison of ^{1}H NMR spectral data of (–)-naloxone

A: Hudlicky's report[5]	B: Our synthetic one	Erro (A-B)
δ (ppm, 300 MHz, CDCl$_3$)	δ (ppm, 400 MHz, CDCl$_3$)	$\Delta\delta$/*ppm*
6.75 (d, *J* = 7.8 Hz, 1H)	6.72 (d, *J* = 8.0 Hz, 1H)	0.03
6.63 (d, *J* = 7.8 Hz, 1H)	6.60 (d, *J* = 8.0 Hz, 1H)	0.03
5.84 (m, 1H)	5.87 – 5.77 (m, 1H)	–
5.22 (m, 2H)	5.25 – 5.17 (m, 2H)	–
4.73 (s, 1H)	4.70 (s, 1H)	0.03
3.19 (m, 2H)	3.17 – 3.15 (m, 2H)	–
3.15 (m, 1H)	3.11 – 2.99 (m, 3H)	–
3.04 (m, 2H)	overlapped	–
2.64 – 2.58 (m, 2H)	2.62 – 2.53 (m, 2H)	0.02
2.46 (ddd, *J* = 12.0, 6.0, 4.2 Hz,1H)	2.40 (td, *J* = 12.4 Hz, 5.2 Hz, 1H)	
2.33 (d, J = 11.4 Hz, 1H)	2.31 (dt, *J* = 14.4 Hz, 3.2 Hz, 1H)	0.02
2.19 (ddd, *J* = 12.0, 8.4, 3.6 Hz, 1H)	2.17 (td, *J* = 12.0 Hz, 3.6 Hz, 1H)	0.02
1.90 (d, *J* = 13.8 Hz, 1H)	1.87 (ddd, *J* = 13.6 Hz, 5.2 Hz, 2.8 Hz, 1H)	0.03
1.66 (td, *J* = 13.8, 3.0 Hz, 1H)	1.67–1.55 (m, 2H)	–
1.58(d, *J* = 13.2 Hz, 1H)	–	–

^{1}H NMR of Hudlicky's synthetic naloxone



^{1}H NMR of our synthetic naloxone

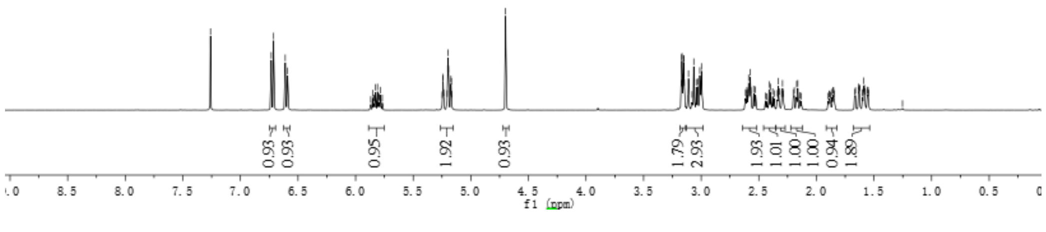
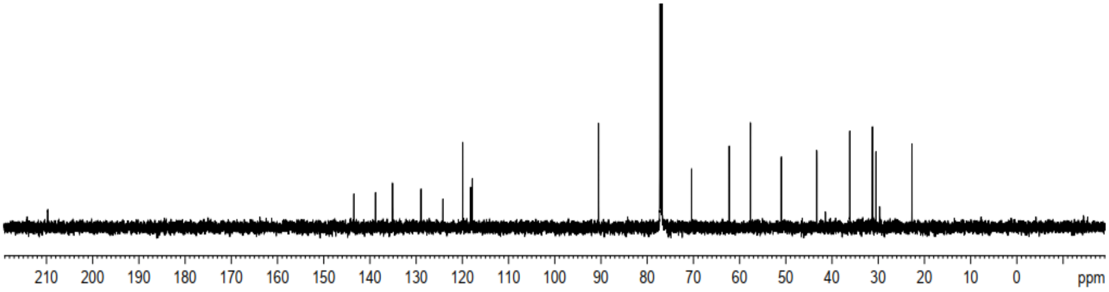


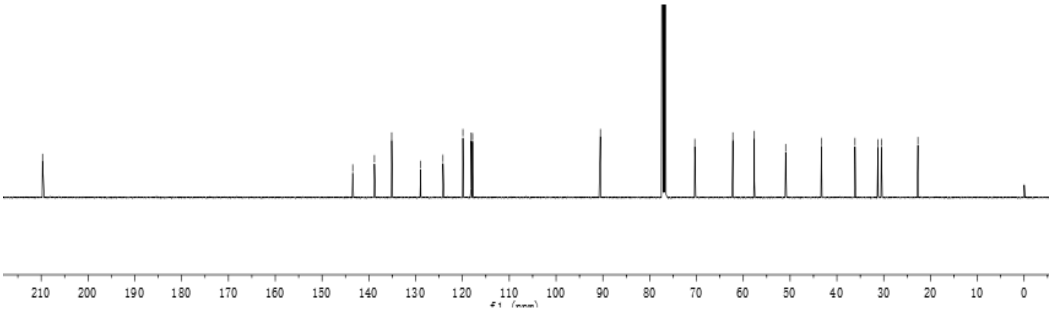
Table S14 Comparison of ^{13}C NMR spectral data of (–)-naloxone

A: Hudlicky's report[5]	B: Our synthetic one	Erro (A-B)
δ (ppm, 150 MHz, $CDCl_3$)	*δ* (ppm, 100 MHz, $CDCl_3$)	*Δδ/ppm*
209.7	209.7	0.0
143.5	143.5	0.0
138.8	138.8	0.0
135.1	135.1	0.0
129.0	128.9	0.1
124.2	124.2	0.0
119.9	119.9	0.0
118.2	118.1	0.1
117.9	117.8	0.1
90.6	90.5	0.1
70.4	70.4	0.0
62.3	62.2	0.1
57.7	57.6	0.1
51.0	50.9	0.1
43.3	43.3	0.0
36.2	36.1	0.1
31.3	31.2	0.1
30.5	30.5	0.0
22.7	22.7	0.0

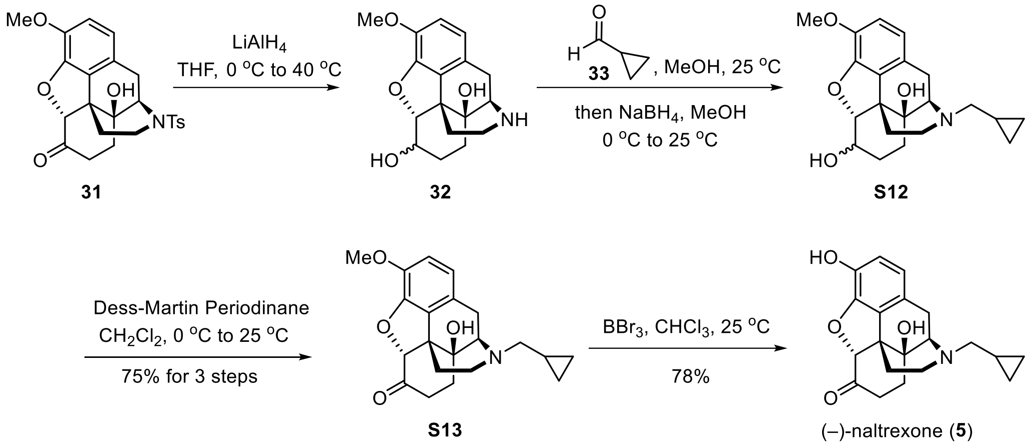
^{13}C NMR of Hudlicky's synthetic naloxone



^{13}C NMR of our synthetic naloxone



16. Synthesis of (–)-naltrexone (5)



(1) Synthesis of compound S13

Under argon, to a solution of compound **31** (25.0 mg, 0.0549 mmol, 1.0 equiv.) in anhydrous THF (2.0 mL) at 0 °C was slowly added $LiAlH_4$ (1 M in THF, 0.28 mL, 0.28 mmol, 5.0 equiv.). The reaction was then stirred at 40 °C for 24 hours, and TLC analysis indicated the complete consumption of the starting material **31**. The reaction was cooled to 0 °C and quenched with isopropanol (35 μL), followed by the sequential treatment with water (15 μL), 15% aqueous NaOH (15 μL) and water (45 μL). The resulting suspension was allowed to warm to 25 °C and stirred for additional 30 min. The mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2/MeOH (10:1, v/v, 1 mL × 5). The filtrate was concentrated *in vacuo* to give the crude compound **32**, which was directly used in the next step without purification.

To a solution of the above compound **32** in MeOH (2.0 mL) was added cyclopropanecarboxyldehyde **33** (17 μL, 0.22 mmol, 4.0 equiv.). The reaction was stirred for 2 hours at 25 °C. Then $NaBH_4$ (16.6 mg, 0.439 mmol, 8.0 equiv.) was added at 0 °C, and the reaction was warmed to 25 °C with stirring. After the TLC and LC-MS analysis showed the reaction was complete, saturated NH_4Cl solution was added. The resulting mixture was diluted with CH_2Cl_2 (2.0 mL) and 15% aqueous NaOH solution was added to adjust the pH = 10. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude compound **S12**, which was directly used in the next step without purification.

To a solution of the above compound **S12** in anhydrous CH_2Cl_2 (1.0 mL) was added Dess-Martin Periodinane (46.7 mg, 0.110 mmol, 2.0 equiv.) at 0 °C. Then the reaction was warmed to 25 ºC with stirring. After the TLC analysis showed the reaction was complete, it was cooled to 0 ºC, followed by the sequential addition of saturated $Na_2S_2O_3$ solution and $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified through silica gel chromatography (dichloromethane/methane = 50:1, v/v) to give the desired product **S13** as a white solid (14.6 mg, 75% yield for 3 steps).

Optical rotation: $[\alpha]_D^{25} = -202$ ($c = 0.6$, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.69 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.21 (brs, 1H), 4.67 (s, 1H), 3.89 (s, 3H), 3.17 (d, J = 5.4 Hz, 1H), 3.07 – 3.00 (m, 2H), 2.69 (dd, J = 12.6, 5.4 Hz, 1H), 2.58 (dd, J = 18.0, 6.0 Hz, 1H), 2.44 – 2.39 (m, 3H), 2.30 (dt, J = 14.4, 3.0 Hz, 1H), 2.13 (td, J = 12.0, 3.6 Hz, 1H), 1.89 – 1.86 (m, 1H), 1.66 – 1.56 (m, 2H), 0.88 – 0.85 (m, 1H), 0.56 – 0.54 (m, 2H), 0.15 – 0.14 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 208.6, 145.0, 142.9, 129.5, 124.9, 119.3, 114.8, 90.4, 70.1, 62.0, 59.2, 56.8, 50.8, 43.6, 36.2, 31.5, 30.7, 22.6, 9.4, 3.9, 3.8.

IR (neat): 3381, 2928, 1726, 1502, 1439, 1278, 1258, 1048, 941, 799, 748.

HRMS (m/z): $[M + H]^+$ calculated for $C_{21}H_{28}NO_4^+$, 356.1856; found, 356.1857.

(2) Synthesis of (–)-naltrexone (5)

Under argon, compound **S13** (10.0 mg, 0.0281 mmol, 1.0 equiv.) was dissolved in anhydrous $CHCl_3$ (0.6 mL), and a solution of BBr_3 (1 M in CH_2Cl_2, 169 μL, 0.169 mmol, 6.0 equiv.) in anhydrous $CHCl_3$ (0.4 mL) was dropwise added at 25 ºC with stirring. After 4 hours, TLC indicated the complete consumption of compound **S13**. The reaction was poured into ice water, basified with ammonia solution (pH = 10 was achieved) and diluted with brine. The resulting mixture was extracted with $CHCl_3$ (2 mL × 10). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified through silica gel chromatography (dichloromethane/methane = 40:1, v/v) to give (–)-naltrexone (**5**) as a white solid (7.5 mg, 78%).

M.p.: 160–162 ºC.

Optical rotation: $[\alpha]_D^{25}$ = –206 (*c* = 0.18, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): *δ* 6.71 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 4.72 (s, 1H), 3.18 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.02 (m, 2H), 2.69 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.55 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.44 – 2.37 (m, 3H), 2.43 – 2.30 (m, 1H), 2.16 (td, *J* = 12.0, 3.6 Hz, 1H), 1.89 (d, *J* = 13.2 Hz, 1H), 1.67 – 1.62 (m, 1H), 1.56 (d, *J* = 13.2 Hz, 1H), 0.88 – 0.84 (m, 1H), 0.55 – 0.54 (m, 2H), 0.15 – 0.14 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): *δ* 209.8, 143.4, 138.7, 129.0, 124.3, 119.9, 117.8, 90.6, 70.3, 62.1, 59.2, 51.0, 43.6, 36.2, 31.3, 30.7, 22.6, 9.4, 4.0, 3.8.

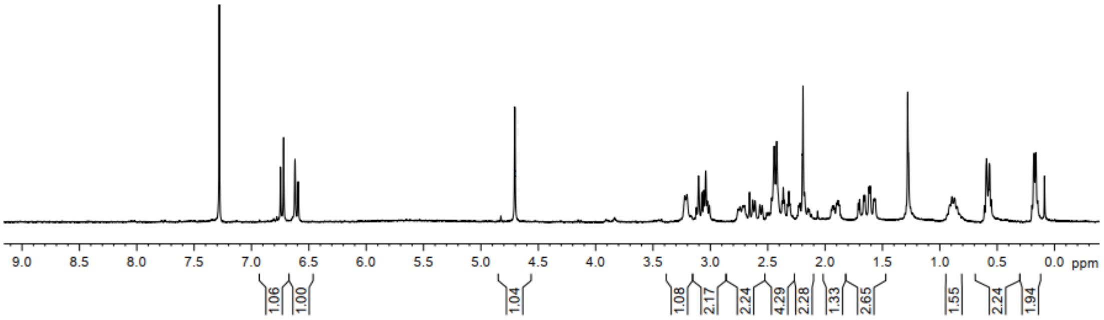
IR (neat): 3356, 2924, 1724, 1455, 1259, 1015, 796, 757.

HRMS (m/z): $[M + H]^+$ calculated for $C_{20}H_{24}NO_4^+$, 342.1700; found, 342.1702.

Table S15 Comparison of ^{1}H NMR spectral data of (–)-naltrexone

A: Hudlicky's report[5]	B: Our synthetic one	Erro (A-B)
δ (ppm, 300 MHz, $CDCl_3$)	*δ* (ppm, 600 MHz, $CDCl_3$)	*Δδ/ppm*
6.74 (d, *J* = 8.1 Hz, 1H)	6.71 (d, *J* = 8.4 Hz, 1H)	0.03
6.60 (d, *J* = 8.1 Hz, 1H)	6.57 (d, *J* = 8.4 Hz, 1H)	0.03
5.82 (brs, 1H)	–	–
4.74 (s, 1H)	4.72 (s, 1H)	0.02
3.21 (d, *J* = 5.9 Hz, 1H)	3.18 (d, *J* = 6.0 Hz, 1H)	0.03
3.11 – 3.03 (m, 2H)	3.09 – 3.02 (m, 2H)	0.02
2.72 (m, 1H)	2.69 (dd, *J* = 12.0, 4.8 Hz, 1H)	0.03
2.58 (m, 1H)	2.55 (dd, *J* = 18.0, 6.0 Hz, 1H)	0.03
2.49 – 2.39 (m, 3H)	2.44 – 2.37 (m, 3H)	–
2.34 (m, 1H)	2.43 – 2.30 (m, 1H)	–
2.18 (m, 1H)	2.16 (td, *J* = 12.0, 3.6 Hz, 1H)	0.02
1.91 (m, 1H)	1.89 (d, *J* = 13.2 Hz, 1H)	0.02
1.66 (m, 1H)	1.67 – 1.62 (m, 1H)	–
1.59 (m, 1H)	1.56 (d, *J* = 13.2 Hz, 1H)	0.03
0.88 (m, 1H)	0.88 – 0.84 (m, 1H)	–
0.57 (m, 2H)	0.55 – 0.54 (m, 2H)	–
0.16 (m, 2H)	0.15 – 0.14 (m, 2H)	–

^{1}H NMR of Hudlicky's synthetic naltrexone



^{1}H NMR of our synthetic naltrexone

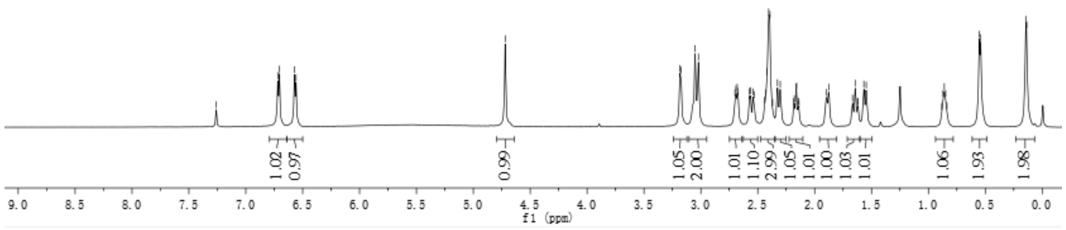
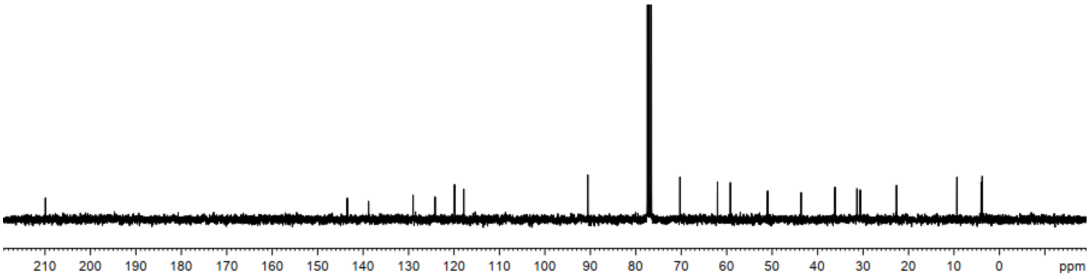


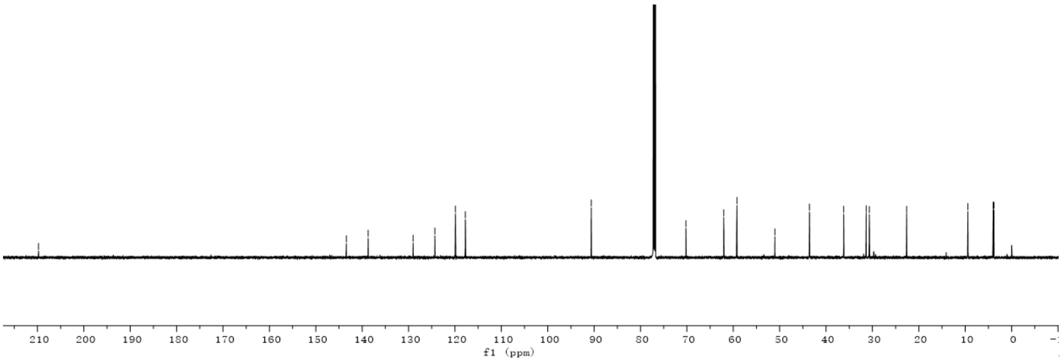
Table S16 Comparison of ^{13}C NMR spectral data of (–)-naltrexone

A: Hudlicky's report[5]	B: Our synthetic one	Erro (A-B)
δ (ppm, 150 MHz, CDCl$_3$)	δ (ppm, 150 MHz, CDCl$_3$)	$\Delta\delta/ppm$
210.0	209.8	0.2
142.5	143.4	–0.9
138.8	138.7	0.1
129.1	129.0	0.1
124.3	124.3	0.0
119.9	119.9	0.0
117.9	117.8	0.1
90.6	90.6	0.0
70.3	70.3	0.0
62.0	62.1	–0.1
59.2	59.2	0.0
51.1	51.0	0.1
43.6	43.6	0.0
36.2	36.2	0.0
31.4	31.3	0.1
30.7	30.7	0.0
22.6	22.6	0.0
9.4	9.4	0.0
4.0	4.0	0.0
3.8	3.8	0.0

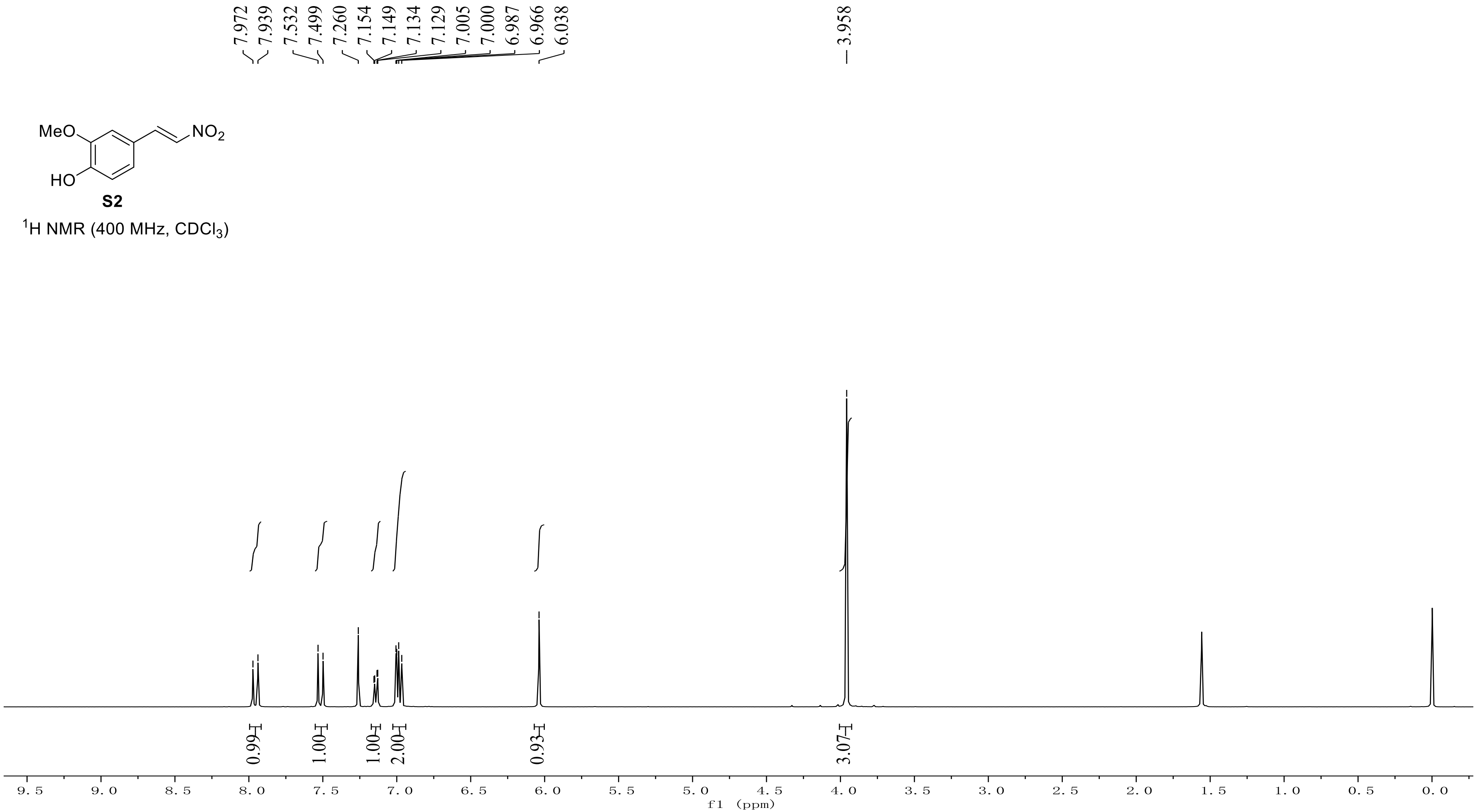
^{13}C NMR of Hudlicky's synthetic naltrexone



^{13}C NMR of our synthetic naltrexone



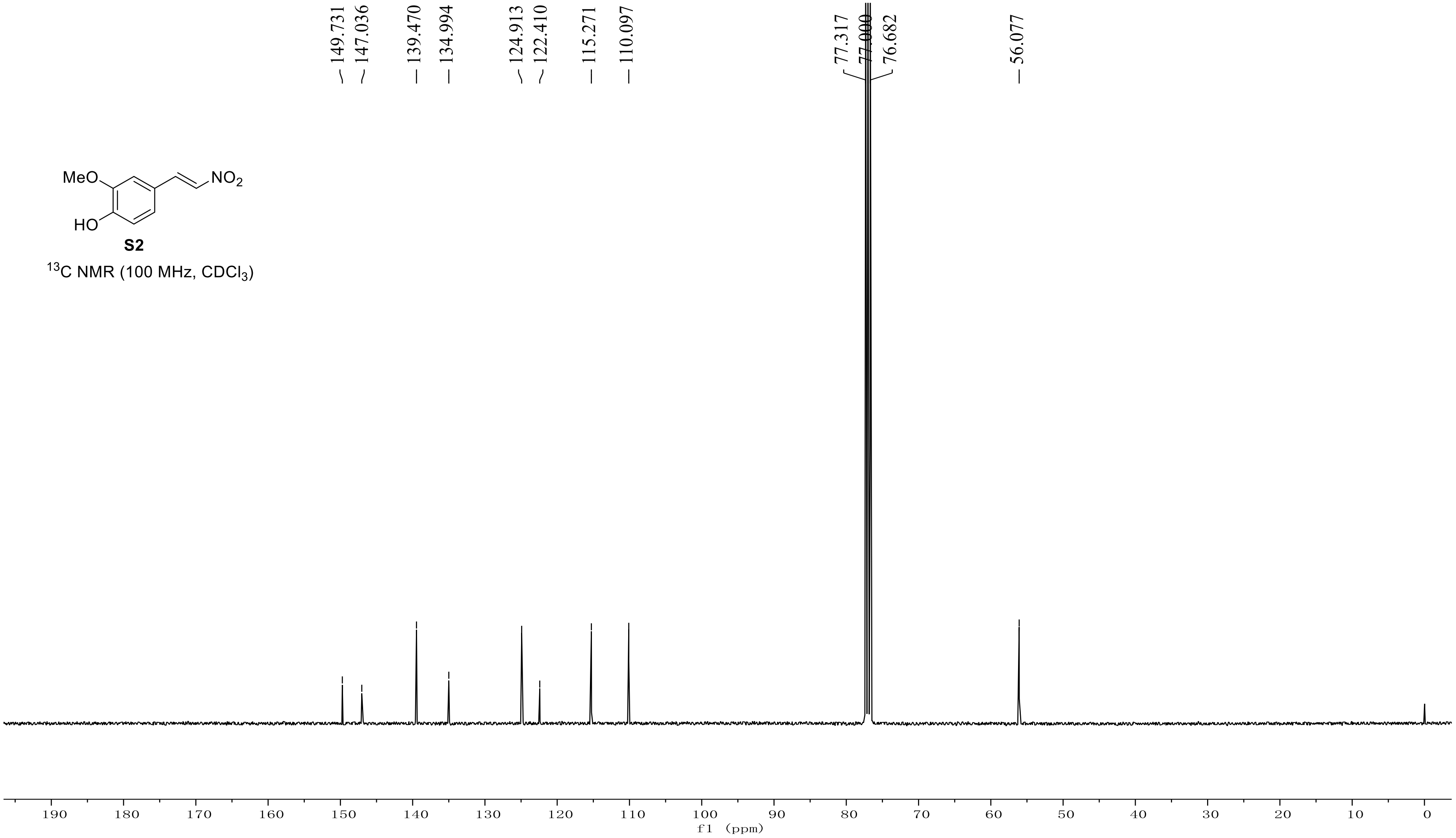
III. NMR Spectra

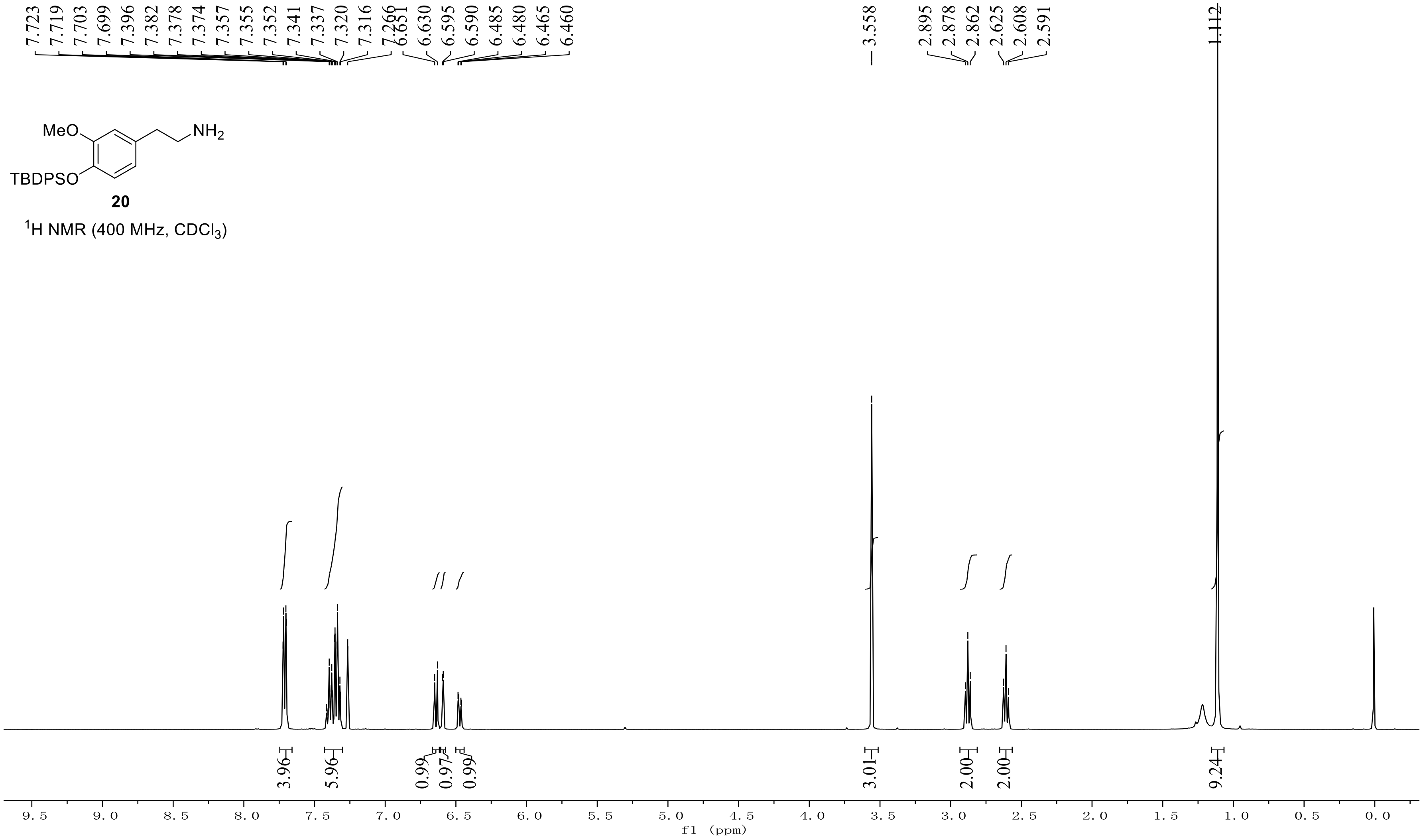

S2

^1H NMR (400 MHz, $CDCl_3$)

S2

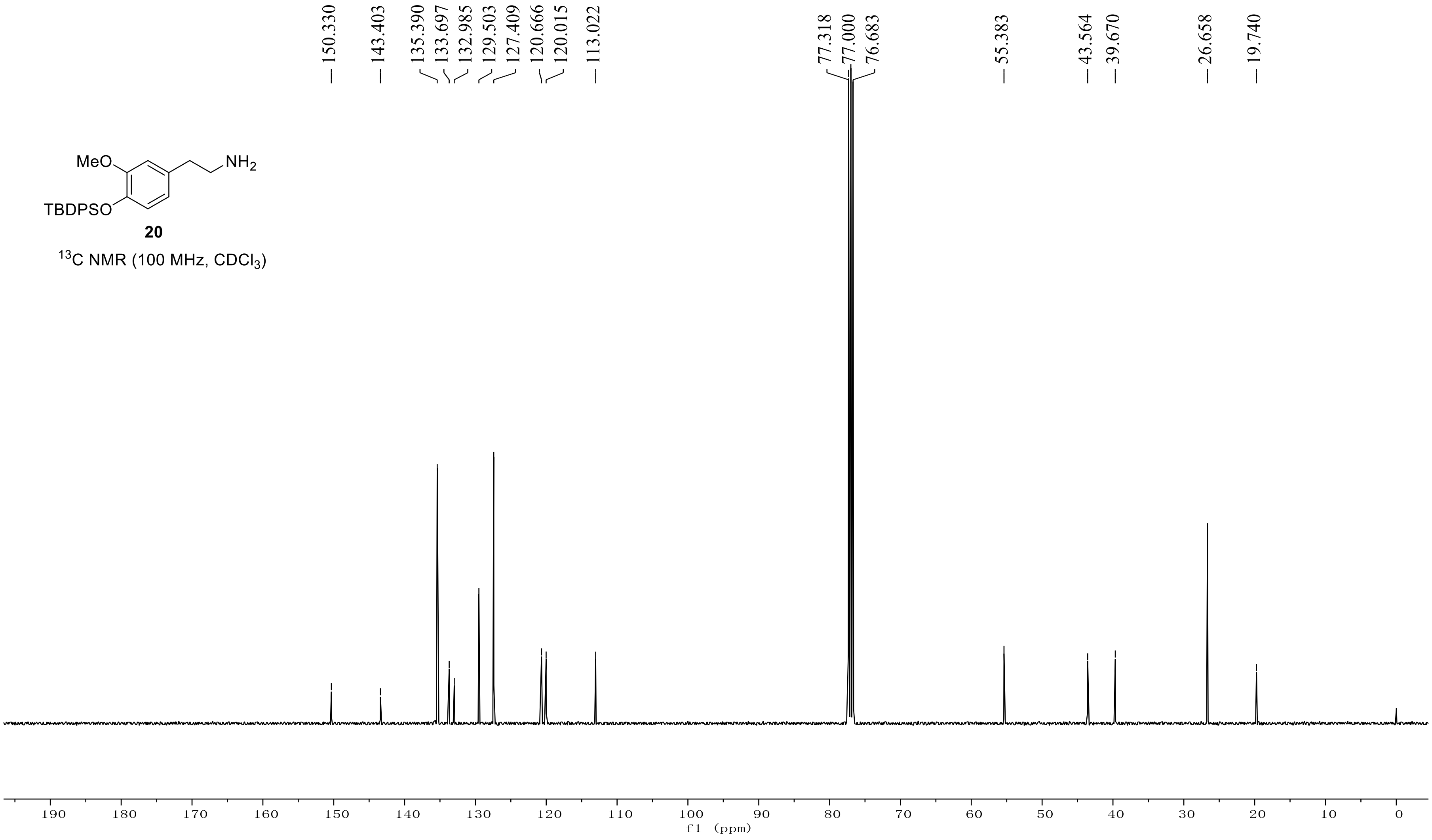
^{13}C NMR (100 MHz, CDCl$_3$)





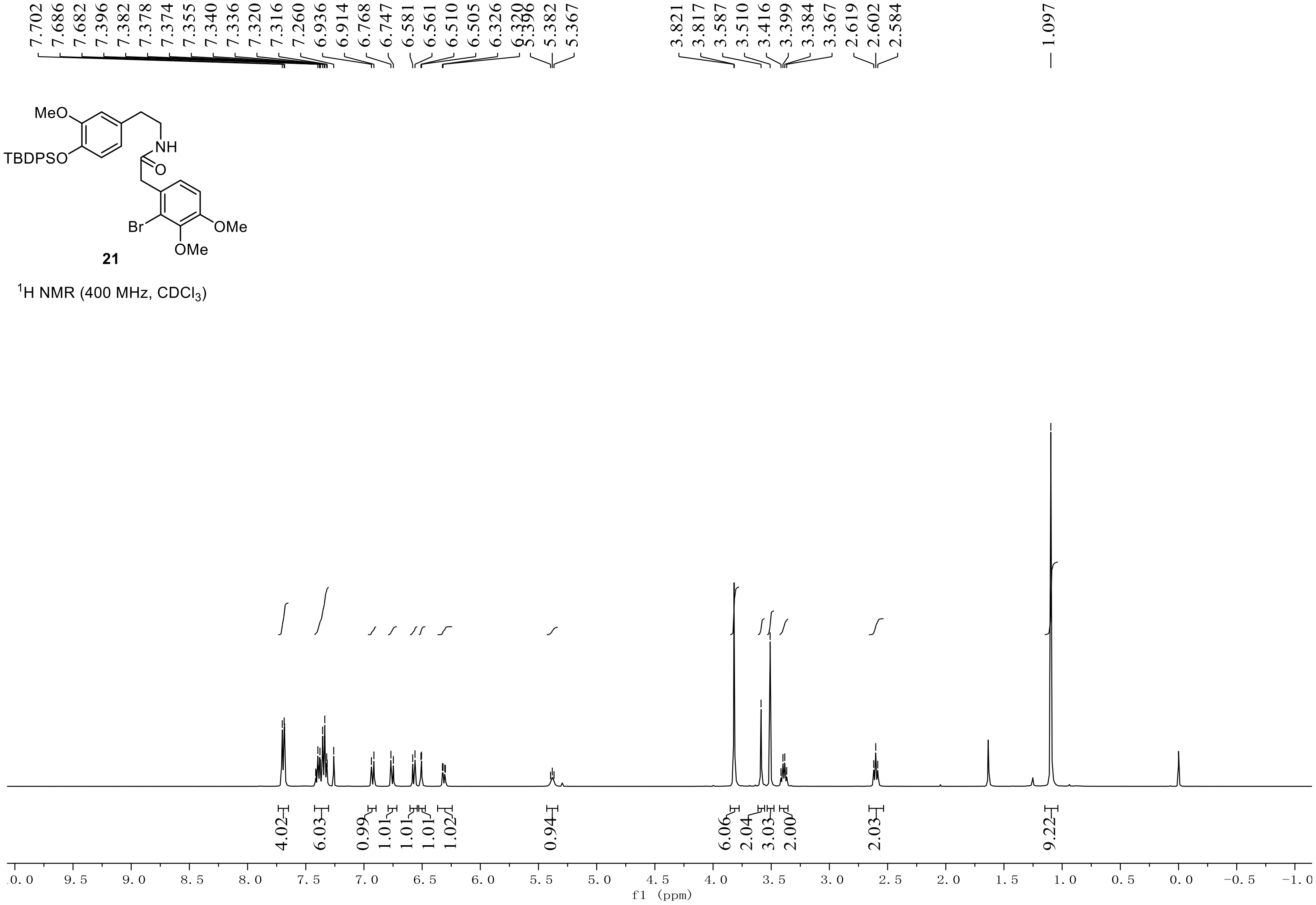
20

^{1}H NMR (400 MHz, $CDCl_3$)



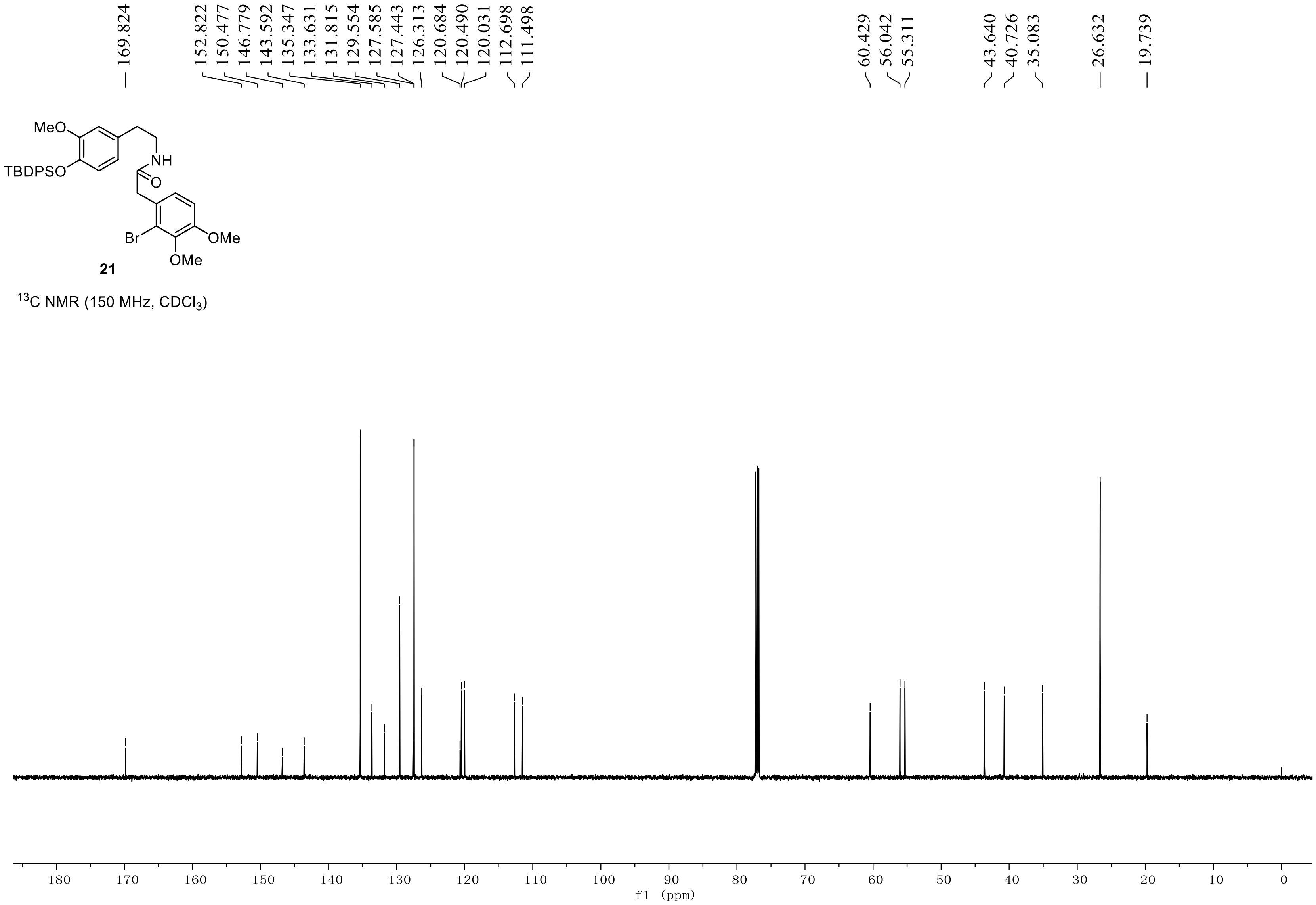
20

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



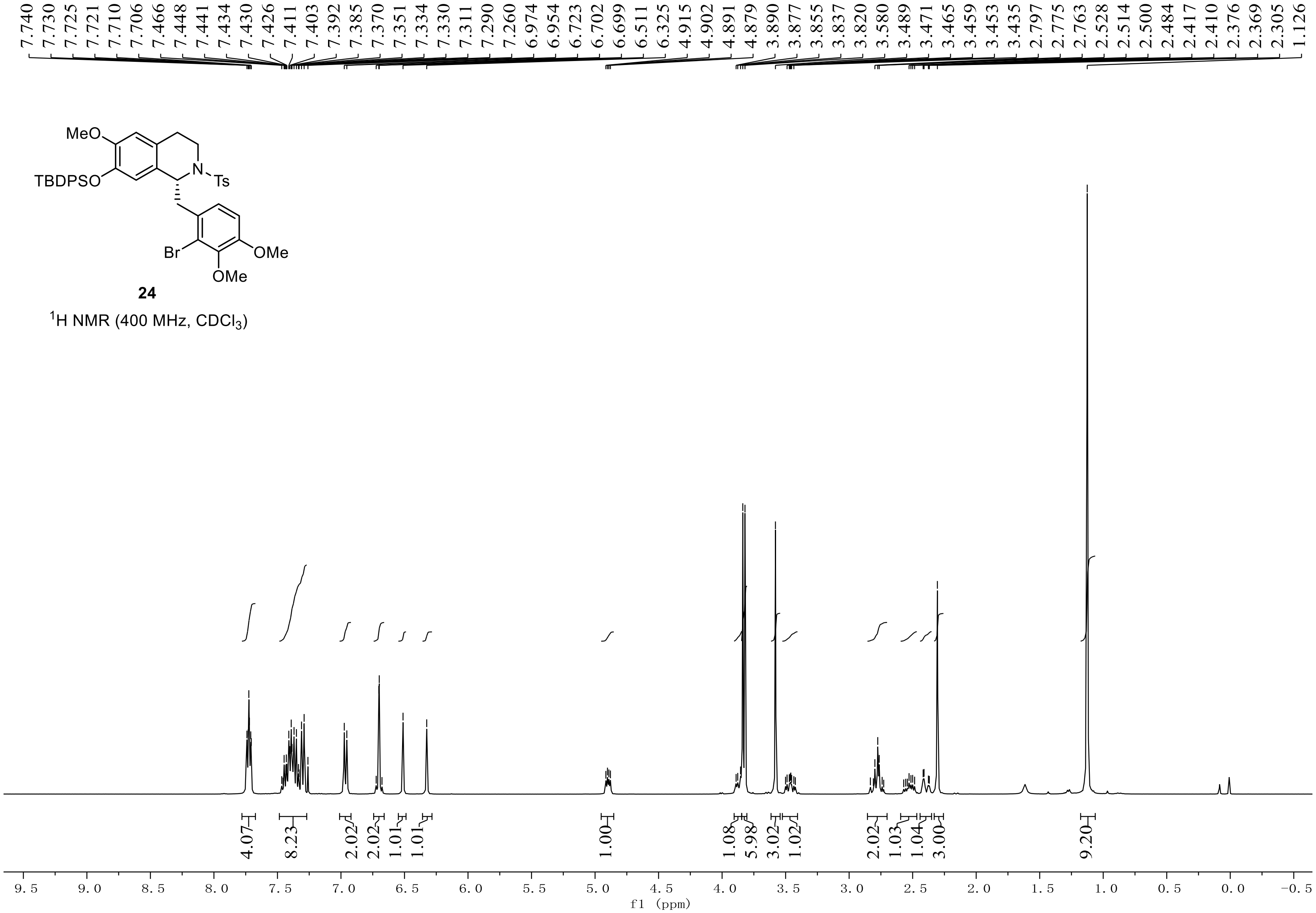
21

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



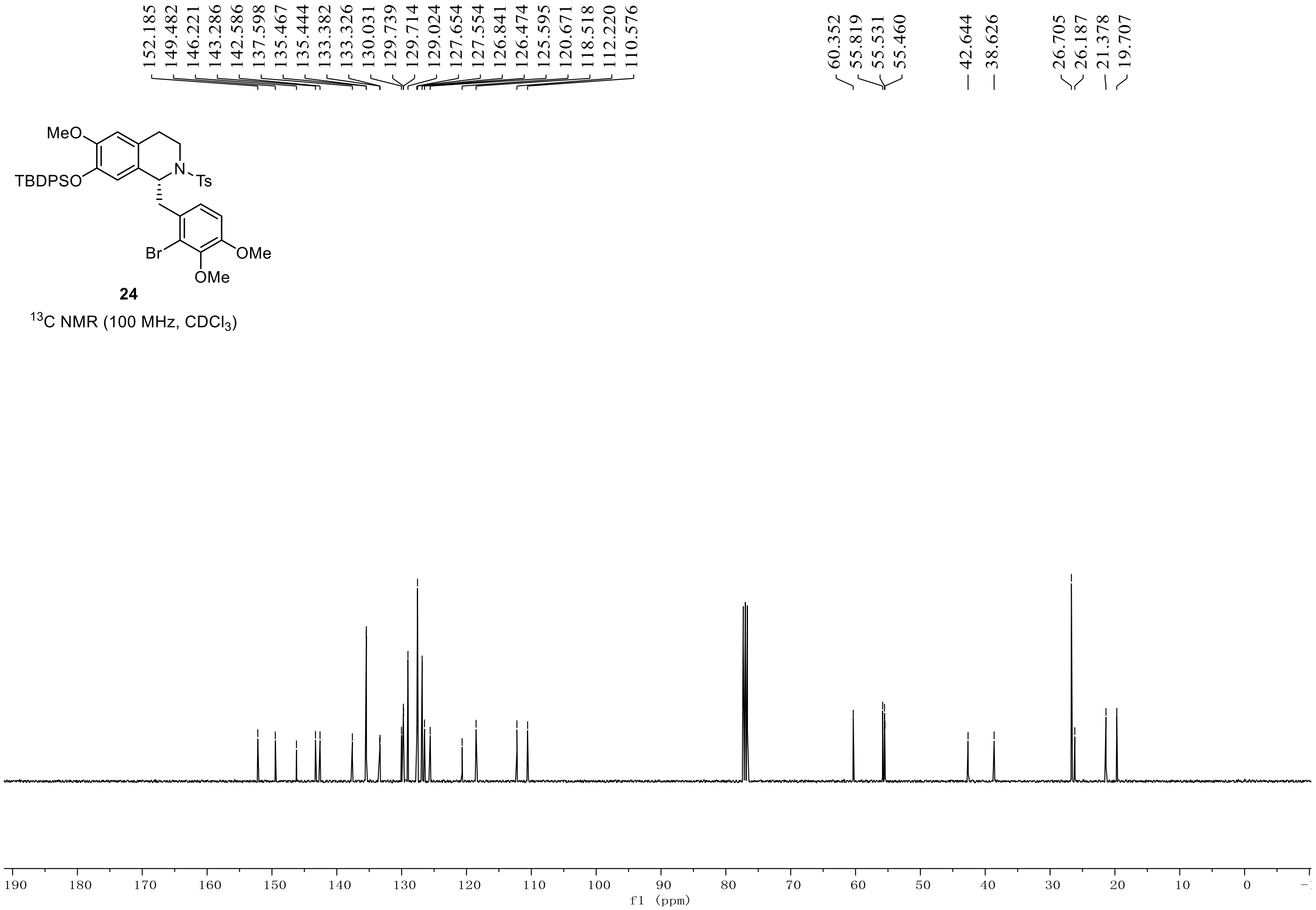
21

^{13}C NMR (150 MHz, CDCl$_3$)



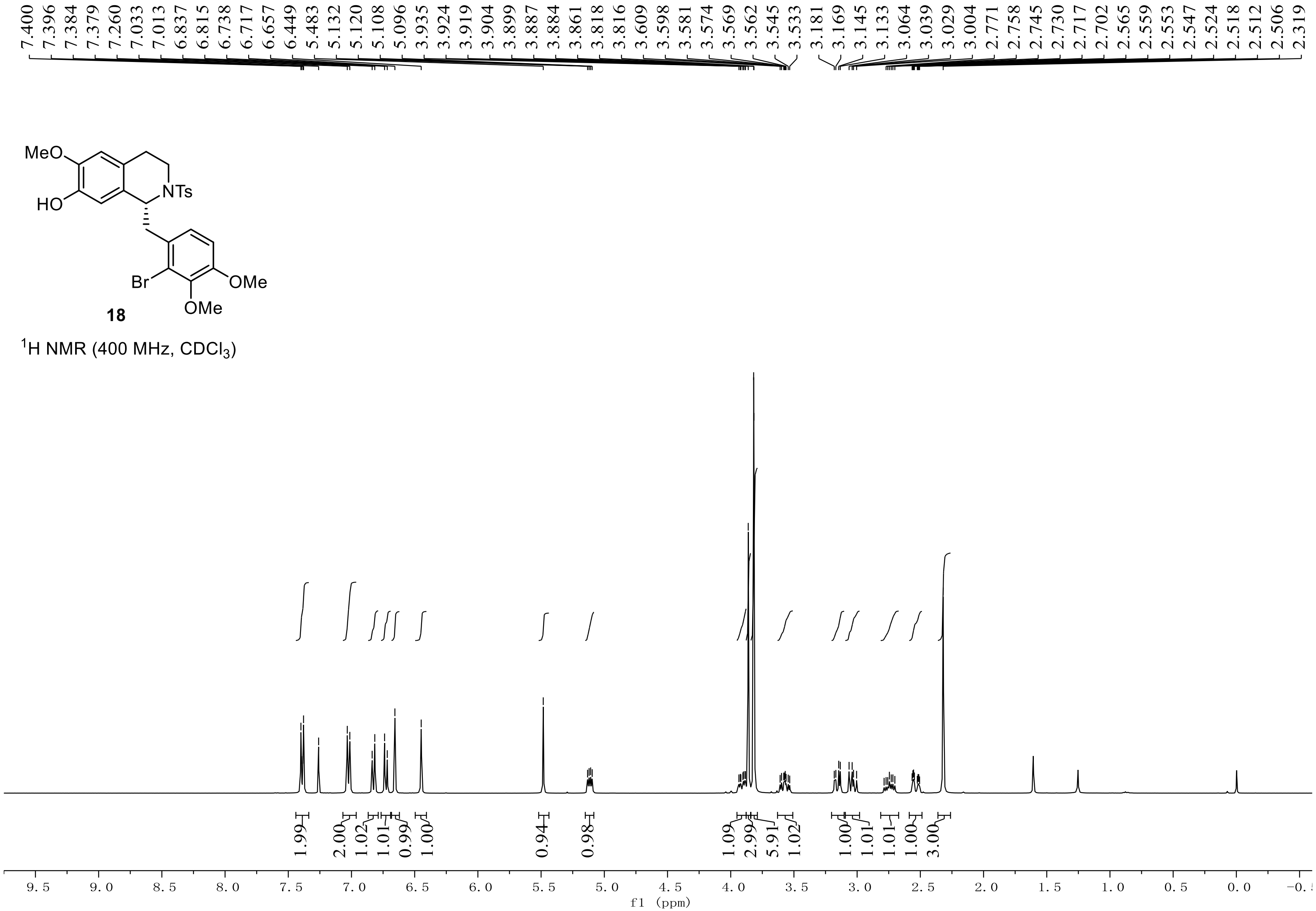
24

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



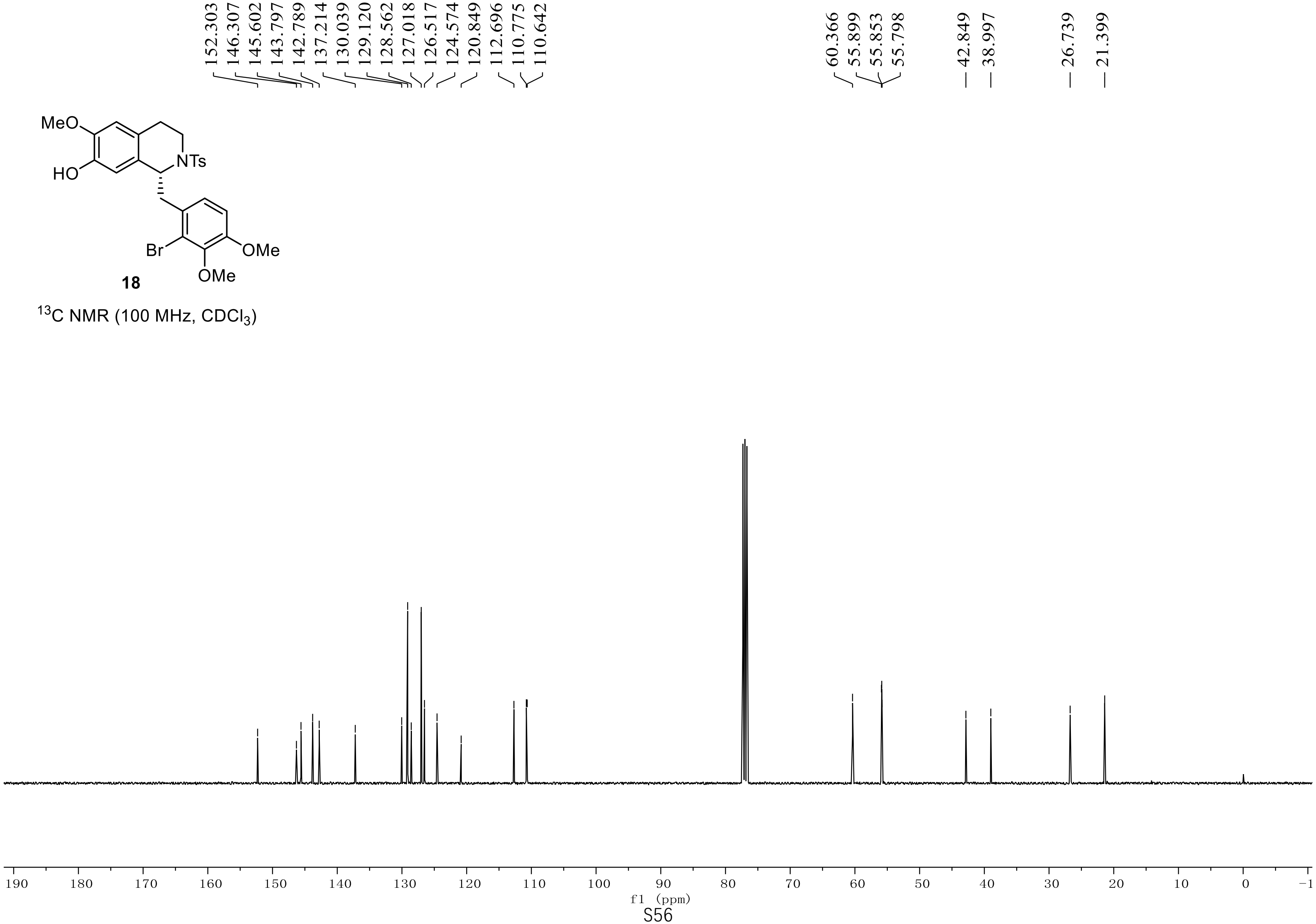
24

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



18

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

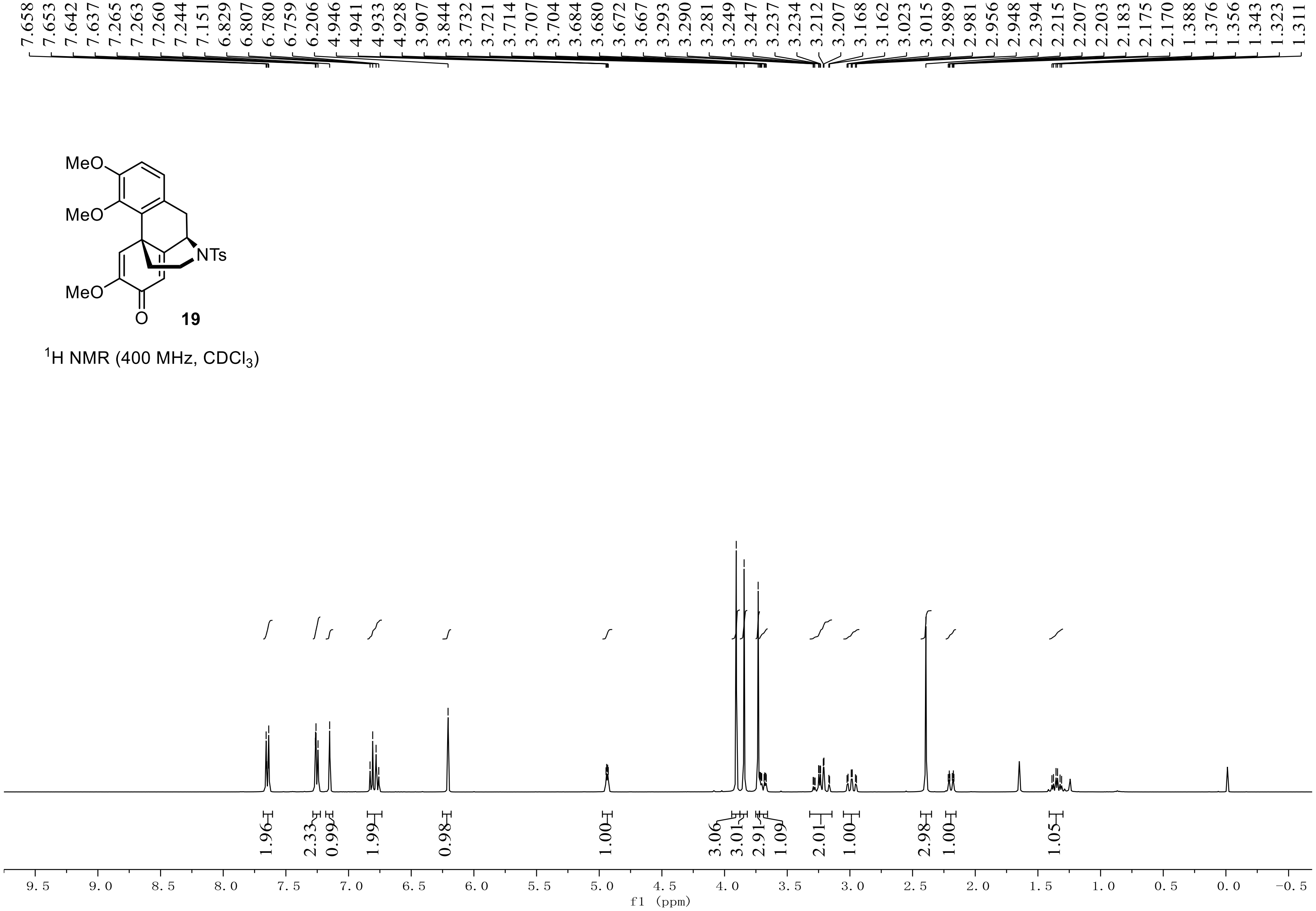


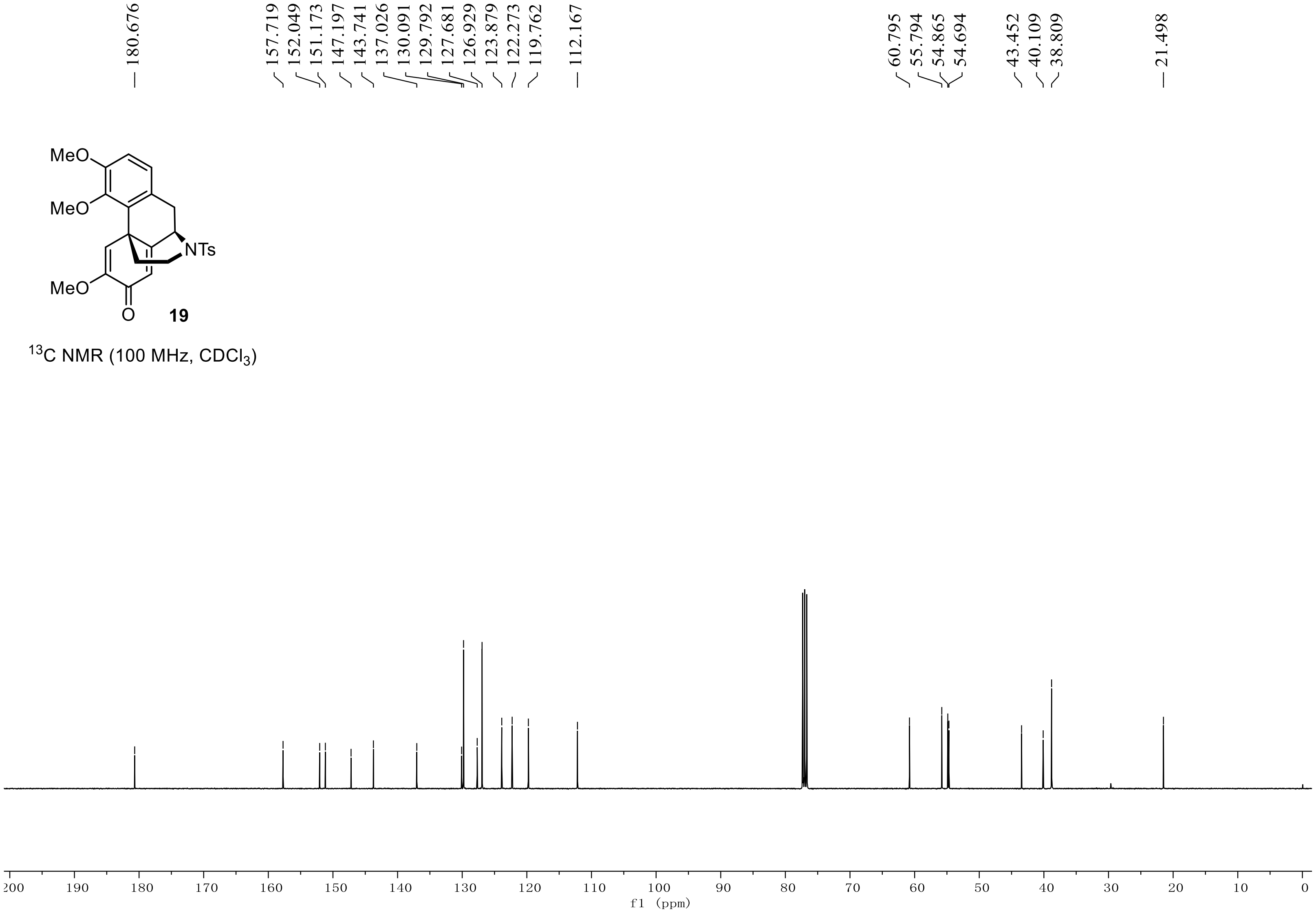
18

^{13}C NMR (100 MHz, $CDCl_3$)

19

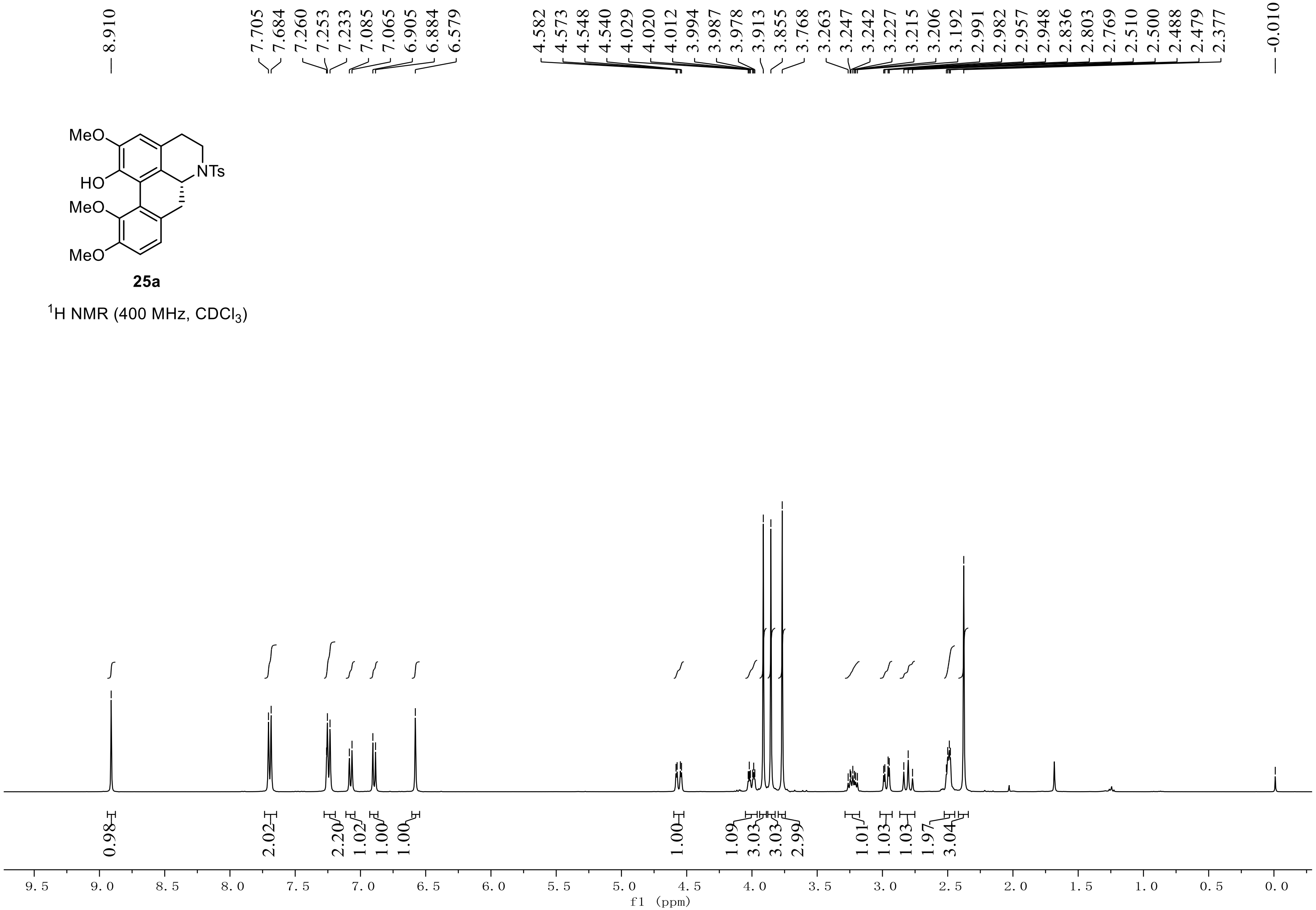
^{1}H NMR (400 MHz, CDCl$_3$)





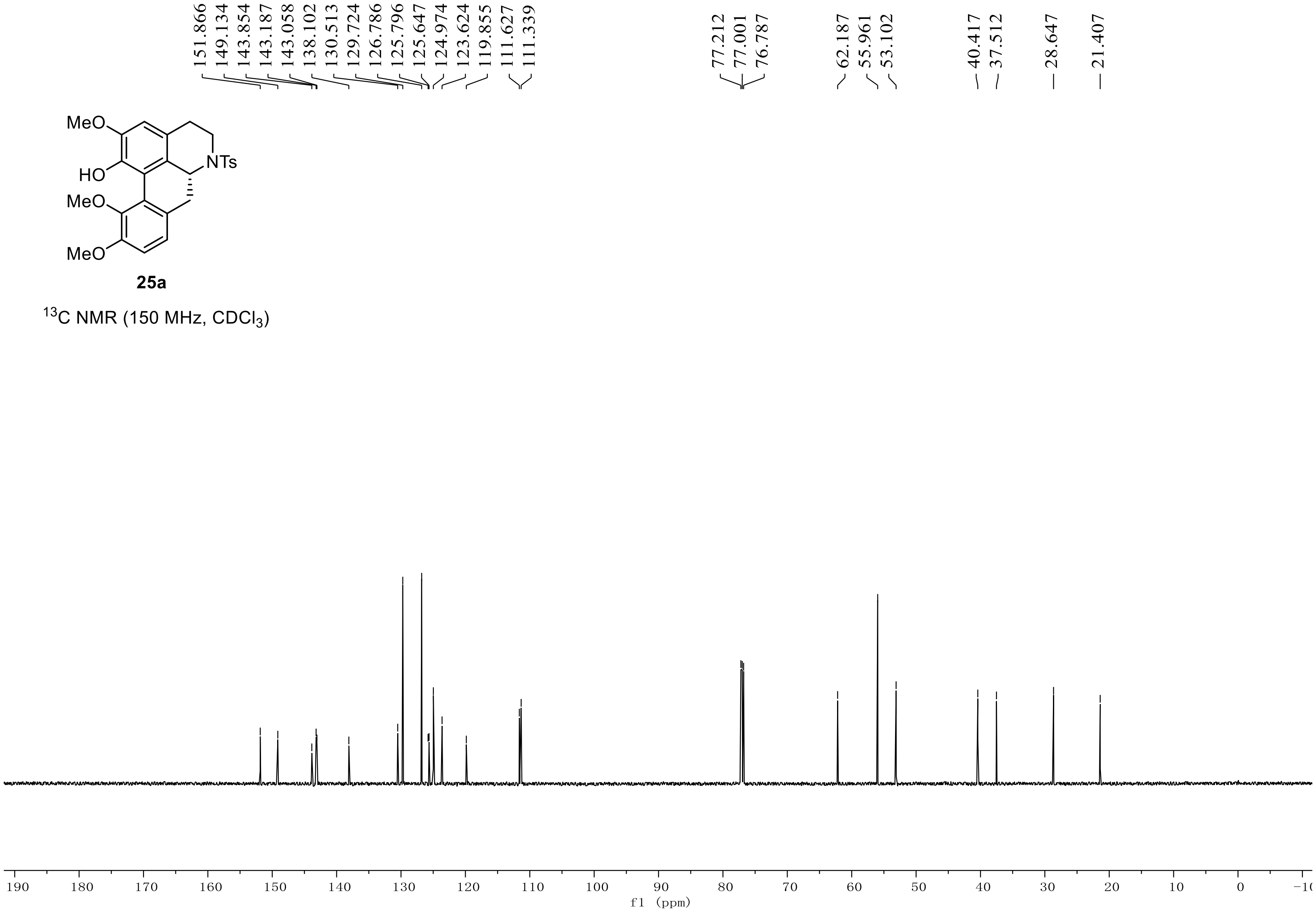
19

^{13}C NMR (100 MHz, $CDCl_3$)



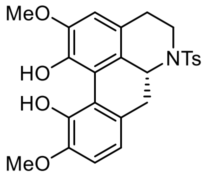
25a

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



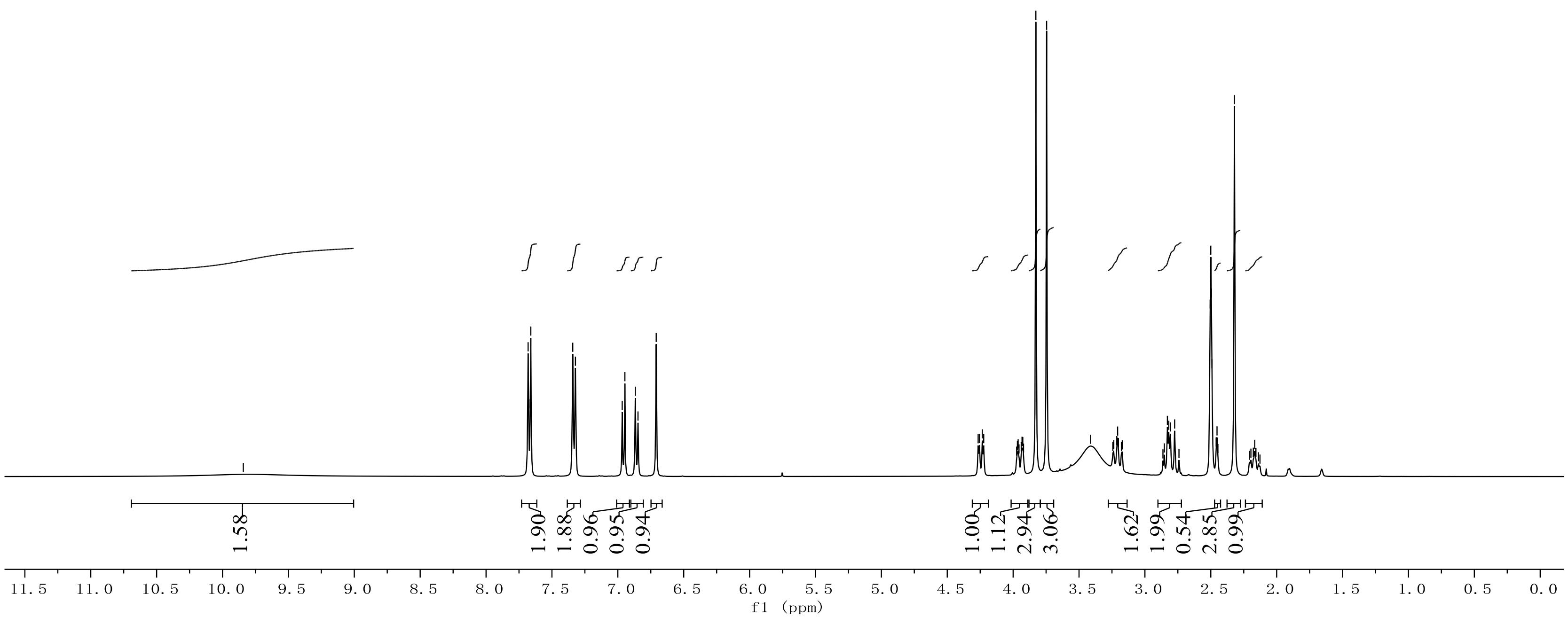
25a

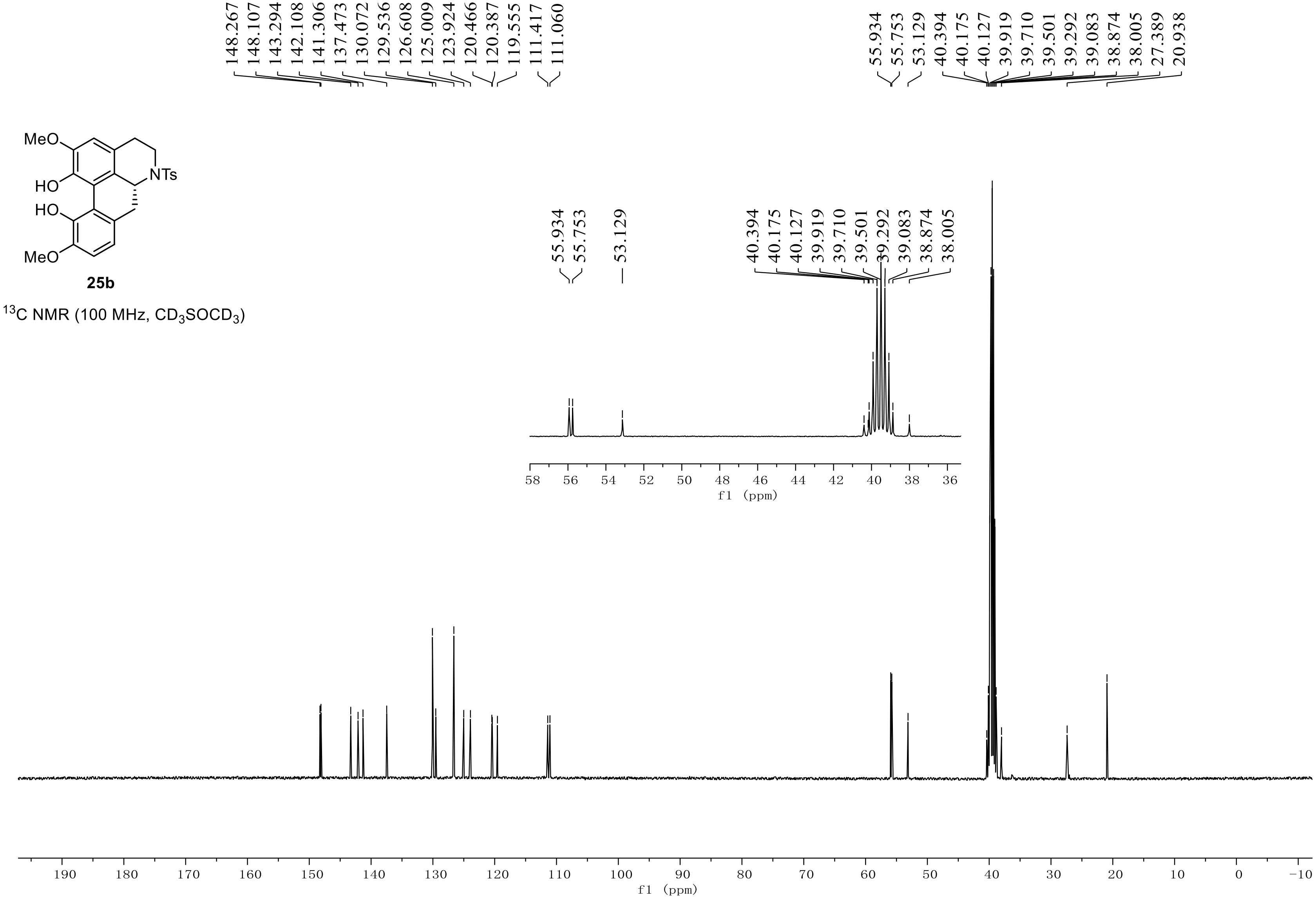
^{13}C NMR (150 MHz, CDCl$_3$)



25b

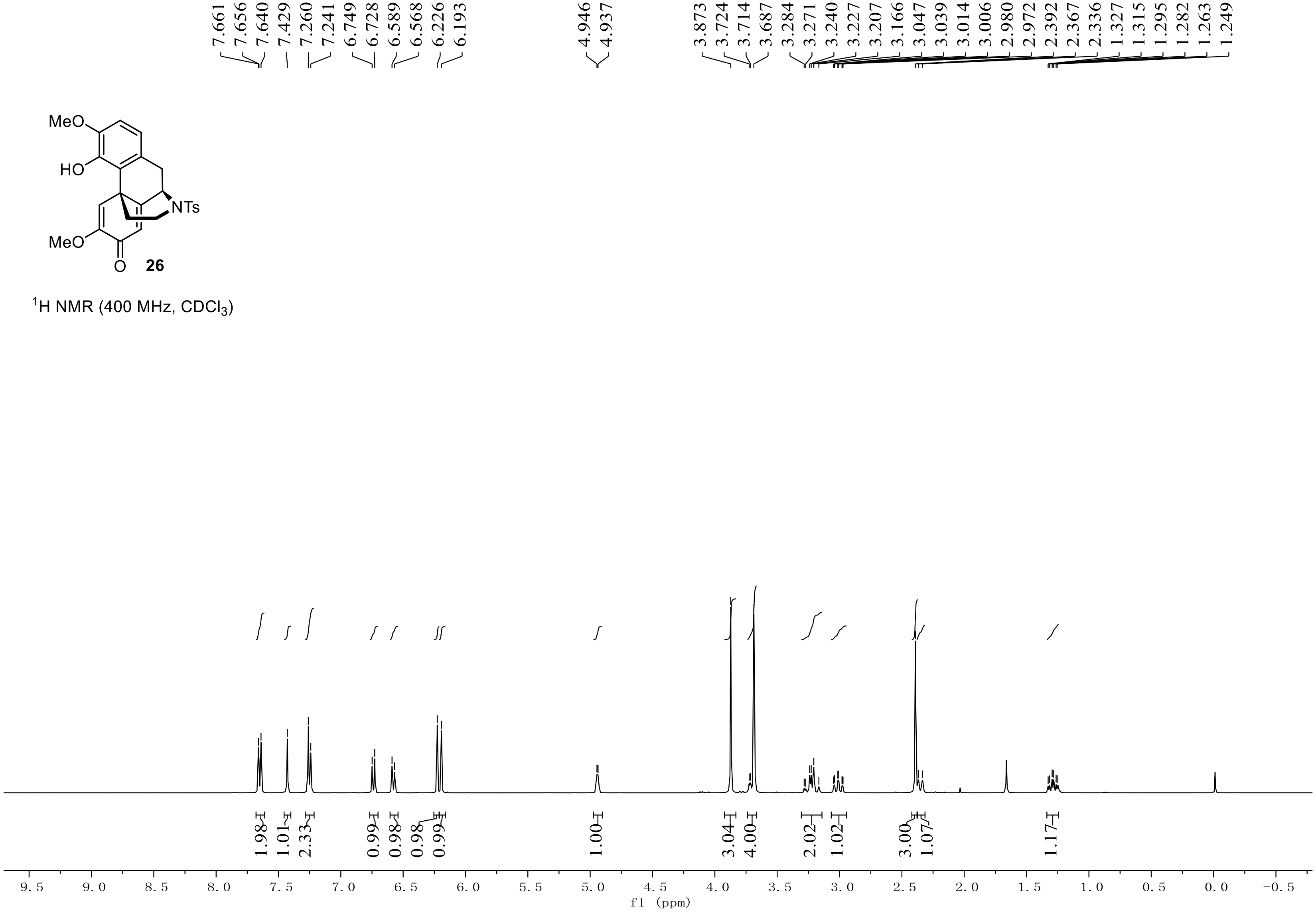
^{1}H NMR (400 MHz, CD_3SOCD_3)





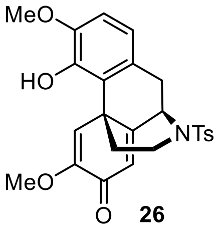
25b

^{13}C NMR (100 MHz, CD_3SOCD_3)



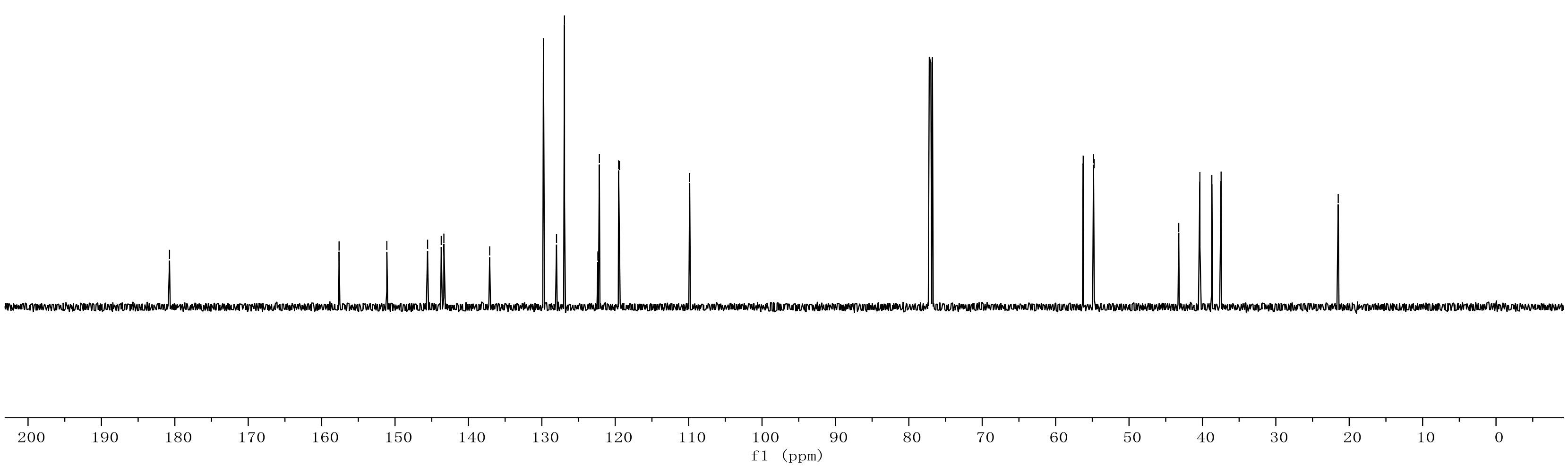
26

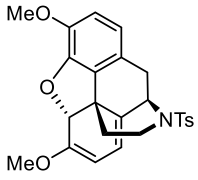
^{1}H NMR (400 MHz, CDCl$_3$)



26

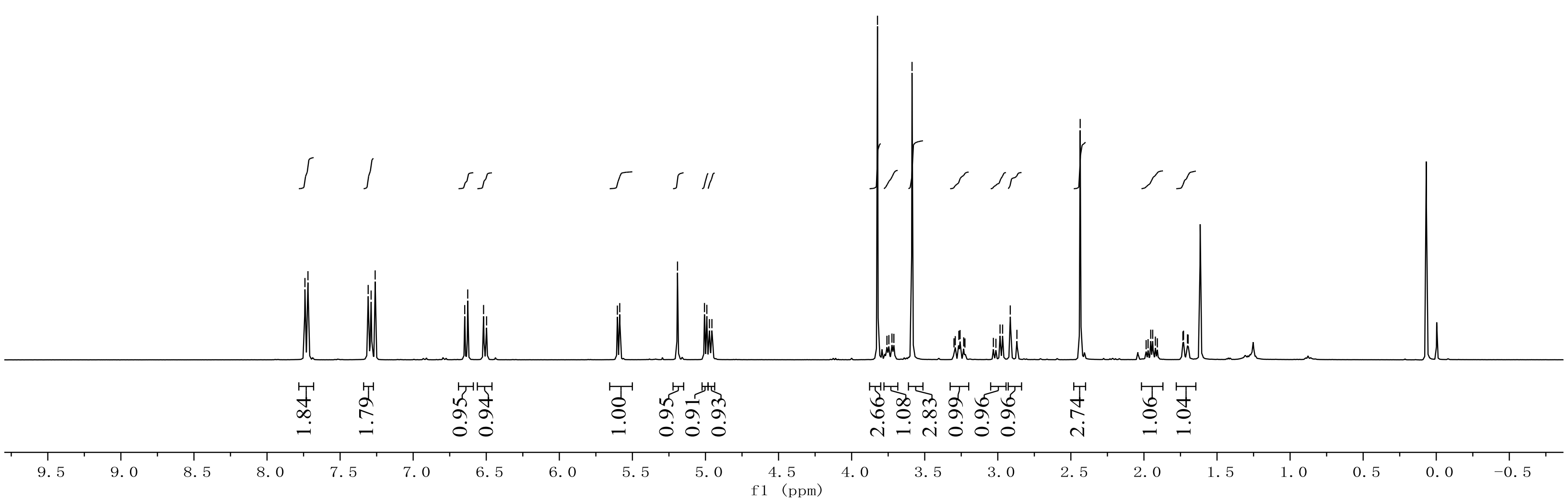
^{13}C NMR (150 MHz, CDCl$_3$)

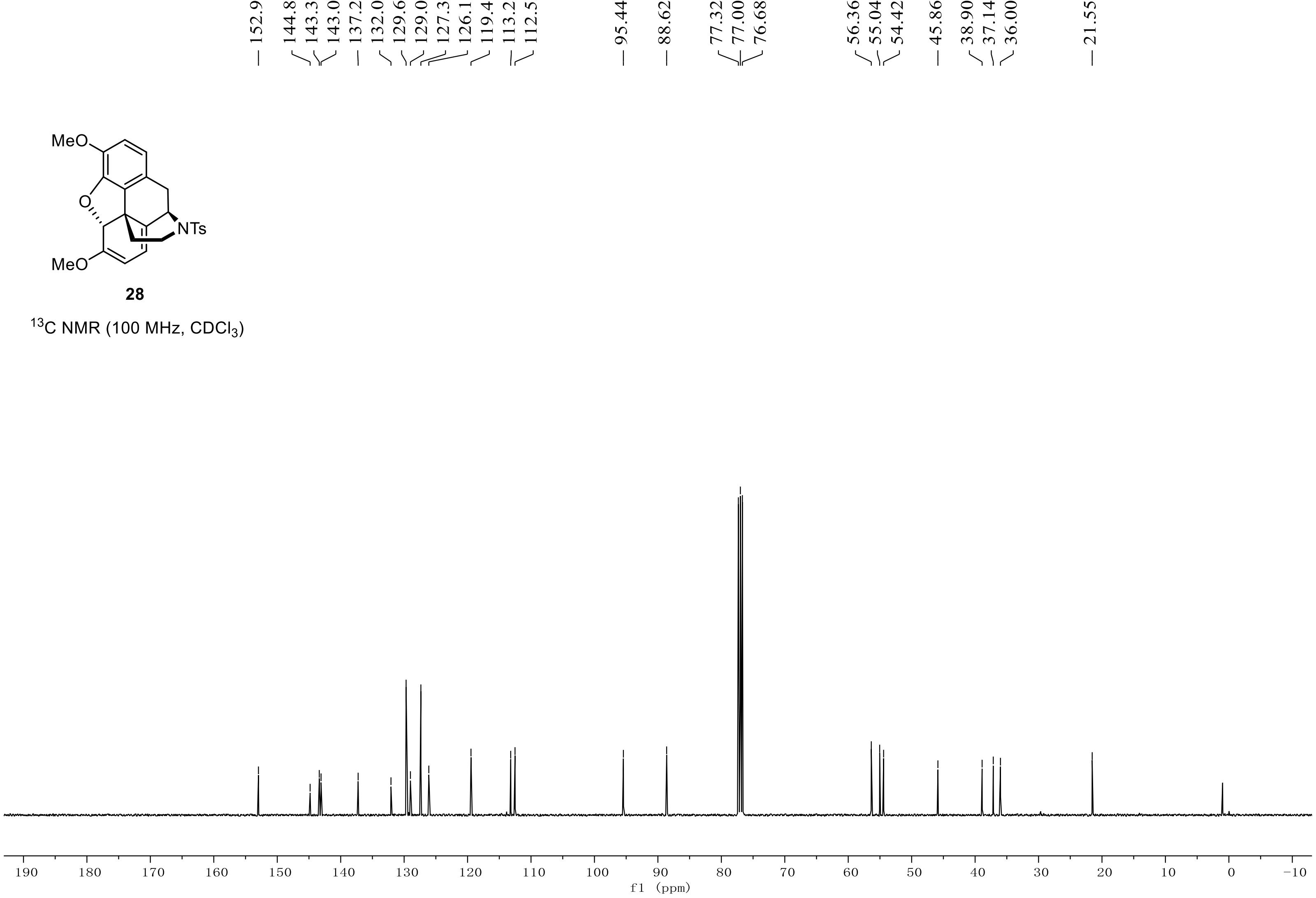




28

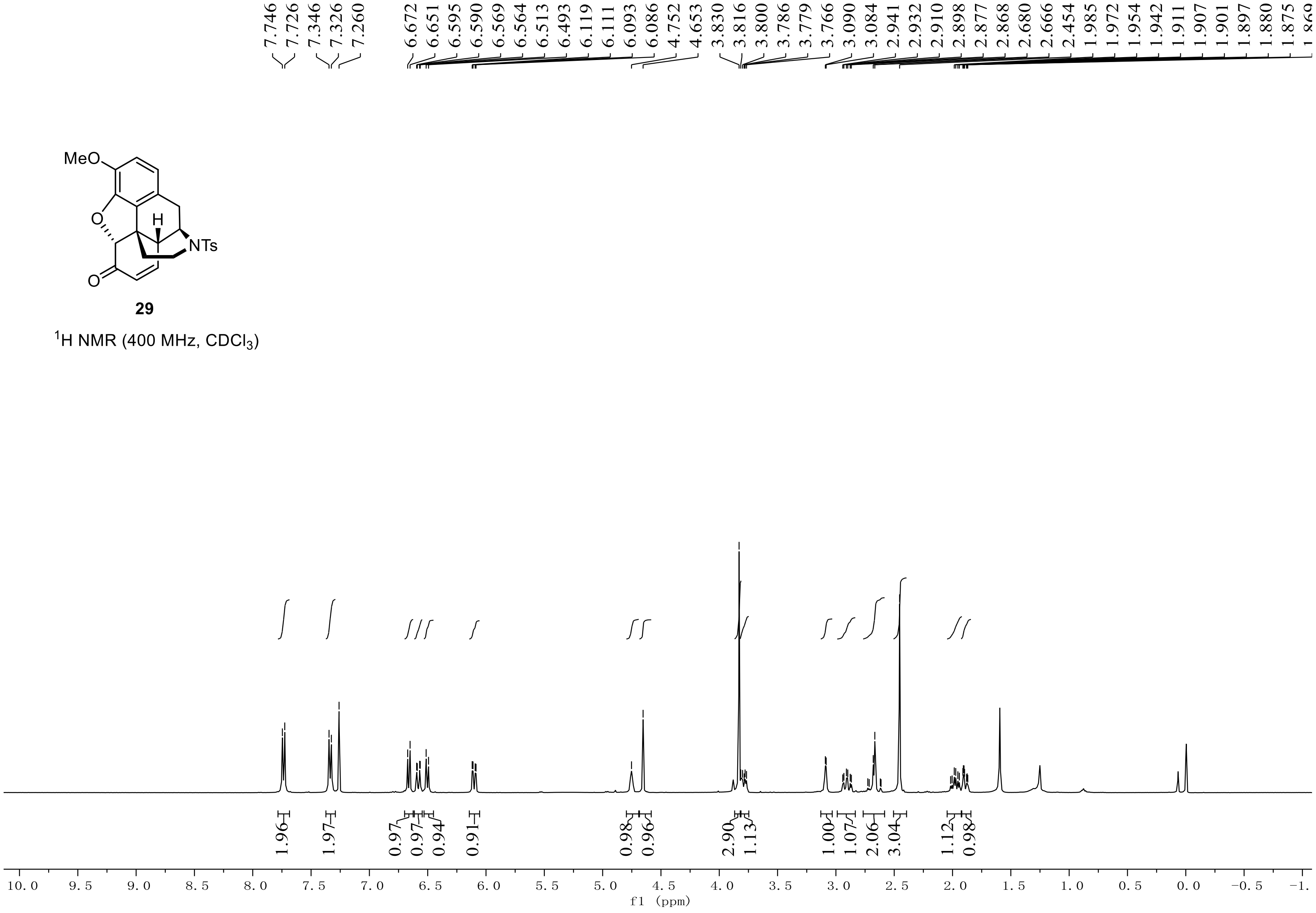
^{1}H NMR (400 MHz, $CDCl_3$)





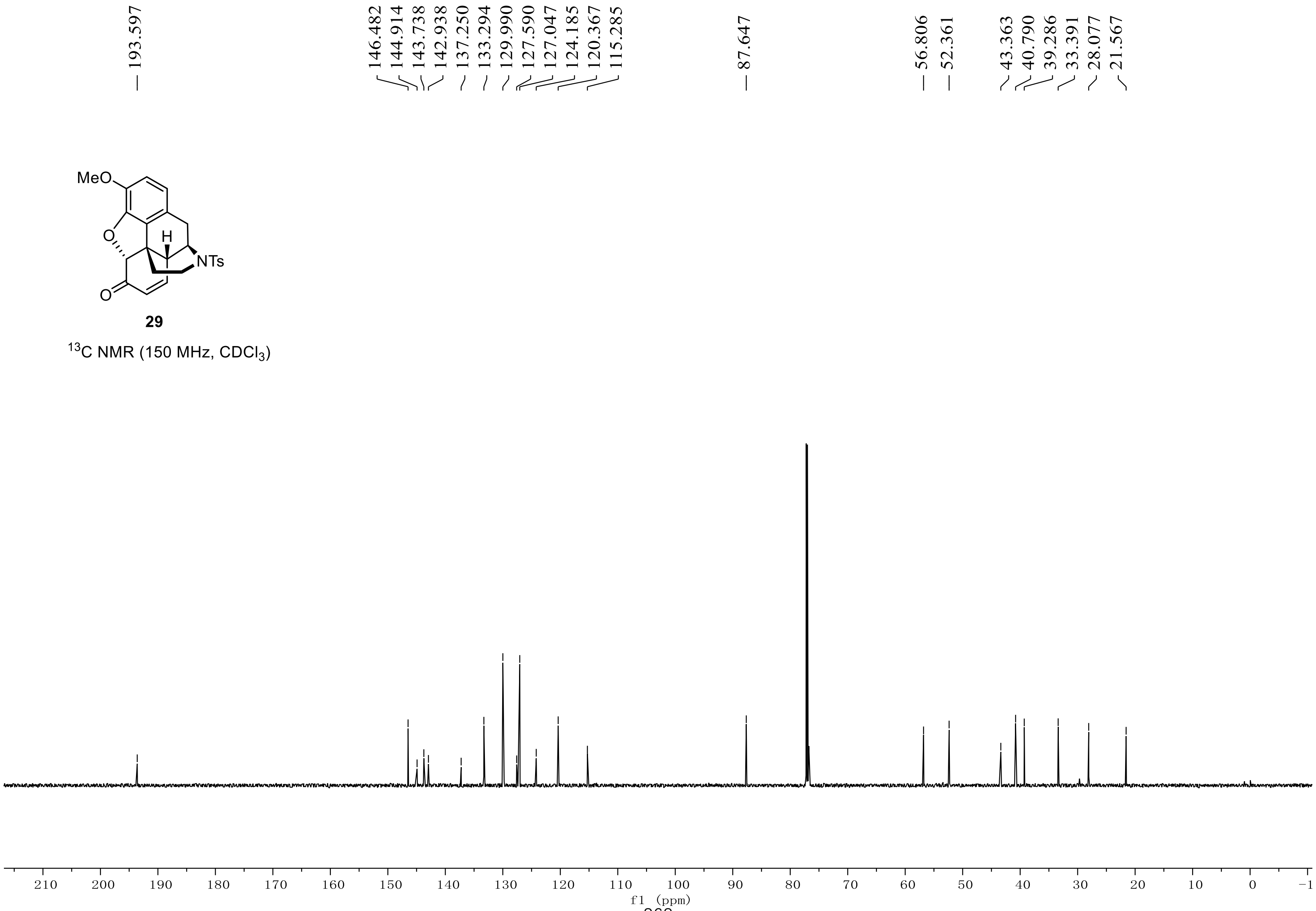
28

^{13}C NMR (100 MHz, $CDCl_3$)



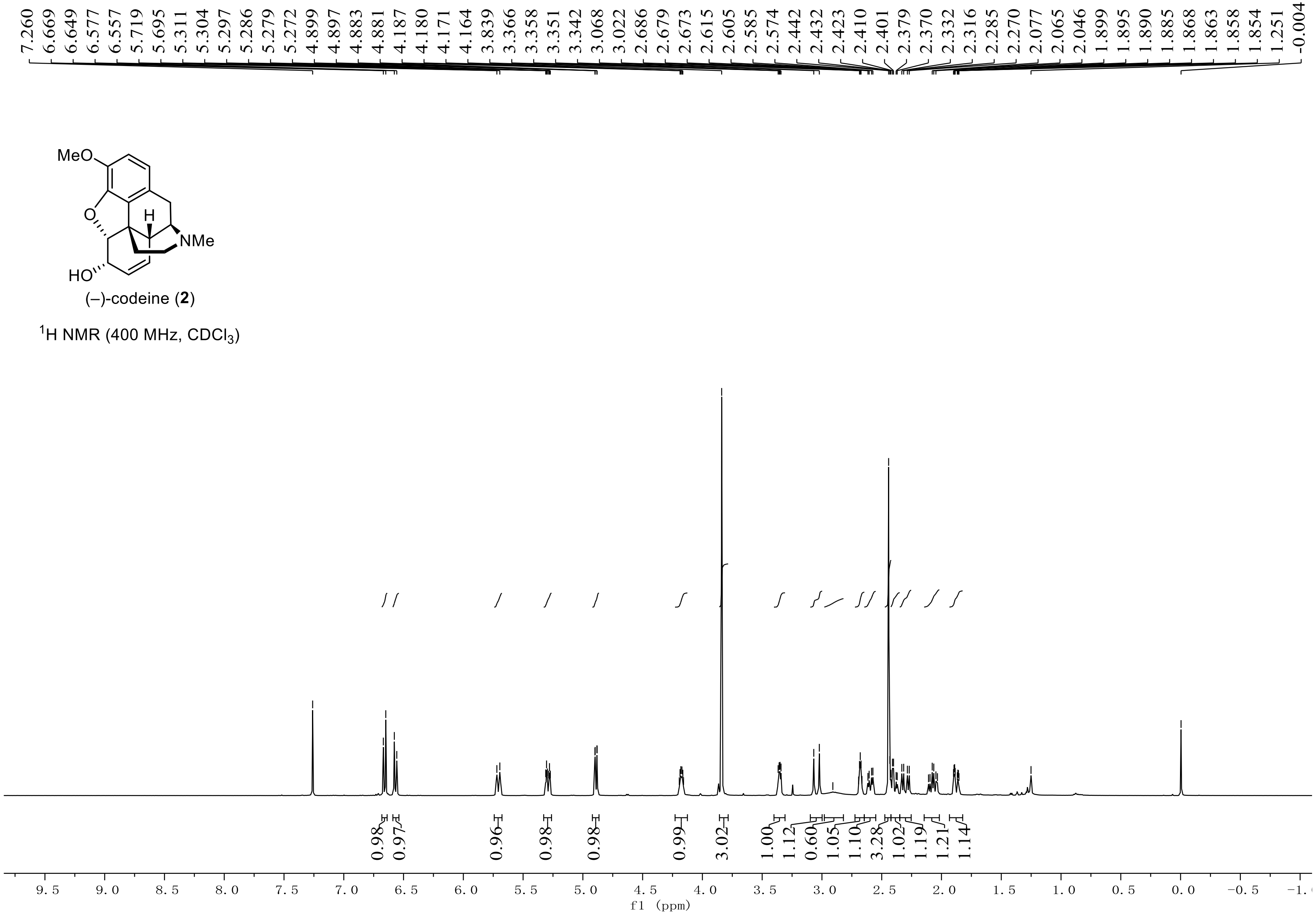
29

^{1}H NMR (400 MHz, $CDCl_3$)



29

^{13}C NMR (150 MHz, CDCl$_3$)

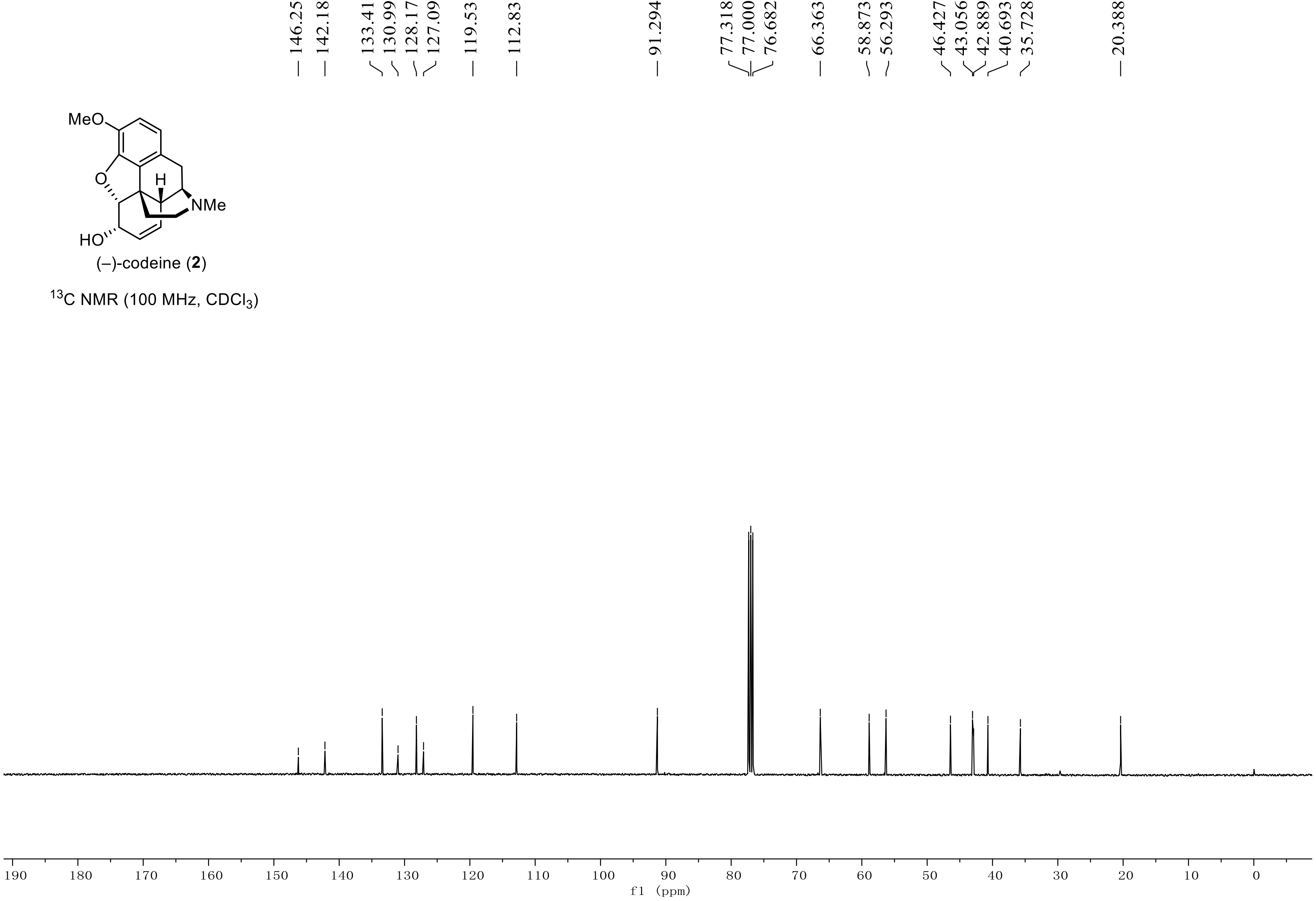


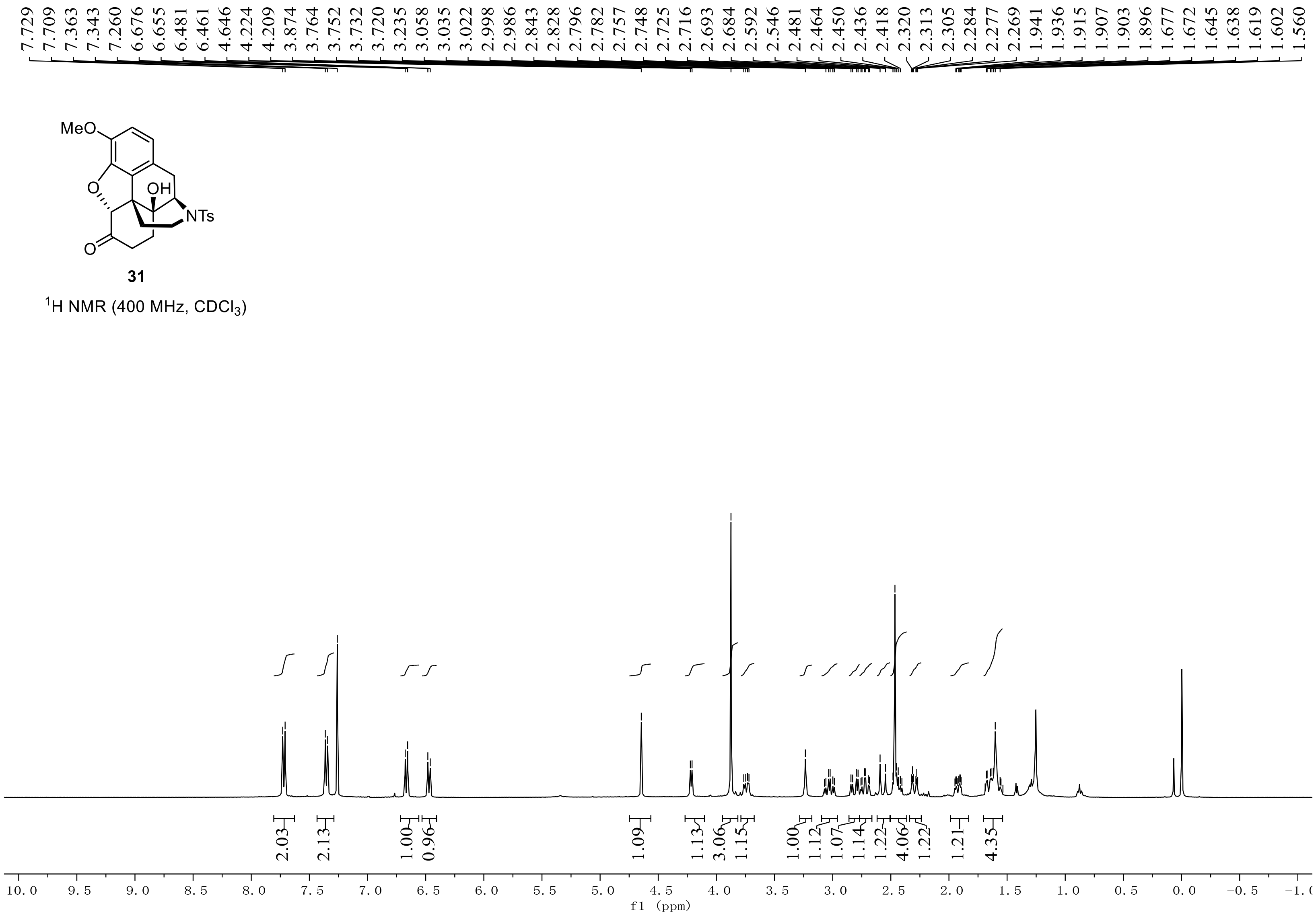
(–)-codeine (**2**)

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

(–)-codeine (**2**)

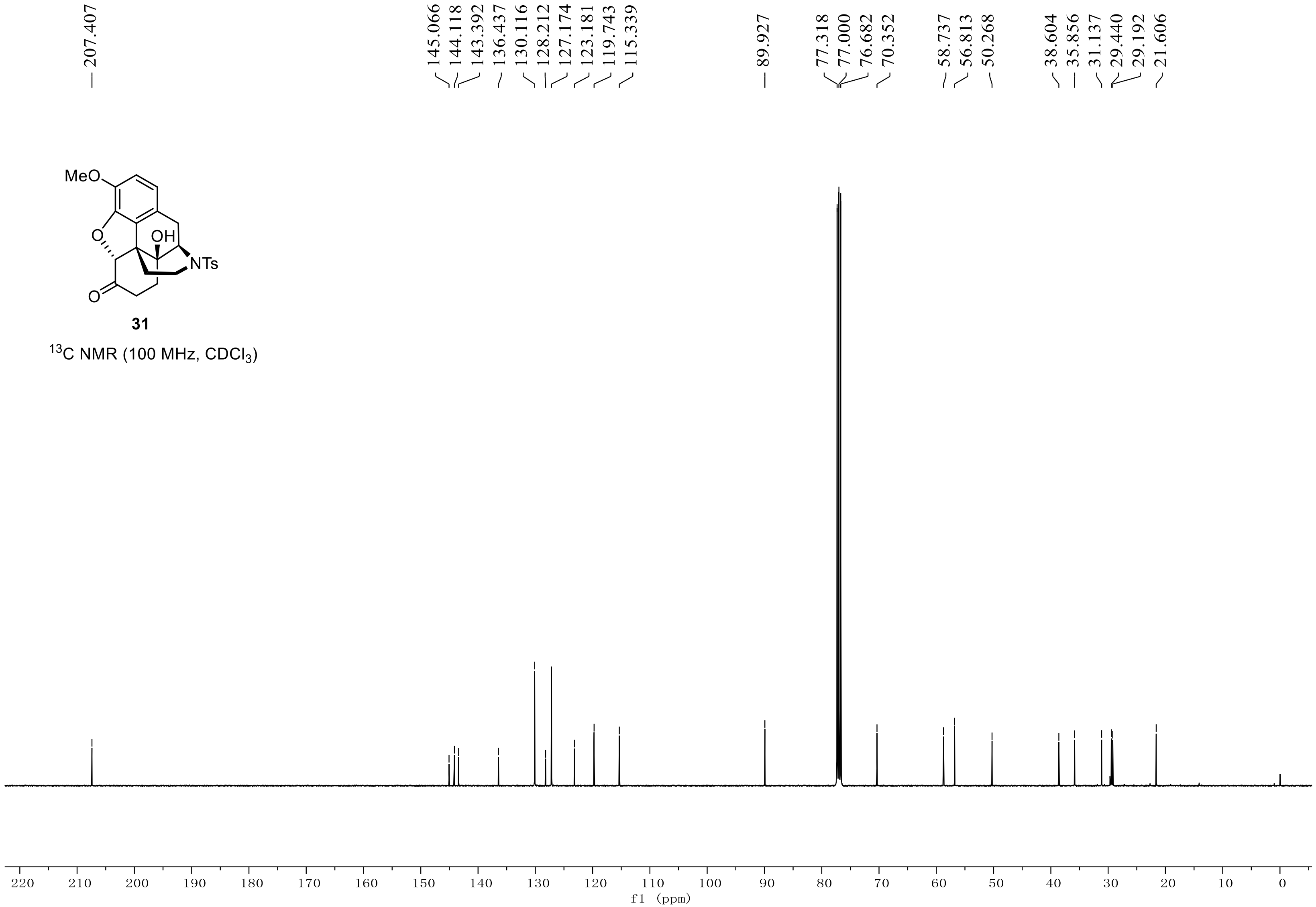
^{13}C NMR (100 MHz, $CDCl_3$)





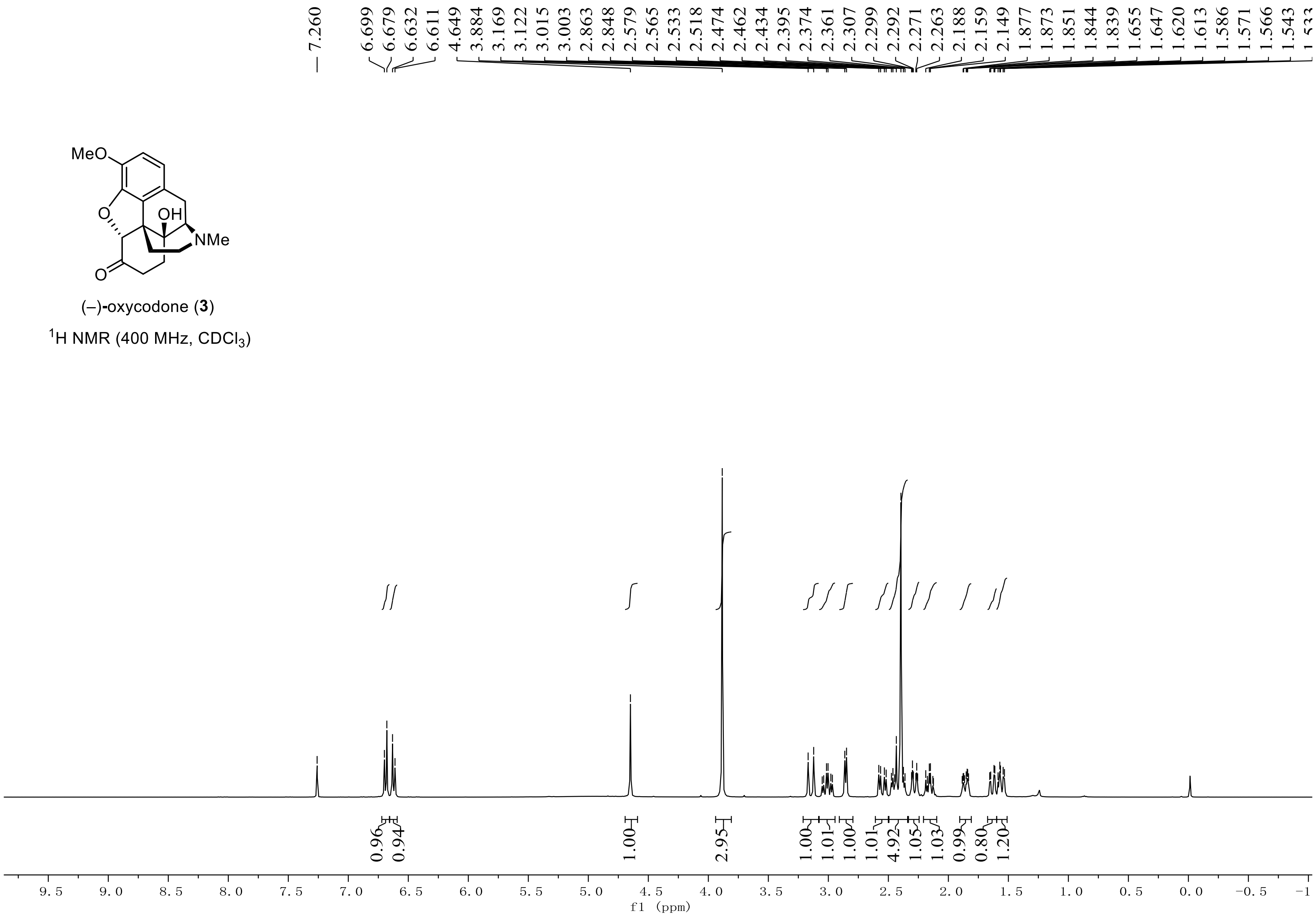
31

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



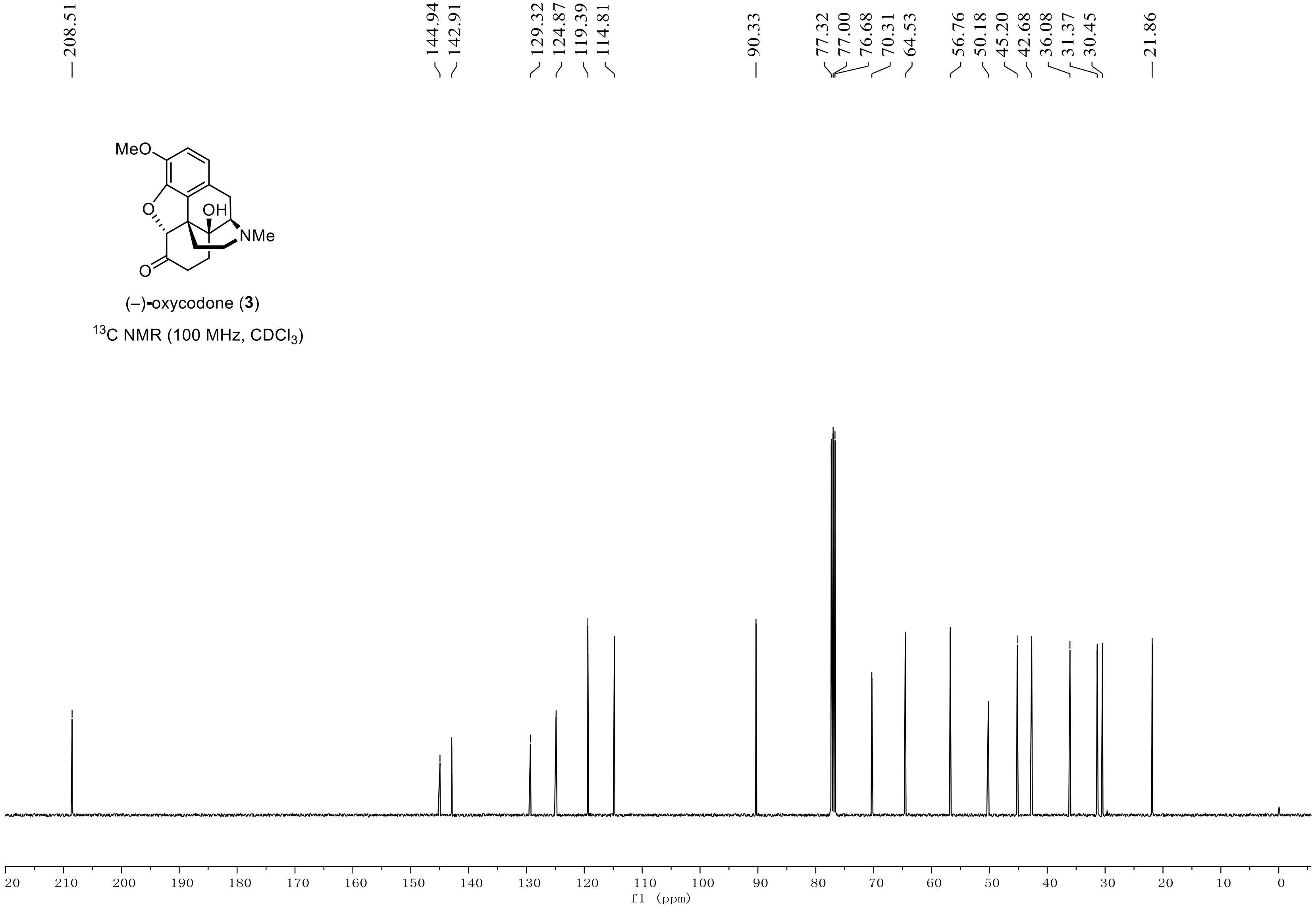
31

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



(–)-oxycodone (**3**)

^{1}H NMR (400 MHz, $CDCl_3$)

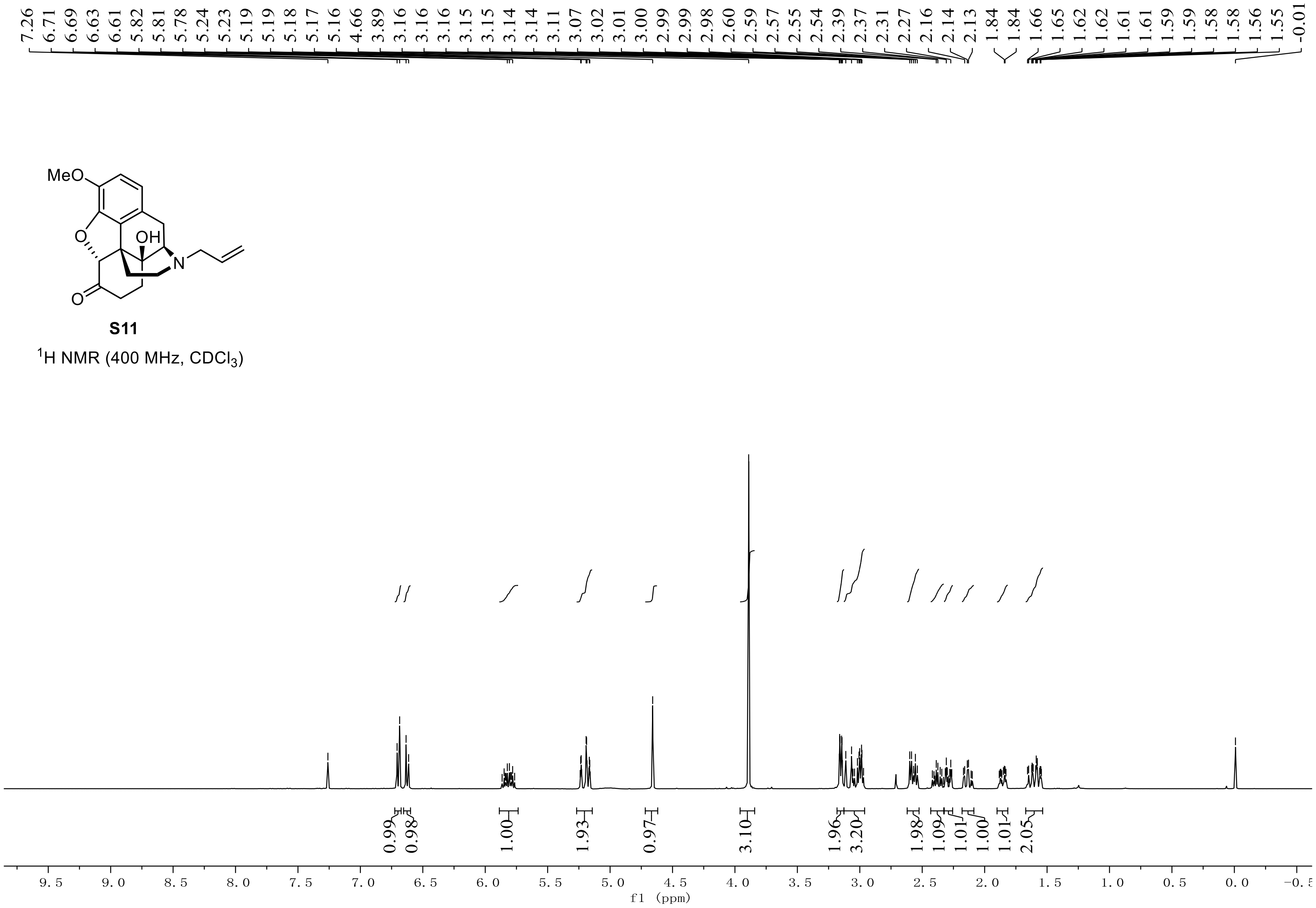


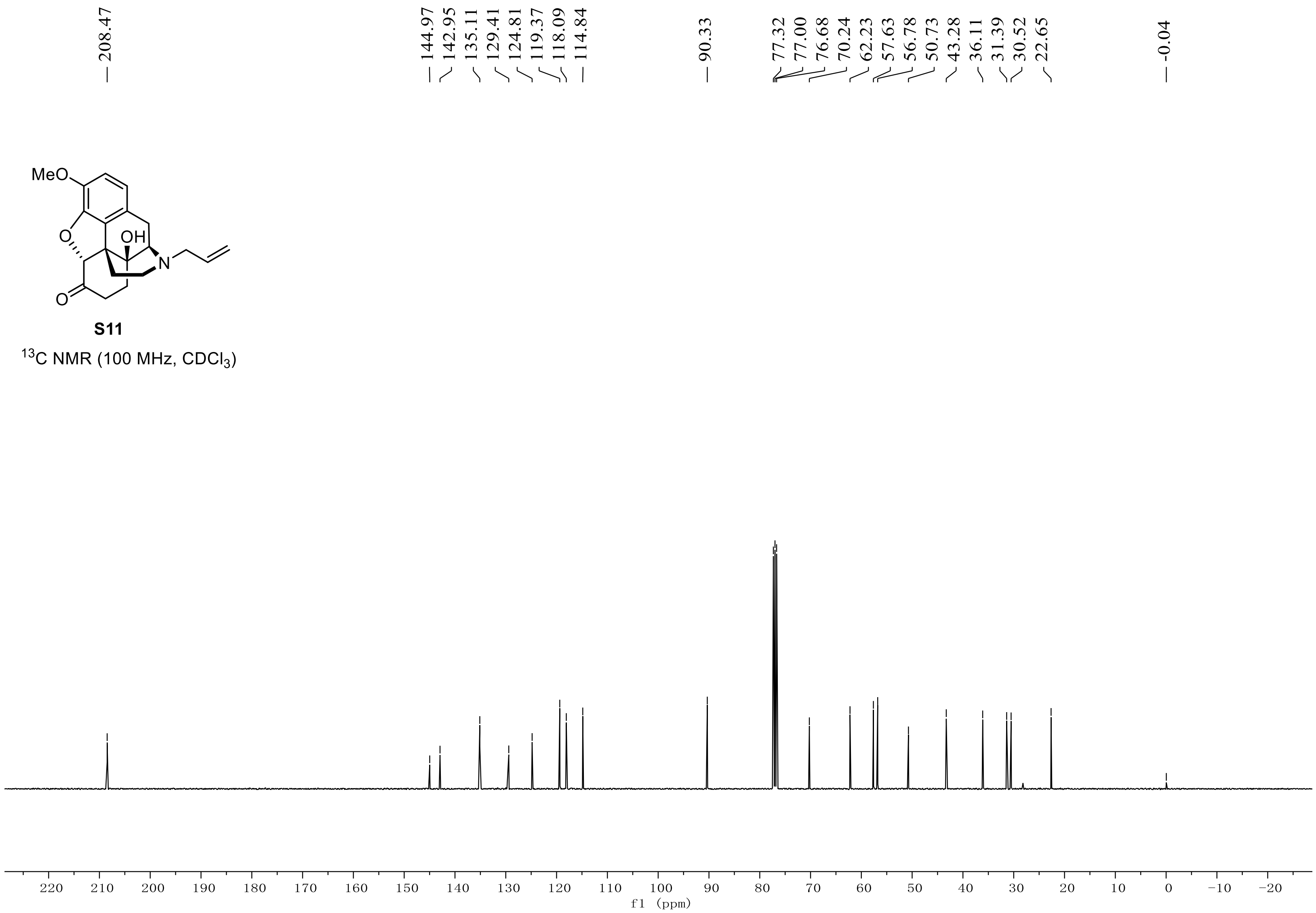
(–)-oxycodone (**3**)

^{13}C NMR (100 MHz, $CDCl_3$)

S11

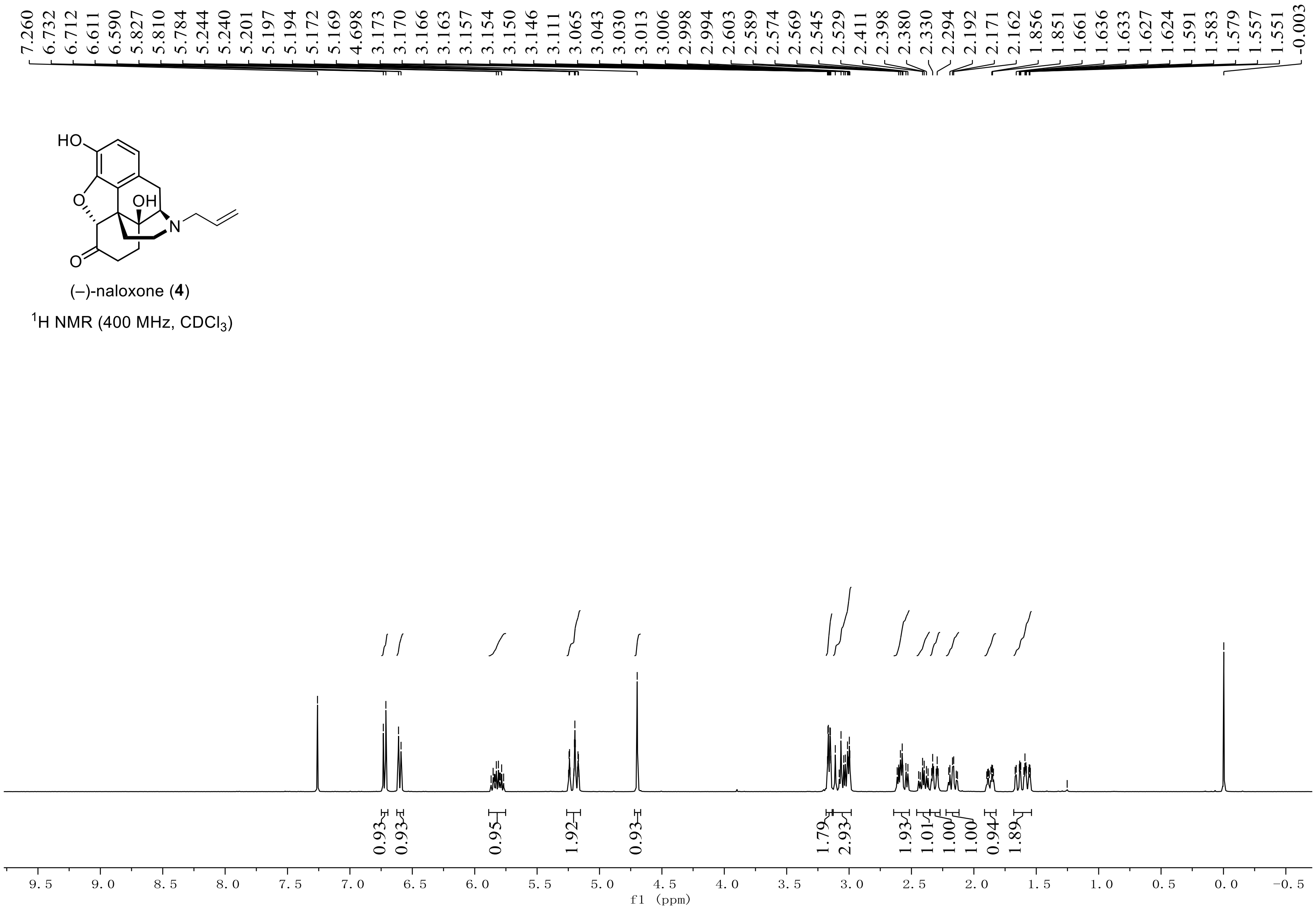
^{1}H NMR (400 MHz, CDCl$_3$)





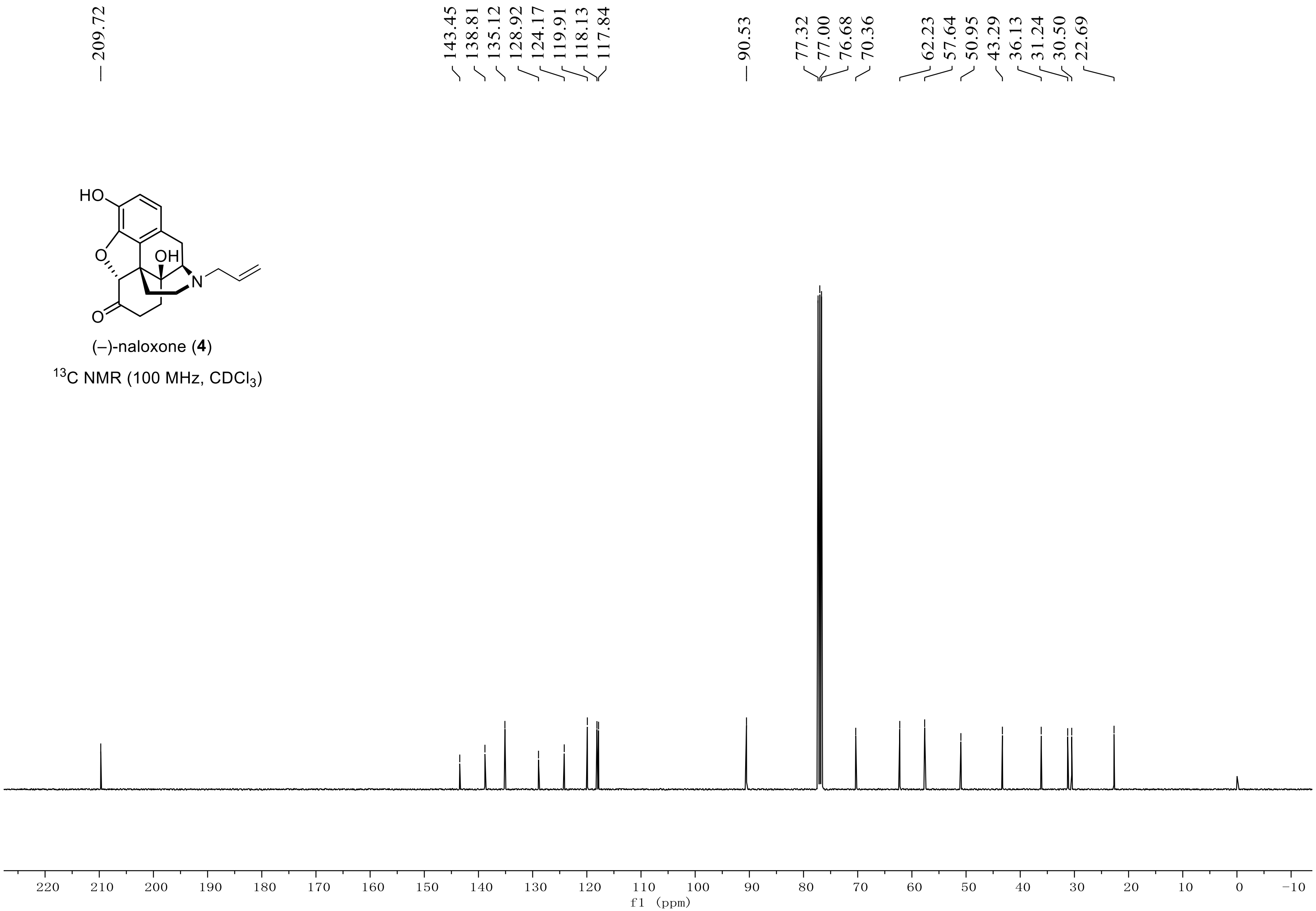
S11

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

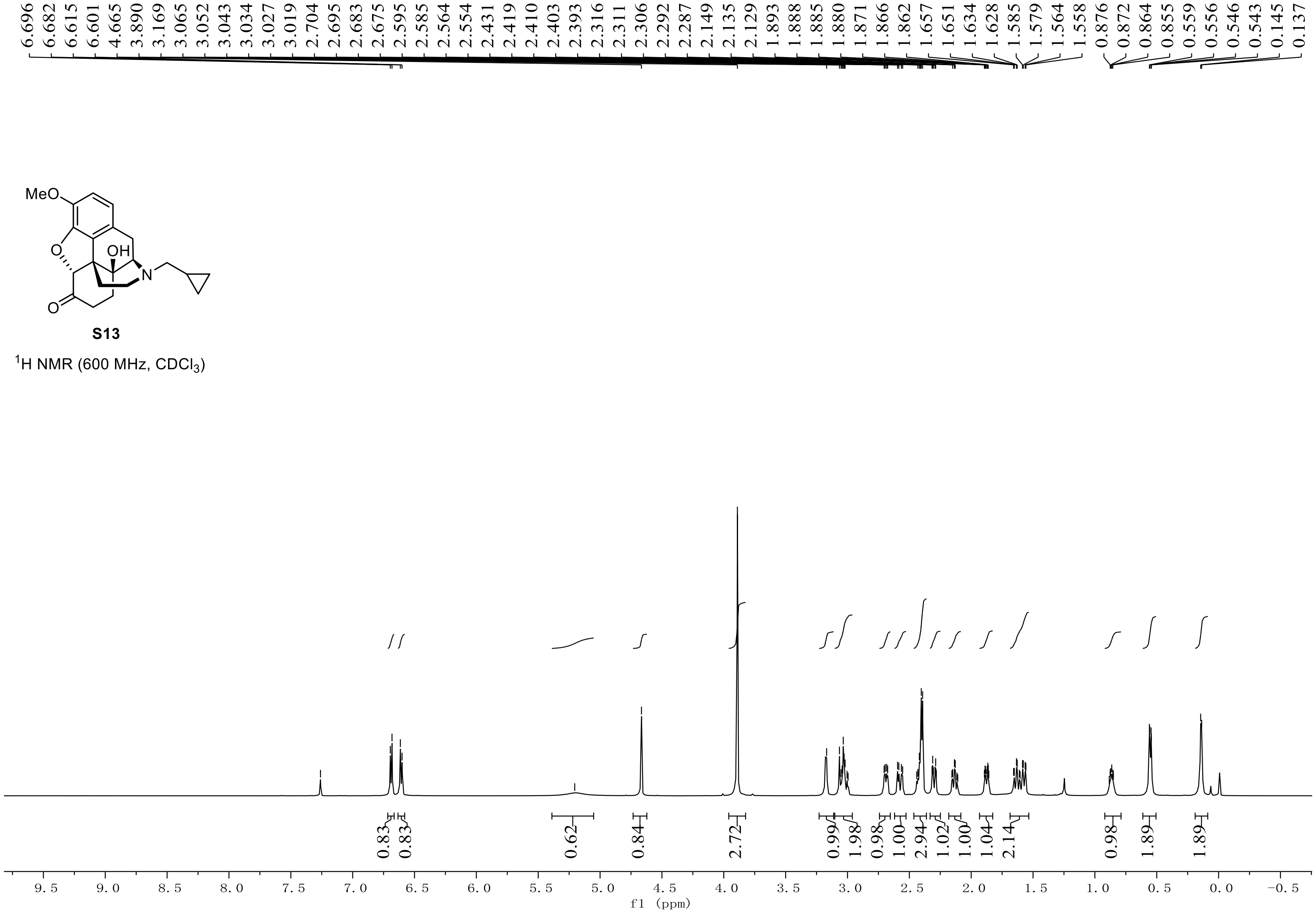


(–)-naloxone (**4**)

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


(–)-naloxone (**4**)

^{13}C NMR (100 MHz, $CDCl_3$)

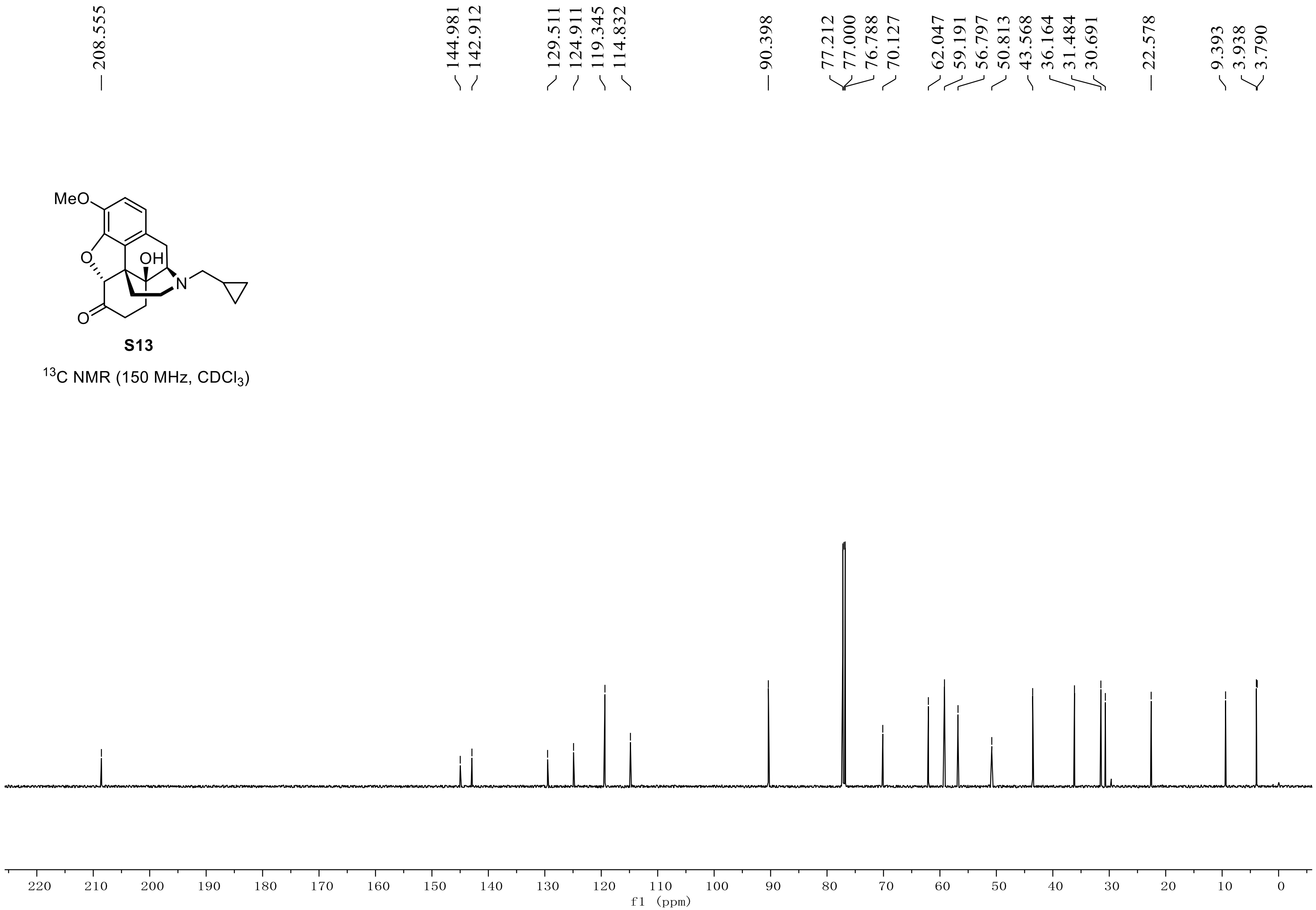


S13

^{1}H NMR (600 MHz, CDCl$_3$)

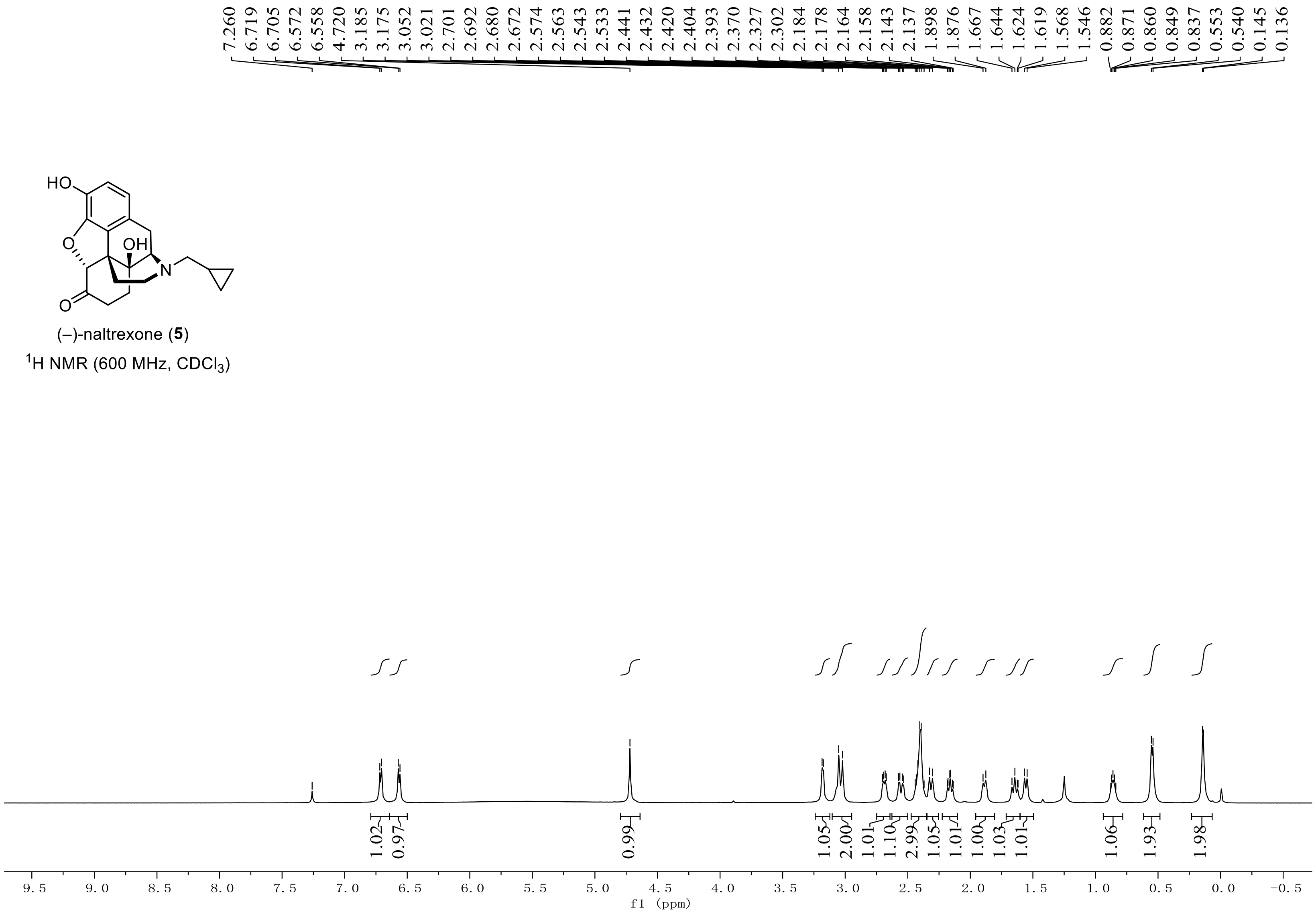
S13

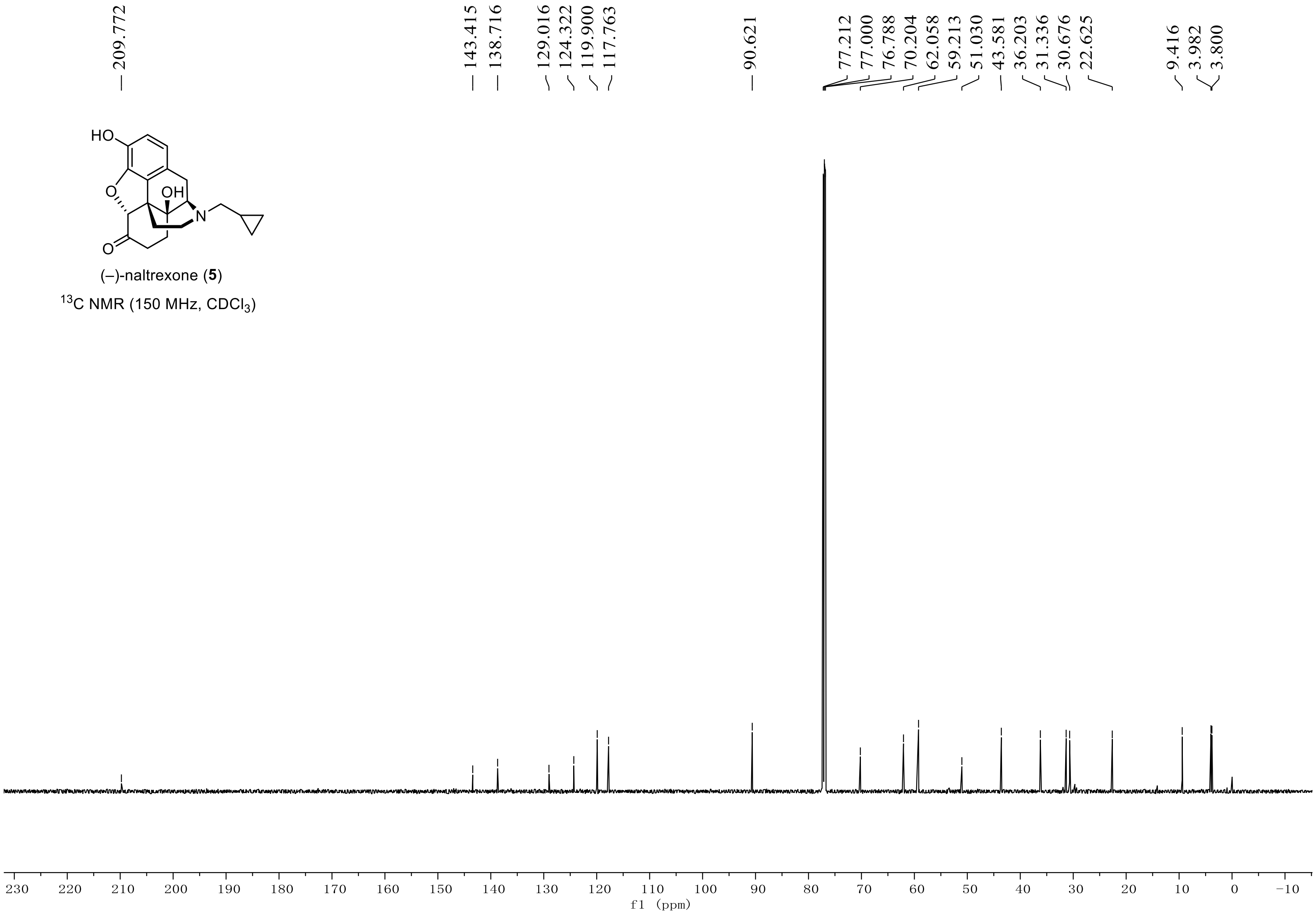
^{13}C NMR (150 MHz, CDCl$_3$)



(–)-naltrexone (**5**)

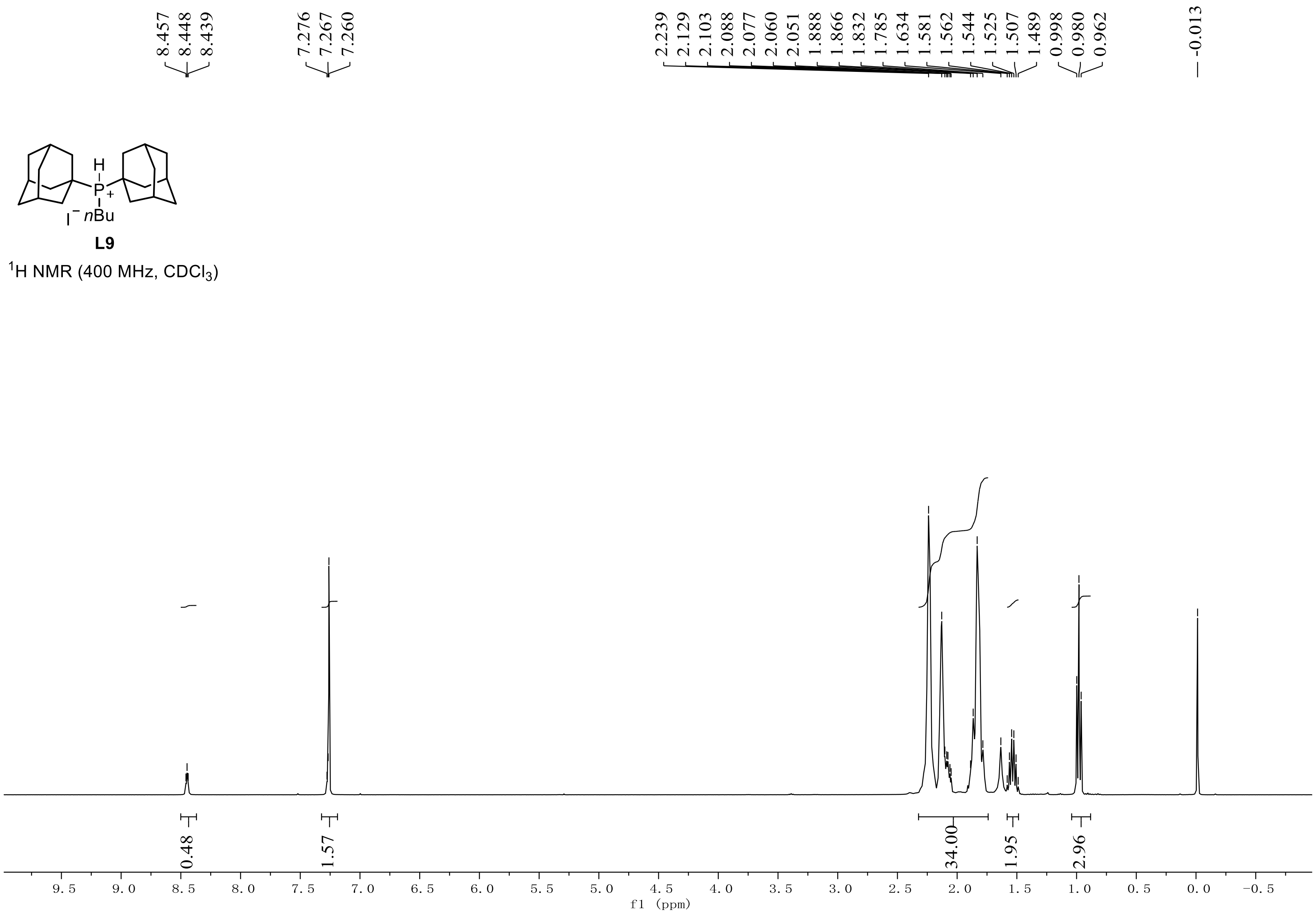
^{1}H NMR (600 MHz, $CDCl_3$)



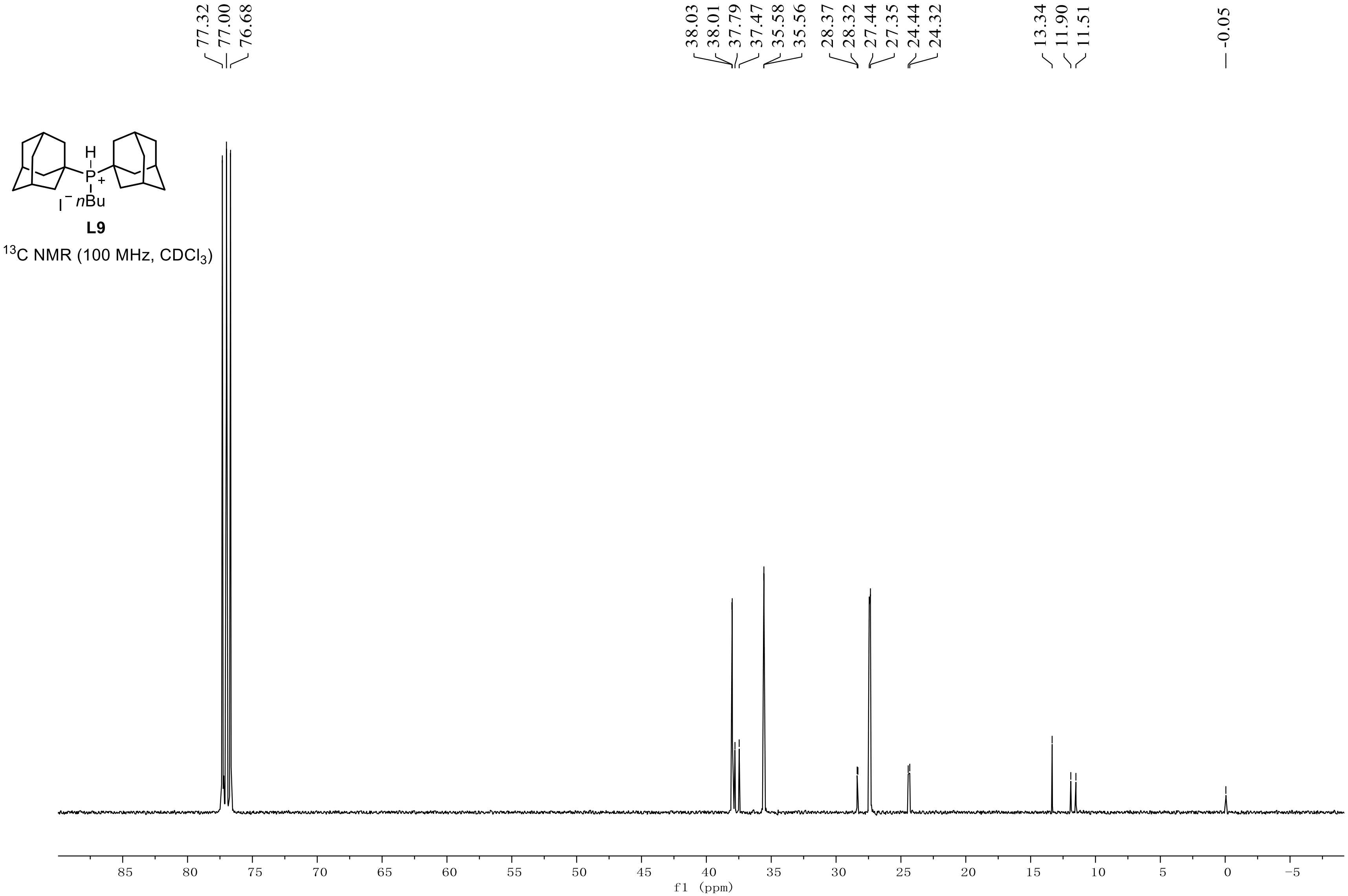


(–)-naltrexone (**5**)

^{13}C NMR (150 MHz, $CDCl_3$)


L9

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

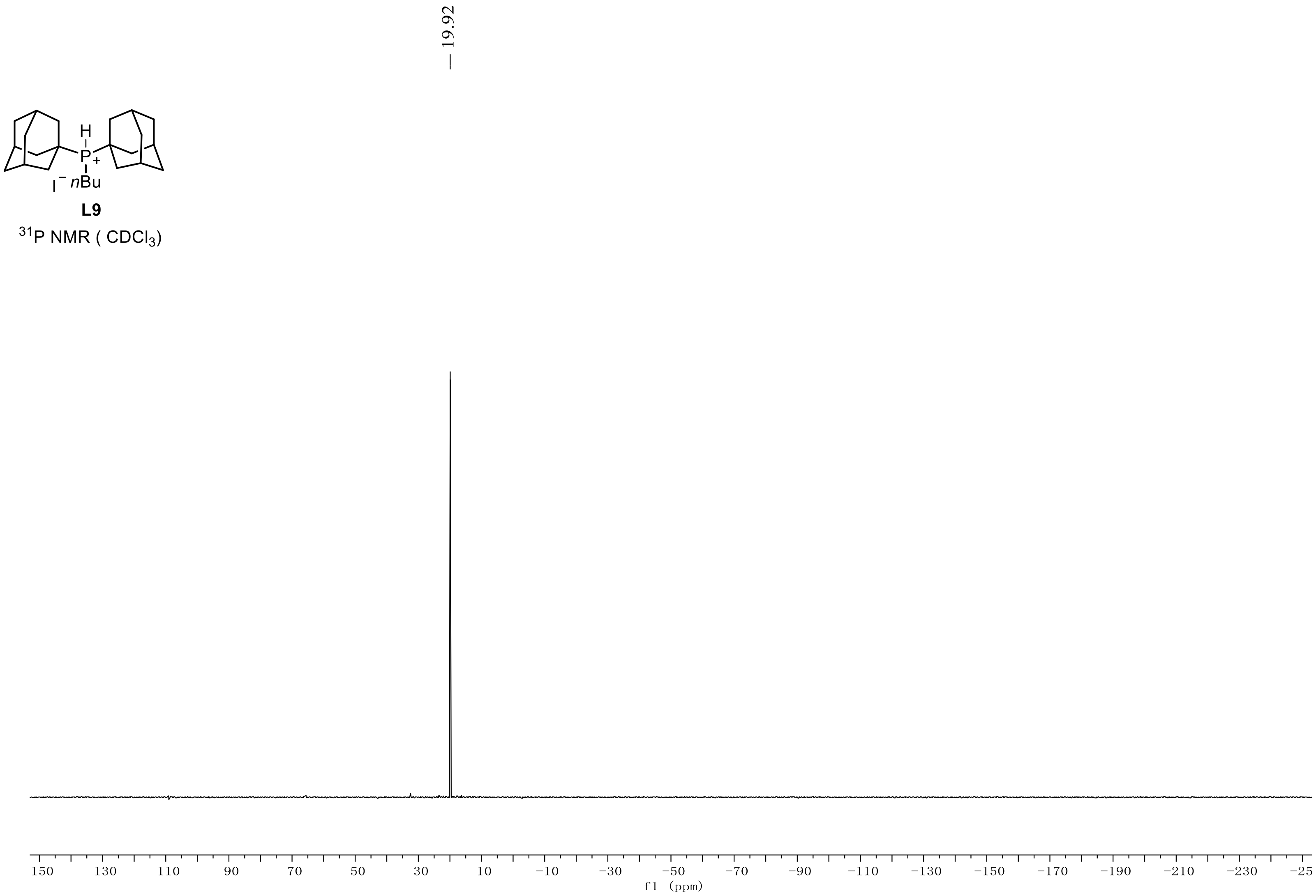


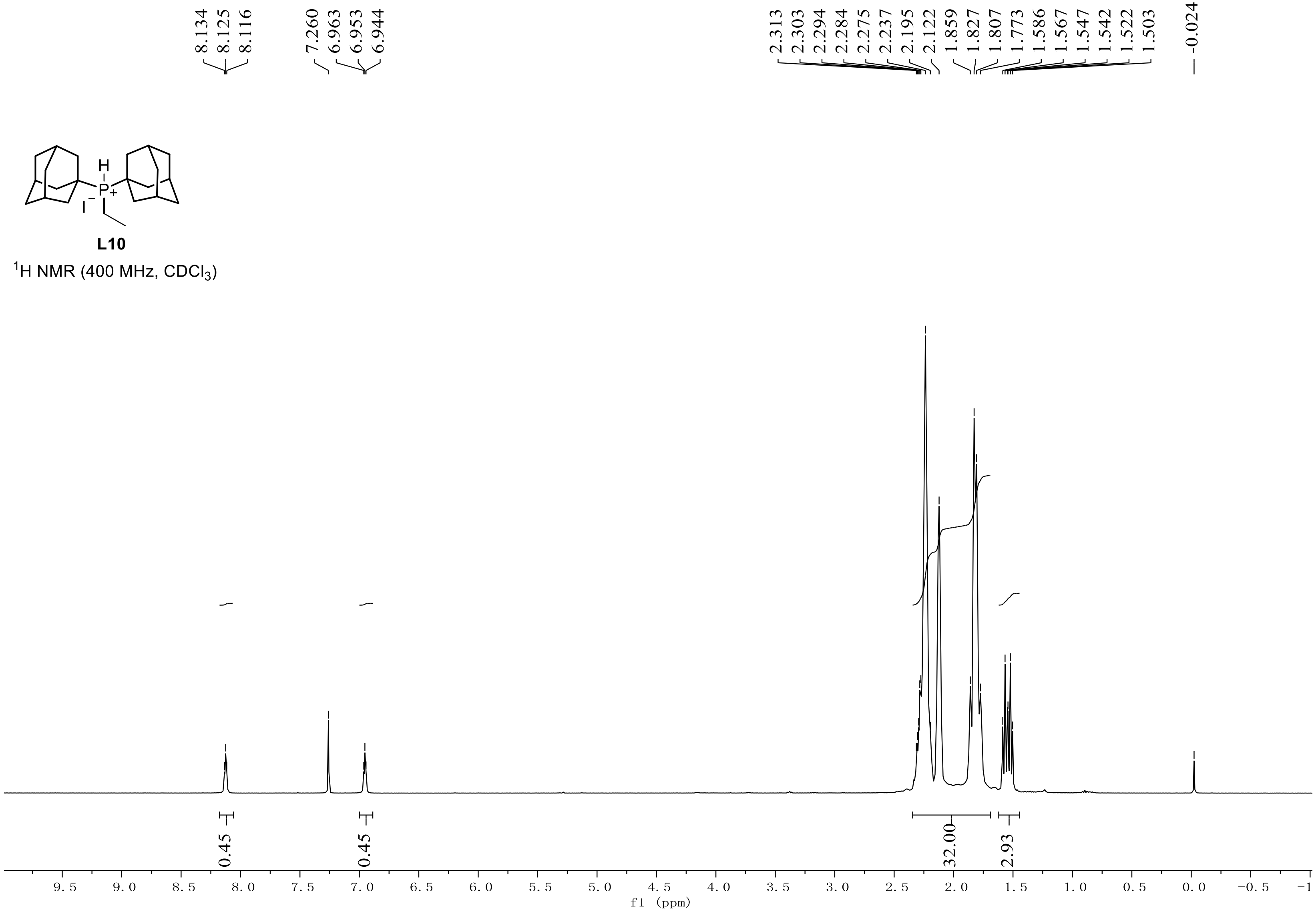
L9

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

L9

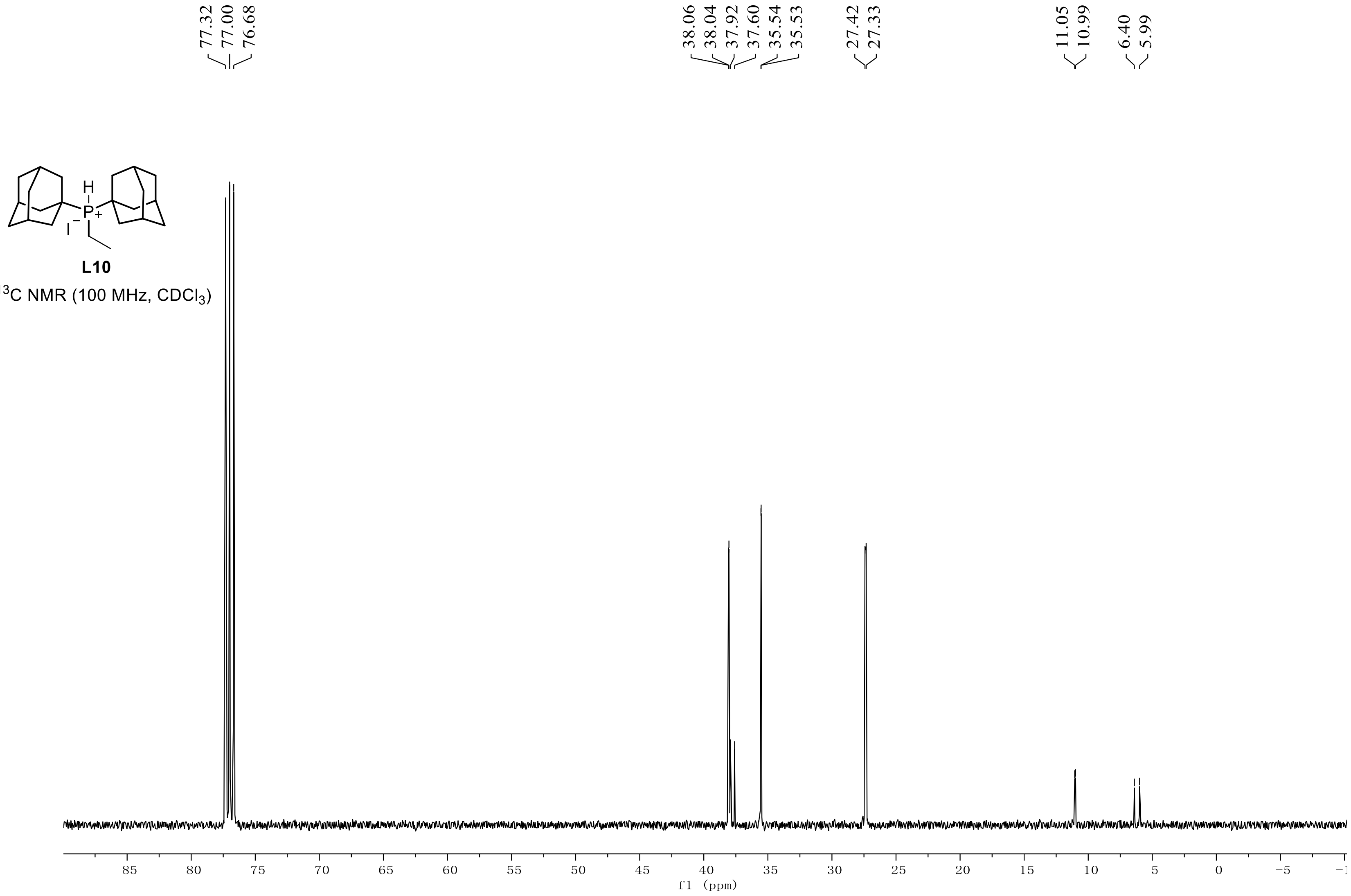
^{31}P NMR ($CDCl_3$)





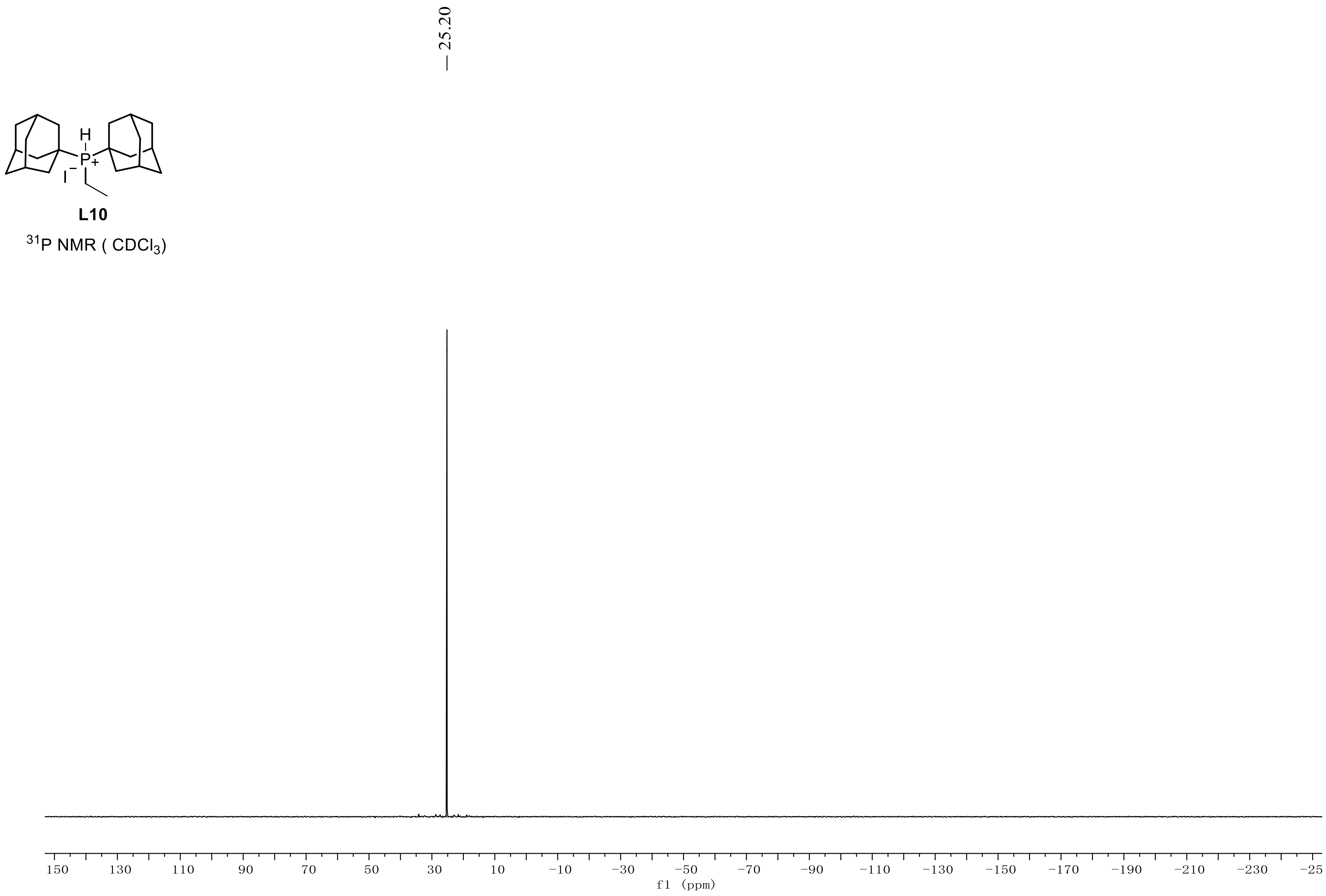
L10

^{1}H NMR (400 MHz, $CDCl_3$)



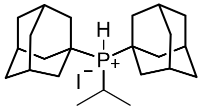
L10

^{13}C NMR (100 MHz, $CDCl_3$)



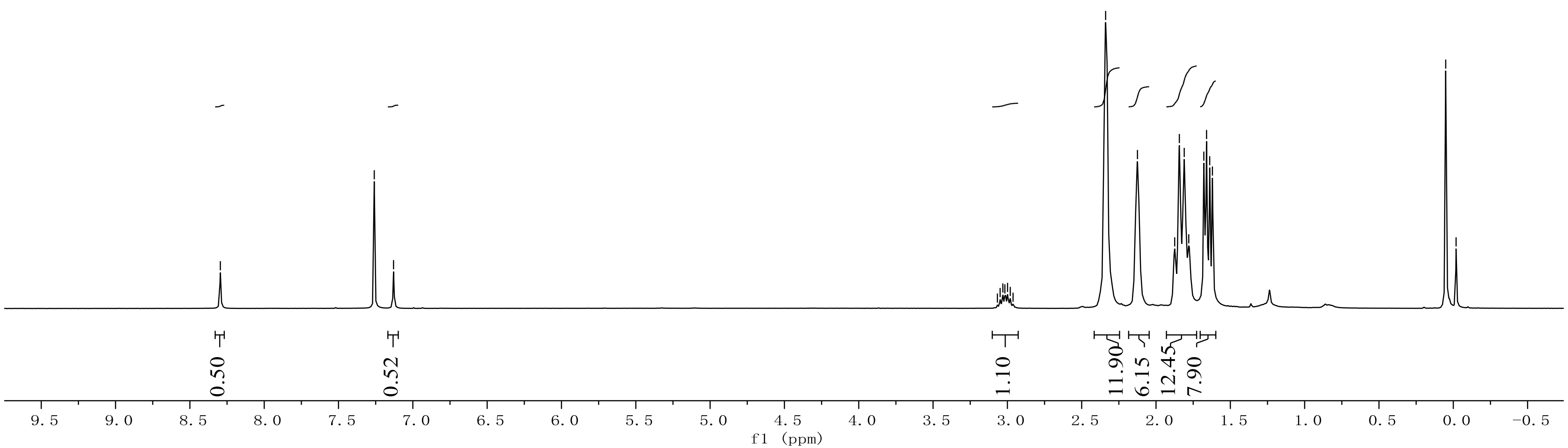
L10

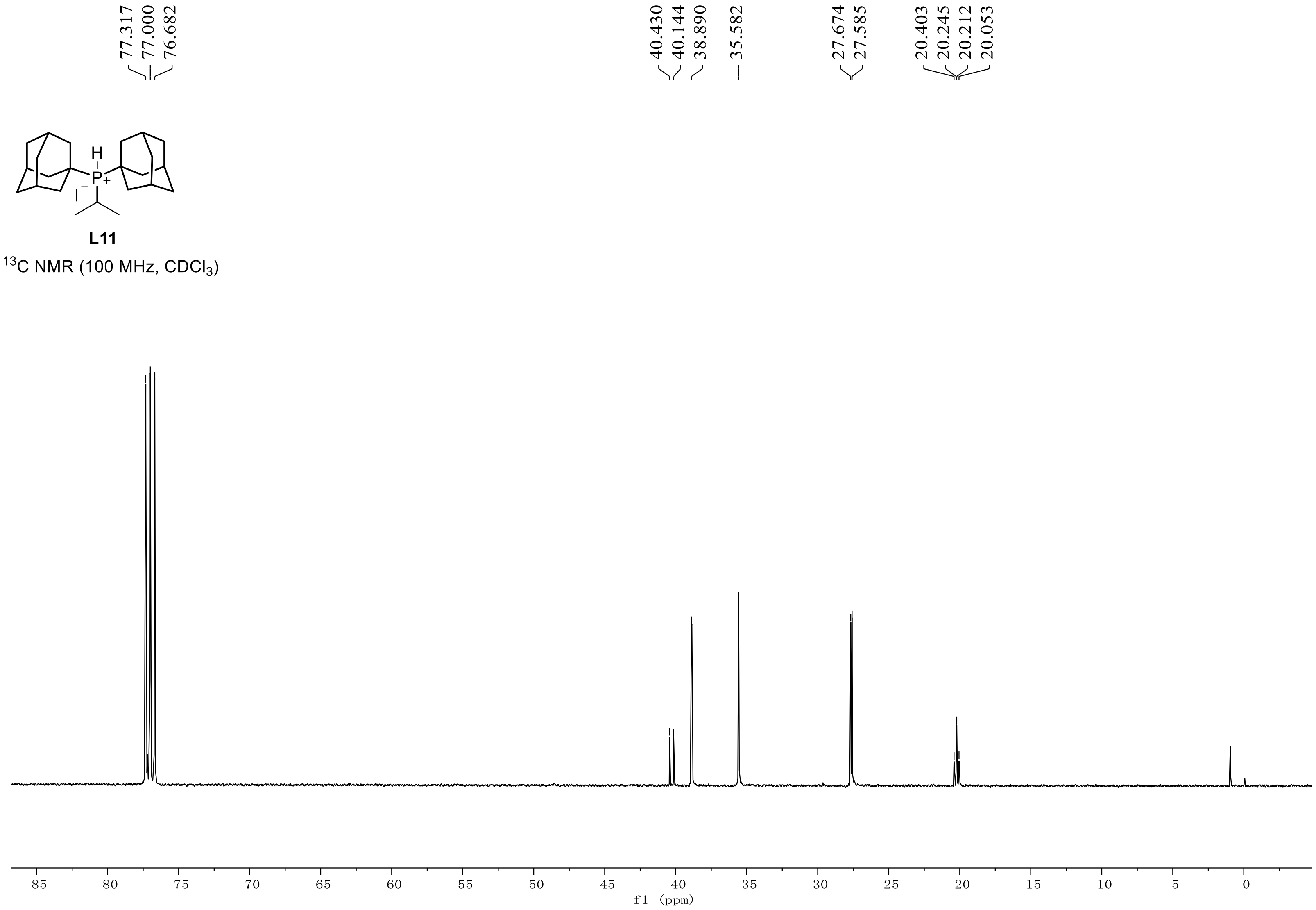
^{31}P NMR (CDCl$_3$)



L11

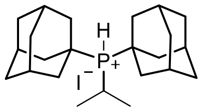
^{1}H NMR (400 MHz, CDCl$_3$)





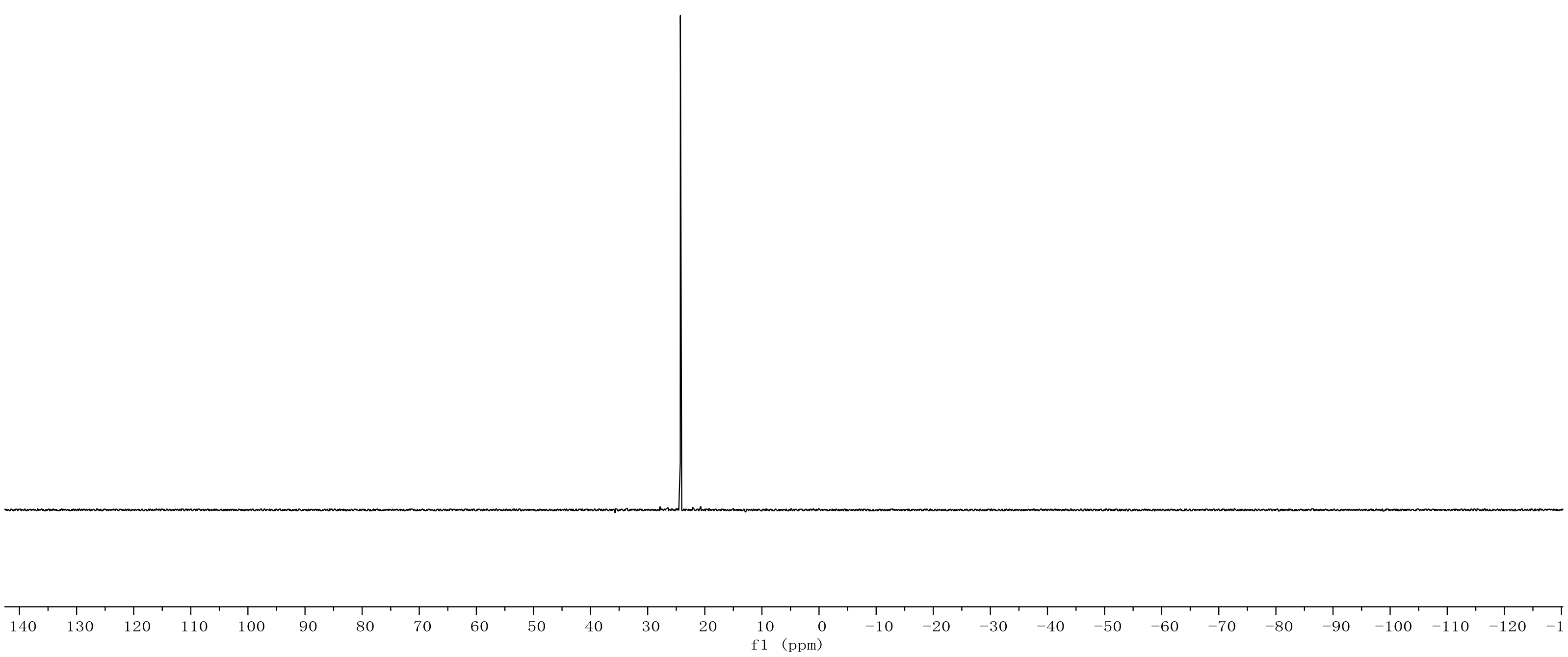
L11

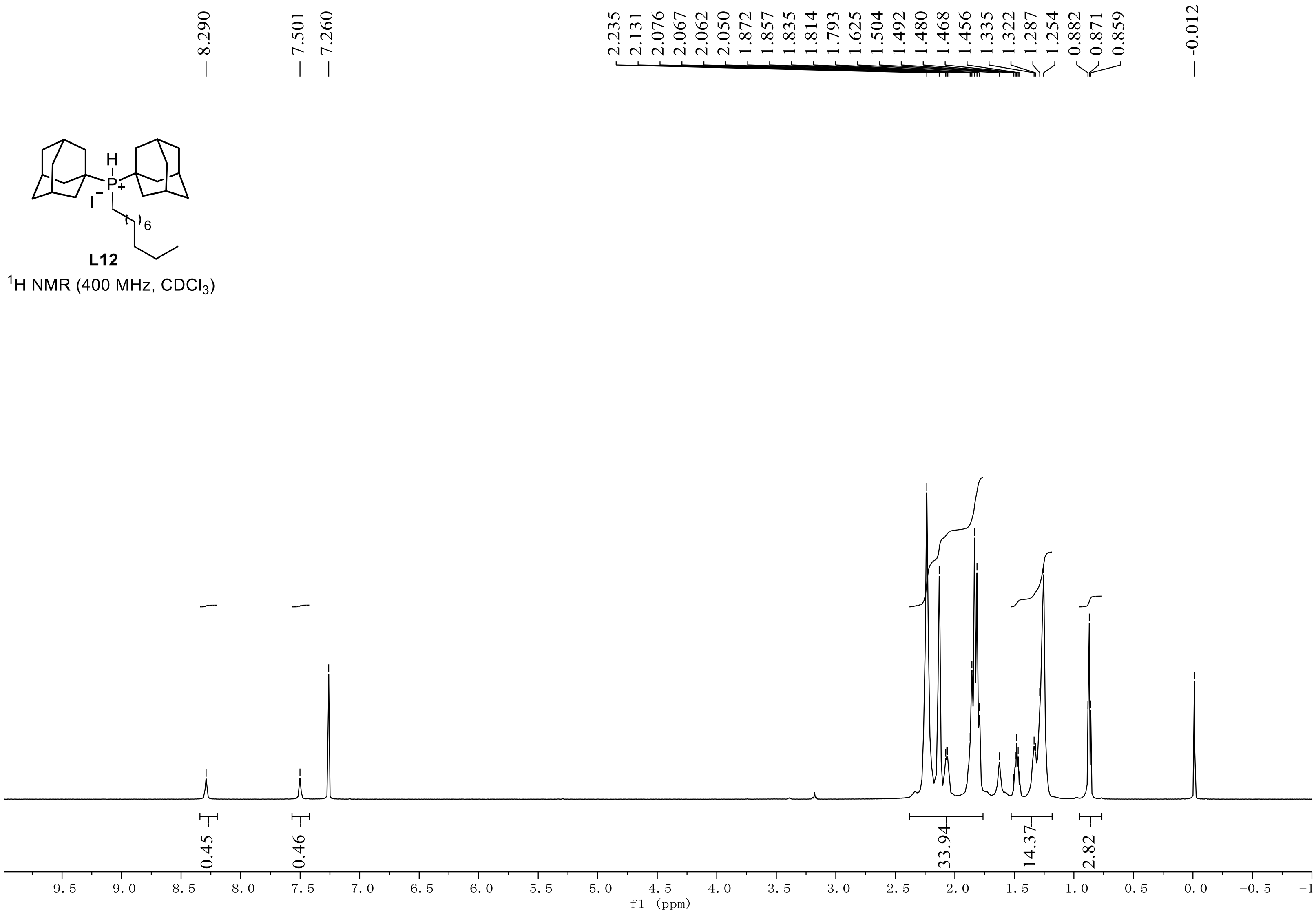
^{13}C NMR (100 MHz, $CDCl_3$)



L11

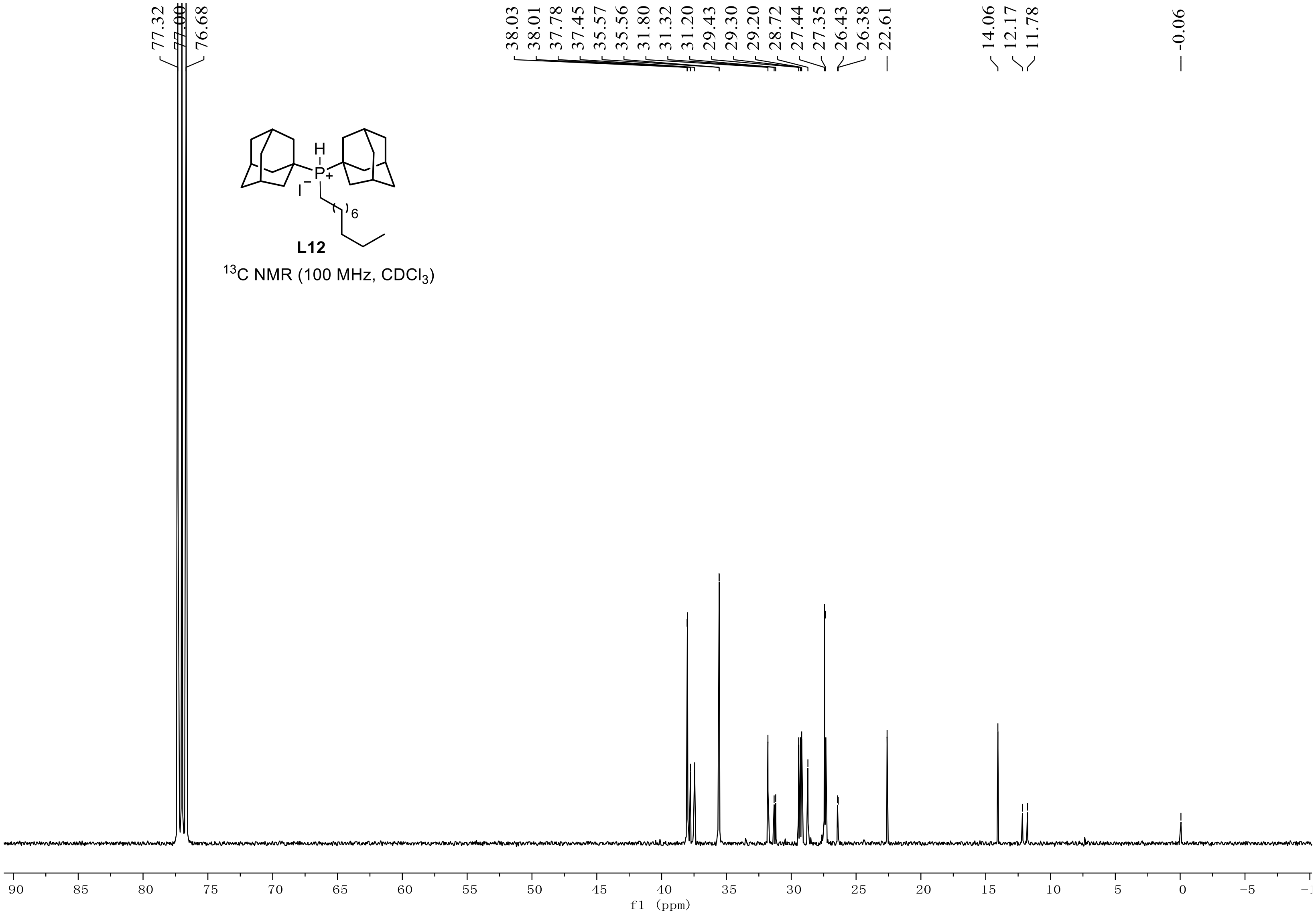
^{31}P NMR ($CDCl_3$)





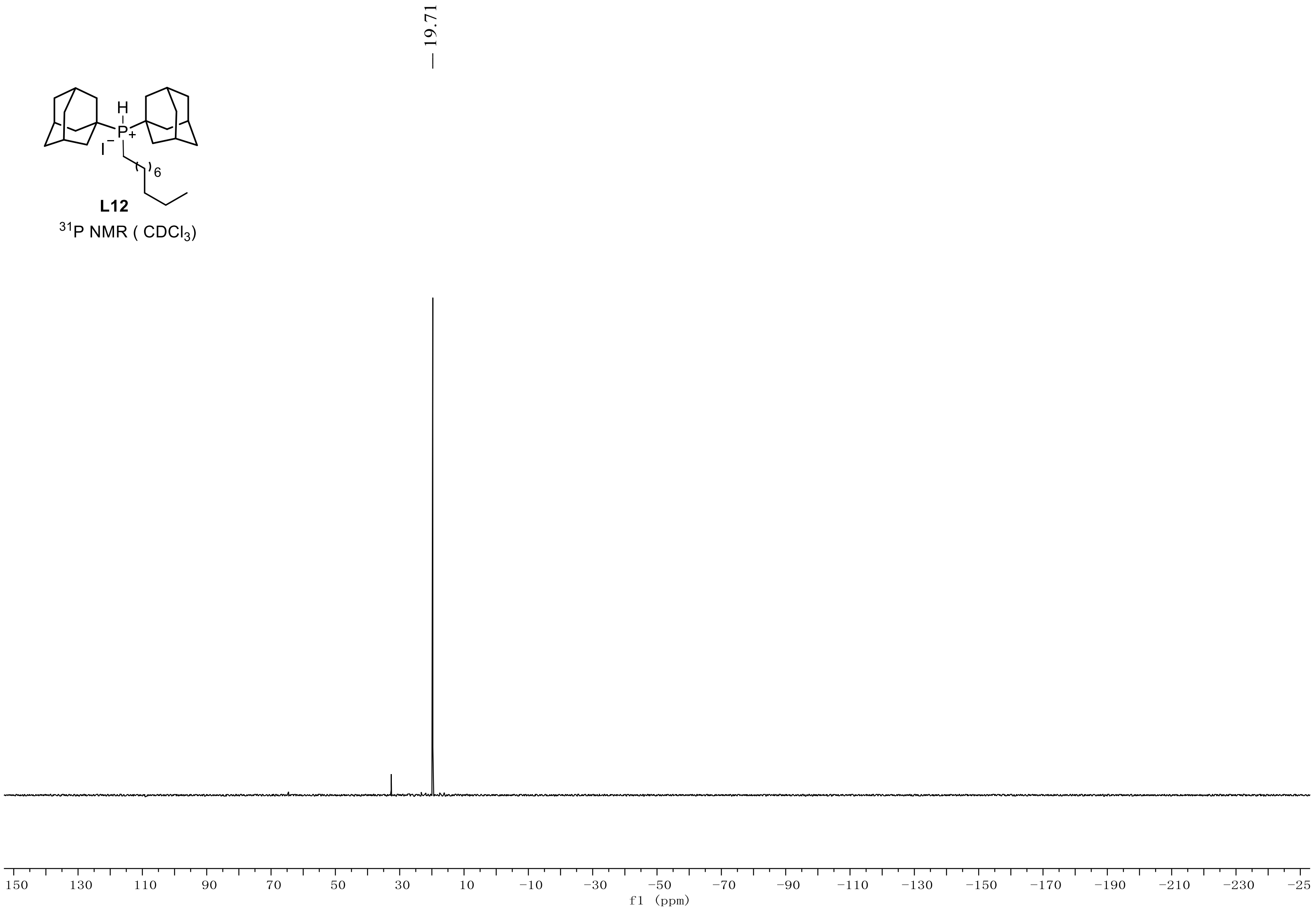
L12

^{1}H NMR (400 MHz, $CDCl_3$)



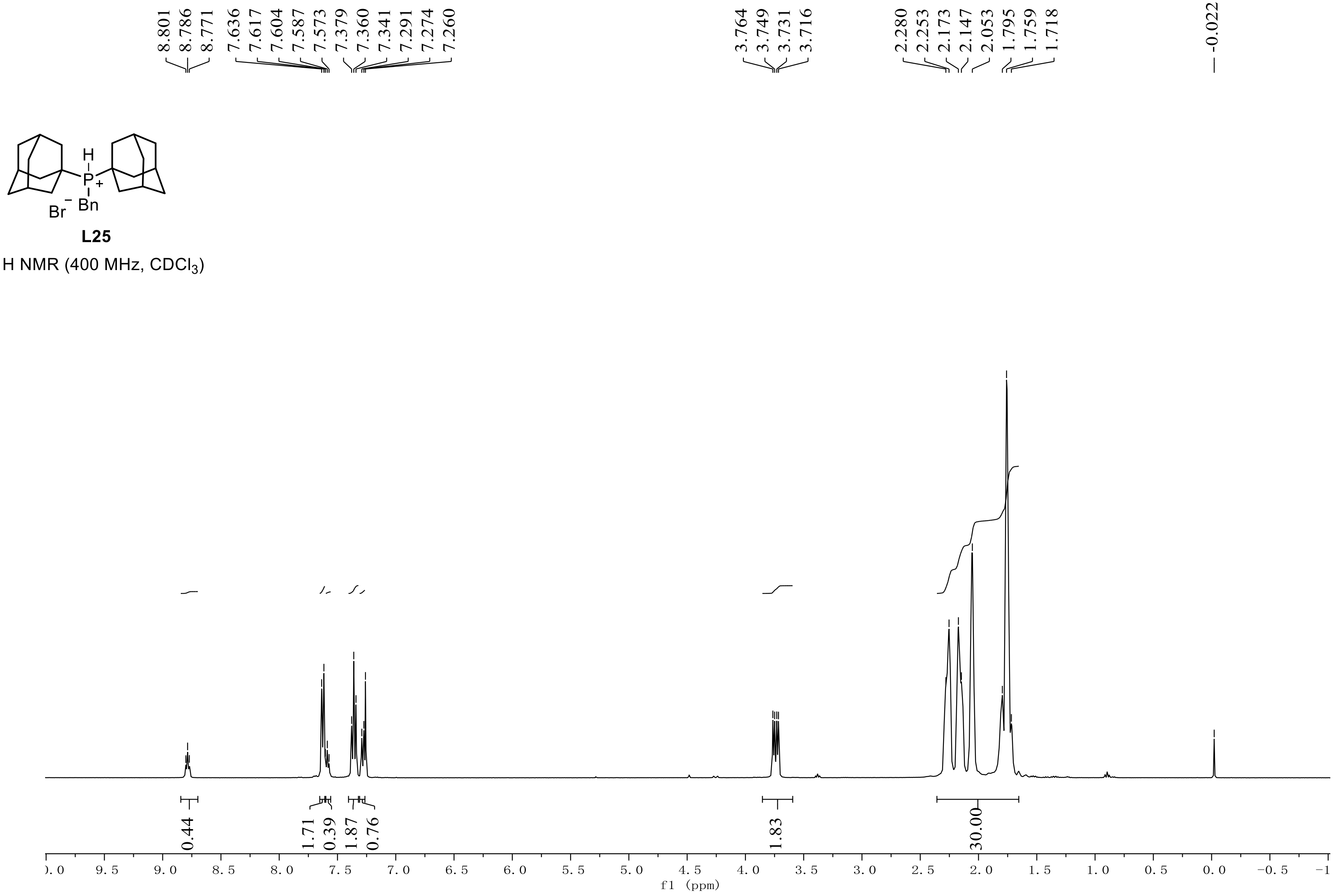
L12

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



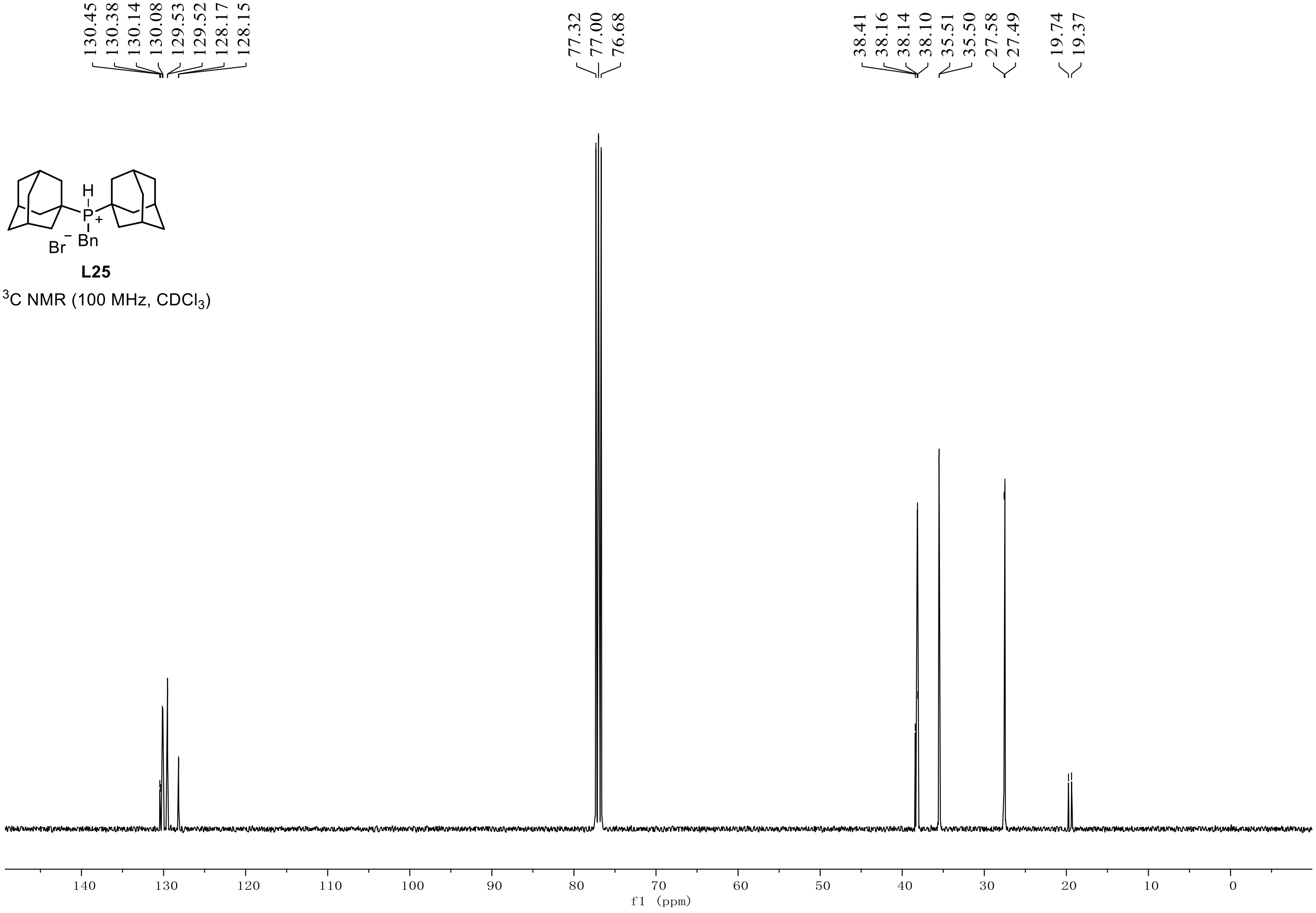
L12

^{31}P NMR ($CDCl_3$)



L25

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

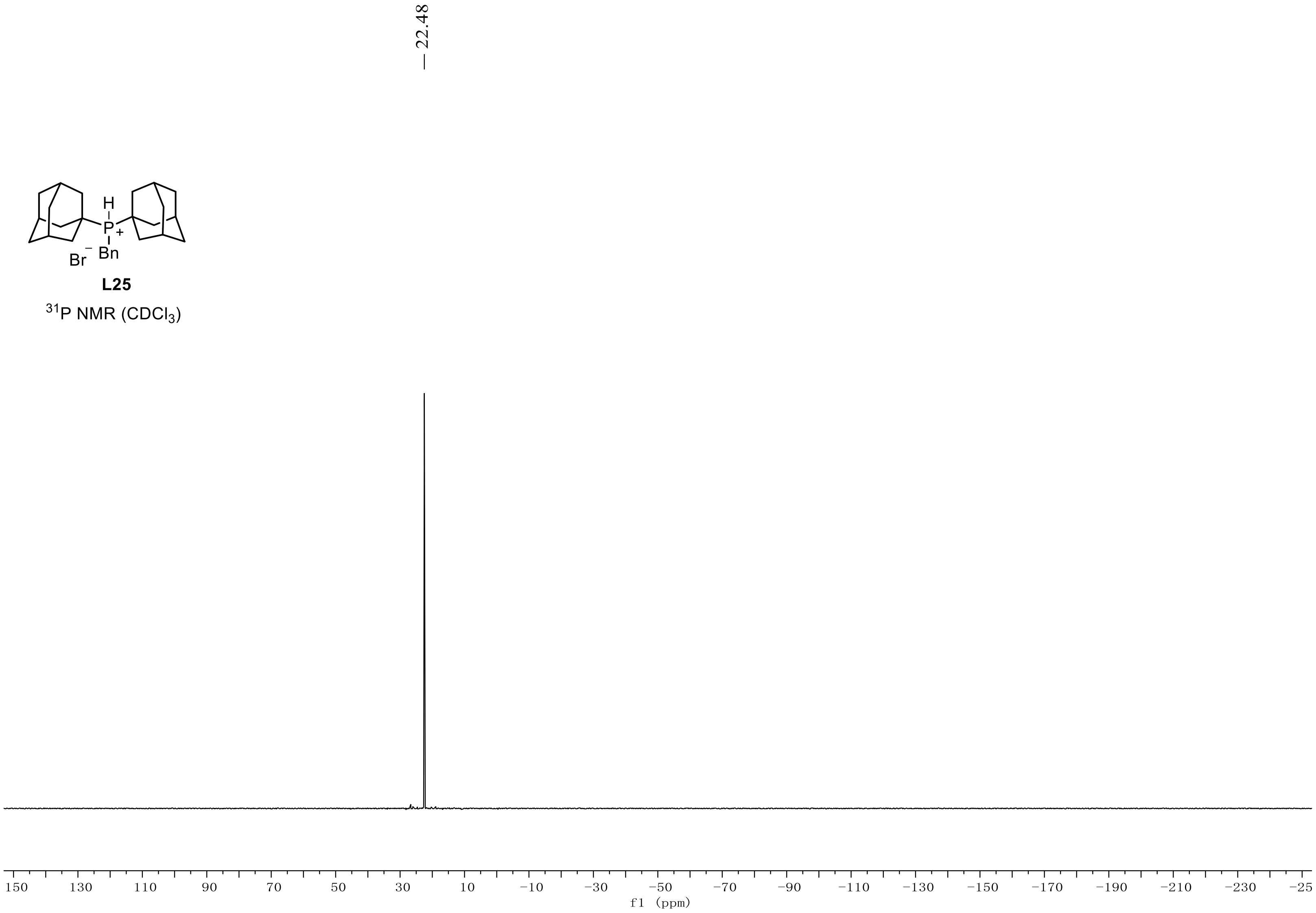


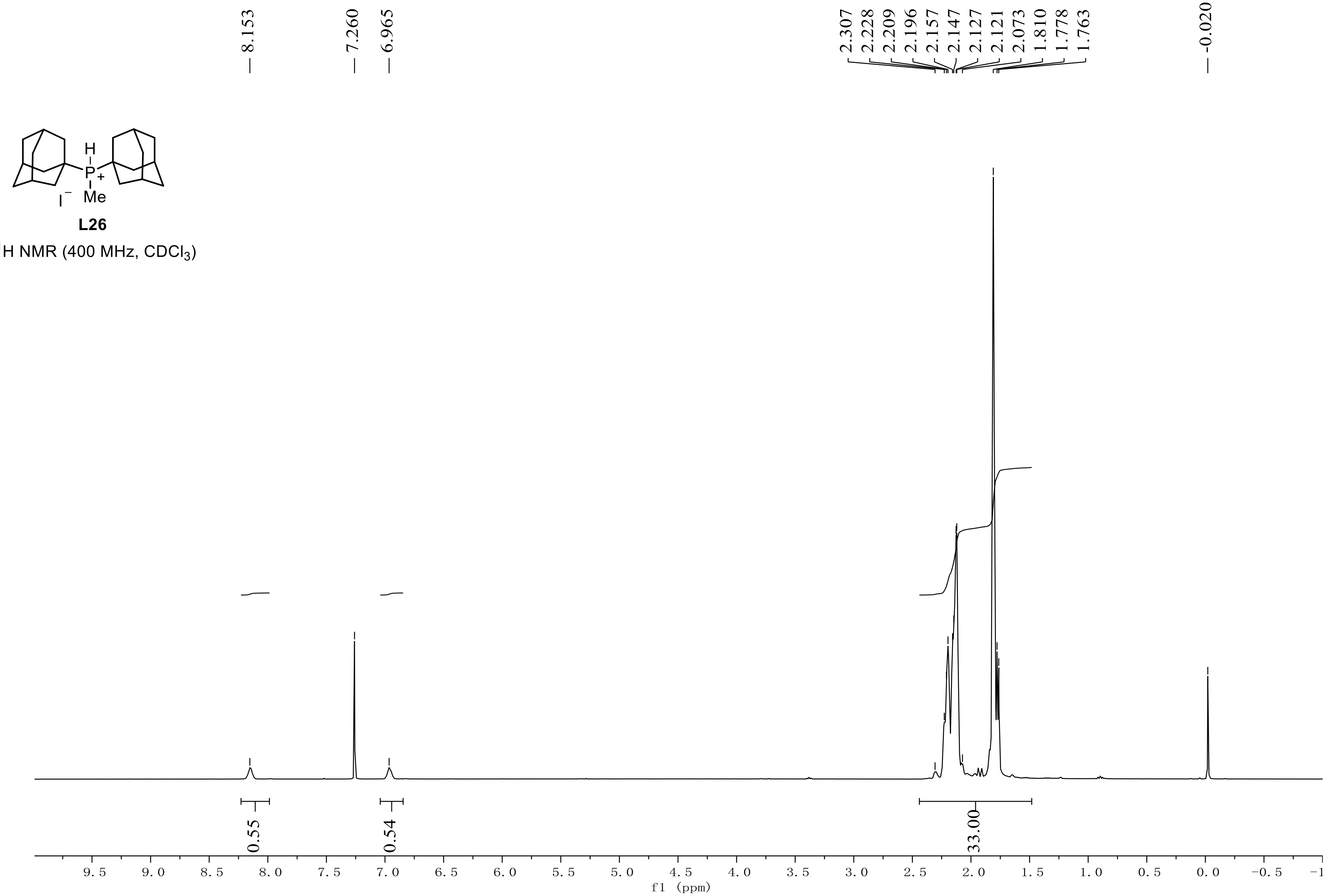
L25

^{13}C NMR (100 MHz, $CDCl_3$)

L25

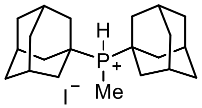
^{31}P NMR ($CDCl_3$)





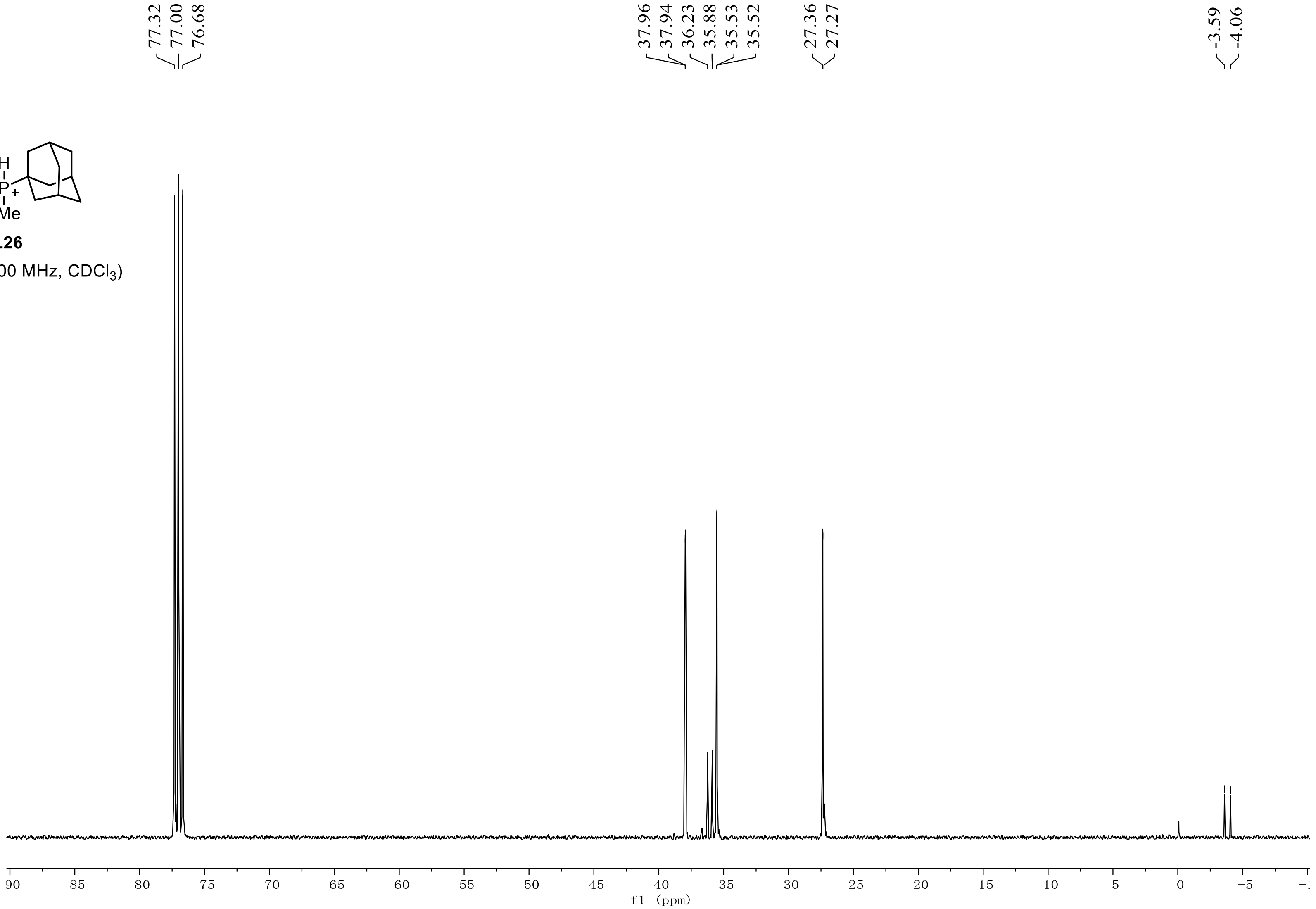
L26

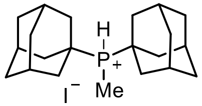
^{1}H NMR (400 MHz, $CDCl_3$)



L26

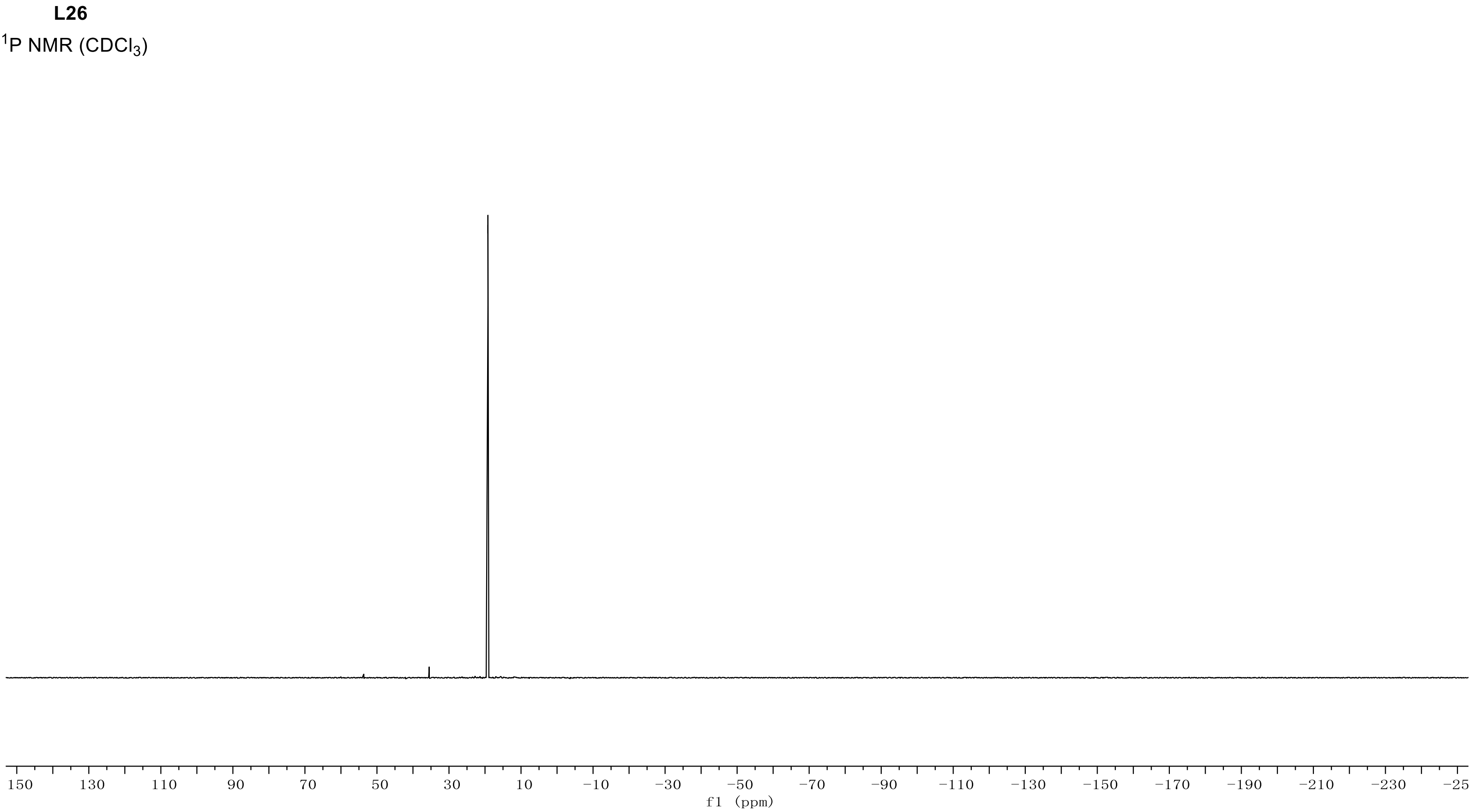
^{13}C NMR (100 MHz, CDCl$_3$)

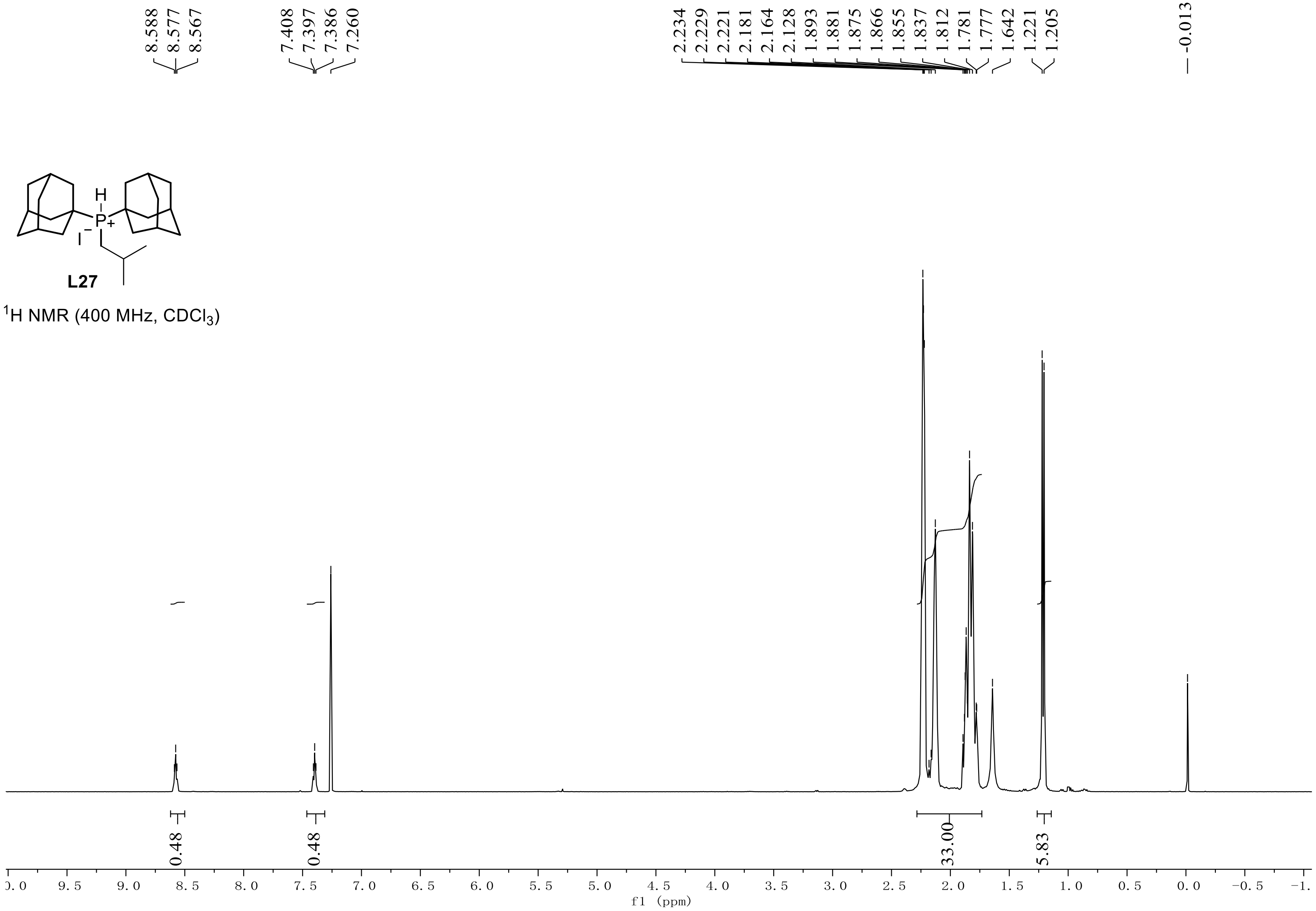




L26

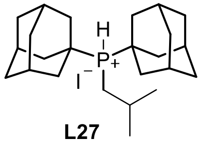
^{31}P NMR (CDCl$_3$)





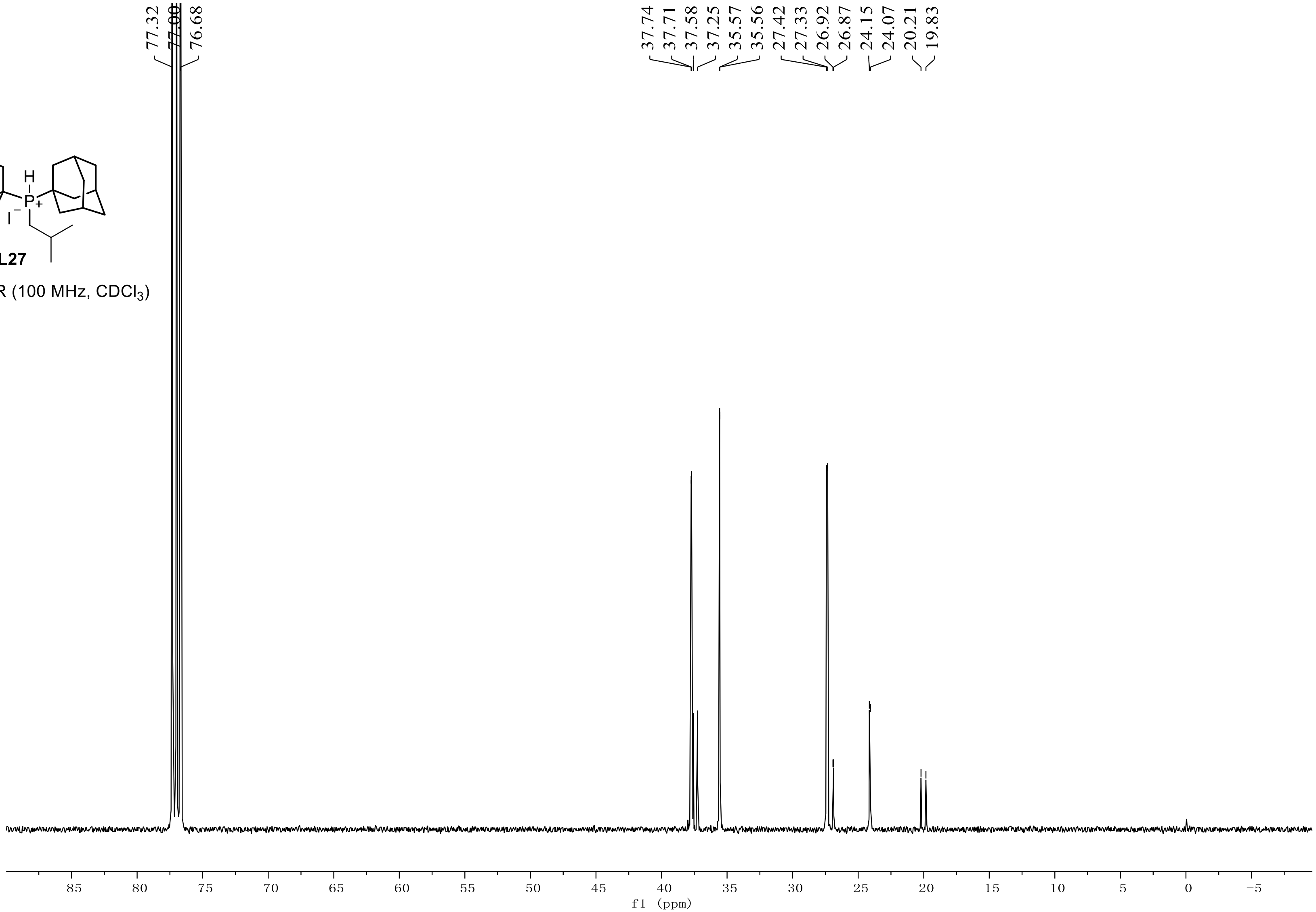
L27

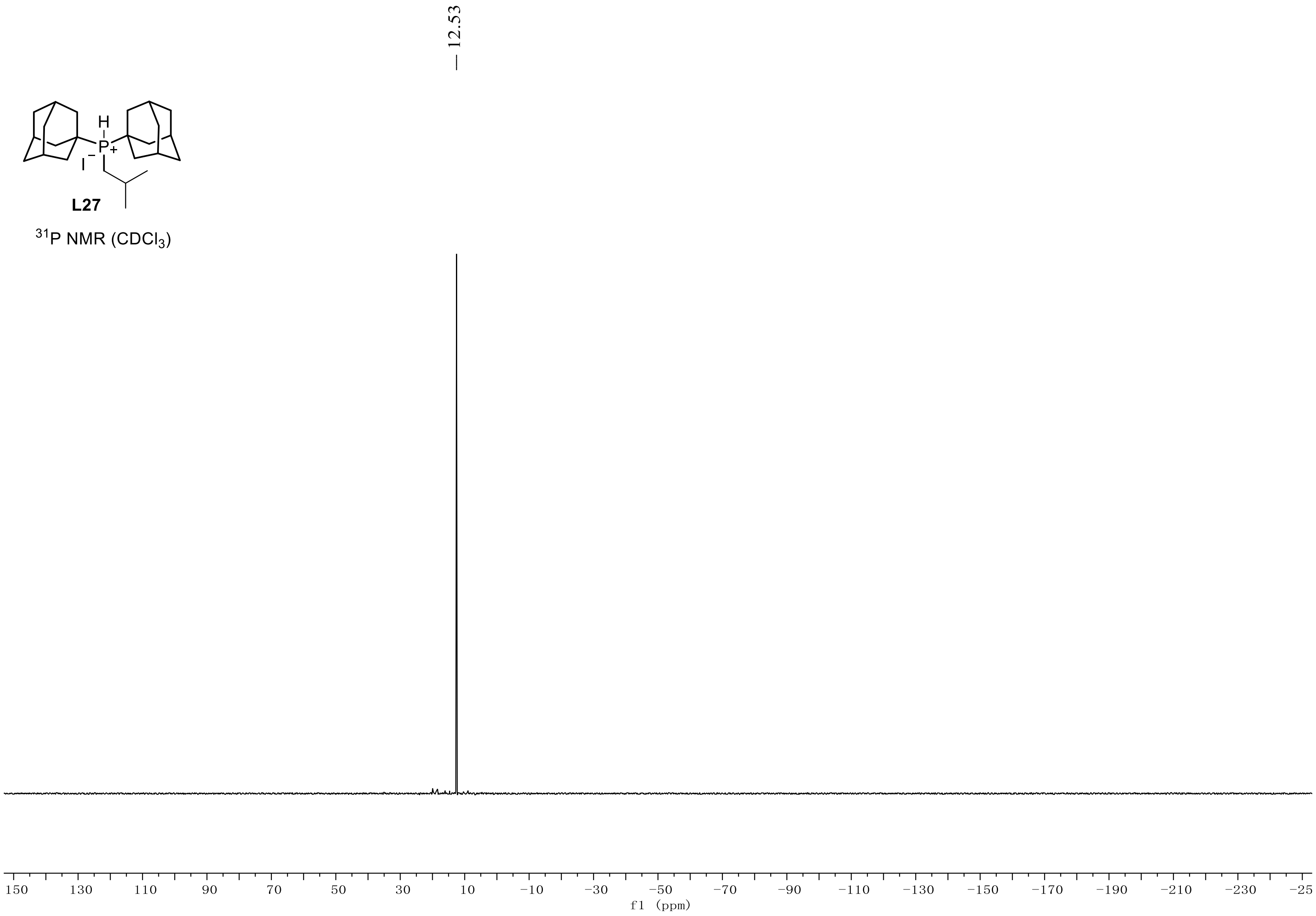
^{1}H NMR (400 MHz, CDCl$_3$)



L27

^{13}C NMR (100 MHz, $CDCl_3$)





L27

^{31}P NMR ($CDCl_3$)

IV. References

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