Supporting Information

Pd-Catalyzed Dimethylation of Tyrosine-Derived Picolinamide for Synthesis of (S)-N-Boc-2,6-dimethyltyrosine and Its Analogues

Xuning Wang,[†] Songtao Niu,[†] Lanting Xu,[‡] Chao Zhang,[‡] Lingxing Meng,[‡] Xiaojing Zhang,[†*] and Dawei Ma[‡]*

[†]*Shenyang Pharmaceutical University, 103 Wenhua Lu, Shenyang 110016, China*

[‡]*State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China*

E-mail: madw@mail.sioc.ac.cn

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1. General Information

Reagents:

All commercial materials were used as received unless otherwise noted. Toluene was distilled from Na. $Pd(OAc)_2$ (98%, TCI) were used in the Pd-catalyzed reactions. Flash chromatography was performed using 230-400 mesh SiliaFlash® P60 (Silicycle Inc.).

Reactions:

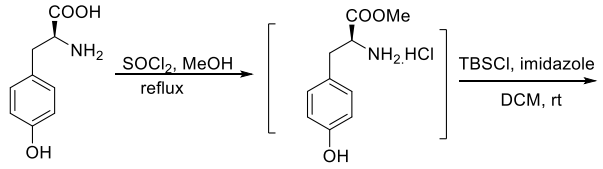
All reactions for the Pd-catalyzed *ortho*-dimethylation of tyrosine-derivatives were set up on bench-top in the open air and carried out in re-sealable test tubes with Teflon septa under different atmosphere. Unless otherwise noted, the reaction test tubes were cooled to room temperature prior to other operations. Unless otherwise noted, the solvents and the solutions of reagents/reactants were transferred via microsyringe or plastic syringe (fitted with metal needle) into the reaction test tubes under a positive pressure (oxygen or argon).

Instruments:

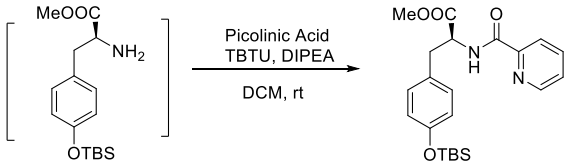
NMR spectra were recorded on Bruker Ultrashield™ 400 Plus, Agilent Technologies 400/54 Premium Shielded, Agilent Technologies 500/54 Premium Shielded instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet. High resolution ESI mass experiments were operated on a Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS instrument and a Thermo Fisher Scientific LTQ FT Ultra instrument. Optical rotations were obtained on a Jasco P1030 Polarimeter instrument and reported as follows: $[\alpha]_D^T$ (*c* = g/100 mL, solvent).

2. Substrate preparation

(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido) propanoate 7.



L-tyrosine



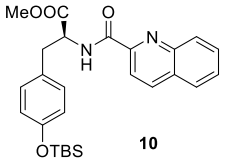
7

To a solution of *L*-tyrosine (9.06 g, 50 mmol) in anhydrous MeOH (50 mL) was added $SOCl_2$ (4.0 mL, 55 mmol) in a dropwise manner. The reaction mixture was heated at reflux overnight. The volatile was removed under vacuum to give the crude methyl *L*-tyrosinate hydrochloride as a white solid, which was used directly for the next step.

To a solution of the above crude product in dry DCM (250 mL) were added imidazole (4.08 g, 60 mmol) and TBSCl (9.04 g, 60 mmol). The reaction mixture was stirred at room temperature overnight before the reaction was quenched by adding saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give the crude TBS-ether as colorless oil, which was used directly for the next step.

A mixture of the above crude product, picolinic acid (7.4 g, 60 mmol,), TBTU (19.25 g, 60 mmol) and DIPEA (21.7 mL, 125 mmol) in anhydrous DCM (250 mL, 0.2 M) was stirred at room temperature overnight before the reaction was quenched by adding saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluting with 10:1 to 4:1 petroleum ether/ethyl acetate) to afford **7** (18.2 g, 88% yield for 3 steps) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.5 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.83 (td, *J* = 7.7, 1.5 Hz, 1H), 7.42 (dd, *J* = 7.2, 5.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.03-4.99 (m, 1H), 3.71 (s, 3H), 3.16 (d, *J* = 6.5 Hz, 2H), 0.96 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125

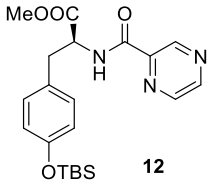
MHz, $CDCl_3$) δ 172.0, 164.1, 154.8, 149.5, 148.4, 137.4, 130.4, 128.8, 126.4, 122.4, 120.3, 53.7, 52.4, 37.7, 25.8, 18.3, -4.3; HRMS (ESI) Calcd. for $C_{22}H_{31}N_2O_4Si$ $(M + H)^+$ 415.2048, Found: 415.2052; $[\alpha]_D^{23.2}$ = +66.86 (*c* = 1, $CHCl_3$).



10

(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(quinoline-2-carboxamido)propanoate 10

Following the same procedure for preparing **7**, **10** was obtained by condensation of the silyl ether with quinalidic acid in 91% yield (4.23 g, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.4 Hz, 1H), 8.31-8.24 (m, 2H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.78-7.74 (m, 1H), 7.63-7.59 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 5.08-5.04 (m, 1H), 3.73 (s, 3H), 3.23 (d, *J* = 6.4 Hz, 2H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 164.2, 154.9, 149.2, 146.6, 137.6, 130.5, 130.2, 130.1, 129.5, 128.8, 128.1, 127.8, 120.3, 118.9, 53.8, 52.4, 37.7, 25.8, 18.3, -4.3; HRMS (ESI) Calcd. for $C_{26}H_{33}N_2O_4Si$ $(M + H)^+$ 465.2204, Found: 465.2207; $[\alpha]_D^{26.4}$ = +7.45 (*c* = 1, $CHCl_3$).

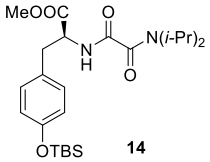


12

(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(pyrazine-2-carboxamido) -propanoate 12

Following the same procedure for preparing **7**, **12** was obtained by condensation of the silyl ether with 2-pyrazinecarboxylic acid in 79% yield (3.26 g, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.74 (d, *J* = 2.0 Hz, 1H), 8.52 (d, *J* = 1.2 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.05-4.99 (m, 1H), 3.73 (s, 3H), 3.18-3.16 (m, 2H), 0.95 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 162.7, 154.9, 147.5, 144.5, 144.1, 142.9, 130.3,

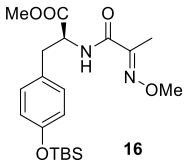
128.4, 120.4, 53.5, 52.5, 37.5, 25.8, 18.3, -4.3; HRMS (ESI) Calcd. for $C_{21}H_{30}N_3O_4Si$ $(M + Na)^+$ 416.2000, Found: 416.2000; $[\alpha]_D^{26.5}$ = +50.60 (*c* = 1, $CHCl_3$).



14

(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(2-(diisopropylamino)-2-oxoacetamido)propanoate 14

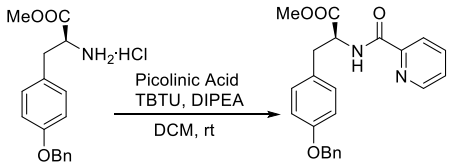
Following the same procedure for preparing **7**, **14** was obtained by condensation of the silyl ether with 2-[bis(1-methylethyl)amino]-2-oxoacetic acid in 64% yield (2.99 g, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.82-4.77 (m, 1H), 4.47- 4.44 (m, 1H), 3.69 (s, 3H), 3.50-3.45 (m, 1H), 3.12-3.00 (m, 2H), 1.41 (d, *J* = 6.4 Hz, 3H),1.40 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 6H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 162.9, 162.6, 154.9, 130.4, 128.3, 120.3, 53.5, 52.5, 49.8, 46.6, 37.4, 25.8, 21.0, 20.9, 20.2, 18.3, -4.3; ESI-HRMS Calcd for $C_2H_{41}N_2O_5Si$ $(M + H)^+$ 465.2779, Found: 465.2784; $[\alpha]_D^{27.1}$ = +30.9 (*c* = 1, $CHCl_3$).



16

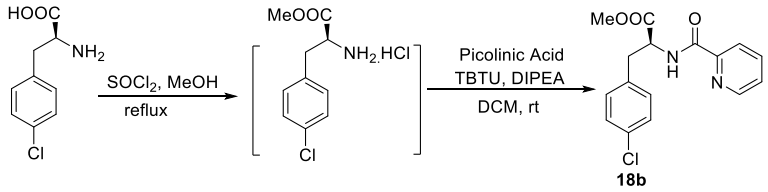
(*S*,*E*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(2-(methoxyimino)-propanamido) propanoate 16

Following the same procedure for preparing **7**, **16** was obtained by condensation of the silyl ether with 2-methoxyiminoacetic acid in 85% yield (3.5 g, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.85-4.80 (m, 1H), 3.94 (s, 3H), 3.68 (s, 3H), 3.05 (d, *J* = 6.0 Hz, 2H), 1.97 (s, 3H), 0.96 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 162. 7, 154.8, 150.0, 130.3, 128.5, 120.3, 63.0, 53.4, 52.3, 37.5, 25.7, 18.3, 9.7, -4.4; HRMS (ESI) Calcd. for $C_{20}H_{33}N_2O_5Si$ $(M + Na)^+$ 409.2153, Found: 409.2156; $[\alpha]_D^{26.5}$ = +23.03 (*c* = 1, $CHCl_3$).



18a

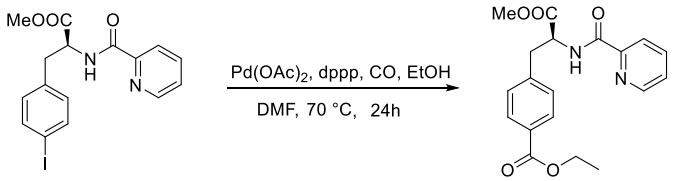
(*S*)-Methyl 3-(4-(benzyloxy)phenyl)-2-(picolinamido)propanoate 18a. A mixture of methyl (*S*)-3-(4-(benzyloxy)- phenyl)propanoate hydrochloride (3.22 g, 10 mmol, commercial available), picolinic acid (1.48 g, 12 mmol), TBTU (3.85 g, 12 mmol) and DIPEA (4.35 mL, 25 mmol) in anhydrous DCM (50 mL, 0.2 M) was stirred at room temperature overnight before the reaction was quenched by adding saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluting with 10:1 to 4:1 petroleum ether/ethyl acetate) to afford **18a** (3.12 g, 80%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 3.6 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 7.2 Hz, 1H), 7.86-7.83 (m, 6H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4Hz, 2H), 5.03 (s, 2H),5.05-5.01(m, 1H), 3.73 (s, 3H), 3.23-3.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 164.0, 158.0, 149.4, 148.4, 137.5, 137.1, 130.5, 128.7, 128.4, 128.1, 127.7, 126.5, 122.5, 115.1, 70.1, 53.8, 52.5, 37.6; HRMS (ESI) Calcd. for $C_{23}H_{23}N_2O_4$ $(M + H)^+$ 391.1652, Found: 391.1650; $[\alpha]_D^{26.5}$ = +55.92 (*c* = 1, $CHCl_3$).



18b

(*S*)-Methyl 3-(4-chlorophenyl)-2-(picolinamido)propanoate 18b. To a solution of 4-chloride-*L*-tyrosine (1.99 g, 10 mmol) in anhydrous MeOH (10 mL) was added dropwise $SOCl_2$ (0.8 mL, 11 mmol). The reaction mixture was heated at reflux overnight. The volatile was removed under vacuum to give the crude methyl *L*-tyrosinate hydrochloride as a white solid, which was used directly for the next step.

A mixture of the above crude ester, picolinic acid (1.48 g, 12 mmol), TBTU (3.85 g, 12 mmol) and DIPEA (4.4 mL, 25 mmol) in anhydrous DCM (50 mL, 0.2 M) was stirred at room temperature overnight before the reaction was quenched by adding saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluting with 10:1 to 4:1 petroleum ether/ethyl acetate) to afford **18b** (2.87 g, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.0 Hz, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.81 (td, *J* = 7.7, 1.6 Hz, 1H), 7.42-7.39 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.07-5.02 (m, 1H), 3.71 (s, 3H), 3.26-3.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 164.0, 149.2, 148.4, 137.5, 134.7, 133.1, 130.7, 128.8, 126.6, 122.4, 53.4, 52.5, 37.7; HRMS (ESI) Calcd. for $C_{16}H_{16}ClN_2O_3$ $(M + H)^+$ 319.0844, Found: 319.0846; $[\alpha]_D^{26.4}$ = +62.46 (*c* = 1, $CHCl_3$).



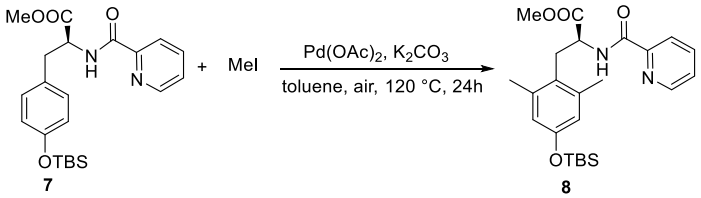
(*S*)-methyl-3-(4-iodophenyl)-2-(picolinamido)propanoate

18c

(*S*)-Ethyl 4-(3-methoxy-3-oxo-2-(picolinamido)propyl)benzoate 18c. A solution of (*S*)-methyl 3-(4-iodophenyl)-2-(picolinamido)propanoate (1.64 g, 4 mmol, prepared from (*S*)-2-amino-3-(4-iodophenyl)propanoic acid), Et_3N (2.2 mL,16 mmol), EtOH (9.3 mL, 160 mmol), $Pd(OAc)_2$ (180 mg, 0.8 mmol), and 1,3-bis(diphenylphosphino)-propane (330 mg, 0.8 mmol) in 20 mL anhydrous DMF was stirred at room temperature until everything dissolved. The mixture was placed under carbon monoxide atmosphere and stirred while heated at 70 ^{o}C with constant charging with additional carbon monoxide. The reaction was completed in about 7 h when TLC showed no remaining iodide. Reaction mixture was filtered through diatomaceous earth and the filtrate was partitioned between diethyl ether (100 mL) and water (100 mL). The aqueous portion was extracted with an additional portion of diethyl ether (200 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Silica gel flash chromatography (eluting with 10:1 to 3:1 petroleum ether/ethyl

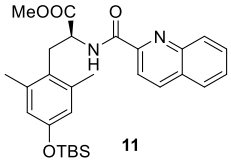
acetate) of the residue afforded **18c** (1.14 g, 80%) as a white solid.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.0 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.85 (dd, *J* = 7.6, 6Hz, 1H), 7.45 (dd, *J* = 6.6, 5.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.12-5.07 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.33 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.26 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 166.6, 164.0, 149.2, 148.4, 141.5, 137.6, 129.9, 129.4, 129.4, 126.7, 122.5, 61.1, 53.4, 52.6, 38.4, 14.5; HRMS (ESI) Calcd. for $C_{19}H_{21}N_2O_5$ $(M + H)^+$ 357.1445, Found: 357.1439; $[\alpha]_D^{26.4}$ = +49.64 (*c* = 1, $CHCl_3$).

3. Pd-catalyzed *ortho*-dimethylation of tyrosine derivatives



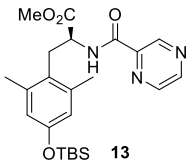
(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylphenyl)-2-(picolinamido) propanoate 8. A mixture of tyrosine derivative **7** (0.2 mmol), MeI (1 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), K_2CO_3 (83 mg, 0.6 mmol) and toluene (1 mL) in a 10 mL sealable test tubes with Teflon septa was heated at 120 ^oC with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and purified by column chromatography (eluting with 20:1 to 12:1 petroleum ether/ethyl acetate) to give **8** (80 mg, 90%) as a white solid. (When the reactions were conducted under oxygen or argon atmosphere, the solvents and the solutions of reagents/reactants were transferred via microsyringe or plastic syringe (fitted with metal needle) into the reaction test tubes under a positive pressure (oxygen or argon)).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.53 (m, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.79 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40 (dd, *J* = 6.4, 4.8 Hz, 1H), 6.49 (s, 2H), 4.97-4.91 (m, 1H), 3.64 (s, 3H), 3.17 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 6H), 0.95 (s, 9H), 0.16 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.81, 163.92, 153.90, 149.29, 148.27, 138.35,

137.31, 126.38, 126.03, 122.26, 119.88, 52.33, 52.10, 32.44, 25.75, 20.33, 18.23, -4.33; HRMS (ESI) Calcd. for $C_{24}H_{35}N_2O_4Si$ $(M + H)^+$ 443.2361, Found: 443.2358; $[\alpha]_D^{23.4}$ = -43.40 (*c* = 1, $CHCl_3$).



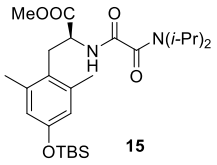
11

(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylphenyl)-2-(quinoline-2-carboxamido) propanoate 11. Compound **11** (14 mg) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.80-7.76 (m, 1H), 7.64-7.60 (m, 1H), 6.51 (s, 2H), 5.02-4.96 (m, 1H), 3.69 (s, 3H), 3.25 (d, *J* = 7.6 Hz, 2H), 2.40 (s, 6H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 164.2, 154.0, 149.2, 146.6, 138.5, 137.6, 130.2, 130, 129.5, 128.1, 127.8, 126.1, 120.0, 118.9, 52.5, 52.3, 32.5, 25.8, 20.5, 18.3, -4.3; HRMS (ESI) Calcd. for $C_{28}H_{37}N_2O_4Si$ $(M + H)^+$ 493.2517, Found: 493.2518; $[\alpha]_D^{28.1}$ = -42.76 (*c* = 1, $CHCl_3$).



13

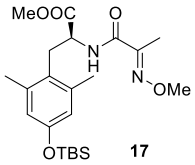
(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylphenyl)-2-(pyrazine-2-carboxamido) propanoate 13. Compound **13** (11 mg) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.74 (d, *J* = 2.4 Hz, 1H), 8.54 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 6.49 (s, 2H), 4.99-4.92 (m, 1H), 3.67 (s, 3H), 3.21-3.11 (m, 2H), 2.32 (s, 6H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 162.6, 154.1, 147.5, 144.5, 144.1, 142.8, 138.4, 125.8, 120.0, 52.5, 52.0, 32.4, 25.8, 20.4, 18.3, -4.3; HRMS (ESI) Calcd. for $C_{21}H_{30}N_3O_4Si$ $(M + Na)^+$ 466.2133, Found: 466.2128; $[\alpha]_D^{26.1}$ = -25.00 (*c* = 1, $CHCl_3$).



15

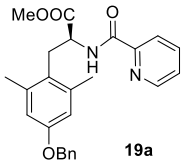
(*S*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylphenyl)-2-

(2-(diisopropylamino)-2-oxoacetamido)propanoate 15. Compound **15** (5 mg) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 1H), 6.49 (s, 2H), 4.78-4.72 (m, 1H), 4.46-4.38 (m, 1H), 3.63 (s, 3H), 3.50-3.43 (m, 1H), 3.12-3.00 (m, 2H), 2.29 (s, 6H), 1.40 (d, *J* = 6.8, 3H), 1.40 (d, *J* = 6.8, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 162.6, 162.4, 154.0, 138.5, 125.7, 119.8, 52.5, 51.8, 49.6, 46.7, 32.4, 25.8, 20.9, 20.9, 20.4, 20.2, 20.1, 18.3, -4.3; HRMS (ESI) Calcd. for $C_{26}H_{44}N_2NaO_5Si$ $(M + Na)^+$ 515.2912, Found: 515.2913; $[\alpha]_D^{24.6}$ = 1.32 (*c* = 1, $CHCl_3$).



17

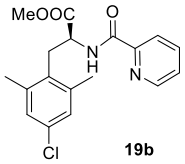
(*S*,*E*)- Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylphenyl)-2-(2-(methoxyimino)propanamido)propanoate 17. Compound **17** (19 mg) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 2H), 4.79-4.72 (m, 1H), 3.97 (s, 3H), 3.63 (s, 3H), 3.08-3.04 (m, 2H), 2.29 (s, 6H), 1.93 (s, 3H), 0.96 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 162.6, 154.0, 150.0, 138.3, 125.8, 119.9, 62.9, 52.3, 51.8, 32.2, 25.7, 20.3, 18.2, 9.6, -4.4; HRMS (ESI) Calcd. for $C_{22}H_{37}N_2O_5Si$ $(M + H)^+$ 437.2466, Found: 437.2465; $[\alpha]_D^{27.1}$ = -15.14 (*c* = 1, $CHCl_3$).



19a

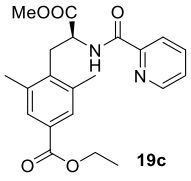
(*S*)-Methyl 3-(4-(benzyloxy)-2,6-dimethylphenyl)-2-(picolinamido)propanoate 19a. Compound **19a** (71 mg) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.56 (m, 2H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.82 (td, *J* = 7.6, 1.6 Hz, 1H), 7.44-7.31 (m, 6H), 6.66 (s, 2H), 5.00 (s, 2H), 5.03-4.92 (m, 1H), 3.68 (s, 3H), 3.21-3.18 (m, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.78, 164.02, 157.21, 149.35, 148.34, 138.56, 137.39, 137.29, 128.62, 127.95, 127.58, 126.45,

125.77, 122.34, 114.66, 69.79, 52.47, 52.29, 32.53, 20.57; HRMS (ESI) Calcd. for $C_{25}H_{27}N_2O_4$ $(M + H)^+$ 419.1965, Found: 419.1972; $[\alpha]_D^{27.7}$ = -164.48 (*c* = 1, $CHCl_3$).



19b

(*S*)-Methyl 3-(4-chloro-2,6-dimethylphenyl)-2-(picolinamido)propanoate 19b. Compound **19b** (7 mg) was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58-8.56 (m, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.81(td, *J* = 7.5, 1.0 Hz, 1H), 7.42 (dd, *J* = 7.5, 4.5 Hz, 1H), 6.97 (s, 2H), 5.00-4.95 (m, 1H), 3.68 (s, 3H), 3.23-3.15 (m, 2H), 2.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 164, 149.2, 148.3, 139.0, 137.5, 132.0, 131.8, 128.1, 126.5, 122.4, 52.5, 51.9, 32.7, 20.2; HRMS (ESI) Calcd. for $C_{18}H_{19}ClN_2NaO_3$ $(M + Na)^+$ 369.0976, Found: 369.0975; $[\alpha]_D^{27.9}$ = -41.02 (*c* = 1, $CHCl_3$).



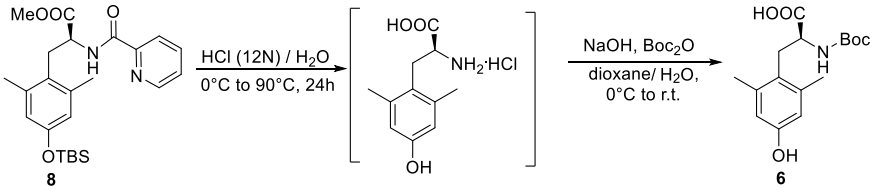
19c

(*S*)-Ethyl 4-(3-methoxy-3-oxo-2-(picolinamido)propyl)-3,5-dimethylbenzoate 19c. Compound **19c** (15 mg) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.8 Hz, 1H), 8.57 (d, *J* = 4.4 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.83-7.79 (m, 1H), 7.66 (s, 2H), 7.43 (dd, *J* = 7.2, 4.8 Hz, 1H), 5.06-4.99 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 3.28 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 6H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 166.8, 164.0, 149.2, 148.3, 138.6, 137.4, 137.4, 129.3, 128.7, 126.5, 122.4, 60.9, 52.5, 51.7, 33.3, 20.2, 14.4; HRMS (ESI) Calcd for $C_{21}H_{25}N_2O_5$ $(M + H)^+$ 385.1758, Found: 385.1754; $[\alpha]_D^{27.4}$ = -45.50 (*c* = 1, $CHCl_3$).

4. Scaling up the dimethylation and synthesis of (S)-N-Boc-2,6-dimethyltyrosine

A mixture of **7** (20.7 g, 50 mmol), MeI (15.6 mL, 250 mmol), $Pd(OAc)_2$ (0.56 g, 2.5

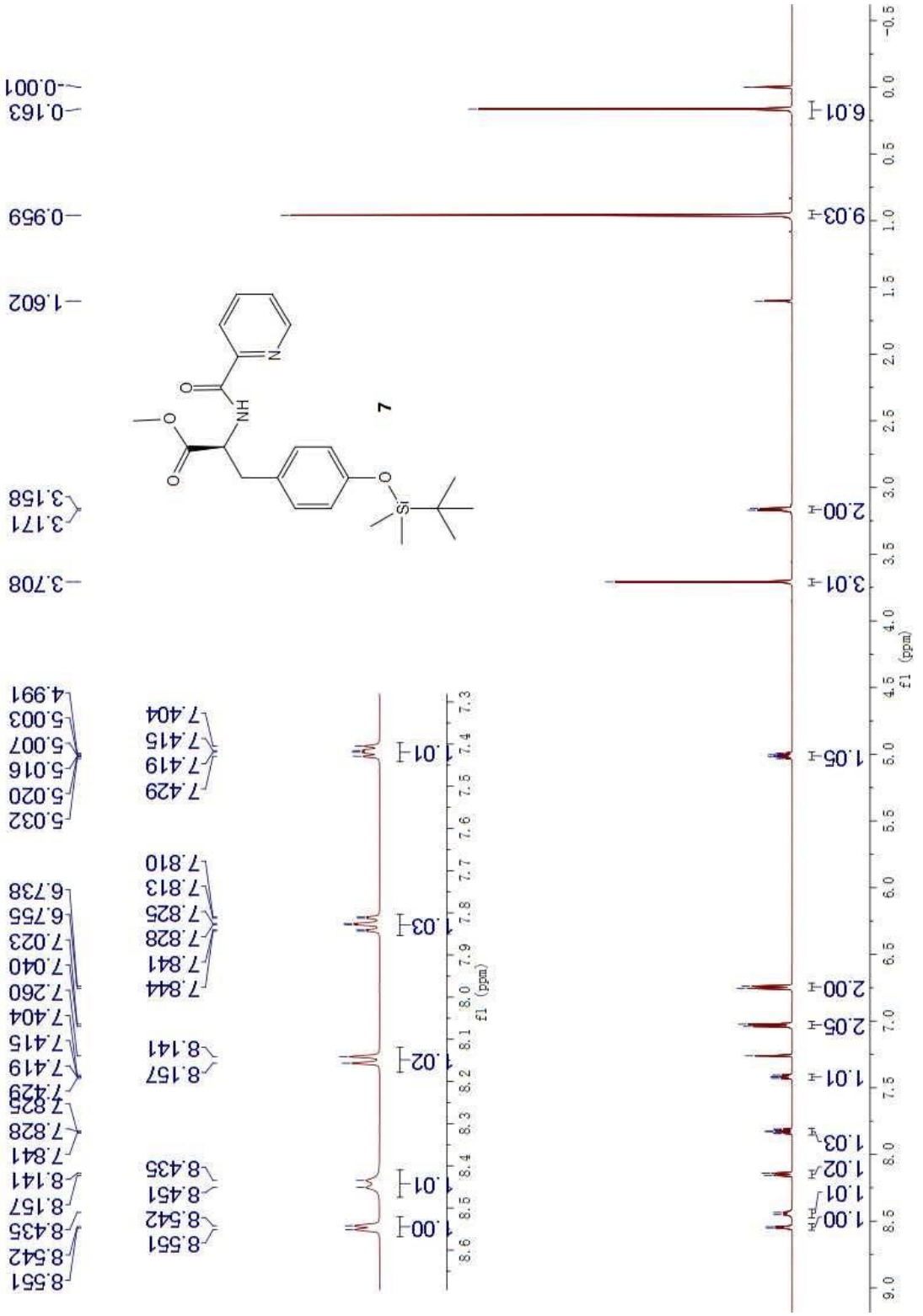
mmol), K_2CO_3 (20.7 g, 150 mmol) and toluene (200 mL) in a pressure-resistant glass bottle was heated at 120 ^oC with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate and filtered through diatomaceous earth. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluting with 20:1 to 12:1 petroleum ether/ethyl acetate) to give **8** (19.9 g, 90%) as a white solid.

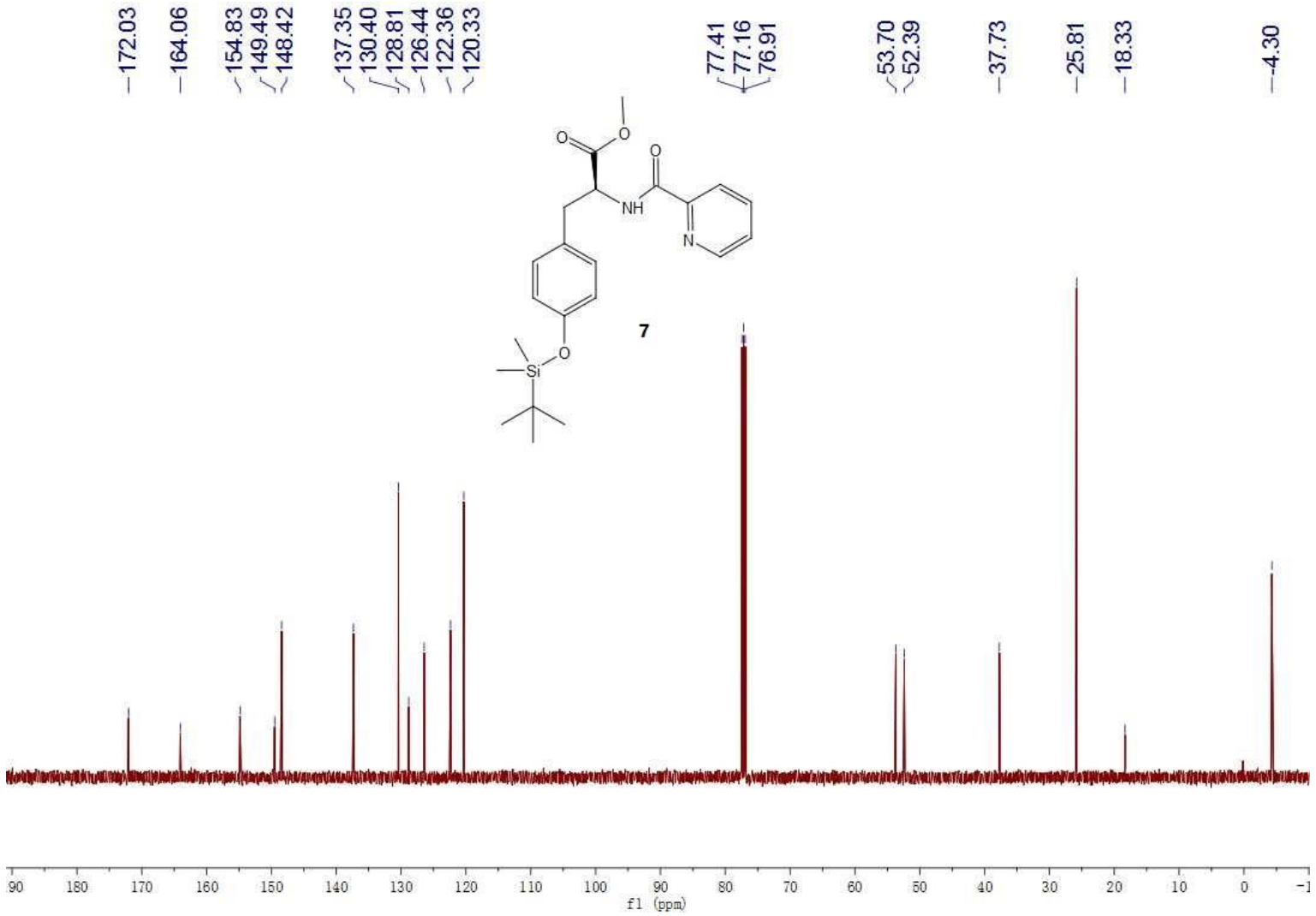


(*S*)-*N*-Boc-2,6-Dimethyltyrosine. The product **8** (8.85 g, 20 mmol) was added to a 250 mL jacketed reactor containing water (28 mL) to give a slurry. Hydrochloric acid (12 N, 28 mL, 340 mmol) was added dropwise at 0 ^oC. The reaction mixture was heated at 90 ^oC for 24 h. The cooled solution was concentrated in vacuo to give crude product, which was used directly for the next step.

To a suspension of the above crude product in water (40 mL) and dioxane (80 mL) at 0 ^oC was added 1 N NaOH to adjust pH to 9~10. After that di-*tert*-butyl dicarbonate (4.3 g, 22 mmol) was added and the mixture was stirred for 4 h at ambient temperature. The dioxane was removed *in vacuo*, the aqueous phase was cooled to 0 ^oC, and the pH was adjusted to 1.4 using HCl (1 N). After the mixture was extracted with ethyl acetate, the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ((eluting with 4:1 to 5:2 petroleum ether/ethyl acetate) to give the product **6** (5.75 g, 93%) as a white solid. ^1H NMR (500 MHz, d_6-DMSO) δ (for major rotamer) 8.92 (s, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.37 (s, 2H), 3.99-3.95 (m, 1H), 2.93 (dd, J = 14, 6.3 Hz, 1H), 2.77 (dd, J =14.5, 8.5 Hz, 1H), 2.17 (s, 6H), 1.32 and 1.17 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO) δ (for major rotamer) 173.9, 155.3, 155.1, 137.8, 125.2, 114.8, 78.0, 53.9, 30.7, 28.2, 20.1; $[\alpha]_D^{24.5}$ = -10.46 (c = 1, MeOH); 99.3% ee

5. Copies of ^{1}H and ^{13}C Spectrum

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126.44
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120.33
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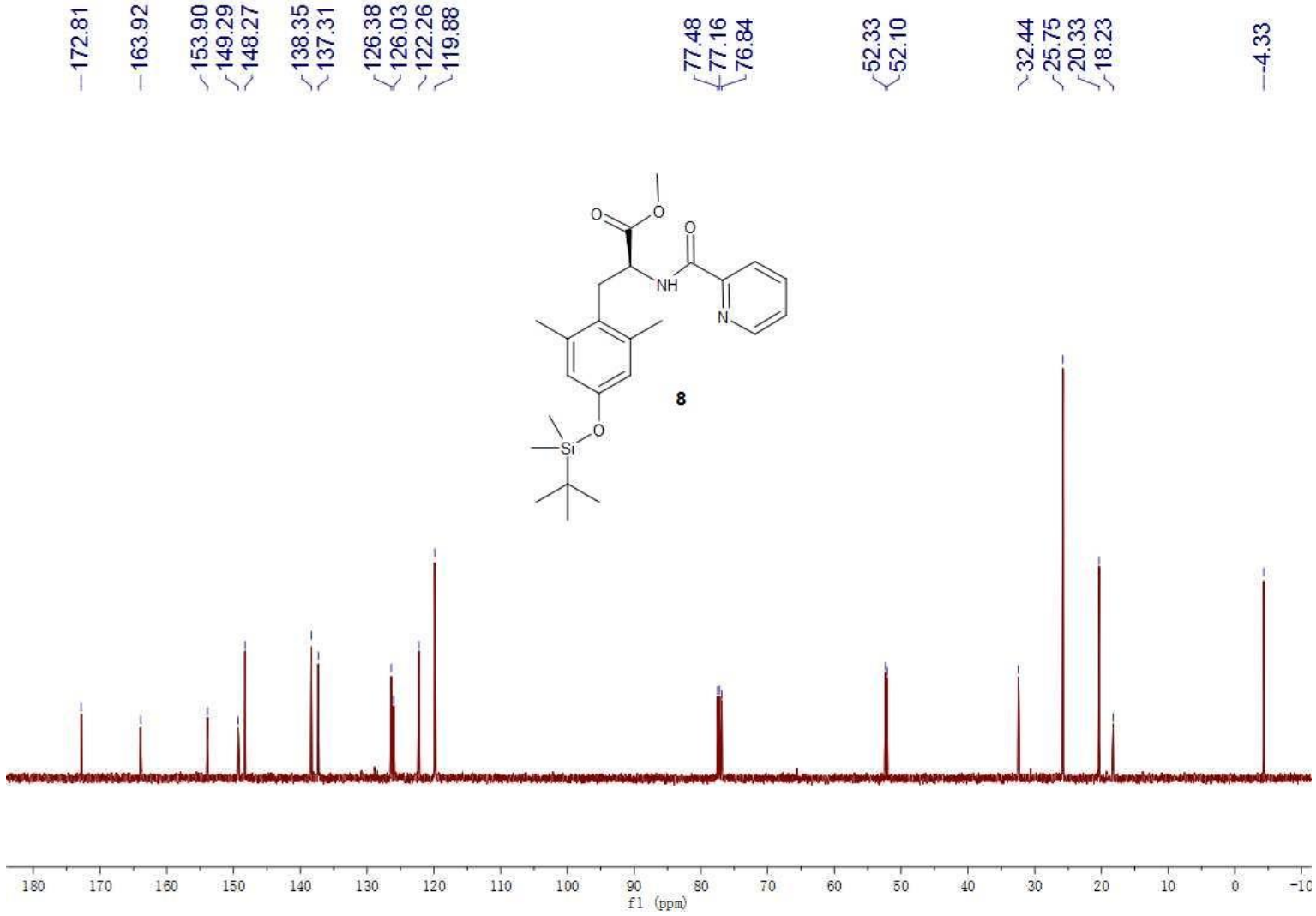
18.33
4.30
7
f1 (ppm)

8
f1 (ppm)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137.31
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52.33
52.10
32.44
25.75
20.33
18.23
4.33
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O
O
NH
N
O
Si
8
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120
110
100
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80
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60
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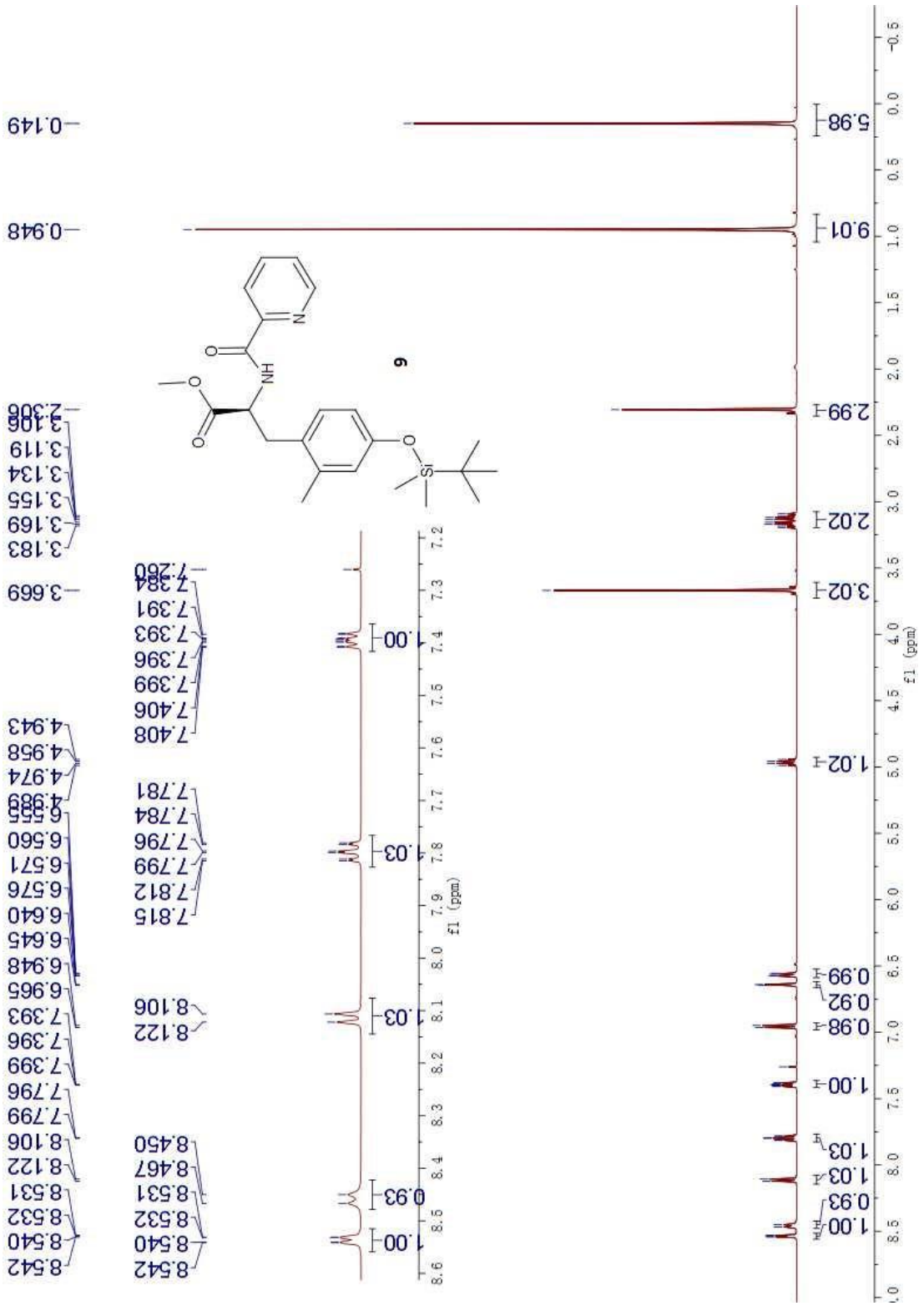
40
30
20
10
0
-10
f1 (ppm)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Si
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4.974
4.989
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6.560
6.571
6.576
6.640
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7.393
7.396
7.399
7.406
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7.784
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7.799
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8.540
8.542
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1.03
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1.00
f1 (ppm)
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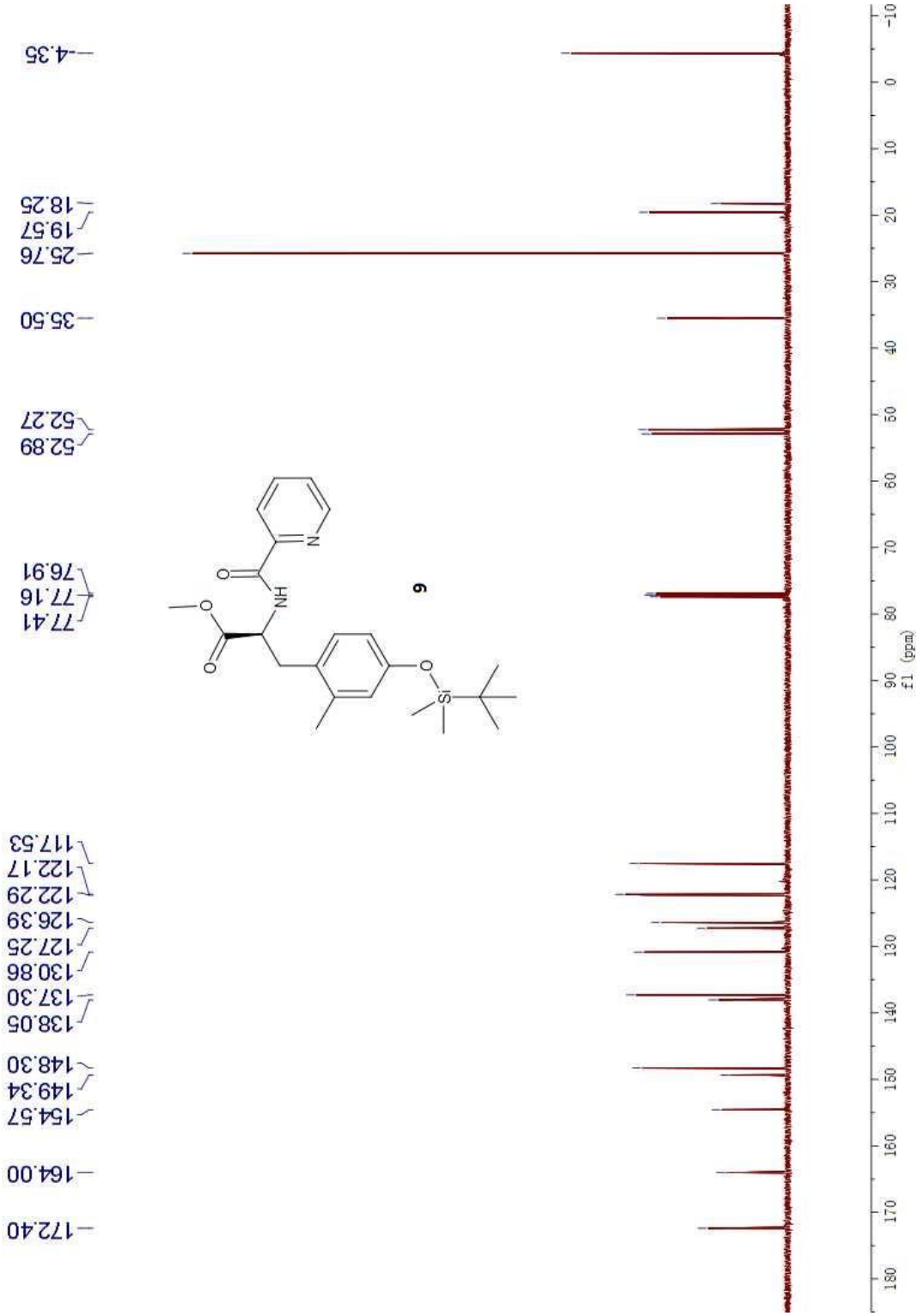
9.01
2.99
2.02
3.02
1.02
0.99
0.92
0.98
1.00
1.03
1.03
0.93
1.00
f1 (ppm)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76.91
77.16
77.41
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122.17
122.29
126.39
127.25
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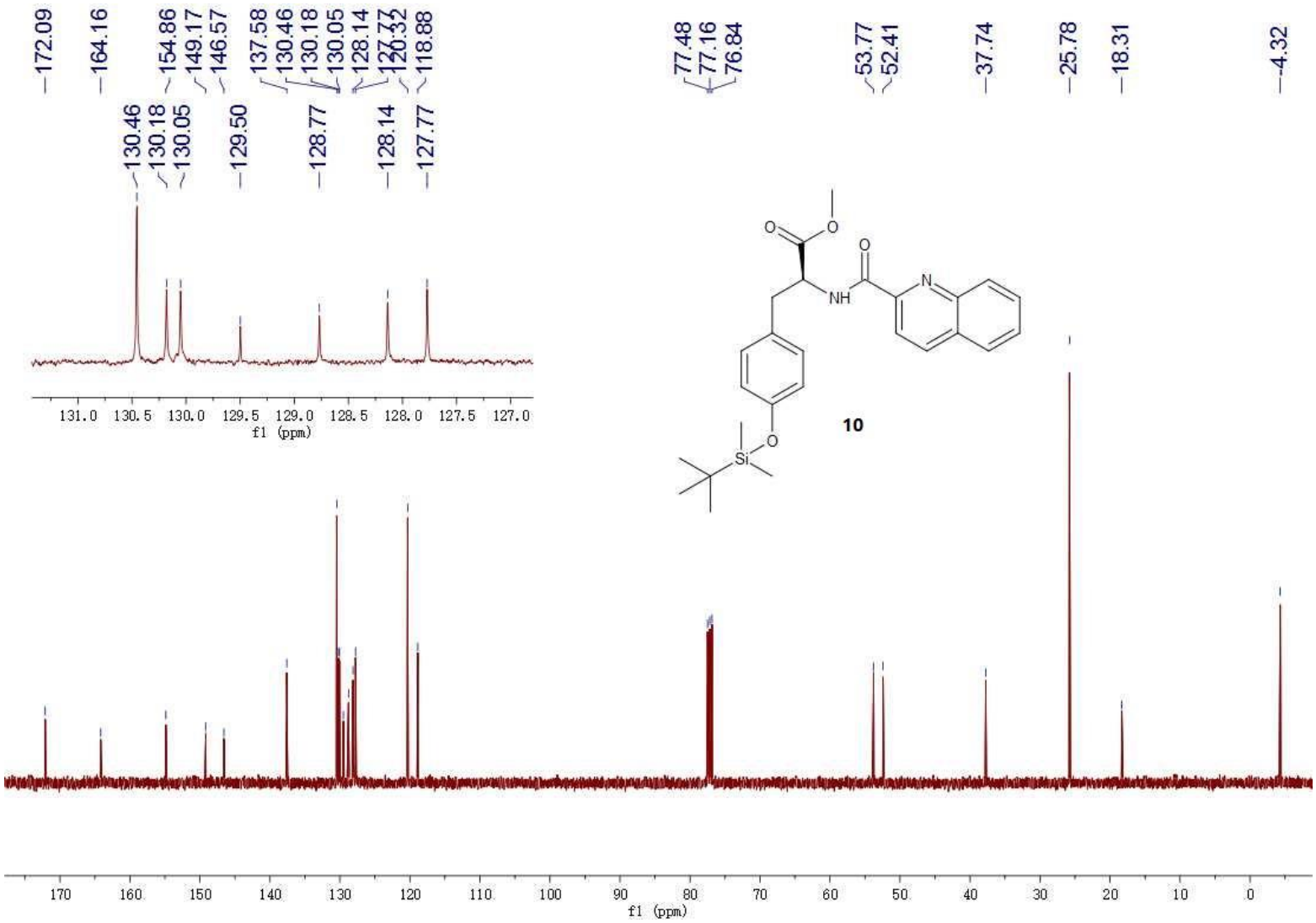
137.30
138.05
148.30
149.34
154.57
164.00
172.40
6
f1 (ppm)

10
f1 (ppm)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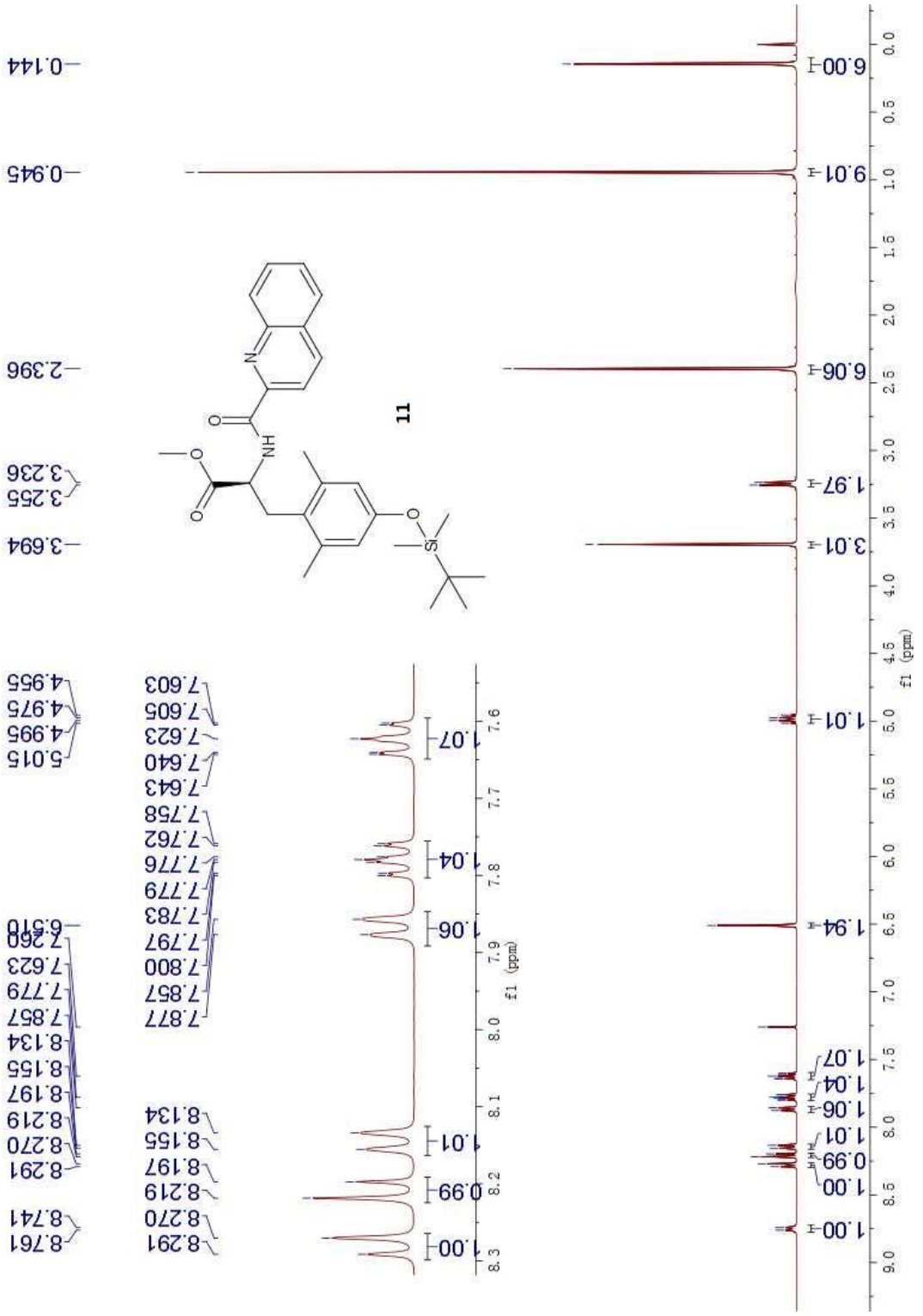
25.78
18.31
4.32
10
f1 (ppm)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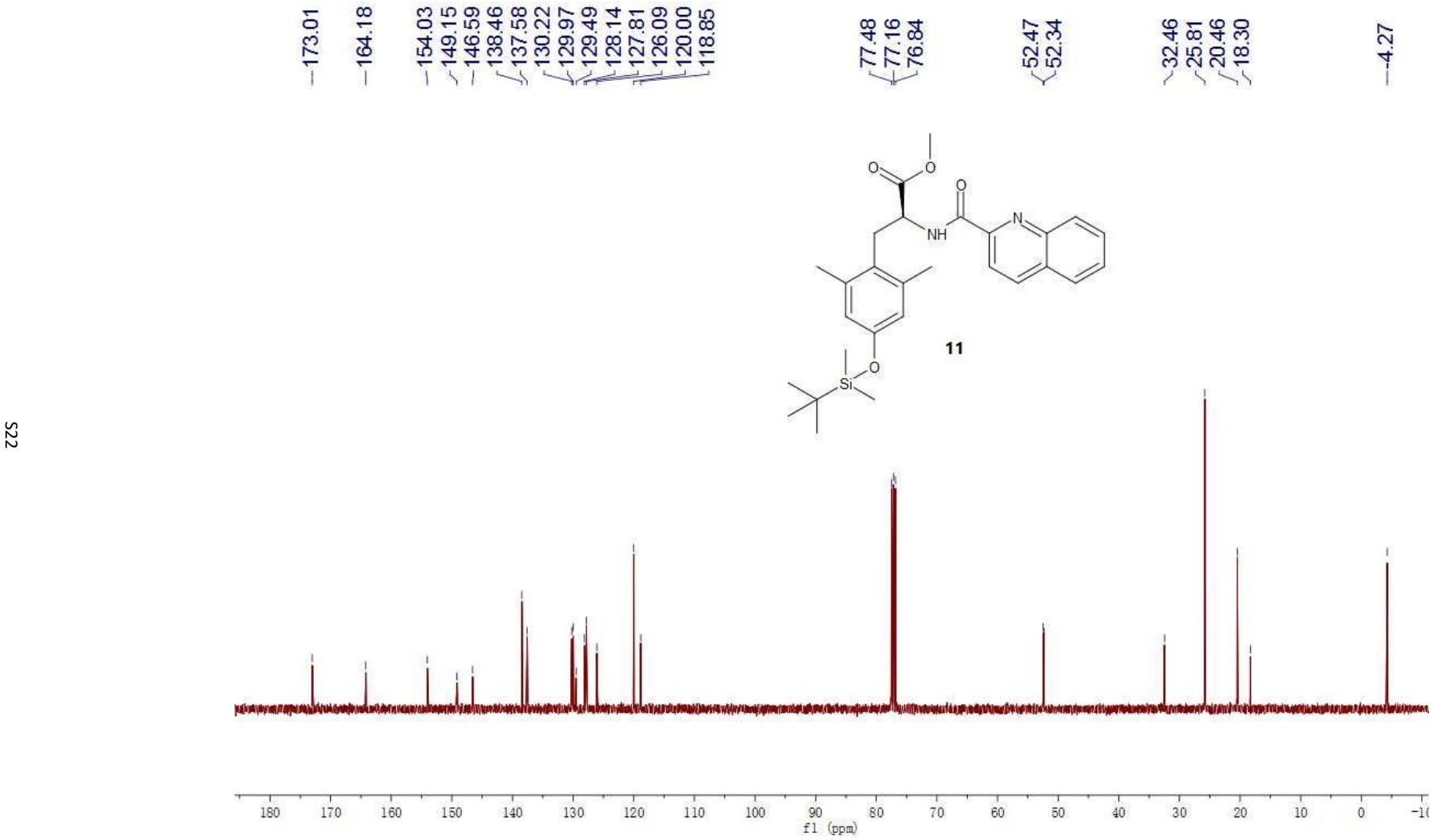
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128.14
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O
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180
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120
110
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50
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30
20
10
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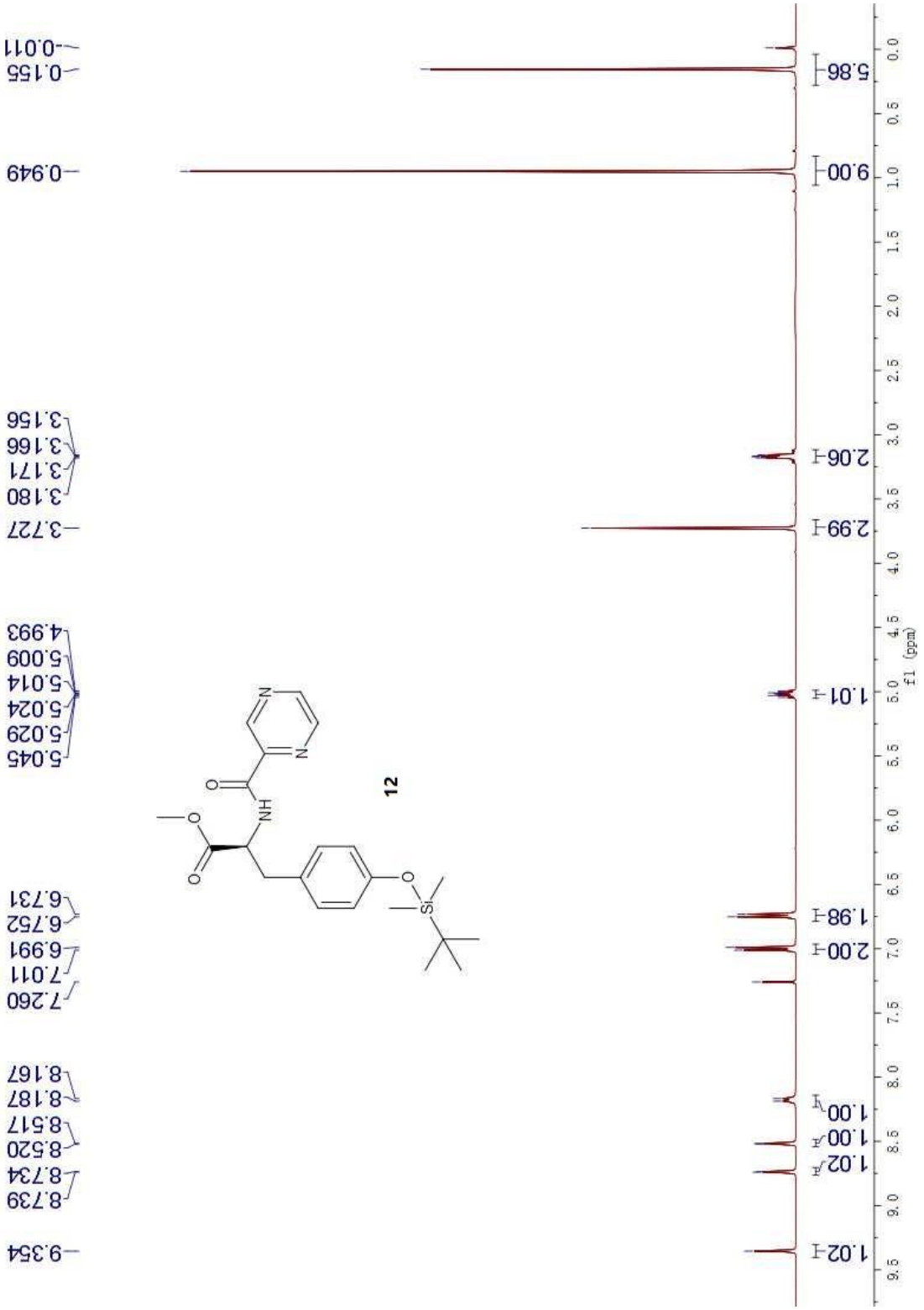
f1 (ppm)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5.029
5.024
5.014
5.009
4.993
3.727
3.180
3.171
3.166
3.156
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0.155
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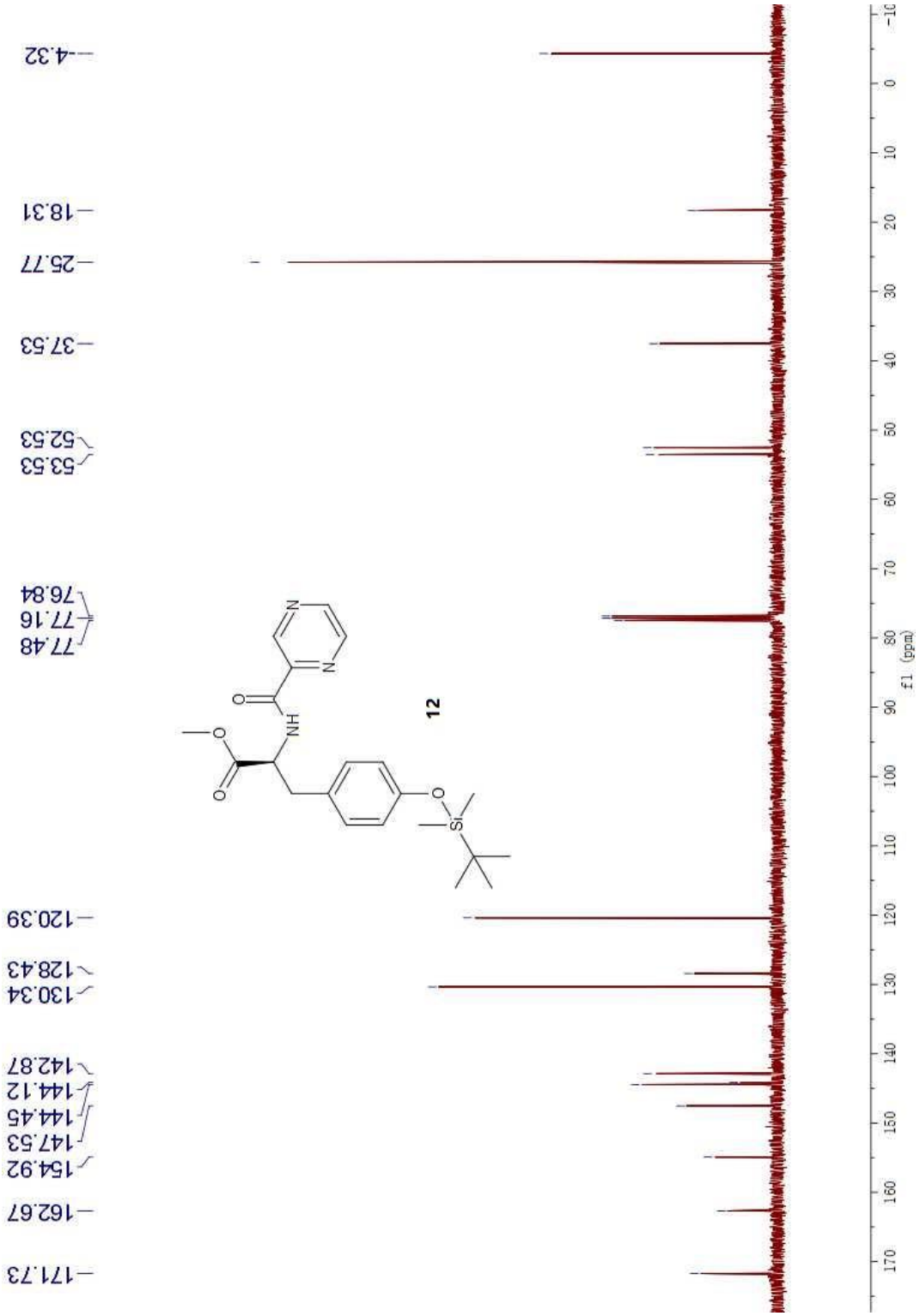
f1 (ppm)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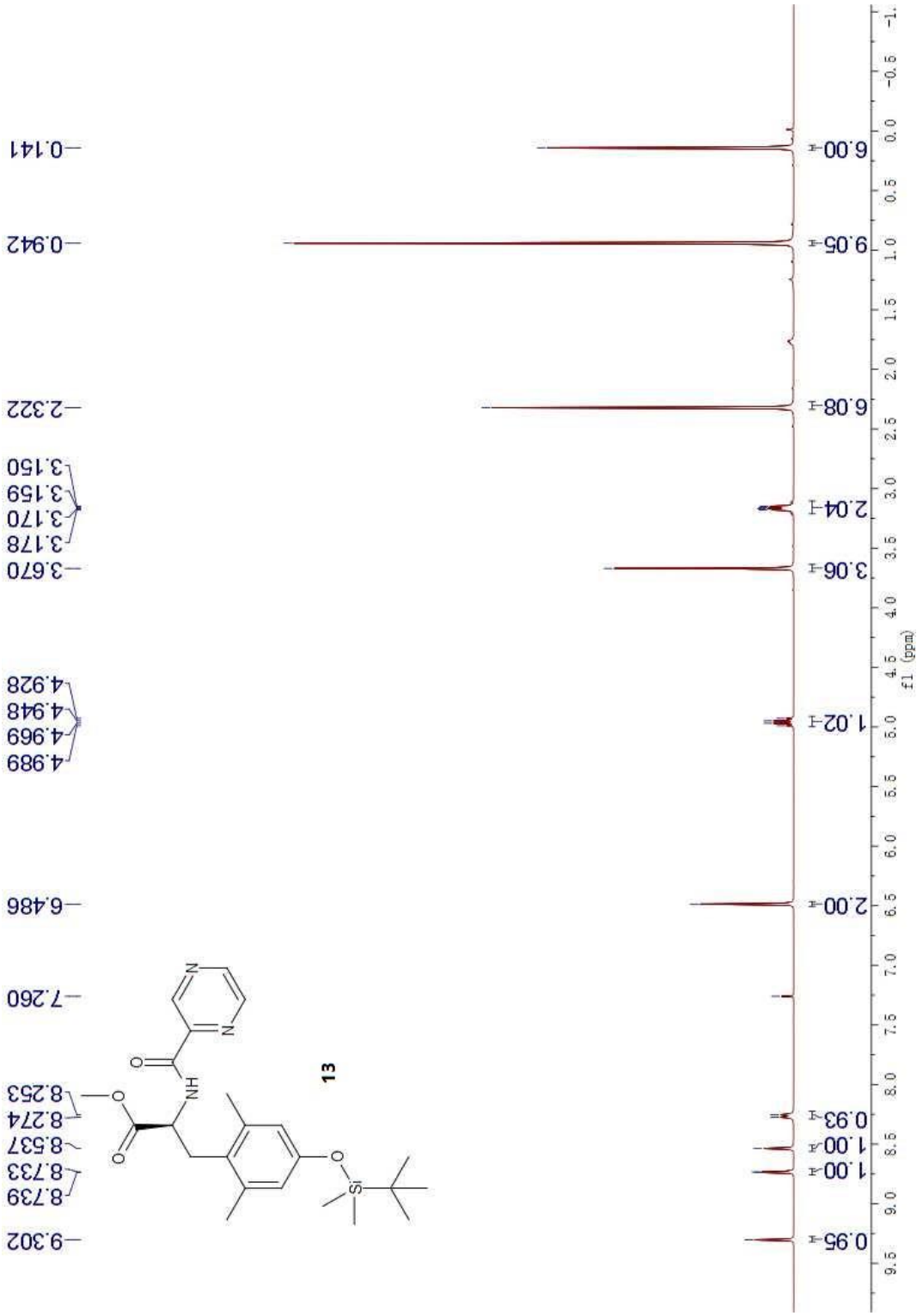
f1 (ppm)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3.178
3.170
3.159
3.150
2.322
0.942
0.141
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1.00
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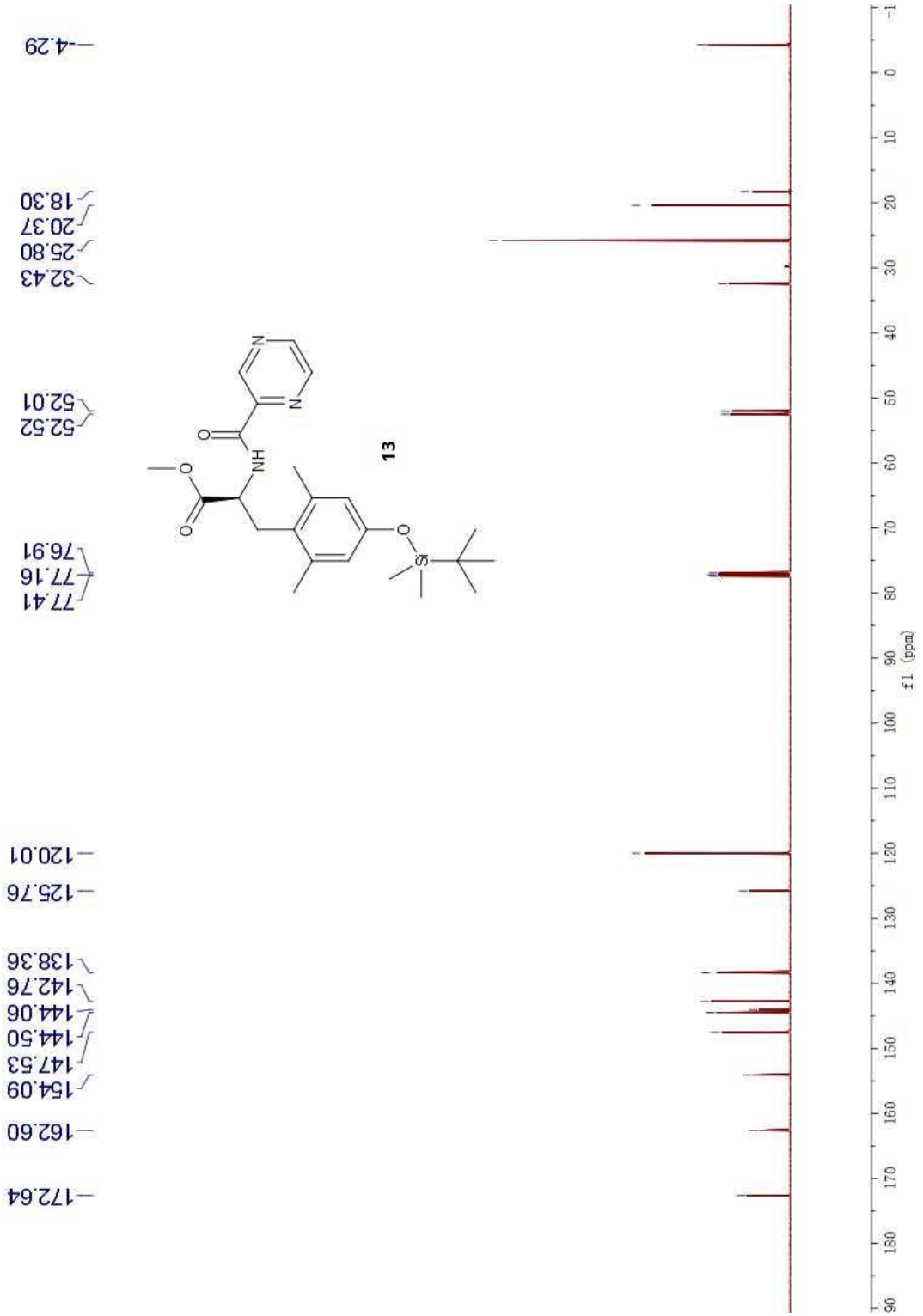
0.93
2.00
1.02
3.06
2.04
6.08
9.05
6.00
f1 (ppm)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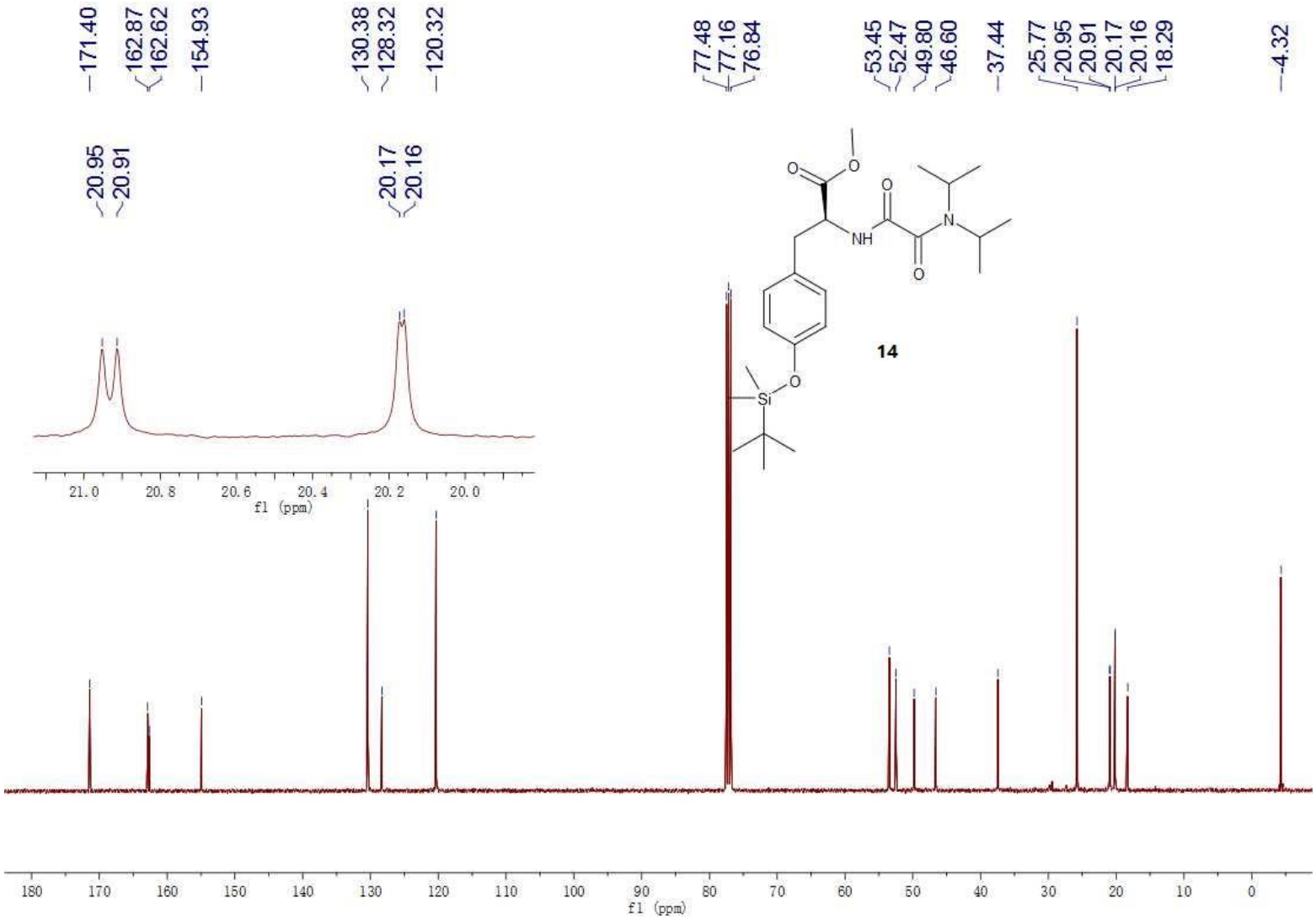
172.64
13
f1 (ppm)

14
f1 (ppm)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18.29
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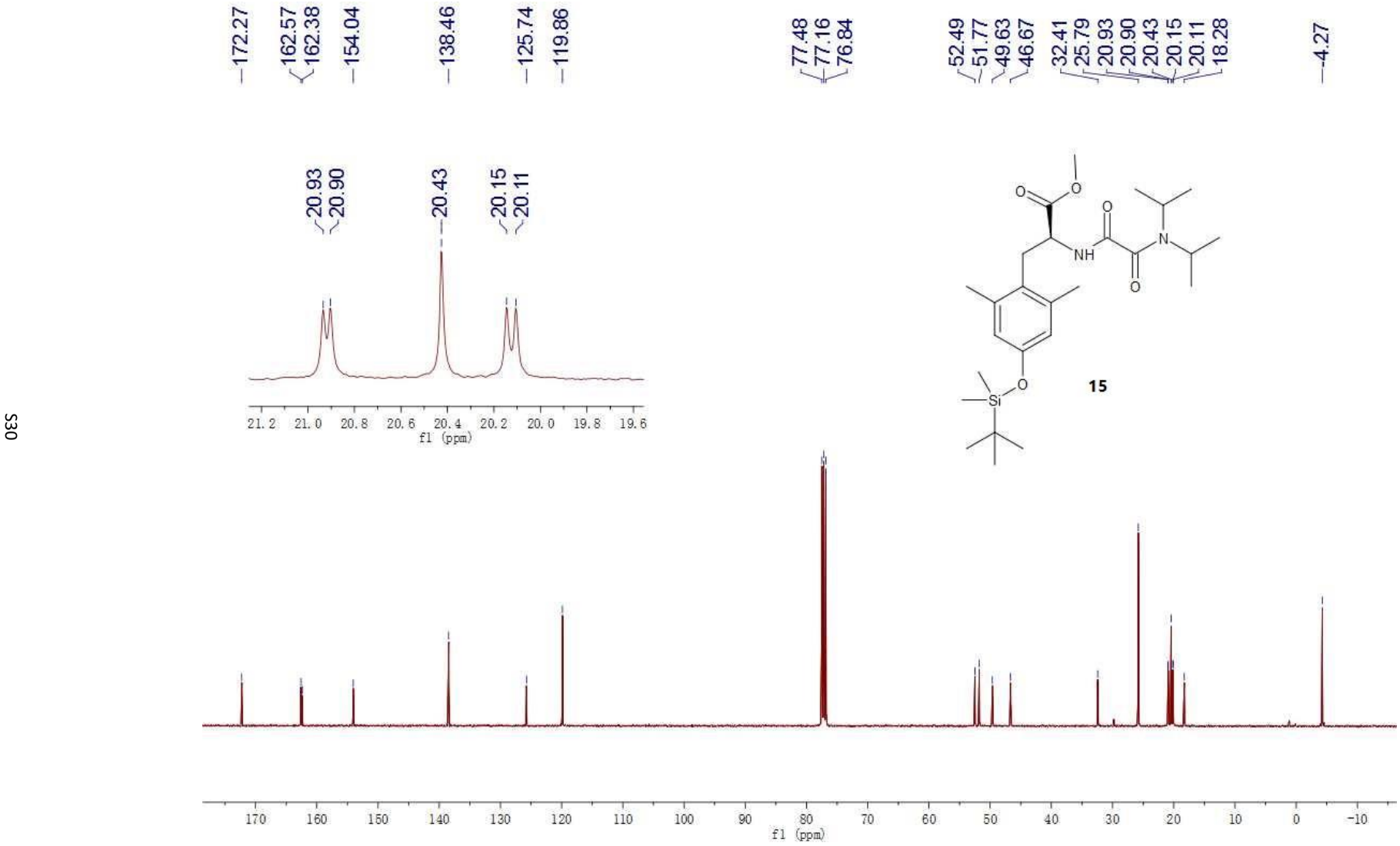
14
f1 (ppm)

15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20.90
20.43
20.15
20.11
18.28
4.27
20.93
20.90
20.43
20.15
20.11
21.2 21.0 20.8 20.6 20.4 20.2 20.0 19.8 19.6
f1 (ppm)
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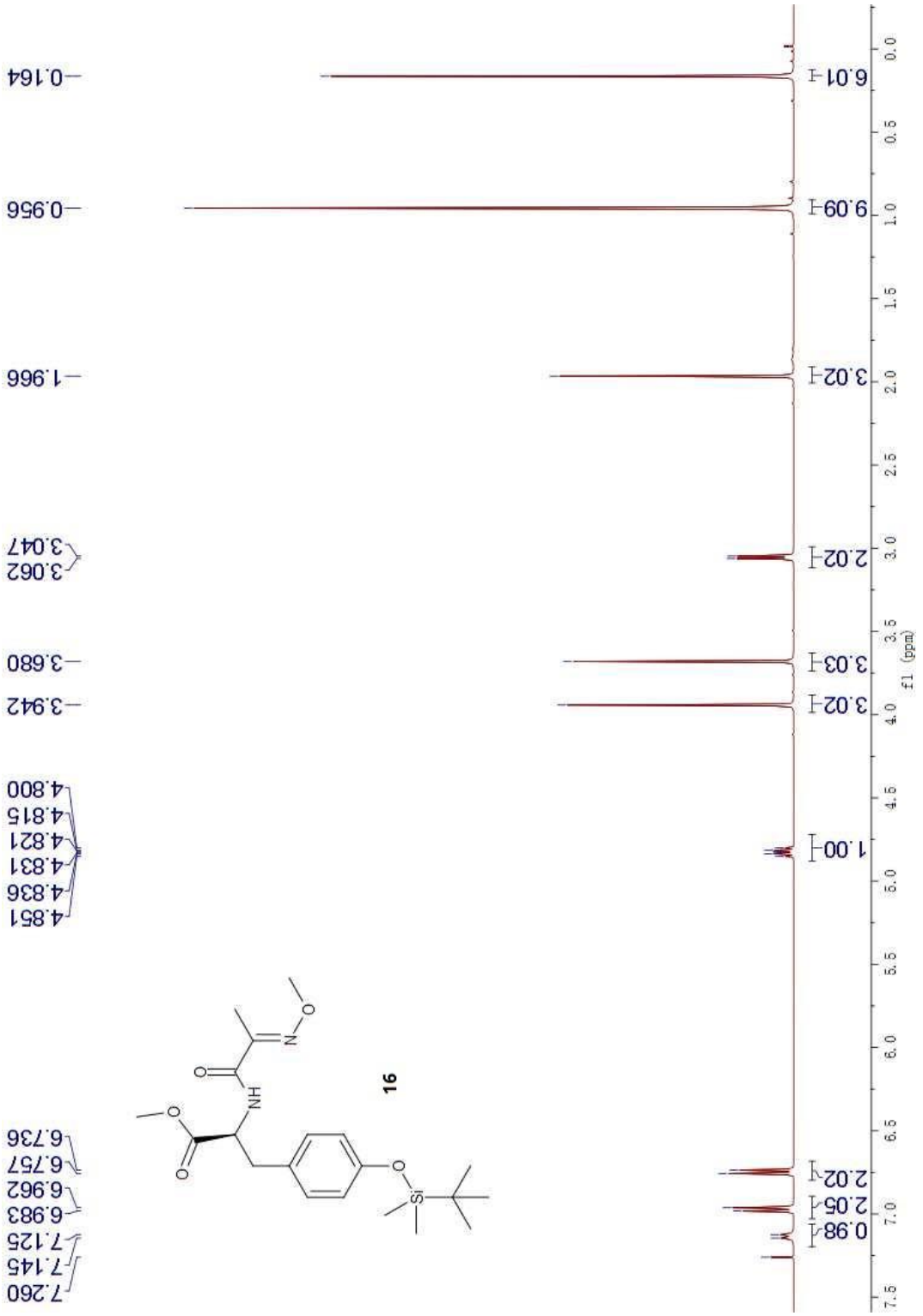
f1 (ppm)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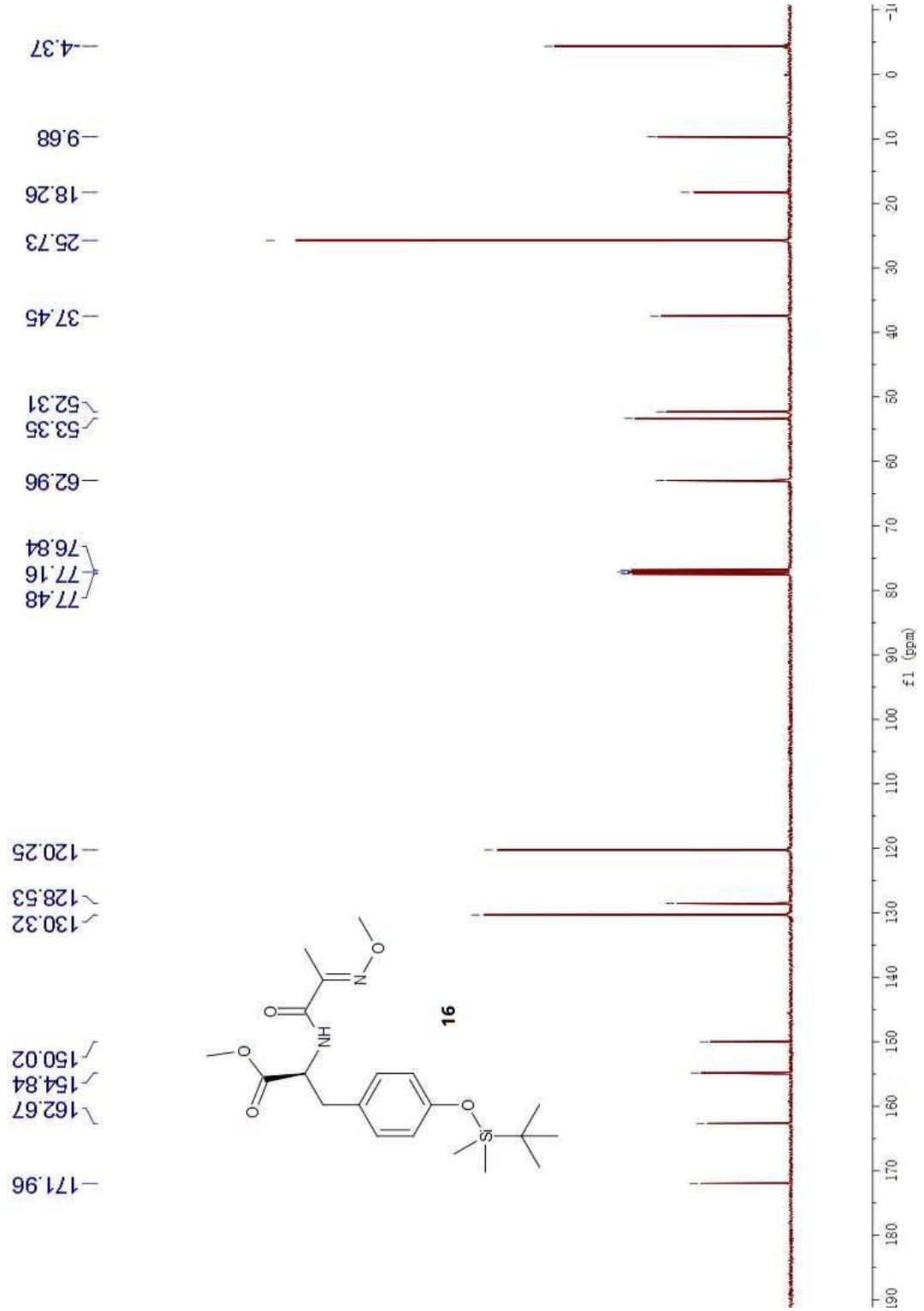
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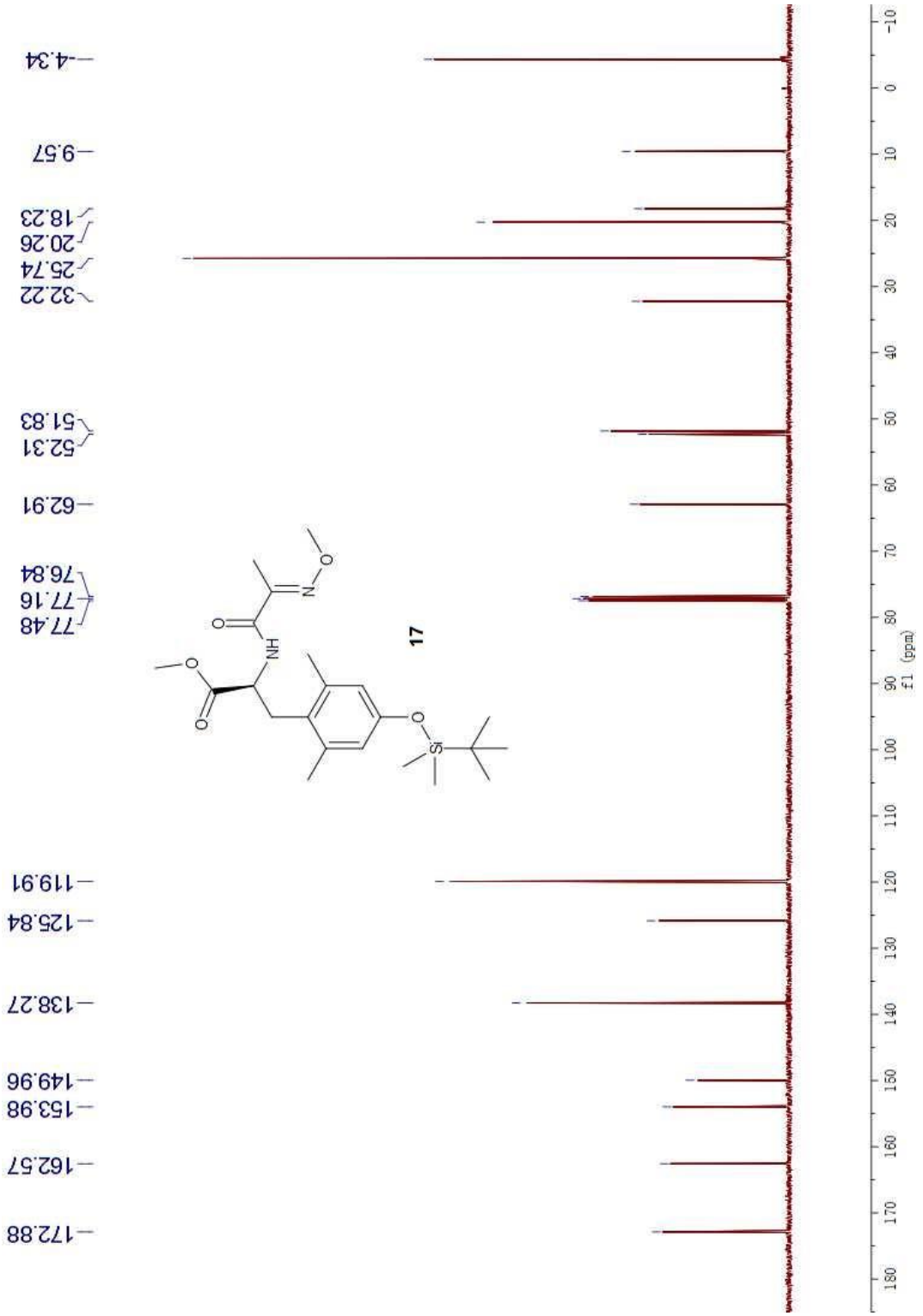
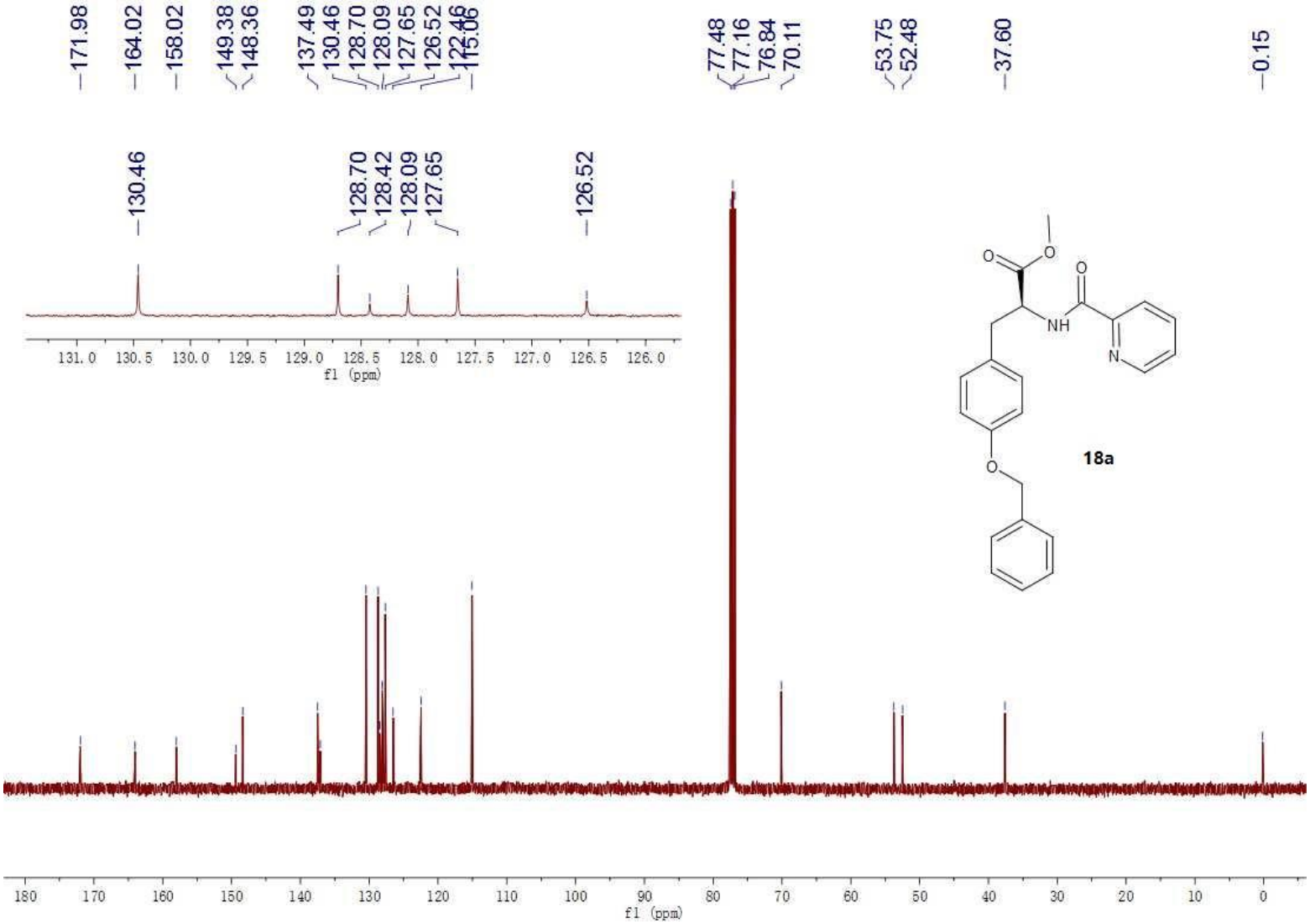
77.16
77.48
120.25
128.53
130.32
150.02
154.84
162.67
171.96
16
HN
O
N
Si
f1 (ppm)

0.163
0.958
1.929
2.294
3.046
3.057
3.066
3.077
3.630
3.972
4.725
4.745
4.765
4.786
6.495
7.202
7.222
7.260
6.00
9.01
3.03
6.03
2.02
3.07
3.06
1.00
2.01
1.05
f1 (ppm)
17

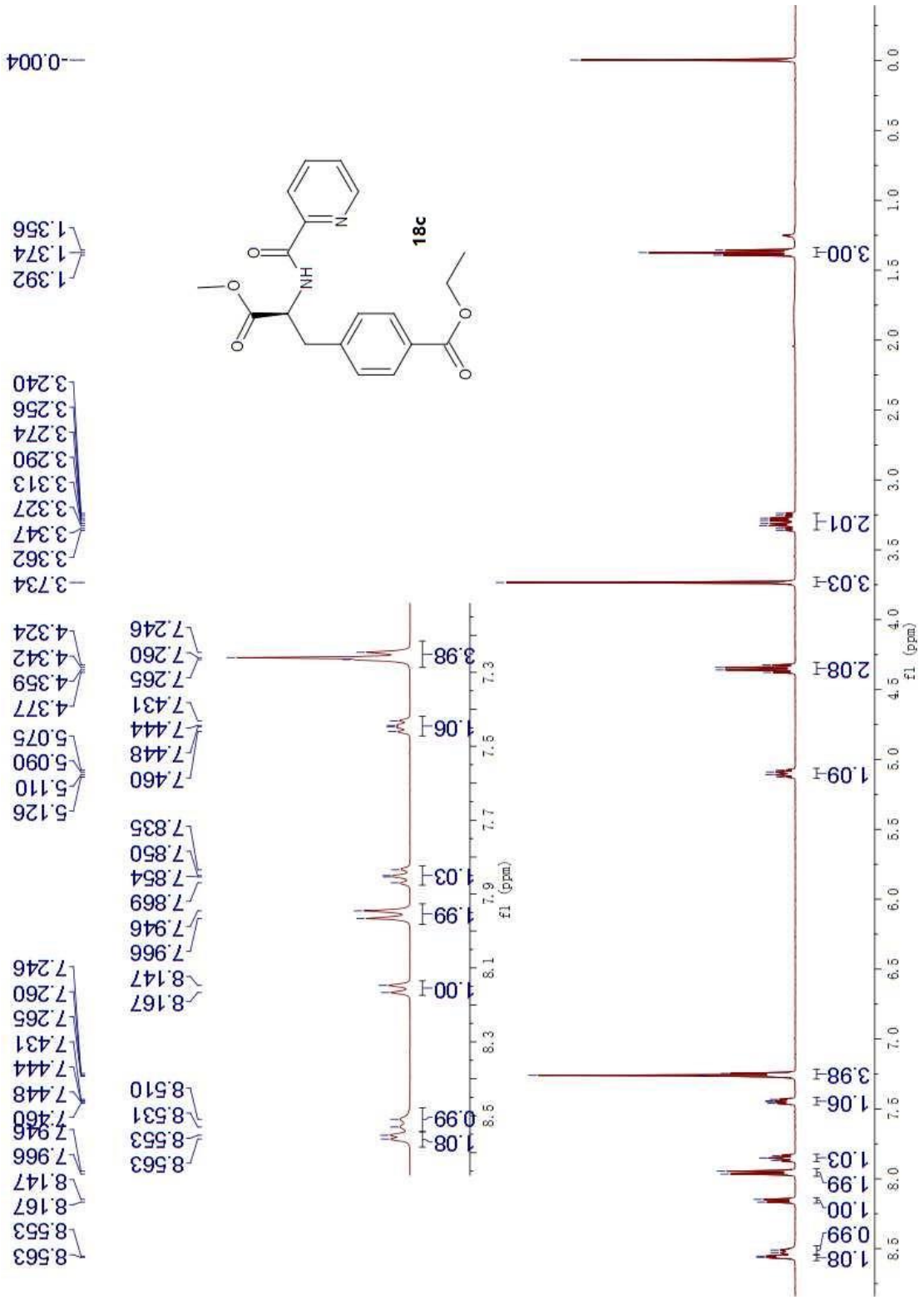

-4.34
9.57
18.23
20.26
25.74
32.22
51.83
52.31
62.91
76.84
77.16
77.48
119.91
125.84
138.27
149.96
153.98
162.57
172.88
17
f1 (ppm)

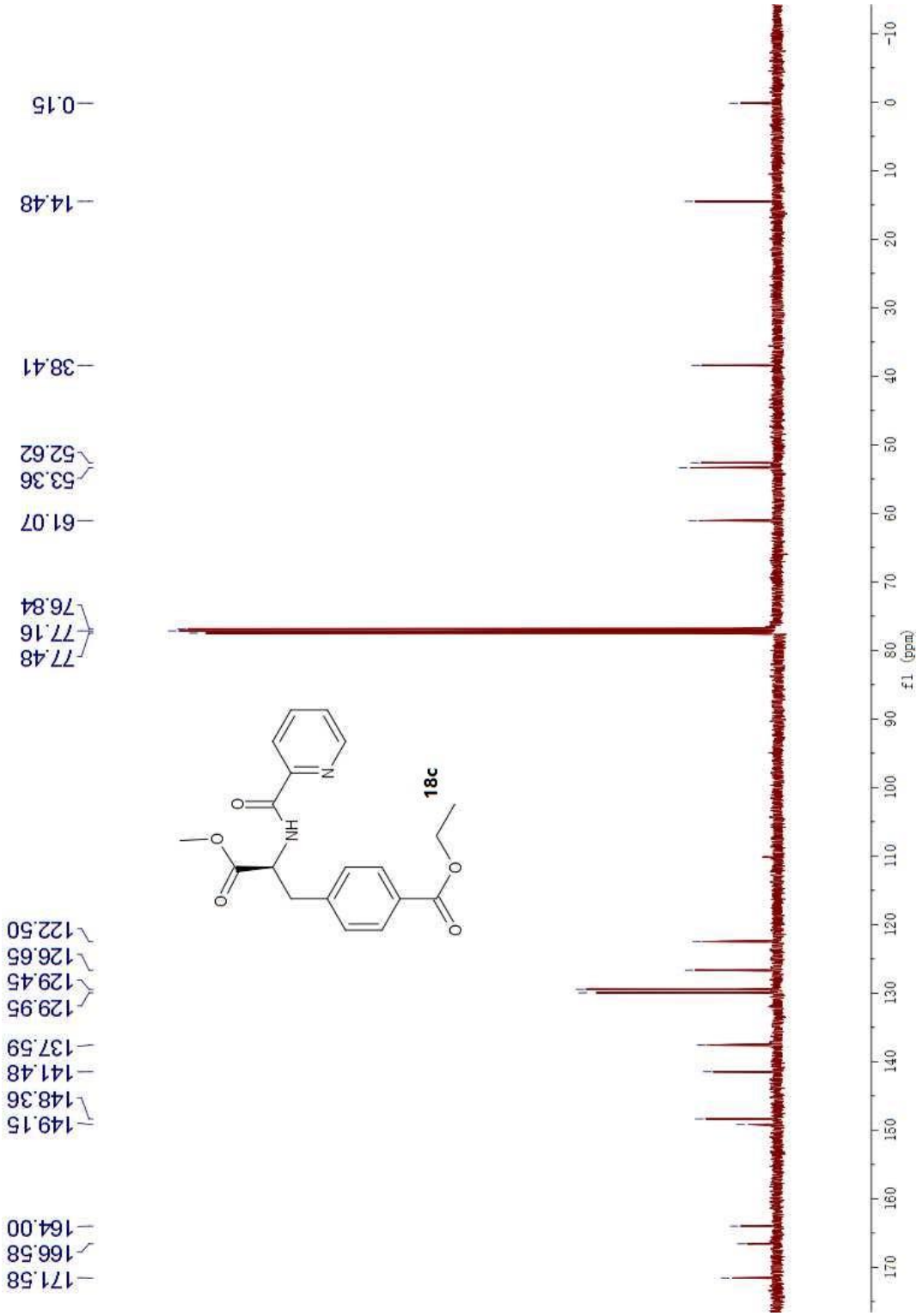
18a
0.000
3.727
3.234
3.220
3.200
3.191
3.185
3.176
3.156
3.140
8.563
8.554
8.503
8.175
8.155
7.844
7.827
7.863
7.449
7.428
7.410
7.394
7.376
7.357
7.334
7.317
7.112
7.091
6.903
6.882
5.054
5.038
5.024
5.003
7.300
7.317
7.334
7.357
7.376
7.394
7.428
7.449
5.97
1.09
2.06
3.00
2.95
5.97
1.99
2.00
1.09
1.02
1.01
1.01
f1 (ppm)

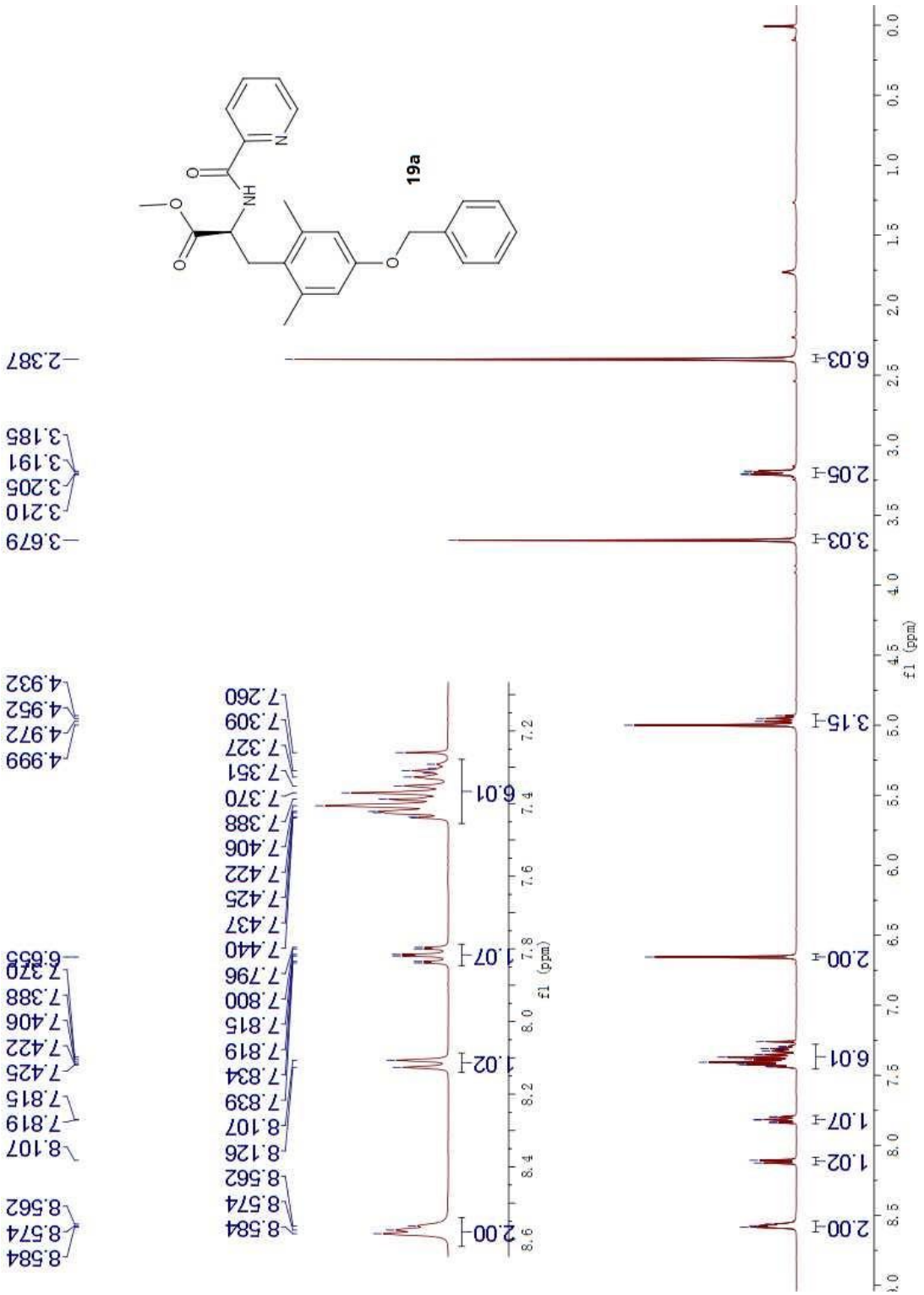

171.98
164.02
158.02
149.38
148.36
137.49
130.46
128.70
128.09
127.65
126.52
77.48
77.16
76.84
70.11
53.75
52.48
37.60
0.15
130.46
128.70
128.42
128.09
127.65
126.52
131.0 130.5 130.0 129.5 129.0 128.5 128.0 127.5 127.0 126.5 126.0
f1 (ppm)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
O
O
NH
O
N
O
18a

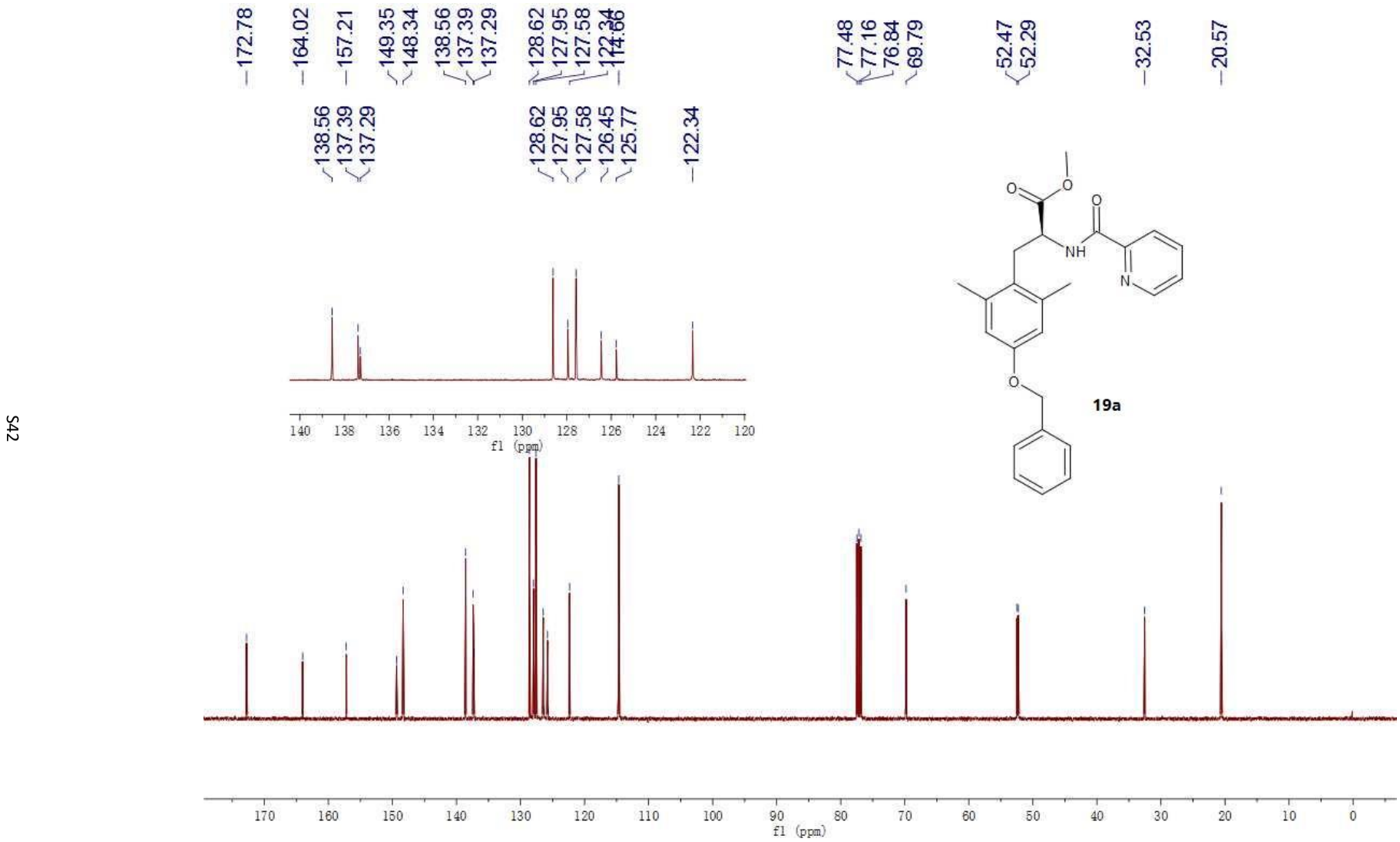
18b
8.532
8.522
8.484
8.464
8.140
8.121
7.814
7.810
7.791
7.795
7.810
7.814
7.829
7.834
7.423
7.420
7.411
7.408
7.404
7.401
7.392
7.390
7.231
7.210
7.104
7.083
5.068
5.052
5.047
5.037
5.032
5.016
3.714
3.259
3.244
3.224
3.210
3.189
3.173
3.154
3.138
1.04
0.93
1.00
1.01
1.02
1.99
2.04
3.04
1.02
1.99
2.04
1.01
1.02
1.99
2.04
f1 (ppm)

18b
171.61
164.02
149.17
148.38
137.47
134.65
133.05
130.72
128.80
126.58
122.39
77.48
77.16
76.84
53.38
52.54
37.70
f1 (ppm)


18c
f1 (ppm)

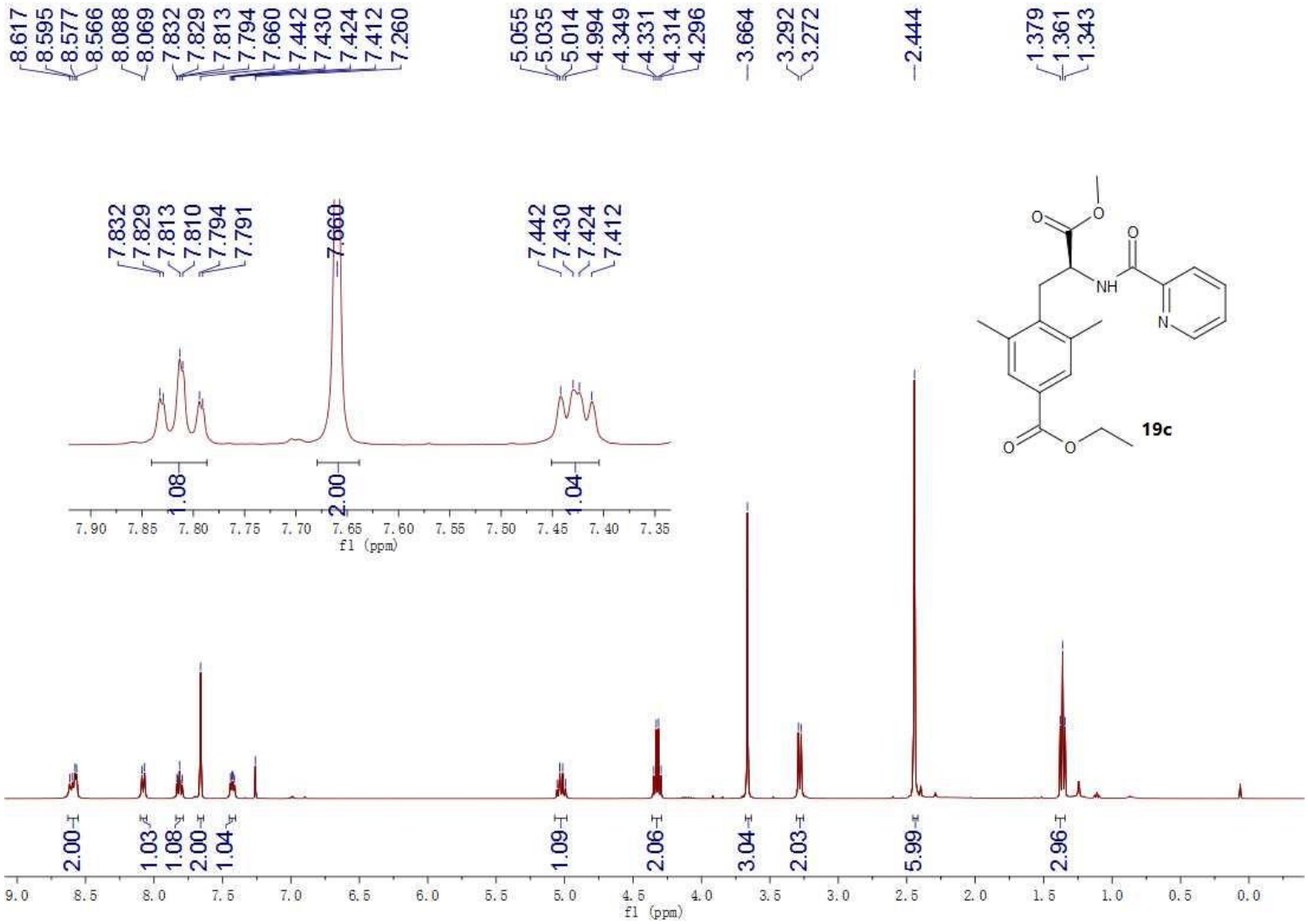

0.15
14.48
38.41
52.62
53.36
61.07
76.84
77.16
77.48
122.50
126.65
129.45
129.95
137.59
141.48
148.36
149.15
164.00
166.58
171.58
18c
f1 (ppm)

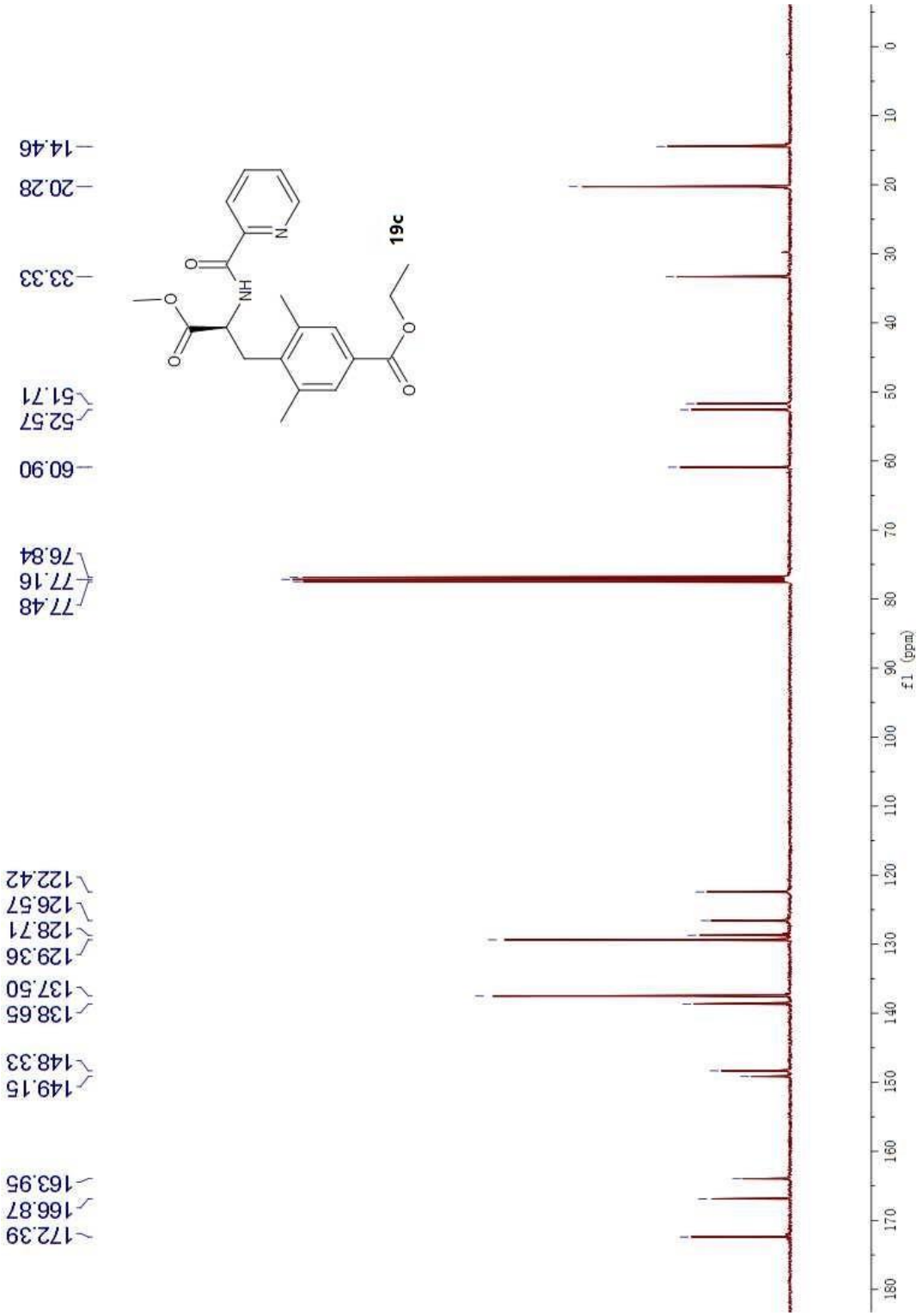

19a
2.387
3.185
3.191
3.205
3.210
3.679
4.932
4.952
4.972
4.999
6.553
7.320
7.388
7.406
7.422
7.425
7.815
7.819
8.107
8.562
8.574
8.584
7.260
7.309
7.327
7.351
7.370
7.388
7.406
7.422
7.425
7.437
7.440
7.796
7.800
7.815
7.819
7.834
7.839
8.107
8.126
8.562
8.574
8.584
6.03
2.05
3.03
3.15
2.00
6.01
1.07
1.02
2.00
6.01
1.07
1.02
2.00
f1 (ppm)


172.78
164.02
157.21
149.35
148.34
138.56
137.39
137.29
128.62
127.95
127.58
122.34
77.48
77.16
76.84
69.79
52.47
52.29
32.53
20.57
138.56
137.39
137.29
128.62
127.95
127.58
126.45
125.77
122.34
f1 (ppm)
f1 (ppm)
19a

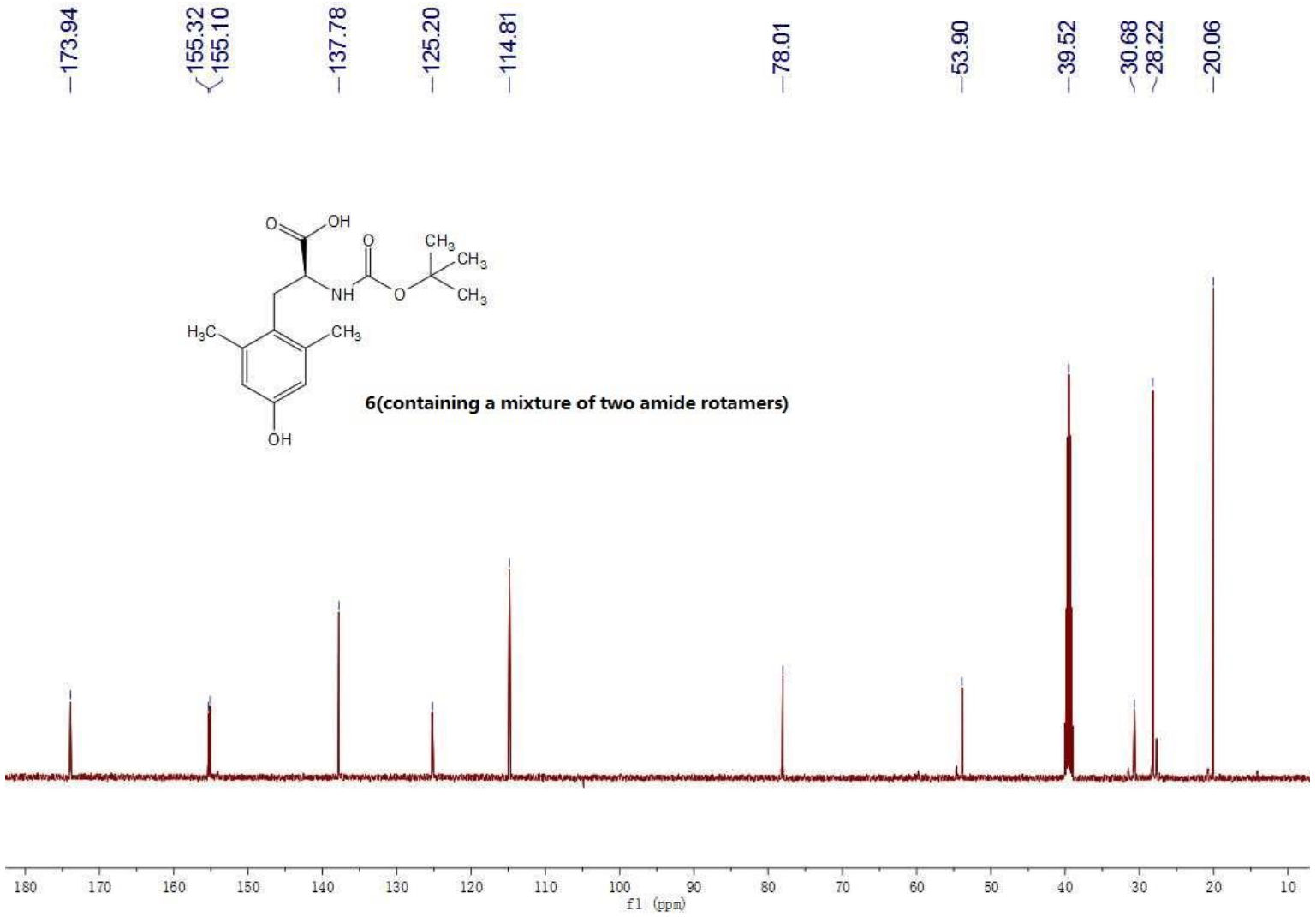
19b
N
HN
O
O
O
Cl
8.583
8.569
8.562
8.097
8.081
7.812
7.810
7.433
7.424
7.419
7.409
7.260
6.970
5.000
4.984
4.967
4.951
3.675
3.232
3.216
3.203
3.188
3.185
3.172
3.156
2.365
8.583
8.569
8.562
8.097
8.081
7.828
7.825
7.812
7.810
7.797
7.795
7.433
7.424
7.419
7.409
1.98
1.07
1.08
1.09
2.00
1.05
3.06
2.00
6.07
f1 (ppm)

172.43
163.95
149.18
148.31
139.03
137.47
132.04
131.84
128.13
126.53
122.38
77.41
77.16
76.91
52.52
51.85
32.72
20.15
19b
O
NH
O
O
N
Cl
f1 (ppm)


8.617
8.595
8.577
8.566
8.088
8.069
7.832
7.829
7.813
7.794
7.660
7.442
7.430
7.424
7.412
7.260
5.055
5.035
5.014
4.994
4.349
4.331
4.314
4.296
3.664
3.292
3.272
2.444
1.379
1.361
1.343
19c
f1 (ppm)


19c
14.46
20.28
33.33
51.71
52.57
60.90
76.84
77.16
77.48
122.42
126.57
128.71
129.36
137.50
138.65
148.33
149.15
163.95
166.87
172.39
f1 (ppm)

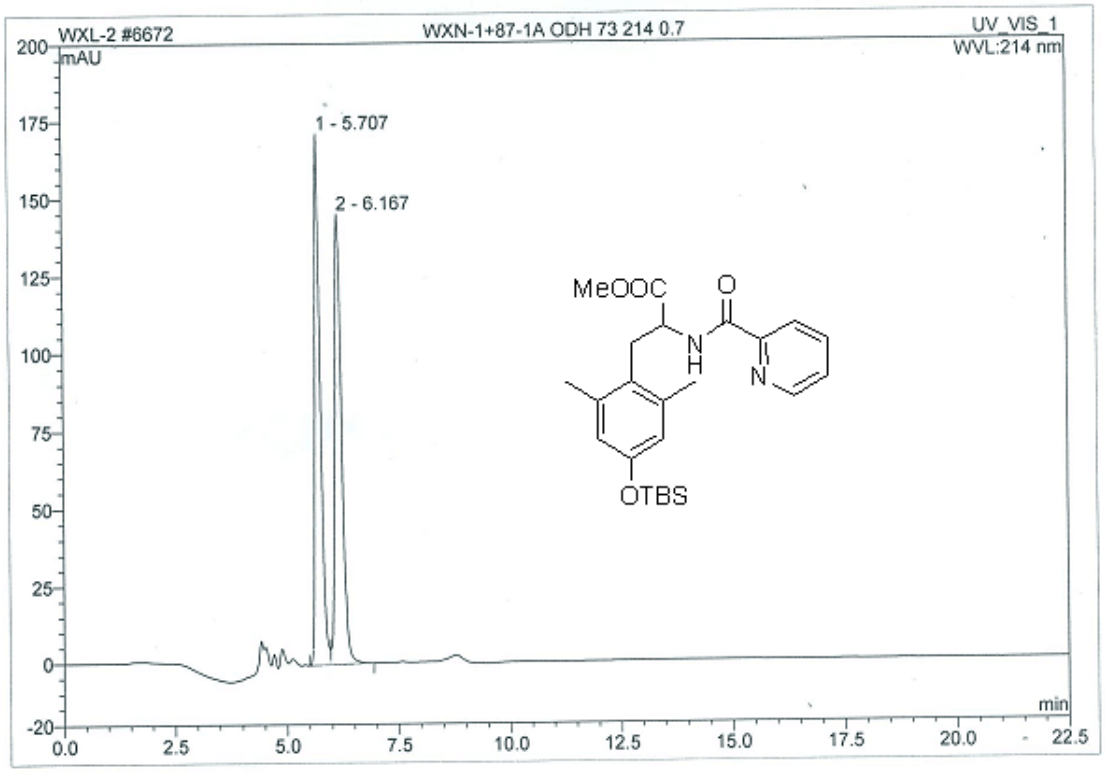
6 (containing a mixture of two amide rotamers)
f1 (ppm)
1.322
2.174
2.497
2.500
2.504
2.747
2.764
2.775
2.792
2.920
2.933
2.949
3.947
3.964
3.978
3.994
6.366
7.064
7.081
8.919
1.08
0.92
2.00
1.13
1.30
1.11
6.01
7.13
1.86
OH
HN
O
OH


173.94
155.32
155.10
137.78
125.20
114.81
78.01
53.90
39.52
30.68
28.22
20.06
O
OH
NH
O
O
CH3
CH3
CH3
H3C
CH3
OH
6(containing a mixture of two amide rotamers)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Racemic and optically active **8** were analyzed with HPLC [ODH (0.46*25cm, 5um) column, hexane/ isopropanol = 70:30, 0.7 mL/min, 214 nm) to determine retention time and enantiomeric excesses. **8**, ee = 99.7%.

6672 WXN-1+87-1A ODH 73 214 0.7

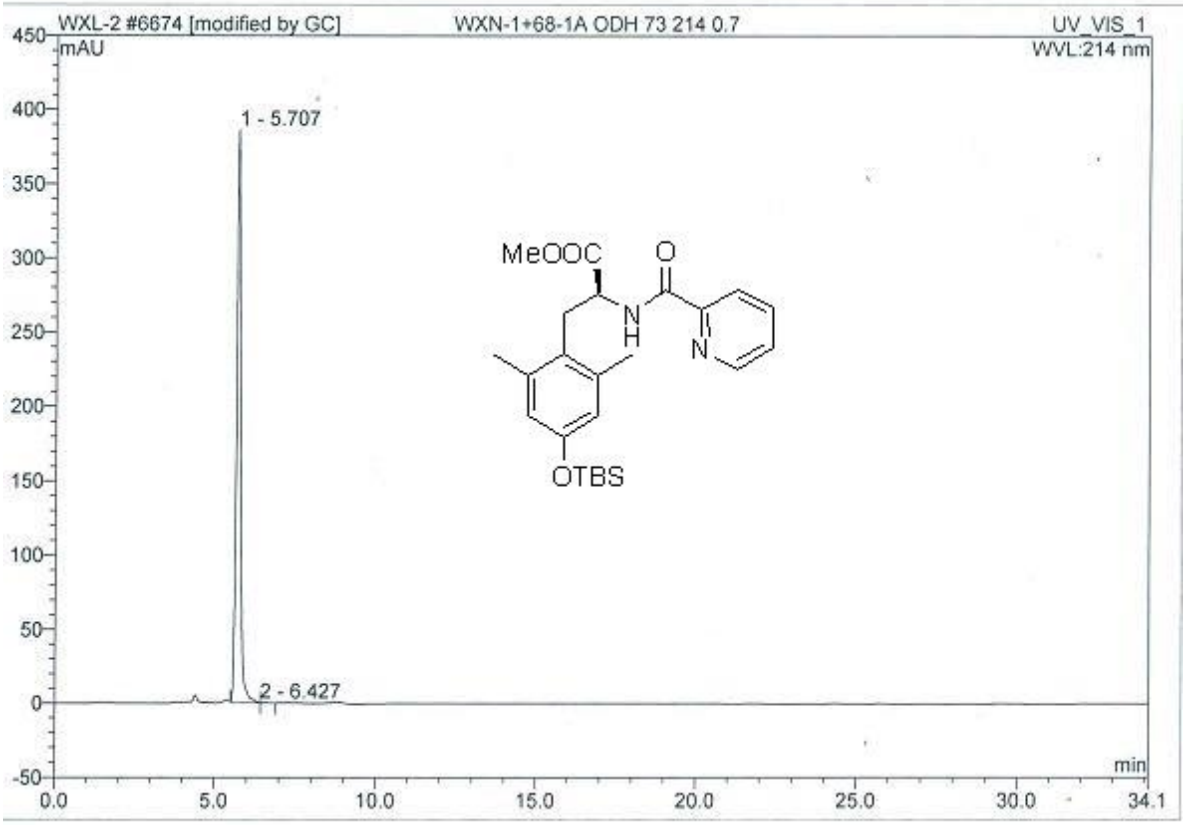
Sample Name:	**WXN-1+87-1A ODH 73 214 0.7**	*Injection Volume:*	**3.0**
Vial Number:	**RD3**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**214**
Control Program:	**WXL-2014**	*Bandwidth:*	**n.a.**
Quantif. Method:	**WXL**	*Dilution Factor:*	**1.0000**
Recording Time:	**2016/3/23 12:51**	*Sample Weight:*	**1.0000**
Run Time (min):	**22.51**	*Sample Amount:*	**1.0000**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.71	n.a.	171.635	25.537	49.83	n.a.	BM
2	6.17	n.a.	145.430	25.715	50.17	n.a.	MB
Total:			317.066	51.253	100.00	0.000	

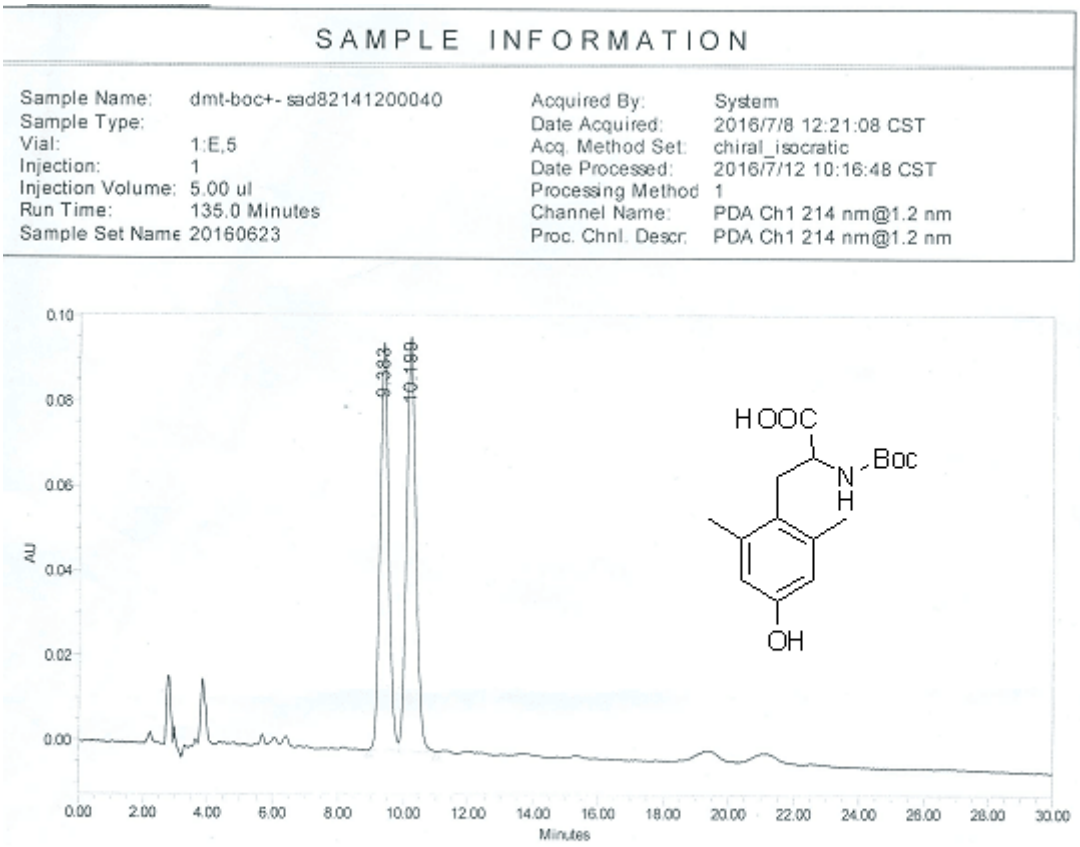
6674 WXN-1+68-1A ODH 73 214 0.7

Sample Name:	**WXN-1+68-1A ODH 73 214 0.7**	*Injection Volume:*	**2.0**
Vial Number:	**RD4**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**214**
Control Program:	**WXL-2014**	*Bandwidth:*	**n.a.**
Quantif. Method:	**WXL**	*Dilution Factor:*	**1.0000**
Recording Time:	**2016/3/23 13:30**	*Sample Weight:*	**1.0000**
Run Time (min):	**34.11**	*Sample Amount:*	**1.0000**



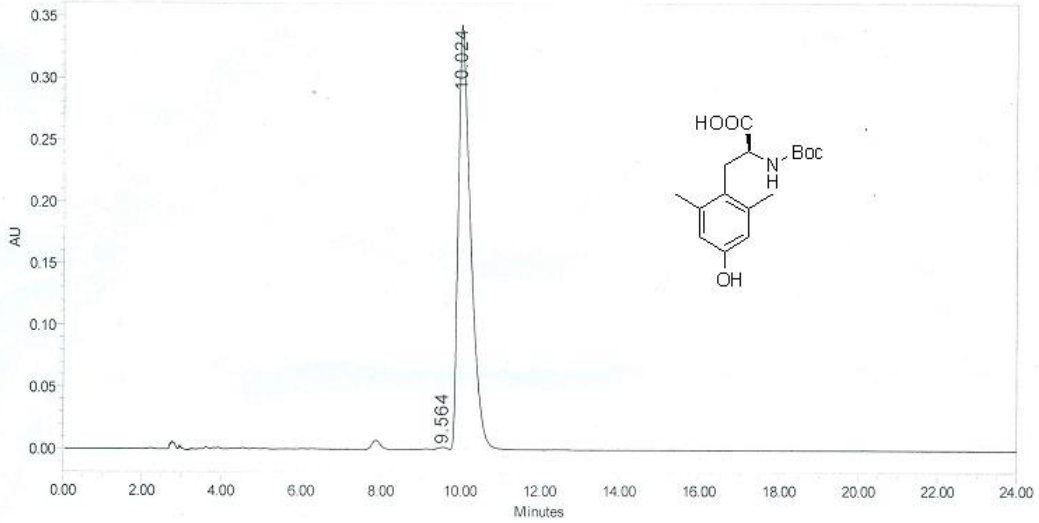
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.71	n.a.	386.126	59.012	99.85	n.a.	M *
2	6.43	n.a.	0.380	0.088	0.15	n.a.	MB*
Total:			386.506	59.100	100.00	0.000	

Racemic and optically active **6** were analyzed with HPLC(Sino-Chiral AD (0.46*25cm, 5um) column, CO_2/ MeOH= 80/20(V/V%), 1.0 mL/min, UV 214 nm, 0.7 mL/min, T= 40℃， background press: 2000 psi) to determine retention time and enantiomeric excesses. **6**, ee = 99.34%.



SAMPLE INFORMATION

Sample Name:	wxn-2-94 sad82141200040	Acquired By:	System
Sample Type:		Date Acquired:	2016/7/8 14:23:45 CST
Vial:	1:E,6	Acq. Method Set:	chiral_isocratic
Injection:	1	Date Processed:	2016/7/12 10:15:44 CST
Injection Volume:	5.00 ul	Processing Method	1
Run Time:	35.0 Minutes	Channel Name:	PDA Ch1 214 nm@1.2 nm
Sample Set Name	20160623	Proc. Chnl. Descr:	PDA Ch1 214 nm@1.2 nm



Peak Results

	RT	Area	Height	% Area
1	9.564	24462	1756	0.33
2	10.024	7407790	343232	99.67