Electronic Supplementary Material (ESI) for Chemical Communications.
This journal is © The Royal Society of Chemistry 2018

Electronic Supplementary Material (ESI) for ChemComm.
This journal is © The Royal Society of Chemistry 2018

Asymmetric synthesis of the fully functionalized six-membered ring of trigoxyphin A

Jing Feng,[a] Tianzi Yu,[a] Zhijiang Zhang,[a] Jinpeng Li,[a] Shaomin Fu,[a] Juan Chen,[b] and Bo Liu *[a]

[a.] *Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China.*

[b.] Analytical & Testing Center, Sichuan University, Chengdu 610064, P. R. China.

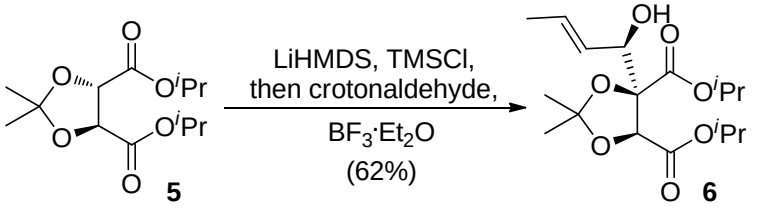
SUPPORTING INFORMATION

General Information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. DCM, DIPA, Et_3N, HMDS, TMSCl, $BF_3{\cdot}OEt_2$, MeCN and toluene were distilled from calcium hydride under argon; tetrahydrofuran was distilled from sodium-benzophenone under argon; EtOH was distilled from dry magnesium turnings and iodine under argon. All the other chemicals were purchased commercially and used without further purification, unless otherwise stated. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm), I_2 and by developing the plates with *p*-anisaldehyde or phosphomolybdic acid. ^1H and ^{13}C NMR were recorded on Bruker DRX-400 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^1H NMR = 7.26, ^{13}C NMR = 77.16). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) were reported in Hertz (Hz). Optical rotations were measured at the sodium D line with a 100 mm path length cell, and were reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. High resolution mass spectra (HRMS) were recorded by using FTMS-7 spectrometers. Infrared (IR) spectra were recorded on a NEXUS 670 FT-IR Fourier transform infrared spectrophotometer and were reported in wavenumbers (cm^{-1}).

Experimental Procedures

Procedure for the Preparation of Compound 6



Preparation of LiHMDS: To a solution of HMDS (70.3 mL, 337 mmol) in THF (200 mL) at -40 °C, ^{n}BuLi (2.5 M in hexane, 130 mL, 325 mmol) was added dropwise. After stirring at -40 °C for 30 min, the LiHMDS was prepared.

To a solution of compound **5**[1] (70.2 g, 256 mmol) and TMSCl (41.2 mL, 326 mmol) in THF (1.10×10^3 mL) at -78 °C, the prepared LiHMDS was added. After finishing addition, the reaction was stirred at -78 °C for 30 min, then warmed up to room temperature and stirred for another 30 min. The mixture was then evaporated, diluted with PE (300 mL), filtered through 4 cm pad of celite and washed with PE (100 mL × 4). The filtrate was concentrated under reduced pressure to give a residue, which was diluted with dry CH_2Cl_2 (1.20×10^3 mL) and cooled down to -40 °C. Then fresh distilled crotonaldehyde (20.8 mL, 253 mmol) and $BF_3{\cdot}OEt_2$ (42.7 mL, 347 mmol) were added in turn. After stirring at -40 °C for 2.3 h, the reaction mixture was quenched with saturated $NaHCO_3$ (500 mL) and separated. The organic phase was washed with saturated $NaHCO_3$ (100 mL). Combined the aqueous phases and extracted with EtOAc (200 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (10:1 PE/EtOAc) to provide **6** (55.0 g, 62%) as a colorless oil.

$[\alpha]_D^{21.6} = +6.73$ (*c* = 1.93, $CHCl_3$).

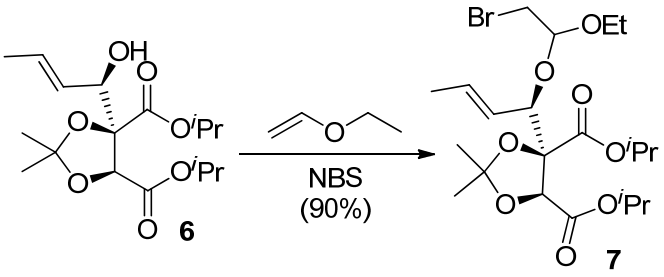
IR (thin film): 3509, 2981, 2933, 1767, 1732, 1376, 1208, 1103 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dq, *J* = 15.2, 6.4 Hz, 1H), 5.63 (ddd, *J* = 15.4, 7.5, 1.5 Hz, 1H), 5.13-5.01 (m, 2H), 4.52 (s, 1H), 4.45 (t, *J* = 6.3 Hz, 1H), 2.54 (d, *J* = 6.4 Hz, 1H), 1.76 (dd, *J* = 6.4, 0.9 Hz, 3H), 1.63 (s, 3H), 1.41 (s, 3H), 1.32-1.24 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.1, 131.4, 127.8, 112.5, 88.3, 79.2, 75.1, 69.9, 69.5, 26.7, 26.6, 21.8, 21.7, 21.6, 17.9.

HRMS (m/z): calcd for $C_{17}H_{28}O_7Na$, $[M+Na]^+$, 367.1733; found, 367.1731.

Procedure for the Preparation of Compound 7



To a solution of compound **6** (55.0 g, 160 mmol) and ethyl vinyl ether (170 mL) in CH_2Cl_2 (170 mL) at -8 ^oC, NBS (114 g, 640 mmol) were added. After stirring for 1.5 h, the reaction mixture was quenched with saturated $NaHCO_3$ (300 mL) and separated. The aqueous phase was extracted with EtOAc (300 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (10:1 PE/EtOAc) to provide **7** (71.4 g, 90%) (two inseparable diastereoisomers) as a colorless oil.

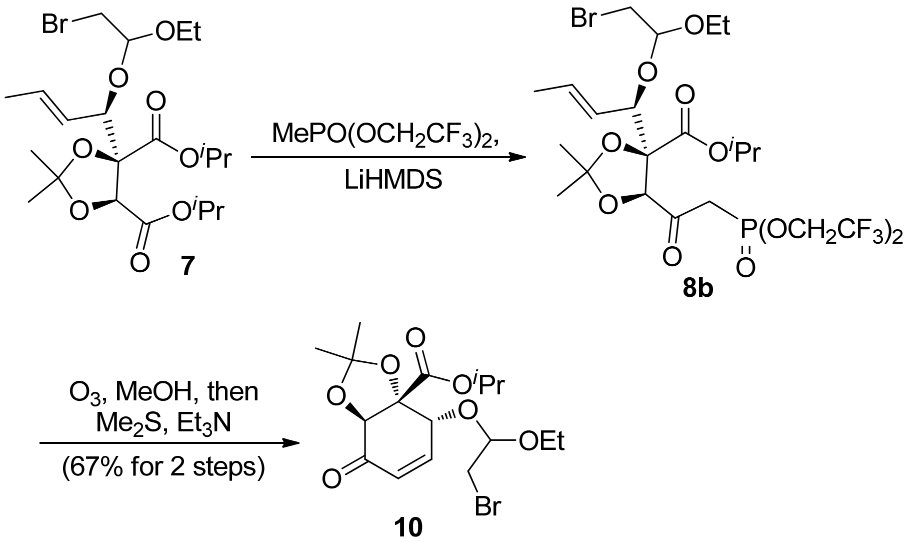
IR (thin film): 2982, 2938, 1763, 1726, 1375, 1206, 1105, 1034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94-5.80 (m, 1H), 5.67-5.46 (m, 1H), 5.12-4.97 (m, 2H), 4.72-4.61 (m, 1H), 4.61-4.58 (m, 0.4H), 4.42 (d, *J* = 9.0 Hz, 0.6H), 4.38-4.34 (m, 1H), 3.70-3.60 (m, 0.6H), 3.58-3.43 (m, 0.9H), 3.42-3.36 (m, 0.6H), 3.33-3.20 (m, 2H), 1.83-1.76 (m, 3H), 1.63 (s, 3H), 1.37-1.22 (m, 15H), 1.20-1.10 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.6, 166.5, 166.4, 135.6, 133.6, 127.0, 125.5, 112.4, 112.3, 102.0, 98.4, 88.4, 88.0, 80.1, 78.8, 78.7, 70.1, 69.9, 69.6, 69.4, 62.4, 60.9, 31.7 (2C), 26.7, 26.6, 26.3 (2C), 22.0, 21.9, 21.8 (2C), 21.7, 18.1, 18.0, 15.1, 14.7.

HRMS (m/z): calcd for $C_{21}H_{35}BrO_8Na$, $[M+Na]^+$, 517.1413，519.1393; found, 517.1411, 519.1392.

Procedure for the Preparation of Compound 10



Preparation of LiHMDS: To a solution of HMDS (83.4 mL, 400 mmol) in THF (400 mL) at -78 °C, ^{n}BuLi (2.5 M in hexane, 160 mL, 400 mmol) was added dropwise. After stirring at -78 °C for 30 min, the LiHMDS was prepared.

To a solution of compound **7** (49.5 g, 100 mmol) and *bis*-trifluoroethyl methylphosphonate[2] (78.0 g, 300 mmol) in dry THF (1.00 × 10^3 mL) at -78 °C, LiHMDS (keep at -78 °C before use) was transferred quickly. After stirring for 5 min, the reaction mixture was quenched by quickly transferred the mixture into the aqueous solution (NaOH, 40.0 g, KH_2PO_4, 500 g, H_2O, 1.00 × 10^3 mL) at 0 °C. The mixture was separated and the aqueous phase was extracted with EtOAc (500 mL × 3). The combined organic extracts were concentrated under reduced pressure to give a residue. Repeated the procedure for the second time and combined the residues, which were used directly for the ozonization reaction.

To a solution of crude **8b** in MeOH (1.00 × 10^3 mL) at -78 °C was imported O_3/O_2 gas. After the solution turned blue, only O_2 was imported. 1.0 h later, Me_2S (40.0 mL, 545 mmol), Et_3N (40.0 mL, 288 mmol) was added in turn and then slowly warmed up to room temperature. After the TLC has shown the aldehyde intermediate was consumed totally, quenched the reaction by transferring the mixture into the aqueous solution (NaOH, 80.0 g, KH_2PO_4, 500 g, H_2O, 1.50 × 10^3 mL) at 0 °C. Removed the MeOH, and the aqueous phase was extracted with EtOAc (500 mL × 4). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and

concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (10:1 to 6:1 PE/EtOAc) to provide **10** (56.8 g, 67%) (two inseparable diastereoisomers) as a colorless oil.

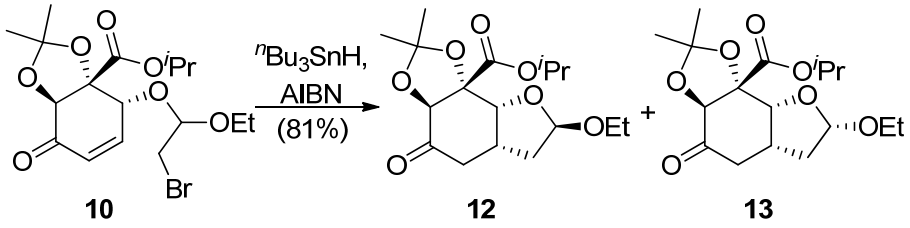
IR (thin film): 2983, 2937, 1739, 1375, 1153, 1107, 1033 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (ddd, *J* = 13.0, 10.2, 5.5 Hz, 2H), 6.07 (d, *J* = 10.2 Hz, 2H), 5.08 (t, *J* = 5.2 Hz, 1H), 5.01-4.92 (m, 3H), 4.90 (d, *J* = 7.4 Hz, 2H), 4.87 (dd, *J* = 5.4, 2.2 Hz, 2H), 3.90-3.81 (m, 1H), 3.80-3.74 (m, 1H), 3.72-3.63 (m, 2H), 3.46-3.38 (m, 4H), 1.50 (s, 3H), 1.49(s, 6H), 1.47(s, 3H) 1.31-1.22 (m, 12H), 1.17 (dd, *J* = 6.1, 3.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 190.0, 168.9(2C), 141.1, 140.5, 131.9 (2C), 113.5 (2C), 102.6, 101.7, 84.4, 83.9, 77.4, 77.3, 70.5(2C), 70.0, 67.8, 63.9, 63.1, 31.9, 31.4, 27.0 (2C), 26.2, 26.0, 21.5, 21.2 (2C), 15.3, 15.1.

HRMS (m/z): calcd for $C_{17}H_{25}BrO_7Na$, $[M+Na]^+$, 443.0681， 445.0661; found, 443.0678, 445.0662.

Procedure for the Preparation of Compound 12/13



10 **12** **13**

To a solution of compound **10** (100 g, 237 mmol) in dry toluene (600 mL) at room temperature was added ^{n}Bu_3SnH（95.8 mL，356 mmol）、AIBN（19.5 g，119 mmol）. The reaction mixture was stirred at 80 °C until the substrate consumed. Concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (5:1 to 3:1 PE/EtOAc) to provide the mixture **12/13** (65.7 g, 81%, **12**:**13**=1.2:1 as determined by ^1H NMR of the mixture) as a white solid. Further purification afforded **12** as a colorless oil and **13** as a white solid.

12：$[\alpha]_D^{21.6}$ = -97.8 (*c* = 1.39, $CHCl_3$).

IR (thin film): 2983, 2933, 1798, 1747, 1376, 1179, 1107, 1084 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.28 (dd, *J* = 5.1, 2.2 Hz, 1H), 5.03-4.93 (m, 1H), 4.60 (d, *J* = 0.8 Hz, 1H), 4.55 (d, *J* = 6.5 Hz, 1H), 3.77 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.43 (dq,

J = 9.5, 7.0 Hz, 1H), 2.85-2.76 (m, 1H), 2.63 (dd, J = 18.2, 8.1 Hz, 1H), 2.20-2.10 (m, 2H), 1.79 (dt, J = 13.5, 5.4 Hz, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.20 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 169.9, 113.7, 103.9, 85.4, 79.1, 75.1, 70.6, 63.6, 42.6, 41.7, 36.4, 26.8, 26.1, 21.7, 21.5, 15.2.

HRMS (m/z): calcd for $C_{17}H_{26}O_7Na$, $[M+Na]^+$, 365.1576; found, 365.1575.

13: mp 107-110 ^oC.

$[\alpha]_D^{18.4}$ = -50.3 (405 nm, c = 0.780, $CHCl_3$).

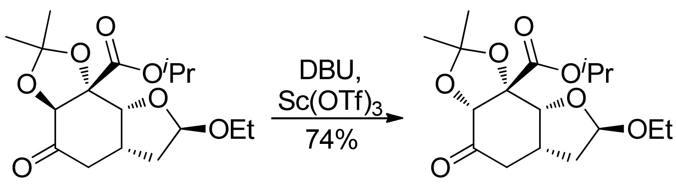
IR (thin film): 2984, 2968, 2899, 1739, 1377, 1290, 1178, 1104 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (d, J = 5.5 Hz, 1H), 5.04-4.94 (m, 1H), 4.79 (s, 1H), 4.42 (d, J = 4.9 Hz, 1H), 3.74 (dq, J = 9.6, 7.1 Hz, 1H), 3.44 (dq, J = 9.6, 7.1 Hz, 1H), 2.72-2.61 (m, 3H), 2.20 (dt, J = 13.6, 6.1 Hz, 1H), 1.95 (d, J = 13.4 Hz, 1H), 1.48 (s, 3H), 1.42 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 170.1, 112.8, 106.0, 86.9, 79.7, 78.6, 70.5, 64.1, 43.8, 40.4, 37.1, 26.6, 26.0, 21.5, 21.4, 15.1.

HRMS (m/z): calcd for $C_{17}H_{26}O_7Na$, $[M+Na]^+$, 365.1576; found, 365.1571.

Procedure for the Preparation of Compound 14



12 **14**

To a solution of $Sc(OTf)_3$ (6.07 g, 12.3 mmol) in MeCN (250 mL) was added DBU (14.7 mL, 98.4 mmol) and the solution of compound **12** (32.5 g, 94.9 mmol) in MeCN (66.0 mL). After stirring at 50 ^oC for 16.5 h, the reaction mixture was filtrated through a 4 cm pad of silica gel and washed with EtOAc (50 mL × 4). The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (4:1 to 3:1 PE/EtOAc) to provide **14** (24.2 g, 74%) as a colorless oil.

$[\alpha]_D^{22.6}$ = -41.0 (c = 0.952, $CHCl_3$).

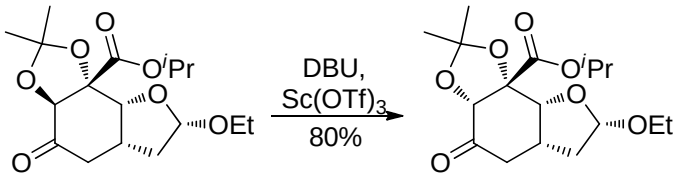
IR (thin film): 2980, 2938, 1733, 1377, 1262, 1092, 1009 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.20-5.10 (m, 1H), 5.07-5.00 (m, 1H), 4.77 (s, 1H), 4.41 (d, *J* = 4.5 Hz, 1H), 3.73-3.64 (m, 1H), 3.44-3.34 (m, 1H), 2.87-2.79 (m, 1H), 2.66 (dd, *J* = 13.3, 9.9 Hz, 1H), 2.18 (ddd, *J* = 13.6, 7.6, 3.8 Hz, 1H), 2.09-2.00 (m, 1H), 1.96 (d, *J* = 13.4 Hz, 1H), 1.55 (s, 3H), 1.38 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 170.6, 112.5, 102.8, 86.3, 79.8, 76.3, 70.5, 63.8, 42.5, 40.7, 37.6, 26.2, 25.5, 21.7, 21.6, 15.2.

HRMS (m/z): calcd for $C_{17}H_{26}O_7Na$, $[M+Na]^+$, 365.1576; found, 365.1581.

Procedure for the Preparation of Compound 15



13 **15**

To a solution of $Sc(OTf)_3$ (0.213 g，0.433 mmol) in MeCN (10 mL) was added DBU (0.52 mL, 3.48 mmol) and the solution of compound **13** (1.14 g, 3.33 mmol) in MeCN (5.00 mL). After stirring at 55 ^oC for 11.5 h, the reaction mixture was filtrated through a 4 cm pad of silica gel and washed with EtOAc (30.0 mL × 5). The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (3:1 PE/EtOAc) to provide **15** (0.910 g, 80%) as a colorless oil.

$[\alpha]_D^{17.8}$ = + 89.6 (*c* = 0.55, $CHCl_3$).

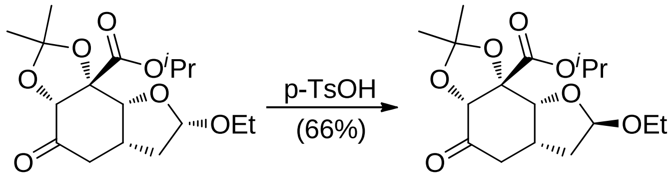
IR (thin film): 2980, 2937, 2877, 1733, 1374, 1263, 1176, 1089 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.17-5.09 (m, 1H), 5.08 (d, *J* = 6.0 Hz, 1H), 4.64 (s, 1H), 4.25 (d, *J* = 4.1 Hz, 1H), 3.63 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.25 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.78-2.63 (m, 2H), 2.33 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.27 (d, *J* = 14.1 Hz, 1H), 1.91 (d, *J* = 13.5 Hz, 1H), 1.55 (s, 3H), 1.38 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 171.0, 111.9, 102.7, 85.5, 78.8 (2C), 70.3, 63.0, 42.2, 40.3, 35.4, 26.0, 25.2, 21.7, 21.6, 14.7.

HRMS (m/z): calcd for $C_{17}H_{26}O_7Na$, $[M+Na]^+$, 365.1576; found, 365.1571.

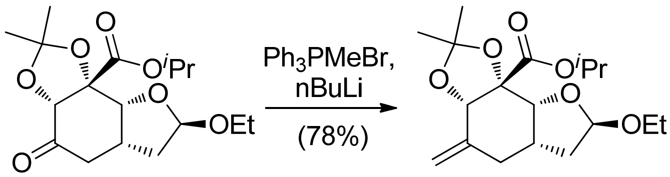
Procedure for the Preparation of Compound 14 from 15



15 14

To a solution of compound **15** (0.630 g, 1.84 mmol) in CH_2Cl_2/EtOH (5.00 mL, 1.50 mL) was added *p*-TsOH·H_2O (0.318 g, 1.67 mmol). After stirring at room temperature for overnight, the reaction mixture was cooled down to 0 °C and quenched with saturated $NaHCO_3$ (5.00 mL). Diluted with EtOAc (20.0 mL) and separated. The organic phase was washed with saturated $NaHCO_3$ (10.0 mL), brine (10.0 mL). Combined the aqueous phase and extracted with EtOAc (15.0 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (3:1 PE/EtOAc) to provide **14** (0.418 g, 66%) as a colorless oil.

Procedure for the Preparation of Compound 16



14 16

To a solution of Ph_3PMeBr (1.90 g, 5.32 mmol) in THF (13.0 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexane, 1.82 mL, 4.55 mmol). After stirring at 0 °C for 25 min, a solution of compound **14** (0.520 g, 1.52 mmol) in THF (3.0 mL) was added dropwise. 5 min later, the reaction mixture was warmed up to rt and stirred at rt for 5.3 h. The reaction mixture was then cooled down to 0 °C and quenched with saturated NH_4Cl (20.0 mL). Diluted with EtOAc (30.0 mL) and separated. The organic phase was washed with saturated NH_4Cl (10.0 mL), brine (10.0 mL). Combined the aqueous phases and extracted with EtOAc (15.0 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and

concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (9:1 PE/EtOAc) to provide **16** (0.404 g, 78%) as a colorless oil.

$[\alpha]_D^{21.4}$ = -193 (*c* = 1.30, $CHCl_3$).

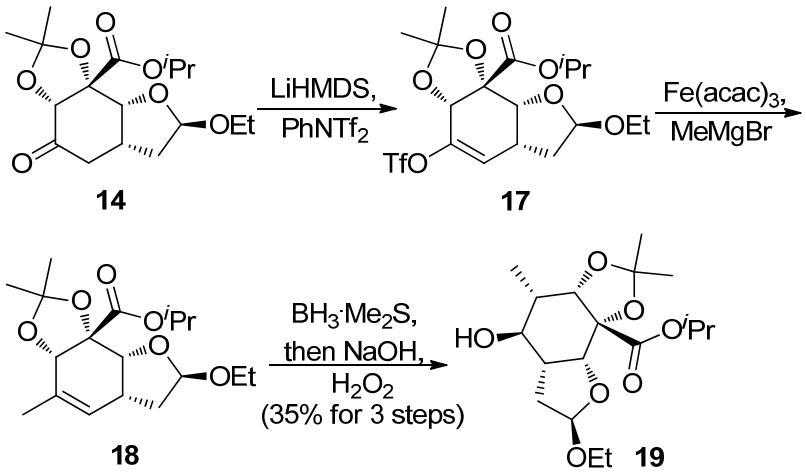
IR (thin film): 2981, 2937, 1755, 1721, 1263, 1103, 1089.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (d, *J* = 4.8 Hz, 1H), 5.11 (dt, *J* = 12.6, 6.3 Hz, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.79 (s, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 3.60 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.34 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.74-2.63 (m, 1H), 2.34 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.22 (dd, *J* = 12.7, 9.6 Hz, 1H), 1.99 (dd, *J* = 12.2, 7.6 Hz, 1H), 1.80 (ddd, *J* = 12.2, 10.6, 5.0 Hz, 1H), 1.49 (s, 3H), 1.30 (s, 3H), 1.26-1.21 (m, 6H), 1.07 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 142.6, 114.2, 111.3, 104.0, 85.6, 80.3, 78.5, 69.4, 62.7, 39.9, 36.9, 30.5, 26.9, 25.9, 21.6, 21.5, 15.1.

HRMS (m/z): calcd for $C_{18}H_{28}O_6Na$, $[M+Na]^+$, 363.1784; found, 363.1779.

Procedure for the Preparation of Compound 19



To a solution of HMDS (0.63 mL, 3.02 mmol) in THF (12.0 mL) at -78 °C was added ^{n}BuLi (2.5 M in hexane, 1.08 mL, 2.70 mmol). After 30 min, the solution of compound **14** (0.616 g, 1.80 mmol) in THF (4.50 mL) was added dropwise. After 0.5 h later, the solution of $PhNTf_2$ (0.865 g, 2.42 mmol) in THF (4.5 mL) was added. After stirring for another 0.5 h, the reaction mixture was slowly warmed up to -33 °C and stirred at this temperature for overnight. The reaction mixture was quenched with saturated NH_4Cl (10.0 mL). Diluted with EtOAc (40.0 mL) and separated. The

organic phase was washed with brine (10.0 mL). Combined the aqueous phase and extracted with EtOAc (20.0 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (7:1 PE/EtOAc) to provide the crude **17** (a mixture of compound **17** and PhNHTf) (0.760 g) as a colorless oil with compound **14** (0.129 g, 21%) recovered.

$[\alpha]_D^{22.2}$ = -60.6 (*c* = 2.03, $CHCl_3$).

IR (thin film): 2982, 2938, 1758, 1725, 1421, 1215, 1141, 1104 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 4.6 Hz, 1H), 5.36 (d, *J* = 4.6 Hz, 1H), 5.21-5.12 (m, 1H), 4.97 (d, *J* = 1.6 Hz, 1H), 4.61 (d, *J* = 7.3 Hz, 1H), 3.72 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.48-3.40 (m, 1H), 3.40-3.31 (m, 1H), 2.20 (ddd, *J* = 12.1, 10.5, 5.2 Hz, 1H), 2.08 (ddd, *J* = 12.2, 7.7, 1.1 Hz, 1H), 1.50 (s, 3H), 1.50 (s, 3H), 1.31 (d, *J* = 6.3 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 144.7, 120.1, 117.0, 113.8, 104.7, 85.5, 77.1, 75.1, 70.5, 63.3, 37.6, 37.3, 27.7, 27.5, 21.8, 21.7, 15.3.

HRMS (m/z): calcd for $C_{18}H_{25}F_3O_9SNa$, $[M+Na]^+$, 497.1069; found, 497.1074.

To a solution of $Fe(acac)_3$ (0.0923 g, 0.261 mmol) and crude **17** (0.760 g) in THF/NMP (12.5 mL, 0.46 mL) at -35 ^oC was added MeMgBr (3.0 M in Me-THF, 2.2 mL, 6.6 mmol). After stirring at -35 ^oC for 20 min, the reaction mixture was quenched with saturated NH_4Cl (15.0 mL). The mixture was extracted with EtOAc (25.0 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (10:1 PE/EtOAc) to provide the crude **18** (0.458 g) as a colorless oil.

$[\alpha]_D^{21.6}$ = -113 (*c* = 1.00, $CHCl_3$).

IR (thin film): 2978, 2936, 1754, 1717, 1377, 1275, 1240, 1105, 1045 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.50-5.47 (m, 1H), 5.32 (d, *J* = 5.0 Hz, 1H), 5.18-5.10 (m, 1H), 4.68 (s, 1H), 4.57 (d, *J* = 7.7 Hz, 1H), 3.71 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.41 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.11-3.01 (m, 1H), 2.09 (td, *J* = 11.6, 5.2 Hz, 1H), 1.95 (dd, *J* = 12.1, 7.6 Hz, 1H), 1.78 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.28 (dd, *J* = 6.3, 1.4 Hz,

6H), 1.14 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 132.0, 123.2, 111.8, 104.7, 84.2, 79.6, 78.5, 69.6, 63.0, 38.1, 37.0, 27.7, 27.5, 21.8, 21.7, 19.6, 15.3.

HRMS (m/z): calcd for $C_{18}H_{28}O_6Na$, $[M+Na]^+$, 363.1784; found, 363.1781.

To a solution of the crude **18** (0.458 g) in THF (10.0 mL) at 0 ^oC was added $BH_3{\cdot}Me_2S$ (10.0 M in Me_2S, 0.540 mL, 5.40 mmol). 10 min later, the reaction mixture was warmed up to room temperature and stirred for 1.6 h. Cooled down to 0 ^oC and 15% NaOH (5.0 mL), 30% H_2O_2 (5.0 mL) were added in turn. After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (10.0 mL). The mixture was extracted with EtOAc (50.0 mL × 3). The combined organic extracts were washed with saturated NH_4Cl (20.0 mL), brine (20.0 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (2:1 PE/EtOAc) to provide **19** (0.225 g, 35% over 3 steps) as a colorless oil.

$[\alpha]_D^{22.3}$ = -143 (c = 1.17, $CHCl_3$).

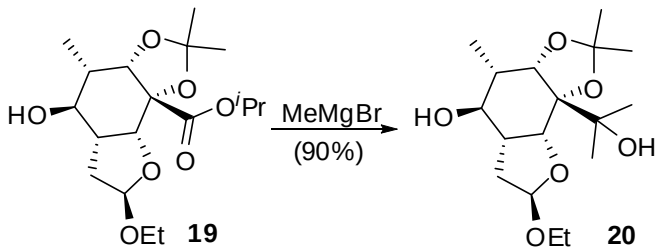
IR (thin film): 3478, 2981, 2937, 1752, 1718, 1375, 1267, 1100, 1050 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (d, J = 4.8 Hz, 1H), 5.21-5.12 (m, 1H), 4.54 (d, J = 2.9 Hz, 1H), 4.34 (d, J = 9.6 Hz, 1H), 3.68-3.59 (m, 2H), 3.40 (dq, J = 9.7, 7.1 Hz, 1H), 2.61-2.52 (m, 1H), 2.18 (dd, J = 12.0, 7.6 Hz, 1H), 1.89 (td, J = 11.8, 4.9 Hz, 2H), 1.77 (br, 1H), 1.74-1.63 (m, 1H), 1.46 (s, 3H), 1.31-1.26 (m, 9H), 1.12 (t, J = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 110.3, 104.2, 83.8, 81.1, 79.6, 71.8, 69.7, 62.8, 45.3, 38.9, 38.0, 26.7, 25.5, 21.8, 21.6, 15.2, 12.6.

HRMS (m/z): calcd for $C_{18}H_{30}O_7Na$, $[M+Na]^+$, 381.1889; found, 381.1884.

Procedure for the Preparation of Compound 20



To a solution of compound **19** (0.106 g, 0.296 mmol) in dry THF (3.0 mL) at 0 °C was added MeMgBr (3.0 M in Me-THF, 0.700 mL, 2.10 mmol). After stirring for 40 min, the reaction mixture was quenched with saturated NH_4Cl (10.0 mL). Diluted with EtOAc (30.0 mL) and separated. The organic phase was washed with brine (5.0 mL). Combined the aqueous phase and extracted with EtOAc (20.0 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (1:1 PE/EtOAc) to provide **20** (0.0877 g, 90%) as a colorless oil.

$[\alpha]_D^{21.7}$ = -24.7 (*c* = 2.99, $CHCl_3$).

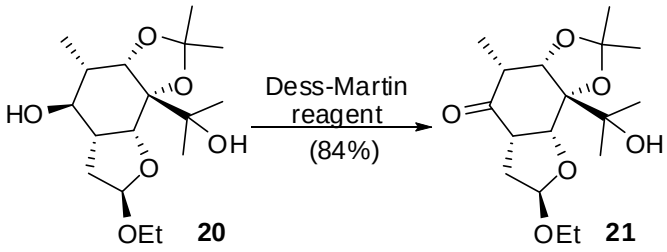
IR (thin film): 3432, 2980, 2934, 1732, 1460, 1373, 1008 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.16-5.13 (m, 1H), 4.38 (d, *J* = 2.3 Hz, 1H), 4.20 (d, *J* = 4.7 Hz, 1H), 3.77 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.50-3.40 (m, 2H), 2.37 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.27 (s, 1H), 2.09-1.97 (m, 2H), 1.79-1.65 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.20-1.15 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 108.4, 101.4, 84.5, 79.5, 76.2, 72.5, 70.7, 63.4, 47.4, 39.5, 38.0, 26.9, 26.2, 26.0, 24.7, 15.3, 14.9.

HRMS (m/z): calcd for $C_{17}H_{30}O_6Na$, $[M+Na]^+$, 353.1940; found, 353.1939.

Procedure for the Preparation of Compound 21



To a solution of compound **20** (7.50 g, 22.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added $NaHCO_3$ (4.08 g, 48.6 mmol) and Dess-Martin reagent (17.5 g, 41.3 mmol) in turn. After stirring at 0 °C for 1.8 h, the reaction mixture was quenched with

saturated $Na_2S_2O_3$ (50.0 mL) and saturated $NaHCO_3$ (50.0 mL). Diluted with EtOAc (200 mL) and separated. The organic phase was washed with saturated $Na_2S_2O_3$ (25.0 mL), saturated $NaHCO_3$ (25.0 mL) and brine (25.0 mL). Combined the aqueous phase and extracted with EtOAc (100 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (3:1 to 2:1 PE/EtOAc) to provide **21** (6.29 g, 84%) as a white solid.

mp 96 - 98 ^oC.

$[\alpha]_D^{21.8}$ = -115 (*c* = 3.45, $CHCl_3$).

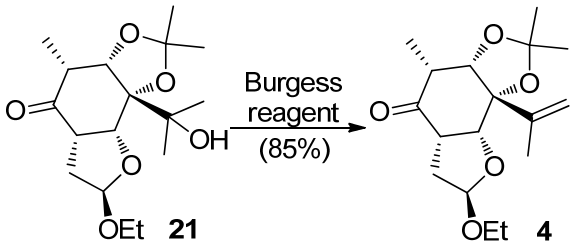
IR (thin film): 3504, 2977, 2937, 1723, 1457, 1368, 1055, 1006 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (d, *J* = 4.8 Hz, 1H), 4.60 (d, *J* = 9.4 Hz, 1H), 4.58 (d, *J* = 2.1 Hz, 1H), 3.69 (dq, *J* = 9.8, 7.1 Hz, 1H), 3.45 (dq, *J* = 9.8, 7.1 Hz, 1H), 3.18 (q, *J* = 9.1 Hz, 1H), 2.78 (qd, *J* = 6.8, 1.7 Hz, 1H), 2.25 (ddd, *J* = 13.2, 9.2, 5.2 Hz, 1H), 2.17 (s, 1H), 2.12 (ddd, *J* = 13.2, 9.0, 0.8 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.34 (s, 6H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.15 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 109.3, 102.6, 84.7, 81.6, 76.0, 73.1, 63.0, 49.2, 45.4, 34.3, 27.4, 26.5, 26.3, 24.6, 15.3, 11.5.

HRMS (m/z): calcd for $C_{17}H_{28}O_6Na$, $[M+Na]^+$, 351.1784; found, 351.1780.

Procedure for the Preparation of Compound 4



To a solution of Burgess reagent (8.50 g, 35.7 mmol) in dry THF (70.0 mL) at 0 ^oC was added the solution of compound **21** (7.80 g, 23.8 mmol) in THF (40.0 mL). 20 min later, the reaction mixture was warmed up to water-bath (rt). After stirring at water-bath (rt) for 3.3 h, the reaction mixture was subjected to flash column chromatography directly (4:1 to 3:1 PE/EtOAc). After concentration, the crude was purified (4:1 PE/EtOAc) for the second time to afford **4** (6.25 g, 85%) as a colorless

oil.

$[\alpha]_D^{22.0}$ = -215 (*c* = 1.08, $CHCl_3$).

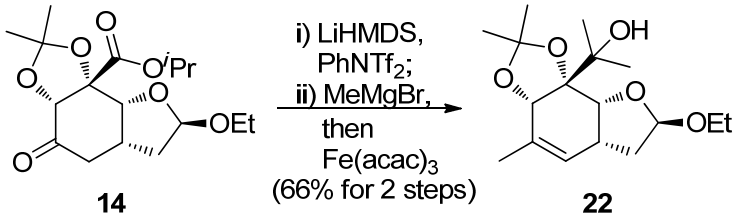
IR (thin film): 2976, 2935, 1729, 1383, 1372, 1108, 1065, 1044 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (d, *J* = 4.8 Hz, 1H), 5.08 (s, 2H), 4.60 (d, *J* = 4.0 Hz, 1H), 4.57 (d, *J* = 9.3 Hz, 1H), 3.70 (dq, *J* = 9.2, 7.1 Hz, 1H), 3.42 (dq, *J* = 9.3, 7.1 Hz, 1H), 3.23 (dt, *J* = 11.2, 9.0 Hz, 1H), 2.69-2.62 (m, 1H), 2.22-2.08 (m, 2H), 1.96 (s, 3H), 1.27 (s, 6H), 1.14 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 148.1, 112.4, 109.9, 104.3, 85.8, 82.8, 82.1, 63.0, 49.1, 47.1, 34.0, 27.3, 26.6, 20.4, 15.2, 9.9.

HRMS (m/z): calcd for $C_{17}H_{26}O_5$ Na, $[M+Na]^+$, 333.1678; found, 333.1674.

Procedure for the Preparation of Compound 22



To a solution of HMDS (23.4 mL, 112 mmol) in THF (270 mL) at -78 °C was added ^{n}BuLi (2.5 M in hexane, 39.6 mL, 99.0 mmol). After 0.5 h, a solution of compound **14** (22.6 g, 66.0 mmol) in THF (37.0 mL) was added dropwise. After stirring for another 0.5 h, a solution of $PhNTf_2$ (33.0 g, 92.4 mmol) in THF (80.0 mL) was added. After 30 min, the reaction mixture was slowly warmed up to -35 °C and stirred at this temperature for 2.5 h. The reaction mixture was quenched with saturated NH_4Cl (100 mL). Diluted with EtOAc (400 mL) and separated. The organic phase was washed with saturated NH_4Cl (50.0 mL), brine (50.0 mL). Combined the aqueous phase and extracted with EtOAc (100 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (7:1 PE/EtOAc) to provide the crude **17**.

To a solution of crude **17** in THF (500 mL) at 0 °C was added MeMgBr (3.0 M in Me-THF, 105 mL, 315 mmol). After stirring at 0 °C for 1.3 h, cooled down to -40 °C and the solution of $Fe(acac)_3$ (7.07 g, 19.8 mmol) in THF/NMP (30.0 mL, 20.0 mL)

was added. After stirring at -40 °C for 4 h, the reaction mixture was quenched with saturated NH_4Cl (200 mL). Diluted with EtOAc (500 mL) and separated. The organic phase was washed with saturated NH_4Cl (100 mL), brine (100 mL). Combined the aqueous phase, and extracted with EtOAc (300 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to provide **22** (13.5g, 66% over 2 steps) as a white solid.

mp 46 - 48 °C.

$[\alpha]_D^{22.1}$ = -75.5 (*c* = 2.11, $CHCl_3$).

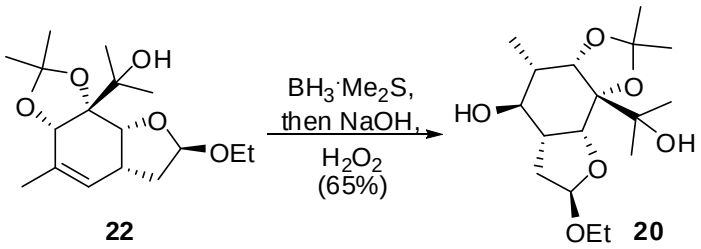
IR (thin film): 3566, 3488, 2978, 2939, 1377, 1213, 1061 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.10-5.06 (m, 1H), 4.36 (s, 1H), 4.22 (d, *J* = 4.3 Hz, 1H), 3.79-3.71 (m, 1H), 3.44-3.35 (m, 1H), 2.76 (s, 1H), 2.53 (s, 1H), 2.13-2.08 (m, 2H), 1.82 (s, 3H), 1.55 (s, 3H), 1.46 (s, 3H), 1.29 (s, 3H), 1.16 (td, *J* = 7.1, 1.8 Hz, 3H), 1.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.8, 126.8, 109.4, 101.6, 86.0, 74.4, 73.8, 71.1, 63.5, 40.7, 40.0, 27.1, 26.1, 23.6, 21.8, 15.3.

HRMS (m/z): calcd for $C_{17}H_{28}O_5Na$, $[M+Na]^+$, 335.1834; found, 335.1832.

Procedure for the Preparation of Compound 20 from Compound 22



22 **20**

To a solution of compound **22** (0.955 g, 3.06 mmol) in THF (11.3 mL) at 0 °C was added $BH_3{\cdot}Me_2S$ (10.0 M in Me_2S, 0.920 mL, 9.20 mmol). 10 min later, warmed up to room temperature and stirred for 21 h. The reaction mixture was then cooled down to 0 °C and 3M NaOH (8.50 mL), 35% H_2O_2 (4.2 mL) were added in turn. After stirring at room temperature for 10.5 h, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (10.0 mL). Repeated the procedure for 13 times. The quality of compound **22** varied from 0.613 g to 0.955 g (totally 12.3 g). Combined all the reaction mixture and diluted with EtOAc (400 mL), H_2O (200 mL). Separated and the organic phase

was washed with brine (20.0 mL × 2). Combined the aqueous phase and extracted with EtOAc (200 mL × 5). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (2:1 to 1:1 PE/EtOAc) to provide **20** (8.41 g, 65%) as a colorless oil.

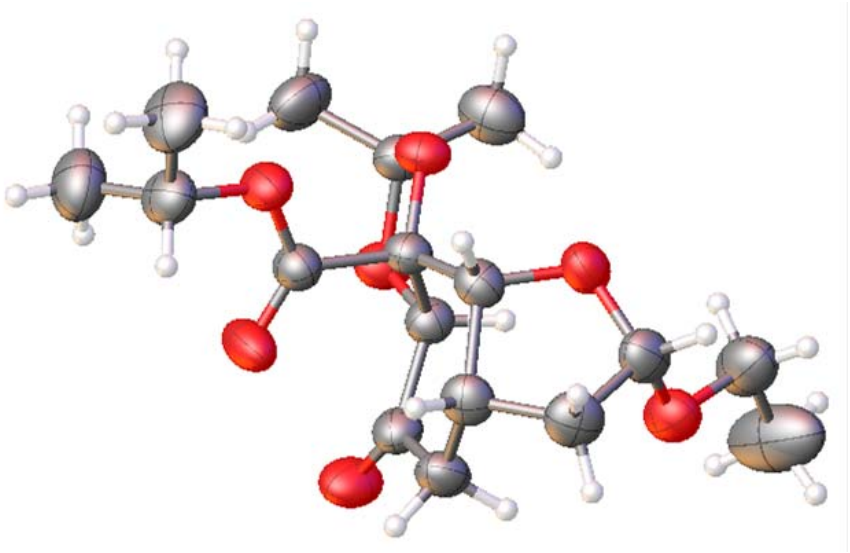
References:

[1] S. Saito, O. Narahara, T. Ishikawa, M. Asahara, T. Moriwake, J. Gawronski and F. Kazmierczak, *J. Org. Chem*., 1993, **58**, 6292.

[2] Submitted by C. Patois, P. Savignac1, E. About-Jaudet and N. Collignon, *Org. Synth.,* 1996, **73**, 152.

X-Ray Crystallographic Data

X-Ray Crystallographic Data for 13



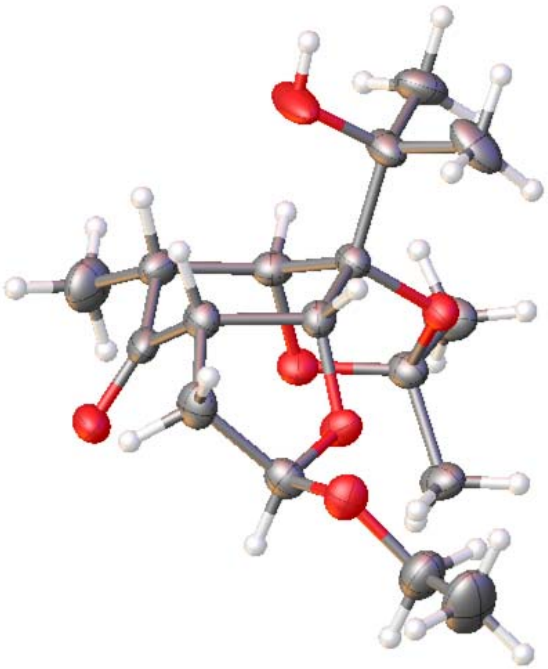
Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1828462)

Crystal data and structure refinement for CCDC 1828462.

Empirical formula	$C_{17}H_{26}O_7$
Formula weight	342.38
Temperature/K	292.85(19)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.9598(3)
b/Å	11.7903(3)
c/Å	17.2249(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1819.62(9)
Z	4
ρ_{calc}g/cm^3	1.250
μ/mm^{-1}	0.807

F(000)	736.0
Crystal size/mm^3	0.8 × 0.6 × 0.4
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.09 to 134.1
Index ranges	$-10 \leq h \leq 9$, $-14 \leq k \leq 11$, $-19 \leq l \leq 20$
Reflections collected	9626
Independent reflections	3245 [R_{int} = 0.0339, R_{sigma} = 0.0280]
Data/restraints/parameters	3245/0/222
Goodness-of-fit on F^2	1.108
Final R indexes [I>=2σ (I)]	R_1 = 0.0555, wR_2 = 0.1315
Final R indexes [all data]	R_1 = 0.0570, wR_2 = 0.1343
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.44
Flack parameter	0.03(11)

X-Ray Crystallographic Data for 21



Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1843135)

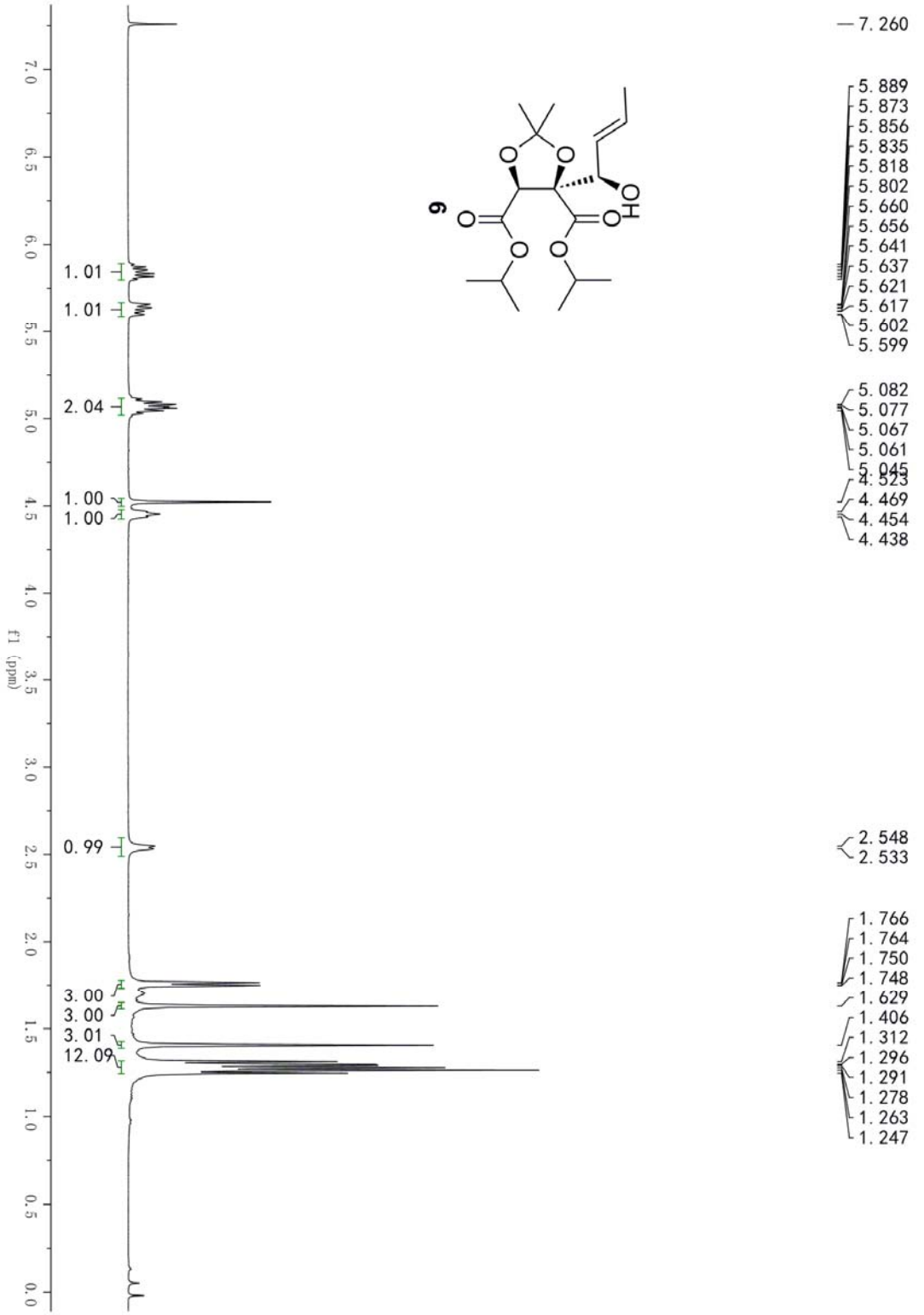
Crystal data and structure refinement for CCDC 1843135.

Empirical formula	C17H28O6
Formula weight	328.39
Temperature/K	170.(2)
Crystal system	orthorhombic
Space group	P212121
a/Å	7.6651(3)
b/Å	12.4842(6)
c/Å	18.5353(8)
α/°	90
β/°	90
γ/°	90
Volume/Å3	1773.69(13)
Z	4
ρcalcg/cm3	1.230

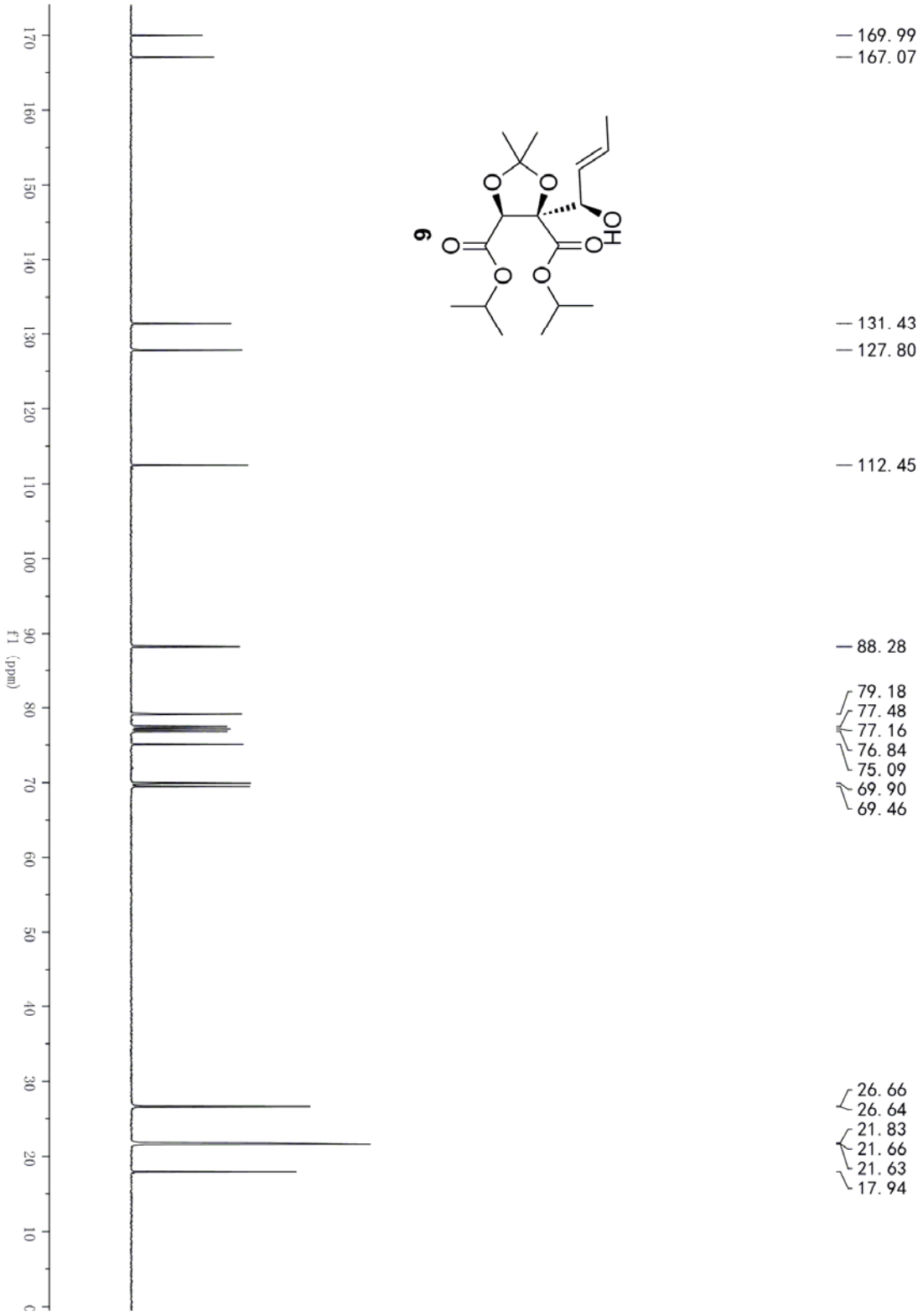
μ/mm-1	0.760
F(000)	712.0
Crystal size/mm3	0.40 × 0.38 × 0.30
Radiation	? (λ = 1.54178)
2Θ range for data collection/°	9.54 to 136.48
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 14, -22 ≤ l ≤ 22
Reflections collected	9910
Independent reflections	3216 [Rint = 0.0322, Rsigma = 0.0316]
Data/restraints/parameters	3216/0/215
Goodness-of-fit on F2	1.157
Final R indexes [I>=2σ (I)]	R1 = 0.0370, wR2 = 0.1103
Final R indexes [all data]	R1 = 0.0374, wR2 = 0.1108
Largest diff. peak/hole / e Å-3	0.28/-0.32
Flack parameter	0.07(5)

NMR Spectra

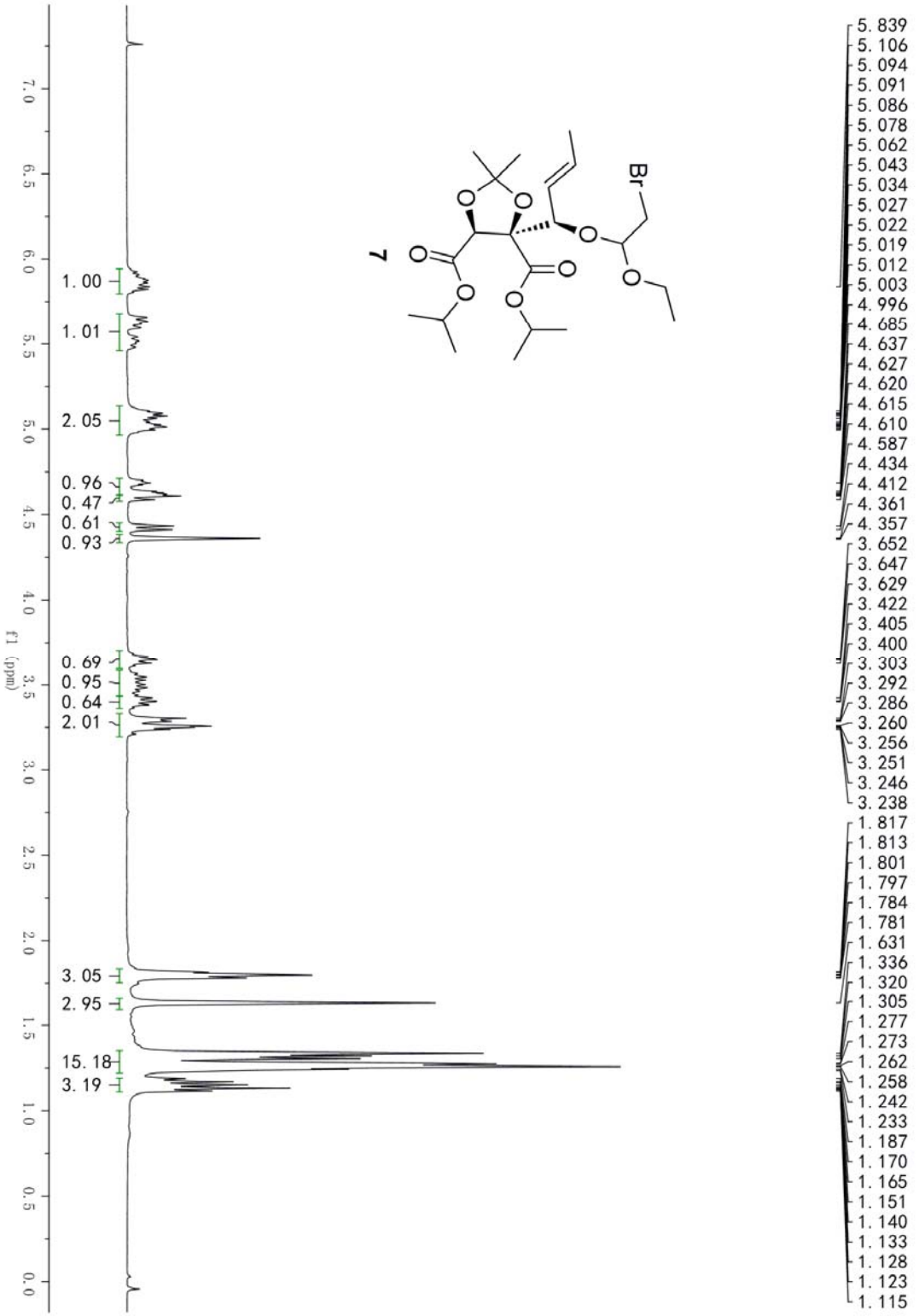
^{1}H NMR Spectrum of compound 6 (400 MHz, $CDCl_3$)



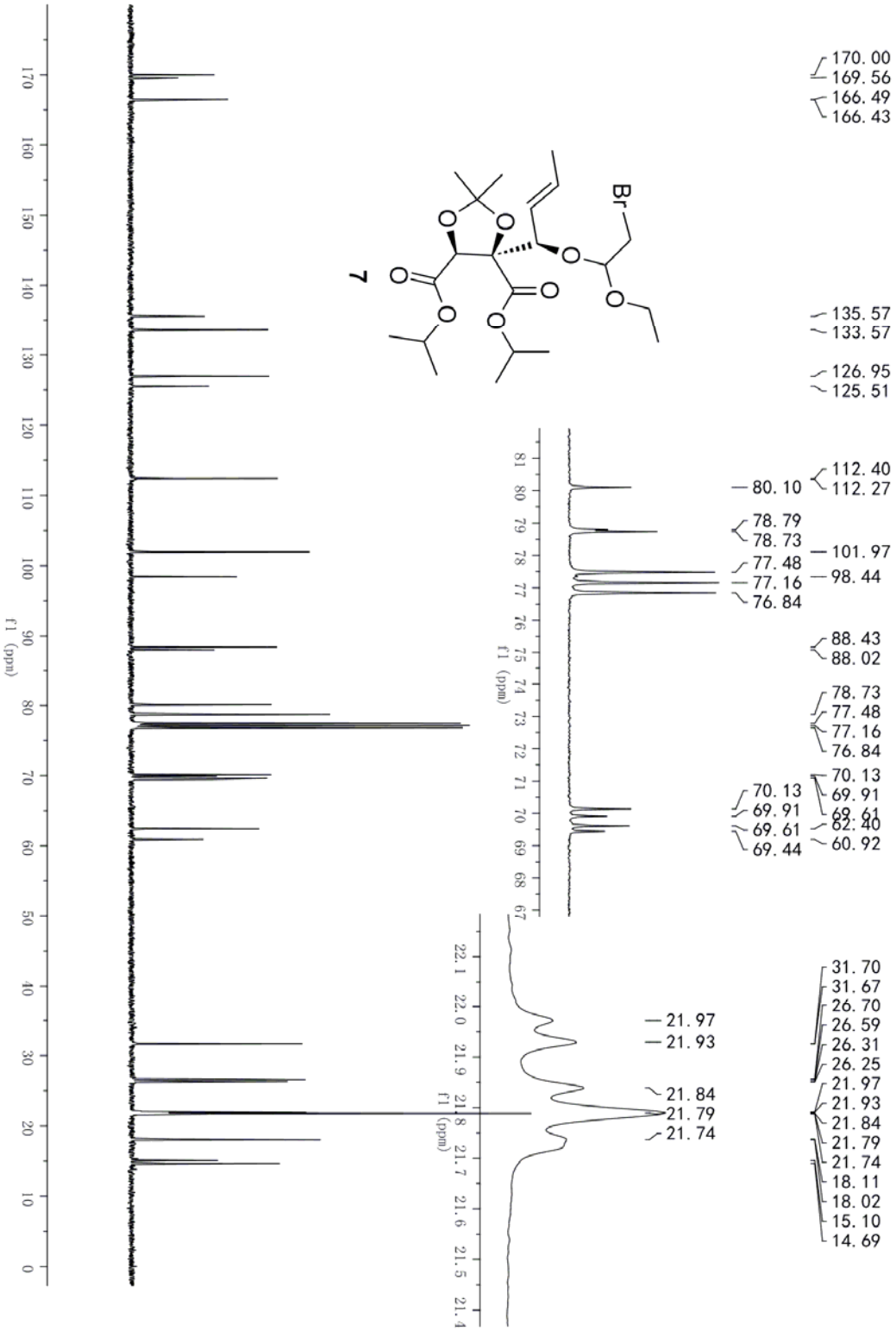
^{13}C NMR Spectrum of compound 6 (100 MHz, $CDCl_3$)



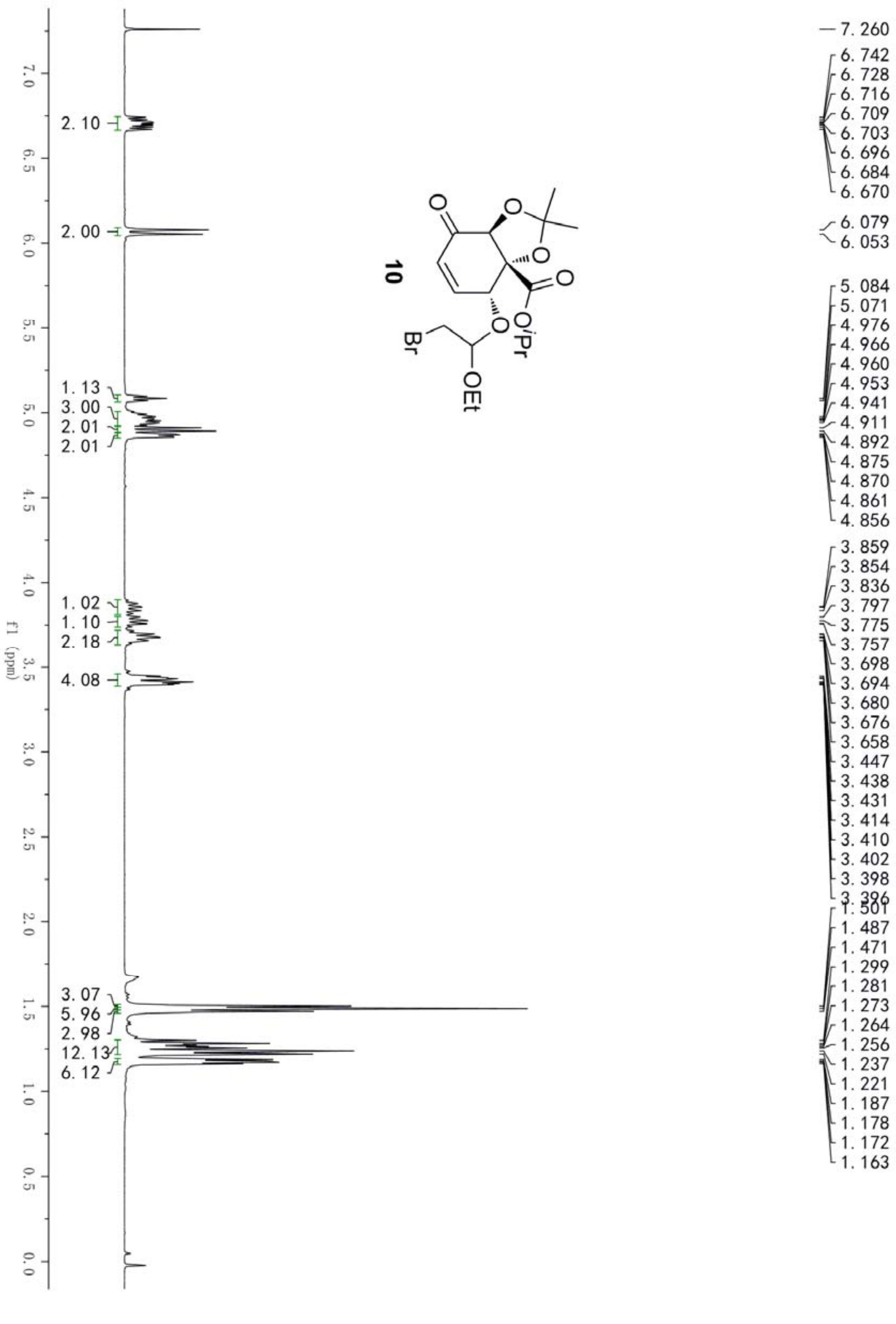
^{1}H NMR Spectrum of compound 7 (400 MHz, $CDCl_3$)



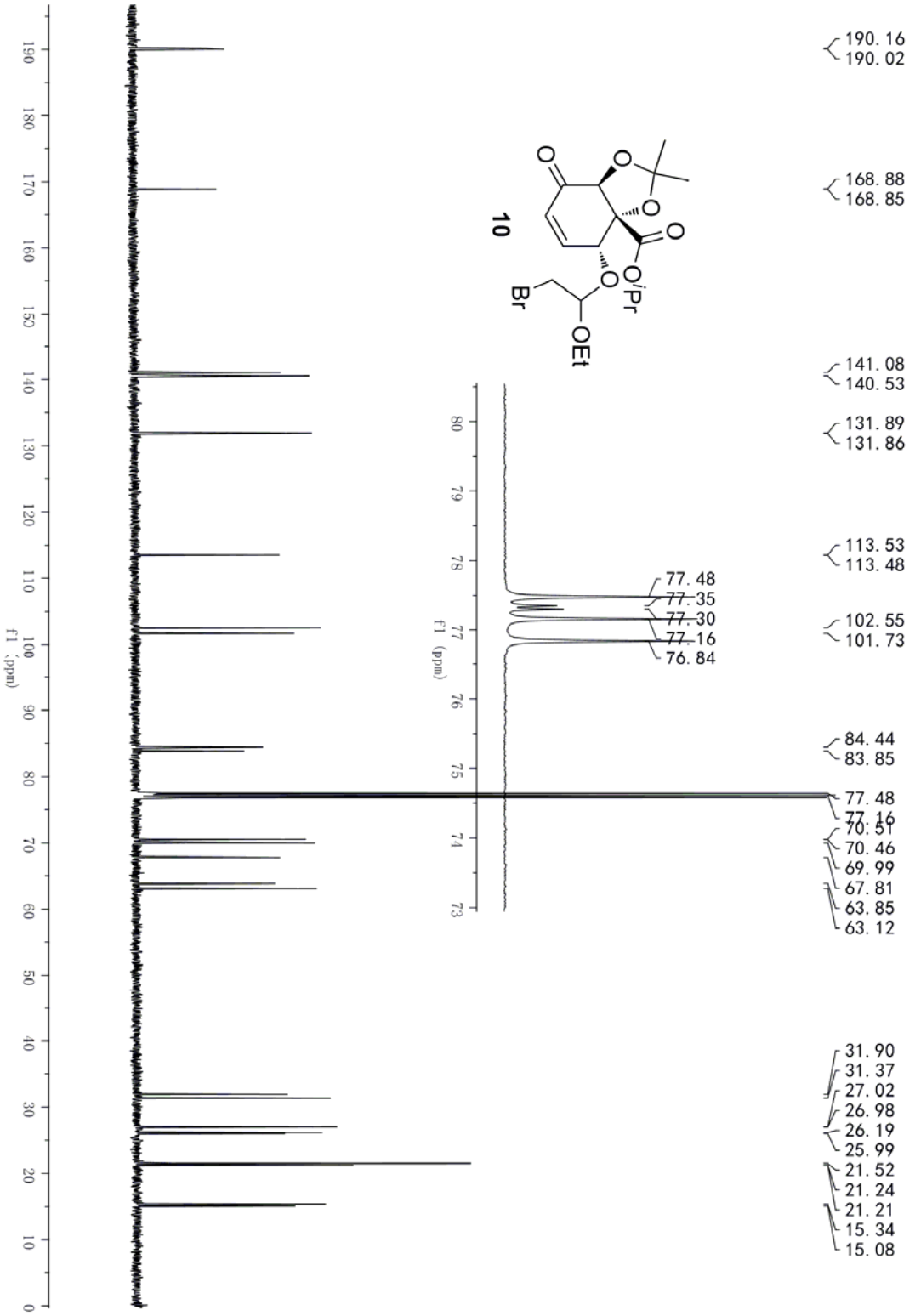
^{13}C NMR Spectrum of compound 7 (100 MHz, $CDCl_3$)



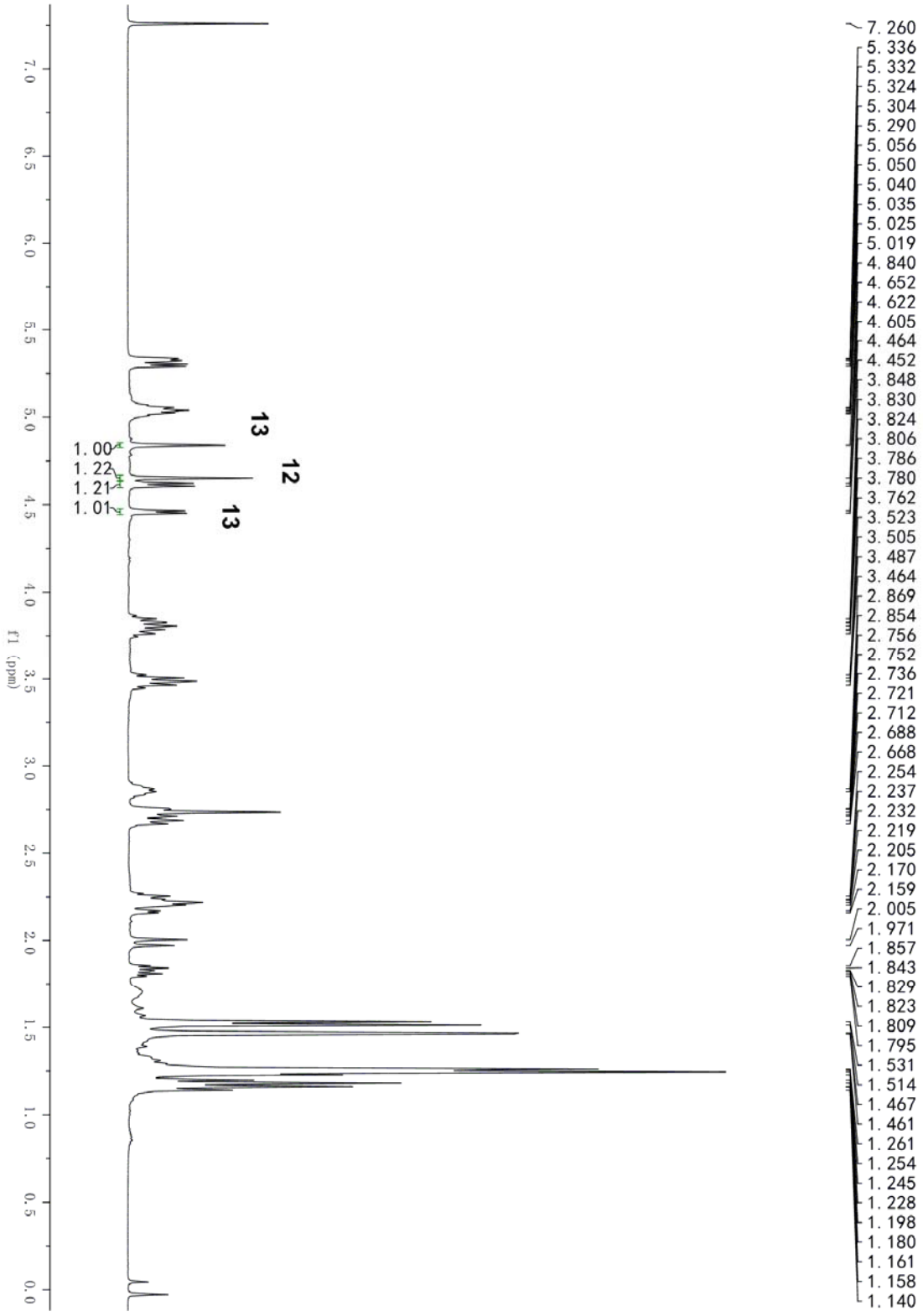
^{1}H NMR Spectrum of compound 10 (400 MHz, $CDCl_3$)



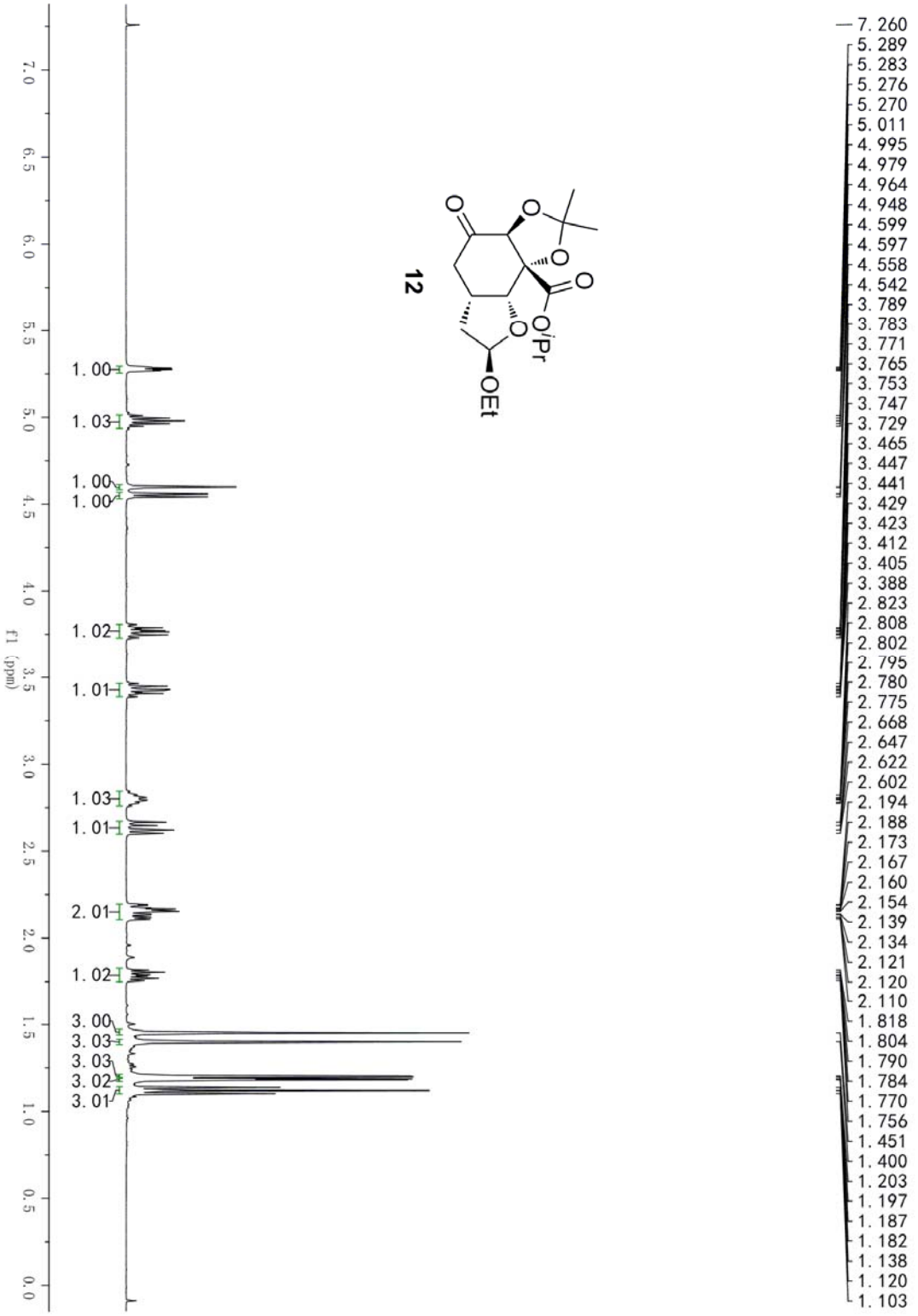
^{13}C NMR Spectrum of compound 10 (100 MHz, $CDCl_3$)



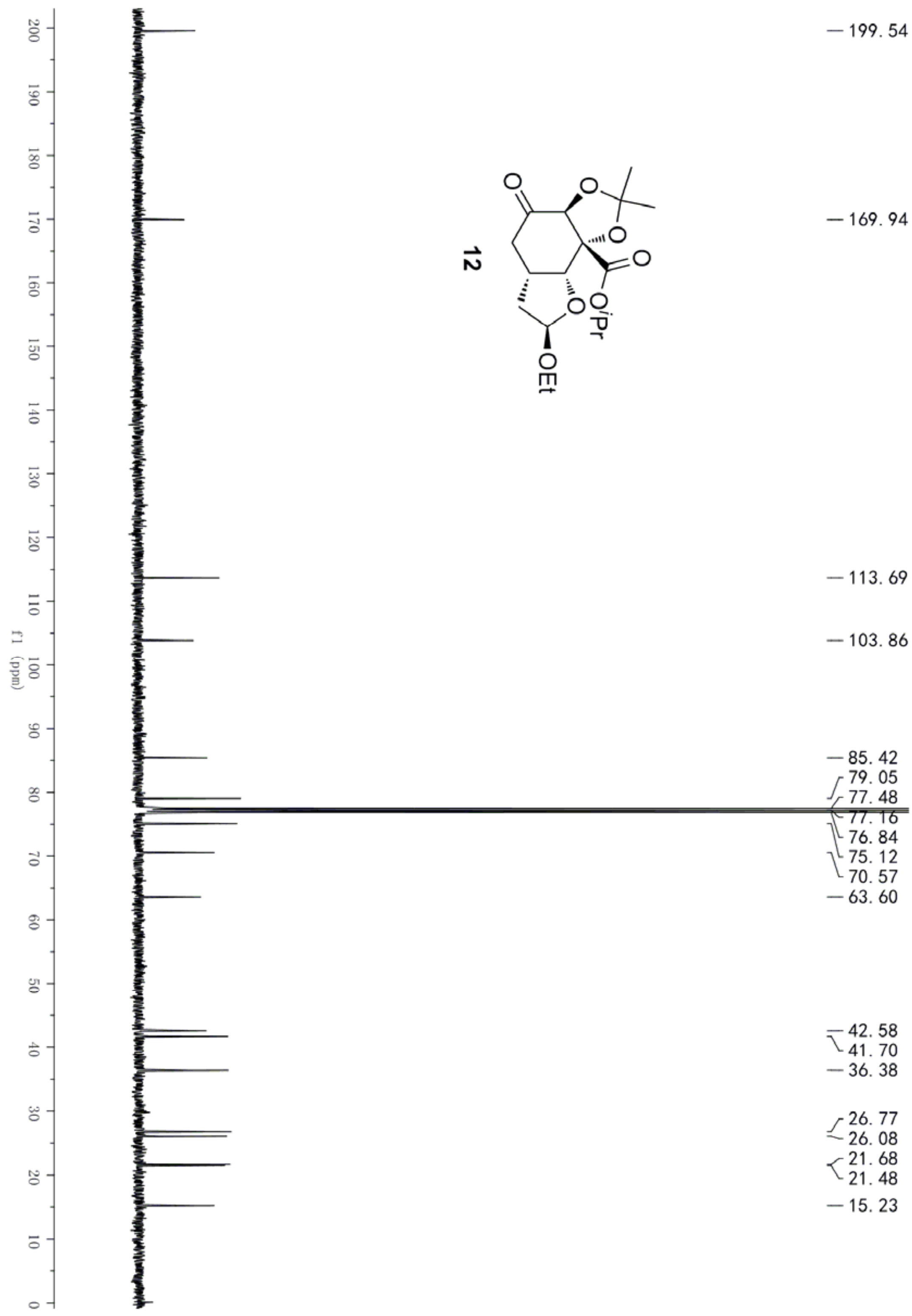
^{1}H NMR Spectrum of the mixture of compounds 12/13 (400 MHz, $CDCl_3$)



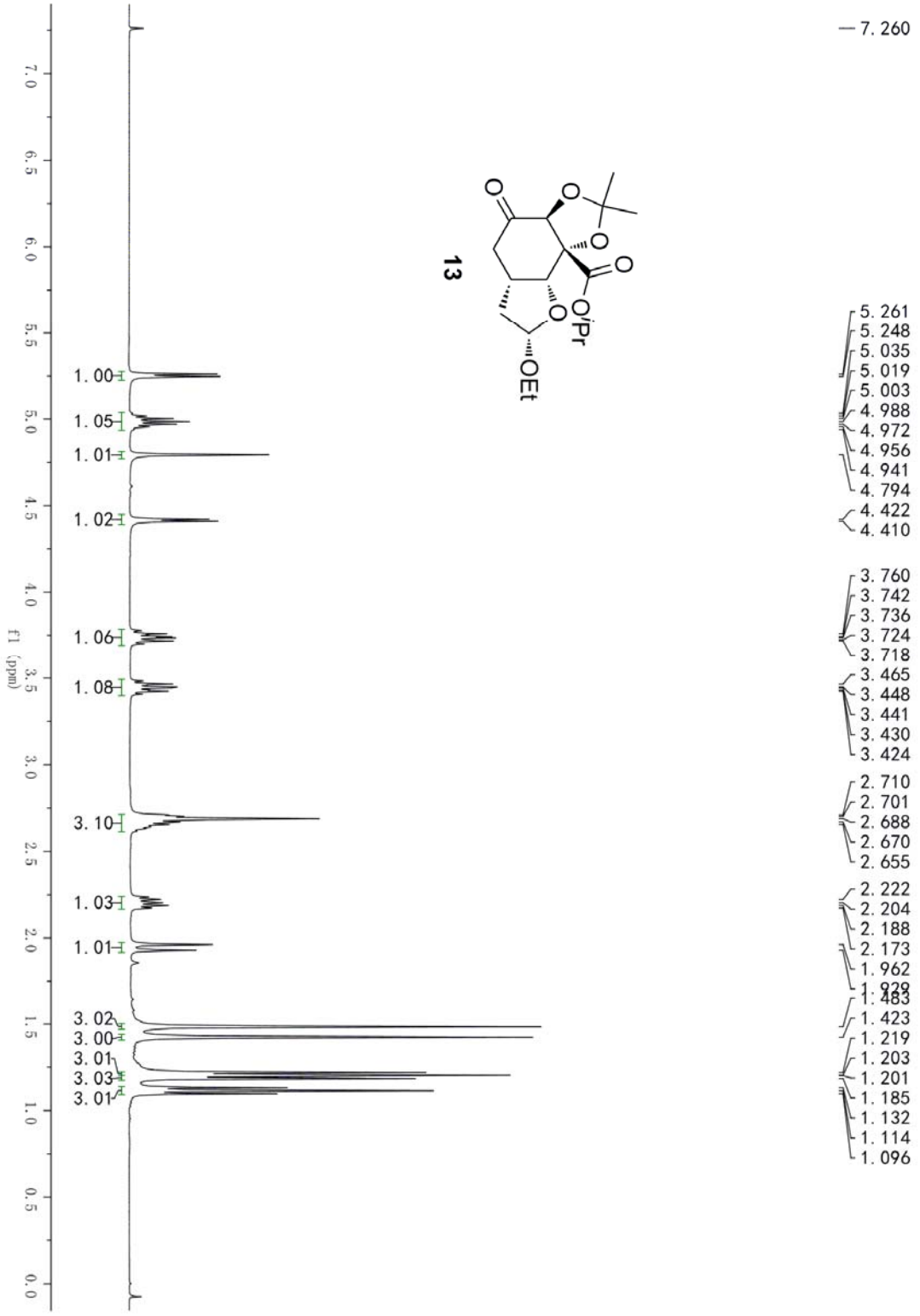
^{1}H NMR Spectrum of compound 12 (400 MHz, $CDCl_3$)



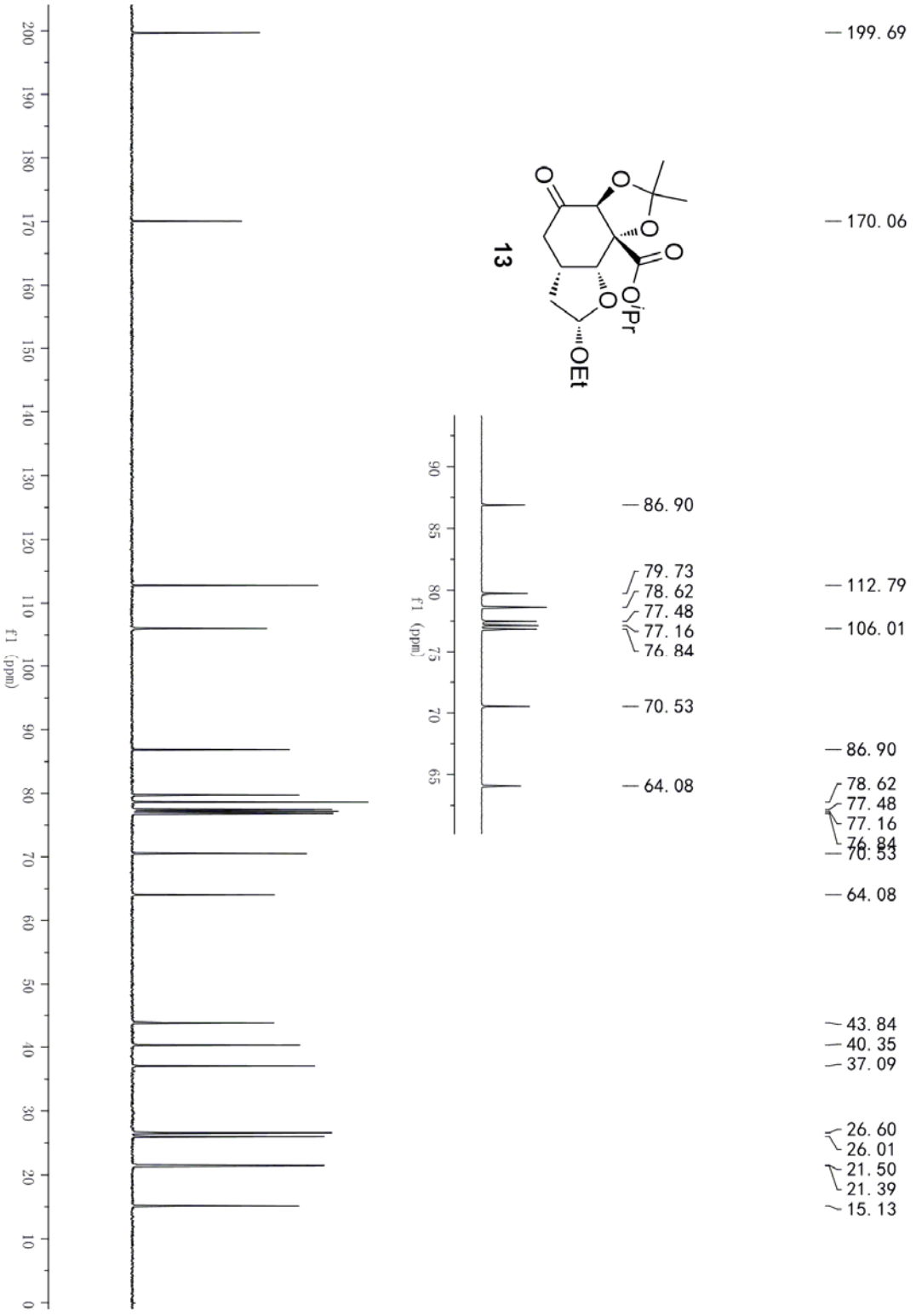
^{13}C NMR Spectrum of compound 12 (100 MHz, $CDCl_3$)



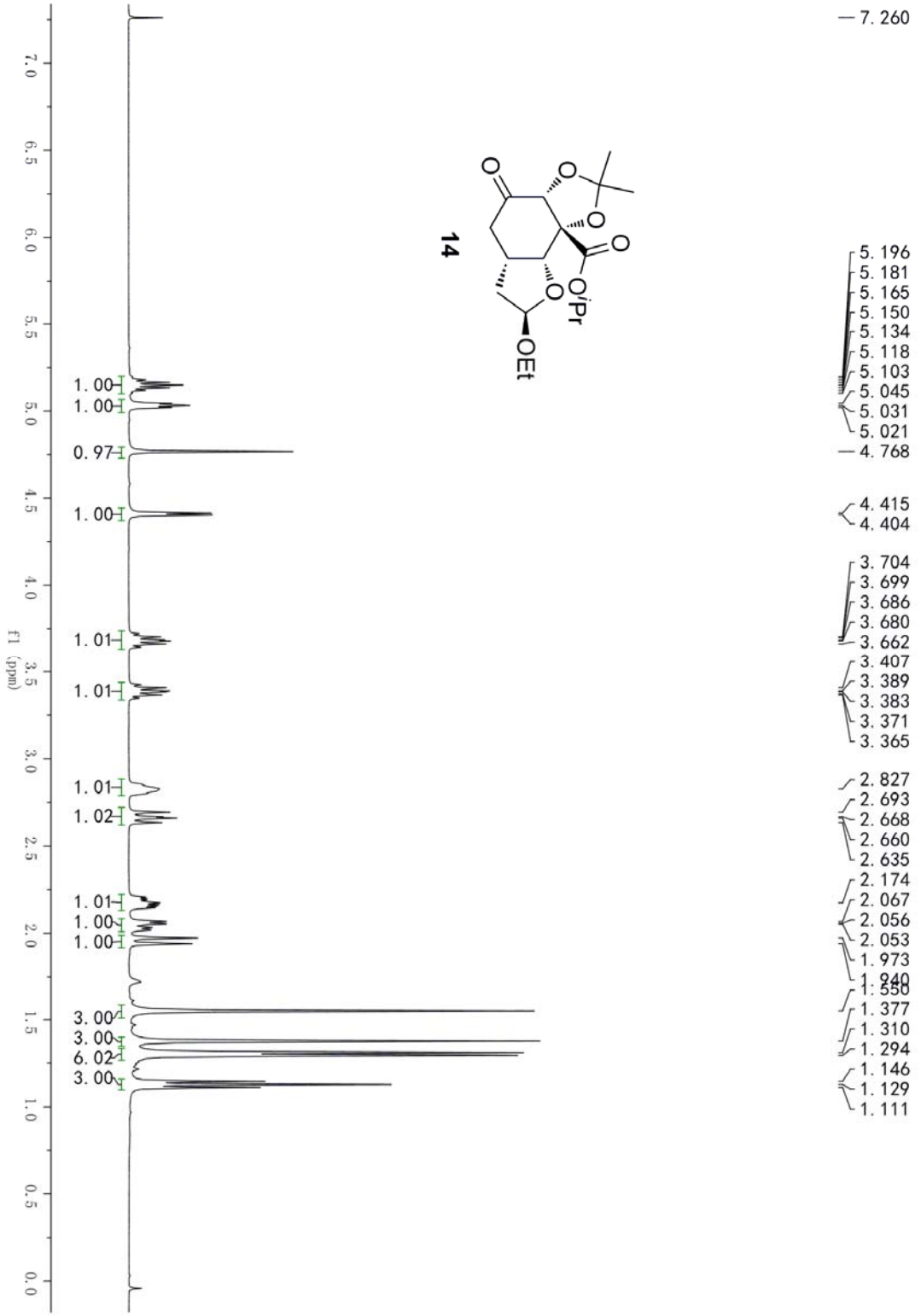
^{1}H NMR Spectrum of compound 13 (400 MHz, $CDCl_3$)



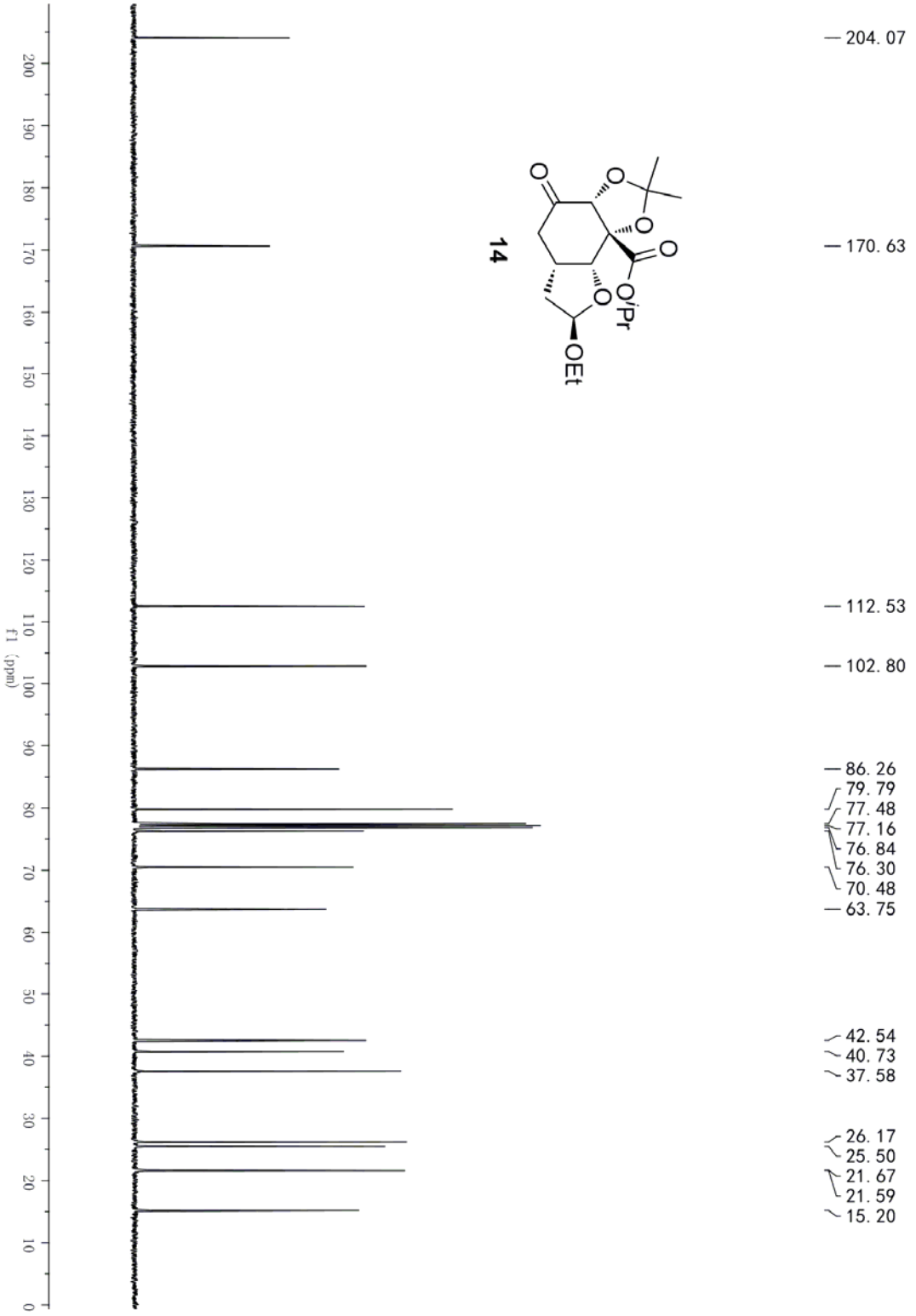
^{13}C NMR Spectrum of compound 13 (100 MHz, $CDCl_3$)



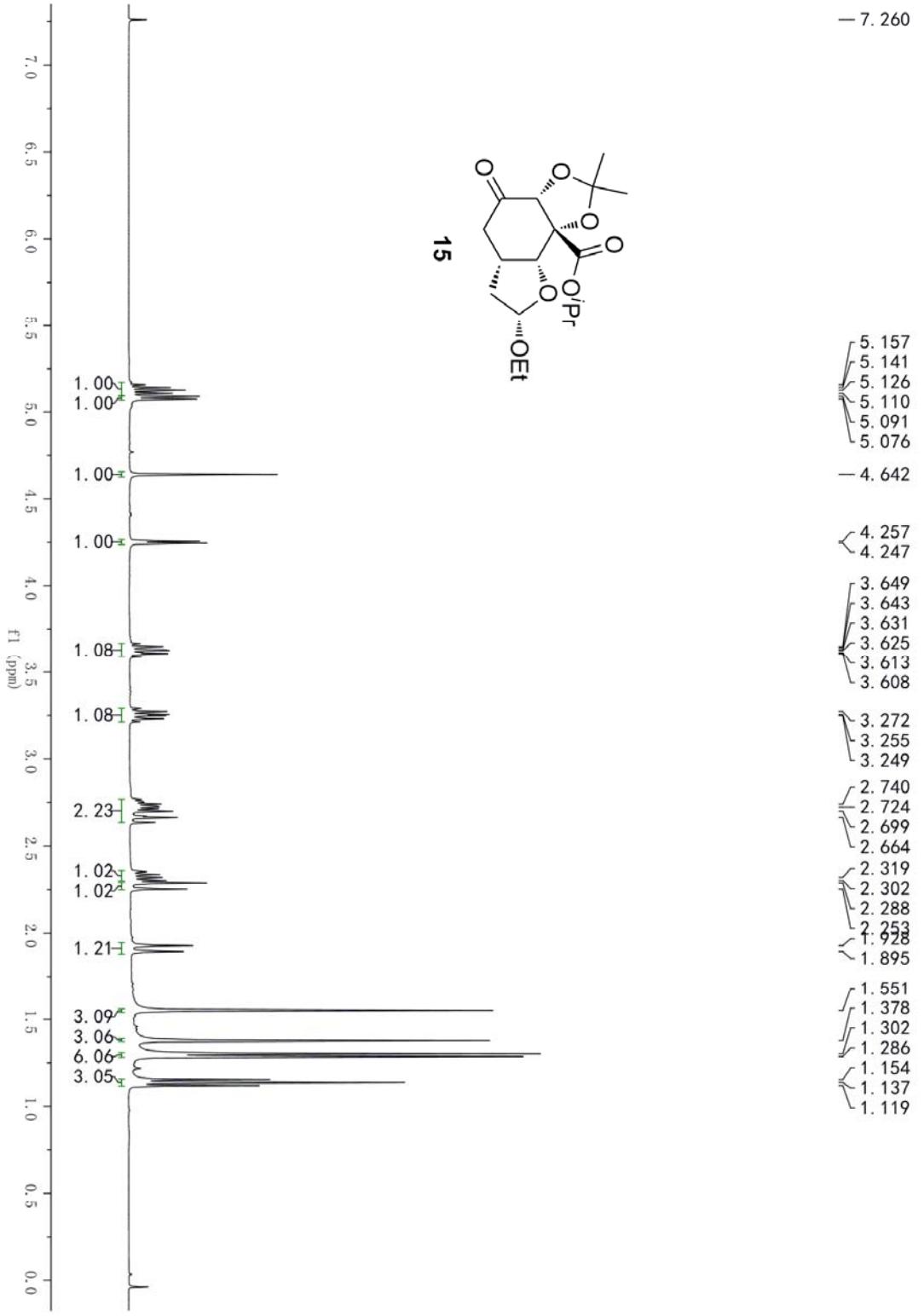
^{1}H NMR Spectrum of compound 14 (400 MHz, $CDCl_3$)



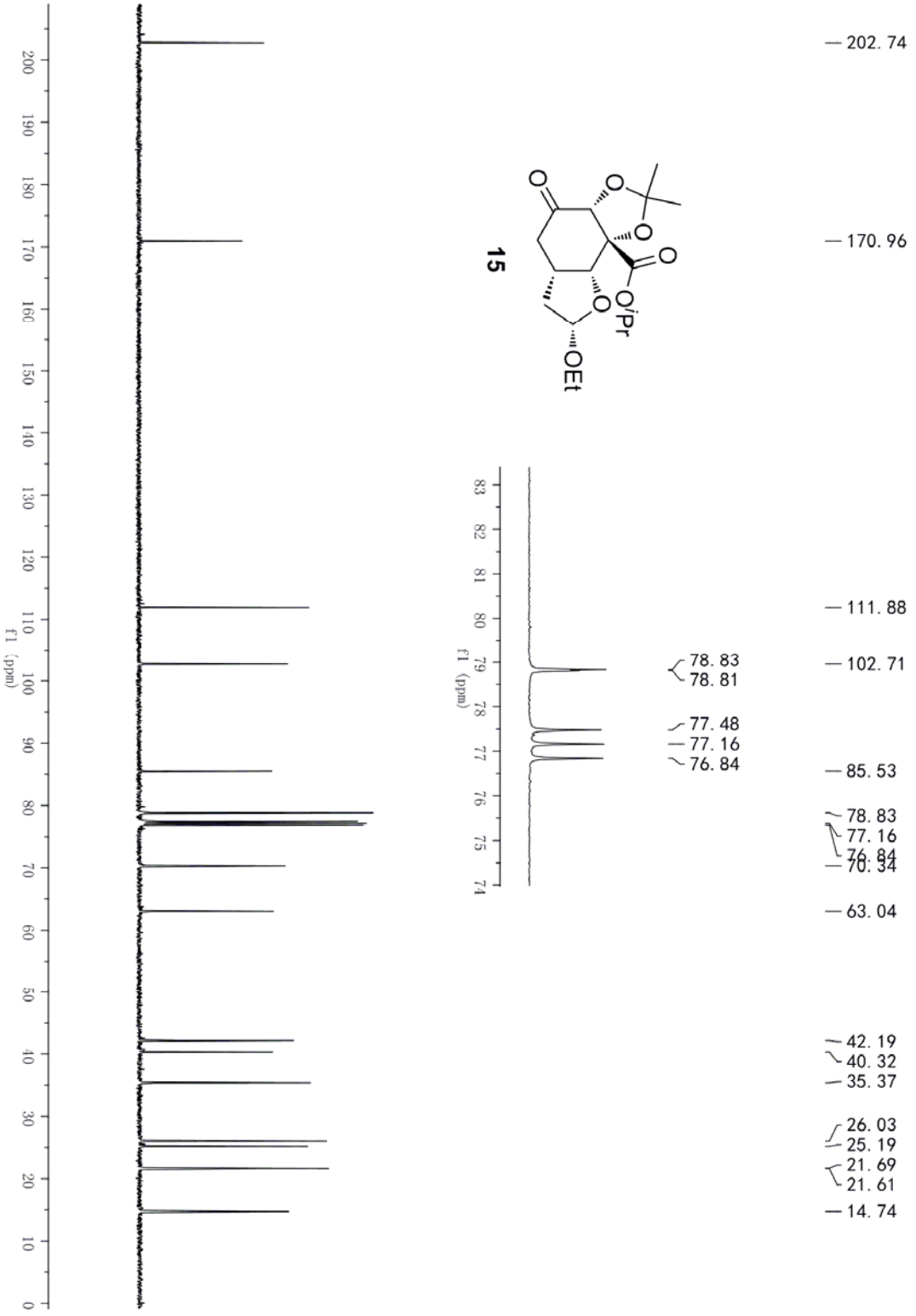
^{13}C NMR Spectrum of compound 14 (100 MHz, $CDCl_3$)



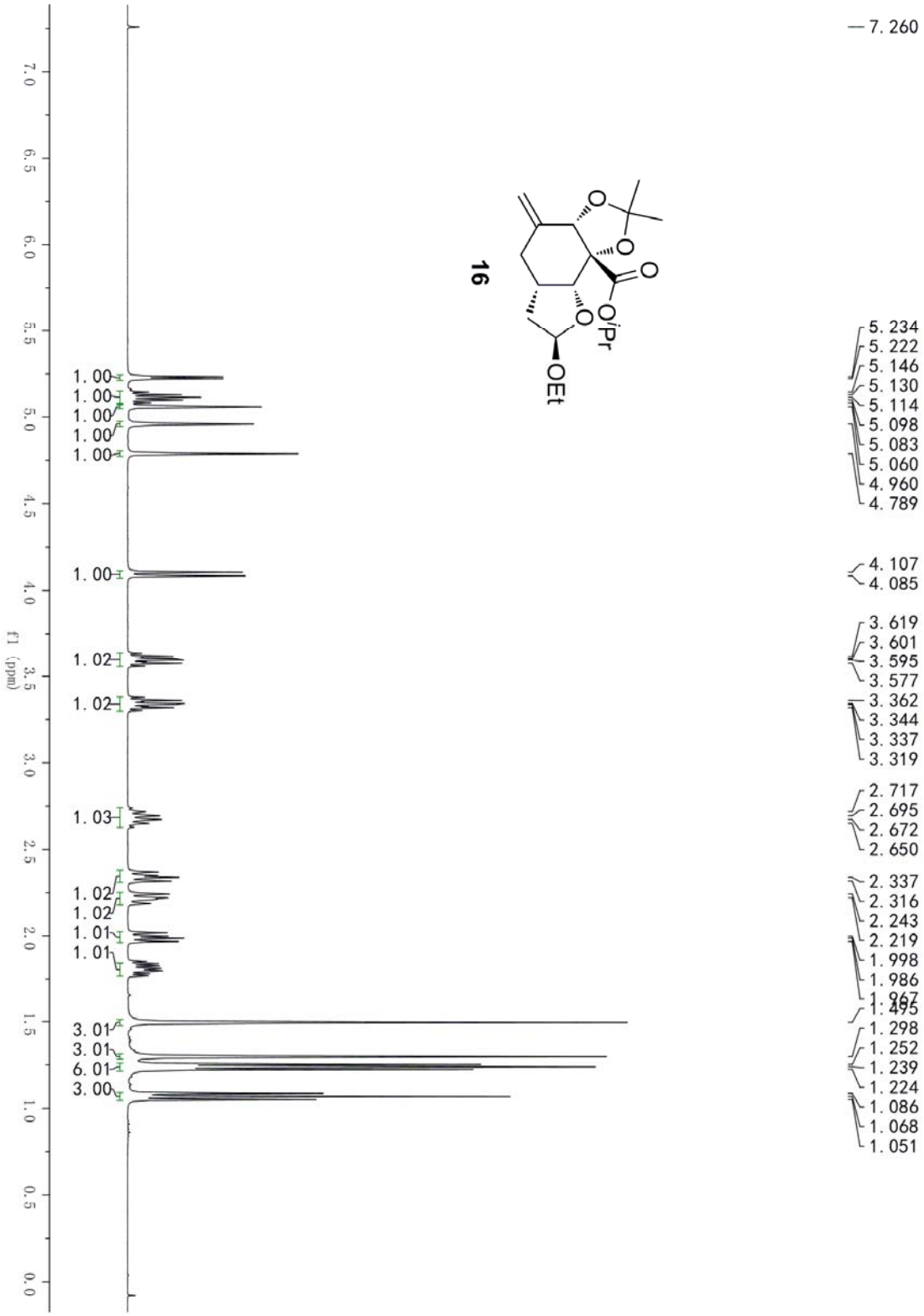
^{1}H NMR Spectrum of compound 15 (400 MHz, $CDCl_3$)



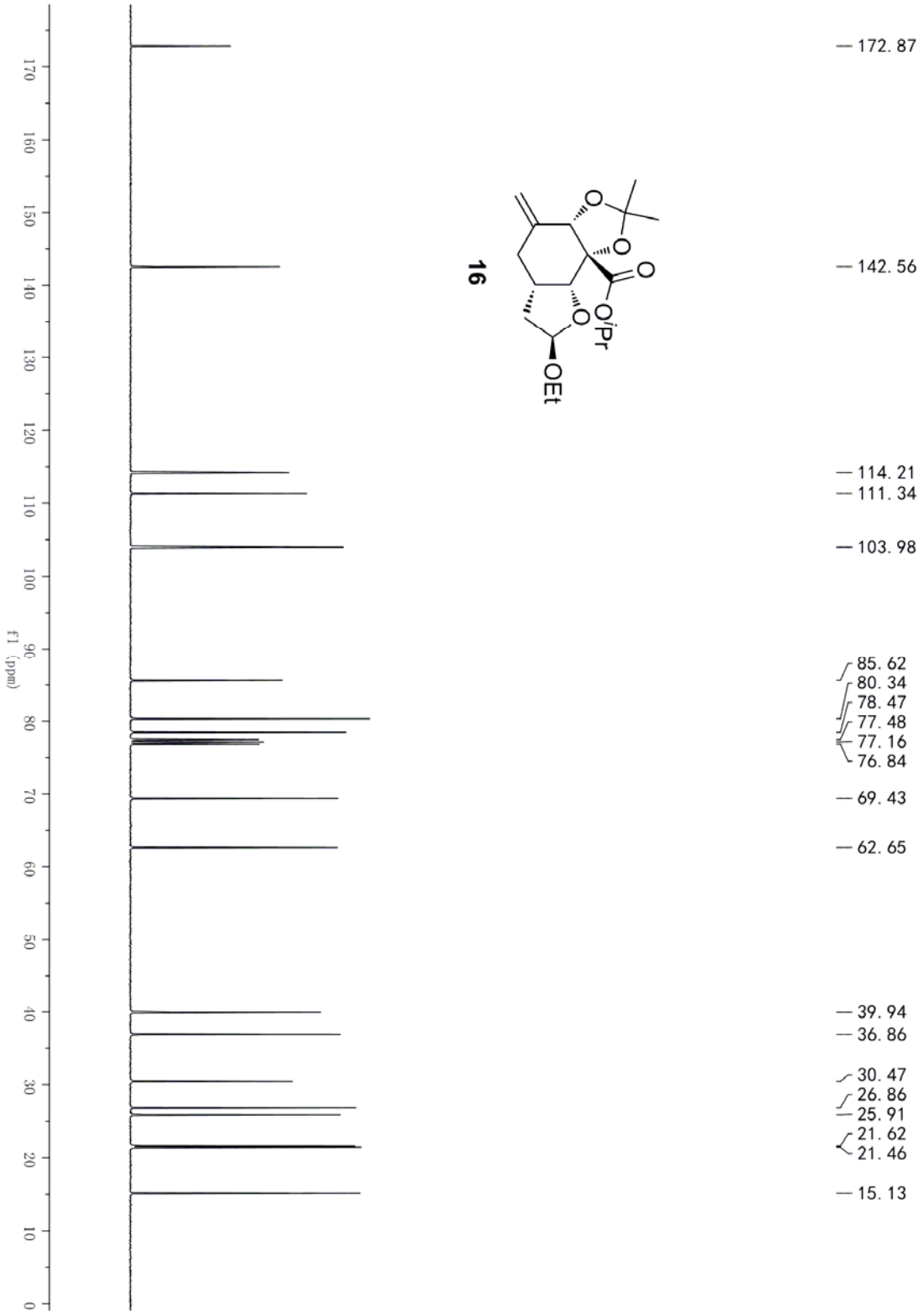
^{13}C NMR Spectrum of compound 15 (100 MHz, $CDCl_3$)



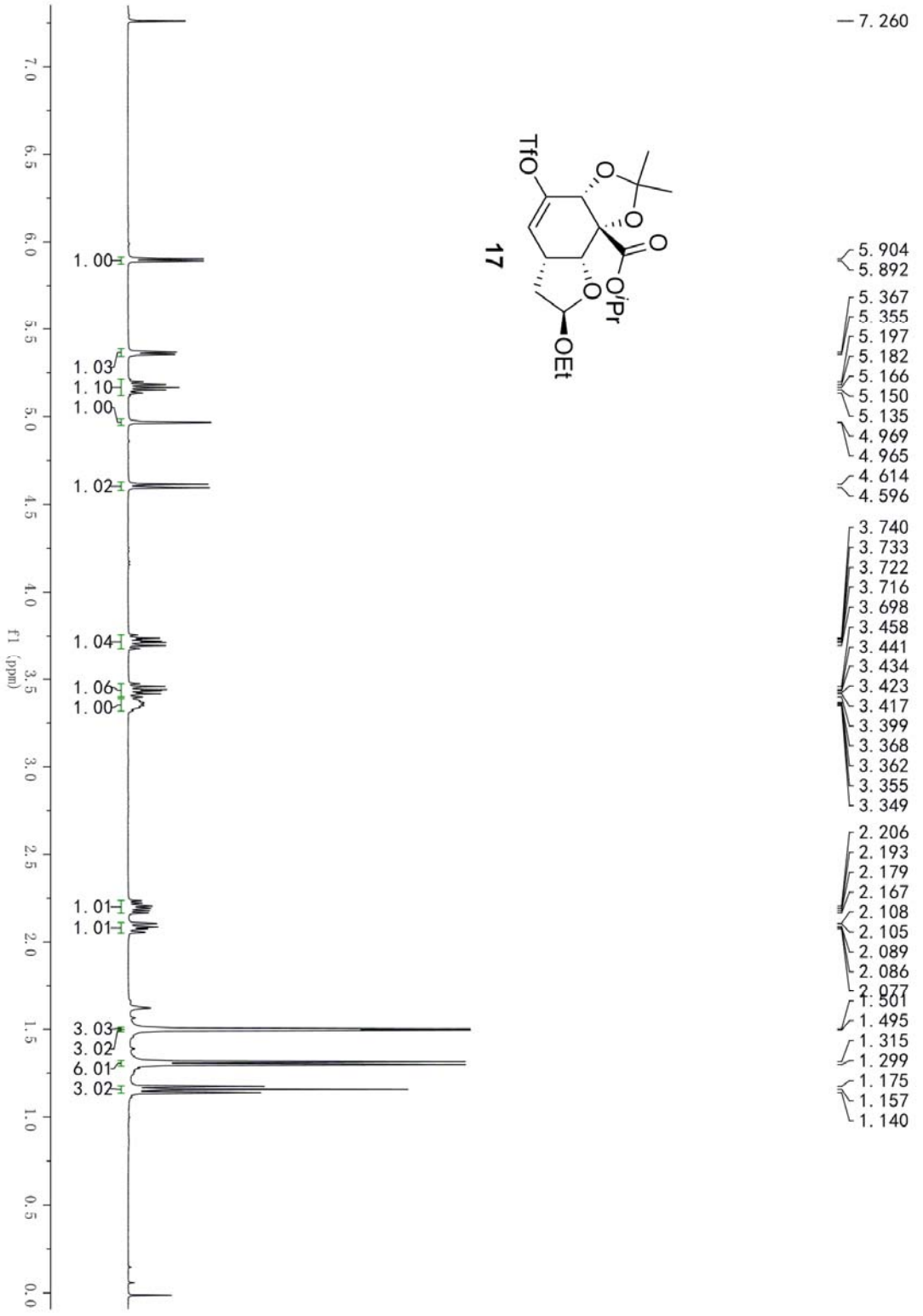
^{1}H NMR Spectrum of compound 16 (400 MHz, $CDCl_3$)



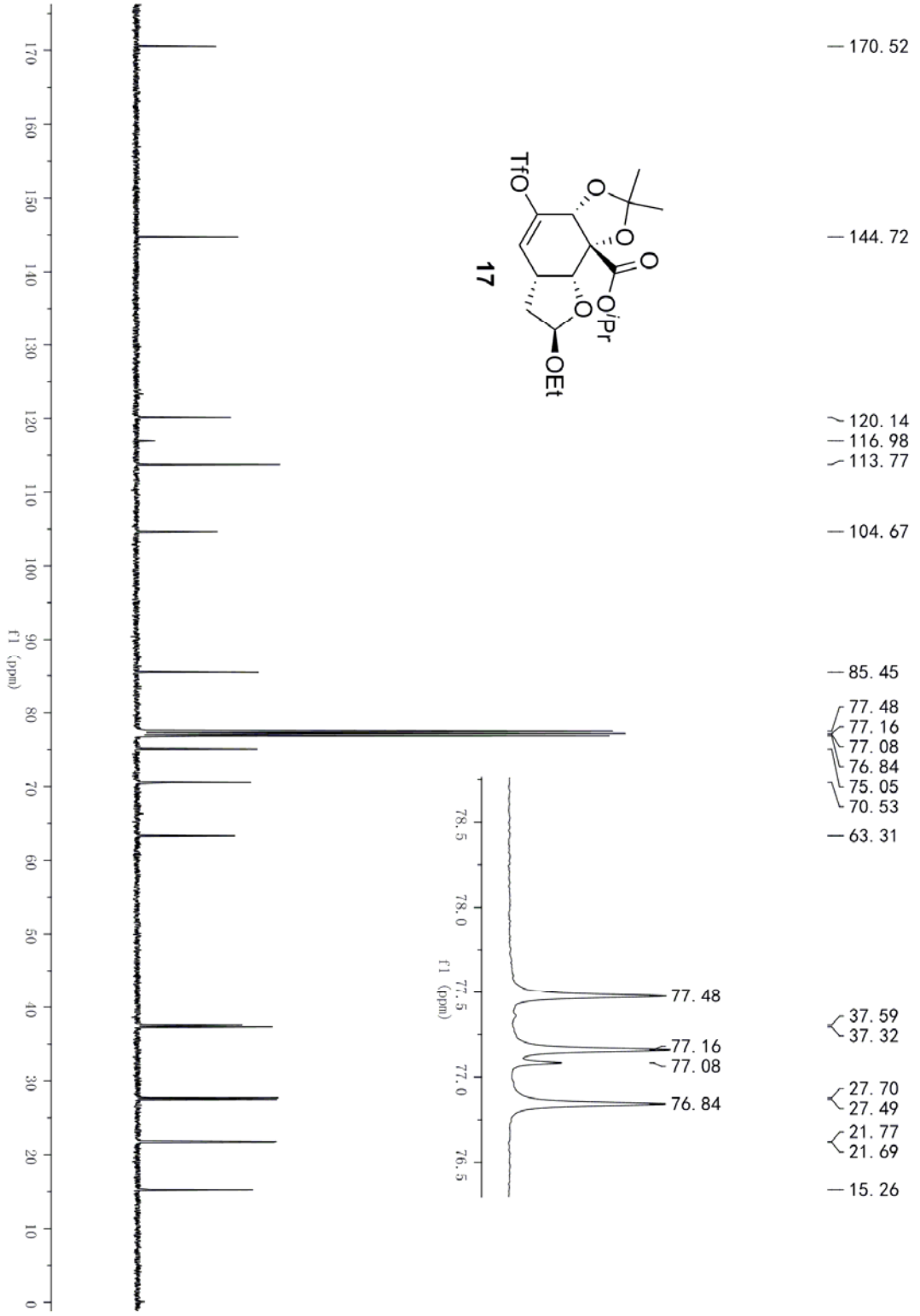
^{13}C NMR Spectrum of compound 16 (100 MHz, $CDCl_3$)



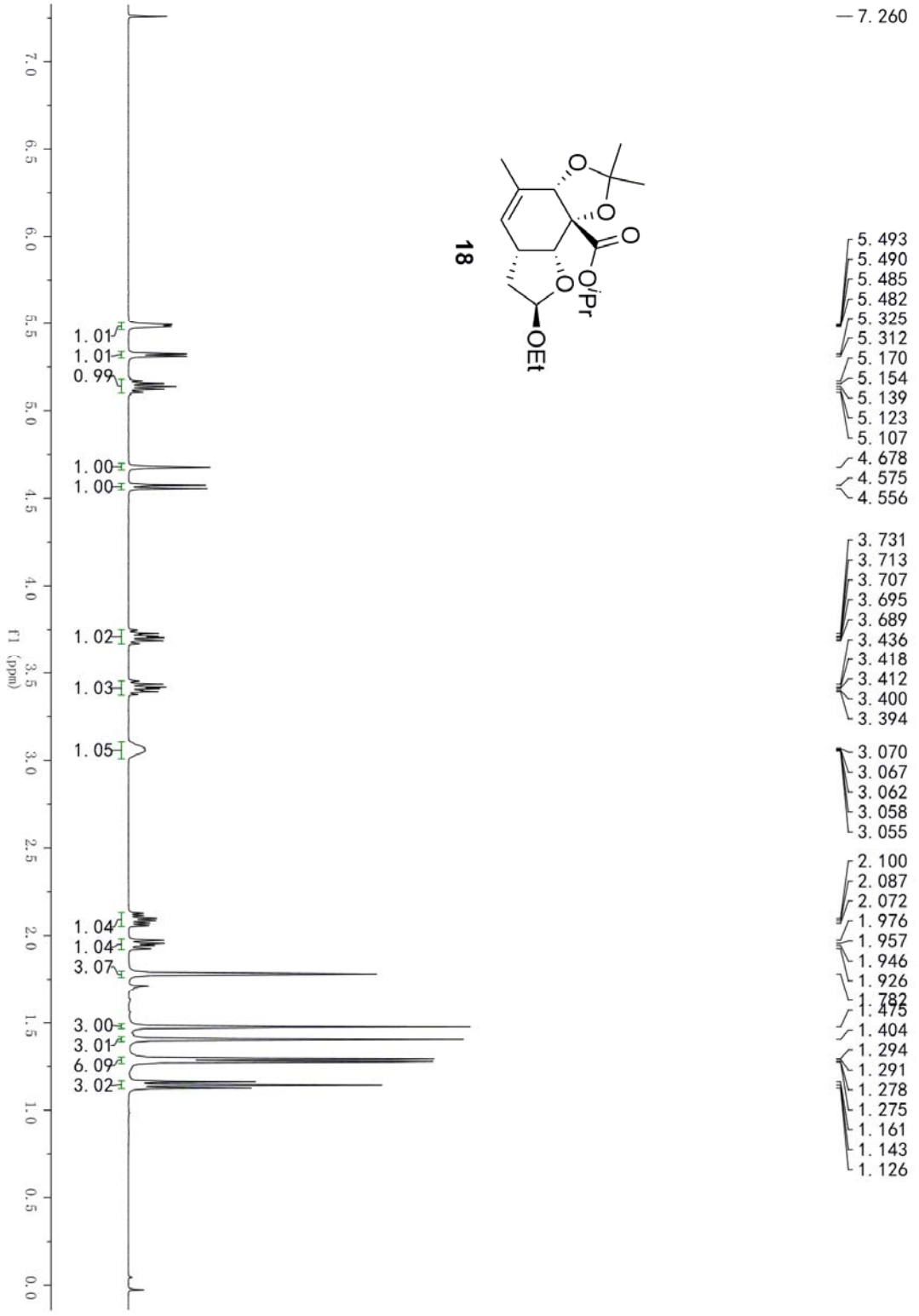
^{1}H NMR Spectrum of compound 17 (400 MHz, $CDCl_3$)



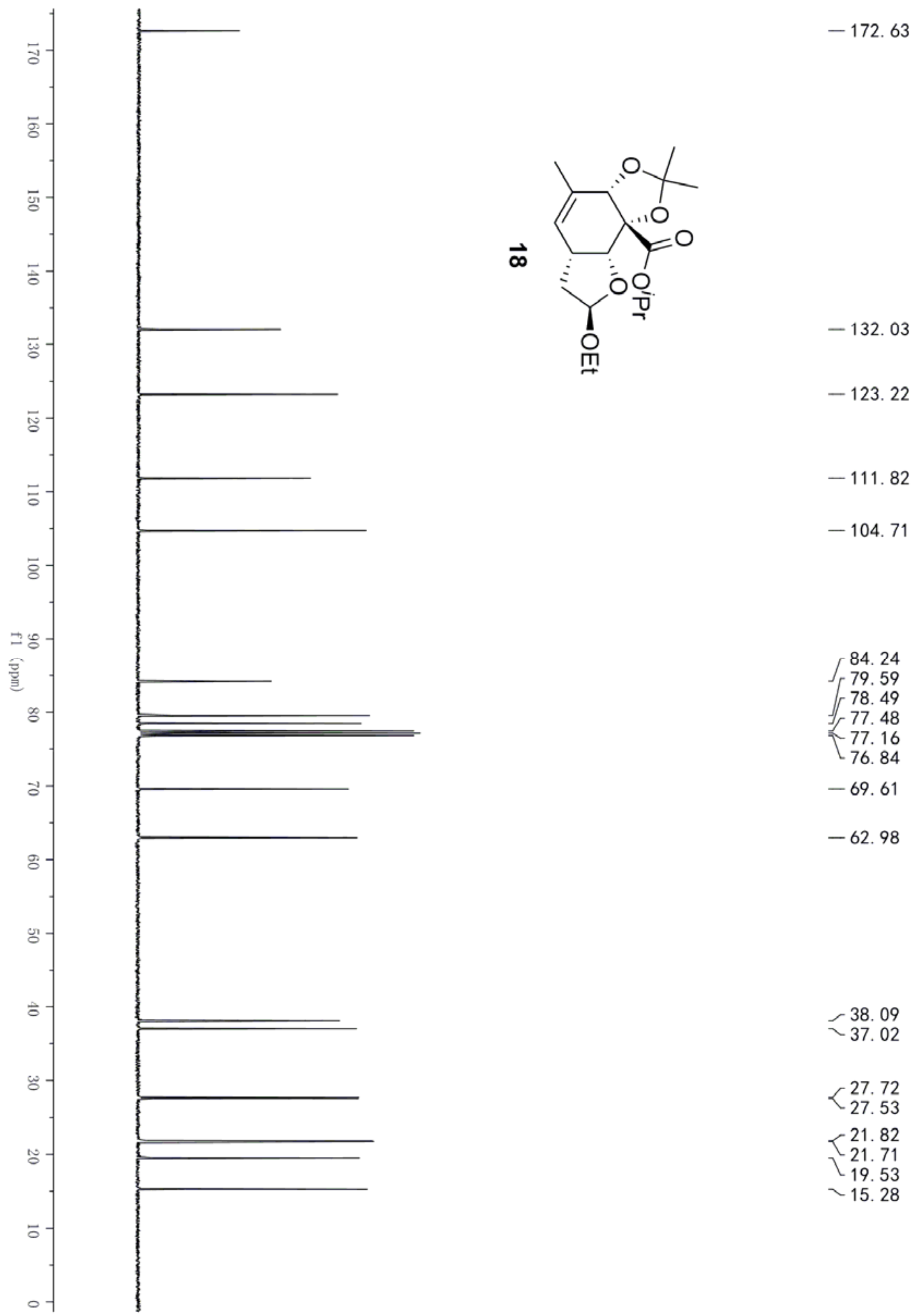
^{13}C NMR Spectrum of compound 17 (100 MHz, $CDCl_3$)



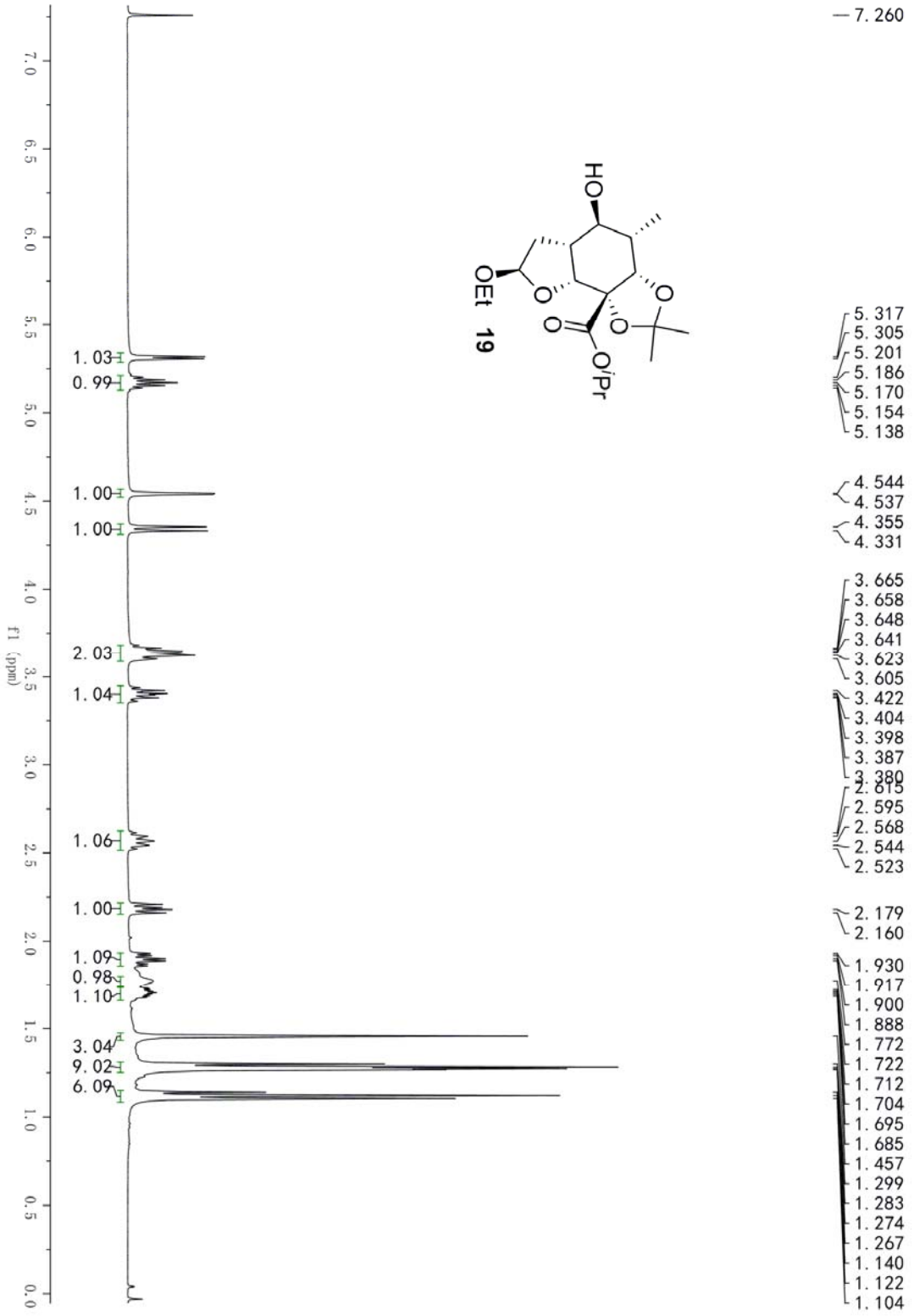
^{1}H NMR Spectrum of compound 18 (400 MHz, $CDCl_3$)



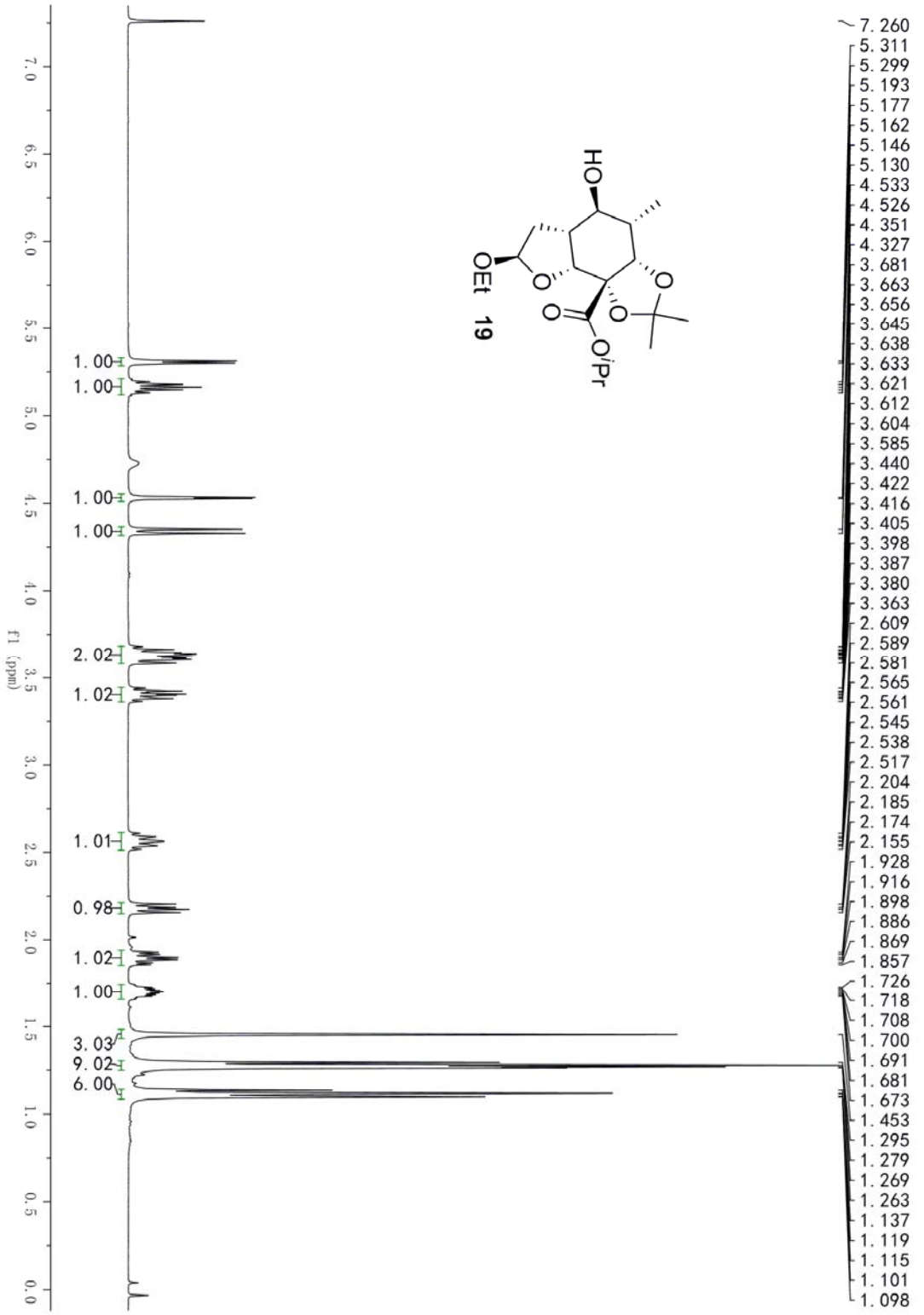
^{13}C NMR Spectrum of compound 18 (100 MHz, $CDCl_3$)



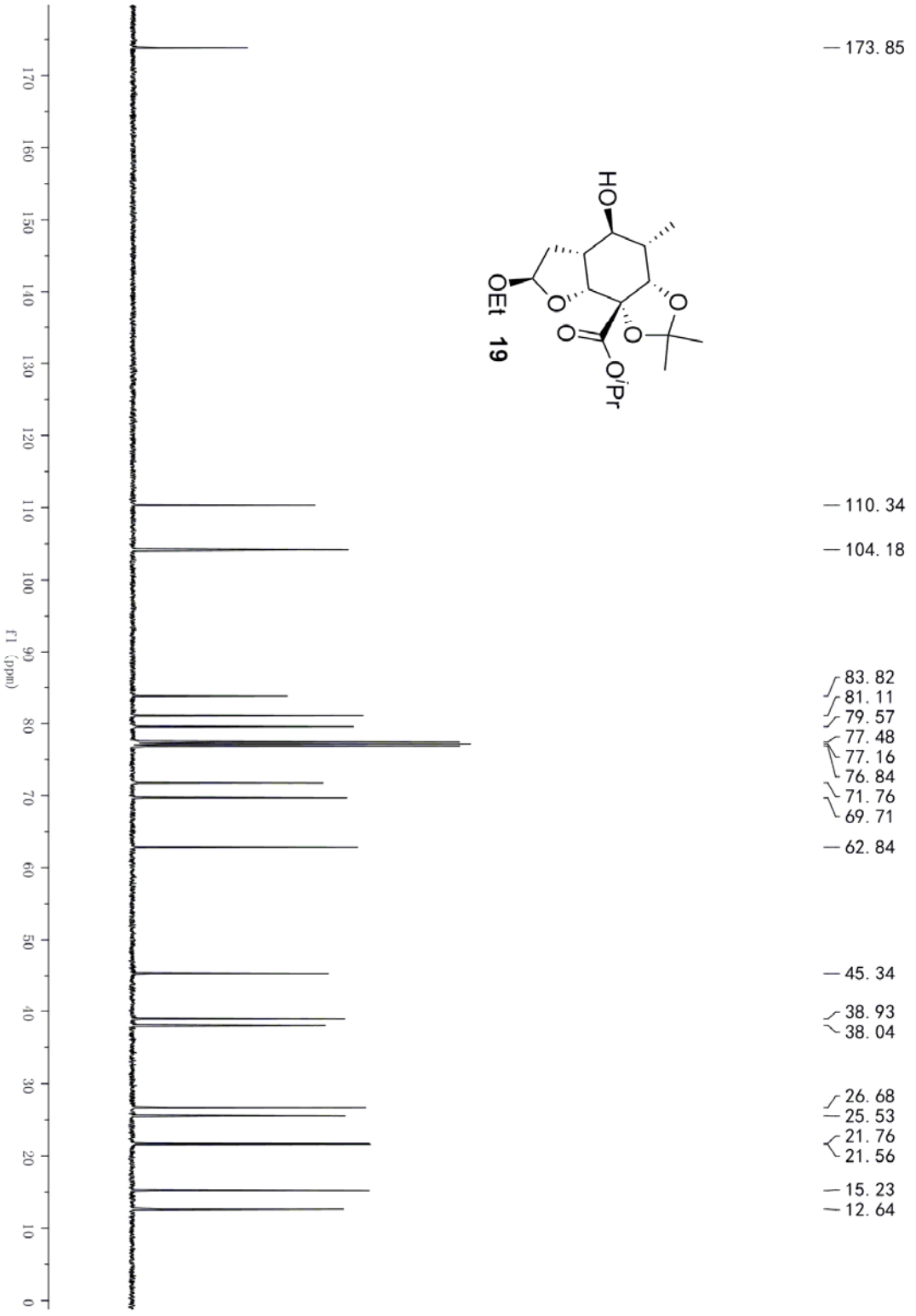
^{1}H NMR Spectrum of compound 19 (400 MHz, $CDCl_3$)



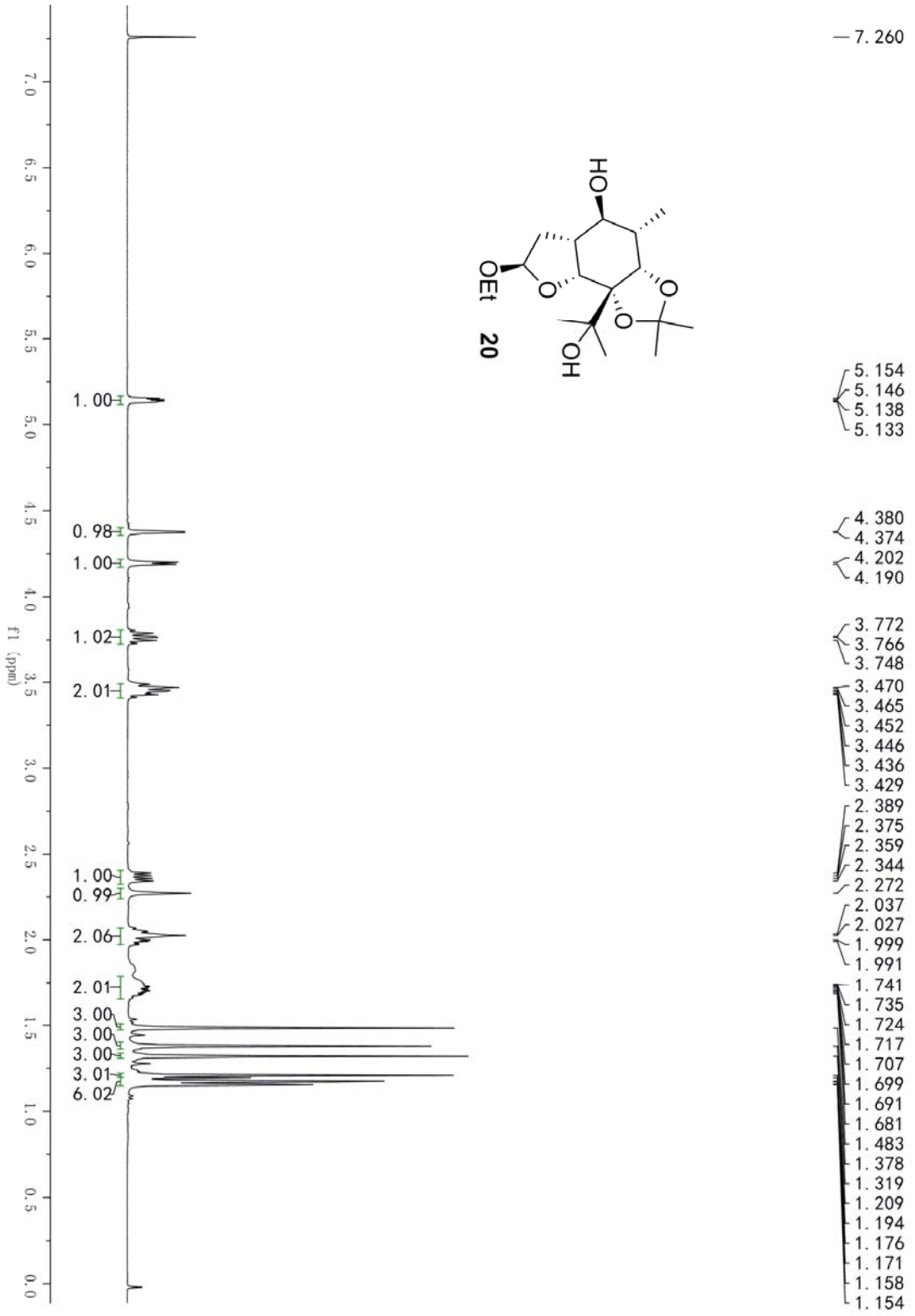
^{1}H NMR Spectrum of compound 19 (400 MHz, $CDCl_3/D_2O$)



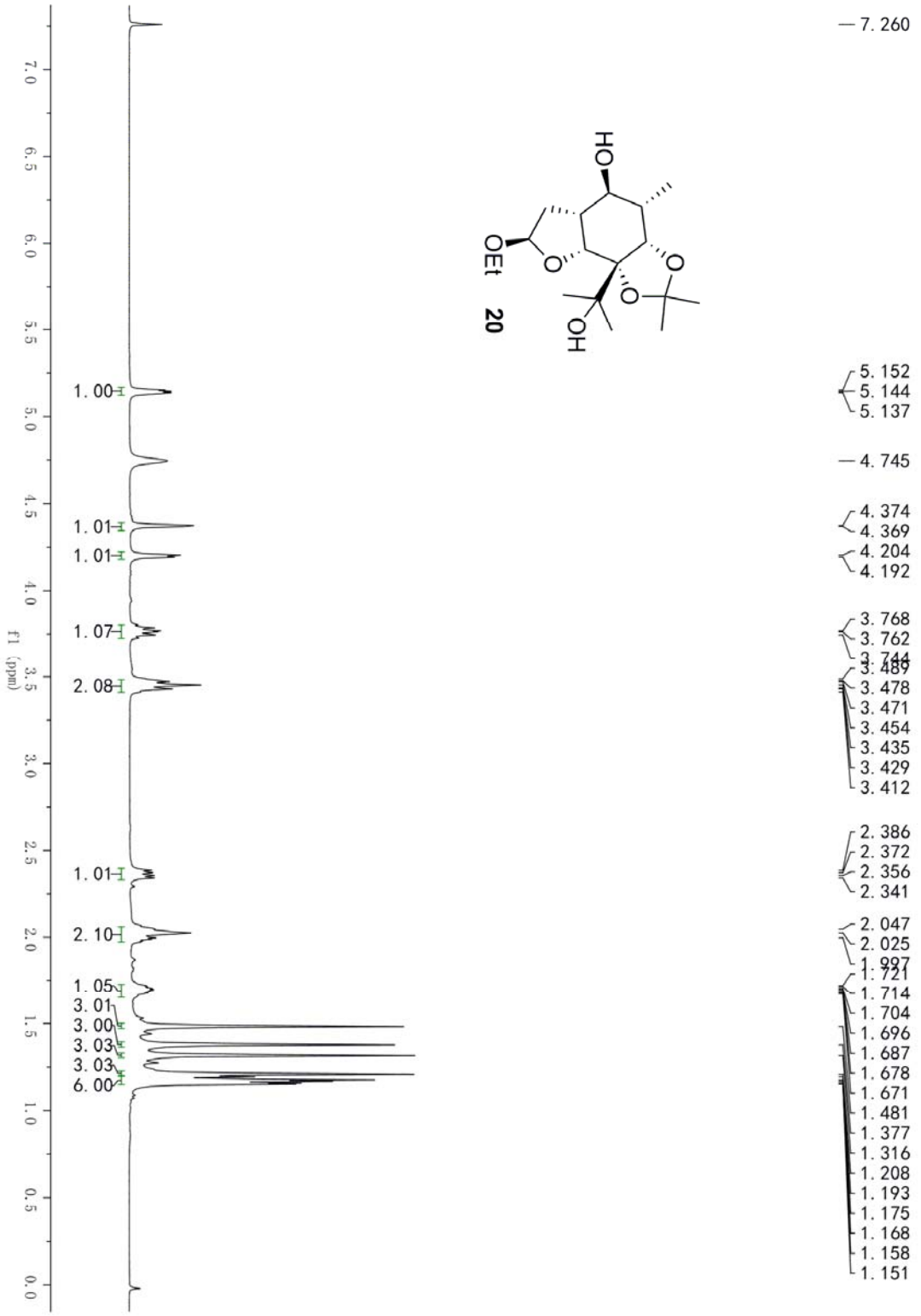
^{13}C NMR Spectrum of compound 19 (100 MHz, $CDCl_3$)



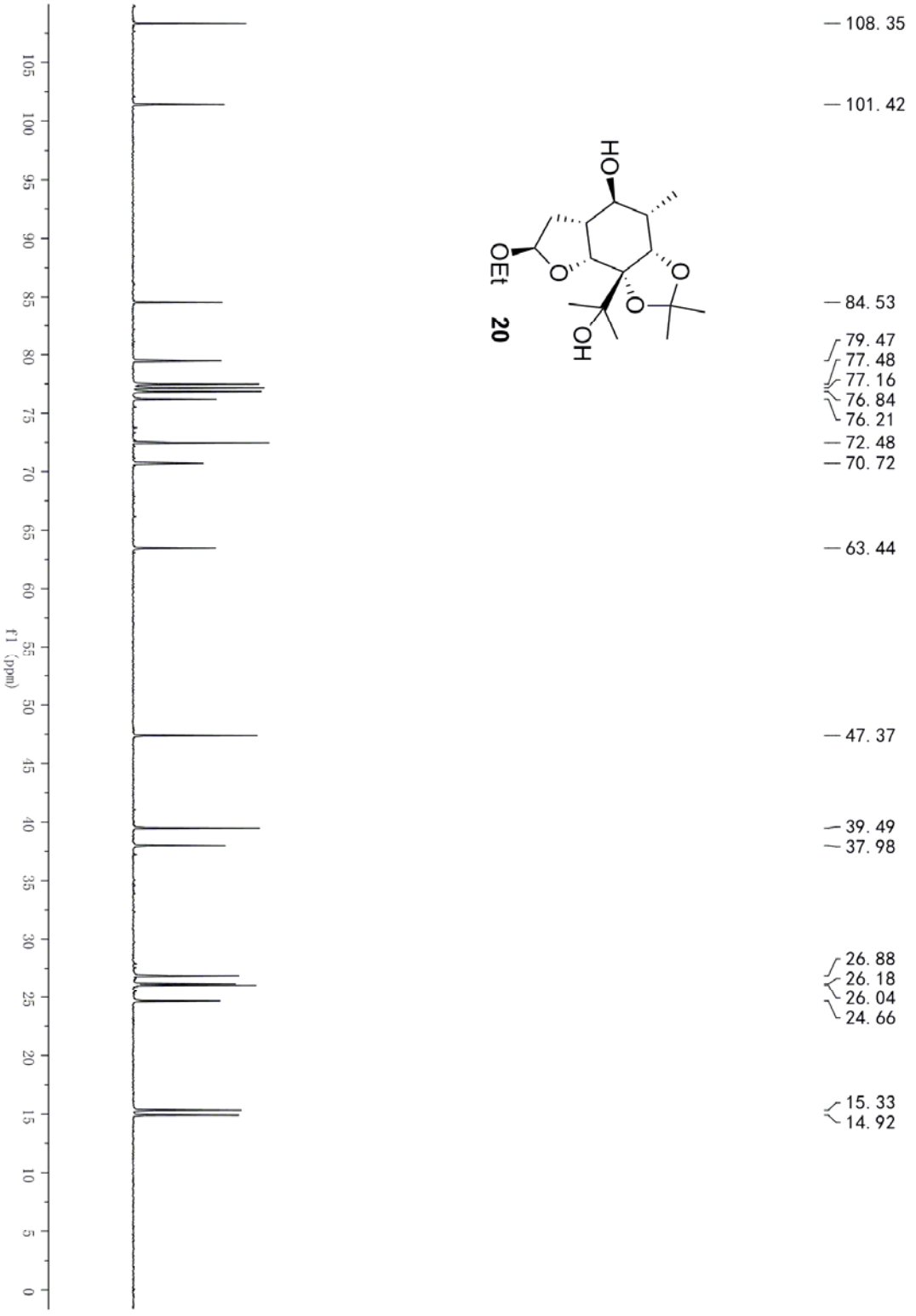
^{1}H NMR Spectrum of compound 20 (400 MHz, $CDCl_3$)



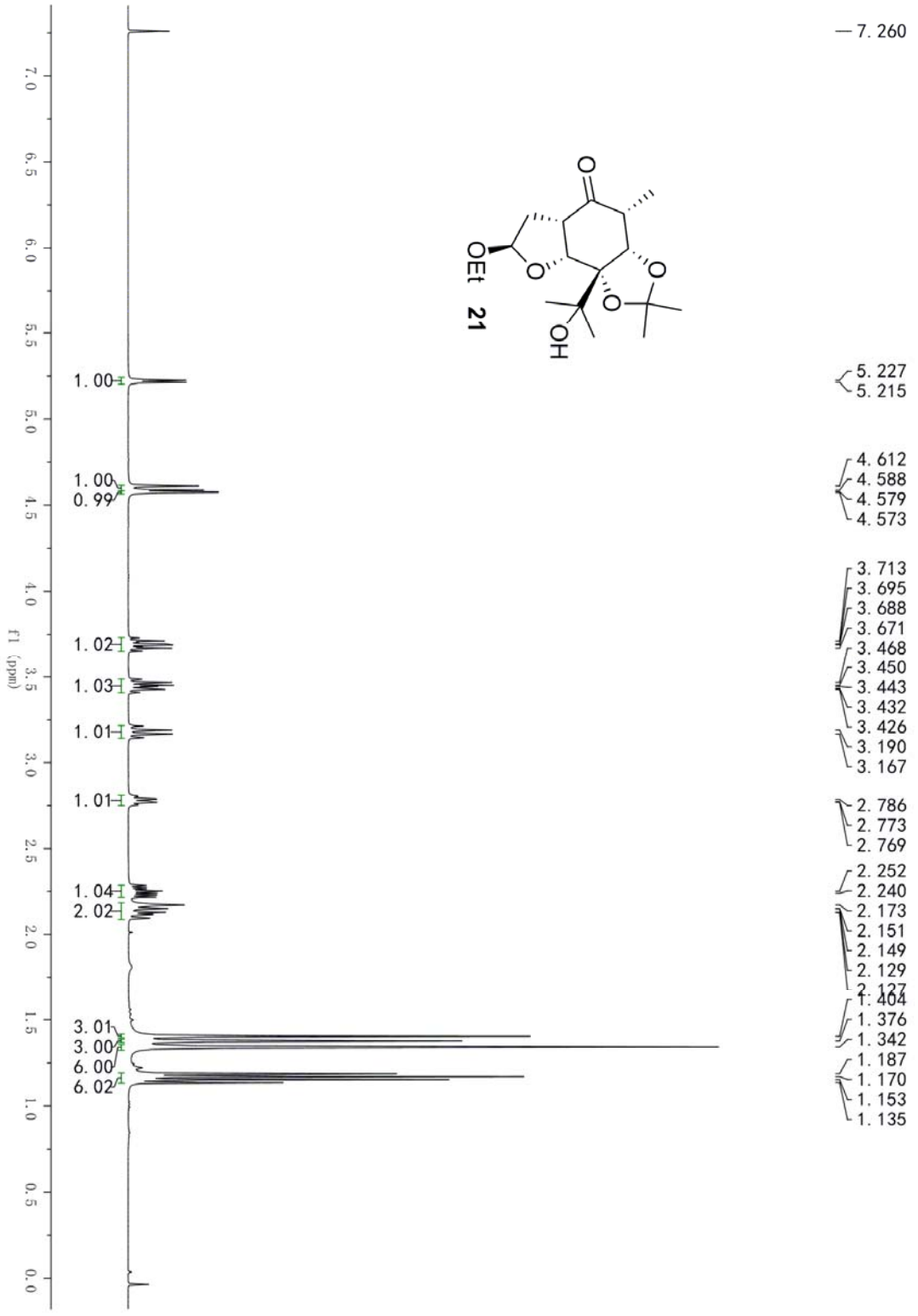
^{1}H NMR Spectrum of compound 20 (400 MHz, $CDCl_3/D_2O$)



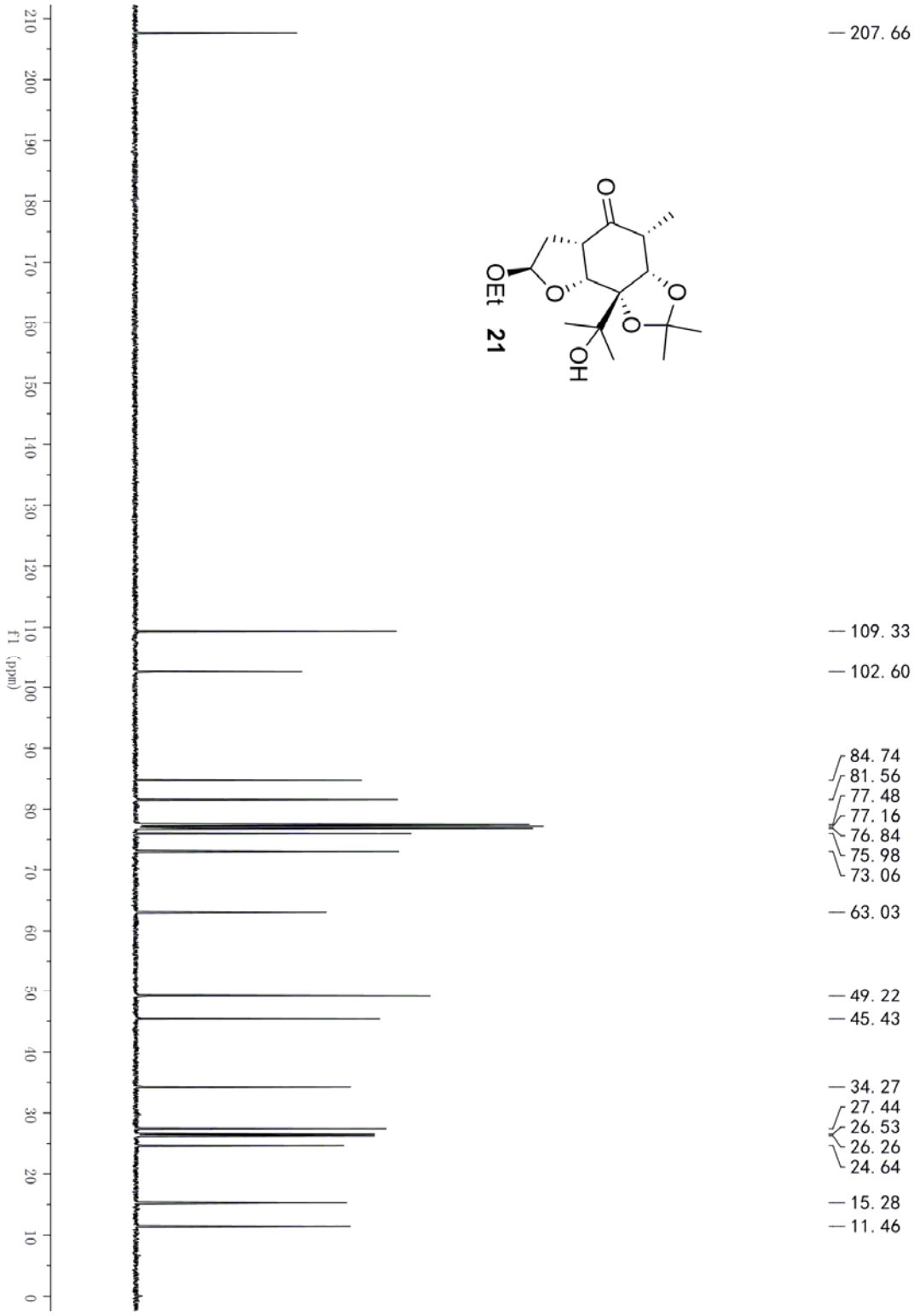
^{13}C NMR Spectrum of compound 20 (100 MHz, $CDCl_3$)



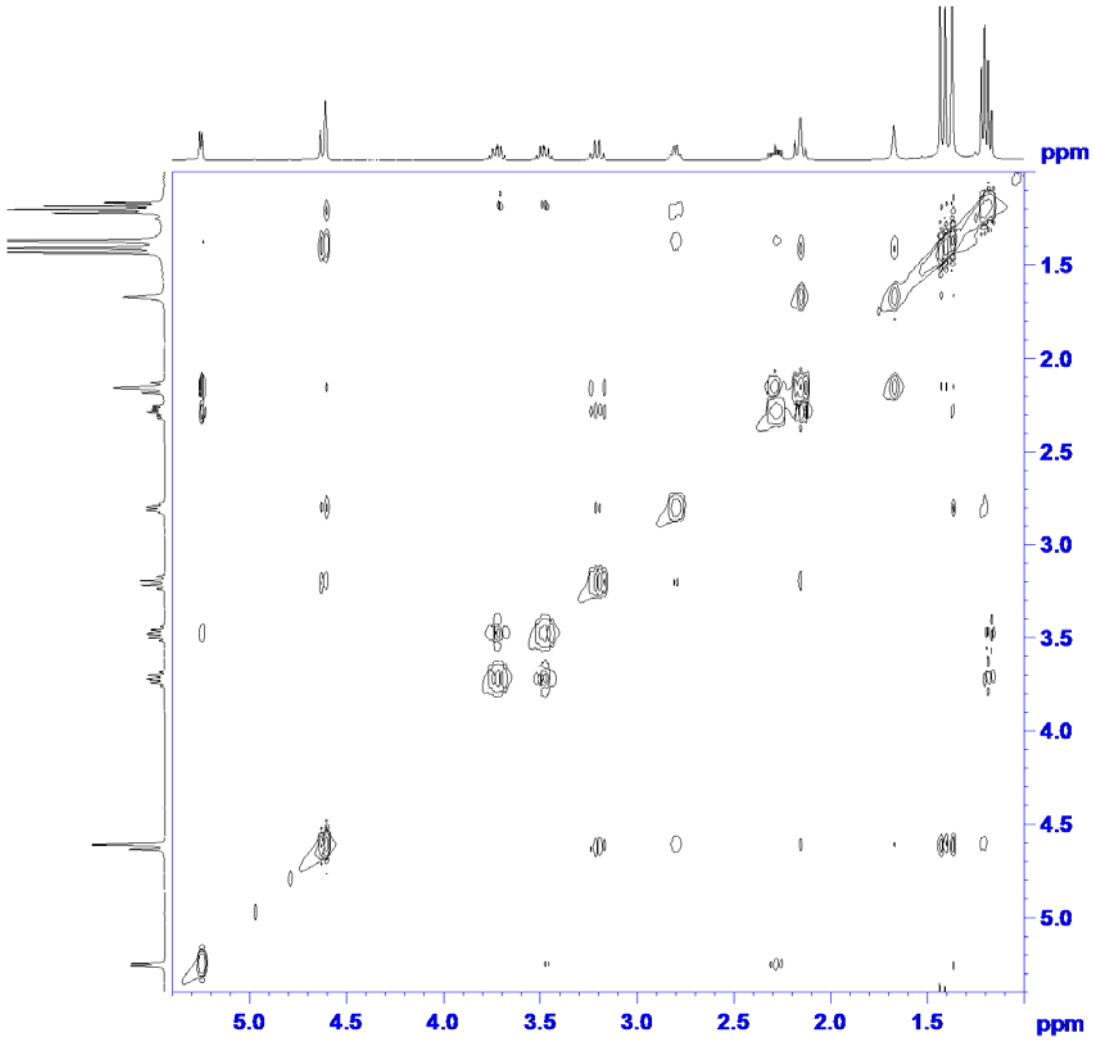
^{1}H NMR Spectrum of compound 21 (400 MHz, $CDCl_3$)



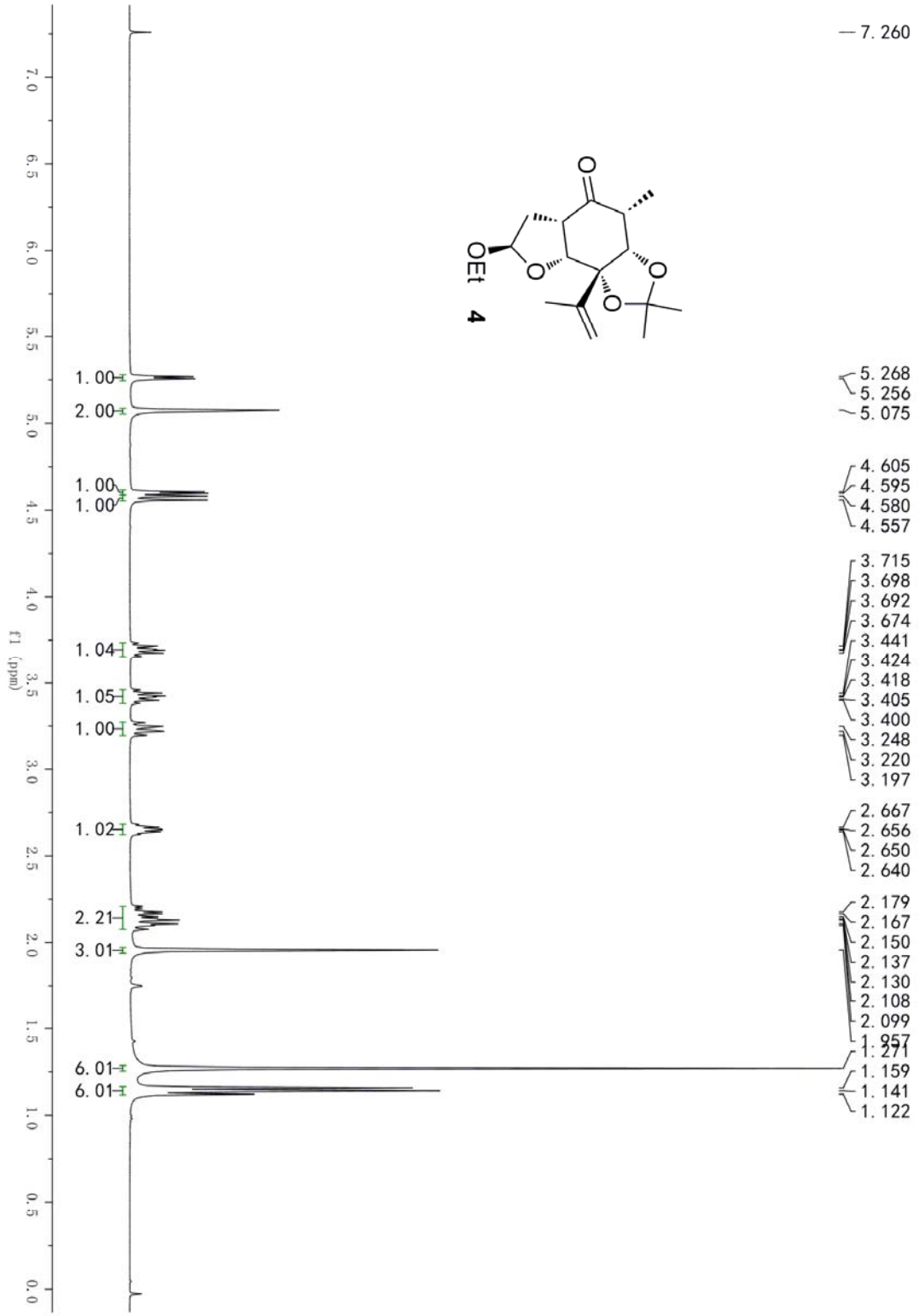
^{13}C NMR Spectrum of compound 21 (100 MHz, $CDCl_3$)



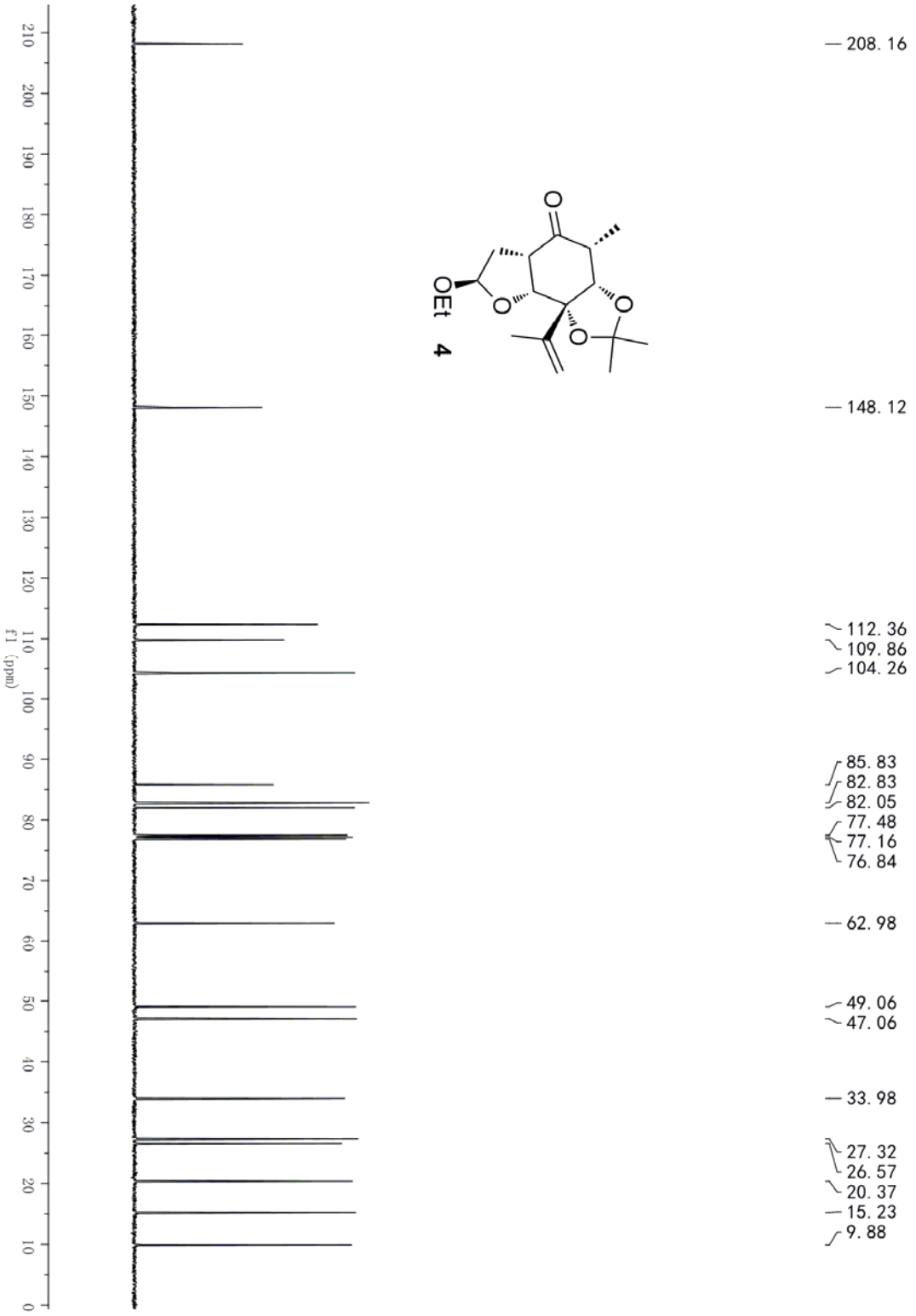
NOESY of compound 21 (400 MHz, $CDCl_3$)



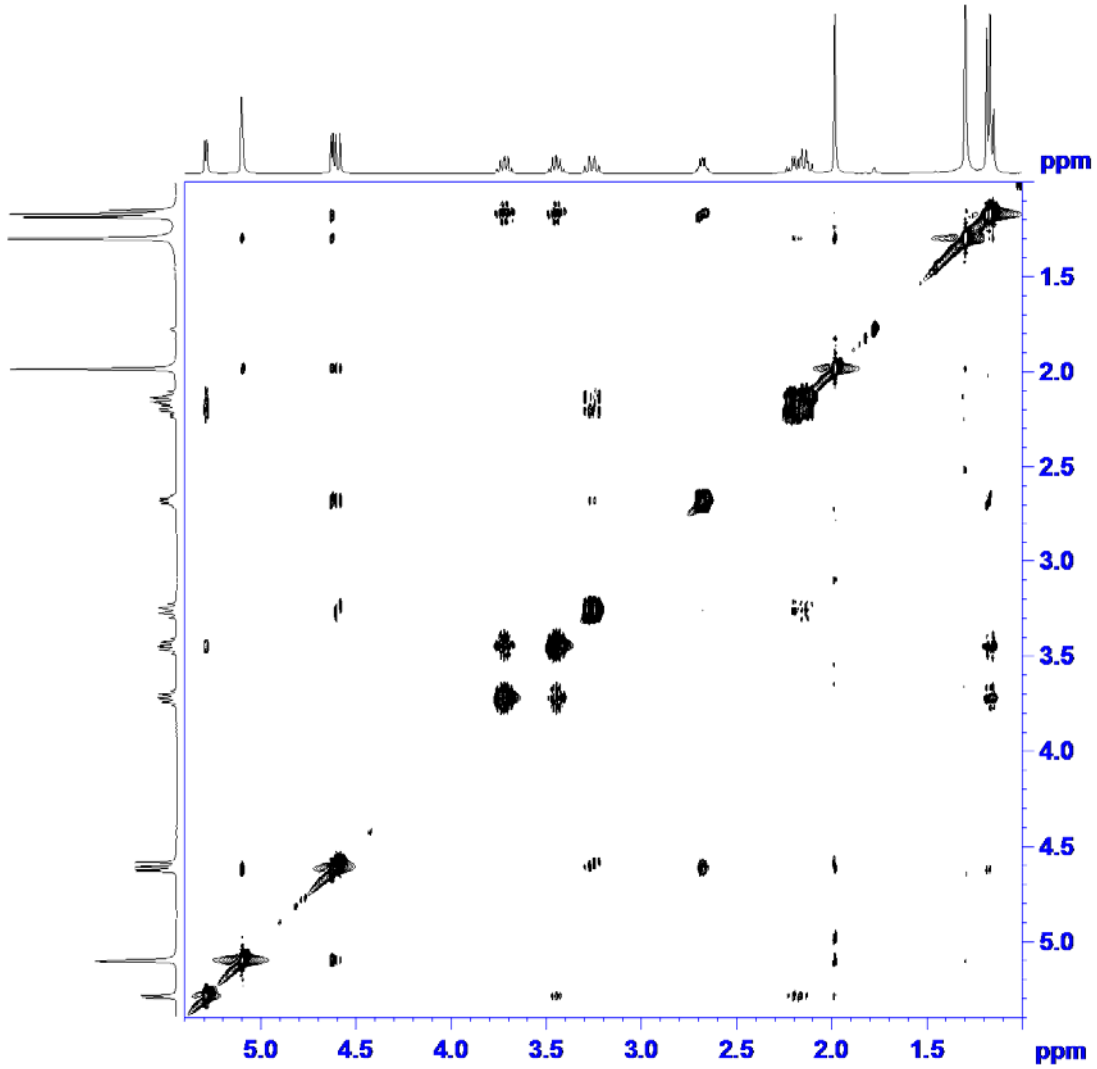
^{1}H NMR Spectrum of compound 4 (400 MHz, $CDCl_3$)



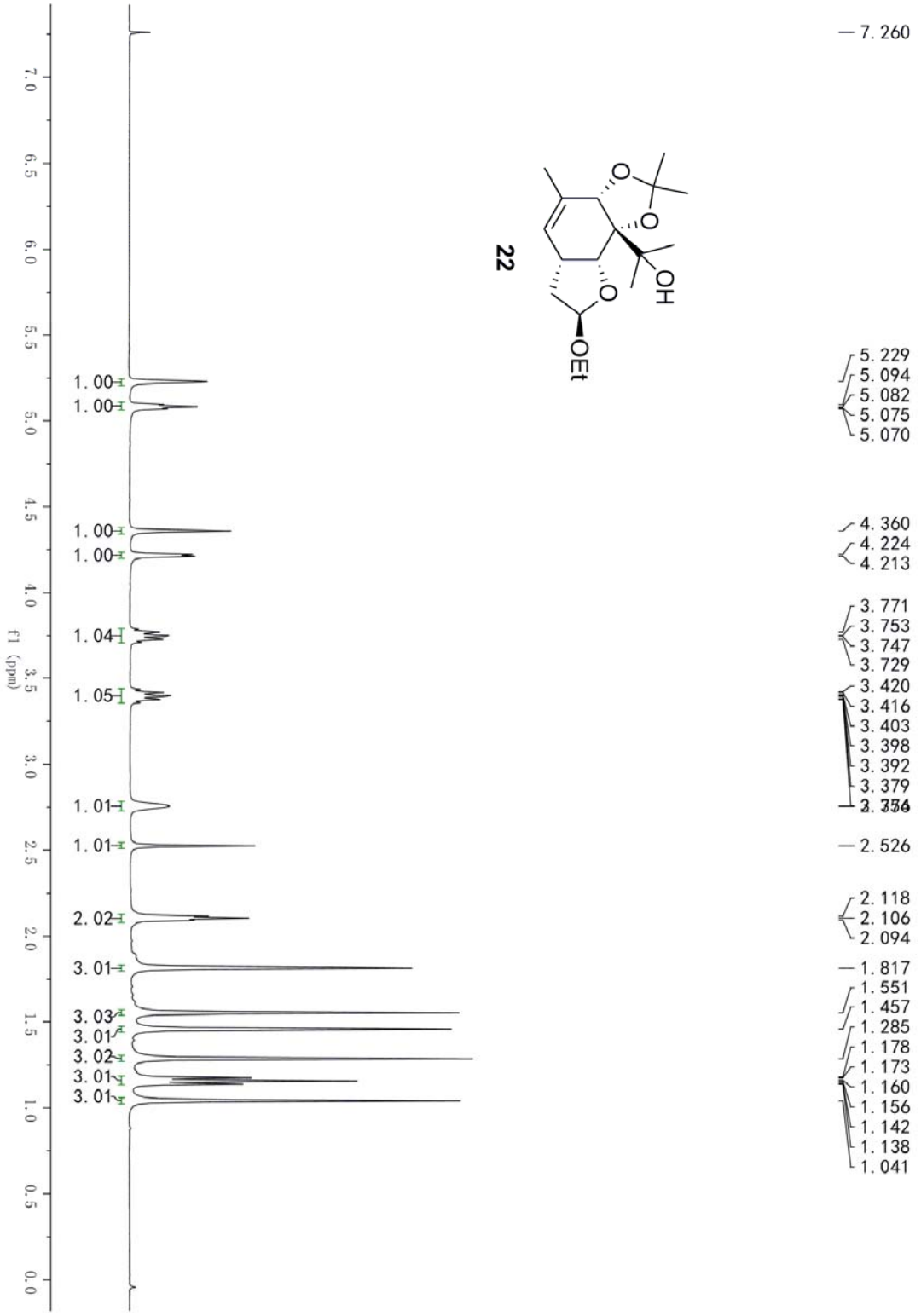
^{13}C NMR Spectrum of compound 4 (100 MHz, $CDCl_3$)



NOESY of compound 4 (400 MHz, $CDCl_3$)



^{1}H NMR Spectrum of compound 22 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of compound 22 (100 MHz, $CDCl_3$)