Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information

Hydrolytic Dynamic Kinetic Resolution of Racemic 3-Phenyl-2-oxetanone to Chiral Tropic Acid

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1. General information

Materials were purchased from commercial suppliers and used directly without further purification unless otherwise noted. *N*-Benzylcinchoninium chloride (**11**, Sigma-Aldrich), *N*-benzylquinidinium chloride (**14**, Tokyo Chemical Industry), *N*-benzylcinchonidinium chloride (**18**, Sigma-Aldrich) and *N*-benzylquininium chloride (**19**, J & K Scientific) were used as received. Other Chemicals were purchased from FUJIFILM Wako Pure Chemical, Tokyo Chemical Industry, KANTO Chemical, and Merck. Racemic 3-Phenyl-2-oxetanone ((*RS*)-**4**) was synthesized as described in the literature.

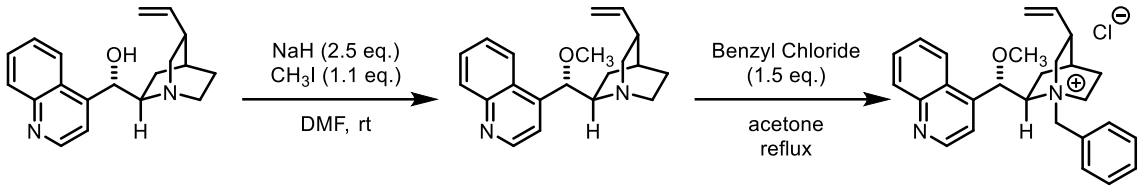
The strongly basic anion exhange resin prepared from Dowex-1® x 8(Cl-) or equivarent (CAS Registry Number 69011-19-4) purchased from FUJIFILM Wako Pure Chem. Corporation.

^{1}H-NMR spectra were recorded on a JEOL JNM-ECA500 (495.1 MHz) spectrometer and chemical shifts were reported in parts per million δ downfield from internal tetramethylsilane (TMS). ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA500 (124.5 MHz) spectrometer. ^{19}F-NMR spectra were recorded on a JEOL JNM-ECA500 (465.9 MHz) spectrometer and chemical shifts were reported in parts per million δ downfield from internal hexafluorobenzene (δ −164.9 ppm). IR spectra were obtained from a JASCO FT/IR-4100 spectrometer. Specific rotation was measured by JASCO P1020 polarimeter. High-resolution mass spectra (ESI, positive and negative) were recorded on a JEOL JMS-T100TD mass spectrometer or Thermo Fisher Scientific Q Exactive mass spectrometer. Melting points (m.p.) were recorded using BÜCHI melting point apparatus B-540.

The products were isolated by silica gel flash column chromatography (Fuji Silysia Chemical, PSQ100B). Chiral HPLC was performed on JASCO HPLC system using Daicel CHIRALPAK (4.6 × 250 mm) and HPLC grade solvents purchased from FUJIFILM Wako Pure Chemical.

2. Synthesis of chiral phase-transfer catalysts

Synthesis of *N*-benzyl-*O*-methylcinchonium chloride (12) [1]



Cinchonine **O-Methylcinchonine** **12**

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-Methoxy(quinolin-4-yl)methyl)-5-vinylquinuclidine (*O*-Methylcinchonine)

Under Ar atmosphere, 60% NaH (1.00 g, 25.0 mmol) was added to the solution of cinchonine (2.94 g, 10.0 mmol) in dry DMF (24 mL), and the mixture was stirred at room temperature for 20 min. Then, the solution of CH_3I (685 μL, 11.0 mmol) in dry DMF (6.8 mL) was added dropwise to the alkoxide solution of cinchonine and stirred overnight. After confirming the completion of the reaction by TLC, the reaction was quenched with brine (50 mL) and extracted with ethyl acetate (1 × 50 mL), ethyl acetate/hexane (1/1, 2 × 50 mL), and the combined organic layer was washed with brine (2 × 25 mL), water (1 × 20 mL), dried over anhydrous K_2CO_3, and the solvent was evaporated. The crude product was purified by silica gel column chromatography (CH_2Cl_2 : methanol : acetone = 20 : 1 :1). The product was solidified by the addition of diethyl ether (4.0 mL) and collected by suction filtration to give *O*-methylcinchonine in a yield of 863 mg (28%).

m.p. 117.4-117.6 °C, lit. 105.9-106.2 °C. [1]

$[\alpha]_D^{21.6}$ +266.5 (c 1.36, $CHCl_3$), lit. $[\alpha]_D^{24}$ +228.6 (c 1.28, $CHCl_3$). [1]

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 8.91 (1H, d, *J* = 4.5 Hz), 8.15 (1H, dd, *J* = 1.0, 8.5 Hz), 8.10 (1H, d, *J* = 8.5 Hz), 7.72 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz), 7.57 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz), 7.48 (1H, d, *J* = 4.5 Hz), 6.11 (1H, ddd, *J* = 8.0, 11.0, 17.0 Hz), 5.11-5.07 (3H, m), 3.31 (3H, s), 3.26 (1H, ddd, *J* = 2.0, 8.0, 14.0 Hz), 3.01 (1H, dt, *J* = 4.0, 9.0 Hz), 2.93 (1H, dd, *J* = 10.0, 11.0 Hz), 2.88-2.82 (1H, m), 2.78-2.72 (1H, m), 2.24 (1H, q, *J* = 8.5 Hz), 2.09-2.04 (1H, m), 1.74 (1H, brs), 1.54-1.41 (2H, m), 1.22-1.17 (1H, m).

^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 150.1, 148.5, 146.3, 141.0, 130.5, 128.9, 126.6, 125.5, 123.1, 118.4, 114.3, 83.4, 60.2, 57.3, 50.1, 49.6, 40.3, 28.2, 26.6, 21.7.

IR (KBr): 3444, 3063, 2983, 2945, 2939, 2929, 2885, 2865, 2847, 2813, 1593, 1570, 1508, 1462, 1447, 1108, 914, 846, 827, 776 cm^{-1}.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O$ 309.1967; found: 309.1976.

(1*S*,2*R*,4*S*,5*R*)-1-Benzyl-2-((*S*)-methoxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium chloride (12)

Under an Ar atmosphere, *O*-methylcinchonine (300 mg, 0.970 mmol) and benzyl chloride (170 μL, 1.46 mmol) were suspended in dry acetone (7.3 mL), and the reaction solution was heated under reflux for 3 days. Then, it was cooled to room temperature and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (CH_2Cl_2 : methanol : acetone = 20 : 3 : 3) gave *N*-benzyl-*O*-methylcinchonium chloride **12** (225 mg) in 54% yield.

m.p. 133.6-137.9 °C, lit. 125.2 °C (decomp.). [1]

$[\alpha]_D^{21.9}$ +220.5 (c 0.41, $CHCl_3$), lit. $[\alpha]_D^{24}$ +179.6 (c 0.40, $CHCl_3$). [1]

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 9.01 (1H, d, *J* = 6.5 Hz), 8.99 (1H, d, *J* = 4.5 Hz), 8.15 (1H, dd, *J* = 1.0, 8.0 Hz), 7.97-7.92 (3H, m), 7.79 (1H, ddd, *J* = 1.0, 7.0, 8.0 Hz), 7.52-7.50 (4H, m), 6.60 (1H, d, *J* = 11.5 Hz), 6.05 (1H, d, *J* = 2.5 Hz), 5.91 (1H, ddd, *J* = 7.0, 10.0, 17.0 Hz), 5.39-5.35 (1H, m), 5.30 (1H, d, *J* = 10.5 Hz), 5.22 (1H, d, *J* = 17.0 Hz), 4.83 (1H, brs), 4.36 (1H, d, *J* = 11.5 Hz), 4.12 (1H, ddd, *J* = 2.5, 9.0, 12.0 Hz), 3.60 (1H, t, *J* = 11.0 Hz), 3.53 (3H, s), 2.80 (1H, q, *J* = 9.5 Hz), 2.47 (1H, q, *J* = 9.0 Hz), 2.33-2.27 (2H, m), 2.03-1.95 (1H, m), 1.78 (1H, t, *J* = 11.0 Hz), 1.12-1.07 (1H, m).

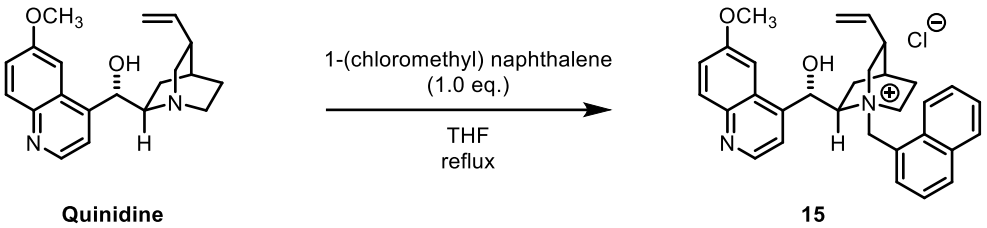
^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 149.4, 148.5, 139.4, 135.4, 134.1, 130.5, 130.2, 129.8, 129.2, 128.8, 127.2, 125.5, 125.0, 119.3, 118.0, 77.3, 66.0, 61.8, 57.1, 55.6, 54.4, 38.0, 27.2, 23.5, 22.0.

^{13}C-NMR (CD_2Cl_2, 124.5 MHz): δ 150.0, 149.1, 140.0, 136.1, 134.5, 130.7, 130.2, 130.1, 129.4, 128.5, 128.1, 126.0, 125.8, 119.9, 117.9, 77.6, 66.6, 62.1, 57.4, 56.1, 54.9, 38.3, 27.8, 23.9, 22.4.

IR (KBr): 3658, 3418, 3065, 3006, 2951, 2836, 1640, 1588, 1572, 1509, 1456, 1373, 1071, 1050, 920, 782, 766, 714, 706, 551 cm^{-1}.

HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{27}H_{31}N_2O$ 399.2436; found: 399.2432.

Synthesis of 1-*N*-(α-naphthylmethyl) quinidinium chloride (15)



(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-Hydroxy(6-methoxyquinolin-4-yl)methyl)-1-(naphthalen-1-ylmethyl)-5-vinylquinuclidin-1-ium chloride (14)

Under an Ar atmosphere, quinidine (1.62 g, 5.00 mmol) and 1-(chloromethyl) naphthalene (883 mg, 5.00 mmol) were dissolved in dry THF (20 mL), and the reaction solution was heated under reflux for 1 day. Then, it was cooled to room temperature and the precipitate was collected by filtration. The crude product was recrystallized from methanol and ether to give **15** in a yield of 993 mg (40%).

m.p. 170-171 °C, lit. 187 °C (decomp.). [2]

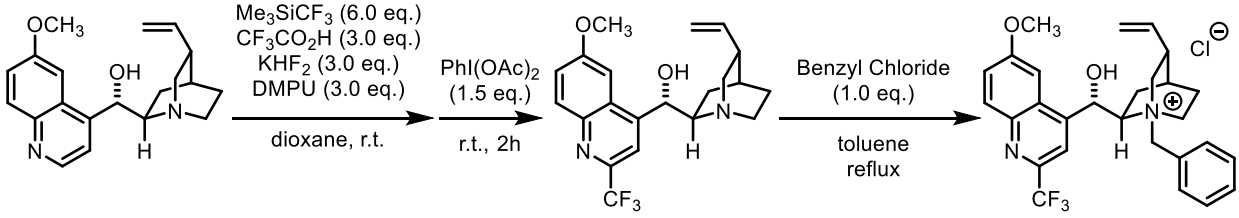
^{1}H-NMR (DMSO-d_6, 495.1 MHz): δ 8.83 (1H, d, J = 4.5 Hz), 8.51 (1H, d, J = 8.5 Hz), 8.19 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 8.0 Hz), 8.06 (1H, d, J = 6.5 Hz), 8.03 (1H, d, J = 9.5 Hz), 7.83 (1H, d, J = 4.0 Hz), 7.75-7.64 (3H, m), 7.58 (1H, d, J = 2.5 Hz), 7.51 (1H, dd, J = 2.5, 9.0 Hz), 6.06 (1H, ddd, J = 7.0, 10.5, 17.5 Hz), 5.83 (1H, d, J = 13.5 Hz), 5.27-5.16 (3H, m), 4.44-4.39 (1H, m), 4.19-4.12 (5H, m), 3.46-3.37 (1H, m), 2.91-2.82 (1H, m), 2.59-2.54 (1H, m), 2.46-2.36 (1H, m), 1.91-1.72 (4H, m).

^{13}C-NMR (DMSO-d_6, 124.5 MHz): δ 157.37, 147.36, 143.71, 137.31, 134.34, 133.71, 133.01, 131.25, 129.14, 127.33, 126.24, 125.46, 125.37, 123.92, 123.88, 121.56, 120.35, 116.95, 102.34, 67.49, 64.62, 59.34, 55.94, 55.52, 54.23, 36.96, 26.01, 23.90, 23.37, 20.86, 11.25.

IR (KBr): 3651, 3641, 3082, 2948, 2880, 2832, 1620, 1586, 1509, 1473, 1353, 1241, 1227, 1209, 1025, 862, 812, 784, 623, 508 cm^{-1}.

HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{31}H_{33}N_2O_2$ 465.2542; found: 465.2552.

***N*-Benzyl-2-trifluoromethylquinidinium chloride (16)**



Quinidine **16**

(1*S*,2*R*,4*S*,5*R*)-1-Benzyl-2-((*S*)-hydroxy(6-methoxy-2-(trifluoromethyl)quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium chloride (16)

Under an Ar atmosphere, a mixture of 2-trifluoromethylquinidine (838 mg, 2.10 mmol) synthesized according to a published procedure[3] and benzyl chloride (242 μL, 2.10 mmol) in dry toluene (10 mL), was heated under reflux for 4 days. Then, it was cooled to room temperature and the precipitate was collected by filtration. The compounds were washed from hexane to give **16** in a yield of 72.2 mg (7%).

m.p. 182.0-182.4 °C.

$[\alpha]_D^{24.9}$ +219.2 (c 0.5, MeOH).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 8.25 (1H, s), 7.93 (1H, d, *J* = 9.0 Hz), 7.90 (1H, brs), 7.64 (2H, d, *J* = 7.0 Hz), 7.36 (1H, d, *J* = 3.0 Hz), 7.31-7.22 (2H, m), 7.18 (1H, dd, *J* = 2.5, 9.5 Hz), 6.53 (1H, brs), 5.94-5.87 (2H, m), 5.67 (1H, d, *J* = 12.5 Hz), 5.25 (1H, d, *J* = 10.5 Hz), 5.20 (1H, d, *J* = 17.0 Hz), 4.62-4.57 (1H, m), 4.01 (1H, d, *J* = 9.5 Hz), 3.91-3.85 (1H, m), 3.84 (1H, s), 3.38 (1H, t, *J* = 11.8 Hz), 2.94-2.88 (1H, m), 2.38-2.32 (1H, m), 2.26-2.21 (1H, m), 1.87-1.77 (3H, m), 0.86-0.82 (1H, m).

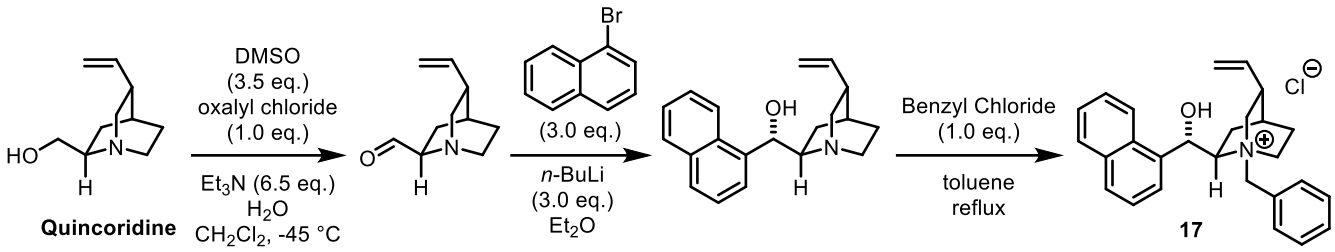
^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 159.6, 145.8, 144.9 (F-coupling is overlapped), 142.9, 135.3, 134.0, 132.6, 130.2, 128.9, 127.2, 126.6, 121.8 (q, *J* = 275 Hz),121.3, 118.4, 116.4, 102.4, 67.6, 65.8, 62.7, 56.8, 56.5, 53.8, 38.2, 27.2, 24.1, 21.9.

^{19}F-NMR ($CDCl_3$, 465.9 MHz): δ −70.1.

IR (KBr): 3566, 3420, 3029, 2949, 2840, 1621, 1508, 1481, 1457, 1364, 1306, 1279, 1233, 1184, 1138, 1102, 1026, 926, 764, 705 cm^{-1}.

HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{28}H_{30}F_3N_2O_2$ 483.2259; found: 483.2274.

Synthesis of (1*S*,2*R*,4*S*,5*R*)-1-benzyl-2-[(hydroxyl)(1-naphthyl)methyl]-5-vinylquinuclidinium chloride (17) [4]



(1*S*,2*R*,4*S*,5*R*)-5-Vinylquinuclidine-2-carbaldehyde

Under Ar atmosphere, DMSO (1.80 mL, 25.9 mmol) in dry CH_2Cl_2 (3.0mL) was cooled to −45 °C, and oxalyl chloride (635 µL, 7.40 mmol) in dry CH_2Cl_2 (10 mL) was added slowly whilst stirring, over 30 min. After a further 30 min at −45 °C, quincoridine (1.24 g 7.41 mmol) in dry CH_2Cl_2 (14 mL) was added dropwise over 1.0 h at −45 °C. The mixture was stirred for an additional 1.0 h at this temperature, and then treated with triethylamine (6.70 mL, 48.1 mmol) and finally warmed up to room temperature and stirred for 50min. The reaction was quenched by the addition of H_2O (12 mL) at 0 °C. The phases were separated, and the organic layer was washed twice with 5.0 mL of H_2O, dried over $NaSO_4$, and the solvent was removed under reduced pressure. The residue was distilled using a kugelrohr apparatus (bath temperature 200 °C, 2 mmHg) to give (*S*)-naphthalen-1-yl((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol as a clear liquid with a yield of 755 mg (62%).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 9.80 (1H, d, *J* = 7.5 Hz), 5.92-5.74 (1H, m), 5.10-4.96 (2H, m), 3.50-2.66 (5H, m), 2.38-2.04 (2H, m), 1.86-1.43 (4H, m). The sensitive compound must be used immediately.

(*S*)-Naphthalen-1-yl((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol

Dry ether (140 mL) and a solution of butyllithium in hexane (1.59 M, 7.29 mL, 11.6 mmol) were combined and cooled to −70 °C. 1-Bromonaphthalene (1.62 mL, 11.6 mmol) in dry THF (70 mL) was added slowly at this temperature. Stirring was then continued for another 30 min, and (1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidine-2-carbaldehyde (642 mg, 3.88 mmol) in dry ether (35 mL) was added dropwise. The reaction was stirred for 6.5 h at −70 °C, then warmed up to room temperature overnight. The reaction was quenched by the addition of H_2O (24 mL) at 0 °C. The phases were separated, and aqueous one was extracted twice with 20 mL of ether. The combined organic layer was washed with 20 mL of brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate : triethylamine = 9 : 1) to give (*S*)-naphthalen-1-yl((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol, which was recrystallized from EtOH with a yield of 148 mg (16%).

m.p. 215.3-220.1 °C, lit. 212-217 °C. [4]

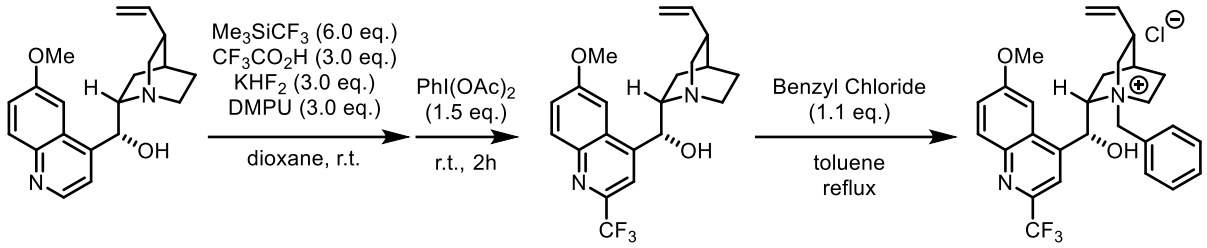
$[\alpha]_D^{25}$ +223.5 (c 0.40, MeOH), lit. $[\alpha]_D^{23}$ +123.0 (c 0.40, MeOH). [4]

^{1}H-NMR (DMSO-d_6, 495.1 MHz): δ 8.17 (1H, d, J = 8.5 Hz), 7.90 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 8.5 Hz), 7.57 (1H, d, J = 6.5 Hz), 7.56-7.44 (3H, m), 6.10 (1H, ddd, J = 8.0, 10.5, 18.0 Hz), 5.41 (1H, d, J = 4.5 Hz), 5.30 (1H, t, J = 5.8 Hz), 5.10-5.04 (2H, m), 3.04-2.98 (2H, m), 2.67-2.56 (3H, m), 2.19-2.14 (1H, m), 1.94-1.90 (1H, m), 1.67 (1H, brs), 1.46-1.34 (3H, m).
^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 140.9, 139.1, 133.8, 130.5, 129.0, 128.0, 126.1, 125.5, 125.4, 123.5, 123.1, 114.2, 73.2, 60.1, 50.1, 49.6, 40.2, 28.4, 26.7, 21.8.
IR (KBr): 3067, 3045, 3002, 2940, 2915, 2876, 2714, 2585, 1637, 1508, 1457, 1387, 1324, 1110, 991, 906, 880, 835, 778, 754 cm^{-1}.
HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{24}NO$ 294.1858; found: 294.1840.

(1*S*,2*R*,4*S*,5*R*)-1-Benzyl-2-((*S*)-hydroxy(naphthalen-1-yl)methyl)-5-vinylquinuclidin-1-ium chloride (17)

Under an Ar atmosphere, the second step product (132 mg, 0.450 mmol) and benzyl chloride (52.0 μL, 0.450 mmol) were suspended in dry toluene (2.0 mL), and the reaction solution was heated under reflux for 1.5 days. Then, it was cooled to room temperature and the precipitate was collected by filtration. The compounds were recrystallized from CH_2Cl_2 and 2-propanol to give **17** in a yield of 140 mg (74%).
m.p. 264.2-264.7 °C, lit. 262-264 °C. [4]
$[\alpha]_D^{24.9}$ +187.9 (c 0.86, MeOH), lit. $[\alpha]_D^{25}$ +114.7 (c 0.86, MeOH). [4]
^{1}H-NMR (DMSO-d_6, 495.1 MHz): δ 8.24 (1H, d, J = 8.5 Hz), 8.01 (1H, d, J = 8.5 Hz), 7.94 (1H, d, J = 8.0 Hz), 7.88 (1H, d, J = 7.5 Hz), 7.78-7.76 (2H, m), 7.67 (1H, t, J = 7.5 Hz), 7.63-7.57 (5H, m), 6.94 (1H, d, J = 4.0 Hz), 6.49 (1H, brs), 6.01 (1H, ddd, J = 7.0, 10.5, 17.0 Hz), 5.24-5.21 (2H, m), 5.15 (1H, d, J = 12.0 Hz), 5.06 (1H, d, J = 12.5 Hz), 4.29 (1H, t, J = 9.3 Hz), 3.93 (1H, t, J = 11.0 Hz), 3.84 (1H, t, J = 9.8 Hz), 3.44 (1H, t, J = 11.5 Hz), 2.98-2.92 (1H, m), 2.66-2.61 (1H, m), 2.35-2.31 (1H, m), 1.86 (1H, brs), 1.76-1.72 (2H, m), 1.02-0.97 (1H, m).
^{13}C-NMR (DMSO-d_6, 124.5 MHz): δ 137.2, 135.2, 133.8, 133.1, 130.0, 129.1, 128.9, 128.8, 128.3, 128.0, 126.7, 125.7, 125.3, 125.2, 123.1, 116.8, 67.6, 64.8, 62.1, 55.9, 53.5, 36.7, 26.4, 23.0, 20.8.
IR (KBr): 3055, 2978, 2963, 2907, 2892, 2843, 2721, 1509, 1469, 1460, 1410, 1394, 1374, 1126, 1112, 923, 809, 784, 768, 703 cm^{-1}.
HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{27}H_{30}NO$ 384.2327; found: 384.2314.

***N*-Benzyl-2-trifluoromethylquininium chloride (20)**



(1*S*,2*S*,4*S*,5*R*)-1-Benzyl-2-((*R*)-hydroxy(6-methoxy-2-(trifluoromethyl)quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium chloride (20)

Under an Ar atmosphere, a mixture of 2-trifluoromethylquinine (126 mg, 0.320 mmol) synthesized according to a published procedure[3] and benzyl chloride (40.3 μL, 0.350 mmol) in dry toluene (3.2 mL), was heated under reflux for 3 days. Then, it was cooled to room temperature and the precipitate was collected by filtration. The compound was washed from hexane to give **20** in a yield of 63.7 mg (38%).

m.p. 186.1-190.1 °C.

$[\alpha]_D^{23.9}$ −206 (c 0.50, MeOH).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 8.13 (1H, s), 8.11 (1H, d, *J* = 9.5 Hz), 7.83 (1H, brs), 7.75 (2H, d, *J* = 7.0 Hz), 7.47-7.38 (4H, m), 7.25 (1H, d, *J* = 2.5 Hz), 6.73 (1H, brs), 6.29 (1H, d, *J* = 12.0 Hz), 5.59 (1H, ddd, *J* = 7.5, 10.5, 17.5 Hz), 5.14-5.05 (3H, m), 4.69 (1H, d, *J* = 12.0 Hz), 3.98-3.92 (4H, m), 3.76 (1H, t, *J* = 8.8 Hz), 3.51 (1H, dd, *J* = 11.0, 13.0 Hz), 3.26-3.21 (1H, m), 3.13-3.07 (1H, m), 2.62-2.55 (1H, m), 2.43-2.35 (1H, m), 2.26-2.23 (1H, m), 2.08-2.02 (1H, m), 1.49-1.44 (1H, m).

^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 159.7, 146.0, 145.3 (q, *J* = 35.0 Hz), 143.3, 136.3, 133.8, 132.9, 130.7, 129.3, 129.1, 128.2, 126.9, 126.8, 122.4, 121.8 (q, *J* = 274 Hz), 118.1, 116.4, 101.6, 69.9, 64.1, 63.9, 61.3, 56.4, 51.0, 38.1, 26.7, 24.8, 21.7.

^{19}F-NMR ($CDCl_3$, 465.9 MHz): δ −70.2.

IR (KBr): 3442, 3194, 2947, 1622, 1508, 1481, 1458, 1439, 1365, 1309, 1261, 1232, 1178, 1132, 1097, 1026, 927, 830, 765, 706 cm^{-1}.

HRMS (ESI) *m/z*: $[M-Cl]^+$ Calcd for $C_{28}H_{30}F_3N_2O_2$ 483.2259; found: 483.2237.

3. Synthesis of racemic tropic acid esters ((*RS*)-5, (*RS*)-9, (*RS*)-10)

(*RS*)-Butyl tropanoate ((*RS*)-5)

Tropic acid (5.00 g, 30.1 mmol) was dissolved in *n*-butyl alchol (30 mL), sulfuric acid (1.0 mL) was added, and the mixture was heated under reflux for overnight. After completion of the reaction, the reaction solution was poured into ice water (100 mL), neutralized by $NaHCO_3$ until pH 8, extracted with ethyl acetate/hexane (=1/1, 3 × 100 mL) and combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 17 : 3) to give (*RS*)-**5** as a clear liquid with a yield of 4.86 g (73%).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 7.36-7.26 (5H, m), 4.17-4.09 (3H, m), 3.86-3.80 (2H, m), 2.29-2.25 (1H, m), 1.60-1.54 (2H, m), 1.32-1.24 (2H, m), 0.87 (3H, t, *J* = 7.3 Hz).

^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 173.1, 135.7, 128.6, 128.0, 127.5, 64.8, 64.4, 54.0, 30.4, 18.8, 13.5.

IR (neat): 3448, 3063, 3031, 2960, 2935, 2874, 1731, 1602, 1496, 1455, 1390, 1349, 1311, 1246, 1170, 1119, 1063, 1042, 962, 939 cm^{-1}.

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{18}NaO_3$ 245.1154; found: 245.1147.

(*RS*)-Methyl tropanoate ((*RS*)-9)

Tropic acid (5.00 g, 30.1 mmol) was dissolved in methanol (30 mL), sulfuric acid (1.0 mL) was added, and the mixture was heated under reflux for 1.5 hours. After completion of the reaction, the reaction solution was poured into ice water (100 mL), neutralized by $NaHCO_3$ until pH 8, extracted with ethyl acetate/hexane (=1/1, 3 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: hexane : ethyl acetate = 1 : 1) to give (*RS*)-**9** as a clear liquid with a yield of 5.28g (98%).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 7.36-7.29 (5H, m), 4.13 (1H, ddd, *J* = 6.5, 8.5, 11.0 Hz), 3.87-3.71 (2H, m), 3.71 (3H, s), 2.34 (1H, t, *J* = 6.5 Hz).

^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 173.6, 135.5, 128.8, 128.1, 127.7, 64.5, 53.9, 52.2.

IR (neat): 3447, 3062, 3031, 3005, 2952, 2883, 1736, 1603, 1493, 1455, 1436, 1355, 1316, 1252, 1200, 1168, 1067, 1043, 969, 849 cm^{-1}.

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{12}NaO_3$ 203.0684; found: 203.0679.

(*RS*)-1,1,1,3,3,3-Hexafluoroisopropyl tropanoate ((*RS*)-10)

To a solution of Tropic acid (1.66 g, 10.0 mmol) in DMF (20 mL) were added 1,1,1,3,3,3-hexafluoro-2-propanol (2.10 mL, 20.0 mmol) and triethylamine (2.78 mL, 20.0 mmol) at room temperature under an Ar atmosphere. (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (4.42 g, 10.0 mmol) was added to the above mixture, followed by stirring at room temperature for overnight. After confirming the completion of the reaction by TLC, aqueous 1 mol/L HCl (50 mL) was added. The mixture was extracted with ethyl acetate (3 × 50 mL) and combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: hexane : ethyl acetate = 17 : 3) to give (*RS*)-**10** as a pale yellow liquid with a yield of 2.08 g (66%).

^{1}H-NMR (DMSO-d_6, 495.1 MHz): δ 7.39-7.30 (5H, m), 6.83 (1H, quin., J = 6.4 Hz), 5.24 (1H, dd, J = 4.3, 5.8 Hz), 4.05 (1H, dd, J = 4.3, 9.8 Hz), 3.97 (1H, td, J = 9.8, 10.0 Hz), 3.69 (1H, td, J = 4.3, 10.0 Hz).

^{13}C-NMR (DMSO-d_6, 124.5 MHz): δ 169.4, 134.4, 128.7, 128.3, 127.9, 120.6 (q, J = 282 Hz), 66.8, 66.6, 66.3, 66.0, 65.7, 65.5, 65.2, 62.9, 55.4, 53.3.

^{19}F-NMR ($CDCl_3$, 465.9 MHz): δ −76.4 (d, J = 21.9 Hz).

IR (neat): 3387, 3092, 3069, 3035, 2969, 2889, 1777, 1604, 1497, 1457, 1387, 1359, 1290, 1268, 1204, 1112, 1059, 919, 906, 697 cm^{-1}.

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{10}F_6NaO_3$ 339.0426; found: 339.0426.

4. Synthesis of 3-phenyl-2-oxetanone ((*RS*)-4, (*S*)-4, (*R*)-4) [5]

(*RS*)-3-Phenyl-2-oxetanone ((*RS*)-4)

Diethyl azodicarboxylate (2.2 mol/L in toluene; 10.9 mL, 24.0 mmol) was added dropwise to a stirred solution of triphenylphosphine (6.30 g, 24.0 mmol) in THF (80 mL) at −78 °C. After about 30 min, the suspension became white and then a solution of tropic acid (3.99 g, 24.0 mmol) in THF (80 mL) was added dropwise. The resulting mixture was stirred and warmed up to −10 °C over 2 h, and reaction mixture was left stirring overnight. After concentrating at room temperature, triphenylphosphine oxide was filtered off by suction. After silica gel column chromatography (hexane : ethyl acetate = 17 : 3), (*RS*)-**4** was isolated as a clear liquid with a yield of 2.08 g (58%).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 7.41-7.26 (5H, m), 4.93 (1H, dd, *J* = 5.0, 7.0 Hz), 4.67 (1H, dd, *J* = 5.0, 7.0 Hz), 4.36 (1H, t, *J* = 5.0 Hz).

^{13}C-NMR ($CDCl_3$, 124.5 MHz): δ 169.5, 132.6,129.2, 128.3, 127.1, 66.3, 56.9.

IR (neat): 3628, 3064, 3031, 2986, 2914, 2216, 1990, 1818, 1604, 1582, 1498, 1473, 1454, 1313, 1180, 1110, 943, 884, 758, 700 cm^{-1}.

(*S*)-3-Phenyl-2-oxetanone ((*S*)-4) [6]

A mixture of racemic tropic acid (5.00 g, 30.1 mmol) and D-(−)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol (3.06 g, 14.4 mmol) in isopropanol was heated to 65 °C and stirred for 1 h. The mixture was then cooled to room temperature for 4.5 h, filtered, and washed with isopropanol (25 mL × 2). The resulting white crystals (5.00 g, 13.2 mmol) in Isopropyl acetate (70 mL) was added aqueous 1 mol/L HCl (30 mL, 30 mmol). The mixture was heated to 60 °C and stirred for 1 h and then cooled to room temperature. The phases were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compounds were recrystallized from benzene to obtain (*S*)-tropic acid in a yield of 1.48 g (30%).

CHIRALCELL (4.6 × 250 mm), Daicel IC, eluent: *t*-butyl methyl ether : TFA = 100 : 0.1, flow rate = 1.0 mL/min, t_1 = 7.85 min ((*S*)-**3**, 99.7%); t_2 = 9.97 min ((*R*)-**3**, 0.30%).

$[\alpha]_D^{23.2}$ −83.4 (c 1.11, acetone, >99% ee for (*S*)-**3**), lit. $[\alpha]_D$ +70 (c 1.11, acetone, for (*R*)-**3**) [7].

Diethyl azodicarboxylate (2.2 mol/L in toluene; 3.64 mL, 8.00 mmol) was added dropwise to a stirred solution of triphenylphosphine (2.10 g, 8.00 mmol) in THF (27 mL) at −78 °C. After about 30 min, the suspension became white and then a solution of (*S*)-**3** (1.33 g, 8.00 mmol) in THF (27 mL) was added dropwise. The resulting mixture was stirred and warmed up to −10 °C over 2 h, and reaction mixture was left stirring overnight. After concentrating at room temperature, triphenylphosphine oxide was filtered off by suction. After purification by silica gel column chromatography (hexane : ethyl acetate = 17 : 3), (*S*)-**4** was isolated as a colorless crystal with a yield of 721 mg (61%).

$[\alpha]_D^{26.6}$ +10.9 (c 1.60, MeOH for (*S*)-**4**), lit. $[\alpha]_D$ +5.0 (c 1.6, MeOH). [8]

(*R*)-3-Phenyl-2-oxetanone ((*R*)-4) [6]

A mixture of racemic tropic acid (5.00 g, 30.1 mmol) and (1*S*,2*S*))-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (3.06 g, 14.4 mmol) in 2-propanol was heated to 65 °C and stirred for 1 h. The mixture was then cooled to room temperature in 2.0 h, filtered, and washed with 2-propanol (25 mL × 2). The resulting white crystals (5.00 g, 13.2 mmol) in isopropyl acetate (70 mL) was added aqueous 1 mol/L HCl (30 mL, 30 mmol). The mixture was heated to 60 °C and stirred for 1 h and then cooled to room temperature. The phases were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compounds were recrystallized from benzene to obtain (*S*)-tropic acid in a yield of 1.57 g (31%).

CHIRALCELL (4.6 × 250 mm), Daicel IC, eluent: *t*-butyl methyl ether : TFA = 100 : 0.1, flow rate = 1.0 mL/min, t_1 = 7.88 min ((*S*)-**3**, 0.20 %); t_2 = 9.88 min ((*R*)-**3**, 99.8 %).

$[\alpha]_D^{24.9}$ +87.0 (c 1.11, acetone, >99 %ee for (*R*)-**3**), lit. $[\alpha]_D$ +70 (c 1.11, acetone, for (*R*)-**3**) [7].

Diethyl azodicarboxylate (2.2 mol/L in toluene; 3.64 mL, 8.00 mmol) was added dropwise to a stirred solution of triphenylphosphine (2.10 g, 8.00 mmol) in THF (27 mL) at −78 °C. After about 30 min, the suspension became white and then a solution of (*S*)-**3** (1.33 g, 8.00 mmol) in THF (27 mL) was added dropwise. The resulting mixture was stirred and warmed up to −10 °C over 2 h, and reaction mixture was left stirring overnight. After concentrating at room temperature, triphenylphosphine oxide was washed with hexane and filtered off by suction. After purification of the crude product by silica gel column chromatography (hexane : ethyl acetate = 17 : 3), (*R*)-**4** was isolated as a colorless crystal with a yield of 487 mg (41%).

$[\alpha]_D^{26.6}$ −11.4 (c 1.60, MeOH for (*S*)-**4**), lit. $[\alpha]_D$ −8.0 (c 1.6, MeOH). [8]

5. General procedure of the enantioselective hydrolysis of (*RS*)-4 using alkaline hydroxide under aqueous biphasic condition (Table 1, 2)

3-Phenyl-2-oxetanone ((*RS*)-**4**, 74.1 mg, 0.500 mmol), chiral phase transfer catalyst (**11**, 21.1 mg, 0.0500 mmol, 10 mol%), and solvent (2.5 mL) in a glass test tube were mixed and stirred at 0 °C. Then, a solution of KOD (1 mol/L, 140 mg KOH, 2.50 mmol in D_2O 2.5 mL) was added to above solution. After having been stirred for 24 h, water (5 mL) and solvent (5 mL) were added to separate layers. The combined aqueous layer was washed with CH_2Cl_2 or solvent used for reaction (5 mL). Then, aqueous 1 mol/L HCl (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: ethyl acetate : HCO_2H = 100 : 1) to give tropic acid (**3**) as colorless solid. The enantiomeric ratio of the product was determined by chiral HPLC (Daicel CHIRALPAK IC, 4.6×250 mm, 5 μm, *t*-butyl methyl ether : TFA = 100 : 0.1, 254 nm, flow rate = 1.0 mL/min).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 7.38-7.26 (5H, m), 4.15 (1H, dd, *J* = 8.5, 10.5 Hz), 3.92-3.85 (2H, m).

6. General procedure of the enantioselective hydrolysis of (*RS*)-4 using resin ($R_4N^+OH^-$) under <u>non-biphasic</u> condition (Table 3, 4)

A strongly basic anion exchange resin (8% cross-linked, Cl- form, 30 g) washed three times with distilled water was filled in to glass column, then, an aqueous NaOH solution (5 g /45 mL) was passed through it over 10 minutes followed by complete washing by distilled water until the eluent became phenolphthalein negative. The wet resin was collected on a glass filter and washed with anhydrous THF (10 × 20 mL) by suction, then it was dried *in vacuo* to complete dryness.

The resin (5 g) prepared as above, PTC (0.0500 mmol, 10 mol%) and CH_2Cl_2 (16 mL) were placed in a glass test tube and cooled to 0 °C. Then, (*RS*)-**4** (74.1 mg, 0.500 mmol)/ CH_2Cl_2 (4 mL) was added and stirred vigorously. The reaction was monitored by TLC. After completion of the reaction, the resin was washed with CH_2Cl_2 (50 mL) and charged into glass column. Then, aqueous 1 mol/L HCl and methanol (100 mL) were passed through the column and aqueous HCl eluent and methanol eluent were collected separately. The extract from aqueous HCl with ethyl acetate (3 × 50 mL) and the evaporated residue of methanol eluent were combined, and washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate : HCO_2H = 100 : 1) to give tropic acid (**3**) as colorless solid. The enantiomeric ratio was determined by chiral HPLC (Daicel IC, *t*-butyl methyl ether : TFA = 100 : 0.1, flow rate = 1.0 mL/min).

^{1}H-NMR ($CDCl_3$, 495.1 MHz): δ 7.38-7.26 (5H, m), 4.15 (1H, dd, *J* = 8.5, 10.5 Hz), 3.92-3.85 (2H, m).

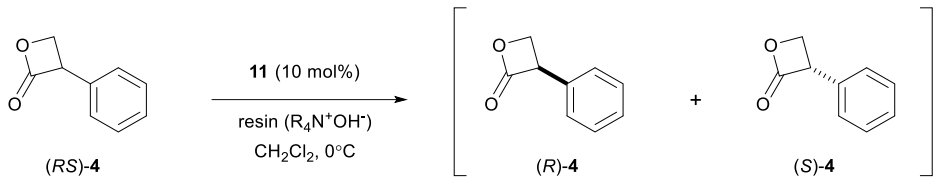
$[\alpha]_D^{22.5}$ −53.5 (c 1.11, acetone, 81% ee for (*S*)-**3**, entry 2 in Table 2), lit. $[\alpha]_D$ +70 (c 1.11, acetone, for (*R*)-**3**). [7]

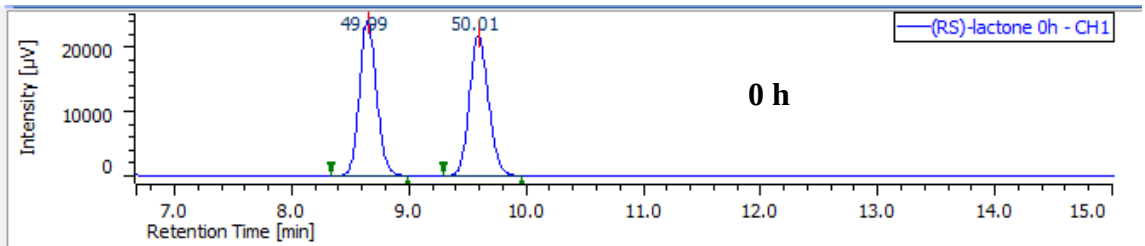
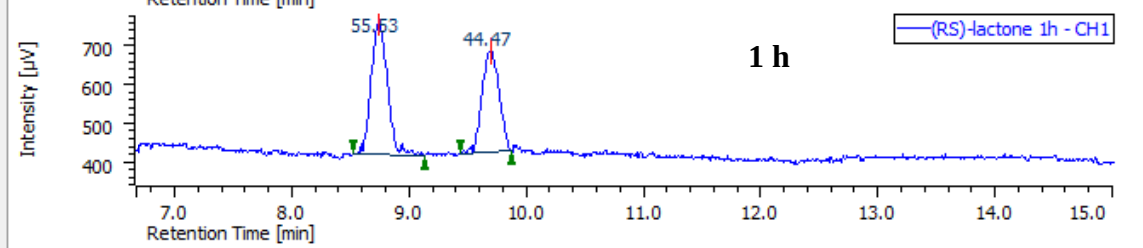
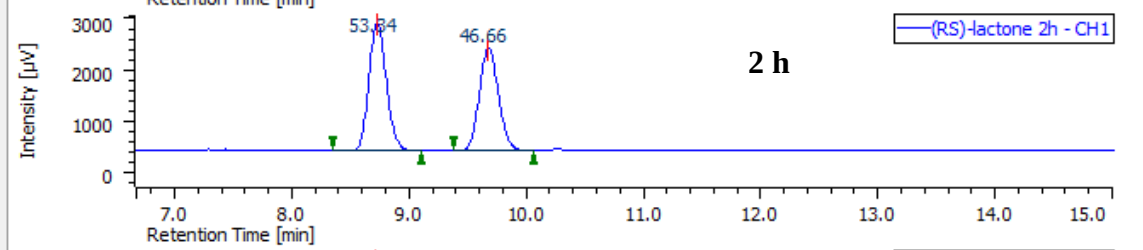
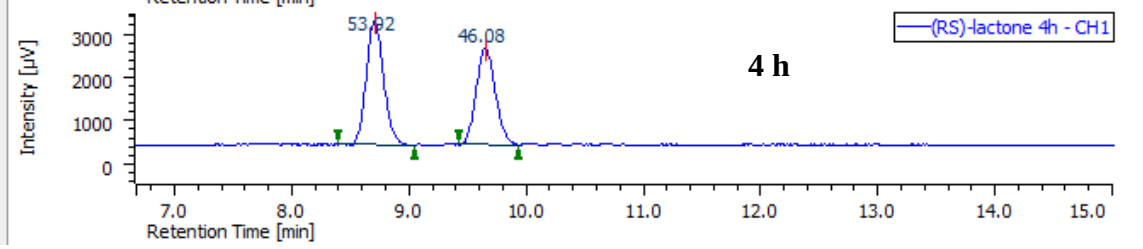
7. Demonstration of the presence of racemization equilibrium between both β-lactone enantiomers (deuterium incorporation experiment)

The deuteration experiment was performed under the general biphasic hydrolysis procedure using (*RS*)-**4** (74.1 mg, 0.500 mmol), **11** (21.1 mg, 0.0500 mmol, 10 mol%), $CDCl_3$ (2.5 mL), and KOH (140 mg, 2.5 mmol) in D_2O (2.5mL). After acidic workup, the hydrolyzed tropic acid (**3**) was isolated as a colorless solid with a yield of 61.9 mg (74%, (24% D incorporation)).
The incorporated ratio of deuterium *via* β-lactone enolate was determined by ^{1}H-NMR.

8. Racemization equilibrium of β-lactone in the reaction system

entry 1, Racemization equilibrium of (*RS*)-**4**

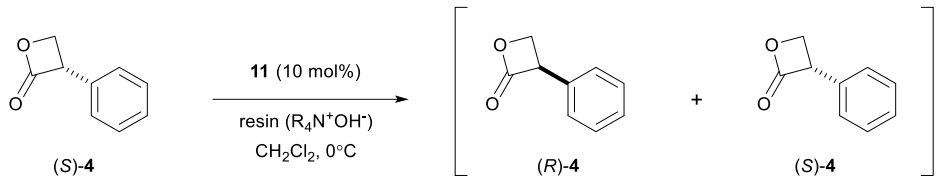


	(*R*)-**4** (*S*)-**4**	(*R*)-**4** : (*S*)-**4**
0 h		**50 : 50**
1 h		**56 : 44**
2 h		**53 : 47**
4 h		**54 : 46**

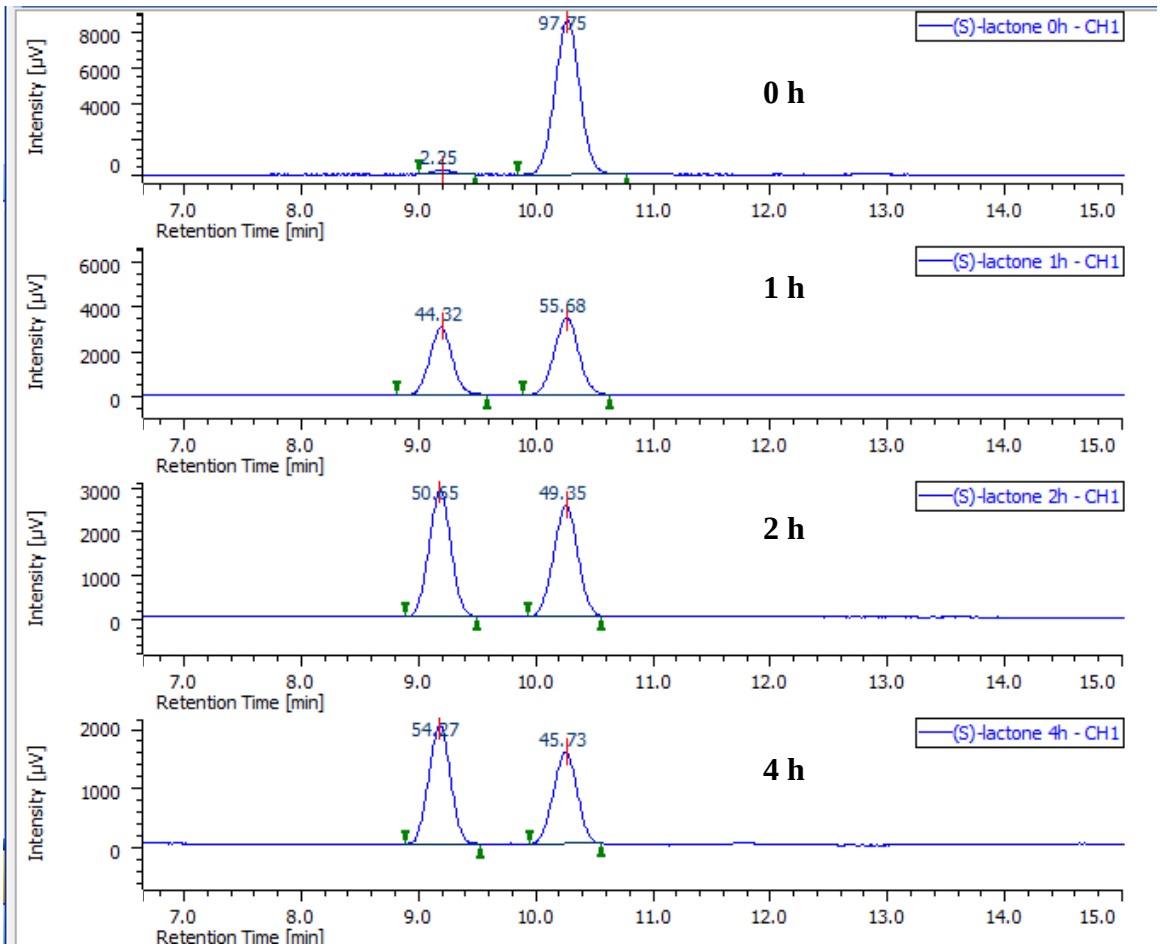
Daicel CHIRALPAK IC, 4.6×250 mm, 5 μm

Hexane: IPA = 80 : 20, 254 nm, flow rate = 1.0 mL/min.

entry 2, Racemization equilibrium of (*S*)-**4**



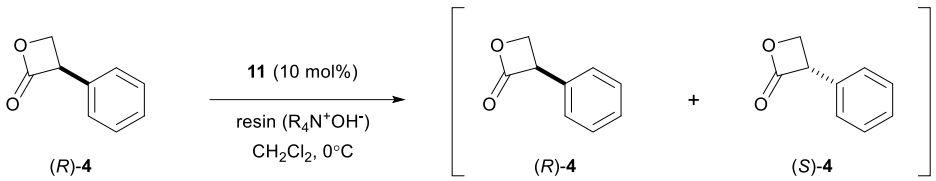
	(*R*)-**4**	(*S*)-**4**	(*R*)-**4** : (*S*)-**4**
0 h	97.75	2.25	**2 : 98**
1 h	44.32	55.68	**44 : 56**
2 h	50.65	49.35	**51 : 49**
4 h	54.27	45.73	**54 : 46**



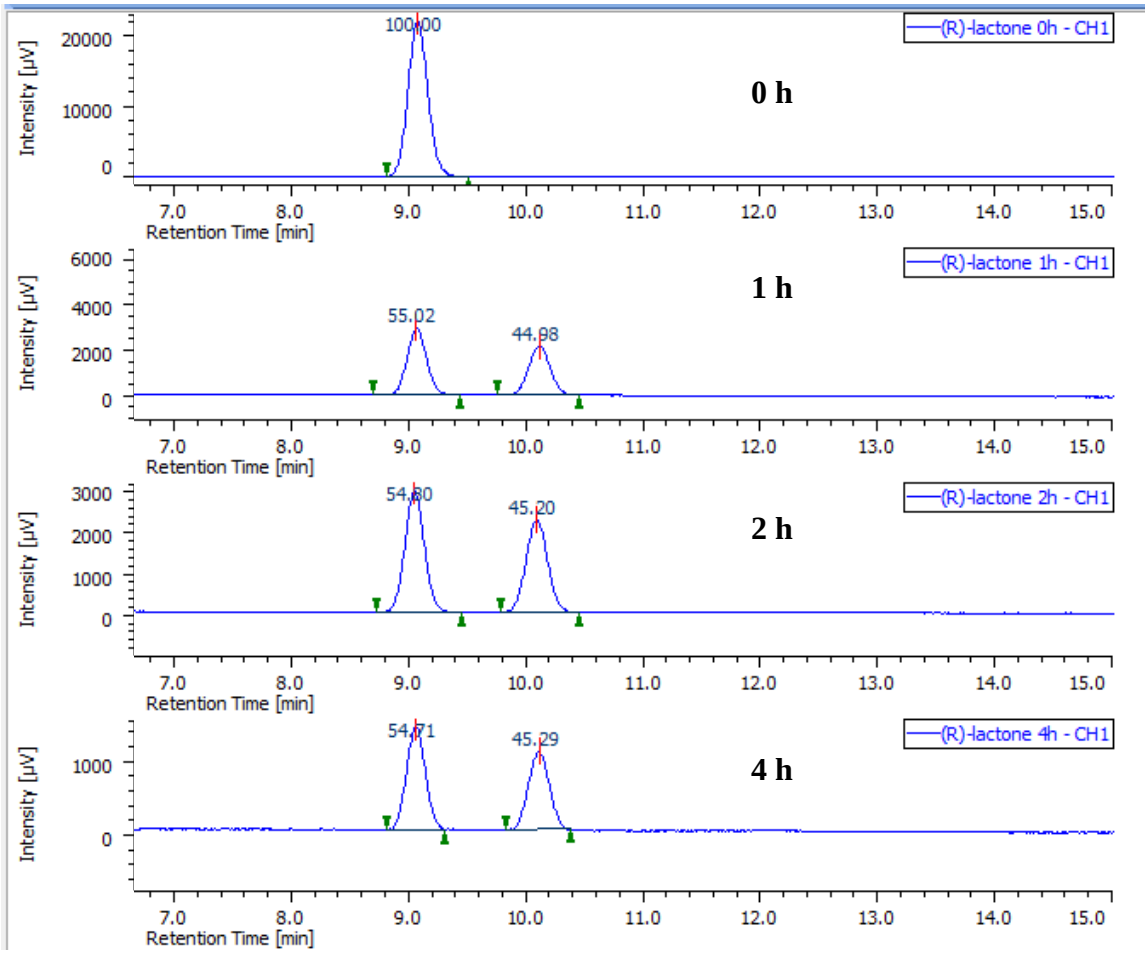
Daicel CHIRALPAK IC, 4.6×250 mm, 5 µm

Hexane: IPA = 80 : 20, 254 nm, flow rate = 1.0 mL/min.

entry 3, Racemization equilibrium of (*R*)-**4**



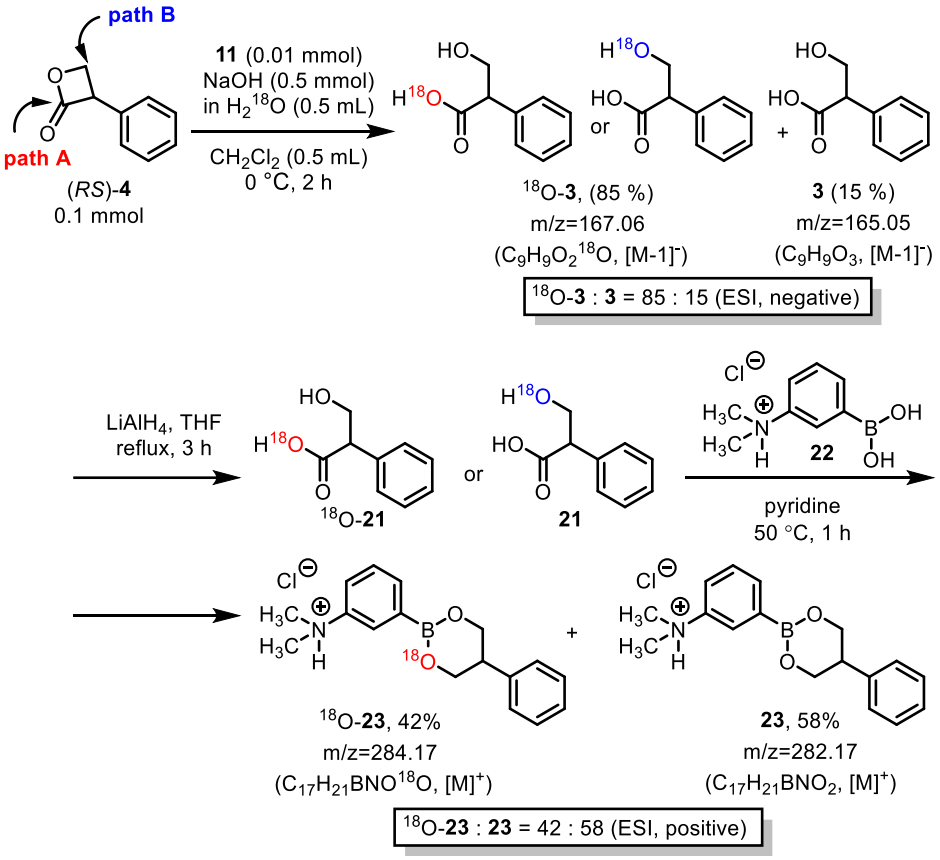
	(*R*)-**4**	(*S*)-**4**	(*R*)-**4** : (*S*)-**4**
0 h	100.00		**100 : 0**
1 h	55.02	44.98	**55 : 45**
2 h	54.80	45.20	**55 : 45**
4 h	54.71	45.29	**55 : 45**



Daicel CHIRALPAK IC, 4.6×250 mm, 5 µm

Hexane: IPA = 80 : 20, 254 nm, flow rate = 1.0 mL/min.

9. Synthesis of ^{18}O incorporated tropic acid (^{18}O-3) and cyclic boronate (^{18}O-23)



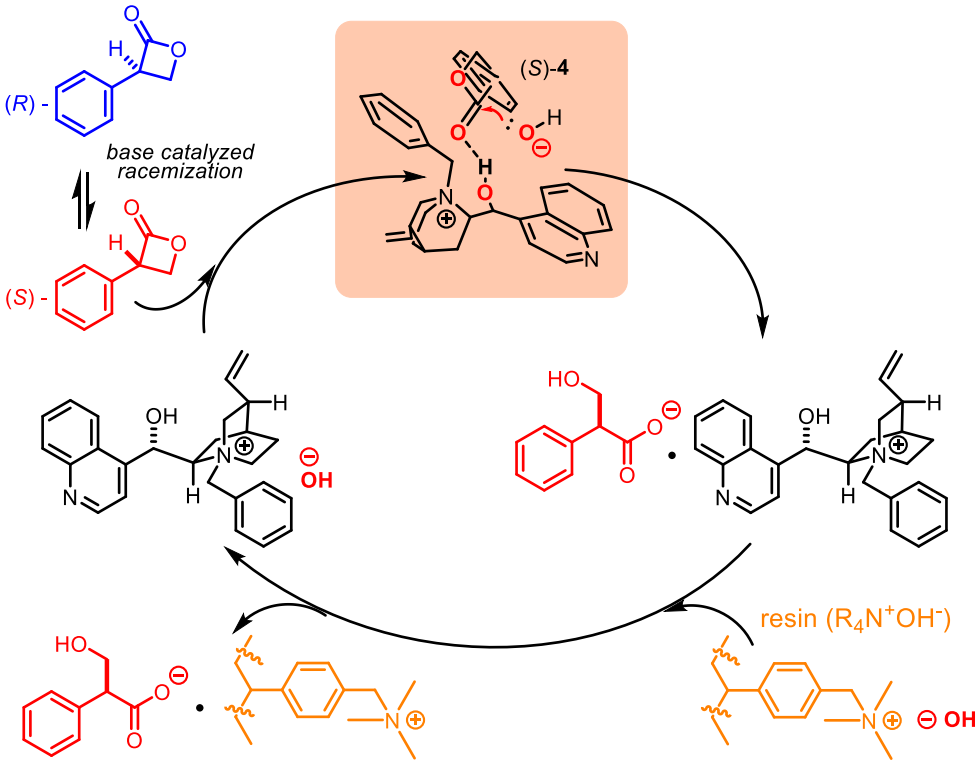
The labeling experiment using $H_2{}^{18}O$ was performed according to the general biphasic procedure. ^{18}O Incorporated tropic acid (^{18}O-**3**) was synthesized using (*RS*)-**4**, (14.8 mg, 0.100 mmol), **11** (4.21 mg, 0.0100 mmol, 10 mol%), CH_2Cl_2 (0.5 mL), and NaOH (20.00 mg, 0.500 mmol) in $H_2{}^{18}O$ (0.5 mL) to give 15 mg of colorless solid (^{18}O-**3**) in 89% yield.

HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_9H_9{}^{16}O_2{}^{18}O$ 167.0594; found: 167.0592. $[M-H]^-$ Calcd for $C_9H_9{}^{16}O_3$ 165.0552; found: 165.0539. ratio (^{18}O-**3** : **3** = 85 : 15).

To a suspension of $LiAlH_4$ (56.9 mg, 1.50 mmol) in THF (2.5 mL) was added a solution of ^{18}O-**3**, (13.3 mg, 0.0800 mmol) in THF (2.5 mL), and the mixture was refluxed for 3 h. Under ice cooling, the reaction was quenched by the addition of water (60 μL), 15% aqueous NaOH (60 μL), water (180 μL), and precipitate white solid precipitate was removed by filtration. Evaporation of the filtrate gave ^{18}O incorporated 2-phenyl-1,3-propanediol (^{18}O-**21**, 8.9 mg) as colorless solid. Then, the mixture of ^{18}O-**21** (0.75 mg, 4.88 μmol), 3-dimethylaminophenylboronic acid (**22**, 1.65 mg, 8.20 μmol) and pyridine (50 μL) was heated at 50 °C for 1 h. After pyridine was removed *in vacuo*, the residue (^{18}O-**23**) was analyzed by HRMS [9].

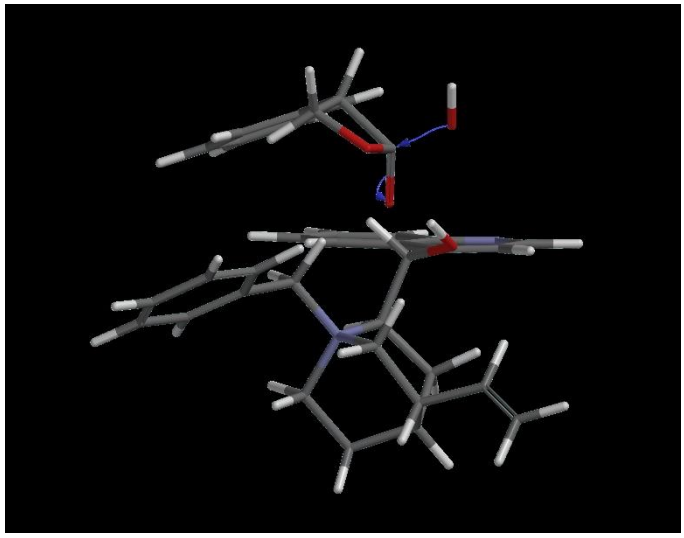
HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}BN{}^{16}O{}^{18}O$ 284.1708; found: 284.1712. $[M+H]^+$ Calcd for $C_{17}H_{21}BN{}^{16}O_2$ 282.1665; found: 282.1668. ratio (^{18}O-**23** : **23** = 42 : 58).

10. Proposed catalytic cycle of hydrolytic dynamic kinetic resolution



11. Density functional theory (DFT) calculation of the geometry optimized orientation of TS-1 ((*S*)-4·11·OH^-) and TS-2 ((*R*)-4·11·OH^-) in CH_2Cl_2 (Figure 1)

TS-1: Summary



Formula: $C_{26}H_{29}N_2O$. $C_9H_8O_2$. HO

Job type: Equilibrium Geometry
Applying: Constraints
Solvent: CPCM: dichloromethane
Method: ωB97X-D
Basis set: 6-31G*
Energy: -1766.446181 hartrees

Output

SPARTAN'20 MECHANICS PROGRAM: (Win/64b) Release 1.1.2

Frequency Calculation

Adjusted 14 (out of 237) low frequency modes

Reason for exit: Successful completion
Mechanics CPU Time: 8.91
Mechanics Wall Time: 0.420

SPARTAN'20 Quantum Mechanics Driver: (Win/64b) Release 1.1.4

Job type: Geometry optimization.
Method: RWB97X-D
Basis set: 6-31G(D)
Number of basis functions: 691
Number of electrons: 294
Parallel Job: 24 threads

SCF model:
A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization
Polarizable Continuum solvation model will be applied
Solvation: C-PCM dielectric=8.82

Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-1766.385556	0.032316	0.116010
2	-1766.407555	0.028386	0.092867
3	-1766.417644	0.021578	0.151577
4	-1766.424934	0.013854	0.055931
5	-1766.429580	0.015284	0.065054
6	-1766.432719	0.010000	0.081824

7	-1766.435497	0.005410	0.106681	
8	-1766.437083	0.003539	0.080949	
9	-1766.438830	0.003722	0.066152	
10	-1766.440020	0.005923	0.073886	
11	-1766.440958	0.005044	0.057788	
12	-1766.441645	0.005256	0.121080	
13	-1766.442054	0.006969	0.109194	
14	-1766.442415	0.007522	0.126821	
15	-1766.442715	0.005100	0.126633	
15	-1766.442715	0.009382	0.164245	Switching to cartesian
16	-1766.442722	0.004691	0.126745	
17	-1766.441095	0.017527	0.123399	
18	-1766.442556	0.009076	0.101571	
19	-1766.440903	0.020208	0.113807	
20	-1766.441625	0.015036	0.096719	
21	-1766.442131	0.009540	0.100704	
22	-1766.442236	0.010111	0.082306	
23	-1766.442304	0.008567	0.137548	
24	-1766.442885	0.004185	0.151766	
25	-1766.442820	0.006426	0.074600	
26	-1766.443010	0.006185	0.099320	
27	-1766.442432	0.008292	0.063731	
28	-1766.443308	0.002760	0.078874	
29	-1766.443198	0.003162	0.081956	
30	-1766.443280	0.002983	0.081766	
31	-1766.442851	0.006179	0.069246	
32	-1766.443333	0.003762	0.094136	
33	-1766.442845	0.007502	0.046023	
34	-1766.443475	0.001001	0.053732	
35	-1766.443471	0.001907	0.038547	
36	-1766.443523	0.000644	0.069512	
37	-1766.443540	0.001441	0.053085	
38	-1766.443583	0.001551	0.098828	
39	-1766.443635	0.001343	0.064079	
40	-1766.443639	0.002281	0.089588	
41	-1766.443729	0.001439	0.098501	
42	-1766.443762	0.002112	0.082077	
43	-1766.443841	0.001517	0.086567	
44	-1766.443899	0.002326	0.093262	
45	-1766.443975	0.001276	0.074998	
46	-1766.444063	0.001093	0.094387	
47	-1766.444118	0.001635	0.071913	
48	-1766.444189	0.001363	0.082009	
49	-1766.444263	0.001181	0.080049	
50	-1766.444348	0.001879	0.085542	
51	-1766.444412	0.001563	0.089575	
52	-1766.444481	0.001364	0.087093	
53	-1766.444553	0.001234	0.084027	
54	-1766.444615	0.001309	0.077488	
55	-1766.444682	0.001183	0.085839	
56	-1766.444744	0.000819	0.086773	
57	-1766.444821	0.000736	0.092341	
58	-1766.444902	0.001023	0.090758	
59	-1766.444968	0.001075	0.094811	
60	-1766.445038	0.001382	0.088644	
61	-1766.445106	0.000998	0.090000	
62	-1766.445174	0.000981	0.087661	
63	-1766.445257	0.000744	0.086110	

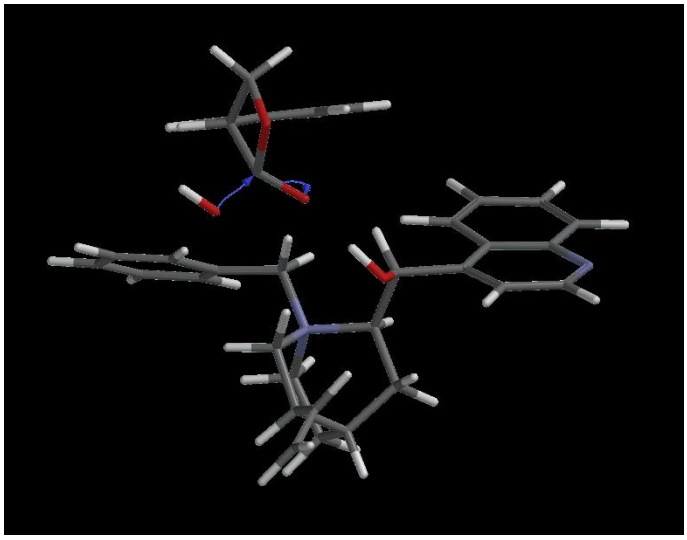
64	-1766.445346	0.000738	0.085488
65	-1766.445432	0.000916	0.086776
66	-1766.445517	0.000936	0.087158
67	-1766.445594	0.001159	0.084539
68	-1766.445672	0.001715	0.091876
69	-1766.445751	0.001323	0.096268
70	-1766.445837	0.001197	0.094433
71	-1766.445913	0.001161	0.097028
72	-1766.445978	0.001664	0.093655
73	-1766.446034	0.001518	0.093564
74	-1766.446079	0.001152	0.095422
75	-1766.446123	0.000966	0.089230
76	-1766.446142	0.001218	0.054223
77	-1766.446139	0.001563	0.060099
78	-1766.446160	0.001297	0.019167
79	-1766.446172	0.000746	0.031085
80	-1766.446181	0.000539	0.031492

Reason for exit: Successful completion
Quantum Calculation CPU Time: 330:40:38.47
Quantum Calculation Wall Time: 16:51:58.80

SPARTAN'20 Properties Program: (Win/64b) Release 1.1.2

Reason for exit: Successful completion
Properties CPU Time: 5.36
Properties Wall Time: 5.39

TS-2: Summary



Formula: $C_{26}H_{29}N_2O$. $C_9H_8O_2$. HO

Job type: Equilibrium Geometry
Applying: Constraints
Solvent: CPCM: dichloromethane
Method: ωB97X-D
Basis set: 6-31G*
Energy: -1766.443446 hartrees

Output

SPARTAN'20 MECHANICS PROGRAM: (Win/64b) Release 1.1.2

Frequency Calculation

Adjusted 13 (out of 237) low frequency modes

Reason for exit: Successful completion
Mechanics CPU Time: 0.234
Mechanics Wall Time: 0.257

SPARTAN'20 Quantum Mechanics Driver: (Win/64b) Release 1.1.4

Job type: Geometry optimization.
Method: RWB97X-D
Basis set: 6-31G(D)
Number of basis functions: 691
Number of electrons: 294
Parallel Job: 24 threads

SCF model:
A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization
Polarizable Continuum solvation model will be applied
Solvation: C-PCM dielectric=8.82

Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-1766.370829	0.110724	0.070253
2	-1766.394299	0.094997	0.066934
3	-1766.403409	0.072267	0.104089
4	-1766.411460	0.045886	0.076117
5	-1766.414328	0.024065	0.080001
6	-1766.419823	0.014355	0.063455
7	-1766.424019	0.005498	0.090619
8	-1766.426450	0.005836	0.056327
9	-1766.428169	0.007994	0.073085
10	-1766.429915	0.009360	0.068947
11	-1766.431302	0.009677	0.082738
12	-1766.432586	0.010650	0.089496
13	-1766.433882	0.011276	0.104584

14	-1766.435292	0.010104	0.101041
15	-1766.436821	0.008873	0.102913
16	-1766.438640	0.005984	0.086176
17	-1766.440544	0.006717	0.087350
18	-1766.441078	0.011909	0.075306
19	-1766.441659	0.006203	0.188006
20	-1766.442154	0.006124	0.241824
21	-1766.442395	0.003852	0.068633
22	-1766.442431	0.009038	0.097801
23	-1766.442642	0.004508	0.168006
24	-1766.442845	0.002765	0.272713
25	-1766.443022	0.001971	0.127180
26	-1766.443022	0.002633	0.276612
27	-1766.443147	0.003617	0.016927
28	-1766.443193	0.001882	0.206002
29	-1766.443232	0.001200	0.023900
30	-1766.443237	0.001118	0.083324
31	-1766.443253	0.001178	0.044317
32	-1766.443260	0.000659	0.007074

Reason for exit: Successful completion
Quantum Calculation CPU Time: 115:25:13.67
Quantum Calculation Wall Time: 6:02:12.55

SPARTAN'20 Properties Program: (Win/64b) Release 1.1.2

Reason for exit: Successful completion
Properties CPU Time: 5.63
Properties Wall Time: 5.67

12. References

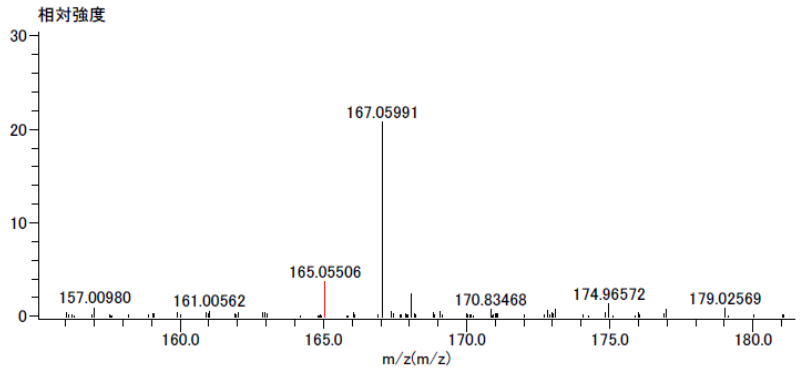
1. E. M. Tanzer, W. B. Schweizer, M. O. Ebert and R. Gilmour, *Chem. Eur. J.*, 2012, **18**, 2006-2013.
2. A. Berkessel, B. Seelig, S. Schwengberg, J. Hescheler and A. Sachinidis, *ChemBioChem*, 2010, **11**, 208-217.
3. T. Shirai, M. Kanai and Y. Kuninobu, *Org. Lett.*, 2018, **20**, 1593-1596.
4. Eckehard V. Dehmlow, S. Düttmann, B. Neumann and H.-G. Stammler, *Eur. J. Org. Chem.*, 2002, **2002**.
5. D. Klomp, J. A. Peters and U. Hanefeld, *Tetrahedron Asymmetry*, 2005, **16**, 3892-3896.
6. B. Latli, M. Stiasni, M. Hrapchak, Z. Li, N. Grinberg, H. Lee, C. A. Busacca and C. H. Senanayake, *J. Labelled Comp. Radiopharm.*, 2016, **59**, 557-564.
7. James M. Takacs, Mohamad R. Jaber and A. S. Vellekoop, *J. Org. Chem.*, 1998, **63**, 2742–2748.
8. M. Hmamouchi and R. E. Prud'homme, *J. Polym. Sci. A Polym. Chem.*, 1991, **29**, 1281-1291.
9. T. Higashi, K. Kawasaki, N. Matsumoto, S. Ogawa, K. Mitamura and S. Ikegawa, *Chem. Pharm. Bull.*, 2013, **61**, 326–332.

13. HRMS spectra

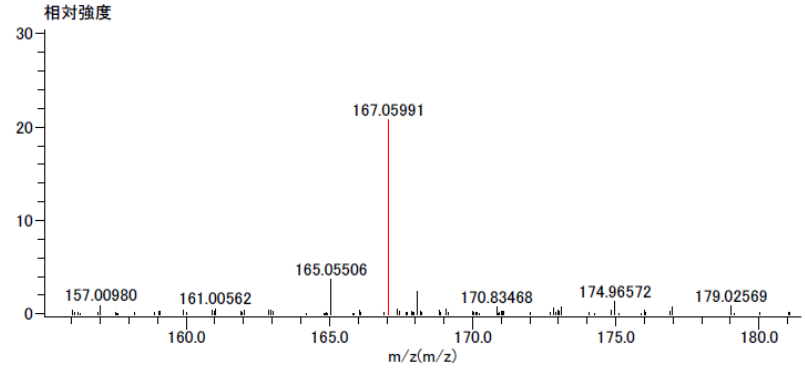
HRMS spectra of tropic acid (3 and ^{18}O-3)

3, 15 %
m/z: 165.05
([M-1]$^-$ $C_9H_9O_3$)

^{18}O-**3**, 85 %
m/z: 167.06
([M-1]$^-$ $C_9H_9O_2{}^{18}O$)

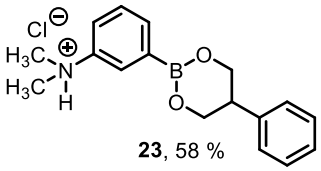


質量	強度	計算質量	質量差 mmu	質量差 ppm	推定組成式	不飽和数
165.05506	2170.16	165.05517	−0.11	−0.66	$^{12}C_9{}^{1}H_9{}^{16}O_3$	5.5



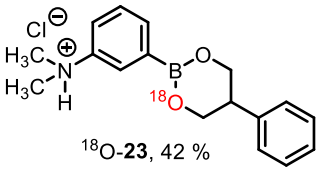
質量	強度	計算質量	質量差 mmu	質量差 ppm	推定組成式	不飽和数
167.05991	12097.25	167.05941	0.49	2.94	$^{12}C_9{}^{1}H_9{}^{16}O_2{}^{18}O_1$	5.5

HRMS spectra of cyclic boronates (23 and ^{18}O-23)

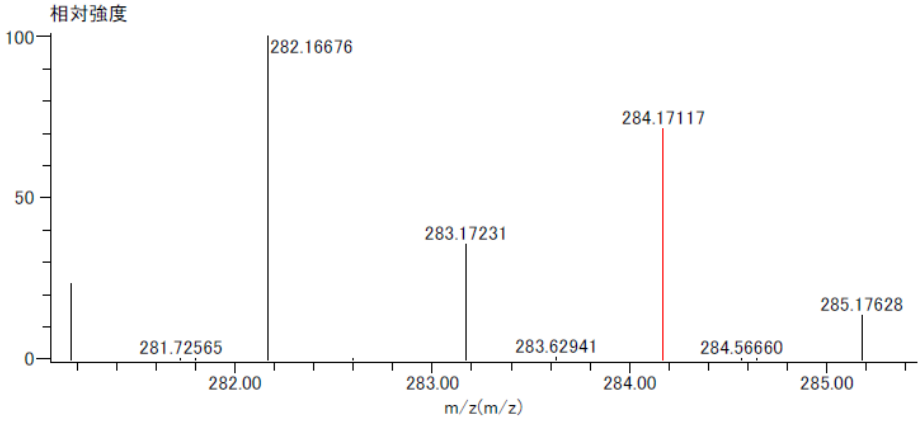


23, 58 %
m/z: 282.17
([M]$^+$ $C_{17}H_{21}BNO_2$)

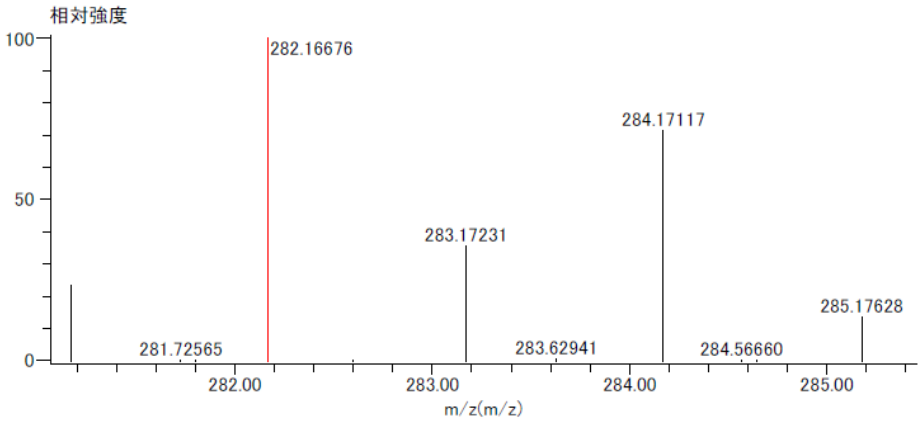
+



^{18}O-**23**, 42 %
m/z: 284.17
([M]$^+$ $C_{17}H_{21}BNO^{18}O$)

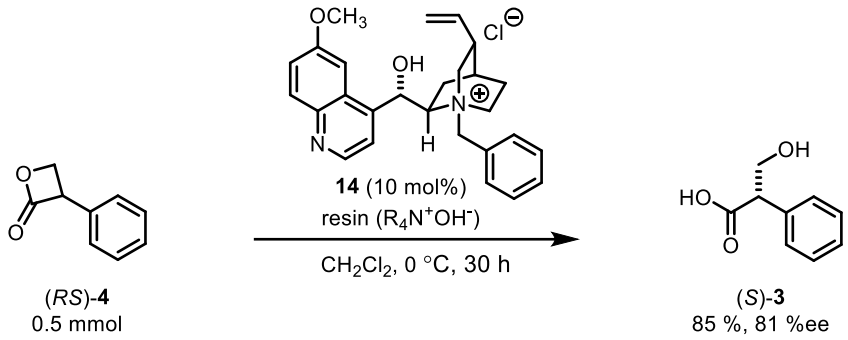


質量	強度	計算質量	質量差 mmu	質量差 ppm	推定組成式	不飽和数
284.17117	466641.63	284.17078	0.39	1.37	$^{12}C_{17}{}^{1}H_{21}{}^{11}B_1{}^{14}N_1{}^{16}O_1{}^{18}O_1$	8.5



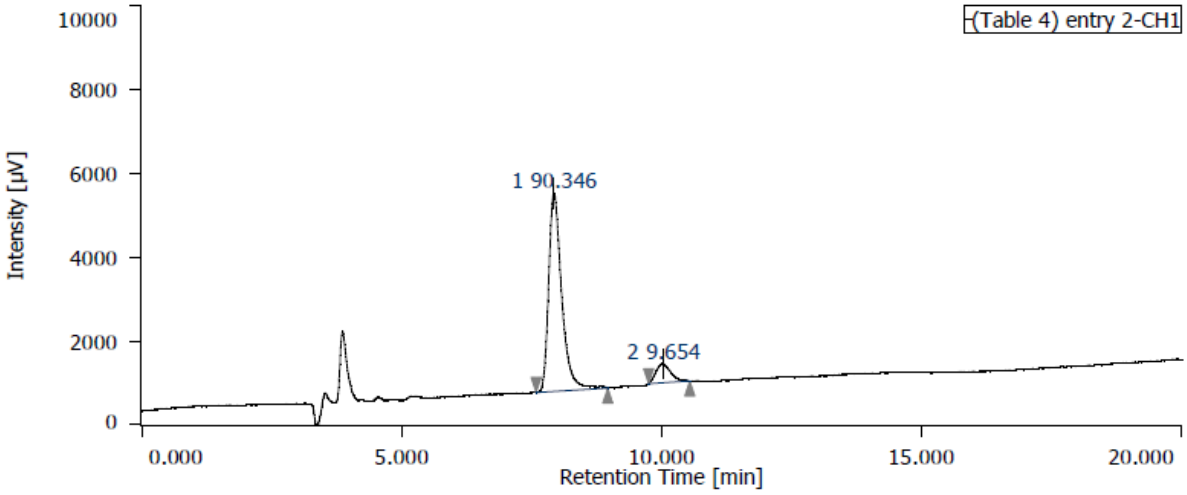
質量	強度	計算質量	質量差 mmu	質量差 ppm	推定組成式	不飽和数
282.16676	653671.40	282.16653	0.23	0.80	$^{12}C_{17}{}^{1}H_{21}{}^{11}B_1{}^{14}N_1{}^{16}O_2$	8.5

14. Chart of chiral HPLC analysis (Table 4, entry 2)



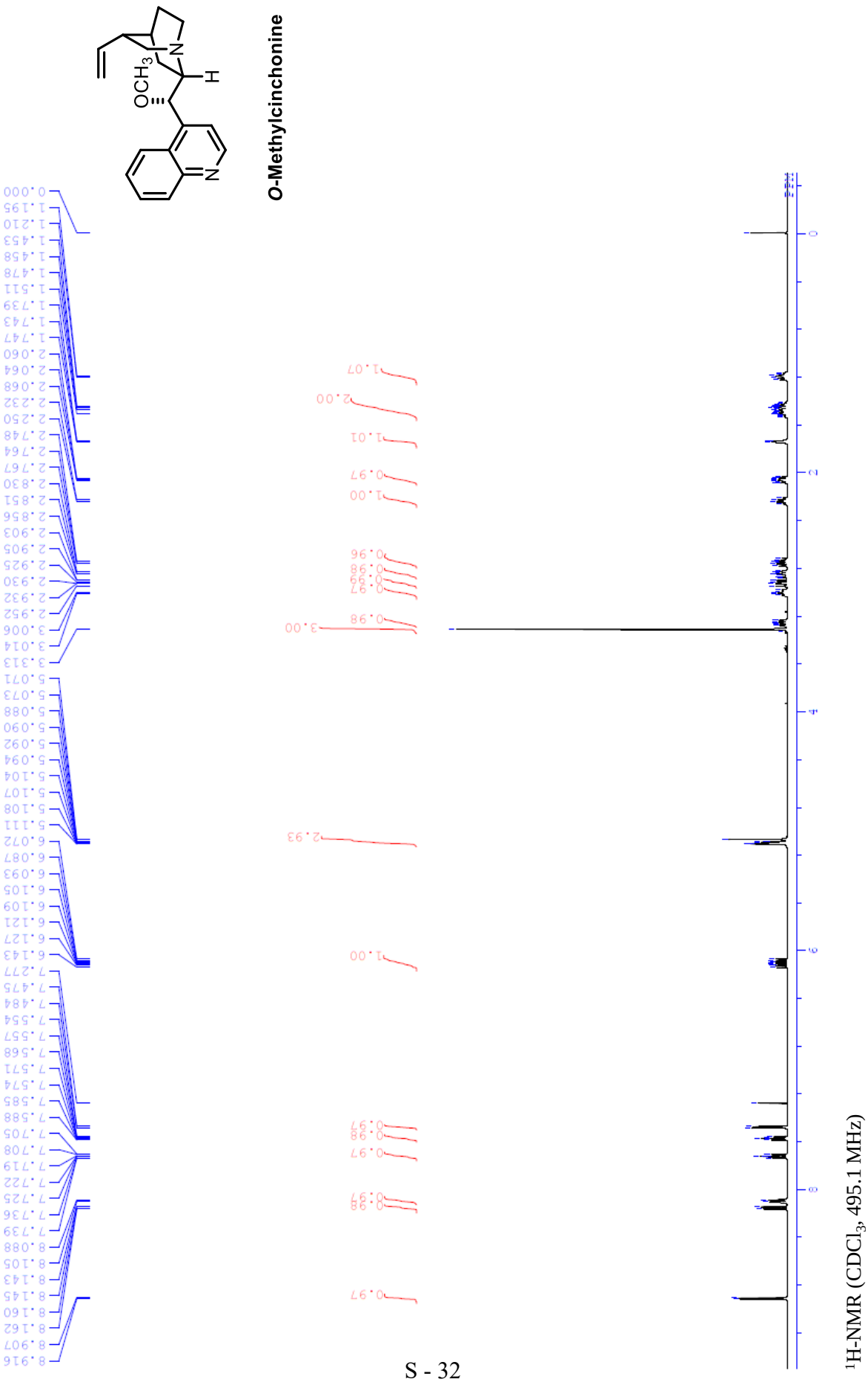
(*RS*)-**4**
0.5 mmol

(*S*)-**3**
85 %, 81 %ee

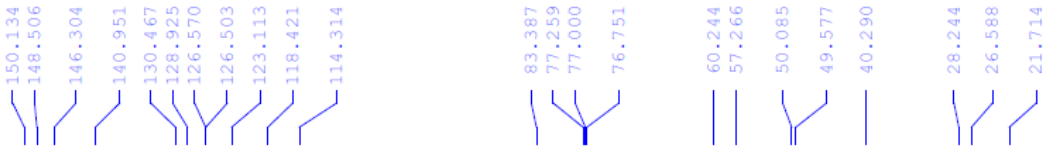


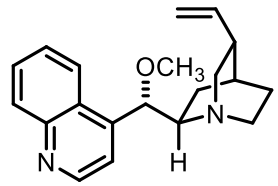
Daicel CHIRALPAK IC, 4.6×250 mm, 5 µm, *t*-butyl methyl ether : TFA = 100 : 0.1, 254 nm, flow rate = 1.0 mL/min, t_1 = 7.93 min (*S*)-**3**, 90.3%; t_2 = 10.03 min (*R*)-**3**, 9.7%.

15. NMR spectra

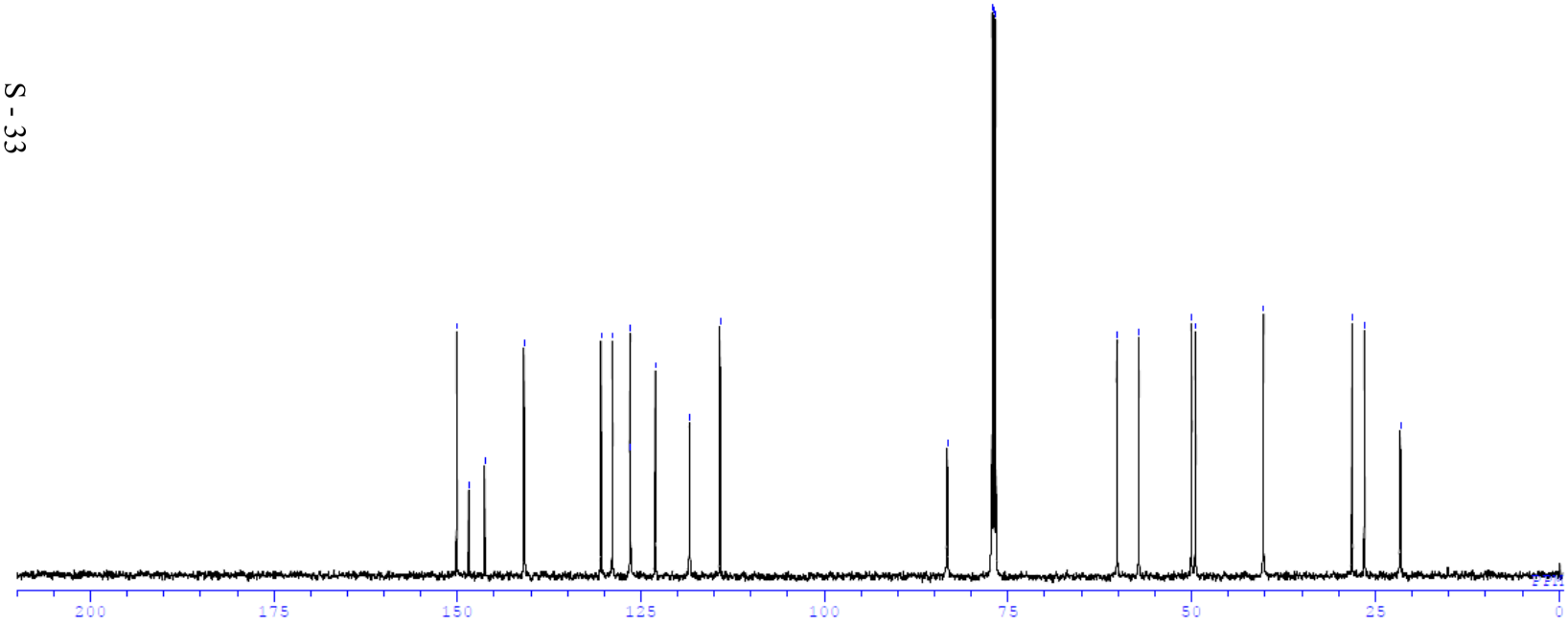


^{1}H-NMR ($CDCl_3$, 495.1 MHz)

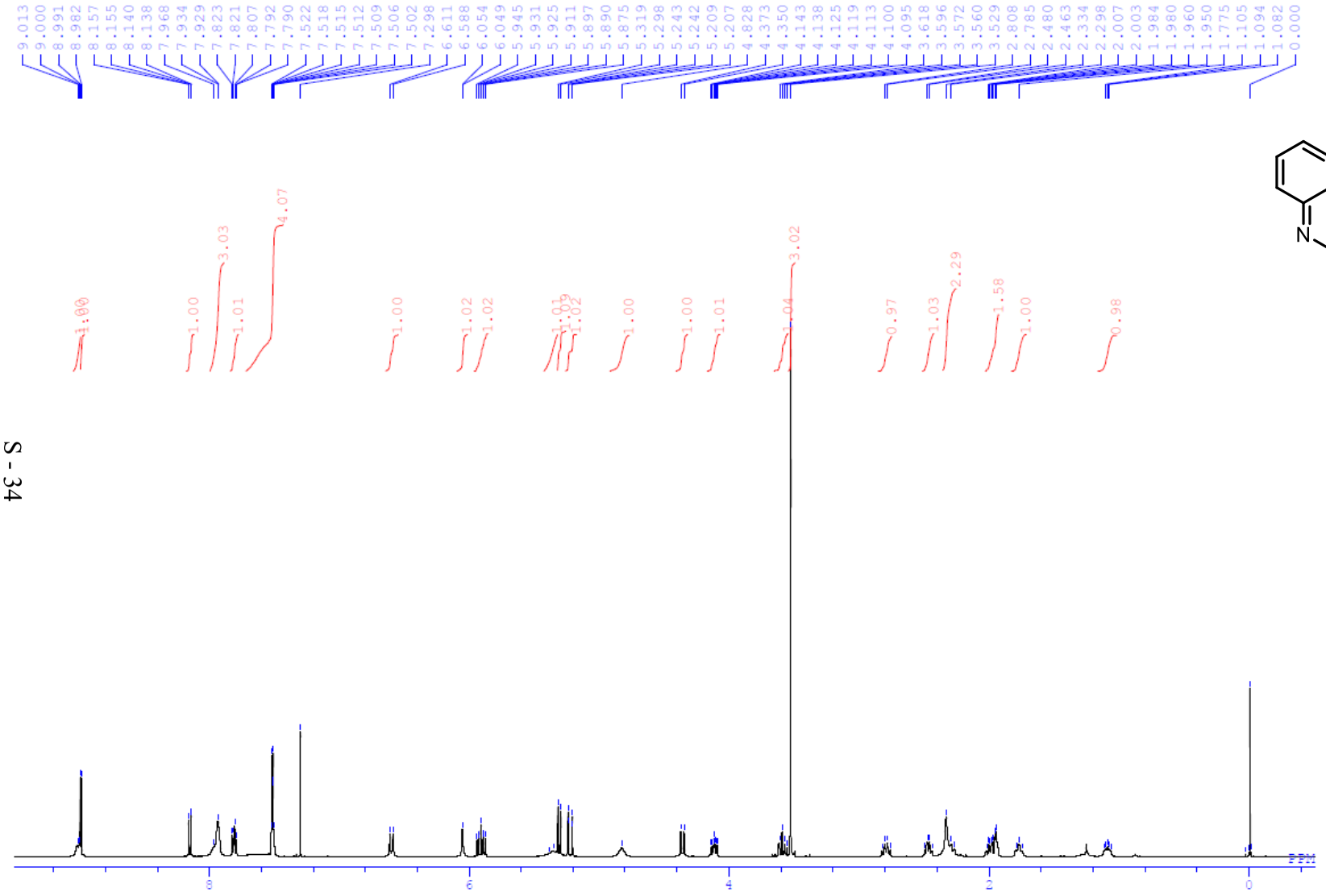


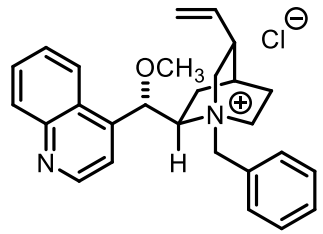


***O*-Methylcinchonine**



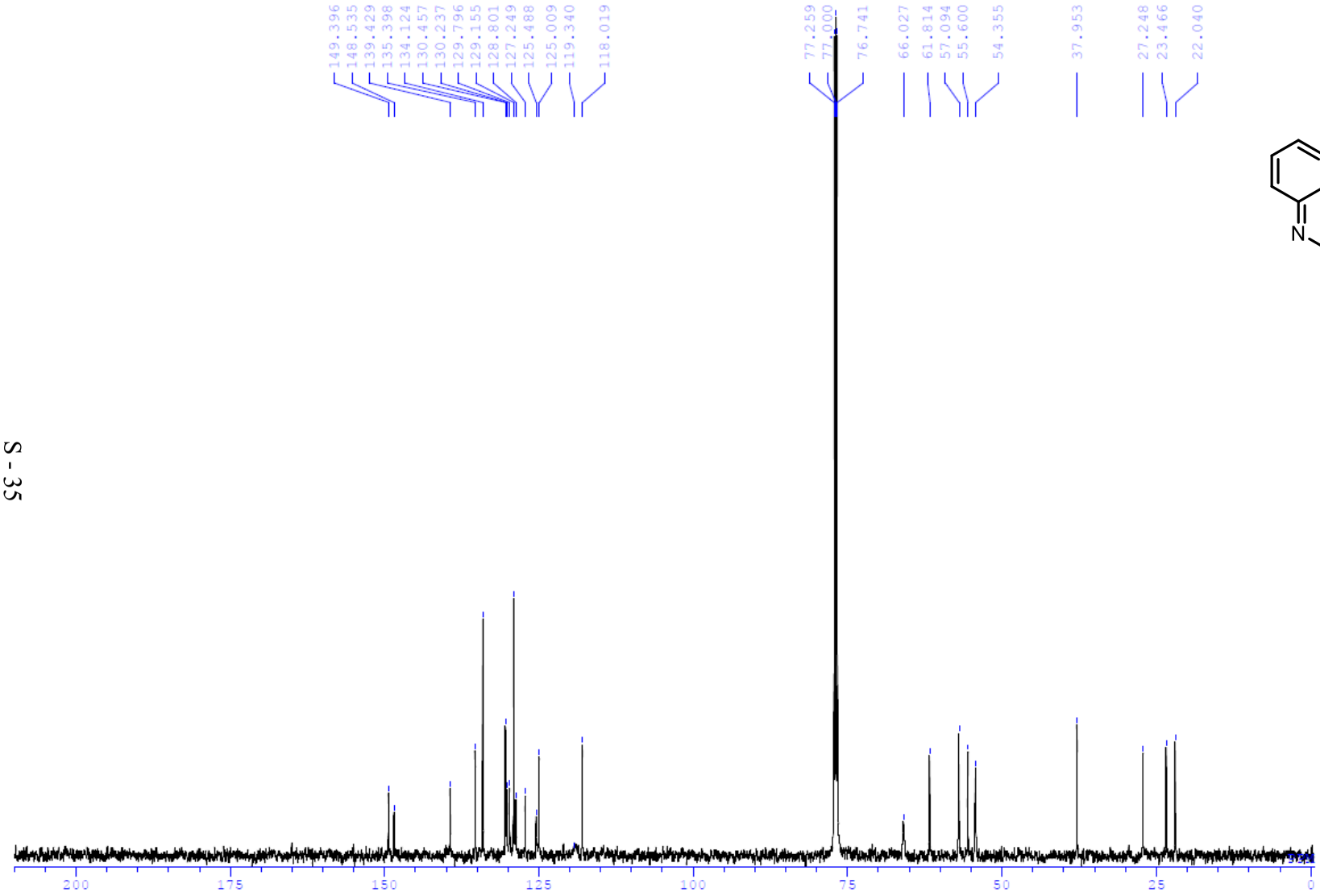
^{13}C-NMR ($CDCl_3$, 124.5 MHz)

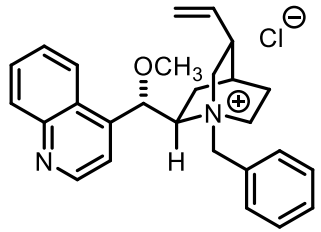




12

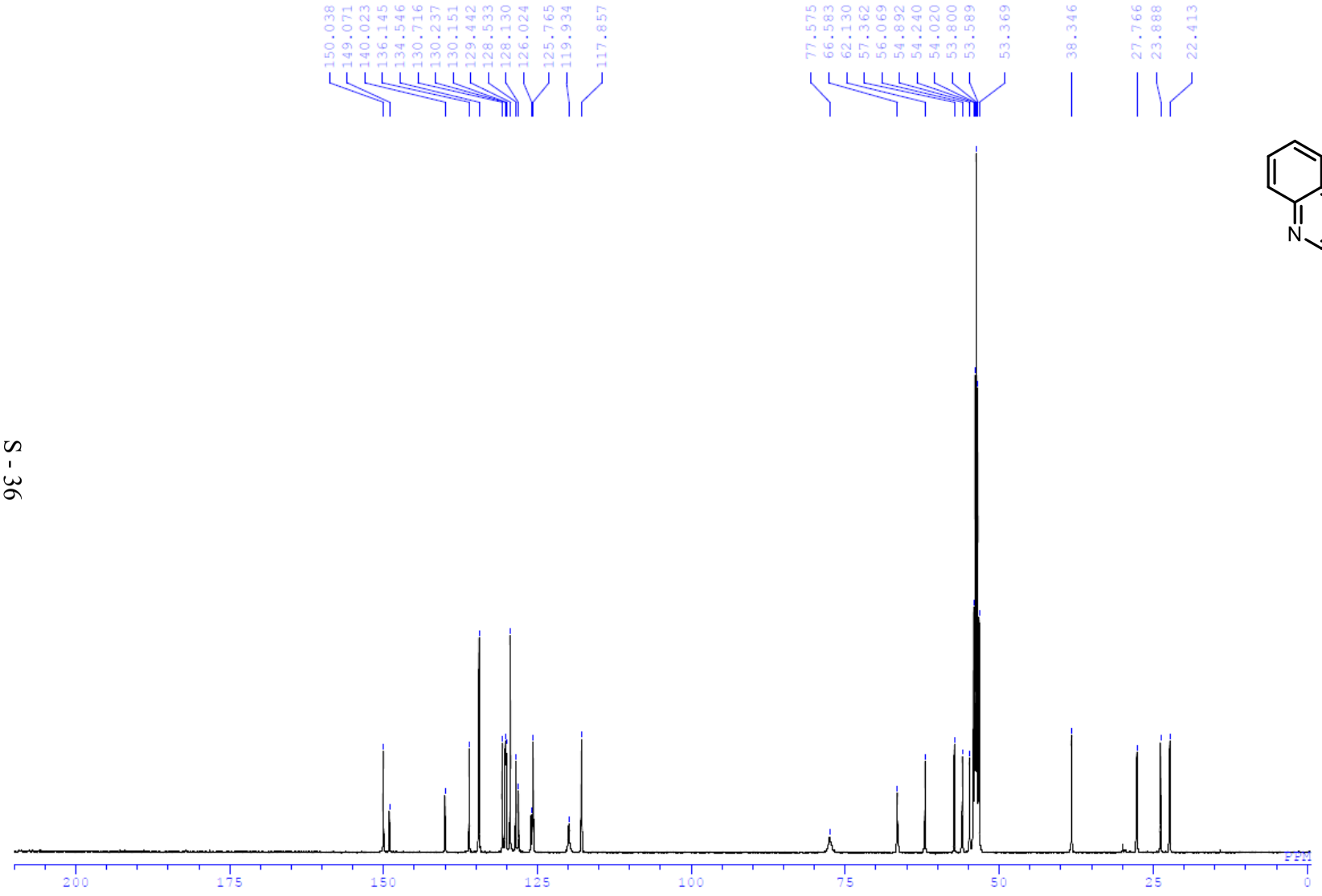
^{1}H-NMR ($CDCl_3$, 495.1 MHz)

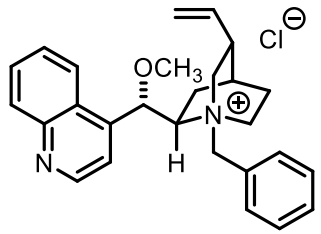




12

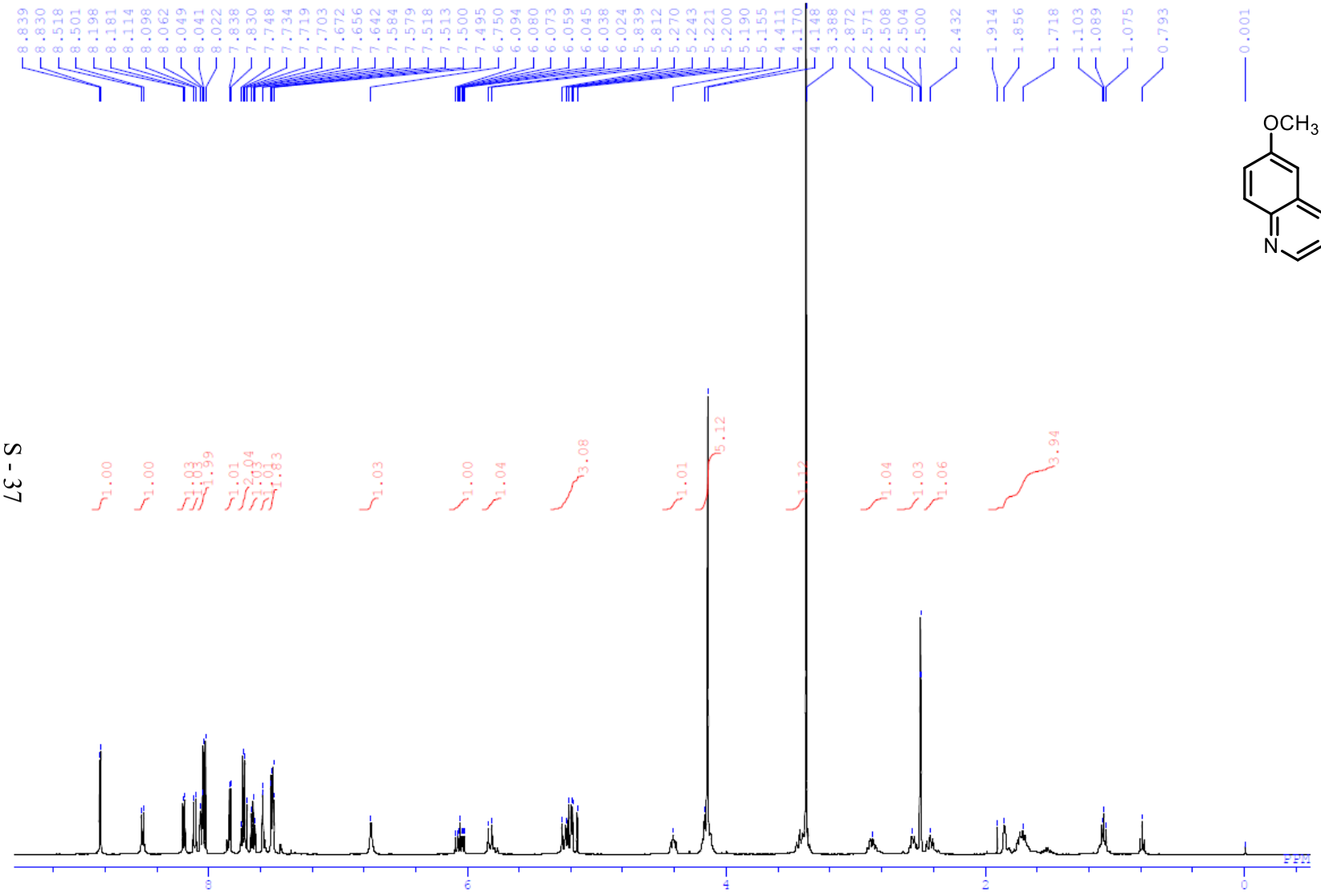
^{13}C-NMR ($CDCl_3$, 124.5 MHz)

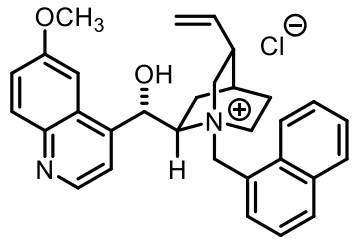




12

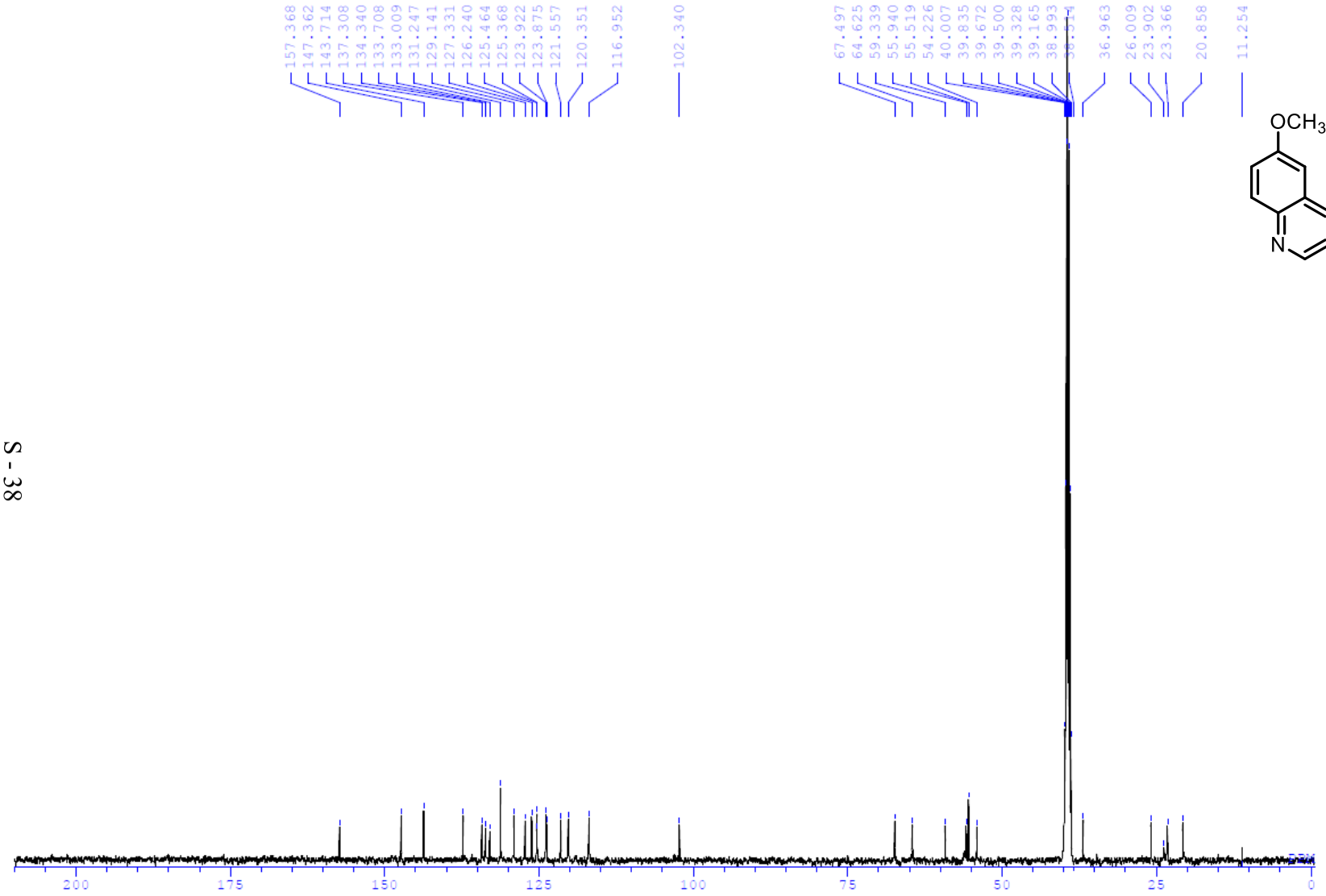
^{13}C-NMR (CD_2Cl_2, 124.5 MHz)

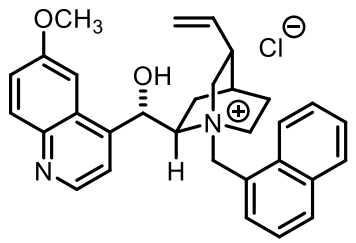




15

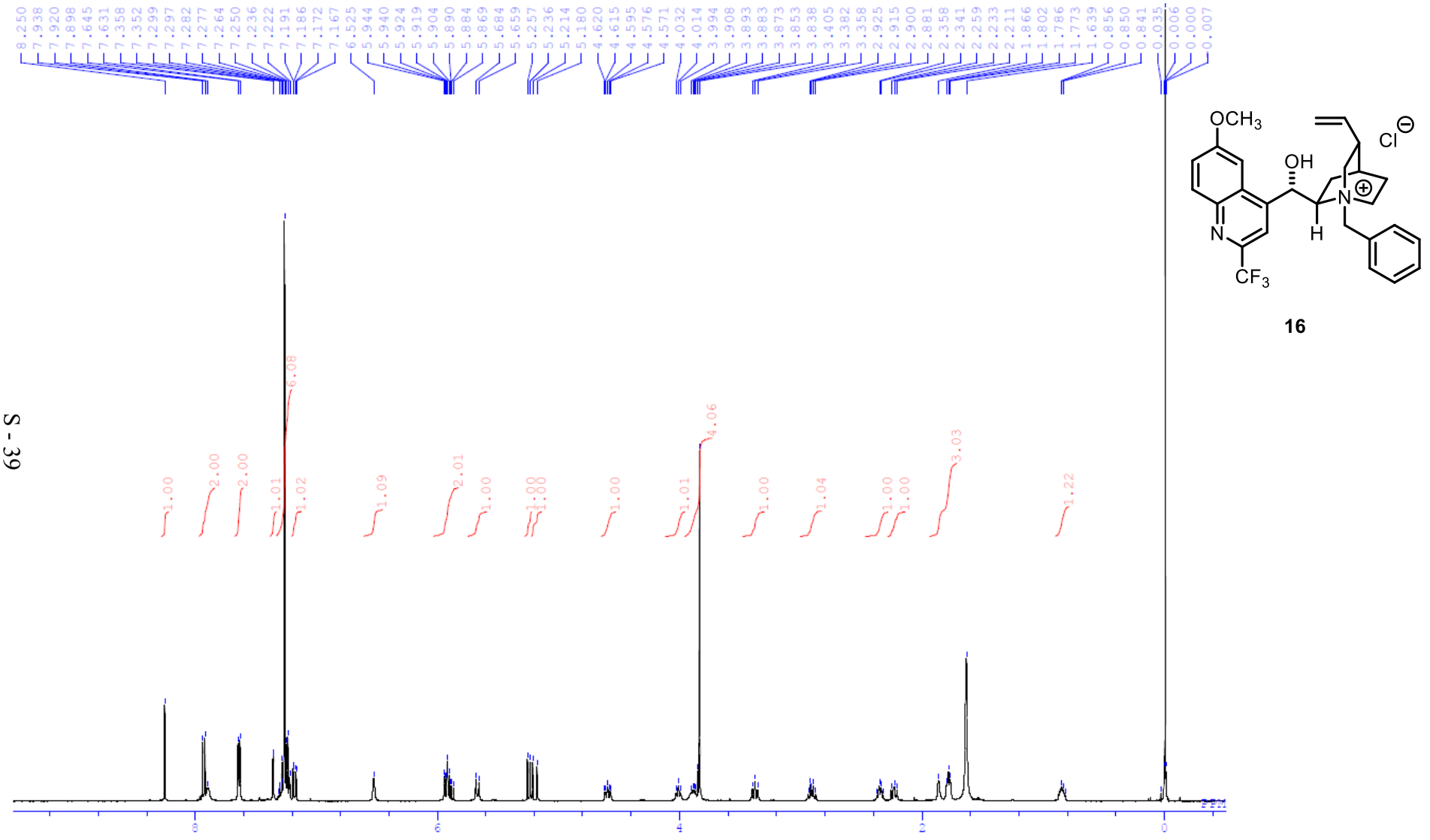
[1]H-NMR (DMSO-d_2, 495.1 MHz)





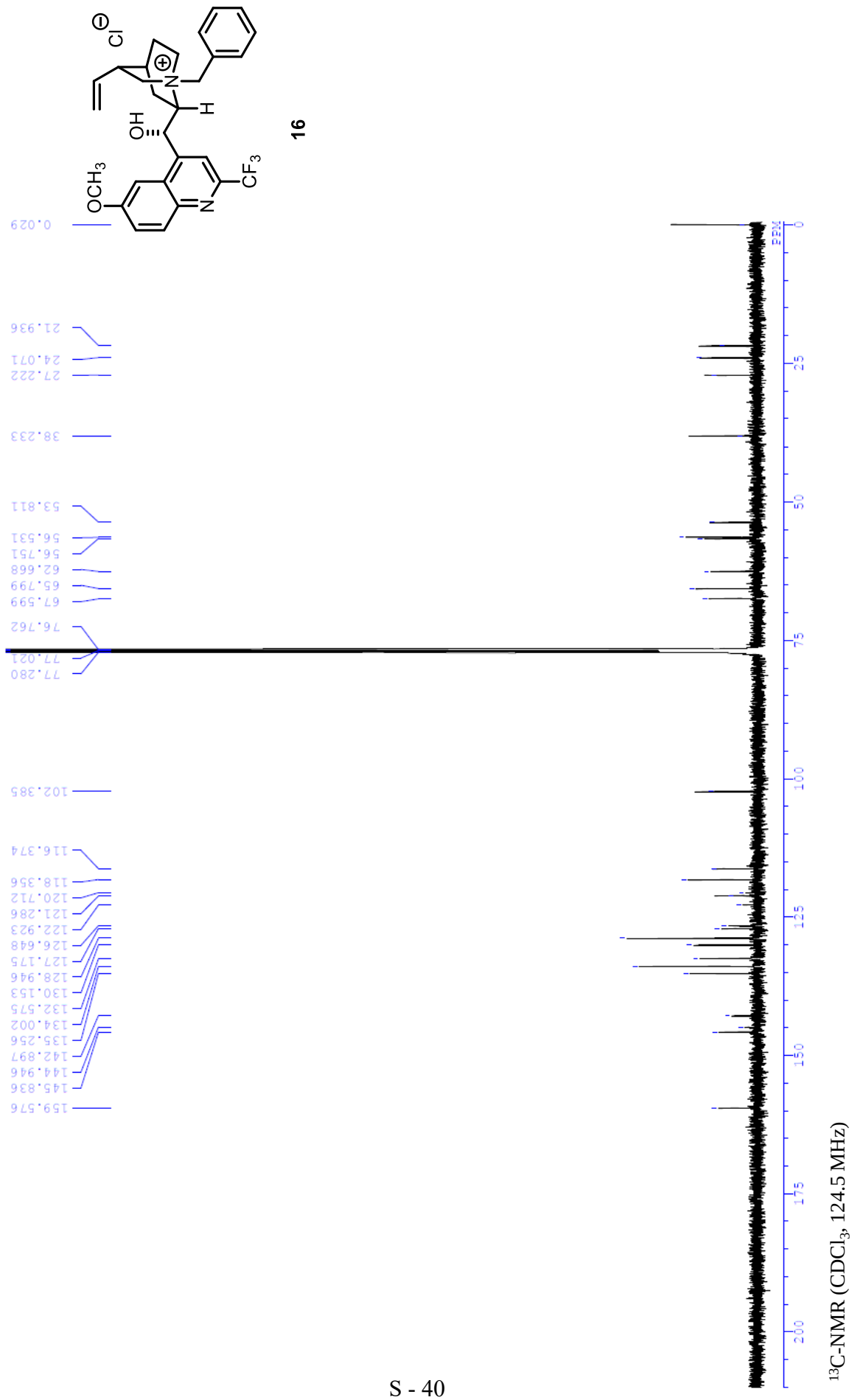
15

^{13}C-NMR (DMSO-d_2, 124.5 MHz)

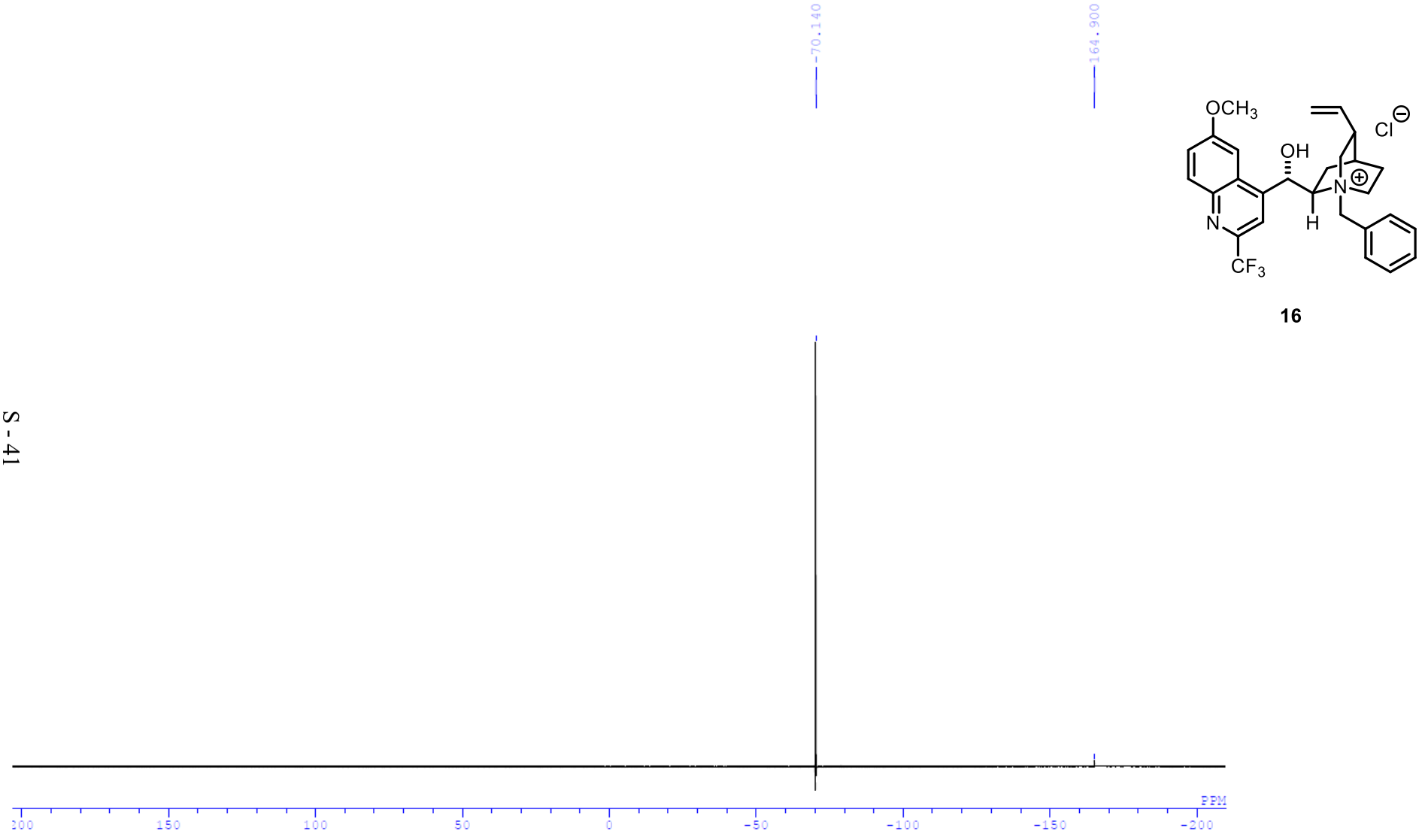


16

^{1}H-NMR ($CDCl_3$, 495.1 MHz)

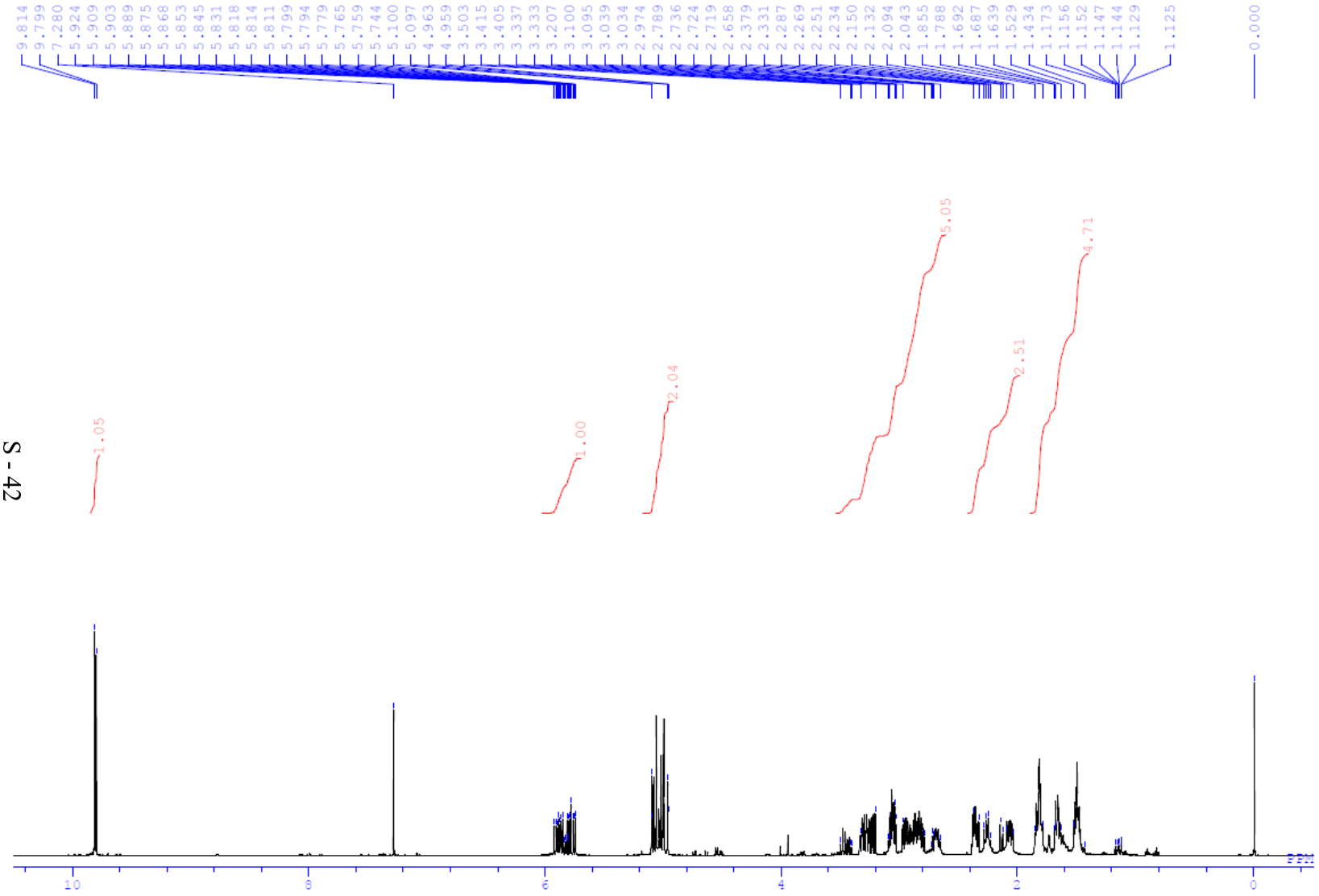


^{13}C-NMR ($CDCl_3$, 124.5 MHz)

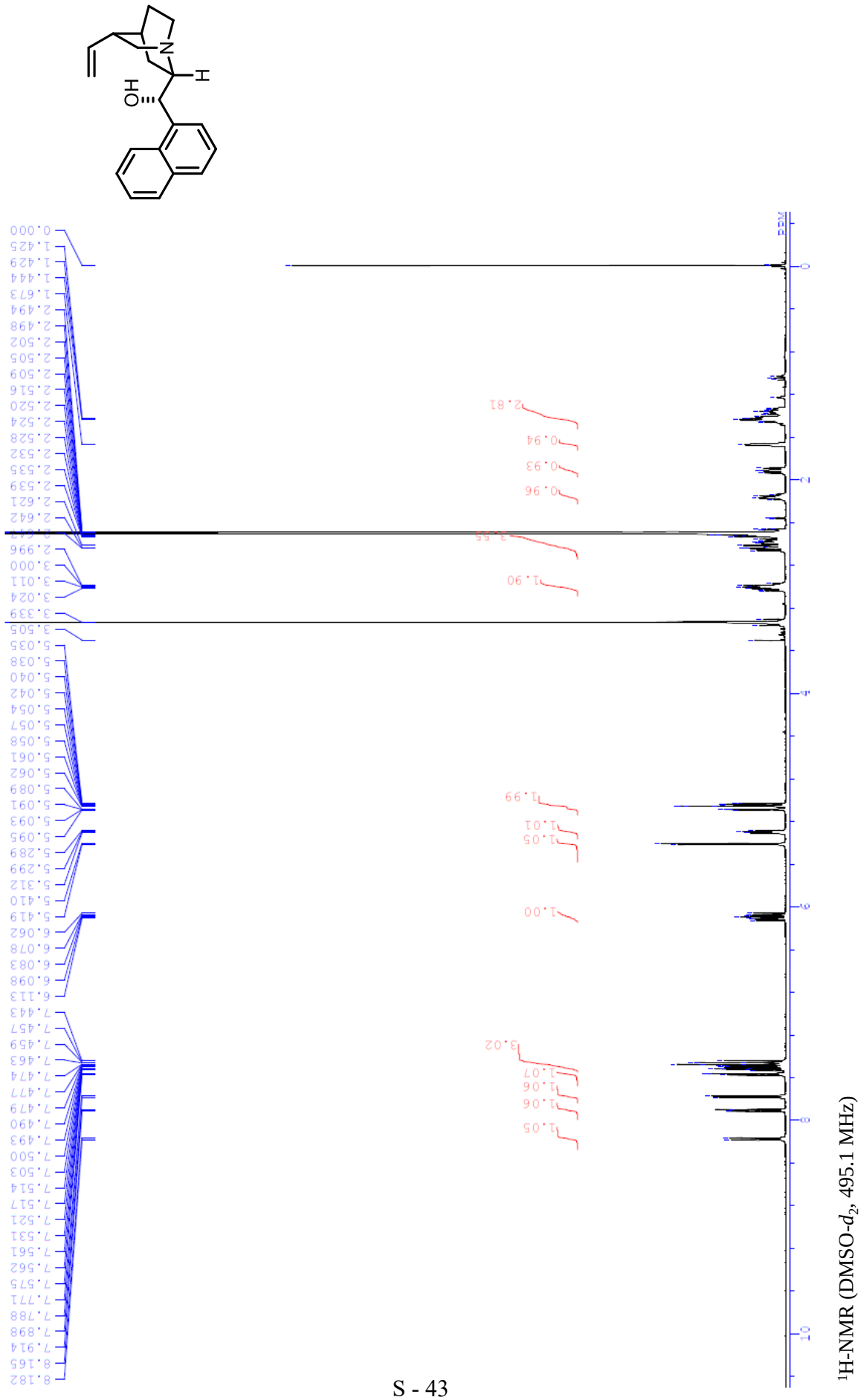


16

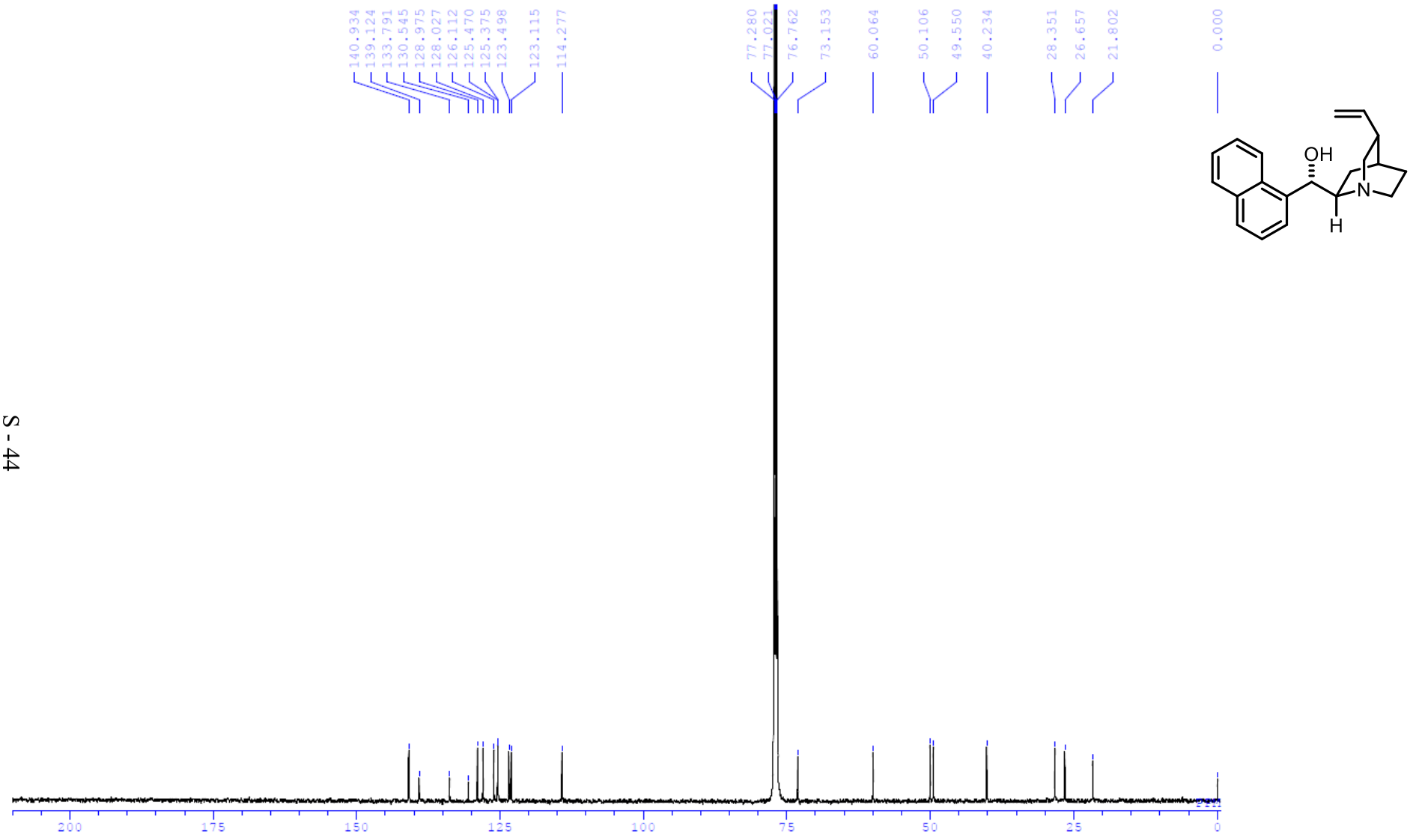
^{19}F-NMR ($CDCl_3$, 465.9 MHz)



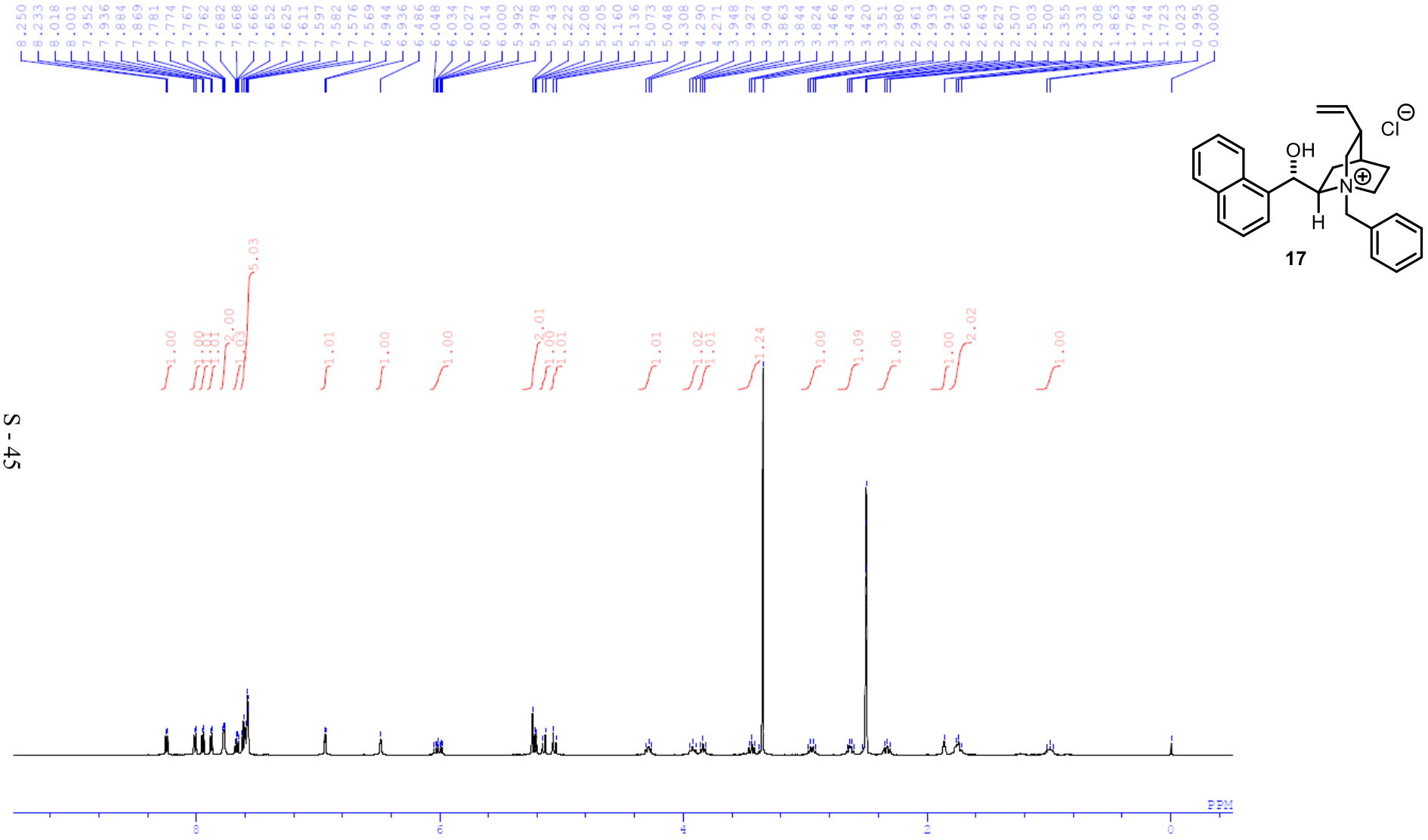
^{1}H-NMR ($CDCl_3$, 495.1 MHz)



^{1}H-NMR (DMSO-d_2, 495.1 MHz)

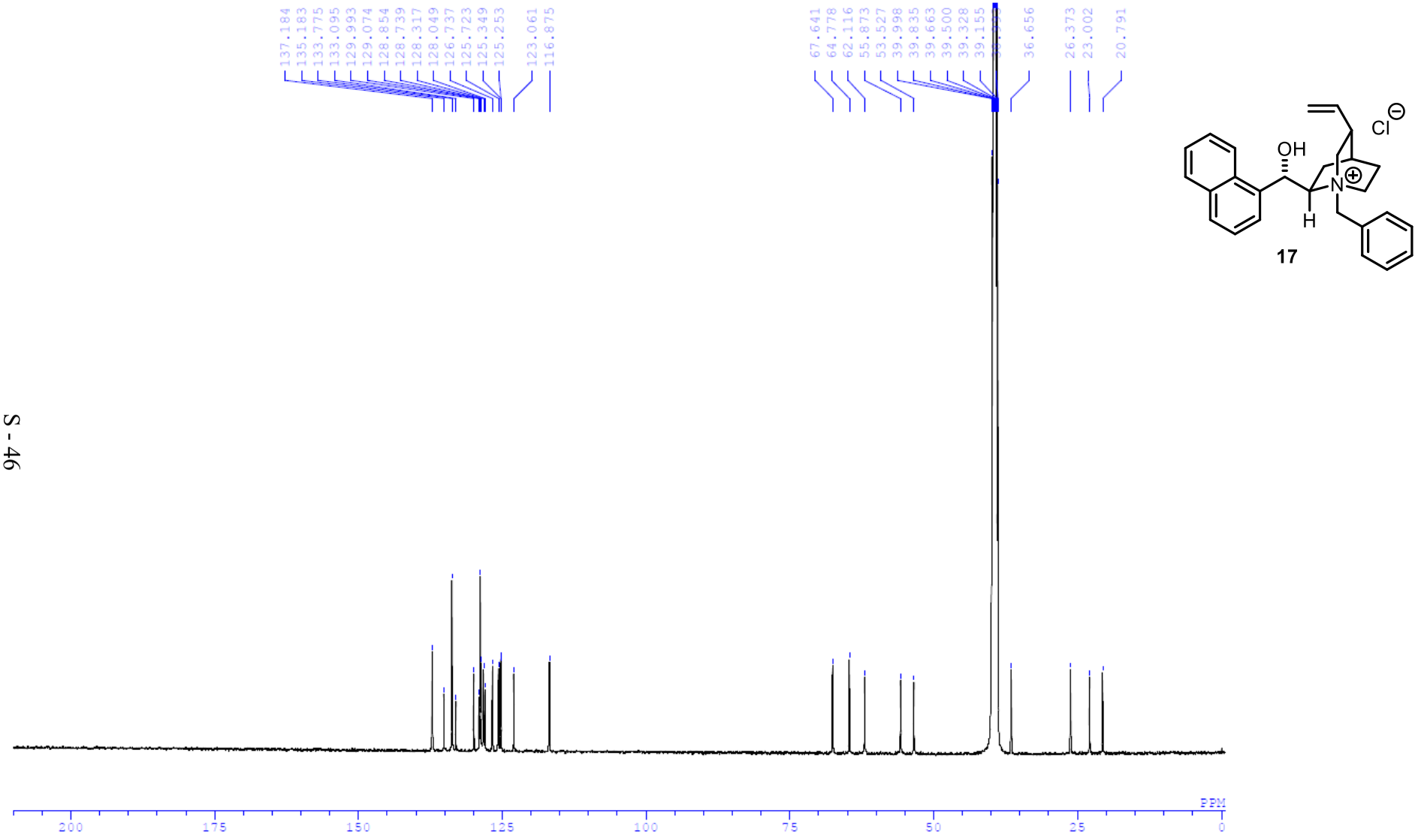


^{13}C-NMR ($CDCl_3$, 124.5 MHz)

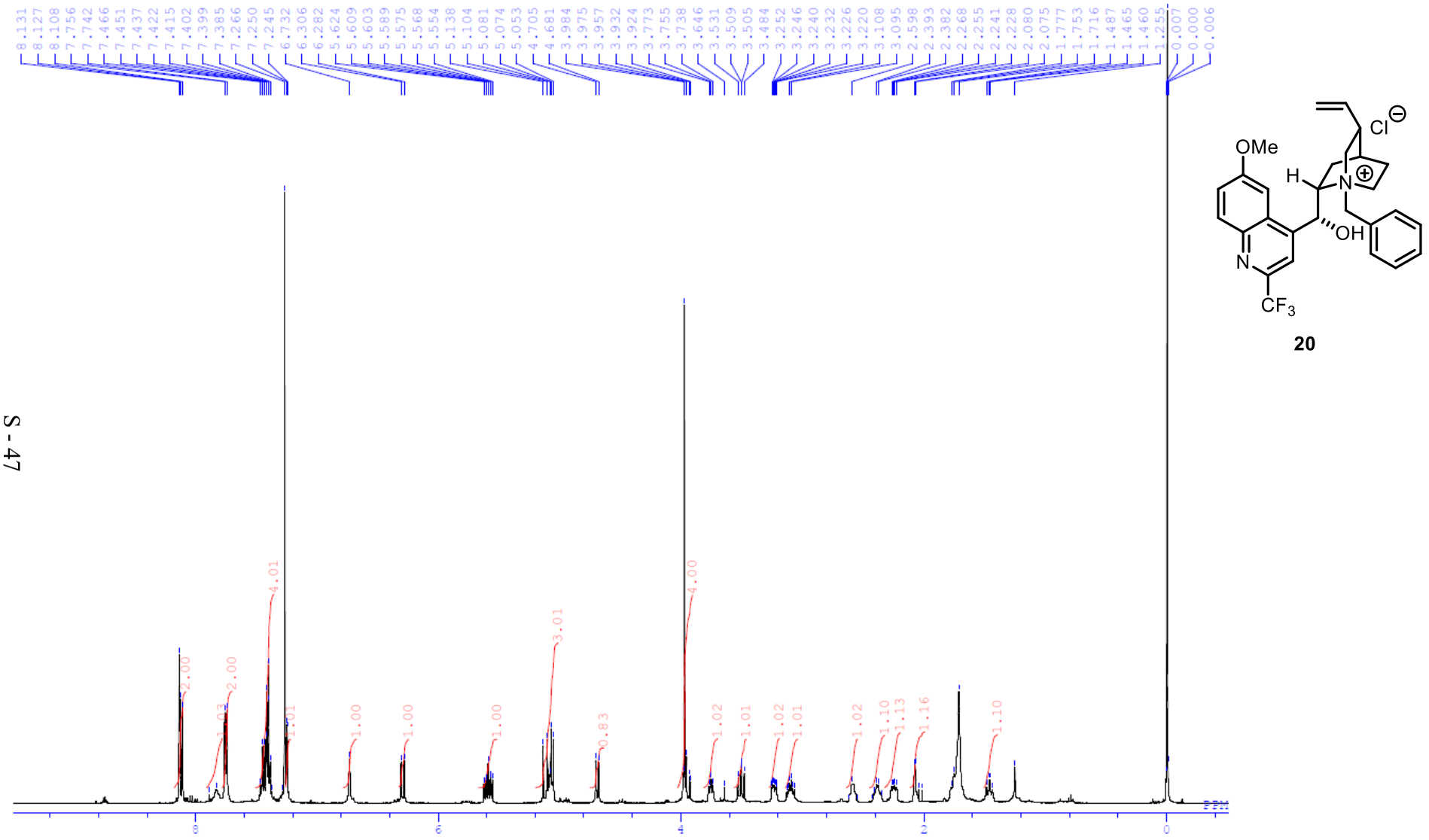


17

^{1}H-NMR (DMSO-d_2, 495.1 MHz)

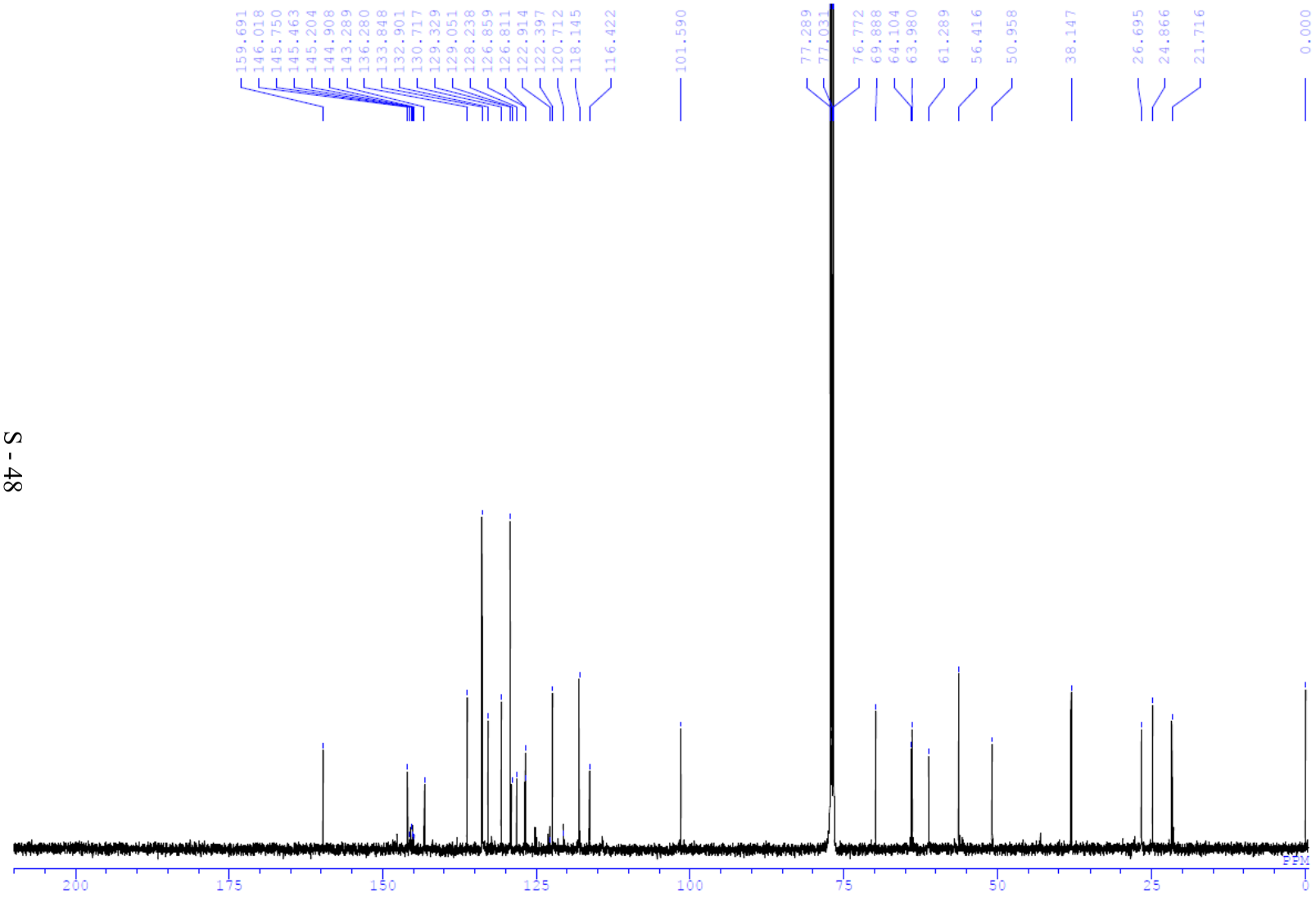


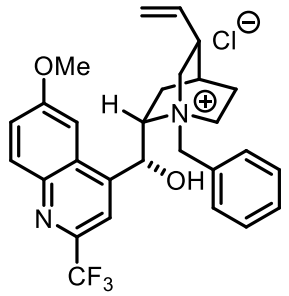
^{13}C-NMR (DMSO-d_2, 124.5 MHz)



20

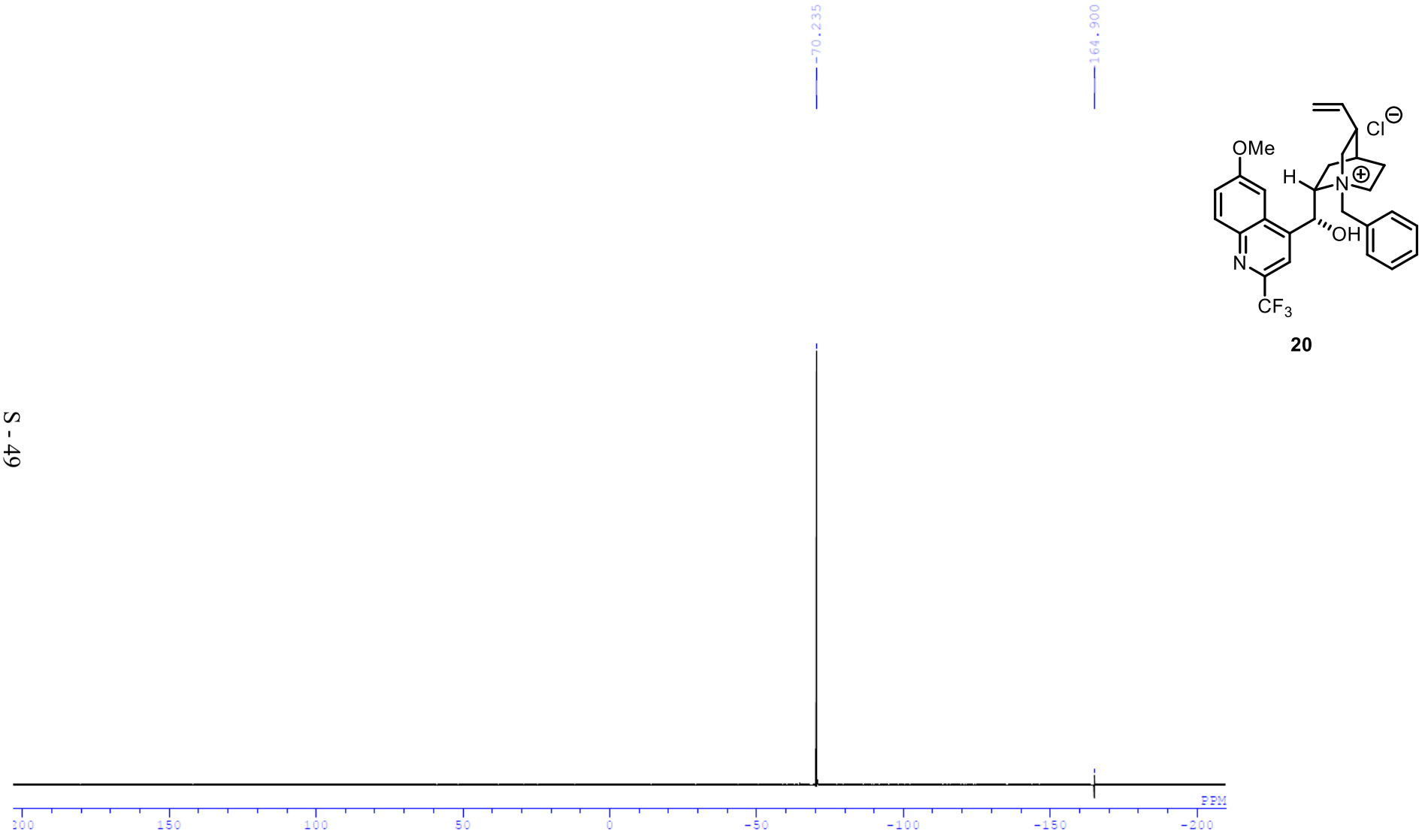
^{1}H-NMR ($CDCl_3$, 495.1 MHz)





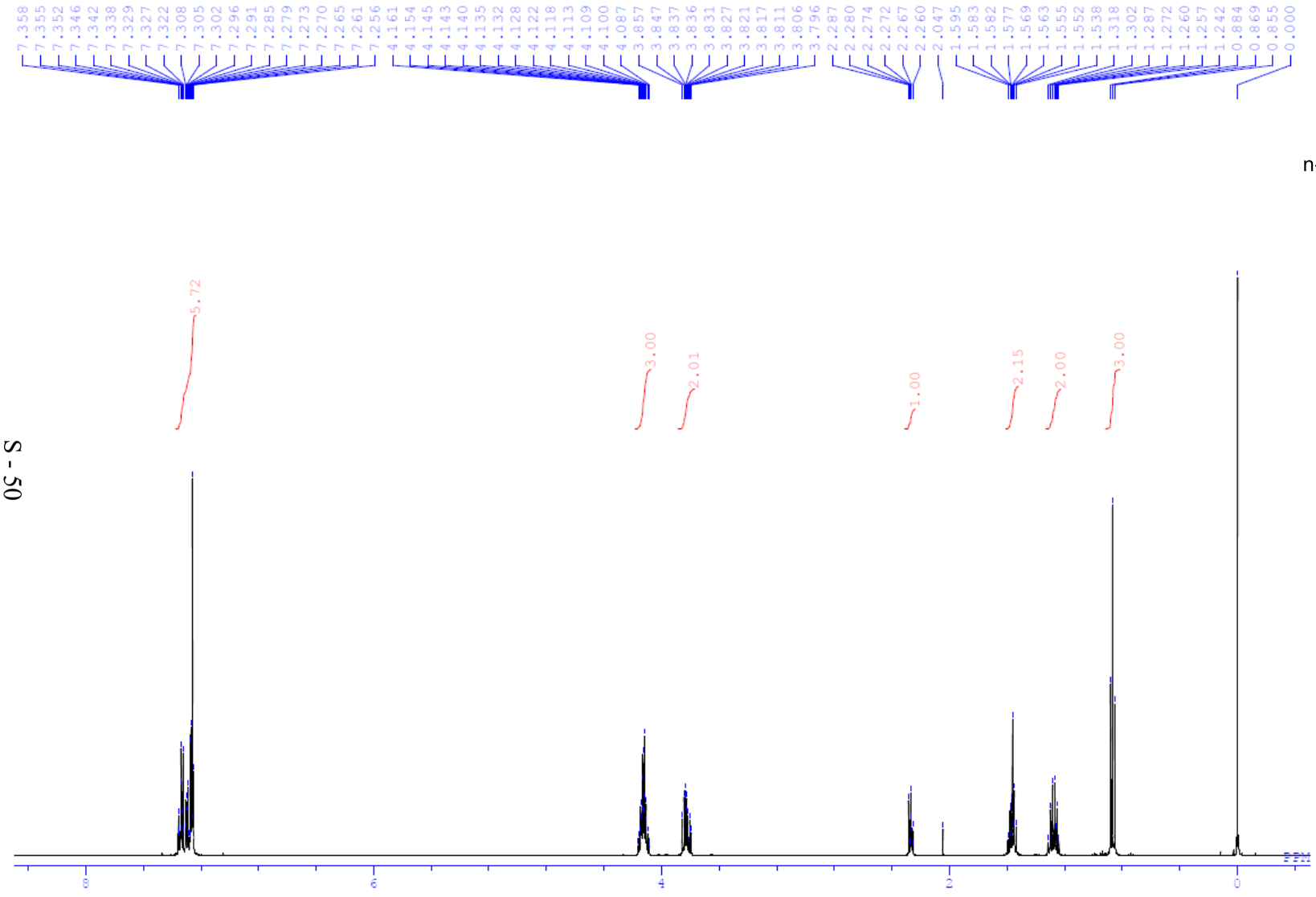
20

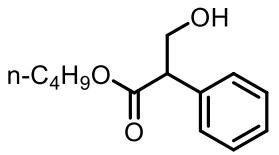
^{13}C-NMR ($CDCl_3$, 124.5 MHz)



20

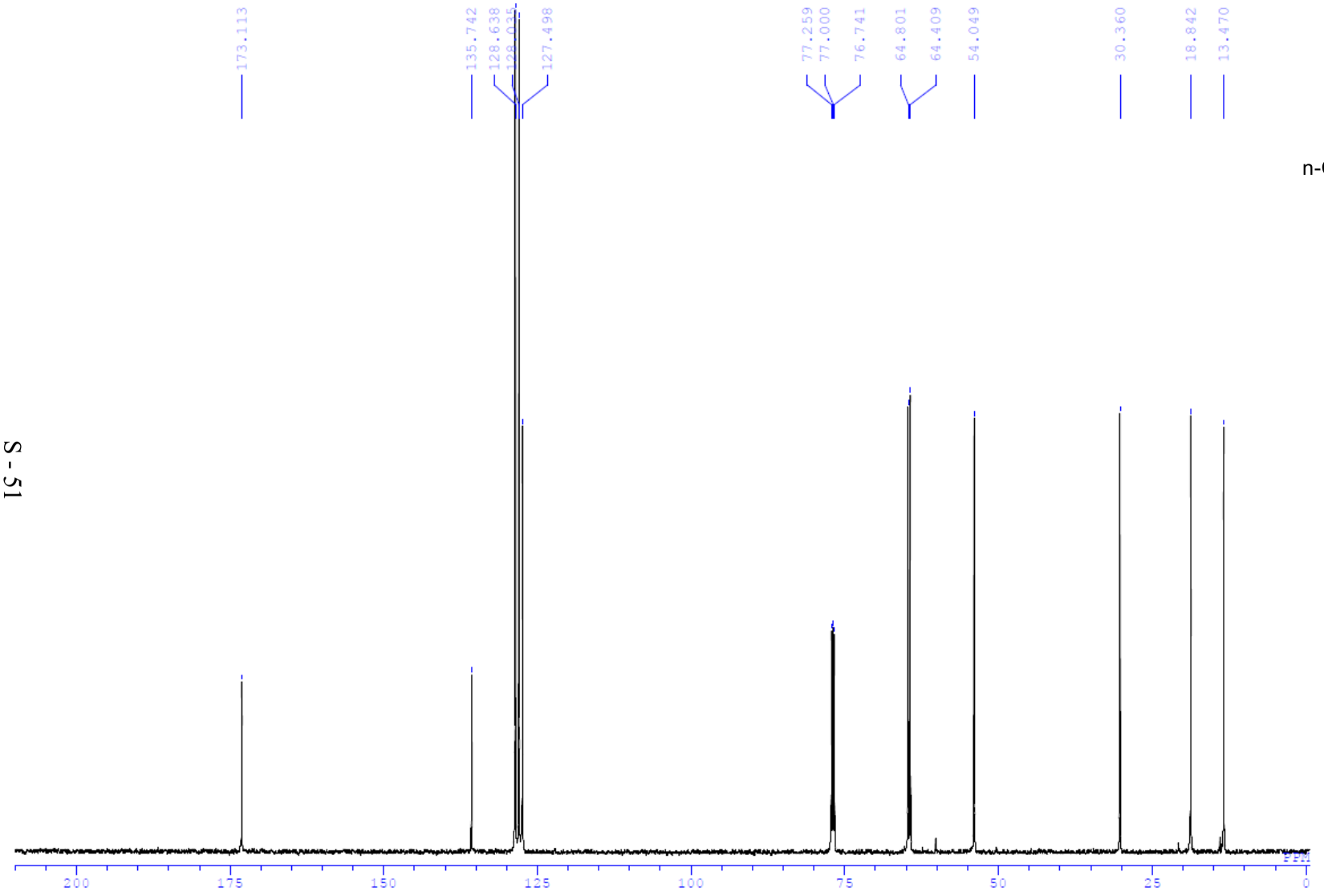
^{19}F-NMR ($CDCl_3$, 465.9 MHz)

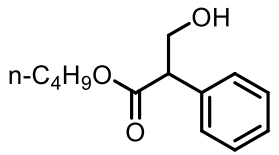




(*RS*)-**5**

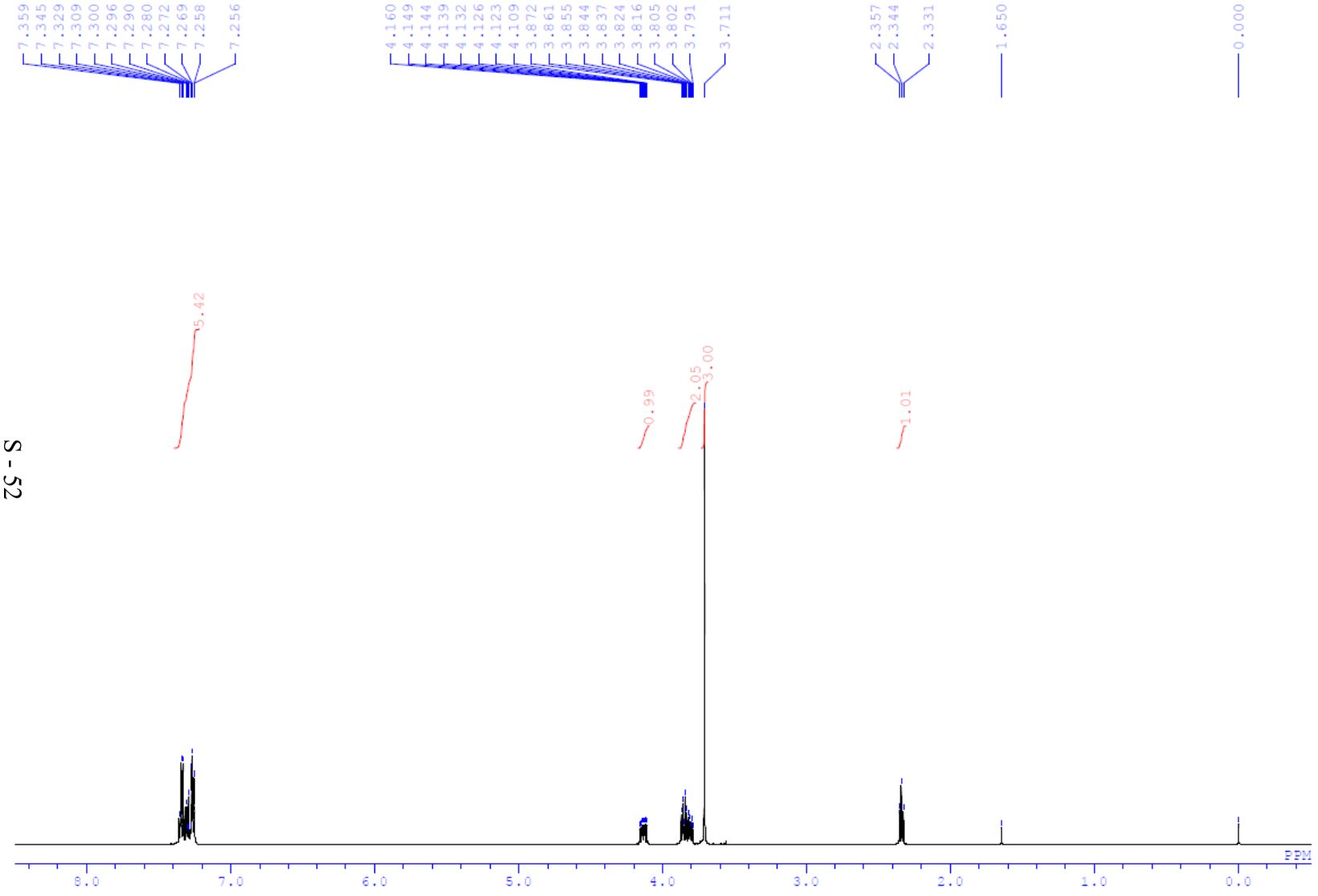
^{1}H-NMR ($CDCl_3$, 495.1 MHz)

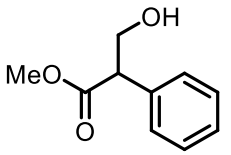




(*RS*)-**5**

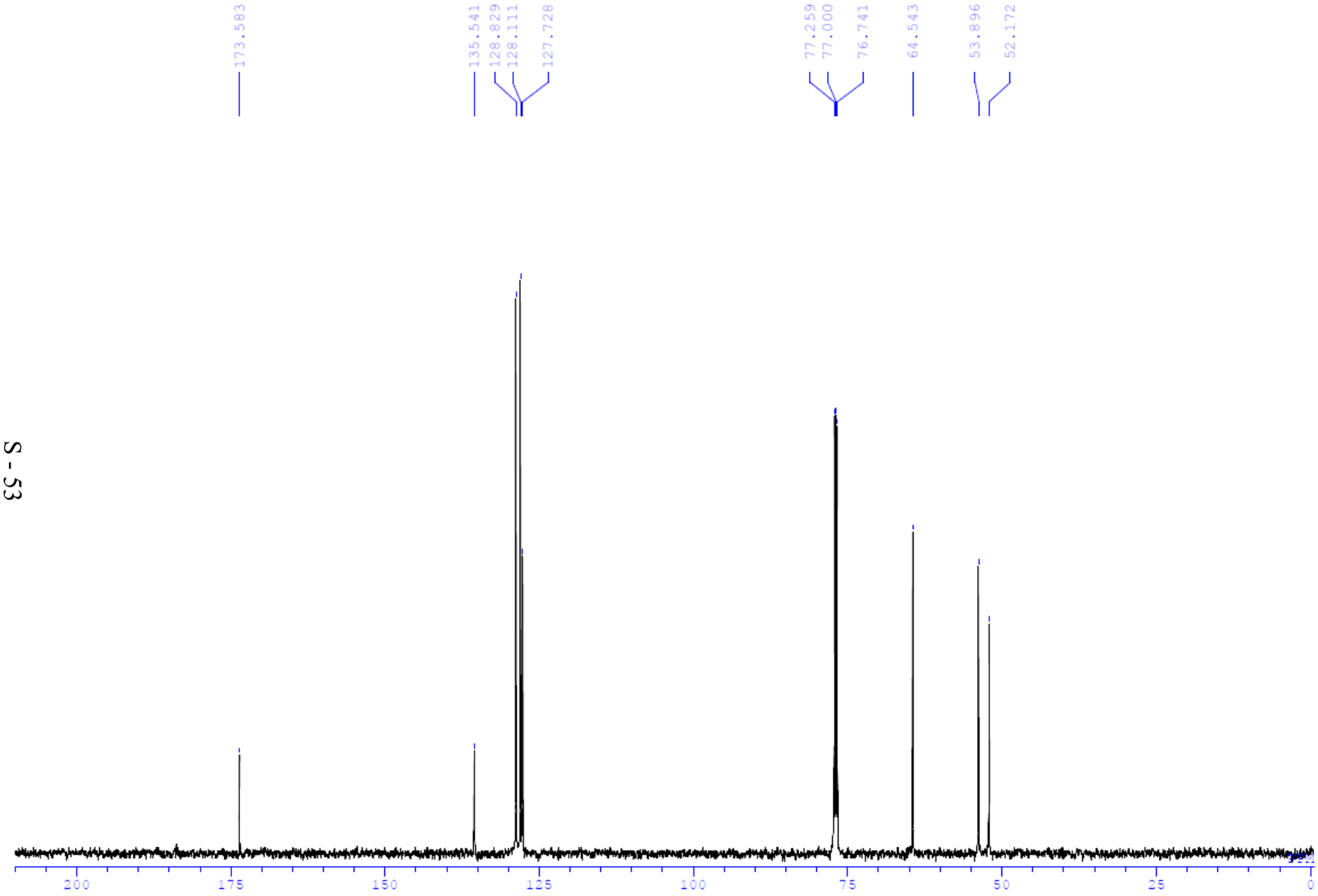
^{13}C-NMR ($CDCl_3$, 124.5 MHz)

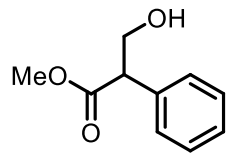




(*RS*)-**9**

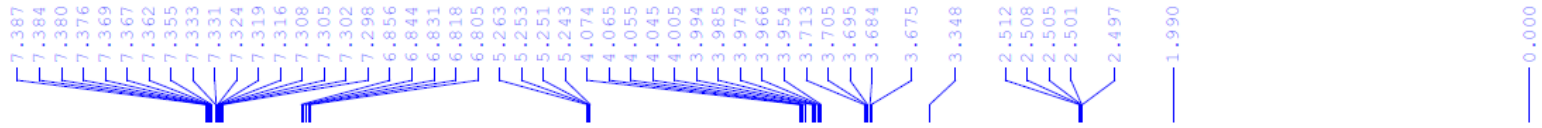
^{1}H-NMR ($CDCl_3$, 495.1 MHz)

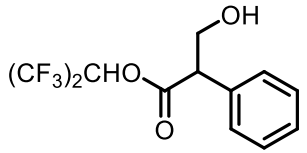




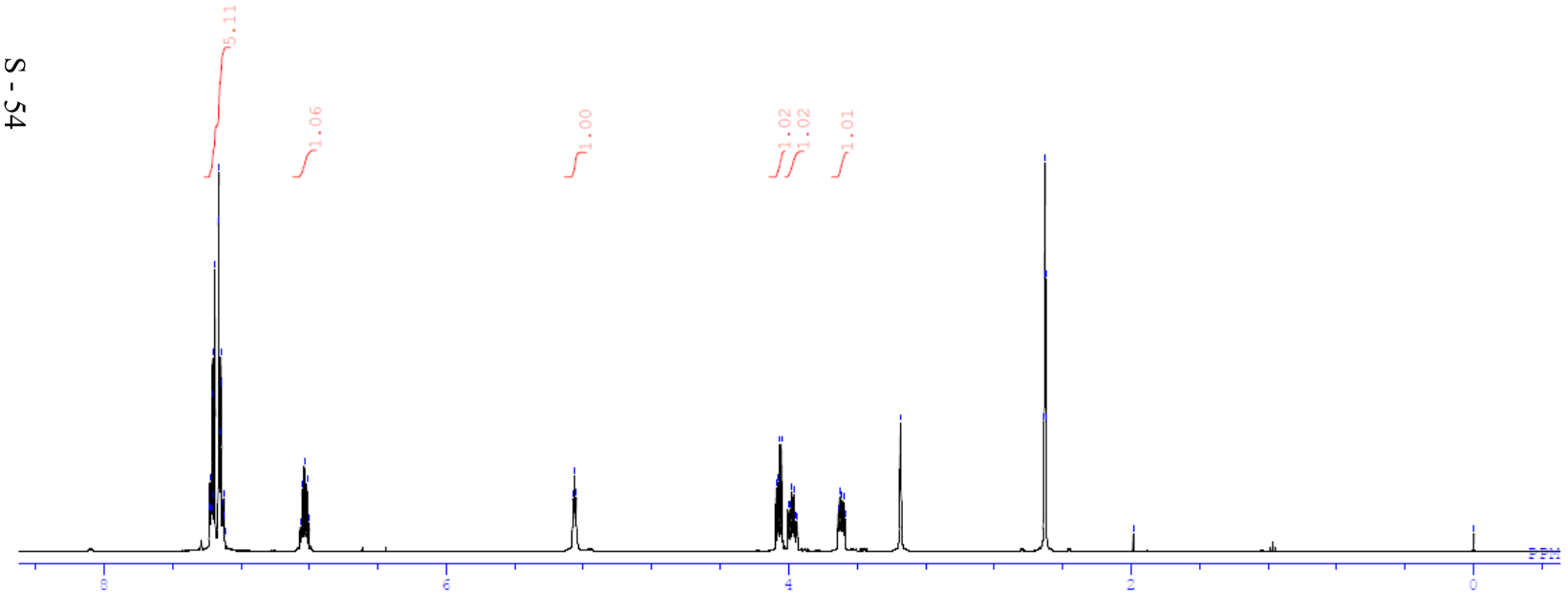
(*RS*)-**9**

^{13}C-NMR ($CDCl_3$, 124.5 MHz)

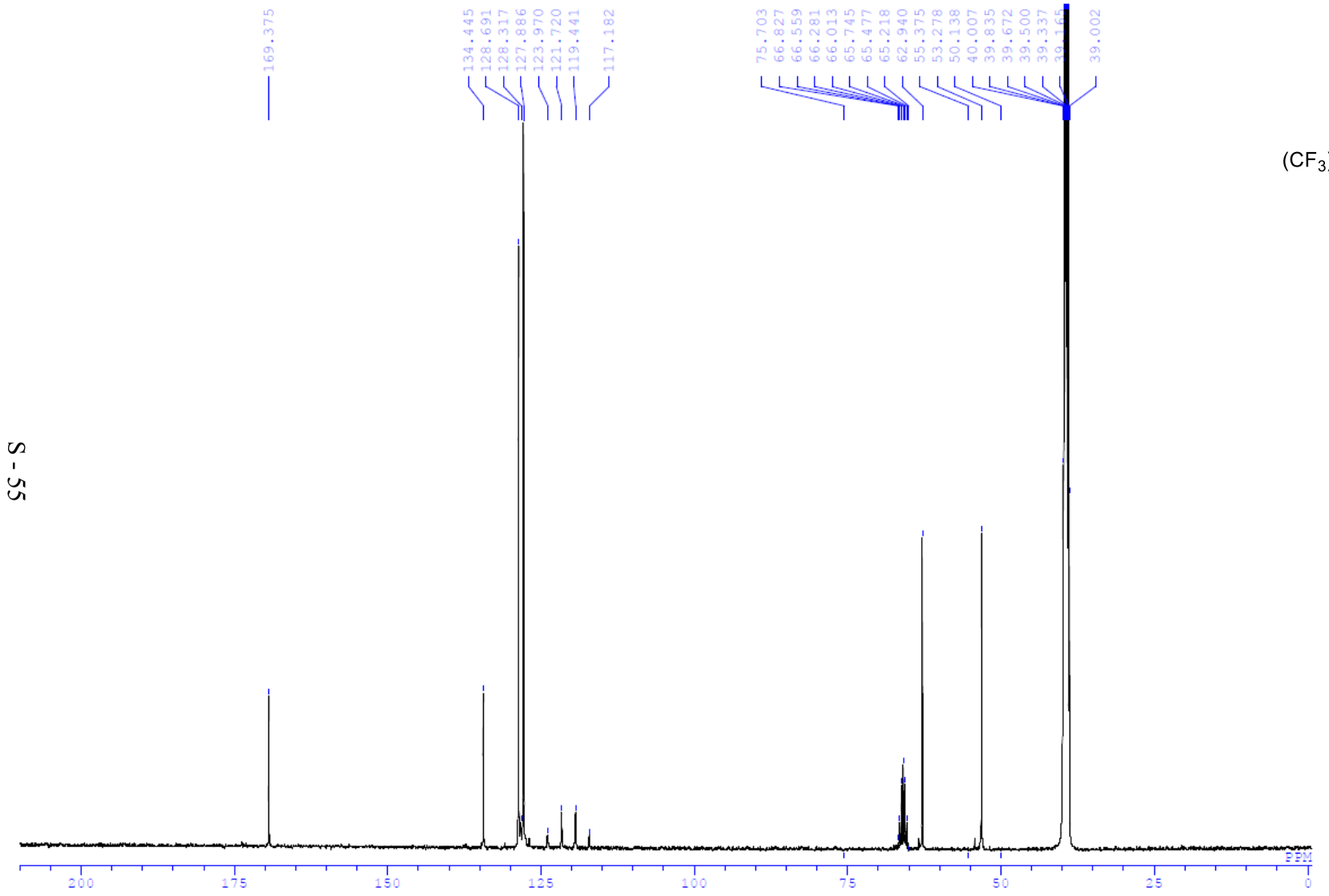


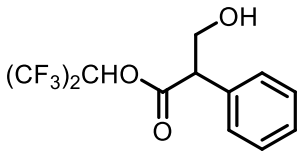


(*RS*)-**10**



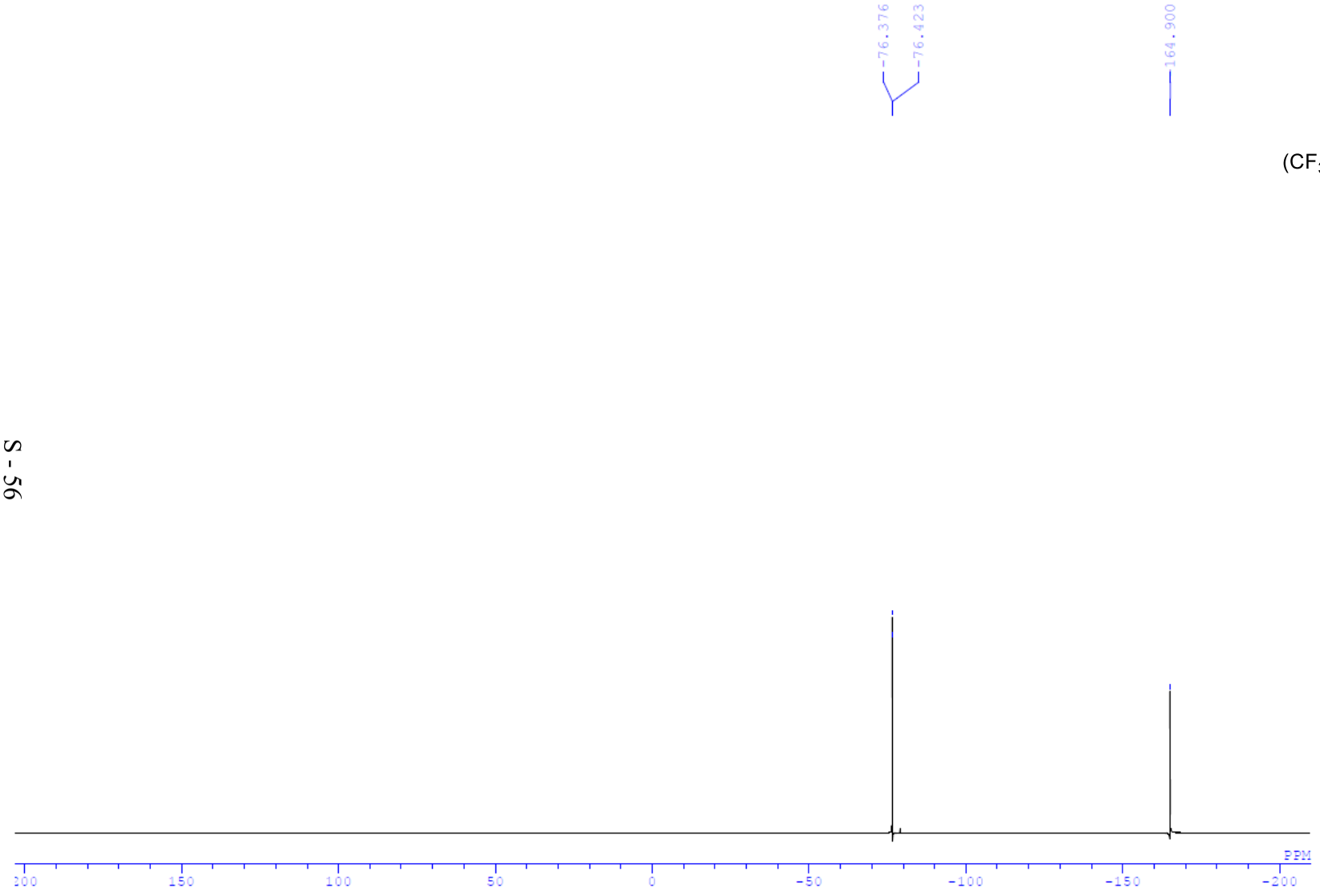
^{1}H-NMR (DMSO-d_6, 495.1 MHz)

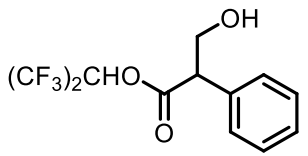




(*RS*)-**10**

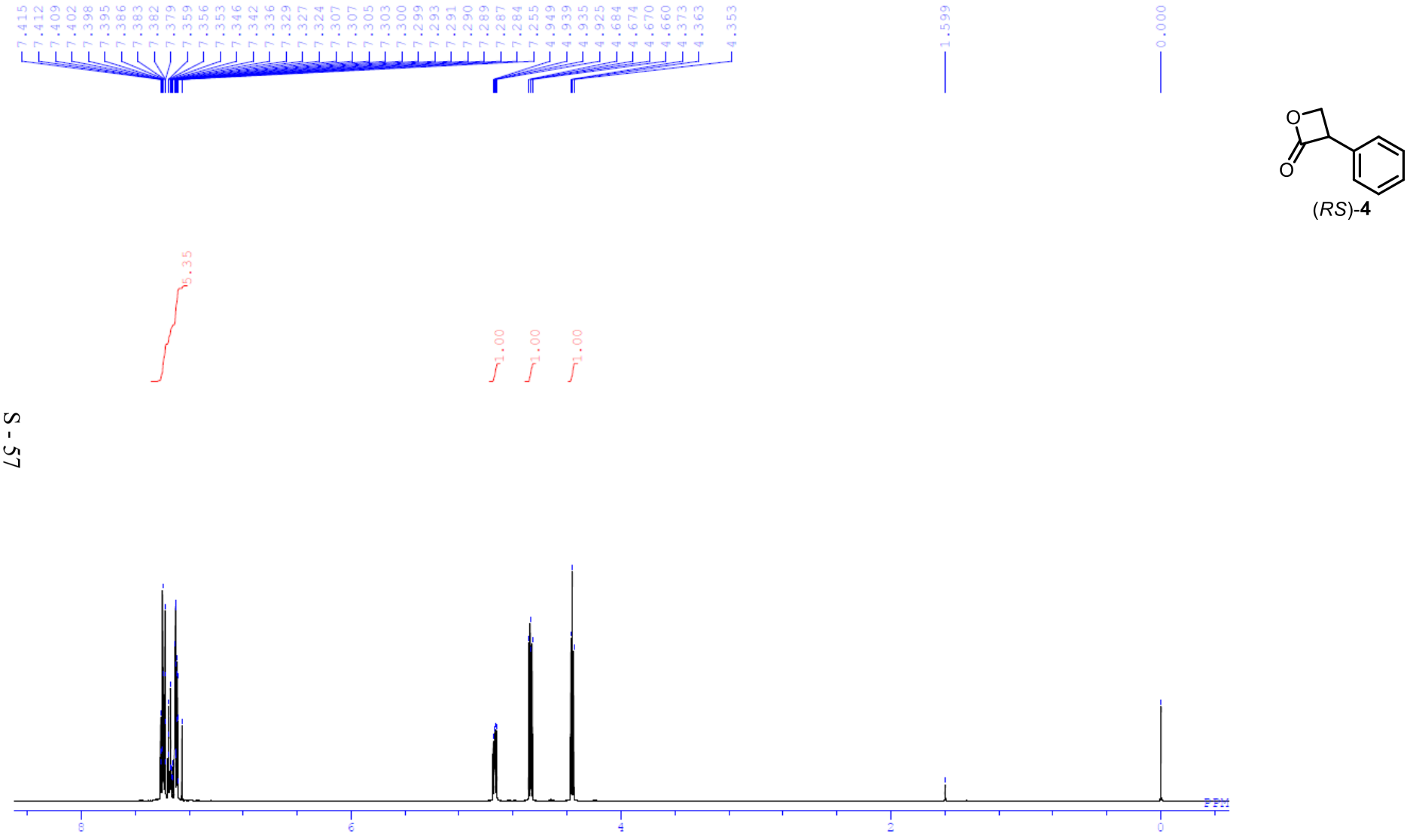
^{13}C-NMR (DMSO-d_6, 124.5 MHz)





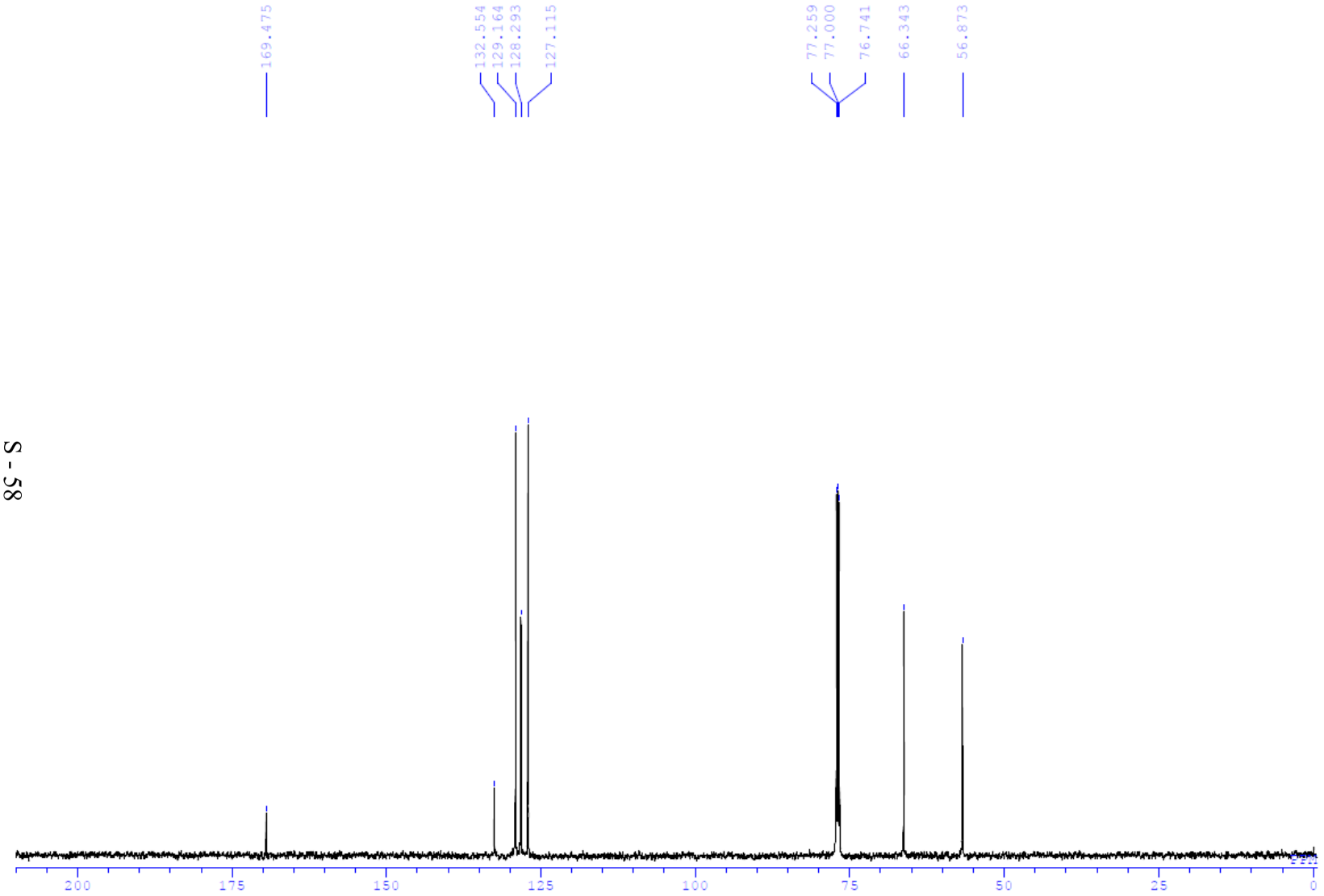
(*RS*)-**10**

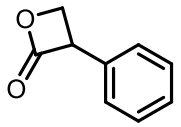
^{19}F-NMR ($CDCl_3$, 465.9 MHz)



(*RS*)-**4**

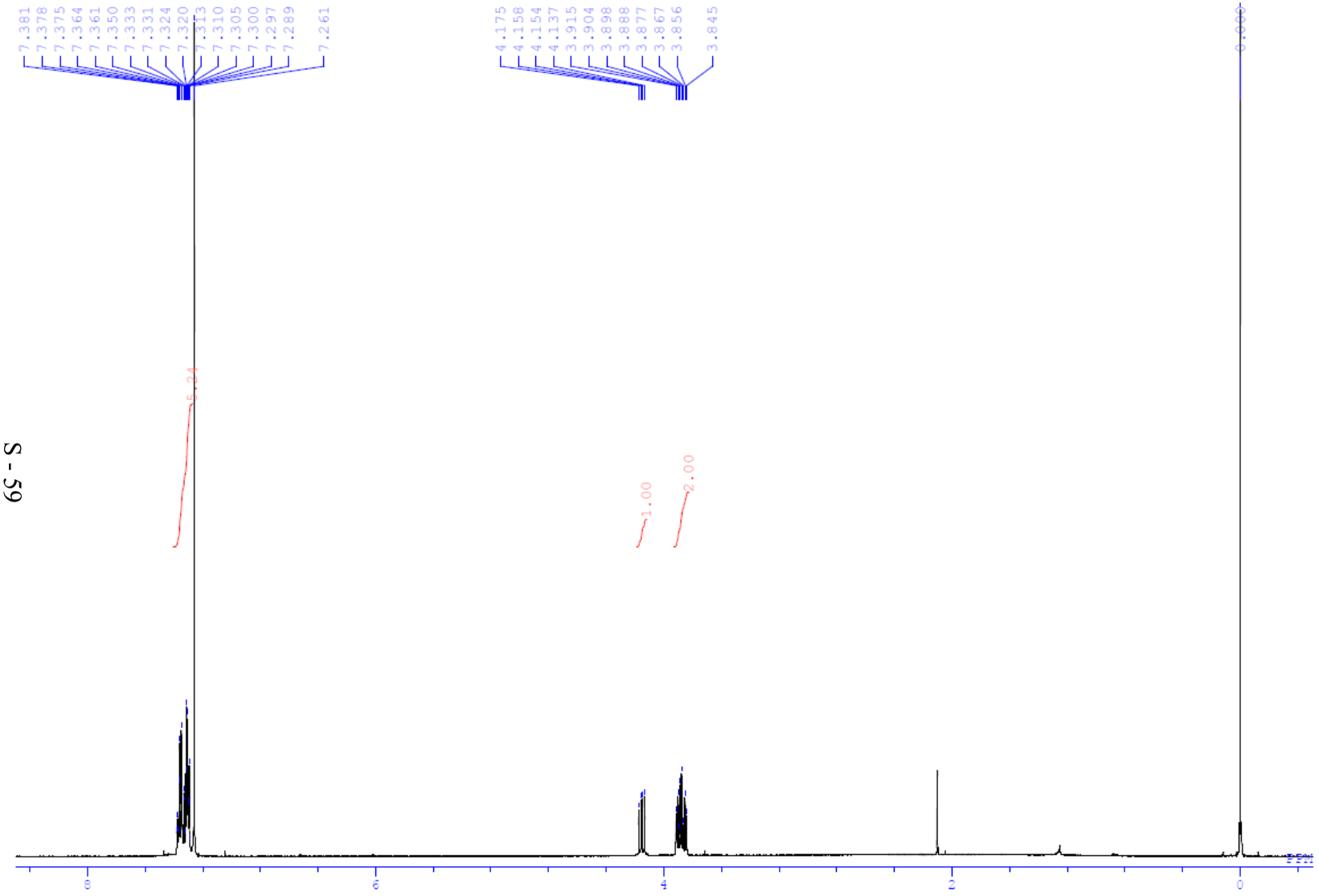
^{1}H-NMR ($CDCl_3$, 495.1 MHz)

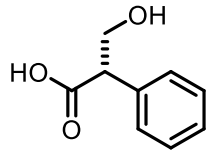




(*RS*)-**4**

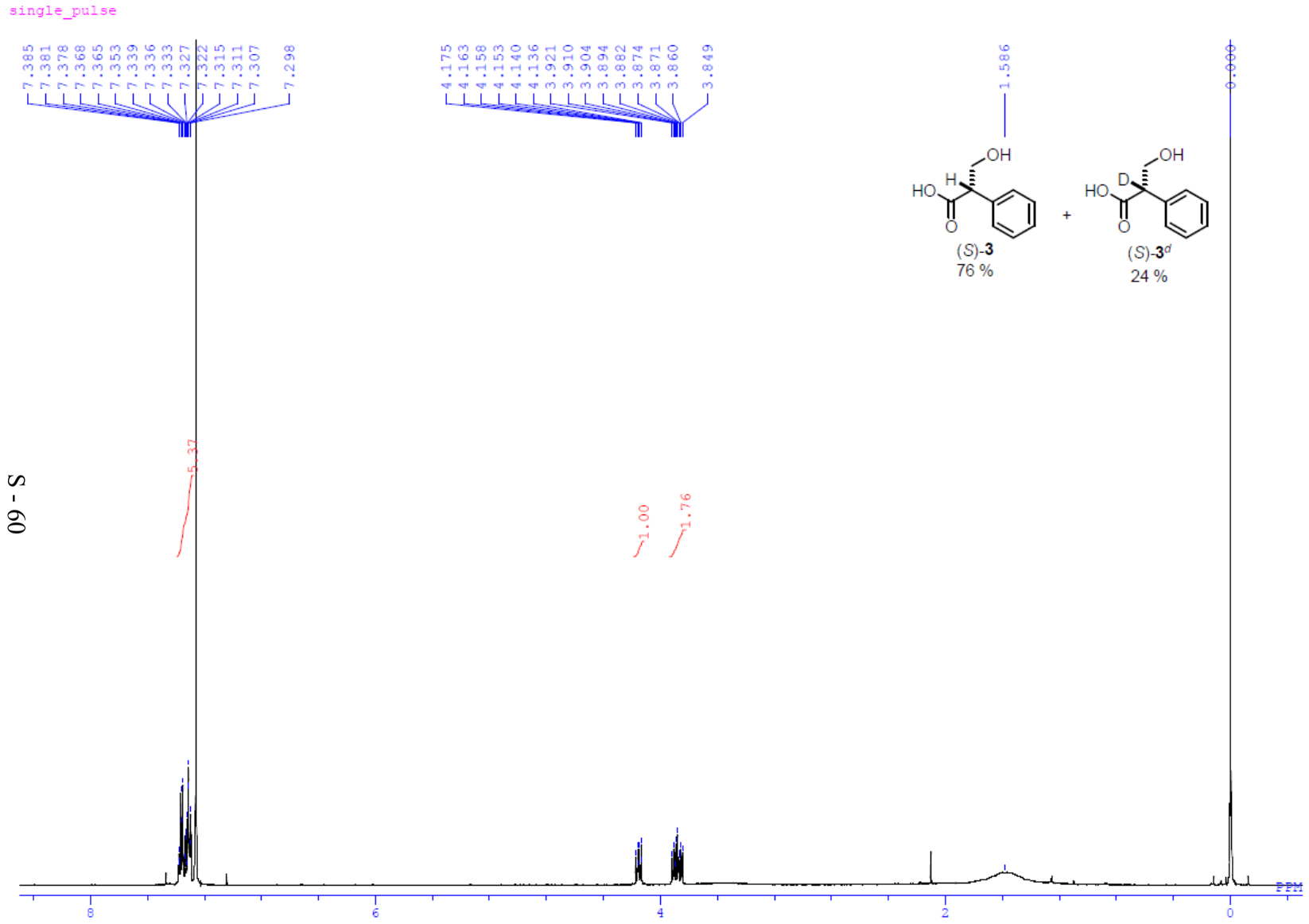
^{13}C-NMR ($CDCl_3$, 124.5 MHz)





(*S*)-**3**

^{1}H-NMR ($CDCl_3$, 495.1 MHz)



^{1}H-NMR ($CDCl_3$, 495.1 MHz)