Enantioselective Syntheses of (+)-Sertraline and (+)-Indatraline using Lithiation/Borylation – Protodeboronation Methodology

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Supporting Information

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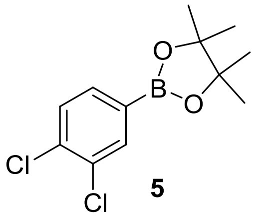
1. General experimental information

Reaction mixtures were stirred magnetically. Air- and moisture-sensitive reactions were carried out in flame-dried glassware under argon atmosphere using standard Schlenk manifold technique. All required fine chemicals were purchased from Aldrich, Acros or Frontier Scientific and used directly without purification. Anhydrous solvents were prepared using anhydrous solvent drying columns.[1] ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded in $CDCl_3$ at 301, 400 or 500 MHz on a Jeol Lambda 300, a Joel Delta 400, a Varian 400 or a Varian 500 Fourier transform spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referred to $CHCl_3$ (7.27 ppm). ^{1}H NMR coupling constants are reported in Hertz and refer to apparent multiplicities. Data are reported as follows: chemical shift, multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, etc.), integration and assignment. ^{13}C NMR spectra were recorded at 101 MHz on a Jeol Delta 400 or a Varian 400 instrument respectively. Chemical shifts (δ_C) are quoted in ppm referenced to $CHCl_3$ (77.0 ppm). ^{11}B NMR spectra were recorded at 96 MHz on a Jeol Lambda 300 with complete proton decoupling using $BF_3{\cdot}Et_2O$ (0.0 ppm) as an external standard. Mass spectra were recorded by the University of Bristol, School of Chemistry departmental mass spectrometry service or the EPSRC National Mass Spectrometry Service Centre at Swansea University using Electron Impact Ionisation (EI), Chemical Ionisation (CI) or Electrospray Ionisation (ESI) techniques for low- and high-resolution mass spectra. All infrared spectra were recorded on the neat compounds using a PerkinElmer Spectrum One FT-IR spectrometer, irradiating between 4000 cm^{-1} and 600 cm^{-1}. Analytical TLC was performed on aluminium backed silica plates (Merck, Silica Gel 60 F_{254}, 0.25 mm). Compounds were visualised by exposure to UV light or by staining the plates with 5% solution of phosphomolybdic acid ($H_3PMo_{12}O_{40}$) in EtOH followed by heating. Flash column chromatography was performed on silica gel (Aldrich, Silica Gel 60, 40–63 µm). All mixed solvent eluents are reported as v/v solutions. Optical rotations were obtained using a Bellingham + Stanley Ltd. ADP220 polarimeter. Melting points were measured with a Reichert hot stage apparatus and are uncorrected. Chiral HPLC separations were performed on an Agilent 1100 Series HPLC unit equipped with UV-VIS Diode-Array detector using Daicel Chiralpak IA or IB columns (4.6 × 250 mm, 5 µm) fitted with respective guards (4 × 10 mm). Supercritical fluid chromatography was performed on a Thar SFC investigator using a Viridis SFC 2-Ethylpyridine column (4.6 × 250 mm, 5 µm).

2. Detailed procedures and analytical data

2-(3,4-Dichlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (5)



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Based on a procedure by *Roush*,[2] 3,4-dichlorophenylboronic acid (9.54 g, 50.0 mmol, 1.0 equiv) and pinacol (5.91 g, 50.0 mmol, 1.0 equiv) were dissolved in anhydrous diethyl ether (75 mL). The mixture was stirred at ambient temperature for 17 h. $MgSO_4$ (14.3 g, 119 mmol, 2.4 equiv) was added and the reaction mixture was stirred for additional 2 h at room temperature. The ethereal solution was filtered through a plug of anhydrous $MgSO_4$ and the solids were thoroughly washed with diethyl ether. The combined filtrates were concentrated *in vacuo* and dried under high vacuum to give the boronic ester **5** (13.65 g, 50.0 mmol, 100%) as a white solid, which showed no impurities in its NMR spectra.

mp 35−36 °C (diethyl ether).

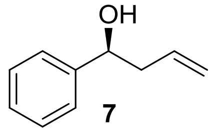
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.87 (d, *J* = 1.4 Hz, 1 H, H_{Ar}), 7.61 (dd, *J* = 8.0, 1.4 Hz, 1 H, H_{Ar}), 7.45 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 1.35 (s, 12 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 136.5 (CH), 135.5 (C), 133.7 (CH), 132.2 (C), 130.0 (CH), 84.3 ($OC(CH_3)_2$), 24.8 (CH_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ_B ppm 29.3 (br. s).

All spectral data match those reported in literature.[3]

(*S*)-1-Phenylbut-3-en-1-ol (7)



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Enzymatic Resolution

Based on a protocol by *Jones*,[4] allyl magnesium bromide solution (22.5 mL, 1.0 M in diethyl ether, 22.5 mmol, 1.5 equiv) was added slowly to a stirred solution of benzaldehyde (1.59 g, 15.0 mmol, 1.0 equiv) in anhydrous diethyl ether (10 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 20 h. Then, an aq. NH_4Cl solution (2%, 100 mL) was added at 0 °C and the mixture was stirred for another 2 h at ambient temperature. The solution was extracted with diethyl ether (4 × 80 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to give racemic alcohol **7** (2.22 g, 15.0 mmol, >99%) as a pale yellow oil, which was used without further purification. According to a procedure by *Kumar*,[5] amino lipase PS (815 mg) was added to a solution of racemic alcohol **7** (2.22 g, 15.0 mmol, 1.0 equiv) in vinyl acetate (50 mL). The mixture was stirred for 70 h at room temperature. The reaction was then filtered, the solids were thoroughly washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (SiO_2, pentane/EtOAc 9:1) to obtain (*S*)-alcohol **7** (889 mg, 6.0 mmol, 40%) as a colourless oil and (*R*)-1-phenylbut-3-enyl acetate (350 mg, 1.8 mmol, 44%) as a colourless oil.

R_f (pentane/EtOAc 9:1) 0.15.

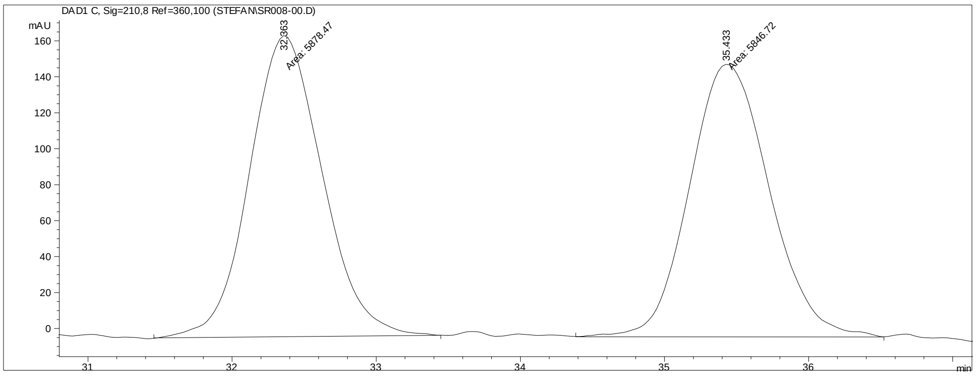
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.40–7.33 (m, 4 H, H_{Ar}), 7.33–7.27 (m, 1 H, H_{Ar}), 5.83 (dddd, *J* = 17.5, 10.3, 7.6, 6.8 Hz, 1 H, C*H*CH$_2$), 5.22–5.13 (m, 2 H, CHC*H$_2$*), 4.75 (ddd, *J* = 7.8, 5.1, 2.8 Hz, 1 H, C*H*OH), 2.60–2.46 (m, 2 H, CH_2), 2.06 (br. s, 1 H, OH).

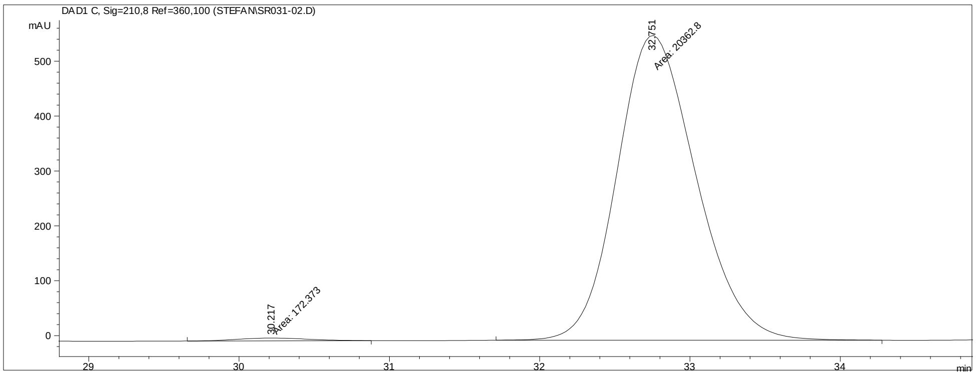
^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 143.8 (C), 134.4 (*C*HCH$_2$), 128.4 (CH), 127.5 (CH), 125.8 (CH), 118.4 (CH*C*H$_2$), 73.3 (CHOH), 43.8 (CH_2).

$[\alpha]_D^{24}$ –69.0 (*c* 1.04, $CHCl_3$, for 98% ee). Lit. $[\alpha]_D^{25}$ –61.2 (*c* 1.05, $CHCl_3$, for 92% ee).[6]

^{1}H and ^{13}C NMR spectra are consistent with the known product.[7]

HPLC separation conditions: Chiralpak IB column with guard, 1.0% *i*PrOH in hexane, flow rate 0.5 mL/min, 20 °C; t_R 30.2 min for (*R*)-enantiomer (minor) and t_R 32.8 min for (*S*)-enantiomer (major).
e.r. = 99.0:1.0.

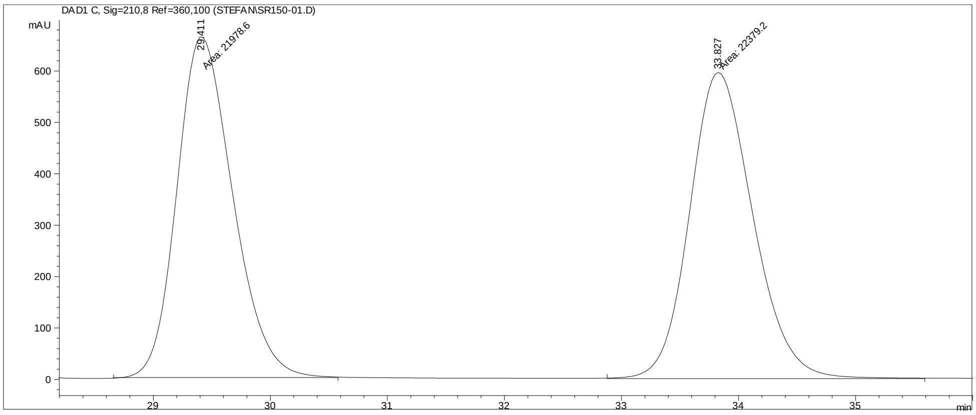


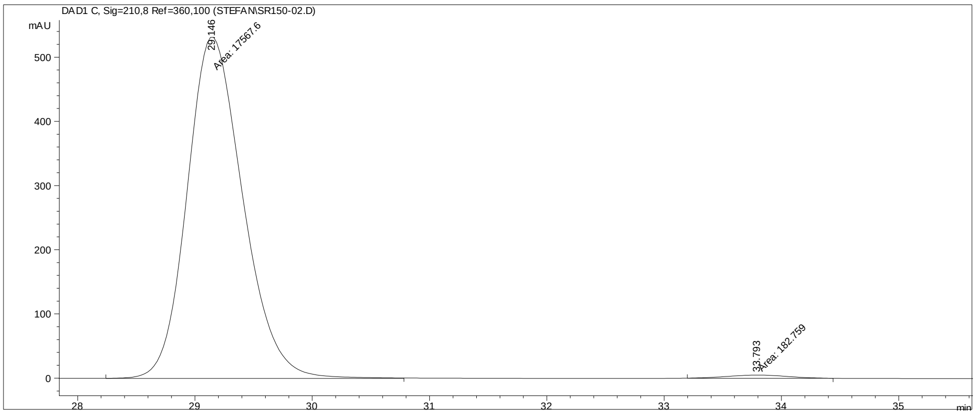


Asymmetric Allylation

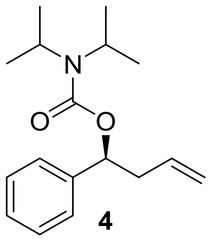
The antipode of the (*S*)-alcohol **7** was prepared according to a procedure by *Leighton*.[8]

HPLC separation conditions: Chiralpak IB column with guard, 1.0% *i*PrOH in hexane, flow rate 0.5 mL/min, 20 °C; t_R 29.1 min for (*R*)-enantiomer (major) and t_R 33.8 min for (*S*)-enantiomer (minor).
e.r. = 99.0:1.0.





(*S*)-1-Phenylbut-3-enyl diisopropylcarbamate (4)



4

To a suspension of sodium hydride (60% dispersion in mineral oil, 1.87 g, 47.0 mmol, 1.5 equiv) in anhydrous THF (130 mL) (*S*)-alcohol **7** (4.63 g, 31.3 mmol, 1.0 equiv) was added dropwise and the mixture was stirred for 75 min at room temperature. A solution of diisopropylcarbamoyl chloride (6.14 g, 37.5 mmol, 1.2 equiv) in anhydrous THF (20 mL) was added and the reaction mixture was heated under reflux for 24 h. The solvent was removed *in vacuo* and the residue was portioned between water (80 mL) and diethyl ether (80 mL). The phases were separated and the aqueous layer was re-extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography

(SiO_2, pentane/EtOAc 6:1) to obtain 7.11 g (*S*)-carbamate **4** (25.8 mmol, 83% or 99% BRSM) as a pale yellow oil. 740 mg of alcohol **7** (5.0 mmol, 16%) could be reisolated.

R_f (pentane/EtOAc 6:1) 0.43.

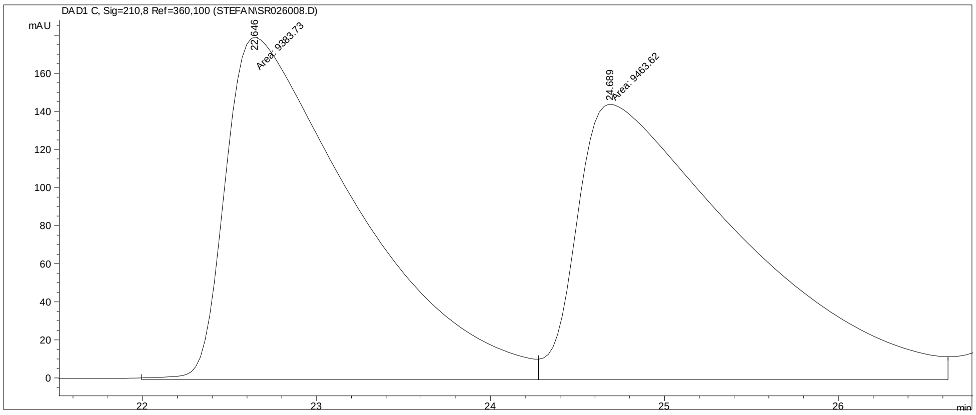
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.35–7.25 (m, 5 H, H_{Ar}), 5.79 (dd, *J* = 7.2, 6.1 Hz, 1 H, CHOCb), 5.78–5.68 (m, 1 H, C*H*CH_2), 5.10–5.01 (m, 2 H, CHC*H*$_2$), 4.05 (br. s, 1 H, C*H*$(CH_3)_2$), 3.84 (br. s, 1 H, C*H*$(CH_3)_2$), 2.74–2.55 (m, 2 H, CH_2), 1.22 (br. s, 12 H, CH_3).

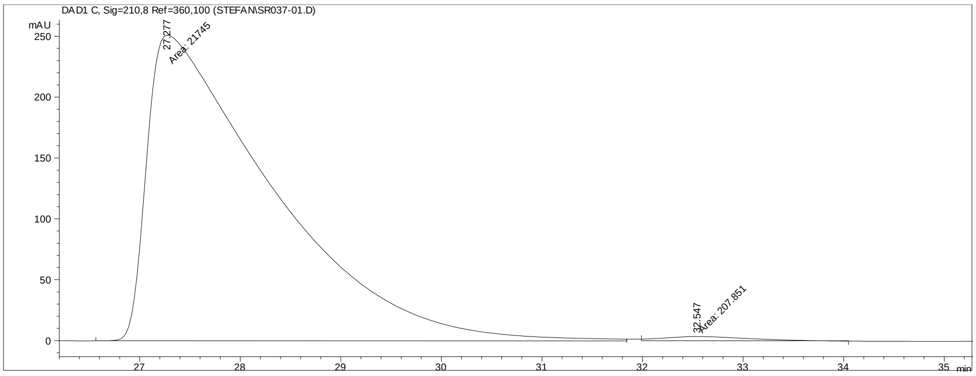
^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 154.9 (NCO), 141.1 (C), 133.8 (*C*HCH_2), 128.3 (CH), 127.5 (CH), 126.5 (CH), 117.7 (CH*C*H$_2$), 75.8 (CH), 45.6 (br., *C*H$(CH_3)_2$), 41.4 (CH_2), 21.1 (br., CH_3).

$[\alpha]_D^{25}$ −3.2 (*c* 1.56, $CHCl_3$, for 98% ee). Lit. $[\alpha]_D^{20}$ −3.3 (*c* 1.56, $CHCl_3$, for 90% ee).[9a]

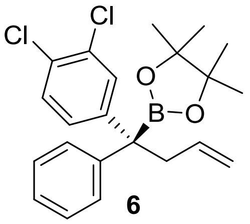
The analytical data are consistent with the known product.[9b]

HPLC separation conditions: Chiralpak IB column with guard, 0.1% *i*PrOH in hexane, flow rate 0.5 mL/min, 0 °C; t_R 27.3 min for (*S*)-enantiomer (major) and t_R 32.5 min for (*R*)-enantiomer (minor).
e.r. = 99.0:1.0.





(R)-2-(1-(3,4-Dichlorophenyl)-1-phenylbut-3-enyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (6)



6

(S)-Carbamate **4** (826 mg, 3.00 mmol, 1.0 equiv) was dissolved in anhydrous diethyl ether (10 mL) and chilled to −78 °C. *sec*-Butyllithium (3.0 mL, 1.3 M solution in cyclohexane/hexane 98:2, 3.9 mmol, 1.3 equiv) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. A solution of boronic ester **5** (1.23 g, 4.50 mmol, 1.5 equiv) in anhydrous toluene (5.0 mL) was added dropwise and the mixture was stirred for 2 h at −78 °C. Afterwards, a solution of 12-crown-4 (582 µL, 3.60 mmol, 1.2 equiv) and H_2O (5.4 µL, 0.30 mmol, 0.1 equiv) was added dropwise to the reaction mixture. The solution was stirred at this temperature for 1 h, and then trimethylsilyl chloride (459 µL, 3.60 mmol, 1.2 equiv) was added slowly. After 5 min, the cooling bath was removed and stirring was continued at room temperature overnight (ca. 16 h). Then, the reaction mixture was cooled to 0 °C and 1 M aqueous KH_2PO_4 (10 mL) was added slowly. After stirring for 10 min at room temperature, the phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 30:1 to give a mixture of tertiary boronic ester **6** (979 mg, 2.43 mmol, 81%) and boronic ester **5** (311 mg, 1.14 mmol, 25%) in a ratio of 76:24 as a colourless oil. In order to obtain an analytical pure sample, an aliquot was washed with 0.5 M aq. NaOH to give tertiary boronic ester **6** as a white solid. Enantiomeric excess of the chiral boronic ester was determined by HPLC analysis of an aliquot oxidised according to the following procedure (see below).

mp 44−45 °C (pentane/EtOAc).

R_f (pentane/EtOAc 30:1) 0.25.

^{1}H NMR (301 MHz, $CDCl_3$) δ_H ppm 7.36 (d, J = 2.0 Hz, 1 H, H_{Ar}), 7.30 (d, J = 8.5 Hz, 1 H, H_{Ar}), 7.29−7.12 (m, 5 H, H_{Ar}), 7.07 (dd, J = 8.4, 2.2 Hz, 1 H, H_{Ar}), 5.57 (ddt, J = 17.0, 10.2, 7.1 Hz, 1 H, C*H*CH_2), 4.97−4.88 (m, 2 H, $CHC\textit{H}_2$), 3.94 (dd, J = 13.2, 7.0 Hz, 1 H, C*H*H), 3.82 (dd, J = 13.2, 7.0 Hz, 1 H, CH*H*), 1.17 (s, 6 H, CH_3), 1.15 (s, 6 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 146.5 (C), 144.6 (C), 135.5 (*C*HCH_2), 131.6 (C), 131.4 (CH), 129.5 (CH), 129.4 (C), 129.2 (CH), 129.0 (CH), 128.0 (CH), 125.9 (CH), 117.6 ($CH\textit{C}H_2$), 84.0 (C), 41.8 (CH_2), 24.4 (CH_3), 24.3 (CH_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ_B ppm 32.4 (br. s).

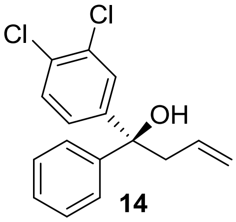
ν_{max} (neat) = 2975, 1640, 1470, 1335, 1235, 1140, 1028, 912, 848, 700, 519 cm^{-1}.

m/z (%) (EI^+) 402 ([^{35,35}M]$^+$, 1), 387 ([^{35,35}M-CH_3]$^+$, 2), 361 ([^{35,35}M-CH_2CHCH_2]$^+$, 100), 191 (29), 101 (75), 83 (49), 55 (21).

HRMS (ESI^+) calcd. for $C_{22}H_{26}O_2{}^{35}Cl_2{}^{11}B$ [M+H]$^+$ 403.1397, found 403.1408.

$[\alpha]_D^{25}$ +11.7 (*c* 2.4, $CHCl_3$, for 98% ee).

(*S*)-1-(3,4-Dichlorophenyl)-1-phenylbut-3-en-1-ol (14)



14

A solution of tertiary boronic ester **6** (43 mg, 0.11 mmol, 1.0 equiv) in THF (4.0 mL) was cooled to 0 °C and a mixture of 2 M aq. NaOH (2.0 mL) and 30% H_2O_2 (1.0 mL) was added under vigorous stirring. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was portioned between water (15 mL) and diethyl ether (15 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc 7:1) to give tertiary alcohol **14** (26 mg, 87 µmol, 83%) as a colourless oil.

R_f (pentane/EtOAc 7:1) 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.59 (d, *J* = 2.2 Hz, 1 H, H_{Ar}), 7.47–7.42 (m, 2 H, H_{Ar}), 7.40–7.32 (m, 3 H, H_{Ar}), 7.30–7.23 (m, 2 H, H_{Ar}), 5.65 (ddt, *J* = 17.2, 10.0, 7.3 Hz, 1 H, C*H*CH_2), 5.31–5.20 (m, 2 H, CHC*H*$_2$), 3.09 (dd, *J* = 13.9, 7.0 Hz, 1 H, C*H*H), 3.00 (dd, *J* = 13.9, 7.0 Hz, 1 H, CH*H*), 2.59 (br. s, 1 H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 146.9 (C), 145.4 (C), 132.6 (*C*HCH_2), 132.3 (C), 130.9 (C), 130.1 (CH), 128.5 (CH), 128.1 (CH), 127.4 (CH), 125.8 (CH), 125.5 (CH), 121.3 (CH*C*H$_2$), 76.2 (CHOH), 46.4 (CH_2).

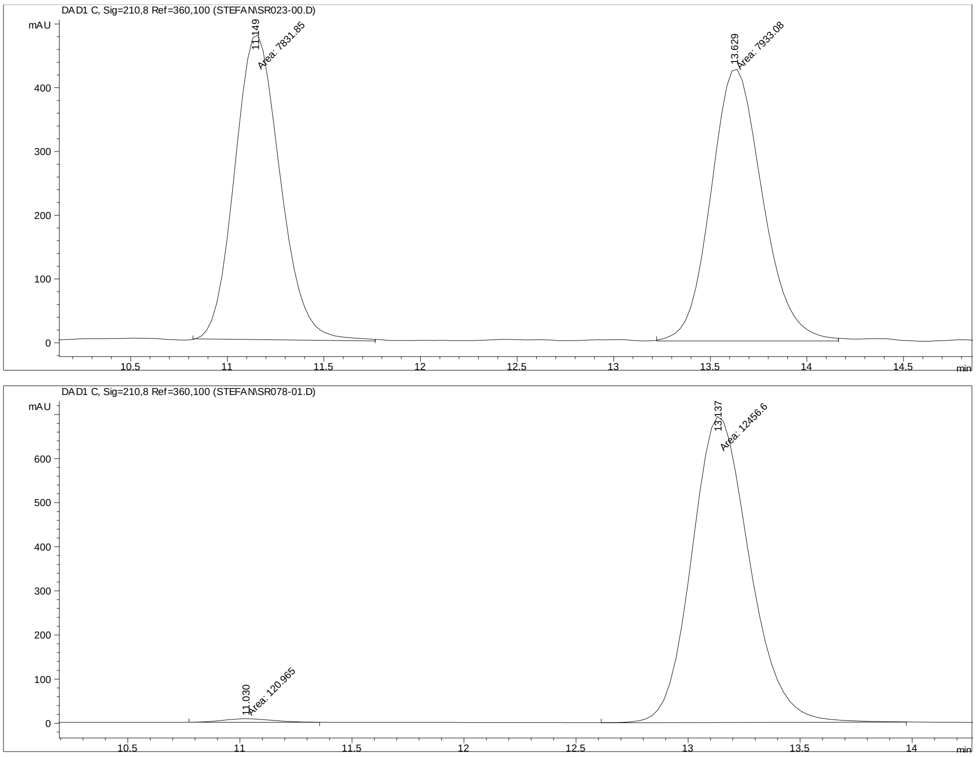
ν_{max} (neat) = 3548, 2927, 1731, 1467, 1447, 1378, 1170, 1028, 921, 821, 766, 698, 540 cm^{-1}.

m/z (%) (CI^+) 293 ([^{35,35}M]$^+$, 40), 275 ([^{35,35}M-OH]$^+$, 68), 251 ([^{35,35}M-CH_2CHCH_2]$^+$, 100), 239 (42), 173 (73), 129 (77), 105 (95), 91 (39), 75 (46).

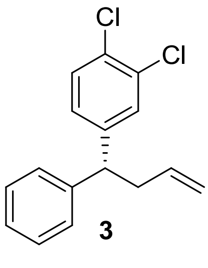
HRMS (CI^+) calcd. for $C_{16}H_{15}O^{35}Cl_2$ [M+H]$^+$ 293.0500, found 293.0510.

$[\alpha]_D^{25}$ +41.5 (*c* 0.87, $CHCl_3$, for 98% ee).

HPLC separation conditions: Chiralpak IB column with guard, 5.0% *i*PrOH in hexane, flow rate 0.7 mL/min, 20 °C; t_R 11.0 min for (*R*)-enantiomer (minor) and t_R 13.1 min for (*S*)-enantiomer (major).
e.r. = 99.0:1.0.



(*R*)-1,2-Dichloro-4-(1-phenylbut-3-enyl)benzene (3)



3

After drying caesium fluoride (576 mg, 3.80 mmol, 1.5 equiv) under high vacuum at 120 °C for 24 h, a solution of tertiary boronic ester **6** (1.02 g, 2.53 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (25.3 mL) and water (114 µL, 6.33 mmol, 2.5 equiv) were added. The reaction mixture was stirred at ambient temperature overnight (ca. 16 h), when diethyl ether (15 mL) was added. The solution was washed with 0.5 M aq. NaOH (15 mL), water (2 × 15 mL), and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (SiO_2, pentane /EtOAc 30:1) to give (*R*)-olefin **3** (679 mg, 2.45 mmol, 97%) as a colourless oil.

$\mathbf{R_f}$ (pentane/EtOAc 30:1) 0.35.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.35 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.34–7.29 (m, 3 H, H_{Ar}), 7.25–7.19 (m, 3 H, H_{Ar}), 7.07 (dd, *J* = 8.3, 2.2 Hz, 1 H, H_{Ar}), 5.69 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H, C*H*CH_2), 5.08–4.95 (m, 2 H, CHCH_2), 3.98 (t, *J* = 7.9 Hz, 1 H, H_{Benzyl}), 2.86–2.71 (m, 2 H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 144.8 (C), 143.2 (C), 135.9 (*C*HCH_2), 132.3 (C), 130.3 (CH), 130.1 (C), 129.9 (CH), 128.6 (CH), 127.8 (CH), 127.4 (CH), 126.6 (CH), 116.9 (CH*C*H_2), 50.4 (CH), 39.6 (CH_2).

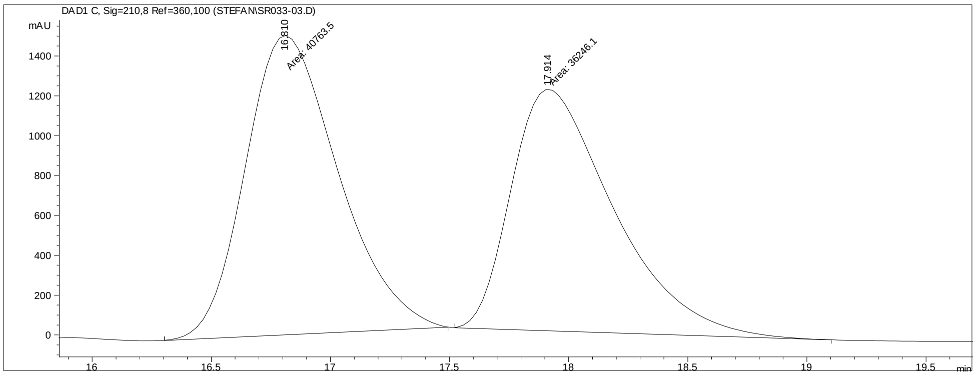
ν_{max} (neat) = 2927, 1641, 1559, 1471, 1398, 1132, 1030, 915, 763, 697 cm^{-1}.

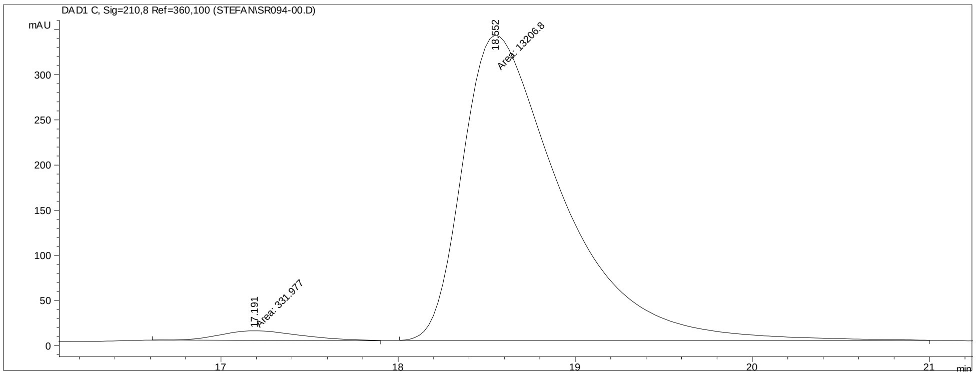
m/z (%) (EI^+) 276 ($[^{35,35}M]^+$, 1), 235 ($[^{35,35}M\text{-}CH_2CHCH_2]^+$, 100), 200 ($[^{35,35}M\text{-}Ph]^+$, 29), 165 (88).

HRMS (EI^+) calcd. for $C_{16}H_{14}{}^{35}Cl_2$ $[M]^+$ 276.0467, found 276.0468.

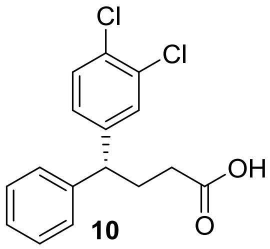
$[\alpha]_D^{24}$ +1.0 (*c* 1.02, $CHCl_3$, for 95% ee).

HPLC separation conditions: Chiralpak IA column with guard, 0.1% *i*PrOH in hexane, flow rate 0.4 mL/min, 0 °C; t_R 17.2 min for (*S*)-enantiomer (minor) and t_R 18.6 min for (*R*)-enantiomer (major).
e.r. = 97.5:2.5.





(*R*)-4-(3,4-Dichlorophenyl)-4-phenylbutanoic acid (10)



10

A solution of 9-BBN (3.0 mL, 0.5 M in THF, 1.5 mmol, 1.5 equiv) was added to a solution of olefin **3** (277 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (2.0 mL) and stirred for 2 h at ambient temperature. The reaction mixture was cooled to 0 °C and a mixture of 2 M aq. NaOH (2.0 mL) and 30% H_2O_2 (1.0 mL) was added. The reaction mixture was stirred vigorously for 20 h at ambient temperature. The solution was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic layers were concentrated under reduced pressure, the residue was dissolved in acetone (18 mL) and Jones reagent[10] (2.6 M, prepared from chromium trioxide (200 mg, 2.0 mmol, 2.0 equiv), water (0.58 mL), and conc. sulfuric acid (0.17 mL)), was added dropwise to the reaction mixture at 0 °C until the colour remained orange. After being stirred for 1 h at room temperature, the mixture was cooled to 0 °C and *i*PrOH was added dropwise until the solution remained colourless. The solution was stirred for 1 h at ambient temperature and then sonicated for 10 min. The mixture was filtered through celite and the precipitate was rinsed thoroughly with diethyl ether. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether (30 mL). The mixture was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, pentane/EtOAc 2:1) to give a pale yellow oil, which crystallised on standing. Carboxylic acid **10** (303 mg, 0.98 mmol, 98%) was obtained as an off-white solid.

mp 116–117 °C (pentane/EtOAc). Lit. 118–120 °C (hexane).[11]

R_f (pentane/EtOAc 2:1) 0.07.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 10.08 (br. s, 1 H, COOH), 7.36 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.35–7.29 (m, 3 H, H_{Ar}), 7.26–7.18 (m, 3 H, H_{Ar}), 7.08 (dd, *J* = 8.3, 2.1 Hz, 1 H, H_{Ar}), 3.93 (t, *J* = 7.4 Hz, 1 H, H_{Benzyl}), 2.41–2.29 (m, 4 H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 178.9 (CO), 144.3 (C), 142.5 (C), 132.5 (C), 130.5 (CH), 130.5 (C), 129.7 (CH), 128.8 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 49.4 (CH), 32.1 (CH_2), 30.0 (CH_2).

ν_{max} (neat) = 3028, 2924, 1705, 1470, 1401, 1132, 1029, 820, 699 cm^{-1}.

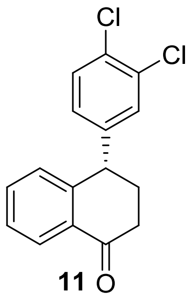
m/z (%) (ESI$^+$) 331 ([^{35,35}M+Na]$^+$, 100), 326 (18), 304 (13), 282 (15), 236 (11), 214 (14), 110 (5).

HRMS (ESI$^+$) calcd. for $C_{16}H_{14}O_2{}^{35}Cl_2Na$ [M+Na]$^+$ 331.0263, found 331.0274.

$[\alpha]_D^{25}$ −4.9 (*c* 1.02, $CHCl_3$, for 94% ee). Lit. $[\alpha]_D^{23}$ −12.5 (*c* 2.5, benzene, for 100% ee).[12]

All analytical data match those reported in literature.[13]

(*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (11)



11

Based on a procedure by *Sawamura,*[13] carboxylic acid **10** (110 mg, 0.35 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (15 mL) and chlorosulfonic acid (73 µL, 1.1 mmol, 3.1 equiv) was added slowly. After being stirred for 45 min at room temperature, the solution was diluted with saturated aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to afford a light yellow oil, which crystallised on standing. Tetralone **11** (95 mg, 0.33 mmol, 93%) was obtained as a white solid, which required no further purification.

mp 77 °C (heptane). Lit. 84 °C (hexane/EtOAc).[12,14]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.14 (dd, *J* = 7.8, 1.6 Hz, 1 H, H_{Ar}), 7.51–7.38 (m, 3 H, H_{Ar}), 7.24 (d, *J* = 2.2 Hz, 1 H, H_{Ar}), 6.96 (dd, *J* = 8.2, 2.0 Hz, 2 H, H_{Ar}), 4.29 (dd, *J* = 8.0, 4.5 Hz, 1 H, H_{Benzyl}), 2.73 (ddd, *J* = 17.2, 7.7, 4.6 Hz, 1 H, C*H*HCO), 2.64 (ddd, *J* = 17.2, 9.2, 4.6 Hz, 1 H, CH*H*CO), 2.52–2.44 (m, 1 H, C*H*H), 2.32–2.22 (m, 1 H, CH*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 197.4 (CO), 144.8 (C), 144.0 (C), 133.9 (CH), 132.8 (C), 132.7 (C), 131.0 (C), 130.6 (CH), 130.5 (CH), 129.3 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 44.5 (CH), 36.5 (*C*H_2CO), 31.7 (CH_2).

ν_{max} (neat) = 2926, 1674, 1590, 1466, 1400, 1329, 1284, 1202, 1029, 881, 824, 770, 720, 674 cm^{-1}.

m/z (%) (EI^+) 290 ($[^{35,35}M]^+$, 95), 275 (24), 262 (48), 248 (52), 227 (100), 199 (75), 163 (45), 131 (26), 115 (24), 100 (31), 91 (57).

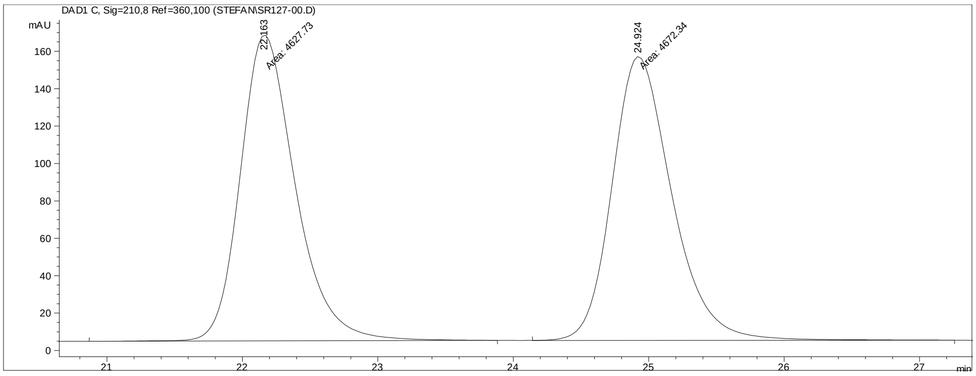
HRMS (EI^+) calcd. for $C_{16}H_{12}O^{35}Cl_2$ $[M]^+$ 290.0265, found 290.0261.

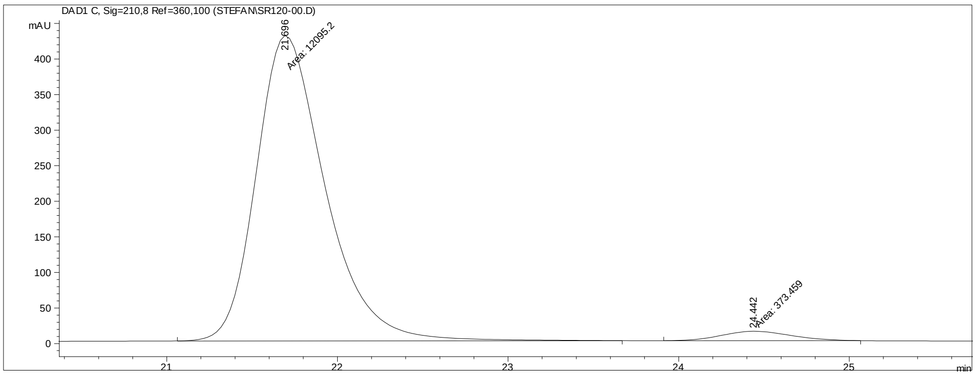
$[\alpha]_D^{25}$ +63.8 (*c* 1.16, benzene, for 94% ee). Lit. $[\alpha]_D^{23}$ +71.3 (*c* 1.1, benzene, for 100% ee).[12]

The analytical data are in accordance with the literature values.[15]

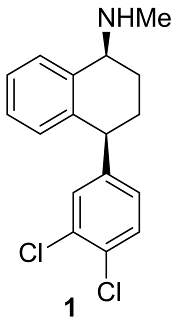
HPLC separation conditions: Chiralpak IB column with guard, 2.0% *i*PrOH in hexane, flow rate 0.5 mL/min, 20 °C; t_R 21.7 min for (*S*)-enantiomer (major) and t_R 24.4 min for (*R*)-enantiomer (minor).

e.r. = 97.0:3.0.





(+)-Sertraline (1)



Following a procedure of *Vukics*,[16] tetralone **11** (75 mg, 0.26 mmol, 1.0 equiv), *N*-methylhydroxylamine hydrochloride (43 mg, 0.52 mmol, 2.0 equiv), and anhydrous NaOAc (42 mg, 0.52 mmol, 2.0 equiv) were dissolved in anhydrous ethanol (5.0 mL). The reaction mixture was heated under reflux for 15 h. Then, the solvent was evaporated and the residue was portioned between water (10 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in anhydrous ethanol (5.0 mL) and *N*-methylhydroxylamine hydrochloride (43 mg, 0.52 mmol, 2.0 equiv) and anhydrous NaOAc (42 mg, 0.52 mmol, 2.0 equiv) were added. The mixture was heated under reflux for 22 h and the solvent was removed *in vacuo*. Water (10 mL) and CH_2Cl_2 (10 mL) were added, the phases were separated, and the aqueous one was re-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (20 mL), dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was dissolved in a mixture of anhydrous MeOH (2.0 mL) and anhydrous CH_2Cl_2 (0.5 mL). Pd on $CaCO_3$ (5 wt. %, 64 mg) was added and the mixture was hydrogenated for 20 h at atmospheric pressure and room temperature. Then, the mixture was filtered through celite and the precipitate was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (SiO_2 treated with Et_3N, pentane/EtOAc 2:3) to give (+)-sertraline (**1**) (37 mg, 0.12 mmol, 47% over two steps) as a yellow oil. The *cis*/*trans* ratio was determined by supercritical fluid chromatography and amounted to 96.5:3.5.

R_f (pentane/EtOAc 2:3) 0.07.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H ppm 7.40–7.33 (m, 2 H, H_{Ar}), 7.27 (d, *J* = 1.3 Hz, 1 H, H_{Ar}), 7.22 (t, *J* = 7.4 Hz, 1 H, H_{Ar}), 7.13 (td, *J* = 7.5, 1.3 Hz, 1 H, H_{Ar}), 6.99 (dd, *J* = 8.3, 2.1 Hz, 1 H, H_{Ar}), 6.81 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 4.00 (dd, *J* = 9.3, 5.4 Hz, 1 H, H_{Benzyl}), 3.75 (t, *J* = 4.1 Hz, 1 H, CHN), 2.56 (s, 3 H, CH_3), 2.14–1.98 (m, 3 H, CH_2, C*H*H), 1.88–1.80 (m, 1 H, CH*H*), 1.60 (br. s, 1 H, NH).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 147.5 (C), 139.5 (C), 138.6 (C), 132.2 (C), 130.7 (CH), 130.3 (CH), 130.0 (C), 129.8 (CH), 129.2 (CH), 128.2 (CH), 127.2 (CH), 126.6 (CH), 57.3 (CHN), 45.4 (CH), 34.4 (CH_3N), 28.4 (CH_2CN), 25.7 (CH_2).

ν_{max} (neat) = 3337, 2925, 2853, 1594, 1469, 1097, 1030, 821, 781, 741 cm^{-1}.

m/z (%) (ESI^+) 306 ($[^{35,35}M]^+$, 100), 272 (61), 238 (48), 207 (5).

HRMS (ESI^+) calcd. for $C_{17}H_{18}N^{35}Cl_2$ $[M+H]^+$ 306.0811, found 306.0804.

The analytical data are in accordance with the literature values.[17]

The secondary amine **1** was converted to the corresponding HCl salt and its absolute stereochemistry was determined by optical rotation.

mp 215–216 °C (diethyl ether). Lit. 243–245 °C (diethyl ether).[11]

$[\alpha]_D^{25}$ +34.5 (*c* 1.16, MeOH). Lit. $[\alpha]_D^{20}$ +37.9 (*c* 2.0, MeOH).[11]

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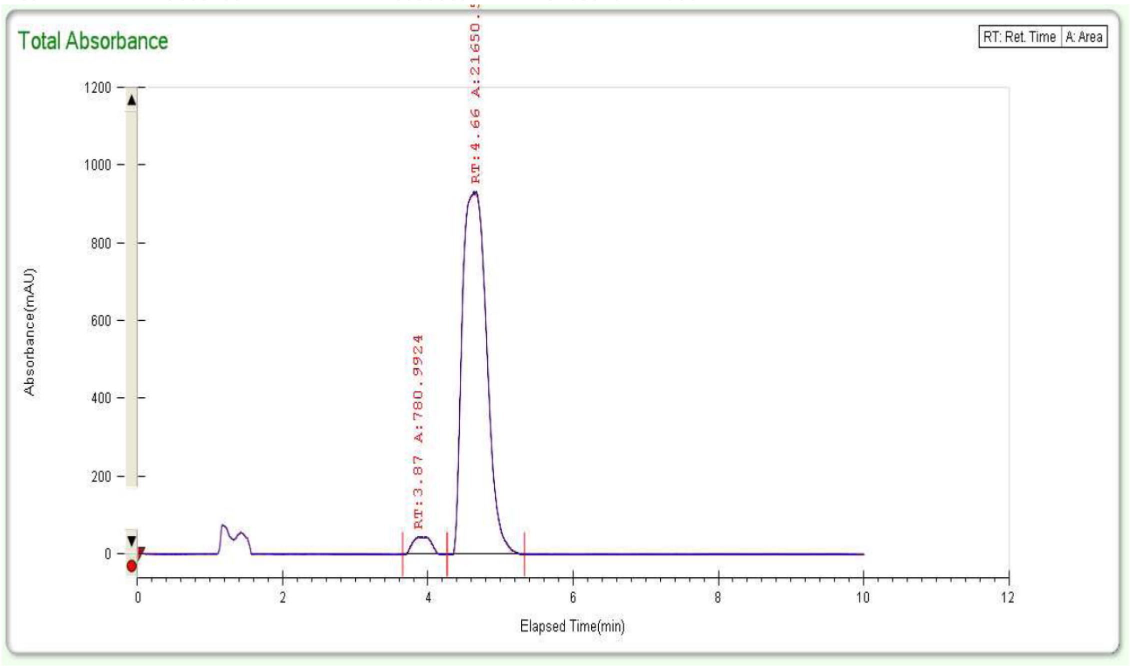
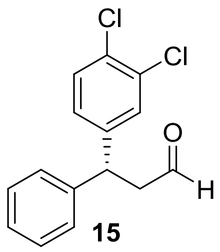


(*R*)-3-(3,4-Dichlorophenyl)-3-phenylpropanal (15)



15

Following the procedure of *Jin*,[18] (*R*)-olefin **3** (139 mg, 0.500 mmol, 1.0 equiv) was dissolved in 1,4-dioxane/H_2O 3:1 (4.0 mL), and $K_2OsO_4 \cdot 2H_2O$ (4 mg, 0.01 mmol, 0.02 equiv), $NaIO_4$ (0.43 g, 2.0 mmol, 4.0 equiv) and 2,6-lutidine (0.11 g, 1.0 mmol, 2.0 equiv) were added to the solution. The reaction mixture was stirred for 4 h at room temperature. Then, water (10 mL) and EtOAc (20 mL) were added, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aq. $Na_2S_2O_3$ (40 mL) and brine (40 mL), and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, pentane/EtOAc 4:1) to afford aldehyde **15** (126 mg, 0.450 mmol, 90%) as a pale yellow oil.

R$_f$ (pentane/EtOAc 4:1) 0.26.

^{1}H NMR (500 MHz, CDCl$_3$) δ_H ppm 9.75 (t, *J* = 1.5 Hz, 1 H, CHO), 7.37 (d, *J* = 8.3 Hz, 1 H, H$_{Ar}$) 7.35−7.29 (m, 3 H, H$_{Ar}$), 7.26−7.18 (m, 3 H, H$_{Ar}$), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1 H, H$_{Ar}$), 4.60 (t, *J* = 7.7 Hz, 1 H, H$_{Benzyl}$), 3.20 (ddd, *J* = 17.4, 7.5, 1.5 Hz, 1 H, C*H*H), 3.16 (ddd, *J* = 17.4, 7.8, 1.5 Hz, 1 H, CH*H*).

^{13}C NMR (101 MHz, CDCl$_3$) δ_C ppm 199.8 (CO), 143.6 (C), 142.0 (C), 132.7 (C), 130.8 (C), 130.6 (CH), 129.7 (CH), 129.0 (CH), 127.6 (CH), 127.1 (CH), 127.1 (CH), 49.1 (CH$_2$), 43.9 (CH).

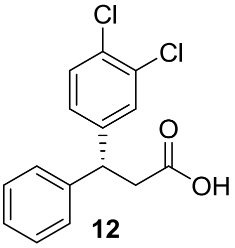
ν$_{max}$ (neat) = 2826, 2726, 1721, 1469, 1389, 1133, 1029, 814, 699 cm^{-1}.

m/z (%) (EI$^+$) 278 ([^{35,35}M]$^+$, 54), 260 (21), 235 (76), 199 (32), 165 (100), 105 (21), 91 (23), 77 (14).

HRMS (EI$^+$) calcd. for $C_{15}H_{12}O^{35}Cl_2$ [M]$^+$ 278.0265, found 278.0272.

$[\alpha]_D^{25}$ −7.3 (*c* 0.95, CHCl$_3$, for 93% ee).

(*R*)-3-(3,4-Dichlorophenyl)-3-phenylpropanoic acid (12)



12

To a solution of (*R*)-aldehyde **15** (51 mg, 0.18 mmol, 1.0 equiv) in *t*BuOH (2.5 mL), $NaH_2PO_4\cdot 2H_2O$ (0.14 g, 0.90 mmol, 5.0 equiv) in H_2O (1.3 mL) and $NaClO_2$ (49 mg, 0.54 mmol, 3.0 equiv) in H_2O (1.3 mL) were added, and the mixture was stirred for 30 min at ambient temperature. Then, brine (4.5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (5 × 10 mL). The aqueous layer was acidified to pH 2 (3 M aq. HCl) and further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, pentane/EtOAc 2:1) afforded (*R*)-carboxylic acid **12** (51 mg, 0.17 mmol, 95%) as a pale yellow oil.

R$_f$ (pentane/EtOAc 2:1) 0.05.

^{1}H NMR (400 MHz, CDCl$_3$) δ_H ppm 10.61 (br. s, 1 H, COOH), 7.36 (d, *J* = 8.3 Hz, 1 H, H$_{Ar}$), 7.34−7.28 (m, 3 H, H$_{Ar}$), 7.26−7.17 (m, 3 H, H$_{Ar}$), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1 H, H$_{Ar}$), 4.48 (t, *J* = 7.9 Hz, 1 H, H$_{Benzyl}$), 3.09 (dd, *J* = 16.2, 7.5 Hz, 1 H, C*H*H), 3.05 (dd, *J* = 16.2, 8.2 Hz, 1 H, CH*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 176.9 (COOH), 143.4 (C), 142.0 (C), 132.6 (C), 130.8 (C), 130.6 (CH), 129.7 (CH), 128.9 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 45.8 (CH), 40.0 (CH_2).

ν_{max} (neat) = 3149, 2911, 1706, 1471, 1412, 1263, 1132, 1080, 1029, 812, 762, 701 cm^{-1}.

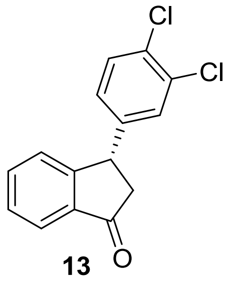
m/z (%) (ESI^-) 297 ($[^{37,37}M]^-$, 9), 295 ($[^{35,37}M]^-$, 62), 293 ($[^{35,35}M]^-$, 100).

HRMS (ESI^-) calcd. for $C_{15}H_{11}O_2{}^{35}Cl_2$ $[M]^-$ 293.0142, found 293.0136.

$[\alpha]_D^{26}$ +3.9 (*c* 1.03, $CHCl_3$, for 93% ee). Lit. $[\alpha]_D^{20}$ –5.8 (*c* 0.8, $CHCl_3$, for 96% ee of the (*S*)-isomer).[19]

The analytical data are in accordance with the literature values.[20a]

(*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (13)



13

Based on a procedure by *Correia,*[20a] (*R*)-carboxylic acid **12** (51 mg, 0.17 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (4.0 mL). Chlorosulfonic acid (101 mg, 0.86 mmol, 5.0 equiv) was added dropwise, and the reaction mixture was stirred for 1.5 h at ambient temperature. A saturated aq. solution of $NaHCO_3$ (25 mL) was added slowly and the reaction mixture was stirred for 10 min at room temperature. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and diethyl ether (1 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a light yellow oil, which crystallised upon standing. Indenone **13** (47 mg, 0.17 mmol, 98%) was afforded as a white solid with an ee of 93%, which required no further purification. The e.r. could be improved to 99.2:0.8 by recrystallisation from hot heptane.

mp 96–97 °C (heptane). Lit. 110–111 °C (hexane/EtOAc).[20b]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.84 (d, J = 7.7 Hz, 1 H, H_{Ar}), 7.62 (td, J = 7.4, 1.3 Hz, 1 H, H_{Ar}), 7.46 (t, J = 7.5 Hz, 1 H, H_{Ar}), 7.39 (d, J = 8.3 Hz, 1 H, H_{Ar}), 7.27 (ddd, J = 7.7, 1.8, 0.9 Hz, 1 H, H_{Ar}), 7.24 (d, J = 2.2 Hz, 1 H, H_{Ar}), 6.96 (dd, J = 8.3, 2.2 Hz, 1 H, H_{Ar}), 4.56 (dd, J = 8.2, 3.9 Hz, 1 H, H_{Benzyl}), 3.24 (dd, J = 19.3, 8.2 Hz, 1 H, C*H*H), 2.63 (dd, J = 19.3, 3.9 Hz, 1 H, CH*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 204.8 (CO), 156.5 (C), 143.9 (C), 136.7 (C), 135.3 (CH), 132.9 (C), 131.1 (C), 130.9 (CH), 129.6 (CH), 128.3 (CH), 127.0 (CH), 126.7 (CH), 123.6 (CH), 46.4 (CH_2), 43.5 (CH).

ν_{max} (neat) = 2921, 1695, 1601, 1470, 1396, 1202, 1091, 1043, 887, 816, 760, 706 cm^{-1}.

m*/*z (%) (CI$^+$) 281 ([^{37,37}M]$^+$, 10), 279 ([^{35,37}M]$^+$, 63), 277 ([^{35,35}M]$^+$, 100).

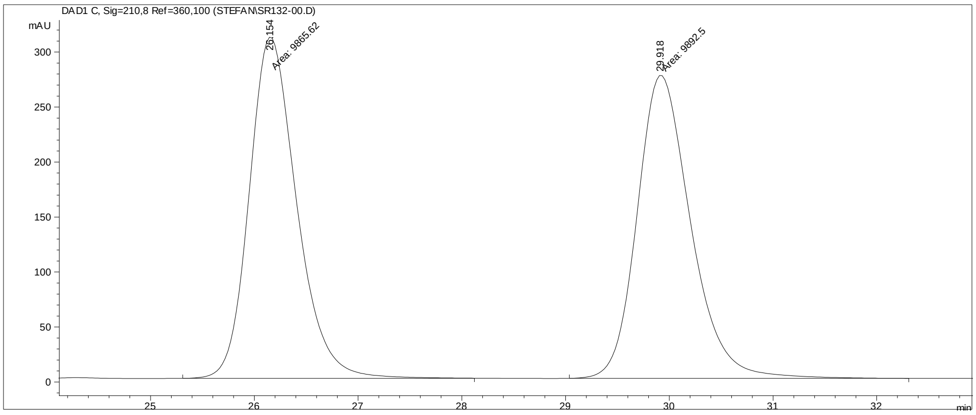
HRMS (CI$^+$) calcd. for $C_{15}H_{11}O^{35}Cl_2$ [M+H]$^+$ 277.0181, found 277.0183.

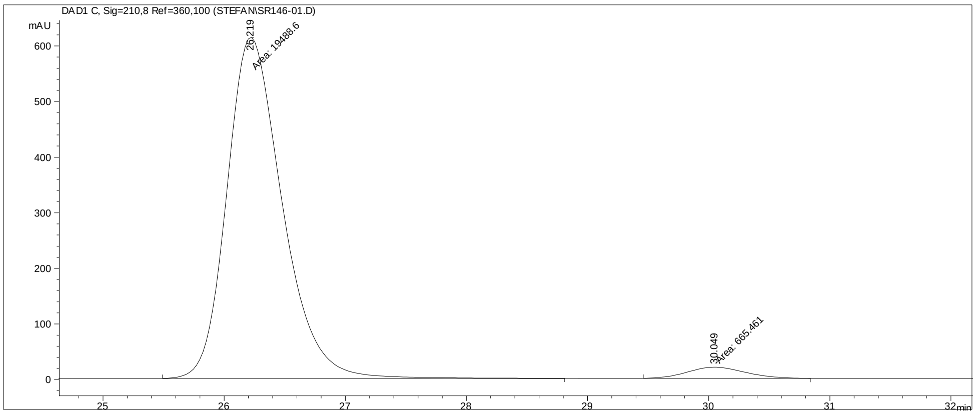
$[\alpha]_D^{24}$ +49.5 (*c* 1.33, $CHCl_3$, for 98% ee). Lit. $[\alpha]_D^{20}$ −50.0 (*c* 1.1, $CHCl_3$, for 89% ee).[20b, Note 1]

The analytical data are in accordance with the literature values.[20a]

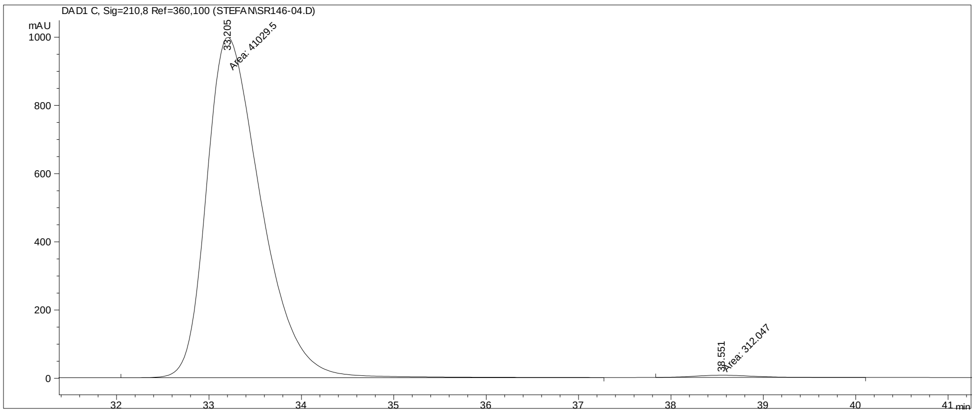
HPLC separation conditions: Chiralpak IB column with guard, 2.0% *i*PrOH in hexane, flow rate 0.5 mL/min, 20 °C; t_R 26.2 min for (*S*)-enantiomer (major) and t_R 30.0 min for (*R*)-enantiomer (minor).

e.r. = 96.5:3.5.





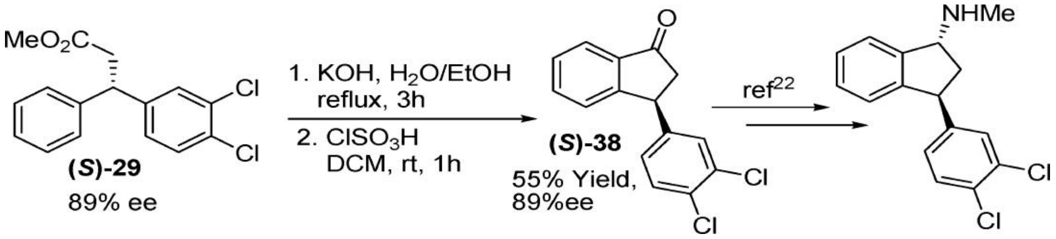
e.r. = 99.2:0.8.



Note 1:

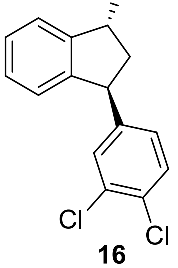
Taylor and Correia reported recently the synthesis of the same compound ((*S*)-**13**), but obtained an $[\alpha]_{\mathrm{D}}^{20}$ of –50.0 (*c* 1.1, $CHCl_3$, for 89% ee). We believe this is a mistake and that the error occurred due to an accidental inversion of the stereocentre when drawing the conversion of **(*S*)-29** to **(*S*)-38** in Scheme 4 in literature reference 20b.

SCHEME 4. Enantioselective Formal Synthesis of (−)-Indatraline



The above scheme is taken from their paper, but the structure of **(*S*)-38** is incorrect and should be drawn with the opposite stereochemistry. This is because the configuration of the stereocentre should not change during basic ester cleavage and an intramolecular Friedel-Crafts reaction. Thus, we believe that Taylor and Correia actually synthesised and reported the $[\alpha]_{\mathrm{D}}^{20}$ of the (*R*)-indenone.

(1*S*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (16)



16

Based on a procedure by *Davies,*[21] indenone **13** (95 mg, 0.34 mmol, 1.0 equiv) was dissolved in anhydrous THF (1.0 mL) and cooled to −10 °C. K-Selectride (0.69 mL, 1 M solution in THF, 0.69 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred for 4 h at −10 °C. Then, water (1.0 mL) was added slowly and the solution was stirred for 30 min at ambient temperature. THF was removed under reduced pressure and the mixture was portioned between water (10 mL) and EtOAc (10 mL). The phases were separated and the aqueous was re-extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (20 mL) and with brine (20 mL), and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (SiO_2, pentane/EtOAc 4:1) to give *cis* alcohol **16** (88 mg, 0.32 mmol, 92%) as a white solid.

mp 102–103 °C (pentane/EtOAc). Lit. 90–91 °C (diisopropyl ether/hexane).[22]

R_f (pentane/EtOAc 4:1) 0.17.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.49 (d, J = 7.3 Hz, 1 H, H_{Ar}), 7.39 (d, J = 8.3 Hz, 1 H, H_{Ar}), 7.37–7.31 (m, 2 H, H_{Ar}), 7.30–7.25 (m, 1 H, H_{Ar}), 7.08 (dd, J = 8.2, 2.1 Hz, 1 H, H_{Ar}), 6.95 (d, J = 7.3 Hz, 1 H, H_{Ar}), 5.30 (t, J = 7.0 Hz, 1 H, C*H*OH), 4.17 (t, J = 8.2 Hz, 1 H, H_{Benzyl}), 3.03 (dt, J = 13.0, 7.2 Hz, 1 H, C*H*H), 2.13 (br. s, 1 H, OH), 1.90 (ddd, J = 13.0, 8.8, 7.3 Hz, 1 H, CH*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 145.1 (C), 144.7 (C), 144.4 (C), 132.5 (C), 130.5 (C), 130.5 (CH), 130.2 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 124.9 (CH), 123.9 (CH), 74.9 (CHOH), 47.5 (CH), 46.7 (CH_2).

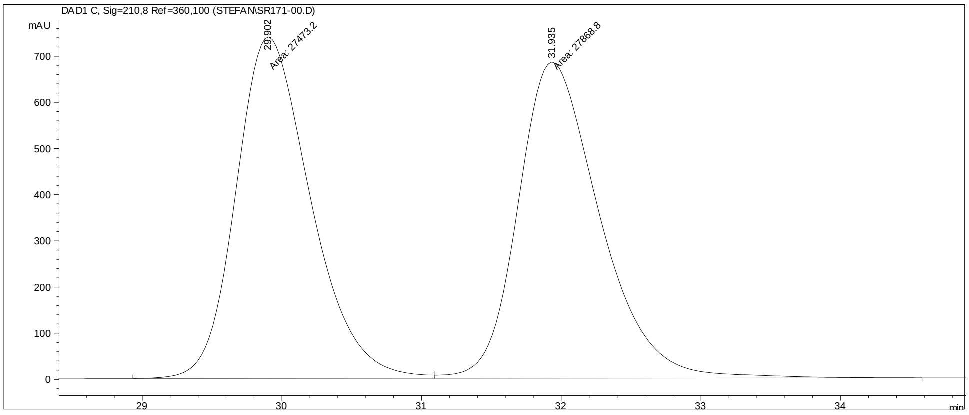
ν_{max} (neat) = 3206, 1736, 1466, 1401, 1095, 1049, 1028, 818, 763, 746 cm^{-1}.

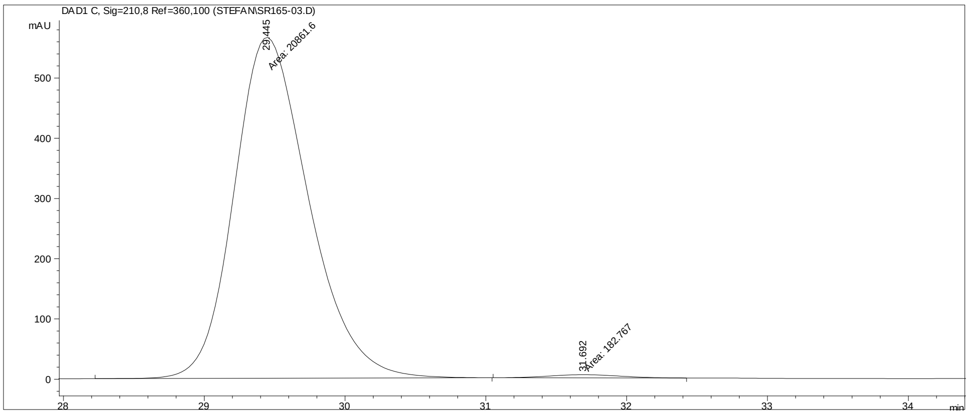
m/z (%) (ESI^+) 305 ($[^{37,37}M+Na]^+$, 12), 303 ($[^{35,37}M+Na]^+$, 66), 301 ($[^{35,35}M+Na]^+$, 100), 265 ($[^{37,37}M-OH]^+$, 4), 263 ($[^{35,37}M-OH]^+$, 24), 261 ($[^{35,35}M-OH]^+$, 34).

HRMS (ESI^+) calcd. for $C_{15}H_{12}O^{35}Cl_2Na$ $[M+Na]^+$ 301.0157, found 301.0151.

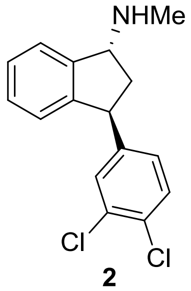
$[\alpha]_D^{23}$ +19.1 (*c* 1.1, $CHCl_3$, for 98% ee).

HPLC separation conditions: Chiralpak IB column with guard, 2.0% *i*PrOH in hexane, flow rate 0.7 mL/min, 20 °C; t_R 29.4 min for (*S*,*S*)-enantiomer (major) and t_R 31.7 min for (*R*,*R*)-enantiomer (minor).
e.r. = 99.1:0.9.





(+)-Indatraline (2)



2

Following a protocol of *Froimowitz*,[23] Et_3N (66 µL, 0.47 mmol, 4.0 equiv) was added to a solution of *cis* alcohol **16** (33 mg, 0.12 mmol, 1.0 equiv) in anhydrous THF (1.0 mL). The mixture was cooled to −20 °C, methananesulfonyl chloride (18 µL, 0.24 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was stirred for 1 h at −20 °C. Then, a solution of methylamine (1.22 mL, 2.0 M in THF, 2.44 mmol, 20.0 equiv) was added slowly. Over 90 min, the mixture was allowed to warm to ambient temperature and stirred for 20 h. The solvent was removed *in vacuo*, and water (10 mL) and EtOAc (10 mL) were added. The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the residue was subjected to column chromatography (SiO_2 treated with Et_3N, pentane/EtOAc 2:3, then EtOAc) to give (+)-indatraline (**2**) (29 mg, 98 µmol, 83%) as a yellow oil.

$\mathbf{R_f}$ (pentane/EtOAc 2:3) 0.04.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H ppm 7.41 (dd, J = 6.8, 1.3 Hz, 1 H, H_{Ar}), 7.36 (d, J = 8.2 Hz, 1 H, H_{Ar}), 7.31–7.22 (m, 3 H, H_{Ar}), 7.01–6.96 (m, 2 H, H_{Ar}), 4.52 (t, J = 7.7 Hz, 1 H), 4.28 (dd, J = 6.7, 3.2 Hz, 1 H), 2.52 (s, 3 H, NCH_3), 2.46 (ddd, J = 13.2, 7.8, 3.2 Hz, 1 H, C*H*H), 2.30–2.21 (m, 1 H, CH*H*), 1.43 (br. s, 1 H, N*H*CH_3).

^{13}**C NMR** (101 MHz, $CDCl_3$) δ_C ppm 145.5 (C), 145.4 (C), 145.0 (C), 132.4 (C), 130.4 (CH), 130.2 (C), 129.8 (CH), 128.2 (CH), 127.4 (CH), 127.2 (CH), 125.2 (CH), 124.6 (CH), 63.7 (CHN), 48.5 (CH), 43.3 (CH_2), 34.3 (NCH_3).

$\boldsymbol{\nu}_{\mathbf{max}}$ (neat) = 3280, 2931, 2789, 1468, 1398, 1029, 820, 756 cm^{-1}.

m/z (%) (ESI^+) 296 ($[^{37,37}M+H]^+$, 13), 294 ($[^{35,37}M+H]^+$, 68), 292 ($[^{35,35}M+H]^+$, 100), 265 ($[^{37,37}M\text{-NHMe}]^+$, 8), 263 ($[^{35,37}M\text{-NHMe}]^+$, 43), 261 ($[^{35,35}M\text{-NHMe}]^+$, 64).

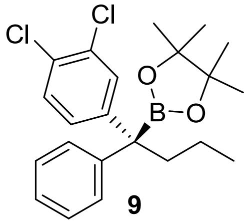
HRMS (ESI$^+$) calcd. for $C_{16}H_{16}{}^{35}Cl_2N$ [M+H]$^+$ 292.0654, found 292.0660.

$[\alpha]_D^{22}$ −18.9 (*c* 1.1, $CHCl_3$).[24]

The secondary amine **2** was treated with 0.5 equiv L-(+)-tartaric acid in MeOH to give a white solid, which was recrystallised from EtOAc/MeOH. The absolute stereochemistry of the tartrate salt was determined by optical rotation.

$[\alpha]_D^{21}$ +29.0 (*c* 0.83, MeOH). Lit. $[\alpha]_D^{25}$ +33.5 (*c* 3, MeOH).[25]

(*R*)-2-(1-(3,4-Dichlorophenyl)-1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9)



9

(*S*)-Carbamate **8** (455 mg, 1.64 mmol, 1.0 equiv) was dissolved in anhydrous diethyl ether (5.5 mL) and chilled to −78 °C. *sec*-Butyllithium (1.51 mL, 1.3 M solution in cyclohexane/hexane 98:2, 1.97 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred at this temperature for 30 min. A solution of boronic ester **5** (672 mg, 2.46 mmol, 1.5 equiv) in anhydrous toluene (2.7 mL) was added dropwise and the mixture was stirred for 2 h at −78 °C. Afterwards, the cooling bath was removed and stirring was continued at room temperature overnight (ca. 16 h). Then, the reaction mixture was cooled to 0 °C and 1 M aqueous KH_2PO_4 (5.0 mL) was added slowly. After stirring for 10 min at room temperature, the phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 30:1 to give a mixture of tertiary boronic ester **9** (476 mg, 1.18 mmol, 72%) and boronic ester **5** (88 mg, 0.32 mmol, 28%) in a ratio of 4:1 as a colourless oil. In order to obtain an analytical pure sample, an aliquot was washed with 0.5 M aq. NaOH to give tertiary boronic ester **9** as a white solid. Enantiomeric excess of the chiral boronic ester was determined by HPLC analysis of an aliquot oxidised according to the following procedure (see below).

mp 98−100 °C ($CHCl_3$).

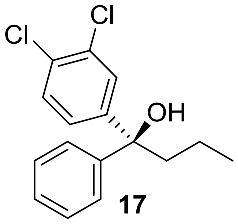
R_f (pentane/EtOAc 30:1) 0.26.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.39 (d, *J* = 2.2 Hz, 1 H, H_{Ar}), 7.29 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.27−7.14 (m, 5 H, H_{Ar}), 7.09 (dd, *J* = 8.4, 2.2 Hz, 1 H, H_{Ar}), 2.15−1.99 (m, 2 H, CCH_2CH_2), 1.17 (s, 6 H, CH_3), 1.16 (s, 6 H, CH_3), 1.14−0.99 (m, 2 H, $CH_2CH_2CH_3$), 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 147.3 (C), 145.4 (C), 131.6 (C), 131.2 (CH), 129.5 (CH), 129.2 (C), 129.1 (CH), 129.1 (CH), 128.0 (CH), 125.7 (CH), 83.8 (C), 39.7 (CH_2), 24.4 (CH_3), 24.3 (CH_3), 20.0 (CH_2), 14.7 (CH_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ_B ppm 32.6 (br. s).

(*S*)-1-(3,4-Dichlorophenyl)-1-phenylbutan-1-ol (17)



17

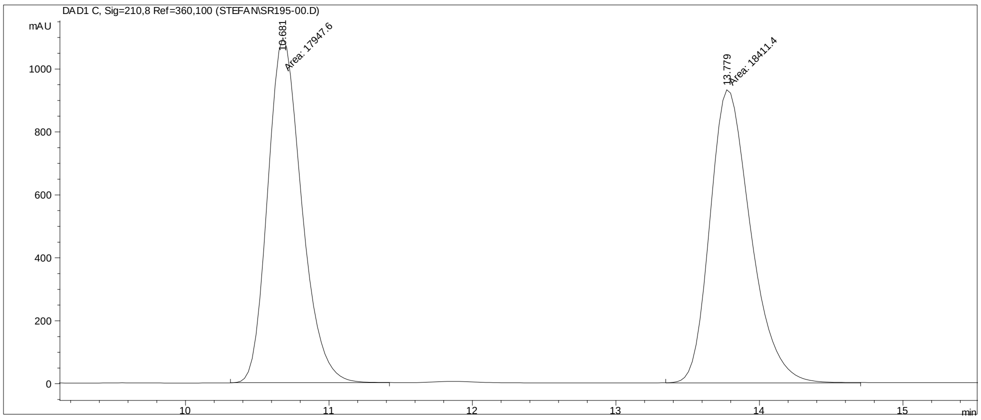
A solution of tertiary boronic ester **9** (81 mg, 0.20 mmol, 1.0 equiv) in THF (6.0 mL) was cooled to 0 °C and a mixture of 2 M aq. NaOH (2.0 mL) and 30% H_2O_2 (1.0 mL) was added under vigorous stirring. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was portioned between water (15 mL) and diethyl ether (15 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc 9:1) to give tertiary alcohol **17** (40 mg, 0.14 mmol, 68%) as a colourless oil.

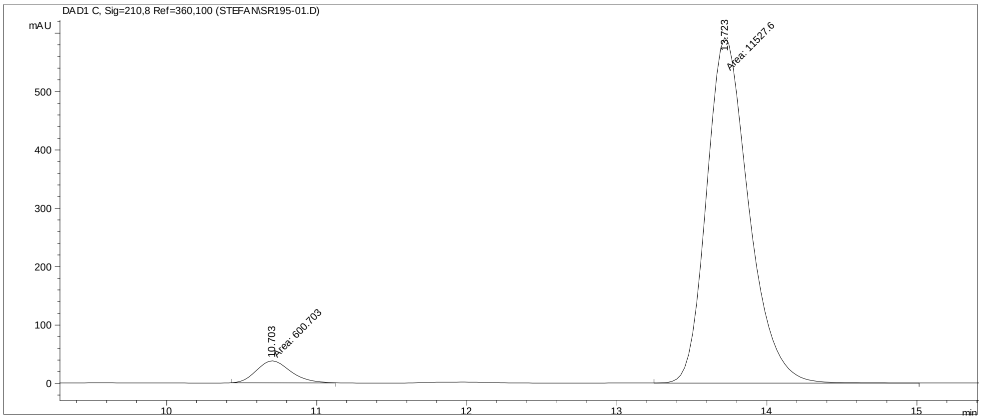
R_f (pentane/EtOAc 9:1) 0.27.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.57 (d, J = 2.2 Hz, 1 H, H_{Ar}), 7.44–7.39 (m, 2 H, H_{Ar}), 7.39–7.32 (m, 3 H, H_{Ar}), 7.30–7.25 (m, 1 H, H_{Ar}), 7.22 (dd, J = 8.4, 2.2 Hz, 1 H, H_{Ar}), 2.30–2.17 (m, 2 H, CCH_2CH_2), 2.07 (br. s, 1 H, OH), 1.41–1.18 (m, 2 H, $CH_2CH_2CH_3$), 0.96 (t, J = 7.3 Hz, 3 H, CH_3).

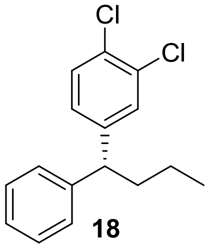
^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 147.5 (C), 146.1 (C), 132.2 (C), 130.6 (C), 130.0 (CH), 128.4 (CH), 128.1 (CH), 127.3 (CH), 125.8 (CH), 125.6 (CH), 77.7 (C), 44.0 (CH_2), 16.9 (CH_2), 14.3 (CH_3).

HPLC separation conditions: Chiralpak IB column with guard, 5.0% *i*PrOH in hexane, flow rate 0.7 mL/min, 20 °C; t_R 10.7 min for (*R*)-enantiomer (minor) and t_R 13.7 min for (*S*)-enantiomer (major).
e.r. = 95.0:5.0.





(*R*)-1,2-Dichloro-4-(1-phenylbutyl)benzene (18)



18

After drying caesium fluoride (46 mg, 0.30 mmol, 1.5 equiv) under high vacuum at 120 °C for 24 h, a solution of tertiary boronic ester **9** (81 mg, 0.20 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL) and water (9.0 µL, 0.5 mmol, 2.5 equiv) were added. The reaction mixture was stirred at ambient temperature overnight (ca. 16 h), when diethyl ether (5.0 mL) was added. The solution was washed with 0.5 M aq. NaOH (5.0 mL), water (2 × 5.0 mL), and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (SiO_2, pentane /EtOAc 30:1) to give compound **18** (40 mg, 0.14 mmol, 72%) as a colourless oil.

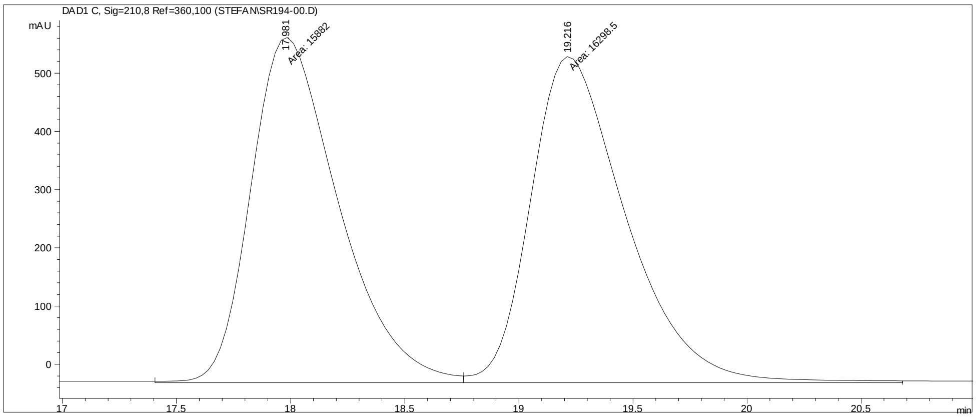
R_f (pentane/EtOAc 30:1) 0.55.

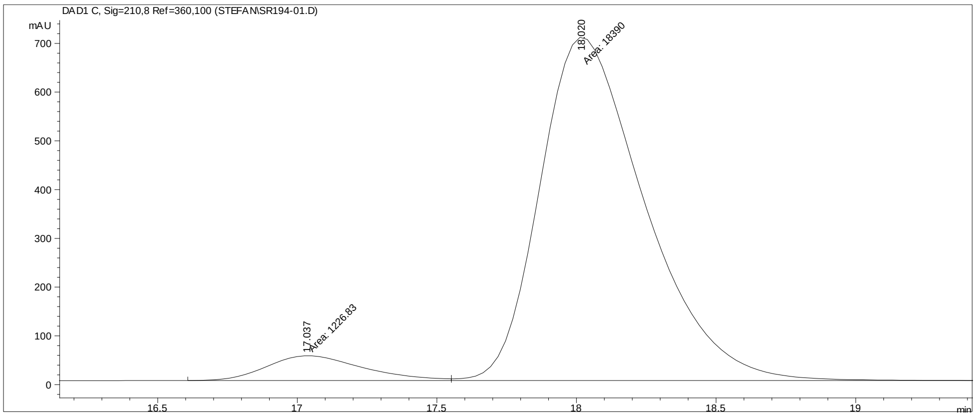
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.36–7.27 (m, 4 H, H_{Ar}), 7.24–7.18 (m, 3 H, H_{Ar}), 7.07 (dd, *J* = 8.2, 2.2 Hz, 1 H, H_{Ar}), 3.87 (t, *J* = 7.8 Hz, 1 H, H_{Benzyl}), 2.06–1.92 (m, 2 H, $CHC\mathit{H_2}CH_2$), 1.28 (sext, *J* = 7.4 Hz, 2 H, $CH_2C\mathit{H_2}CH_3$), 0.94 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C ppm 145.7 (C), 144.0 (C), 132.3 (C), 130.3 (CH), 129.9 (C), 129.8 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.5 (CH), 50.2 (CH), 37.6 (CH_2), 21.0 (CH_2), 14.0 (CH_3).

HPLC separation conditions: Chiralpak IB column with guard, 0.1% *i*PrOH in hexane, flow rate 0.4 mL/min, 0 °C; t_R 17.0 min for (*S*)-enantiomer (minor) and t_R 18.0 min for (*R*)-enantiomer (major).

e.r. = 93.7:6.3.

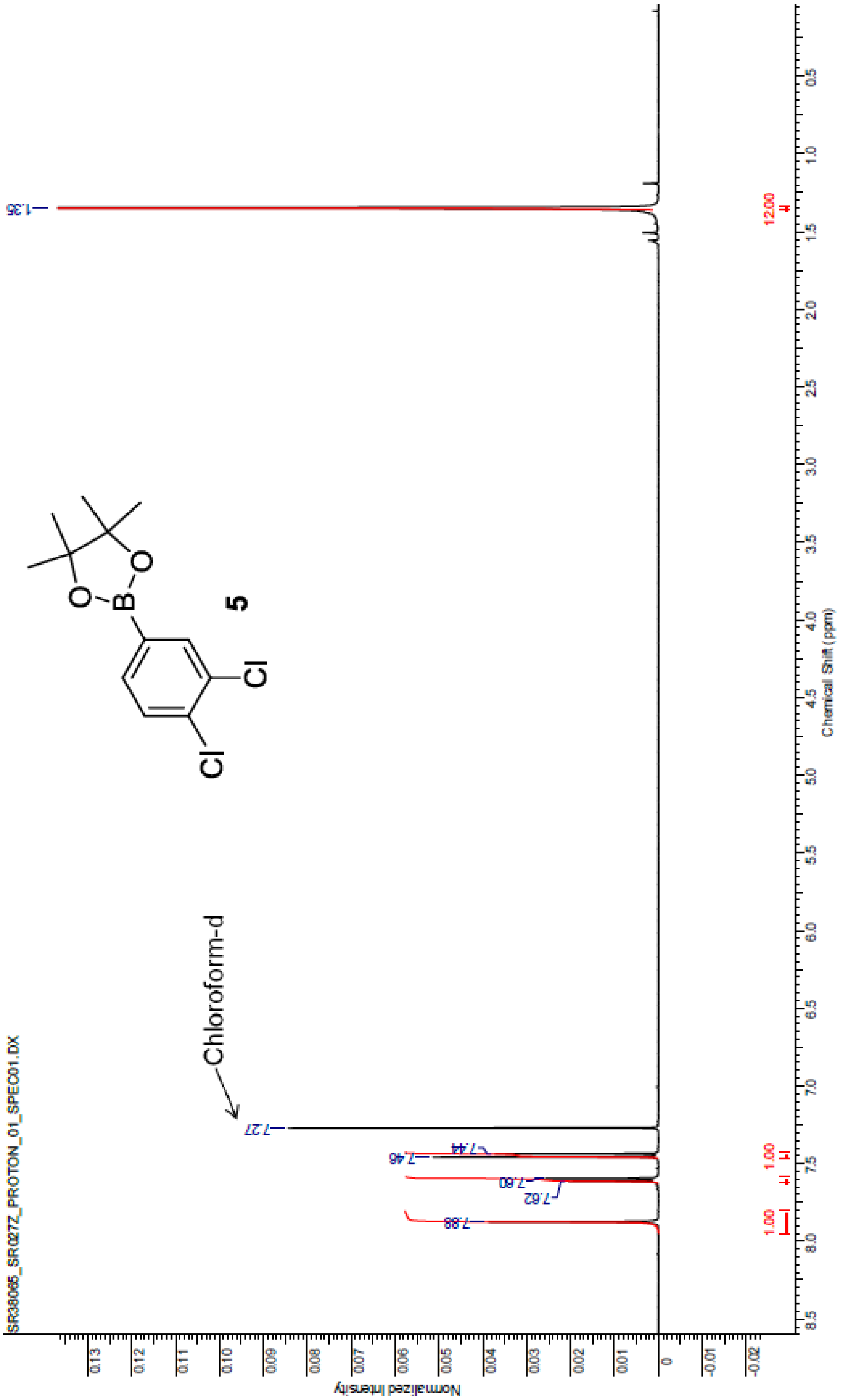




3. ^{1}H NMR and ^{13}C NMR spectra

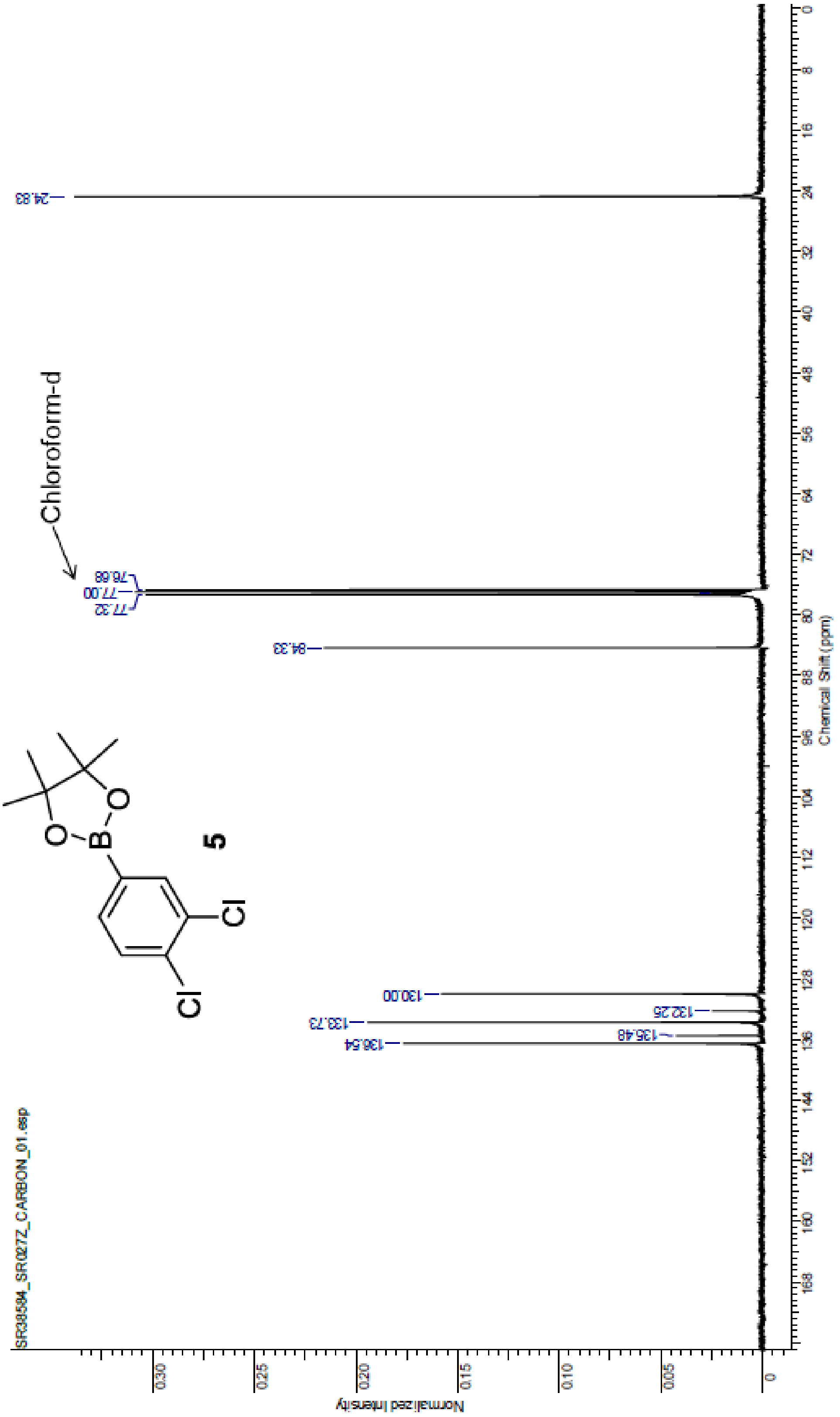
2-(3,4-Dichlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (5)

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



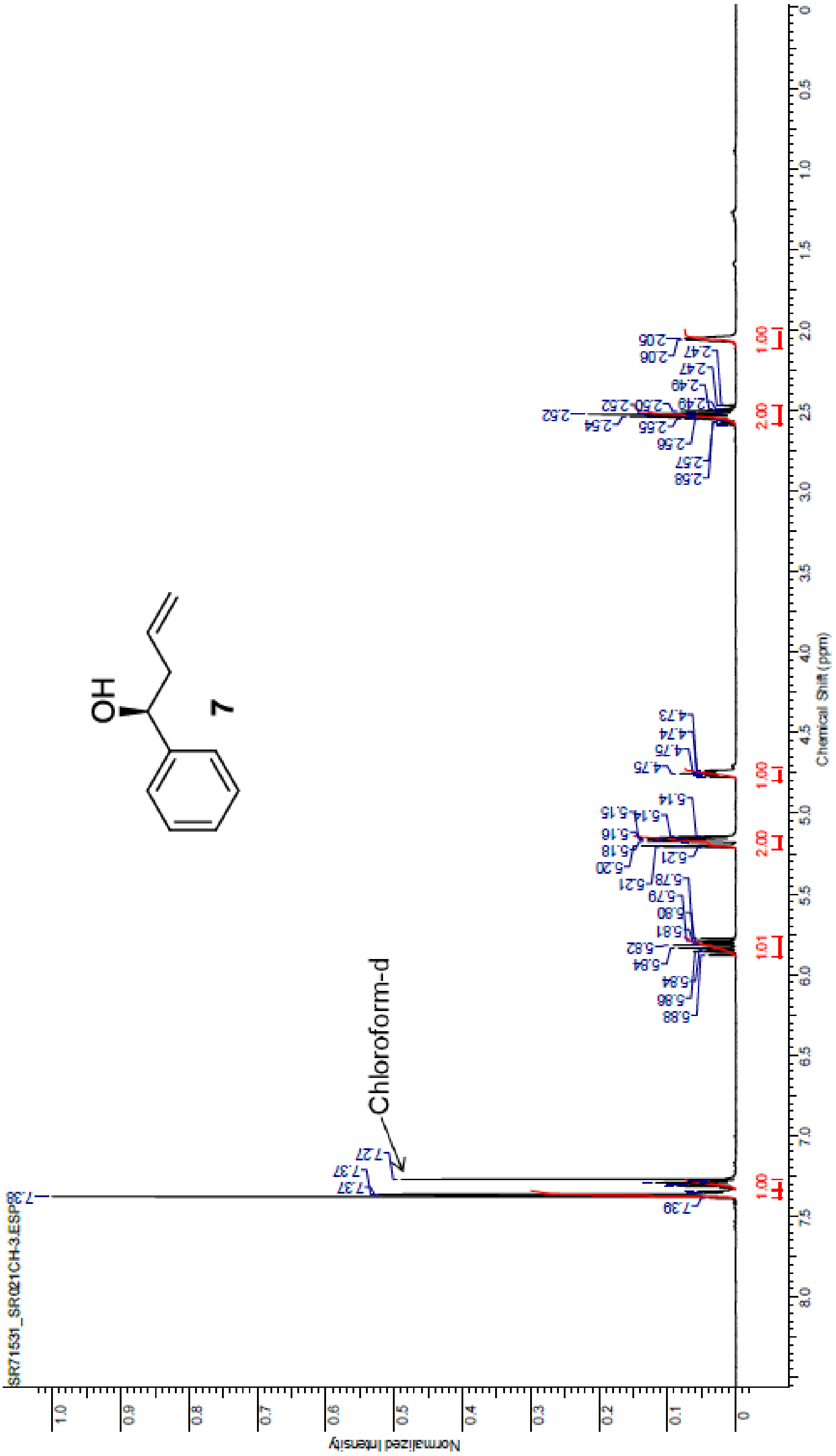
2-(3,4-Dichlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (5)

^{13}C NMR (101 MHz, $CDCl_3$)



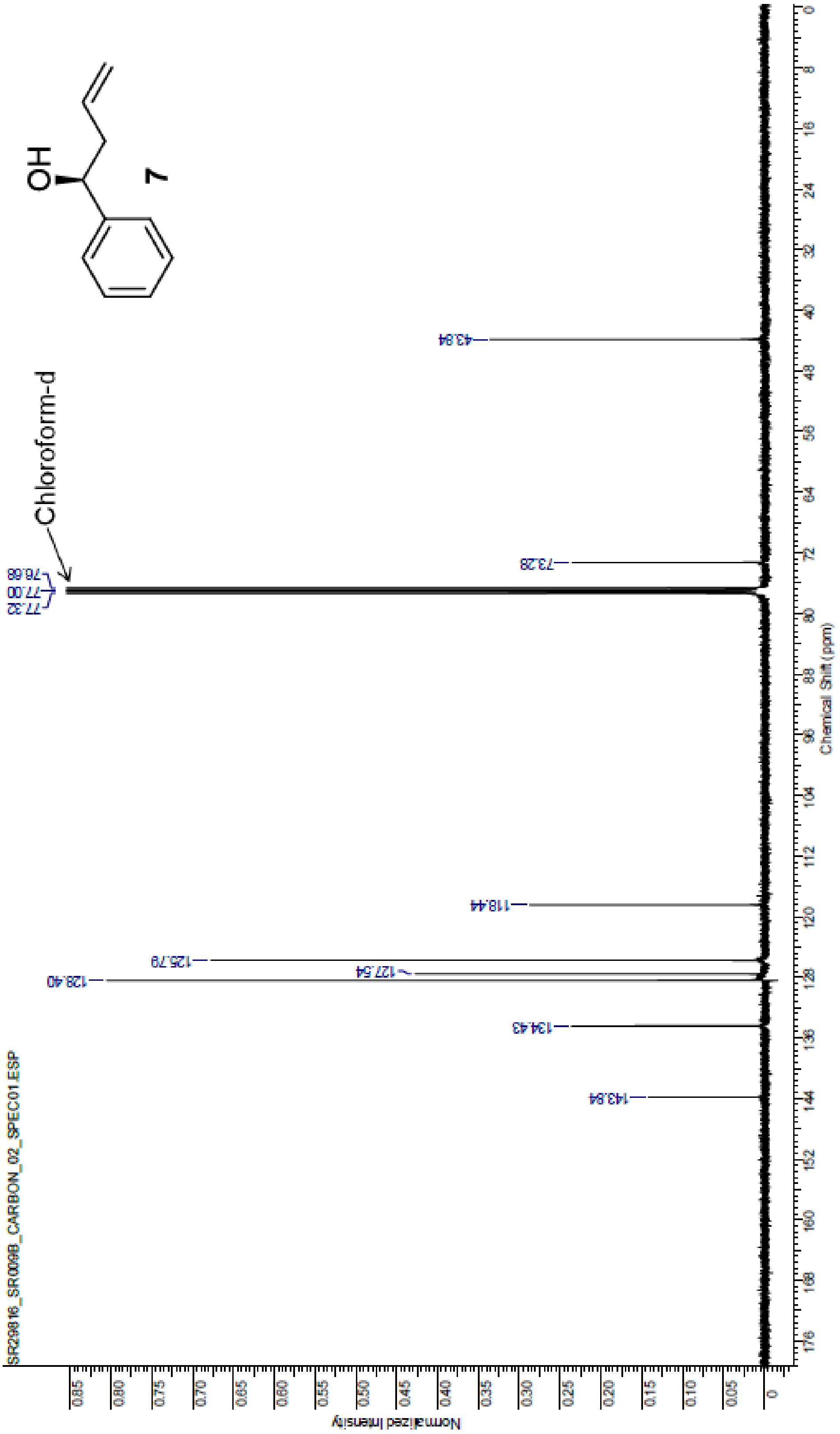
(*S*)-1-Phenylbut-3-en-1-ol (7)

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



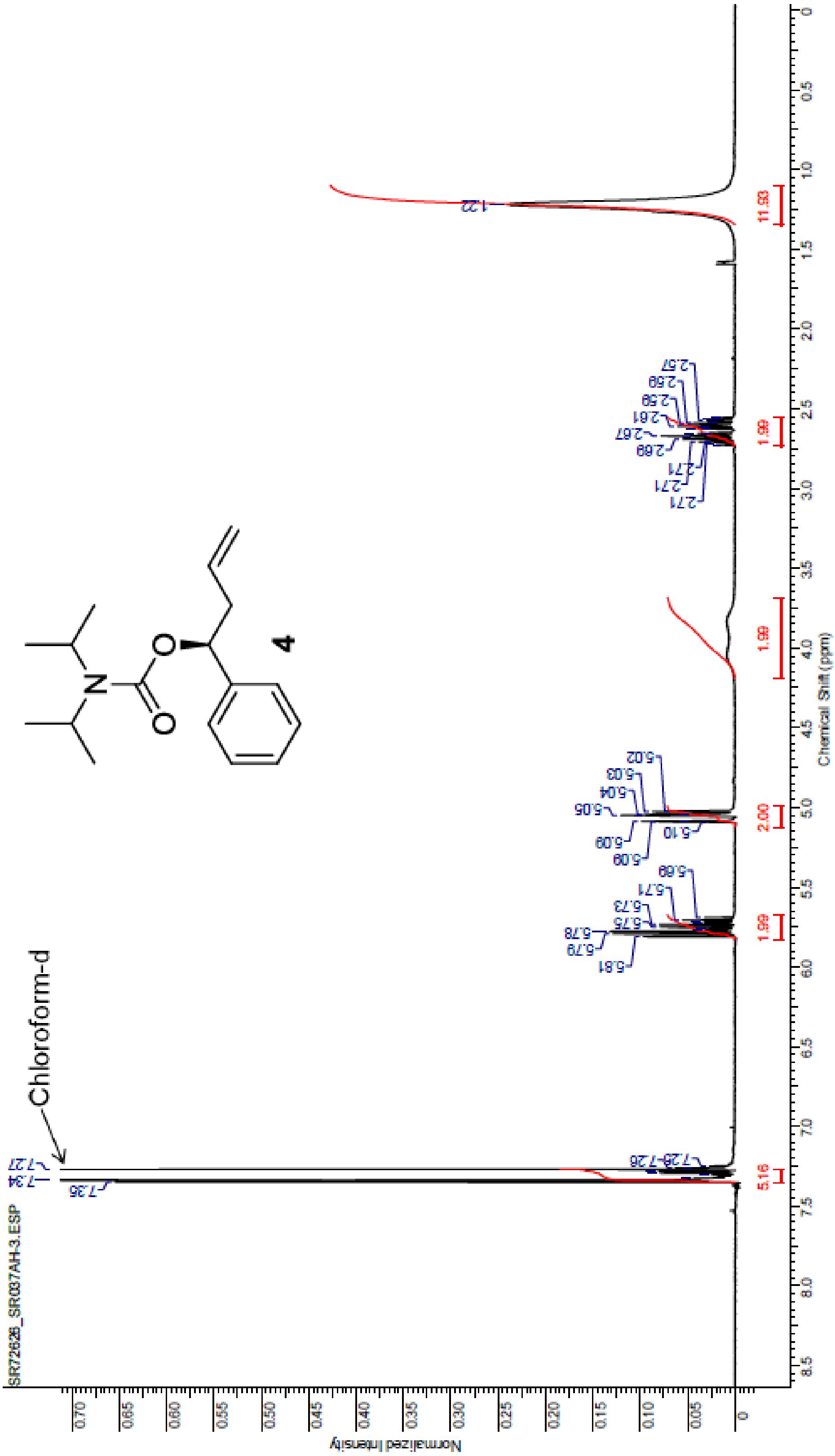
(*S*)-1-Phenylbut-3-en-1-ol (7)

^{13}C NMR (101 MHz, $CDCl_3$)



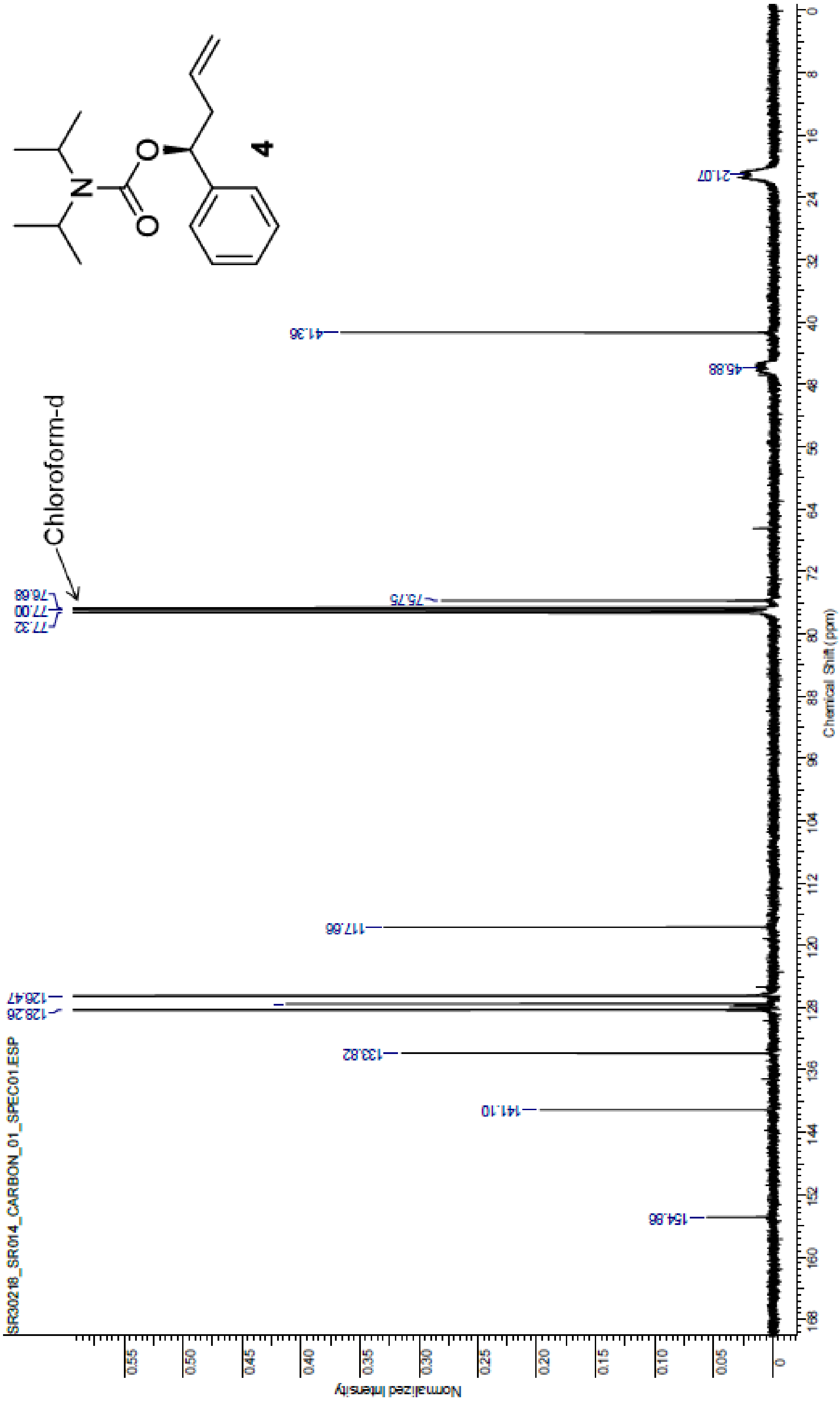
(*S*)-1-Phenylbut-3-enyl diisopropylcarbamate (4)

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



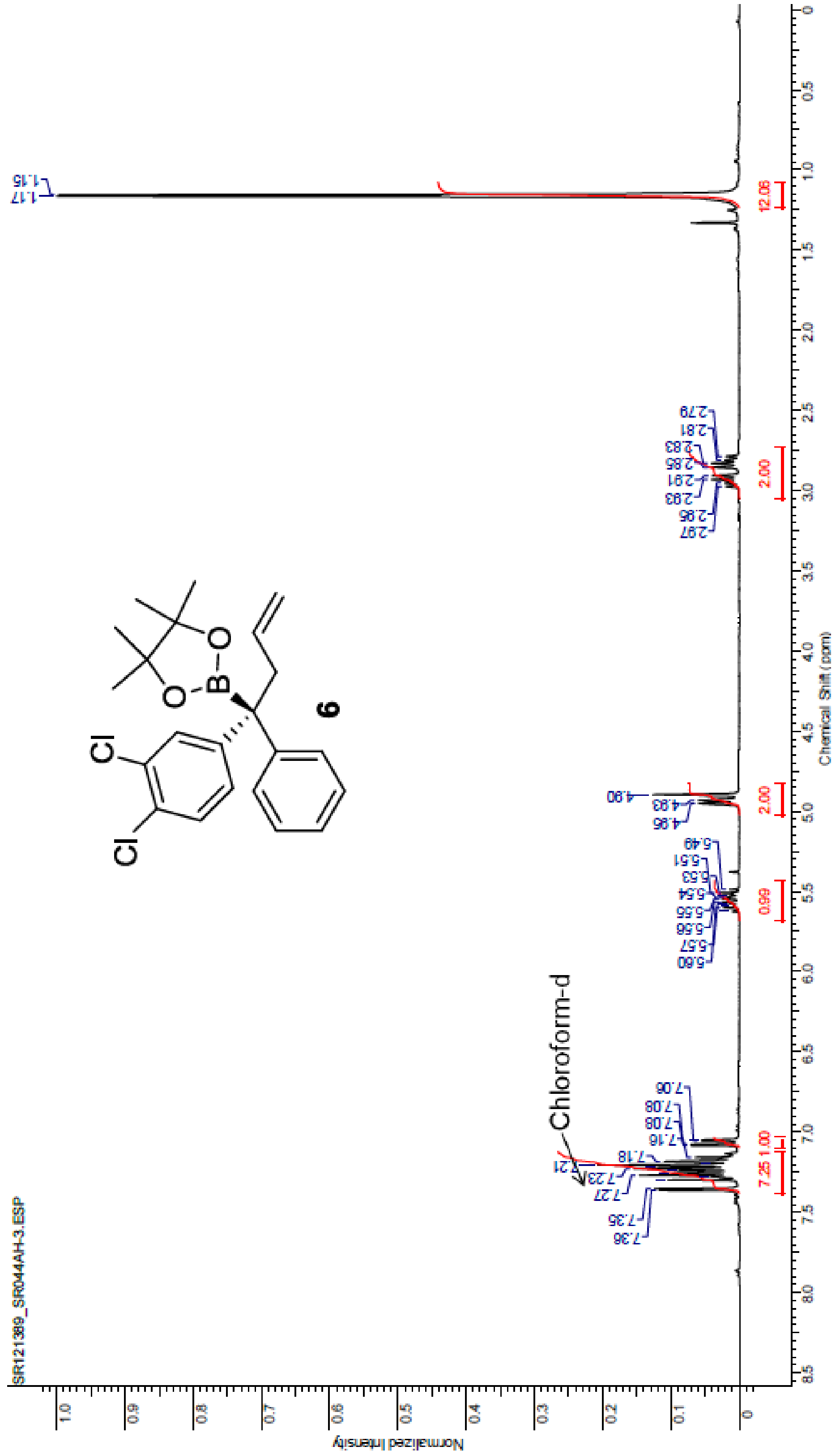
(*S*)-1-Phenylbut-3-enyl diisopropylcarbamate (4)

^{13}C NMR (101 MHz, CDCl$_3$)



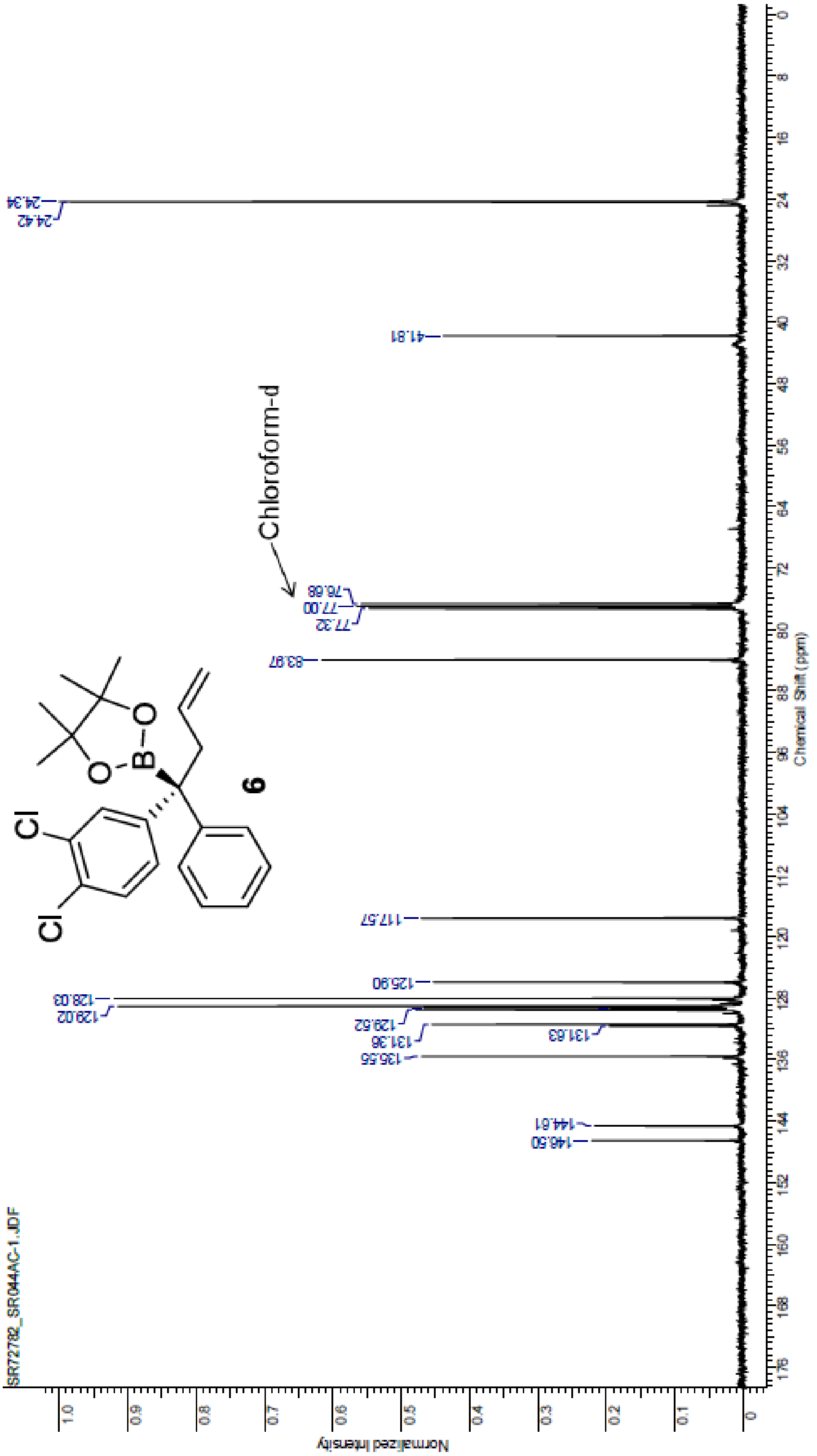
(*R*)-2-(1-(3,4-Dichlorophenyl)-1-phenylbut-3-enyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (6)

^{1}H NMR (301 MHz, $CDCl_3$)



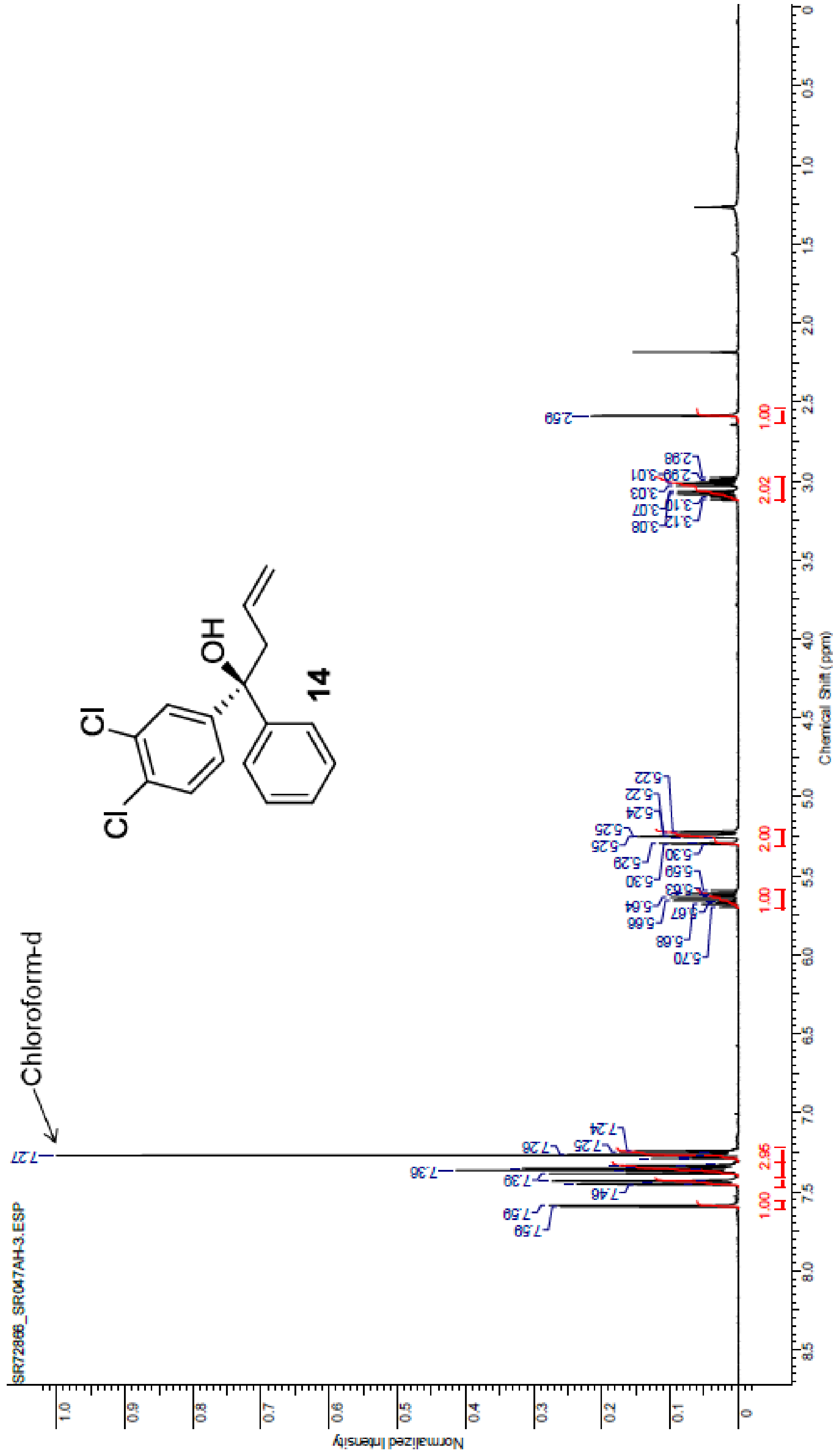
(*R*)-2-(1-(3,4-Dichlorophenyl)-1-phenylbut-3-enyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (6)

^{13}C NMR (101 MHz, CDCl$_3$)



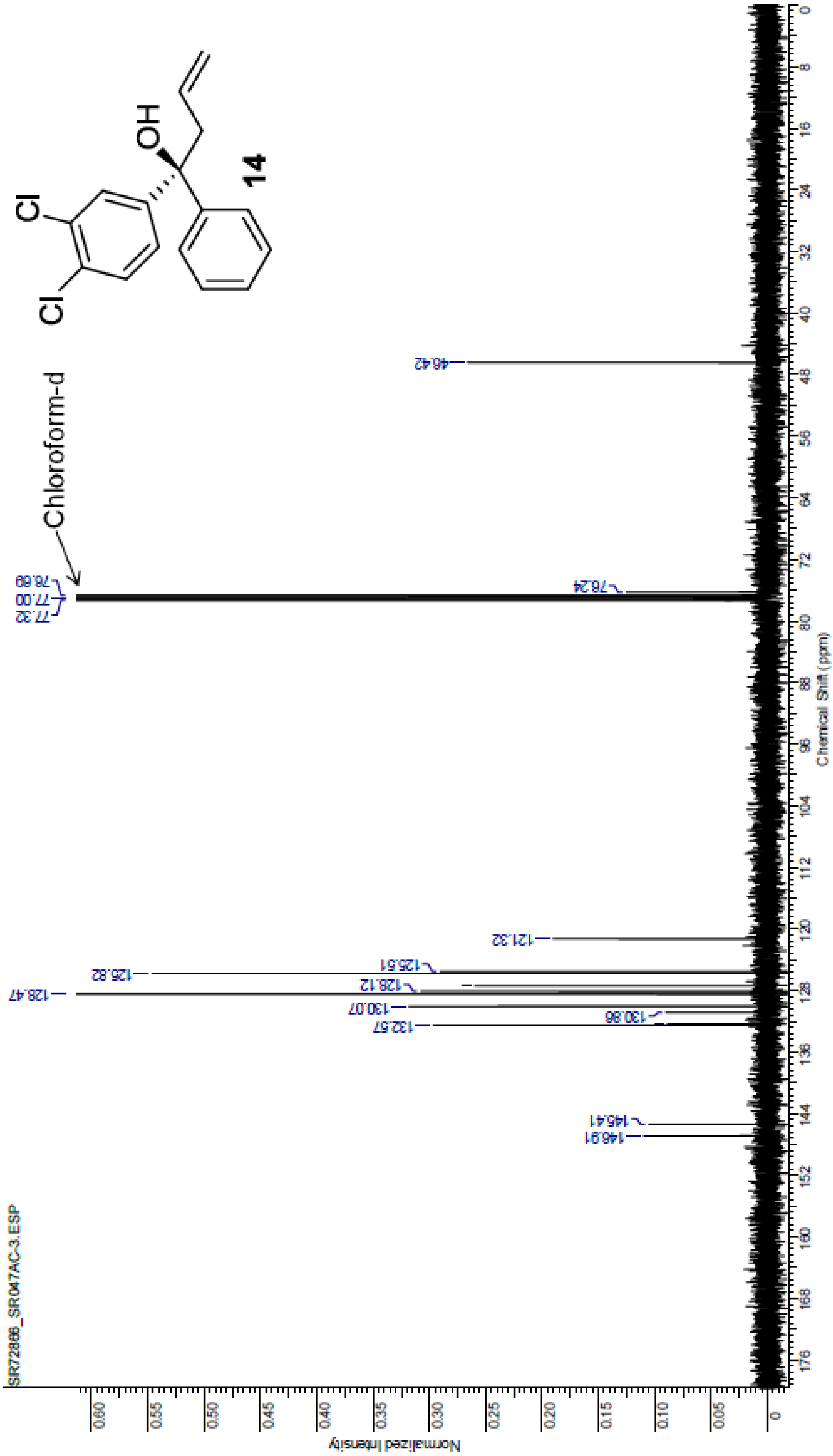
(*S*)-1-(3,4-Dichlorophenyl)-1-phenylbut-3-en-1-ol (14)

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



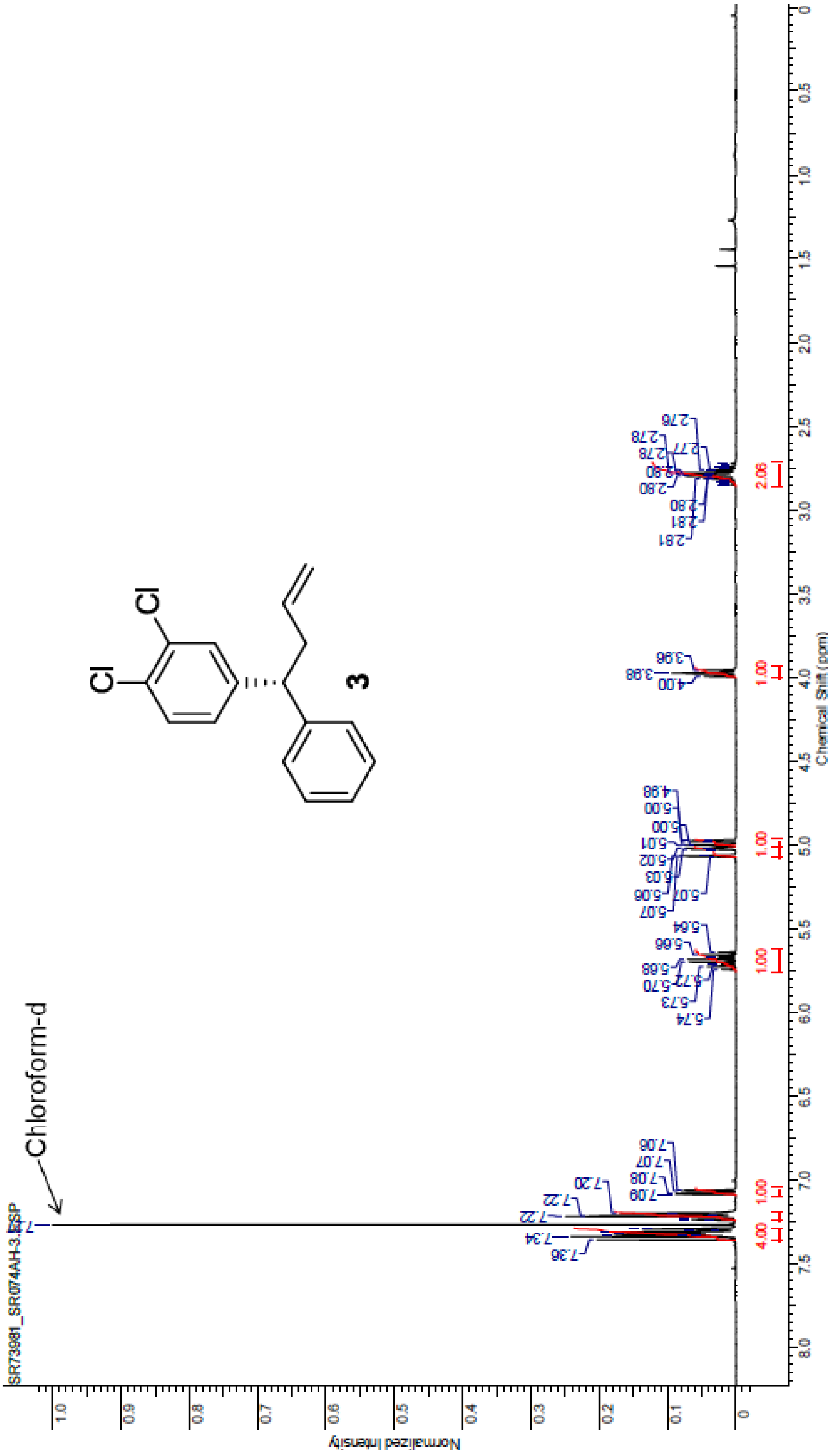
(*S*)-1-(3,4-Dichlorophenyl)-1-phenylbut-3-en-1-ol (14)

^{13}C NMR (101 MHz, CDCl$_3$)



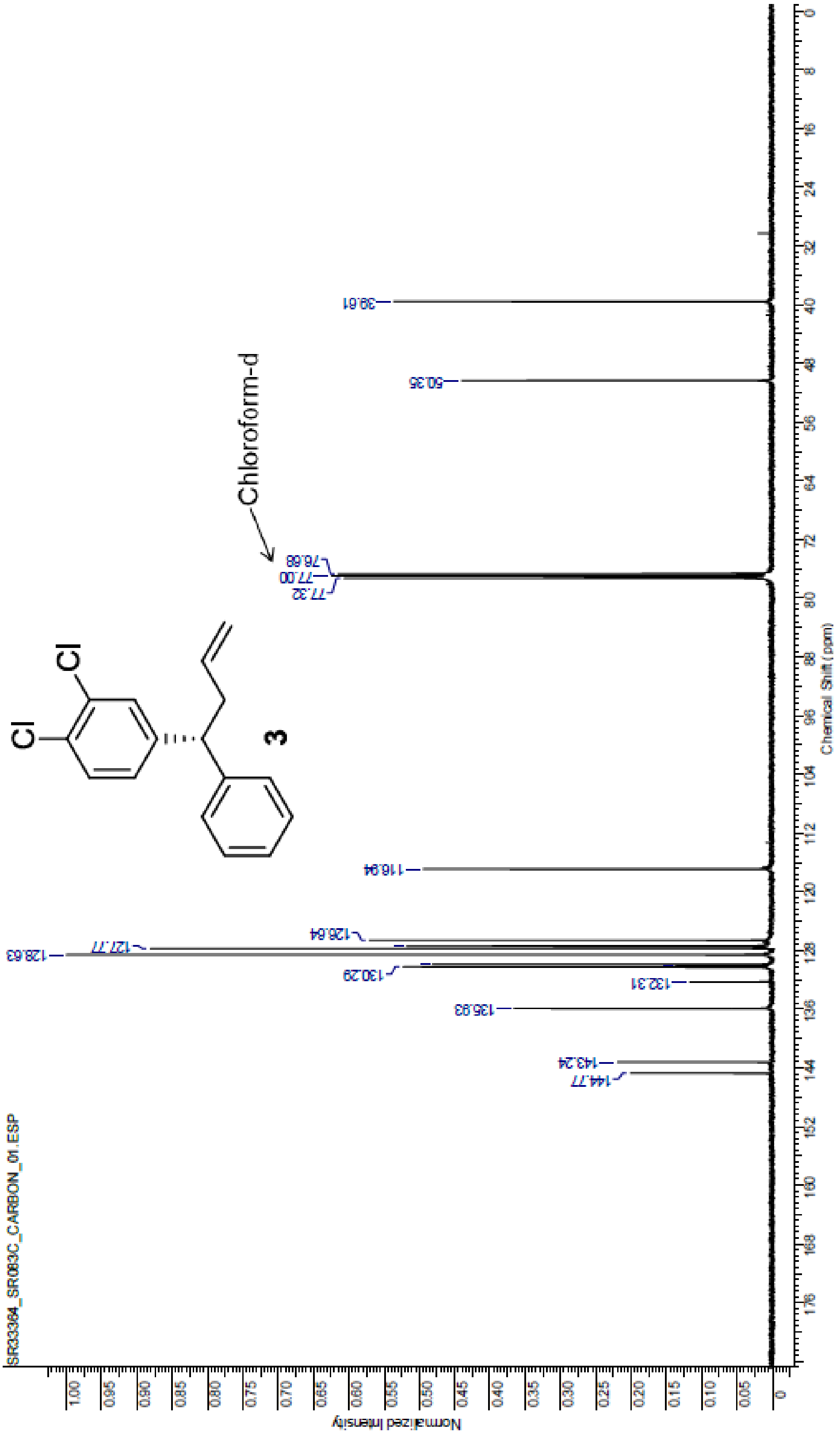
(*R*)-1,2-Dichloro-4-(1-phenylbut-3-enyl)benzene (3)

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



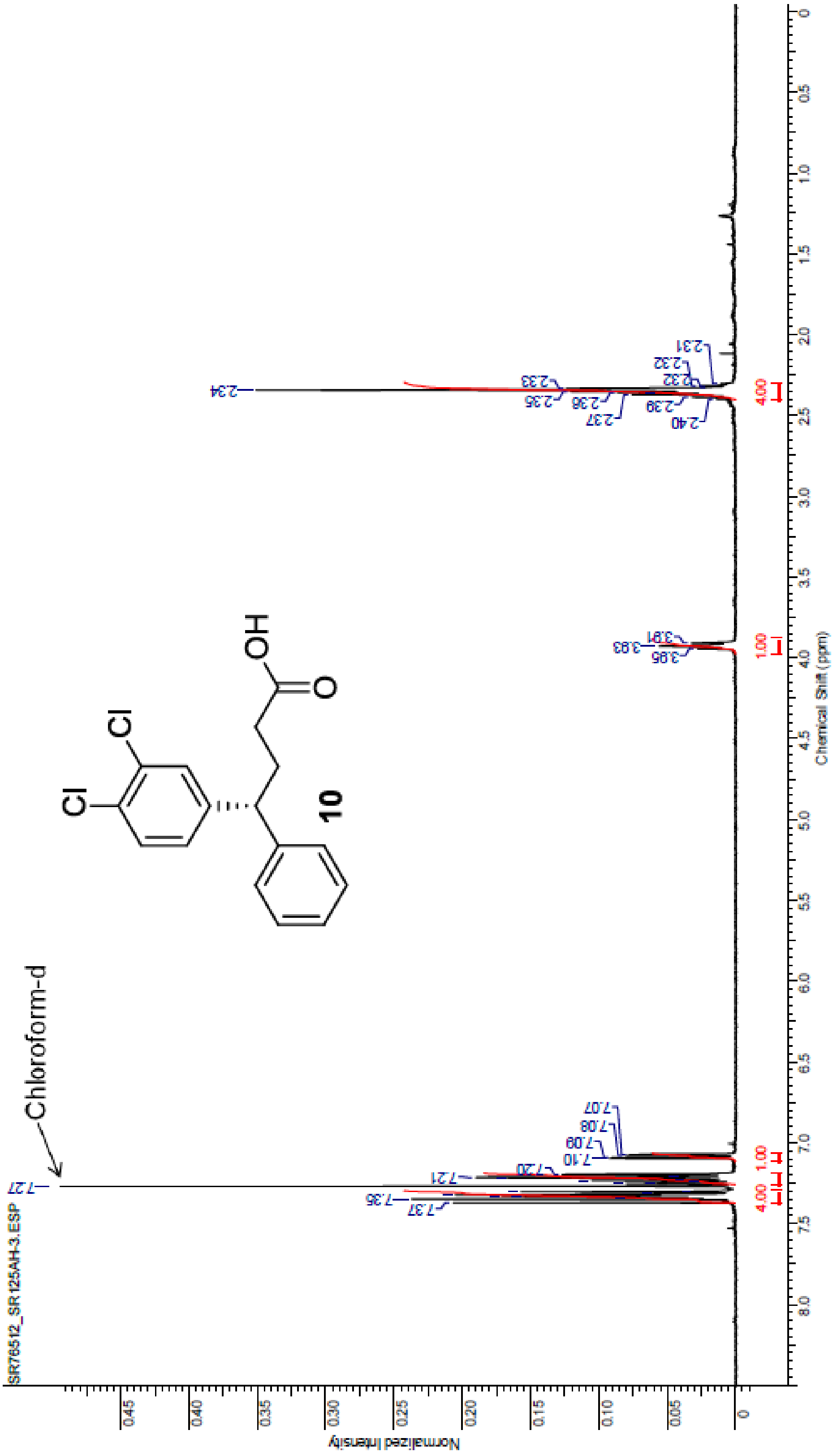
(*R*)-1,2-Dichloro-4-(1-phenylbut-3-enyl)benzene (3)

^{13}C NMR (101 MHz, $CDCl_3$)



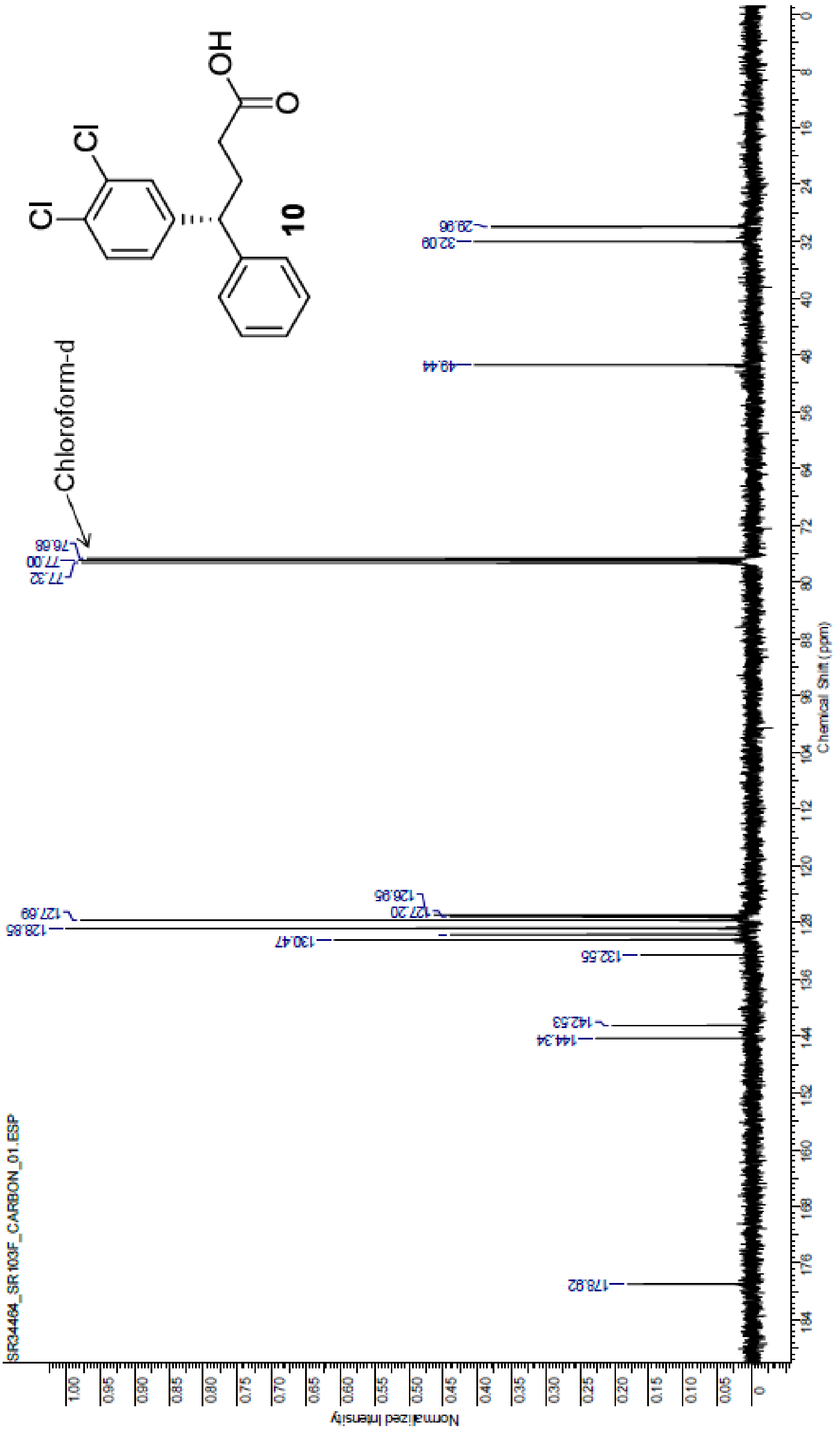
(*R*)-4-(3,4-Dichlorophenyl)-4-phenylbutanoic acid (10)

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



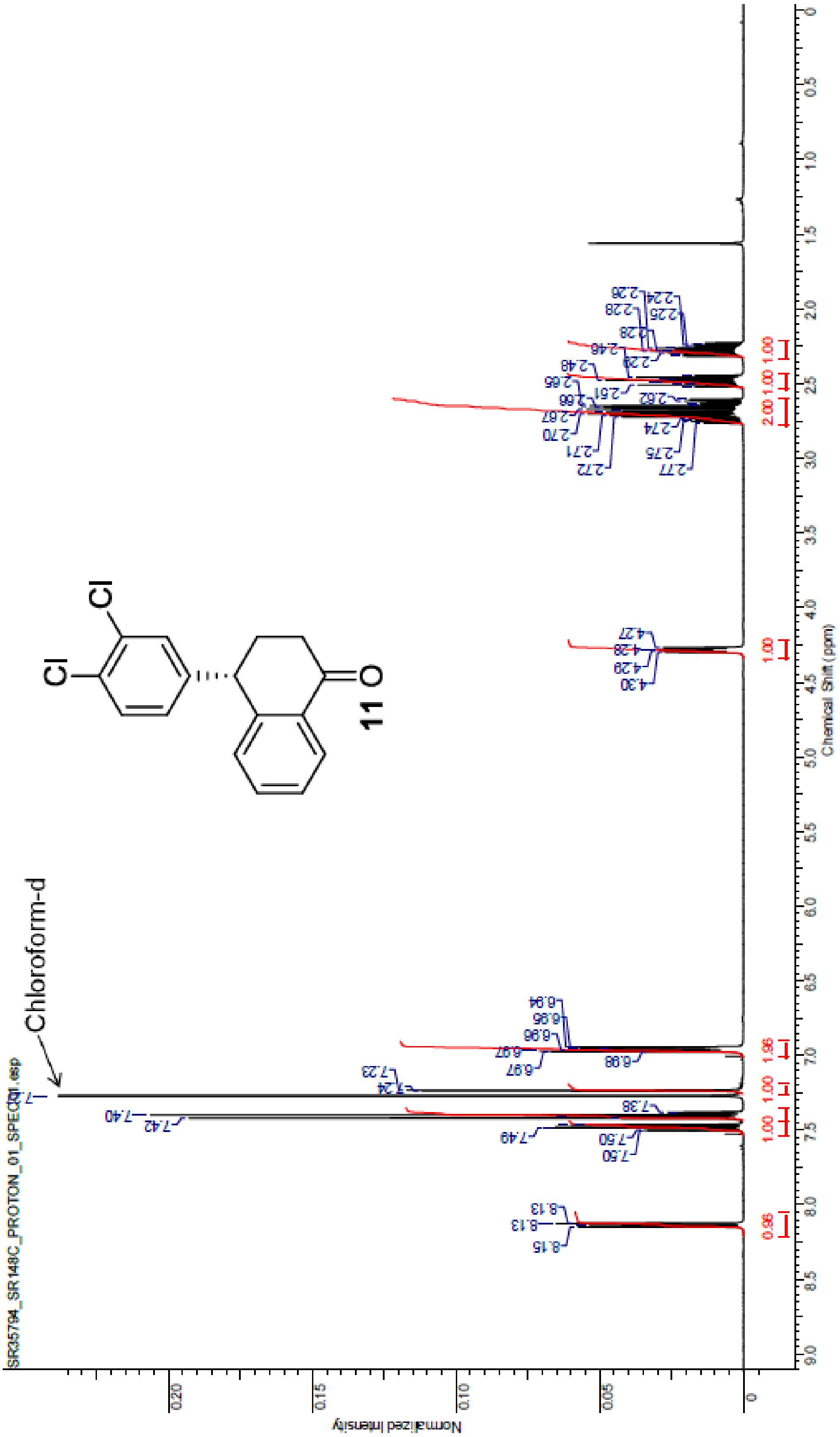
(*R*)-4-(3,4-Dichlorophenyl)-4-phenylbutanoic acid (10)

^{13}C NMR (101 MHz, CDCl$_3$)



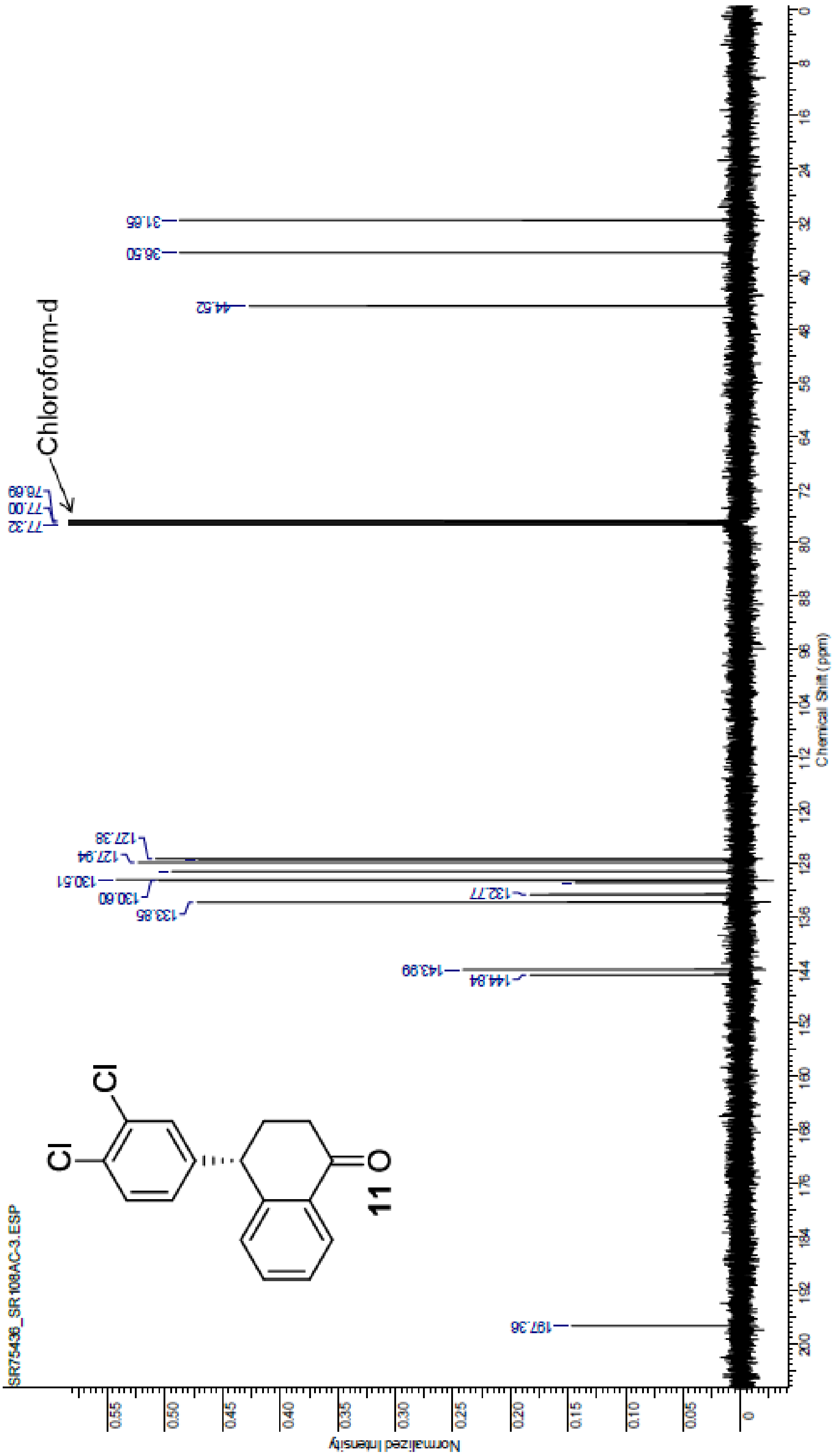
(*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (11)

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



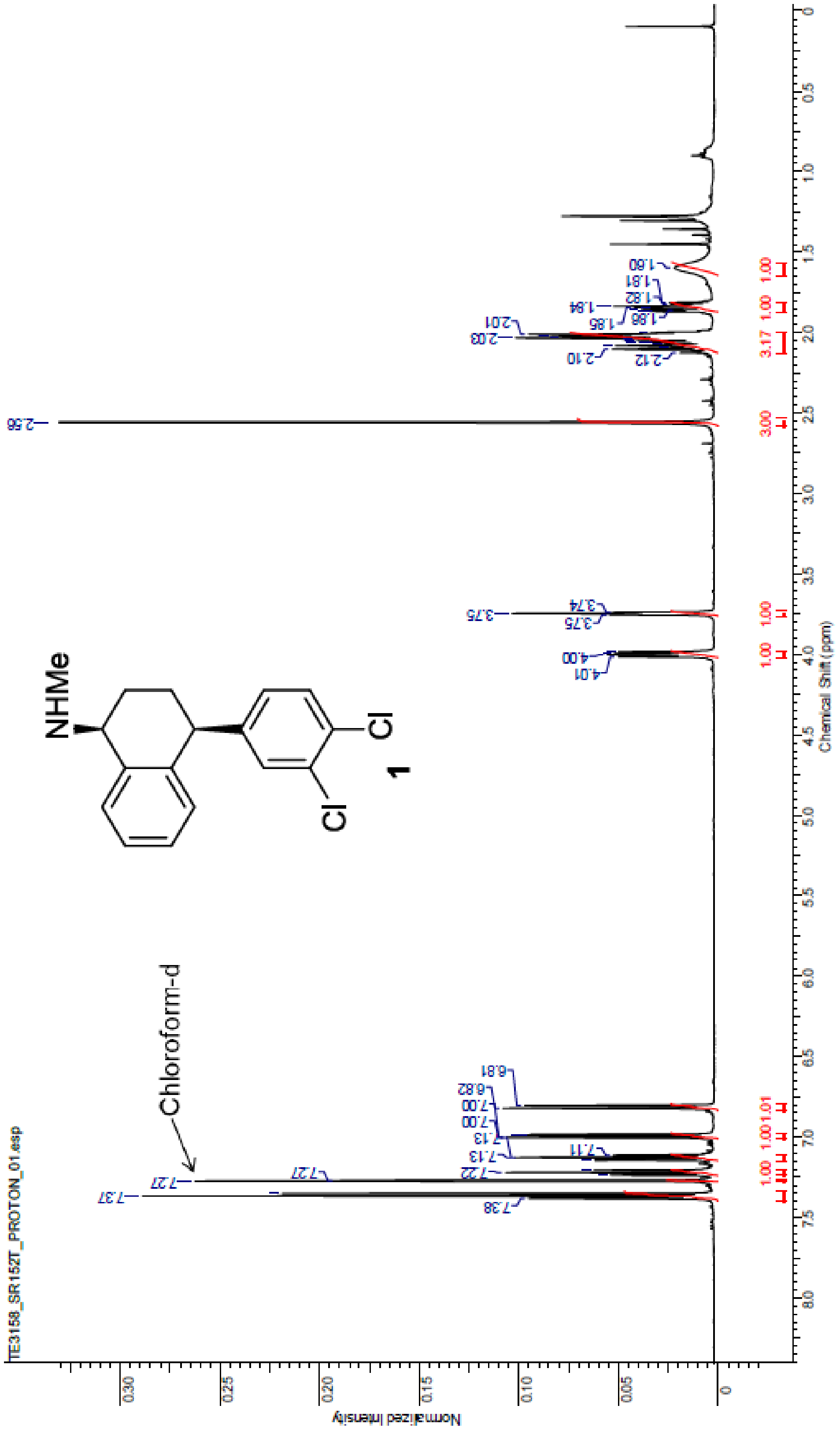
(*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (11)

^{13}C NMR (101 MHz, CDCl$_3$)



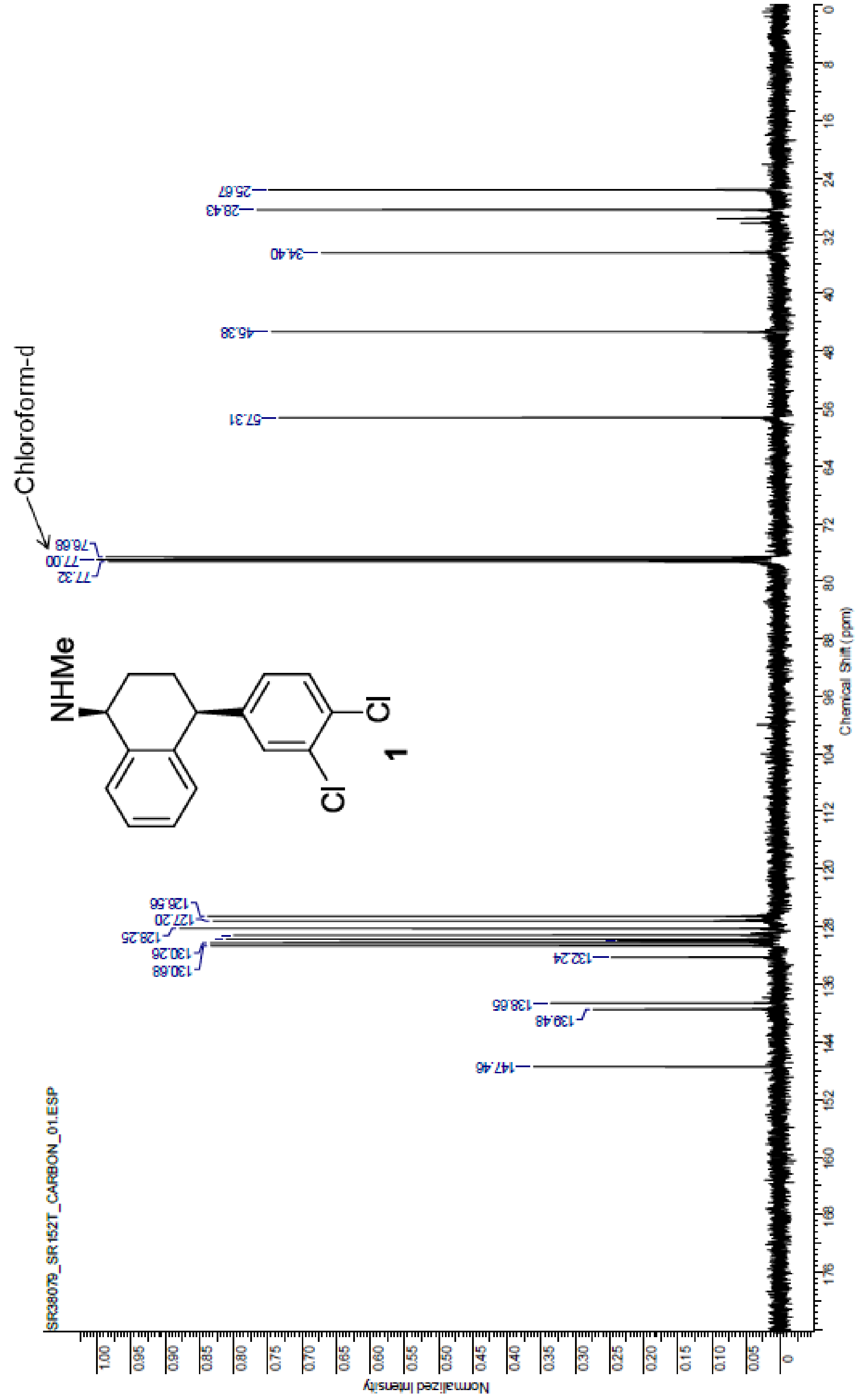
(+)-Sertraline (1)

^{1}H NMR (500 MHz, $CDCl_3$)



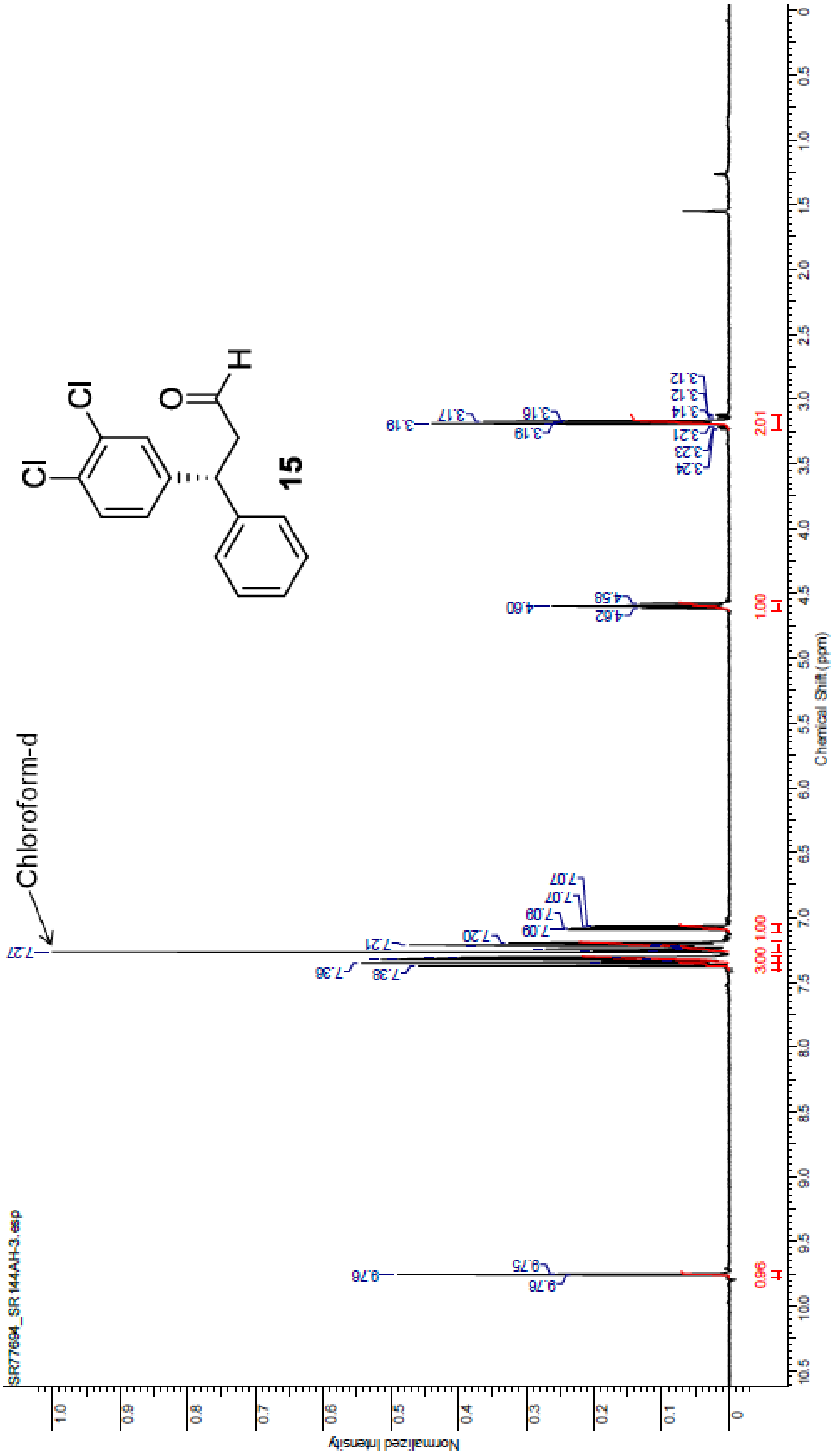
(+)-Sertraline (1)

^{13}C NMR (101 MHz, $CDCl_3$)



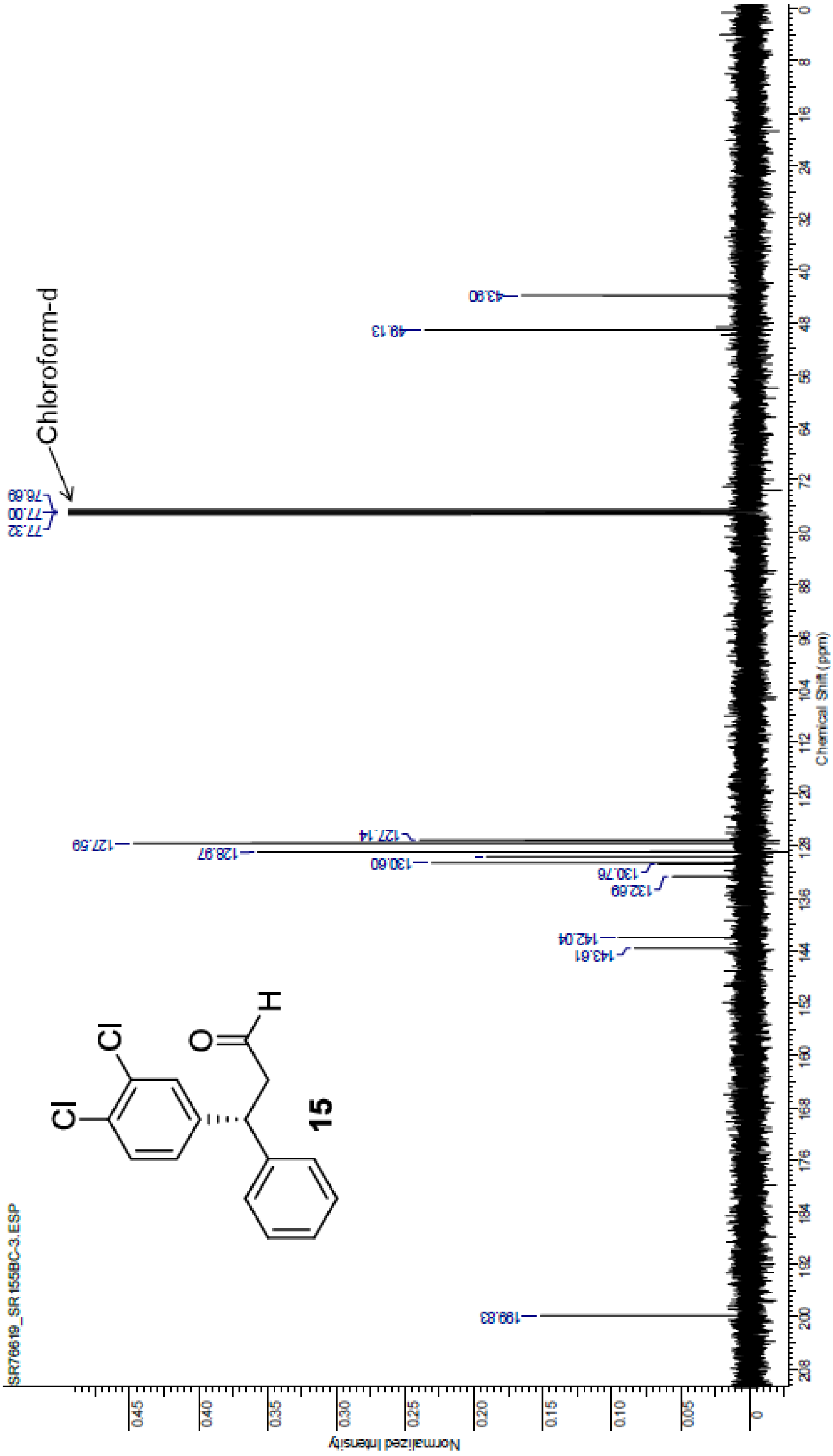
(*R*)-3-(3,4-Dichlorophenyl)-3-phenylpropanal (15)

^{1}H NMR (500 MHz, $CDCl_3$)



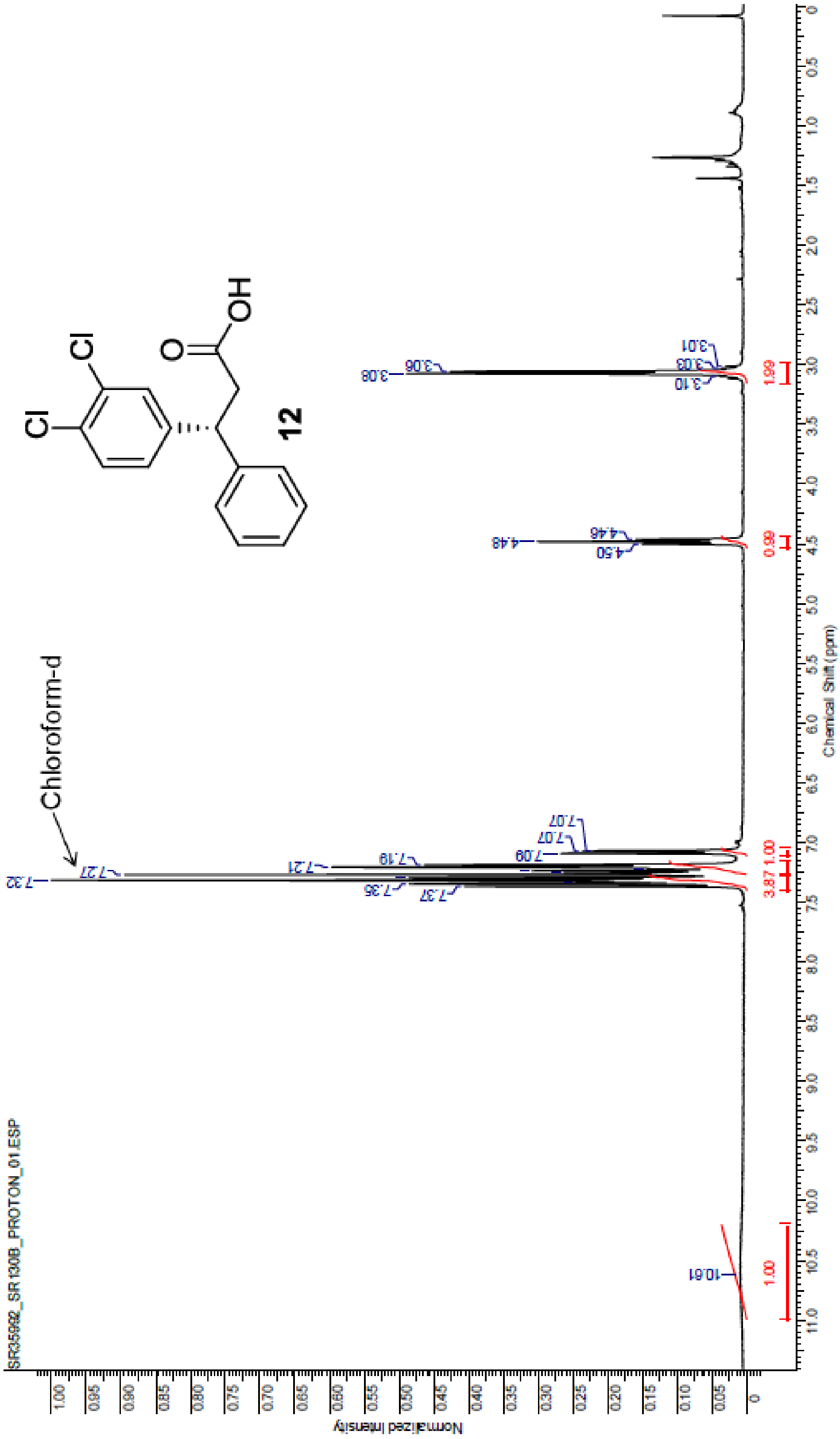
(*R*)-3-(3,4-Dichlorophenyl)-3-phenylpropanal (15)

^{13}C NMR (101 MHz, CDCl$_3$)



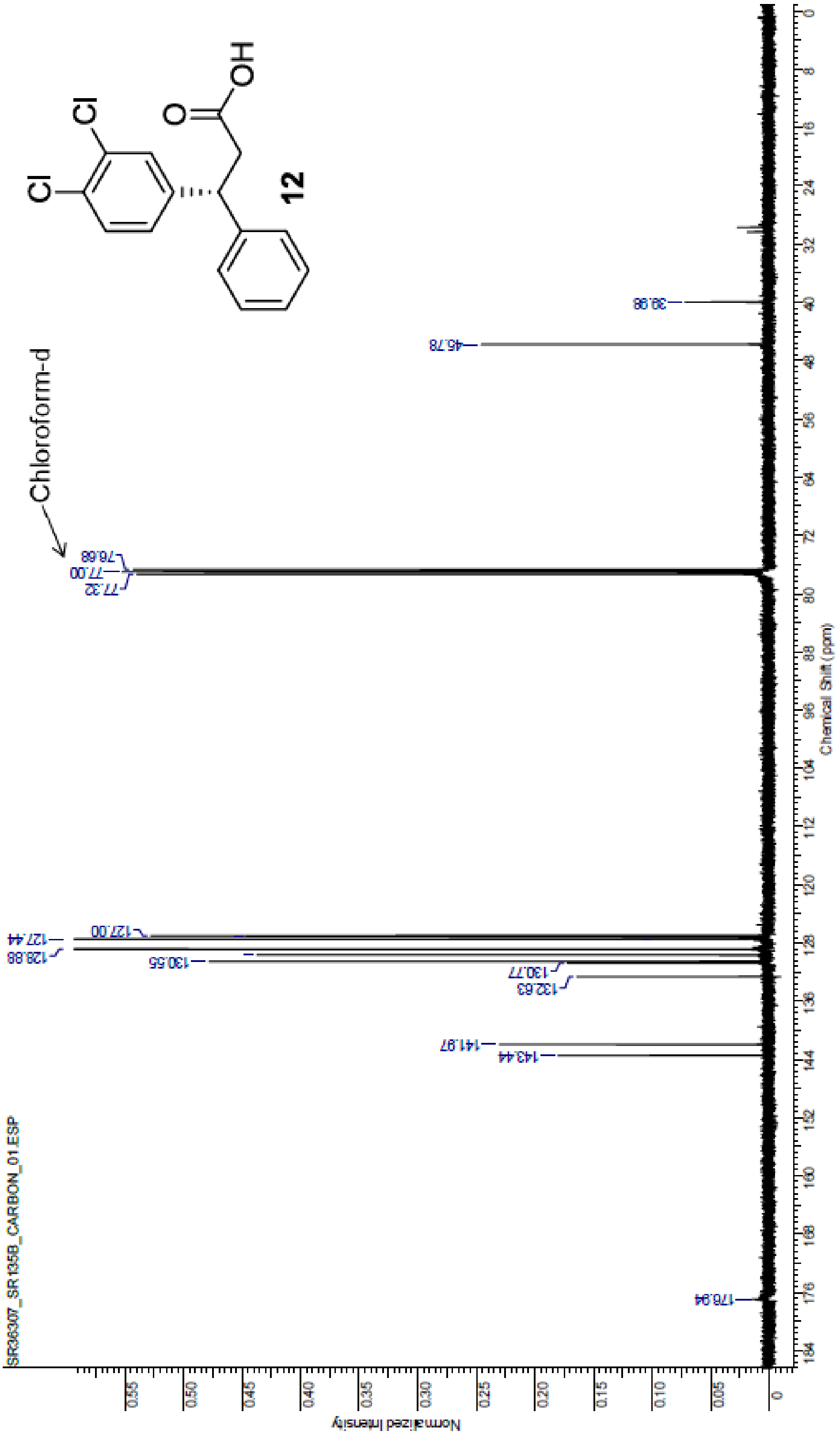
(*R*)-3-(3,4-Dichlorophenyl)-3-phenylpropanoic acid (12)

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



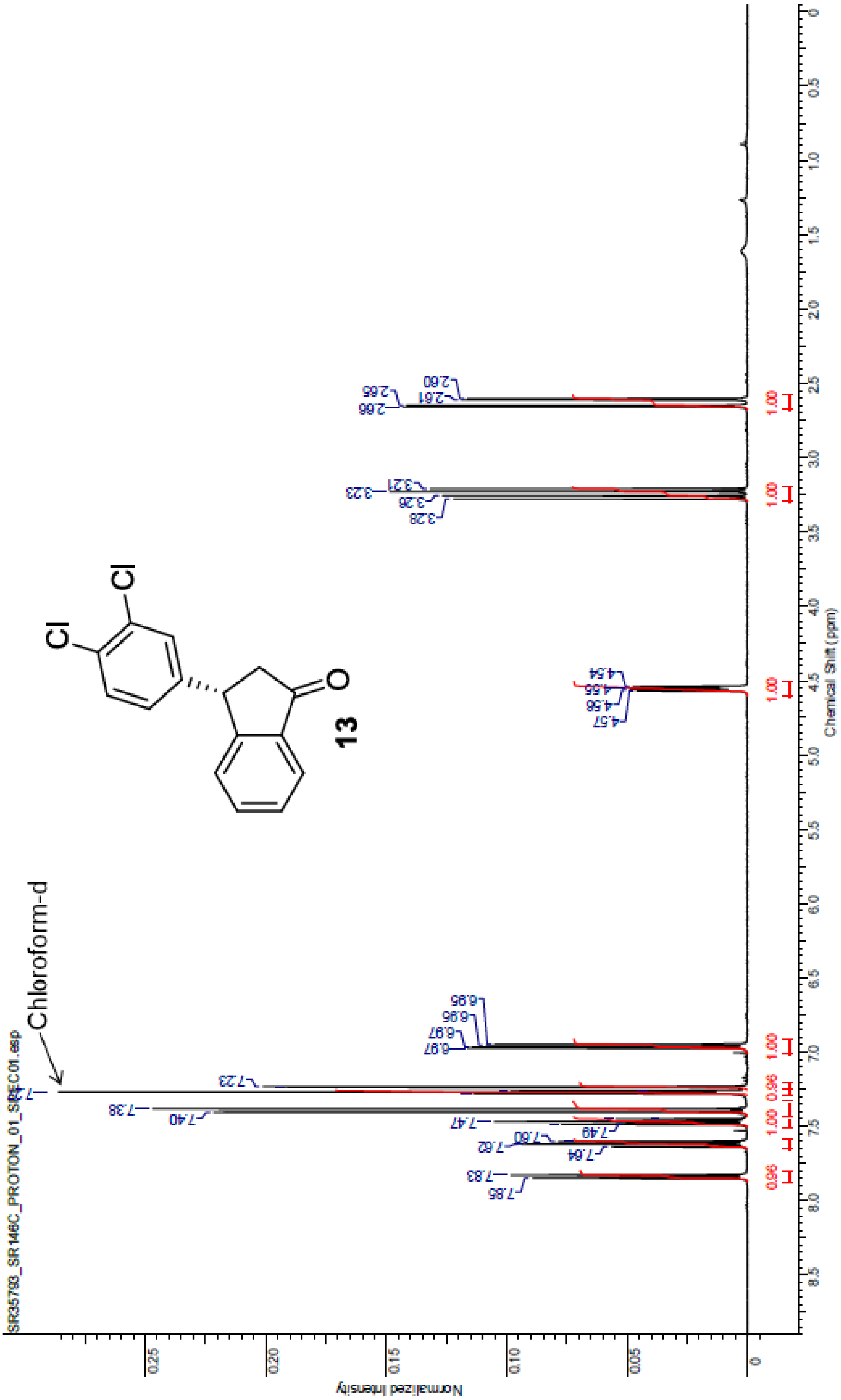
(*R*)-3-(3,4-Dichlorophenyl)-3-phenylpropanoic acid (12)

^{13}C NMR (101 MHz, CDCl$_3$)



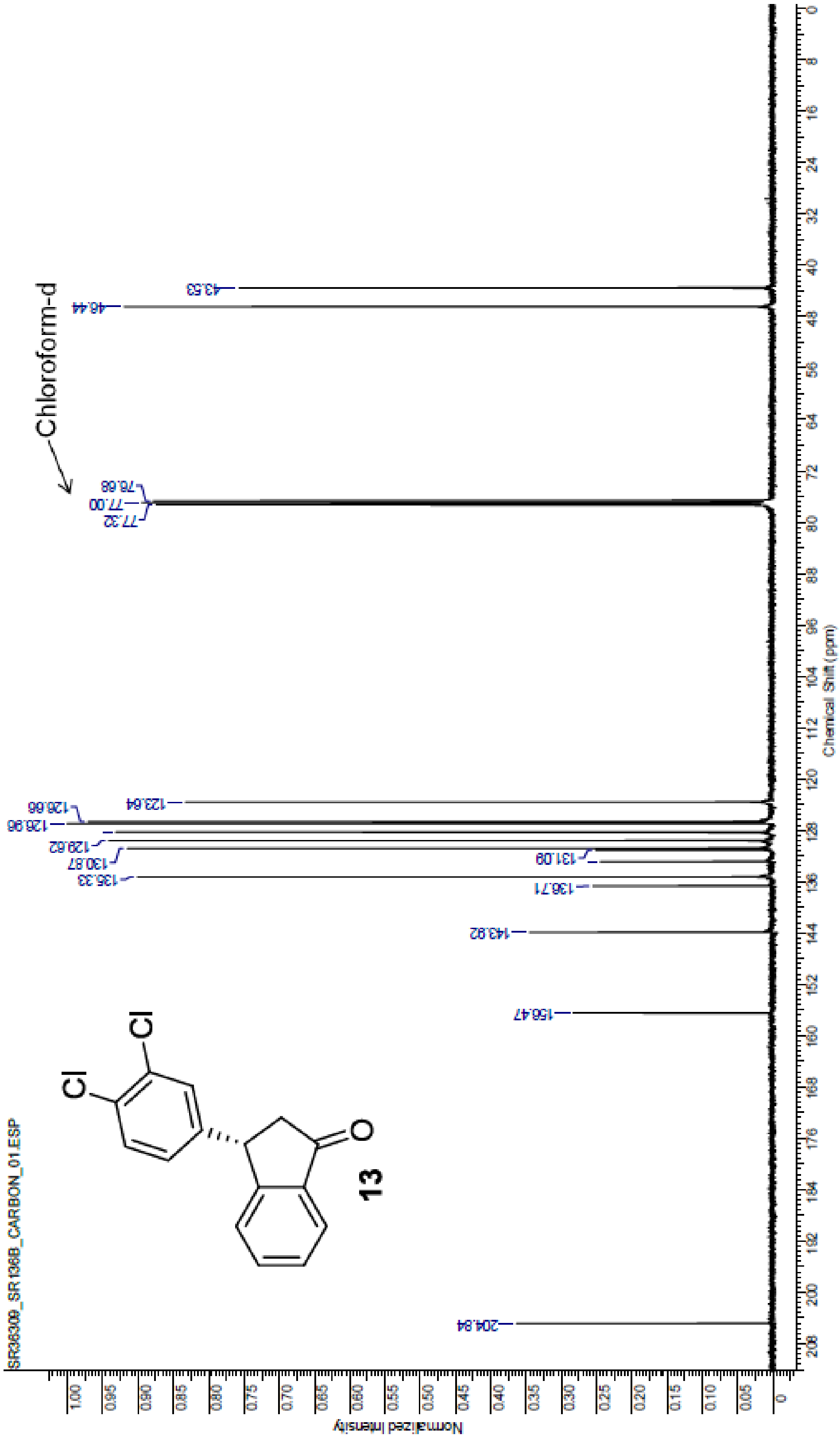
(*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (13)

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



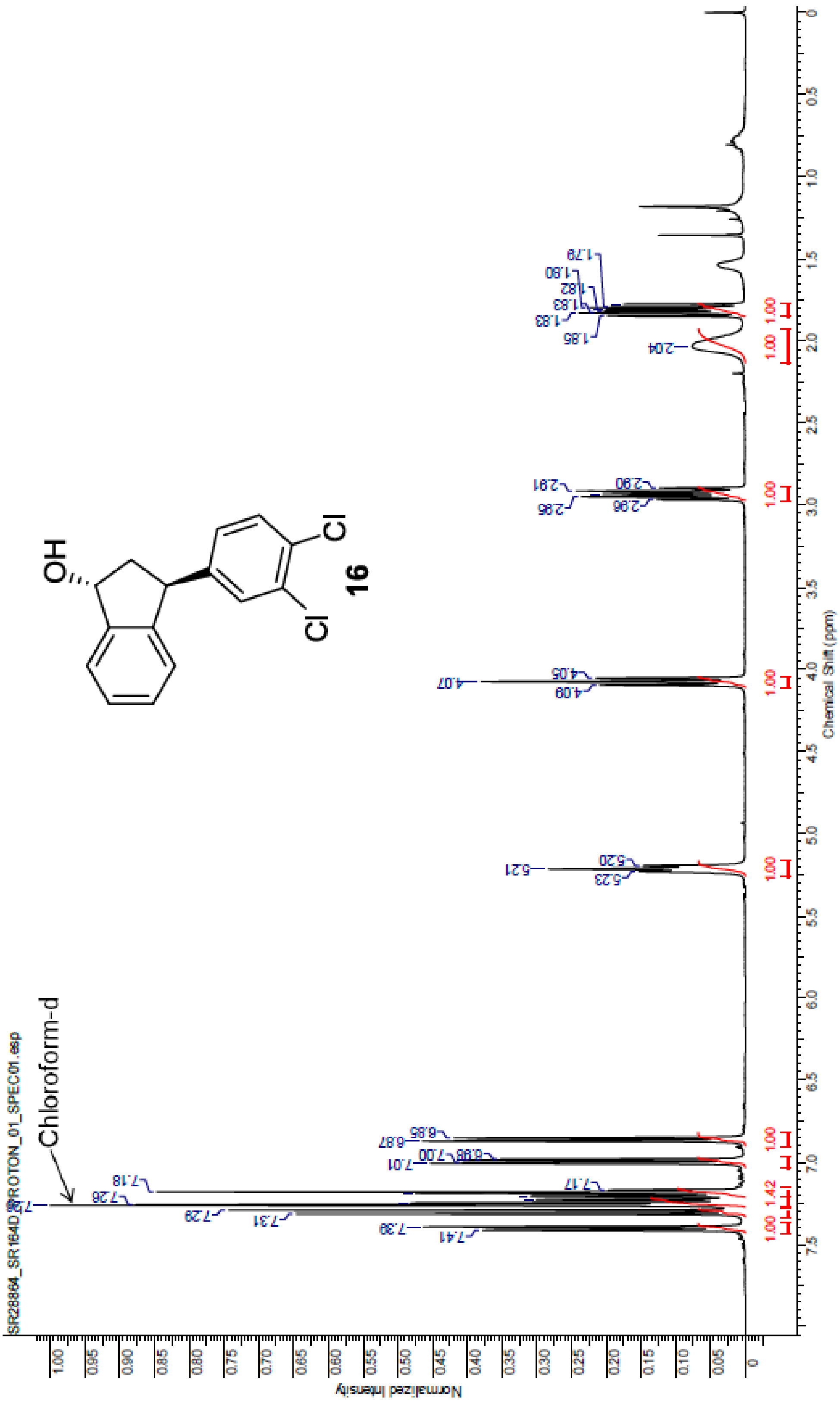
(*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (13)

^{13}C NMR (101 MHz, $CDCl_3$)



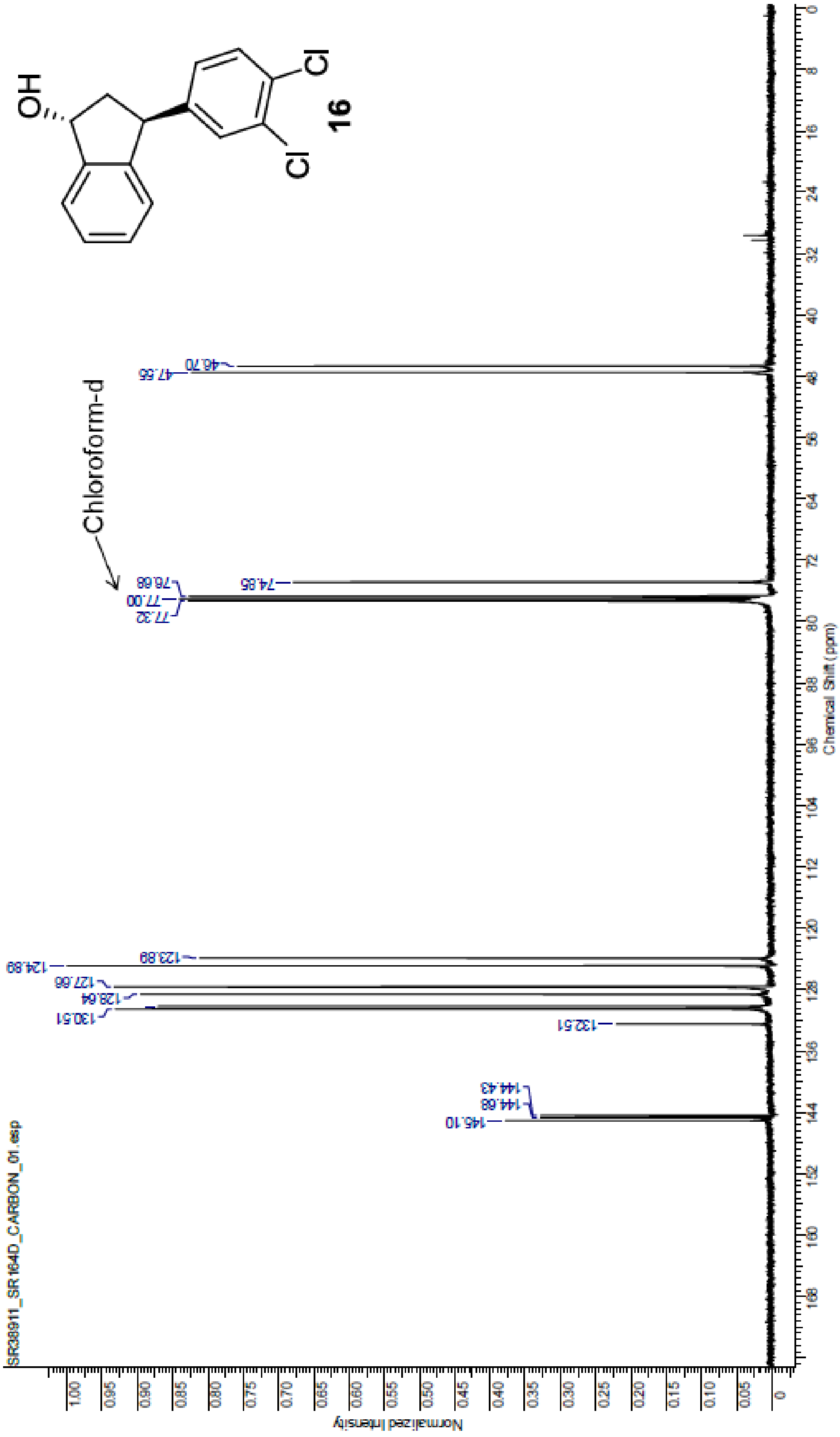
(1*S*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (16)

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



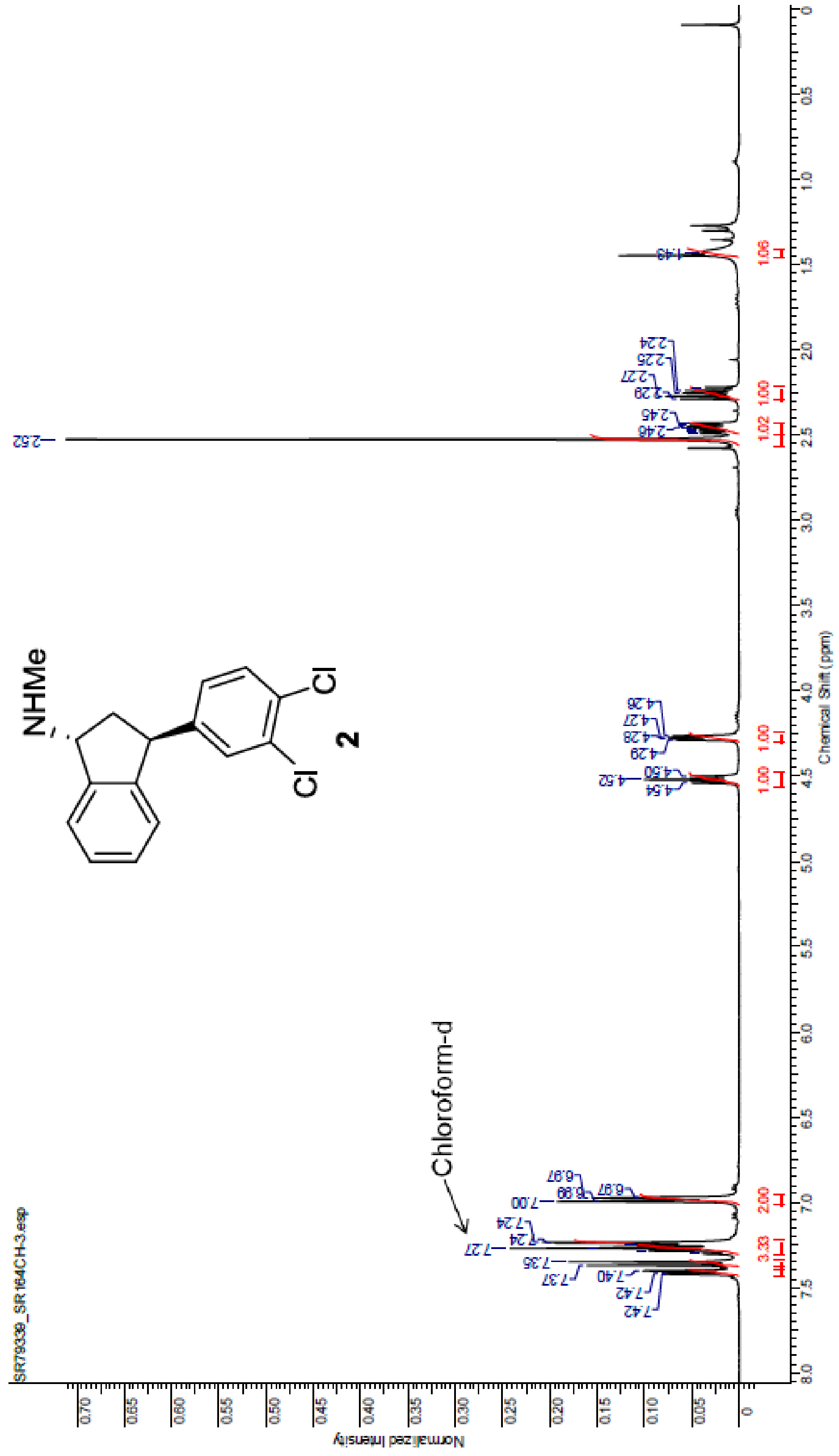
(1*S*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (16)

^{13}C NMR (101 MHz, CDCl$_3$)



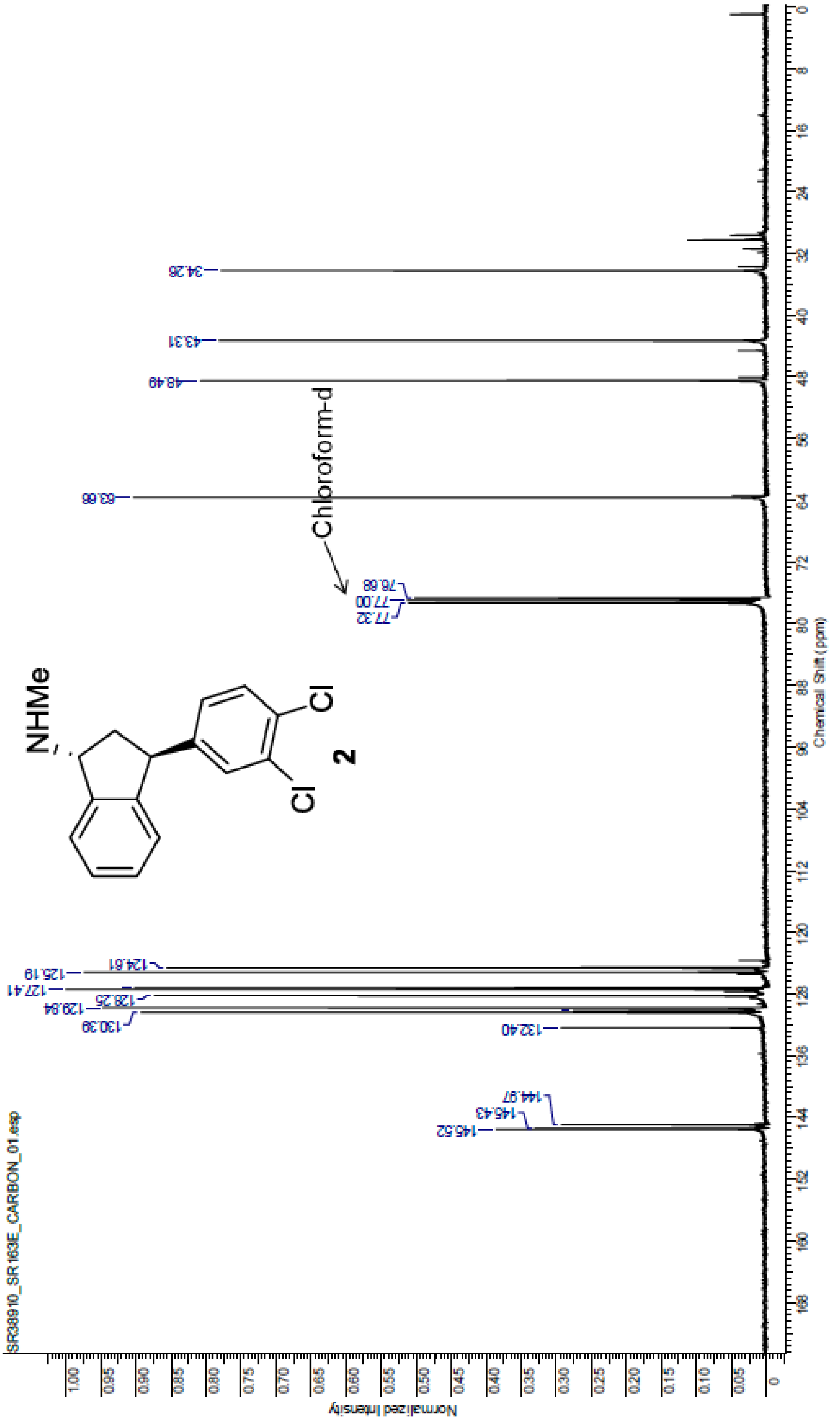
(+)-Indatraline (2)

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



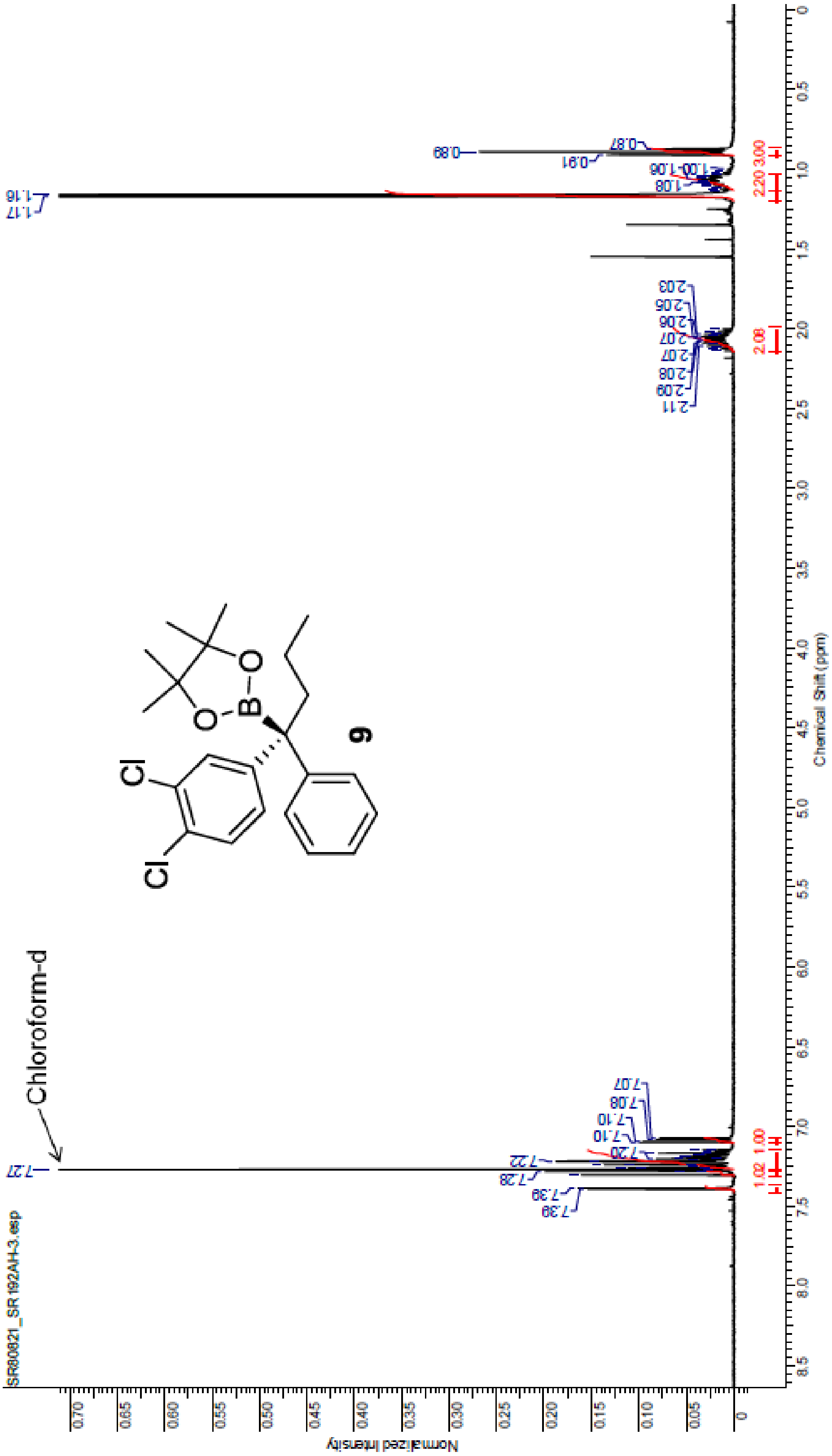
(+)-Indatraline (2)

^{13}C NMR (101 MHz, $CDCl_3$)



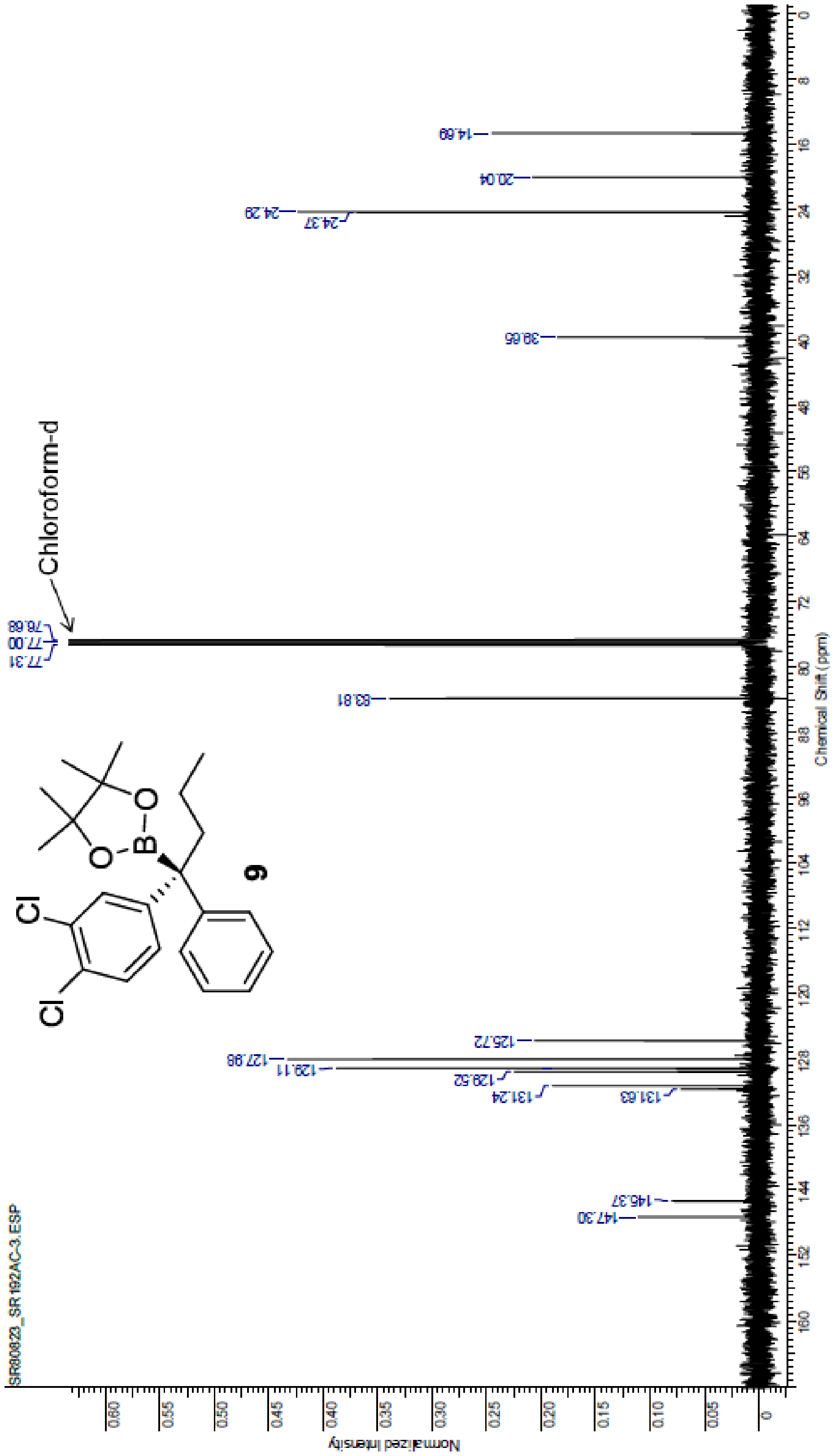
(*R*)-2-(1-(3,4-Dichlorophenyl)-1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9)

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



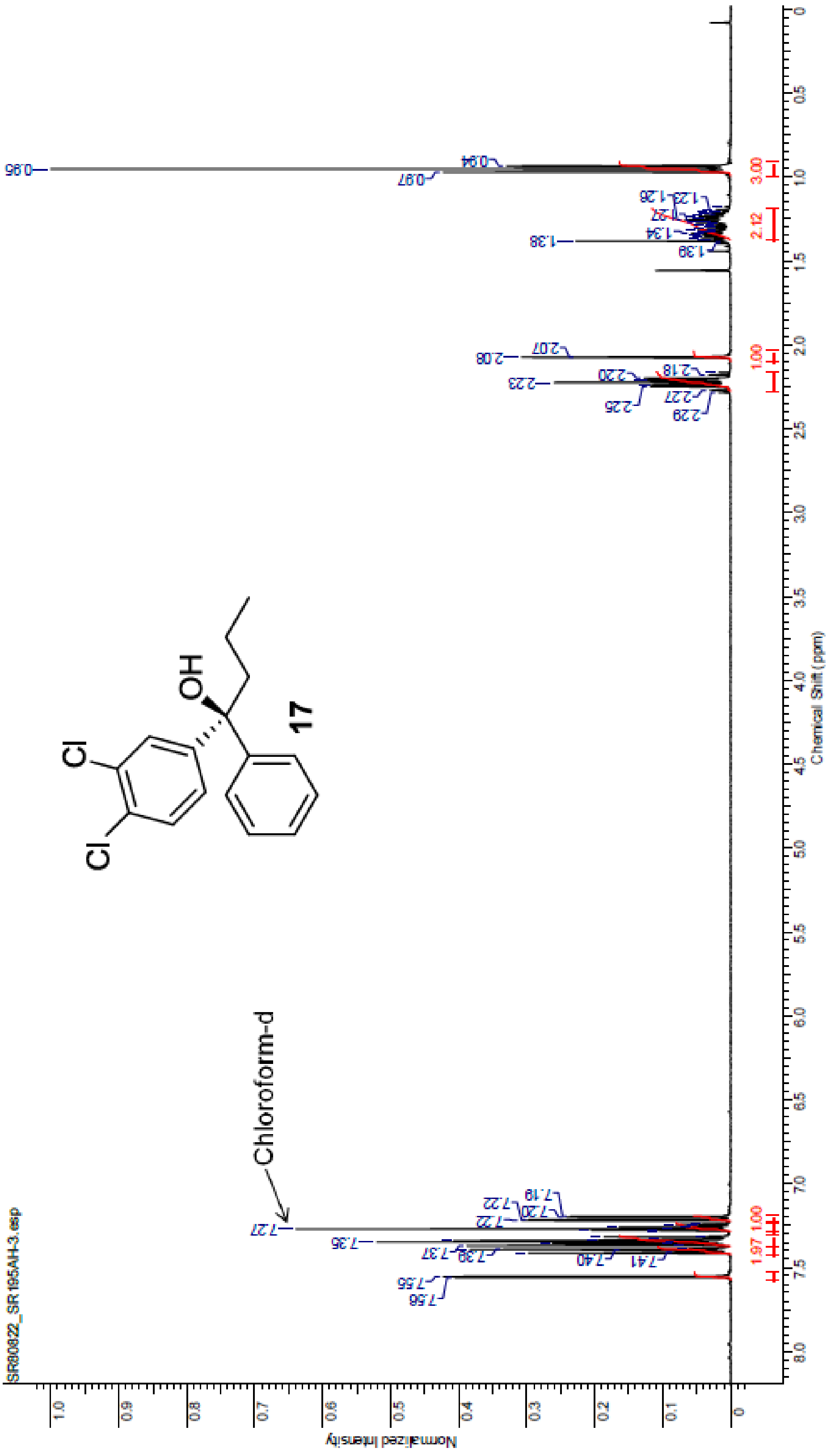
(*R*)-2-(1-(3,4-Dichlorophenyl)-1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9)

^{13}C NMR (101 MHz, $CDCl_3$)



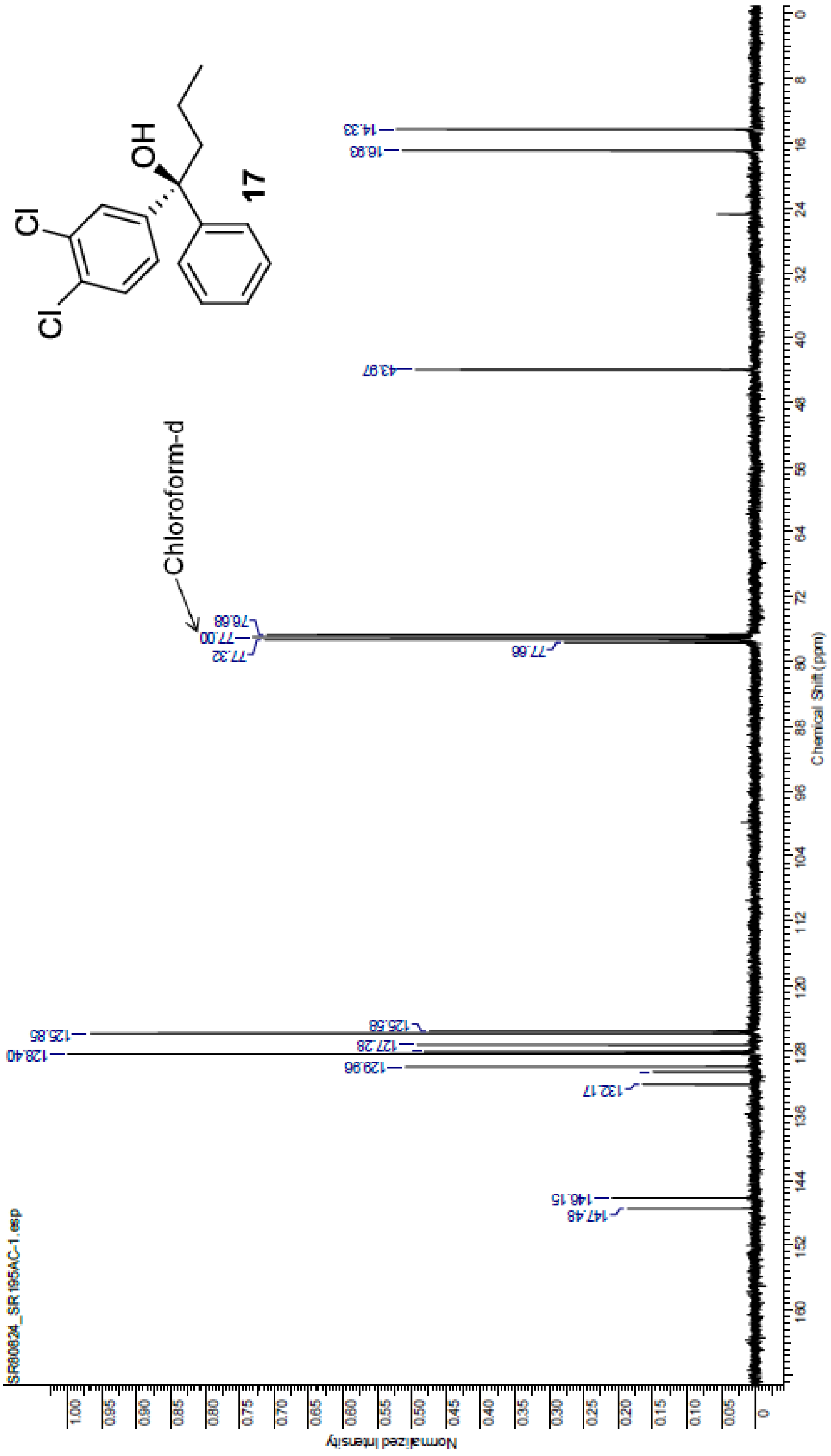
(*S*)-1-(3,4-Dichlorophenyl)-1-phenylbutan-1-ol (17)

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



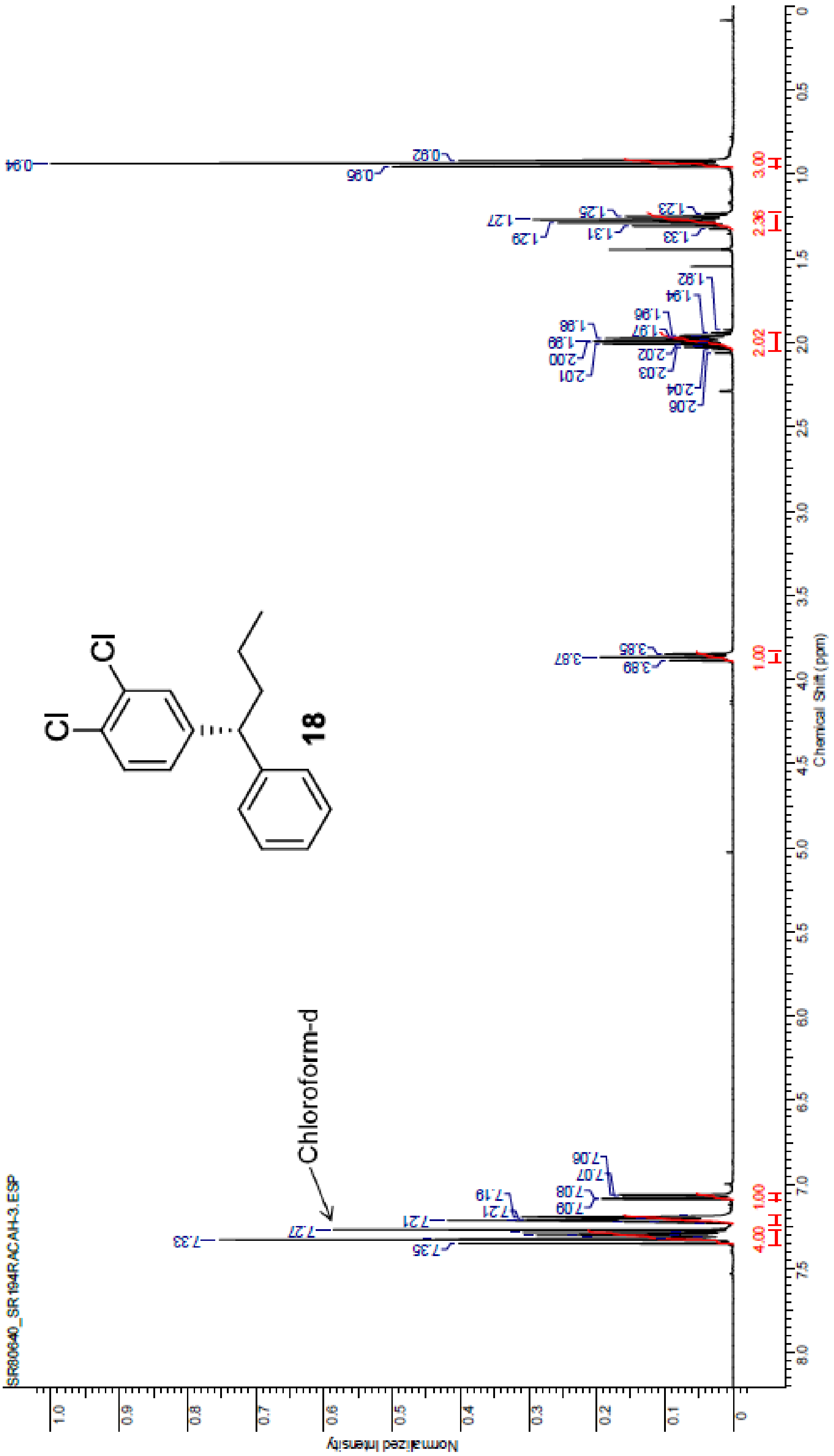
(*S*)-1-(3,4-Dichlorophenyl)-1-phenylbutan-1-ol (17)

^{13}C NMR (101 MHz, $CDCl_3$)



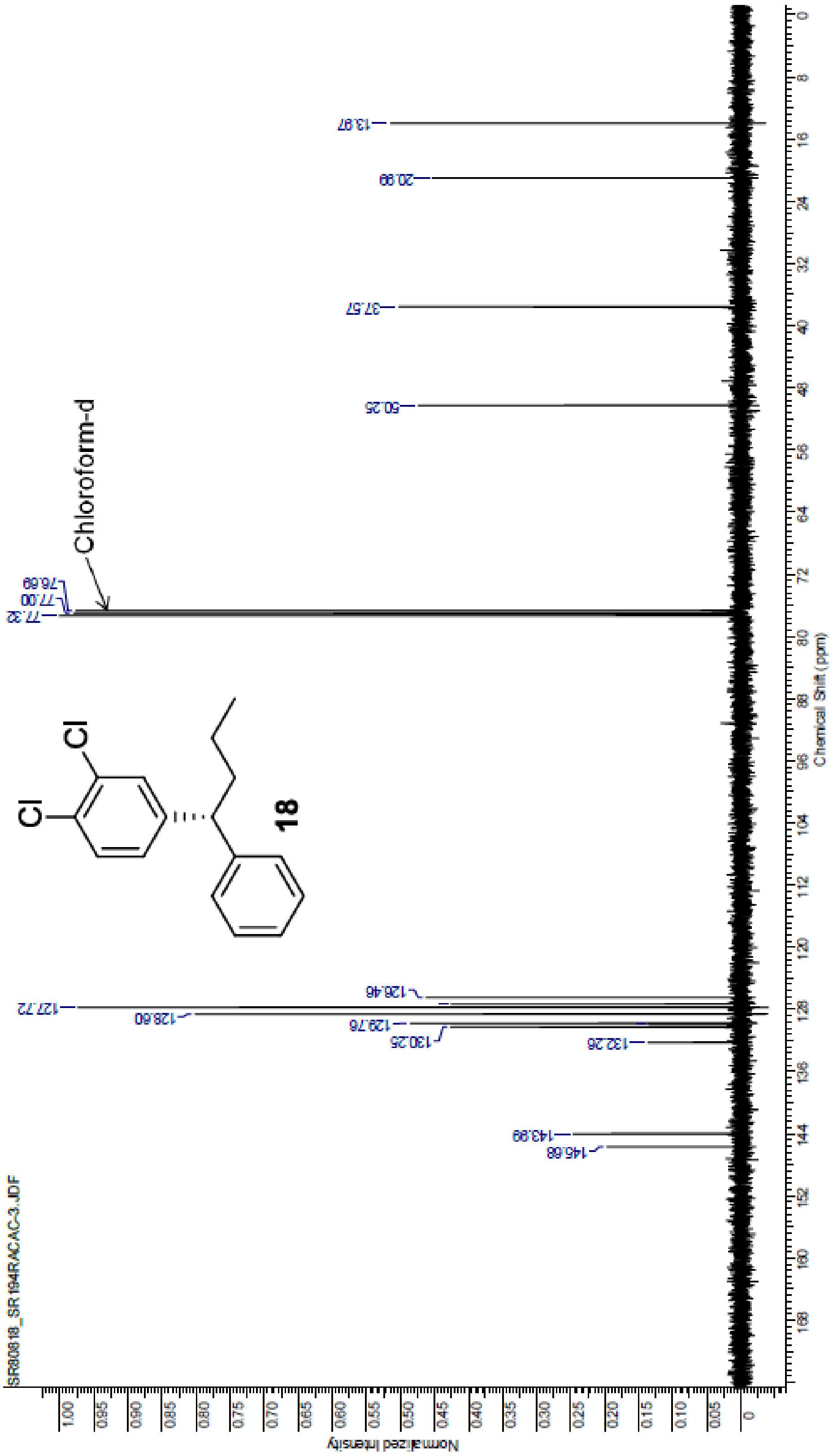
(*R*)-1,2-Dichloro-4-(1-phenylbutyl)benzene (18)

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



(*R*)-1,2-Dichloro-4-(1-phenylbutyl)benzene (18)

^{13}C NMR (101 MHz, $CDCl_3$)



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