A Short Stereodivergent Synthesis of (*R*) and (*S*)-Nicotine

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Supporting Information

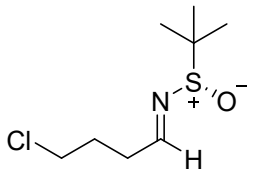
Contents of Supporting Information

1. General experimental procedures

All reagents were purchased from commercial sources and used without additional purification unless stated otherwise. Under nitrogen gas, tetrahydrofuran (THF) was freshly distilled over sodium and benzophenone. Dry toluene, MeOH, and DMF were purchased. (±)-Nicotine was purchased from Scientific Laboratory Supplies (SLS) Ltd. All reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen or argon. Brine is a saturated aqueous solution of sodium chloride. Petroleum ether refers to light petroleum ether (b.p. 40-60 °C). Solvent evaporation was performed using a rotary evaporator under reduced pressure. TLC was performed on Merck silica gel 60 F_{254} and visualised by a UV lamp and aqueous alkaline potassium permanganate. Flash column chromatography was performed over silica gel Fluka 60. ^{1}H and ^{13}C NMR spectral data were recorded using a Bruker AV400 spectrometer. Chemical shifts are quoted in ppm downfield from tetramethylsilane (TMS) as internal standard or deuterated chloroform either in ^{1}H NMR or ^{13}C NMR as a reference (δ_H 7.26 ppm or δ_C 77.16 ppm, respectively). Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant values *J* are given in Hertz. FT-IR spectral data were recorded using a Perkin-Elmer 1600 FTIR spectrometer. Mass spectrometry data were recorded using a Bruker MicroTOF spectrometer in ESI mode. Specific rotation values were measured at ambient temperature in MeOH solution on a BS Bellingham Stanley Ltd. ADP-440 Polarimeter 37-440 using a sodium lamp at 589 nm and a 4 mL capacity cell with a 15 cm path length. All yields refer to isolated material that is homogenous by TLC or NMR, unless otherwise stated. Where isomeric compounds are present in purified materials, the ratios have been determined by ^{1}H NMR analysis, where possible. In most cases, the ^{1}H NMR data is reported for only the major isomer. Chiral HPLC analysis was performed on an Agilent 1260 instrument using 4.6 x 250 mm columns. Compound names are assigned according to standard IUPAC nomenclature.

1. Synthesis of (*S*)-(-)-nicotine (1)

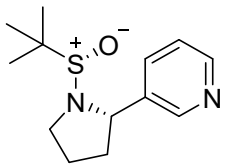
(*Ss*,*E*)-*N*-(4-chlorobutylidene)-2-methylpropane-2-sulfinamide (4)



To a solution of 4-chloro-1-butanol **3** (5 mL, 50.2 mmol, 1.0 eq.) in DCM (50 mL), PCC (13.5 g, 62.75 mmol, 1.25 eq.) and silica gel (13.5 g) were added. The reaction mixture was stirred overnight (*circa* 16 hours). The reaction mixture was then filtered through a pad of silica gel and washed with ethyl acetate (50 mL). The solvents were then evaporated under reduced pressure to produce the crude aldehyde analogue of **3** (2 g) as brown-green oil, which was then used in the next step without further purification. To a solution of titanium (IV) ethoxide (11.89 mL, 56.7 mmol, 3.0 eq.) in dry THF (50 mL), the crude aldehyde analogue of **3** (2 g, 18.9 mmol, 1.0 eq.) was added, and the mixture was stirred at room temperature for 15 minutes. Followed by the slow addition of (*S*)-(-)-*tert*-butyl-sulfinamide (2.52 g, 20.79 mmol, 1.1 eq.), and the reaction mixture was heated at reflux for 6 hours. When the reaction had reached completion, as monitored by TLC, the reaction was allowed to cool to room temperature. The reaction was then quenched with brine (40 mL), and the resulting slurry was filtered through a pad of Celite®, and the filter cake was washed with ethyl acetate (2 × 20 mL). The filtrate was then transferred to a separating funnel, where the organic layer was washed with brine (20 mL). The aqueous layer was extracted once with ethyl acetate (20 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was obtained as a deep yellow oil and purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford **4** (3.52 g, 16.82 mmol, 89%; single isomer) as a yellow oil. $[\alpha]_D^{26}$ = +230.3 (*c* = 1.0, MeOH); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 2961, 2928, 2903, 2870 (C-H_{ali}), 1723 (C=N), 1072 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.07 (1H, t, *J* = 4.0), 3.59 (2H, td, *J* = 6.4 and 1.9), 2.70-2.65 (2H, m), 2.14-

2.08 (2H, m), 1.16 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.0, 56.7, 44.1, 33.2, 28.0, 22.4; HRMS (ESI) calculated for $C_8H_{17}{}^{35}ClNOS^+$ $[M+H]^+$ 210.0714, found 210.0711. The data is consistent with the literature.[1]

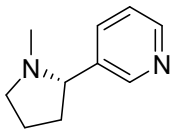
3-((2*S*)-1-((*Ss*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)pyridine (6)



To a solution of *m*-bromopyridine (1 mL, 10.38 mmol, 1.0 eq.) in dry toluene (15 mL) under a nitrogen atmosphere at -78 °C, *i*-PrMgCl (2.0 M in toluene, 5.19 mL, 10.38 mmol, 1.0 eq.) was added dropwise. After completion of the addition, the reaction mixture was stirred for 4 hours, after which TLC indicated the complete consumption of the starting materials.[2] Subsequently, a solution of **4** (2.18 g, 10.38 mmol, 1.0 eq.) in dry toluene (25 mL) was added to the reaction mixture drop by drop through a rubber septum, and the reaction mixture was stirred at -78 °C for 3 hours before saturated aqueous NH_4Cl (30 mL) was added. The organic layer was then separated, and the aqueous washed with ethyl acetate (2 × 15 mL). The combined organic layers were then evaporated under reduced pressure to provide the crude sulfinamide **5** (2.29 g, 7.79 mmol, 75%) with >25:1 *dr*, which was used in the next step without further purification. The crude sulfinamide **5** (750 mg, 2.3 mmol, 1.0 eq.) was dissolved in dry THF (20 mL) at -78 °C, before adding LDA (2.0 M in hexane, 1.5 mL, 3.0 mmol, 1.3 eq.). After stirring for 3 hours at room temperature, a saturated aqueous solution of NH_4Cl (20 mL) was added to the reaction mixture and stirred for 15 minutes, and the reaction mixture extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ before filtration and concentration *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to afford **6** (522 mg, 2.07 mmol, 90%) as a yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. $[\alpha]_D^{26}$ = -122.0 (*c* = 1.0, MeOH); IR

$\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3082, 3064, 3047 (C-H_{aro}), 2999, 2928, 2857 (C-H_{ali}), 1635 (C=N), 1062 (S-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.59 (1H, s), 8.49 (1H, s), 7.72 (1H, s), 7.24-7.21 (1H, m), 3.24-3.19 (1H, m), 3.12-3.08 (1H, m), 2.31-2.20 (2H, m), 1.87-1.71 (3H, m), 1.19 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 149.7, 148.6, 138.9, 135.1, 123.7, 68.9, 57.5, 56.6, 35.4, 22.9, 22.1; HRMS (ESI) calculated for $C_{13}H_{20}N_2NaOS^+$ $[M+Na]^+$ 275.1189, found 275.1188.

(*S*)-3-(1-methylpyrrolidin-2-yl)pyridine [(*S*)-(-)-nicotine (1)]

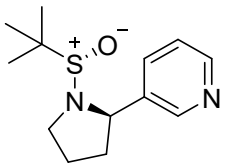


To a solution of **6** (500 mg, 1.98 mmol, 1.0 eq.) in dry MeOH (20 mL) at 0 °C, HCl (1.0 M in Et_2O, 9.9 mL, 9.9 mmol, 5.0 eq.) was then added slowly over 15 minutes. After completion of the addition, the reaction mixture was stirred at room temperature for 4 hours, after which TLC and LCMS indicated the consumption of starting material **6**. Then, a saturated solution of aqueous $NaHCO_3$ (15 mL) was added, and the organic layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over Mg_2SO_4 and concentrated *in vacuo* to provide a crude amine derivative **7** (276 mg, 1.86 mmol, 94%) as yellow oil, $[\alpha]^{27}_D$ = -86.4 (c = 1.0, MeOH), which was used in the next step without further purification.[3] The desired (*S*)-nicotine (**1**) was prepared according to a modified literature procedure.[4] To a solution of the crude amine derivative **7** (200 mg, 1.35 mmol, 1.0 eq.) in DMF (5 mL), a mixture of TMEDA (20 μL, 135 μmol, 0.1 eq.), DMC (568 μL, 6.75 mmol, 5.0 eq.), and DMF (10 mL) was added slowly. After completion of the addition, the mixture was heated at 90 °C for 6 hours. The reaction was monitored by TLC (petroleum ether/ethyl acetate) until no amine derivative **7** remained. Brine (15 mL) was then added to the reaction mixture and stirred for 15 minutes. Ethyl acetate (15 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ before filtration and concentration *in vacuo*. The crude residue was purified by flash column chromatography over silica gel

(eluting with 6:1 petroleum ether/ethyl acetate) to afford the desired (*S*)-(-)-nicotine (**1**) (182 mg, 1.12 mmol, 83%) as a colourless oil. Enantiomeric excess (*ee*) was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); tr (major) = 17.3 minutes, tr (minor) = 18.7 minutes; 93.2% *ee* (96.6:3.4 *er*) (Figure 1); $[\alpha]_D^{27}$ = -166.3 (*c* = 1.0, MeOH); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3056, 3016 (C-H_{aro}), 2976, 2957, 2921, 2863 (C-H_{ali}), 1680 (C=N); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.55 (1H, s), 8.45 (1H, s), 7.72 (1H, s), 7.22-7.18 (1H, m), 3.23-3.11 (2H, m), 2.30-2.21 (2H, m), 2.12 (3H, s), 1.95-1.70 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 149.4, 148.5, 138.8, 134.9, 123.5, 68.8, 56.9, 40.3, 35.2, 22.6; HRMS (ESI) calculated for $C_{20}H_{28}N_4Na^+$ $[2M+Na]^+$ 347.2206, found 347.2205.

2. Synthesis of (*R*)-(+)-nicotine (2)

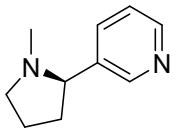
3-((2*R*)-1-((*Ss*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)pyridine (9)



To a solution of 3-bromopyridine (1.5 mL, 15.57 mmol, 1.0 eq.) in dry THF (20 mL) under a nitrogen atmosphere at -78 °C, *i*-PrMgCl (1.0 M in THF, 15.57 mL, 15.57 mmol, 1.0 eq.) was then added dropwise through the rubber septum. After completion of the addition, the reaction mixture was stirred for 5 hours, which TLC indicated the complete consumption of the starting materials.[2] Subsequently, a solution of **4** (3.27 g, 15.57 mmol, 1.0 eq.) in dry THF (30 mL) was added to the reaction mixture drop by drop through a rubber septum. After the final addition, the reaction mixture was stirred at -78 °C for 4 hours before saturated aqueous NH_4Cl (25 mL) was added. The organic layer was then separated with ethyl acetate (2 × 20 mL). The solvent was then evaporated under reduced pressure to provide the crude sulfinamide **8** (3.24 g, 11.21 mmol, 72%) with >25:1 *dr*, which was used in the next step without further purification. The crude sulfinamide **8** (1.2 g, 4.15 mmol, 1.0 eq.) was dissolved in dry THF (25 mL) before adding LDA (2.0 M in hexane, 2.7 mL, 5.40 mmol, 1.3 eq.) at -78

°C. After stirring for 3 hours at room temperature, a saturated aqueous solution of NH_4Cl (30 mL) was added to the reaction mixture and stirred for 15 minutes, and the organic layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentration *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to afford **9** (891 mg, 3.53 mmol, 85%) as a pale-yellow oil. The product was isolated as a >25:1 mixture of diastereomers; only data for the major diastereomer is shown. IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3064, 3031 (C-H_{aro}), 2976, 2959, 2922, 2863 (C-H_{ali}), 1639 (C=N), 1066 (S-O); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.58 (1H, s), 8.48 (1H, s), 7.70 (1H, s), 7.24-7.19 (1H, m), 3.23-3.17 (1H, m), 3.11-3.06 (1H, m), 2.30-2.20 (2H, m), 1.85-1.70 (3H, m), 1.20 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 149.6, 148.5, 138.7, 135.0, 123.6, 68.7, 57.6, 56.5, 35.3, 22.8, 22.0; HRMS (ESI) calculated for $C_{13}H_{20}N_2NaOS^+$ $[M+Na]^+$ 275.1189, found 275.1190; $[\alpha]_D^{26}$ = +122.9 (*c* = 1.0, MeOH).

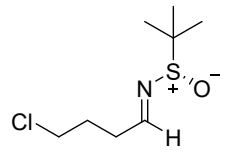
(*R*)-3-(1-methylpyrrolidin-2-yl)pyridine [(*R*)-(+)-nicotine (2)]



To a solution of **9** (700 mg, 2.77 mmol, 1.0 eq.) in dry MeOH (25 mL) at 0 °C, HCl (1.0 M in Et_2O, 13.85 mL, 13.85 mmol, 5.0 eq.) was then added slowly over 15 minutes. After completion of the addition, the reaction mixture was stirred at room temperature for 4 hours, after which TLC and LCMS indicated the consumption of starting material **9**. Subsequently, a saturated solution of aqueous $NaHCO_3$ (20 mL) was added, and the organic layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over Mg_2SO_4 and concentrated *in vacuo* to provide a crude amine derivative **10** (390 mg, 2.63 mmol, 95%) as yellow oil, $[\alpha]^{25}_D$ = +86.1 (c = 1.0, MeOH), which was used in the next step without further purification.[3] The desired (*R*)-nicotine (**2**) was prepared according to a modified literature procedure.[4] To a solution of the crude amine derivative **10** (230 mg, 1.55 mmol, 1.0 eq.) in DMF

(5 mL), a mixture of TMEDA (23 μL, 155 μmol, 0.1 eq.), DMC (653 μL, 7.75 mmol, 5.0 eq.), and DMF (10 mL) was added slowly. After completion of the addition, the mixture was heated at 90 °C for 7 hours. The reaction was monitored by TLC (petroleum ether/ethyl acetate) until no amine derivative **10** remained. Brine (15 mL) was then added to the reaction mixture and stirred for 15 minutes. Ethyl acetate (20 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ before filtration and concentration *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) to afford the desired (*R*)-(+)-nicotine (**2**) (201 mg, 1.24 mmol, 80%) as a colourless oil. Enantiomeric excess (*ee*) was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); tr (major) = 18.7 minutes, tr (minor) = 17.1 minutes; 94.4% *ee* (97.2:2.8 *er*) (Figure 2); $[\alpha]_D^{25}$ = +165.9 (*c* = 1.0, MeOH). IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ (neat) = 3058, 3024 (C-H_{aro}), 2951, 2923, 2874, 2851 (C-H_{ali}), 1683 (C=N); ^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.54 (1H, s), 8.44 (1H, s), 7.70 (1H, s), 7.23-7.18 (1H, m), 3.21-3.10 (2H, m), 2.30-2.20 (2H, m), 2.11 (3H, s), 1.95-173 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 149.3, 148.4, 138.7, 134.8, 123.4, 68.6, 56.8, 40.2, 35.1, 22.5; HRMS (ESI) calculated for $C_{20}H_{28}N_4Na^+$ $[2M+Na]^+$ 347.2206, found 347.2204.

4. ^{1}H and ^{13}C NMR spectra



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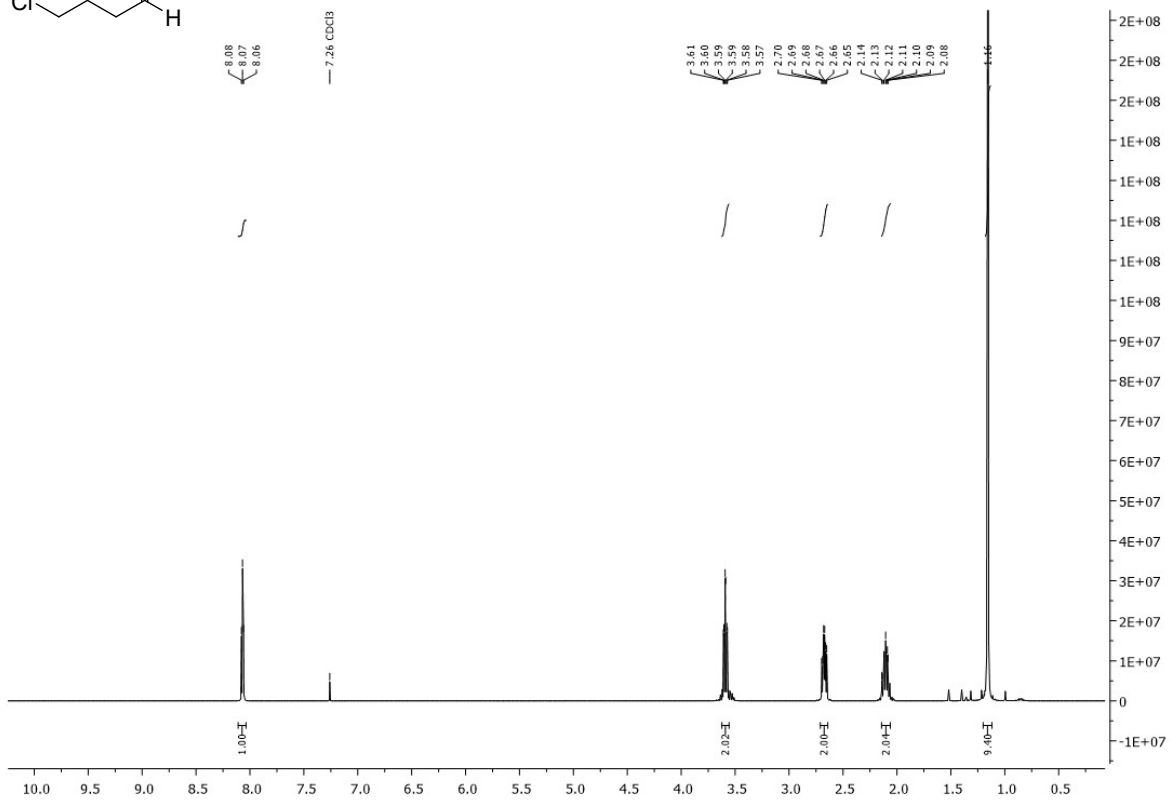

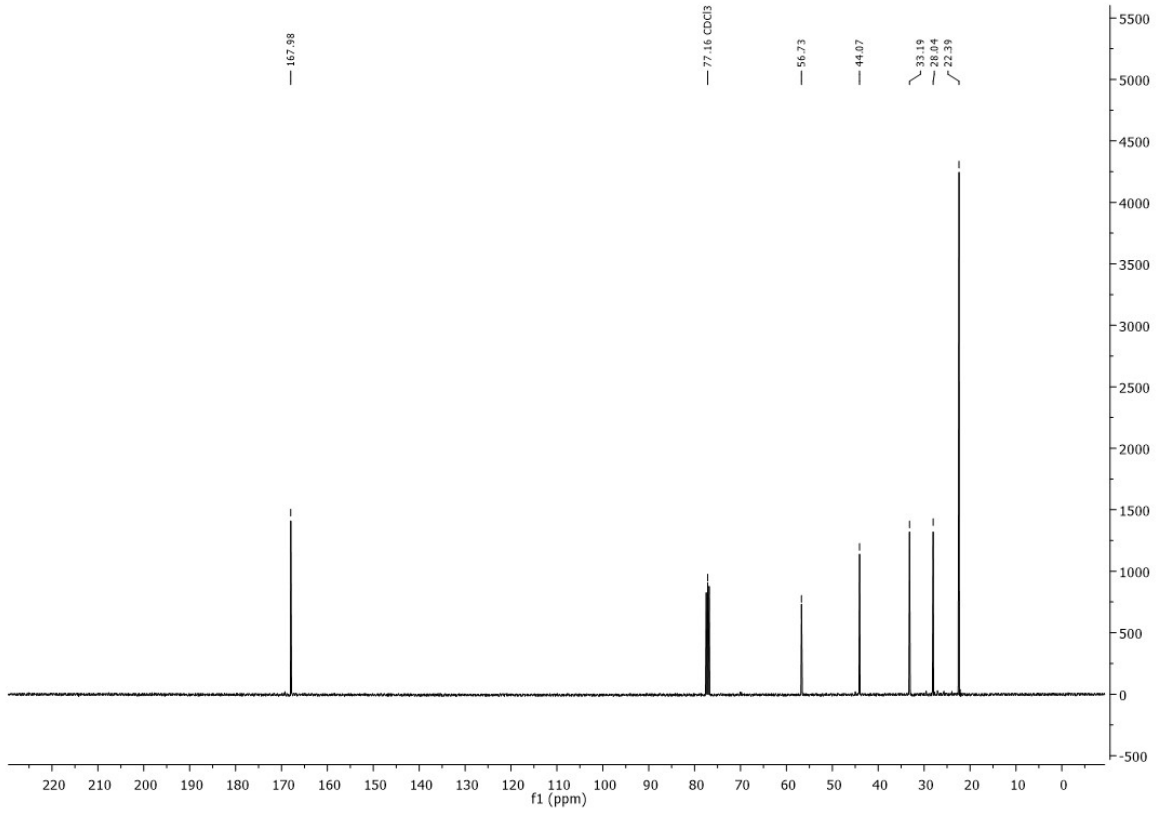

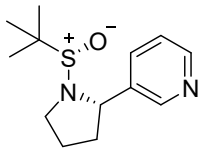

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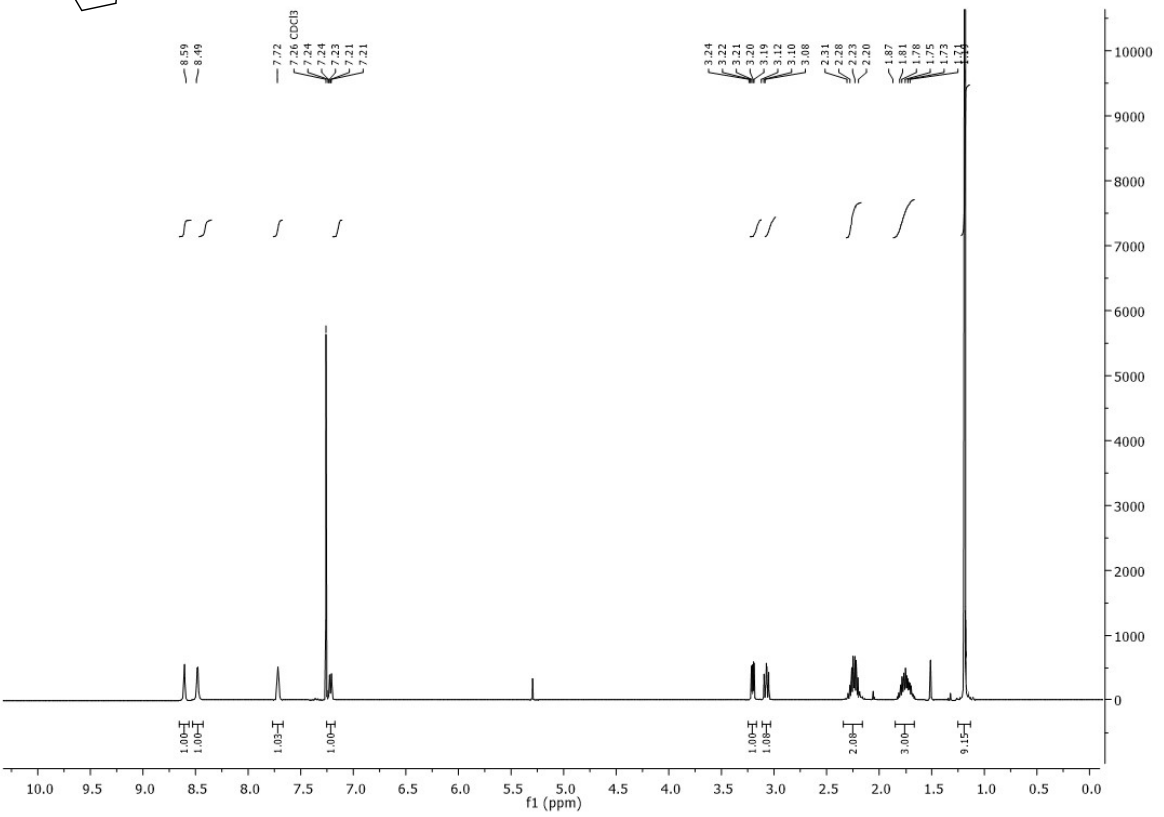
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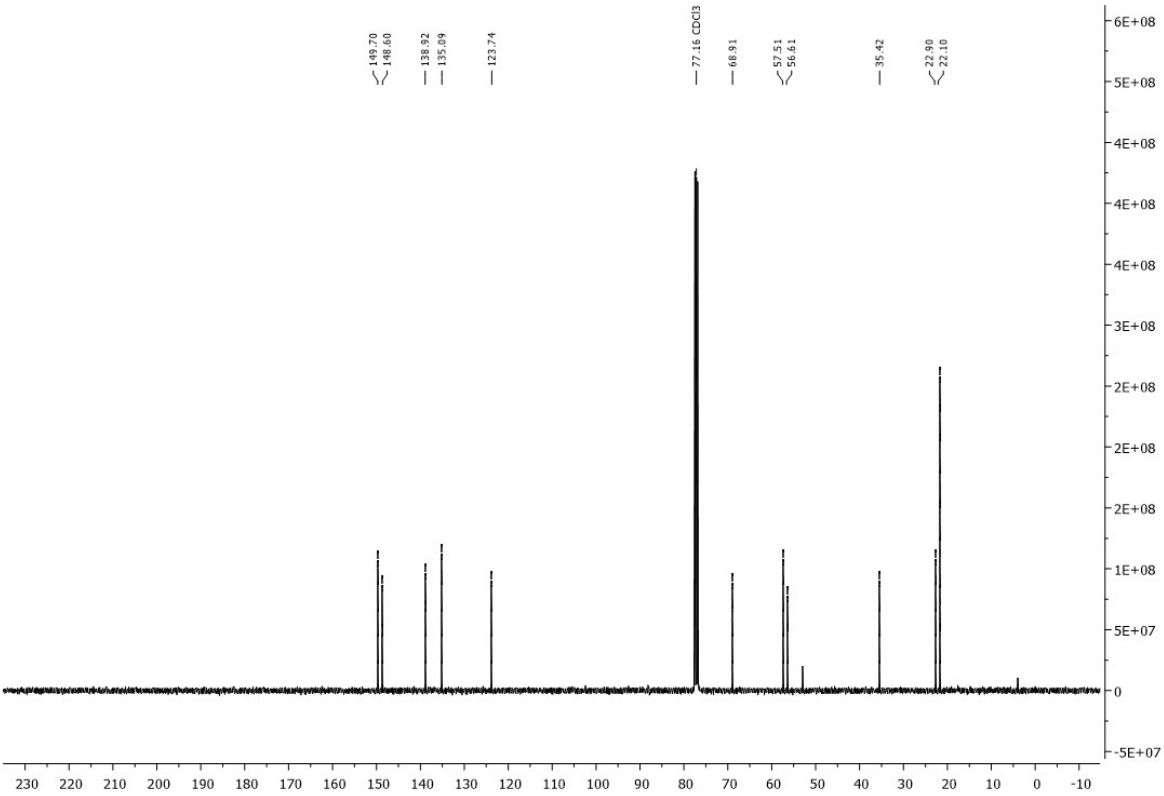
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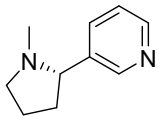

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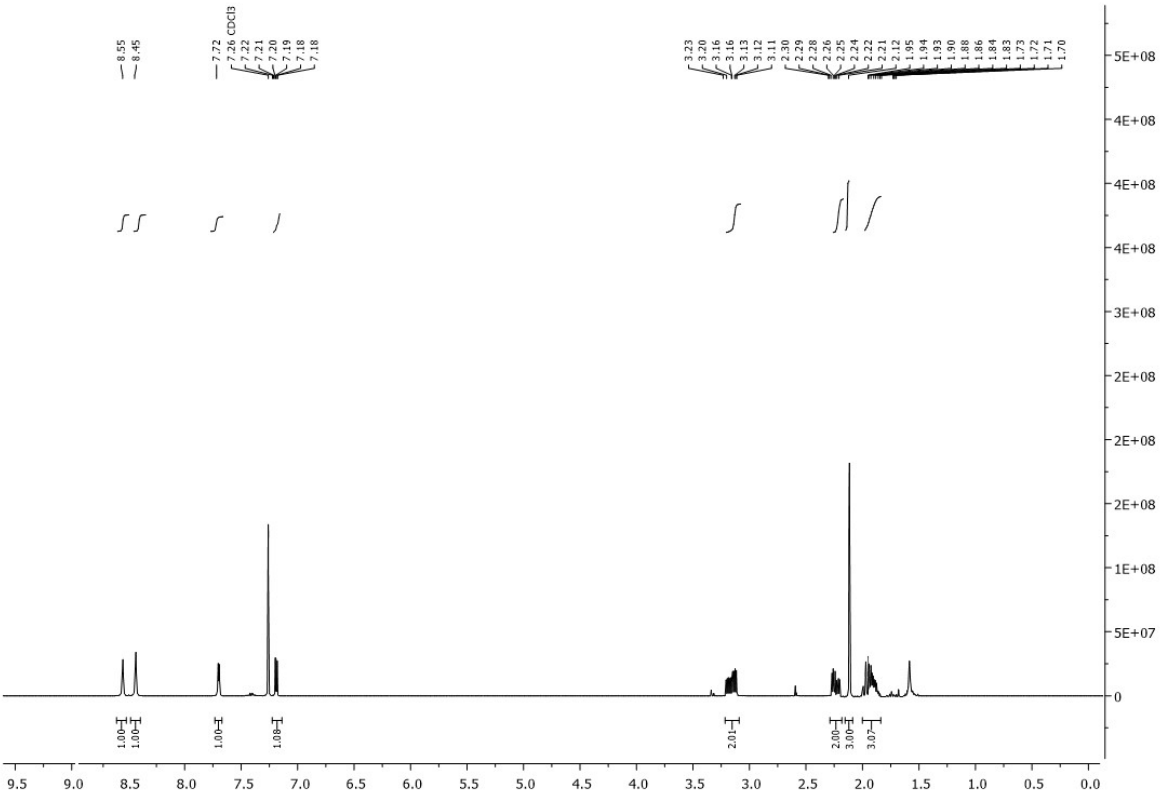
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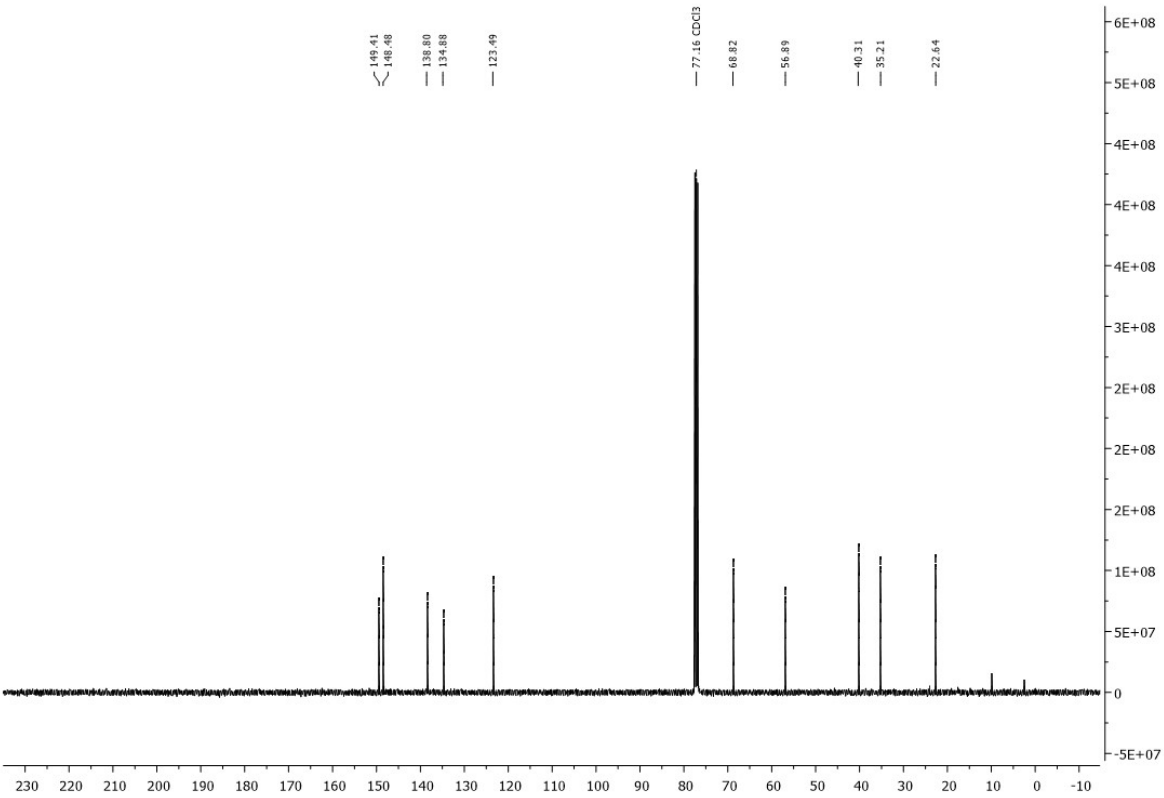
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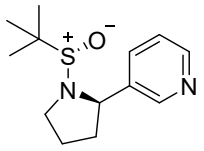

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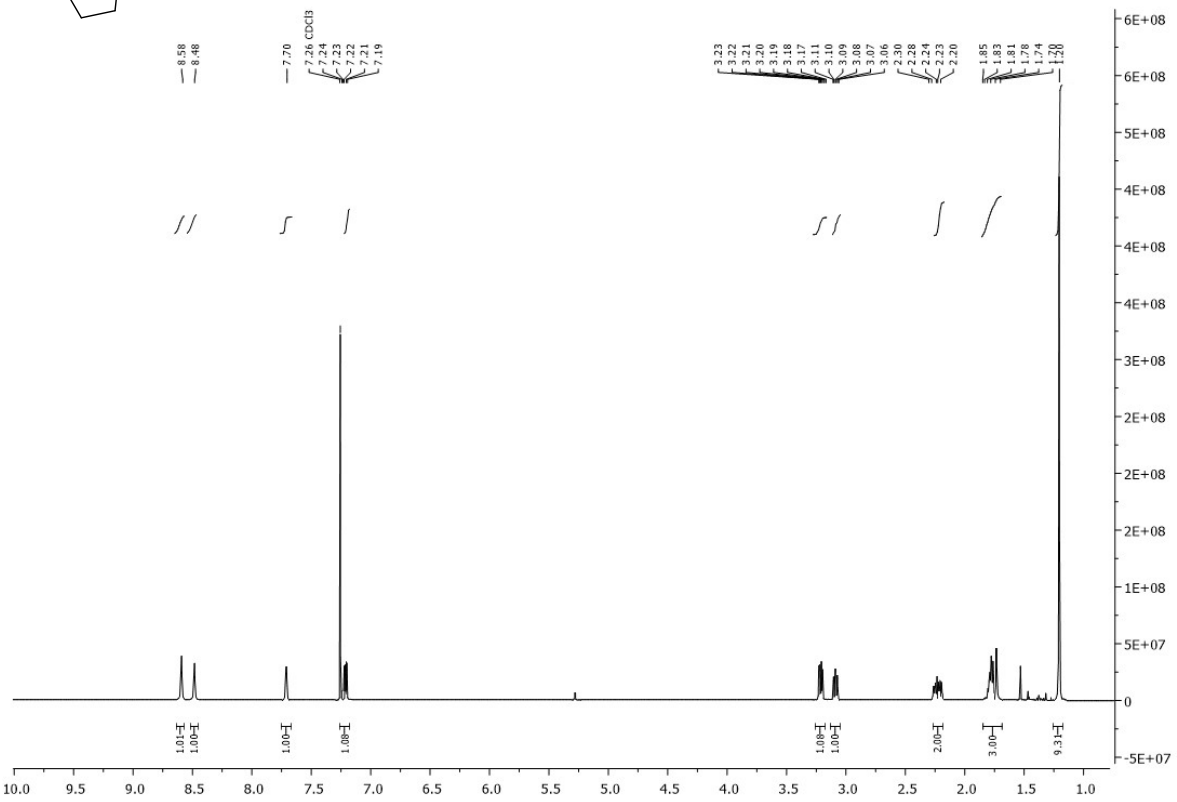
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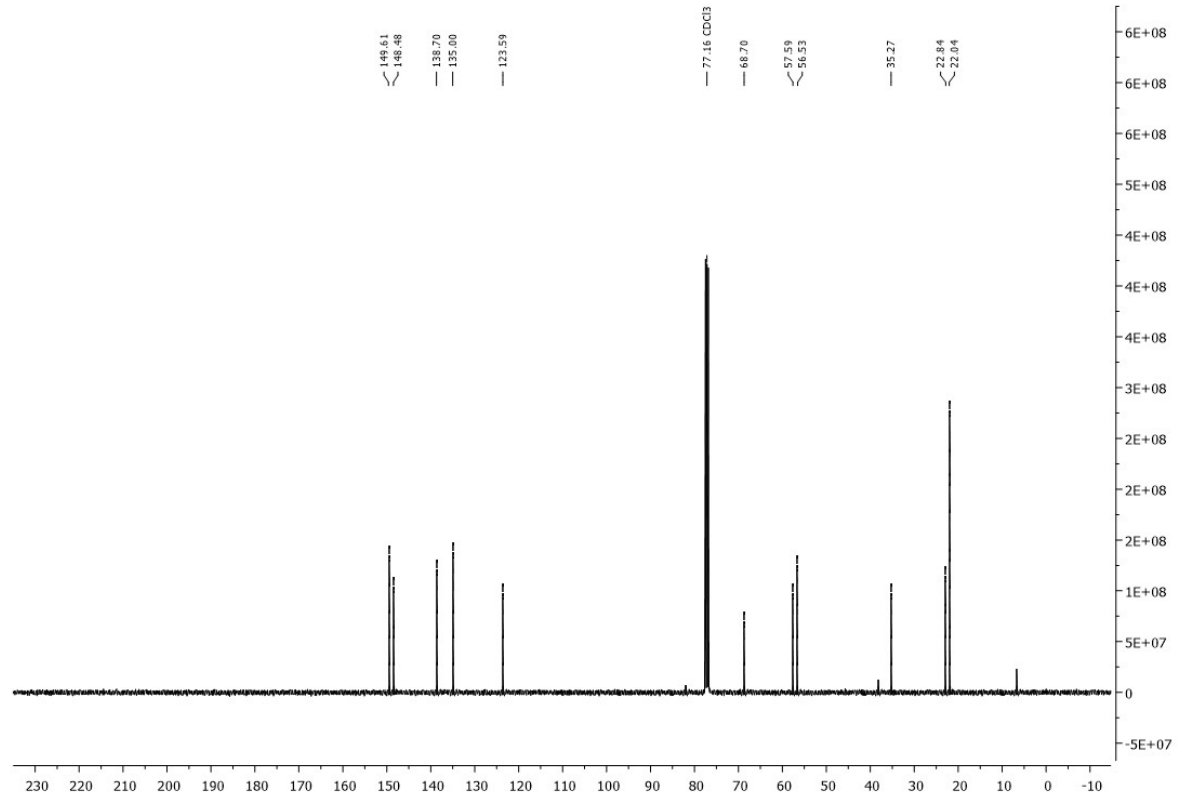
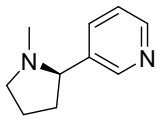
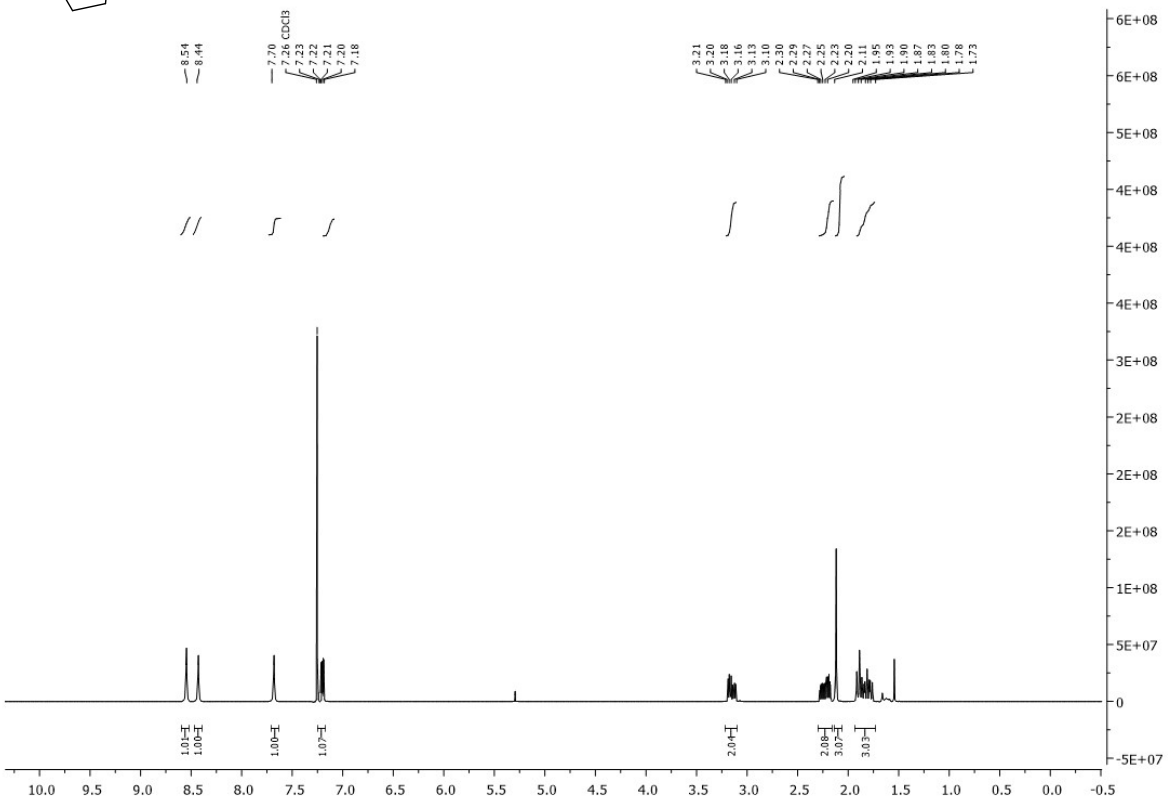
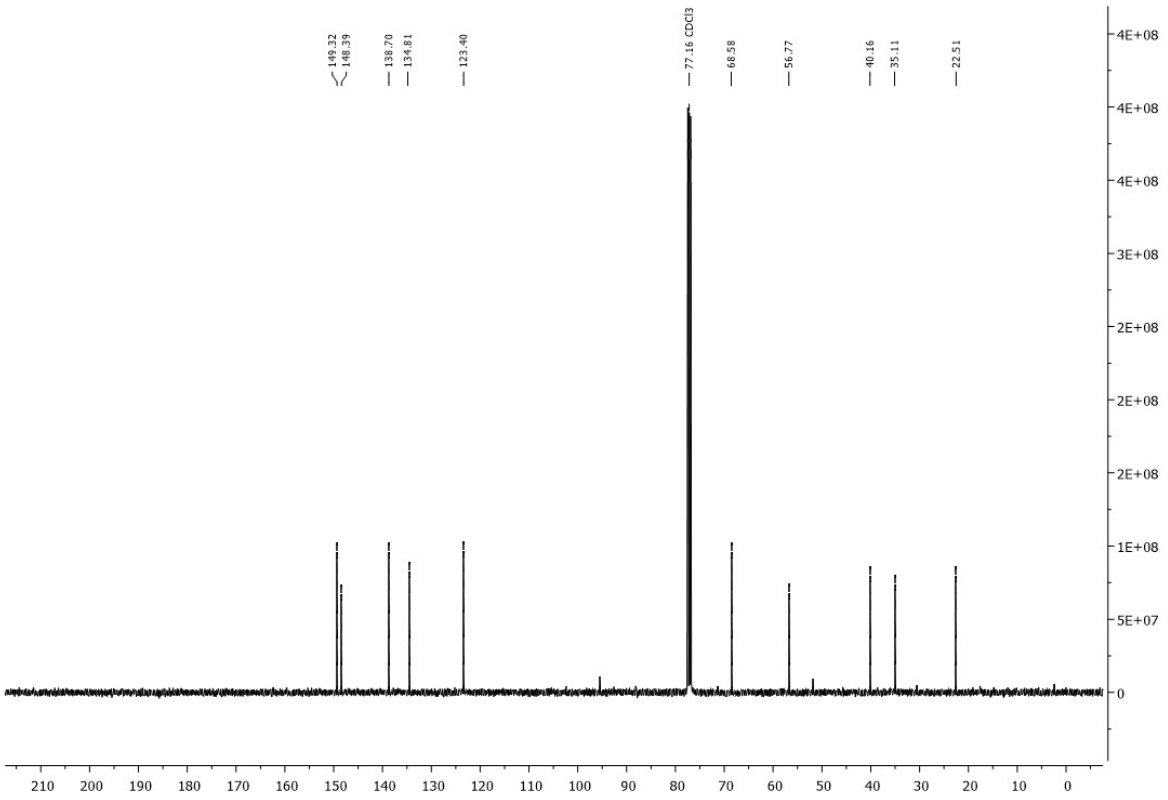
-5E+07


149.61
148.48
138.70
135.00
123.59
77.16 CDCl3
68.70
57.59
56.53
35.27
22.84
22.04
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
5E+07
0
-5E+07

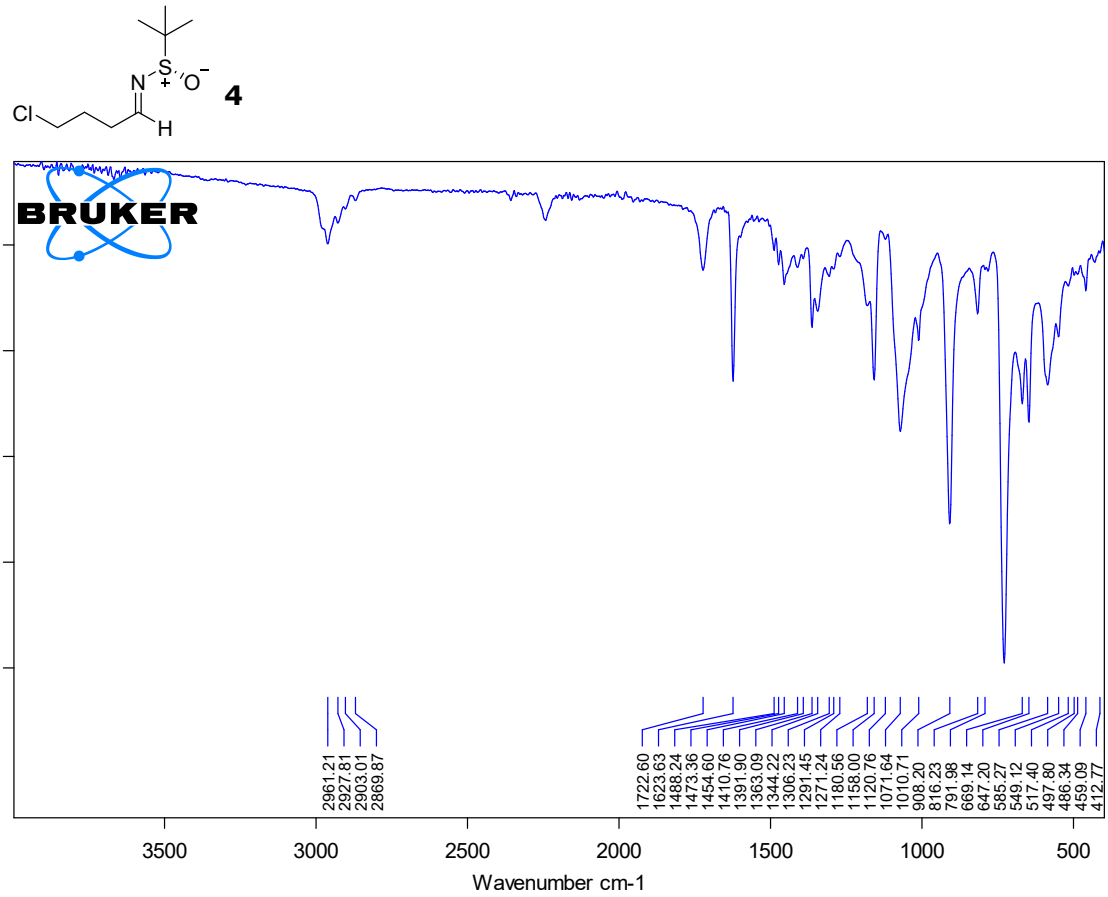


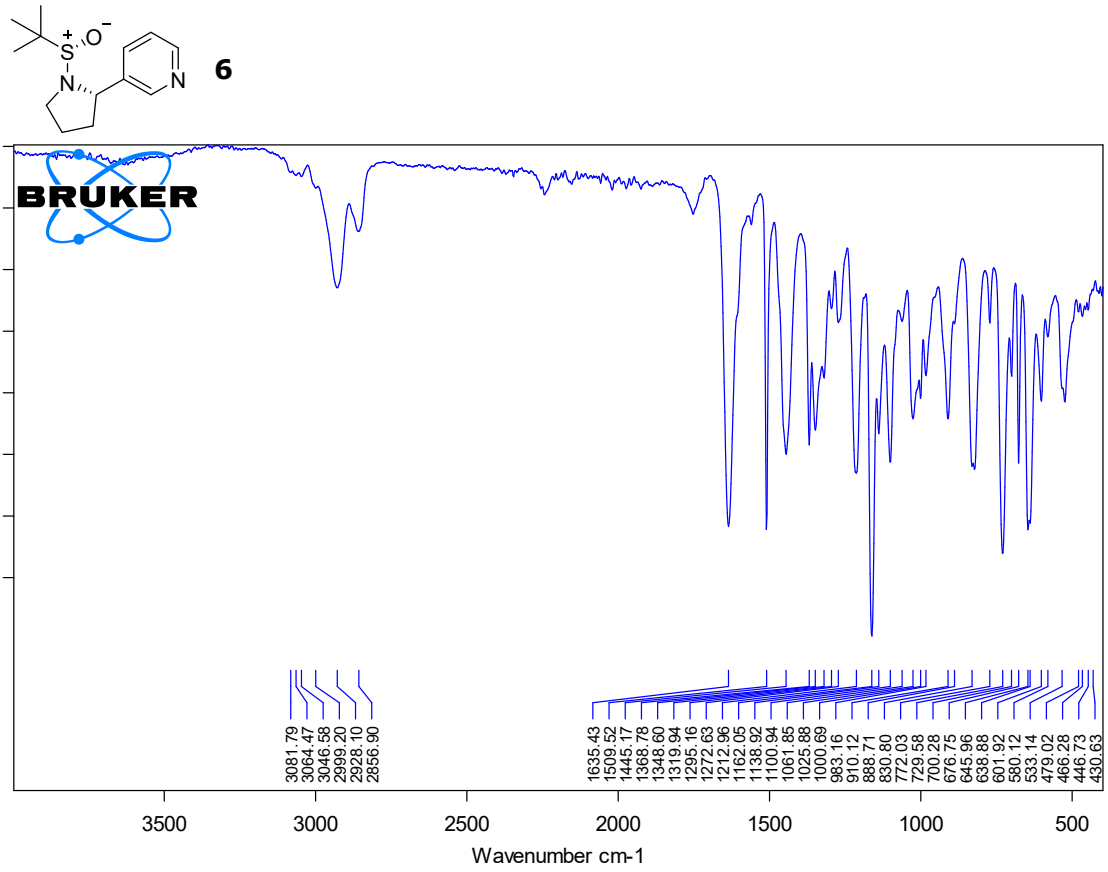
2

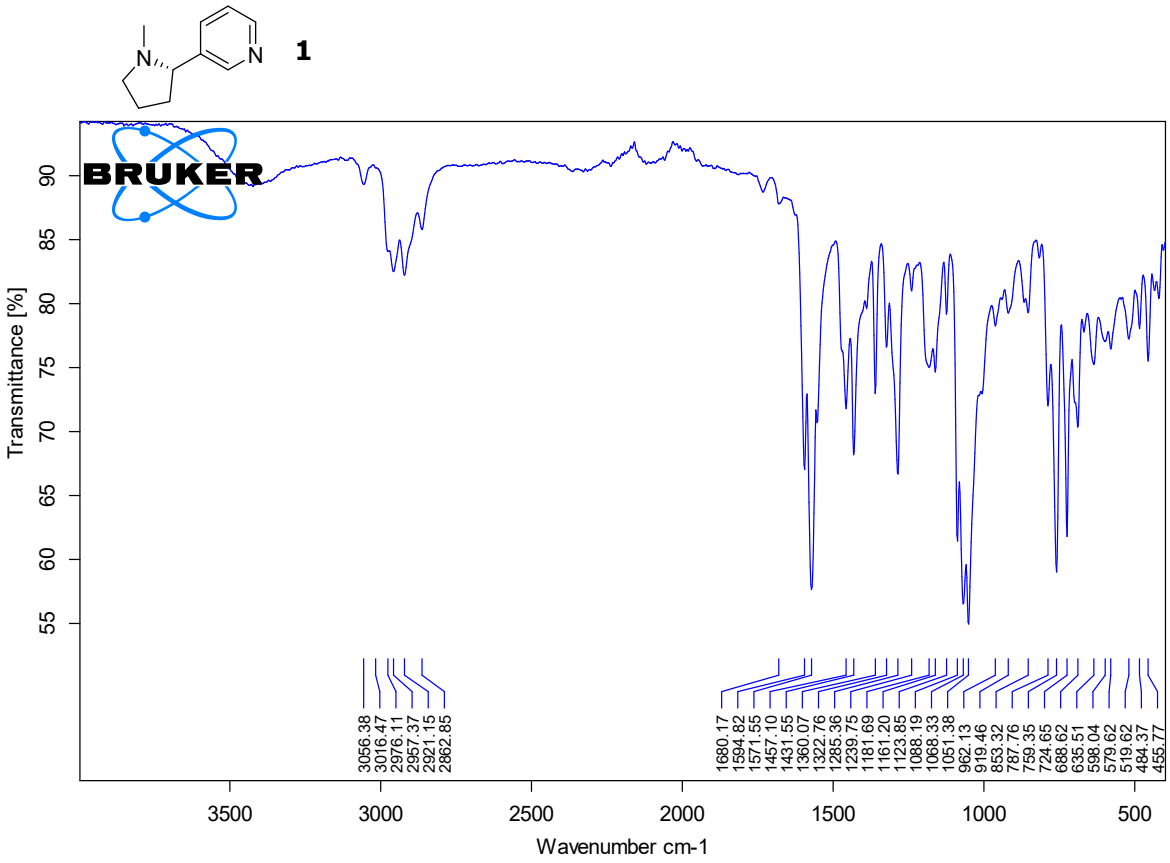

8.54
8.44
7.70
7.26 CDCl3
7.23
7.22
7.21
7.20
7.18
3.21
3.20
3.18
3.16
3.13
3.10
2.30
2.29
2.27
2.25
2.23
2.20
2.11
1.95
1.93
1.90
1.87
1.83
1.80
1.78
1.73
1.01
1.00
1.00
1.07
2.04
2.08
3.07
3.03

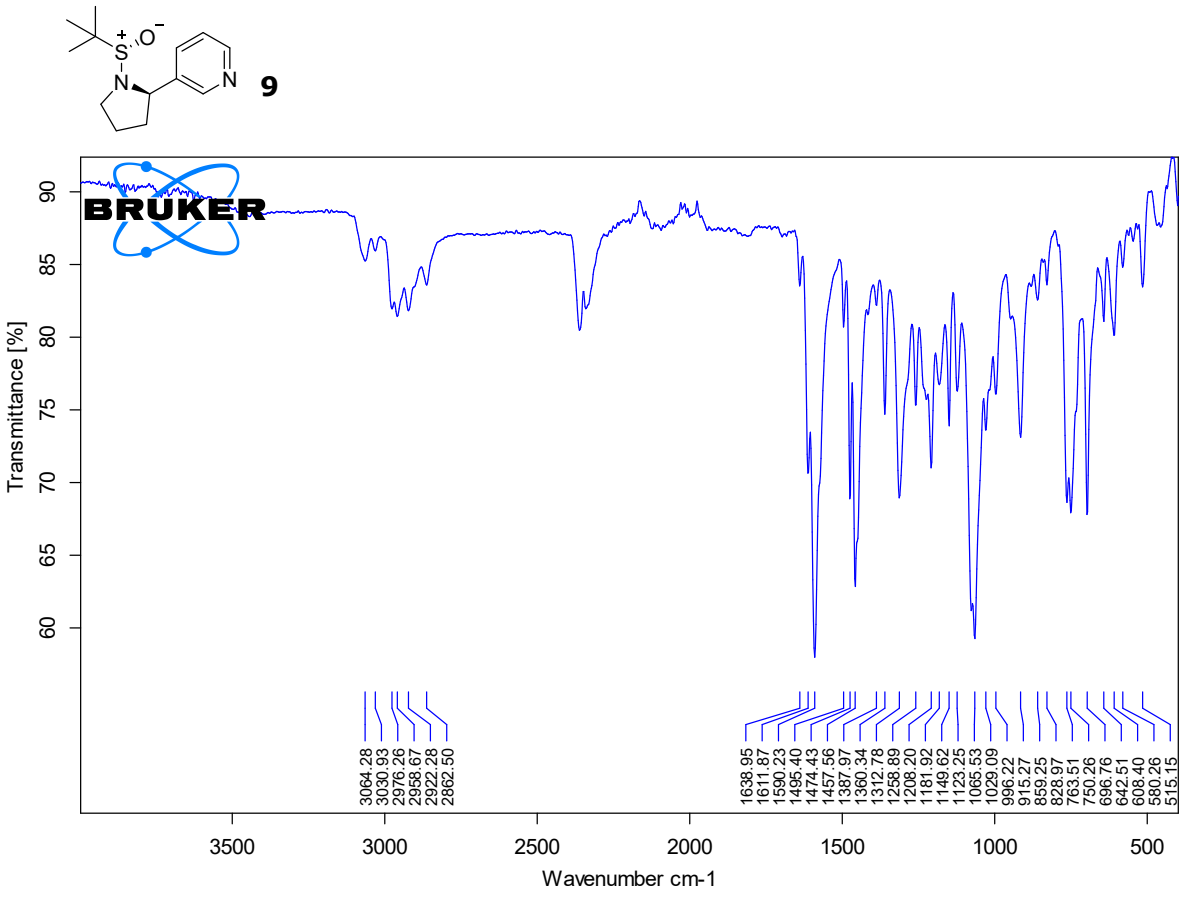

149.32
148.39
138.70
134.81
123.40
77.16 CDCl3
68.58
56.77
40.16
35.11
22.51

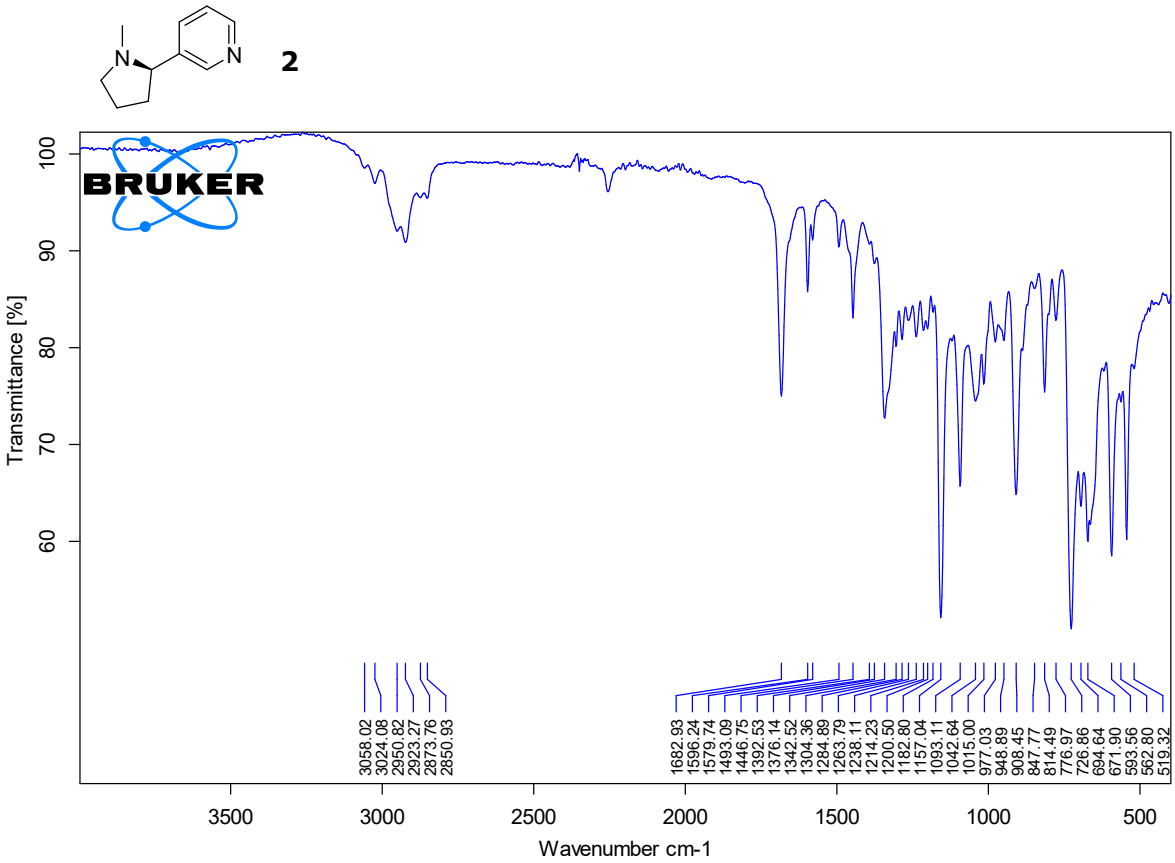
5. FT-IR spectra





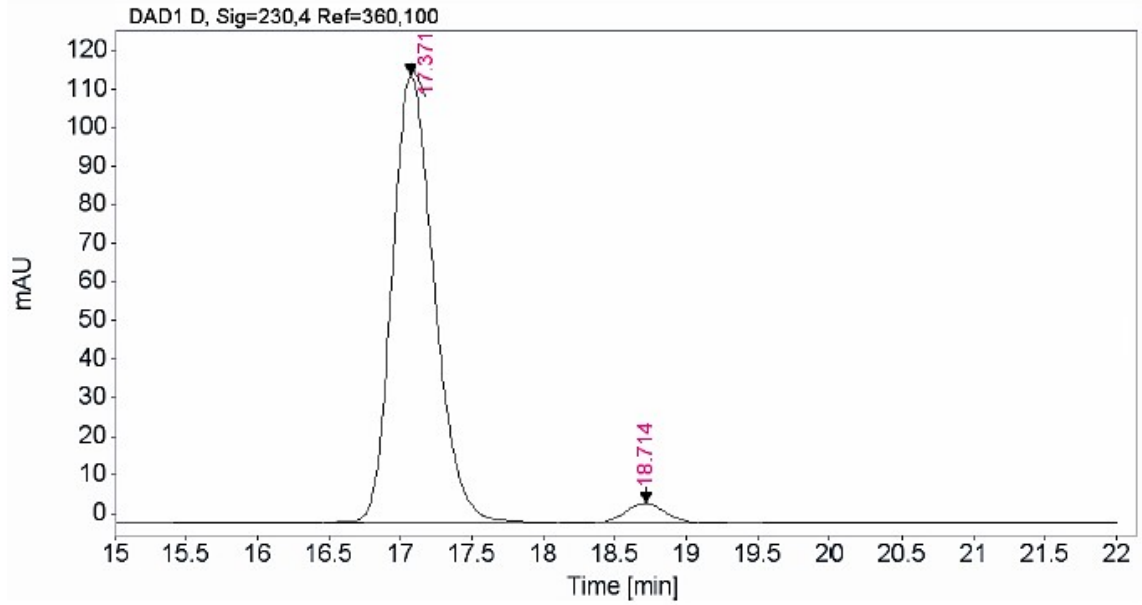

1
BRUKER
Transmittance [%]
90
85
80
75
70
65
60
55
3056.38
3016.47
2976.11
2957.37
2921.15
2862.85
1680.17
1594.82
1571.55
1457.10
1431.55
1360.07
1322.76
1285.36
1239.75
1181.69
1161.20
1123.85
1088.19
1068.33
1051.38
962.13
919.46
853.32
787.76
759.35
724.65
688.62
635.51
598.04
579.62
519.62
484.37
455.77
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1


9
BRUKER
Transmittance [%]
90
85
80
75
70
65
60
3064.28
3030.93
2976.26
2958.67
2922.28
2862.50
1638.95
1611.87
1590.23
1495.40
1474.43
1457.56
1387.97
1360.34
1312.78
1258.89
1208.20
1181.92
1149.62
1123.25
1065.53
1029.09
996.22
915.27
859.25
828.97
763.51
750.26
696.76
642.51
608.40
580.26
515.15
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1


2
BRUKER
Transmittance [%]
100
90
80
70
60
3058.02
3024.08
2950.82
2923.27
2873.76
2850.93
1682.93
1596.24
1579.74
1493.09
1446.75
1392.53
1376.14
1342.52
1304.36
1284.89
1263.79
1238.11
1214.23
1200.50
1182.80
1157.04
1093.11
1042.64
1015.00
977.03
948.89
908.45
847.77
814.49
776.97
726.86
694.64
671.90
593.56
562.80
519.32
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

6. HPLC chromatogram of (*S*)-nicotine (1), (*R*)-nicotine (2), and racemic mixture of nicotine

Data file:	C:\CHEM32\1\DATA\YL\DEF_LC A		
Sample name:	ED9651-0		
Instrument:	AGILENT 1260	**Acq. operator:**	SYSTEM
Injection date:	6/30/2024 11:13:46 AM		
Acq. method:	HDH100C.0.4ML.50MI		

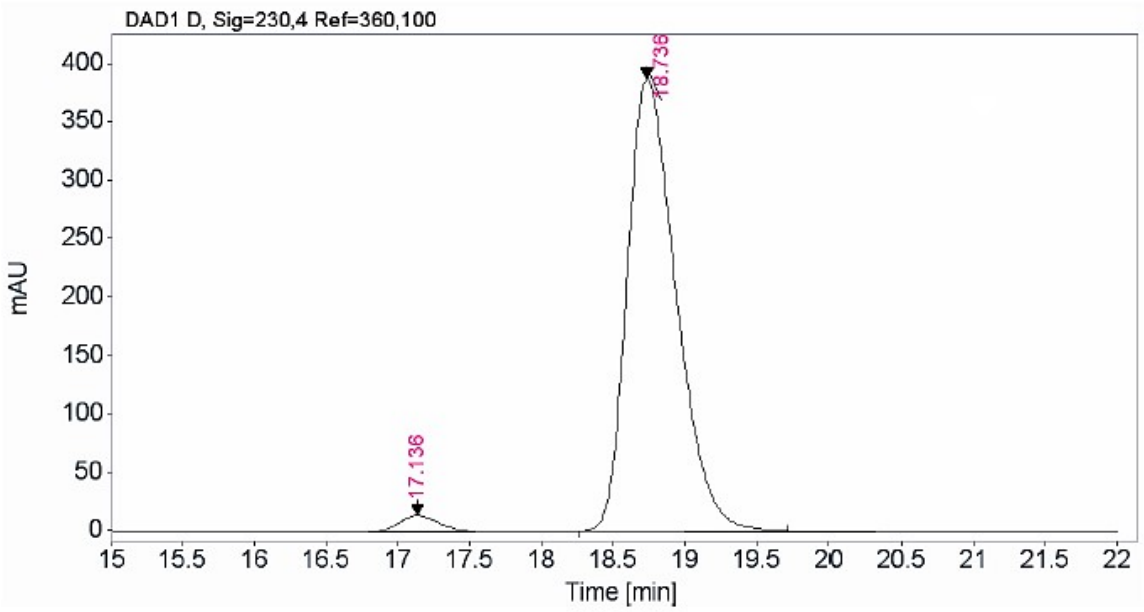


Signal: DAD1 D, Sig=230,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
17.371	MM	0.3420	1330.838	116.2280	96.57
18.714	MM	0.2102	47.242	11.0260	3.43

Figure 1: HPLC chromatogram showing (*S*)-nicotine (**1**) (major enantiomer) and (*R*)-nicotine (**2**) (minor enantiomer) peaks[5]

Data file:	C:\CHEM32\1\DATA\YL\DEF_LC		
Sample name:	ED9551-1		
Instrument:	AGILENT 1260	**Acq. operator:**	SYSTEM
Injection date:	6/26/2024 1:23:54 PM		
Acq. method:	HDH100C.0.3ML.50MI		

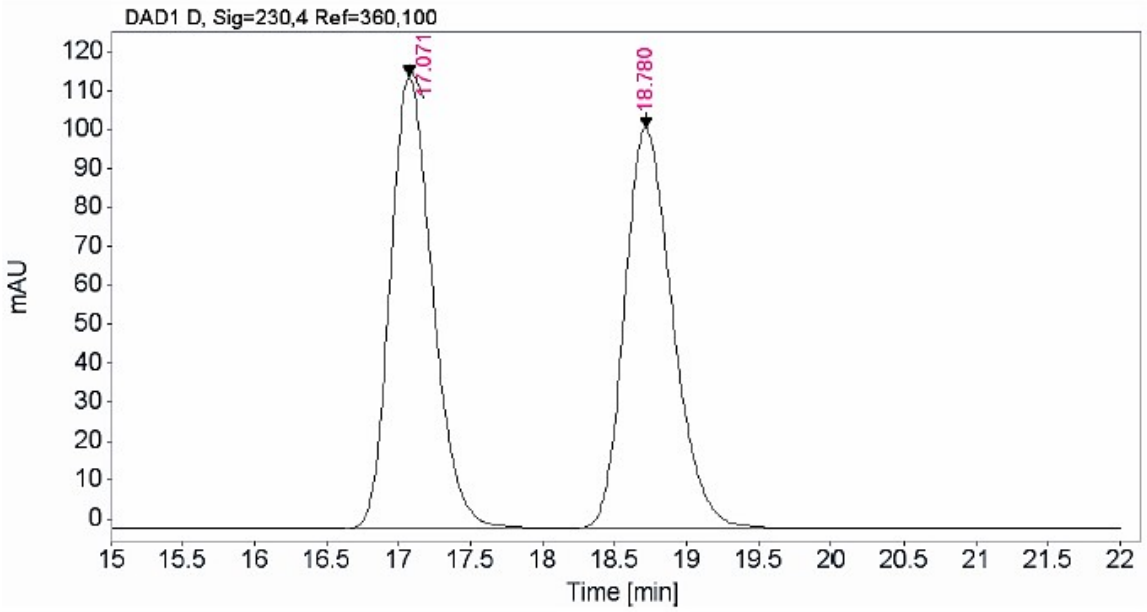


Signal: DAD1 D, Sig=230,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
17.136	MM	0.3204	269.774	14.0332	2.85
18.736	MM	0.3955	9188.608	387.2544	97.15

Figure 2: HPLC chromatogram showing (*R*)-nicotine (**2**) (major enantiomer) and (*S*)-nicotine (**1**) (minor enantiomer) peaks[5]

Data file:	C:\CHEM32\1\DATA\YL\DEF_LC
Sample name:	ED9691-2
Instrument:	AGILENT 1260
Acq. operator:	SYSTEM
Injection date:	7/2/2024 11:13:46 AM
Acq. method:	HDH100C.0.3ML.50MI



Signal: DAD1 D, Sig=230,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
17.071	MM	0.3420	2384.885	116.2280	49.94
18.780	MM	0.3871	2390.468	102.9248	50.06

Figure 3: HPLC chromatogram showing racemic mixture of (*S*)-nicotine (**1**) and (*R*)-nicotine (**2**) peaks[5]

According to Figure 3, the retention times for (*S*)-nicotine (**1**) and (*R*)-nicotine (**2**) are 14.071 and 18.780 minutes, respectively. This was compared with the literature HPLC data for racemic nicotine.[5]

7. References

1. L. R. Reddy and M. Prashad. *Chem. Commun.*, **2010**, 46, 222-224.
2. R. Kumar, K. K. Bhasin, J. S. Dhau, and A. Singh. *Inorg. Chem. Commun.*, **2022**, 139, 109344,.
3. R. S. Dawood and R. A. Stockman. *Eur. J. Org. Chem.*, **2021**, 3850-3853.
4. S. Y. Zhao, H. Q. Zhang, D. Q. Zhang, and Z. Y. Shao. *Synth. Comm.*, **2012**, 42, 128-135.
5. R. K. Agarthimoole, S. Gagan, S. Parida, T. K. Dinesh, M. S. Karatholuvhu, N. Palani, and S. Mukherjee. *Int. J. Org. Chem.*, **2022**, 12, 189-199.