Electrochemical N-demethylation of tropane alkaloids

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Supporting Information

Introduction

Table S1 Conditions and advantages/disadvantages of different catalytic methods for the N-demethylation of tropane alkaloids (References order is based on the main manuscript).

Ref.	Catalyst	Temp.	Solvent	Yield %	Oxidant	Time	Disadvantages	Advantages
[9]	NA	RT	Chloroform	90.5 (noratropine)	2,2,2-Trichloroethyl chloroformate 5 equiv.	20 h	1) A carbamate intermediate is produced which needs to be cleaved. 2) Very toxic oxidant. 3) Toxic solvent. 4) Long time. 5)Requires 8.8 equiv. of Zn dust	1) High yield
[10]	NA	RT	Chloroform	100 (noratropine)	α-chloroethyl chloroformate 5 equiv.	4 h	1) A carbamate intermediate is produced which needs to be cleaved. 2) Very toxic oxidant. 3) Toxic solvent. 4) Requires 10.2 equiv. of sodium hydrogen carbonate	1) Excellent yield
[10]	NA	30	Water (0.5 M sulfuric acid)	79.8 (norscopolamine)	$KMnO_4$ 2.5 equiv.	1 h	1) Toxic and hazardous oxidant. 2) Requires 2.5 equiv. of oxidants	1) Only water as solvent
[11]	NA	RT	Water	16.8 (noratropine)	$KMnO_4$ 2 equiv.	10 min	1) Toxic oxidant, 2) Very low yield	1) Quick reaction. 2) Only water as solvent
[12]	Light, Bengal rose, TPP (Photochemistry)	RT	Dichloromethane	66 (noratropine)	Photochemical reaction, oxygen and light	6 h	1) Toxic solvent. 2) Complex reaction mixture	1) No toxic oxidants. 2) Medium yield.
[15]	$FeSO_4.7H_2O$ 1.5 equiv.	RT	Methanol	51 (noratropine)	Magnesium bis (monoperoxyphthalate) hexahydrate 1.1 equiv.	45 min	1) N-oxide formation. 2) HCl isolation. 3) TPPS for iron chelating/separation. 4) Toxic solvent. 5) Low yield	1) No toxic oxidants
[17]	Fe(II)TPPS	-80-0 °C	Chloroform or methanol	42 (noratropine)	H_2O_2 or m-CPBA	NA	1) N-oxide formation. 2) Hazardous oxidant, 3) HCl salt isolation, 4) Catalyst separation, 5) Low temperature. 6) Toxic solvent. 7) Low yield	1) Stabilizing the catalyst by acetate buffer
[8]	Ferrocene 0.1 equiv.	80 °C	Chloroform and isopropanol	60 (noratropine)	H_2O_2 or m-CPBA	24 h	1) Toxic catalyst. 2) Hazardous oxidants. 3) Low yield. 4) Toxic solvents in part of the process. 5) Catalyst separation	1) Application of green solvent in part of the process
[2]	Iron powder 1 equiv.	RT	Chloroform	81 (noratropine)	H_2O_2 or m-CPBA	2 h	1)N-oxide formation 2) HCl salt isolation. 3) hazardous oxidants. 4)toxic solvents. 5)catalyst separation	1) High yield
[18] Green Chemistry	Iron nanoparticles (FeSO4 and $NaBH_4$) 1 equiv.	RT	Chloroform and isopropanol	85 (noratropine)	m-CPBA 1.2 equiv.	3 h	1) toxic sodium borohydride for nanoparticle synthesis. 2)N-oxide formation 3)HCl salt isolation 4)hazardous oxidant. 5)Catalyst separation. 6)Toxic solvent in part of the process.	1) High yield. 2) Application of isopropanol in part of the process
[18] Green Chemistry	$Fe_3(CO)_{12}$ 0.05 equiv.	RT	Chloroform and isopropanol/ethyl acetate	79 (noratropine)	m-CPBA 1.2 equiv.	19 h	1) Dangerous catalyst. 2) N-oxide formation. 3) HCl salt isolation. 4 Hhazardous oxidants 3) Long reaction time. 4) Toxic solvent in part of the reaction	1) Medium yield. 2) Application of isopropanol in part of the reaction. 3) Low catalyst load
[3] and [6] Green Chemistry	Fe(II)-TAML 0.1 equiv.	RT	Ethanol Acetone DMSO	75 (noratropine) 77 (norscopolamine)	H_2O_2, 50 equiv.	1 h	1) Deactivating of H_2O_2 by MnO_2. 2) Very high equivalent of H_2O_2	1) Application of green solvent. 2) High yield. 3) Low catalyst load

Experimental section

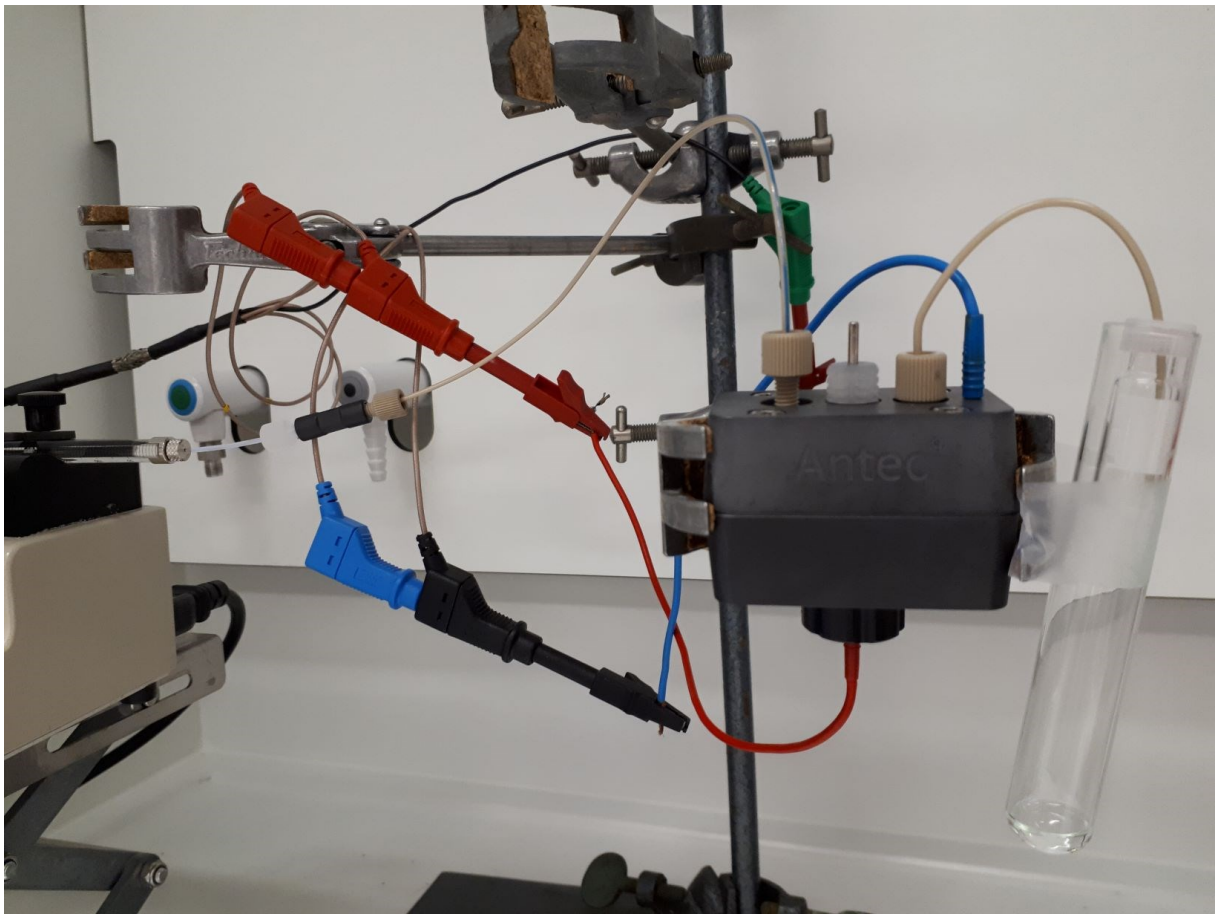
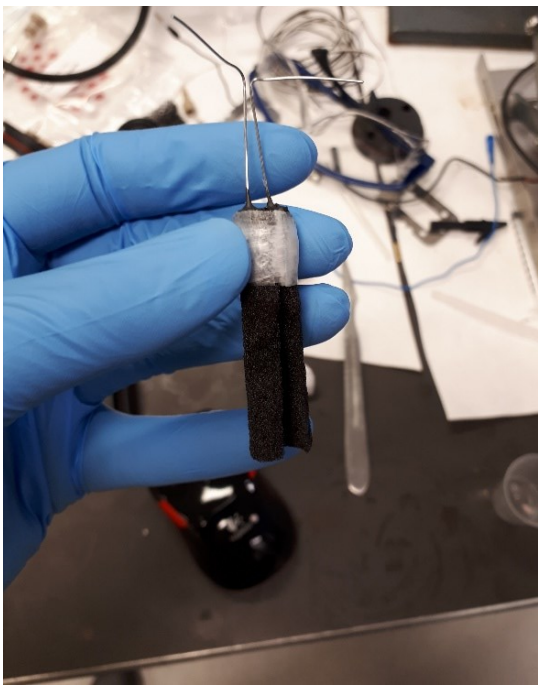


Fig S1, Set-up of the analytical electrochemical flow-cell (µ-PrepCell, Antec Scientific)



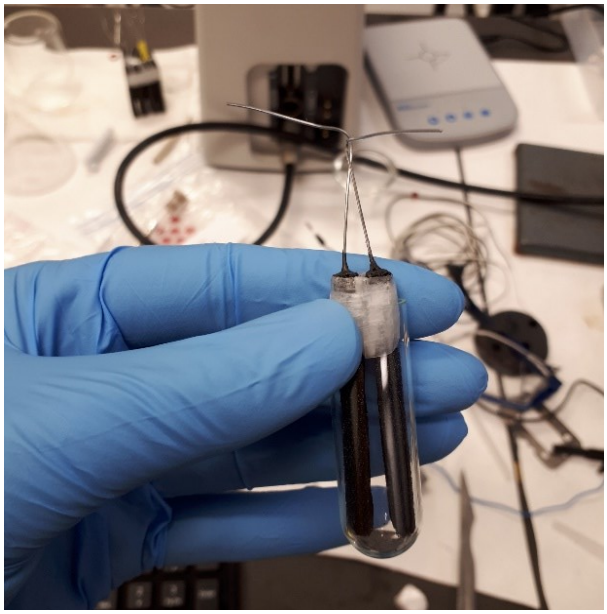


Fig S2, Set-up of the home-made electrochemical cell using a 100 PPI GC electrode, a stainless steel wire and a half-cut glass test tube

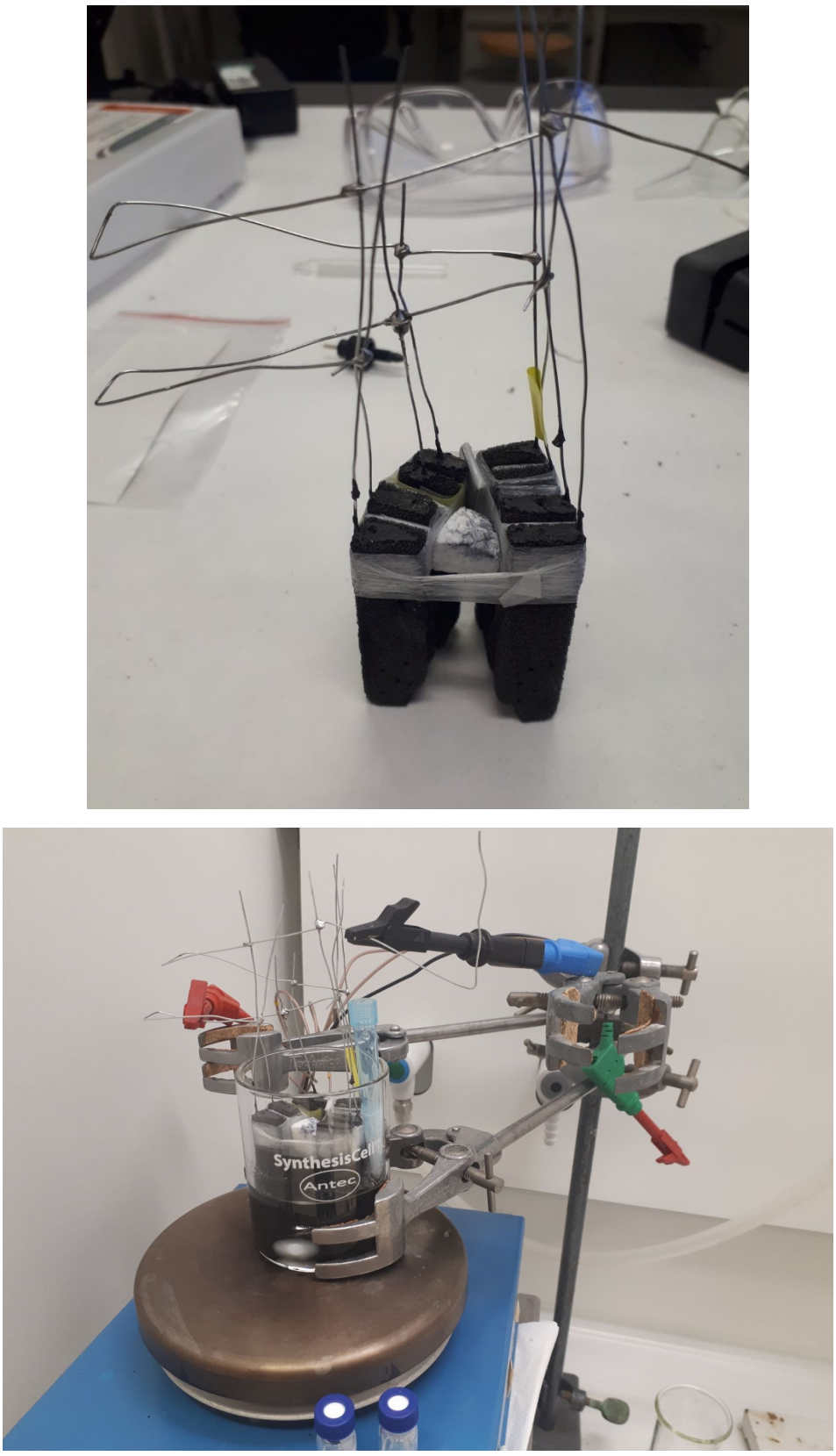


Fig S3, Home-made electrochemical cell with a stack of four paired anode-cathode electrodes for gram-scale synthesis

LC-MS chromatograms

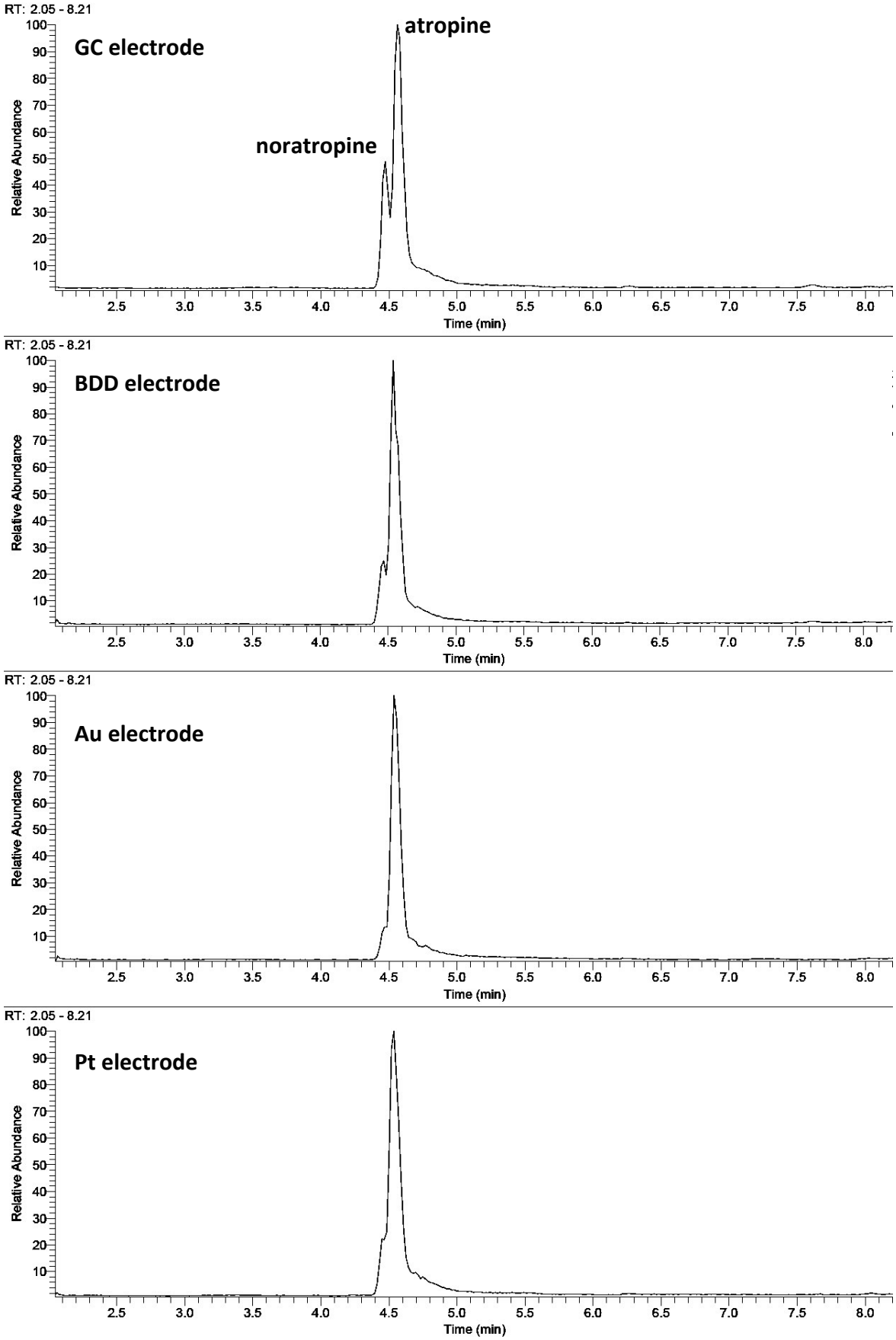


Fig S4, LC-MS chromatogram of flow-cell experiment with different electrode materials. Reaction condition: 10 mM, 5 µL/min, 200 µA, ethanol, $NaClO_4$ (4 equivalent).

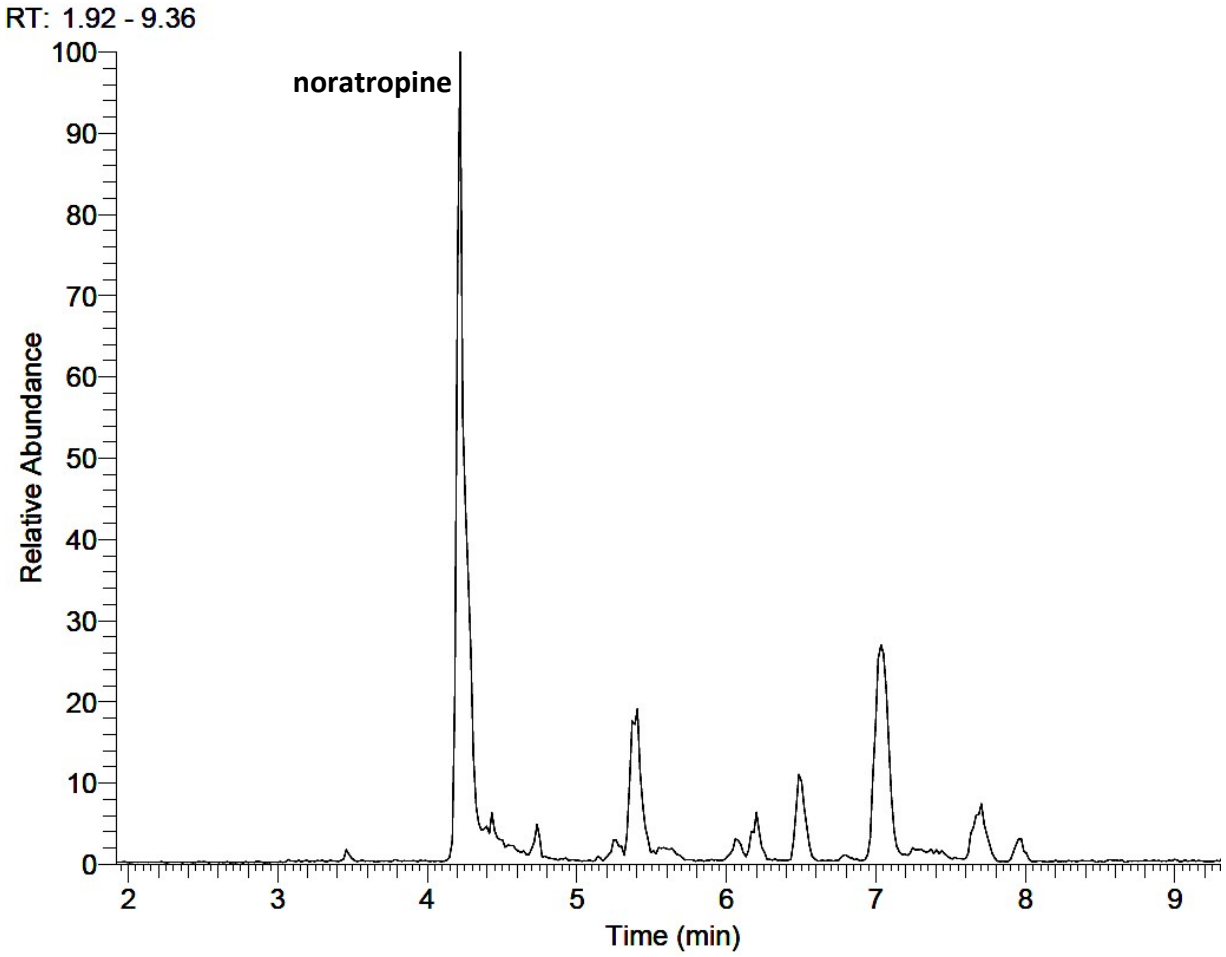


Fig S5, LC-MS chromatogram of final reaction mixture of entry 5, Table 1.
57 mM atropine, ethanol/water 2:1, 8 mA/3 h.

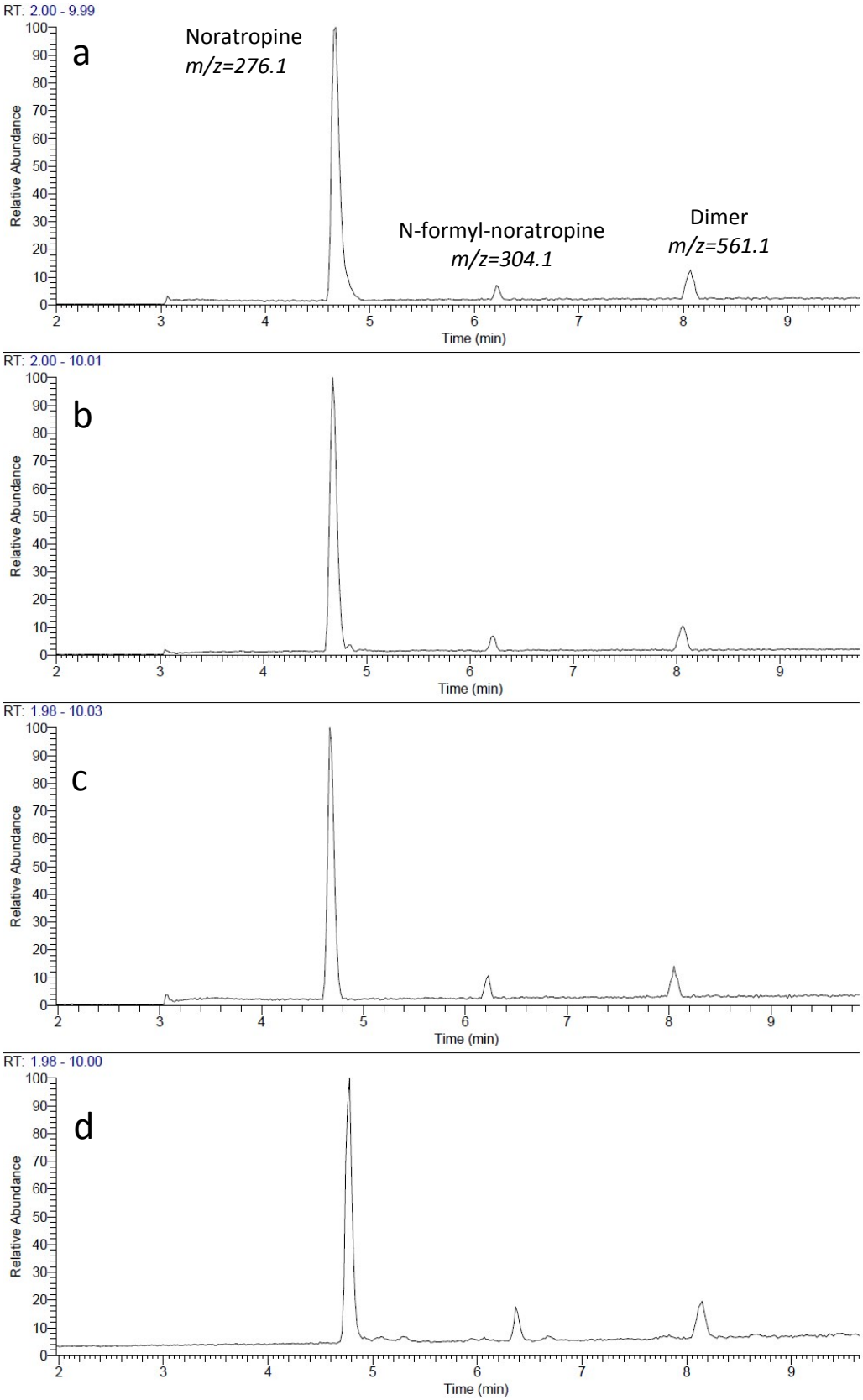


Fig S6, LC-MS chromatogram of final reaction mixture in four different conditions, entry 9-12, Table 1 (panels a-d, respectively).
57 mM atropine, ethanol/water 2:1, 4 mA/4.5 h.

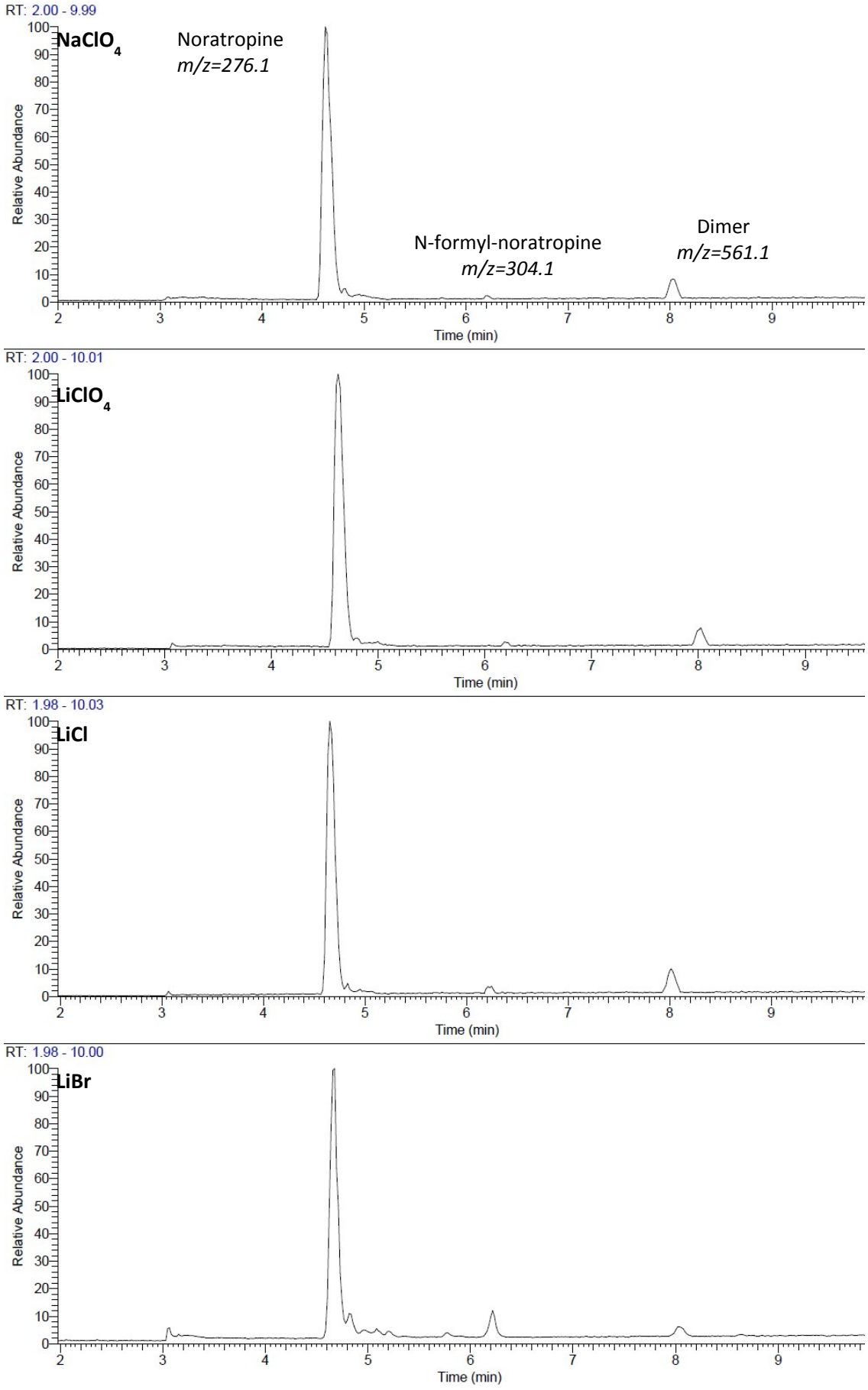


Fig S7, LC-MS chromatogram of final reaction mixture with four different supporting electrolytes, entry 1-4, Table 3. 57 mM atropine, methanol/water 2:1.

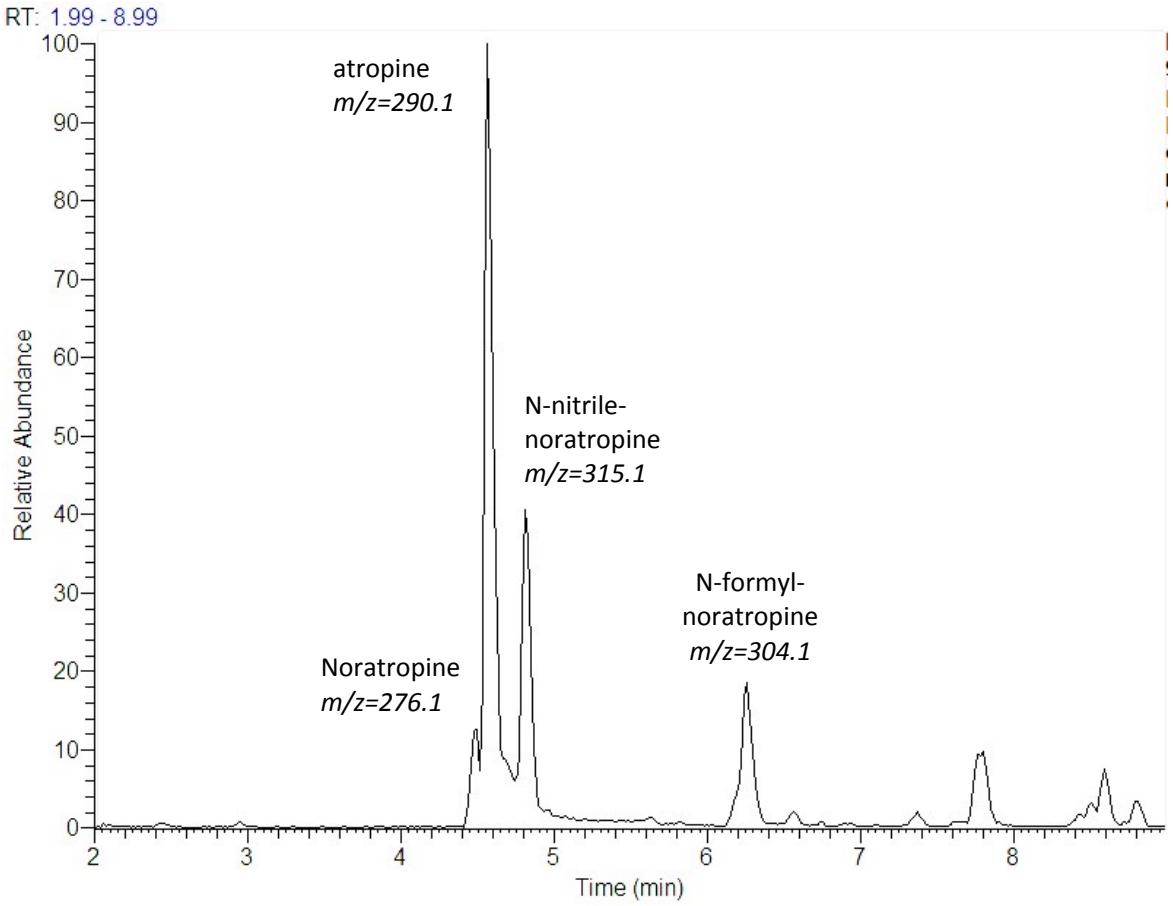


Fig S8, LC-MS chromatogram of flow-cell experiment with added KCN. Reaction condition: 10 mM atropine, 1 µL/min, 200 µA, ethanol/water 1:1, $NaClO_4$ (4 equivalent), KCN (4 equivalent).

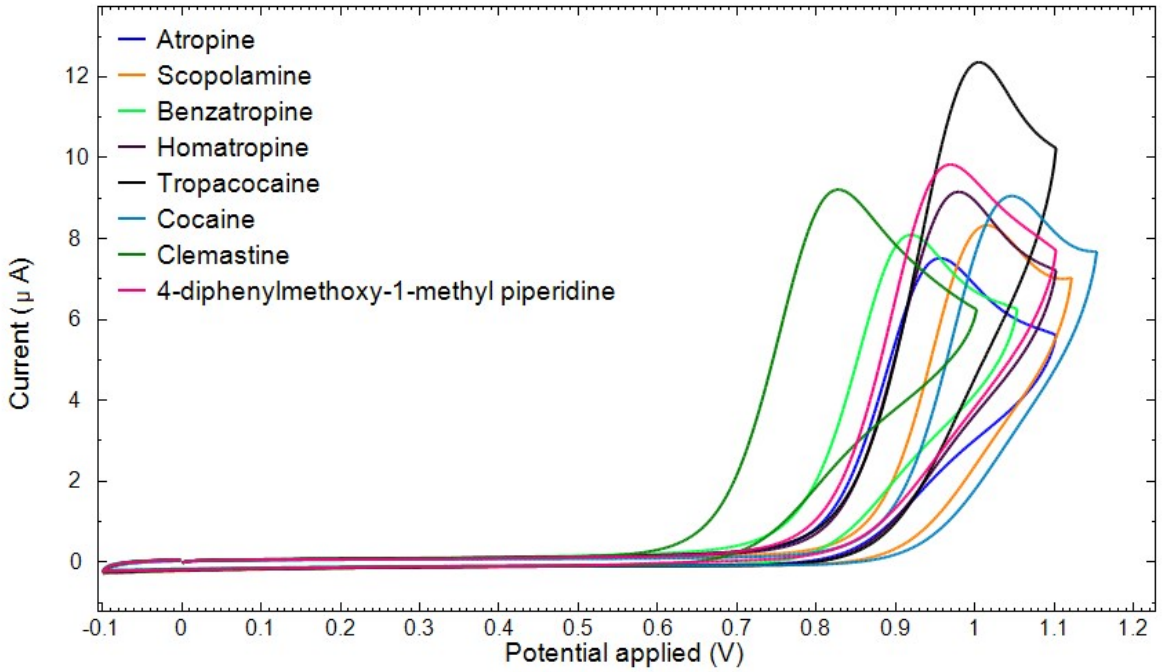


Fig S9, Cyclic voltammetry of different compounds (5 mM) in ethanol/water (2:1) with $NaClO_4$ (0.1 M) as supporting electrolyte, glassy carbon both as working and counter electrodes, scan rate = 100 mV/s.

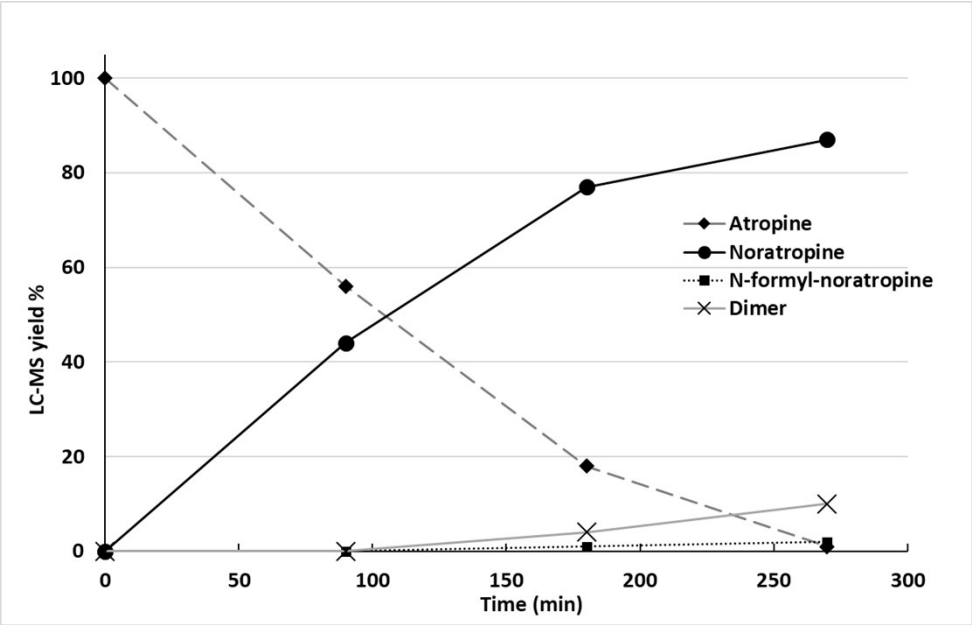


Fig S10, Product distribution during the reaction period for the electrochemical N-demethylation of atropine (Table 2, entry 10).

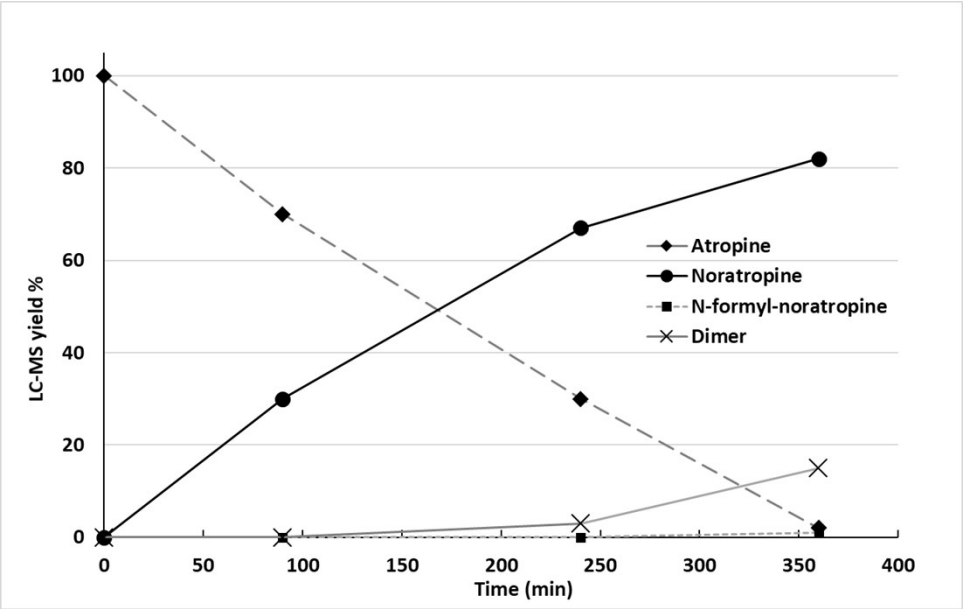


Fig S11, Product distribution during the reaction period for the electrochemical N-demethylation of atropine in gram-scale (Table 4, entry 2).

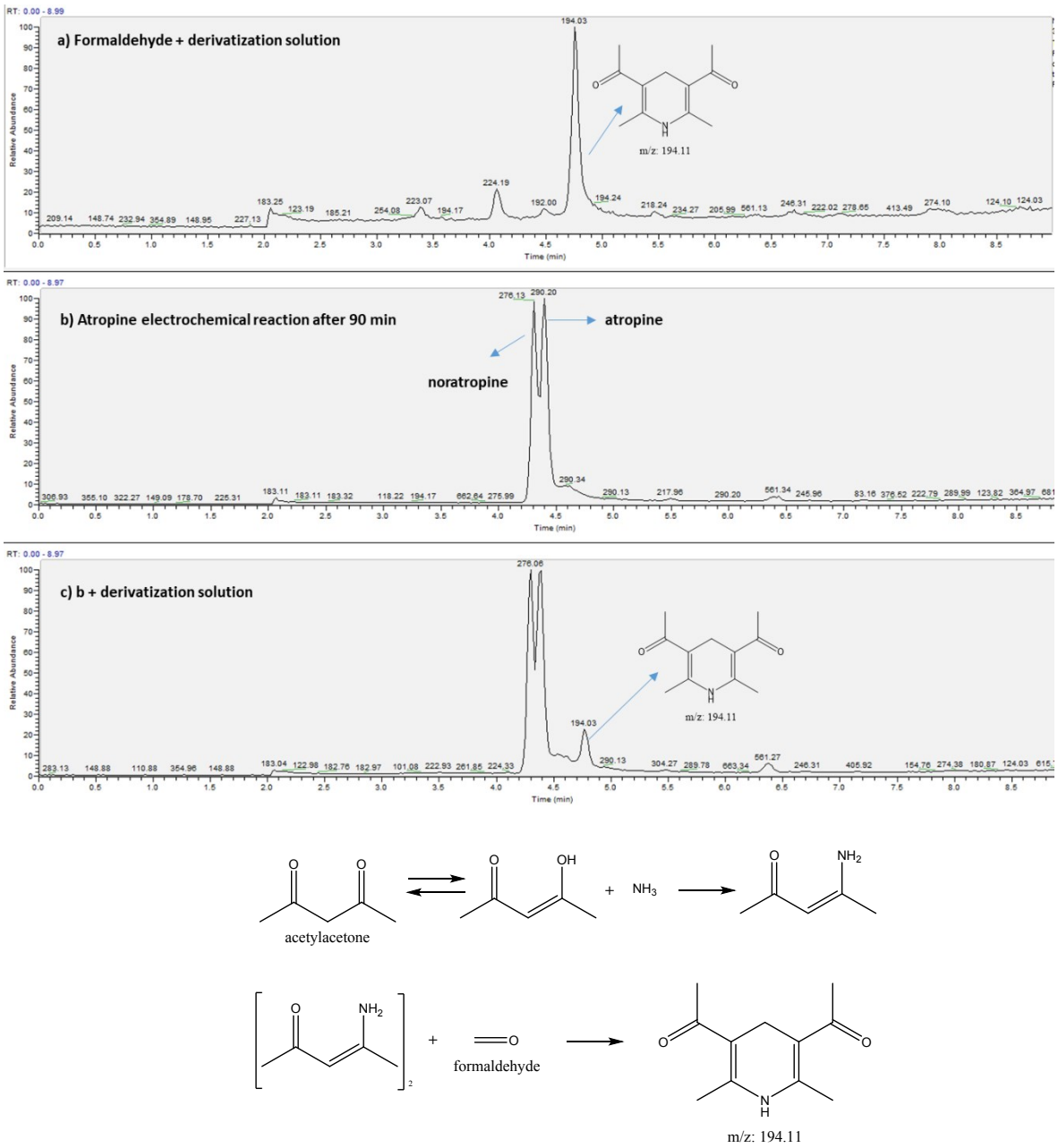


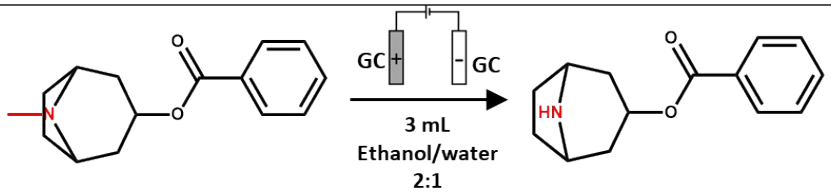
Fig S12, LC-MS chromatogram and reaction scheme of the derivatization reaction of formaldehyde in the reaction solution.

Table S2, electrochemical N-demethylation of atropine to noratropine using another set of electrodes. 50 mg atropine, 3 mL, ethanol, $NaClO_4$ (4 equiv.) (the same condition as Table 2, entry 9-12)

Entry	Current/time	Added water	Conversion (%)[a]	Yield (%)
1	4 mA / 4.1 h	18.5 M (33% v/v)	99	74[b]
2	4 mA / 4.1 h	18.5 M (33% v/v)	99	70[b]
3	4 mA / 4.1 h	18.5 M (33% v/v)	99	70[b]
4	4 mA / 4.1 h	18.5 M (33% v/v)	99	76[b]

[a] determined by LC-MS. [b] Isolated yield after 2-step-NH_4OH-LLE

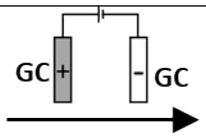
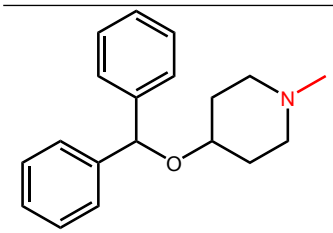
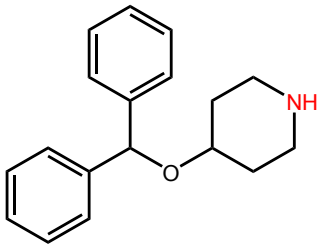
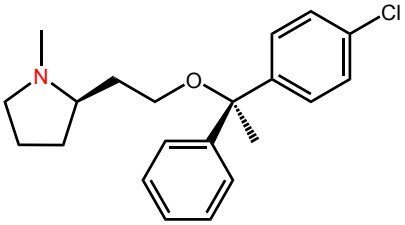
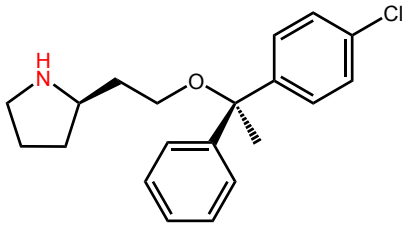
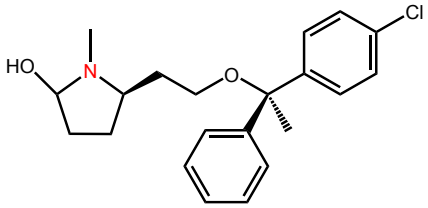
Table S3, electrochemical N-demethylation of tropacocaine at different pH values.



Entry	Current/time	Supporting electrolyte (4 equiv.)	Conversion (%)[a]	Yield (%)	pH[b]
1[c, d]	4 mA / 7 h	$NaClO_4$	99	70[e]	11
2[c]	4 mA / 4 h	LiCl	0	-	4
3[f]	4 mA / 1 h	$NaClO_4$	2	-	5
4[f, g]	4 mA / 1 h	$NaClO_4$	95	81[h]	10

[a] determined by LC-MS. [b] measured by pH paper. [c] 54 mM. [d] reaction with free amine. [e] isolated yield by 2-step-NH_4OH LLE. [f] 20 mM. [g] pH increased by adding equimolar amount of sodium carbonate. [h] yield determined by LC-MS.

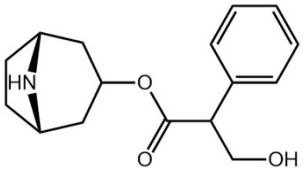
Table S4, electrochemical N-demethylation of N-methylpiperidine and N-methylpyrrolidine examples.

Starting compound	 **60 mg** **3 mL** **Ethanol/water (2:1)** **$NaClO_4$ (4 equiv.)**	Synthesized compound
 4-diphenylmethoxy-1-methyl piperidine **13**	0.96 V [a] 4 mA / 12 h	 44 % [b]
 Clemastine **14**	0.82 V [a] 4 mA / 9 h	 19% [c] +  52% [c]

[a] electrochemical oxidation potential versus Ag/AgCl. [b] Isolated yield after silica-gel chromatography.
[c] Isolated yield after C18 chromatography.

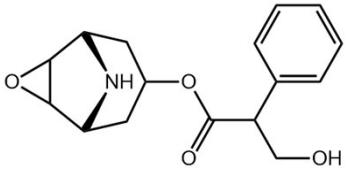
^{1}H and ^{13}C NMR of compounds

Noratropine



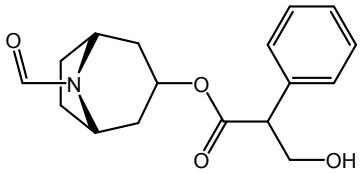
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 5H), 5.07 (t, J = 5.2 Hz, 1H), 4.21 – 4.12 (m, 1H), 3.86 – 3.74 (m, 2H), 3.43 (dt, J = 6.8, 3.1 Hz, 1H), 3.31 (dt, J = 6.7, 3.0 Hz, 1H), 2.45 (br.s, 2H), 2.00 (dddd, J = 15.1, 5.3, 3.7, 1.5 Hz, 1H), 1.96 – 1.83 (m, 2H), 1.74 (dt, J = 15.1, 1.8 Hz, 1H), 1.70 – 1.59 (m, 1H), 1.53 (dq, J = 15.0, 1.8 Hz, 1H), 1.52 – 1.40 (m, 1H), 1.31 (ddd, J = 13.1, 9.2, 4.5 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl3) δ 172.36 (C=O), 135.92 (C), 128.94 (CH), 128.25 (CH), 127.79 (CH), 68.73 (CH), 64.03 (CH_2), 54.66 (CH), 53.17 (CH), 53.09 (CH), 37.20 (CH2), 36.92 (CH2), 28.98 (CH2), 28.59 (CH2). **HRMS;** Calculated for $C_{16}H_{22}NO_3$ $[M+H^+]$=276.1597, observed = 276.1594. Data are consistent with literature [1,2].

Norscopolamine



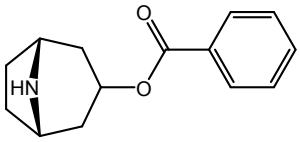
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 2H), 7.36 – 7.29 (m, 1H), 7.32 – 7.20 (m, 2H), 5.03 (t, J = 5.2 Hz, 1H), 4.17 (dd, J = 11.0, 8.8 Hz, 1H), 3.81 (dd, J = 11.0, 5.3 Hz, 1H), 3.76 (dd, J = 8.8, 5.2 Hz, 1H), 3.27 (d, J = 3.0 Hz, 1H), 3.22 (dd, J = 3.9, 2.3 Hz, 1H), 3.07 (dd, J = 3.9, 2.2 Hz, 1H), 2.61 (br.s, 1H), 2.72 (s, 1H), 2.52 (d, J = 3.0 Hz, 1H), 2.13 (ddd, J = 15.2, 5.4, 3.9 Hz, 1H), 2.04 (ddd, J = 15.3, 5.2, 3.9 Hz, 1H), 1.67 (dq, J = 15.3, 1.8 Hz, 1H), 1.44 (dq, J = 15.5, 1.8 Hz, 1H).**^{13}C NMR** (126 MHz, CDCl3) δ 171.86 (C=O), 135.82 (C), 129.13 (CH), 128.17 (CH), 128.11 (CH), 66.94 (CH), 63.95 (CH_2-OH), 54.40 (CH), 53.97 (CH), 53.47 (CH), 51.92 (CH), 51.80 (CH), 31.34 (CH_2), 31.14 (CH_2). **HRMS:** Calculated for $C_{16}H_{20}NO_4$ $[M+H^+]$=290.1387, observed = 290.1388. Data are consistent with literature [1–3].

N-formyl-noratropine



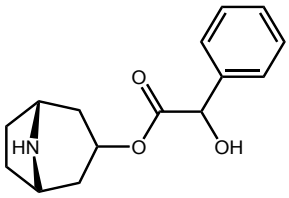
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 0.5H), 8.06 (s, 0.5H), 7.40 – 7.25 (m, 5H), 5.21 – 5.15 (m, 1H), 4.56 (dt, J = 6.8, 3.0 Hz, 0.5H), 4.43 (dt, J = 6.8, 2.9 Hz, 0.5H), 4.22 (ddd, J = 9.9, 7.9, 1.3 Hz, 1H), 4.01 (dt, J = 6.7, 2.8 Hz, 0.5H), 3.91 – 3.80 (m, 2.5H), 2.46 (broad s, 1H), 2.20 – 1.55 (m, 7H), 1.28 (m, 1H). **^{13}C NMR** (126 MHz, CDCl3) δ 172.16 (OC=O), 172.14 (OC=O), 157.37 (CH=O), 135.41 (C), 135.33 (C), 129.06 (CH), 129.04 (CH), 128.11 (CH), 128.08 (CH), 128.00 (CH), 127.96 (CH), 68.23 (HC-O), 64.12 (CH_2-OH), 64.08 (CH_2-OH), 54.34 (CH), 54.31 (CH), 53.37 (CH), 53.27 (CH), 48.52 (CH), 48.44 (CH), 38.47 (CH_2), 38.14 (CH_2), 35.82 (CH_2), 35.57 (CH_2), 27.88 (CH_2), 27.40 (CH_2), 27.11 (CH_2), 26.68 (CH_2). **HRMS:** Calculated for $C_{17}H_{22}NO_4$ $[M+H^+]$ = 304.1543, observed = 304.1544. Data are consistent with literature [2].

Nortropacocaine



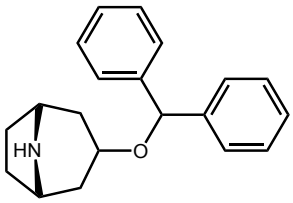
^{1}H NMR (500 MHz, CD_3OD) δ 8.05 – 7.94 (m, 2H), 7.59 (dd, J = 8.3, 6.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 5.29 (tt, J = 11.2, 6.1 Hz, 1H), 3.61 (p, J = 3.0 Hz, 2H), 2.10 (ddd, J = 13.6, 6.1, 2.9 Hz, 2H), 1.94 – 1.79 (m, 4H), 1.82 – 1.69 (m, 2H). **^{13}C NMR** (126 MHz, CDCl3) δ 166.56 (C=O), 133.36 (C), 130.58 (CH), 129.53 (CH), 128.27 (CH), 67.50 (CH), 54.31 (CH), 38.98 (CH_2), 29.15 (CH_2). **HRMS:** Calculated for $C_{14}H_{18}NO_2$ [M+H$^+$]=232.1332, observed = 232.1333. Data are consistent with literature [4,5].

Norhomatropine



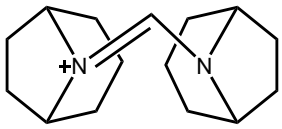
^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 – 7.27 (m, 5H), 5.14 – 5.00 (m, 2H), 3.45 – 3.38 (m, 1H), 3.32 (s, 1H), 3.29 – 3.24 (m, 1H), 2.12 – 1.95 (m, 1H), 1.94 – 1.86 (m, 1H), 1.85 – 1.71 (m, 2H), 1.64 (tq, J = 12.3, 6.4, 5.9 Hz, 1H), 1.49 – 1.35 (m, 2H), 1.14 – 0.95 (m, 1H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 172.91 (C=O), 138.54 (C), 128.62 (CH), 128.49 (CH), 126.72 (CH), 73.29 (CH), 70.12 (CH), 52.93 (CH), 52.83 (CH), 36.97 (CH2), 36.74 (CH2), 28.87 (CH2), 28.36 (CH2). **HRMS:** Calculated for $C_{15}H_{20}NO_3$ [M+H$^+$] = 262.1438, observed = 262.1438.

Norbenzatropine



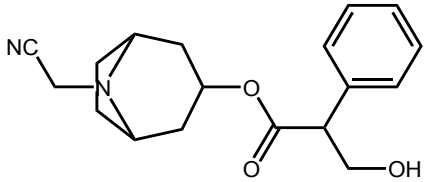
^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.22 (m, 10H), 5.42 (s, 1H), 4.75 (s, 3H), 4.06 – 4.01 (m, 2H), 3.84 – 3.75 (m, 1H), 2.50 – 2.36 (m, 4H), 2.26 – 2.17 (m, 2H), 2.06 (d, J = 15.3 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 141.98 (C), 128.55 (CH), 127.65 (CH), 126.71 (CH), 81.60 (CH), 67.66 (CH), 53.99 (CH), 33.42 (CH2), 26.31 (CH2). **HRMS:** Calculated for $C_{20}H_{24}NO$ [M+H$^+$] = 294.1852, observed = 294.1852.

8-((8-azabicyclo[3.2.1]octan-8-yl)methylene)-8-azabicyclo[3.2.1]octan-8-ium



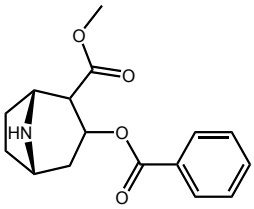
^{1}H NMR (500 MHz, Chloroform-d) δ 8.18 (s, 1H), 4.52 – 4.37 (m, 4H), 2.29 – 2.17 (m, J = 5.6, 4.7 Hz, 4H), 2.04 – 1.92 (m, 4H), 1.91 – 1.72 (m, 11H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 143.22 (CH), 63.85 (CH), 56.54 (CH), 33.21 (CH2), 32.09 (CH2), 28.35 (CH2), 25.68 (CH2), 16.22 (CH2). **HRMS:** Calculated for $C_{15}H_{25}N_2^+$ [M]= 233.2012, observed = 233.2012.

8-(cyanomethyl)-8-azabicyclo[3.2.1]octan-3-yl 3-hydroxy-2-phenylpropanoate



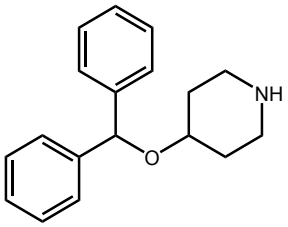
^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.23 (m, 5H), 5.05 (t, J = 5.3 Hz, 1H), 4.18 (dd, J = 11.0, 8.6 Hz, 1H), 3.86 – 3.76 (m, 2H), 3.27 (d, J = 13.7 Hz, 3H), 3.19 – 3.12 (m, 1H), 2.44 – 2.24 (br.s, 1H), 2.21 – 2.05 (m, 2H), 1.87 – 1.74 (m, 3H), 1.66 – 1.51 (m, 2H), 1.26 – 1.20 (m, 1H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 172.20 (CO), 135.46 (C), 129.01 (CH), 128.14 (CH), 127.90 (CH), 116.95 (CN), 67.54 (CH), 64.15 (CH_2-OH), 58.95 (CH), 58.86 (CH), 54.28 (CH), 40.81 (CH_2), 36.65 (CH), 36.45 (CH), 25.25 (CH), 24.70 (CH). **HRMS:** Calculated for $C_{18}H_{23}N_2O_3$ [M+H$^+$] = 315.1703 , observed = 315.1703. Data are consistent with literature [6,7].

Norcocaine



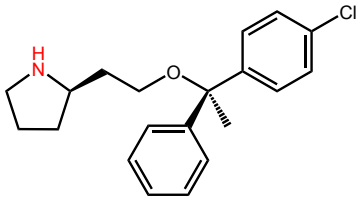
^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 – 7.91 (m, 2H), 7.55 (td, J = 7.3, 1.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 5.44 (dt, J = 11.6, 6.5 Hz, 1H), 3.82 (td, J = 7.6, 2.6 Hz, 2H), 3.64 (s, 3H), 3.47 (s, 1H), 3.11 (dd, J = 6.8, 2.2 Hz, 1H), 2.20 – 1.95 (m, 4H), 1.80 – 1.70 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 172.83 (C=O), 165.64 (C=O), 133.32 (CH), 129.94 (C), 129.64 (CH), 128.52 (CH), 66.75 (CH), 56.07 (CH), 53.40 (CH), 51.96 (CH_3), 48.02 (CH), 34.82 (CH_2), 28.10 (CH_2), 27.20 (CH_2). **HRMS:** Calculated for $C_{16}H_{20}NO_4$ [M+H$^+$] = 290.1386 , observed = 290.1386 .

4-(benzhydryloxy)piperidine



^{1}H NMR (500 MHz, Chloroform-d) 7.32 (d, *J* = 5.5 Hz, 8H), 7.26 – 7.23 (m, 2H), 5.44 (s, 1H), 3.81 – 3.67 (m, 2H), 3.45 (ddd, *J* = 14.0, 10.5, 3.9 Hz, 2H), 3.27 (dt, *J* = 12.7, 4.6 Hz, 2H), 1.99 (qt, *J* = 14.8, 4.0 Hz, 4H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 142.01 (C), 128.72 (CH), 127.92 (CH), 127.01 (CH), 81.52 (CH), 67.49 (CH), 41.68 (CH_2), 27.59 (CH_2). **HRMS:** Calculated for $C_{18}H_{22}NO$ [M+H$^+$]=268.1696, observed = 268.1696 .

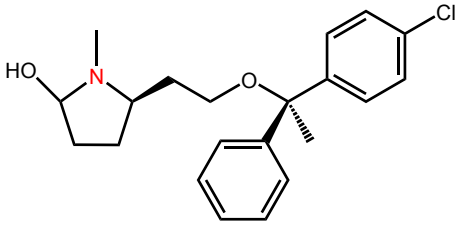
(R)-2-(2-((R)-1-(4-chlorophenyl)-1-phenylethoxy)ethyl)pyrrolidine formate



. HCOOH

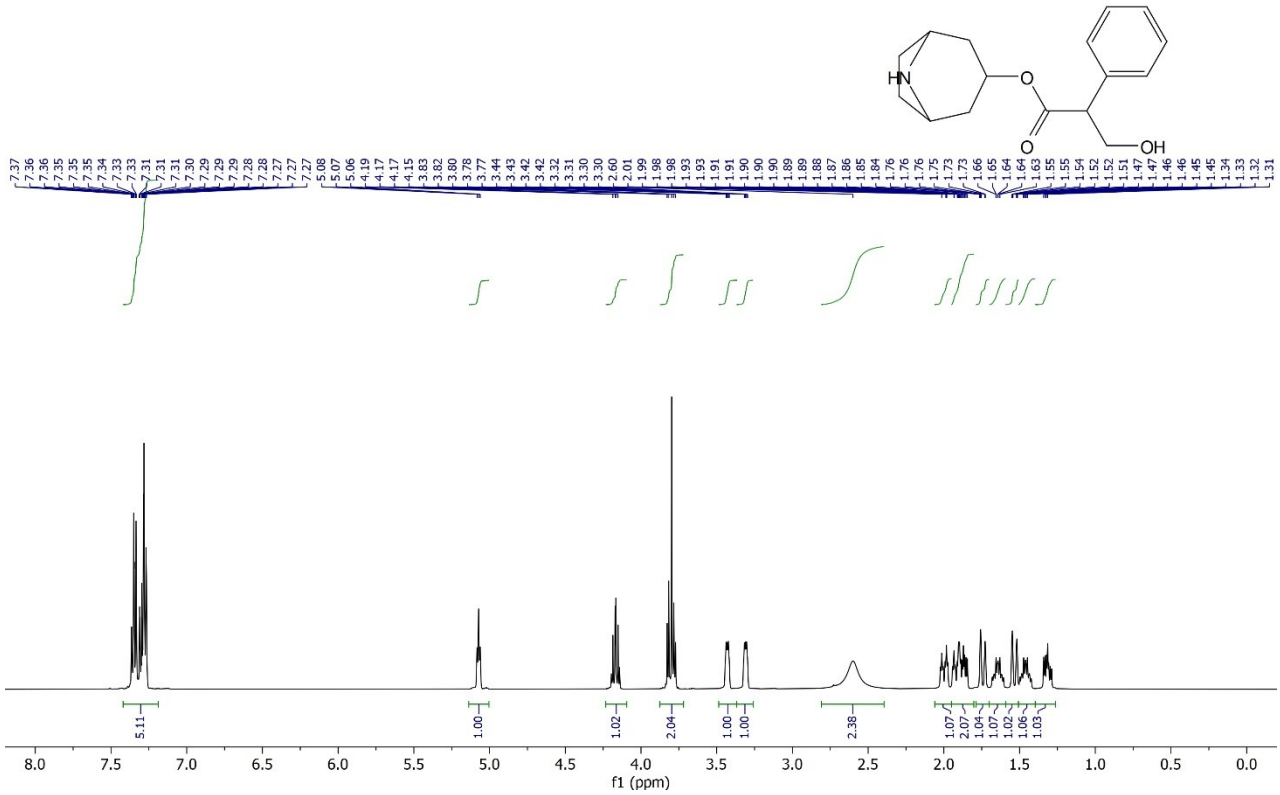
^{1}H NMR (500 MHz, Chloroform-d) 8.58 (s, 1H), 7.35 – 7.23 (m, 10H), 3.66 (tt, *J* = 8.9, 6.5 Hz, 1H), 3.43 – 3.17 (m, 4H), 2.25 – 1.87 (m, 6H), 1.86 (d, *J* = 4.4 Hz, 3H), 1.68 (dq, *J* = 12.8, 8.8 Hz, 1H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 169.07 (C=O), 145.84 (C), 145.10 (C), 132.95 (CCl), 128.32 (CH), 128.30 (CH), 128.27 (CH), 127.34 (CH), 126.72 (CH), 80.70 (C), 59.76 (CH_2), 57.78 (CH), 44.15 (CH_2), 32.72 (CH_2), 30.56 (CH_2), 25.63 (CH_3), 23.84 (CH_2). **HRMS:** Calculated for $C_{20}H_{25}NOCl$[M+H$^+$] = 330.1619, observed = 330.1616 .

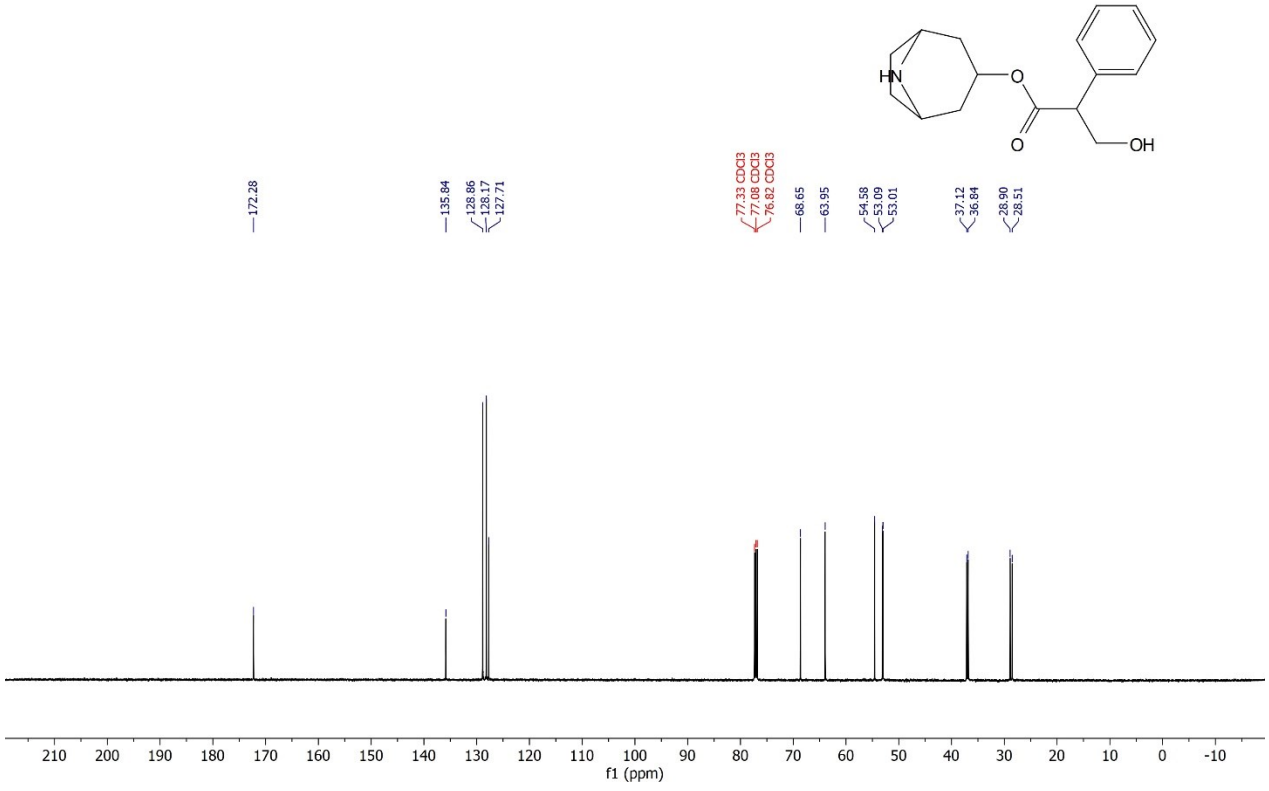
(5R)-5-(2-((R)-1-(4-chlorophenyl)-1-phenylethoxy)ethyl)-1-methylpyrrolidin-2-ol

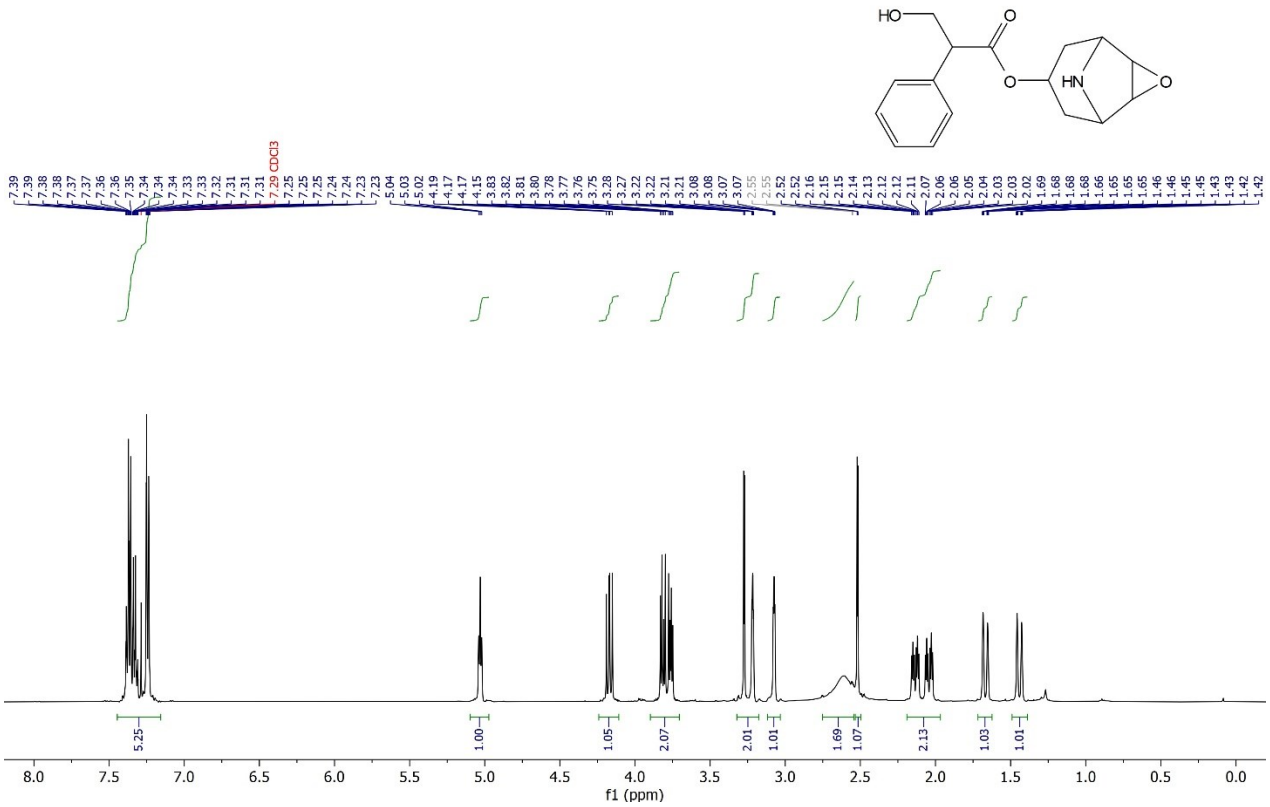


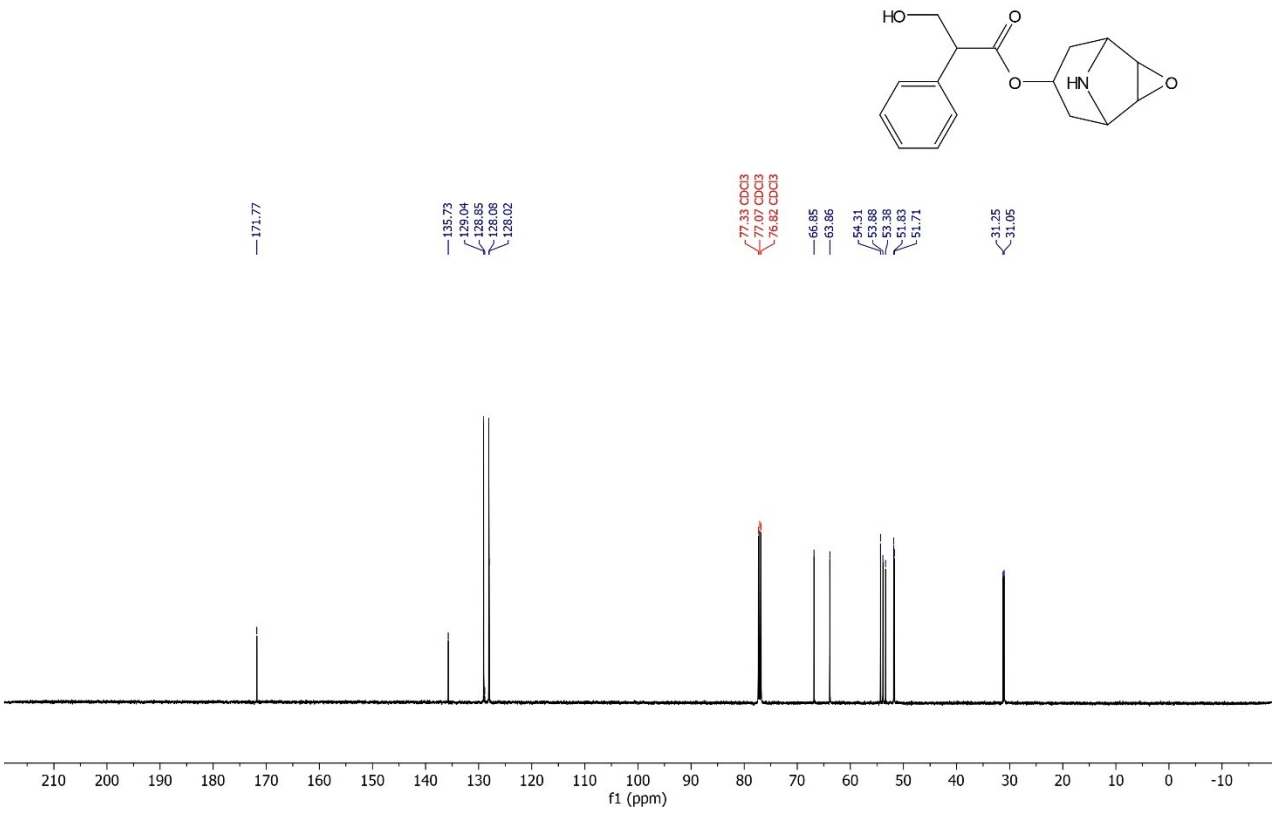
^{1}H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.24 (m, 9H), 3.99 (ddd, *J* = 11.4, 8.4, 2.6 Hz, 1H), 3.81 (dq, *J* = 14.2, 8.8, 8.1 Hz, 2H), 3.45 (s, 3H), 3.39 (dq, *J* = 8.3, 4.2, 3.1 Hz, 1H), 3.29 (td, *J* = 9.0, 4.0 Hz, 1H), 2.33 – 2.09 (m, 4H), 2.02 – 1.88 (m, 2H), 1.85 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 145.15 (C), 145.01 (C) , 132.85 (CCl), 128.30 (CH), 128.26 (CH), 128.09 (CH), 127.41 (CH), 126.71 (CH), 80.80 (CH), 76.39 (C), 69.18 (CH), 58.77 (CH_2), 51.82 (CH_3), 28.24 (CH_2), 27.76 (CH_2), 25.49 (CH_2), 19.56 (CH_3). **HRMS:** Calculated for $C_{21}H_{27}ClNO_2$ [M+H$^+$] = 360.1725, observed = 360.1720.

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






HO
O
O
HN
O
7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.34 7.34 7.34 7.33 7.32 7.31 7.31 7.31 7.29 CDCl3 7.25 7.25 7.24 7.24 7.23 7.23
5.04 5.03 5.02 4.19 4.17 4.17 4.15 3.83 3.82 3.81 3.80 3.78 3.77 3.76 3.75 3.28 3.27 3.22 3.22 3.21 3.21 3.08 3.08 3.07 3.07 2.55 2.52 2.52 2.16 2.15 2.15 2.14 2.13 2.12 2.12 2.11 2.07 2.06 2.06 2.05 2.04 2.03 2.03 2.02 1.69 1.68 1.68 1.66 1.65 1.65 1.65 1.46 1.46 1.45 1.45 1.43 1.42 1.42
5.25
1.00
1.05
2.07
2.01
1.01
1.69
1.07
2.13
1.03
1.01
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


HO
O
O
HN
O
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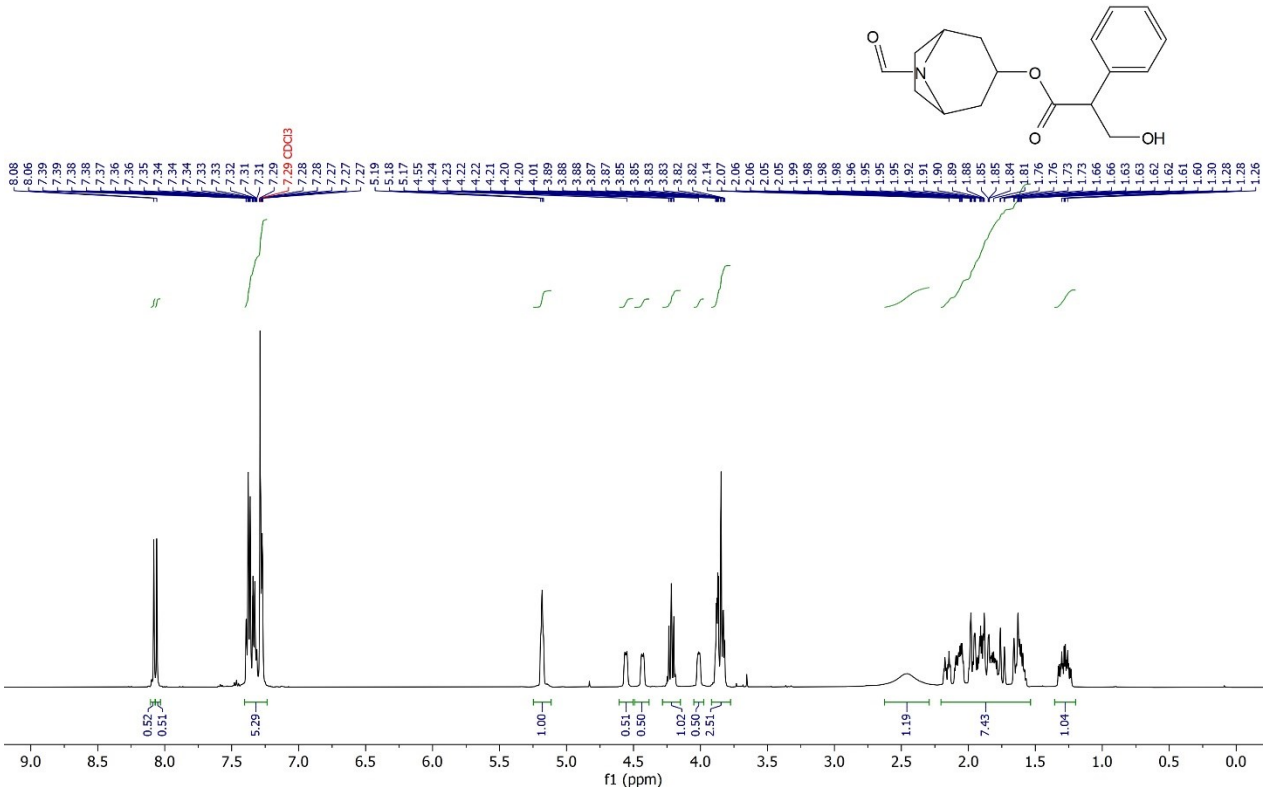
135.73
129.04
128.85
128.08
128.02
77.33 CDCl3
77.07 CDCl3
76.82 CDCl3
66.85
63.86
54.31
53.88
53.38
51.83
51.71
31.25
31.05
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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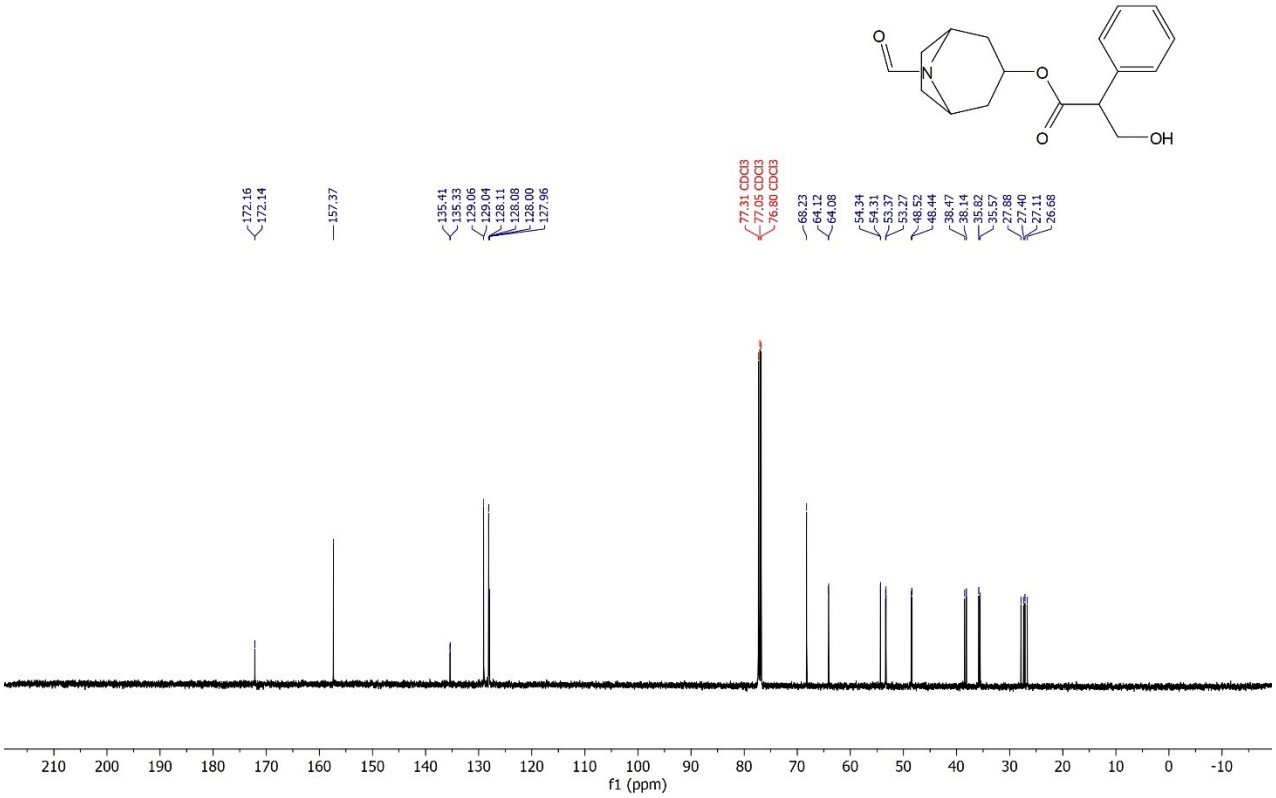
N
O
O
OH
f1 (ppm)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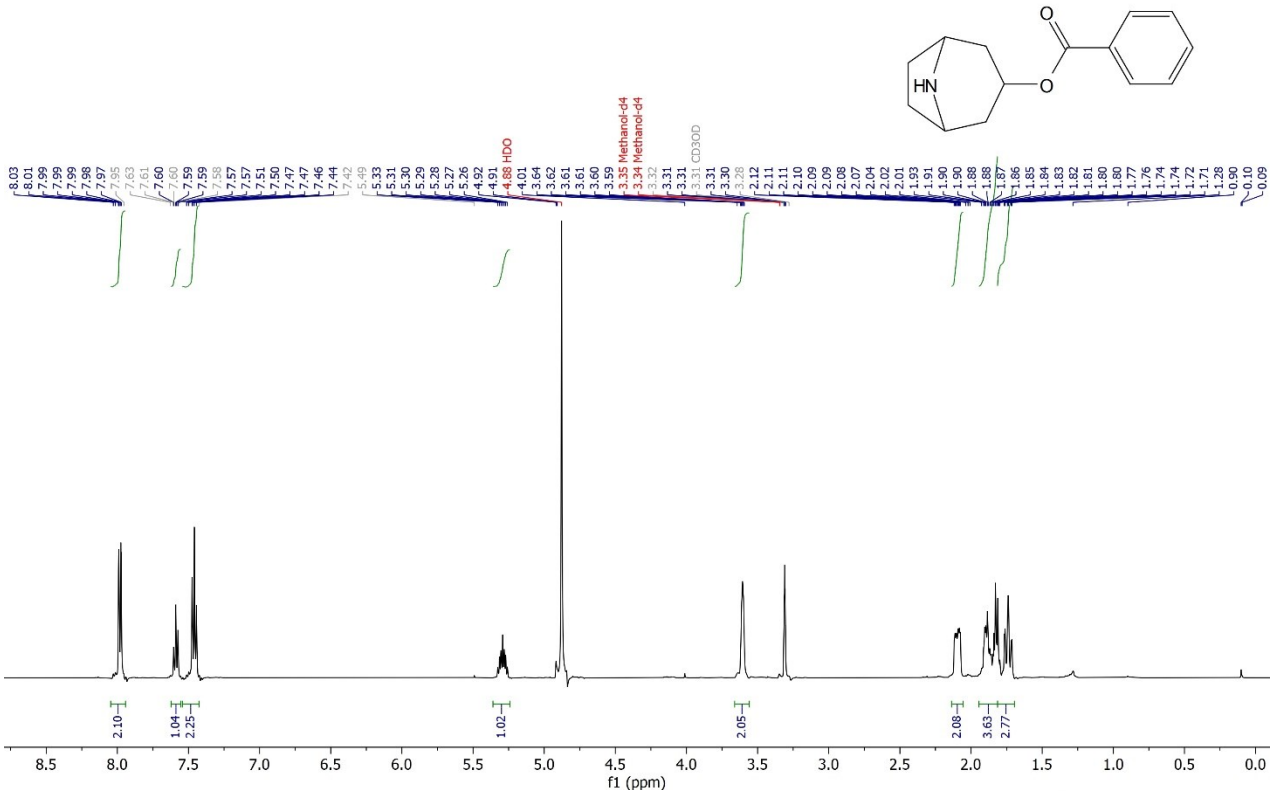
N
O
O
OH
f1 (ppm)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O
O
HDO
Methanol-d4
Methanol-d4
CD3OD
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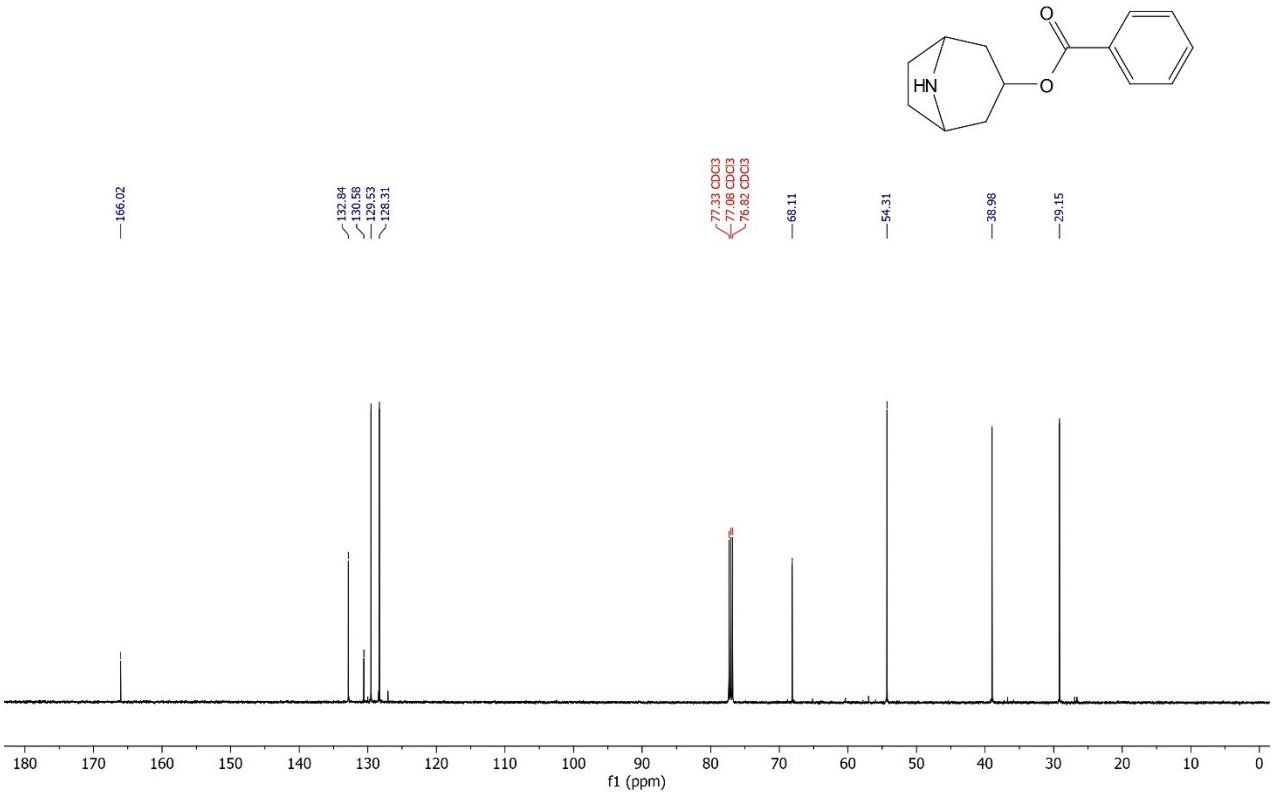
1.04
2.25
1.02
2.05
2.08
3.63
2.77
f1 (ppm)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O
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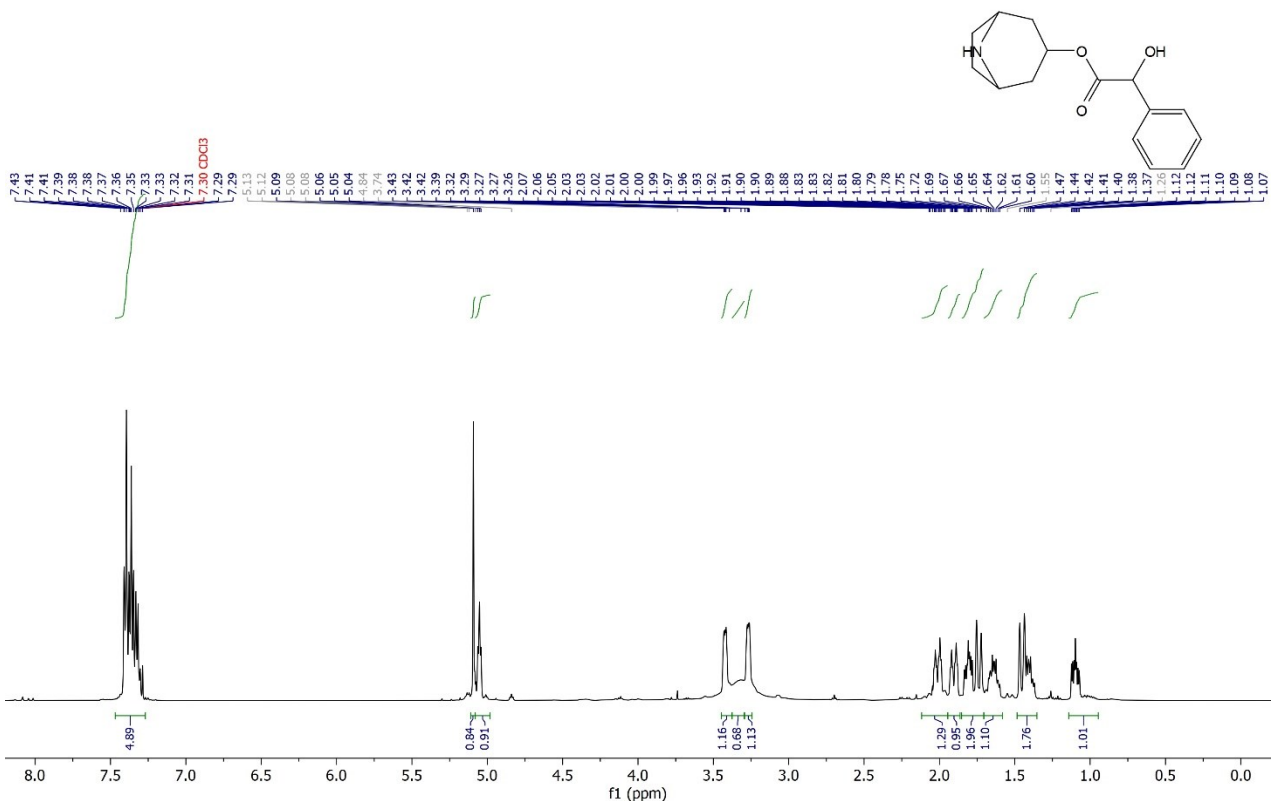
132.84
130.58
129.53
128.31
77.33 CDCl3
77.08 CDCl3
76.82 CDCl3
68.11
54.31
38.98
29.15
f1 (ppm)


HN
O
OH
O
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5.13 5.12 5.09 5.08 5.08 5.06 5.05 5.04 4.84 3.74 3.43 3.42 3.42 3.39 3.32 3.29 3.27 3.27 3.26 2.07 2.06 2.05 2.03 2.03 2.02 2.01 2.00 2.00 1.99 1.97 1.96 1.93 1.92 1.91 1.90 1.90 1.89 1.88 1.83 1.83 1.82 1.81 1.80 1.79 1.78 1.75 1.72 1.69 1.67 1.66 1.65 1.64 1.62 1.61 1.60 1.55 1.47 1.44 1.42 1.41 1.40 1.38 1.37 1.26 1.12 1.12 1.11 1.10 1.09 1.08 1.07
4.89
0.84
0.91
1.16
0.68
1.13
1.29
0.95
1.96
1.10
1.76
1.01
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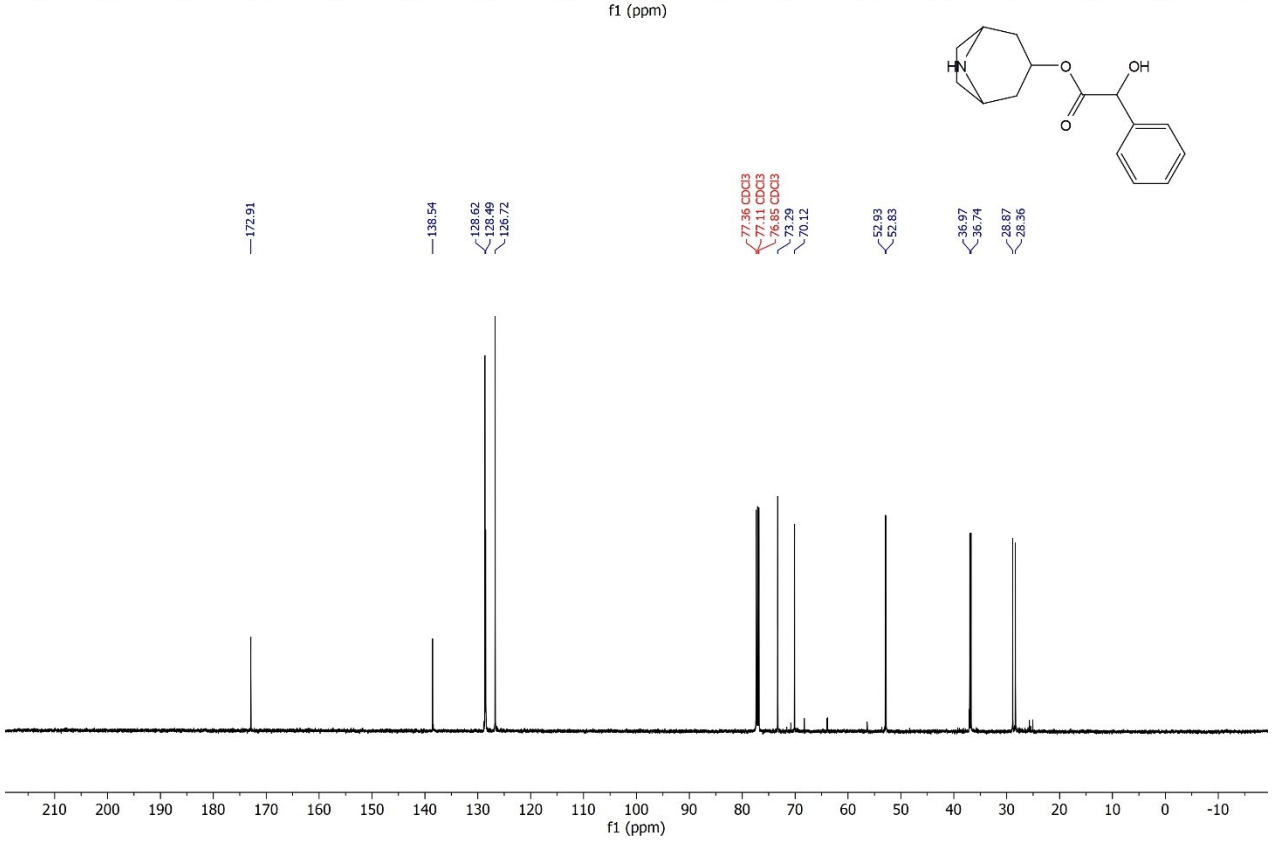
f1 (ppm)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O
OH
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172.91
138.54
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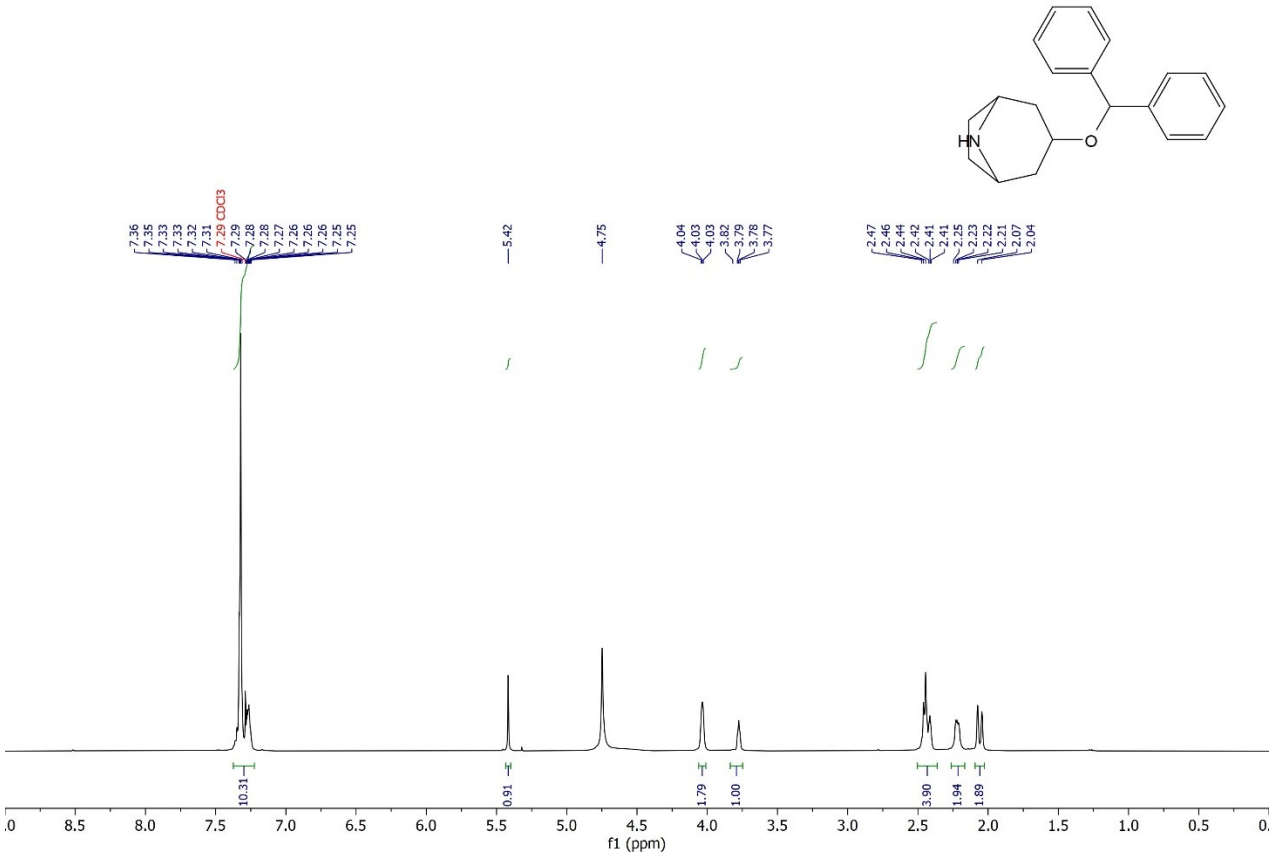
128.49
126.72
77.36 CDCl3
77.11 CDCl3
76.85 CDCl3
73.29
70.12
52.93
52.83
36.97
36.74
28.87
28.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HN
O
7.36
7.35
7.33
7.33
7.32
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7.29 CDCl3
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2.46
2.44
2.42
2.41
2.41
2.25
2.23
2.22
2.21
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2.04
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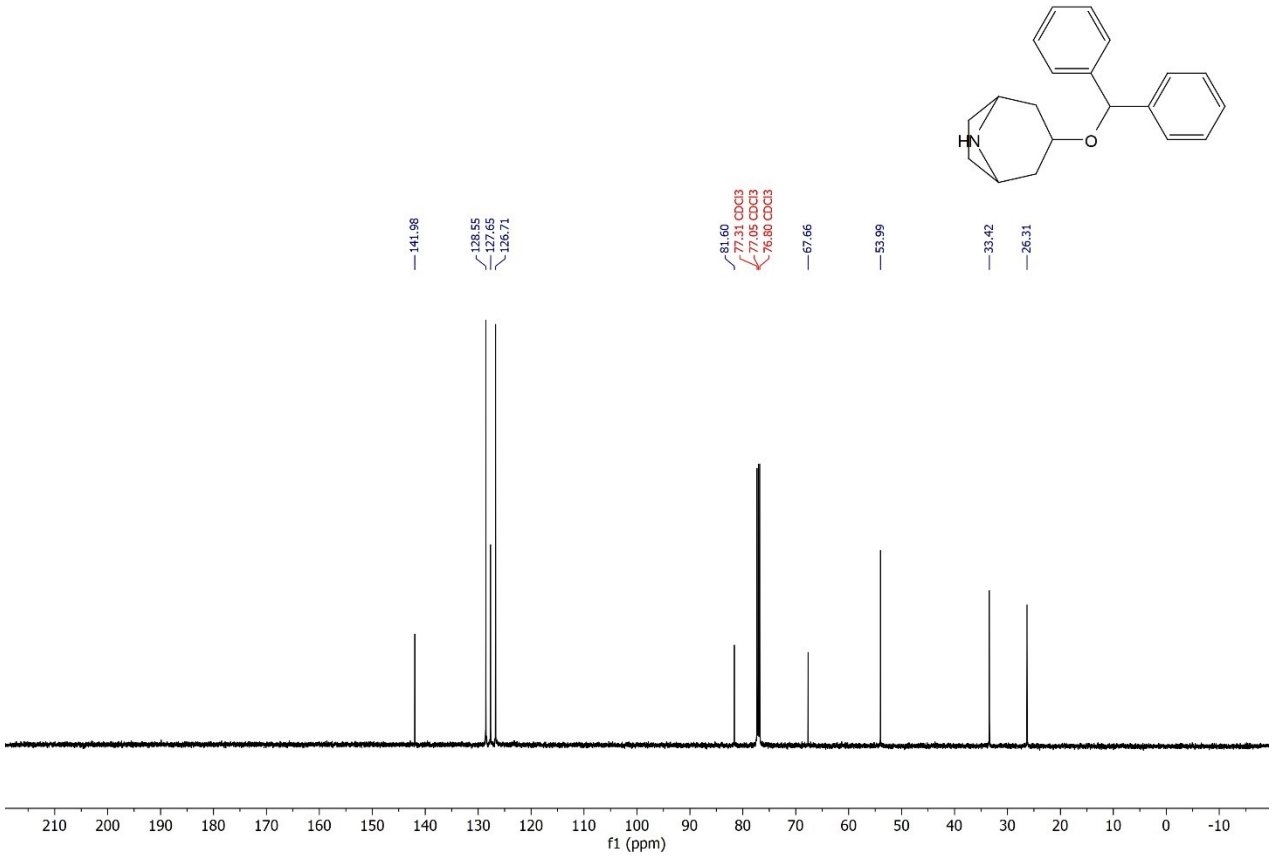
1.89
f1 (ppm)


HN
O
141.98
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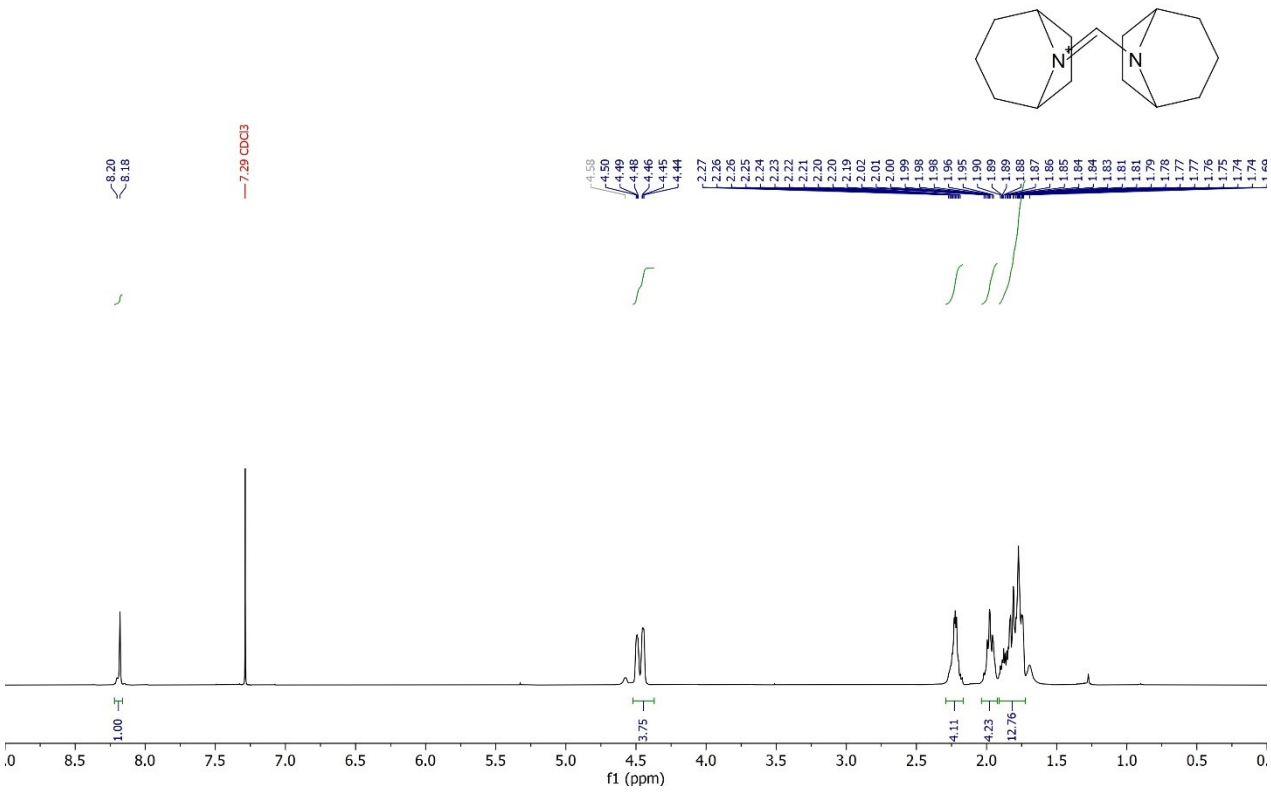
127.65
126.71
81.60
77.31 CDCl3
77.05 CDCl3
76.80 CDCl3
67.66
53.99
33.42
26.31
f1 (ppm)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N
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8.18
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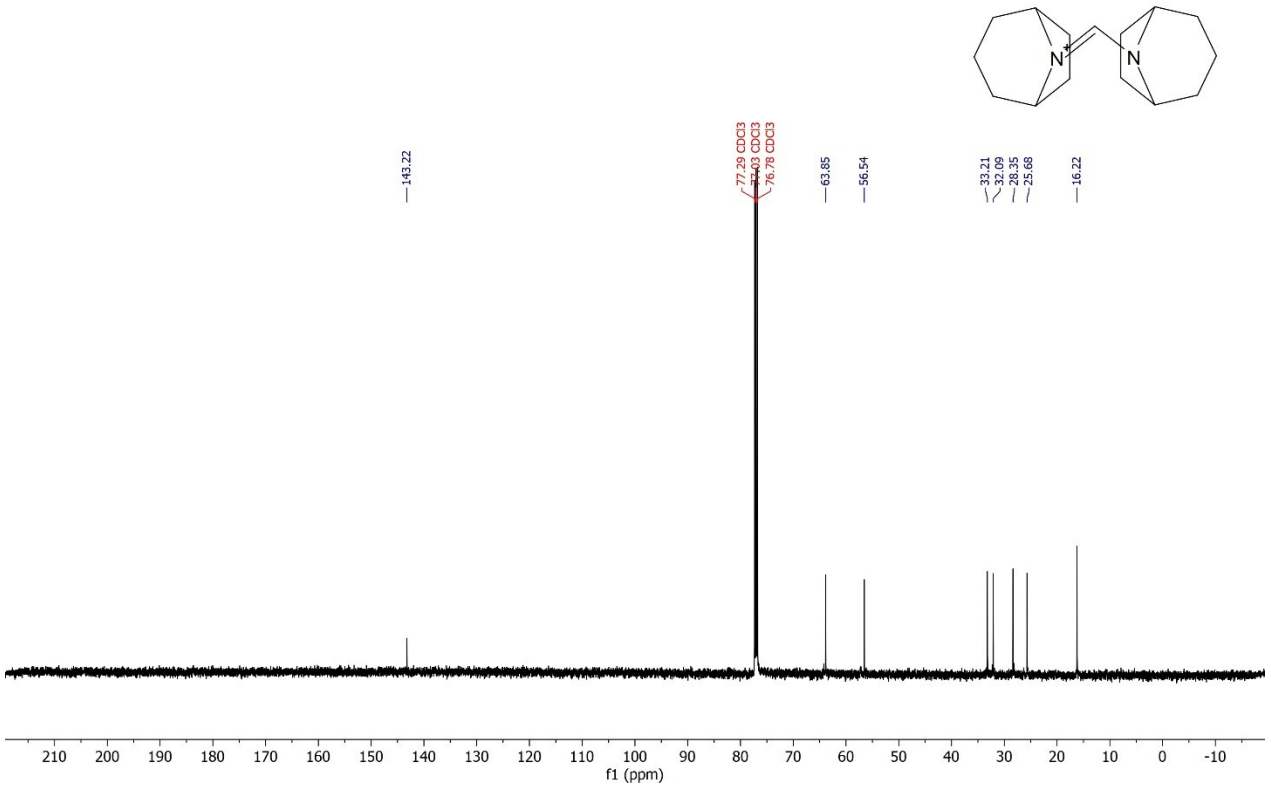
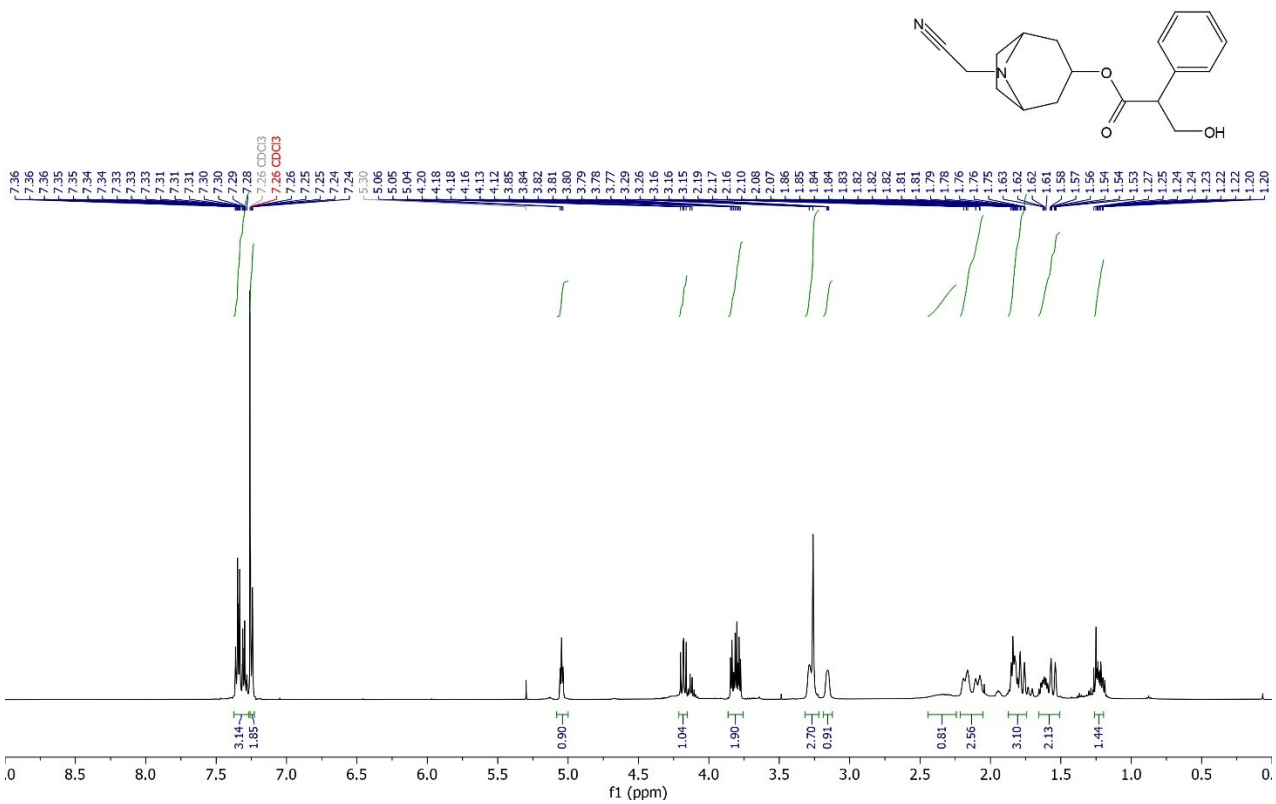
4.46
4.45
4.44
1.00
3.75
4.11
4.23
12.76
f1 (ppm)


N+
N
143.22
77.29 CDCl3
77.03 CDCl3
76.78 CDCl3
63.85
56.54
33.21
32.09
28.35
25.68
16.22
f1 (ppm)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O
OH
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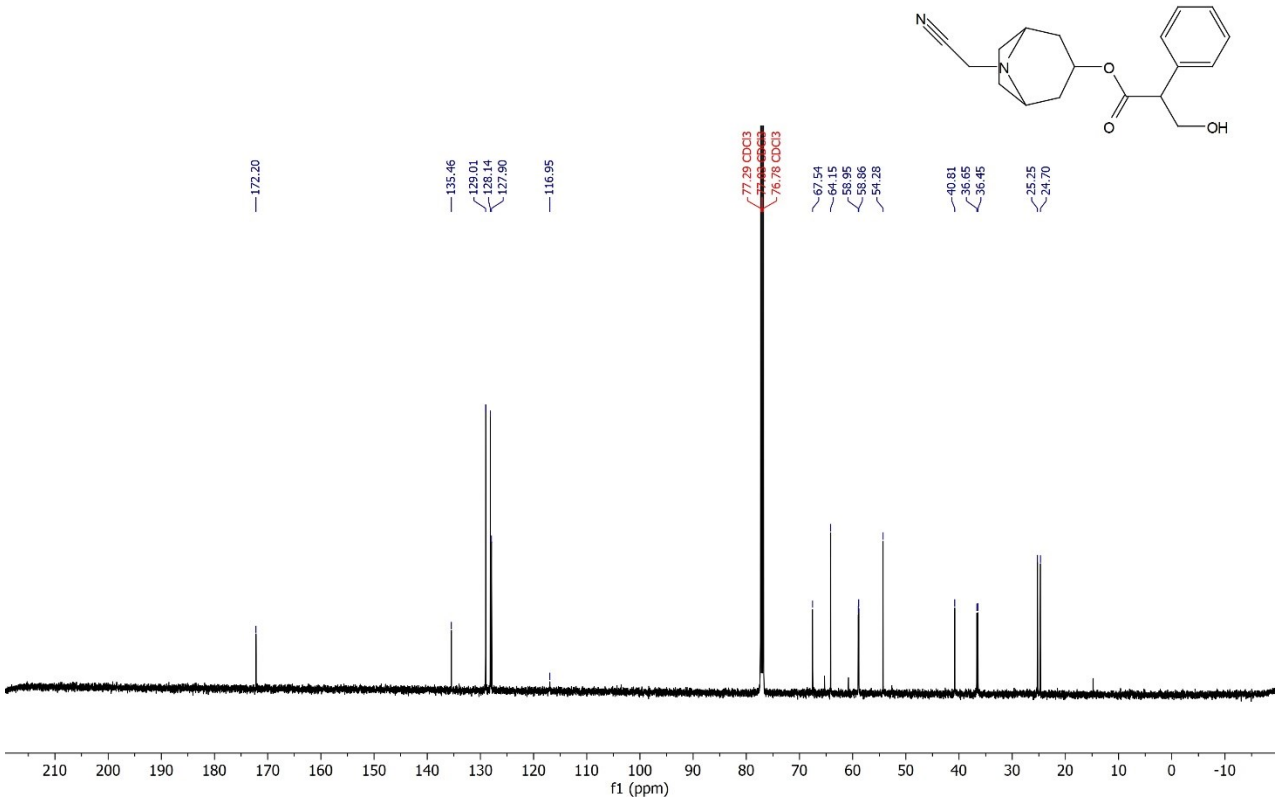
0.91
0.81
2.56
3.10
2.13
1.44
f1 (ppm)


N
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O
O
OH
172.20
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129.01
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127.90
116.95
77.29 CDCl3
76.78 CDCl3
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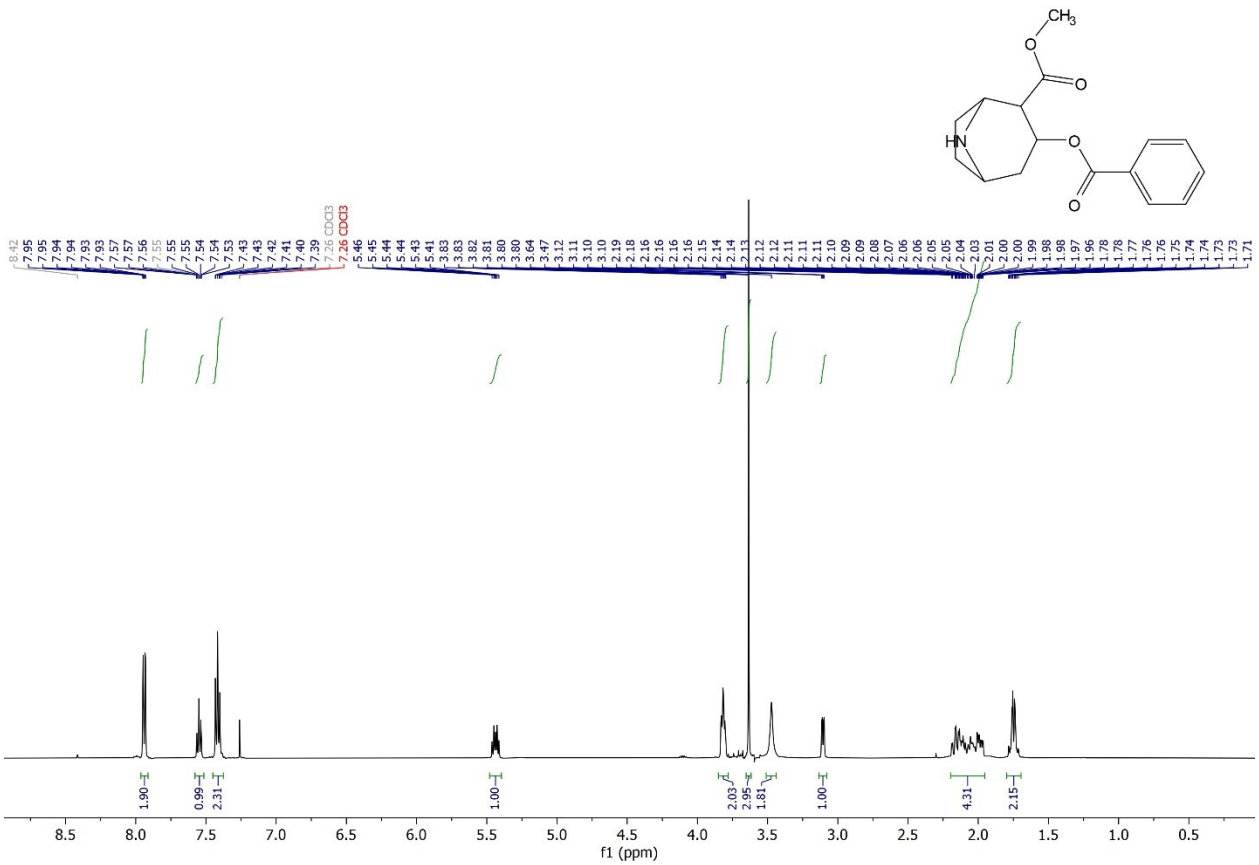
58.95
58.86
54.28
40.81
36.65
36.45
25.25
24.70
f1 (ppm)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O
HN
O
O
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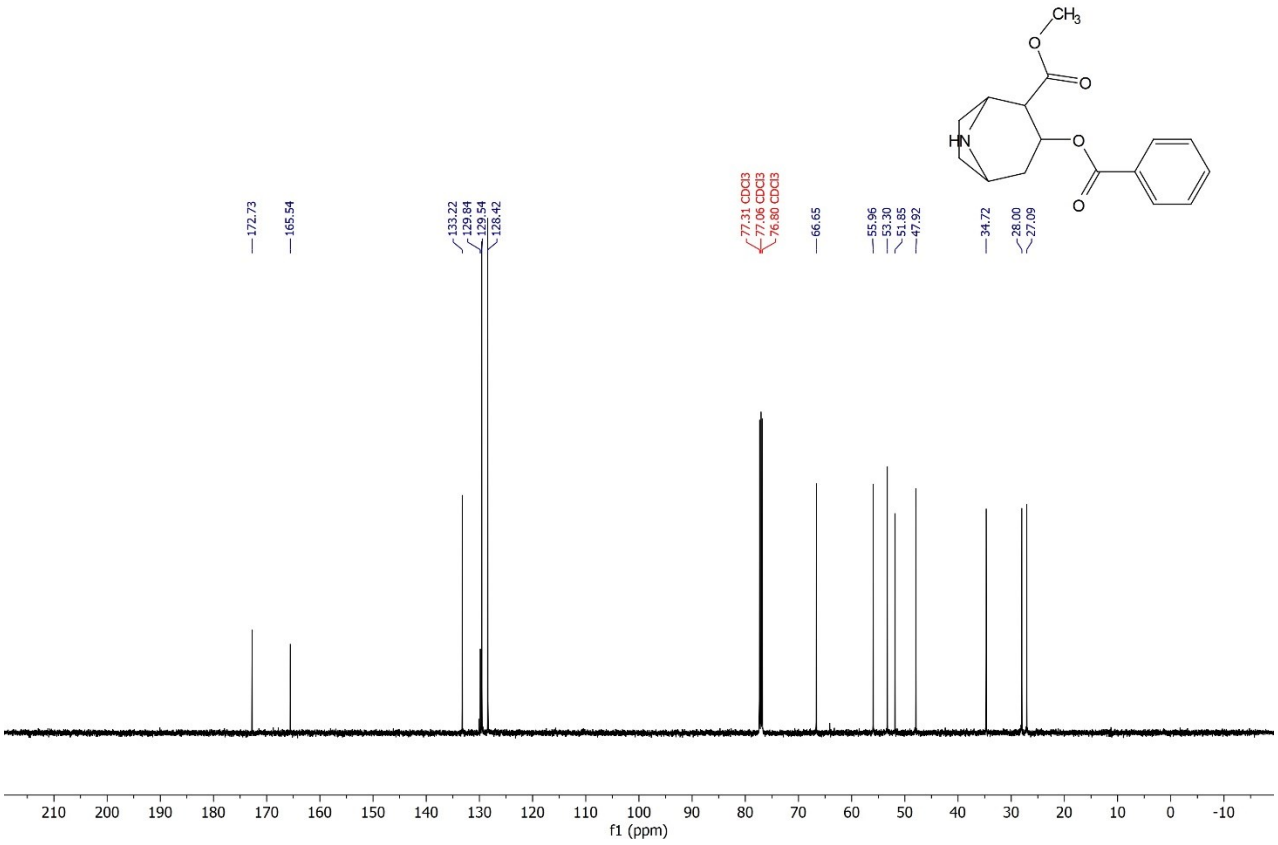
2.03
2.95
1.81
1.00
4.31
2.15
f1 (ppm)


CH3
O
O
HN
O
O
172.73
165.54
133.22
129.84
129.54
128.42
77.31 CDCl3
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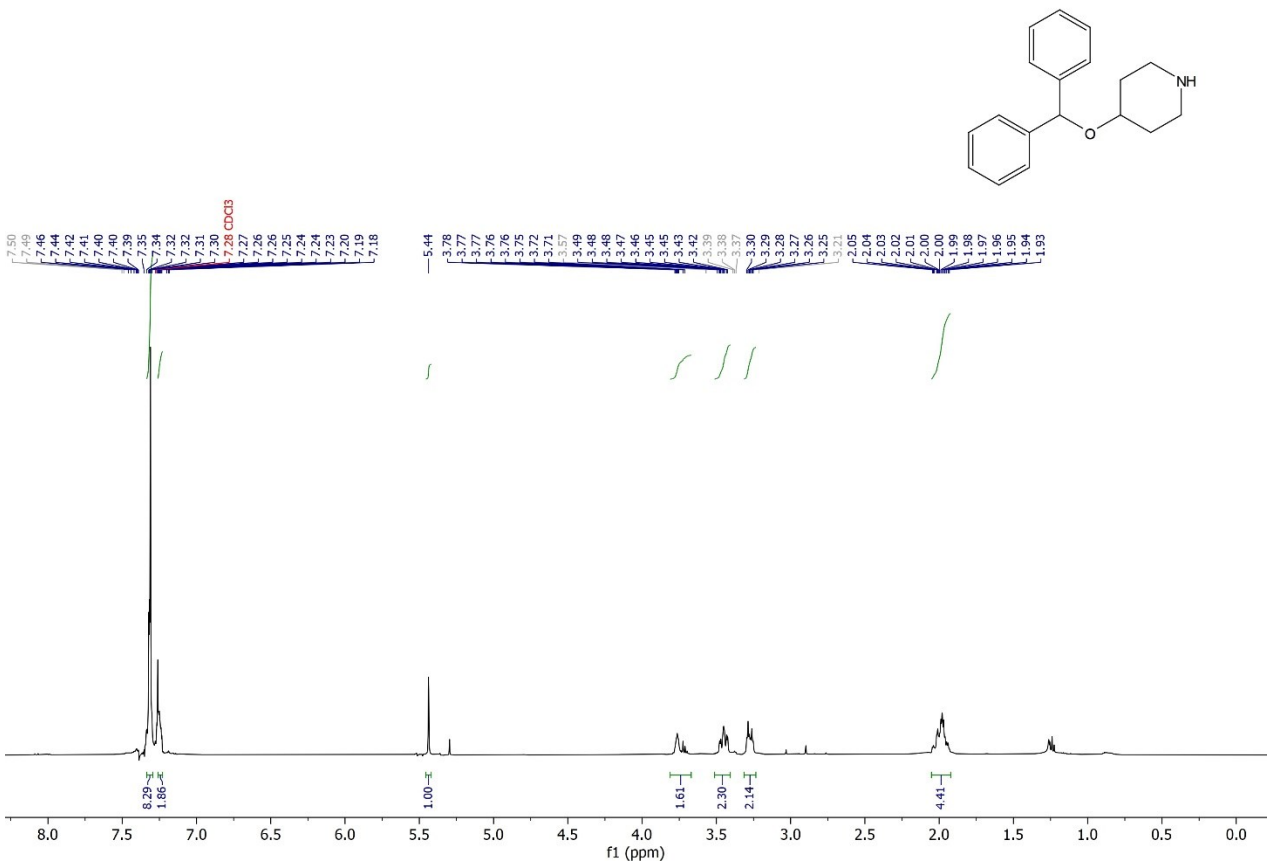
66.65
55.96
53.30
51.85
47.92
34.72
28.00
27.09
f1 (ppm)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1.00
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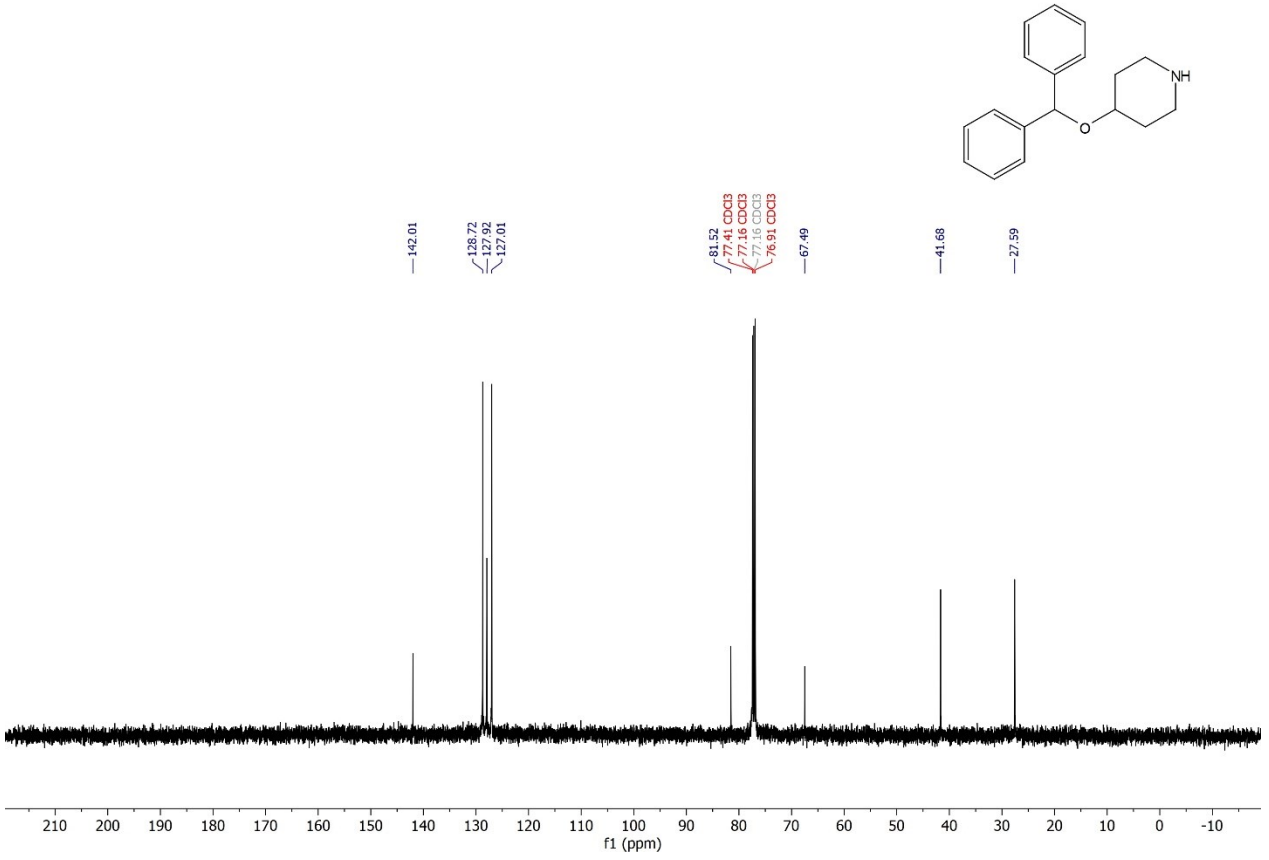
2.30
2.14
4.41
f1 (ppm)


NH
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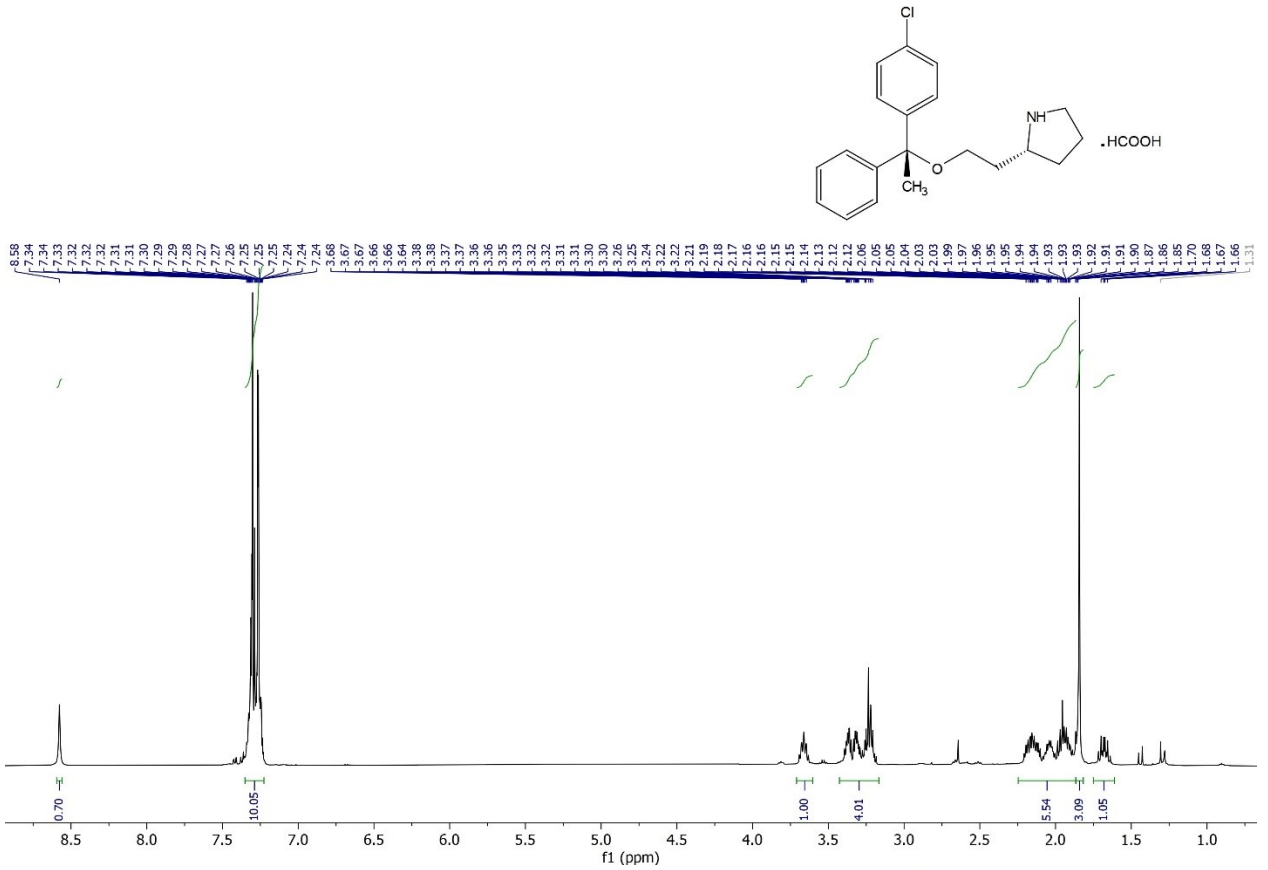
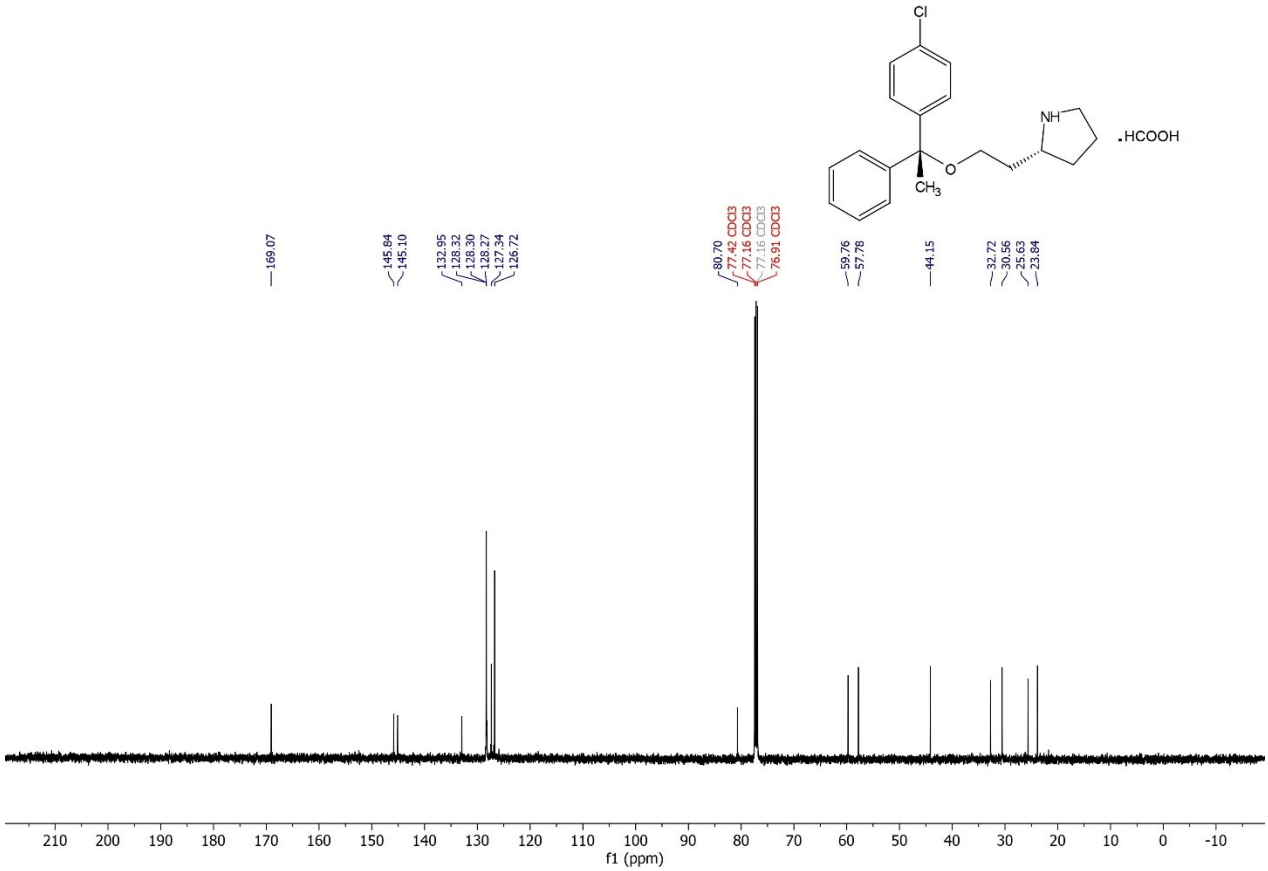
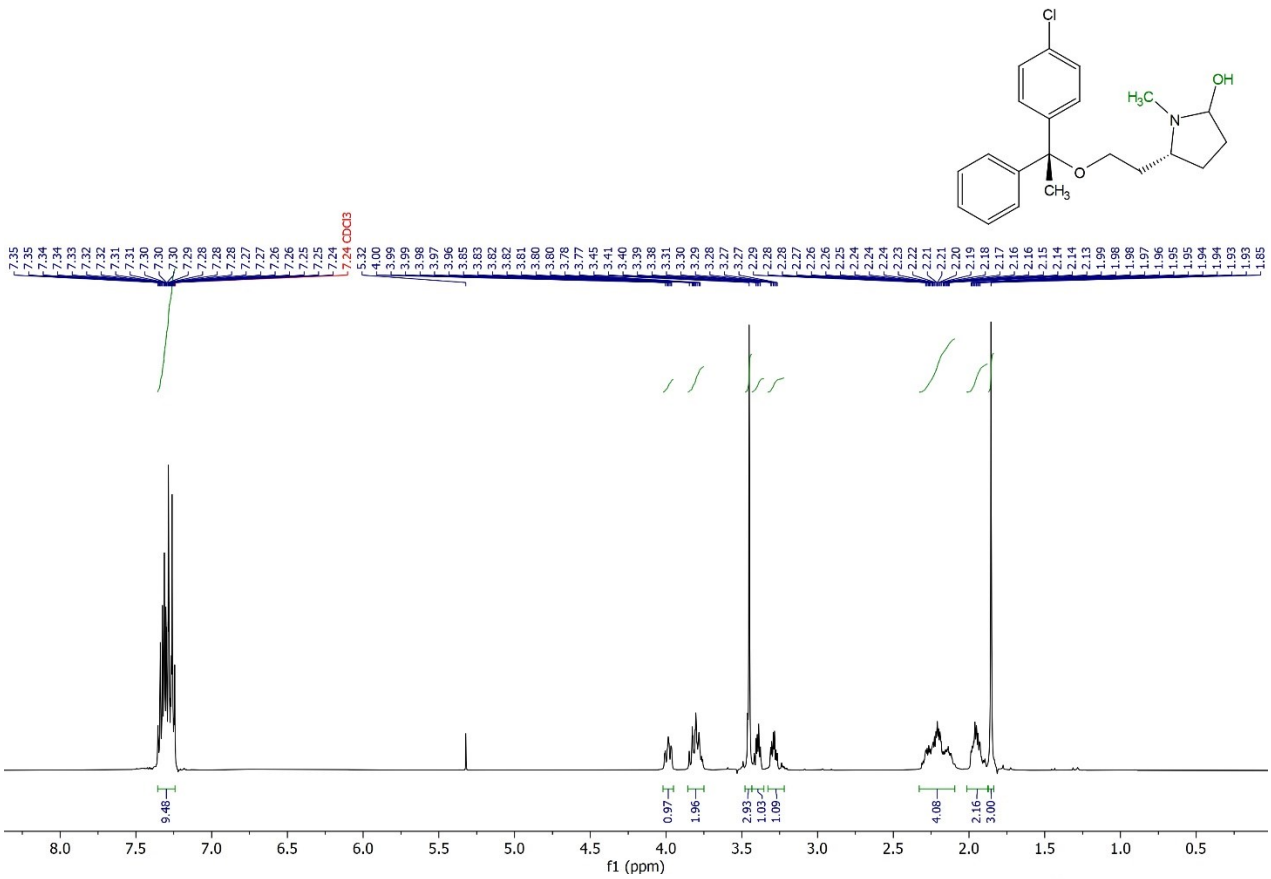
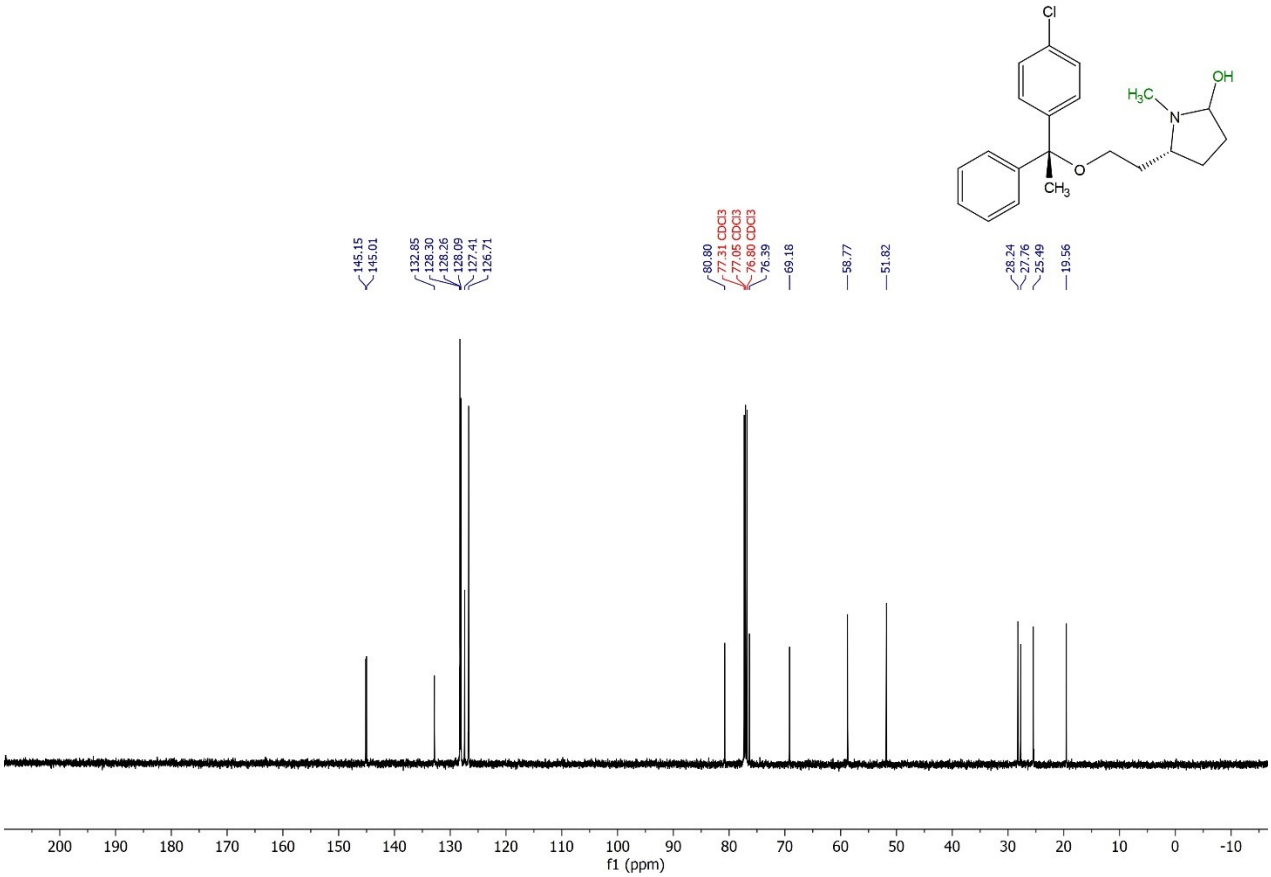
127.01
81.52
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
67.49
41.68
27.59
f1 (ppm)

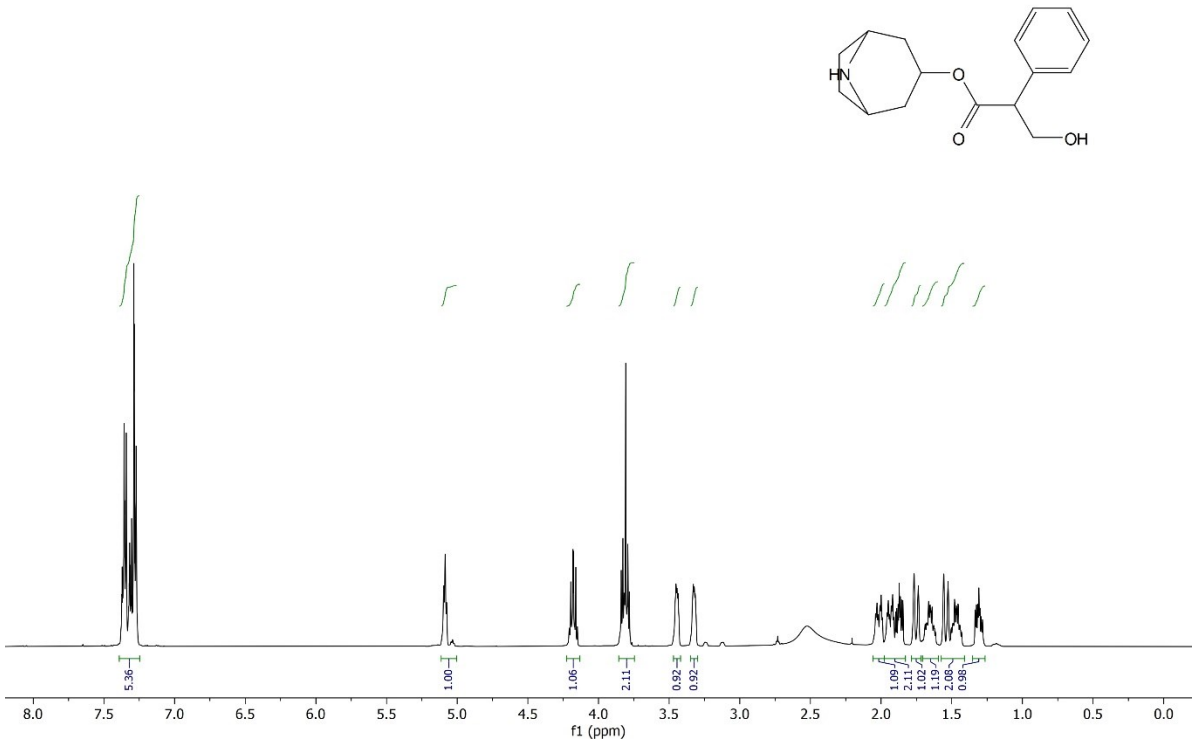

Cl
NH
O
CH3
.HCOOH
0.70
10.05
1.00
4.01
5.54
3.09
1.05
f1 (ppm)


Cl
NH
O
CH3
.HCOOH
169.07
145.84
145.10
132.95
128.32
128.30
128.27
127.34
126.72
80.70
77.42 CDCl3
77.16 CDCl3
77.16 CDCl3
76.91 CDCl3
59.76
57.78
44.15
32.72
30.56
25.63
23.84
f1 (ppm)


Cl
OH
H3C
N
O
CH3
7.24 CDCl3
9.48
0.97
1.96
2.93
1.03
1.09
4.08
2.16
3.00
f1 (ppm)


Cl
OH
H3C
N
O
CH3
145.15
145.01
132.65
128.30
128.26
128.09
127.41
126.71
80.80
77.31 CDCl3
77.05 CDCl3
76.80 CDCl3
76.39
69.18
58.77
51.82
28.24
27.76
25.49
19.56
f1 (ppm)

^{1}H NMR of gram-scale synthesized noratropine (Table 5, entry 1)



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