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Supplementary Information

Towards a chemo-enzymatic method for the asymmetric synthesis of ß-amino tertiary alcohols

Andrea March-Cortijos[a] and Timothy J. Snape*[b]

[a] Andrea March-Cortijos, School of Chemistry, Manchester Interdisciplinary Biocentre, University of Manchester, 131 Princess Street, Manchester, M1 7DN
[b] Timothy J. Snape, School of Pharmacy and Pharmaceutical Sciences, Maudland Building, University of Central Lancashire, Preston, PR1 2HE, UK

* Correspondence should be addressed to tjsnape@uclan.ac.uk

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General.

Commercially available reagents were used as received without purification. Analytical thin layer chromatography (TLC) was performed with Keiselgel 60 F_{254}, in a variety of solvents on aluminium-backed plates. The plates were visualised by UV light (254 nm), *p*-anisaldehyde and $KMnO_4$. Flash column chromatography was conducted with Merck silica gel 60H (40-60 μm, 230-400 mesh) under bellows pressure. Nominal and high resolution mass spectra were recorded on a Waters LCT mass spectrometer connected to a Waters Alliance 1100 LC autosampler and controlled by Waters Masslynx 4.1 and OpenAccess software using electrospray (ES) and fast atom bombardment (FAB) ionization. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (300 MHz) or a Bruker DPX 400 (400 MHz) spectrometer. All chemical shifts (d) are quoted in parts per million (ppm) relative to a calibration reference of the residual protic solvent; C*H*Cl_3 (d_H 7.24, s) was used as the internal standard in ^{1}H NMR spectra, and ^{13}C NMR shifts were referenced using *C*DCl_3 (d_C 77.4, t) with broad band decoupling. The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and the *J* values are measured in Hertz.

Synthesis of tertiary alcohols.

To a solution of (±)-(2-(hydroxymethyl)oxiran-2-yl)methyl acetate, **2** (200mg, 1.37 mmol) in ethanol (14 ml, 0.1 M) was added the corresponding amine (3 equivalents). The solution was heated at reflux for 1 hour. The mixture was reduced *in vacuo* and the crude material was purified by column chromatography (SiO_2; MeOH/ EtOAc).

Synthesis of chiral tertiary alcohols.

To a solution of (*S*)-(+)-**2** (100 mg, 0.96 mmol), Amano L, AK (200 mg, 2 wt. eq.) and molecular sieves (4 Å) in dichloromethane (10 ml, 0.1 M) was added acetic anhydride (1.8 equivalents) and left for one hour at 37 ºC. The mixture was filtered through Celite® and the filtrate was reduced *in vacuo*. Ethanol (10 ml, 0.1 M) and the corresponding amine (see Table 1) was added and the mixture heated at reflux for 4 hours. The mixture was reduced *in vacuo* and purified by column chromatography (SiO_2; 20% EtOH in EtOAc). The enantiomeric purity was determined by HPLC; Agilent 1100 Series. Chiralpack AD, 1 ml/min, 80/20 *iso*-hexene in EtOH at 25 ºC.

Synthesis of 2,3-dihydroxy-2-(piperidin-1-ylmethyl)propyl acetate 6.

Yield 55%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 1.56 (6H, m), 2.07 (3H, s), 2.51 (6H, m), 3.53 (1H, d, *J* = 11.6 ($\underline{H}_aH_b$)), 3.58 (1H, d, *J* = 11.6 ($H_a\underline{H}_b$)), 3.96 (1H, d, *J* = 11.2 ($\underline{H}_cH_d$)), 3.99 (1H, d, *J* = 11.2 ($H_c\underline{H}_d$)); ^{13}C NMR (100 MHz) 21.0 (CH_3), 23.7, 26.5, 57.0, 62.3, 66.3, 66.6 (CH_2), 71.7, 171.3 (C); MS ES (+ve) found *m/z* 232.1 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 232.1542, $C_{11}H_{21}O_4N+H^+$ requires 232.1549; IR (cm^{-1}) 3416, 1737.

Synthesis of 2,3-dihydroxy-2-(morpholinomethyl)propyl acetate 7.

Yield 76%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.10 (3H, s), 2.55 (2H, d, *J*=4.0), 2.59 (2H, m), 2.72 (2H, m), 3.54 (1H, d, *J* = 11.4 ($\underline{H}_aH_b$)), 3.58 (1H, d, *J* = 11.4 ($H_a\underline{H}_b$)), 3.70 (4H, t, *J* = 4.8), 4.00 (1H, d, *J* = 11.6 ($\underline{H}_cH_d$)), 4.03 (1H, d, *J* = 11.6 ($H_c\underline{H}_d$)); ^{13}C NMR (100 MHz) 20.3 (CH_3), 55.6, 61.7, 65.9, 66.0, 67.2 (CH_2), 72.2, 171.9 (C); MS ES (+ve) found *m/z* 234.1 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 234.1336, $C_{10}H_{19}O_5N+H^+$ requires 234.1341; IR (cm^{-1}) 3420, 1735, 1113.

Synthesis of 3-(2,6-dimethylmorpholino)-2-hydroxy-2-(hydroxymethyl)propyl acetate 8.

Yield 84%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H major isomer: 1.14 (6H, d *J* = 5.6), 2.02 (1H, d, *J* = 10.0), 2.07 (1H, d, *J* = 10.0), 2.12 (3H, s), 2.48 (1H, d, *J* = 9.2), 2.53 (1H, d, *J* = 6.4), 2.72 (1H, d, *J* = 11.2), 2.93 (1H, d, *J* = 11.2), 3.56 (1H, d, *J* = 12.4 ($\underline{H}_aH_b$)), 3.61 (1H, d, *J* = 12.4 ($H_a\underline{H}_b$)), 3.64-

3.70 (2H, m), 4.0-4.06 (2H, m); ^{13}C NMR (100 MHz) 19.1, 21.0 (CH_3), 61.4, 61.5, 66.2, 66.9 (CH_2), 71.9 (CH), 72.0, 171.3 (C); MS ES (+ve) found *m/z* 262.2 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 262.1648, $C_{12}H_{23}O_5N+H^+$ requires 262.1654; IR (cm^{-1}) 3435, 1736.

Synthesis of 2,3-dihydroxy-2-((4-(2-hydroxyethyl)piperidin-1-yl)methyl)propyl acetate 9.

Yield 77%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 1.27-1.35 (2H, m), 1.49-1.58 (3H, m), 1.71-1.76 (2H, m), 2.13 (3H, s), 2.29-2.40 (2H, m), 2.57-2.62 (2H, m), 2.88 (1H, m), 3.09 (1H, m), 3.60-3.64 (2H, m), 3.71-3.76 (2H, m), 4.03-4.07 (2H, m); ^{13}C NMR (100 MHz) 20.9 (CH_3), 31.7 (CH), 32.7, 32.9, 39.2, 56.1, 60.5, 66.4, 66.9 (CH_2), 71.6, 170.9 (C); MS ES (+ve) found *m/z* 276.2 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 276.1814, $C_{10}H_{19}O_5N+H^+$ requires 276.1811; IR (cm^{-1}) 3376, 1735.

Synthesis of *N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl)-*N*-(2-morpholinoethyl)acetamide 10.

Yield 89%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.13 (3H, s), 2.46 (4H, t, J = 4.0), 2.61 (2H, t, J = 5.2), 3.41 (4H, s), 3.50 (2H, t, J = 6.0), 3.54 (2H, s), 3.65 (4H, t, J = 4.8); ^{13}C NMR (100 MHz) 21.8 (CH_3), 48.6, 52.3, 54.0, 58.9, 65.3, 66.4 (CH_2), 74.6, 174.1 (C); MS ES (+ve) found *m/z* 277.2 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 277.1773, $C_{12}H_{24}O_5N_2+H^+$ requires 277.1763; IR (cm^{-1}) 3376, 1612, 1113.

Synthesis of *N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl)-*N*-isopropylacetamide 11.

Yield 21%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 1.24 (6H, d, J = 6.8), 2.20 (3H, s), 3.43 (2H, s), 3.48 (4H, m), 4.03 (1H, m); ^{13}C NMR (100 MHz) 21.2, 22.6 (CH_3), 46.9 (CH_2), 51.2 (CH), 64.5 (CH_2), 74.3, 174.6 (C); MS ES (+ve) found *m/z* 206.1 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 206.1393, $C_9H_{19}O_4N+H^+$ requires 206.1392; IR (cm^{-1}) 3242, 1613.

Synthesis of *N*-cyclopentyl-*N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl) acetamide 12.

Yield 31%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 1.56 (4H, m), 2.69 (2H, m), 1.80 (2H, m), 2.15 (3H, s), 3.37 (2H, s), 3.41 (4H, t, J = 3.2), 3.98 (1H, m); ^{13}C NMR (100 MHz) 21.4 (CH_2), 22.2 (CH_3), 28.7, 46.4 (CH_2), 60.2 (CH), 63.2 (CH_2), 73.2, 173.8 (C); MS ES (+ve) found *m/z* 232.2 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 232.1546, $C_{11}H_{21}O_4N+H^+$ requires 232.1549; IR (cm^{-1}) 3363, 1601.

Synthesis of *N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl)-*N*-(prop-2-ynyl)acetamide 13.

Yield 93%, solid. M.p. 76 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.27 (3H, s), 2.35 (1H, t, J = 2.4), 3.49 (6H, m), 4.21 (2H, d, J = 2.4); ^{13}C NMR (100 MHz) 21.6 (CH_3), 40.8, 49.4, 64.0 (CH_2), 73.2 (CH), 75.6, 78.2, 174.1 (C); MS ES (+ve) found *m/z* 202.2 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 202.1085, $C_9H_{15}O_4N+H^+$ requires 202.1079; IR (cm^{-1}) 3232, 1729.

Synthesis of *N*-(2,3-dihydroxy-2-((methyl(prop-2-ynyl)amino)methyl)propyl acetate 14.

Yield 80%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.10 (3H, s), 2.25 (1H, t, J = 2.4), 2.46 (3H, s), 2.62 (1H, d, J = 14.0 ($\underline{H_a}H_b$)), 2.67 (1H, d, J = 14.0 ($H_a\underline{H_b}$)), 3.41 (2H, d, J = 2.4), 3.53 (1H, d, J = 11.2 ($\underline{H_c}H_d$)), 3.57 (1H, d, J = 11.2 ($H_c\underline{H_d}$)), 4.03 (2H, s); ^{13}C NMR (100 MHz) 21.0, 44.6 (CH_3), 48.0, 58.8, 65.9, 66.5 (CH_2), 72.5, 73.4 (C), 78.7 (CH), 171.3 (C); MS ES (+ve) found *m/z* 216.1 ($[M+H]^+$, 100%); HRMS FAB $[M+H]^+$ 216.1232, $C_{10}H_{17}O_4N+H^+$ requires 216.1236; IR (cm^{-1}) 3419, 1729.

Synthesis of *N*-allyl-*N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl)acetamide 15.

Yield 96%, solid. M.p. 84 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.14 (3H, s), 3.44 (6H, m), 4.07 (2H, d, J = 4.0), 5.12 (1H, d, J = 17.6), 5.25 (1H, d, J = 12.0), 5.79 (1H, ddt, J = 4.0, 12.0, 17.6); ^{13}C NMR (100 MHz) 21.3 (CH_3), 48.8, 53.0, 63.8 (CH_2), 75.5 (C), 116.8 (CH_2), 131.9 (CH), 174.4 (C);

MS ES (+ve) found *m/z* 204.1 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 204.1246, $C_9H_{17}O_4N+H^+$ requires 204.1236; IR (cm^{-1}) 3216, 1611.

Synthesis of 3-(allyl(methyl)amino)-2-hydroxy-2-(hydroxymethyl)propyl acetate 16.

Yield 55%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.09 (3H, s), 2.39 (3H, s), 2.52 (1H, d, *J* = 13.8 ($\underline{H_a}H_b$)), 2.64 (1H, d, *J* = 13.8 ($H_a\underline{H_b}$)), 3.06 (1H, dd, *J* = 7.2, 14.0), 3.19 (1H, dd, *J* = 6.4, 14.0), 3.53 (1H, d, *J* = 11.4 ($\underline{H_c}H_d$)), 3.57 (1H, d, *J* = 11.4 ($H_c\underline{H_d}$)), 3.99 (1H, d, *J* = 11.8 ($\underline{H_e}H_f$)), 4.02 (1H, d, *J* = 11.8 ($H_e\underline{H_f}$)), 5.17 (1H, s), 5.20 (1H, d, *J* = 3.6), 5.85 (1H, m); ^{13}C NMR (100 MHz) 21.1, 45.1 (CH_3), 60.2, 62.9, 66.4, 66.9 (CH_2), 72.0 (C), 118.8 (CH_2), 135.0 (CH), 171.4 (C); MS ES (+ve) found *m/z* 218.1 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 218.1384, $C_{10}H_{19}O_4N+H^+$ requires 218.1392; IR (cm^{-1}) 3384, 1736.

Synthesis of *N*-benzyl-*N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl)acetamide 17.

Yield 74%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.11 (3H, s), 3.43 (6H, m), 4.68 (2H, s), 7.07 (2H, d, *J* = 6.8), 7.30 (1H, m), 7.37 (2H, m); ^{13}C NMR (100 MHz) 21.8 (CH_3), 49.2, 54.2, 64.2 (CH_2), 76.0 (C), 126.3, 128.0, 129.3 (CH), 136.3, 174.7 (C); MS ES (+ve) found *m/z* 254.2 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 254.1380, $C_{13}H_{19}O_4N+H^+$ requires 254.1292; IR (cm^{-1}) 3295, 1605.

Synthesis of 3-(benzyl(methyl)amino)-2-hydroxy-2-(hydroxymethyl)propyl acetate 18.

Yield 63%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.06 (3H, s), 2.38 (3H, s), 2.58 (1H, d, *J* = 13.6 ($\underline{H_a}H_b$)), 2.69 (1H, d, *J* = 13.6 ($H_a\underline{H_b}$)), 3.46 (1H, d, *J* = 11.4 ($\underline{H_c}H_d$)), 3.49 (1H, d, *J* = 11.4 ($H_c\underline{H_d}$)), 3.54 (1H, d, *J* = 12.8 ($\underline{H_e}H_f$)), 3.72 (1H, d, *J* = 12.8 ($H_e\underline{H_f}$)), 3.97 (2H, s), 7.32 (5H, m); ^{13}C NMR (100 MHz) 20.9, 45.0 (CH_3), 60.2, 64.3, 66.1, 66.7 (CH_2), 72.1 (C), 127.6, 128.6, 129.2 (CH), 138.1, 171.1 (C); MS ES (+ve) found *m/z* 268.2 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 268.1542, $C_{14}H_{21}O_4N+H^+$ requires 268.1549; IR (cm^{-1}) 3386, 1735.

Synthesis of *N*-(2,3-dihydroxy-2-(hydroxymethyl)propyl)-*N*-phenethylacetamide 19.

Yield 54%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 1.97 (3H, s), 2.88 (2H, t, *J* = 7.6), 3.38-3.49 (6H, m), 3.66 (2H, t, *J* = 7.6), 7.15–7.33 (5H, m); ^{13}C NMR (100 MHz) 21.3 (CH_3), 34.8, 48.5, 52.4, 64.2 (CH_2), 75.8 (C), 127.1, 129.0, 129.1 (CH), 137.9, 174.0 (C); MS ES (+ve) found *m/z* 268.2 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 268.1542, $C_{14}H_{21}O_4N+H^+$ requires 268.1538; IR (cm^{-1}) 3272, 1602.

Synthesis of 3-(4-fluorophenylamino)-2-hydroxy-2-(hydroxymethyl)propyl acetate 20.

Yield 96%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.13 (3H, s), 3.17 (1H, d, *J* = 12.8 ($\underline{H_a}H_b$)), 3.21 (1H, d, *J* = 12.8 ($H_a\underline{H_b}$)), 3.61 (2H, s), 4.17 (1H, d, *J* = 11.6 ($\underline{H_c}H_d$)), 4.20 (1H, d, *J* = 11.6 ($H_c\underline{H_d}$)), 6.61-6.65 (2H, m), 6.87-6.92 (2H, m); ^{13}C NMR (100 MHz) 20.9 (CH_3), 48.1, 64.4, 65.6 (CH_2), 73.3 (C), 114.6, 115.7 (CH), 144.6, 157.5, 171.7 (C); MS ES (+ve) found *m/z* 258.0 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 258.1135, $C_{12}H_{16}O_4NF+H^+$ requires 258.1141; IR (cm^{-1}) 3372, 1720. [a_D] (EtOH, c=0.9) +5.6.

Synthesis of 2,3-dihydroxy-2-((2-methoxyphenylamino)methyl)propyl acetate 21.

Yield 93%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) d_H 2.14 (3H, s), 3.25 (1H, d, *J* = 13.2 ($\underline{H_a}H_b$)), 3.32 (1H, d, *J* = 13.2 ($H_a\underline{H_b}$)), 3.63 (2H, s), 3.85 (3H, s), 4.20 (2H, s), 6.70-6.74 (2H, m), 6.79 (1H, dd, J = 1.4, 8.0), 6.85-6.89 (1H, m); ^{13}C NMR (100 MHz) 20.9 (CH_3), 47.2 (CH_2), 55.5 (CH_3), 64.5, 66.0 (CH_2), 73.4 (C), 109.7, 110.7, 117.6, 121.2 (CH), 138.1, 147.3, 171.6 (C); MS ES (+ve) found *m/z* 270.1 ([M+H]$^+$, 100%); HRMS FAB [M+H]$^+$ 270.1329, $C_{13}H_{19}O_5N+H^+$ requires 270.1341; IR (cm^{-1}) 3401, 1720. [a_D] (EtOH, c=0.6) +11.2.

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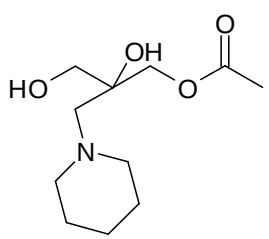

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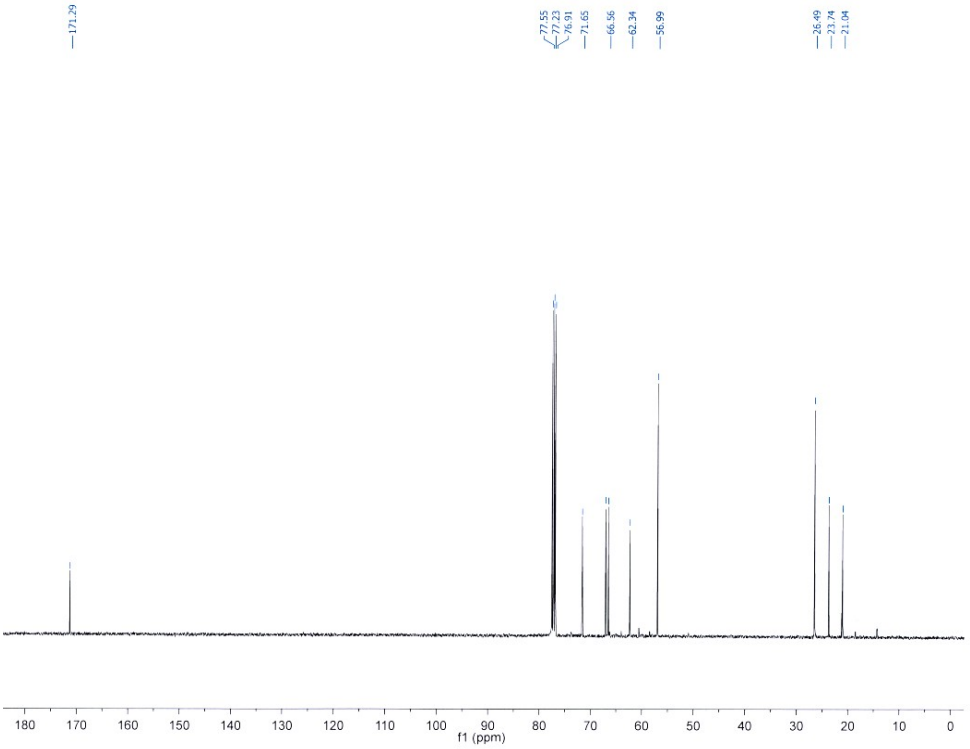

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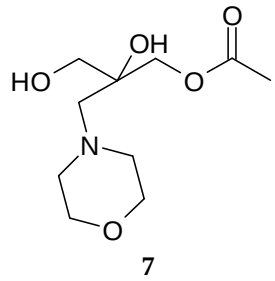

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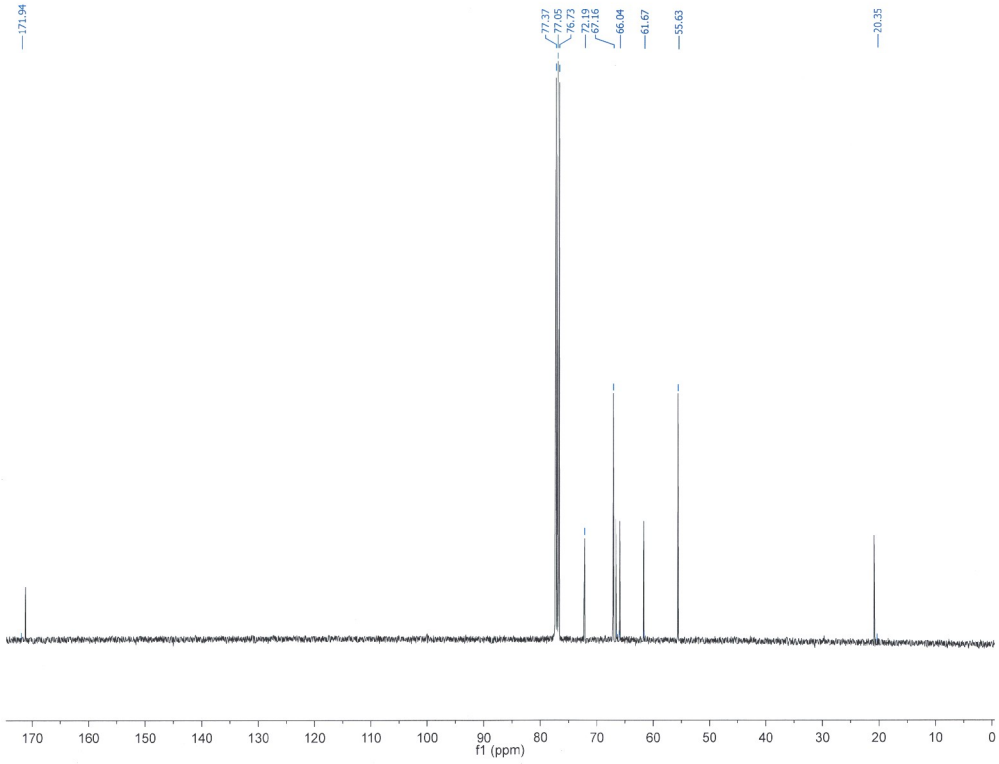

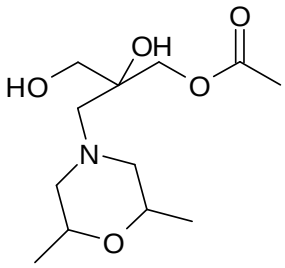
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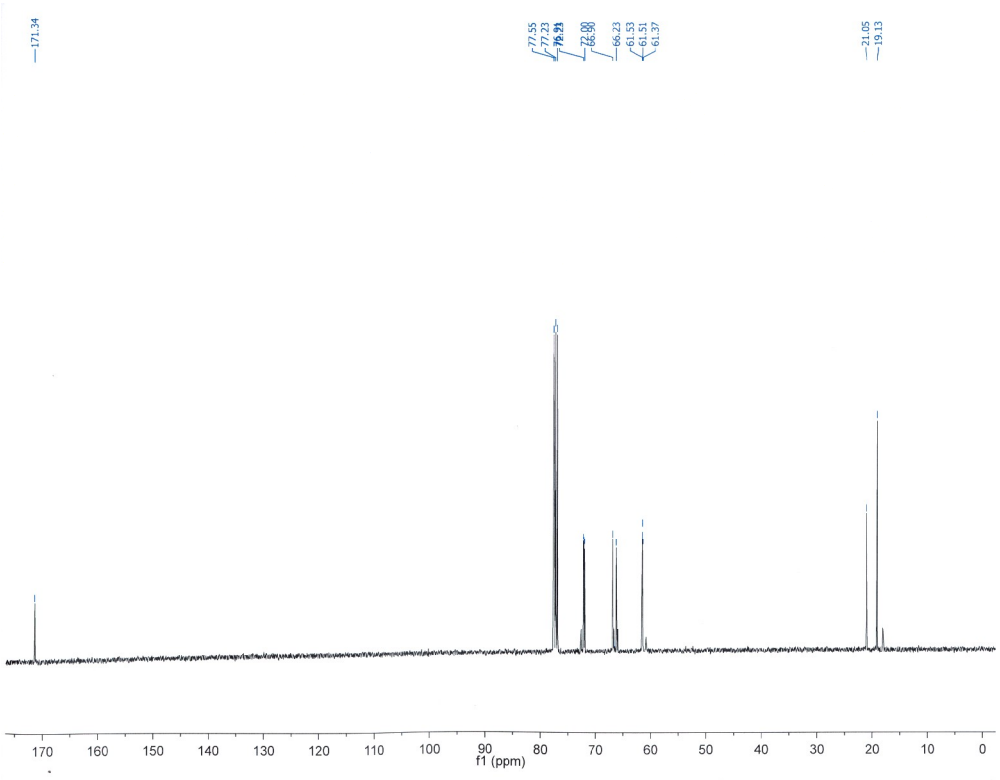
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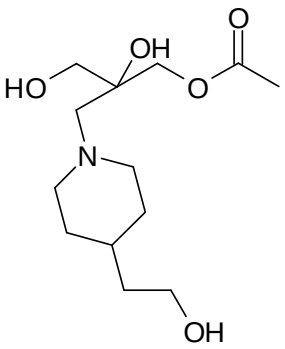

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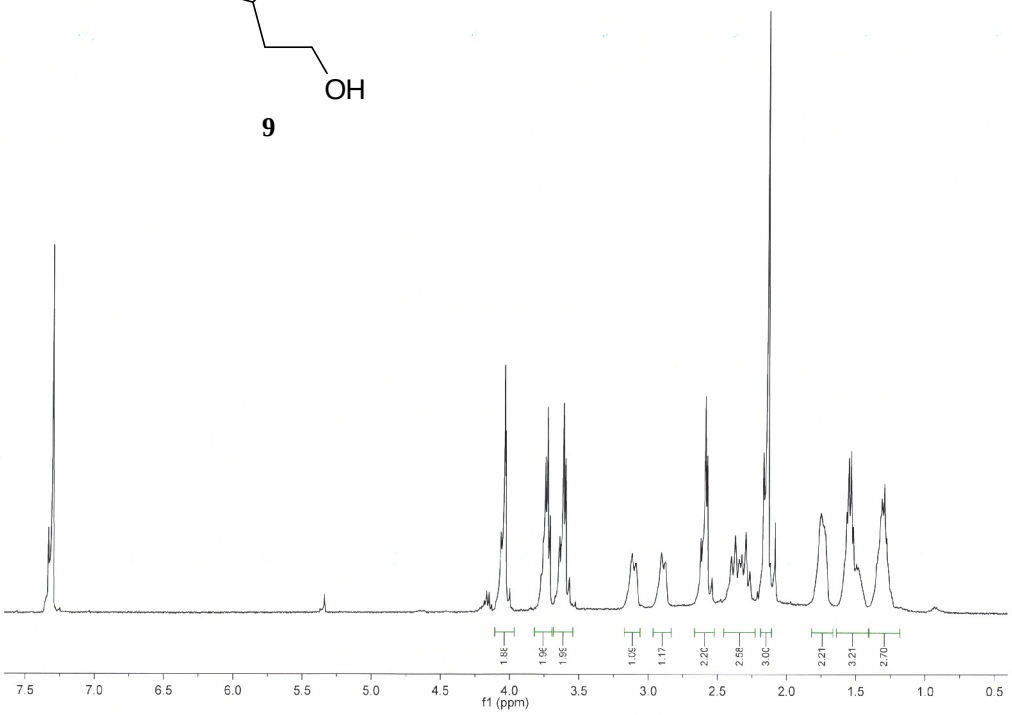

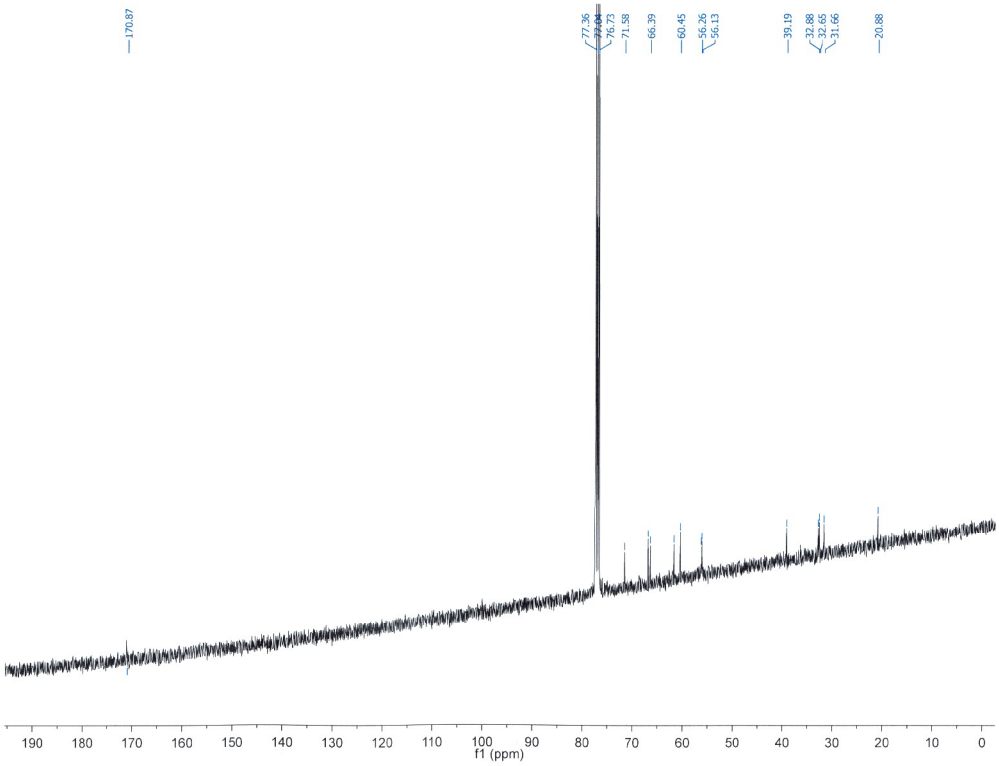

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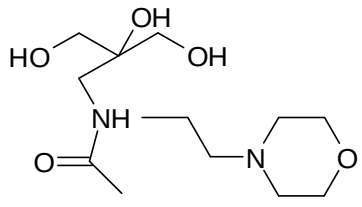

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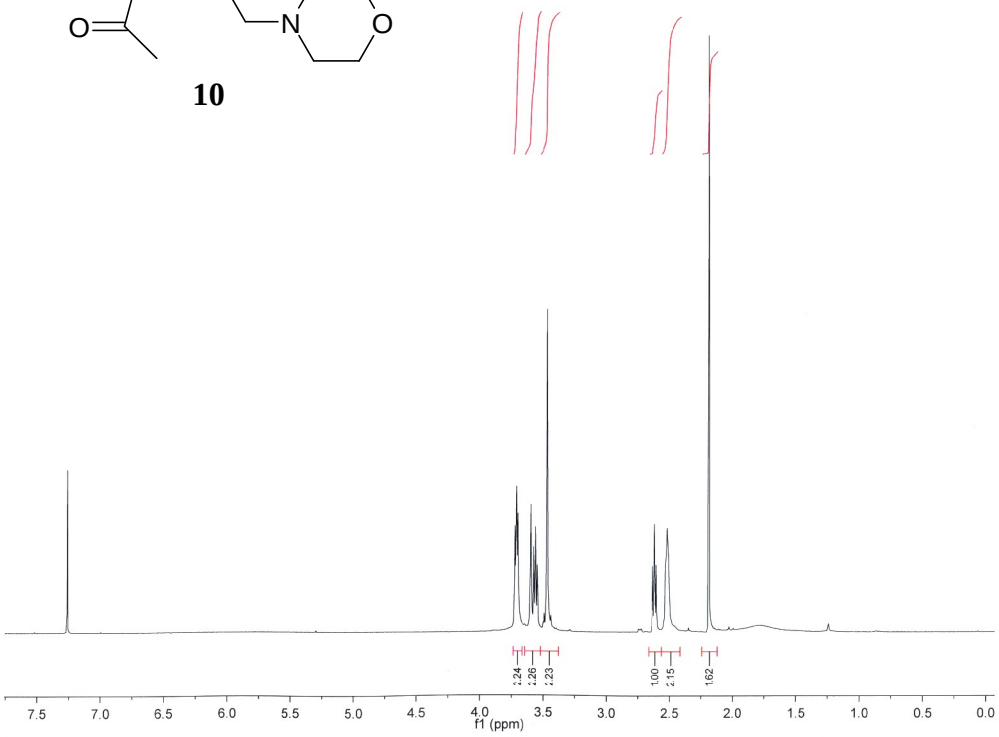

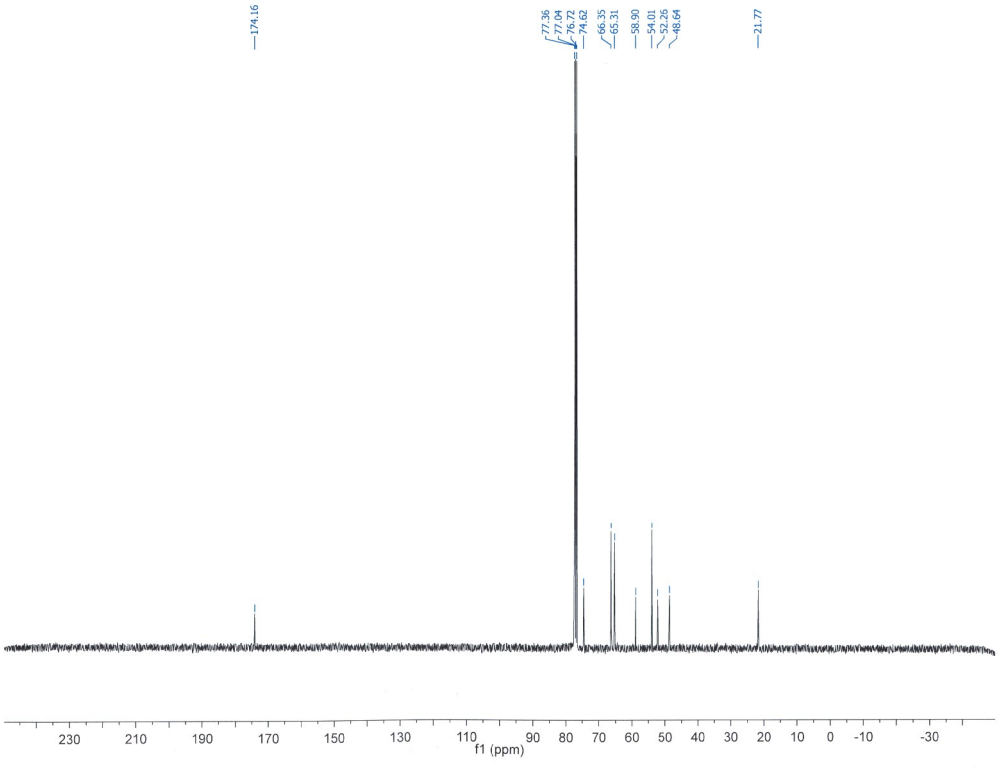

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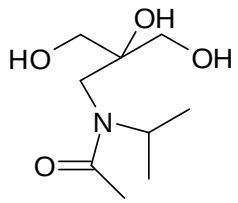

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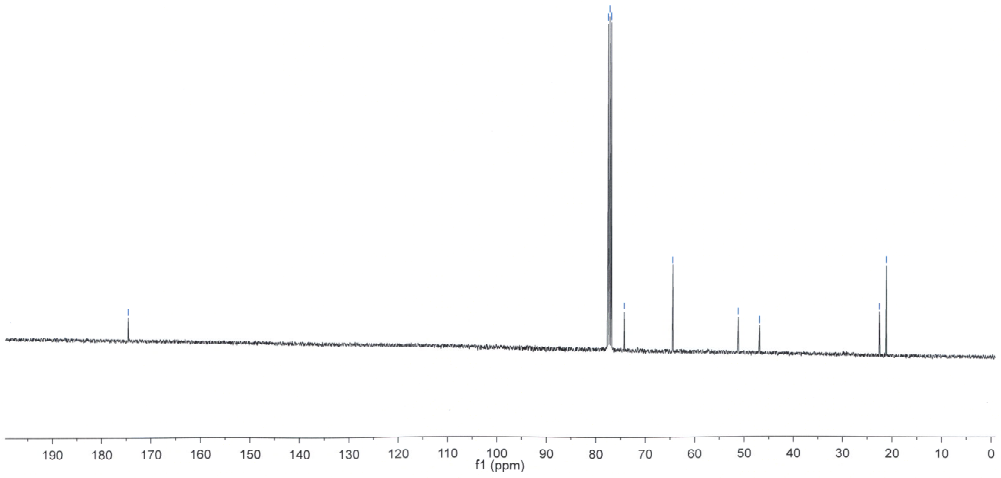

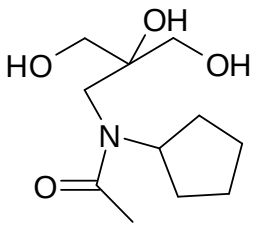
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HO
OH
N
O

12

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1.06
5.97
1.80
3.00
2.16
2.12
4.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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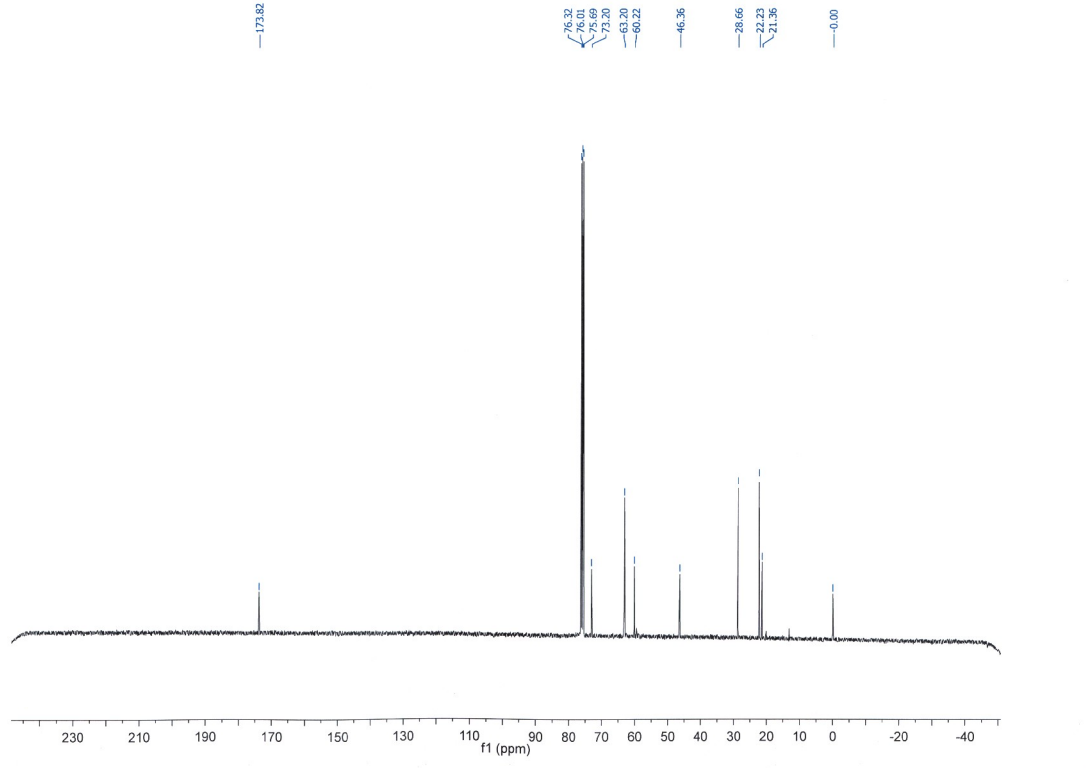
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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22.23
21.36
0.00
230
210
190
170
150
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-20
-40
f1 (ppm)

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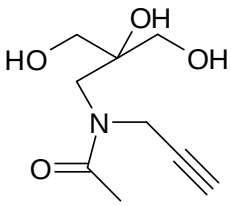

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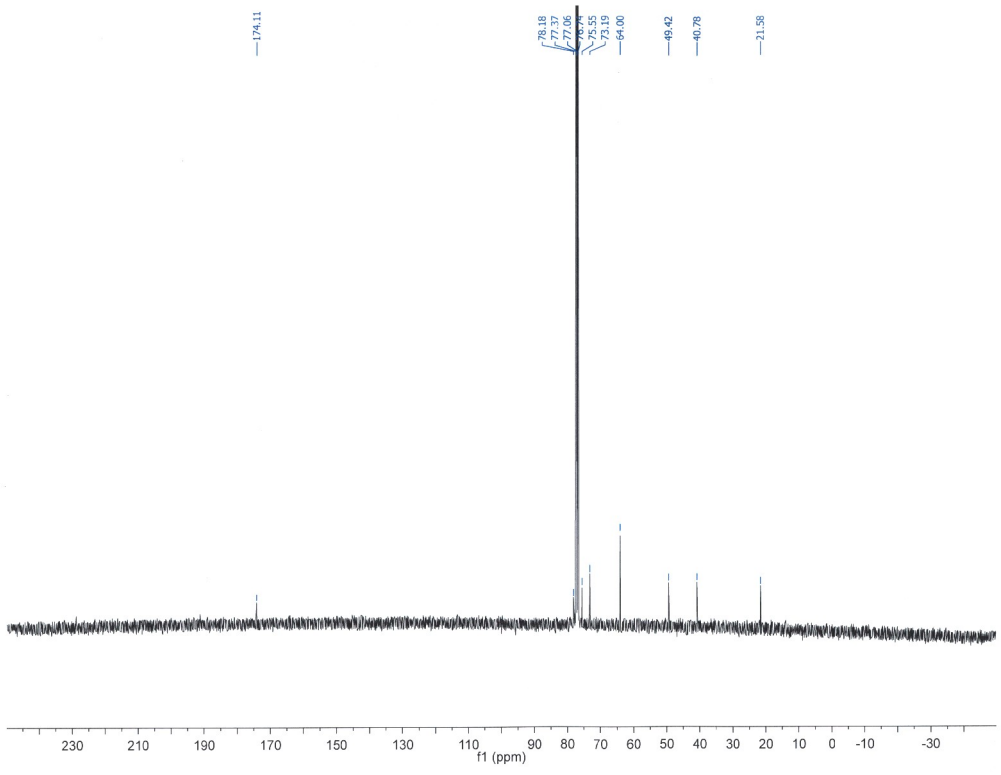

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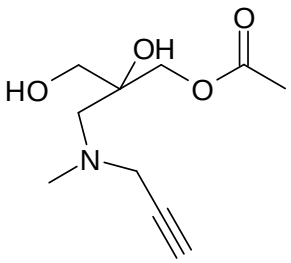

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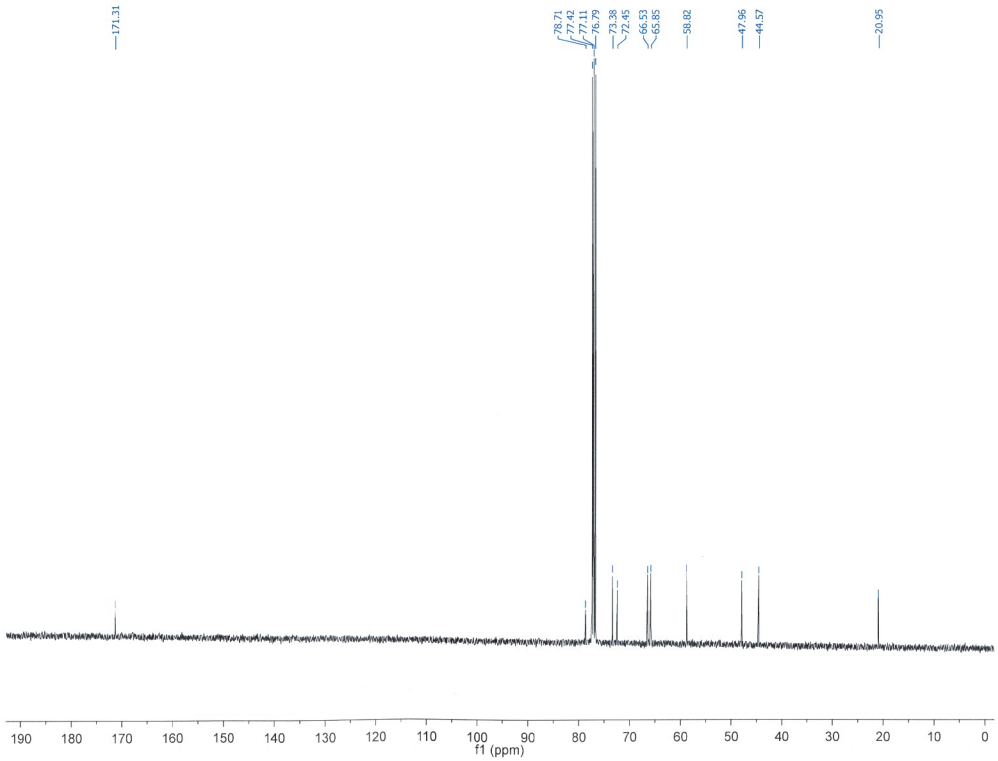

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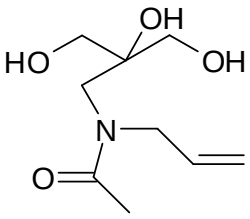

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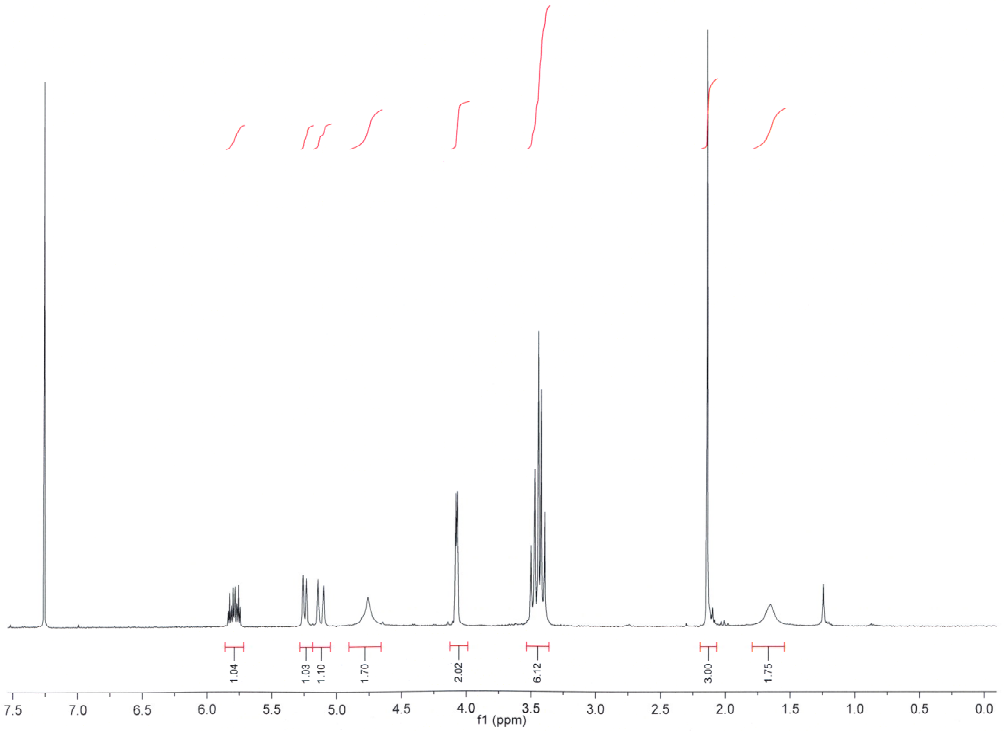

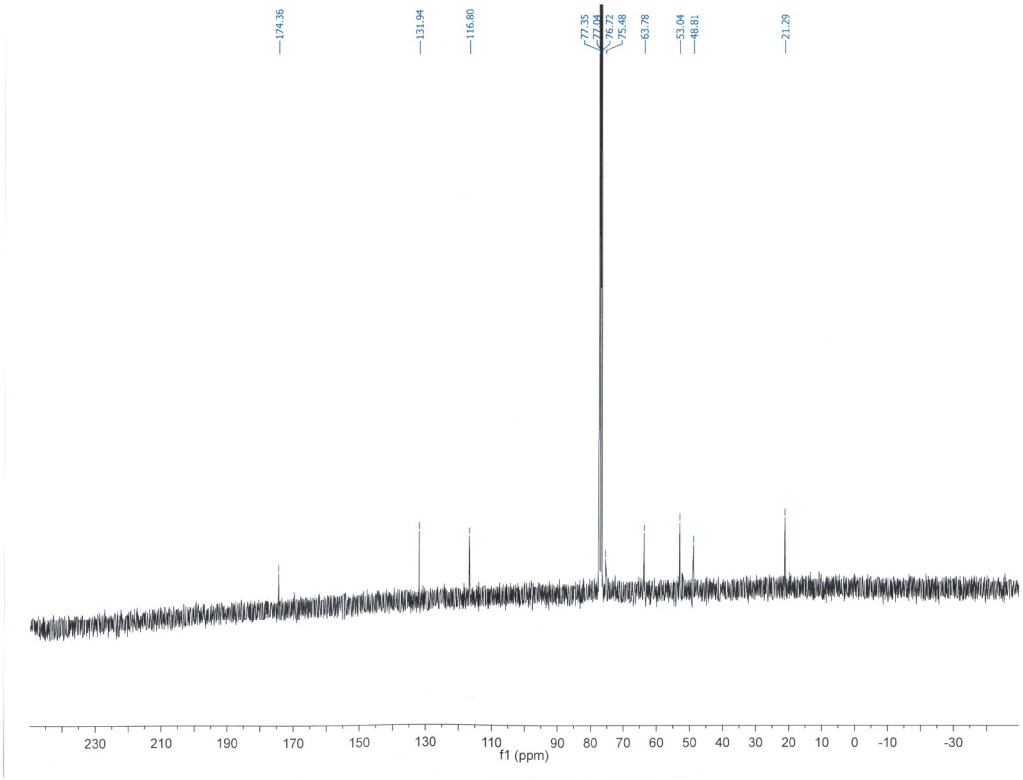

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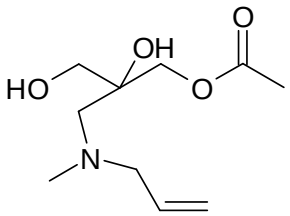

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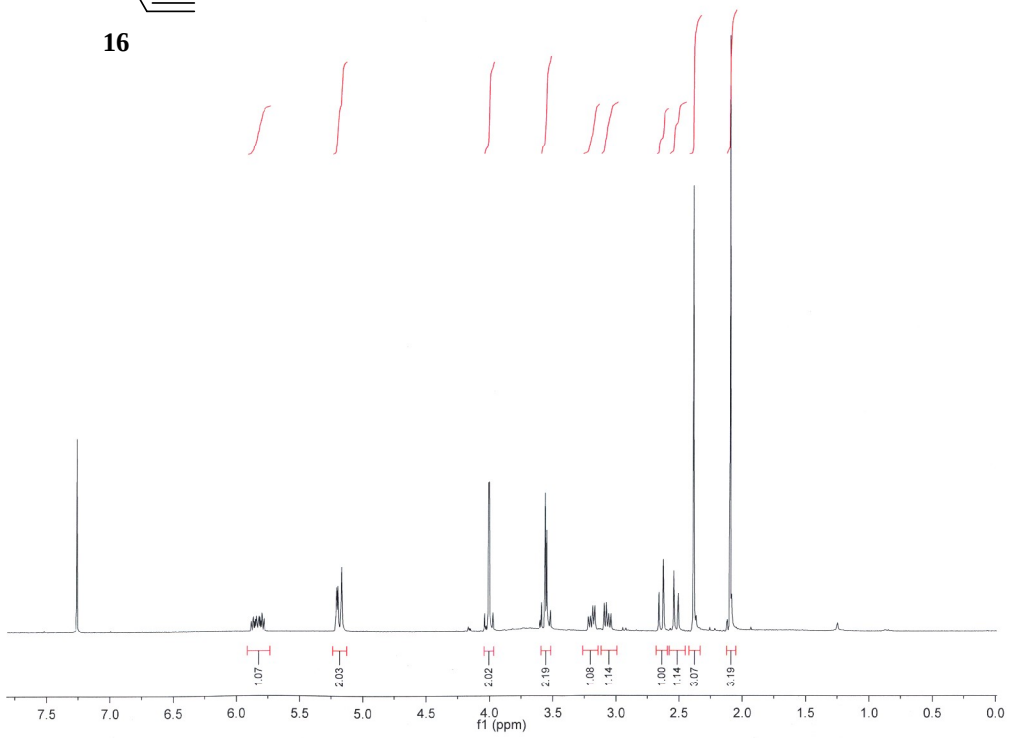

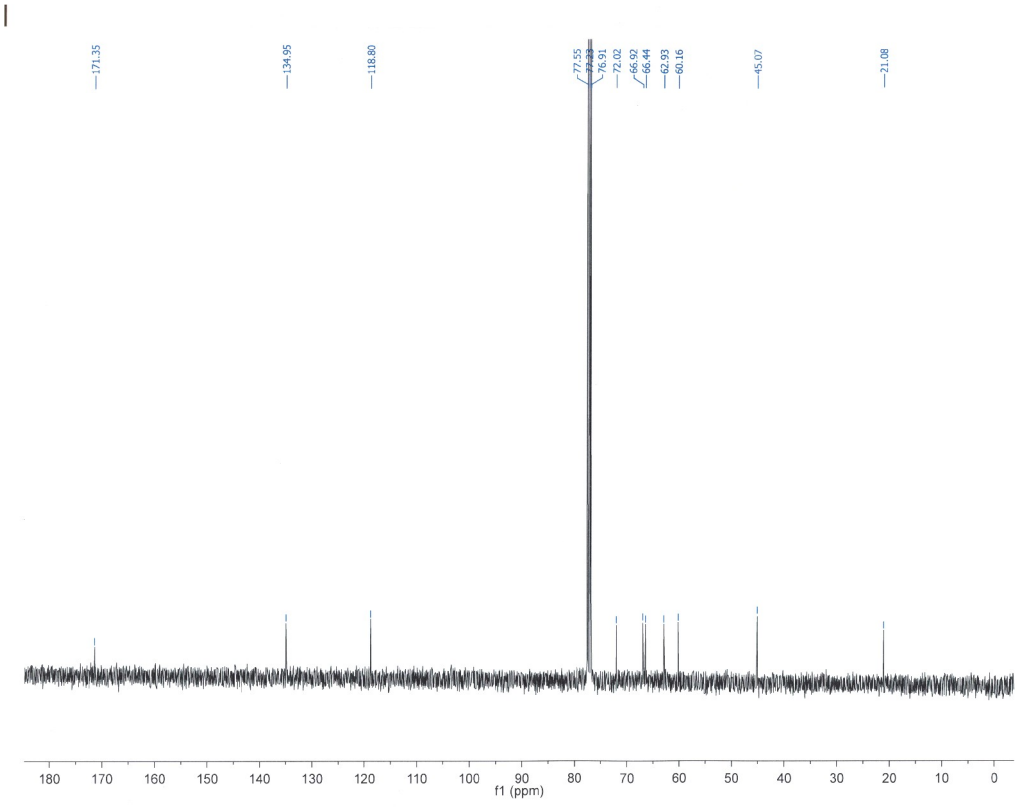

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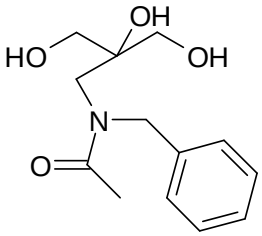

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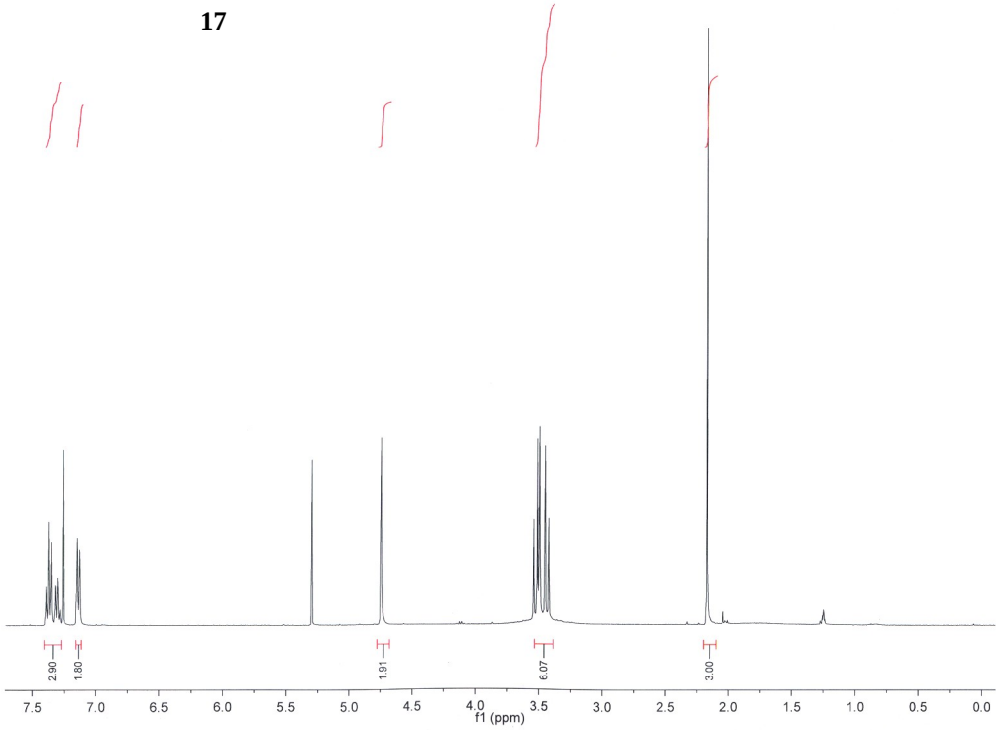

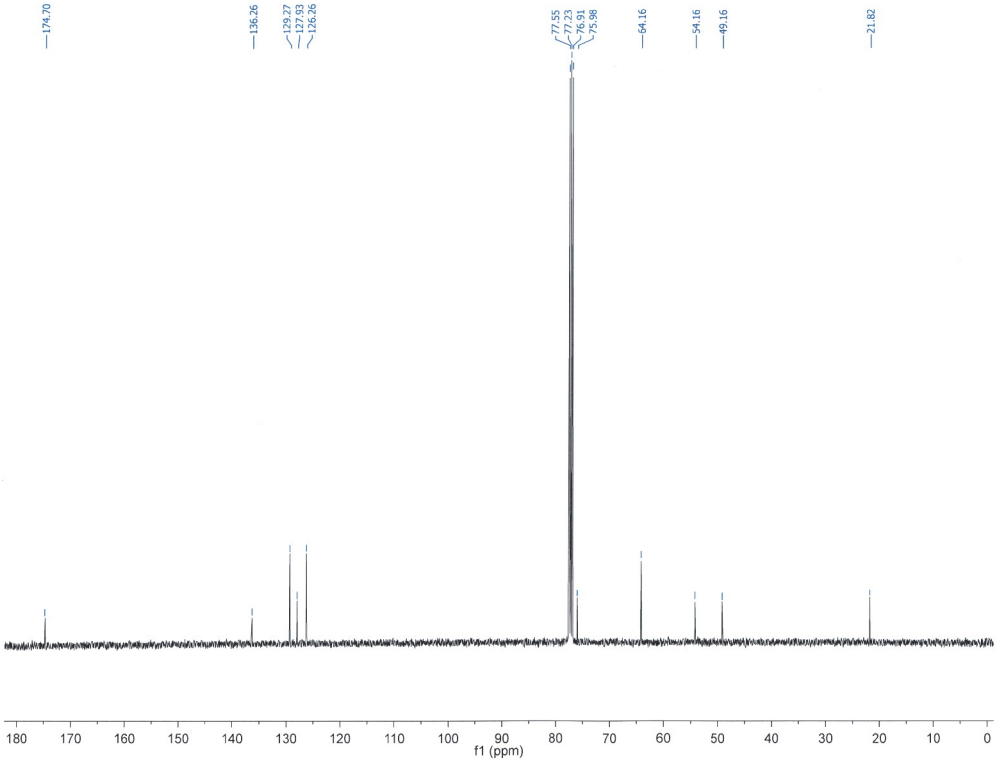

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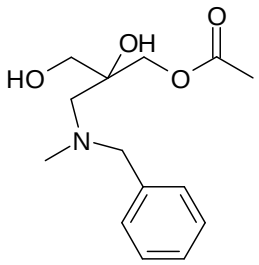

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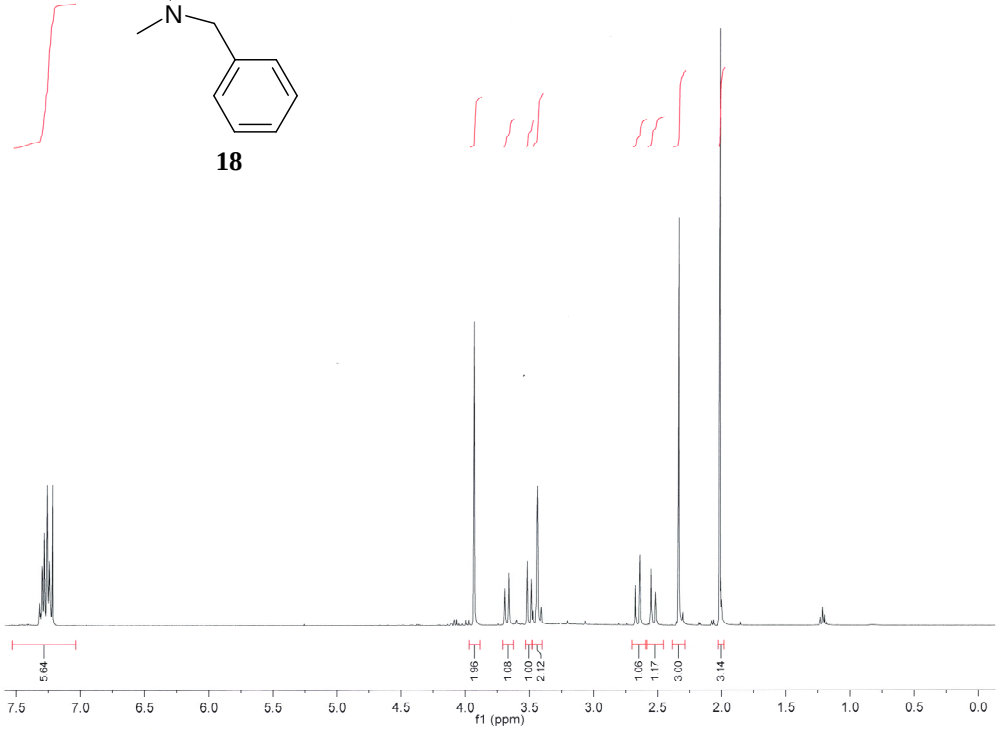

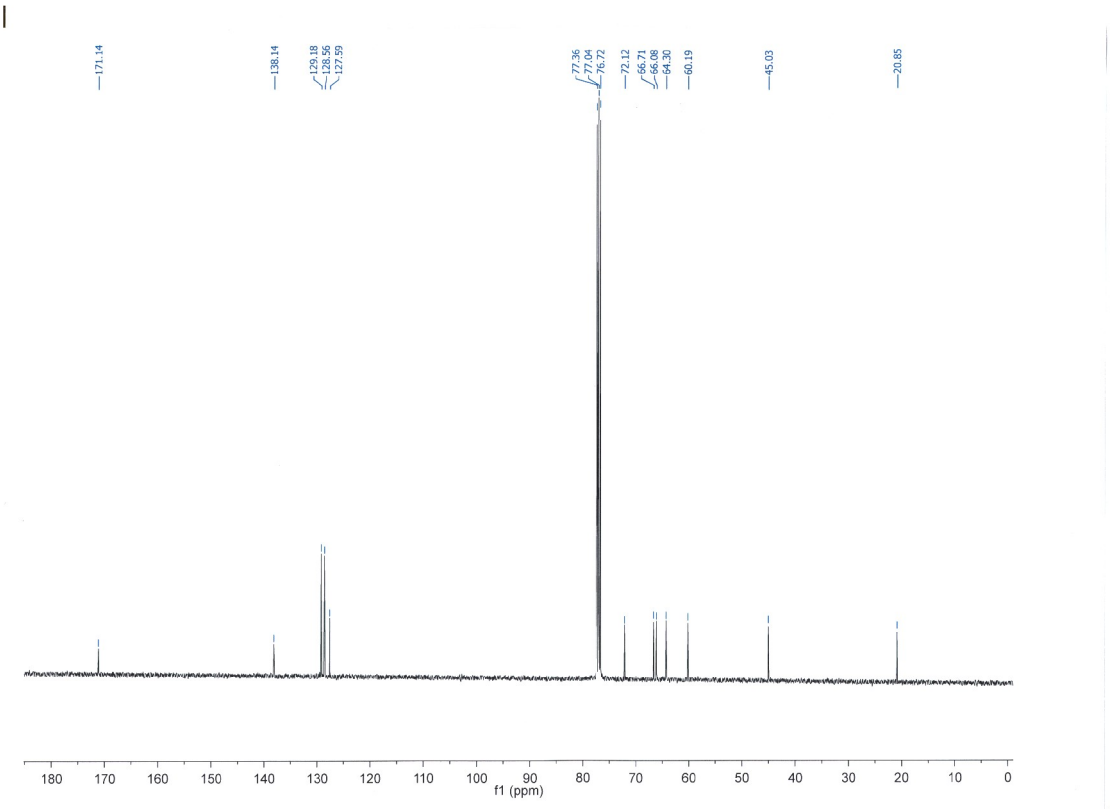

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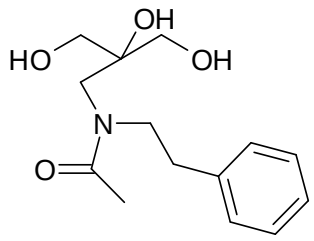

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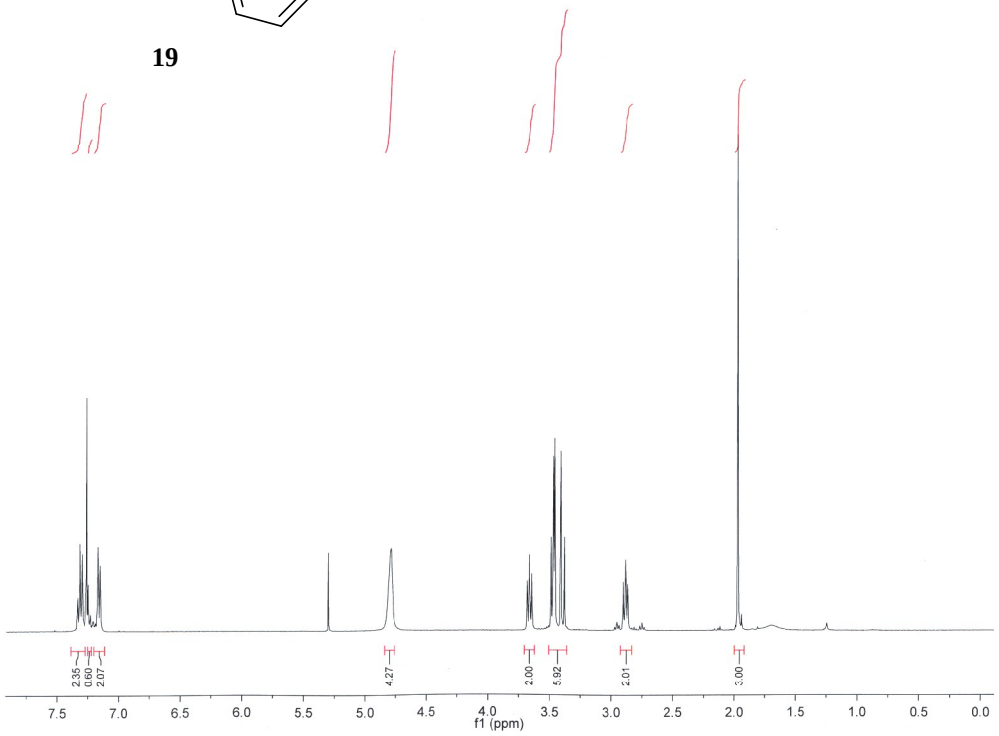

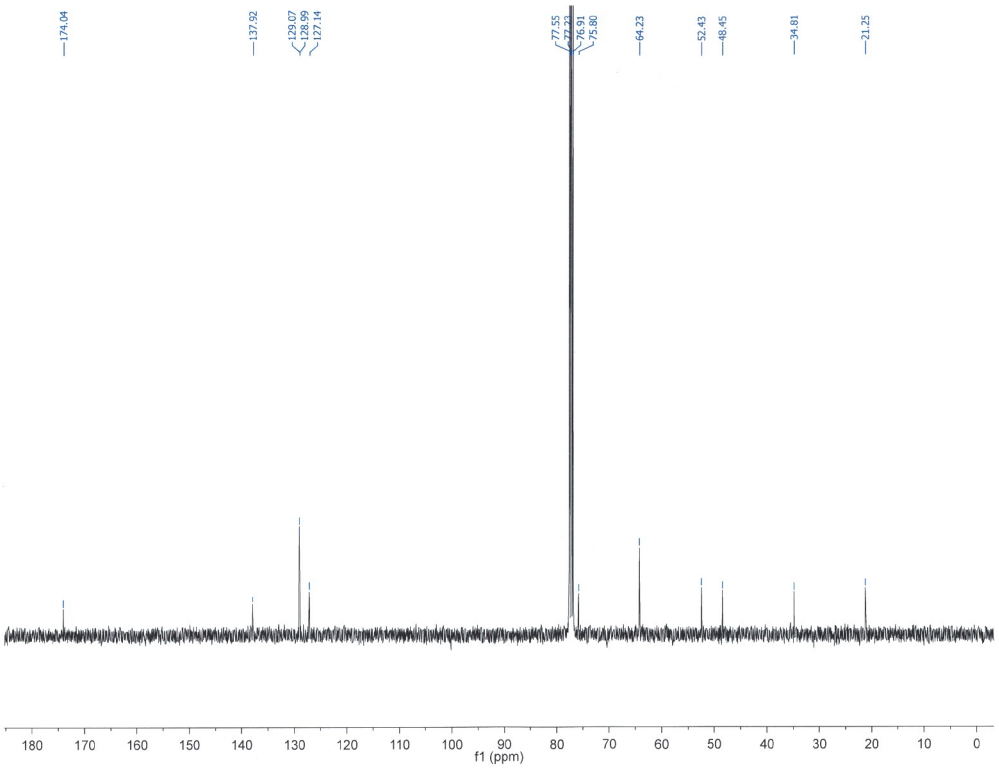

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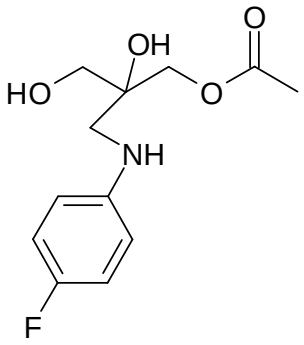

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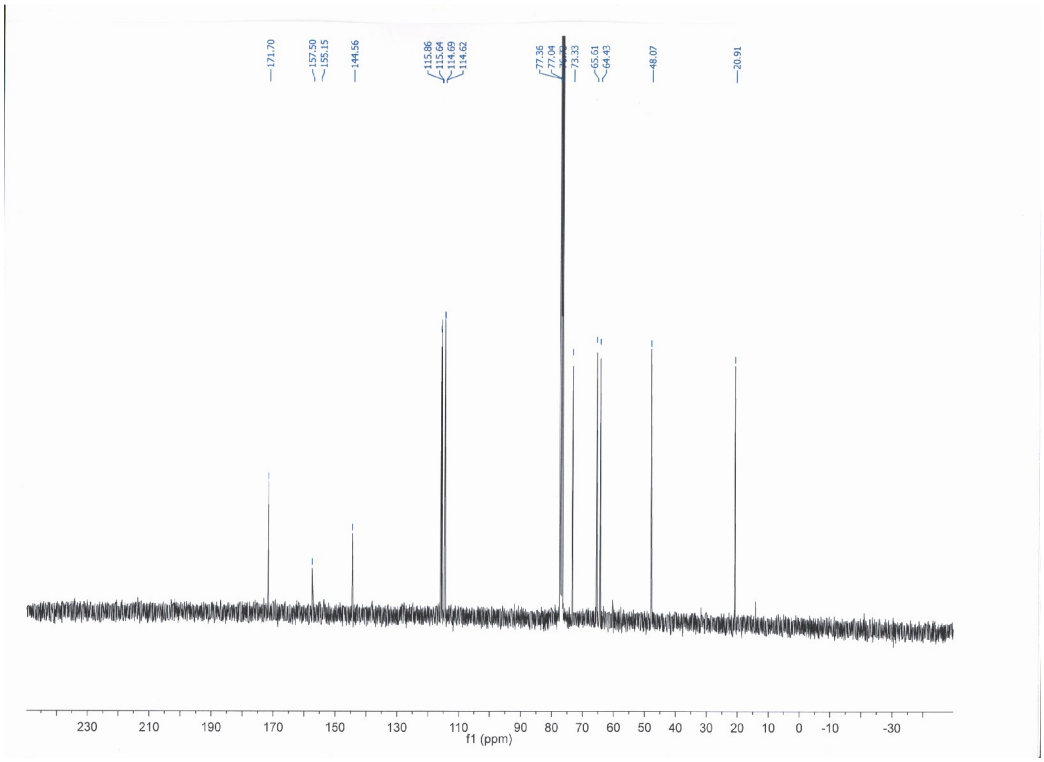

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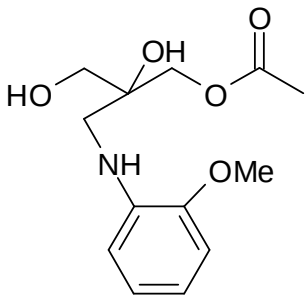

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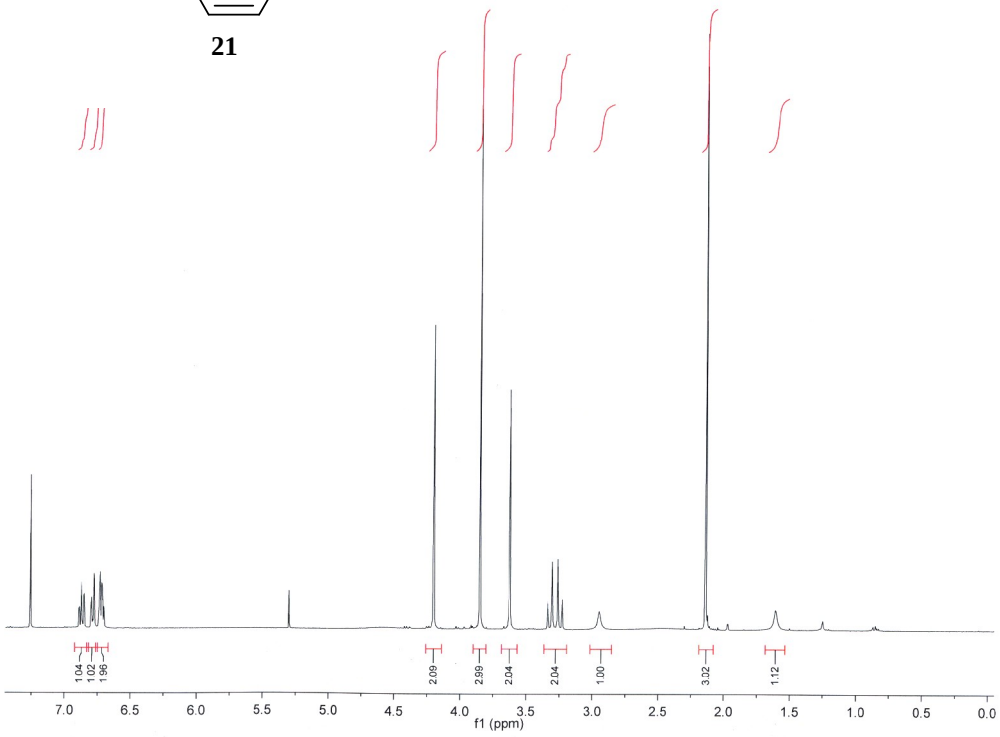

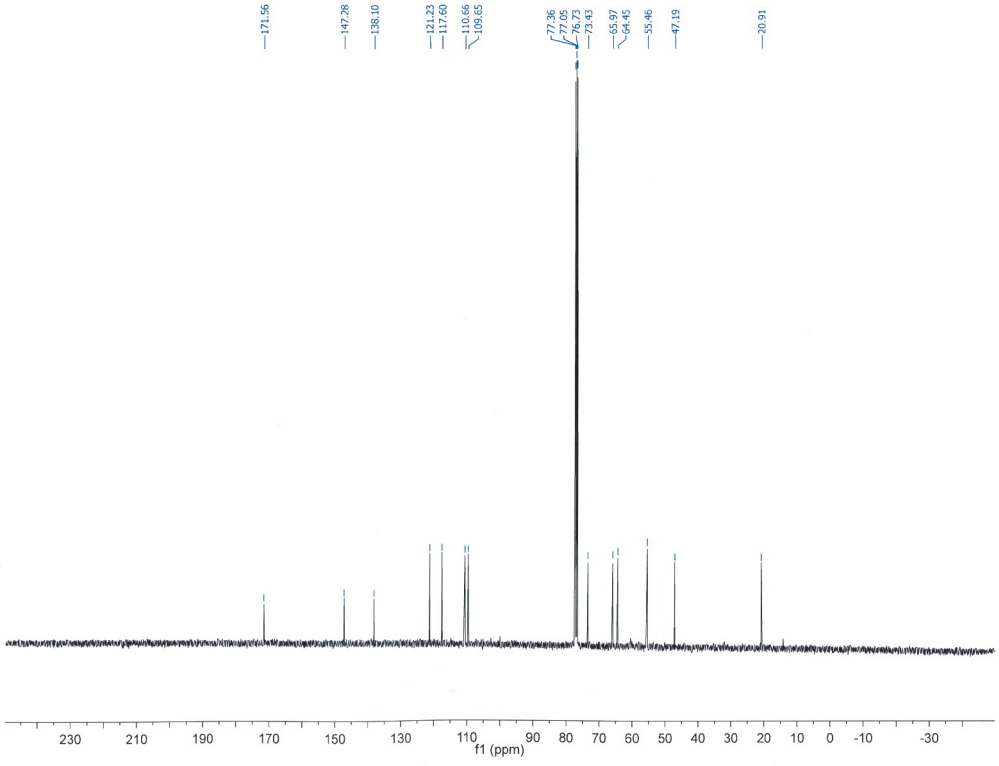

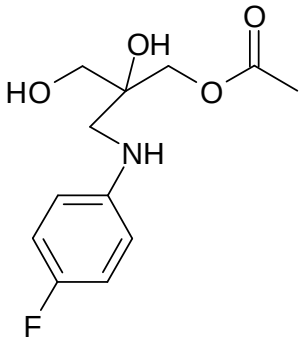

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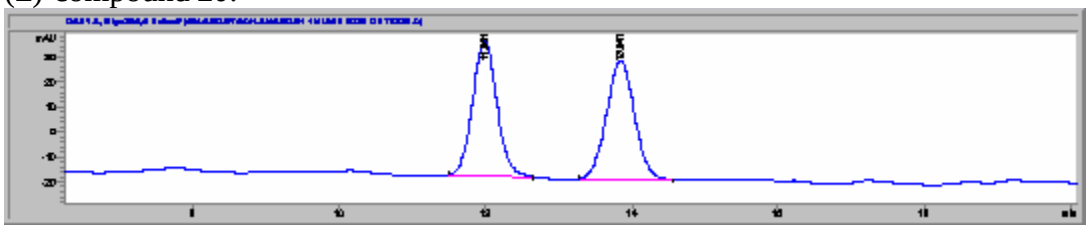

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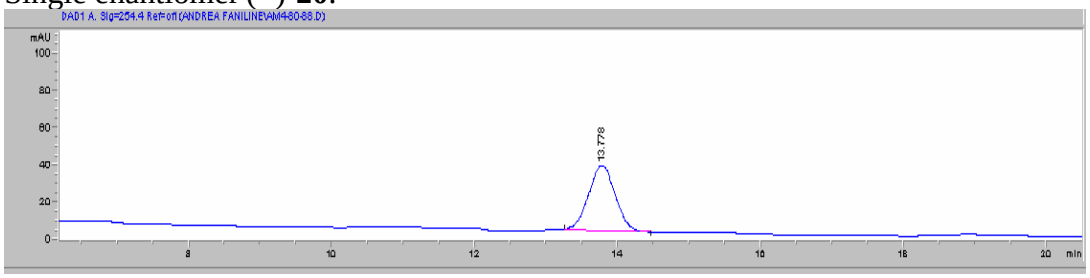

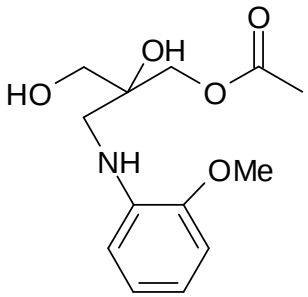

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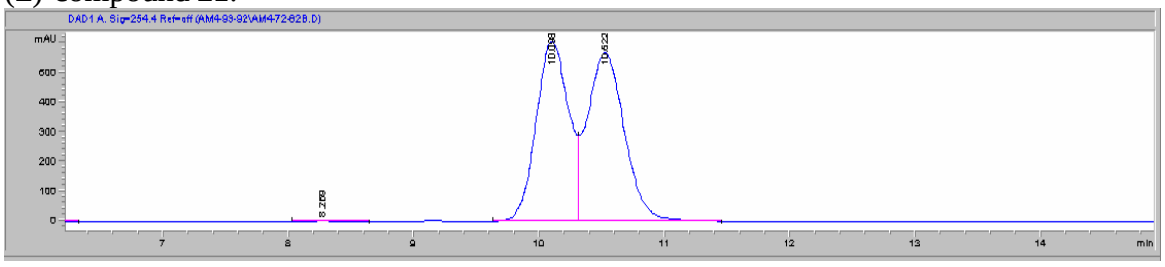

Single enantiomer (+)-**21**: