**SUPPORTING INFORMATION**

# A Temporary-Bridge Strategy for Enantioselective Organocatalyzed Synthesis of Aza-Seven-Membered Rings

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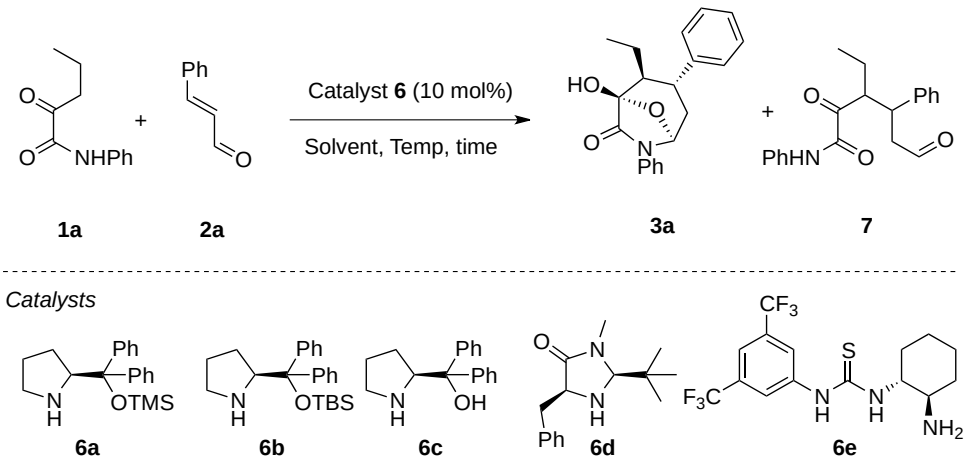
## 1. General information

All reagents were weighed and handled in air at room temperature. $^{1}$H NMR spectra were measured on a *Brucker AC 400* (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm referenced to the internal solvent signal (peak at 7.26 ppm in the case of $CDCl_3$; peak at 5.32 in the case of $CH_2Cl_2$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad), coupling constants (Hz), and assignment. $^{13}$C NMR spectra were measured on a *Brucker AC 400* (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the internal solvent signal (peak at 77 ppm in the case of $CDCl_3$). High performance liquid chromatography (HPLC) was performed on VWR Hitachi (pump L-2130/Diode Array detector L-2455) instrument. High-resolution mass spectra (HRMS) were performed on a *QStar Elite* (Applied Biosystems SCIEX) spectrometer equipped with atmospheric pressure ionization source (API) pneumatically assisted. Samples were ionized by positive electrospray mode as follows: electrospray tension (ISV): 5500 V; opening tension (OR): 50 V; nebulization gas pressure (air): 20 psi. Low resolution mass spectra were recorded on ion trap *Brucker Esquire 6000*, equipped with an electrospray source (methanolic sodium chloride solution). Optical rotations were measured at 30 °C in $CH_3Cl$ with a PERKIN ELMER 241 micropolarimeter. Melting points (mp) were determined with a Büchi Melting-point B-450 apparatus and were not corrected. Thin layer chromatography (TLCs) were developed on silica *Merck 60F$_{254}$*. Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with *p*-anisaldehyde reagent or phosphomolybdic acid reagent. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh). All reagents were obtained from commercial suppliers unless otherwise stated. Catalyst **6a**, **6b**, **6c**, **6d**, were purchased from Sigma Aldrich. Catalyst **6e**, was prepared following the literature procedure.[1] All unsaturated aldehydes were commercially available and purified according standard methods to remove any traces of the corresponding acid. Trichloroethanol was brought from Sigma Aldrich and contains 23 ppm of water (Karl-Fischer titration method). For experiments using this solvent, 4% v/v of water was added allowing to lower its freezing point to –7 °C.

(1) Berkessel, A.; Seelig, B. *Synthesis* **2009**, 2113.

## 2. Reaction optimization

We first investigated this reaction with ketoamide **1a** and cinnamaldehyde (**2a**) as starting materials with Hayashi-Jørgensen catalyst **6a** (Table 1). The reaction conducted in toluene did not proceed at all after 15 h (entry 1) and we only observed the very slow formation of Michael adduct **7** (11%, dr > 20:1) when benzoic acid was used as an additive (entry 2). Dichloromethane as well as acetonitrile proved unsuitable solvents for this reaction, as only small quantities of Michael adduct were recovered after similar reaction times (entries 3 and 4). Gratifyingly, the use of ethanol afforded the desired product **3a** in very good yield, as only two diastereomers (dr = 3:1) and excellent enantioselectivity for both diastereomers (entry 5). The addition of benzoic acid completely inhibited the reaction (entry 6). Catalyst **6b**, bearing a bulkier silyl group was also efficient even if we noticed a slightly lower yield and diastereoselectivity (entry 7). Other iminium activation catalysts **6c-e** did not promote this three-bond forming domino reaction (entries 8-10). Methanol was also a good solvent for this transformation (entry 11) with no significant increase of yield or selectivity but the slightly more acidic trichloroethanol allowed the formation of **3a** with a better diastereoselectivity while high yield and high enantioselectivity were maintained (entry 12). However, conducting the reaction in trifluroroethanol totally inhibited the reaction (entry 13). Clearly, the use of acidic media (either additive or solvent) is detrimental for this reaction, possibly due to unfavorable enolization of the a-ketoamide resulting in the inhibition of the initial conjugate addition. Finally the reaction temperature was lowered to –7 °C, which resulted in an increase of the diastereoselectivity to 8:1 even if prolonged reaction time was required to drive the reaction to completion (entry 14).



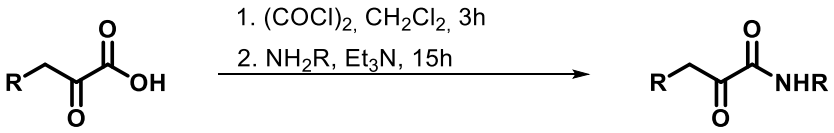
| Entry | Catalyst | Solvent | Temp | Time | Yield of **3a** (%)[b] | dr[c] | ee (%)[d,e] |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | toluene | 0 °C | 15 h | 0 | - | - |
| 2[g] | **6a** | toluene | 0 °C | 15 h | 0[f] | - | - |
| 3 | **6a** | $CH_2Cl_2$ | 0 °C | 15 h | 0[f] | - | - |
| 4 | **6a** | $CH_3CN$ | 0 °C | 15 h | 0[f] | - | - |
| 5 | **6a** | EtOH | 0 °C | 15 h | 92 | 3:1 | 97 [86] |
| 6[g] | **6a** | EtOH | 0 °C | 15 h | 0 | - | - |
| 7 | **6b** | EtOH | 0 °C | 15 h | 84 | 2:1 | 99 [50] |
| 8 | **6c** | EtOH | 0 °C | 15 h | 0 | - | - |
| 9 | **6d** | EtOH | 0 °C | 15 h | 0 | - | - |
| 10 | **6e** | EtOH | 0 °C | 15 h | 0 | - | - |
| 11 | **6a** | MeOH | 0 °C | 15 h | 94 | 3:1 | 98 [93] |
| 12 | **6a** | $CCl_3CH_2OH$ | 0 °C | 24 h | 91 | 5:1 | 99 [88] |
| 13 | **6a** | $CF_3CH_2OH$ | 0 °C | 24 h | 0 | - | - |
| 14 | **6a** | $CCl_3CH_2OH$ | –7 °C | 3 d | 94 | 8:1 | 99 |

[a]Reaction conditions: Ketoamide **1a** (0.2 mmol, 1.0 equiv), catalyst **6a** (10 mol%) were dissolved in the solvent (2 mL) and stirred for 15 min (0 °C or –7 °C). Then, cinnamaldehyde (**2a**) (2.0 equiv) was added and the mixture was stirred for the time and the temperature indicated. [b]Isolated yield after flash chromatography. [c]Determined by $^1$H NMR of the crude reaction product. [d]Determined by chiral HPLC analysis. [e]Values in brackets are for the minor diastereomer. [f]10-15% of the Michael adduct **7** were isolated. [g]20 mol% of benzoic acid was added.

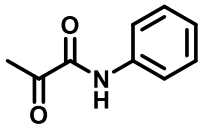
## 3. Experimental procedures

### *a. α-ketoamides preparation*

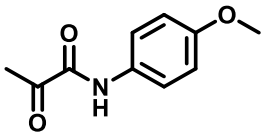
α-ketoamides were prepared according to the general procedure:



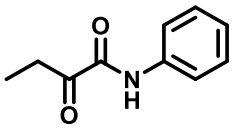

In a dried round-bottom flask was solubilized the 1,2-ketoacid (1.20 equiv) in dry dichloromethane (0.4 M). The solution was cooled to 0 °C and oxalyl chloride (1.20 eq) was added followed by two drops of DMF. After 3 hr of stirring at room temperature, the solution was cooled to 0 °C and a solution of triethylamine (1.50 equiv) and the amine (1.00 equiv) in dichloromethane (0.8 M related to the amine) was added dropwise. White fumes appeared immediately and a precipitation occurred during the process. The reaction mixture was stirred at room temperature for 15 hours and was then washed with a 1N HCl solution, water and brine (except for 2-oxo-*N*-(pyridin-3-yl)pentanamide which is only washed with water and brine). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude reaction mixture was purified by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether).



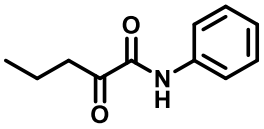

2-oxo-N-phenylpropanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afforded the ketoamide (1.3 g, 80%) as a yellow amorphous solid. Mp = 85 – 86 °C. Rf (EtOAc/PE, 10 : 90) = 0.36. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.72 (br s, 1H, NH), 7.64 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 2.57 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.46 (C), 157.68 (C), 136.39 (C), 129.40 (2CH), 125.45 (CH), 119.85 (2CH), 24.19 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 164.0706, $C_9H_{10}NO_2^+$ calculated 164.0706].



N-(4-methoxyphenyl)-2-oxopropanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afforded the ketoamide (1.8 g, 93%) as a yellow amorphous solid. Mp = 127 – 128 °C. Rf (EtOAc/PE, 10 : 90) = 0.39 $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.67 (br s, 1H), 7.58 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 2.58 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.66 (C), 157.45 (C), 157.17 (C), 129.58 (C), 121.37 (2CH), 114.52 (2CH), 55.62 ($CH_3$), 24.25 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 194.0811, $C_{10}H_{12}NO_3$+ calculated 194.0812].

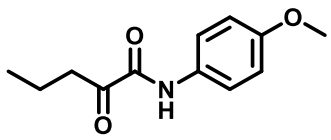


2-Oxo-N-phenylbutanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afforded the ketoamide (1.26 g, 71%) as a white amorphous solid. Mp = 91 – 92 °C. Rf (EtOAc/PE, 10 : 90) = 0.46. NMR $^{1}$H (400 MHz, $CDCl_3$): δ 8.74 (br s, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 3.06 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). NMR $^{13}$C (100 MHz, $CDCl_3$): δ 200.06 (C), 157.67 (C), 136.47 (C), 129.38 (2CH), 125.40 (CH), 119.89 (2CH), 30.14 ($CH_2$), 7.36 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 178.0862, $C_{10}H_{12}NO_2^+$ calculated 178.0863].

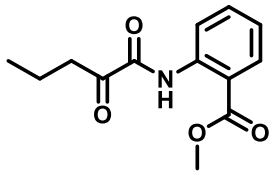


2-Oxo-N-phenylpentanamide (**1a**): The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afforded the ketoamide **1a** (1.72 g, 90%) as a white amorphous solid. Mp = 79 – 80 °C. Rf (EtOAc/PE, 10 : 90) = 0.57 $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.75 (br s, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 3.0 (t, *J* = 7.2 Hz, 2H), 1.71 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.54 (C), 157.73 (C), 136.49

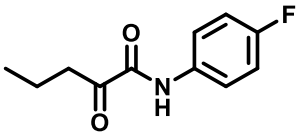
(C), 129.37 (2CH), 125.38 (CH), 119.87 (2CH), 38.35 ($CH_2$), 16.99 ($CH_2$), 13.77 ($CH_3$). MS: m/z (ES+) 204 [$(M+Na)^+$, 100%], 236 (40). m/z [Found (ES+): $[M+H]^+$ 192.1019, $C_{11}H_{14}NO_2^+$ calculated 192.1019].



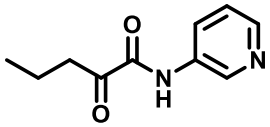
2-oxo-N-(4-methoxyphenyl)pentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 1:9) afforded the ketoamide (339 mg, 77%) as a light yellow oil. Rf (ethyl acetate/petroleum ether, 1:9) = 0.37 Mp = 112 – 113 °C; NMR $^1$H (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 9.00 Hz, 2H), 6.90 (d, *J* = 9.00 Hz, 2H), 3.81 (s, 3H), 3.00 (t, *J* = 7.22 Hz, 2H), 1.70 (sext, *J* = 7.35 Hz, 2H), 0.99 (t, *J* = 7.43 Hz, 3H) NMR $^{13}$C (100 MHz, $CDCl_3$): δ 199.56 (C), 157.34 (C), 156.98 (C), 129.53 (C), 121.23 (2CH), 114.37 (2CH), 55.48 ($CH_2$), 38.26 ($CH_3$), 16.86 ($CH_2$), 13.65 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 222.1125, $C_{11}H_{16}NO_3^+$ calculated 222.1125].



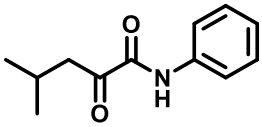
Methyl 2-(2-oxopentanamido)benzoate: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 30:70) afforded the ketoamide (1.35 g, 54%) as a white amorphous solid. Mp = 145 – 148 °C. Rf (EtOAc/PE, 10 : 90) = 0.13 NMR $^1$H (400 MHz, $CDCl_3$): δ 12.34 (br s, 1H), 8.75 (d, *J* = 8.4 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 3.97 (s, 3H), 2.99 (t, *J* = 7.2 Hz, 2H), 1.83 – 1.62 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). NMR $^{13}$C (100 MHz, $CDCl_3$): δ 198.87 (C), 168.18 (C), 158.92 (C), 139.79 (C), 134.68 (CH), 131.38 (CH), 123.87 (CH), 120.49 (CH), 116.74 (C), 52.74 ($CH_3$), 38.47 ($CH_2$), 16.95 ($CH_2$), 13.79 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 250.1074, $C_{13}H_{16}NO_4^+$ calculated 250.1074].



N-(4-fluorophenyl)-2-oxopentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afforded the ketoamide (1.53 g, 73%) as a yellow amorphous solid. Mp = 103 – 104 °C. Rf (EtOAc/PE, 10 : 90) = 0.54 $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.74 (br s, 1H), 7.62 (dd, *J* = 9.0, 4.7 Hz, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 1.75 – 1.63 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.42 (C), 159.97 (C, d, *J* = 245.1 Hz), 157.63 (C) , 132.59 (C, d, *J* = 2.9 Hz), 121.57 (CH x2, d, *J* = 8.0 Hz), 116.12 (CH x2, d, *J* = 22.7 Hz), 38.36 ($CH_2$), 16.97 ($CH_2$), 13.76 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 210.0925, $C_{11}H_{13}FNO_2^+$ calculated 210.0925].

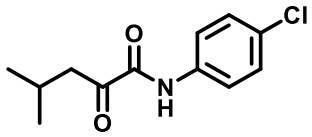


2-oxo-N-(pyridin-3-yl)pentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 50:50) afford the ketoamide (1.48 g, 77%) as a yellow amorphous solid. Mp = 95 – 96 °C. Rf (EtOAc/PE, 50 : 50) = 0.39 $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.81 (br s, 1H), 8.68 (d, *J* = 2.4 Hz, 1H), 8.36 (dd, *J* = 4.7, 1.1 Hz, 1H), 8.16 (ddd, *J* = 8.3, 2.4, 1.4 Hz, 1H), 7.26 (dd, *J* = 8.3, 4.8 Hz, 1H), 2.93 (t, *J* = 7.2 Hz, 2H), 1.64 (h, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **$^{13}$C** NMR (100 MHz, $CDCl_3$): δ 198.80 (C) , 158.19 (C), 146.38 (CH), 141.56 (CH), 133.38 (C), 126.91(CH) , 123.90 (CH), 38.35 ($CH_2$), 16.93 ($CH_2$), 13.74 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 193.0972, $C_{10}H_{13}N_2O_2^+$ calculated 193.0972].

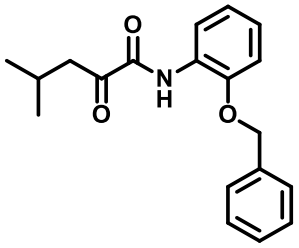


4-methyl-2-oxo-N-phenylpentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afford the ketoamide (1.74 g, 85%) as a white amorphous solid. Mp = 94 – 95 °C. Rf (EtOAc/PE, 10 : 90) = 0.64 $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.77 (br s, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 2.90 (d, *J* = 6.9

Hz, 2H), 2.24 (n, *J* = 6.7, 1H), 0.99 (d, *J* = 6.9 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.27 (C), 157.8 (C), 136.51 (C), 129.38 (2CH), 125.37 (CH), 119.85 (2CH), 44.98 ($CH_2$), 24.73 (CH), 22.71 ($2CH_3$). m/z [Found (ES+): $[M+H]^+$ 206.1176, $C_{12}H_{16}NO_2^+$ calculated 206.1176].

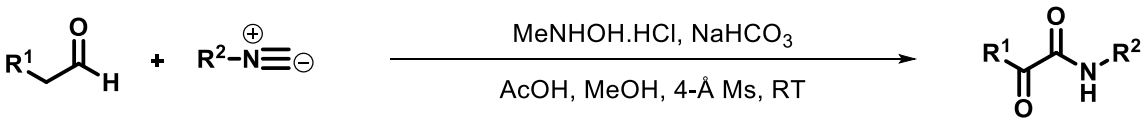



N-(4-chlorophenyl)-4-methyl-2-oxopentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afford the ketoamide (1.9 g, 80%) as a white crystalline solid. Mp = 112 – 113 °C. Rf (EtOAc/PE, 10 : 90) = 0.68 $^1$H NMR (400 MHz, $CDCl_3$): δ 8.76 (br s, 1H), 7.6 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 2.88 (d, *J* = 6.9 Hz, 2H), 2.23 (n, *J* = 6.7, 1H), 0.99 (d, *J* = 6.7 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.96 (C), 157.75 (C), 135.1 (C), 130.47 (C), 129.44 (2CH), 121.07 (2CH), 44.95 ($CH_2$), 24.71 (CH), 22.69 ($2CH_3$). m/z [Found (ES+): $[M+H]^+$ 240.0785, $C_{12}H_{15}ClNO_2^+$ calculated 240.0786].

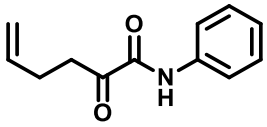



N-(2-(benzyloxy)phenyl)-4-methyl-2-oxopentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afford the ketoamide (2 g, 64%) as a yellow solid. Mp = 62 – 63 °C. Rf (EtOAc/PE, 10 : 90) = 0.58. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.53 (brs, 1H), 8.43 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.45 – 7.40 (m, 4H), 7.38 – 7.32 (m, 1H), 7.08 (td, *J* = 7.8, 1.6 Hz, 1H), 7.03 – 6.93 (m, 2H), 5.18 (s, 1H), 2.88 (d, *J* = 6.9 Hz, 1H), 2.24 (n, 6.7 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.90 (C), 157.85 (C), 148.08 (C), 136.37 (C), 128.91 (CH x2), 128.37 (CH), 127.27 (CH x2), 126.72 (C), 125.07 (CH), 121.62 (CH), 119.93 (CH), 112.23 (CH), 71.00 ($CH_2$), 45.02 ($CH_2$), 24.72 (CH), 22.74 ($2CH_3$). m/z [Found (ES+): $[M+H]^+$ 312.1594, $C_{19}H_{22}NO_3^+$ calculated 312.1594].

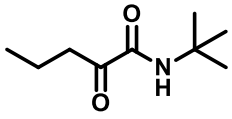
When the desired α-ketoacide is not commercially available, α-ketoamides can also be synthesized *via* an Ugi-type four-component reaction starting with aldehydes.[2] General procedure:




The aldehyde (1.0 equiv) was added to a solution of *N*-methyl hydroxylamine hydrochloride (1.1 equiv), $NaHCO_3$ (2 equiv) and 4Å molecular sieves (0.75 g/mmol) in dry methanol (1.0 M) and the mixture was stirred for 30 min at room temperature. The isocyanide (1.05 equiv) and acetic acid (9 equiv) were then added. The solution was stirred at room temperature until the reaction reached completion. The reaction mixture was then filtrated and the solvent evaporated, affording a crude product that was purified by flash chromatography on silica gel.



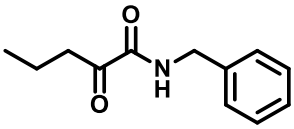

2-Oxo-N-phenylhex-5-enamide: The general procedure described above was performed on a 5 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 5:95) afforded the ketoamide (437 mg, 43%) as a white crystalline solid. Rf (EtOAc/PE, 10 : 90) = 0.54. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.72 (br s, 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 5.85 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.09 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.14 (t, *J* = 7.3 Hz, 2H), 2.44 (q, *J* = 7.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.83 (C), 157.57 (C), 136.44 (CH), 136.42 (C),129.40 (2CH), 125.46 (CH), 119.89 (2CH), 115.96 ($CH_2$), 35.67 ($CH_2$), 27.38 ($CH_2$). m/z [Found (ES+): $[M+H]^+$ 204,1017, $C_{12}H_{14}NO_2^+$ calculated 204,1019].




2-Oxo-N-(tert-butyl)-pentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum

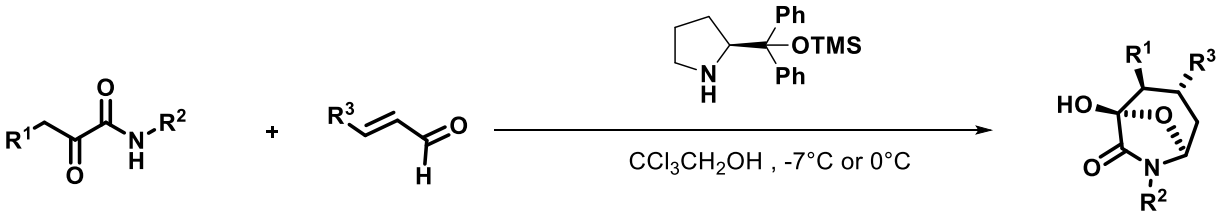
(2) Grassot, J.-M. ; Masson, G. ; Zhu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 947.

ether, 1:9) afforded the ketoamide (875 mg, 53%) as a colorless liquid. Rf (ethyl acetate/petroleum ether, 1:9) = 0.32. NMR $^{1}H$ (400 MHz, $CDCl_3$): 6.82 (br, 1H), 2.87 (t, *J* = 7.30 Hz, 2H), 1.61 (sext, *J* = 7.30 Hz, 2H), 1.38 (s, 9H), 0.94 (t, *J* = 7.30 Hz, 3H). NMR $^{13}C$ (100 MHz, $CDCl_3$): δ 200.25 (C), 159.44 (C), 51.18 (C), 38.04 ($CH_2$), 28.29 ($3CH_3$), 16.78 ($CH_2$), 13.63 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 171.1333, $C_9H_{17}NO_2^+$ calculated 171.1332].

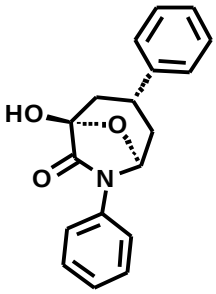



2-Oxo-N-benzylpentanamide: The general procedure described above was performed on a 10 mmol scale. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 1:8) afforded the ketoamide (1.21 g, 59%) as a light yellow crystalline solid. Rf (ethyl acetate/petroleum ether, 1:9) = 0.30 Mp = 40 – 41 °C; NMR $^{1}H$ (400 MHz, $CDCl_3$): δ 7.40-7.22 (m, 5H), 4.46 (d, *J* = 6.07 Hz, 2H), 2.92 (t, *J* = 7.27 Hz, 2H), 1.64 (sxt, *J* = 7.35 Hz, 2H), 0.96 (t, *J* = 7.35 Hz, 3H) NMR $^{13}C$ (100 MHz, $CDCl_3$): δ 199.04 (C), 160.03 (C), 137.03 (C), 128.83 (2CH), 127.89 (2CH), 127.85 (CH), 43.40 ($CH_2$), 38.69 ($CH_2$), 16.70 ($CH_2$), 13.62 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 206.1173, $C_{12}H_{15}NO_2^+$ calculated 206.1176].

### *b. 7-aza-8-oxa-bicyclo[3.2.1]octane derivatives synthesis*

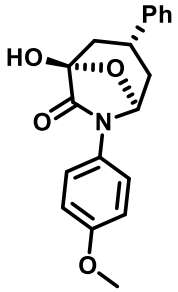



**General procedure:** The unsaturated aldehyde (0.4 mmol, 2 equiv) was added in one portion to a solution of the ketoamide (0.2 mmol, 1.0 equiv) and the Hayashi-Jørgensen catalyst (0.02 mmol, 0.1 equiv) in 1 mL of trichloroethanol (0.2 M) at –7° C or 0 °C. The reaction mixture was stirred for 3 days at the indicated temperature and then directly purified by chromatography (silica gel, eluent: ethyl acetate/petroleum ether). Racemic compounds were synthetized by mixing equivalent amounts of both enantiomers of the Hayashi-Jørgensen catalyst. The diastereomeric ratio was determined by $^{1}$H NMR spectroscopy of a crude reaction sample after solvent removal by high vacuum exposure. The enantiomeric excess was determined by HPLC analysis on a chiral phase. Scale up experiments were done under the same conditions.



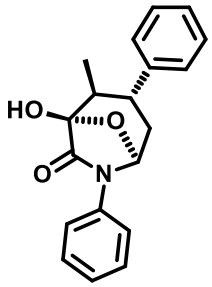
(1R,2S,3R,5S)-1-hydroxy-3,6-diphenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3f**): The general procedure described above was performed on a 0.2 mmol scale; dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 1:5) afforded the bicyclic compound **3f** (33 mg, 56%) as a white amorphous solid. Mp = 119 – 120 °C; Rf (ethyl acetate/petroleum ether, 1:4) = 0.22; HPLC (Lux-Cellulose-4, heptane/ethanol = 60/40, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 8.08 min, $t_{minor}$ = 10.53 min, ee = 97%; [$\alpha_D^{25°C}$ ($CHCl_3$, *c* = 2.4 M) = + 21; NMR $^{1}$H (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.07, 2H),

7.41 (dd, *J* = 7.11, 7.36, 2H), 7.22 (m, 4H), 5.91 (s, 1H), 4.44 (br, 1H), 3.03 (m, 1H), 2.29 (dd, *J* = 13.50, 5.73, 1H), 2.23-2.03 (m, 3H) NMR $^{13}$C (100 MHz, $CDCl_3$): δ 169.60 (C), 142.16 (C), 135.77 (C), 129.48 (2CH), 128.78 (2CH), 127.18 (2CH), 127.06 (C), 125.49 (C), 118.77 (2CH), 100.39 (C), 85.84 (C), 37.107 (C), 35.61 (C), 32.67 (C); m/z [Found (ES+): $[M+H]^+$ 296.1282, $C_{18}H_{18}NO_3^+$ calculated 296.1281].

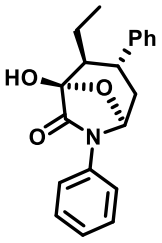



(1R,3R,5S)-1-hydroxy-6-(4-methoxyphenyl)-3-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3g**): The general procedure described above was performed on a 0.2 mmol scale; dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 40:60) afforded the bicyclic compound **3g** (60 mg, 92%) as a yellow amorphous solid. Mp = 160 – 161 °C; Rf = 0.32 (ethyl acetate/petroleum ether 40/60); HPLC (Chiralpak ID, heptane/ethanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 13.53 min, $t_{minor}$ = 11.42 min, ee = 97 %; $\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 37; $^1$H NMR(400 MHz, $CD_2Cl_2$): δ 7.48 (d, *J* = 9.1 Hz, 2H), 7.33 – 7.29 (m, 2H), 7.24 – 7.21 (m, 3H), 6.94 (d, *J* = 9.1 Hz, 2H), 5.83 (s, 1H), 4.50 (s, 1H), 3.80 (s, 3H), 3.04 (s, *J* = 5.8 Hz, 1H), 2.22 (dd, *J* = 13.1, 5.7 Hz, 1H), 2.11 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.02 – 2.00 (m, 2H); $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ 169.53 (C), 157.95 (C), 143.11 (C), 129.42 (C), 129.25 (2CH), 127.78 (2CH), 127.48 (CH), 121.71 (2CH), 115.12 (2CH), 100.66 (C), 86.92 (CH), 56.04 (CH), 37.83 ($CH_2$), 36.21 (CH), 33.19 ($CH_2$); m/z [Found (ES+): $[M+H]^+$ 326.1386, $C_{19}H_{20}NO_4^+$ calculated 326.1387].

**Gram-scale experiment :** 3 mmol of α-ketoamide as SM, yield 88% (859mg of **3g**) with same ee and dr.



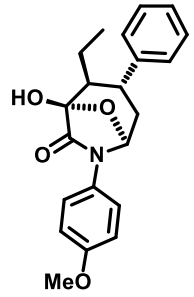

(1R,2S,3R,5S)-2-methyl-1-hydroxy-3-phenyl-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3h**): The general procedure described above was performed on a 0.2 mmol scale; dr = 10:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 20:80) afforded the bicyclic compound **3h** (74 mg, 90%) as a white amorphous solid. Mp = 110 – 111 °C; Rf (ethyl acetate/petroleum ether, 1:4) = 0.28; HPLC (Chiralpak ID, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 14.88 min, $t_{minor}$ = 11.65 min, ee = 99 %; $\alpha_D^{25°C}$ ($CHCl_3$, *c* = 1.0 M) = + 62; NMR $^1$H (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.98 Hz, 2H), 7.35 (t, *J* = 7.39 Hz, 2H), 7.30 (t, *J* = 7.39 Hz, 2H), 7.24-7.16 (m, 2H), 7.13 (d, *J* = 7.39 Hz, 2H), 5.92 (s, 1H), 4.64 (br, 1H), 3.27 (dt, *J* = 12.80, 5.12 Hz, 1H), 2.40 (m, 2H), 2.01 (ddd, *J* = 13.14, 4.78, 1.70 Hz, 1H), 0.87 (d, *J* = 6.90 Hz, 3H). NMR $^{13}$C (100 MHz, $CDCl_3$): δ 170.54 (C), 139.85 (C), 135.75 (C), 129.42 (2CH), 128.51 (2CH), 127.61 (2CH), 126.79 (CH), 125.38 (CH), 118.66 (2CH), 101.99 (C), 85.73 (CH), 38.11 (CH), 25.79 ($CH_2$), 6.78 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 310.1437, $C_{19}H_{20}NO_3^+$ calculated 310.1438].




(1R,2S,3R,5S)-2-ethyl-1-hydroxy-3,6-diphenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3a**): The general procedure described above was performed on a 0.2 mmol scale; dr = 7:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicyclic compound **3a** (61 mg, 94%) as a white amorphous solid. Mp = 80 – 81 °C; Rf = 0.45 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak IE, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 14.45 min, $t_{minor}$ = 12.85 min, ee = 99 %, minor diastereomer, $t_{major}$ = 9.39 min, $t_{minor}$ = 12.07 min, ee = 89 %; $\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 42; $^1$H NMR(400 MHz, $CD_2Cl_2$): δ 7.56 (d, *J* = 7.9

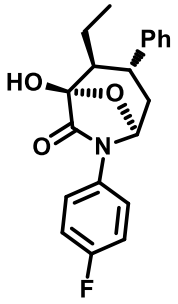
Hz, 2H), 7.40 – 7.27 (m, 4H), 7.25 – 7.14 (m, 4H), 5.93 (s, 1H), 4.55 (s, 1H), 3.26 (dt, *J* = 12.5, 4.9 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.10 (dd, *J* = 9.9, 4.8 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.81 – 1.70 (m, 1H), 1.27 – 1.15 (m, 1H), 0.56 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR(100 MHz, $CD_2Cl_2$): δ 171.16 (C), 140.71 (C), 136.53 (C), 129.87 (2CH), 128.98 (2CH), 128.30 (2CH), 127.24 (CH), 125.78 (CH), 119.18 (CH), 103.31 (C), 86.31 (CH), 45.78 (CH), 38.73 (CH), 26.91 ($CH_2$), 16.89 ($CH_2$), 15.04 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 324,1594, $C_{20}H_{22}NO_3^+$ calculated 324,1594].

**Gram scale experiment :** 3 mmol of α-ketoamide as SM, yield 90% (873 mg of **3g**) with same ee and dr.

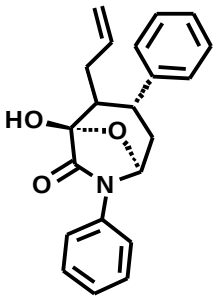



(1R,2S,3R,5S)-2-ethyl-1-hydroxy-6-(4-methoxyphenyl)-3-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3k**): The general procedure described above was performed on a 2 mmol scale; dr = 6:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 1:5 then 1:2) afforded the bicyclic compound **3k** (59 mg, 84%) as a white amorphous solid. Mp = 146 – 147 °C; Rf (ethyl acetate/petroleum ether, 1:4) = 0.19 ; HPLC (Lux-Amylose-2, heptane/ethanol = 60/40, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 14.07 min, $t_{minor}$ = 11.09 min, ee = 99 %, minor diastereomer, $t_{major}$ = 12.41 min, $t_{minor}$ = 16.78 min, ee = 91 %; $[\alpha_D^{25°C}$ ($CHCl_3$, *c* = 1.3 M) = + 95°; m/z [Found (ES+): $[M+H]^+$ 354.1703, $C_{21}H_{24}NO_4^+$ calculated 354.1700]; NMR $^1$H (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 9.10 Hz, 2H), 7.31 (t, *J* = 7.30 Hz, 2H), 7.22 (t, *J* = 7.30 Hz, 1H), 7.19 (d, *J* = 7.30 Hz, 2H), 6.88 (d, *J* = 9.10 Hz, 2H), 5.84 (s, 1H), 4.58 (br, 1H), 3.78 (s, 3H), 3.29 (dt, *J* = 12.76, 4.88 Hz, 1H), 2.36 (t, *J* = 12.36 Hz, 1H), 2.16 (q, *J* = 4.67 Hz, 1H), 1.96 (ddd, *J* = 13.61, 4.53, 1.65 Hz, 1H), 1.79 (m, 1H), 1.22 (m, 1H), 0.58 (t, *J* = 7.52 Hz, 3H). NMR $^{13}$C (100 MHz, $CDCl_3$): δ 170.15 (C), 157.19 (C), 139.96 (C), 128.51 (2CH), 127.69 (2CH), 126.79 (CH), 120.89 (2CH), 114.60 (2CH), 102.75 (C), 86.09 (CH), 55.49 (CH), 45.32 (CH), 38.19 (CH), 26.33 ($CH_2$), 16.37 ($CH_2$), 14.69 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 354.1703, $C_{20}H_{22}NO_3^+$ calculated 354.1700].

**Gram-scale experiment:** 2 mmol of α-ketoamide as SM, yield 92% (653 mg of **3k**) with same ee and dr.

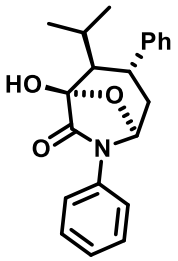



(1R,2S,3R,5S)-2-ethyl-6-(4-fluorophenyl)-1-hydroxy-3-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3l**): The general procedure described above was performed on a 0.2 mmol scale; dr = 5:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicycic compound **3l** (53 mg, 78%) as a white amorphous solid. Mp = 132 – 133 °C; Rf = 0.64 (ethyl acetate/petroleum ether 30/70); HPLC (Chiralpak AD-H, heptane/ethanol = 60/40, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 28.49 min, $t_{minor}$ = 13.22 min, ee = 99 %, minor diastereomer, $t_{major}$ = 16.25 min, $t_{minor}$ = 15.01 min, ee = 88 %; [$\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 76; $^1$H NMR (400 MHz, $CD_2Cl_2$): δ 7.56 – 7.51 (m, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.19 (m, 3H), 7.10 – 7.03 (m, 2H), 5.88 (s, 1H), 4.64 (s, 1H), 3.24 (dt, *J* = 12.5, 4.9 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.11 (q, *J* = 5.0 Hz, 1H), 1.98 (ddd, *J* = 13.8, 4.7, 1.8 Hz, 1H), 1.75 (dqd, *J* = 15.1, 7.6, 5.1 Hz, 1H), 1.21 (dqd, *J* = 14.8, 7.5, 5.1 Hz, 1H), 0.56 (t, *J* = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ 171.01 (C), 160.36 (d, *J* = 245.0 Hz), 140.56 (C), 132.65 (C, d, *J* = 2.9 Hz), 129.01 (2CH), 128.26 (2CH), 127.30 (CH), 121.15 (2CH, d, *J* = 8.1 Hz), 116.61 (2CH, d, *J* = 22.7 Hz), 103.28 (C), 86.50 (CH), 45.77 (CH), 38.69 (CH), 26.79 ($CH_2$), 16.87 ($CH_2$), 15.02 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 342.1499, $C_{20}H_{21}NO_3F^+$ calculated 342.1500].

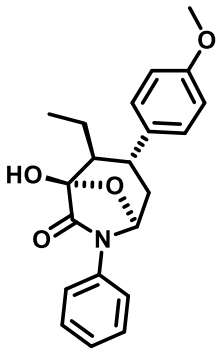



(1R,2S,3R,5S)-2-allyl-1-hydroxy-3,6-diphenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3j**): The general procedure described above was performed on a 0.2 mmol scale; dr = 4:1. Purification

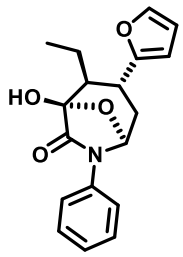
by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 1:5) afforded the bicyclic compound **3j** (51 mg, 76%) as a white amorphous solid. Mp = 145 – 146 °C; Rf (ethyl acetate/petroleum ether, 1:4) = 0.30; HPLC (Chiralpak AZ-H, heptane/ethanol = 60/40, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 10.25 min, $t_{minor}$ = 11.03 min, ee = 98 %; minor diastereomer, $t_{major}$ = 8.61 min, $t_{minor}$ = 7.31 min, ee = 88%; [$\alpha_D^{25°C}$ ($CHCl_3$, *c* = 0.9 M) = + 105.04°; m/z [Found (ES+): $[M+H]^+$ 336.1594, $C_{21}H_{22}NO_3^+$ calculated 336.1591]; NMR $^1H$ (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.38 Hz, 2H), 7.39 (dd, *J* = 8.38, 7.56 Hz, 2H), 7.31 (dd, *J* = 7.56, 7.43 Hz, 2H), 7.23 (t, *J* = 7.02 Hz, 1H), 7.18 (d, *J* = 7.56 Hz, 1H), 7.16 (d, *J* = 7.56 Hz, 2H), 5.99 (s, 1H), 5.67 (m, H), 4.97 (d, *J* = 16.82 Hz, 1H), 4.89 (d, *J* = 10.23 Hz, 1H), 4.31 (s, 1H), 3.33 (dt, *J* = 12.74, 5.06 Hz, 1H), 2.60-2.30 (m, 3H), 2.07 (ddd, *J* = 13.65, 4.39, 1.38 Hz, 1H), 1.94 (m, 1H). NMR $^{13}C$ (100 MHz, $CDCl_3$): δ 169.67 (C), 139.49 (C), 138.59 (CH), 135.76 (C), 129.41 (2CH), 128.60 (2CH), 127.70 (2CH), 126.99 (CH), 125.34 (CH), 118.61 (2CH), 115.99 ($CH_2$), 102.77 (C), 85.66 (CH), 43.37 (CH), 38.06 (CH), 27.90 ($CH_2$), 26.39 ($CH_2$); m/z [Found (ES+): $[M+H]^+$ 336.1591, $C_{21}H_{22}NO_3^+$ calculated 336.1594].




(1R,2S,3R,5S)-1-hydroxy-2-isopropyl-3,6-diphenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3i**): The general procedure described above was performed on a 0.2 mmol scale; dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicyclic compound **3i** (52 mg, 77%) as a white amorphous solid. Mp = 115 – 116 °C; Rf = 0.51 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak IF, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 12.37 min, $t_{minor}$ = 10.69 min, ee = 96 %; [$\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 67; $^1H$ NMR (400 MHz, $CD_2Cl_2$): δ 7.56 (d, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.32 – 7.16 (m, 6H), 5.76 (s, 1H), 4.59 (s, 1H), 3.04 (td, *J* = 11.6, 6.0 Hz, 1H), 2.38 (dd, *J* = 11.9, 1.3 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.15 – 2.00 (m, 2H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.66 (d, *J* = 7.3 Hz, 3H). $^{13}C$ NMR (100 MHz, $CD_2Cl_2$): δ 170.27 (C), 143.54 (C), 136.77 (C), 129.93 (2CH), 129.19 (2CH), 128.75 (2CH), 127.35 (CH), 125.80 (CH), 119.41 (2CH), 102.85 (C), 86.27 (CH), 52.20 (CH), 39.73 (CH), 37.64 ($CH_2$), 27.20 (CH), 21.78 ($CH_3$), 20.44 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 444,2169, $C_{28}H_{30}NO_4^+$ calculated 444,2169].

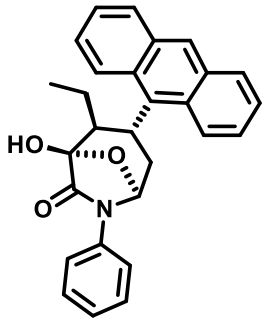


(1R,2S,3R,5S)-2-ethyl-1-hydroxy-3-(4-methoxyphenyl)-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3b**): The general procedure described above was performed on a 0.2 mmol scale; dr = 4:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afford the bicyclic compound **3b** (55 mg, 78%) as a white amorphous solid. Mp = 115 – 116 °C; Rf = 0.48 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak AZ-H, heptane/ethanol = 60/40, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 15.33 min, $t_{minor}$ = 13.85 min, ee = 97 %, minor diastereomer, $t_{major}$ = 11.44 min, $t_{minor}$ = 9.26 min, ee = 82 %; $[\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 66; NMR $^1$H (400 MHz, $CD_2Cl_2$): δ 7.56 (d, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.20 – 7.13 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.92 (s, 1H), 4.37 (s, 1H), 3.76 (s, 1H), 3.21 (dt, *J* = 12.6, 4.9 Hz, 1H), 2.34 (t, *J* = 13.3 Hz, 1H), 2.06 – 2.02 (m, 1H), 1.99 (ddd, *J* = 13.7, 4.7, 1.7 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.27 – 1.16 (m, 1H), 0.58 (t, *J* = 7.5 Hz, 1H). NMR $^{13}$C (100 MHz, $CD_2Cl_2$): δ 171.03 (C), 158.98 (C), 136.58 (C), 132.62 (C), 129.87 (2CH), 129.19 (2CH), 125.71 (CH), 119.12 (2CH), 114.28 (2CH), 103.20 (C), 86.30 (CH), 55.71 (CH), 45.92 (CH), 37.95 (CH), 27.19 ($CH_2$), 16.79 ($CH_2$), 15.09 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 354.1700, $C_{21}H_{24}NO_4^+$ calculated 354.1700].



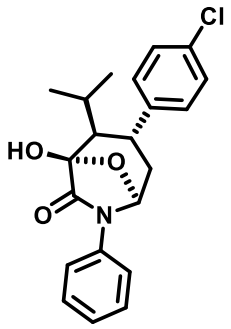
(1R,2S,3R,5S)-2-ethyl-3-(furan-2-yl)-1-hydroxy-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3e**): The general procedure described above was performed on a 0.2 mmol scale; dr = 4:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicyclic compound **3e** (55 mg, 88%) as a white amorphous solid. Mp =

114 – 115 °C; Rf = 0.45 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak AD-H, heptane/ethanol = 60/40, flow rate = 2.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 33.84 min, $t_{minor}$ = 9.79 min, ee = 97 %, minor diastereomer, $t_{major}$ = 8.34 min, $t_{minor}$ = 14.61 min, ee = 85 %; $[\alpha_D]^{22}$ ($CHCl_3$, *c* = 1.06) = + 41; NMR $^1$H (400 MHz, $CD_2Cl_2$): δ 7.57 – 7.55 (m, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 1.7 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.90 (s, 1H), 4.18 (s, 1H), 3.29 (dt, *J* = 12.2, 5.1 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.16 – 2.12 (m, 1H), 2.03 (ddd, *J* = 13.9, 4.9, 1.8 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.34 – 1.23 (m, 1H), 0.61 (t, *J* = 7.6 Hz, 3H). NMR $^{13}$C (100 MHz, $CD_2Cl_2$): δ 170.58 (C), 155.04 (C), 141.92 (CH), 163.43 (C), 129.94 (2CH), 125.85 (CH), 119.21 (2CH), 110.77 (CH), 106.67 (CH), 102.48 (C), 86.10 (CH), 44.02 (CH), 33.40 (CH), 26.33 ($CH_2$), 17.24 ($CH_2$), 14.19 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 314.1388, $C_{18}H_{20}NO_4^+$ calculated 314.1387].



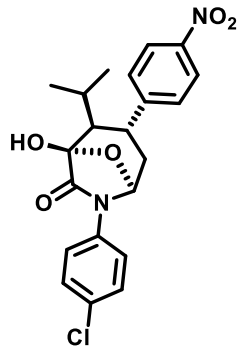

(1R,2S,3R,5S)-3-(anthracen-9-yl)-2-ethyl-1-hydroxy-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3d**): The general procedure described above was performed on a 0.2 mmol scale, dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicyclic compound **3d** (60 mg, 71%) as a white amorphous solid. Mp = 139 – 140 °C; Rf = 0.31 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak AD-H, heptane/ethanol = 60/40, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 21.54 min, $t_{minor}$ = 14.34 min, ee = 95 %; $[\alpha_D]^{22}$ ($CHCl_3$, *c* = 1.06) = + 135; NMR $^1$H (500 MHz, $CD_2Cl_2$): δ 8.80 (d, *J* = 9.0 Hz, 1H), 8.43 (s, 1H), 8.15 – 8.11 (m, 1H), 8.09 – 8.04 (m, 1H), 8.00 (dq, *J* = 6.5, 3.1 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.59 (ddd, *J* = 9.0, 6.5, 1.4 Hz, 1H), 7.52 – 7.45 (m, 3H), 7.43 (dq, *J* = 6.5, 3.3 Hz, 2H), 7.29 – 7.24 (m, 1H), 6.07 (d, *J* = 1.3 Hz, 1H), 4.41 – 4.35 (m, 1H), 4.36 (s, 1H), 3.16 (ddd, *J* = 11.4, 7.0, 4.7 Hz, 1H), 3.05 (ddd, *J* = 14.3, 11.6, 2.6 Hz, 1H), 2.24 (ddd, *J* = 14.5, 7.0, 0.9 Hz, 1H), 1.84 – 1.71 (m, 1H), 1.12 (dqd, *J* = 15.1, 7.6, 4.7 Hz, 1H), 0.46 (t, *J* = 7.5 Hz, 3H). NMR $^{13}$C (126 MHz, $CD_2Cl_2$): δ 169.32 (C), 136.70 (C), 133.27 (C), 132.90 (C), 132.03 (C), 131.42 (C), 130.67 (CH), 130.14 (2CH), 130.03 (CH), 129.84 (C), 128.46

(CH), 127.12 (CH), 126.23 (CH), 126.20 (CH), 125.79 (CH), 125.36 (CH), 125.26 (CH), 123.71 (CH), 120.04 (CH), 103.47 (C), 87.39 (CH), 47.49 (CH), 36.69 (CH), 33.00 ($CH_2$), 23.77 ($CH_2$), 13.93 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 424.1904, $C_{28}H_{26}NO_3^+$ calculated 424.1907].



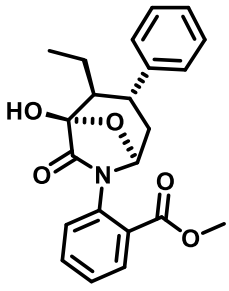

(1R,2S,3R,5S)-3-(4-chlorophenyl)-1-hydroxy-2-isopropyl-6-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3c**): The general procedure described above was performed on a 0.2 mmol scale, dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicyclic compound **3c** (66 mg, 89%) as a white amorphous solid. Mp = 182 – 183 °C; Rf = 0.5 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak IE, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 8.72 min, $t_{minor}$ = 9.89 min, ee = 94 %; $[a]_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 29; NMR $^1H$ (400 MHz, $CD_2Cl_2$): δ 7.59 – 7.56 (m, 2H), 7.44 – 7.38 (m, 2H), 7.30 – 7.28 (m, 2H), 7.23 – 7.20 (m, 3H), 5.77 (s, 1H), 4.20 (s, 1H), 3.04 (td, *J* = 11.6, 5.9 Hz, 1H), 2.32 (dd, *J* = 11.9, 1.6 Hz, 1H), 2.19 (ddd, *J* = 14.0, 5.8, 1.5 Hz, 1H), 2.12 – 2.00 (m, 2H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.67 (d, *J* = 7.3 Hz, 3H). NMR $^{13}C$ (100 MHz, $CD_2Cl_2$): δ 169.90 (C), 142.15 (C), 136.73 (C), 132.90 (C), 130.16 (2CH), 129.97 (2CH), 129.31 (2CH), 125.82 (CH), 119.29 (2CH), 102.54 (C), 86.12 (CH), 52.19 (CH), 39.18 (CH), 37.51 ($CH_2$), 27.17 (CH), 21.89 ($CH_3$), 20.38 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 372.1357, $C_{21}H_{23}NO_3Cl^+$ calculated 372.1361].

**Gram-scale experiment :** 3 mmol of α-ketoamide as SM, yield 93% (1.03 g of **3c**) with same ee and dr.



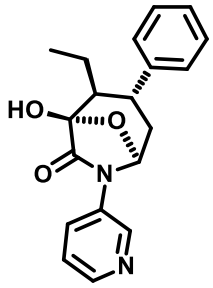
(1R,2S,3R,5S)-6-(4-chlorophenyl)-1-hydroxy-2-isopropyl-3-(4-nitrophenyl)-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3p**): The general procedure described above was performed on a 0.2 mmol scale, dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 30:70) afforded the bicyclic compound **3p** (74 mg, 89%) as a white amorphous solid. Mp = 197 – 198 °C; Rf = 0.58 (ethyl acetate/petroleum ether 30/70); HPLC (Chiralpak IF, heptane/ethanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 12.47 min, $t_{minor}$ = 10.23 min, ee = 96%; $[\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 78; $^1$H NMR (400 MHz, $CD_2Cl_2$): $^1$H NMR (400 MHz, $CD_2Cl_2$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.59 – 7.49 (m, 2H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.41 – 7.36 (m, 2H), 5.78 (s, 1H), 4.35 (s, 1H), 3.15 (td, *J* = 11.6, 6.0 Hz, 1H), 2.41 (dd, *J* = 11.9, 1.7 Hz, 1H), 2.23 – 1.91 (m, 2H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.66 (d, *J* = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ 169.88 (C), 151.01 (C), 147.57 (C), 135.12 (C), 131.02 (C), 130.02 (2CH), 129.67 (2CH), 124.53 (2CH), 120.33 (2CH), 102.50 (C), 85.80 (CH), 51.82 (CH), 39.71 (CH), 36.95 ($CH_2$), 27.32 (CH), 22.03 ($CH_3$), 20.36 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 417.1209, $C_{21}H_{22}N_2O_5Cl^+$ calculated 417.1212].

**Gram-scale experiment :** 3 mmol of α-ketoamide as SM, yield 92% (1.15 g of **p**) with same ee and dr.

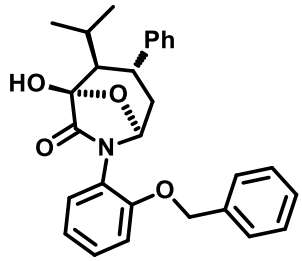


methyl 2-((1R,2S,3R,5S)-2-ethyl-1-hydroxy-7-oxo-3-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-6-yl)benzoate (**3n**): The general procedure described above was performed on a 0.2 mmol scale, dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 40:60) afforded the bicyclic compound **3n** (39 mg, 51%) as a colorless oil; Rf

= 0.15 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak IA, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 15.68 min, $t_{minor}$ = 13.41 min, ee = 92 %, [$\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 34; $^1$H NMR (400 MHz, $CD_2Cl_2$): $^1$H NMR (400 MHz, $CD_2Cl_2$) δ 8.00 – 7.91 (m, 1H), 7.63 (td, J = 7.7, 1.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.36 – 7.31 (m, 5H), 7.27 – 7.20 (m, 1H), 5.65 (s, 1H), 4.62 (s, 1H), 3.83 (s, 3H), 3.12 (dd, *J* = 20.1, 8.8 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.08 – 2.00 (m, 2H), 1.63 (dt, *J* = 14.7, 7.3 Hz, 1H), 1.27 (dqd, *J* = 14.9, 7.5, 3.8 Hz, 1H), 0.79 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ 169.99 (C), 166.65 (C), 143.31 (C), 134.69 (C), 133.60 (C), 132.14 (C), 129.21 (2CH), 128.91 (C), 128.77 (2CH), 128.53 (CH), 127.39 (CH), 127.13 (CH), 102.51 (C), 88.56 (CH), 53.04 ($CH_3$), 48.80 (CH), 43.70 (CH), 37.72 ($CH_2$), 21.95 ($CH_2$), 14.14 ($CH_3$); m/z [Found (ES+): $[M+NH_4]^+$ 382.1650, $C_{22}H_{24}NO_5^+$ calculated 382.1649].




(1R,2S,3R,5S)-2-ethyl-1-hydroxy-3-phenyl-6-(pyridin-2-yl)-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3o**): The general procedure described above was performed on a 0.2 mmol scale; dr = 4:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 60:40) afforded the bicyclic compound **3o** (55 mg, 85%) as a white amorphous solid. Mp = 95 – 96 °C; Rf = 0.4 (ethyl acetate/petroleum ether 60/40); HPLC (Chiralpak IA, heptane/ethanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 9.93 min, $t_{minor}$ = 13.61 min, ee = 88 %, minor diastereomer, $t_{major}$ = 19.55 min, $t_{minor}$ = 12.13 min, ee = 84 %; [$\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 36; $^1$H NMR (400 MHz, $CD_2Cl_2$) δ 8.77 (d, *J* = 2.5 Hz, 1H), 8.42 – 8.38 (m, 1H), 8.04 (ddd, *J* = 8.4, 2.6, 1.4 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.22 (dt, *J* = 14.6, 6.8 Hz, 3H), 5.85 (s, 1H), 5.35 (s, 1H), 2.63 (td, *J* = 10.9, 7.1 Hz, 1H), 2.24 – 2.08 (m, 3H), 1.68 – 1.61 (m, 1H), 1.27 – 1.12 (m, 1H), 0.78 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ 170.02 (C), 146.30 (CH), 142.51 (C), 140.03 (CH), 133.74 (C), 129.23 (CH x2), 128.67 (CH x2), 127.53 (CH), 126.14 (CH), 124.52 (CH), 102.74 (C), 85.75 (CH), 48.28 (CH), 43.64 (CH), 36.69 ($CH_2$), 21.74 ($CH_2$), 14.14 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 325.1545, $C_{19}H_{21}N_2O_3^+$ calculated 325.1547].

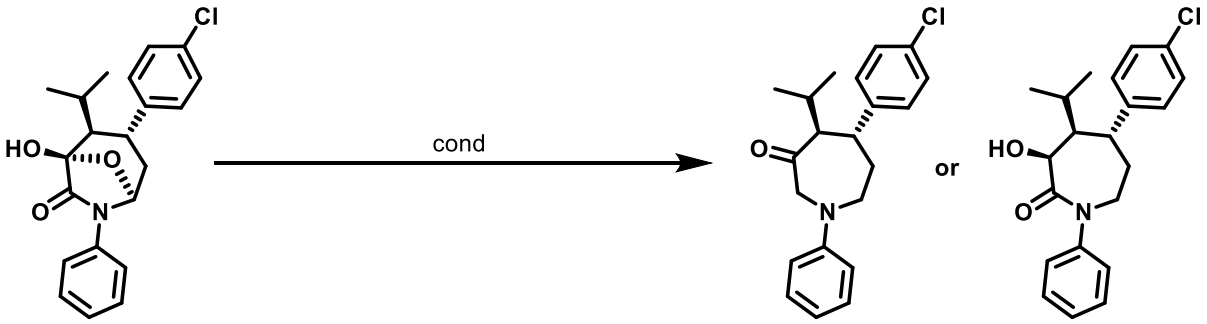



(1R,2S,3R,5S)-6-(2-(benzyloxy)phenyl)-1-hydroxy-2-isopropyl-3-phenyl-8-oxa-6-azabicyclo[3.2.1]octan-7-one (**3m**): The general procedure described above was performed on a 0.2 mmol scale; dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 10:90 then 40:60) afforded the bicyclic compound **3m** (48 mg, 46%) as a white amorphous solid. Mp = 173 – 174 °C; Rf = 0.21 (ethyl acetate/petroleum ether 40/60); HPLC (Chiralpak ID, heptane/ethanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 8.32 min, $t_{minor}$ = 9.97 min, ee = 95 %; $[\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 53; $^1$H NMR(400 MHz, $CD_2Cl_2$): 7.46 (d, *J* = 7.2 Hz, 1H), 7.42 – 7.22 (m, 7H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 7.09 – 7.00 (m, 2H), 5.65 (s, 1H), 5.18 (d, *J* = 1.5 Hz, 2H), 4.37 (s, 1H), 3.41 – 3.31 (m, 1H), 2.34 (dd, *J* = 11.9, 1.5 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.95 (s, 1H), 1.93 (dd, *J* = 3.8, 1.8 Hz, 1H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.65 (d, *J* = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ 170.80 (C), 154.51 (C), 144.11 (C), 137.00 (C), 129.91 (CH), 129.28 (CH x2), 129.05 (CH x2), 128.76 (CH x2), 128.51 (CH), 128.11 (CH x2), 127.09 (CH), 124.33 (C), 121.89 (CH), 114.35 (CH), 102.05 (C), 88.05 (CH), 71.16 ($CH_2$), 52.72 (CH), 39.76 (CH), 38.06 ($CH_2$), 27.31 (CH), 21.66 ($CH_3$), 20.67 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 444.2168, $C_{28}H_{30}NO_4^+$ calculated 444.2169].

### *c. Ring opening of bicyclic compounds 3 and access to azepanes derivatives:*

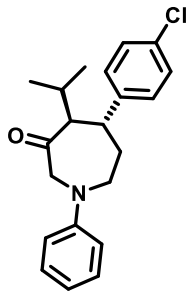
## Compound 4a, 4b, 4e

The reduction reaction optimization key entries are showed here. Reactions with LAH were only monitored by TLC. Isolated yields for reactions with $BH_3$.THF complex (as described in the following procedures for reduction).




3c 4a 4b

| Entry | Solvent | Reducing agent | equivalents | T (°C) | T(h) | Yield |
|---|---|---|---|---|---|---|
| 1 | THF | LAH | 2.00 | 0 | | (degradation) |
| 2 | THF | LAH | 2.00 | rt | | (degradation) |
| 3 | THF | $BH_3$.THF | 1.05 | rt | | 0% (no reaction) |
| 4 | THF | $BH_3$.THF | 1.05 | reflux | 3 | 37% **4a** |
| 5 | THF | $BH_3$.THF | 1.05 | reflux | 15 | 78% **4a** |
| 6 | THF | $BH_3$.THF | 3 | reflux | 15 | 89% **4b** |



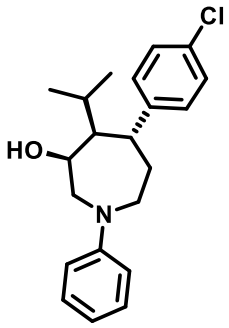

(4S,5R)-5-(4-chlorophenyl)-4-isopropyl-1-phenylazepan-3-one (**4a**): $BH_3$.THF complex 1M solution in THF (1.05 equiv, 210 µL, 0.21 mmol) was added to a stirred solution of the bicyclic compound **3c** (1 equiv, 74.4 mg, 0.2 mmol) in dry THF (1 mL, 0.2 M) at rt, under argon and in a sealed tube. The reaction was refluxed for 15 h in the sealed tube (bath temperature 95°C) After reaction completion, the reaction mixture was carefully quenched by dropwise addition of $H_2O$ (2 mL). $K_2CO_3$ (7 equiv per mole of $BH_3$.THF, 203 mg, 1.47 mmol) was added and the reaction was stirred at room temperature for 15 min. The reaction mixture was extracted with 20% EtOH in EtOAc (4x3 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 0:100 then 5:95) afforded the azepane **4a** (53 mg, 78%) as a colorless oil, dr > 20:1. Rf = 0.7 (ethyl acetate/petroleum ether 10/90); HPLC (Chiralpak IE, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 6.85 min, $t_{minor}$ = 4.41 min, ee = 94 %; $\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 37. NMR $^1$H (400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.9 Hz, 2H), 7.26 – 7.24 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.88 (t, *J* = 8.5 Hz, 3H), 4.07 (d, *J* = 18.1 Hz, 1H), 3.87 (d, *J* = 18.0 Hz, 1H), 3.41 (ddd, *J* = 12.9, 8.4, 4.4 Hz, 1H), 3.19 – 3.12 (m, 2H), 2.96 (td, *J* = 7.6, 3.6 Hz, 1H), 2.11 – 1.96 (m, 1H), 1.93 – 1.85 (m, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); NMR $^{13}$C (100 MHz, $CDCl_3$): δ 214.40 (C), 149.61 (C), 143.62 (C), 132.22 (C), 129.66 (2CH), 129.21 (2CH), 128.95 (2CH), 119.17 (CH), 114.51 (2CH), 61.71 ($CH_2$), 60.36 (CH), 47.95 ($CH_2$), 44.31 (CH), 34.98 ($CH_2$), 29.41 (CH), 21.13 ($CH_3$), 20.72 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 342.1619, $C_{21}H_{25}NOCl^+$ calculated 342.1619].

**General procedure for the reduction of bicyclic compounds to azepanols:**

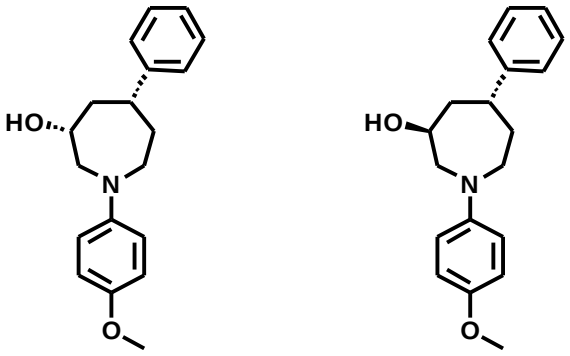
$BH_3$.THF complex 1M solution in THF (3 equiv, 600 µL, 0.6 mmol) was added to a stirred solution of the bicyclic compound (1 equiv, 74.4 mg, 0.2 mmol) in dry THF (1 mL) at rt under argon and in a sealed tube. The reaction was then refluxed for 15 h in the sealed tube ( bath temperature 95°C) After completion, the reaction mixture was carefully quenched dropwise

with $H_2O$ (2 mL). $K_2CO_3$ (7equiv per mol of $BH_3$.THF complex, 581 mg, 4.2 mmol) was added and the reaction was stirred at rt for 15 min. The reaction mixture was extracted with 20% ethanol in EtOAc (4x3 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated in vacuo. Purification over silica gel petroleum ether/EtOAc gradient 100:0 to 95:5) afforded the azepanols.

***Azepan-3-ol derivatives were found to be sensitive on silica gel. Azepan-3-ol derivatives decomposed rapidly in solution. Decomposition rate observed : $CDCl_3$ > $CD_2Cl_2$ > $C_6D_6$ (best observed stability). Azepan-3-ol derivatives can be kept for more than one month neat and at –20 °C.***

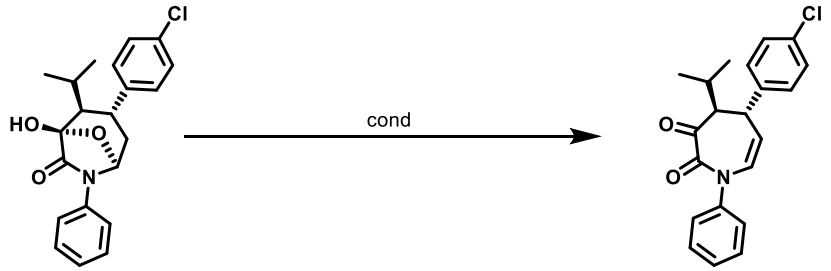



(3S,4S,5R)-5-(4-chlorophenyl)-4-isopropyl-1-phenylazepan-3-ol (**4b**): The general procedure described above was performed on a 0.2 mmol scale; crude dr > 20:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 0:100 then 5:95) afforded the bicyclic compound **4b** (61 mg, 89%) as a colorless oil; Rf = 0.51 (ethyl acetate/petroleum ether 10/90); HPLC (Chiralpak IA, heptane/ethanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 8.60 min, $t_{minor}$ = 4.30 min, ee = 94 %; $[\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 57; $^1$H NMR (400 MHz, $C_6D_6$) δ 7.32 – 7.24 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 3.98 – 3.89 (m, 1H), 3.29 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.20 (td, *J* = 12.3, 11.5, 3.5 Hz, 1H), 3.09 (dt, *J* = 13.1, 3.9 Hz, 1H), 3.01 (dd, *J* = 14.2, 2.3 Hz, 1H), 2.74 (td, *J* = 10.8, 3.3 Hz, 1H), 1.64 – 1.47 (m, 2H), 1.41 – 1.32 (m, 2H), 1.28 (ddd, *J* = 11.4, 3.0, 1.5 Hz, 1H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (101 MHz, $C_6D_6$) δ 151.03 (C), 145.56 (C), 131.60 (C), 129.37 (2CH), 129.08 (2CH), 128.77 (2CH), 117.48 (CH), 113.11 (2CH), 67.75 (CH), 54.73 ($CH_2$), 52.46 (CH), 47.47 ($CH_2$), 42.19 (CH), 37.87 ($CH_2$), 29.01 (CH), 22.00 ($CH_3$), 17.46 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 344.1776, $C_{21}H_{27}NOCl^+$ calculated 344.1776].



This compound was isolated as a 1:1 mixture of two diastereomers (inseparable) (**4e**): (3R,5R)-1-(4-methoxyphenyl)-5-phenylazepan-3-ol and (3S,5R)-1-(4-methoxyphenyl)-5-phenylazepan-3-ol : The general procedure described above was performed on a 0.2 mmol scale or on a 1 mmol scale; crude dr = 1:1. Purification by flash chromatography (silica gel, eluent: ethyl acetate/petroleum ether, 0:100 then 5:95) afforded the azepane derivative (**4e**) (on 0.2 mmol scale, 54 mg, 91%) (on a 1 mmol scale, 283 mg, 95%) as a colorless oil; Rf = 0.34 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak IA, heptane/ethanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm): diastereomer 1, $t_{major}$ = 17.12 min, $t_{minor}$ = 21.78 min, ee = 97 %, diastereomer 2, $t_{major}$ = 8.13 min, $t_{minor}$ = 6.77 min, ee = 97 %; $\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 36; $^1$H NMR (500 MHz, $CDCl_3$): 7.20 – 7.13 (m, 4H), 7.07 (dd, *J* = 15.8, 7.6 Hz, 2H), 7.02 (d, *J* = 7.3 Hz, 2H), 6.91 (dd, *J* = 16.8, 7.9 Hz, 6H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 3.91 (br s, 1H), 3.73 (br s, 1H), 3.60 (dd, *J* = 14.3, 4.0 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 3.34 (dd, *J* = 15.1, 3.1 Hz, 1H), 3.26 – 3.15 (m, 2H), 3.15 – 3.02 (m, 2H), 2.94 – 2.82 (m, 3H), 2.43 (t, *J* = 11.2 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 1H), 1.84 (d, *J* = 13.4 Hz, 3H), 1.77 – 1.57 (m, 4H), 1.56 – 1.49 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 152.73 (C dia1), 152.09 (C dia2), 149.15 (C dia1), 148.79 (C dia2), 145.27 (C dia1), 144.32 (C dia2), 128.81 (2CHdia1), 128.78 (2CHdia2), 126.99 (2CH dia1), 126.90 (2CH dia2), 126.24 (CH dia1), 126.19 (CH dia2), 115.47 (2CH dia1), 115.23 (2CH dia2), 114.79 (2CH dia1), 113.40 (2CH dia2), 70.20 ($CH_3$ dia1), 67.93 ($CH_3$ dia2), 56.98 ($CH_2$ dia1), 55.49 ($CH_2$ dia2), 55.45 (CH dia1), 55.39 (CH dia2), 50.18 ($CH_2$ dia1), 48.99 ($CH_2$ dia2), 45.54 ($CH_2$ dia1), 45.51 ($CH_2$ dia2), 40.68 (CH dia1), 38.38 (CH dia1), 36.55 ($CH_2$ dia1), 36.46 ($CH_2$ dia2); m/z [Found (ES+): $[M+H]^+$ 298.1801, $C_{19}H_{24}NO_2^+$ calculated 298.1802].

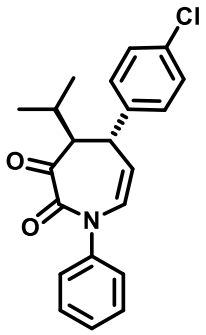
**Optimization of the remote dehydration (Synthesis of compound 4c, 4d)**



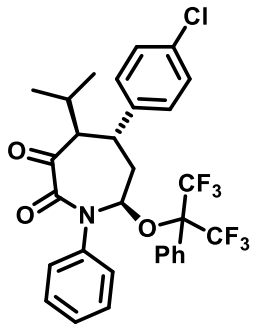

3c 4c

| Entry | Solvent | "Dehydrating agent" | eq | T (°C) | T(h) | Yield 4d (%) |
|---|---|---|---|---|---|---|
| 1 | THF | Burgess reagent | 2 | reflux | overnight | 0 (degradation) |
| 2 | $CH_2Cl_2$ | $BF_3.Et_2O$ | 2 | rt | overnight | 0 (No reaction, SM recovered) |
| 3 | $CH_2Cl_2$ | $BF_3.Et_2O$ | 2 | reflux | overnight | 0 (No reaction, SM recovered) |
| 4 | $CH_2Cl_2$ | $TiCl_4$ | 2 | rt | 4h | 0 (unidentified byproducts) |
| 5 | $CH_2Cl_2$ | TsOH | 2 | rt | overnight | 0 (SM recovered+ slight degradation) |
| 6 | $CH_2Cl_2$ | $CF_3SO_3H$ | 1 | rt | overnight | 0 (extensive degradation) |
| 7 | $CH_2Cl_2$ | $SOCl_2$ | 2 | rt | overnight | <10 (+SM recovered) |
| 8 | $CH_2Cl_2$ | $SOCl_2$ | 2 | reflux | overnight | <10 (+SM recovered) |
| 9 | $CH_2Cl_2$ | $SOCl_2$ + 2eq pyridine | 2 | reflux | overnight | <10 (+SM recovered) |
| 10 | dioxane | $SOCl_2$ | 2 | rt | overnight | 0 (SM recovered) |
| 11 | dioxane | $SOCl_2$ | 2 | reflux | overnight | 0 (SM recovered) |
| 12 | dioxane | $SOCl_2$ + 2eq pyridine | 2 | reflux | overnight | 0 (SM recovered) |
| 13 | $CH_2Cl_2$ | Martin sulfurane | 1.3 | rt | 2h | 62% |

***Note: the Martin sulfurane dehydrating agent must be handled in a glove box.***




(4S,5R)-5-(4-chlorophenyl)-4-isopropyl-1-phenyl-4,5-dihydro-1H-azepine-2,3-dione (**4c**): Martin's sulfurane (1.3 equiv, 174.9 mg, 0.26 mmol) was added to a stirred solution of the bicyclic compound (**3c**) (1.0 equiv, 74.4 mg, 0.2 mmol) in dry $CH_2Cl_2$ (2 mL) at rt under argon in a sealed tube. The reaction was stirred for 3 h at rt. After completion, solvent was evaporated and the crude product was purified over silica gel (eluent: petroleum ether/EtOAc gradient 100:0 to 95:5) to give the enamide (44 mg, 62%) as white solid; Rf = 0.6 (ethyl acetate/petroleum ether 30/70); HPLC (Chiralpak IF, heptane/ethanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm): $t_{major}$ = 9.15 min, $t_{minor}$ = 7.39 min, ee = 97 %; $\alpha_D^{22}$ ($CHCl_3$, *c* = 1.06) = + 82; $^1$H NMR (400 MHz, $CD_2Cl_2$): δ 7.48 – 7.42 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 4H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.12 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.90 – 5.85 (m, 1H), 4.32 – 4.08 (m, 1H), 3.11 (d, *J* = 4.5 Hz, 1H), 1.72 – 1.58 (m, 1H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$) δ 202.96 (C), 167.92 (C), 139.60 (C), 138.86 (C), 133.68 (C), 129.92 (2CH), 129.76 (2CH), 129.64 (2CH), 129.35 (CH), 128.46 (CH), 127.97 (CH), 125.41 (2CH), 71.75 (CH), 42.30 (CH), 29.71 (CH), 21.85 ($CH_3$), 17.45 ($CH_3$); m/z [Found (ES+): $[M+H]^+$ 354.1255, $C_{21}H_{21}ClNO_2^+$ calculated 354.1255].



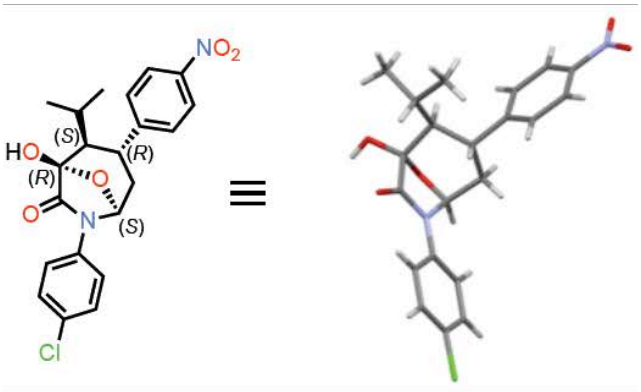

(4S,5R,7R)-5-(4-chlorophenyl)-7-((1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-yl)oxy)-4-isopropyl-1-phenylazepan-3-one (**4d**): Martin's sulfurane (1.3 equiv, 174.9 mg, 0.26 mmol) was adde to a stirred solution of the bicyclic compound (4e) (1equiv, 74.4 mg, 0.2 mmol) and 1,1,1,3,3,3-Hexafluoro-2-phenyl-2-propanol (2 equiv, 67 μg, 0.4 mmol) in dry $CH_2Cl_2$ (2 mL)

at rt under argon in a sealed tube. The reaction was stirred for 3 h at rt. After completion, solvent was evaporated and the crude product was purified over silica gel (eluent: petroleum ether/EtOAc gradient 100:0 to 95:5) to give the enamide (95 mg, 81%) as colorless oil; Rf = 0.51 (ethyl acetate/petroleum ether 20/80); HPLC (Chiralpak IE, heptane/ethanol = 95/5, flow rate = 1.0 mL/min, λ = 254 nm): major diastereomer, $t_{major}$ = 10.33 min, $t_{minor}$ = 8.41 min, ee = 94 %, minor diastereomer, $t_{major}$ = 12.92 min, $t_{minor}$ = 12.24 min, ee = 94 %; $\alpha^{22}$ ($CHCl_3$, *c* = 1.06) = + 95; $^1$H NMR (400 MHz, $CD_2Cl_2$): δ 7.58 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.41 – 7.34 (m, 4H), 7.33 – 7.21 (m, 5H), 6.93 (d, *J* = 7.6 Hz, 2H), 5.40 (d, *J* = 6.2 Hz, 1H), 3.68 (td, *J* = 11.9, 3.4 Hz, 1H), 3.11 (dd, *J* = 11.7, 3.3 Hz, 1H), 2.65 (ddd, *J* = 14.6, 6.3, 3.5 Hz, 1H), 2.38 (dd, *J* = 14.4, 12.5 Hz, 1H), 1.62 (ddp, *J* = 10.3, 7.0, 3.3 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H). $^{13}$C NMR (101 MHz, $CD_2Cl_2$) δ 201.13 (C), 169.46 (C), 141.14 (C), 139.47 (C), 133.28 (C), 131.36 (CH), 129.64 (2CH), 129.33 (4CH), 129.30 (2CH), 128.78 (2CH), 127.78 (CH), 127.26 (C), 125.59 (2CH), 122.82 (q, *J* = 289.8 Hz, $CF_3$), 122.34 (q, *J* = 288.8 Hz, $CF_3$), 86.19 (CH), 84.41 (h, *J* = 29 Hz, C), 58.24 (CH),45.30 ($CH_2$), 40.27 (CH), 28.13 (CH), 20.70 ($CH_3$), 16.72 ($CH_3$). m/z [Found (ES+): $[M+H]^+$ 598.1578, $C_{30}H_{27}ClF_6NO_3^+$ calculated 598.1578].

COSY, HSQC and NOESY analysis are available for this compound at the end of this supporting information.

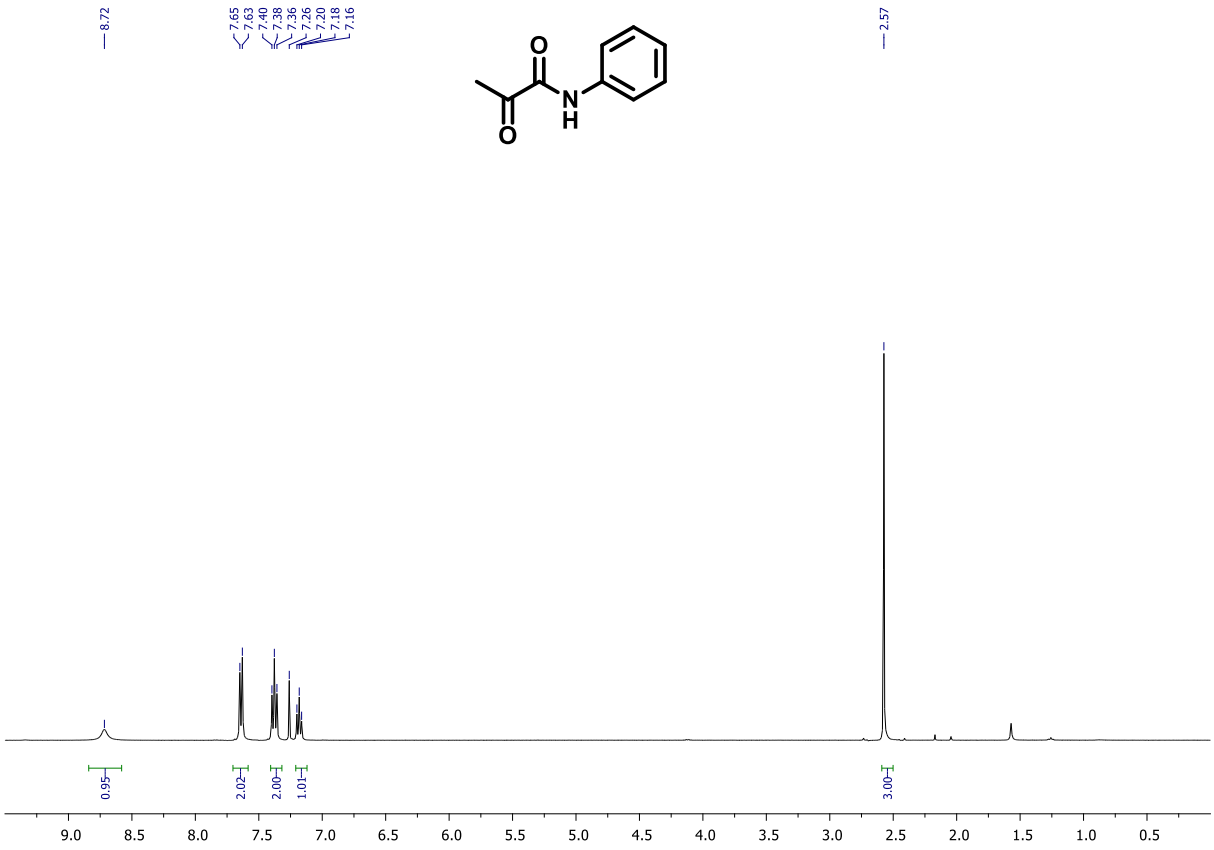
## 4. X-ray analysis

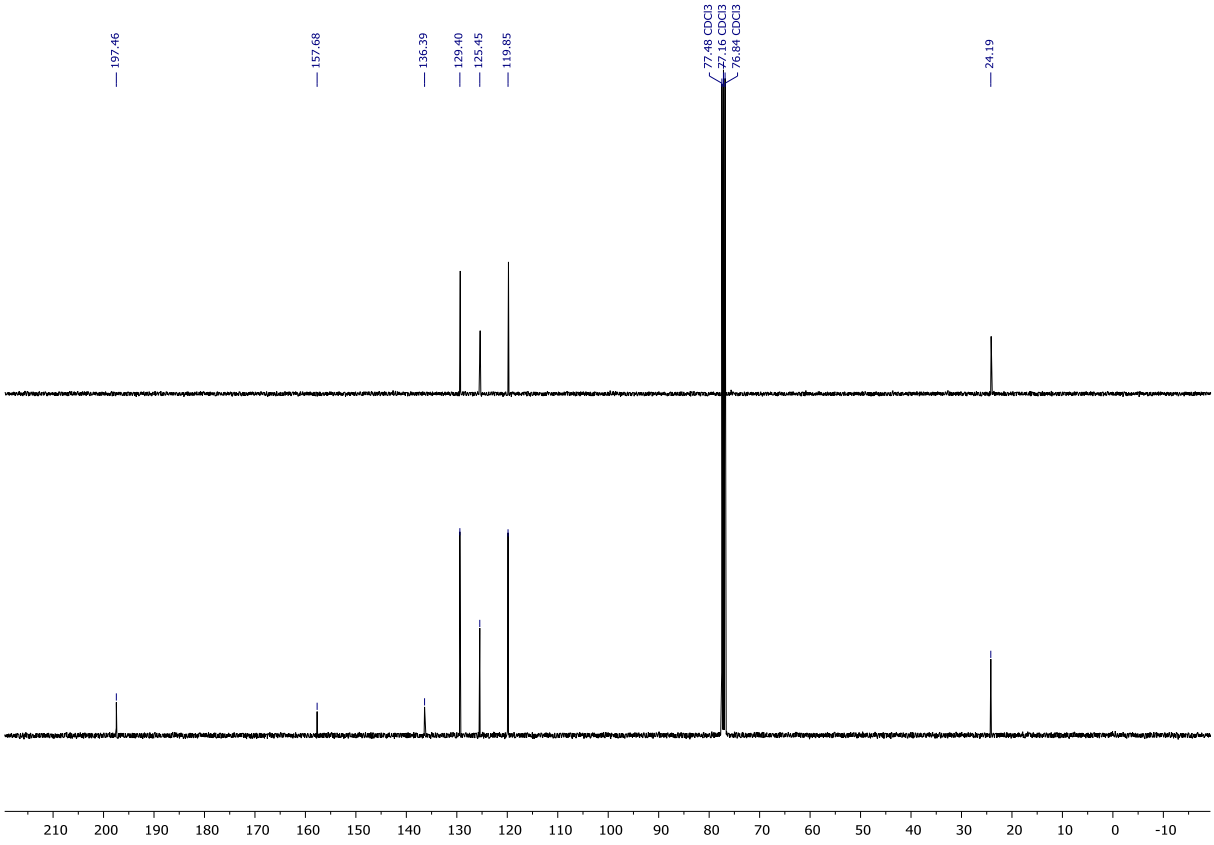
X-ray diffraction analysis has been done establishing the relative and absolute configurations for the compound **3p**.




CCDC 1015393 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## 5. NMR of ketoamides




197.46
157.68
136.39
129.40
125.45
119.85
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
24.19
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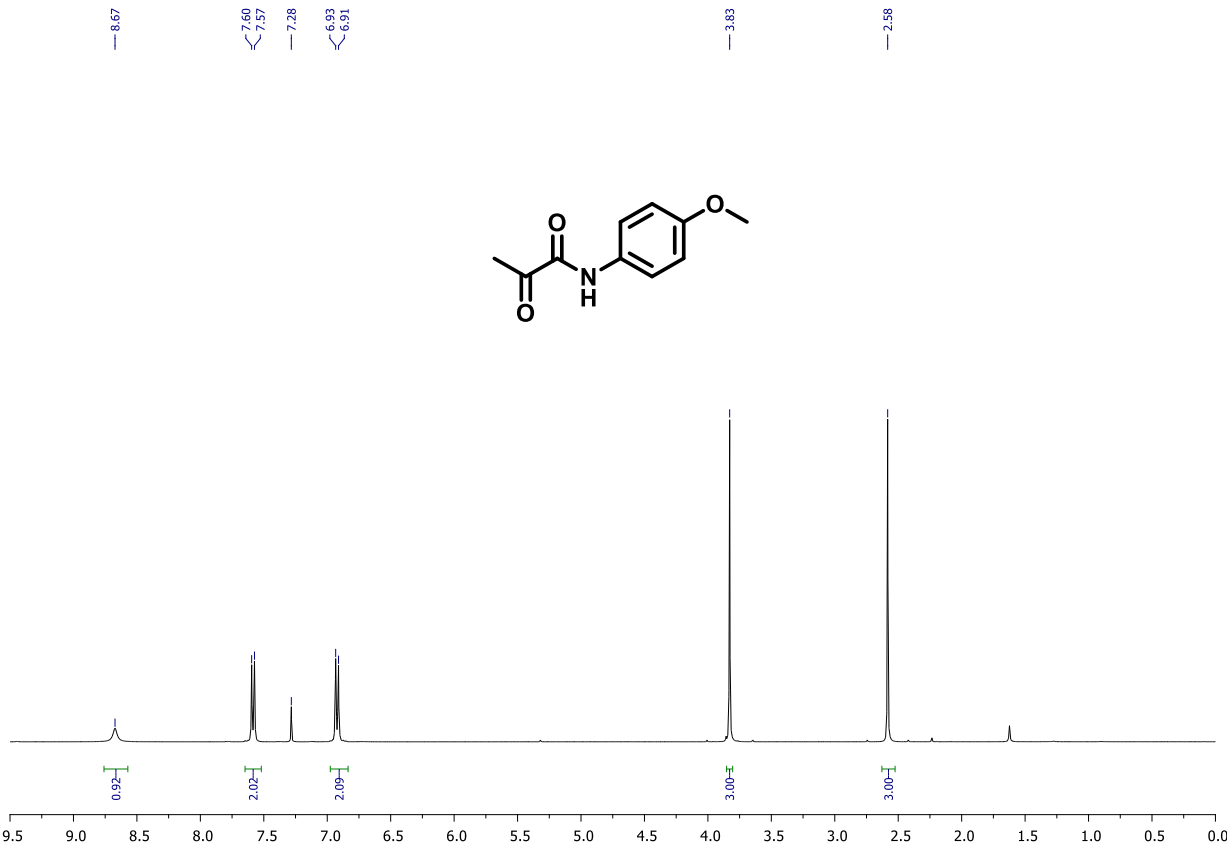
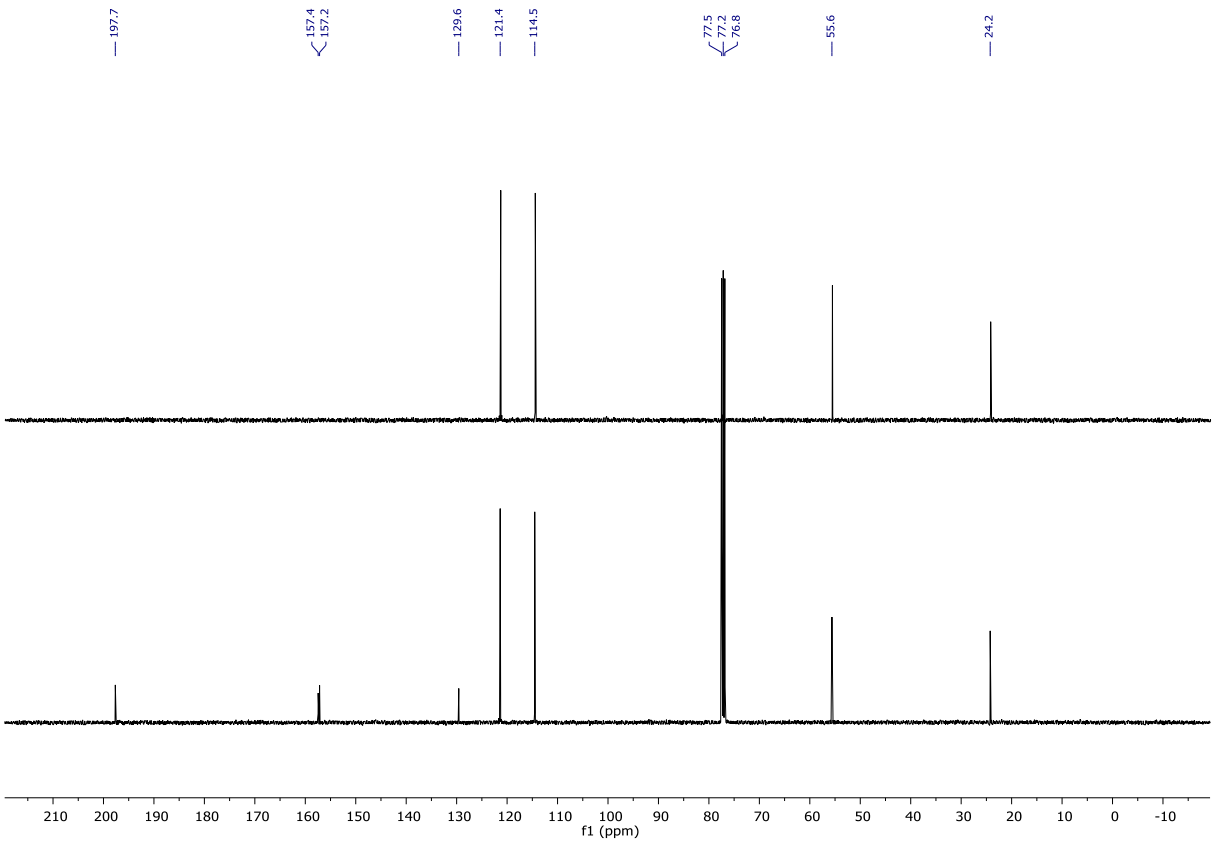

8.67
7.60
7.57
7.28
6.93
6.91
3.83
2.58
O
O
N
H
O
0.92
2.02
2.09
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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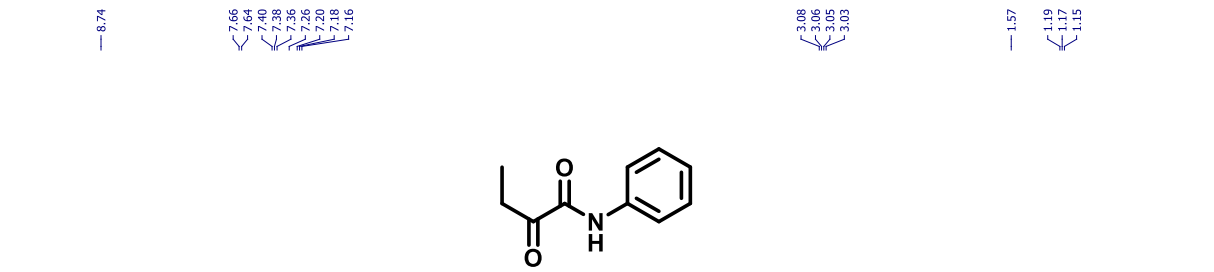
157.2
129.6
121.4
114.5
77.5
77.2
76.8
55.6
24.2
f1 (ppm)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7.36
7.26
7.20
7.18
7.16
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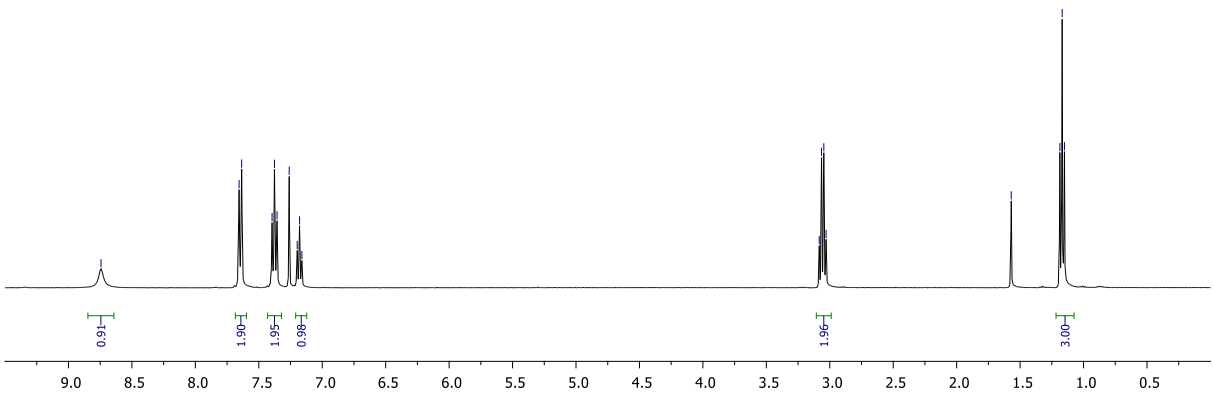
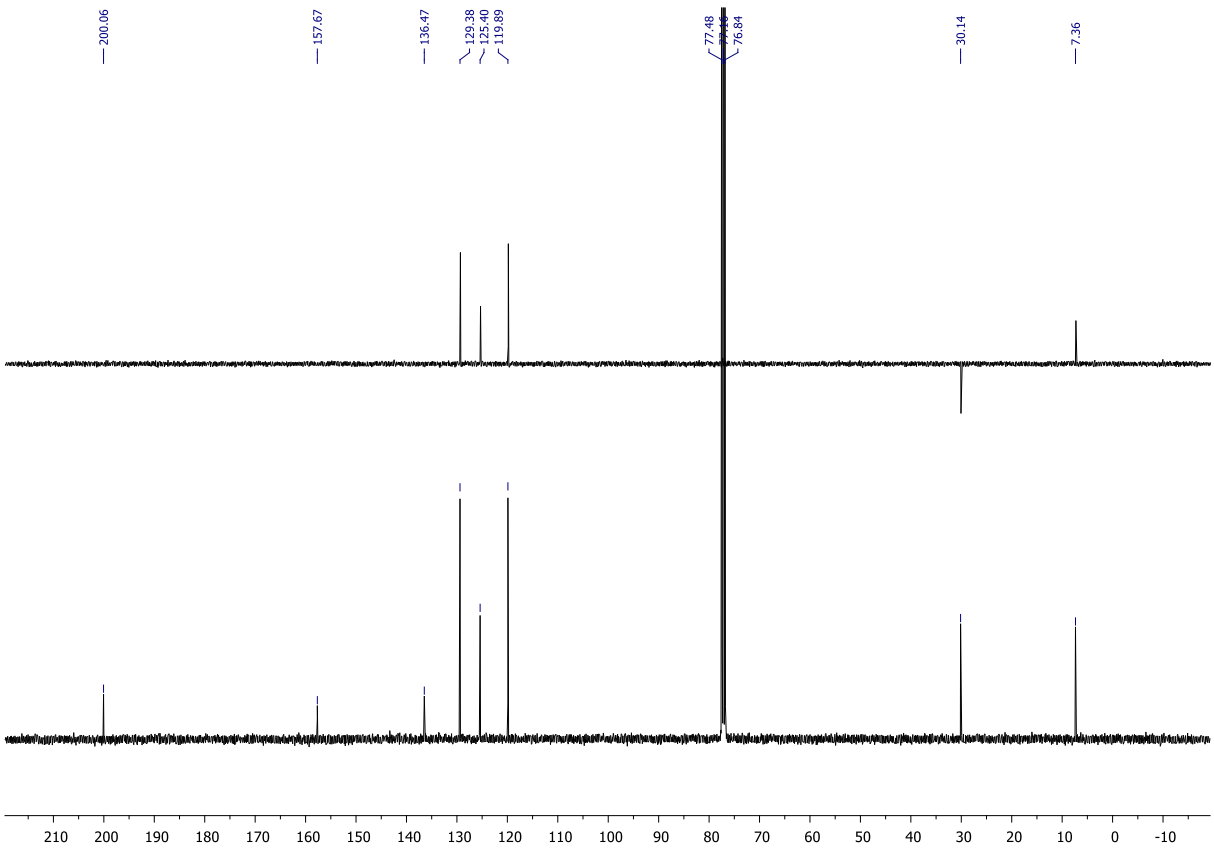
3.06
3.05
3.03
1.57
1.19
1.17
1.15


O
N
H
O


0.91
1.90
1.95
0.98
1.96
3.00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129.38
125.40
119.89
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76.84
30.14
7.36
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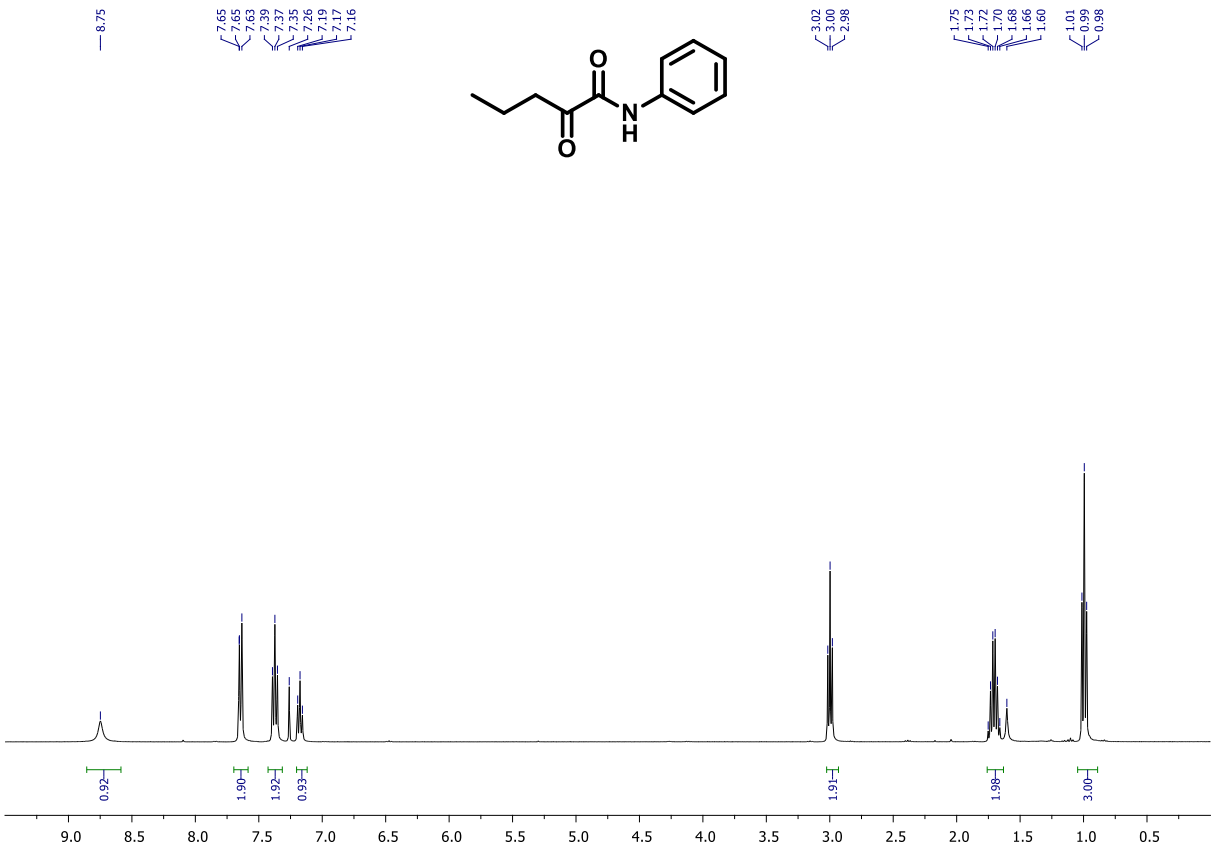
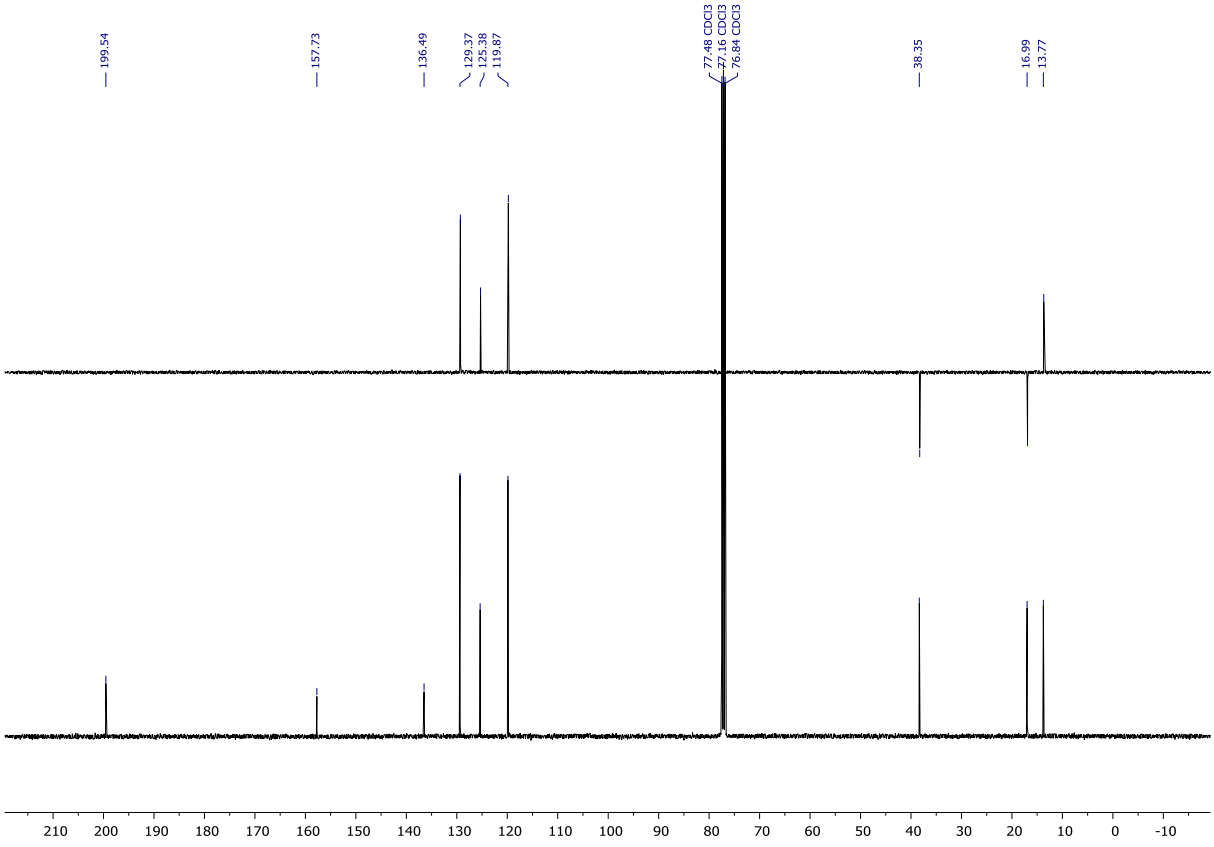
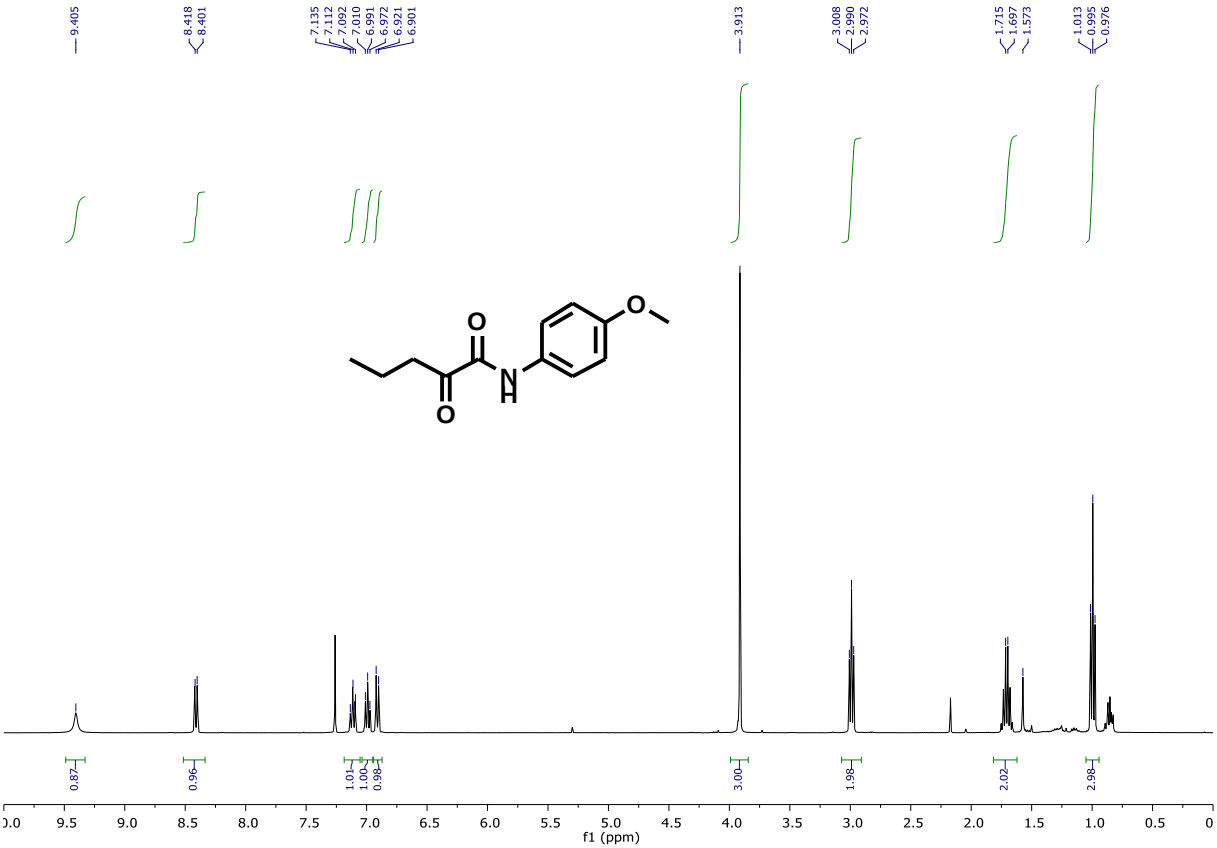
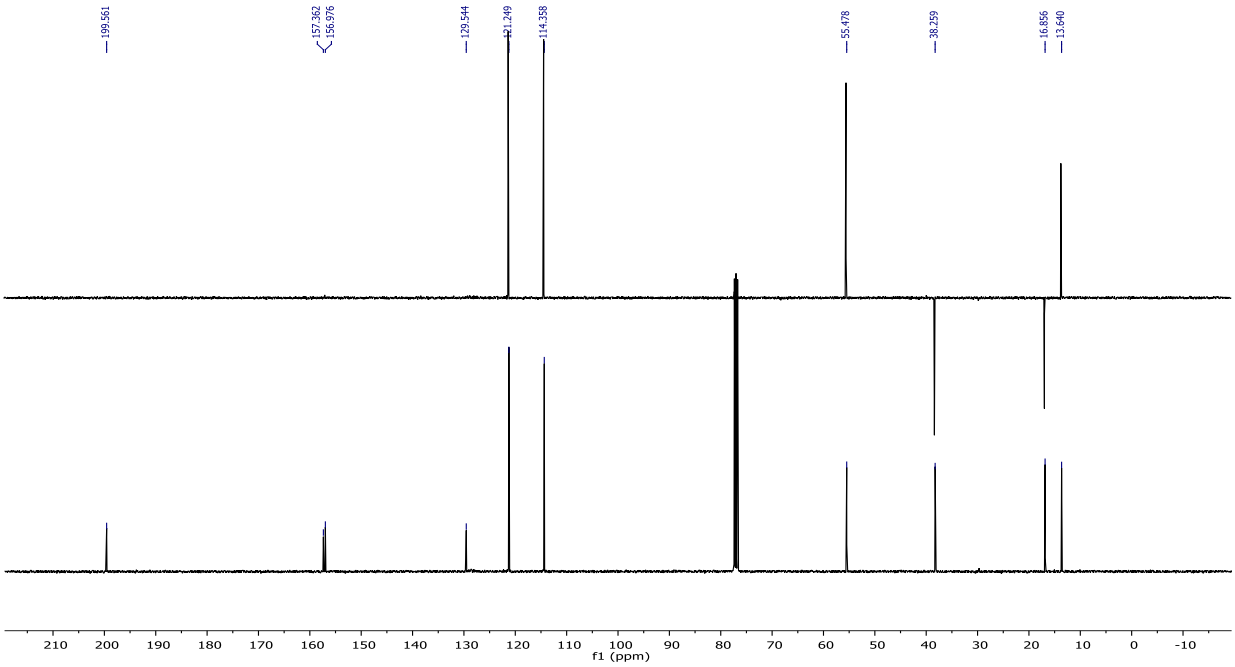
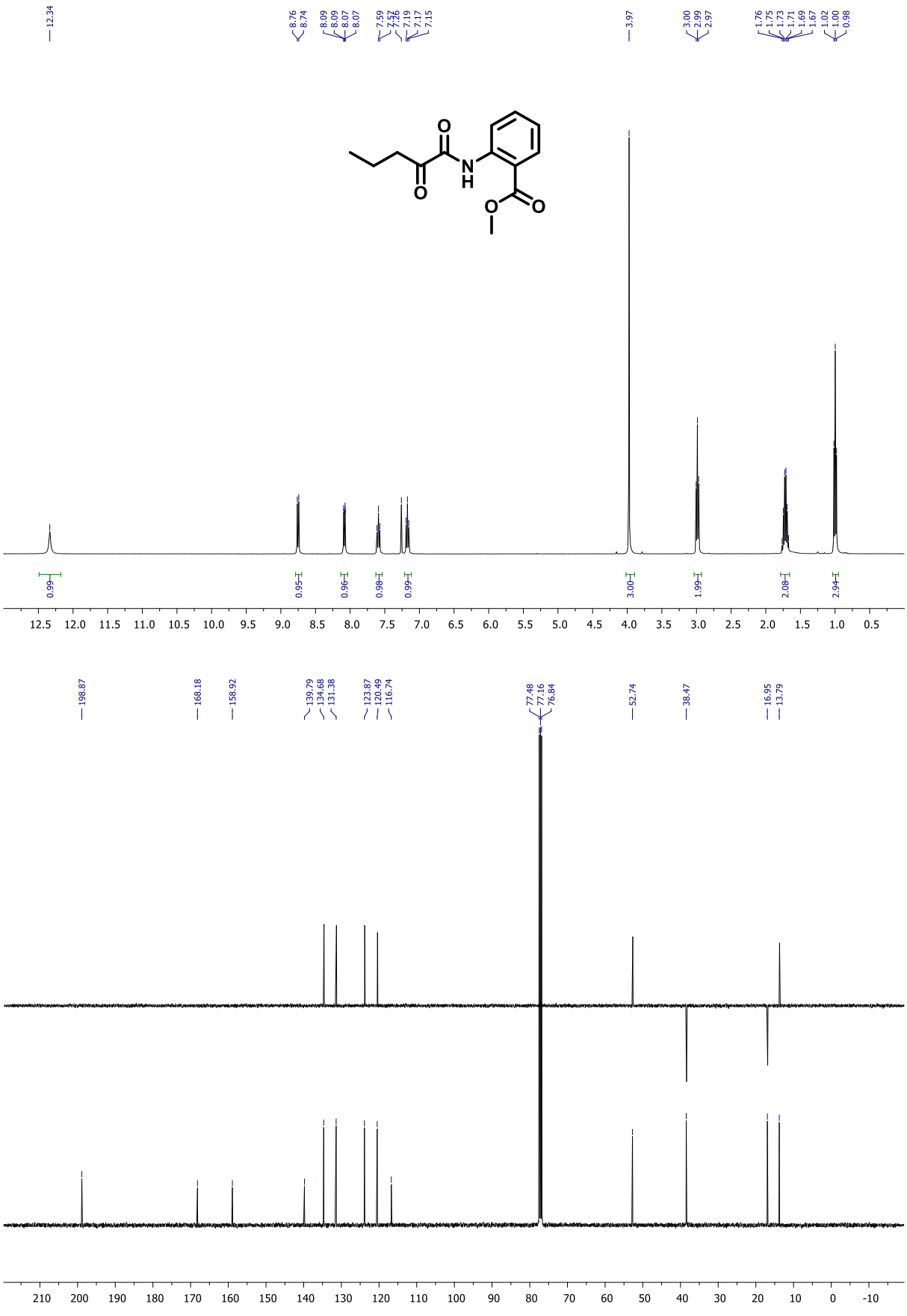
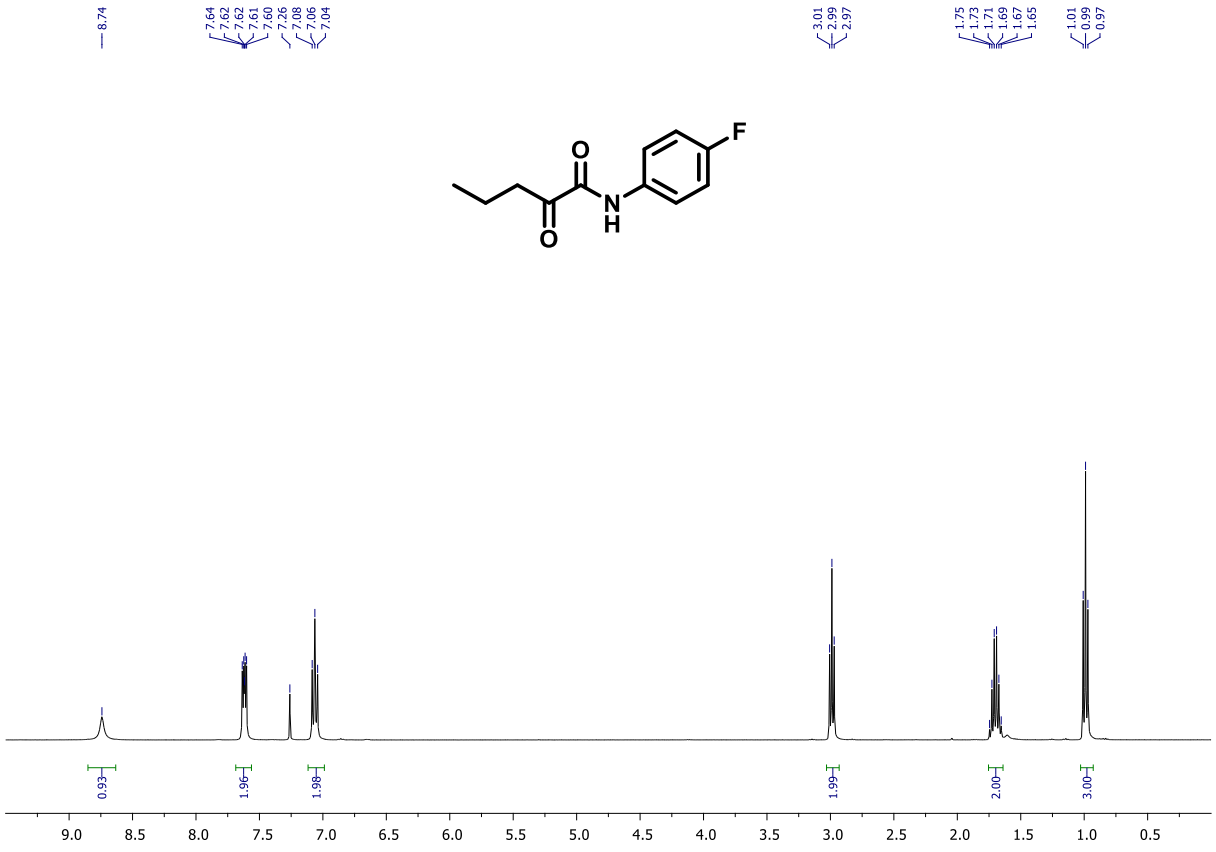

8.75
7.65
7.65
7.63
7.39
7.37
7.35
7.26
7.19
7.17
7.16
3.02
3.00
2.98
1.75
1.73
1.72
1.70
1.68
1.66
1.60
1.01
0.99
0.98
O
N
H
O
0.92
1.90
1.92
0.93
1.91
1.98
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

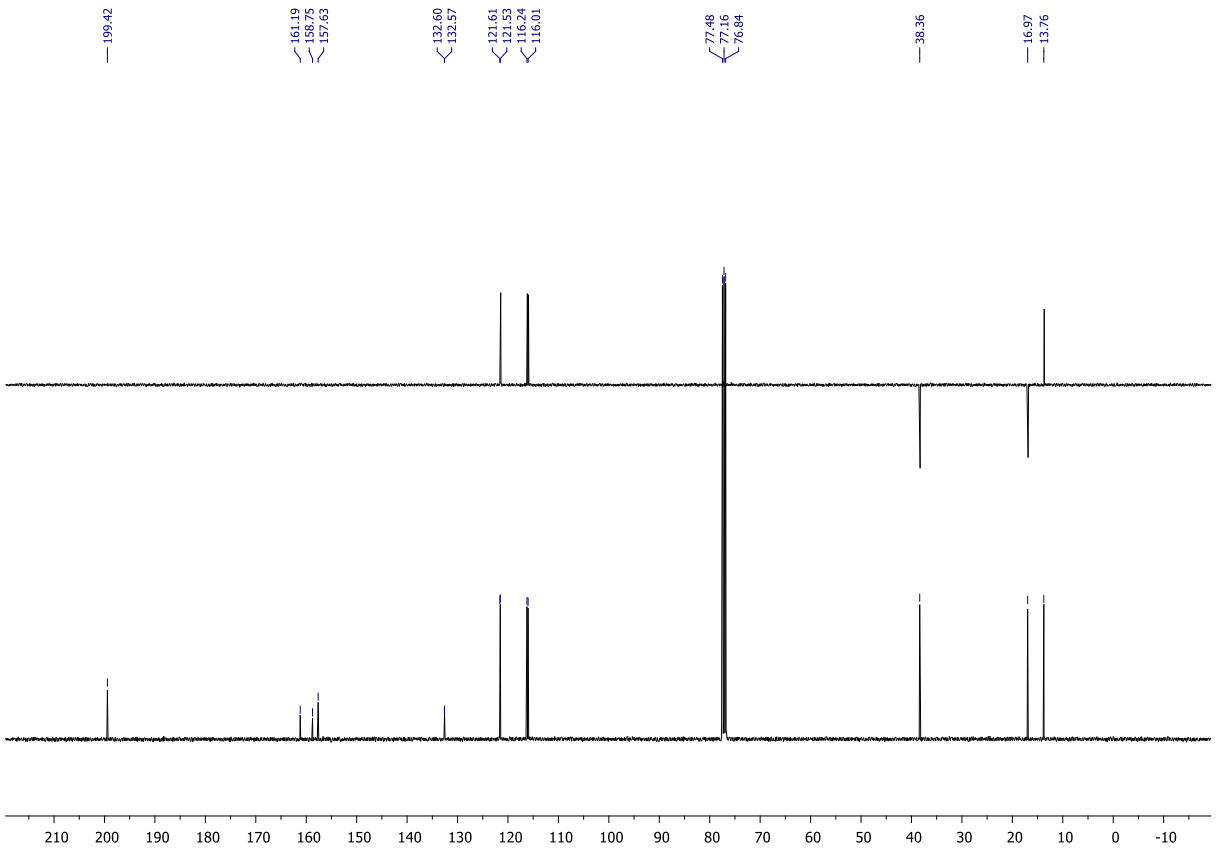

199.54
157.73
136.49
129.37
125.38
119.87
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.35
16.99
13.77
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

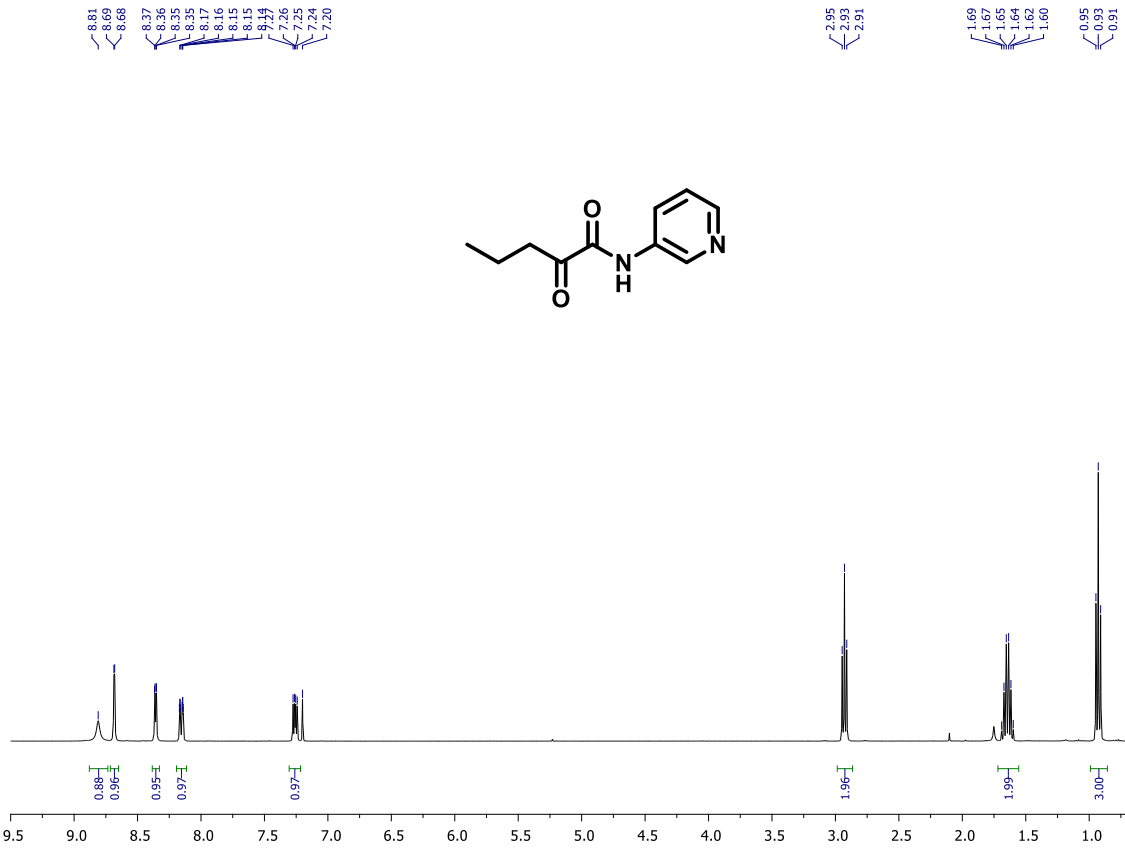

9.405
8.418
8.401
7.135
7.112
7.092
7.010
6.991
6.972
6.921
6.901
3.913
3.008
2.990
2.972
1.715
1.697
1.573
1.013
0.995
0.976
O
O
N
H
O
0.87
0.96
1.01
1.00
0.98
3.00
1.98
2.02
2.98
f1 (ppm)

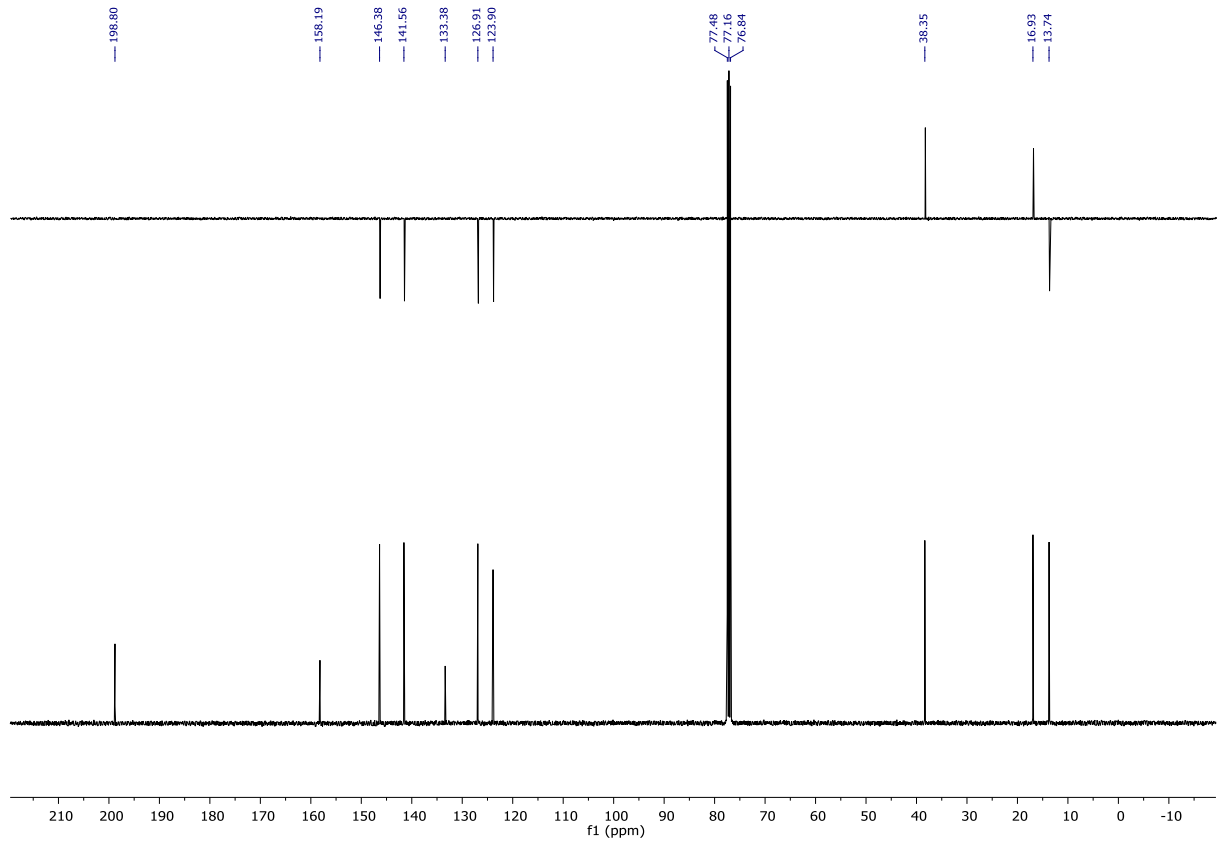

199.561
157.362
156.976
129.544
121.249
114.358
55.478
38.359
16.856
13.640
f1 (ppm)

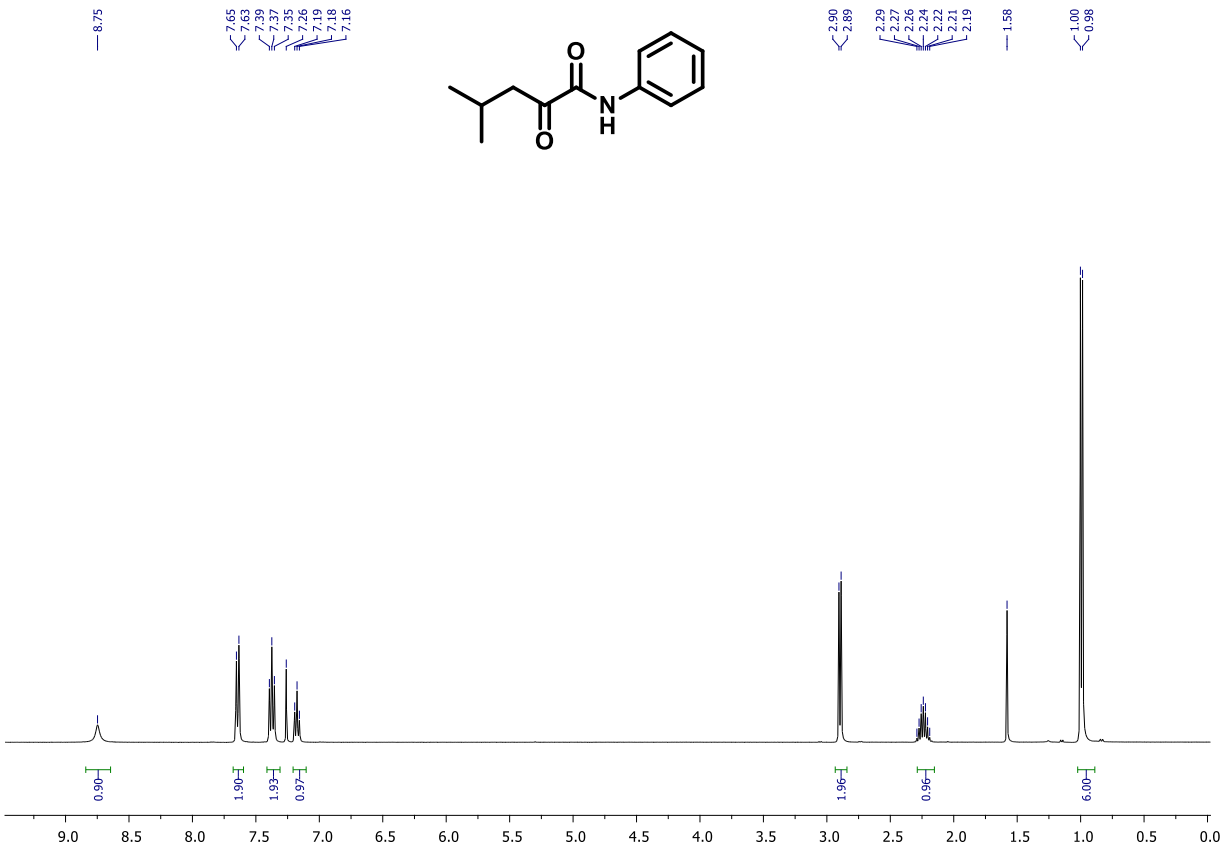

12.34
8.76
8.74
8.09
8.09
8.07
8.07
7.59
7.57
7.56
7.19
7.17
7.15
3.97
3.00
2.99
2.97
1.76
1.75
1.73
1.71
1.69
1.67
1.02
1.00
0.98
O
N
H
O
O
O
0.99
0.95
0.96
0.98
0.99
3.00
1.99
2.08
2.94
198.87
168.18
158.92
139.79
134.68
131.38
123.87
120.49
116.74
77.48
77.16
76.84
52.74
38.47
16.95
13.79

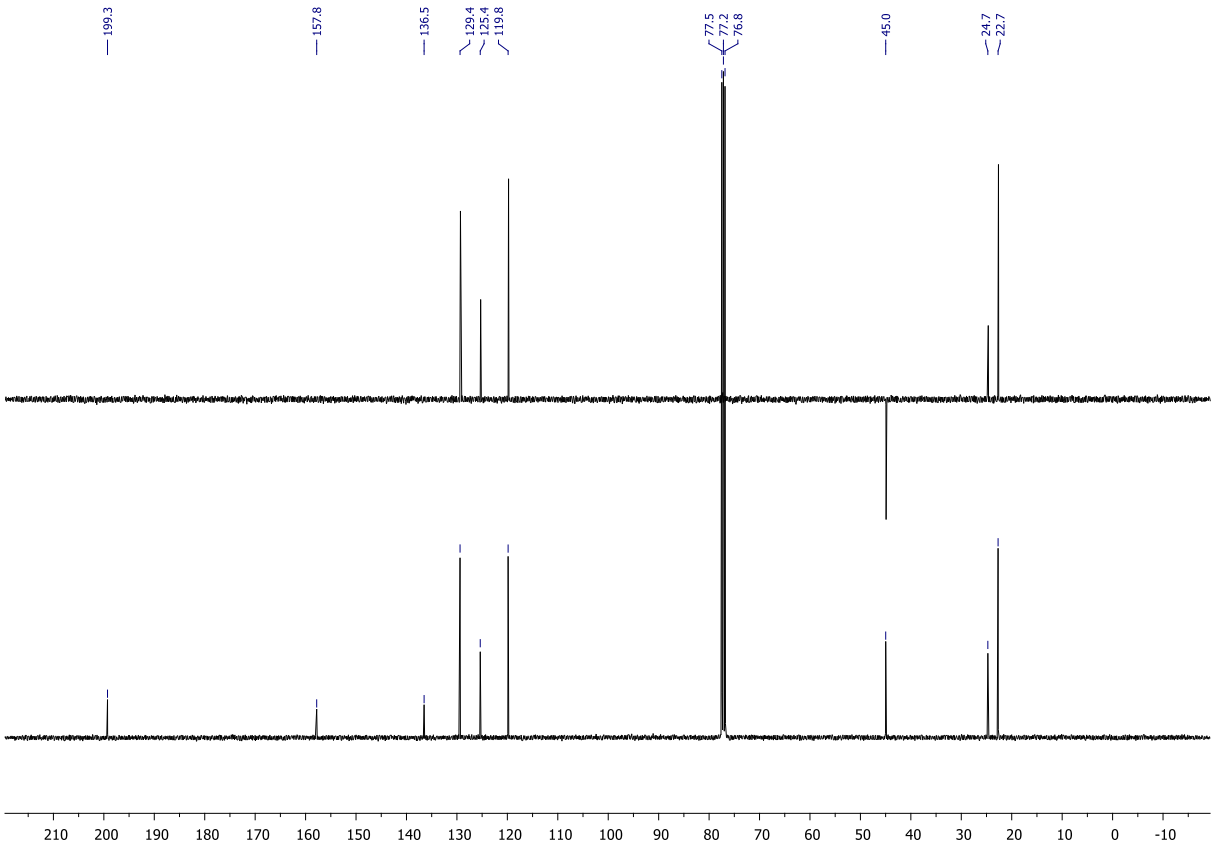

8.74
7.64
7.62
7.62
7.61
7.60
7.26
7.08
7.06
7.04
3.01
2.99
2.97
1.75
1.73
1.71
1.69
1.67
1.65
1.01
0.99
0.97
F
O
N
H
O
0.93
1.96
1.98
1.99
2.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

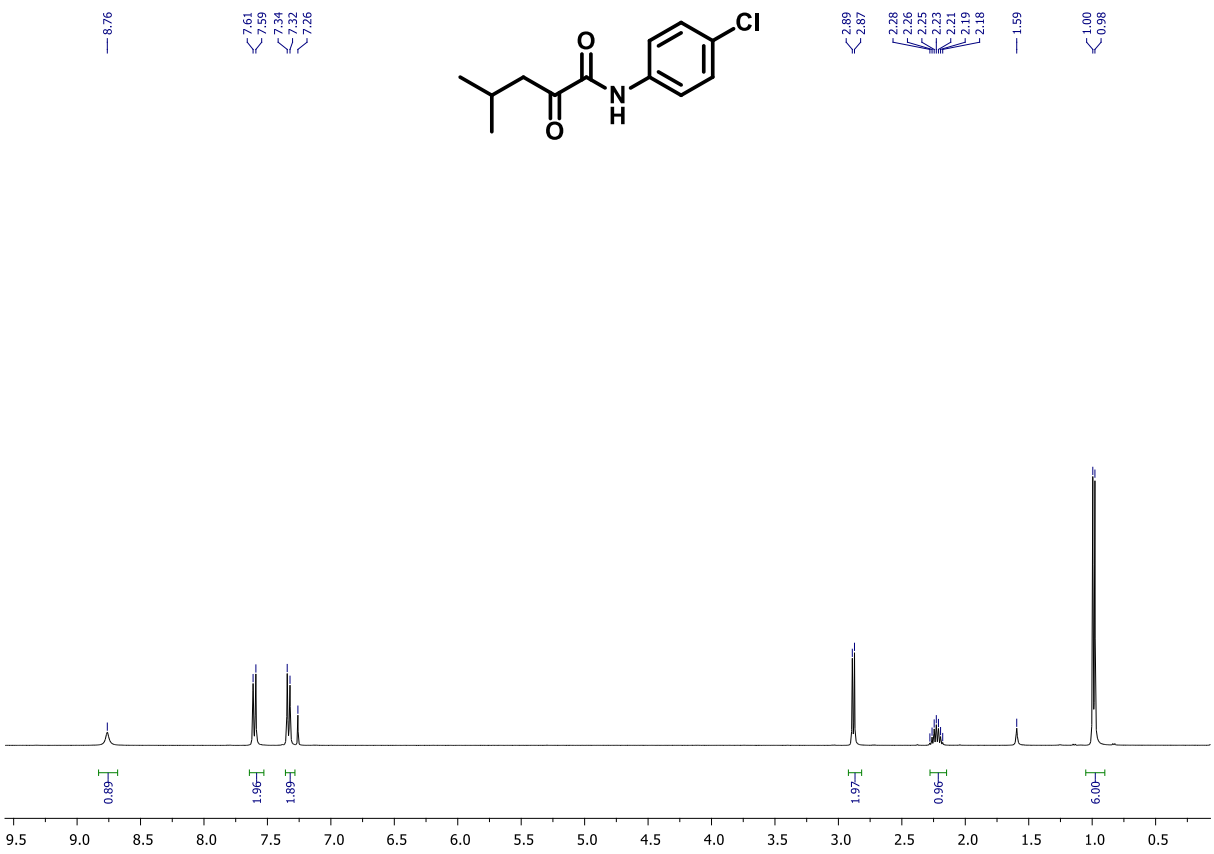

199.42
161.19
158.75
157.63
132.60
132.57
121.61
121.53
116.24
116.01
77.48
77.16
76.84
38.36
16.97
13.76
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

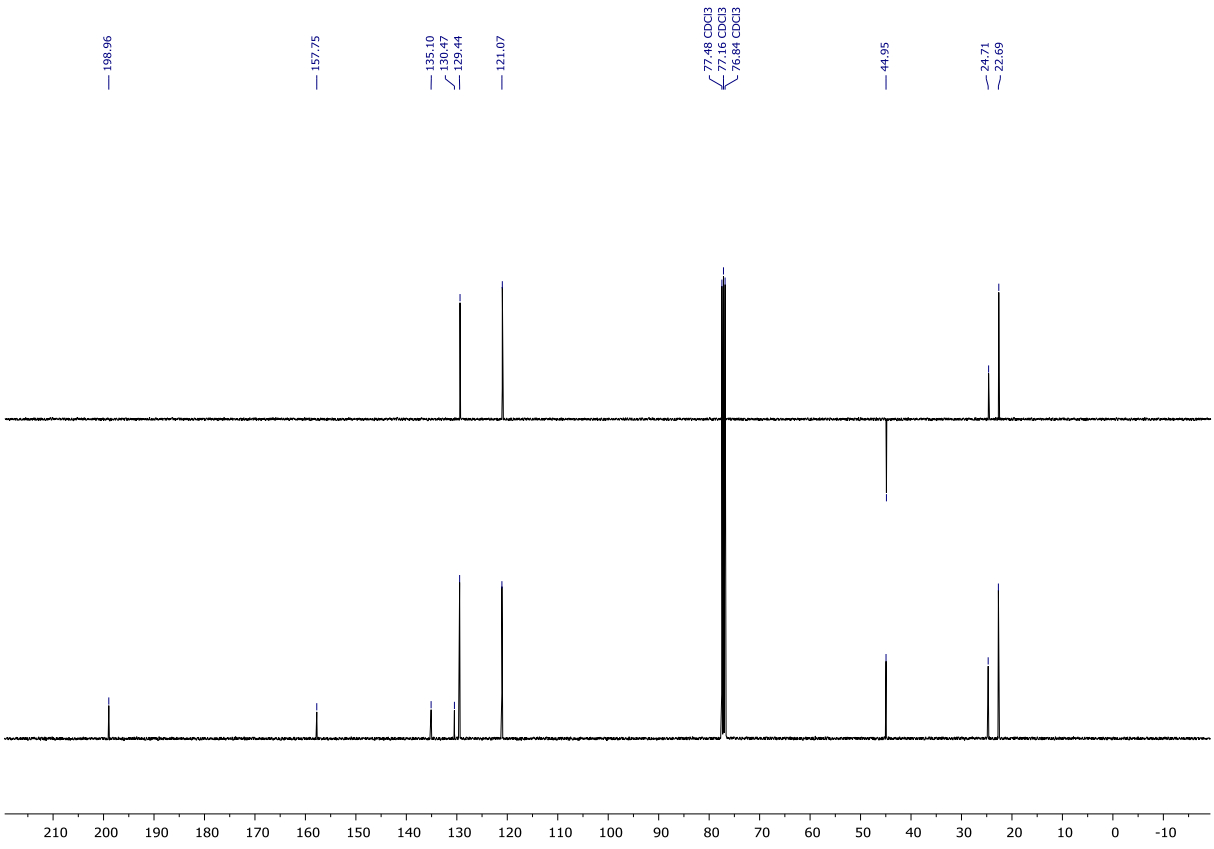

8.81
8.69
8.68
8.37
8.36
8.35
8.35
8.17
8.16
8.15
8.15
7.27
7.26
7.25
7.24
7.20
2.95
2.93
2.91
1.69
1.67
1.65
1.64
1.62
1.60
0.95
0.93
0.91
O
N
H
N
O
0.88
0.96
0.95
0.97
0.97
1.96
1.99
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

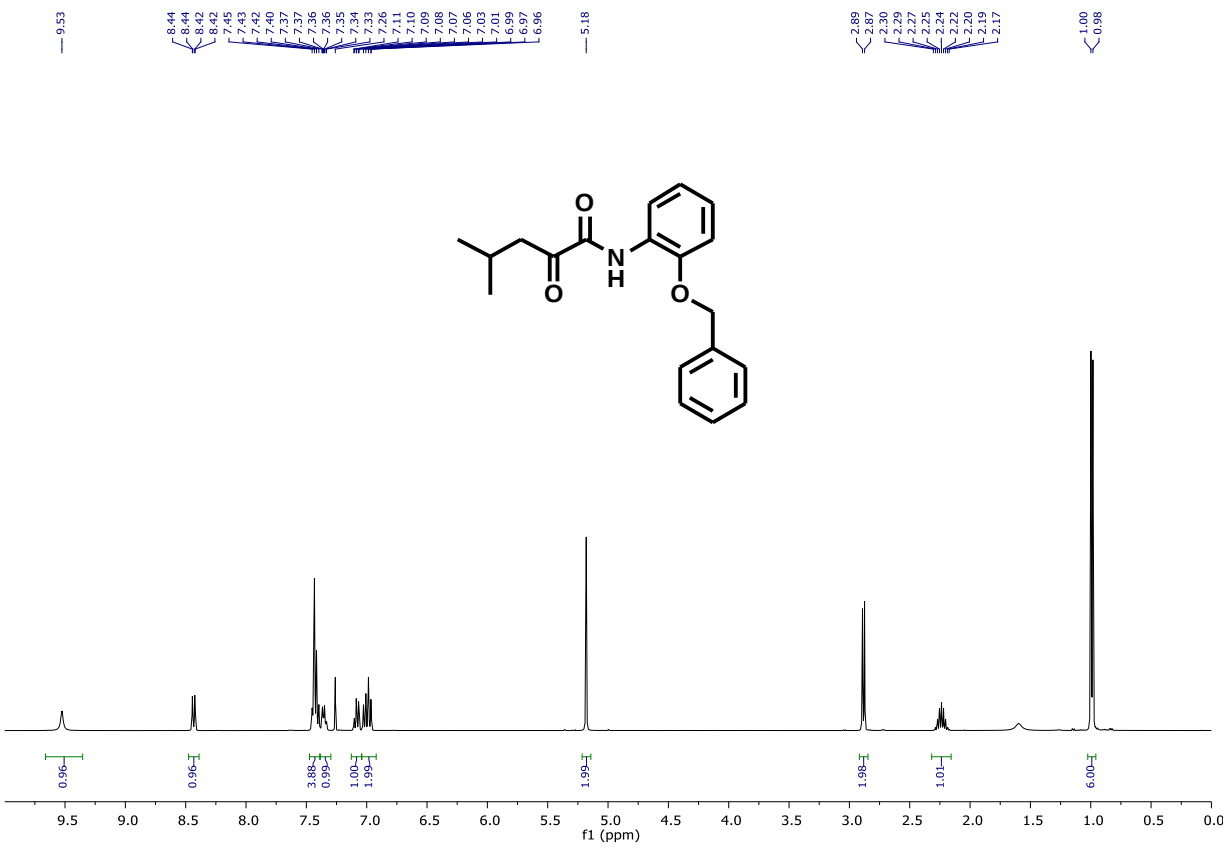

198.80
158.19
146.38
141.56
133.38
126.91
123.90
77.48
77.16
76.84
38.35
16.93
13.74
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

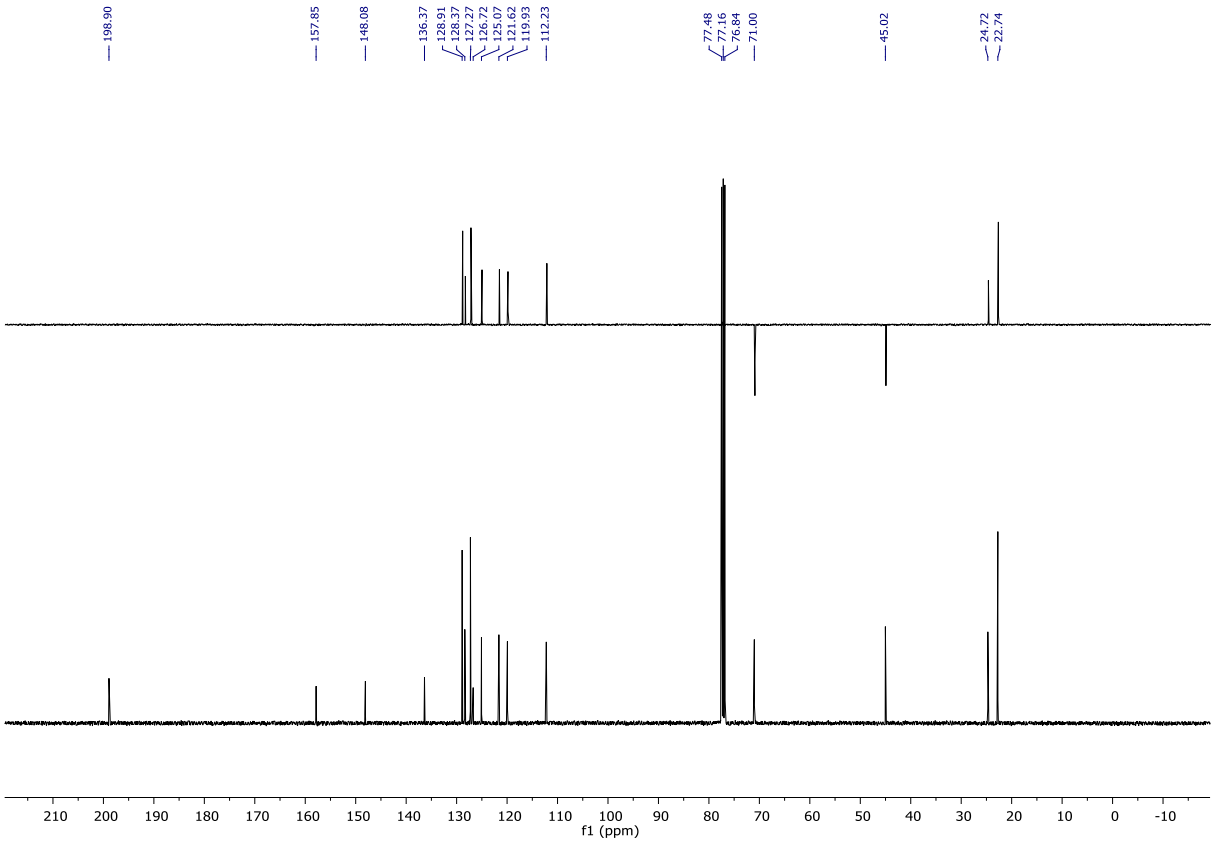

8.75
7.65
7.63
7.39
7.37
7.35
7.26
7.19
7.18
7.16
2.90
2.89
2.29
2.27
2.26
2.24
2.22
2.21
2.19
1.58
1.00
0.98
O
N
H
O
0.90
1.90
1.93
0.97
1.96
0.96
6.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

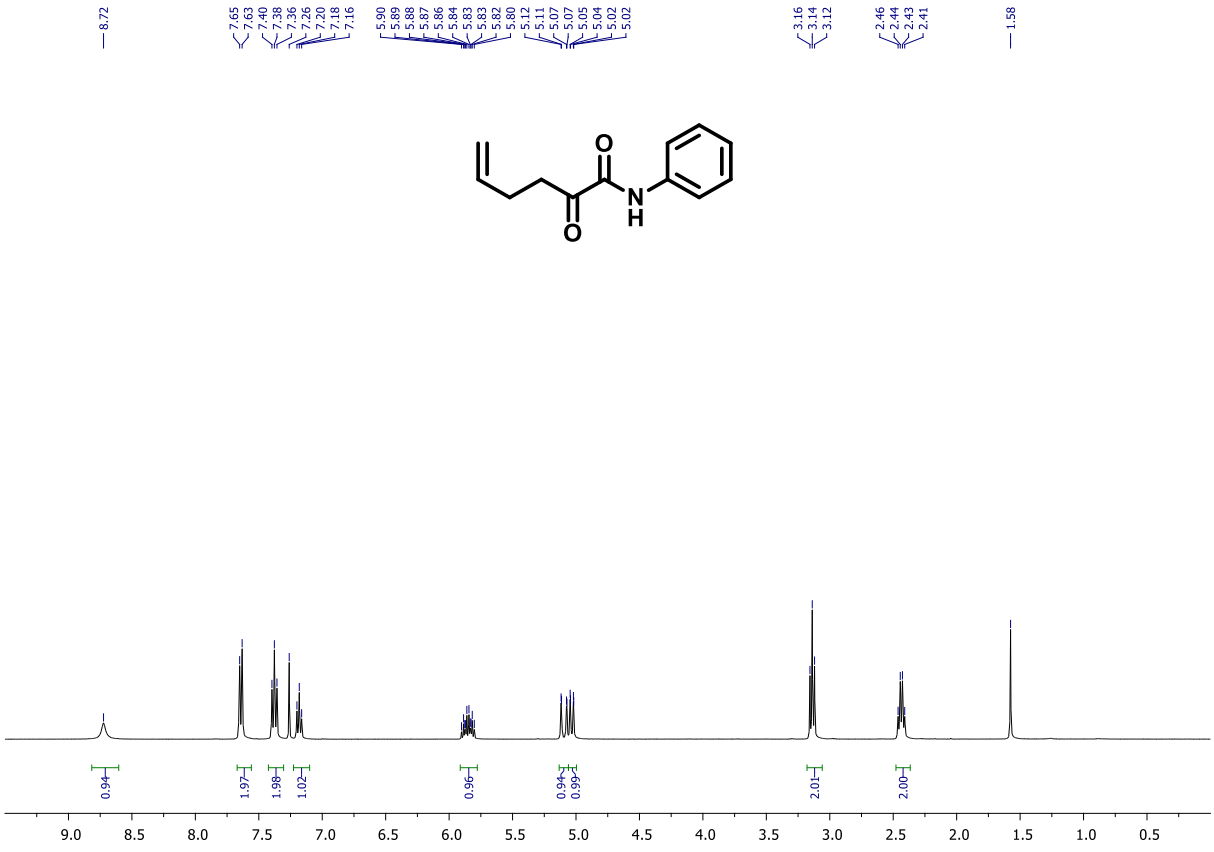

199.3
157.8
136.5
129.4
125.4
119.8
77.5
77.2
76.8
45.0
24.7
22.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

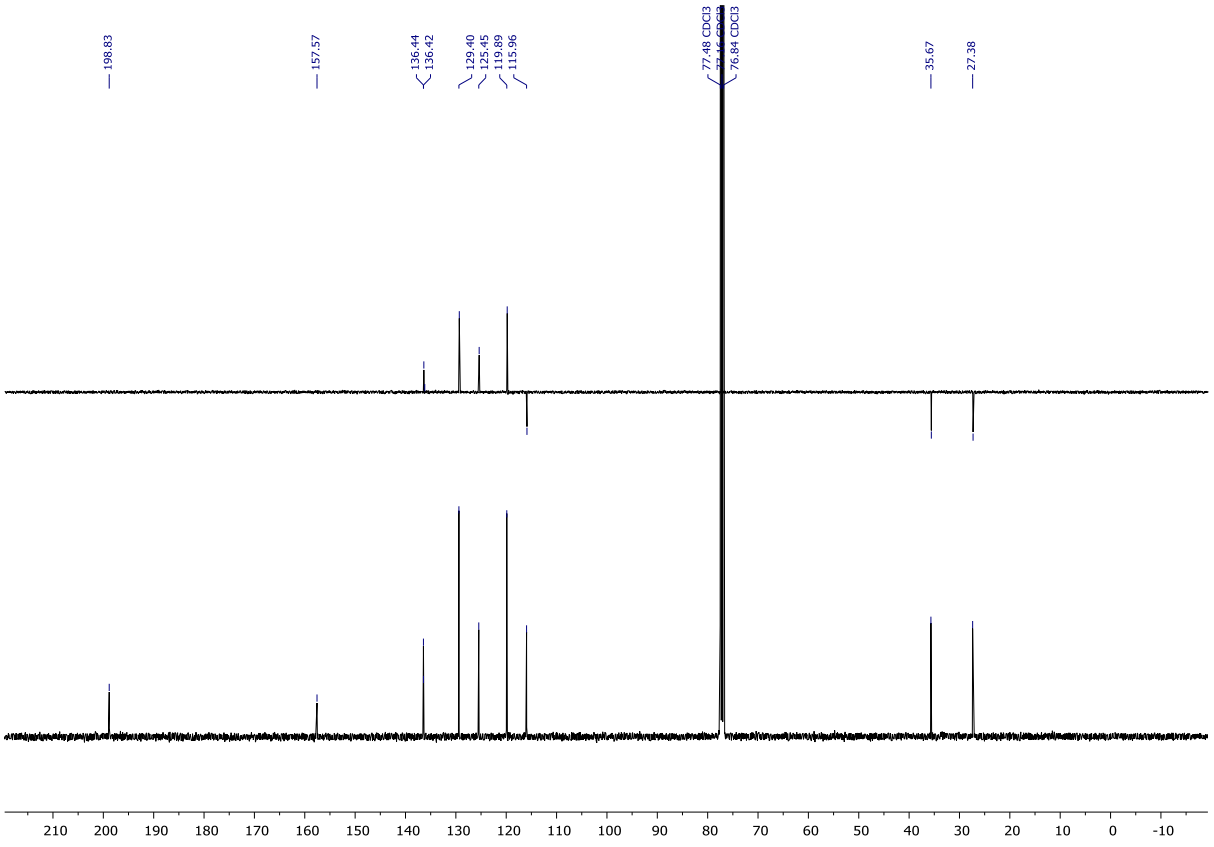

8.76
7.61
7.59
7.34
7.32
7.26
2.89
2.87
2.28
2.26
2.25
2.23
2.21
2.19
2.18
1.59
1.00
0.98
Cl
O
N
H
O
0.89
1.96
1.89
1.97
0.96
6.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

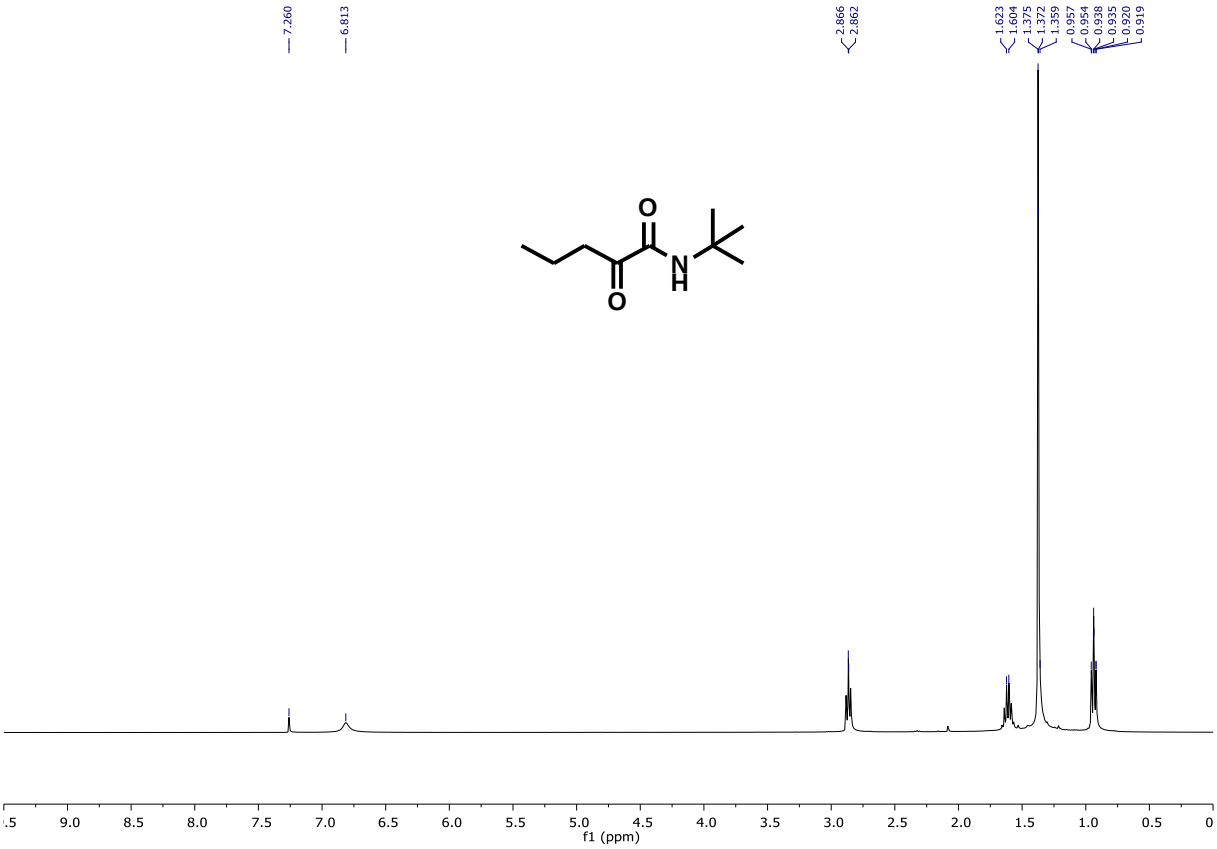

198.96
157.75
135.10
130.47
129.44
121.07
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
44.95
24.71
22.69
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

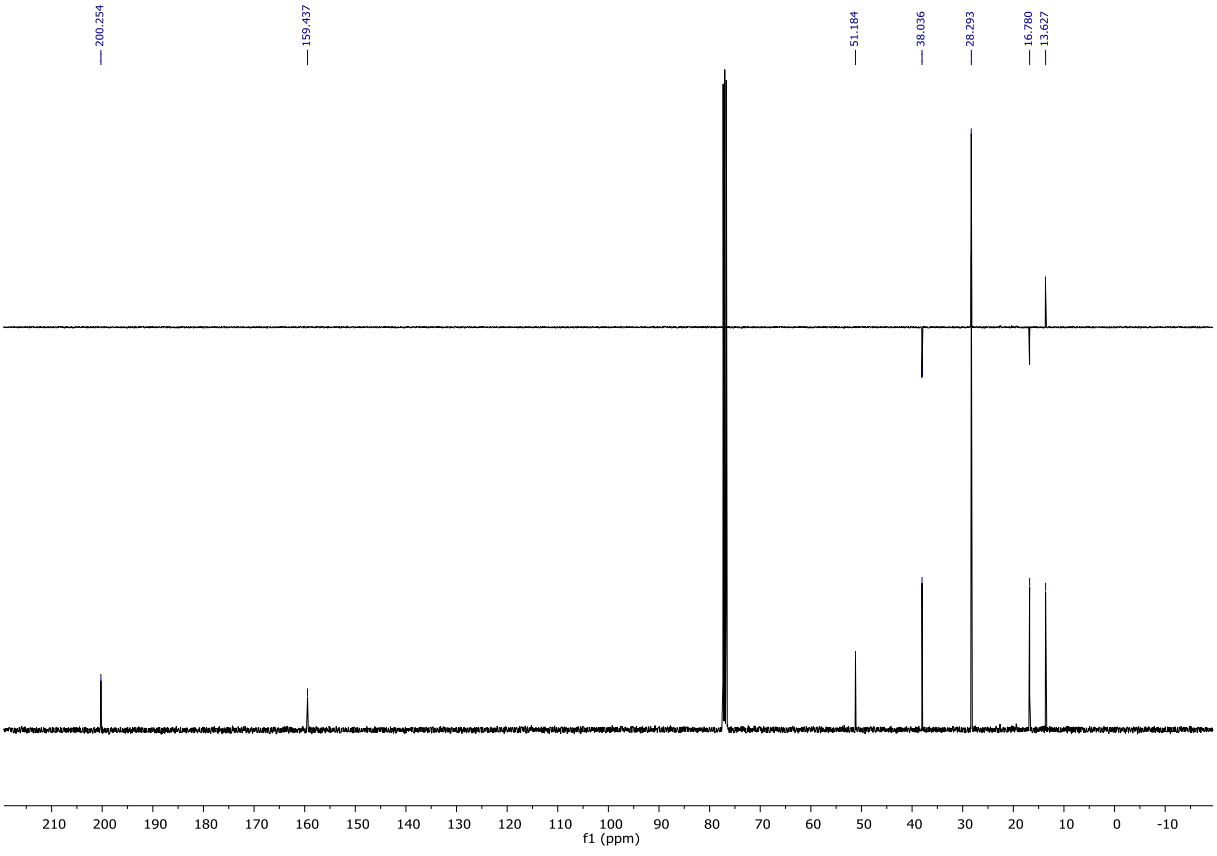

9.53
8.44
8.44
8.42
8.42
7.45
7.43
7.42
7.40
7.37
7.37
7.36
7.36
7.35
7.34
7.33
7.26
7.11
7.10
7.09
7.08
7.07
7.06
7.03
7.01
6.99
6.97
6.96
5.18
2.89
2.87
2.30
2.29
2.27
2.25
2.24
2.22
2.20
2.19
2.17
1.00
0.98
O
N
H
O
O
0.96
0.96
3.88
0.99
1.00
1.99
1.99
1.98
1.01
6.00
f1 (ppm)

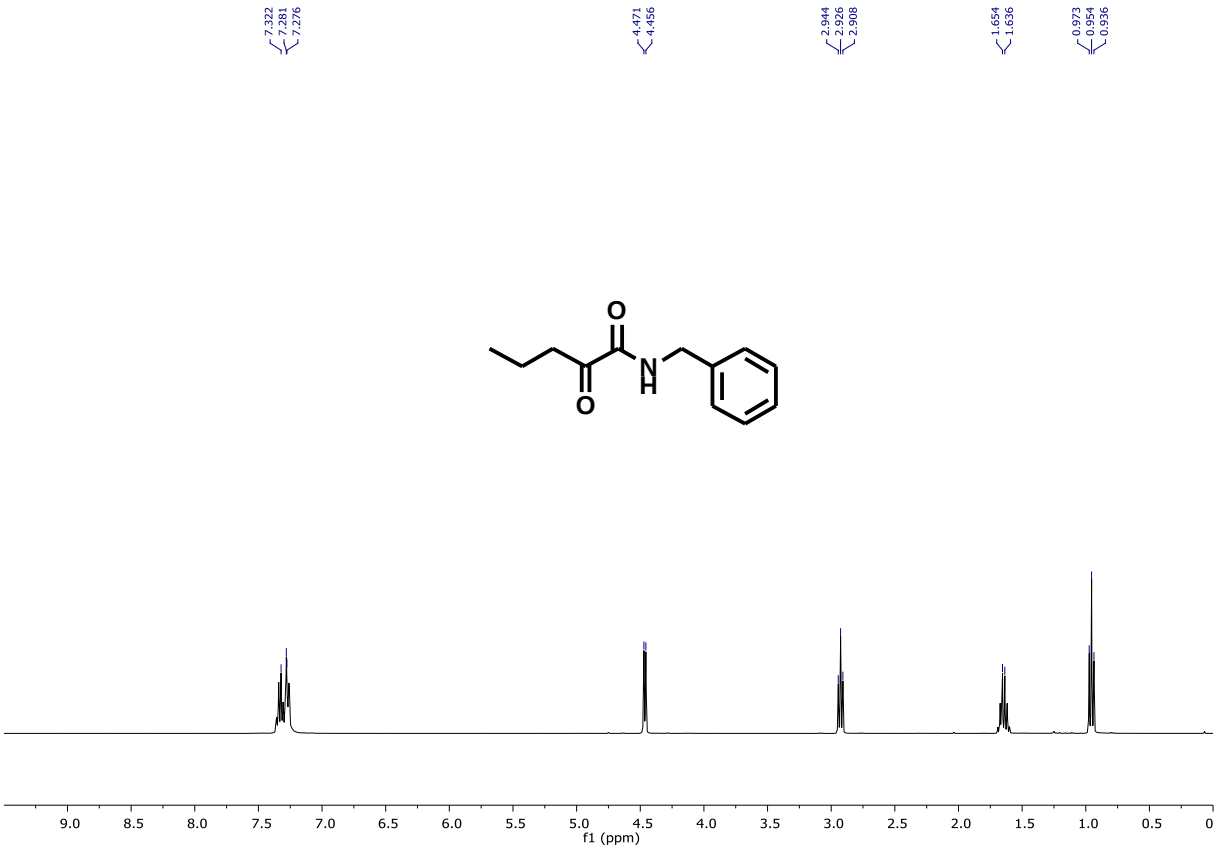

198.90
157.85
148.08
136.37
128.91
128.37
127.27
126.72
125.07
121.62
119.93
112.23
77.48
77.16
76.84
71.00
45.02
24.72
22.74
f1 (ppm)

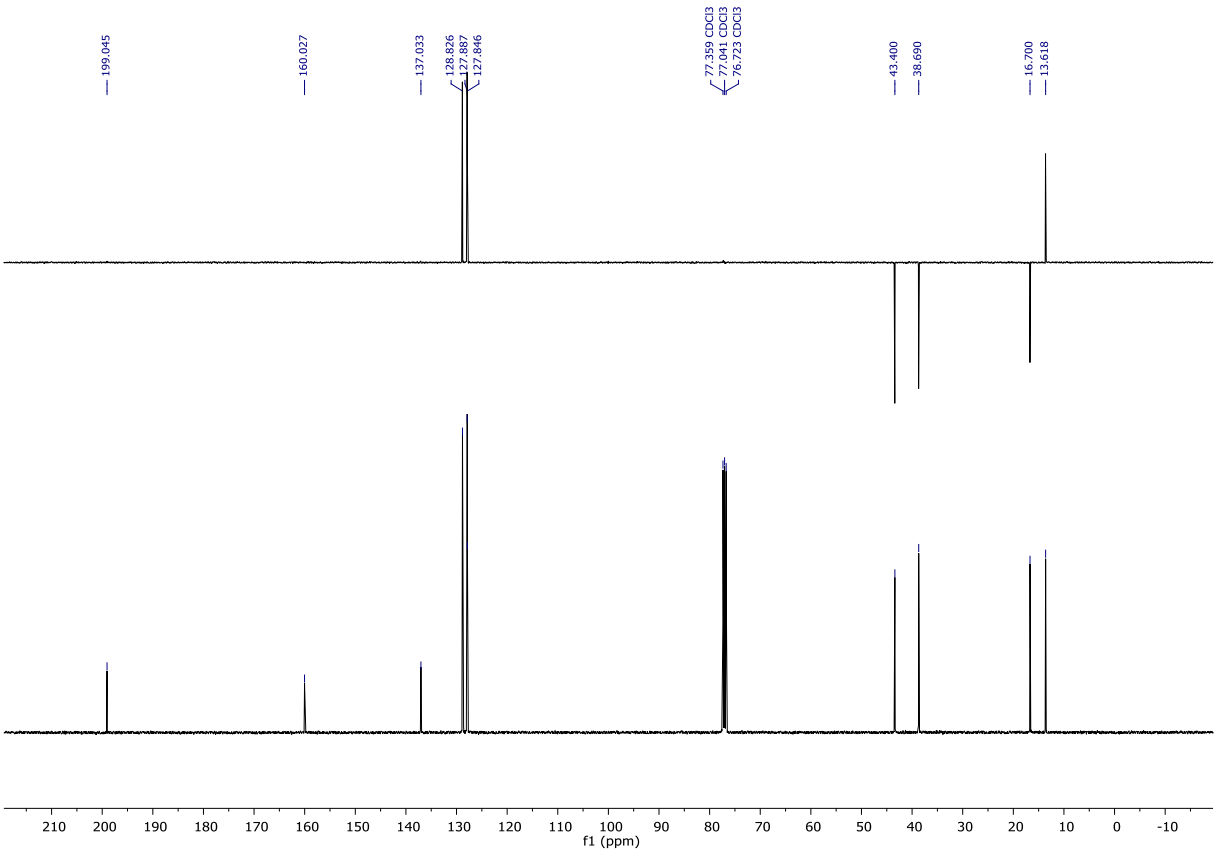

8.72
7.65
7.63
7.40
7.38
7.36
7.26
7.20
7.18
7.16
5.90
5.89
5.88
5.87
5.86
5.84
5.83
5.83
5.82
5.80
5.12
5.11
5.07
5.07
5.05
5.04
5.02
5.02
3.16
3.14
3.12
2.46
2.44
2.43
2.41
1.58
O
N
H
O
0.94
1.97
1.98
1.02
0.96
0.94
0.99
2.01
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


198.83
157.57
136.44
136.42
129.40
125.45
119.89
115.96
77.48 CDCl3
76.84 CDCl3
35.67
27.38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

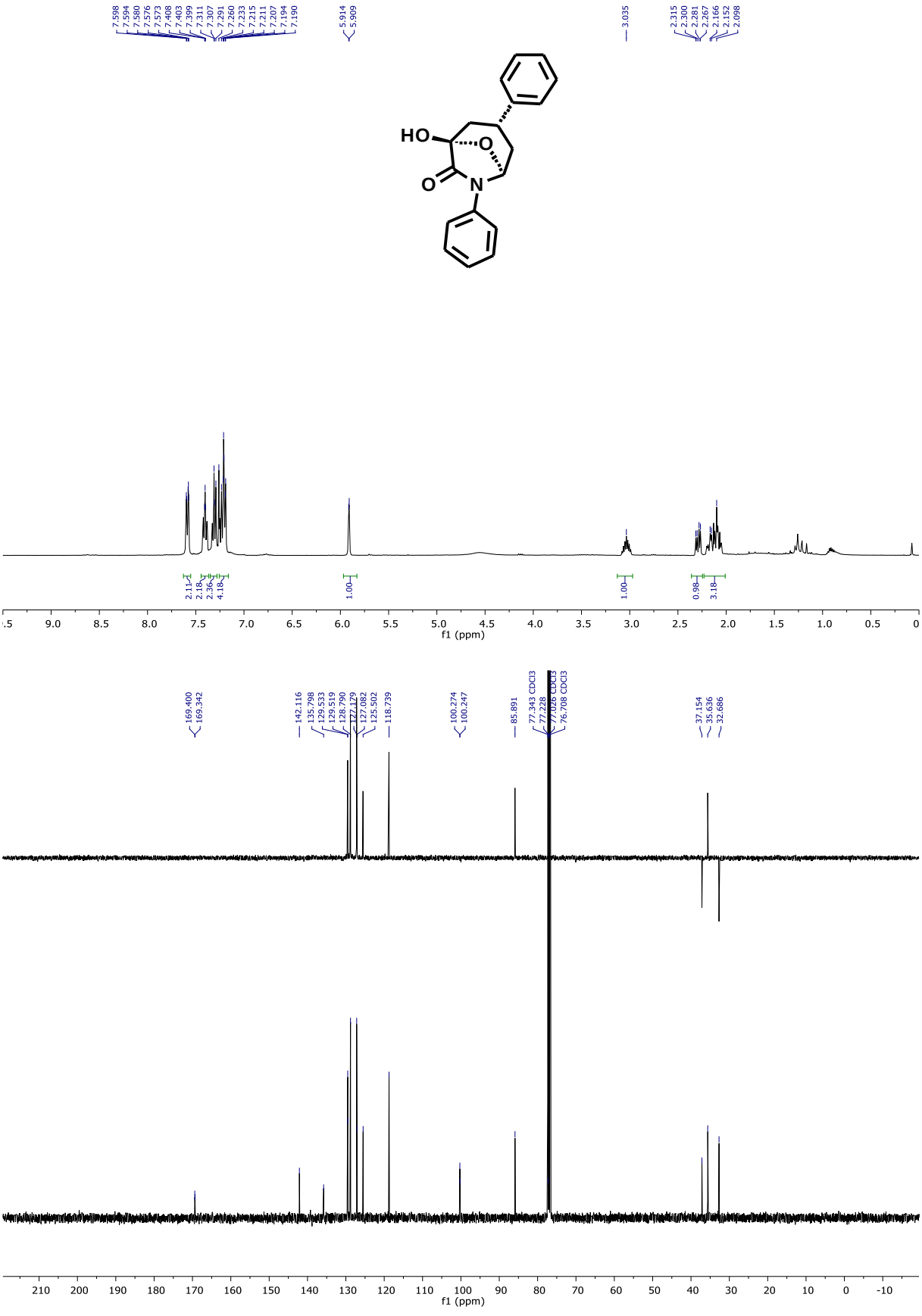

7.260
6.813
2.866
2.862
1.623
1.604
1.375
1.372
1.359
0.957
0.954
0.938
0.935
0.920
0.919
O
N
H
O
f1 (ppm)

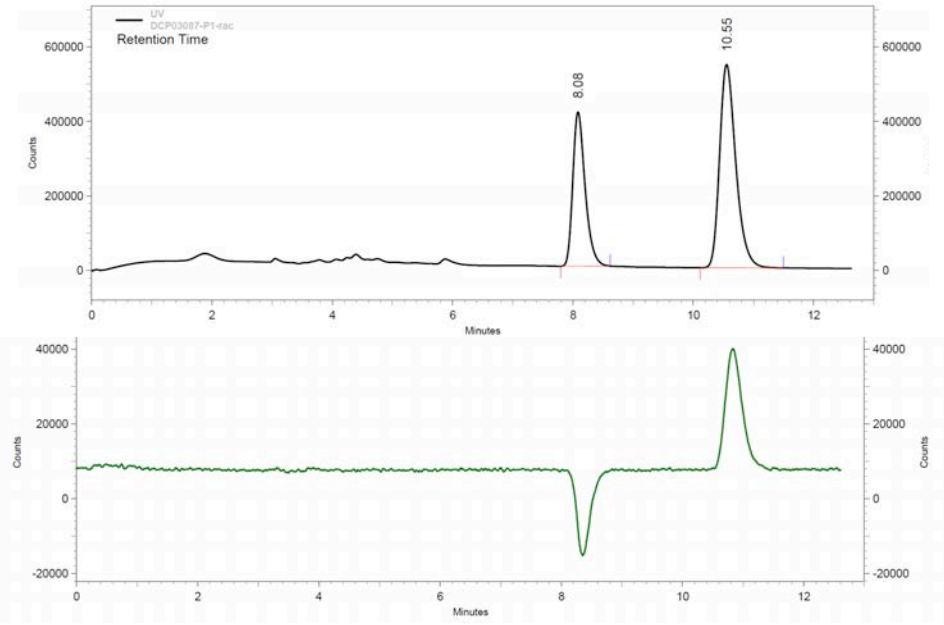

200.254
159.437
51.184
38.036
28.293
16.780
13.627
f1 (ppm)


7.322
7.281
7.276
4.471
4.456
2.944
2.926
2.908
1.654
1.636
0.973
0.954
0.936
O
O
N
H
9.0
8.5
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
f1 (ppm)

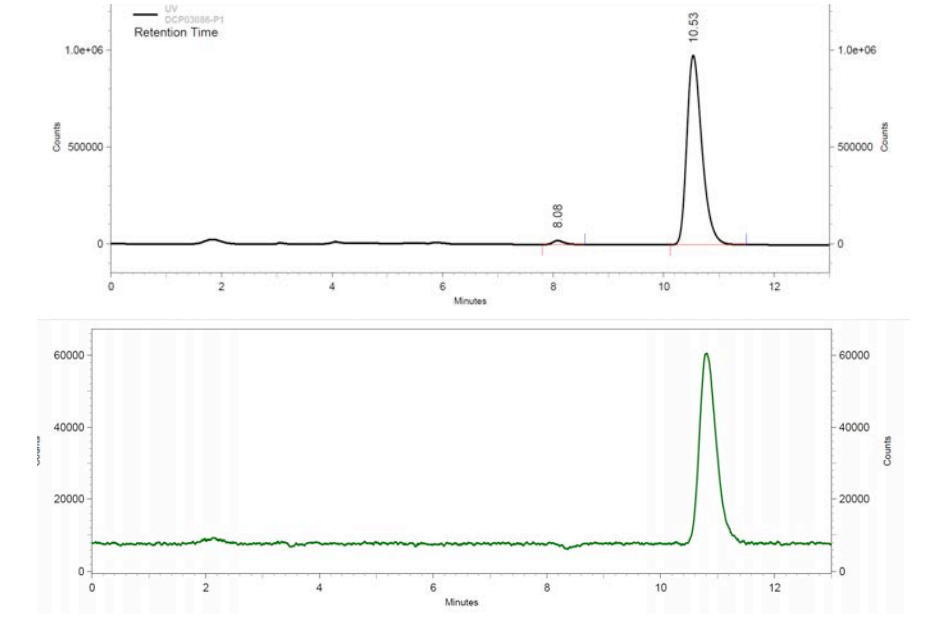

199.045
160.027
137.033
128.826
127.887
127.846
77.359 CDCl3
77.041 CDCl3
76.723 CDCl3
43.400
38.690
16.700
13.618
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

## 6. NMR spectra and HPLC of 7-aza-8-oxa-bicyclo[3.2.1]octane derivatives

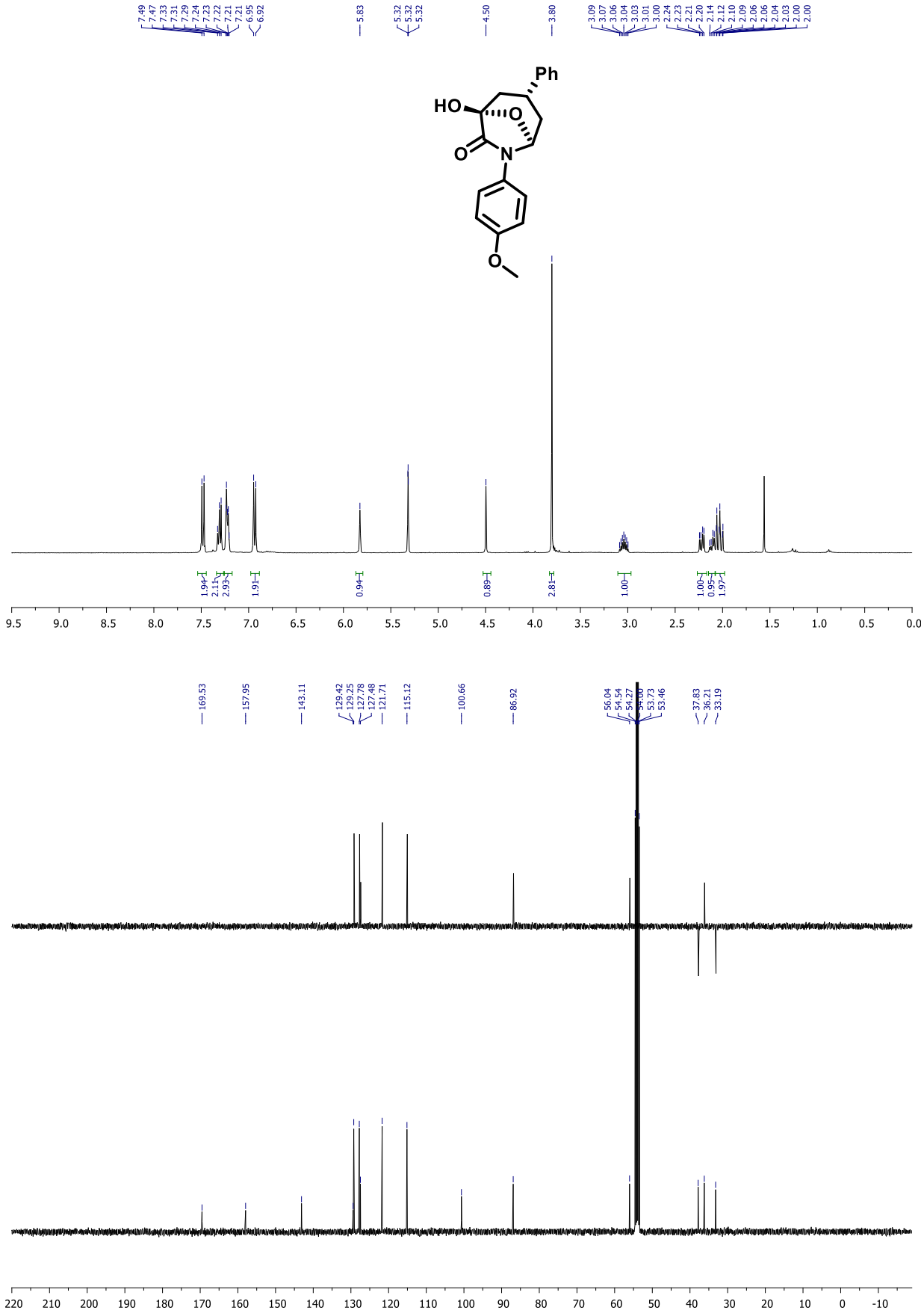


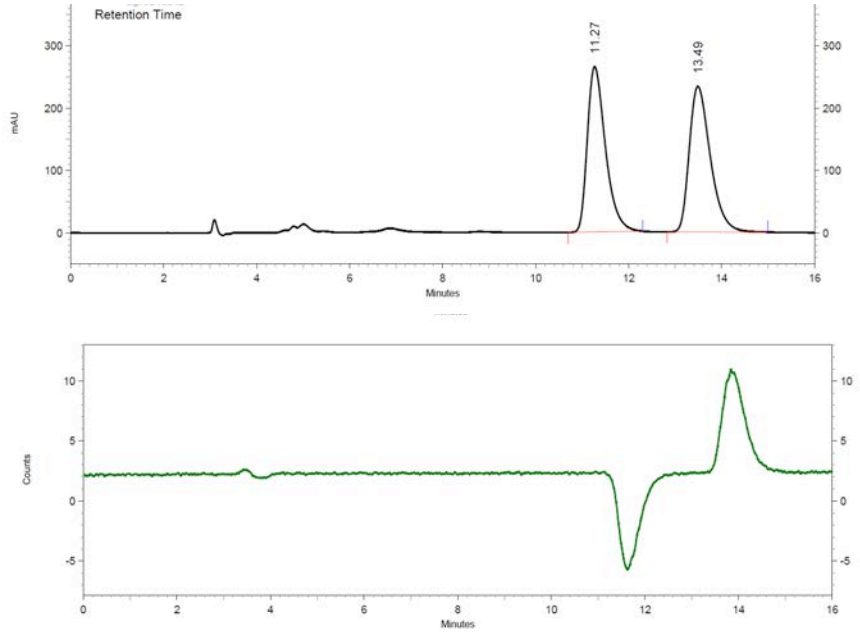



| UV Results<br>Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.08 | 5880311 | 36.60 | 1.69 | 1.00 | 0.00 |
| 10.55 | 10187671 | 63.40 | 2.52 | 1.49 | 5.71 |
| Totals | 16067982 | 100.00 | | | |




| UV Results<br>Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.08 | 287670 | 1.53 | 1.69 | 1.00 | 0.00 |
| 10.53 | 18551935 | 98.47 | 2.51 | 1.48 | 5.64 |
| Totals | 18839605 | 100.00 | | | |

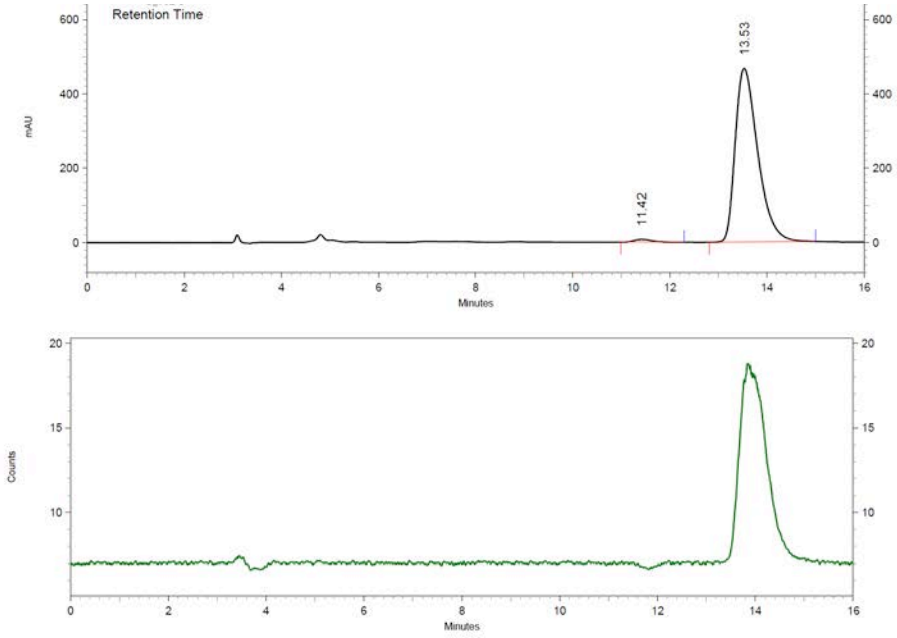

7.49
7.47
7.33
7.31
7.29
7.24
7.23
7.22
7.21
7.21
6.95
6.92
5.83
5.32
5.32
5.32
4.50
3.80
3.09
3.07
3.06
3.04
3.03
3.01
3.00
2.24
2.23
2.21
2.20
2.14
2.12
2.10
2.09
2.06
2.06
2.04
2.03
2.00
2.00
Ph
HO
O
O
N
O
1.94
2.11
2.93
1.91
0.94
0.89
2.81
1.00
1.00
0.95
1.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
169.53
157.95
143.11
129.42
129.25
127.78
127.48
121.71
115.12
100.66
86.92
56.04
54.54
54.27
54.00
53.73
53.46
37.83
36.21
33.19
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10




1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.27 | 28733303 | 49.45 | 2.76 | 0.00 | 0.00 |
| 13.49 | 29368205 | 50.55 | 3.50 | 0.00 | 2.89 |
| Totals | 58101508 | 100.00 | | | |

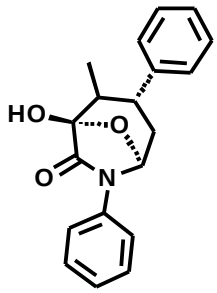


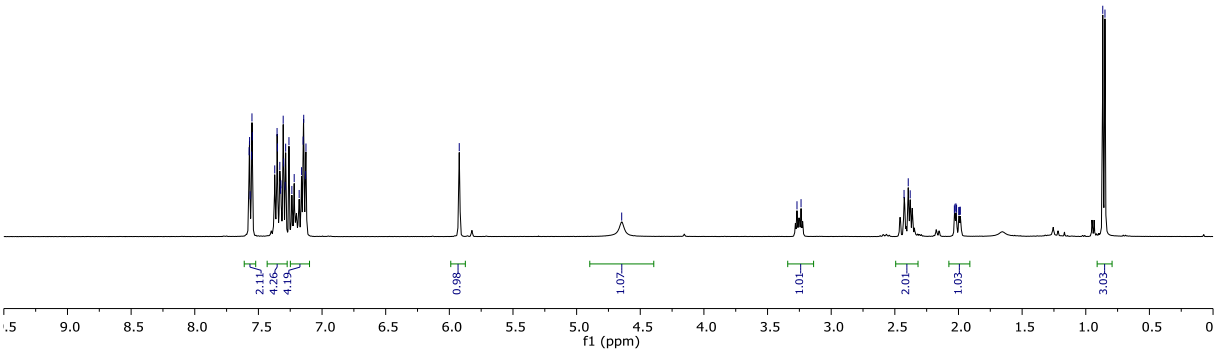

1: 254 nm, 4 nm

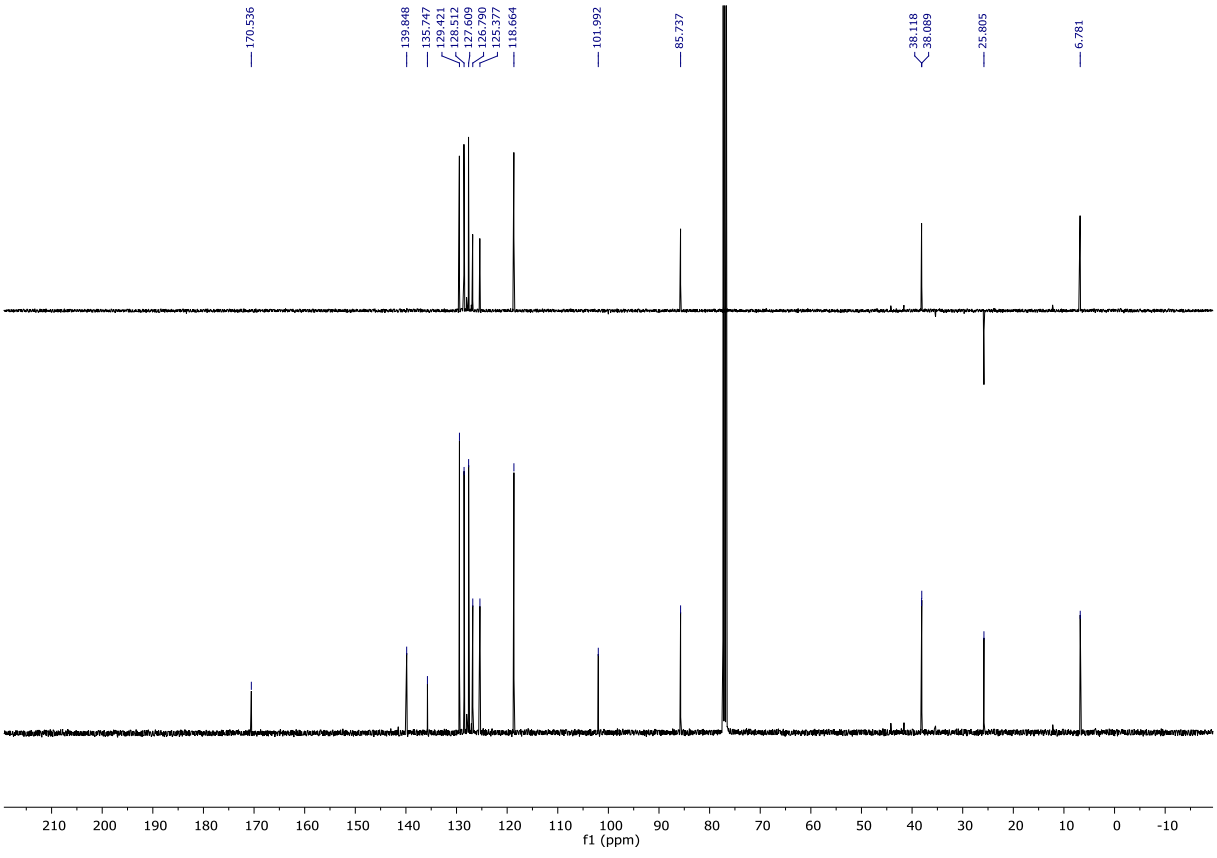
Results

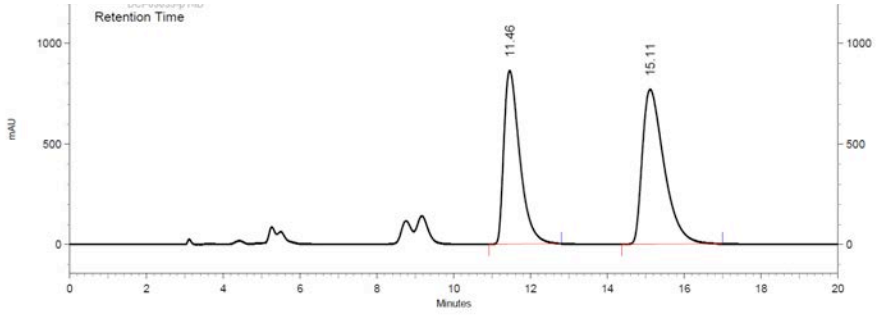
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.42 | 824554 | 1.35 | 2.81 | 0.00 | 0.00 |
| 13.53 | 60139073 | 98.65 | 3.51 | 0.00 | 2.74 |
| Totals | 60963627 | 100.00 | | | |

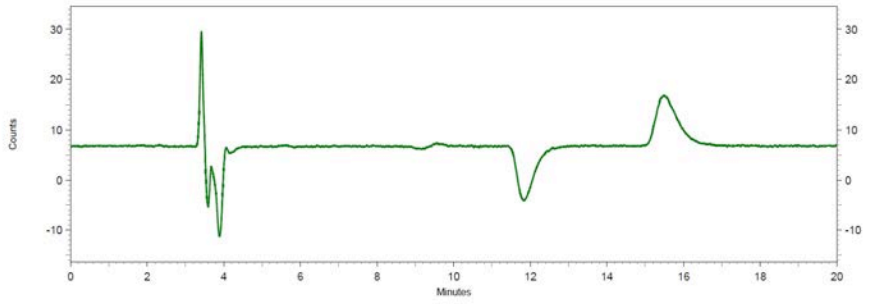

7.573
7.569
7.565
7.554
7.551
7.548
7.372
7.353
7.350
7.332
7.326
7.323
7.305
7.302
7.290
7.286
7.260
7.237
7.219
7.180
7.161
7.149
7.144
7.131
7.126
5.922
4.646
3.269
3.237
2.428
2.395
2.379
2.032
2.027
2.020
2.015
1.998
1.993
1.985
0.866
0.849


HO
O
O
N


2.11
4.26
4.19
0.98
1.07
1.01
2.01
1.03
3.03
f1 (ppm)


170.536
139.848
135.747
129.421
128.512
127.609
126.790
125.377
118.664
101.992
85.737
38.118
38.089
25.805
6.781
f1 (ppm)

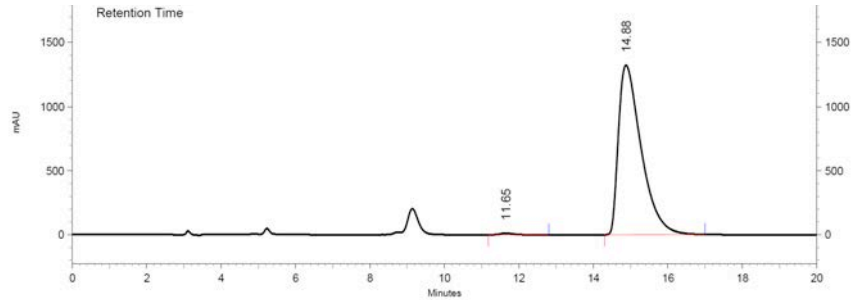


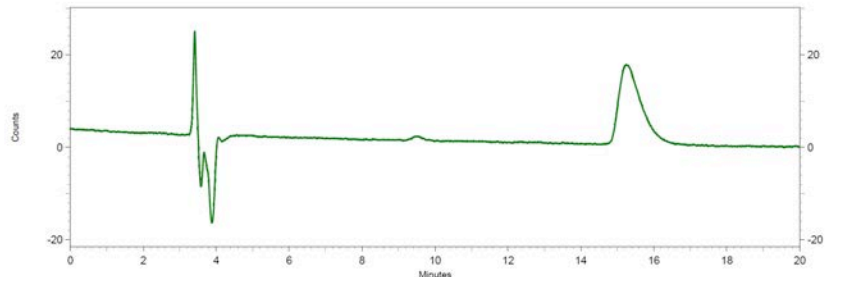




1: 254 nm, 4 nm

Results

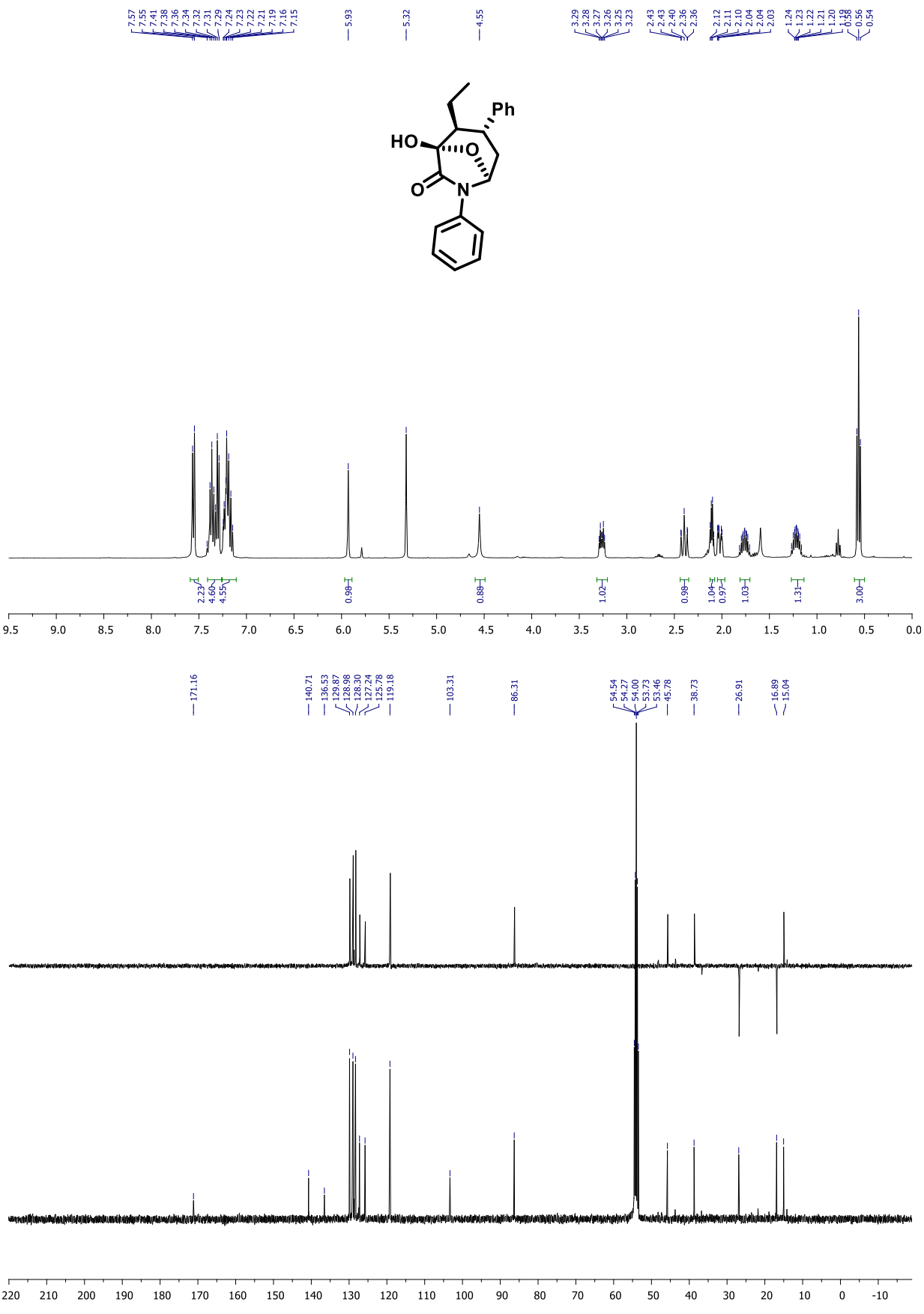
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.46 | 99447042 | 44.97 | 2.82 | 0.00 | 0.00 |
| 15.11 | 121689581 | 55.03 | 4.04 | 0.00 | 4.07 |
| Totals | 221136623 | 100.00 | | | |

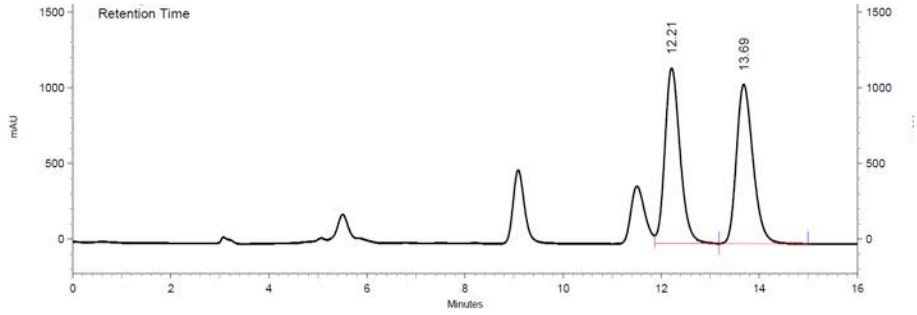


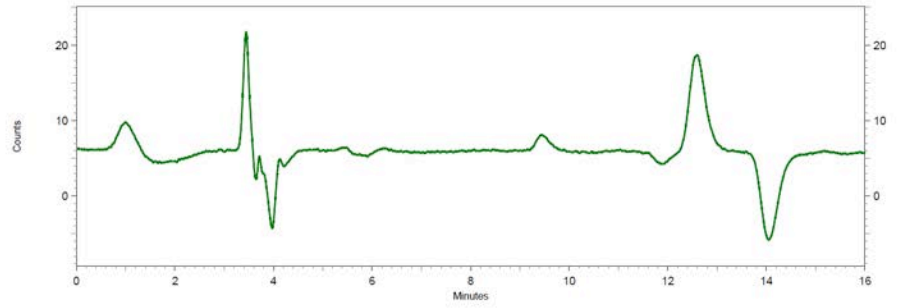




Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.65 | 1359421 | 0.60 | 2.88 | 0.00 | 0.00 |
| 14.88 | 224799241 | 99.40 | 3.96 | 0.00 | 3.58 |
| Totals | 226158662 | 100.00 | | | |


7.57
7.55
7.41
7.38
7.36
7.34
7.32
7.31
7.29
7.24
7.23
7.22
7.21
7.19
7.16
7.15
5.93
5.32
4.55
3.29
3.28
3.27
3.26
3.25
3.23
2.43
2.43
2.40
2.36
2.36
2.12
2.11
2.10
2.04
2.04
2.03
1.24
1.23
1.22
1.21
1.20
1.19
0.58
0.56
0.54
Ph
HO
O
O
N
2.23
4.60
4.55
0.98
0.88
1.02
0.98
1.04
0.97
1.03
1.31
3.00
9.5
9.0
8.5
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
171.16
140.71
136.53
129.87
128.98
128.30
127.24
125.78
119.18
103.31
86.31
54.54
54.27
54.00
53.73
53.46
45.78
38.73
26.91
16.89
15.04
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

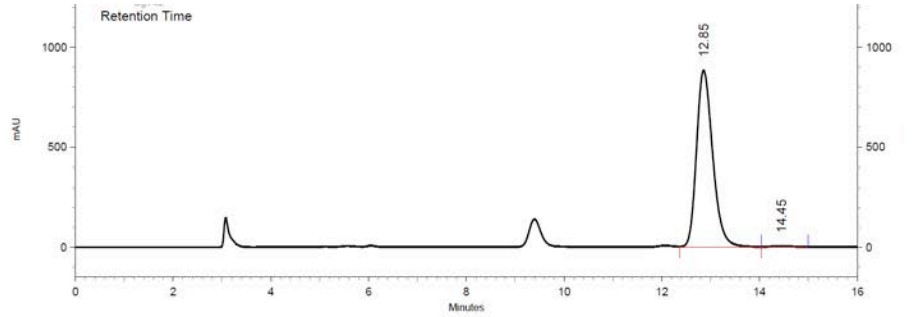


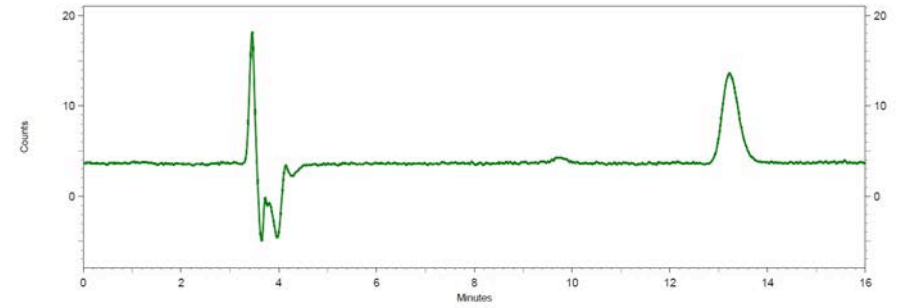




1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 12.21 | 99635537 | 50.26 | 3.07 | 1.00 | 0.00 |
| 13.69 | 98589318 | 49.74 | 3.56 | 1.16 | 2.50 |
| Totals | 198224855 | 100.00 | | | |

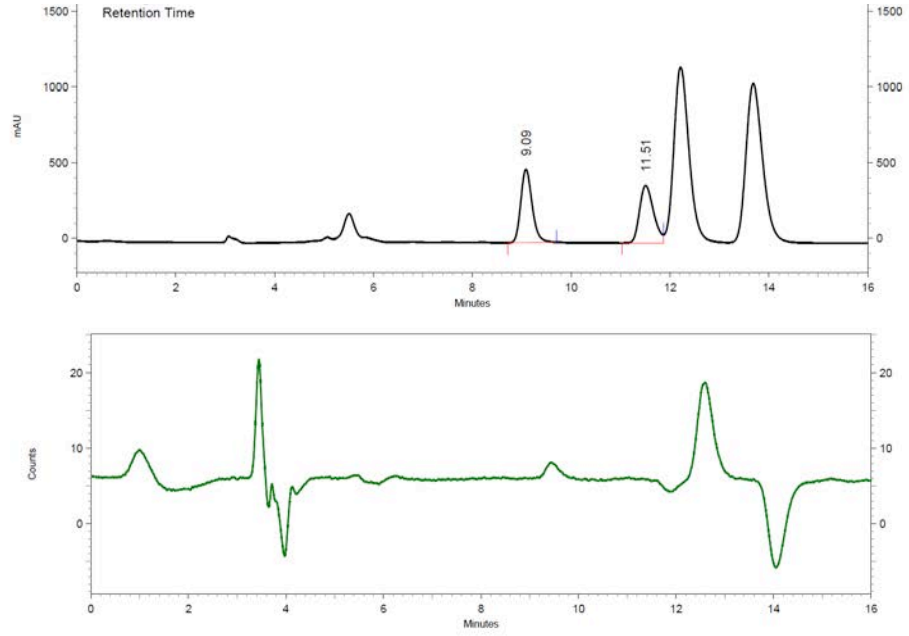



1: 254 nm, 4 nm

Results

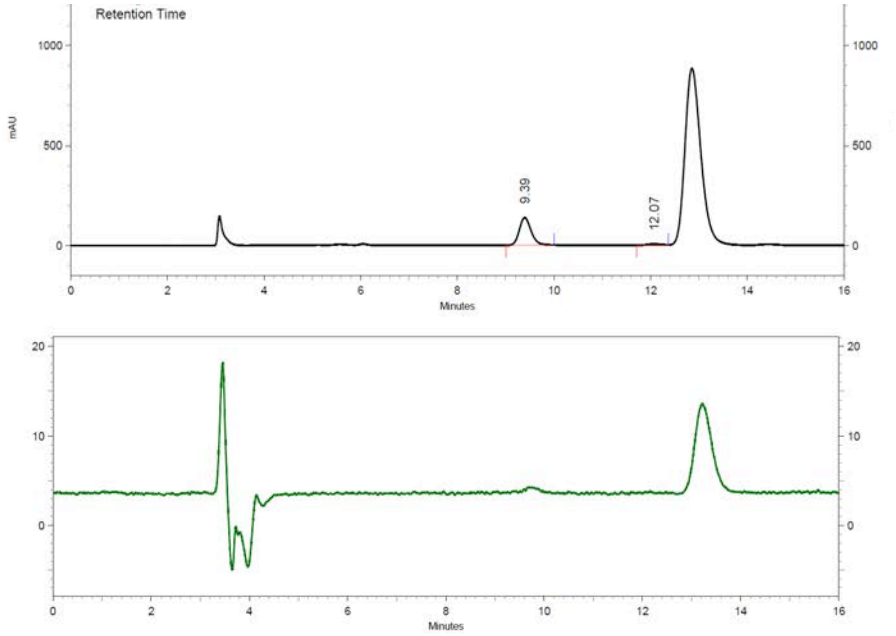
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 12.85 | 81246510 | 99.40 | 3.28 | 0.00 | 0.00 |
| 14.45 | 493174 | 0.60 | 3.82 | 0.00 | 2.52 |
| Totals | 81739684 | 100.00 | | | |




1: 254 nm, 4 nm

Results

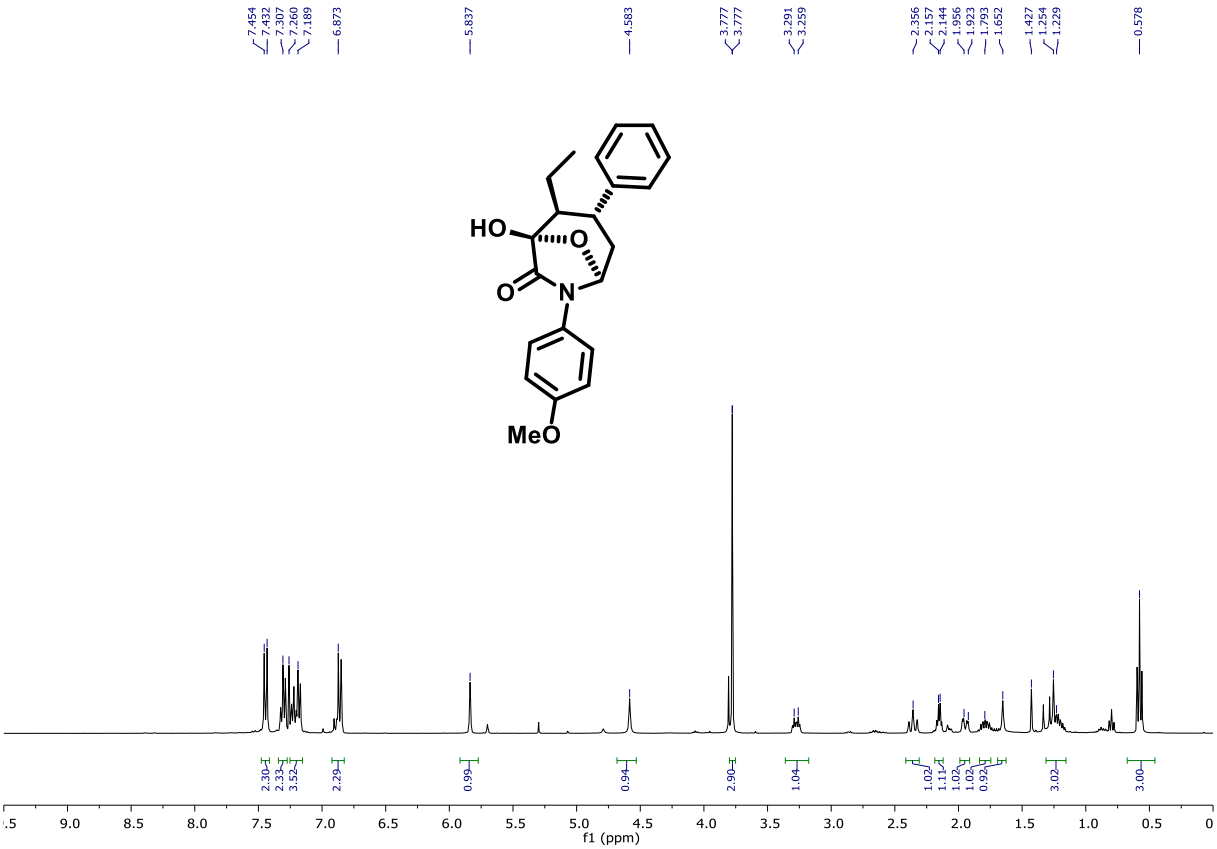
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.09 | 31018388 | 50.82 | 2.03 | 1.00 | 0.00 |
| 11.51 | 30020321 | 49.18 | 2.84 | 1.40 | 5.07 |
| Totals | 61038709 | 100.00 | | | |

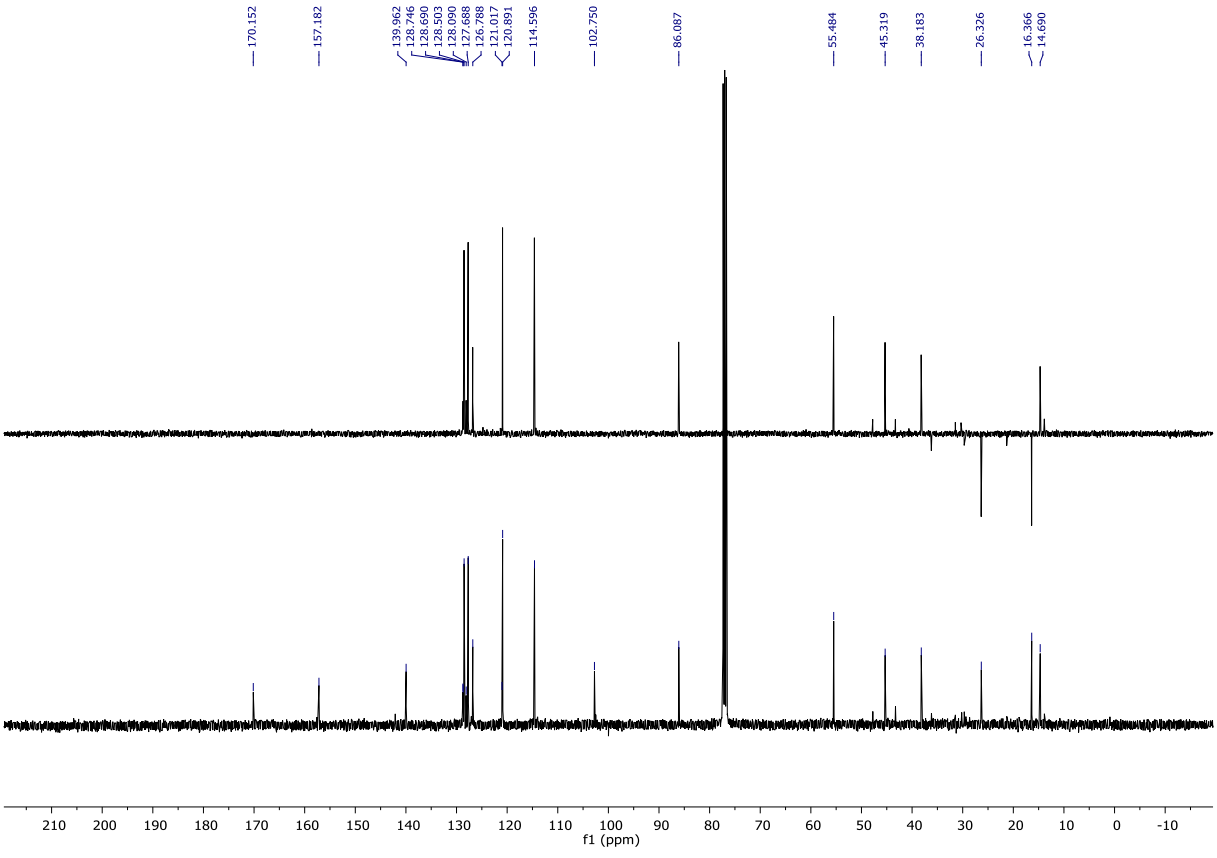


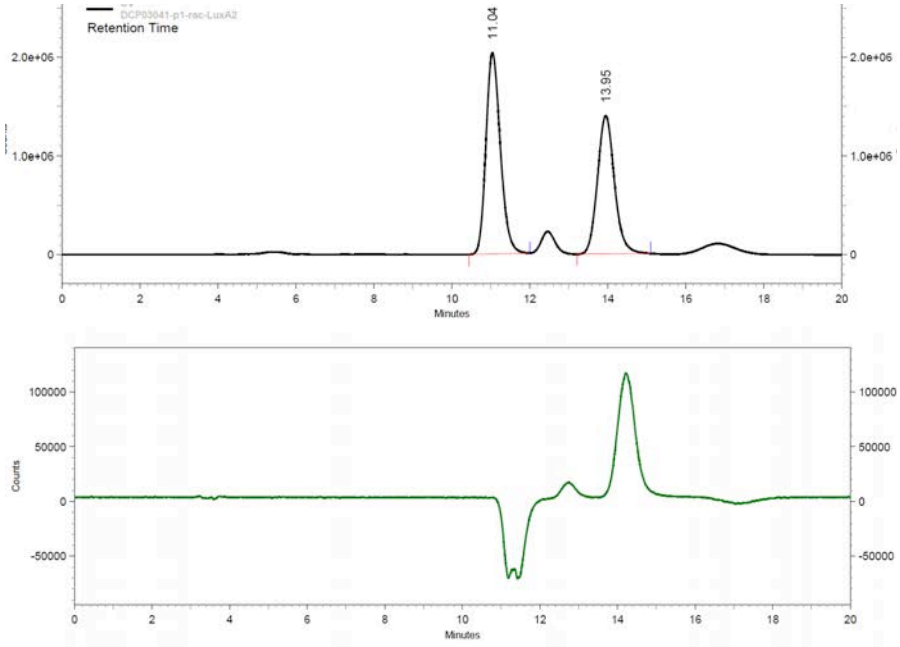

1: 254 nm, 4 nm

Results

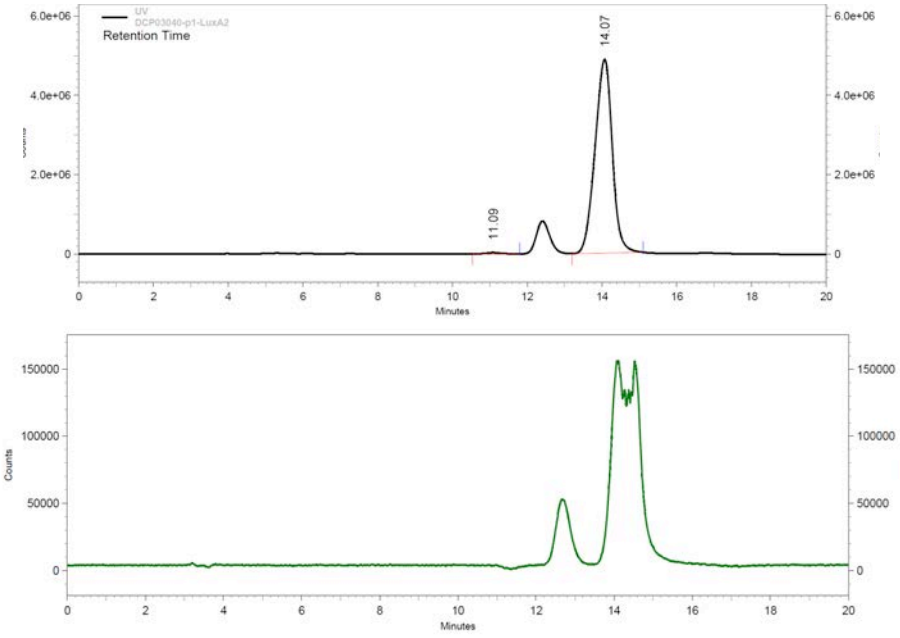
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.39 | 9318553 | 94.54 | 2.13 | 0.00 | 0.00 |
| 12.07 | 538697 | 5.46 | 3.02 | 0.00 | 0.00 |
| Totals | 9857250 | 100.00 | | | |


7.454
7.432
7.307
7.260
7.189
6.873
5.837
4.583
3.777
3.777
3.291
3.259
2.356
2.157
2.144
1.956
1.923
1.793
1.652
1.427
1.254
1.229
0.578
HO
O
O
N
MeO
2.30
2.33
3.52
2.29
0.99
0.94
2.90
1.04
1.02
1.11
1.02
0.92
3.02
3.00
f1 (ppm)


170.152
157.182
139.962
128.746
128.690
128.503
128.090
127.688
126.788
121.017
120.891
114.596
102.750
86.087
55.484
45.319
38.183
26.326
16.366
14.690
f1 (ppm)

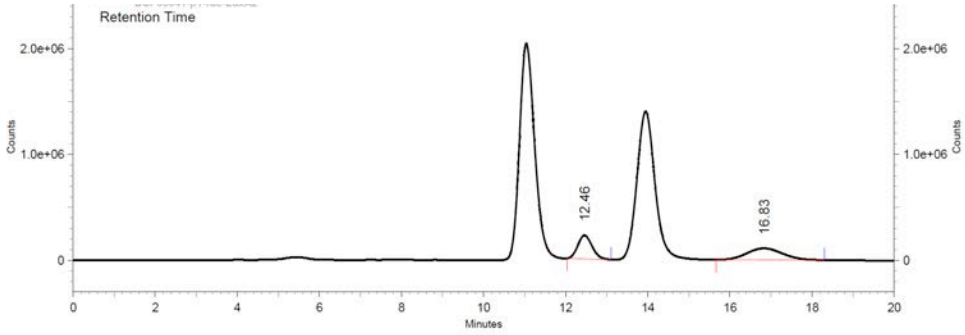


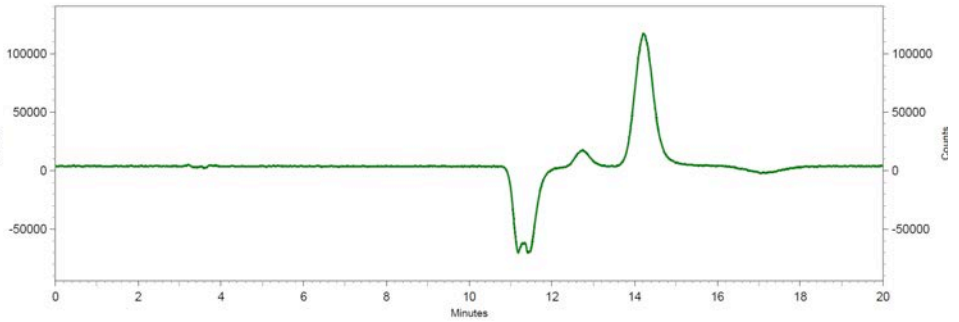

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.04 | 52430660 | 55.22 | 2.68 | 1.00 | 0.00 |
| 13.95 | 42522016 | 44.78 | 3.65 | 1.36 | 3.92 |
| Totals | 94952676 | 100.00 | | | |




UV Results

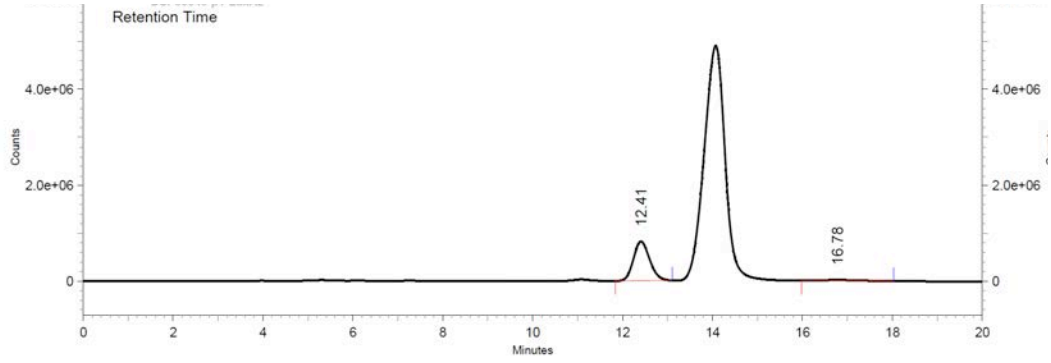
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.09 | 880506 | 0.56 | 2.70 | 1.00 | 0.00 |
| 14.07 | 156808063 | 99.44 | 3.69 | 1.37 | 3.88 |
| Totals | 157688569 | 100.00 | | | |

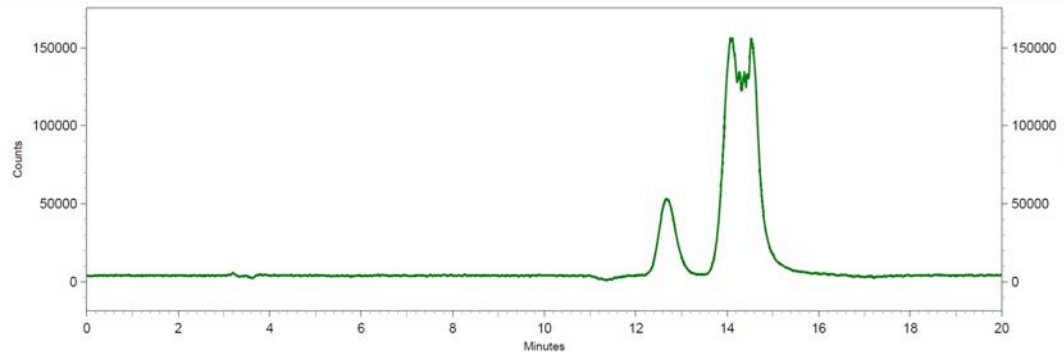



UV Results

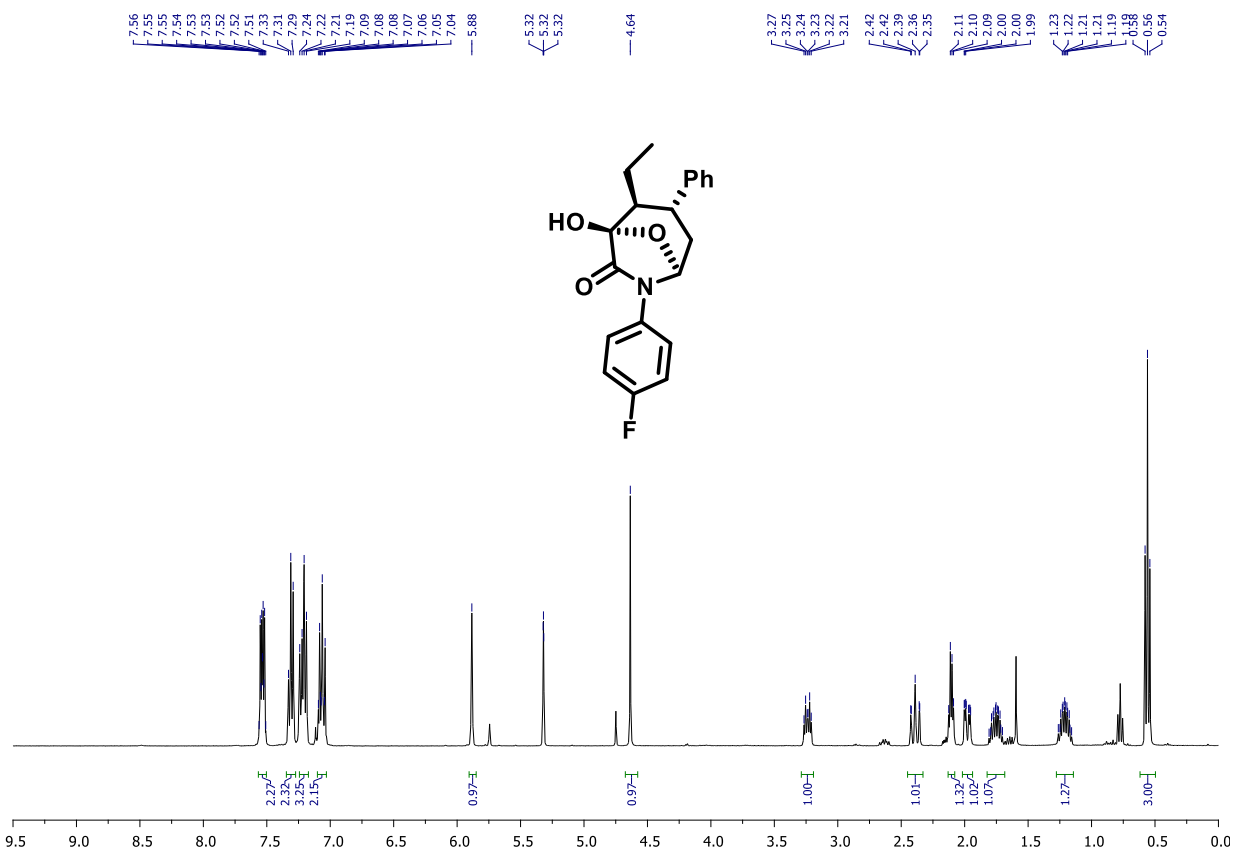
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 12.46 | 5380430 | 44.73 | 3.15 | 0.00 | 0.00 |
| 16.83 | 6648267 | 55.27 | 4.61 | 0.00 | 3.81 |
| Totals | 12028697 | 100.00 | | | |

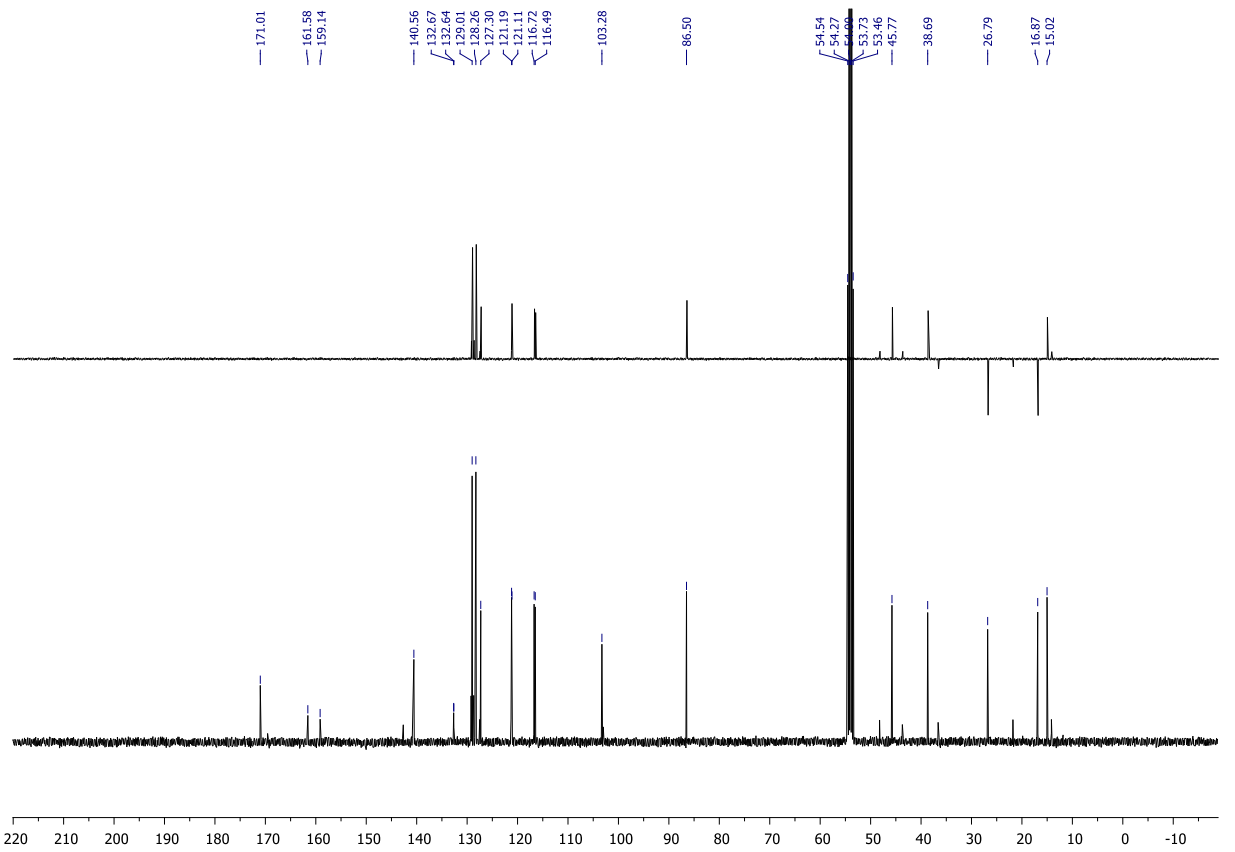


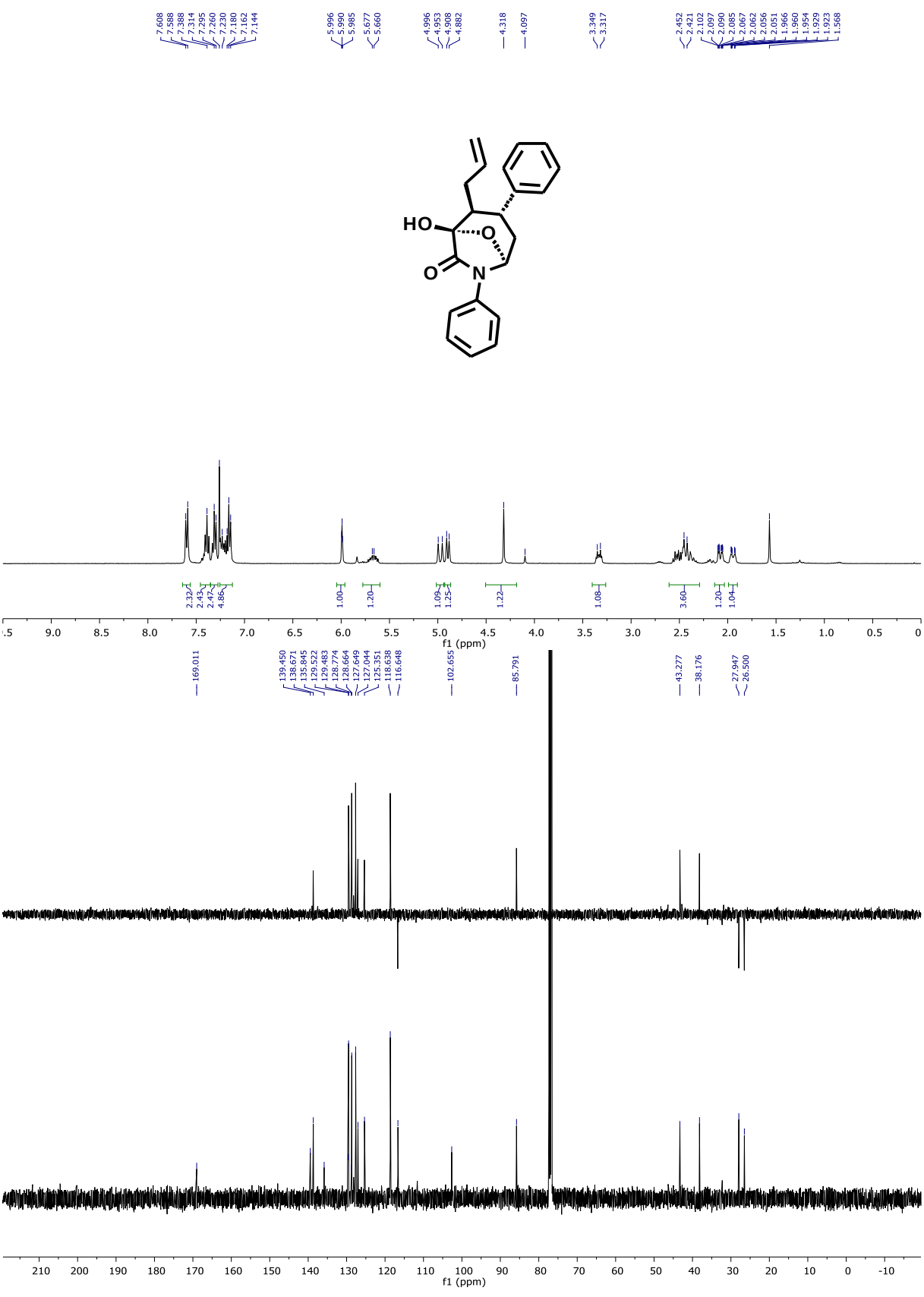



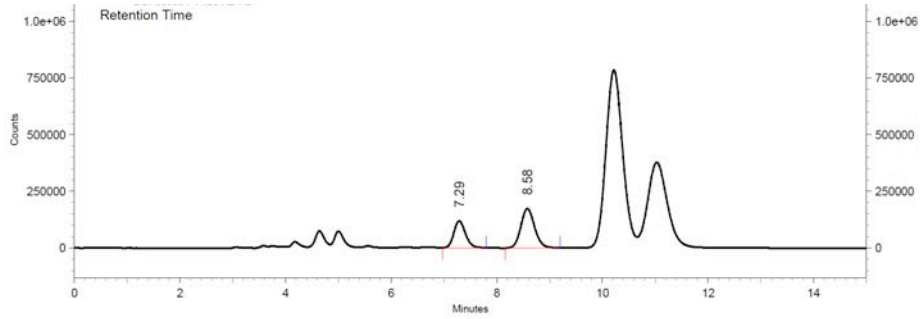

UV Results

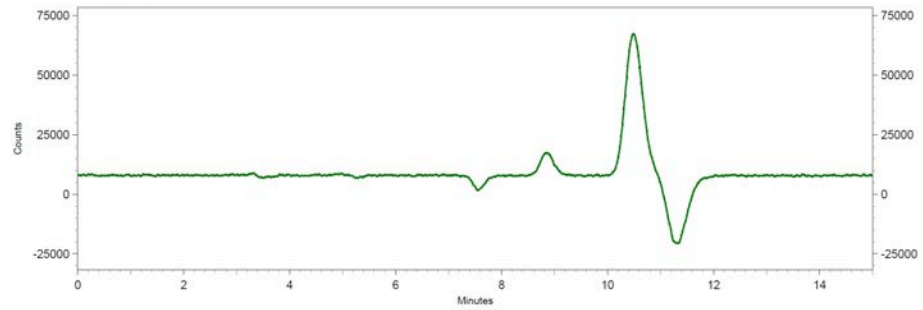
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.09 | 880506 | 0.56 | 2.70 | 1.00 | 0.00 |
| 14.07 | 156808063 | 99.44 | 3.69 | 1.37 | 3.88 |
| Totals | 157688569 | 100.00 | | | |


Ph
HO
O
O
N
F

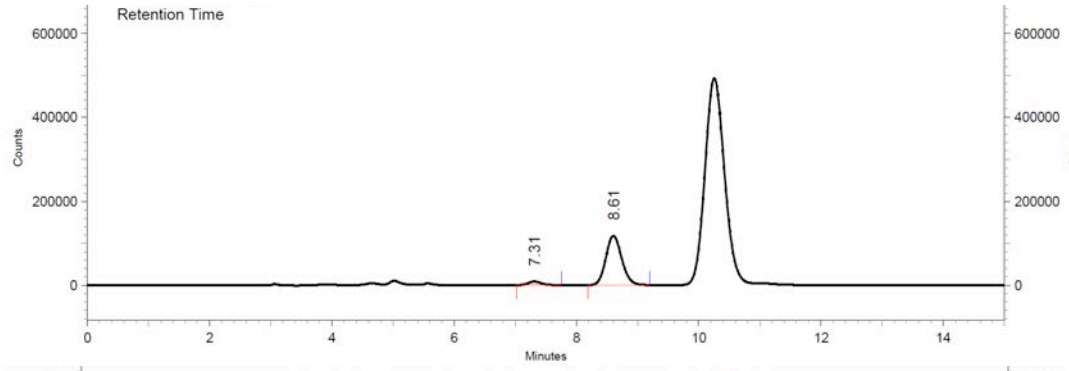


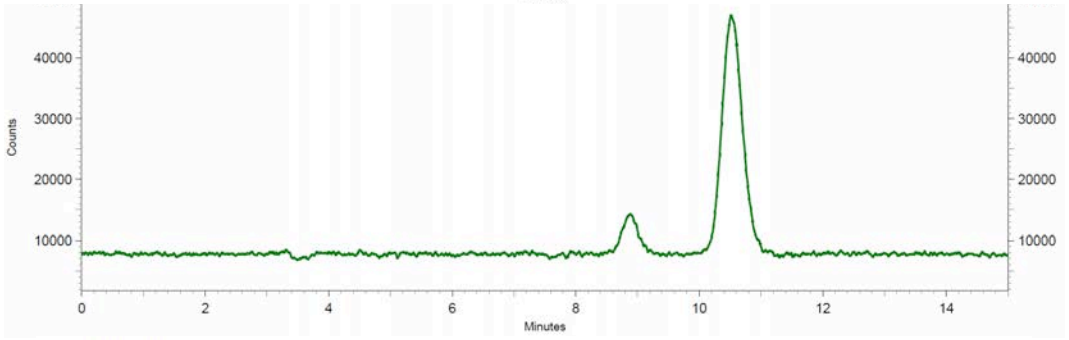

7.608
7.588
7.388
7.314
7.295
7.260
7.230
7.180
7.162
7.144
5.996
5.990
5.985
5.677
5.660
4.996
4.953
4.908
4.882
4.318
4.097
3.349
3.317
2.452
2.421
2.102
2.097
2.090
2.085
2.067
2.062
2.056
2.051
1.966
1.960
1.954
1.929
1.923
1.568
HO
O
O
N
2.32
2.43
2.42
4.86
1.00
1.20
1.09
1.25
1.22
1.08
3.60
1.20
1.04
f1 (ppm)
169.011
139.450
138.671
135.845
129.522
129.483
128.774
128.664
127.649
127.044
125.351
118.638
116.648
102.655
85.791
43.277
38.176
27.947
26.500
f1 (ppm)



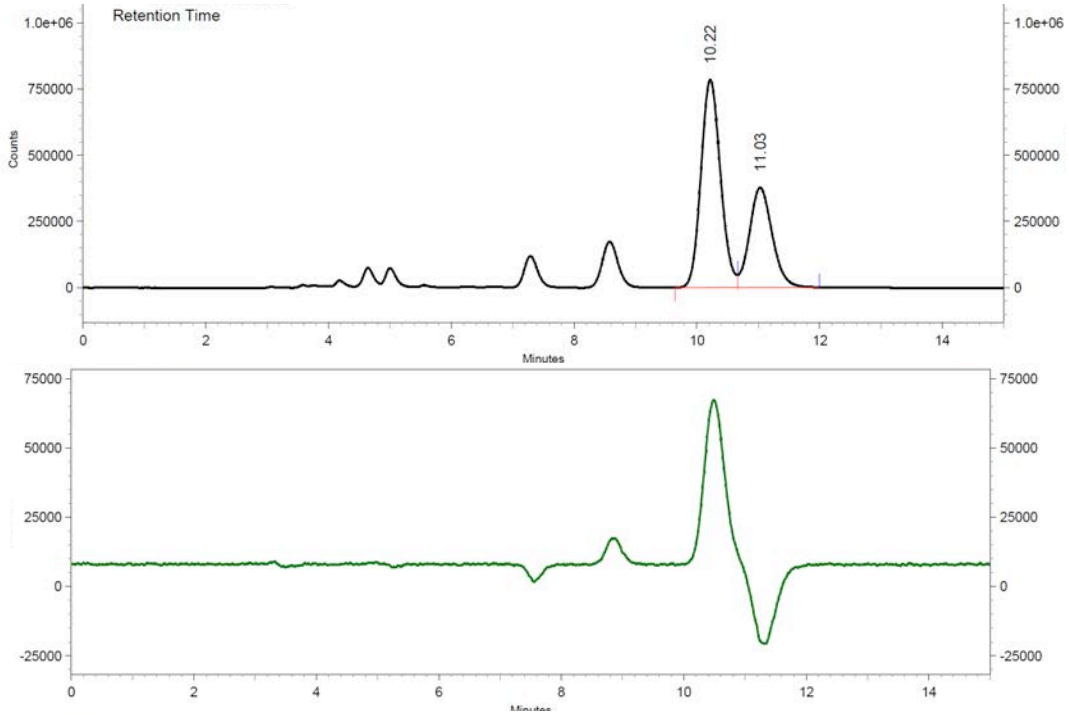




| UV Results<br>Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 7.29 | 1809471 | 36.62 | 1.43 | 1.00 | 0.00 |
| 8.58 | 3131348 | 63.38 | 1.86 | 1.30 | 2.90 |
| Totals | 4940819 | 100.00 | | | |

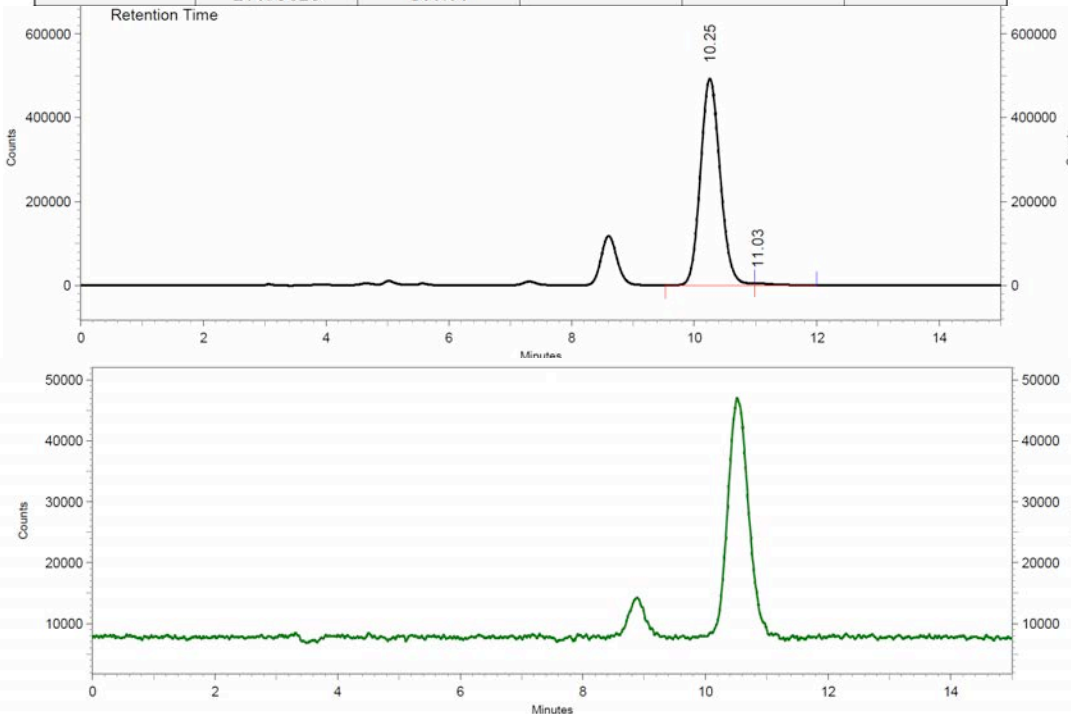


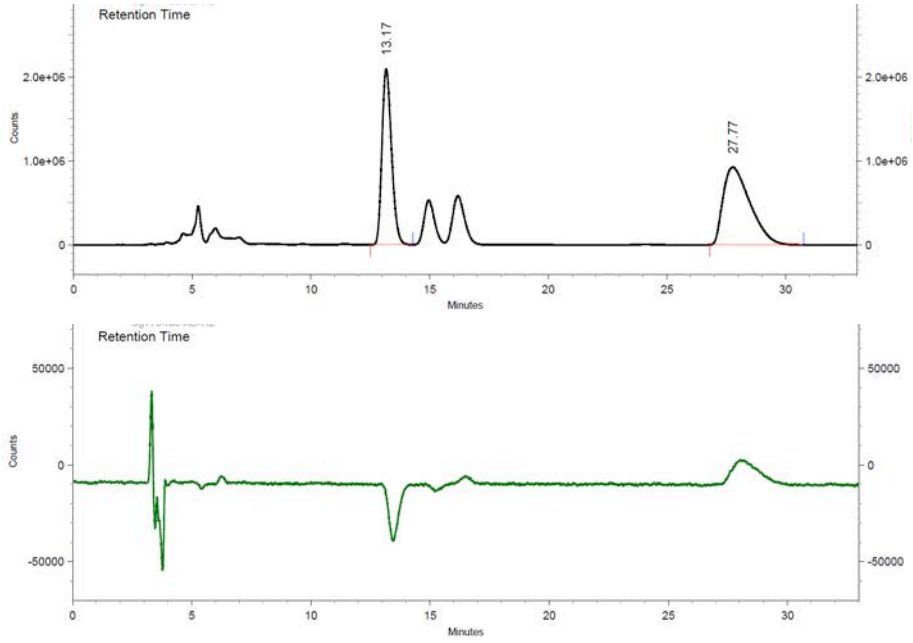

| UV Results<br>Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 7.31 | 130524 | 5.76 | 1.44 | 1.00 | 0.00 |
| 8.61 | 2135118 | 94.24 | 1.87 | 1.30 | 2.92 |
| Totals | 2265642 | 100.00 | | | |



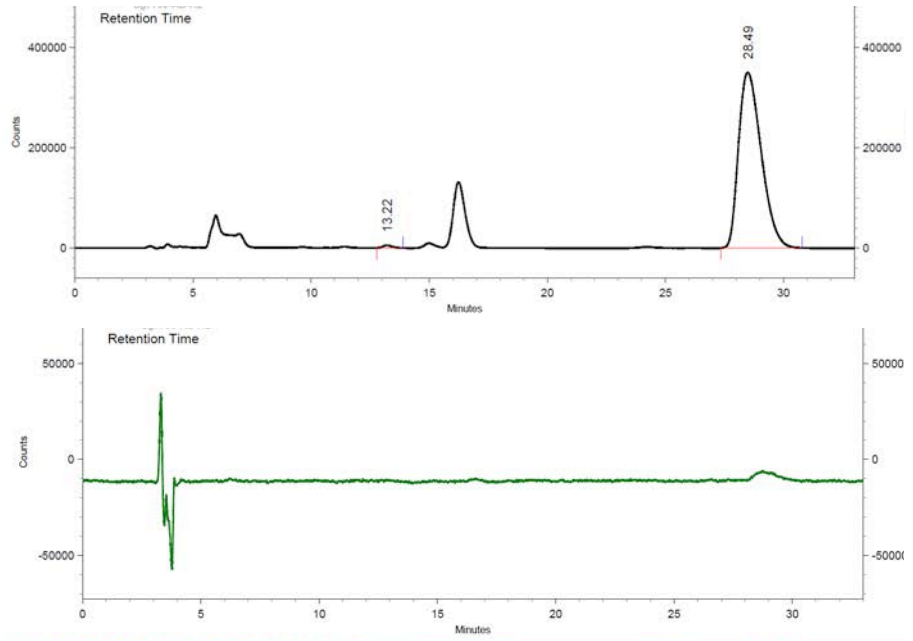

| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 10.22 | 17362594 | 64.08 | 2.41 | 1.00 | 0.00 |
| 11.03 | 9731034 | 35.92 | 2.68 | 1.11 | 1.27 |
| Totals | 27093628 | 100.00 | | | |



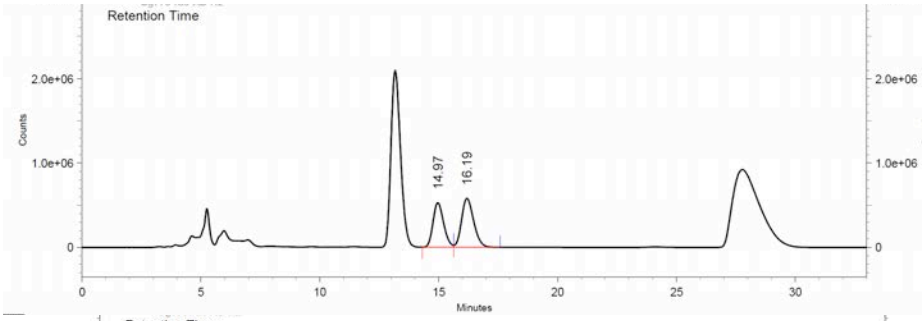

| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 10.25 | 11033505 | 99.18 | 2.42 | 1.00 | 0.00 |
| 11.03 | 91477 | 0.82 | 2.68 | 1.11 | 0.00 |
| Totals | 11124982 | 100.00 | | | |

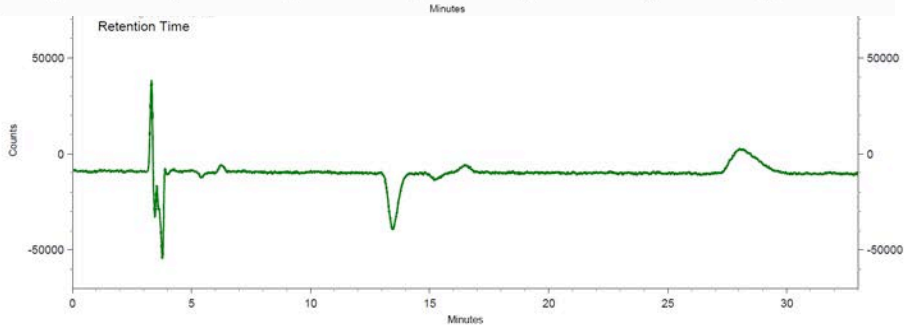



| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 13.17 | 58873156 | 44.69 | 3.39 | 0.00 | 0.00 |
| 27.77 | 72861411 | 55.31 | 8.26 | 0.00 | 10.07 |
| Totals | 131734567 | 100.00 | | | |

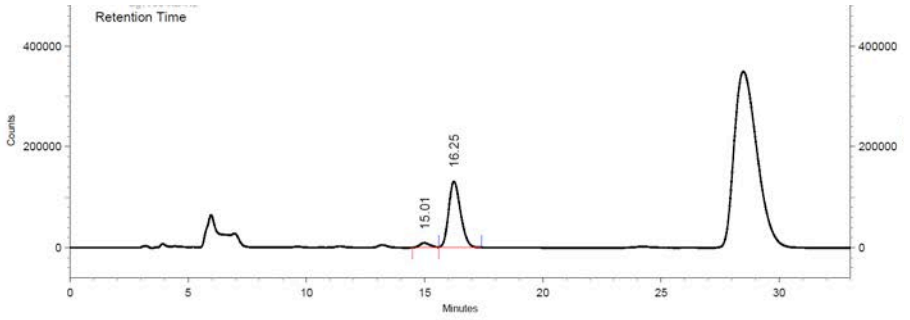


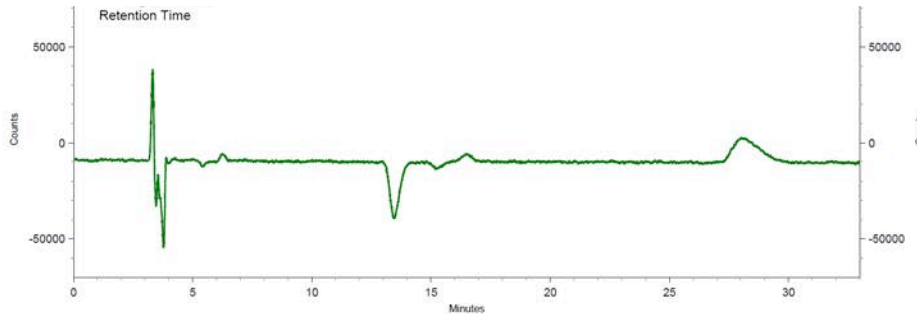

| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 13.22 | 142314 | 0.60 | 3.41 | 0.00 | 0.00 |
| 28.49 | 23429918 | 99.40 | 8.50 | 0.00 | 12.07 |
| Totals | 23572232 | 100.00 | | | |



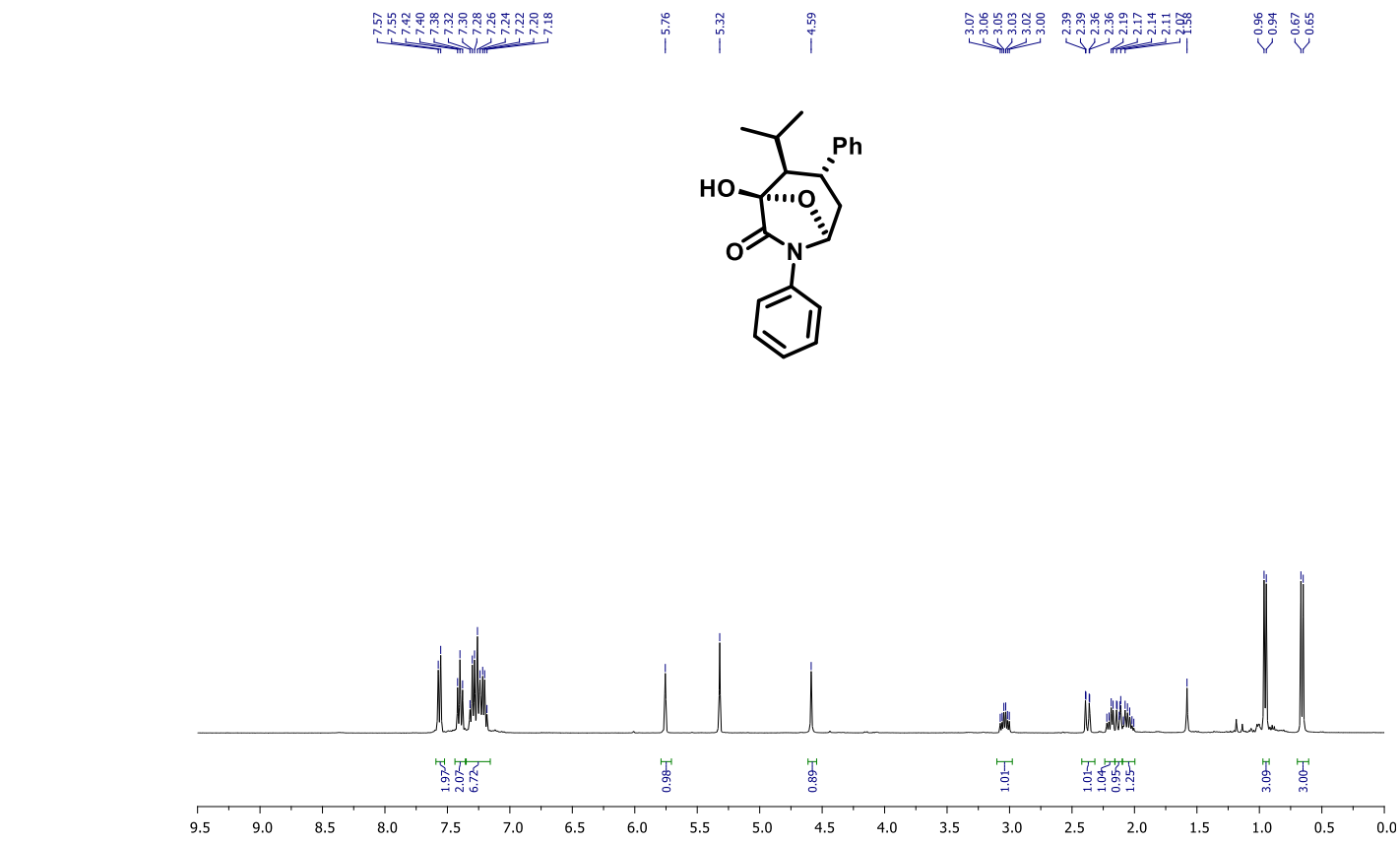




| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 14.97 | 16400059 | 44.40 | 3.99 | 0.00 | 0.00 |
| 16.19 | 20534724 | 55.60 | 4.40 | 0.00 | 1.38 |
| Totals | 36934783 | 100.00 | | | |




| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 15.01 | 283692 | 5.82 | 4.00 | 0.00 | 0.00 |
| 16.25 | 4593911 | 94.18 | 4.42 | 0.00 | 1.39 |
| Totals | 4877603 | 100.00 | | | |


7.57
7.55
7.42
7.40
7.38
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7.28
7.26
7.24
7.22
7.20
7.18
5.76
5.32
4.59
3.07
3.06
3.05
3.03
3.02
3.00
2.39
2.39
2.36
2.36
2.19
2.17
2.14
2.11
2.07
1.58
0.96
0.94
0.67
0.65
Ph
HO
O
O
N
1.97
2.07
6.72
0.98
0.89
1.01
1.01
1.04
0.95
1.25
3.09
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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2.0
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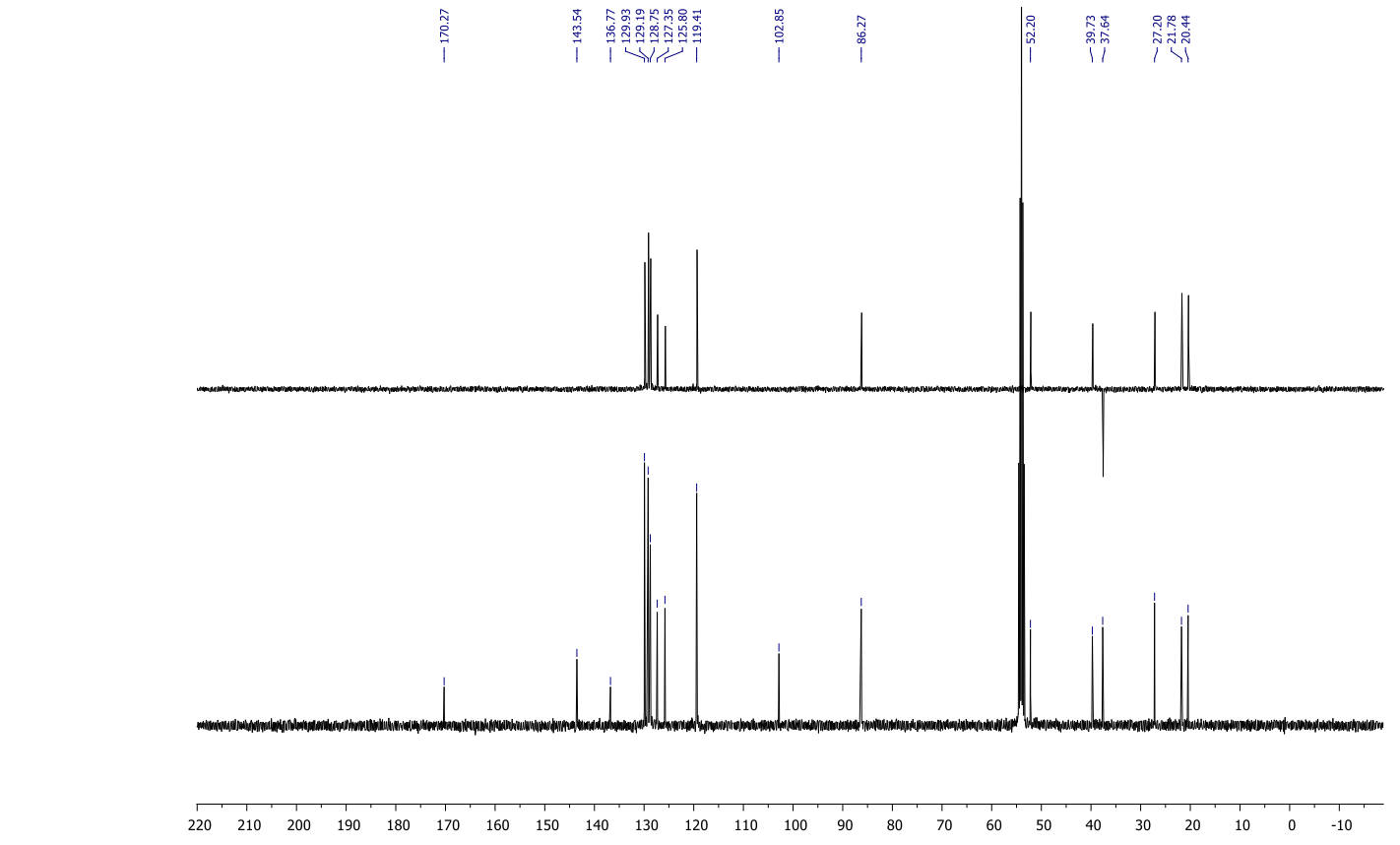
0.0


170.27
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136.77
129.93
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127.35
125.80
119.41
102.85
86.27
52.20
39.73
37.64
27.20
21.78
20.44
220
210
200
190
180
170
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120
110
100
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80
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60
50
40
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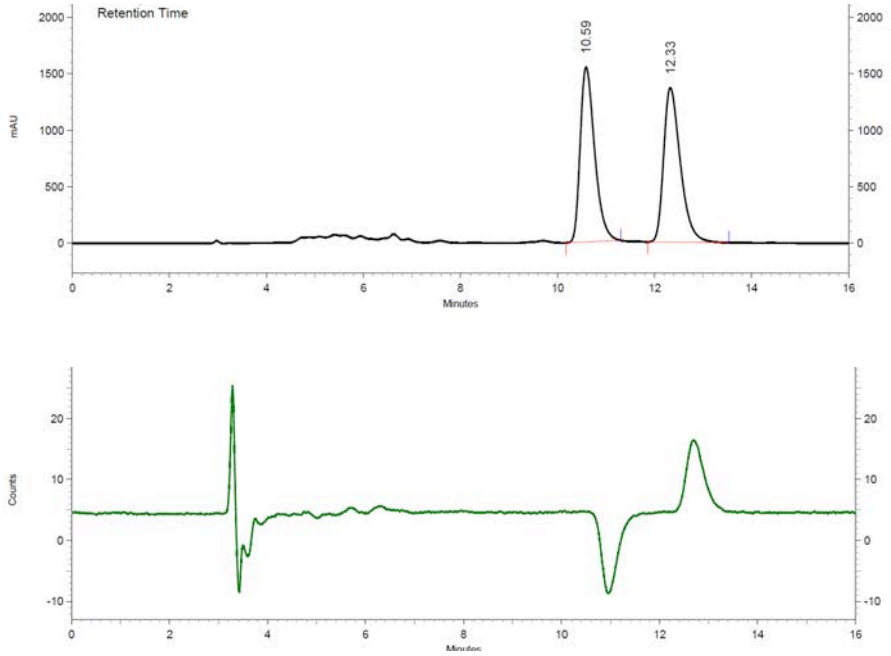
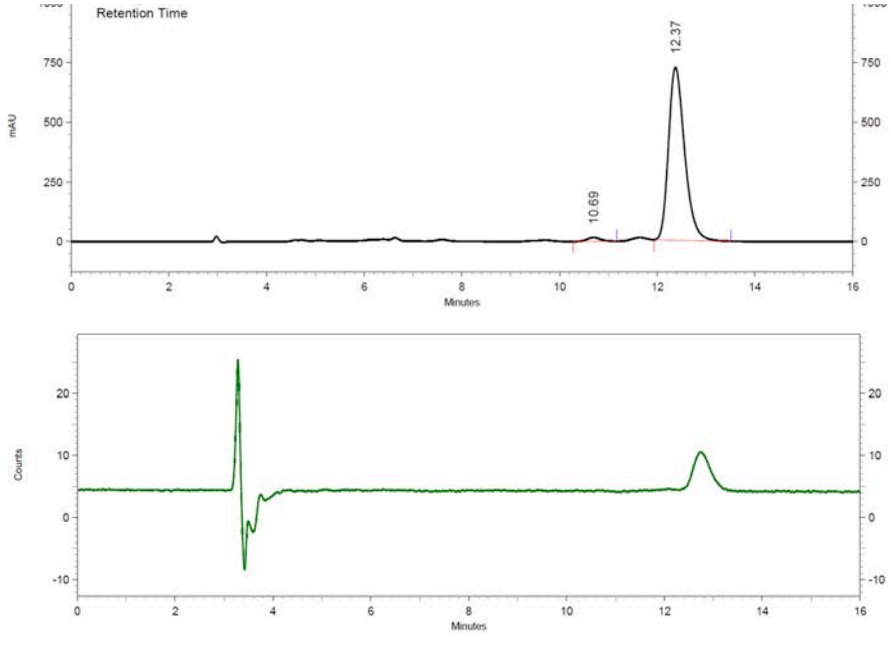
20
10
0
-10




1: 254 nm, 4 nm

Results

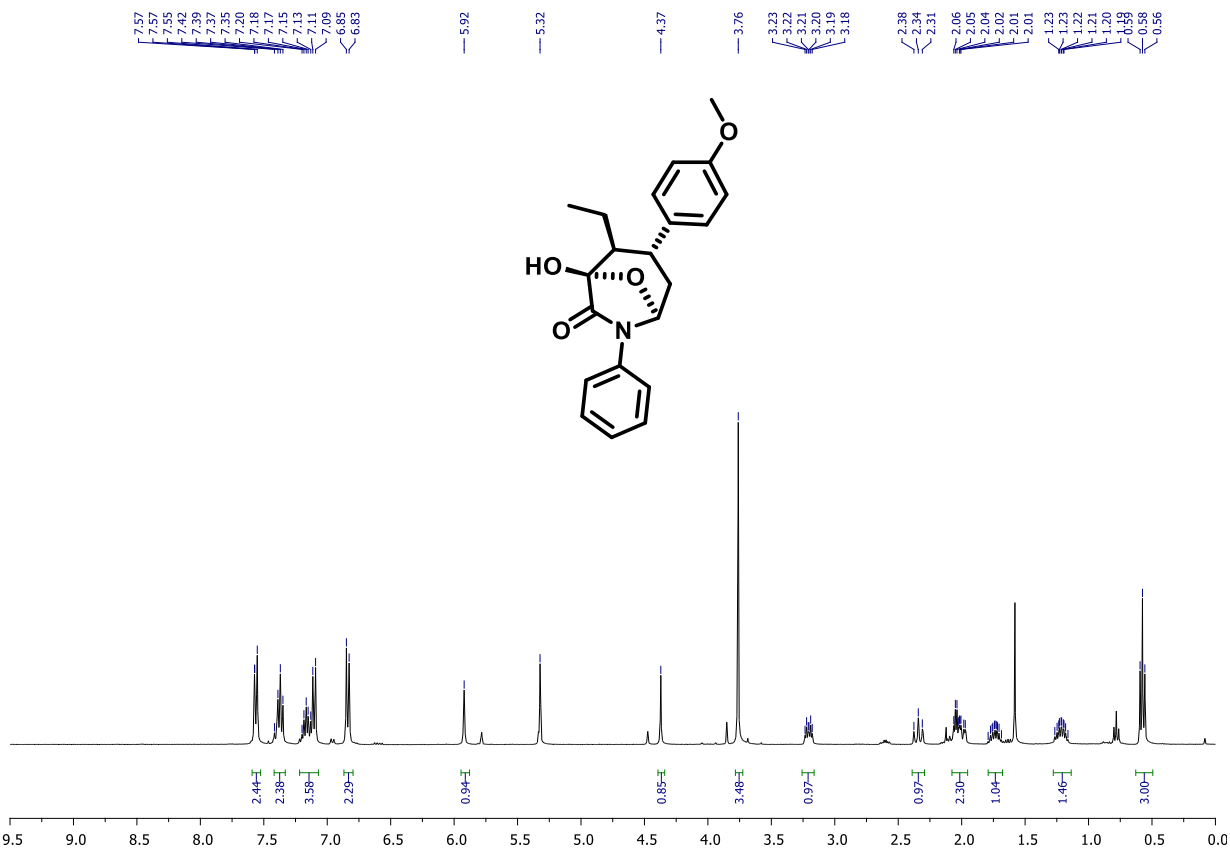
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 10.59 | 128282460 | 49.39 | 2.53 | 1.00 | 0.00 |
| 12.33 | 131437674 | 50.61 | 3.11 | 1.23 | 2.96 |
| Totals | 259720134 | 100.00 | | | |




1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 10.69 | 1229290 | 1.81 | 2.56 | 1.00 | 0.00 |
| 12.37 | 66513280 | 98.19 | 3.12 | 1.22 | 3.02 |
| Totals | 67742570 | 100.00 | | | |


7.57
7.57
7.55
7.42
7.39
7.37
7.35
7.20
7.18
7.17
7.15
7.13
7.11
7.09
6.85
6.83
5.92
5.32
4.37
3.76
3.23
3.22
3.21
3.20
3.19
3.18
2.38
2.34
2.31
2.06
2.05
2.04
2.02
2.01
2.01
1.23
1.23
1.22
1.21
1.20
0.59
0.58
0.56
HO
O
O
O
N
2.44
2.38
3.58
2.29
0.94
0.85
3.48
0.97
0.97
2.30
1.04
1.46
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
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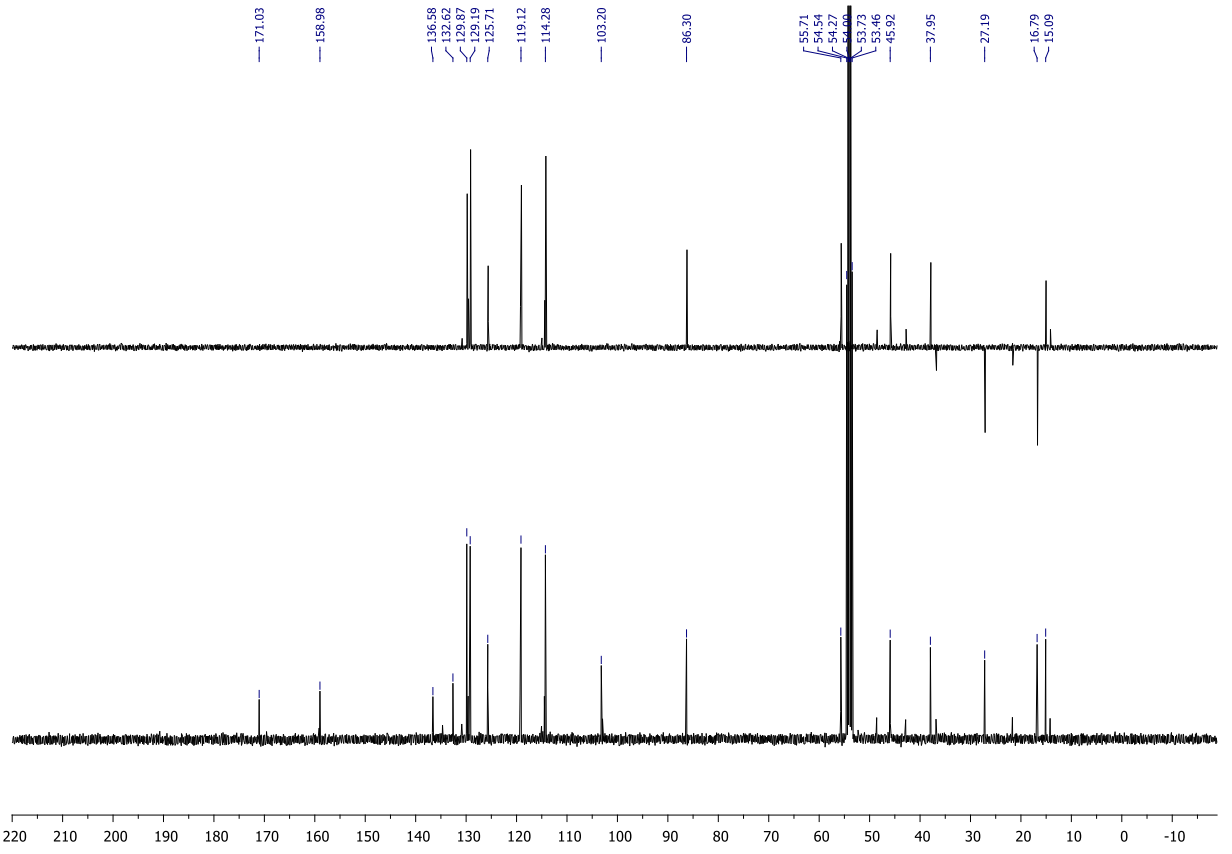
2.0
1.5
1.0
0.5
0.0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103.20
86.30
55.71
54.54
54.27
54.00
53.73
53.46
45.92
37.95
27.19
16.79
15.09
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190
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170
160
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140
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120
110
100
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80
70
60
50
40
30
20
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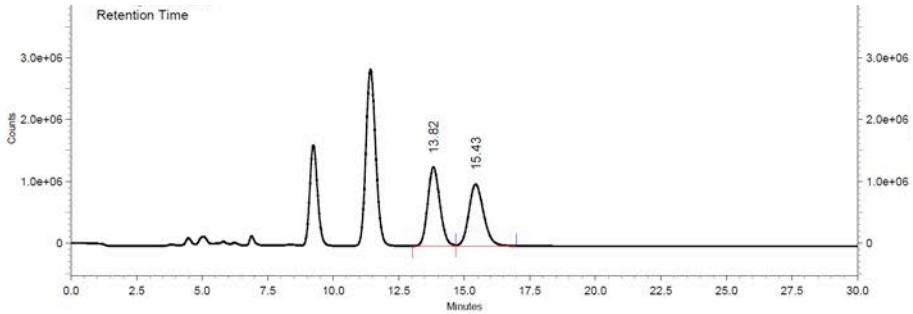
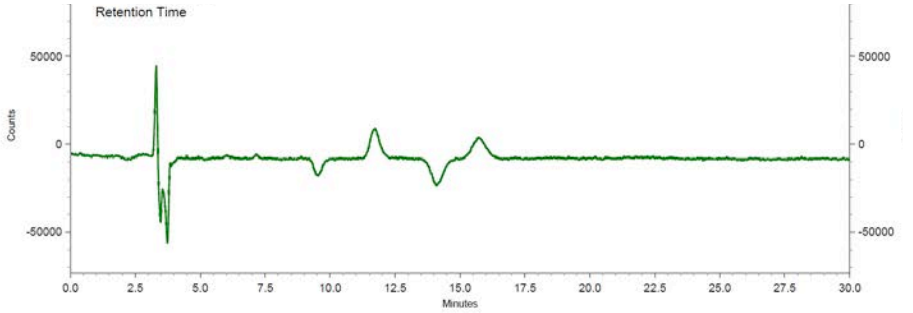
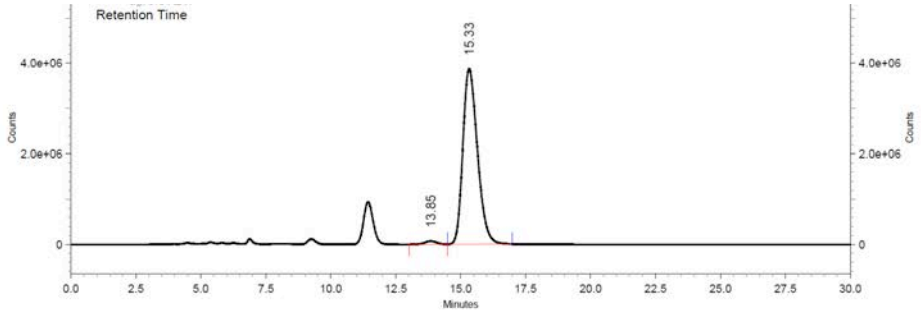
0
-10

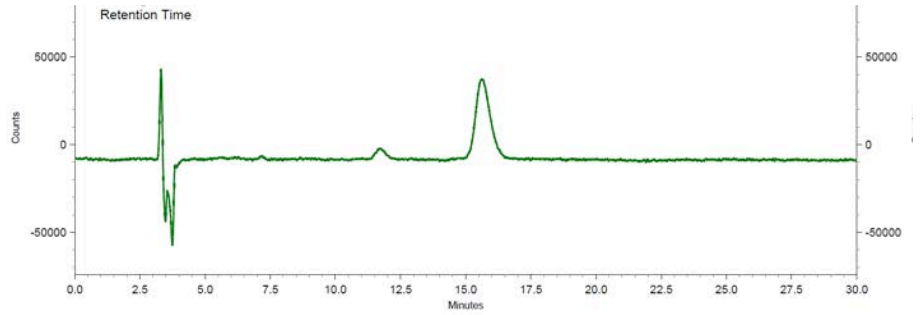
Major diastereomer



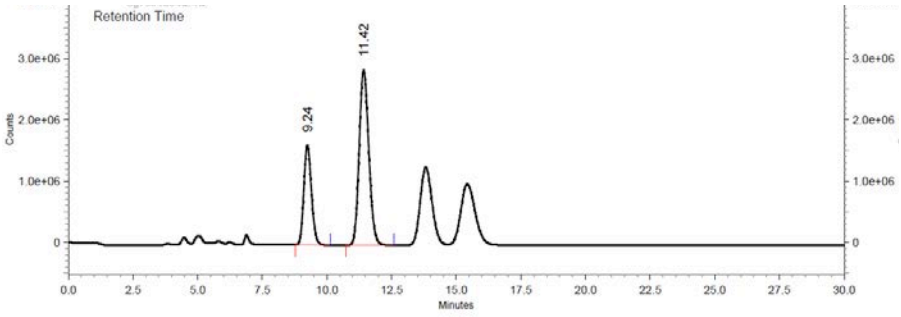

| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 13.82 | 40946775 | 51.14 | 3.61 | 0.00 | 0.00 |
| 15.43 | 39119185 | 48.86 | 4.14 | 0.00 | 1.70 |
| Totals | 80065960 | 100.00 | | | |

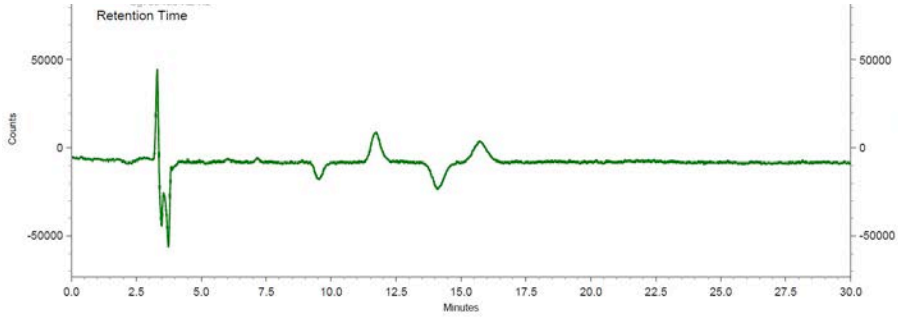


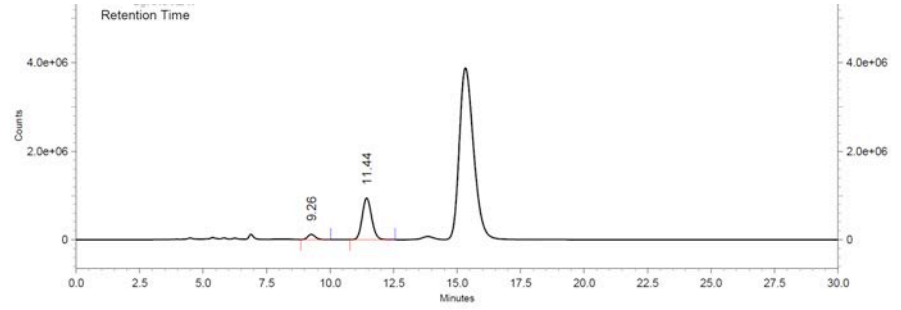

| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 13.85 | 2215689 | 1.45 | 3.62 | 0.00 | 0.00 |
| 15.33 | 150994781 | 98.55 | 4.11 | 0.00 | 1.57 |
| Totals | 153210470 | 100.00 | | | |

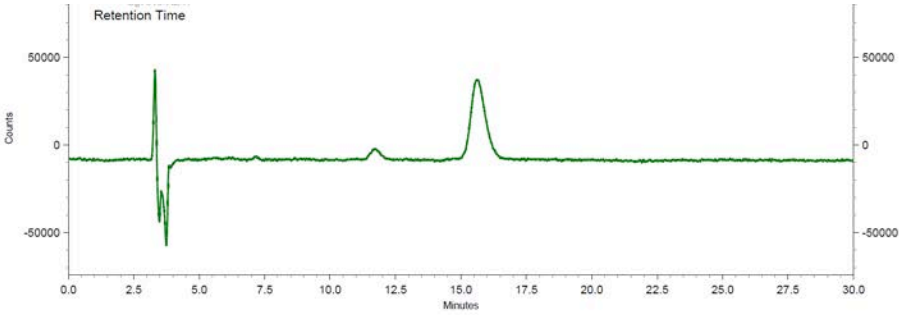
Minor diastereomer



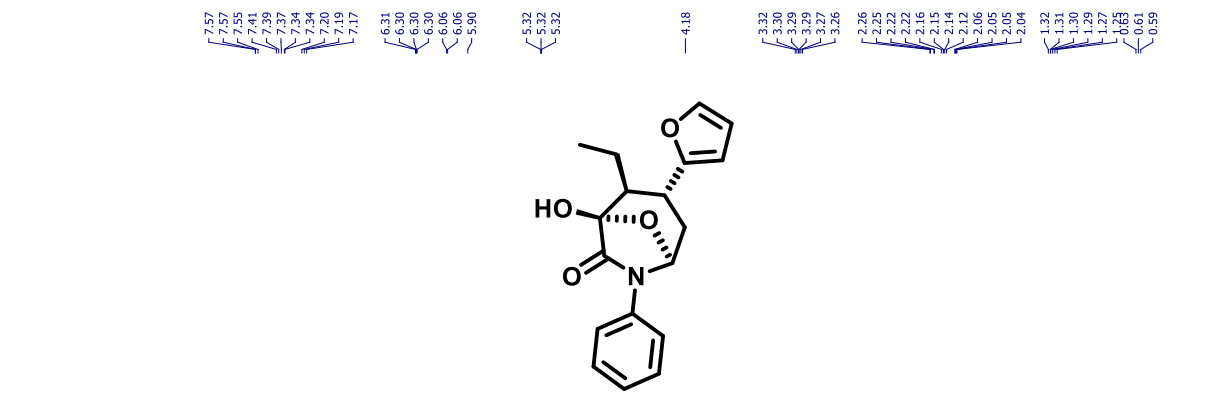




| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.24 | 33513300 | 31.19 | 2.08 | 0.00 | 0.00 |
| 11.42 | 73942002 | 68.81 | 2.81 | 0.00 | 3.50 |
| Totals | 107455302 | 100.00 | | | |




| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.26 | 2392433 | 9.00 | 2.09 | 0.00 | 0.00 |
| 11.44 | 24185803 | 91.00 | 2.81 | 0.00 | 3.54 |
| Totals | 26578236 | 100.00 | | | |


7.57
7.57
7.55
7.41
7.39
7.37
7.34
7.34
7.20
7.19
7.17
6.31
6.30
6.30
6.30
6.06
6.06
5.90
5.32
5.32
5.32
4.18
3.32
3.30
3.29
3.29
3.27
3.26
2.26
2.25
2.22
2.22
2.16
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2.14
2.12
2.06
2.05
2.05
2.04
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1.31
1.30
1.29
1.27
0.63
0.61
0.59


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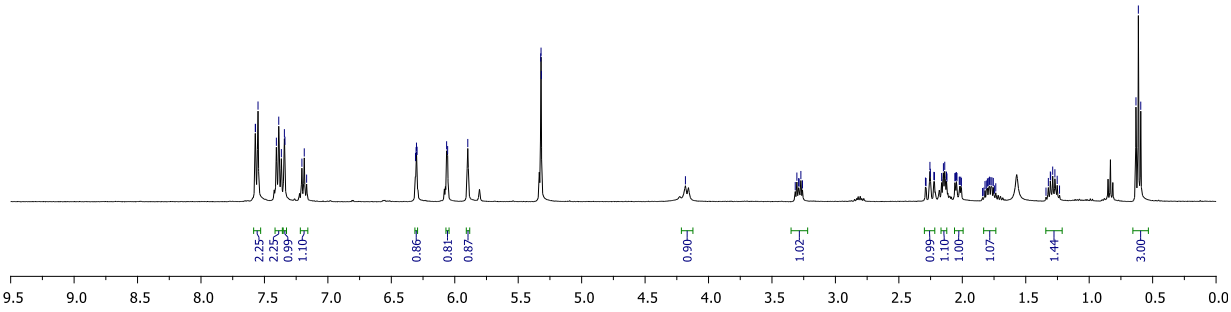
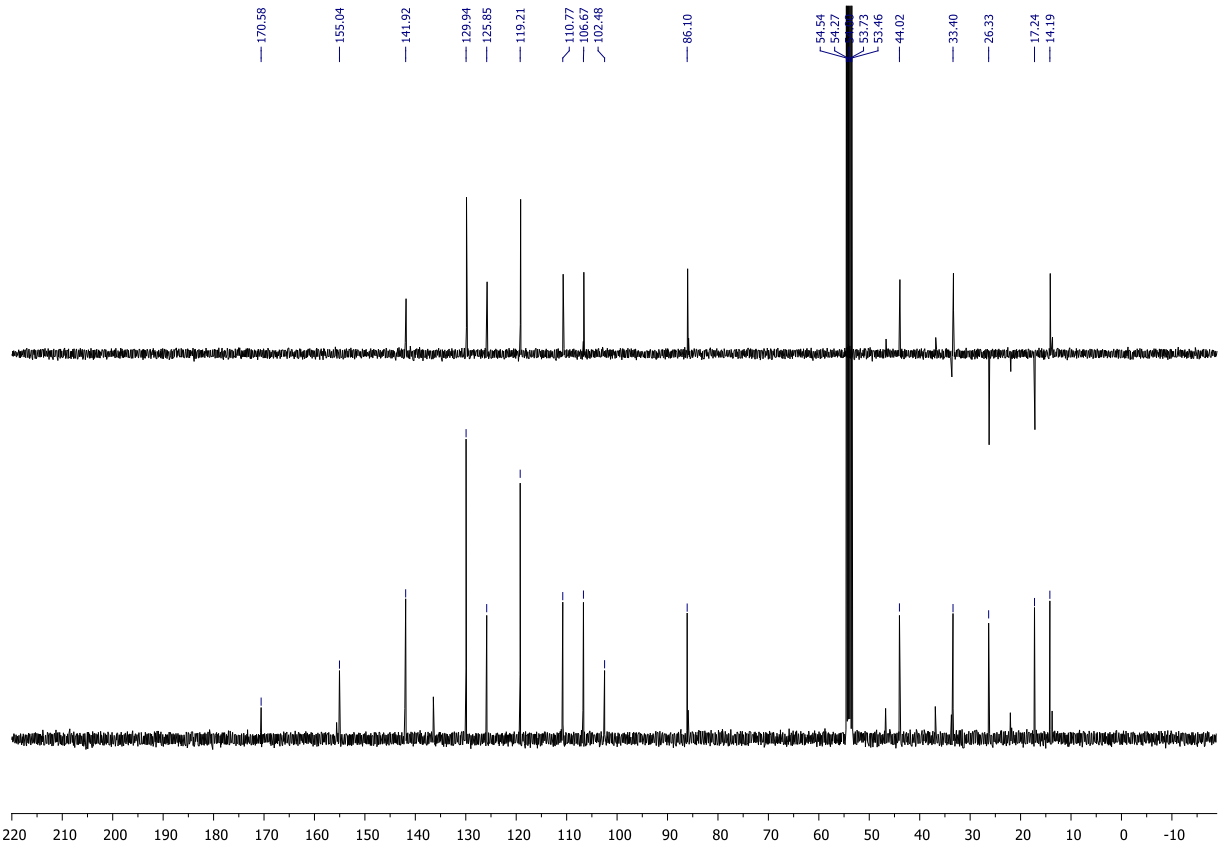

2.25
2.25
0.99
1.10
0.86
0.81
0.87
0.90
1.02
0.99
1.10
1.00
1.07
1.44
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


170.58
155.04
141.92
129.94
125.85
119.21
110.77
106.67
102.48
86.10
54.54
54.27
53.73
53.46
44.02
33.40
26.33
17.24
14.19
220
210
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190
180
170
160
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140
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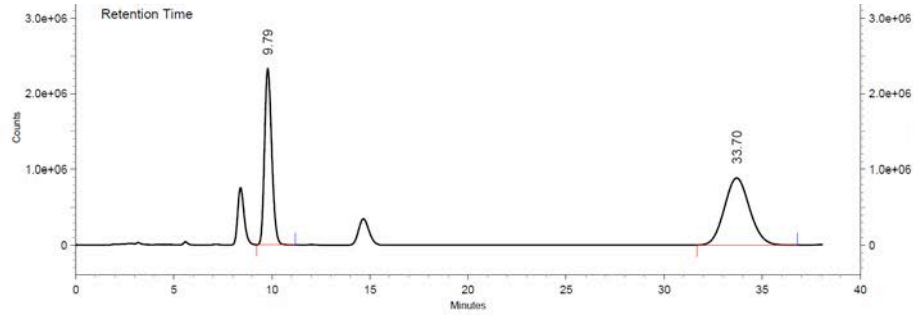
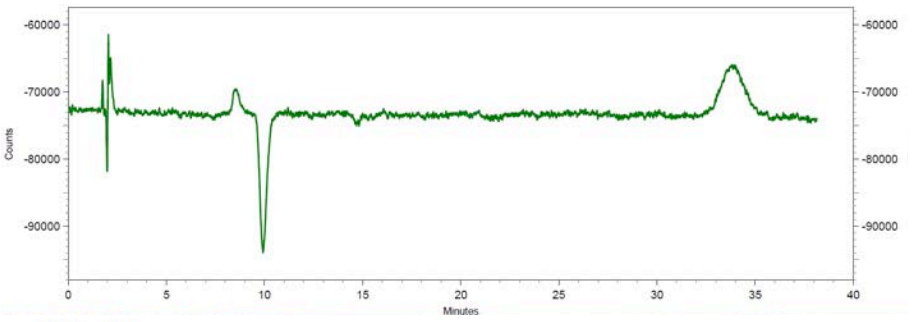
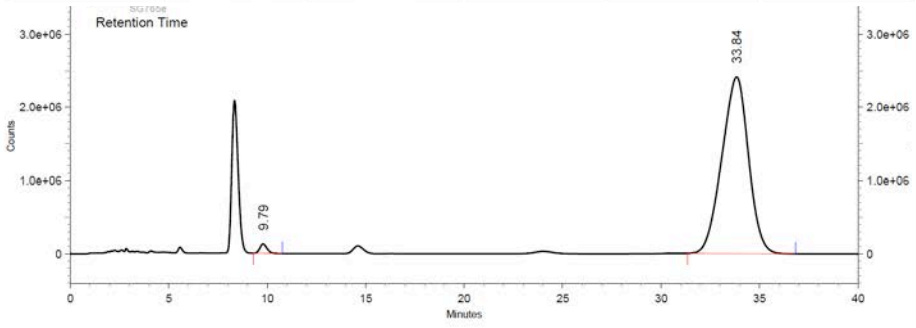
80
70
60
50
40
30
20
10
0
-10

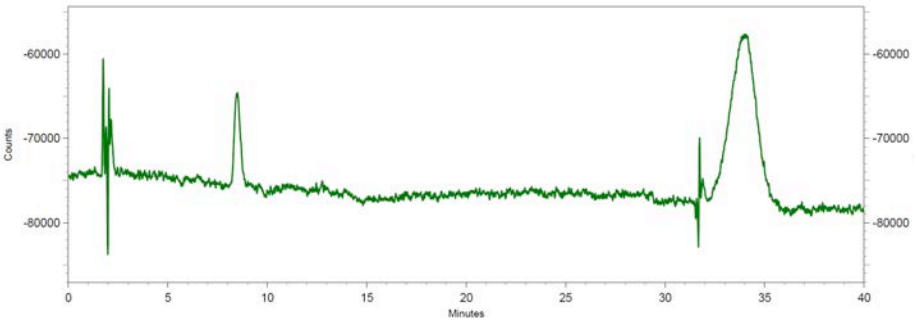



UV Results

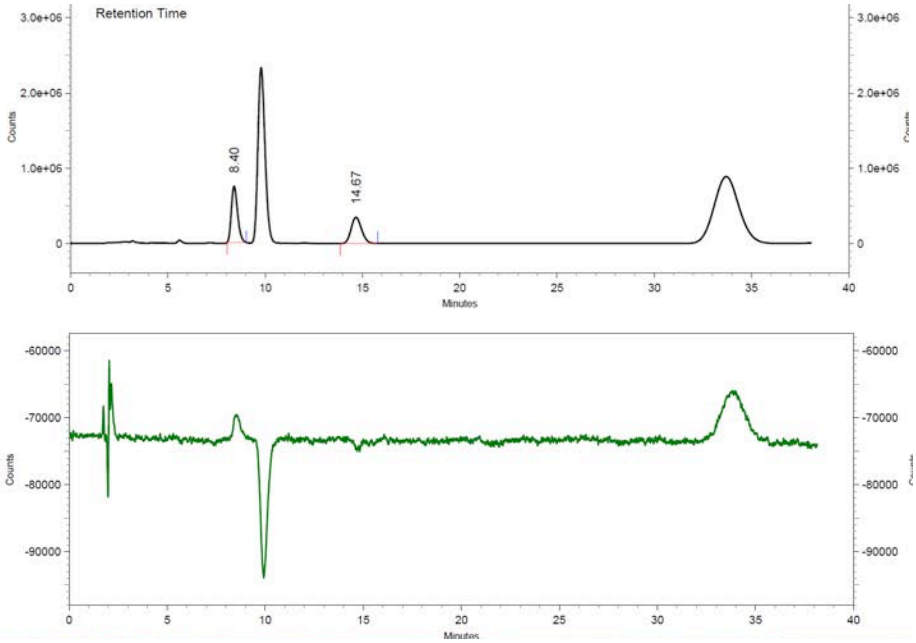
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.79 | 59487520 | 42.78 | 2.26 | 1.00 | 0.00 |
| 33.70 | 79555114 | 57.22 | 10.23 | 4.52 | 15.48 |
| Totals | 139042634 | 100.00 | | | |



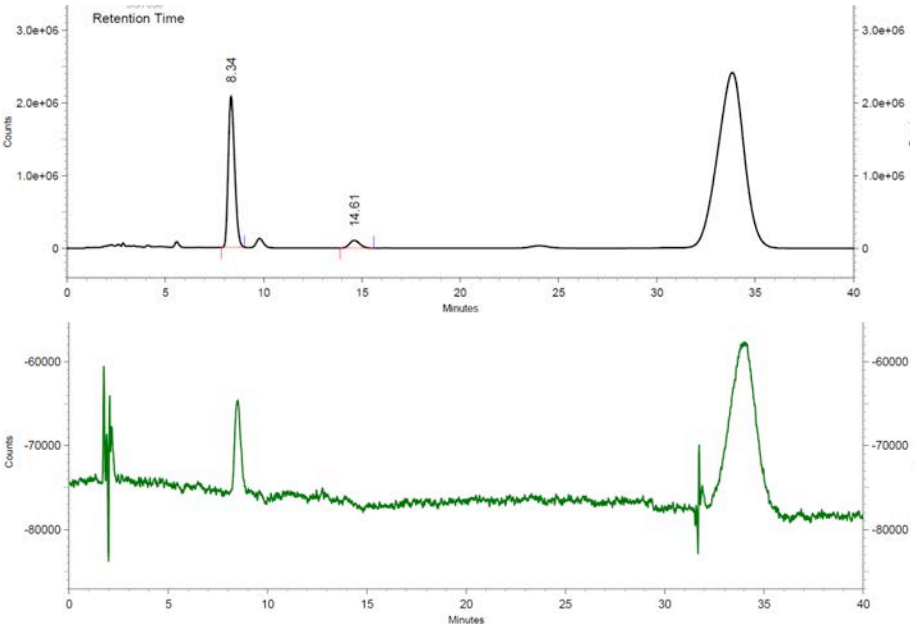




UV Results

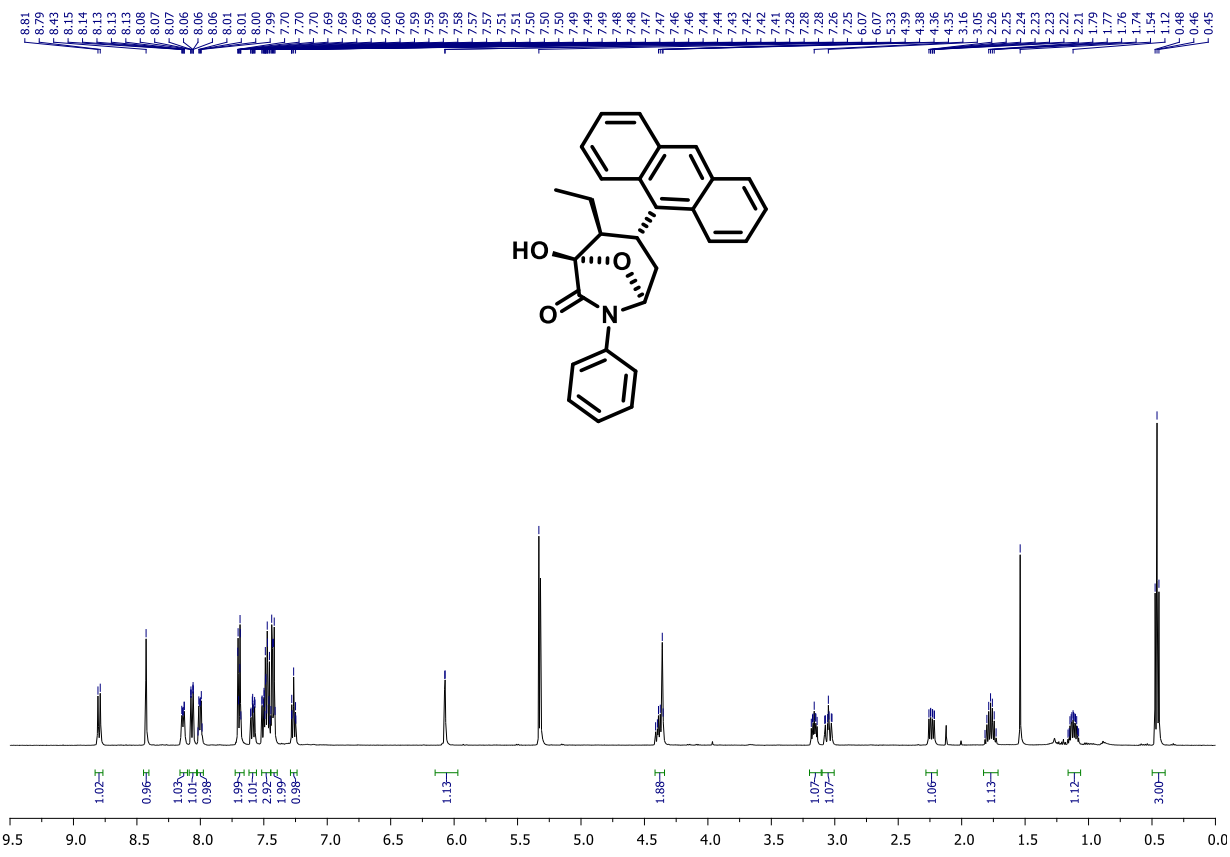
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.79 | 3186199 | 1.39 | 2.26 | 1.00 | 0.00 |
| 33.84 | 226640948 | 98.61 | 10.28 | 4.54 | 14.78 |
| Totals | 229827147 | 100.00 | | | |




| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.40 | 16709084 | 56.30 | 1.80 | 1.00 | 0.00 |
| 14.67 | 12967327 | 43.70 | 3.89 | 2.16 | 7.89 |
| Totals | 29676411 | 100.00 | | | |




| UV Results Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.34 | 46903049 | 92.40 | 1.78 | 1.00 | 0.00 |
| 14.61 | 3856842 | 7.60 | 3.87 | 2.17 | 7.91 |
| Totals | 50759891 | 100.00 | | | |


HO
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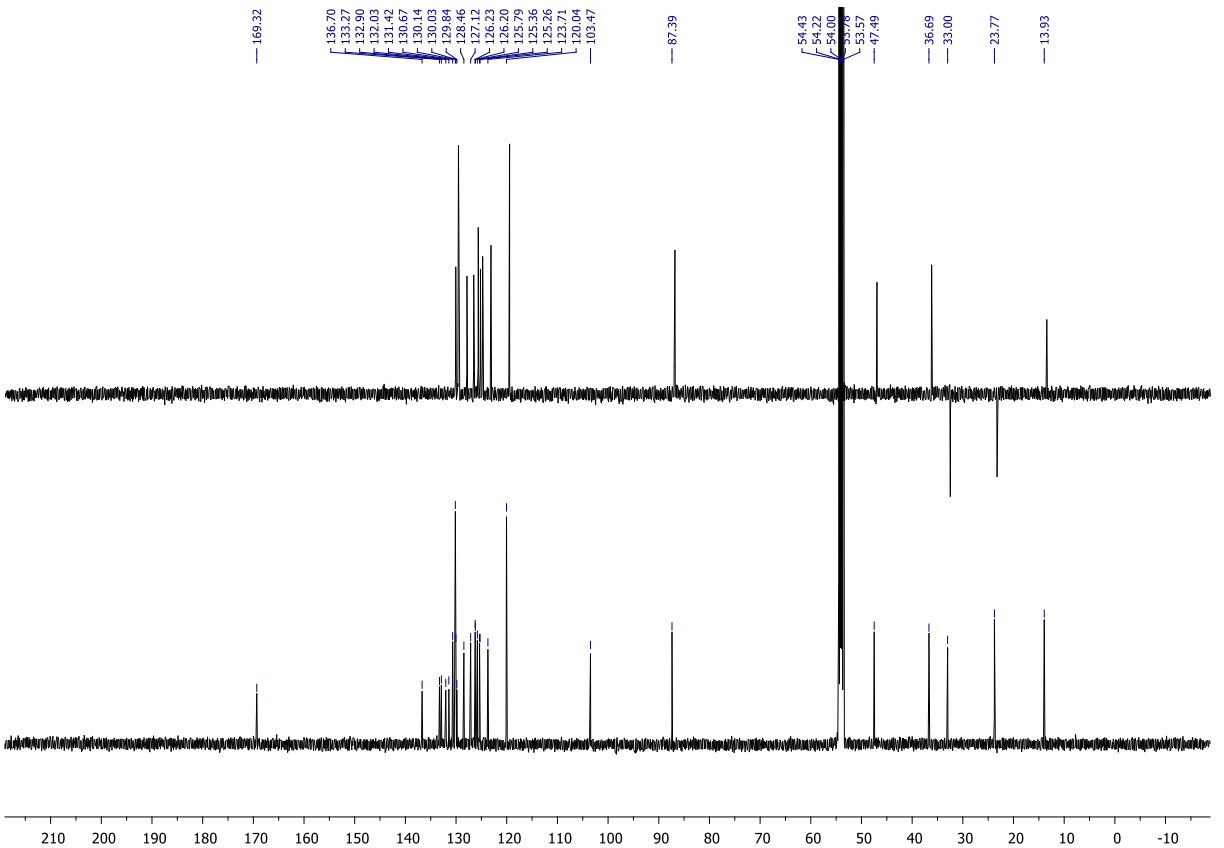
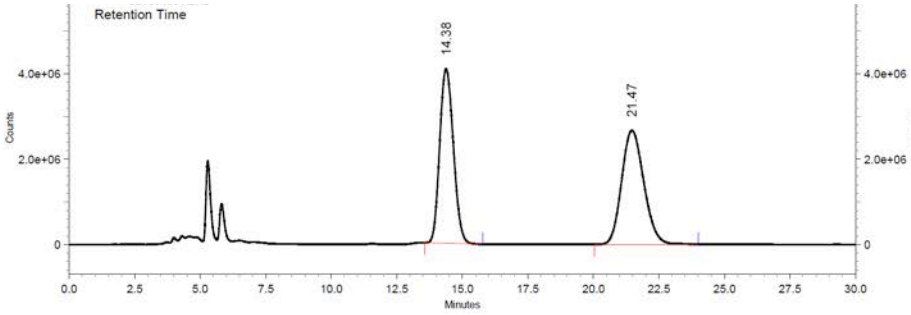
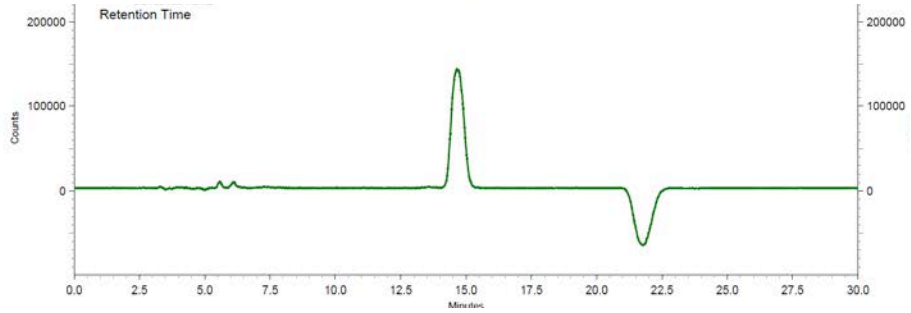
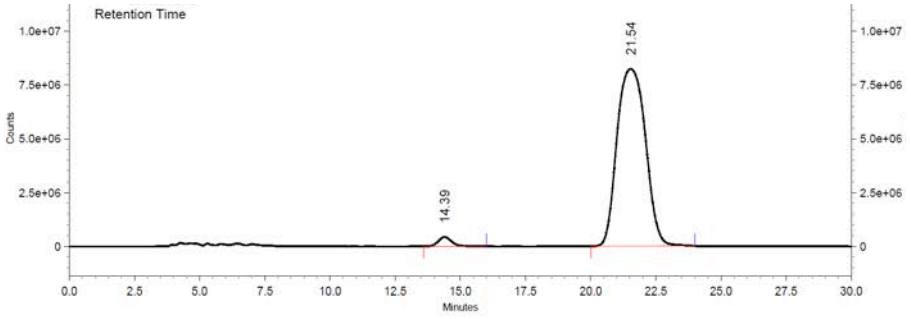


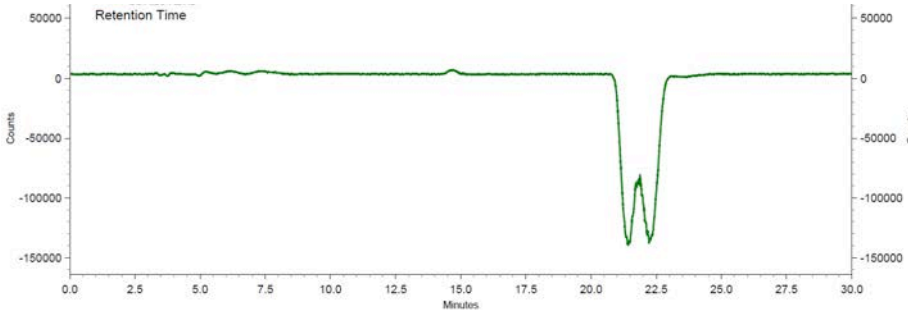



UV Results

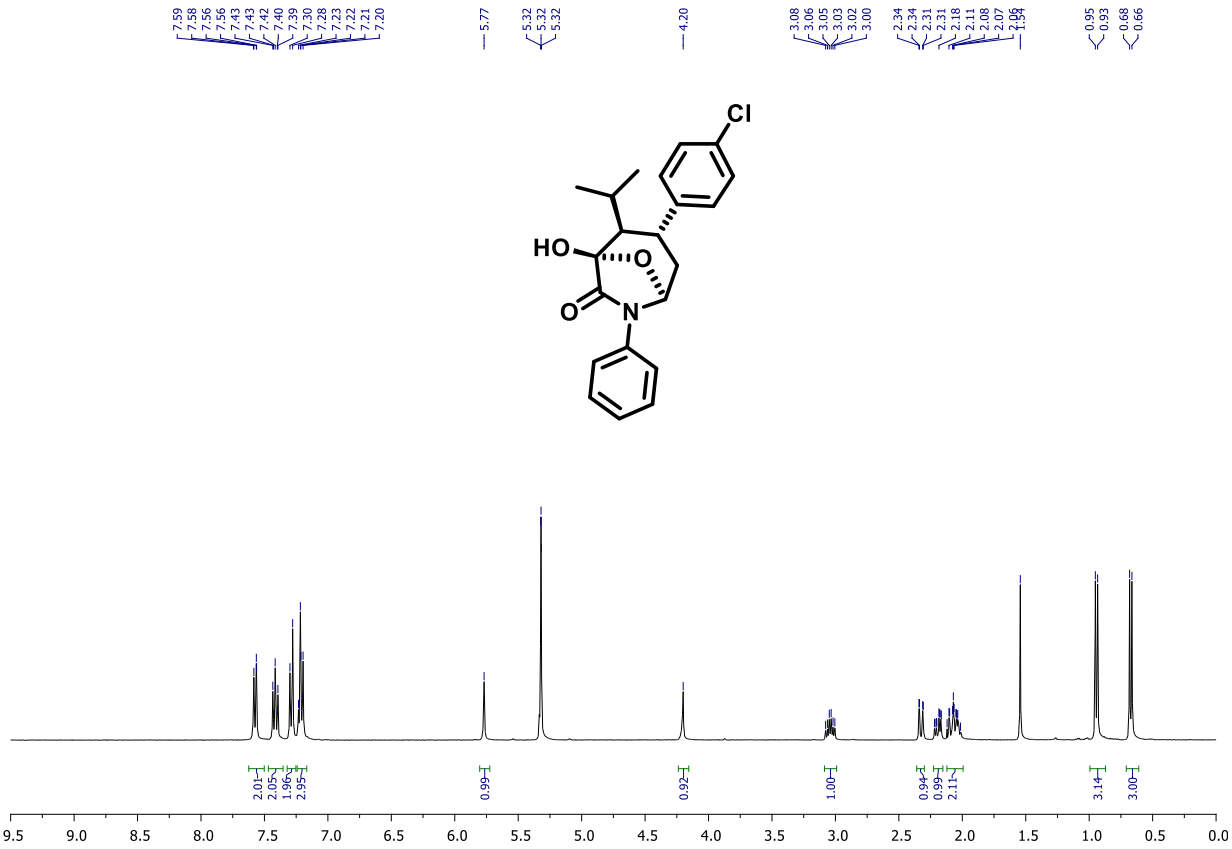
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 14.38 | 148575739 | 48.66 | 3.79 | 1.00 | 0.00 |
| 21.47 | 156758233 | 51.34 | 6.16 | 1.62 | 5.58 |
| Totals | 305333972 | 100.00 | | | |




UV Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 14.39 | 15172288 | 2.37 | 3.80 | 1.00 | 0.00 |
| 21.54 | 626267310 | 97.63 | 6.18 | 1.63 | 5.07 |
| Totals | 641439598 | 100.00 | | | |


7.59
7.58
7.56
7.56
7.43
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7.28
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8.0
7.5
7.0
6.5
6.0
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4.0
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2.0
1.5
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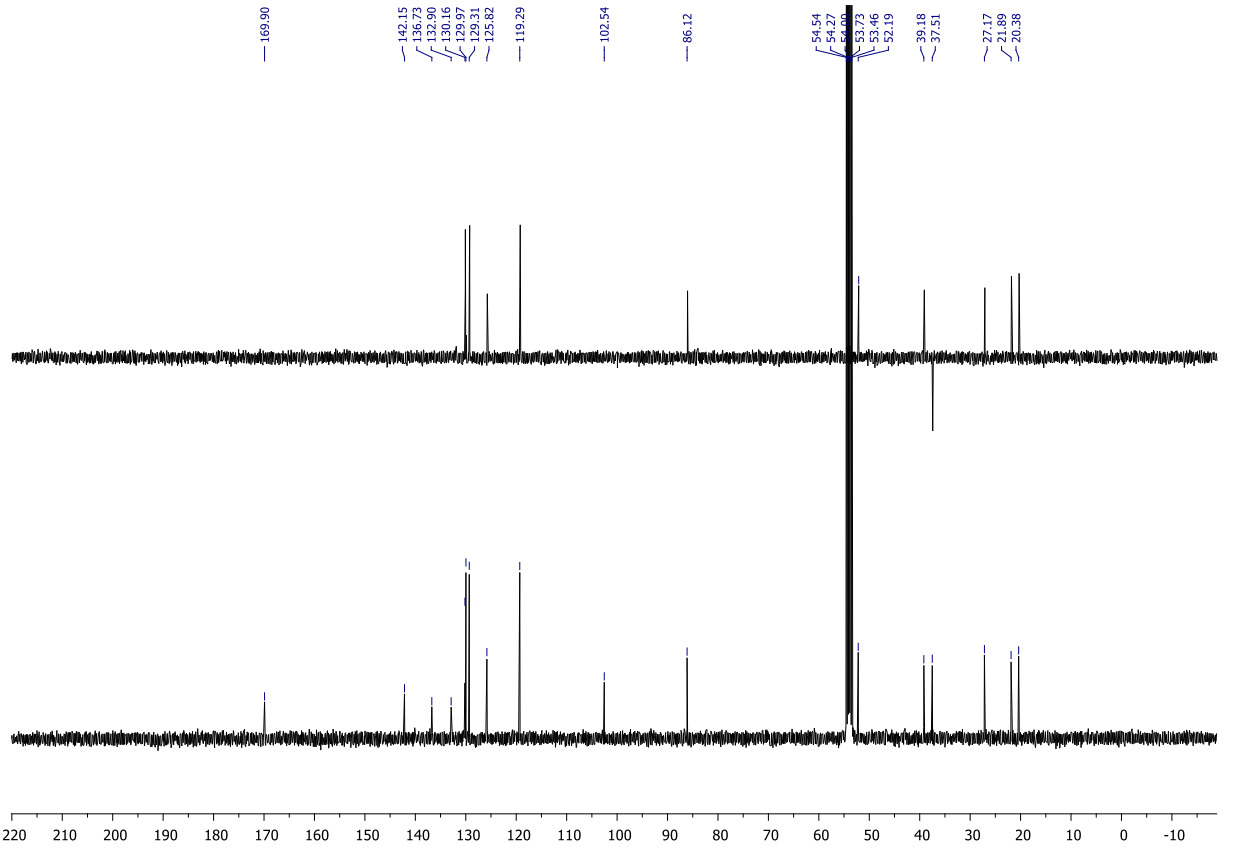
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125.82
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102.54
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54.27
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37.51
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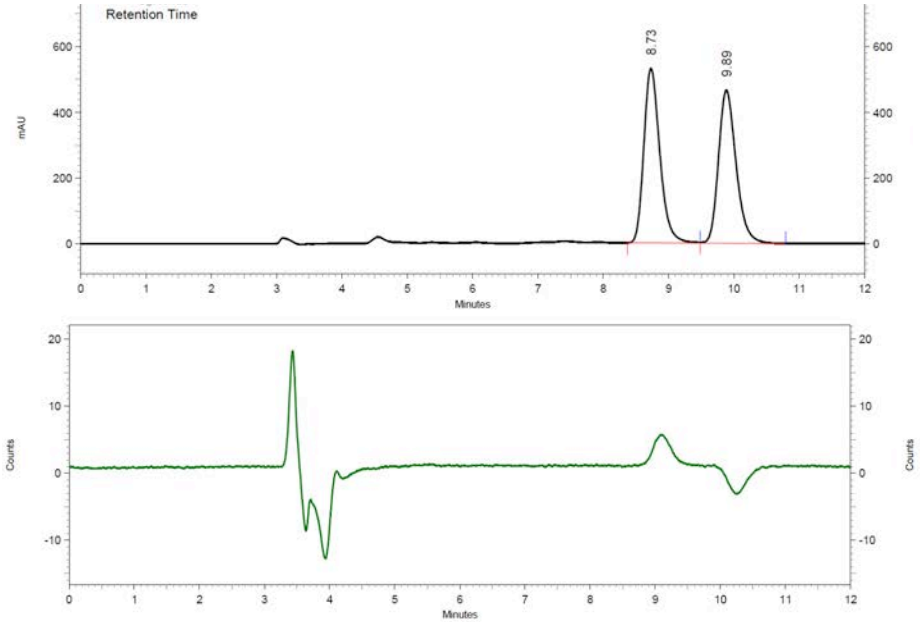
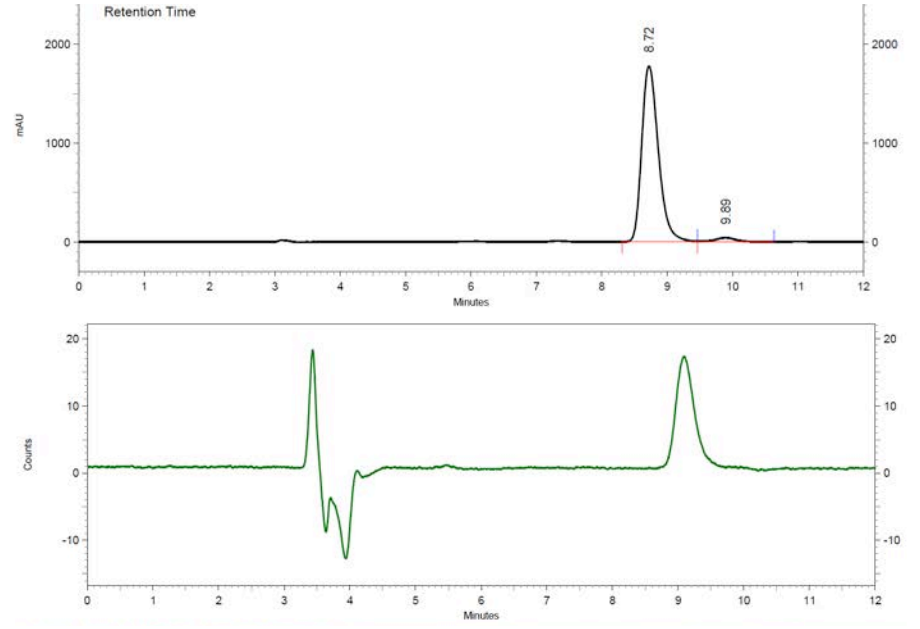
0
-10




1: 254 nm, 4 nm

Results

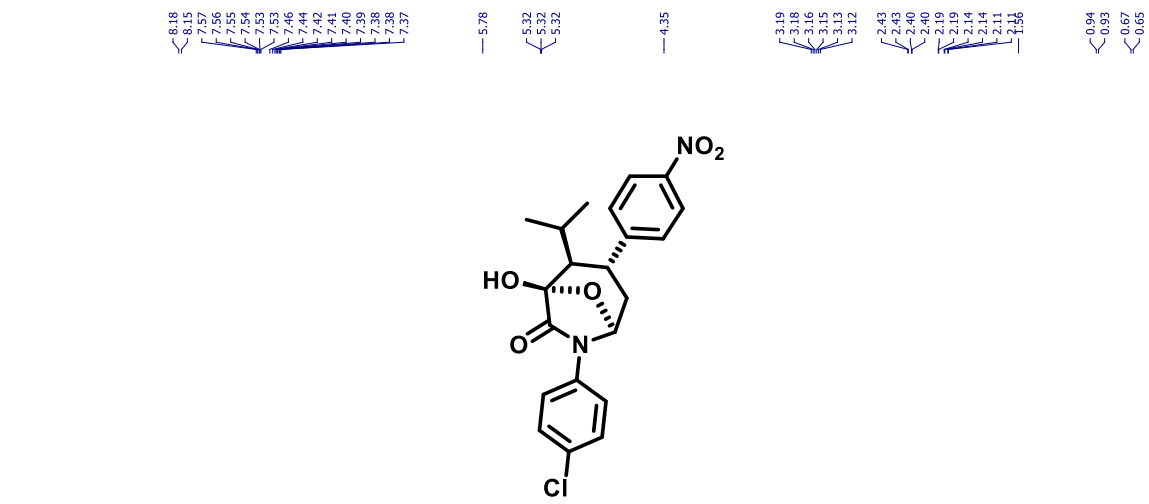
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.73 | 36232432 | 50.93 | 1.91 | 1.00 | 0.00 |
| 9.89 | 34915301 | 49.07 | 2.30 | 1.20 | 2.46 |
| Totals | 71147733 | 100.00 | | | |

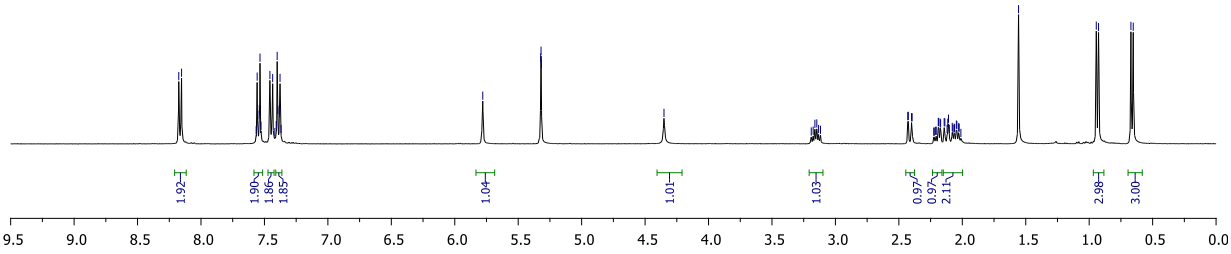


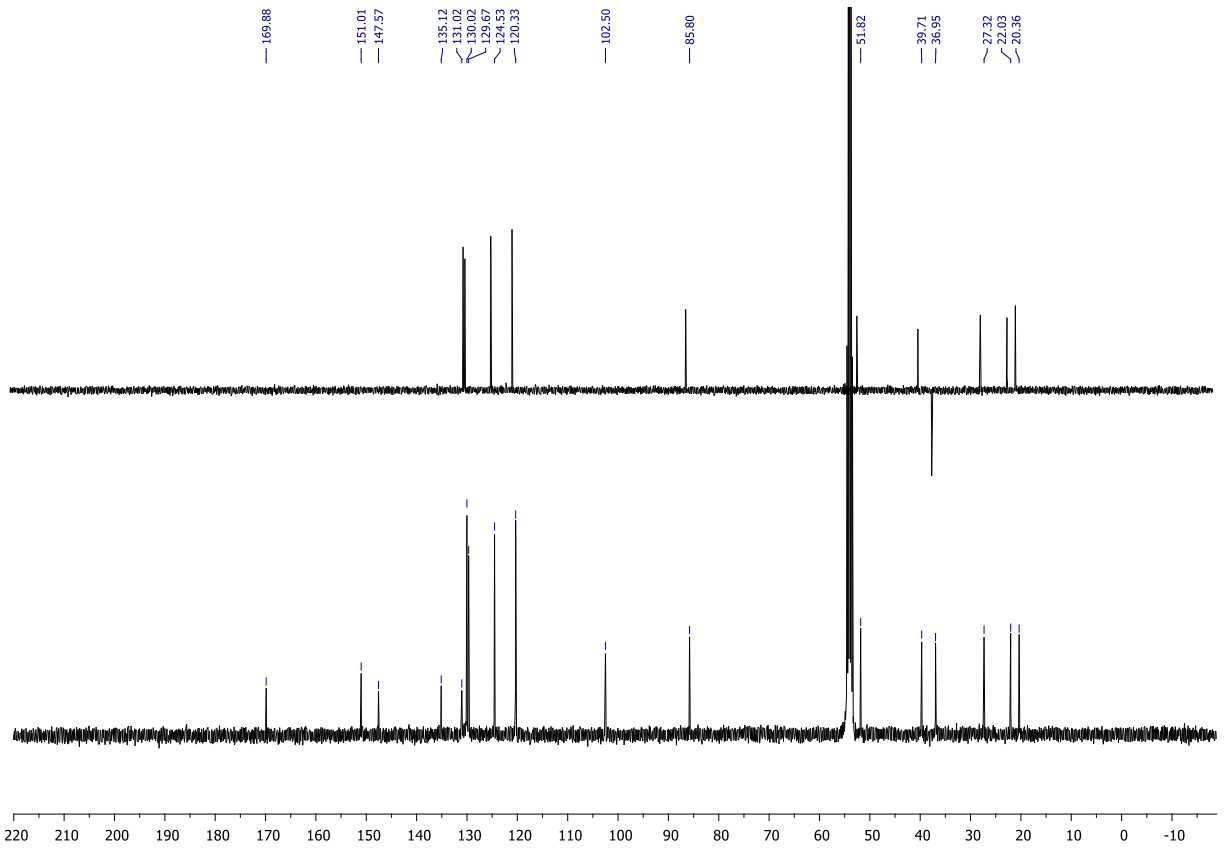

1: 254 nm, 4 nm

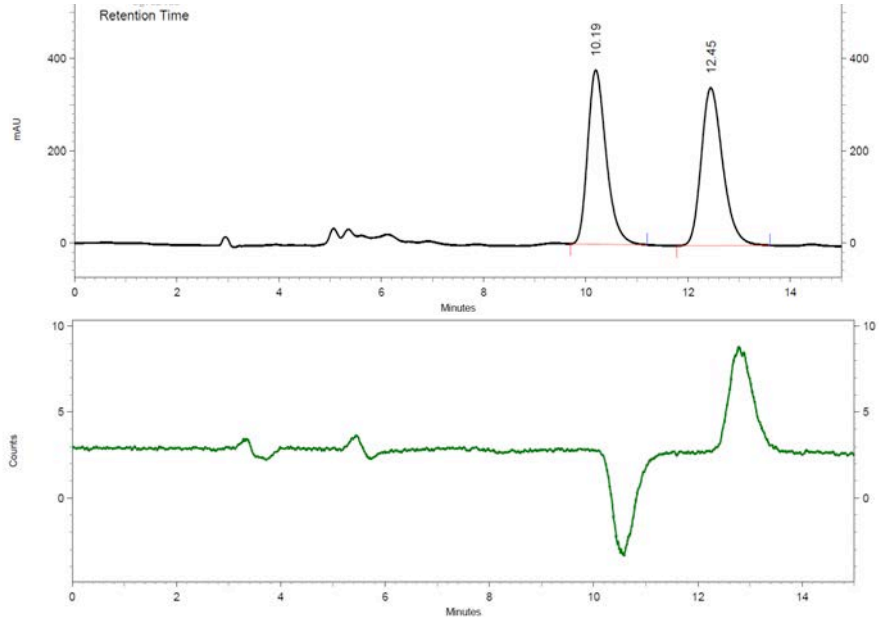
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.72 | 125826651 | 97.17 | 1.91 | 1.00 | 0.00 |
| 9.89 | 3668233 | 2.83 | 2.30 | 1.21 | 2.32 |
| Totals | 129494884 | 100.00 | | | |


8.18
8.15
7.57
7.56
7.55
7.54
7.53
7.53
7.46
7.44
7.42
7.41
7.40
7.39
7.38
7.38
7.37
5.78
5.32
5.32
5.32
4.35
3.19
3.18
3.16
3.15
3.13
3.12
2.43
2.43
2.40
2.40
2.19
2.19
2.14
2.14
2.11
2.11
1.58
0.94
0.93
0.67
0.65
NO2
HO
O
O
N
Cl


1.92
1.90
1.86
1.85
1.04
1.01
1.03
0.97
0.97
2.11
2.98
3.00
9.5
9.0
8.5
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

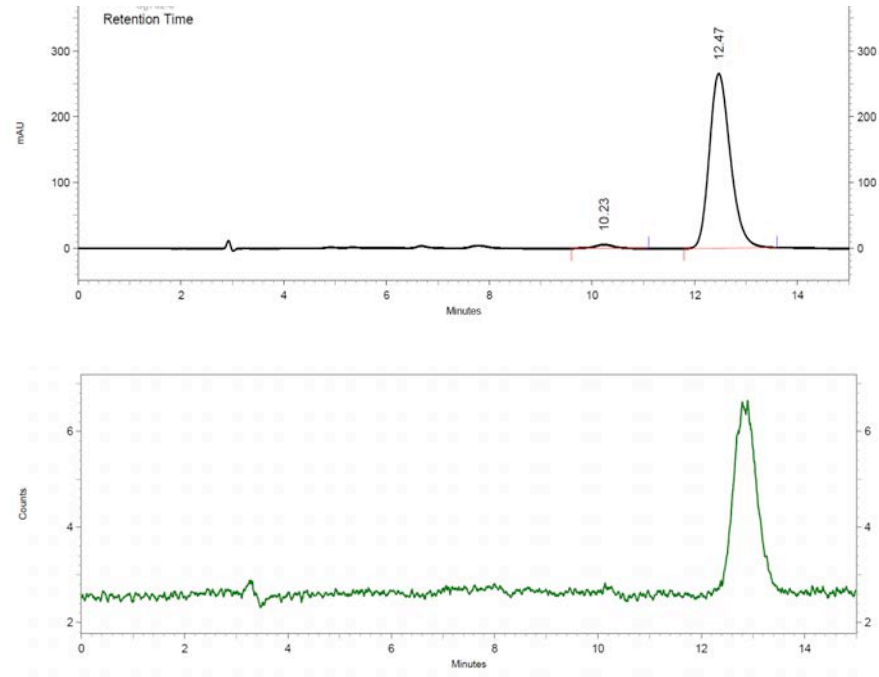

169.88
151.01
147.57
135.12
131.02
130.02
129.67
124.53
120.33
102.50
85.80
51.82
39.71
36.95
27.32
22.03
20.36
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10




1: 254 nm, 4 nm

Results

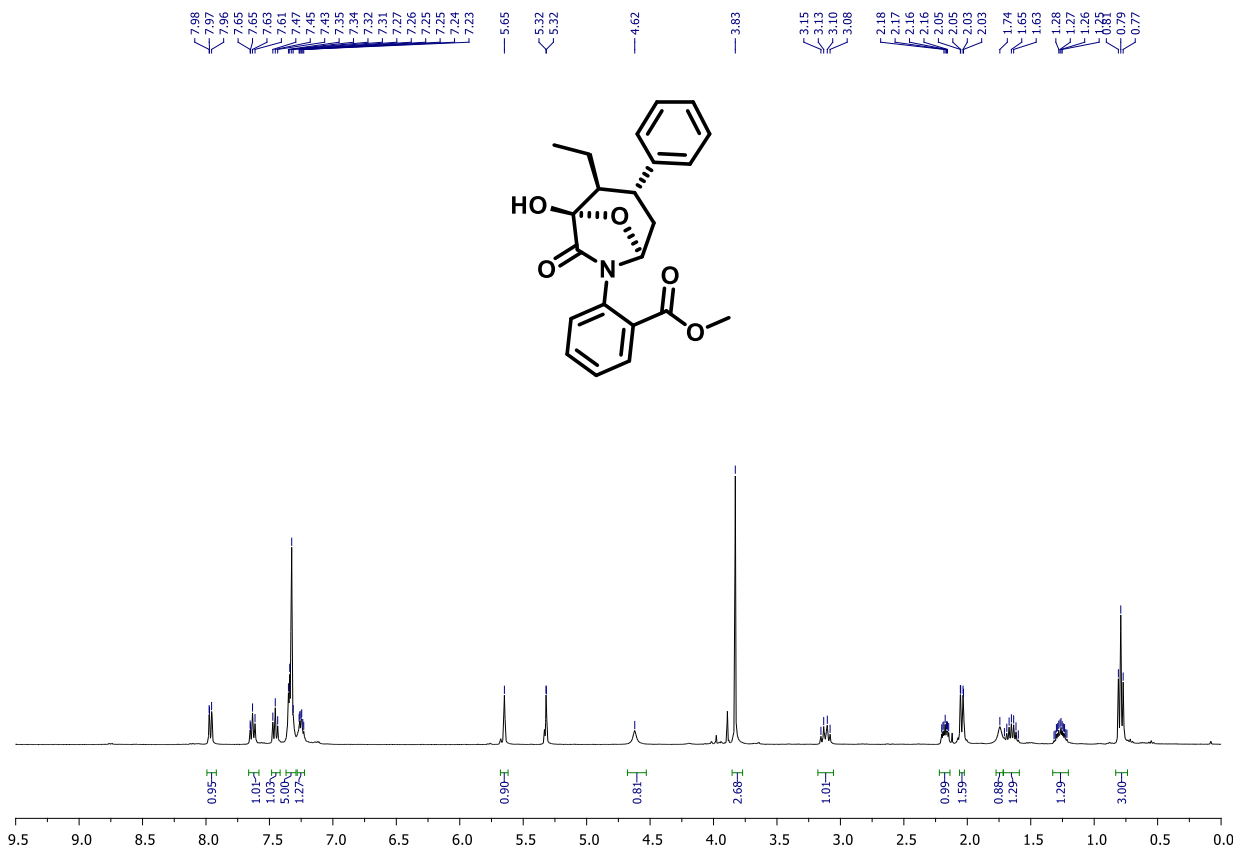
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 10.19 | 38130065 | 48.70 | 2.40 | 0.00 | 0.00 |
| 12.45 | 40158877 | 51.30 | 3.15 | 1.00 | 3.15 |
| Totals | 78288942 | 100.00 | | | |

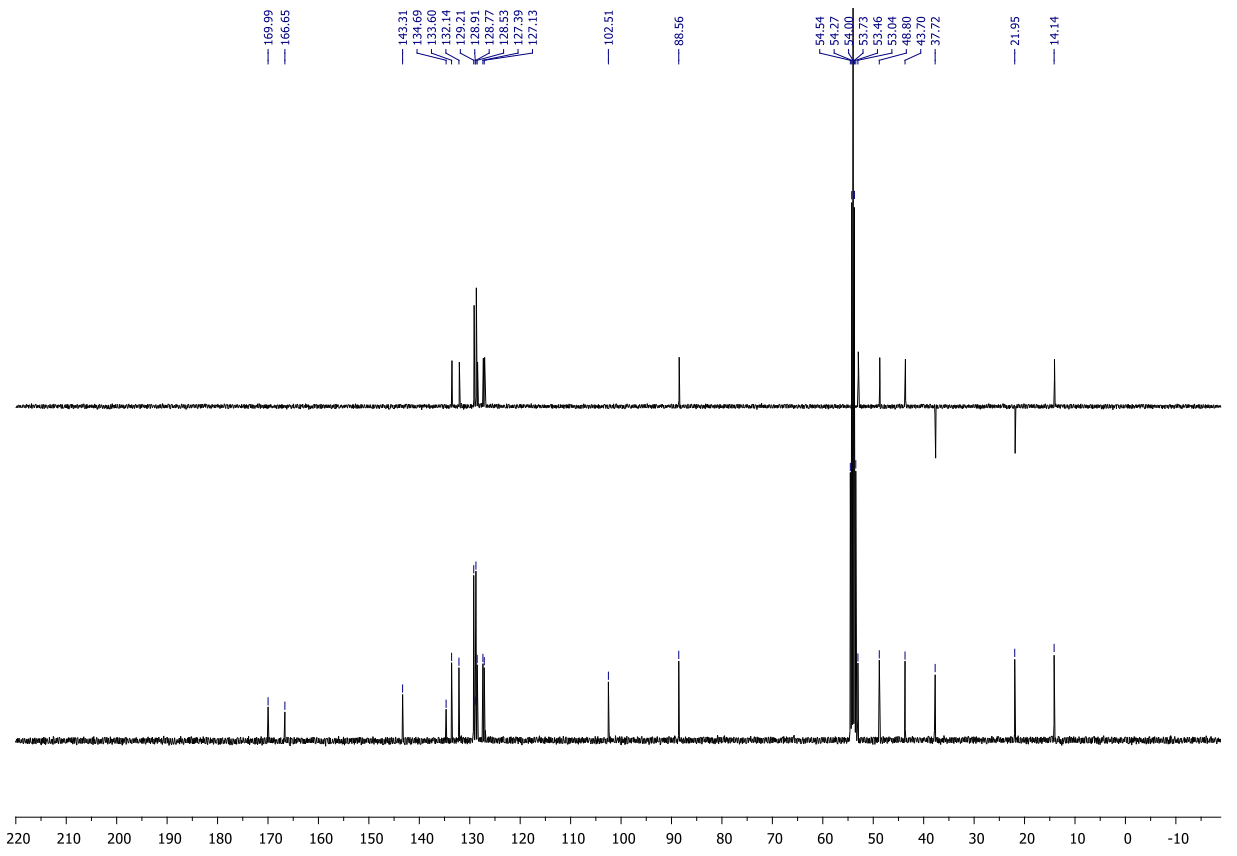


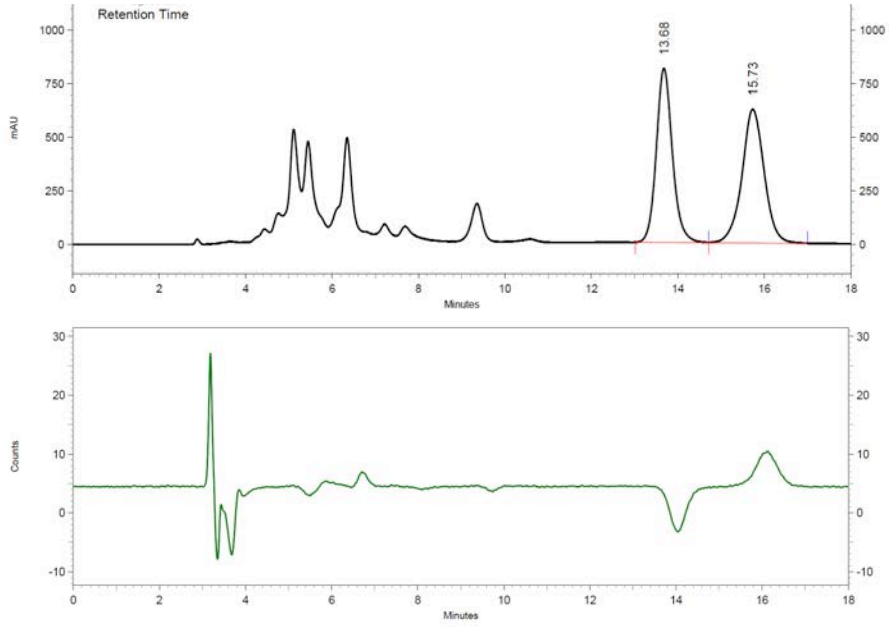

1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 10.23 | 644734 | 2.09 | 2.41 | 0.00 | 0.00 |
| 12.47 | 30171389 | 97.91 | 3.16 | 1.00 | 3.10 |
| Totals | 30816123 | 100.00 | | | |


7.98
7.97
7.96
7.65
7.65
7.63
7.61
7.47
7.45
7.43
7.35
7.34
7.32
7.31
7.27
7.26
7.25
7.25
7.24
7.23
5.65
5.32
5.32
4.62
3.83
3.15
3.13
3.10
3.08
2.18
2.17
2.16
2.16
2.05
2.05
2.03
2.03
1.74
1.65
1.63
1.28
1.27
1.26
1.25
0.81
0.79
0.77
HO
O
O
N
O
O
0.95
1.01
1.03
5.00
1.27
0.90
0.81
2.68
1.01
0.99
1.59
0.88
1.29
1.29
3.00
9.5
9.0
8.5
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

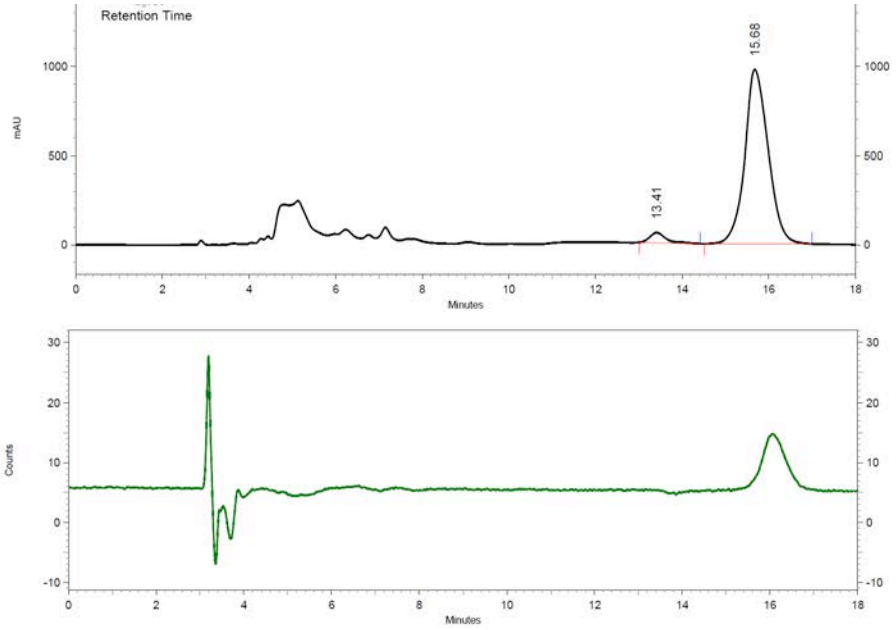

169.99
166.65
143.31
134.69
133.60
132.14
129.21
128.91
128.77
128.53
127.39
127.13
102.51
88.56
54.54
54.27
54.00
53.73
53.46
53.04
48.80
43.70
37.72
21.95
14.14
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10




1: 254 nm, 4 nm

Results

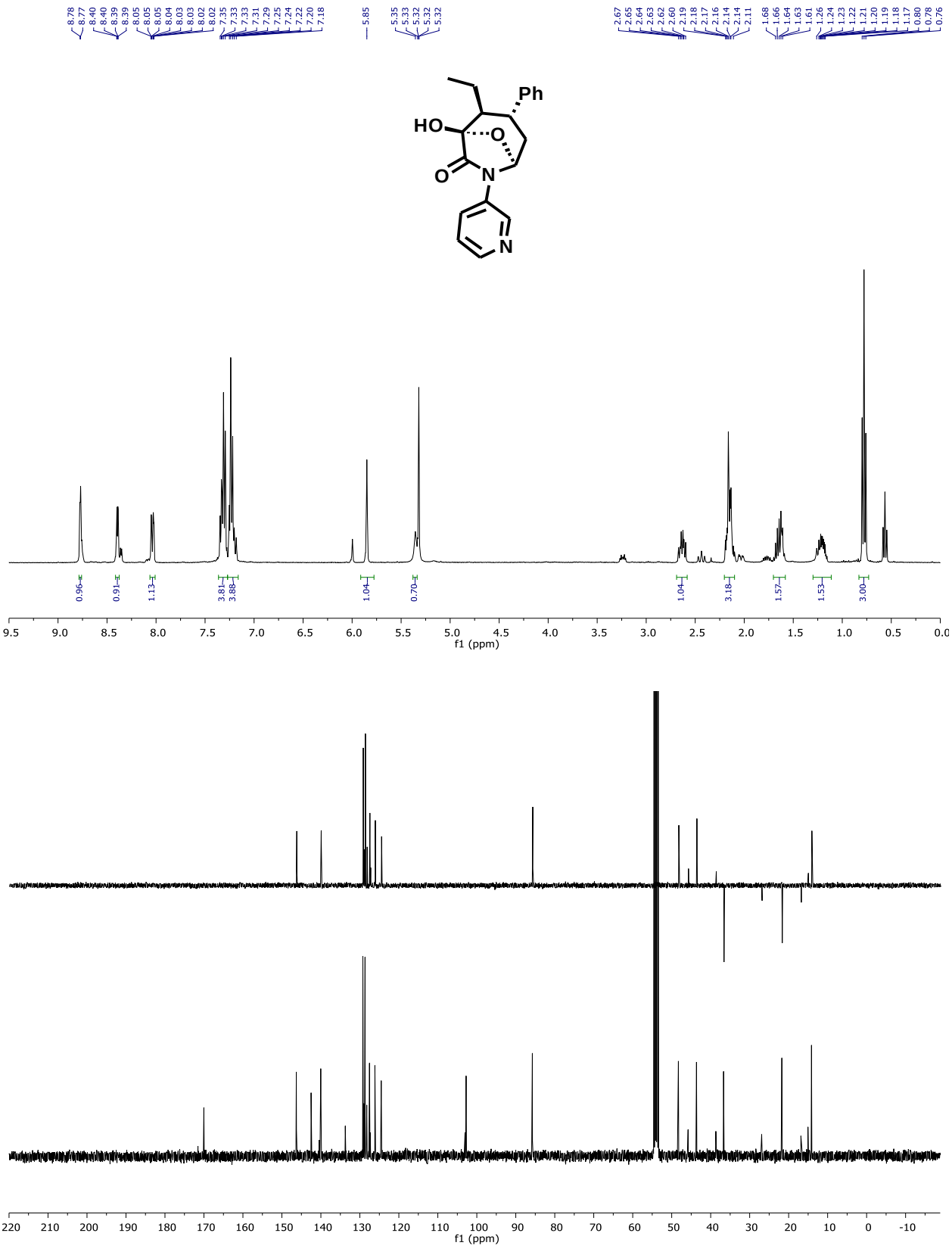
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 13.68 | 84609857 | 48.65 | 3.56 | 0.00 | 0.00 |
| 15.73 | 89298454 | 51.35 | 4.24 | 0.00 | 2.57 |
| Totals | 173908311 | 100.00 | | | |

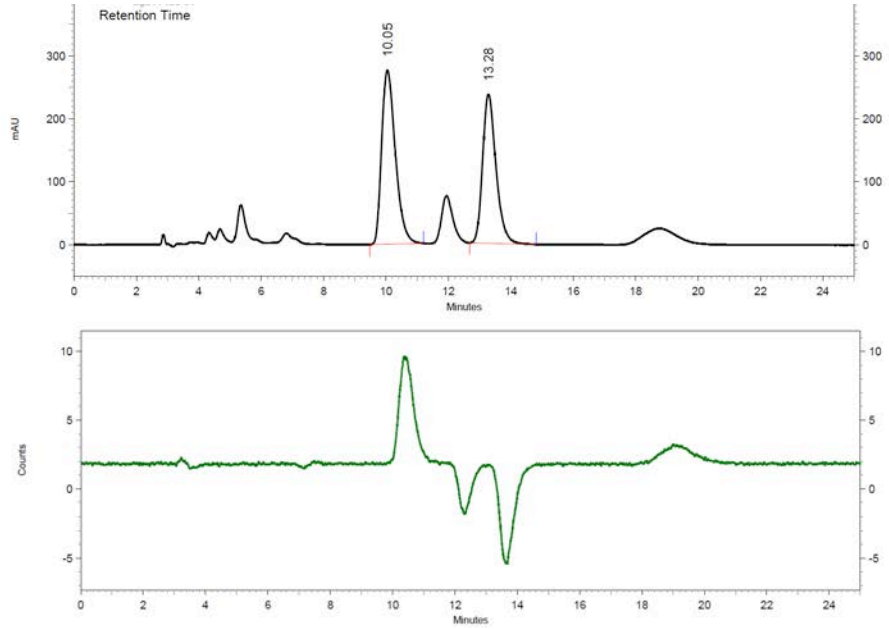



1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 13.41 | 5926965 | 3.88 | 3.47 | 0.00 | 0.00 |
| 15.68 | 146656577 | 96.12 | 4.23 | 0.00 | 2.77 |
| Totals | 152583542 | 100.00 | | | |

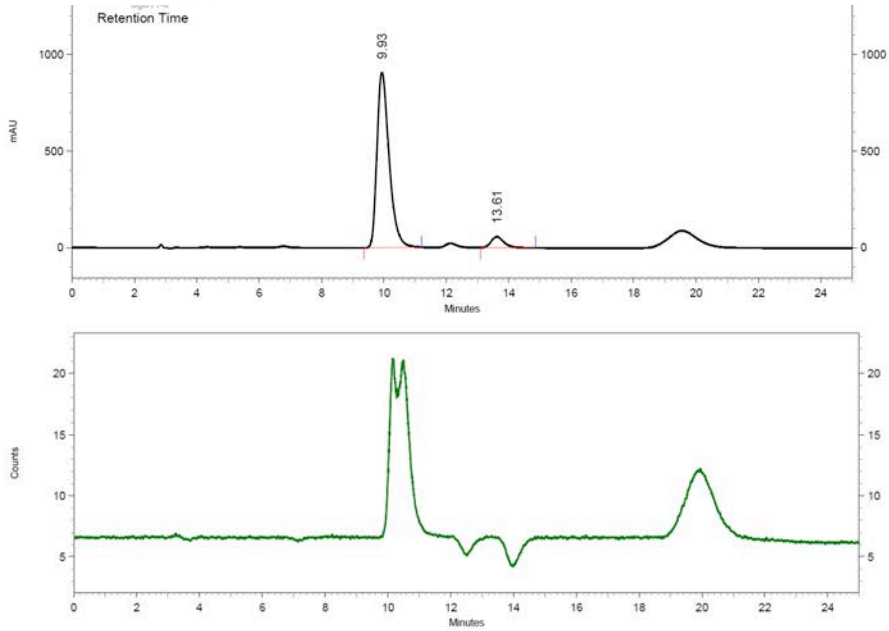

8.78 8.77 8.40 8.40 8.39 8.39 8.05 8.05 8.05 8.04 8.03 8.03 8.02 8.02 7.35 7.33 7.33 7.31 7.29 7.25 7.24 7.22 7.20 7.18
5.85
5.35 5.33 5.32 5.32 5.32
2.67 2.65 2.64 2.63 2.62 2.60 2.19 2.18 2.17 2.16 2.14 2.14 2.11
1.68 1.66 1.64 1.63 1.61
1.26 1.24 1.23 1.22 1.21 1.20 1.19 1.18 1.17 0.80 0.78 0.76
Ph
HO
O
O
N
N
0.96 0.91 1.13 3.81 3.88 1.04 0.70 1.04 3.18 1.57 1.53 3.00
9.5 9.0 8.5 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)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)




1: 254 nm, 4 nm

Results

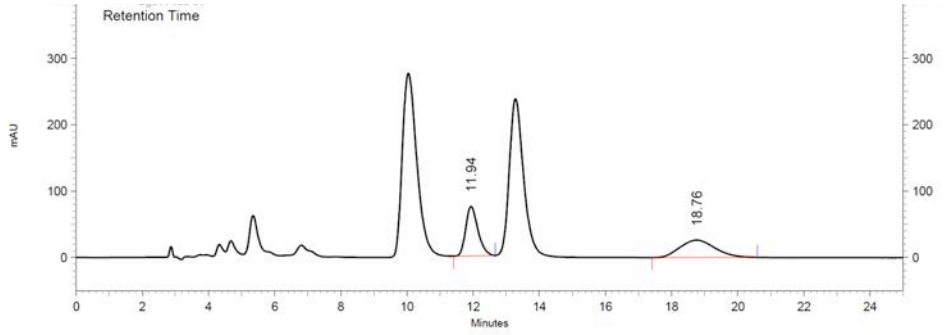
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.94 | 7637260 | 49.88 | 2.98 | 1.00 | 0.00 |
| 18.76 | 7673122 | 50.12 | 5.25 | 0.00 | 5.06 |
| Totals | 15310382 | 100.00 | | | |

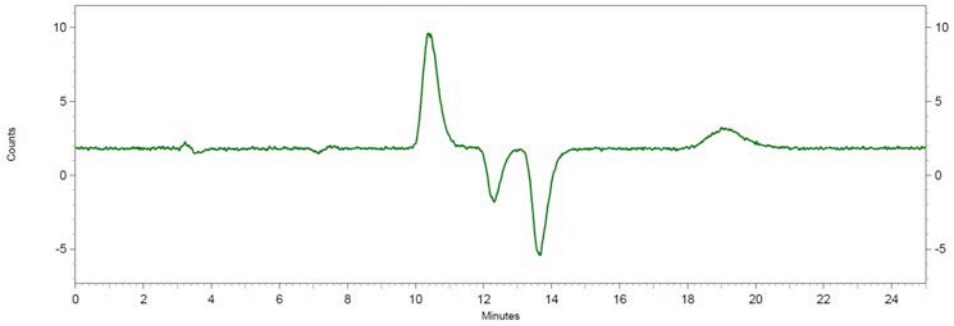



1: 254 nm, 4 nm

Results

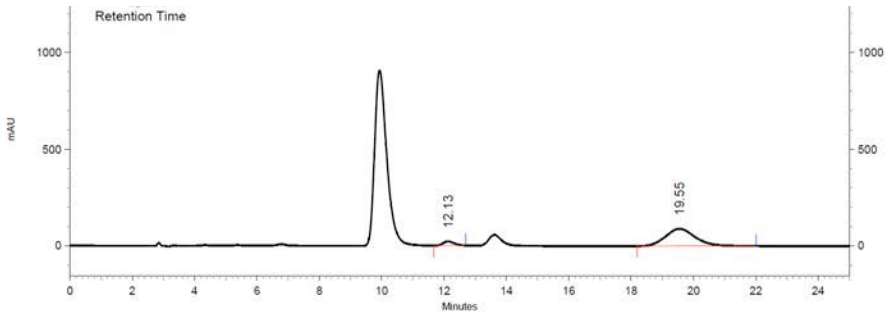
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 9.93 | 98310091 | 93.84 | 2.31 | 0.00 | 0.00 |
| 13.61 | 6457686 | 6.16 | 3.54 | 0.00 | 5.04 |
| Totals | 104767777 | 100.00 | | | |

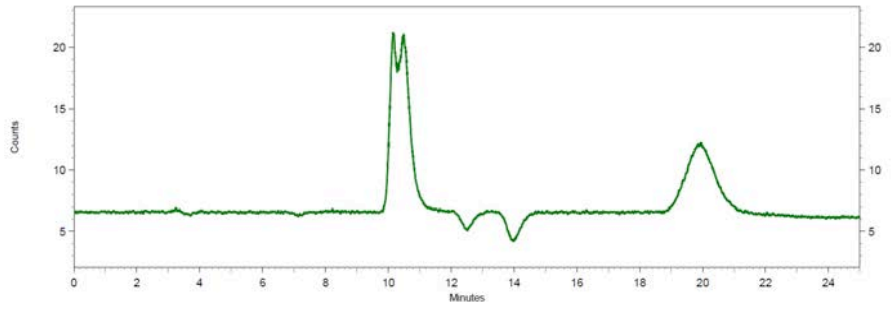



1: 254 nm, 4 nm
Results

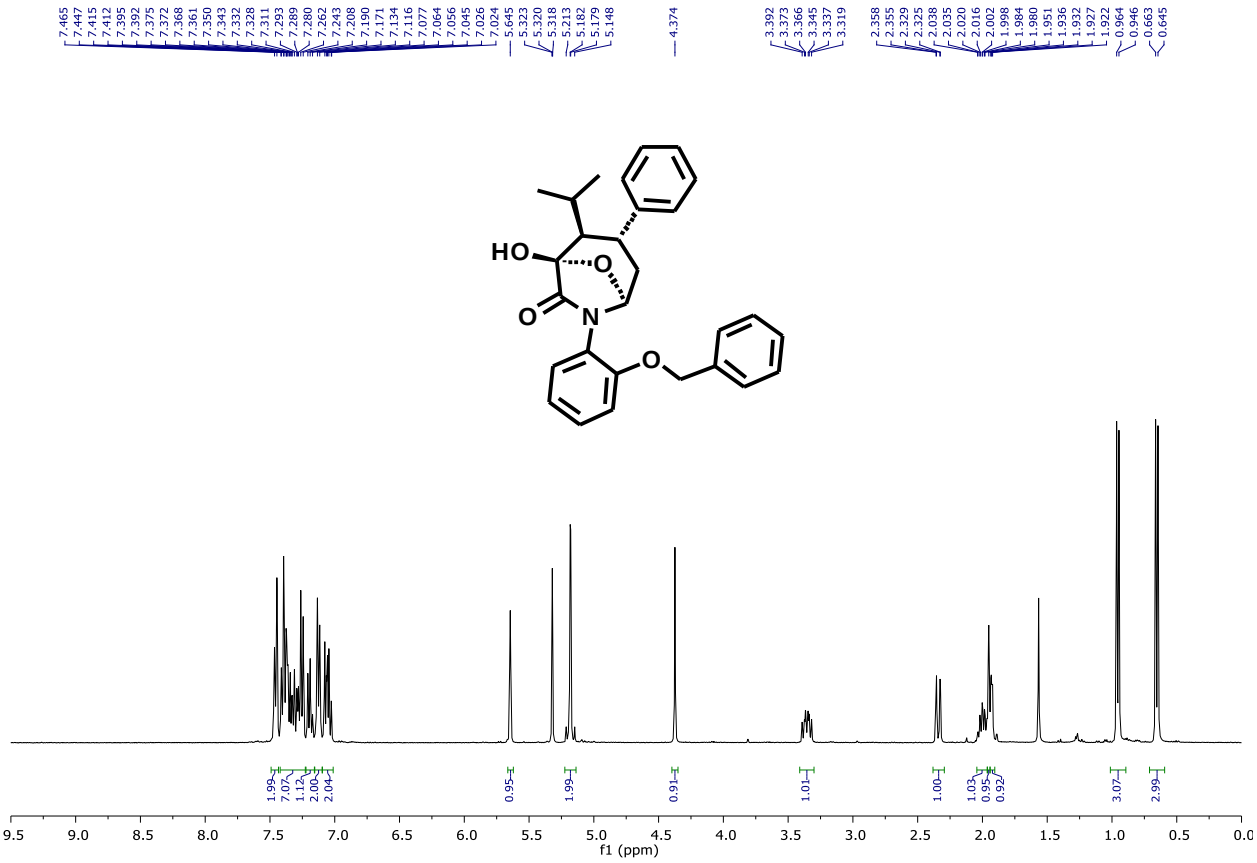
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.94 | 7637260 | 49.88 | 2.98 | 1.00 | 0.00 |
| 18.76 | 7673122 | 50.12 | 5.25 | 0.00 | 5.06 |
| Totals | 15310382 | 100.00 | | | |

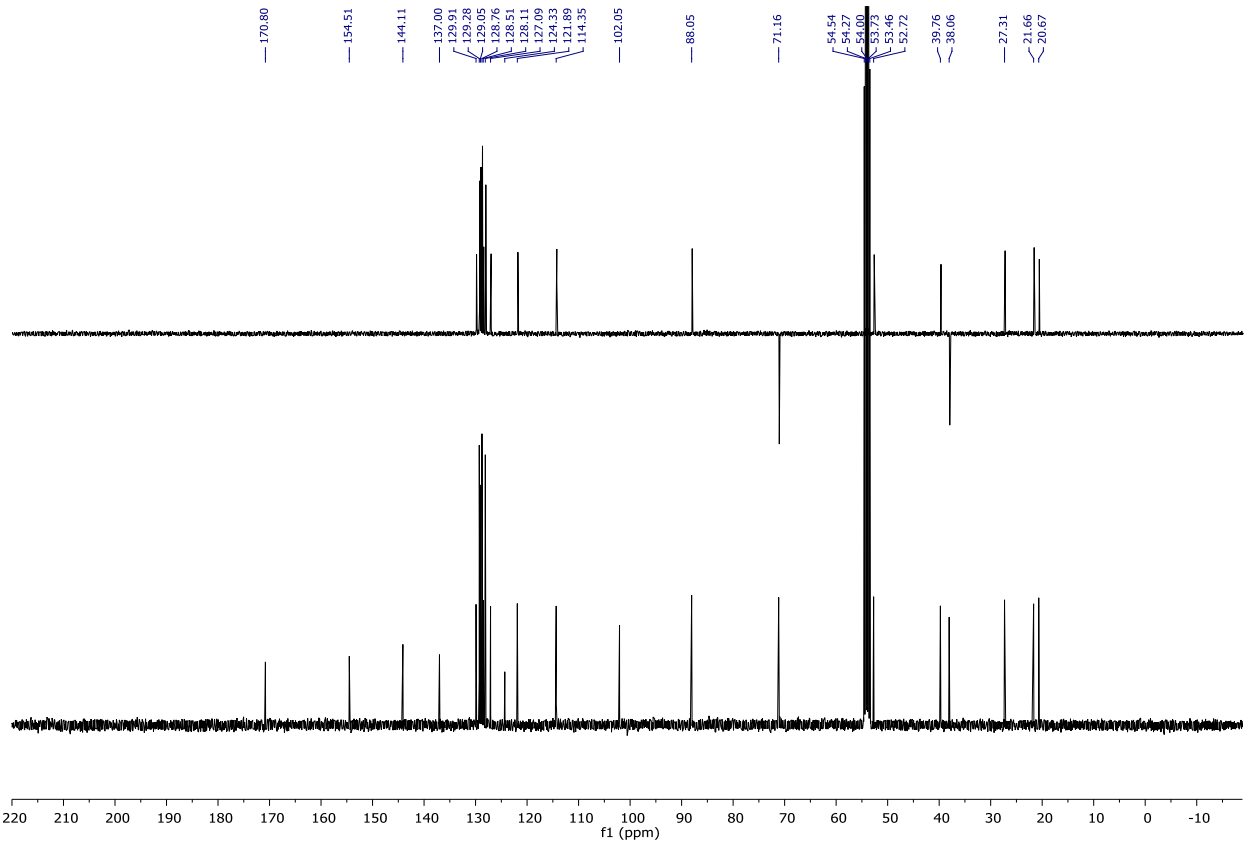


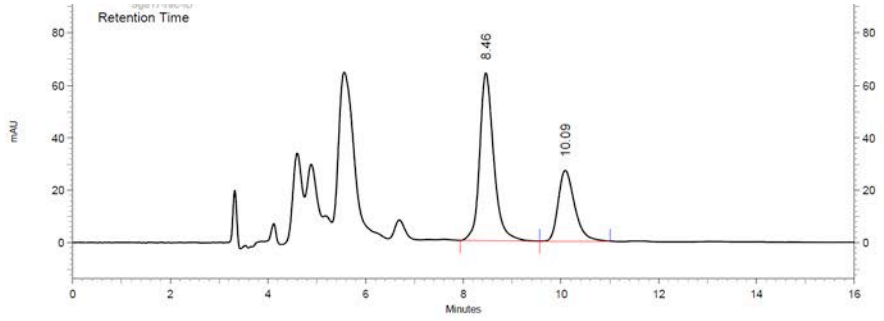



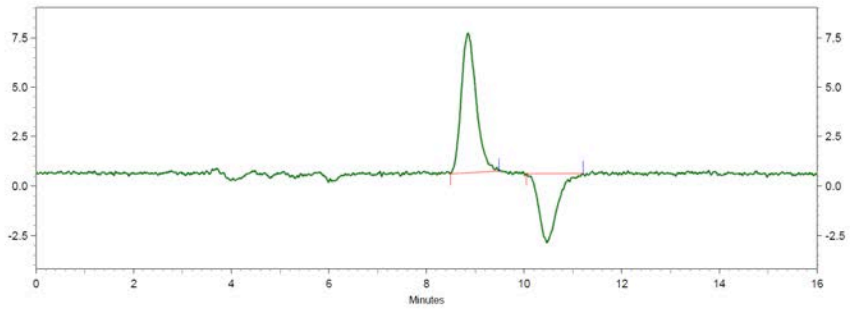

1: 254 nm, 4 nm
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 12.13 | 2039706 | 8.03 | 3.04 | 1.00 | 0.00 |
| 19.55 | 23363984 | 91.97 | 5.52 | 0.00 | 6.17 |
| Totals | 25403690 | 100.00 | | | |


7.465
7.447
7.415
7.412
7.395
7.392
7.375
7.372
7.368
7.361
7.350
7.343
7.332
7.328
7.311
7.293
7.289
7.280
7.262
7.243
7.208
7.190
7.171
7.134
7.116
7.077
7.064
7.056
7.045
7.026
7.024
5.645
5.323
5.320
5.318
5.213
5.182
5.179
5.148
4.374
3.392
3.373
3.366
3.345
3.337
3.319
2.358
2.355
2.329
2.325
2.038
2.035
2.020
2.016
2.002
1.998
1.984
1.980
1.951
1.936
1.932
1.927
1.922
0.964
0.946
0.663
0.645
HO
O
O
N
O
1.99
7.07
1.12
2.00
2.04
0.95
1.99
0.91
1.01
1.00
1.03
0.95
0.92
3.07
2.99
f1 (ppm)


170.80
154.51
144.11
137.00
129.91
129.28
129.05
128.76
128.51
128.11
127.09
124.33
121.89
114.35
102.05
88.05
71.16
54.54
54.27
54.00
53.73
53.46
52.72
39.76
38.06
27.31
21.66
20.67
f1 (ppm)

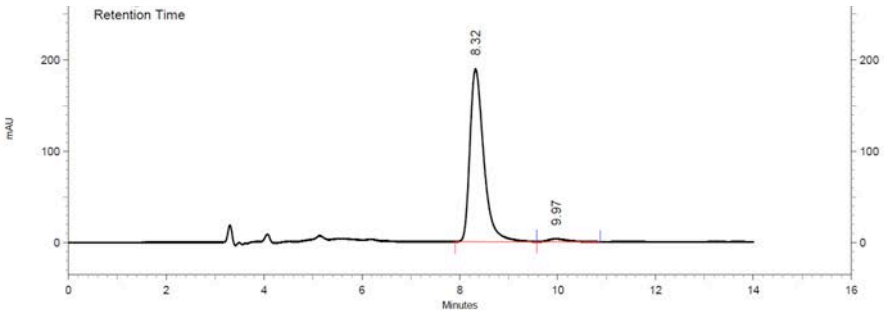


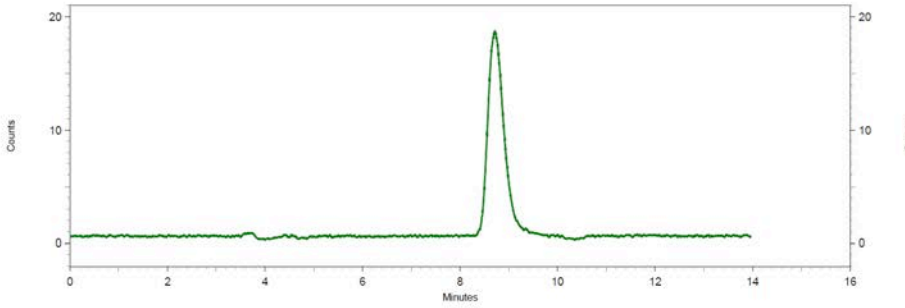




1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.46 | 5104213 | 66.85 | 1.82 | 0.00 | 0.00 |
| 10.09 | 2531120 | 33.15 | 2.36 | 0.00 | 2.93 |
| Totals | 7635333 | 100.00 | | | |



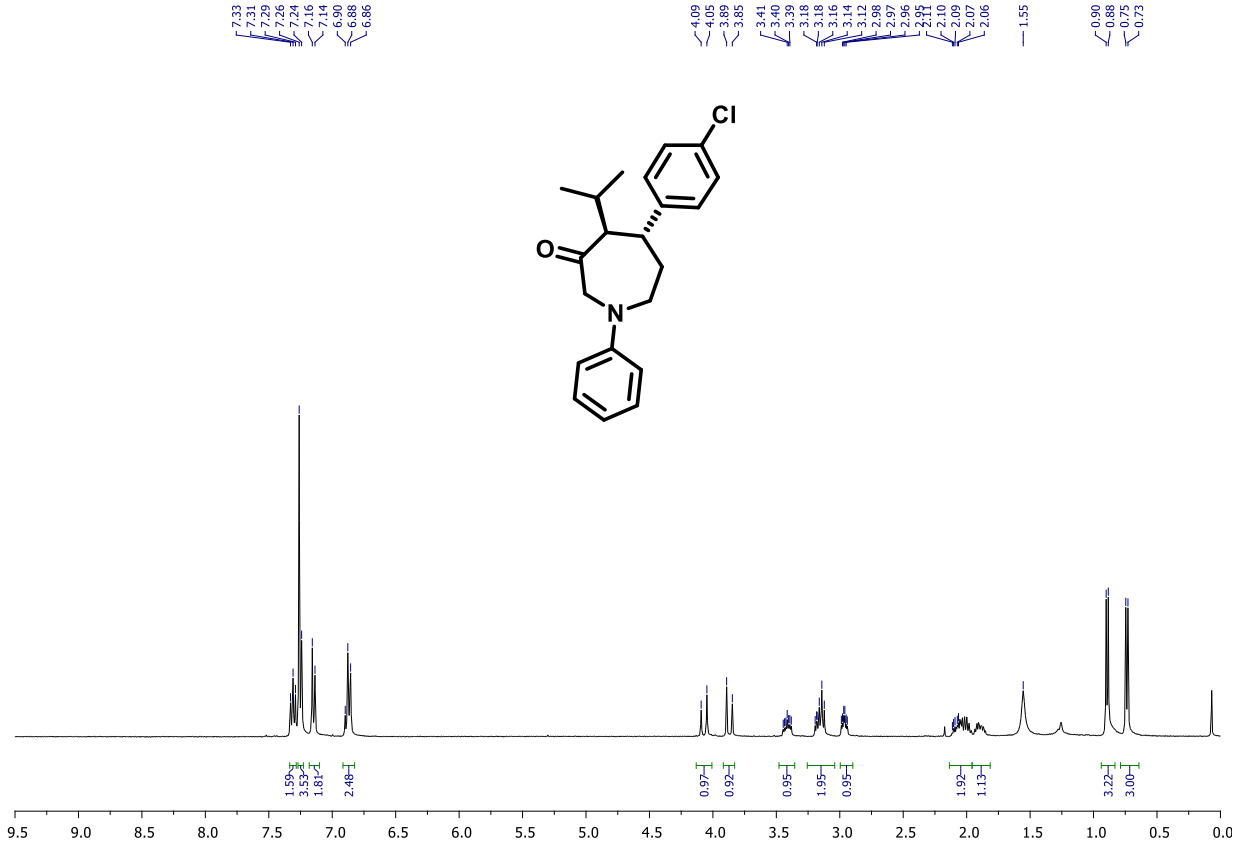



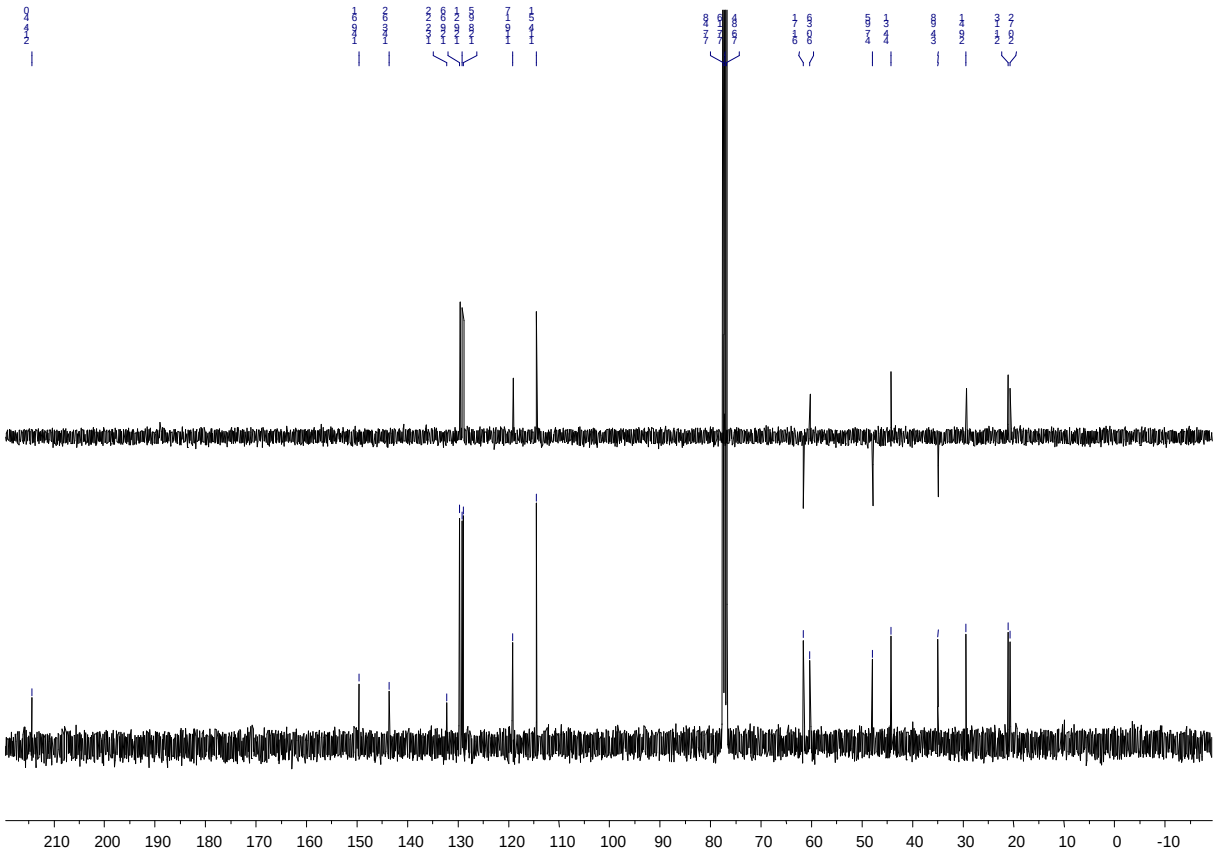

1: 254 nm, 4 nm

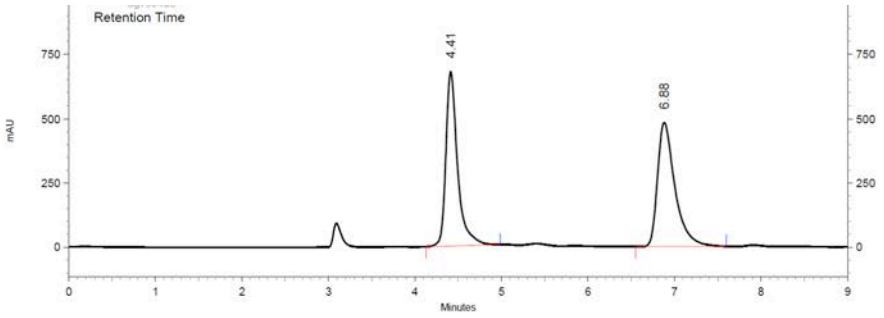
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.32 | 14896023 | 97.72 | 1.77 | 0.00 | 0.00 |
| 9.97 | 347954 | 2.28 | 2.32 | 0.00 | 2.75 |
| Totals | 15243977 | 100.00 | | | |

## 7. NMR spectra of monocyclic azepanes derivatives



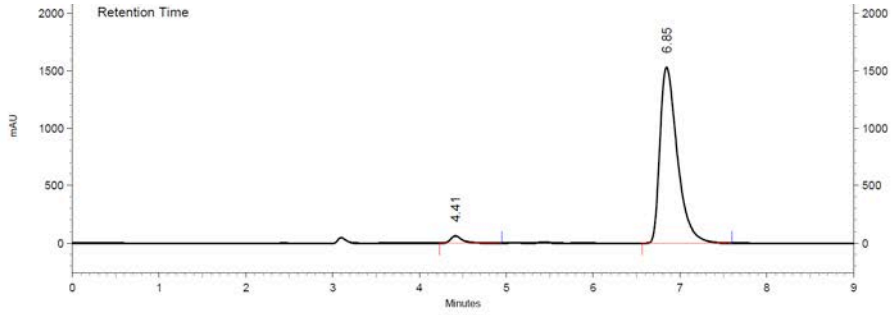



1: 254 nm, 4 nm

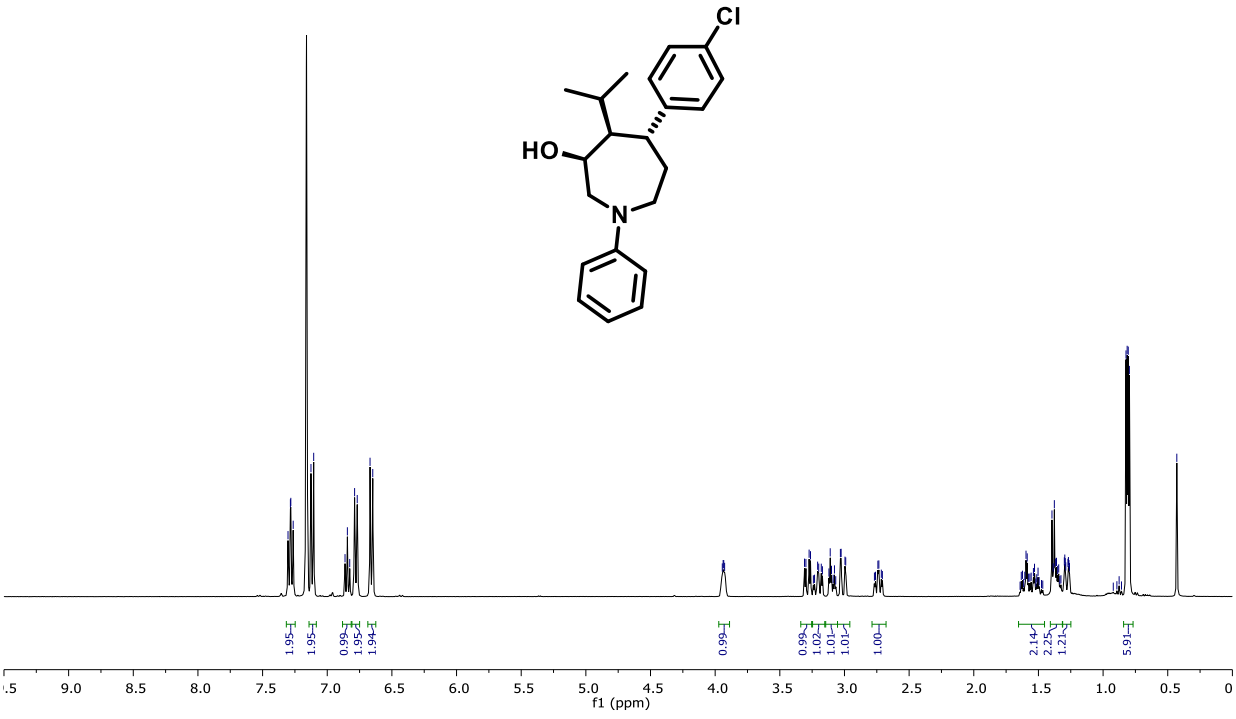
Results

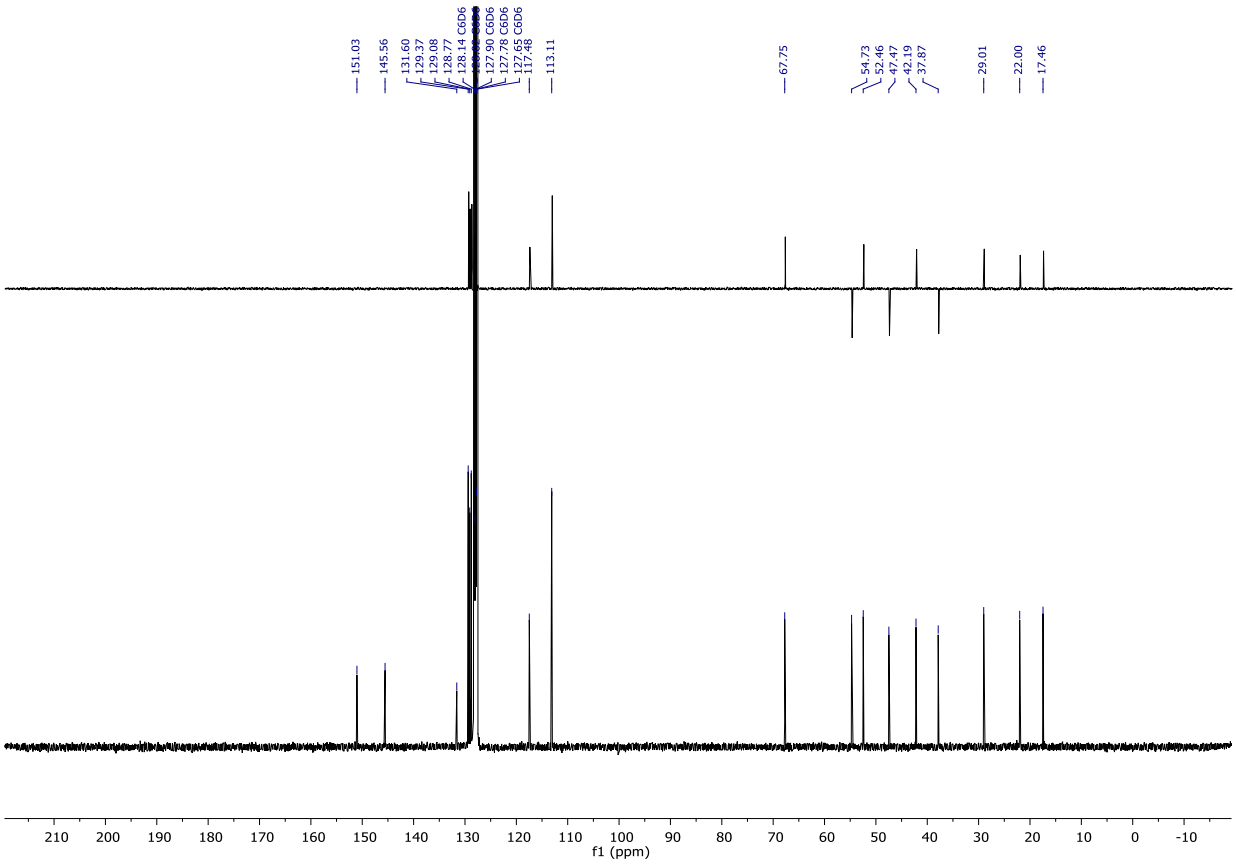
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 4.41 | 25594668 | 48.65 | 0.47 | 0.00 | 0.00 |
| 6.88 | 27020208 | 51.35 | 1.29 | 0.00 | 8.44 |
| Totals | 52614876 | 100.00 | | | |

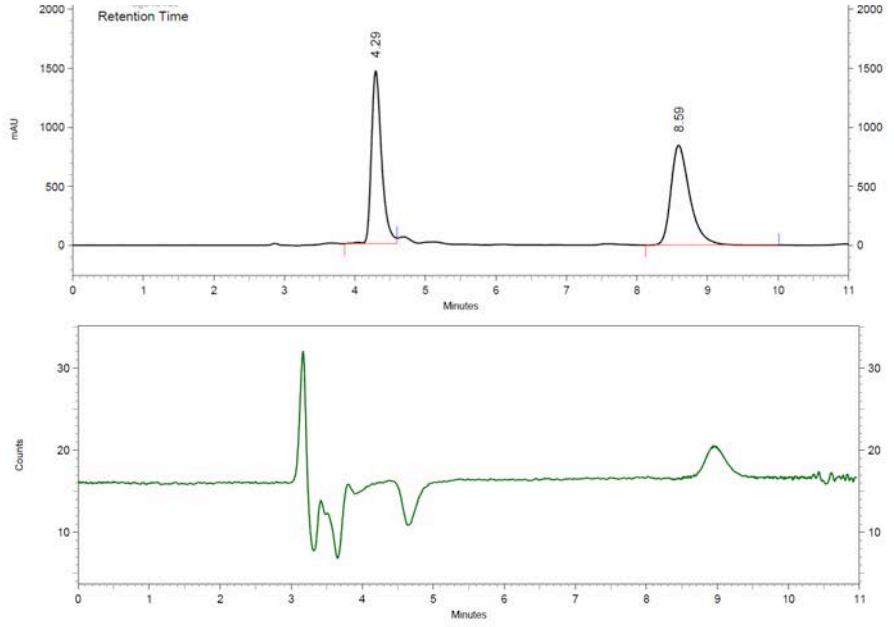



1: 254 nm, 4 nm
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 4.41 | 2275550 | 2.60 | 0.47 | 0.00 | 0.00 |
| 6.85 | 85162398 | 97.40 | 1.28 | 0.00 | 8.34 |
| Totals | 87437948 | 100.00 | | | |



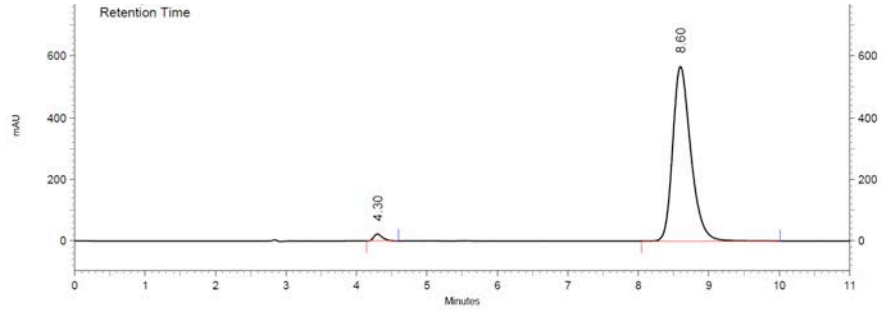


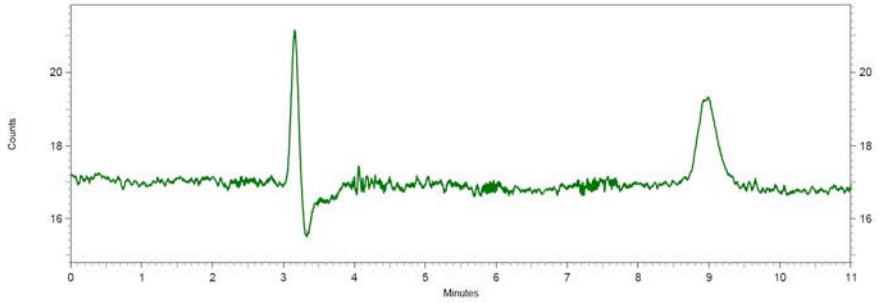




1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 4.29 | 59109009 | 48.28 | 0.43 | 0.00 | 0.00 |
| 8.59 | 63314209 | 51.72 | 1.86 | 0.00 | 11.62 |
| Totals | 122423218 | 100.00 | | | |

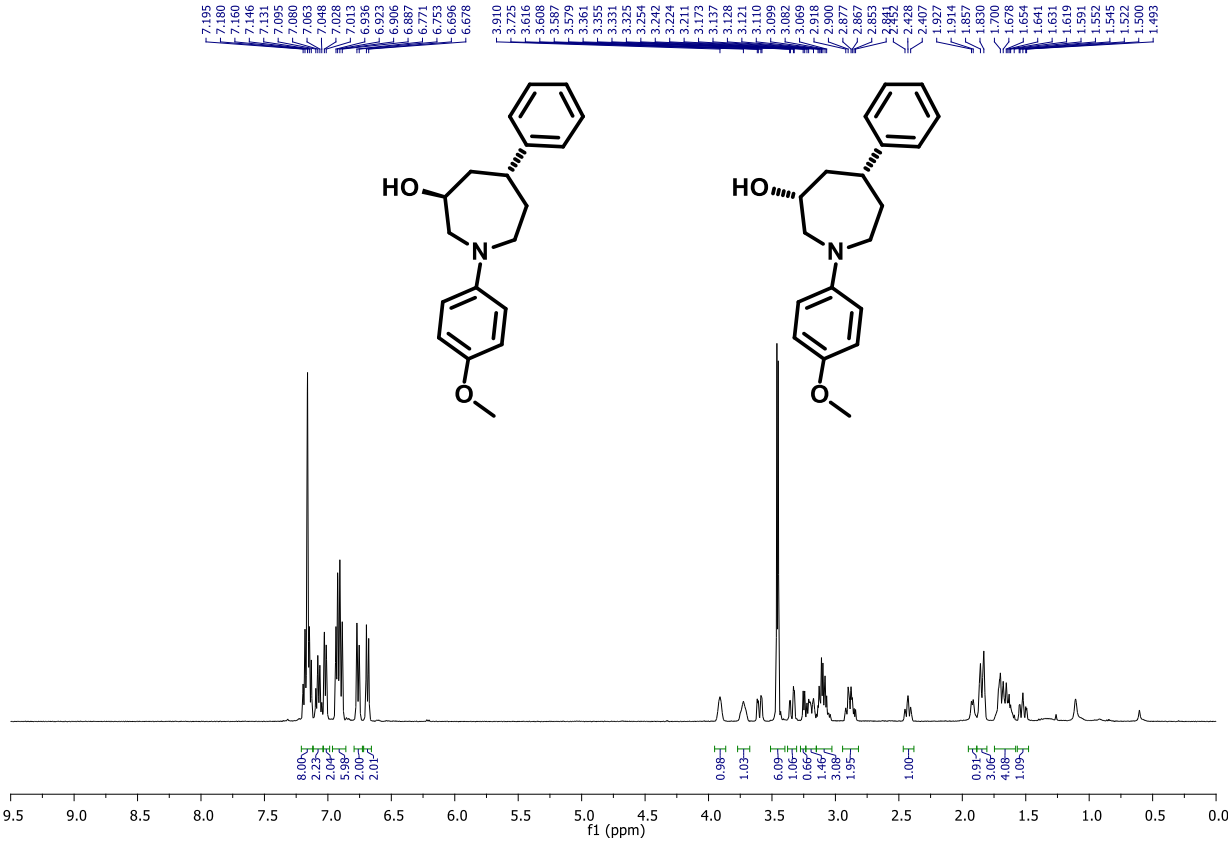


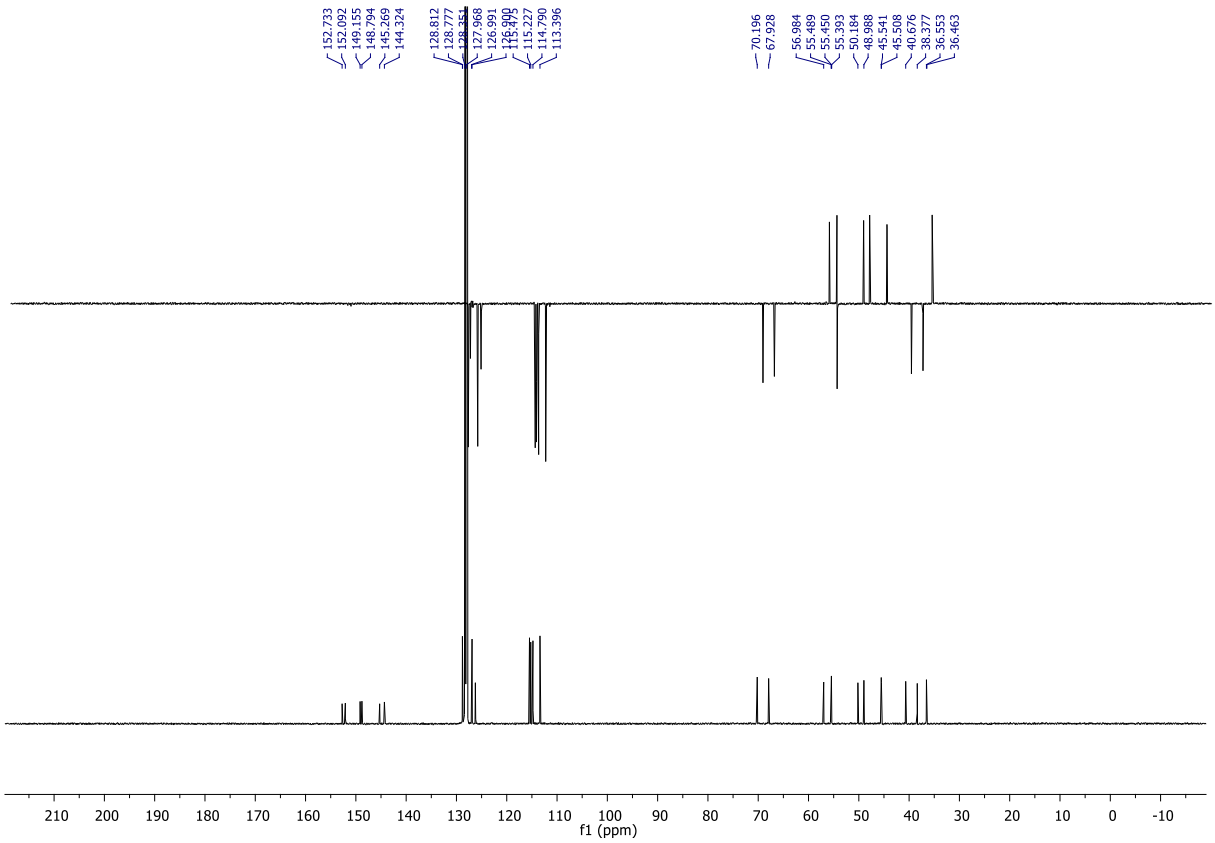



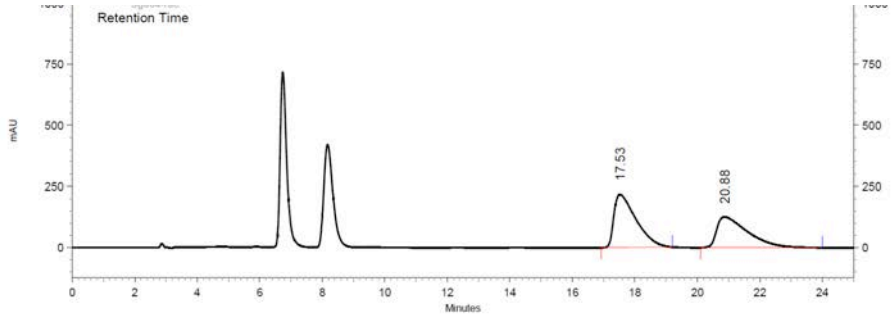

1: 254 nm, 4 nm

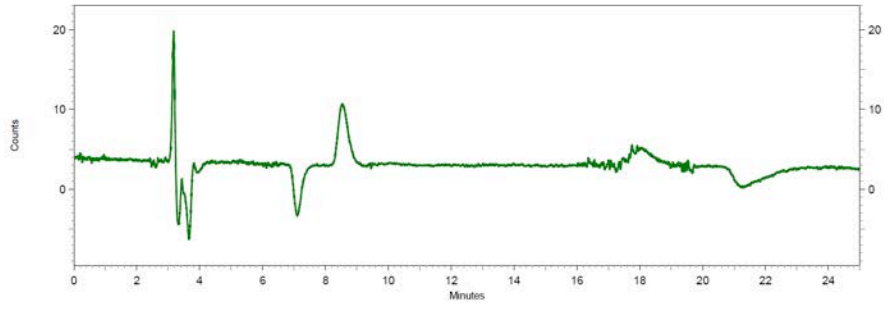
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 4.30 | 787161 | 1.91 | 0.43 | 0.00 | 0.00 |
| 8.60 | 40398803 | 98.09 | 1.87 | 0.00 | 12.38 |
| Totals | 41185964 | 100.00 | | | |





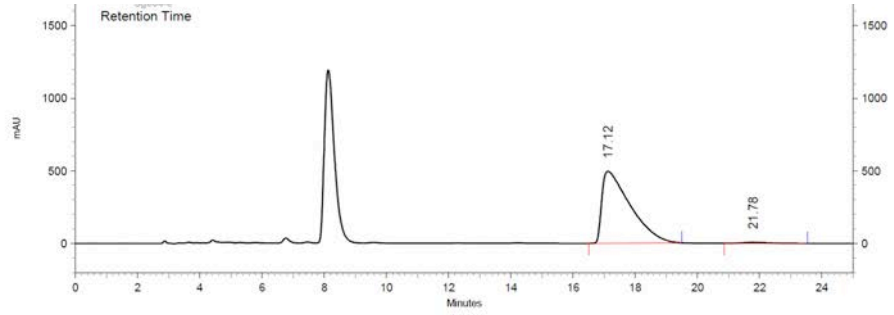



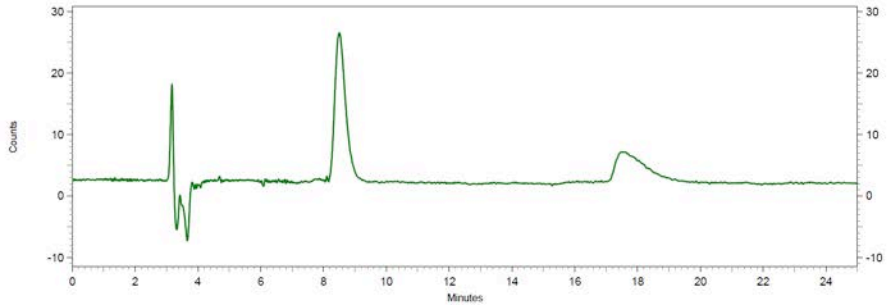




2: 270 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 17.53 | 42859374 | 55.32 | 4.84 | 0.00 | 0.00 |
| 20.88 | 34612483 | 44.68 | 5.96 | 0.00 | 2.12 |
| Totals | 77471857 | 100.00 | | | |

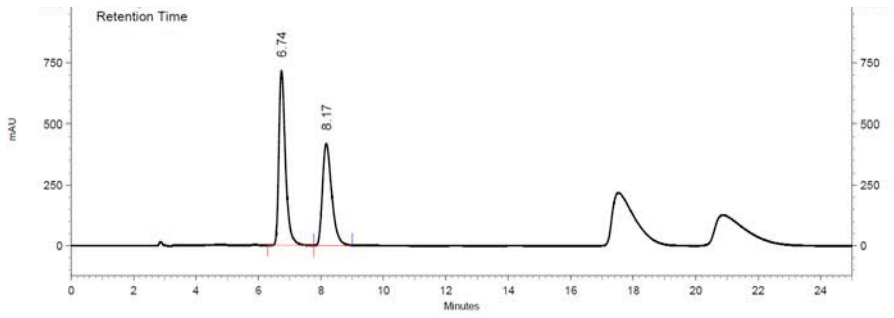


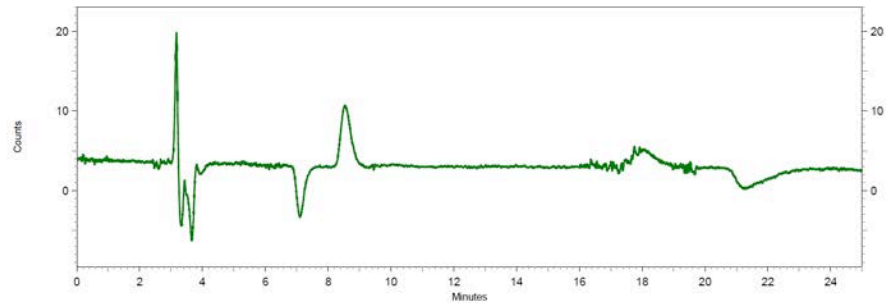




2: 270 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 17.12 | 125512387 | 98.77 | 4.71 | 0.00 | 0.00 |
| 21.78 | 1559292 | 1.23 | 6.26 | 0.00 | 2.85 |
| Totals | 127071679 | 100.00 | | | |

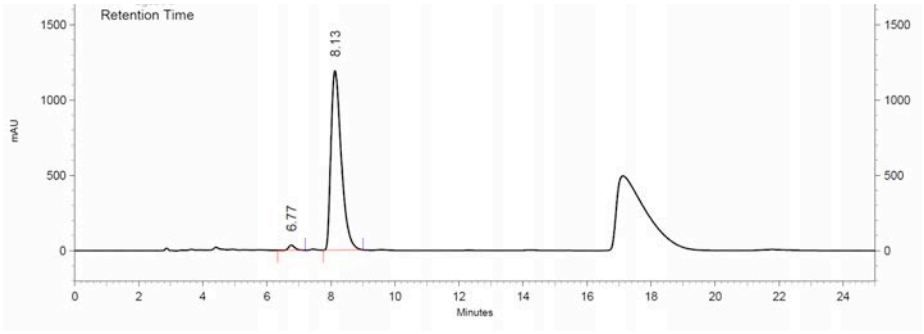


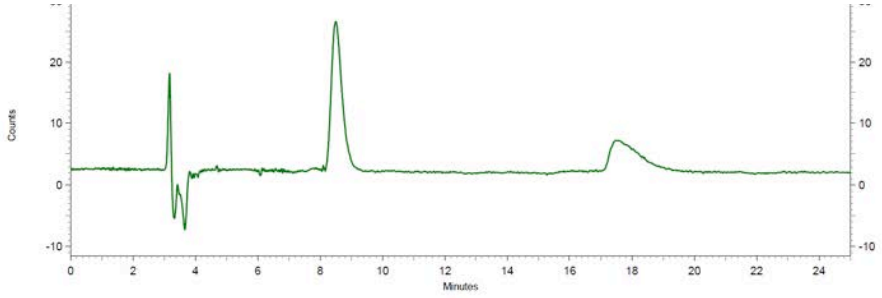



2: 270 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 6.74 | 42126881 | 55.03 | 1.25 | 0.00 | 0.00 |
| 8.17 | 34431030 | 44.97 | 1.72 | 0.00 | 3.13 |
| Totals | 76557911 | 100.00 | | | |

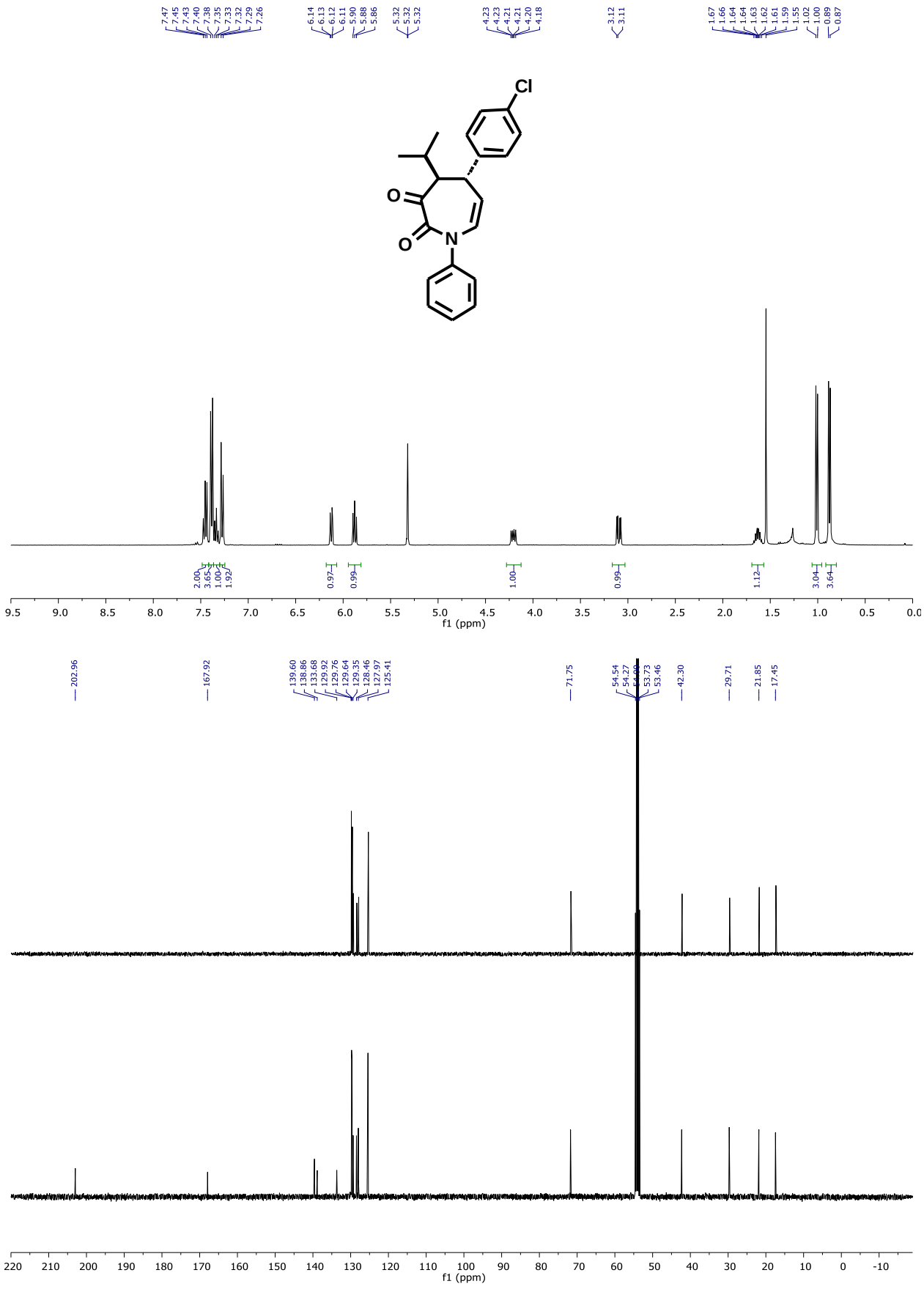


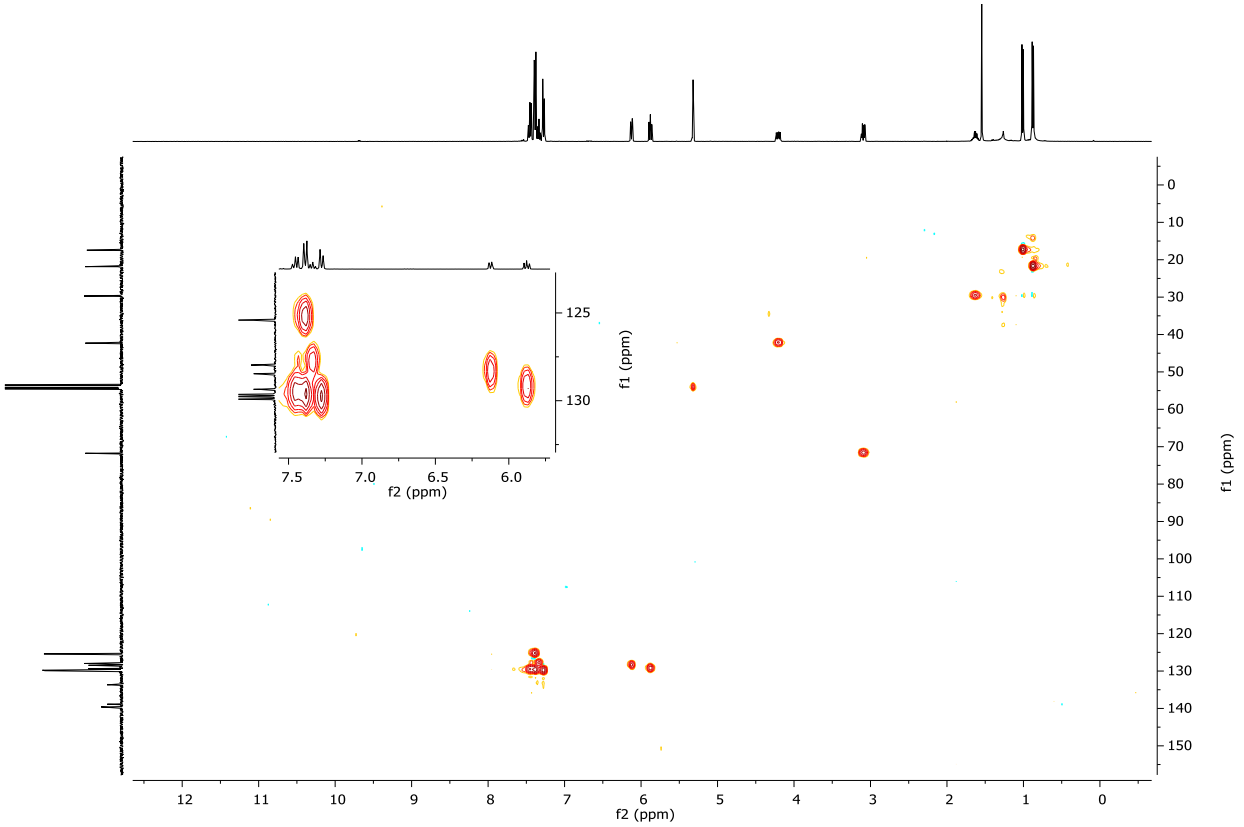



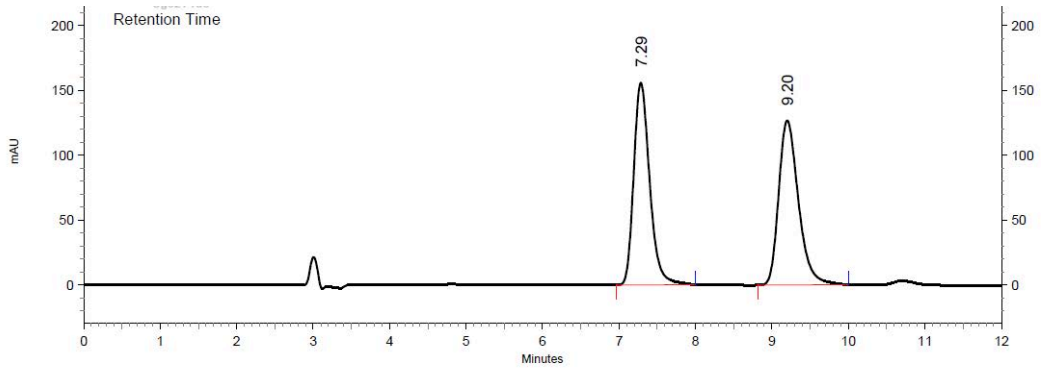

2: 270 nm, 4 nm

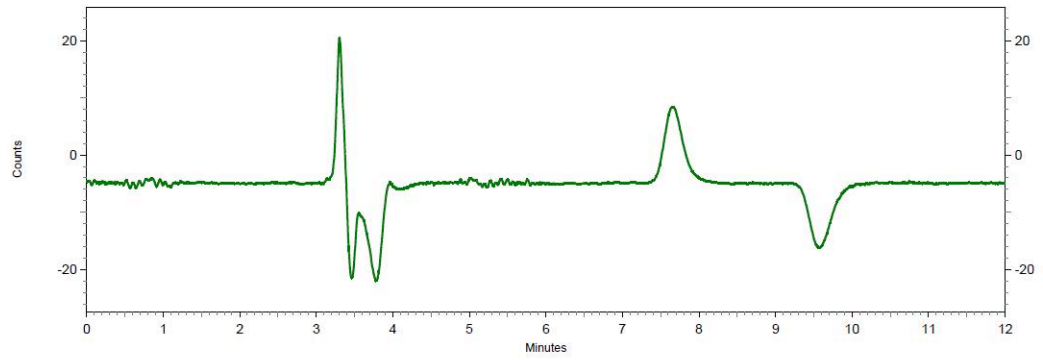
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 6.77 | 1848677 | 1.70 | 1.26 | 0.00 | 0.00 |
| 8.13 | 106857632 | 98.30 | 1.71 | 0.00 | 2.88 |
| Totals | 108706309 | 100.00 | | | |


7.47
7.45
7.43
7.40
7.38
7.35
7.33
7.32
7.29
7.26
6.14
6.13
6.12
6.11
5.90
5.88
5.86
5.32
5.32
5.32
4.23
4.23
4.21
4.21
4.20
4.18
3.12
3.11
1.67
1.66
1.64
1.64
1.63
1.62
1.61
1.59
1.55
1.02
1.00
0.89
0.87
Cl
O
O
N
2.00
3.65
1.00
1.92
0.97
0.99
1.00
0.99
1.12
3.04
3.64
9.5 9.0 8.5 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)
202.96
167.92
139.60
138.86
133.68
129.92
129.76
129.64
129.35
128.46
127.97
125.41
71.75
54.54
54.27
54.00
53.73
53.46
42.30
29.71
21.85
17.45
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



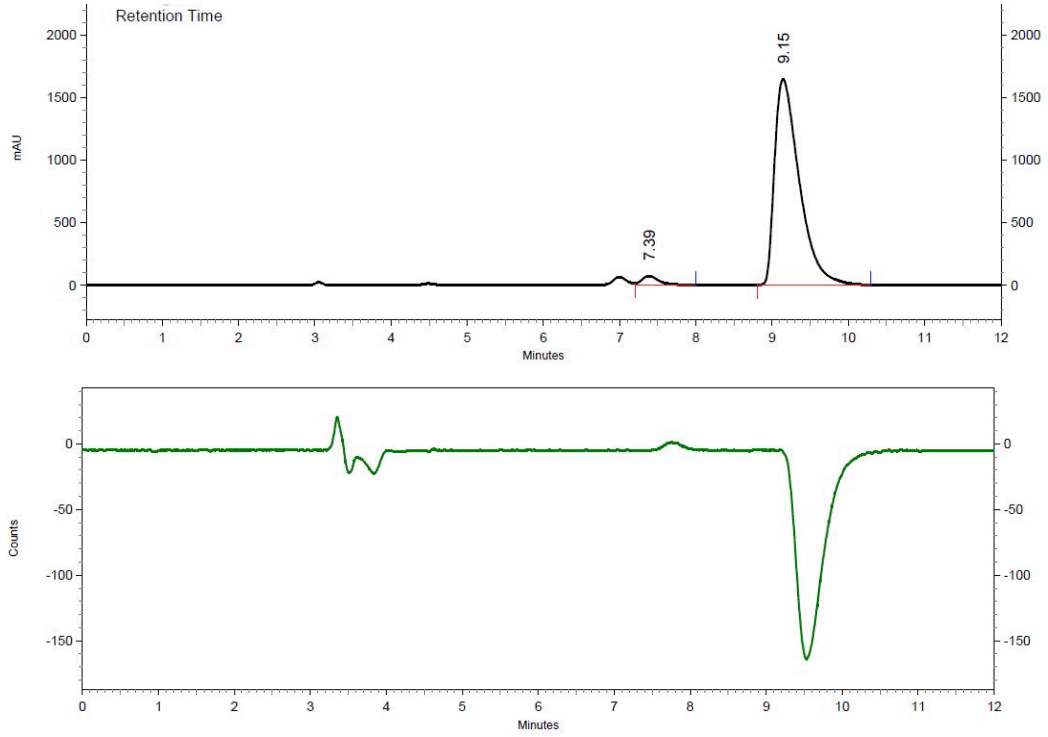




1: 254 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 7.29 | 9039494 | 49.80 | 1.43 | 1.00 | 0.00 |
| 9.20 | 9111465 | 50.20 | 2.07 | 1.45 | 4.53 |
| Totals | 18150959 | 100.00 | | | |



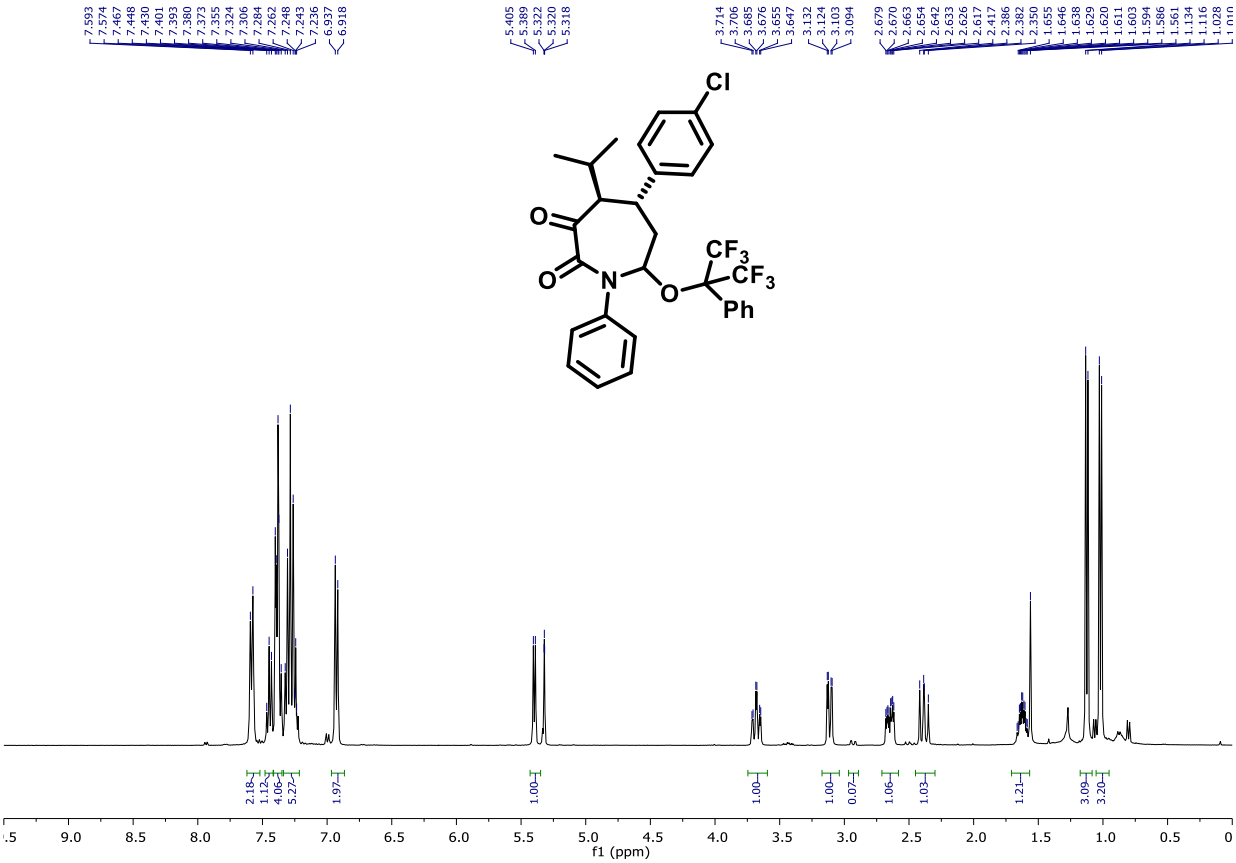


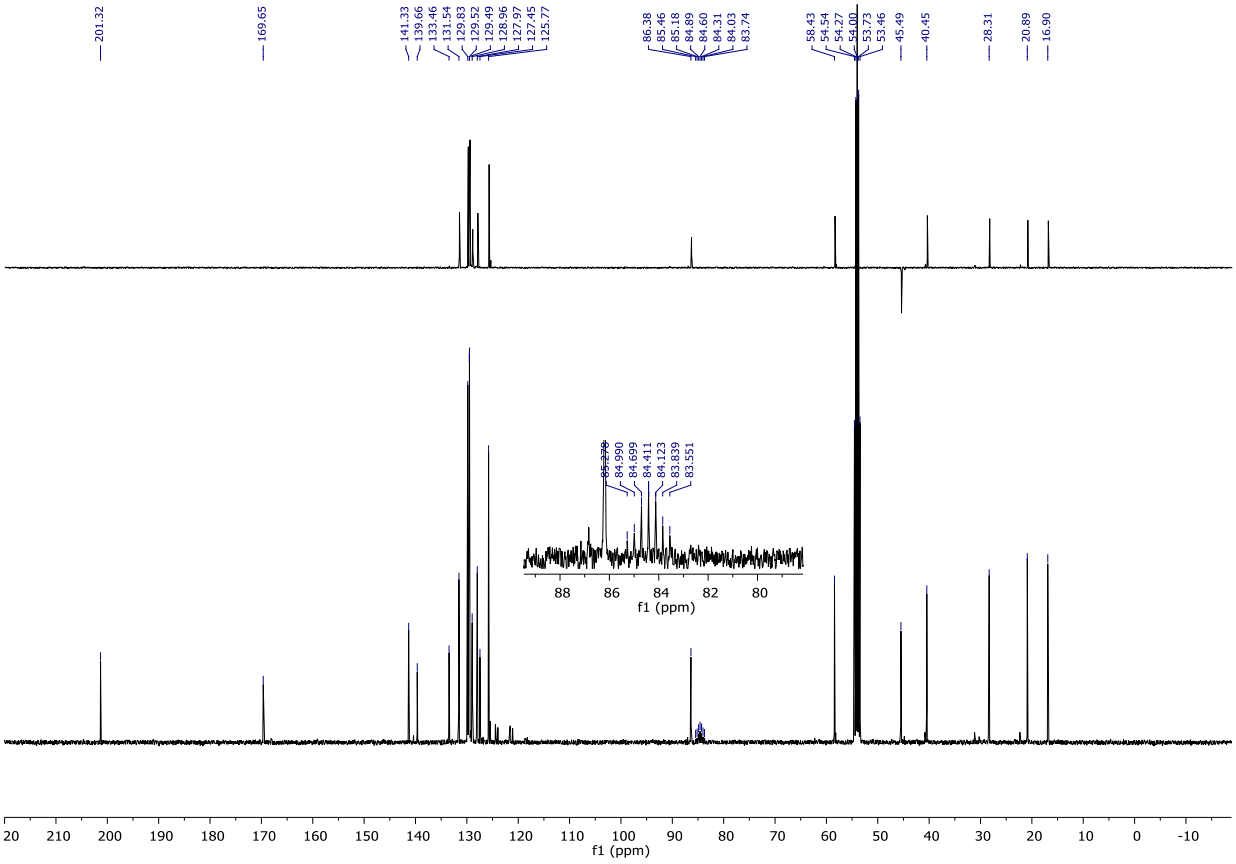


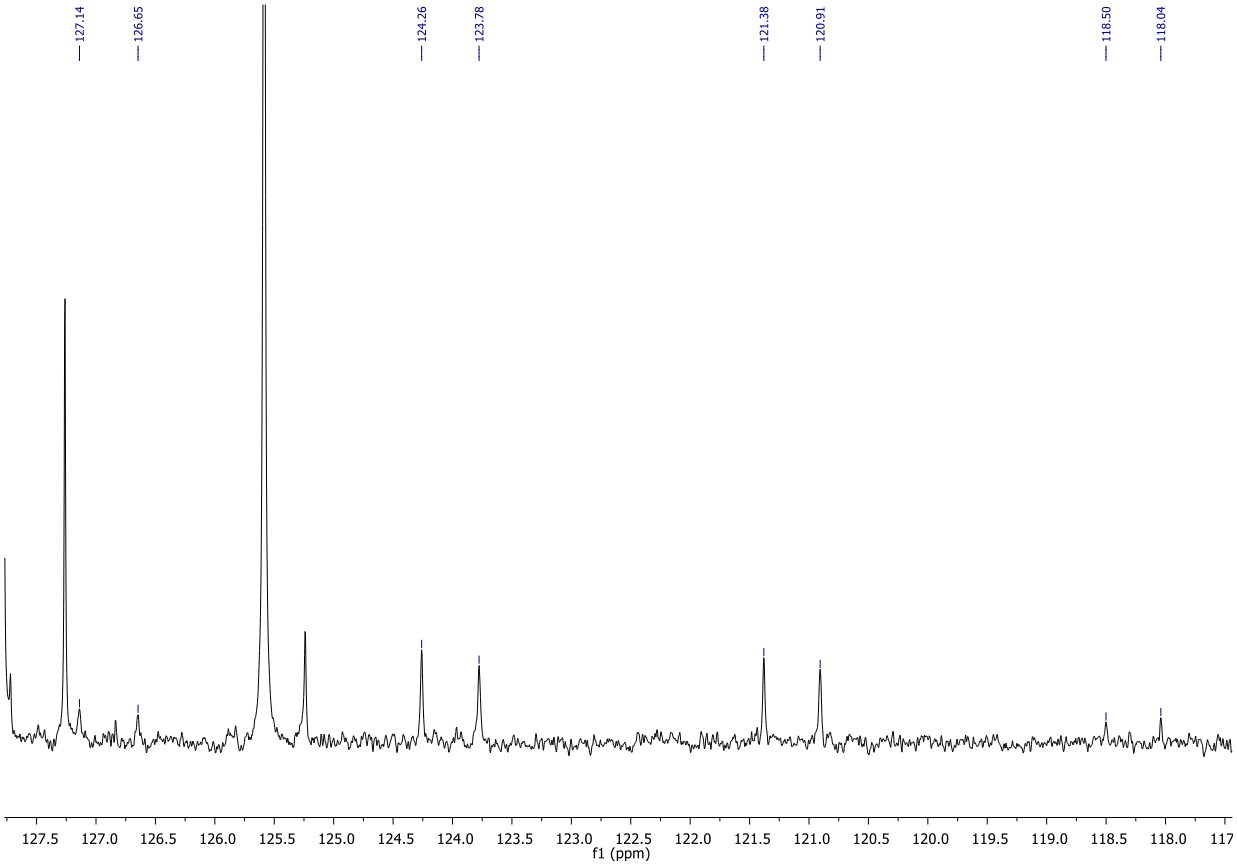
1: 254 nm, 4 nm

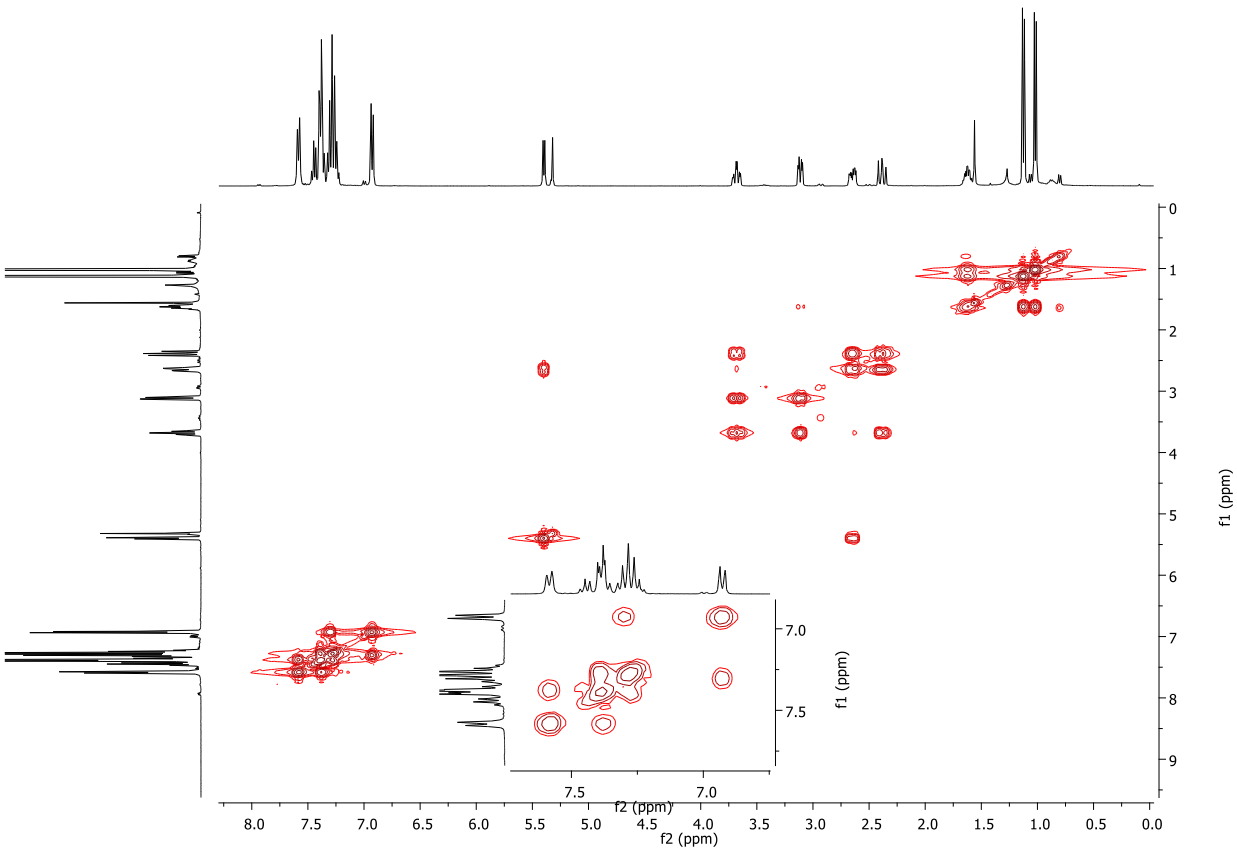
Results

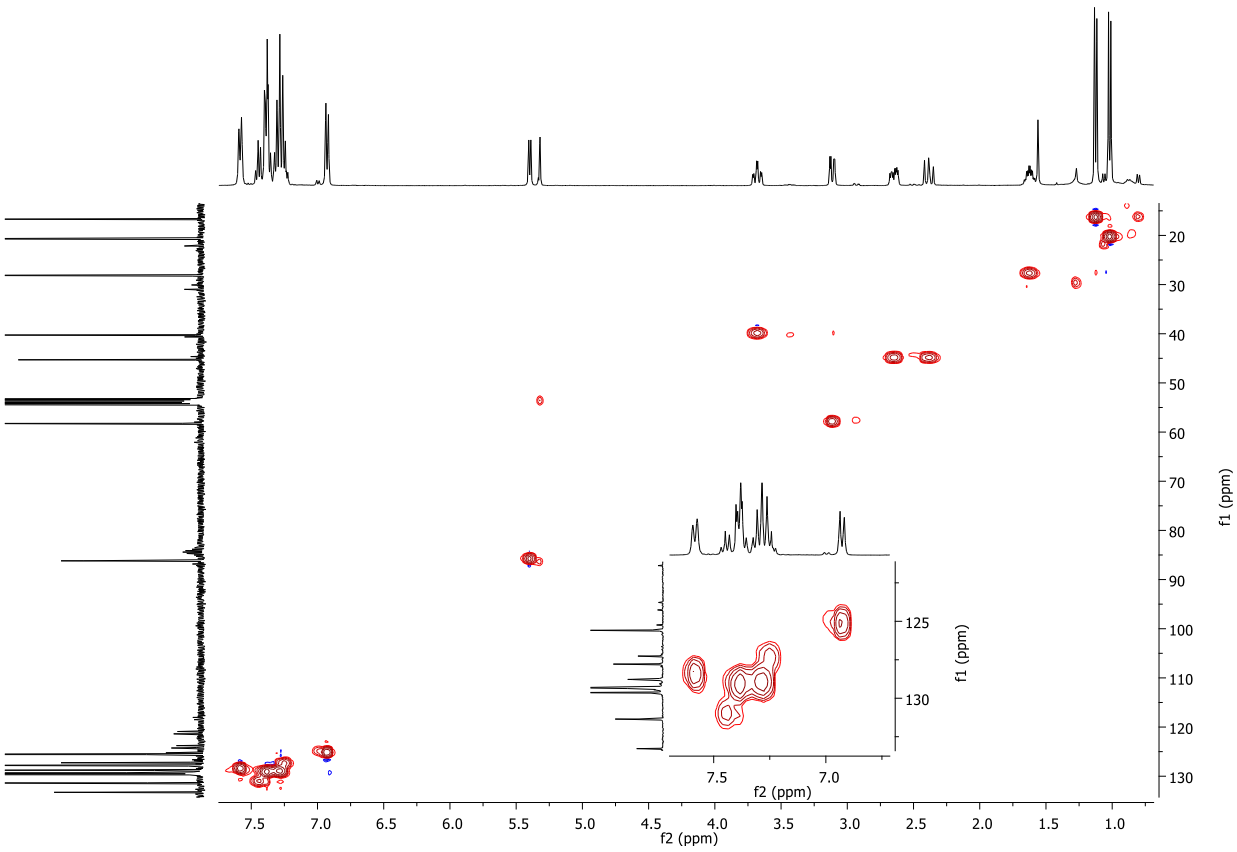
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 7.39 | 4508861 | 2.95 | 1.46 | 1.00 | 0.00 |
| 9.15 | 148133606 | 97.05 | 2.05 | 1.40 | 3.57 |
| Totals | 152642467 | 100.00 | | | |

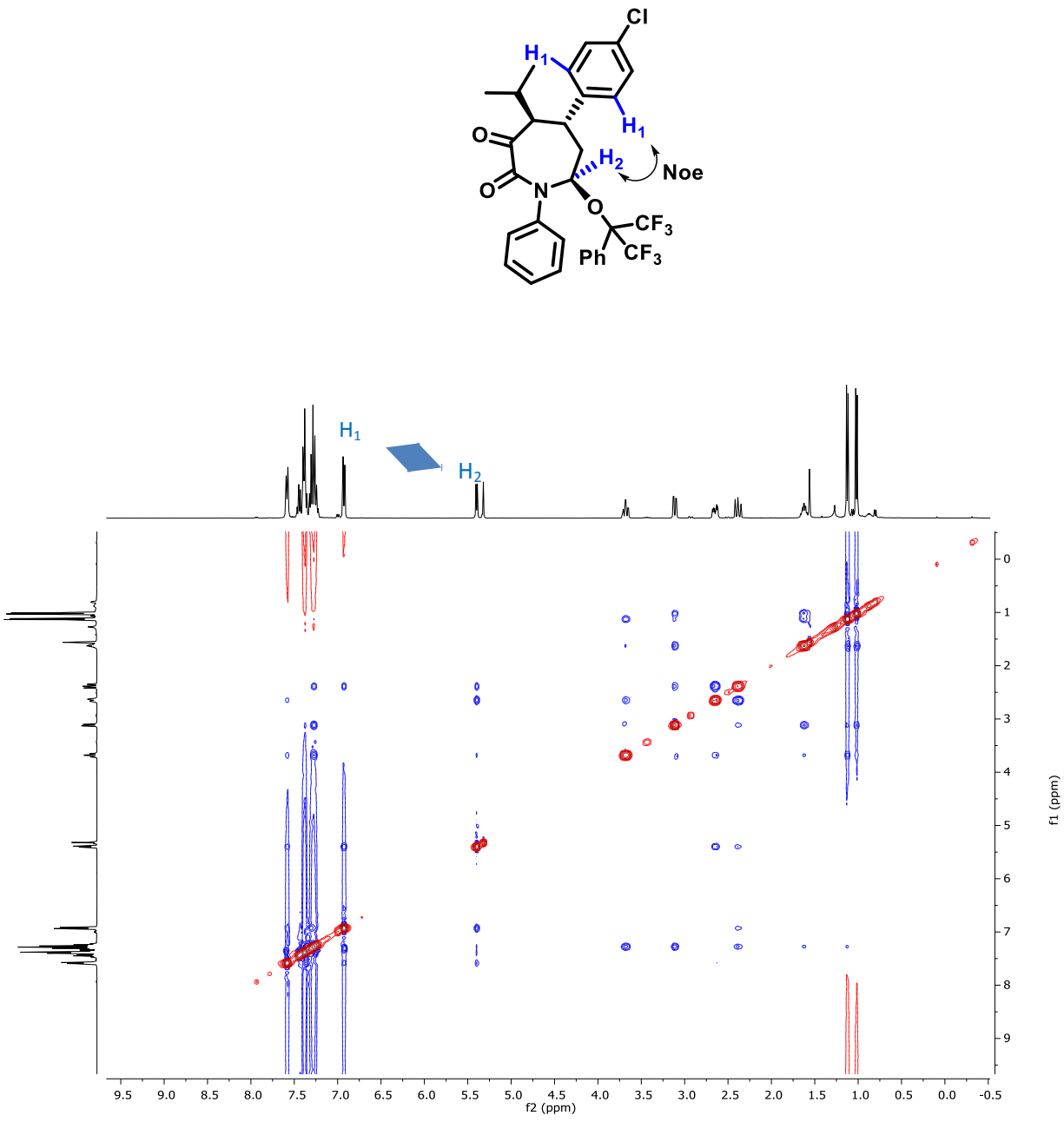

7.593
7.574
7.467
7.448
7.430
7.401
7.393
7.380
7.373
7.355
7.324
7.306
7.284
7.262
7.248
7.243
7.236
6.937
6.918
5.405
5.389
5.322
5.320
5.318
3.714
3.706
3.685
3.676
3.655
3.647
3.132
3.124
3.103
3.094
2.679
2.670
2.663
2.654
2.642
2.633
2.626
2.617
2.417
2.386
2.382
2.350
1.655
1.646
1.638
1.629
1.620
1.611
1.603
1.594
1.586
1.561
1.134
1.116
1.028
1.000
Cl
O
O
N
O
CF3
CF3
Ph
2.18
1.12
4.06
5.27
1.97
1.00
1.00
1.00
0.07
1.06
1.03
1.21
3.09
3.20
f1 (ppm)

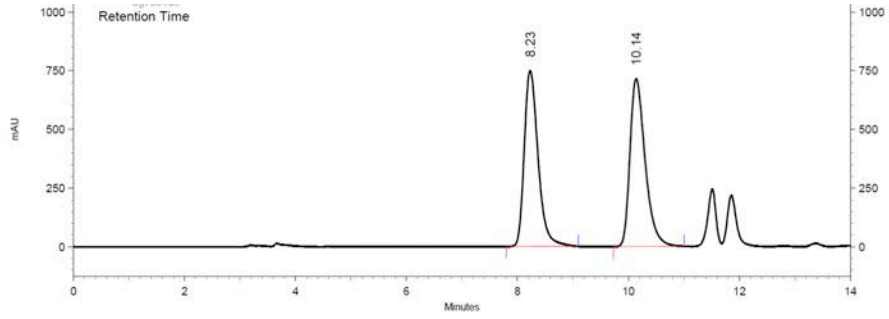

201.32
169.65
141.33
139.66
133.46
131.54
129.83
129.52
129.49
128.96
127.97
127.45
125.77
86.38
85.46
85.18
84.89
84.60
84.31
84.03
83.74
58.43
54.54
54.27
54.00
53.73
53.46
45.49
40.45
28.31
20.89
16.90
85.276
84.990
84.699
84.411
84.123
83.839
83.551
f1 (ppm)
f1 (ppm)

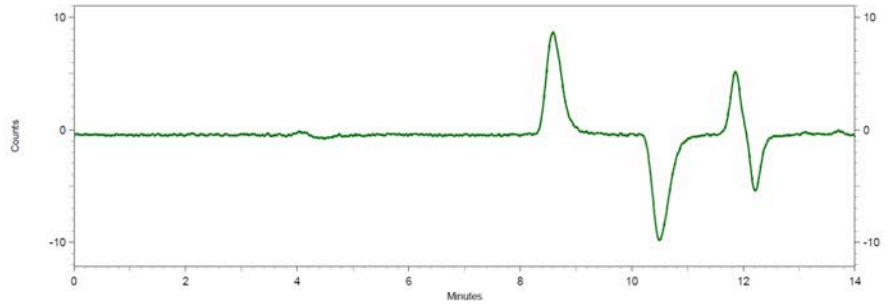

127.14
126.65
124.26
123.78
121.38
120.91
118.50
118.04
f1 (ppm)


f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)
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
20
30
40
50
60
70
80
90
100
110
120
130
125
130

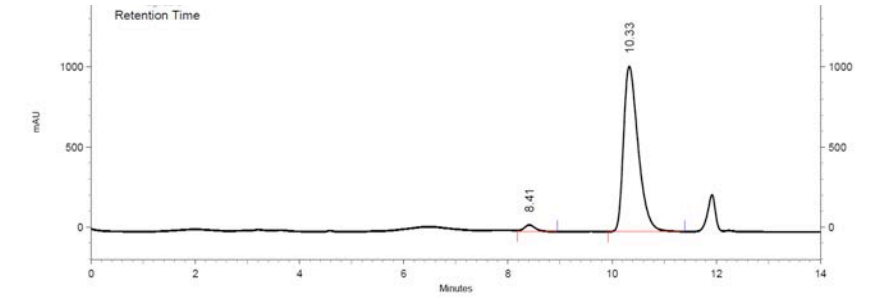

Cl
H1
H1
H2
Noe
O
O
N
O
CF3
Ph
CF3
H1
H2
f2 (ppm)
f1 (ppm)

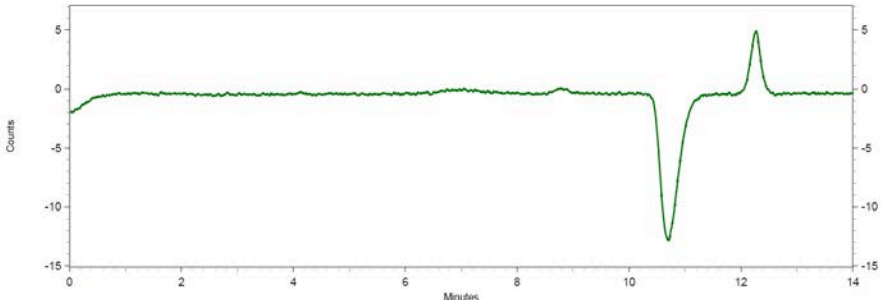



1: 220 nm, 4 nm
Results

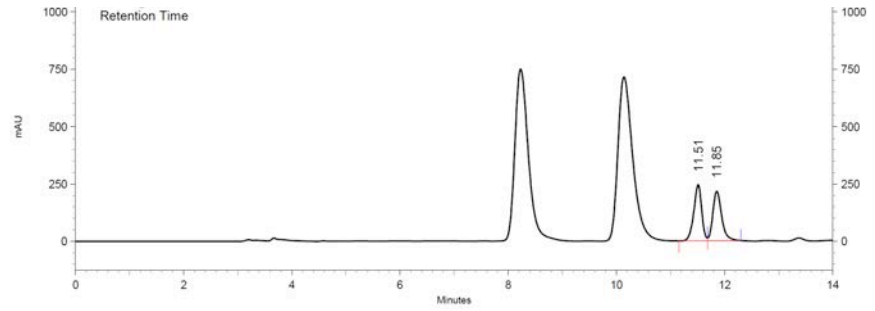
| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.23 | 51865570 | 48.82 | 1.74 | 0.00 | 0.00 |
| 10.14 | 54374427 | 51.18 | 2.38 | 0.00 | 4.05 |
| Totals | 106239997 | 100.00 | | | |

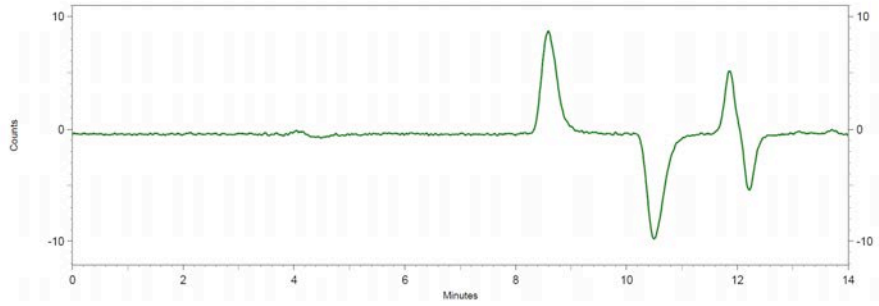



1: 220 nm, 4 nm
Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 8.41 | 2571972 | 3.10 | 1.80 | 0.00 | 0.00 |
| 10.33 | 80300098 | 96.90 | 2.44 | 0.00 | 4.22 |
| Totals | 82872070 | 100.00 | | | |

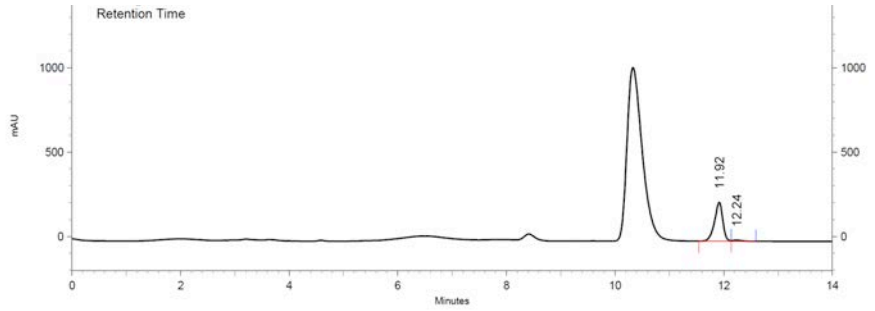


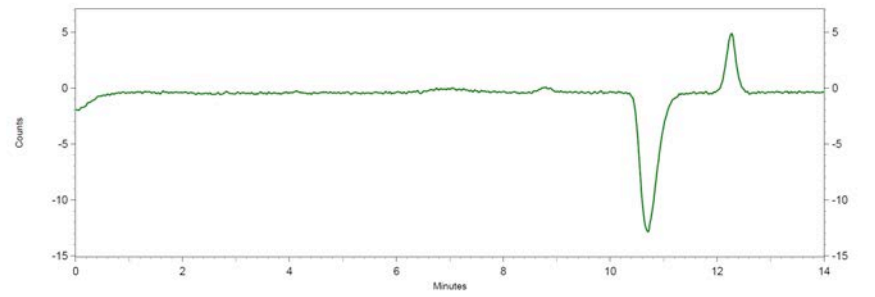




1: 220 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.51 | 9958848 | 50.45 | 2.84 | 0.00 | 0.00 |
| 11.85 | 9781368 | 49.55 | 2.95 | 0.00 | 1.21 |
| Totals | 19740216 | 100.00 | | | |




1: 220 nm, 4 nm

Results

| Retention Time | Area | Area % | Capacity factor | Relative RT | Resolution (USP) |
|---|---|---|---|---|---|
| 11.92 | 9671017 | 97.23 | 2.97 | 0.00 | 0.00 |
| 12.24 | 275617 | 2.77 | 3.08 | 0.00 | 1.05 |
| Totals | 9946634 | 100.00 | | | |