Electronic Supplementary Material (ESI) for ChemComm.

Phosphine-Catalyzed Dearomatizing [3+2] Annulations of Isoquinolinium Methylides with Allenes

Zhi-Jun Jia,[a,b] Constantin Gabriel Daniliuc[c], Andrey P. Antonchick[a,b]* and Herbert Waldmann[a,b]*

[a] Max-Planck-Institut für Molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany.
[b] Technische Universität Dortmund, Fakultät Chemie und Chemische Biologie, Chemische Biologie, Otto-Hahn-Strasse 6, 44227 Dortmund, Germany.
[c] Organisch-Chemisches Institut, Universität Münster, Corrensstrasse 40, D-48149 Münster, Germany.

General

Unless otherwise noted, all commercially available compounds were used as provided without further purifications. Solvents for chromatography were technical grade.

Analytical thin-layer chromatography (TLC) was performed on *Merck silica gel aluminium plates* with F-254 indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Column chromatography was performed using *silica gel Merck 60* (particle size 0.040-0.063 mm). Solvent mixtures are understood as volume/volume. ^{1}H-NMR and ^{13}C-NMR were recorded on a *Bruker DRX400* (400 MHz), *Bruker DRX500* (500 MHz) and *INOVA500* (500 MHz) using $CDCl_3$ or DMSO-d_6 as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C); multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are given in Hertz (Hz).

High resolution mass spectra were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Acceka HPLC*-System (HPLC column: *Hypersyl GOLD*, 50 mm x 1 mm, particle size 1.9 μm, ionization method: electron spray ionization). Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a *Bruker Tensor 27* spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured in a *Schmidt + Haensch Polartronic HH8* polarimeter.

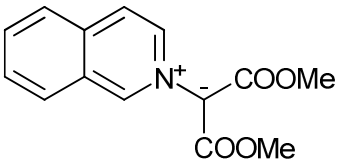
Procedures for the synthesis of isoquinolinium methylides[1,2,3]

For **1a**, **1b**:[3]

To a mixture of 2-bromomalonate and 30 mL acetone was added isoquinoline. The mixture was stirred for 24 h at r.t., and the resulting precipitate was filtered and recrystallized from *i*-PrOH and ether to give a colorless solid. The solid was dissolved in water, the pH was adjusted to alkaline conditions and the solution extracted with $CHCl_3$. Recrystallization gave yellow needles.

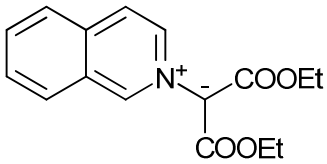
For **1c-1p**:[1,2]

To a solution of $Cu(acac)_2$ (1 mol %) in 5 mL of CH_2Cl_2 were added the corresponding isoquinoline (1.0 mmol) and iodonium ylide (1.2 mmol). The reaction mixture was stirred at room temperature to 40 ℃. After completion of the reaction (monitored by TLC), the solution was concentrated and purified by chromatography on silica gel to give the corresponding isoquinolinium methylides **1a-1p**.

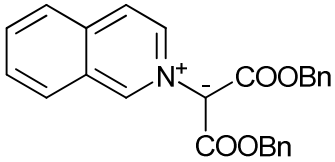


1a, 65% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.28 (s, 1H), 8.30 (d, *J* = 6.8 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.00 – 8.01 (m, *J* = 4.5 Hz, 2H), 7.97 (d, *J* = 6.9 Hz, 1H), 7.83 (ddd, *J* = 8.1, 5.3, 2.8 Hz, 1H), 3.73 ppm(s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.49, 141.41, 136.37, 135.64, 130.21, 129.75, 127.74, 126.85, 123.55, 97.35, 54.93, 50.74 ppm; FT-IR: $\tilde{\nu}$ = 3067, 2948, 1702, 1589, 1440, 1368, 1075 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{14}NO_4$: 260.09173, found: 260.09195.

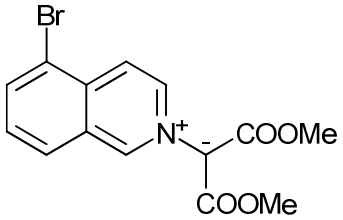
1. S. b. R. Goudreau, D. Marcoux and A. B. Charette, *The Journal of Organic Chemistry*, 2008, **74**, 470.
2. B. Xin, W. Tang, Y. Wang, G. Lin, H. Liu, Y. Jiao, Y. Zhu, H. Yuan, Y. Chen and T. Lu, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4783.
3. O. Tsuge, S. Kanemasa, K. Sakamoto and S. Takenaka, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2513-2524.



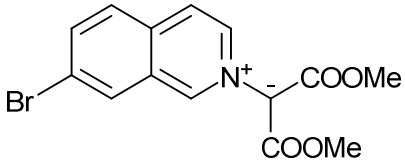
1b, 73% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.28 (s, 1H), 8.31 (d, *J* = 6.9 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.00 – 7.88 (m, 2H), 7.94 (d, *J* = 6.9 Hz, 1H), 7.88 – 7.77 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 4H), 1.29 ppm (t, *J* = 7.0 Hz, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.26, 141.40, 136.22, 135.46, 130.11, 129.68, 127.69, 126.81, 123.32, 97.59, 64.64, 59.12, 14.95 ppm; FT-IR: $\tilde{\nu}$ = 3081, 2976, 1655, 1605, 1409, 1372, 1330, 1170, 1049 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{16}H_{18}NO_4$: 288.12303, found: 288.12299.



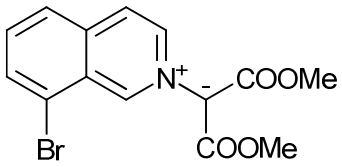
1c, 78% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.37 (d, *J* = 6.8 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.03 – 7.99 (m, 2H), 7.96 (d, *J* = 6.9 Hz, 1H), 7.83 (dt, *J* = 8.2, 4.0 Hz, 1H), 7.44 – 7.36 (m, 4H), 7.33 – 7.23 (m, 6H), 5.28 ppm(s, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.38, 141.32, 137.98, 136.29, 135.57, 130.15, 129.73, 128.41, 127.78, 127.69, 127.41, 126.81, 123.43, 64.97 ppm; FT-IR: $\tilde{\nu}$ = 3031, 2949, 1709, 1575, 1384, 1282, 1052 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{22}NO_4$: 412.15433, found: 412.15440.



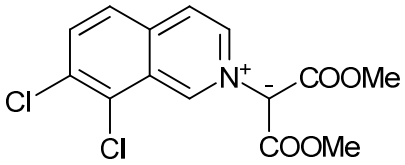
1d, 52% yield; Only ^{1}H-NMR is available due to its poor solubility even in all the solvents, ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 8.42 (d, *J* = 6.2 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.87 – 7.76 (m, 1H), 3.76 ppm (s, 6H); FT-IR: $\tilde{\nu}$ = 3023, 2943, 1701, 1590, 1440, 1377, 1359, 1080 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{79}BrNO_4$: 338.00225, found: 338.00255; calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{81}BrNO_4$: 340.00020, found: 340.00045;



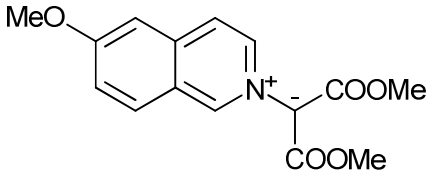
1e, 80% yield; Only ^{1}H-NMR is available due to its poor solubility even in all the solvents, ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1H), 8.47 – 8.21 (m, 2H), 8.15 – 8.00 (m, 1H), 8.00 – 7.78 (m, 2H), 3.76 ppm (s, 6H); FT-IR: $\tilde{\nu}$ = 3112, 2947, 1701, 1587, 1442, 1374, 1083, 1077 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{79}BrNO_4$: 338.00225, found: 338.00268; calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{81}BrNO_4$: 340.00020, found: 340.00052;



1f, 62% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 8.40 (d, *J* = 6.8 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.81 (t, *J* = 7.9 Hz, 1H), 3.76 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.60, 153.44, 142.27, 137.90, 135.69, 134.21, 127.26, 126.39, 124.30, 123.68, 50.93 ppm; FT-IR: $\tilde{\nu}$ = 3064, 2948, 1626, 1597, 1439, 1337, 1187, 1075 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{79}BrNO_4$: 338.00225, found: 338.00257; calcd. for $[M+H]^+$ $C_{14}H_{13}{}^{81}BrNO_4$: 340.00020, found: 340.00050;

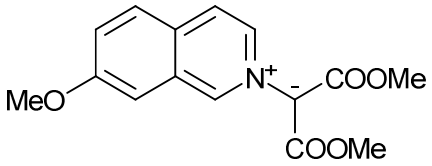


1g, 51% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 8.43 (dd, *J* = 6.8, 1.0 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 6.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 3.76 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.56, 150.42, 142.40, 136.66, 135.75, 135.30, 131.80, 127.04, 126.22, 123.35, 50.94 ppm; FT-IR: $\tilde{\nu}$ = 3039, 2944, 1585, 1436, 1337, 1183, 1111, 1054 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{14}H_{12}Cl_2NO_4$: 328.01379, found: 328.01438.

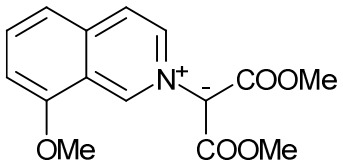


1h, 55% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.04 (s, 1H), 8.16 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.81 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.25 – 7.20 (m, 1H), 4.04 (s, 3H), 3.72 ppm (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 167.88, 165.48, 152.34, 141.80, 139.40,

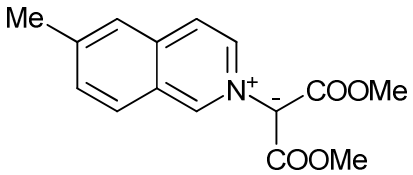
131.57, 123.48, 123.21, 122.09, 104.86, 56.36, 50.68 ppm; FT-IR: $\tilde{\nu}$ = 2944, 2847, 1588, 1434, 1337, 1266, 1184, 1091 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.10230, found: 290.10282.



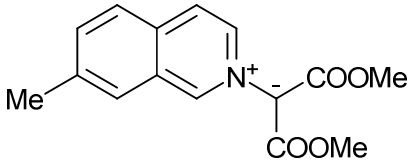
1i, 58% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 8.18 (d, *J* = 6.8 Hz, 1H), 7.97 – 7.78 (m, 2H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.33 (s, 1H), 3.97 (s, 3H), 3.72 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.82, 160.56, 151.68, 139.68, 132.28, 129.56, 129.19, 128.27, 123.29, 106.17, 56.09, 50.72 ppm; FT-IR: $\tilde{\nu}$ = 3084, 2946, 1705, 1587, 1436, 1375, 1263, 1078 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.10230, found: 290.10236.



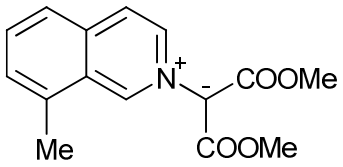
1j, 61% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 8.21 (d, *J* = 6.9 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 3.72 ppm (s, 6H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.92, 157.75, 150.07, 141.73, 137.38, 137.14, 122.99, 120.39, 118.28, 107.90, 56.39, 50.64 ppm; FT-IR: $\tilde{\nu}$ = 3045, 2938, 1596, 1428, 1344, 1213, 1085 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.10230, found: 290.10268.



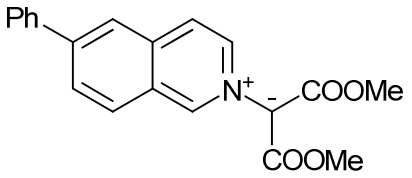
1k, 55% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 8.23 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 6.8 Hz, 1H), 7.82 – 7.71 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 3.73 (s, 6H), 2.66 ppm (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.96, 153.09, 147.64, 141.46, 136.81, 132.53, 129.52, 126.12, 125.92, 122.87, 96.87, 50.72, 22.80 ppm; FT-IR: $\tilde{\nu}$ = 3033, 2943, 1585, 1334, 1189, 1090 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_4$: 274.10738, found: 274.10747.



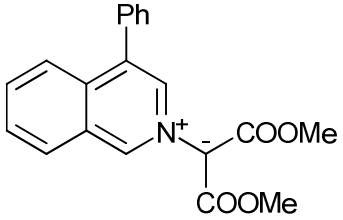
1l, 58% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.23 (d, *J* = 6.7 Hz, 1H), 7.95 – 7.87 (m, 3H), 7.85 – 7.78 (m, 1H), 3.72 (s, 6H), 2.61 ppm (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.79, 152.91, 140.91, 140.67, 138.02, 134.77, 130.08, 128.31, 128.05, 126.56, 123.30, 50.68, 21.90 ppm; FT-IR: $\tilde{\nu}$ = 3093, 2948, 1702, 1588, 1438, 1372, 1071 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_4$: 274.10738, found: 274.10748.



1m, 60% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1H), 8.29 (d, *J* = 6.7 Hz, 1H), 7.95 (d, *J* = 6.7 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.62 (d, *J* = 6.7 Hz, 1H), 3.74 (s, 6H), 2.80 ppm (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 165.71, 151.10, 141.11, 138.33, 137.08, 135.59, 130.88, 127.44, 124.97, 123.97, 50.73, 18.57 ppm; FT-IR: $\tilde{\nu}$ = 3042, 2940, 1592, 1432, 1346, 1198, 1091 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{15}H_{16}NO_4$: 274.10738, found: 274.10751.

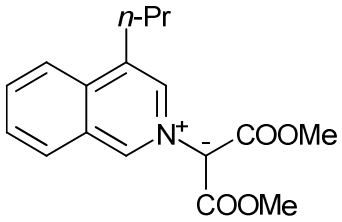


1n, 67% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 8.30 (s, 1H), 8.25 – 8.13 (m, 2H), 8.13 – 8.03 (m, 1H), 8.03 – 7.94 (m, 1H), 7.83 – 7.68 (m, 2H), 7.65 – 7.44 (m, 3H), 3.76 ppm (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.80, 153.06, 152.00, 141.68, 140.83, 138.61, 130.26, 130.01, 129.76, 129.56, 127.91, 126.75, 124.16, 123.55, 50.81 ppm; FT-IR: $\tilde{\nu}$ = 3017, 2952, 1574, 1439, 1350, 1186, 1080 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{18}BrNO_4$: 336.12303, found: 336.12326.



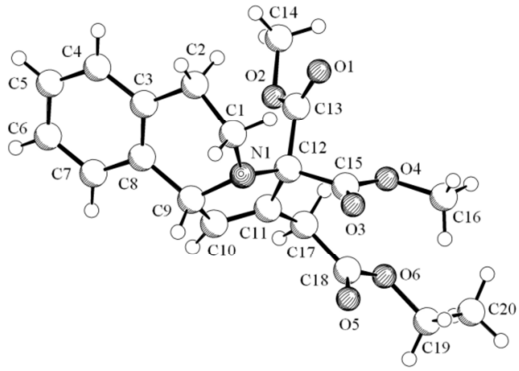
1o, 72% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 8.33 – 8.16 (m, 2H), 8.04 (d, 1H), 8.00 – 7.93 (m, 1H), 7.90 – 7.78 (m, 1H), 7.61 – 7.46 (m, 5H), 3.76 ppm (s, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 167.87, 165.84, 152.15, 140.40, 137.39, 136.96, 135.64,

134.28, 133.60, 130.07, 129.59, 129.25, 128.06, 125.51, 50.86 ppm; FT-IR: $\tilde{\nu}$ = 2945, 1611, 1434, 1364, 1176, 1074 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{18}BrNO_4$: 336.12303, found: 336.12375.



1p, 72% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.14 (s, 1H), 8.18 – 8.10 (m, 3H), 8.06 – 7.96 (m, 1H), 7.87 – 7.76 (m, 1H), 3.73 (s, 6H), 3.06 (t, *J* = 7.3 Hz, 2H), 1.87 – 1.71 (m, 3H), 1.07 ppm (t, *J* = 7.3 Hz, 3H).; ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 151.84, 140.04, 136.26, 135.97, 135.28, 130.57, 129.72, 127.88, 123.48, 50.71, 32.06, 23.04, 14.05 ppm; FT-IR: $\tilde{\nu}$ = 2943, 1707, 1624, 1434, 1367, 1171, 1072 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{17}H_{20}NO_4$: 302.13868, found: 302.13920.

Crystal data and structure refinement for compound 4a



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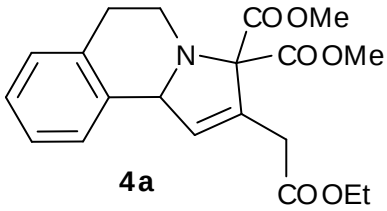
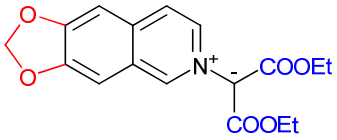


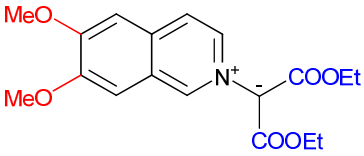
4a

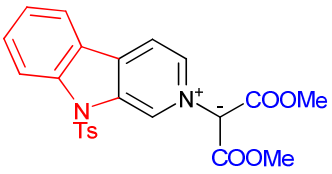
Empirical formula	C_{20} H_{23} N O_6
Formula weight	373.39
Temperature	223(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, $P2_1/c$ (No. 14)
Unit cell dimensions	a = 8.7052(2) Å
	b = 7.8790(2) Å β = 93.841(1)°
	c = 27.3581(9) Å
Volume	1872.23(9) $Å^3$
Z, Calculated density	4, 1.325 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	792
Crystal size	0.30 x 0.15 x 0.03 mm
Theta range for data collection	4.48 to 26.37°
Limiting indices	-10<=h<=10, -9<=k<=8, -34<=l<=34
Reflections collected / unique	16357 / 3784 [R(int) = 0.073]
Completeness to theta = 26.37	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9971 and 0.9712
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3784 / 0 / 247
Goodness-of-fit on F^2	1.060
Final R indices [I>2σ(I)]	R1 = 0.0643, wR^2 = 0.1242
R indices (all data)	R1 = 0.1122, wR^2 = 0.1476
Largest diff. peak and hole	0.192 and -0.220 e.$Å^{-3}$

Other failed substrates

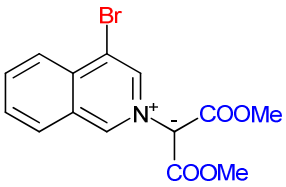
No Reaction:



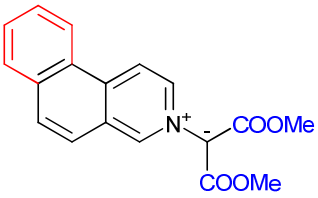




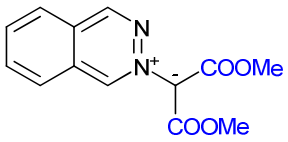
Product is too instable to characterization:

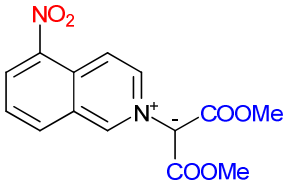


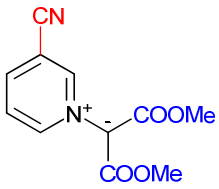
Low reactivty:



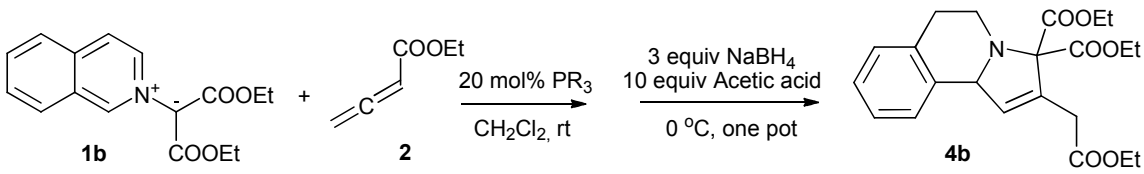
Complicated Reactivity:

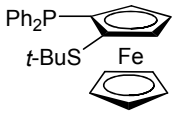




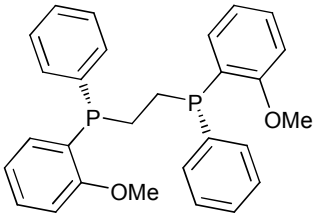


Attempts to enantioseletive [3+2] cycloaddition reactions

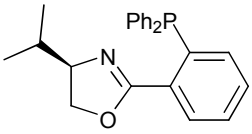




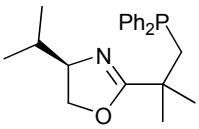
t = 12 h,
yield = 67%,
ee = 0.



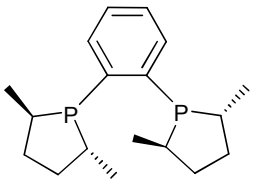
t = 10 min,
yield = 94%,
ee = 0.



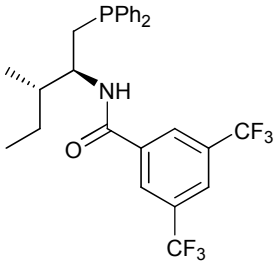
t = 2 h,
yield = 76%,
ee = 0.



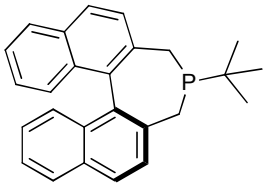
t = 12 h,
yield = 67%,
ee = 0.



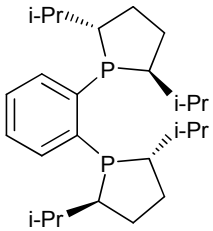
t = 10 min,
yield = 98%,
ee = 0.



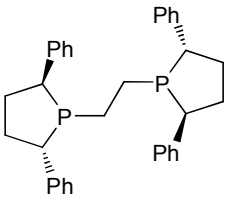
t = 10 min.
mess.



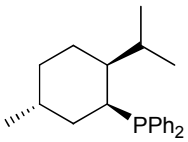
t = 2 h,
yield = 76%,
ee = 0.



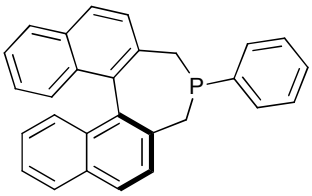
low conversion.



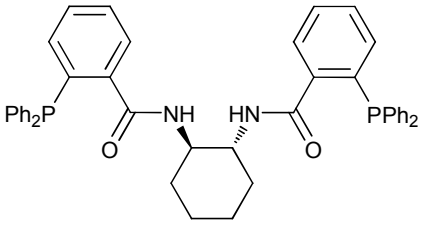
low conversion.



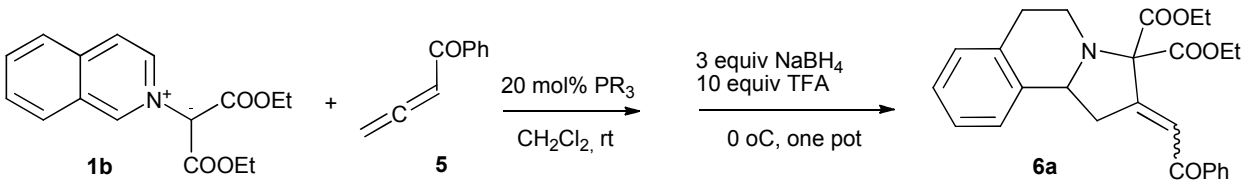
low conversion.

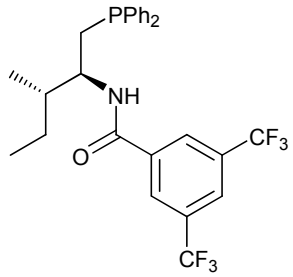


low conversion.

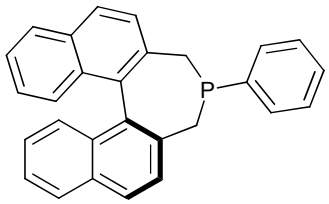


low conversion.

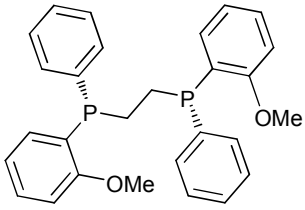




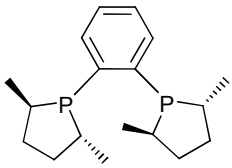
t = 5h
Ratio of isomers > 5:1
yiled = 87%
ee = 37%



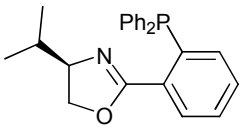
t = 24h
Ratio of isomers = 2:1
yiled = 60%
ee = 7%, 0.



t = 5h
Ratio of isomers = 1:1
yiled = 85%
ee = 0.



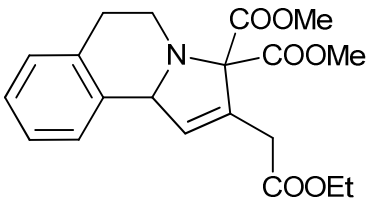
t = 5h
Ratio of isomers = 1.2:1
yiled = 87%
ee = 0.



t = 7h
Ratio of isomers = 2:1
yiled = 72%
ee = 0.

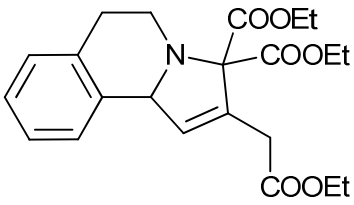
General procedure and substrate scope for [3+2] cycloaddition reactions

Reactions were performed with **1a** (0.1 mmol), **2** or **5** (0.15 mmol) and PBu_3 (0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature. After completion of the reaction, $NaBH_4$ (0.3 mmol) and acetic acid or trifluoroacetic acid (1 mmol) were added sequentially at 0 °C, and the reaction mixture was stirred for 10 minutes. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by silica gel flash chromatography to give the desired product.



Dimethyl 2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

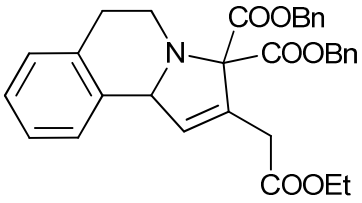
4a: 75% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.19 – 7.07 (m, 4H), 6.51 (d, *J* = 1.3 Hz, 1H), 5.17 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.63 (s, 3H), 3.45 – 3.34 (m, 2H), 3.33 (d, *J* = 1.3 Hz, 2H), 2.95 – 2.83 (m, 1H), 2.70 (dd, *J* = 12.2, 8.0 Hz, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.57, 169.31, 169.26, 137.08, 134.77, 133.21, 133.05, 129.01, 126.43, 126.04, 124.39, 81.51, 65.53, 60.94, 52.64, 52.52, 42.47, 33.98, 28.34, 14.32 ppm; FT-IR: $\tilde{\nu}$ = 2953, 2841, 1731, 1452, 1235, 1138, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{24}NO_6$: 374.15981, found: 374.15949.



Diethyl 2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

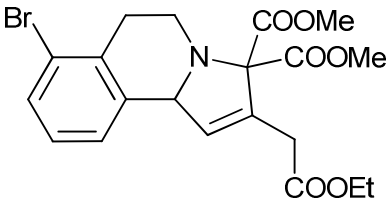
4b: 95% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.20 – 7.07 (m, 4H), 6.54 (s, 1H), 5.23 (s, 1H), 4.33 – 4.22 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.11 – 4.01 (m, 2H), 3.48 (s, 1H), 3.41 – 3.30 (m, 3H), 2.98 – 2.87 (m, 1H), 2.83 – 2.71 (m, *J* = 15.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H),

1.26 (t, *J* = 7.1 Hz, 3H), 1.06 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.55, 168.59, 136.40, 134.94, 133.20, 132.47, 128.70, 126.68, 126.20, 124.40, 81.81, 65.60, 61.90, 60.96, 43.10, 33.99, 28.54, 14.31, 14.25, 13.79 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2932, 1728, 1447, 1369, 1225, 1147, 1027 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{22}H_{28}NO_6$: 402.19111, found: 402.19064.



Dibenzyl 2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

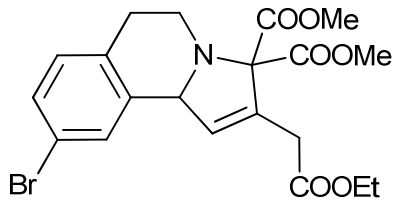
4c: 84% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.38 – 7.31 (m, 5H), 7.31 – 7.24 (m, 3H), 7.20 – 7.13 (m, 2H), 7.14 – 7.06 (m, 4H), 6.56 (d, *J* = 1.4 Hz, 1H), 5.28 – 5.24 (m, 1H), 5.21 (s, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.08 (qd, *J* = 7.1, 3.5 Hz, 2H), 3.39 (ddd, *J* = 8.7, 5.3, 3.5 Hz, 2H), 3.34 (d, *J* = 8.7 Hz, 2H), 2.89 – 2.76 (m, 1H), 2.65 (dt, *J* = 16.1, 4.4 Hz, 1H), 1.22 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.54, 137.17, 135.49, 135.03, 134.92, 133.01, 132.97, 128.99, 128.66, 128.59, 128.38, 128.34, 128.23, 128.18, 126.47, 126.03, 124.31, 81.81, 67.47, 67.39, 65.62, 60.88, 42.56, 33.91, 28.44, 14.25 ppm; FT-IR: $\tilde{\nu}$ = 2979, 1731, 1454, 1368, 1139, 1026 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{32}H_{32}NO_6$: 526.22241, found: 526.22278.



Dimethyl 7-bromo-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

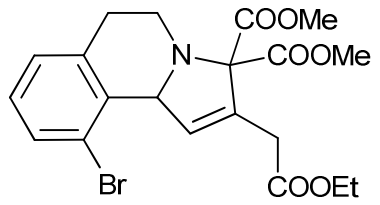
4d: 51% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.5 Hz, 1H), 7.11 – 6.99 (m, 2H), 6.47 (d, *J* = 1.2 Hz, 1H), 5.13 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.82 (dd, *J* = 7.8, 2.3 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.55 (ddd, *J* = 12.8, 6.7, 2.8 Hz, 1H), 3.37 – 3.28 (m, 3H), 2.81 (dd, *J* = 9.9, 6.9 Hz, 1H), 2.74 (d, *J* = 3.4 Hz, 1H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.50, 169.05, 139.35, 134.34, 133.60, 132.87, 130.57, 127.26, 125.69, 123.62, 81.05, 65.64, 61.02, 52.86, 52.63, 42.21, 33.93, 29.31, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2953, 1731, 1562, 1437, 1240, 1143, 1030 cm^{-1}; HRMS: calcd. for $[M+H]^+$

$C_{20}H_{23}{}^{79}BrNO_6$: 452.07033, found: 452.06829; calcd. for $[M+H]^+$ $C_{220}H_{23}{}^{81}BrNO_6$: 454.06828, found: 454.06794.



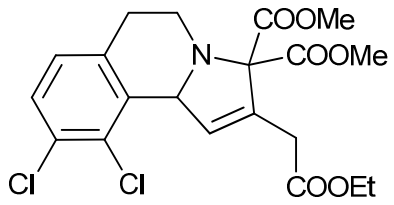
Dimethyl 9-bromo-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4e: 69% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28 – 7.24 (m, 1H), 7.24 – 7.21 (m, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.46 (d, *J* = 1.4 Hz, 1H), 5.13 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.82 (dd, *J* = 6.6, 3.0 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 3.47 – 3.28 (m, 3H), 2.86 – 2.73 (m, 1H), 2.63 (dt, *J* = 16.3, 4.3 Hz, 1H), 1.26 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.44, 169.12, 139.17, 133.74, 133.60, 132.49, 130.69, 129.51, 127.50, 119.61, 81.37, 65.13, 61.06, 52.77, 52.65, 42.14, 33.94, 27.69, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2986, 1731, 1568, 1234, 1173, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{23}{}^{79}BrNO_6$: 452.07033, found: 452.06919; calcd. for $[M+H]^+$ $C_{220}H_{23}{}^{81}BrNO_6$: 454.06828, found: 454.06799.



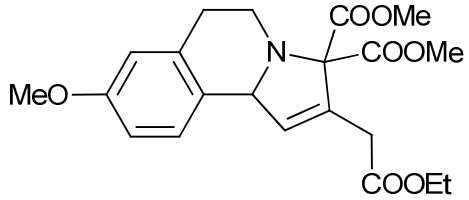
Dimethyl 10-bromo-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4f: 62% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.3 Hz, 1H), 7.08 – 6.94 (m, 2H), 6.88 (s, 1H), 5.45 (s, 1H), 4.24 – 4.04 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.60 – 3.45 (m, 1H), 3.39 – 3.21 (m, 2H), 3.17 (ddd, *J* = 14.7, 11.4, 3.7 Hz, 1H), 2.72 (ddd, *J* = 16.5, 11.5, 5.4 Hz, 1H), 2.51 (d, *J* = 16.5 Hz, 1H), 1.27 ppm (dt, *J* = 14.3, 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.53, 169.80, 169.72, 137.82, 134.91, 133.64, 132.29, 131.28, 129.07, 127.67, 122.08, 82.15, 66.65, 60.99, 52.96, 52.79, 41.67, 33.96, 27.52, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2953, 1731, 1558, 1434, 1226, 1138, 1027 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{23}{}^{79}BrNO_6$: 452.07033, found: 452.06934; calcd. for $[M+H]^+$ $C_{220}H_{23}{}^{81}BrNO_6$: 454.06828, found: 454.06767.



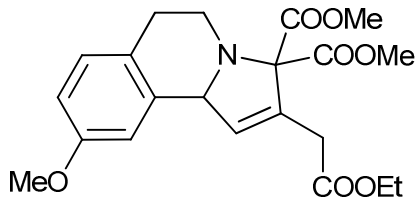
Dimethyl 9,10-dichloro-2-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4g: 52% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.27 – 7.24 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 1.1 Hz, 1H), 5.49 (s, 1H), 4.16 – 4.09 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.56 (ddd, *J* = 14.2, 5.5, 2.2 Hz, 1H), 3.34 – 3.24 (m, 2H), 3.21 – 3.12 (m, 1H), 2.70 (ddd, *J* = 17.0, 11.4, 5.7 Hz, 1H), 2.53 (d, *J* = 17.0 Hz, 1H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.42, 169.62, 169.44, 135.70, 135.64, 132.89, 132.84, 131.05, 130.31, 128.96, 128.12, 81.87, 65.63, 61.05, 53.02, 52.85, 41.40, 33.95, 27.10, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1731, 1432, 1225, 1138, 1028 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{20}H_{22}Cl_2NO_6$: 442.08187, found: 442.08248.



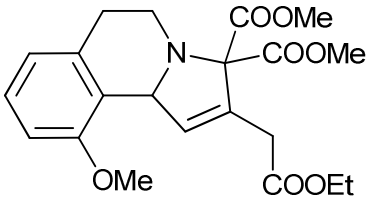
Dimethyl 2-(2-ethoxy-2-oxoethyl)-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4h: 59% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.48 (s, 1H), 5.13 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H), 3.41 – 3.33 (m, 2H), 3.32 (d, *J* = 1.2 Hz, 2H), 2.94 – 2.79 (m, 1H), 2.67 (dd, *J* = 11.9, 4.2 Hz, 1H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.58, 169.22, 158.15, 136.09, 133.40, 132.80, 129.42, 125.42, 114.01, 112.04, 81.57, 65.14, 60.95, 55.39, 52.70, 52.56, 42.47, 33.98, 28.62, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2930, 2840, 1761, 1719, 1609, 1434, 1306, 1018 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_7$: 404.17038, found: 404.16921.



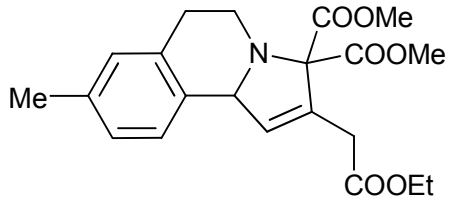
Dimethyl 2-(2-ethoxy-2-oxoethyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4i: 79% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.3 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 6.48 (s, 1H), 5.16 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.74 (m, 6H), 3.65 (s, 3H), 3.43 (ddd, *J* = 12.4, 6.2, 3.6 Hz, 1H), 3.38 – 3.27 (m, 3H), 2.86 – 2.73 (m, 1H), 2.68 – 2.52 (m, 1H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.56, 169.31, 157.90, 137.91, 133.15, 133.05, 129.96, 126.66, 112.21, 109.96, 81.45, 65.67, 60.95, 55.43, 52.68, 52.53, 42.54, 33.95, 27.28, 14.31 ppm; FT-IR: $\tilde{\nu}$ = 3004, 2954, 2928, 1726, 1606, 1500, 1350, 1064 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_7$: 404.17038, found: 404.16866.



Dimethyl 2-(2-ethoxy-2-oxoethyl)-10-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

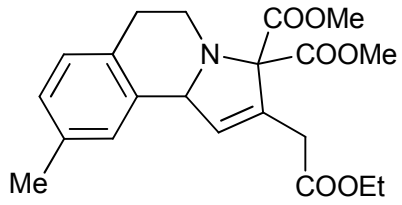
4j: 84% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.15 – 7.03 (m, *J* = 7.9 Hz, 1H), 6.75 – 6.59 (m, 3H), 5.31 (s, 1H), 4.12 (dd, *J* = 14.1, 7.0 Hz, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.54 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.32 – 3.23 (m, 2H), 3.25 – 3.11 (m, 1H), 2.79 – 2.63 (m, 1H), 2.58 – 2.45 (m, 1H), 1.25 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.80, 170.04, 156.24, 136.06, 134.91, 130.95, 126.97, 124.82, 121.88, 107.74, 81.44, 63.48, 60.84, 55.21, 52.77, 52.56, 41.67, 34.04, 27.32, 14.30 ppm; FT-IR: $\tilde{\nu}$ = 2953, 2838, 1730, 1581, 1468, 1248, 1088 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_7$: 404.17038, found: 404.16929.



Dimethyl 2-(2-ethoxy-2-oxoethyl)-8-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

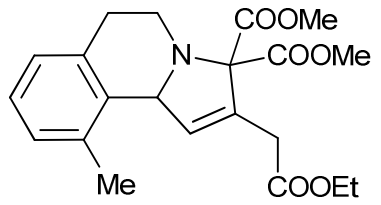
4k: 67% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.02 – 6.94 (m, 2H), 6.94 – 6.88 (m, 1H), 6.48 (s, 1H), 5.15 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.45 – 3.33 (m, 2H), 3.33 – 3.26 (m, 2H), 2.89 – 2.77 (m, 1H), 2.64 (dt, *J* = 16.2, 4.2 Hz, 1H), 2.28 (s, 3H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.58, 169.26, 135.89,

134.54, 134.06, 133.41, 132.77, 129.62, 126.81, 124.30, 81.54, 65.40, 60.92, 52.65, 52.51, 42.48, 33.98, 28.21, 21.17, 14.32 ppm; FT-IR: $\tilde{\nu}$ = 2981, 2953, 1731, 1550, 1433, 1235, 1140, 1030 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_6$: 388.17546, found: 388.17670.



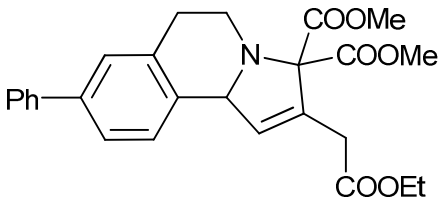
Dimethyl 2-(2-ethoxy-2-oxoethyl)-9-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4l: 72% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.03 – 6.85 (m, 3H), 6.50 (s, 1H), 5.16 (s, 1H), 4.19 – 4.04 (m, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.46 – 3.38 (m, 1H), 3.36 – 3.23 (m, 3H), 2.83 – 2.79 (m, 1H), 2.65 – 2.60 (m, 1H), 2.30 (s, 3H), 1.26 ppm (td, *J* = 7.1, 2.7 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.48, 169.26, 135.40, 133.24, 132.71, 131.37, 128.83, 127.10, 124.94, 122.02, 81.37, 65.45, 60.82, 52.55, 52.41, 42.38, 33.84, 27.61, 21.13, 14.19 ppm; FT-IR: $\tilde{\nu}$ = 2953, 2918, 1731, 1433, 1217, 1150, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_6$: 388.17546, found: 388.17688.



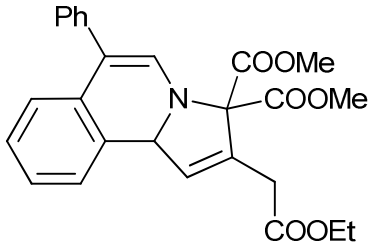
Dimethyl 2-(2-ethoxy-2-oxoethyl)-10-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4m: 80% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.50 (s, 1H), 5.45 (s, 1H), 4.18 – 4.09 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.50 (ddd, *J* = 13.6, 5.4, 2.6 Hz, 1H), 3.34 – 3.27 (m, 2H), 3.17 (ddd, *J* = 13.6, 11.1, 3.8 Hz, 1H), 2.79 – 2.70 (m, 1H), 2.62 – 2.51 (m, *J* = 18.3 Hz, 1H), 2.34 (s, 3H), 1.25 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.63, 169.76, 135.05, 134.47, 134.23, 133.35, 132.28, 128.75, 127.53, 126.23, 81.90, 65.36, 60.92, 52.85, 52.68, 41.96, 33.88, 28.18, 20.17, 14.31 ppm; FT-IR: $\tilde{\nu}$ = 2980, 2953, 1730, 1433, 1224, 1133, 1031 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{21}H_{26}NO_6$: 388.17546, found: 388.17725.



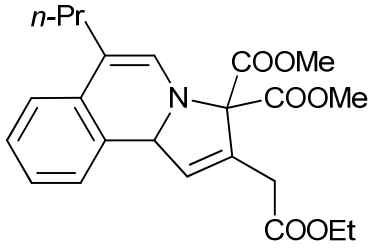
Dimethyl 2-(2-ethoxy-2-oxoethyl)-8-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4n: 76% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.58 – 7.53 (m, 2H), 7.45 – 7.37 (m, 3H), 7.37 – 7.29 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 1.4 Hz, 1H), 5.23 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 3.52 – 3.44 (m, 1H), 3.45 – 3.36 (m, 1H), 3.36 – 3.30 (m, 2H), 2.95 (ddd, *J* = 15.9, 9.2, 6.8 Hz, 1H), 2.76 (dt, *J* = 15.9, 3.9 Hz, 1H), 1.27 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.58, 169.34, 141.14, 139.45, 136.11, 135.11, 133.19, 133.06, 128.82, 127.83, 127.24, 127.15, 124.94, 124.90, 81.47, 65.44, 60.98, 52.73, 52.57, 42.41, 33.97, 28.37, 14.33 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1731, 1433, 1234, 1148, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{28}NO_6$: 450.19111, found: 450.19098.



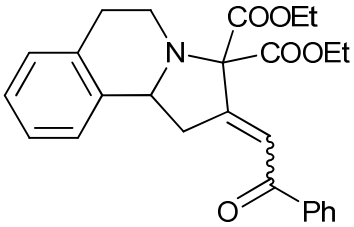
Dimethyl 2-(2-ethoxy-2-oxoethyl)-6-phenylpyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4o: 60% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 7.20 – 7.04 (m, 4H), 6.81 – 6.73 (m, 2H), 5.58 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.47 (s, 2H), 1.29 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.42, 168.39, 167.90, 138.83, 133.30, 132.50, 130.72, 129.83, 129.27, 128.63, 128.59, 127.03, 126.41, 126.38, 123.02, 122.85, 118.08, 80.41, 65.62, 61.16, 53.24, 53.15, 33.66, 14.34 ppm; FT-IR: $\tilde{\nu}$ = 2954, 1732, 1607, 1443, 1244, 1178, 1029 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{26}NO_6$: 448.17546, found: 448.17365.



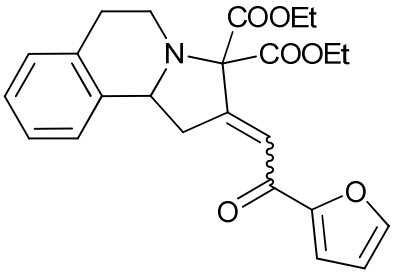
Dimethyl 2-(2-ethoxy-2-oxoethyl)-6-propylpyrrolo[2,1-*a*]isoquinoline-3,3(10b*H*)-dicarboxylate

4p: 87% yield; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.21 – 7.10 (m, 3H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 0.5 Hz, 1H), 6.40 (s, 1H), 5.45 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.60 (s, 3H), 3.44 – 3.34 (m, 2H), 2.56 (ddd, *J* = 13.7, 8.2, 5.4 Hz, 1H), 2.26 – 2.18 (m, 1H), 1.67 – 1.58 (m, 1H), 1.56 – 1.44 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 170.43, 168.61, 168.20, 133.25, 132.44, 131.08, 130.42, 127.76, 126.97, 126.00, 122.76, 121.16, 115.22, 80.79, 65.62, 61.08, 53.01, 52.92, 33.70, 32.18, 22.52, 14.33, 14.06 ppm; FT-IR: $\tilde{\nu}$ = 2956, 1735, 1686, 1441, 1244, 1173, 1129, 1031 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{23}H_{28}NO_6$: 414.19111, found: 414.19033.



Diethyl 2-(2-oxo-2-phenylethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate

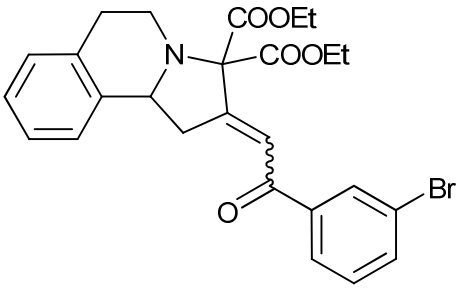
6a: 91% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.92 (m, 2H), 7.61 – 7.53 (m, 1H), 7.51 – 7.44 (m, 2H), 7.45 – 7.39 (m, 1H), 7.21 – 7.10 (m, 4H), 4.39 – 4.22 (m, 4H), 4.19 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.96 (ddd, *J* = 18.2, 6.2, 1.9 Hz, 1H), 3.59 (dd, *J* = 11.1, 5.9 Hz, 1H), 3.30 – 3.18 (m, 1H), 2.98 – 2.79 (m, 3H), 1.35 (t, *J* = 6.1 Hz, 3H), 1.31 ppm (t, *J* = 6.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.56, 168.03, 167.64, 156.95, 138.73, 137.98, 134.29, 132.98, 128.92, 128.78, 128.40, 126.65, 126.06, 125.55, 120.33, 79.07, 62.28, 61.95, 60.32, 44.54, 37.80, 30.19, 14.62, 14.25 ppm; FT-IR: $\tilde{\nu}$ = 2980, 1727, 1671, 1368, 1228, 1040 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{28}NO_5$: 434.19620, found: 434.19605.



Diethyl 2-(2-(furan-2-yl)-2-oxoethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate

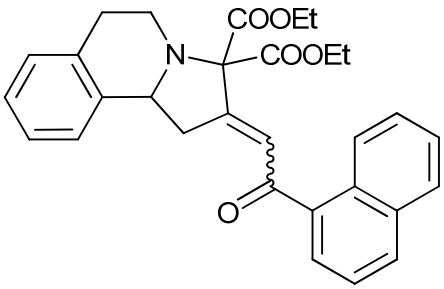
6b: 83% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 – 7.54 (m, 1H), 7.31 – 7.28 (m, 1H), 7.23 – 7.21 (m, 1H), 7.18 – 7.11 (m, 4H), 6.60 – 6.48 (m, 1H), 4.42 – 4.21 (m, 4H), 4.23 – 4.12 (m, 1H), 4.03 (ddd, *J* = 18.5, 6.3, 1.9 Hz, 1H), 3.57 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.32 – 3.16 (m, 1H), 2.97 – 2.76 (m, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.30 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C-

NMR (101 MHz, $CDCl_3$): δ = 178.52, 167.87, 167.44, 157.59, 154.24, 146.47, 137.97, 134.27, 128.91, 126.66, 126.09, 125.57, 119.36, 117.26, 112.58, 79.10, 62.28, 61.94, 60.34, 44.53, 37.89, 30.17, 14.60, 14.23 ppm; FT-IR: $\tilde{\nu}$ = 2980, 1727, 1667, 1621, 1466, 1232, 1040 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{24}H_{26}NO_6$: 424.17546, found: 424.17525.



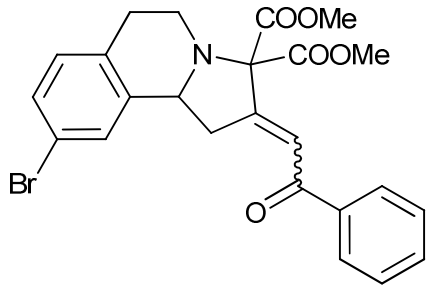
Diethyl 2-(2-(3-bromophenyl)-2-oxoethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate

6c: 83% yield; Ratio of isomer, 78:22; For major product: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 – 8.04 (m, 1H), 7.91 – 7.84 (m, 1H), 7.68 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.22 – 7.06 (m, 4H), 4.37 – 4.24 (m, 4H), 4.18 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.93 (ddd, *J* = 18.4, 6.3, 1.8 Hz, 1H), 3.59 (dd, *J* = 11.1, 6.3 Hz, 1H), 3.30 – 3.15 (m, 1H), 2.96 – 2.78 (m, 3H), 1.40 – 1.29 ppm (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 189.01, 167.91, 167.49, 158.26, 140.50, 137.87, 135.79, 134.28, 131.44, 130.38, 128.94, 126.89, 126.69, 126.08, 125.51, 123.12, 119.74, 79.10, 62.37, 62.03, 60.26, 44.51, 37.94, 30.18, 14.63, 14.26 ppm; FT-IR: $\tilde{\nu}$ = 2980, 1727, 1673, 1368, 1220, 1038 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{26}H_{27}{}^{79}BrNO_5$: 512.10671, found: 512.10677; calcd. for $[M+H]^+$ $C_{22}H_{21}{}^{81}BrNO_6$: 514.10467, found: 514.10462; For minor isomer, ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17 – 8.07 (m, 1H), 7.91 – 7.87 (m, 1H), 7.68 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.35 (dd, *J* = 10.4, 5.4 Hz, 1H), 7.20 – 7.11 (m, 4H), 7.09 – 7.05 (m, 1H), 4.31 – 4.24 (m, 3H), 4.18 – 4.12 (m, 1H), 4.06 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.77 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.33 (dd, *J* = 15.6, 5.4 Hz, 1H), 3.25 – 3.14 (m, 1H), 2.91 – 2.72 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.09 ppm (t, *J* = 7.1 Hz, 3H).



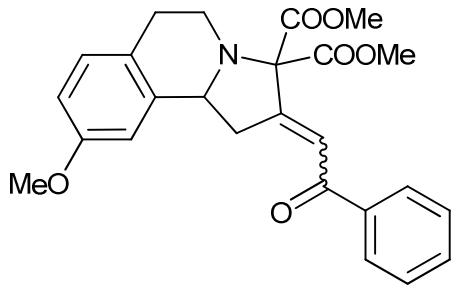
Diethyl 2-(2-(naphthalen-1-yl)-2-oxoethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarboxylate

6d: 79% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.26 – 7.23 (m, 1H), 7.21 – 7.10 (m, 4.9 Hz, 4H), 4.38 – 4.22 (m, 5H), 4.00 (dd, *J* = 18.3, 6.2 Hz, 1H), 3.62 (dd, *J* = 11.4, 6.2 Hz, 1H), 3.34 – 3.22 (m, 1H), 3.06 – 2.81 (m, 3H), 1.31 ppm (q, *J* = 7.2 Hz, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = ^{13}C NMR (101 MHz, $cdcl_3$) δ 194.17, 167.69, 167.39, 137.67, 134.25, 134.10, 132.65, 128.99, 128.70, 128.16, 127.85, 126.87, 126.66, 126.24, 125.88, 125.64, 124.80, 124.62, 79.13, 62.49, 62.18, 60.58, 44.74, 37.70, 30.13, 14,68, 14.28 ppm; FT-IR: $\tilde{\nu}$ = 2978, 2924, 1727, 1673, 1368, 1230, 1039 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{30}H_{30}NO_5$: 484.21185, found: 484.21150.



Dimethyl 9-bromo-2-(2-oxo-2-phenylethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylate

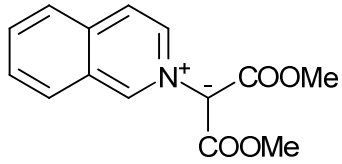
6e: 64% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.93 (m, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.46 (m, 2H), 7.40 (dd, *J* = 3.1, 1.9 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.92 (ddd, *J* = 11.7, 8.0, 2.7 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.54 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.14 (dd, *J* = 14.7, 8.0 Hz, 1H), 2.91 – 2.74 ppm (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.37, 168.45, 167.92, 155.98, 139.88, 138.53, 133.17, 133.12, 130.59, 129.78, 128.83, 128.52, 128.45, 120.56, 119.65, 78.99, 59.98, 53.43, 52.66, 44.25, 37.56, 29.61 ppm; FT-IR: $\tilde{\nu}$ = 2955, 1755, 1728, 1672, 1443, 1220, 1118, 1033 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{24}H_{23}{}^{79}BrNO_5$: 484.07541, found: 484.07507; calcd. for $[M+H]^+$ $C_{24}H_{23}{}^{81}BrNO_5$: 486.07337, found: 486.07296.



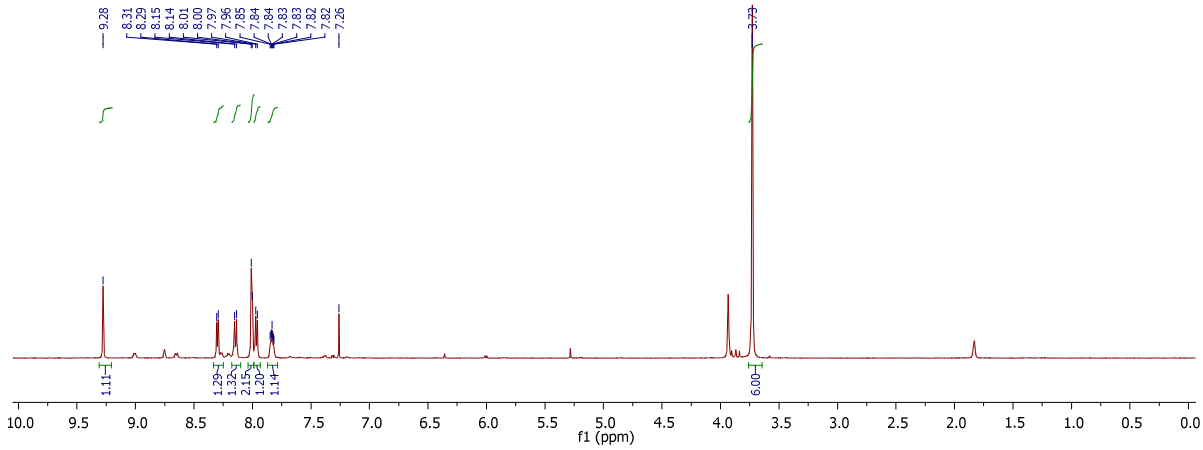
Dimethyl 9-methoxy-2-(2-oxo-2-phenylethylidene)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarboxylatedimethyl

6f: 78% yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 – 7.92 (m, 2H), 7.59 – 7.55 (m, 1H), 7.51 – 7.42 (m, 2H), 7.40 (dd, *J* = 3.2, 1.9 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 4.14 (dd, *J* = 9.7, 6.1 Hz, 1H), 3.94 (ddd, *J* = 8.1, 6.1, 3.0 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.53 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.22 – 3.11 (m, 1H), 2.94 – 2.82 (m, 2H), 2.81 – 2.74 ppm (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.52, 168.64, 168.02, 158.04, 156.57, 138.67, 138.61, 133.06, 129.88, 128.81, 128.43, 126.16, 120.46, 113.27, 110.21, 79.22, 60.48, 55.55, 53.38, 52.54, 44.69, 37.64, 29.27 ppm; FT-IR: $\tilde{\nu}$ = 2953, 1730, 1672, 1614, 1503, 1443, 1226, 1040 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_{25}H_{26}NO_6$: 436.17546, found: 436.17547.

Spectra


N+
COOMe
COOMe

1a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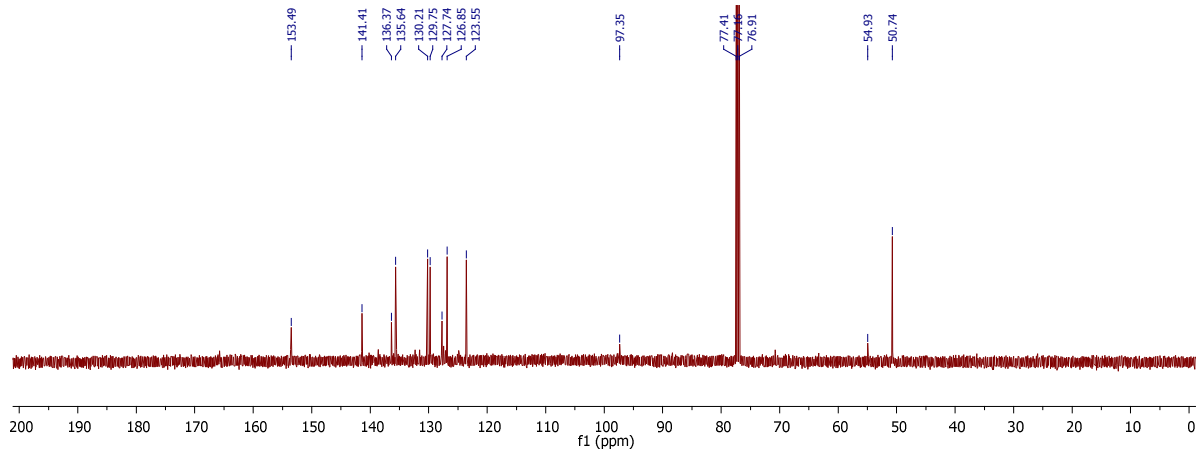
8.15
8.14
8.01
8.00
7.97
7.96
7.85
7.84
7.84
7.83
7.83
7.82
7.82
7.26
3.73
1.11
1.29
1.32
2.15
1.20
1.14
6.00
f1 (ppm)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141.41
136.37
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126.85
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97.35
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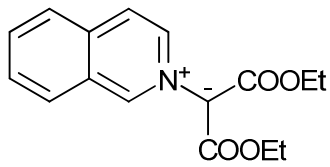
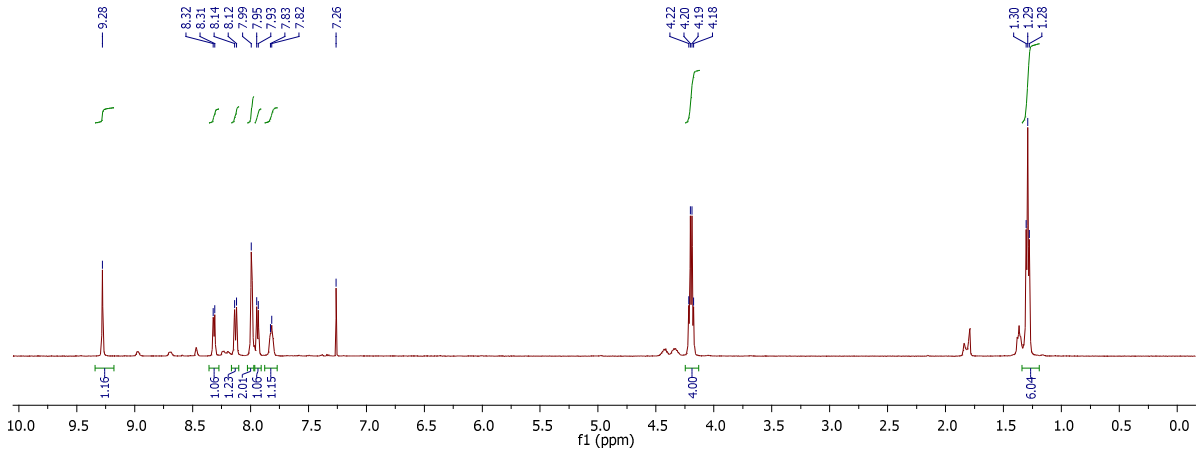
77.16
76.91
54.93
50.74
f1 (ppm)


N+
COOEt
COOEt

1b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8.32
8.31
8.14
8.12
7.99
7.95
7.93
7.83
7.82
7.26
4.22
4.20
4.19
4.18
1.30
1.29
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1.16
1.06
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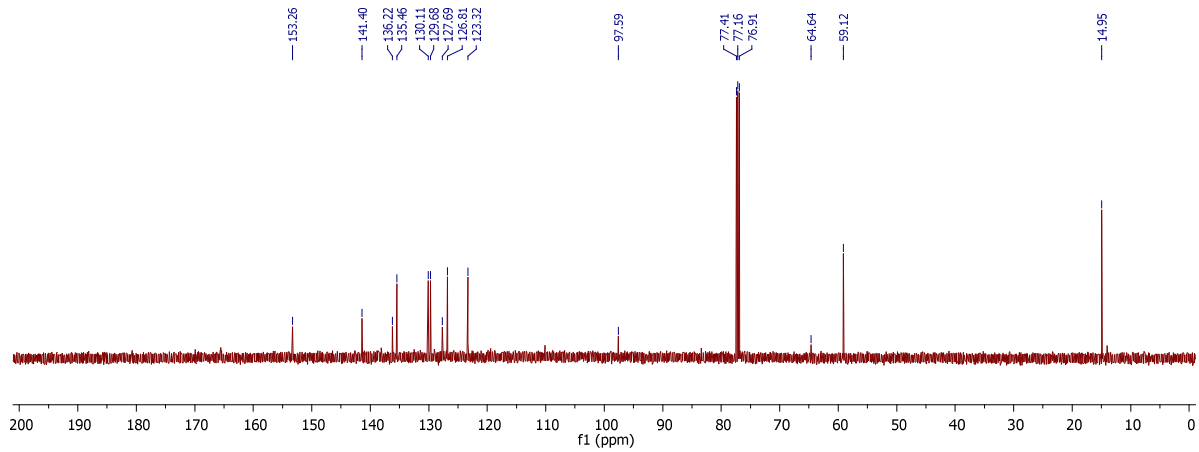
2.01
1.06
1.15
4.00
6.04
f1 (ppm)


153.26
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97.59
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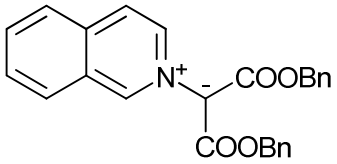
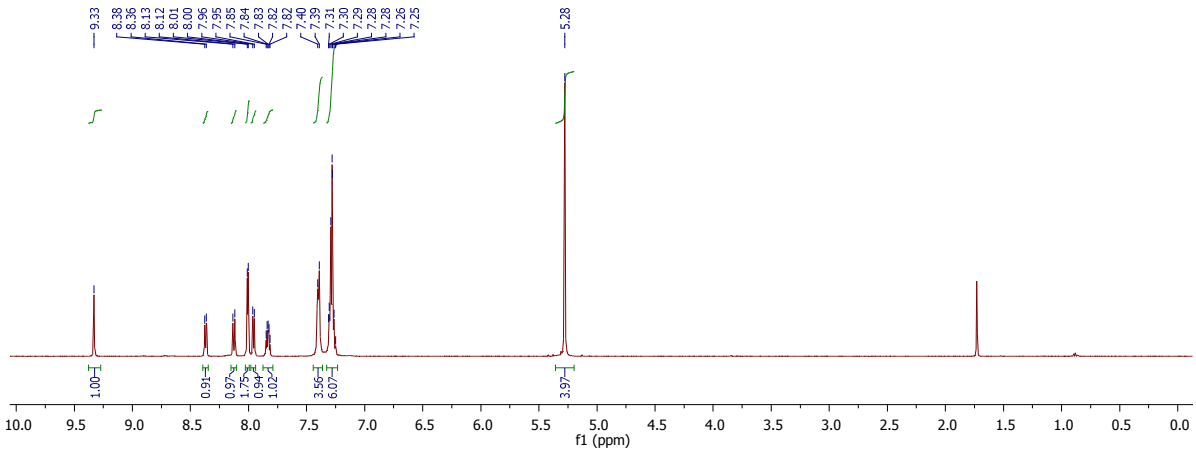
77.16
76.91
64.64
59.12
14.95
f1 (ppm)


N+
COOBn
COOBn

1c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8.13
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8.01
8.00
7.96
7.95
7.85
7.84
7.83
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7.40
7.39
7.31
7.30
7.29
7.28
7.28
7.26
7.25
5.28
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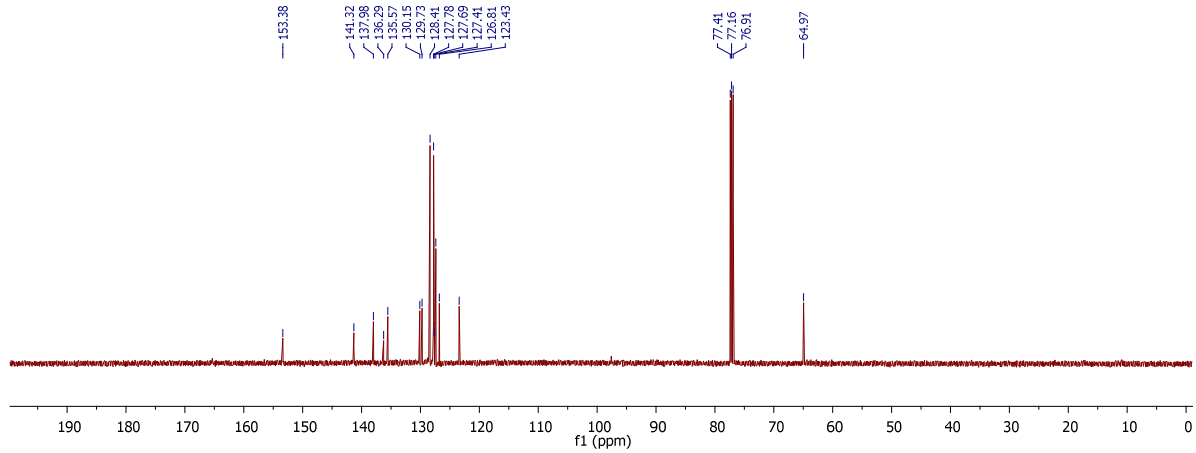
0.97
1.75
0.94
1.02
3.56
6.07
3.97
f1 (ppm)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126.81
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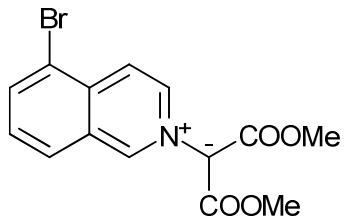
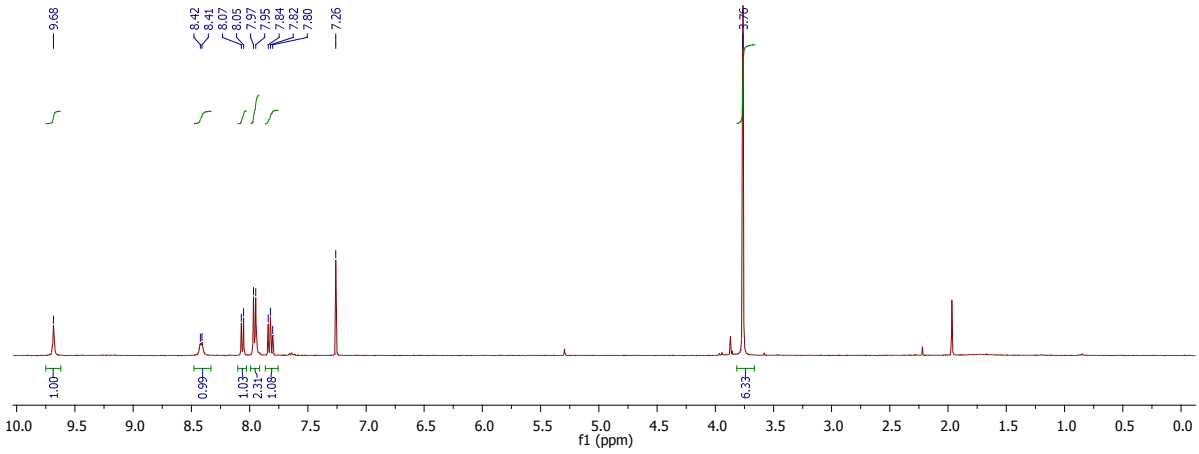
77.41
77.16
76.91
64.97
f1 (ppm)


Br
N+
-
COOMe
COOMe

1d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7.95
7.84
7.82
7.80
7.26
3.76
1.00
0.99
1.03
2.31
1.08
6.33
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
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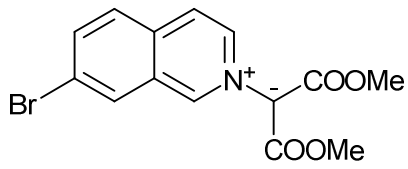
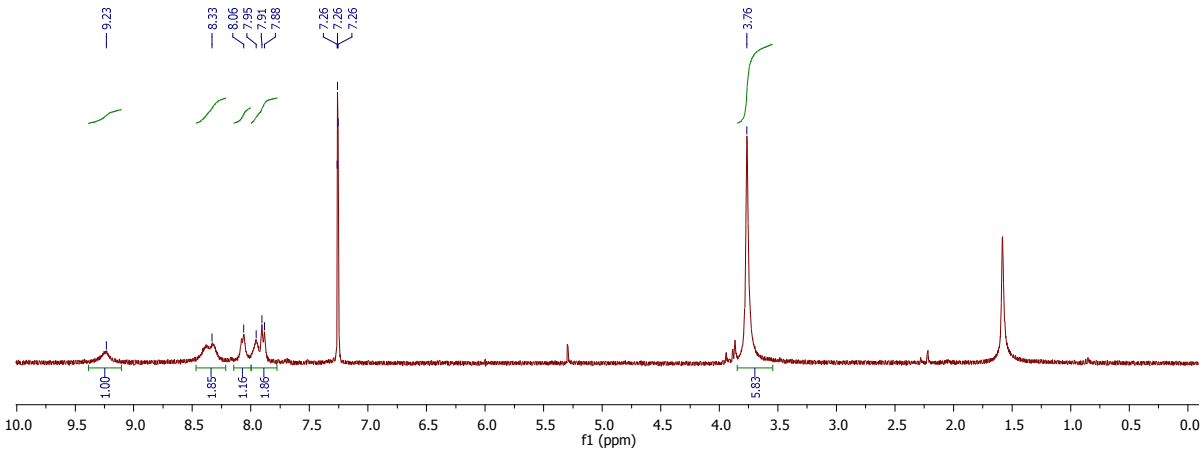
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Br
N+
-
COOMe
COOMe

1e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7.26
7.26
7.26
3.76
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1.85
1.16
1.86
5.83
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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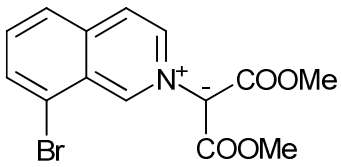
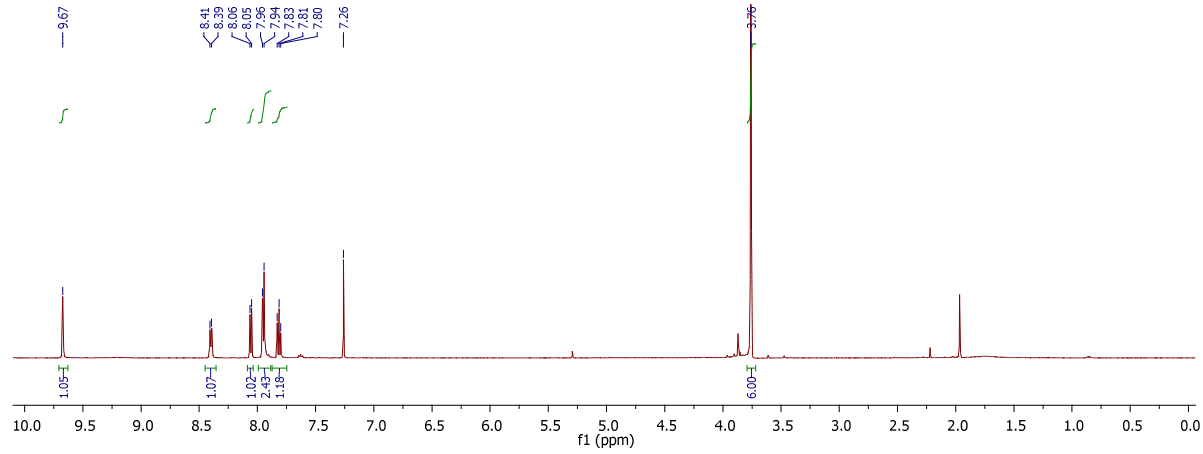
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


N+
-
COOMe
COOMe
Br

1f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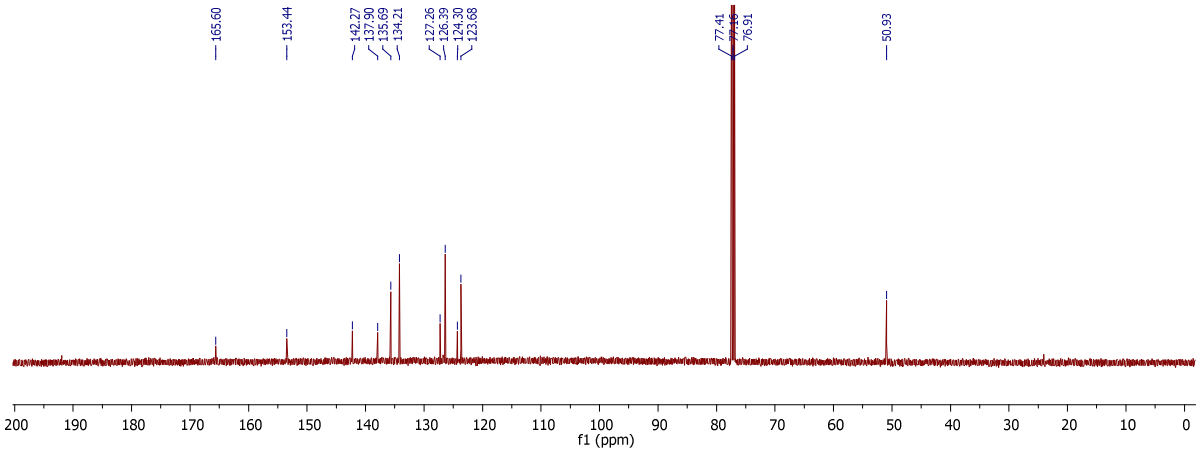
1.02
2.43
1.18
6.00
f1 (ppm)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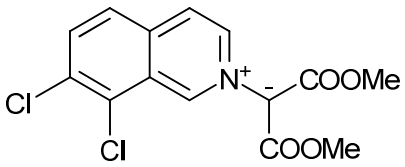
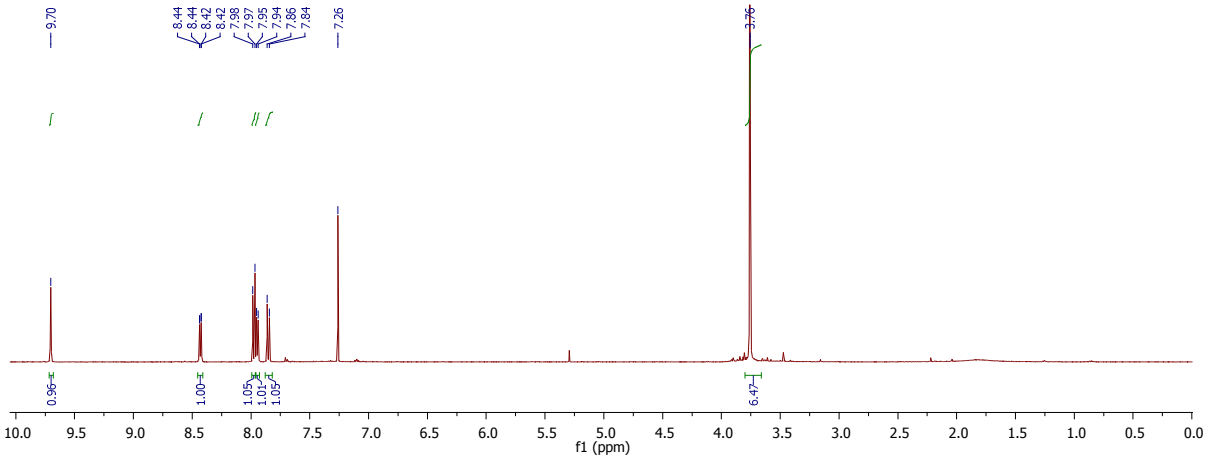
123.68
77.41
77.16
76.91
50.93
f1 (ppm)


Cl
Cl
N+
-
COOMe
COOMe

1g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0.96
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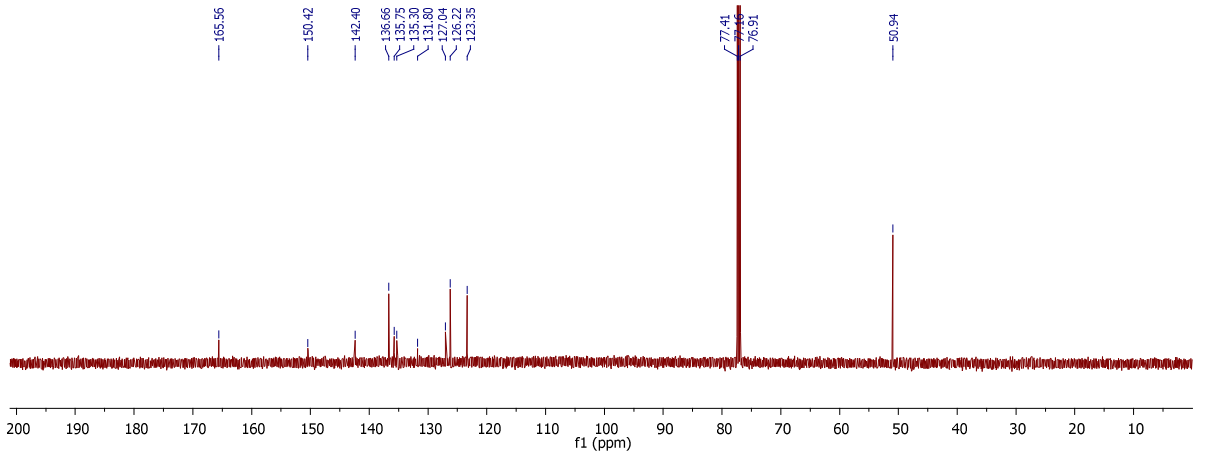
1.01
1.05
6.47
f1 (ppm)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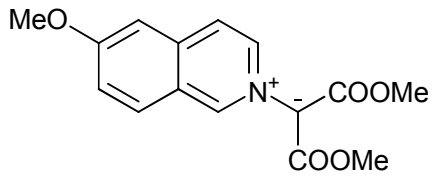
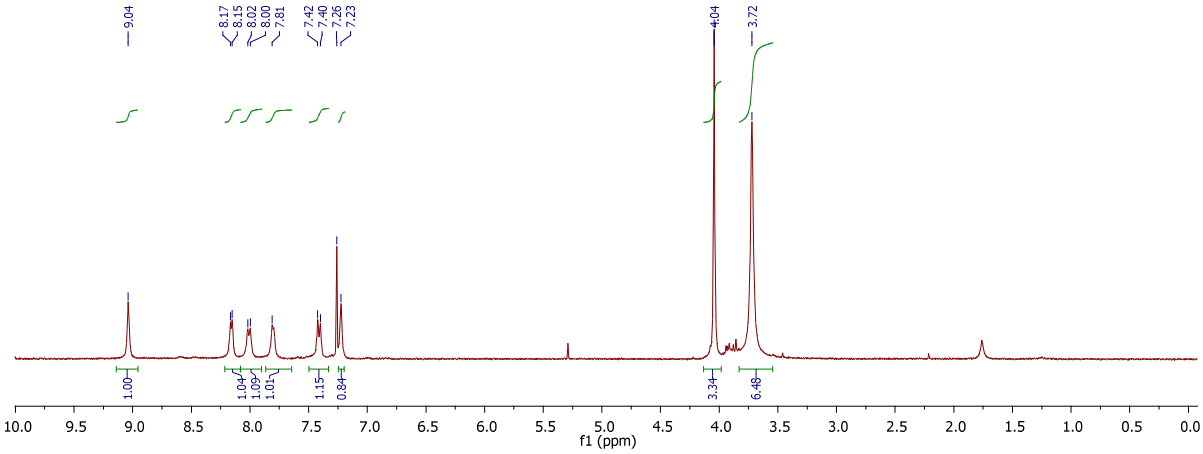
50.94
f1 (ppm)


MeO
N+
COOMe
COOMe

1h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1.01
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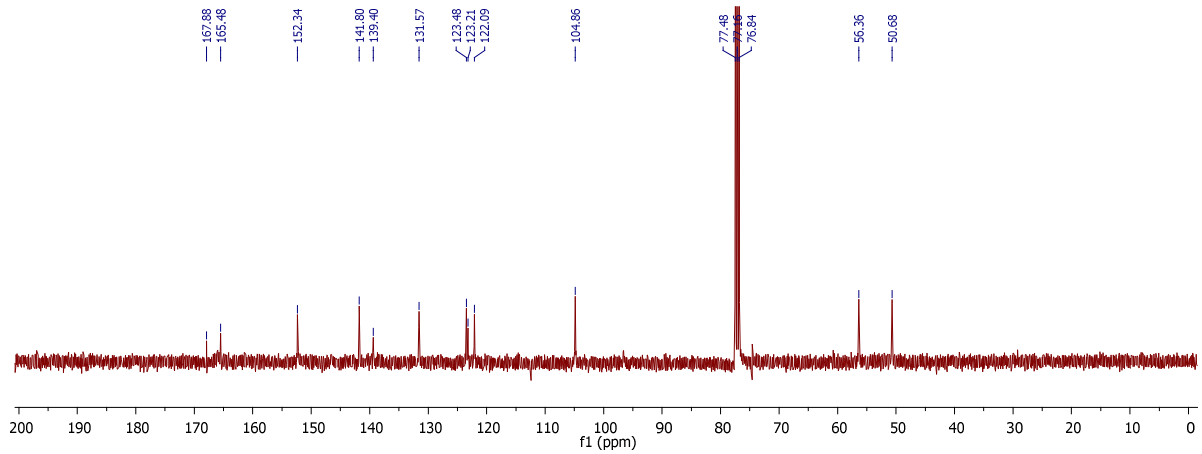
f1 (ppm)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122.09
104.86
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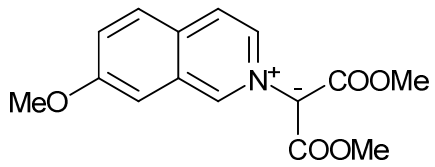
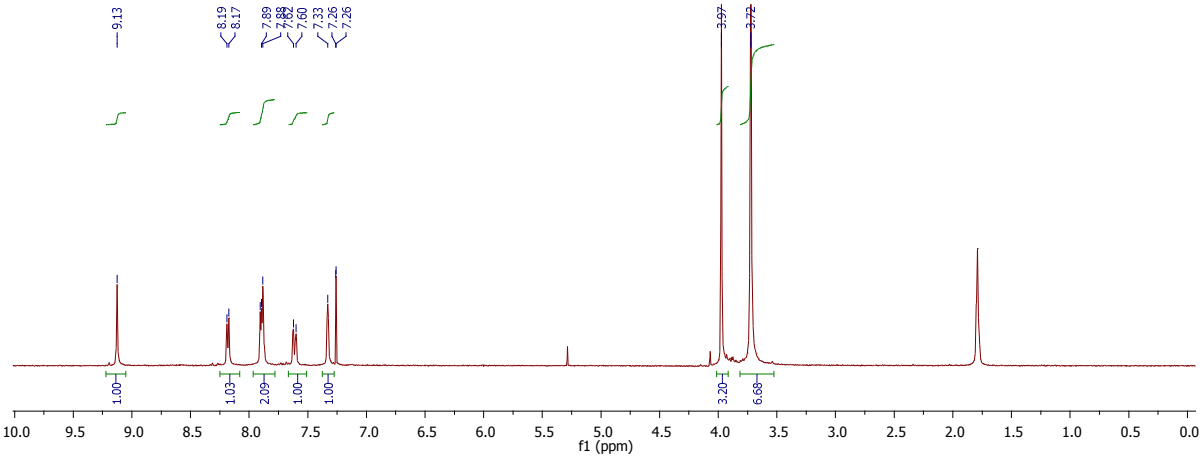
77.16
76.84
56.36
50.68
f1 (ppm)


MeO
N+
COOMe
COOMe

1i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1.00
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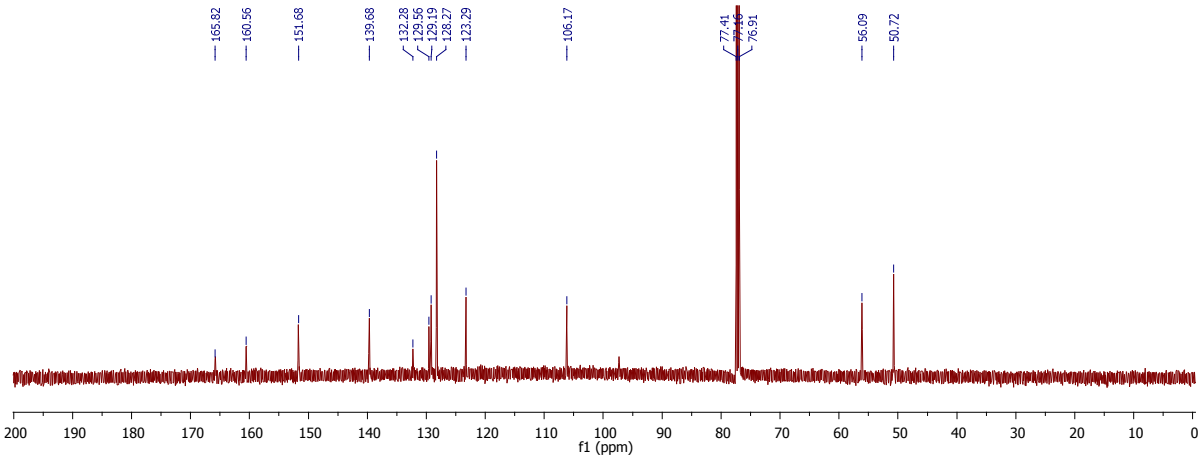
6.68
f1 (ppm)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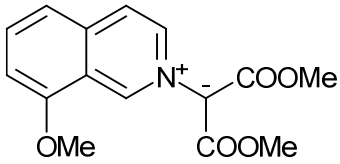
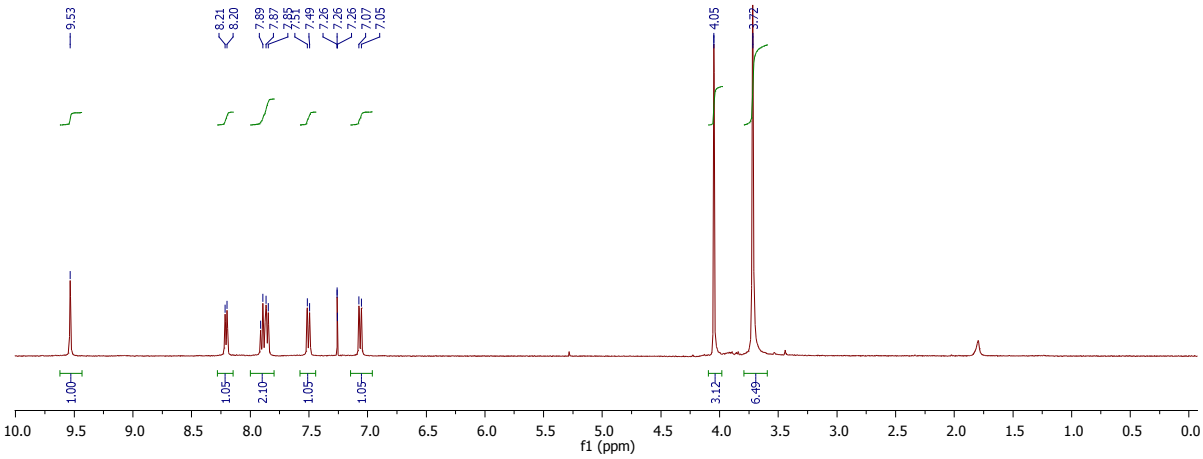
56.09
50.72
f1 (ppm)


N+
-
COOMe
OMe
COOMe

1j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1.05
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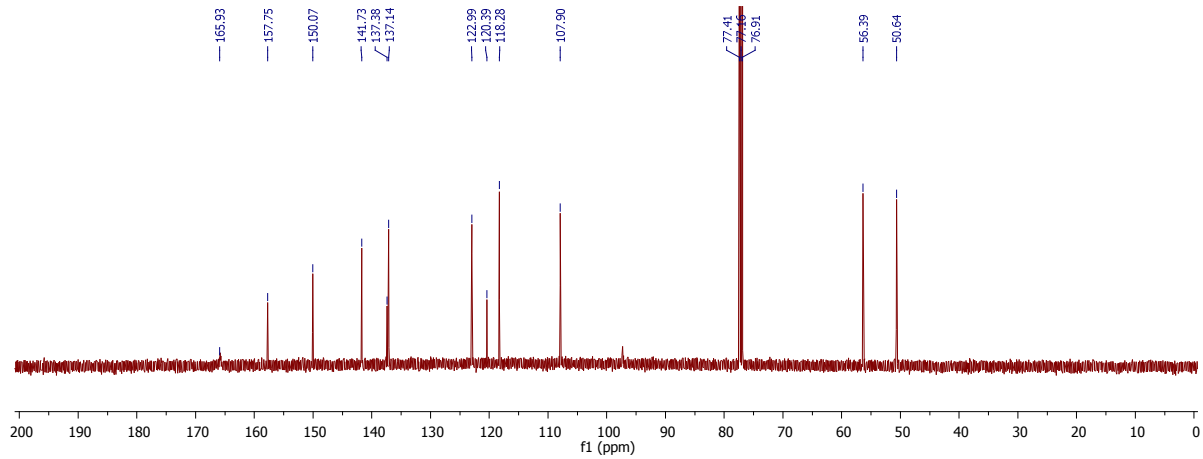
6.49
f1 (ppm)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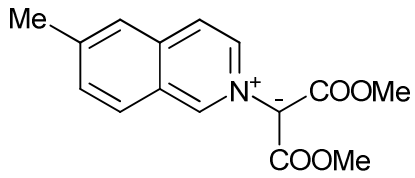
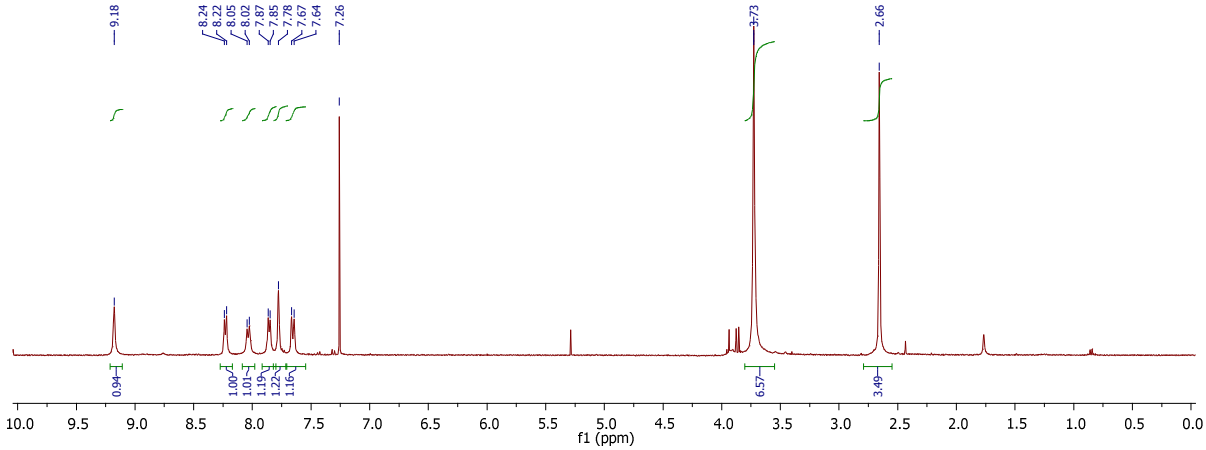
107.90
77.41
77.16
76.91
56.39
50.64
f1 (ppm)


Me
N+
COOMe
COOMe

1k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7.85
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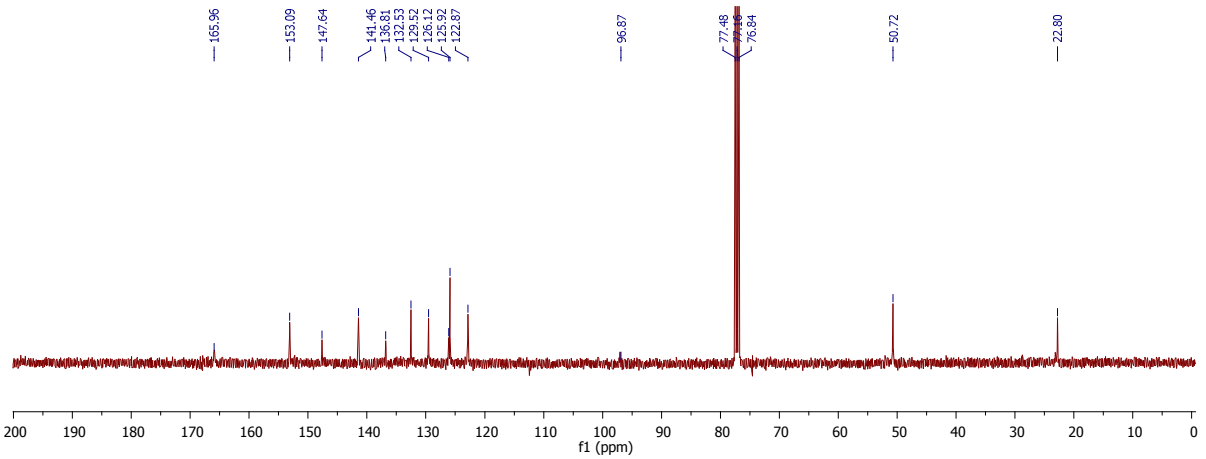
7.67
7.64
7.26
3.73
2.66
0.94
1.00
1.01
1.19
1.22
1.16
6.57
3.49
f1 (ppm)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147.64
141.46
136.81
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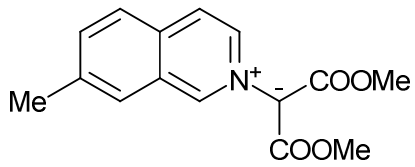
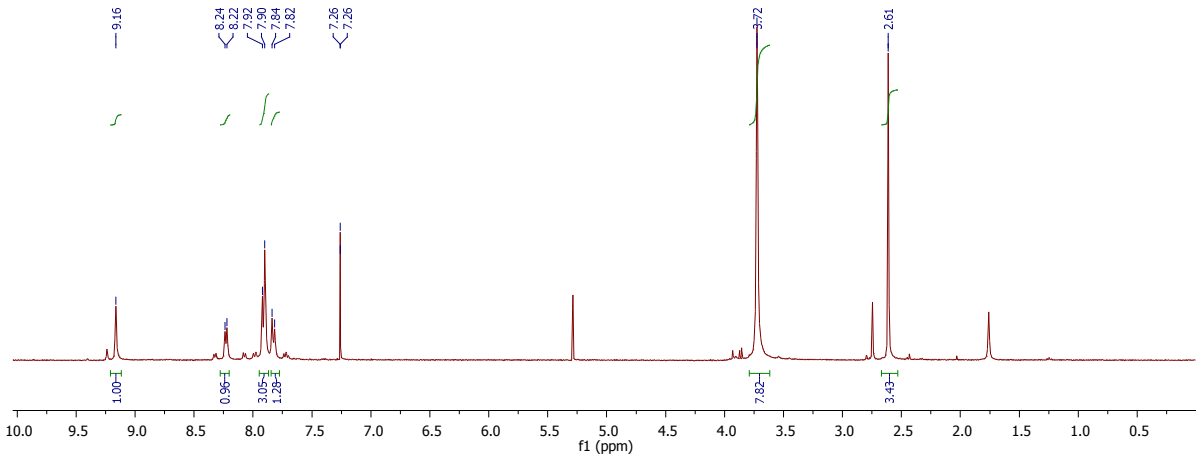
122.87
96.87
77.48
77.16
76.84
50.72
22.80
f1 (ppm)


Me
N+
COOMe
COOMe

1l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8.24
8.22
7.92
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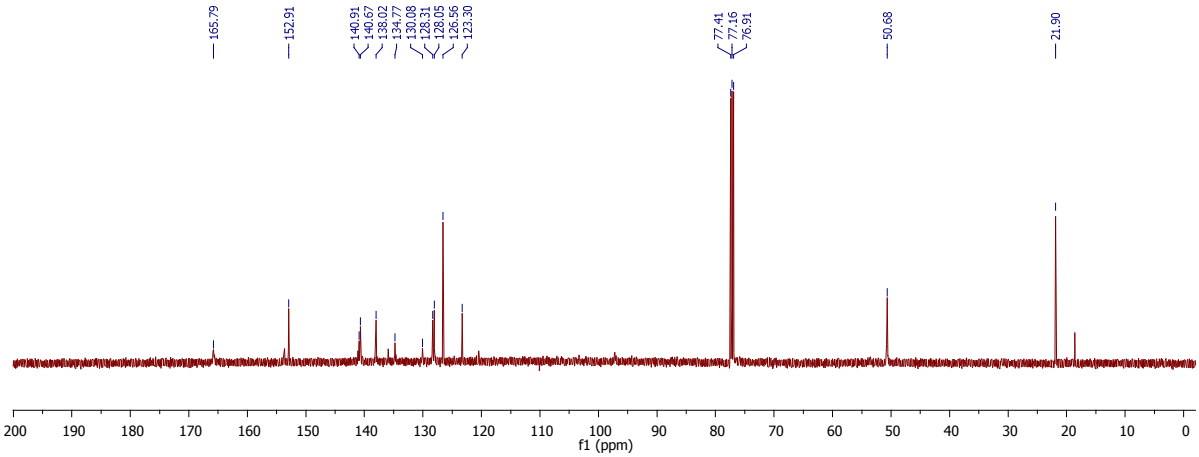
7.84
7.82
7.26
7.26
3.72
2.61
1.00
0.96
3.05
1.28
7.82
3.43
f1 (ppm)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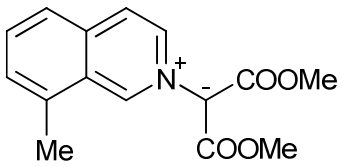
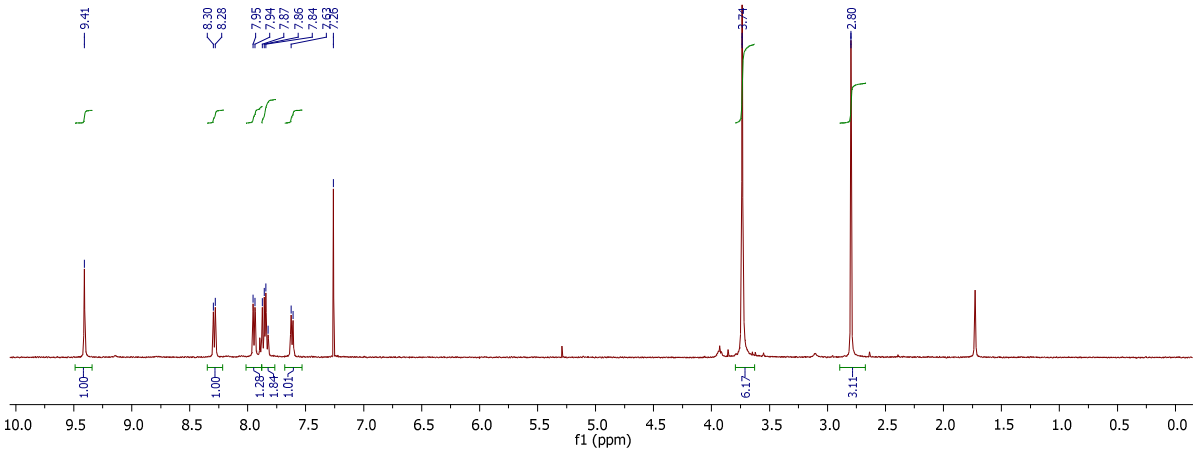
138.02
134.77
130.08
128.31
128.05
126.56
123.30
77.41
77.16
76.91
50.68
21.90
f1 (ppm)


N+
-
COOMe
COOMe
Me

1m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8.30
8.28
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7.94
7.87
7.86
7.84
7.63
7.28
3.74
2.80
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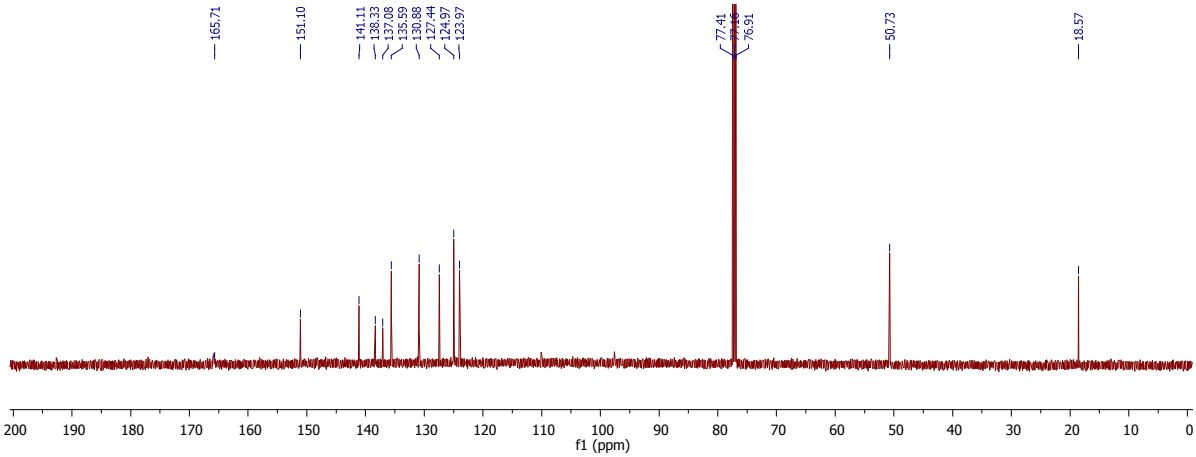
1.84
1.01
6.17
3.11
f1 (ppm)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141.11
138.33
137.08
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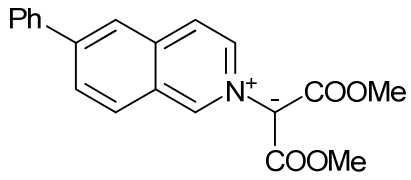
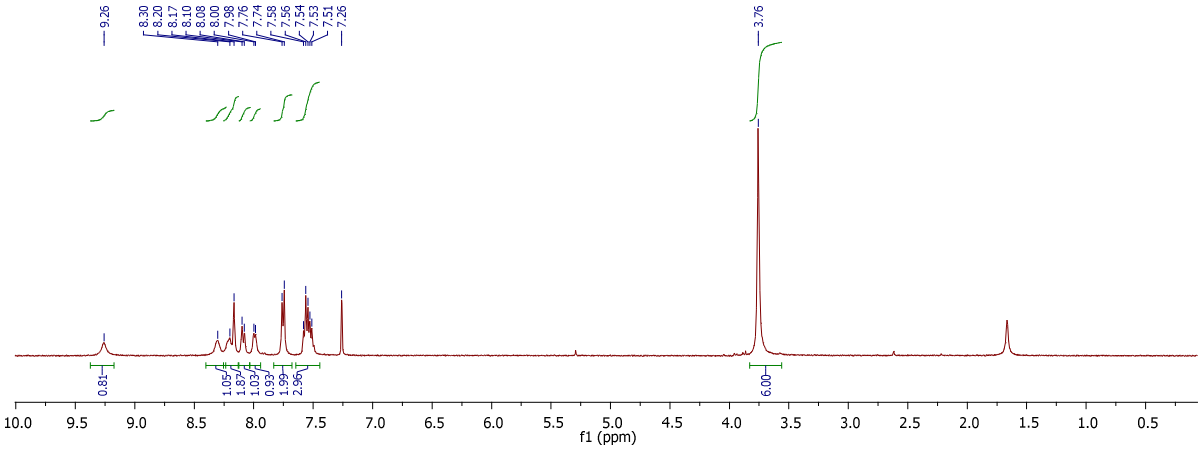
127.44
124.97
123.97
77.41
77.16
76.91
50.73
18.57
f1 (ppm)


Ph
N+
COOMe
COOMe

1n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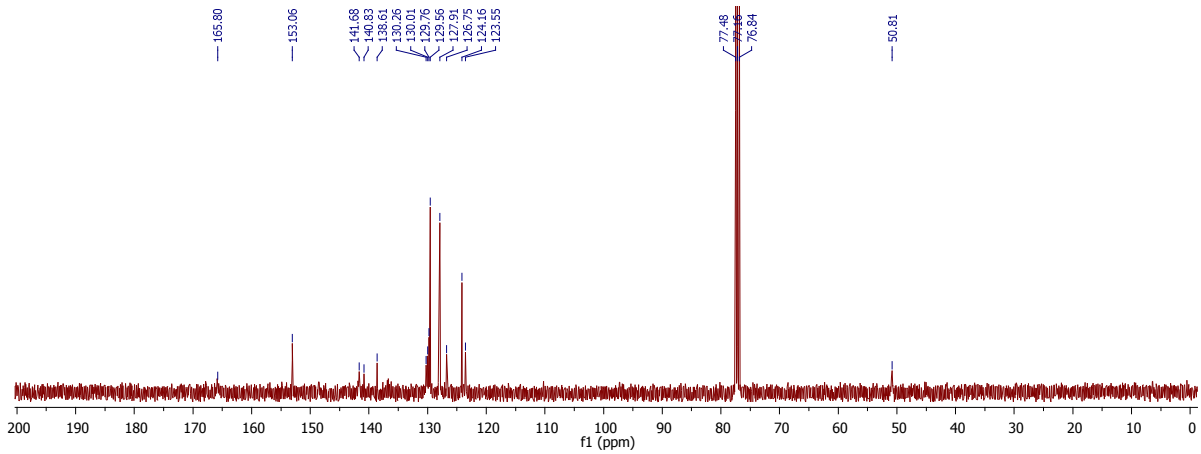
8.10
8.08
8.00
7.98
7.76
7.74
7.58
7.56
7.54
7.53
7.51
7.26
3.76
0.81
1.05
1.87
1.03
0.93
1.99
2.96
6.00
f1 (ppm)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140.83
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130.26
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129.76
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126.75
124.16
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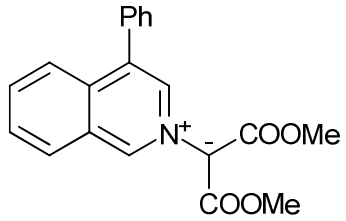
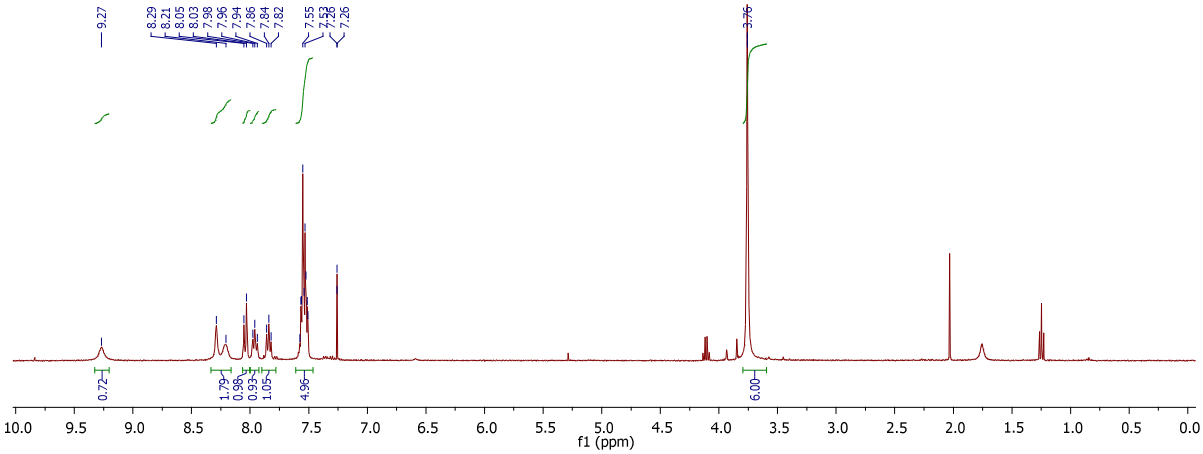
77.48
77.16
76.84
50.81
f1 (ppm)


Ph
N+
COOMe
COOMe

1o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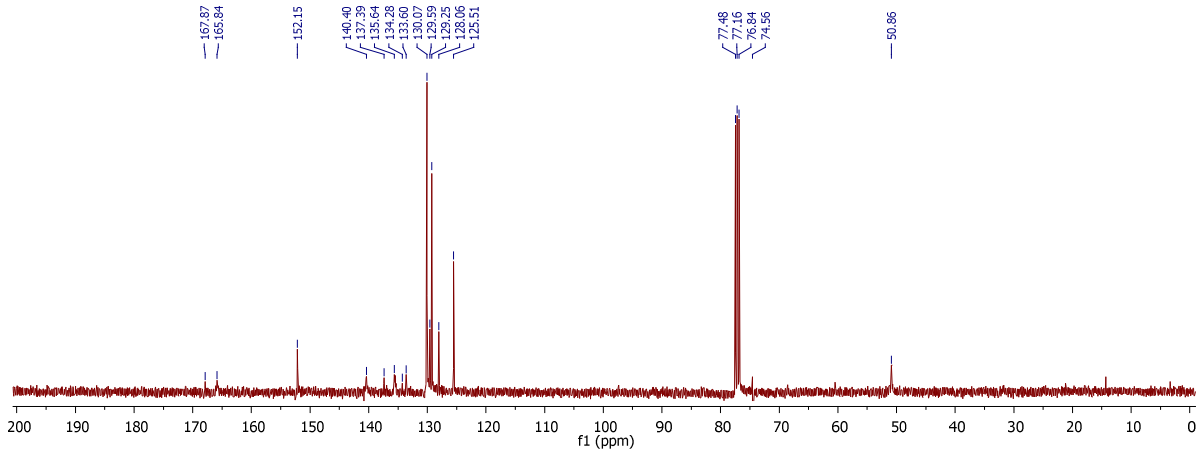
8.29
8.21
8.05
8.03
7.98
7.96
7.94
7.86
7.84
7.82
7.55
7.53
7.28
7.26
3.76
0.72
1.79
0.98
0.93
1.05
4.96
6.00
f1 (ppm)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152.15
140.40
137.39
135.64
134.28
133.60
130.07
129.59
129.25
128.06
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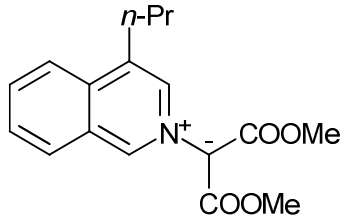
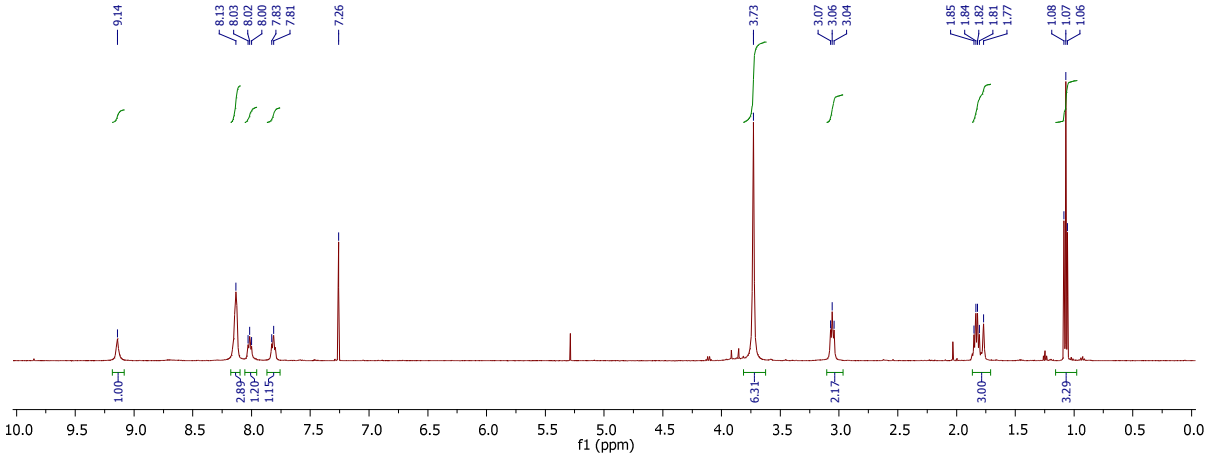
77.16
76.84
74.56
50.86
f1 (ppm)


n-Pr
N+
COOMe
COOMe

1p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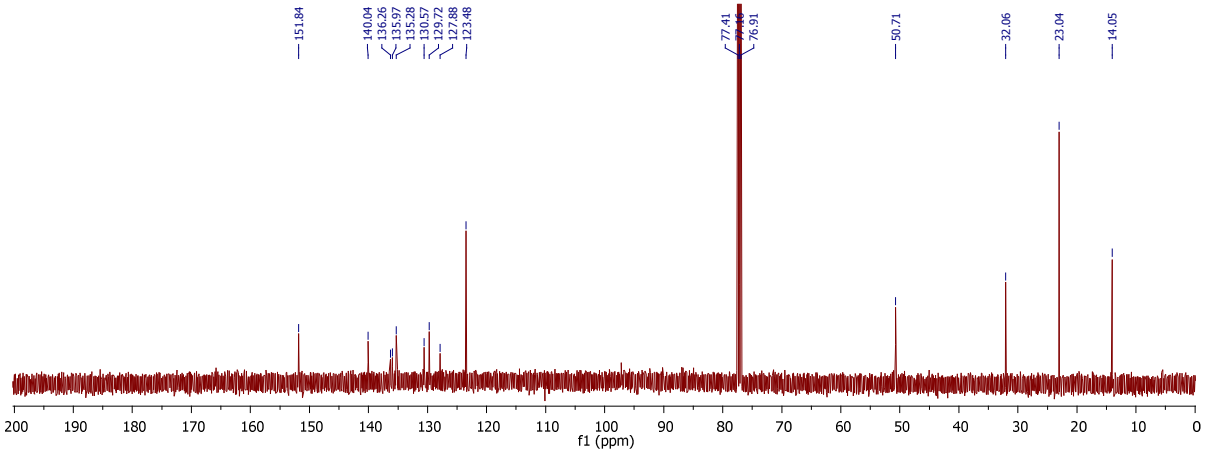
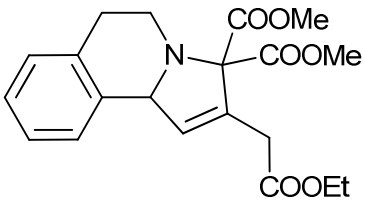
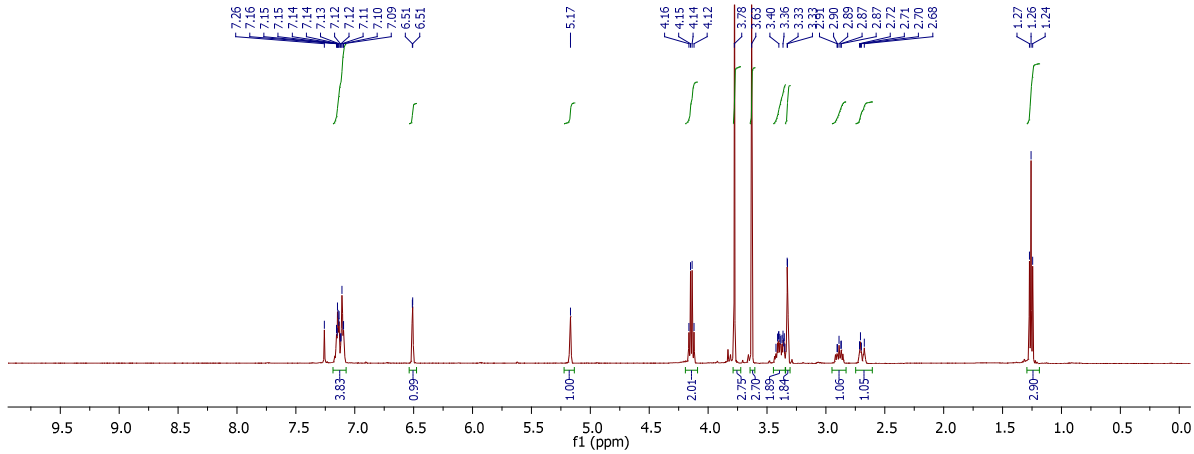
8.13
8.03
8.02
8.00
7.83
7.81
7.26
3.73
3.07
3.06
3.04
1.85
1.84
1.82
1.81
1.77
1.08
1.07
1.06
1.00
2.89
1.20
1.15
6.31
2.17
3.00
3.29
f1 (ppm)


151.84
140.04
136.26
135.97
135.28
130.57
129.72
127.88
123.48
77.41
77.16
76.91
50.71
32.06
23.04
14.05
f1 (ppm)


COOMe
COOMe
N
COOEt

4a


7.26
7.16
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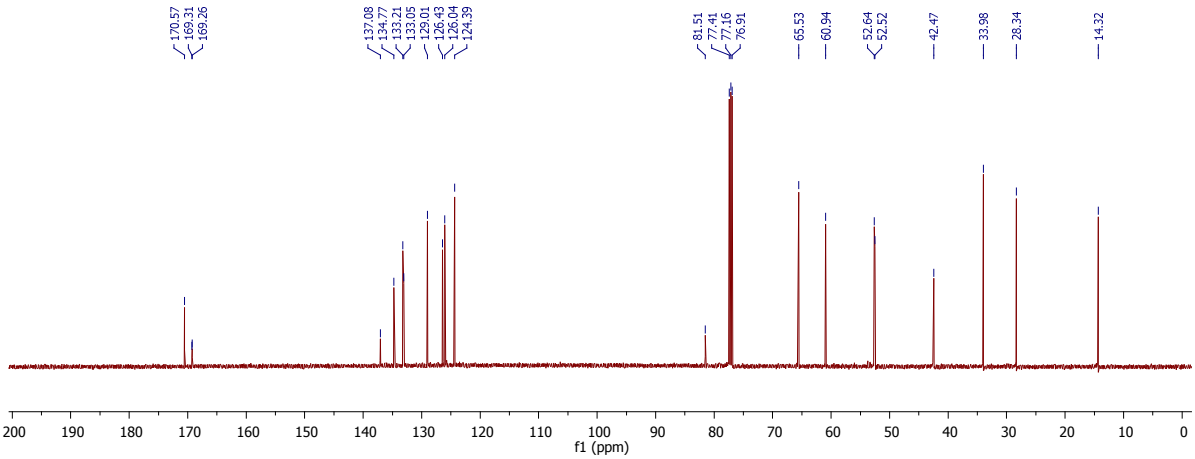
7.15
7.14
7.14
7.13
7.12
7.12
7.11
7.10
7.09
6.51
6.51
5.17
4.16
4.15
4.14
4.12
3.78
3.63
3.40
3.36
3.33
2.91
2.90
2.89
2.87
2.87
2.72
2.71
2.70
2.68
1.27
1.26
1.24
3.83
0.99
1.00
2.01
2.75
2.70
1.89
1.84
1.06
1.05
2.90
f1 (ppm)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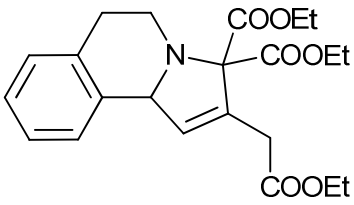
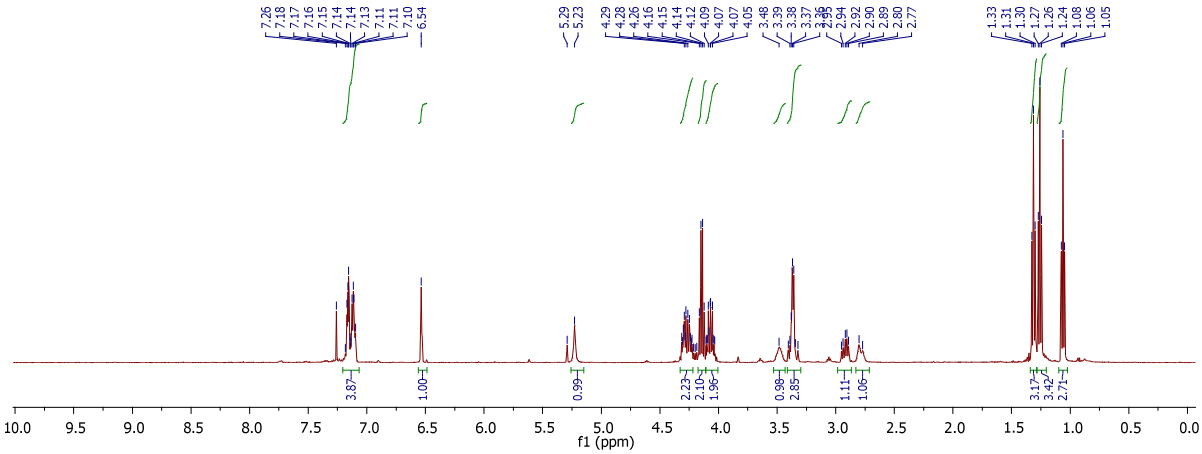
134.77
133.21
133.05
129.01
126.43
126.04
124.39
81.51
77.41
77.16
76.91
65.53
60.94
52.64
52.52
42.47
33.98
28.34
14.32
f1 (ppm)


COOEt
N
COOEt
COOEt

4b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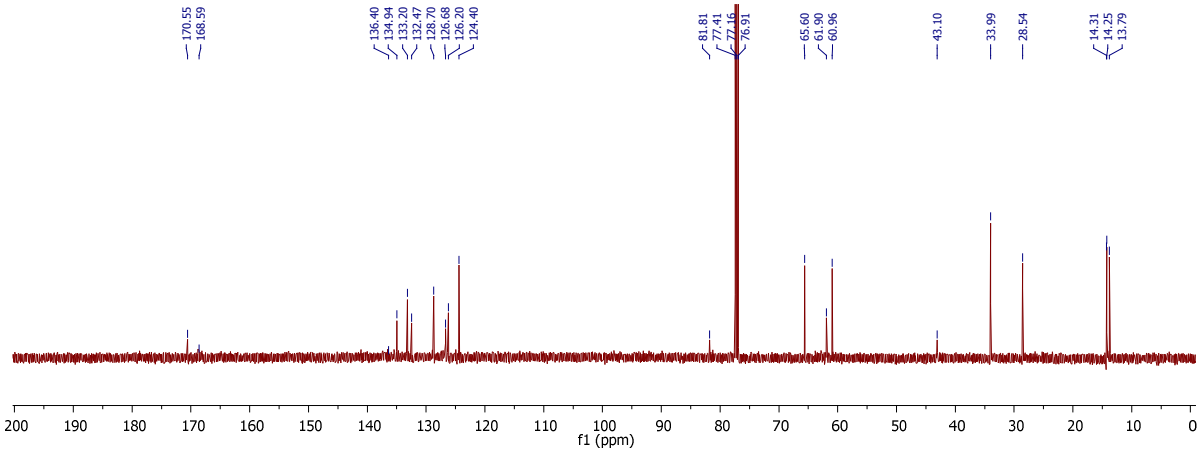
7.16
7.15
7.14
7.14
7.13
7.11
7.11
7.10
6.94
5.29
5.23
4.29
4.28
4.26
4.16
4.15
4.14
4.12
4.09
4.07
4.07
4.05
3.48
3.39
3.38
3.37
2.95
2.94
2.92
2.90
2.89
2.80
2.77
1.33
1.31
1.30
1.27
1.26
1.24
1.08
1.06
1.05
3.87
1.00
0.99
2.23
2.10
1.96
0.98
2.85
1.11
1.06
3.12
3.42
2.71
f1 (ppm)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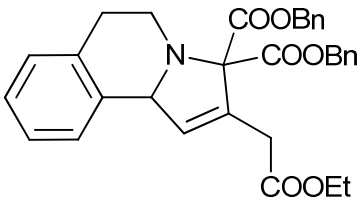
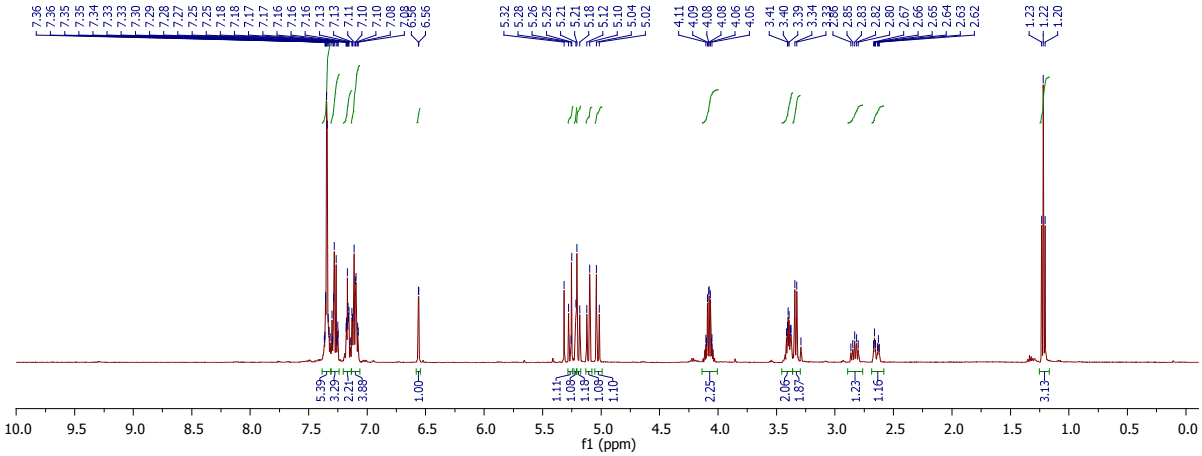
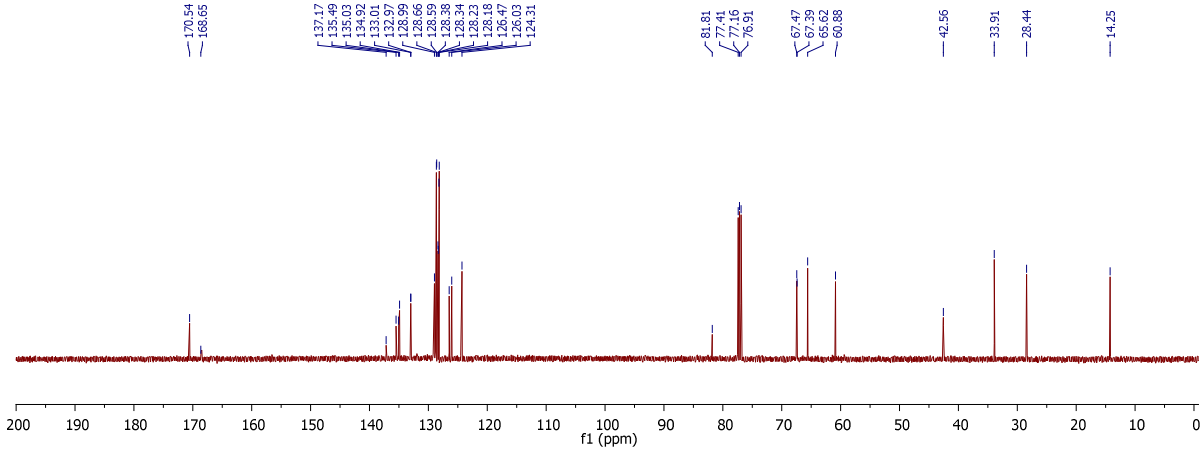
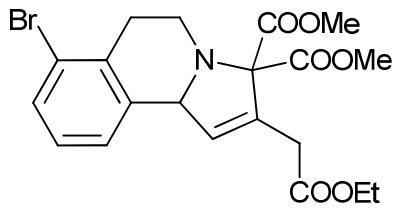
132.47
128.70
126.68
126.20
124.40
81.81
77.41
77.16
76.91
65.60
61.90
60.96
43.10
33.99
28.54
14.31
14.25
13.79
f1 (ppm)



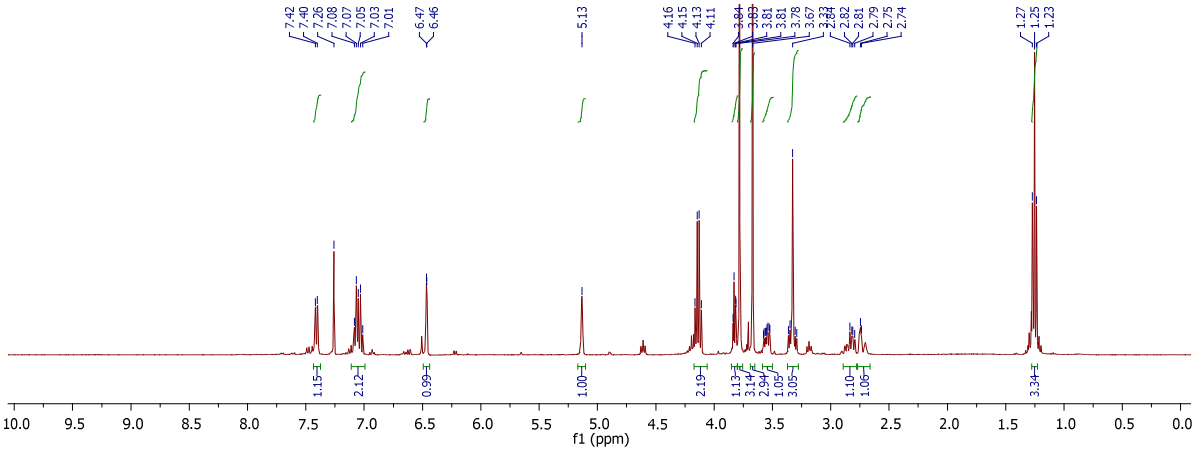
4c






Br
N
COOMe
COOMe
COOEt

4d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7.01
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6.46
5.13
4.16
4.15
4.13
4.11
3.84
3.83
3.81
3.81
3.78
3.67
2.82
2.81
2.79
2.75
2.74
1.27
1.25
1.23
1.15
2.12
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1.00
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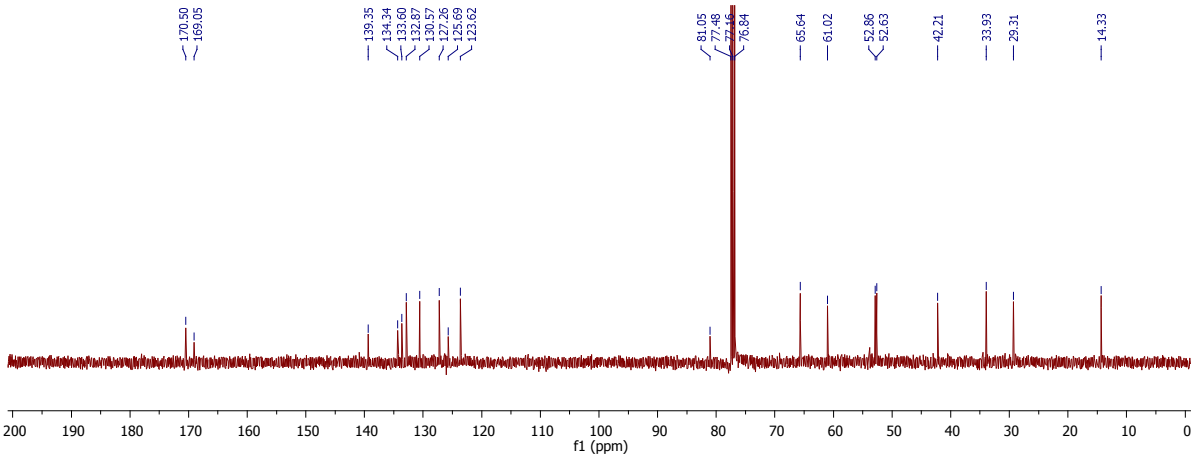
1.13
3.14
2.94
1.05
3.05
1.10
1.06
3.34
f1 (ppm)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123.62
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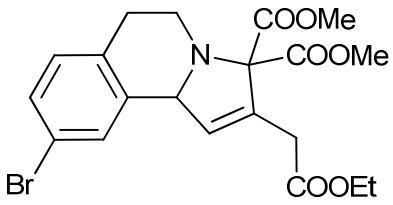
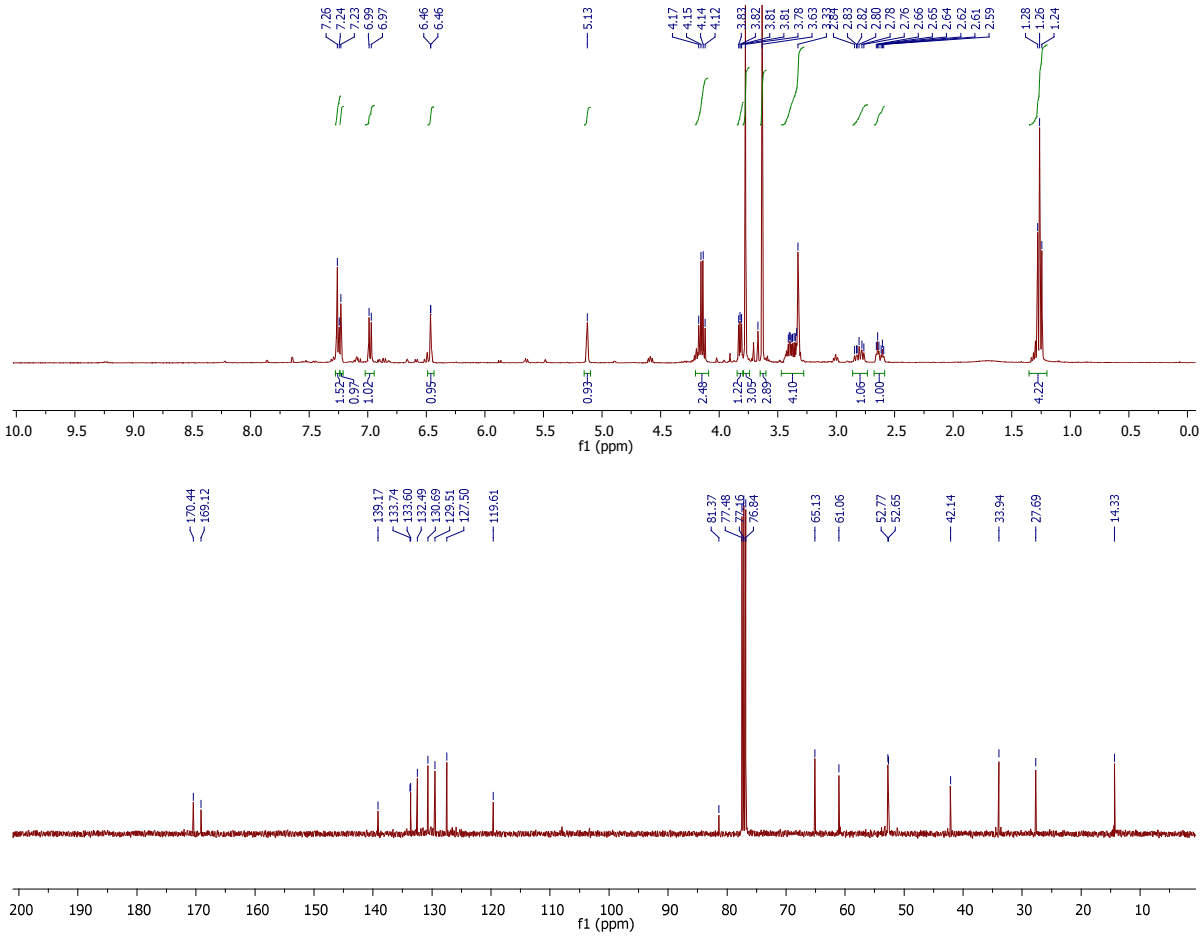
61.02
52.86
52.63
42.21
33.93
29.31
14.33
f1 (ppm)


COOMe
COOMe
N
Br
COOEt

4e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6.46
5.13
4.17
4.15
4.14
4.12
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3.82
3.81
3.81
3.78
3.63
2.83
2.82
2.80
2.78
2.76
2.66
2.65
2.64
2.62
2.61
2.59
1.28
1.26
1.24
1.52
0.97
1.02
0.95
0.93
2.48
1.22
3.05
2.89
4.10
1.06
1.00
4.22
f1 (ppm)
170.44
169.12
139.17
133.74
133.60
132.49
130.69
129.51
127.50
119.61
81.37
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77.16
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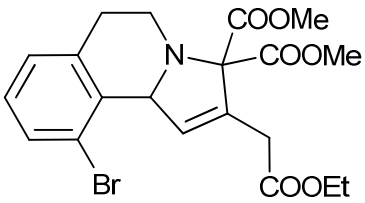
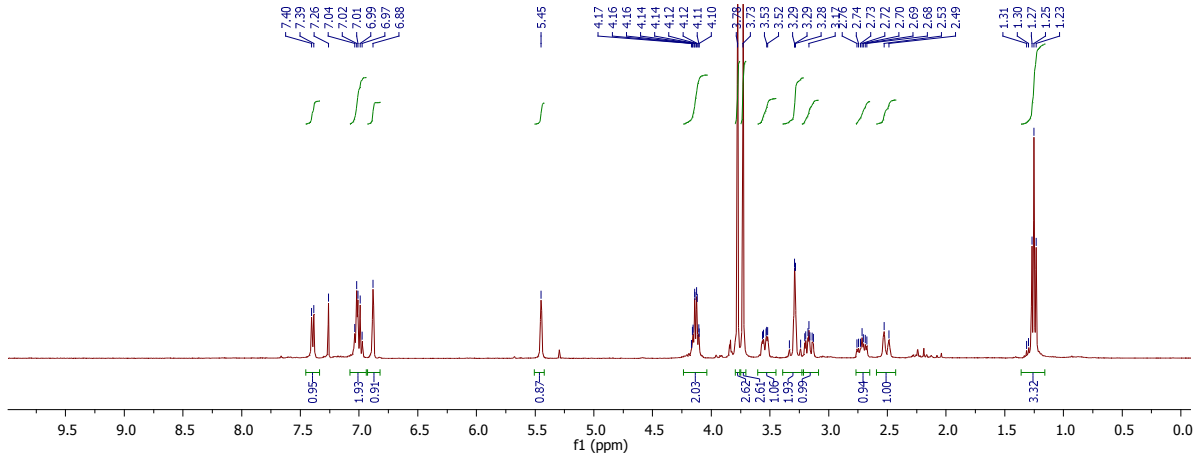
65.13
61.06
52.77
52.65
42.14
33.94
27.69
14.33
f1 (ppm)


COOMe
COOMe
N
Br
COOEt

4f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7.01
6.99
6.97
6.88
5.45
4.17
4.16
4.16
4.14
4.14
4.12
4.12
4.11
4.10
3.73
3.53
3.52
3.29
3.29
3.28
2.74
2.73
2.72
2.70
2.69
2.68
2.53
2.49
1.31
1.30
1.27
1.25
1.23
0.95
1.93
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0.87
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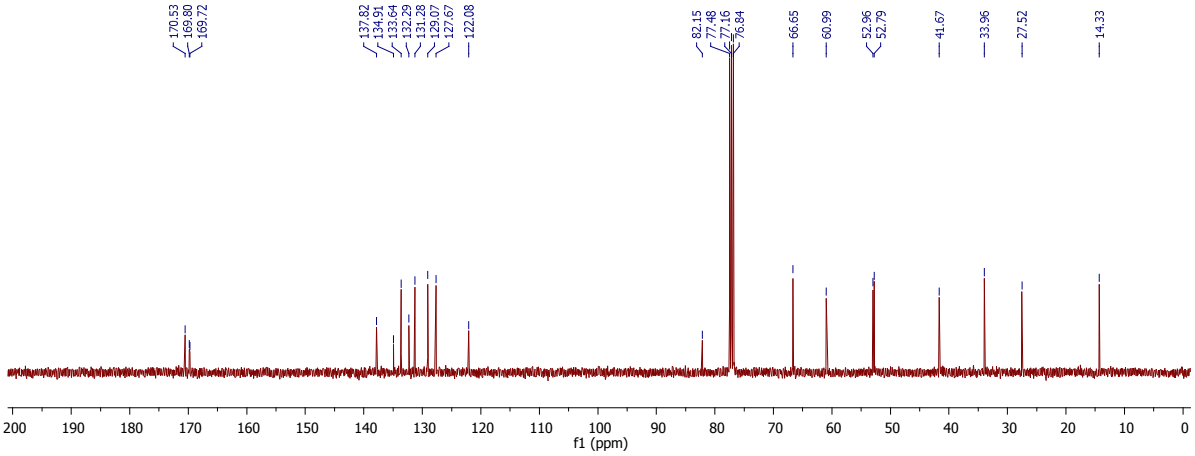
2.62
2.61
1.06
1.93
0.99
0.94
1.00
3.32
f1 (ppm)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122.08
82.15
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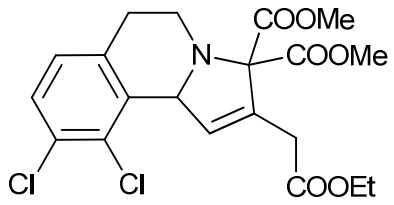
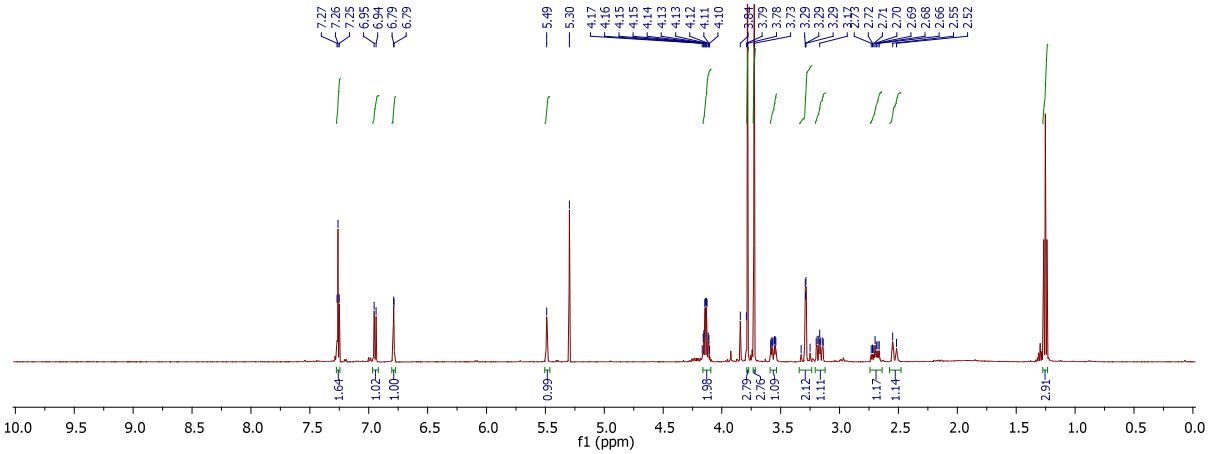
41.67
33.96
27.52
14.33
f1 (ppm)


COOMe
N
COOMe
Cl
Cl
COOEt

4g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7.26
7.25
6.95
6.94
6.79
6.79
5.49
5.30
4.17
4.16
4.15
4.15
4.14
4.13
4.13
4.12
4.11
4.10
3.81
3.79
3.78
3.73
3.29
3.29
3.29
3.17
2.73
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2.71
2.70
2.69
2.68
2.66
2.55
2.52
1.64
1.02
1.00
0.99
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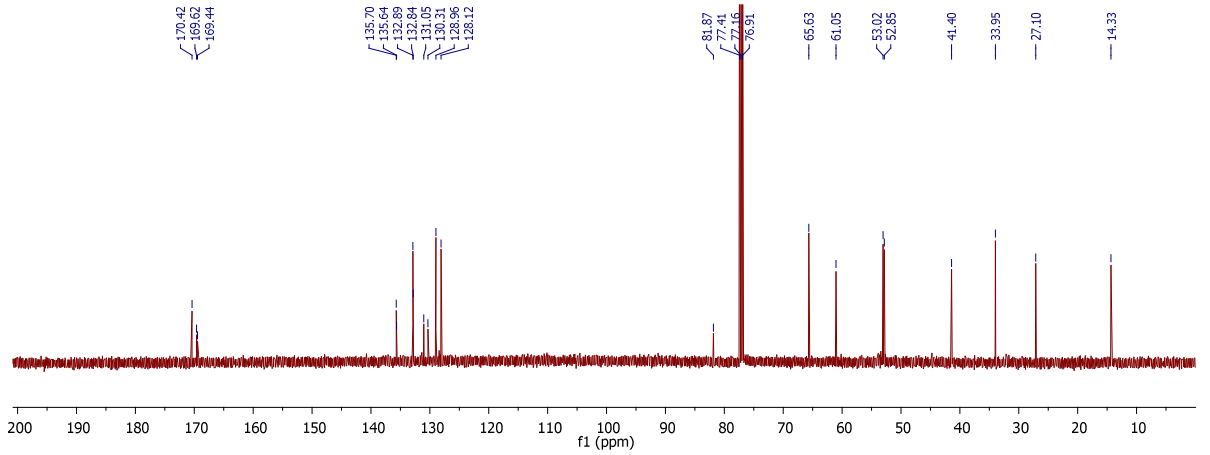
2.79
2.76
1.09
2.13
1.11
1.17
1.14
2.91
f1 (ppm)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169.62
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135.64
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132.84
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130.31
128.96
128.12
81.87
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53.02
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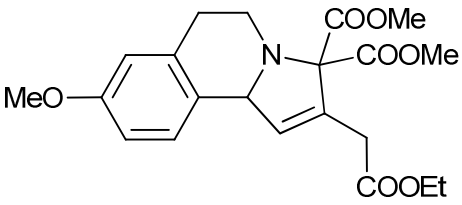
14.33
f1 (ppm)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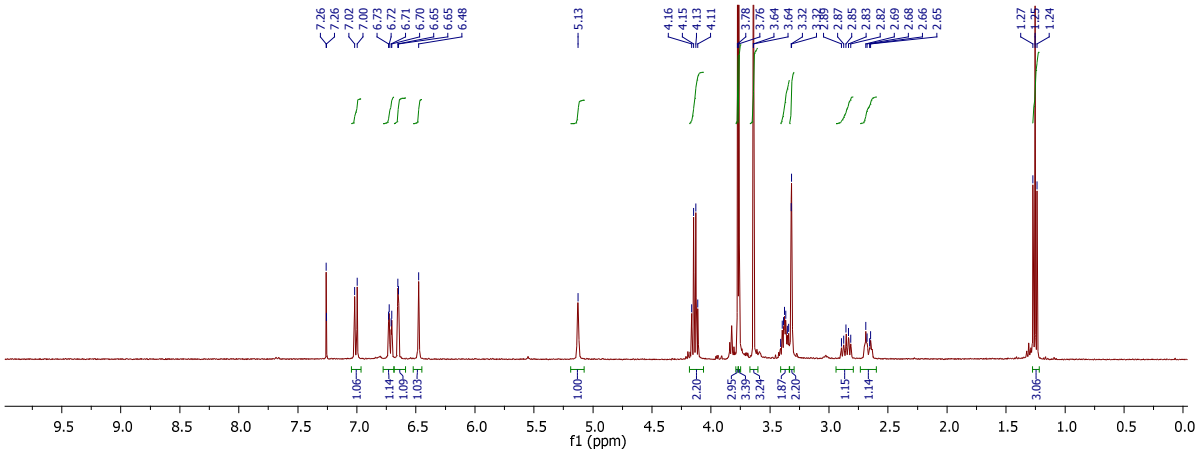
COOMe
MeO
COOEt

4h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4.15
4.13
4.11
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3.76
3.64
3.64
3.32
2.87
2.85
2.83
2.82
2.69
2.68
2.66
2.65
1.27
1.25
1.24
1.06
1.14
1.09
1.03
1.00
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3.24
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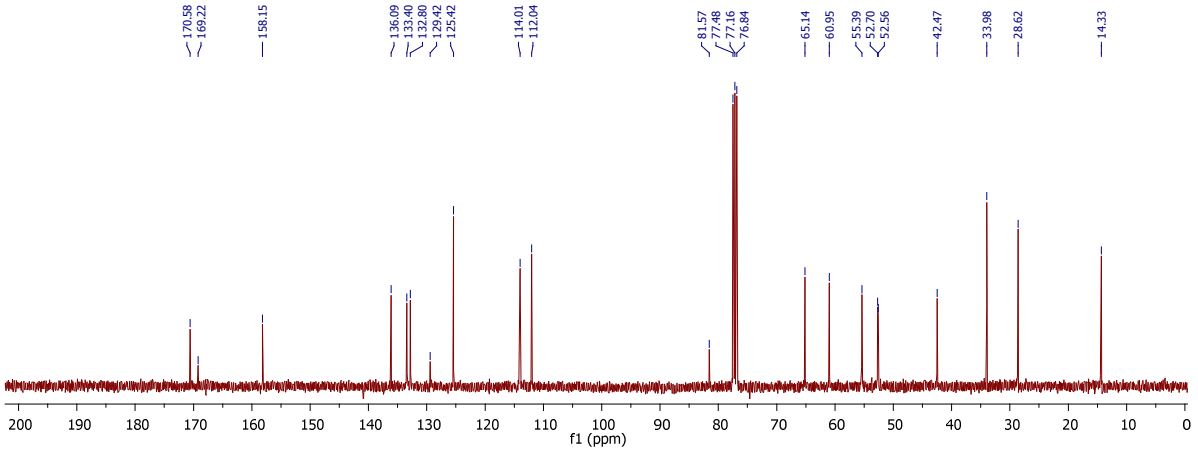
1.14
3.06
f1 (ppm)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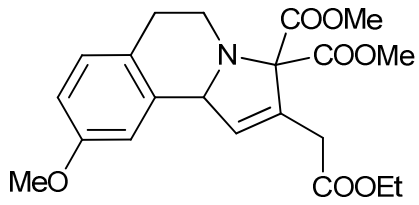
f1 (ppm)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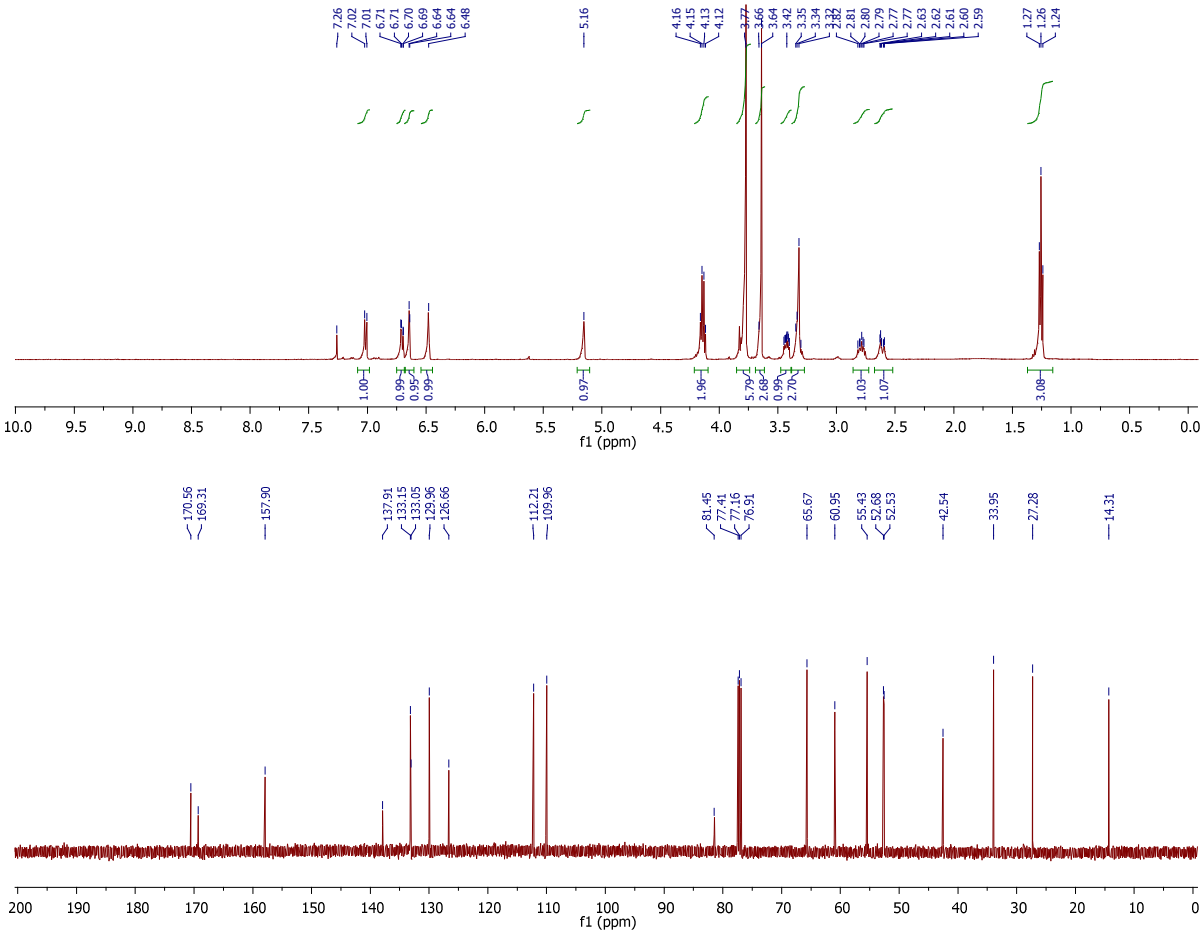
COOMe
MeO
COOEt

4i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4.12
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3.64
3.42
3.35
3.34
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2.79
2.77
2.77
2.63
2.62
2.61
2.60
2.59
1.27
1.26
1.24
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0.95
0.99
0.97
1.96
5.79
2.68
0.99
2.70
1.03
1.07
3.08
f1 (ppm)
170.56
169.31
157.90
137.91
133.15
133.05
129.96
126.66
112.21
109.96
81.45
77.41
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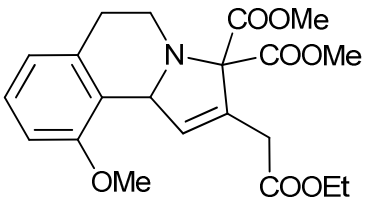
14.31
f1 (ppm)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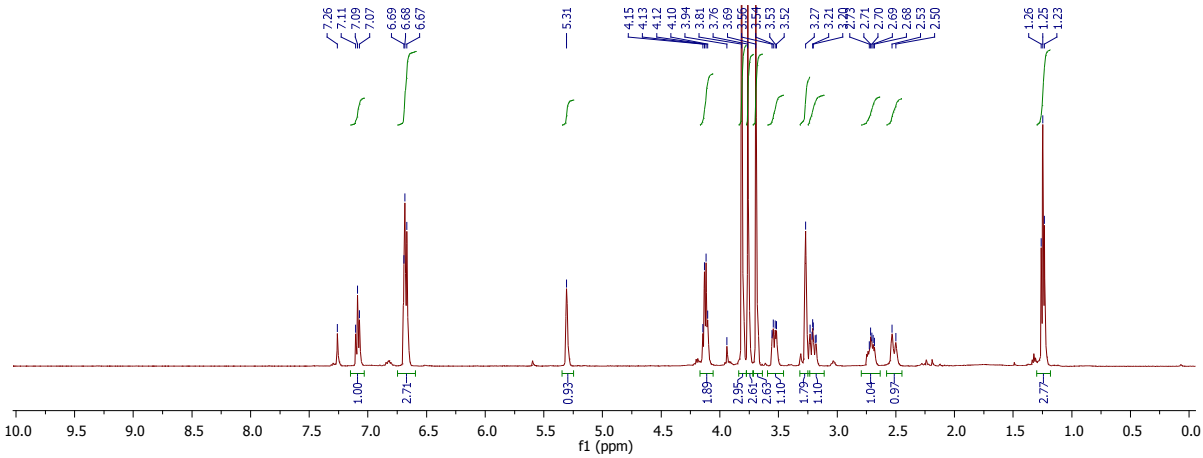
COOMe
OMe
COOEt

4j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3.81
3.76
3.69
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3.54
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3.52
3.27
3.21
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1.25
1.23
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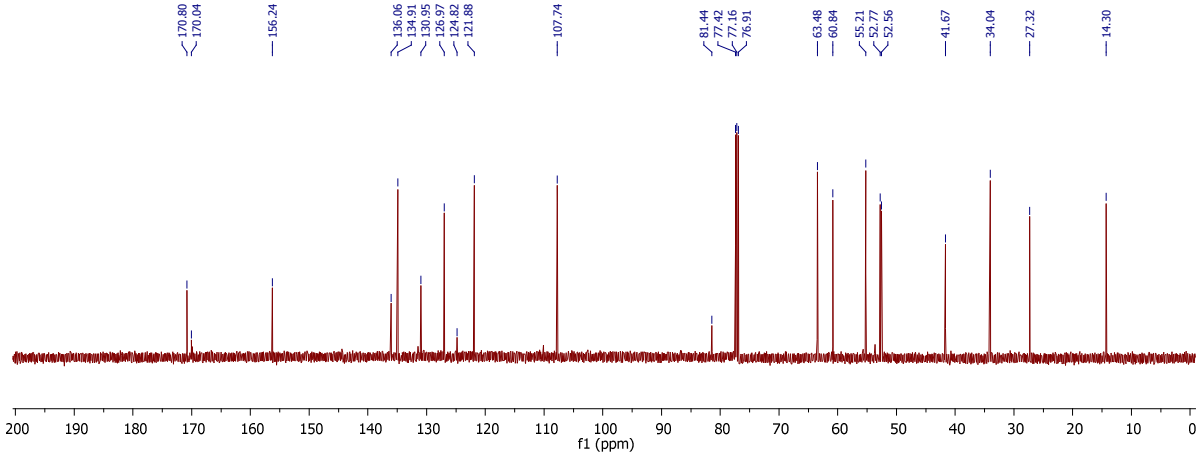
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41.67
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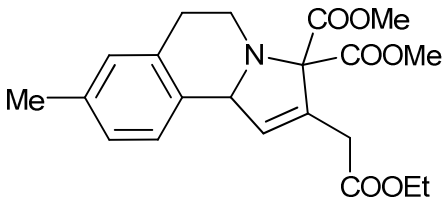
27.32
14.30
f1 (ppm)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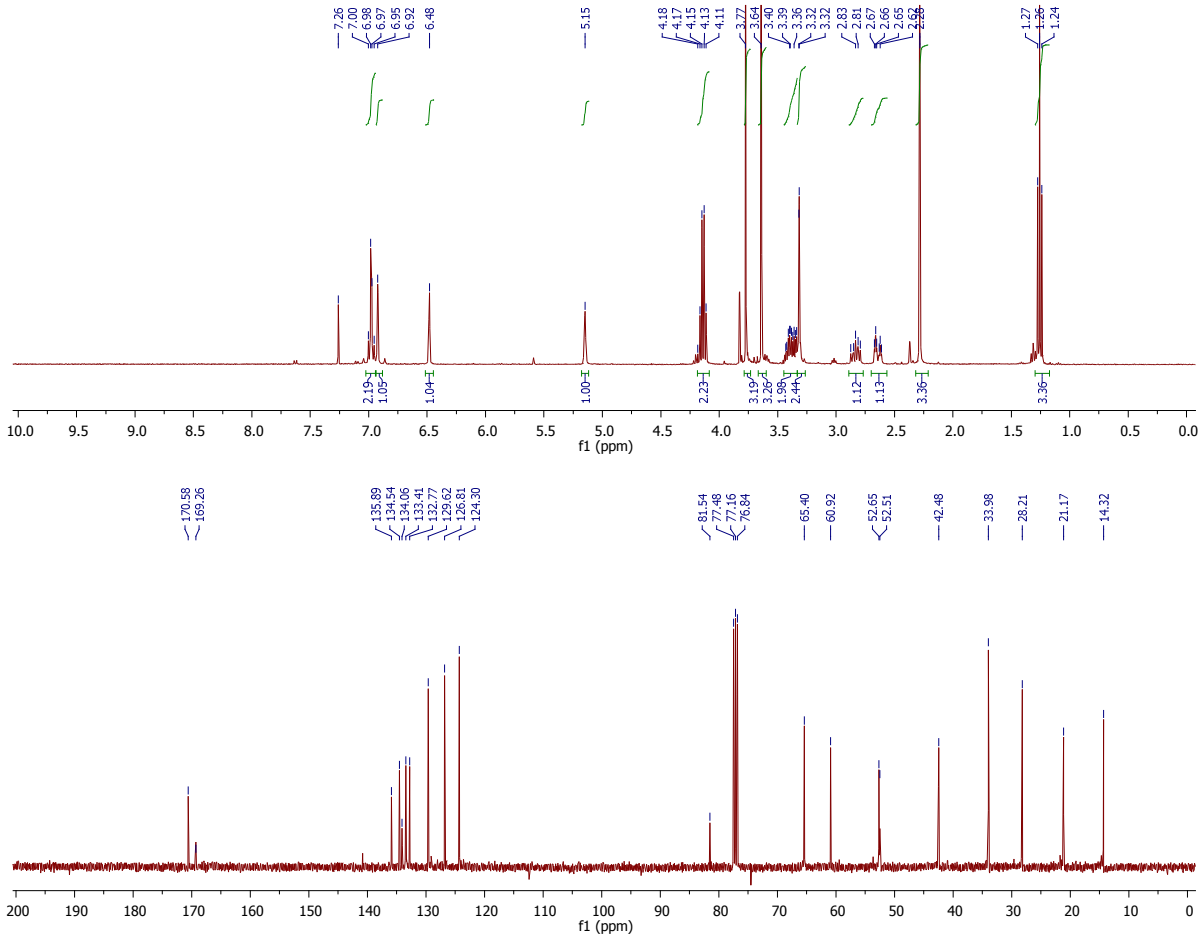
N
COOMe
Me
COOEt

4k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2.67
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2.65
2.62
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1.26
1.24
2.19
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3.26
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1.12
1.13
3.36
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f1 (ppm)
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135.89
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128.81
124.30
81.54
77.48
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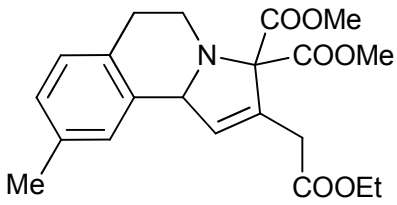
f1 (ppm)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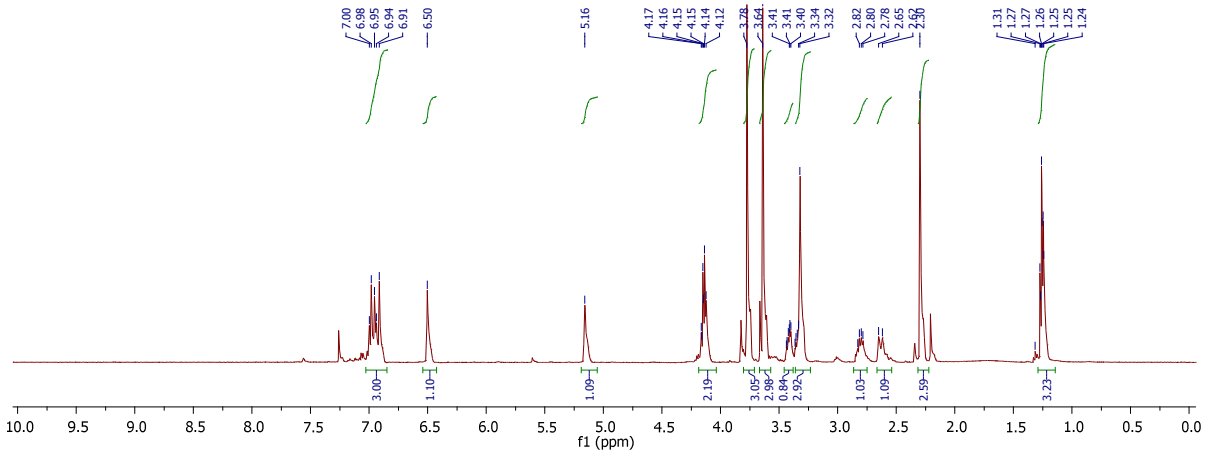
N
COOMe
Me
COOEt

4l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4.12
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3.32
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1.24
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1.09
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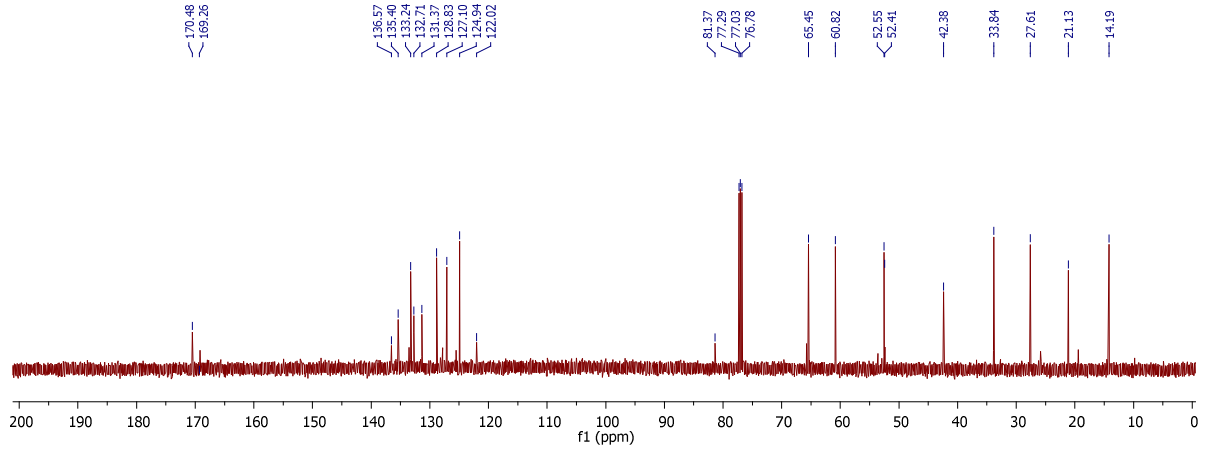
f1 (ppm)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52.41
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27.61
21.13
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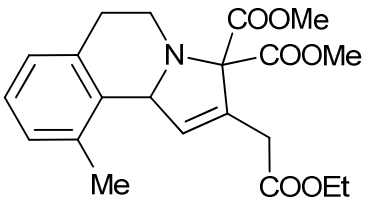
f1 (ppm)



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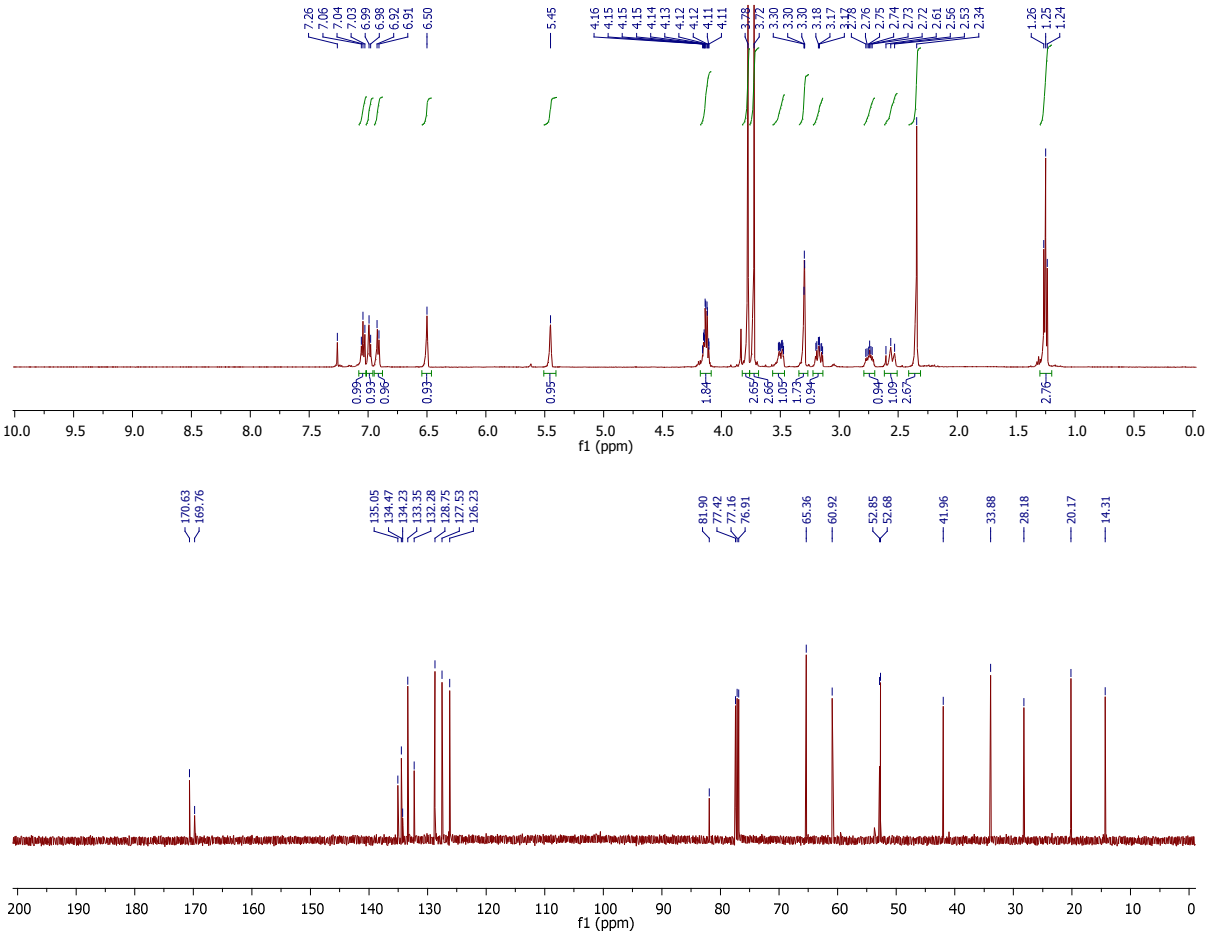

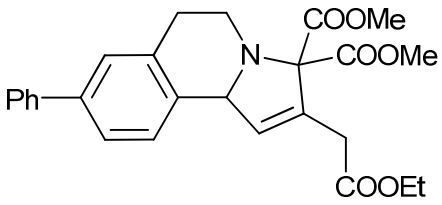
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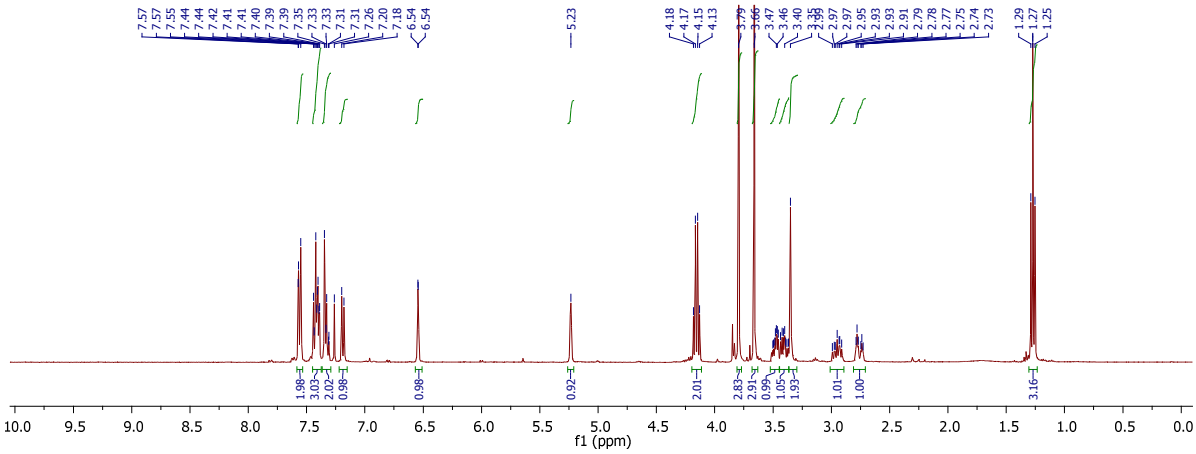
COOMe
Ph
COOEt

4n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4.13
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3.40
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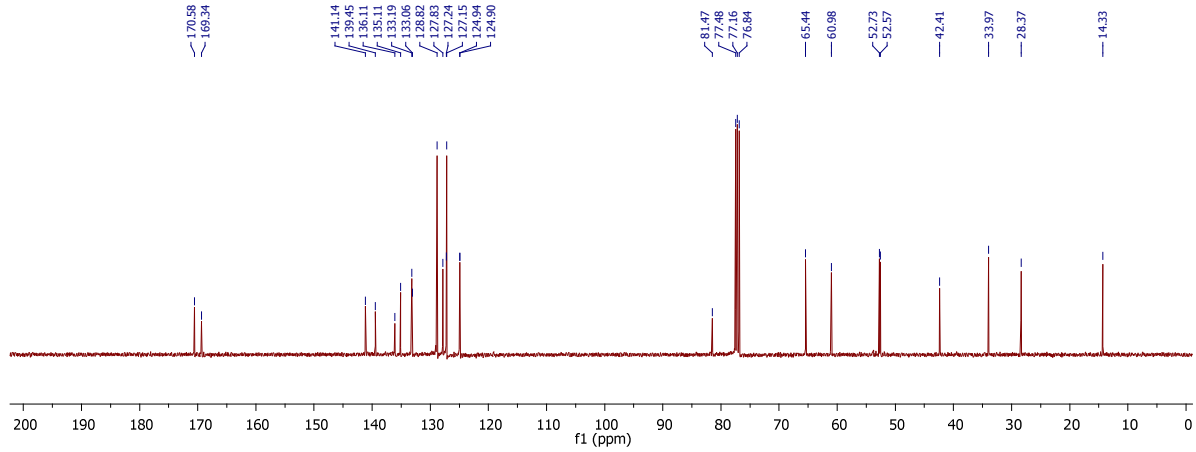
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124.90
81.47
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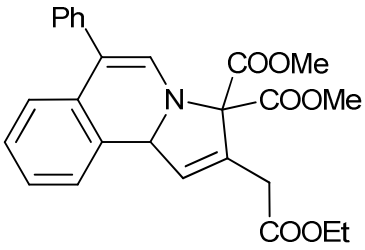
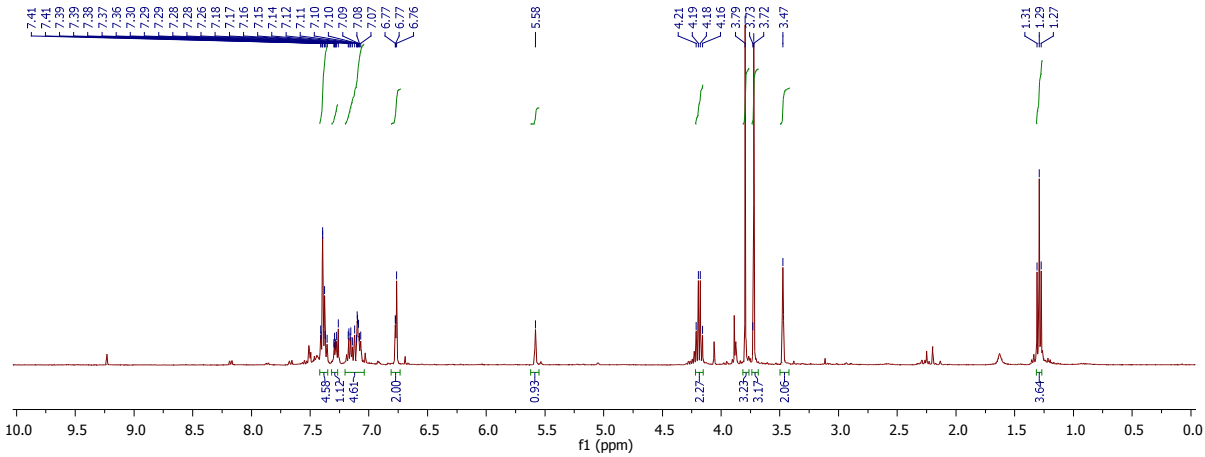
52.73
52.57
42.41
33.97
28.37
14.33
f1 (ppm)


Ph
COOMe
N
COOMe
COOEt

4o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7.12
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7.10
7.10
7.09
7.08
7.07
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6.77
6.76
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1.29
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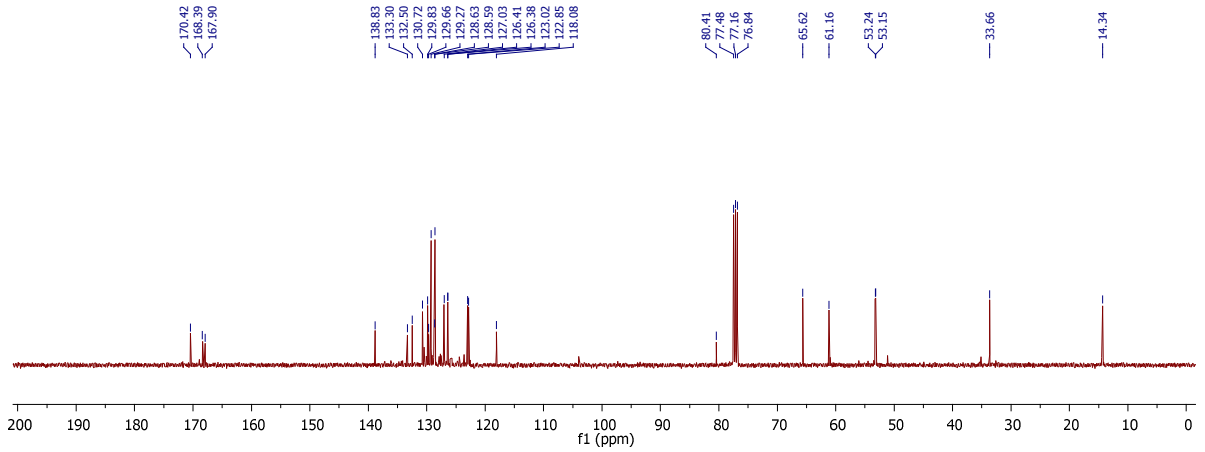
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128.63
128.59
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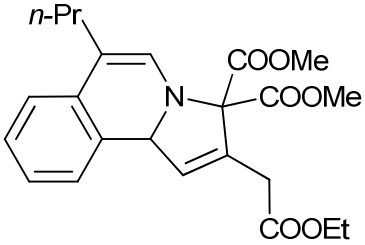
53.24
53.15
33.66
14.34
f1 (ppm)


n-Pr
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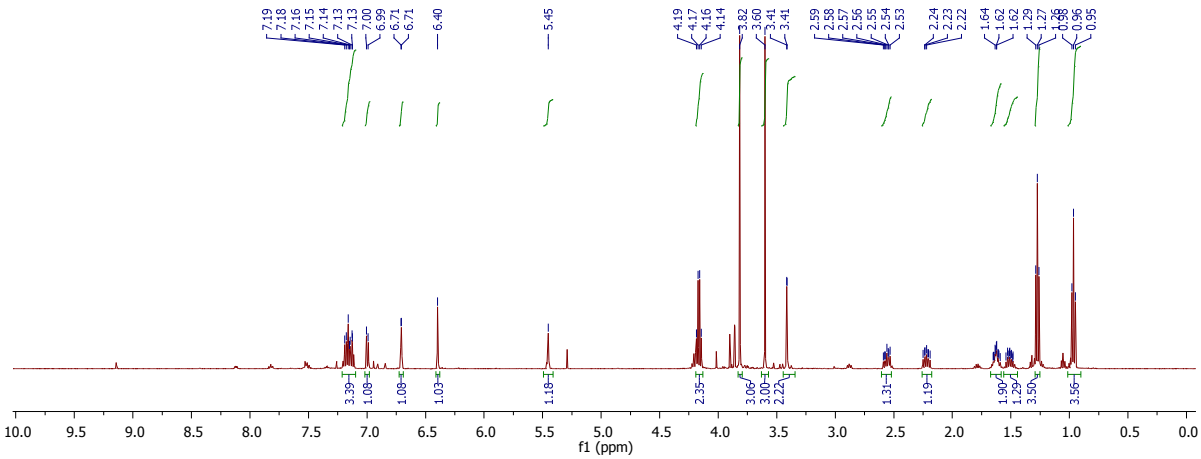
COOMe
N
COOEt

4p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2.54
2.53
2.24
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0.95
3.39
1.08
1.08
1.03
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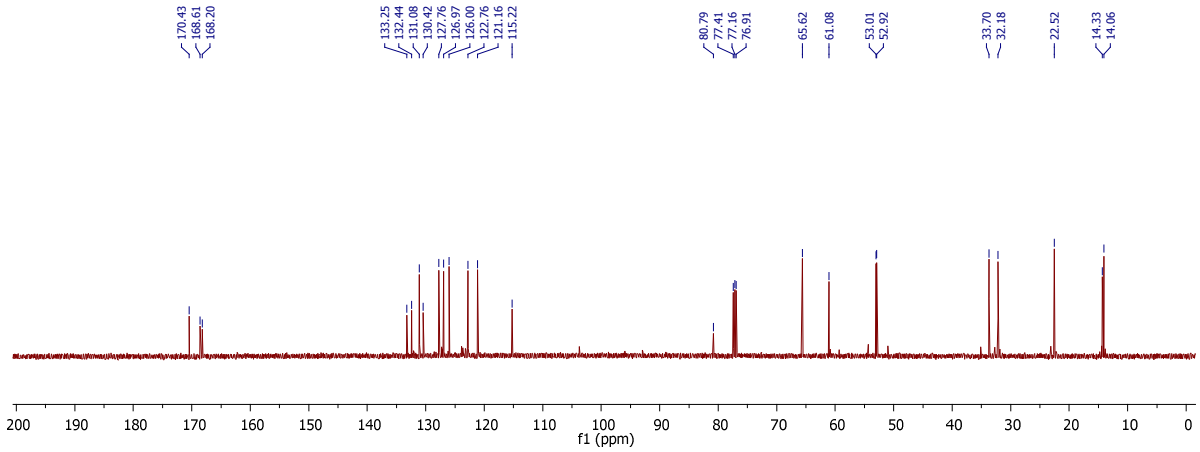
f1 (ppm)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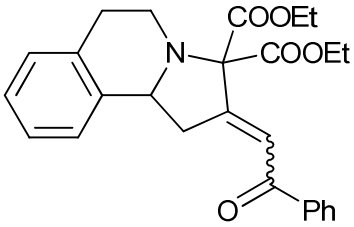
32.18
22.52
14.33
14.06
f1 (ppm)



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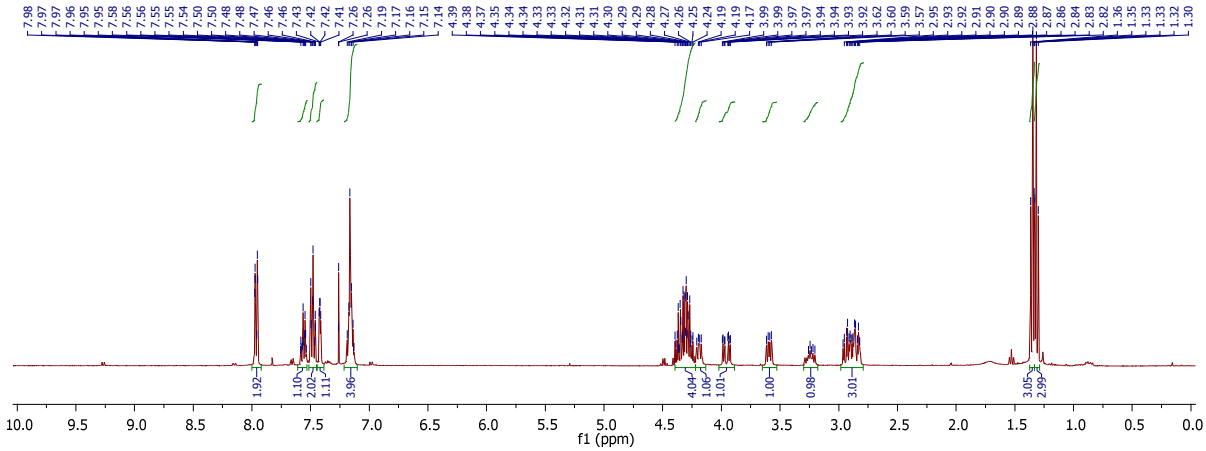

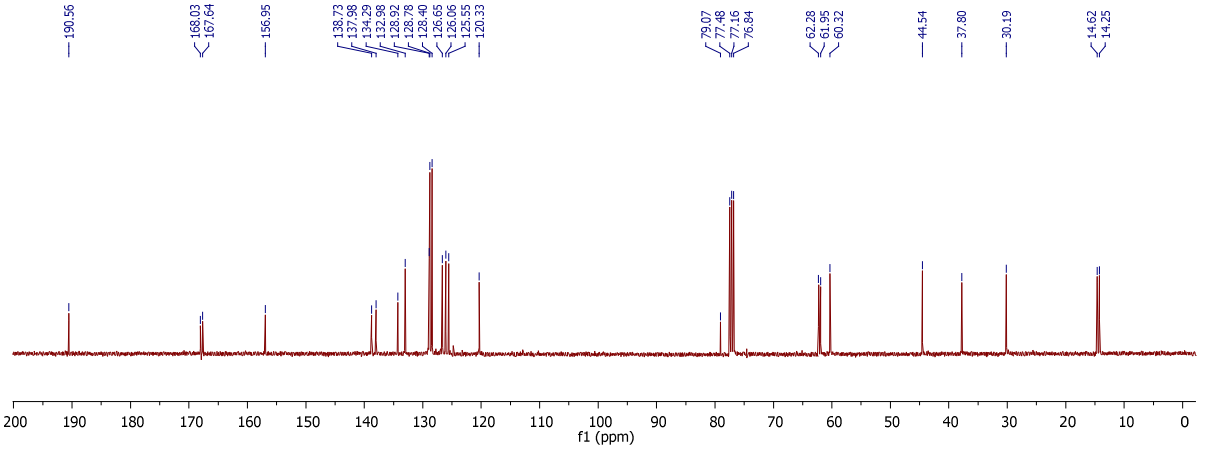

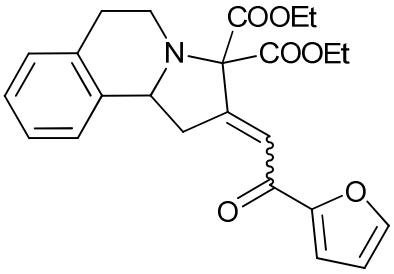

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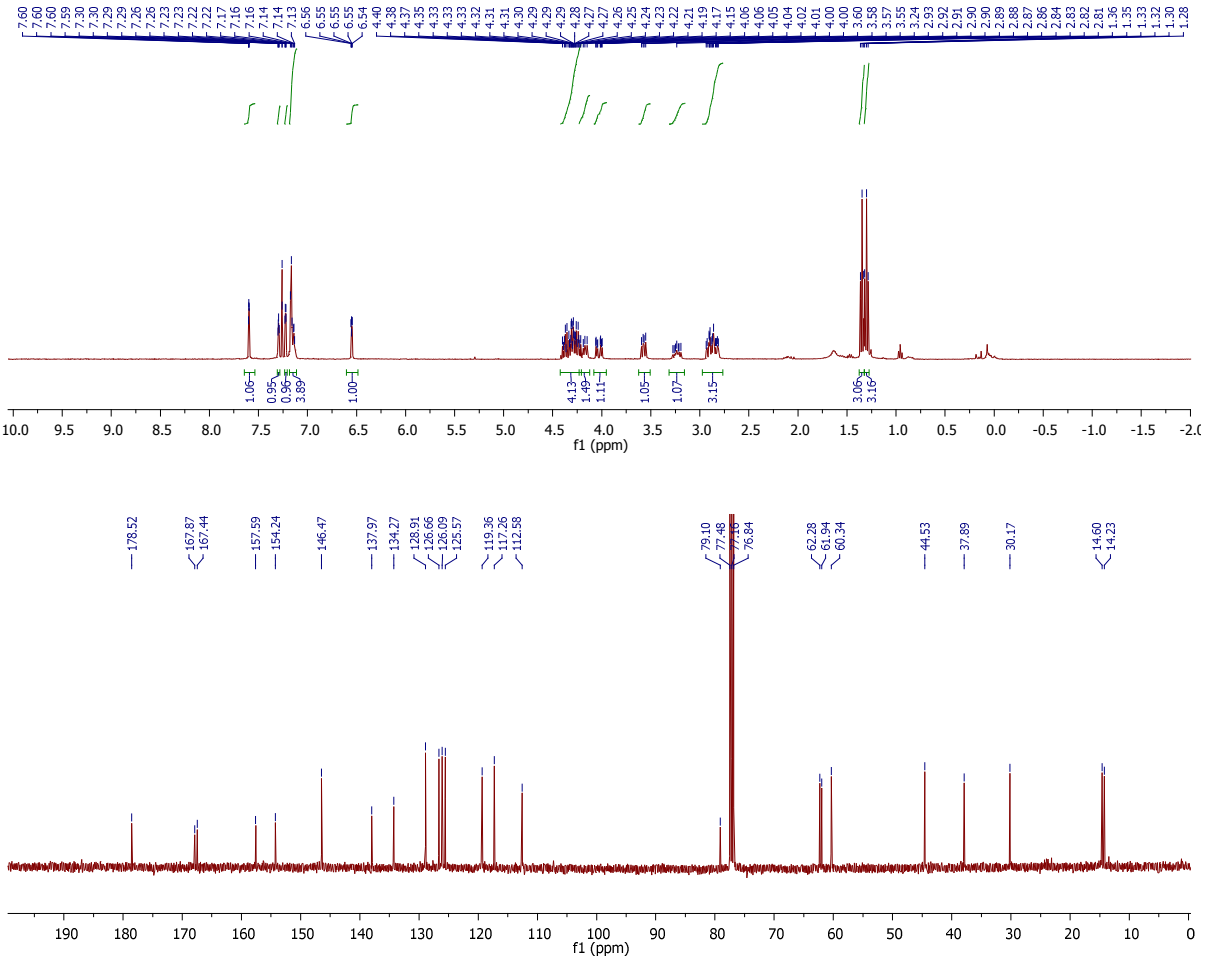
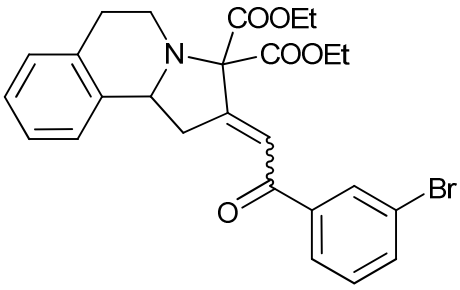
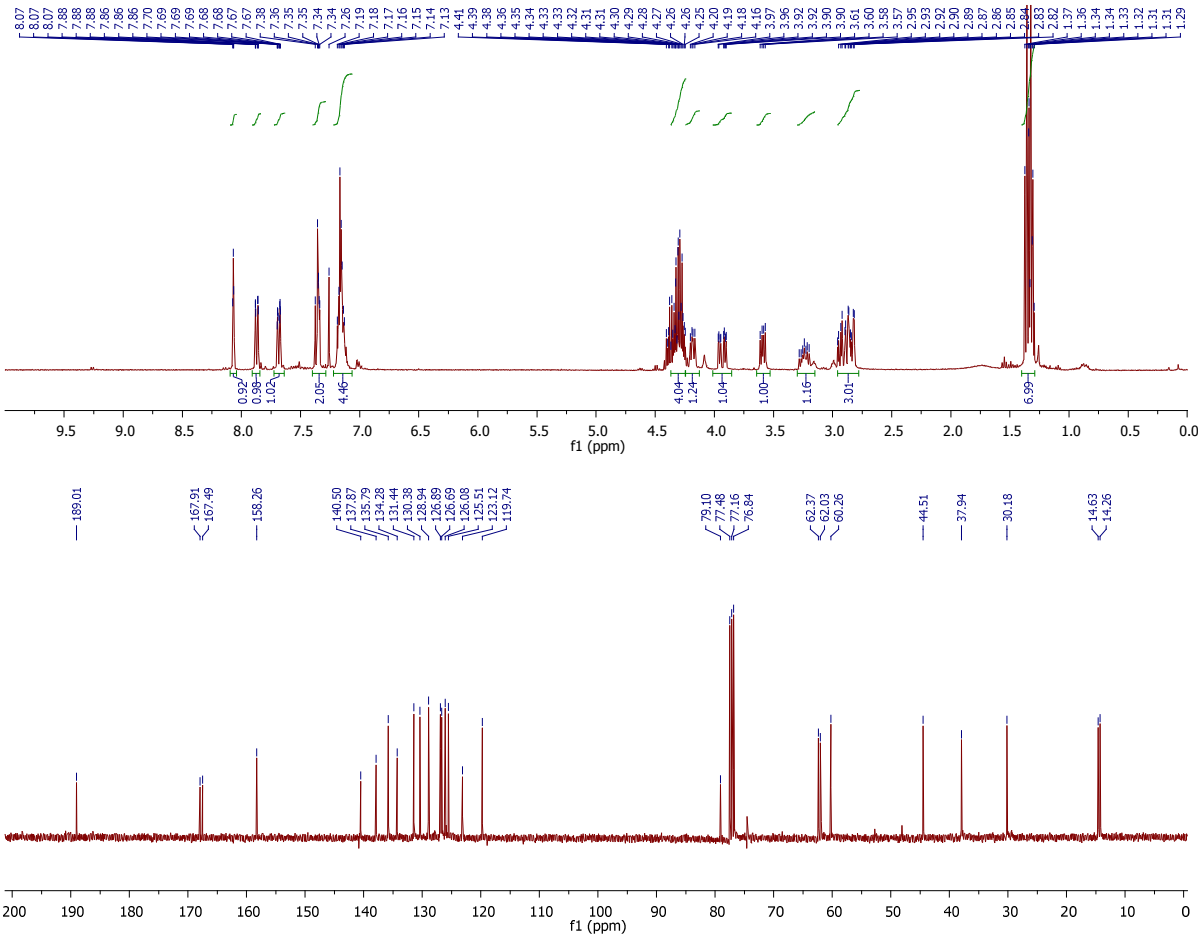
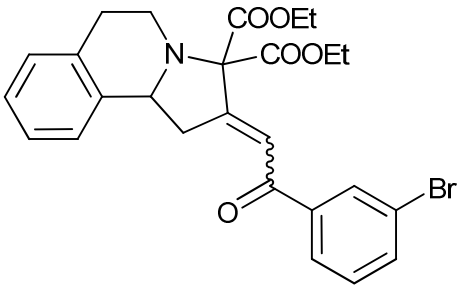


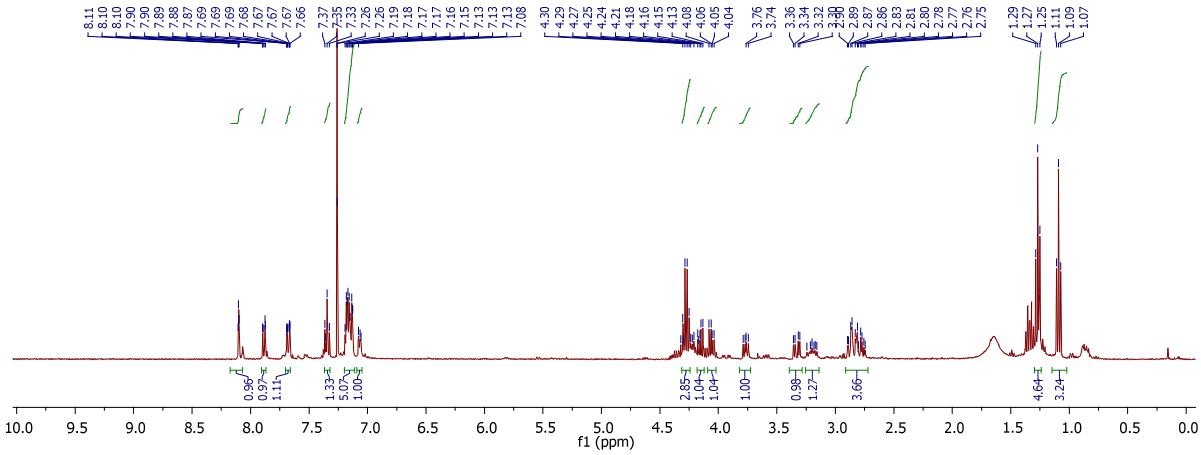


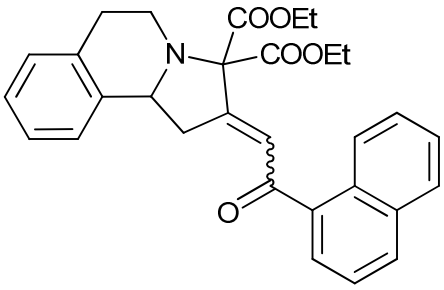
6c- major



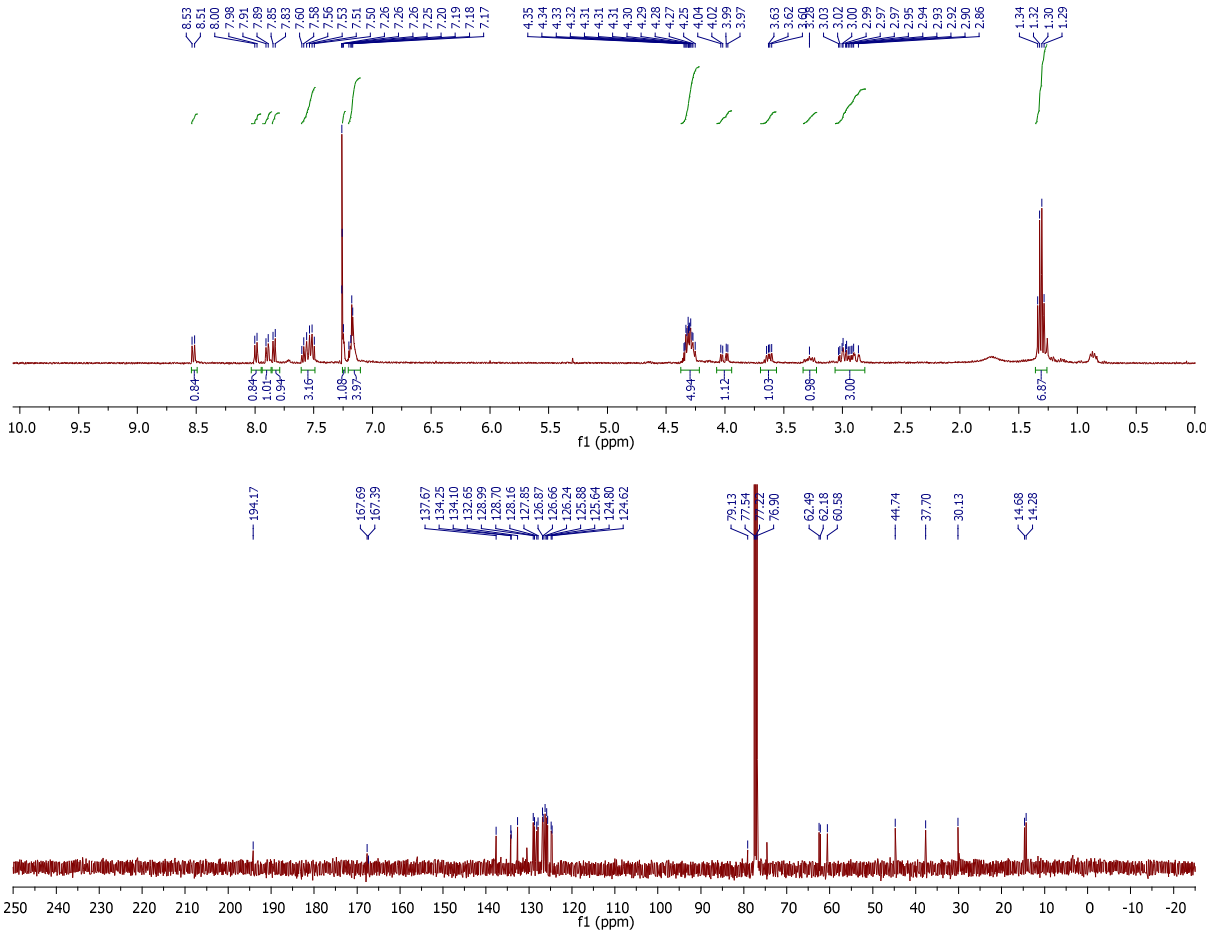


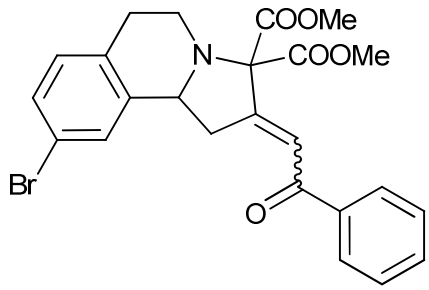
6c-minor





6d




COOMe
COOMe
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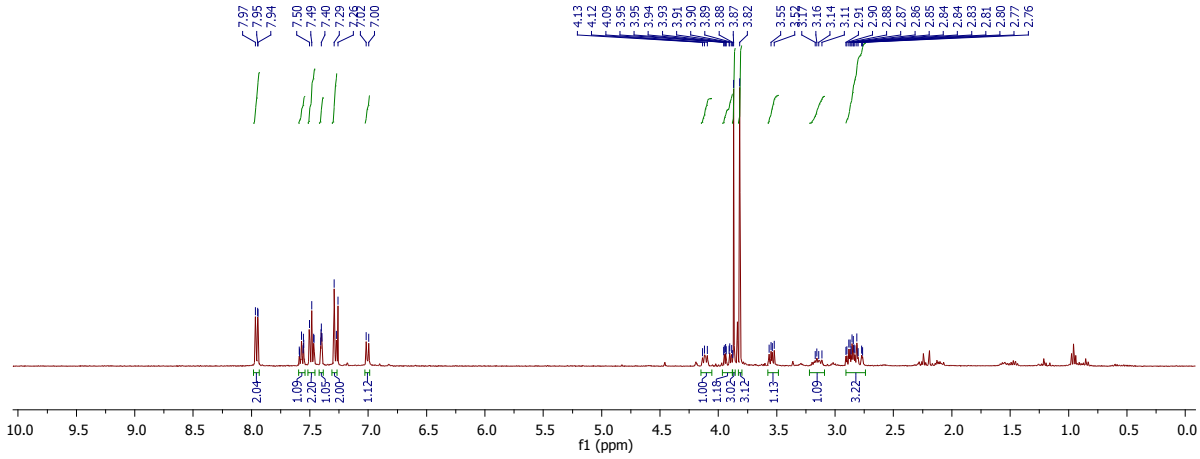
Br
O

6e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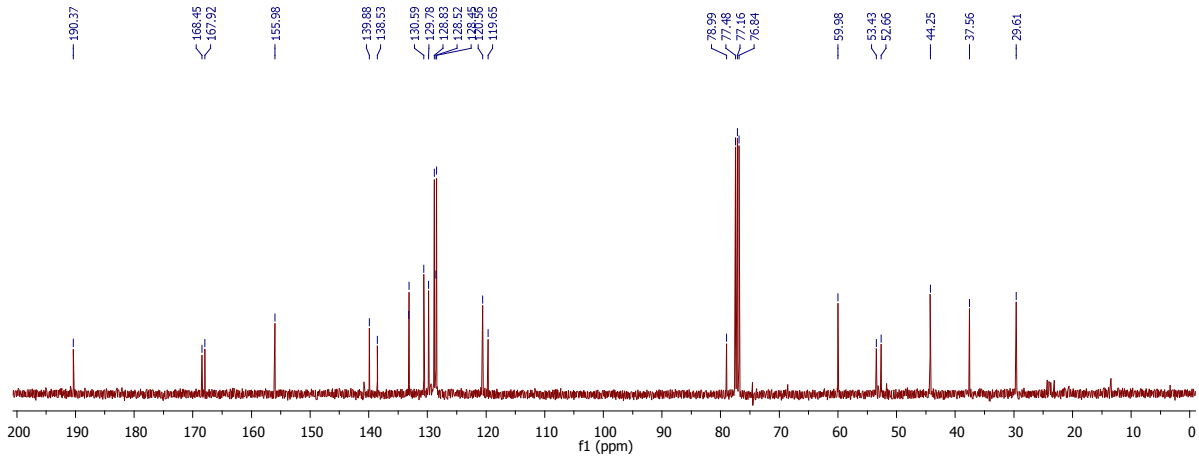
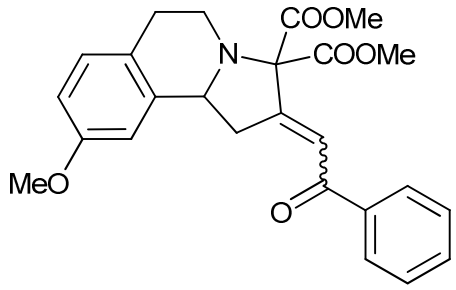
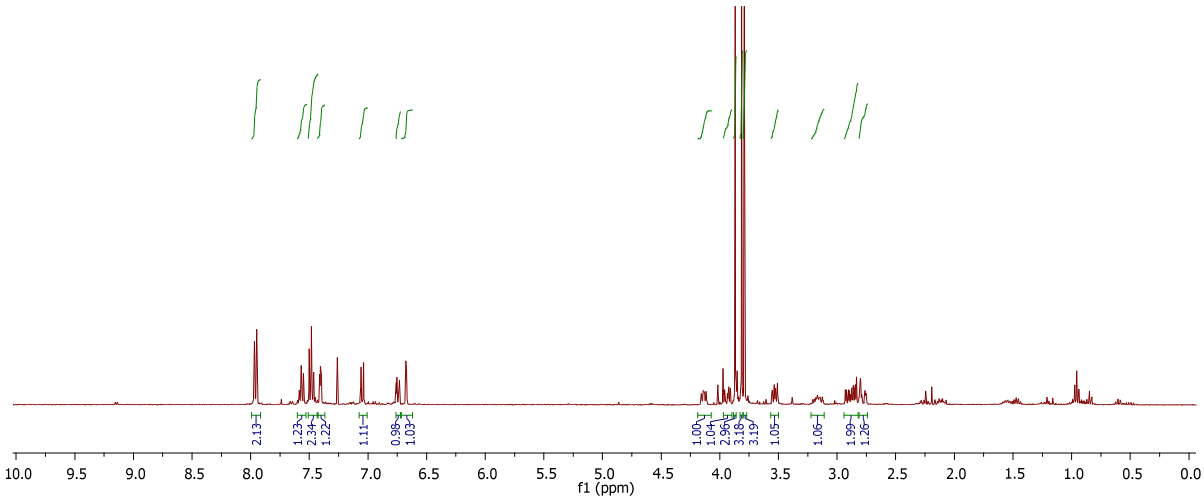
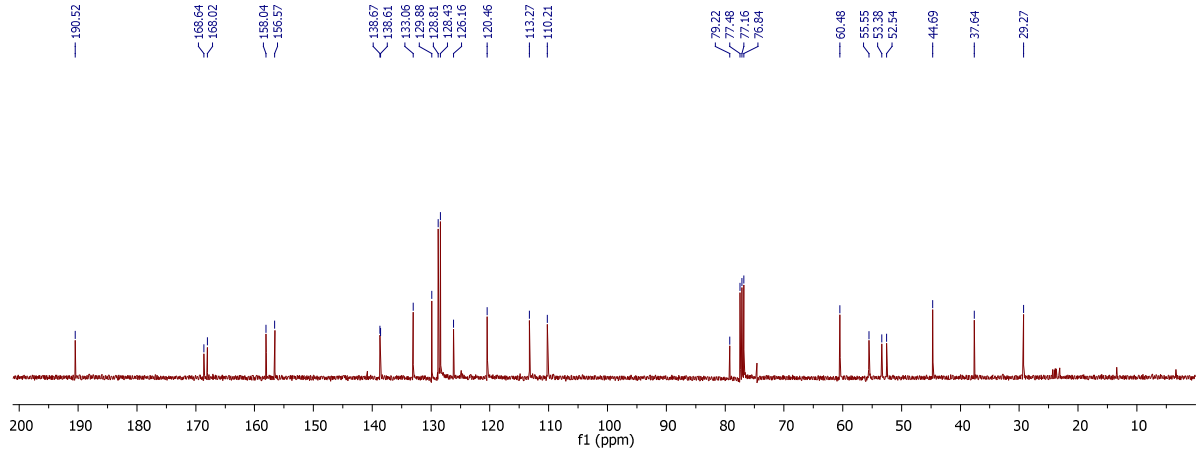
7.50
7.49
7.40
7.29
7.26
7.02
7.00
4.13
4.12
4.09
3.95
3.95
3.94
3.93
3.91
3.90
3.89
3.88
3.87
3.82
3.55
3.52
3.17
3.16
3.14
3.11
2.91
2.90
2.88
2.87
2.86
2.85
2.84
2.84
2.83
2.81
2.80
2.77
2.76
2.04
1.09
2.20
1.05
2.00
1.12
1.00
1.16
3.02
3.12
1.13
1.09
3.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190.37
168.45
167.92
155.98
139.88
138.53
130.59
129.78
128.83
128.52
128.45
120.56
119.65
78.99
77.48
77.16
76.84
59.98
53.43
52.66
44.25
37.56
29.61
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


COOMe
COOMe
N
MeO
O

6f


2.13
1.23
2.34
1.22
1.11
0.98
1.03
1.00
1.04
2.96
3.18
3.19
1.05
1.06
1.99
1.26
10.0 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)


190.52
168.64
168.02
158.04
156.57
138.67
138.61
133.06
129.88
128.81
128.43
126.16
120.46
113.27
110.21
79.22
77.48
77.16
76.84
60.48
55.55
53.38
52.54
44.69
37.64
29.27
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

Biological Methods: The hedgehog signaling inhibition and cell viability assay:

For assaying signal transduction through the HH pathway mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. These multipotent mesenchymal progenitor cells can differentiate into osteoblasts upon treatment with the SMO agonist Purmorphamine. During differentiation osteoblast specific genes such as alkaline phosphatase (ALK), which plays an essential role in bone formation, are highly expressed. Activity of ALK can directly be monitored by following substrate hydrolysis yielding a highly luminescent product. Inhibition of the pathway results in reduction of luminescence.[1]

The screening for small molecule inhibitors of the HH pathway was carried out in 384 well format. Shortly, 800 cells per well were seeded and allowed to grow overnight. The next day, compounds were added to a final concentration of 10 µM using the acoustic nanoliter dispenser ECHO 520. After one hour, Purmorphamine was added to a final concentration of 1.5 µM; control cells did not receive Purmorphamine. After four days, the cell culture medium was aspirated and a commercial luminogenic ALK substrate (CDP-Star, Roche) was added. After one hour, luminescence was read. To identify and exclude toxic compounds that also lead to a reduction in the luminescent signal, cell viability measurements were carried out in parallel. The cell viability assay followed the same workflow as the HH assay, except that only 200 cells per well were seeded. Cell culture medium alone served as control for the cell viability assay. For the measurement of cell viability, Cell Titer Glo reagent (Promega) which determines the cellular ATP content was used. Hits were scored as showing at least a 50% reduction in the luminescent signal in the HH assay, and a minimum of 80% cell viability. Dose-response analysis for hit compounds was done using a three-fold dilution curve starting from 30 µM. IC_{50} values were calculated using the Quattro software suite (Quattro Research GmbH).

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1. a) X. Wu, S. Ding, Q. Ding, N. S. Gray, P. G. Schultz *J. Am. Chem. Soc.* **2002**, *124*, 14520-14521; b) M. M. Beloti, L. S. Bellesini, A. L. Rosa, *Cell Biol. Int.* **2005**, *29*, 537-541; b) X. Wu,1 J. Walker, J. Zhang, S Ding, P. G. Schultz *Chem. Biol.* 2004, 11, 1229-1238; c) X.-J Li, B.-Y. Hu, S. A. Jones, Y.-S. Zhang, Y. Sha, T. Lavaute, Z.-W. Du, *Stem Cells* **2008**, *26*, 886-893; (d) S. Sinha, J. K. Chen, *Nat. Chem. Biol.* **2006**, *2*, 29-30.