Synthesis of Natural-Product-Like Scaffolds in Unprecedented Efficiency via a 12-Fold Branching Pathway

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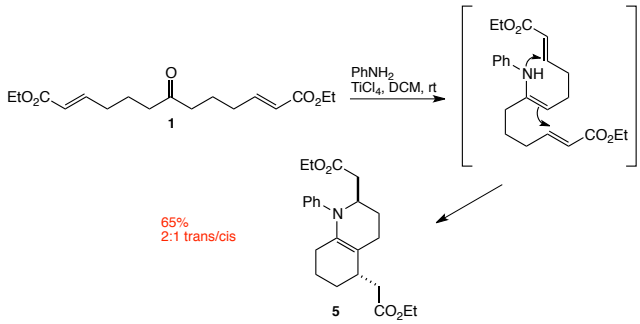
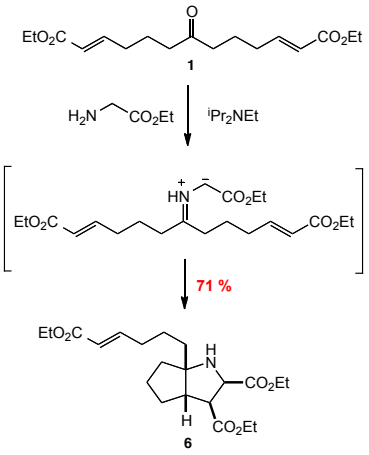
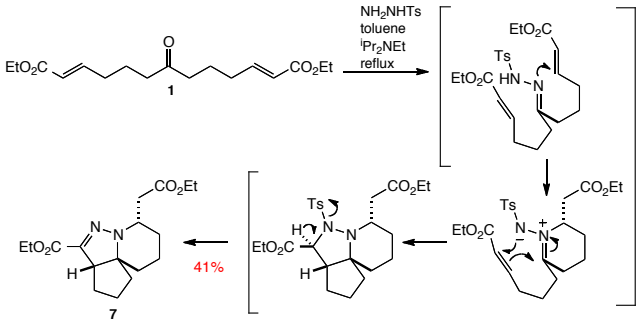
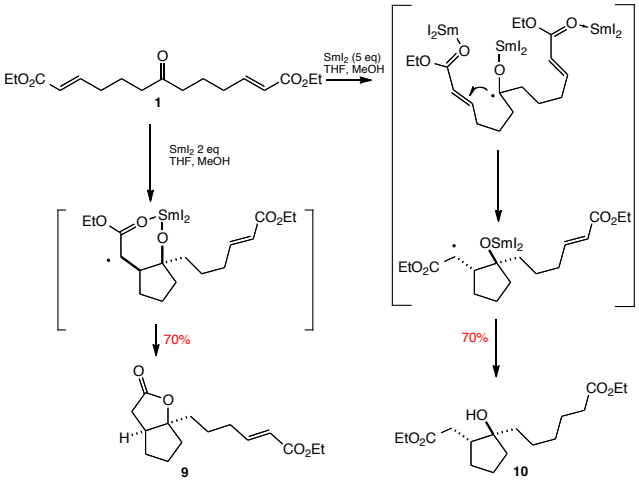
Supplementary Information

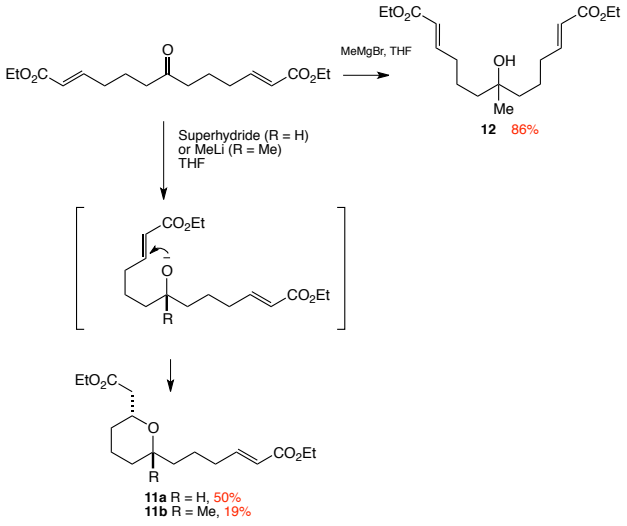
Postulated mechanisms not detailed in the manuscript

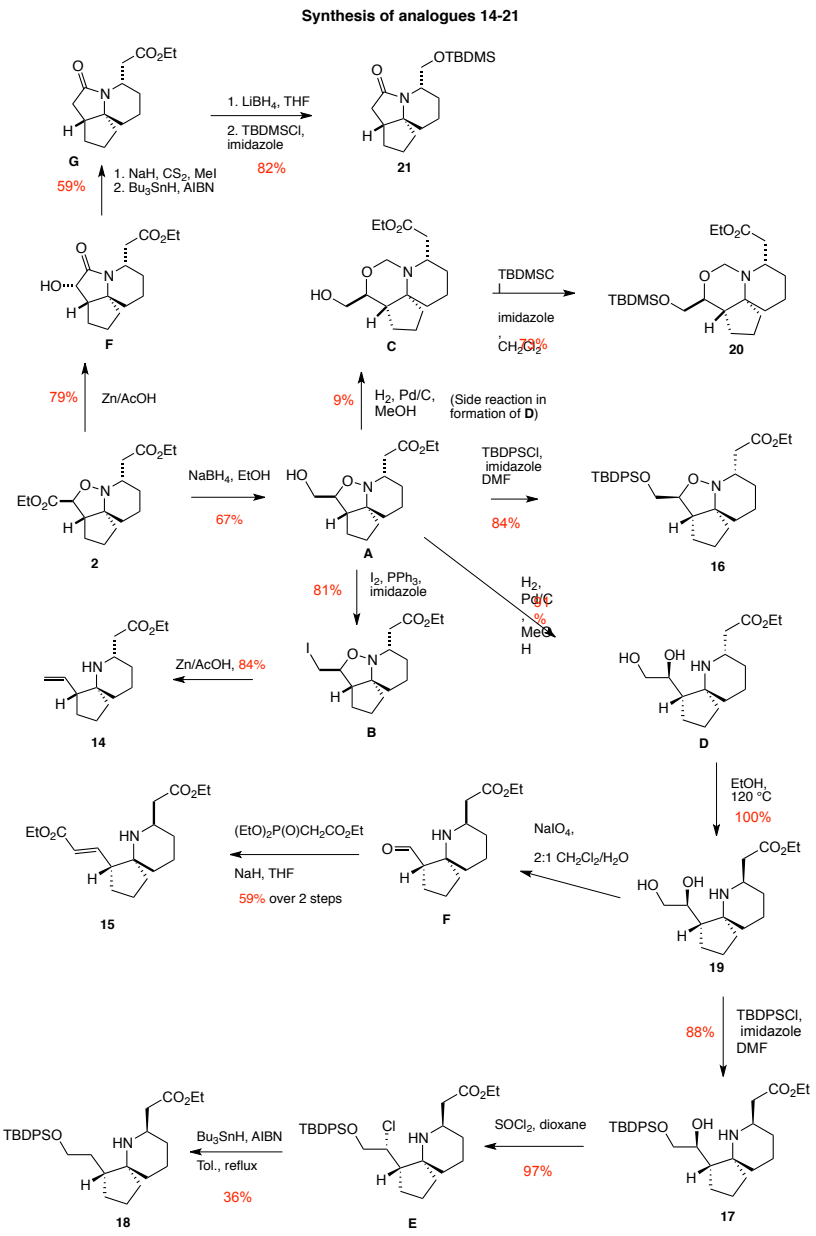










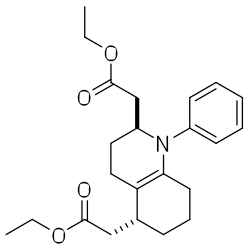


Biological screening assays

The human HL-60, THP-1 and A549 cancer cell lines (from ECACC) were cultured in RPMI 1640 medium with 10% foetal calf serum, 2mM L-glutamine, 100U/ml penicillin and 100 μg/ml streptomycin (Invitrogen). Cells were maintained in a humidified atmosphere at 37°C and 5% CO_2.

Inhibition of cancer cell proliferation was measured by MTS assay using the CellTiter 96 Aq_{ueous} One Solution Cell Proliferation Assay (Promega) and following the manufacturer's instructions. Briefly, cells (1 x 10^4/100μl for A549 or 3 x 10^4/100μl for other cells) were seeded in 96-well plates and left untreated or treated with DMSO (vehicle control) or analogues (1 x 10^{-10} to 1 x 10^{-10} M) in triplicate for 72 hr at 37°C with 5% CO_2. Following this, MTS assay reagent was added for 3 hr and absorbance measured at 490nm using a Polarstar Optima microplate reader (BMG Labtech). IC_{50} values were calculated using GraphPad Prism Version 5.0 software.

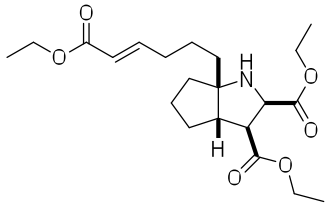
Ethyl 2-[8-(2-ethoxy-2-oxoethyl)-1-phenyl-1,2,3,4,5,6,7,8-octahydroquinolin-2-yl]acetate (5)



To a solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in dichloromethane (10 mL) at -10 °C was added titanium (IV) chloride (1M solution in dichloromethane, 0.64 mL, 0.64 mmol). The mixture was stirred at -10 °C for 30 minutes, then aniline (40.0 µL, 0.48 mmol) was added. The mixture was allowed to warm to room temperature, then heated to reflux overnight. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and filtered through a pad of celite. The filtrate was extracted with ethyl acetate (3 x 10 mL), the combined organics washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting product was purified using column chromatography on silica gel (6:1 petroleum ether / ethyl acetate) to give the title compound as a yellow oil (80.0 mg, 65%), and a 3:1 mixture of diastereomers (data for major diastereomer detailed).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24 - 7.30 (2H, m), 6.96 - 7.06 (3H, m), 4.16 – 4.23 (4H, m), 4.04 - 4.15 (1H, m), 2.77 (1H, ddd, J = 14.6, 9.6, 4.1 Hz), 2.73 - 2.81 (1H, m), 2.59 - 2.72 (2H, m), 2.27 - 2.44 (2H, m), 1.78 - 1.93 (3H, m), 1.62 - 1.74 (3H, m), 1.45 - 1.61 (3H, m), 1.31 (3H, t, *J*=7.1 Hz), 1.32 (3H, t, *J*=7.0 Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.5, 172.8, 149.2, 133.9, 128.7, 124.5, 122.5, 116.4, 60.4, 60.3, 58.0, 39.7, 38.7, 36.5, 29.7, 29.3, 28.1, 22.7, 21.0, 14.4, 14.3; *m/z* (ES) 386 (M+1, 100 %), 408 (16); HRMS: Found: 386.2335 $C_{23}H_{32}NO_4$ ($M+H^+$) Requires 386.2326; ν_{max} (thin film)/cm^{-1} 3664, 3008, 1724.

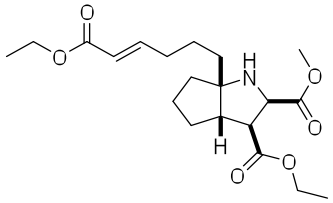
Diethyl 6a-((*E*)-5-(ethoxycarbonyl)pent-4-enyl)octahydrocyclopenta[b]pyrrole-2,3-dicarboxylate (6a)



To a solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (50.0 mg, 0.16 mmol) in toluene (1.5 mL) was added glycine ethyl ester hydrochloride (30.0 mg, 0.24 mmol) and *N,N*-di*iso*propylethylamine (80.0 µL, 0.48 mmol) and the mixture heated to reflux overnight. The solution was cooled to room temperature and the remaining solvent removed *in vacuo*. The resulting residue was purified using column chromatography on silica gel (5:1 petroleum ether / ethyl acetate then 1:1 petroleum ether / ethyl acetate) to give the title compound as colourless oil (50.0 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.94 (1H, dt, *J*=15.6, 6.8 Hz), 5.82 (1H, dt, *J*=15.6, 1.5 Hz), 4.13 - 4.22 (4H, m), 4.05 - 4.13 (2H, m), 3.98 (1H, d, *J*=6.2 Hz), 2.90 (1H, dd, *J*=6.2, 2.5 Hz), 2.35 - 2.44 (1H, m), 2.13 - 2.30 (3H, m), 1.95 - 2.04 (1H, m), 1.59 (8H, m), 1.19 - 1.31 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.2, 171.2, 166.6, 148.7, 121.7, 74.3, 62.9, 61.1, 60.7, 60.2, 55.7, 52.7, 40.2, 38.5, 33.5, 32.7, 25.4, 23.8, 14.3, 14.2, 14.2; *m/z* (ES) 396 (M+1, 100 %), 418 (20); HRMS: Found: 396.2429 $C_{21}H_{34}NO_6$ ($M+H^+$) Requires 396.2386; ν_{max} (thin film)/cm^{-1} 3305, 1717, 1654, 1095, 979.

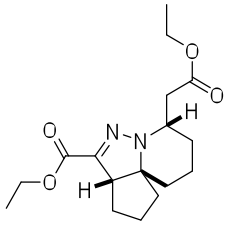
3-ethyl 2-methyl 6a-[(4E)-6-ethoxy-6-oxohex-4-en-1-yl]-octahydrocyclopenta [b]pyrrole-2,3-dicarboxylate (6b)



To a solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (50.0 mg, 0.16 mmol) in toluene (1.5 mL) was added glycine methyl ester hydrochloride (30.0 mg, 0.24 mmol) and *N,N*-di*iso*propylethylamine (80.0 µL, 0.48 mmol) and the mixture heated to reflux overnight. The solution was cooled to room temperature and the remaining solvent removed *in vacuo*. The resulting residue was purified using column chromatography on silica gel (5:1 petroleum ether / ethyl acetate then 1:1 petroleum ether / ethyl acetate) to give the title compound as a colourless oil (30.0 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.96 (1H, dt, J = 15.6, 7.0 Hz), 5.84 (1H, dt, J = 15.6, 1.5 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.12 (2H, qd, J = 7.2, 1.6 Hz), 4.01 (1H, d, J = 6.4 Hz), 3.74 (3H, s), 2.92 (1H, dd, J = 6.4, 2.3 Hz), 2.42 (1H, ddd, J = 8.5, 6.4, 2.3 Hz), 2.28 - 2.18 (2H, m), 2.05 - 1.98 (1H, m), 1.75 - 1.84 (1H, m), 1.71 - 1.39 (8H, m), 1.25 (3H, t, *J*=7.1 Hz),, 1.30 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.8, 174.1, 172.7, 60.5, 60.4, 55.9, 53.8, 45.7, 41.6, 39.8, 36.5, 29.2, 26.9, 25.8, 19.0, 14.3, 14.2; *m/z* (ES) *m/z* (ES) 382 ($M+1^+$, 100 %), 404 (13); HRMS: Found: 382.2230 $C_{20}H_{32}O_6N$ ($M+H^+$) Requires 382.2224; ν_{max} (thin film)/cm^{-1} 3305, 1717, 1654, 1095, 979

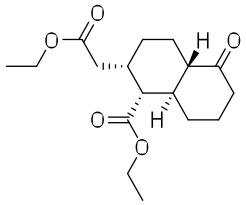
Ethyl 9-(2-ethoxy-2-oxoethyl)-7,8-diazatricyclo[6.4.0.0^{1,5}]dodec-6-ene-6-carboxylate (7)



To a stirred solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in toluene (15 mL) was added *p*-toluenesulfonyl hydrazide (70.0 mg, 0.35 mmol) and the mixture heated to reflux for 6 hours. The solvent was removed *in vacuo* and the resulting residue purified by column chromatography on silica gel (10:1 petroleum ether / ethyl acetate) to give the title compound as a yellow solid (40.0 mg, 41%). m.p 78-80 °C.

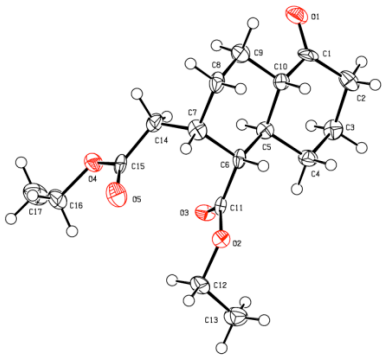
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.26 (2H, q, *J*=7.0 Hz), 4.17 (1H, q, *J*=7.2 Hz), 3.77 - 3.88 (1H, m), 3.19 (1 H, dd, *J*=9.1, 4.1 Hz), 3.07 (1 H, dd, *J*=16.2, 6.1 Hz), 2.67 (1H, dd, *J*=16.2, 7.8 Hz), 2.19 - 2.30 (1H, m), 1.44 - 2.07 (11H, m), 1.33 (3H, t, *J*=7.0 Hz), 1.28 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.7, 163.8, 138.3, 80.3, 60.5, 60.2, 55.6, 53.3, 38.3, 36.2, 33.5, 33.0, 32.8, 26.6, 21.9, 14.5, 14.2; *m/z* (ES) 345 (M+23, 52 %), 323 (13); HRMS: Found: 345.1818 $C_{17}H_{26}N_2O_4Na$ (M+Na^+) Requires 345.1785; ν_{max} (thin film)/cm^{-1} 1726, 1685.

Ethyl 2-[6-(2-ethoxy-2-oxoethyl)-9-oxobicyclo[3.3.1]nonan-2-yl]acetate (8)

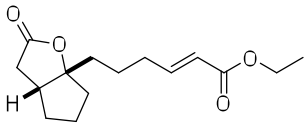


To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 26 mg, 0.64 mmol) in tetrahydrofuran (5 mL) at 0 °C was added (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol). The mixture was stirred at 0 °C for 3 hours, then warmed to room temperature and stirred for a further 72 hours. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated. The resulting residue was recrystallized from light petroleum to give the title compound as white needles (70.0 mg, 70%). m.p. 62-64 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.07 - 4.23 (4H, m), 2.26 - 2.55 (5H, m), 1.37 - 2.18 (11H, m), 1.22 - 1.33 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.8, 174.1, 172.7, 60.5, 60.4, 55.9, 53.8, 45.7, 41.6, 39.8, 36.5, 29.2, 26.9, 25.8, 19.0, 14.3, 14.2; *m/z* (ES) 333 ($M+23^+$, 100 %), 328 (28), 311 (26); HRMS: Found: 333.1685 $C_{17}H_{26}O_5Na$ ($M+Na^+$) Requires 333.1672; ν_{max} (thin film)/cm^{-1} 1725.



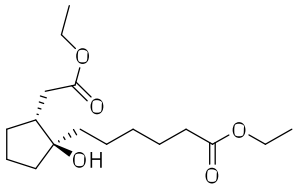
(*E*)-Ethyl 6-(2-oxohexahydro-2H-cyclopenta[b]furan-6a-yl)hex-2-enoate (9)



To a stirred solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in tetrahydrofuran (12 mL) was added methanol (4 mL). The mixture was cooled to 0 °C and argon was bubbled through for 15 minutes. Samarium diiodide (0.1 M in THF, 6.40 mL, 0.64 mmol) was added dropwise *via* a cannula and the mixture was stirred at 0 °C for 30 minutes then warmed to room temperature and stirred for a further 30 minutes. The reaction was quenched with HCl (1 M, 10 mL) and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo.* The resulting residue was purified using column chromatography on silica gel (6:1 petroleum ether / ethyl acetate) to give the title compound as a yellow oil (60.0 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.92 (1H, dt, *J*=15.5, 7.0 Hz), 5.82 (1H, d, *J*=15.5 Hz), 4.19 (2H, q, *J*=7.2 Hz), 2.86 (1H, dd, *J*=18.5, 10.2 Hz), 2.46 - 2.55 (1H, m), 2.30 (1H, dd, *J*=18.5, 2.9 Hz), 2.24 (2H, q, *J*=7.0 Hz), 2.01 - 2.11 (1H, m), 1.90 (1H, ddd, *J*=17.0, 12.9, 8.5 Hz), 1.49 - 1.80 (8H, m), 1.29 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.2, 166.6, 148.1, 122.0, 97.7, 60.3, 42.3, 38.9, 38.0, 36.9, 34.4, 32.1, 23.9, 22.9, 14.3; *m/z* (ES) 289 (M+23, 100 %), 267 (21), 284 (13); HRMS: Found: 289.1408 $C_{15}H_{22}O_4Na$ ($M+Na^+$) Requires 289.1416; ν_{max} (thin film)/cm^{-1} 1759, 1710, 1654, 1191, 980.

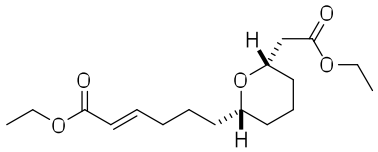
Ethyl 6-((1S*,2R*)-2-(2-ethoxy-2-oxoethyl)-1-hydroxycyclopentyl)hexanoate (10)



To a stirred solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in tetrahydrofuran (12 mL) was added methanol (4 mL). The mixture was cooled to 0 °C and argon was bubbled through for 15 minutes. Samarium diiodide (0.1 M in THF, 16 mL, 1.6 mmol) was added dropwise *via* a cannula and the mixture was stirred at 0 °C for 30 minutes then warmed to room temperature and stirred for a further 30 minutes. The reaction was quenched with HCl (1 M, 10 mL) and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel (6:1 petroleum ether / ethyl acetate) to give the title compound as a yellow oil (70.0 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.14 (4H, observed quin, *J*=7.0 Hz), 2.43 (1H, dd, *J*=13.6, 5.3 Hz), 2.18 - 2.35 (4H, m), 1.93 - 2.05 (1H, m), 1.48 - 1.81 (8H, m), 1.32 - 1.42 (5H, m), 1.27 (3H, t, *J*=7.0 Hz), 1.26 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1, 173.9, 81.7, 60.7, 60.2, 47.0, 37.3, 35.4, 35.3, 34.4, 30.2, 29.9, 25.0, 23.3, 20.8, 14.3, 14.2; *m/z* (ES) 337 (M+23, 100 %), 315 (18); HRMS: Found: 337.1996 $C_{17}H_{30}O_5Na$ ($M+Na^+$) Requires 337.1991; ν_{max} (thin film)/cm^{-1} 3602, 1724.

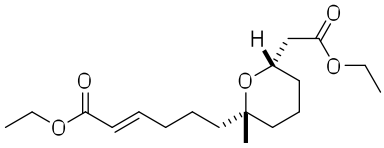
(*E*)-ethyl 6-((2*S,6*S**)-6-(2-ethoxy-2-oxoethyl)tetrahydro-2H-pyran-2-yl)hex-2-enoate (11)**



To a stirred solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (50.0 mg, 0.16 mmol) in tetrahydrofuran (3 mL) at 0 °C was added SuperHydride® (1 M, 0.18 mL, 0.18 mmol). The solution was warmed to room temperature and stirred overnight. The reaction was quenched with acetone (2 mL) and the solvent removed *in vacuo.* Water (3 mL) and ethyl acetate (3 mL) were added to the resulting oil and the aqueous phase extracted with ethyl acetate (2 x 5 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo.* The resulting residue was purified using column chromatography on silica gel (6:1 petroleum ether / ethyl acetate) giving rise to the title compound as a colourless oil (25.0 mg, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.96 (1H, dt, *J*=15.6, 6.9 Hz), 5.82 (1H, dt, *J*=15.6, 1.6 Hz), 4.19 (2H, q, *J*=7.2 Hz), 4.15 (2H, q, *J*=7.0 Hz), 3.76 (1H, dddd, *J*=11.0, 7.9, 5.5, 2.1 Hz), 3.19 - 3.38 (1H, m), 2.52 (1H, dd, *J*=14.8, 8.1 Hz), 2.39 (1H, dd, *J*=14.8, 5.5 Hz), 2.16 - 2.25 (2H, m), 1.43 - 1.69 (8H, m), 1.24 - 1.38 (2H, m), 1.27 (3H, t, *J*=7.2 Hz), 1.30 (3H, t, *J*=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.6, 164.7, 149.3, 121.4, 77.7, 74.6, 60.4, 60.2, 41.9, 35.7, 32.1, 31.3, 31.2, 24.1, 23.5, 14.3; *m/z* (ES) 335 (M+23, 100 %), 313 (27), 330 (12); HRMS: Found: 335.1853 $C_{17}H_{28}O_5Na$ ($M+Na^+$) Requires 335.1834; ν_{max} (thin film)/cm^{-1} 1718, 1191, 1653, 1191, 980.

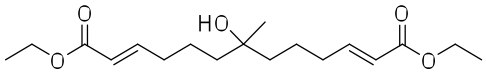
(*E*)-Ethyl 6-(6-((ethoxycarbonyl)methyl)-tetrahydro-2-methyl-2H-pyran-2-yl)hex-2-enoate



To a stirred solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate 100 mg, 0.32 mmol) in toluene (5 mL) at 0 °C was added methyl lithium (1.4 M, 0.27 mL, 0.38 mmol) dropwise and the reaction was stirred at 0 °C for 3 hours. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel (3:1 petroleum ether / ethyl acetate) to give the title compound as colourless oil (20.0 g, 19%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.99 (1H, dt, *J* = 15.6, 7.0 Hz), 5.84 (1H, ddt, *J* = 15.6, 10.5, 1.5 Hz), 4.26-4.07 (4H, m), 4.04-3.84 (1H, m), 2.51-2.30 (2H, m), 2.28-2.13 (2H, m), 1.74-1.34 (10H, m), 1.29 (6H, dtd, *J*=11.1, 7.2, 0.7 Hz), 1.13 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.7, 166.8, 146.3, 121.3, 73.6, 67.3, 60.3, 60.2, 44.1, 42.2, 34.4, 32.7, 31.4, 31.00, 21.5, 19.7, 14.3, 14.3; *m/z* (ES) 249 ($M+23^+$, 100 %), HRMS: Found: 349.1966 $C_{18}H_{30}O_5Na$ ($M+Na^+$) Requires 349.1985; ν_{max} (thin film)/cm^{-1} 1715, 1653, 1191, 980.

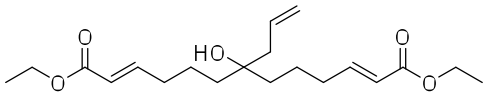
1,13-Diethyl (2*E*,11*E*)-7-hydroxy-7-methyltrideca-2,11-dienedioate (12a)



A solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in tetrahydrofuran (3 mL) was cooled to -78 °C and methyl magnesium bromide (1.1 M solution in tetrahydrofuran, 0.32 mL, 0.35 mmol) was added. The reaction was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as a colourless oil (90.0 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.94 (2H, dt, *J*=15.6, 6.8 Hz), 5.81 (2H, dt, *J*=15.6, 1.5 Hz), 4.17 (4H, q, *J*=7.2 Hz), 2.20 (4H, q, *J*=6.8 Hz), 1.53 – 1.41 (8H, m), 1.27 (6H, t, *J*=7.2 Hz), 1.15 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.6, 148.8, 121.6, 72.3, 60.2, 41.4, 32.6, 26.8, 22.4, 14.2; *m/z* (ES) 349 (M+23, 100 %); HRMS: Found: 349.1994 $C_{18}H_{30}O_5Na$ ($M+Na^+$) Requires 349.1985; ν_{max} (thin film)/cm^{-1} 3494, 1707, 1654, 979.

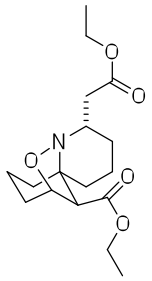
(2*E*,11*E*)-diethyl 7-allyl-7-hydroxytrideca-2,11-dienedioate (12b)



A solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in tetrahydrofuran (3 mL) was cooled to -78 °C and allyl magnesium chloride (1.5 M solution in tetrahydrofuran, 0.23 mL, 0.35 mmol) was added. The reaction was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting product was purified using column chromatography on silica gel (3:1 petroleum ether / ethyl acetate) to give the title compound as a colourless oil (20.0 mg, 20%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.96 (2H, dt, *J*=15.7, 6.9 Hz), 5.69 - 5.91 (3H, m), 5.04 - 5.23 (2H, m), 4.20 (4H, q, *J*=7.2 Hz), 2.13 - 2.28 (6H, m), 1.38 - 1.58 (8H, m), 1.30 (6H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.7, 148.7, 133.4, 121.7, 119.10, 73.6, 60.2, 43.7, 38.6, 32.6, 22.1, 14.3; *m/z* (ES) 375 (M+23, 100 %), 370 (9), 353 (4); HRMS: Found: 375.2159 $C_{20}H_{32}O_5Na$ ($M+Na^+$) Requires 375.2147; ν_{max} (thin film)/cm^{-1} 3603, 3079, 1710, 1654, 983.

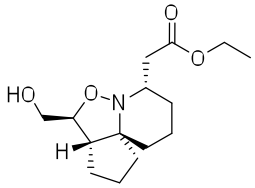
Ethyl (5*S*)-5-(2-ethoxy-2-oxoethyl)-7-oxa-6- azatricyclo[6.3.1.0^{1,6}]dodecane-12-carboxylate (13)



To a solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (100 mg, 0.32 mmol) in anhydrous methanol (5 mL) was added hydroxylamine hydrochloride (24.0 mg, 0.35 mmol) and sodium acetate (80.0 mg, 0.96 mmol) and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue taken up in dichloromethane (10 mL) and filtered. The solvent was removed and the resulting oil taken up in toluene (3 mL) and irradiated in the microwave at 140 °C for 2 hours. The solvent was removed *in vacuo* and the resulting product purified using column chromatography on silica gel (3:1 petroleum ether / ethyl acetate) to give the title compound as a colourless oil (40 mg, 38%).

^{1}H NMR (270 MHz, C_6D_6, 70 °C) δ_H 4.06 (1H, d, *J*=5.8 Hz), 3.98 (2H q, *J*=7.1 Hz), 3.96 (2H, q, *J*=7.1, 1.2 Hz), 3.42 (1H, dddd, *J*=11.4, 7.6, 6.3, 3.7 Hz), 2.96 (1H, dd, *J*=15.6, 6.2 Hz), 2.42 - 2.60 (1H, m), 2.48 (1H, dd, *J*=15.6, 7.6 Hz), 1.66 - 1.94 (3H, m), 1.34 - 1.66 (6H, m), 1.02 - 1.32 (3H m), 0.98 (3H, t, *J*=7.0 Hz), 0.95 (3H, t, *J*=7.1 Hz); ^{13}C NMR (67.5 MHz, C_6D_6, 70 °C) δ_C 171.3, 170.5, 81.9, 74.4, 60.6, 60.2, 59.6, 55.4, 39.8, 33.2, 31.1, 30.8, 26.2, 25.4 and 21.7, 14.0, 13.8; *m/z* (ES) 348 (M+23, 100%),326 (20); HRMS: Found:348.1777 $C_{17}H_{27}NO_5Na$ (M+Na^+) Requires 348.1781; ν_{max} (thin film)/cm^{-1} 1727.

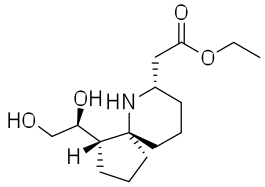
Ethyl 2-[(3a*S,4*S**,7*S**,10a*S**)-4-hydroxymethyloctahydrocyclopenta[3,4]-isoxazolo[2,3a]pyridin-7-yl]acetate (A)**



A solution of tricycle **2** (920 mg, 2.83 mmol) in anhydrous ethanol (40 mL) was cooled to 0 ºC and sodium borohydride (332 mg, 8.77 mmol) was added in one portion. The reaction mixture was warmed to room temperature and stirred for 48 h. Acetone (40 mL) was added and the reaction mixture was stirred for another hour before the solvent was evaporated *in vacuo*. The residue was dissolved in water (40 mL) and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo*. The yellow residue was purified by column chromatography on silica gel (2:1 petroleum ether / ethyl acetate) to afford the title compound as a pale yellow oil (488.0 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.14 (2H, q, *J* 7.2 Hz), 3.80 (1H, dd, *J* 11.3, 3.7 Hz), 3.74-3.62 (1H, m), 3.57 (1H, dd, *J* 11.3, 7 Hz), 3.29-3.20 (1H, m), 2.74-2.62 (2H, m), 2.27 (1H, dd, *J* 14.9, 3.8 Hz), 2.11-1.34 (12H, m), 1.27 (3H, t, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.1, 88.1, 76.6, 62.0, 61.9, 61.0, 45.5, 41.9, 37.7, 31.7, 31.0, 29.3, 26.5, 20.3, 14.0; *m/z* (ES) 306 (M+23, 100%), 284 (39), 589 (16); HMRS: Found: 306.1676 $C_{15}H_{26}NNaO_4$ ($M+Na^+$) Requires 306.1676; ν_{max} (solution cell)/cm^{-1} 3445, 1709, 1242, 1172.

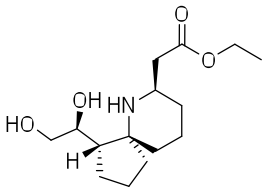
Ethyl 2-[(1*S,5*S**,7*S**)-1-[(1*S**)-1',2'-dihydroxyethyl]-6-azaspiro[4.5]dec-7-yl]acetate (D)**



To a solution of alcohol **A** (516 mg, 1.76 mmol) in anhydrous methanol (45 mL) was added palladium on activated carbon (516 mg, 100 wt %). The mixture was hydrogenated at room temperature under atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to afford the title compound as a white solid (468.0 mg, 91 %). m.p. 74-80 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.16 (2H, q, *J* 7.1 Hz), 3.74-3.66 (2H, m), 3.51-3.44 (1H, m), 3.31-3.19 (1H, m), 2.38 (2H, d, *J* 6.0 Hz), 2.18-2.08 (1H, m), 1.89-0.98 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2, 74.0, 65.2, 64.6, 60.6, 51.6, 50.0, 40.9, 38.9, 37.0, 31.2, 26.6, 20.1, 19.6, 14.1; *m/z* (ES) 286 (M+1, 100%), 308 (5); HMRS: Found: 286.2004 $C_{15}H_{28}NO_4$ ($M+H^+$) Requires 286.2013; ν_{max} (solution cell)/cm^{-1} 3312, 1728, 1294, 1192.

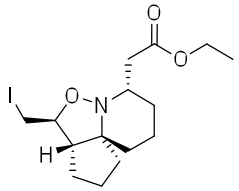
Ethyl 2-[(1*S,5*S**,7*R**)-1-[(1*S**)-1',2'-dihydroxyethyl]-6-azaspiro[4.5]dec-7-yl]acetate (19)**



A solution of diol **D** (343 mg, 1.20 mmol) in ethanol (16 mL) was irradiated in the microwave reactor at 120 ºC for 10 h. The reaction mixture was concentrated *in vacuo* to afford the title compound as a light brown solid (343.0 mg, 100%). m.p. 46-49 °C (Found: C, 62.90; H, 9.44; N, 4.56. $C_{15}H_{27}NO_4$ Requires C, 63.13; H, 9.54; N, 4.91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.15 (2H, q, *J* 7.2 Hz), 3.76-3.68 (2H, m), 3.50 (1H, dd, *J* 11.4, 6.4 Hz), 3.08 (1H, m), 2.42 (1H, dd, *J* 16.6, 3.4 Hz), 2.29 (1H, dd, *J* 16.6, 9.0 Hz), 2.03-1.95 (1H, m), 1.78-1.38 (12H, m), 1.26 (3H, t, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 172.5, 74.1, 65.8, 63.9, 60.5, 51.2, 50.2, 41.4, 38.0, 31.9, 29.1, 24.5, 22.1, 20.4, 14.2; *m/z* (ES) 286 (M+1, 100%), 270 (27); HMRS: Found: 286.2025 $C_{15}H_{28}NO_4$ ($M+H^+$) Requires 286.2013; ν_{max} (solution cell)/cm^{-1} 3300, 1721, 1294, 1180.

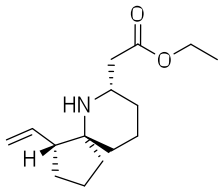
Ethyl 2-[(3a*S,4*S**,7*S**,10a*S**)-4-iodomethyloctahydrocyclopenta[3,4]-isoxazolo[2,3a]pyridin-7-yl]acetate (B)**



A solution of triphenylphosphine (739 mg, 2.81 mmol) and imidazole (192 mg, 2.80 mmol) in a 3:1 mixture of diethyl ether-acetonitrile (9 mL) was cooled to 0 °C. Iodine (716 mg, 2.80 mmol) was added in one portion and the resulting yellow suspension was stirred for 20 min at room temperature and then was cooled to 0 °C. A solution of alcohol **A** (400 mg, 1.41 mmol) in a 3:1 mixture of diethyl ether-acetonitrile (9 mL) was added. The resulting mixture was stirred overnight at room temperature, filtered through a pad of celite and washed with ethyl acetate. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (5:1 petroleum ether / ethyl acetate) to afford the title compound as white crystals (445.0 mg, 81%). m.p. 44-45 °C (Found: C, 46.00; H, 6.14; N, 3.48. $C_{15}H_{24}INO_3$ Requires C, 45.81; H, 6.15; N, 3.56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.13 (2H, q, *J* 7.2 Hz), 3.97 (1H, ddd, *J* 9.8, 6.9, 4.9 Hz), 3.46 (1H, dd, *J* 9.8, 4.9 Hz), 3.35 (1H, t, *J* 9.8 Hz), 3.10 (1H, ddd, *J* 15.2, 8.0, 3.5 Hz), 2.94 (1H, dd, *J* 15.2, 4.2 Hz), 2.51 (1H, d, *J* 6.4 Hz), 2.27 (1H, dd, *J* 15.3, 8.3 Hz), 2.05-1.40 (12H, m), 1.27 (3H, t, *J* 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 172.4, 85.8, 77.8, 62.6, 60.4, 53.9, 40.1, 38.8, 32.8, 30.1, 29.7, 21.2, 20.2, 14.3, 9.3; *m/z* (ES) 394 (M+1, 100%), 416 (81); HMRS: Found: 394.0861 $C_{15}H_{25}{}^{127}INO_3$ ($M+H^+$) Requires 394.0874; ν_{max} (solution cell)/cm^{-1} 2942, 1724, 1169.

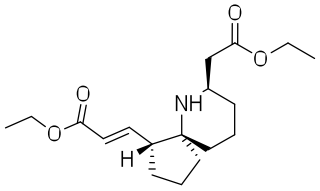
Ethyl 2-[(1*R,5*S**,7*S**)-1-vinyl-6-azaspiro[4.5]decan-7-yl)]acetate (14)**



To a stirred solution of the iodide **B** (108 mg, 0.27 mmol) in acetic acid (5 mL) was added zinc dust (179 mg, 2.74 mmol). The resulting suspension was stirred at room temperature for 2 h, and then stirred at 70 °C for 1 h. The reaction mixture was quenched by adding dichloromethane (25 mL) and solid sodium hydrogen carbonate. The mixture was filtered, washed with saturated aqueous sodium hydrogen carbonate (2 × 30 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the title compound as a yellow oil (66.0 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.87 (1H, ddd, *J* 16.0, 10.0, 9.4 Hz), 5.12 (1H, dd, *J* 16.0, 2.0 Hz), 5.08 (1H, dd, *J* 10.0, 2.0 Hz), 4.10 (2H, q, *J* 7.2 Hz), 3.07 (1H, m), 2.75 (1H, t, *J* 8.2 Hz), 2.32 (2H, d, *J* 6.4 Hz), 1.95-1.16 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c 172.0, 138.8, 115.3, 64.4, 60.3, 49.0, 45.9, 41.9, 39.7, 34.5, 31.8, 29.8, 20.9, 19.3, 14.2; *m/z* (ES) 252 (M+1, 100%); HMRS: Found: 252.1963 $C_{15}H_{26}NO_2$ ($M+H^+$) Requires 252.1958; ν_{max} (solution cell)/cm^{-1} 3078, 2936, 1725, 1636, 917.

(2*E*)-Ethyl-3-[(1*R,5*S**,7*R**)-7-(2-ethoxy-2-oxoethyl)-6-azaspiro[4.5]decan-1-yl]acrylate (15)**

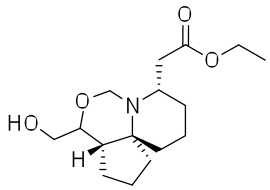


An anhydrous solution of diol **19** (260 mg, 0.91 mmol) in a 7:3 mixture of dichloromethane-water (52 mL) was cooled to 0 °C and then sodium periodate (390 mg, 1.82 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 80 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The resulting aldehyde was used directly with no further purification.

Sodium hydride (60% dispersion in mineral oil, 54 mg, 1.36 mmol) was added at room temperature to a stirred solution of triethylphosphonoacetate (0.27 mL, 1.36 mmol) in dry tetrahydrofuran (20 mL). The reaction mixture was stirred for 30 min and then cooled to 0 °C. A solution of the crude aldehyde in THF (10 mL) was added via a syringe. The reaction mixture was slowly warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride (50 mL) was added and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and evaporated *in vacuo.* Purification of the residue by column chromatography on silica gel (2:1 petroleum ether / ethyl acetate) afforded the title compound as a yellow oil (173.0 mg, 59 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.07 (1H, dd, *J* 15.7, 8.4 Hz), 5.81 (1H, d, *J* 15.7 Hz), 4.20 (2H, q, *J* 7.2 Hz), 4.12 (2H, q, *J* 7.2 Hz), 3.05 (1H, m), 2.28 (3H, m), 1.89-1.38 and 1.1-0.9 (12H, m), 1.31 (3H, t, *J* 7.0 Hz), 1.26 (3H, t, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 172.5, 166.6, 149.7, 122.0, 65.0, 60.2, 60.1, 53.8, 48.5, 41.8, 35.0, 33.7, 32.5, 28.9, 22.4, 21.7, 14.3, 14.2; *m/z* (ES) 324 (M+1,100%); HMRS: Found: 324.2155 $C_{18}H_{30}NO_4$ ($M+H^+$) Requires 324.2169; ν_{max} (solution cell)/cm^{-1} 3011, 1716, 1650, 1262, 1186, 1036.

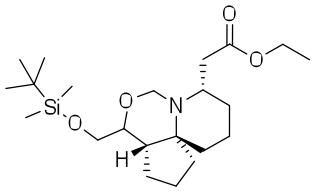
Ethyl 2-[((3a*S,8*S**,11a*S**)-4-(hydroxymethyl)decahydrocyclopenta[d]pyrido [1,2-c][1,3]oxazin-8-yl)acetate (C)**



To a solution of alcohol **A** (485 mg, 1.76 mmol) in anhydrous methanol (100 mL) was added palladium on activated carbon (514 mg, 106 wt %). The mixture was hydrogenated at room temperature under atmospheric pressure for 48 h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. Purification of the residue by column chromatography on alumina (ethyl acetate then 99:1 to 98:1 dichloromethane / methanol) afforded the title compound as colourless oil (44.0 mg, 9%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.50 (1H, d, *J* 9.9 Hz), 4.38 (1H, d, *J* 9.9 Hz), 4.10 (2H, q, *J* 7.1 Hz), 3.75-3.60 (1H, m), 3.55-3.42 (2H, m), 3.34-3.22 (1H, m), 2.40-2.25 (2H, m), 2.10 and 1.89-1.32 (13H, m), 1.23 (3H, t, *J* 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 172.4, 78.5, 77.1, 64.4, 63.7, 60.4, 52.7, 40.7, 37.8, 36.1, 30.7, 28.1, 23.7, 19.9, 17.6, 14.2; *m/z* (ES) 298 (M+1, 100%); HMRS: Found: 298.2008 $C_{16}H_{27}NO_4$ ($M+H^+$) Requires 298.2013; ν_{max} (solution cell)/cm^{-1} 3431, 2932, 1731, 1160.

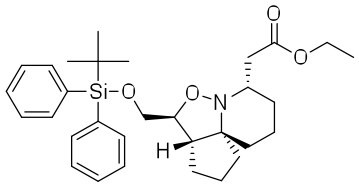
Ethyl 2-((3a*S,8*S**,11a*S**)-4-(((tert-butyldimethylsilyl)oxy)methyl)decahydro-cyclopenta[d]pyrido[1,2-c][1,3]oxazin-8-yl)acetate (20)**



To a stirred solution of alcohol **C** (44 mg, 0.15 mmol) in dry dichloromethane (5 mL), was added imidazole (20 mg, 0.30 mmol). The reaction mixture was cooled to 0 °C and *tert*-butylchlorodimethylsilane (45 mg, 0.30 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. Water (10 mL) was added and the aqueous phase was extracted with dichloromethane (2 × 10 mL). Organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography over silica gel (ethyl acetate) afforded the title compound as colourless oil (45.0 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.50 (1H, d, *J* 9.9 Hz), 4.38 (1H, d, *J* 9.9 Hz), 4.10 (2H, q, *J* 7.1 Hz), 3.75-3.60 (2H, m), 3.49 (1H, dd, J 9.1, 5.1 Hz), 3.26 (1H, ddd, *J* 10.4, 5.4, 3.2 Hz), 2.50 (1H, m), 2.30 (1H, m), 2.18-2.04 and 1.90-1.28 (13H, m), 1.23 (3H, t, *J* 7.1 Hz), 0.89 (9H, m), 0.06 (6H, d, *J* 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c 172.4, 79.3, 77.0, 66.1, 63.9, 60.3, 52.6, 41.1, 37.8, 36.2, 30.6, 28.5, 23.9, 19.9, 17.7, 26.0, 18.5, 14.2, -5.1; *m/z* (ES) 412 (M+1, 100%), 434 (M+23, 5); HMRS: Found: 434.2680 $C_{22}H_{41}NaNO_4Si$ ($M+H^+$) Requires 434.2697; ν_{max} (solution cell)/cm^{-1} 2930, 1735, 1251, 1080.

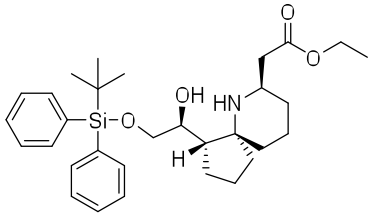
Ethyl 2-[(1*S,5*S**,6*S**,9*S**)-6-([(*tert*-butyldiphenylsilyl)oxy]methyl)-7-oxa-8-azatricyclo[6.4.0.0^{1,5}] dodecan-9-yl]acetate (16)**



To a solution of **A** (1.0 g, 3.53 mmol) in tetrahydrofuran (50 mL), was added a solution of imidazole (240 mg, 7.06 mmol) and *tert*-butyldiphenylchlorosilane (970 mg, 3.88 mmol) in tetrahydrofuran (50 mL) was added and the resulting solution was stirred for 72 h. The reaction was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (1:0 to 2:1 hexane / ethyl acetate) afforded the title compound as a clear oil (1.54 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (4H, t, *J* 7.9 Hz), 7.54-7.31 (6H, m), 4.03 (2H, q, *J* 7.2 Hz), 3.95-3.84 (1H, m), 3.82-3.73 (2H, m), 3.00 (1H, ddt, *J* 11.2, 8.8, 3.8 Hz), 2.89 (1H, dd, *J* 15.0, 3.8 Hz), 2.53-2.47 (1H, m), 2.25 (1H, dd, *J* 15.0, 8.8 Hz), 2.07-1.20 (12H, m), 1.16 (3H, t, *J* 7.2 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2 , 135.7, 134.8, 129.7, 127.7, 85.9, 76.4, 66.7, 61.1, 60.0, 51.3, 40.2, 38.6, 31.8, 28.9, 28.2, 26.9, 26.6, 21.6, 19.3, 14.2; HMRS: Found: 522.3024 $C_{31}H_{44}NO_4Si$ ($M+H^+$) Requires 522.3034; ν_{max} (thin film)/cm^{-1} 2957, 1731.

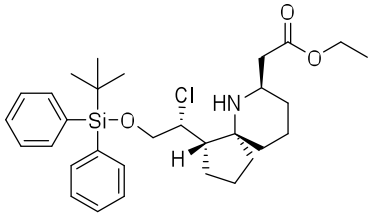
Ethyl 2-[(1*S,5*S**,7*R**)-1-[(1*S**)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-hydroxy-ethyl]-6-azaspiro[4.5] decan-7-yl]acetate (17)**



To a stirring solution of imidazole (25 mg, 0.36 mmol) in tetrahydrofuran (1.5 mL) was added *tert*-butyldiphenylchlorosilane (49 mg, 0.18 mmol) and the resulting solution was stirred for 15 minutes and then cooled to 0 °C. A solution of **19** (51 mg, 0.18 mmol) in tetrahydrofuran (1.5 mL) was added and the resulting reaction mixture was stirred warming to rt for 96 h. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (1:0 to 20:1 dichloromethane / methanol) gave the title compound as a clear oil (83.0 mg, 88%). (Found: C, 71.13; H 8.54; N, 2.75. $C_{31}H_{45}NO_4Si$ Requires C, 71.09; H, 8.66; N, 2.67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76-7.69 (4H, m), 7.46-7.37 (6H, m), 4.16 (2H, q, *J* 7.0 Hz), 3.82-3.59 (3H, m), 3.13-3.04 (1H, m), 2.40 (1H, dd, *J* 16.6, 3.8 Hz), 2.32 (1H, dd, *J* 16.6, 9.0 Hz), 2.18-2.06 (1H, m), 1.94-1.32 (12H, m), 1.29 (3H, t, *J* 7.0 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.7, 135.7, 133.9, 129.6, 127.7, 74.8, 67.7, 63.9, 60.5, 51.5, 48.5, 41.6, 37.9, 37.4, 32.2, 29.4, 26.9, 24.5, 22.4, 19.4, 14.3; HMRS: Found: 524.3172 $C_{31}H_{46}NO_4Si$ ($M+H^+$) Requires 524.3191; ν_{max} (thin film)/cm^{-1} 3301, 3072, 1724.

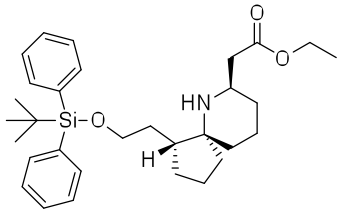
Ethyl 2-[(1*S,5*S**,7*R**)-1-[(1*S**)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-chloro-ethyl]-6-azaspiro[4.5]decan-7-yl]acetate (E)**



To a stirring solution of **17** (475 mg, 0.907 mmol) in 1,4-dioxane (20 mL) was added thionyl chloride (0.13 mL, 1.81 mmol). The solution was stirred for 18 h, whereupon a quench of saturated aqueous sodium hydrogen carbonate (30 mL) was added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried over potassium carbonate and sodium sulfate and the solvent was removed *in vacuo* to yield the title compound as a pale orange oil (476.0 mg, 97%) which was deemed sufficiently pure to carry forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71-7.65 (4H, m), 7.47-7.36 (6H, m), 4.39 (1H, ddd, *J* 7.2, 5.7, 3.5 Hz), 4.13 (2H, q, *J* 7.0 Hz), 3.84 (1H, dd, *J* 10.4, 5.7 Hz), 3.76 (1H, dd, *J* 10.4, 7.2 Hz), 3.06 (1H, ddt, *J* 8.9, 4.7, 2.3 Hz), 2.34 (1H, dd, *J* 15.7, 4.7 Hz), 2.26 (1H, dd, *J* 15.7, 8.9 Hz), 2.12 (1H, td, *J* 8.4, 3.5 Hz), 1.93-1.32 (12H, m), 1.26 (3H, t, *J* 7.0 Hz), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.6, 135.7, 133.4, 129.7, 127.7, 66.9, 63.6, 63.2, 60.3, 50.6, 48.8, 42.2, 36.5, 36.1, 32.2, 26.9, 26.4, 22.9, 22.2, 19.3, 14.3; HMRS: Found: 542.2857 $C_{31}H_{45}{}^{35}ClNO_3Si$ ($M+H^+$) Requires 542.2852; ν_{max} (thin film)/cm^{-1} 2933, 1724.

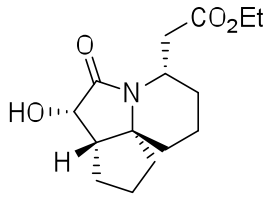
Ethyl 2-[(1*R,5*S**,7*R**)-1-(2-[(*tert*-butyldiphenylsilyl)oxy]ethyl)-6-azaspiro-[4.5]decan-7-yl] acetate (18)**



A solution of **E** (592 mg, 1.092 mmol) in degassed toluene (10 mL) was heated to 90 °C. A solution of azobis*iso*butyronitrile (89 mg, 0.546 mmol) and tributyltin hydride (0.59 mL, 2.184 mmol) in degassed toluene (5 mL) was added drop-wise over 4 h. The reaction mixture was heated to reflux for 18 h, whereupon a quench of saturated aqueous sodium hydrogen carbonate (30 mL) was added. The resulting solution was extracted with hexane (3 x 30 mL), the combined organic were dried over sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography on alumina (100:1 hexane / ethyl acetate) yielded the product as a pale yellow oil (197.0 mg, 36%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79-7.60 (4H, m), 7.52-7.33 (6H, m), 4.14 (2H, q, *J* 7.2 Hz), 3.76 (1H, dq, *J* 7.4, 4.8 Hz), 3.65 (1H, dd, *J* 14.6, 7.4 Hz), 3.08 (1H, ddt, *J* 8.3, 5.1, 2.6 Hz), 2.37 (1H, dd, *J* 15.5, 5.1 Hz), 2.30 (1H, dd, *J* 15.5, 8.3 Hz), 2.19-1.31 (14H, m), 1.27 (3H, t, *J* 7.2 Hz), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.6, 135.6, 134.2, 129.5, 127.6, 63.6, 63.0, 60.2, 48.3, 46.6, 42.1, 34.9, 34.0, 32.9, 31.8, 29.6, 26.9, 22.5, 21.4, 19.2, 14.3; HMRS: Found: 508.3218 $C_{31}H_{46}NO_3Si$ ($M+H^+$) Requires 508.3241; ν_{max} (solution cell)/cm^{-1} 2933, 2861, 1723, 1110, 909.

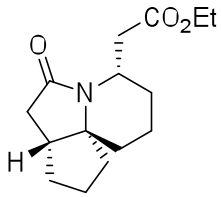
Ethyl 2-((4*S,7*S**,7a*S**,10a*S**)-7-hydroxy-6oxodecahydrocyclopenta[i]indolizin-4-yl)acetate (F)**



To a stirred solution of tricyclic diester **2** (1.17 g, 3.6 mmol) in 50% aqueous acetic acid (100 mL) was added activated zinc metal (3.5 g, 54 mmol) and the solution was heated at 70 °C for 24 hours. The solvent was then evaporated and the resulting slurry was taken up in dichloromethane (75 mL) and washed with water (50 mL). The organic layer was then washed with saturated aqueous sodium hydrogen carbonate (50 mL), dried over sodium sulfate and concentrated *in vacuo*. The product was purified by column chromatography over silica gel (2:1 hexane / ethyl acetate) to give the title compound as colourless opaque crystals (789.0 mg, 79%). mp 98-100C (from hexane).

^{1}H NMR δ_H (400MHz; $CDCl_3$) 4.80 – 4.70 (1H, m), 4.30 (1H, d, *J* 9.6 Hz), 4.14 (2H, q, *J* 7.2 Hz), 2.70 – 2.55 (2H, m), 2.41 (1H, m), 1.98 - 1.36 (12H, m, H_2-7, H_2-8, H_2-8, H_2-10, H_2-11 and H_2-12), 1.26 (3H, m, H_3-18); ^{13}C NMR (100MHz, $CDCl_3$) δ_C 173.6, 170.7, 77.3, 69.3, 60.7, 48.1, 45.9, 38.8, 37.6, 36.8, 27.9, 25.8, 23.9, 17.4, 14.2; *m/z* (CI) 282 (M+1, 100%); HRMS: Found: 282.1705 $C_{15}H_{24}NO_4$ Requires 282.1705; ν_{max} (thin film)/cm^{-1} 3324, 1731, 1664.

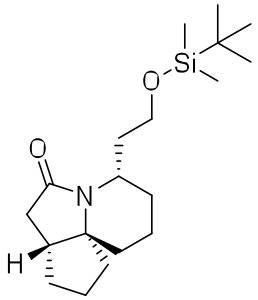
Ethyl 2-((4*S,7a*R**,10a*S**)-6-oxodecahydrocyclopenta[i]indolizin-4-yl)acetate (G)**



A dispersion of 60% NaH in mineral oil (58 mg, 1.5 mmol) was suspended in anhydrous tetrahydrofuran (10 mL). A solution of tricyclic lactanol **F** (196 mg, 7 mmol) in anhydrous tetrahydrofuran (5 mL) was then added and the solution was warmed to 40°C. A solution of carbon disulfide (14.6 µL, 0.24 mmol) in anhydrous tetrahydrofuran (5 mL) was then added and the solution was heated at 40 °C for a further 20 minutes before being recooling to room temperature. Methyl iodide (13.4 µL, 0.22 mmol) was then added and the solution was stirred for a further 20 minutes before being diluted with diethyl ether (10 mL) and the reaction was quenched with saturated sodium hydrogen carbonate (10 mL). The product was then extracted with ethyl acetate (3 × 10 mL), dried over sodium sulfate and concentrated *in vacuo* to give the xanthate intermediate as a colourless oil (259 mg). This was then dissolved in anhydrous toluene (20 mL) and tributyl tin hydride (300 µL, 0.83 mmol) was added, followed by azobisisobutyronitrile (~2 mg). The solution was then heated at 80 °C for 6 hours before being concentrated to dryness, taken up in diethyl ether and washed with water. The organic fraction was then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (1:1 hexane / ethyl acetate) to give the title compound as a colourless oil (109 mg, 59% overall).

^{1}H NMR δ_H (400MHz; $CDCl_3$) 4.73 (1H, q, *J* 7.2 Hz), 4.06 (2H, dq, *J* 7.0, 4.0, Hz), 2.72 – 2.53 (3H, m), 2.30 – 2.08 (1H, m), 2.06 (1H, dd, *J* 17.2, 5.6 Hz), 1.95 - 1.27 (12H, m), 1.18 (3H, t, *J* 7.0 Hz); ^{13}C NMR δ_C (100MHz, $CDCl_3$) 173.1, 171.3, 70.3, 60.9, 45.0, 43.9, 37.7, 33.1, 30.1, 27.8, 26.2, 17.1, 14.1; *m/z* (EI) 266 (M+1, 100%); HRMS: Found: 266.1754 $C_{15}H_{23}NO_3$ Requires 266.1751; ν_{max} (thin film)/cm^{-1} 1731, 1681.

Ethyl 2-(4*S,7a*R**,10a*S**)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)octahydro-cyclopenta[i]indolizin-6(7H))-one (21)**

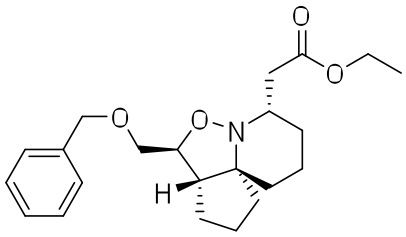


A solution of tricycle **G** (279 mg, 1.05 mmol) in tetrahydrofuran (10 mL) was cooled to 0 ºC and lithium borohydride (165 mg, 7.57 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 2 h. Acetone (10 mL) was added and the reaction mixture was stirred for another hour before the solvent was evaporated *in vacuo*. The residue was dissolved in water (30 mL) and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to afford the alcohol as a colourless oil.

To a stirred solution of alcohol in dry dichloromethane (10 mL), was added imidazole (220 mg, 3.20 mmol, followed by *tert*-butylchlorodimethylsilane (340 mg, 2.33 mmol). The reaction mixture was stirred at room temperature for 18 h. Water (10 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 15 mL). Organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography over silica gel (6:4 to 1:1 petroleum ether / ethyl acetate) afforded the title compound as colourless oil (289.0 mg, 82%).

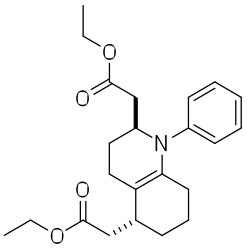
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.32 (1H, q, *J* 7.0 Hz), 3.69 - 3.61 (1H, m), 3.55 (1H, ddd, *J* 10.2, 8.5, 5.8 Hz), 2.59 (1H, dd, *J* 17.1, 10.4 Hz), 2.19 - 2.08 (2H, m), 1.98 - 1.41 (12H, m), 1.38 - 1.25 (2H, m), 0.85 (9H, s), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.3, 70.5, 61.3, 45.9, 43.4, 38.3, 38.0, 37.6, 35.9, 33.4, 28.3, 25.8, 25.5, 18.1, 17.4, -5.4; *m/z* (ES) 360 ($M+23^+$, 100 %), 338 (59); HRMS: Found: 338.2512 $C_{19}H_{36}NO_2Si$ ($M+H^+$) Requires 338.2510; ν_{max} (thin film)/cm^{-1} 2931, 1683, 1405, 1255, 1098.

Ethyl 2-[(1*S,5*S**,6*S**,9*S**)-6-[(benzyloxy)methyl]-7-oxa-8-azatricyclo-[6.4.0.0^{1,5}] dodecan-9-yl]acetate (22)**



To a stirring solution of alcohol **A** (1.06 g, 3.741 mmol) in tetrahydrofuran (100 mL) was added sodium hydride (60% dispersion in mineral oil, 165 mg, 4.115 mmol) and the suspension was stirred for 10 min. Benzyl bromide (0.42 mL, 3.741 mmol) was added drop-wise and the resulting solution was stirred at room temperature for 24 h, after which time the reaction was quenched with HCl (1 M, 100 mL). The solution was extracted with diethyl ether (80 mL). The aqueous layer was neutralised with saturated aqueous sodium hydrogen carbonate (80 mL) and further extracted with diethyl ether (2 x 80 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel (10:1 to 1:1 hexane / ethyl acetate) to afford the title compound as a colourless oil (236.0 mg, 17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 - 7.32 (5H, m), 4.60 (2H, dd, *J* 17.2, 12.0 Hz), 4.10 (2H, q, *J* 7.1 Hz), 3.88 (1H, dt, *J* 7.6, 5.6 Hz), 3.68 (2H, d, *J* 5.6 Hz), 3.13 (1H, ddt, *J* 11.6, 8.7, 3.8 Hz), 2.96 (1H, dd, *J* 15.2, 3.8 Hz), 2.51 (1H, dt, *J* 7.6, 3.5 Hz), 2.28 (1H, dd, *J* 15.2, 8.7 Hz), 2.07 - 1.29 (12H, m), 1.24 (3H, t, *J* 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.4, 138.3, 128.3, 127.5, 127.5, 84.8, 76.4, 73.4, 73.3, 61.2, 60.2, 51.0, 40.2, 38.4, 31.8, 29.3, 27.8, 21.4, 19.8, 14.2; *m/z* (ES) 374 (M+1, 100 %), 396 (27); HRMS: Found: 374.2326 $C_{22}H_{32}NO_4$ ($M+H^+$) Requires 374.2326; ν_{max} (thin film)/cm^{-1} 3011, 2941, 2872, 1724.



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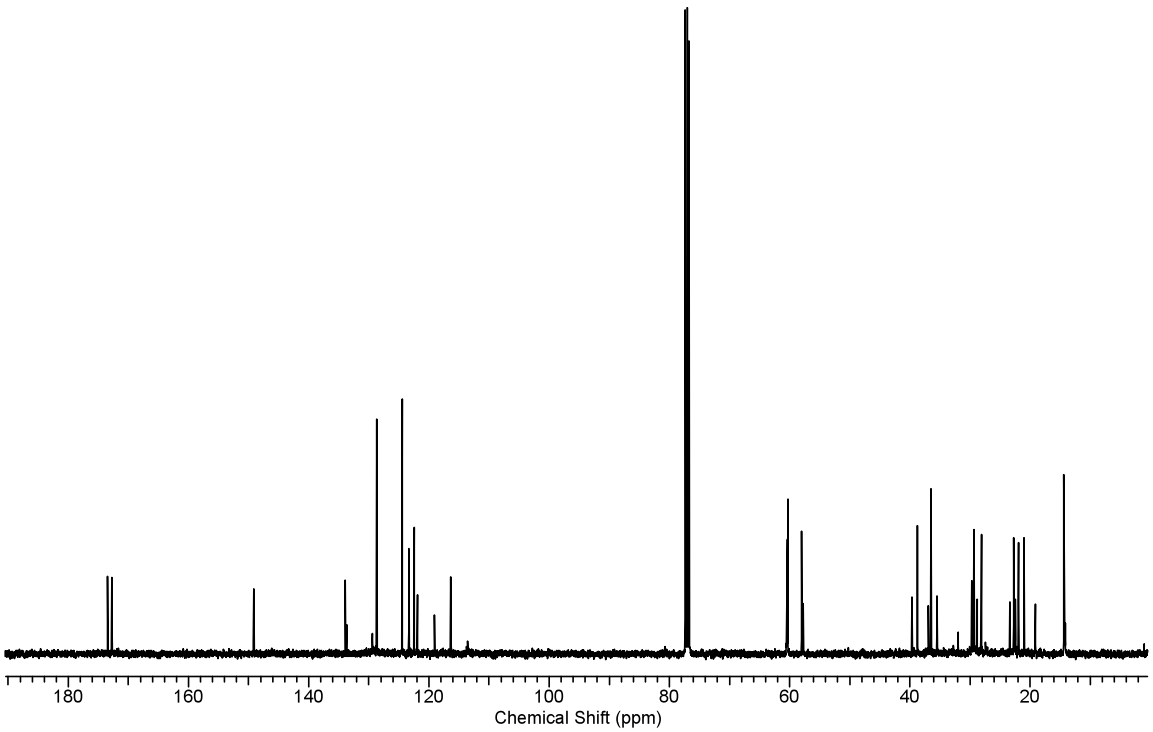

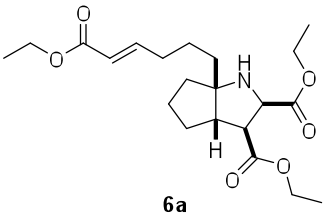

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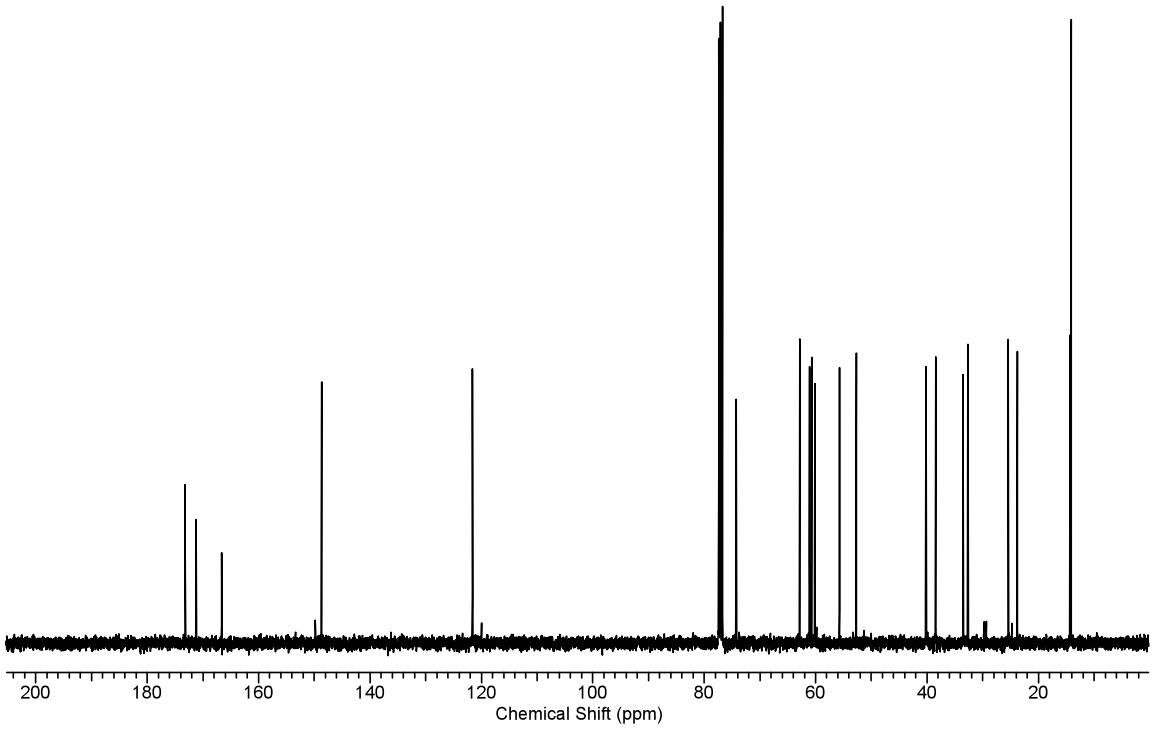
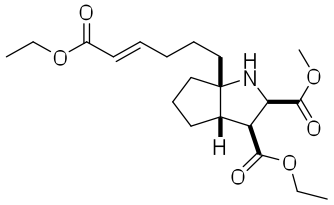
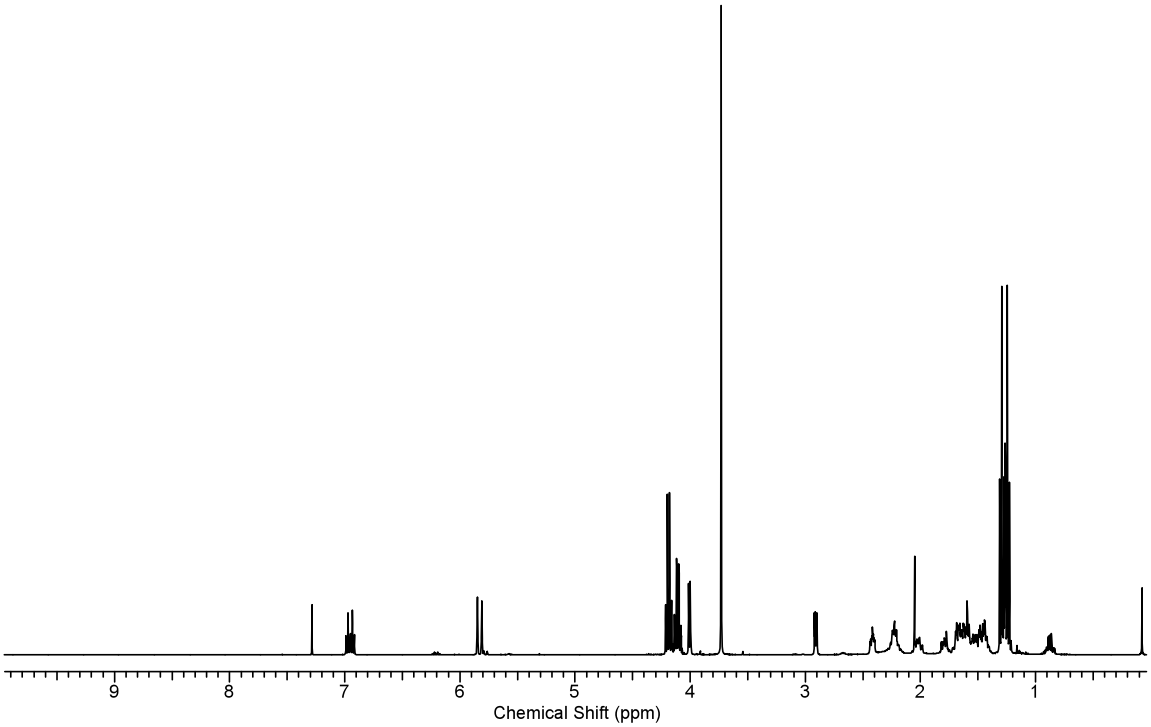
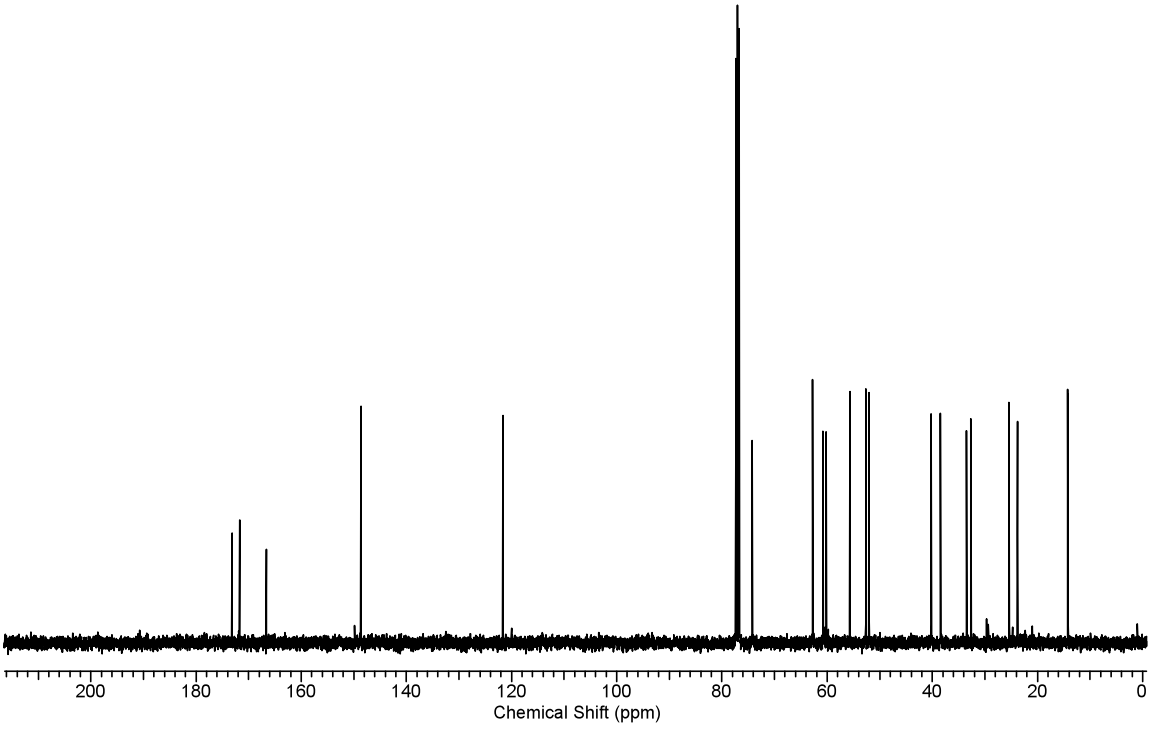
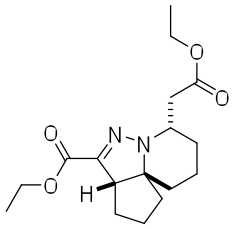




6b







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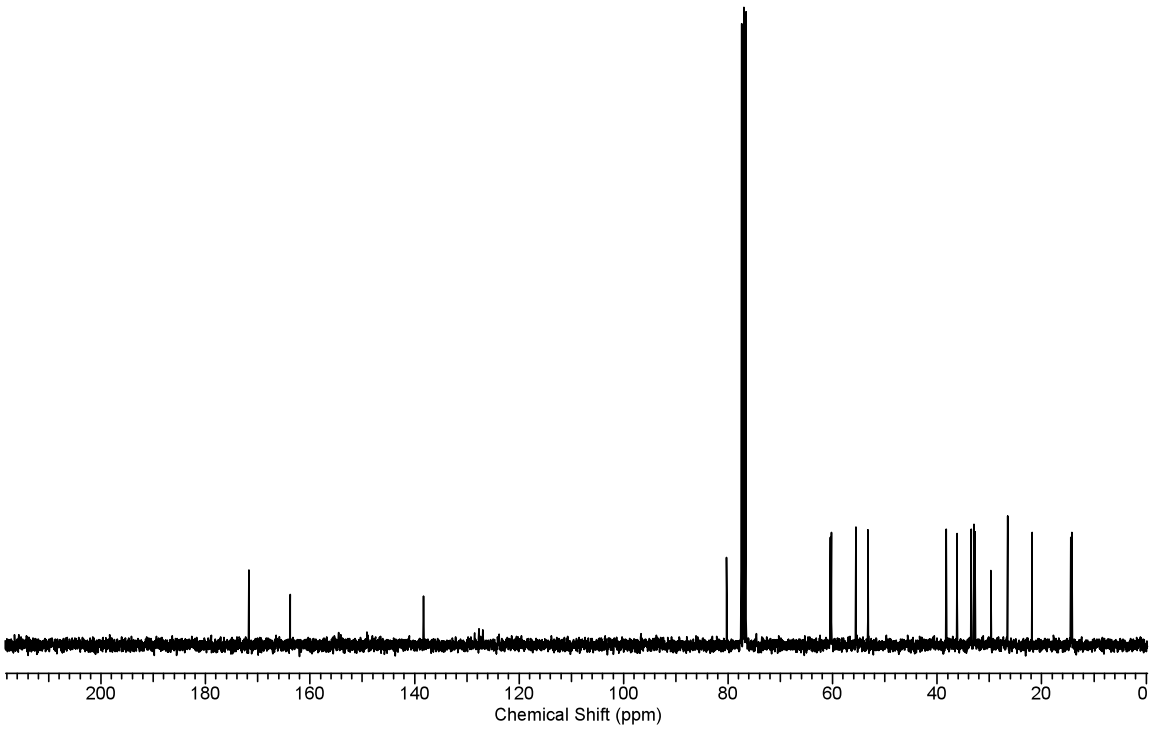

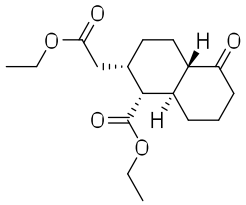

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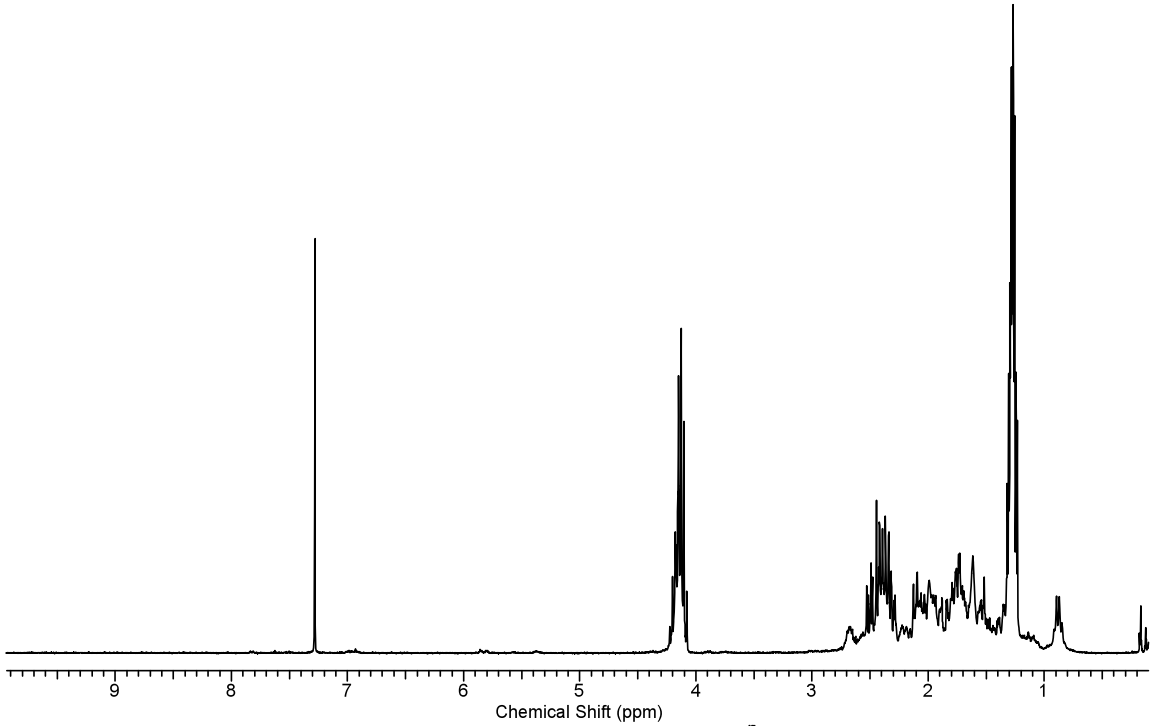

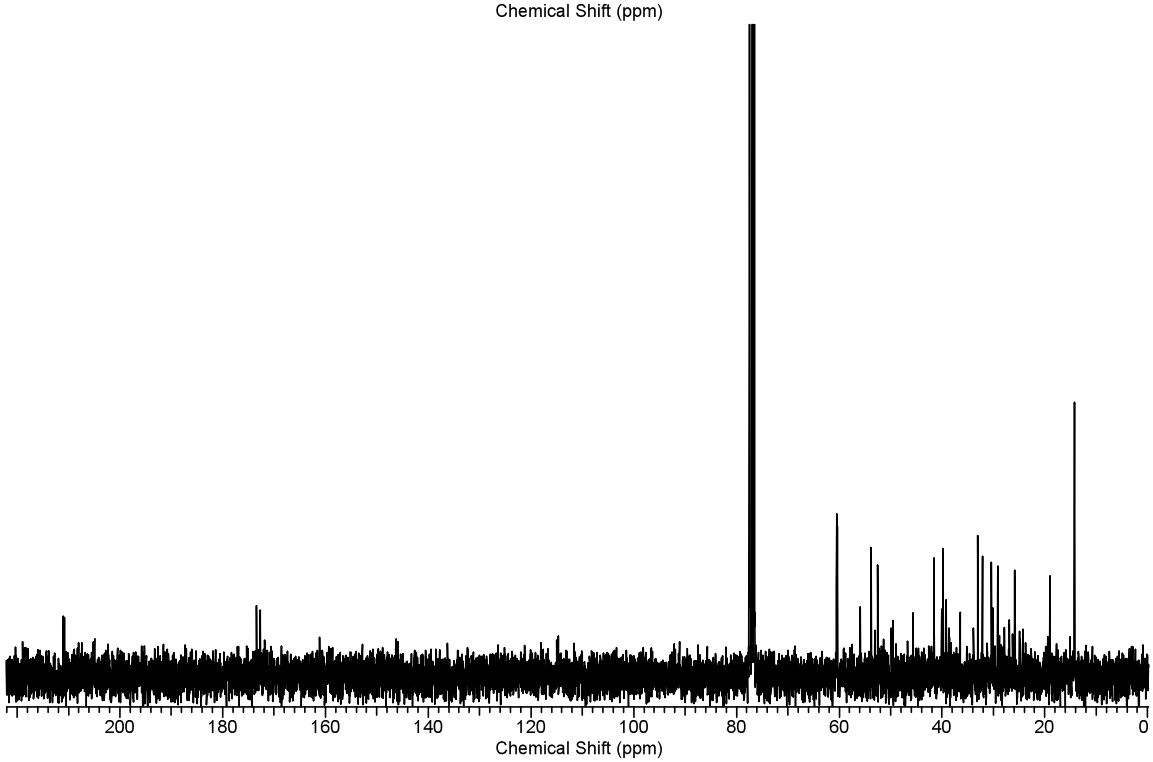

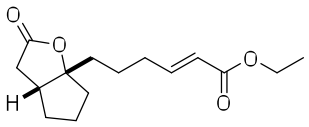

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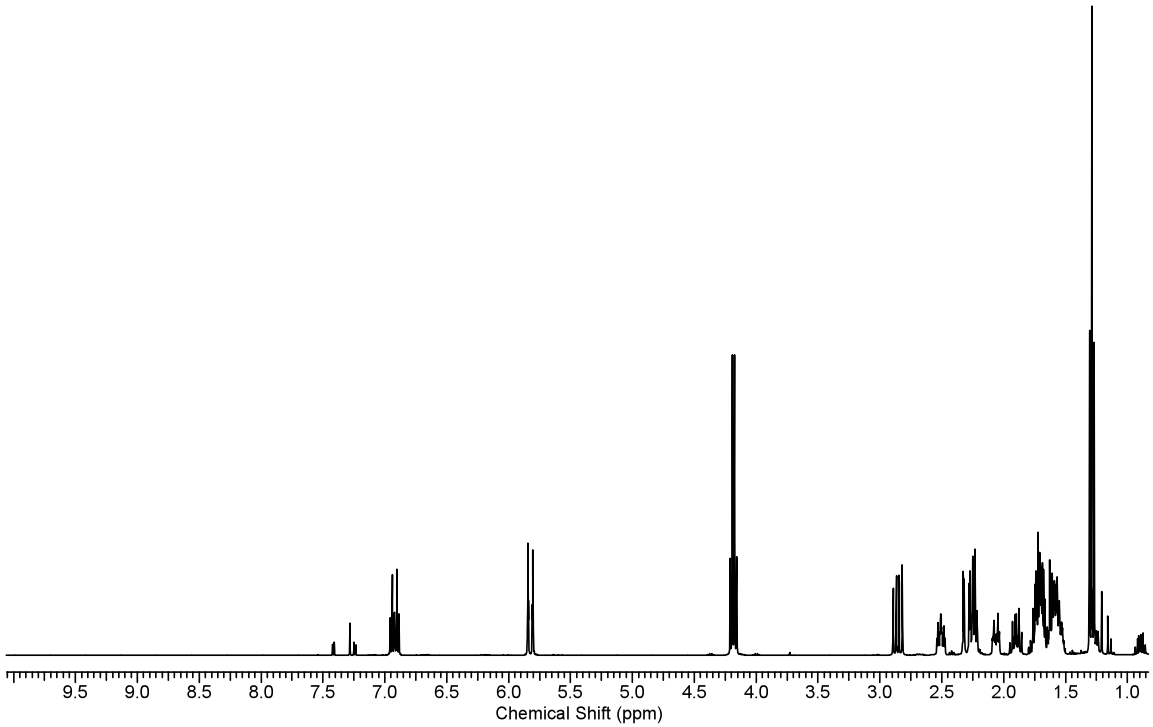

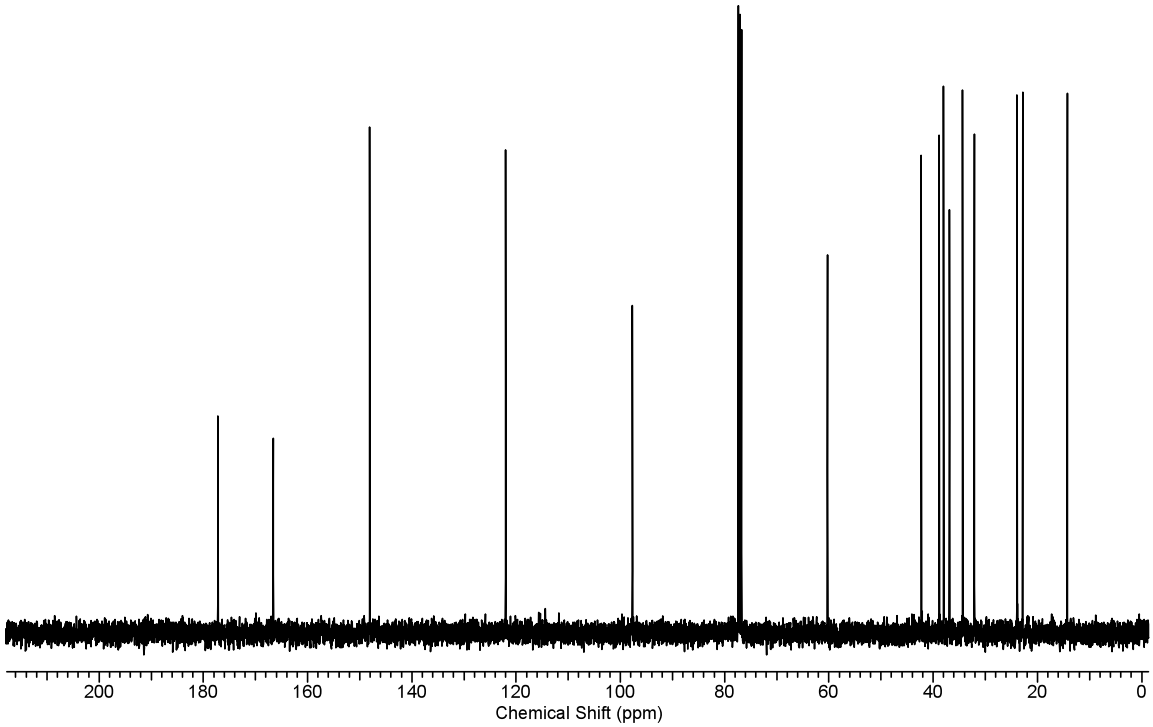

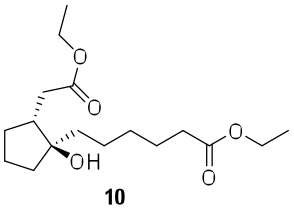

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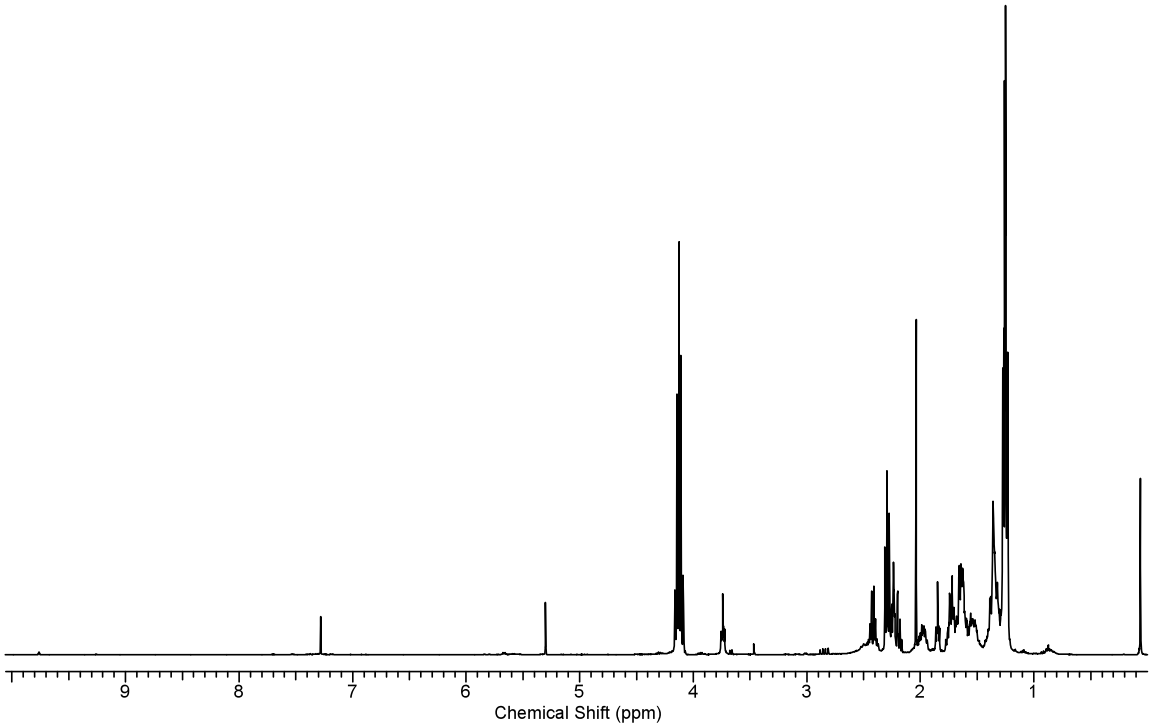

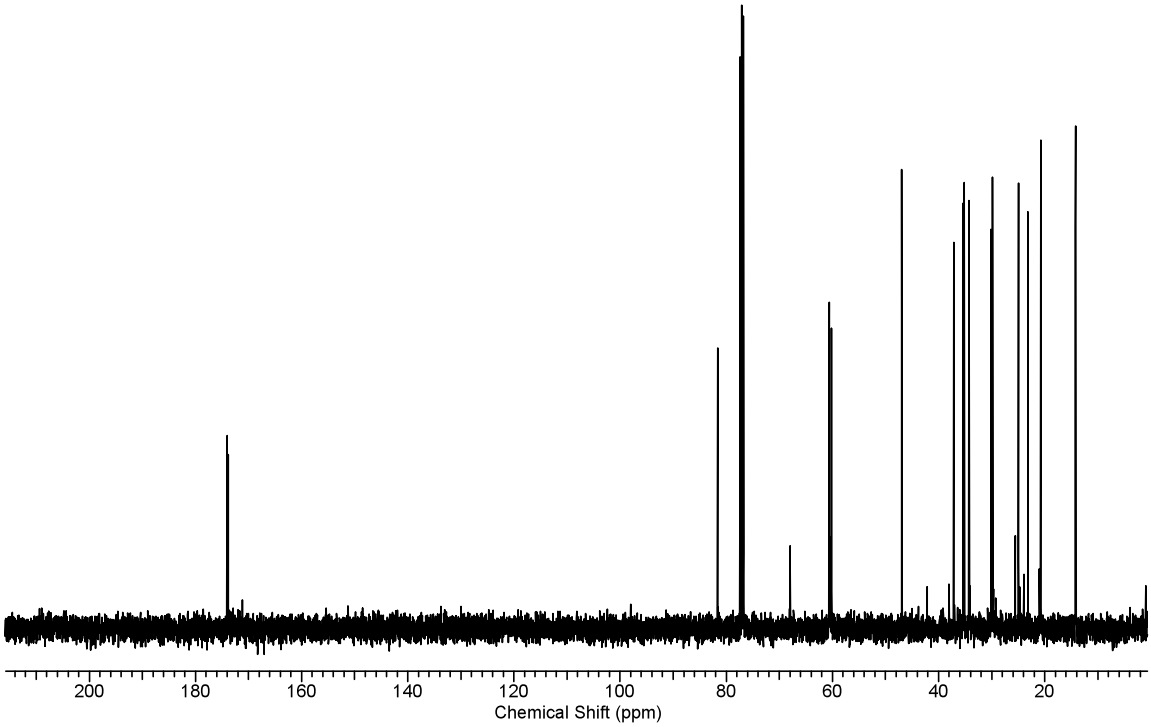

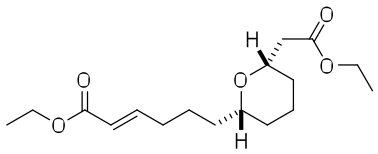

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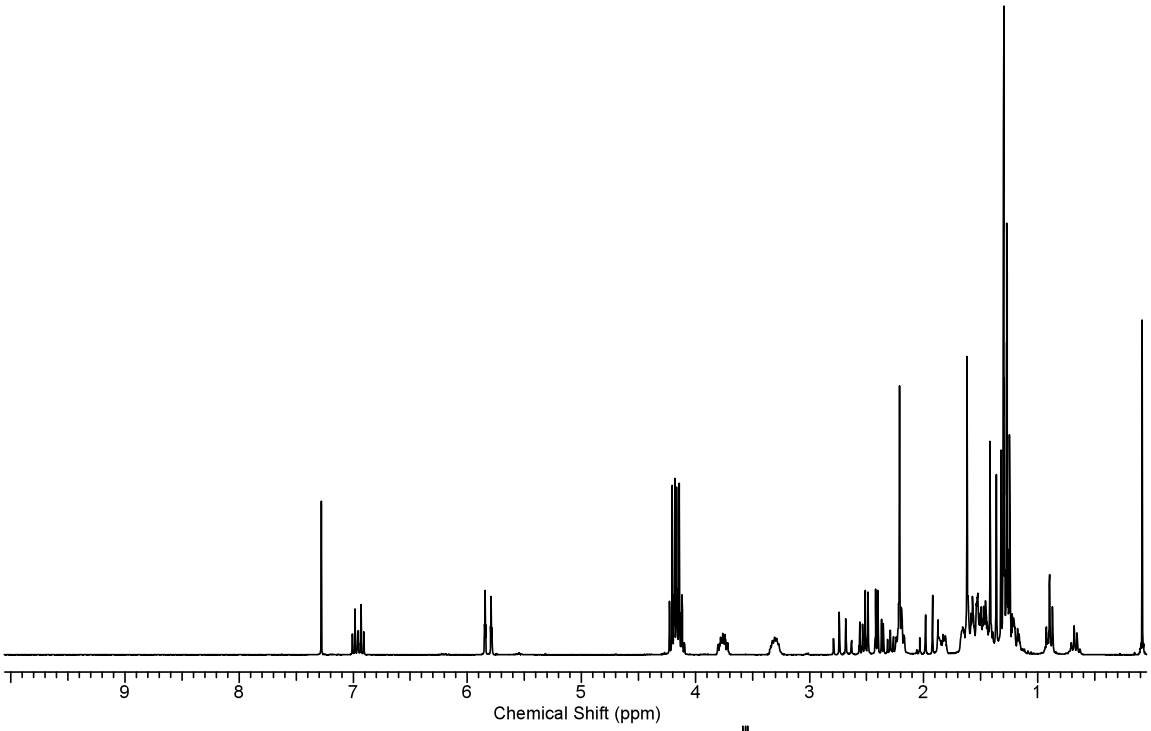

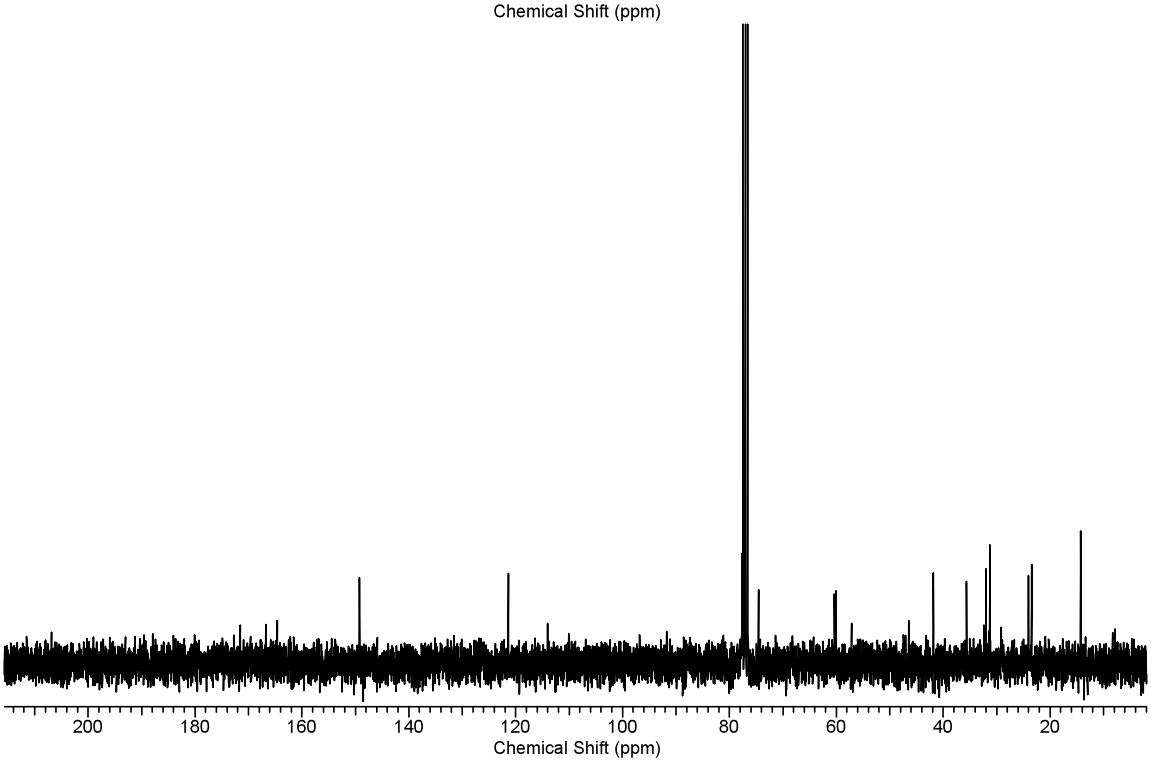

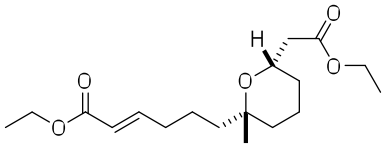

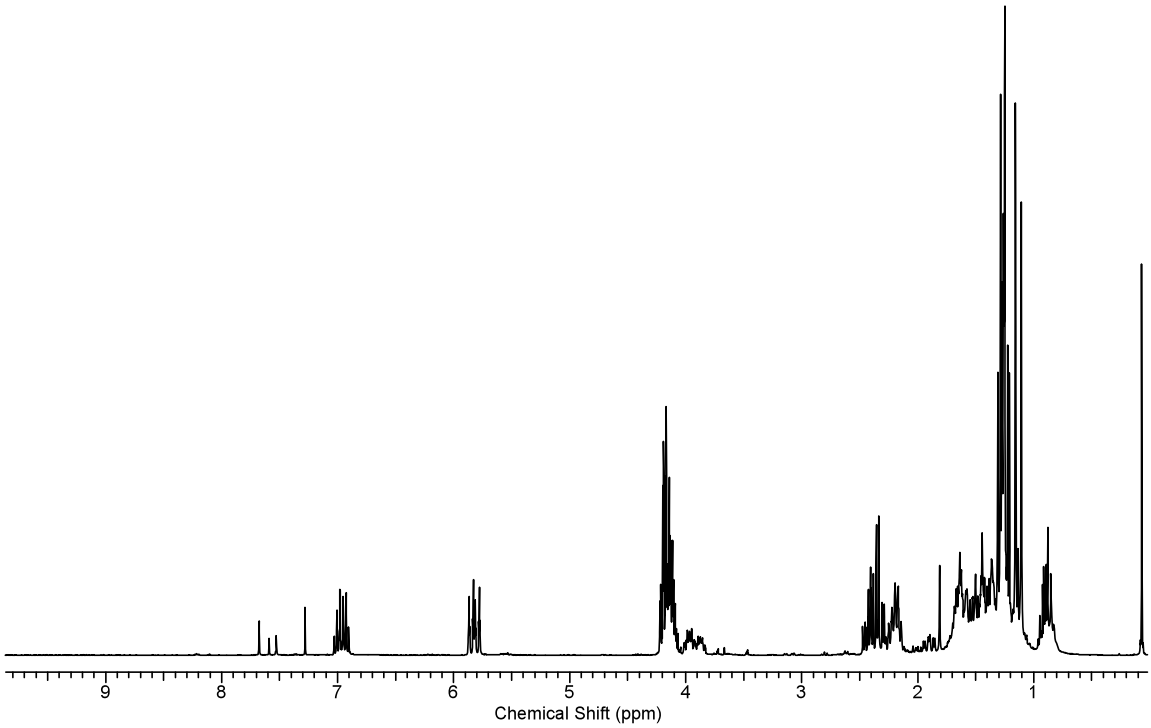

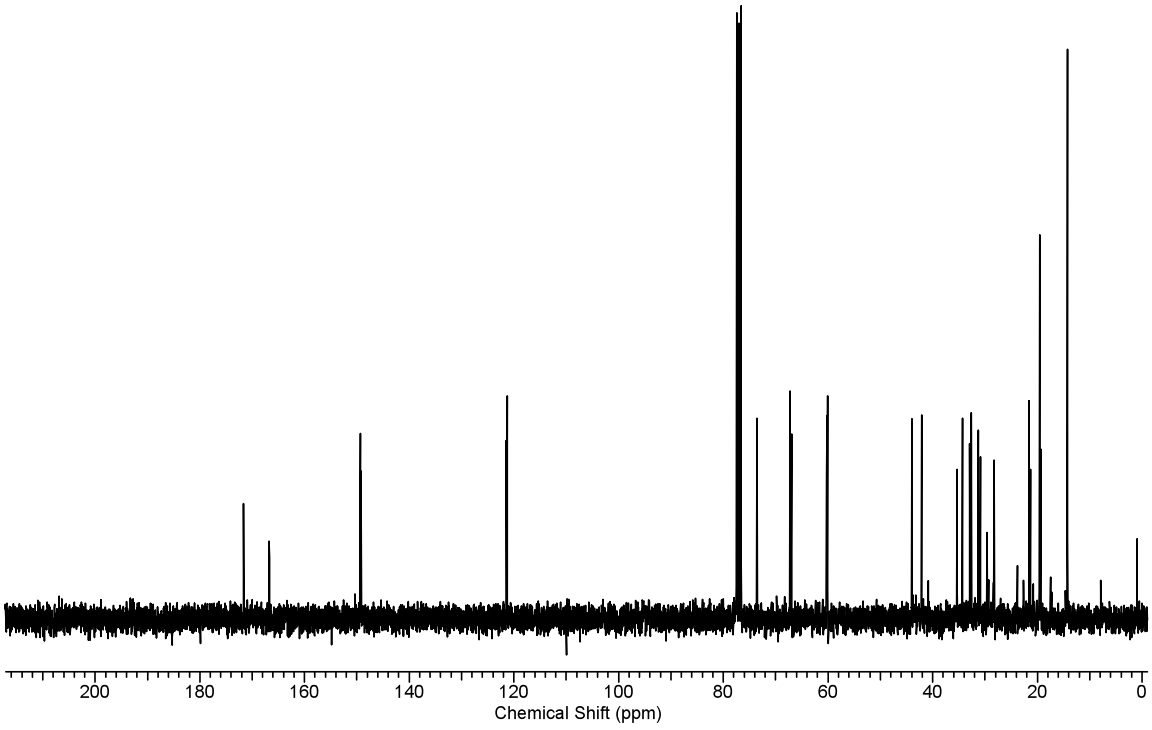

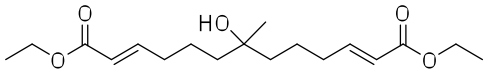

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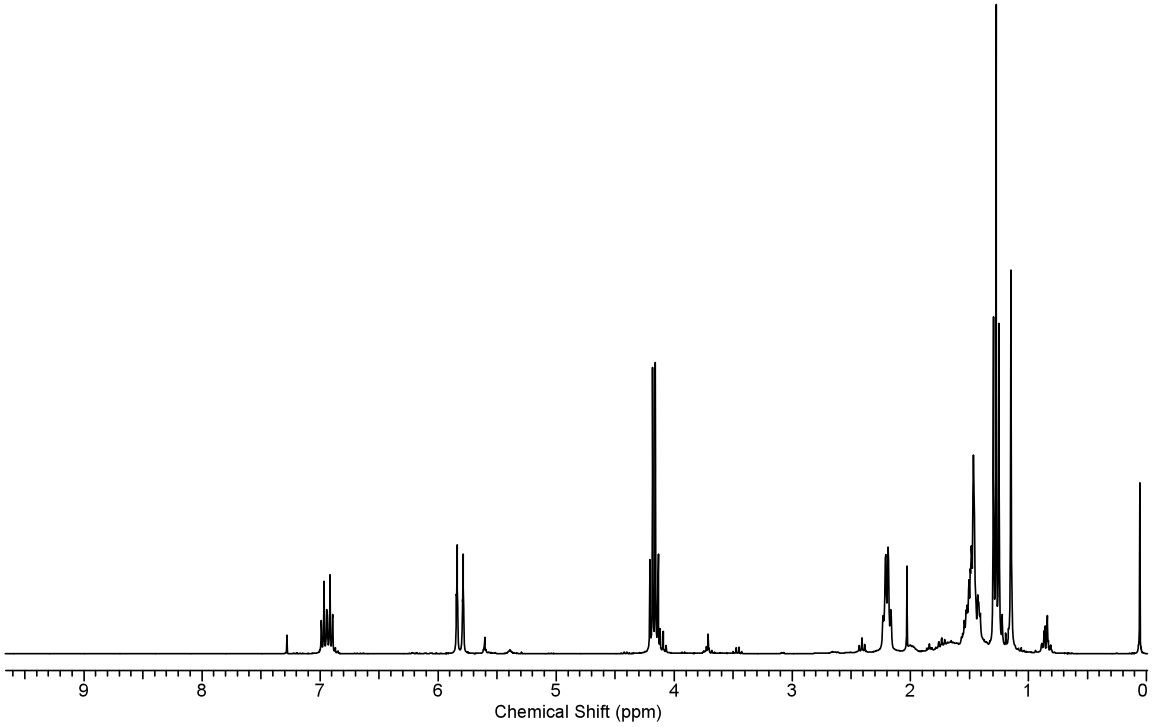

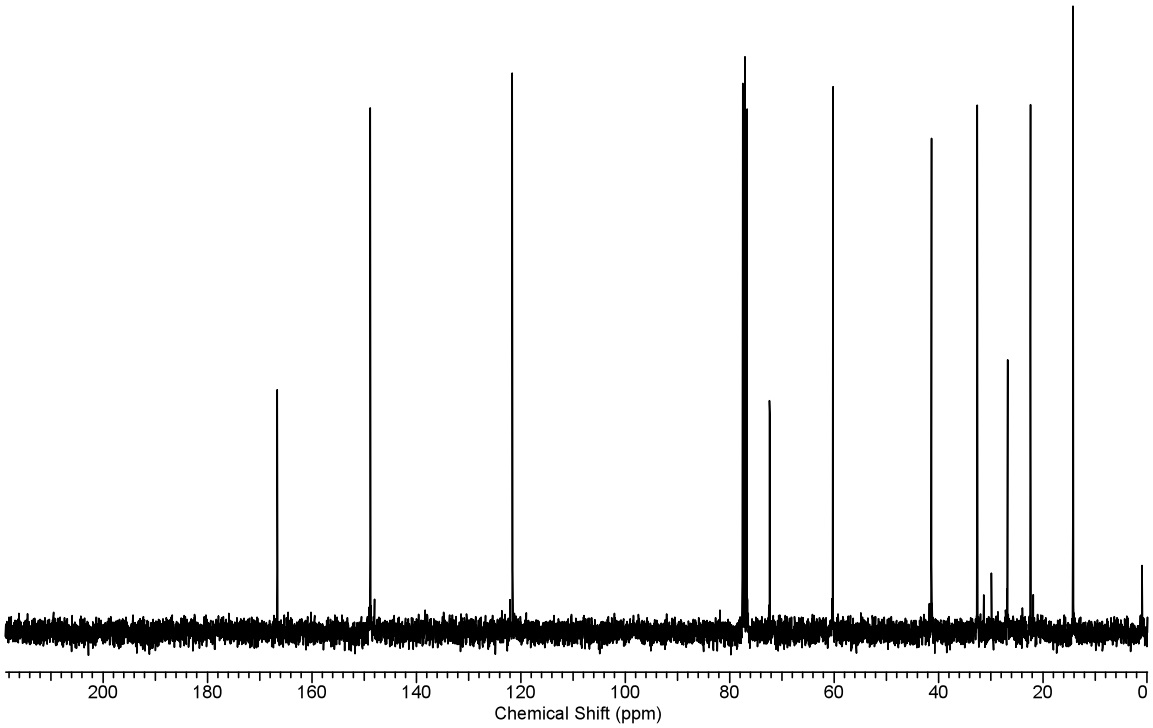

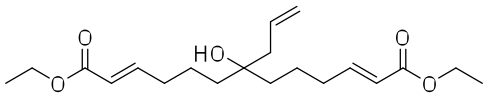

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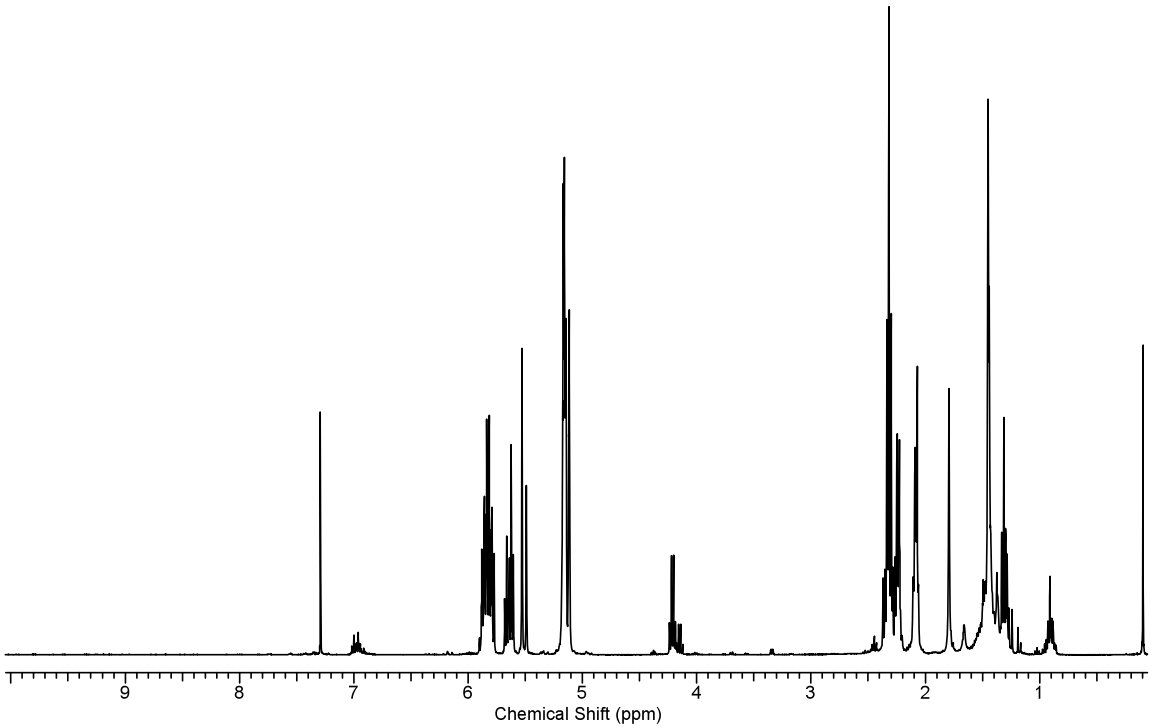

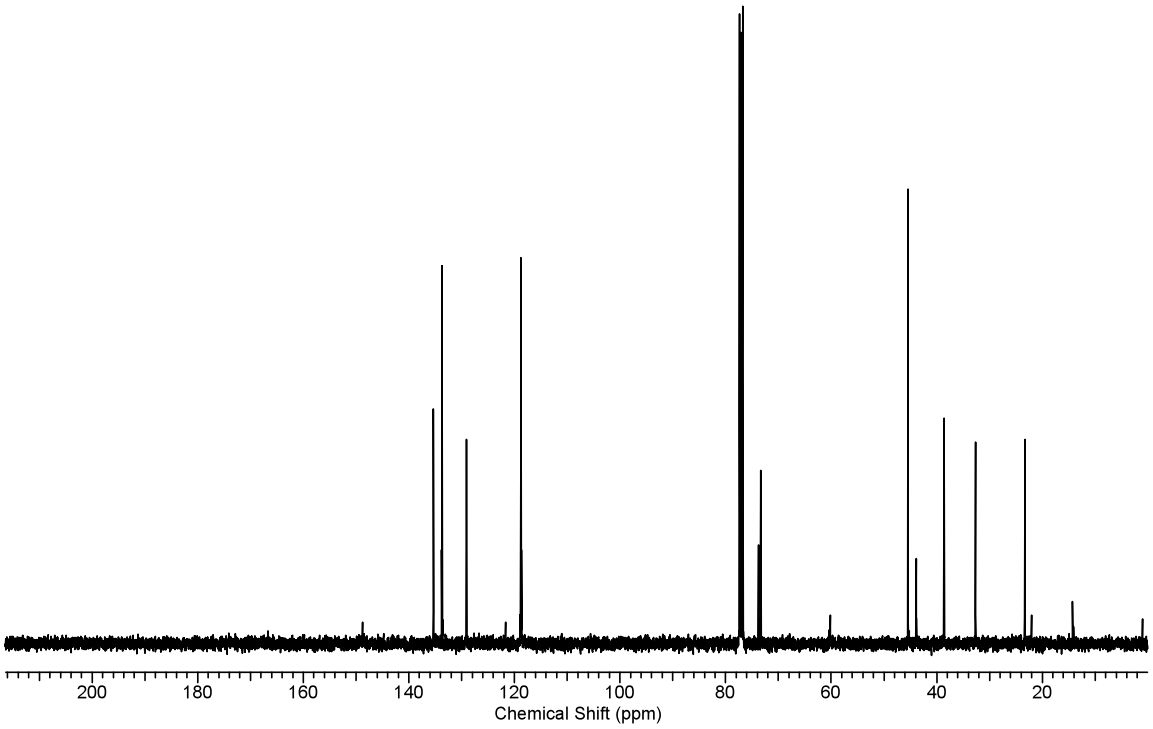

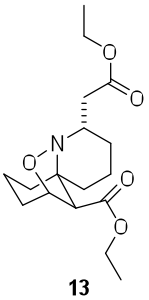

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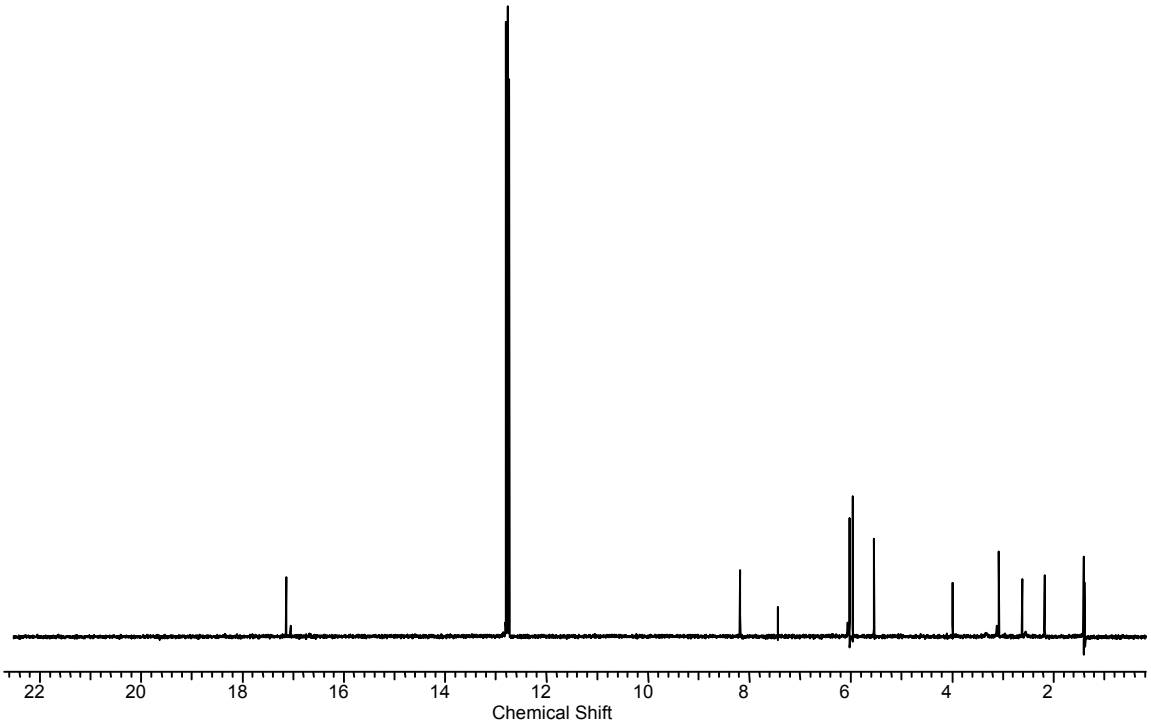

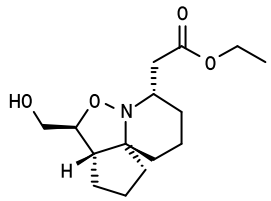

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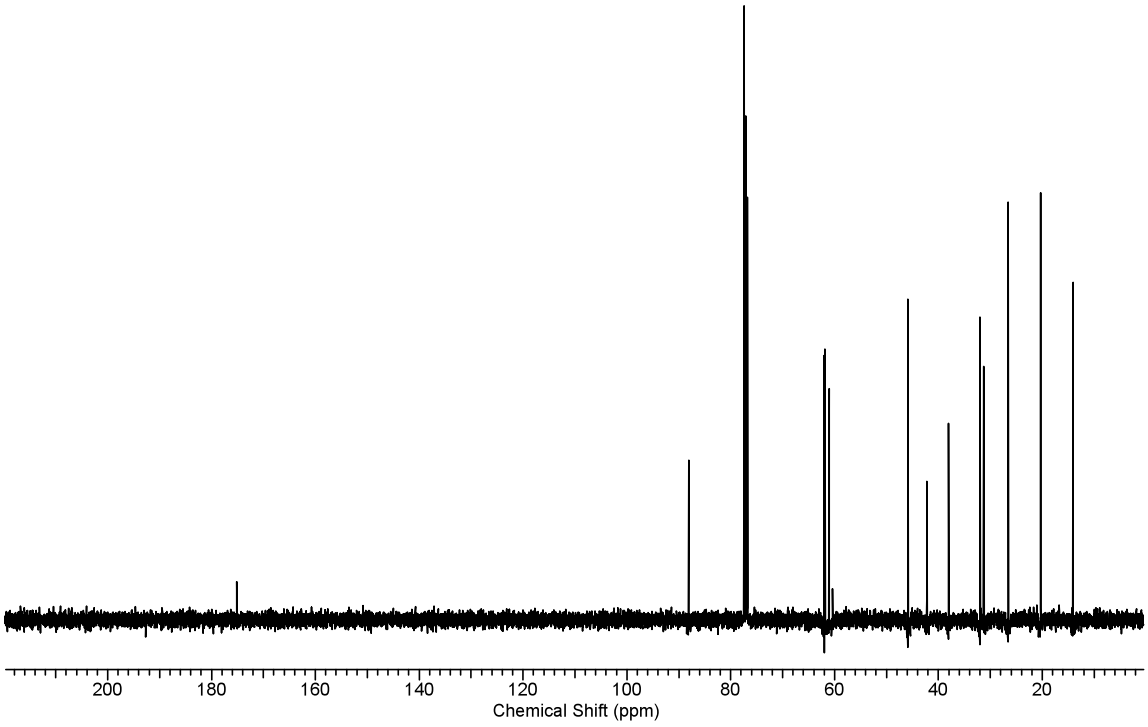

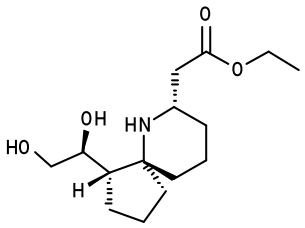

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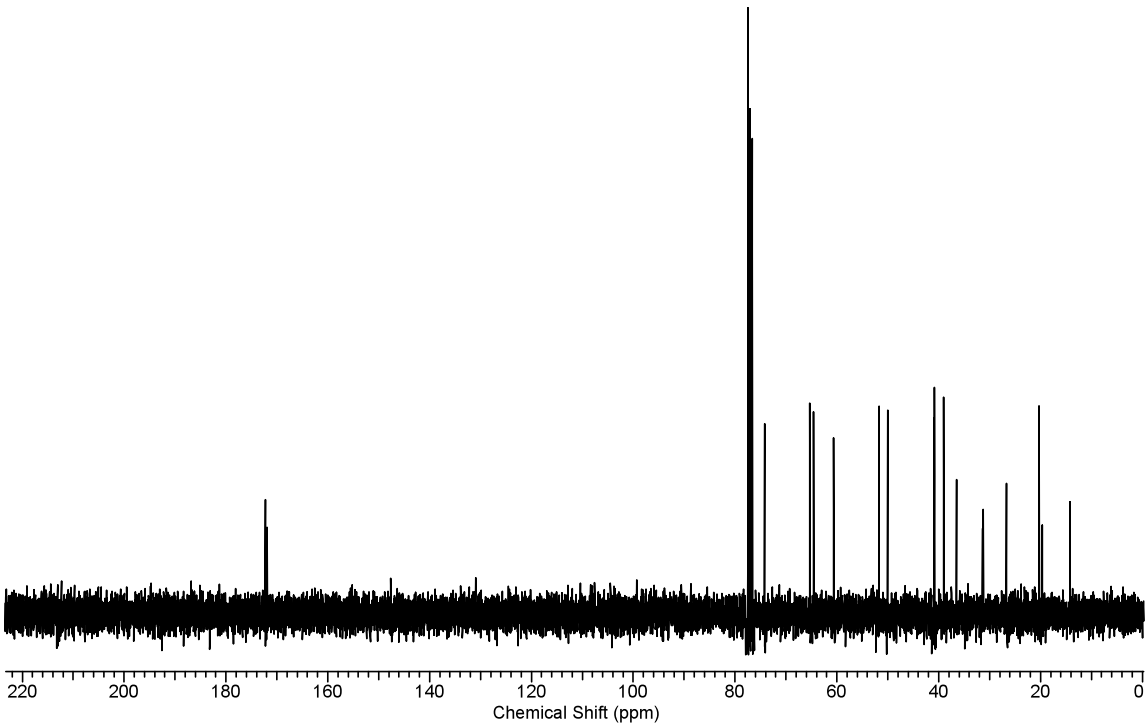

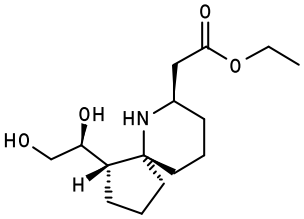

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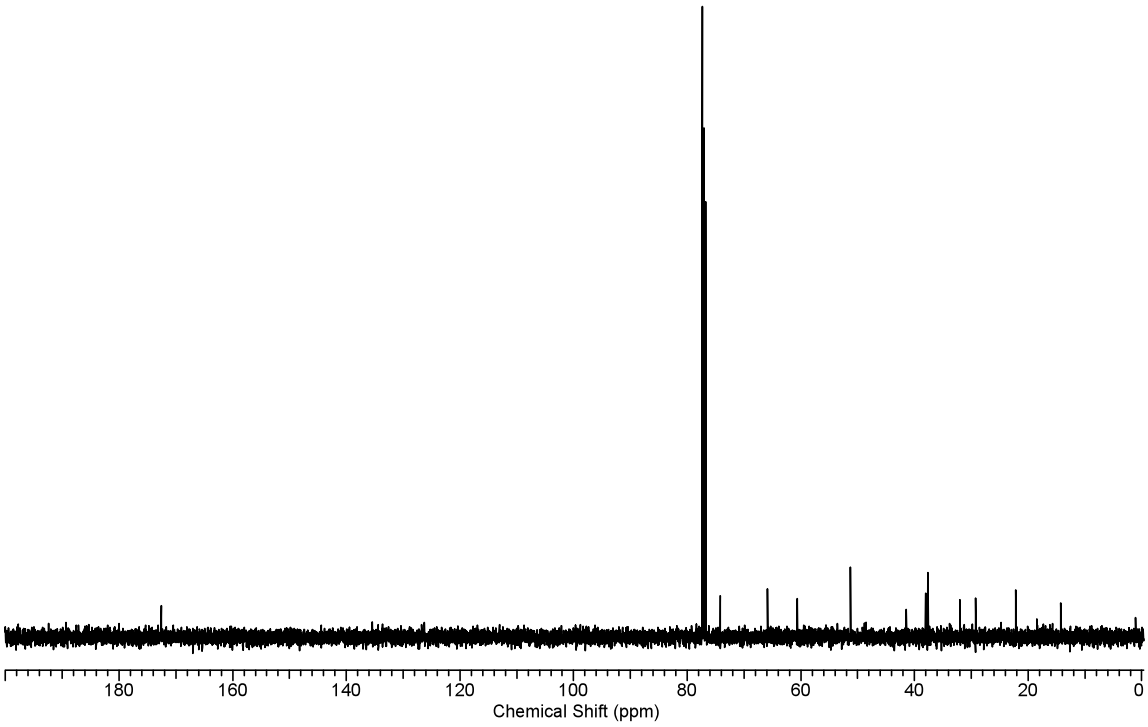

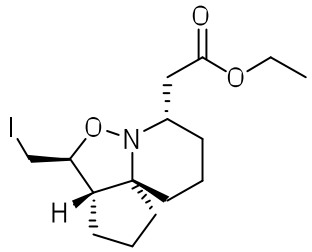

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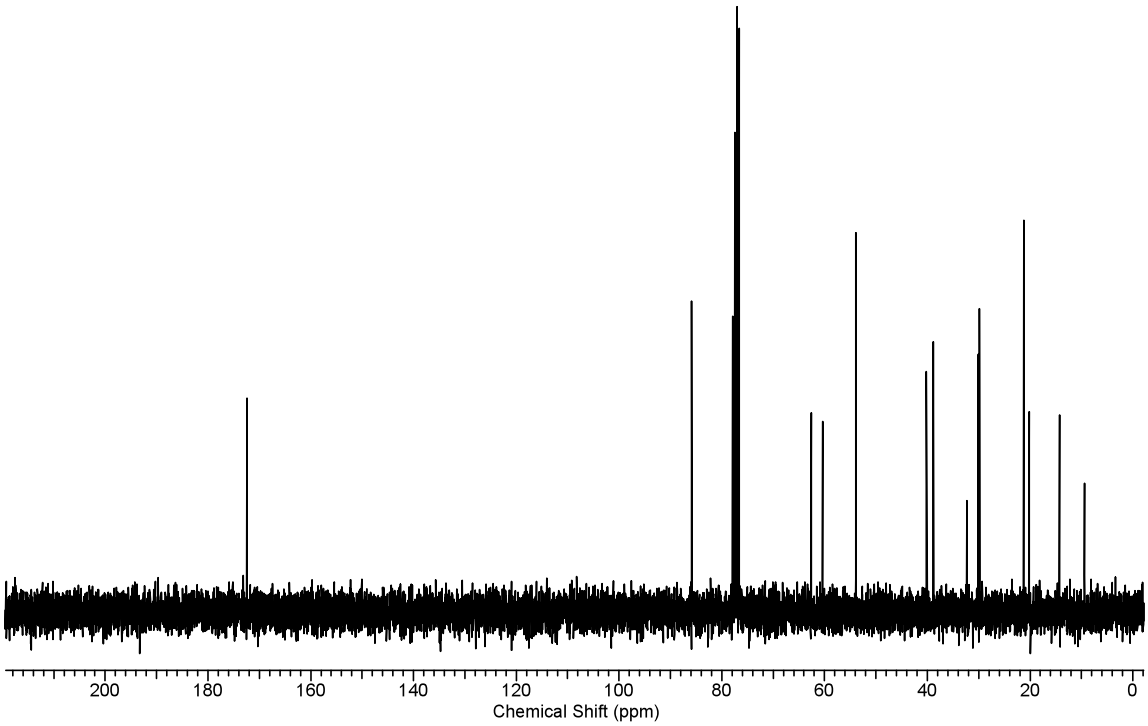

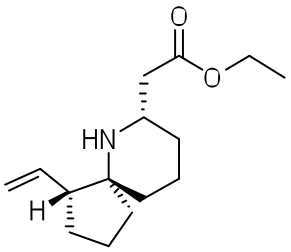

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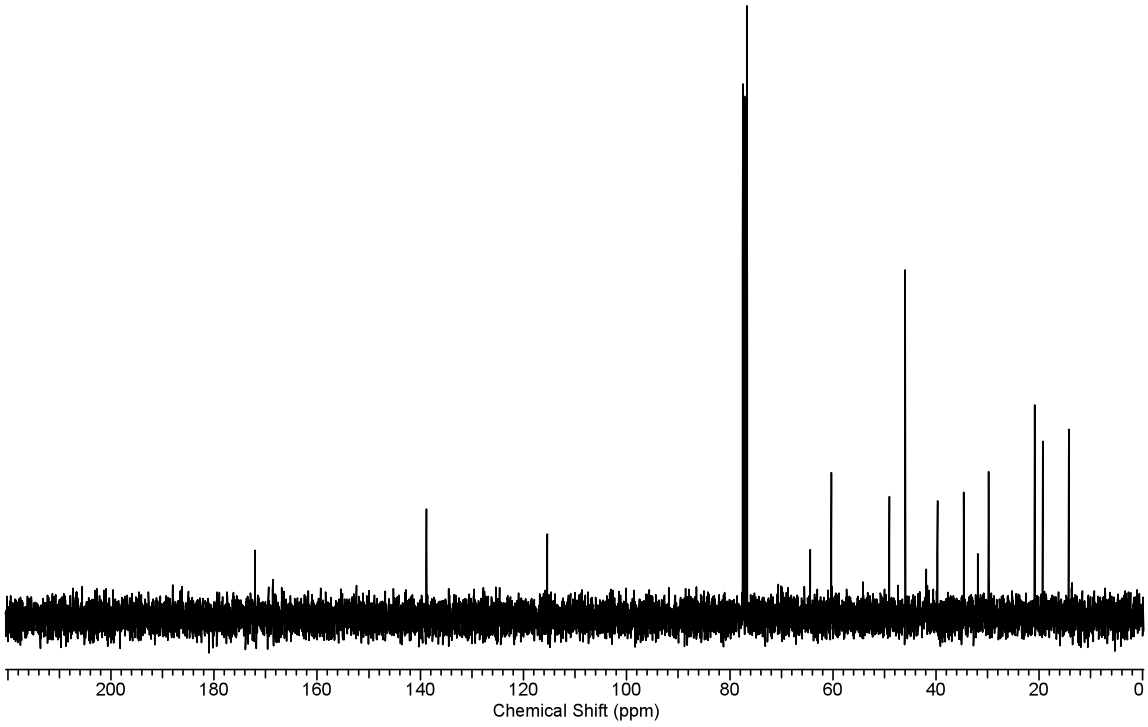

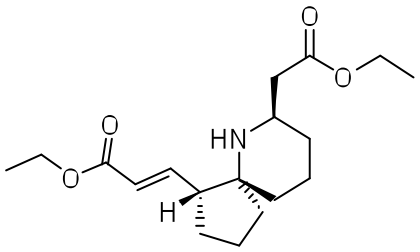

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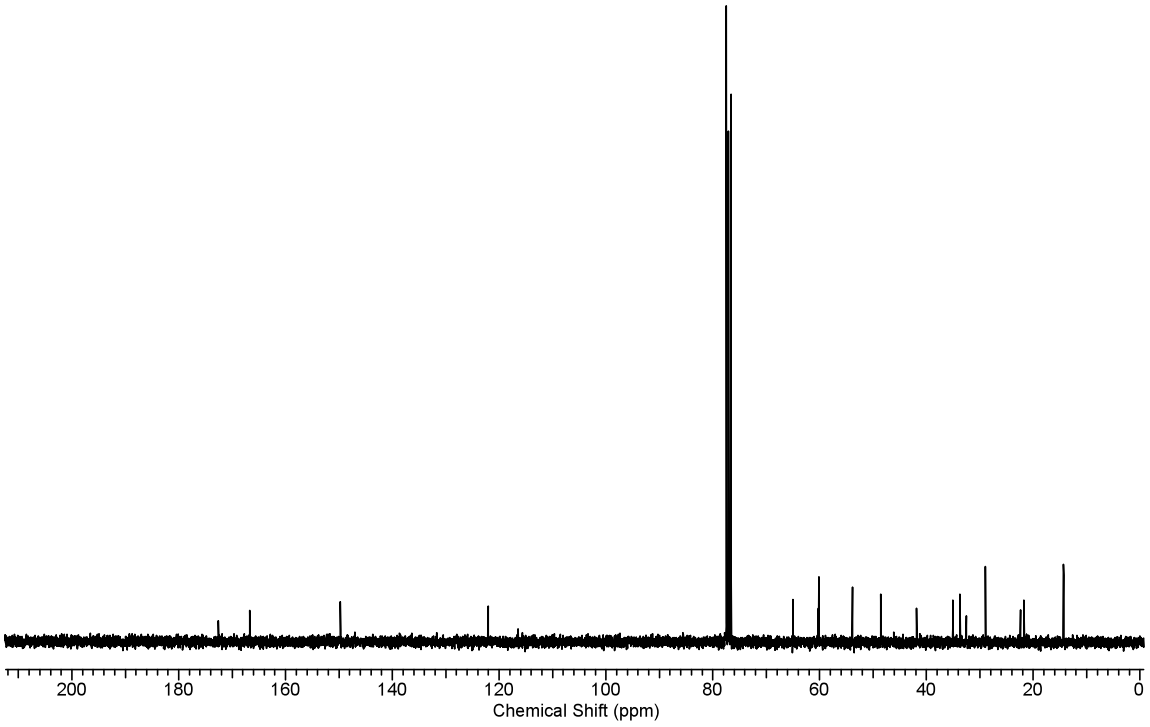

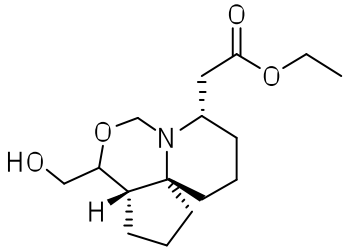

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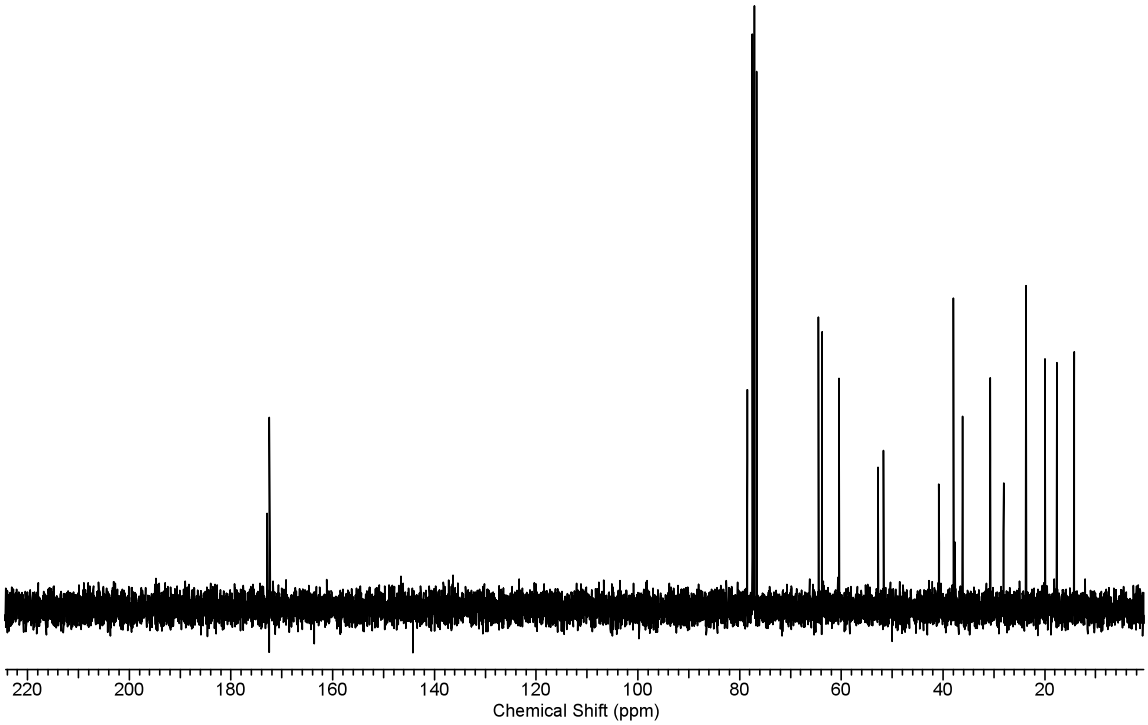

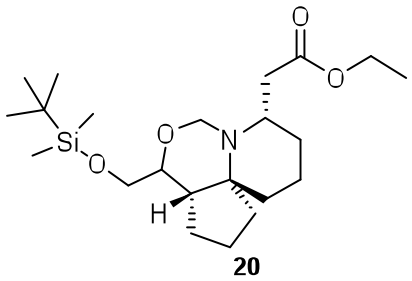

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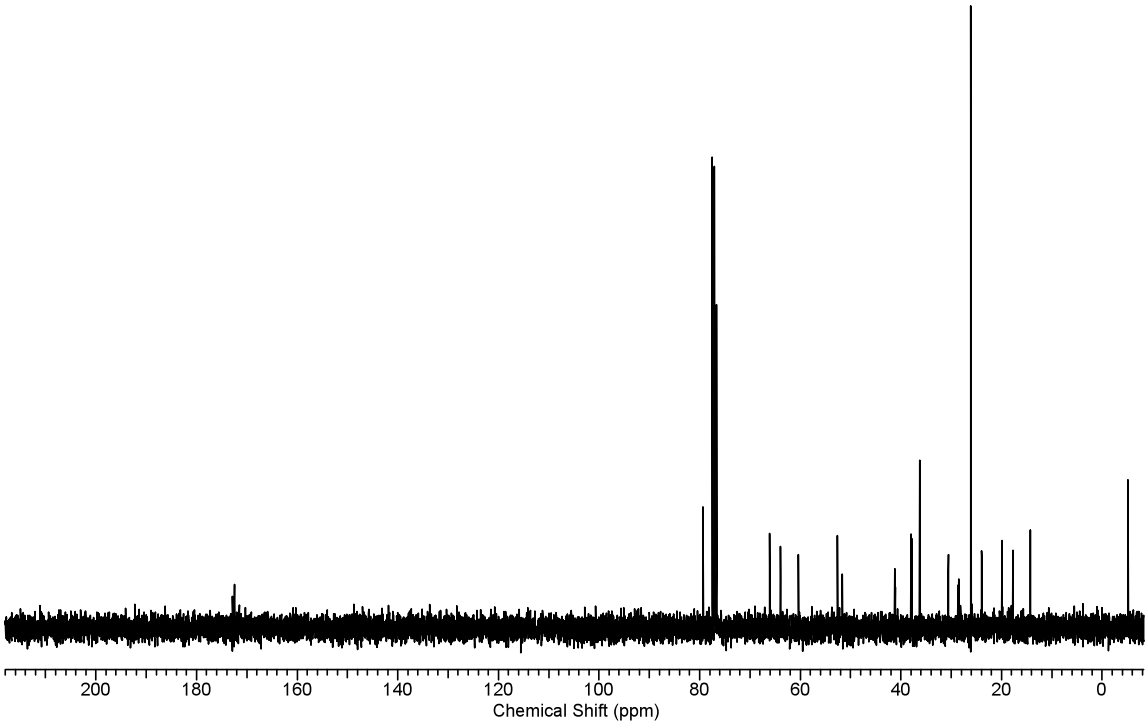

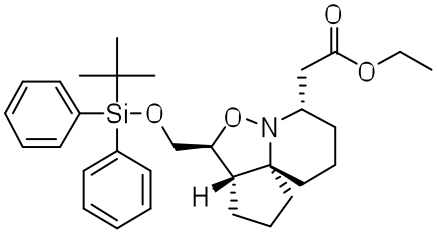

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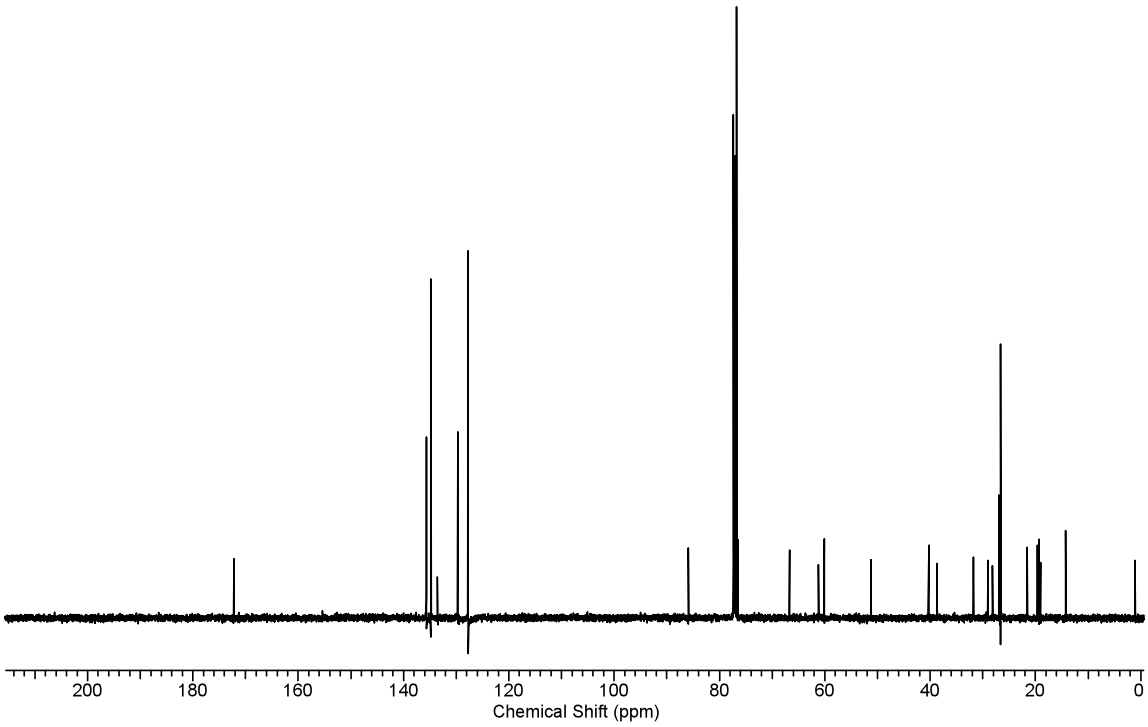

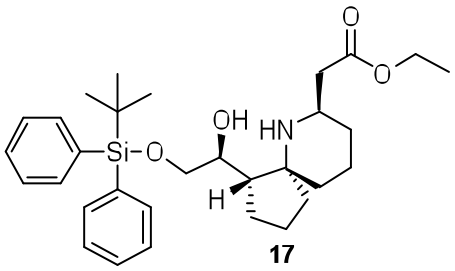

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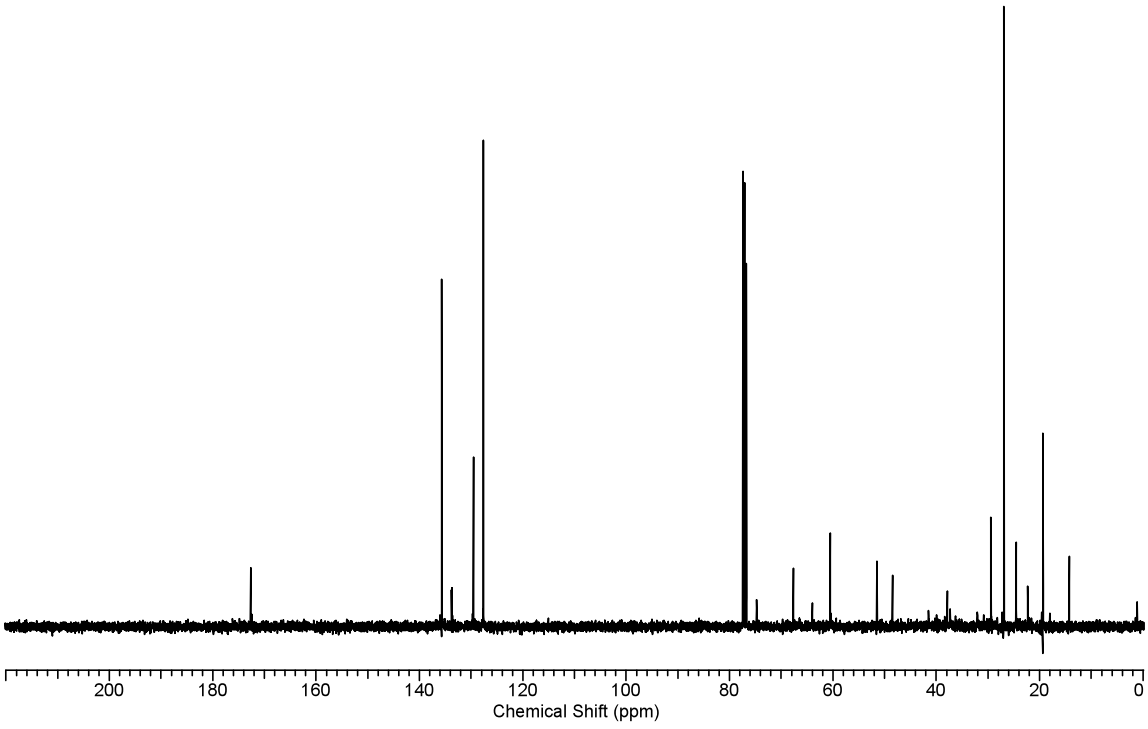

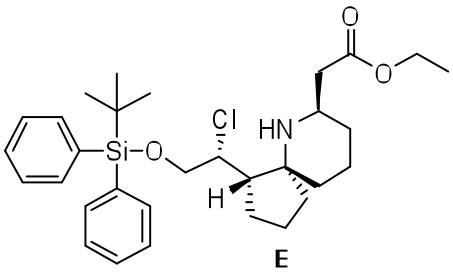

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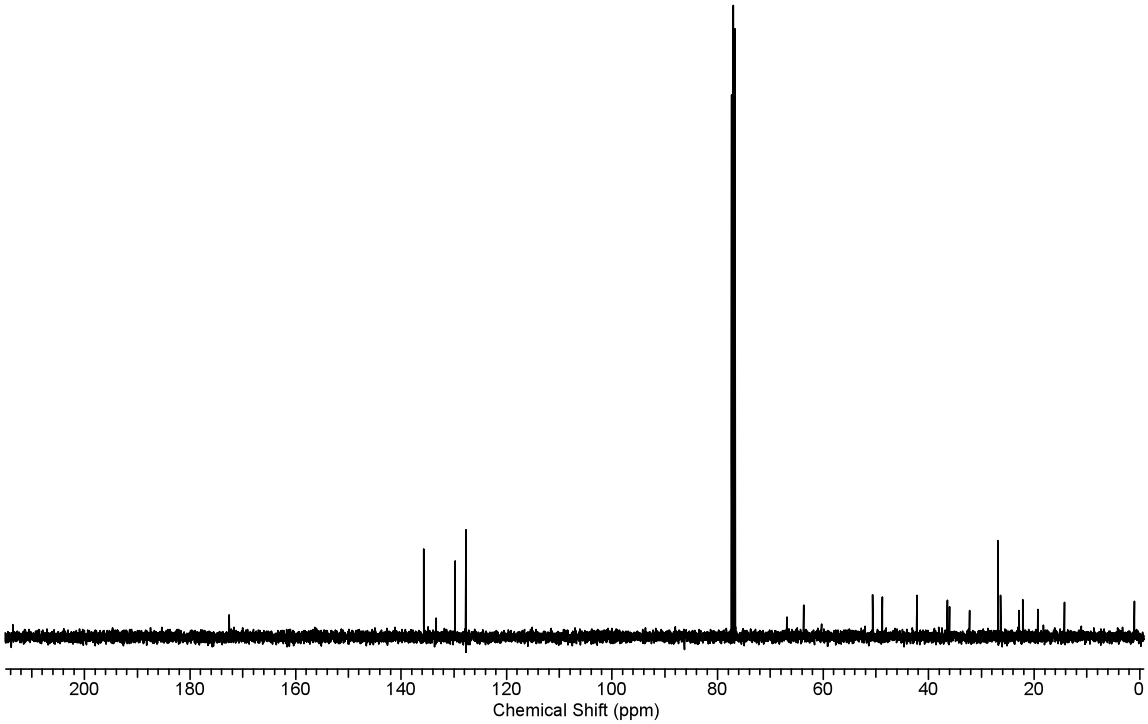

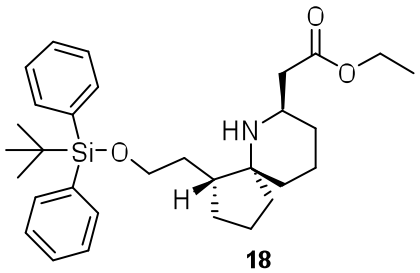

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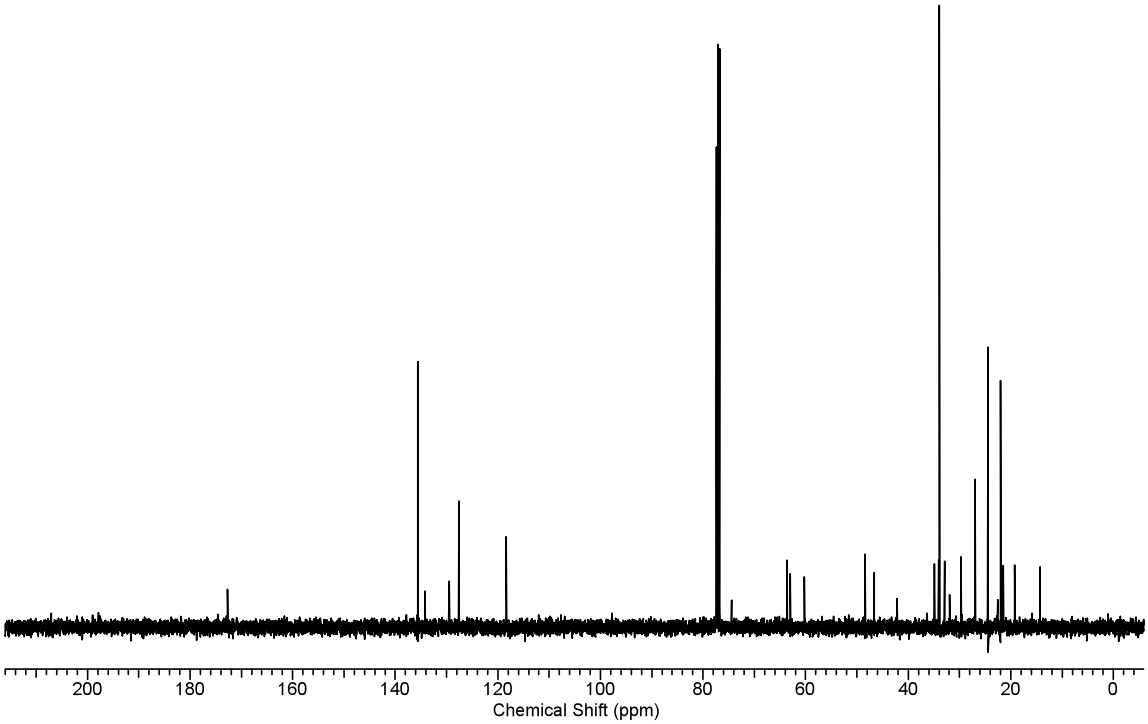

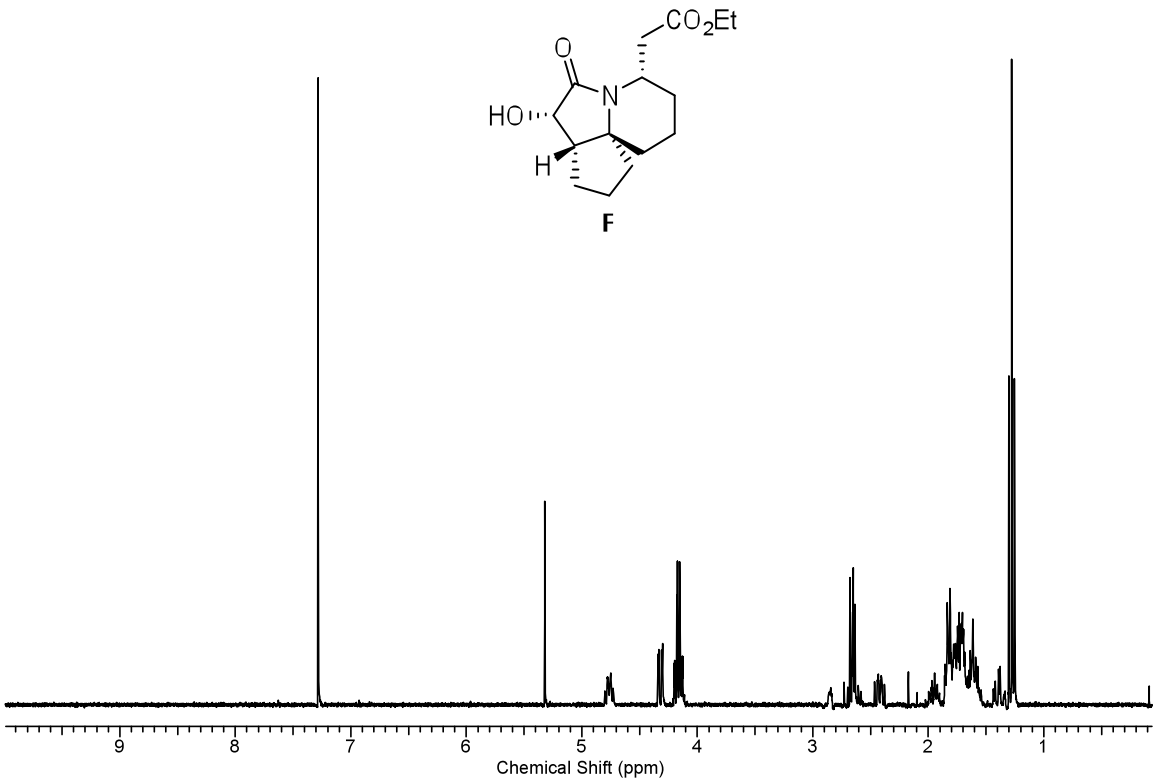

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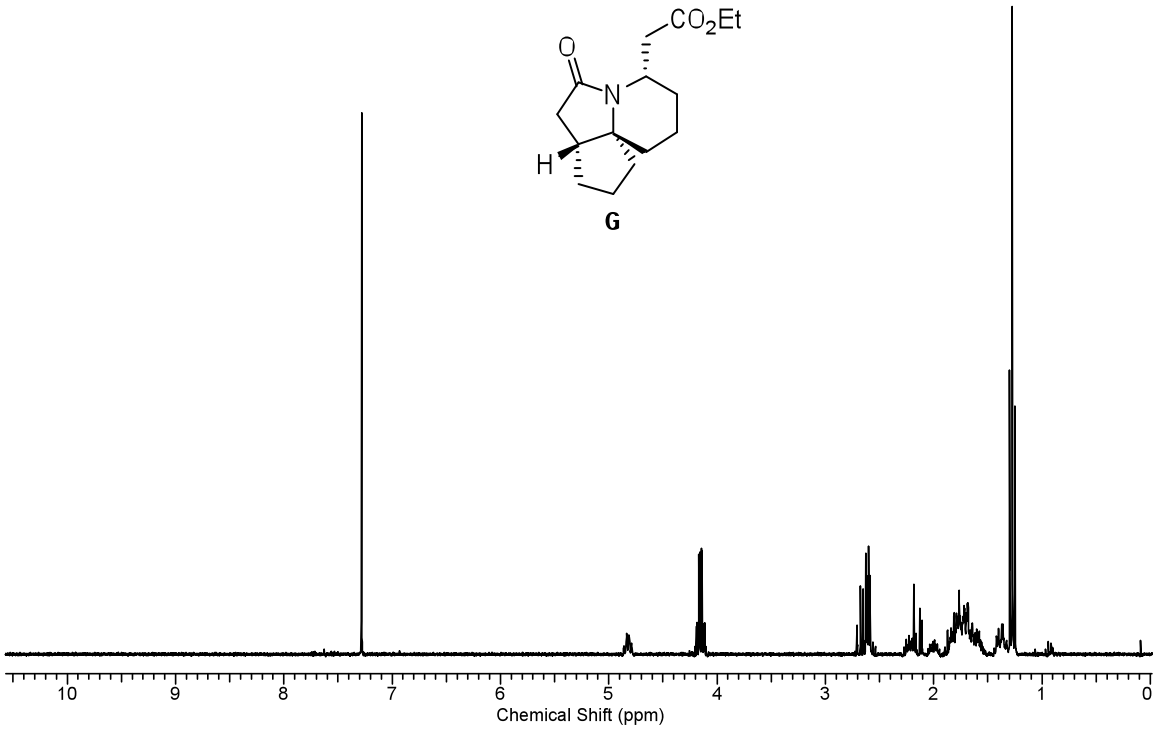

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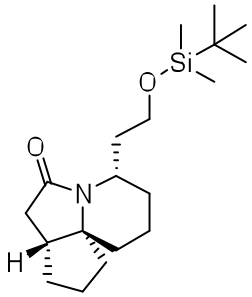

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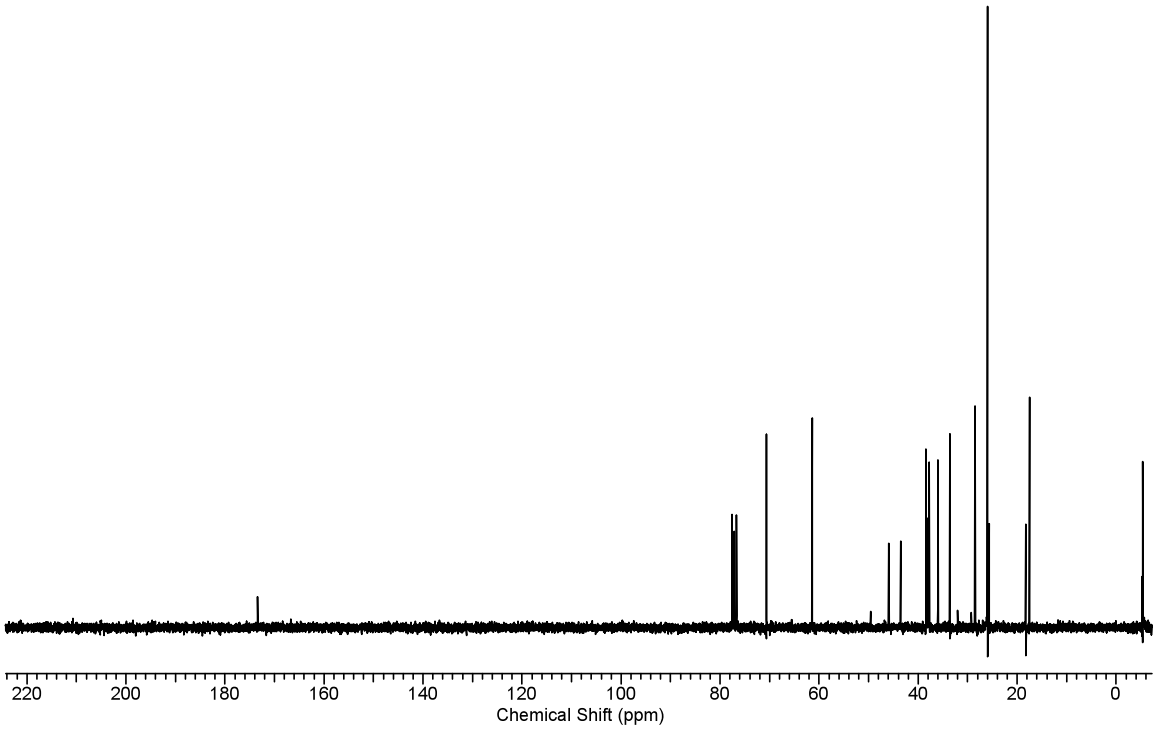

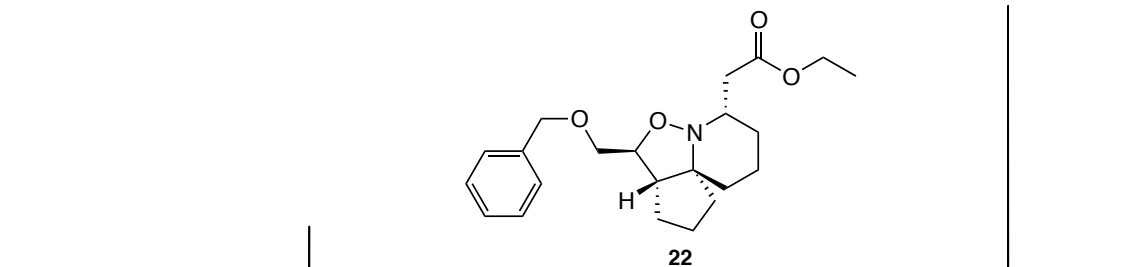

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