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Supporting Information

69451 Weinheim, Germany

Supplementary Information
for
“Total Synthesis of (+)-Fawcettidine”

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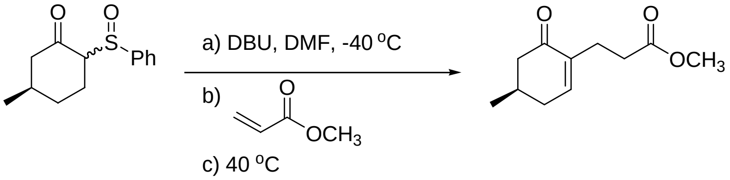
Contents

General Experimental

All reactions sensitive to air or moisture were carried out in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Dichloromethane and toluene were distilled from calcium hydride prior to use. All commercial reagents or materials were used without purification unless otherwise noted. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Triethylamine washed silica gel was stirred with triethylamine before packing and then sequentially flushing the silica gel with ethyl acetate followed by hexanes. Buffered (pH 8) saturated aqueous ammonium chloride was prepared by adding 50 mL of ammonium hydroxide to 950 mL of saturated aqueous ammonium chloride solution. Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform. Chemical shifts are recorded in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.27 ppm ^{1}H NMR; δ 77.0 ppm ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz). Optical rotations were determined on a Jasco digital P-1010 polarimeter at 589 nm. All solutions were made using chloroform ($CHCl_3$) and are reported as follows: $[\alpha]^t_D$ (c = g per 100 mL, solvent).

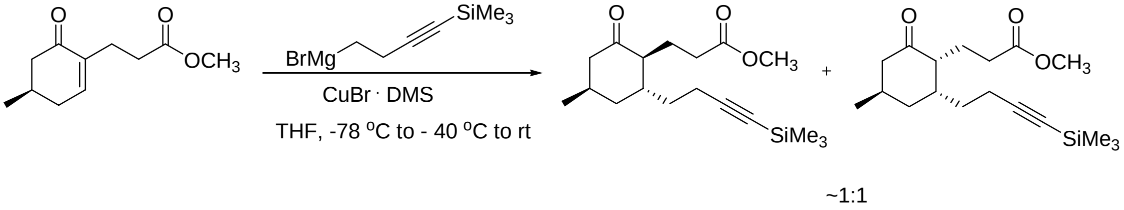
Experimental Procedures for Scheme 2:



(*R*)-Methyl 3-(4-methyl-6-oxocyclohex-1-enyl)propanoate (4)

To a solution of 8.11 g of (*R*)-5-methyl-2-(phenylsulfinyl)cyclohexanone (34.3 mmol) in 200 mL of DMF at −40 °C was added 6.16 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (41.2 mmol) dropwise via syring. The resulting orange solution was stirred at −40 °C for 0.25 h. Methyl methacrylate (3.71 mL, 41.2 mmol) was added dropwise via syringe. The reaction mixture was stirred for 1 h at −40 °C and then warmed to rt. The solution was heated to 40 °C for 2 h and then cooled to rt. The reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organics were washed five times with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a crude brown oil. The oil was purified by column chromatography on silica gel (5:1→4:1 hexanes:ethyl acetate) to give 4.23 g (63 %) of the title compound **4** as a light yellow oil.

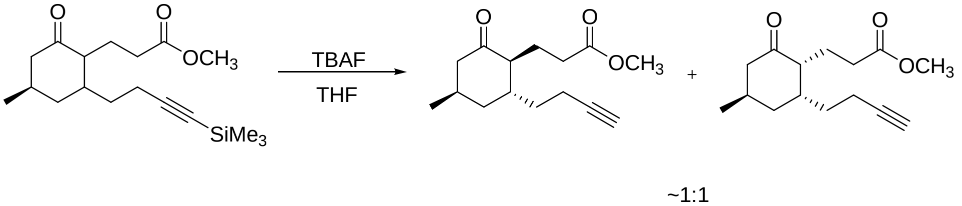
IR (neat): 2995, 1739, 1673 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73-6.71 (m, 1H), 3.63 (s, 3H), 2.49-2.36 (m, 6H), 2.20-1.98 (m, 3H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 174.5, 146.5, 138.7, 52.4, 47.5, 35.3, 34.0, 31.5, 26.3, 22.1. MS (ESI): 219 (M + Na$^+$). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.56; H, 8.29. $[\alpha]^{20}_D$ = -39° (c = 0.63, $CHCl_3$).



Methyl 3-((4*R*)-4-methyl-2-oxo-6-(4-(trimethylsilyl)but-3-ynyl)cyclohexyl)propanoate

To a suspension of 5.73 g of magnesium (236 mmol) in 200 mL of THF was added 34.9 g of 4-trimethylsilyl-1-bromo-3-butyne (170 mmol) in one portion via syringe. The reaction mixture was immediately cooled to 0 °C and stirred for 1 h. The cloudy grey solution was transferred dropwise via cannula to a suspention of 34.9 g of copper(I) bromide-dimethyl sulfide complex (170 mmol) in 400 mL of THF at −78 °C and stirred for 1 h. To the resulting dark red reaction mixture was added 12.7 mL of chlorotrimethylsilane (99.1 mmol) dropwise via syringe. A solution of 18.5 g of (*R*)-methyl 3-(4-methyl-6-oxocyclohex-1-enyl)propanoate (94.4 mmol) in 50 mL of THF was added to the red mixture dropwise via cannula. The resulting reaction mixture was stirred at −78 °C for 1 h then at −40 °C for 1 h before warming to rt. The mixture was

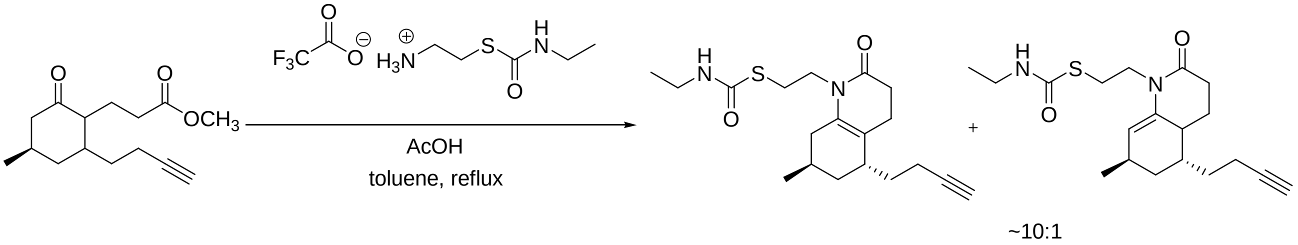
quenched with basic ammonium chloride solution, diluted with diethyl ether, and the layers were separated. The organic layer was washed with basic ammonium chloride solution until the aqueous fraction was no longer blue. The organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil. The crude oil was dissolved in 300 mL of methanol and 3 mL of 3M HCl. The solution was stirred for 2 h at rt. The solvents were removed *in vacuo* to yield a crude yellow oil. The oil was purified by column chromatography on silica gel (10:1→5:1→3:1 hexanes:ethyl acetate) to give 25.6 g (84 %) of the title compound as a pale yellow oil.
IR (neat): 2955, 2174, 1740, 1708 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 2.38-1.87 (m, 1H), 1.71-1.43 (m, 4H), 1.01-0.94 (dd, J = 14.0, 6.1 Hz, 3H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.2, 212.5, 174.8, 174.6, 107.2, 107.1, 86.3, 86.2, 55.0, 53.8, 52.5, 52.4, 51.2, 48.1, 40.5, 39.3, 37.3, 35.0, 33.0, 32.8, 32.7, 30.9, 30.5, 26.6, 25.8, 23.2, 22.7, 22.1, 18.6, 18.5, 1.1. MS (ESI): 345 ($M + Na^+$). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.02; H, 9.33.



Methyl 3-((4*R*)-2-(but-3-ynyl)-4-methyl-6-oxocyclohexyl)propanoate (5)

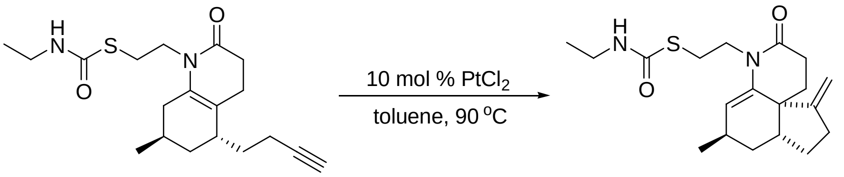
To a solution of 23.73 g of methyl 3-((4*R*)-4-methyl-2-oxo-6-(4-(trimethylsilyl)but-3-ynyl)cyclohexyl)propanoate (73.58 mmol) in 400 mL of THF was added 73.58 mL of tetrabutylammonium fluoride (73.58 mmol, 1M in THF) in portions of 10 mL. The resulting dark red reaction mixture was stirred for 0.10 h at rt before being diluted with diethyl ether. The solution was washed once with water and once with brine. The combined aqueous fractions were extracted three times with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give an orange-brown oil. The crude oil was purified by column chromatography on silica gel (4:1 hexanes:ethyl acetate) to afford 17.73 g (96 %) of the title compound **5** as a yellow oil.
IR (neat): 3288, 2953, 2360, 1738, 1708 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.42-1.88 (m, 12H), 1.74-1.46 (m, 4H), 1.00 (dd, J = 13.1, 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.3, 212.5, 174.8, 174.5, 84.4, 84.3, 69.9, 55.0, 53.9, 52.6, 52.5, 51.2, 48.1, 40.3, 39.4, 37.2, 34.9, 32.9, 32.8, 30.9, 30.5, 26.4, 26.1, 23.2, 22.8, 22.2, 17.1, 17.0. MS (ESI): 273 ($M + Na^+$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.63; H, 8.82.

Experimental Procedures for Scheme 3:



S-2-((5R,7R)-5-(But-3-ynyl)-7-methyl-2-oxo-3,4,5,6,7,8-hexahydroquinolin-1(2H)-yl)ethyl ethylcarbamothioate (7)

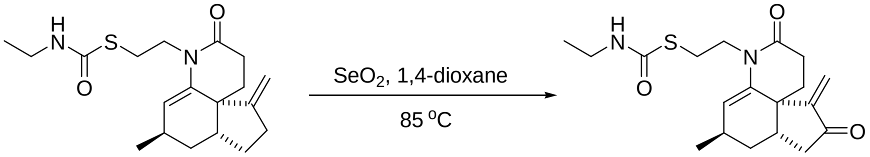
To a solution of 3.968 g of compound **5** (15.85 mmol) and 14.55 g of 2-(ethylcarbamoylthio)ethanaminium 2,2,2-trifluoroacetate (**6**) (55.48 mmol) in 40 mL of toluene was added 15.85 mL of acetic acid via syringe. A Deak-Stark apparatus was attached and the reaction mixture was heated to reflux and stirred for 4.5 h. The reaction mixture was cooled to rt, diluted with diethyl ether, and washed twice with a saturated solution of sodium bicarbonate. The combined aqueous fractions were extracted once with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1→0:1 hexanes:ethyl acetate) to afford 3.891 g (70 %) of the title compound **7** as a white solid, mp: 94-99 ^{o}C. IR (neat): 3290, 2930 2360, 1651, 1525 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.12 (br s, 1H), 3.73-3.66 (m, 2H), 3.29-3.26 (m, 2H), 2.93-2.89 (m, 2H), 2.44-1.99 (m, 8H), 1.94 (t, J = 2.4 Hz, 1H), 1.83-1.65 (m, 3H), 1.53-1.20 (m, 3H), 1.11 (t, J = 7.3 Hz, 3H), 0.99 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.1, 167.8, 133.0, 119.5, 85.6, 70.2, 42.6, 38.3, 37.7, 35.1, 34.8, 33.4, 33.1, 29.5, 26.0, 25.3, 22.9, 18.3, 16.3. Additional peaks associated with the minor isomer: δ 170.7, 170.4, 138.8, 129.8, 128.0, 112.9, 85.4, 70.1, 41.7, 35.6, 34.5, 34.0, 29.2, 26.6, 17.5, 15.7. MS (APCI): 349 (M + H^{+}). Anal. Calcd for $C_{19}H_{28}N_2O_2S$: C, 65.48; H, 8.10; N, 8.04. Found: C, 65.22; H, 8.10; N, 7.78. $[\alpha]^{20}_{D}$ = +24^{o} (c = 0.57, CHCl$_3$).



S-2-((9R)-9-Methyl-5-methylene-2-oxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[e]quinolin-1(2H)-yl)ethyl ethylcarbamothioate (8)

A solution of 3.33 g containing both constitutional isomers of compound **7** (9.57 mmol) and 0.255 g of platinum(II) chloride (0.957 mmol) in 35 mL of toluene were heated to 90 ^{o}C and stirred for 5 h. The reaction mixture was then cooled to rt and filtered through a plug of triethylamine washed silica gel. The solvents were removed *in vacuo* to give a thick brown oil. The crude oil was purified by column chromatography on triethylamine

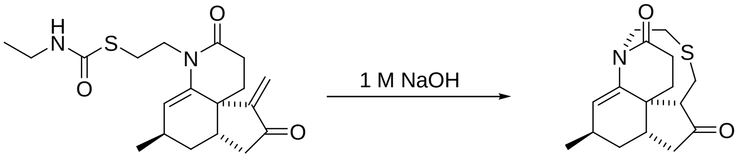
washed silica gel (3:1→1:1→0:1 hexanes:ethyl acetate) to afford 2.91 g (87 %) of the title compound **8** as a yellow foam.
IR (neat): 3288, 2955, 2244, 1657, 1631, 1527 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (br s, 1H), 5.45 (d, *J* = 3.5 Hz, 1H), 4.87 (s, 1H), 4.63 (s, 1H), 4.02-3.95 (m, 1H), 3.74-3.67 (m, 1H), 3.29 (t, *J* = 5.7 Hz, 2H), 3.00-2.98 (m, 2H), 2.51-2.30 (m, 5H), 2.03-1.95 (m, 2H), 1.79-1.75 (m, 1H), 1.38-1.33 (m, 1H), 1.22-1.17 (m, 1H), 1.12 (t, *J* = 7.0, 3H), 0.99 (t, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 167.5, 154.3, 139.0, 112.7, 109.3, 49.3, 45.6, 41.8, 37.3, 33.5, 30.3, 29.7, 29.4, 29.3, 27.6, 27.4, 22.4, 15.9. MS (APCI): 349 (M + H$^+$), 371 (M + Na$^+$). $[\alpha]^{21}_D$ = +92° (c = 0.99, $CHCl_3$).



S-2-((9*R*)-9-Methyl-5-methylene-2,6-dioxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2H)-yl)ethyl ethylcarbamothioate (9)

A solution of 0.11 g of annulation product **8** (0.30 mmol) and 0.034 g of selenium dioxide (0.30 mmol) in 7 mL of 1,4-dioxane was heated to 85 °C and stirred for 1.75 h. The resulting brown solution was cooled to rt and the solvents were removed *in vacuo* to give a red-brown residue. The residue was purified by column chromatography on triethylamine washed silica gel (3:1→1:1→1:2→0:1 hexanes:ethyl acetate) to afford 0.060 g (54 %) of the title enone **9** as a pale yellow oil.
IR (neat): 3290, 2932, 2360, 1728, 1667, 1636, 1524 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H), 5.80 (br s, 1H), 5.66 (d, *J* = 4.8 Hz, 1H), 5.20 (s, 1H), 4.09-4.02 (m, 1H), 3.78-3.70 (m, 1H), 3.33 (quint., *J* = 6.1 Hz, 2H), 3.10-3.01 (m, 2H), 2.75 (dd, *J* = 18.7, 7.4 Hz, 1H), 2.60-2.30 (m, 4H), 2.15 (s, 1H), 1.91-1.79 (m, 2H), 1.44-1.41 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.9, 169.4, 167.4, 149.0, 138.5, 120.6, 113.3, 46.7, 46.0, 42.8, 37.4, 36.1, 34.0, 30.3, 29.8, 29.0, 27.5, 22.3, 15.9. MS (ESI): 385 (M + Na$^+$). $[\alpha]^{20}_D$ = +40.6° (c = 1.58, $CHCl_3$).

Experimental Procedures for Scheme 4:

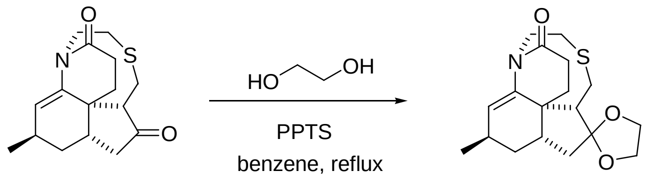


Sulfide (10)

A solution of 134 mg of enone **9** (0.37 mmol) in 20 mL of freshly sparged 1 M NaOH and 5 drops of dry dichloromethane was stirred vigorously for 12 h. The aqueous solution was extracted five times with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a clear oil.

The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1→1:2→0:1 hexanes:ethyl acetate) to yield 82.0 mg (76 %) of sulfide **10** as a white solid, mp: 155 °C (dec).

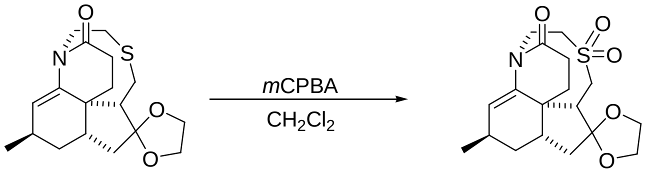
IR (film): 2928, 1734, 1636 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (d, *J* = 4.3 Hz, 1H), 4.71-4.64 (m, 1H), 3.36 (dt, *J* = 13.4, 4.6 Hz, 1H), 3.00-2.87 (m, 3H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.65-2.58 (m, 3H), 2.51 (d, *J* = 9.4 Hz, 1H), 2.36 (septet, *J* = 4.7 Hz, 1H), 2.17 (dd, *J* = 18.6, 4.3 Hz, 1H), 2.00-1.97 (m, 2H), 1.60-1.51 (m, 2H), 1.11 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.9, 169.9, 139.1, 120.6, 78.2, 61.5, 44.1, 43.5, 38.9, 37.1, 34.5, 33.6, 31.3, 29.6, 28.1, 22.1. MS (APCI): 292 (M + H^+). $[\alpha]^{21}_D$ = +335° (c = 0.75, $CHCl_3$).



Synthesis of Ketal Intermediate

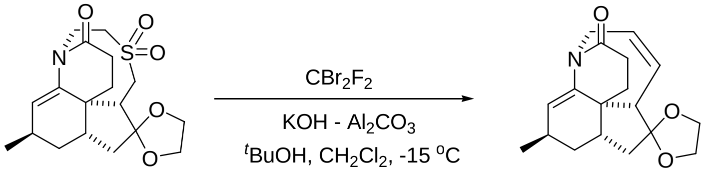
A solution of 0.345 g of sulfide **10** (1.18 mmol), 0.297 g of pyridinium *p*-toluenesulfonate (1.18 mmol), and 0.40 mL of ethylene glycol (7.10 mmol) in 15 mL of benzene was heated to reflux using a Dean-Stark apparatus. The reaction was refluxed with stirring for 30 h. It was then cooled to rt, diluted with diethyl ether, and poured into a solution of saturated sodium bicarbonate. The aqueous layer was separated and subsequently extracted three times with ethyl acetate. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated to yield a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→0:1 hexanes:ethyl acetate) to afford 0.346 g (87 %, 93 % BRSM) of the ketal as a pale yellow oil.

IR (neat): 2926, 1636 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.24 (d, *J* = 3.1 Hz, 1H), 4.66 (ddd, *J* = 13.7, 11.3, 5.9 Hz, 1H), 3.93-3.78 (m, 4H), 3.30 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.09 (d, *J* = 14.8 Hz, 1H), 3.05-2.97 (m, 1H), 2.82-2.57 (m, 3H), 2.38-2.32 (m, 1H), 2.23-2.06 (m, 4H), 1.92-1.85 (m, 1H), 1.80-1.57 (m, 3H), 1.41-1.33 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 140.4, 120.0, 116.6, 65.6, 64.8, 57.8, 44.5, 41.6, 41.2, 40.2, 35.3, 34.4, 34.2, 34.1, 30.3, 27.3, 22.4. MS (ESI): 358 (M + Na^+). Anal. Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; H, 7.51; N, 4.18. Found: C, 64.36; H, 7.58; N, 3.99. $[\alpha]^{21}_D$ = + 206° (c = 0.26, $CHCl_3$).



Sulfone 11

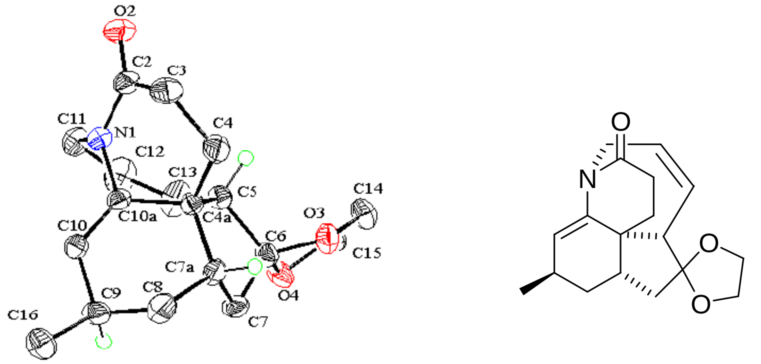
To a solution of 0.014 g of the ketal (0.042 mmol) in 1.5 mL of dichloromethane at −78 °C was added a solution of 0.021 g of *m*-chloroperbenzoic acid (0.12 mmol) in 2.5 mL of dichloromethane, dropwise via cannula. The white suspension was stirred for 0.25 h at −78 °C, warmed to rt and stirred for a subsequent 2.5 h. The reaction mixture was diluted with dichloromethane, washed once with a saturated solution of sodium bicarbonate, once with a saturated solution of sodium bisulfite, and once with brine. The combined aqueous fractions were extracted once with dichloromethane. The combined organics were dried over sodium sulfate, filtered, and concentrated to afford a white film. The crude product was purified by column chromatography on triethylamine washed silica gel (1:1→0:1 hexanes:ethyl acetate) to afford 0.015 g (98 %) of sulfone **11** as a clear oil.
IR (neat): 2931, 1717, 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.41 (d, *J* = 3.9 Hz, 1H), 5.22 (ddd, *J* = 14.6, 12.4, 6.1 Hz, 1H), 4.02-3.80 (m, 5H), 3.46 (d, *J* = 16.1, 1H), 3.34 (dd, *J* = 14.4, 5.8 Hz, 1H), 3.20-3.15 (m, 1H), 3.05-2.98 (m, 1H), 2.70-2.61 (m, 2H), 2.51-2.41 (m, 3H), 2.28-2.11 (m, 2H), 1.75-1.66 (m, 2H), 1.62-1.56 (m, 2H), 1.09 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 139.1, 119.9, 116.4, 65.7, 65.4, 58.3, 53.6, 48.0, 45.3, 41.4, 40.1, 37.0, 35.5, 33.9, 30.4, 28.2, 22.1. MS (APCI): 368 ($M + H^+$). $[\alpha]^{20}_D = +149^o$ (c = 1.23, $CHCl_3$).



Olefin 12

A suspention of 0.031 g of sulfone **11** (0.084 mmol) and 0.30 g of alumina-supported potassium hydroxide[1] in 1.75 mL of *tert*-butyl alcohol and 0.75 mL of dichloromethane was cooled to -15 °C. To the cold suspension was added 0.10 mL of dibromodifluoromethane (1.1 mmol) slowly via syringe. The reaction mixture was stirred at -15 °C for 2.2 h and warmed to rt. The mixture was filtered over Celite, rinsing exhaustively with dichloromethane, and concentrated to give a yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:0→3:1→1:1→0:1 hexanes:ethyl acetate) to afford 0.012 g (46 %) of olefin **12** as a clear film.
IR (neat): 2958, 1695, 1661 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.65-5.62 (m, 1H), 5.54 (s, 1H), 5.39-5.35 (m, 1H), 5.04-5.00 (m, 1H), 3.95-3.89 (m, 4H), 3.62 (dd, *J* = 17.5, 2.0 Hz, 1H), 2.51-2.33 (m, 3H), 2.31-2.14 (m, 3H), 1.95-1.88 (m, 1H), 1.75-1.61 (m, 3H), 1.34 (ddd, *J* = 13.6, 10.8, 5.2 Hz, 1H), 1.04 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 141.6, 129.1, 127.1, 125.4, 116.5, 65.7, 64.4, 54.4, 51.0, 50.5, 41.1,

39.4, 37.2, 32.2, 31.3, 26.6, 22.3. MS (APCI): 302 (M + H$^+$). $[\alpha]^{21}_D$ = +142° (c = 0.27, $CHCl_3$).



Structure of product **12** as determined from X-ray diffraction

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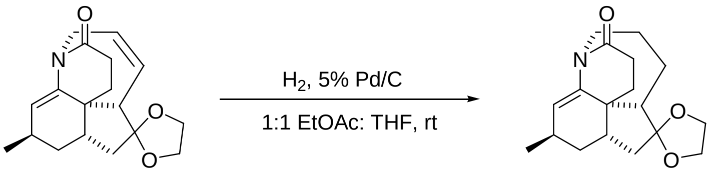
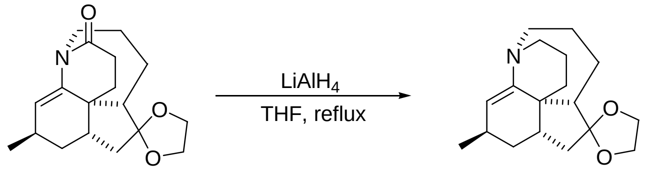


Synthesis of Enamide Intermediate

The nitrogen atmosphere of a solution of 0.026 g of olefin **12** (0.086 mmol) and 9.0 mg of 5 % palladium on carbon (0.0043 mmol) in 3 mL of a 1:1 ethyl acetate:THF mixture was replaced by purging with hydrogen gas. A full hydrogen balloon was then attached and the reaction mixture was stirred at rt for 12 h. The black suspension was filtered through Celite, rinsing exhaustively with methanol. The solution was then concentrated to give a yellow film. The crude film was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→1:5→0:1 hexanes:ethyl acetate) to afford 0.015 g (57 %) of the enamide as a white solid.

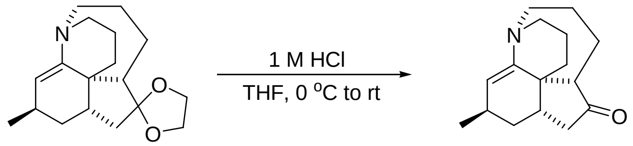
IR (film): 2927, 1738, 1688, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (s, 1H), 4.38 (dt, *J* = 12.8, 3.0 Hz, 1H), 3.93-3.83 (m, 4H), 2.87 (ddd, *J* = 13.3, 9.3, 6.4 Hz, 1H), 2.40-2.20 (m, 4H), 2.16-2.09 (m, 1H), 1.95-1.85 (m, 2H), 1.78-1.57 (m, 6H), 1.34-1.25 (m, 2H), 1.05 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 143.0, 126.4, 115.8, 64.8, 63.5, 57.5, 49.9, 47.6, 41.5, 37.8, 37.6, 31.5, 31.3, 28.7, 28.3, 25.8, 21.5. MS (APCI): 304 (M + H$^+$). $[\alpha]^{20}_D$ = +106° (c = 0.76, $CHCl_3$).



Synthesis of Enamine Intermediate

To a suspension of 0.018 g of lithium aluminum hydride (0.48 mmol) in 2 mL of THF was added a solution of 0.015 g of the enamide (0.048 mmol) in 2 mL of THF via cannula. The reaction mixture was heated to reflux and stirred for 8 h. The grey suspension was cooled to rt, followed by the slow addition of 18 μL of water, 16 μL of 15 % NaOH, then another 54 μL of water. The biphasic mixture was stirred for 15 minutes at rt after which 0.2 g of magnesium sulfate was added. After stirring for another 30 minutes at rt, the mixture was filtered through a pad of Celite and rinsed exhaustively with diethyl ether. The filtrate was concentrated *in vacuo* to afford a clear film. The crude product was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→1:5→0:1 hexanes:ethyl acetate) to afford 9.8 mg (71 %) of the enamine as a clear oil.

IR (neat): 2925, 2852, 1656, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (d, *J* = 1.7 Hz, 1H), 3.95-3.87 (m, 4H), 3.09-2.96 (m, 4H), 2.20-2.18 (m, 1H), 1.98-1.84 (m, 4H), 1.78-1.44 (m, 7H), 1.26-1.11 (m, 3H), 0.98 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 129.0, 117.3, 65.6, 64.4, 60.8, 56.3, 53.0, 46.8, 43.1, 40.5, 38.9, 33.3, 33.0, 30.0, 27.0, 25.2, 22.6. MS (APCI): 290 (M + H$^+$). $[\alpha]^{20}_D = +91^\circ$ (c = 0.95, $CHCl_3$).



(+)-Fawcettidine (1)

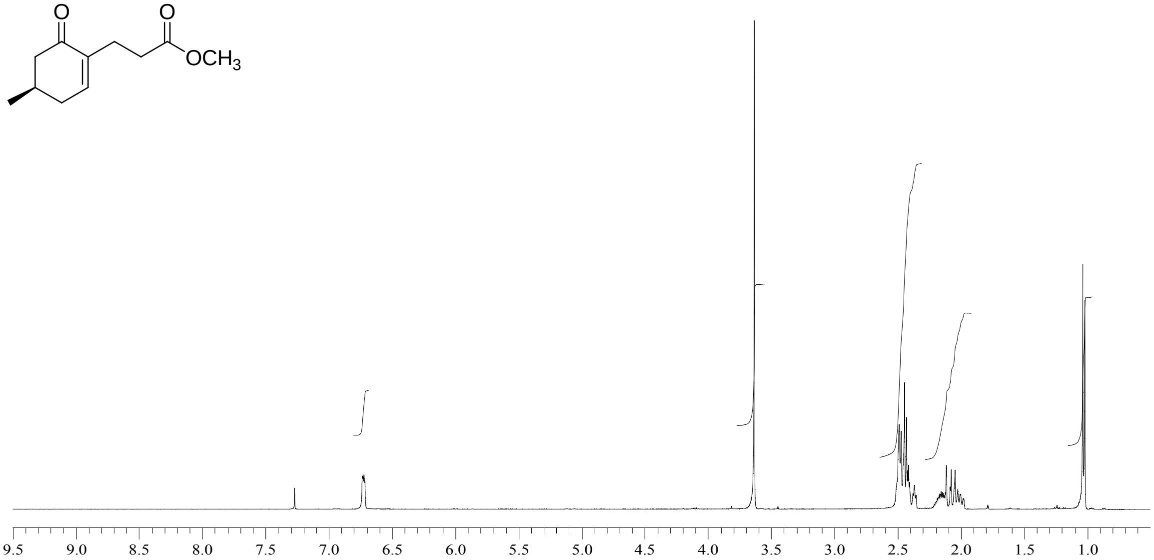
To a solution of 5.0 mg of the enamine (0.018 mmol) in 0.5 mL of THF at 0 °C was added 0.05 mL of 1 M HCl. The solution was stirred at rt for 17 h. The reaction mixture was neutralized with 0.05 mL of 1 M NaOH and then extracted twice with ethyl acetate. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→0:1 hexanes:ethyl acetate) to afford 3.0 mg (60 %) of (+)-fawcettidine (**1)** as a clear oil.

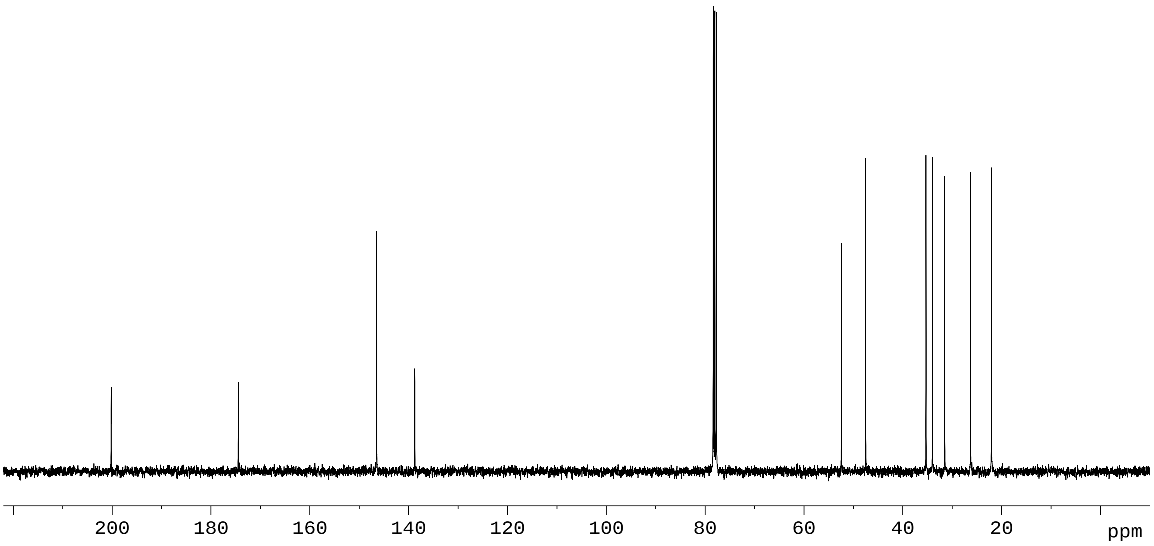
IR (neat): 2925, 2853, 1741, 1663 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (d, *J* = 5.2 Hz, 1H), 3.14-2.98 (m, 4H), 2.74 (ddd, *J* = 16.6, 7.4, 1.3 Hz, 1H), 2.34-2.24 (m, 2H), 2.20-2.05 (m, 3H), 1.99-1.93 (m, 1H), 1.91-1.83 (m, 1H), 1.79-1.59 (m, 3H), 1.41-1.34 (m, 2H), 1.28-1.21 (m, 2H), 1.05 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.9, 147.0, 128.2, 61.4, 57.2, 53.0, 47.1, 45.1, 40.2, 38.3, 35.1, 32.4, 30.2, 28.7, 24.8, 21.8. MS (APCI): 246 (M + H$^+$). $[\alpha]^{21}_D = +92^\circ$ (c = 0.41, $CHCl_3$), $[\alpha]^{19}_D = +61^\circ$ (c = 0.25, EtOH).

References:

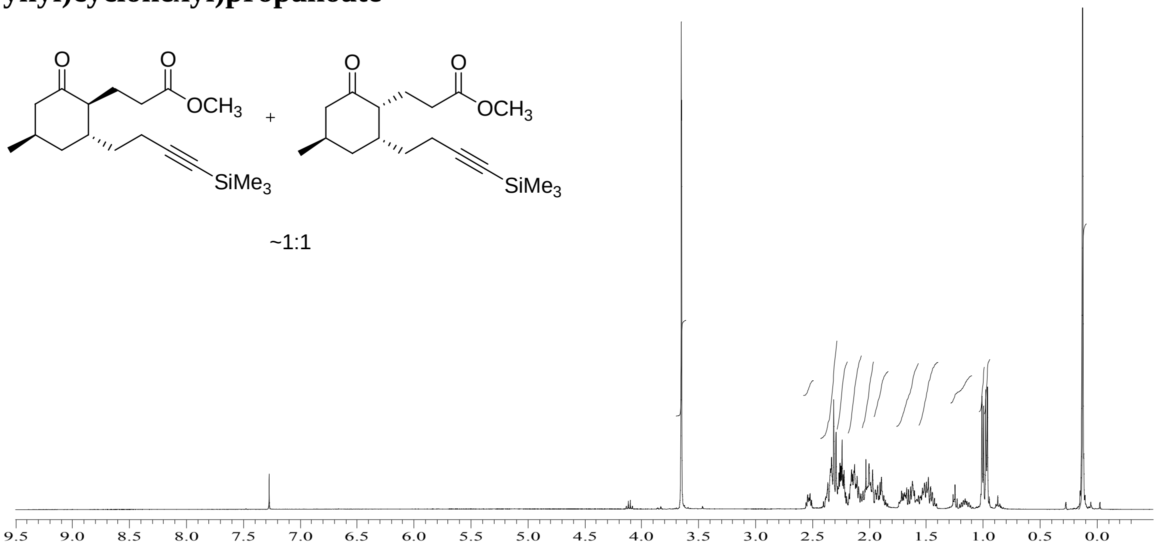
1. R. J. K. Taylor, G. Casy, *Org. React.* **2003**, *62*, 357-475.

(*R*)-Methyl 3-(4-methyl-6-oxocyclohex-1-enyl)propanoate (4)





Methyl 3-((4*R*)-4-methyl-2-oxo-6-(4-(trimethylsilyl)but-3-ynyl)cyclohexyl)propanoate



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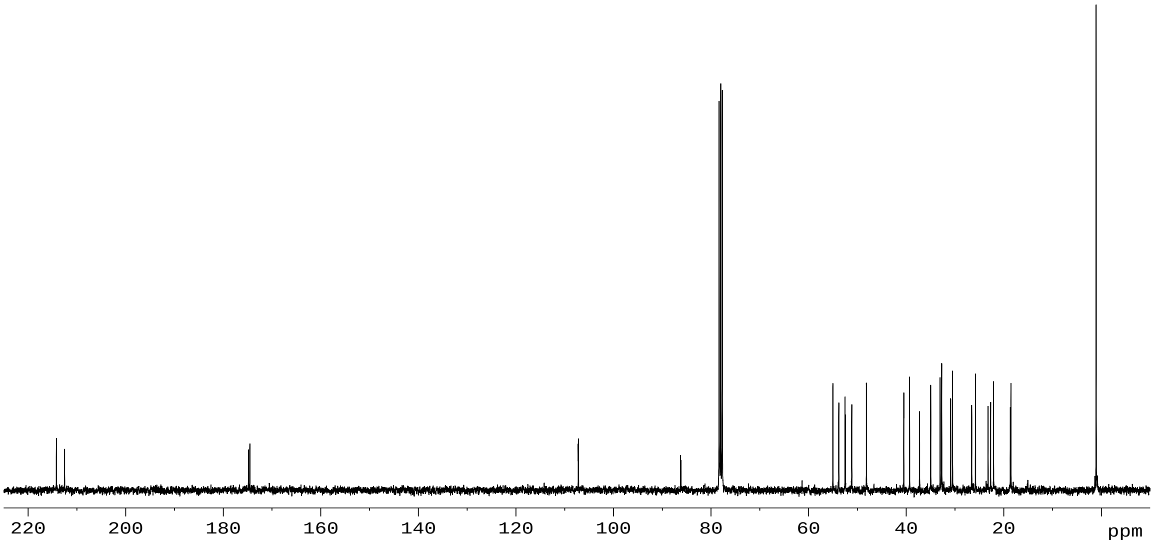
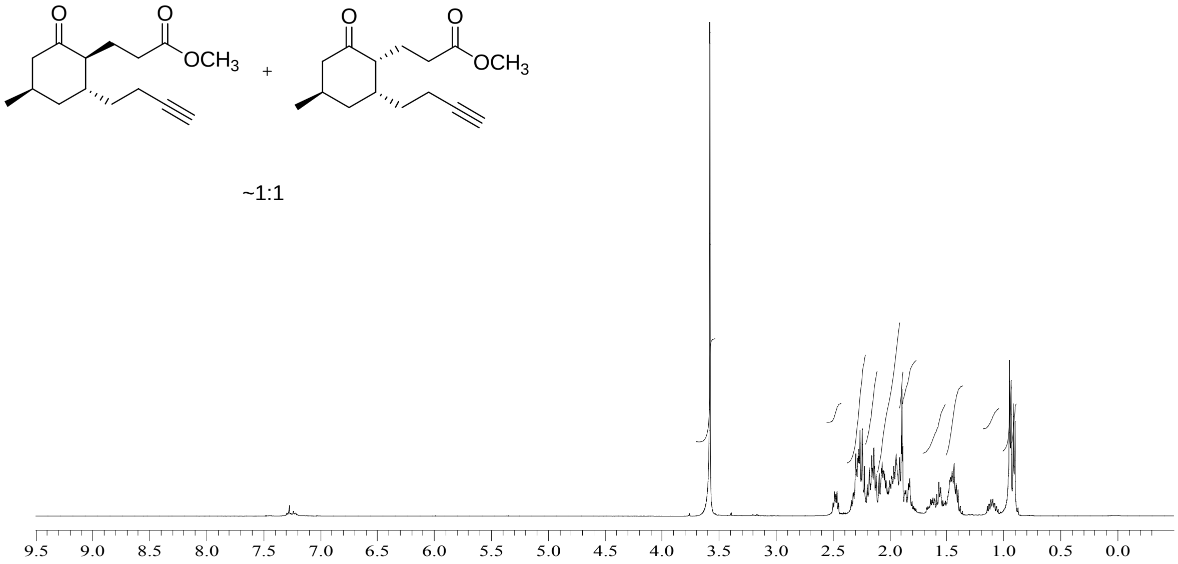
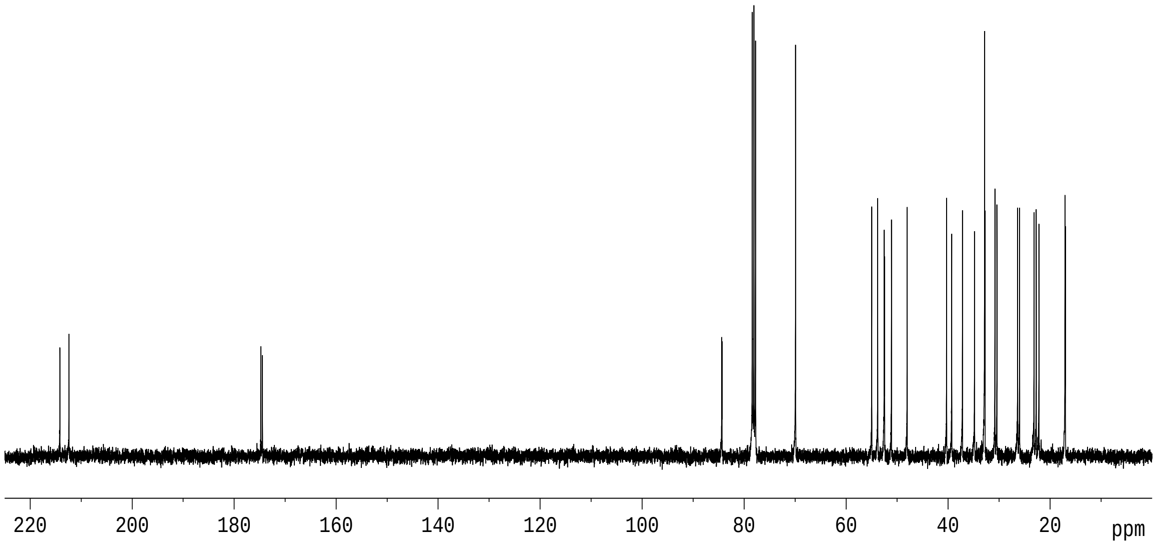
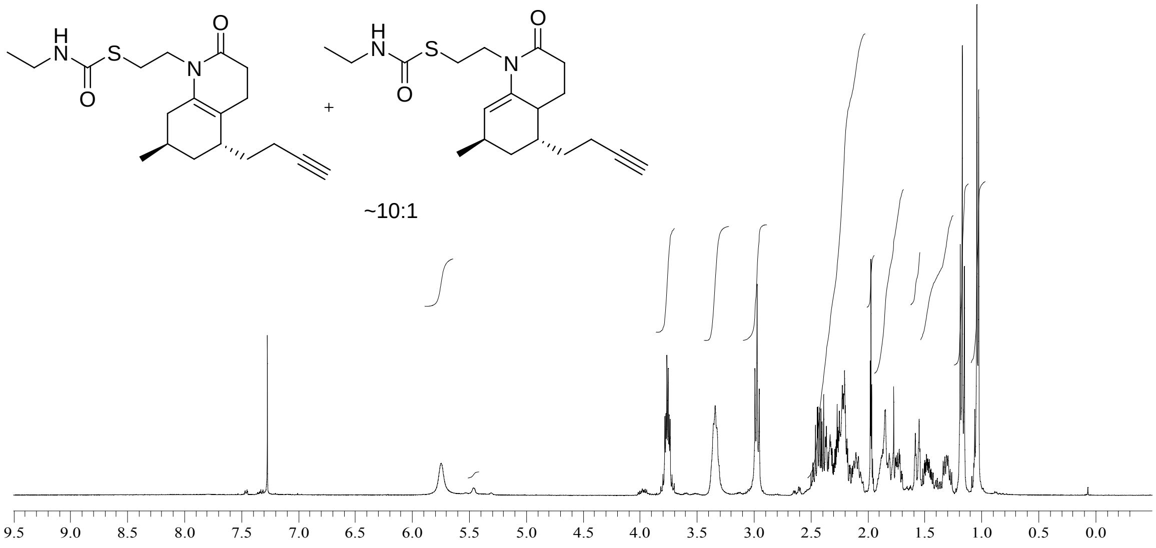


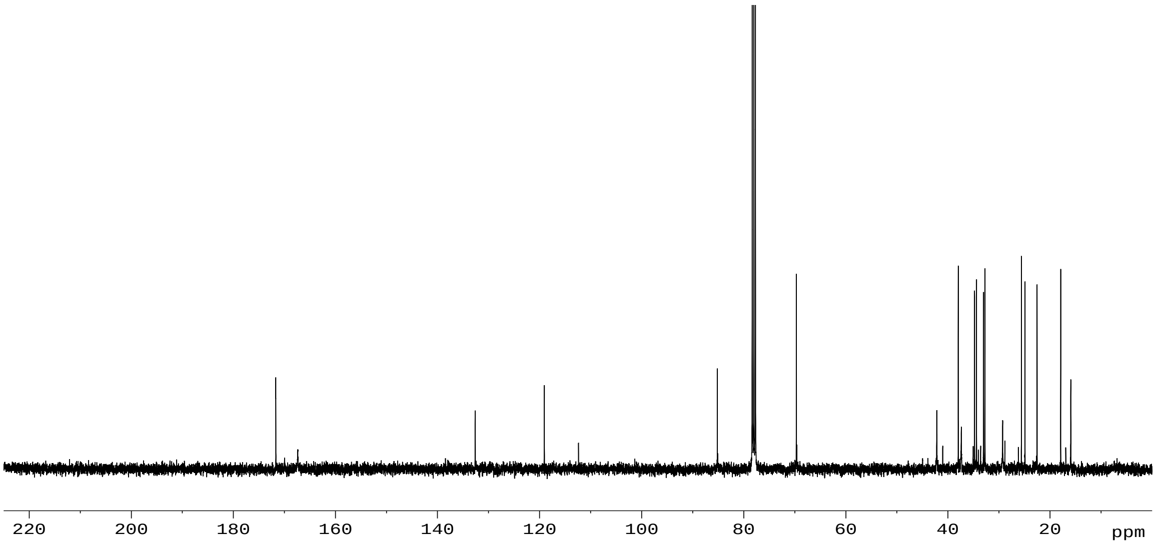
Methyl 3-((4*R*)-2-(but-3-ynyl)-4-methyl-6-oxocyclohexyl)propanoate (5)



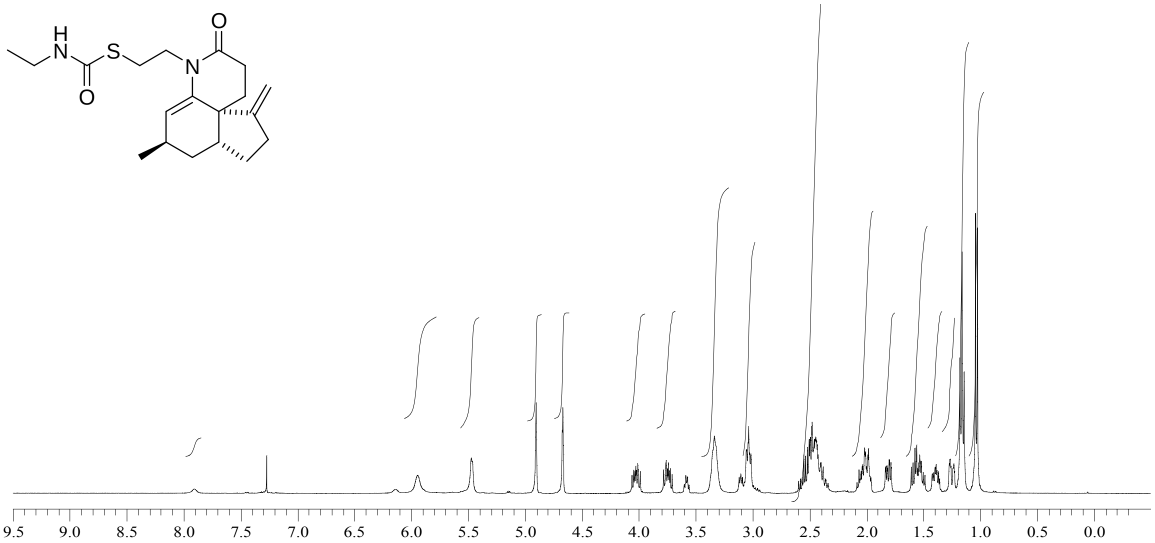


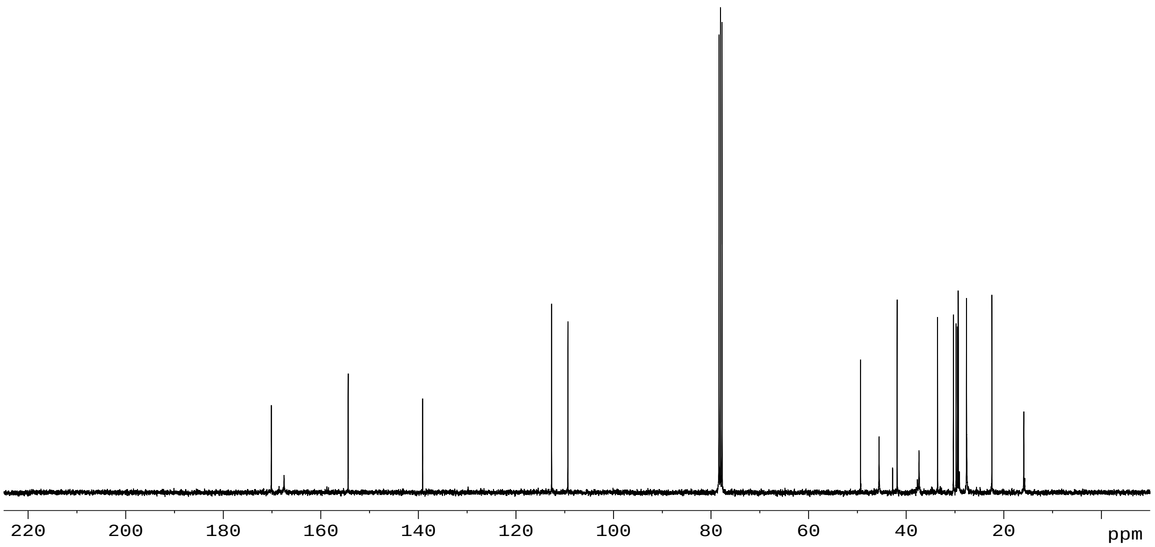
***S*-2-((5*R*,7*R*)-5-(But-3-ynyl)-7-methyl-2-oxo-3,4,5,6,7,8-hexahydroquinolin-1(2*H*)-yl)ethyl ethylcarbamothioate (7)**



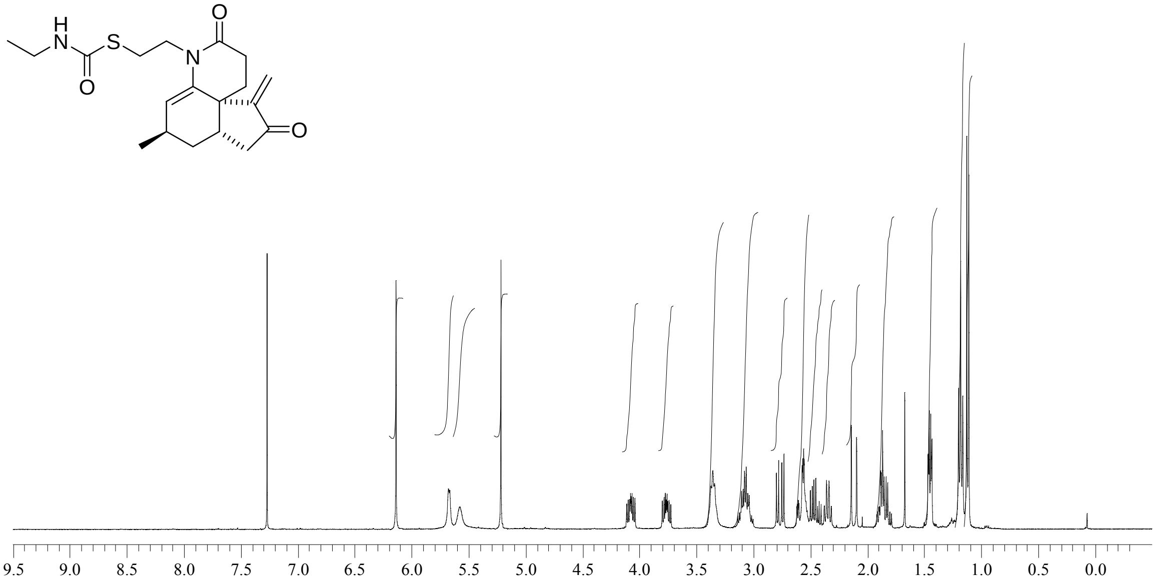


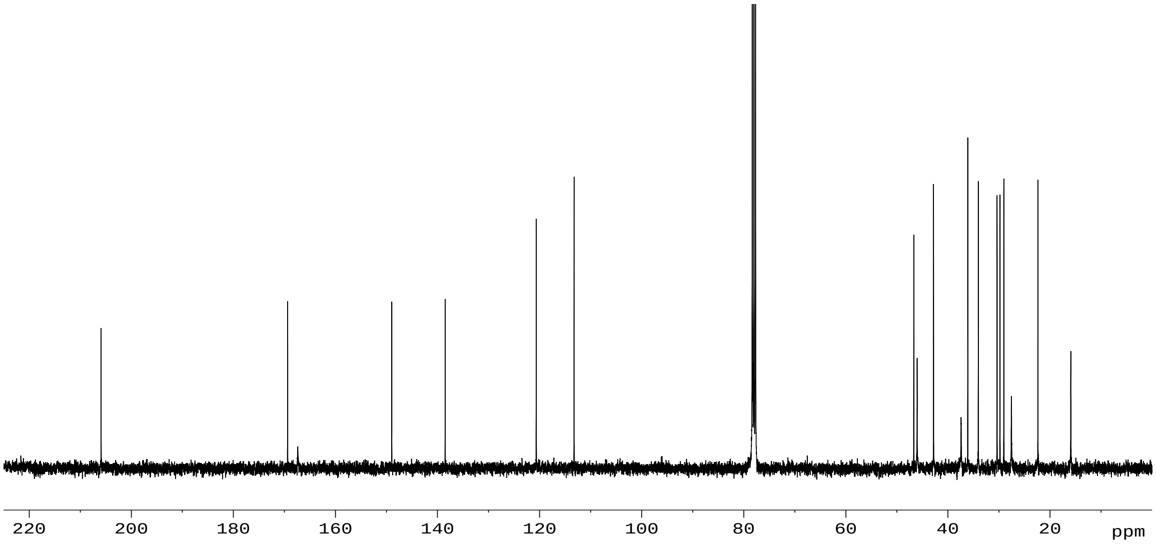
S-2-((9*R*)-9-Methyl-5-methylene-2-oxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2H)-yl)ethyl ethylcarbamothioate (8)





***S*-2-((9*R*)-9-Methyl-5-methylene-2,6-dioxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2H)-yl)ethyl ethylcarbamothioate (9)**





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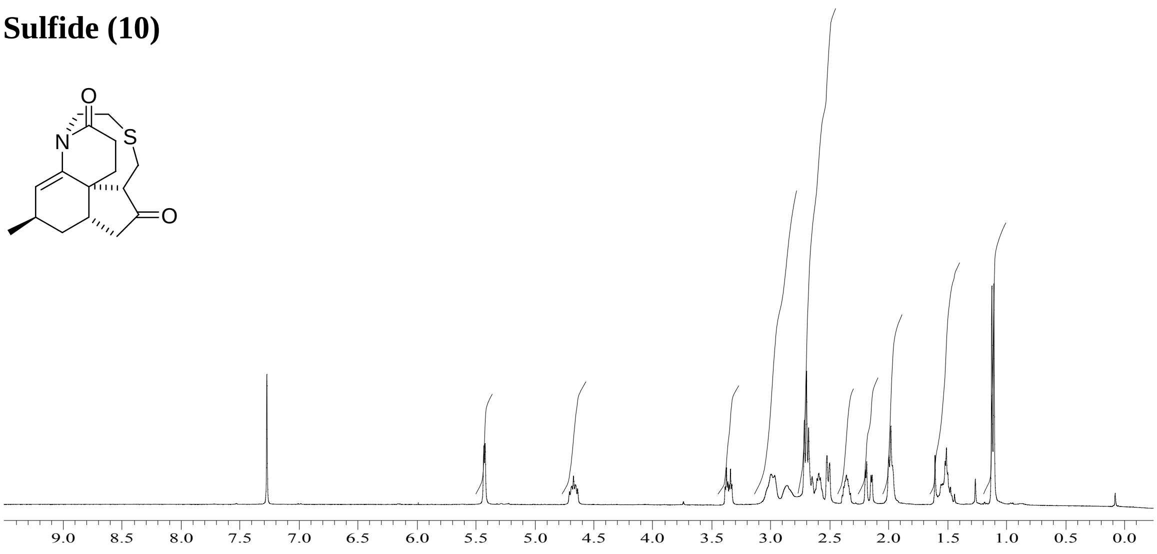
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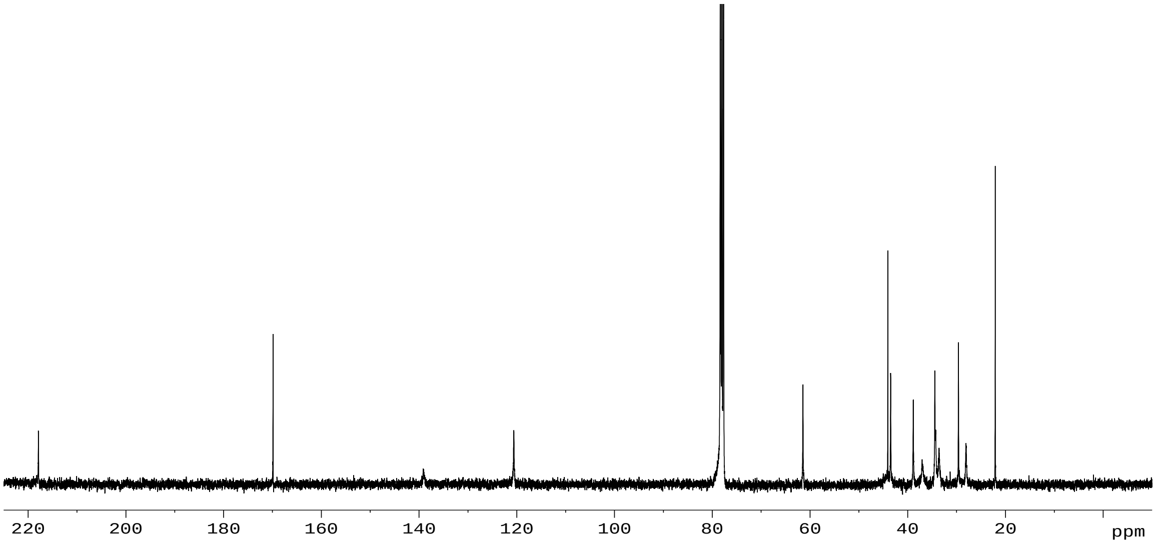
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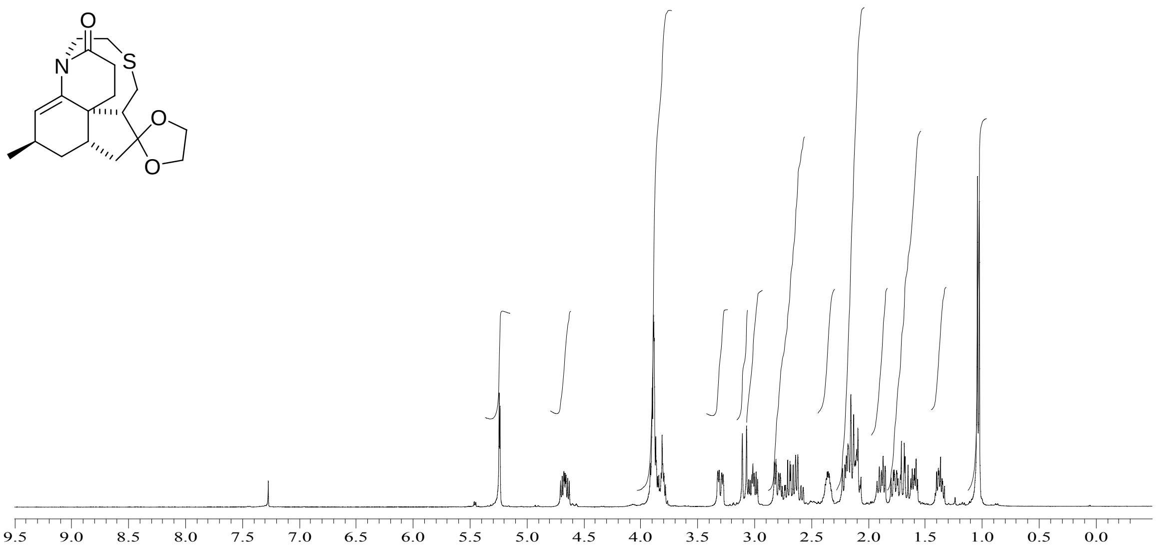
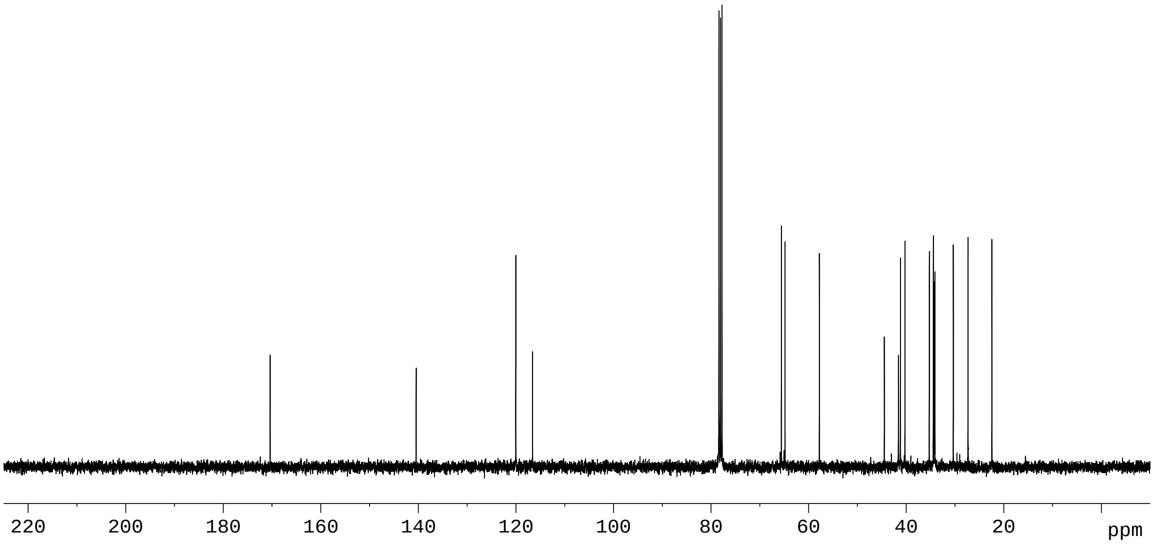
Ketal Intermediate





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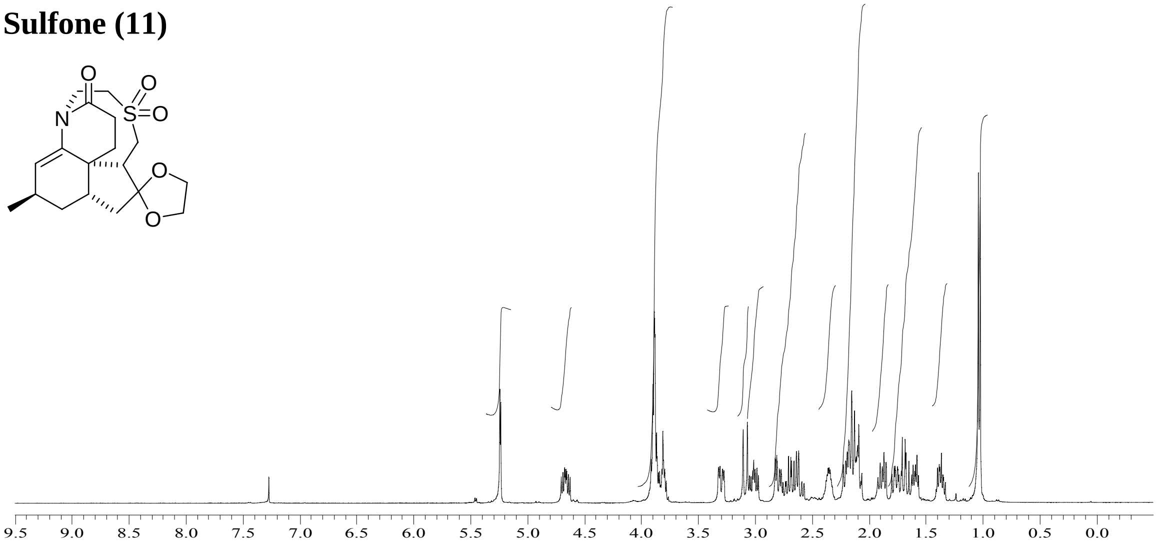
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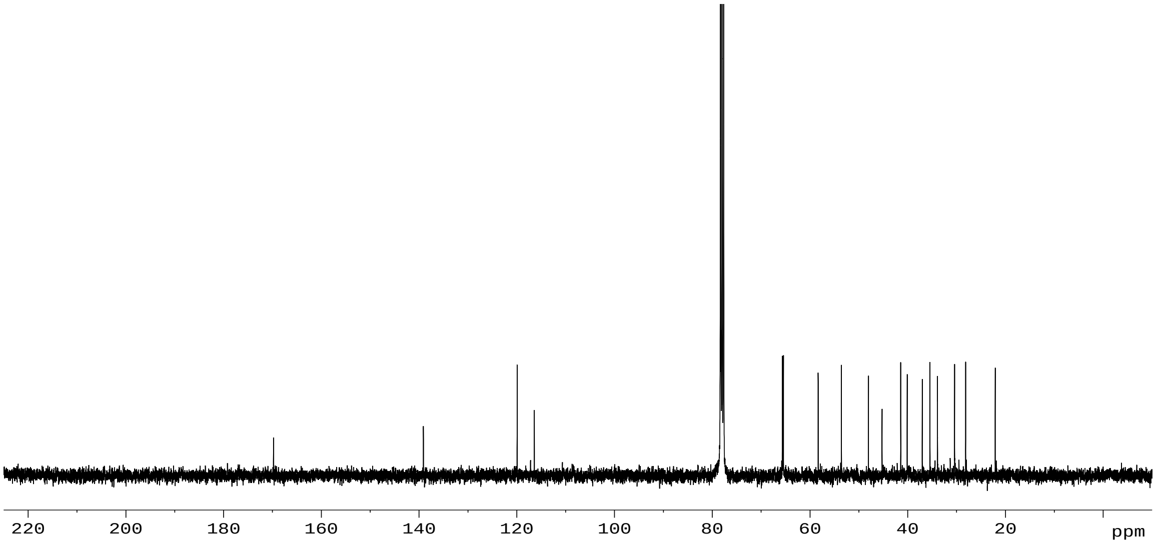
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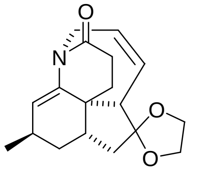
Olefin 12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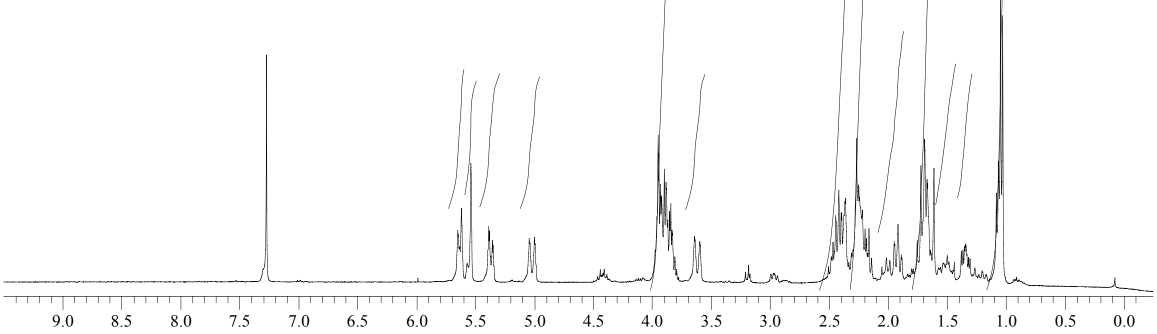
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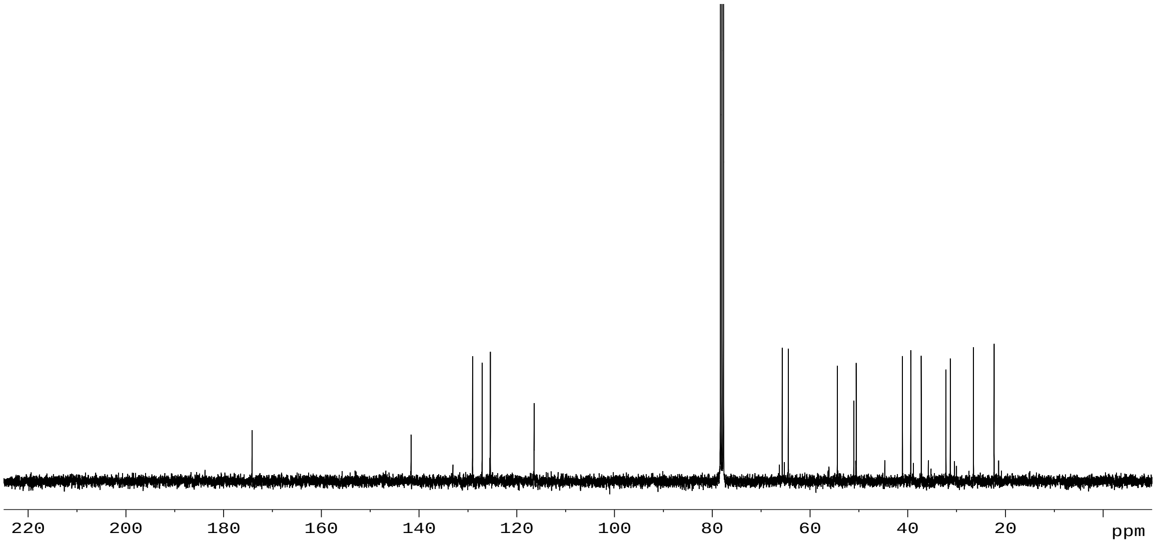
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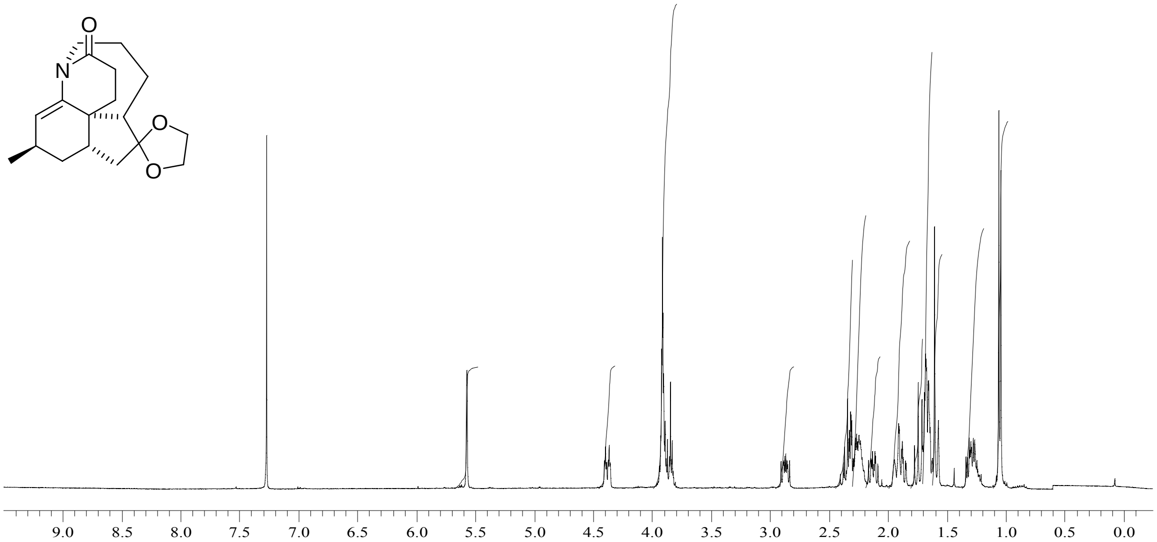
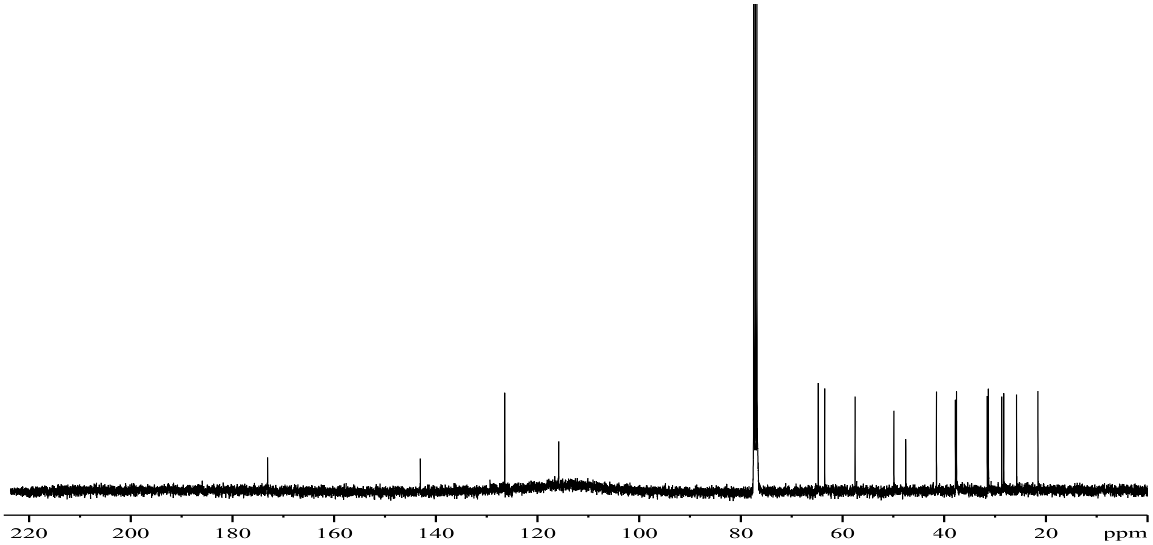
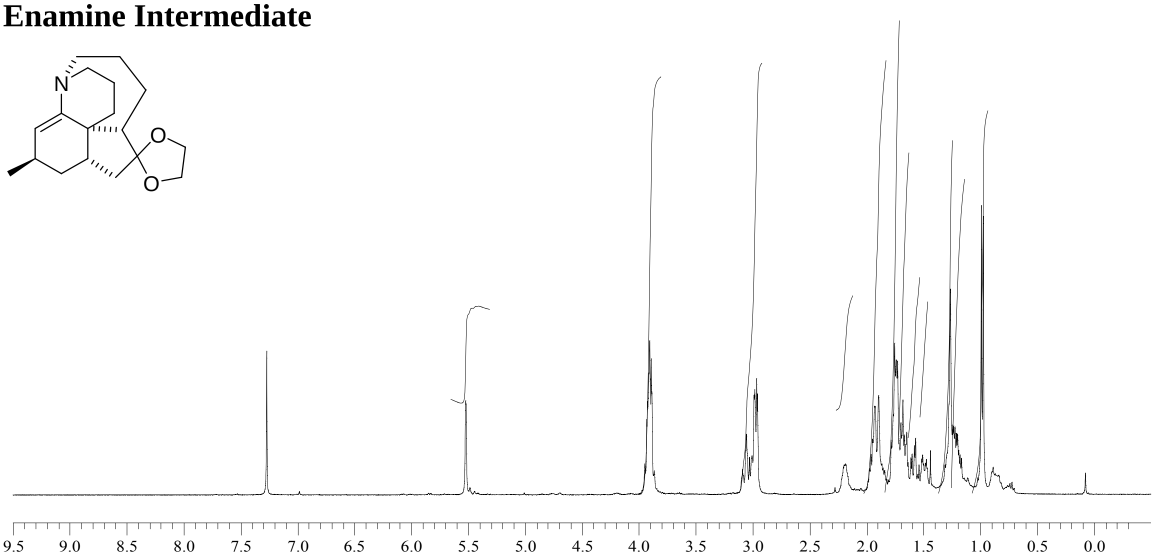
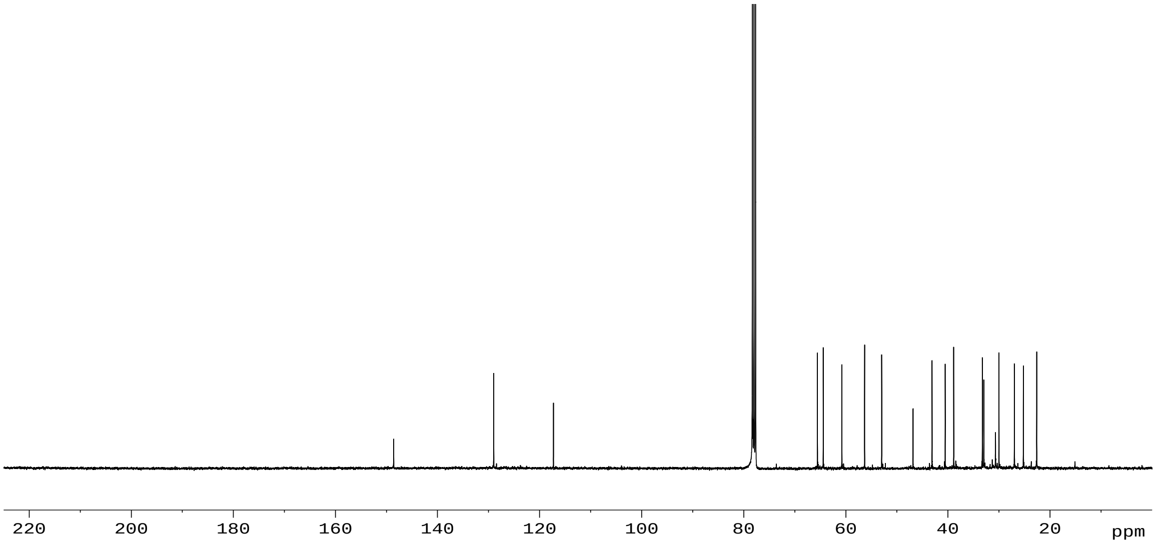
Enamide Intermediate





Enamine Intermediate





(+)-Fawcettidine (1)