Universitat Autònoma de Barcelona
Facultat de Ciències
Departament de Química

Iterative Synthetic Strategy for Azaphenalene Alkaloids.

Total Synthesis of (-)-9a-*epi*-hippocasine

Ph.D. THESIS

Ph.D. in Chemistry

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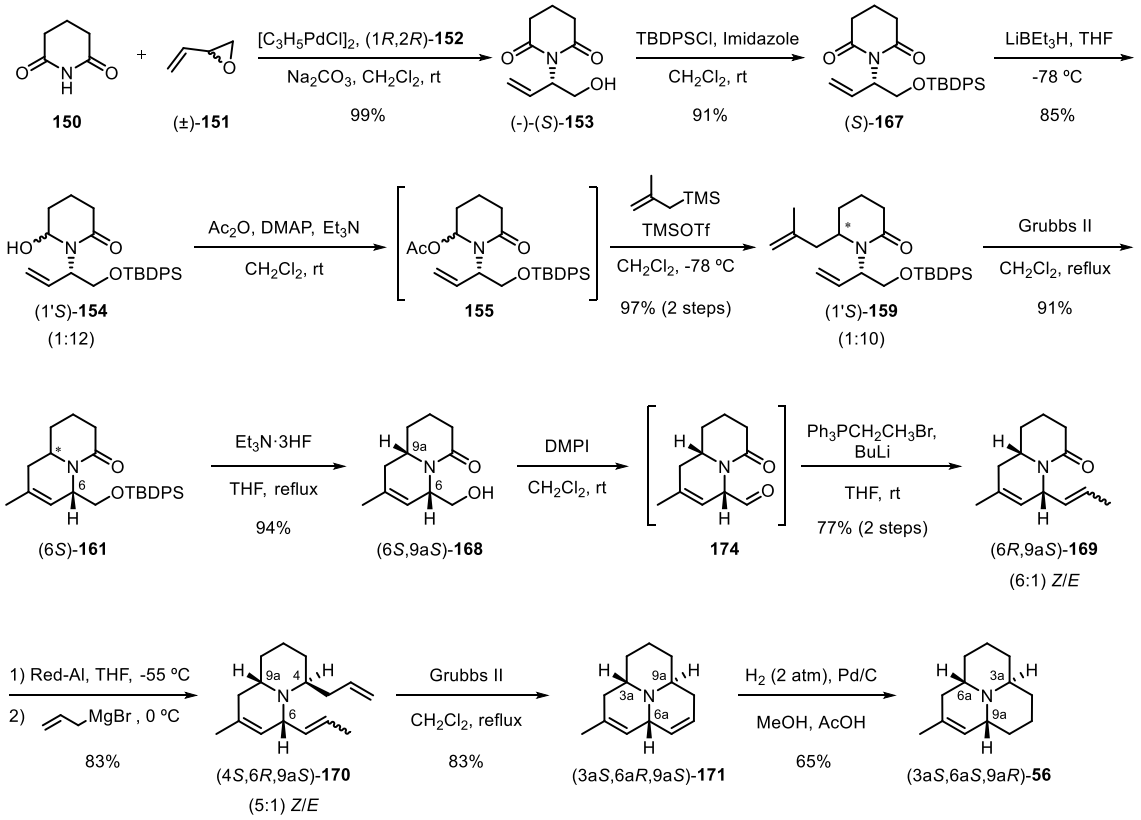
V. Summary and Conclusions

Summary and Conclusions

A non-natural alkaloid, (-)-9a-*epi*-hippocasine, **56**, has been synthesized in 11 steps and 22% overall yield starting from glutarimide, **150**, and racemic butadiene monoepoxide, **151** (Scheme 66). The enantioselectivity is originated in an initial palladium-catalyzed asymmetric allylation. A key point of the approach is the generation of the acyliminium ion derived from **154** previously synthesized in our research group.[55] An iterative strategy has been developed, encompassing two nucleophilic allylations and two ring closing metathesis processes.

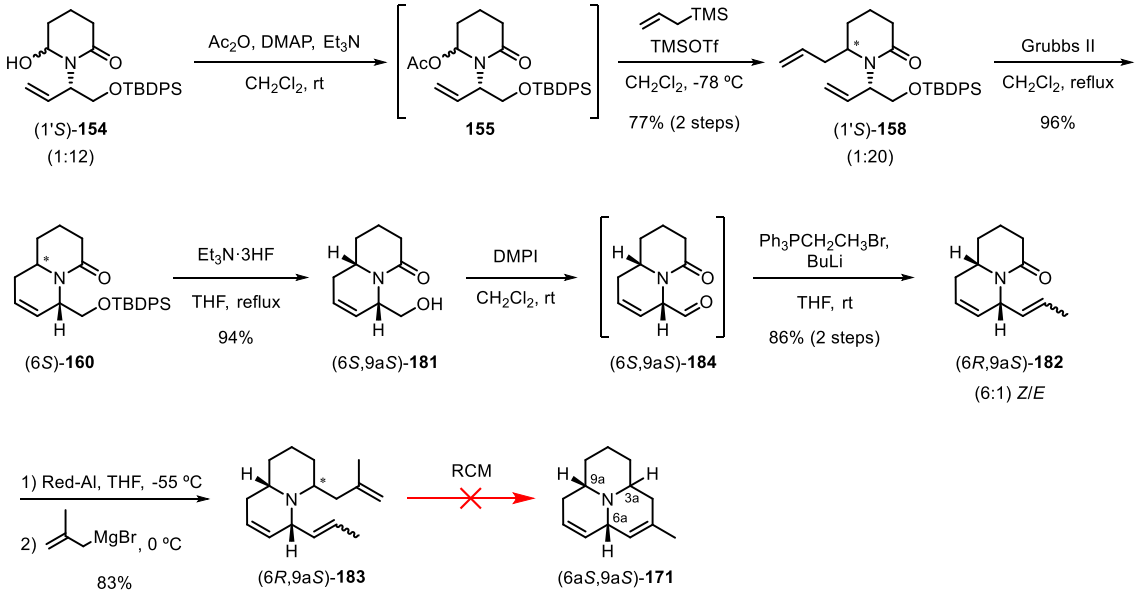


Scheme 66. Total synthesis of (-)-9a-*epi*-hippocasine, **56**.

Once the absolute configuration of **171** was confirmed, a chemoselective hydrogenation was necessary to keep the sterochemical information and avoid the synthesis of a *meso* alkaloid.

For this reason, the synthetic tactic was modified with the aim of changing the configuration of one stereogenic center (Scheme 67). As expected, the selectivity of the nucleophilic allylation steps did not change by altering the order in which the allylic residues were introduced and the configuration of the major isomer of **183** was the one required to furnish a final chiral alkaloid. Unfortunately, the second RCM leading to the construction of the

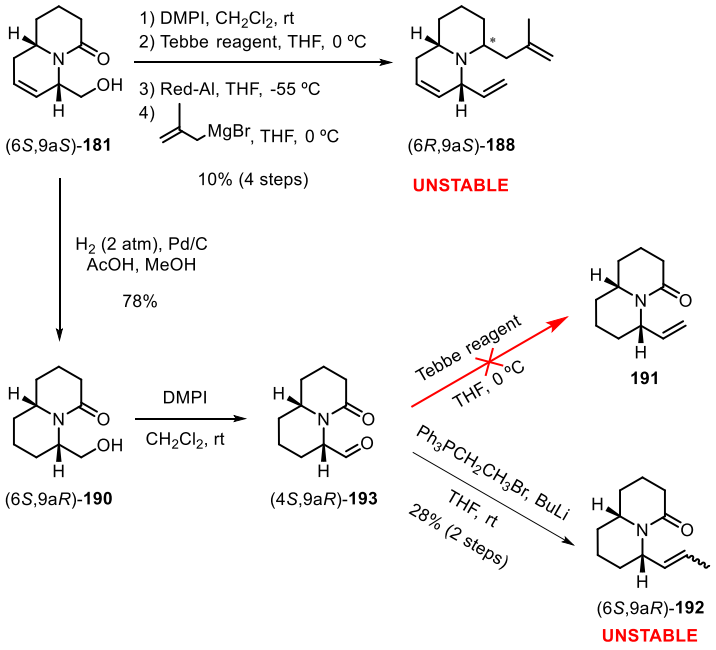
third six-membered ring was not accomplished, presumably due to steric hindrance and/or the instability of the starting material and/or products.



Scheme 67. Change of synthetic tactic. Synthetic approach to a saturated chiral alkaloid.

Two alternative approaches were tested, but none of them gave the desired results, because the involved intermediates showed low stability (Scheme 68).

Some preliminary studies based on a Relay Ring-Closing Metathesis alternative were also performed.



Scheme 68. Alternative synthetic approaches assayed.

VI. Experimental Section

1. General Procedures

1.1. Reagents and solvents

All commercially available reagents were used as received. Solvents were dried by distillation over the appropriate drying agents: CH_2Cl_2 (CaH_2), DCE (CaH_2), CH_3CN (CaH_2), THF (Na^0), toluene (Na^0). When needed, reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere.

1.2. Spectroscopy

Nuclear magnetic resonance spectra (NMR) have been registered at *Servei de Ressonància Magnètica Nuclear* in the *Universitat Autònoma de Barcelona*. ^{1}H NMR spectra were recorded on Bruker DPX250 (250 MHz), Bruker DPX360 (360 MHz) and Bruker ARX400 (400 MHz) spectrometers. Proton chemical shifts (δ) are reported in ppm ($CDCl_3$, 7.26 ppm). ^{13}C NMR spectra were recorded with complete proton decoupling on Bruker DPX250 (63 MHz), Bruker DPX360 (91 MHz) and Bruker ARX400 (101 MHz) spectrometers. Carbon chemical shifts are reported in ppm ($CDCl_3$, 77.16 ppm). NMR signals were assigned with the help of COSY, DEPT135, HSQC, HMBC, NOESY and selective n.O.e. experiments. All spectra have been registered at 298 K.

The abbreviations used to describe signal multiplicities are: s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (double doublet), tt (triple triplet), ddd (double double duplet), ddt (double double triplet), m (multiplet) and qn (quintet).

Infrared spectra (IR) were recorded on a Bruker Tensor 27 Spectrophotometer equipped with Golden Gate Single Refraction Diamond ATR (Attenuated Total Reflectance) accessory at Servei d'Anàlisi Química in the Universitat Autònoma de Barcelona. Peaks are reported in cm^{-1}.

1.3. Mass spectrometry

High resolution mass spectra (HRMS) were recorded at *Servei d'Anàlisi Química* in the *Universitat Autònoma de Barcelona* in a Bruker micrOTOFQ spectrometer using ESIMS (QTOF) or at *Parque Científico Tecnológico* at the *Universidad de Burgos* in a Micromass AutoSpec using EI-HR.

1.4. Optical Rotation

Specific optical rotations ($[\alpha]_D$) were measured at 20 ± 2 ^oC and 589.3 nm using a JASCO J-715 polarimeter in a 0.1 dm long cuvette at *Servei d'Anàlisi Química* in the *Universitat Autònoma de Barcelona* or by using a Perkin Elmer 341 spectometer at 20 and 589 nm and a 1 dm long cuvette at CSIC in Barcelona.

1.5. Chromatography

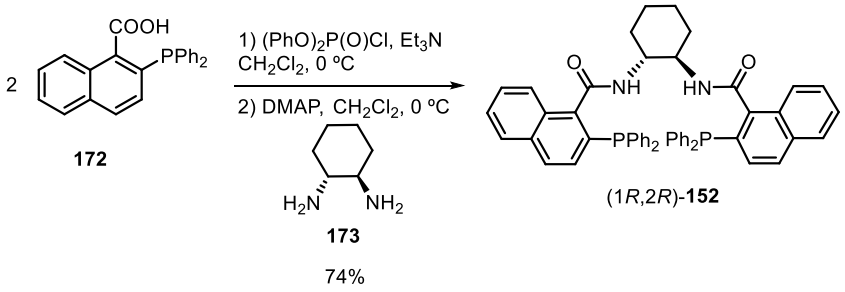
Thin-layer chromatography (TLC) were performed using silica gel 60 with fluorescent indicator UV_{254} pre-coated aluminium sheets (0.2 mm thickness) or aluminium oxide N/UV_{254} pre-coated aluminium sheets (0.2 mm thickness) and they were visualized using a 254 nm UV lamp or developing with $KMnO_4$/NaOH aqueous solution or ethanolic solution of molybdenum ammonium and cerium sulfate.

Flash column chromatography were performed using silica gel (pore size: 40-63 μm) or neutral aluminium oxide (pore size: 58 Å)

Chiral High-Performance Liquid Chromatography (CHPLC) analyses were performed using a Waters 2690 chromatograph coupled to a UV-visible Waters 996 Photodiode Array Detector with a Daicel Chiralcel IC 0.46 x 25 cm column (detector at 210 nm). All analyses were performed with a flow of 1 ml/min and 75:25 hexane:isopropanol as mobile phase.

2. Synthesis of (-)-9a-*epi*-hippocasine

2.1. Synthesis of the Trost ligand, (1*R*,2*R*)-152.



To a solution of 3.22 g (9.05 mmol) of 2-diphenylphosphino-1-naphtoic acid, **172**, in 71 mL of anhydrous CH_2Cl_2 at 0 ºC, was added 4.26 mL (30.5 mmol) of Et_3N followed by the dropwise addition of 2.12 mL (10.2 mmol) of $(PhO)_2P(O)Cl$. The reaction mixture was stirred at room temperature for 5 hours.

Meanwhile, 516.7 mg (4.5 mmol) of (1*R*,2*R*)-cyclohexane-1,2-diamine, **173**, was dissolved in 19 ml of anhydrous CH_2Cl_2 and then, 55.3 mg (0.45 mmol) of DMAP were added to the solution.

After the five hours, the solution of **172** was transferred via cannula to the solution of diamine **173** and the mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with 80 mL of CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulphate and concentrated under vacuum.

The crude was purified by flash column chromatography with neutral aluminium oxide (gradient, 100% hexane to hexane:ethyl acetate 7:2) to afford 2.63 g (3.33 mmol, 74% yield) of (1*R*,2*R*)-**152** as a pale yellow solid.

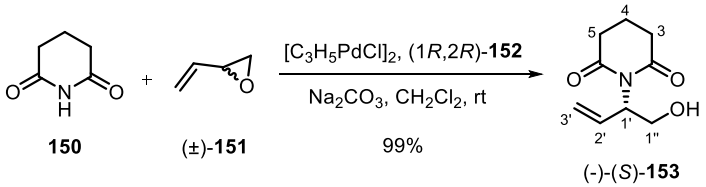
Physical and spectroscopic data of (1*R*,2*R*)-**152**

R_f = 0.75 (1:1, hexane:ethyl acetate)

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 – 7.79 (d, *J* = 8.7 Hz, 2H), 7.76 – 7.65 (m, 4H), 7.43 – 7.12 (m, 22H), 7.09 – 6.96 (m, 4H), 6.55 – 6.47 (m, 2H), 3.88 – 3.76 (m, 2H), 2.41 – 2.24 (m, 2H), 1.76 – 1.65 (m, 2H), 1.33 – 1.22 (m, 4H).

2.2. Assymmetric Allylic Alkylation (AAA)

2.2.1. Synthesis of 1-[(1*S*)-1-(hydroxymethyl)prop-2-en-1-yl]piperidine-2,6-dione, (*S*)-153[57]



To a solution of 3.33 g (29.5 mmol) of glutarimide, **150**, in 243 mL of anhydrous CH_2Cl_2 were added 630.7 mg (0.75 mmol) of the Trost ligand (1*R*,2*R*)-**152**, 103.2 mg (0.28 mmol) of π-allylpalladium chloride dimer and 323.9 mg (3.05 mmol) of sodium carbonate. 2.4 mL (30 mmol) of racemic butadiene monoxide, **151**, were then added. The resulting mixture was stirred overnight at room temperature.

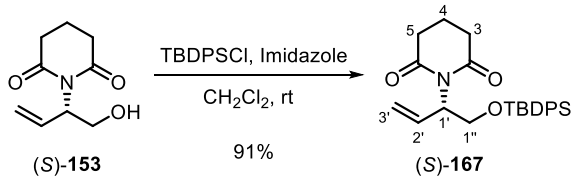
Afterwards, the reaction mixture was filtered through Celite® washing with ethyl acetate, CH_2Cl_2 and then concentrated under vacuum. The crude residue was purified by flash column chromatography (gradient, hexane:ethyl acetate from 1:1 to 2:3) to furnish 5.33 g (29 mmol, 99% yield) of (*S*)-**153** as a yellow oil in a 95% of enantiomeric excess determined by CHPLC.

Physical and spectroscopic data of (*S*)-**153**

R_f = 0.33 (100% ethyl acetate)

^{1}H NMR (250 MHz, $CDCl_3$) δ 6.12 (ddd, *J* = 17.4 Hz, 10.1 Hz, 7.0 Hz, 1H: H-2'), 5.41 (m, 1H: H-1'), 5.21 (m, 2H: H-3'), 4.08 – 3.78 (m, 2H: H-1''), 2.68 (t, *J* = 6.55 Hz, 4H: 2H-3 + 2H-5), 2.50 (dd, *J* = 8.5 Hz, 3.7 Hz, 1H: OH), 1.95 (qn, *J* = 6.6 Hz, 2H: 2H-4).

2.2.2. Synthesis of 1-[(1S)-1-({[tert-butyl(diphenyl)silyl]oxy}methyl)prop-2-en-1-yl]piperidine-2,6-dione, 167



A solution of 5.11 g (27.9 mmol) of the starting imine (*S*)-**153** in 253 mL of anhydrous CH_2Cl_2 was cooled to 0 ^oC. Then, 9.1 g (133.9 mmol) of imidazole and 7.4 mL (28.5 mmol) of TBDPSCl were added. The reaction mixture was stirred at room temperature for 14 h.

After that time, the reaction mixture was concentrated under vacuum and filtered through Celite®, removing a white solid (Imidazole·HCl), washing with ethyl acetate. The filtrate was concentrated under vacuum to obtain the crude product as a yellow oil.

The residue was purified by flash column chromatography (gradient, hexane:ethyl acetate from 7:1 to 1:2) to give 10.7 g (25.4 mmol, 91% yield) of the protected imide (*S*)-**167** as a white solid.

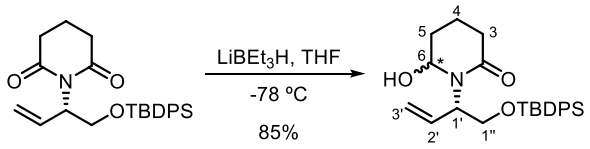
Physical and spectroscopic data of (*S*)-**167**

R_f = 0.43 (3:1, hexane:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H: 4H-Ph), 7.41 (m, 6H: 6H-Ph), 6.06 (ddd, *J* = 17.4 Hz, 10.3 Hz, 7.2 Hz, 1H: H-2'), 5.54 (m, 1H: H-1'), 5.16 (m, 2H: 2H-3'), 4.23 (t, *J* = 9.6 Hz, 1H: H-1''), 3.83 (dd, *J* = 9.9 Hz, 6.2 Hz, 1H: H-1''), 2.64 (t, *J* = 6.6 Hz, 4H: 2H-3 + 2H-5), 1.90 (qn, *J* = 6.6 Hz, 2H: H-4), 1.02 (s, 9H: 9H-*t*-Bu).

2.3. First nucleophilic allylation

2.3.1. Synthesis of 1-[(1*S*)-1-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)prop-2-en-1-yl]-6-hydroxypiperidin-2-one, 154



(*S*)-**167** (1'*S*)-**154** (1:12)

A solution of 4.43 g (10.5 mmol) of the protected imide (*S*)-**167** in 42 mL of anhydrous THF was cooled down to -78 ºC. Subsequently, 16.8 mL (16.8 mmol) of a $LiBEt_3H$ solution (1M in THF) were added dropwise. The resulting mixture was stirred during 45 minutes at the same temperature.

Afterwards, 60 mL of saturated $NaHCO_3$ solution and 12 mL of H_2O_2 30% solution were slowly added and the mixture was allowed to reach room temperature. Then, it was filtered through Celite® and washed with ethyl acetate. The two phases of the filtrate were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give an oily residue which was purified by flash column chromatography (gradient, hexane:ethyl acetate from 5:1 to 3:1) to

furnish 3.78 g (8.93 mmol, 85% yield) of a diastereomeric mixture 1:12 of (1'*S*)-**154** as a yellow oil.

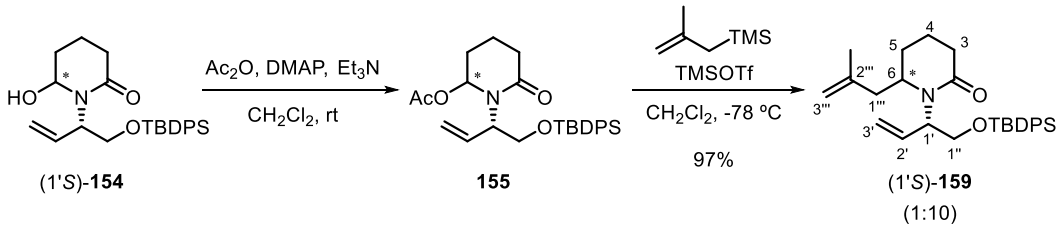
Physical and spectroscopic data of (1'*S*)-**154**

R_f = 0.43 (1:1, hexane:ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) **major isomer** δ 7.67 (m, 4H: 4H-Ph), 7.44 (m, 6H: 6H-Ph), 5.79 (ddd, *J* = 16.7 Hz, 10.6 Hz, 5.9 Hz, 1H: H-2'), 5.29 – 5.00 (m, 5H: 2H-3', H-1', H-6, OH), 3.97 (dd, *J* = 11.2 Hz, 3.5 Hz, 1H: H-1''), 3.85 (dd, *J* = 11.3 Hz, 6.1 Hz, 1H: H-1''), 2.65 – 1.63 (m, 6H: 2H-3 + 2H-4+ 2H-5), 1.08 (s, 9H: 9H-*t*-Bu).

^{1}H NMR (250 MHz, $CDCl_3$) **characteristic signals of minor isomer** δ 6.17 (ddd, *J* = 17.6 Hz, 10.5 Hz, 7.2 Hz, 1H: H-2'), 4.32 (m, 1H: H-6), 4.10 (m, 1H: H-1'), 3.66 (m, 1H: H-1'').

2.3.2. Synthesis of 1-[(1*S*)-1-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)prop-2-en-1-yl]-6-(2-methylprop-2-en-1-yl)piperidin-2-one, 159



(1'*S*)-**154** **155** (1'*S*)-**159** (1:10)

A solution of 3.36 g (7.94 mmol) of a diastereomeric mixture (1:12) of aminal (1'*S*)-**154** with 42 mL of anhydrous CH_2Cl_2 was cooled down to 0 ^oC. Then, 447.5 mg (3.66 mmol) of DMAP, 1.88 mL (19.9 mmol) of acetic anhydride and 2.77 mL (19.9 mL) of anhydrous triethylamine were added. The resulting mixture was stirred at room temperature overnight.

After that time, 30 mL of saturated $NaHCO_3$ solution and 30 mL of water were slowly added. After the extraction with CH_2Cl_2, the combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to obtain intermediate **155** as a yellow oil which was dissolved in 42 mL of anhydrous CH_2Cl_2. This solution is cooled down to -78 ^oC. Then, 2.8 mL (15.9 mmol) of methylallyltrimethylsilane were added, followed by the dropwise addition of 2.2 mL (11.9 mmol) of TMSOTf. The resulting mixture was stirred at the same temperature during 4 h.

Afterwards, 30 mL of saturated $NaHCO_3$ solution were added. The mixture was allowed to reach room temperature and 30 mL of water were then added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4.

The solvent was removed under vacuum and the crude residue obtained was purified by flash column chromatography (gradient, hexane: Et_2O from 7:3 to 1:1) affording 3.55 g (7.7 mmol, 97% yield) of a diastereomeric mixture 1:10 of amide (1'*S*)-**159** as yellow oil.

Physical and spectroscopic data of (1'*S*)-**159**

R_f = 0.67 (3:1 Et_2O:hexane)

^{1}H NMR (250 MHz, $CDCl_3$) **major isomer** δ 7.66 (m, 4H: 4H-Ph), 7.49 – 7.31 (m, 6H: 6H-Ph), 6.20 (ddd, *J* = 17.3 Hz, 10.6 Hz, 6.8 Hz, 1H: H-2'), 5.15 – 4.99 (m, 2H: 2H-3'), 4.82 (bs, 1H: H-3'''), 4.72 (bs, 1H: H-3'''), 4.38 – 4.24 (m, 1H: H-1'), 3.95 – 3.76 (m, 2H: H-1''), 3.69 – 3.51 (m, 1H: H-6), 2.49 – 2.13 (m, 4H: 2H-3, 2H-5), 1.88 – 1.72 (m, 2H: 2H-4), 1.70 (s, 3H: 3H-Me), 1.06 (s, 9H: 9H-*t*-Bu).

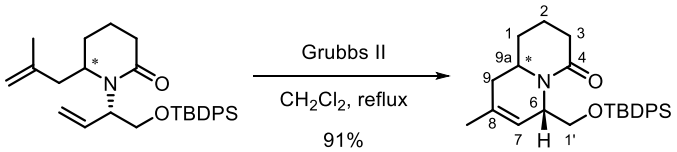
^{1}H NMR (250 MHz, $CDCl_3$) **characteristic signals of minor isomer** δ 6.15 – 6.02 (m, 1H: H-2'), 4.04 (dd, *J* = 15.5 Hz, 6.3 Hz, 2H: H-1'').

^{13}C NMR (101 MHz, $CDCl_3$) **major isomer** δ 169.8 (C-2), 141.9 (C-2'''), 135.7 (C-Ph), 135.6 (C-2'), 135.4 (C-Ph), 129.7 (C-Ph), 127.7 (C-Ph), 117.0 (C-3'), 113.5 (C-3'''), 66.1 (C-1'), 64.2 (C-1''), 57.4 (C-6), 41.4 (C-1'''), 32.5 (C-5), 26.9 (C(**C**H_3)$_3$), 25.2 (C-3), 22.2 (C-Me), 19.2 (**C**(CH_3)$_3$), 16.0 (C-4).

^{13}C NMR (101 MHz, $CDCl_3$) **characteristic signals of minor isomer** δ 170.1 (C-2), 142.0 (C-2'''), 134.8 (C-2'), 133.6 (C-Ph), 133.5 (C-Ph), 133.4 (C-Ph), 117.5 (C-3'), 113.3 (C-3'''), 64.5 (C-1'), 62.9 (C-1''), 54.2 (C-6), 41.8 (C-1'''), 32.0 (C-5), 22.1 (C(**C**H_3)$_3$), 19.3 (**C**(CH_3)$_3$), 15.9 (C-4).

2.4. First ring-closing metathesis

2.4.1. Synthesis of (6*S*)-6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-8-methyl-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 161



(1'*S*)-**159** (6*S*)-**161**

To a solution of 2.15 g (4.65 mmol) of a diastereomeric mixture (1:10) of lactam (1'*S*)-**159** in 521 mL of anhydrous and previously degassed CH_2Cl_2, 118.4 mg (0.14 mmol) of second generation Grubbs catalyst were added portionwise. The resulting mixture was heated at reflux during 48 h.

After cooling down to room temperature, the reaction mixture was filtered through a short pad of silica gel washing with Et_2O. The filtrate was concentrated under vacuum and the crude product was purified by flash column chromatography (gradient, hexane:Et_2O from 9:1 to 1:1) to obtain 1.84 g (4.23 mmol, 91% yield) of a yellowish oil identified as pure bicyclic compound (6*S*)-**161**, obtained as a single isomer.

Physical and spectroscopic data of (6*S*)-**161**

R_f = 0.56 (3:1, Et_2O: hexane)

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.64 (m, 4H: 4H-Ph), 7.37 (m, 6H: 6H-Ph), 5.62 (m, 1H: H-7), 4.60 (m, 1H: H-6), 3.93 (dd, *J* = 9.4, 5.2 Hz, 1H: 1H-1''), 3.78 (dd, *J* = 9.4, 2.9 Hz, 1H: 1H-1''), 3.33 (tt, *J* = 11.1, 2.9 Hz, 1H: H-9a), 2.49 – 2.31 (m, 2H: 2H-3), 2.24 (m, 1H: 1H-9), 1.95 – 1.65 (m, 7H: 2H-1 + 2H-2 + 3H-Me), 1.49 (m, 1H: 1H-9), 1.04 (s, 9H: 9H-*t*-Bu).

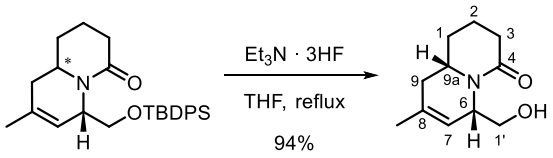
^{13}C NMR (91 MHz, $CDCl_3$) δ 171.0 (C-4), 135.7 (C-Ph), 135.4 (C-Ph), 133.9 (C-8), 129.6 (C-Ph), 127.6 (C-Ph), 127.6 (C-Ph), 121.2 (C-7), 65.3 (C-1'), 54.9 (C-9a), 54.0 (C-6), 37.0 (C-9), 32.9 (C-3), 31.0 (C-1), 26.9 (C(**C**H_3)$_3$), 23.3 (C-Me), 20.9 (C-2), 19.4 (**C**(CH_3)$_3$).

HRMS:

Calculated for $C_{27}H_{35}NO_2Si$: 456.2335 (MNa^+)

Found: 456.2337 (MNa^+)

2.4.2. Synthesis of (6*S*,9a*S*)-6-(hydroxymethyl)-8-methyl-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 168



(6*S*)-**161** (6*S*,9a*S*)-**168**

To a solution of 1.92 g (4.43 mmol) of bicycle **161** in 63 mL of anhydrous THF, 4.3 mL (26.6 mmol) of $Et_3N{\cdot}3HF$ were added. The resulting mixture was stirred under reflux overnight.

After cooling down to room temperature, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and then 50 mL of saturated $NaHCO_3$ solution were added dropwise. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to obtain a residue which was purified by flash

column chromatography (gradient, hexane:ethyl acetate from 1:5 to 100% ethyl acetate) to give 813.9 mg (4.16 mmol, 94% yield) of alcohol (6*S*,9a*S*)-**168** as a white solid.

Physical and spectroscopic data of (6*S*,9a*S*)-**168**

R_f = 0.19 (100% ethyl acetate)

$[\alpha]^{20}_D$ = +33.5 (*c* 0.01, CH_2Cl_2)

IR (ATR) = 3366, 2928, 2873, 1610, 1407, 1286, 1047 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.43 (m, 1H: H-7), 4.60 (m, 1H: H-6), 4.27 (bs, 1H: H-OH), 3.73 (dd, *J* = 11.5 Hz, 2.5 Hz, 1H: H-1'), 3.49 (dd, *J* = 11.5 Hz, 6.5 Hz, 1H: H-1'), 3.37 (tt, *J* = 11.3 Hz, 3.0 Hz, 1H: H-9a), 2.52 (m, 2H: 2H-3), 2.19 (m, 1H: H-9), 1.99 – 1.50 (m, 5H: 2H-1 + 2H-2 + 1H-9), 1.75 (s, 3H: 3H-Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C-4), 135.61 (C-8), 120.0 (C-7), 68.1 (C-1'), 57.2 (C-6), 55.7 (C-9a), 36.5 (C-1), 32.7 (C-9), 30.6 (C-3), 23.1 (C-Me), 20.1 (C-2).

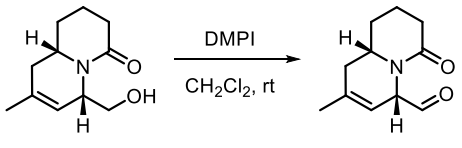
HRMS:

Calculated for $C_{11}H_{17}NO_2$: 218.1157 (MNa^+)

Found: 218.1152 (MNa^+).

2.5. Oxidation and Wittig alkenylation

2.5.1. Synthesis of (6S,9aS)-8-methyl-4-oxo-1,3,4,6,9,9a-hexahydro-2H-quinolizine-6-carbaldehyde, 174



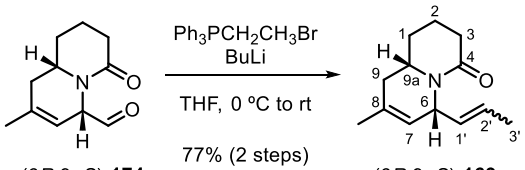
(6*S*,9a*S*)-**168** (6*S*,9a*S*)-**174**

To a solution of 862.5 mg (4.42 mmol) of alcohol **168** in 80 mL anhydrous CH_2Cl_2, 11 mL (5.3 mmol) of Dess-Martin perdiodinane (15%wt in CH_2Cl_2) were added. The resulting clear mixture was stirred at room temperature for 3 h.

Then, the reaction mixture was quenched by adding 50 mL of $NaHCO_3$ and $NaS_2O_3{\cdot}(H_2O)_5$ saturated aqueous solution. After vigorous stirring for 45 min, the solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. The

solvent was removed under vacuum obtaining the aldehyde **174** as a yellowish oil, which was used in the next step without further purification due to its instability.

2.5.2. Synthesis of (6*R*,9a*S*)-8-methyl-6-(prop-1-en-1-yl)-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 169



(6*R*,9a*S*)-**174** → (6*R*,9a*S*)-**169** (6:1) *Z*/*E*

On one hand, a solution of 10.34 g (27.9 mmol) of $Ph_3PCH_2CH_3Br$ in 42 mL of anhydrous THF was cooled down to 0 ºC. Then, 9.2 mL (23 mmol) of BuLi solution (2.5 M in hexanes) were added. The resulting mixture was stirred at room temperature for 1 h to form the corresponding ylide.

A solution of aldehyde **174** in 80 mL of anhydrous THF was treated with the solution of the phosphonium ylide and the new reaction mixture was stirred at room temperature overnight.

After that time, 80 mL of Et_2O were added in order to precipitate PPh_3O. The solid was filtered through Celite® and the filtrate was concentrated under vacuum. The crude residue was purified by flash column chromatography (gradient, hexane:Et_2O from 7:3 to 1:1) to give 851.8 mg (3.4 mmol, 77% yield) of lactam (6*R*,9a*S*)-**169** as yellow oil in a 6:1 *Z*/*E* ratio.

Physical and spectroscopic data of (6*R*,9a*S*)-**169**

R_f = 0.50 (100% Et_2O)

$[\alpha]^{20}_D$ = -72.1 (*c* 2.14, $CHCl_3$)

IR (ATR): 3458, 3015, 2916, 2854, 1643 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) **major isomer (*Z*)** δ 5.32 (m, 1H: H-2'), 5.23 (m, 1H: H-7), 4.98 (m, 1H: H-6), 4.89 (m, 1H: H-1'), 3.25 (m, 1H: H-9a), 2.31 (m, 2H: H-3), 2.03 (m, 1H: 1H-1), 1.92 – 1.72 (m, 3H: 1H-1 + 1H-9 + 1H-2), 1.72 – 1.55 (m, 6H: 3H-3' + 3H-Me), 1.55 – 1.37 (m, 2H: 1H-9 + 1H-2).

^{1}H NMR (400 MHz, $CDCl_3$) **significant signals of minor isomer (*E*)** δ 5.41 (m, 1H: H-2'), 4.76 (t, *J* = 5.5 Hz, 1H: H-6).

^{13}C NMR (101 MHz, $CDCl_3$) **major isomer (*Z*)** δ 170.3 (C-4*E*), 132.2 (C-8), 131.3 (C-1'), 122.7 (C-2'), 121.2 (C-7), 54.7 (C-9a), 50.5 (C-6), 36.8 (C-1), 32.9 (C-3), 31.1 (C-9), 22.9 (C-Me), 20.5 (C-2), 12.7 (C-3').

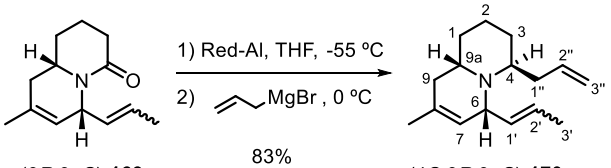
^{13}C NMR (101 MHz, $CDCl_3$) **minor isomer (*E*)** δ170.2 (C-4), 133.2 (C-8), 130.9 (C-1'), 124.3 (C-2'), 122.1 (C-7), 54.9 (C-9a), 53.8 (C-6), 36.4 (C-1), 32.7 (C-3), 31.0 (C-9), 22.8 (C-Me), 20.5 (C-2), 17.5 (C-3').

HRMS:

Calculated for $C_{13}H_{19}NO$: 228.1359 (MNa^+)

Found: 228.1363 (MNa^+)

2.6. Second nucleophilic allylation. Synthesis of (4*R*,6*R*,9a*S*)-4-allyl-8-methyl-6-[1-propenyl]-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine, 170



(6*R*,9a*S*)-**169**
(6:1) *Z*/*E*

(4*S*,6*R*,9a*S*)-**170**
(5:1) Z/E

A solution containing 370.4 mg (1.8 mmol) of a mixture *Z*/*E* (6:1) of lactam **169** in 25.7 mL of anhydrous THF was cooled down to -55 ºC. Once reached the desired temperature, 0.66 mL (2.16 mmol) of Red-Al solution (65% in THF) were added. The resulting mixture was stirred at the same temperature for 3 hours.

After that time, 18 mL (18 mmol) of allylmagnesium bromide solution (1 M in THF) was added and the solution was then stirred at 0 ºC for 3 h.

Then, the reaction mixture was treated with 30 mL of saturated $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum obtaining an oily residue which was purified by flash column chromatography on silica gel (gradient, 100% hexane to hexane:ethyl acetate 7:3 + 3 drops of Et_3N/10 mL of eluent) to afford 345 mg (1.49 mmol, 83% yield) of a 5:1 *Z*/*E* mixture of amines (4*S*,6*R*,9a*S*)-**170**, respectively, as yellow oil.

Physical and spectroscopic data of (4*S*,6*R*,9a*S*)-**170**

R_f = 0.56 (9:1, CH_2Cl_2: MeOH + 3 drops of Et_3N/10 mL of eluent)

IR (ATR): 3074, 3016, 2921, 2854, 1638, 1446 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) **major isomer (*Z*)** δ 5.67 (m, 1H: H-2''), 5.54 (m, 1H: H-2'), 5.25 (m, 1H: H-1'), 5.14 – 4.93 (m, 3H: H-7 + 2H-3''), 4.07 (m, 1H: H-6), 3.09 (m, 1H: H-4), 2.66 (m, 1H: H-9a), 2.42 – 2.13 (m, 2H: 2H-1''), 1.70 (dd, *J* = 6.9, 1.7 Hz, 3H: 3H-3'), 1.64 (bs, 3H: 3H-Me), 1.93-1.38 (m, 8H: 2H-1 + 2H-2 + 2H-3 + 2H-9)

^{1}H NMR (400 MHz, $CDCl_3$) **significant signals of minor isomer (*E*)** δ 3.62 (m, 1H: H-6), 3.15 (m, 1H: H-4)

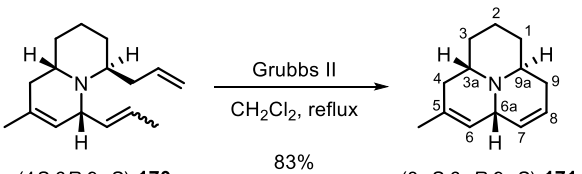
^{13}C NMR (101 MHz, $CDCl_3$) **major isomer** δ 137.5 (C-2''), 133.8 (C-1'), 131.2 (C-8), 124.9 (C-2'), 122.8 (C-7), 115.9 (C-3''), 54.3 (C-4), 53.6 (C-6), 49.3 (C-9a), 39.4 (C-1), 34.8 (C-3), 28.1 (C-9), 26.7 (C-1''), 22.8 (C-Me), 18.2 (C-2), 13.4 (C-3).

HRMS:

Calculated for $C_{16}H_{25}N$: 232.2060 (MH^+)

Experimental: 232.2059 (MH^+)

2.7. Second ring-closing metathesis. Synthesis of (3a*S*,6a*R*,9a*S*)-5-methyl-1,2,3,3a,4,6a,9,9a-octahydropyrido[2,1,6-de]quinolizine, 171



(4*S*,6*R*,9a*S*)-**170**
(5:1) Z/E

(3a*S*,6a*R*,9a*S*)-**171**

To a solution of 345 mg (1.5 mmol) of a *Z*/*E* mixture (5:1) of amine **170** in 200 mL of anhydrous and previously degassed CH_2Cl_2, 127.3 mg (0.15 mmol) of second generation Grubbs catalyst were added in one portion. The resulting mixture was heated at reflux overnight.

After cooling down to room temperature, the reaction mixture was filtered through a short pad of silica gel washing with Et_2O. The filtrate was concentrated under vacuum and the crude product was purified by flash column chromatography on neutral alumina (gradient, 100% hexane to hexane:ethyl acetate 7:3 + 3 drops of Et_3N/10 mL of eluent) to furnish 245.8 mg (1.25 mmol, 83% yield) of a yellow oil corresponding to tricyclic amine (3a*S*,6a*R*,9a*S*)-**171**.

Physical and spectroscopic data of (3a*S*,6a*R*,9a*S*)-**171**

R_f = 0.51 (9:1, CH_2Cl_2: MeOH + 3 drops of Et_3N/10 mL of eluent)

[α] $^{20}_{D}$ = -52.1 (*c* 1.14, $CHCl_3$)

IR: 2924, 2854, 1735, 1638, 1446, 633 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.66 (m, 2H: H-8 + H-7), 5.22 (m, 1H: H-6), 4.02 (m, 1H: H-6a), 3.28 (m, 1H: H-3a), 2.67 (m, 1H: H-9a), 2.51 – 2.26 (m, 2H: 2H-4), 2.10 – 1.22 (m, 8H: 2H-1 + 2H-2 + 2H-3 + 2H-9), 1.68 (s, 3H: 3H-Me).

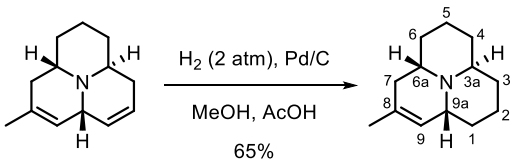
^{13}C NMR (63 MHz, $CDCl_3$) δ 130.6 (C-5), 128.3 (C-7), 123.4 (C-6), 121.4 (C-8), 56.7 (C-6a), 53.5 (C-9a), 42.2 (C-3a), 34.6 (C-3), 33.9 (C-1), 30.0 (C-4), 27.6 (C-9), 23.3 (C-Me), 19.0 (C-2).

HRMS:

Calculated for $C_{13}H_{19}N$: 190.1590 (MH^+)

Experimental: 190.1583 (MH^+)

2.8. Synthesis of (3a*S*,6a*S*,9a*R*)-8-methyl-1,2,3,3a,4,5,6,6a,7,9a-decahydropyrido[2,1,6-*de*]quinolizine, 56



(3a*S*,6a*R*,9a*S*)-**171** (3a*S*,6a*S*,9a*R*)-**56**

A solution containing 40.5 mg (0.21 mmol) of tricyclic amine **171** in 1.5 mL of methanol and 3 drops of acetic acid was hydrogenated in presence of 4 mg (10%) of Pd/C (10%) at 2 atm for 48 h. After that time, the solution was filtered through Celite® washing with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue obtained was purified by flash column chromatography in neutral alumina (gradient, 100% hexane to hexane:Et_2O 1:1 + 3 drops of Et_3N/10 mL of eluent) to furnish 26.6 mg (0.14 mmol, 65% yield) of (-)-9a-*epi*-hippodamine, **56**, as a single isomer. A solution of target compound in $CDCl_3$ (600 µL) was treated with TFA (100 µL) in order to obtain the corresponding salt, which was fully characterized by NMR.

Physical and spectroscopic data of (3a*S*,6a*S*,9a*R*)-**56**

R_f = 0.45 (100% Et_2O + 3 drops of Et_3N/10 mL of eluent)

[α]$_D^{20}$ = -0.71 (*c* 0.27, $CHCl_3$)

IR: 2926, 2854, 2363, 2344, 1686, 1199, 1129, 631 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) **56**·TFA δ 5.23 (m, 1H: H-9), 4.26 (m, 1H: H-9a), 3.84 (m, 1H: H-6a), 3.15 (m, 1H: H-3a), 2.49 (m, 1H: 1H-7), 2.25-2.00 (m, 3H: 2H-1 + 1H-7), 1.95-1.55 (m, 11H: 1H-1 + 2H-2 + 2H-3 + 2H-4 + 2H-5 + 2H-6), 1.85 (s, 3H: 3H-Me).

^{13}C-NMR (101 MHz, $CDCl_3$) **56**·TFA δ 134.4 (C-8), 118.5 (C-9), 56.9 (C-9a), 56.0 (C-6a), 52.7 (C-3a), 30.4 (C-3 or C-4), 30.3 (C-3 or C-4), 28.7 (C-1), 28.5 (C-7), 26.8 (C-6), 22.6 (C-Me), 17.8 (C-5), 17.2 (C-2).

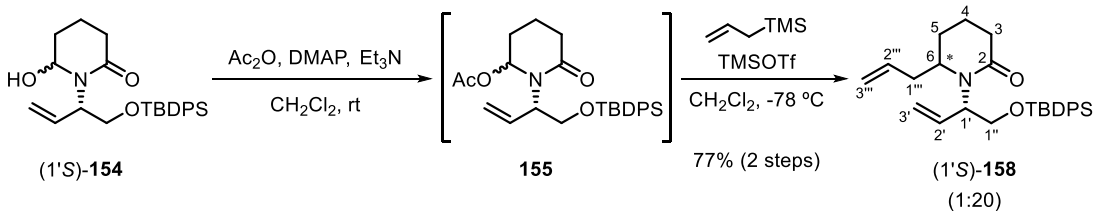
HRMS:

Calculated for $C_{13}H_{22}N$: 191.1747 (MH^+)

Found: 191.1752 (MH^+)

3. Towards other azaphenalene alkaloids

3.1. First nucleophilic allylation. Synthesis of 6-allyl-1-[(1'*S*)-1-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)prop-2-en-1-yl]piperidin-2-one, 158



A solution of 4.45 g (10.5 mmol) of a diastereomeric mixture (1:12) of aminal (1'*S*)-**154** with 55.3 mL of anhydrous CH_2Cl_2 was cooled down to 0 ºC. Once reached the desired temperature, 592.2 mg (4.84 mmol) of DMAP, 2.49 mL (26.3 mmol) of acetic anhydride and 3.66 mL (26.3 mL) of anhydrous triethylamine were added. The resulting mixture was stirred at room temperature overnight.

The reaction mixture was treated with 30 mL of saturated $NaHCO_3$ solution and 30 mL of water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to obtain intermediate **155** as a yellow oil which was dissolved in 55.3 mL of anhydrous CH_2Cl_2. This solution was cooled down to -78 ºC. Then, 3.34 mL (21 mmol) of allyltrimethylsilane were added, followed by the dropwise addition of 2.86 mL (15.8 mmol) of TMSOTf. The reaction mixture was stirred at the same temperature during 4 h.

Afterwards, 30 mL of saturated $NaHCO_3$ solution were added. The mixture was warmed up to room temperature and 30 mL of water were then added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue obtained was purified by flash column chromatography (gradient, hexane: Et_2O from 8:2 to 1:1) to get 3.62 g (8.1 mmol, 77% yield) of a diastereomeric mixture 20:1 of amide (1'*S*)-**158** as yellow oil.

Physical and spectroscopic data of (1'*S*)-**158**

R_f = 0.46 (3:1 Et_2O:hexane)

IR (ATR): 3071, 2931, 2857, 1637, 1427, 1107 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) **major isomer** δ 7.69 – 7.61 (m, 4H: 4H-Ph), 7.48 – 7.33 (m, 6H: 6H-Ph), 6.20 (ddd, *J* = 17.3 Hz, 10.5 Hz, 6.6 Hz, 1H: 1H-2'), 5.74 – 5.53 (m, 1H: 1H-2'''), 5.15 – 4.99 (m, 4H: 2H-3' + 2H-3'''), 4.34 – 4.20 (m, 1H: 1H-1'), 3.90 – 3.77 (m, 2H: 2H-1''), 3.47 – 3.32 (m, 1H: 1H-6), 2.55 – 2.10 (m, 4H: 2H-3 + 2H-1'''), 1.87 – 1.59 (m, 4H: 2H-4 + 2H-5), 1.05 (s, 9H: 9H-*t*-Bu).

^{1}H NMR (250 MHz, $CDCl_3$) **significant signals of minor isomer** δ 6.12 – 5.99 (m, 1H: 1H-2') 5.18 (m, 4H: 2H-3' + 2H-3'''), 4.18 – 3.90 (m, 2H: 2H-1'')

^{13}C NMR (63 MHz, $CDCl_3$) **major isomer** δ 169.9 (C-2), 135.7 (C-Ph), 135.7 (C-Ph), 135.3 (C-Ph), 134.6 (C-Ph), 133.7 (C-2 or C-2'''), 133.5 (C-2 or C-2'''), 129.8 (C-Ph), 127.8 (C-Ph), 117.9 (C-3 or C-3'''), 117.1 (C-3 or C-3''') 66.0 (C-1''), 64.2 (C-1'), 59.0 (C-6), 37.7 (C-3), 32.6 (C-1'''), 27.0 (C(**C**H_3)$_3$), 25.7 (C-4 or C-5), 19.3 (C-4 or C-5), 16.28 (**C**(CH_3)$_3$).

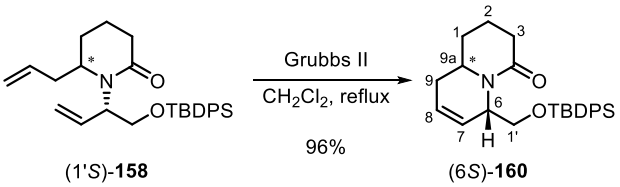
HRMS:

Calculated for $C_{28}H_{36}NO_2Si$: 470.2486 (MNa^+)

Found: 470.2491 (MNa^+)

3.2. First ring-closing metathesis

3.2.1. Synthesis of (6*S*)-6-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 160



(1'*S*)-**158** (6*S*)-**160**

To a solution of 2.74 g (6.12 mmol) of a diastereomeric mixture (20:1) of lactam (1'*S*)-**158** in 227 mL of anhydrous and previously degassed CH_2Cl_2, 51 mg (0.06 mmol) of second generation Grubbs catalyst were added. The resulting mixture was heated at reflux overnight.

After cooling down to room temperature, the reaction mixture was filtered through a short pad of silica gel washing with Et_2O. The filtrate was concentrated under vacuum and the crude residue was purified by flash column chromatography (gradient, hexane:Et_2O from 9:1 to 1:1) to obtain 2.47 g (5.88 mmol, 96% yield) of a yellow oil corresponding to bicycle (6*S*)-**160**, which was isolated as a single isomer.

Physical and spectroscopic data of (6*S*)-**160**

R_f = 0.38 (3:1, Et_2O:hexane)

IR (ATR): 2928, 2854, 1668, 1612, 1406, 1095 cm^{-1}.

$[\alpha]_D^{20}$ = -85.8 (*c* 1.00, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H: 4H-Ph), 7.38 (m, 6H: 6H-Ph), 6.06 (ddd, *J* = 9.5, 6.7, 2.4 Hz, 1H: H-7), 5.98 (ddd, *J* = 10.0, 5.0, 2.7 Hz, 1H: H-8), 4.65 (m, 1H: H-6), 3.88 (m, 2H: 2H-1'), 3.30 (tt, *J* = 11.0, 3.1 Hz, 1H: H-9a), 2.40 (m, 2H: 2H-3), 2.14 (m, 2H: 2H-9), 1.86 (m, 2H: 1H-1 + 1H-2), 1.74 (m, 1H: 1H-2), 1.51 (m, 1H: 1H-1), 1.05 (s, 9H: 9H-*t*-Bu).

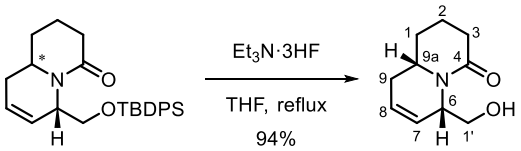
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C-4), 135.7 (C-Ph), 133.9 (C-Ph), 133.8 (C-Ph), 129.6 (C-Ph), 128.0 (C-7), 127.7 (C-Ph), 127.6 (C-Ph), 127.0 (C-8), 65.3 (C-1'), 55.0 (C-9a), 53.9 (C-6), 32.9 (C-3), 32.0 (C-9), 31.1 (C-1), 27.0 (C(**C**H_3)$_3$), 20.8 (C-2), 19.4 (**C**(CH_3)$_3$).

HRMS:

Calculated for $C_{26}H_{33}NO_2Si$: 419.2281 (M^+)

Found: 419.2287 (M^+)

3.2.2. Synthesis of (6*S*,9a*S*)-6-(hydroxymethyl)-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 181



(6*S*)-**160** (6*S*,9a*S*)-**181**

To a solution of 2.38 g (5.66 mmol) of bicycle (6*S*)-**160** in 81 mL of anhydrous THF, 5.5 mL (34 mmol) of $Et_3N{\cdot}3HF$ were added. The resulting mixture was stirred under reflux overnight.

After cooling down to room temperature, the reaction mixture was diluted with 25 mL of CH_2Cl_2 and then 55 mL of saturated $NaHCO_3$ solution were added dropwise. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to obtain a residue which was purified by flash column chromatography (gradient, hexane:ethyl acetate from 1:5 to 100% ethyl acetate) affording 966.2 mg (5.33 mmol, 94% yield) of alcohol (6*S*,9a*S*)-**181** as a white solid.

Physical and spectroscopic data of (6*S*,9a*S*)-**181**

R_f = 0.2 (100% ethyl acetate)

$[\alpha]^{20}_D$ = -35.5 (*c* 1.30, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.97 (m, 1H: H-7), 5.75 (m, 1H: H-8), 4.56 (m, 1H: H-6), 3.68 (dd, *J* = 11.4, 3.0 Hz, 1H: 1H-1'), 3.49 (dd, *J* = 11.4, 5.8 Hz, 1H: 1H-1'), 3.29 (m, 1H: H-9a), 2.45 (m, 2H: 1H-3 + 1H-9), 2.08 (m, 2H: 1H-3 + 1H-9), 1.95 – 1.43 (m, 4H: 2H-1 + 2H-2).

^{13}C NMR (91 MHz, $CDCl_3$) δ 172.9 (C-4), 126.9 (C-7 or C-8), 126.5 (C-7 or C-8), 66.9 (C-1'), 56.4 (C-9a), 55.4 (C-6), 32.5 (C-3 or C-9 or C-1), 31.3 (C-3 or C-9 or C-1), 30.4 (C-3 or C-9 or C-1), 20.0 (C-2).

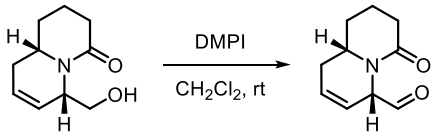
HRMS:

Calculated for $C_{10}H_{15}NO_2$: 204.1000 (MNa^+)

Found: 204.1995 (MNa^+)

3.3. Dess-Martin oxidation and Wittig alkenylation.

3.3.1. Synthesis of (6*S*,9a*S*)-4-oxo-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine-6-carbaldehyde, 184

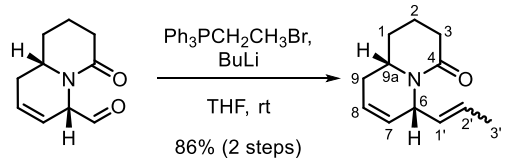


(6*S*,9a*S*)-**181** (6*S*,9a*S*)-**184**

To a solution of 562.5 mg (3.1 mmol) of alcohol **181** in 56 mL anhydrous CH_2Cl_2, 18 mL (4.6 mmol) of Dess-Martin perdiodinane (8%wt in CH_2Cl_2) were added. The resulting mixture was stirred at room temperature for 3 h.

Then, the reaction mixture was treated with 50 mL of $NaHCO_3$ and $NaS_2O_3{\cdot}(H_2O)_5$ saturated aqueous solution. After vigorous stirring for 45 min, the solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum obtaining aldehyde **184** which was used in the next step without further purification due to its instability.

3.3.2. Synthesis of (6*R*,9a*S*)-6-(prop-1-en-1-yl)-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 182



(6*S*,9a*S*)-**184** (6*R*,9a*S*)-**182**
(6:1) *Z*/*E*

A solution of 7.25 g (19.5 mmol) of $Ph_3PCH_2CH_3Br$ in 114.8 mL of anhydrous THF was cooled down to 0 ^oC. Then, 6.5 mL (16.1 mmol) of BuLi solution (2.5 M in hexanes) were added. The resulting mixture was stirred at room temperature for 1 h.

When the formation of the phosphonium ylide had finished, a solution of the aldehyde **184** dissolved in 28 mL of anhydrous THF was transferred over the solution of the phosphonium ylide. The reaction mixture was stirred at room temperature overnight.

After that time, 80 mL of Et_2O were added in order to precipitate PPh_3O. The solid was filtered through Celite® and the filtrate was concentrated under vacuum.

The crude residue was purified by flash column chromatography (gradient, hexane:Et_2O from 7:3 to 1:1) to give 510.5 mg (2.67 mmol, 86% yield) of lactam (6*R*,9a*S*)-**182** as a yellow oil with a *Z*/*E* ratio of 6:1.

Physical and spectroscopic data of (6*R*,9a*S*)-**182**

R_f = 0.47 (100% Et_2O)

$[\alpha]^{20}_D$ = -99.7 (*c* 0.97, $CHCl_3$)

IR (ATR): 3500, 2923, 2852, 1641, 1444, 1405, 1336 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$) **major isomer (*Z*)** δ 5.84 (m, 1H: H-8), 5.64 (ddd, J = 9.8 Hz, 4.8 Hz, 2.8 Hz, 1H: H-7), 5.44 (m, 1H: H-2'), 5.11 (m, 1H: H-6), 4.98 (m, 1H: H-1'), 3.31 (tt, J = 10.7 Hz, 3.4 Hz, 1H: H-9a), 2.39 (m, 2H: 2H-3), 2.19 – 2.00 (m, 1H: 2H-9), 1.95 – 1.81 (m, 2H: 2H-2), 1.75 (dd, J = 6.9 Hz, 1.7 Hz, 3H: H-Me), 1.72 – 1.49 (m, 2H: 2H-1).

^{1}H NMR (360 MHz, $CDCl_3$) **significant signals of minor isomer (*E*)** δ 5.90 (m, 1H: H-8), 5.74 (ddd, J = 9.7 Hz, 5.2 Hz, 2.9 Hz, 1H: H-7), 5.55 (m, 1H: H-2'), 5.31 (m, 1H: H-1'), 4.87 (m, 1H: H-6).

^{13}C NMR (63 MHz, $CDCl_3$) **major isomer (*Z*)** δ 171.0 (C-4), 131.1 (C-1'), 128.1 (C-7), 124.1 (C-8), 123.9 (C-2'), 55.1 (C-9a), 50.8 (C-6), 33.2 (C-3), 32.2 (C-1), 31.5 (C-9), 20.8 (C-2), 13.1 (C-3').

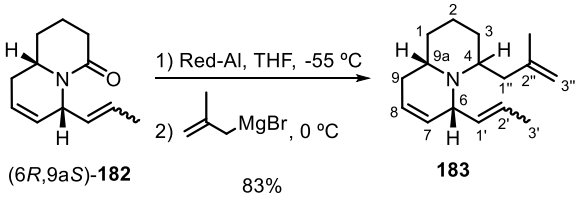
^{13}C NMR (63 MHz, $CDCl_3$) **minor isomer (*E*)** δ 130.6 (C-1'), 129.3 (C-7), 125.4 (C-8), 125.0 (C-2'), 55.4 (C-9a), 54.0 (C-6), 33.0 (C-3), 32.1 (C-1), 31.3 (C-9), 22.8 (C-2), 14.3 (C-3').

HRMS:

Calculated for $C_{12}H_{17}NO$: 191.1388 (M^+H^+)

Found: 191.1379 (M^+H^+)

3.4. Second nucleophilic allylation. Synthesis of (6*R*,9a*S*)-4-(2-methylprop-2-en-1-yl)-6-(prop-1-en-1-yl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine, 183



A solution with 94.7 mg (1.8 mmol) of a mixture *Z*/*E* (6:1) of lactam (6*R*,9a*S*)-**182** in 25.7 mL of anhydrous THF was cooled down to -55 °C. Once reached the desired temperature, 0.66

mL (2.16 mmol) of Red-Al solution (65% in THF) were added. The resulting mixture was stirred at the same temperature for 3 hours.

After that time, 18 mL (18 mmol) of allylmagnesium bromide solution (1 M in THF) prepared in situ was added and the solution was then stirred at 0 ^{o}C for 4 h.

The reaction mixture was treated with 30 mL of saturated $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum obtaining an oily residue which was purified by flash column chromatography (gradient, 100% hexane to hexane:ethyl acetate 7:3 + 3 drops of Et_3N/10 mL of eluent) to afford 307.7 mg (1.33 mmol, 74% yield) of (*Z*,4*S*,6*R*,9a*S*)-**183** and 37 mg (0.16 mmol, 9% yield) of (*Z*,4*R*,6*R*,9a*S*)-**183**.

Physical and spectroscopic data of (*Z*,4*S*,6*R*,9a*S*)-**183**

R_f = 0.75 (9:1, CH_2Cl_2: MeOH + 3 drops of Et_3N/10 mL of eluent)

IR (ATR): 3314, 3025, 2920, 2359, 1647, 1443 cm^{-1}.

$[\alpha]_D^{20}$ = -101.4 (*c* 1.00, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (m, 1H: H-7), 5.53 (m, 1H: H-2'), 5.35 (m, 1H: H-8), 5.28 (m, 1H: H-1'), 4.72 (s, 1H: 1H-3''), 4.68 (s, 1H: 1H-3''), 4.12 (m, 1H: H-6), 3.21 (m, 1H: H-4), 2.70 (m, 1H: H-9a), 2.36 – 2.19 (m, 2H: 2H-1''), 2.08 – 1.93 (m, 1H: 1H-9), 1.90 – 1.80 (m, 1H: 1H-9), 1.76 – 1.15 (m, 6H: 2H-1 + 2H-2 + 2H-3), 1.69 (dd, *J* = 7.0, 1.4 Hz, 3H: 3H-3'), 1.65 – 1.62 (m, 3H: 3H-Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C-2''), 133.8 (C-1'), 128.7 (C-8), 125.0 (C-2'), 123.5 (C-7), 112.0 (C-3''), 53.4 (C-6), 52.3 (C-4), 48.8 (C-9a), 34.9 (C-1), 34.5 (C-9), 30.1 (C-1''), 27.7 (C-3), 22.14 (C-Me), 18.3 (C-2), 13.6 (C-3').

HRMS:

Calculated for $C_{16}H_{25}N$: 232.2065 (M^+H^+)

Found: 232.2056 (M^+H^+)

Physical and spectroscopic data of (*Z*,4*R*,6*R*,9a*S*)-**183**

R_f = 0.20 (9:1, CH_2Cl_2: MeOH + 3 drops of Et_3N/10 mL of eluent)

$[\alpha]_D^{20}$ = -50.7 (*c* 0.41, $CHCl_3$)

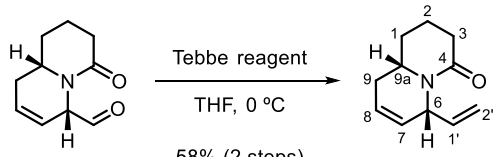
^{1}H NMR (360 MHz, $CDCl_3$) δ 5.77 (m, 1H: H-7), 5.55 (m, 1H: H-2'), 5.46 (m, 1H: H-2), 5.32 (ddd, *J* = 10.7, 9.0, 1.7 Hz, 1H: H-1'), 4.88 (s, 1H: 1H-3''), 4.79 (s, 1H: 1H-3''), 4.32 (m, 1H: H-6), 3.73 (m,

1H: H-4), 2.83 (m, 1H: H-9a), 2.25 – 1.97 (m, 4H: 2H-1'' + 1H-3 + 1H-9), 1.91 – 1.35 (m, 6H: 2H-1 + 2H-2 + 2H-3), 1.75 (s, 3H: 3H-Me), 1.70 (dd, *J* = 6.9, 1.7 Hz, 3H: 3H-3').

^{13}C NMR (91 MHz, $CDCl_3$) δ 142.9 (C-2''), 132.6 (C-1'), 129.8 (C-8), 125.9 (C-2'), 125.8 (C-7), 113.7 (C-3''), 68.6 (C-4), 53.2 (C-9a), 52.5 (C-6), 46.4 (C-1''), 37.3 (C-2), 36.9 (C-3), 32.1 (C-9), 22.6 (C-Me), 22.2 (C-1), 13.4 (C-3').

3.5. Alternative approaches

3.5.1. Tebbe alkenylation. Synthesis of (6*R*,9a*S*)-6-vinyl-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one, 187



(6*S*,9a*S*)-**184** (6*R*,9a*S*)-**187**

A solution of 89.6 mg (0.494 mmol) of the unpurified aldehyde (6*S*,9a*S*)-**184** in 19.7 mL of anhydrous THF was cooled down to 0 ºC. Once reached the desired temperature, 0.99 mL (0.494 mmol) of Tebbe reagent (1M in THF) was added and the reaction mixture was stirring at the same temperature for 50 min.

After that time, some drops of a 5% NaOH aqueous solution were added to the reaction mixture and, after 5 min, 10 mL of Et_2O were added. The solution was filtered through Celite®, washed with Et_2O and then concentrated under vacuum.

The crude residue was purified by column chromatography over silica gel (gradient, hexane:Et_2O from 9:1 to 1:1) to obtain 50.78 mg (0.286 mmol, 58% yield) of the alkene (6*R*,9a*S*)-**187** as a yellow oil.

Physical and spectroscopic data of (6*R*,9a*S*)-**187**

R_f = 0.5 (100% Et_2O)

IR (ATR): 3268, 3043, 2924, 2853, 1637, 1443 cm^{-1}.

$[\alpha]_D^{20}$ = -102.3 (*c* 0.53, $CHCl_3$)

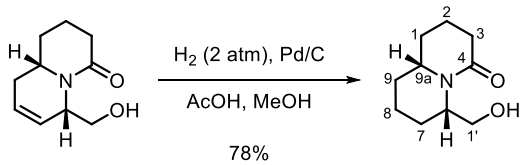
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 9.7, 7.1, 2.4 Hz, 1H: H-8), 5.82 – 5.69 (m, 2H: H-7 + H-1'), 5.12 (dt, *J* = 17.1, 1.2 Hz, 1H: 1H-2'), 5.01 (dt, *J* = 10.1, 1.2 Hz, 1H: 1H-2'), 4.98 – 4.91 (m, 1H:

H-6), 3.34 (tt, *J* = 11.1, 3.2 Hz, 1H: H-9a), 2.45 (m, 2H: 2H-3), 2.17 (m, 1H: 1H-9), 2.06 (m, 1H: 1H-9), 1.96 – 1.85 (m, 2H: 1H-1 + 1H-2), 1.82 – 1.68 (m, 1H: 1H-2), 1.63 – 1.52 (m, 1H: 1H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.89 (C-4), 137.79 (C-1'), 128.39 (C-7), 125.58 (C-8), 113.61 (C-2'), 55.25 (C-9a), 54.71 (C-6), 32.94 (C-3), 31.71 (C-9), 31.23 (C-1), 20.73 (C-2).

3.5.2. Hydrogenation – Dess-Martin Oxidation – Wittig olefination

3.5.2.1. Synthesis of (6*S*,9a*R*)-6-(hydroxymethyl)octahydro-4*H*-quinolizin-4-one, 190



(6*S*,9a*S*)-**181** (6*S*,9a*R*)-**190**

A solution containing 103 mg (0.57 mmol) of alcohol (6*S*,9a*S*)-**181** in 2 mL of methanol and 3 drops of acetic acid was hydrogenated in presence of 10.3 mg (10%) of Pd/C (10%) at 2 atm. of H_2 overnight.

After that time, the solution was filtered through Celite® washing with CH_2Cl_2. The filtrate was washed with saturated $NaHCO_3$ solution and the organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum.

The residue was filtered through a short pad of silica gel to give 82 mg (0.45 mmol, 78% yield) of alcohol (6*S*,9a*R*)-**190**.

Physical and spectroscopic data of (6*S*,9a*R*)-**190**

R_f = 0.2 (100% ethyl acetate)

IR (ATR): 3371, 2940, 2872, 1603, 1410, 1343, 1050 cm^{-1}.

$[\alpha]^{20}_D$ = -80.0 (*c* 0.60, CH_2Cl_2)

^{1}H NMR (250 MHz, $CHCl_3$) δ 4.94 (dd, *J* = 7.5, 5.6 Hz, 1H: H-OH), 3.82 (m, 2H: 2H-1'), 3.52 (m, 1H: H-6), 3.39 (m, 1H: H-9a), 2.42 (m, 2H: 2H-3), 2.05 – 1.43 (m, 10H: 2H-1 + 2H-2 + 2H-7 + 2H-8 + 2H-9).

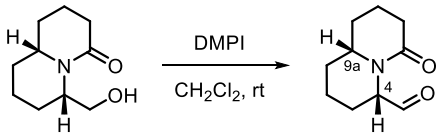
^{13}C NMR (101 MHz, $CHCl_3$) δ 171.2 (C-4), 65.4 (C-1), 62.2(C-9a), 57.6 (C-6), 33.4 (C-1 or C-3 or C-7 or C-9), 31.8 (C-1 or C-3 or C-7 or C-9), 29.9 (C-1 or C-3 or C-7 or C-9), 26.0 (C-1 or C-3 or C-7 or C-9), 21.4 (C-2 or C-8), 18.7 (C-2 or C-8).

HRMS:

Calculated for $C_{10}H_{17}NO_2$: 183.1338 (MH^+)

Found: 183.1360 (MH^+)

3.5.2.2. Synthesis of (4*S*,9a*R*)-6-oxooctahydro-2*H*-quinolizine-4-carbaldehyde, 193

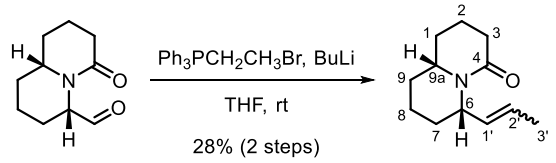


(6*S*,9a*R*)-**19** (4*S*,9a*R*)-**193**

To a solution of 38.3 mg (0.21 mmol) of (6*S*,9a*R*)-**190** in 3.8 mL of anhydrous CH_2Cl_2, 106.9 mg (0.252 mmol) of DMPI were added. The resulting mixture was stirred at room temperature for 3 hours.

After that time, the reaction mixture was treated with 5 mL of $NaHCO_3$ and $NaS_2O_3{\cdot}(H_2O)_5$ saturated aqueous solution. After 45 min of stirring, the aqueous phase was extracted with CH_2Cl_2 (3x5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, to give aldehyde (4*S*,9a*R*)-**193** as yellow oil, which was used in the next step without further purification due to its instability.

3.5.2.3. Synthesis of (6*S*,9a*R*)-6-(prop-1-en-1-yl)octahydro-4*H*-quinolizin-4-one, 192



(4*S*,9a*R*)-**193** (6*S*,9a*R*)-**192**

A solution of 93.6 mg (0.25 mmol) of $Ph_3PCH_2CH_3Br$ in 1.6 mL of anhydrous THF was cooled down to 0 ^oC and 0.1 mL (0.25 mmol) of BuLi solution (2.5 M in hexane) were then added. The resulting mixture was stirred at room temperature during 1 hour.

On the other hand, the aldehyde (4*S*,9a*R*)-**193** was dissolved in 3.8 mL of anhydrous THF. When the phosphorous ylide was formed, the previous solution was transferred over the solution of the aldehyde and the new reaction mixture was stirred at room temperature overnight.

After that time, 10 mL of Et_2O were added in order to precipitate triphenylphosphine oxide. The solution was filtered through Celite® washing with Et_2O and the filtrate was concentrated under vacuum obtaining the residue which was purified by flash column

chromatography (gradient, 100% hexane to 100% Et_2O) to give 11 mg (0.06 mmol, 28% yield) of lactam (6*S*,9a*R*)-**192** as yellow oil.

Physical and spectroscopic data of (6*S*,9a*R*)-**192**

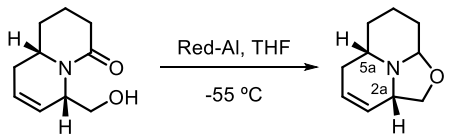
R_f = 0.21 (100% Et_2O)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (m, 1H: H-2'), 5.42 (m, 1H: H-1'), 4.91 (m, 1H: H-6), 3.49 (m, 1H: H-9a), 2.37 (m, 2H: 2H-3), 1.98 – 1.30 (m, 3H: 2H-1 + 2H-2 + 2H-7 + 2H-8 + 2H-9), 1.74 (d, *J* = 6.6 Hz, 3H: 3H-3').

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C-4), 132.3 (C-1'), 124.9 (C-2'), 53.4 (C-9a), 49.5 (C-6), 32.9 (C-3), 31.4 (C-1, C-2, C-7, C-8 or C-9), 26.1 (C-1, C-2, C-7, C-8 or C-9), 20.4 (C-1, C-2, C-7, C-8 or C-9), 16.7(C-1, C-2, C-7, C-8 or C-9), 13.1 (C-3').

3.5.3. Preliminary studies for the RRCM

3.5.3.1. Synthesis of (2a*S*,5a*S*)-2,2a,5,5a,6,7,8,8a-octahydrooxazolo[2,3,4-de]quinolizine, 198

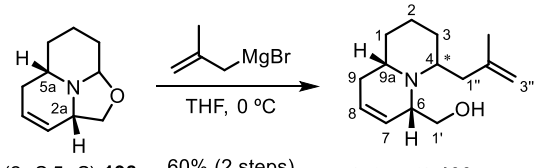


(6*S*,9a*S*)-**181** (2a*S*,5a*S*)-**198**

A solution of 619.6 mg (3.42 mmol) of alcohol (6*S*,9a*S*)-**181** in 50 mL of anhydrous THF was cooled down to -55 ºC. Once reached the desired temperature, 3.33 mL (10.3 mmol) of Red-Al solution (65% in THF) were added slowly and the resulting mixture was stirring overnight at the same temperature.

The reaction mixture was treated with 30 mL of 5% NaOH solution and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum obtaining (2a*S*,5a*S*)-**198**, which was used in the following step without further purification due to its instability.

3.5.3.2. Synthesis of [(6*S*,9a*S*)-4-(2-methylprop-2-en-1-yl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizin-6-yl]methanol, 199



The residue obtained in the previous step was dissolved in 50 mL of anhydrous THF and cooled down to 0 ºC. Then, 34.2 mL (34.2 mmol) of methylallylmagnesium bromide solution (1 M in THF, prepared in situ) were added. The reaction mixture was stirred during 4 h at the same temperature.

After that time, it was treated with 30 mL of 5% HCl solution and washed with CH_2Cl_2. Then, the aqueous phase was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The lasts organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to obtain 453.8 mg (2.05 mmol, 60% yield) of amine (6*S*,9a*S*)-**199** in a diastereomeric ratio of 1:5, as a brown oil, which were pure enough to use in the next step without further purification.

Physical and spectroscopic data of (6*S*,9a*S*)-**199**

R_f = 0.46 (3:7, hexane:ethyl acetate)

IR (ATR): 3336, 3072, 3035, 2928, 2865, 1723, 1643, 1445 cm^{-1}.

$[\alpha]_D^{20}$ = -15.4 (*c* 0.50, $CHCl_3$)

^{1}H NMR (400 MHz, $CHCl_3$) **major isomer** δ 5.85 (ddd, *J* = 8.0, 6.2, 1.9 Hz, 1H: H-8), 5.57 (dt, *J* = 10.0, 3.0 Hz, 1H: H-7), 4.76 (s, 1H: H-3''), 4.70 (s, 1H: H-3''), 3.75 (dd, *J* = 10.5, 4.0 Hz, 1H: 1H-1'), 3.42 (s, 1H: H-6), 3.33 (dd, *J* = 10.4, 1.8 Hz, 1H: 1H-1'), 3.18 (m, 1H: H-4), 2.78 (m, 1H: H-9a), 2.39 (dd, *J* = 13.5, 10.6 Hz, 1H: 1H-1''), 2.18 (d, *J* = 13.4 Hz, 1H: 1H-1''), 2.03 – 1.78 (m, 2H: 2H-9), 1.76 – 1.72 (m, 2H: 2H-2), 1.69 (s, 3H: 3H-Me), 1.67 – 1.44 (m, 4H: 2H-2 + 2H-3).

^{1}H NMR (400 MHz, $CHCl_3$) **significant signals of minor isomer** δ 5.97 (m, 1H: H-8), 4.78 (s, 1H: 1H-3''), 4.73 (s, 1H: 1H-3''), 2.66 (m, 1H: H-9a), 2.53 (d, *J* = 10.6 Hz, 1H: H-4).

^{13}C NMR (101 MHz, $CHCl_3$) **major isomer** δ 143.8 (C-2''), 127.5 (C-7), 126.3 (C-8), 112.5 (C-3''), 61.4 (C-1'), 56.9 (C-6), 52.5 (C-4), 48.7 (C-9a), 34.5 (C-1), 33.1 (C-9), 32.0 (C-1''), 28.1 (C-3), 22.4 (C-Me), 18.2 (C-2).

HRMS:

Calculated for $C_{14}H_{23}NO$: 222.1848 (M^+H^+)

Found: 222.1838 (M^+H^+)

VII. References

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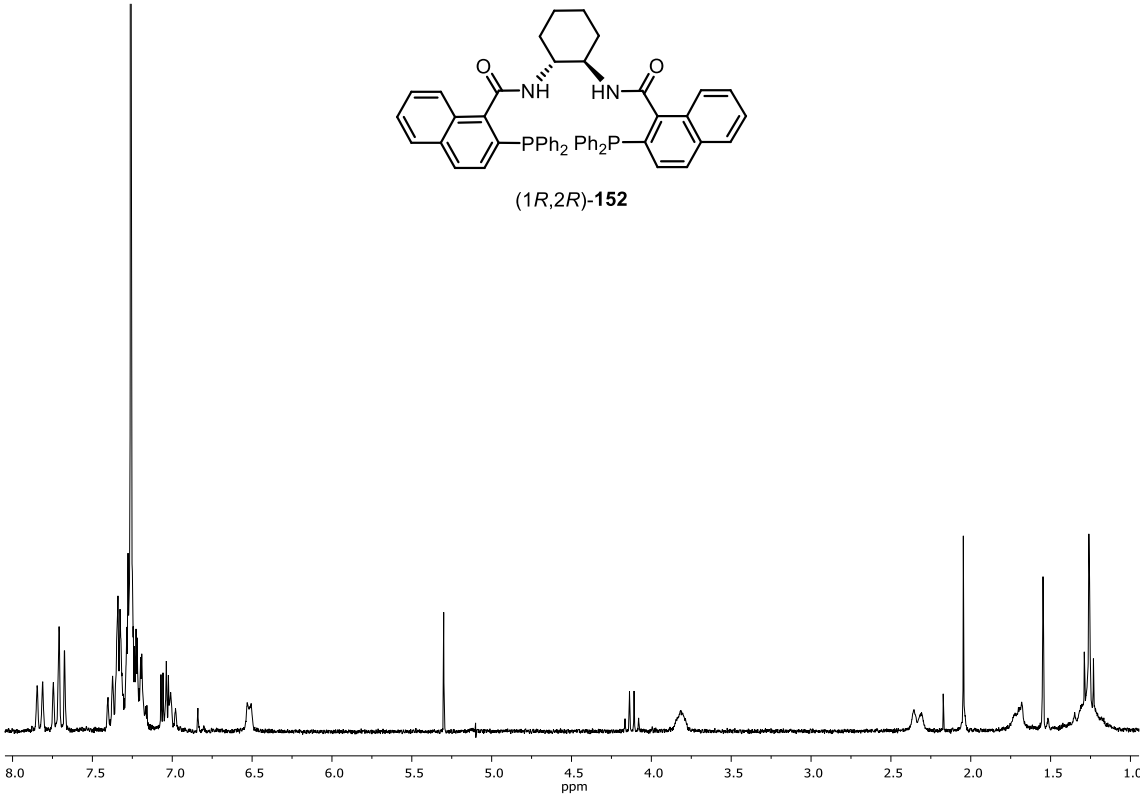
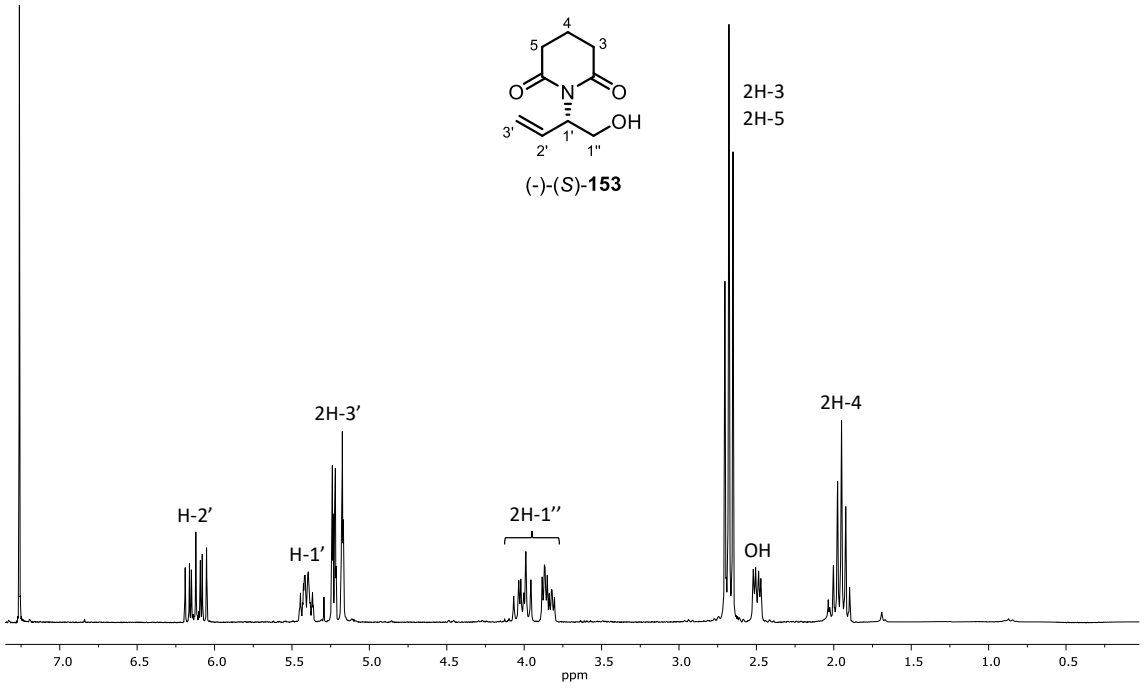
VIII. Spectra



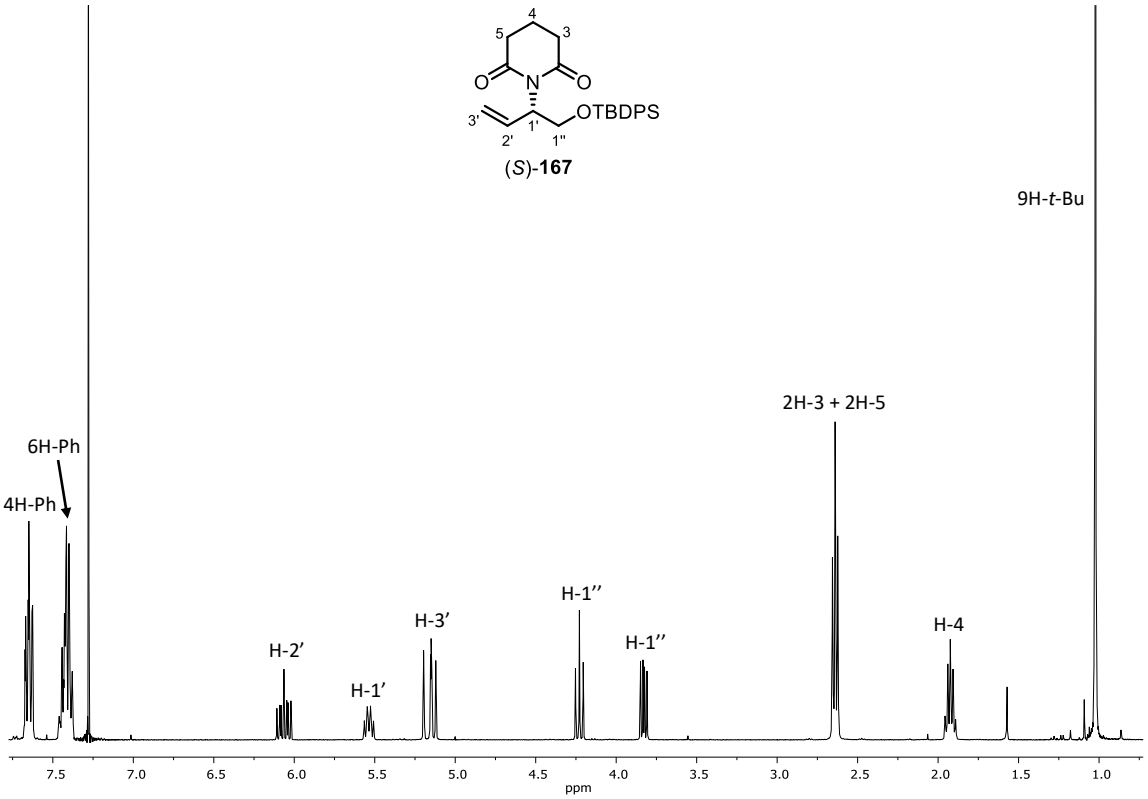
(1*R*,2*R*)-**152**

^{1}H NMR (250 MHz, $CDCl_3$)



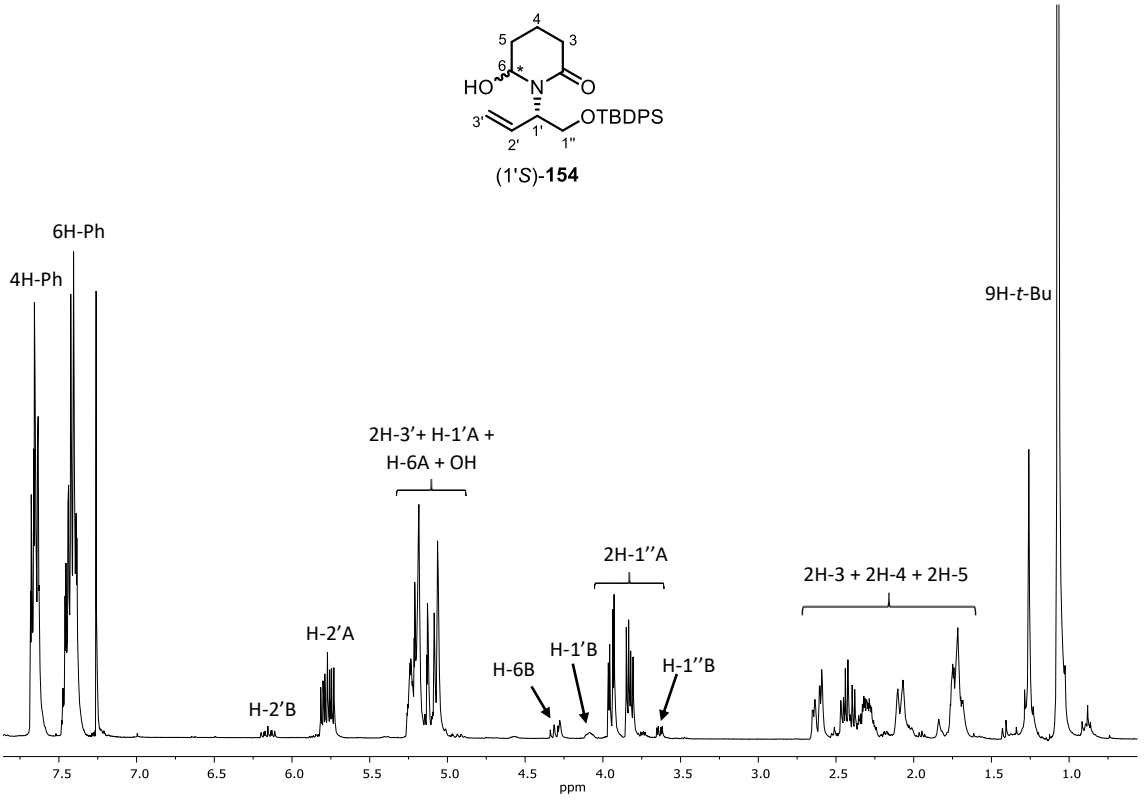
(-)-(*S*)-**153**

^{1}H NMR (250 MHz, $CDCl_3$)



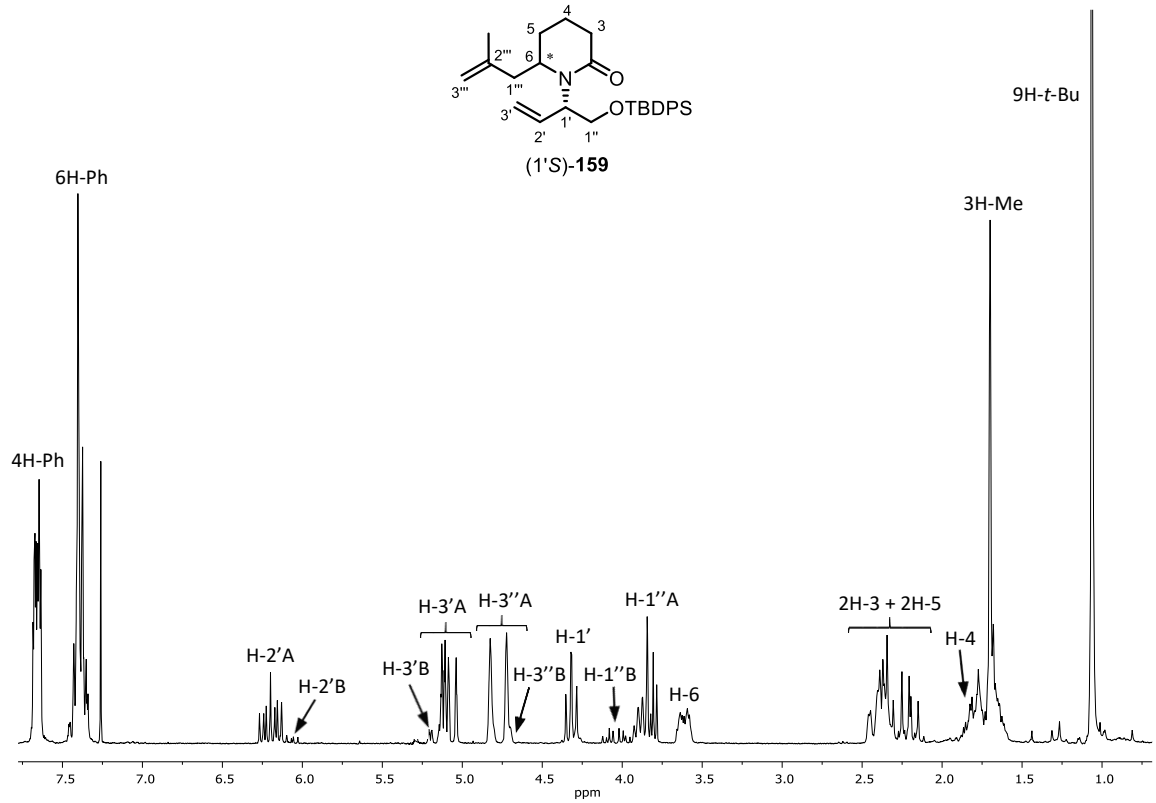
(*S*)-**167**

^{1}H NMR (400 MHz, $CDCl_3$)



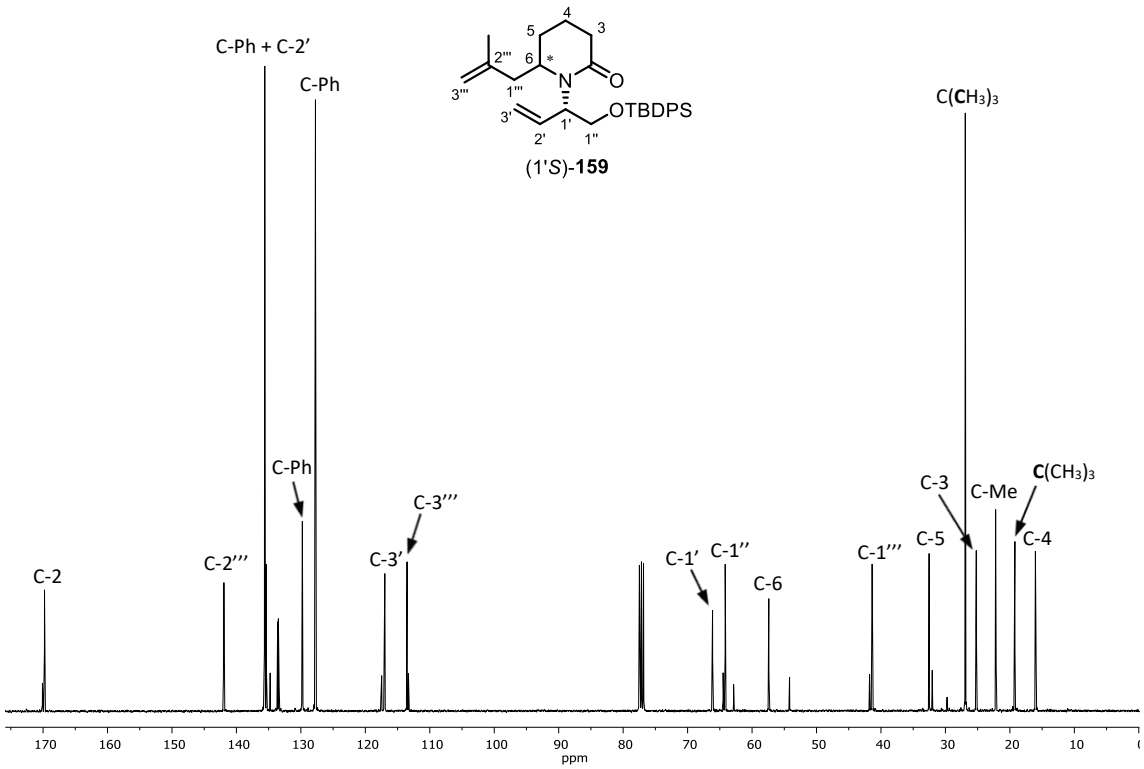
(1'*S*)-**154**

^{1}H NMR (400 MHz, $CDCl_3$)



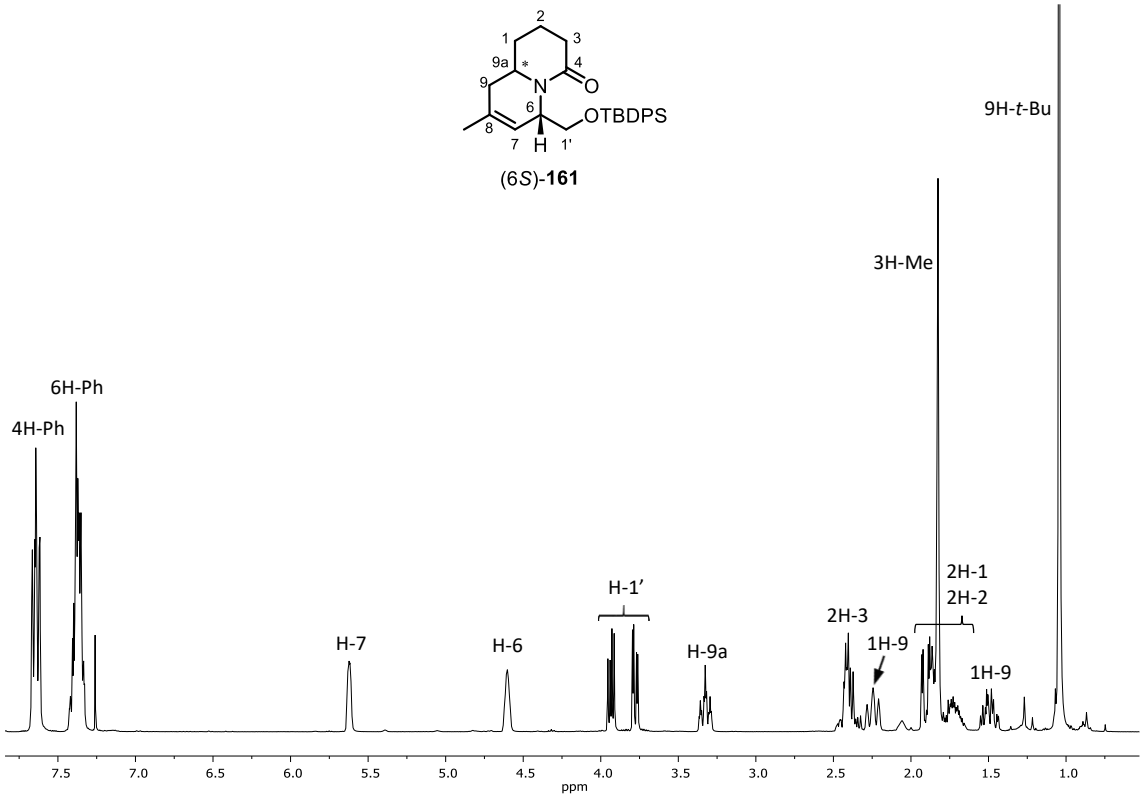
(1'*S*)-**159**

^{1}H NMR (250 MHz, $CDCl_3$)



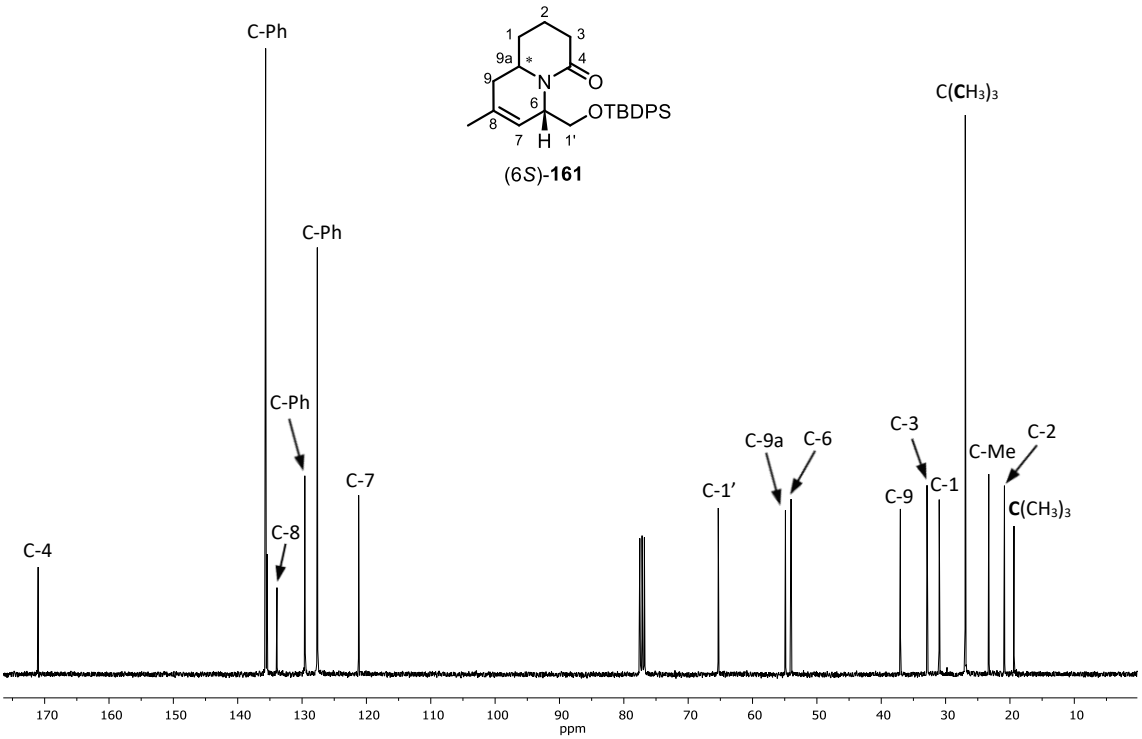
(1'*S*)-**159**

^{13}C NMR (101 MHz, $CDCl_3$)



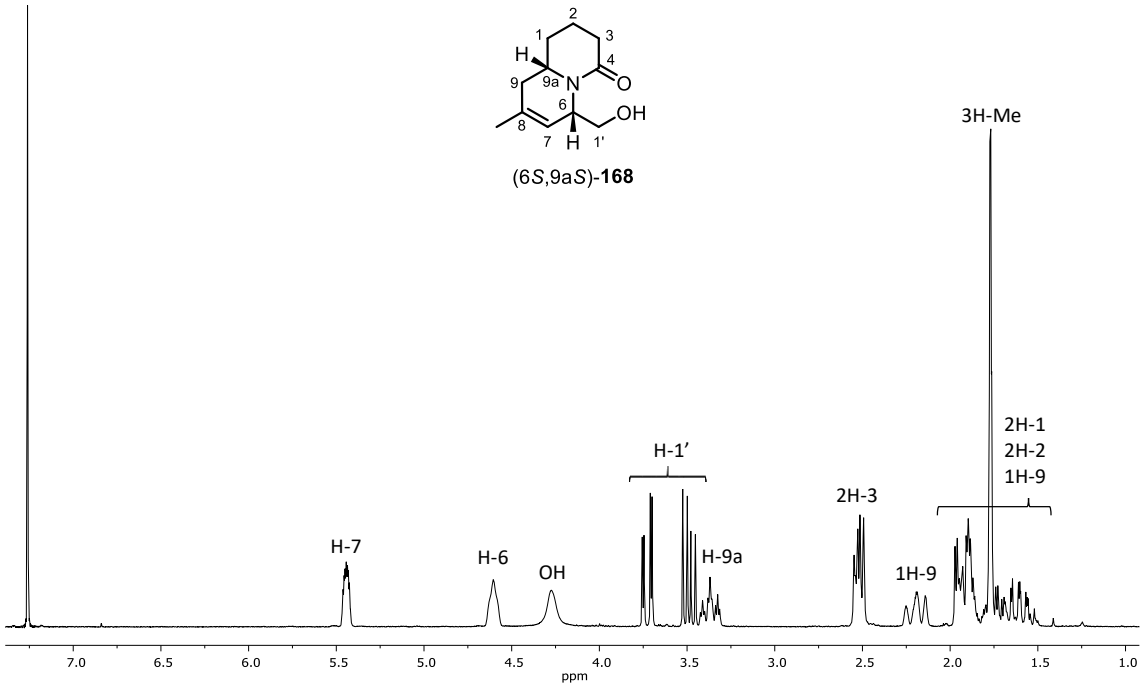
(6*S*)-**161**

^{1}H NMR (360 MHz, $CDCl_3$)

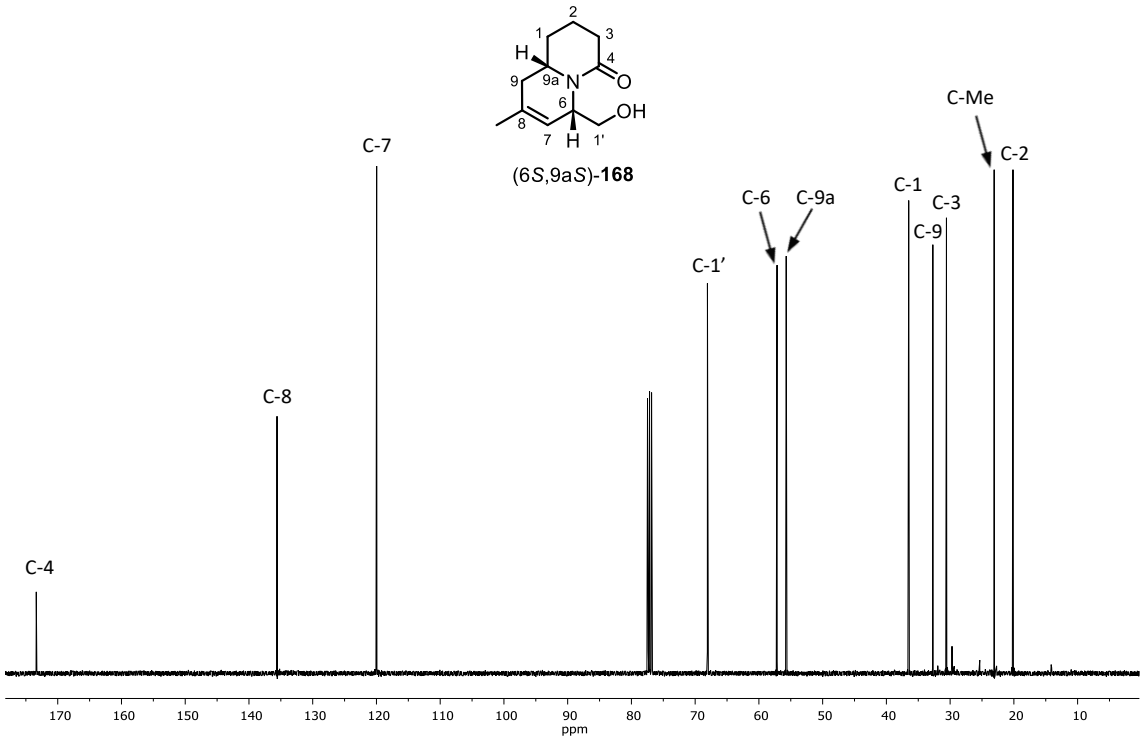


(6*S*)-**161**

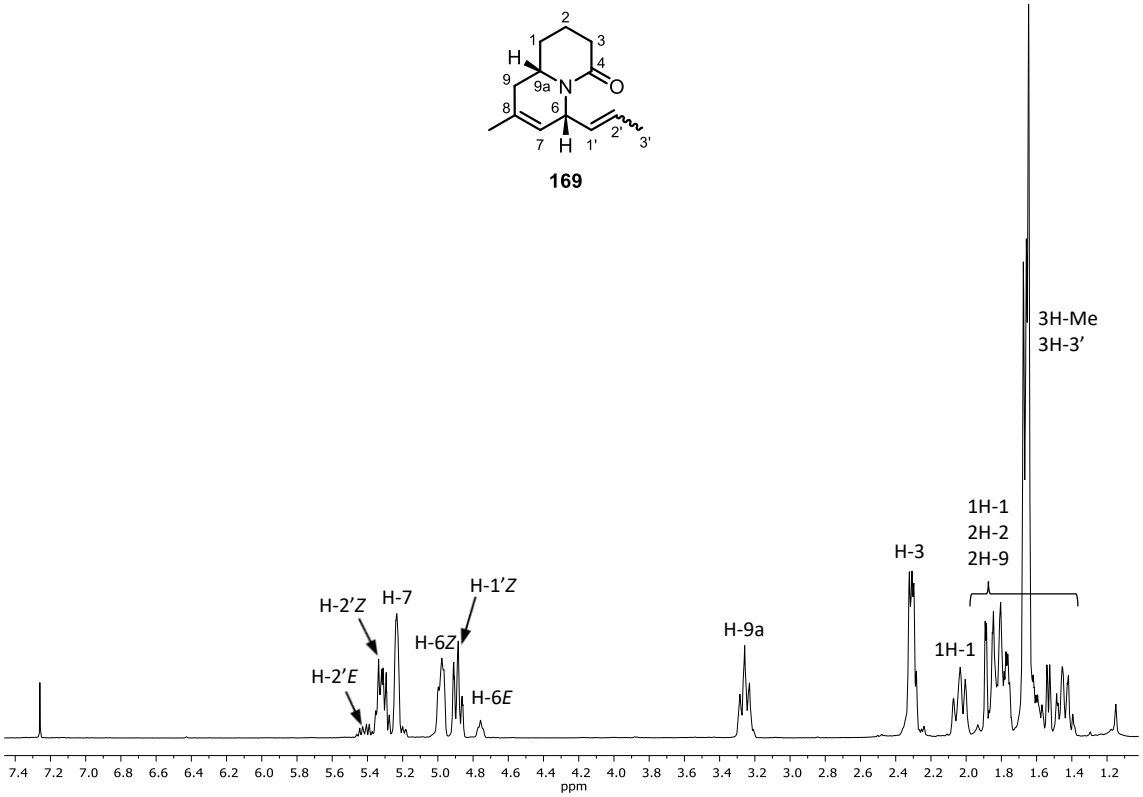
^{13}C NMR (91 MHz, $CDCl_3$)



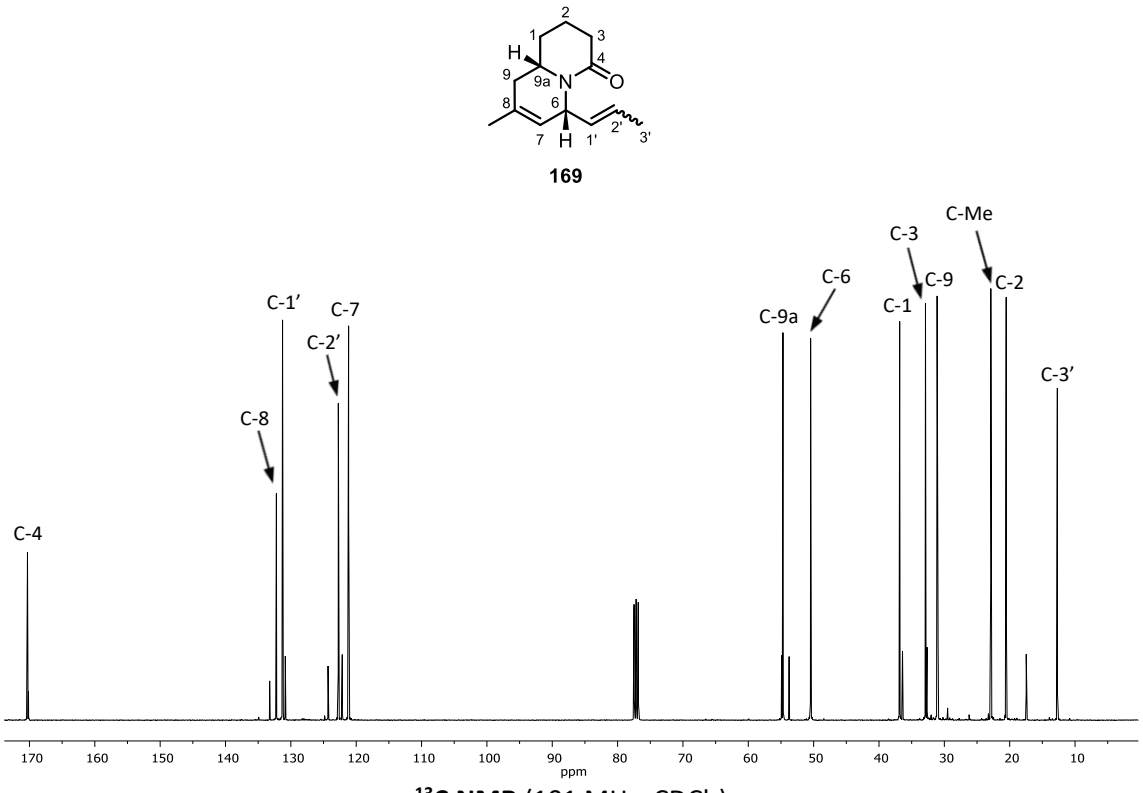
^{1}H NMR (250 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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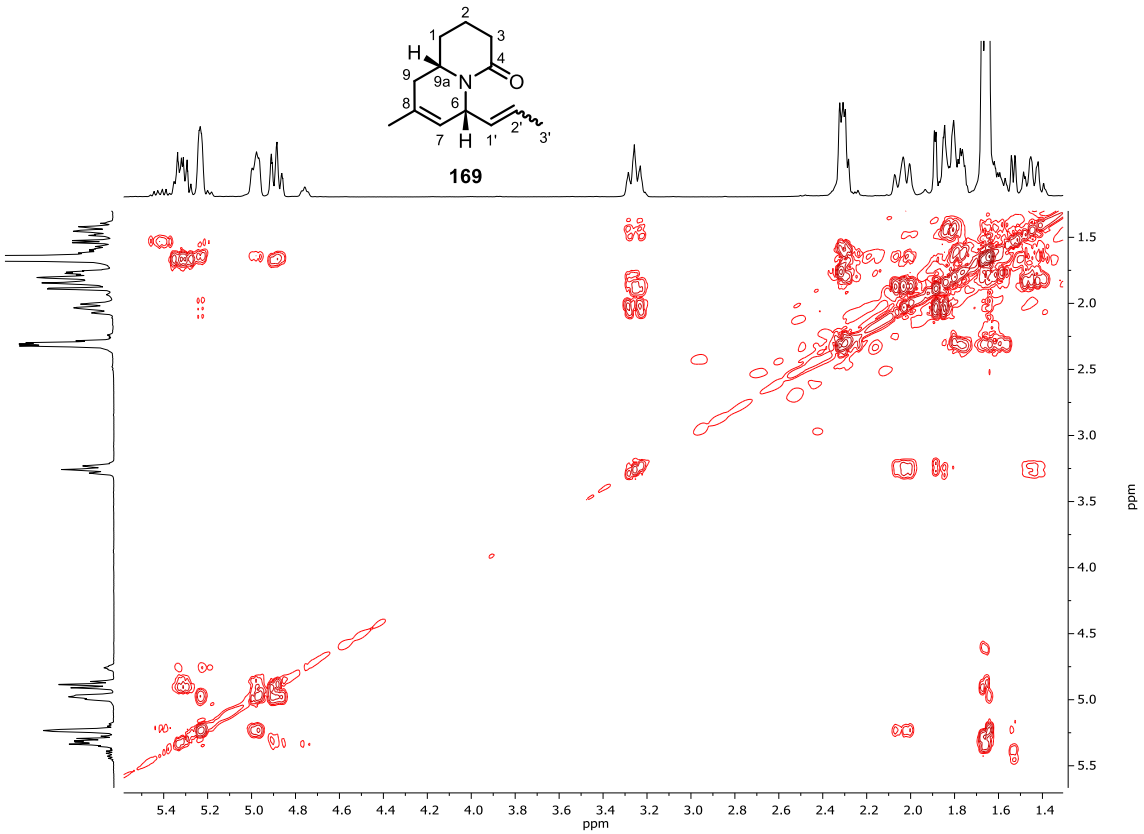
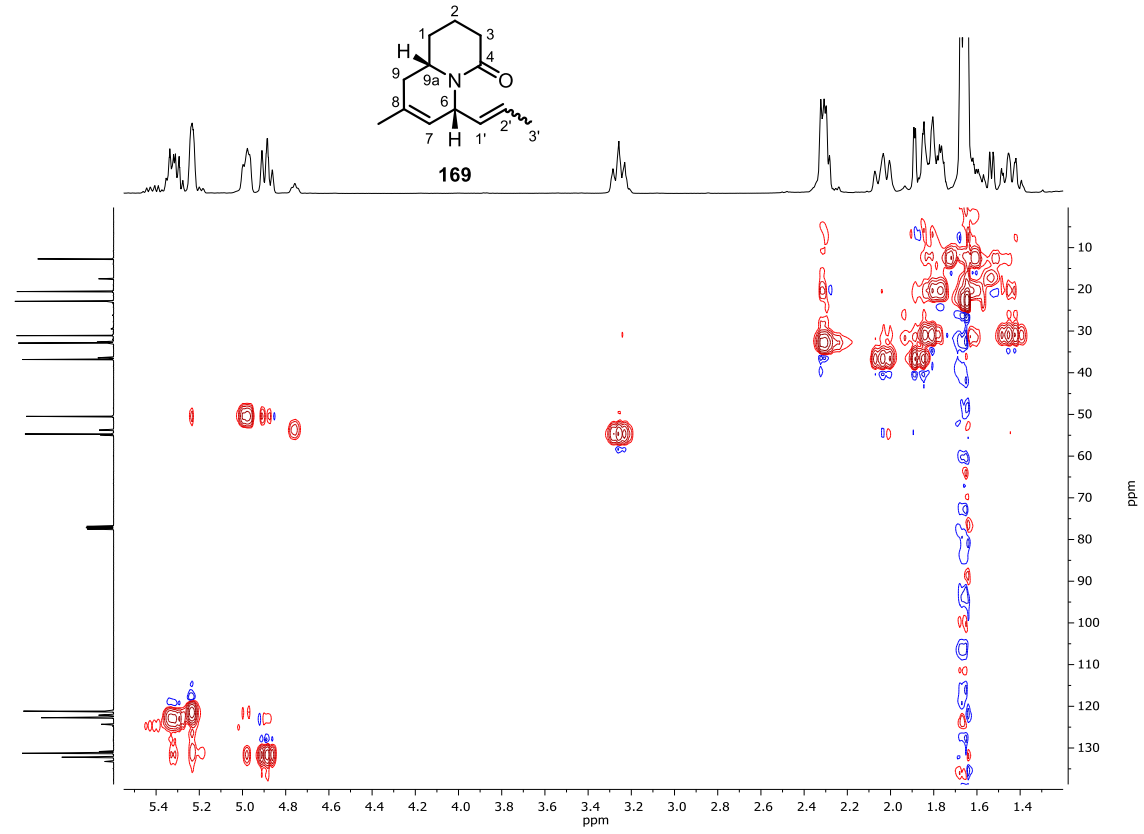
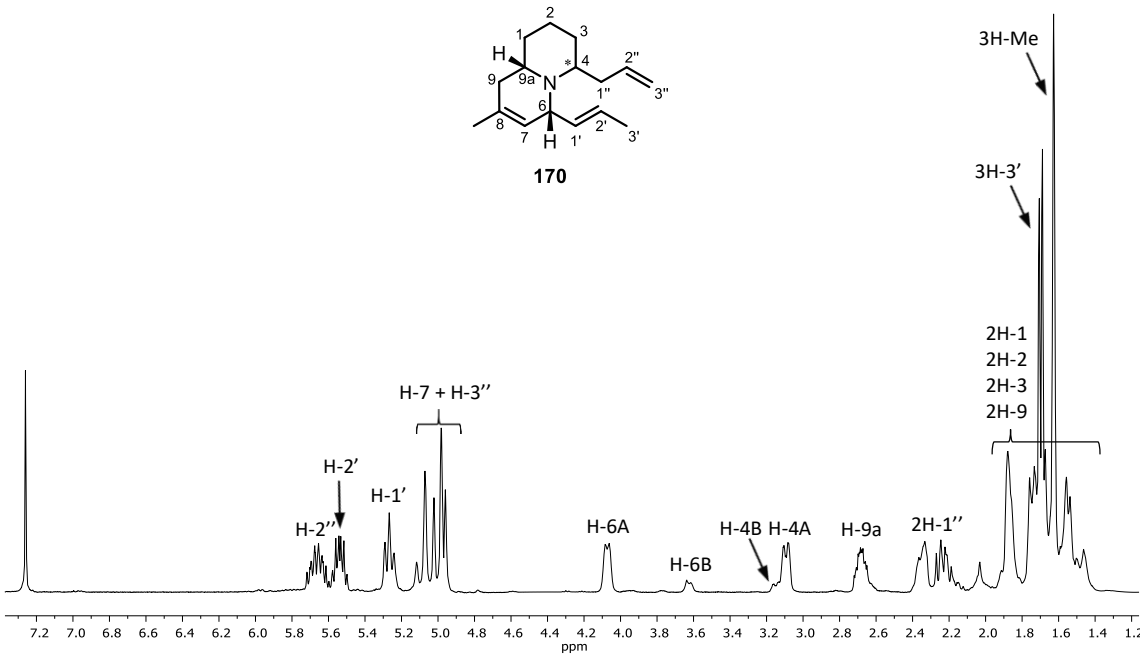


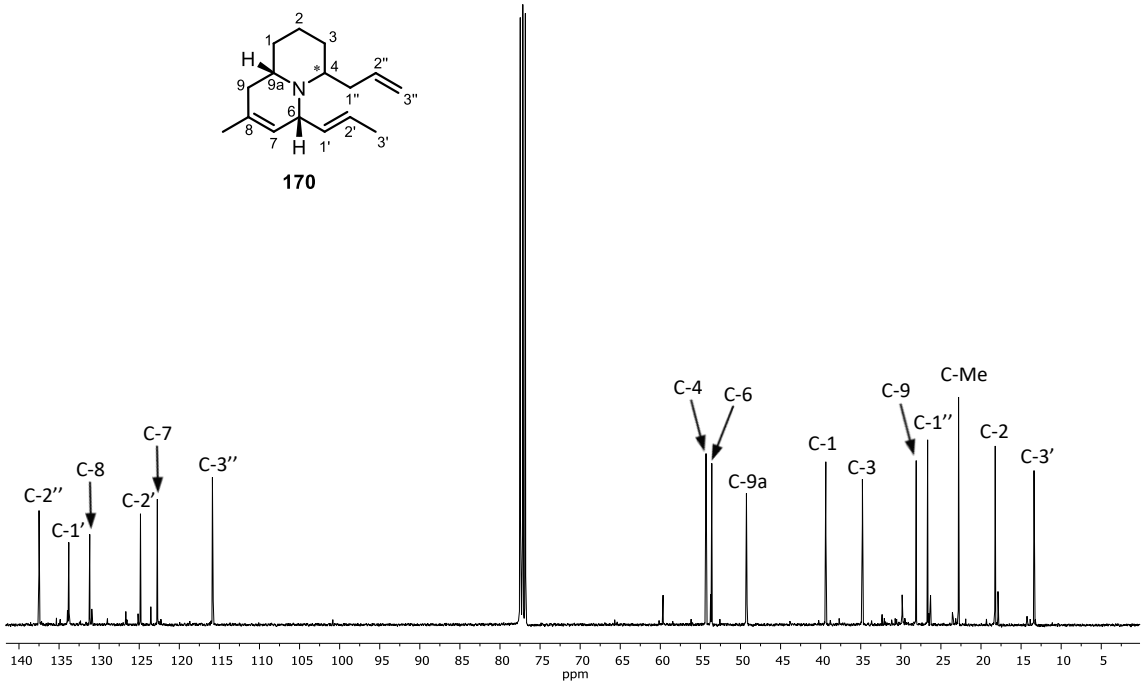
2D COSY (400 MHz, $CDCl_3$)



HSQC (400 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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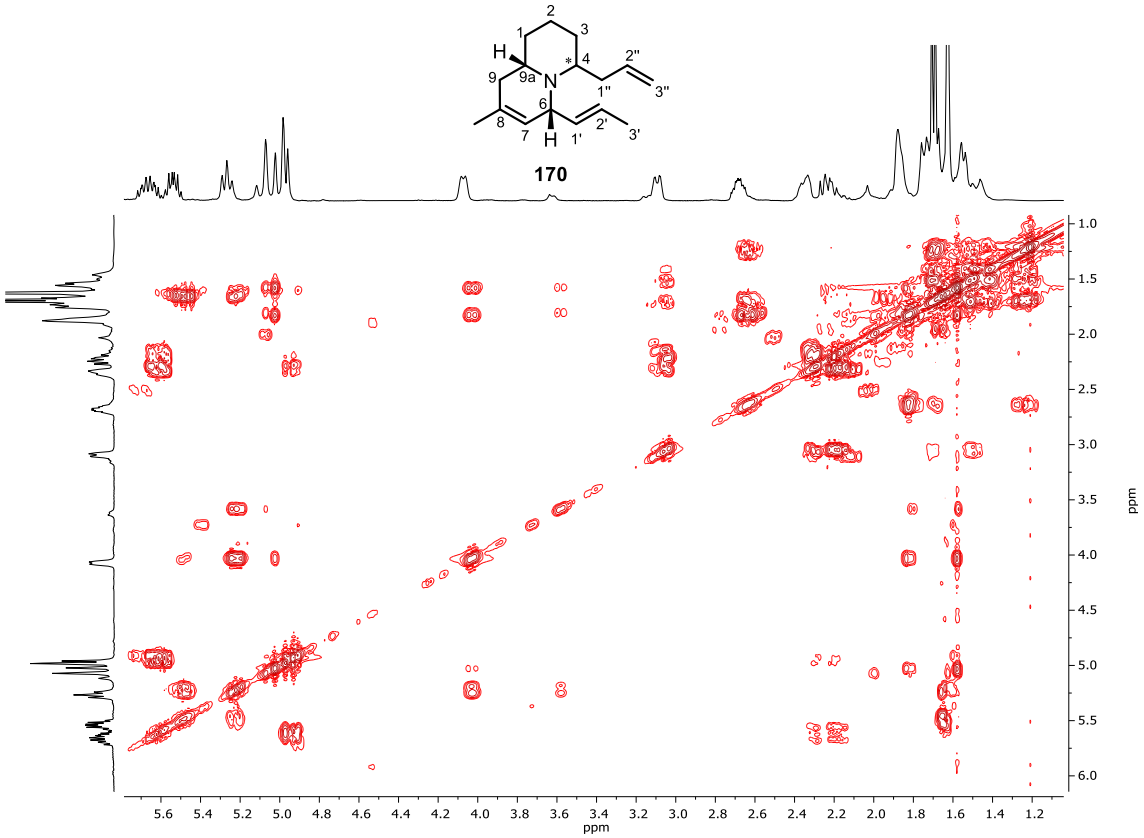

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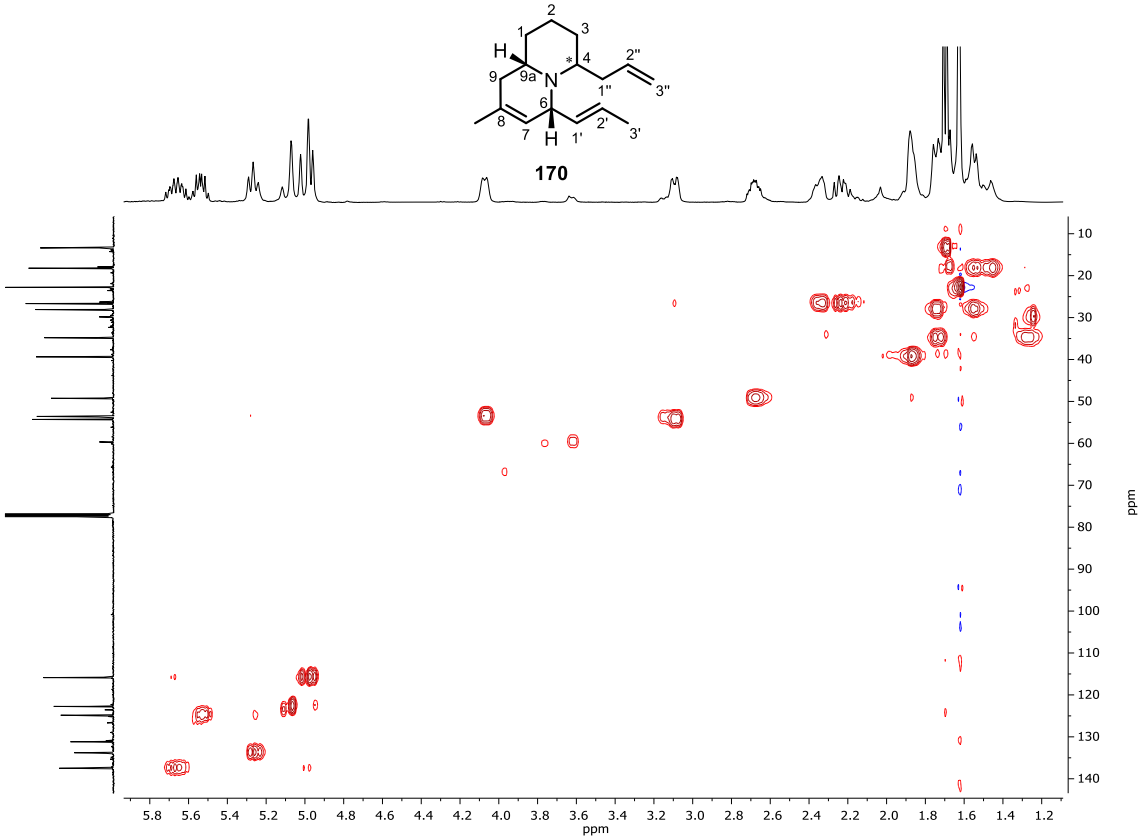

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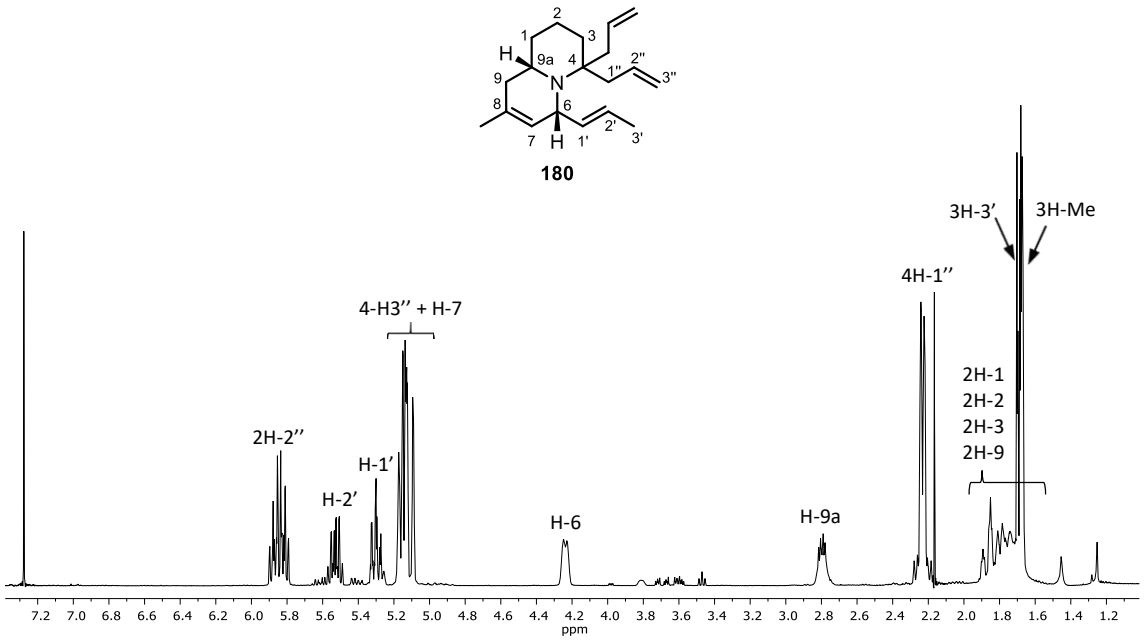

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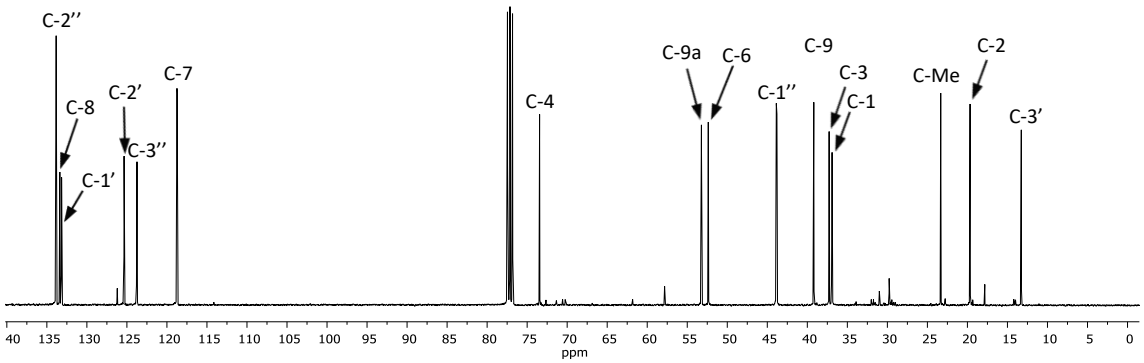

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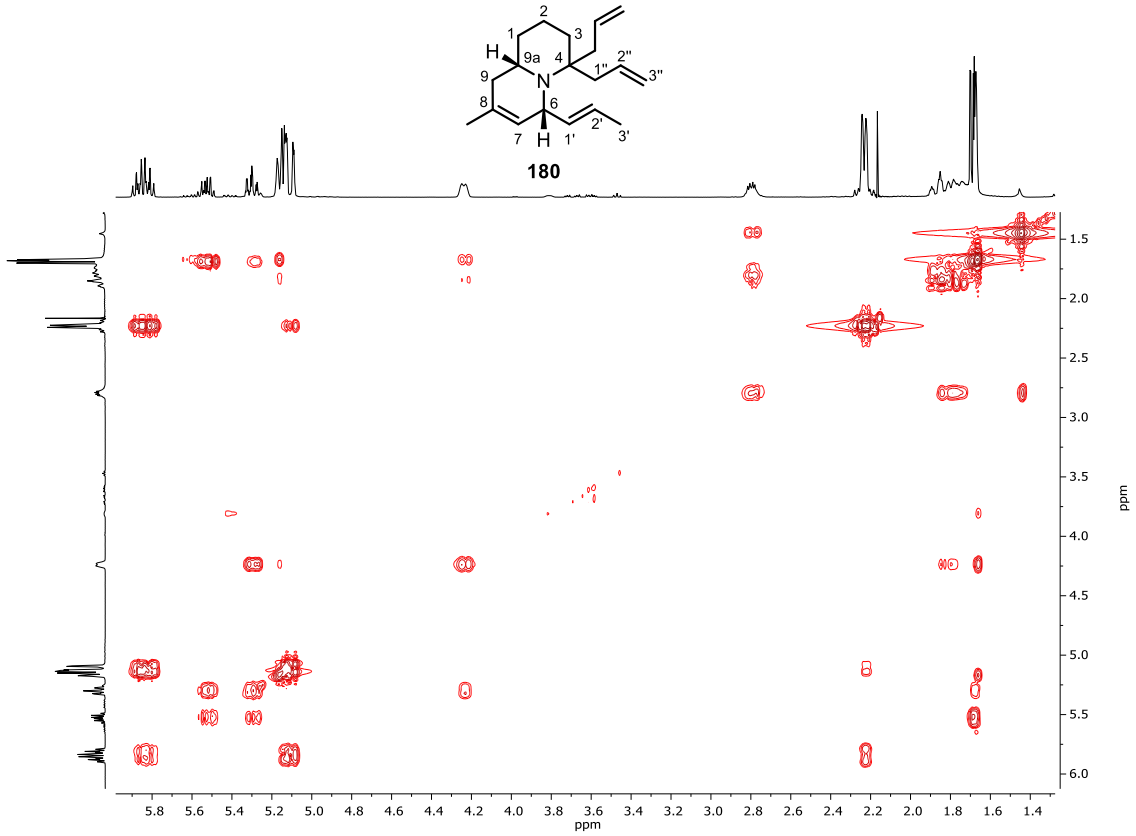

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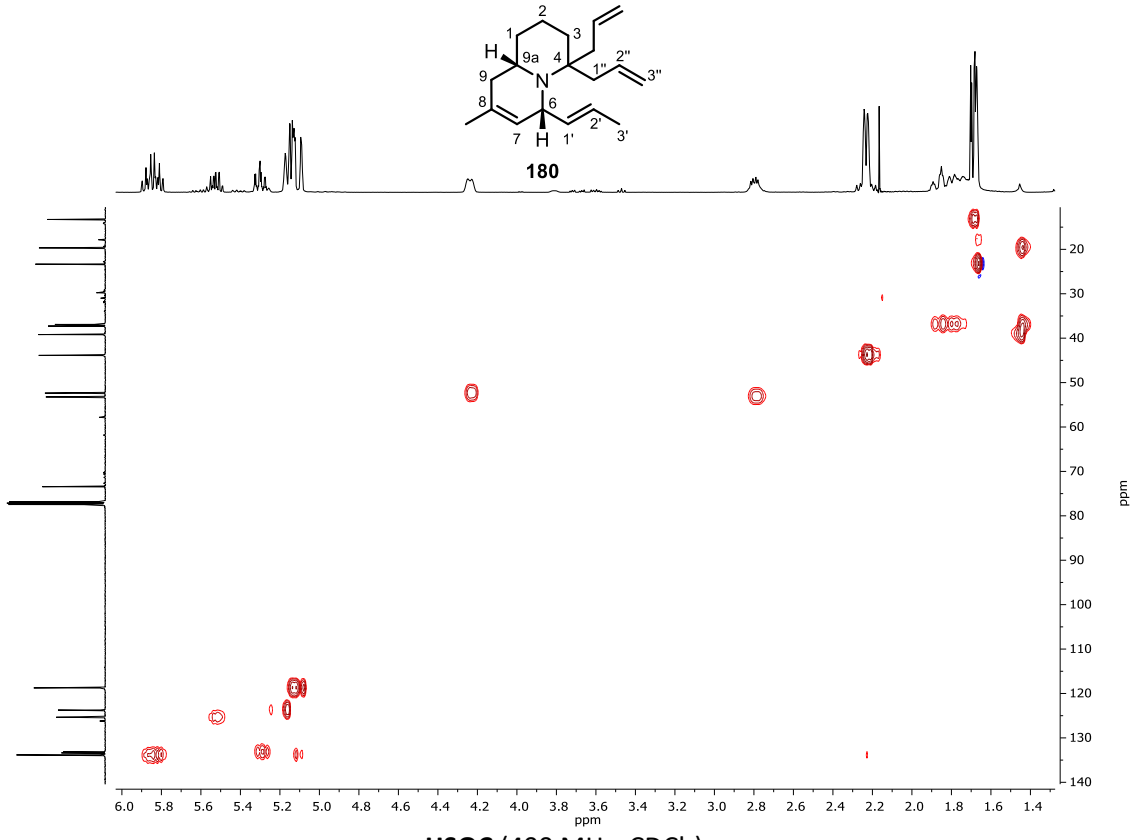

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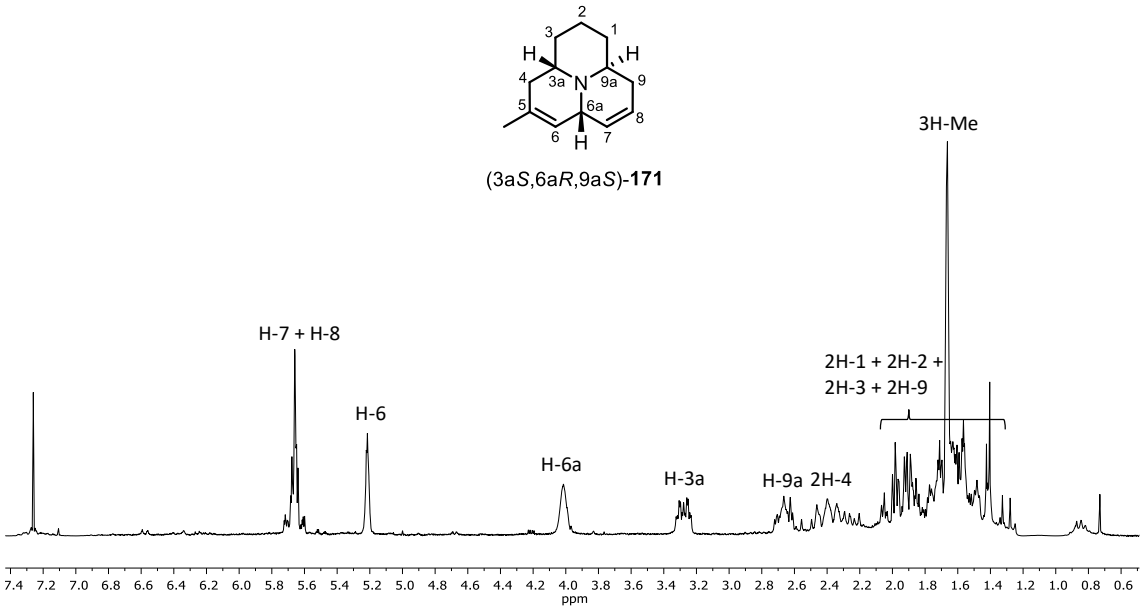

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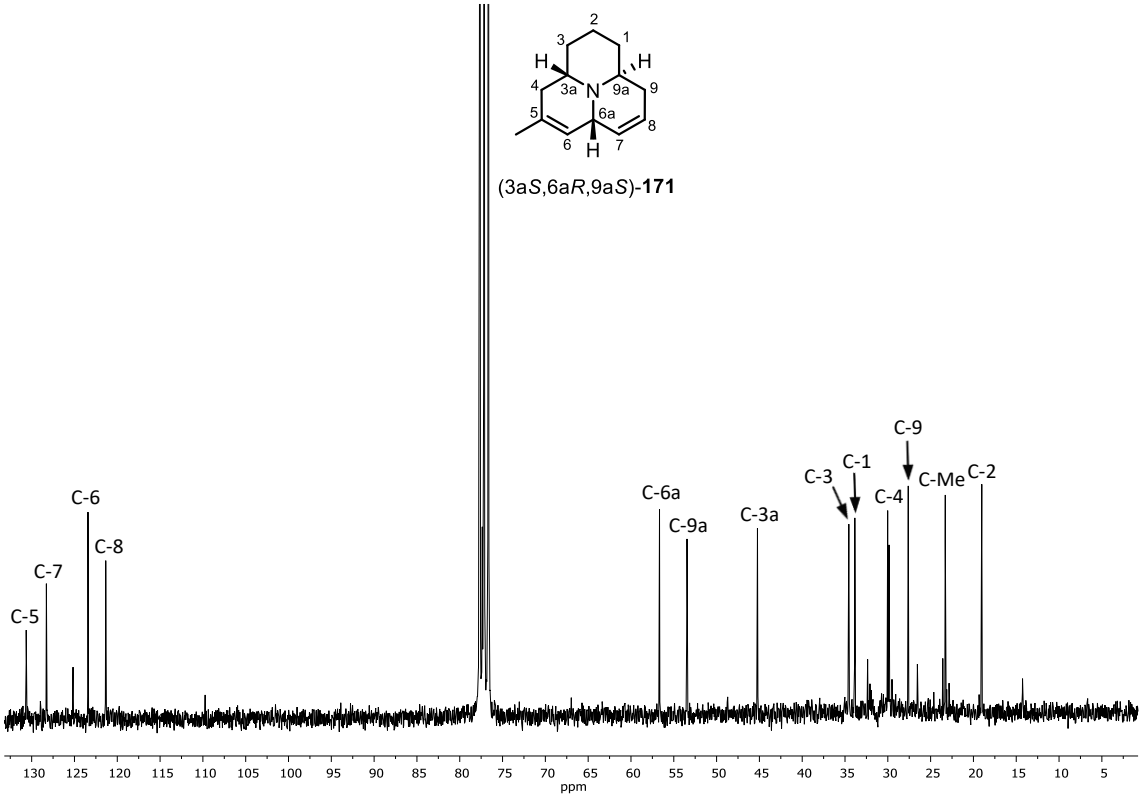

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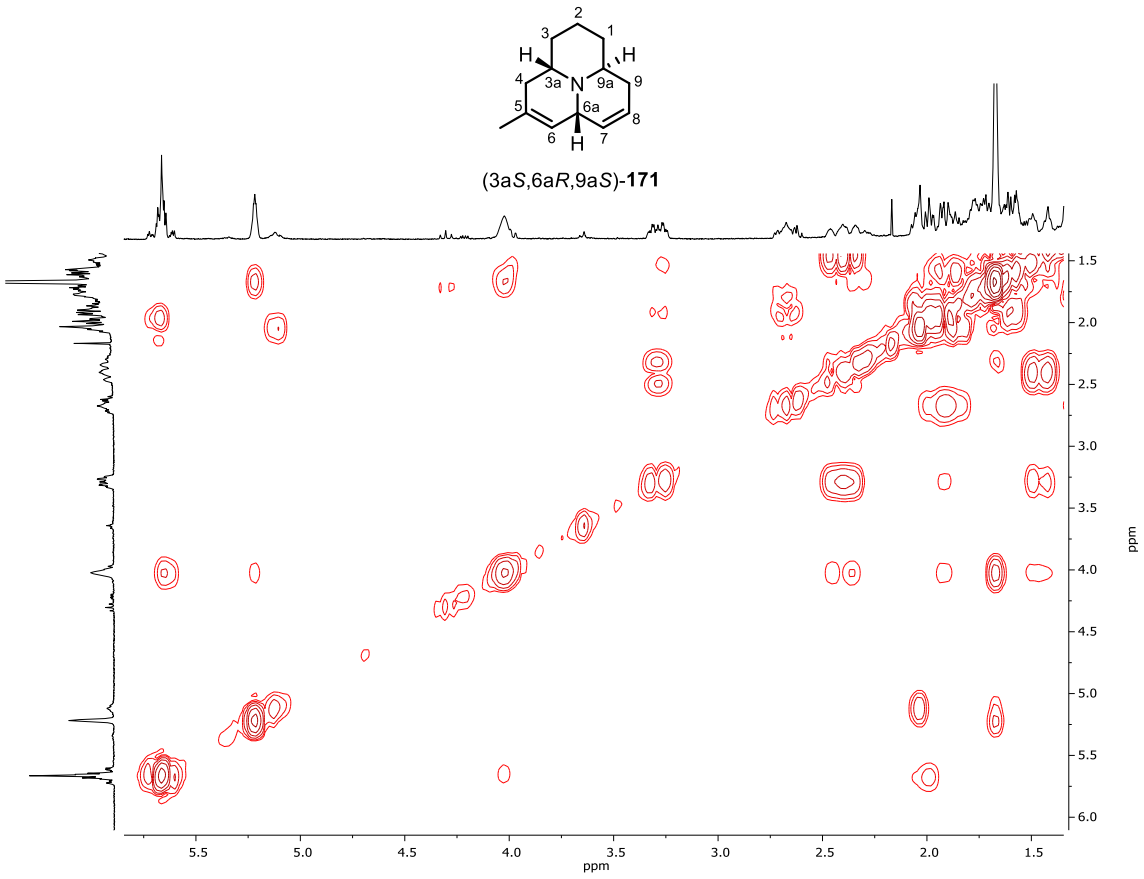

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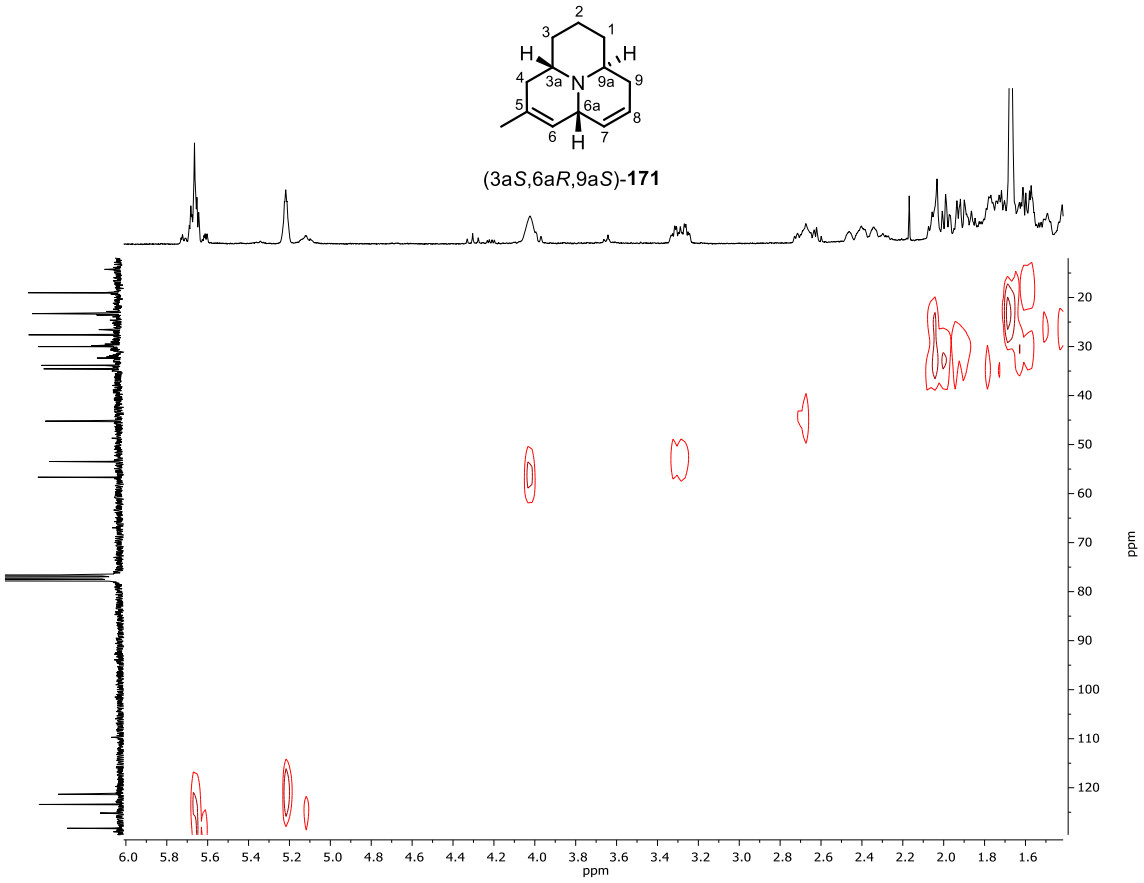

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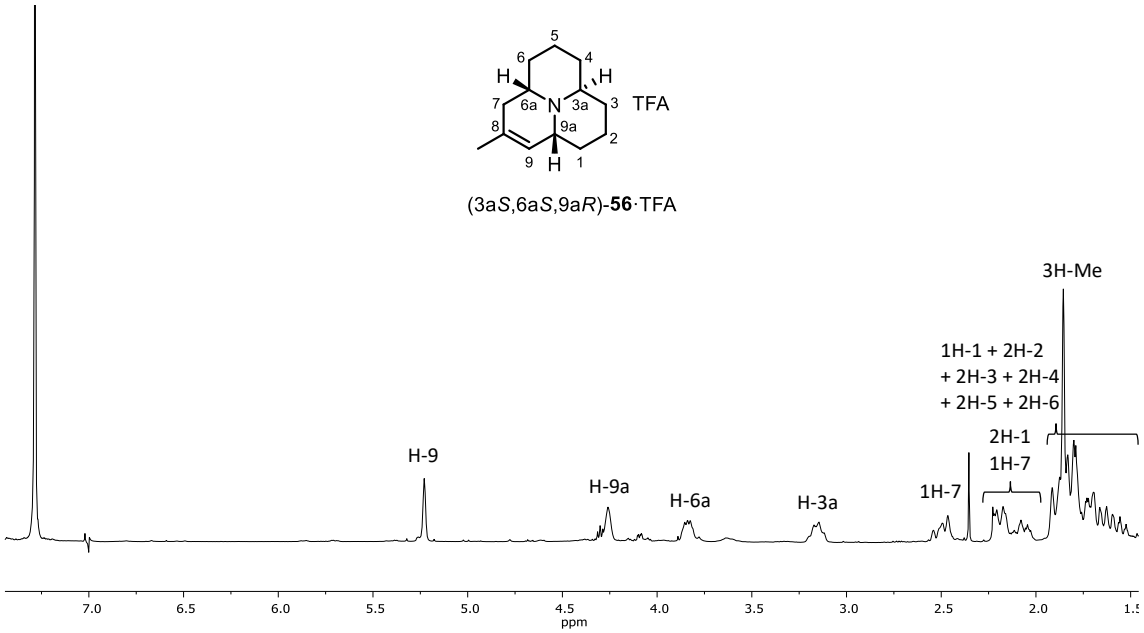

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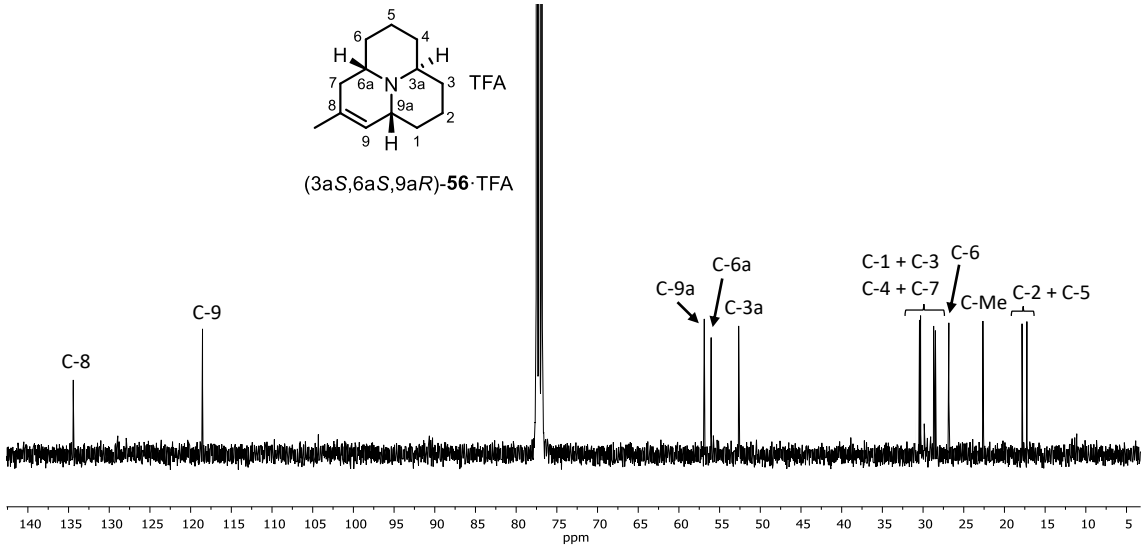

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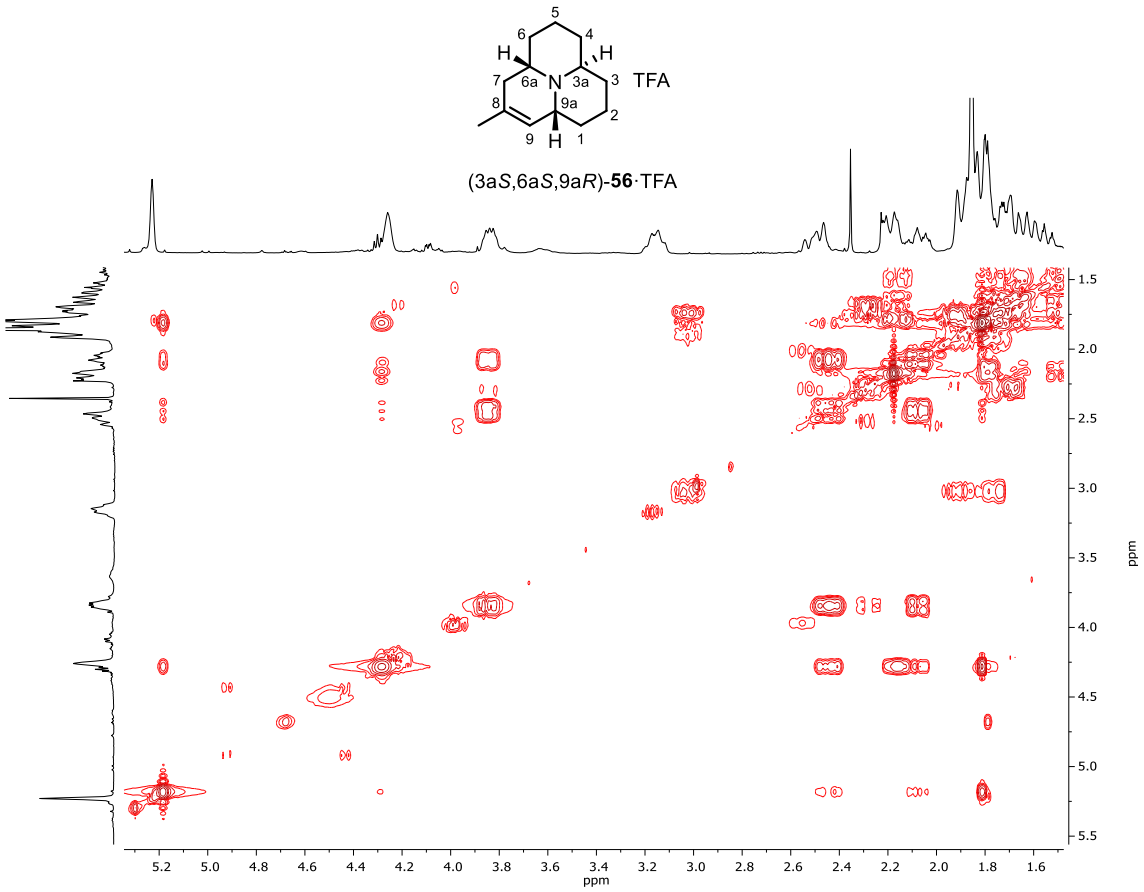

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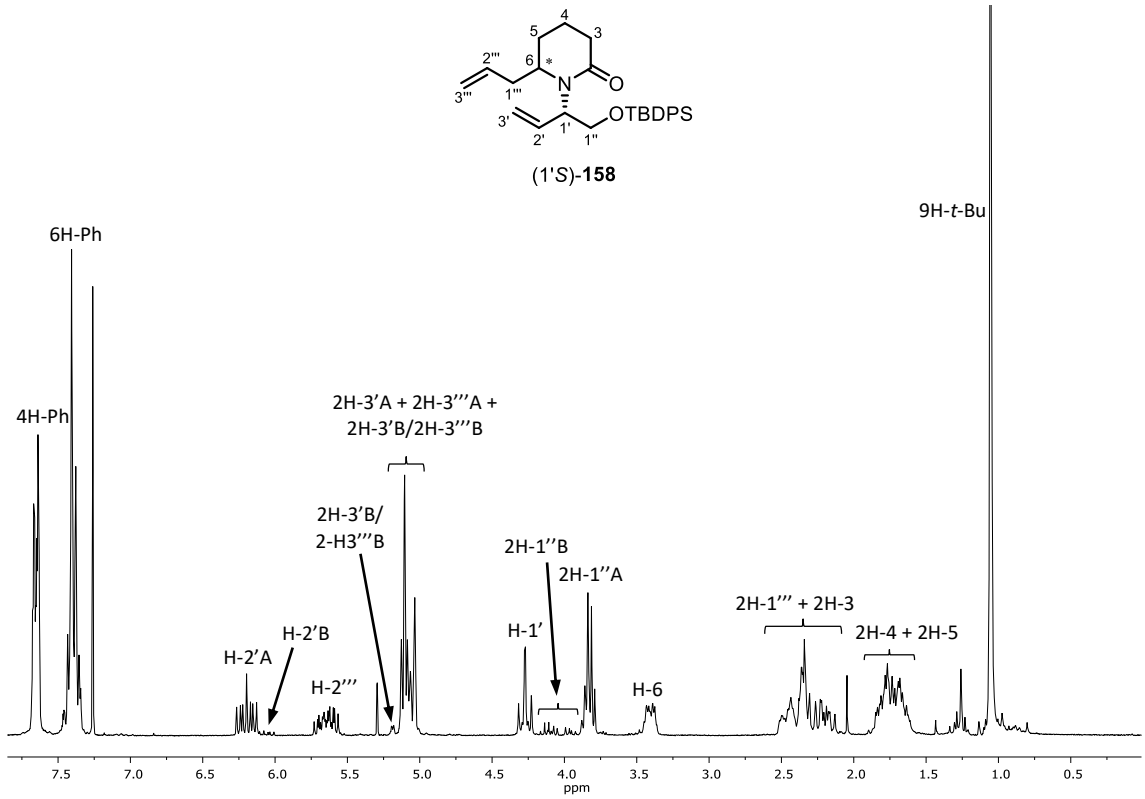

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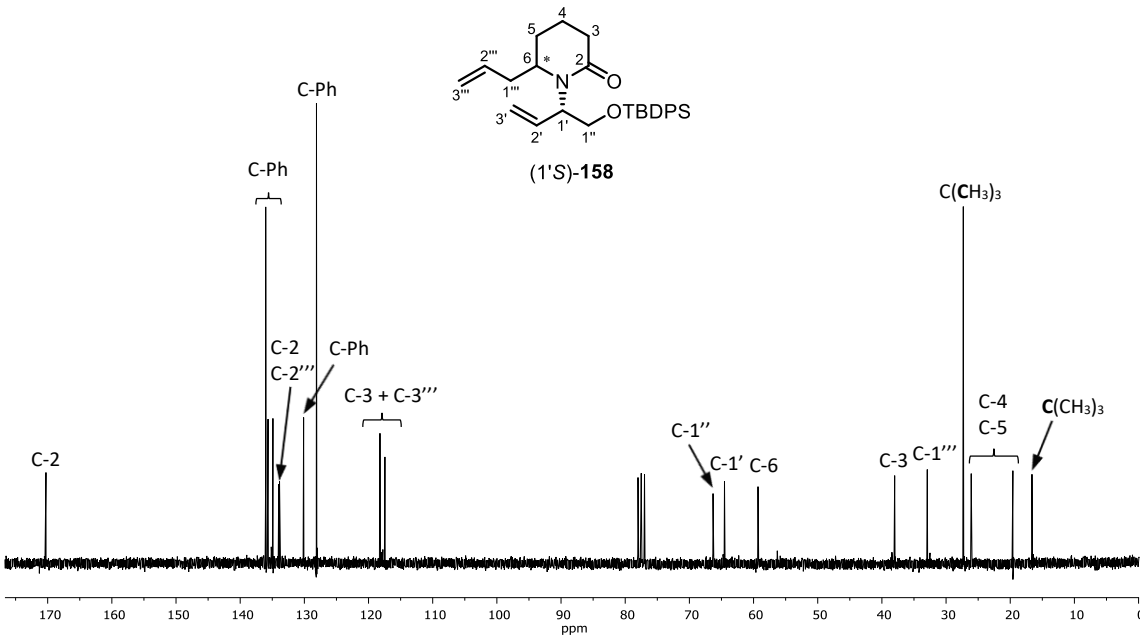
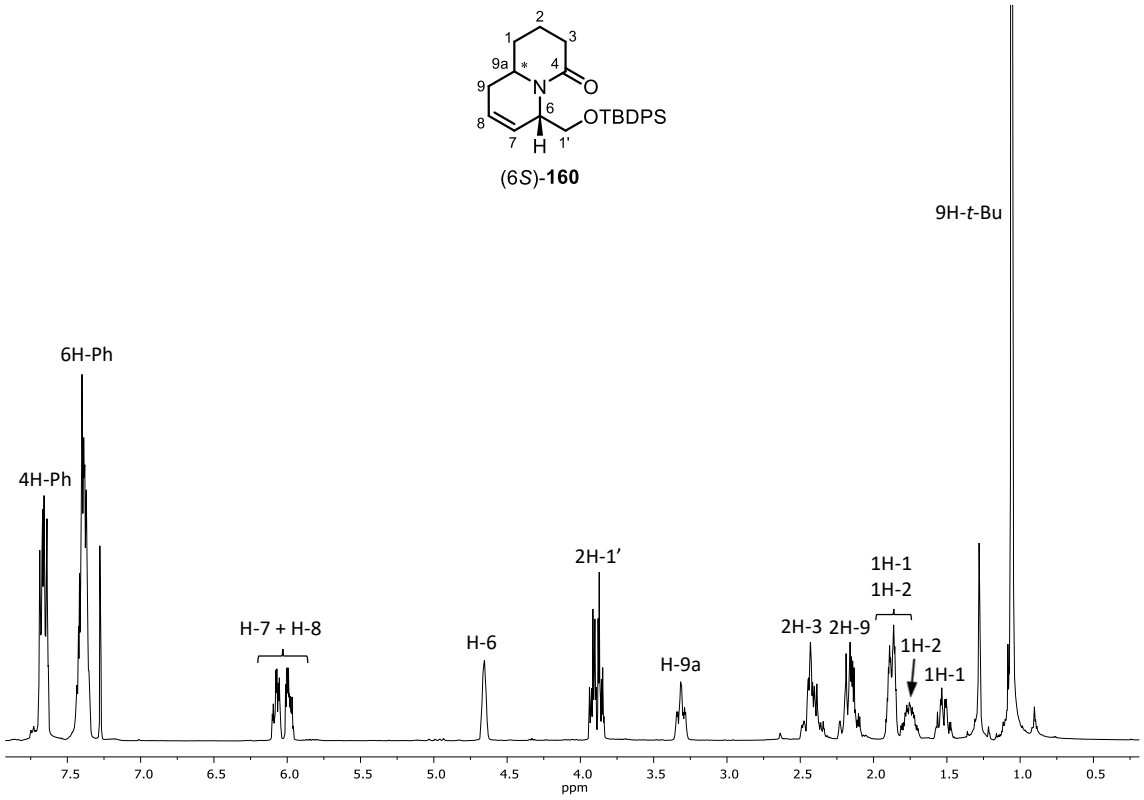
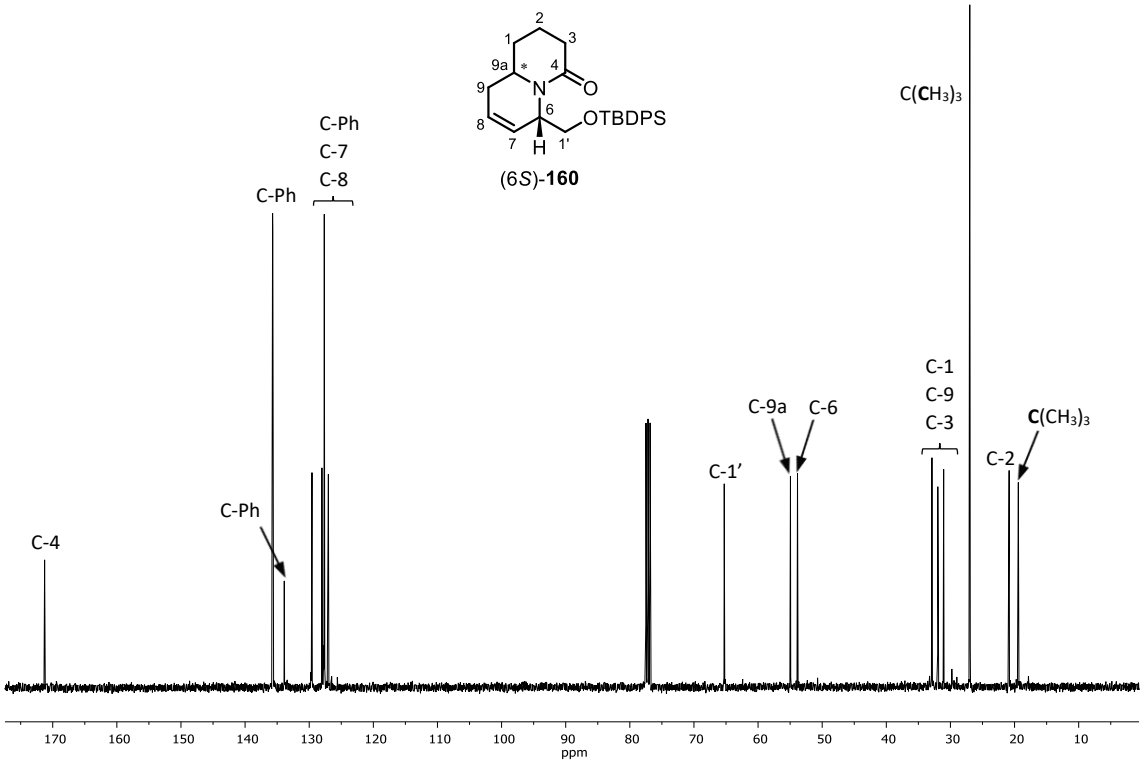


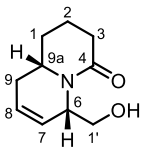
^{13}C NMR (63 MHz, $CDCl_3$)



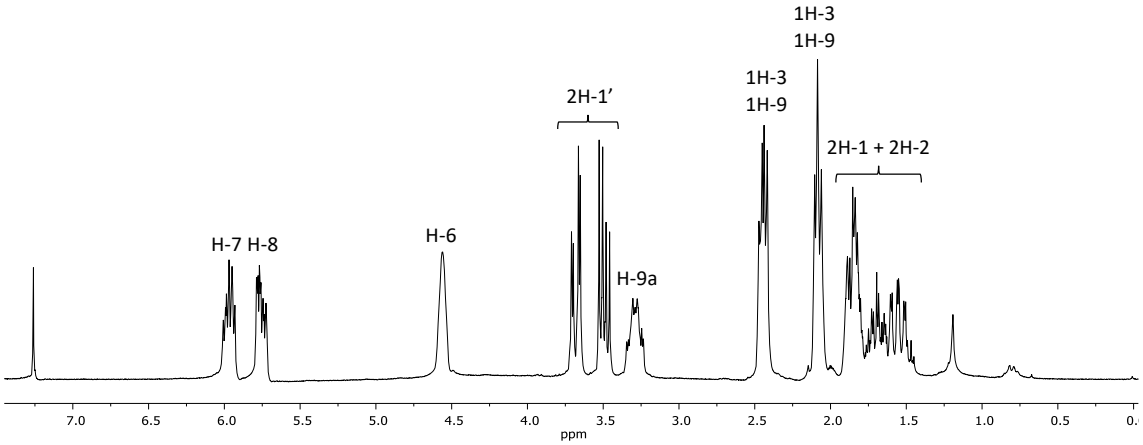
^{1}H NMR (400 MHz, $CDCl_3$)



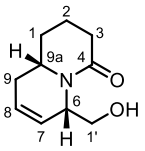
^{13}C NMR (101 MHz, $CDCl_3$)



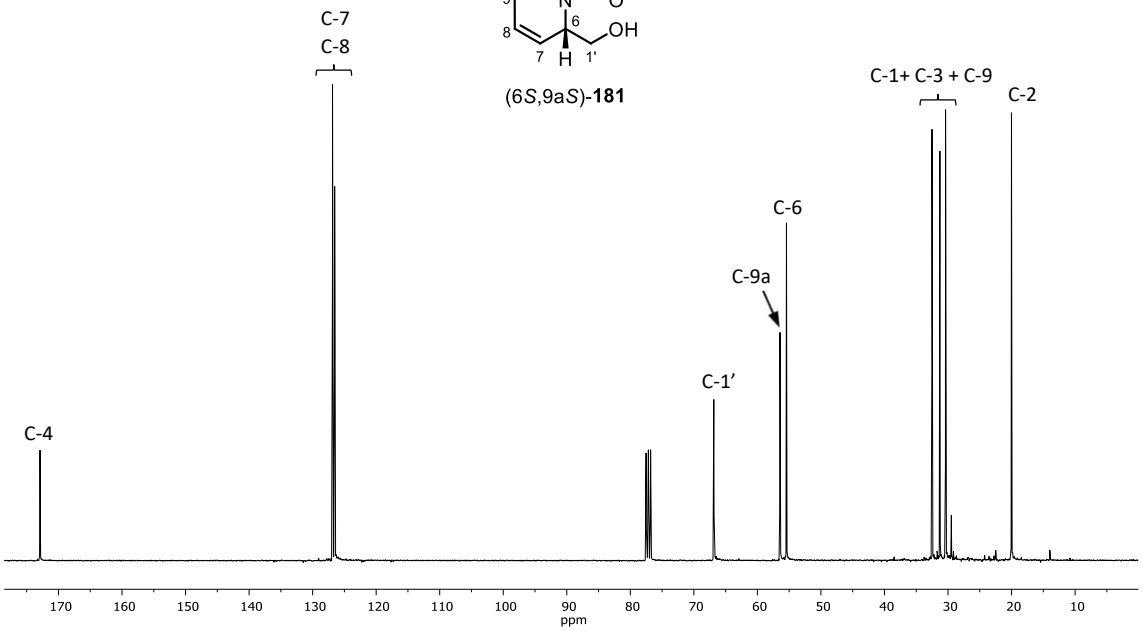
(6*S*,9a*S*)-**181**



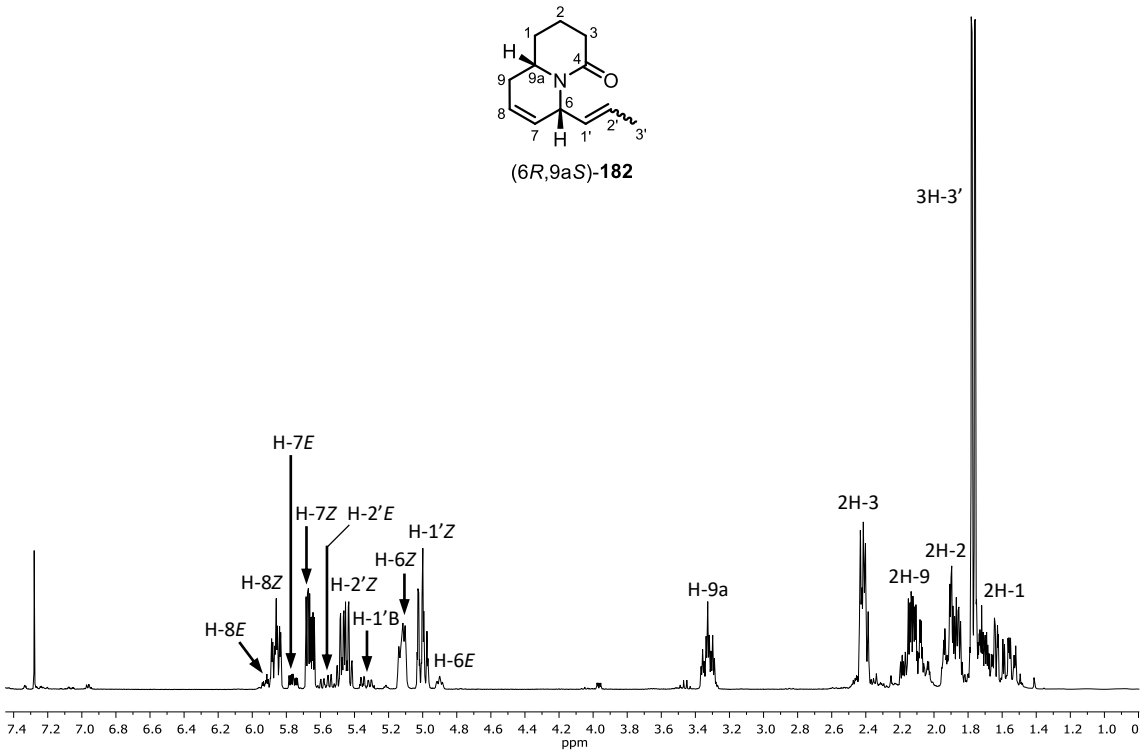
^{1}H NMR (250 MHz, $CDCl_3$)



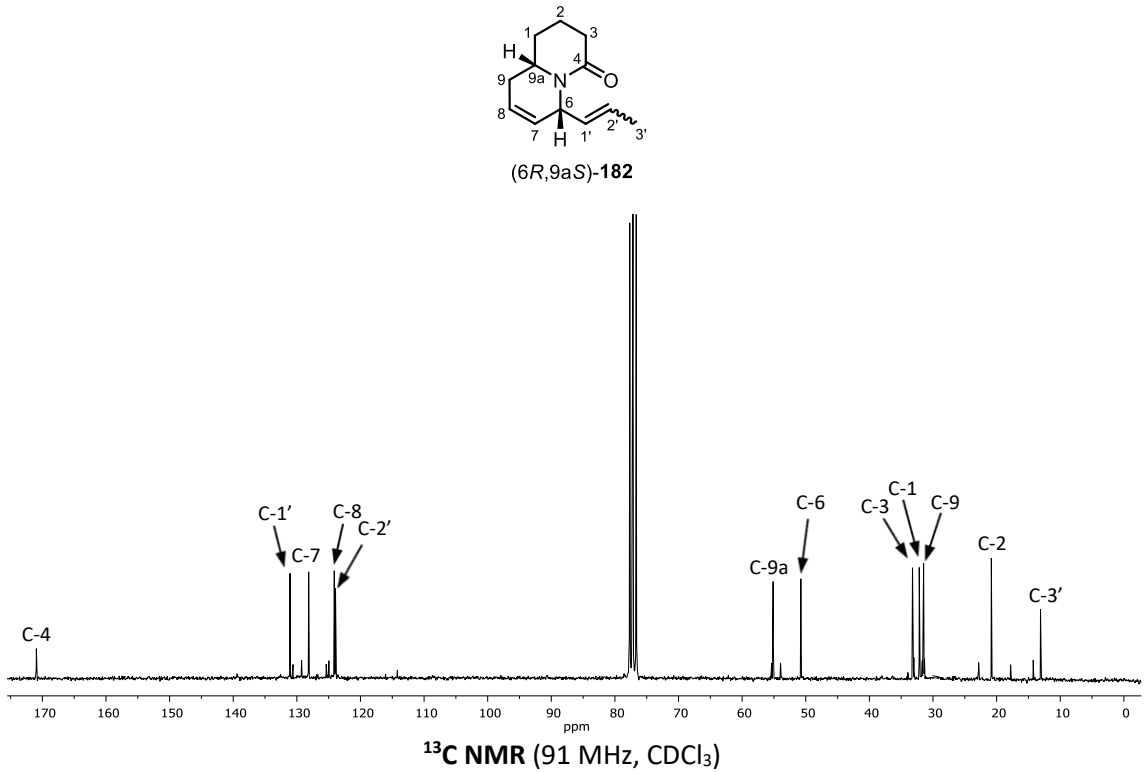
(6*S*,9a*S*)-**181**



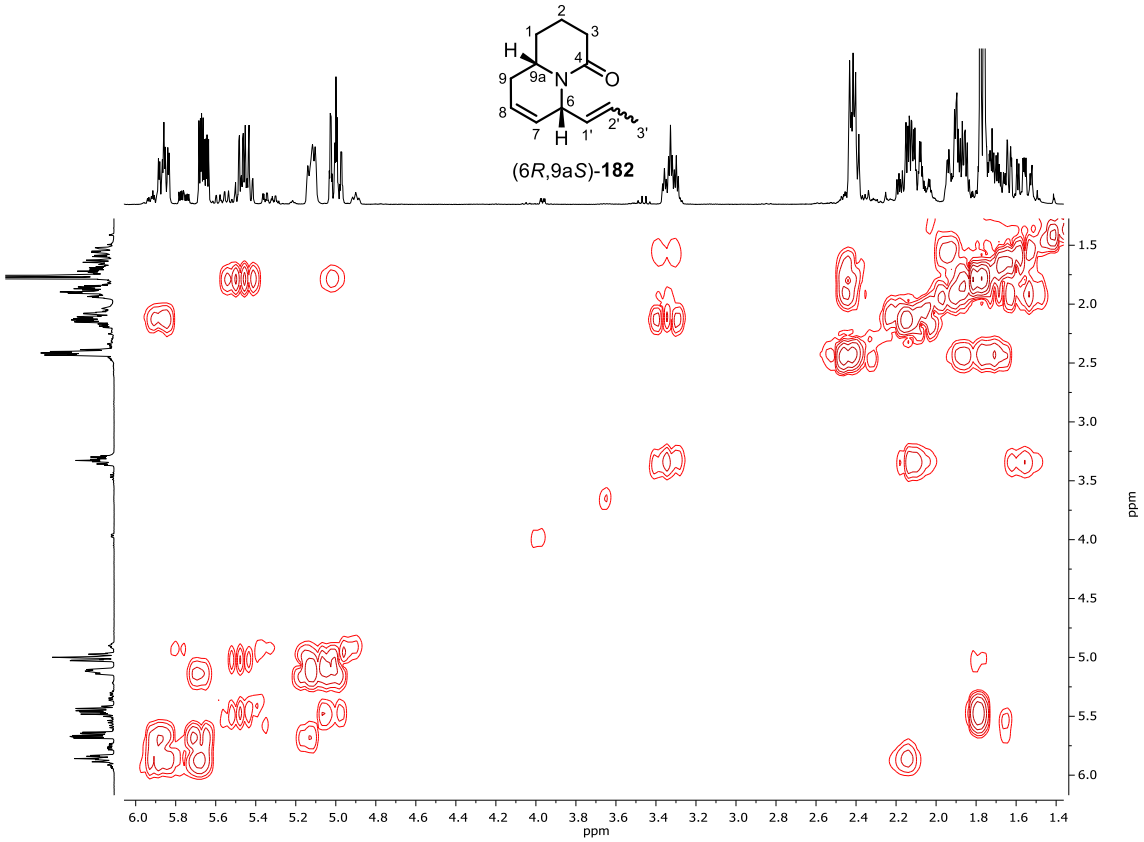
^{13}C NMR (91 MHz, $CDCl_3$)



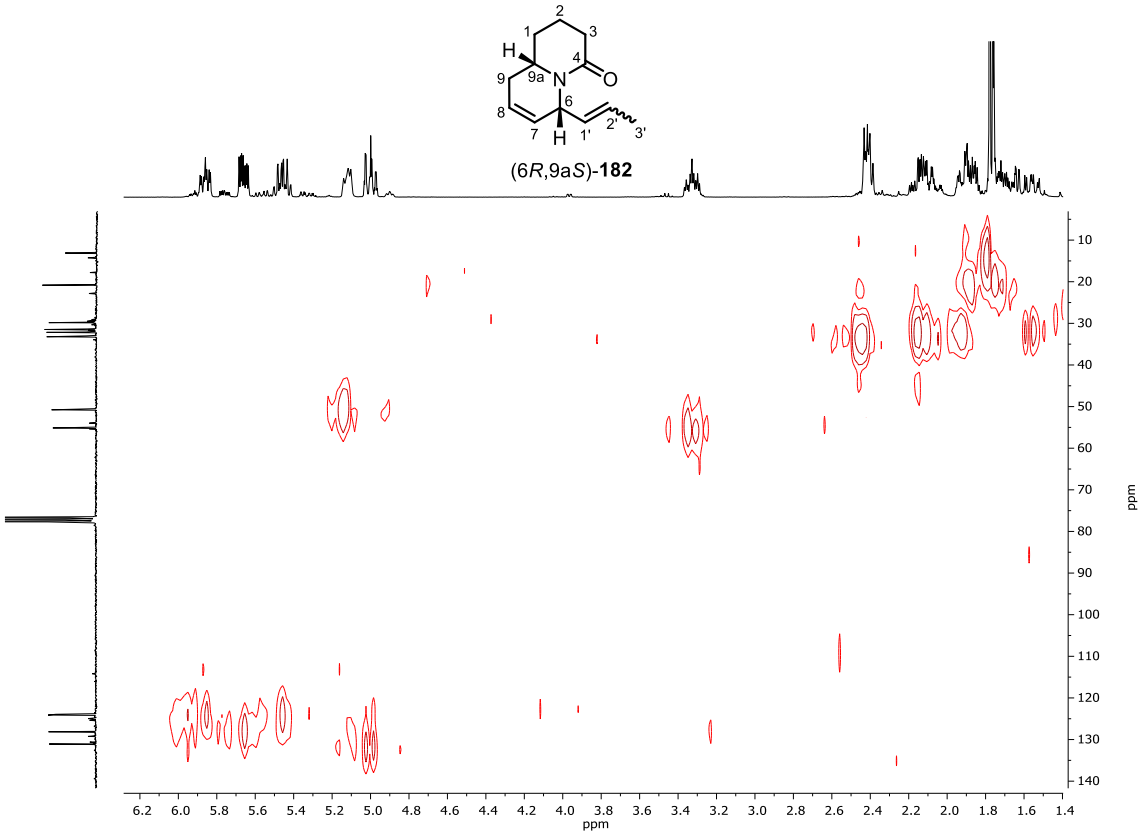
^{1}H NMR (360 MHz, $CDCl_3$)



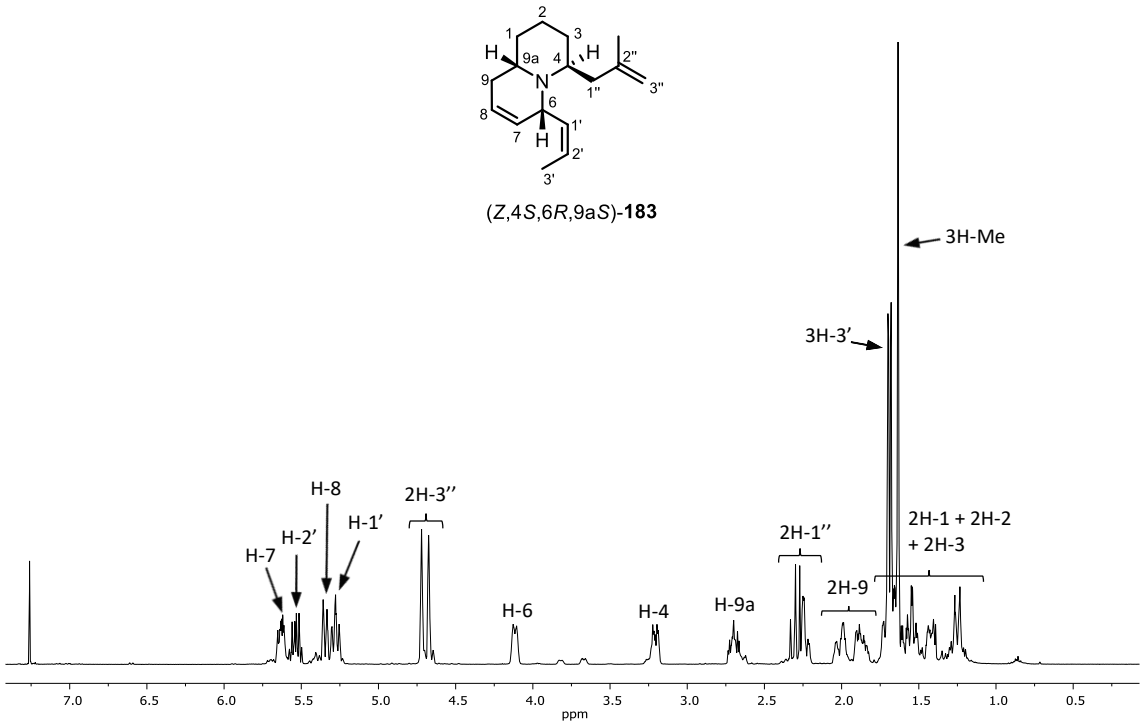
^{13}C NMR (91 MHz, $CDCl_3$)



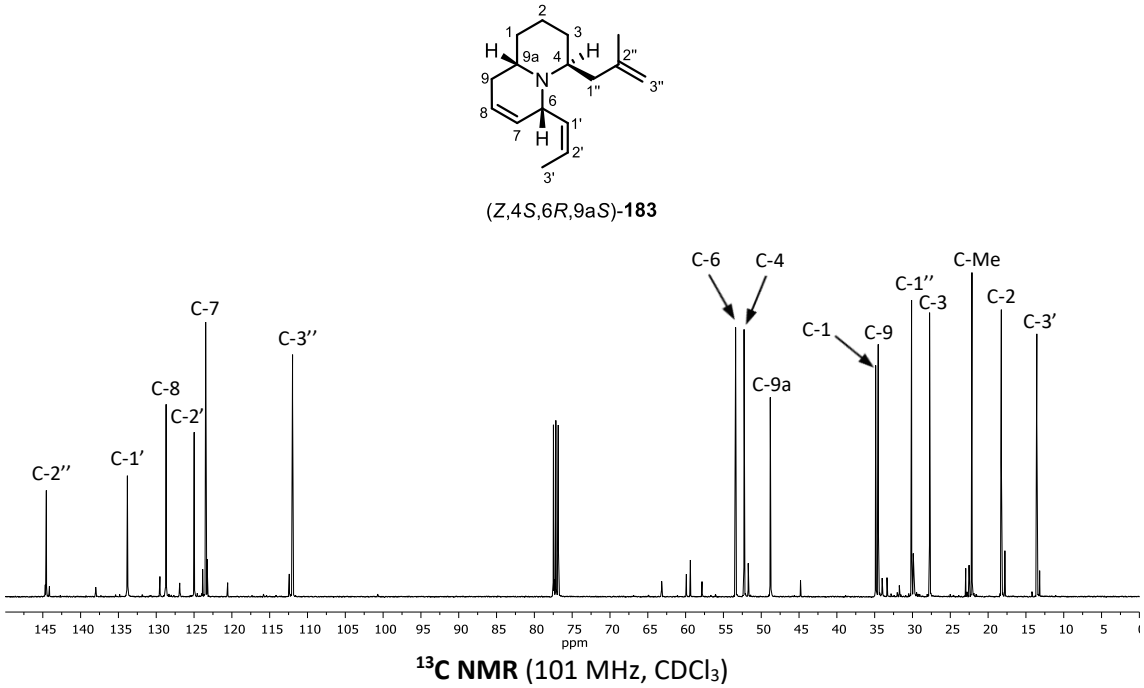
2D COSY (250 MHz, $CDCl_3$)



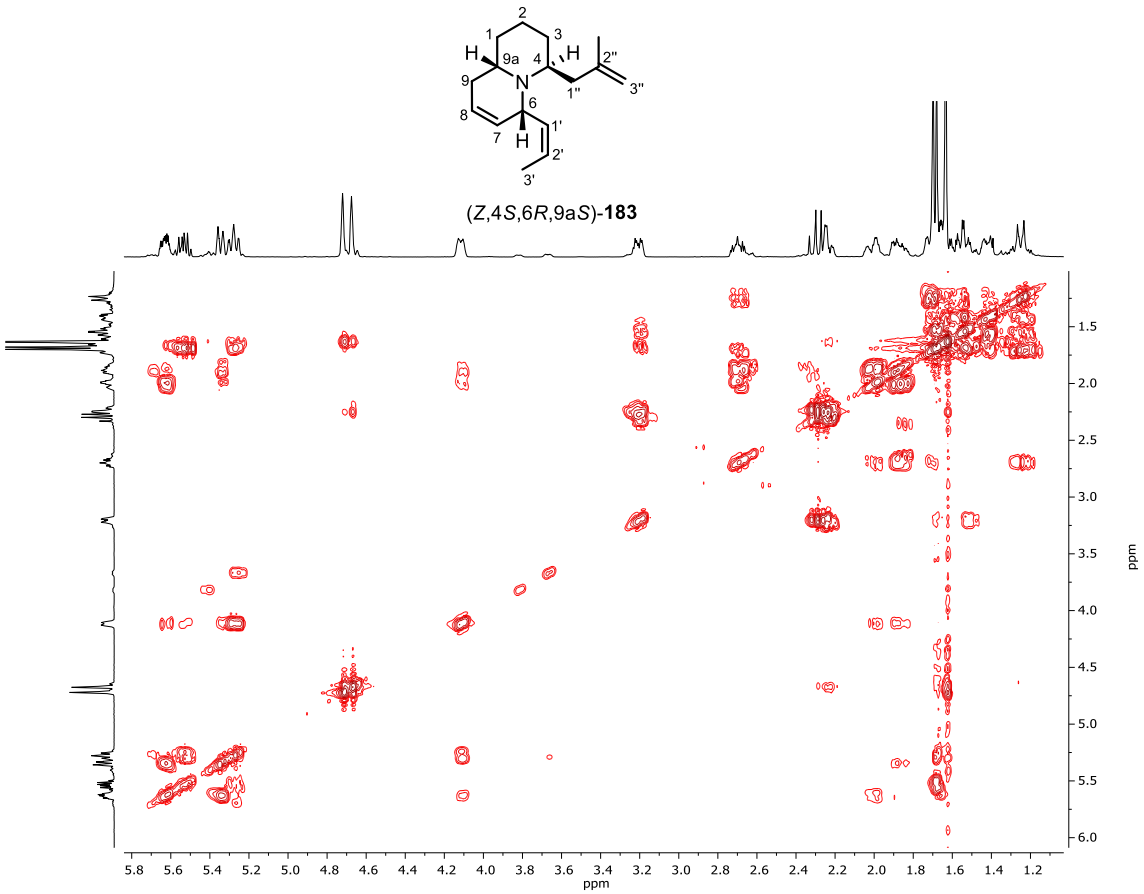
HSQC (250 MHz, $CDCl_3$)



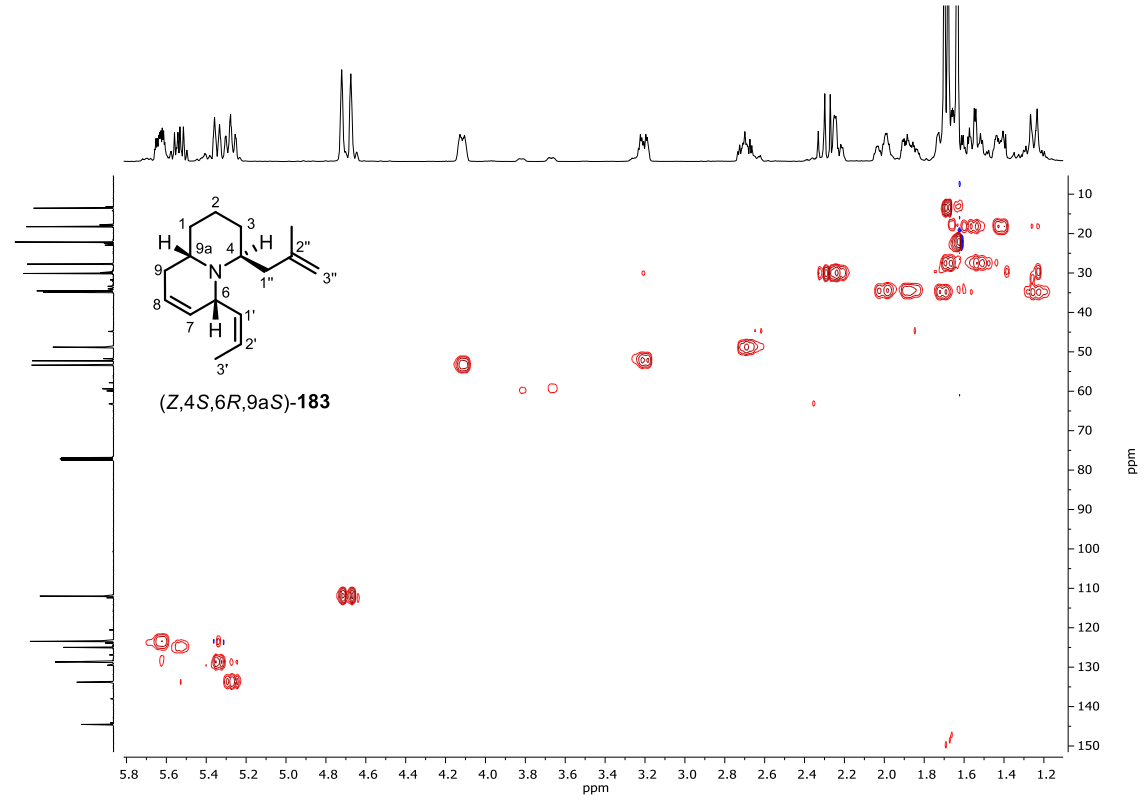
^{1}H NMR (400 MHz, $CDCl_3$)



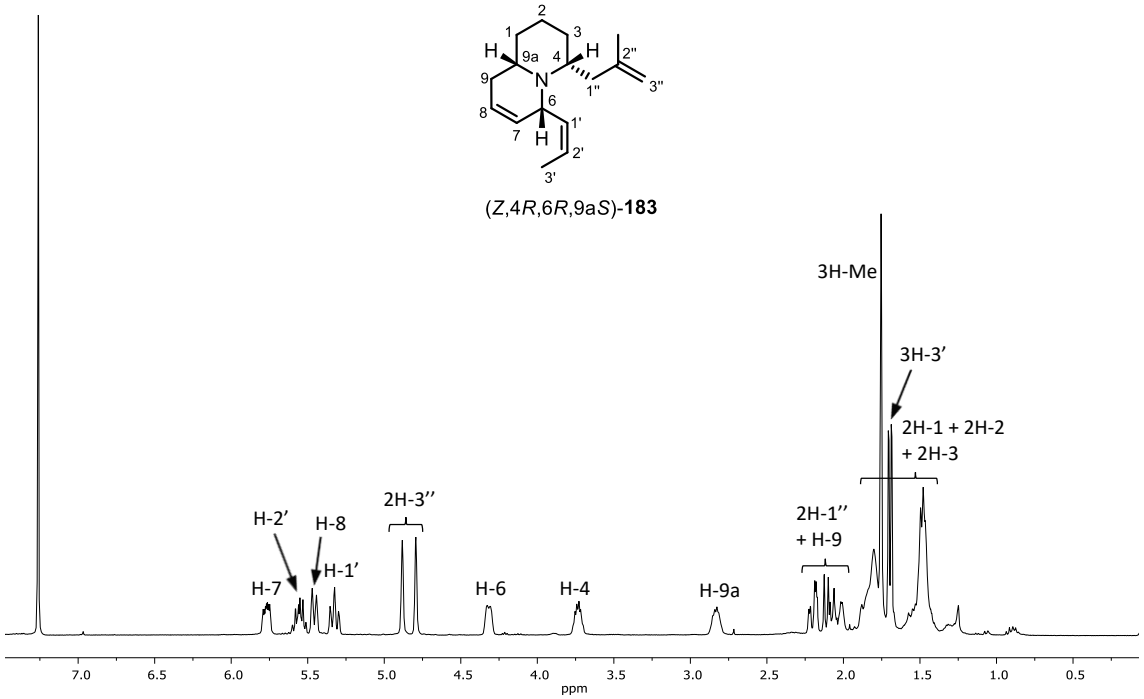
^{13}C NMR (101 MHz, $CDCl_3$)



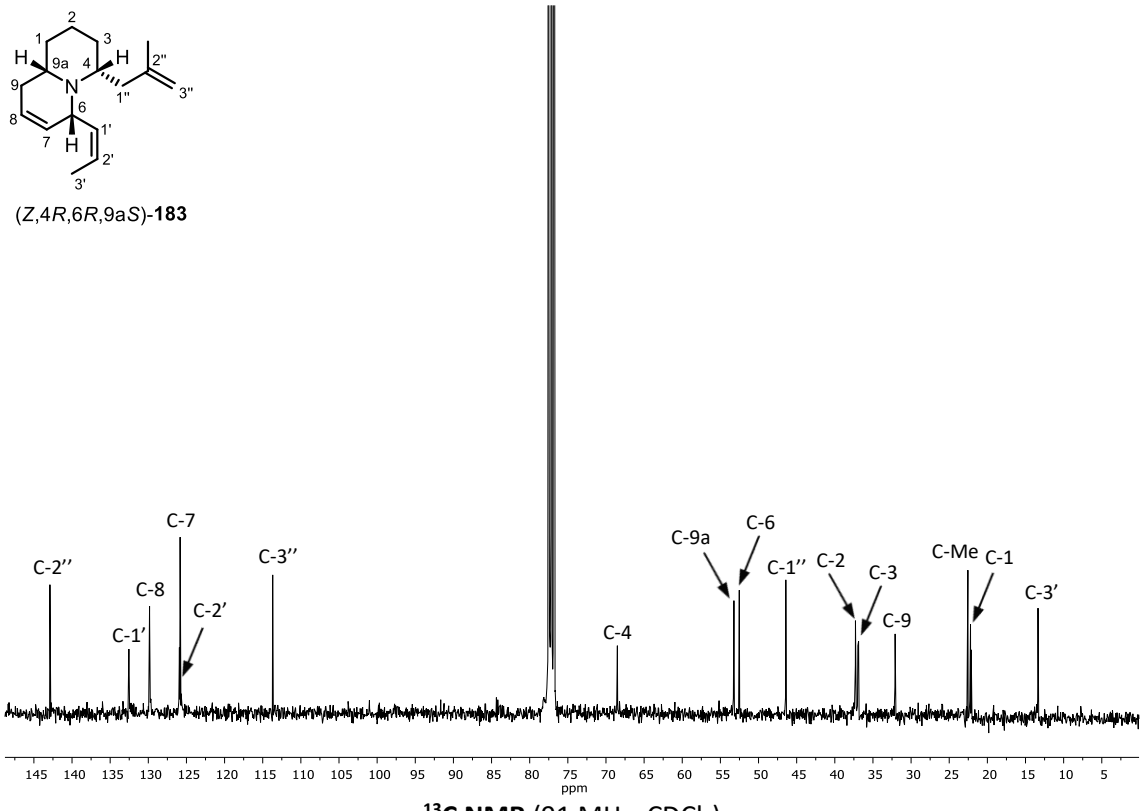
2D COSY (400 MHz, $CDCl_3$)



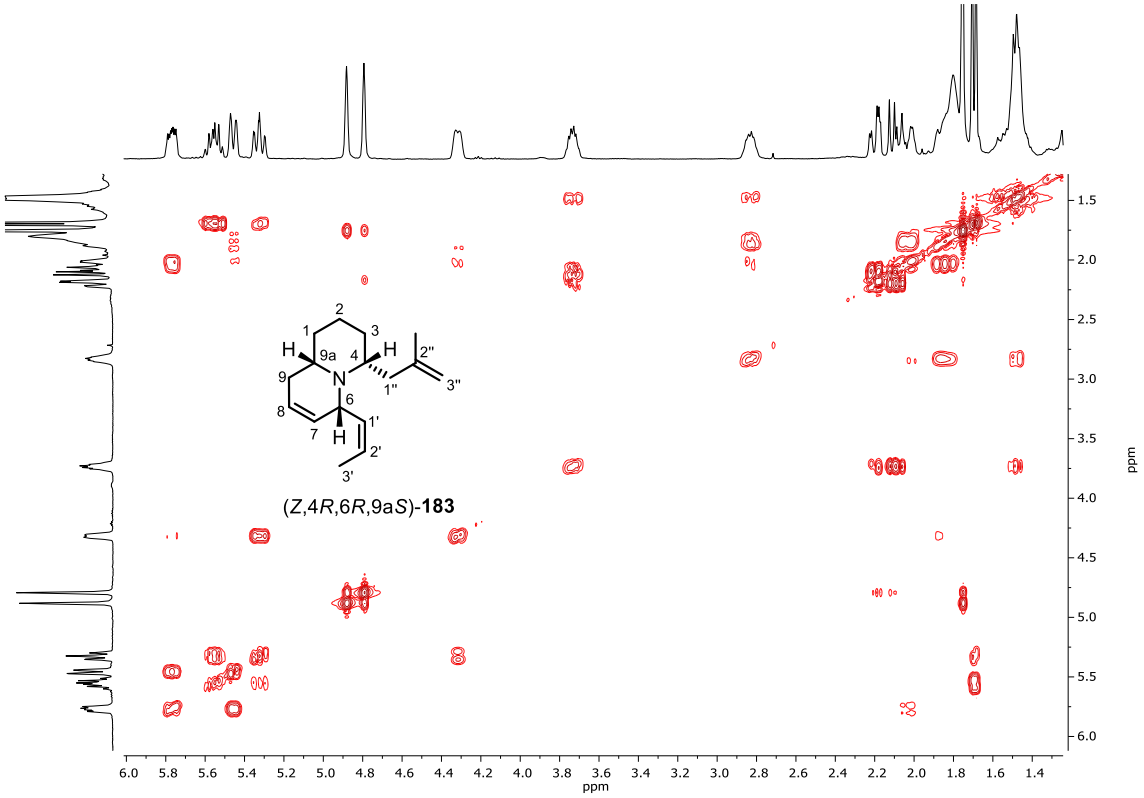
HSQC (400 MHz, $CDCl_3$)



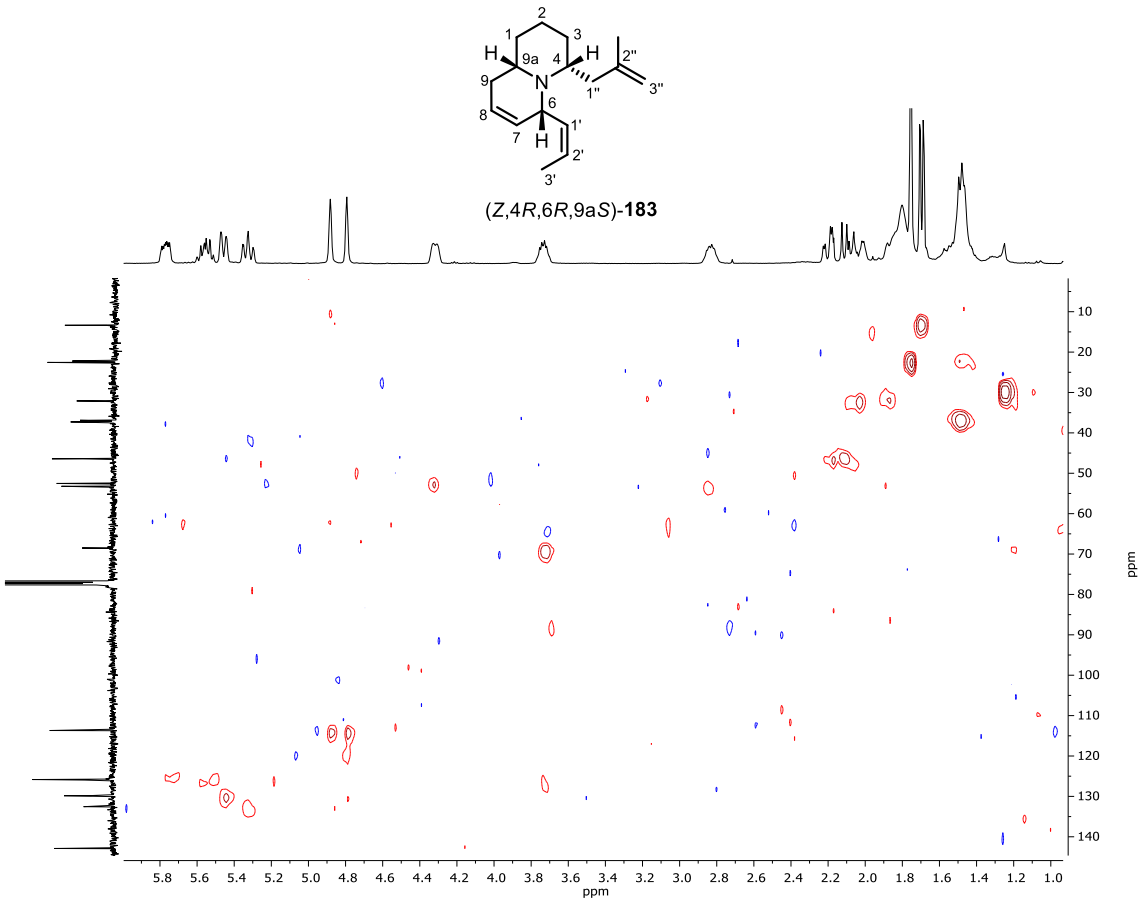
^{1}H NMR (360 MHz, $CDCl_3$)



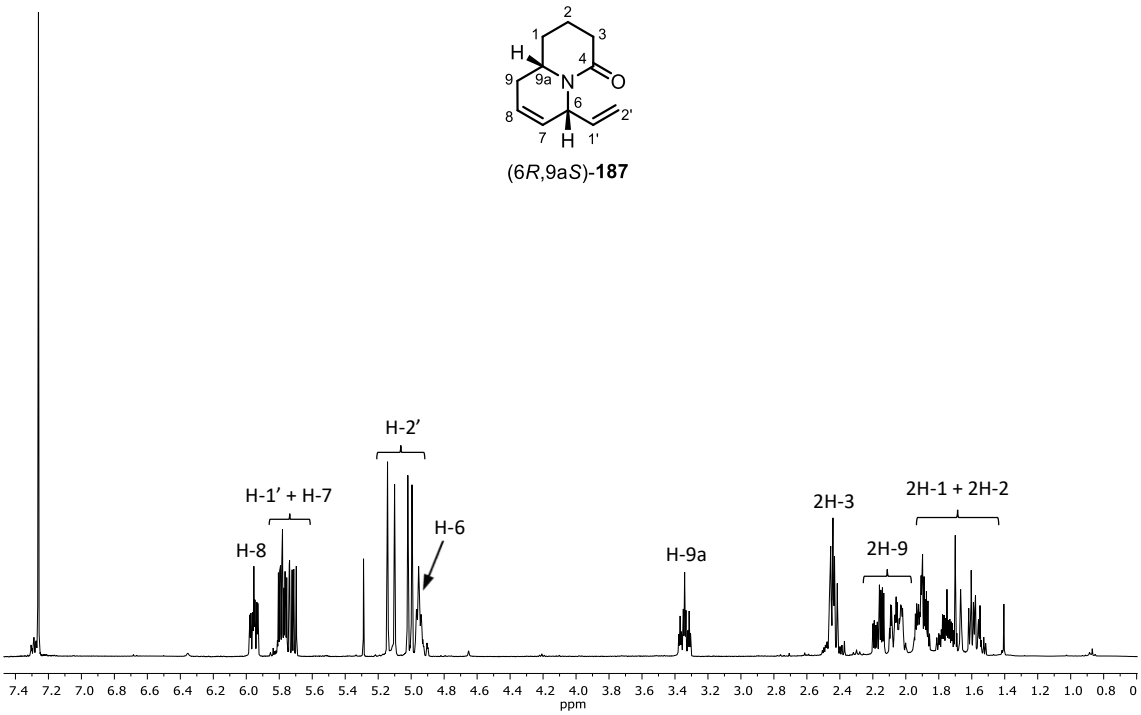
^{13}C NMR (91 MHz, $CDCl_3$)



2D COSY (360 MHz, $CDCl_3$)

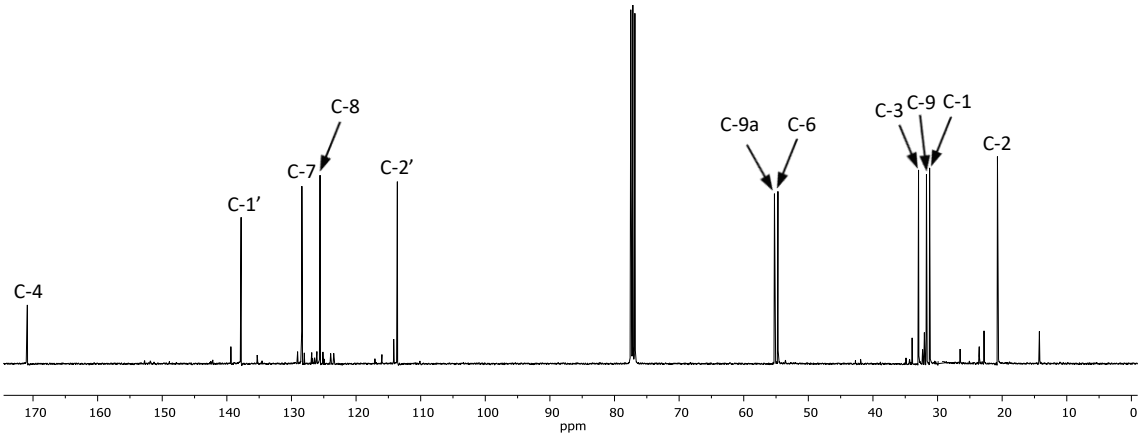


HSQC (360 MHz, $CDCl_3$)



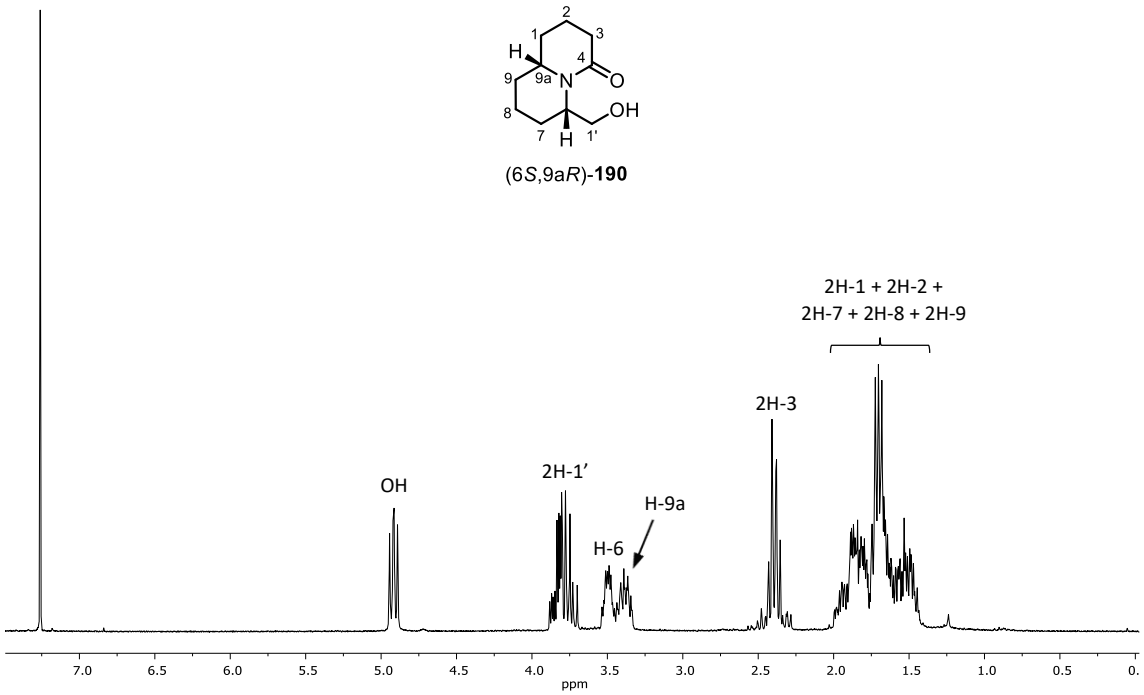
(6*R*,9a*S*)-**187**

^{1}H NMR (400 MHz, $CDCl_3$)



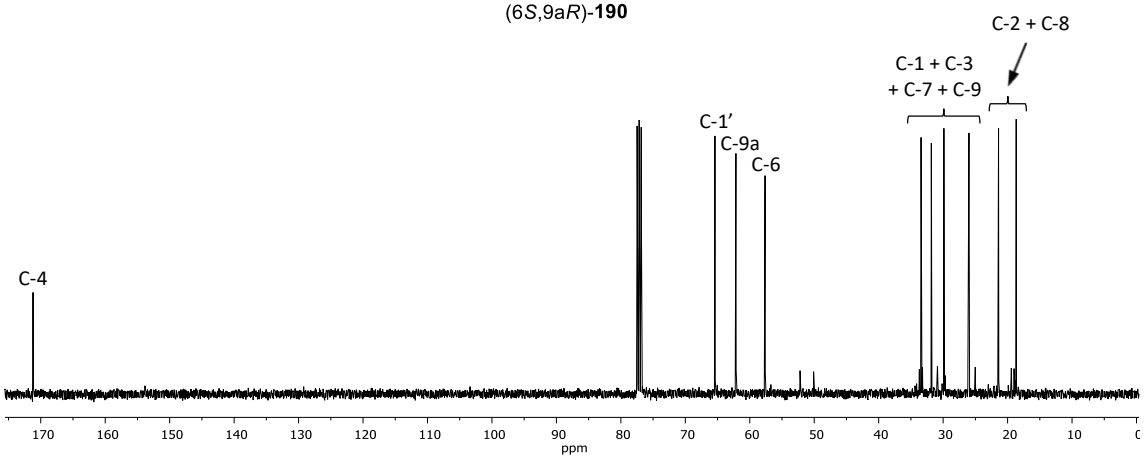
(6*R*,9a*S*)-**187**

^{13}C NMR (101 MHz, $CDCl_3$)



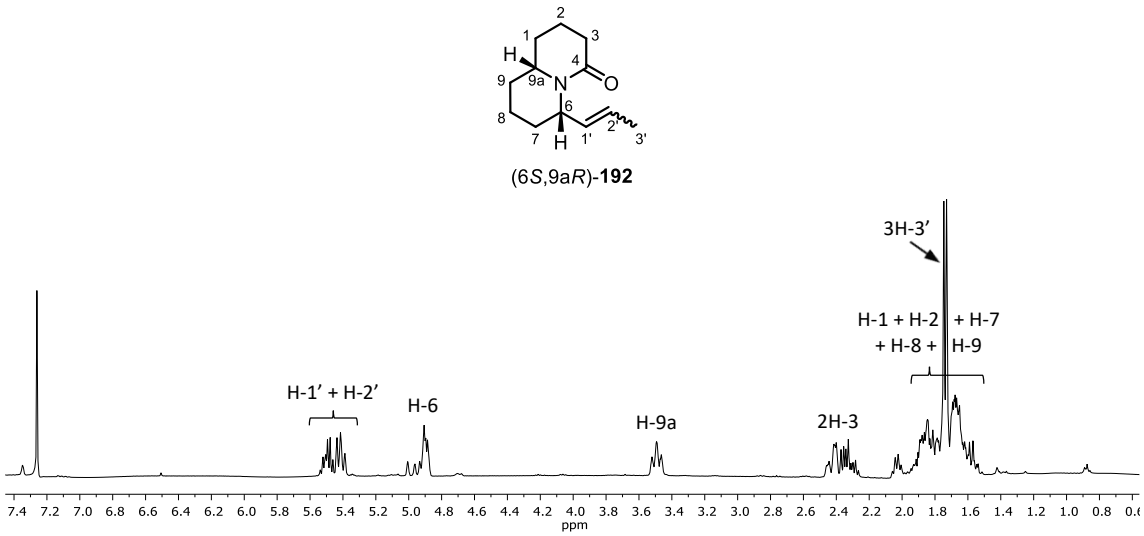
(6*S*,9a*R*)-**190**

^{1}H NMR (400 MHz, $CDCl_3$)



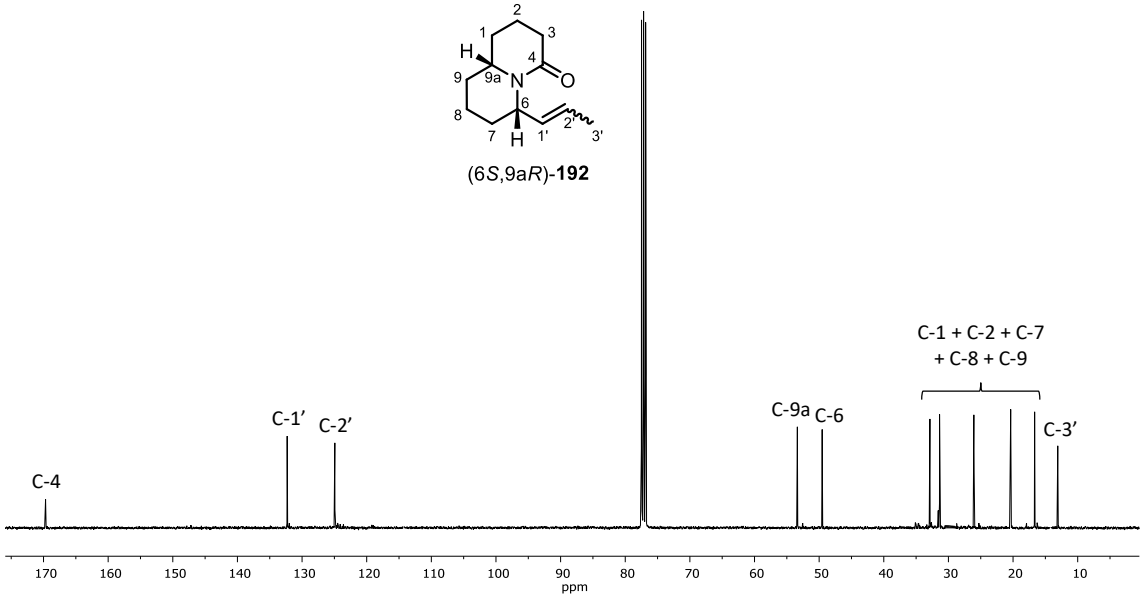
(6*S*,9a*R*)-**190**

^{13}C NMR (101 MHz, $CDCl_3$)



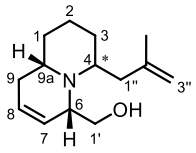
(6*S*,9a*R*)-**192**

^{1}H NMR (400 MHz, $CDCl_3$)



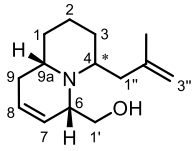
(6*S*,9a*R*)-**192**

^{13}C NMR (101 MHz, $CDCl_3$)



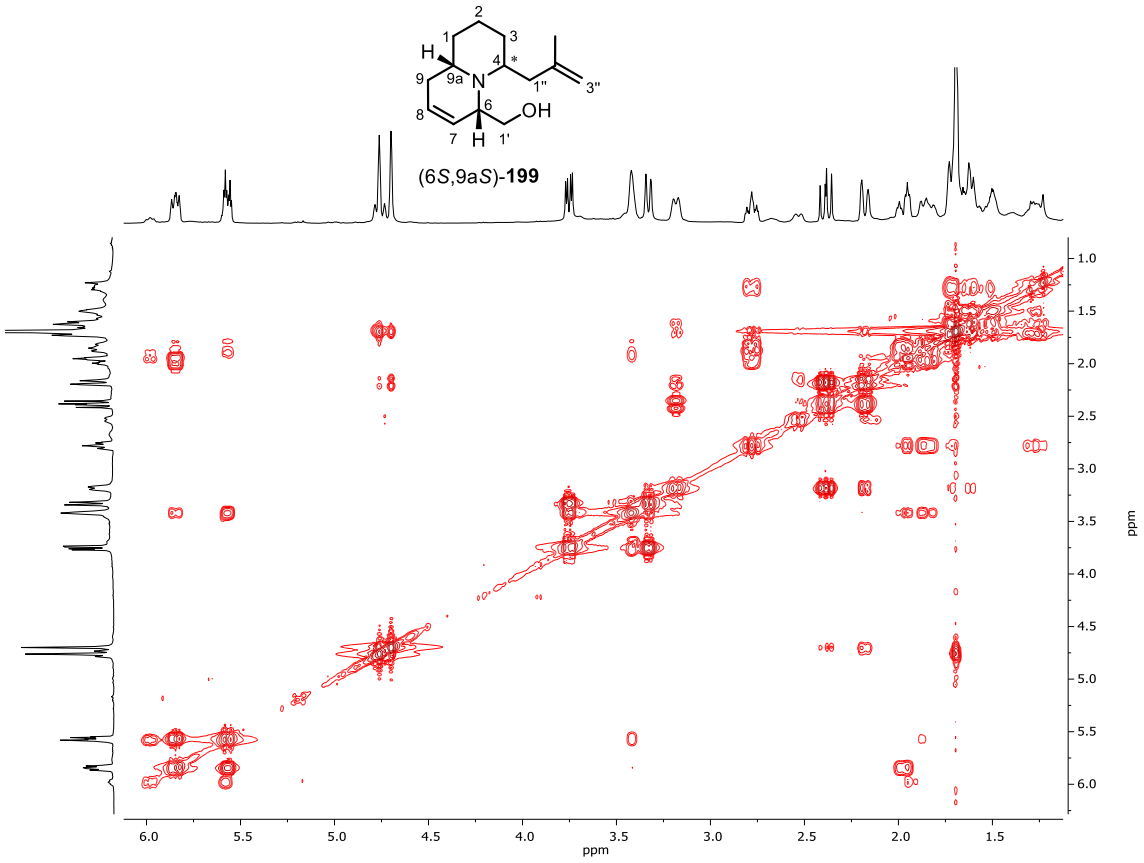
(6*S*,9a*S*)-**199**

^{1}H NMR (400 MHz, $CDCl_3$)

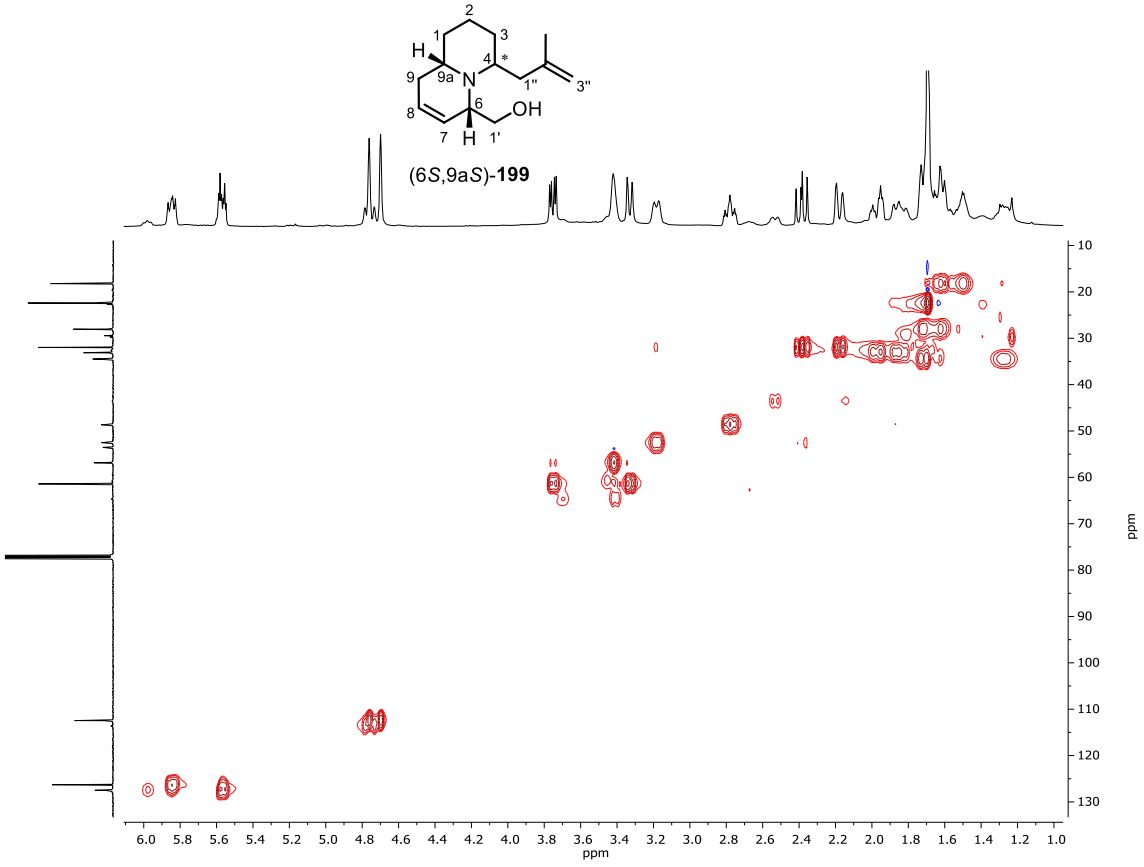


(6*S*,9a*S*)-**199**

^{13}C NMR (101 MHz, $CDCl_3$)



2D COSY (400 MHz, $CDCl_3$)



HSQC (400 MHz, $CDCl_3$)