

A Regio- and Diastereoselective Intramolecular Nitrone Cycloaddition for Practical 3- and 2,3-Substituted Piperidine Synthesis from γ -Butyrolactone

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Benzyl 2-(<i>bis</i> (2- <i>tert</i> -butylphenoxy)phosphoryl)acetate	30
¹ H NMR (400 MHz, CDCl ₃)	30
¹³ C NMR (101 MHz, CDCl ₃)	31
³¹ P NMR (162 MHz, CDCl ₃)	32
(<i>Z</i>)-Ethyl 6-hydroxy-2-hexenoate (<i>cis</i> - 5a):	33
¹ H NMR (400 MHz, CDCl ₃)	33
¹³ C NMR (101 MHz, CDCl ₃)	34
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¹ H NMR (400 MHz, CDCl ₃)	35
¹³ C NMR (101 MHz, CDCl ₃)	36
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¹ H NMR (400 MHz, CDCl ₃)	37
¹³ C NMR (101 MHz, CDCl ₃)	38
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¹ H NMR (400 MHz, CDCl ₃)	39
¹³ C NMR (101 MHz, CDCl ₃)	40
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<i>rac</i> -(5 <i>R</i> ,6 <i>S</i>)-Benzyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (<i>cis</i> -3b):	53
^1H NMR (400 MHz, CDCl_3)	53
^{13}C NMR (101 MHz, CDCl_3)	54
COSY (400 MHz, CDCl_3)	55
HSQC (400 MHz, CDCl_3)	55
2D NOESY (600 MHz, CDCl_3)	56
^1H NMR (400 MHz, CDCl_3)	57
^{13}C NMR (101 MHz, CDCl_3)	58
2D NOESY (600 MHz, CDCl_3)	59
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^{13}C NMR (101 MHz, CDCl_3)	61
COSY (400 MHz, CDCl_3)	62
HSQC (600 MHz, CDCl_3)	62
HMBC (600 MHz, CDCl_3)	63
2D NOESY (600 MHz, CDCl_3)	63
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^1H NMR (400 MHz, CDCl_3)	64
^{13}C NMR (101 MHz, CDCl_3)	65
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^1H NMR (400 MHz, CDCl_3)	66
^{13}C NMR (101 MHz, CDCl_3)	67
<i>rac</i> -(5 <i>S</i> ,6 <i>R</i> ,8 <i>S</i>)-ethyl 8-heptyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18c):	68
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^{13}C NMR (101 MHz, CDCl_3)	69
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^1H NMR (400 MHz, CDCl_3)	70
^{13}C NMR (101 MHz, CDCl_3)	71
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^1H NMR (400 MHz, CDCl_3)	72
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^1H NMR (400 MHz, CDCl_3)	74
^{13}C NMR (101 MHz, CDCl_3)	75
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^1H NMR (400 MHz, CDCl_3)	76
COSY (400 MHz, CDCl_3)	78
HSQC (400 MHz, CDCl_3)	78
HMBC (400 MHz, CDCl_3)	79
2D NOESY (600 MHz, CDCl_3)	79
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^1H NMR (400 MHz, CDCl_3)	80
^{13}C NMR (101 MHz, CDCl_3)	81
<i>rac</i> -(5 <i>R</i> ,6 <i>R</i> ,7 <i>S</i>)-ethyl 7-(4-bromophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19f):	82
^1H NMR (400 MHz, CDCl_3)	82
^{13}C NMR (101 MHz, CDCl_3)	83
<i>rac</i> -(5 <i>S</i> ,6 <i>R</i> ,8 <i>S</i>)-ethyl 8-(4-methoxyphenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18g):	84
^1H NMR (400 MHz, CDCl_3)	84
^{13}C NMR (101 MHz, CDCl_3)	85
<i>rac</i> -(5 <i>R</i> ,6 <i>R</i> ,7 <i>S</i>)-ethyl 7-(4-methoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19g):	86
^1H NMR (400 MHz, CDCl_3)	86
^{13}C NMR (101 MHz, CDCl_3)	87
<i>rac</i> -(5 <i>S</i> ,6 <i>R</i> ,8 <i>S</i>)-ethyl 8-(2-nitrophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18h):	88
^1H NMR (400 MHz, CDCl_3)	88
^{13}C NMR (101 MHz, CDCl_3)	89
<i>rac</i> -(5 <i>R</i> ,6 <i>R</i> ,7 <i>S</i>)-ethyl 7-(2-nitrophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19h):	90

^1H NMR (400 MHz, CDCl_3).....	90
^{13}C NMR (101 MHz, CDCl_3)	91
<i>rac</i> -(5 <i>S</i> ,6 <i>R</i> ,8 <i>S</i>)-ethyl 8-(2-methoxyphenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18i):	92
^1H NMR (400 MHz, CDCl_3).....	92
^{13}C NMR (101 MHz, CDCl_3)	93
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^1H NMR (400 MHz, CDCl_3).....	94
^{13}C NMR (101 MHz, CDCl_3)	95
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^1H NMR (400 MHz, CDCl_3).....	96
^{13}C NMR (101 MHz, CDCl_3)	97
<i>rac</i> -(5 <i>R</i> ,6 <i>R</i> ,7 <i>S</i>)-ethyl 7-(4-fluoro-2-(trifluoromethyl)phenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19j):.....	98
^1H NMR (400 MHz, CDCl_3).....	98
^{13}C NMR (101 MHz, CDCl_3)	99
<i>rac</i> -(<i>R</i>)-Ethyl 2-hydroxy-2-((<i>R</i>)-piperidin-3-yl)acetate (20a):	100
^1H NMR (400 MHz, CDCl_3).....	100
^{13}C NMR (101 MHz, CDCl_3)	101
COSY (400 MHz, CDCl_3).....	102
HSQC (400 MHz, CDCl_3).....	102
HMBC (400 MHz, CDCl_3)	103
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^1H NMR (400 MHz, D_2O).....	104
^{13}C NMR (101 MHz, D_2O)	105
COSY (400 MHz, D_2O).....	106
HSQC (400 MHz, D_2O).....	106
HMBC (400 MHz, D_2O)	107
2D NOESY (600 MHz, D_2O).....	107
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^1H NMR (400 MHz, CDCl_3).....	108
^{13}C NMR (101 MHz, CDCl_3)	109
COSY (400 MHz, CDCl_3).....	110
HSQC (400 MHz, CDCl_3).....	110
HMBC (400 MHz, CDCl_3)	111
<i>rac</i> -(<i>R</i>)-3-((<i>S</i>)-2-Ethoxy-1-hydroxy-2-oxoethyl)piperidinium chloride	112
^1H NMR (400 MHz, CDCl_3).....	112
^{13}C NMR (101 MHz, CDCl_3)	113
<i>rac</i> -(<i>R</i>)-2-Hydroxy-2-((<i>S</i>)-piperidin-3-yl)acetic acid (21b):	114
^1H NMR (400 MHz, D_2O).....	114
^{13}C NMR (101 MHz, D_2O)	115
COSY (400 MHz, D_2O).....	116
HSQC (400 MHz, D_2O).....	116
HMBC (400 MHz, D_2O)	117
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^{13}C NMR (101 MHz, CDCl_3)	119
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^1H NMR (400 MHz, CDCl_3).....	120
^{13}C NMR (101 MHz, CDCl_3)	121
<i>rac</i> -(<i>R</i>)-ethyl 2-((2 <i>S</i> ,3 <i>S</i>)-2-heptylpiperidin-3-yl)-2-hydroxyacetate (22c)	122
^1H NMR (400 MHz, CDCl_3).....	122
^{13}C NMR (101 MHz, CDCl_3)	123
<i>rac</i> -(<i>R</i>)-ethyl 2-hydroxy-2-((2 <i>R</i> ,3 <i>S</i>)-2-(pyridin-3-yl)piperidin-3-yl)acetate (22d):	124
^1H NMR (400 MHz, CDCl_3).....	124
^{13}C NMR (101 MHz, CDCl_3)	125

<i>rac</i> -(<i>R</i>)-ethyl 2-((2 <i>R</i> ,3 <i>S</i>)-2-(4-aminophenyl)piperidin-3-yl)-2-hydroxyacetate (22e):	126
¹ H NMR (400 MHz, CDCl ₃)	126
¹³ C NMR (101 MHz, CDCl ₃)	127
<i>rac</i> -(<i>R</i>)-ethyl 2-((2 <i>R</i> ,3 <i>S</i>)-2-(4-bromophenyl)piperidin-3-yl)-2-hydroxyacetate (22f):	128
¹ H NMR (400 MHz, CDCl ₃)	128
¹³ C NMR (101 MHz, CDCl ₃)	129
<i>rac</i> -(<i>R</i>)-ethyl 2-hydroxy-2-((2 <i>R</i> ,3 <i>S</i>)-2-(4-methoxyphenyl)piperidin-3-yl)acetate (22g):	130
¹ H NMR (400 MHz, CDCl ₃)	130
¹³ C NMR (101 MHz, CDCl ₃)	131
<i>rac</i> -(<i>R</i>)-ethyl 2-((2 <i>R</i> ,3 <i>S</i>)-2-(2-aminophenyl)piperidin-3-yl)-2-hydroxyacetate (22h):	132
¹ H NMR (400 MHz, CDCl ₃)	132
¹³ C NMR (101 MHz, CDCl ₃)	133
<i>rac</i> -(<i>R</i>)-ethyl 2-((2 <i>R</i> ,3 <i>S</i>)-2-(2-methoxyphenyl)piperidin-3-yl)-2-hydroxyacetate (22i):	134
¹ H NMR (400 MHz, CDCl ₃)	134
¹³ C NMR (101 MHz, CDCl ₃)	135
<i>rac</i> -(<i>R</i>)-ethyl 2-((2 <i>R</i> ,3 <i>S</i>)-2-(4-fluoro-2-(trifluoromethyl)phenyl)piperidin-3-yl)-2-hydroxyacetate (22j):	136
¹ H NMR (400 MHz, CDCl ₃)	136
¹³ C NMR (101 MHz, CDCl ₃)	137

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General Information

Solvents and Reagents. Unless otherwise specified, all reagents were purchased from commercial sources and used without further purification. “Diatomaceous earth” refers to Celite 545. MS3Å powder, MS3Å beads (8–12 mesh) and MS4Å beads (4–8 mesh) were always activated¹ before use in a muffle furnace at 320 °C for 15 hr and stored in a desiccator over P₂O₅. Anhydrous K₂CO₃ and Cs₂CO₃ were prepared by heating, under air and at atmospheric pressure, the reagent grade salts in a muffle furnace at 300 °C for one day.² Anhydrous K₃PO₄ was prepared by an analogous procedure, but with a muffle furnace temperature of 900 °C.³ Anhydrous CH₃CN was obtained by refluxing the HPLC grade solvent over P₂O₅ for three hours, then distilling it onto MS3Å beads.^{1,4} DCM and toluene were obtained from a solvent purification system and stored over MS4Å beads. 1,2-Dichlorobenzene was distilled under atmospheric pressure from sodium onto activated MS3Å beads.⁵ DIEA and triethylamine were stored over MS3Å beads.⁶ Methanol was distilled from Mg/I₂ onto MS3Å beads under argon.^{7,8} Petroleum ether was distilled before use and refers to the fraction boiling between 60 °C and 80 °C. THF was distilled from Na–benzophenone onto MS4Å beads.^{1,4,9}

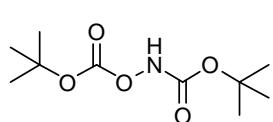
Chromatography. TLC was performed on aluminium or glass backed silica gel 60 F254 plates and visualization was accomplished using either a UV lamp (254 nm) or heating with basic KMnO₄ solution (olefins, aromatic isoxazolidines, phosphites and phosphonoacetates), ninhydrin (2° amines), iodine-modified Dragendorff’s reagent¹⁰ (all isoxazolidines) or ceric ammonium molybdate (some isoxazolidines). Dry column vacuum chromatography (DCVC)¹¹ was performed using 15–40 µm silica gel 60 and a two-stage diaphragm pump. Flash column chromatography was performed using 230–400 mesh (40–63 µm) silica gel 60 and N₂ gas.

NMR. ^1H NMR spectra were recorded at 25 °C on either 400 MHz or 600 MHz spectrometers and are reported in ppm using the specified solvent as internal standard (CDCl_3 at 7.26 ppm, HDO at 4.79 ppm¹²). ^{13}C NMR spectra are reported in ppm using the specified solvent as internal standard (CDCl_3 at 77.0 ppm). When ^{13}C NMR was performed on samples dissolved in D_2O , one drop of methanol, known to appear at 49.50 ppm in D_2O ,¹² was used as the internal standard.

All two-dimensional spectra were recorded with quadrature detection in both dimensions using time proportional phase incrementation (TPPI). For DQF-COSY experiments, 2048 data points were collected in t_2 and 512 in t_1 , and between 16 and 32 transients were collected at each increment. NOESY spectra were acquired in the phase-sensitive mode with 2048 data points in t_2 and 512 in t_1 , and 32 transients at each increment. An optimized mixing time of 1000 ms was used and processing was carried out using a sine-bell squared function shifted by $\pi/2$ and a states-TPPI method. Special precautions, such as degassing of the sample, were not taken. Carbon–hydrogen correlation (HSQC) was achieved via a sensitivity enhanced double INEPT transfer using echo/antiecho-TPPI gradient (80:20.1) selection. 2048 data points were collected in t_2 with a 1.3 s recycle delay and decoupling during acquisition. In t_1 , 512 increments were used. A gradient ratio of 80:20.1 was used to select echo/antiecho-TPPI phase sensitivity. HMBC spectra were obtained via zero and double quantum coherence with a low-pass J -filter to suppress one-bond couplings. No decoupling was used during the acquisition and the results were magnitude calculated.

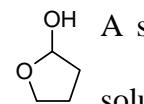
Experimental Section

*N,O-bis(tert-butoxycarbonyl)hydroxylamine.*¹³



A solution of Boc₂O (44.7 g, 0.205 mol) and NEt₃ (21.2 g, 29.2 mL, 0.210 mol) in 5:1 petroleum ether/MTBE (70 mL) maintained at -5 °C was cannulated into a vigorously stirred solution of NH₂OH•HCl (6.95 g, 0.10 mol) in water (69 mL) maintained at 0 °C over a period of 80 minutes. The biphasic mixture was allowed to warm to room temperature overnight with vigorous stirring. The layers were separated, and the organic phase was washed with saturated aqueous NH₄Cl (2 × 30 mL) and brine (30 mL), then dried over MgSO₄. After filtration and evaporation of the solvent at reduced pressure (8 Torr, 35 °C), the resulting colorless oil was dried under high vacuum (5×10^{-3} Torr, rt) until crystals began to form. The mixture was then stored at -20 °C overnight and the white solid obtained slurried with ice-cold petroleum ether, filtered, and washed with more ice-cold petroleum ether. Drying under vacuum (5×10^{-3} Torr, rt) for 12 hours gave the title compound (16.9 g, 73 mmol; 73%) as a white solid that was stored under dry nitrogen at -20 °C: m.p. 67–69 °C (lit. m.p.¹³ 67–68 °C); IR (KBr) ν_{max} (cm⁻¹): 3274, 2988, 2941, 1797, 1737, 1720, 1484, 1397, 1374, 1242, 1156, 1122, 962, 887, 849, 809, 772, 617; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (br. s, 1H, NH), 1.51 (s, 9H, (CH₃)₃), 1.48 (s, 9H, (CH₃)₃).

Tetrahydrofuran-2-ol.¹⁴



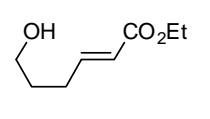
A solution of DIBAL-H (1 M in toluene, 39 mL, 39 mmol) was added dropwise to a solution of γ -butyrolactone (2.24 g, 26 mmol) in dry toluene (50 mL) maintained at -78 °C (acetone/CO₂(s)) over a period of 1.5 hours. The reaction mixture was stirred for a further 4.5 hours at -78 °C, then quenched by the dropwise addition of methanol (3.3 mL). The mixture was allowed to warm to 0 °C (ice-bath), diluted with water (8.8 mL) and mixed with diatomaceous

earth (8.8 g) and MgSO₄ (8.8 g). After mechanically stirring for 30 minutes, the brown slurry was filtered and washed thoroughly with distilled diethyl ether (5 × 100 mL). The filtrate was concentrated at reduced pressure to afford crude product as a colorless oil (2.1 g, 92%) that was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 5.54 (br. m, 1H, OCH(OH)), 4.05 (dt, 1H, *J* = 8.1 Hz, 5.3 Hz, CH₂O), 3.86 (m, 1H, CH₂O), 2.43 (br. d, 1H, OH), 2.12–1.81 (m, 4H, CH₂CH₂); ¹³C NMR (CDCl₃) δ 98.4, 67.4, 33.2, 23.4.

Benzyl 2-(bis(2-tert-butylphenoxy)phosphoryl)acetate.

A vigorously stirred mixture of benzyl bromoacetate (8.0 g, 5.5 mL, 35 mmol) and *bis*(2-*tert*-butylphenyl) ethyl phosphite^{15a} (26.2 g, 70 mmol) under an atmosphere of argon was heated at 130 °C for 18 hours. The resulting brown oil was allowed to cool to room temperature, then purified by dry column vacuum chromatography¹¹ (SiO₂, 0–20% EtOAc in petroleum ether) to afford the title compound (12.4 g, 72%) as a colorless oil: IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3056, 2968, 2873, 1740, 1578, 1489, 1442, 1180, 1084, 953; ¹H NMR (400 MHz, CDCl₃) δ 7.67 (m, 2H), 7.34 (m, 2H), 7.32–7.21 (m, 5H), 7.11 (m, 2H), 5.09 (s, 1H, PhCH₂), 3.41 (d, 2H, *J* = 21.7 Hz, PCH₂), 1.34 (s, 18H, (C(CH₃)₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 164.3 (d, *J* = 6.1 Hz), 150.0 (d, *J* = 8.8 Hz), 139.1 (d, *J* = 8.4 Hz), 134.8, 128.49, 128.47, 128.40, 127.7, 127.4, 124.6, 119.6 (d, *J* = 3.0 Hz), 67.7, 35.6 (d, *J* = 138.5 Hz), 34.6, 30.0; ³¹P NMR (162 MHz, CDCl₃) δ 12.3; HRMS (ESI) *m/z* calcd for C₂₉H₃₆O₅P [M + H]⁺, 495.2300, found 495.2275.

(E)-Ethyl 6-hydroxy-2-hexenoate (*trans*-5a).

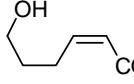
 (Ethoxycarbonylmethylene)triphenylphosphorane¹⁶ (948 mg, 2.72 mmol) was added to a solution of tetrahydrofuran-2-ol (100 mg, 1.14 mmol) in CH₂Cl₂ (41

mL). After 48 hours CH_2Cl_2 was removed at reduced pressure (8 Torr, 35 °C) and, following purification of the resulting orange oil by flash chromatography (SiO_2 , 10% then 20–35% EtOAc in petroleum ether, 5% increments), *trans*-**5a** (154 mg, 85%) was obtained as a colorless oil with spectral data matching those reported¹⁷ previously: ^1H NMR (400 MHz, CDCl_3) δ 6.97 (dt, 1H, J = 15.7 Hz, 7.0 Hz, $\text{CH}=\text{CHC(O)}$), 5.84 (dt, 1H, J = 15.6, 1.6 Hz, $\text{CH}=\text{CHC(O)}$), 4.17 (q, 2H, J = 7.1 Hz, OCH_2), 3.67 (t, 2H, J = 6.3 Hz, $\text{HO}-\text{CH}_2$), 2.30 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 1.72 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.28 (t, 3H, J = 7.1 Hz, CH_3).

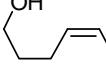
General Procedure for the Preparation of Z-Olefins.

K_3PO_4 (2 equiv) was added to a stirred solution of phosphonoacetate (1 equiv) in CH_3CN (1 mL mmol⁻¹) at room temperature. After five minutes the mixture was cooled to 0 °C and stirred vigorously during the addition of tetrahydrofuran-2-ol (1.1 equiv). Once ^1H NMR analysis indicated the reaction was complete (generally 48 hours) the mixture was filtered, and the residue washed with toluene (2 × 2 mL mmol⁻¹). The combined filtrates were evaporated under reduced pressure. The Z-olefin was isolated after purification of the resulting yellow oil by flash chromatography (SiO_2 , 10% then 20–35% EtOAc in petroleum ether, 5% increments).

(Z)-Ethyl 6-hydroxy-2-hexenoate (*cis*-5a**).**

Obtained as a colorless oil (2.80 g, 79%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm⁻¹): 3424

 (br), 2983, 2938, 2875, 1711, 1644, 1448, 1415, 1390, 1195, 1034, 821; ^1H NMR (400 MHz, CDCl_3) δ 6.22 (dt, 1H, J = 11.5 Hz, 8.2 Hz, $\text{CH}=\text{CHC(O)}$), 5.85 (dt, 1H, J = 11.5, 1.4 Hz, $\text{CH}=\text{CHC(O)}$), 4.18 (q, 2H, J = 7.1 Hz, OCH_2), 3.61 (m, 2H, $\text{HO}-\text{CH}_2$), 2.73 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 2.56 (br., 1H, OH), 1.72 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.29 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 167.1, 149.1, 120.8, 61.0, 60.2, 31.0, 24.9, 14.2; HRMS (EI) m/z calcd for $\text{C}_8\text{H}_{14}\text{O}_3$ [M]⁺, 158.0943, found 158.0943.

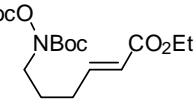
(Z)-Benzyl 6-hydroxy-2-hexenoate (*cis*-5b).

Obtained as a colorless oil (2.15 g, 66%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3487
 (br), 3037, 2940, 2879, 1713, 1643, 1454, 1415, 1168, 818, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 6.27 (dt, 1H, J = 11.5, 8.2 Hz, CH=CHC(O)), 5.91 (dt, 1H, J = 11.5, 1.4 Hz, CH=CHC(O)), 5.17 (s, 2H, PhCH₂), 3.62 (t, 2H, J = 6.0 Hz, HOCH₂), 2.75 (m, 2H, CH₂CH=CH), 2.41 (br., 1H, OH), 1.73 (m, 2H, CH₂CH₂CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 166.7, 149.9, 135.8, 128.6, 128.3, 120.4, 66.0, 61.1, 31.1, 25.0; HRMS (EI) *m/z* calcd for C₁₃H₁₆O₃ [M]⁺, 220.1100, found 220.1099.

General Procedure for the Mitsunobu Reaction.

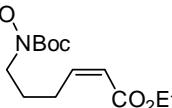
DIAD (1.23 equiv) was introduced into a stirred solution of PPh₃ (1.24 equiv) in dry THF (4.9 mL mmol⁻¹) under argon at 0 °C. This solution, from which a white solid rapidly precipitated, was first stirred for 30 minutes, then combined with *N,O*-bis(*tert*-butoxycarbonyl)hydroxylamine (0.90 equiv) and the primary alcohol (1 equiv) in dry THF (2.9 mL mmol⁻¹). The mixture was allowed to stir at room temperature until judged complete by TLC and ¹H NMR analysis (generally 8–24 hours). THF was then removed at reduced pressure and the resulting paste was purified by the methods specified for each compound below.

(E)-Ethyl 6-(*tert*-butoxycarbonyl)(*tert*-butoxycarbonyloxy)amino)hex-2-enoate (*trans*-6a).

 Flash chromatography (SiO₂, 1% then 2–6% EtOAc in petroleum ether, 2% increments) gave *trans*-6a (802 mg, 95%) as a pale yellow oil: IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 2983, 2937, 1785, 1716, 1654, 1458, 1395, 1370, 1147, 981; ¹H NMR (400 MHz, CDCl₃) δ 6.94 (dt, J = 15.6, 6.9 Hz, 1H, CH=CHC(O)), 5.84 (dt, J = 15.6, 1.4 Hz, 1H, CH=CHC(O)), 4.18 (q, J = 7.1 Hz, 2H, OCH₂), 3.60 (br. m, 2H, NCH₂), 2.28 (m, 2H, CH₂CH=CH), 1.76 (qn., J = 7.2 Hz, 2H, CH₂CH₂CH₂), 1.53 (s, 9H, C(CH₃)₃), 1.48 (s, 9H, C(CH₃)₃), 1.28 (t, J = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.5, 154.8, 152.3,

147.8, 122.0, 84.9, 82.4, 60.2, 49.4, 29.1, 28.1, 27.6, 25.6, 14.3; HRMS (ESI) m/z calcd for $C_{18}H_{31}NO_7K$ [M + K]⁺, 412.1738, found 412.1736.

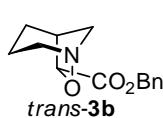
(Z)-Ethyl 6-(tert-butoxycarbonyl(tert-butoxycarbonyloxy)amino)hex-2-enoate (*cis*-6a).

 Flash chromatography (SiO₂, 1% then 2–6% EtOAc in petroleum ether, 2% increments) yielded *cis*-6a (3.3 g, 94%) as a colorless oil: IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 2983, 2937, 1784, 1716, 1645, 1456, 1394, 1370, 1111, 832, 781; ¹H NMR (400 MHz, CDCl₃) δ 6.21 (dt, J = 11.5, 7.6 Hz, 1H, CH=CHC(O)), 5.78 (dt, J = 11.5, 1.7 Hz, 1H, CH=CHC(O)), 4.16 (q, J = 7.1 Hz, 2H, OCH₂), 3.60 (br. m, 2H, NCH₂), 2.71 (dq, J = 7.5, 1.7 Hz, 2H, CH₂CH=CH), 1.76 (qn, J = 7.5 Hz, 2H, CH₂CH₂CH₂), 1.53 (s, 9H, C(CH₃)₃), 1.47 (s, 9H, C(CH₃)₃), 1.28 (t, J = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.3, 154.8, 152.3, 148.7, 120.5, 84.8, 82.3, 59.9, 49.7, 28.1, 27.6, 26.4, 26.1, 14.3; HRMS (ESI) m/z calcd for $C_{18}H_{31}NO_7K$ [M + K]⁺, 412.1738, found 412.1746.

(Z)-Benzyl 6-(tert-butoxycarbonyl(tert-butoxycarbonyloxy)amino)hex-2-enoate (*cis*-6b).

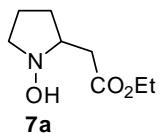
 After flash chromatography (SiO₂, 1% then 2.5–12.5% EtOAc in petroleum ether, 2.5% increments) the title compound (3.1 g, 82%) was obtained as a colorless oil: IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 2984, 1786, 1718, 1643, 1395, 1370, 1167, 751, 729, 704; ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.28 (m, 5H), 6.25 (dt, J = 11.5, 7.6 Hz, 1H, CH=CHC(O)), 5.85 (dt, J = 11.5, 1.7 Hz, 1H, CH=CHC(O)), 5.15 (s, 2H, PhCH₂), 3.60 (br. m, 2H, NCH₂), 2.73 (dq, J = 7.6, 1.7 Hz, 2H, CH₂CH=CH), 1.76 (qn, J = 7.4 Hz, 2H, CH₂CH₂CH₂), 1.53 (s, 9H, C(CH₃)₃), 1.47 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 165.9, 154.7, 152.3, 149.5, 136.1, 128.52, 128.2, 128.1, 84.7, 82.3, 65.7, 49.6, 28.1, 27.6, 26.4, 26.1; HRMS (ESI) m/z calcd for $C_{23}H_{34}NO_7$ [M + H]⁺, 436.2335, found 436.2340.

***rac*-(5*R*,6*R*)-Benzyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*trans*-3b).**



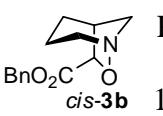
Obtained as an orange oil (1.04 g, 92%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3055, 2949, 2867, 1748, 1456, 1381, 1190, 1168, 1110, 1019, 999, 784, 736, 701; ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.27 (m, 5H), 5.17 (d, J = 12.3 Hz, 1H, OCH₂), 5.13 (d, J = 12.3 Hz, 1H, OCH₂), 4.62 (s, 1H, H-6), 3.32 (dd, J = 14.2, 6.1 Hz, 1H, H-2_{eq}), 3.25 (m, 1H, H-8_{eq}), 2.96 (d, J = 11.3 Hz, 1H, H-8_{ax}), 2.80 (m, 1H, H-5), 2.74 (ddd, J = 14.1, 12.0, 5.3 Hz, 1H, H-2_{ax}), 1.90 (m, 1H, H-3_{ax}), 1.82–1.66 (m, 2H, H-4), 1.53 (m, 1H, H-3_{eq}); ¹³C NMR (101 MHz, CDCl₃) δ 171.2 (C=O), 135.3, 128.5, 128.3, 128.2, 81.3 (C-6), 66.7 (OCH₂), 59.0 (C-8), 55.7 (C-2), 43.1 (C-5), 27.8 (C-4), 19.1 (C-3); HRMS (ESI) *m/z* calcd for C₁₄H₁₈NO₃ [M + H]⁺, 248.1287, found 248.1286.

Ethyl 2-(1-hydroxypyrrolidin-2-yl)acetate (7a).



Obtained as a byproduct in cycloaddition reactions as a yellow oil with spectral data corresponding to those reported¹⁸: ¹H NMR (400 MHz, CDCl₃) δ 4.14 (q, 2H, J = 7.1 Hz, OCH₂), 3.27 (m, 1H, H-5'), 3.17 (qn, 1H, J = 7.7 Hz, H-2'), 2.81 (m, 1H, H-5'), 2.75 (m, 1H, H-2), 2.41 (dd, 1H, J = 15.1, 7.7 Hz, H-2), 2.06 (m, 1H, H-3'), 1.80 (m, 2H, H-4'), 1.47 (m, 1H, H-3'), 1.26 (t, 1H, J = 7.2 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 172.3 (C=O), 64.9 (C-2'), 60.5 (OCH₂), 57.5 (C-5'), 38.3 (br., C-2), 27.3 (C-3'), 19.9 (br., C-4'), 14.2 (CH₃).

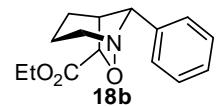
***rac*-(5*R*,6*S*)-Benzyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*cis*-3b).**



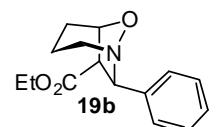
Purified by flash column chromatography (SiO₂, 20–50% EtOAc in petroleum ether, 10% increments) and obtained as an orange oil (54 mg, 68%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3055, 2953, 2873, 1749, 1498, 1456, 1381, 1201, 1188, 1116, 1024; ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.30 (m, 5H), 5.28 (d, J = 12.1 Hz, 1H, OCH₂), 5.24 (d, J = 12.1 Hz, 1H, OCH₂), 4.62 (d, J = 4.9 Hz, 1H, H-6), 3.44 (dd, J = 14.3, 6.6 Hz, 1H, H-2_{eq}), 3.36 (m, 1H, H-8_{eq}), 3.10 (d, J = 11.3 Hz, 1H, H-8_{ax}), 2.86–2.76 (m, 2H, H-5, H-2_{ax}), 2.16–2.00 (m, 1H, H-3_{ax}), 1.73–1.62

(m, 2H, H-4), 1.39–1.30 (m, 1H, H-3_{eq}); ¹³C NMR (101 MHz, CDCl₃) δ 169.4 (C=O), 135.3, 128.58, 128.56, 128.5, 81.8 (C-6), 66.8 (OCH₂), 61.3 (C-8), 56.1 (C-2), 41.1 (C-5), 25.0 (C-4), 18.1 (C-3); HRMS (ESI) *m/z* calcd for C₁₄H₁₈NO₃ [M + H]⁺, 248.1287, found 248.1280.

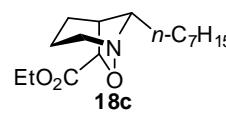
***rac*-(5*S*,6*R*,8*S*)-Ethyl 8-phenyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18b).**

 Purified by flash column chromatography (SiO₂, 10–25% EtOAc in petroleum ether, 5% increments) and obtained as a colorless oil (24.9 mg, 71%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3059, 2945, 2873, 1748, 1450, 1372, 1208, 1188, 1038; ¹H NMR (400 MHz, CDCl₃) δ 7.47 (m, 2H), 7.34 (m, 2H), 7.25 (m, 1H), 4.29–4.20 (m, 4H, OCH₂, H-6, H-8), 3.70 (dd, 1H, *J* = 6.7, 14.2 Hz, H-2), 3.06 (ddd, 1H, *J* = 5.7, 11.9, 14.3 Hz, H-2), 2.97 (m, 1H, H-5), 2.18 (m, 1H, H-3), 2.02–1.95 (m, 2H, H-4), 1.49 (m, 1H, H-3), 1.28 (t, 3H, *J* = 7.1 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 139.4, 128.4, 127.2, 125.8, 79.7 (C-6), 73.4 (OCH₂), 61.1(C-8), 57.0 (C-2), 47.5 (C-5), 26.8 (C-4), 17.9 (C-3), 14.2 (CH₃); HRMS (MALDI–TOF) *m/z* calcd for C₁₅H₂₀NO₃ [M + H]⁺, 262.1443, found 262.1466.

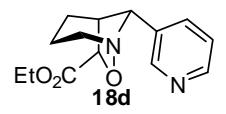
***rac*-(5*R*,6*R*,7*S*)-Ethyl 7-phenyl-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19b).**

 Purified by flash column chromatography (SiO₂, 10–25% EtOAc in petroleum ether, 5% increments) and obtained as a colorless oil (7.9 mg, 23%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3056, 2962, 1728, 1448, 1373, 1335, 1232, 1191, 1047; ¹H NMR (400 MHz, CDCl₃) δ 7.44 (m, 2H), 7.32 (m, 2H), 7.23 (m, 1H), 4.82 (d, 1H, *J* = 5.9 Hz, H-7), 4.70 (m, 1H, H-5), 4.24 (m, 2H, OCH₂), 3.68–3.58 (m, 2H, H-6, H-2), 3.07 (m, 1H, H-2), 2.18–1.98 (m, 2H, H-3, H-4), 1.75 (m, 1H, H-4), 1.48 (m, 1H, H-3), 1.30 (t, 3H, *J* = 7.1 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.3, 144.1, 128.6, 127.0, 126.1, 78.1 (C-5), 68.0 (C-7), 63.0 (C-6), 61.3 (OCH₂), 55.5 (C-2), 25.8 (C-4), 15.5 (C-3), 14.2 (CH₃); HRMS (MALDI–TOF) *m/z* calcd for C₁₅H₂₀NO₃ [M + H]⁺, 262.1443, found 262.1453.

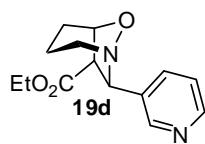
***rac*-(5*S*,6*R*,8*S*)-Ethyl 8-heptyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18c).**


Purified by flash column chromatography (SiO_2 , 10–25% EtOAc in petroleum ether, 5% increments) and obtained as a colorless oil (35.2 mg, 84%): IR ($\text{CHCl}_3/\text{NaCl}$) ν_{max} (cm^{-1}): 2929, 2857, 1745, 1463, 1374, 1286, 909; ^1H NMR (400 MHz, CDCl_3) δ 4.58 (d, 1H, J = 4.9 Hz, H-6), 4.27 (m, 2H, OCH₂), 3.51 (dd, 1H, J = 6.8, 14.1 Hz, H-2), 2.96 (t, 1H, J = 6.8 Hz, H-8), 2.88 (ddd, 1H, J = 5.9, 11.9, 14.1 Hz, H-2), 2.65 (m, 1H, H-5), 2.05 (m, 1H, H-3), 1.84 (m, 1H), 1.68 (m, 1H), 1.61–1.22 (m, 16H), 0.86 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.9, 80.6, 72.3, 61.1, 56.7, 44.2, 31.7, 31.6, 29.4, 29.2, 26.7, 26.4, 22.6, 17.6, 14.2, 14.0; HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{30}\text{NO}_3$ [M + H]⁺, 284.2226, found 284.2231.

***rac*-(5*S*,6*R*,8*S*)-Ethyl 8-(pyridin-3-yl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18d).**

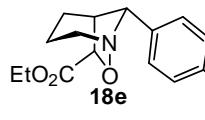

Purified by flash column chromatography (SiO_2 , 1–5% EtOH in toluene, 1% increments) and obtained as a red oil (23.2 mg, 64%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3051, 2946, 2874, 1748, 1576, 1471, 1423, 1373, 1274, 1209, 1188, 1097, 1035, 793, 737; ^1H NMR (400 MHz, CDCl_3) δ 8.88 (s, 1H), 8.65 (m, 1H), 8.32 (m, 1H), 7.65 (m, 1H, J = 5.3, 8.0 Hz), 4.37 (s, 1H, H-8), 4.25 (m, 2H, OCH₂), 4.10 (d, 1H, J = 4.76 Hz, H-6), 3.71 (dd, 1H, J = 6.4, 14.5 Hz, H-2_{ax}), 3.11–3.01 (m, 2H, H-2_{eq}, H-5), 2.16 (m, 1H, H-3_{ax}), 2.03 (m, 2H, H-4), 1.54 (m, 1H, H-3_{eq}), 1.28 (t, 3H, J = 7.1 Hz, CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 168.8, 143.4, 143.0, 139.6, 137.9, 125.4, 79.5 (C-6), 70.8 (C-8), 61.5 (OCH₂), 56.6 (C-2), 47.0 (C-5), 26.4 (C-4), 17.6 (C-3), 14.2 (CH₃); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3$ [M + H]⁺, 263.1396, found 263.1415.

rac-(5R,6R,7S)-Ethyl 7-(pyridin-3-yl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19d).



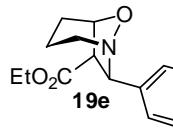
Purified by flash column chromatography (SiO_2 , 1–5% EtOH in toluene, 1% increments) and obtained as a red oil (12.2 mg, 34%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3051, 2962, 1728, 1577, 1466, 1428, 1373, 1235, 1194, 1046, 1008, 738; ^1H NMR (400 MHz, CDCl_3) δ 8.65 (m, 1H), 8.50 (m, 1H), 7.84 (dt, 1H, J = 1.8, 8.1 Hz), 7.84 (m, 1H), 4.85 (d, 1H, J = 5.7 Hz, H-7), 4.71 (m, 1H, H-5), 4.26 (m, 2H, OCH_2), 3.64 (ddd, 1H, J = 4.5, 12.6, 14.3 Hz, H-2), 3.54 (m, 1H, H-6), 3.06 (m, 1H, H-2), 2.18–1.94 (m, 2H, H- 3_{ax} , H-4), 1.78 (m, 1H, H-4), 1.50 (m, 1H, H- 3_{eq}), 1.31 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.9, 148.1, 147.6, 139.9, 134.2, 123.8, 78.2 (C-5), 65.8 (C-7), 62.9 (C-6), 61.5 (OCH_2), 55.5 (C-5), 25.7 (C-4), 15.5 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}]^+$, 263.1396, found 263.1414.

rac-(5S,6R,8S)-Ethyl 8-(4-nitrophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18e).



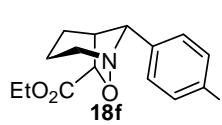
Purified by flash column chromatography (SiO_2 , 10–35% EtOAc in petroleum ether, 5% increments) and obtained as a yellow solid (21.3 mg, 44%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 2982, 1946, 2874, 1748, 1603, 1522, 1449, 1349, 1209, 1187, 1037; ^1H NMR (400 MHz, CDCl_3) δ 8.20 (m, 2H), 7.67 (m, 2H), 4.33 (br. s, 1H, H-8), 4.26 (m, 2H, OCH_2), 4.14 (d, 1H, J = 4.8 Hz, H-6), 3.72 (dd, 1H, J = 6.6, 14.3 Hz, H- 2_{ax}), 3.07 (m, 1H, H- 2_{eq}), 3.02 (m, 1H, H-5), 2.17 (m, 1H, H- 3_{ax}), 2.09–1.95 (m, 2H, H-4), 1.53 (m, 1H, H- 3_{eq}), 1.28 (t, 1H, J = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.2, 147.3, 146.5, 127.0, 123.7, 79.6 (C-6), 73.0 (C-8), 61.3 (OCH_2), 56.8 (C-2), 47.3 (C-5), 26.7 (C-4), 17.7 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5$ [$\text{M} + \text{H}]^+$, 307.1294, found 307.1293.

***rac*-(5*R*,6*R*,7*S*)-Ethyl 7-(4-nitrophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19e).**



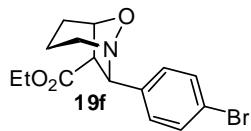
Purified by flash column chromatography (SiO_2 , 10–35% EtOAc in petroleum ether, 5% increments) and obtained as a yellow solid (14.6 mg, 30%): IR (CHCl_3) ν_{max} (cm^{-1}): 2962, 1726, 1603, 1520, 1462, 1348, 905; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (m, 2H, H-11), 7.62 (m, 2H, H-10), 4.92 (d, 1H, $J = 5.7$ Hz, H-7), 4.70 (m, 1H, H-5), 4.28 (m, 2H, OCH₂), 3.65 (ddd, 1H, $J = 4.6, 12.7, 14.4$ Hz, H-2_{eq}), 3.50 (m, 1H, H-6), 3.06 (m, 1H, H-2_{ax}), 2.13 (m, 1H, H-4), 2.00 (m, 1H, H-3_{ax}), 1.78 (m, 1H, H-4), 1.51 (m, 1H, H-3_{eq}), 1.31 (t, 3H, $J = 7.1$ Hz, CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 169.9 (C=O), 151.4 (C-9), 147.0 (C-12), 127.0 (C-10), 123.9 (C-11), 78.2 (C-5), 67.3 (C-7), 62.8 (C-6), 61.6 (OCH₂), 55.5 (C-2), 25.8 (C-4), 15.6 (C-3), 14.2 (CH₃); HRMS (MALDI–TOF) m/z calcd for C₁₅H₁₉N₂O₅ [M + H]⁺, 307.1288, found 307.1275.

***rac*-(5*S*,6*R*,8*S*)-Ethyl 8-(4-bromophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18f).**



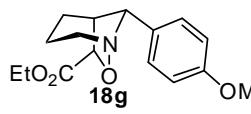
Purified by flash column chromatography (SiO_2 , 10–25% EtOAc in petroleum ether, 5% increments) and obtained as a colorless solid (36.1 mg, 65%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3056, 2981, 2943, 2873, 1748, 1489, 1372, 1207, 1187, 1038; ^1H NMR (400 MHz, CDCl_3) δ 7.47 (m, 2H), 7.35 (m, 2H), 4.29–4.20 (m, 4H, OCH₂, H-6, H-8), 3.69 (dd, 1H, $J = 6.8, 14.3$ Hz, H-2_{ax}), 3.06 (ddd, 1H, $J = 5.7, 11.9, 14.3$ Hz, H-2_{eq}), 2.93 (m, 1H, H-5), 2.17 (m, 1H, H-3_{ax}), 2.04–1.90 (m, 2H, H-4), 1.50 (m, 1H, H-3_{eq}), 1.28 (t, 3H, $J = 7.1$ Hz, CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 138.2, 131.5, 127.7, 121.2, 79.7 (C-6), 72.9 (C-8), 61.2 (OCH₂), 56.8 (C-2), 47.3 (C-5), 26.6 (C-4), 17.7 (C-3), 14.2 (CH₃); HRMS (MALDI–TOF) m/z calcd for C₁₅H₁₉⁷⁹BrNO₃ [M + H]⁺, 340.0549, found 340.0551.

rac-(5R,6R,7S)-Ethyl 7-(4-bromophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19f).



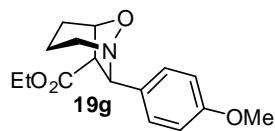
Purified by flash column chromatography (SiO_2 , 10–25% EtOAc in petroleum ether, 5% increments) and obtained as a colorless oil (14.8 mg, 27%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3055, 2964, 1728, 1488, 1372, 1229, 1191, 1010; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (m, 2H, ArH), 7.32 (m, 2H, ArH), 4.77 (d, 1H, $J = 5.9$ Hz, H-7), 4.68 (m, 1H, H-5), 4.25 (m, 2H, OCH_2), 3.62 (m, 1H, H- 2_{eq}), 3.52 (m, 1H, H-6), 3.04 (m, 1H, H- 2_{ax}), 2.16–1.93 (m, 2H, H-4, H- 3_{ax} , H-4), 1.78–1.71 (m, 1H, H-4), 1.48 (m, 1H, H- 3_{eq}), 1.30 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 143.3, 131.7, 127.9, 120.8, 78.1 (C-5), 67.4 (C-7), 63.0 (C-6), 61.4 (OCH_2), 55.5 (C-2), 25.8 (C-4), 15.5 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{15}\text{H}_{19}{^{79}\text{BrNO}_3} [\text{M} + \text{H}]^+$, 340.0549, found 340.0561.

rac-(5S,6R,8S)-Ethyl 8-(4-methoxyphenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18g).



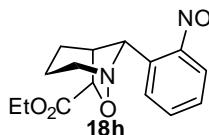
Purified by flash column chromatography (SiO_2 , 10–30% EtOAc in petroleum ether, 5% increments) and obtained as a colorless oil (24.9 mg, 63%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3055, 2984, 1746, 1612, 1513, 1445, 1423, 1373, 1209, 1182, 1036, 738, 706; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (m, 2H), 6.87 (m, 2H), 4.33 (d, 1H, $J = 4.8$ Hz, H-6), 4.27 (m, 1H, H-8), 4.25 (m, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 3.69 (d, 1H, $J = 6.7$, 14.2 Hz, H- 2_{ax}), 3.11 (ddd, 1H, $J = 5.7$, 12.0, 14.2 Hz, H- 2_{eq}), 2.93 (m, 1H, H-5), 2.18 (m, 1H, H- 3_{ax}), 2.01–1.94 (m, 2H, H-4), 1.51 (m, 1H, H- 3_{eq}), 1.29 (t, 3H, $J = 7.1$ Hz, OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.7 (C=O), 158.8, 130.9, 126.9, 113.8, 79.8 (C-6), 73.1 (C-8), 61.1 (OCH_2), 56.8 (C-2), 55.3 (OCH_3), 47.5 (C-5), 26.5 (C-4), 17.6 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4 [\text{M} + \text{H}]^+$, 292.1549, found 292.1552.

rac-(5*R*,6*R*,7*S*)-Ethyl 7-(4-methoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19g).



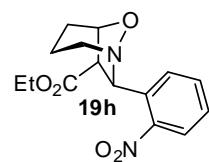
Purified by flash column chromatography (SiO_2 , 10–30% EtOAc in petroleum ether, 5% increments) and obtained as a colorless oil (9.5 mg, 25%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3054, 2962, 1729, 1612, 1514, 1464, 1443, 1372, 1248, 1190; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (m, 2H), 6.85 (m, 2H), 4.78 (d, 1H, $J = 5.9$ Hz, H-7), 4.71 (m, 1H, H-5), 4.23 (m, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 3.66–3.56 (m, 2H, H- 2_{eq} , H-6), 3.08 (m, 1H, H- 2_{ax}), 2.17–1.97 (m, 2H, H- 3_{ax} , H-4), 1.74 (m, 1H, H-4), 1.48 (m, 1H, H- 3_{eq}), 1.29 (t, 3H, $J = 7.14$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 158.7, 136.1, 127.3, 114.0, 78.2 (C-5), 67.6 (C-7), 63.0 (C-6), 61.2 (OCH_2), 55.4, 55.3, 25.7 (C-4), 15.4 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ [$\text{M} + \text{H}]^+$, 292.1549, found 292.1562.

rac-(5*S*,6*R*,8*S*)-Ethyl 8-(2-nitrophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18h).



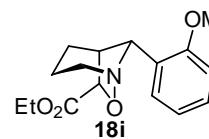
Purified by flash column chromatography (SiO_2 , 1–5% EtOAc in CH_2Cl_2 , 1% increments) and obtained as a yellow oil (29.4 mg, 69%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 2979, 2943, 2875, 1749, 1527, 1466, 1450, 1346, 1208, 1187, 1039, 738; ^1H NMR (400 MHz, CDCl_3) δ 8.10 (m, 1H), 8.05 (m, 1H), 7.66 (m, 1H), 7.46 (m, 1H), 4.96 (s, 1H, H-8), 4.25 (m, 2H, OCH_2), 4.19 (d, 1H, $J = 4.8$ Hz, H-6), 3.73 (m, 1H, H-2), 3.12 (m, 1H, H-2), 2.85 (m, 1H, H-5), 2.29–2.10 (m, 2H, H-4, H- 3_{ax}), 1.98 (m, 1H, H-4), 1.55 (m, 1H, H- 3_{eq}), 1.27 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.3, 146.8, 134.9, 134.1, 129.5, 128.4, 125.2, 79.7 (C-6), 71.6 (C-8), 61.3 (OCH_2), 57.4 (C-2), 47.6 (C-5), 26.9 (C-4), 17.8 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5$ [$\text{M} + \text{H}]^+$, 307.1294, found 307.1314.

***rac*-(5*R*,6*R*,7*S*)-Ethyl 7-(2-nitrophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19h).**



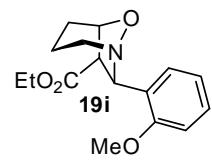
Purified by flash column chromatography (SiO_2 , 1–5% EtOAc in CH_2Cl_2 , 1% increments) and obtained as a yellow oil (10.2 mg, 24%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3054, 2986, 1735, 1530, 1422, 1356, 1178; ^1H NMR (400 MHz, CDCl_3) δ 7.86 (m, 1H), 7.73 (m, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 5.39 (d, 1H, J = 6.0 Hz, H-7), 4.73 (m, 1H, H-5), 4.22 (m, 2H, OCH_2), 3.62 (m, 1H, H-2), 3.56 (m, 1H, H-6), 3.16 (m, 1H, H-2), 2.29–2.07 (m, 2H, H-3_{ax}, H-4), 1.81 (m, 1H, H-4), 1.49 (m, 1H, H-3_{eq}), 1.28 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.3, 148.5, 138.6, 133.4, 129.3, 127.9, 123.6, 78.6 (C-5), 63.2, 62.6, 61.5, 55.5, 25.7 (C-4), 15.3 (C-3), 14.1 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5$ [M + H]⁺, 307.1294, found 307.1297.

***rac*-(5*S*,6*R*,8*S*)-Ethyl 8-(2-methoxyphenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18i).**



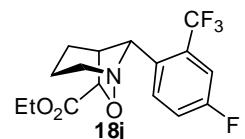
Purified by flash column chromatography (SiO_2 , 1–9% EtOAc in CH_2Cl_2 , 2% increments) and obtained as a colorless oil (34.7 mg, 84%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 2943, 2873, 1746, 1604, 1491, 1462, 1371, 1287, 1242, 1207, 1187, 1033; ^1H NMR (400 MHz, CDCl_3) δ 7.62 (m, 1H), 7.24 (m, 1H), 6.96 (m, 1H), 6.85 (m, 1H), 4.41 (br. s, 1H, H-8), 4.31 (d, 1H, J = 4.8 Hz, H-6), 4.24 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.70 (dd, 1H, J = 6.7, 14.1 Hz, H-2), 3.07 (ddd, 1H, J = 5.7, 11.9, 14.2 Hz, H-2), 2.91 (m, 1H, H-5), 2.21 (m, 1H, H-3_{ax}), 2.02 (m, 1H, H-4), 1.93 (m, 1H, H-4), 1.49 (m, 1H, H-3_{ax}), 1.27 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 155.9, 128.3, 127.5, 127.3, 120.7, 109.7, 79.9 (C-6), 70.0 (C-8), 61.0 (OCH_2), 57.4, 55.2, 46.3 (C-5), 26.5 (C-4), 17.9 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ [M + H]⁺, 292.1549, found 292.1565.

rac-(5*R*,6*R*,7*S*)-Ethyl 7-(2-methoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19i).



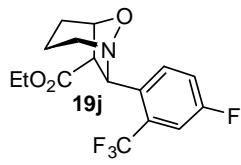
Purified by flash column chromatography (SiO_2 , 1–9% EtOAc in CH_2Cl_2 , 2% increments) and obtained as a colorless oil (6.1 mg, 15%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 2937, 1736, 1603, 1490, 1464, 1373, 1245, 1178; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (m, 1H), 7.29 (m, 1H), 6.97 (m, 1H), 6.87 (m, 1H), 5.41 (d, 1H, J = 6.3 Hz, H-7), 4.86 (m, 1H, H-5), 4.24 (q, 2H, J = 7.1 Hz, OCH_2), 3.84–3.80 (m, 4H), 3.70 (m, 1H), 3.36 (m, 1H), 2.40 (m, 1H), 2.17 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.30 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.1, 156.8, 129.5, 127.12, 127.09, 120.9, 110.6, 79.1 (C-5), 63.3 (C-7), 61.4 (OCH_2), 58.9, 55.4, 54.6, 25.2 (C-4), 14.8 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ [M + H] $^+$, 292.1549, found 292.1560.

rac-(5*S*,6*R*,8*R*)-Ethyl 8-(4-fluoro-2-(trifluoromethyl)phenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18j).



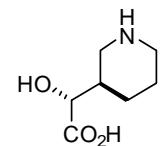
Purified by flash column chromatography (SiO_2 , 0.5–2.5% EtOAc in CH_2Cl_2 , 0.5% increments) and obtained as a colorless oil (30.6 mg, 65%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 2944, 2876, 1749, 1620, 1596, 1498, 1428, 1315, 1280, 1212, 1168, 1127, 1045, ^1H NMR (400 MHz, CDCl_3) δ 7.96 (dd, 1H, J = 5.6, 8.8 Hz), 7.36 (dd, 1H, J = 2.8, 9.0 Hz), 7.25 (m, 1H), 4.51 (br. s, 1H, H-8), 4.34 (d, 1H, J = 4.8 Hz, H-6), 4.27 (m, 2H, OCH_2), 3.72 (dd, 1H, J = 6.8, 14.3 Hz, H-2), 3.11 (ddd, 1H, J = 5.8, 11.7, 14.3 Hz, H-2), 2.89 (m, 1H, H-5), 2.21 (m, 1H, H-3_{ax}), 2.07–1.93 (m, 2H, H-4), 1.53 (m, 1H, H-3_{eq}), 1.29 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.4, 161.4 (d, J = 249.2 Hz, C–F), 133.8 (m, C–CF₃), 130.9 (d, J = 7.7 Hz), 128.5 (dd, J = 7.7, 31.4 Hz), 123.7 (qd, J = 2.7, 174.1 Hz, CF₃), 119.1 (d, J = 19.9 Hz), 113.8 (dq, J = 5.9, 25.3 Hz), 79.4 (C-6), 71.3 (d, J = 2.1 Hz, C-8), 61.3 (OCH_2), 57.8 (C-2), 47.9 (C-5), 26.8 (C-4), 17.6 (C-3), 14.2 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{F}_4\text{NO}_3$ [M + H] $^+$, 348.1223, found 348.1229.

rac-(5R,6R,7S)-Ethyl 7-(4-fluoro-2-(trifluoromethyl)phenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19j).



Purified by flash column chromatography (SiO_2 , 0.5–2.5% EtOAc in CH_2Cl_2 , 0.5% increments) and obtained as a colorless oil (3.9 mg, 8%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 2984, 1739, 1500, 1434, 1372, 1320, 1220, 1165, 1131, 1050, 918; ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dd, 1H, $J = 5.5, 8.6$ Hz), 7.32–7.24 (m, 2H), 5.17 (d, 1H, $J = 5.7$ Hz, H-7), 4.80 (m, 1H, H-5), 4.20 (q, 2H, $J = 7.1$ Hz, OCH_2), 3.66 (m, 1H, H-6), 3.58 (ddd, 1H, $J = 4.8, 12.7, 14.3$ Hz, H-2), 3.10 (m, 1H, H-2), 2.28 (m, 1H, H- 3_{ax}), 2.14 (m, 1H, H-4), 1.72 (m, 1H, H-4), 1.46 (m, 1H, H- 3_{eq}), 1.27 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 169.1, 161.1 (d, $J = 248.4$ Hz, C–F), 139.1 (m), 131.4 (d, $J = 8.4$ Hz), 129.0 (dd, $J = 7.7, 30.7$ Hz), 123.3 (qd, $J = 2.7, 274.1$ Hz, CF_3), 119.8 (d, $J = 20.7$ Hz), 112.4 (dq, $J = 6.0, 24.9$ Hz), 78.8 (C-5), 63.5 (m, C-7), 63.1, 61.3 (OCH_2), 55.2, 25.8 (C-4), 15.1 (C-3), 14.1 (CH_3); HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{F}_4\text{NO}_3$ [$\text{M} + \text{H}]^+$, 348.1223, found 348.1223.

rac-(R)-2-Hydroxy-2-((R)-piperidin-3-yl)acetic acid (20b).



Crystallized from H_2O –acetone. Drying under high vacuum (rt, 5×10^{-3} Torr) gave the title compound (621 mg, 97%) as colorless needles: IR (KBr) ν_{max} (cm^{-1}): 3420, 2961, 2767, 2727, 2533, 2472, 2440, 1645, 1603, 1481, 1420, 1356, 1079, 945, 732, 591, 542; ^1H NMR (400 MHz, D_2O) δ 3.95 (d, 1H, $J = 4.0$ Hz, H-2), 3.38 (m, 1H, H- $6'_{eq}$), 3.25 (m, 1H, H- $2'_{eq}$), 2.94–2.84 (m, 2H, H- $2'_{ax}$, H- $6'_{ax}$), 2.15 (m, 1H, H- $3'_{ax}$), 2.00 (m, 1H, H- $5'_{eq}$), 1.88 (m, 1H, H- $4'_{eq}$), 1.74 (m, 1H, H- $5'_{ax}$), 1.49 (m, 1H, H- $4'_{ax}$); ^{13}C NMR (101 MHz, D_2O) δ 179.5 (C=O), 74.6 (C-2), 45.4 (C-2'), 44.7 (C-6'), 38.0 (C-3'), 25.5 (C-4'), 22.3 (C-5'); HRMS (ESI) m/z calcd for $\text{C}_7\text{H}_{14}\text{NO}_3$ [$\text{M} + \text{H}]^+$, 160.0974, found 160.0967.

***rac*-(*R*)-Ethyl 2-hydroxy-2-((*S*)-piperidin-3-yl)acetate (**21a**).**

Purification by flash chromatography (SiO₂, 18:1:1 CHCl₃/MeOH/30% NH₄OH) gave **21a** (104 mg, 86%) as a colorless solid: IR (CH₂Cl₂/NaCl) ν_{\max} (cm⁻¹): 3526, 2984, 2938, 2859, 1732, 1446, 1369, 1215, 1134, 1121; ¹H NMR (400 MHz, CDCl₃) δ 4.20 (m, 2H, OCH₂), 4.04 (d, 1H, J = 3.8 Hz, H-2), 2.99 (m, 1H, H-2'), 2.91 (m, 1H, H-6'), 2.79 (br. s, 2H, NH, OH), 2.64 (dd, 1H, J = 12.0 Hz, 10.2 Hz, H-2'), 2.52 (m, 1H, H-6'), 1.86 (m, 1H, H-3'), 1.69 (m, 1H, H-5'), 1.52 (m, 1H, H-4'), 1.46–1.33 (m, 2H, H-4', H-5'), 1.26 (t, 3H, J = 7.1 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 174.2 (C=O), 73.3 (C-2), 61.4 (OCH₂), 49.3 (C-2'), 46.4 (C-6'), 40.4 (C-3'), 25.9 (C-5'), 24.7 (C-4'), 14.2 (CH₃); MS (ESI) *m/z* 188 [M + H]⁺; HRMS (ESI) *m/z* calcd for C₉H₁₈NO₃ [M + H]⁺, 188.1287, found 188.1284.

***rac*-(*R*)-2-Hydroxy-2-((*S*)-piperidin-3-yl)acetic acid (**21b**).**

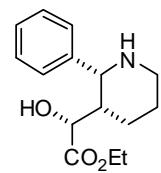
Crystallized from H₂O–acetone and obtained as colorless crystals (34 mg, 93%): IR (KBr) ν_{\max} (cm⁻¹): 3424, 3050, 2938, 2863, 2537, 1638, 1604, 1412, 1358, 1344, 1133, 1094, 934, 809, 701, 586, 539; ¹H NMR (400 MHz, D₂O) δ 3.97 (d, 1H, J = 3.5 Hz, C-2), 3.45–3.33 (m, 2H, H-2'_{eq}, H-6'_{eq}), 2.92–2.83 (m, 2H, H-2'_{ax}, H-6'_{ax}), 2.18 (m, 1H, H-3'_{ax}), 1.98 (m, 1H, H-5'_{eq}), 1.76–1.62 (m, 2H, H-5'_{ax}, H-4'_{eq}), 1.46 (m, 1H, H-4'_{ax}); ¹³C NMR (101 MHz, D₂O) δ 179.5 (C=O), 73.8 (C-2), 47.2 (C-2'), 44.7 (C-6'), 38.0 (C-3'), 22.9 (C-4'), 22.4 (C-5'); MS (ESI) *m/z* 160 [M + H]⁺; HRMS (ESI) *m/z* calcd for C₇H₁₃NO₃Na [M + Na]⁺, 182.0793, found 182.0796.

***rac*-(*R*)-Ethyl 2-((2*S*,3*S*)-2-cyclohexylpiperidin-3-yl)-2-hydroxyacetate (**22a**).**

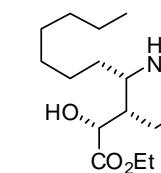
Purified by flash column chromatography (SiO₂, 100:1:0.5, 100:2:0.5, 100:3:0.5 CH₂Cl₂/MeOH/30% NH₄OH) and obtained as a colorless oil (25.9 mg, 97%): IR (CH₂Cl₂/NaCl) ν_{\max} (cm⁻¹): 3137 (br), 3058, 2933, 2856, 1748, 1677, 1448, 1370, 1202, 1070; ¹H NMR (400 MHz, CDCl₃) δ 4.70 (d, 1H, J = 3.3 Hz, H-2), 4.24 (q, 2H, J = 7.1

Hz, OCH₂), 3.32 (m, 1H, H-6'), 2.78 (m, 1H, H-6'), 2.67 (dd, 1H, *J* = 3.1, 9.9 Hz, H-2'), 2.28 (m, 1H), 2.19 (m, 1H), 1.97 (m, 1H), 1.88–1.64 (m, 6H), 1.61–1.46 (m, 2H), 1.35–1.07 (m, 6H), 1.05–0.89 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 173.5, 72.4 (C-2), 65.6, 61.1, 46.8, 37.5, 33.5, 29.5, 29.2, 26.7, 26.0, 25.7, 25.5, 21.3, 14.3 (CH₃); HRMS (MALDI–TOF) *m/z* calcd for C₁₅H₂₈NO₃ [M + H]⁺, 270.2069, found 270.2074.

***rac*-(R)-Ethyl 2-hydroxy-2-(2*R*,3*S*)-2-phenylpiperidin-3-yl)acetate (22b).**

 Purified by flash column chromatography (SiO₂, 100:1:0.5, 100:2:0.5, 100:3:0.5 CH₂Cl₂/MeOH/30% NH₄OH) and obtained as a colorless oil (20.6 mg, 96%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3600–2800 (br), 3056, 2938, 2859, 1746, 1467, 1452, 1368, 1199, 1138, 1066; ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.35 (m, 4H), 7.29 (m, 1H), 4.22–4.12 (m, 3H), 4.11 (d, 1H, *J* = 3.1 Hz), 3.32 (ddt, 1H, *J* = 4.9, 11.3 Hz, H-6'), 2.88 (ddd, 1H, *J* = 3.4, 11.3, 12.6 Hz, H-6'), 2.24 (m, 1H), 2.17 (m, 1H), 1.91 (m, 1H), 1.76 (m, 1H), 1.58 (m, 1H), 1.23 (t, 3H, *J* = 7.1 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 173.5, 141.2, 128.7, 127.6, 126.1, 73.2 (C-2), 65.8, 60.6, 47.7, 40.3, 27.3, 22.6, 14.3; HRMS (MALDI–TOF) *m/z* calcd for C₁₅H₂₂NO₃ [M + H]⁺, 264.1600, found 264.1622.

***rac*-(R)-Ethyl 2-((2*S*,3*S*)-2-heptylpiperidin-3-yl)-2-hydroxyacetate (22c).**

 Purified by flash column chromatography (SiO₂, 100:1:0.5, 100:2:0.5, 100:3:0.5 CH₂Cl₂/MeOH/30% NH₄OH) and obtained as a colorless oil (23.2 mg, 91%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3452 (br), 2929, 2857, 1745, 1467, 1369, 1203; ¹H NMR (400 MHz, CDCl₃) δ 4.71 (d, 1H, *J* = 3.6 Hz, H-2), 4.24 (m, 2H, OCH₂), 3.12 (m, 1H), 2.83 (m, 1H), 2.69 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.79–1.41 (m, 5H), 1.40–1.18 (m, 13H), 0.92–0.82 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 174.0, 73.4 (C-2), 61.2, 60.6, 47.2,

36.7, 33.0, 31.8, 29.6, 29.1, 27.4, 26.2, 22.9, 22.6, 14.4, 14.1; HRMS (MALDI–TOF) m/z calcd for $C_{16}H_{32}NO_3 [M + H]^+$, 286.2382, found 286.2384.

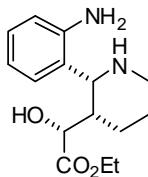
***rac*-(*R*)-Ethyl 2-((2*R*,3*S*)-2-(4-aminophenyl)piperidin-3-yl)-2-hydroxyacetate (22e).**

Purified by flash column chromatography (SiO_2 , 100:1:0.5, 100:2:0.5, 100:3:0.5 $CH_2Cl_2/MeOH/30\% NH_4OH$) and obtained as a colorless solid (18.5 mg, 90%): IR ($CH_2Cl_2/NaCl$) ν_{max} (cm^{-1}): 3450, 3352, 3308, 3238, 2985, 2916, 2855, 1741, 1621, 1519, 1428, 1217, 1200, 1136, 1066, 1022; 1H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 2H), 6.69 (m, 2H), 4.28 (m, 1H), 4.18 (m, 2H, OCH_2), 4.01 (d, 1H, $J = 3.1$ Hz), 3.67 (br. s, 2H, NH_2), 3.30 (ddt, $J = 4.9, 11.2$ Hz, H-6'), 2.87 (ddd, 1H, $J = 3.3, 11.3, 12.8$ Hz, H-6'), 2.21 (m, 1H), 2.09 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 1.24 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 145.8, 130.9, 127.2, 115.2, 73.2, 65.4, 60.7, 47.7, 40.4, 27.2, 22.5, 14.3; HRMS (MALDI–TOF) m/z calcd for $C_{15}H_{23}N_2O_3 [M + H]^+$, 279.1709, found 279.1713.

***rac*-(*R*)-Ethyl 2-hydroxy-2-((2*R*,3*S*)-2-(4-methoxyphenyl)piperidin-3-yl)acetate (22g).**

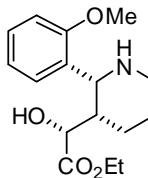
Purified by flash column chromatography (SiO_2 , 100:1:0.5, 100:2:0.5, 100:3:0.5 $CH_2Cl_2/MeOH/30\% NH_4OH$) and obtained as a colorless oil (25.0 mg, 93%): IR ($CH_2Cl_2/NaCl$) ν_{max} (cm^{-1}): 3434 (br), 3056, 2957, 2938, 2859, 2838, 1745, 1613, 1515, 1466, 1368, 1248, 1198, 1138, 1034; 1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 6.90 (m, 2H), 4.21 (dd, 1H, $J = 1.1, 3.1$ Hz), 4.17 (m, 2H, OCH_2), 4.06 (d, 1H, $J = 3.1$ Hz), 3.80 (s, 3H, OCH_3), 3.31 (ddt, 1H, $J = 4.9, 11.2$ Hz), 2.87 (ddd, 1H, $J = 3.4, 11.3, 12.7$ Hz), 2.22 (m, 1H), 2.11 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.57 (m, 1H), 1.23 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 159.0, 133.2, 127.2, 114.1, 73.2, 65.3, 60.6, 55.3, 47.7, 40.4, 27.2, 22.6, 14.3; HRMS (MALDI–TOF) m/z calcd for $C_{16}H_{24}NO_4 [M + H]^+$, 294.1705, found 294.1705.

***rac*-(*R*)-Ethyl 2-((2*R*,3*S*)-2-(2-aminophenyl)piperidin-3-yl)-2-hydroxyacetate (22h).**



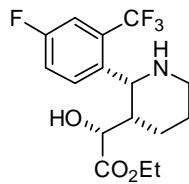
Purified by flash column chromatography (SiO_2 , 100:1:0.5, 100:2:0.5, 100:3:0.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}/30\% \text{ NH}_4\text{OH}$) and obtained as a colorless solid (16.1 mg, 83%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3468, 3354, 3225, 3055, 2985, 2943, 2823, 1742, 1625, 1497, 1454, 1435, 1211, 1134, 1063, 1020, 738, 705; ^1H NMR (400 MHz, CDCl_3) δ 7.45 (m, 1H), 7.12 (m, 1H), 6.84 (m, 1H), 6.72 (m, 1H), 4.28 (m, 1H), 4.18 (m, 2H), 4.09 (d, 1H, $J = 2.9$ Hz), 3.33 (dddd, 1H, $J = 4.9, 11.3$ Hz), 2.90 (ddd, 1H, $J = 3.4, 11.3, 12.7$ Hz), 2.35–2.21 (m, 2H), 1.93 (m, 1H), 1.73 (m, 1H), 1.60 (m, 1H), 1.24 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 173.5, 143.0, 128.2, 125.8, 125.4, 119.4, 116.6, 73.7, 61.3, 60.7, 48.1, 36.6, 27.1, 22.8, 14.3; HRMS (MALDI–TOF) m/z calcd for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}]^+$, 279.1709, found 279.1736.

***rac*-(*R*)-Ethyl 2-((2*R*,3*S*)-2-(2-methoxyphenyl)piperidin-3-yl)-2-hydroxyacetate (22i).**



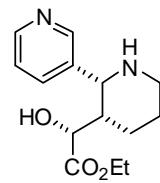
Purified by flash column chromatography (SiO_2 , 100:1:0.5, 100:2:0.5, 100:3:0.5, 100:4:0.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}/30\% \text{ NH}_4\text{OH}$) and obtained as a colorless solid (26.8 mg, 91%): IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3429 (br), 3055, 2939, 1744, 1602, 1493, 1464, 1367, 1245, 1205, 1140, 1029; ^1H NMR (400 MHz, CDCl_3) δ 7.54 (m, 1H), 7.27 (m, 1H), 6.98 (m, 1H), 6.89 (m, 1H), 4.41 (d, 1H, $J = 2.9$ Hz), 4.21–4.14 (m, 3H), 3.84 (s, 3H, OCH_3), 3.31 (dddd, 1H, $J = 4.9, 11.2$ Hz), 2.90 (ddd, 1H, $J = 3.3, 11.2, 12.8$ Hz), 2.32 (m, 1H), 2.24 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.58 (m, 1H), 1.24 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 173.8, 156.1, 129.3, 128.3, 125.8, 120.8, 110.3, 74.0, 60.6, 59.4, 55.3, 47.9, 37.1, 27.0, 22.9, 14.3; HRMS (MALDI–TOF) m/z calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_4$ [$\text{M} + \text{H}]^+$, 294.1705, found 294.1712.

***rac*-(*R*)-Ethyl 2-((2*R*,3*S*)-2-(4-fluoro-2-(trifluoromethyl)phenyl)piperidin-3-yl)-2-hydroxyacetate (**22j**).**



Purified by flash column chromatography (SiO₂, 100:1:0.5, 100:2:0.5 CH₂Cl₂/MeOH/30% NH₄OH) and obtained as a colorless solid (16.9 mg, 95%): IR (CH₂Cl₂/NaCl) ν_{max} (cm⁻¹): 3327, 3055, 2860, 1745, 1620, 1598, 1500, 1432, 1314, 1214, 1166, 1132, 1048, 886; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (dd, 1H, *J* = 5.5, 8.8 Hz), 7.43 (dd, 1H, *J* = 2.7, 9.0 Hz), 7.30 (m, 1H), 4.42 (m, 1H), 4.28 (d, 1H, *J* = 2.7 Hz), 4.19 (q, 2H, *J* = 7.1 Hz, OCH₂), 3.33 (dd, 1H, *J* = 5.0, 11.4 Hz), 2.94 (m, 1H), 2.26 (m, 1H), 2.17 (m, 1H), 1.91 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 173.2, 161.5 (d, *J* = 249.2 Hz), 135.4 (m), 130.1 (d, *J* = 8.4 Hz), 129.9 (dd, *J* = 7.2, 30.4 Hz), 123.4 (qd, *J* = 2.7, 274.2 Hz), 119.1 (d, 20.8 Hz), 114.3 (dq, *J* = 6.3, 24.9 Hz), 73.1, 61.8 (m), 61.0, 48.2, 38.6, 27.3, 22.4, 14.2; HRMS (MALDI-TOF) *m/z* calcd for C₁₆H₂₀F₄NO₃ [M + H]⁺, 350.1379, found 350.1383.

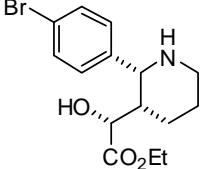
Preparation of *rac*-(*R*)-Ethyl 2-hydroxy-2-((2*R*,3*S*)-2-(pyridin-3-yl)piperidin-3-yl)acetate (22d**).**



Activated zinc powder (16.4 mg, 0.63 mmol) was added to a solution of **18d** (8.9 mg, 0.034 mmol) in acetic acid (0.63 mL) and the mixture was stirred at room temperature until TLC indicated the reaction was complete (approximately 12 hours). The mixture was filtered through diatomaceous earth, the diatomaceous earth was extracted with MeOH, and the combined filtrates were evaporated under reduced pressure. The white solid residue obtained suspended in saturated aqueous NaHCO₃ (5 mL) and CHCl₃ (10 mL). After phase separation, the aqueous layer was further extracted with CHCl₃ (10 mL × 4) and the combined organic layers were dried over MgSO₄ and evaporated under reduced pressure. The oily residue obtained was purified by flash column chromatography (SiO₂, 100:1:0.5, 100:3:0.5, 100:5:0.5 CH₂Cl₂/MeOH/30% NH₄OH) to afford **22d** (7.9 mg, 88%) as a

hygroscopic, colorless solid: IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3600–2800 (br), 2937, 2861, 1746, 1577, 1426, 1368, 1330, 1208, 1139, 1070, 1023, 738; ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, 1H, J = 2.2 Hz), 8.57 (dd, 1H, J = 1.6, 4.9 Hz), 7.84 (m, 1H), 7.33 (m, 1H), 4.22–4.13 (m, 3H), 3.35 (dddd, 1H, J = 4.9, 11.3 Hz), 2.90 (ddd, 1H, J = 3.4, 11.5, 12.7 Hz), 2.30–2.15 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.61 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 149.2, 148.5, 136.6, 133.6, 123.6, 72.9, 63.5, 60.9, 47.6, 40.0, 27.1, 22.4, 14.3; HRMS (MALDI–TOF) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$]⁺, 265.1552, found 265.1574.

Preparation of *rac*-(*R*)-Ethyl 2-((2*R*,3*S*)-2-(4-bromophenyl)piperidin-3-yl)-2-hydroxyacetate (22f).

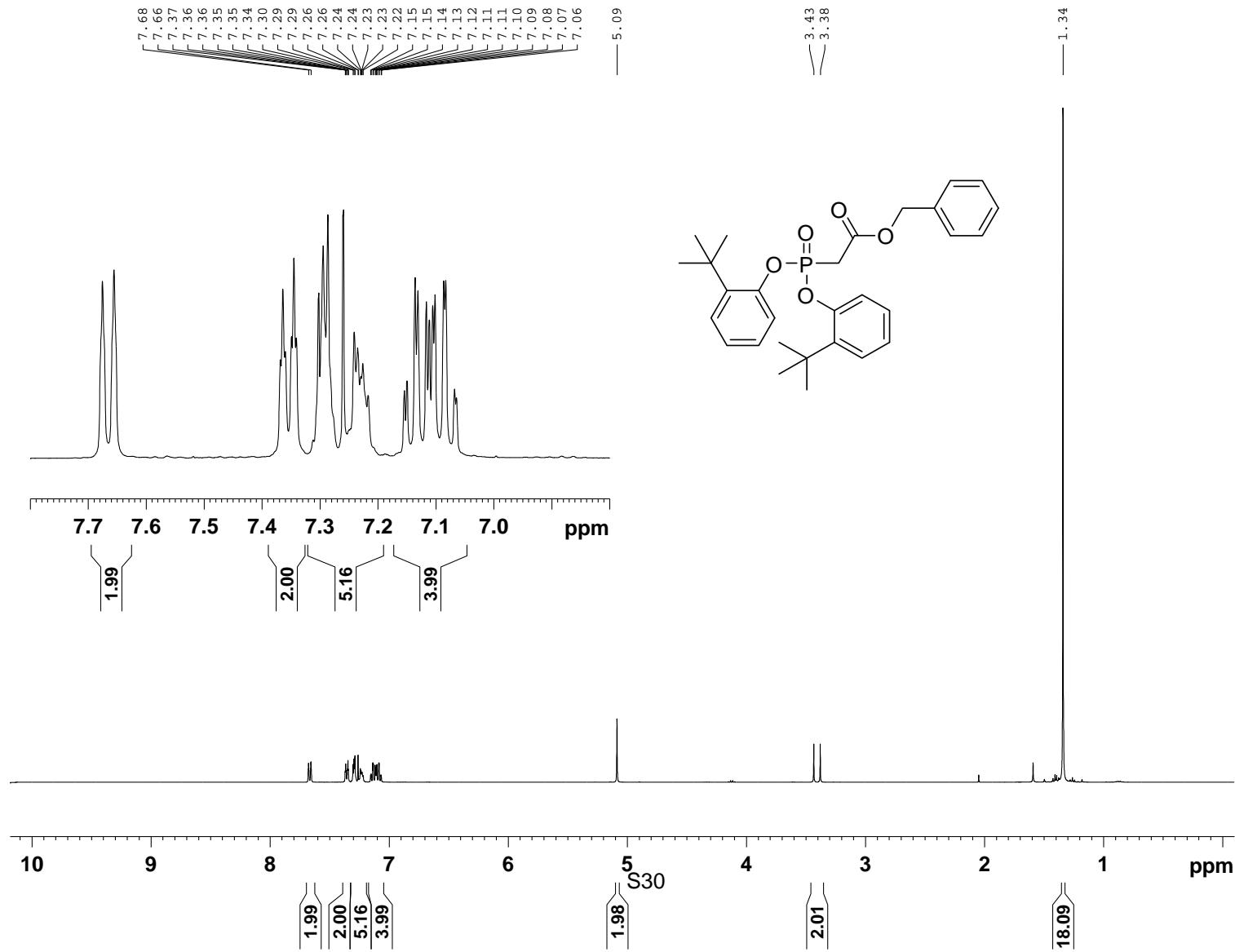
 Activated zinc powder (44 mg, 0.031 mmol) was added to a solution of **18f** (10 mg, 0.031 mmol) in HCl (10%, 0.33 mL) and the mixture was stirred at room temperature until TLC indicated the reaction was complete (1–2 hours). The mixture was diluted with MeOH and filtered through a pad of diatomaceous earth. After extraction of the diatomaceous earth with MeOH, the combined filtrates were evaporated under reduced pressure. The residue was dissolved in minimal MeOH and diluted with sufficient 1:1 $\text{CHCl}_3\text{--NH}_3$ (7 N in MeOH) to induce precipitation of a white solid, which was removed by filtration through a pad of diatomaceous earth. The diatomaceous earth was extracted with CHCl_3 and the combined filtrates were concentrated *in vacuo*. After purification of the residue by flash column chromatography (SiO_2 , 100:1:0.5, 100:2:0.5, 100:3:0.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}/30\%$ NH_4OH), **22f** (9.9 mg, 98%) was obtained as a colorless solid: IR ($\text{CH}_2\text{Cl}_2/\text{NaCl}$) ν_{max} (cm^{-1}): 3600–2700 (br), 3296, 3062, 2933, 2861, 1746, 1488, 1448, 1366, 1274, 1249, 1206, 1139, 103, 1012, 964, 885, 860, 828, 802; ^1H NMR (400 MHz, CDCl_3) δ 7.51 (m, 2H), 7.30 (m, 2H), 4.22–4.13 (m, 3H), 4.09 (d, 1H, J = 3.1 Hz), 3.33 (ddt, 1H, J = 4.9, 11.3 Hz), 2.89 (ddd, 1H, J = 3.3, 11.5, 12.8 Hz), 2.21 (m, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 1.75 (m, 1H), 1.59 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 149.2, 148.5, 136.6, 133.6, 123.6, 72.9, 63.5, 60.9, 47.6, 40.0, 27.1, 22.4, 14.3; HRMS (MALDI–TOF) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$]⁺, 265.1552, found 265.1574.

3H , $J = 7.1$ Hz, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 173.3, 140.0, 131.9, 127.9, 121.5, 73.0, 65.1, 60.8, 47.5, 40.1, 27.1, 22.4, 14.3; HRMS (MALDI–TOF) m/z calcd for $\text{C}_{15}\text{H}_{21}^{79}\text{BrNO}_3$ [M + H] $^+$, 342.0705, found 342.0706.

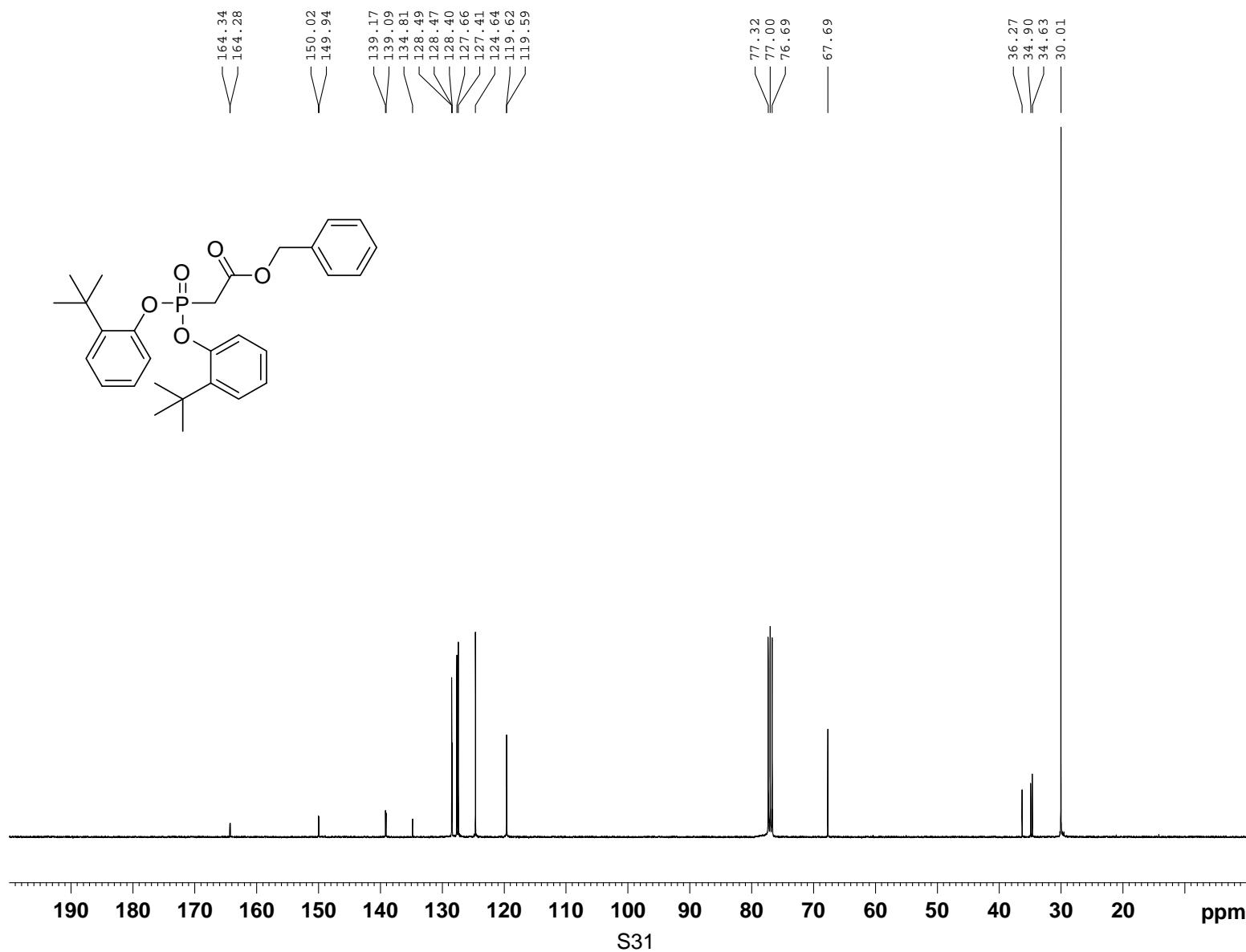
Spectral Data for New Compounds

Benzyl 2-(bis(2-tert-butylphenoxy)phosphoryl)acetate

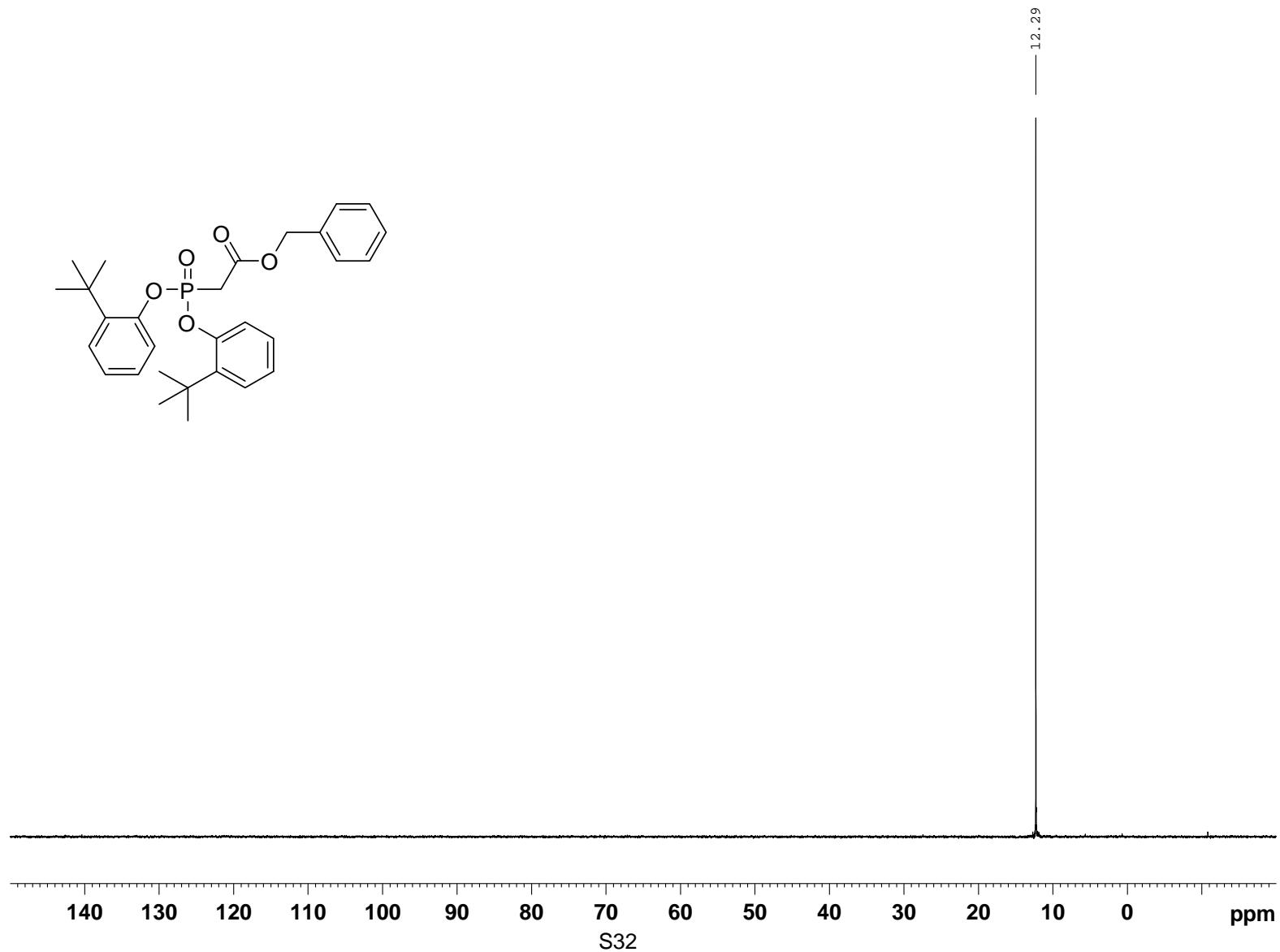
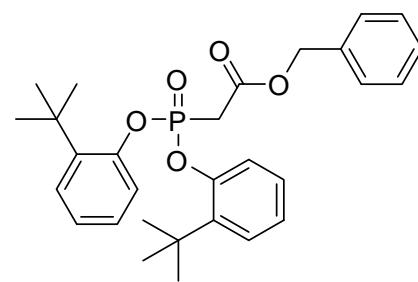
^1H NMR (400 MHz, CDCl_3)



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

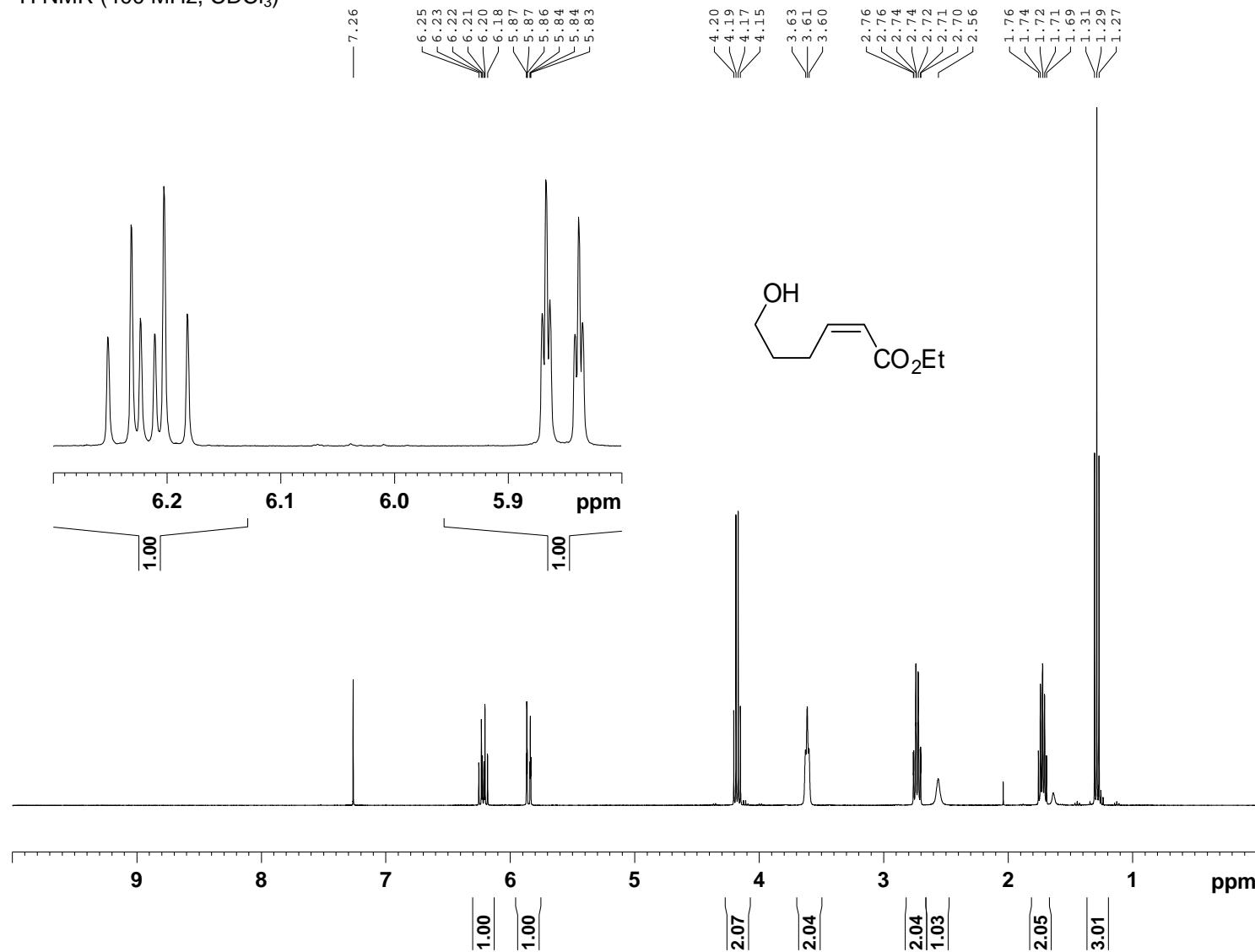


^{31}P NMR (162 MHz, CDCl_3)

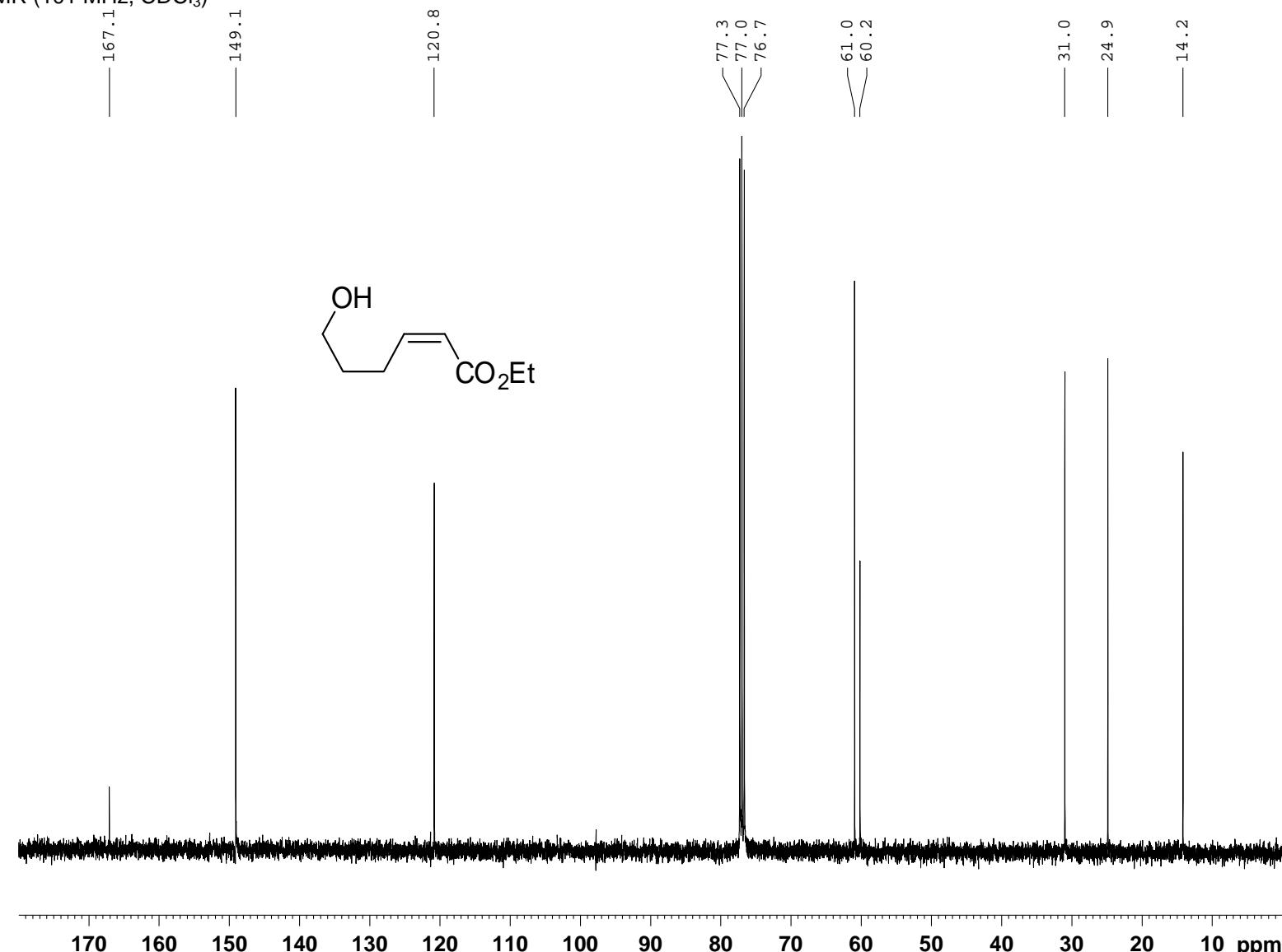


(Z)-Ethyl 6-hydroxy-2-hexenoate (*cis*-5a):

¹H NMR (400 MHz, CDCl₃)

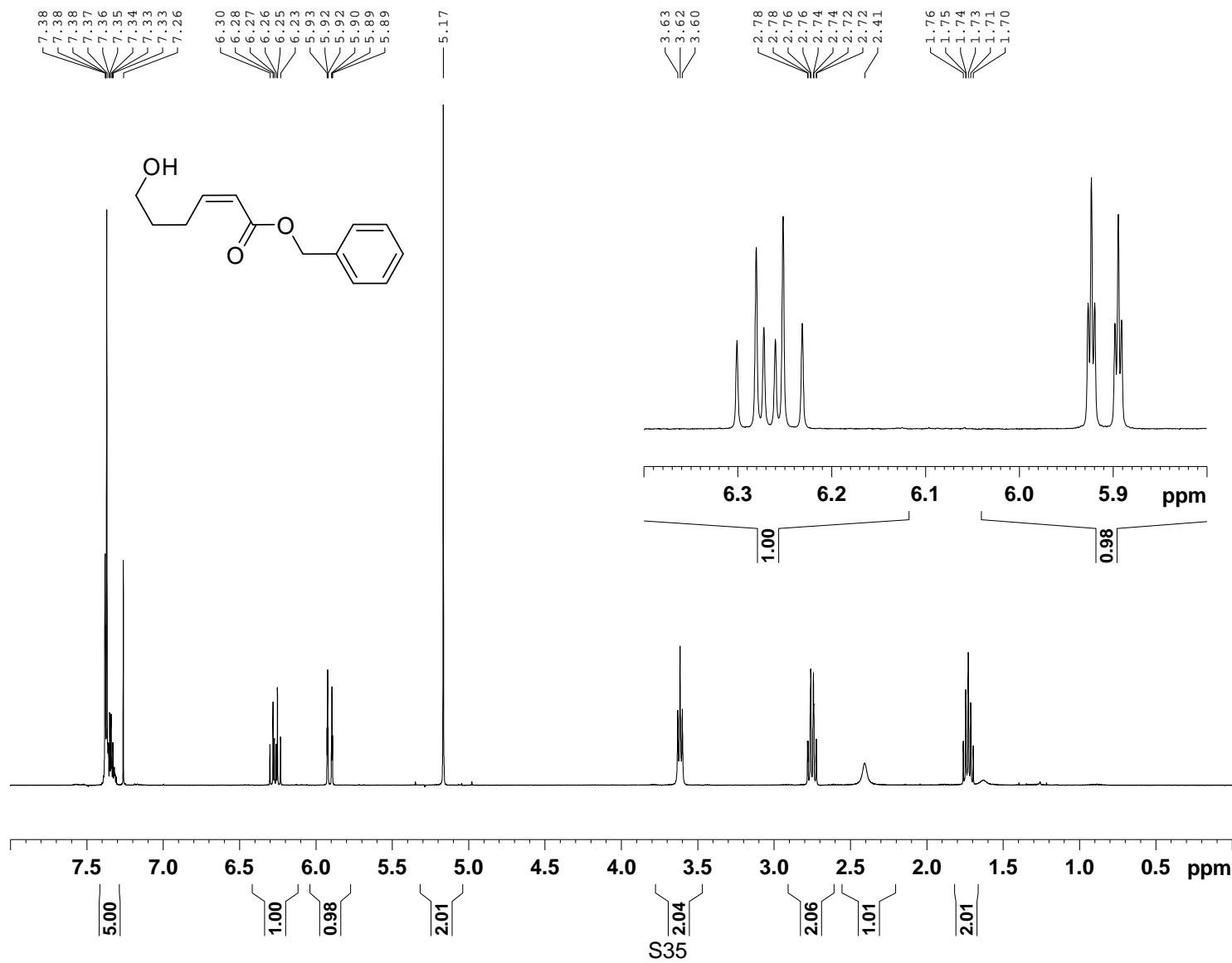


¹³C NMR (101 MHz, CDCl₃)

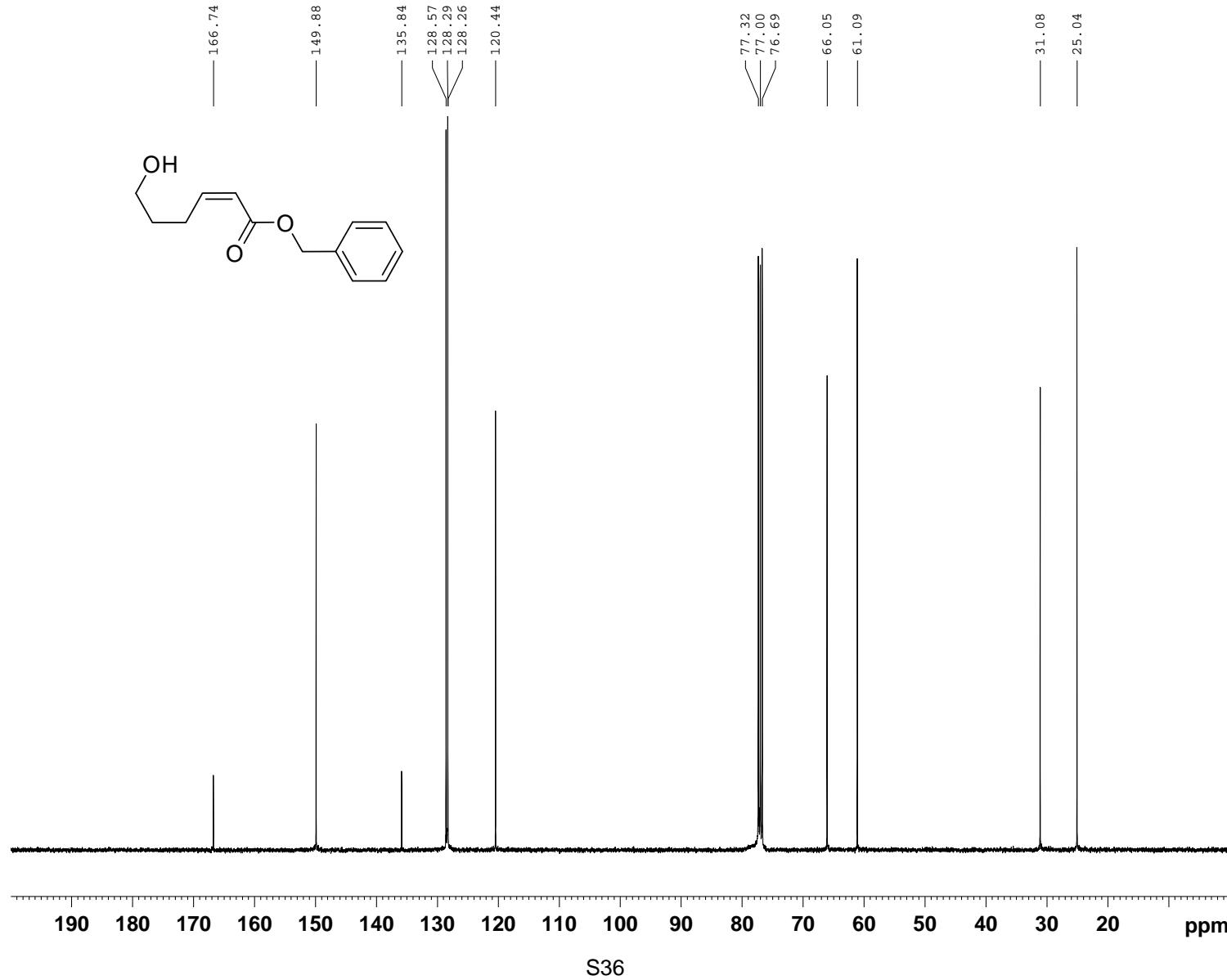
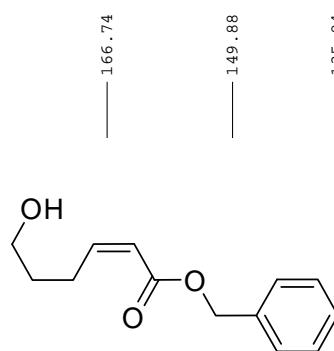


(Z)-Benzyl 6-hydroxy-2-hexenoate (*cis*-5b):

¹H NMR (400 MHz, CDCl₃)

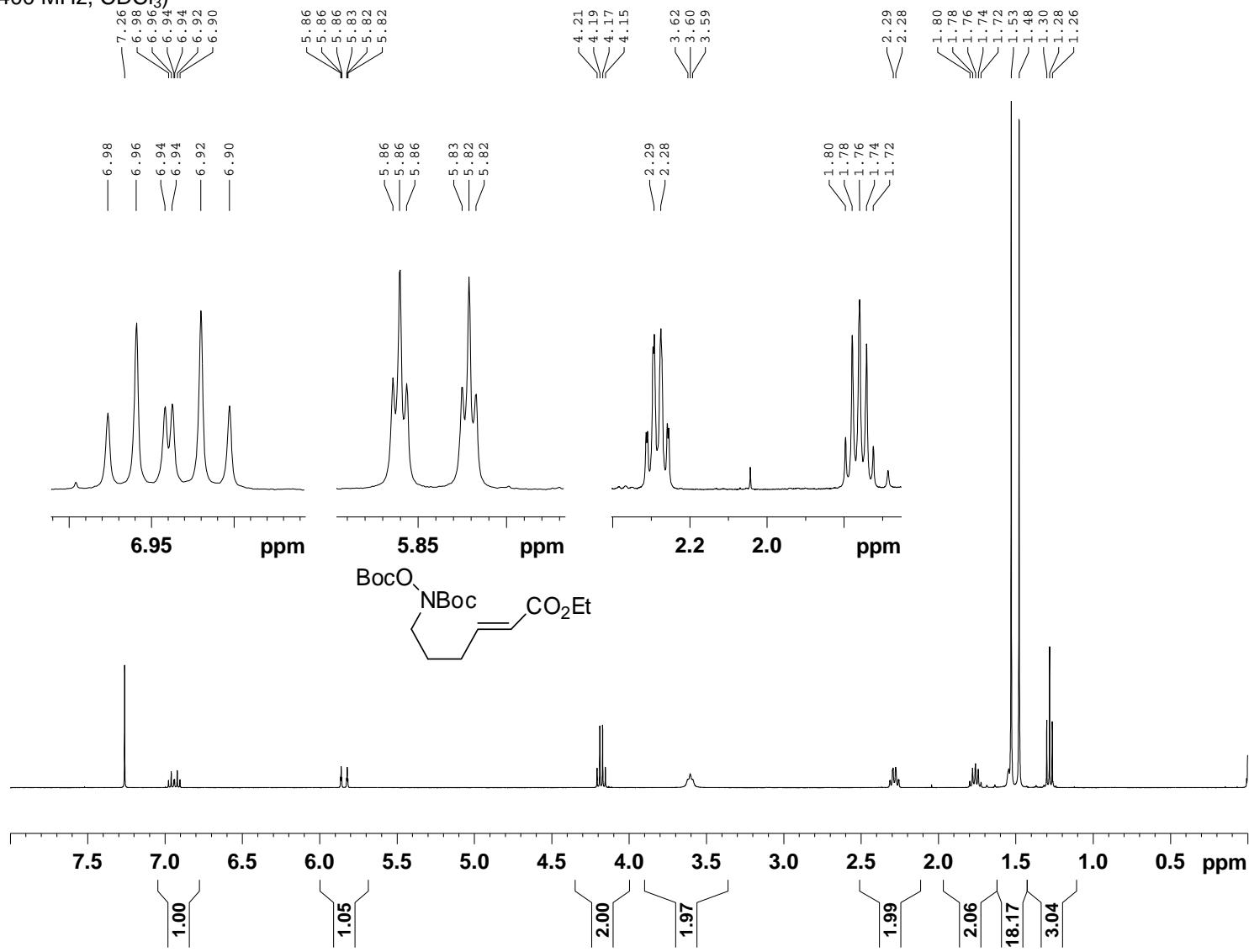


¹³C NMR (101 MHz, CDCl₃)



(E)-Ethyl 6-(tert-butoxycarbonyl(tert-butoxycarbonyloxy)amino)hex-2-enoate (*trans*-6a):

^1H NMR (400 MHz, CDCl_3)



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

— 166.5
— 154.8
— 152.3
— 147.8

— 122.0

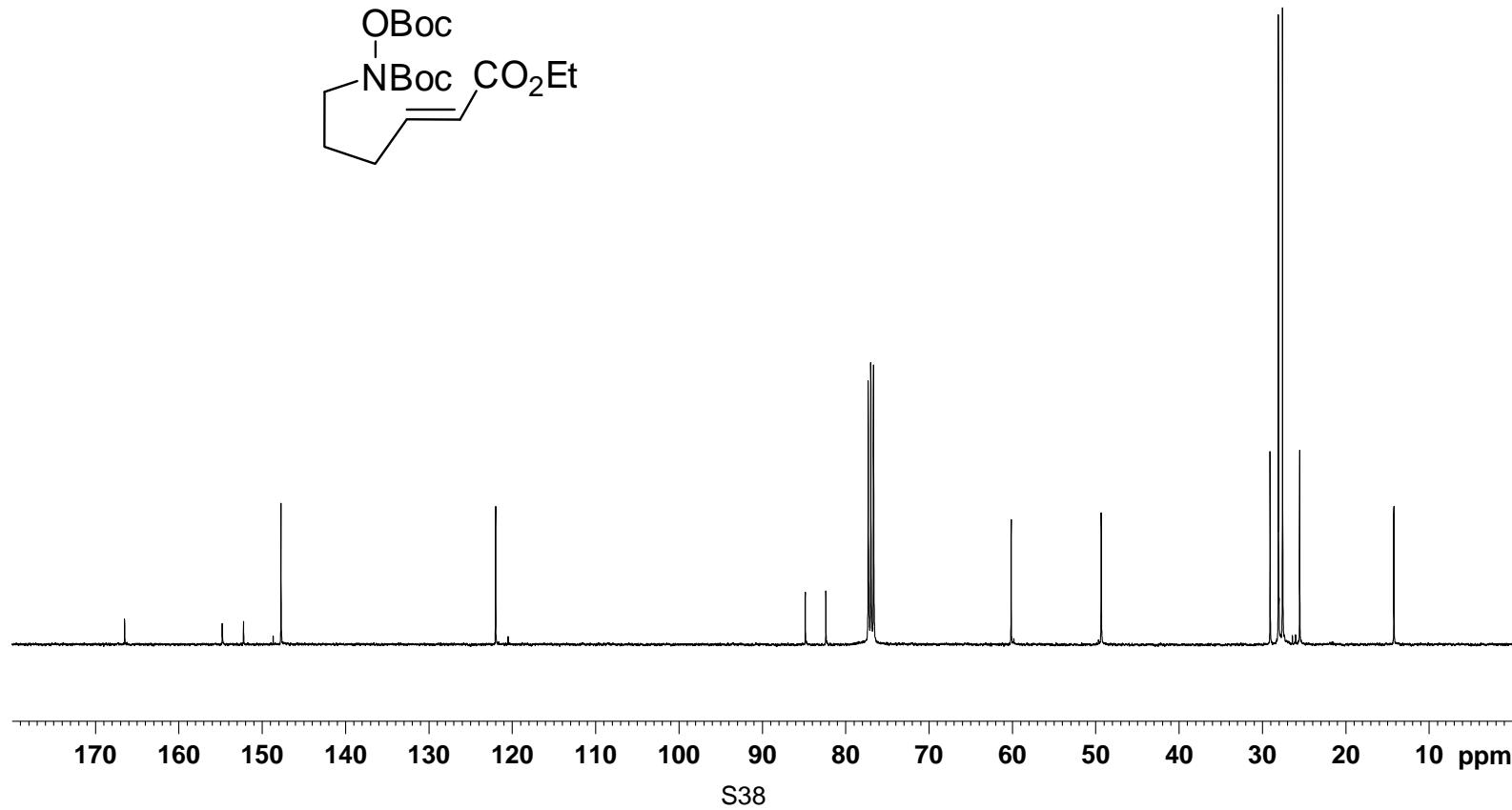
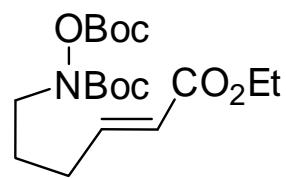
— 84.9
— 82.4
— 77.3
— 77.0
— 76.7

— 60.2

— 49.4

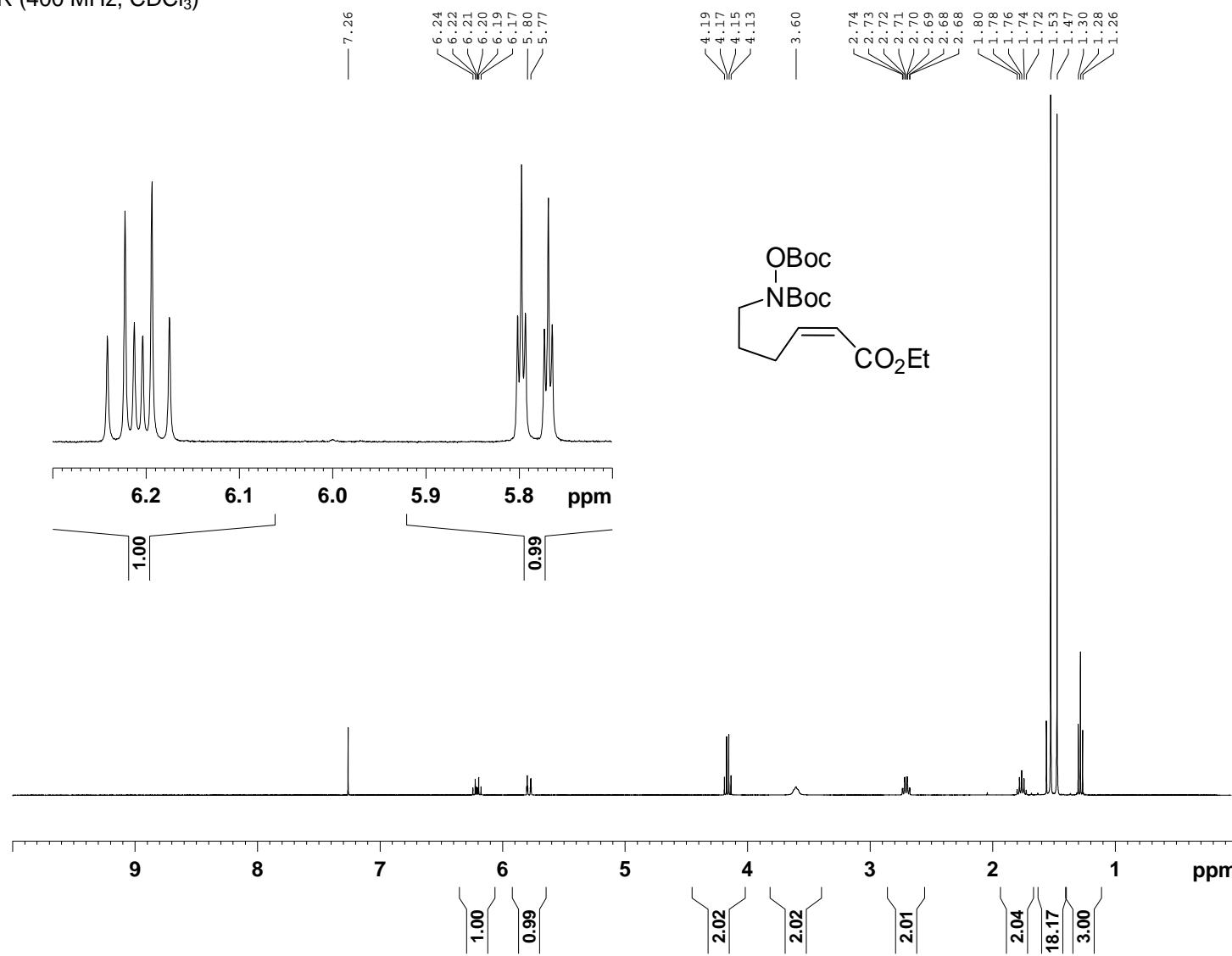
— 29.1
— 28.1
— 27.6
— 25.6

— 14.2



(Z)-Ethyl 6-(tert-butoxycarbonyl(tert-butoxycarbonyloxy)amino)hex-2-enoate (*cis*-6a):

¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)

— 166.3
— 154.8
— 152.3
— 148.7

— 120.5

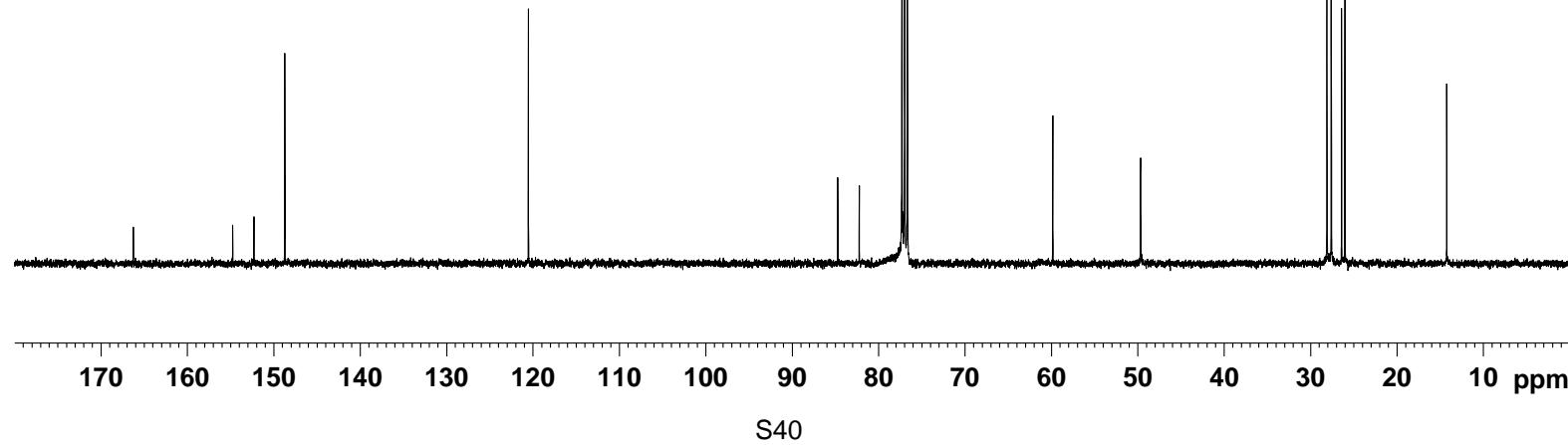
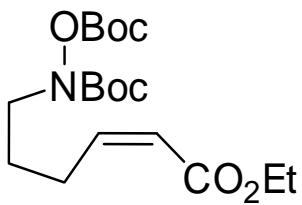
— 84.8
— 82.3
— 77.3
— 77.0
— 76.7

— 59.9

— 49.7

— 28.1
— 27.6
— 26.4
— 26.1

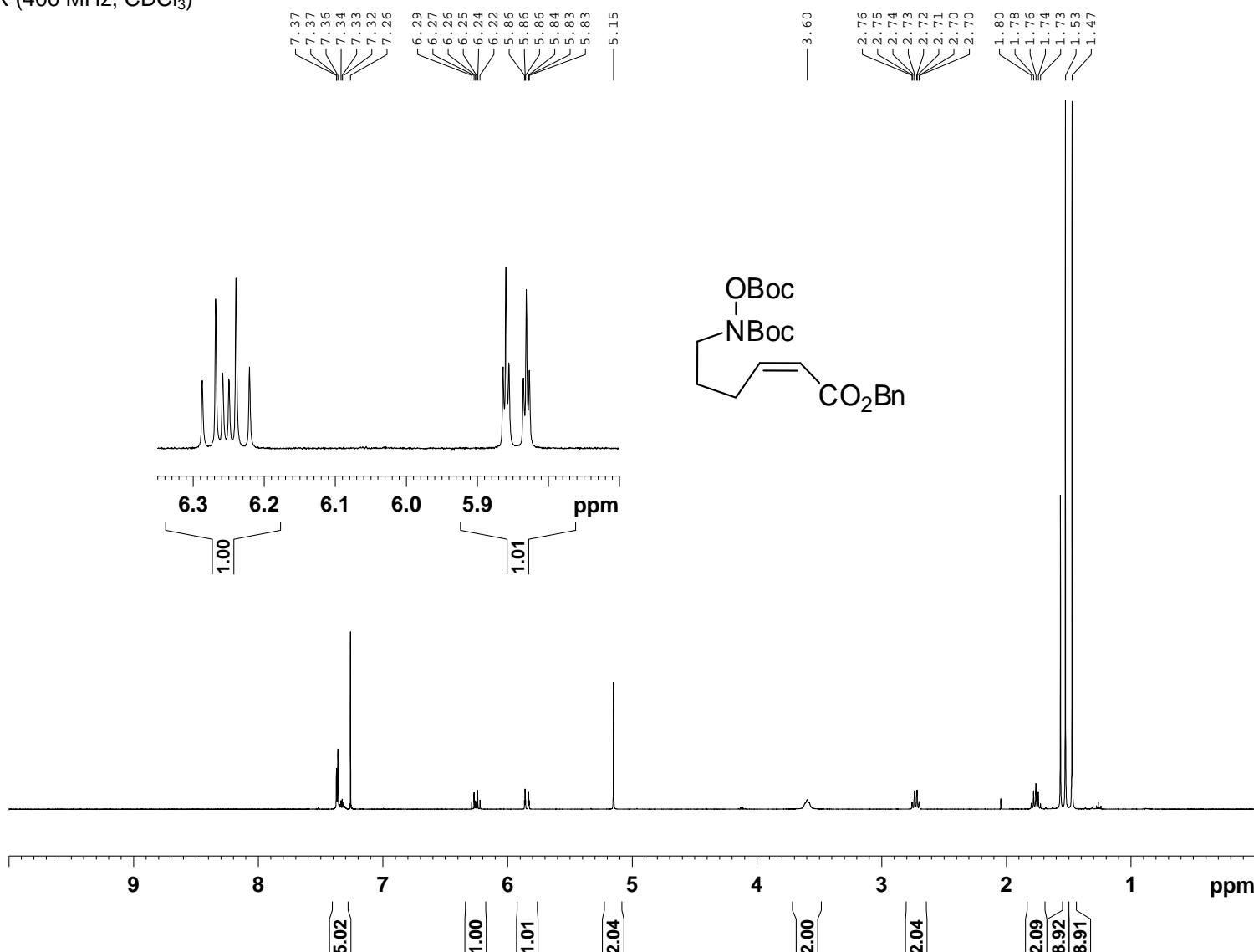
— 14.3



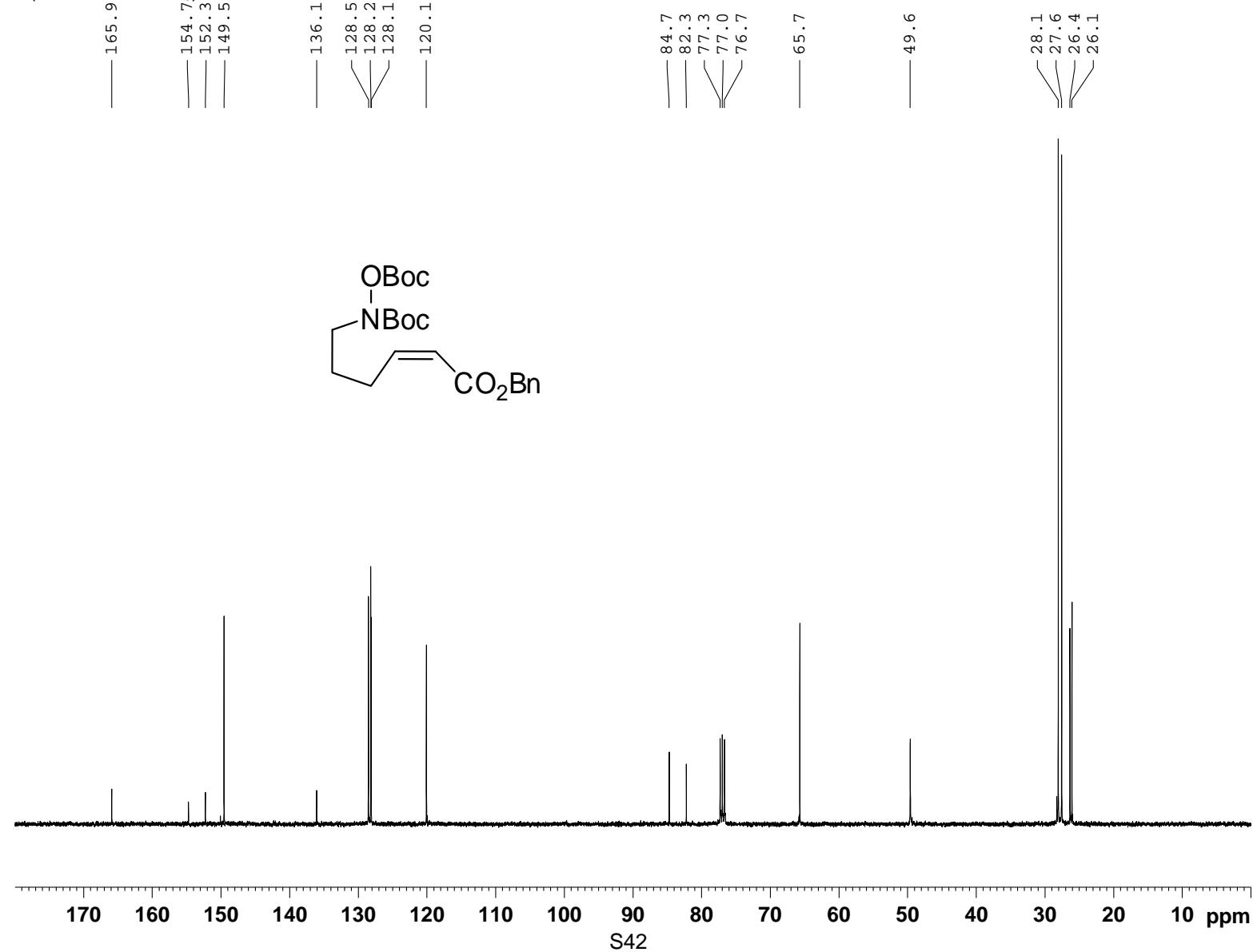
S40

(Z)-Benzyl 6-(tert-butoxycarbonyl(tert-butoxycarbonyloxy)amino)hex-2-enoate (*cis*-6b):

^1H NMR (400 MHz, CDCl_3)

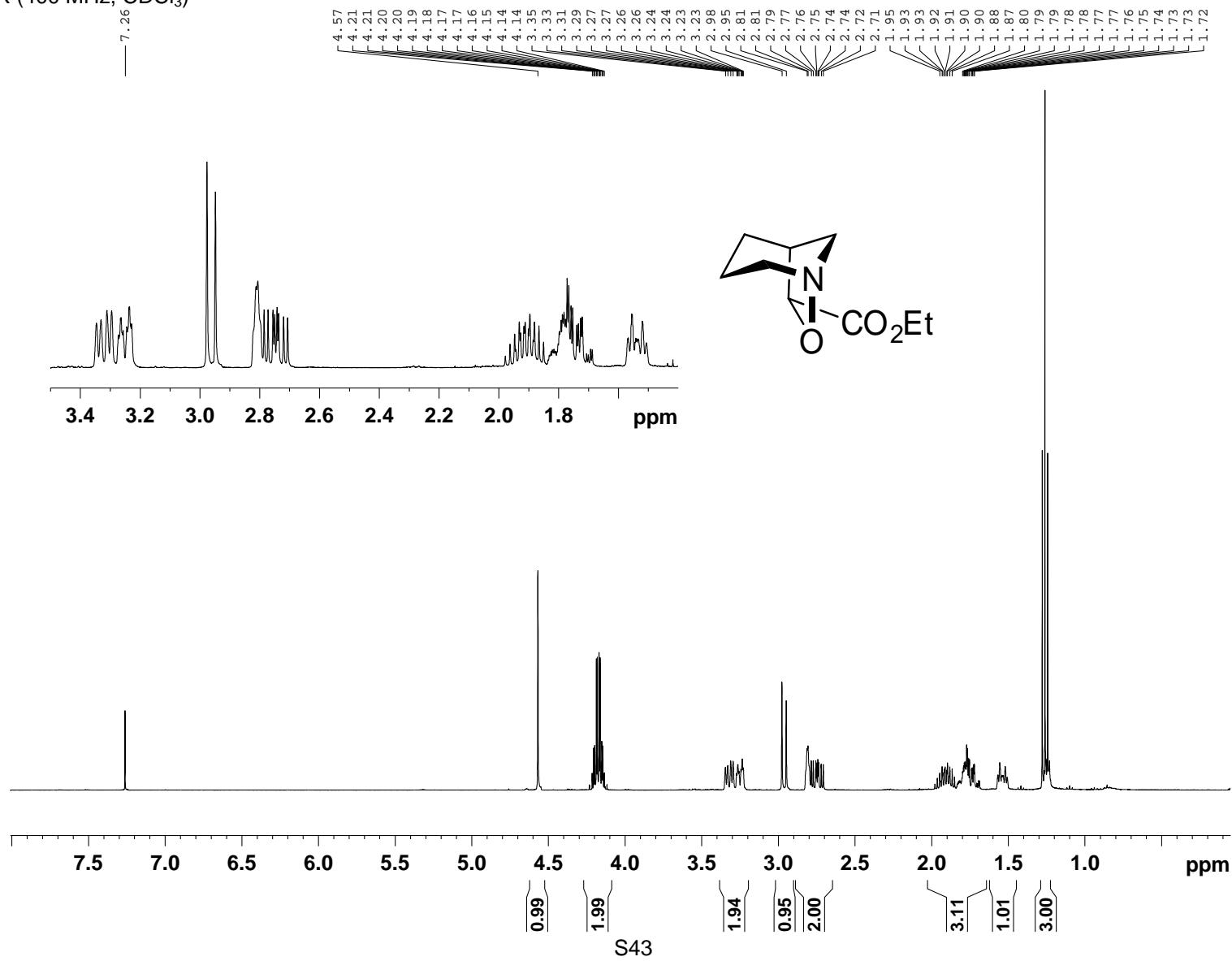


^{13}C NMR (101 MHz, CDCl_3)

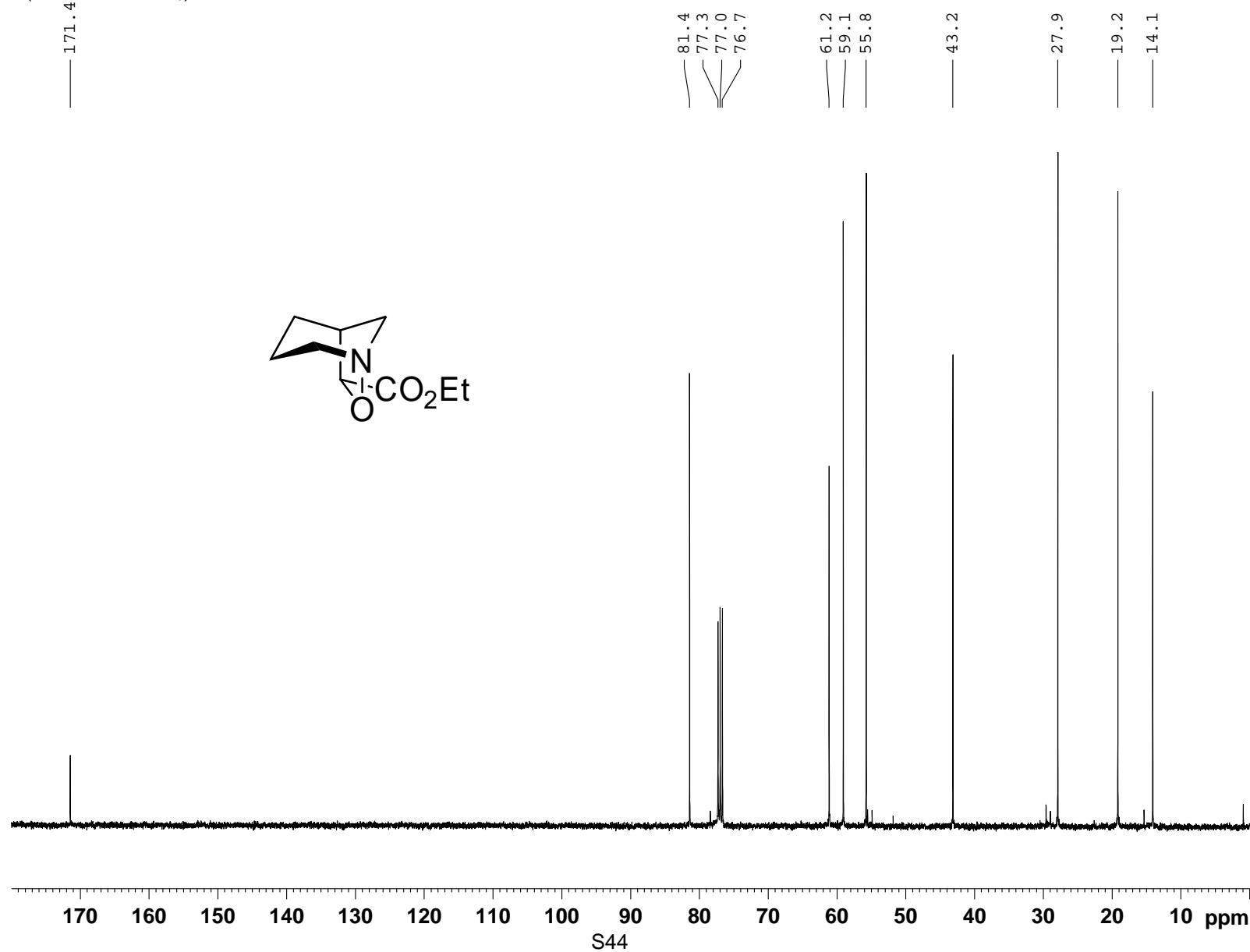


rac-(5*R*,6*R*)-Ethyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*trans*-3a):

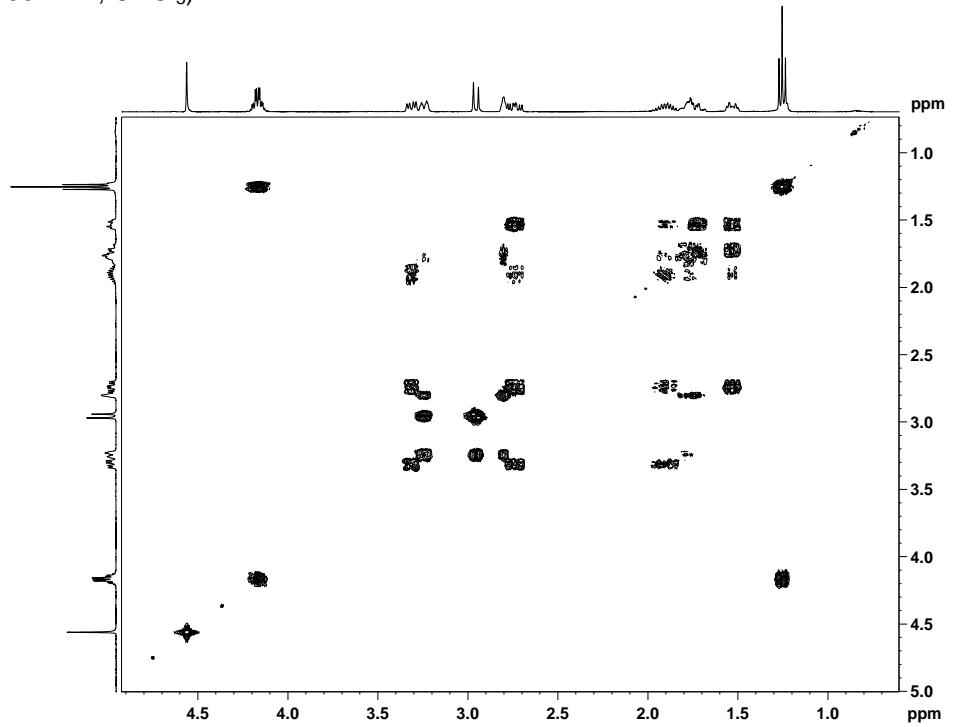
¹H NMR (400 MHz, CDCl₃)



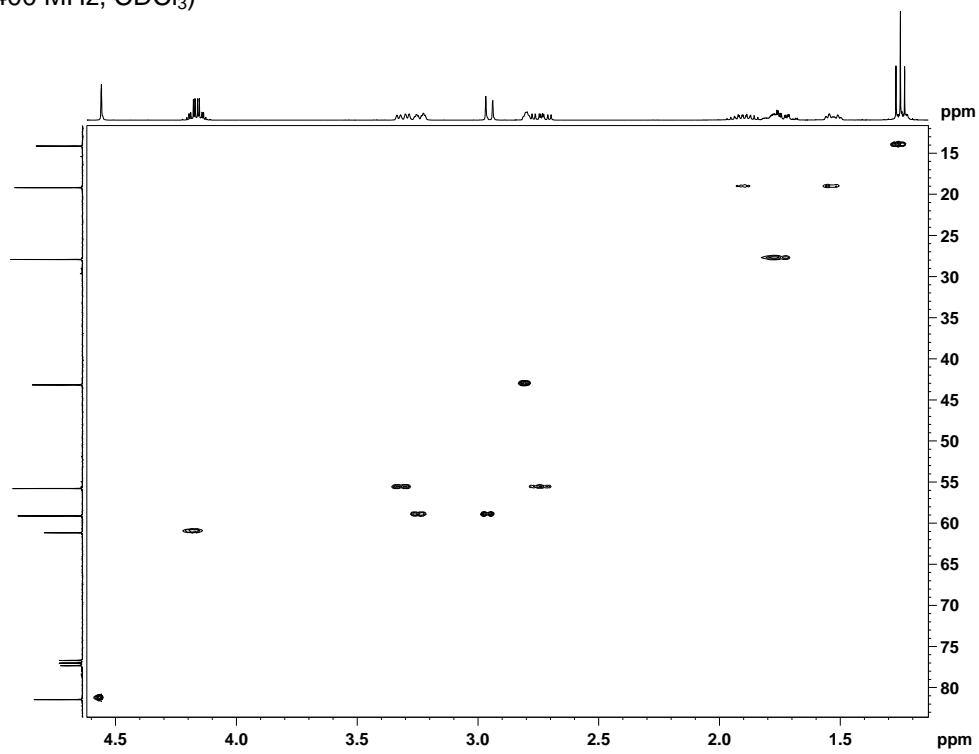
^{13}C NMR (101 MHz, CDCl_3)



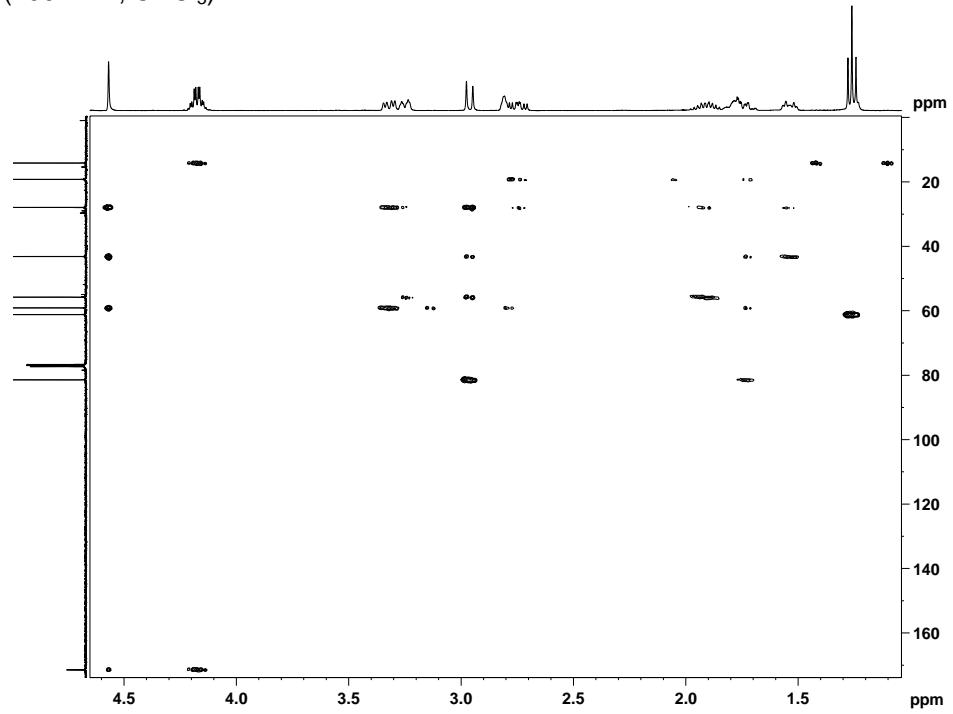
COSY (400 MHz, CDCl_3)



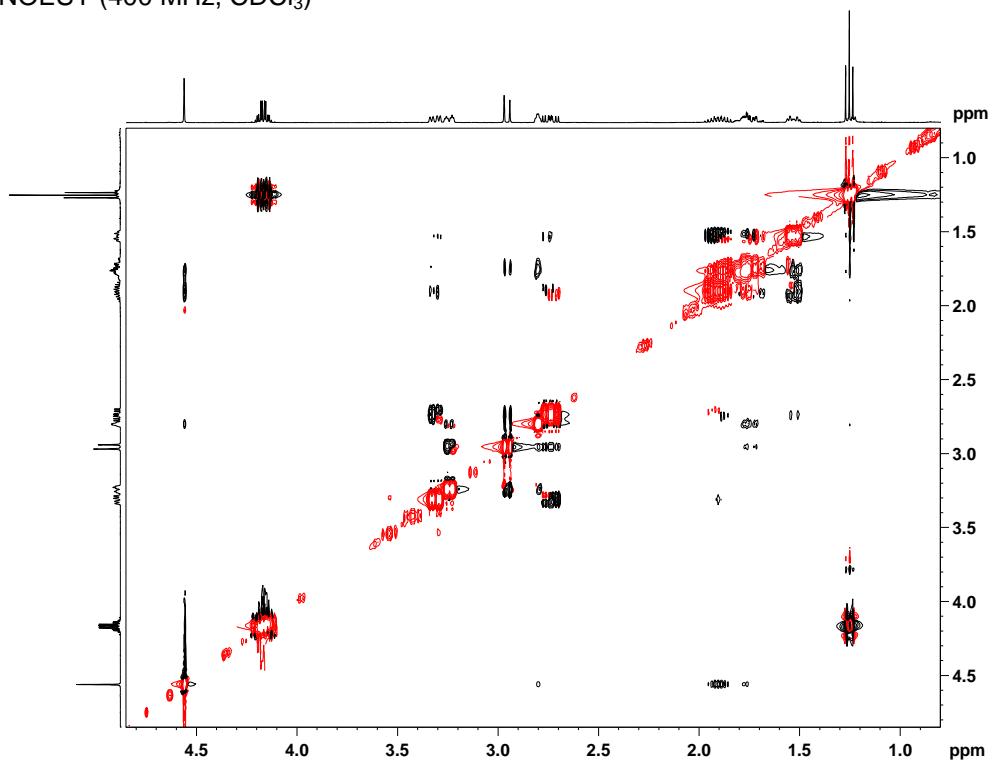
HSQC (400 MHz, CDCl_3)



HMBC (400 MHz, CDCl_3)

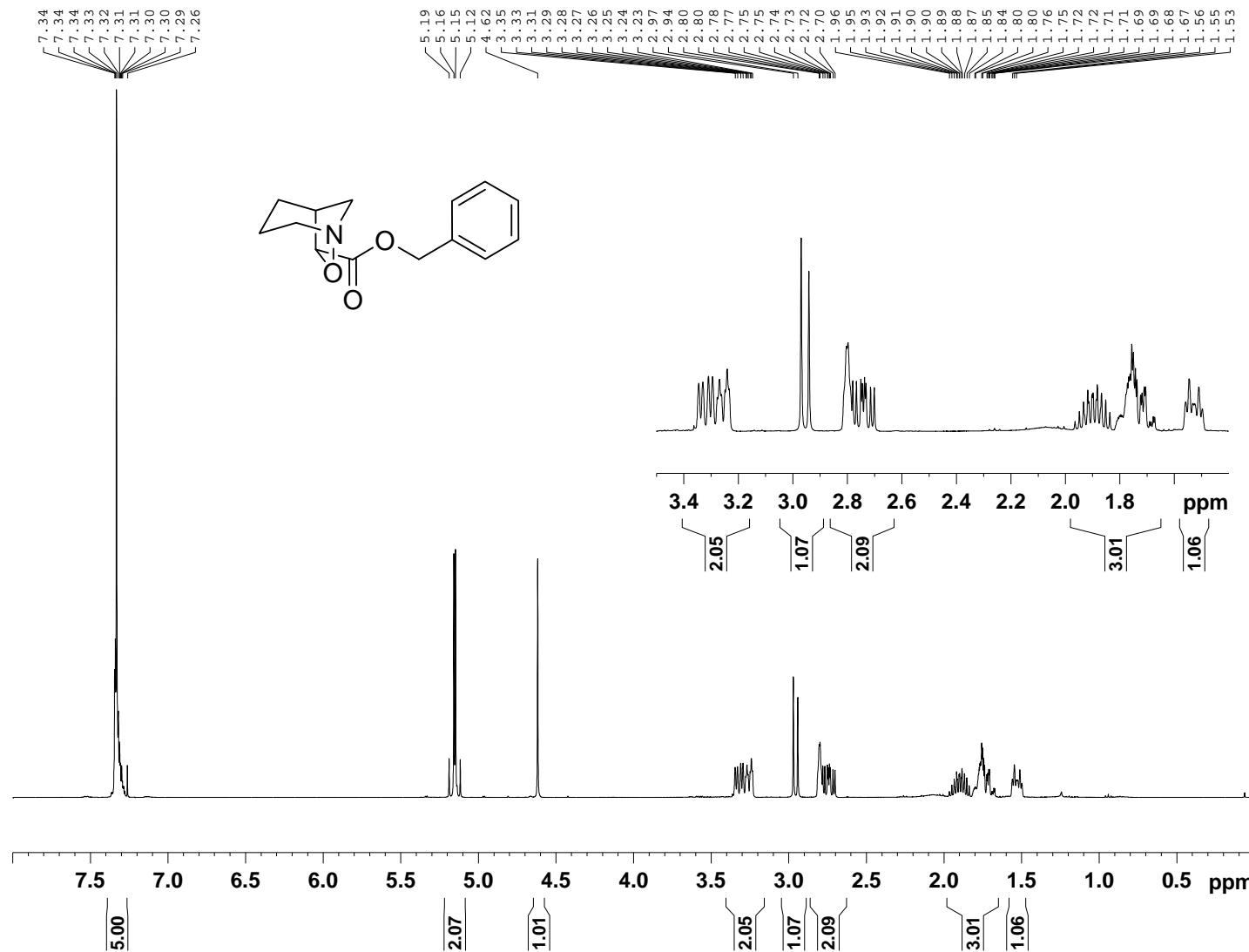


2D NOESY (400 MHz, CDCl_3)

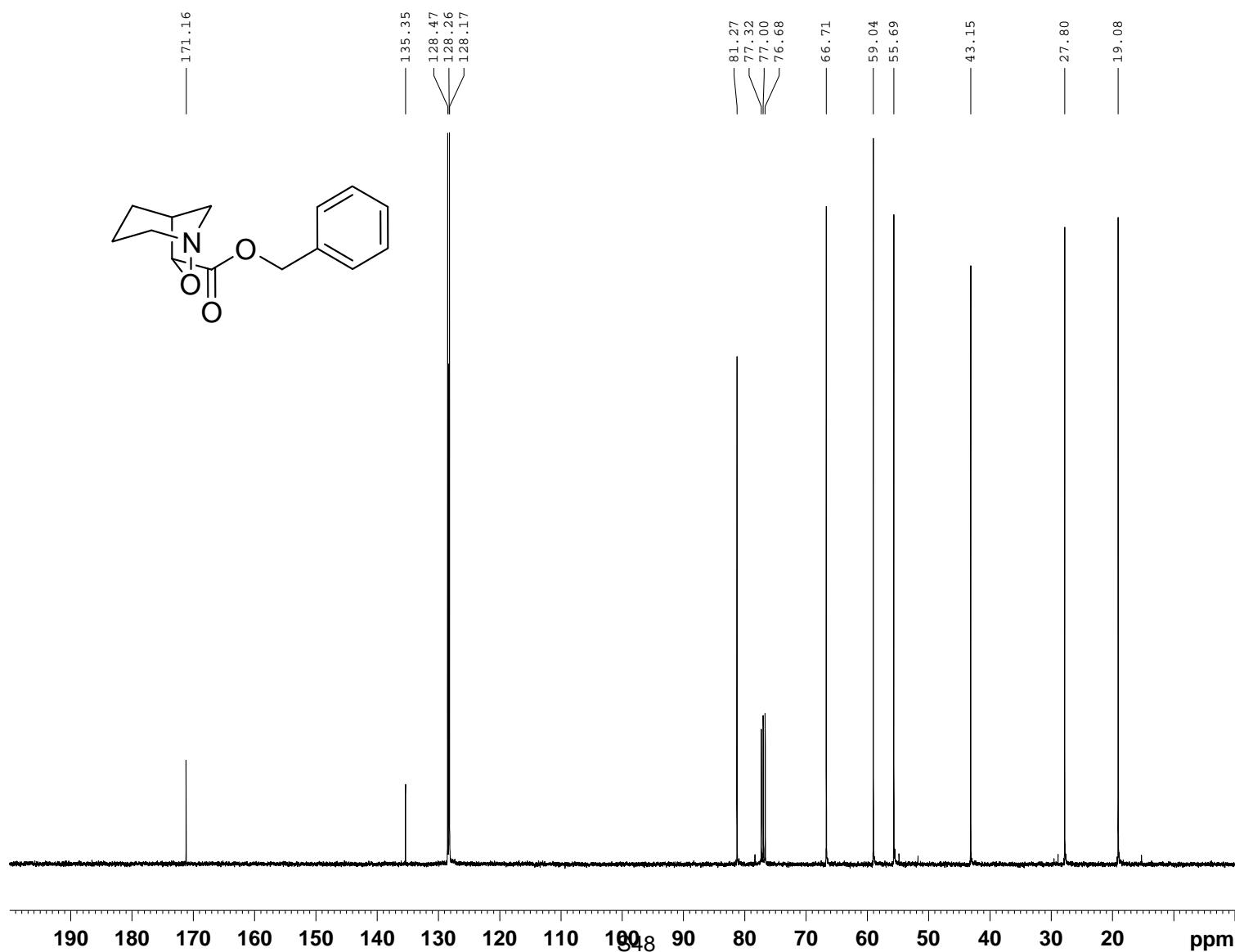


***rac*-(5*R*,6*R*)-Benzyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*trans*-3b):**

¹H NMR (400 MHz, CDCl₃)

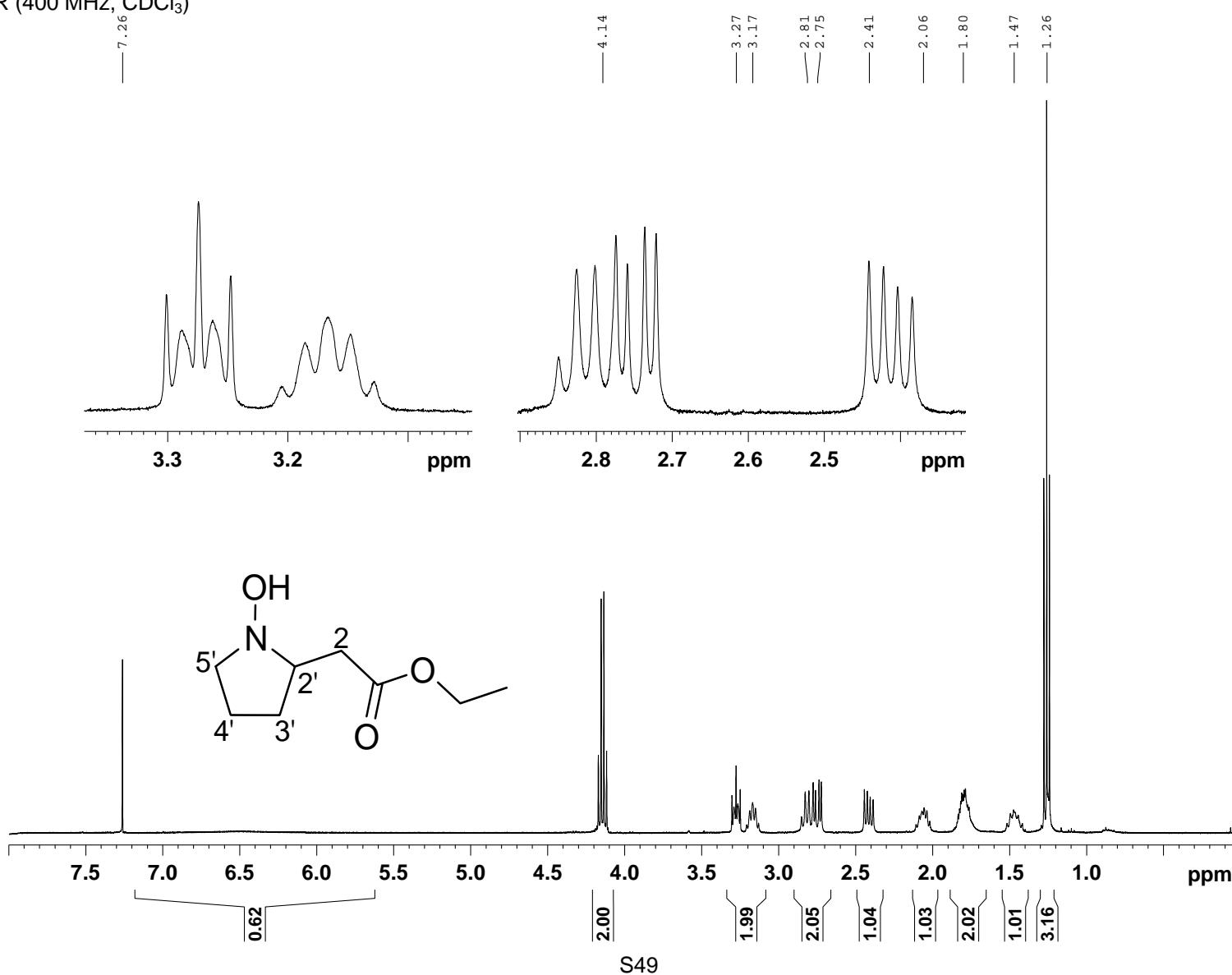


¹³C NMR (101 MHz, CDCl₃)

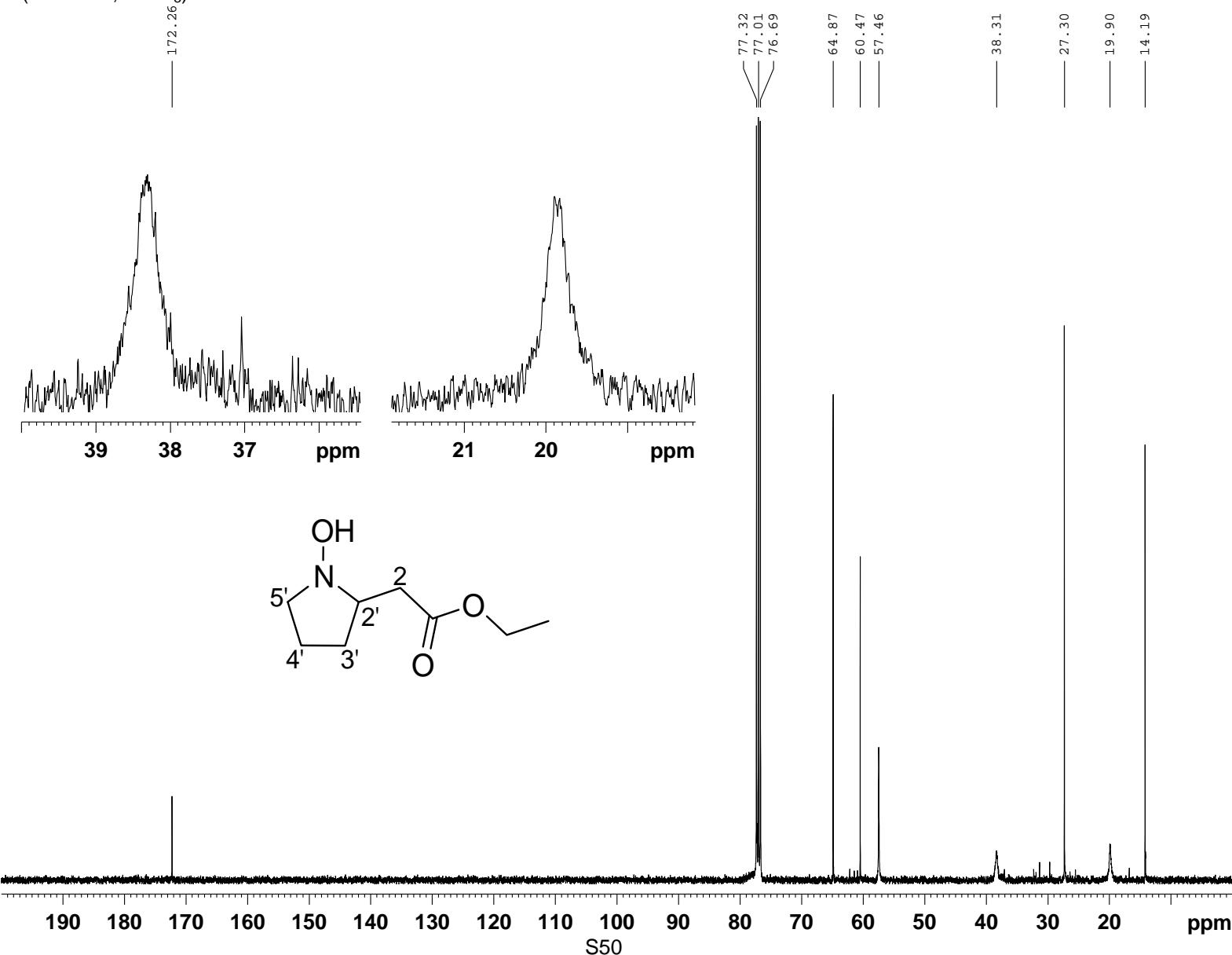


Ethyl 2-(1-hydroxypyrrolidin-2-yl)acetate (7a):

¹H NMR (400 MHz, CDCl₃)

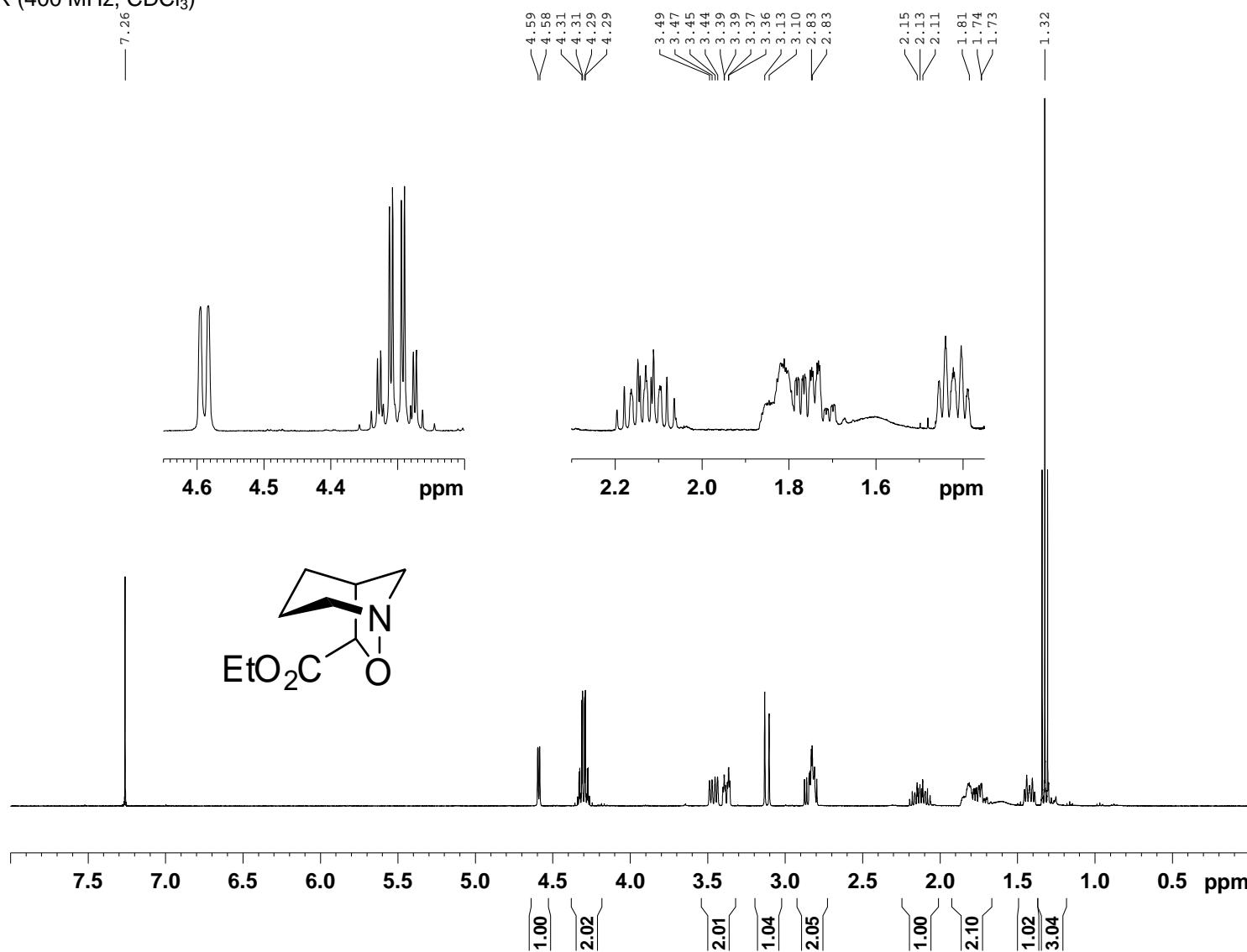


^{13}C NMR (101 MHz, CDCl_3)

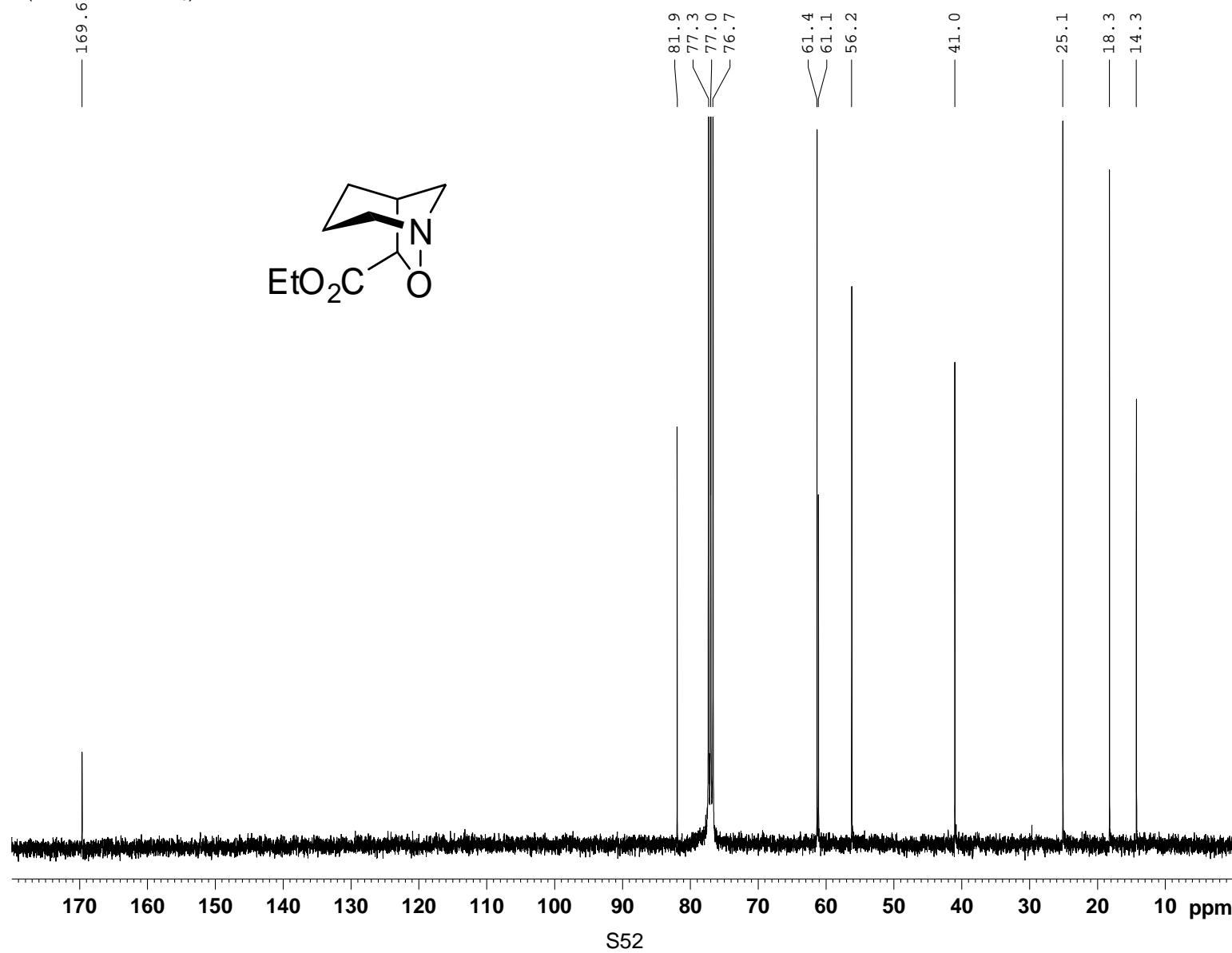


rac-(5*R*,6*S*)-Ethyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*cis*-3a):

^1H NMR (400 MHz, CDCl_3)

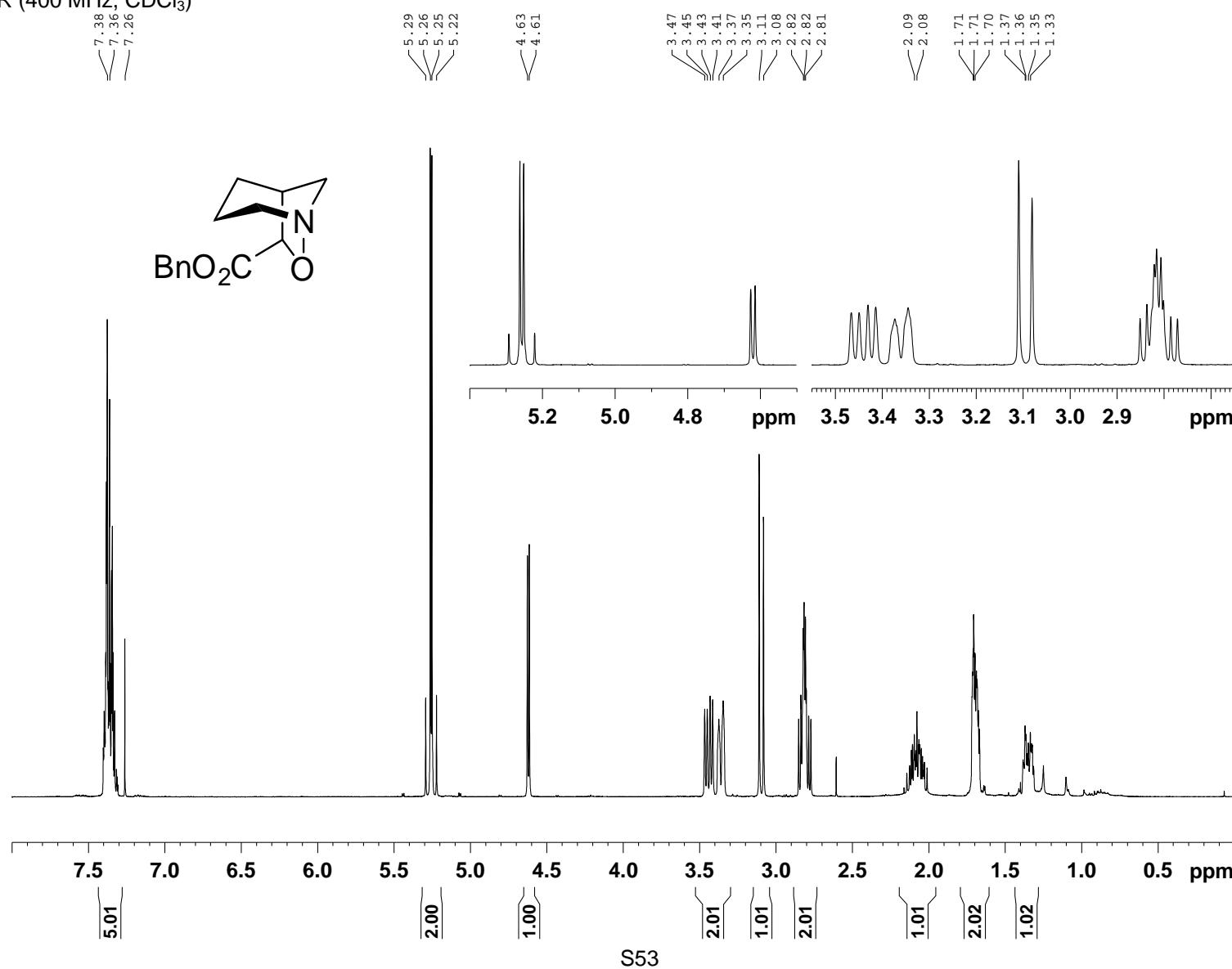


¹³C NMR (101 MHz, CDCl₃)

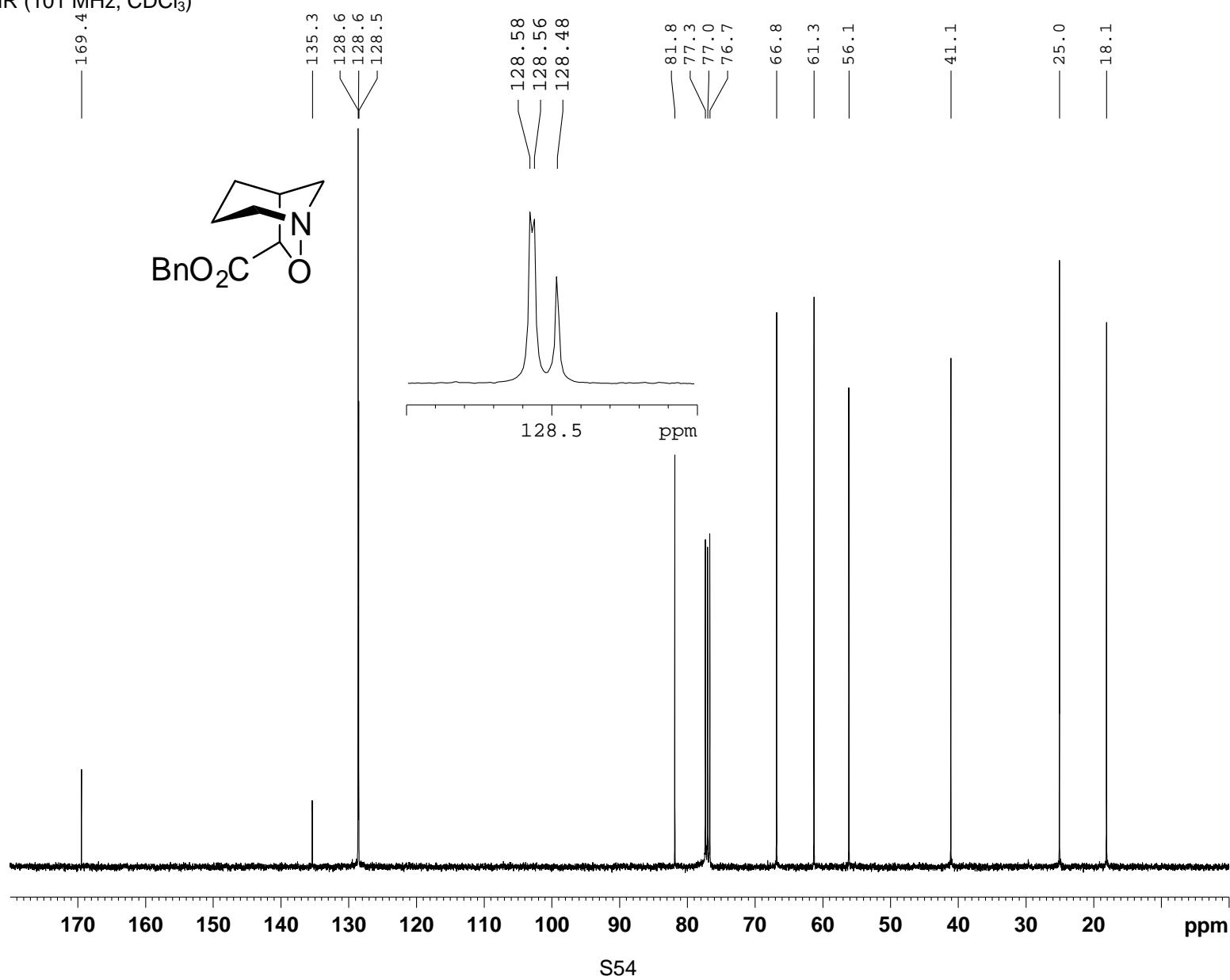


***rac*-(5*R*,6*S*)-Benzyl 7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*cis*-3b):**

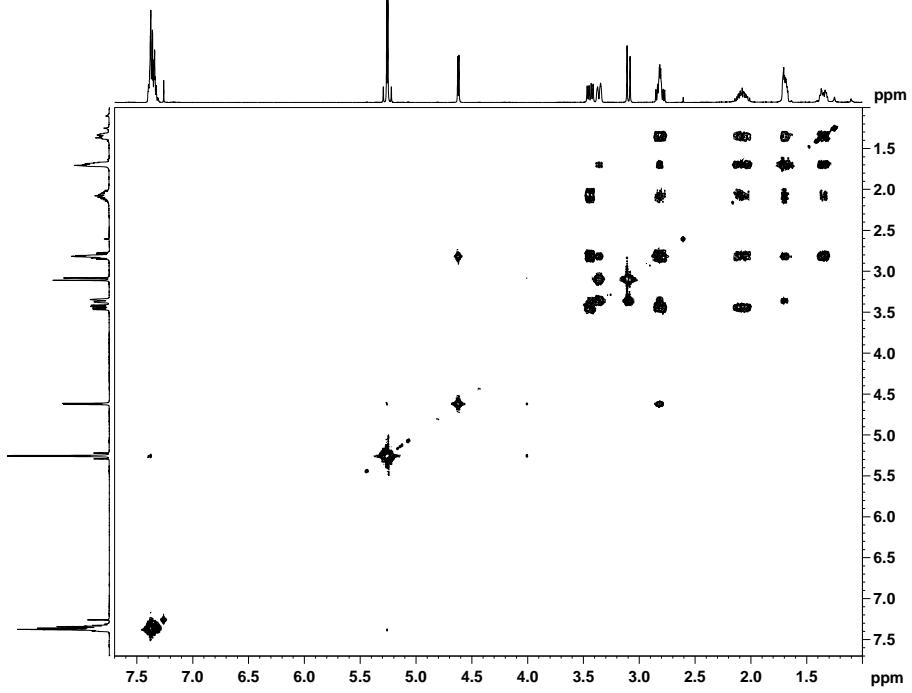
¹H NMR (400 MHz, CDCl₃)



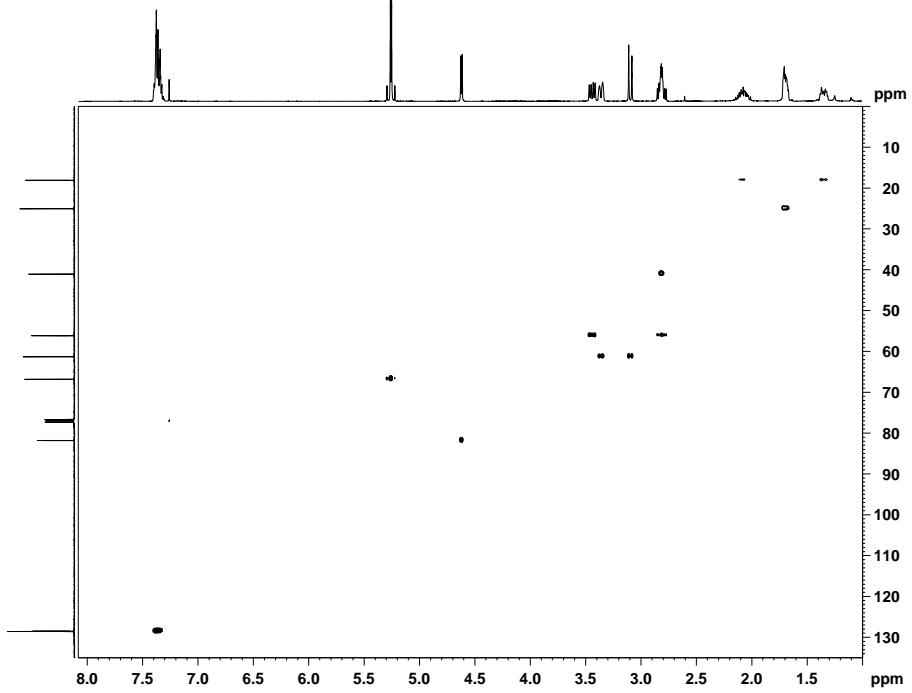
¹³C NMR (101 MHz, CDCl₃)



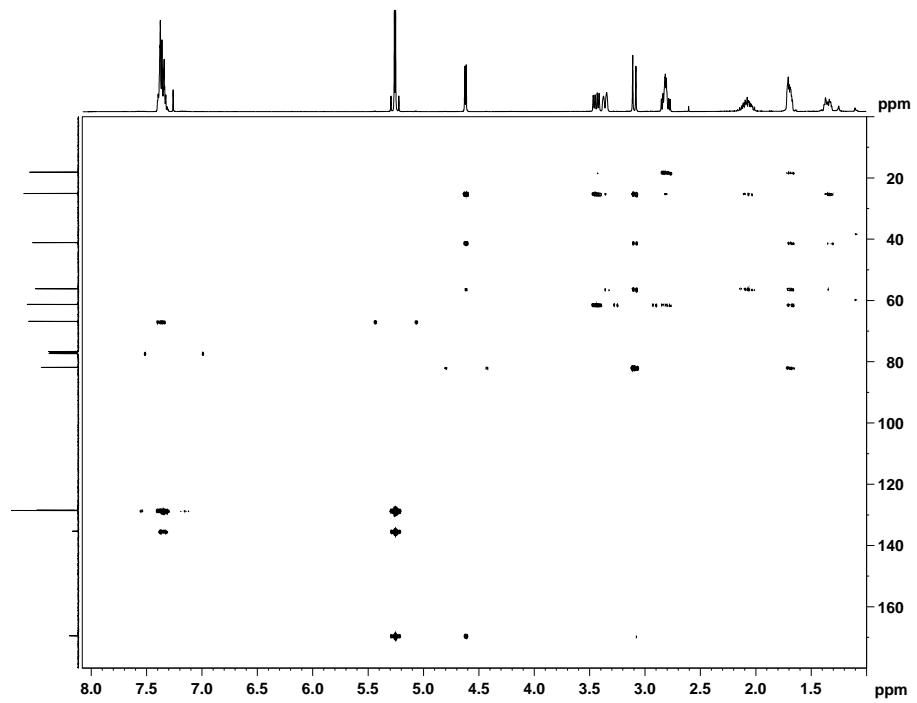
COSY (400 MHz, CDCl_3)



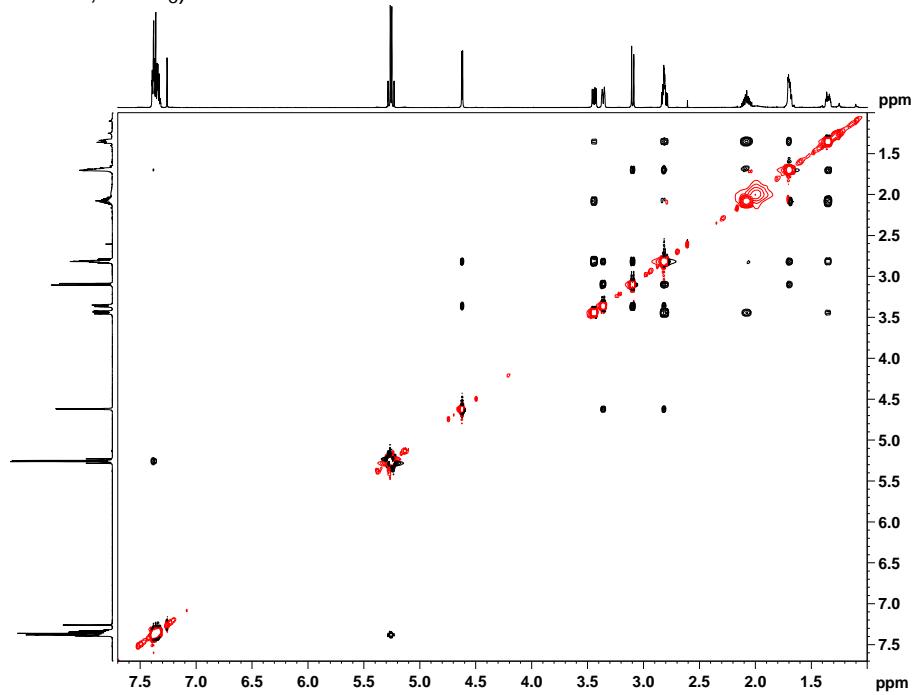
HSQC (400 MHz, CDCl_3)



HMBC (400 MHz, CDCl_3)

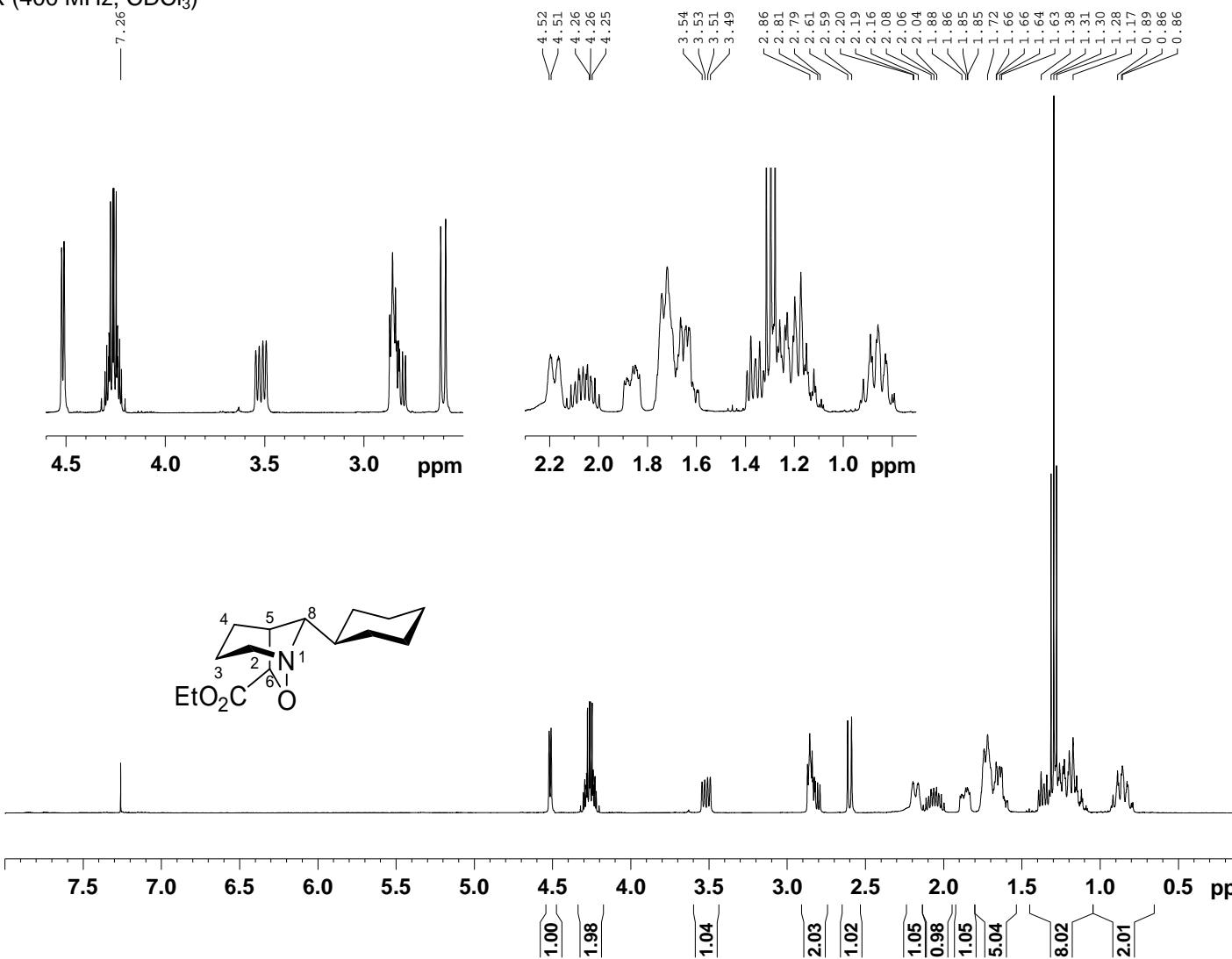


2D NOESY (600 MHz, CDCl_3)

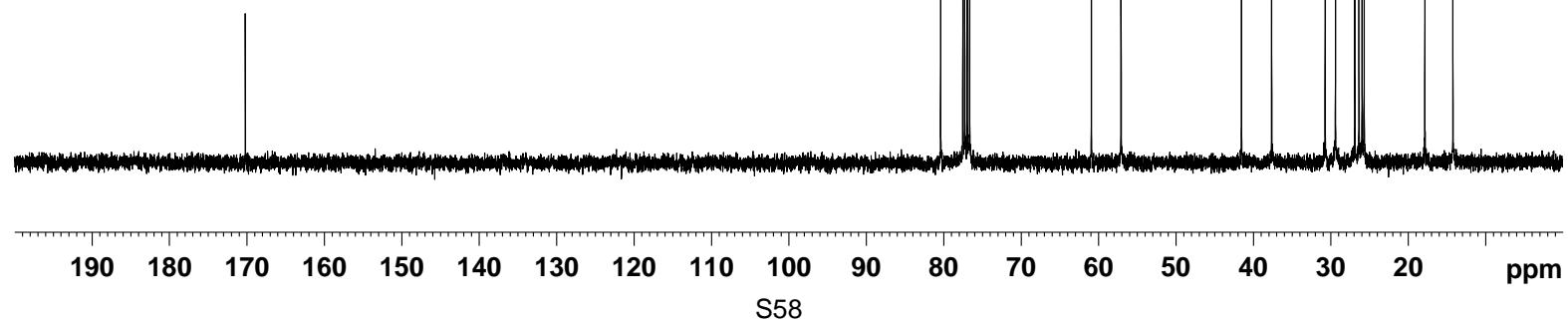
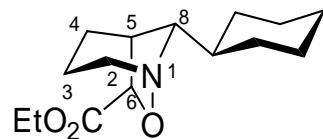
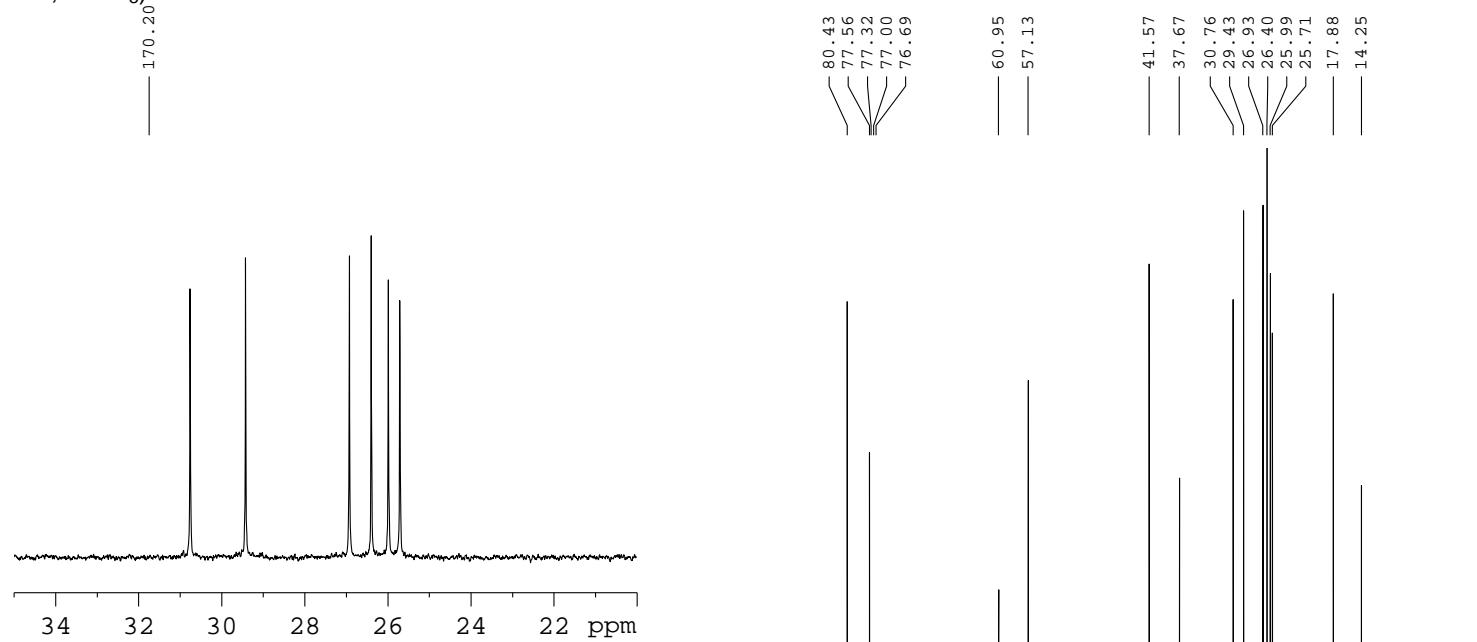


rac-(5*S*,6*R*,8*S*)-ethyl 8-cyclohexyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18a):

¹H NMR (400 MHz, CDCl₃)

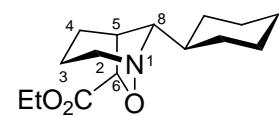
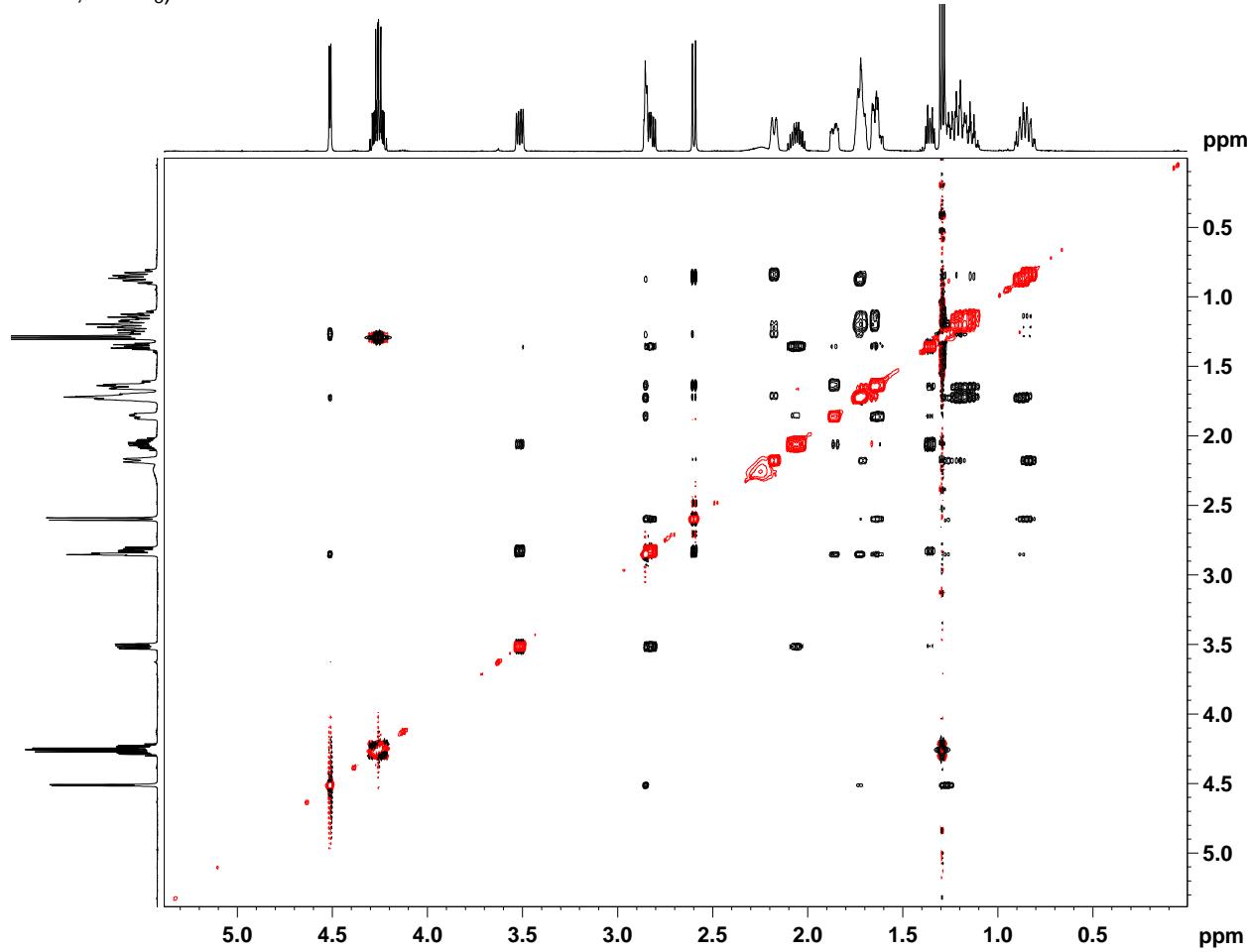


¹³C NMR (101 MHz, CDCl₃)



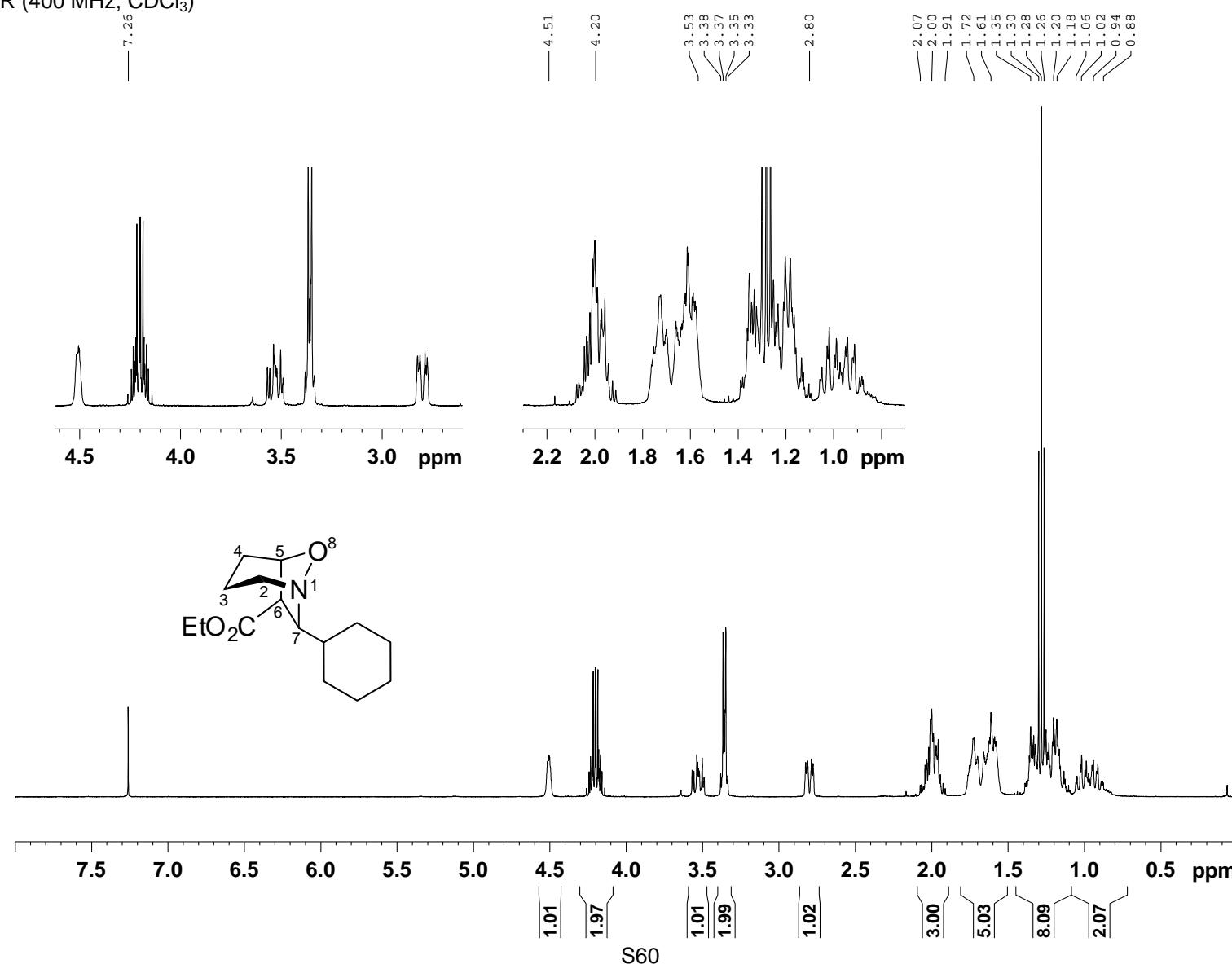
S58

2D NOESY (600 MHz, CDCl_3)

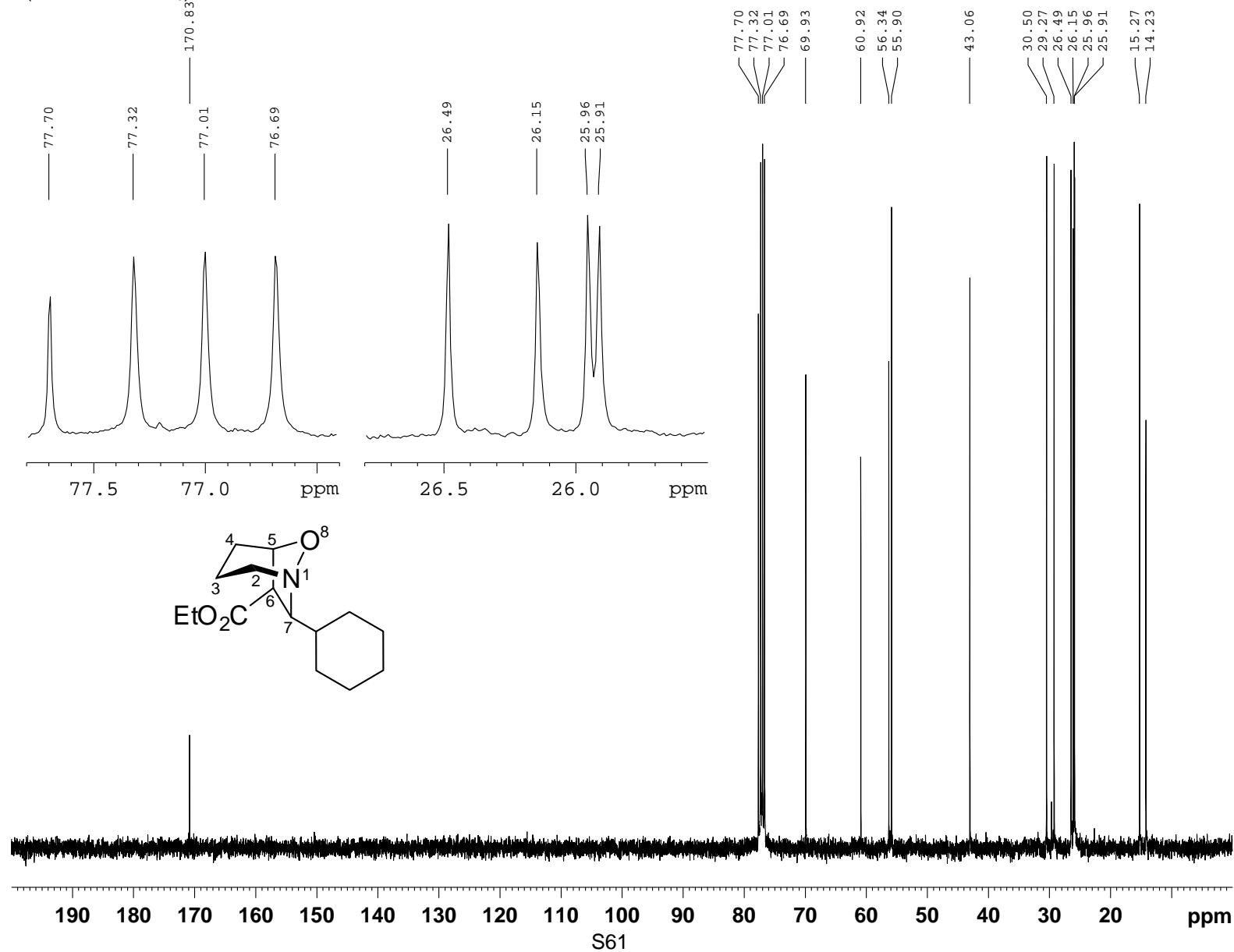


rac-(5R,6R,7R)-ethyl 7-cyclohexyl-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19a):

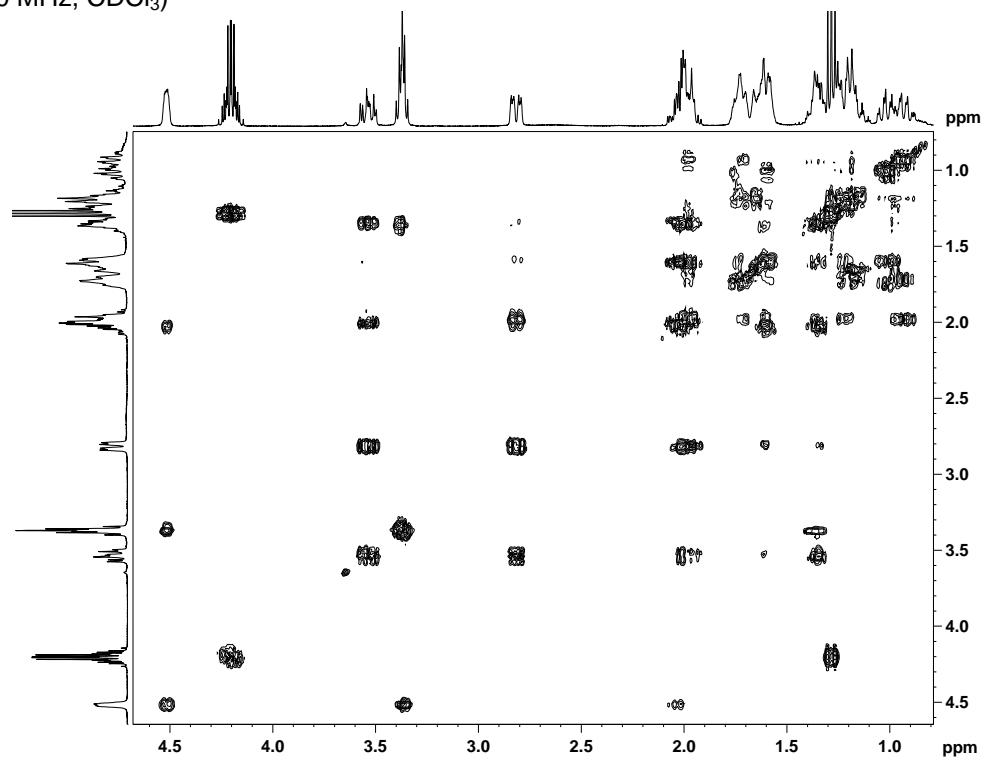
¹H NMR (400 MHz, CDCl₃)



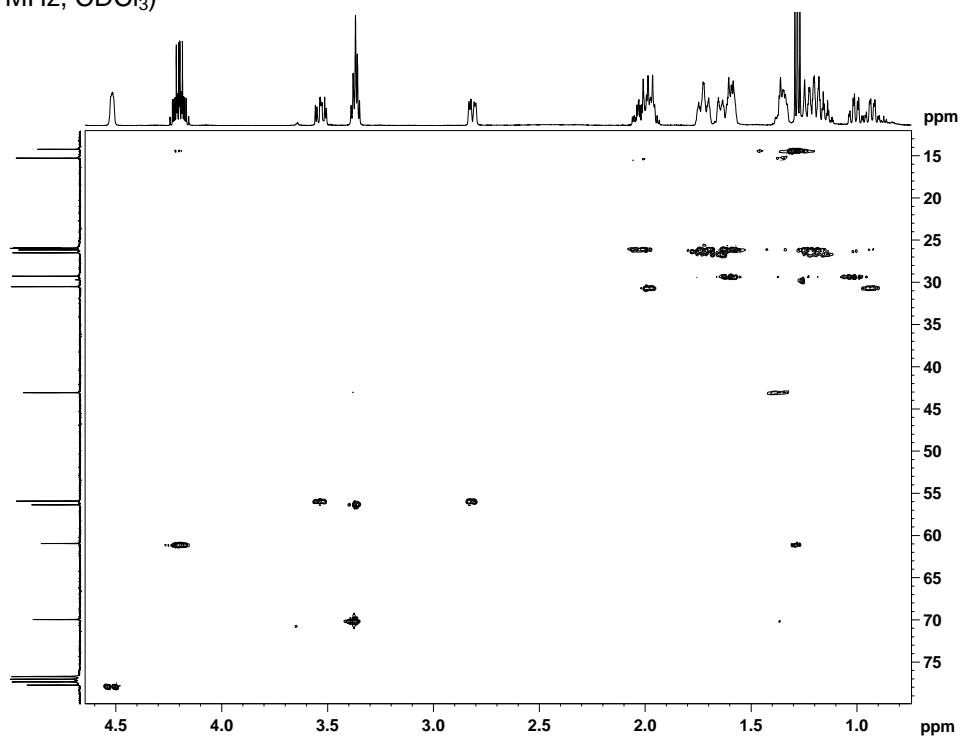
¹³C NMR (101 MHz, CDCl₃)



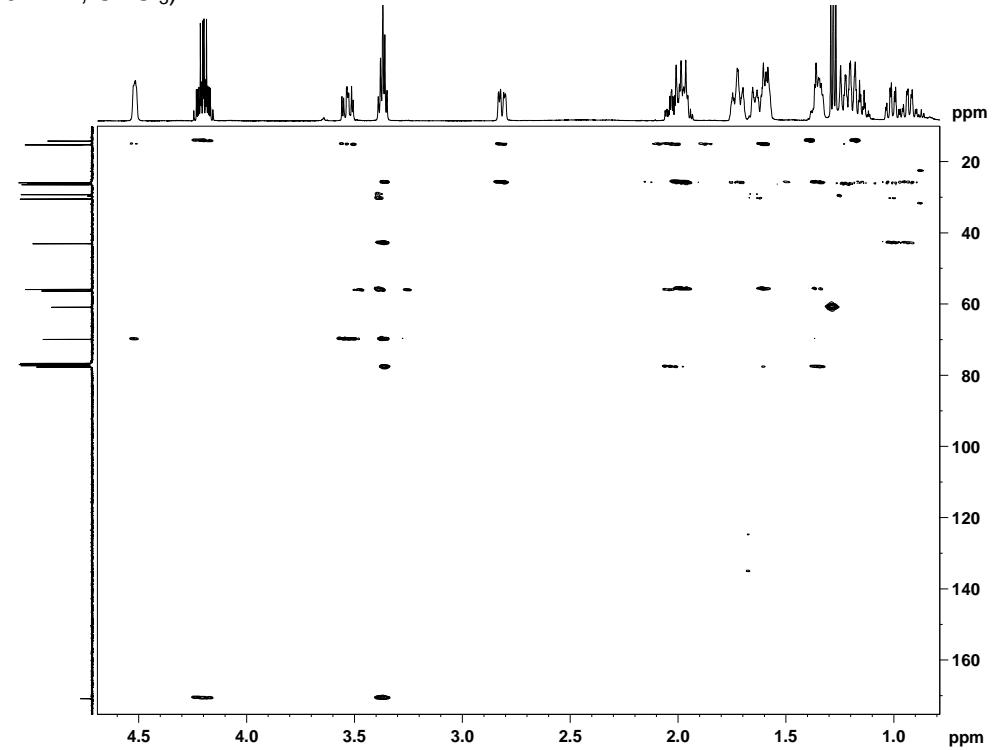
COSY (400 MHz, CDCl_3)



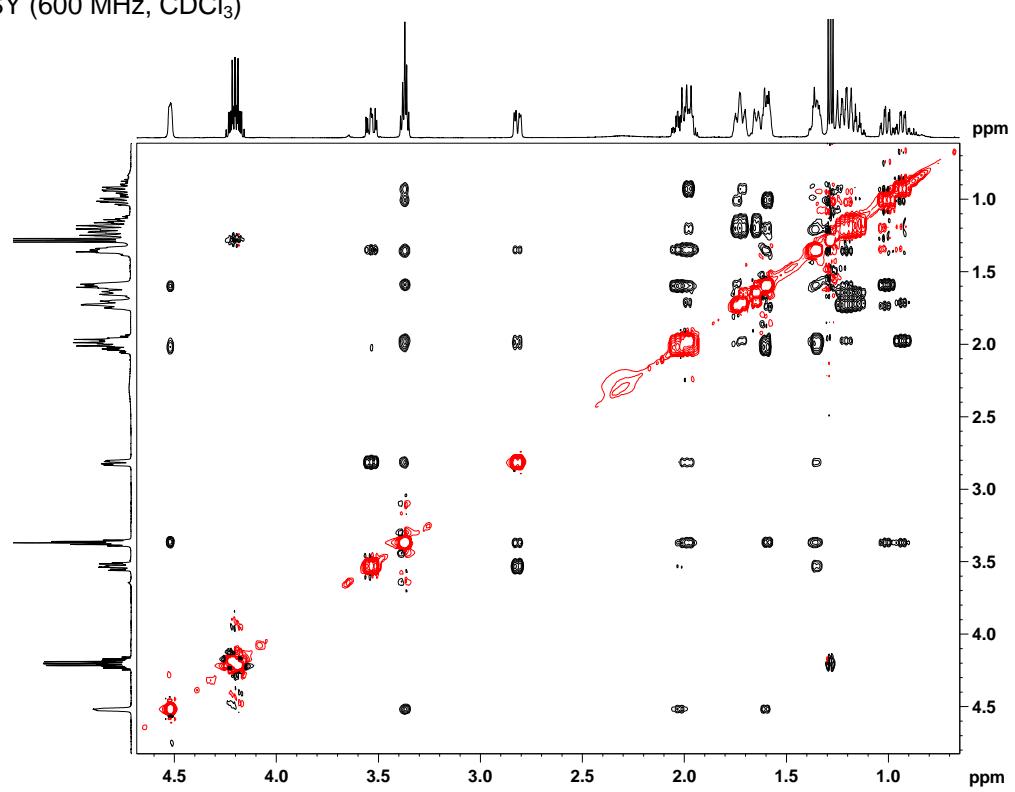
HSQC (600 MHz, CDCl_3)



HMBC (600 MHz, CDCl_3)

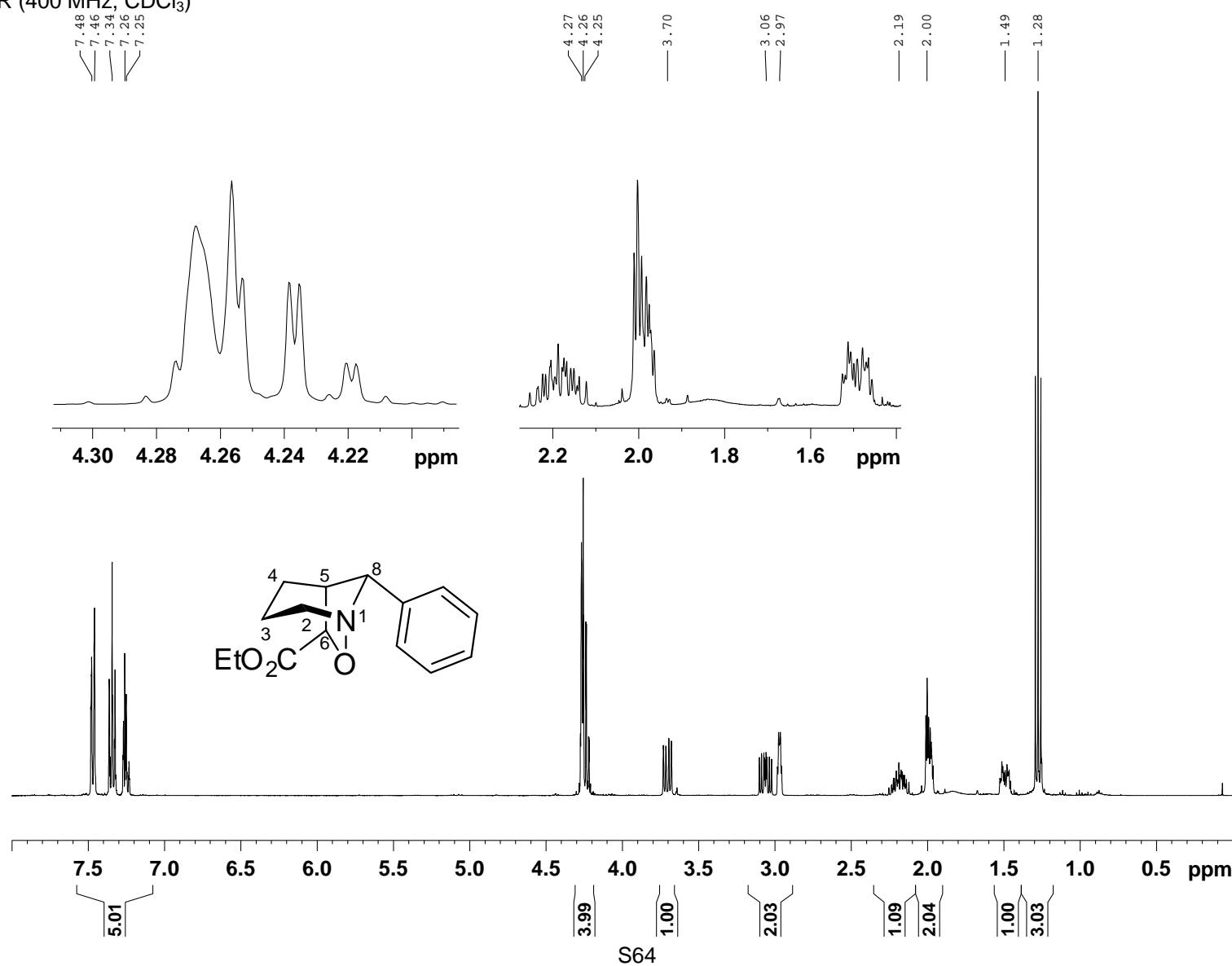


2D NOESY (600 MHz, CDCl_3)

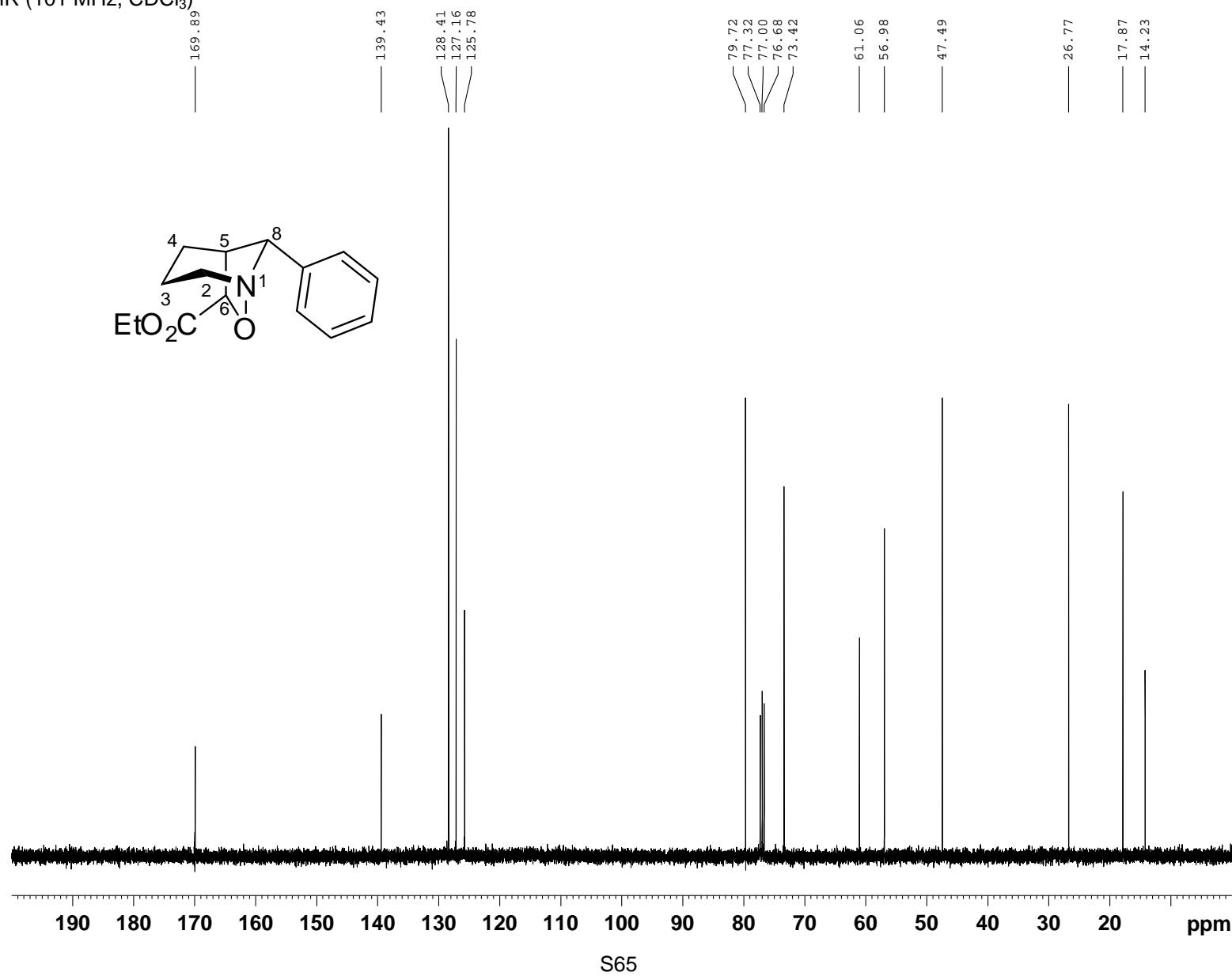
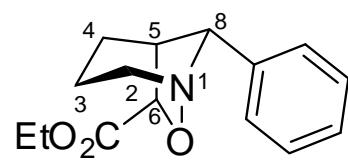


rac-(5*S*,6*R*,8*S*)-ethyl 8-phenyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (**18b**):

^1H NMR (400 MHz, CDCl_3)

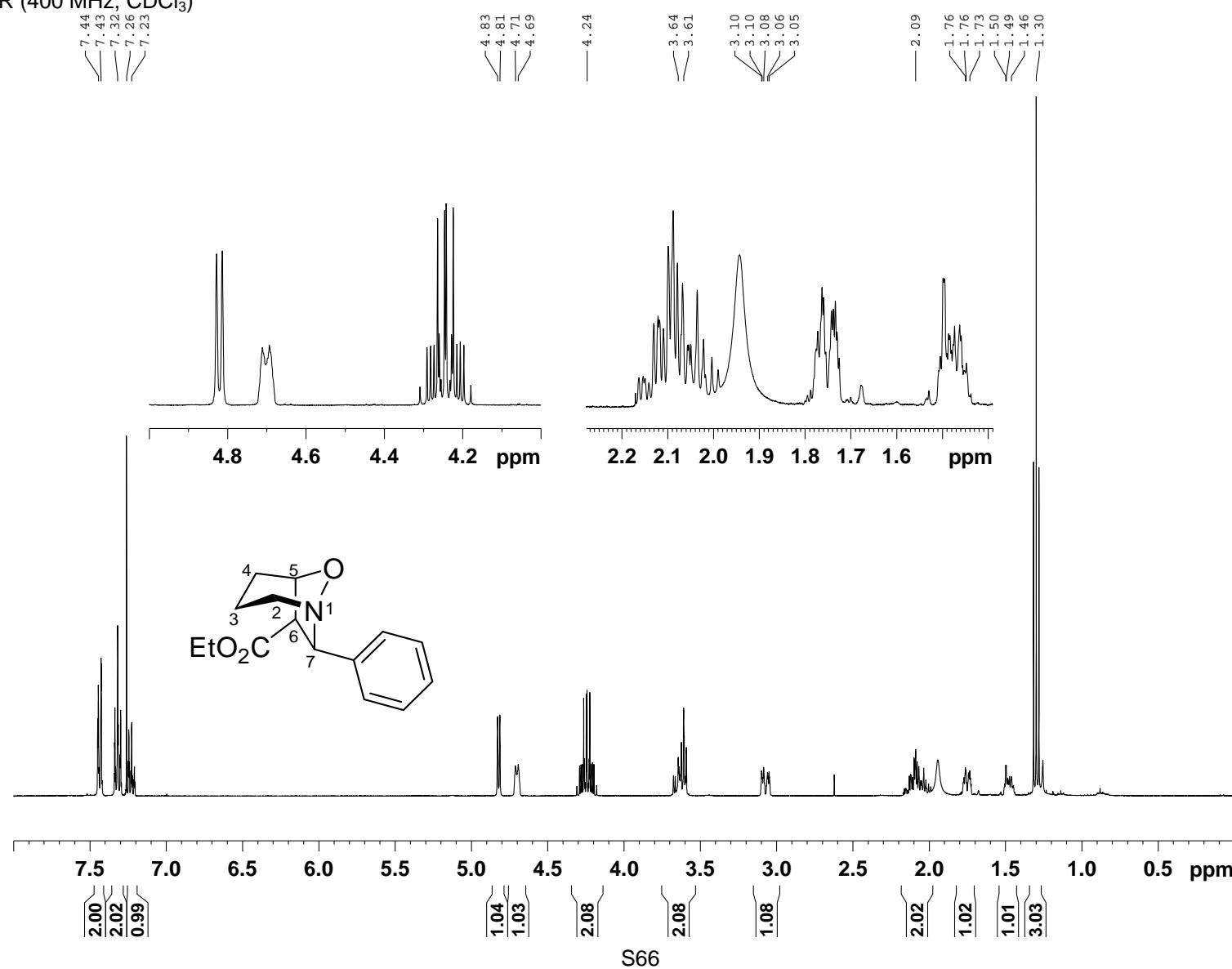


¹³C NMR (101 MHz, CDCl₃)

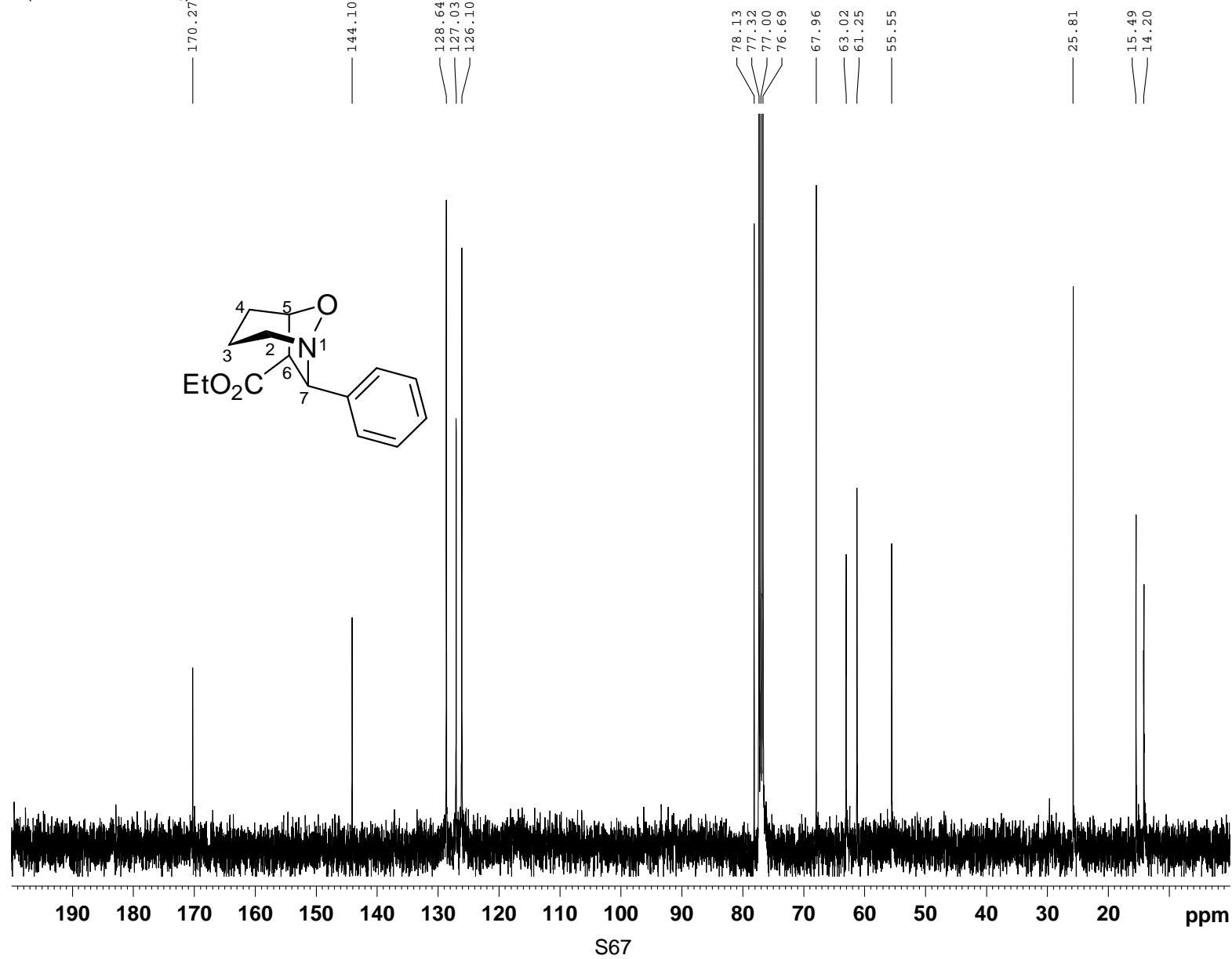


rac-(5*R*,6*R*,7*S*)-ethyl 7-phenyl-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (**19b**):

^1H NMR (400 MHz, CDCl_3)

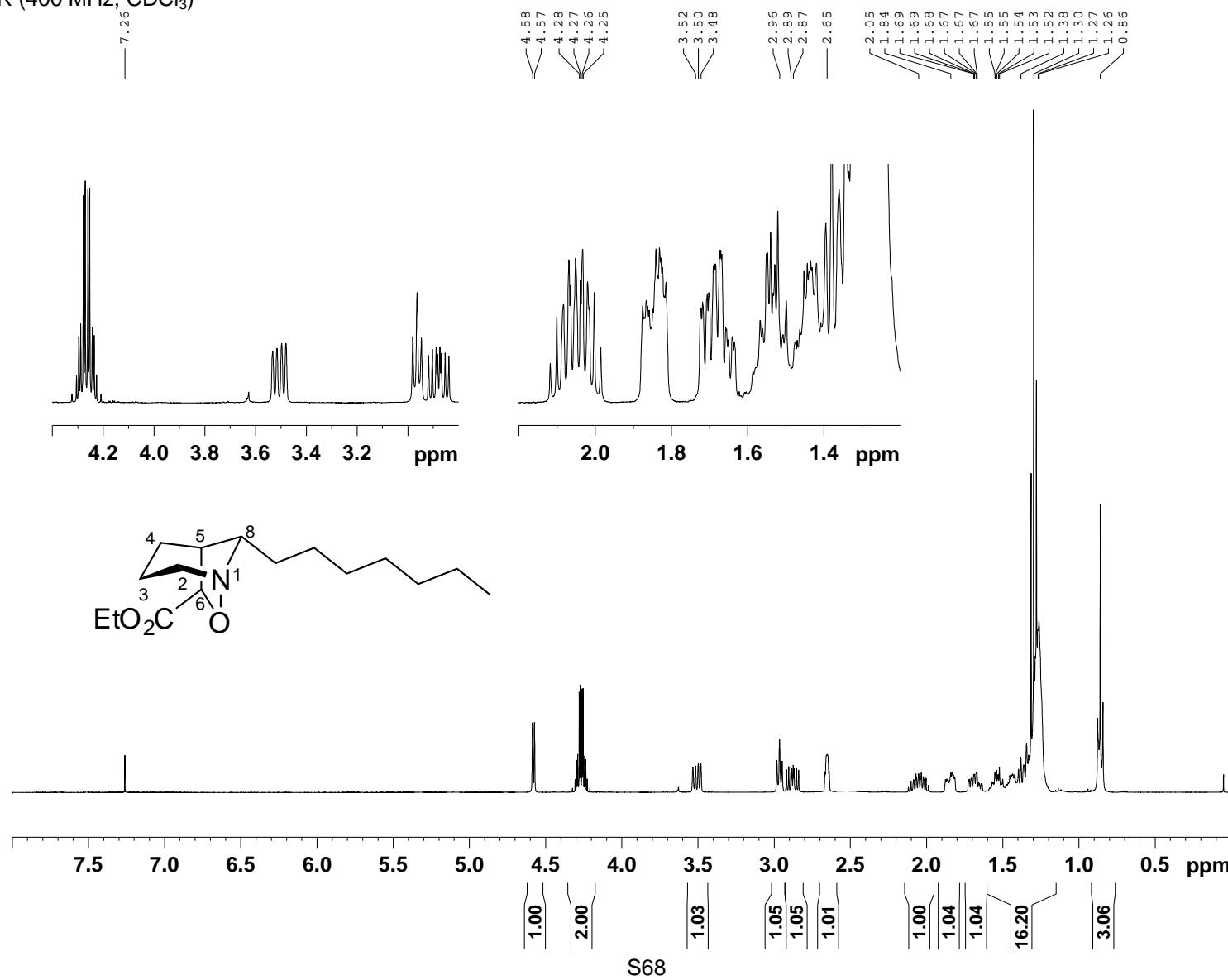


¹³C NMR (101 MHz, CDCl₃)

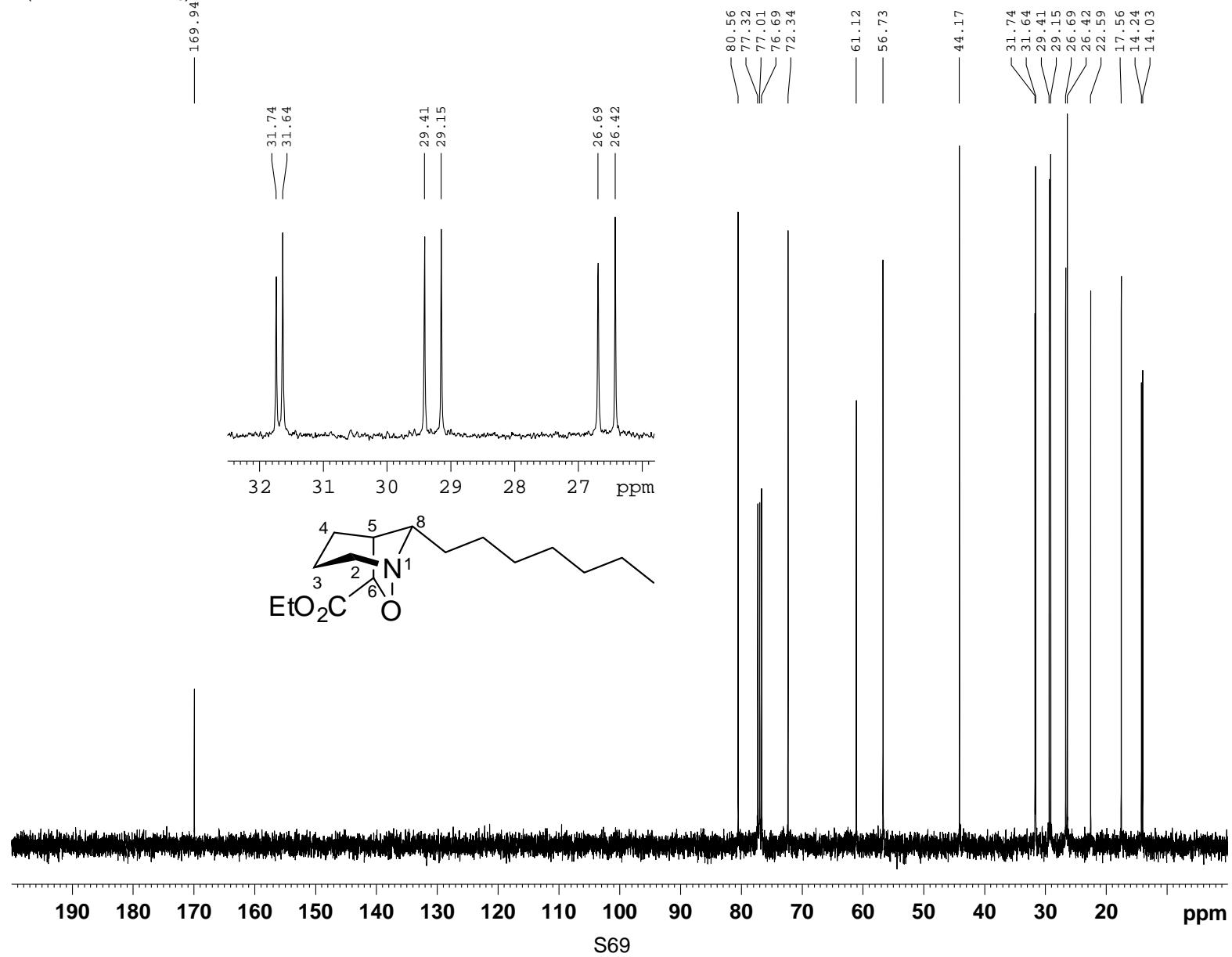


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-heptyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18c):**

¹H NMR (400 MHz, CDCl₃)

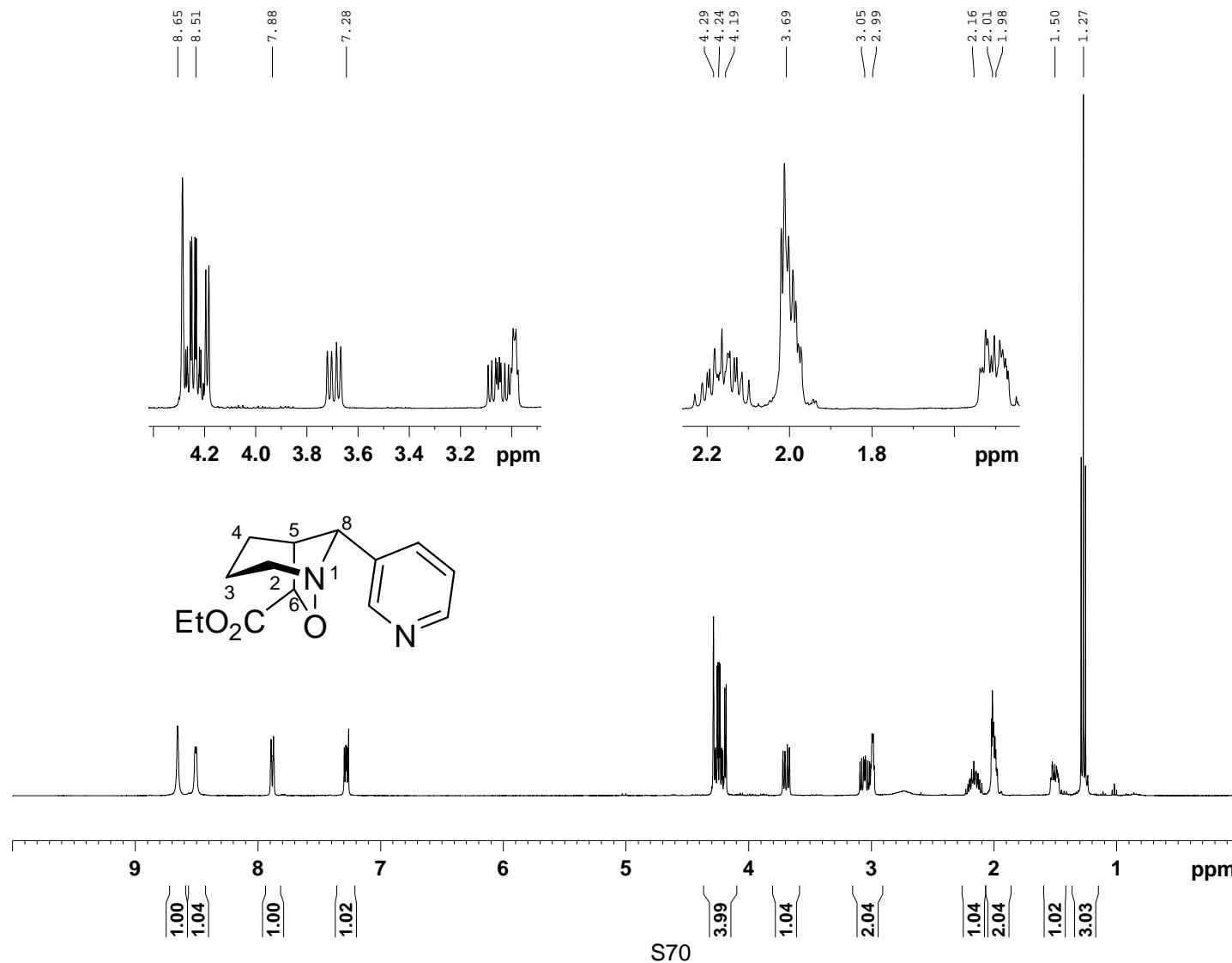


¹³C NMR (101 MHz, CDCl₃)

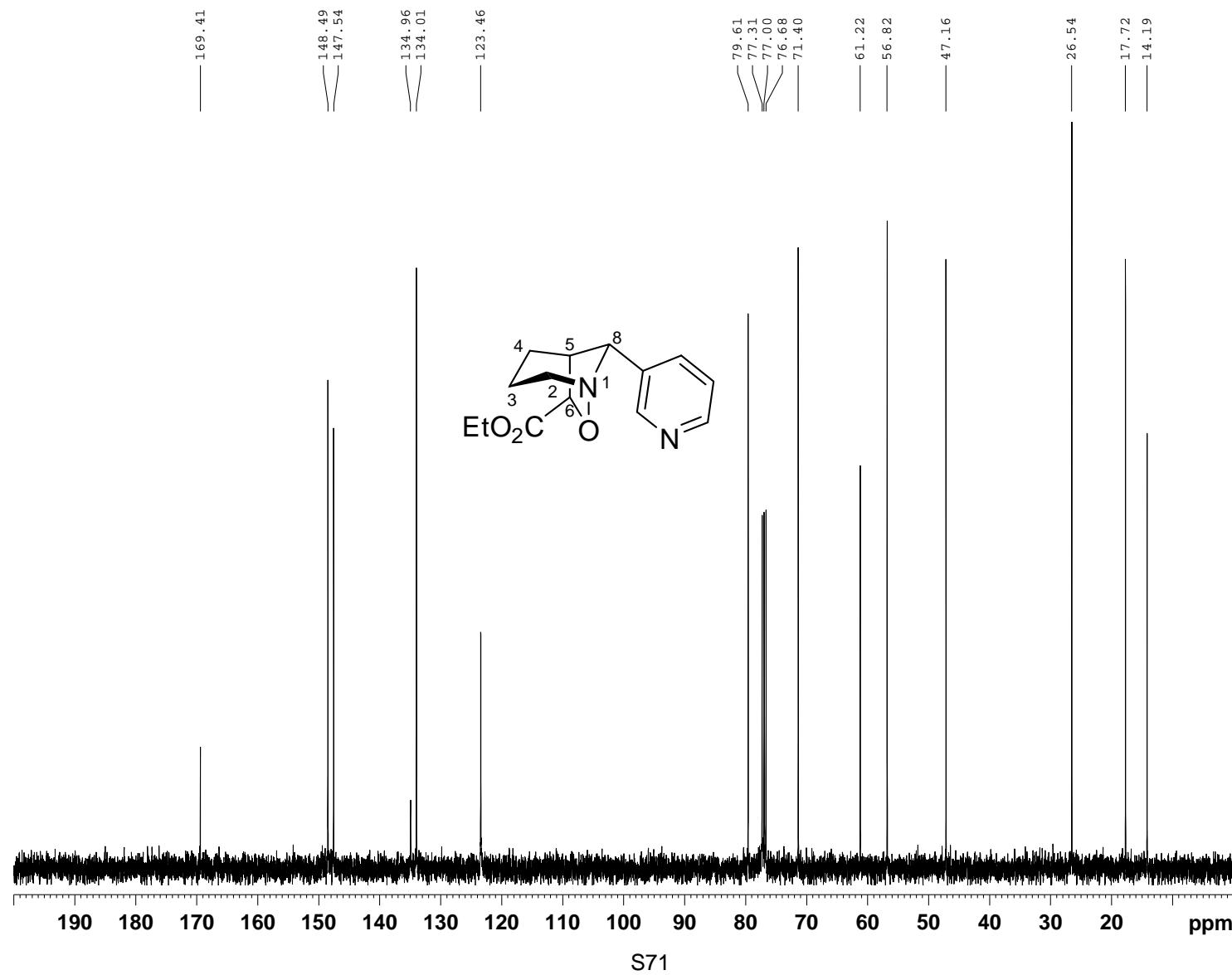


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-(pyridin-3-yl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18d):**

¹H NMR (400 MHz, CDCl₃)

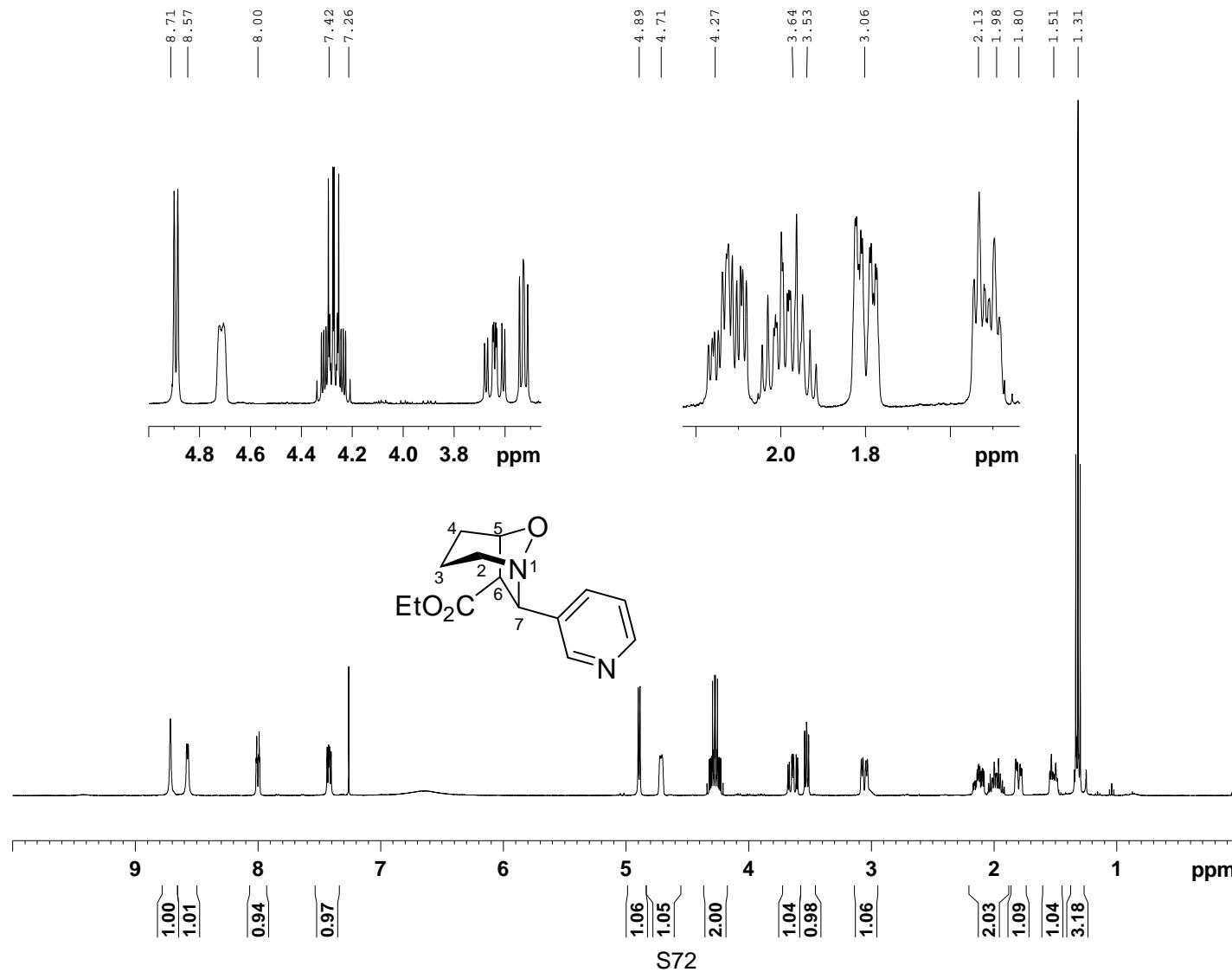


¹³C NMR (101 MHz, CDCl₃)

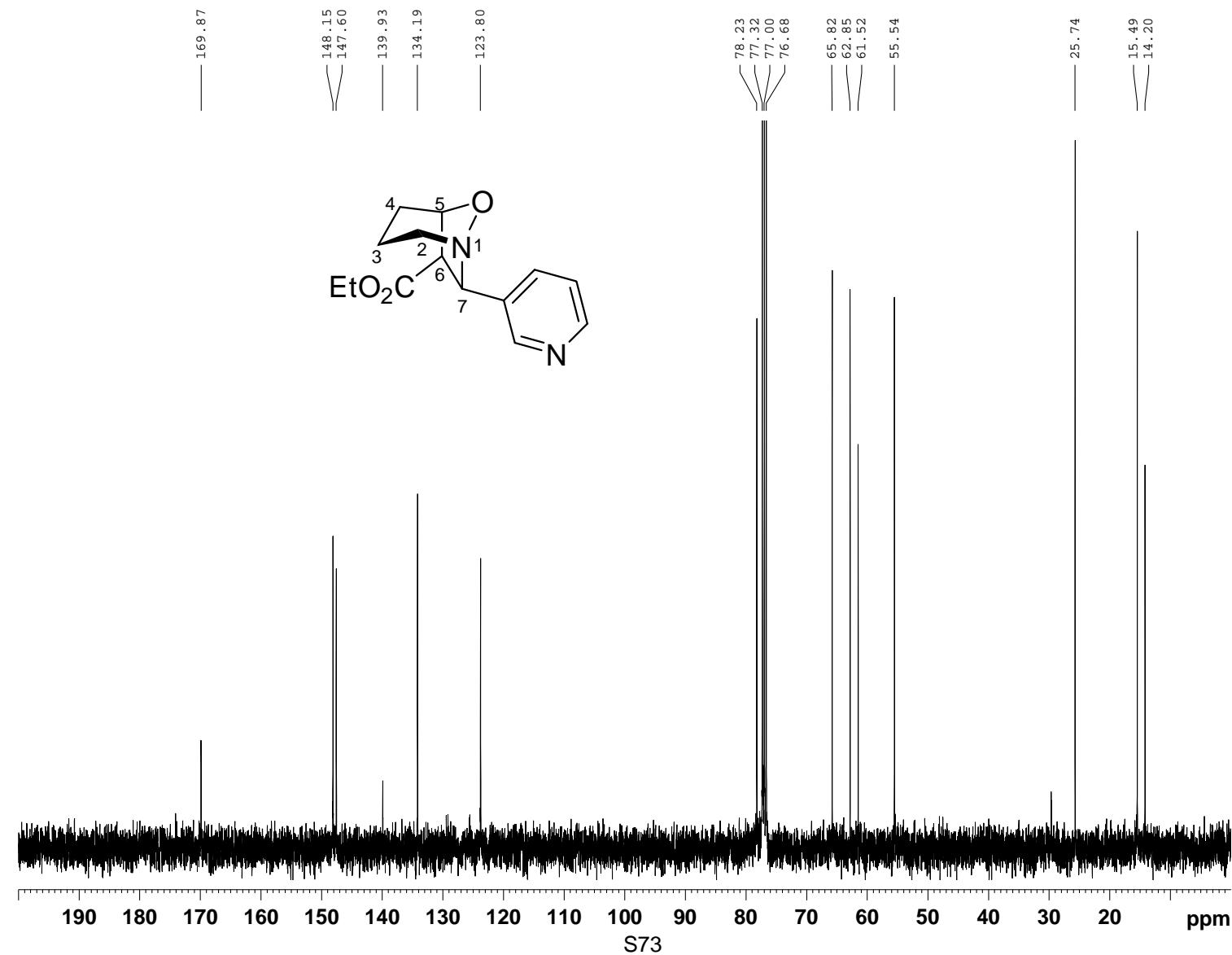


rac-(5*R*,6*R*,7*S*)-ethyl 7-(pyridin-3-yl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (**19d**):

¹H NMR (400 MHz, CDCl₃)

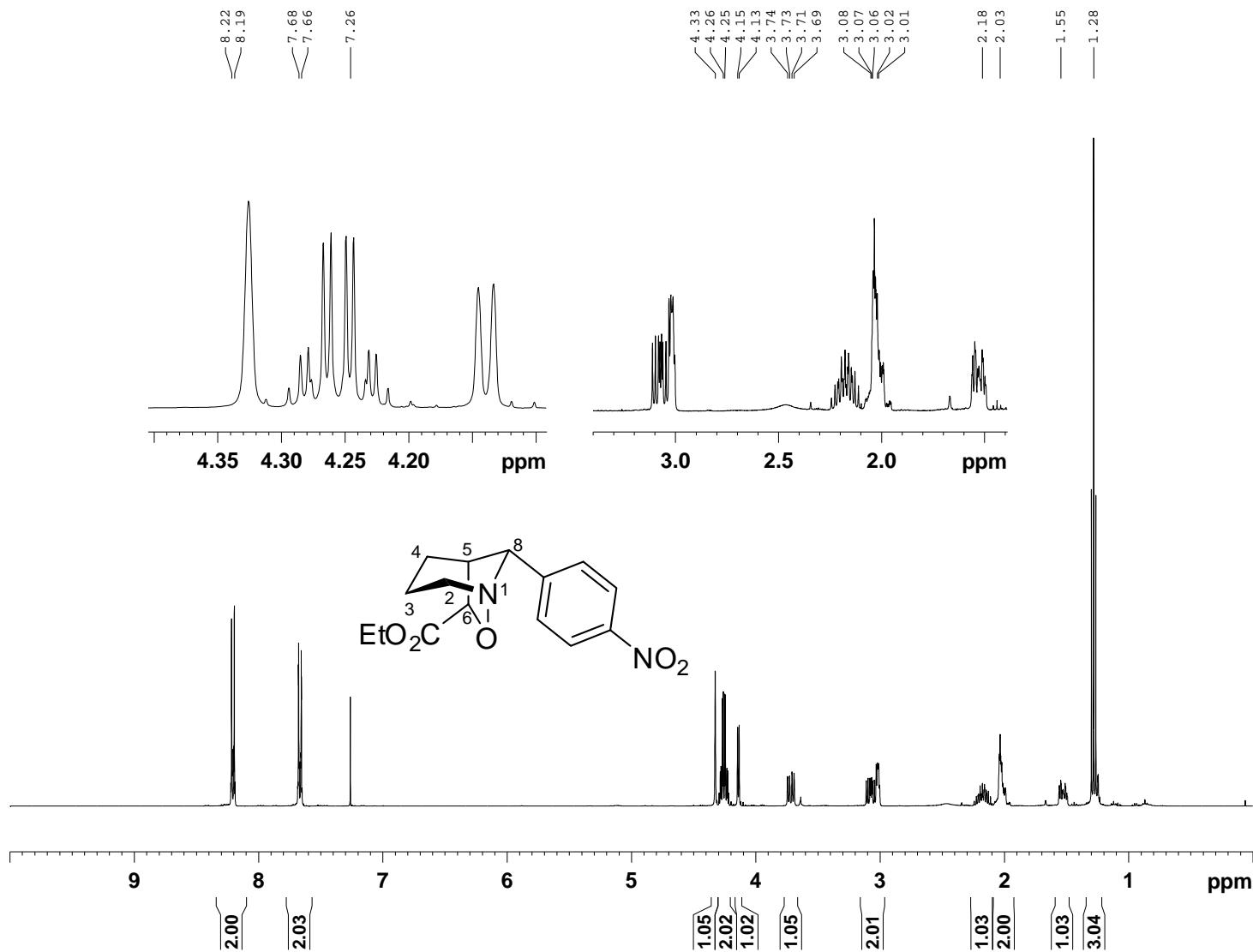


¹³C NMR (101 MHz, CDCl₃)

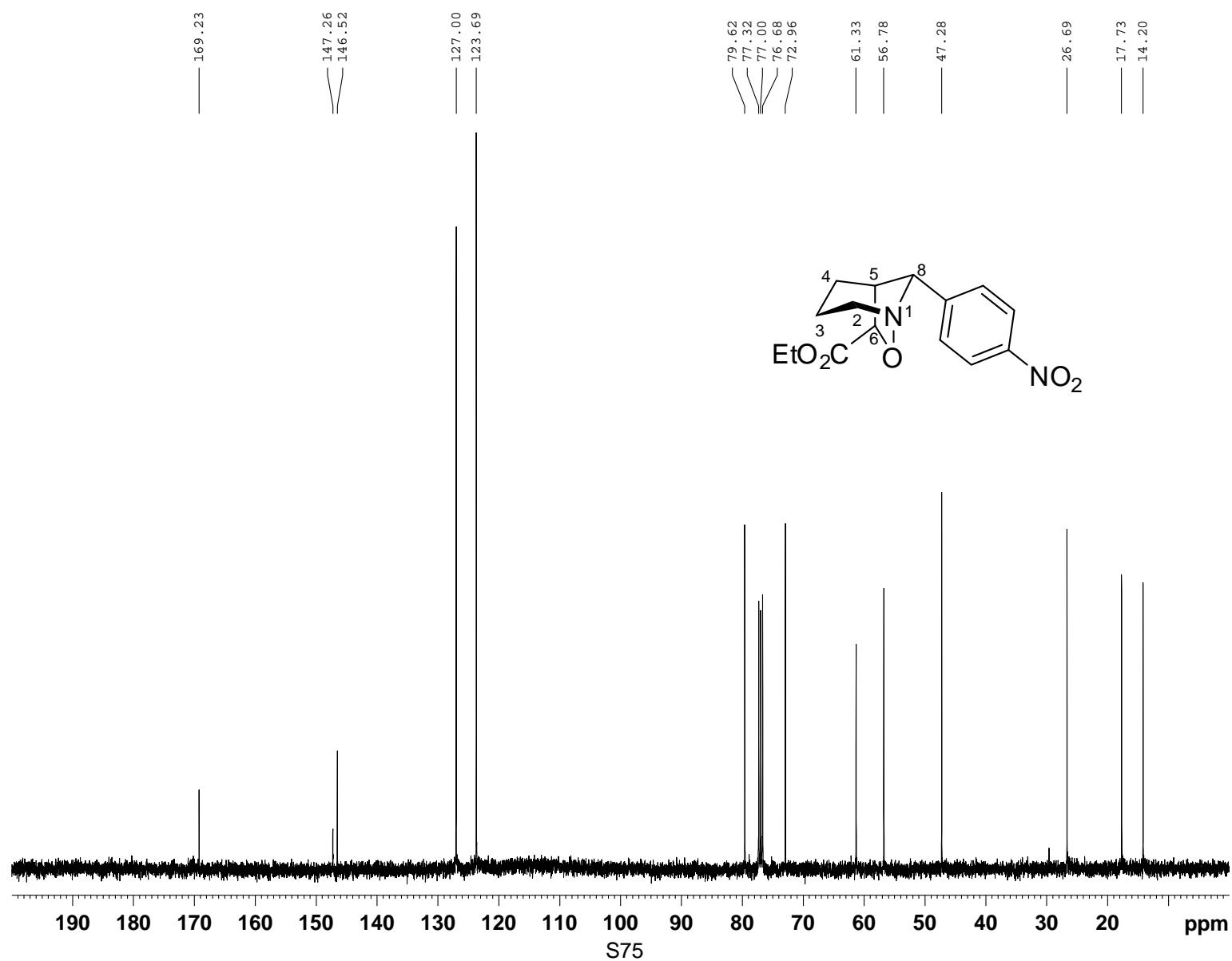


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-(4-nitrophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18e):**

¹H NMR (400 MHz, CDCl₃)

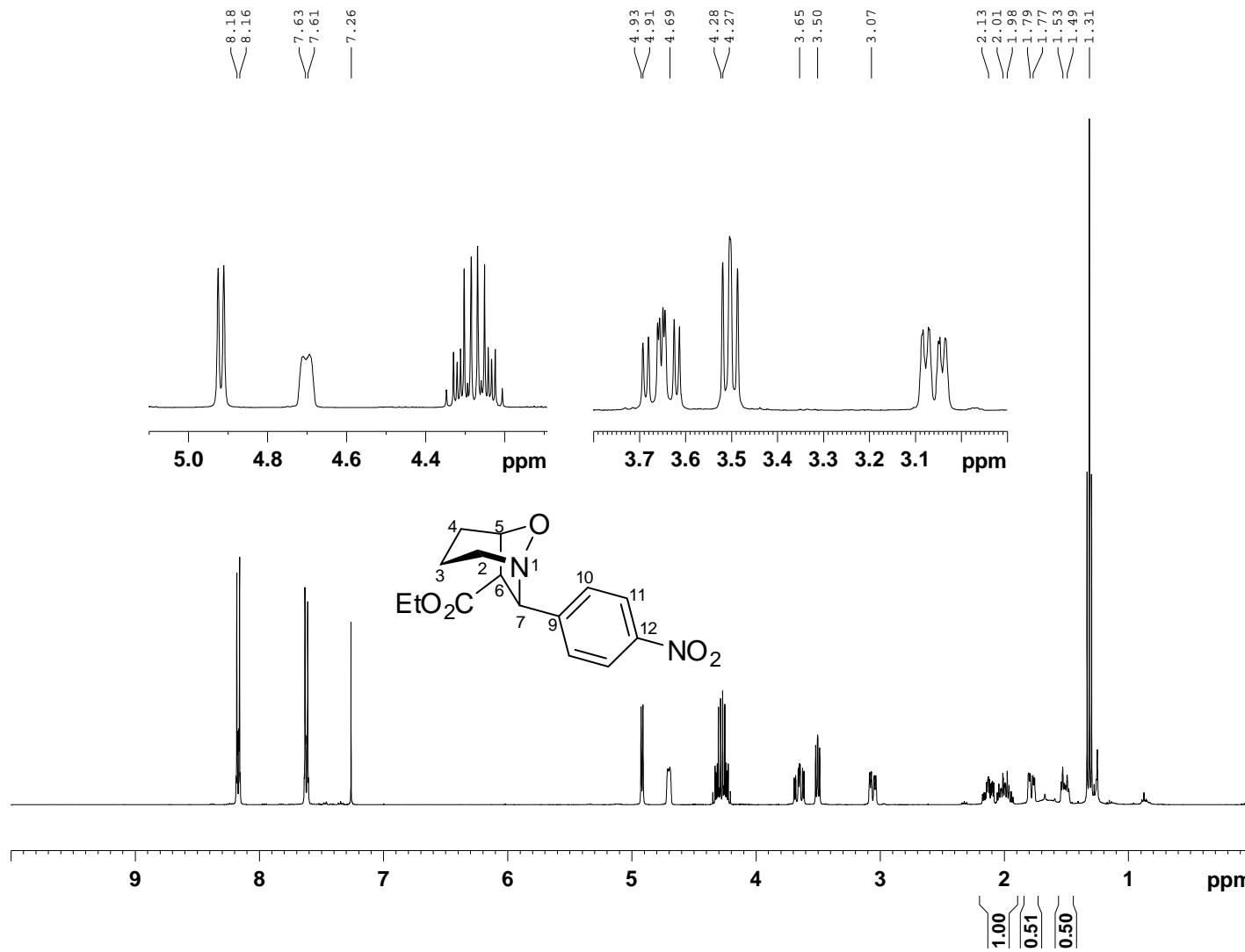


¹³C NMR (101 MHz, CDCl₃)

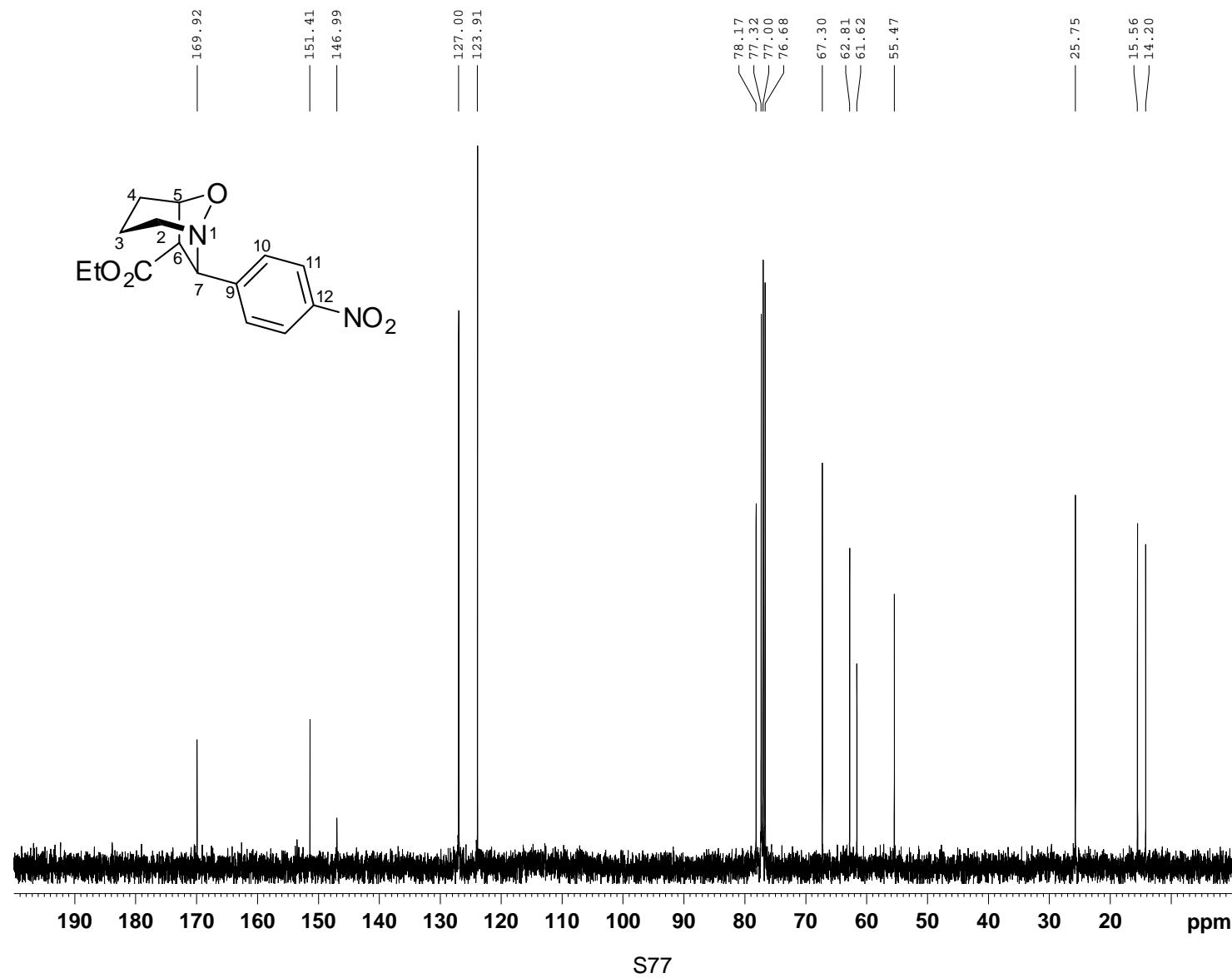


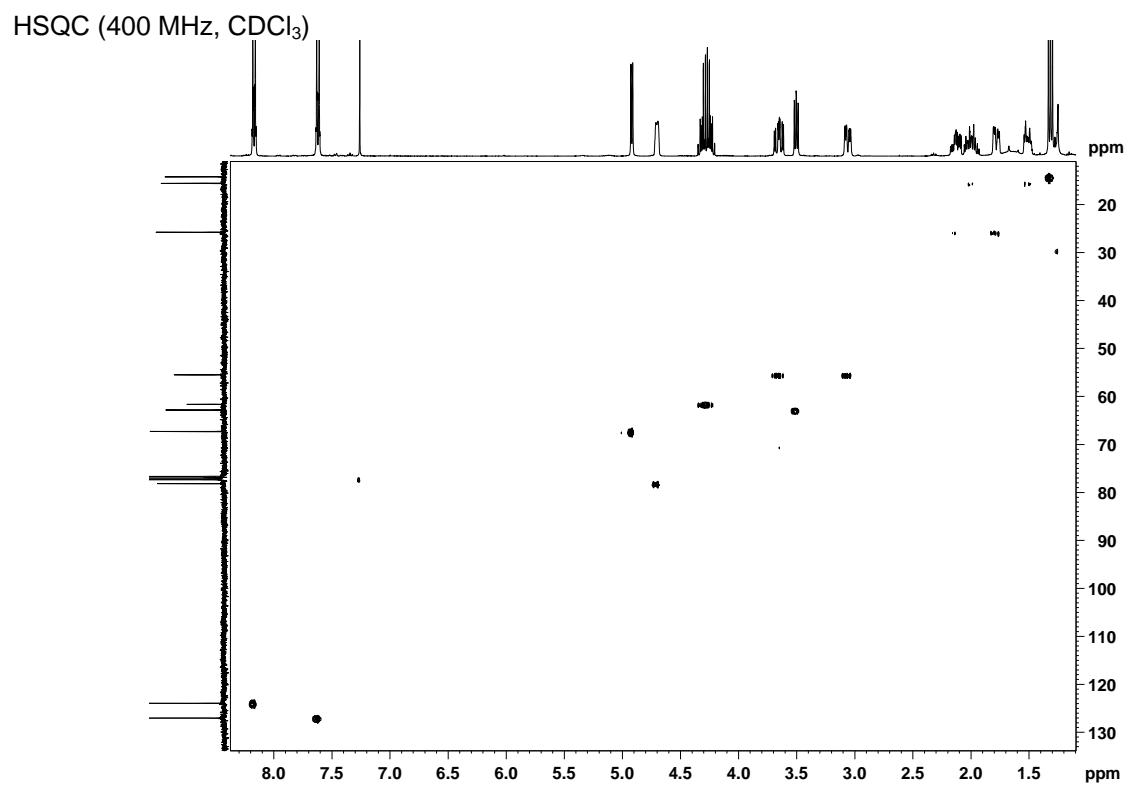
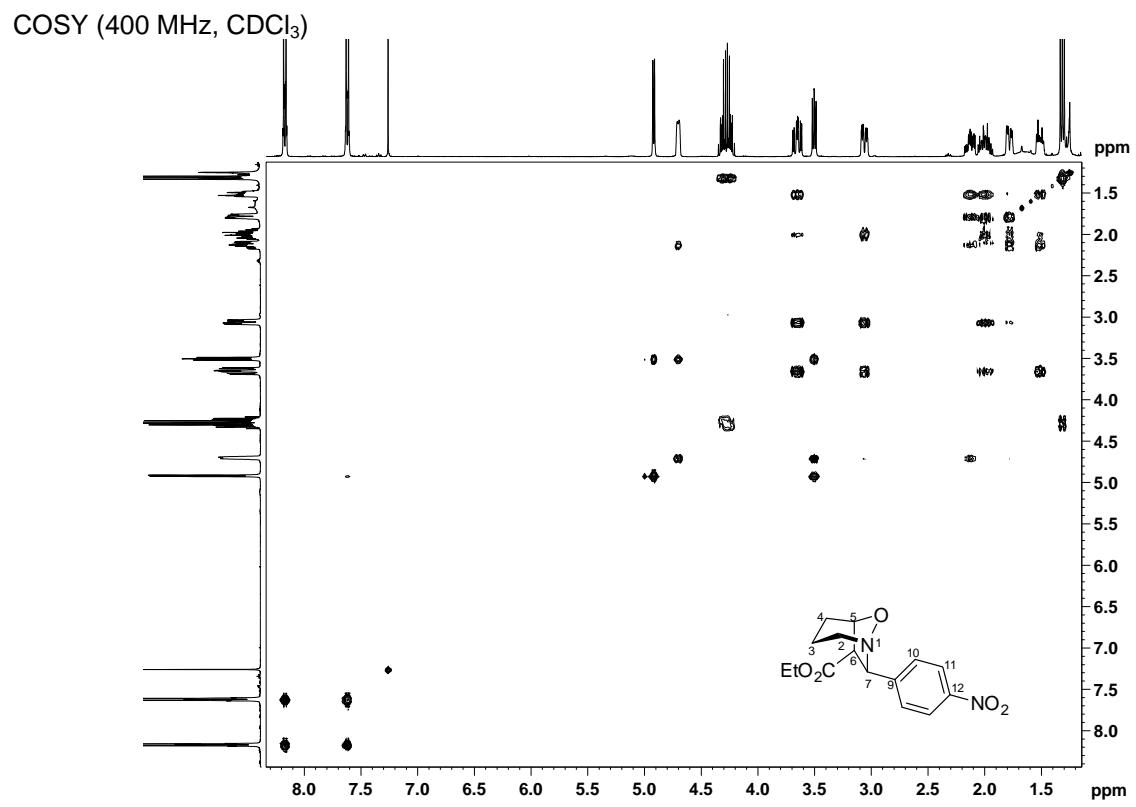
rac-(5*R*,6*R*,7*S*)-ethyl 7-(4-nitrophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (**19e**):

¹H NMR (400 MHz, CDCl₃)

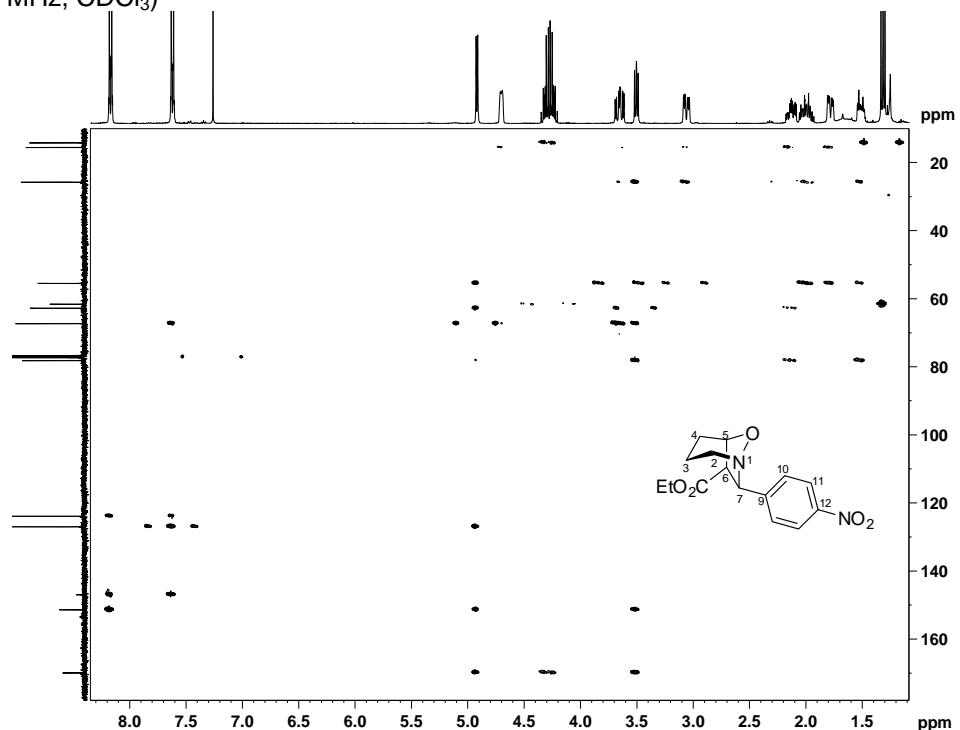


¹³C NMR (101 MHz, CDCl₃)

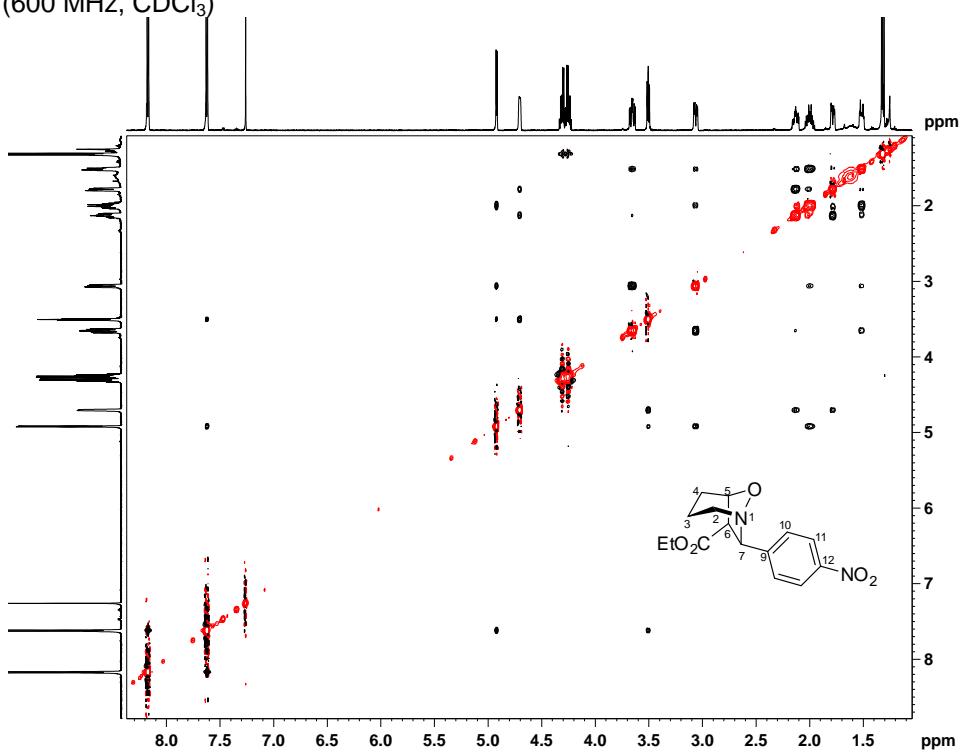




HMBC (400 MHz, CDCl_3)

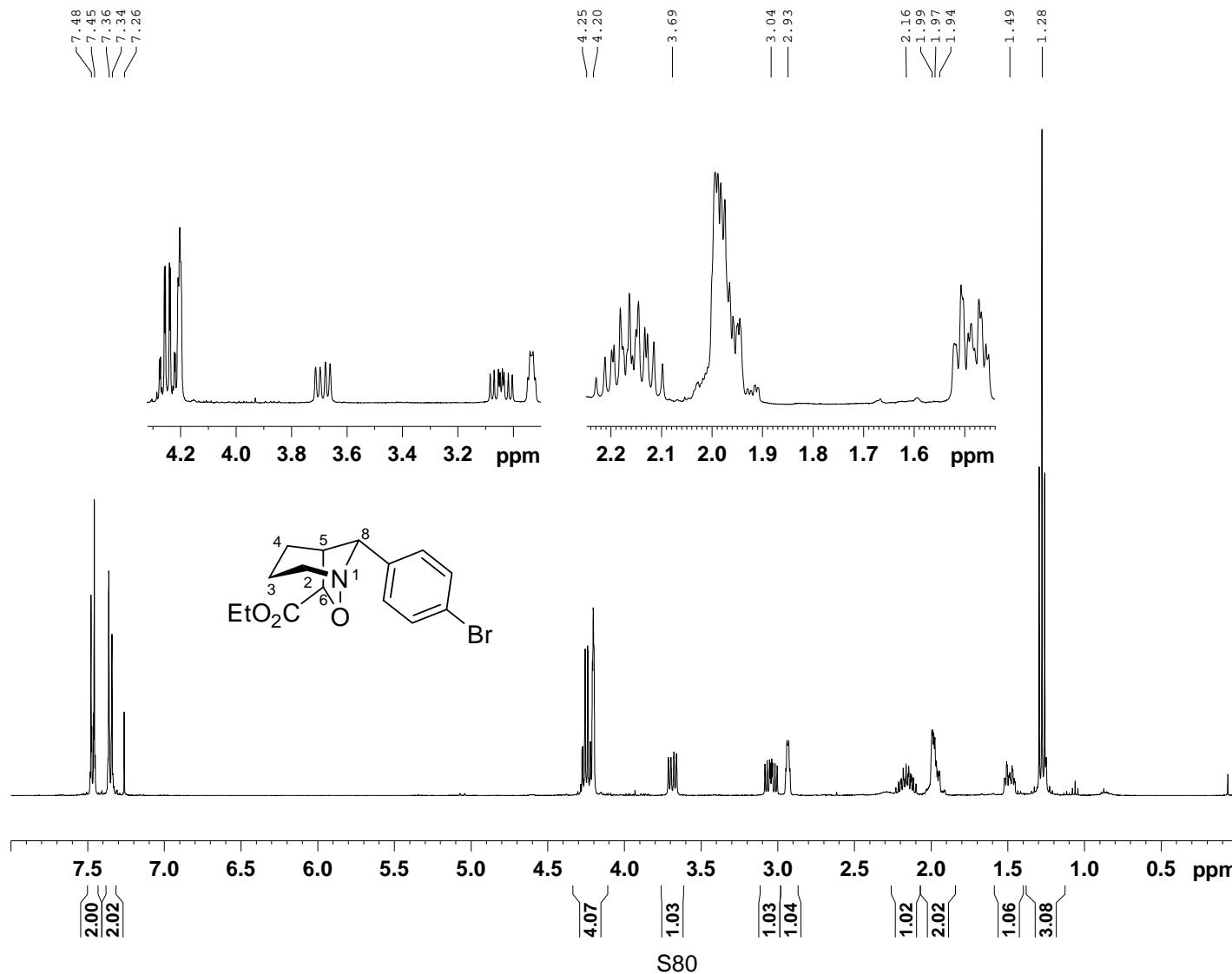


2D NOESY (600 MHz, CDCl_3)

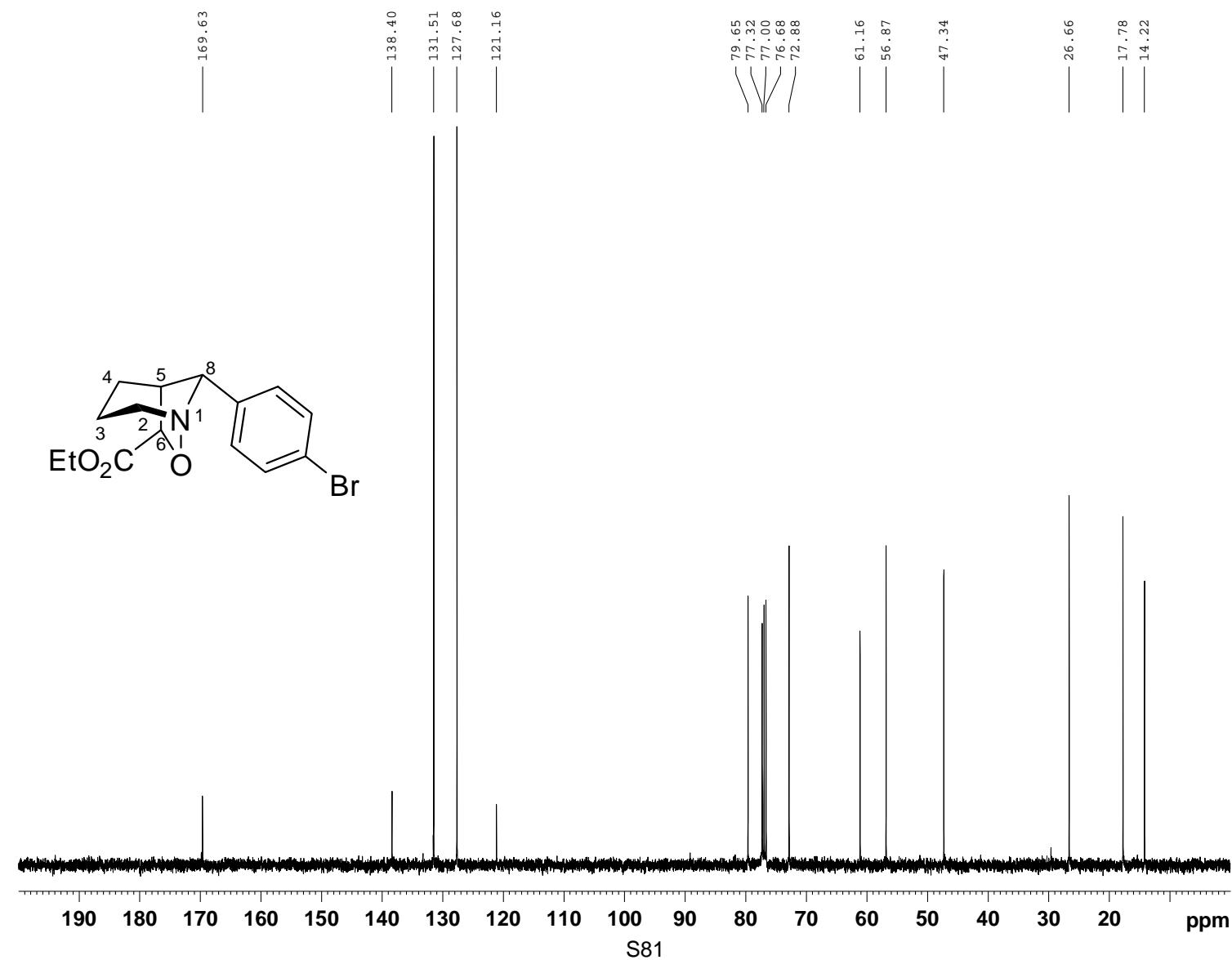


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-(4-bromophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18f):**

¹H NMR (400 MHz, CDCl₃)

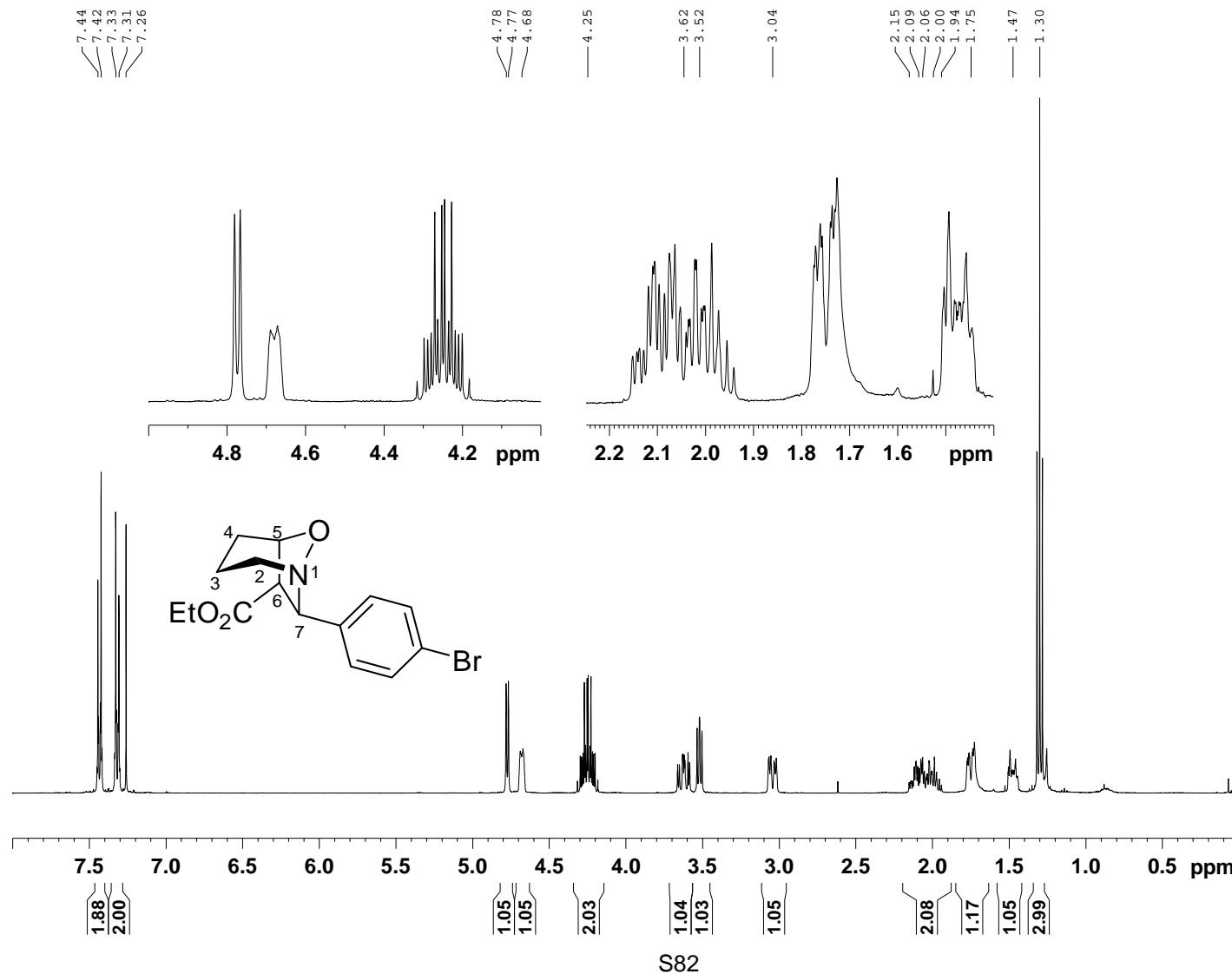


¹³C NMR (101 MHz, CDCl₃)

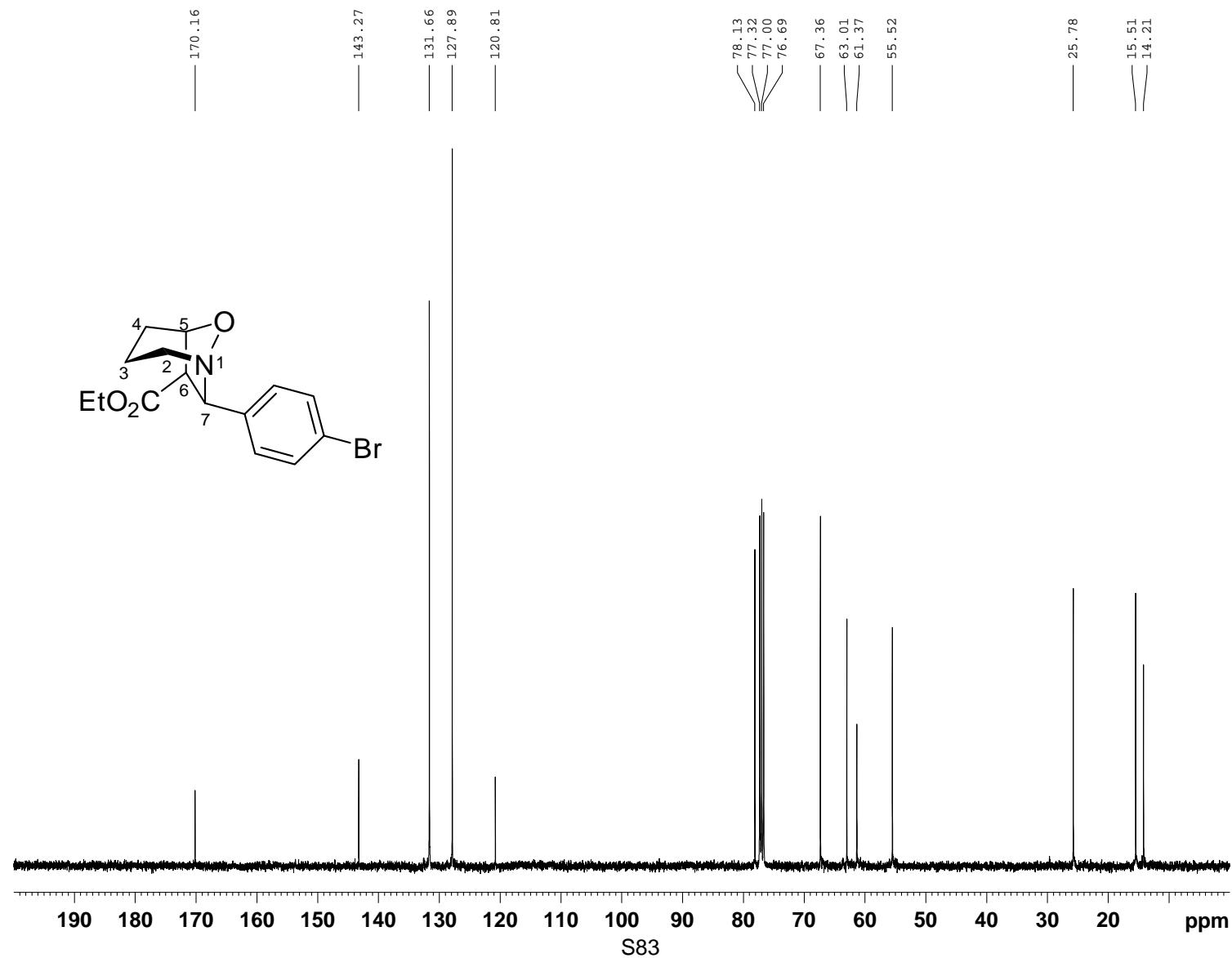


***rac*-(5*R*,6*R*,7*S*)-ethyl 7-(4-bromophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19f):**

¹H NMR (400 MHz, CDCl₃)

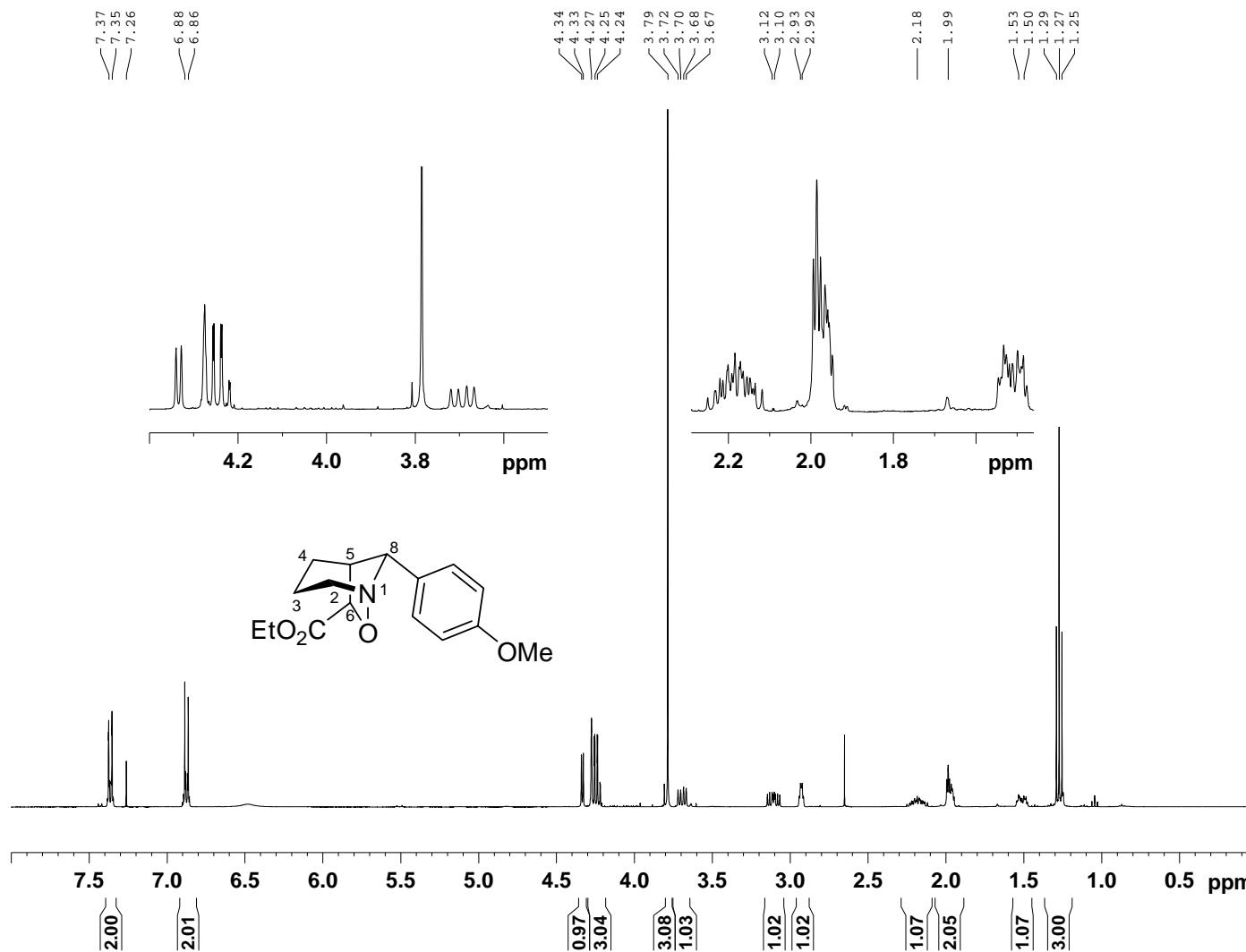


¹³C NMR (101 MHz, CDCl₃)

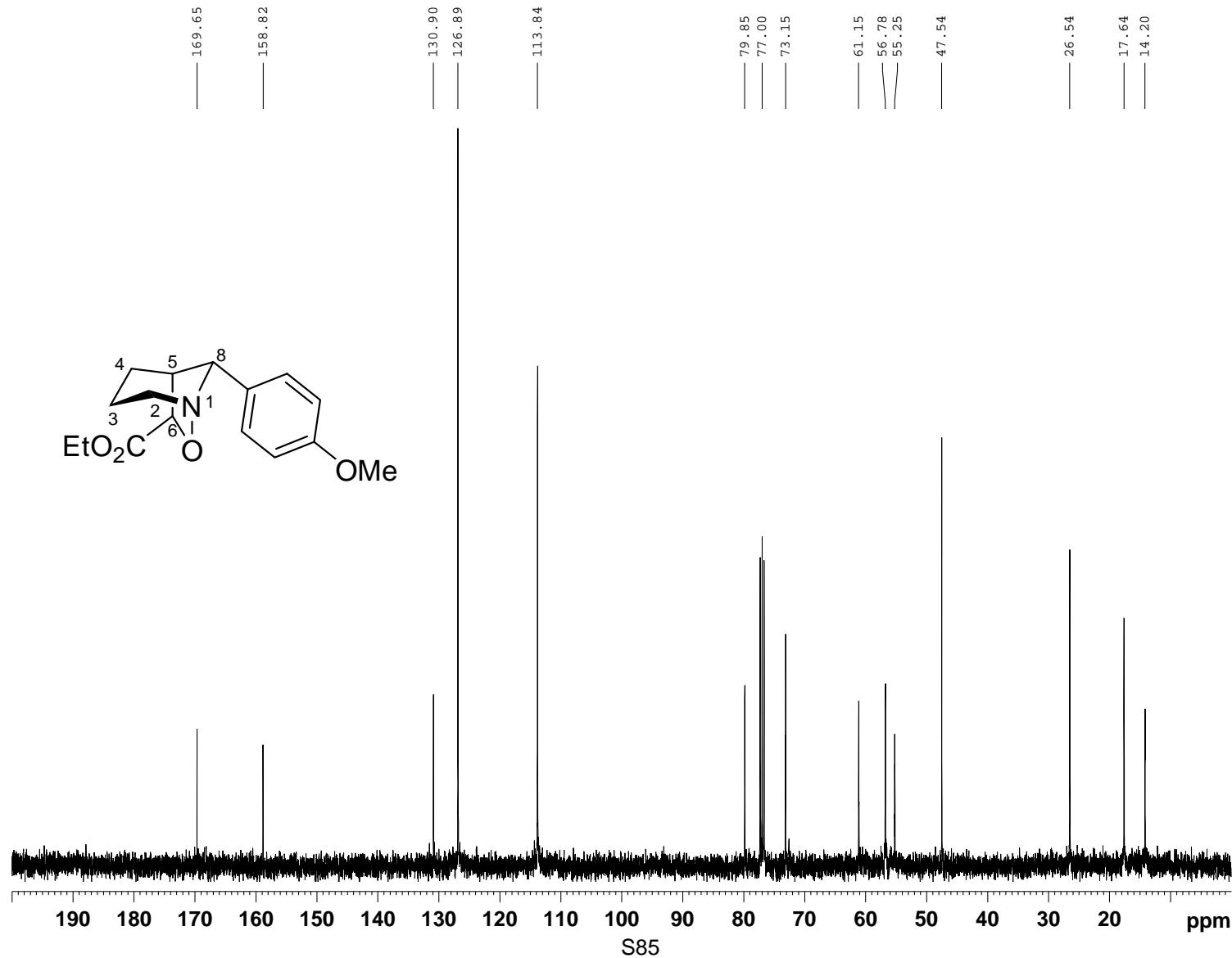
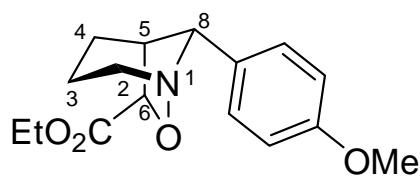


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-(4-methoxyphenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18g):**

¹H NMR (400 MHz, CDCl₃)

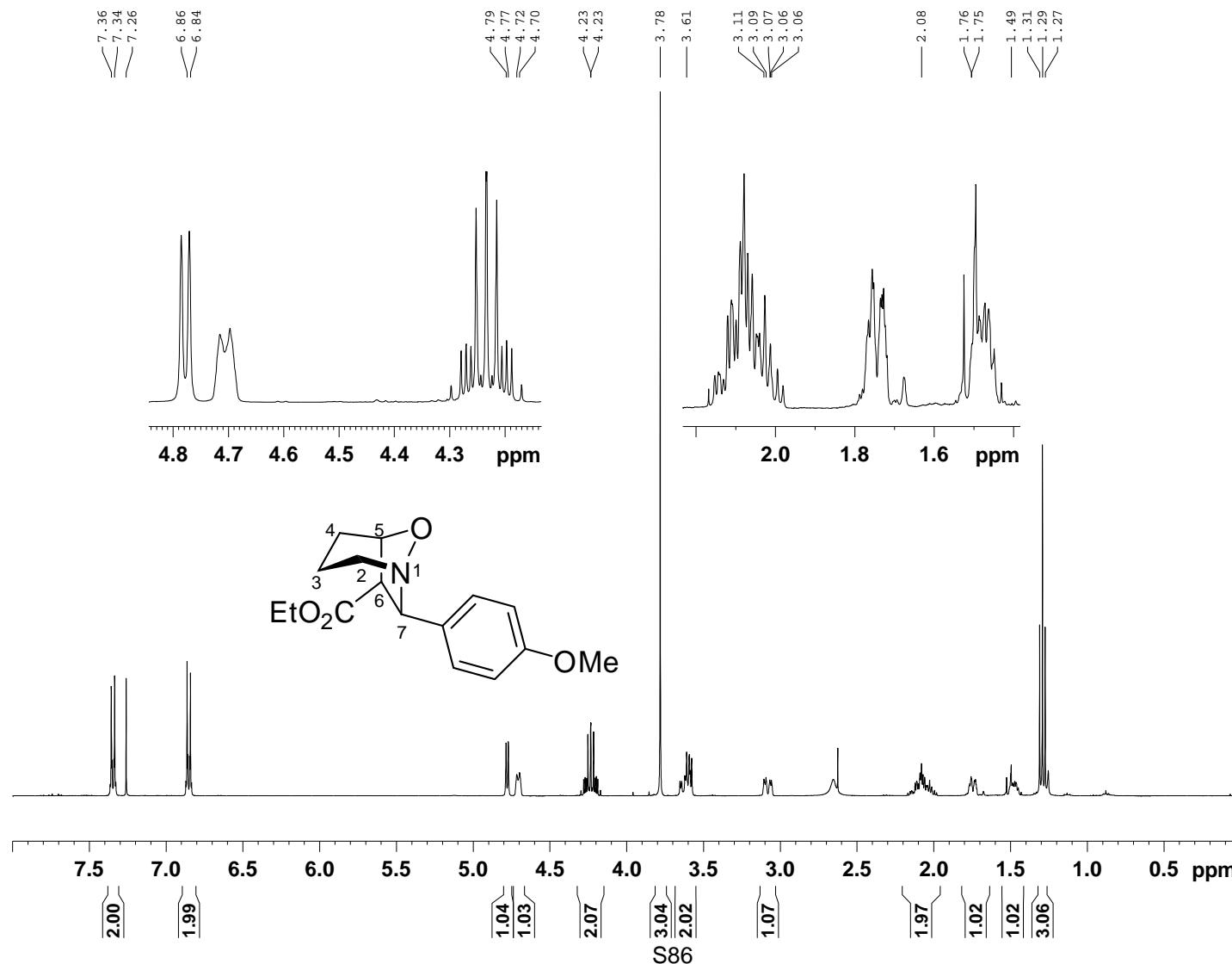


¹³C NMR (101 MHz, CDCl₃)

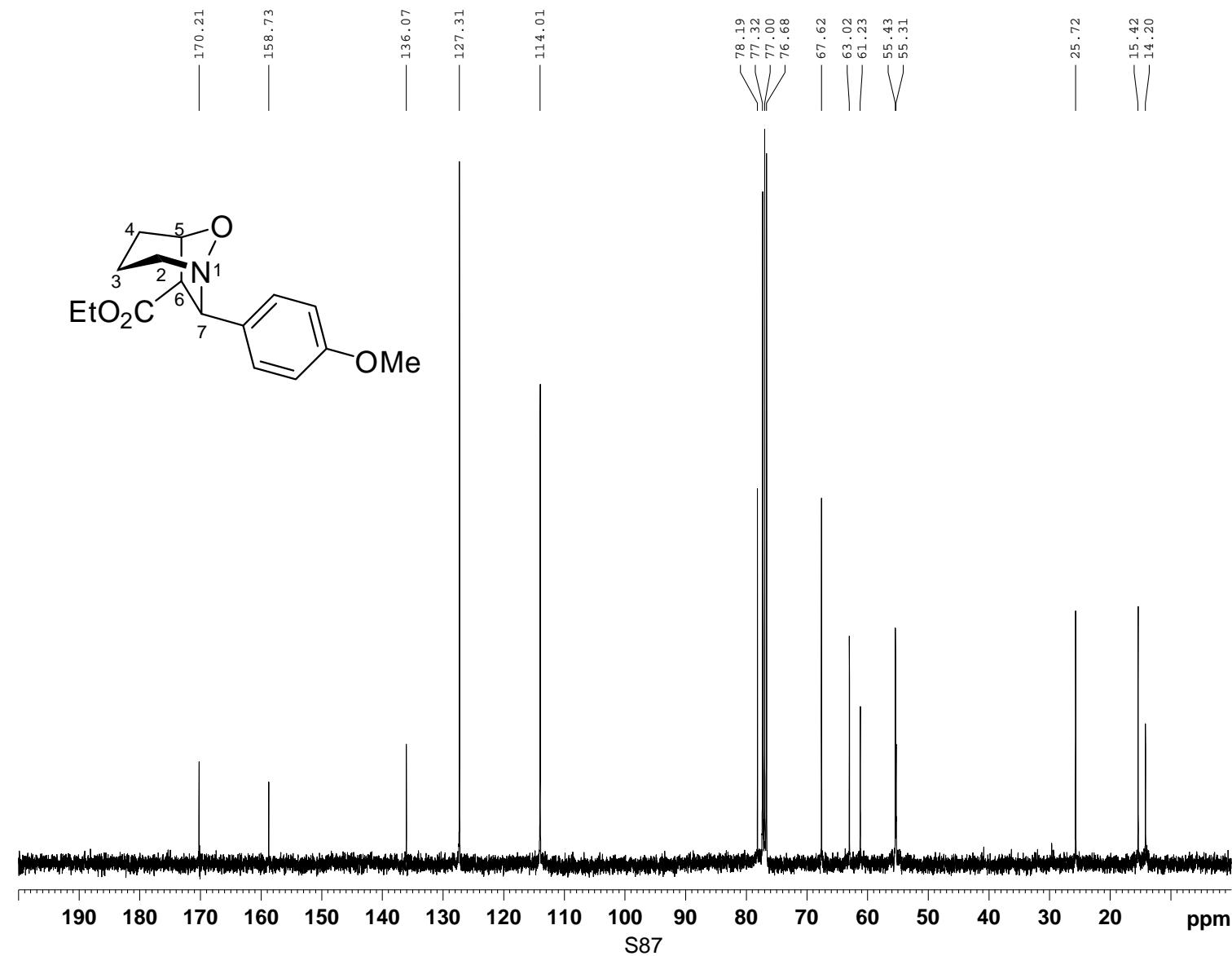


***rac*-(5*R*,6*R*,7*S*)-ethyl 7-(4-methoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19g):**

¹H NMR (400 MHz, CDCl₃)

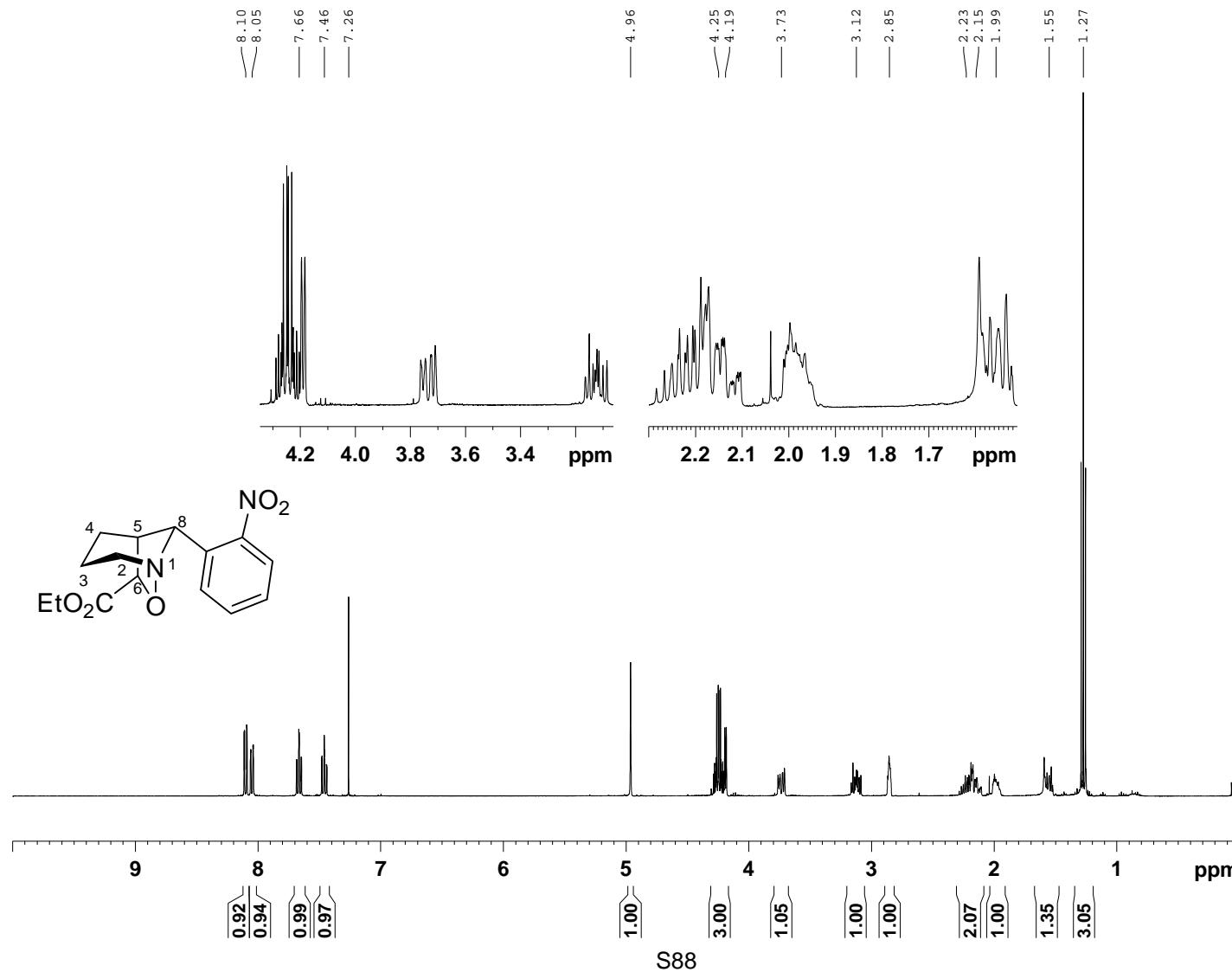


¹³C NMR (101 MHz, CDCl₃)

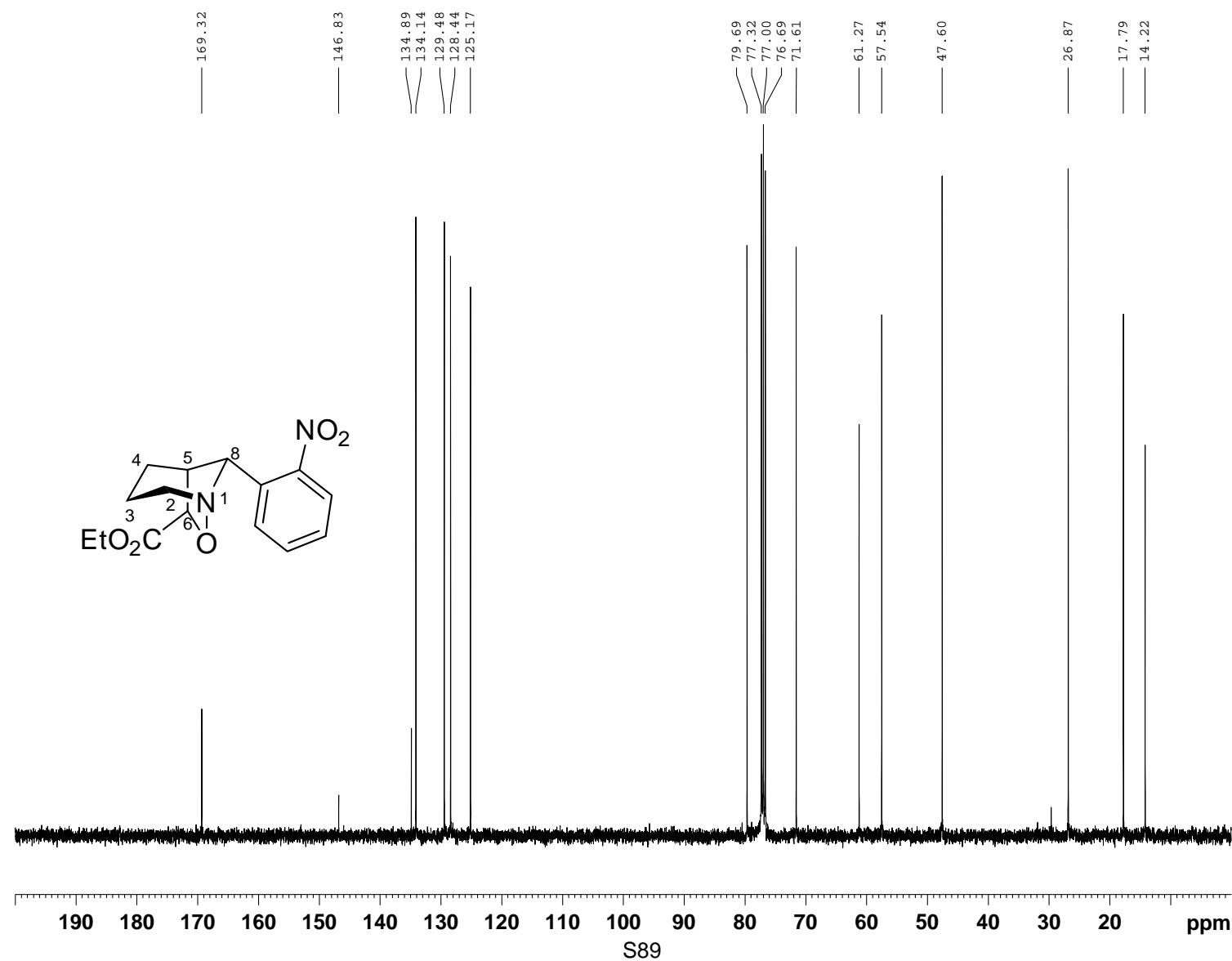


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-(2-nitrophenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18h):**

¹H NMR (400 MHz, CDCl₃)

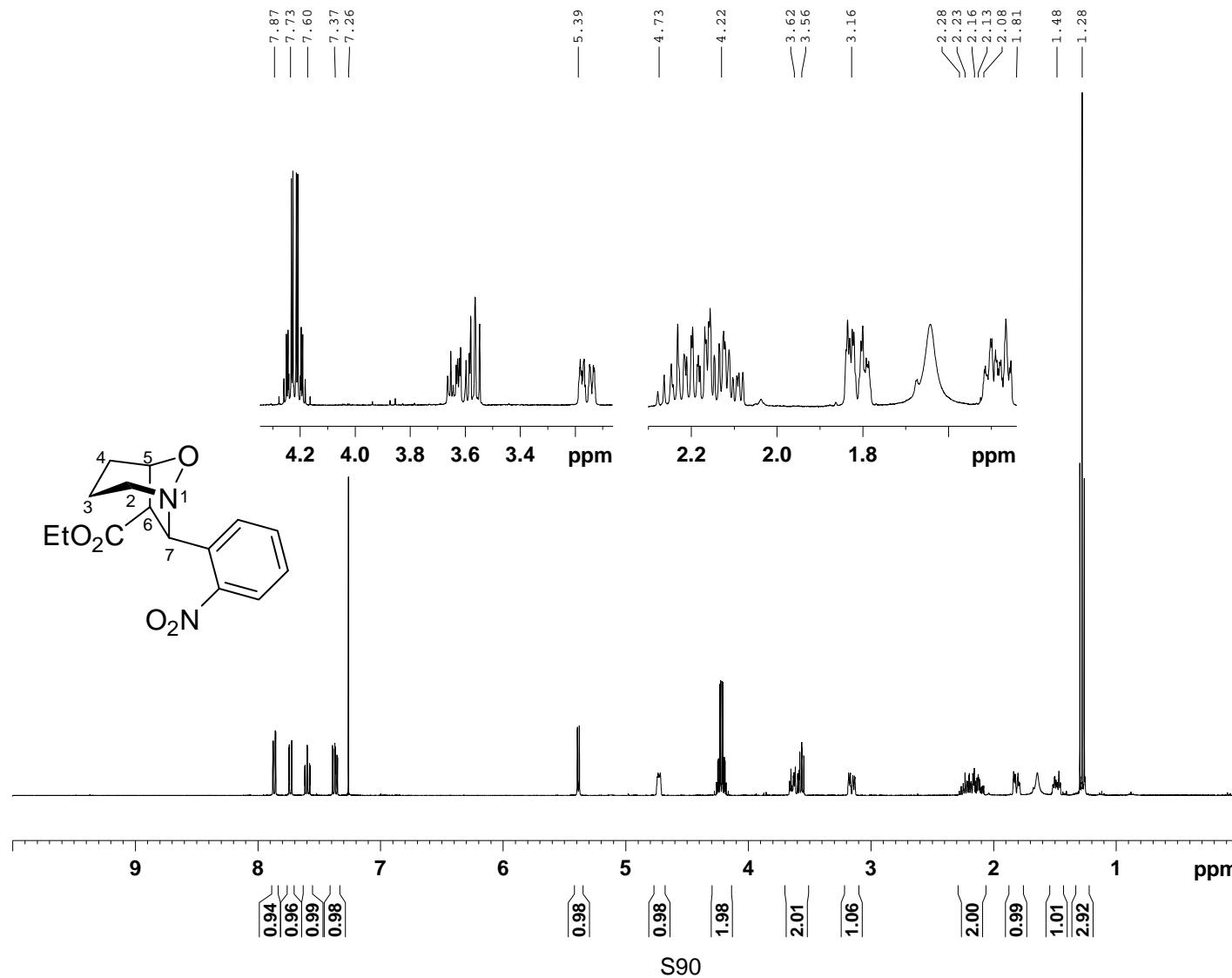


¹³C NMR (101 MHz, CDCl₃)

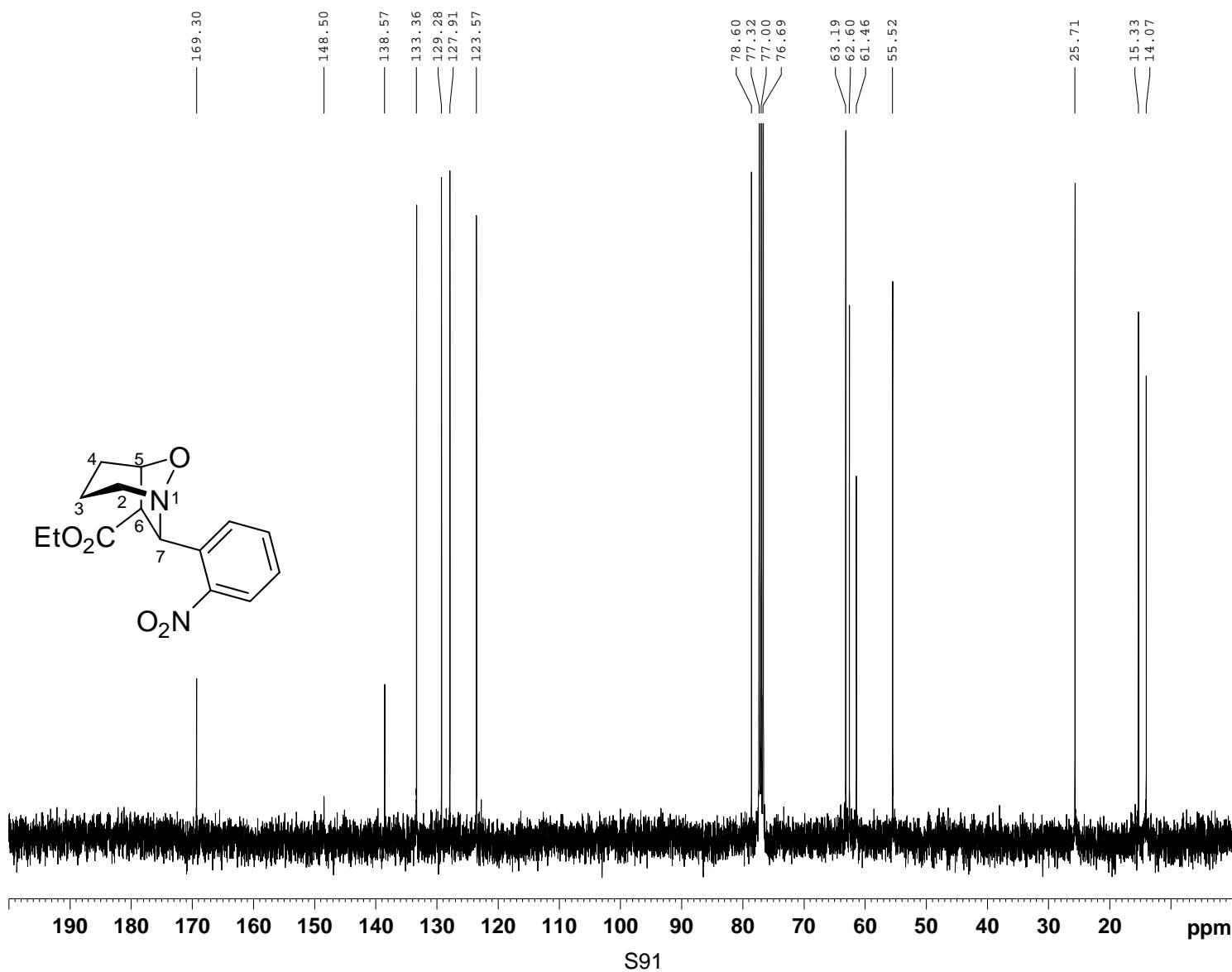


rac-(5*R*,6*R*,7*S*)-ethyl 7-(2-nitrophenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (**19h**):

¹H NMR (400 MHz, CDCl₃)

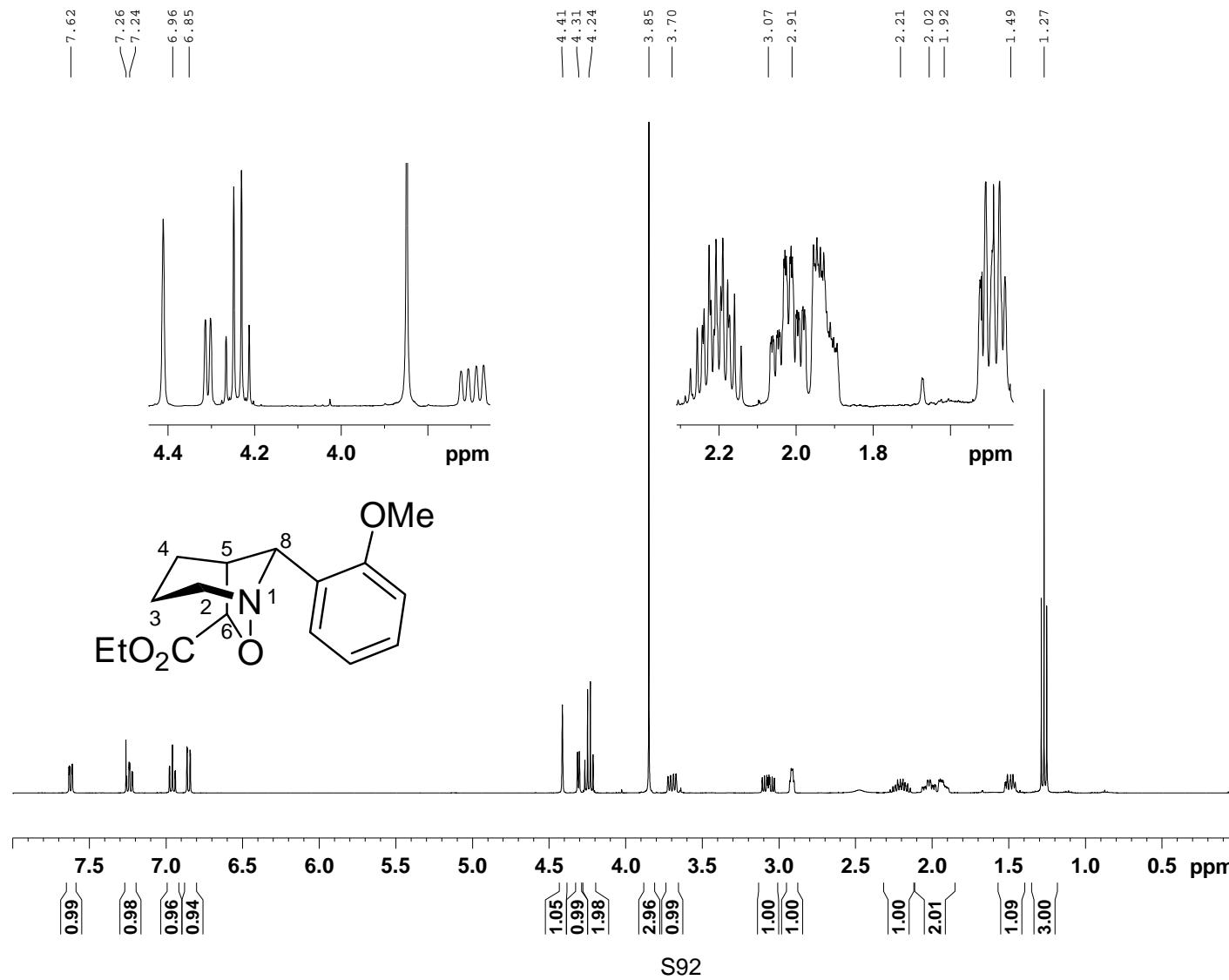


¹³C NMR (101 MHz, CDCl₃)

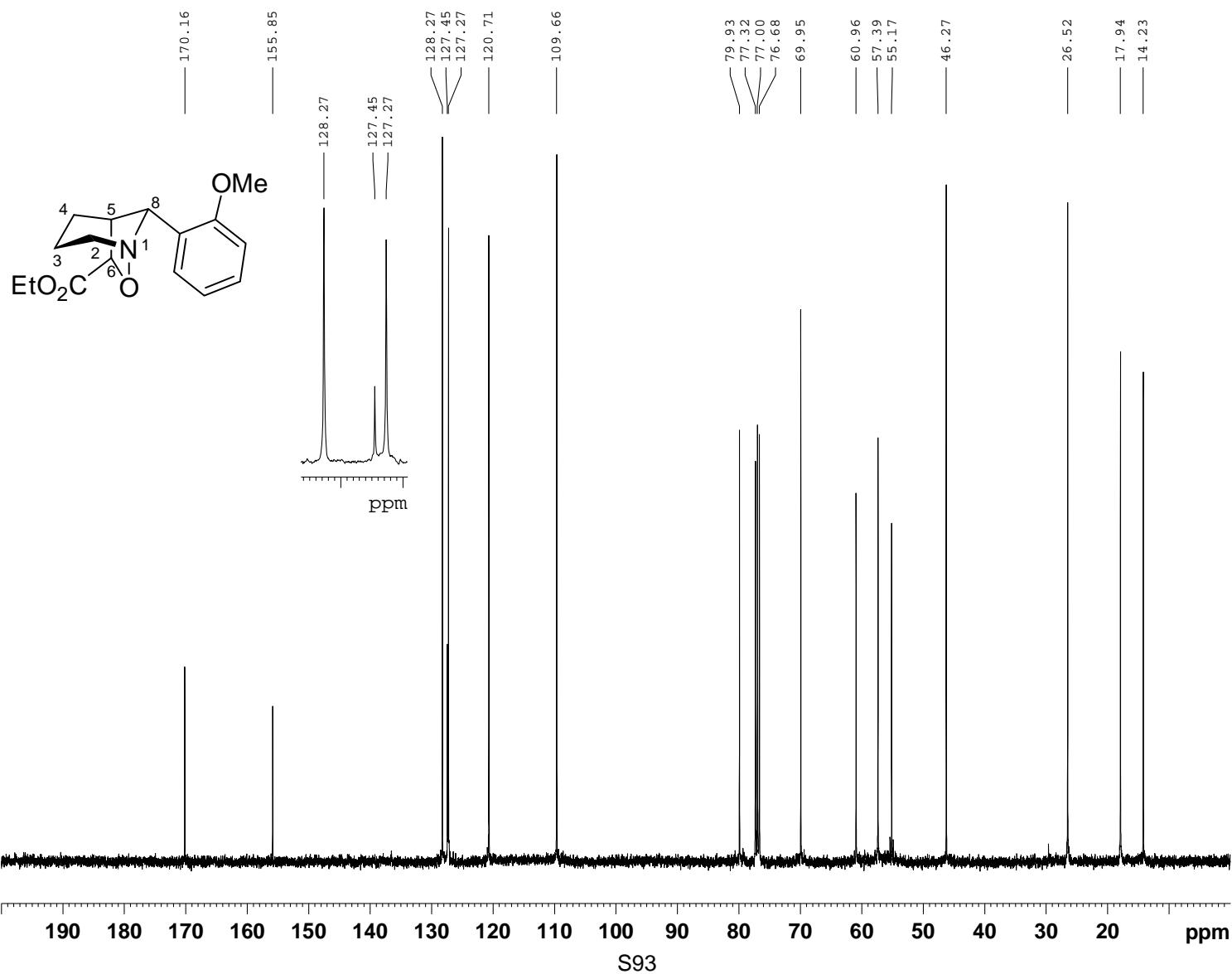


***rac*-(5*S*,6*R*,8*S*)-ethyl 8-(2-methoxyphenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18i):**

¹H NMR (400 MHz, CDCl₃)

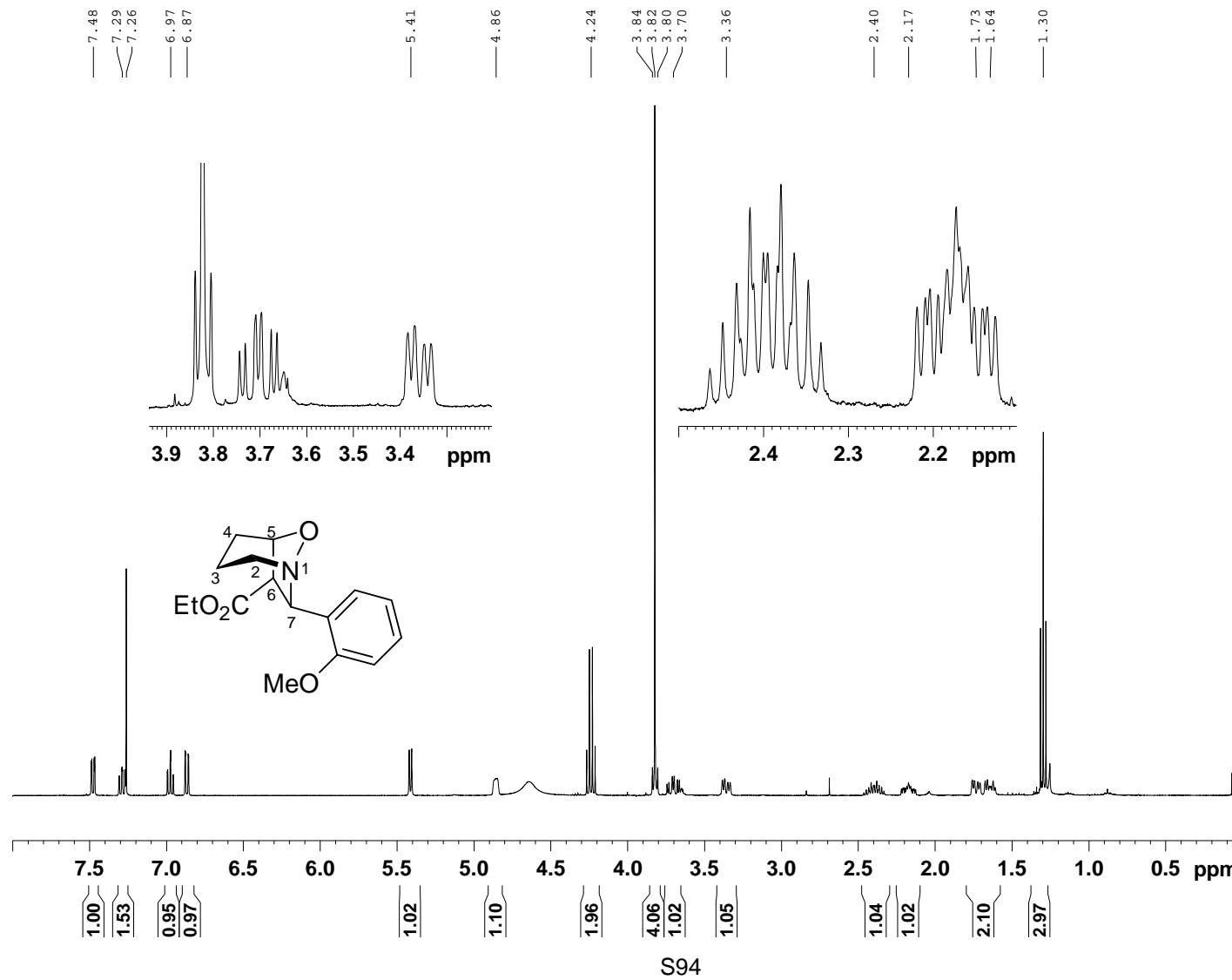


¹³C NMR (101 MHz, CDCl₃)

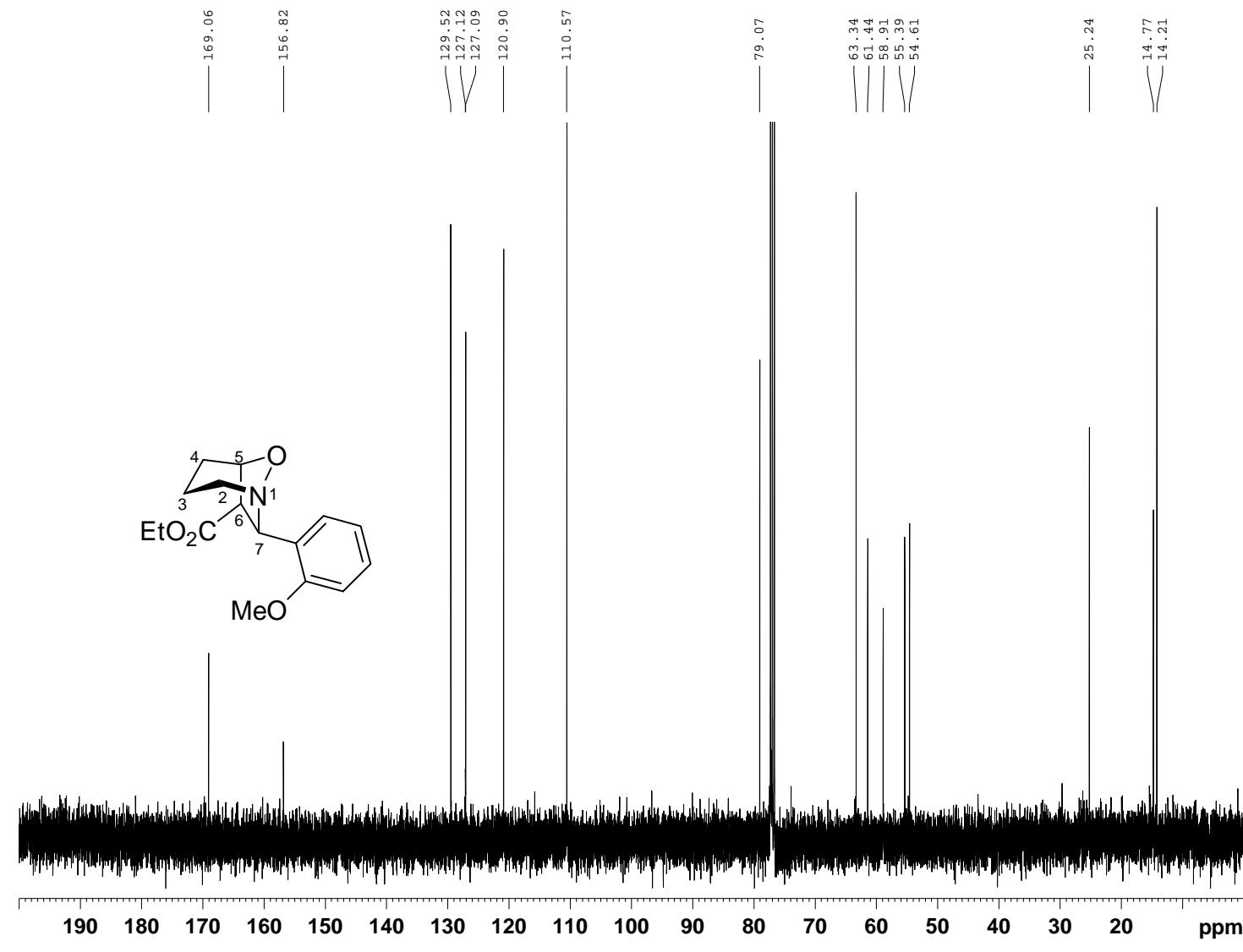


rac-(5*R*,6*R*,7*S*)-ethyl 7-(2-methoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19i):

^1H NMR (400 MHz, CDCl_3)

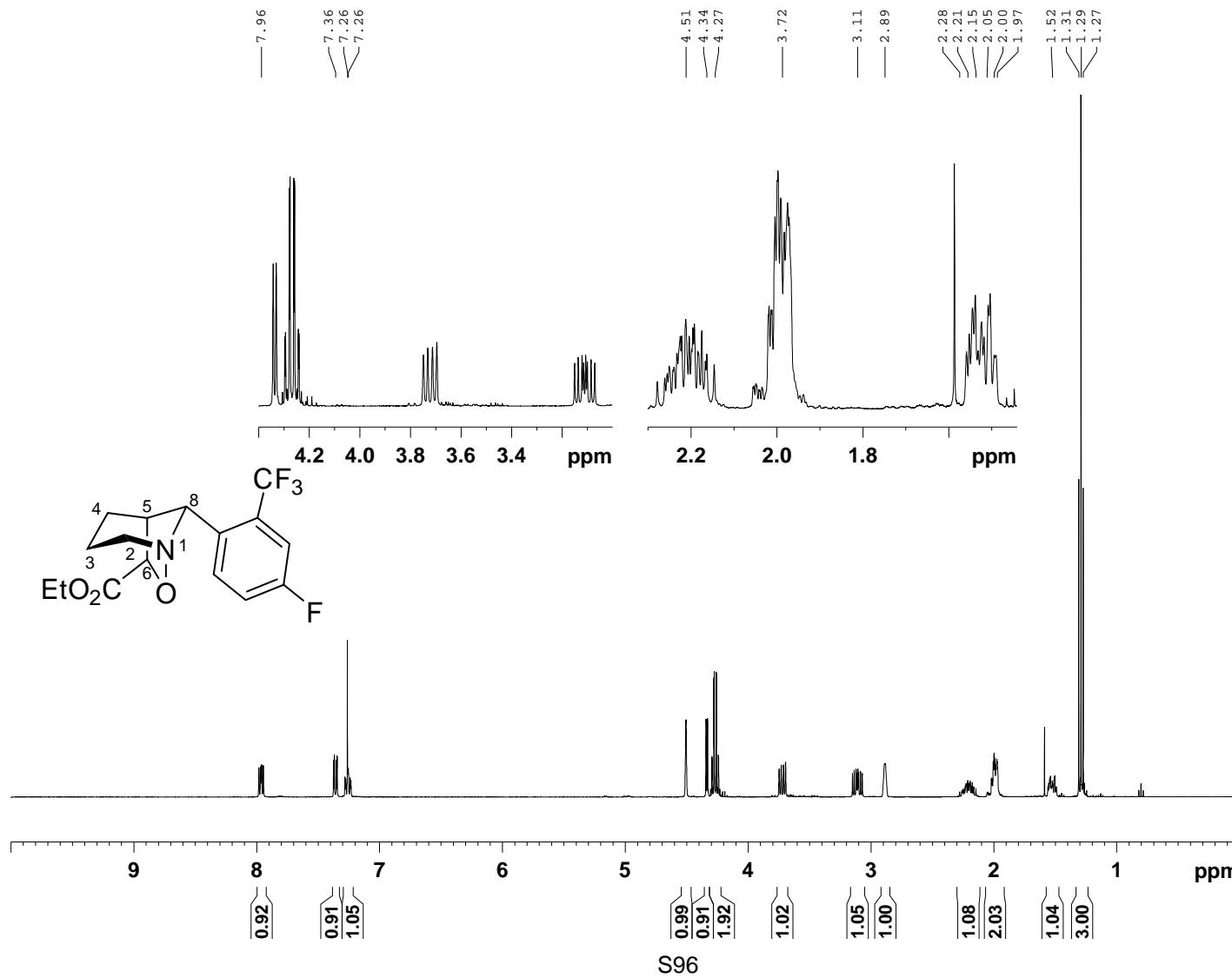


¹³C NMR (101 MHz, CDCl₃)

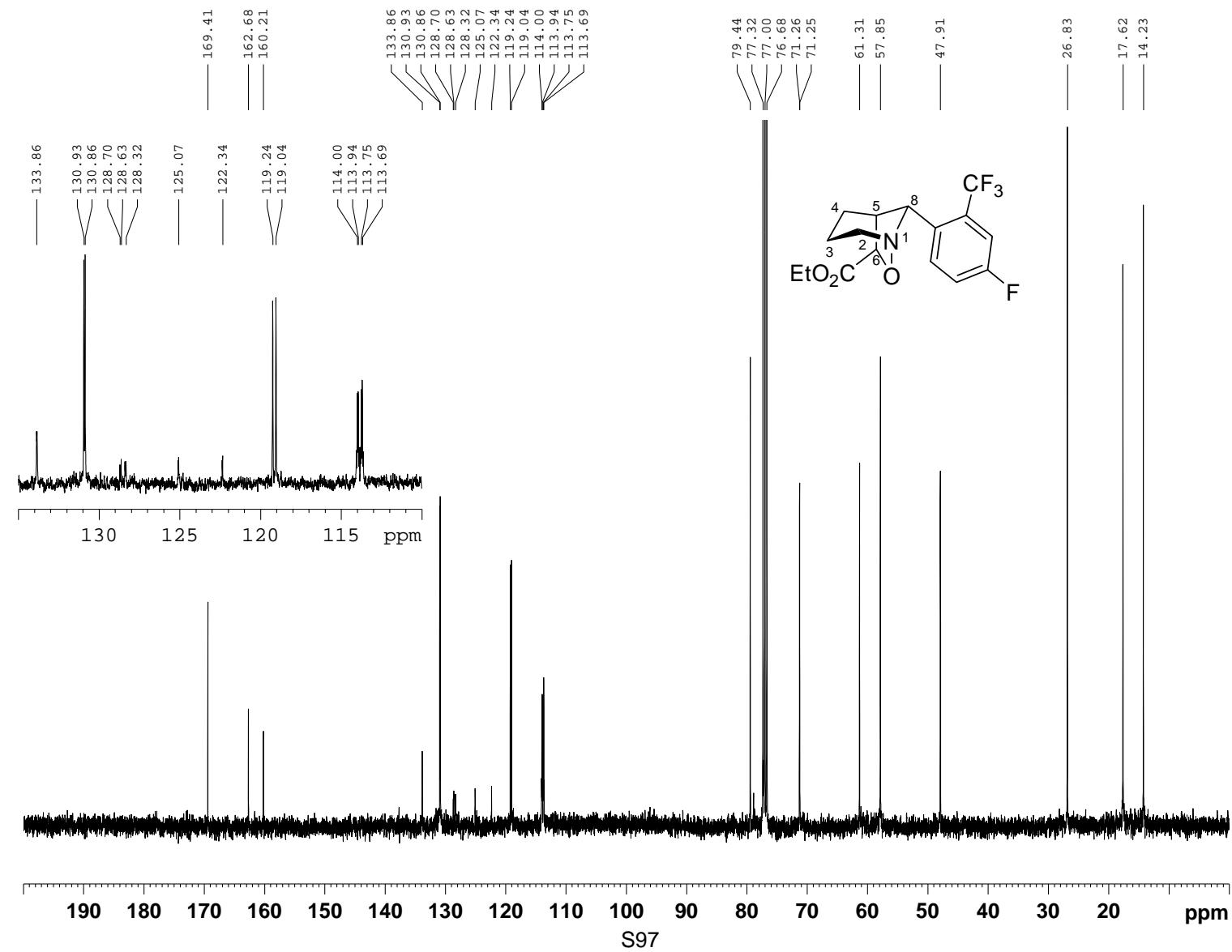


***rac*-(5*S*,6*R*,8*R*)-ethyl 8-(4-fluoro-2-(trifluoromethyl)phenyl)-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18j):**

¹H NMR (400 MHz, CDCl₃)

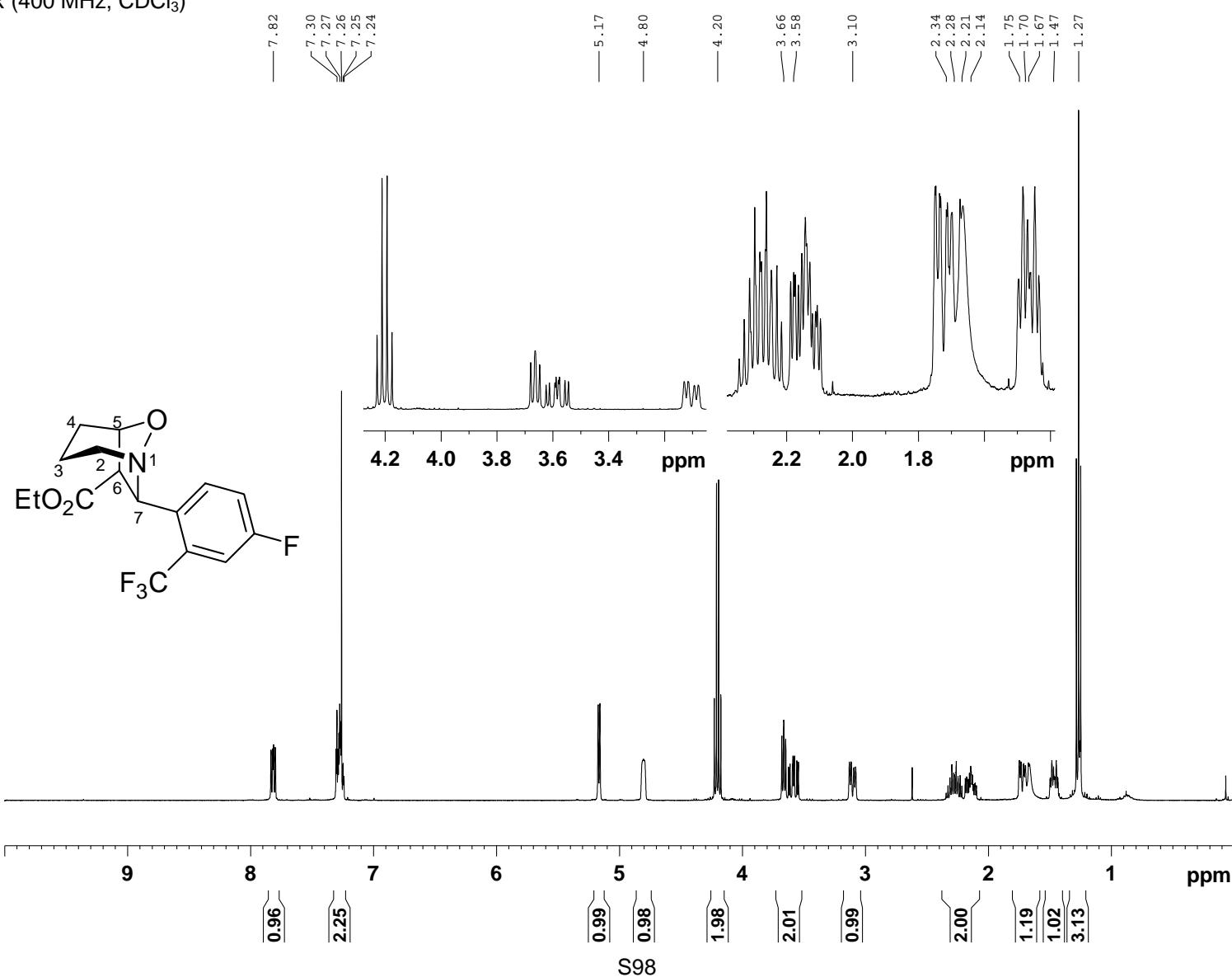


¹³C NMR (101 MHz, CDCl₃)

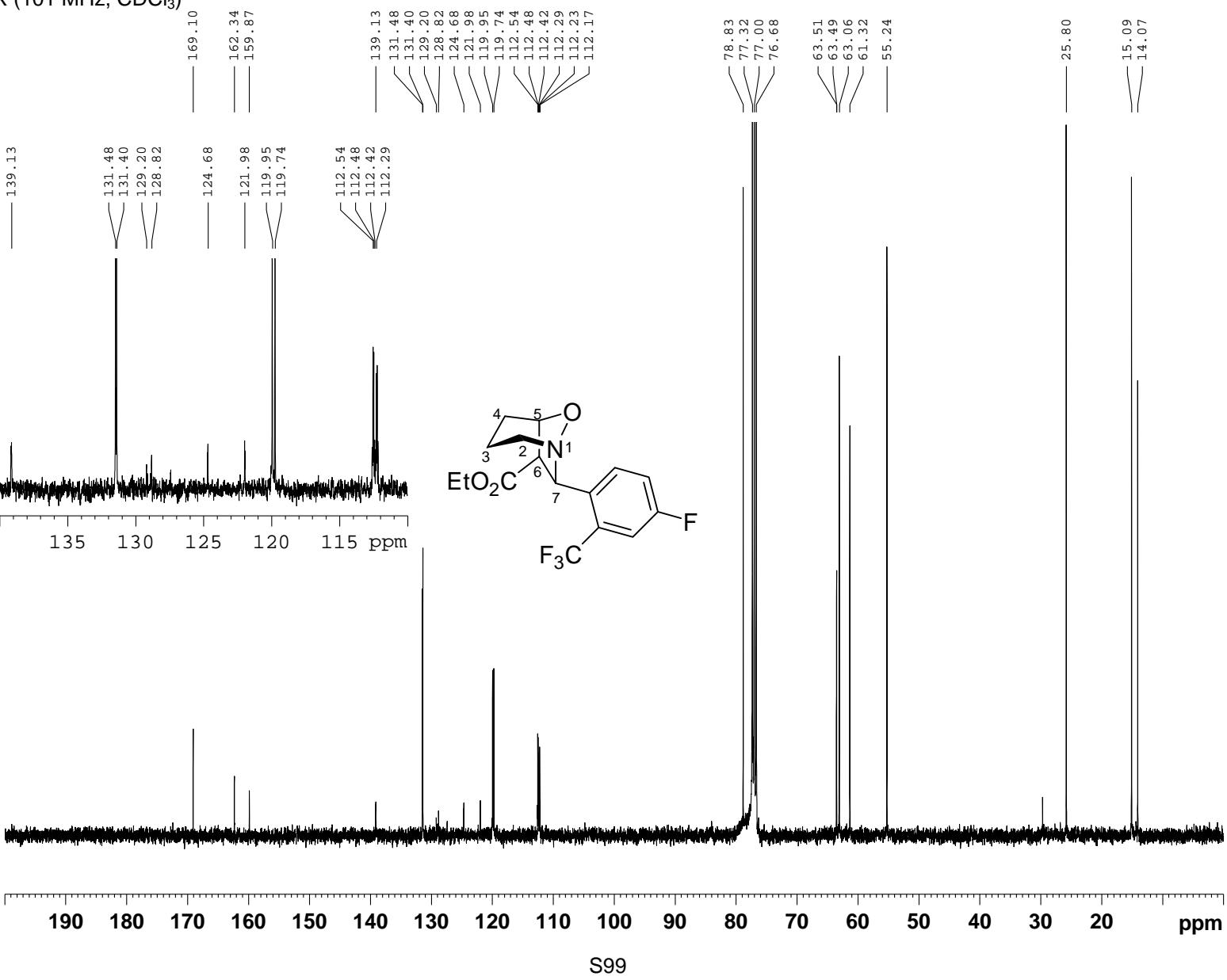


rac-(5*R*,6*R*,7*S*)-ethyl 7-(4-fluoro-2-(trifluoromethyl)phenyl)-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19j):

^1H NMR (400 MHz, CDCl_3)



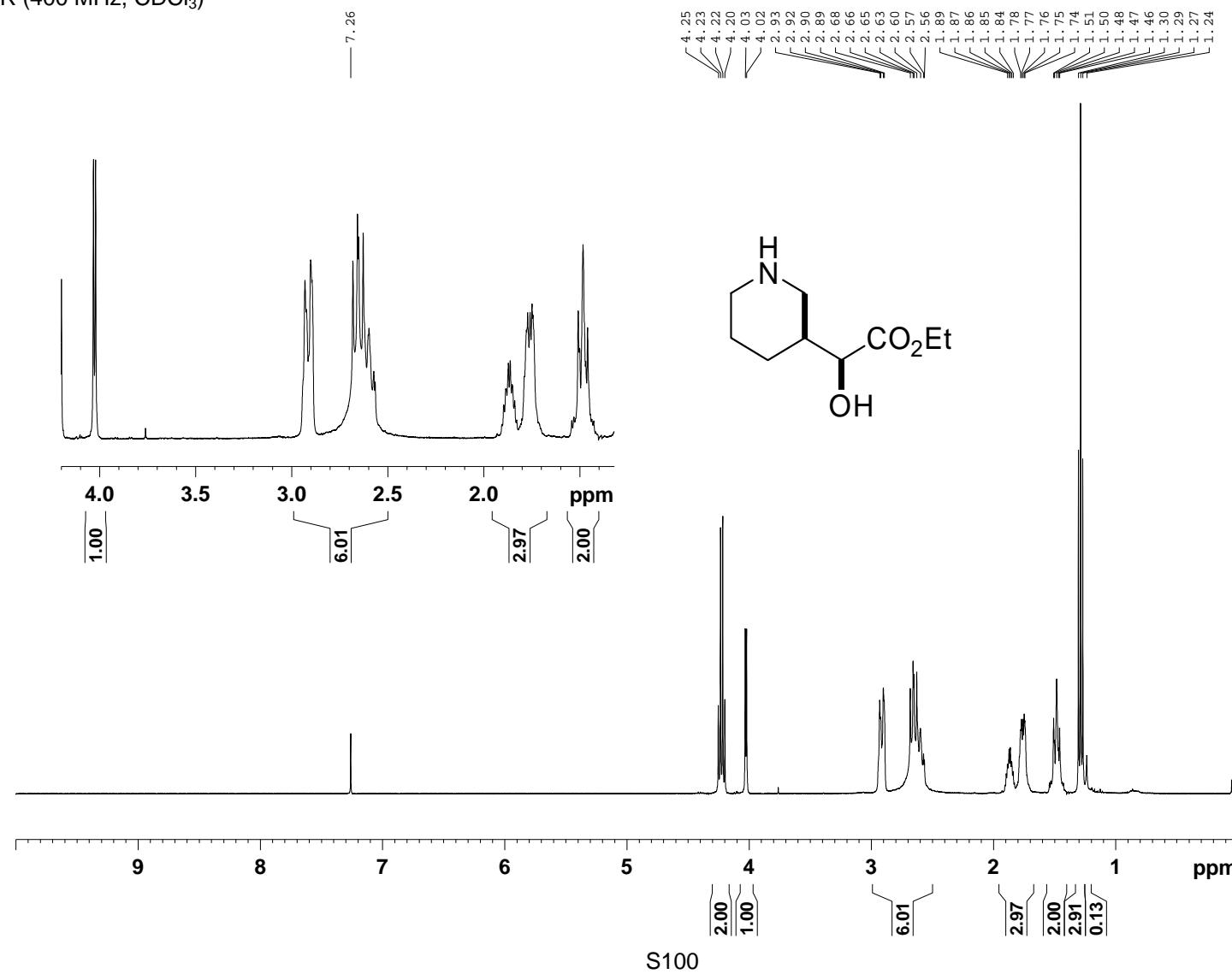
¹³C NMR (101 MHz, CDCl₃)



S99

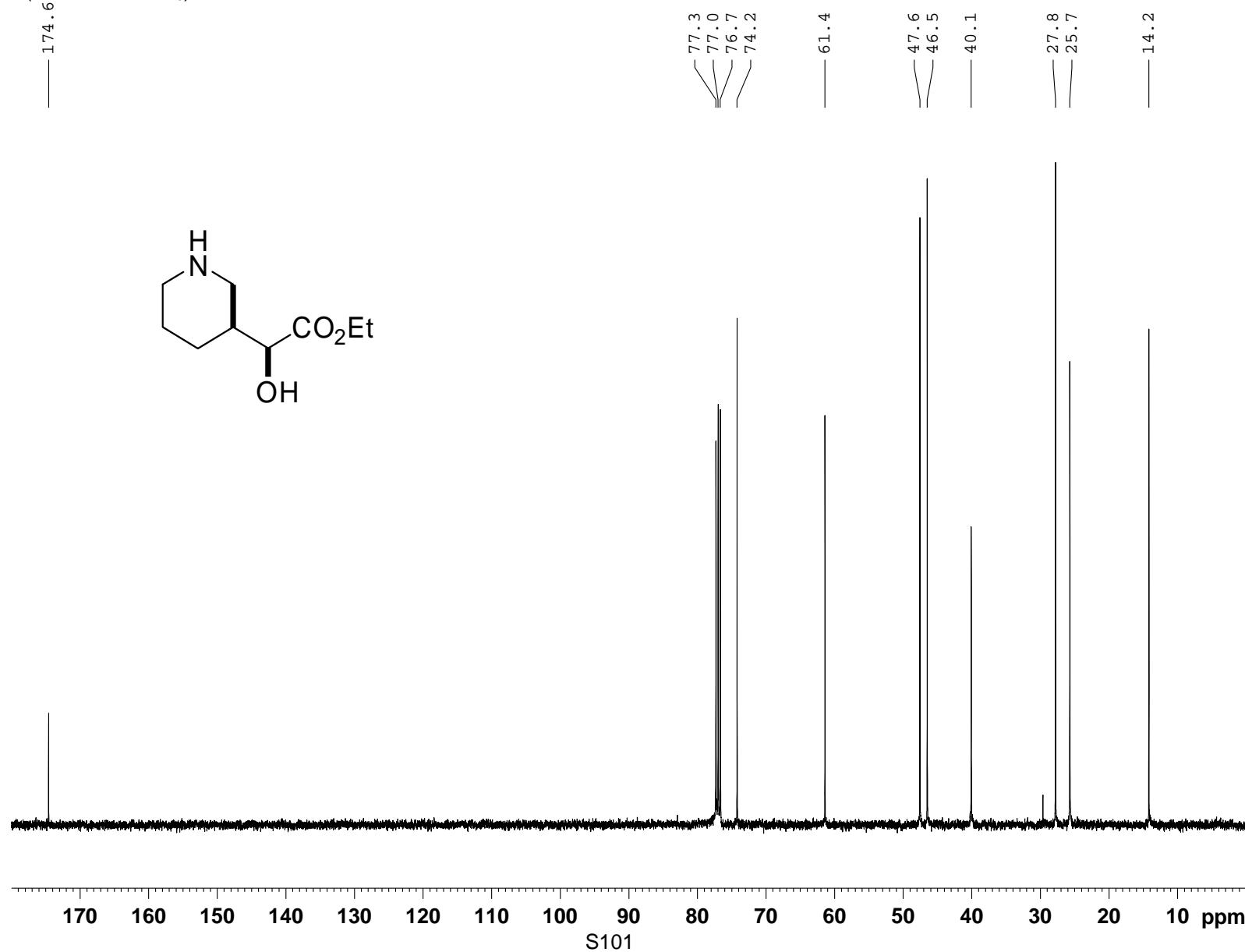
***rac*-(*R*)-Ethyl 2-hydroxy-2-((*R*)-piperidin-3-yl)acetate (20a):**

^1H NMR (400 MHz, CDCl_3)

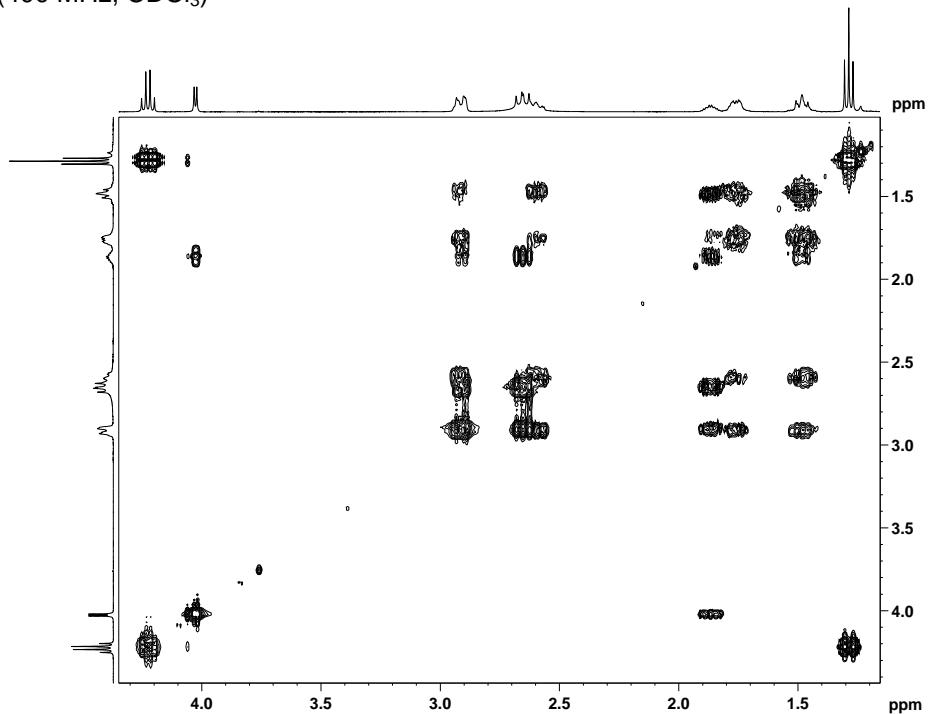


S100

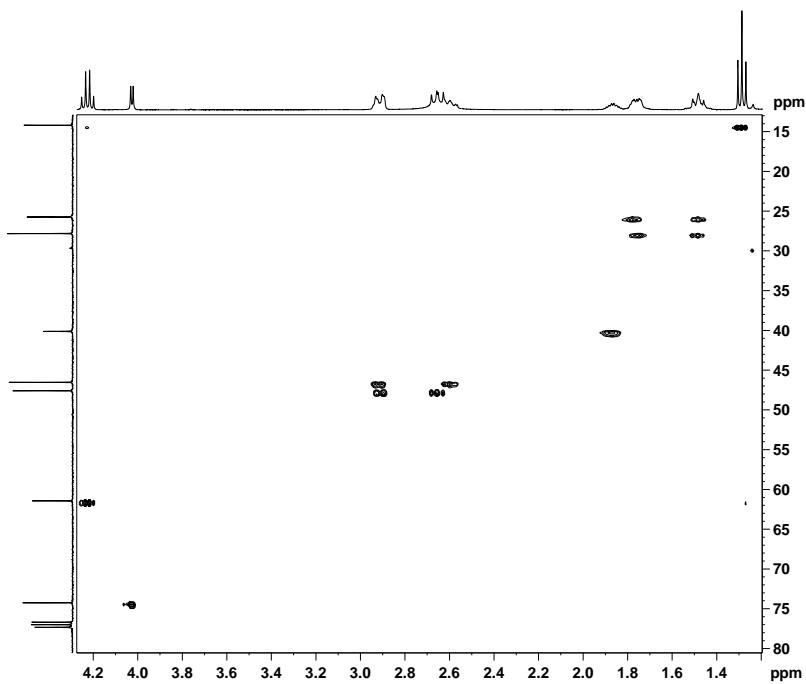
^{13}C NMR (101 MHz, CDCl_3)



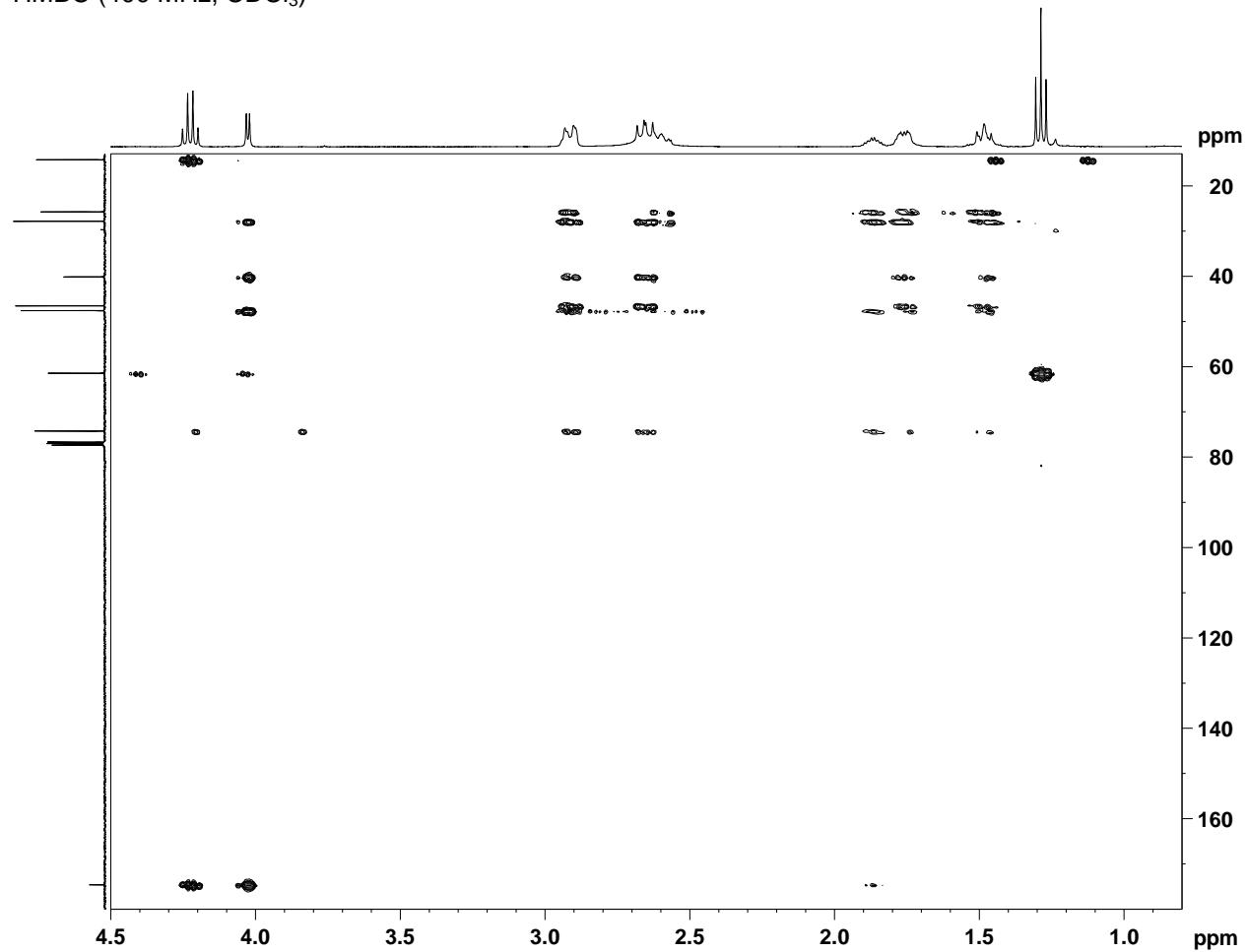
COSY (400 MHz, CDCl_3)



HSQC (400 MHz, CDCl_3)

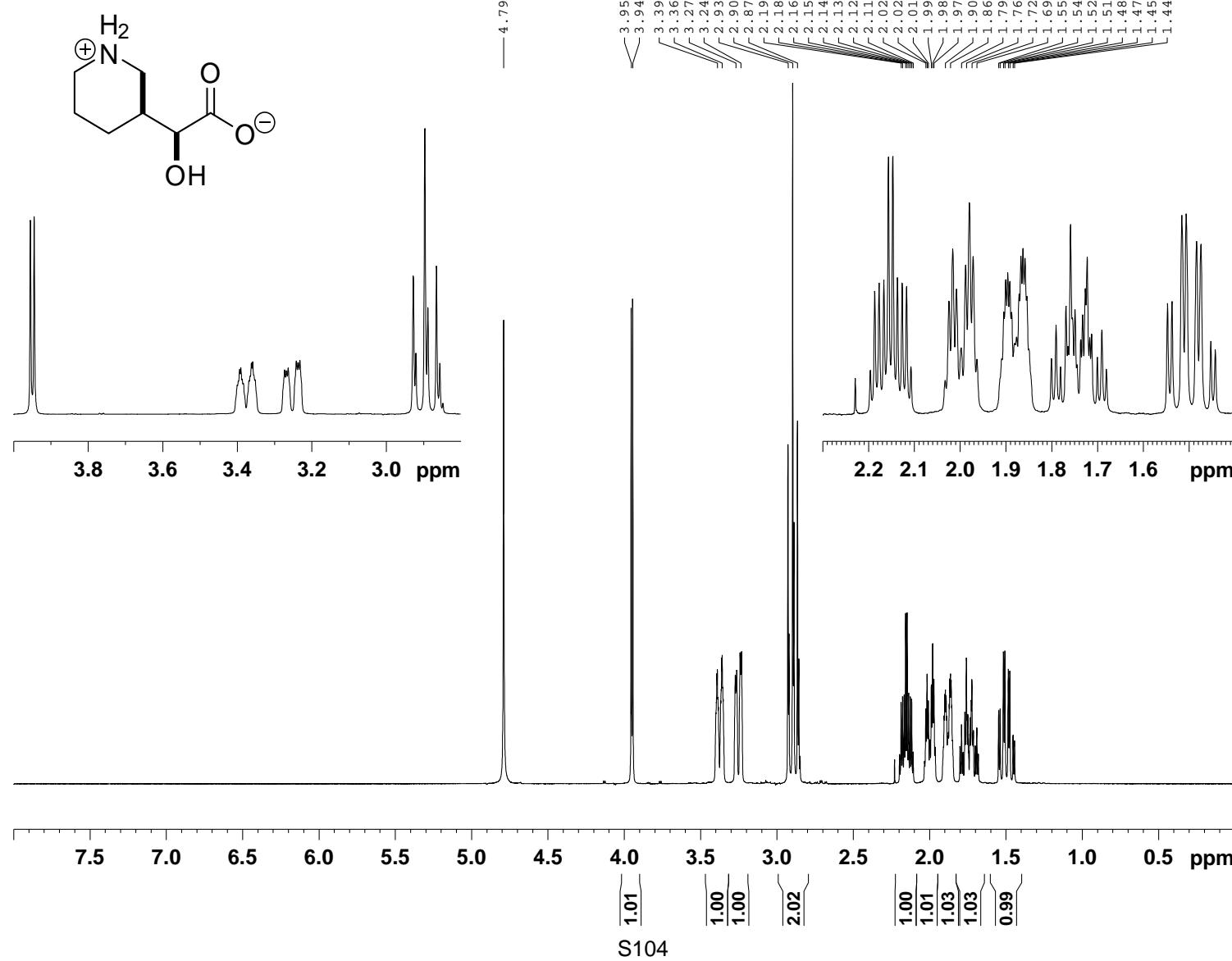


HMBC (400 MHz, CDCl₃)



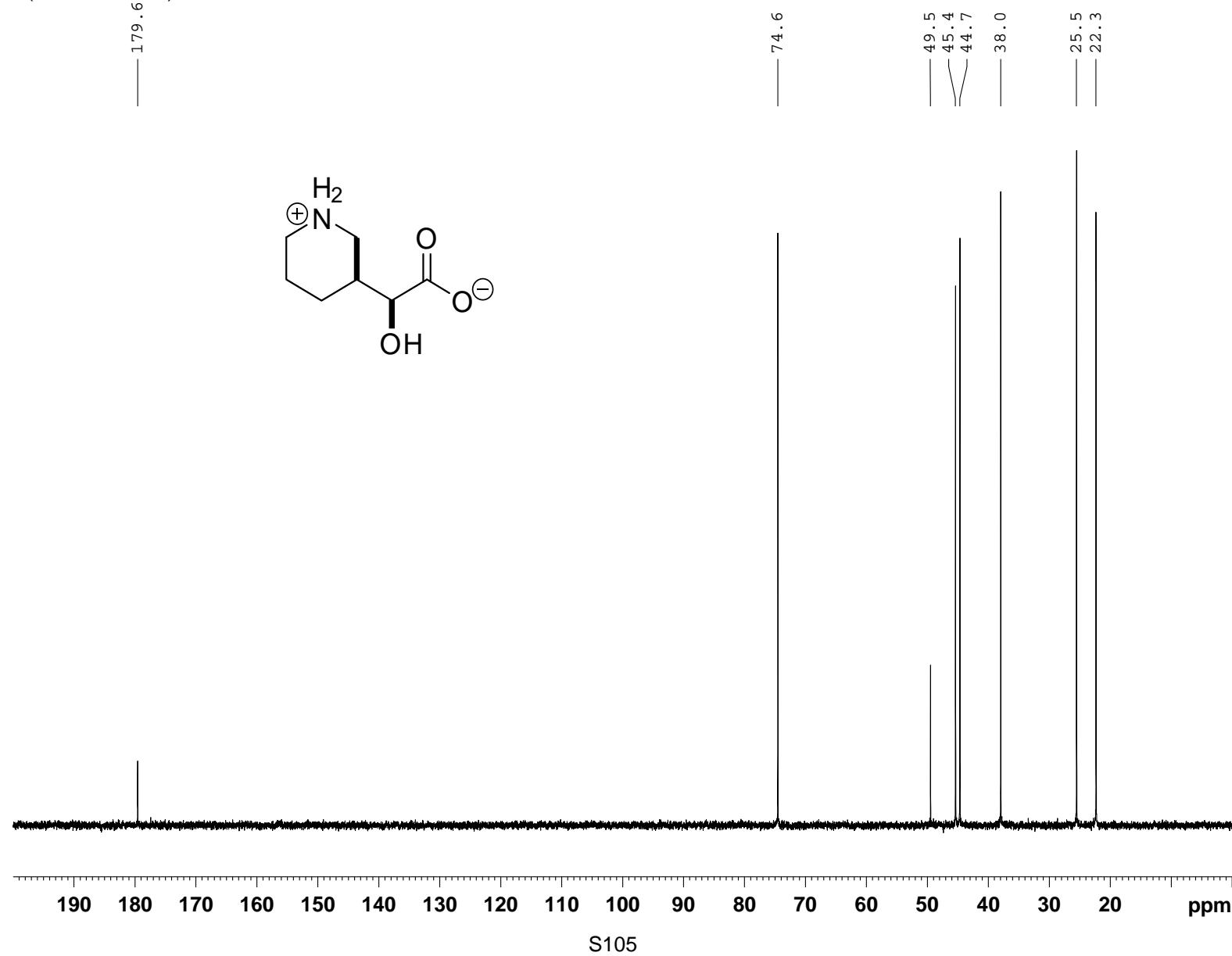
***rac*-(*R*)-2-Hydroxy-2-((*R*)-piperidin-3-yl)acetic acid (20b):**

^1H NMR (400 MHz, D_2O)

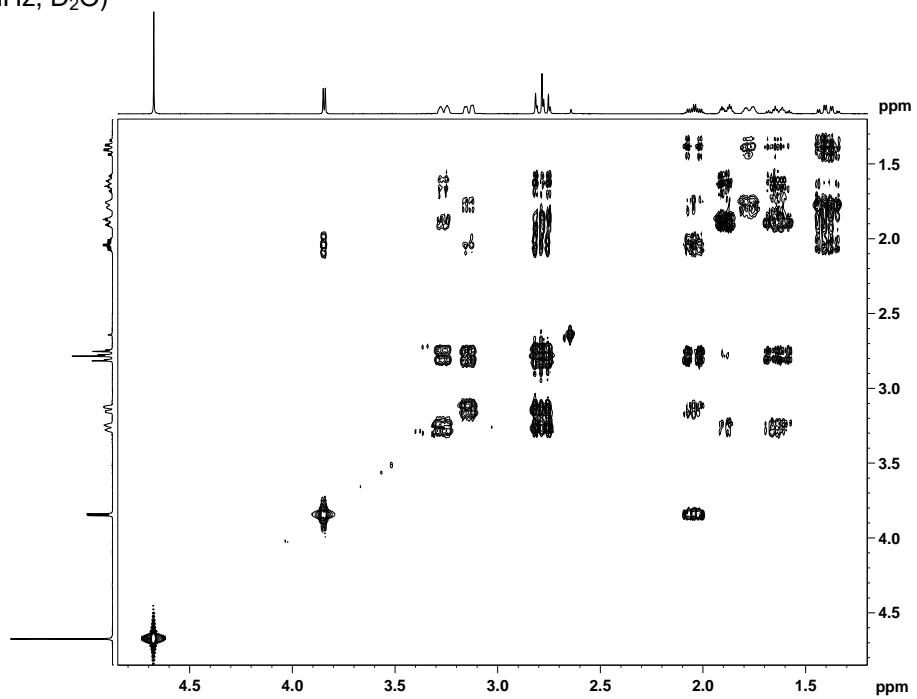


S104

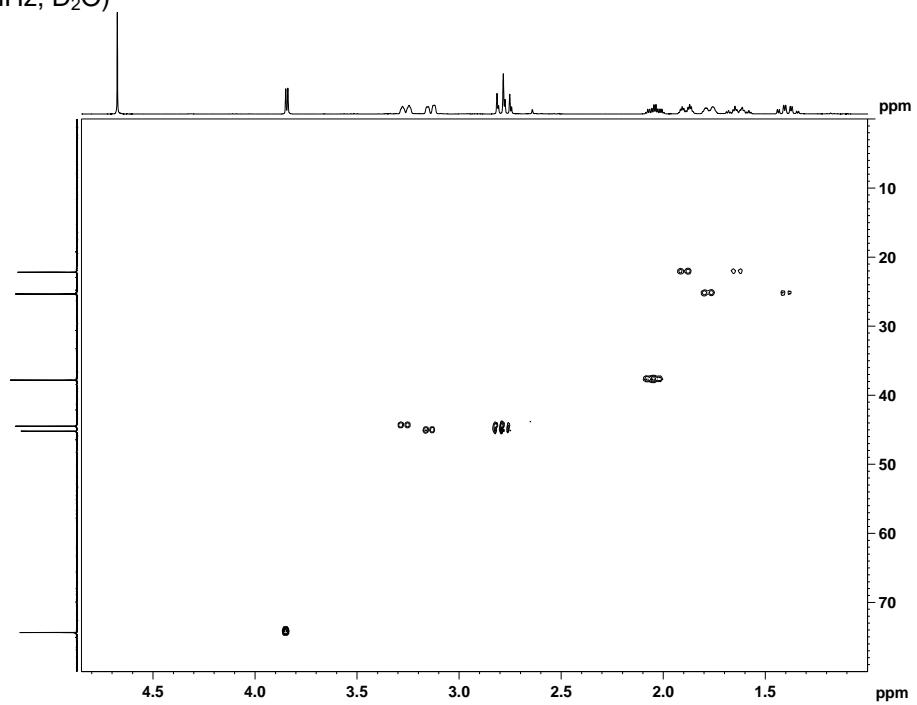
¹³C NMR (101 MHz, D₂O)



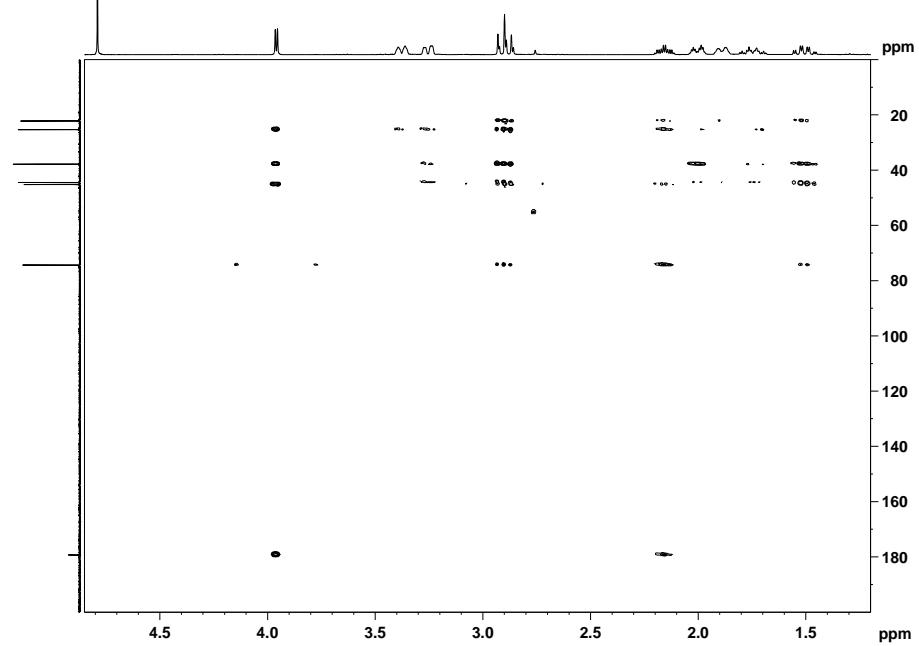
COSY (400 MHz, D₂O)



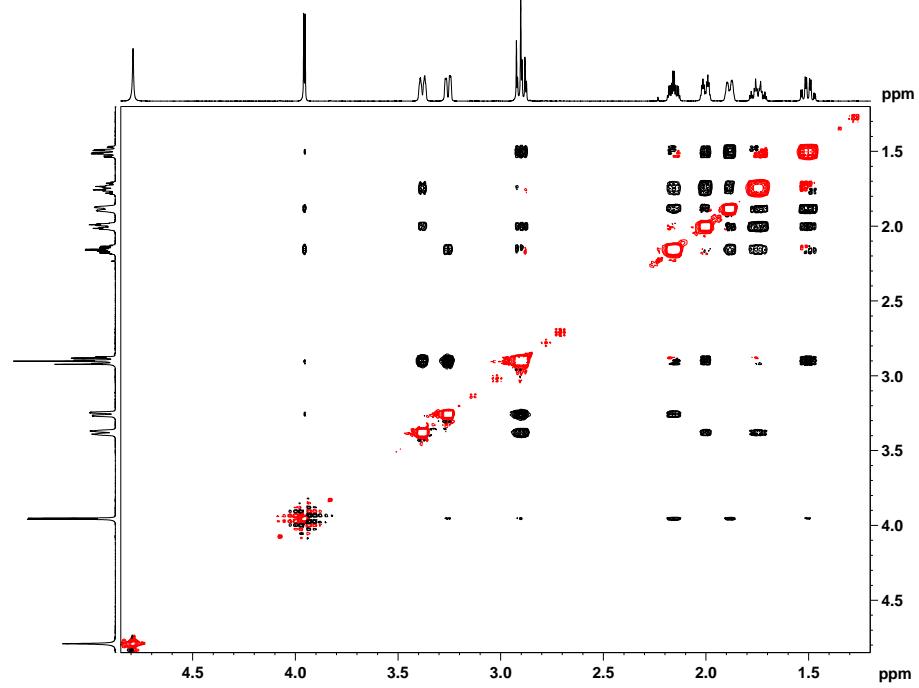
HSQC (400 MHz, D₂O)



HMBC (400 MHz, D₂O)

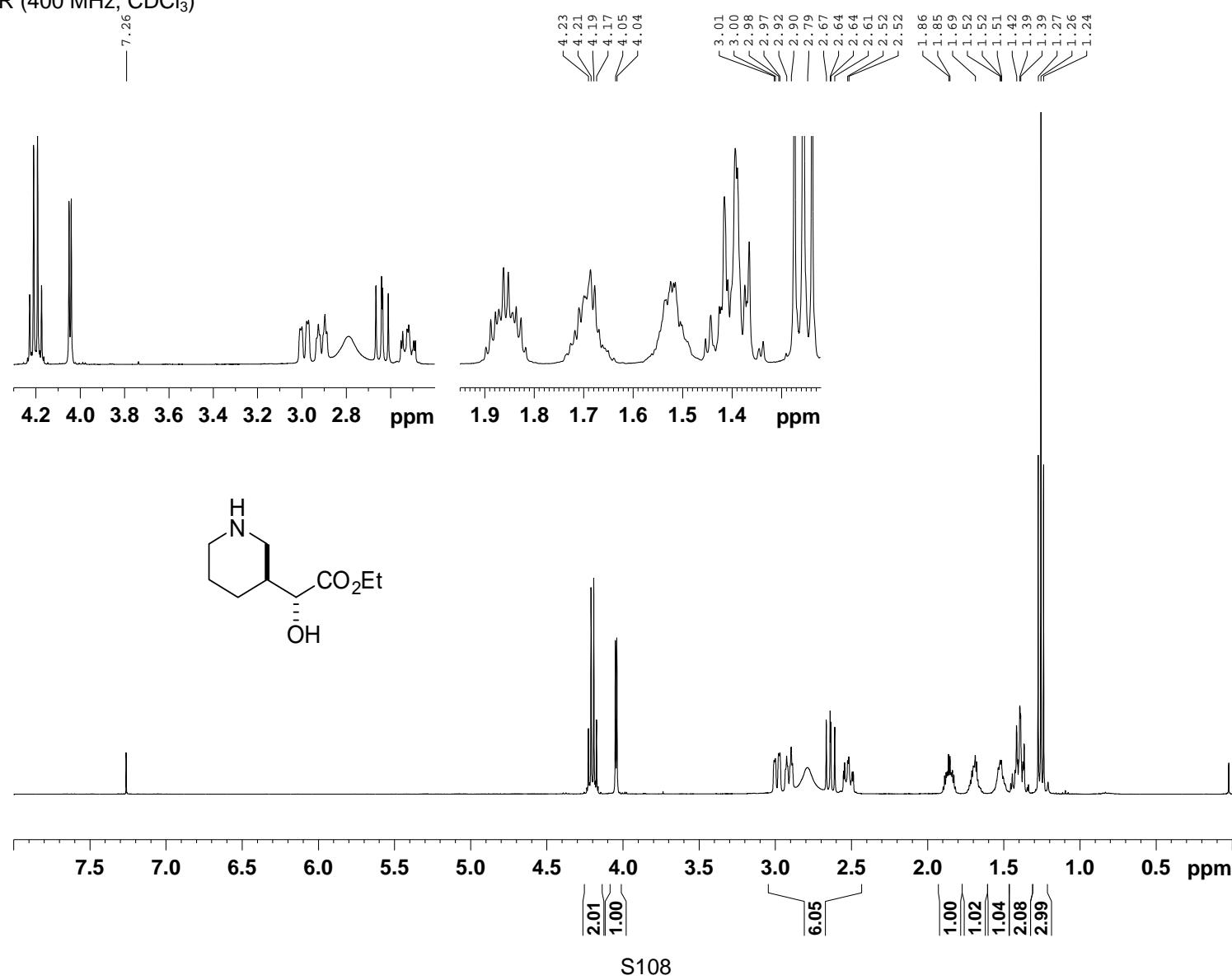


2D NOESY (600 MHz, D₂O)

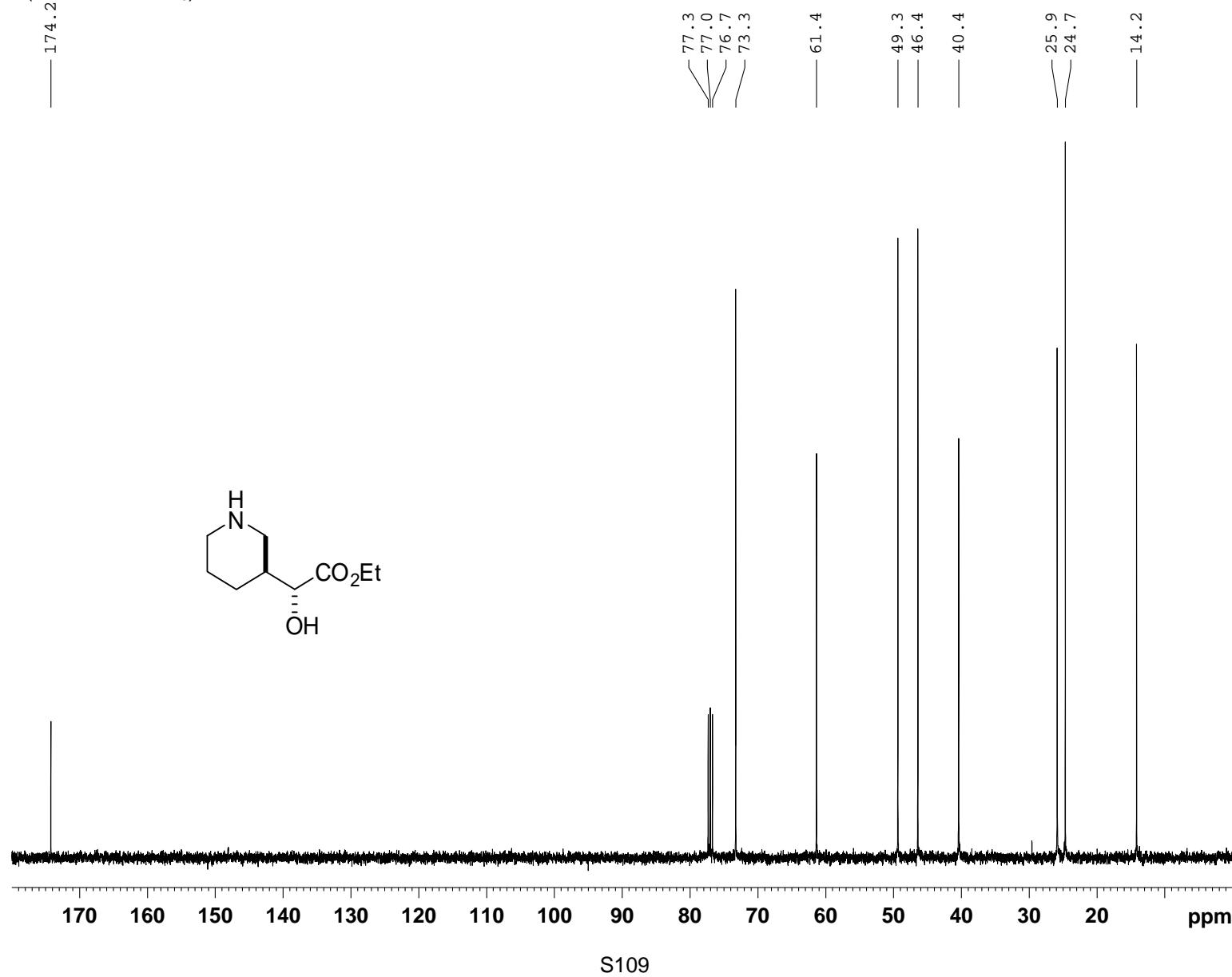


rac-(*R*)-Ethyl 2-hydroxy-2-((*S*)-piperidin-3-yl)acetate (21a):

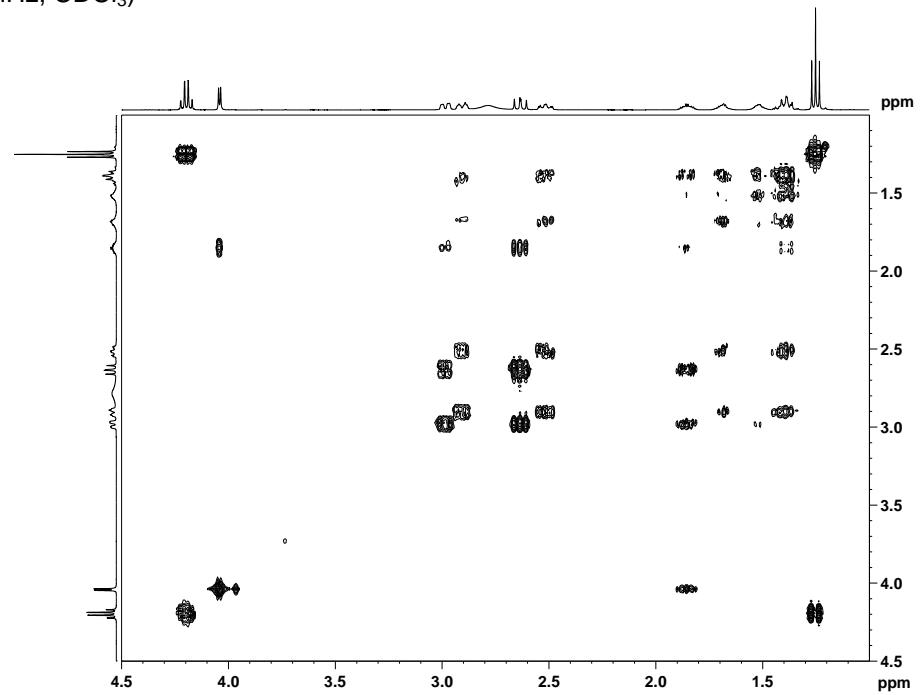
^1H NMR (400 MHz, CDCl_3)



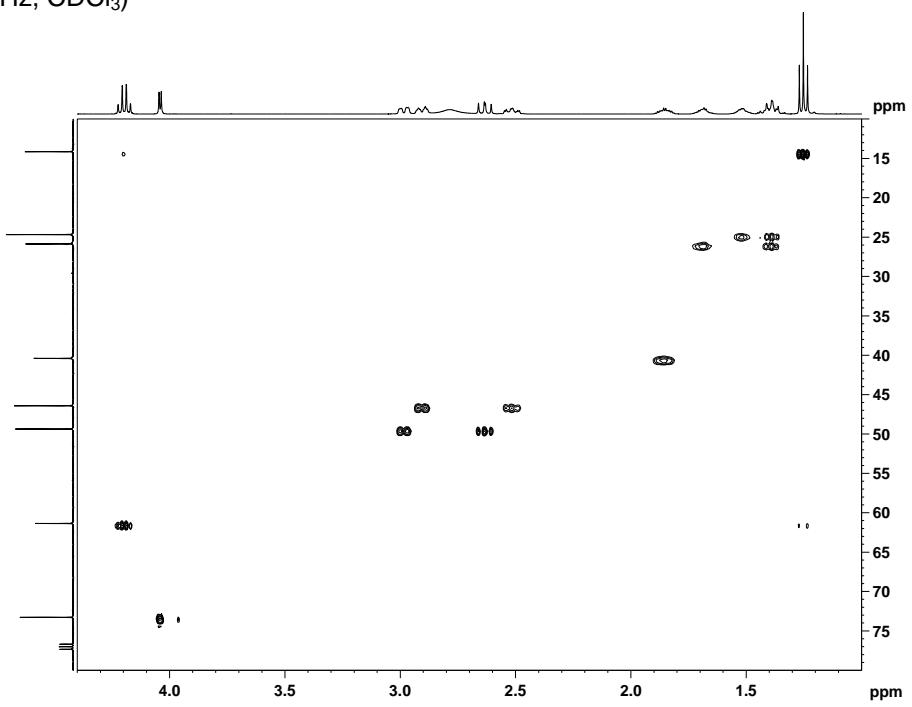
¹³C NMR (101 MHz, CDCl₃)



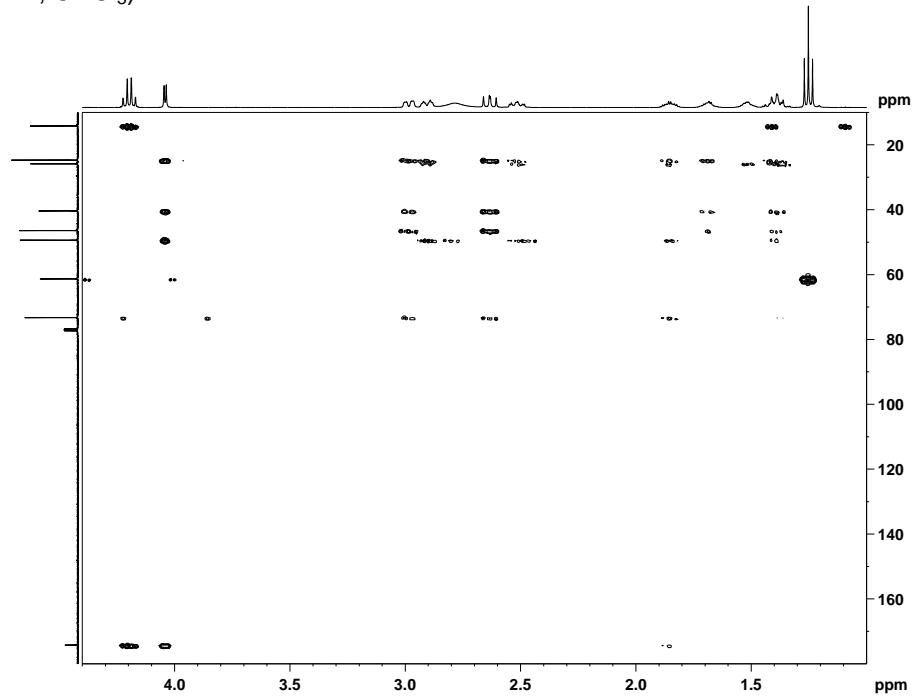
COSY (400 MHz, CDCl_3)



HSQC (400 MHz, CDCl_3)

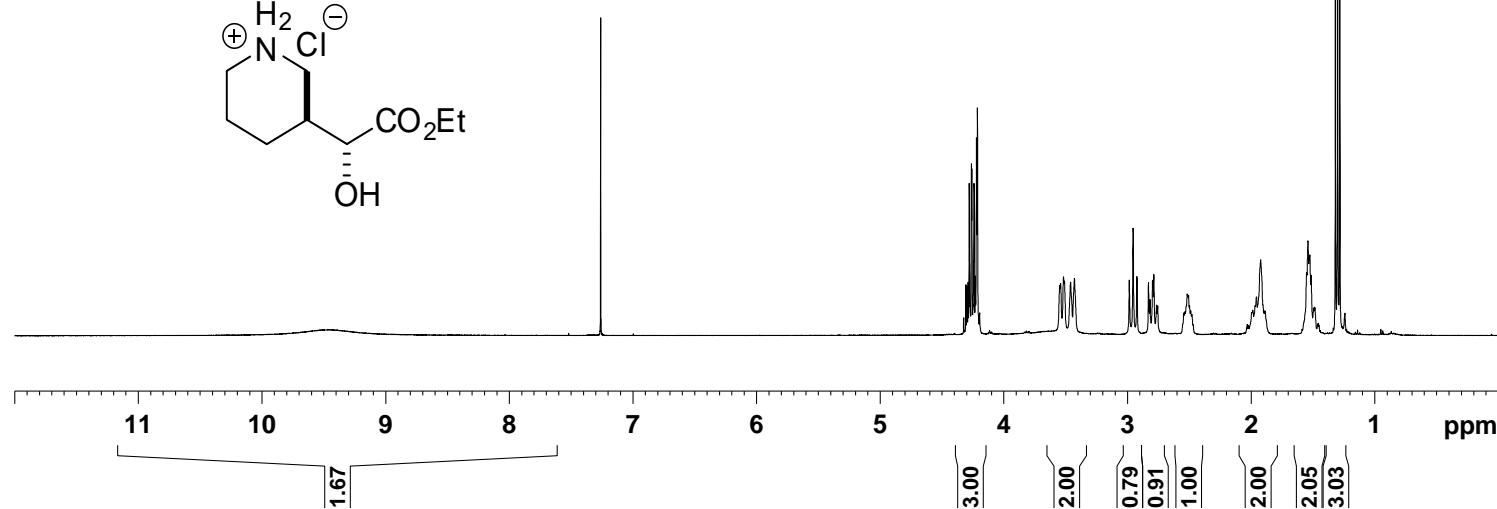
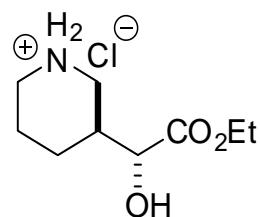
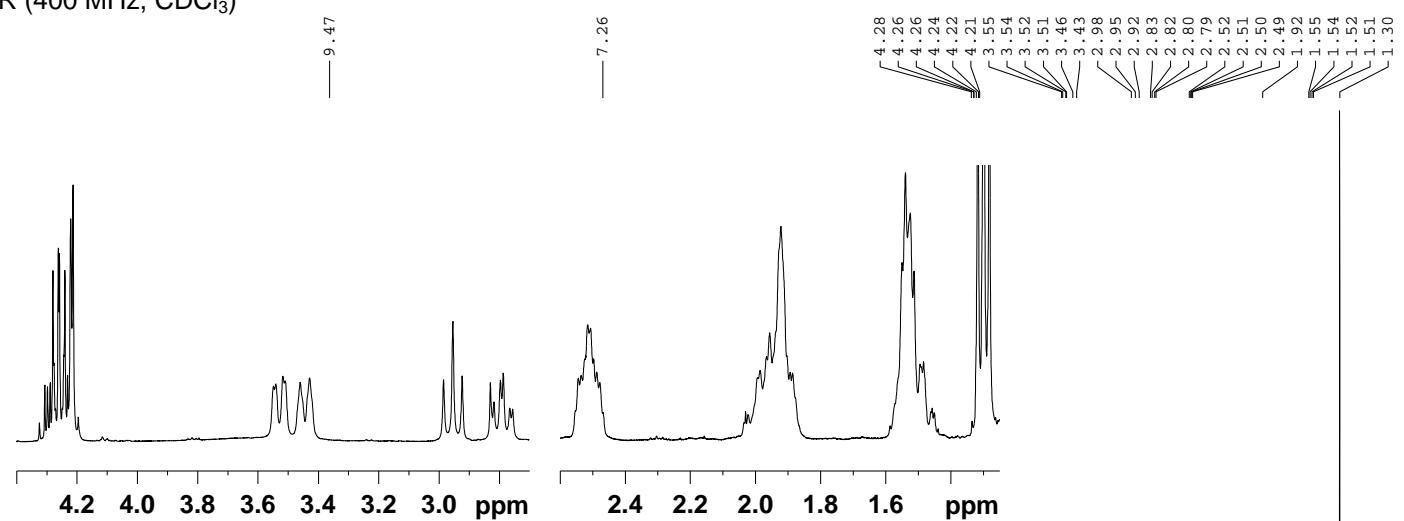


HMBC (400 MHz, CDCl₃)

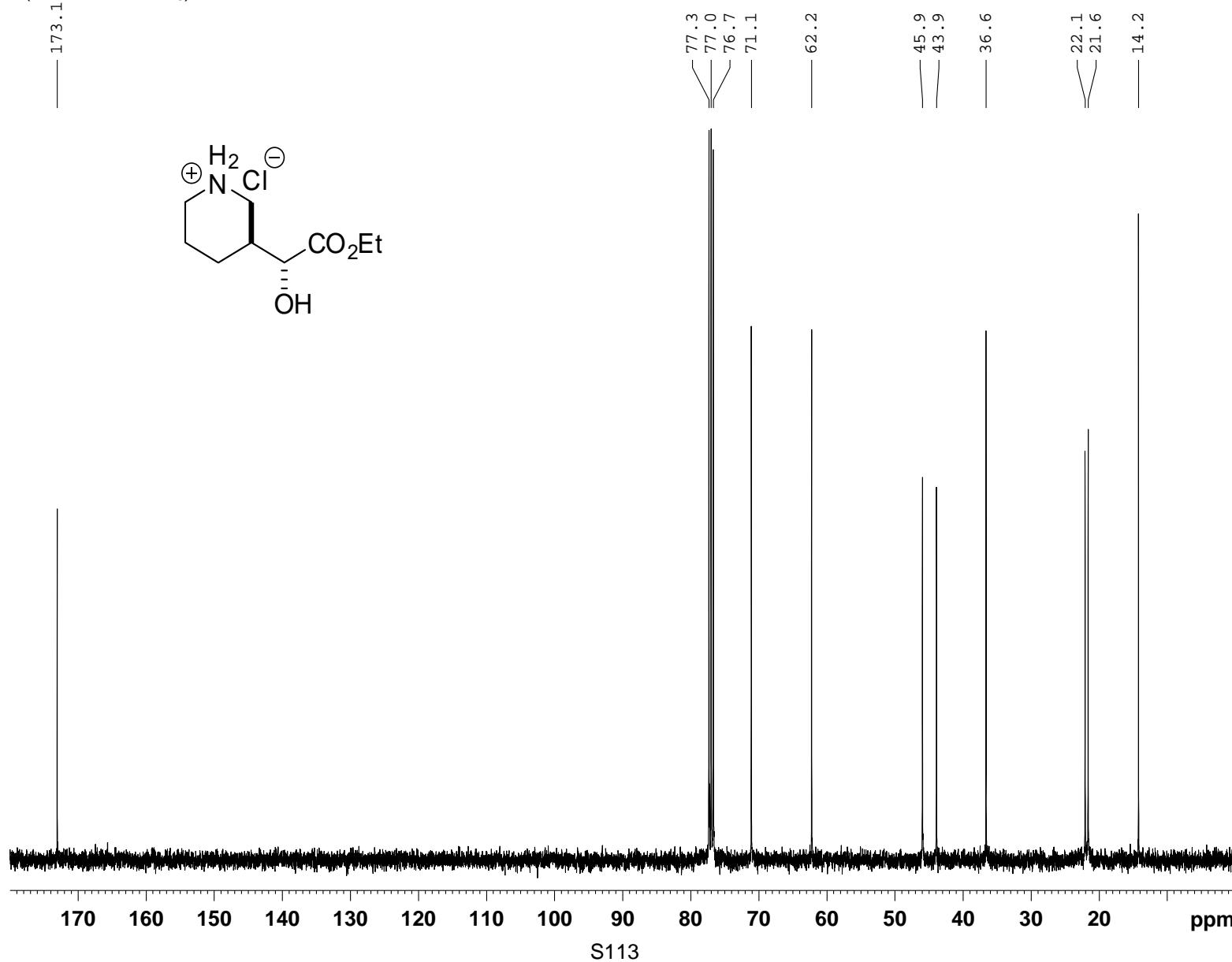


rac-(*R*)-3-((*S*)-2-Ethoxy-1-hydroxy-2-oxoethyl)piperidinium chloride

^1H NMR (400 MHz, CDCl_3)

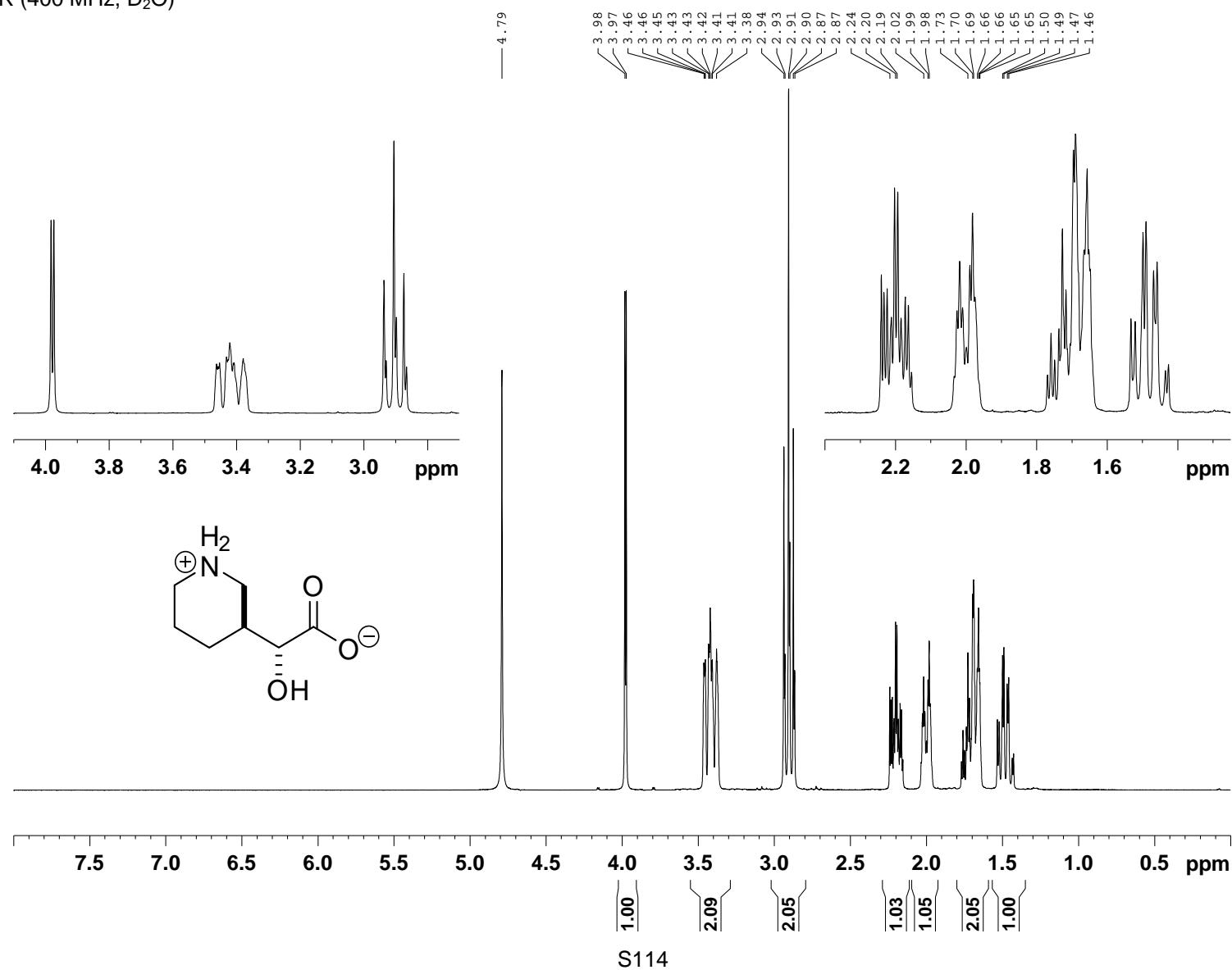


¹³C NMR (101 MHz, CDCl₃)

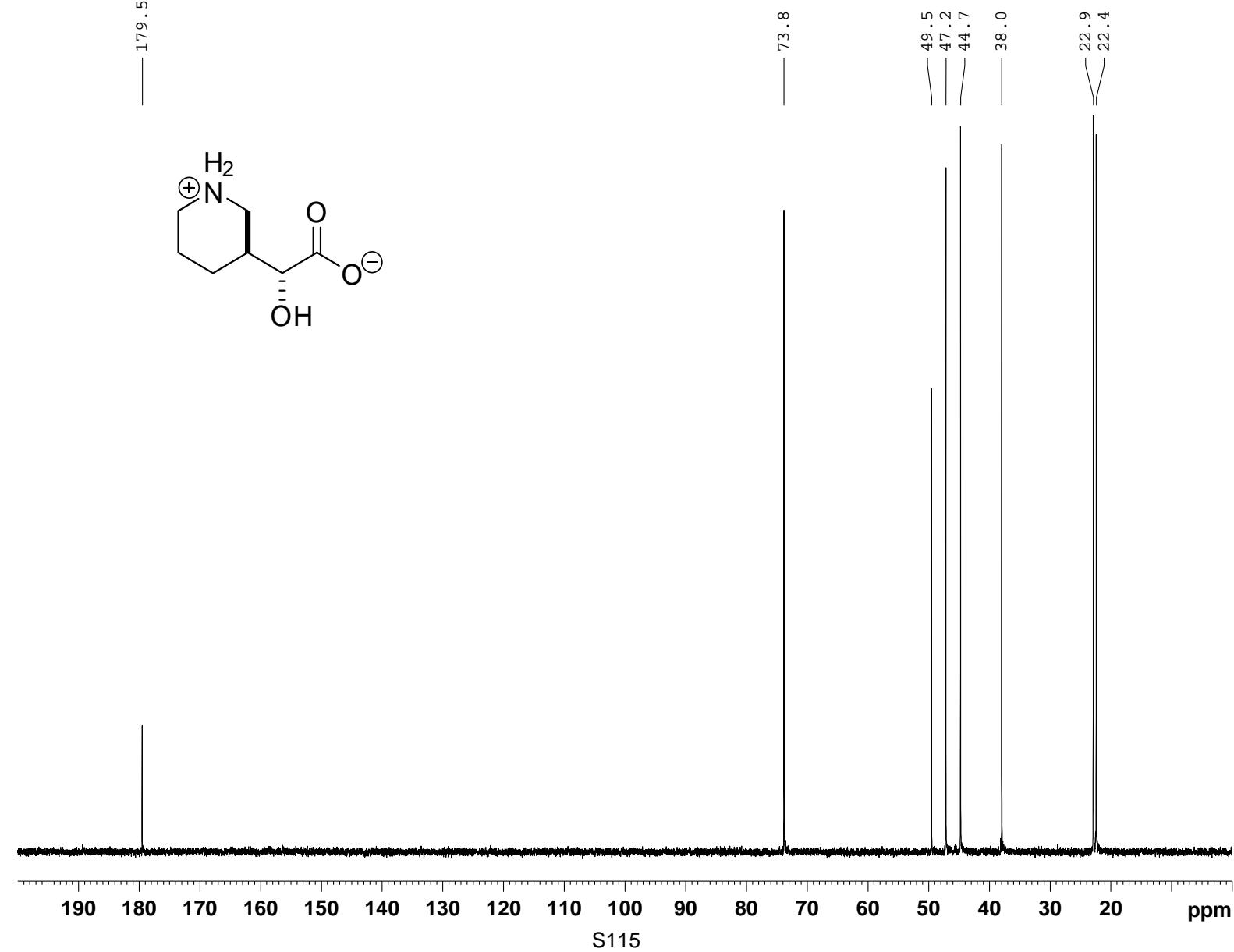


rac-(*R*)-2-Hydroxy-2-((*S*)-piperidin-3-yl)acetic acid (**21b**):

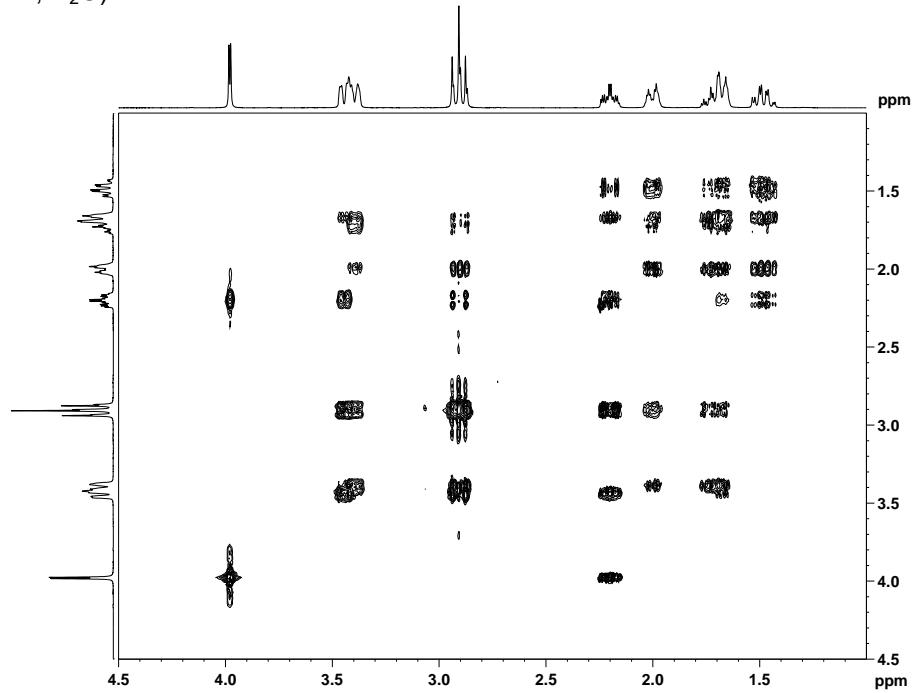
^1H NMR (400 MHz, D_2O)



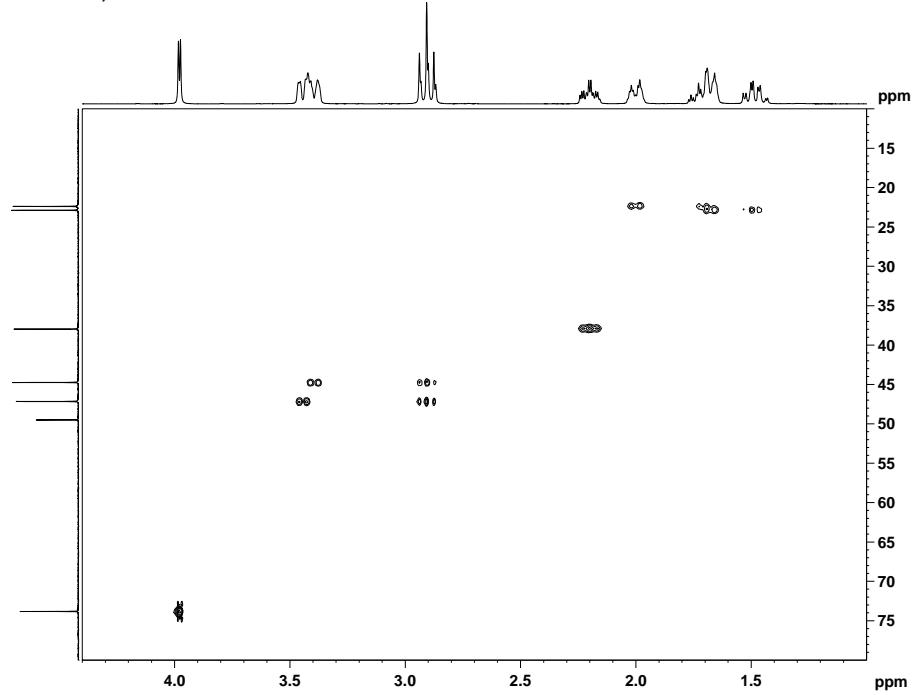
¹³C NMR (101 MHz, D₂O)



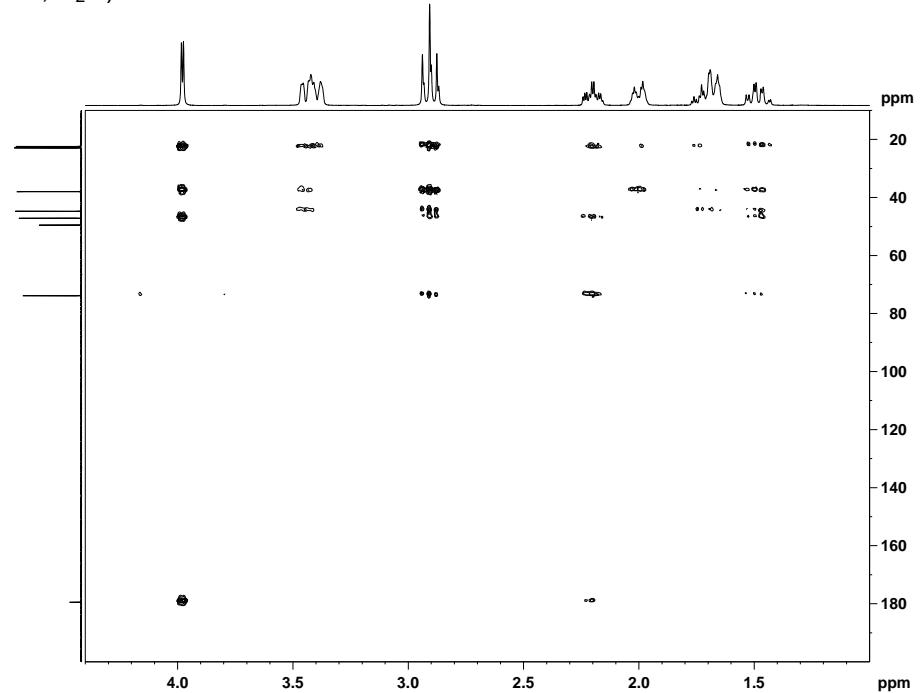
COSY (400 MHz, D₂O)



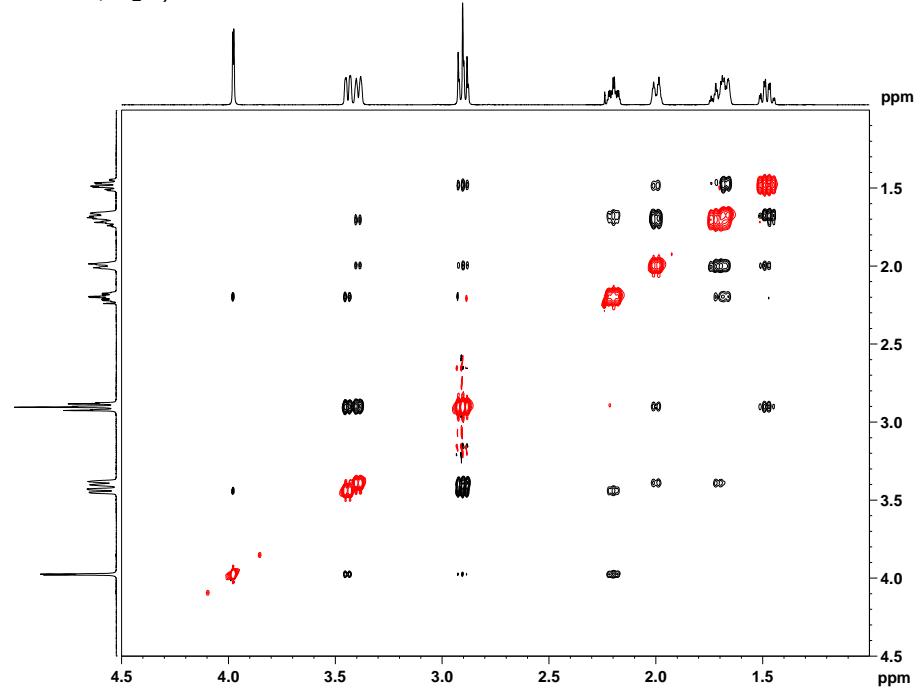
HSQC (400 MHz, D₂O)



HMBC (400 MHz, D₂O)

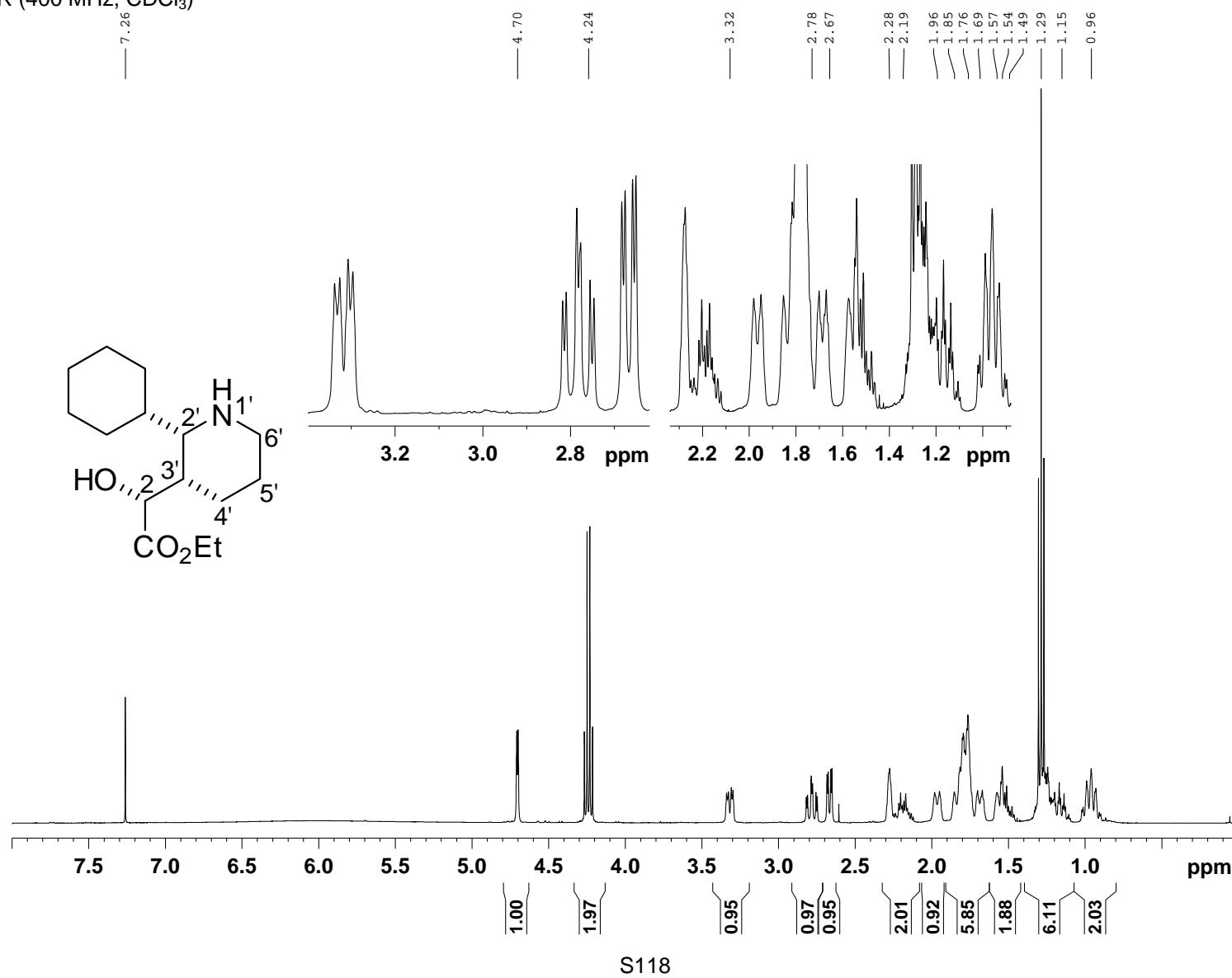


2D NOESY (600 MHz, D₂O)

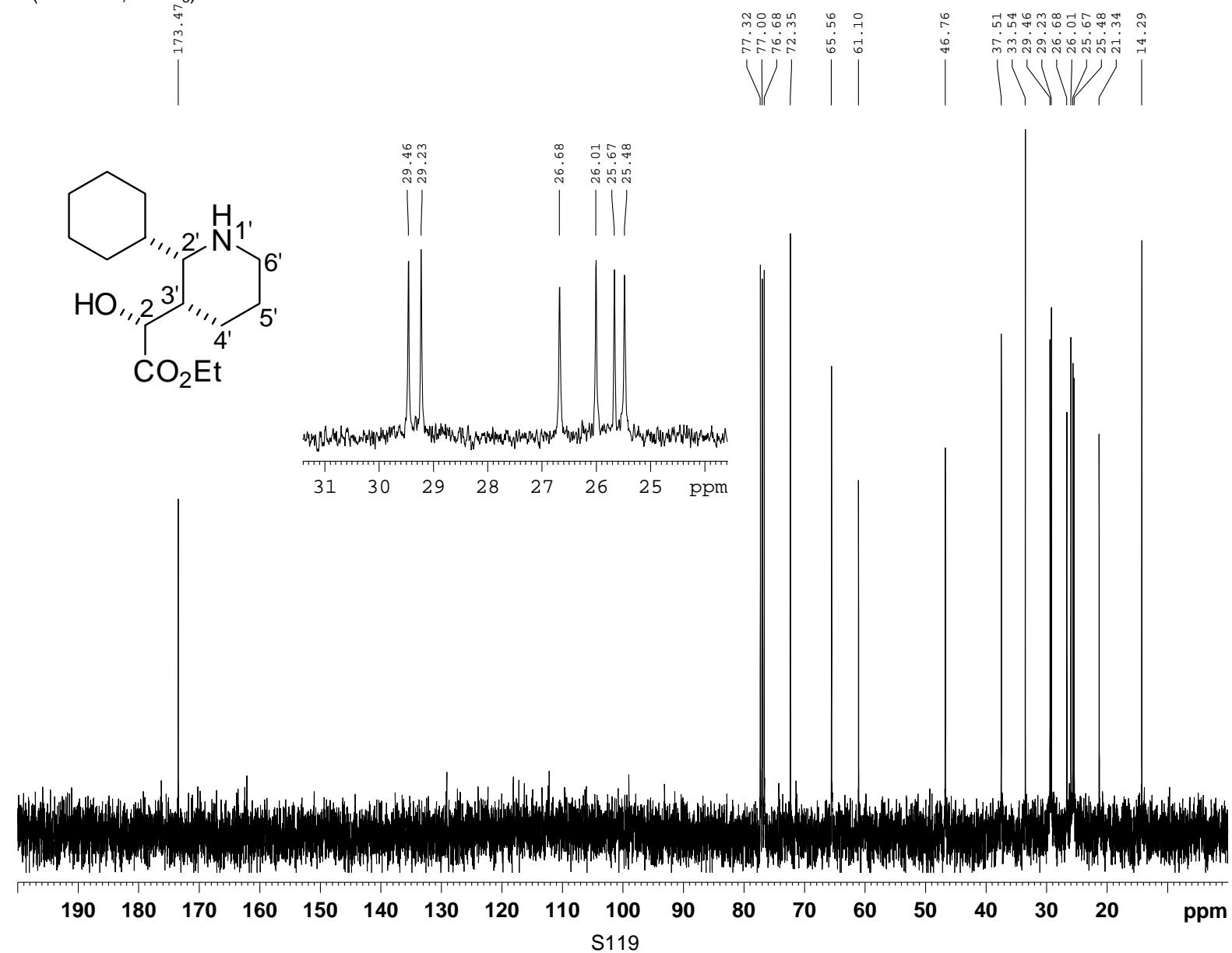


rac-(*R*)-ethyl 2-((2*S*,3*S*)-2-cyclohexylpiperidin-3-yl)-2-hydroxyacetate (**22a**):

^1H NMR (400 MHz, CDCl_3)

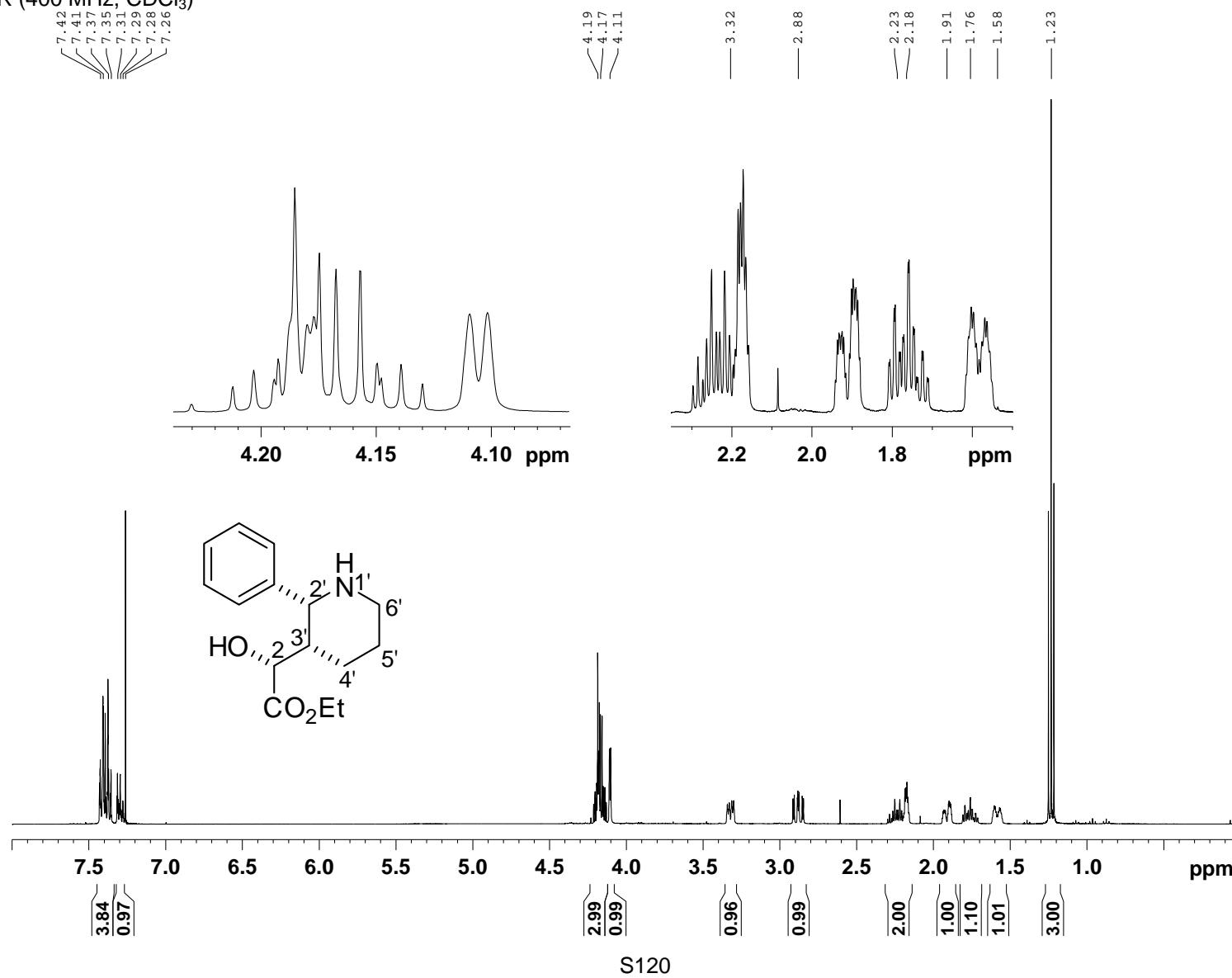


¹³C NMR (101 MHz, CDCl₃)

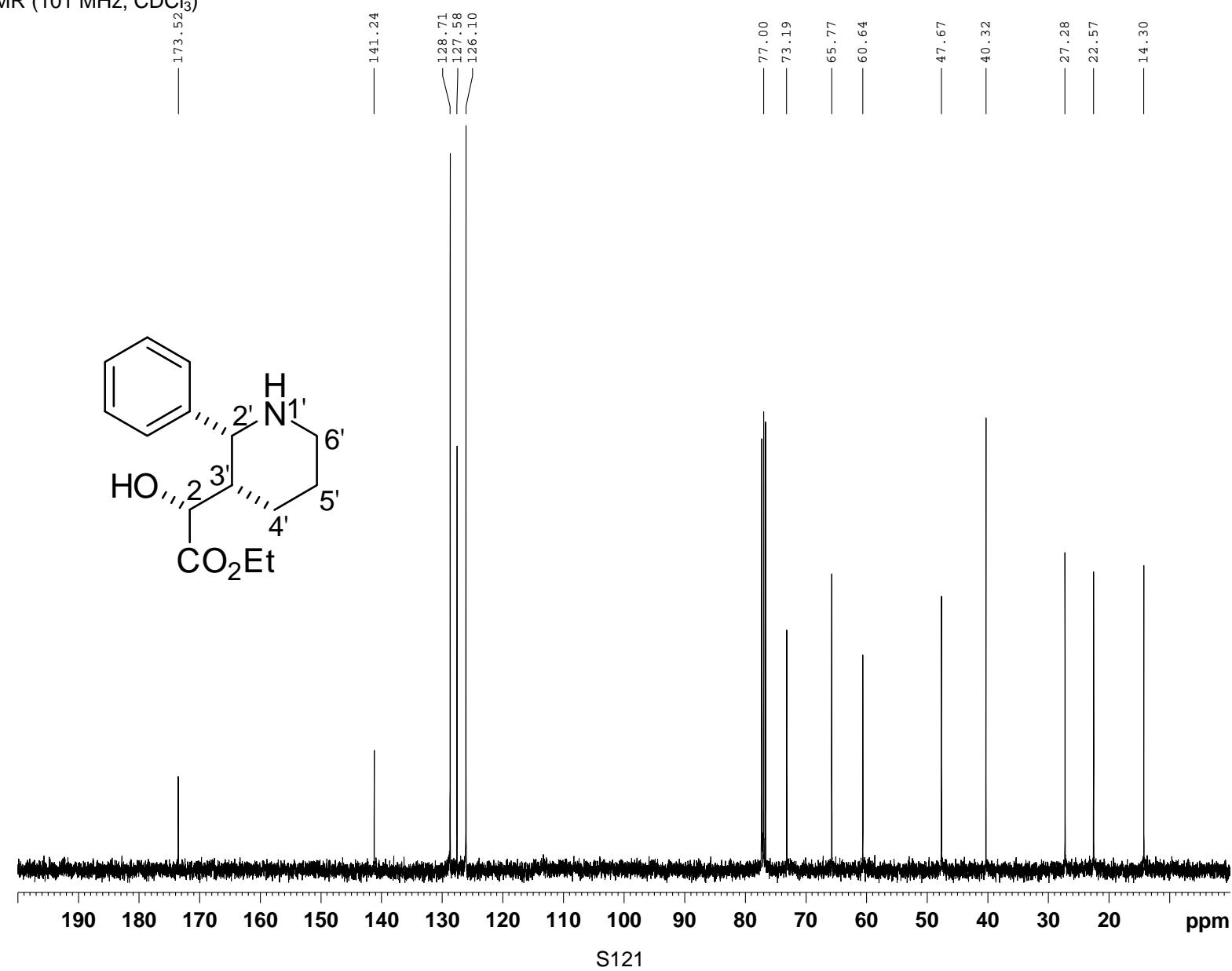


rac-(*R*)-ethyl 2-hydroxy-2-((2*R*,3*S*)-2-phenylpiperidin-3-yl)acetate (22b)

^1H NMR (400 MHz, CDCl_3)

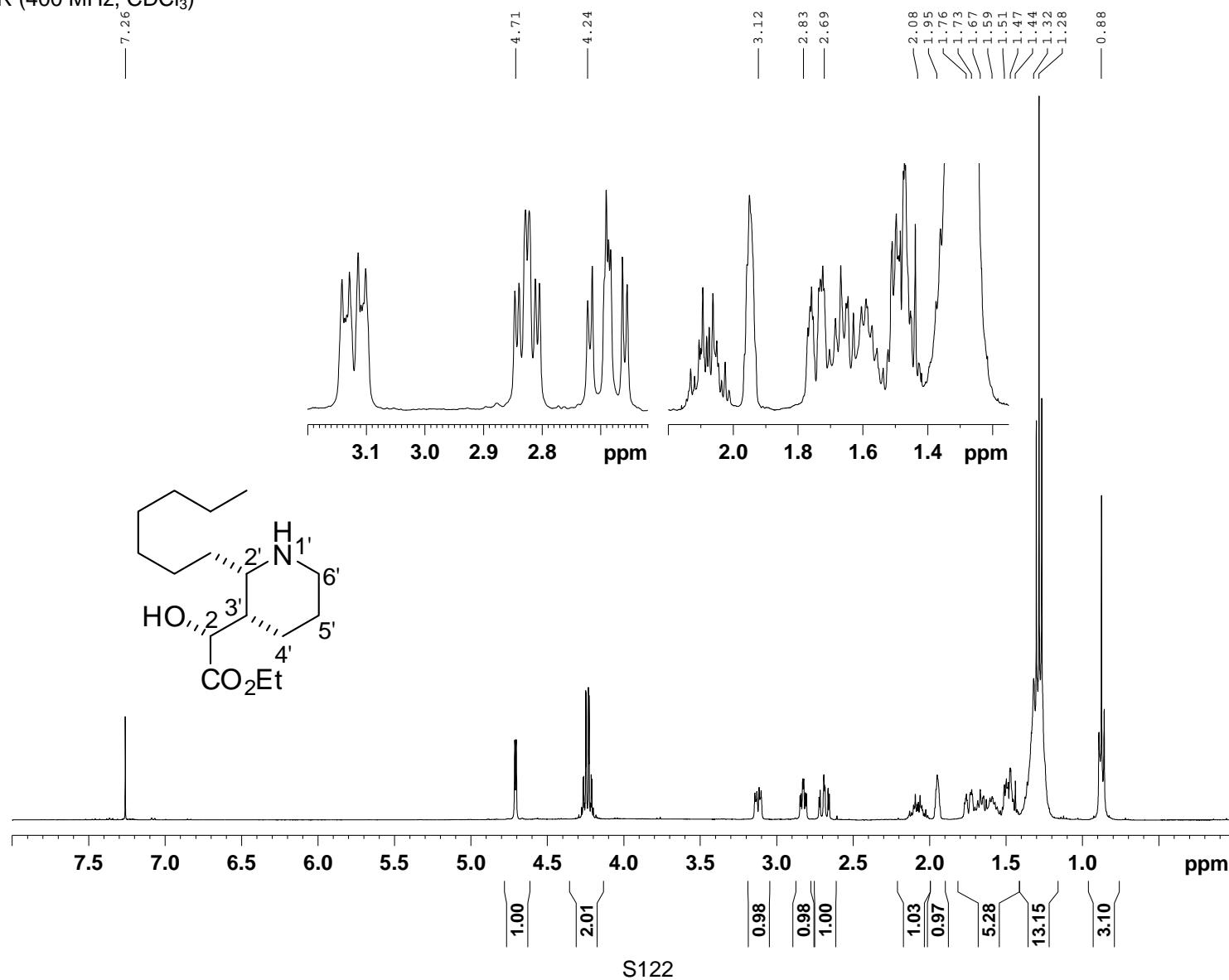


¹³C NMR (101 MHz, CDCl₃)

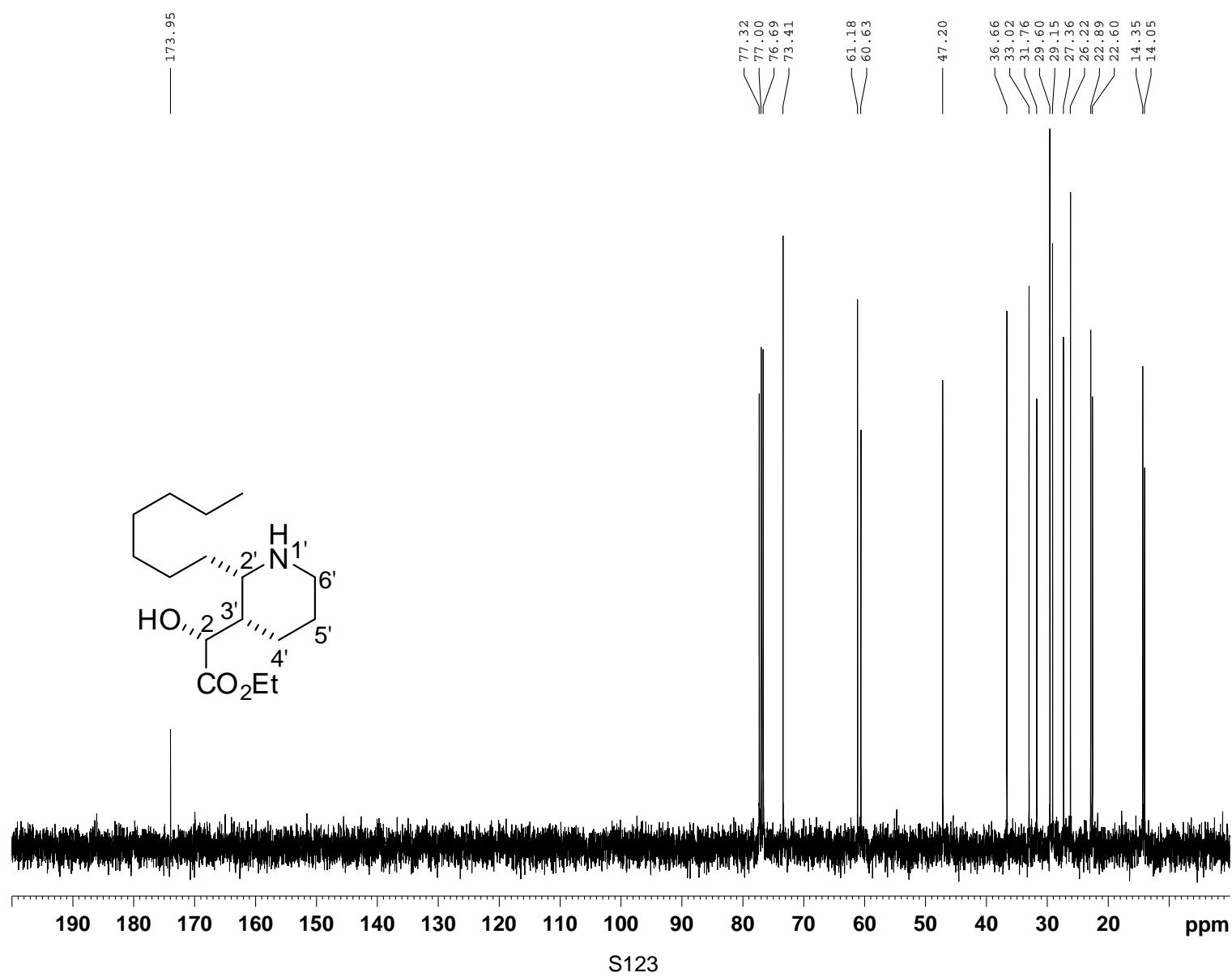


rac-(*R*)-ethyl 2-((2*S*,3*S*)-2-heptylpiperidin-3-yl)-2-hydroxyacetate (**22c**)

¹H NMR (400 MHz, CDCl₃)

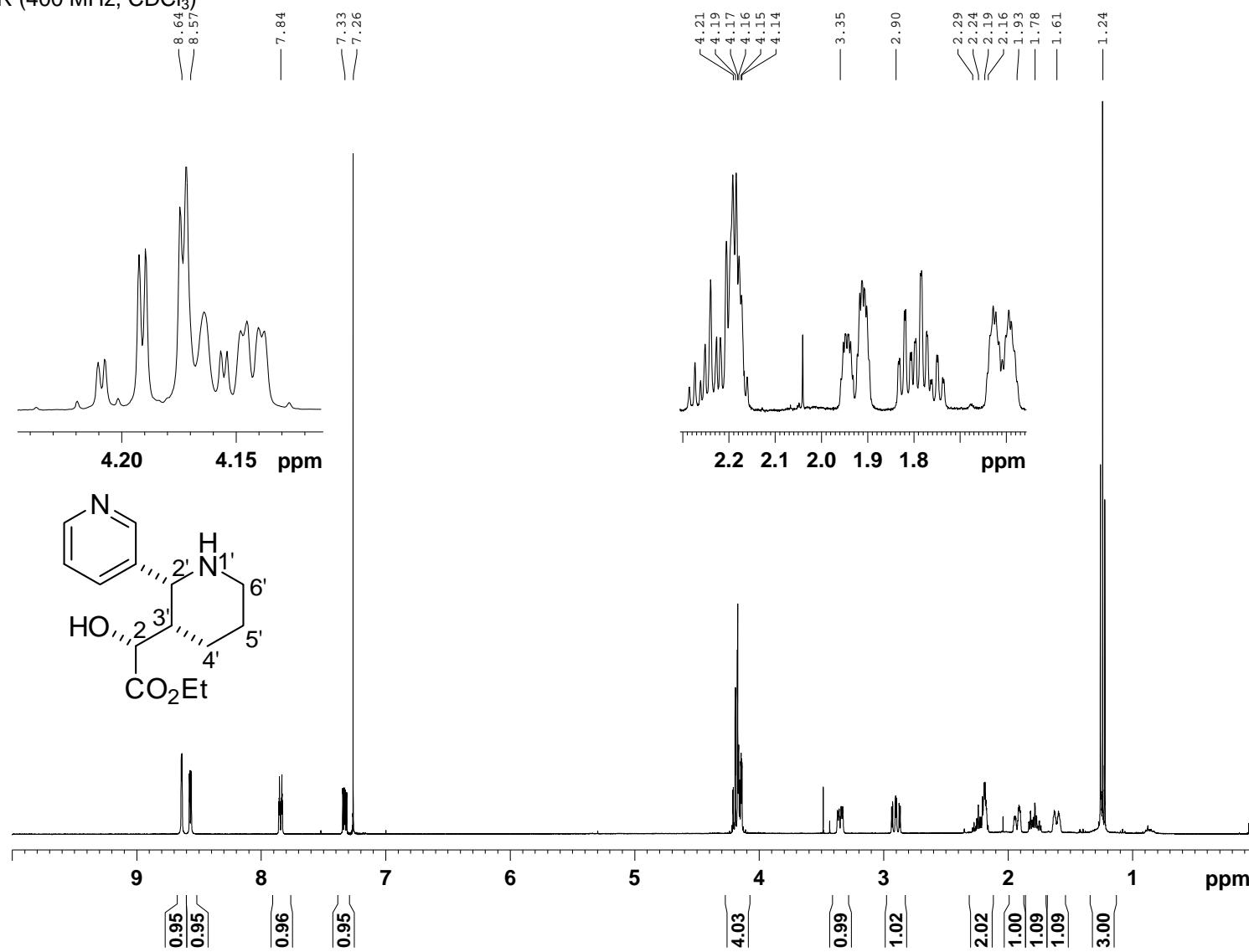


¹³C NMR (101 MHz, CDCl₃)

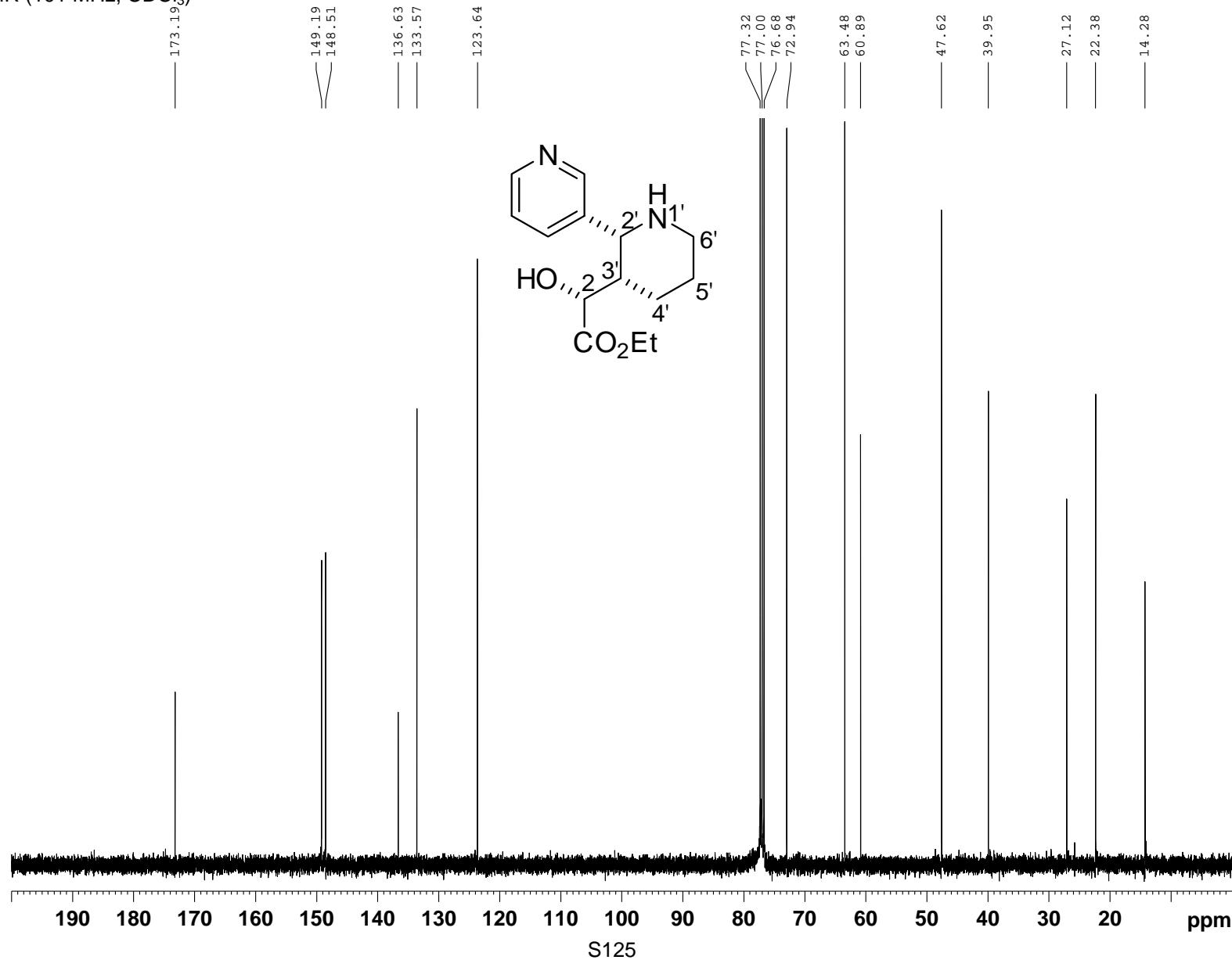


rac-(*R*)-ethyl 2-hydroxy-2-((2*R*,3*S*)-2-(pyridin-3-yl)piperidin-3-yl)acetate (**22d**):

^1H NMR (400 MHz, CDCl_3)

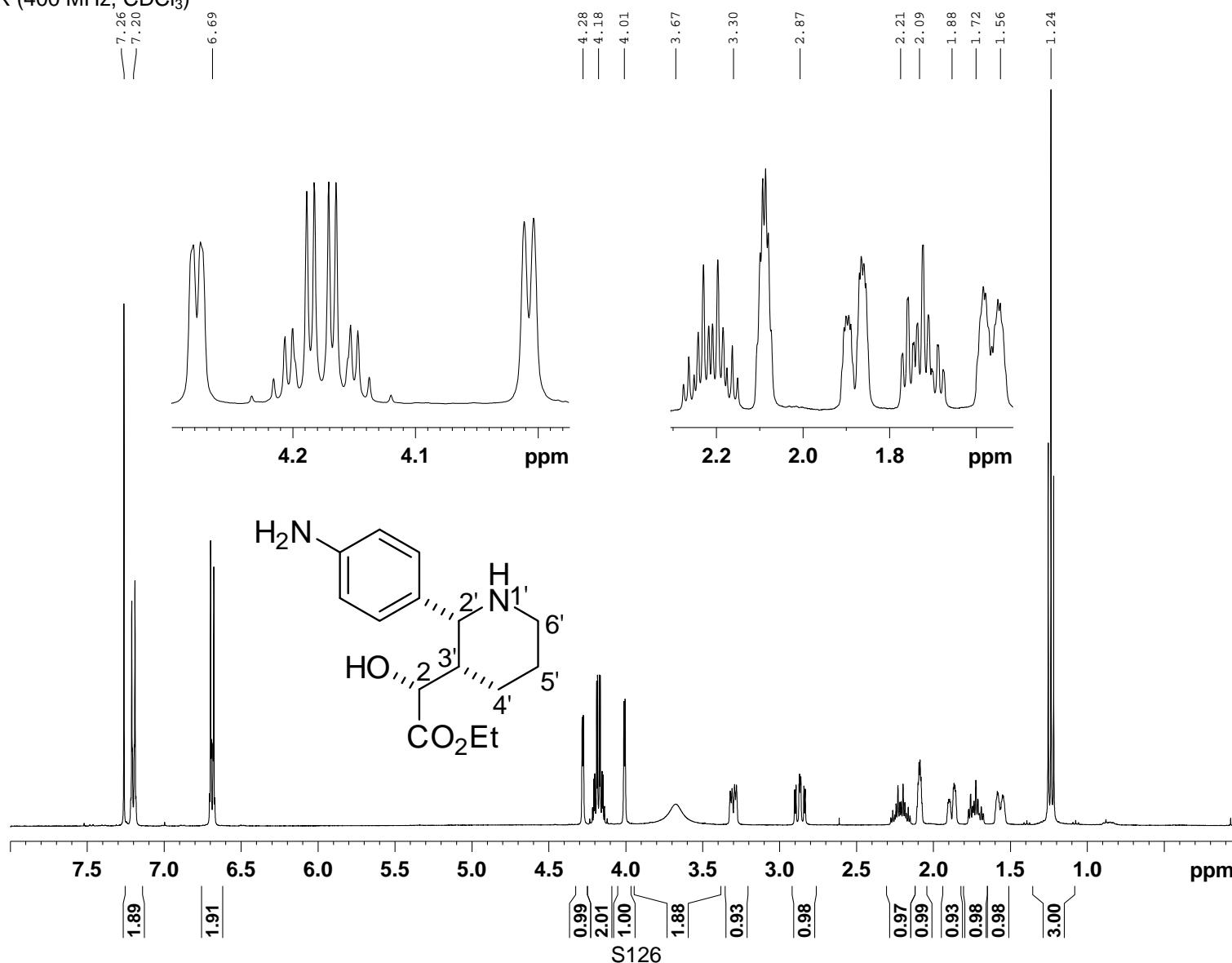


¹³C NMR (101 MHz, CDCl₃)

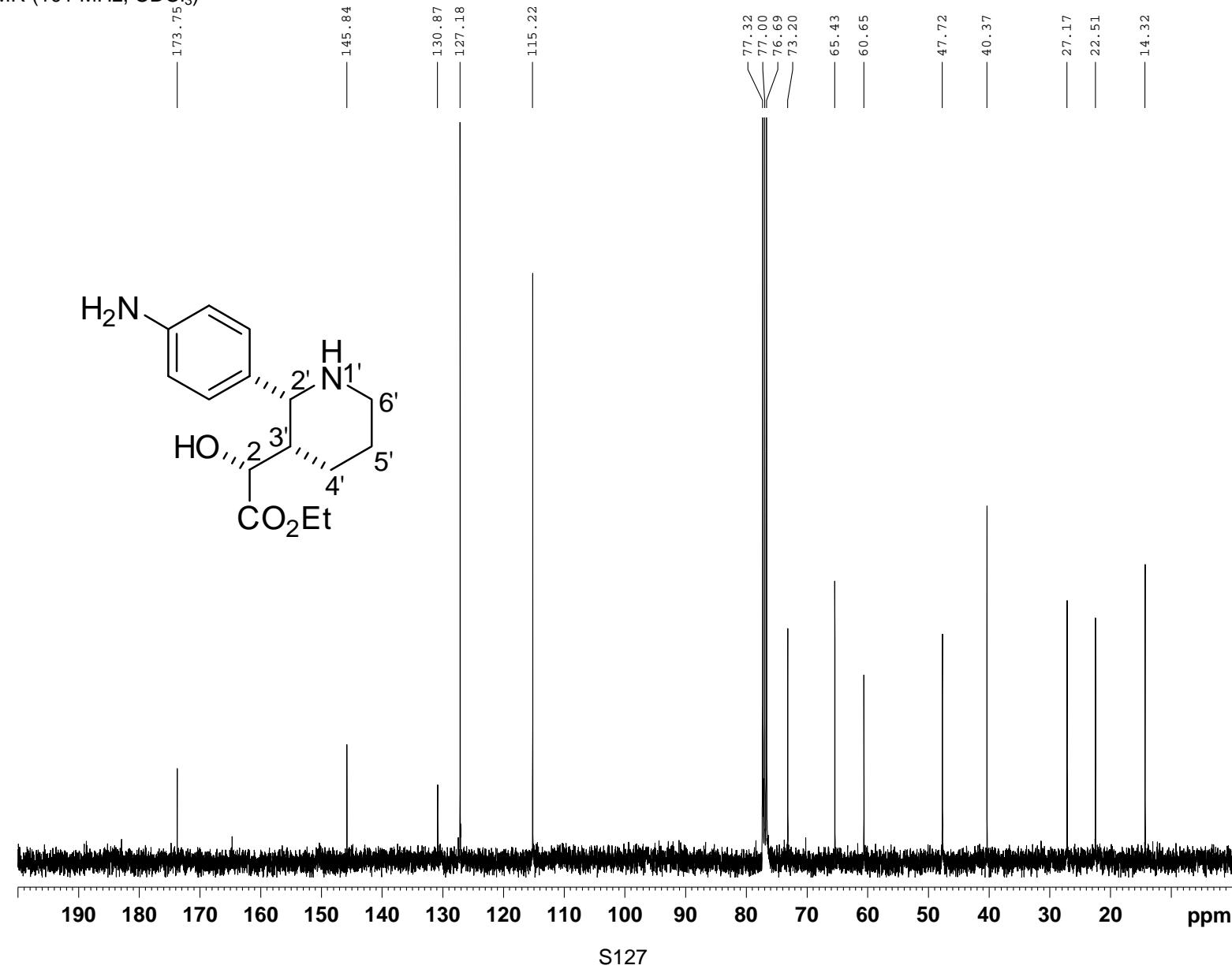


rac-(*R*)-ethyl 2-((2*R*,3*S*)-2-(4-aminophenyl)piperidin-3-yl)-2-hydroxyacetate (**22e**):

^1H NMR (400 MHz, CDCl_3)

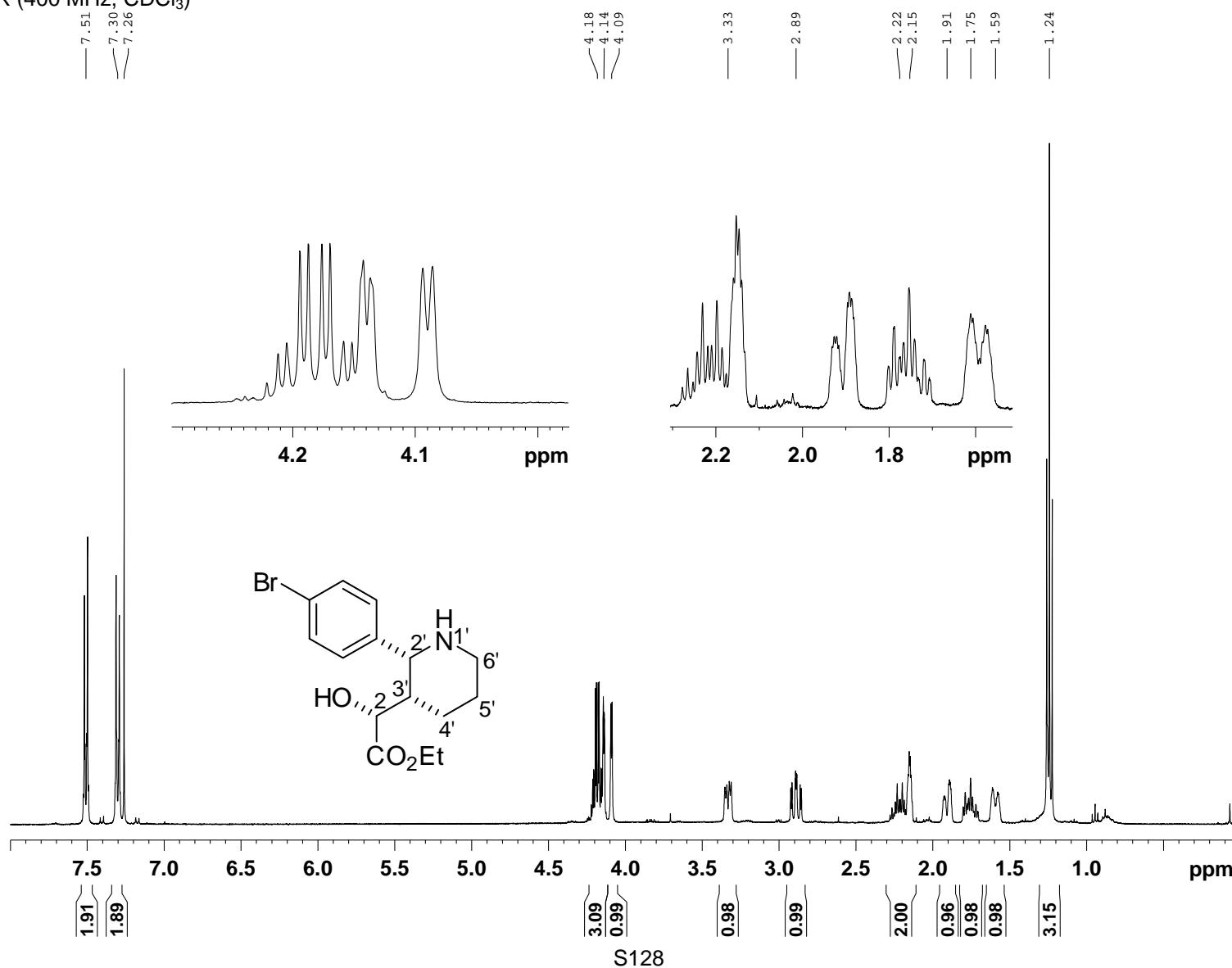


¹³C NMR (101 MHz, CDCl₃)

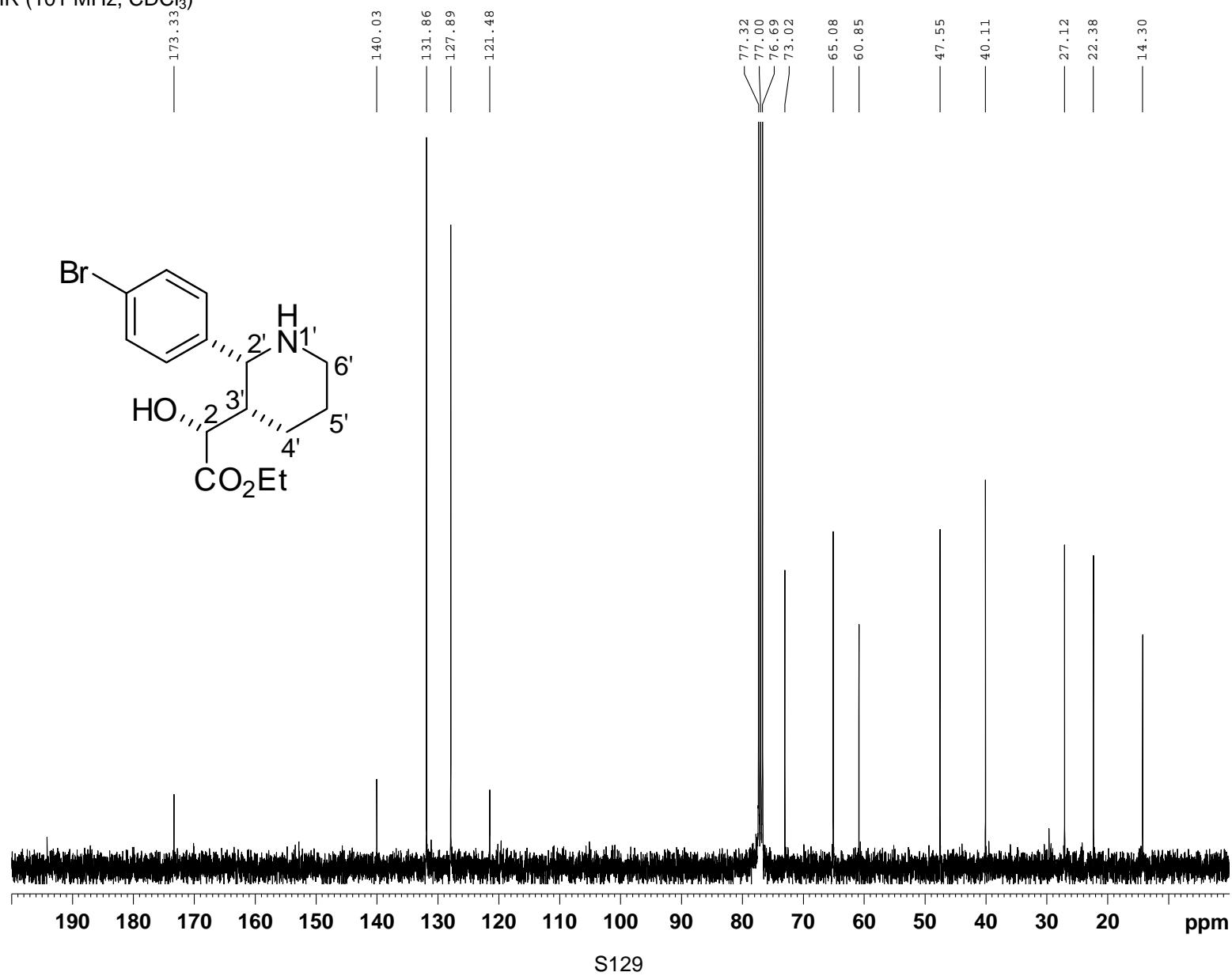
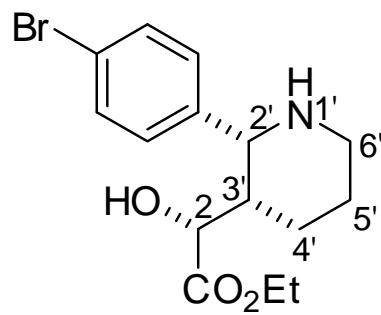


rac-(*R*)-ethyl 2-((2*R*,3*S*)-2-(4-bromophenyl)piperidin-3-yl)-2-hydroxyacetate (**22f**):

¹H NMR (400 MHz, CDCl₃)

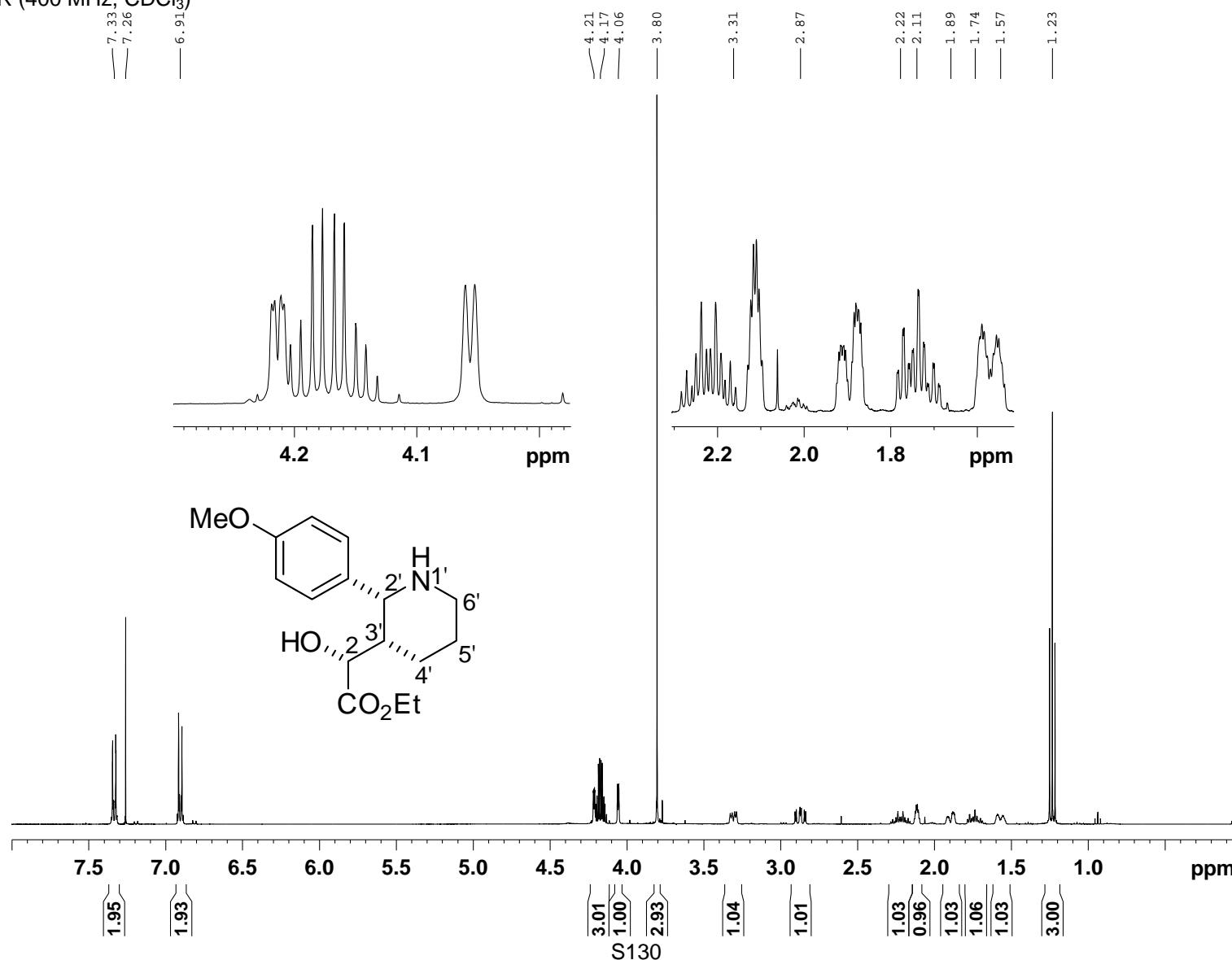


¹³C NMR (101 MHz, CDCl₃)

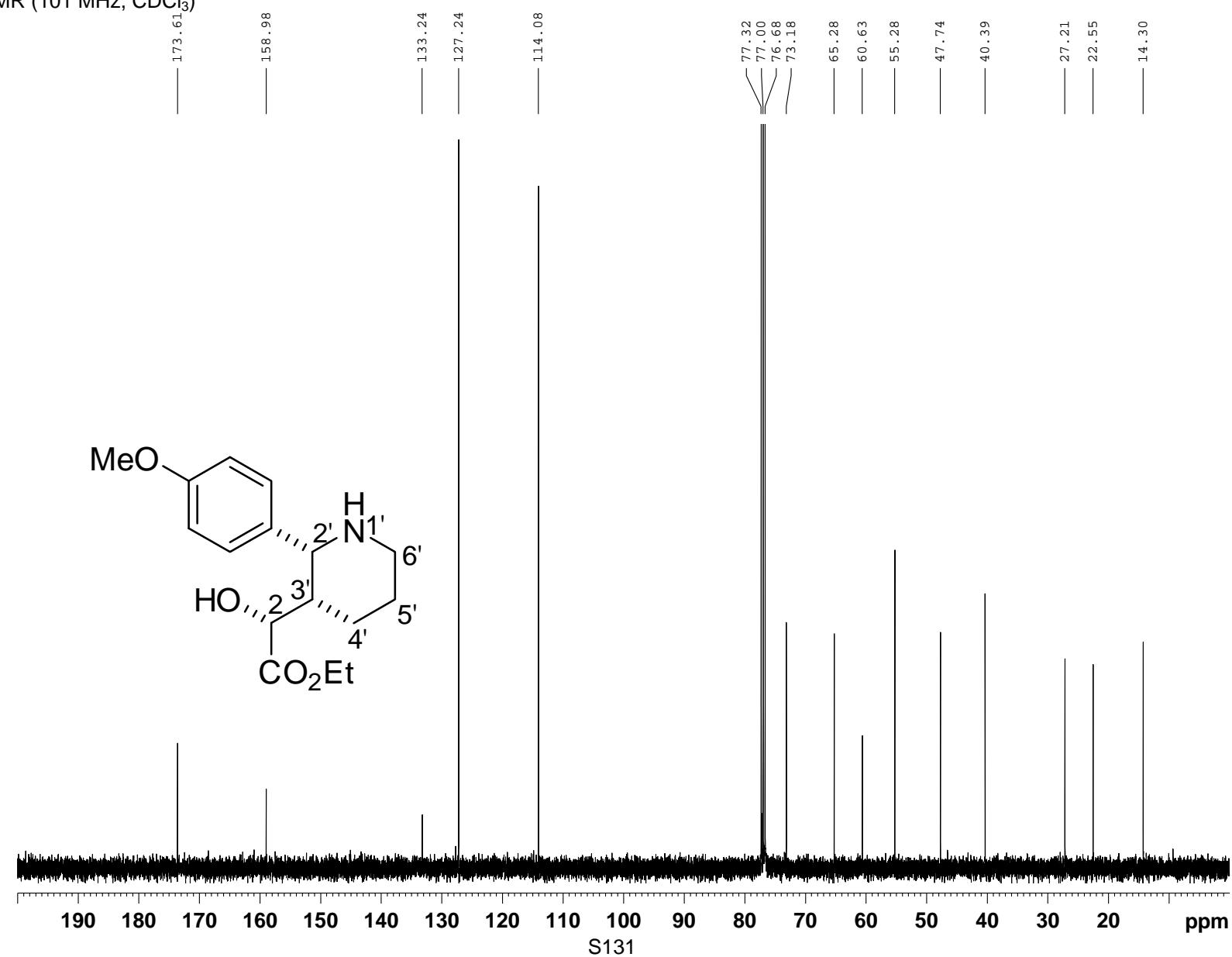


rac-(*R*)-ethyl 2-hydroxy-2-((2*R*,3*S*)-2-(4-methoxyphenyl)piperidin-3-yl)acetate (22g):

^1H NMR (400 MHz, CDCl_3)

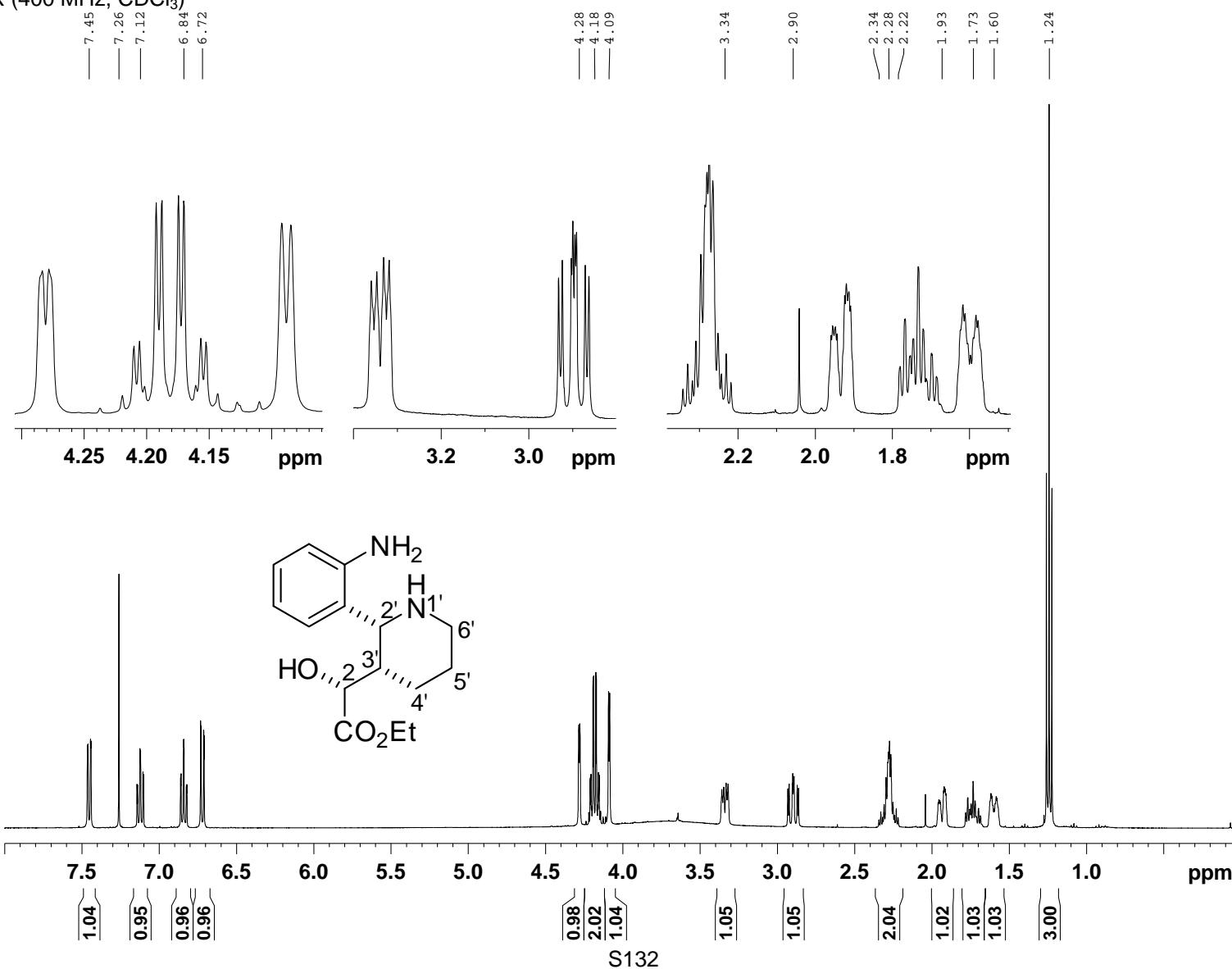


¹³C NMR (101 MHz, CDCl₃)

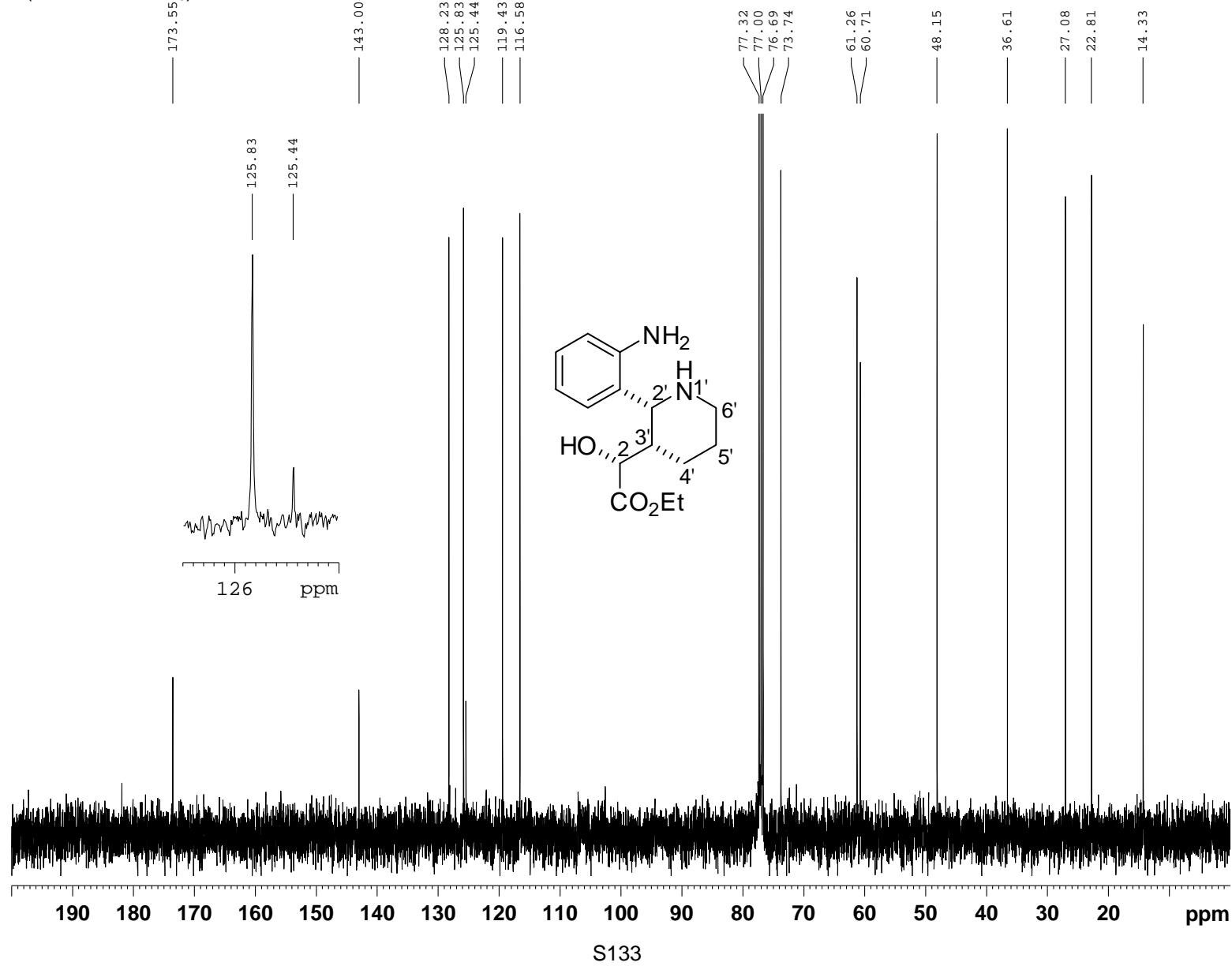


rac-(*R*)-ethyl 2-((2*R*,3*S*)-2-(2-aminophenyl)piperidin-3-yl)-2-hydroxyacetate (**22h**):

¹H NMR (400 MHz, CDCl₃)

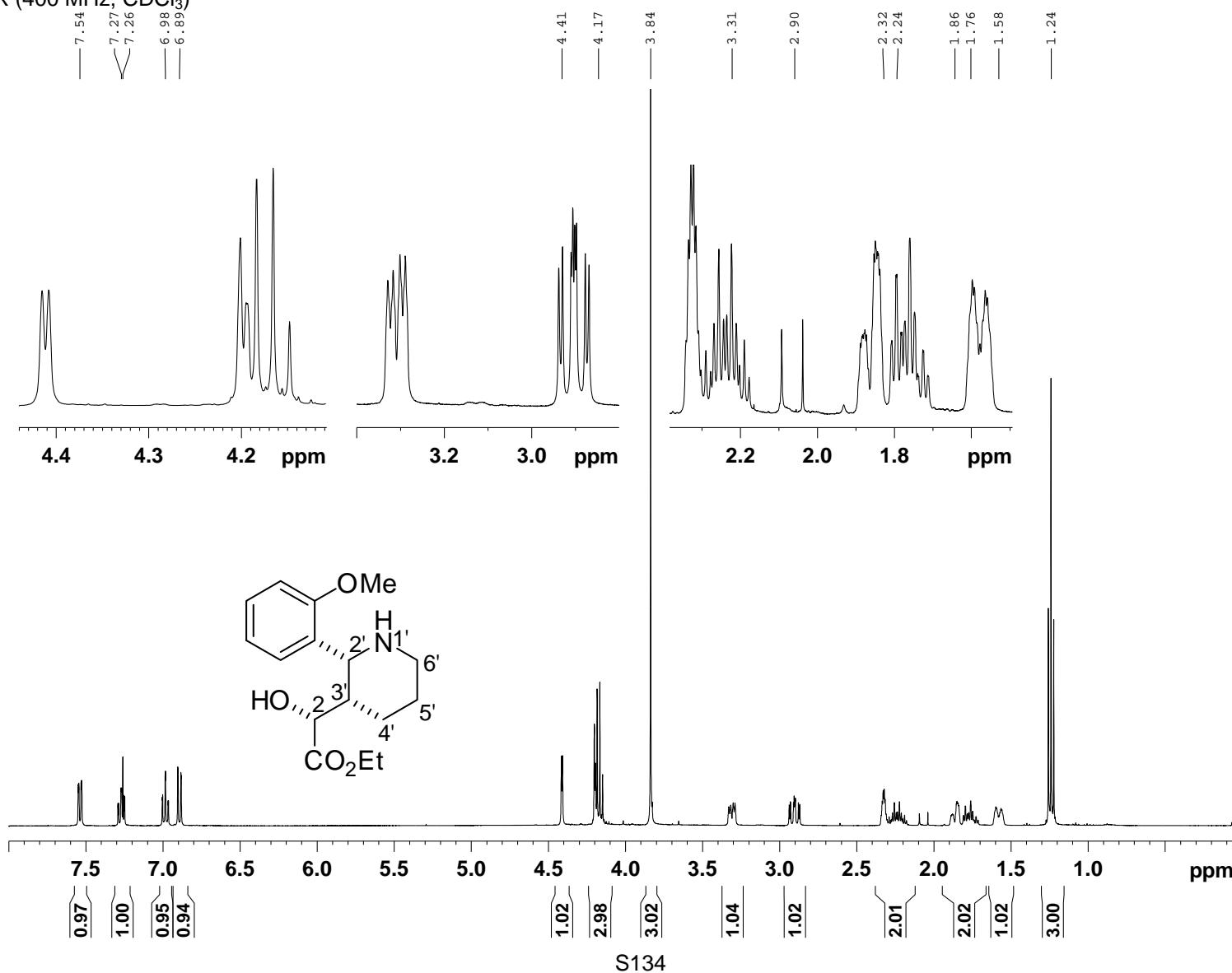


¹³C NMR (101 MHz, CDCl₃)

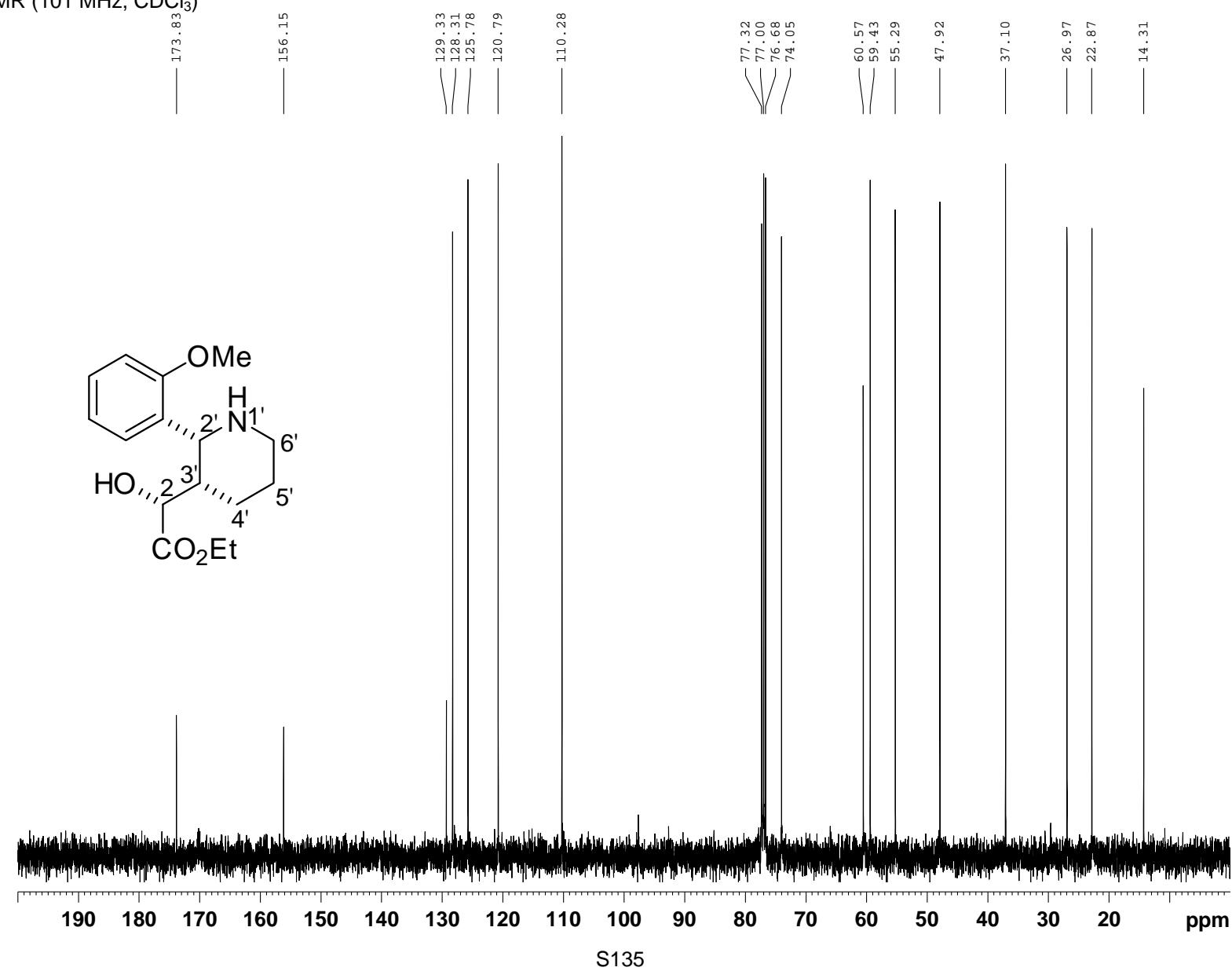


rac-(*R*)-ethyl 2-((2*R*,3*S*)-2-(2-methoxyphenyl)piperidin-3-yl)-2-hydroxyacetate (**22i**):

^1H NMR (400 MHz, CDCl_3)

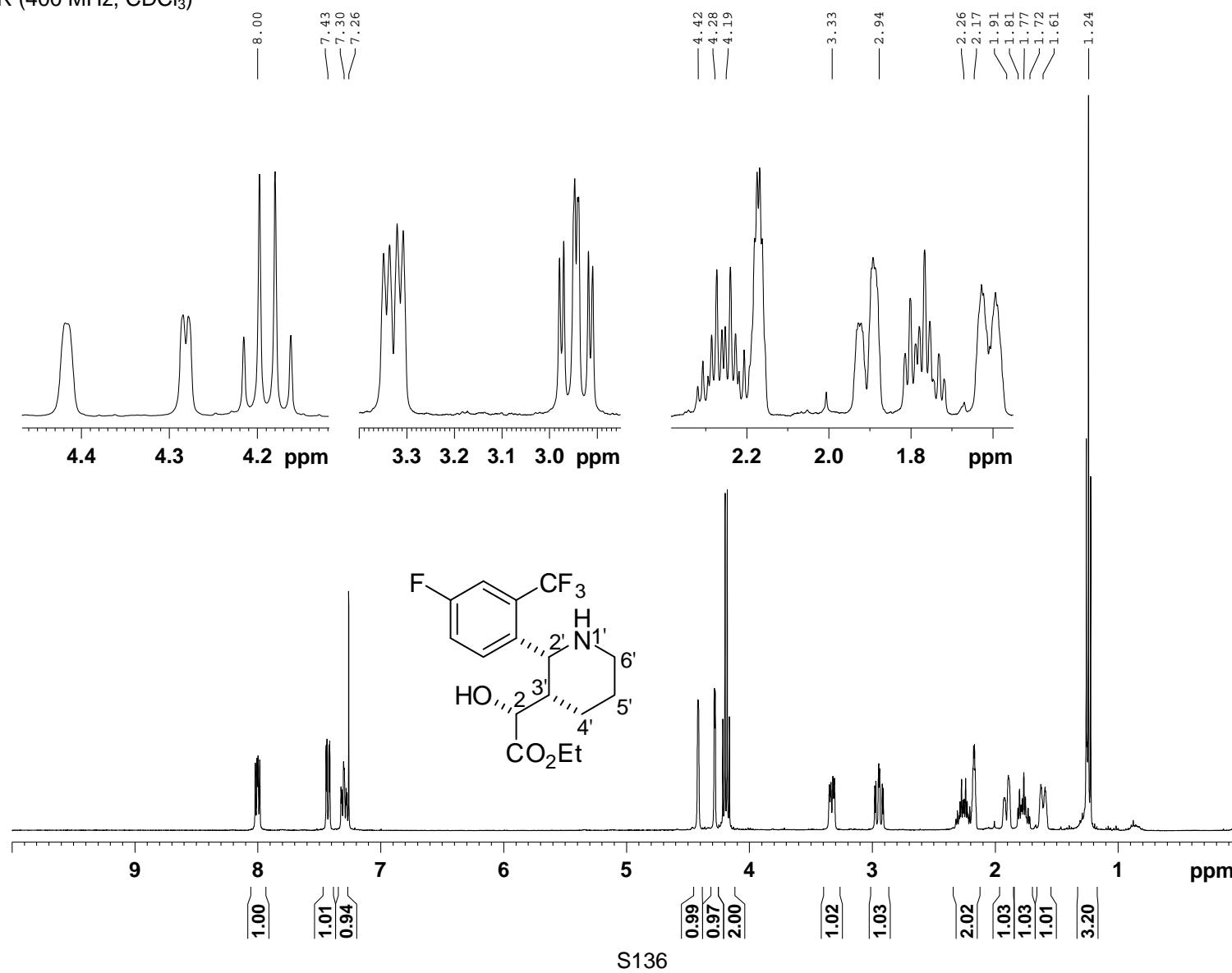


¹³C NMR (101 MHz, CDCl₃)

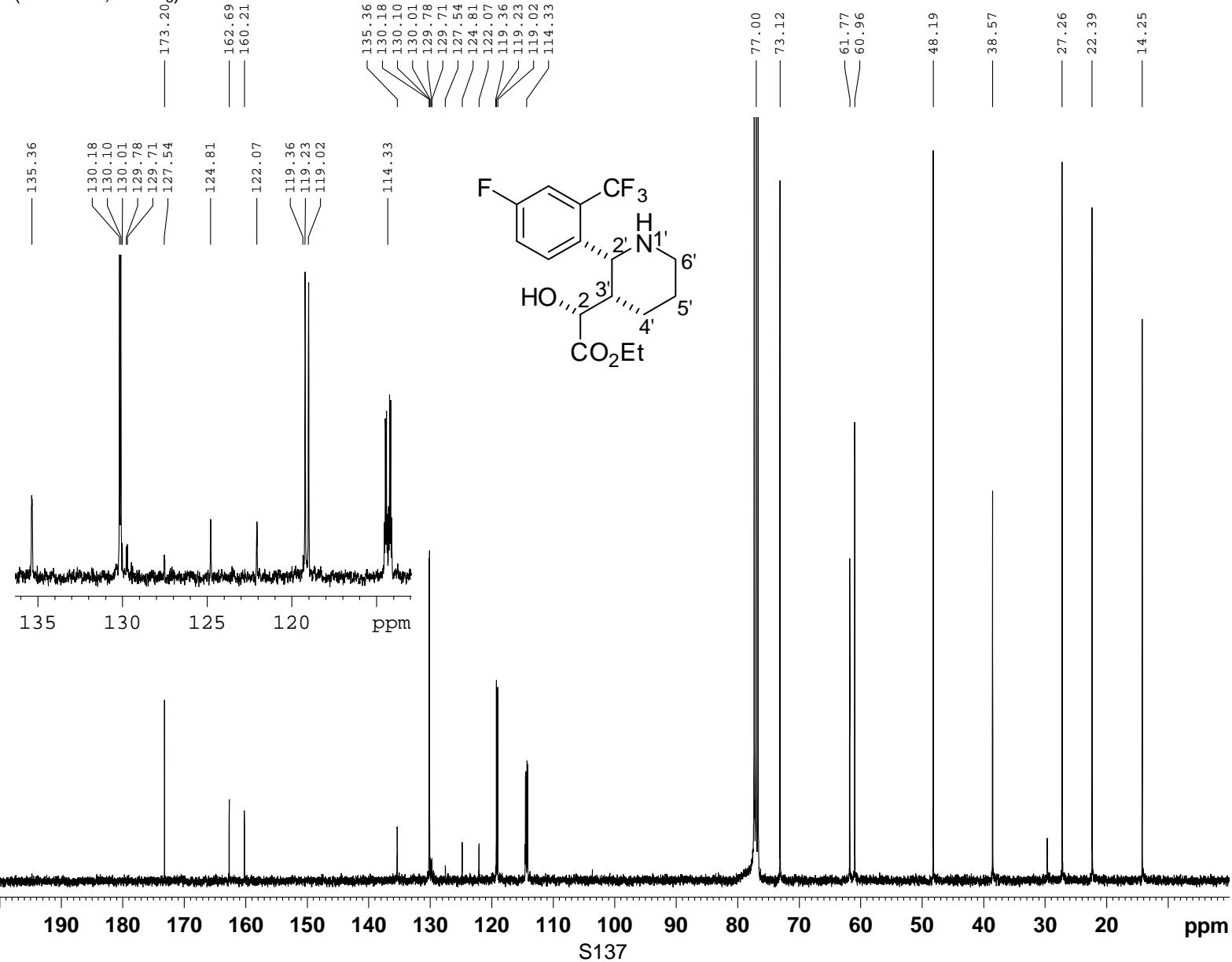


***rac*-(*R*)-ethyl 2-((2*R*,3*S*)-2-(4-fluoro-2-(trifluoromethyl)phenyl)piperidin-3-yl)-2-hydroxyacetate (22j):**

¹H NMR (400 MHz, CDCl₃)



¹³C NMR (101 MHz, CDCl₃)



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