SUPPORTING INFORMATION
FOR

Total Synthesis of the Initially Reported and Revised Structures of the Neuroprotective Agent Palmyrolide A

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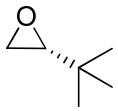
CONTENTS

GENERAL TECHNIQUES

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at λ = 598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/ TMS solvent, or the residual chloroform (δ 7.26 ppm), DMSO (δ 2.50 ppm) or methanol (δ 3.31 ppm) peaks. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm) or methanol (δ 49.0 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^1H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in Hz) and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV.

EXPERIMENTAL PROCEDURES

(*R*)-2-*tert*-Butyloxirane [(*R*)-8]



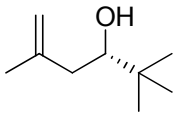
Following the procedure outlined by Jacobsen *et al.*[1] the *title compound* (2.15 g, 21.5 mmol, 43%) was isolated as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.89 (s, 9 H, ^{t}Bu), 2.55-2.57 (m, 1 H, CH of CH_2), 2.59-2.61 (m, 1 H, CH), 2.68-2.70 (m, 1 H, CH of CH_2).

Spectroscopic data is consistent with that reported in the literature.[1,2]

[α] $^{20}_{D}$ -13.9 (*c* 2.13, PhH); lit. [α] $^{20}_{D}$ -14.6 (*c* 2.16, PhH).[2]

(*S*)-2,2,5-Trimethylhex-5-en-3-ol



To a stirred suspension of CuI (0.16 g, 0.82 mmol, 10 mol%) in THF (10 mL) -78 ºC was added a solution of isopropenylmagnesium bromide in THF (23 mL, 0.5 M, 14 mmol). (*R*)-**8** (1 mL, 8.2 mmol) was added dropwise while the temperature was maintained at -78 ºC, the solution turned a darker red/yellow color and was allowed to warm to -25 ºC and stirred for 16 h. The solution was allowed to warm to 0 ºC and stirred for a further 1 h, then quenched with ammonium chloride solution. The aqueous phase was extracted with ether (2 x 25 mL) and the combined organic phases dried ($MgSO_4$) filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (0.77 g, 5.44 mmol, 66%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.91 (s, 9 H, ^{t}Bu), 1.67 (br s, 1 H, OH), 1.75 (s, 3 H, Me), 1.98 (dd, *J* = 11.2, 13.2 Hz, 1 H, CH of CH_2), 2.23 (d, *J* = 13.6 Hz, 1 H, CH of CH_2), 3.33 (dd, *J* = 2.8, 10.8 Hz, 1 H, CH), 4.80 (s, 1 H, CH of CH_2), 4.88 (s, 1 H, CH of CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.0 (CH_3), 25.7 (^{t}Bu, 3 x CH_3), 34.4 (C), 40.5 (CH_2), 75.6 (CH), 113.3 (CH_2), 143.7 (C).

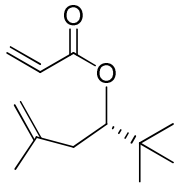
Spectroscopic data is consistent with that reported in the literature for the (*R*)-enantiomer.[3]

[α] $^{20}_{D}$ +9.6 (*c* 1.35, $CHCl_3$); Lit. (*R*)-enantiomer [α] $^{28}_{D}$ -11.3 (*c* 1.25, $CHCl_3$).[4]

IR ν_{max} (neat)/cm^{-1} 2955, 2870, 1731, 1644, 1479, 1363, 1297, 1240, 1170, 891.

HRMS-APCI: *m/z* $[M + H]^+$ calcd. For $[C_9H_{18}O + H]^+$: 143.1436; found: 143.1430.

(*S*)-2,2,5-Trimethylhex-5-en-3-yl acrylate (9)



To a solution of (*S*)-2,2,5-trimethylhex-5-en-3-ol (0.5 g, 3.5 mmol) in dichloromethane (17.5 mL) were added DMAP (0.086 g, 0.7 mmol, 20 mol%), Hünigs base (0.12 mL, 17.5 mmol) and acryloyl chloride (0.95 g, 10.5 mmol) at 0 ºC. The reaction mixture was stirred for 6 h and allowed to warm to room temperature. The reaction was then cooled to 0 ºC and quenched carefully with aqueous sodium bicarbonate solution (25 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (0.6 g, 3.06 mmol, 87% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.92 (s, 9 H, ^{t}Bu), 1.74 (s, 3 H, Me), 2.21 (d, J = 9.2 Hz, 2 H, CH_2), 4.68 (d, J = 16.0 Hz, 2 H, CH_2), 4.96 (dd, J = 3.6, 9.2 Hz, 1 H, CH), 5.77 (dd, J = 1.2, 10.4 Hz, 1 H, CH of CH_2), 6.08 (dd, J = 10.4, 16.4 Hz, 1 H, CH), 6.34 (dd, J = 1.2, 17.2 Hz, 1 H, CH of CH_2).

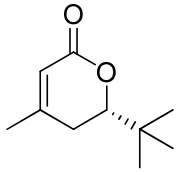
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.1 (Me), 25.9 (^{t}Bu, 3 x Me), 34.6 (C), 38.5 (CH_2), 78.2 (CH), 113.1 (CH_2), 128.7 (CH), 130.0 (CH_2), 142.2 (C), 165.8 (C=O).

[α] $^{20}_{D}$ +14.1 (*c* 1.5, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2967, 1721, 1646, 1432, 1404, 1316, 1295, 1269, 1219, 1192, 1047, 983, 892, 806, 737, 703.

HRMS-APCI: *m/z* $[M + H]^+$ calcd. For $[C_{12}H_{20}O_2 + H]^+$: 197.1536; found: 197.1534.

(*S*)-6-*tert*-Butyl-4-methyl-5,6-dihydro-2*H*-pyran-2-one (10)



To a solution of diene **9** (0.35 g, 1.8 mmol) in dichloromethane (160 mL) at reflux was added a solution of Grubbs 2nd generation catalyst (30 mg, 0.0356 mmol, 2 mol%) in dichloromethane (18 mL) and reflux was maintained for 24 h. A second portion of Grubbs 2nd generation catalyst (30 mg, 2 mol%) in dichloromethane (5 mL) was added to the reaction and reflux was continued for 24 h. The solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (0.29 g, 1.72 mmol, 83% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.00 (s, 9 H, ^{t}Bu), 1.98 (s, 3 H, Me), 2.09 (dd, *J* = 3.6, 17.6 Hz, 1 H, CH of CH_2), 2.35 (t, *J* = 14.0 Hz, 1 H, CH of CH_2), 4.02 (dd, *J* = 3.6, 13.2 Hz, 1 H, CH), 5.79 (s, 1 H, CH).

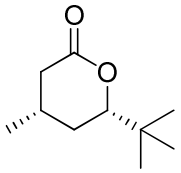
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 23.0 (Me), 25.5 (^{t}Bu, 3 x Me), 29.9 (CH_2), 33.7 (C), 84.5 (CH), 116.3 (CH), 157.4 (CH), 165.6 (C=O).

[α] $^{20}_{D}$ -114.4 (*c* 1.83, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3452, 2960, 2874, 1716, 1698, 1481, 1435, 1385, 1367, 1338, 1292, 1269, 1250, 1221, 1181, 1150, 1097, 1056, 1013, 927, 869, 846, 734, 655.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{10}H_{16}O_2 + H]^+$: 169.1223; found: 169.1228.
$[M + Na]^+$ calcd. for $[C_{10}H_{16}O_2 + Na]^+$: 191.1043; found: 191.1041.

(4*S*,6*S*)-6-*tert*-Butyl-4-methyltetrahydro-2*H*-pyran-2-one (11)



A solution of dihydropyranone **10** (0.54 g, 3.2 mmol) in methanol (55 mL) was passed through an H-cube® flow reactor (20 ºC, at 20 Bar with 10 mol% Pd/C). A further 20 mL of methanol was passed through the apparatus and the combined solvent was concentrated *in vacuo* to give the *title compound* (0.54 g, 3.2 mmol, ~100% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.95 (s, 9 H, ^{t}Bu), 1.02 (d, *J* = 6.0 Hz, 3 H, Me), 1.10-1.23 (m, 1 H, CH of CH_2), 1.83-1.90 (m, 1 H, CH of CH_2), 1.93-2.03 (m, 2 H, CH + CH of CH_2), 2.60-2.69 (m, 1 H, CH of CH_2), 3.94 (dd, *J* = 2.8, 12.0 Hz, 1 H, CH).

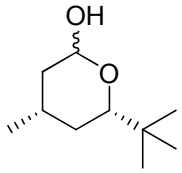
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.7 (Me), 25.4 (^{t}Bu, 3 x Me), 26.6 (CH), 31.6 (CH_2), 34.2 (C), 38.0 (CH_2), 87.9 (CH), 171.7 (C=O).

[α] $^{20}_{D}$ -3.6 (*c* 1.04, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3447, 2957, 2873, 1730, 1481, 1458, 1397, 1367, 1346, 1264, 1240, 1220, 1207, 1164, 1111, 1085, 1004, 929, 887, 862, 819, 655, 616, 602.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{10}H_{18}O_2 + H]^+$: 171.1380; found: 171.1384.
$[M + Na]^+$ calcd. for $[C_{10}H_{18}O_2 + Na]^+$: 193.1199; found: 193.1198.

(4*S*,6*S*)-6-*tert*-Butyl-4-methyltetrahydro-2*H*-pyran-2-ol (12)



To a solution of lactone **11** (100 mg, 0.59 mmol) in dichloromethane (5 mL) at -78 ºC was added a solution of DIBAL-H in toluene (0.88 mL, 1M, 0.88 mmol) and the reaction was stirred for 4 h. The reaction was quenched with methanol (5 mL) and water (5 mL) and allowed to warm to room temperature. An aqueous solution of hydrochloric acid (1M) was added dropwise until cloudiness disappeared. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and combined organics phases washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* as a 1.4:1 mixture of epimers (81 mg, 0.47 mmol, 77%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = (minor epimer peaks denoted with asterix) *0.86 (s, 9 H, ^{t}Bu), 0.88 (d, J = 6.0 Hz, 3 H, Me), 0.90 (s, 9H, ^{t}Bu), *0.94 (d, J = 6.8 Hz, 3 H, Me), 0.87-0.97 (m, 1 H, CH of CH_2), *0.87-0.97 (m, 2 H, CH_2), 1.10-1.20 (m, 1 H, CH of CH_2), *1.48-1.54 (m, 1 H, CH of CH_2), *1.55-1.58 (m, 1 H, CH), 1.58-1.61 (m, 1 H, CH of CH_2), 1.68-1.73 (m, 1 H, CH of CH_2), *1.81-1.86 (m, 1 H, CH of CH_2), 1.90-2.03 (m, 1 H, CH), *2.72 (s, 1 H, OH), 3.00 (dd, J = 2.0, 11.6 Hz, 1 H, CH), 3.32 (s, 1 H, OH), *3.56 (dd, J = 2.0, 11.6 Hz, 1 H, CH), 4.66 (dd, J = 1.6, 9.6 Hz, 1 H, CH), *5.33 (d, J = 3.2 Hz, 1 H, CH).

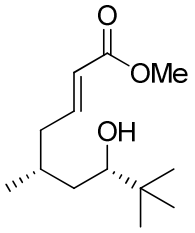
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.9 (Me), *22.4 (Me), *24.2 (CH), *26.0 (^{t}Bu, 3 x Me), 26.1 (^{t}Bu, 3 x Me), 29.3 (CH), 33.3 (CH_2), *33.4 (C), 33.7 (C), *34.0 (CH_2), *38.4 (CH_2), 41.4 (CH_2), *76.0 (CH), 83.2 (CH), *92.1 (CH), 96.5 (CH).

[*α*] $^{20}_{D}$ +33.6 (*c* 1.23, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3378, 2951, 2869, 1479, 1456, 1394, 1363, 1321, 1256, 1123, 1079, 1044, 995, 969, 933, 910, 887, 841, 824, 725, 603.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{10}H_{20}O_2 + Na]^+$: 195.1356; found: 195.1340.

(5*R*,7*S*)-Methyl-7-hydroxy-5,8,8-trimethylnon-2-enoate



A solution of methyl diethylphosphonoacetate **13** (73 mg, 0.064 mL, 0.35 mmol) in THF (2 mL) was added to a suspension of sodium hydride (8 mg, 0.35 mmol) in THF (2 mL) at -78 ºC and the reaction

mixture was stirred for 2 h. A solution of lactol **12** (20 mg, 0.12 mmol) in THF (2 mL) was added to the reaction via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Methanol (5 mL) and water (5 mL) were added and the reaction mixture was stirred for 10 min before extraction of aqueous phase with dichloromethane (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and solvent was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (15 mg, 0.066 mmol, 57% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (s, 9 H, ^{t}Bu), 0.92 (d, J = 3.2 Hz, 3 H, Me), 1.18-1.39 (m, 3 H, CH_2 + OH), 1.86-1.94 (m, 1 H, CH), 2.07-2.27 (m, 2 H, CH_2), 3.29 (dd, J = 2.0, 10.4 Hz, 1 H, CH), 3.72 (s, 3 H, OMe), 5.83 (d, J = 15.6 Hz, 1 H, CH), 6.95 (dt, J = 7.2, 15.2 Hz, 1 H, CH).

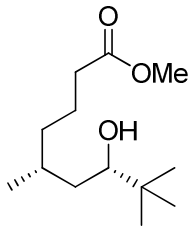
^{13}C NMR (100 MHZ, $CDCl_3$): δ_C = 18.7 (Me), 25.6 (^{t}Bu, 3 x Me), 29.3 (CH), 34.8 (C), 38.4 (CH_2), 40.8 (CH_2), 51.4 (OMe), 77.2 (CH), 122.1 (CH), 148.2 (CH), 167.0 (C=O).

[α] $^{20}_{D}$ +5.0 (*c* 1.17, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3483, 2952, 2870, 1724, 1654, 1437, 1364, 1321, 1271, 1206, 1166, 1114, 1045, 1014, 1007, 984, 900, 720.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{13}H_{24}O_3 + Na]^+$: 251.1618; found: 251.1610.

(5*R*,7*S*)-Methyl-7-hydroxy-5,8,8-trimethylnonanoate



A solution of (5*R*,7*S*)-methyl-7-hydroxy-5,8,8-trimethylnon-2-enoate (130 mg, 0.57 mmol) in methanol (50 mL) was passed through an H-cube® flow reactor (20 ºC, at 20 Bar with 10 mol% Pd/C). A further 20 mL of methanol was passed through the apparatus and the combined solvent was concentrated *in vacuo* to give the *title compound* (130 mg, 0.57 mmol, ~100% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (s, 9 H, ^{t}Bu), 0.89 (d, J = 6.4 Hz, 3 H, Me), 1.14-1.36 (m, 5 H, 2 x CH_2 + OH), 1.60-1.71 (m, 3 H, CH + CH_2), 2.30 (t, J = 7.6 Hz, 2 H, CH_2), 3.28 (dd, J = 2.0, 10.8 Hz, 1 H, CH), 3.66 (s, 3 H, Me).

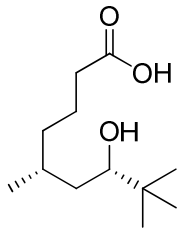
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 18.8 (Me), 22.4 (CH_2), 25.6 (^{t}Bu, 3 x Me), 29.3 (CH), 34.3 (CH_2), 34.8 (C), 37.7 (CH_2), 38.6 (CH_2), 51.4 (OMe), 77.2 (CH), 174.3 (C=O).

[α] $^{20}_{D}$ -21.2 (*c* 1.276, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3459, 3250, 2956, 2917, 2850, 2167, 1739, 1436, 1363, 1258, 1166, 1086, 1012, 864, 798, 698, 660, 620, 611, 603.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{13}H_{26}O_3 + H]^+$: 231.1955; found: 231.1949.

(5*R*,7*S*)-7-Hydroxy-5,8,8-trimethylnonanoic acid



To a solution of (5*R*,7*S*)-methyl-7-hydroxy-5,8,8-trimethylnonanoate (100 mg, 0.4 mmol) in dichloromethane/methanol (5 mL, 9:1), was added a methanolic solution of sodium hydroxide (112 mg, in 1 mL, 2.8 mmol). After 2.5 h stirring at room temperature, the solvents were concentrated *in vacuo* and the residue was diluted with water (10 mL) then washed with ether (2 x 10 mL) and the organic phases discarded. The aqueous phase was cooled (0 ºC) and acidified (pH 2-3) with dilute aqueous hydrochloric acid, then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and solvent was concentrated *in vacuo* to give the *title compound* (89 mg, 0.41 mmol, 94% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (s, 9 H, ^{t}Bu), 0.89 (d, *J* = 6.4 Hz, 3 H, Me), 1.14-1.39 (m, 5 H, 2 x CH_2 + OH), 1.60-1.76 (m, 3 H, CH + CH_2), 2.34 (t, *J* = 7.6 Hz, 2 H, CH_2), 3.29 (dd, *J* = 2.0, 10.8 Hz, 1 H, CH), CO_2H not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 18.8 (Me), 22.2 (CH_2), 25.6 (^{t}Bu, 3 x Me), 29.3 (CH), 34.0 (CH_2), 34.8 (C), 37.6 (CH_2), 38.6 (CH_2), 77.3 (CH), 178.7 (C=O).

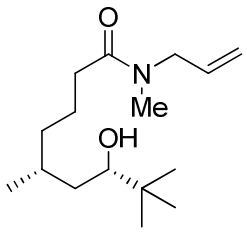
M.P. 93.8-94.7 ºC.

[α] $^{20}_{D}$ -9.6 (*c* 1.2, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3297, 2962, 2933, 2878, 2507, 1672, 1465, 1424, 1394, 1366, 1335, 1307, 1277, 1184, 1125, 1105, 1077, 1052, 1030, 1007, 982, 947, 904, 868, 845, 823, 765, 642, 603.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{12}H_{24}O_3 + Na]^+$: 239.1618; found: 239.1617.

(5*R*,7*S*)-*N*-allyl-7-hydroxy-*N*-5,8,8-tetramethylnonanamide (6)



To a solution of (5*R*,7*S*)-7-hydroxy-5,8,8-trimethylnonanoic acid (1.57 g, 7.3 mmol) in dichloromethane (150 mL) was added HOAt (1.06 g, 7.4 mmol), *N*-methylallylamine (0.6 mL, 7.3 mmol) and EDCI (1.15

g, 7.4 mmol). The reaction mixture was stirred at room temperature for 4 h then concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with methanol-ethyl acetate (1:19) to give the *title compound* as a 1:1 mixture of rotamers (1.54 g, 5.7 mmol, 78%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (s, 9 H, ^{t}Bu), 0.89 (d, *J* = 6.4 Hz, 3 H, Me), 1.14-1.39 (m, 5 H, 2 x CH_2 + OH), 1.58-1.76 (m, 3 H, CH + CH_2), 2.30 (dt, *J* = 8.4, 16.8 Hz, 2 H, CH_2), 2.92 (d, *J* = 8.0 Hz, 3 H, NMe), 3.27 (dt, *J* = 2.0, 10.4, 1 H, CH), 3.89 (d, *J* = 4.8 Hz, 1 H, CH of CH_2), 3.98 (d, *J* = 6.4 Hz, 1 H, CH of CH_2), 5.09-5.23 (m, 2 H, CH_2), 5.68-5.82 (m, 1 H, CH).

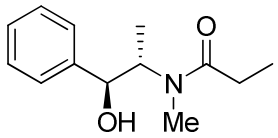
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = (signals for rotamers denoted with asterix) 18.9 (Me), 22.3 (CH_2), *22.6 (CH_2), 25.6 (^{t}Bu, 3 x Me), 29.3 (CH), *29.4 (CH), 33.0 (CH_2), *33.5 (CH_2), 33.7 (NMe), *34.6 (NMe), 34.8 (C), 38.0 (CH_2), 38.6 (CH_2), 49.9 (CH_2), *52.1 (CH_2), 77.2 (CH), 116.5 (CH_2), *117.0 (CH_2), 132.6 (CH), *133.2 (CH). C=O not observed.

[α] $^{20}_{D}$ -18.5 (*c* 0.9, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2940, 2869, 2236, 1732, 1630, 1554, 1479, 1465, 1437, 1373, 1245, 1181, 1119, 1045, 998, 907, 729, 694, 644, 621, 606.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{16}H_{31}NO_2 + Na]^+$: 292.2247; found: 292.2255.

***N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide**



Following the procedure outlined by Myers *et al.*[5] the *title compound* (5.0 g, 22.6 mmol, 94% yield) was isolated as a colourless solid and a mixture of rotamers (~ 3:1).

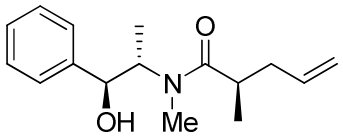
M.P. 112-113 ºC.; Lit. 114-115 ºC.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = (Signals for minor rotamers denoted with asterix) *0.97 (d, *J* = 6.8 Hz, 3 H, Me), 1.11 (dd, *J* = 2.8, 7.6 Hz, 3 H, Me), 1.14 (dt, *J* = 2.0, 8.8 Hz, 3 H, Me), *1.18 (dt, *J* = 1.2, 7.2 Hz, 3 H, Me), 2.27-2.35 (m, 2 H, CH_2), *2.36-2.55 (m, 2 H, CH_2), 2.80 (s, 3 H, NMe), *2.92 (s, 3 H, NMe), *3.96-4.04 (m, 1 H, CH), 4.28 (br s, 1 H, OH), 4.40-4.47 (m, 1 H, CH), 4.55-4.60 (m, 1 H, CH), 7.27-7.40 (m, 5 H, 5 x CH).

Spectroscopic data is consistent with that reported in the literature.[6,7]

[α] $^{20}_{D}$ +111.8 (*c* 1.0, $CHCl_3$); Lit. [α] $^{20}_{D}$ +103.1 (*c* 0.66, MeOH).[7]

(*R*)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide



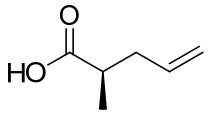
Following the procedure outlined by Myers *et al.*[5] the *title compound* (5.77 g, 22.1 mmol, 97% yield) was isolated as a dark yellow oil and a mixture of rotamers (~ 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = (Signals for minor rotational isomer denoted with an asterix) 1.00-1.10 (m, 6 H, 2 x Me), 2.03-2.10 (m, 1 H, CH of CH_2), *2.12-2.19 (m, 1 H, CH of CH_2), 2.29-2.40 (m, 1 H, CH of CH_2), *2.45-2.52 (m, 1 H, CH), 2.61-2.72 (m, 1 H, CH), 2.85 (s, 3 H, NMe), *2.89 (s, 3 H, NMe), *4.04-4.09 (m, 1 H, CH), 4.45 (br s, 1 H, OH), 4.55-4.60 (m, 1 H, CH), 4.99 (d, J = 10.4 Hz, 1 H, CH of CH_2), 5.03 (d, J = 1.6 Hz, 1 H, CH of CH_2), *5.10 (d, J = 18.0 Hz, 1 H, CH of CH_2), 5.63-5.74 (m, 1 H, CH), *5.74-5.78 (m, 1 H, CH), 7.22-7.38 (m, 5 H, 5 x CH).

Spectroscopic data is consistent with that reported in the literature.[6,8]

[α] $_D^{20.5}$ +75.0 (*c* 2.0, $CHCl_3$). Lit. [α] $_D^{20}$ +76.1 (*c* 1.5, $CHCl_3$).[8]

(*R*)-2-methylpent-4-enoic acid [(*R*)- 7]



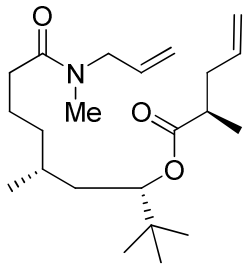
Following the procedure outlined by Myers *et al.*[5] the *title compound* (1.88 g, 16.47 mmol, 92% yield) was isolated as a dark yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.18 (d, J = 6.8 Hz, 3 H, Me), 2.17-2.24 (m, 1 H, CH of CH_2), 2.40-2.48 (m, 1 H, CH of CH_2), 2.51-2.59 (m, 1 H, CH), 5.04-5.11 (m, 2 H, CH_2), 5.71-5.82 (m, 1 H, CH).

Spectroscopic data was consistent with that reported in the literature.[9]

[α] $_D^{20.5}$ -9.6 (*c* 1.13, $CHCl_3$); lit. [α] $_D^{25}$ -8.0 (conc. and solvent not reported).[10]

(*R*)-((3*S*,5*R*)-9-(allyl(methyl)amino)-2,2,5-trimethyl-9-oxononan-3-yl) 2-methylpent-4-enoate (4)



To a solution of acid (*R*)-**7** (63 mg, 0.53 mmol) in benzene (2.0 mL), was added 2,4,6-trichlorobenzoyl chloride (0.113 mL, 0.73 mmol) followed by Hünigs base (0.113 mL, 0.65 mmol), alcohol **6** (0.1 g, 0.38 mmol) and DMAP (0.113 g, 0.93 mmol). The reaction was stirred at room temperature for 12 h, diluted with ethyl acetate (5 mL) and washed with water (2 x 5 mL), brine (5 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* as a 1:1 mixture of rotamers (122 mg, 0.33 mmol, 89% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.85 (s, 9 H, ^{t}Bu), 0.88 (d, *J* = 4.8 Hz, 3 H, Me), 1.01-1.09 (m, 1 H, CH), 1.15 (d, *J* = 6.8 Hz, 3 H, Me), 1.18-1.35 (m, 3 H, CH_2 + CH of CH_2), 1.52-1.65 (m, 3 H, CH_2 + CH of CH_2), 2.13 (dt, *J* = 6.8, 13.6 Hz, 1 H, CH of CH_2), 2.26 (dt, *J* = 7.2, 14.4 Hz, 2 H, CH_2), 2.39-2.54 (m, 2 H, CH + CH of CH_2), 2.90 (d, *J* = 4.4 Hz, 3 H, NMe), 3.86 (d, *J* = 4.8 Hz, 1 H, CH of CH_2), 3.97 (d, *J* = 5.6 Hz, 1 H, CH of CH_2), 4.81 (d, *J* = 10.8 Hz, 1 H, CH), 4.97-5.22 (m, 4 H, 2 x CH_2), 5.68-5.79 (m, 2 H, 2 x CH).

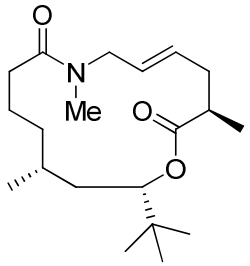
^{13}C NMR (100 MHz, $CDCl_3$): δ_C (Signals for minor rotational isomer denoted with asterix) = 16.9 (Me), *17.0 (Me), 19.0 (Me), *22.5 (CH_2), 22.9 (CH_2), 26.0 (^{t}Bu, 3 x Me), 29.3 (CH), 33.1 (CH_2), 33.5 (C), 33.7 (CH_2), *34.57 (NMe), 34.62 (NMe), *36.77 (CH_2), 36.80 (CH_2), 37.7 (CH_2), *38.0 (CH_2), 39.6 (CH), *49.9 (CH_2), 52.1 (CH_2), *78.10 (CH), 78.13 (CH), *116.5 (CH_2), 116.8 (CH_2), 117.0 (CH_2), 132.6 (CH), *133.2 (CH), 135.6 (CH), 172.7 (C=O), *173.2 (C=O), 175.8 (C=O).

[α] $^{19.4}_{D}$ -24.6 (*c* 1.1, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2960, 1727, 1676, 1650, 1459, 1415, 1376, 1368, 1262, 1173, 1127, 1085, 931, 912.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{22}H_{39}NO_3 + H]^+$: 366.3003; found: 366.2998.

(3*R*,13*R*,15*S*,E)-15-*tert*-butyl-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-5-ene-2,9-dione



To a solution of diene **4** (100 mg, 2.75 mmol) in degassed (Ar bubbled through solvent) 1,2-dichloroethane (80 mL) heated to reflux was added a solution of Grubbs 2nd generation catalyst (10 mg, 5 mol%) in 1,2-dichloroethane (1mL) and the reflux was maintained for 24 h. A second portion of Grubbs 2nd generation catalyst (10 mg, 5 mol%) in 1,2-dichloroethane (1 mL) was added and the reflux continued for a further 24 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (62 mg, 0.18 mmol, 67% yield) as a dark yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (s, 9 H, ^{t}Bu), 0.88 (dd, *J* = 6.0, 14.4 Hz, 3 H, Me), 1.09-1.16 (m, 1 H, CH of CH_2), 1.20 (d, *J* = 6.8 Hz, 3 H, Me), 1.21-1.32 (m, 3 H, CH + CH_2), 1.43 (dd, *J* = 10.0, 14.0

Hz, 1 H, CH of CH_2), 1.63-1.75 (m, 2 H, CH_2), 2.04-2.15 (m, 2 H, 2 x CH of CH_2), 2.28-2.53 (m, 3 H, CH + 2 x CH of CH_2), 2.95 (s, 3 H, NMe), 3.57 (d, J = 18.0 Hz, 1 H, CH of CH_2), 4.01 (dd, J = 5.2, 17.6 Hz, 1 H, CH of CH_2), 4.73 (d, J = 9.2 Hz, 1 H, CH), 5.41-5.57 (m, 2 H, 2 x CH).

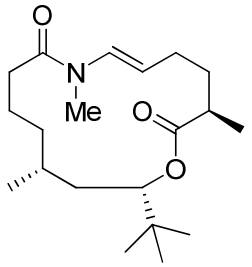
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 19.4 (Me), 19.8 (Me), 20.2 (CH_2), 25.8 (^{t}Bu, 3 x Me), 27.0 (CH), 30.3 (CH_2), 34.3 (NMe), 34.6 (C), 35.3 (CH_2), 36.1 (CH_2), 37.1 (CH_2), 41.0 (CH), 51.1 (CH_2), 79.5 (CH), 126.4 (CH), 129.2 (CH), 172.9 (C=O), 176.3 (C=O).

[α] $^{20}_{D}$ -37.7 (*c* 1.0, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2959, 2934, 1722, 1644, 1458, 1398, 1377, 1252, 1197, 1063, 966, 933.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{20}H_{35}NO_3 + Na]^+$: 360.2509; found: 360.2513.
$[M + K]^+$ calcd. for $[C_{20}H_{35}NO_3 + K]^+$: 376.2249; found: 376.2254.

(3*R*,13*R*,15*S*,E)-15-*tert*-butyl-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (1)



To a solution of (3*R*,13*R*,15*S*,E)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-5-ene-2,9-dione (50 mg, 0.15 mmol) in toluene (10.0 mL) at reflux was added a solution of carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (20 mg, 20 mol%) in toluene (1 mL) and the reflux was maintained for 24 h. The solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (44 mg, 0.13 mmol, 88% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (s, 9 H, ^{t}Bu), 0.93 (d, J = 5.6 Hz, 3 H, Me) 1.23 (d, J = 7.2 Hz, 3 H, Me), 1.22-1.25 (m, 3 H, CH_2 + CH of CH_2), 1.35-1.45 (m, 2 H, CH + CH of CH_2), 1.54-1.63 (m, 1 H, CH of CH_2), 1.68-1.78 (m, 2 H, CH_2), 1.88-1.96 (m, 1 H, CH of CH_2), 2.10-2.20 (m, 1 H, CH of CH_2), 2.21-2.34 (m, 2 H, CH_2), 2.48-2.56 (m, 1 H, CH of CH_2), 2.60-2.67 (dt, J = 8.0, 13.6 Hz, 1 H, CH), 3.06 (s, 3 H, NMe), 4.78 (d, J = 9.6 Hz, 1 H, CH), 4.86 (ddd, J = 4.8, 10.4, 13.6 Hz, 1 H, CH), 6.68 (d, J = 13.6 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 19.4 (Me), 19.5 (Me), 23.3 (CH_2), 25.9 (^{t}Bu, 3 x Me), 27.9 (CH), 29.1 (NMe), 29.7 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 34.9 (C), 35.3 (CH_2), 37.0 (CH), 38.4 (CH_2), 78.6 (CH), 110.3 (CH), 129.9 (CH), 172.1 (C=O), 175.8 (C=O).

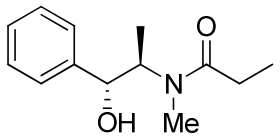
Spectroscopic data is consistent with that reported in the literature.[11]

[α] $^{19.5}_{D}$ -42.6 (*c* 0.97, $CHCl_3$); Lit. $[\alpha]^{24}_{D}$ -44.0 (*c* 0.16, $CHCl_3$).[11]

IR ν_{max} (neat)/cm^{-1} 2958, 2922, 2853, 1727, 1639, 1459, 1366, 1334, 1293, 1199, 1165, 1124, 1085, 932.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{20}H_{35}NO_3 + Na]^+$: 360.2509; found: 360.2514.
$[M + H]^+$ calcd. for $[C_{20}H_{35}NO_3 + H]^+$: 338.2690; found: 338.2688.

***N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide**



Following the procedure outlined by Myers *et al.*[5] the *title compound* (4.84 g, 21.87 mmol, 91% yield) was isolated as a colourless solid and a mixture of rotamers (~ 3:1).

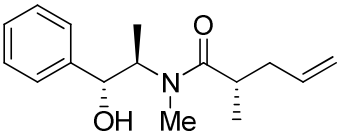
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = (Signals for minor rotamers denoted with asterix) *0.98 (d, *J* = 6.8 Hz, 3 H, Me), 1.12 (dd, *J* = 2.8, 7.6 Hz, 3 H, Me), 1.15 (dt, *J* = 2.0, 8.8 Hz, 3 H, Me), *1.19 (dt, *J* = 1.2, 7.2 Hz, 3 H, Me), 2.24-2.42 (m, 2 H, CH_2), *2.44-2.59 (m, 2 H, CH_2), 2.81 (s, 3 H, NMe), *2.93 (s, 3 H, NMe), *4.01 (t, *J* = 7.2 Hz, 1 H, CH), 4.27 (br s, 1 H, OH), 4.42-4.46 (m, 1 H, CH), 4.56-4.61 (m, 1 H, CH), 7.27-7.36 (m, 5 H, 5 x CH).

M.P. 111-113 ºC.; Lit. 114-115 ºC.[5]

Spectroscopic data is consistent with that reported in the literature.[6]

[α] $^{20}_{D}$ -135.1 (*c* 1.0, $CHCl_3$); Lit. [α] $^{23}_{D}$ -100.0 (*c* 0.57, MeOH).[6]

(*S*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide



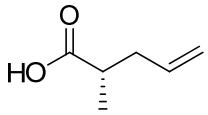
Following the procedure outlined by Myers *et al.*[5] the *title compound* (4.58 g, 17.52 mmol, 76% yield) was isolated as light yellow oil and a mixture of rotamers (~ 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = (Signals for minor rotamers denoted with asterix) 1.00-1.10 (m, 6 H, 2 x Me), 2.04-2.12 (m, 1 H, CH of CH_2), *2.13-2.18 (m, 1 H, CH of CH_2), 2.29-2.40 (m, 1 H, CH of CH_2), *2.46-2.54 (m, 1 H, CH), 2.62-2.73 (m, 1 H, CH), 2.85 (s, 3 H, NMe), *2.89 (s, 3 H, NMe), *4.04-4.09 (m, 1 H, CH), 4.45 (br s, 1 H, OH), 4.55-4.60 (m, 1 H, CH), 4.97 (d, *J* = 10.4 Hz, 1 H, CH of CH_2), 5.04 (d, *J* = 1.6 Hz, 1 H, CH of CH_2), *5.11 (d, *J* = 18.0 Hz, 1 H, CH of CH_2), 5.64-5.74 (m, 1 H, CH), *5.74-5.79 (m, 1 H, CH), 7.25-7.35 (m, 5 H, 5 x CH).

Spectroscopic data is consistent with that reported in the literature.[6]

[α] $^{20.5}_{D}$ -69.9 (*c* 1.03, $CHCl_3$). Lit. [α] $^{20}_{D}$ -74.9 (*c* 1.50, $CHCl_3$).[8]

(*S*)-2-methylpent-4-enoic acid [(*S*)- 7]



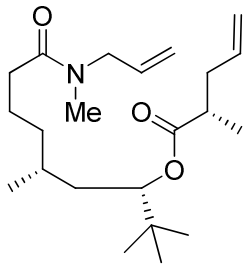
Following procedure outlined by Myers *et al.*[5] the *title compound* (1.84 g, 16.12 mmol, 92% yield) was isolated as a dark yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.19 (d, *J* = 6.8 Hz, 3 H, Me), 2.17-2.24 (m, 1 H, CH of CH_2), 2.41-2.48 (m, 1 H, CH of CH_2), 2.51-2.60 (m, 1 H, CH), 5.04-5.12 (m, 2 H, CH_2), 5.72-5.82 (m, 1 H, CH).

Spectroscopic data was consistent with that reported in the literature.[9]

[α] $_D^{20.5}$ +9.3 (*c* 1.02, $CHCl_3$); lit. [α] $_D^{20}$ +9.7 (*c* 0.4, $CHCl_3$).[9]

(*S*)-((3*S*,5*R*)-9-(allyl(methyl)amino)-2,2,5-trimethyl-9-oxononan-3-yl)-2-methylpent-4-enoate (5)



To a solution of acid (*S*)-**7** (63 mg, 0.53 mmol) in benzene (2.0 mL), was added 2,4,6-trichlorobenzoyl chloride (0.113 mL, 0.73 mmol) followed by Hünigs base (0.113 mL, 0.0.65 mmol), alcohol **6** (100 mg, 0.375 mmol) and finally DMAP (113 mg, 0.93 mmol). The reaction was stirred at room temperature for 12 h, diluted with ethyl acetate (5 mL), washed with water (2 x 5 mL), washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* as a 1:1 mixture of rotamers (120 mg, 0.35 mmol, 92% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (s, 9 H, ^{t}Bu), 0.89 (dd, *J* = 4.4, 6.0 Hz, 3 H, Me), 1.15 (d, *J* = 6.0 Hz, 3 H, Me), 1.18 (d, *J* = 6.8 Hz, 2 H, CH_2), 1.20-1.34 (m, 2 H, CH + CH of CH_2), 1.53-1.67 (m, 3 H, CH_2 + CH of CH_2), 2.10-2.21 (m, 1 H, CH of CH_2), 2.24-2.31 (m, 2 H, CH_2), 2.41-2.47 (m, 1 H, CH of CH_2), 2.48-2.57 (m, 1 H, CH), 2.91 (d, *J* = 4.0 Hz, 3 H, NMe), 3.88 (d, *J* = 6.0 Hz, 1 H, CH of CH_2), 3.99 (d, *J* = 6.4 Hz, 1 H, CH of CH_2), 4.83 (d, *J* = 10.8 Hz, 1 H, CH), 5.00-5.21 (m, 4 H, 2 x CH_2), 5.68-5.80 (m, 2 H, 2 x CH).

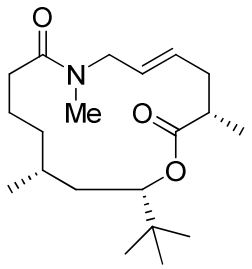
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = (Signals for minor rotational isomer signals denoted with asterix) *16.4 (Me), 17.0 (Me), 19.02 (Me), *19.03 (Me), *22.6 (CH_2), 22.9 (CH_2), *25.9 (^{t}Bu, 3 x Me), 26.0 (^{t}Bu, 3 x Me), 29.3 (CH), 33.1 (NMe), *33.6 (CH_2), 33.7 (CH_2), 34.5 (C), *34.7 (NMe), 36.87 (CH_2), *36.90 (CH_2), *37.5 (CH_2), 37.7 (CH_2), 38.0 (CH_2), 39.7 (CH), *50.0 (CH_2), 52.2 (CH_2), 78.15 (CH), *78.18 (CH), *116.5 (CH_2), 116.8 (CH_2), *117.0 (CH_2), 117.1 (CH_2), *132.6 (CH), 133.2 (CH), *135.3 (CH), 135.7 (CH), *172.8 (C=O), 173.3 (C=O), 175.8 (C=O).

[α] $^{19.7}_{D}$ -12.7 (*c* 0.985, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2960, 1726, 1676, 1649, 1459, 1377, 1363, 1263, 1173, 1127, 1085, 931, 912.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{22}H_{39}NO_3 + Na]^+$: 388.2822; found: 388.2825.
$[M + K]^+$ calcd. for $[C_{22}H_{39}NO_3 + K]^+$: 404.2562; found: 404.2560.

(3*S*,13*R*,15*S*,E)-15-*tert*-butyl-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-5-ene-2,9-dione



To a solution of diene **5** (100 mg, 2.75 mmol) in degassed (Ar bubbled through solvent) 1,2-dichloroethane (80 mL), heated to reflux was added a solution of Grubbs 2nd generation catalyst (10 mg, 5 mol%) in 1,2-dichloroethane (1mL) and reflux was maintained for 24 h. A second portion of Grubbs 2nd generation catalyst (10 mg, 5 mol%) in 1,2-dichloroethane (1 mL) was added, reflux continued for a further 24 h. Solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (59 mg, 0.17 mmol, 63% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86 (s, 9 H, ^{t}Bu), 0.89 (d, *J* = 5.6 Hz, 3 H, Me), 1.17-1.29 (m, 3 H, CH + CH_2), 1.22 (d, *J* = 7.2 Hz, 3 H, Me), 1.40 (dd, *J* = 10.8, 13.6, 1 H, CH of CH_2), 1.51-1.61 (m, 1 H, CH of CH_2), 1.71-1.83 (m, 1 H, CH of CH_2), 2.01-2.12 (m, 1 H, CH of CH_2), 2.28-2.43 (m, 4 H, 2 x CH_2), 2.63-2.72 (m, 1 H, CH), 2.93 (s, 3 H, NMe), 3.60 (d, *J* = 16.4 Hz, 1 H, CH of CH_2), 4.05 (d, *J* = 16.0 Hz, 1 H, CH of CH_2), 4.79 (d, *J* = 10.4 Hz, 1 H, CH), 5.51-5.55 (m, 2 H, 2 x CH).

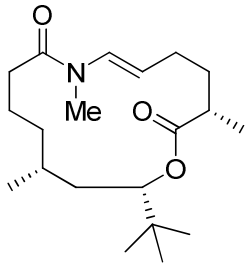
^{13}C NMR (100 MHZ, $CDCl_3$): δ_C = 17.9 (Me), 19.1 (Me), 20.5 (CH_2), 25.7 (CH_2), 25.8 (^{t}Bu, 3 x Me), 26.6 (CH), 29.8 (NMe), 34.2 (C), 34.6 (CH_2), 35.8 (CH_2), 37.5 (CH_2), 40.8 (CH), 51.0 (CH_2), 79.2 (CH), 127.0 (CH), 128.2 (CH), 172.9 (C=O), 174.6 (C=O).

[α] $^{19.5}_{D}$ -37.8 (*c* 1.13, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2962, 2918, 1722, 1645, 1457, 1397, 1365, 1251, 1066, 933.

HRMS-ESI: *m/z* $[M + K]^+$ calcd. for $[C_{20}H_{35}NO_3 + K]^+$: 376.2249; found: 376.2246.

(3*S*,13*R*,15*S*,E)-15-*tert*-butyl-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (*ent*-2)



To a solution of (3*S*,13*R*,15*S*,E)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-5-ene-2,9-dione (50 mg, 0.15 mmol) in toluene (10.0 mL) at reflux was added a solution of carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (20 mg, 20 mol%) in toluene (1 mL) and the reflux was maintained for 24 h. The solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (42 mg, 0.12 mmol, 84% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.9 (s, 9 H, ^{t}Bu), 0.93 (d, *J* = 6.4 Hz, 3 H, Me), 1.10-1.20 (m, 1 H, CH of CH_2), 1.19 (d, *J* = 7.2 Hz, 3 H, Me), 1.23-1.33 (m, 4 H, CH + CH_2 + CH of CH_2), 1.56-1.8 (m, 5 H, 2 x CH_2 + CH of CH_2), 1.83-1.92 (m, 1 H, CH of CH_2), 2.06-2.15 (m, 1 H, CH of CH_2), 2.18-2.26 (m, 1 H, CH of CH_2), 2.40-2.50 (m, 1 H, CH), 2.53-2.62 (m, 2 H, CH_2), 3.05 (s, 3 H, NMe), 4.85 (dd, *J* = 1.2, 10.4 Hz, 1 H, CH), 5.12 (dt, *J* = 7.2, 14.0 Hz, 1 H, CH), 6.65 (d, *J* = 14.0 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 17.4 (Me), 20.5 (Me), 22.7 (CH_2), 26.0 (^{t}Bu, 3 x Me), 27.1 (CH), 27.7 (NMe), 30.7 (CH_2), 32.9 (CH_2), 33.8 (CH_2), 34.8 (C), 36.3 (CH), 36.5 (CH_2), 37.9 (CH_2), 78.9 (CH), 112.9 (CH), 130.9 (CH), 172.5 (C=O), 175.6 (C=O).

Spectroscopic data is consistent with that reported in the literature.[11]

[α] $^{19.5}_{D}$ -43.3 (*c* 1.04, $CHCl_3$); Lit. $[\alpha]^{23.2}_{D}$ -45.5 (*c* 0.5, $CHCl_3$).[11]

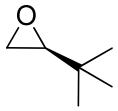
IR ν_{max} (neat)/cm^{-1} 2961, 2931, 1723, 1674, 1641, 1461, 1382, 1366, 1335, 1176, 1081, 919, 730.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{20}H_{35}NO_3 + H]^+$: 338.2690; found: 338.2696.

One pot alternative.

To a solution of diene **5** (10 mg, 0.027 mmol) in degassed (Ar bubbled through solvent) 1,2-dichloroethane (4 mL), heated to reflux was added a solution of Grubbs 2nd generation catalyst (1.5 mg, 5 mol%) in 1,2-dichloroethane (0.5 mL) and reflux was maintained for 24 h. A second portion of Grubbs 2nd generation catalyst (1.5 mg, 5 mol%) in 1,2-dichloroethane (0.5 mL) was added and reflux continued for a further 24 h. Solvent was concentrated *in vacuo* and residue was taken up in toluene (2.0 mL). The reaction mixture was brought to reflux, a solution of carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (4 mg, 20 mol%) in toluene (1 mL) was added and the reflux was maintained for 24 h. The solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (7.6 mg, 0.023 mmol, 84% yield) as a yellow oil.

(*S*)-2-*tert*-Butyloxirane [(*S*)- 8]



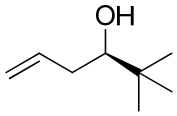
Following the procedure outlined by Jacobsen *et al.*[1] the *title compound* (2.67 g, 26.66 mmol. 44.5% yield) was isolated as a colourless oil.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.90 (s, 9 H, ^{t}Bu), 2.55-2.57 (m, 1 H, CH of CH_2), 2.59-2.62 (m, 1 H, CH), 2.69-2.70 (m, 1 H, CH of CH_2).

Spectroscopic data is consistent with that reported in the literature.[1,2]

[α] $_D^{20}$ +17.0 (*c* 1.51, PhH); lit. [α] $_D^{20}$ +12.8 (*c* 1.92, PhH).[2]

(*R*)-2,2-dimethylhex-5-en-3-ol



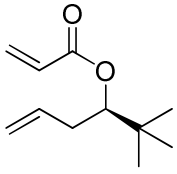
Following the procedure outlined by Porco *et al.*[12] the *title compound* (1.823 g, 14.21 mmol, 65% yield) was isolated as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.91 (s, 9 H, ^{t}Bu), 1.63 (br s, 1 H, OH), 1.93-2.02 (m, 1 H, CH of CH_2), 2.32-2.38 (m, 1 H, CH of CH_2), 3.24 (dd, *J* = 2.0, 10.8 Hz, 1 H, CH), 5.10-5.16 (m, 2 H, CH_2), 5.80-5.91 (m, 1 H, CH).

Spectroscopic data is consistent with that reported in the literature.[13]

[α] $_D^{20}$ +2.6 (*c* 1.00, $CHCl_3$); lit. [α] $_D$ +2.8 (*c* 10.0, C_6H_6).[14]

(*R*)-2,2-dimethylhex-5-en-3-yl acryate (14)



To a solution of (*R*)-2,2-dimethylhex-5-en-3-ol (1.82 g, 0.01 mol) in dichloromethane (50 mL) was added DMAP (0.35 g, 3.0 mmol, 20 mol%), Hünigs base (12.38 mL, 0.07 mol) and acryloyl chloride (3.68 mL, 0.05 mol) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction was then cooled to 0 ºC and quenched carefully with aqueous sodium bicarbonate solution (50 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography

on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (2.48 g, 13.6 mmol, 96% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.93 (s, 9 H, ^{t}Bu), 2.17-2.26 (m, 1 H, CH of CH_2), 2.37-2.43 (m, 1 H, CH of CH_2), 4.86 (dd, *J* = 2.8, 10.4 Hz, 1 H, CH), 4.96-5.05 (m, 2 H, CH_2), 5.67-5.77 (m, 1 H, CH), 5.79 (dd, *J* = 1.6, 10.4 Hz, 1 H, CH of CH_2), 6.11 (dd, *J* = 10.4, 17.2 Hz, 1 H, CH), 6.38 (dd, *J* = 1.6, 17.6 Hz, 1 H, CH of CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 25.9 (^{t}Bu, 3 x Me), 34.6 (CH_2), 34.7 (C), 79.9 (CH), 117.0 (CH_2), 128.8 (CH), 130.2 (CH_2), 135.1 (CH), 166.0 (C=O).

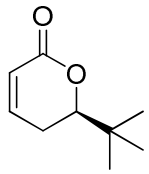
Spectroscopic data is consistent with that reported in the literature for *ent*-(**14**).[15]

[α] $^{20}_{D}$ -19.3 (*c* 1.12, $CHCl_3$); Lit. *ent*-(**14**) [α] $^{20}_{D}$ +18.7 (*c* 7.0, *n*-pentane).[15]

IR ν_{max} (neat)/cm^{-1} 2964, 2873, 1724, 1641, 1480, 1469, 1403, 1367, 1295, 1270, 1188, 1047, 980, 915, 807.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{11}H_{18}O_2 + Na]^+$: 205.1199; found: 205.1201.

(*R*)-6-*tert*-Butyl-5,6-dihydro-2*H*-pyran-2-one (15)



To a solution of diene **14** (1.739 g, 9.5 mmol) in degassed (Ar bubbled through solvent) dichloromethane (55 mL) at reflux was added a solution of Grubbs 2nd generation catalyst (80 mg, 0.094 mmol, 1.0 mol%) in dichloromethane (2 mL) and the reflux was maintained for 24 h. A second portion of Grubbs 2nd generation catalyst (80 mg, 1.0 mol%) was added in dichloromethane (2 mL) and reflux continued for a further 24 h. The solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (1.28 g, 8.32 mmol, 87% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.99 (s, 9 H, ^{t}Bu), 2.24-2.39 (m, 2 H, CH_2), 4.06 (dd, *J* = 4.8, 12.0 Hz, 1 H, CH), 6.01 (ddd, *J* = 1.2, 2.4, 9.6 Hz, 1 H, CH), 6.87-6.91 (m, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 24.5 (CH_2), 25.4 (^{t}Bu, 3 x Me), 33.8 (C), 85.2 (CH), 121.2 (CH), 145.4 (CH), 164.8 (C=O).

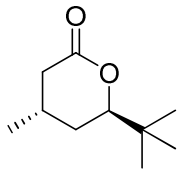
Spectroscopic data is consistent with that reported in the literature for *ent*-(**15**).[15]

[α]$^{19.5}_{D}$ +110.7 (*c* 1.72, $CHCl_3$); Lit. *ent*-(**15**) [α] $^{20}_{D}$ -115.2 (*c* 3.5, *n*-pentane).[15]

IR ν_{max} (neat)/cm^{-1} 2965 2876, 1707, 1482, 1398, 1382, 1369, 1252, 1152, 1123, 1084, 1044, 1028, 962, 946, 928, 818.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_9H_{14}O_2 + Na]^+$: 177.0886; found: 177.0888.

(4*S*, 6*R*)-6-*tert*-Butyl-4-methyltetrahydro-2*H*-pyran-2-one (16)



A suspension of CuI (0.37 g, 1.29 mmol) in ether (6 mL) was cooled to -78 ºC. A solution of methylmagnesium bromide in THF (6.5 mL, 0.6 M, 3.9 mmol) was added and the reaction was stirred at -78 ºC for 2 h. A solution of dihydropyranone **15** (0.2 g, 1.29 mol) in ether (6 mL) was added dropwise over 1 h and the reaction mixture was stirred at -78 ºC for a further 4 h. The reaction was quenched carefully with a saturated ammonium chloride solution and allowed to warm to room temperature. The aqueous phase was extracted with ether (3 x 20 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (0.16 g, 0.94 mmol, 73% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.96 (s, 9 H, ^{t}Bu), 1.11 (d, *J* = 6.4 Hz, 3 H, Me), 1.50 (dt, *J* = 4.0, 14.0 Hz, 1 H, CH of CH_2), 1.81 (ddd, *J* = 7.2, 12.0, 14.0 Hz, 1 H, CH of CH_2), 2.17-2.23 (m, 2 H, CH + CH of CH_2), 2.51 (q, *J* = 9.2 Hz, 1 H, CH of CH_2), 3.98 (dd, *J* = 3.6, 11.6 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.2 (Me), 24.0 (CH), 25.4 (^{t}Bu, 3 x Me), 29.8 (CH_2), 33.9 (C), 36.9 (CH_2), 83.7 (CH), 173.2 (C=O).

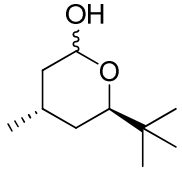
Spectroscopic data was consistent with that reported for *ent*-(**16**).[15,16]

[α] $^{20}_{D}$ -38.8 (*c* 0.95, $CHCl_3$); Lit. *ent*-(**16**) $[\alpha]^{20}_{D}$ +28.3 (*c* 3.2, Et_2O).[14]; +46.5 (*c* 0.3, $CHCl_3$).[16]

IR ν_{max} (neat)/cm^{-1} 3339, 2962, 2874, 1724, 1629, 1481, 1452, 1399, 1369, 1244, 1166, 1122, 1100, 1073, 1046, 1000.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{10}H_{18}O_2 + Na]^+$: 193.1199; found: 193.1200.

(4*S*, 6*R*)-6-*tert*-Butyl-4-methyltetrahydro-2*H*-pyran-2-ol (17)



To a solution of lactone **16** (100 mg, 0.6 mmol) in dichloromethane (5 mL) at -78 ºC was added DIBAL-H (1M in toluene, 0.9 mL, 0.9 mmol) and the reaction was stirred for 4 h. The reaction was quenched with methanol (5 mL) and water (5 mL) and allowed to warm to room temperature. An aqueous solution of hydrochloric acid (1M) was added dropwise until cloudiness disappeared. The aqueous phase was

extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* as a 1:2 mixture of epimers (84 mg, 0.49 mmol, 80% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = (Signals for minor epimer denoted with asterix) *0.87 (s, 9 H, ^{t}Bu), 0.90 (s, 9 H, ^{t}Bu), 1.08 (d, *J* = 7.6 Hz, 3 H, Me), *1.12 (d, *J* = 7.2 Hz, 3 H, Me), 1.25-1.30 (m, 2 H, CH_2), 1.42-1.54 (m, 2 H, CH_2), *1.62-1.69 (m, 2 H, CH_2), *1.78-1.85 (m, 2 H, CH_2), *2.31 (d, *J* = 3.2 Hz, 1 H, CH), 2.63 (d, *J* = 6.0 Hz, 1 H, CH), 3.28 (dd, *J* = 2.0, 12.0 Hz, 1 H, CH), *3.63 (dd, *J* = 4.0, 11.2 Hz, 1 H, CH), 4.92 (ddd, *J* = 2.0, 5.6, 10.0 Hz, 1 H, CH), *5.29-5.31 (m, 1 H, CH), lactol OH not observed.

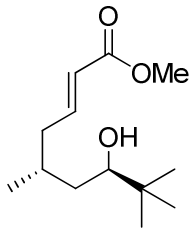
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 18.8 (Me), 24.1 (CH), 26.0 (^{t}Bu, 3 x Me), 30.1 (CH_2), 35.4 (C), 38.6 (CH_2), 78.4 (CH), 93.2 (CH).

[α] $_D^{20.5}$ -4.5 (*c* 0.403, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3372, 2947, 2869, 1480, 1457, 1395, 1366, 1320, 1259, 1177, 1123, 1082, 1043, 997, 969, 887.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{10}H_{20}O_2 + Na]^+$: 195.1356; found: 195.1350.

(5*R*, 7*R*, *E*)-Methyl-7-hydroxy-5,8,8-trimethylnon-2-enoate



A solution of phoshonate **13** (0.37 g, 0.32 mL, 1.74 mmol) in THF (10 mL) was added to a suspension of NaH (40 mg, 1.67 mmol) in THF (10 mL) at -78 ºC and the reaction mixture was stirred for 2 h. A solution of lactol **17** (100 mg, 0.58 mmol) in THF (10 mL) was added and the reaction mixture was stirred for 16 h and allowed to warm to room temperature. The reaction was quenched with a saturated aqueous solution of sodium chloride (20 mL) and diluted with water (20 mL), stirred for 10 min, then extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:4) to give the *title compound* (88 mg, 0.39 mmol, 66% yield) as a yellow oil.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86 (s, 9 H, ^{t}Bu), 0.94 (d, *J* = 6.8 Hz, 3 H, Me), 1.20-1.27 (m, 1 H, CH of CH_2), 1.38 (ddd, *J* = 1.6, 9.2, 14.0 Hz, 1 H, CH of CH_2), 1.85-1.94 (m, 1 H, CH), 1.95-2.03 (m, 1 H, CH of CH_2), 2.31-2.38 (m, 1 H, CH of CH_2), 3.26 (dd, *J* = 2.0, 10.4 Hz, 1 H, CH), 3.70 (s, 3 H, OMe), 5.81 (d, *J* = 15.6 Hz, 1 H, CH), 6.95 (ddd, *J* = 6.8, 7.6, 15.2 Hz, 1 H, CH), OH not observed.

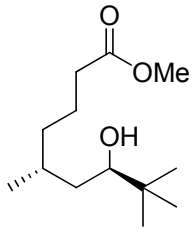
^{13}C NMR (100 MHZ, $CDCl_3$): δ_C = 20.9 (Me), 25.5 (^{t}Bu, 3 x Me), 29.6 (CH), 34.9 (C), 38.1 (CH_2), 38.4 (CH_2), 51.3 (OMe), 77.3 (CH), 122.2 (CH), 148.1 (CH), 166.9 (C=O).

[α] $_D^{20.5}$ +38.9 (*c* 1.00, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3461, 2949, 2870, 1724, 1710, 1437, 1364, 1321, 1276, 1206, 1167, 1074, 1044, 1006, 984.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{13}H_{24}O_3 + Na]^+$: 251.1618; found: 251.1610.

(5*R*, 7*R*)-Methyl 7-hydroxy-5,8,8-trimethylnonanoate



A solution of (5*R*,7*R*,*E*)-Methyl-7-hydroxy-5,8,8-trimethylnon-2-enoate (100 mg, 0.42 mmol) in methanol (10 mL) was passed through an H-cube® flow reactor (20 ºC, at 20 Bar with 10 mol% Pd/C). A further 5 mL of methanol was passed through the apparatus and the combined solvent was concentrated *in vacuo* to give the *title compound* (97 mg, 0.42 mmol, ~ 100% yield) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86 (s, 9 H, ^{t}Bu), 0.93 (d, *J* = 6.8 Hz, 3 H, Me), 1.00-1.09 (m, 1 H, CH of CH_2), 1.14-1.21 (m, 1 H, CH of CH_2), 1.35 (ddd, *J* = 5.6, 14.8, 16.8 Hz, 1 H, CH of CH_2), 1.40-1.49 (m, 1 H, CH of CH_2), 1.50-1.60 (m, 1 H, CH of CH_2), 1.62-1.73 (m, 3 H, OH + CH + CH of CH_2) 2.28 (dt, *J* = 6.4, 8.0 Hz, 2 H, CH_2), 3.24 (dd, *J* = 1.6, 10.0 Hz, 1 H, CH), 3.65 (s, 3 H, OMe).

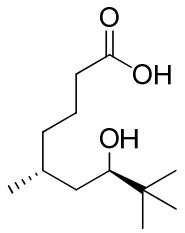
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 20.8 (Me), 22.2 (CH_2), 25.6 (^{t}Bu, 3 x Me), 29.6 (CH), 34.3 (CH_2), 34.8 (CH_2), 34.9 (C), 39.0 (CH_2), 51.4 (OMe), 77.4 (CH), 174.2 (C=O).

[α] $_D^{19.7}$ +45.1 (*c* 1.053, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3463, 2956, 2922, 2850, 2168, 1731, 1460, 1437, 1363, 1258, 1197, 1165, 1087, 1038, 1015, 81, 603.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{13}H_{26}O_3 + Na]^+$: 253.1774; found: 253.1783.

(5*R*,7*R*)-7-Hydroxy-5,8,8-trimethylnonanoic acid



To a solution of methyl 7-hydroxy-5,8,8-trimethylnonanoate (100 mg, 0.43 mmol) in a dichloromethane/methanol (5 mL, 9:1), was added a methanolic solution of sodium hydroxide (112 mg,

in 1 mL, 2.8 mmol). After 2.5 h stirring at room temperature, the solvents were concentrated *in vacuo* and residue was diluted with water (10 mL), then washed with ether (2 x 10 mL) and the organic phases discarded. The aqueous phase was then cooled (0 ºC) and acidified (pH 2-3) with dilute aqueous hydrochloric acid and extracted with dichloromethane (3 x 10 mL). The combined organic phases dried ($MgSO_4$), filtered and the solvent was concentrated *in vacuo* to give the *title compound* (86 mg, 0.39 mmol, 91% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (s, 9 H, ^{t}Bu), 0.94 (d, *J* = 6.8 Hz, 3 H, Me), 1.03-1.14 (m, 1 H, CH of CH_2) ,1.17-1.24 (m, 1 H, CH of CH_2), 1.37 (ddd, *J* = 2.0, 9.6, 14.4 Hz, 1 H, CH of CH_2), 1.43-1.52 (m, 1 H, CH of CH_2), 1.53-1.62 (m, 1 H, CH of CH_2), 1.63-1.77 (m, 2 H, CH + CH of CH_2), 2.34 (dt, *J* = 8.0, 14.8 Hz, 2 H, CH_2), 3.28 (dd, *J* = 1.6, 10.0 Hz, 1 H, CH), CO_2H and OH not observed.

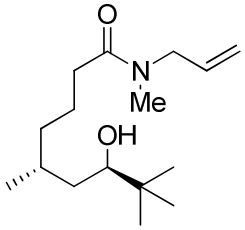
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 20.8 (Me), 21.9 (CH_2), 25.6 (^{t}Bu, 3 x Me), 29.6 (CH), 34.2 (CH_2), 34.7 (CH_2), 34.9 (C), 38.9 (CH_2), 77.5 (CH), 179.2 (C=O).

[α] $_D^{20.5}$ +48.1 (*c* 1.06, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3297, 2963, 2933, 2875, 2511, 1672, 1468, 1424, 1396, 1366, 1336, 1308, 1273, 1184, 1125, 1106, 1077, 1053, 1030, 1007, 983, 947, 868, 846, 765.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{12}H_{24}O_3 + Na]^+$: 239.1618; found: 239.1617.

(5*R*,7*R*)-*N*-allyl-7-hydroxy-*N*,5,8,8-tetramethylnonanamide (18)



To a solution of (5*R*,7*R*)-7-hydroxy-5,8,8-trimethylnonanoic acid (86 mg, 0.4 mmol) in dichloromethane (8.0 mL) was added HOAt (55 mg, 0.4 mmol), *N*-methylallylamine (46 µL, 0.48 mmol), and EDCI (62 mg, 0.4 mmol). The reaction mixture was stirred for 4 h and solvent was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with methanol-ethyl acetate (1:19) to give the *title compound* as a 1:1 mixture of rotamers (92 mg, 0.34 mmol, 85% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.85 (s, 9 H, ^{t}Bu), 0.93 (dd, *J* = 3.6, 6.8 Hz, 3 H, Me), 0.99-1.12 (m, 1 H, CH), 1.16-1.23 (m, 1 H, CH of CH_2), 1.34 (ddd, *J* = 1.6, 9.2, 14.0 Hz, 1 H, CH of CH_2), 1.43-1.52 (m, 1 H, CH of CH_2), 1.54-1.60 (m, 1 H, CH of CH_2), 1.63-1.75 (m, 2 H, CH_2), 1.89 (br s, 1 H, OH), 2.22-2.36 (m, 2 H, CH_2), 2.90 (d, *J* = 10.8 Hz, 3 H, NMe), 3.25 (dd, *J* = 1.2, 10.0 Hz, 1 H, CH), 3.88 (d, *J* = 4.4 Hz, 1 H, CH of CH_2), 3.97 (d, *J* = 6.0 Hz, 1 H, CH of CH_2), 5.07-5.20 (m, 2 H, CH_2), 5.66-5.79 (m, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = (Signals for minor rotamers denoted with asterix) 20.9 (Me), *22.3 (CH_2), 22.6 (CH_2), 25.7 (^{t}Bu, 3 x Me), 29.66 (CH), *29.73 (CH), 33.1 (C), *33.6 (CH_2), 33.7 (CH_2), *34.8

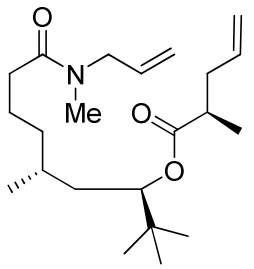
(NMe), 34.9 (NMe), *35.0 (CH_2), 35.1 (CH_2), 39.1 (CH_2), *50.0 (CH_2), 52.2 (CH_2), *77.19 (CH), 77.21 (CH), 116.6 (CH_2), *117.1 (CH_2), 132.7 (CH), *133.2 (CH), 172.9 (C=O), *173.4 (C=O).

[α] $^{19.7}_{D}$ +36.4 (*c* 1.005, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 3431, 2943, 2868, 1634, 1478, 1464, 1401, 1362, 1276, 1241, 1092, 996, 922.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{16}H_{31}NO_2 + Na]^+$: 292.2247; found: 292.2250.

(*R*)-(3*R*,5*R*)-9-(allyl(methyl)amino)-2,2,5-trimethyl-9-oxononan-3-yl 2-methylpent-4-enoate (19)



To a solution of acid (*R*)-**7** (25 mg, 0.21 mmol) in benzene (0.75 mL) was added 2,4,6-trichlorobenzoyl chloride (45 μL, 0.29 mmol) followed by Hünigs base (45 μL, 0.26 mmol), alcohol **18** (40 mg, 0.15 mmol) and DMAP (45 mg, 0.37 mmol). The reaction was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate (5 mL), washed with water (2 x 5 mL), washed with brine, dried (Na_2SO_4), filtered and the solvent was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* as a 1:1 mixture of rotamers (53 mg, 0.14 mmol, 96% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.85 (d, *J* = 1.2 Hz, 9 H, ^{t}Bu), 0.87 (dd, *J* = 2.8, 8.4 Hz, 3 H, Me), 1.00-1.10 (m, 1 H, CH of CH_2), 1.14 (ddd, *J* = 1.6, 2.8, 6.8 Hz, 3 H, Me), 1.25-1.33 (m, 2 H, CH_2), 1.34-1.40 (m, 1 H, CH), 1.42-1.54 (m, 2 H, CH_2), 1.62-1.74 (m, 1 H, CH of CH_2), 2.09-2.16 (m, 1 H, CH of CH_2), 2.21-2.31 (m, 2 H, CH_2), 2.38-2.52 (m, 2 H, CH + CH of CH_2), 2.90 (d, *J* = 10.4 Hz, 3 H, NMe), 3.88 (d, *J* = 4.8 Hz, 1 H, CH of CH_2), 3.96 (d, *J* = 5.6 Hz, 1 H, CH of CH_2), 4.77-4.81 (m, 1 H, CH), 4.98-5.19 (m, 4 H, 2 x CH_2), 5.67-5.79 (m, 2 H, 2 x CH).

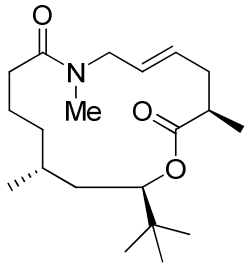
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = (Signals for minor rotational isomer denoted with asterix) *16.90 (Me), 16.93 (Me), *20.60 (Me), 20.62 (Me), 22.1 (CH_2), *22.4 (CH_2), *25.91 (^{t}Bu, 3 x Me), 25.94 (^{t}Bu, 3 x Me), *29.2 (CH), 29.3 (CH), 33.1 (CH_2), *33.4 (CH_2), *33.8 (C), 34.5 (C), *34.58 (CH_2), 34.60 (CH_2), 34.9 (CH_2), 37.21 (CH_2), *37.24 (CH_2), 37.6 (CH_2), *37.7 (CH_2), 39.5 (CH), *39.7 (CH), *49.9 (CH_2), 52.1 (CH_2), *78.26 (CH), 78.30 (CH), *116.5 (CH_2), 116.7 (CH_2), 116.8 (CH_2), 116.9 (CH_2), *132.7 (CH), *133.3 (CH), 135.6 (CH), 172.8 (C=O), *173.3 (C=O), 175.70 (C=O), *175.74 (C=O).

[α] $^{19.7}_{D}$ +15.7 (*c* 1.31, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2939, 1726, 1675, 1648, 1460, 1415, 1396, 1377, 1332, 1264, 1222, 1173, 1128, 1107, 994, 957, 931, 912.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd. for $[C_{22}H_{39}NO_3 + Na]^+$: 388.2822; found: 388.2815.

(3*R*,13*R*,15*R*,*E*)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-5-ene-2,9-dione



To a solution of diene **19** (36 mg, 0.1 mmol) in degassed (Ar bubbled through solvent) 1,2-dichloroethane (30 mL) heated to reflux was added a solution of Grubbs 2nd generation catalyst (4 mg, 5 mol%) in 1,2-dichloroethane (1mL) and the reflux was maintained for 24 h. A second portion of Grubbs 2nd generation catalyst (4 mg, 5 mol%) in 1,2-dichloroethane (1 mL) was added and the reflux was continued for a further 24 h. Solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (25 mg, 0.074 mmol, 74% yield)as a dark yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.84 (s, 9 H, ^{t}Bu), 0.87 (dd, *J* = 6.0, 8.0 Hz, 3 H, Me), 1.23 (d, *J* = 7.2 Hz, 4 H, CH + Me), 1.26-1.34 (m, 1 H, CH of CH_2), 1.39-1.51 (m, 2 H, CH_2), 1.52-1.62 (m, 2 H, CH_2), 1.84-1.93 (m, 1 H, CH of CH_2). 2.11-2.23 (m, 2 H, CH_2), 2.26-2.37 (m, 1 H, CH of CH_2), 2.49-2.58 (m, 1 H, CH of CH_2), 2.66-2.74 (m, 1 H, CH), 2.97 (s, 3 H, NMe), 3.83 (d, *J* = 2.8 Hz, 2 H, CH_2), 4.85 (d, *J* = 10.0 Hz, 1 H, CH), 5.54-5.57 (m, 2 H, 2 x CH).

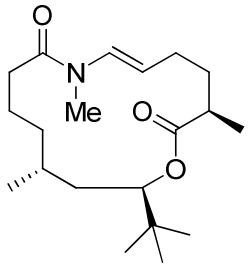
^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 16.5 (Me), 20.0 (Me), 21.7 (CH_2), 25.8 (C), 25.9 (^{t}Bu, 3 x Me), 27.6 (CH), 31.1 (CH_2), 33.6 (CH_2), 34.7 (CH_2), 35.0 (NMe), 37.5 (CH_2), 39.6 (CH), 51.8 (CH_2), 77.0 (CH), 127.0 (CH), 127.6 (CH), 173.7 (C=O), 173.9 (C=O).

[α] $^{19.7}_{D}$ -23.2 (*c* 1.06, $CHCl_3$).

IR ν_{max} (neat)/cm^{-1} 2958, 2929, 2871, 1723, 1645, 1480, 1458, 1397, 1377, 1365, 1252, 1197, 1129, 1064, 967, 933.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{20}H_{35}NO_3 + H]^+$: 338.2690; found: 338.2692.

Palmyrolide A (3)



To a solution of (3*R*,13*R*,15*R*,*E*)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-5-ene-2,9-dione (9.7 mg, 0.029 mmol) in toluene (2.0 mL) at reflux was added a solution of

carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (4 mg, 20 mol%) in toluene (1 mL) and the reflux was maintained for 24 h. Solvent was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) to give the *title compound* (8.5 mg, 0.025 mmol, 87% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (s, 9 H, ^{t}Bu), 0.90 (d, *J* = 6.8 Hz, 3 H, Me), 1.02-1.12 (m, 1 H, CH of CH_2), 1.21 (d, *J* = 7.2 Hz, 3 H, Me), 1.32-1.41 (m, 2 H, CH_2), 1.43-1.52 (m, 1 H, CH), 1.54-1.62 (m, 1 H, CH of CH_2), 1.66 (ddd, *J* = 2.4, 10.8, 14.4 Hz, 1 H, CH of CH_2), 1.73-1.84 (m, 3 H, CH_2 + CH of CH_2), 2.25-2.33 (m, 2 H, CH_2), 2.34-2.42 (m, 2 H, CH_2), 2.44-2.52 (m, 1 H, CH), 3.05 (s, 3 H, NMe), 4.88 (dd, *J* = 1.6, 10.8 Hz, 1 H, CH), 5.28 (dt, *J* = 7.2, 14.0 Hz, 1 H, CH), 6.47 (d, *J* = 14.0 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 16.8 (Me), 20.6 (Me), 24.3 (CH_2), 26.0 (^{t}Bu, 3 x Me), 27.0 (CH_2), 29.3 (CH), 31.7 (NMe), 32.8 (CH_2), 34.4 (CH_2), 34.5 (CH_2), 35.2 (C), 35.7 (CH_2), 38.9 (CH), 77.2 (CH), 117.2 (CH), 130.6 (CH), 172.8 (C=O), 175.2 (C=O).

Spectroscopic data is consistent with that reported in the literature for isolated[17] and synthetic.[11,18]

[α] $_D^{19.9}$ -27.4 (*c* 0.56, $CHCl_3$); Lit. [α] $_D^{23}$ -29 (*c* 0.9, $CHCl_3$)[16]; [α] $_D$ -27 (*c* 0.86, $CHCl_3$).[11,18]

IR ν_{max} (neat)/cm^{-1} 2958, 2927, 2872, 1726, 1674, 1643, 1461, 1414, 1382, 1366, 1315, 1204, 1192, 1171, 1121, 1076, 995, 960, 933.

HRMS-ESI: *m/z* $[M + H]^+$ calcd. for $[C_{20}H_{35}NO_3 + H]^+$: 338.2690; found:338.2700.

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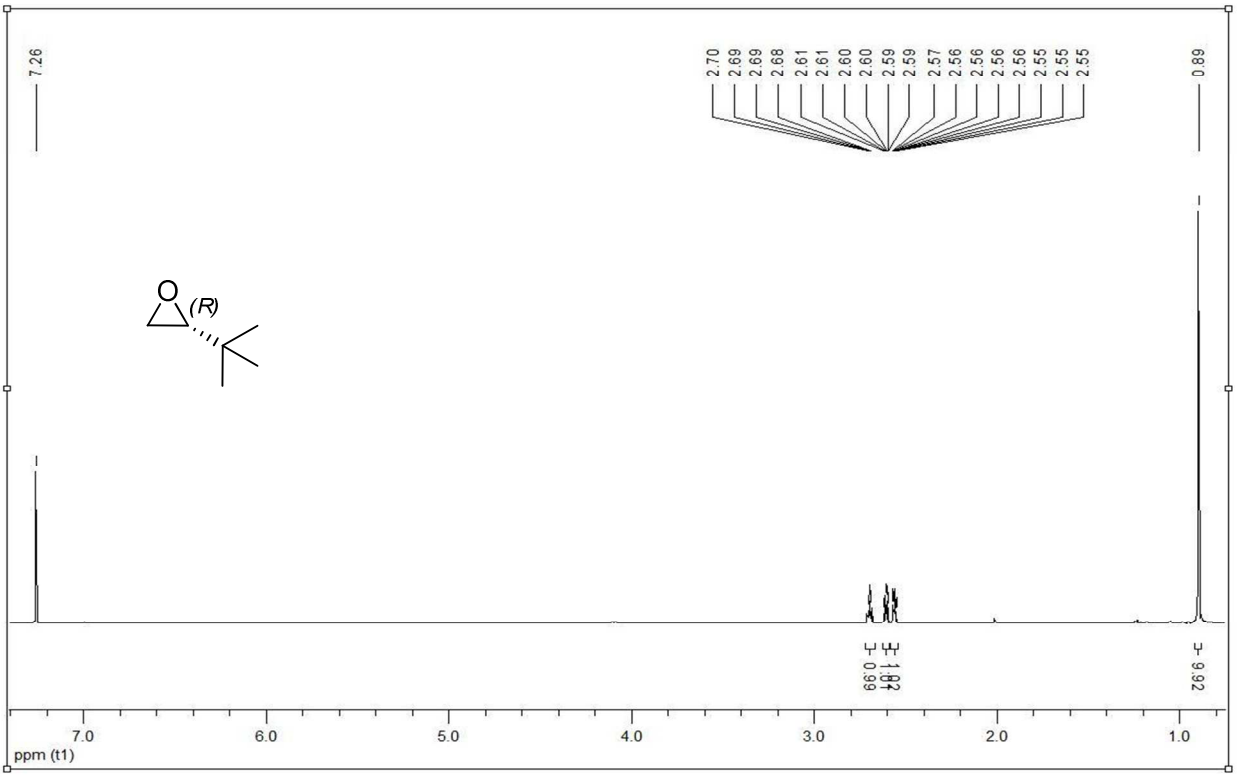
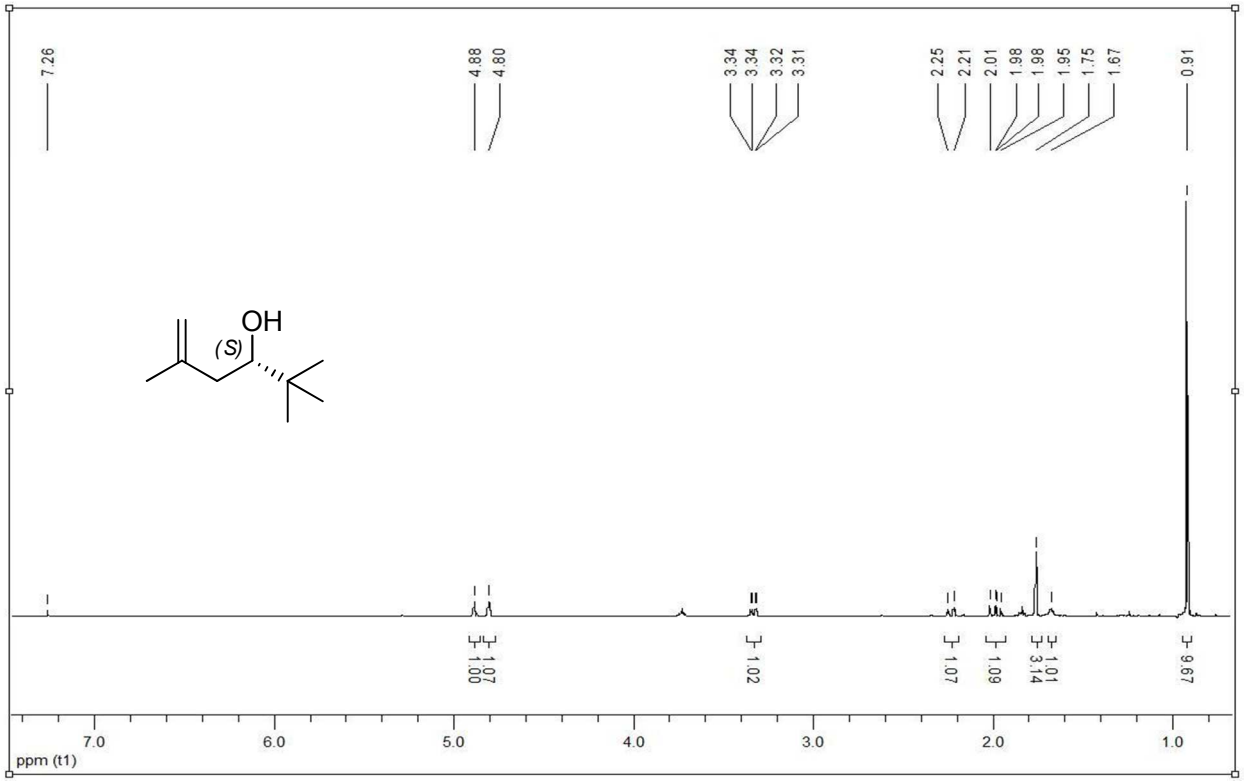
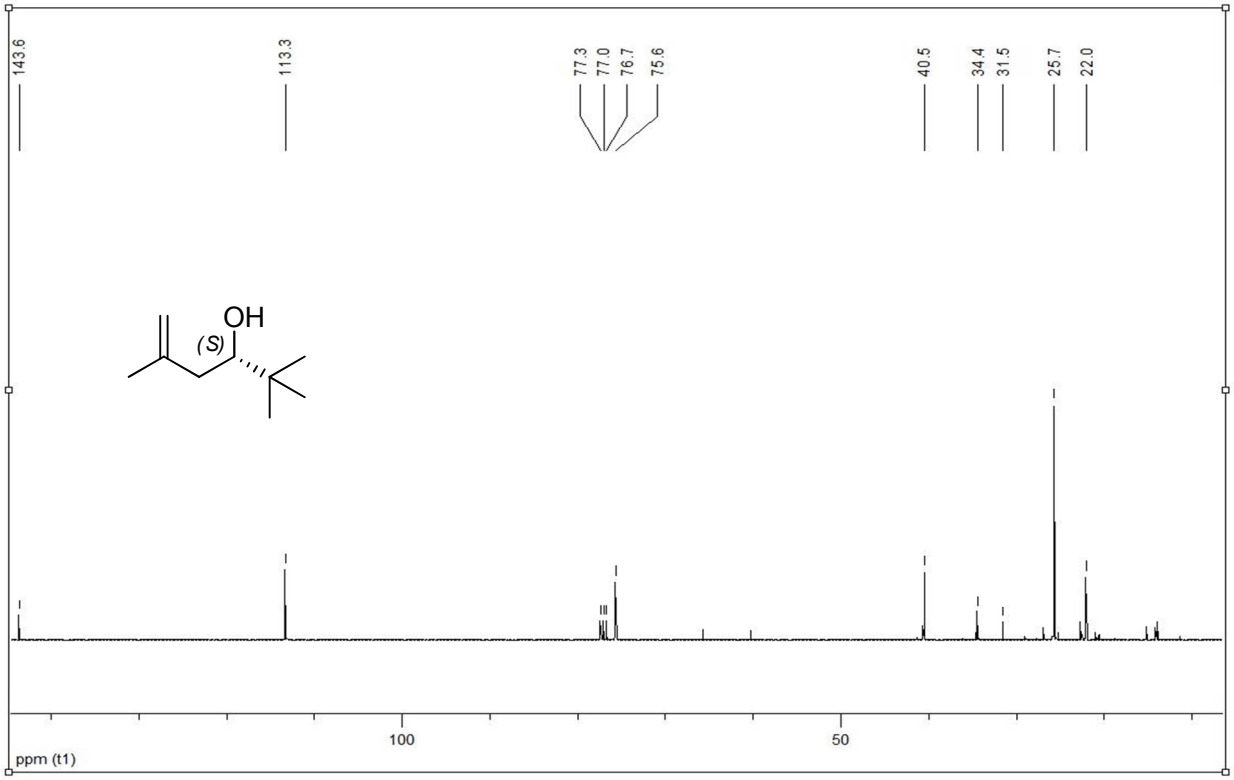
Compound (*R*)-**8** **^{1}H NMR** (400 MHZ, $CDCl_3$)



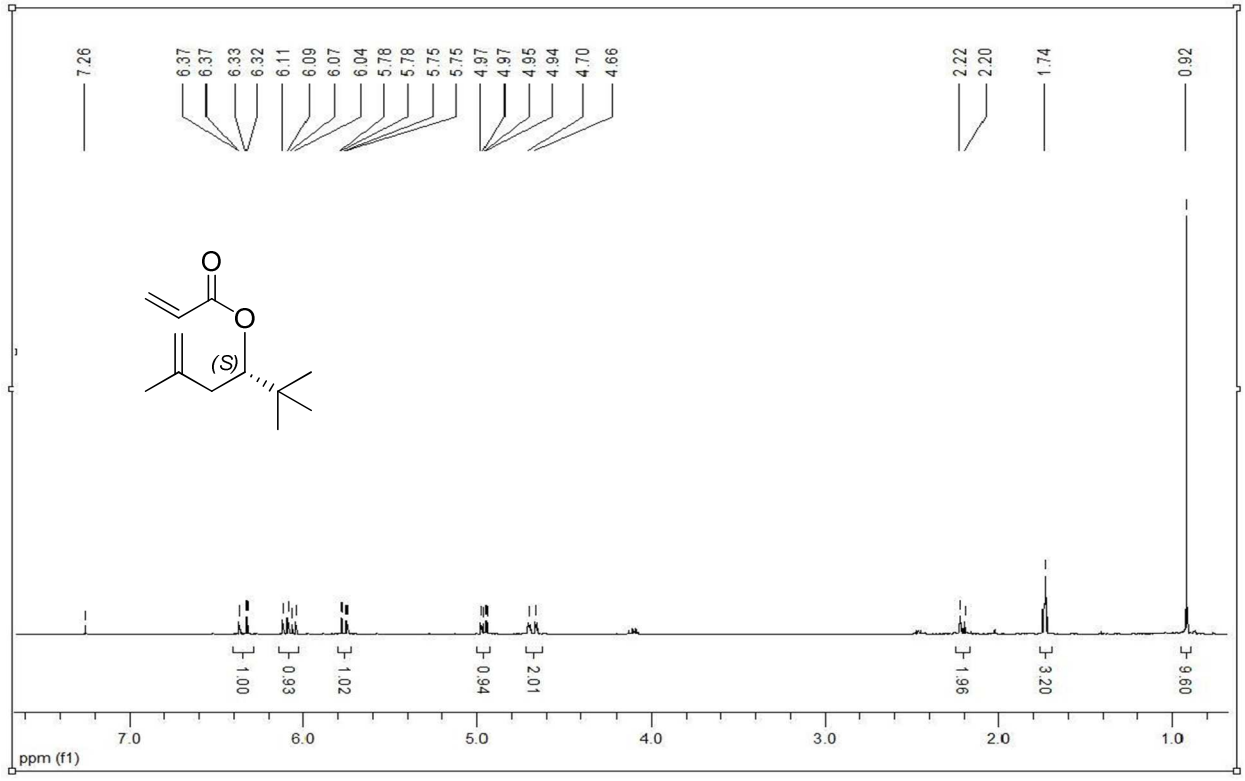
^{1}H NMR (400 MHZ, $CDCl_3$)



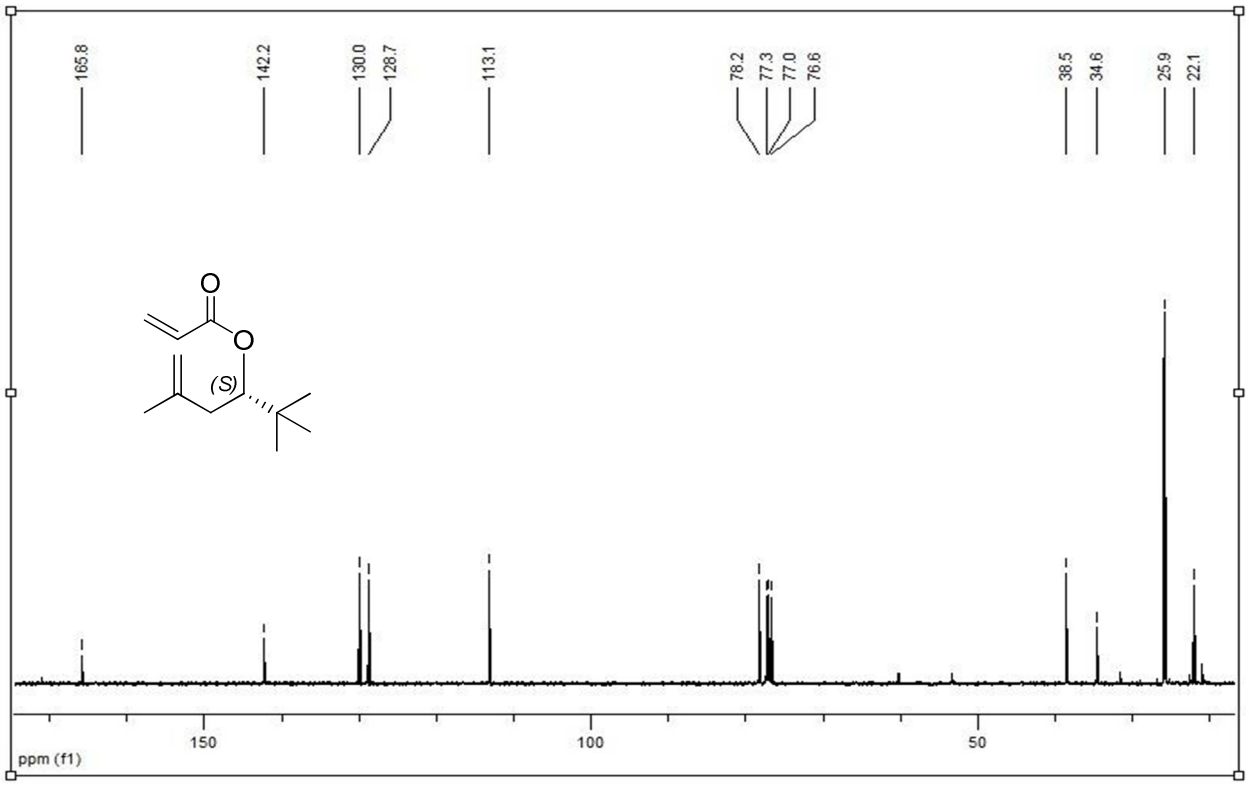
^{13}C NMR (100 MHz, $CDCl_3$)



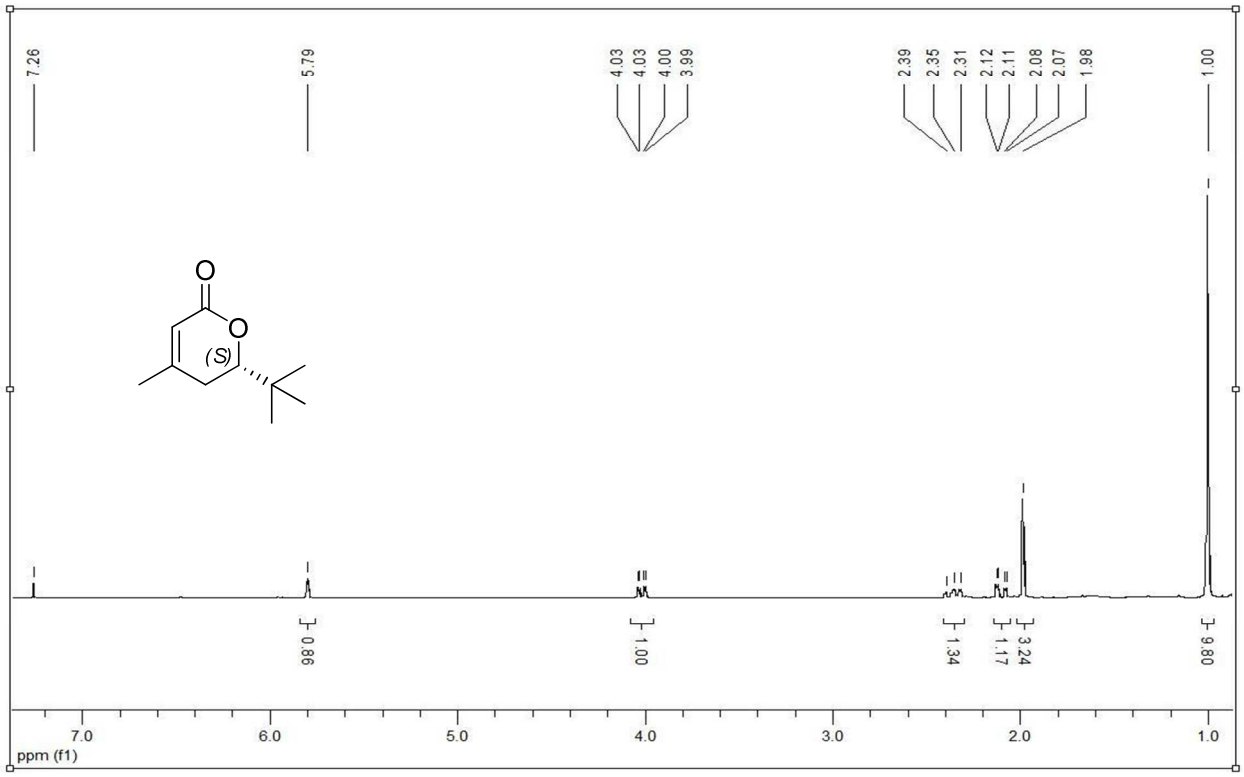
Compound **9** **^{1}H NMR** (400 MHz, $CDCl_3$)



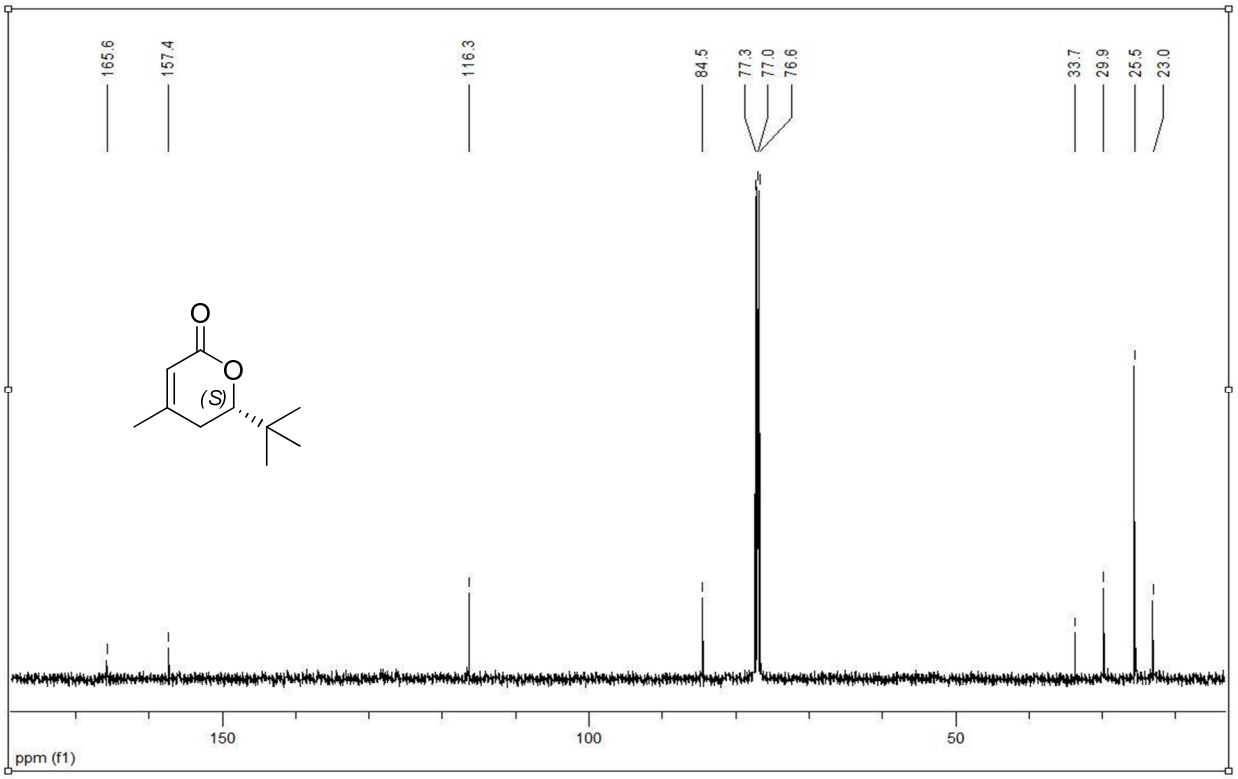
^{13}C NMR (100 MHz, $CDCl_3$)



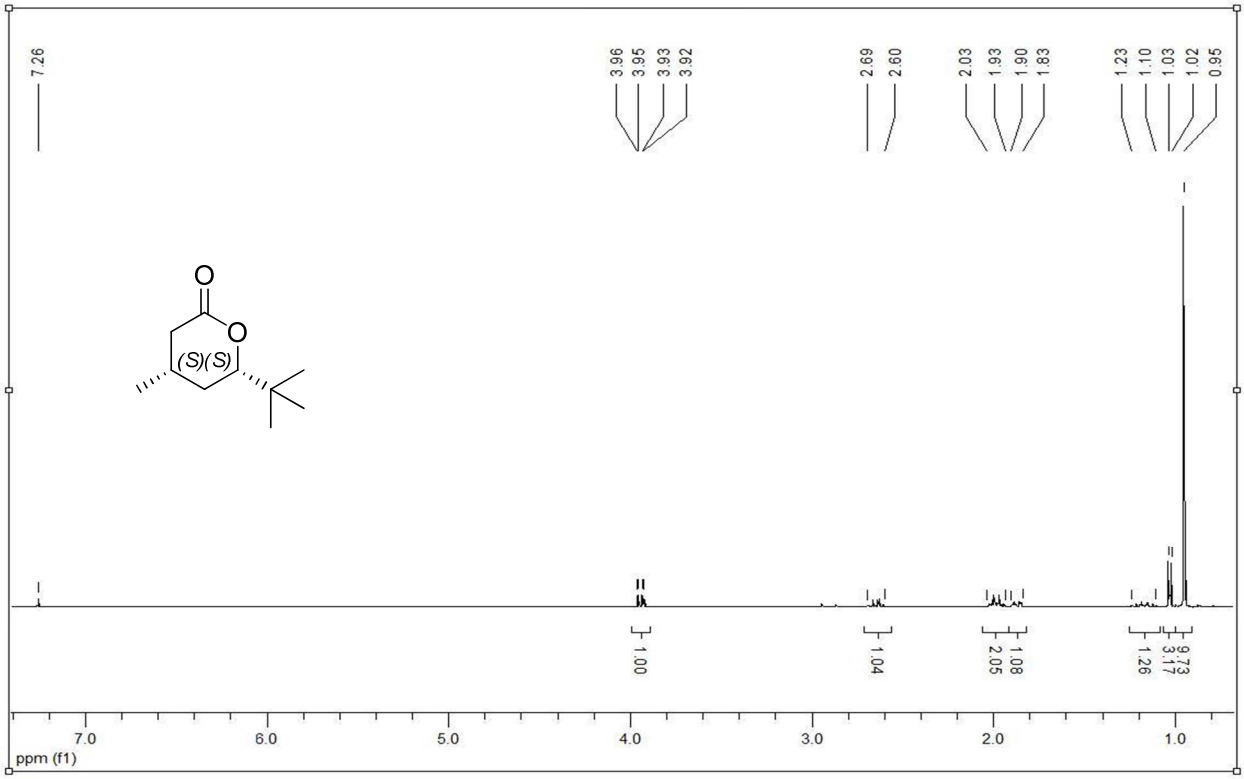
Compound 10 **^{1}H NMR** (400 MHz, $CDCl_3$)



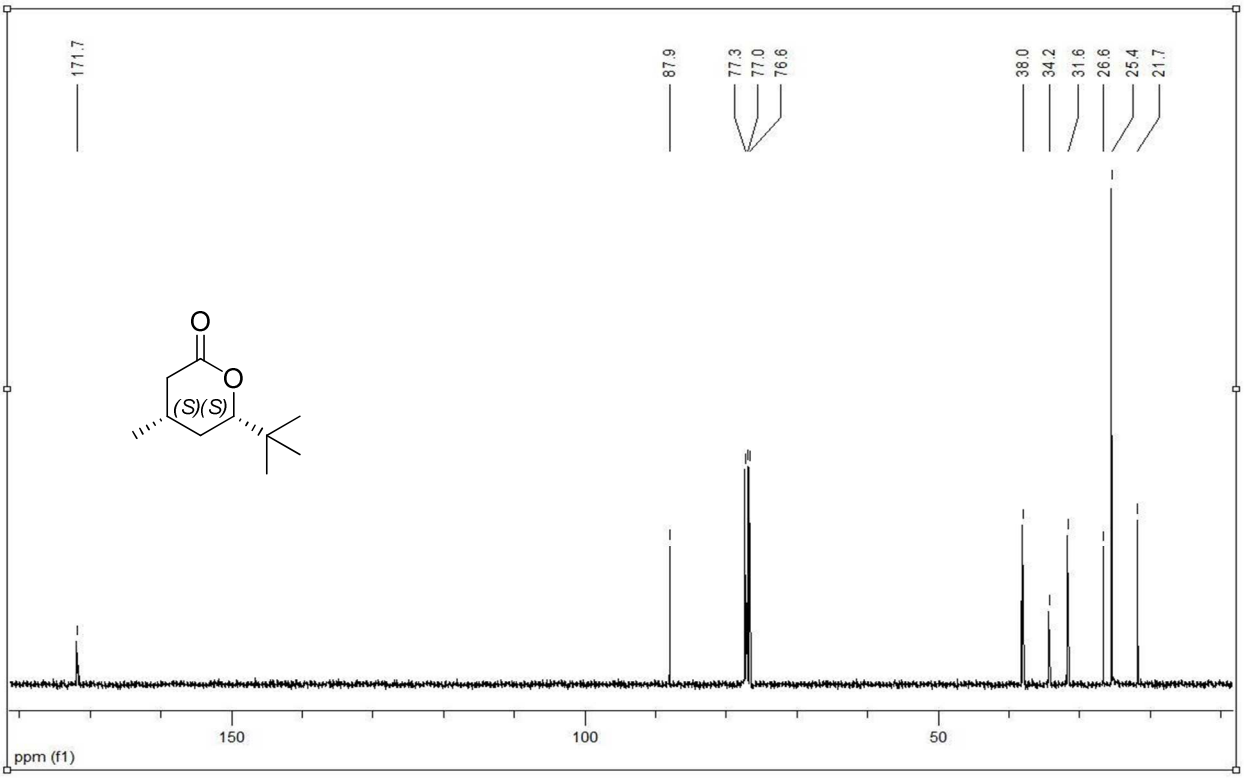
^{13}C NMR (100 MHz, $CDCl_3$)



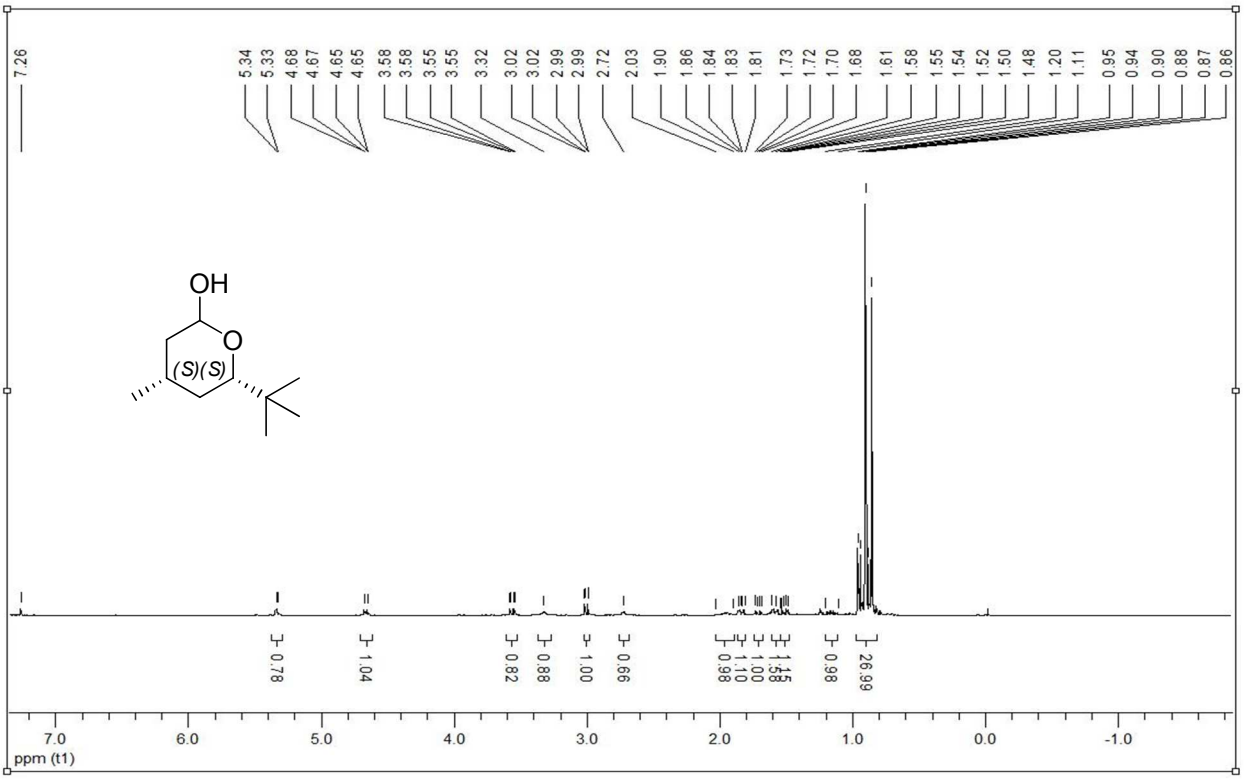
Compound **11** **^{1}H NMR** (400 MHz, $CDCl_3$)



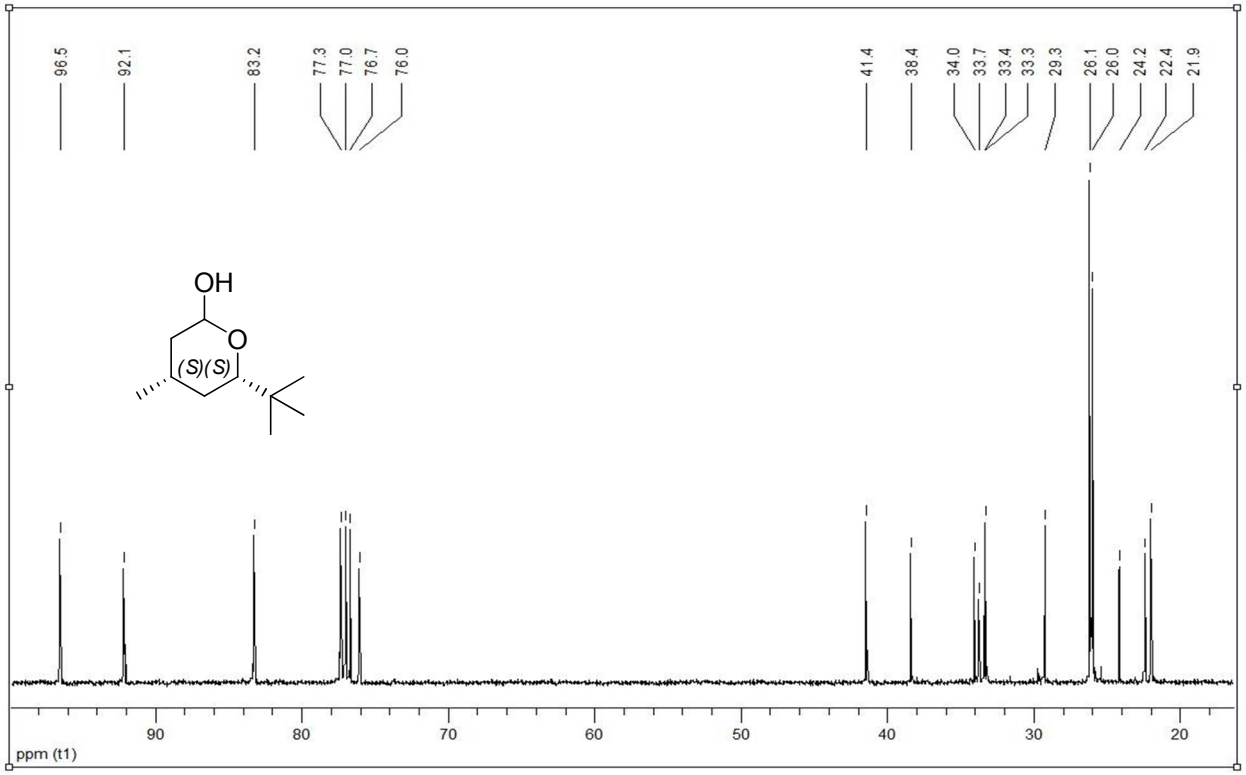
^{13}C NMR (100 MHz, $CDCl_3$)



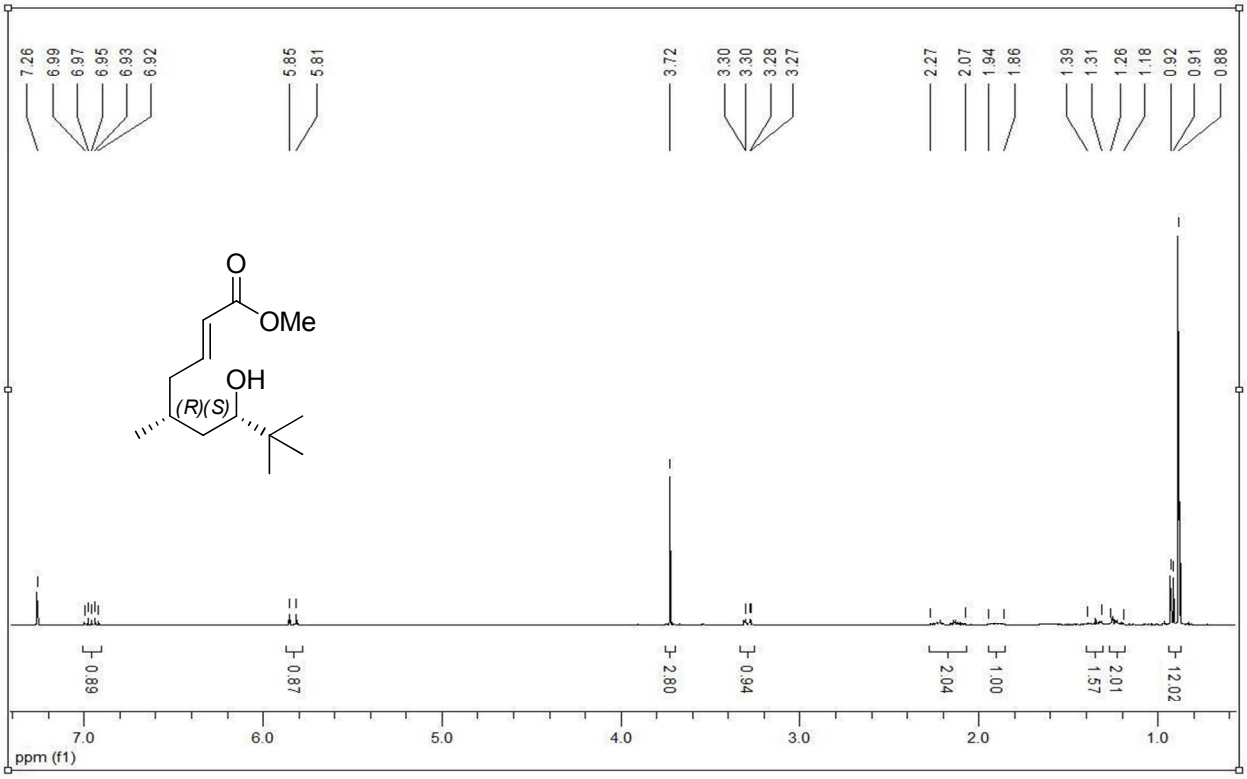
Compound **12** **^{1}H NMR** (400 MHz, $CDCl_3$)



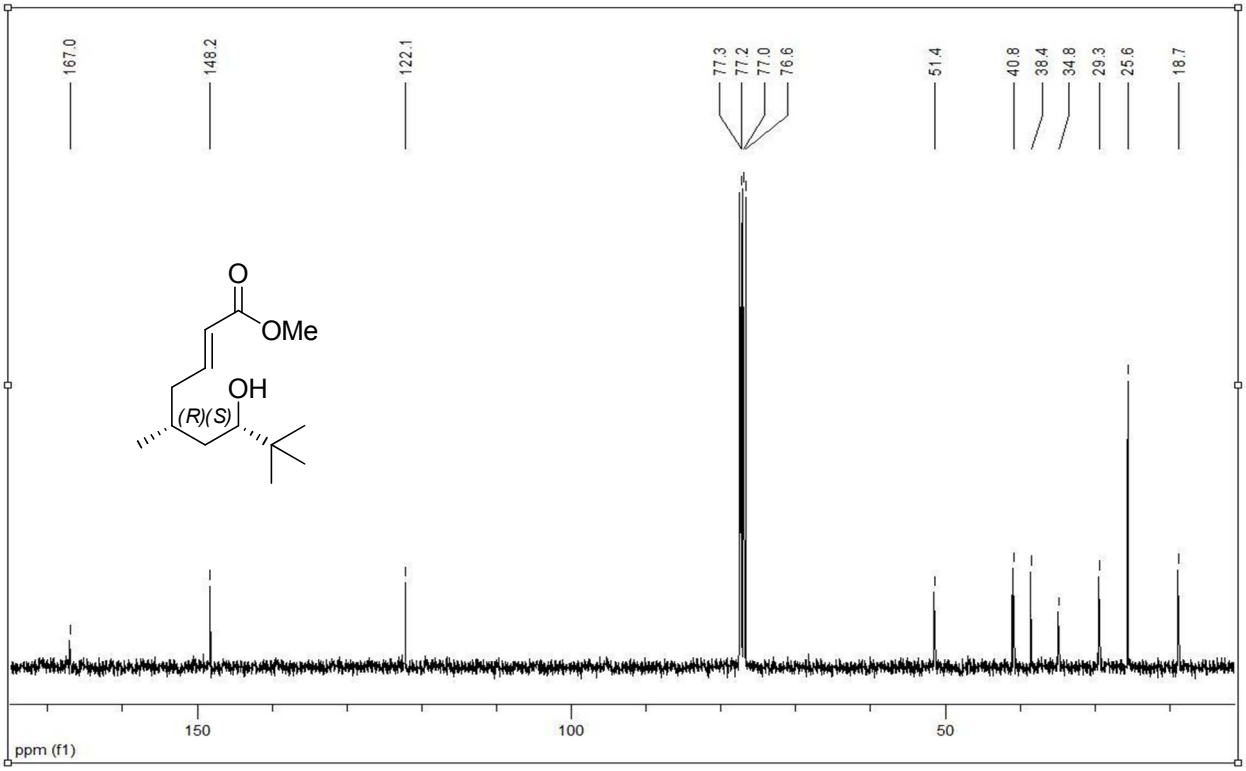
^{13}C NMR (100 MHz, $CDCl_3$)



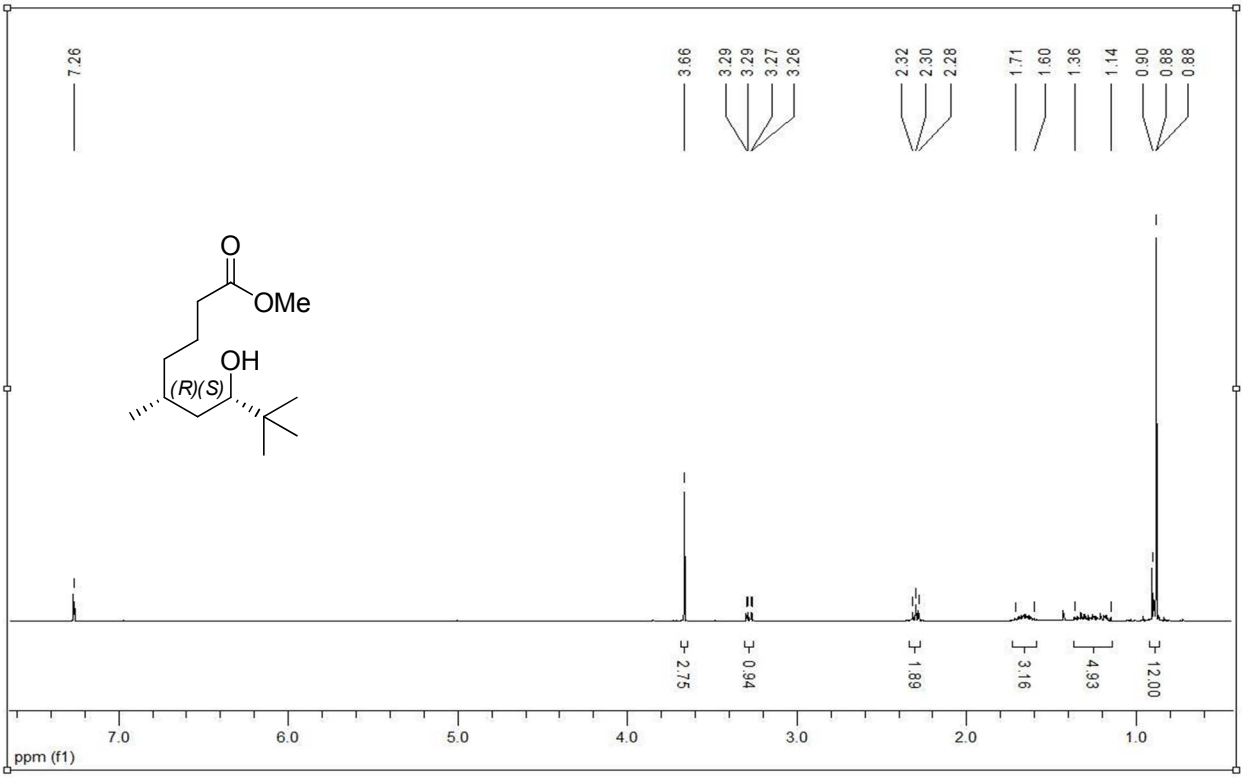
^{1}H NMR (400 MHz, $CDCl_3$)



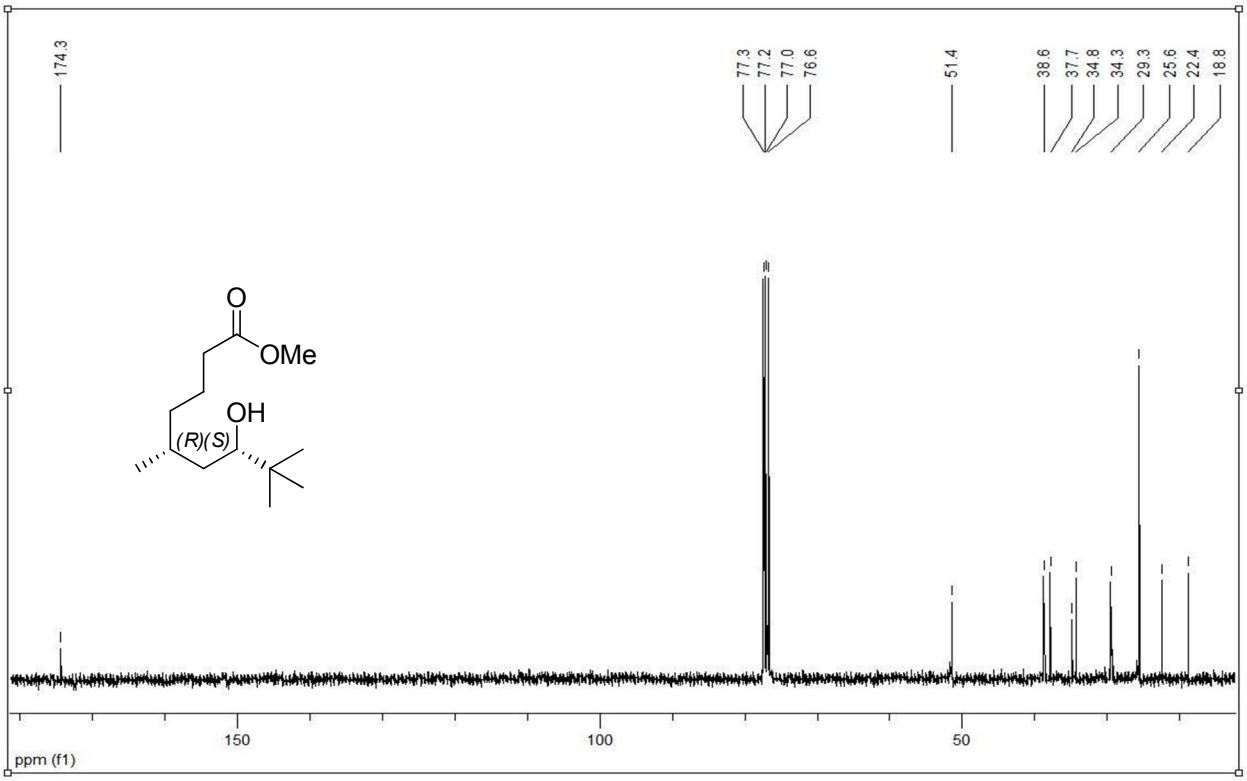
^{13}C NMR (100 MHz, $CDCl_3$)



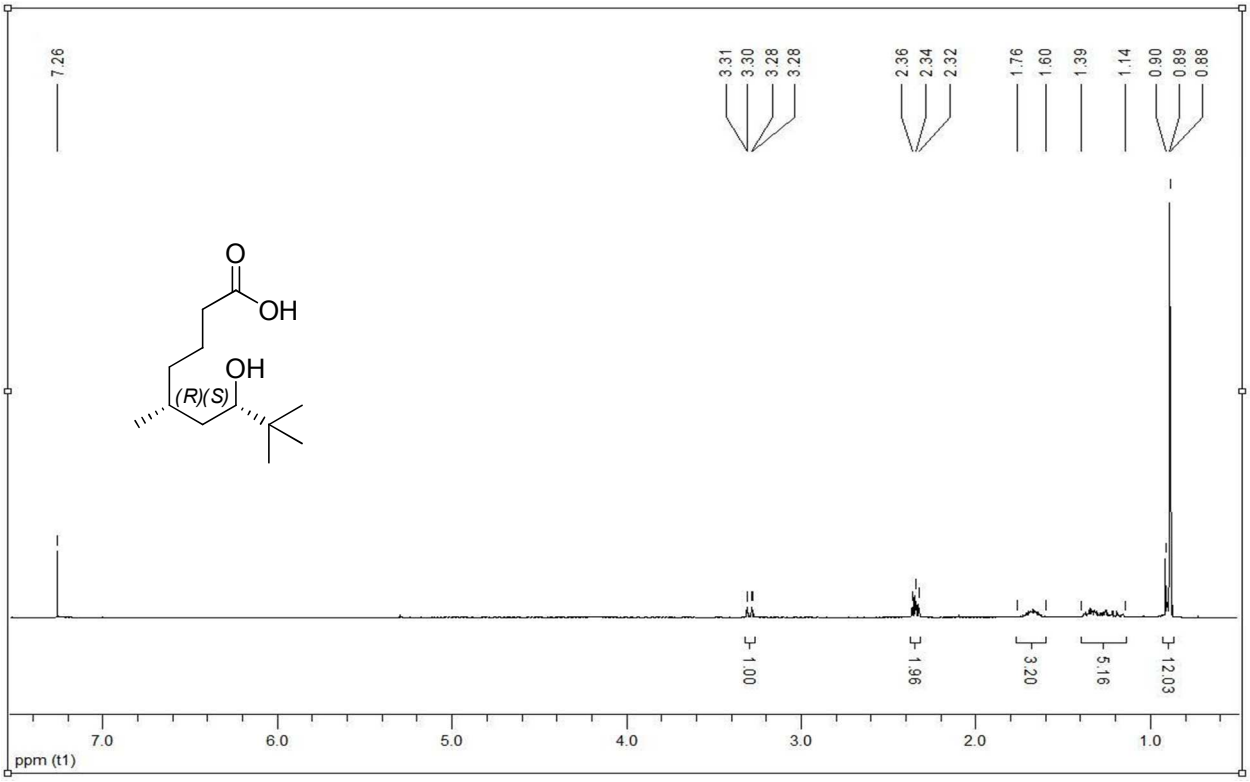
^{1}H NMR (400 MHz, $CDCl_3$)



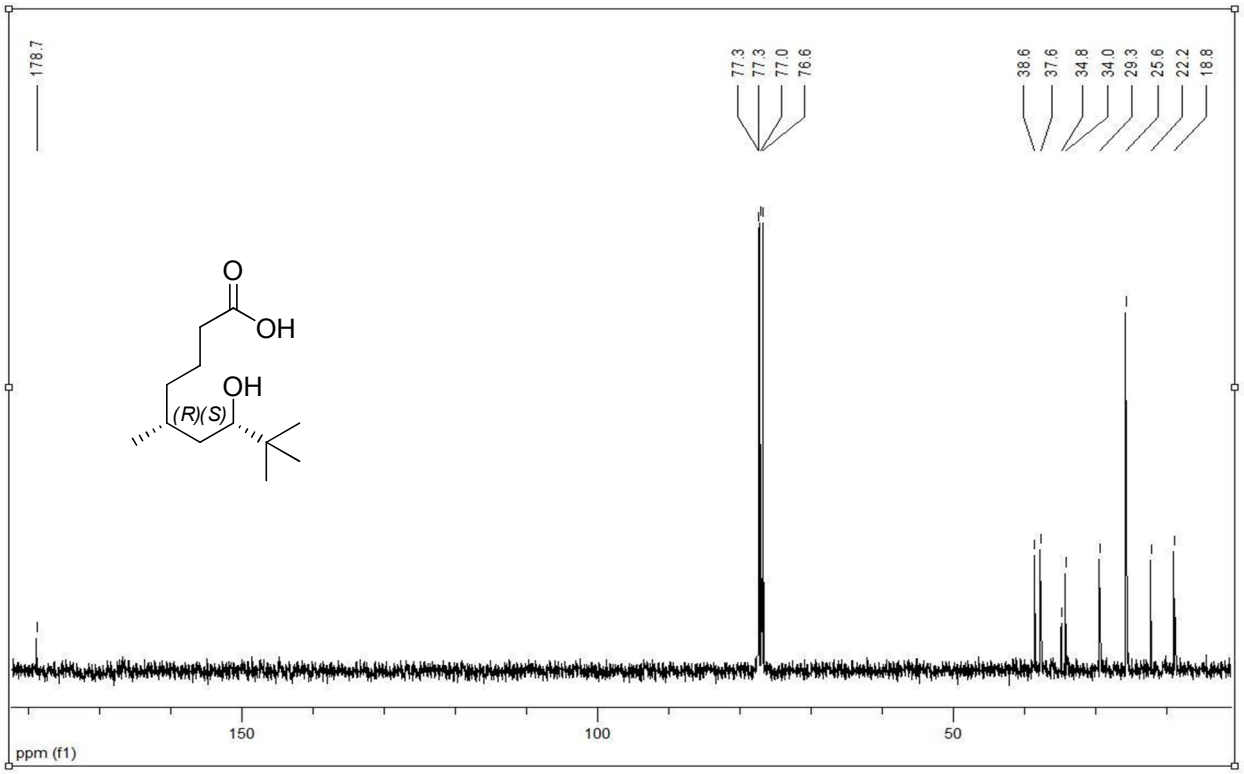
^{13}C NMR (100 MHz, $CDCl_3$)



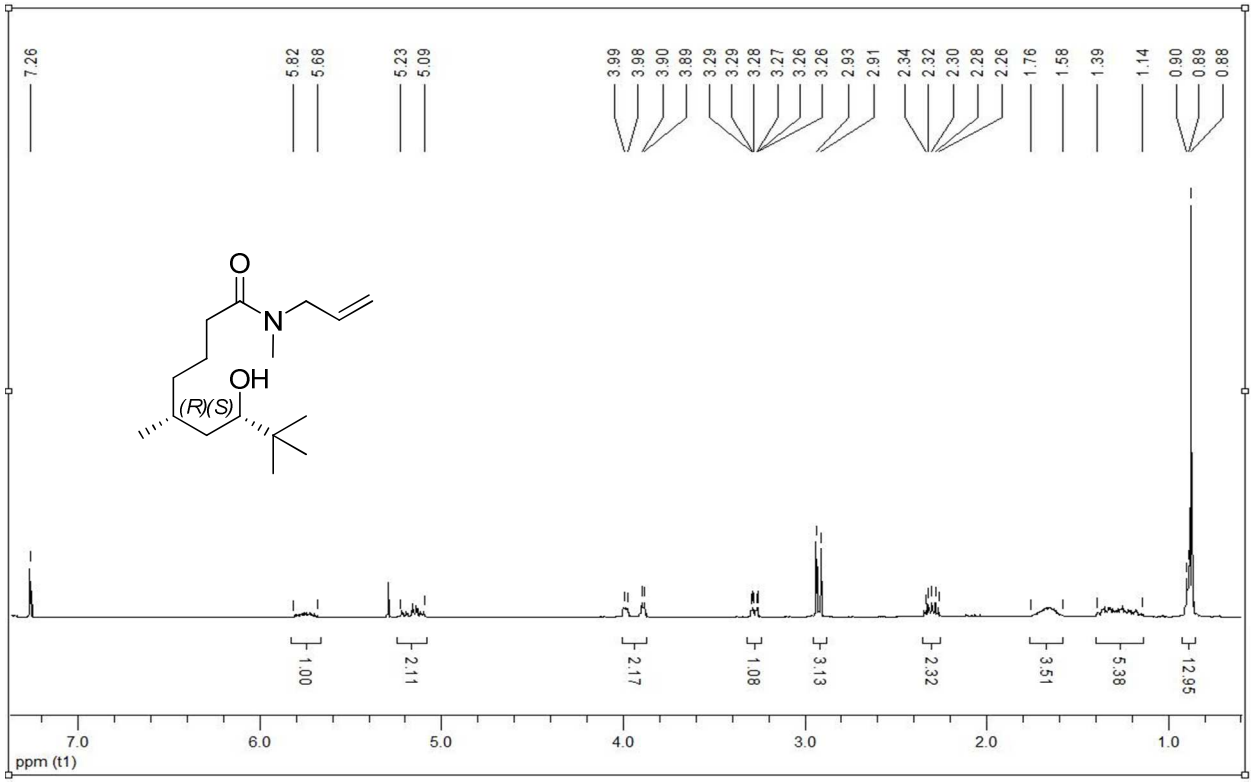
^{1}H NMR (400 MHz, $CDCl_3$)



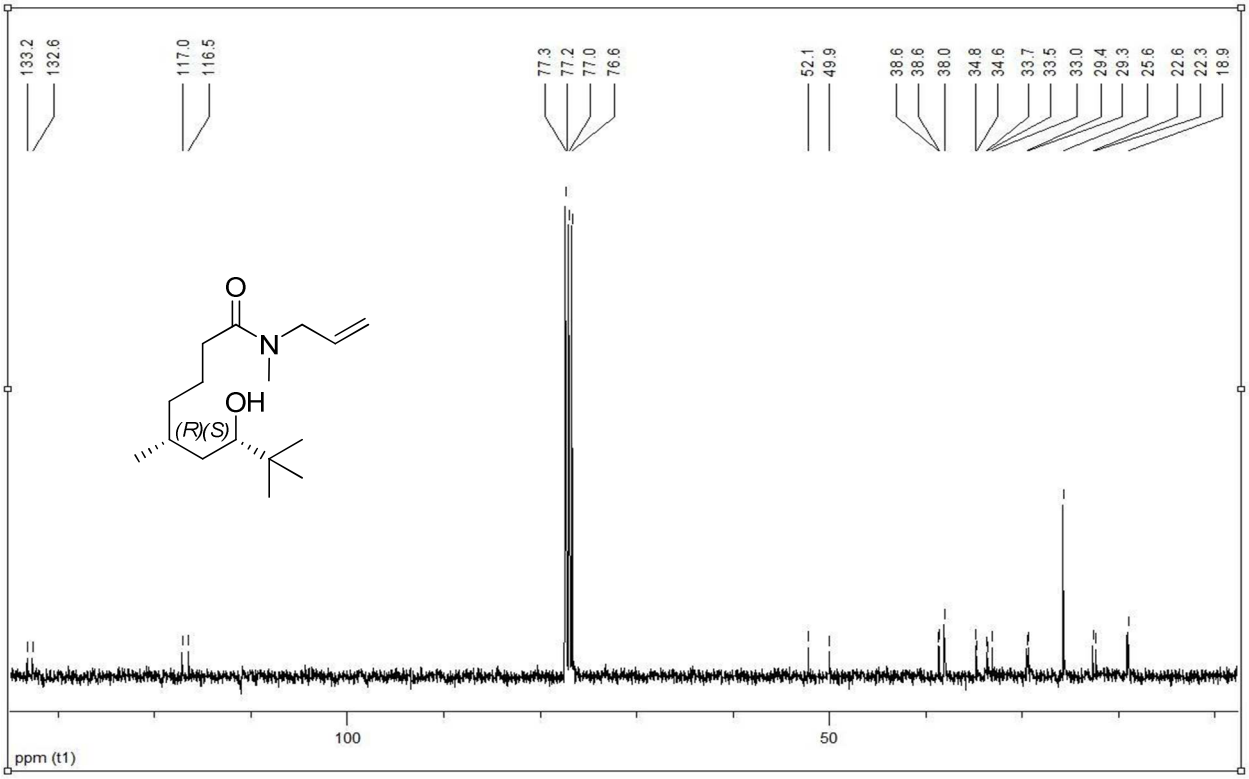
^{13}C NMR (100 MHz, $CDCl_3$)



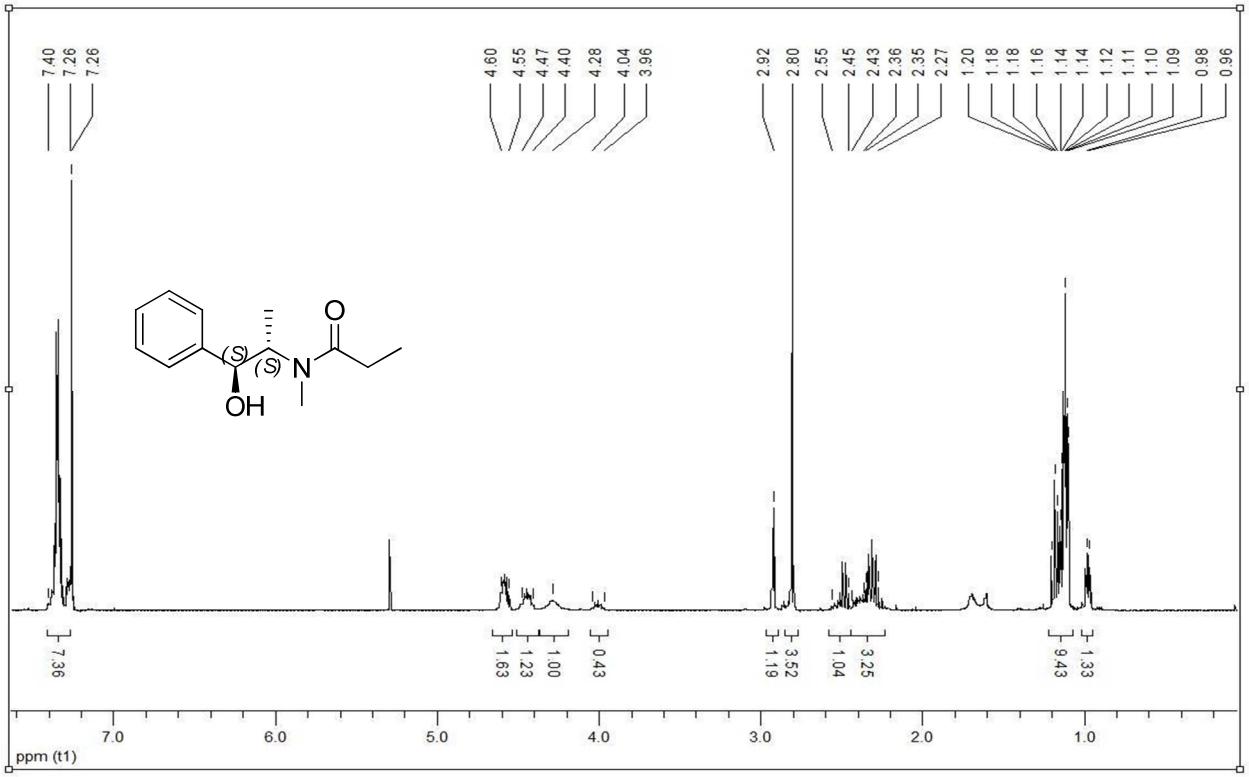
Compound **6** **^{1}H NMR** (400 MHz, $CDCl_3$)



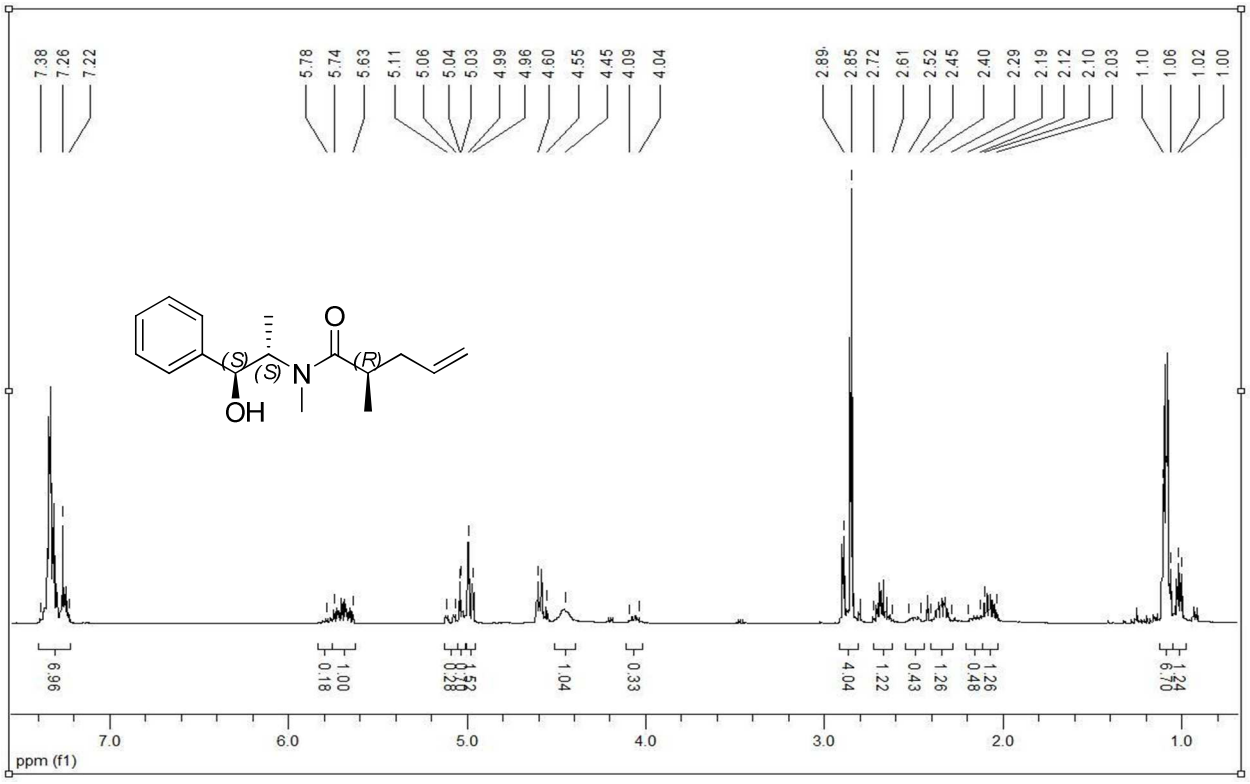
^{13}C NMR (100 MHz, $CDCl_3$)



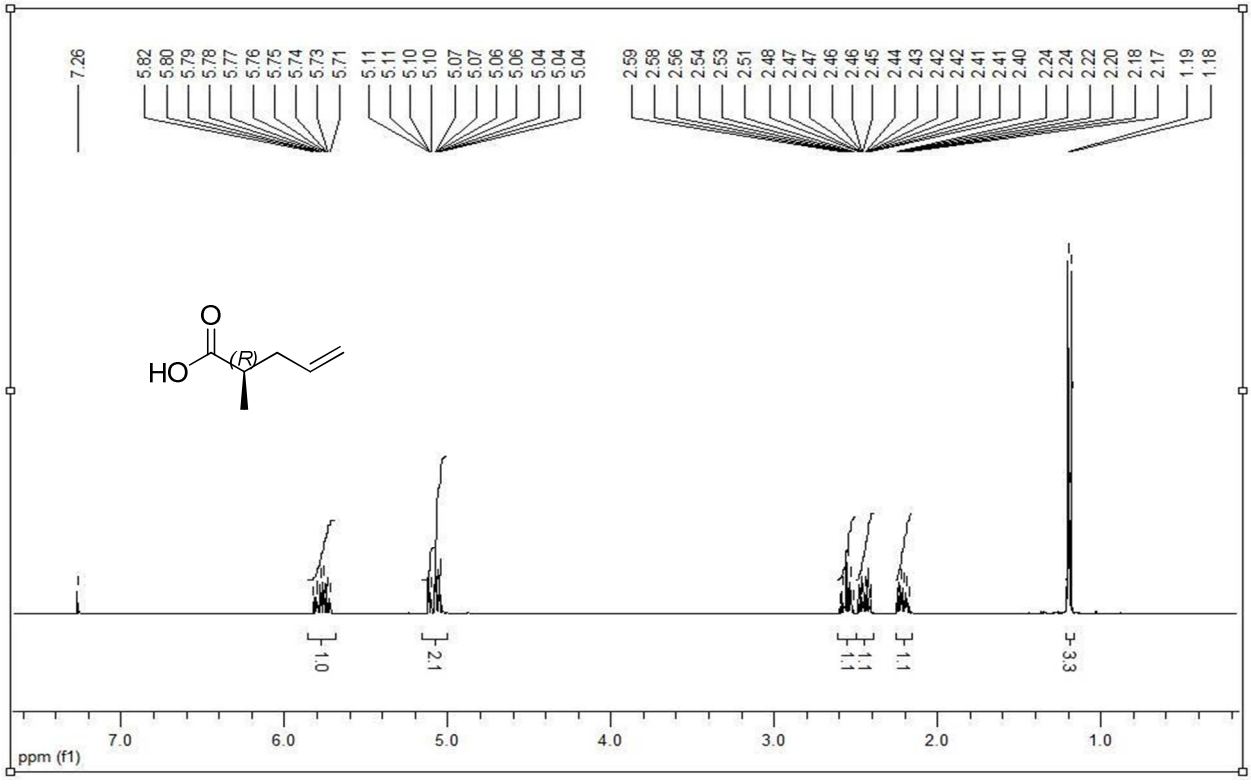
^{1}H NMR (400 MHz, $CDCl_3$)



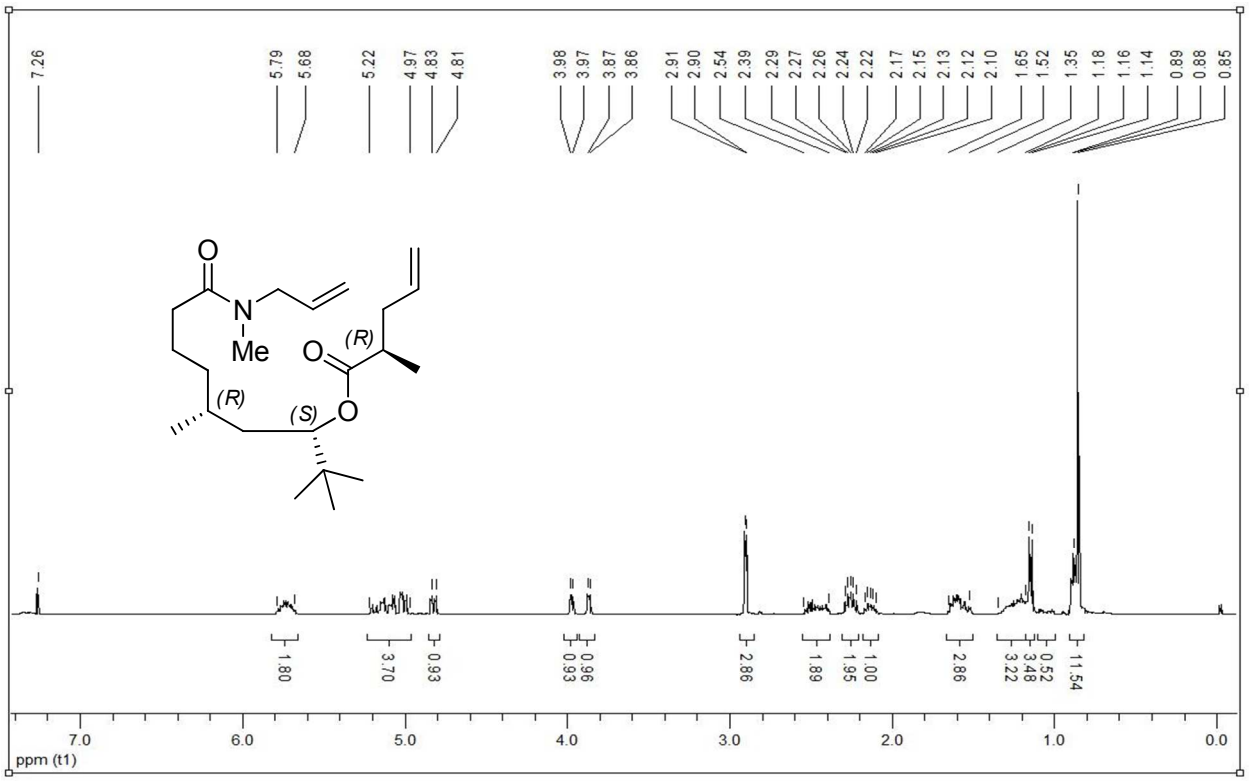
^{1}H NMR (400 MHz, $CDCl_3$)



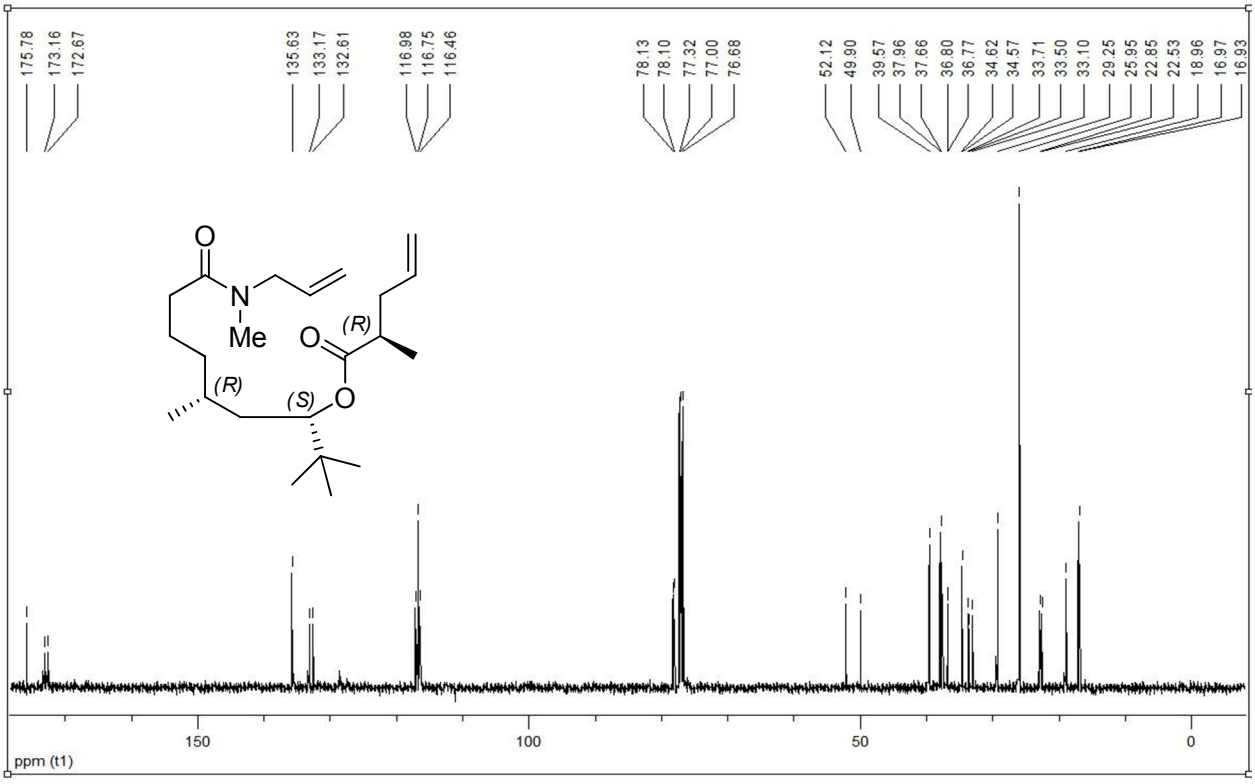
Compound (*R*)-7 **^{1}H NMR** (400 MHz, $CDCl_3$)



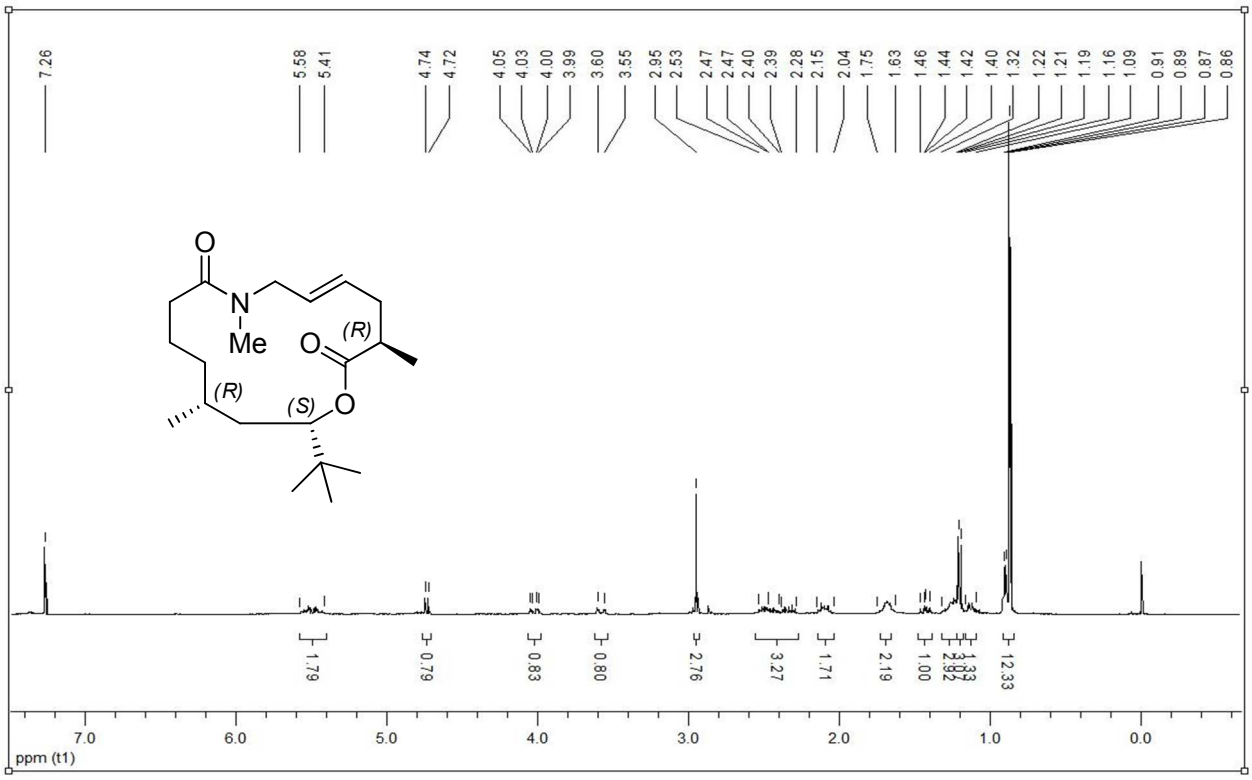
Compound **4** **^{1}H NMR** (400 MHz, $CDCl_3$)



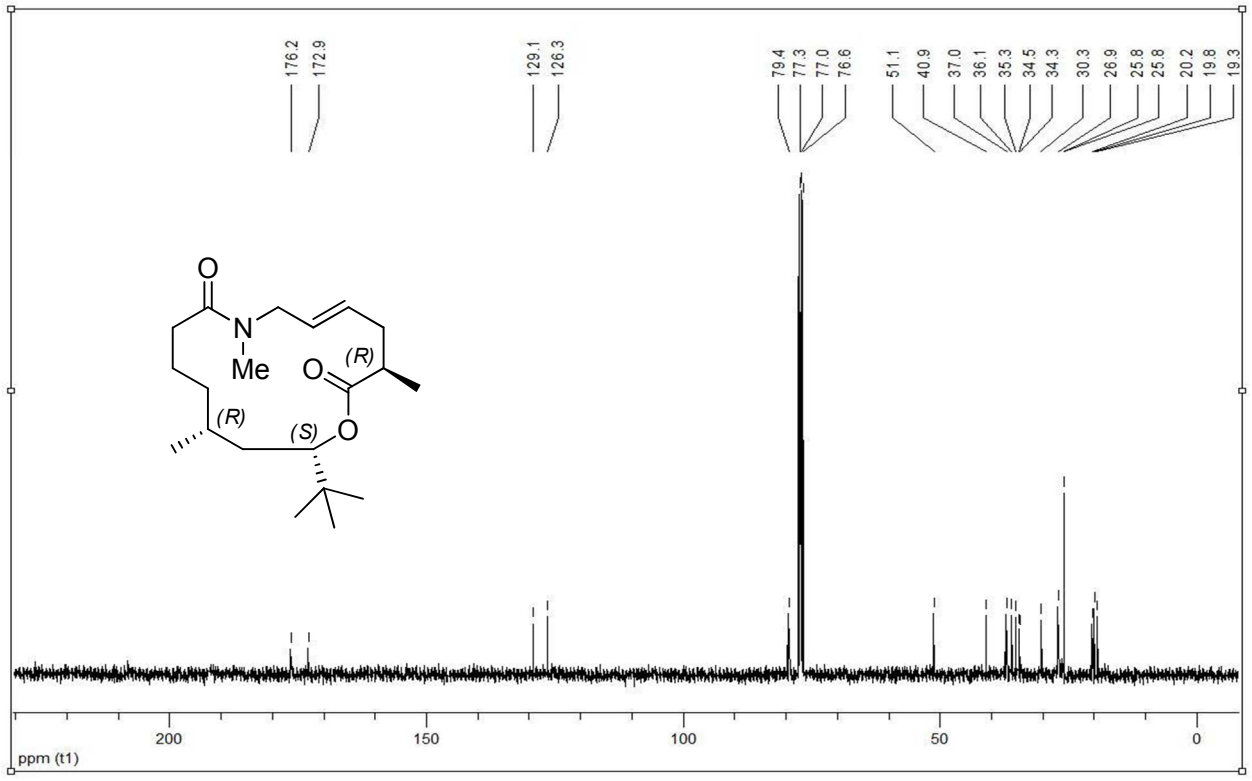
^{13}C NMR (100 MHz, $CDCl_3$)



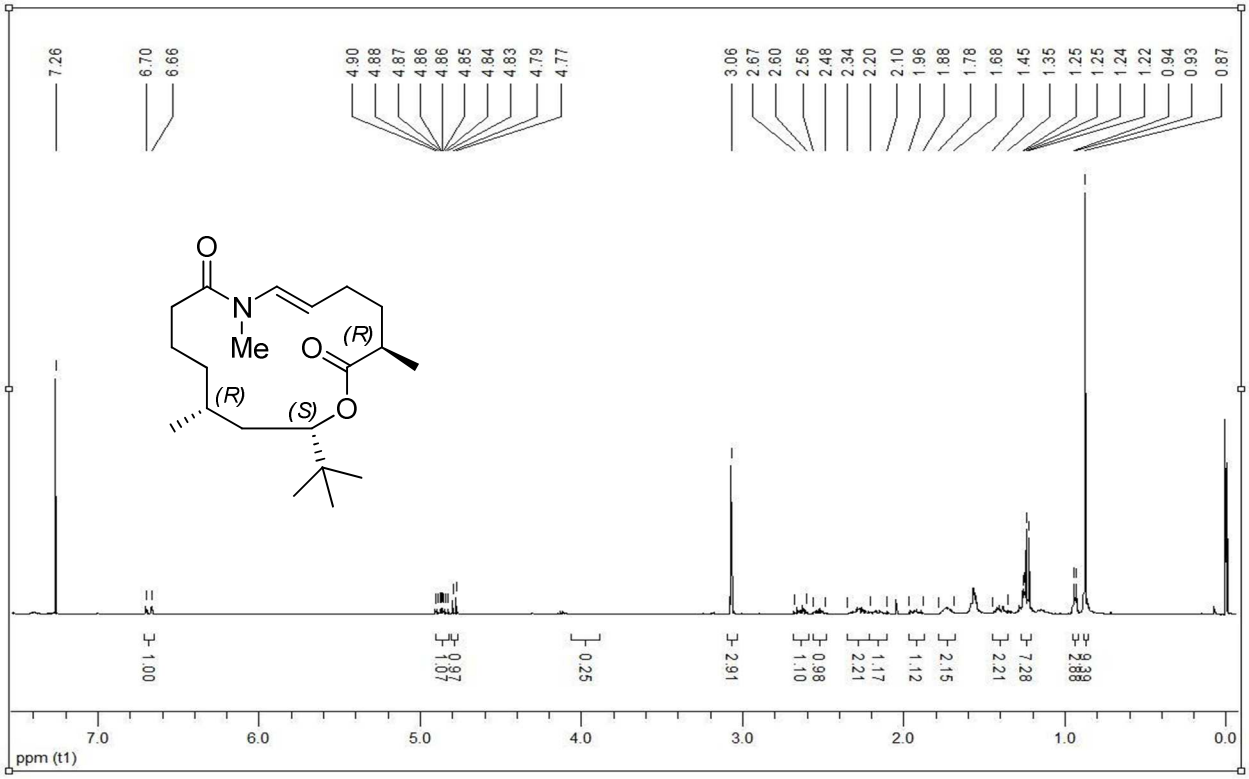
^{1}H NMR (400 MHz, $CDCl_3$)



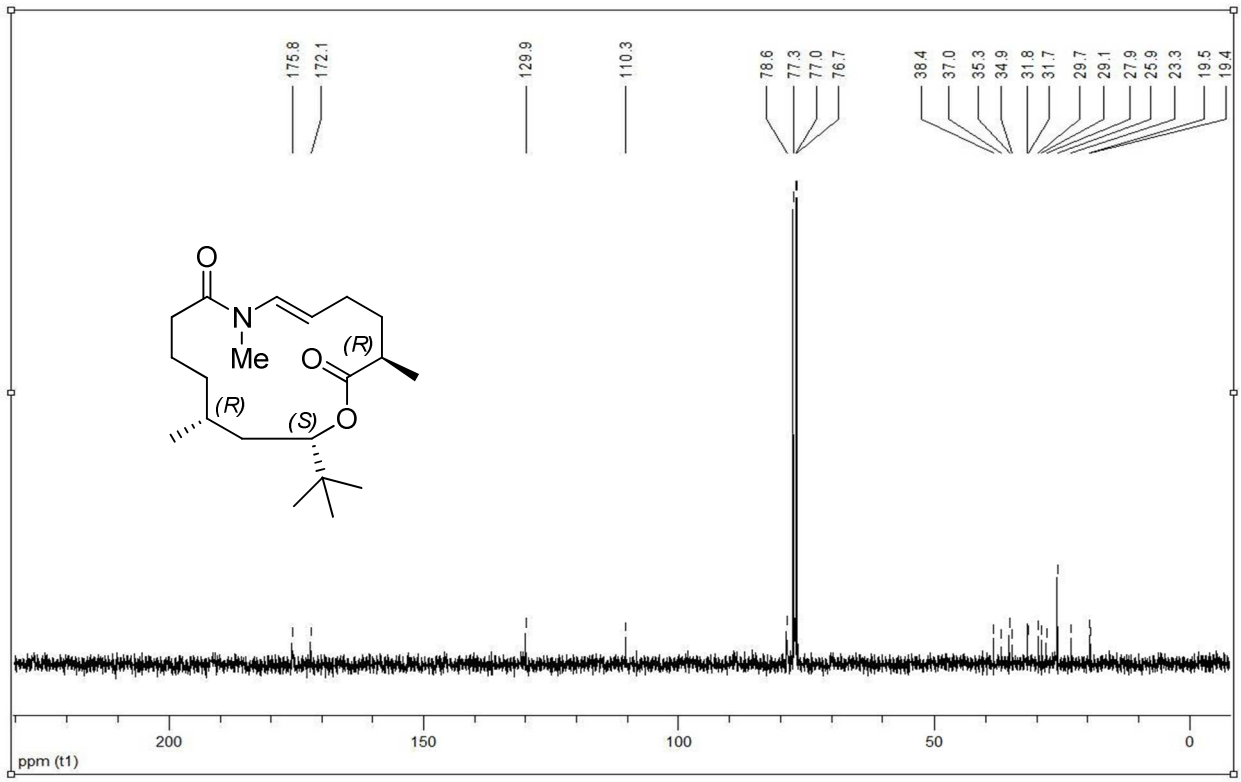
^{13}C NMR (100 MHz, $CDCl_3$)



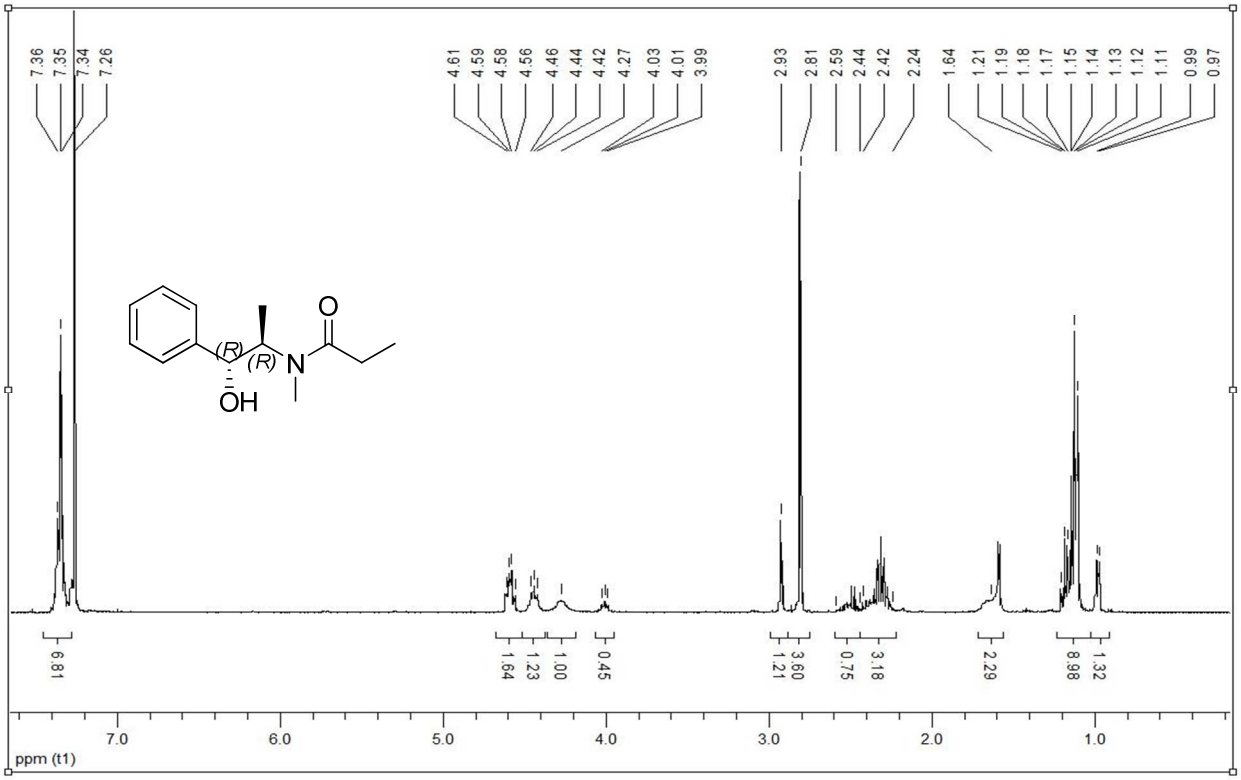
Compound **1** **^{1}H NMR** (400 MHz, $CDCl_3$)



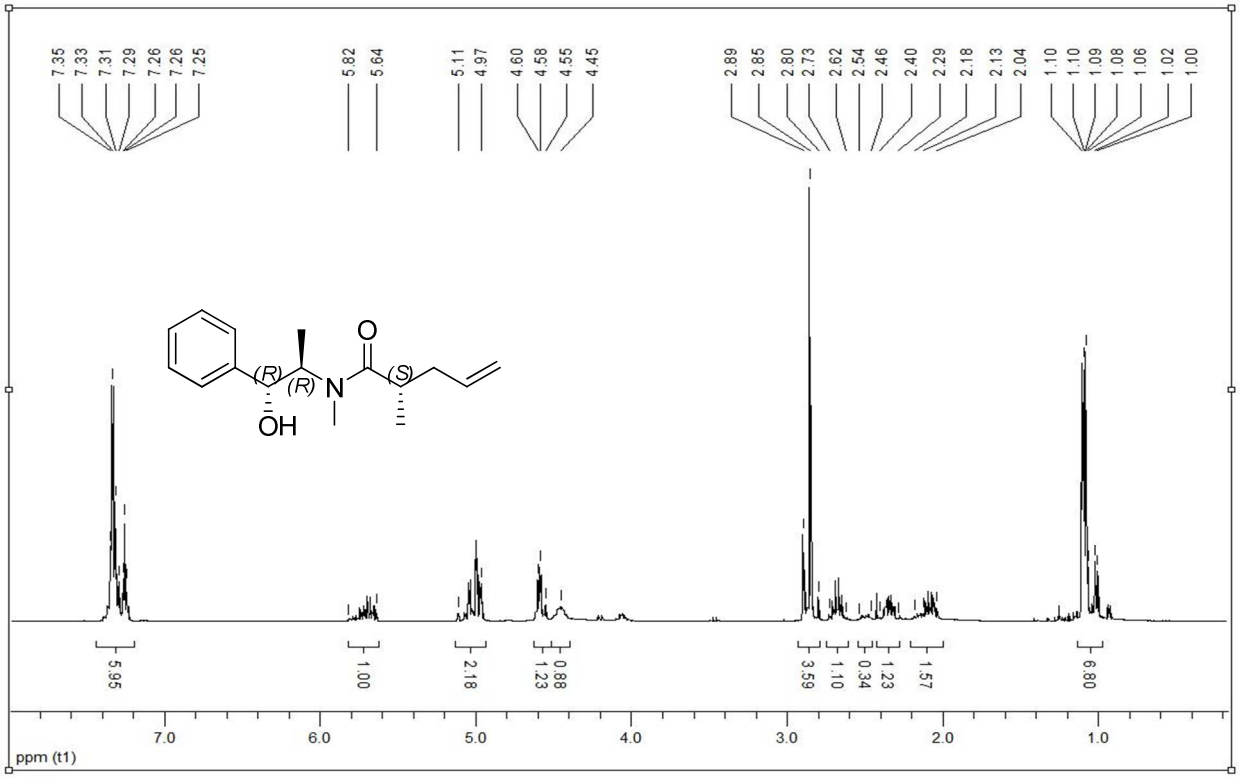
^{13}C NMR (100 MHz, $CDCl_3$)



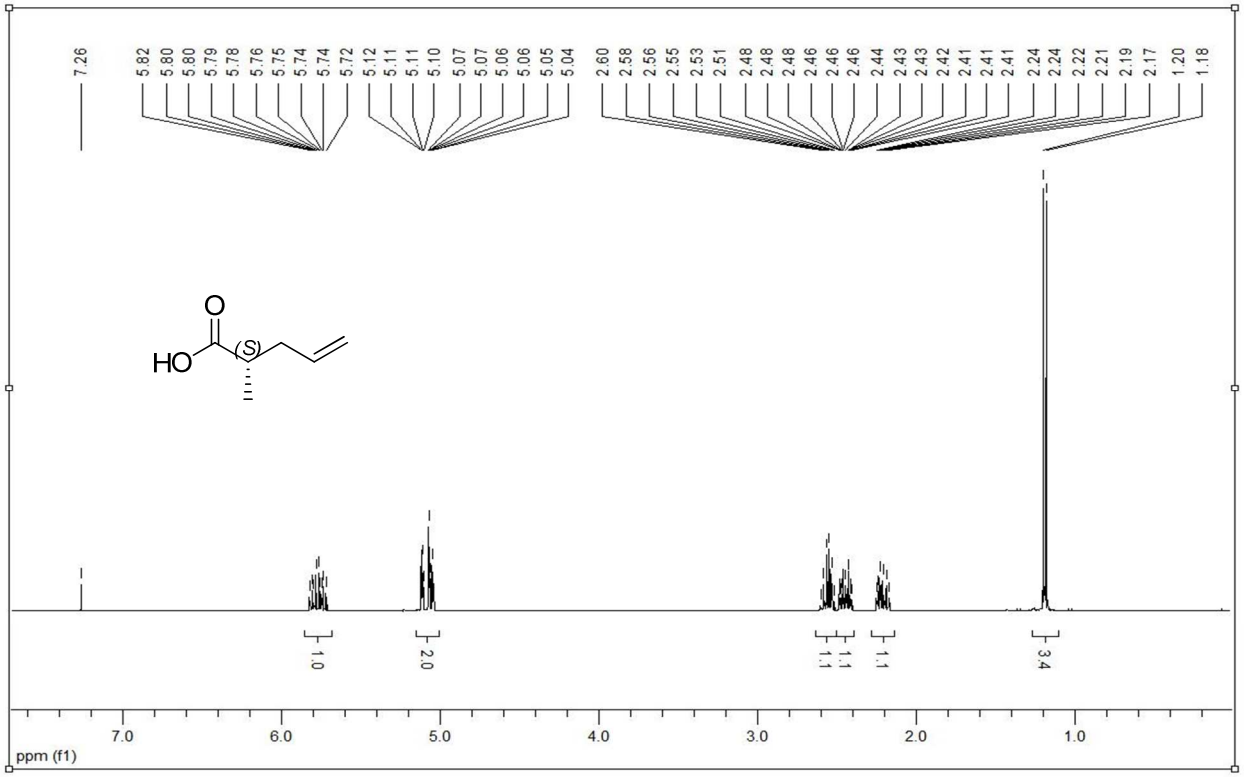
^{1}H NMR (400 MHz, $CDCl_3$)



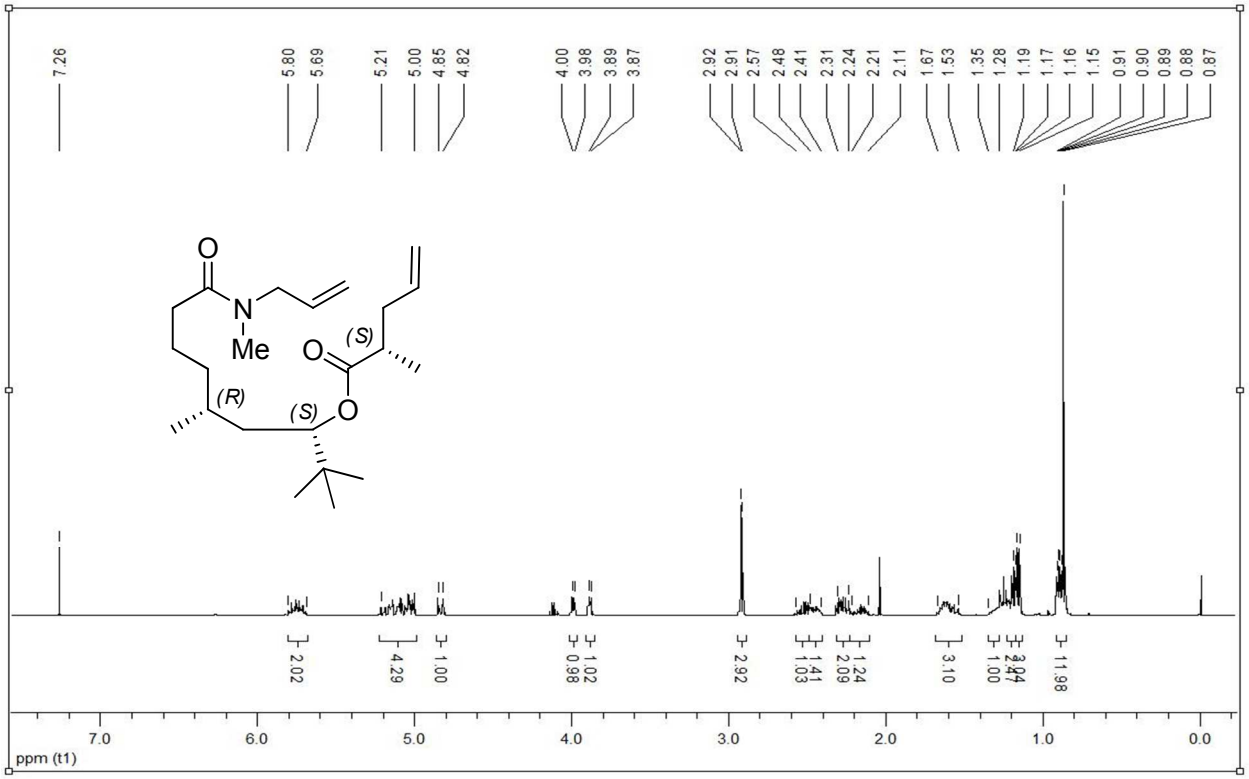
^{1}H NMR (400 MHz, $CDCl_3$)



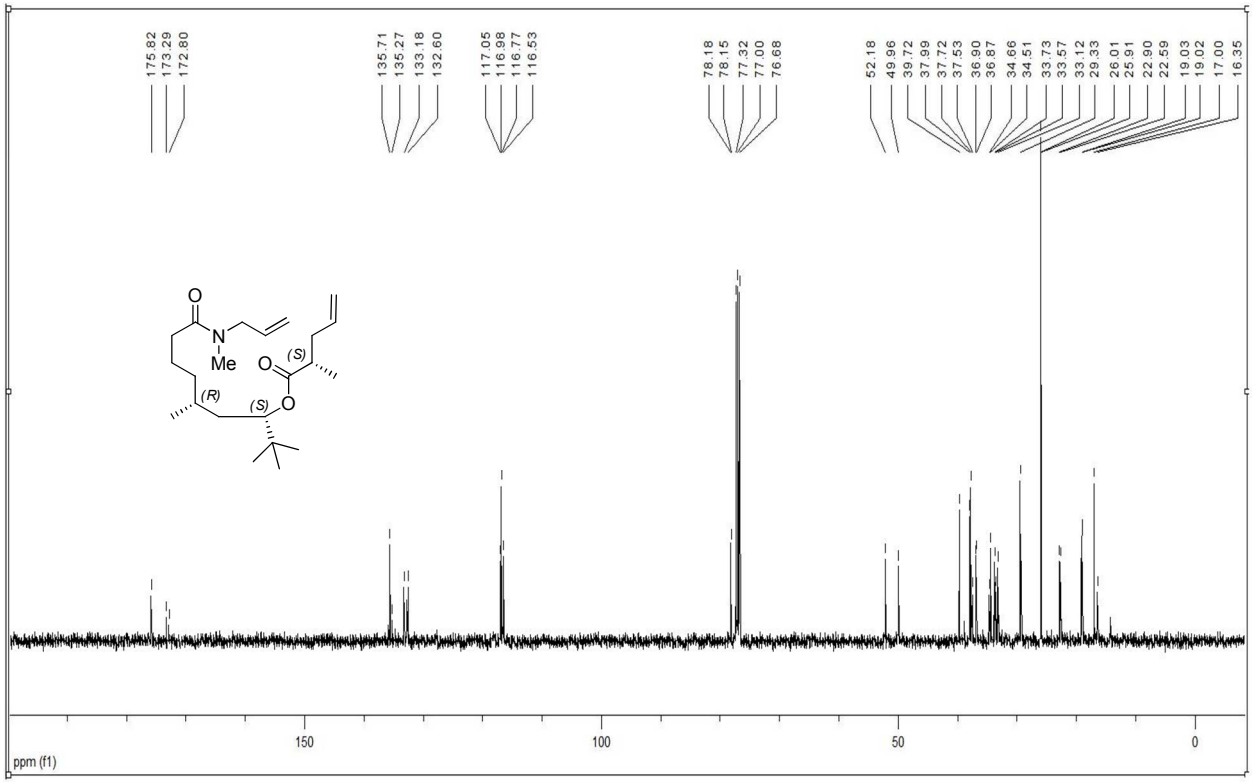
Compound (*S*)-7 **^{1}H NMR** (400 MHz, $CDCl_3$)



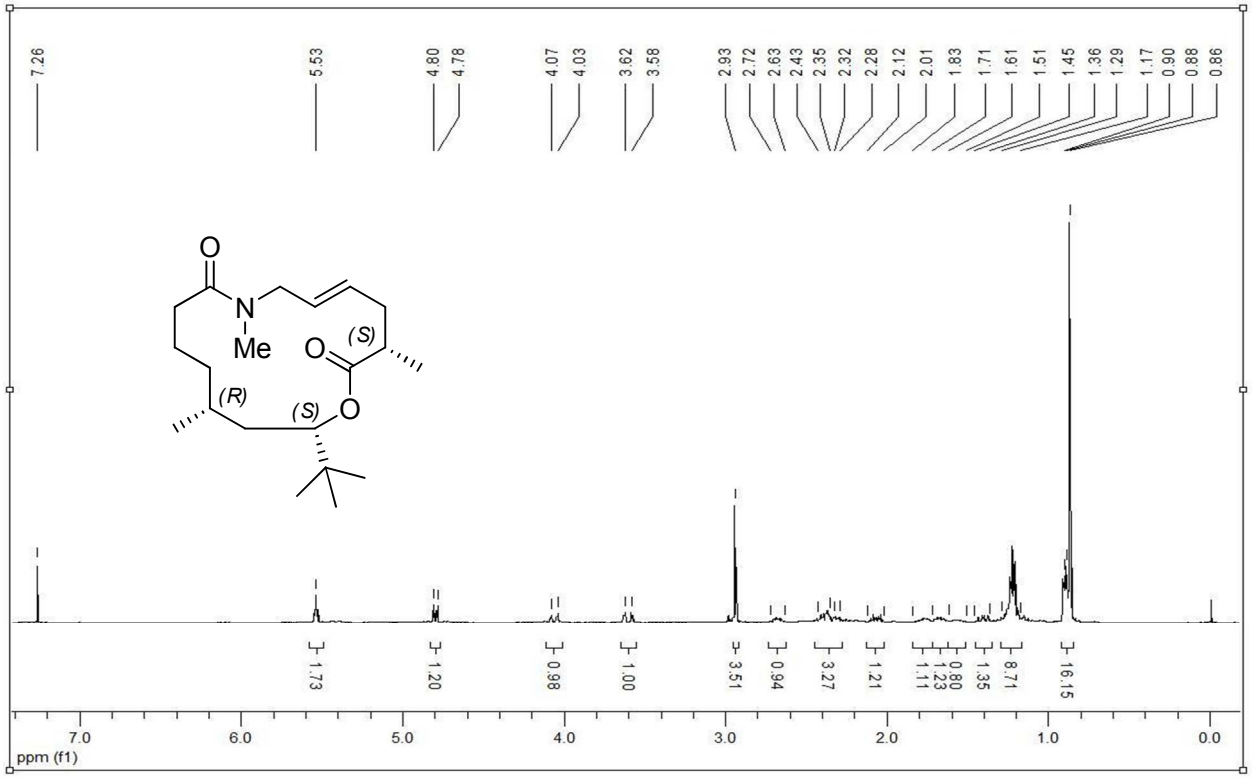
Compound **5** **^{1}H NMR** (400 MHz, $CDCl_3$)



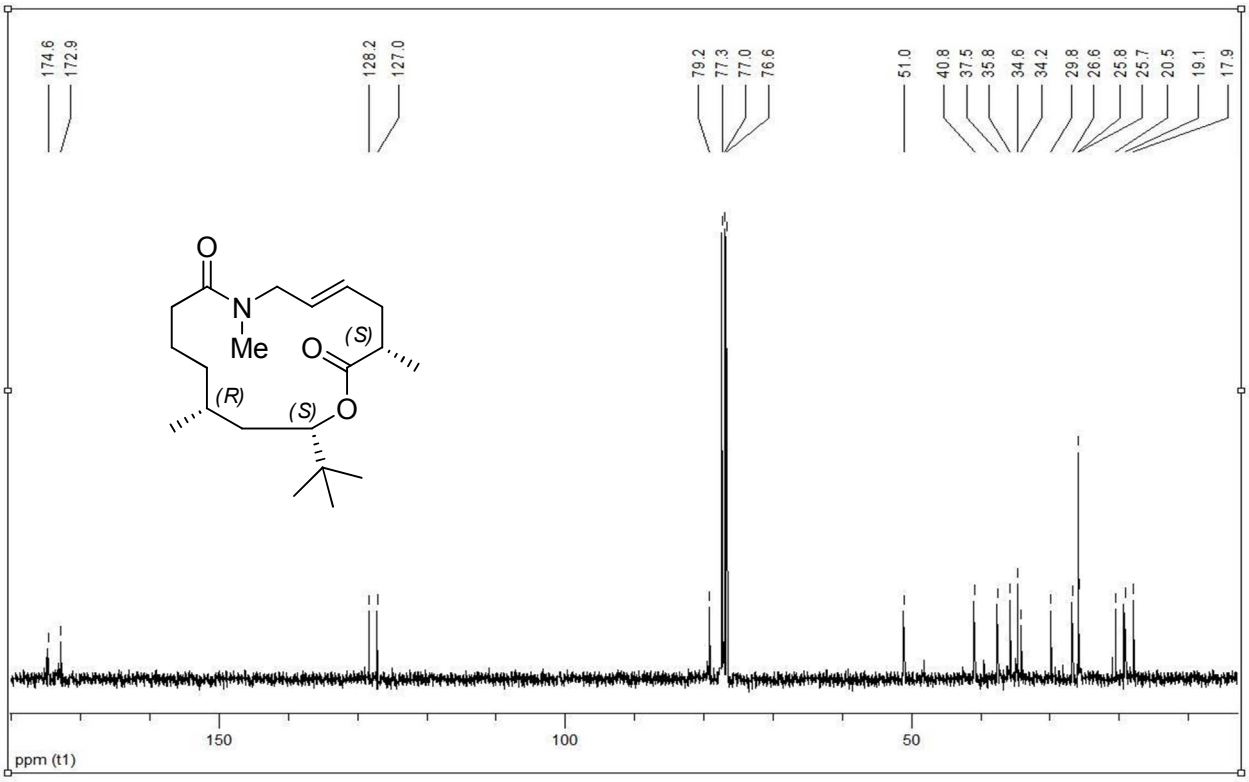
^{13}C NMR (100 MHz, $CDCl_3$)



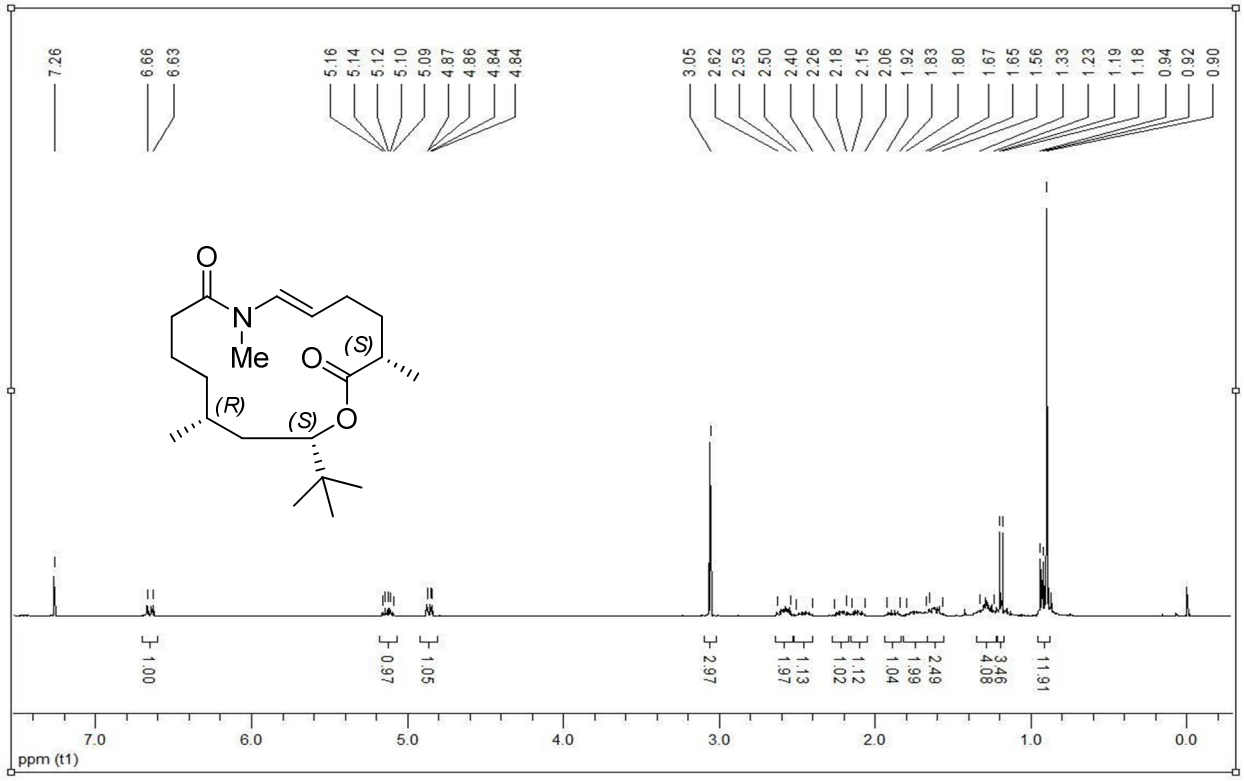
^{1}H NMR (400 MHz, $CDCl_3$)



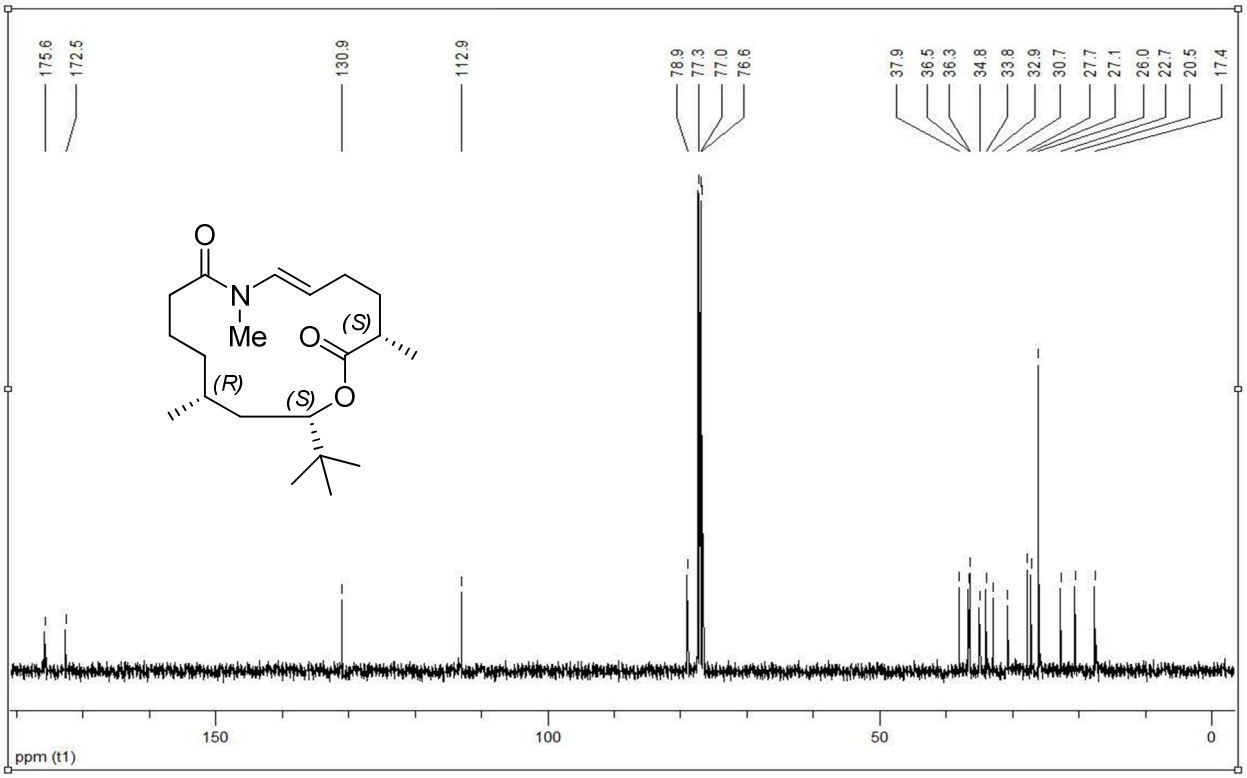
^{13}C NMR (100 MHz, $CDCl_3$)



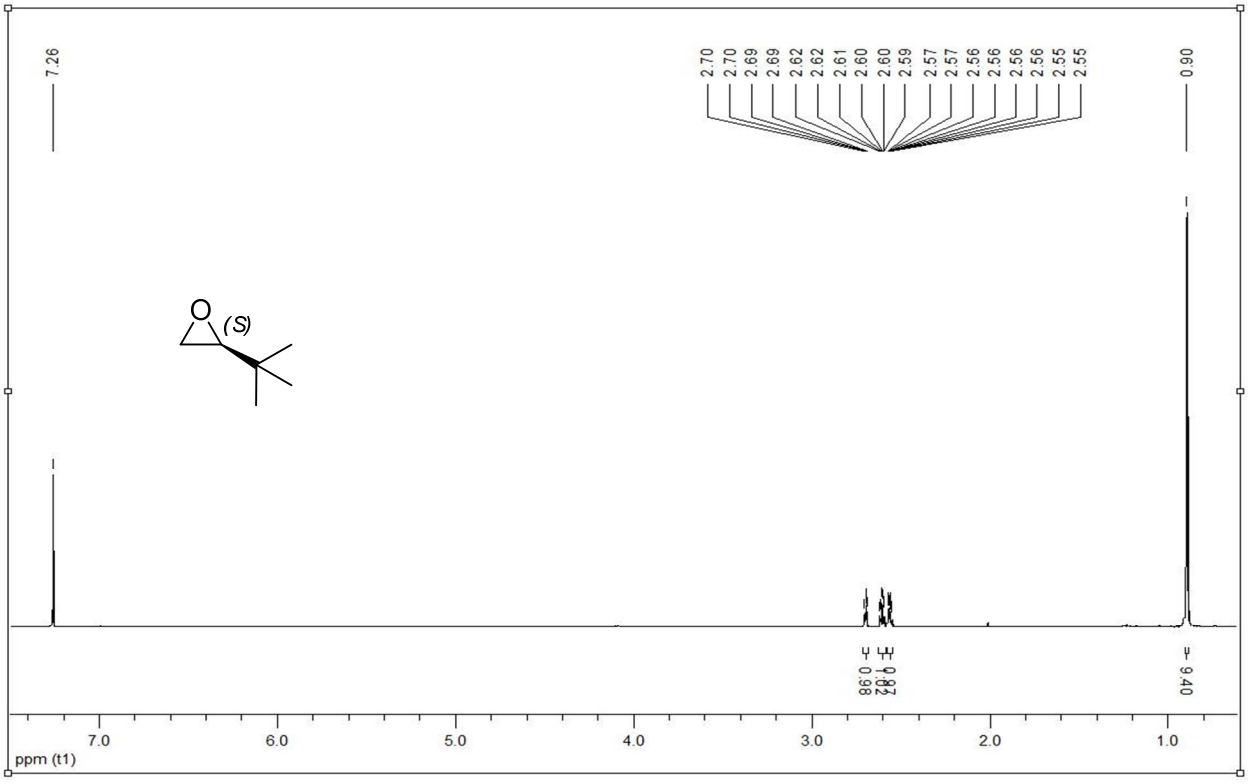
Compound *ent*-(**2**) **^{1}H NMR** (400 MHz, $CDCl_3$)



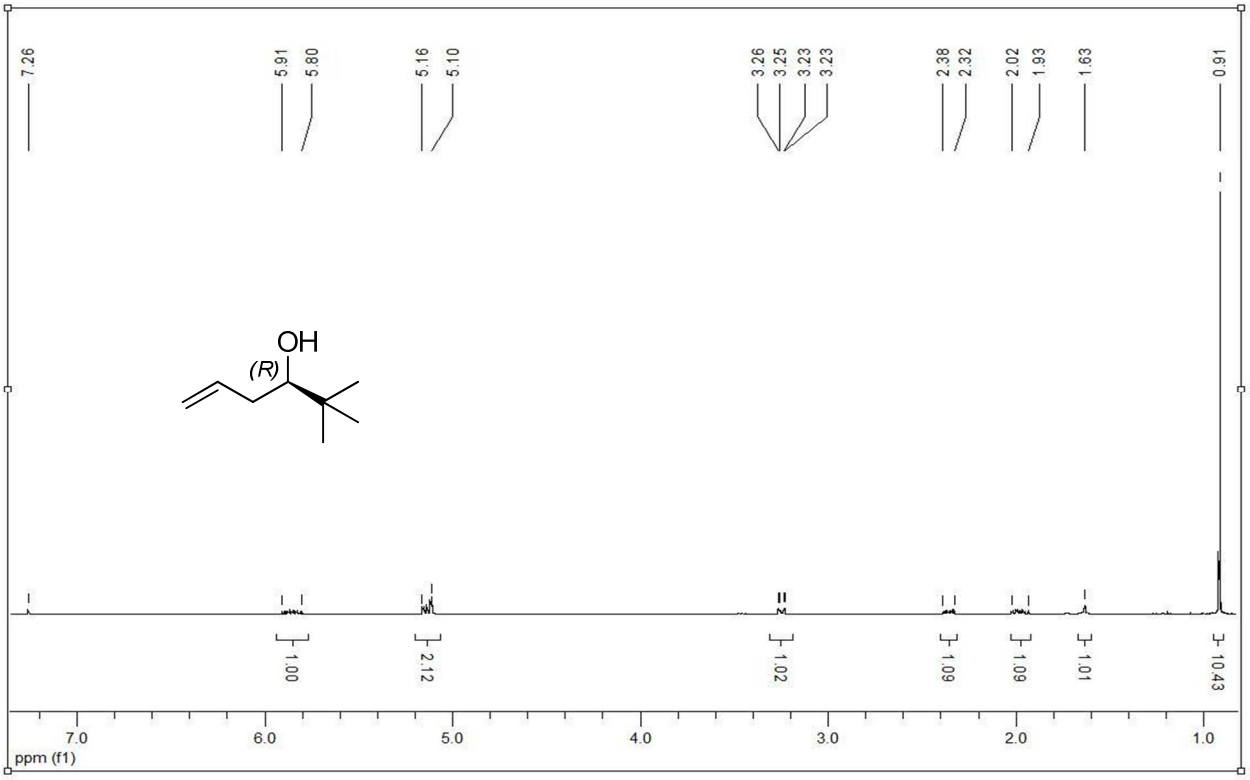
^{13}C NMR (100 MHz, $CDCl_3$)



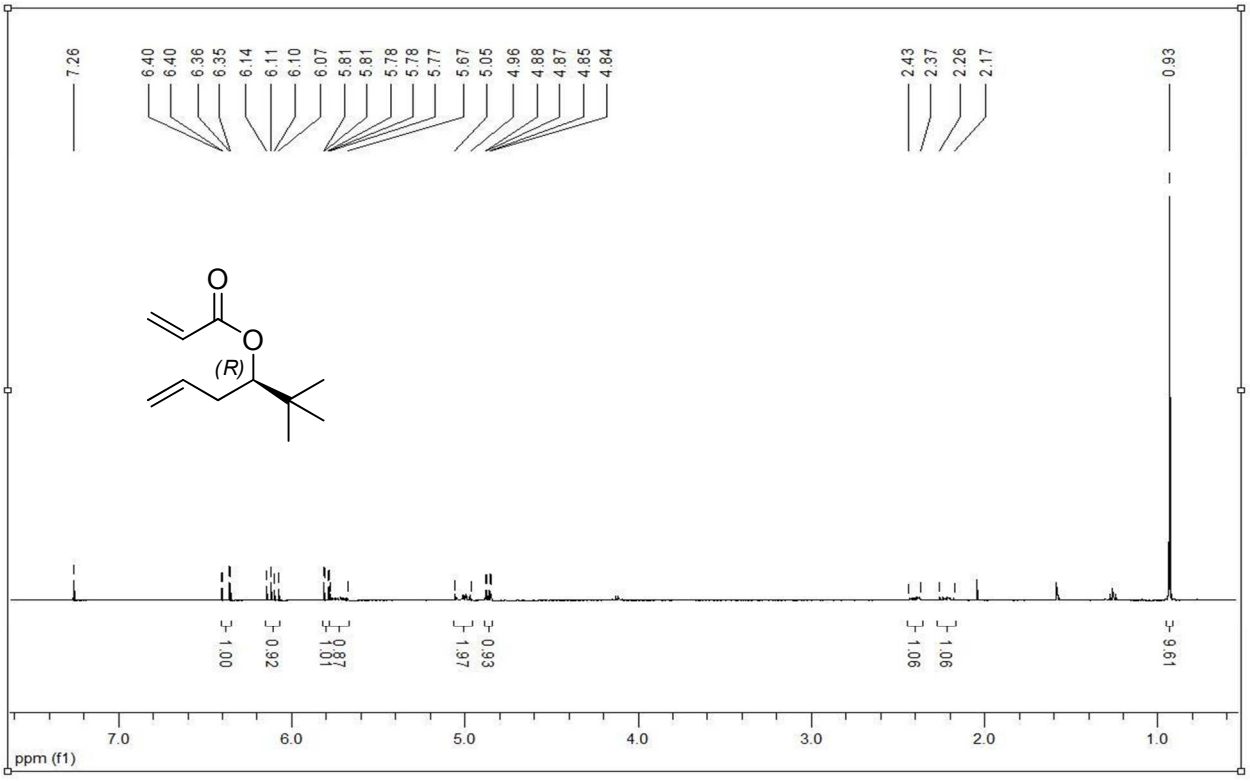
Compound (*S*)-**8** **^{1}H NMR** (400 MHz, $CDCl_3$)



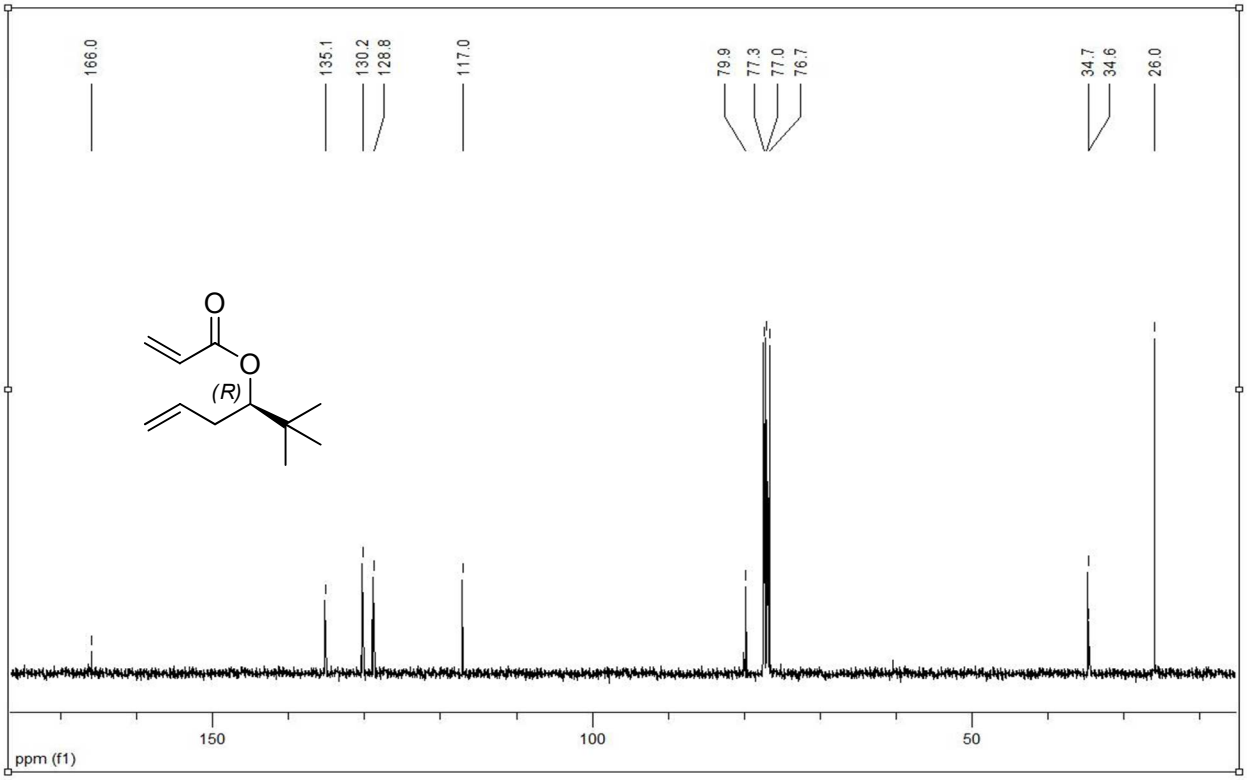
^{1}H NMR (400 MHz, $CDCl_3$)



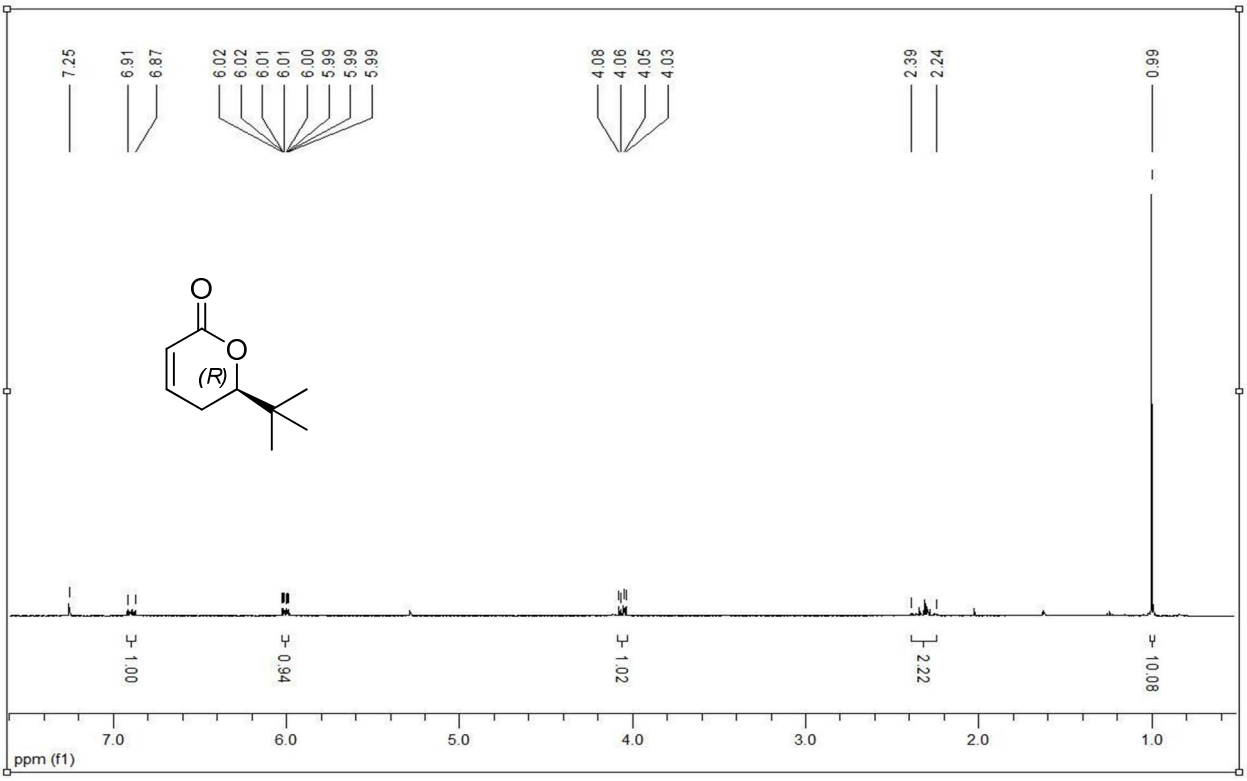
Compound **14** **^{1}H NMR** ($CDCl_3$)



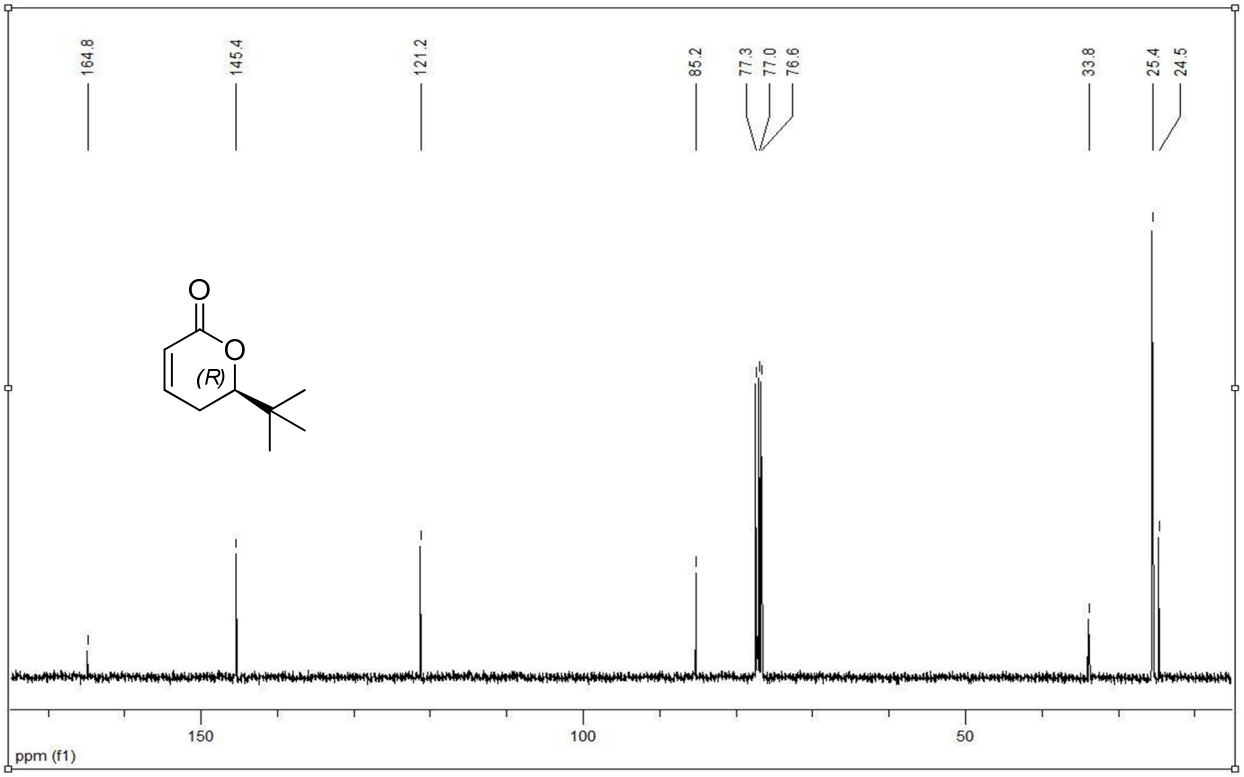
^{13}C NMR ($CDCl_3$)



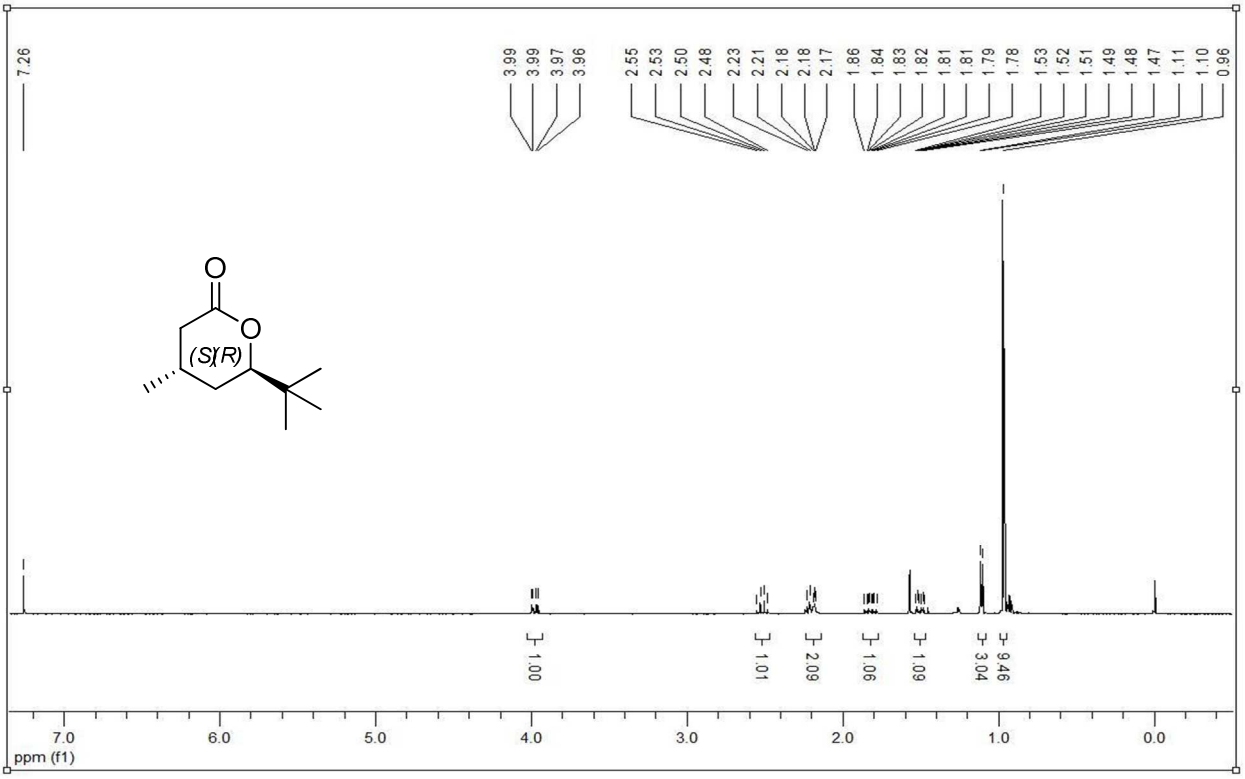
Compound **15** **^{1}H NMR** (400 MHz, $CDCl_3$)



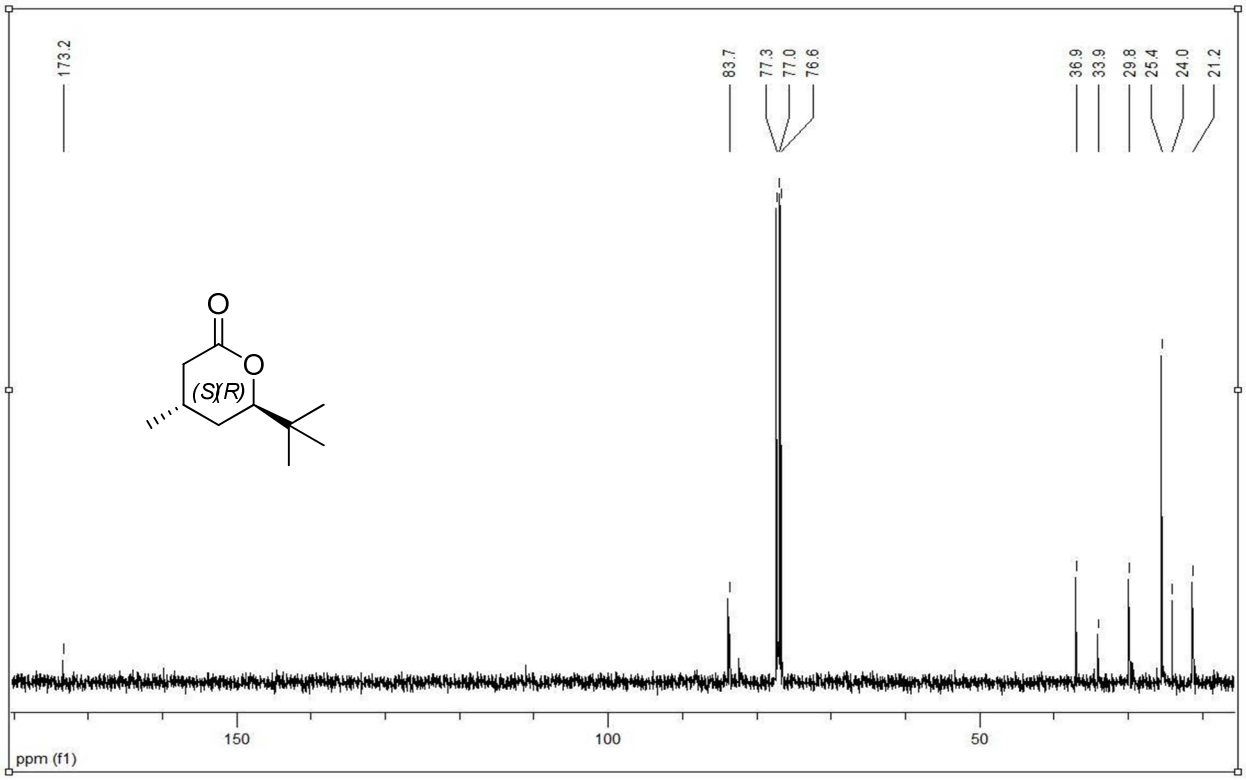
^{13}C NMR (100 MHz, $CDCl_3$)



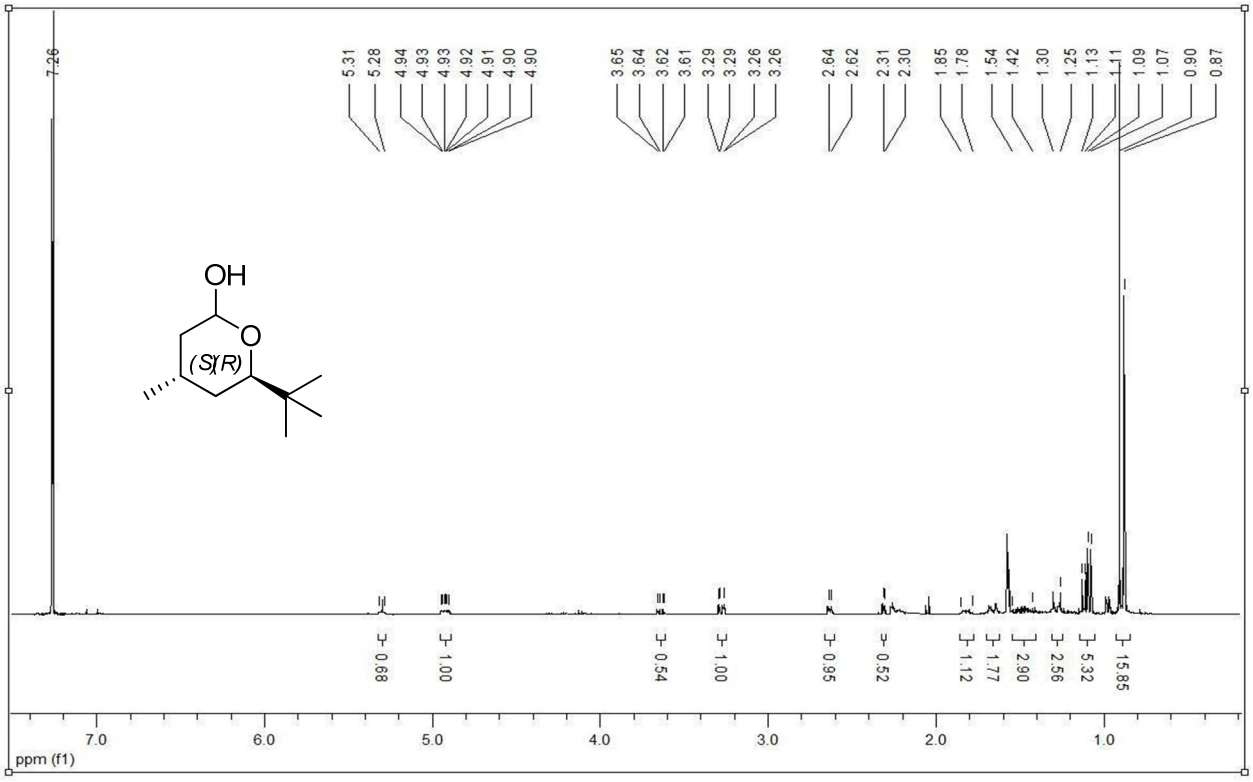
Compound **16** **^{1}H NMR** (400 MHz, $CDCl_3$)



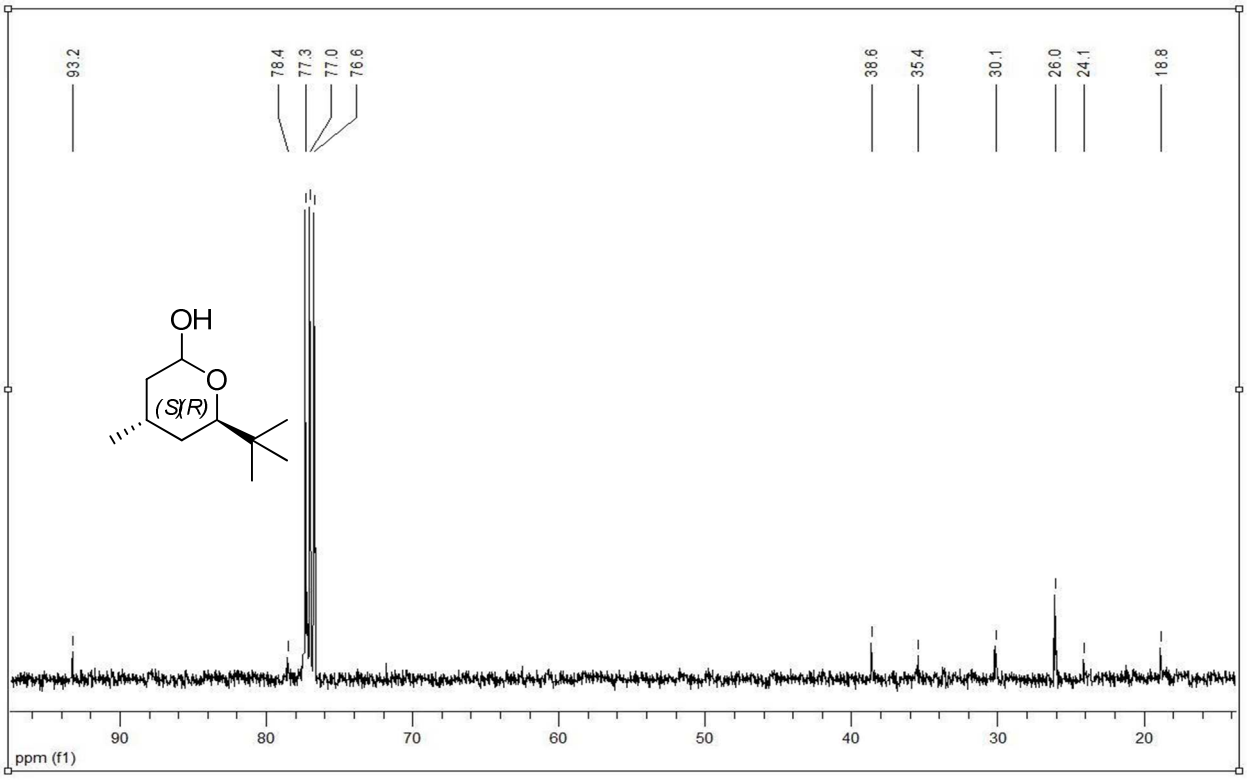
^{13}C NMR (100 MHz, $CDCl_3$)



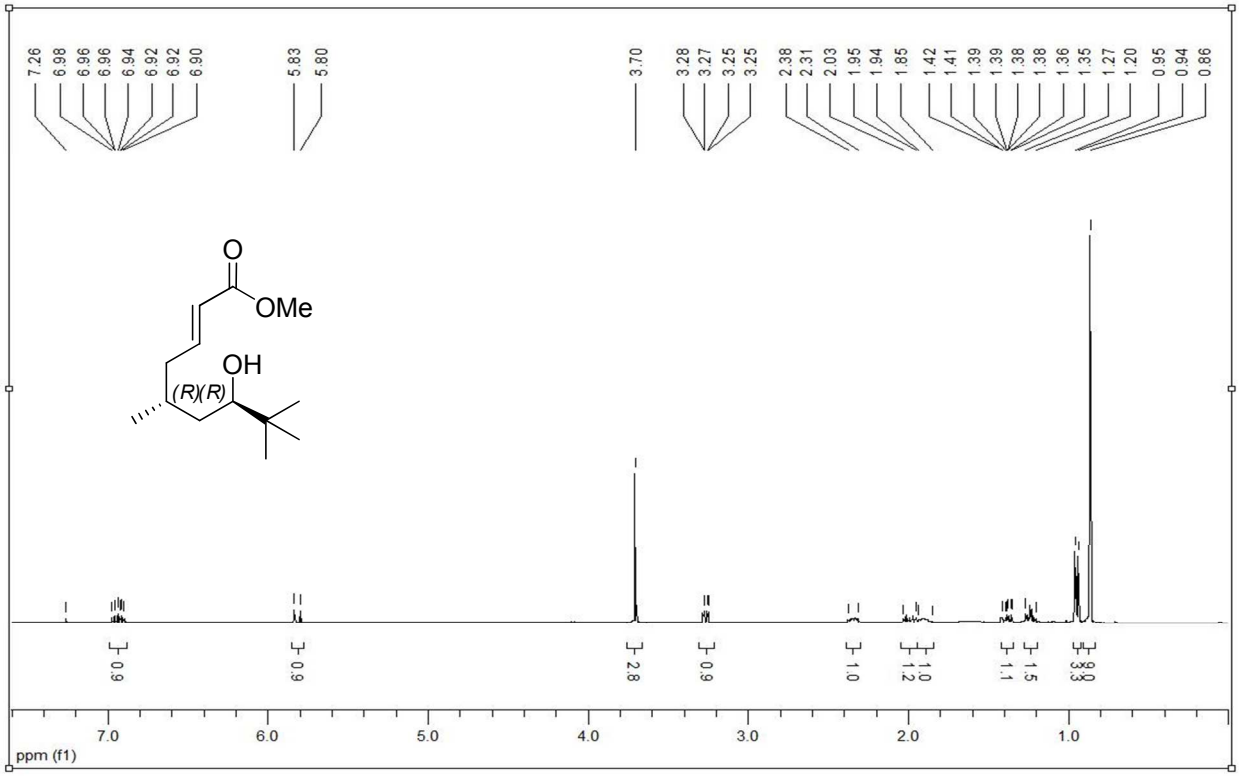
Compound **17** **^{1}H NMR** (400 MHz, $CDCl_3$)



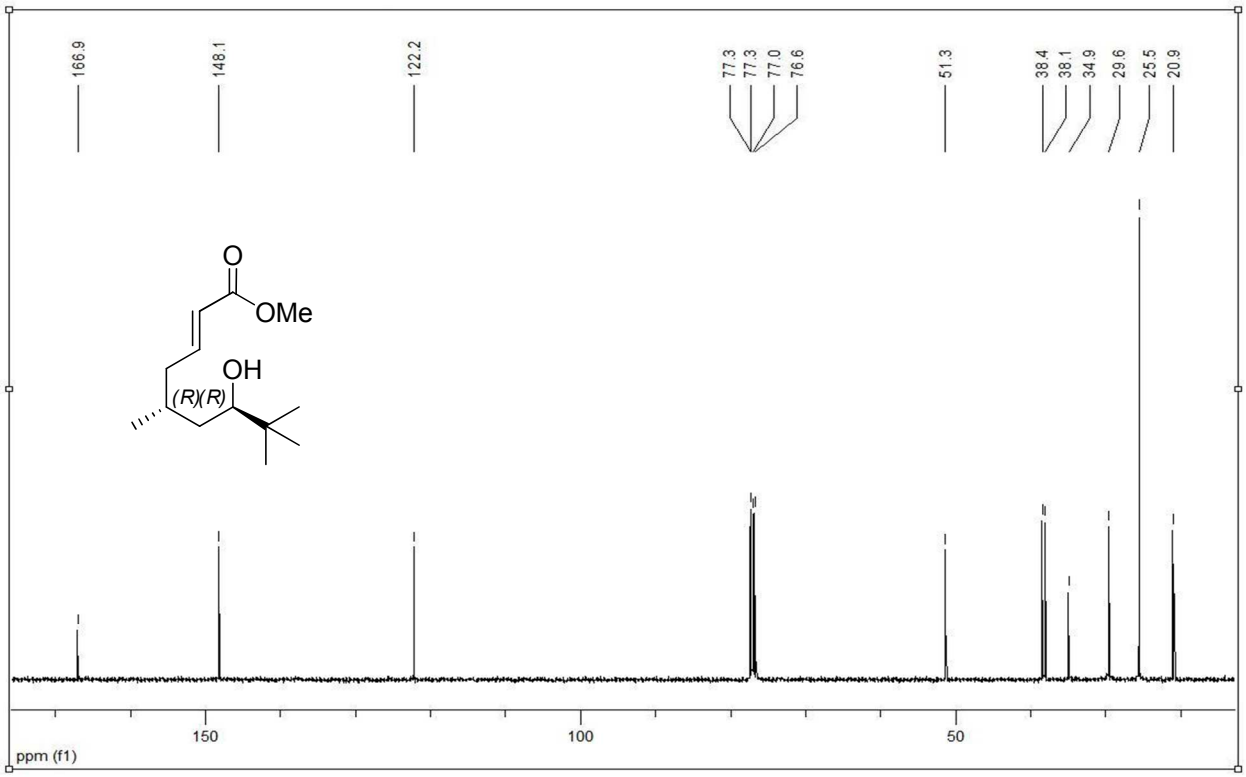
^{13}C NMR (100 MHz, $CDCl_3$)



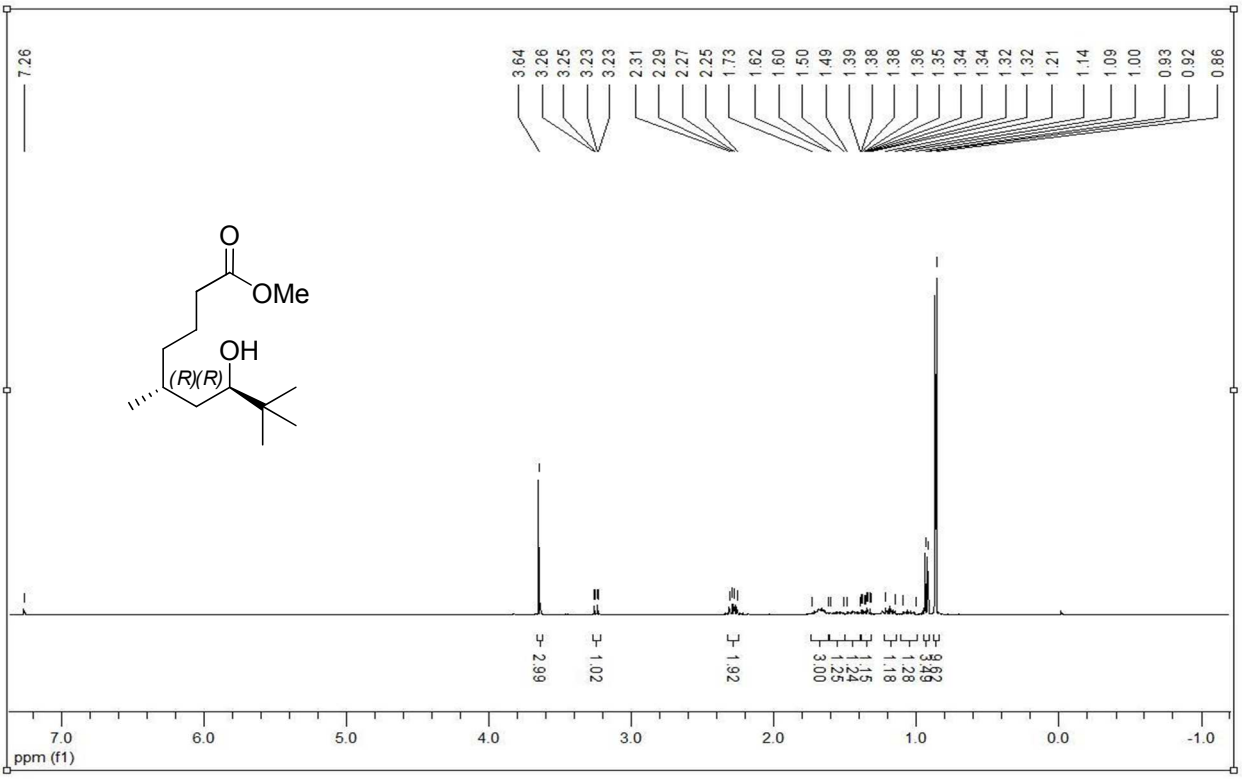
^{1}H NMR (400 MHz, $CDCl_3$)



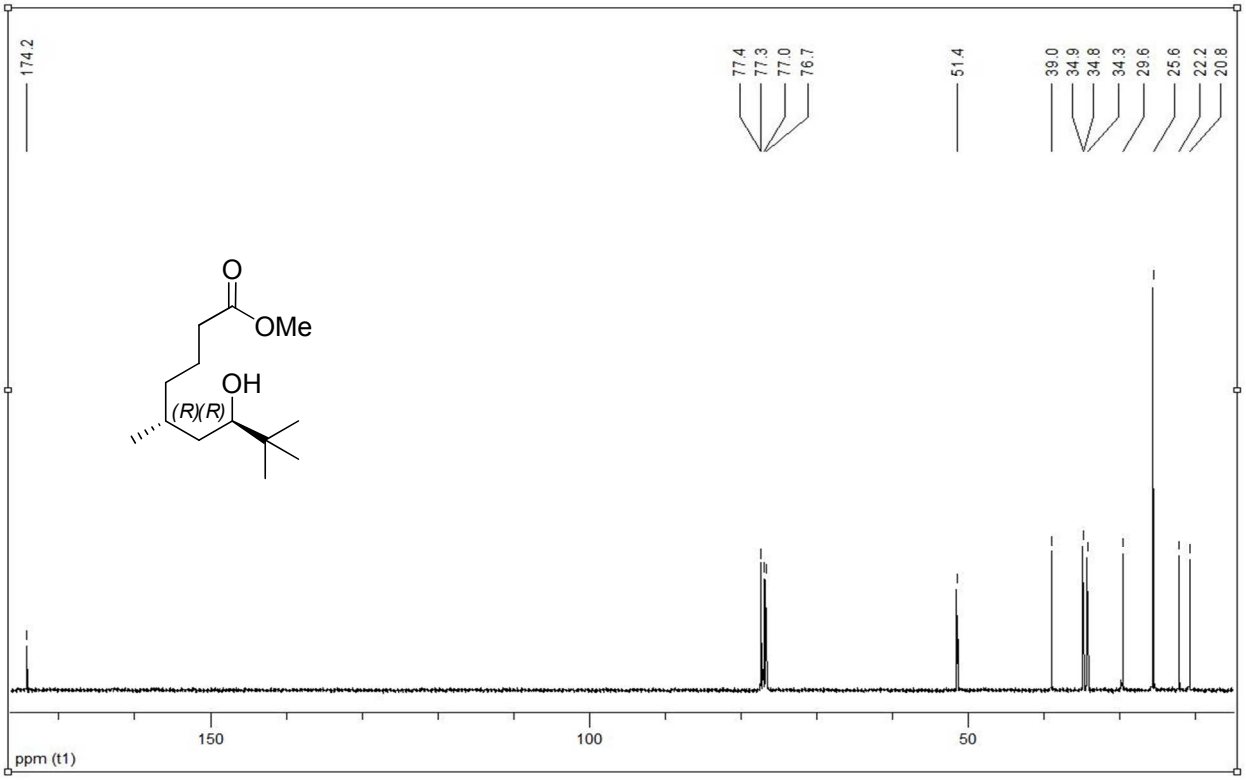
^{13}C NMR (100 MHz, $CDCl_3$)



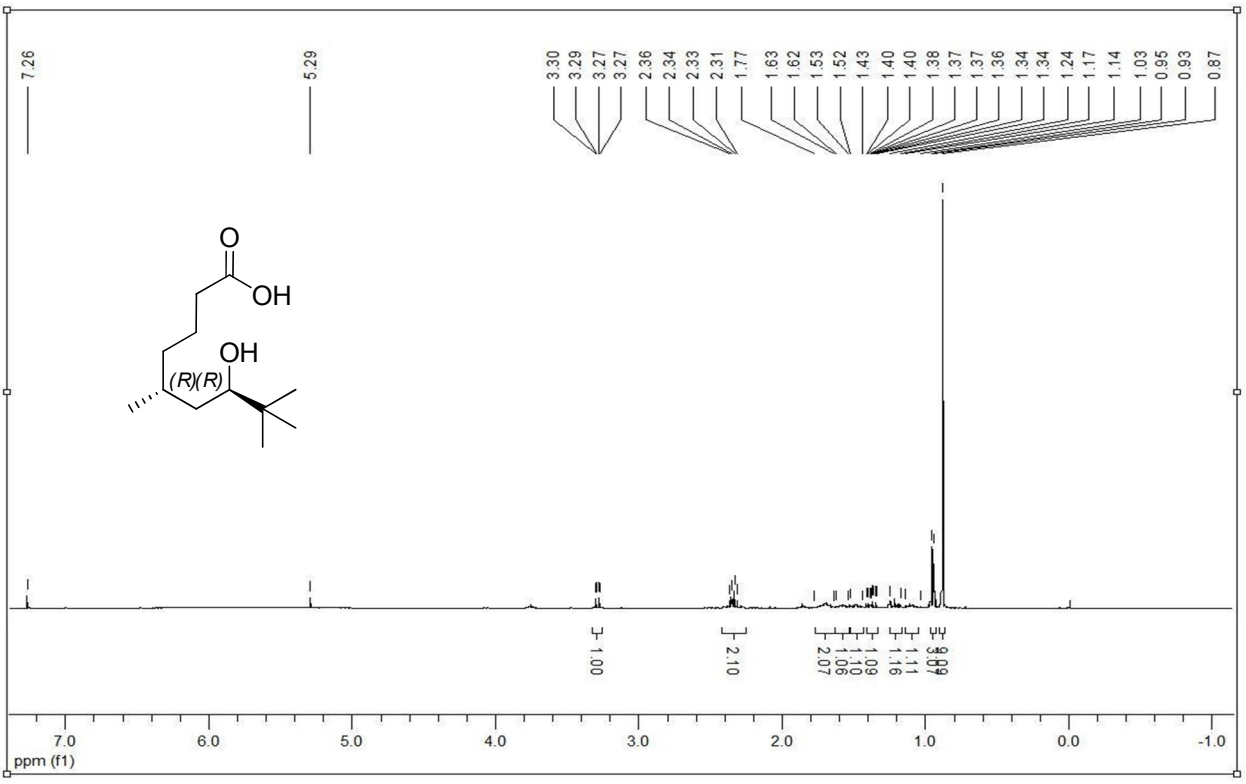
^{1}H NMR (400 MHz, $CDCl_3$)



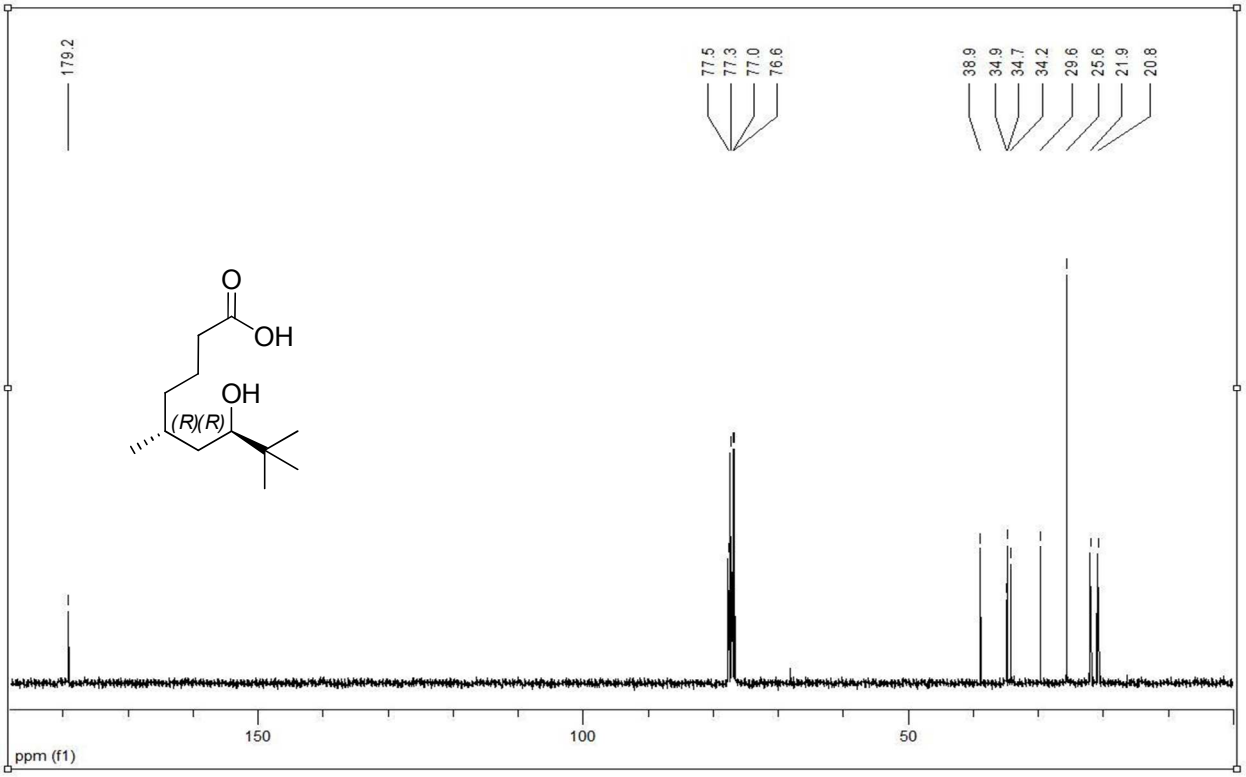
^{13}C NMR (100 MHz, $CDCl_3$)



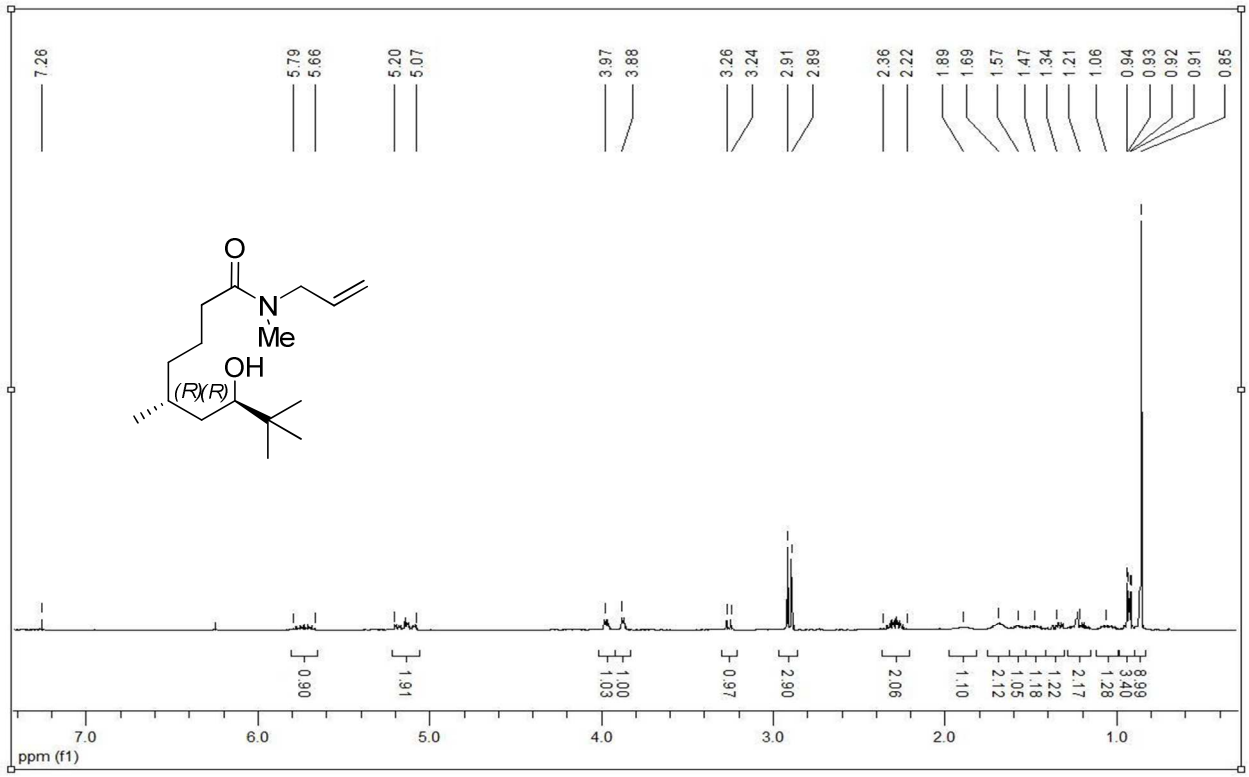
^{1}H NMR (400 MHz, $CDCl_3$)



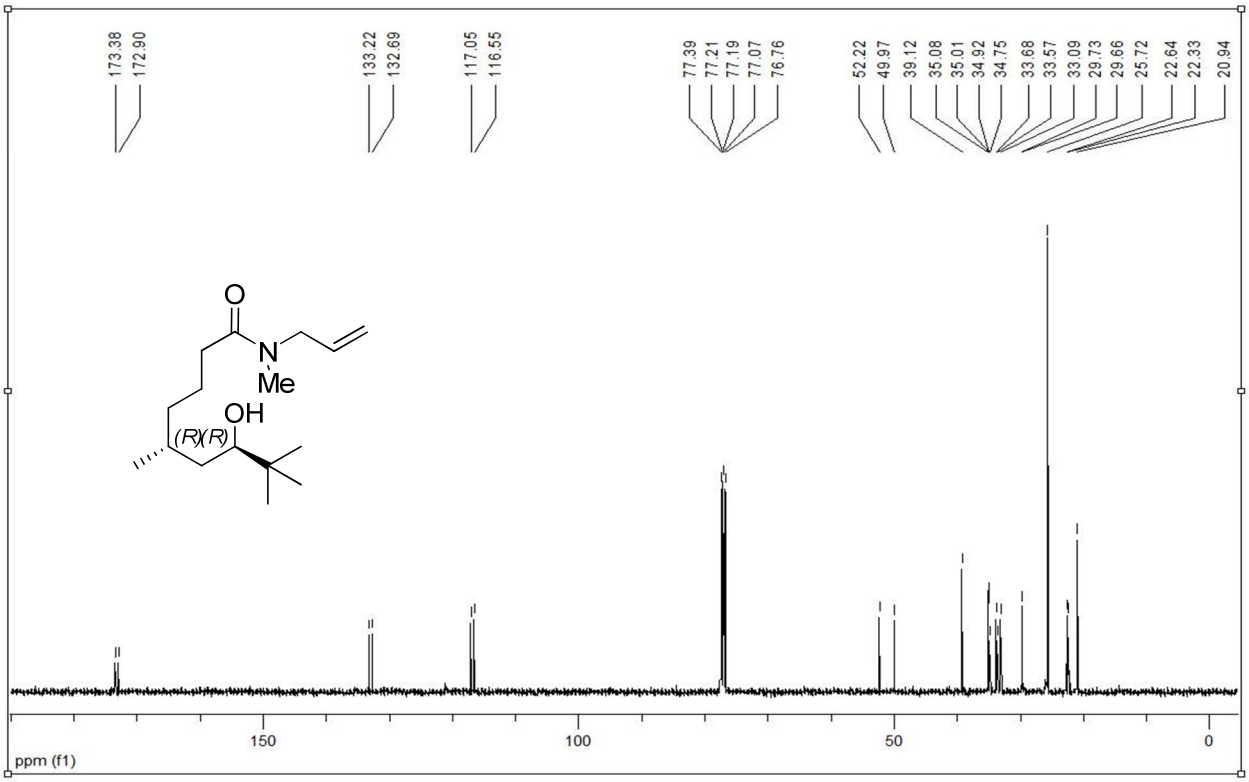
^{13}C NMR (100 MHz, $CDCl_3$)



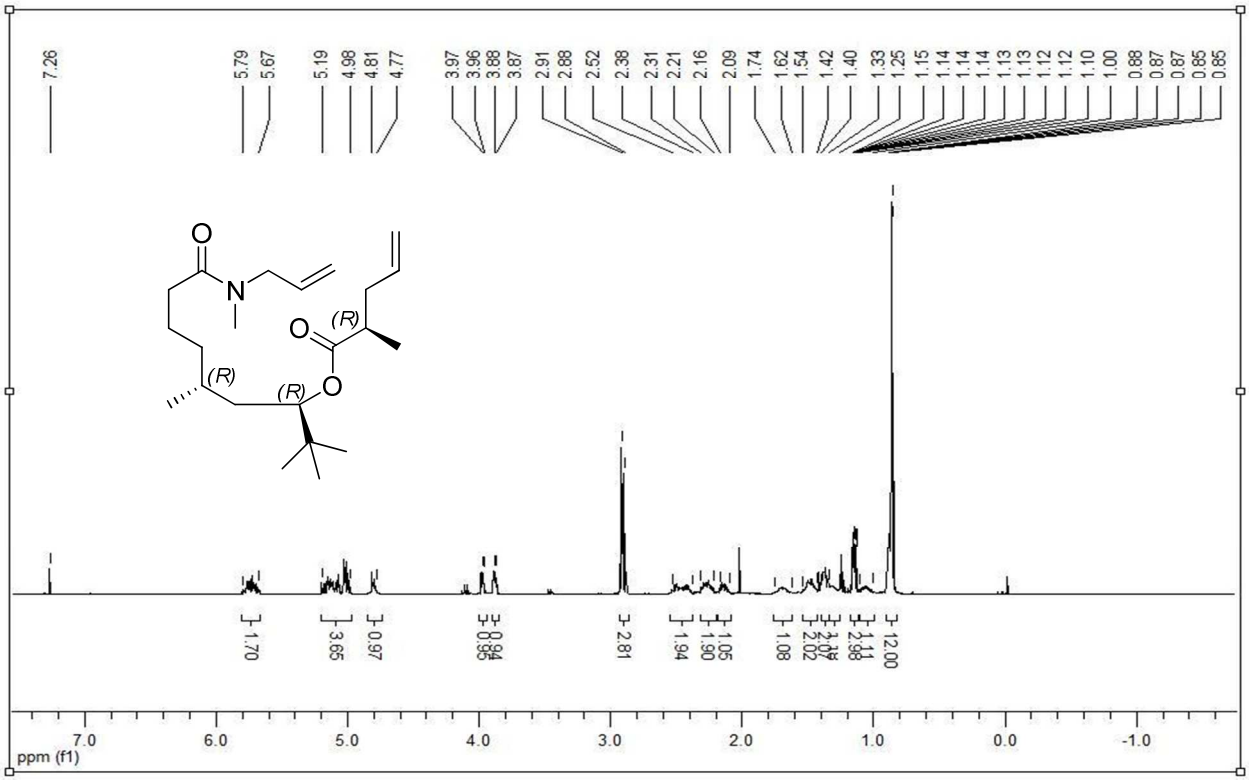
Compound **18** **^{1}H NMR** (400 MHz, $CDCl_3$)



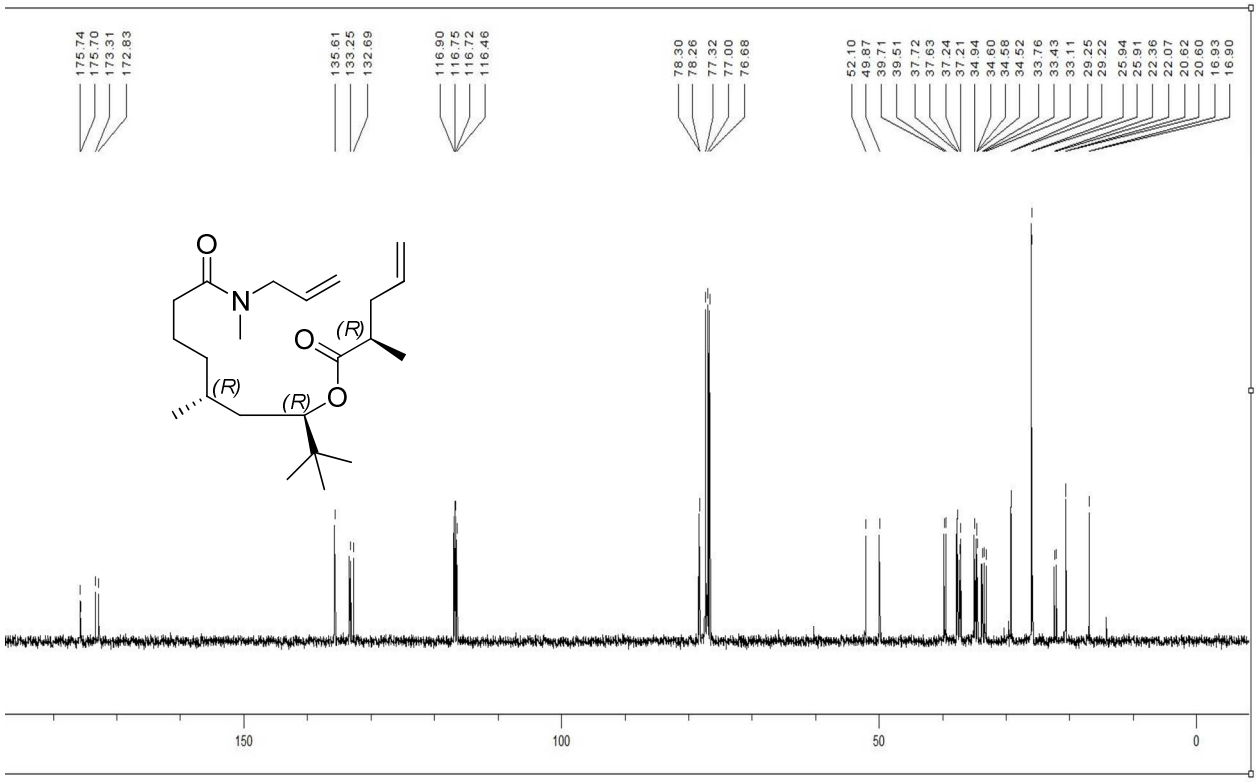
^{13}C NMR (100 MHz, $CDCl_3$)



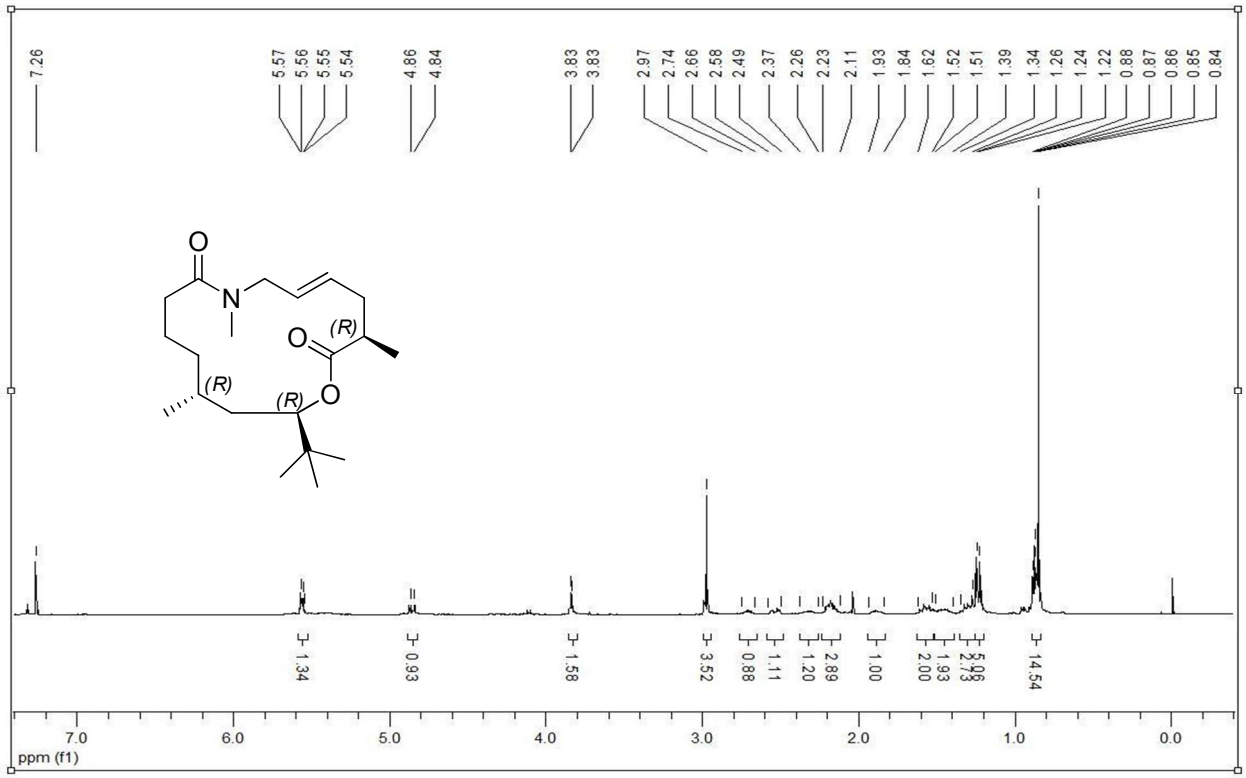
Compound **19** **^{1}H NMR** (400 MHz, $CDCl_3$)



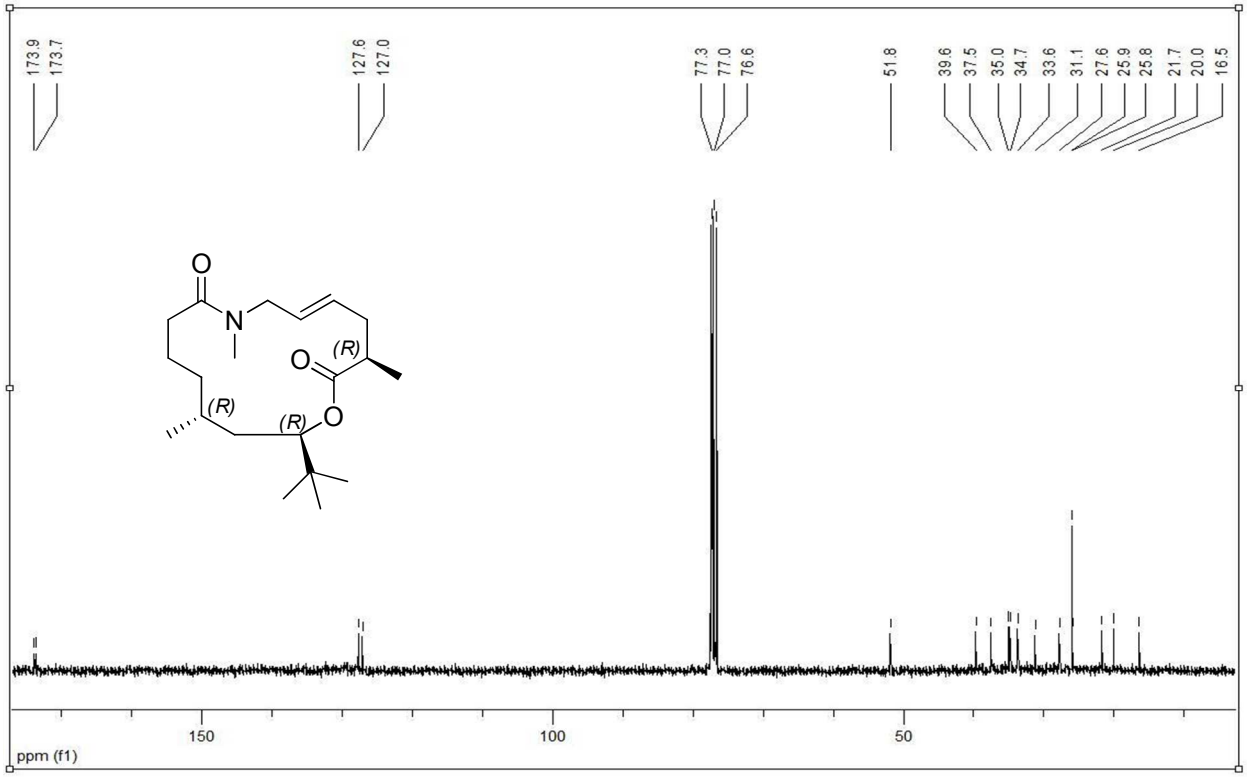
^{13}C NMR (100 MHz, $CDCl_3$)



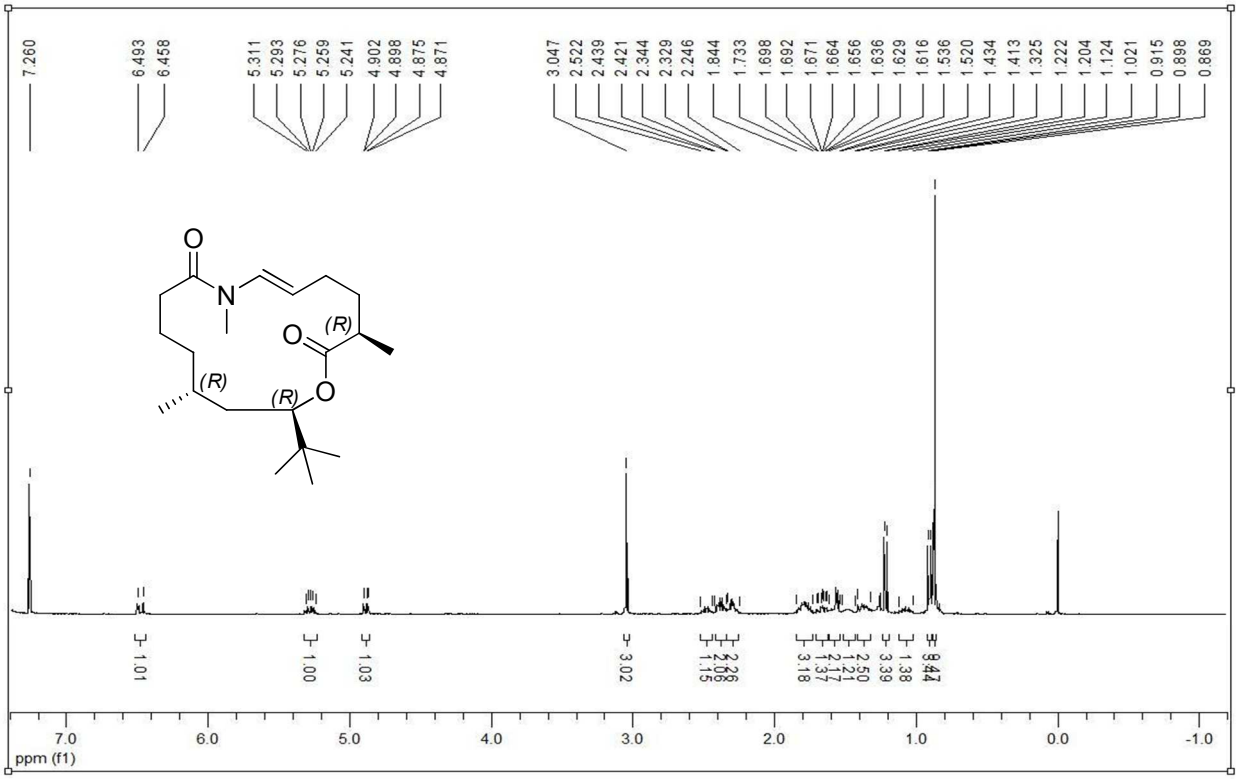
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



Compound **3** **^{1}H NMR** (400 MHZ, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)