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# Supporting Information



69451 Weinheim, Germany

Supporting Information

# Formal Synthesis of (+)-Catharanthine

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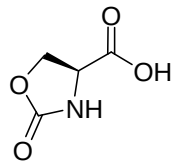
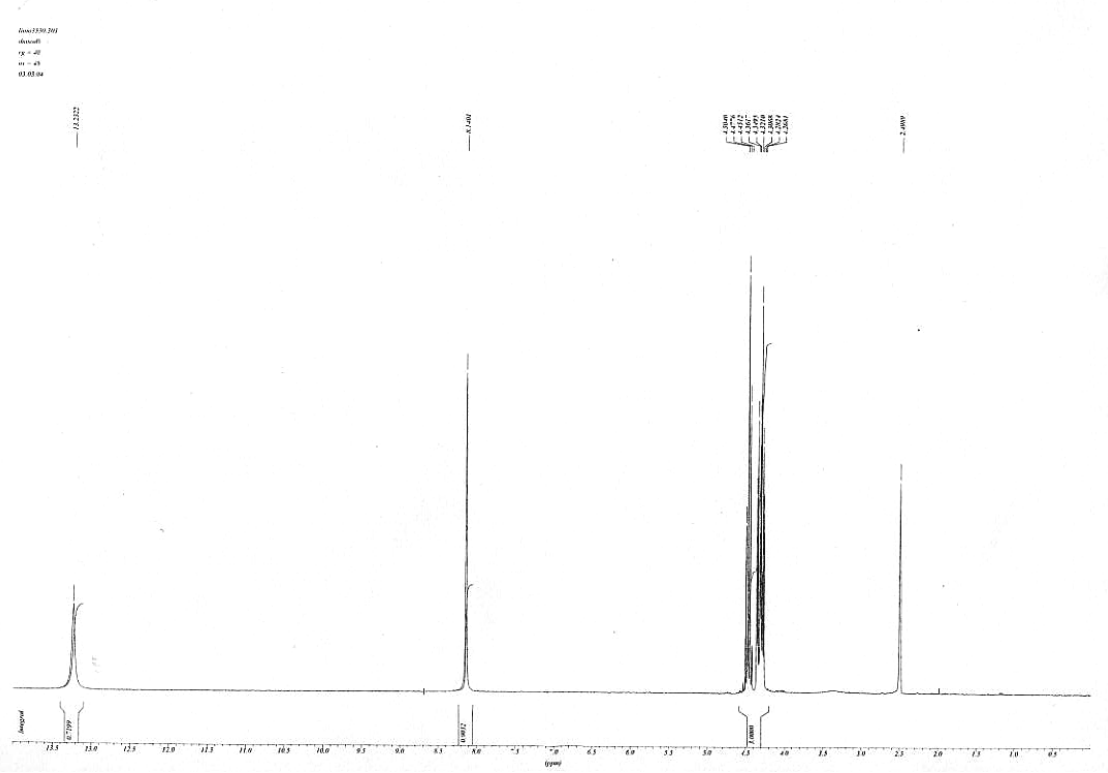
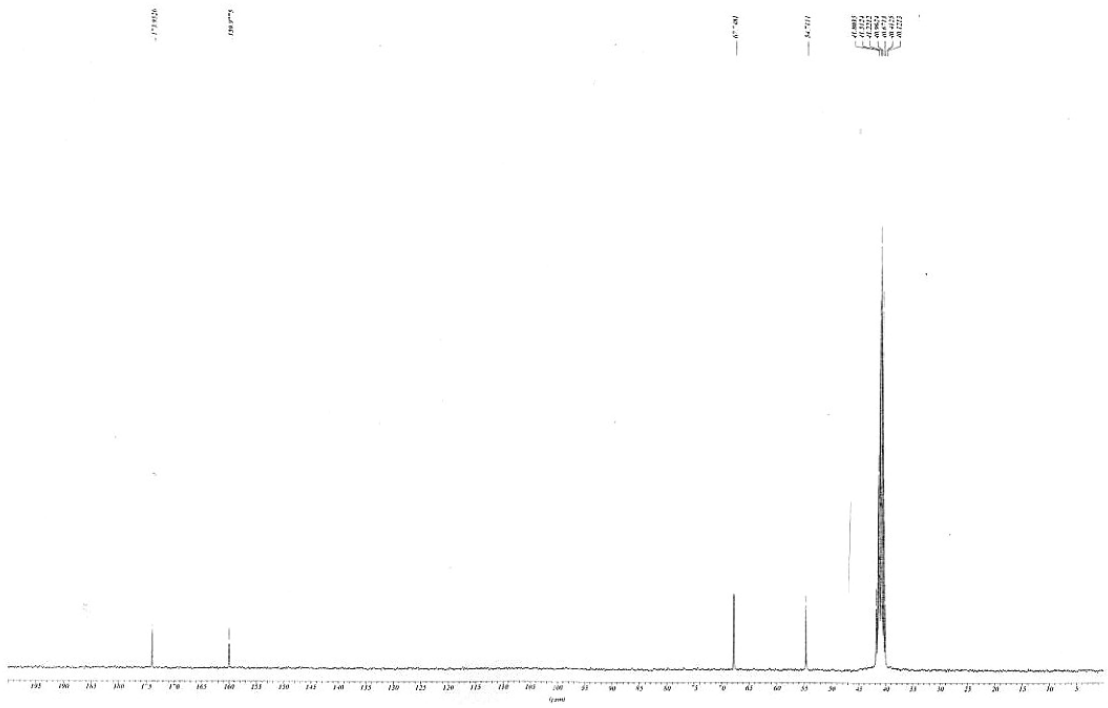
**General procedures.** Unless otherwise specified, chemicals were purchased from Aldrich co. and used without further purification. Reactions were carried out under nitrogen using dry solvent, unless otherwise noted. THF, $Et_2O$ and $CH_2Cl_2$ were distilled respectively from sodium/benzophenone ketyl and calcium hydride before use. Flash chromatography was carried out on Kieselgel 60 (230-240 mesh, Merck) and analytical TLC was performed on Merck precoated silica gel (60 $F_{254}$); visualization was carried out with UV and/or heating with a solution of 5-7% phosphomolybdic acid in ethanol. Melting points were determined using open-ended capillary tubes on a Büchi 535 apparatus and are uncorrected. Microanalyses were performed at the "Service de Microanalyse de l'Institut des Substances Naturelles" in Gif-sur-Yvette (France). Mass spectra were recorded on an ESI-TOF Mariner spectrometer. HRMS were recorded at the "Service de Spectrometrie de Masse de l'Institut des Substances Naturelles" in Gif-sur-Yvette (France). $^1H$ and $^{13}C$ spectra were recorded either on a Bruker AC 300 spectrometer at 300.13 and 75.47 MHz or a Bruker AVANCE DPX 400 spectrometer at 400.13 and 100.61 MHz. Unless otherwise specified, spectra were recorded in $CDCl_3$; chemical shifts (δ) are expressed in ppm and coupling constant (J) in Hertz. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR. Optical rotations were determined using the sodium D line (589 nm) on a Perkin Elmer 341 polarimeter.

**(*S*)-2-Oxo-oxazolidine-4-carboxylic acid (6)**

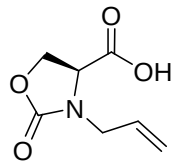



At 0°C, to (L)-carbobenzyloxyserine (25.34 g, 106 mmol, 1 equiv) is added a NaOH solution (8.0 g, 1.9 equiv) in 40 mL of $H_2O$. The solid quickly dissolves and the solution is stirred at rt for 30 min. The mixture is then washed with $Et_2O$ (3x40 mL), carefully acidified to pH 1 using 37% HCl (at 0°C), and extracted with EtOAc (12x50 mL). The organic layers are collected, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. **6** (10.21 g, 73%) is obtained as a white solid. mp = 119-120°C; $[\alpha]_D^{20}$ -21 (c 0.1, $H_2O$); IR (KBr): $\nu_{max}$ 3371, 3017, 1740, 1407, 1258, 1201, 1121, 1045 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 13.2 (brs, 1H, $CO_2H$), 8.15 (brs, 1H, NH), 4.48 (dd, *J* = 8.8 Hz and 8.8 Hz, 1H), 4.38-4.26 (m, 2H); $^{13}C$ NMR (DMSO-$d_6$): δ 173.9, 159.9, 67.7, 54.7; LRMS (ESI-TOF): 263 [2M+$H^+$] (100); 285 [2M+$Na^+$] (15). Anal. Calcd: C 36.66, H 3.86, N 10.65; Found C 36.65, H 3.84, N 10.69.

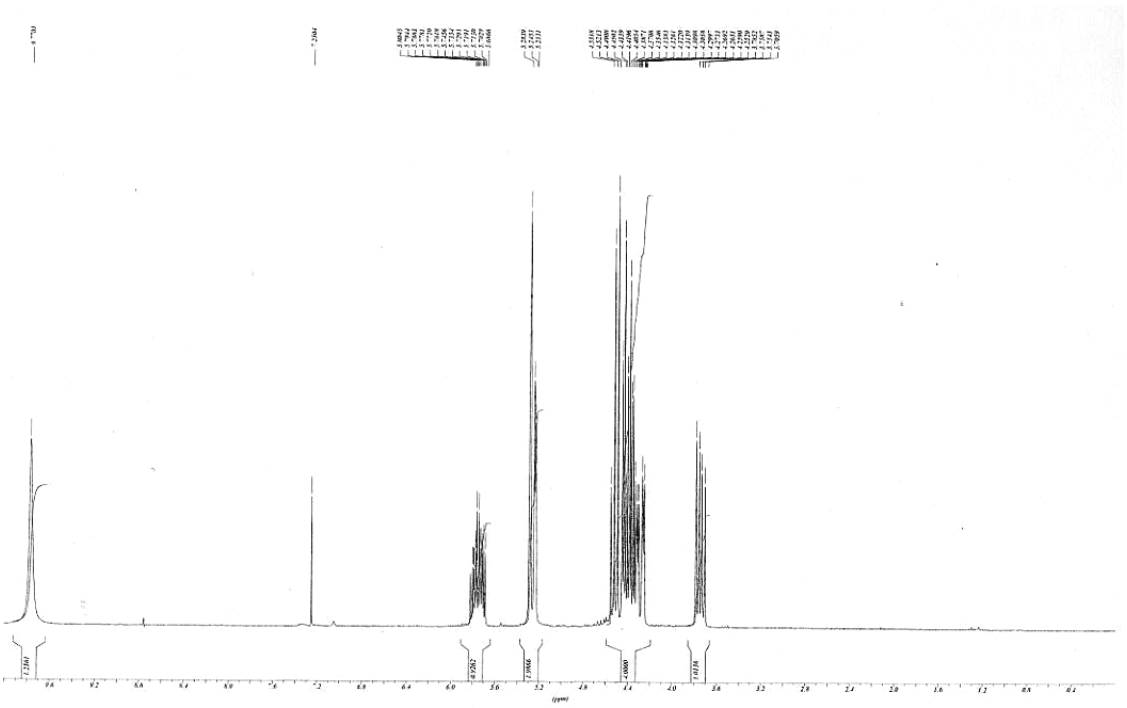


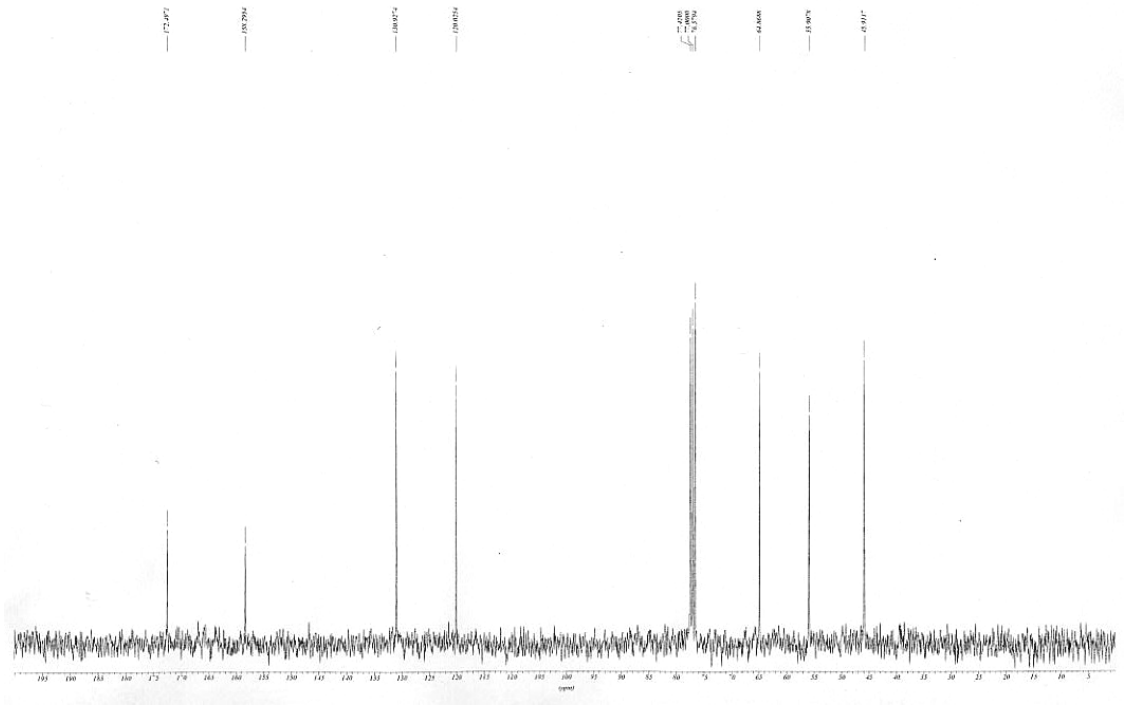


**(*S*)-3-Allyl-2-oxo-oxazolidine-4-carboxylic acid (7)**

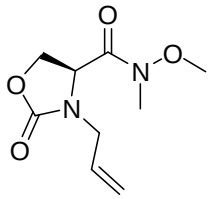



At 0°C, to a solution of **6** (10.78 g, 82.2 mmol, 1 equiv) in 200 mL of DMF, is added portionwise, NaH (6.67 g, 2.02 equiv). After 20 min, allyl iodide (7.5 mL, 1 equiv) is added dropwise. The mixture is warmed to rt and stirred for 16 h. KOH (110 mL of a 1M soln in $H_2O$) is then added, and the mixture is washed with EtOAc (2x200 mL). The aqueous layer is carefully acidified (at 0°C) to pH 1 using 37% HCl, extracted with EtOAc (5x100 mL) and $CH_2Cl_2$ (100 mL). The organic layers are collected, washed with a saturated solution of $Na_2S_2O_3$ (2x20 mL), dried over $Na_2SO_4$, filtered and solvents are removed under reduced pressure. The crude is filtered on silica (EtOAc) to give **7** (8.55 g, 61%) as a white solid. $R_f$ = 0.5 (EtOAc); mp = 118-119°C; $[\alpha]_D^{20}$ = -19 (c 0.25, MeOH); FTIR (KBr): $\nu_{max}$ 3019, 1751, 1702, 1443, 1411, 1186 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 9.94 (brs, 1H, $CO_2H$); 5.79-5.68 (m, 1H), 5.28-5.23 (m, 2H), 4.50-4.25 (m, 4H), 3.74 (dd, *J* = 7.9 Hz and 15.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): δ 172.5, 158.3, 130.9, 120.0, 64.8, 55.9, 45.9; LRMS (ESI-TOF): 172 [$M+H^+$] (100), 343 [$2M+Na^+$] (24).

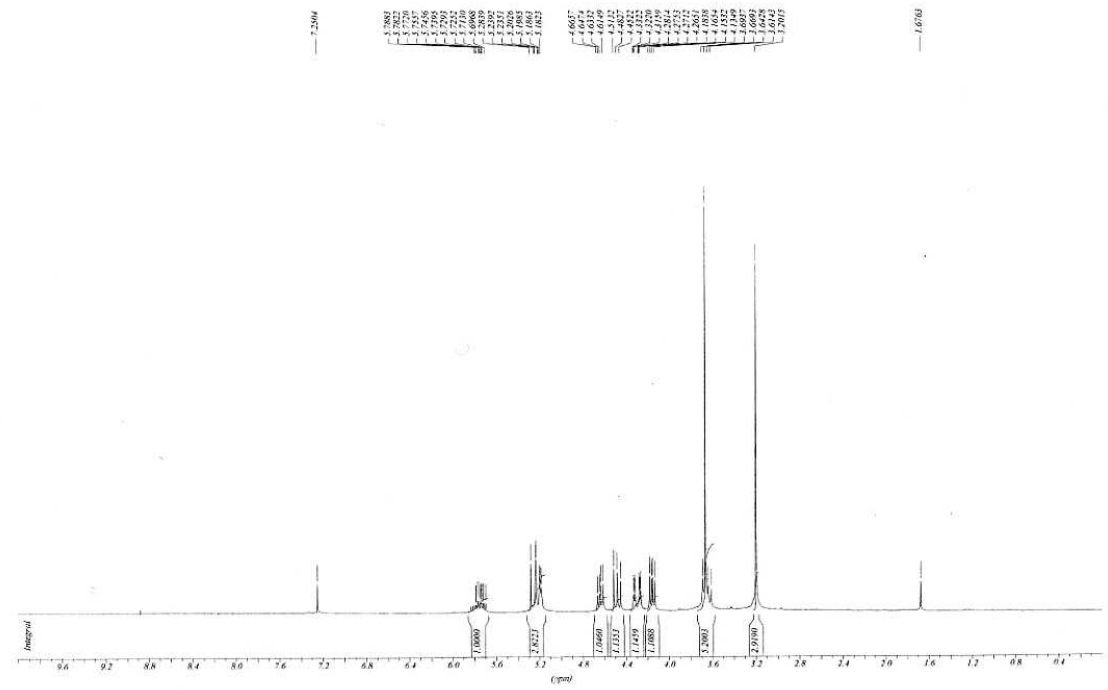


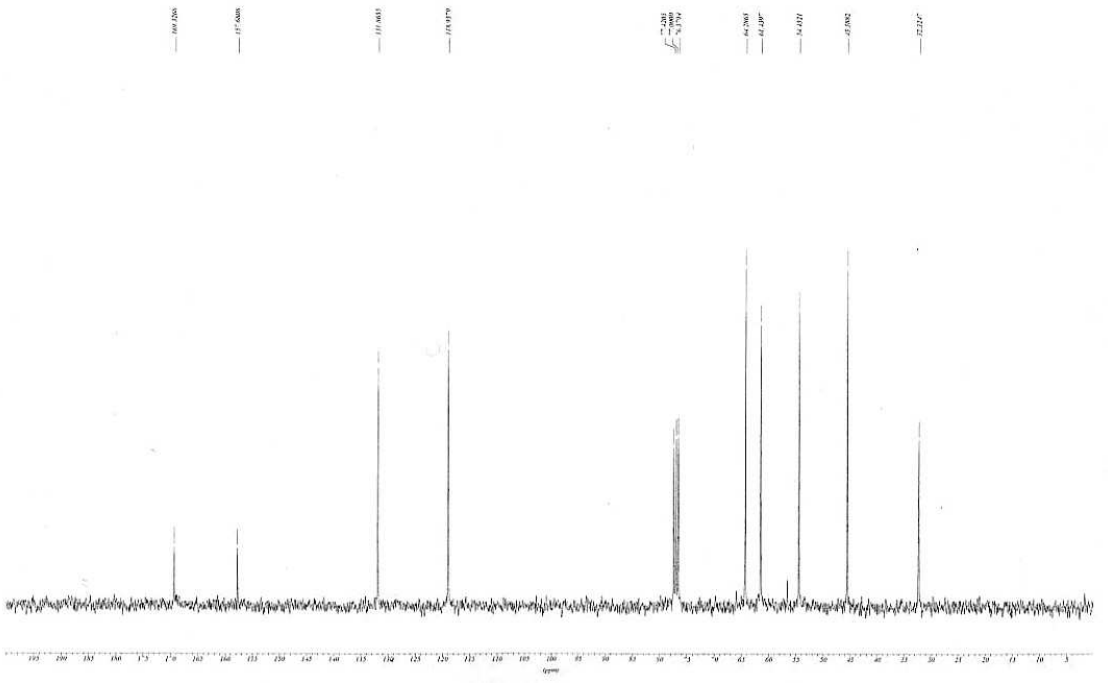


**(*S*)-3-Allyl-*N*-methoxy-*N*-methyl-2-oxo-oxazolidine-4-carboxamide (8)**

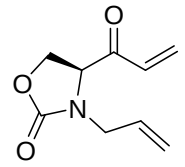


At -5°C, to a solution of 7 (2.32 g, 13.5 mmol, 1 equiv) in 100 mL of $CH_2Cl_2$, are added HCl-HN(OMe)Me (1.32 g, 1 equiv), diisoethylpropylamine (2.35 mL, 1 equiv), and dropwise, a solution of EDCI (2.59 g, 1 equiv) in 50 mL of $CH_2Cl_2$. After 1 h at -5°C, the mixture is washed with 1N HCl (2x10 mL). The organic layer is collected, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue is purified on silica (EtOAc) to afford **8** (2.20 g, 76%) as a white solid. mp = 67-68°C ; $[\alpha]_D^{20}$ = -55 (c 1.2, MeOH); FTIR (KBr): $\nu_{max}$ 2982, 2926, 1756, 1663, 1423, 1333, 1232, 1204, 1081, 1042 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.79-5.70 (m, 1H), 5.28-5.18 (m, 2H), 4.64 (dd, *J* = 9.7 Hz and 5.5 Hz, 1H), 4.45-4.51 (dd, *J* = 9.1 Hz and *J* = 9.1 Hz, 1H), 4.35-4.25 (m, 1H), 4.16 (dd, *J* = 9.1 Hz and 5.5 Hz, 1H), 3.69-3.61 (m, 2H), 3.66 (s, 3H), 3.20 (s, 3H); $^{13}C$ NMR ($CDCl_3$): δ 169.3, 157.8, 132.1, 119.1, 64.3, 61.5, 54.7, 45.7, 32.5; LRMS (ESI-TOF): 215 [$M+H^+$] (100); Anal. Calcd: C 50.46, H 6.59, N 13.08, found C 50.40, H 6.57, N 13.03; HPLC Analysis: Chiralpak OD (UV: 205 nm), Hexane/EtOH: 95/5, Flow rate: 1 mL/min, T=35°C, Retention time: 32.4 min (ee>99%).

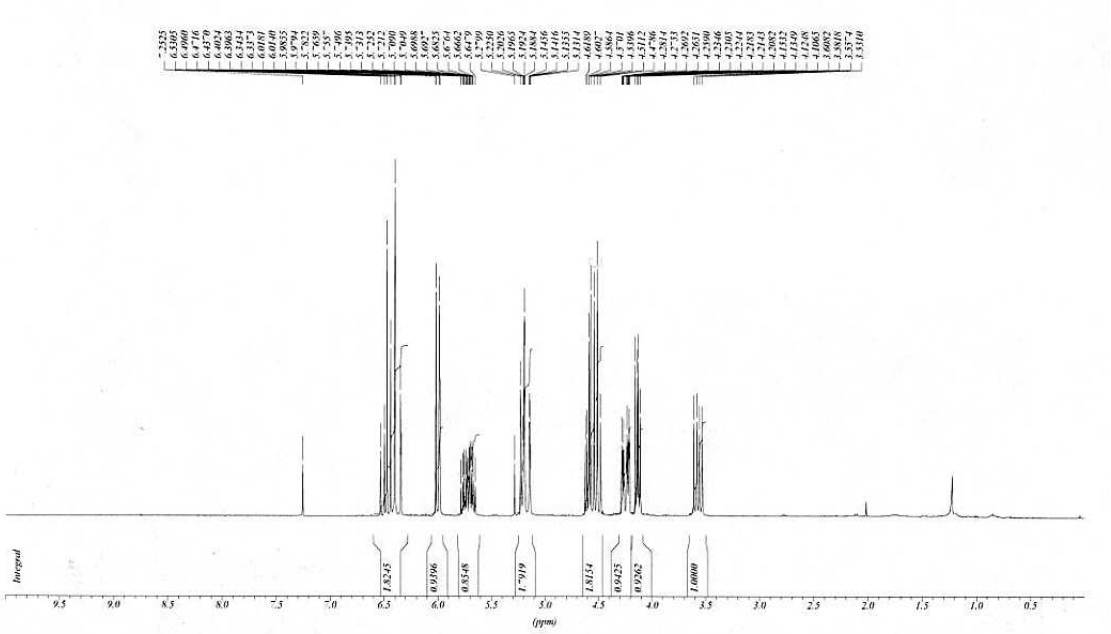


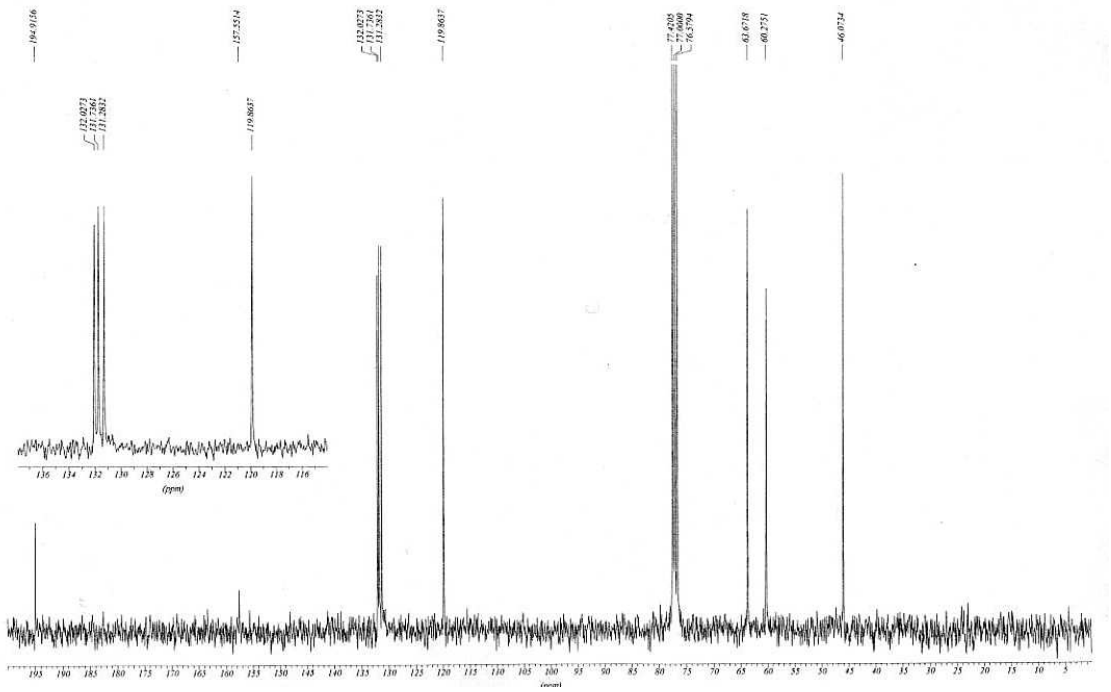


**(*S*)-4-Acryloyl-3-allyl-oxazolidin-2-one (9)**

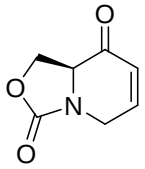


At -5°C, to a solution of **8** (1.49 g, 6.9 mmol, 1 equiv) in 100 mL of THF is added dropwise, vinylmagnesium bromide (14.9 mL of a 1 M soln in THF, 2.1 equiv). A white precipitate quickly appears. The mixture is stirred at -5°C for 1 h and 6 mL of acetic anhydride are added followed by 6 mL of MeOH. The mixture is then concentrated to one fourth, and diluted with 750 mL of $Et_2O$. The organic layer is washed with 10% $NH_4Cl$ (2x25 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue is filtered on silica (EtOAc/Hexane: 1/1) to give **9** (1.01 g, 81%) as a pale yellow oil. $R_f$ = 0.44 (Hexane/AcOEt 3/7); FTIR (film): $\nu_{max}$ 1753, 1702, 1614, 1413, 1216, 1051 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.53-6.33 (m, 2H), 6.02-5.98 (m, 1H), 5.75-5.66 (m, 1H), 5.22-5.13- (m, 2H), 4.62-4.47 (m, 2H), 4.30-4.20 (m, 1H), 4.15-4.10 (m, 1H), 3.57 (dd, $J$ = 14.9 Hz and 8.55 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): δ 194.9, 157.5, 132.0, 131.7, 131.3, 119.9, 63.7, 60.3, 46.1; LRMS (ESI-TOF): 182 [$M+H^+$] (100).

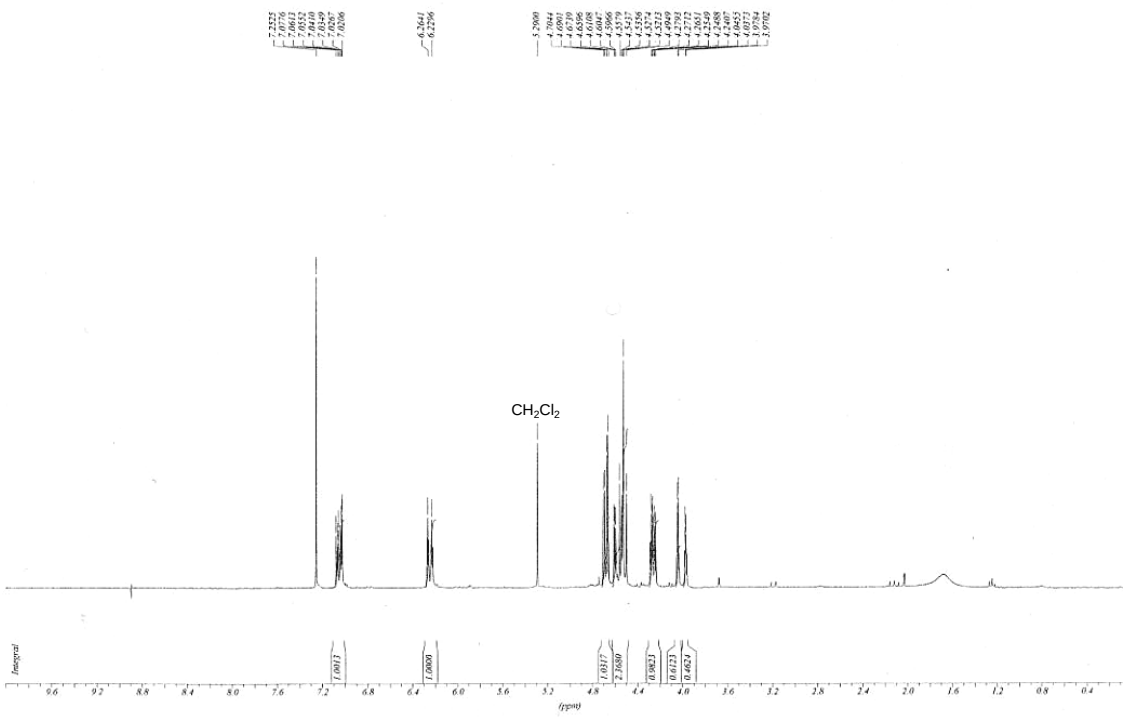


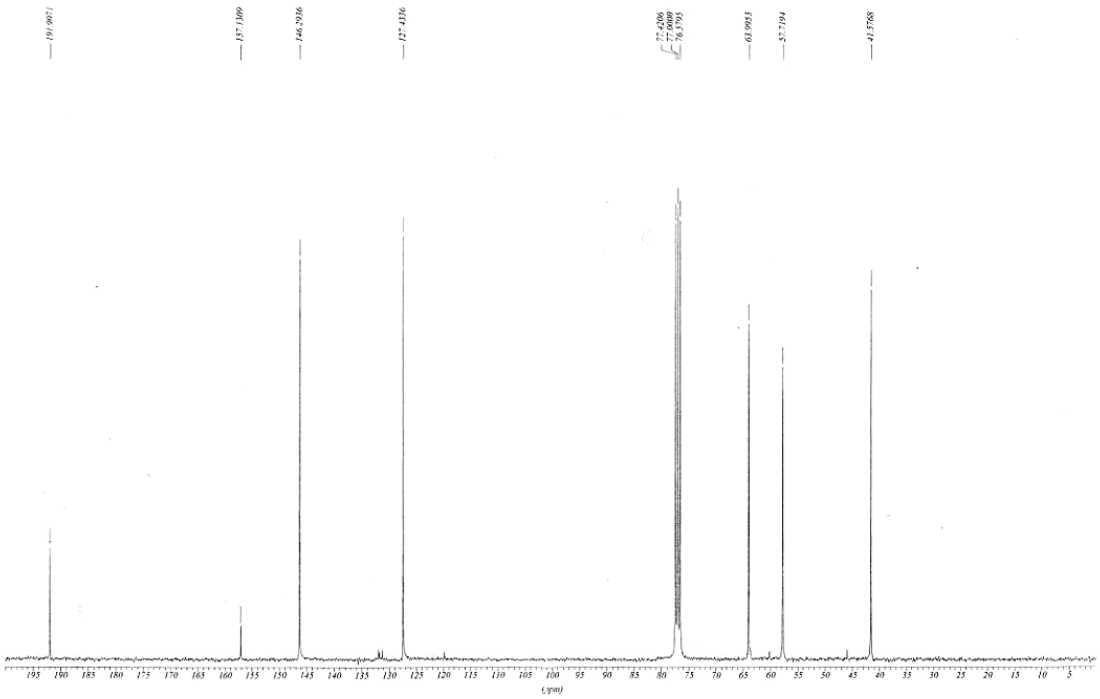


**(*S*)-1H-Oxazolo[3,4-a]pyridine-3,8(5H,8aH)-dione (10)**

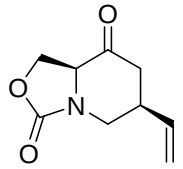


To a solution of **9** (1.01 g, 5.6 mmol, 1 equiv) in 100 mL of $CH_2Cl_2$ is added 115 mg of the second generation of Grubbs catalyst (0.02 equiv). After 2 h under reflux, the solvent is removed under reduced pressure. The crude residue is purified on silica (EtOAc) to afford **10** (745 mg, 87%) as a white solid. $R_f$ = 0.25 (Hexane/EtOAc 3/7); $[\alpha]_D^{20}$ = -59 (c 1.6, MeOH); mp = 88-90°C; IR (KBr): $\nu_{max}$ 1753, 1693, 1433, 1244, 1193 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.09-7.01 (m, 1H), 6.28-6.21 (m, 1H), 4.68 (dd, *J* = 9.1 Hz and 4.3 Hz, 1H), 4.50 (dd, *J* = 9.1 Hz and 9.1 Hz, 1H), 4.26 (ddd, *J* = 1.8 Hz, 4.3 Hz and 9.3 Hz, 1H), 4.06-3.96 (m, 1H); $^{13}C$ NMR ($CDCl_3$): δ 191.9, 157.1, 146.3, 127.4, 64.0, 57.7, 41.6; LRMS (ESI-TOF): 176 [M+$Na^+$] (28); 208 [M+MeOH] (96); 240 [M+2MeOH] (100); HPLC Analysis: Chiralpak AS (UV: 230 nm), Hexane/EtOH: 80/20, Flow rate: 1 mL/min, T=30°C, Retention time: 21.9 min (ee = 99%).

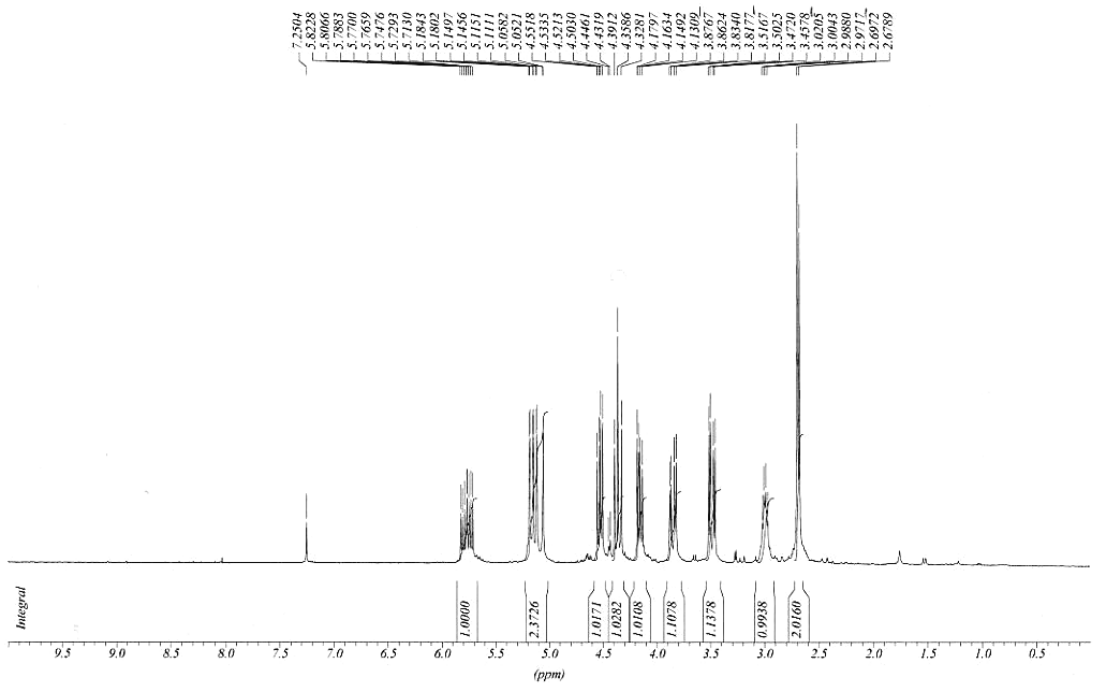

CH2Cl2



**(6*S*,8a*S*)-6-Vinyldihydro-1H-oxazolo[3,4-a]pyridine-3,8(5H,8aH)-dione (11)**




At –78°C, to a suspension of CuI (1.29 g, 1.6 equiv) in 20 mL of THF is added a solution of vinylmagnesium bromide (12 mL of a 1 M soln in THF, 2.9 equiv). After 5 min at -78°C, the mixture is warmed to -5°C over a period of time of 20 min, and cooled again to –78°C. A solution of **10** (634 mg, 4.1 mmol, 1 equiv) in 60 mL of THF is then added dropwise over a period of 2 h. The reaction is further stirred at –78°C for 1 h. The mixture is then poured into 50 mL of saturated $NH_4Cl$ at 0°C. The aqueous layer is extracted with EtOAc (4x100 mL). The organic layers are collected, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude is pure enough to be involved in the next step without any further purification. $R_f$ = 0.5 (Hexane/AcOEt 1/1); $^1$H NMR ($CDCl_3$): δ 5.85-5.75 (m, 1H), 5.23-5.09 (m, 2H), 4.57 (dd, *J* = 5.5 Hz and *J* = 9.1 Hz, 1H), 4.38 (dd, *J* = 9.1 Hz and 9.1 Hz, 1H), 4.17 (dd, 1H, *J* = 5.5 Hz and 9.1 Hz), 3.84 (dd, *J* = 4.7 Hz and 13.0 Hz 1H), 3.58 (dd, 1H, *J* = 4.2 Hz and 13.4 Hz), 3.04 (m, 1H), 2.70 (d, *J* = 5.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 203.3, 156.6, 136.5, 116.5, 61.8, 59.6, 43.4, 42.0, 37.3; SM (ESI-TOF): 182 [$M+H^+$] (100).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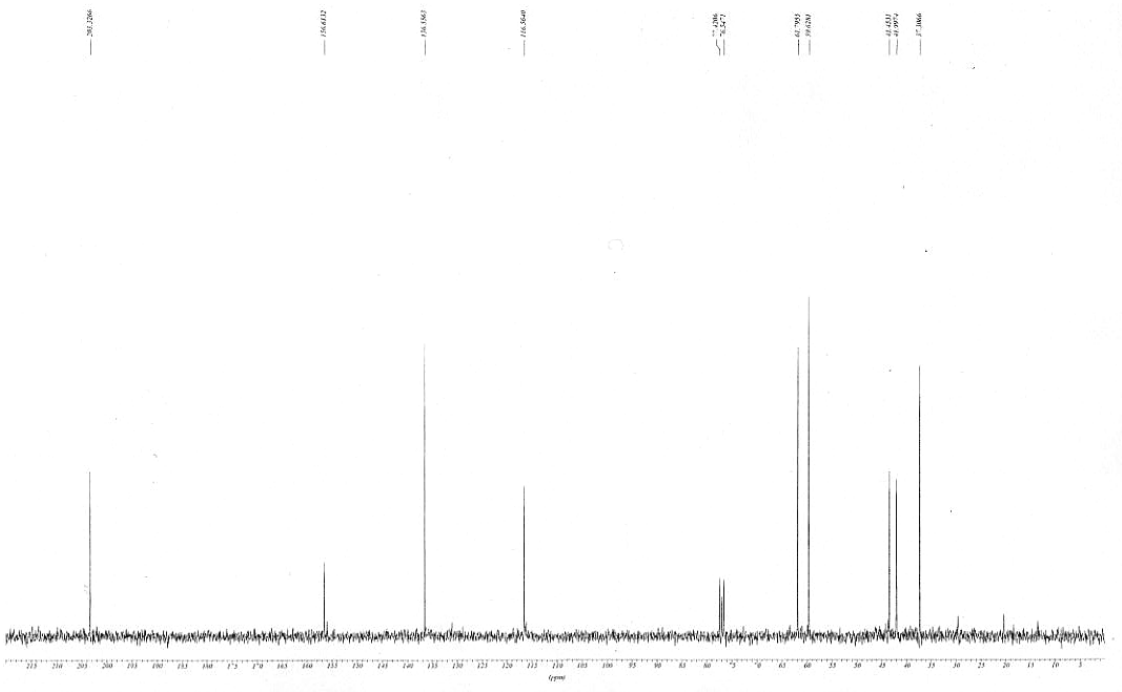
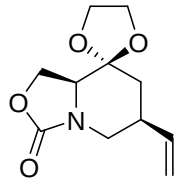
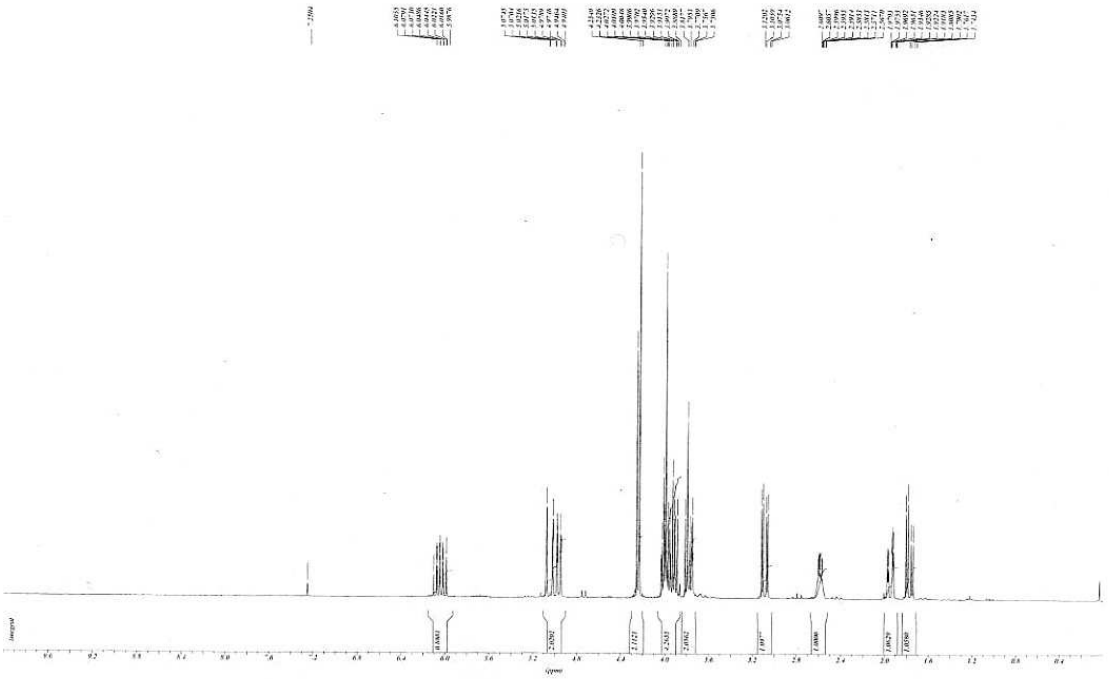
(ppm)

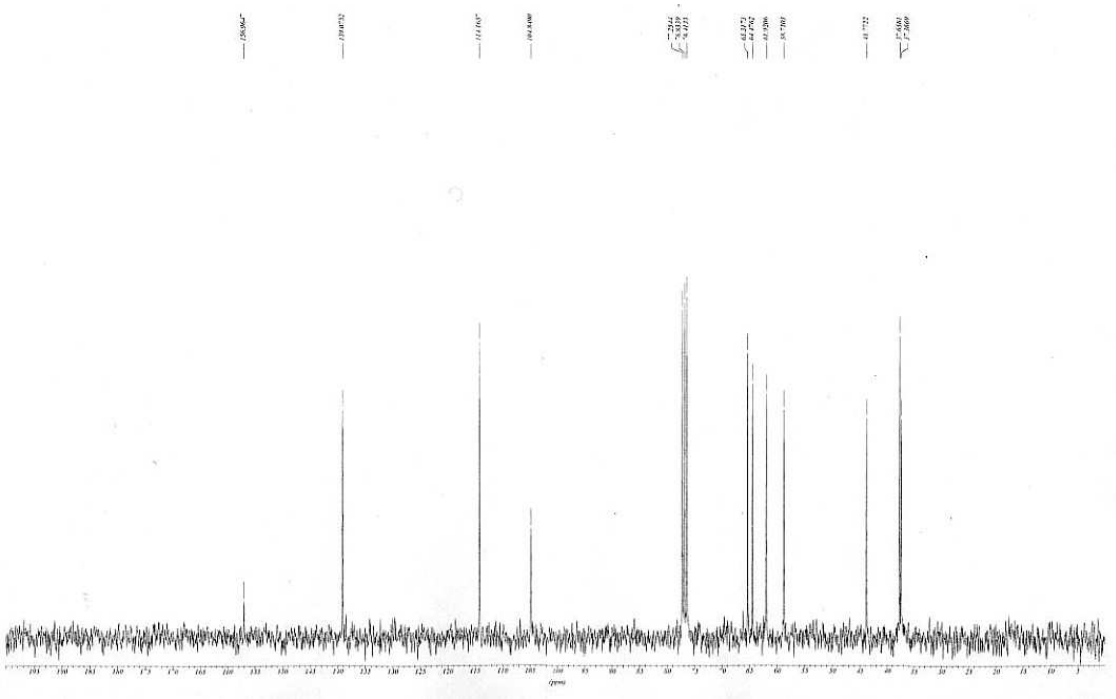


**(6'*S*,8a'*S*)-6'-Vinyltetrahydrospiro[[1,3]dioxolane-2,8'-oxazolo[3,4-a]pyridin]-3'(5'H)-one (12)**

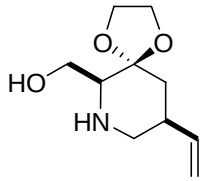


A solution of crude **11** and monohydrated PTSA (60 mg, 0.3 mmol) in 10 mL of $CH_2Cl_2$ is refluxed for 48 h using an inverted Dean-Stark apparatus. The mixture is then cooled to rt, filtered on anhydrous $K_2CO_3$, and concentrated under reduced pressure. The crude residue is purified on silica (Hexane/EtOAc 1/1) and recrystallized in $Et_2O$ to afford **12** (654 mg, 70%) as a white solid. $R_f$ = 0.18 (Hexane/EtOAc 1/1); $[\alpha]_D^{20}$ = +10 (c 1.2, MeOH); mp = 138-140°C; FTIR (KBr): $\nu_{max}$ 3076, 2894, 1735, 1439 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.12-5.98 (m, 1H), 5.09-4.93 (m, 2H), 4.27-4.21 (m, 2H), 4.04-3.86 (m, 4H), 3.83-3.74 (m, 2H), 3.09 (dd, *J* = 13.4 Hz and 4.2 Hz, 1H), 2.64-2.54 (m, 1H), 1.99-1.91 (m, 1H), 1.82-1.73 (m, 1H); $^{13}C$ NMR ($CDCl_3$): δ 157.1, 139.2, 114.3, 105.0, 65.5, 64.6, 62.1, 58.9, 43.9, 37.8, 37.5; LRSM (ESI-TOF): 226 [$M+H^+$] (100), 451 [$2M+H^+$] (19); 473 [$2M+Na^+$] (36); Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found C, 58.67; H, 6.63; N, 6.08; HPLC Analysis: Chiralpak AS (UV: 205 nm), Hexane/EtOH: 85/15, Flow rate: 1 mL/min, T=35°C, Retention time 17.4 min (ee > 99%).

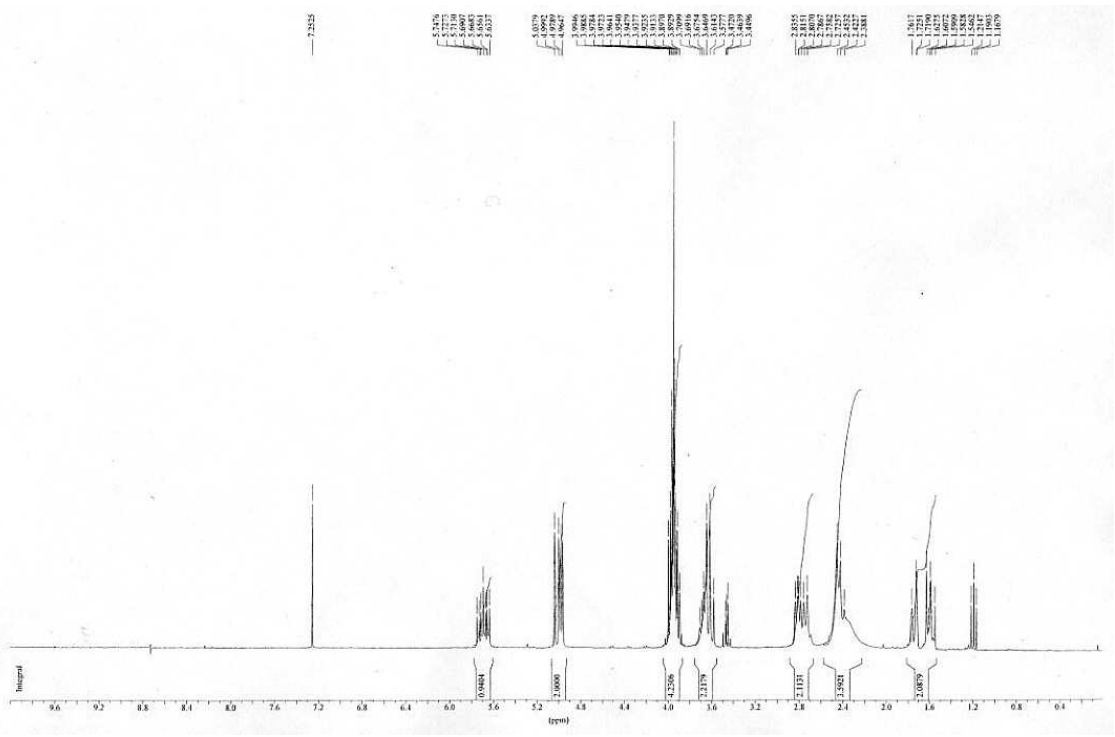


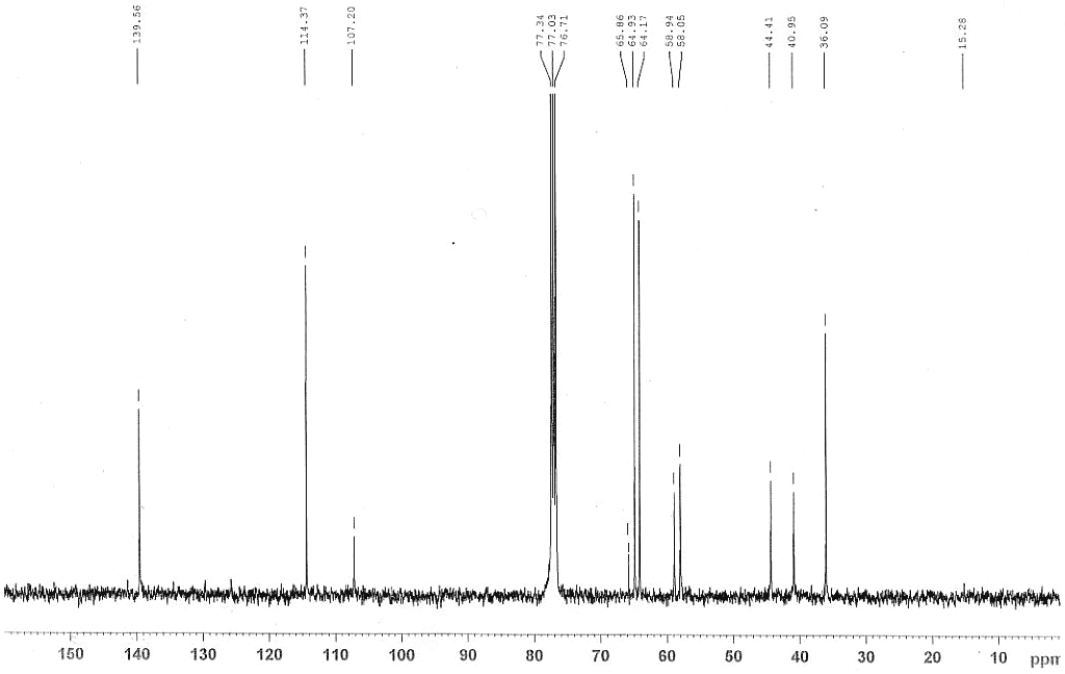


**((6*S*,9*S*)-9-Vinyl-1,4-dioxa-7-azaspiro[4.5]decan-6-yl)methanol (13)**




A solution of **12** (487 mg, 2.16 mmol, 1 equiv) and NaOH (450 mg, 5.2 equiv) in 18 mL of MeOH/$H_2O$ 2/1 is refluxed for 20 h. The reaction mixture is then cooled to rt and concentrated to one third. The aqueous layer is extracted with AcOEt (2x10 mL) and $CH_2Cl_2$ (2x10 mL). The organic layers are collected, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford **13** (411 mg, 95%) as a pale yellow oil. $R_f$ = 0.3 ($CH_2Cl_2$/MeOH 9/1); $[\alpha]_D^{20}$ = +5 (c 0.87, $CHCl_3$); FTIR (KBr): $\nu_{max}$ 3414, 3327, 2930, 2877, 2361, 1641, 1059, 906 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.77-5.62 (m, 1H), 5.08-4.94 (m, 2H), 4.04-3.85 (m, 4H), 3.73-3.56 (m, 2H), 2.81 (m, 1H), 2.56-2.24 (m, 3H), 1.74 (m, 1H), 1.59 (m, 1H); $^{13}C$ NMR ($CDCl_3$): δ 139.5, 114.3, 107.2, 64.9, 64.1, 58.9, 58.0, 44.4, 40.9, 36.0; LRMS (ESI-TOF): 200 [$M+H^+$] (82); 222 [$M+Na^+$] (100); 399 [$2M+H^+$] (44).

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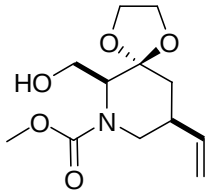
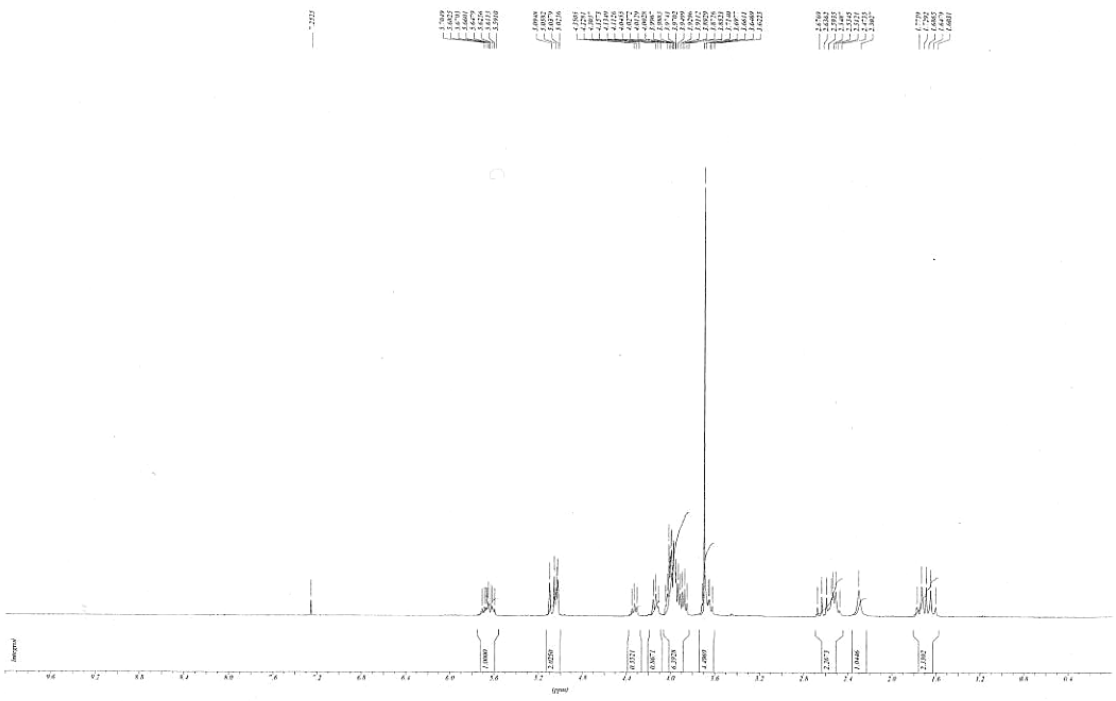
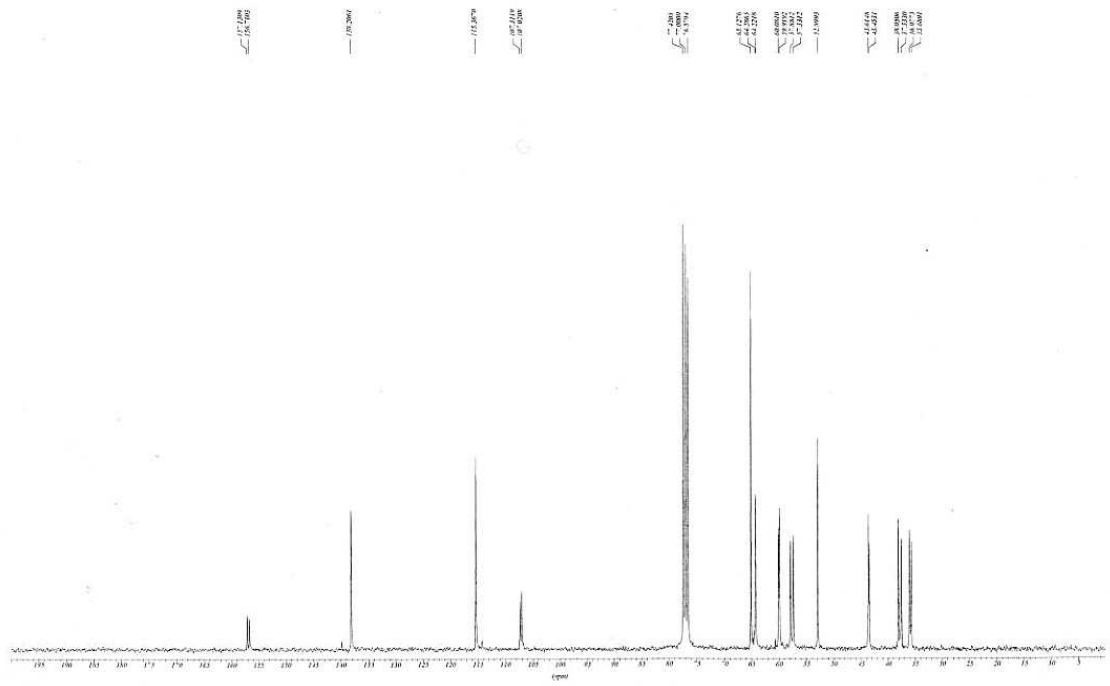
77.24
77.03
76.71
65.86
64.93
64.17
58.94
58.05
44.41
40.95
36.09
15.28
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

**(6*S*,9*S*)-Methyl 6-(hydroxymethyl)-9-vinyl-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (14)**

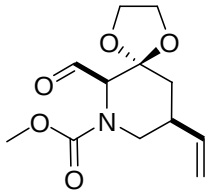



At rt, to a solution of **13** (411 mg, 2.06 mmol, 1 equiv) in 10 mL of THF is added $NaHCO_3$ (173 mg, 1 equiv) and, dropwise, methyl chloroformate (160 µL, 1 equiv). After 18 h the reaction mixture is filtered on a short pad of celite 545. The solvent is concentrated under reduced pressure. The crude residue is purified on silica (Hexane/AcOEt 1/1 → AcOEt) to give **14** (450 mg, 1.7 mmol, 81%) as an amorphous solid which is recrystallized at –20°C in $Et_2O$; $R_f$ = 0.2 (Hexane/AcOEt 3/7); $[\alpha]_D^{20}$ = +11 (c 0.8, MeOH); mp = 56-59°C; FTIR (film): $\nu_{max}$ 3447, 1692, 1458 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) Rotamers A/B 8/5: δ 5.72-5.58 (m, 1H), 5.11-5.01 (m, 2H), 4.38-4.28 (m, 1H B), 4.18-4.08 (m, 1H A), 4.07-3.84 (m, 6H), 3.73-3.61 (m, 1H), 3.69 (s, 3H), 2.70-2.44 (m, 2H), 2.30 (bs, 1H, OH), 1.81-1.58 (m, 2H); $^{13}C$ NMR ($CDCl_3$) Rotamers : δ 157.1, 156.7, 138.2, 115.3, 107.3, 65.1, 64.2 60.0, 59.9, 57.8, 57.3, 52.8 , 43.6, 43.4, 38.0, 37.5, 36.0, 35.7; LRMS (TOF) : 258 $[M+H^+]$ (4); 280 $[M+Na^+]$ (100); 537 $[2M+Na^+]$ (4); Anal. Calcd for $C_{12}H_{19}NO_5$: C 56.02, H 7.44, N 5.44; Found C 56.13, H 7.55, N 5.45.

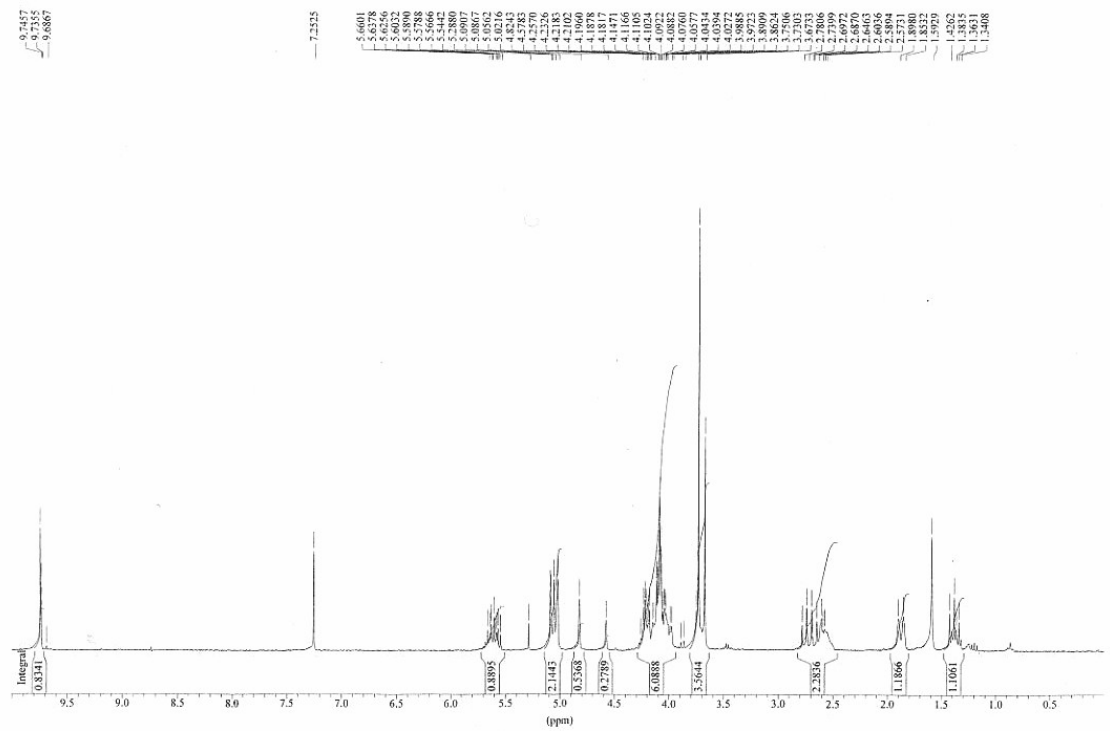


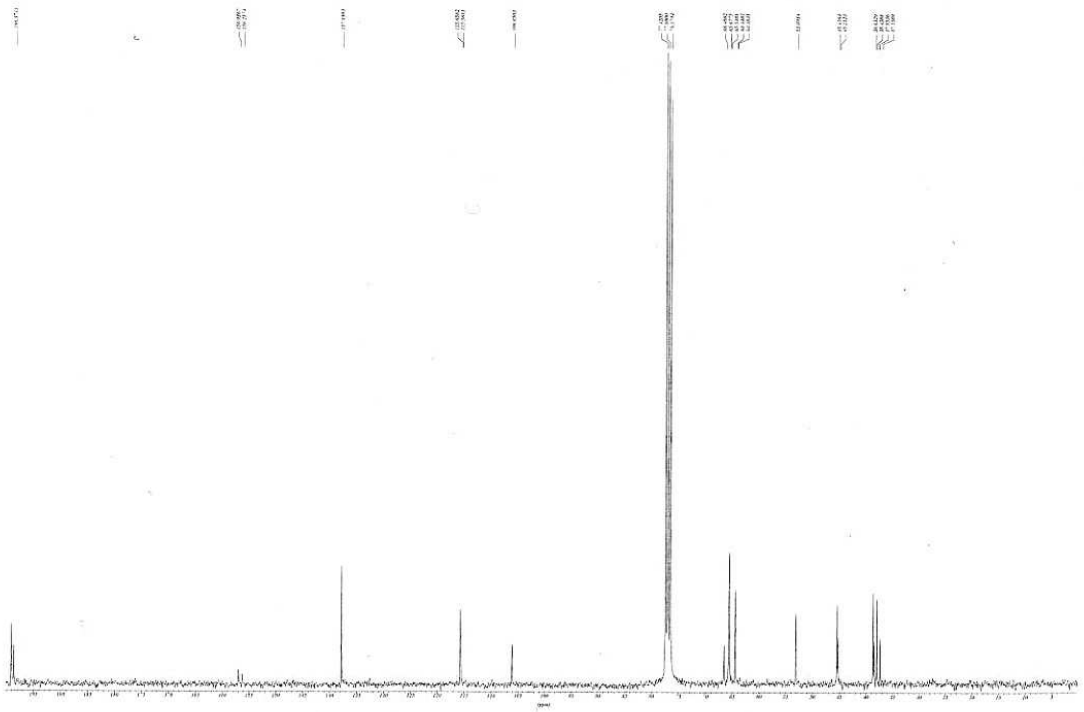


**(6*S*,9*S*)-Methyl 6-formyl-9-vinyl-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (15)**

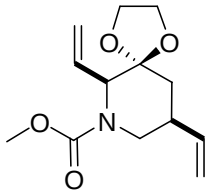


To a solution of **14** (217 mg, 0.84 mmol, 1 equiv) in 10 mL of $CH_2Cl_2$ is added, at 0°C, NMO (150 mg, 1.3 equiv), 4 Å molecular sieves (500 mg) and TPAP (50 mg, 0.16 equiv). After 1 h at rt, the reaction mixture is filtered on a short pad of celite 545 and concentrated under reduced pressure. The crude is purified on silica (Hexane/EtOAc 1/1) to afford **15** (160 mg, 0.6 mmol, 75%) as a colorless oil; $R_f$= 0.4 (Hexane/EtOAc 1/1); $[\alpha]_D^{20}$ = -170 (c 0.9, $CHCl_3$); FTIR (film): $\nu_{max}$ 1731, 1699, 1449 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) mixture of A and B rotamers (2/1): δ 9.74 (s, 1H A), 9.73 (s, 1H B), 5.70-5.53 (m, 1H), 5.12-5.00 (m, 2H), 4.82 (s, 1H A), 4.57 (s, 1H B), 4.28-3.94 (m, 5H), 3.73 (s, 3H A), 3.67 (s, 3H B), 2.80-2.48 (m, 2H), 1.86-1.80 (m, 1H), 1.45-1.29 (m, 1H); $^{13}C$ NMR ($CDCl_3$): δ 198.5, 198.1, 156.9, 156.2, 137.8, 115.6, 115.5, 106.0, 66.4, 65.6, 65.5, 64.4, 64.3, 53.0, 45.4, 45.2, 38.6, 38.4, 37.9, 37.3; LRMS (ESI TOF): 278 [$M+Na^+$] (35); 294 [$M+K^+$] (100).

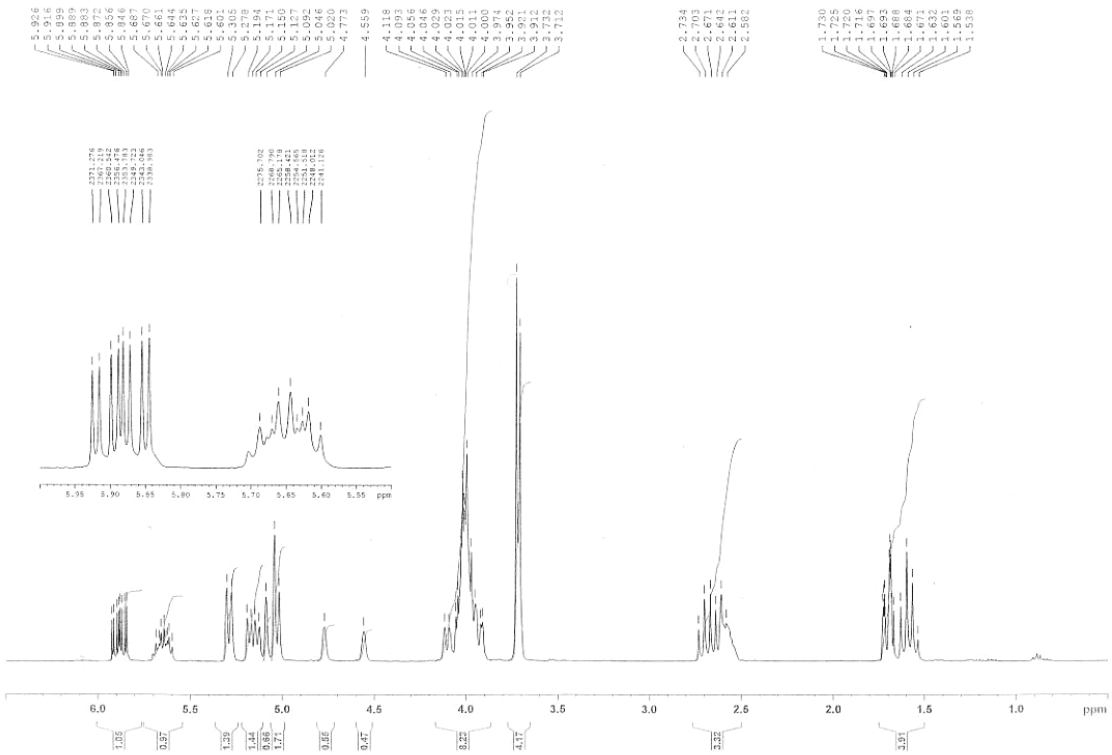

Integral
0.8341
0.8895
2.1443
0.5368
0.2789
6.0858
3.5644
2.2836
1.1866
1.1061
(ppm)

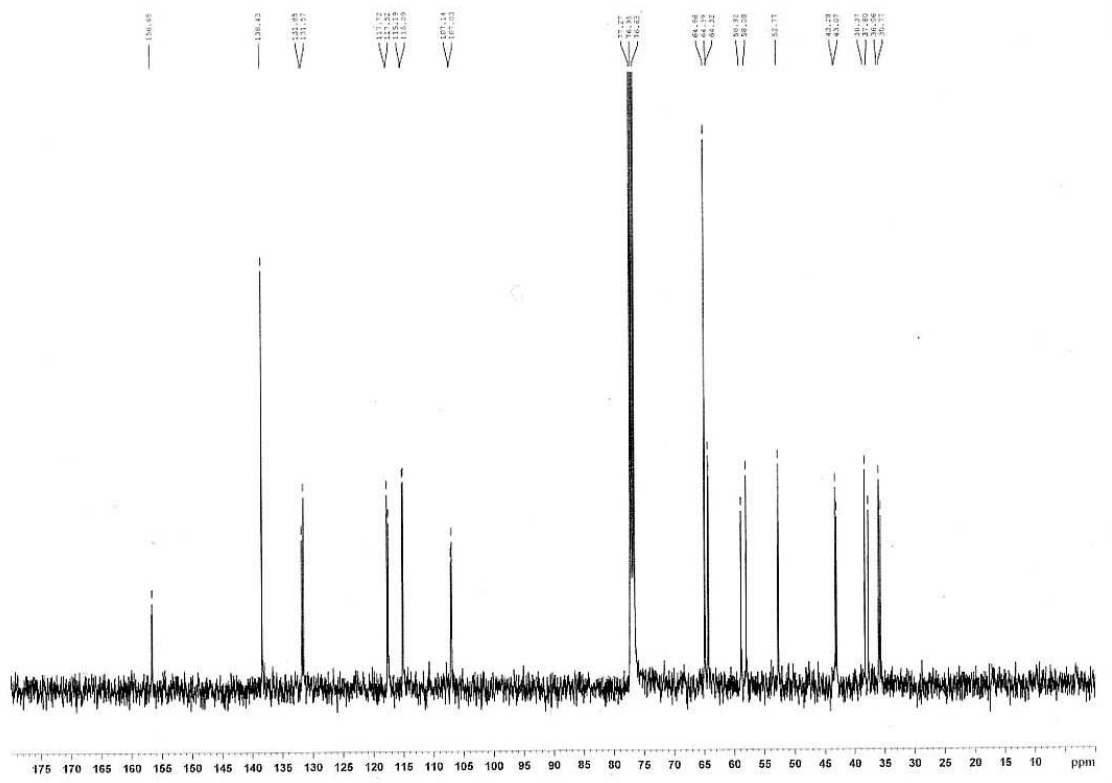


**(6*S*,9*S*)-Methyl 6,9-divinyl-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (16)**

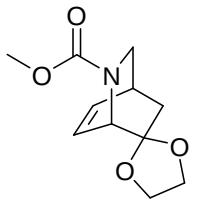


At -60°C, to a solution of **15** (540 mg, 2.1 mmol, 1 equiv) in 10 mL of THF is added dropwise, Tebbe's reagent (5 mL of a 0.5 M soln in toluene, 1.2 equiv). After 1 h, 0.1 mL of 15% NaOH is added dropwise at –10°C. The reaction mixture is then filtered on a pad of celite 545 and concentrated under reduced pressure. The crude is purified on silica (Hexane/EtOAc 8/2) to afford **16** (446 mg, 83%) as a colorless oil; $R_f$ = 0.6 (Hexane/EtOAc 1/1); $[\alpha]_D^{20}$ = -30 (c 1.0, MeOH); FTIR (film): $\nu_{max}$ 3082, 2954, 2928, 1705, 1642, 1452 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) mixture of A and B rotamers (1/1): δ 5.94-5.82 (m, 1H), 5.71-5.59 (m, 1H), 5.34-4.98 (m, 4H), 4.80-4.74 (m, 1H A), 4.59-4.53 (m, 1H B), 4.18-3.84 (m, 4H), 3.73 (s, 3H A), 3.71 (s, 3H B), 2.76-2.50 (m, 2H), 1.76-1.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 156.7, 138.5, 131.9, 131.6, 117.7, 117.5, 115.2, 107.1, 65.0, 64.3, 59.0, 58.1, 52.8, 43.3, 43.2, 38.4, 37.8, 36.1, 35.8; LRMS (ESI-TOF): 276 [$M+Na^+$] (100); 292 [$M+K^+$] (54); 529 [$2M+Na^+$] (19); 545 [$2M+K^+$] (25).

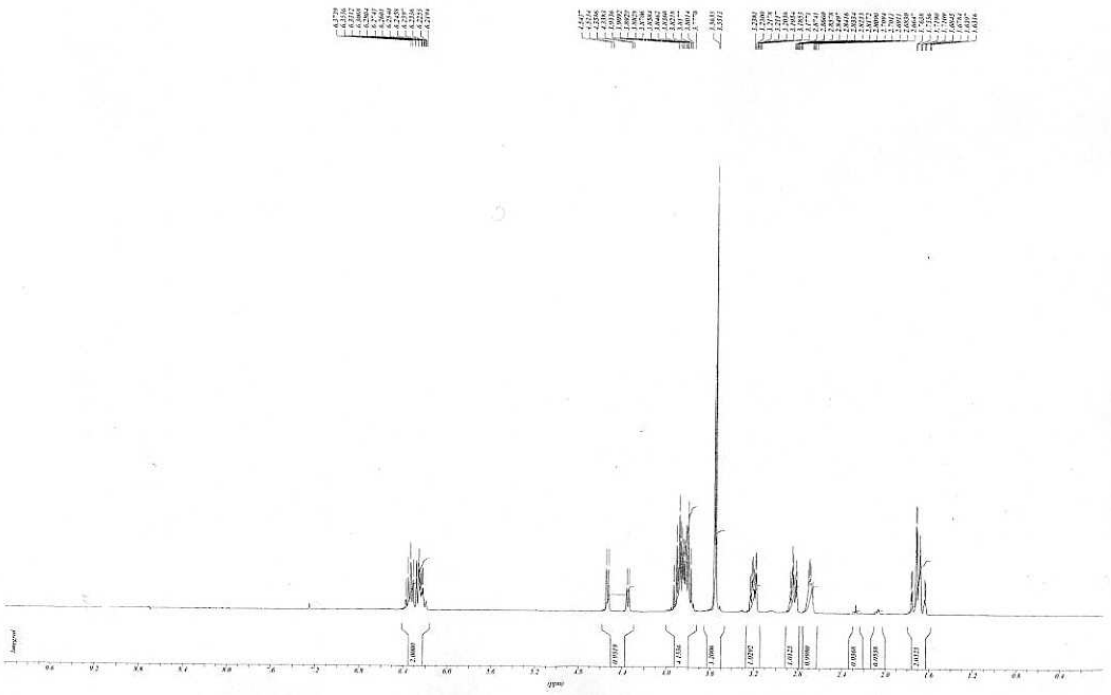


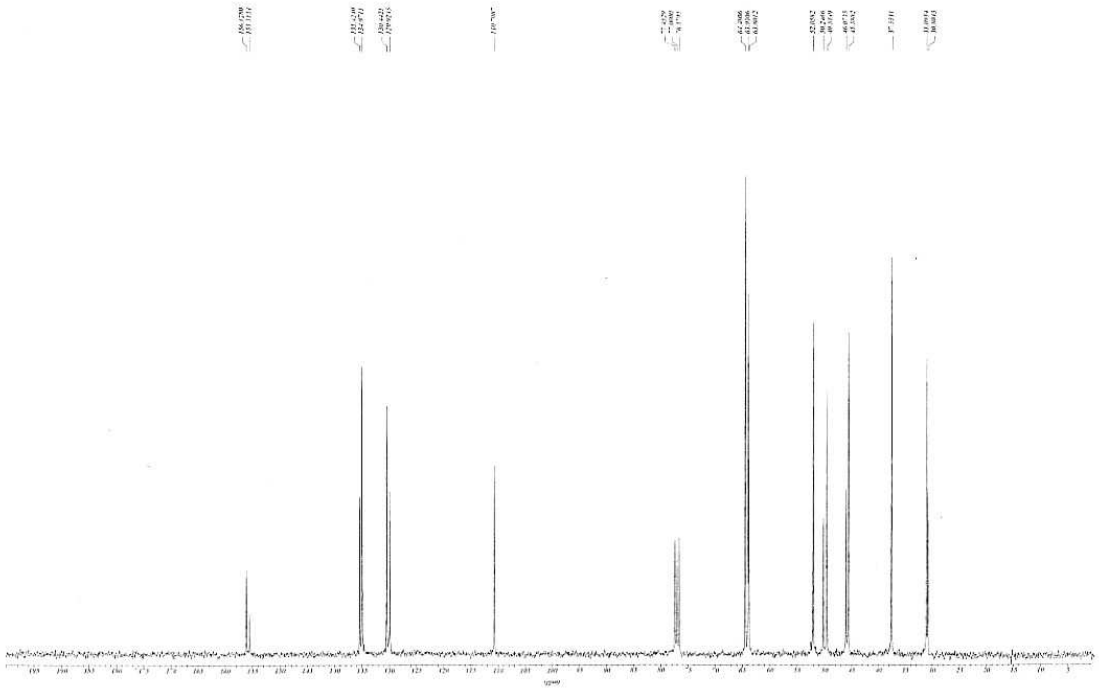


**Methyl 2-azaspiro[bicyclo[2.2.2]oct[5]ene-7,2'-[1,3]dioxolane]-2-carboxylate (17)**

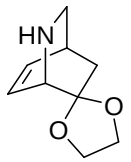


To a solution of **16** (207 mg, 0.81 mmol, 1 equiv) in 15 mL of $CH_2Cl_2$ is added 60 mg of the second generation of Grubbs catalyst (0.1 equiv). After 20 h under reflux, the solvent is removed under reduced pressure. The crude is purified on silica (Hexane/EtOAc 6/4 → 1/1) to afford **17** (154 mg, 84%) as a white solid; $R_f$ = 0.3 (Hexane/AcOEt 1/1); $[\alpha]_D^{20}$ = +70 (c 0.4, MeOH); FTIR (film): $\nu_{max}$ 3568, 2959, 2886, 1697 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) mixture of A and B rotamers (2/1): δ 6.39-6.18 (m, 2H), 4.53 (d, *J* = 6.1 Hz, 1H A), 4.34 (d, *J* = 6.1 Hz, 1H B), 3.97-3.73 (m, 4H), 3.56 (s, 3H B), 3,55 (s, 3H A), 3,25-3,16 (m, 1H), 2.89-2.80 (m, 1H), 2.74-2.65 (m, 1H), 1.78-1.61 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 156.1, 155.5, 135.4, 134.9, 130.4, 129.9, 110.7, 64.4, 63.9, 63.8, 52.0, 50.2, 49.5, 46.0, 45.5, 37.5, 31.1, 30.8; HRMS (TOF MS ES+): Calcd for $C_{11}H_{15}NO_4Na$ ($M+Na^+$) 248.0899; Found 248.0903; Anal. Calcd for $C_{11}H_{15}NO_4$ C 58.66, H 6.71, N 6.22; Found C 58.39, H 6.83, N 6.13; HPLC Analysis: Chiralcel OD (UV: 220 nm), Hexane/iPrOH: 95/5, Flow rate: 0.8 mL/min, T=35°C, Retention time: 15.4 min (ee > 99%).

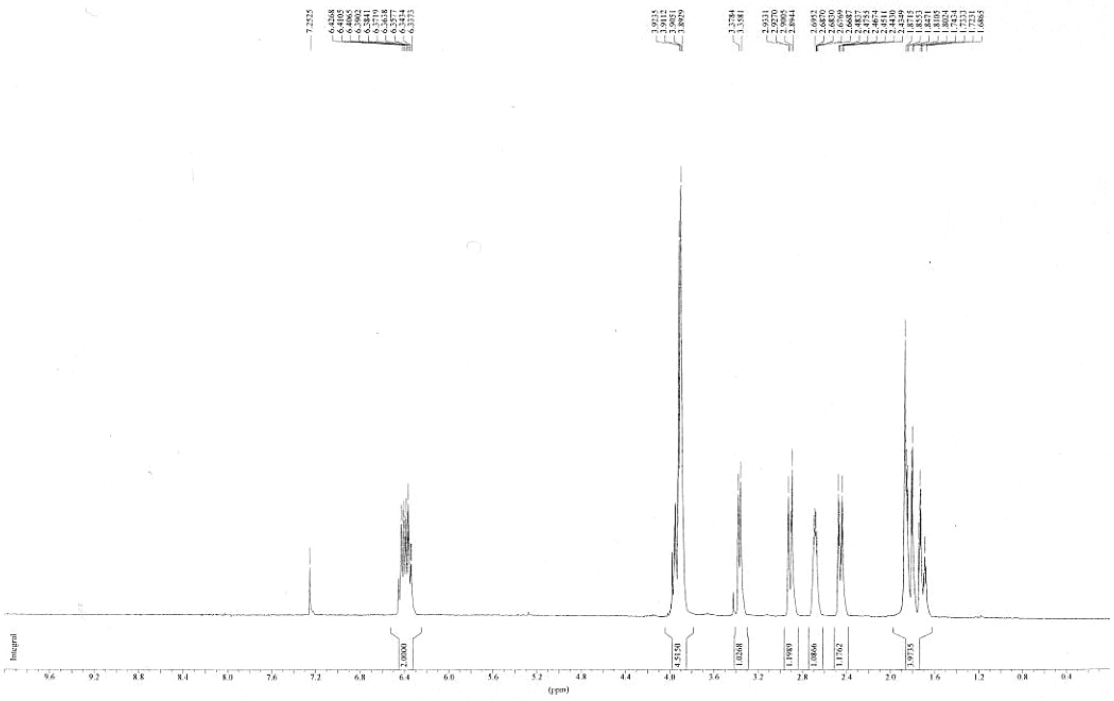


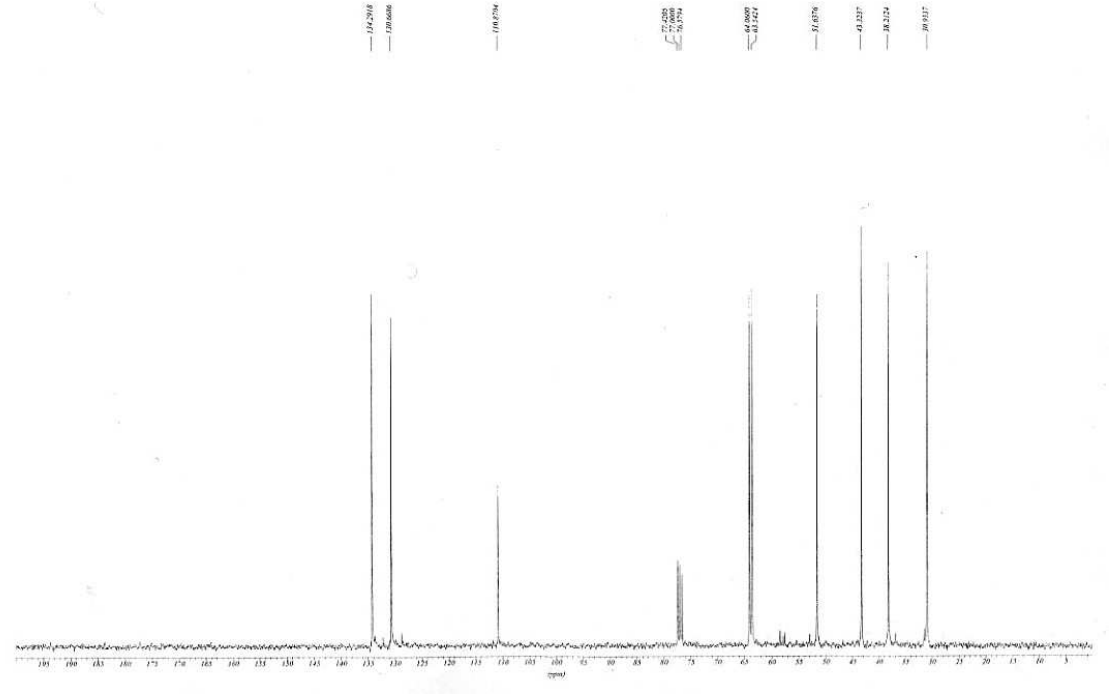


**2-Azaspiro[bicyclo[2.2.2]oct[5]ene-7,2'-[1,3]dioxolane] (18)**

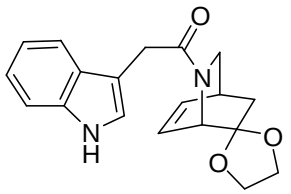



At 0°C, to a solution of **17** (236 mg, 1.05 mmol, 1 equiv) in 8 mL of $Et_2O$ is added dropwise a solution of MeLi (1.7 mL of a 1.6 M soln in $Et_2O$, 2.6 equiv). After 90 min at 0°C, a saturated solution of $NH_4Cl$ (0.5 mL) is added followed by 1 mL of 15% NaOH. The aqueous phase is extracted with EtOAc (2x10 mL) and $CH_2Cl_2$ (10 mL). The organic layer is collected, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude is purified on silica ($CH_2Cl_2$ → $CH_2Cl_2$/MeOH 95/5 → $CH_2Cl_2$ saturated with $NH_3$) to afford **18** (130 mg, 74%) as pale yellow oil. $R_f$ = 0.05 ($CH_2Cl_2$/MeOH 9/1); $[\alpha]_D^{20}$ = -55 (c 1.3, $CHCl_3$) FTIR (film): $\nu_{max}$ 3418, 2966, 2897, 1646, 1533, 1416 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.44-6.28 (m, 2H), 3.93-3.85 (m, 4H), 3.39 (d, *J* = 5.4 Hz), 3.01 (brs, 1H, NH), 2.88 (dd, *J* = 9.7 Hz and 2.4 Hz, 1H), 2.72-2.63 (m, 1H), 2.44 (dt, *J* = 9.7 Hz and 2.4 Hz, 1H), 1.83-1.68 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 134.2, 130.6, 110.8, 64.0, 63.5, 51.6, 43.3, 38.2, 30.9; LRMS (ESI-TOF): 168 [$M+H^+$] (100).

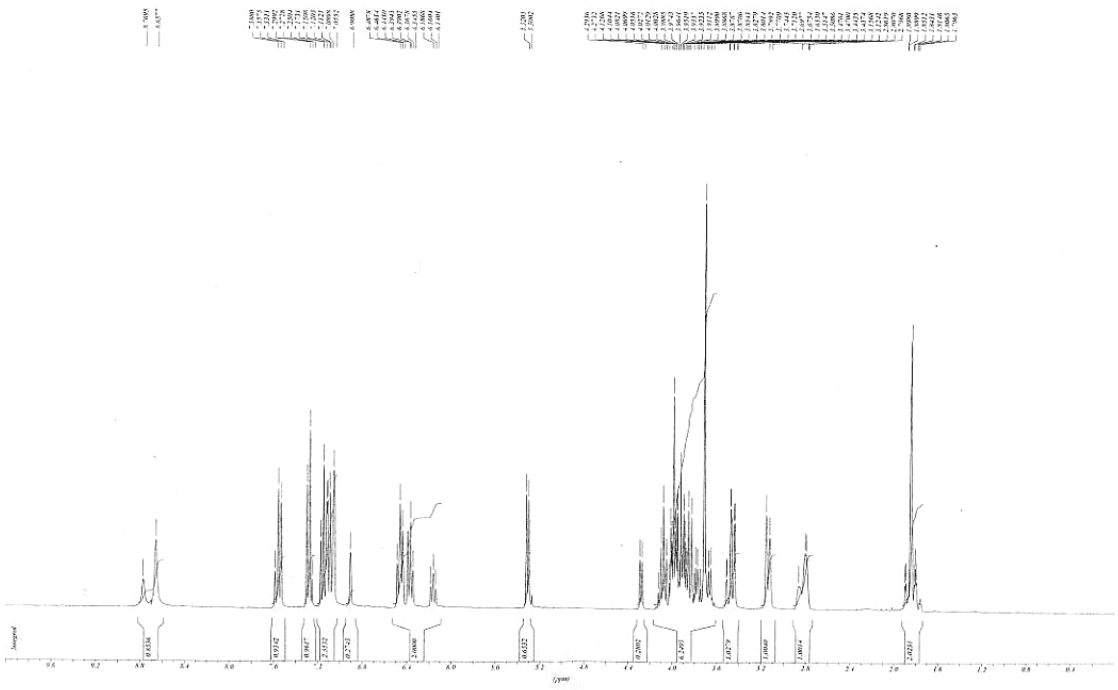


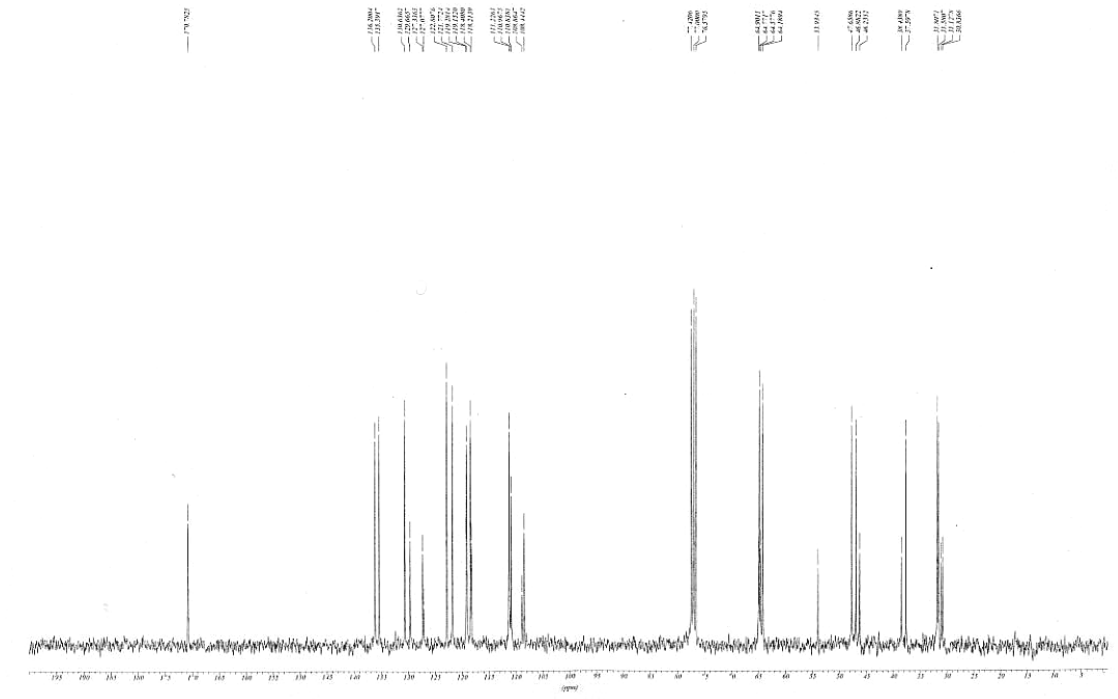


**2-(1H-Indol-3-yl)-1-(2-azaspiro[bicyclo[2.2.2]oct[7]ene-6,2'-[1,3]dioxolane]-2-yl)ethanone (19)**

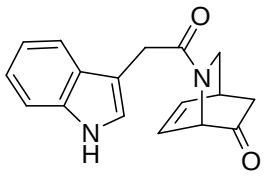


To a solution of **18** (170 mg, 1.0 mmol, 1 equiv) in 20 mL of $CH_2Cl_2$ is added indole carboxylic acid (182 mg, 1 equiv) and EDCI (190 mg, 1 equiv). After 1 h, $CH_2Cl_2$ (100 mL) is added and the mixture is washed successively with HCl 0.01 M (5 mL) and 5 mL of saturated $K_2CO_3$. The organic phase is dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude is purified on silica (EtOAc) to afford **19** (305 mg, 94%) as a white solid. $R_f$ = 0.3 ($CH_2Cl_2$/MeOH 95/5); $[\alpha]_D^{20}$ = +45 (c 1.3, $CHCl_3$); $^1$H NMR ($CDCl_3$) mixture of A and B rotamers (5/2): δ 8.83-8.60 (m, 1H, NH), 7.62-7.50 (m, 1H), 7.33-7.23 (m, 1H), 7.20-7.06 (m, 2H), 7.06-7.02 (m, 1H A), 6.93-6.88 (m, 1H B), 6.51-6.42 (m, 1H), 6.41-6.32 (m, 1H A), 6.21-6.11 (m, 1H B), 5.31 (d, $J$ = 6.1 Hz, 1H A), 4.28 (d, $J$ = 6.1 Hz, 1H B), 4.16-3.60 (m, 6H), 3.54-3.41 (m, 1H), 3.19-3.08 (m, 1H), 2.91-2.74 (m, 1H), 1.93-1.72 (m, 2H); $^{13}$C NMR ($CDCl_3$): δ 170.7, 136.2, 135.3, 130.6, 129.6, 127.3, 127.0, 122.8, 121.7, 119.2, 119.1, 118.4, 118.2, 111.2, 110.9, 110.8, 108.8, 108.4, 64.9, 64.7, 64.5, 64.1, 53.9, 47.6, 46.8, 46.2, 38.4, 37.5, 31.8, 31.5, 31.1, 30.8; FTIR (film): $\nu_{max}$ 3272, 3056, 2970, 2885, 1630, 1434 cm$^{-1}$; HRMS (TOF MS ES+): Calcd for $C_{19}H_{20}N_2O_3Na$ 347.1372; Found 347.1368; Anal. Calcd for $C_{19}H_{20}N_2O_3$ C 70.35, H 6.21, N 8.64; Found C 70.24, H 6.29, N 8.56; HPLC Analysis: Chiralcel OD (UV: 220 nm), Hexane/EtOH: 95/5, Flow rate: 1 mL/min, T=35°C, Retention time: 64.5 min (ee > 99%).

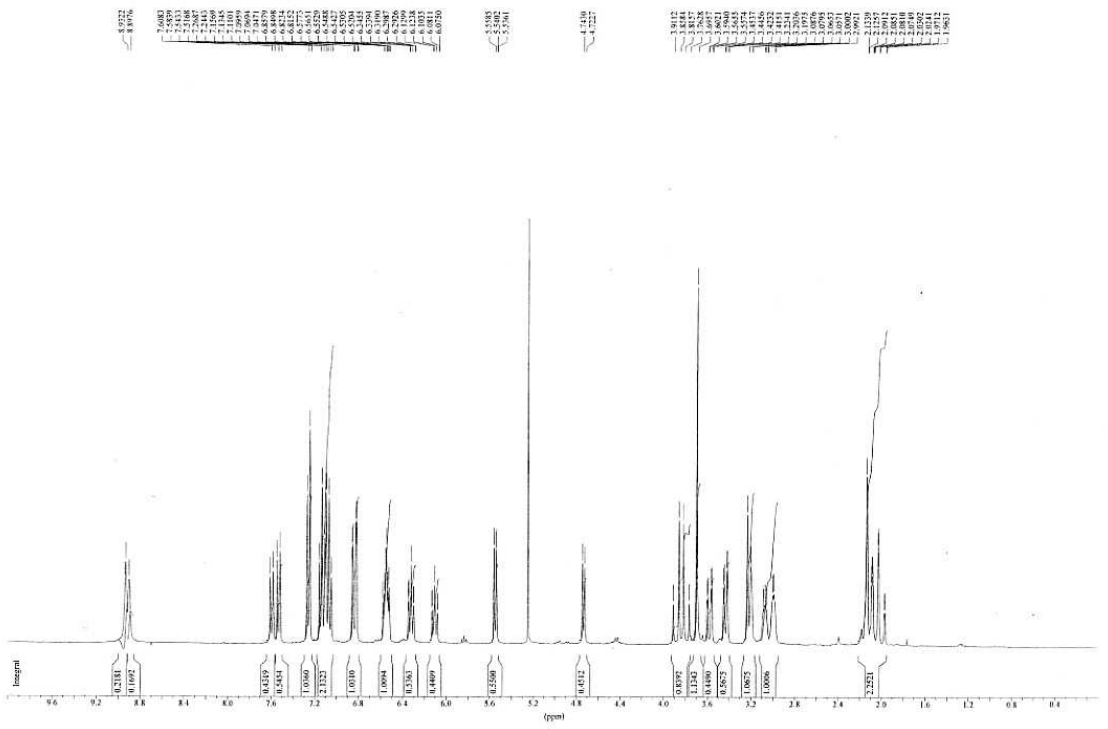


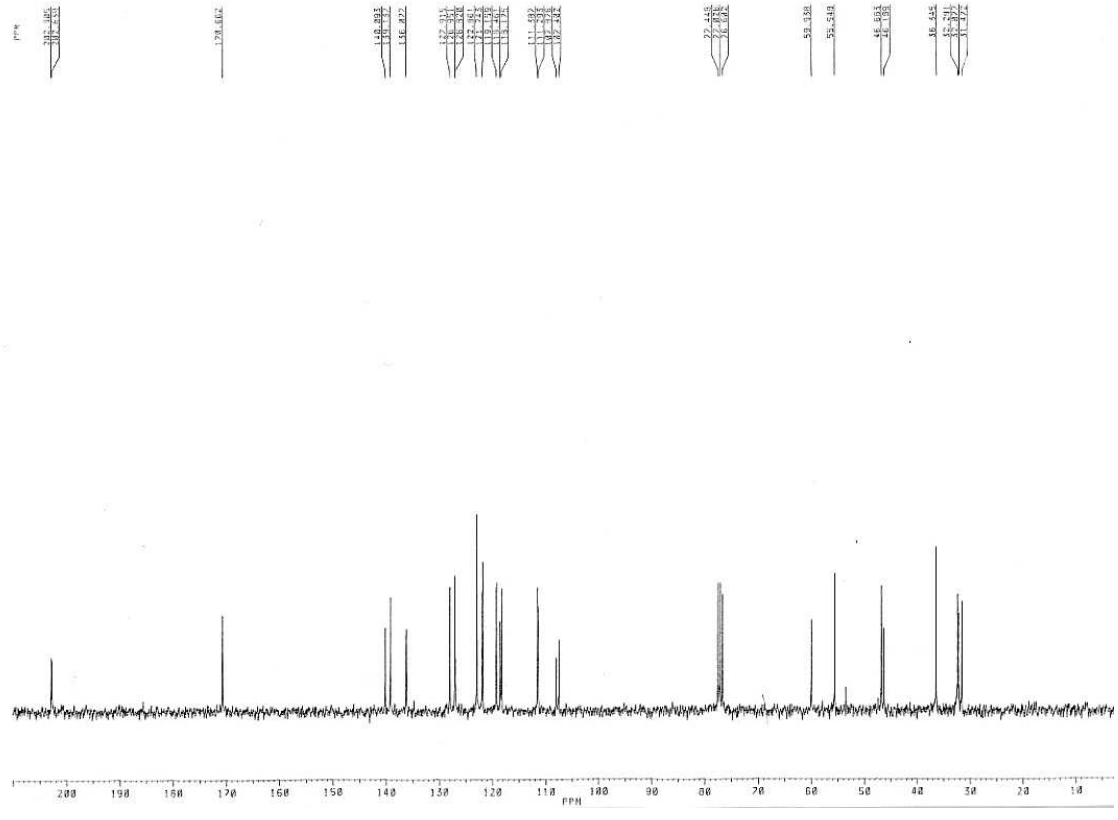


**2-(2-(1H-Indol-3-yl)acetyl)-2-azabicyclo[2.2.2]oct-7-en-6-one (20)**

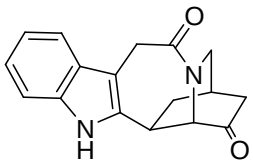


To a solution of **19** (305 mg, 0.94 mmol, 1 equiv) in 4 mL of acetone, are added PTSA (30 mg, 0.1 equiv) and water (0.15 mL). After 96 h at 60°C, anhydrous $K_2CO_3$ is added. The mixture is vigorously stirred for 15 min, filtrated and concentrated under reduced pressure. The crude is purified on silica ($CH_2Cl_2$/MeOH 100/0 → 98/2) to afford **20** (233 mg, 88%) as a white solid; $R_f$ = 0.3 ($CH_2Cl_2$/MeOH 95/5); $[\alpha]_D^{20}$ = -61 (c 1.2, $CHCl_3$); FTIR (KBr): $\nu_{max}$ 3277, 3055, 2924, 1732, 1634, 1413 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) mixture of A and B rotamers (55/45): δ 8.95-8.87 (m, 1H, NH), 7.59 (d, *J* = 7.9 Hz, 1H B), 7.53 (d, *J* = 7.9 Hz, 1H A), 7.25 (d, *J* = 7.3 Hz, 1H), 7.19-7.02 (m, 2H), 6.85 (d, *J* = 2.4 Hz, 1H B), 6.81 (d, *J* = 2.4 Hz, 1H A), 6.61-6.49 (m, 1H), 6.37-6.27 (m, 1H A), 6.15-6.05 (m, 1H B), 5.54 (d, *J* = 6.1 Hz, 1H A), 4.73 (d, *J* = 6.1 Hz, 1H B), 3.88 (d, *J* = 15.8 Hz, 1H B), 3.78 (d, *J* = 15.8 Hz, 1H B), 3.69 (s, 1H A), 3.58 (dd, *J* = 10.9 Hz and 2.4 Hz, 1H B), 3.43 (dd, *J* = 9.1 Hz and 2.4 Hz, 1H A), 3.27-3.15 (m, 1H), 3.12-3.04 (m, 1H B), 3.03-2.95 (m, 1H A), 2.23-1.93 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 202.8, 202.6, 170.6, 140.1, 139.1, 136.0, 127.9, 126.9, 126.8, 122.8, 121.7, 119.1, 118.4, 118.1, 111.3, 111.2, 107.8, 107.4, 59.9, 55.5, 46.6, 46.1, 36.3, 32.2, 32.0, 31.4; HRMS (TOF MS ES+): Calcd for $C_{17}H_{16}N_2O_2Na$: 303.1109; Found 303.1120; HPLC Analysis: Chiralcel OD (UV: 220 nm), Hexane/EtOH: 85/15, Flow rate: 1 mL/min, T=35°C, Retention time: 25.2 min (ee>99%).

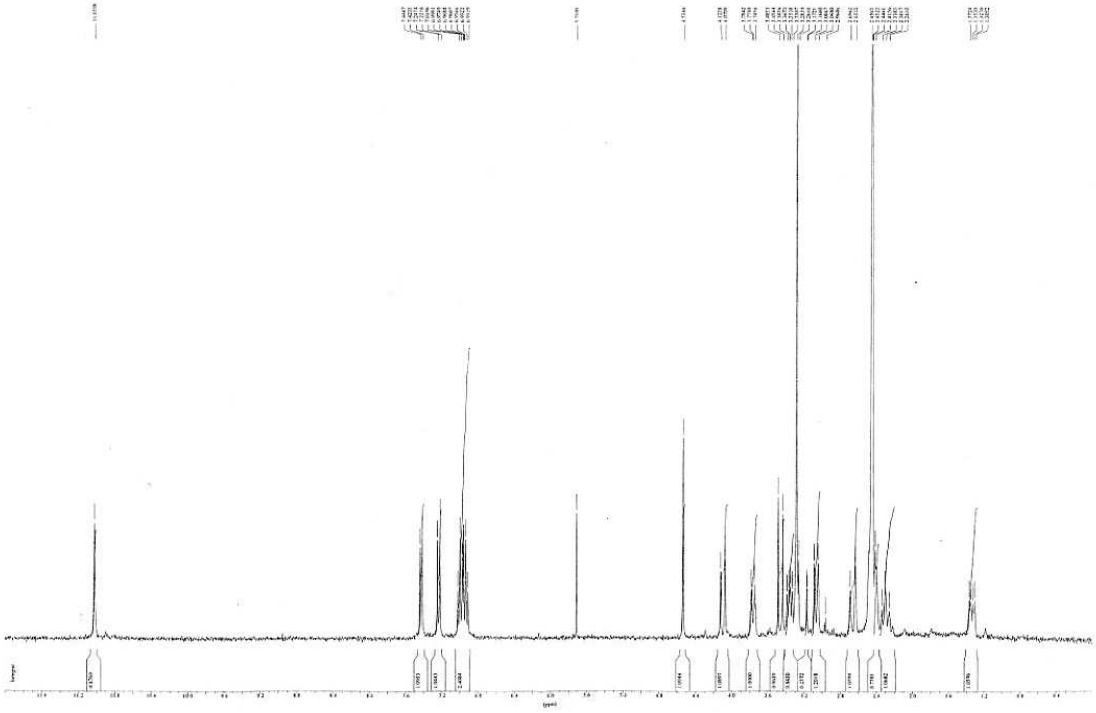


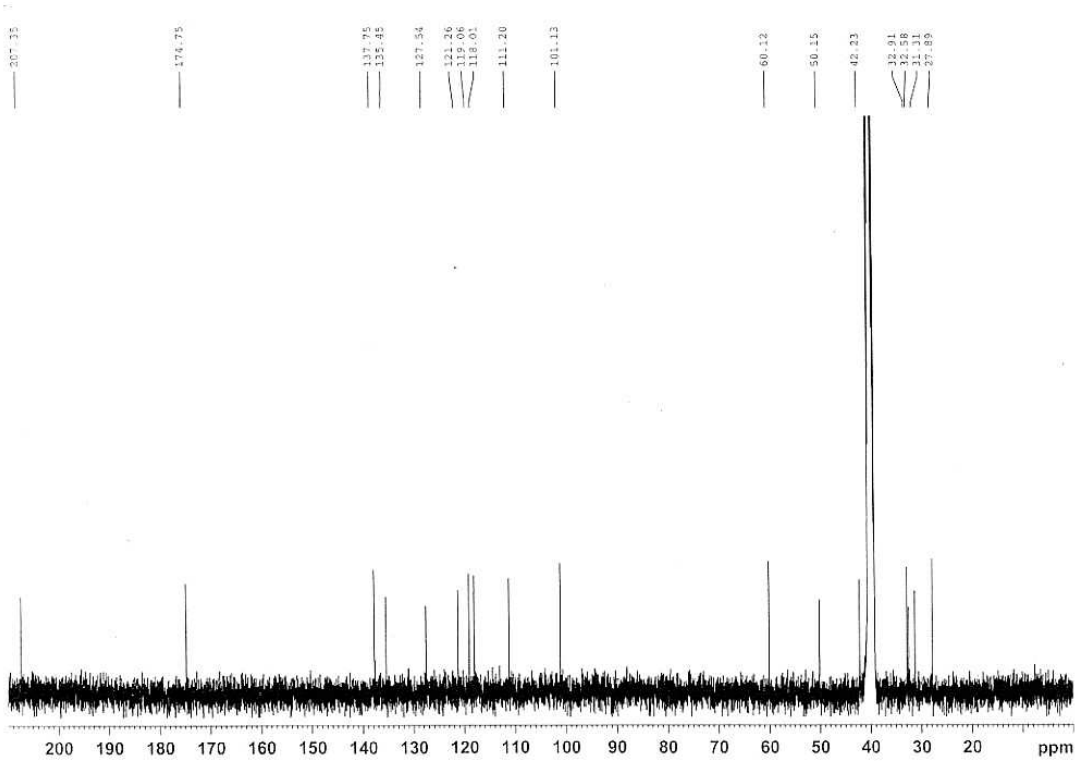


**Ketone (21)**

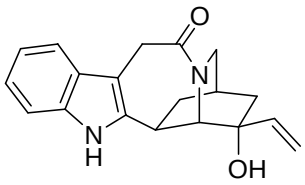



To a suspension of $(CH_3CN)_2PdCl_2$ (75 mg, 1.3 equiv) and $AgBF_4$ (80 mg, 1.4 equiv) in 3 mL of $CH_3CN$ is added a solution of **20** (63 mg, 0.22 mmol, 1 equiv) in 8 mL of $CH_3CN$. After 1 h at rt, the mixture is stirred at 70°C for 18 h. The reaction is then cooled to 0°C and MeOH (2 mL) is added followed by $NaBH_4$ (27 mg, 3.2 equiv). After decantation of $Pd^0$ salts, the mixture is filtered over a pad of celite 545 and concentrated under reduced pressure. The crude is then filtered again over silica ($CH_2Cl_2$/MeOH 98/2) to afford **21** (white solid) which is involved in the next step without further purification. $R_f$ = 0.2 ($CH_2Cl_2$/MeOH 9/1); FTIR (film): $\nu_{max}$ 3275, 2940, 1742, 1632, 1460, 1038, 738 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 11.02 (s, 1H, NH), 7.44 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.04-6.90 (m, 2H), 4.53 (s, 1H), 4.10 (d, *J* = 15.8 Hz, 1H), 3.76 (m, 1H), 3.46 (d, *J* = 15.2 Hz, 1H), 3.36 (m, 1H), 3.07 (d, *J* = 11.6 Hz, 1H), 2.66 (d, *J* = 18.9 Hz, 1H), 2.52-2.38 (m, 2H), 2.30 (m, 1H), 1.34 (m, 1H); $^{13}C$ NMR (DMSO-$d_6$): δ 208.3, 175.7, 138.7, 136.5, 128.5, 122.3, 120.1, 119.0, 112.2, 102.2, 61.2, 51.2, 43.3, 33.9, 33.6, 32.3, 32.3, 28.9; LRMS (ESI TOF): 281 [$M+H^+$] (100).

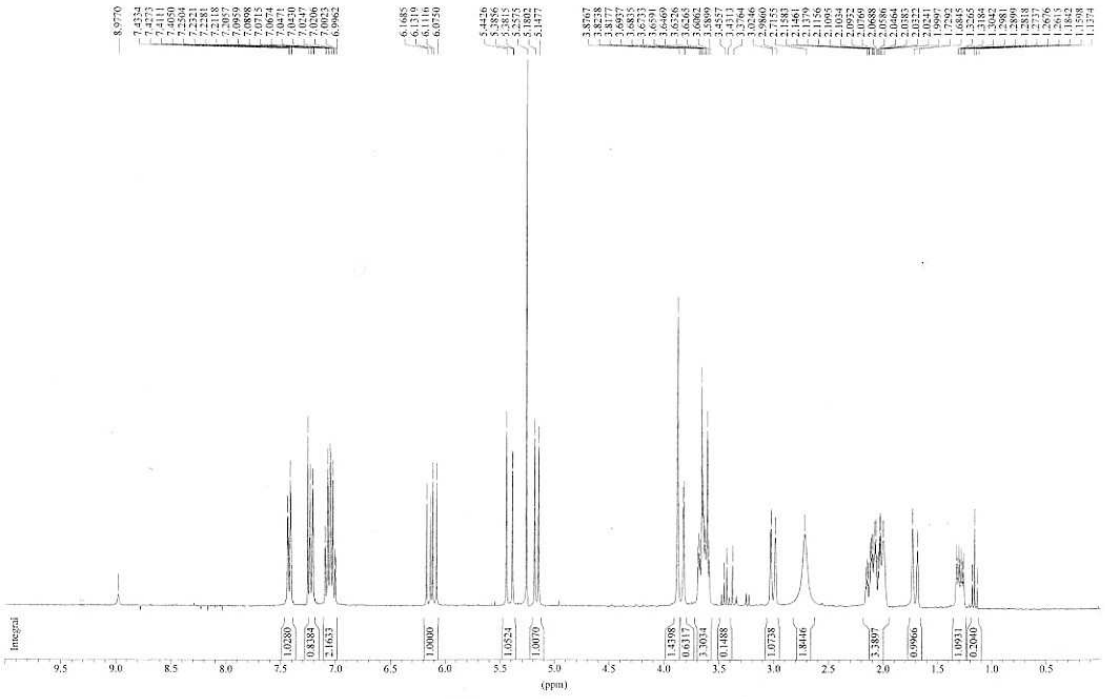


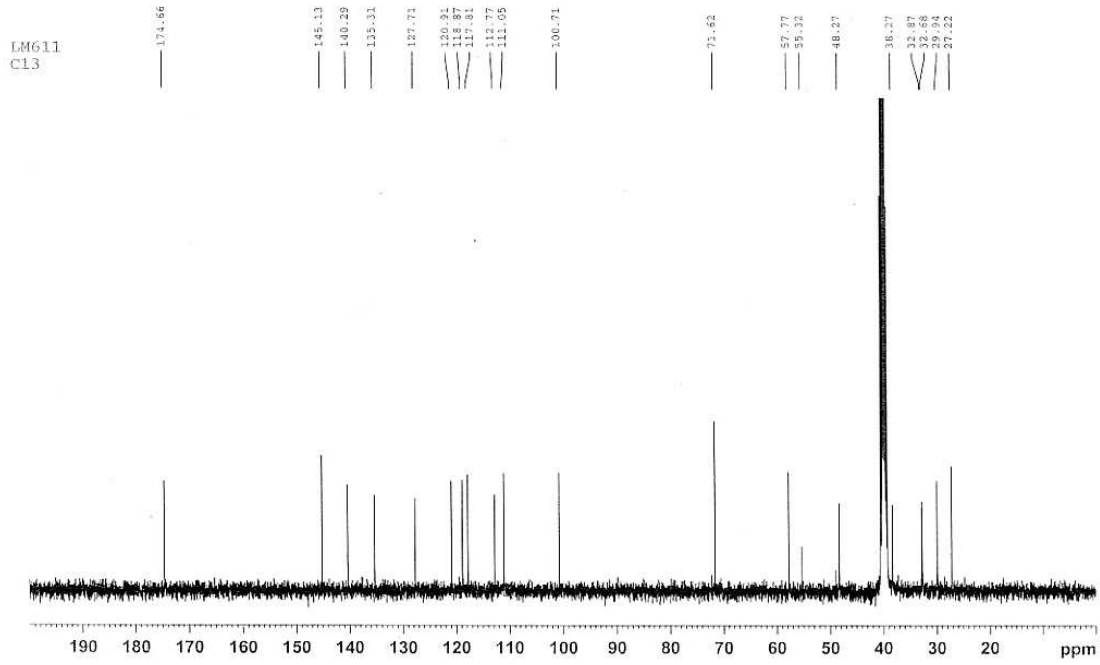

207.35
174.75
137.75
135.45
127.54
121.26
119.06
118.01
111.20
101.13
60.12
50.15
42.23
32.91
32.58
31.31
27.89
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**Allylic alcohol (22)**

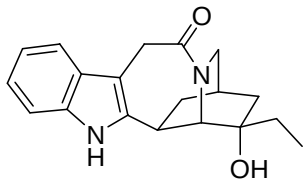



To a solution of **21** (45 mg, 0.16 mmol, 1 equiv) in 2 mL of THF is added dropwise, at 0°C, a solution of vinylmagnesium bromide (0.7 mL of a 1 M soln in THF, 4.3 equiv). After 1 h under vigorous stirring at 0°C, 1 mL of saturated $NH_4Cl$ is added. The aqueous layer is extracted with EtOAc (2x5 mL) and $CH_2Cl_2$ (5 mL). The organic layers are collected, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude is purified on silica ($CH_2Cl_2$/MeOH 96/4) to afford **22** (33 mg, 48% for the two steps) as a white solid; $R_f$ = 0.2 ($CH_2Cl_2$/MeOH 96/4); $[\alpha]_D^{20}$ = -19 (c 1.0, EtOH); FTIR (KBr): $\nu_{max}$ 3438, 3253, 2935, 1640, 1463, 1408, 961, 757 $cm^{-1}$; $^1H$ NMR ($CDCl_3$-$CD_3OD$): δ 7.42 (d, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.07-6.91 (m, 2H), 6.12 (dd, *J* = 10.9 Hz and 17.1 Hz, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 9.1 Hz, 1H), 3.81-3.87 (m, 2H), 3.60-3.69 (m, 3H), 3.00 (d, *J* = 11.5 Hz, 1H), 2.06 (m, 3H), 1.70 (d, *J* = 13.4 Hz, 1H), 1.15 (m, 1H); $^{13}C$ NMR (DMSO-$d_6$): δ 174.6, 145.1, 140.2, 135.3, 127.7, 120.9, 118.8, 117.8, 112.7, 111.0, 100.7, 71.6, 57.7, 48.2, 38.2, 32.8, 32.6, 29.9, 27.2; LRMS (ESI TOF): 309 [$M+H^+$] (15); 331 [$M+Na^+$] (100); 639 [$2M+Na^+$] (68); HPLC Analysis: Chiralcel OD (UV: 254 nm), Hexane/EtOH: 90/10, Flow rate: 1 mL/min, T=35°C, Retention time: 31.0 min (ee > 99%).

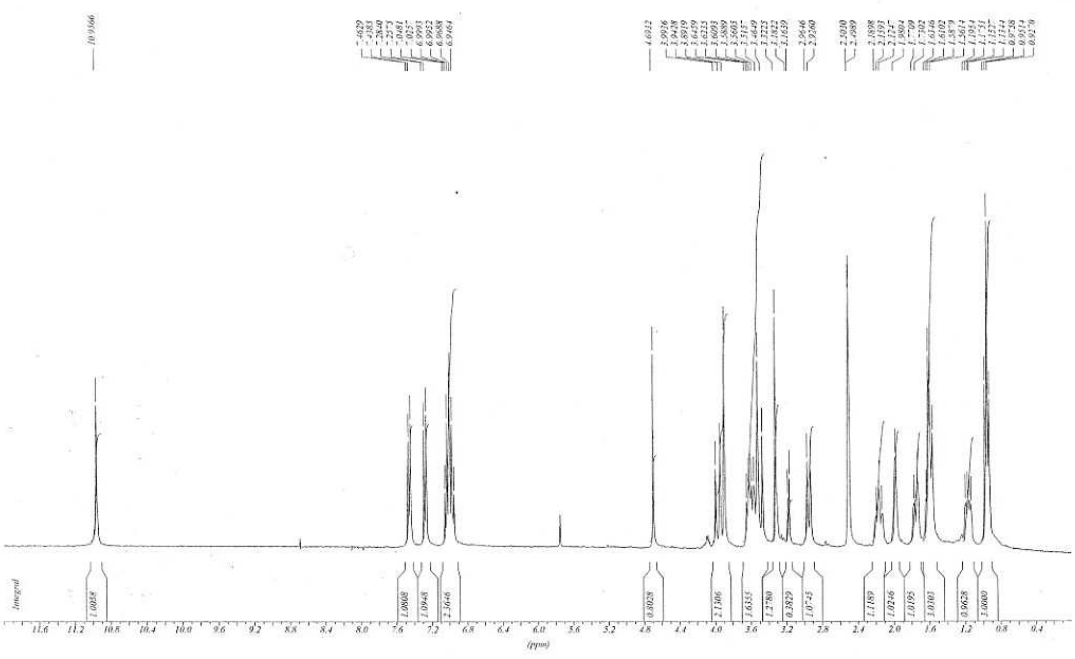


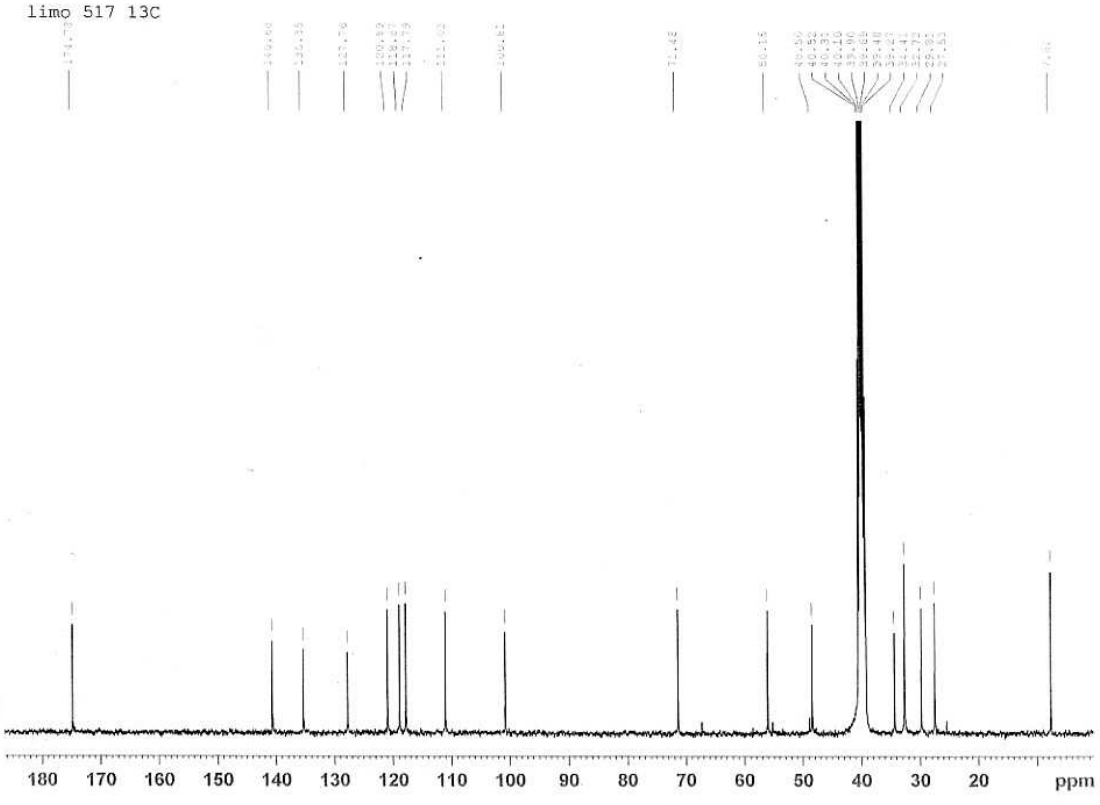

LM611
C13
174.66
145.13
140.29
135.31
127.71
120.91
118.87
117.81
112.77
111.05
100.71
71.62
57.77
55.32
48.27
38.27
32.87
32.68
30.04
27.22
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**Lactam (23)**

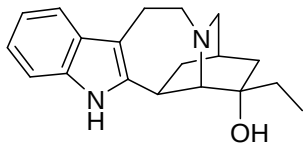



To a solution of **22** (33 mg, 0.107 mmol, 1 equiv) in 2 mL of THF is added $PtO_2$ (1 mg, 0.04 equiv). The mixture is stirred vigorously under 1 bar of $H_2$ for 2 h. Platinum is then filtered and the solvent is concentrated under reduced pressure. The crude is purified on silica ($CH_2Cl_2$/MeOH 98/2) to afford **23** (23 mg, 70 %) as a white solid. $R_f$ = 0.2 ($CH_2Cl_2$/MeOH 96/4); $[\alpha]_D^{20}$ = -29 (c 1.0, EtOH); FTIR (film): $\nu_{max}$ 3272, 2937, 1624, 1461, 1417, 959, 752 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 10.95 (s, 1H, NH), 7.45 (d, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 4.69 (s, 1H, OH), 3.96 (d, *J* = 15.2 Hz, 1H), 3.89 (s, 1H), 3.67-3.44 (m, 3H), 2.94 (d, *J* = 11.6 Hz), 2.23-2.09 (m, 1H), 2.03-1.94 (m, 1H), 1.80-1.70 (m, 1H), 1.67-1.52 (m, 3H), 1.22-1.11 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H); $^{13}C$ NMR (DMSO-$d_6$): δ 174.3, 140.2, 134.9, 127.3, 120.4, 118.4, 117.3, 110.5, 100.3, 71.0, 55.7, 48.0, 38.6, 33.9, 32.2, 29.3, 27.0, 7.1; LRMS (ESI-TOF): 311 [$M+H^+$] (100); HPLC Analysis: Chiralcel OD (UV: 254 nm), Hexane/EtOH: 93/7, Flow rate: 1 mL/min, T=35°C, Retention time: 42.6 min (ee > 99%).

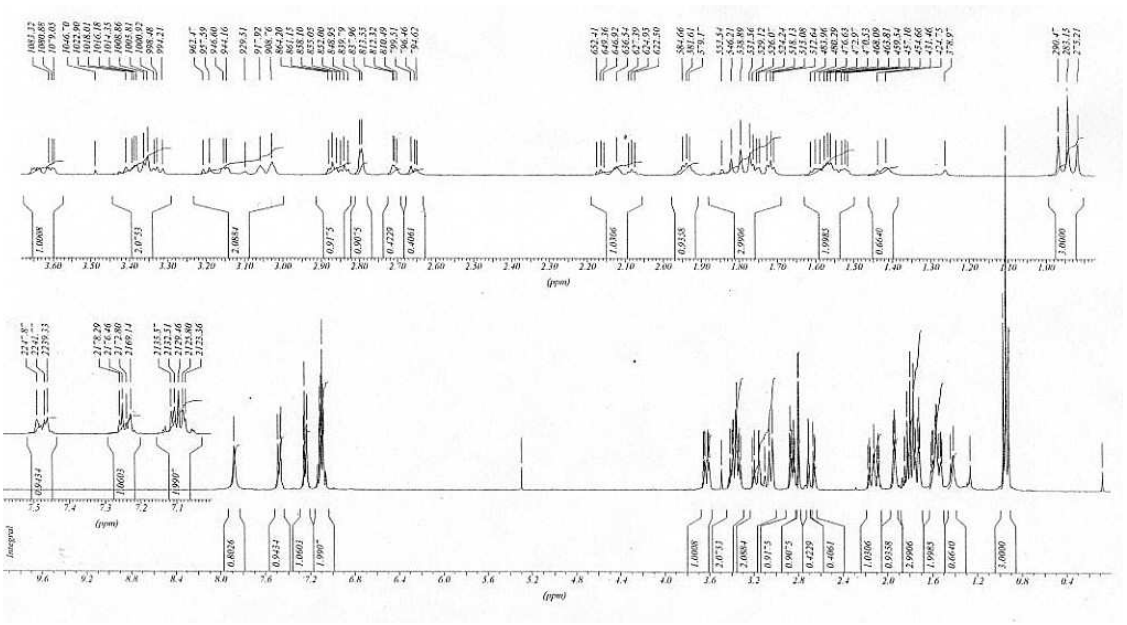



limo 517 13C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

**Büchi's intermediate (24)**




At 0°C, to a suspension of $LiAlH_4$ (46 mg, 20 equiv) in 4 mL of THF, is added dropwise a solution of $AlCl_3$ (117 mg, 14.6 equiv) in 4 mL of THF. After 10 min at 0°C, a solution of **23** (18 mg, 0.06 mmol, 1 equiv) in 4 mL of THF is added dropwise. After 2 h, 2 mL of 15% NaOH is added. The organic layer is extracted with EtOAc (2x10 mL) and $CH_2Cl_2$ (10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude is purified on silica ($CH_2Cl_2$/MeOH 95/5) to afford **24** (14 mg, 77%) as a white solid. $R_f$ = 0.2 ($CH_2Cl_2$/MeOH 95/5); $[\alpha]_D^{20}$ = +32 (c 1.1, MeOH); FTIR (film): $\nu_{max}$ 3399, 3305, 2924, 2852, 1462, 1167, 739 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.88 (brs, 1H, NH), 7.50-7.45 (m, 1H), 7.27-7.21 (m, 1H), 3.62 (ddd, *J* = 11.6 Hz, 4.2 Hz and 1.8 Hz, 1H), 3.44-3.30 (m, 2H), 3.22-3.13 (m, 1H), 3.08-3.00 (m, 1H), 2.90-2.82 (m, 1H), 2.79 (d, *J* = 1.8 Hz, 1H), 2.19-2.06 (m, 1H), 1.97-1.90 (m, 1H), 1.87-1.69 (m, 3H), 1.62-1.51 (m, 2H), 1.41 (brs, 1H, OH), 0.94 (t, *J* = 7.9 Hz, 3H); $^{13}C$ NMR ($CDCl_3$): δ 141.7, 134.4, 129.6, 120.8, 118.9, 117.7, 110.1, 109.2, 75.2, 61.4, 53.8, 48.1, 40.7, 34.0, 33.9, 33.7, 27.3, 20.7, 7.1; HRMS (TOF MS ES+) calcd for $C_{19}H_{25}N_2O$ ($M+H^+$) 297.1967, found 297.1964; HPLC Analysis: Chiralcel OD (UV: 230 nm), Hexane/EtOH: 92/8, Flow rate: 1 mL/min, T=35°C. Retention time: 7.3 min (ee>99%).



limo 522 13C