Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Approach to pactamycin analogues using rhodium(II)-catalyzed alkene aziridination and C(sp^3)—H amination reactions

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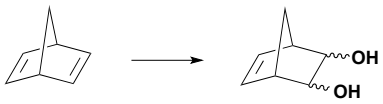
General information: Melting points were measured in capillary tubes on a Büchi B-540v apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP -C13, P31, or Dual C13 probe) and Avance 500 MHz (BB0-ATM probe or BBI - ATM probe). Carbon NMR (^{13}C) spectra were recorded at 125 or 75 MHz, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. NMR experiments were carried out in deuterated chloroform ($CDCl_3$) or deuterated acetone [$(CD_3)_2CO$]. Chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane (TMS) or residual solvent peaks as internal standards. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quadruplet, quint: quintuplet, m: multiplet, br.: broad, app.: apparent. Coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained either with a LCT (Micromass) instrument using electrospray ionization (ES), or from a Time of Flight analyzer (ESI-MS) for the high-resolution mass spectra (HRMS). Thin-layer chromatography was performed on silica gel 60 F254 on aluminum plates (Merck) and visualized under a UVP Mineralight UVLS-28 lamp (254 nm) and by staining with solutions of ninhydrin, phosphomolybdic acid, or acidic p-anisaldehyde in ethanol. Flash chromatography was conducted on Merck silica gel 60 (40-63 µm) at medium pressure (300 mbar) or on CombiFlash (Serlabo Technologies). All reagents were obtained from commercial suppliers unless otherwise stated. The rhodium catalyst $Rh_2(NHCOCF_3)_4$ is prepared

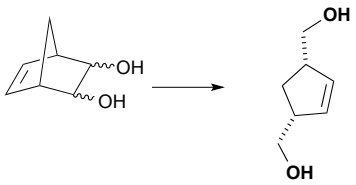
according to the literature from rhodium(II) acetate which was purchased from Alfa Aesar Company.[1] The copper-mediated Sila-Sonogashira-Hagihara reactions were all performed with CuCl 97% purchased from Aldrich. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. Organic extracts were dried over magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4).

(1*R**,4*S**)-bicyclo[2.2.1]hept-5-ene-2,3-diol



In a 250 mL two-necked round bottom flask equipped with an air condenser, OsO_4 (4% wt. in H_2O, 2.00 mL, 0.310 mmol, 0.400 mol %) was added dropwise (2 drops per seconde) to a vigorously stirred solution of norbornadiene (10.0 g, 109 mmol, 1.40 equiv.) and NMO (9.08 g, 77.5 mmol, 1.00 equiv.), in pyridine (10 mL), *t*-BuOH (100 mL), and water (35 mL) at RT. The mixture was heated to reflux and was stirred for 15 h. Then the solution was cooled to RT and a saturated solution of $Na_2S_2O_3$ (50mL) was added. The mixture was stirred for 30 minutes, then filtered over Celite®. The filtrate was extracted with EtOAc (4x50 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 60:40 to 10:90) with dry loading on celite, and the desired compound was obtained as a white solid (6.97 g, 71%).
The data are consistent with the literature.[2]

((1*R**,3*S**)-cyclopent-4-ene-1,3-diyl)dimethanol (**2**)



2

In a 500 mL round bottom flask equipped with an internal thermometer, a solution of diol (15.0 g, 119 mmol, 1.00 equiv.) in HCO_2Me (240 mL) was cooled to 0 °C with an ice bath. Then $NaIO_4$ (38.1 g, 178 mmol, 1.50 equiv.) and water (15 mL) were added: the temperature of the white slurry reaches 23 °C after 10 min, before starting to decrease. The ice bath was removed and the mixture was stirred at RT until no more starting material remains by TLC (PE/EtOAc 4:6). After 1 h, the reaction

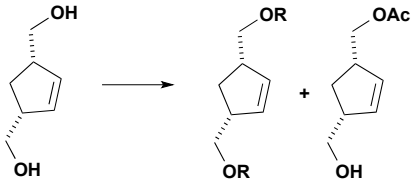
[1] A. M. Dennis, J. D. Korp, I. Bernal, I. R. A. Howard and J. L. Bear, *Inorg. Chem.* 1983, **22**, 1522.
[2] L. Maier, P. Khirsariya, O. Hylse, S. K. Adla, L. Černová, M. Poljak, S. Krajčovičová, E. Weis, S. Drápela, K. Souček, and K. Paruch *J. Org. Chem.* 2017, **82**, 3382.

mixture was filtered over celite, washed with HCO_2Me, the filtrate was dried over Na_2SO_4 then filtered, and the filtrate was concentrated under reduced pressure. The crude unstable dialdehyde was immediately used without further purification.

To a 500 mL two-necked round bottom flask equipped with an addition funnel under argon, was added $LiAlH_4$ (6.77 g, 178 mmol, 1.50 equiv.) and anhydrous THF (180 mL). To this suspension, cooled to 0 °C, was added dropwise a solution of the crude dialdehyde in anhydrous THF (60 mL). After 15 minutes the ice bath was removed and the mixture was allowed to stir at RT for 2 h. The reaction mixture was cooled again to 0 °C, and quenched by successive addition of water (6.8 mL), NaOH 15% (6.8 mL) and water (20.4 mL). The slurry was stirred at RT for 30 minutes, then Na_2SO_4 was added and the mixture was stirred for 5 more minutes before being filtered over celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc 50:50 to 0:100), affording **2** as a pale yellow oil (12.9 g, 85%).

The data are consistent with the literature.[3]

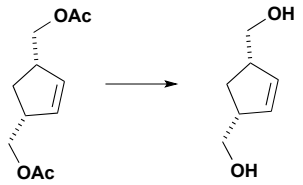
((1*S**,4*R**)-4-(hydroxymethyl)cyclopent-2-en-1-yl)methyl acetate (**3**)



In a 1 L round bottom flask under argon, were added **2** (26.4 g, 206 mmol, 1.00 equiv.) and anhydrous DCM (450 mL). To this solution was added Et_3N (28.7 mL, 206 mmol, 1.00 equiv.) and the mixture was cooled to 0 °C before Ac_2O (19.4 mL, 206 mmol, 1.00 equiv.) was added dropwise. After 5 minutes, the ice bath was removed and the reaction mixture was allowed to stir at RT for 18 h. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 80:20 to 0:100), and three compounds were successively isolated: the diacetylated compound **4** as a pale yellow oil (8.96 g, 20%), the desired compound **3** as a pale yellow oil (18.4 g, 53%) and the remaining starting material **2** (7.31g, 26%).

The data are consistent with the literature.[4]

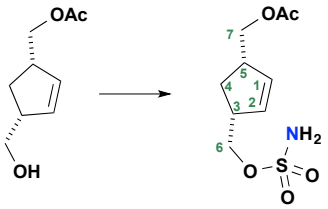
[3] M. J. Cook, T. Rovis, *J. Am. Chem. Soc.* 2007, **129**, 9302.
[4] M. Mekrami, S. Sicsic, *Tetrahedron: Asymmetry* 2011, **22**, 1605.



4 2

Recycling of 4 : To a 500 mL round bottom flask containing **4** (17.5 g, 82.4 mmol, 1.00 equiv.) were added methanol (200 mL) then sodium methoxide (8.91 g, 165 mmol, 2.00 equiv.) and the mixture was stirred at RT overnight. The reaction mixture was then concentrated to 1/5 of its volume and filtered over celite. The filtrate was concentrated, and purified by filtration over a silica plug washed with EtOAc. After concentration under reduced pressure, **2** was obtained as a pale yellow oil (10.4 g, 99%).

((1*S**,4*R**)-4-((sulfamoyloxy)methyl)cyclopent-2-en-1-yl)methyl acetate (**5**)



3 5

In a 100 mL round bottom flask under argon was added chlorosulfonyl isocyanate (2.64 mL, 30.3 mmol, 1.50 equiv.) and the flask was cooled to 0 °C. Formic acid (1.14 mL, 30.3 mmol, 1.50 equiv.) was added dropwise to keep the gas evolution slow (ADDITION MUST BE KEPT PARTICULARLY SLOW UNTIL SOLID STARTS TO FORM). The white solid was left slowly warming up to RT overnight. The solid was cooled again to 0 °C and anhydrous DMA (15 mL) was added slowly (gas evolution may happen again). A solution of **3** (3.44 g, 20.2 mmol, 1.00 equiv.) and pyridine (2.44 mL, 30.3 mmol, 2.00 equiv.) in anhydrous DMA (20 mL) was added slowly to the freshly prepared sulfamoyl chloride solution, and the mixture was stirred at 0 °C for 30 minutes then at RT for 5 h. Water was added, followed by $NH_4Cl_{sat.}$, then the solution was extracted with EtOAc (x4). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 80:20 to 60:40) to afford **5** as a white solid (4.52 g, 90%).

HRMS (ESI) calcd for $C_9H_{14}NO_5S$ $(M+H)^+$ 248.0593, found 248.0593.

mp 64-66 °C

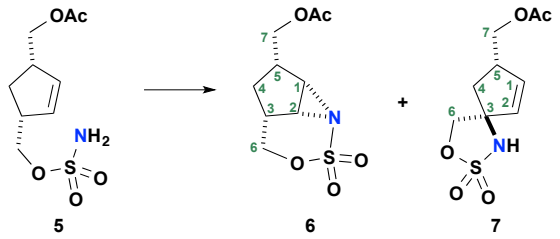
IR (cm^{-1}): 3338, 3205, 2982, 2893, 1704, 1575, 1390, 1362, 1171, 1098, 1056.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (dt, *J* = 2.1, 5.5 Hz, 1H, H_2), 5.77 (dt, *J* = 2.0, 5.5 Hz, 1H, H_1), 4.92 (br. s, 2H, NH_2), 4.16 (dd, *J* = 5.9, 9.4 Hz, 1H, H_{6a}), 4.12 (dd, *J* = 6.3, 9.4 Hz, 1H, H_{6b}), 4.10 (dd, *J* = 7.0, 10.8

Hz, 1H, H_{7a}), 3.96 (dd, *J* = 6.1, 10.8 Hz, 1H, H_{7b}), 3.18-3.10 (m, 1H, H_3), 3.10-3.03 (m, 1H, H_5), 2.28 (dt, *J* = 9.0, 13.7 Hz, 1H, H_{4a}), 2.07 (s, 3H, H_7), 1.38 (dt, *J* = 5.8, 13.7 Hz, 1H, H_{4b}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C_{CO}), 133.9 (C_2), 131.9 (C_1), 73.9 (C_6), 67.7 (C_7), 45.1 (C_3), 45.1 (C_5), 29.5 (C_4), 21.1 (C_{Me}).

((2*S**,2a*S**,2a1*R**,5a*R**)-3,3-dioxidohexahydro-4-oxa-3-thia-2b-azacyclopropa[cd]inden-2-yl)methyl acetate (**6**)



In a 1 L round bottom flask under argon were added **5** (14.2 g, 56.8 mmol, 1.00 equiv.), MgO (4.88 g, 108 mmol, 1.90 equiv.) and $Rh_2(NHCOCF_3)_4$ (127 mg, 0.172 mmol, 0.300 mol %). Anhydrous DCM (320 mL) was added and the solution was cooled to 0 °C. $PhI(OAc)_2$ (26.7 g, 73.8 mmol, 1.30 equiv.) was added in one portion and the mixture was allowed to stir at RT overnight before being filtered over Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc 80:0 to 20:80), affording **6** as a white crystalline solid (13.5 g, 54.6 mmol, 95%) and **7** as a colorless oil (421 mg, 1.70 mmol, 3%).

HRMS (ESI) calcd for $C_9H_{14}NO_5S$ $(M+H)^+$ 248.0587, found 248.059.

mp 112-114 °C

IR (cm^{-1}) 2921, 1734, 1360, 1236, 1174, 1036, 903, 874, 798, 667.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (dd, 1H, *J* = 1.0, 11.3 Hz, H_{6a}), 4.44 (dd, 1H, *J* = 8.4, 11.1 Hz, H_{7a}), 4.38 (dd, 2H, *J* = 7.8, 11.1 Hz, H_{7b}), 4.24 (dd, 1H, *J* = 2.3 ,11.3 Hz, H_{6b}), 3.80 (dd, 1H, *J* = 3.7, 4.5 Hz, H_1), 3.43 (app. t , 1H, *J* = 4.4 Hz, H_2), 3.04-2.92 (m, H_5), 2.77 (dq, 1H, *J* = 10.7, 13.9 Hz, H_{4a}), 2.67-2.60 (m, H_3), 2.08 (s, 3H, Ac), 1.76 (dq, 1H, *J* = 2.4, 13.9 Hz, H_{4b}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C_{CO}), 76.1 (C_6), 63.7 (C_7), 55.5 (C_2), 51.2 (C_1), 39.7 (C_5), 34.7 (C_4), 31.9 (C_3), 21.0 (C_{Me}).

((5*S**,7*S**)-2,2-dioxido-3-oxa-2-thia-1-azaspiro[4.4]non-8-en-7-yl)methyl acetate (**7**)

HRMS (ESI) calcd for $C_9H_{14}NO_5S$ $(M-H)^-$ 246.0436, found 246.0430.

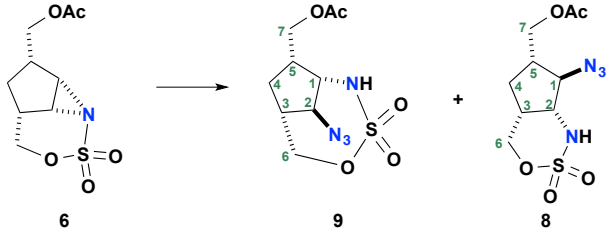
(oil)

IR (cm^{-1}) 3230, 2951, 1719, 1439, 1335, 1188, 1129, 1039, 798.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, 1H, *J* = 5.6 Hz, H_1), 5.88 (d, 1H, *J* = 5.6 Hz, H_2), 5.07 (b.s, 1H, NH), 4.51 (d, 1H, *J* = 8.6 Hz, H_{6a}), 4.47 (d, 1H, *J* = 8.6 Hz, H_{6b}), 4.11 (dd , 1H, *J* = 5.8, 11.0 Hz, H_{7a}), 3.99 (dd , 1H, *J* = 5.8, 11.0 Hz, H_{7b}), 3.30-3.24 (m, 1H, H_5), 2.55 (dd , 1H, *J* = 8.1, 14.0 Hz, H_{4a}), 2.06 (s, 3H, Ac), 1.93 (dd , 1H, *J* = 5.2, 14.0 Hz, H_{4a}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C_{CO}), 139.1 (C_1), 131.6 (C_2), 78.9 (C_6), 73.7 (C_3), 66.1 (C_7), 44.4 (C_5), 40.0 (C_4), 21.0 (C_{Me}).

((4a*R**,6*S**,7*R**,7a*R**)-7-azido-2,2-dioxidohexahydro-1H-cyclopenta[d][1,2,3]oxathiazin-6-yl)methyl acetate (**8**)



For selected examples of promoters used see:

Promoters	Yield 9	Yield 8
TMEDA (0.3 eq)	12%	38%
Tetramethylguanidine (0.3 eq)	18%	41%
HMPT (0.3 eq)	24%	42%
DBU (0.3 eq)	25%	59%
Tris (4-OMePh) phosphine (0.3 eq)	10%	43%
DMAP (0.3 eq)	21%	40%
DBN (0.3 eq)	19%	64%
DBN (0.1 eq)	21%	50%
DBN (0.3 eq)*	15%	40%
TBAF (0.1 eq)	32%	63%
$BF_3.OEt_2$ (0.3 eq)	0%	0%
$ZnOTf_2$ (0.3 eq)	0%	0%

* conducted at 40 °C

In a 250 mL round bottom flask were added **6** (8.00 g, 32.4 mmol, 1.00 equiv.) and anhydrous acetonitrile (150 mL). To this solution were added $TMSN_3$ (8.59 mL, 64.7 mmol, 2.00 equiv.) then TBAF (1 M in THF, 3.2 mL, 3.2 mmol, 0.1 equiv.) and the reaction mixture was stirred at RT for 3 h. $NH_4Cl_{sat.}$ and water were added and then the solution was extracted with EtOAc (x4). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 90:10 to 50:50),

affording **8** as a white crystalline solid (5.90 g, 20.3 mmol, 63%) and the other regioisomere **9** as white crystalline solid (3.20 g, 11.0 mmol, 32%).

HRMS (ESI) calcd for $C_9H_{13}N_4O_5S^-$ $(M-H)^-$ 289.0612, found 289.0623.

mp 102-104 °C

IR (cm^{-1}) 3167, 2965, 2877, 2099, 1713, 1363, 1257, 1181, 1042, 921, 773.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (d, 1H, *J* = 8.1 Hz, NH), 4.83 (dd, 1H, *J* = 3.6, 12 Hz, H_{6a}), 4.47 (dd, 2H, *J* = 3.2, 12 Hz, H_{6b}), 4.21 (dd, 1H, *J* = 3.8, 11.4 Hz, H_{7a}), 4.16 (dd, 1H, *J* = 3.8, 11.4 Hz, H_{7b}), 3.96-3.93 (m, 1H, H_2), 3.86 (dd, 1H, J = 3, 4.3 Hz, H_1), 2.42-2.36 (m, 1H, H_3), 2.35-2.28 (m, 1H, H_5), 2.15 (s, 3H, Ac), 2.13-2.07 (m, 1H, H_{4a}), 1.83-1.77 (m, 1H, H_{4b}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C_{CO}), 72.6 (C_6), 68.0 (C_1), 65.1 (C_7), 63.7 (C_2), 43.3 (C_3), 34.0 (C_5), 26.8 (C_4), 21.0 (C_{Me}).

((1*S**,6*R**,8*S**,9*S**)-9-azido-3,3-dioxido-4-oxa-3-thia-2-azabicyclo[4.2.1]nonan-8-yl)methyl acetate (**9**)

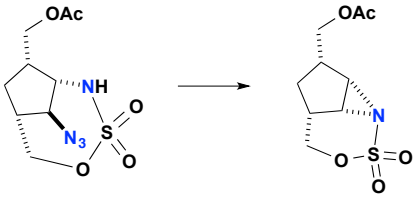
HRMS (ESI) calcd for $C_9H_{15}N_4O_5S^+$ $(M+H)^+$ 291.0749 found 291.0758.

mp 101-103 °C

IR (cm^{-1}) 3302, 2961, 2101, 1736, 1362, 1237, 1170, 1077, 934, 741.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (br. s, 1H, NH), 5.00 (s, 1H, H_2), 4.46 (dd, 1H, *J* = 1.3, 12.1 Hz, H_{6a}), 4.33 (dd, 1H, *J* = 9.9, 12.0 Hz, H_{7a}), 4.18 (dd, 1H, *J* = 4.8, 12.0 Hz, H_{7b}), 4.05 (dd, 1H, *J* = 3.3, 12.1 Hz, H_{6b}), 3.57 (d, 1H, *J* = 4.5 Hz, H_1), 2.78-2.65 (m, 1H, H_5), 2.65-2.57 (m, 1H, H_3), 2.23 (dt, 1H, *J* = 10.2, 13.8 Hz, H_{4a}), 2.10 (s, 3H, Ac), 1.47 (ddd, 1H, *J* = 3.6, 4.8, 13.8 Hz, H_{4b}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C_{CO}), 72.6 (C_6), 66.8 (C_2), 62.3 (C_7), 58.4 (C_1), 45.0 (C_5), 43.0 (C_3), 25.8 (C_5), 20.9 (C_{Me}).

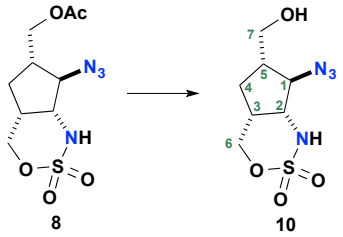


9 6

Recycling of 4 : To a solution of **9** (1.00 g, 3.44 mmol, 1.00 equiv.) in EtOAc (17 mL) was added Pd/C (10 % wt on C, 183 mg, 0.172 mmol, 5.00 mol %). The suspension was purged 5 times with H_2 and was stirred at RT for 4 h. The reaction mixture was filtered over celite, washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was used for the next step without further purification.

To the crude amine in THF (27 mL) and at 0 °C was added AcOH (3.95 mL, 68.9 mmol, 20.0 equiv.), and then a solution of $NaNO_2$ (1.90 g, 27.6 mmol, 8.00 equiv.) was added dropwise. The mixture was vigorously stirred at 0 °C for 30 minutes then the ice bath was removed and the mixture was stirred at RT for 2 h. Water was added and the solution was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 50:50 to 30:70) to afford **6** as a white solid (355 mg, 42% over 2 steps).

(4a*R**,6*S**,7*R**,7a*R**)-7-azido-6-(hydroxymethyl)hexahydro-1H-cyclopenta[d][1,2,3]oxathiazine 2,2-dioxide (**10**)



In a 250 mL round bottom flask was added **8** (5.88 g, 20.3 mmol, 1.00 equiv.) and methanol (120 mL). To this solution was added sodium methoxide (4.38 g, 81.0 mmol, 4.00 equiv.) and the mixture was stirred at RT for 2 h. Then $NH_4Cl_{sat.}$ (100 mL) was added and the reaction mixture was extracted with EtOAc (4 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified flash column chromatography (SiO_2, PE/EtOAc 1:1 to 2:3), affording **10** as a white solid (4.83 g, 96%).

HRMS (ESI) calcd for $C_7H_{11}N_4O_4S^-$ $(M-H)^-$ 247.0506, found 247.0497.

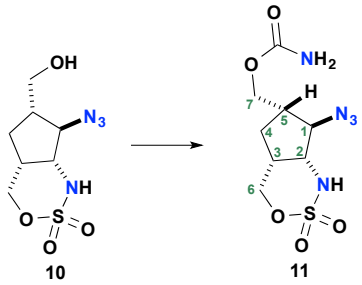
mp 90-92 °C

IR (cm^{-1}) 3499, 3090, 2942, 2892, 2092, 1716, 1455, 1356, 1180, 1064, 910, 788.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, 1H, *J* = 9.4 Hz, NH), 4.91 (dd, 1H, *J* = 2.8, 12 Hz, H_{6a}), 4.45 (d, 2H, *J* = 12 Hz, H_{6b}), 3.95 (dd, 1H, *J* = 3.9, 9.4 Hz, H_2), 3.88 (dd, 1H, *J* = 2.2, 10.0 Hz, H_{7a}), 3.85 (br. s, 1H, H_1), 3.71 (dd, 1H, *J* = 2.2, 10.0 Hz, H_{7b}), 2.71 (br. s, 1H, OH), 2.41-2.33 (m, 1H, H_5), 2.28-2.19 (m, 1H, H_3), 2.18-2.01 (m, 2H, $H_{4a/4b}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 72.5 (C_6), 69.5 (C_1), 63.0 (C_2), 62.5 (C_7), 45.5 (C_5), 35.2 (C_3), 25.9 (C_4).

((4a*R**,6*S**,7*R**,7a*R**)-7-azido-2,2-dioxidohexahydro-1H-cyclopenta[d][1,2,3]oxathiazin-6-yl)methyl carbamate (**11**)



In a 10 mL round bottom flask was added **10** (176 mg, 0.709 mmol, 1.00 equiv.) and anhydrous DCM (3 mL). To this solution was added NaOCN (92.2 mg, 1.42 mmol, 2.00 equiv.) in one portion, and then TFA (109 µL, 1.42 mmol, 2.00 equiv.) was added dropwise. After 17 h, NaOCN (92.2 mg, 1.42 mmol, 2.00 equiv.) and TFA (109 µL, 1.42 mmol, 2.00 equiv.) were added again to reach completion. After 7 more hours, water was added and the reaction mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 100:0 to 60:40), affording **11** as a white solid (136 mg, 66%).

HRMS (ESI) calcd for $C_8H_{12}N_5O_5S^-$ $(M-H)^-$ 290.0565, found 290.0553.

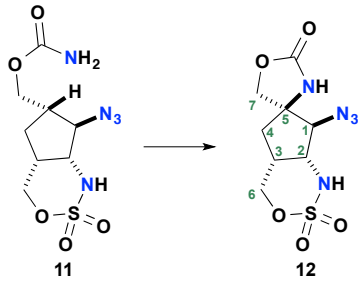
mp 109-111 °C

IR (cm^{-1}) 3441, 3229, 2110, 1705, 1597, 1342, 1174, 1065, 937, 773.

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.75 (br. s, 1H, NH), 5.90 (br. s, NH_2), 4.67 (dd, 1H, *J* = 5, 12 Hz, H_{6a}), 4.53 (dd, 1H, *J* = 6.3, 12 Hz, H_{6b}), 4.13 (d, 2H, *J* = 5.5 Hz, $H_{7a/7b}$), 4.10 (dd, 1H, *J* = 6.5, 7.9 Hz , H_1), 3.90 (dd, 1H, J = 6.5, 12.7 Hz, H_2), 2.54-2.43 (m, 1H, H_3), 2.28-2.17 (m, 1H, H_5), 2.15-2.07 (m, 1H, H_{4a}), 1.61-1.50 (m, 1H, H_{4b}).

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 157.4 (C_{CO}), 73.9 (C_6), 66.7 (C_1), 65.1 (C_7), 64.6 (C_2), 43.8 (C_5), 33.8 (C_3), 27.5 (C_4).

(4a*R**,6*R**,7*S**,7a*R**)-7-azidotetrahydro-1H,4H-spiro[cyclopenta[d][1,2,3]oxathiazine-6,4'-oxazolidin]-2'-one 2,2-dioxide (**12**)



In a seal tube under argon were added **11** (50.0 mg, 0.172 mmol, 1.00 equiv.), $Rh_2(HNCOCF_3)_4$ (11 mg, 17 µmol, 0.10 equiv.), MgO (15.9 mg, 0.395 mmol, 2.30 equiv.) and TCE (1 mL). To this suspension was added $PhI(OPiv)_2$ (126 mg, 0.309 mmol, 1.80 equiv.) in one portion and the mixture was heated to 80 °C and stirred for 12 h. After cooling to RT, the reaction mixture was filtered over celite and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 10:90 to 0:100), affording **12** as a white solid (10 mg, 20%) and some recovered starting material **11** (12 mg, 25%).

HRMS (ESI) calcd for $C_8H_{10}N_5O_5S^-$ $(M-H)^-$ 288.0408, found 288.0408.

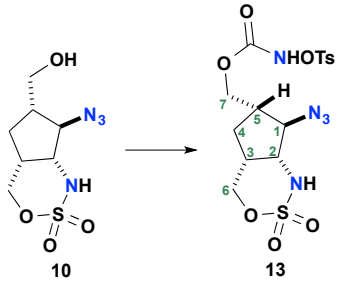
mp 114-116 °C

IR (cm^{-1}) 3356, 3068, 2883, 2111, 1726, 1355, 1179, 936, 760.

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.24 (s, 1H, NH), 7.19 (d, 1H, *J* = 6.1 Hz, NH), 4.63 (dd, 1H, *J* = 5.2, 12.0 Hz, H_{6a}), 4.58 (d, 1H, *J* = 9.4 Hz, H_{7a}), 4.52 (dd, 1H, *J* = 6.3, 12.0 Hz, H_{6b}), 4.36 (d, 1H, *J* = 9.7 Hz, H_1), 4.32 (d, 1H, *J* = 9.4 Hz, H_{7b}), 4.14 (dd, 1H, *J* = 6.1, 9.7 Hz, H_2), 2.82-2.70 (m, 1H, H_3), 2.28 (dd, 1H, *J* = 8.9, 14.5 Hz, H_{4a}), 2.07-2.02 (m, 1H, H_{4b}).

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 158.6 (C_{CO}), 73.9 (C_6), 72.6 (C_7), 68.6 (C_1), 64.6 (C_5), 61.5 (C_2), 36.9 (C_4), 30.9 (C_3).

((4a*R**,6*S**,7*R**,7a*R**)-7-azido-2,2-dioxidohexahydro-1H-cyclopenta[d][1,2,3]oxathiazin-6-yl)methyl (tosyloxy)carbamate (**13**)



In a 5 mL round bottom flask were added 1,1'-carbonyldiimidazole (144 mg, 0.886 mmol, 1.10 equiv.) and anhydrous THF (8 mL). To this solution was added **10** (200 mg, 0.806 mmol, 1.00 equiv.), and the

mixture was stirred at RT for 3 h. The mixture was washed with $NH_4Cl_{sat.}$ (3 mL) and brine (3 mL), and was then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in pyridine (4 mL). Hydroxylamine hydrochloride (168 mg, 2.42 mmol, 3.00 equiv.) was added and the resulting mixture was stirred at RT overnight. Most of the pyridine was removed under reduced pressure and the residue was dissolved in DCM (10 mL). The mixture was washed with $NH_4Cl_{sat.}$ (3 x 5 mL) and brine (5 mL), and was then dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The crude hydroxamic acid was immediately used without further purification.

To a solution of crude hydroxamic acid in anhydrous THF (5 mL) at 0 °C, was added *p*-toluenesulfonyl chloride (169 mg, 0.886 mmol, 1.10 equiv.). Triethylamine (113 µL, 0.814 mmol, 1.01 equiv.) was then slowly added, and the resulting white suspension was stirred at RT for 6 h. The mixture was washed with water (3 mL) and brine (3 mL), and was then dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc 40:60 to 20:80), affording **13** as a white solid (225 mg, 60% over 2 steps).

HRMS (ESI) calcd for $C_{15}H_{18}N_5O_8S_2^-$ $(M-H)^-$ 460.0602, found 460.0599.

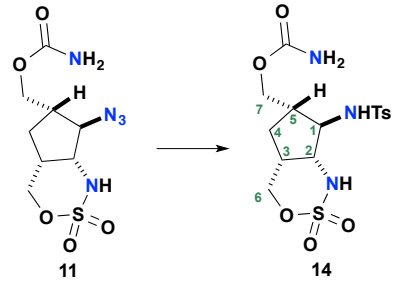
mp 88-90 °C

IR (cm^{-1}) 3272, 2960, 2102, 1739, 1367, 1242, 1174, 922, 737.

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 10.53 (s, 1H, NH), 7.88 (d, 1H, *J* = 8.3 Hz, H_{Ts}), 7.51 (d, 1H, *J* = 8.3 Hz, H_{Ts}), 6.81 (d, 1H, *J* = 6.3 Hz, NH), 4.67 (dd, 1H, *J* = 5.1, 12.0 Hz, H_{6a}), 4.53 (dd, 1H, *J* = 6.4, 12.0 Hz, H_{6b}), 4.23-4.13 (m, 2H, $H_{7a/7b}$), 4.08-4.01 (m, 1H, H_1), 3.96-3.88 (m, 1H, H_2), 2.55-2.43 (m, 4H, $H_{3/Me}$), 2.18-2.01 (m, 2H, $H_{4a/5}$), 1.51-1.41 (m, 1H, H_{4b}).

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 156.7 (C_{CO}), 147.0 ($C_{q(Ts)}$), 131.9 ($C_{q(Ts)}$), 130.7 (2*$C_{Ar(Ts)}$), 130.2 (2*$C_{Ar(Ts)}$), 73.9 (C_6), 67.2 (C_7), 65.9 (C_1), 64.4 (C_2), 43.1 (C_3), 32.8 (C_5), 27.3 (C_4), 21.6 ($Me_{(Ts)}$).

((4a*R**,6*S**,7*R**,7a*R**)-7-((4-methylphenyl)sulfonamido)-2,2-dioxidohexahydro-1H-cyclopenta[d][1,2,3]oxathiazin-6-yl)methyl carbamate (**14**)



In a 250 mL round bottom flask were added **11** (436 mg, 1.50 mmol, 1.00 equiv.), Pd/C (10 % wt on C, 78 mg, 2.5 mol %) and methanol (80 mL). The suspension was purged 5 times with H_2 and was stirred at RT for 30 minutes. The reaction mixture was filtered over celite, washed with MeOH, and the filtrate was concentrated under reduced pressure. The residue was used for the next step without further purification.

To the crude amine in anhydrous MeCN (15 mL) under argon was added triethylamine (303 µL, 2.25 mmol, 1.50 equiv.) and then TsCl (429 mg, 2.25 mmol, 1.50 equiv.). The reaction mixture was stirred at RT for 4 h, then silica was added to make a dry loading, and the suspension was evaporated. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 20:80 to 0:100), affording **14** as a white solid (400 mg, 65%).

HRMS (ESI) calcd for $C_{15}H_{21}N_3NaO_7S_2^+$ $(M+Na)^+$ 442.0713, found 442.0709.

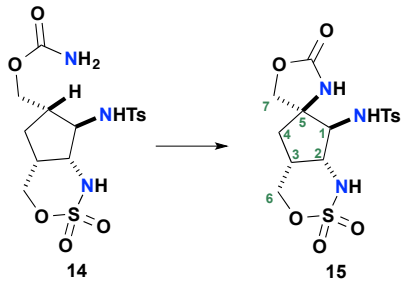
mp 225-227 °C

IR (cm^{-1}) 3483, 3307, 3083, 2905, 1696, 1610, 1356, 1188, 1085, 911, 781.

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.78 (dt, 2H, *J* = 8.3, 1.9 Hz, H_{Ts}), 7.39 (d, 2H, *J* = 8.3 Hz, H_{Ts}), 6.82 (d, *J* = 7.3 Hz 1H, NH_{Ts}), 6.20 (d, 1H, *J* = 7.2 Hz, NH_{Sulf}), 5.72 (br. s, 2H, NH_2), 4.72 (dd, 1H, *J* = 3.8, 12.0 Hz, H_{6a}), 4.46 (dd, 1H, *J* = 2.8, 12.0 Hz, H_{6b}), 3.99 (dd, 1H, *J* = 5.4, 10.6 Hz , H_{7a}), 3.87 (dd, 1H, *J* = 7.2, 10.6 Hz , H_{7b}), 3.86-3.82 (m, 1H, H_2), 3.45 (td, 1H, *J* = 2.4, 7.3 Hz, H_1), 2.41 (s, 3H, H_{Me}), 2.34-2.23 (m, 2H, $H_{5/3}$), 2.02-1.92 (m, 1H, H_{4a}), 1.70 (q, 1H, *J* = 12.2 Hz, H_{4b}).

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 157.3 (C_{CO}), 144.5 ($C_{q(Ts)}$), 139.2 ($C_{q(Ts)}$), 130.5 (2*$C_{Ar(Ts)}$), 128.0 (2*$C_{Ar(Ts)}$), 73.3 (C_6), 65.6 (C_7), 65.1 (C_2), 62.3 (C_1), 46.3 (C_5), 35.2 (C_3), 29.2 (C_4), 21.4 ($Me_{(Ts)}$).

N-((4a*R**,6*R**,7*S**,7a*R**)-2,2-dioxido-2'-oxotetrahydro-1H,4H-spiro[cyclopenta[d][1,2,3]oxathiazine-6,4'-oxazolidin]-7-yl)-4-methylbenzenesulfonamide (**15**)



In a seal tube under argon were added **14** (20 mg, 0.048 mmol, 1.0 equiv.), $Rh_2(HNCOCF_3)_4$ (6.5 mg, 12 µmol, 20 mol %), MgO (5.8 mg, 0.15 mmol, 3.0 equiv.) and anhydrous MeCN (1 mL), followed by $PhI(OAc)_2$ (23 mg, 0.072 mmol, 1.5 equiv.) in one portion. The resulting mixture was stirred at RT for 18 h, and was then filtered over celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, EtOAc), affording **15** as a white solid (9.0 mg, 45%), and some recovered starting material **14** (11 mg, 55%).

HRMS (ESI) calcd for $C_{17}H_{23}N_4O_7S_2^+$ $(M+ACN+H)^+$ 459.1003, found 459.0999.

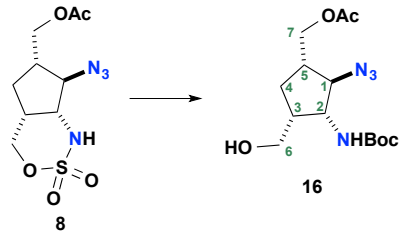
mp 230-232 °C

IR (cm^{-1}) 3266, 2924, 1737, 1319, 1152, 1090, 930, 665.

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.81 (d, 2H, *J* = 8.3, H_{Ts}), 7.34 (d, 2H, *J* = 8.3 Hz, H_{Ts}), 7.01 (d, *J* = 8.6 Hz 1H, NH_{Ts}), 6.94 (br. s, 1H, NH), 6.44 (d, 1H, *J* = 7.6 Hz, NH_{Sulf}), 4.55 (dd, 1H, *J* = 5.1, 11.8 Hz, H_{6a}), 4.40 (dd, 1H, *J* = 6.3, 11.8 Hz, H_{6b}), 4.39 (d, 1H, *J* = 9.0 Hz , H_{7a}), 4.28 (d, 1H, *J* = 9.0 Hz , H_{7b}), 4.05 (app. t, 1H, *J* = 8.6 Hz , H_1), 3.89 (app. q, 1H, *J* = 8.1 Hz, H_2), 2.75-2.63 (m, 1H, H_3), 2.40 (s, 3H, H_{Me}), 2.19 (dd, 1H, *J* = 7.9, 13.8 Hz, H_{4a}), 2.08-2.06 (m, 1H, H_{4b}).

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 158.8 (C_{CO}), 143.9 ($C_{q(Ts)}$), 141.0 ($C_{q(Ts)}$), 130.2 (2*$C_{Ar(Ts)}$), 128.1 (2*$C_{Ar(Ts)}$), 73.2 (C_6), 71.8 (C_7), 65.5 (C_5), 63.8 (C_1), 61.5 (C_2), 37.4 (C_3), 32.1 (C_4), 21.4 ($Me_{(Ts)}$).

((1*S**,2*R**,3*R**,4*R**)-2-azido-3-((*tert*-butoxycarbonyl)amino)-4-(hydroxymethyl)cyclopentyl)methyl acetate (**16**)



In a 100 mL round bottom flask under argon was added **8** (2.00 g, 6.89 mmol, 1.00 equiv.) and anhydrous THF (35 mL). To this solution was added Boc_2O (1.58 g, 7.23 mmol, 1.05 equiv.) in one

portion, and then the solution was stirred at RT. After 1 h, a phosphate buffer solution (pH 8, 0.5 M, 20 mL) was added, and the reaction mixture was heated to 50 °C and stirred for 29 h. The reaction mixture was cooled to RT and was extracted with EtOAc (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 100:0 to 70:30), affording **16** as a colorless viscous oil (1.68 g, 74%).

HRMS (ESI) calcd for $C_{14}H_{24}N_4NaO_5^+$ $(M+Na)^+$ 351.1639, found 351.1634.

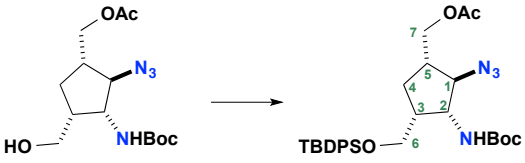
(oil)

IR (cm^{-1}) 3364, 2971, 2098, 1687, 1512, 1365, 1233, 1162, 1034.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, 1H, *J* = 8.3 Hz, NH), 4.13 (dd, 2H, *J* = 3.6, 5.5 Hz, $H_{7a/7b}$), 4.10-4.02 (m, 1H, H_2), 3.75-3.67 (m, 1H, H_{6a}), 3.58-3.49 (m, 2H, $H_{6b/1}$), 2.56 (br. s, 1H, OH), 2.40-2.34 (m, 1H, H_3), 2.20-2.12 (m, 1H, H_5), 2.10 (s, 3H, Ac), 2.01-1.91 (m, 1H, H_{4a}), 1.46 (s, 9H, H_{Boc}), 1.41-1.27 (m, 1H, H_{4b}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 ($C_{CO(Ac)}$), 156.3 ($C_{CO(Boc)}$), 80.3 ($C_{q(Boc)}$), 69.3 (C_1), 65.6 (C_7), 62.1 (C_6), 58.2 (C_2), 41.7 (C_5), 40.8 (C_3), 28.5 (C_{tBu}), 27.5 (C_4), 21.0 ($C_{Me(Ac)}$).

((1*S**,2*R**,3*R**,4*R**)-2-azido-3-((tert-butoxycarbonyl)amino)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopentyl)methyl acetate



In a 100 mL round bottom flask under argon was added **16** (1.63 g, 4.96 mmol, 1.00 equiv.) and anhydrous DMF (25 mL). To this solution was added imidazole (676 mg, 9.93 mmol, 2.00 equiv.) and DMAP (30.3 mg, 0.248 mmol, 5.00 mol %), and the mixture was cooled to 0 °C before TBDPSCl (1.55 mL, 5.96 mmol, 1.20 equiv.) was added dropwise. After 5 minutes, the ice bath was removed and the solution was stirred at RT for 1 h 30. Water was added and the reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 100:0 to 98:2), affording the expected product as a colorless viscous oil (2.70 g, 96%).

HRMS (ESI) calcd for $C_{30}H_{42}N_4NaO_5Si^+$ $(M+Na)^+$ 589.2817, found 589.2813.

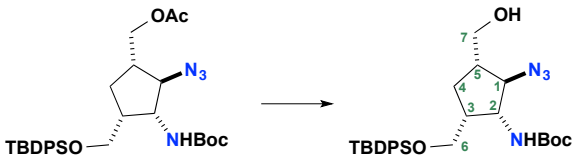
(oil)

IR (cm^{-1}) 3385, 2932, 2099, 1716, 1500, 1365, 1230, 1110, 701.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.61 (m, 4H, H_{TBDPS}), 7.49-7.37 (m, 6H, H_{TBDPS}), 5.79 (d, 1H, *J* = 7.8 Hz, NH), 4.18-4.06 (m, 1H, H_2), 4.13 (dd, 2H, *J* = 2.1, 5.6 Hz, $H_{7a/7b}$), 3.77 (dd, 1H, *J* = 2.8, 10.9 Hz, H_{6a}), 3.60 (dd, 1H, *J* = 3.8, 10.9 Hz, H_{6b}) 3.59-3.52 (m, 1H, H_1), 2.38-2.24 (m, 1H, H_3), 2.14-2.02 (m, 1H, H_5), 2.01 (s, 3H, $H_{Me(Ac)}$), 1.93-1.81 (m, 1H, H_{4a}), 1.71-1.60 (m, 1H, H_{4b}), 1.46 (s, 9H, $H_{tbu(Boc)}$), 1.10 (s, 9H, $H_{tbu(TBDPS)}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 ($C_{CO(Ac)}$), 155.9 ($C_{CO(Boc)}$), 135.7 (4*C_{Ar}), 132.6 (2*$C_{q(Ar)}$), 130.2 (2*C_{Ar}), 128.0 (4*C_{Ar}), 79.7 ($C_{q(Boc)}$), 69.5 (C_1), 65.2 (C_7), 63.6 (C_6), 58.9 (C_2), 44.4 (C_5), 38.8 (C_3), 28.6 ($C_{tbu(Boc)}$), 27.4 (C_4), 27.1 ($C_{tbu(TBDPS)}$), 21.0 ($C_{Me(Ac)}$), 19.3 ($C_{q(TBDPS)}$).

tert-butyl((1*R**,2*R**,3*S**,5*R**)-2-azido-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-(hydroxymethyl)cyclopentyl)carbamate



In a 50 mL round bottom flask were added the substrate (2.67 g, 4.71 mmol, 1.00 equiv.) and methanol (10 mL), and the solution was cooled to 0 °C. To this solution was added a sodium methoxide solution freshly prepared from sodium (433 mg, 18.8 mmol, 4.00 equiv.) and methanol (13 mL). The reaction mixture was stirred at 0 °C for 25 minutes then $NH_4Cl_{sat.}$ was added, followed by water. The reaction mixture was extracted with EtOAc (4 x 30 mL) and then, the combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 98:2 to 80:20), affording the expected product as a colorless viscous oil (2.33 g, 94%).

HRMS (ESI) calcd for $C_{28}H_{40}N_4NaO_4Si^+$ $(M+Na)^+$ 547.2711, found 547.2712.

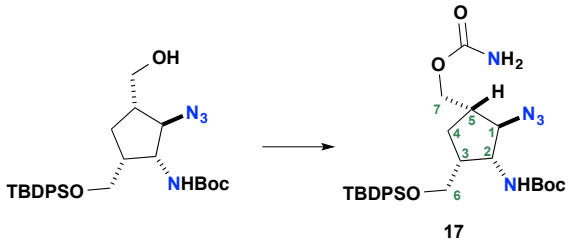
(oil)

IR (cm^{-1}) 3427, 2931, 2097, 1695, 1504, 1365, 1248, 1164, 1110, 700.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H, H_{TBDPS}), 7.42 (m, 6H, H_{TBDPS}), 5.72 (d, 1H, *J* = 8.3 Hz, NH), 4.21-4.08 (m, 1H, H_2), 3.74 (dd, 1H, *J* = 3.2, 10.9 Hz, H_{6a}), 3.70 (d, 2H, *J* = 3.5 Hz, $H_{7a/7b}$), 3.60 (dd, 1H, *J* = 3.9, 10.9 Hz, H_{6b}), 3.55 (t, 1H, *J* = 8.3 Hz, H_1), 2.38-2.27 (m, 1H, H_3), 2.01-1.90 (m, 1H, H_5), 1.90-1.81 (m, 1H, H_{4a}), 1.66-1.57 (m, 1H, H_{4b}), 1.60 (s, 1H, OH), 1.46 (s, 9H, $H_{tbu(Boc)}$), 1.10 (s, 9H, H $C_{tbu(TBDPS)}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (C_{CO}), 135.8 (4*C_{Ar}), 132.8 (2*$C_{q(Ar)}$), 130.1 (2*C_{Ar}), 128.0 (4*C_{Ar}), 79.7 ($C_{q(Boc)}$), 69.4 (C_1), 64.4 (C_7), 63.9 (C_6), 58.7 (C_2), 44.0 (C_5), 38.9 (C_3), 28.6 ($C_{tbu(Boc)}$), 27.1 ($C_{tbu(TBDPS)}$), 27.0 (C_4), 19.3 ($C_{q(TBDPS)}$).

tert-butyl((1*R**,2*R**,3*S**,5*R**)-2-azido-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-((carbamoyloxy)methyl)cyclopentyl)carbamate (**17**)



17

In a 100 mL round bottom flask under argon were added the substrate (2.31 g, 4.40 mmol, 1.00 equiv.) and anhydrous DCM (44 mL). The solution was cooled to 0 °C, and then trichloroacetyl isocyanate (630 µL, 5.28 mmol, 1.20 equiv.) was added. After 2 minutes, the ice bath was removed and the reaction mixture was stirred at RT for 30 minutes before being concentrated under reduced pressure.

The residue was dissolved in MeOH (44 mL), and K_2CO_3 (3.04 g, 22.0 mmol, 5.00 equiv.) was added. The yellow mixture was vigorously stirred for 50 minutes, and then $NH_4Cl_{sat.}$ was added, followed by water. The reaction mixture was extracted with EtOAc (4 x 30 mL) and then, the combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 98:2 to 80:20), affording **17** as a colorless caramel (2.43 g, 97%).

HRMS (ESI) calcd for $C_{29}H_{41}N_5NaO_5Si+$ $(M+Na)^+$ 590.2769, found 590.2763.

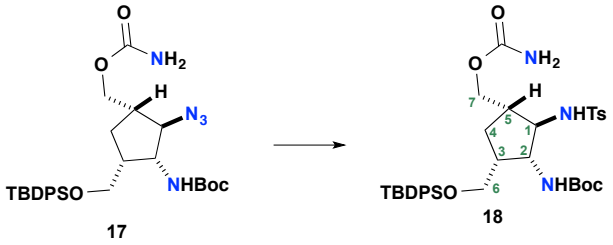
(oil)

IR (cm^{-1}) 3363, 2931, 2099, 1714, 1504, 1328, 1110, 1068, 701.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H, H_{TBDPS}), 7.48-7.39 (m, 6H, H_{TBDPS}), 5.76 (d, 1H, *J* = 8.0 Hz, NH), 4.51 (br. s, 2H, NH_2), 4.15 (dd, 1H, *J* = 5.0, 11.0 Hz, H_{7a}), 4.12-4.06 (m, 2H, $H_{7b/2}$), 3.78 (d, 1H, *J* = 10.8 Hz, H_{6a}), 3.63-3.56 (m, 2H, $H_{6b/1}$), 2.35-2.27 (m, 1H, H_3), 2.12-2.03 (m, 1H, H_5), 1.90-1.83 (m, 1H, H_{4a}), 1.70-1.61 (m, 1H, H_{4b}), 1.46 (s, 9H, $H_{tbu(Boc)}$), 1.10 (s, 9H, $H_{tbu(TBDPS)}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 ($C_{CO(Boc)}$), 155.9 ($C_{CO(Carb)}$), 135.8 (C_{Ar}), 132.8 ($C_{q(Ar)}$), 132.6 ($C_{q(Ar)}$), 130.2 (C_{Ar}), 128.1 (C_{Ar}), 79.8 ($C_{q(Boc)}$), 69.5 (C_1), 65.7 (C_7), 63.7 (C_6), 58.9 (C_2), 41.7 (C_5), 38.7 (C_3), 28.6 ($C_{tbu(Boc)}$), 27.2 ($C_{tbu(TBDPS)}$), 27.1 (C_4), 19.3 ($C_{q(TBDPS)}$).

tert-butyl((1*R**,2*R**,3*S**,5*R**)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-((carbamoyloxy)methyl)-2-((4-methylphenyl)sulfonamido)cyclopentyl)carbamate (**18**)



In a 250 mL round bottom flask were added **17** (2.41 g, 4.24 mmol, 1.00 equiv.), Pd/C (10 % wt on C, 226 mg, 5.00 mol %) and methanol (42 mL). The suspension was purged 5 times with H_2 and was stirred at RT for 1 h 30. The reaction mixture was filtered over celite, washed with MeOH, and the filtrate was concentrated under reduced pressure. The residue was used for the next step without further purification.

To the crude amine in anhydrous DCM (42 mL) under argon was added triethylamine (887 µL, 6.37 mmol, 1.50 equiv.) and then TsCl (971 mg, 5.09 mmol, 1.20 equiv.). The reaction mixture was stirred at RT for 1 h, then water was added, and the solution was extracted with DCM (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 95:5 to 60:40), affording **18** as a white solid (2.24 g, 76%).

HRMS (ESI) calcd for $C_{36}H_{50}N_3O_7SSi^+$ $(M+H)^+$ 696.3133, found 696.3139.

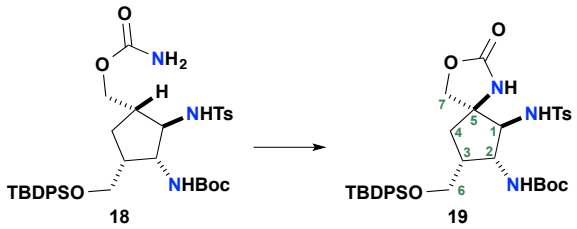
mp 81-83 °C

IR (cm^{-1}) 3370, 2931, 1695, 1508, 1325, 1155, 1092, 701.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (app. d, 2H, *J* = 8.4 Hz, H_{Ts}), 7.66-7.60 (m, 4H, H_{TBDPS}), 7.49-7.37 (m, 6H, H_{TBDPS}), 7.25 (d, 2H, *J* = 8.4 Hz, H_{Ts}), 5.84 (d, 1H, *J* = 8.0 Hz, NH_{Boc}), 5.77 (app. d, 1H, *J* = 8.0 Hz, NH_{Ts}), 4.33 (br. s, 2H, NH_2), 4.09 (dd, 1H, *J* = 3.9, 10.9 Hz, H_{7a}), 3.96 (dt, 1H, *J* = 8.4, 10.5 Hz, H_2), 3.87 (dd, 1H, *J* = 5.1, 10.8 Hz, H_{7b}), 3.60 (dd, 1H, *J* = 3.4, 10.8 Hz, H_{6a}), 3.50 (dd, 1H, *J* = 5.7, 10.8 Hz, H_{6b}), 3.49-3.83 (m, 1H, H_1), 2.40 (s, 3H, H_{Me}), 2.37-2.24 (m, 1H, H_3), 2.09-1.96 (m, 1H, H_5), 1.95-1.84 (m, 1H, H_{4a}), 1.42 (s, 9H, H_{Boc}), 1.40-1.31 (m, 1H, H_{4b}), 1.06 (s, 9H, H_{TBDPS}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2 ($C_{CO(Boc)}$), 156.8 ($C_{CO(Carb)}$), 143.1 ($C_{q(Ts)}$), 138.4 ($C_{q(Ts)}$) 135.8 (C_{Ar}), 133.0 ($C_{q(Ar)}$), 132.5 ($C_{q(Ar)}$), 130.2 ($C_{q(Ar)}$), 129.7 (C_{Ts}), 128.1 (C_{Ar}), 127.2 (C_{Ts}), 79.7 ($C_{q(Boc)}$), 65.1 (C_1), 64.7 (C_7), 60.7 (C_6), 58.6 (C_2), 41.8 (C_5), 40.0 (C_3), 28.5 ($C_{tbu(Boc)}$), 27.1 ($C_{tbu(TBDPS)}$), 26.6 (C_4), 21.7 (C_{Me}), 19.4 ($C_{q(TBDPS)}$).

tert-butyl((5*R**,6*S**,7*R**,8*R**)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6-((4-methylphenyl)sulfonamido)-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl)carbamate (**19**)



In a seal tube under argon were added **18** (14 mg, 20 µmol, 1.0 equiv.), $Rh_2(OAc)_4$ (0.9 mg, 2.0 µmol, 10 mol %), MgO (2.6 mg, 60 µmol, 3.0 equiv.) and anhydrous benzene (0.4 mL), followed by $PhI(OCOCMe_2Ph)_2$ (16 mg, 30 µmol, 1.5 equiv.) in one portion. The resulting mixture was stirred at 50 °C for 18 h, and was cooled to rt. The suspension was directly purified by preparative chromatography (SiO_2, DCM/Acetone 9:1), affording **19** as a white solid (8.8 mg, 63%) and **18** as a white solid (1.8 mg, 13%)

HRMS (ESI) calcd for $C_{36}H_{47}N_3NaO_7SSi^+$ $(M+Na)^+$ 716.2796, found 716.2802.

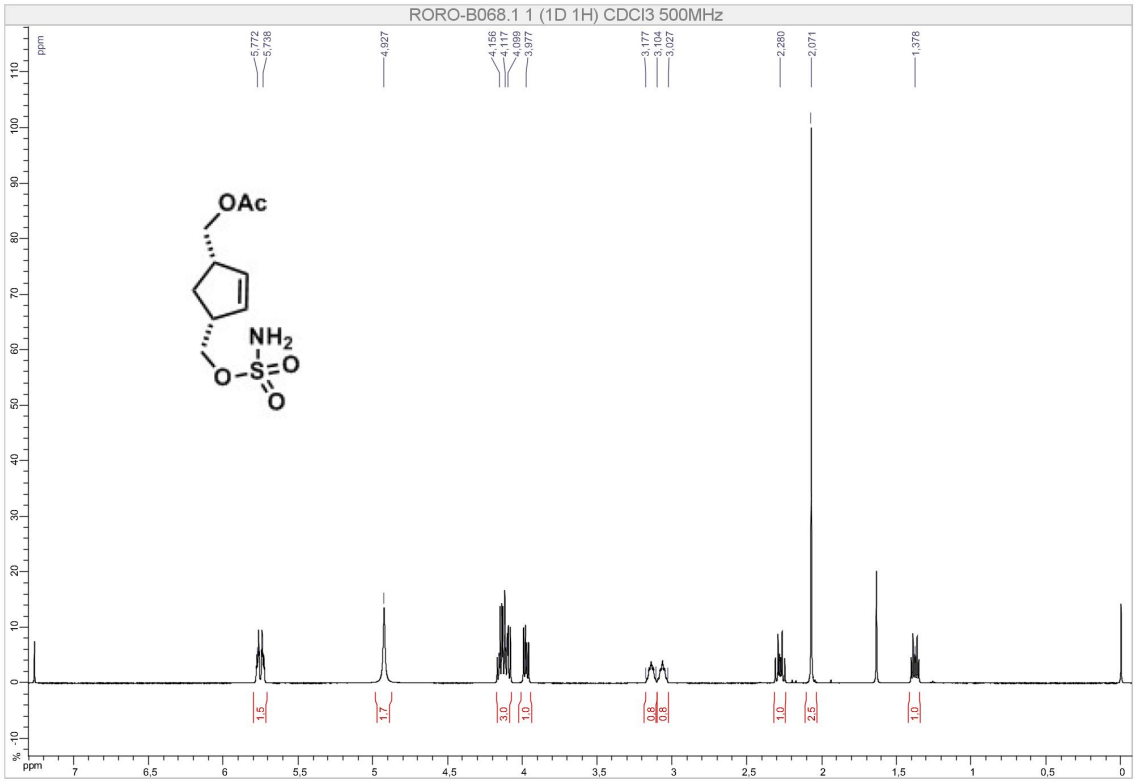
mp 125-127 °C

IR (cm^{-1}) 3243, 2931, 1725, 1504, 1335, 1154, 1094, 1040, 700.

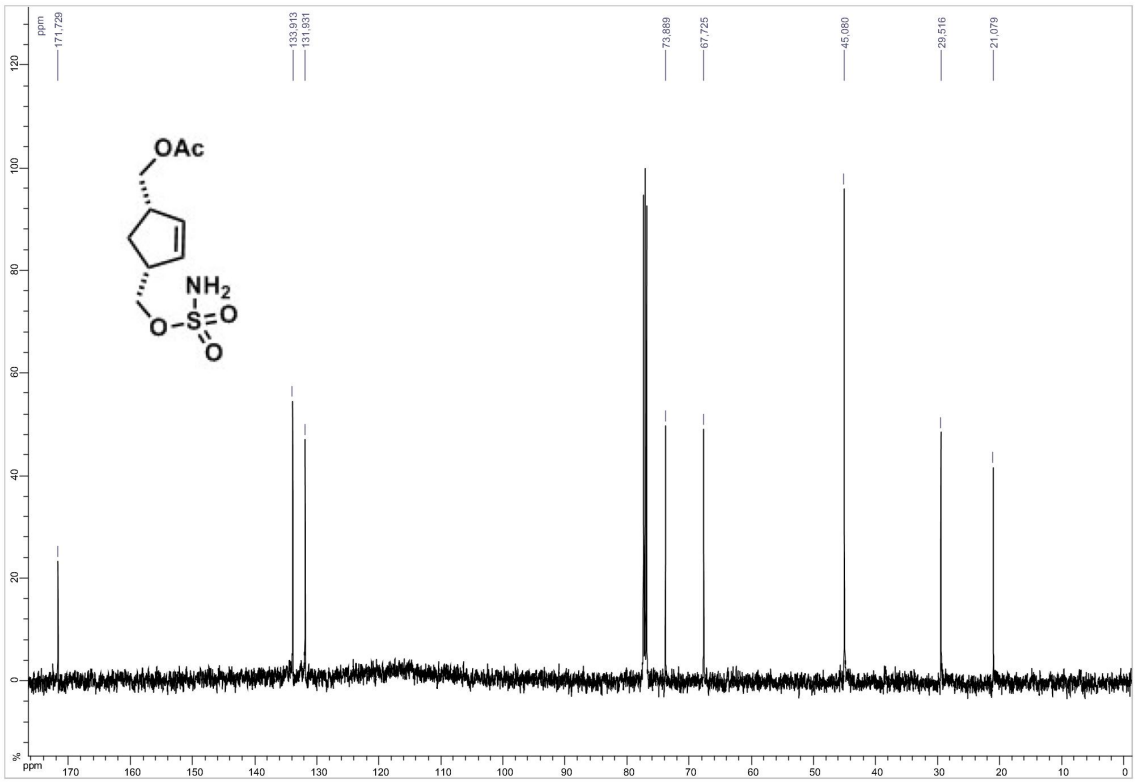
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (app. d, 2H, *J* = 8.4 Hz, H_{Ts}), 7.59 (m, 4H, H_{TBDPS}), 7.49-7.35 (m, 6H, H_{TBDPS}), 7.20 (d, 2H, *J* = 8.4 Hz, H_{Ts}), 7.16 (br. s, 1H, NH_{Carb}), 6.52 (d, 1H, *J* = 9.0 Hz, NH_{Boc}), 5.22 (d, 1H, *J* = 8.4 Hz, NH_{Ts}), 4.11-3.95 (m, 1H, H_2), 4.07 (s, 2H, $H_{7a/7b}$), 3.70 (app. d, 1H, *J* = 10.7 Hz, H_{6a}), 3.59 (app. t, 1H, *J* = 9.7 Hz, H_1), 3.41 (dd, 1H, *J* = 2.5, 10.7 Hz, H_{6b}), 2.45-2.34 (m, 1H, H_3), 2.37 (s, 3H, H_{Me}), 2.19-2.07 (m, 1H, H_{4a}), 1.95-1.86 (m, 1H, H_{4b}), 1.36 (s, 9H, H_{Boc}), 1.08 (s, 9H, H_{TBDPS}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 ($C_{CO(Boc)}$), 156.4 ($C_{CO(Carb)}$), 143.1 ($C_{q(Ts)}$), 138.8 ($C_{q(Ts)}$) 135.7 (C_{Ar}), 132.7 ($C_{q(Ar)}$), 130.2 ($C_{q(Ar)}$), 130.1 ($C_{q(Ar)}$), 129.8 (C_{Ts}), 128.1 (C_{Ar}), 127.2 (C_{Ts}), 79.6 ($C_{q(Boc)}$), 72.3 (C_1), 64.0 (C_7), 63.4 (C_5), 63.1 (C_6), 55.6 (C_2), 36.2 (C_3), 35.3 (C_4), 28.5 ($C_{tbu(Boc)}$), 27.3 ($C_{tbu(TBDPS)}$), 21.7 (C_{Me}), 19.4 ($C_{q(TBDPS)}$).

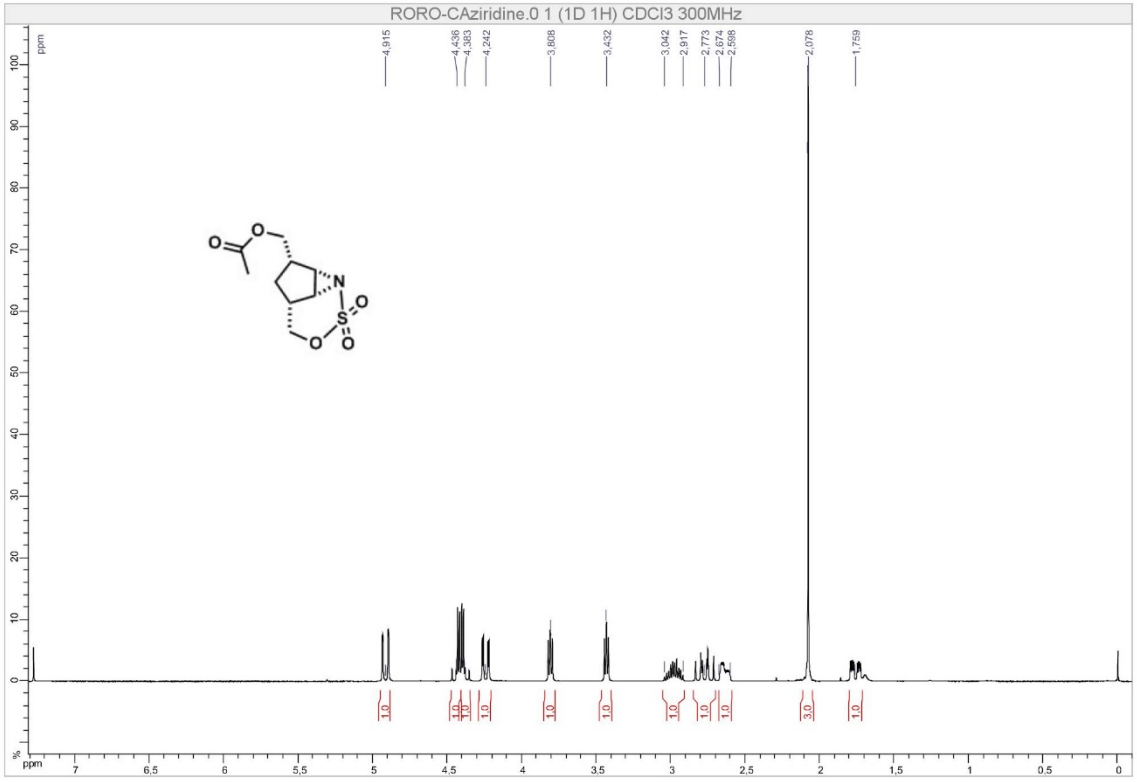
^{1}H NMR ($CDCl_3$, 500 MHz)



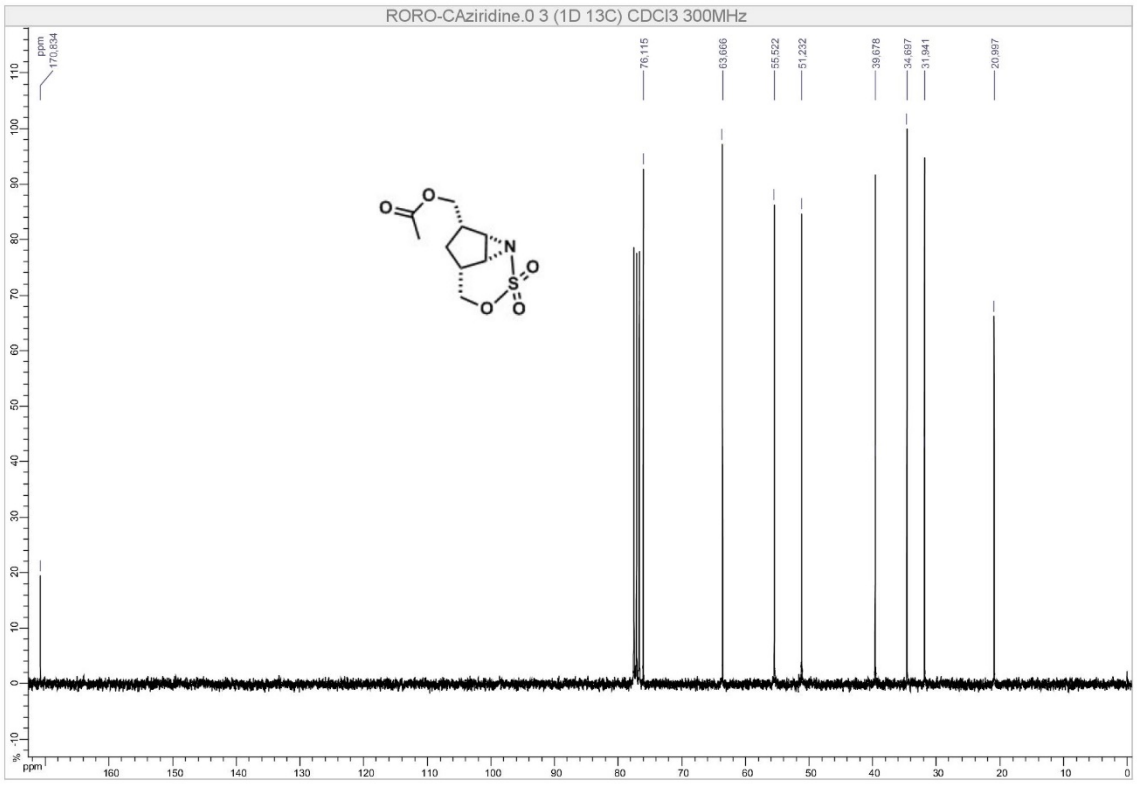
^{13}C NMR ($CDCl_3$, 75 MHz)



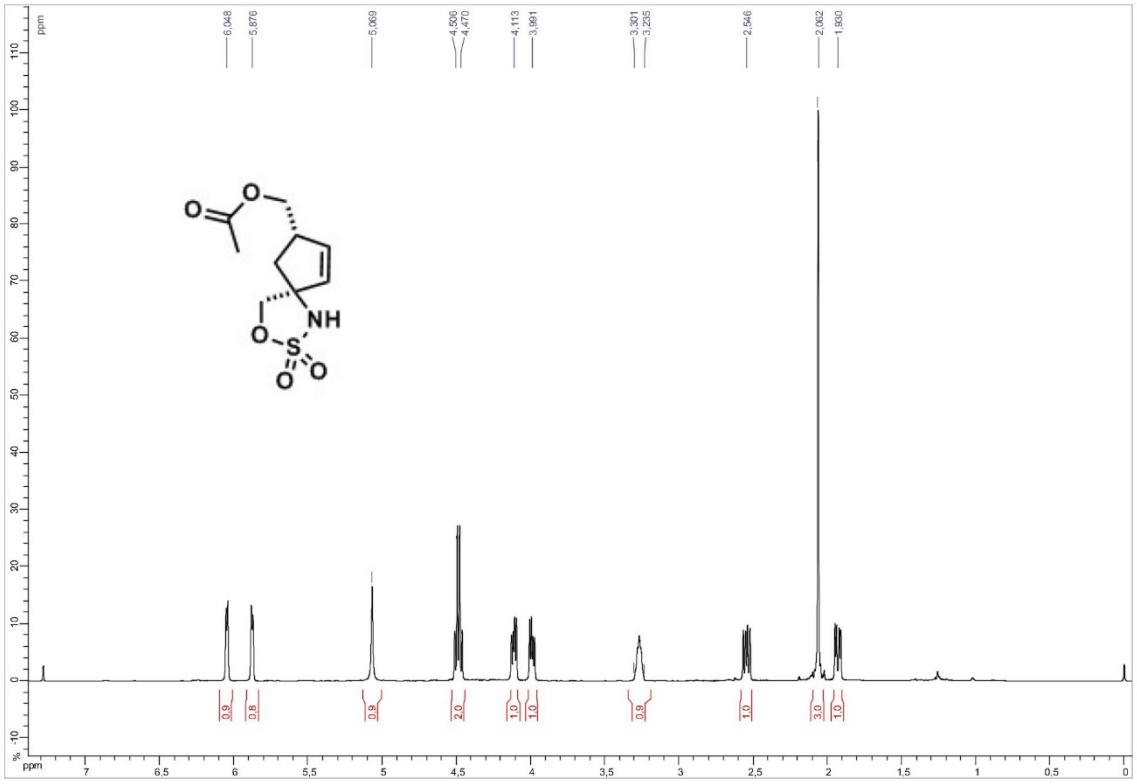
^{1}H NMR ($CDCl_3$, 300 MHz)



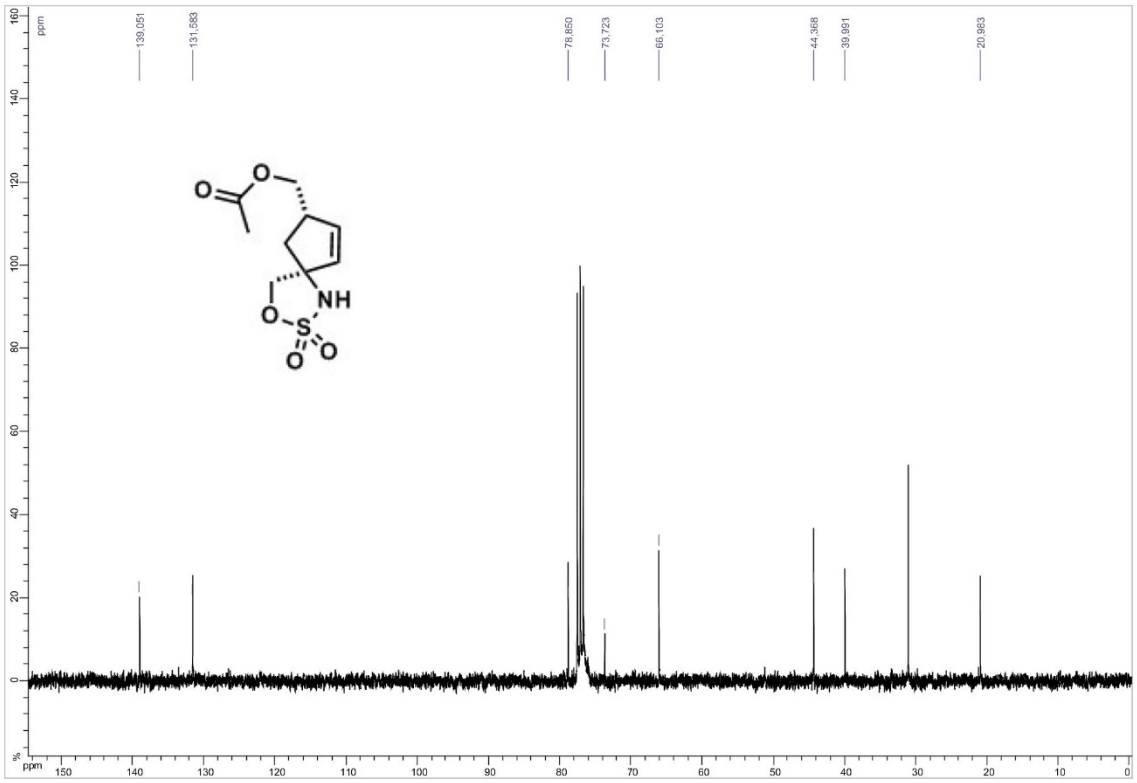
^{13}C NMR ($CDCl_3$, 75 MHz)



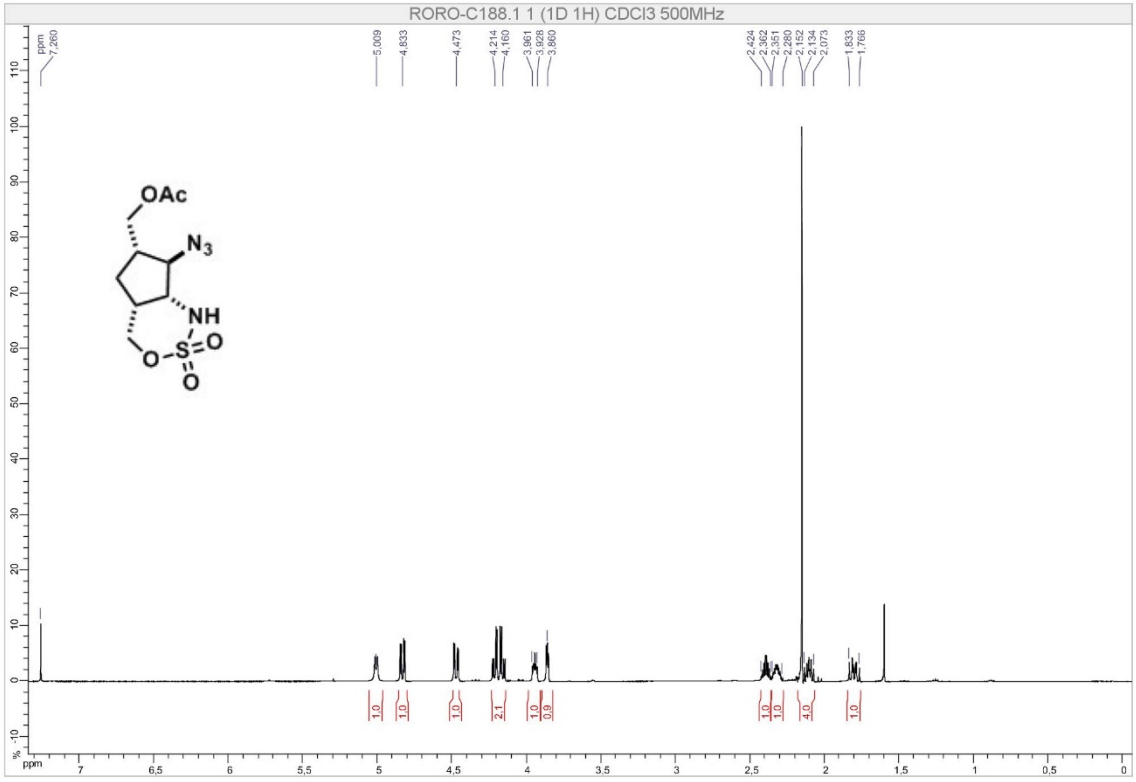
^{1}H NMR ($CDCl_3$, 500 MHz)



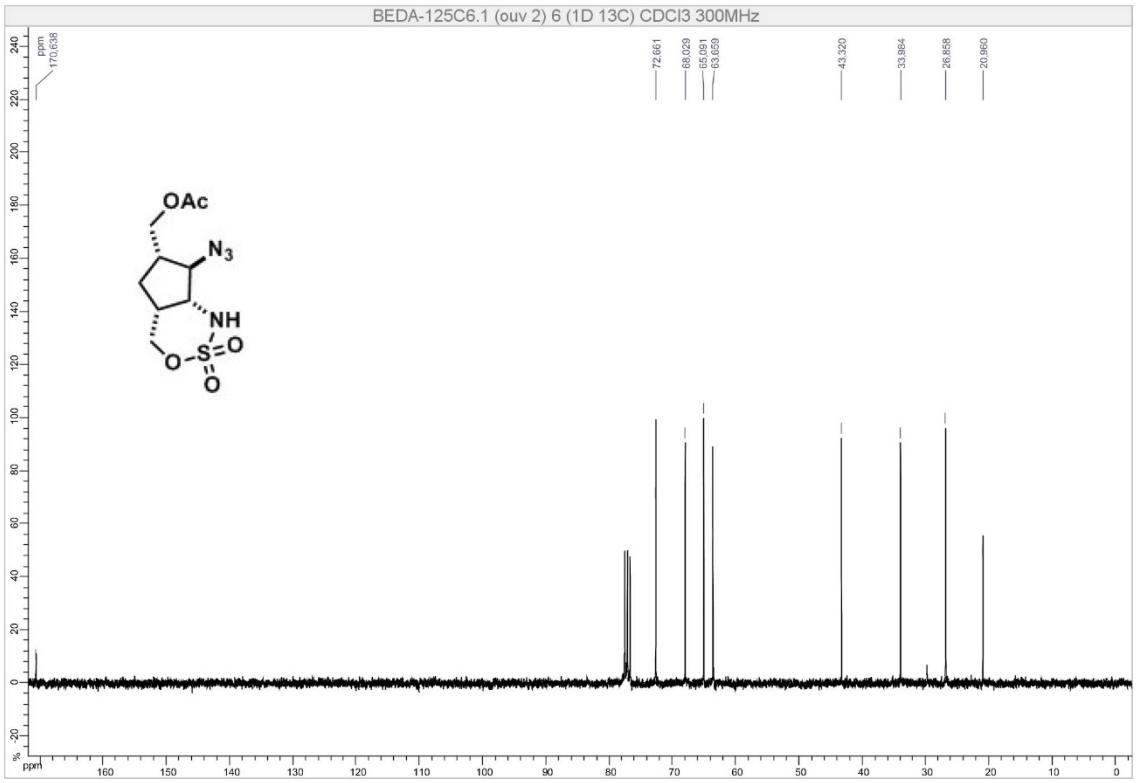
^{13}C NMR ($CDCl_3$, 75 MHz)



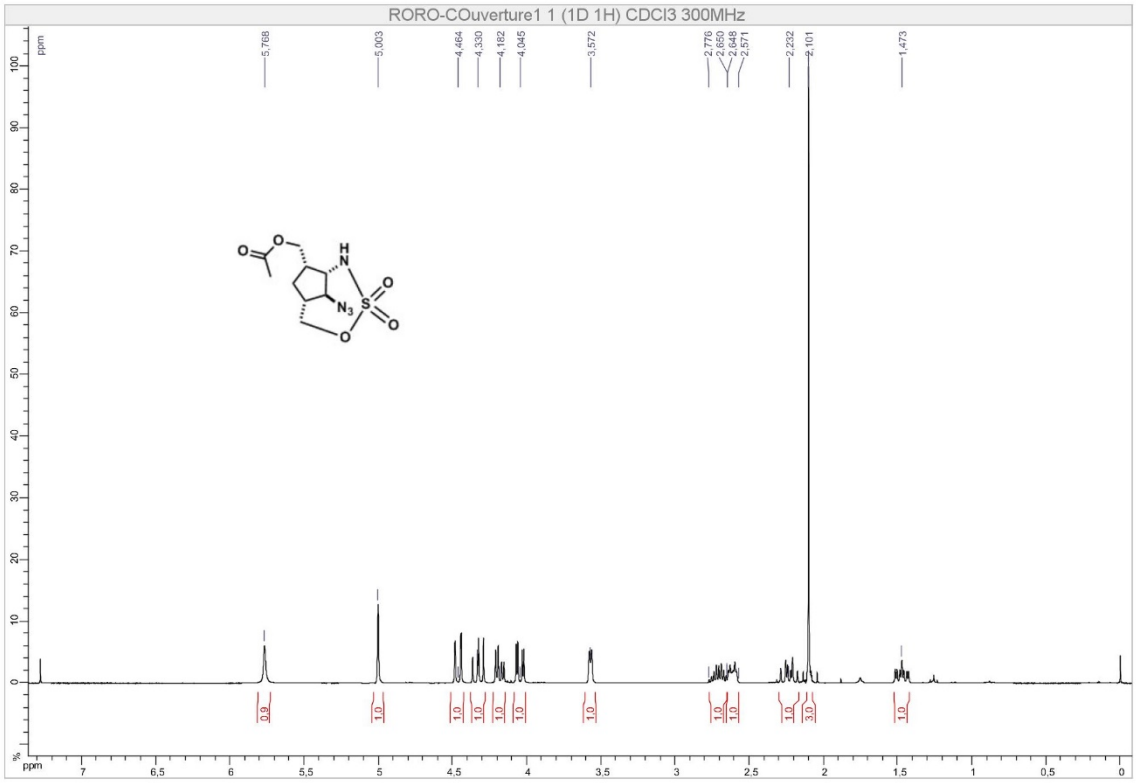
^{1}H NMR ($CDCl_3$, 500 MHz)



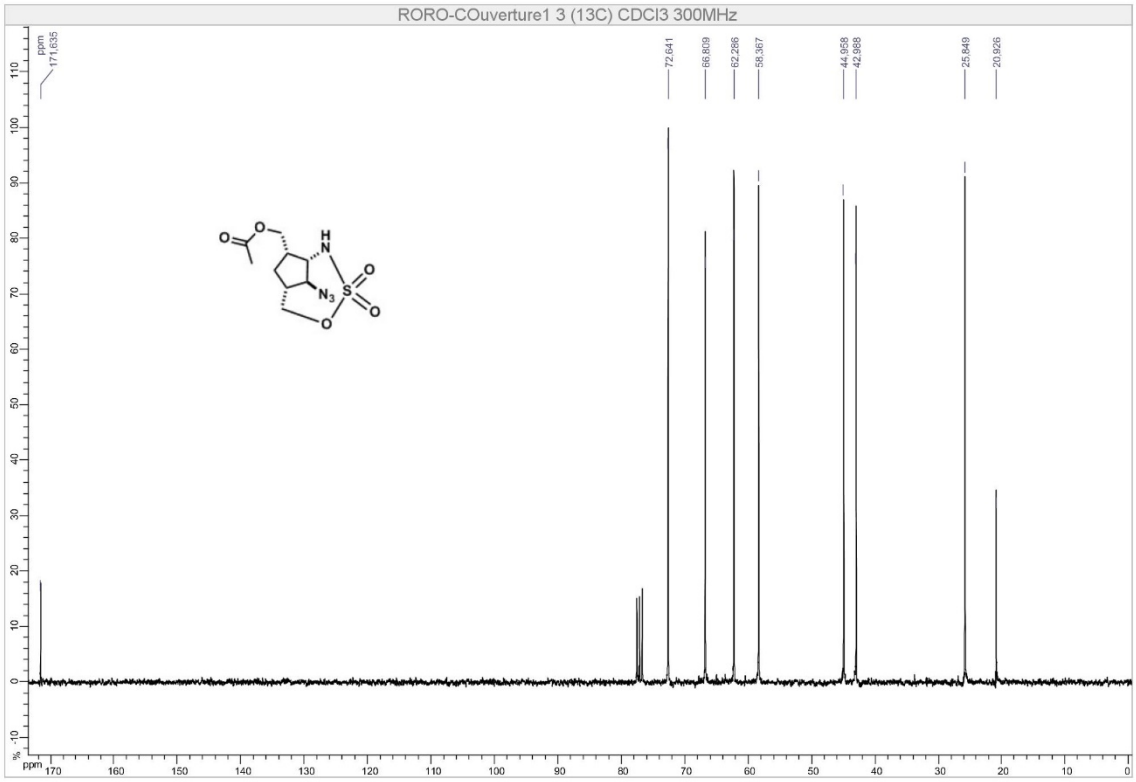
^{13}C NMR ($CDCl_3$, 75 MHz)



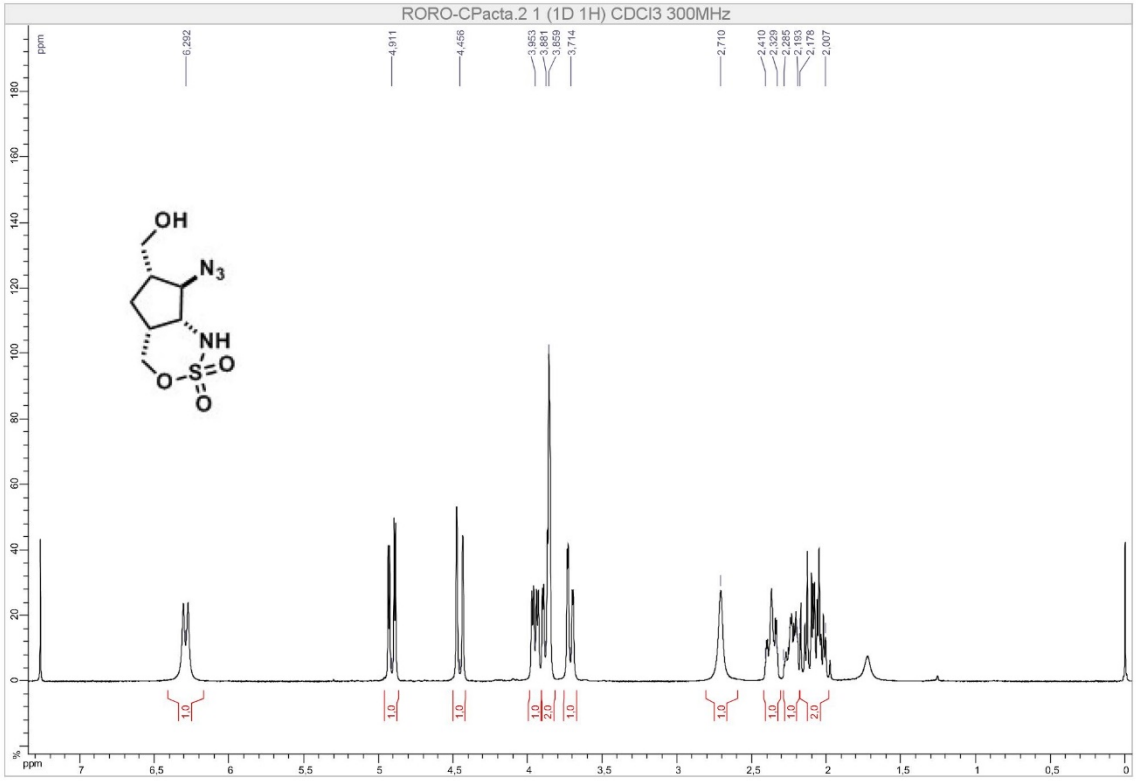
^{1}H NMR ($CDCl_3$, 300 MHz)



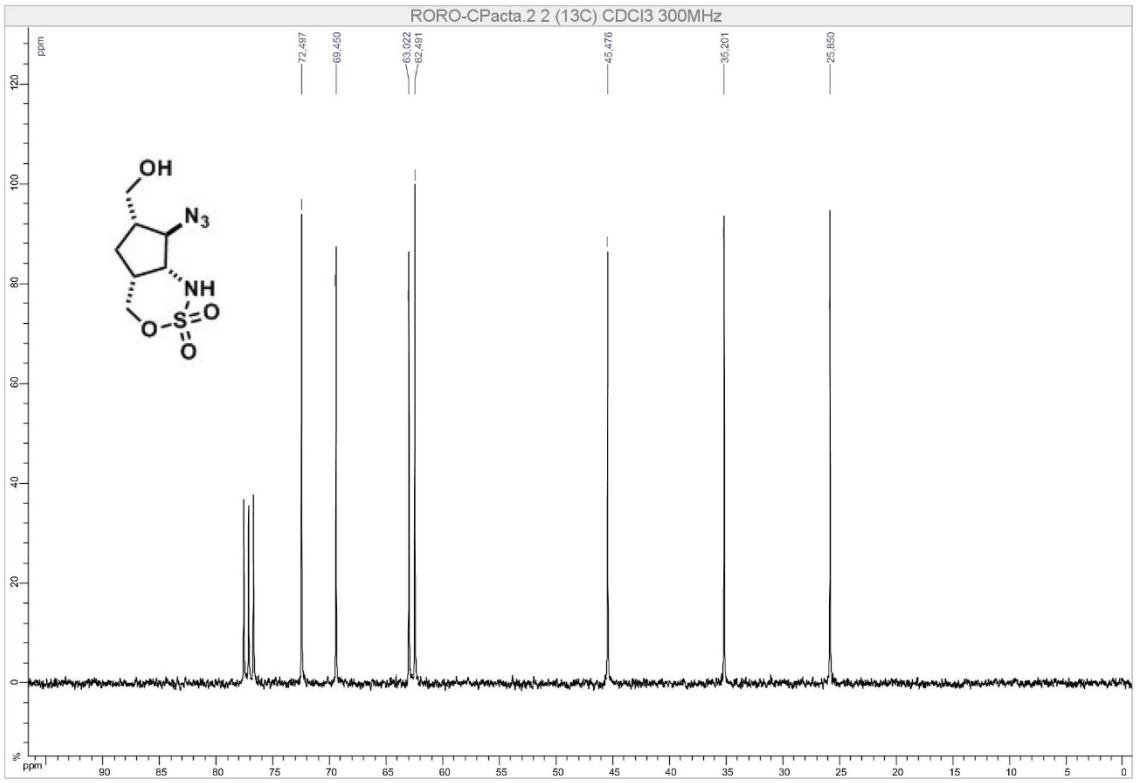
^{13}C NMR ($CDCl_3$, 75 MHz)



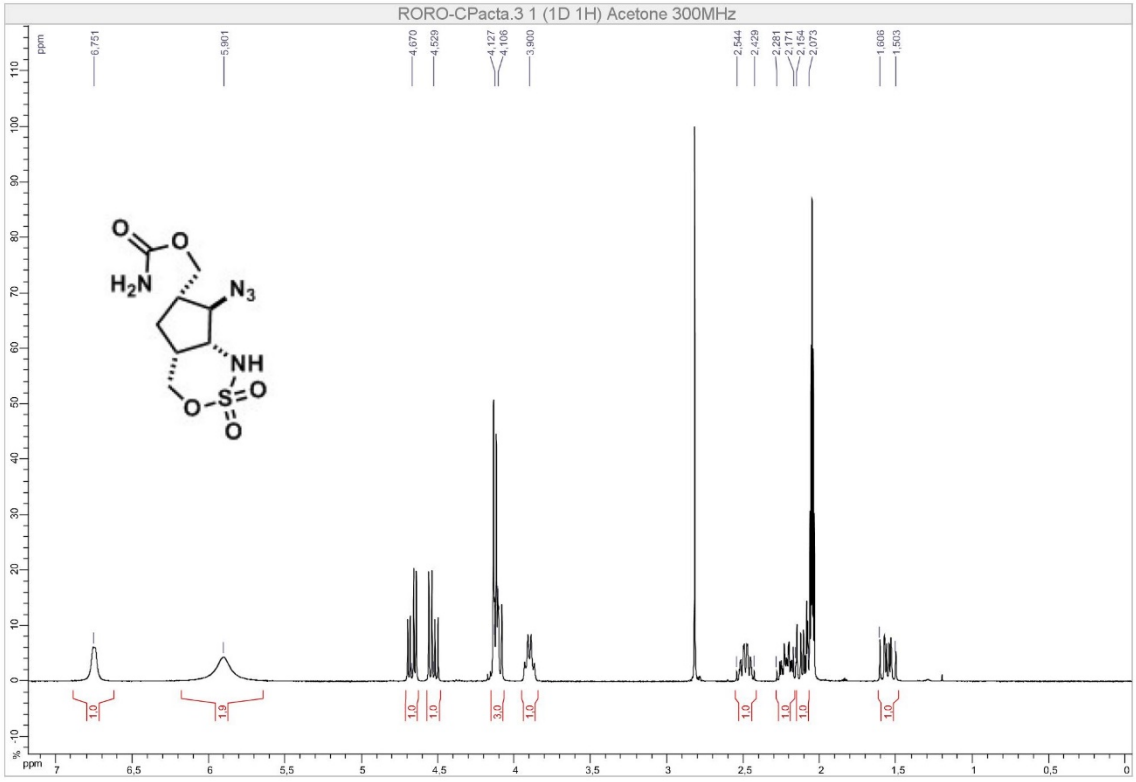
^{1}H NMR ($CDCl_3$, 300 MHz)



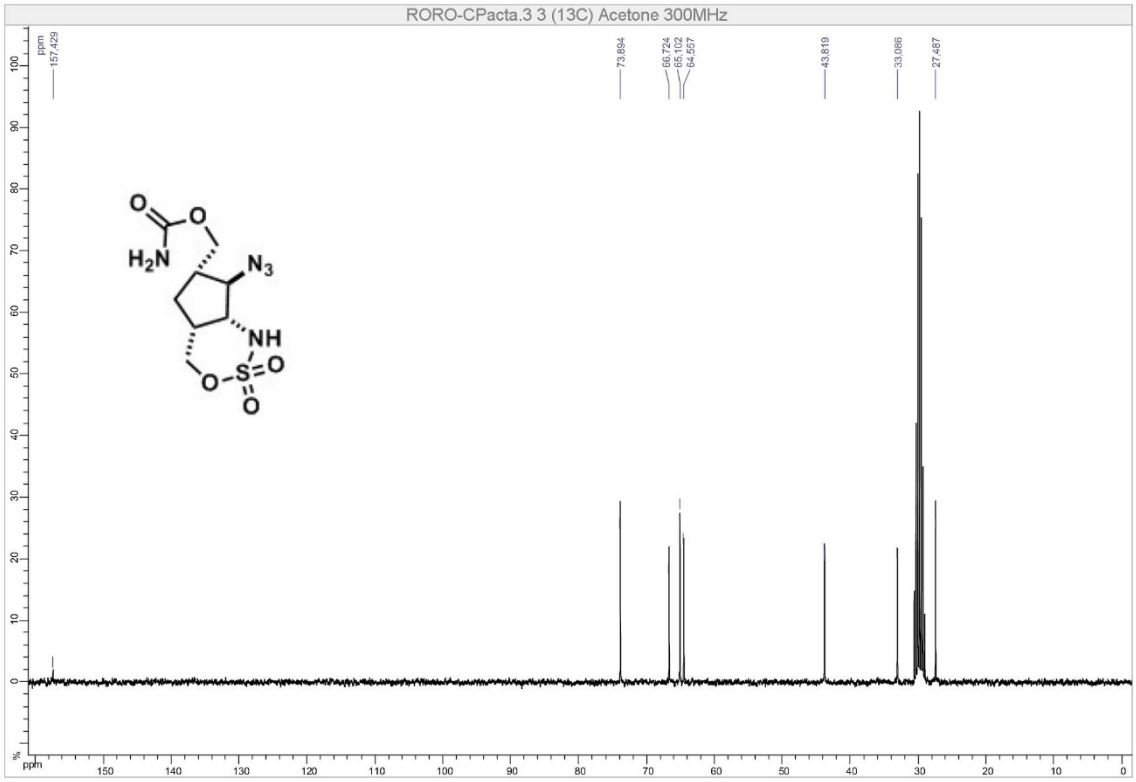
^{13}C NMR ($CDCl_3$, 75 MHz)



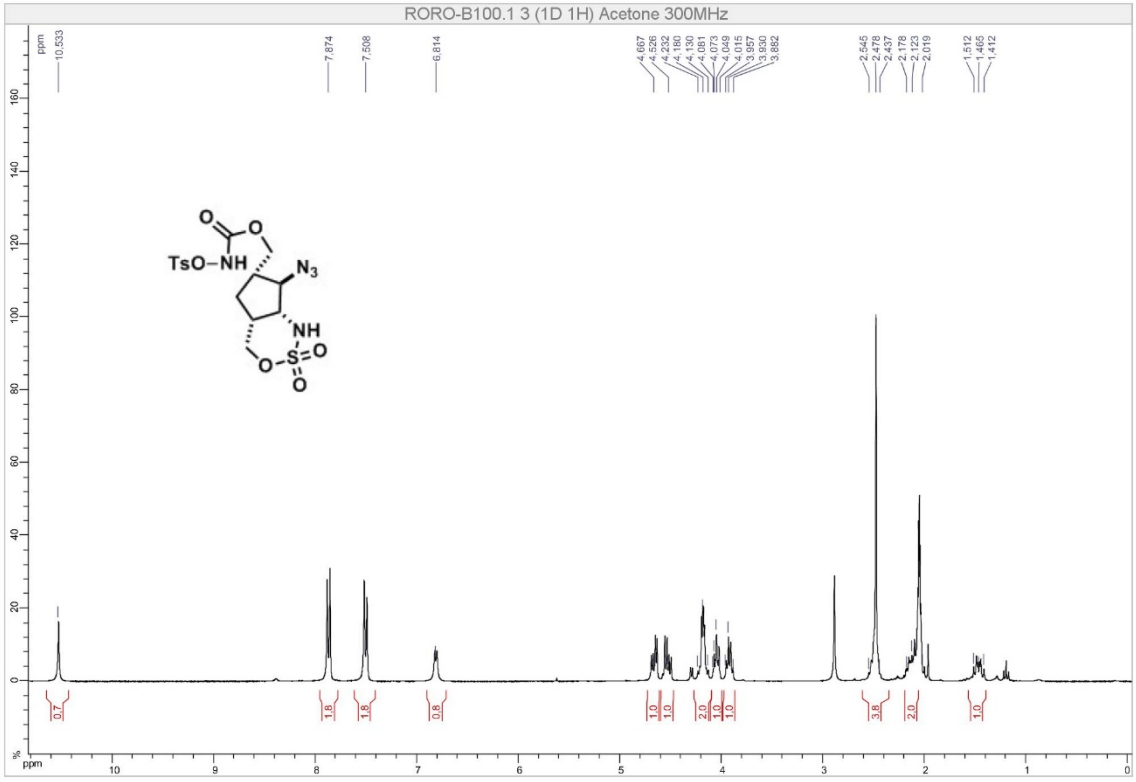
^{1}H NMR ($(CD_3)_2CO$, 300 MHz)



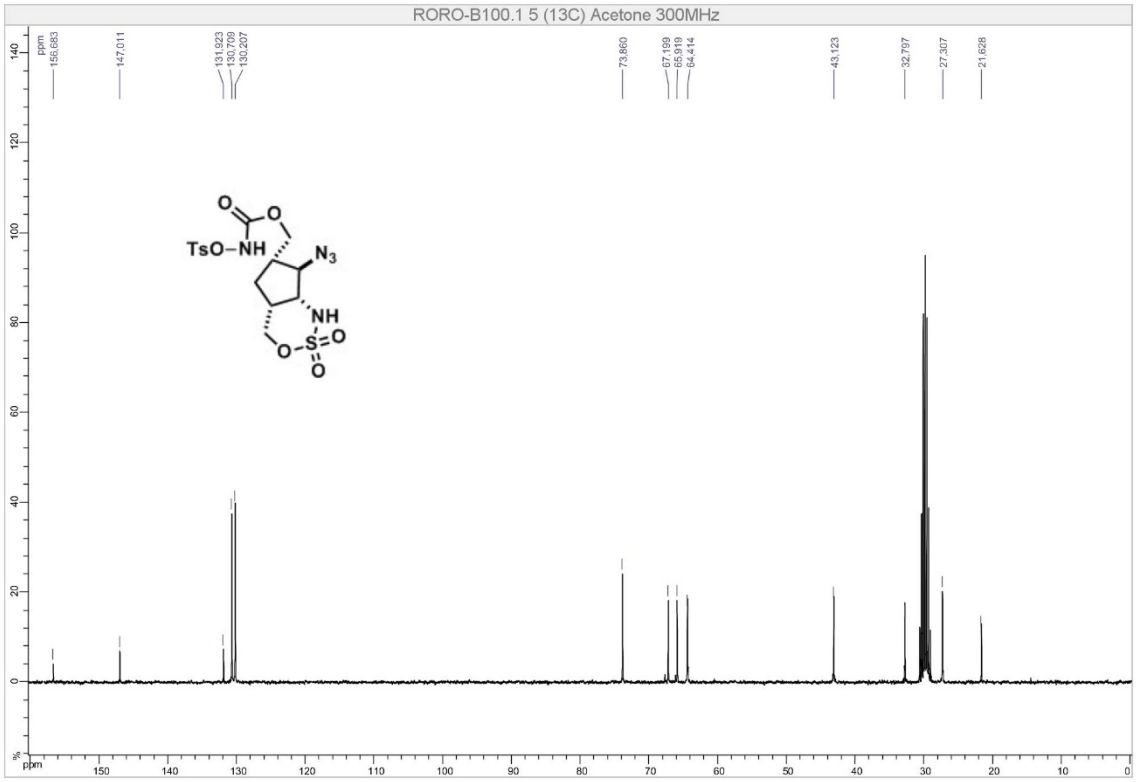
^{13}C NMR ($(CD_3)_2CO$, 75 MHz)



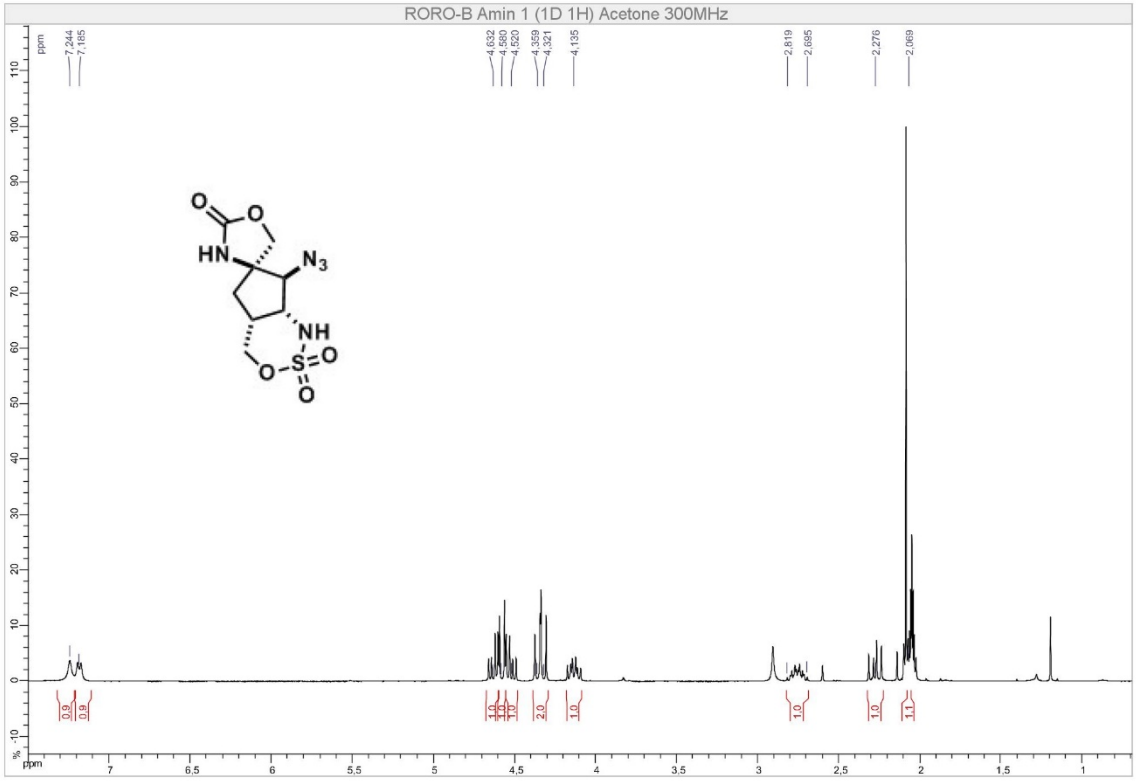
^{1}H NMR ($(CD_3)_2CO$, 300 MHz)



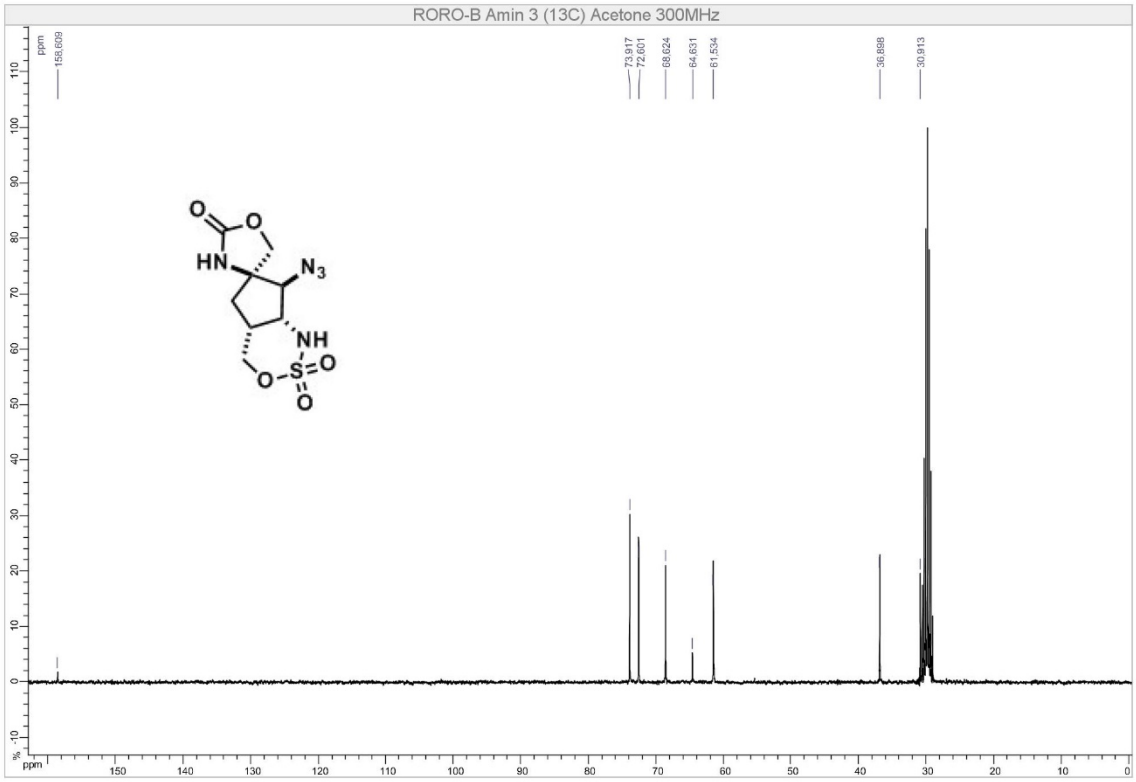
^{13}C NMR ($(CD_3)_2CO$, 75 MHz)



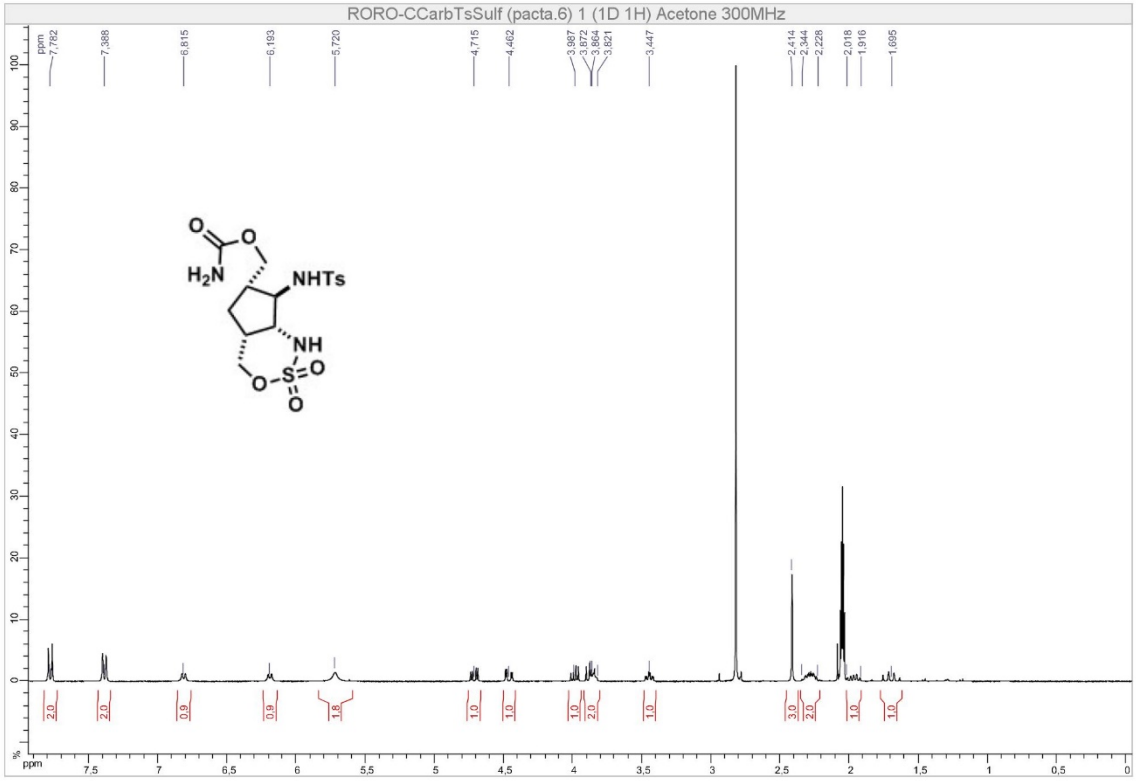
^{1}H NMR ($(CD_3)_2CO$, 300 MHz)



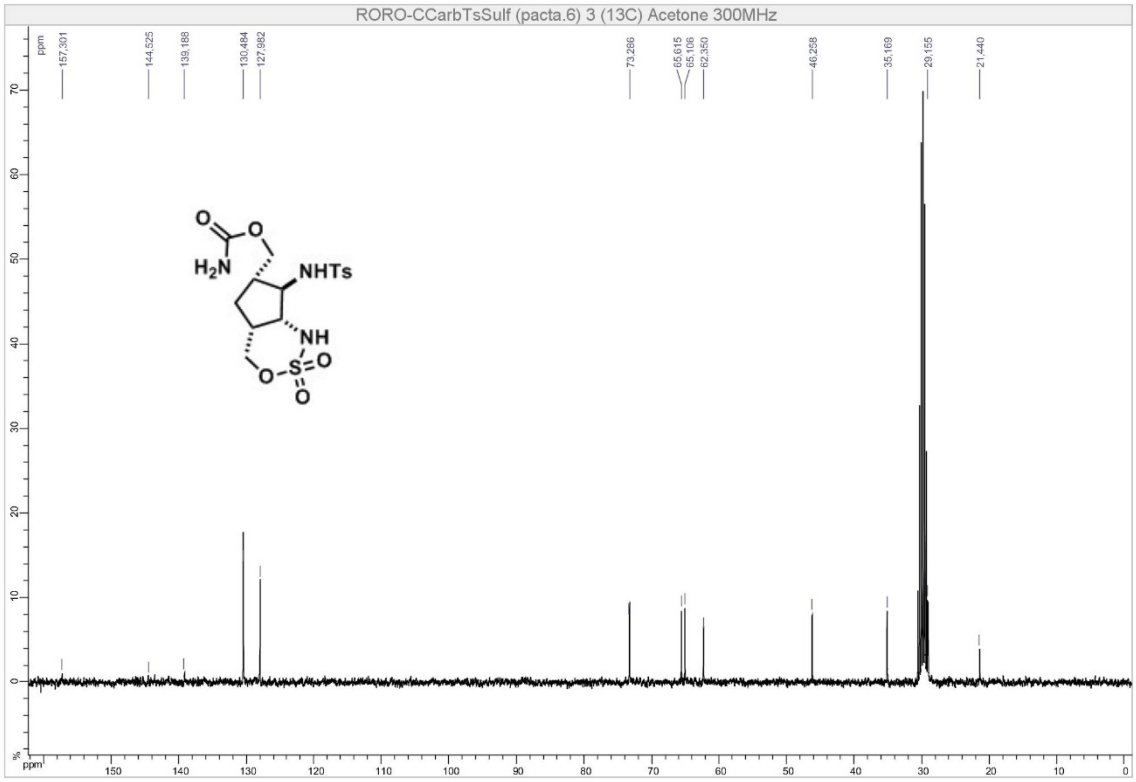
^{13}C NMR ($(CD_3)_2CO$, 75 MHz)



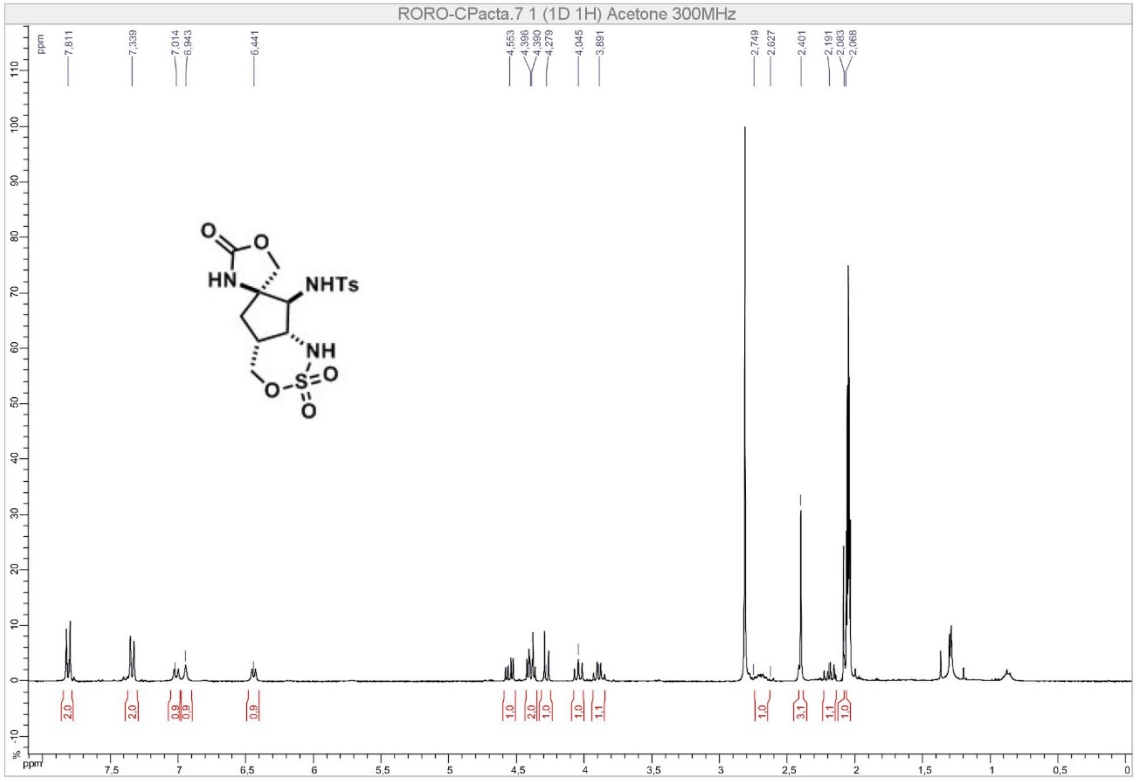
^{1}H NMR ($(CD_3)_2CO$, 300 MHz)



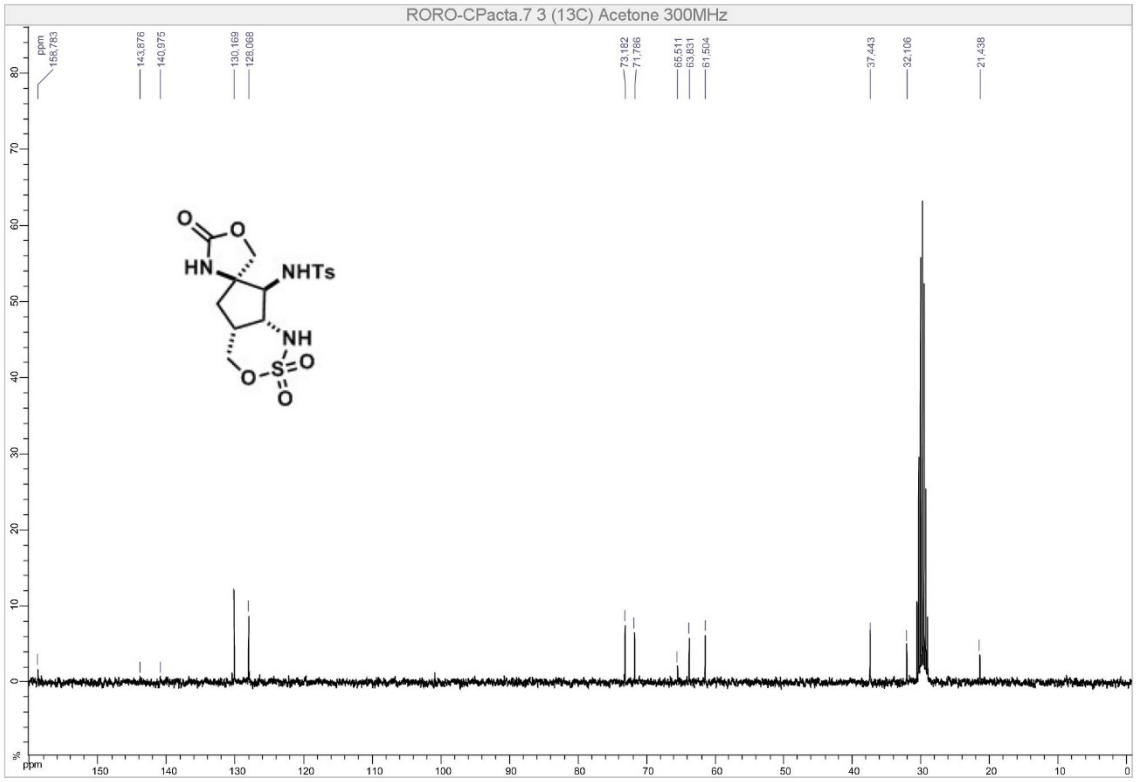
^{13}C NMR ($(CD_3)_2CO$, 75 MHz)



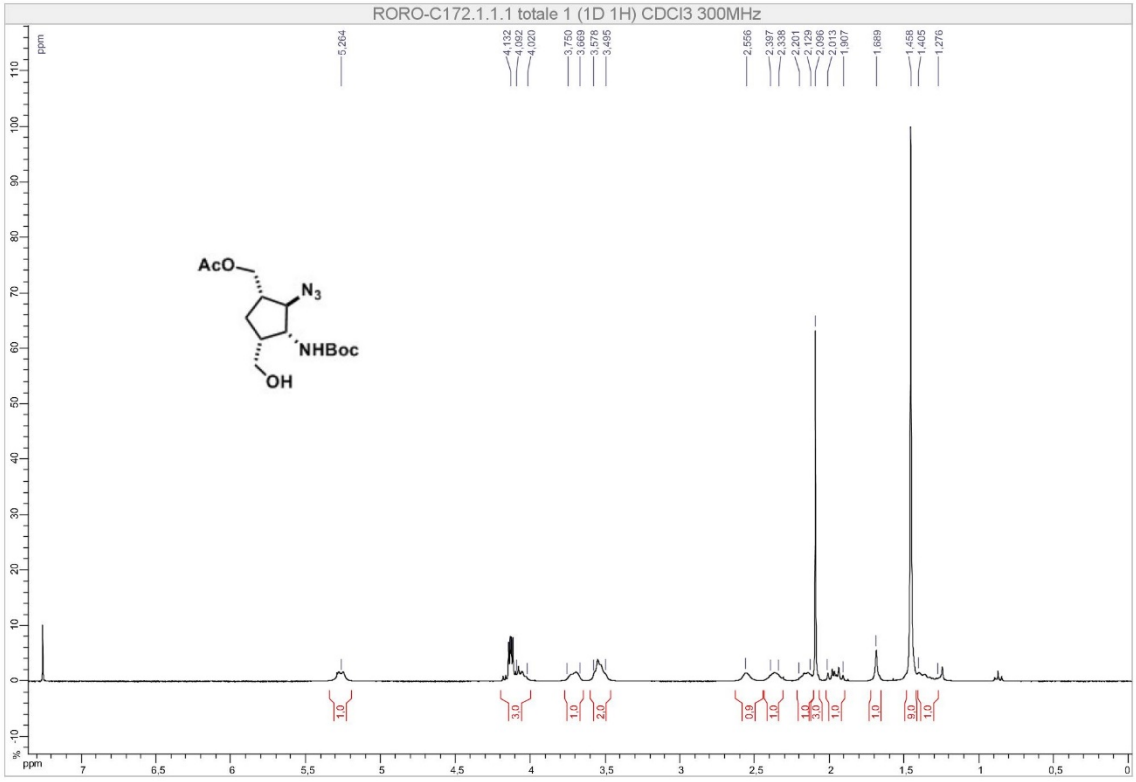
^{1}H NMR ($(CD_3)_2CO$, 300 MHz)



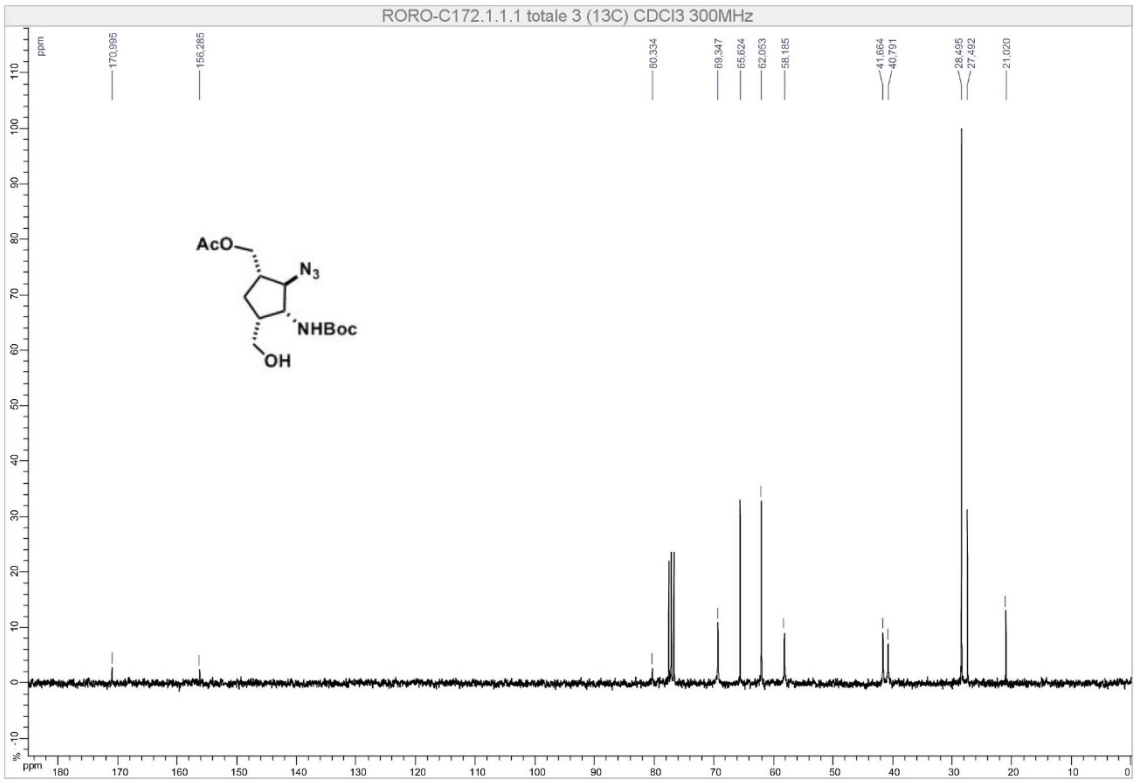
^{13}C NMR ($(CD_3)_2CO$, 75 MHz)



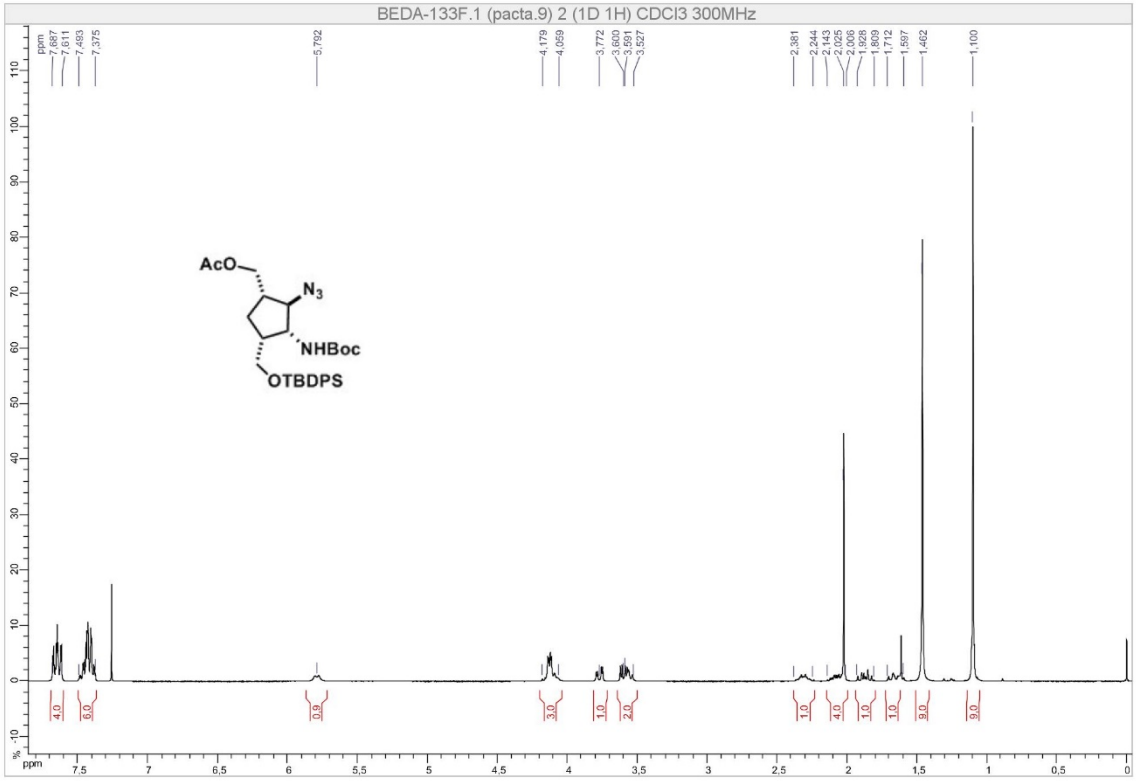
^{1}H NMR ($CDCl_3$, 300 MHz)



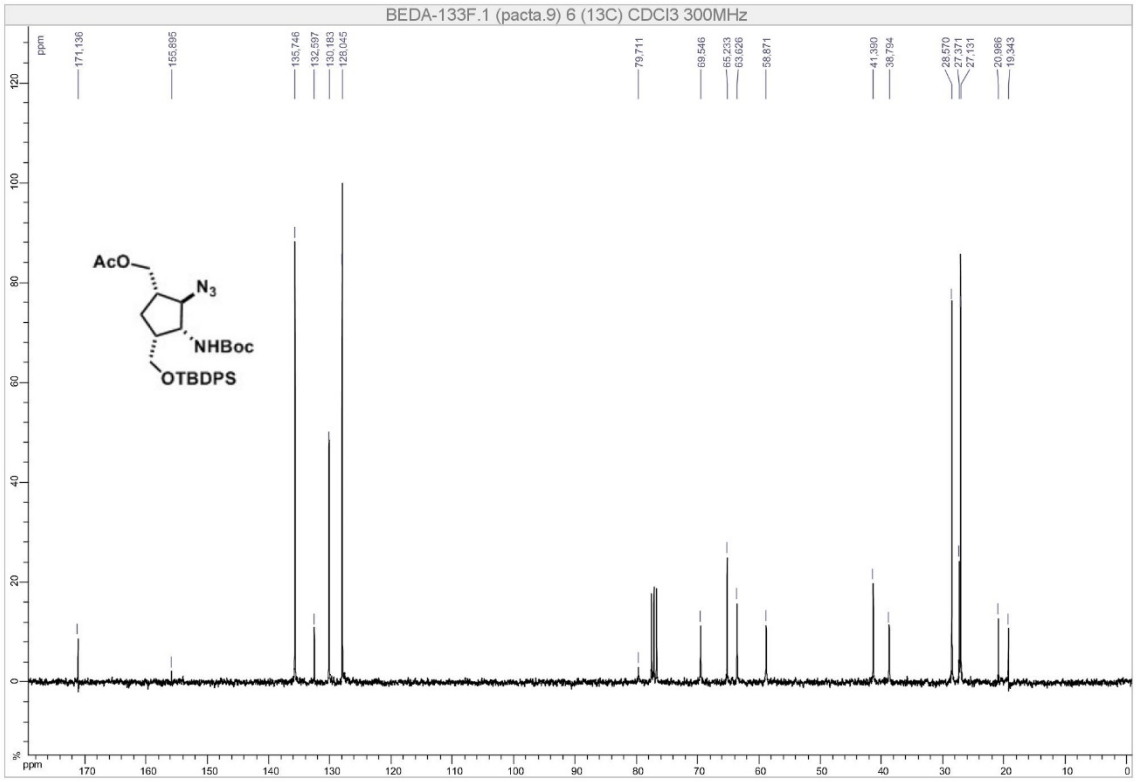
^{13}C NMR ($CDCl_3$, 75 MHz)



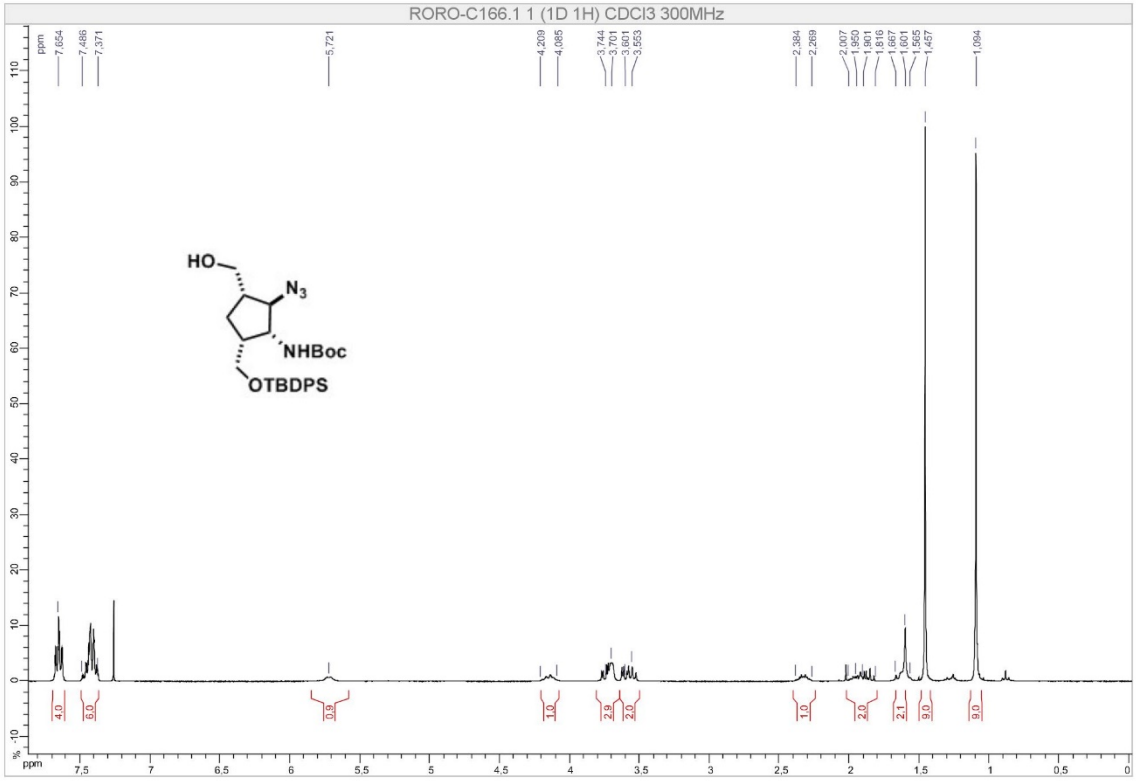
^{1}H NMR ($CDCl_3$, 300 MHz)



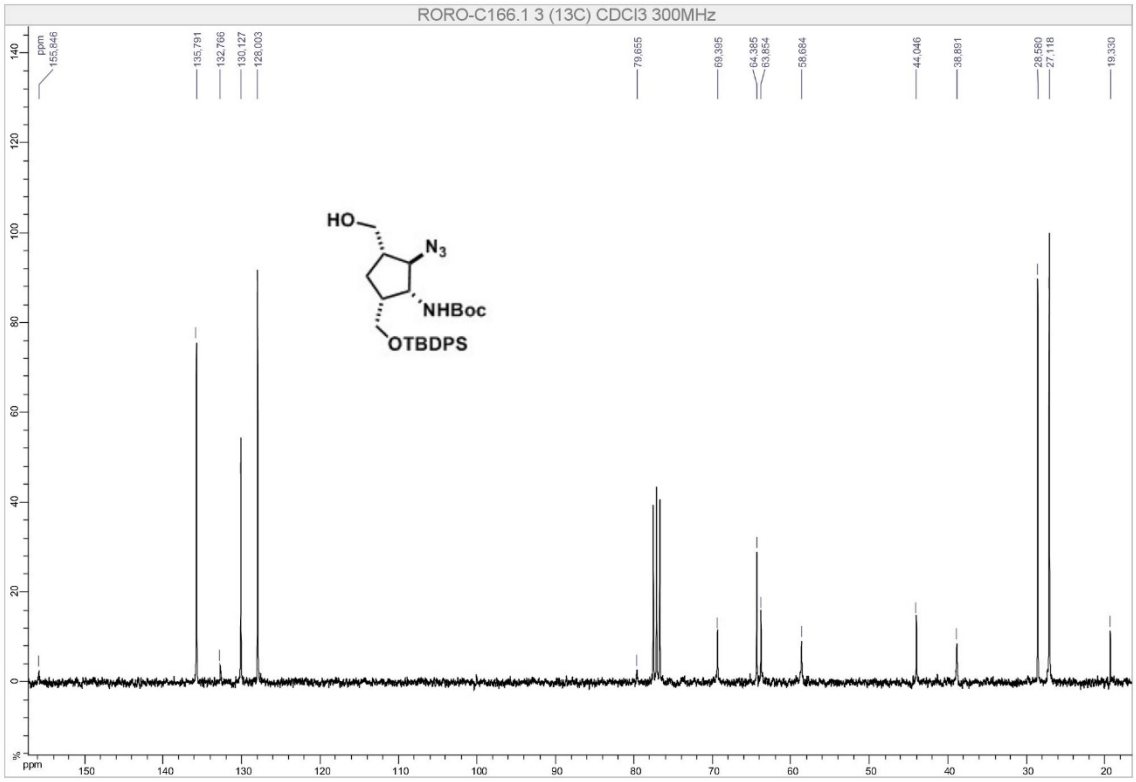
^{13}C NMR ($CDCl_3$, 75 MHz)



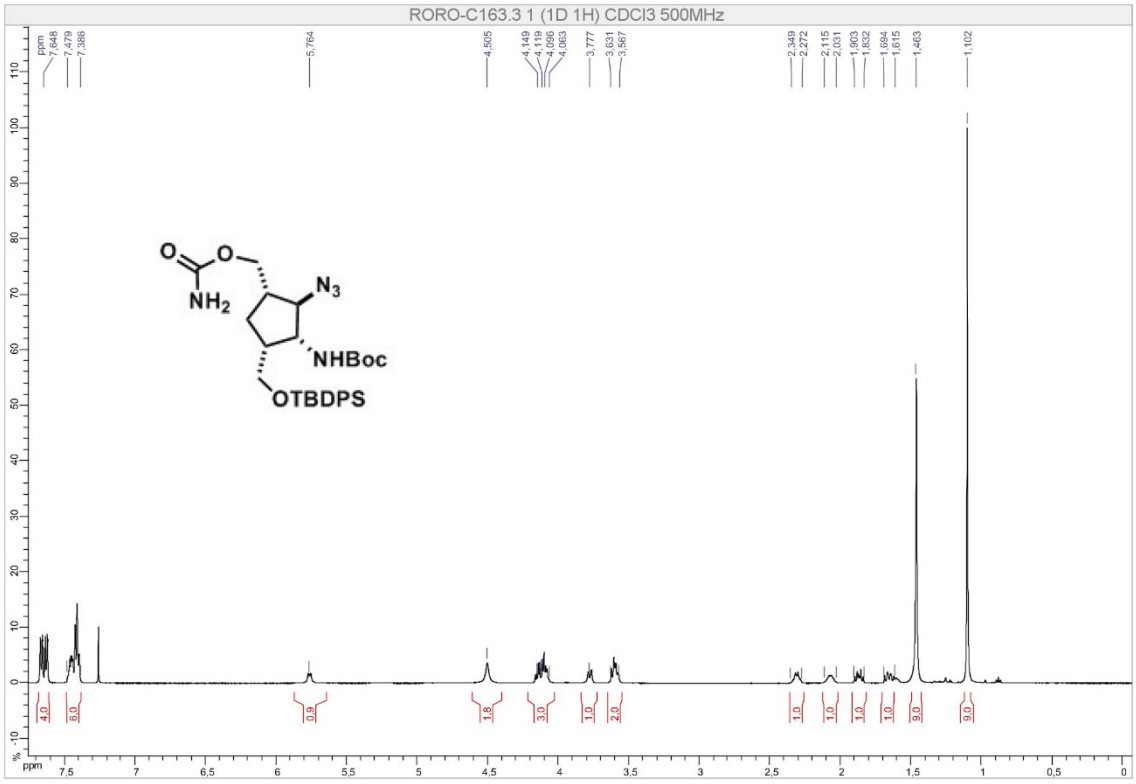
^{1}H NMR ($CDCl_3$, 300 MHz)



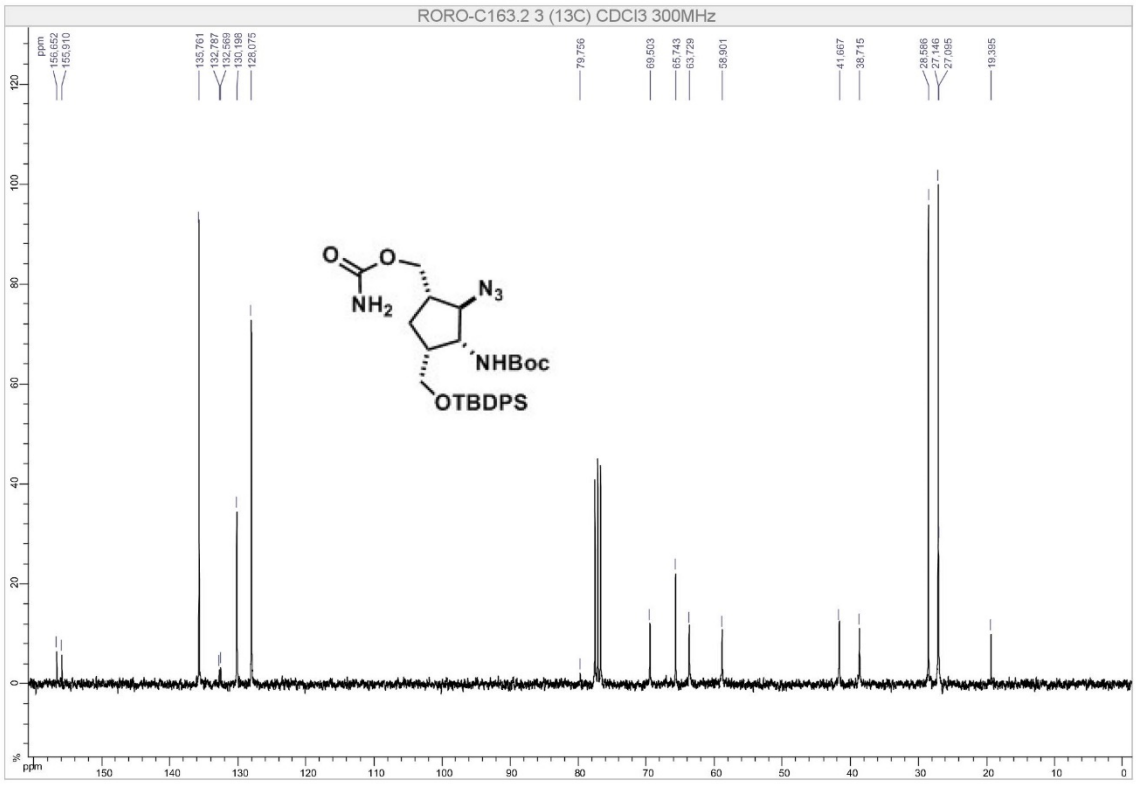
^{13}C NMR ($CDCl_3$, 75 MHz)



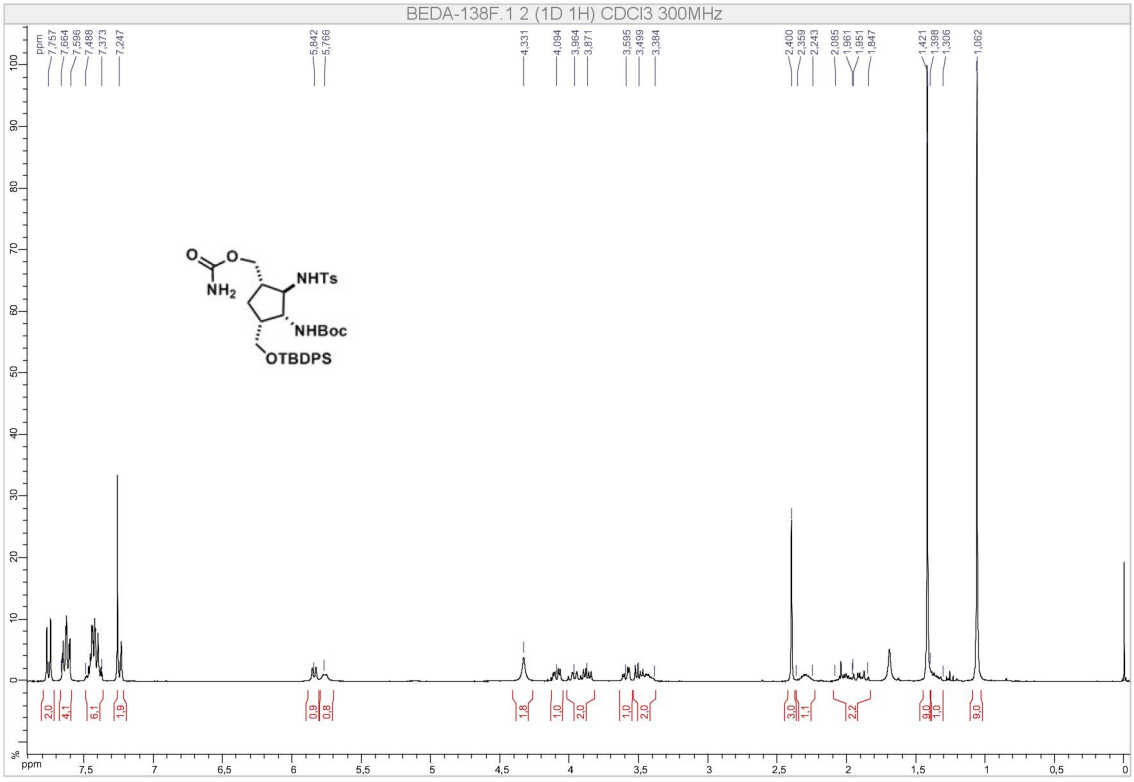
^{1}H NMR ($CDCl_3$, 500 MHz)



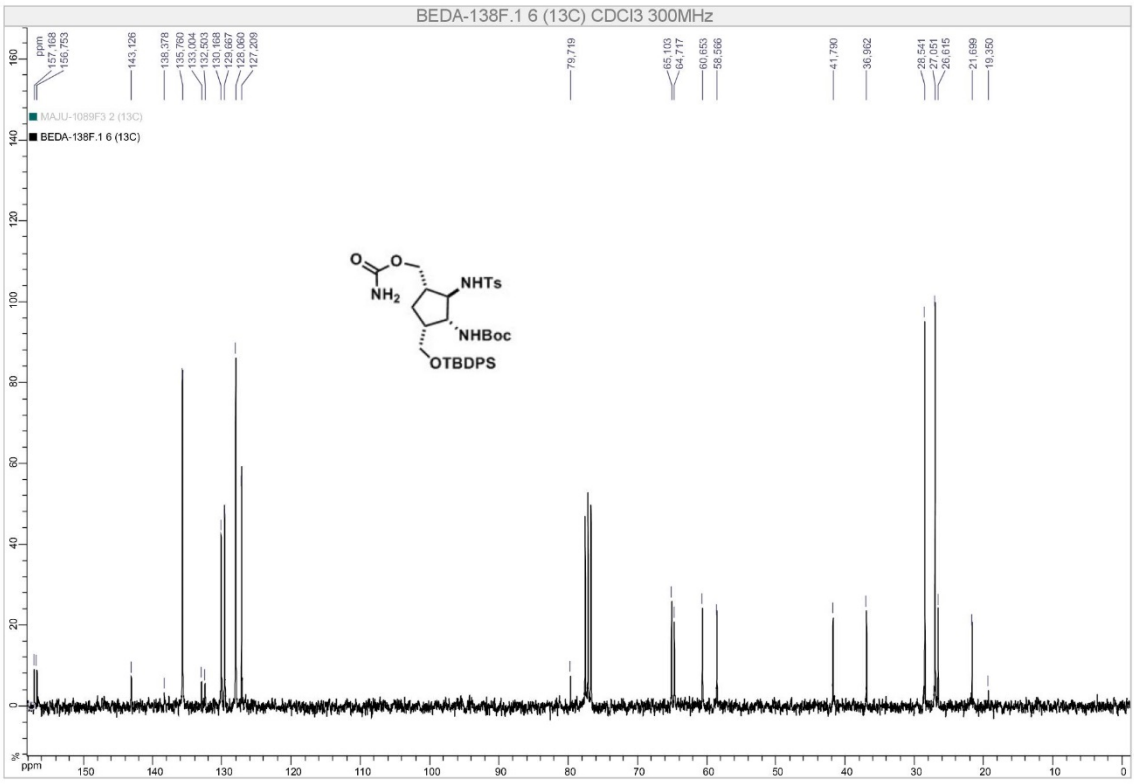
^{13}C NMR ($CDCl_3$, 75 MHz)



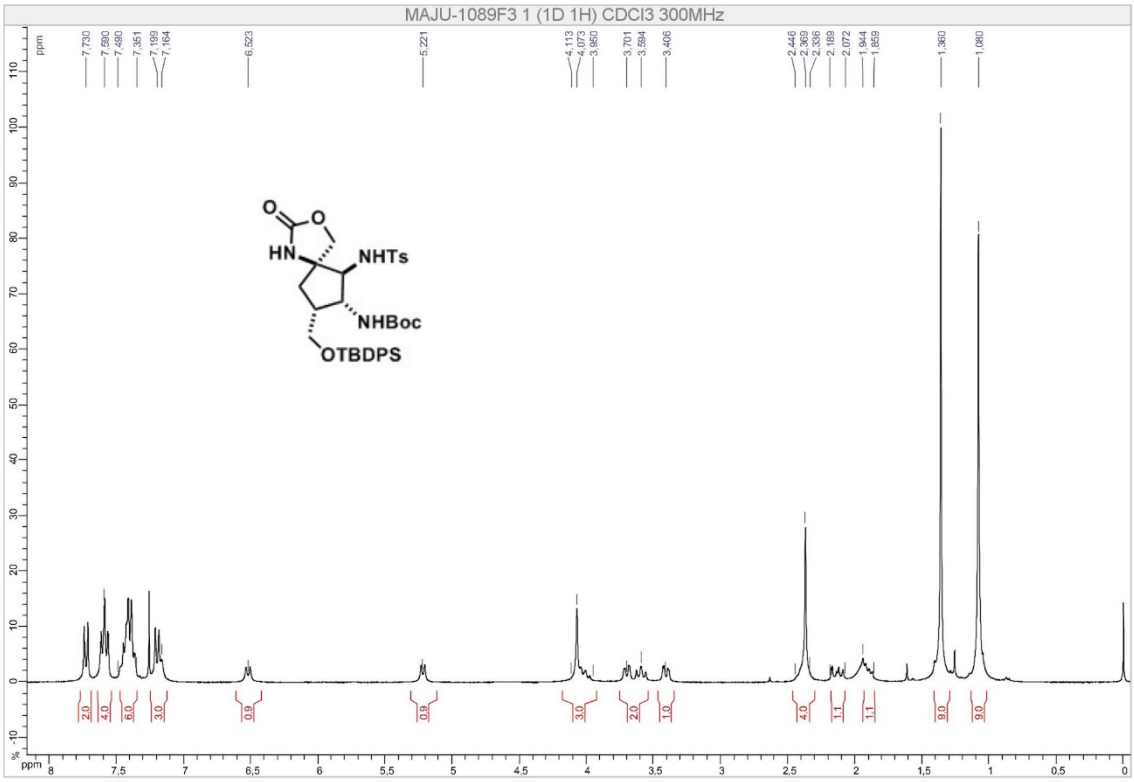
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)