Biologically Inspired Total Synthesis of Ulbactin F, an Iron-Binding Natural Product

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Supporting Information

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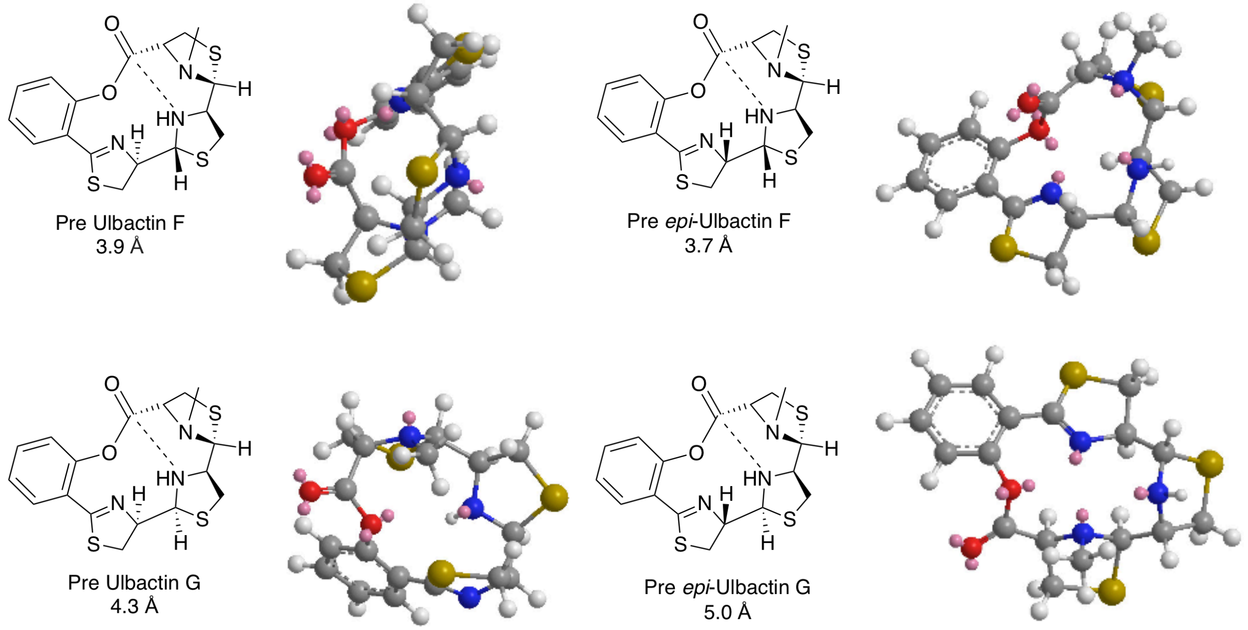
1. Supplementary Figures:



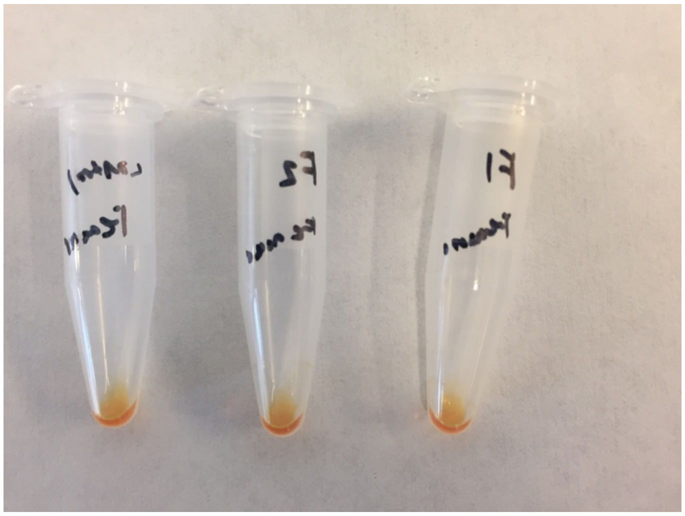
Pre Ulbactin F
3.9 Å

Pre *epi*-Ulbactin F
3.7 Å

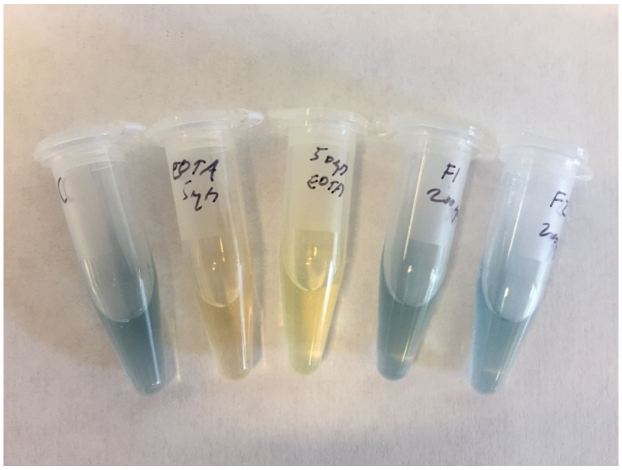
Pre Ulbactin G
4.3 Å

Pre *epi*-Ulbactin G
5.0 Å

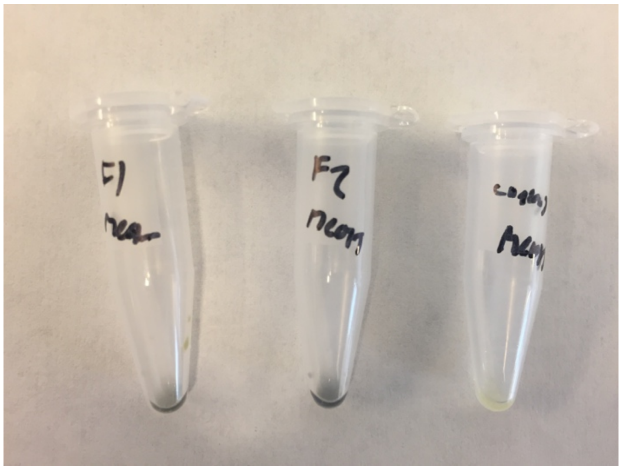
Supplementary Figure 1: Energy minimizations of proposed macrocycles leading to various epimers of Ulbactins with relevant atom-to-atom distance highlighted. Structures and calculations are generated in Chem3D. Dashed atom-to-atom distances are reported in Ångströms.



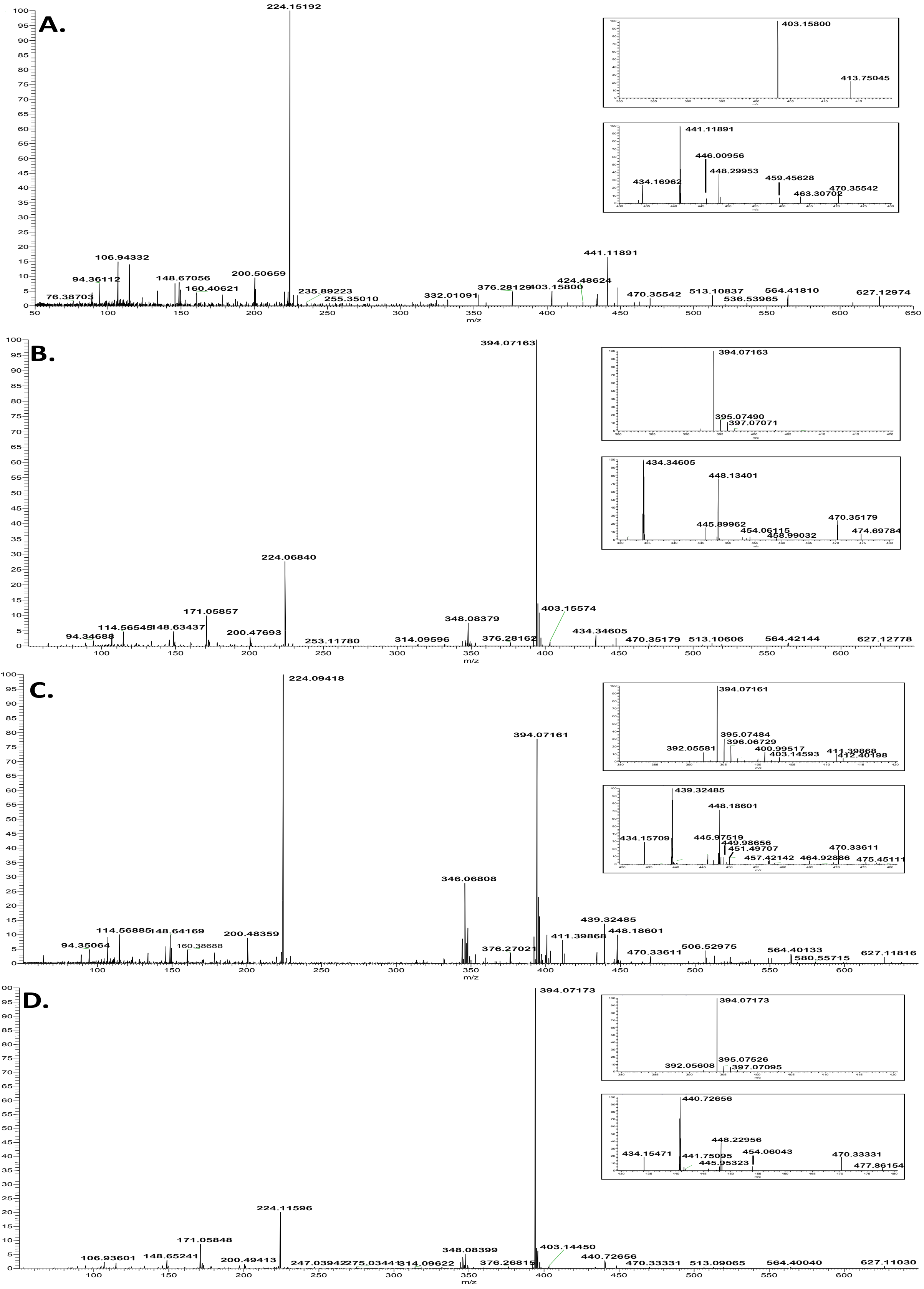
Supplementary Figure 2: (Left) Methanol containing 100 μM iron (III) acetylacetonate. (Middle) Methanol containing 100 μM *epi*-ulbactin F and 100 μM iron (III) acetylacetonate. (Right) Methanol containing 100 μM ulbactin F and 100 μM iron (III) acetylacetonate.



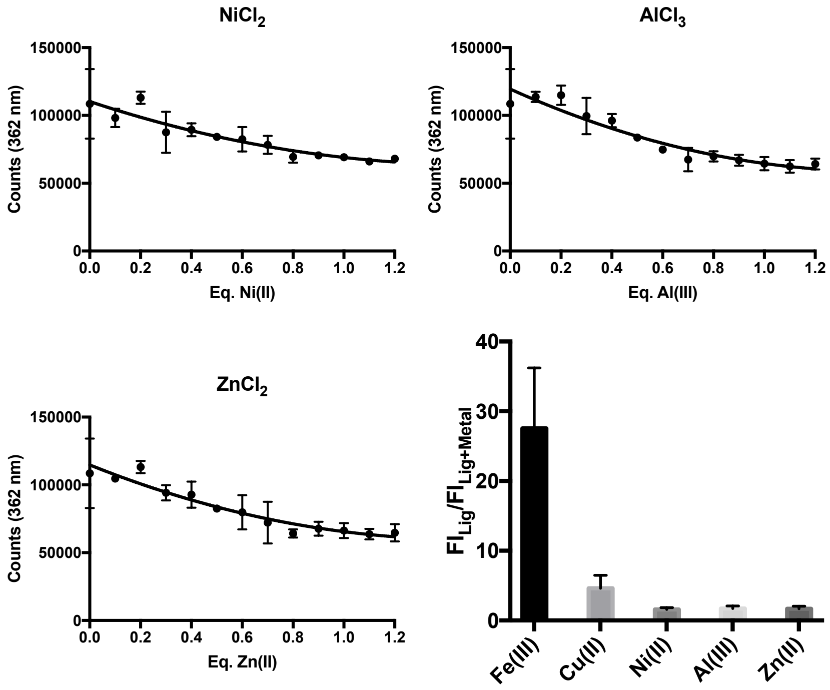
Supplementary Figure 3: From left to right: CAS media, CAS media containing 5 μM EDTA, CAS media containing 50 μM EDTA, CAS media containing 200 μM ulbactin F, and CAS media containing 200 μM *epi*-ulbactin F.



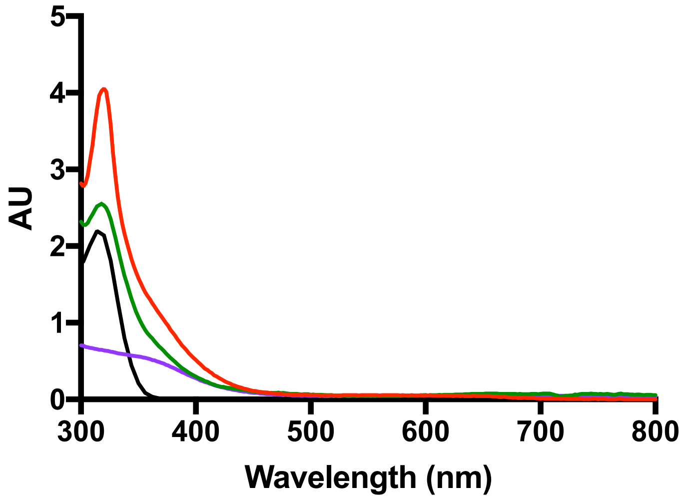
Supplementary Figure 4: (Left) Methanol containing 100 μM ulbactin F and 100 μM iron (III) chloride. (Middle) Methanol containing 100 μM *epi*-ulbactin F and 100 μM iron (III) chloride. (Right) Methanol containing 100 μM iron (III) chloride.



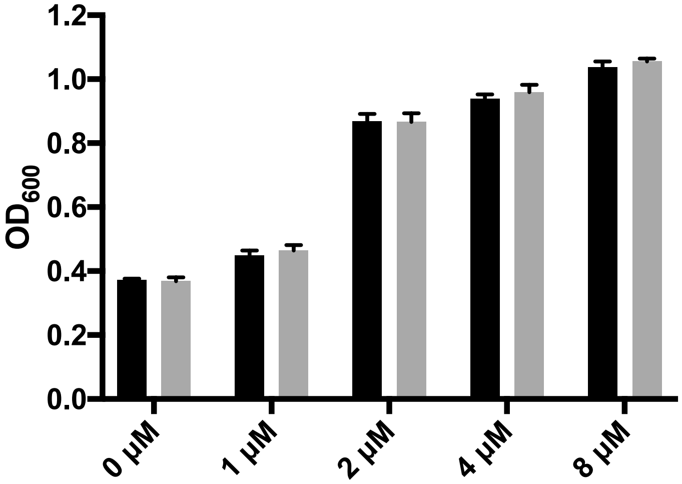
Supplementary Figure 5: Mass Chromatograms of ulbactin F samples. (A) Background chromatogram (B) Ulbactin F before treatment with iron (III) chloride (C) Ulbactin F after treatment with iron (III) chloride (D) ulbactin F after treatment with iron (III) chloride and subsequent extraction between ethyl acetate and 5% aqueous sodium citrate. All samples dissolved in methanol.



Supplementary Figure 6: Fluorescence titrations of ulbactin F with (Top left) Nickel (II) chloride, (Top right) Aluminum (III) chloride, and (Bottom left) Zinc (II) chloride. Ratio of fluorescence of 400 μM ligand over fluorescence of 400 μM ligand + 400 μM metal (Bottom right). Measurements taken in methanol.



Supplementary Figure 7: UV-Vis spectra of 400 μM Fe^{3+}-ulbactin F complex (Red), 400 μM Fe^{3+}-ulbactin F complex + 500 μM catechol (Green), 400 μM ulbactin F (black), and 100 μM catechol$_3$-Fe^{3+} complex. All spectra taken in methanol.



Supplementary Figure 8: Growth of *Pseudomonas aeruginosa* PAO1 cultures grown in M9 minimal media containing 300 µM 2,2'-dipyridyl and supplemented with Fe^{3+}-ulbactin F complex (black bars) or $FeCl_3$ (grey bars).

2. Methods

General: NMR spectra were recorded using the following spectrometers: Varian INOVA500, Varian INOVA400, VNMR400, and Bruker Ascend 600. All NMR spectra were recorded under ambient temperature. Chemical shifts are quoted in ppm relative to solvents used (^{1}H: δ = 7.26 and ^{13}C: δ = 77.16 for residual $CHCl_3$, ^{1}H: δ = 3.49, 1.09 and ^{13}C: δ = 50.41 for residual CH_3OH, ^{1}H: δ = 1.56 for residual H_2O. The abbreviations used to describe splitting are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), etc.

Accurate mass spectra were recorded on a Thermo LTQ-FTMS using either APCI or ESI techniques.

Infrared spectra were obtained using a Thermoscientific Nicolet with an attenuated total reflectance (ATR) with a Germanium crystal. Samples were tested neat or in chloroform. Peaks are reported in cm^{-1} and described as either weak (w), strong (s), or broad (b).

Specific rotations were obtained with 1 dm path length using a Perkin Elmer Model 341 Polarimeter with a Na/Hal lamp set to 598 nm. Samples were dissolved in either chloroform or water depending on the solubility restrictions of some compounds. In all cases, the polarimeter was zeroed to the solvent first. Measurements were taken over several minutes and then adjusted based on concentration.

Non-aqueous reactions were performed under an atmosphere of argon in flame-dried glassware with HPLC-grade solvents dried by passage through alumnina. Amine bases were freshly distilled over CaH_2 prior to use. Brine refers to a saturated aqueous solution of sodium chloride. Purification via flash chromatography refers to usage of Biotage Isolera One Automated column. Reactions monitored via thin-layer chromatography (TLC) using EMD Millipore® TLC silica gel glass plates with various stains specified in each procedure. Reactions monitored by LCMS were injected into an Agilent Technologies 1220 Infinity HPLC Liquid Chromatograph connected to an Advion Expression Compact Mass Spectrometer. Solvents used were HPLC grade water and acetonitrile each spiked with 0.1% formic acid.

Fluorescence measurements were recorded on a FluoroMax spectrophotometer (Horiba Scientific, Edison, New Jersey) in a quartz fluorescence cuvette with a 1 cm pathlength, an integration range of 285-550 nm and an excitation and emission slit width of 2 nm.

3. Biological Assays

Growth studies were conducted using *Pseudomonas aeruginosa* PAO1. A test-tube culture of liquid LB media was inoculated with PAO1 and grown overnight at 37° C, 200 RPM. Overnight culture was diluted 1:100 in fresh media and grown at 37° C, 200 RPM. OD_{600} was monitored until exponential growth, approximately 0.2, was reached. Regrown culture was then diluted into M9 minimal media containing 600 μM 2,2'-dipyridyl to achieve a 0.5 McFarland standard inoculum. Stock solutions of either 10 mM Fe^{3+}-ulbactin F complex or 10 mM $FeCl_3$ in methanol were diluted into M9 minimal media to a concentration of 512 μM and added to separate wells of the first column of a sterile 96-well microtiter plate (200 μL per well). All other wells were filled with 100 μL of M9 minimal media and the first column was serially diluted across the plate. Inoculum was added (100 μL per well) to achieve a final volume of 200 μL per well, 300 μM 2,2'-dipyridyl and 256->1 μM iron (III) source. The plate was then grown at 37° C for 24 hours and OD_{600} was monitored by plate reader.

4. Metal Chelation Assays

All fluorescence titrations were performed in methanol. Briefly, a 350 μL stock solution of 400 μM ulbactin F was prepared and an emission spectrum was recorded ($\lambda_{excitation}$ = 316 nm, integration time = 1 second, accumulations = 10). Metal chloride stock solution (10 mM) was added in 1.4 μL portions, the solution was gently mixed, and an emission spectrum was recorded after each addition.

Isolation of Fe^{3+}-ulbactin F complex was conducted by treating ulbactin F in methanol with excess iron (III) chloride. Once addition of iron resulted in no further color change, the solution was concentrated by rotary evaporation and excess iron (III) chloride was removed by triteration with diethyl ether. The complex was then dissolved in methanol.

HRMS analysis of ulbactin F samples treated with iron and citrate was conducted by ionizing samples through Atmospheric-Pressure Chemical Ionization (APCI) using Atmospheric Solids Analysis Probe (ASAP) to load each sample. Ulbactin F (1 mg) was dissolved in minimal methanol and an aliquot was taken (**Supplementary Figure 5b**). Sample was then treated with excess iron (III) chloride methanol solution. The sample was concentrated and triturated with ether to remove excess iron. Sample was redissolved in methanol and an aliquot was taken (**Supplementary Figure 5c**). Sample was concentrated, redissolved in ethyl acetate and washed with 5% aqueous sodium citrate. Ethyl acetate was partitioned and concentrated. Sample was redissolved in methanol and an aliquot was taken (**Supplementary Figure 5d**).

CAS liquid media was prepared as described previously [1].

Reference:

[1] Louden, B. C.; Haarmann, D.; Lynne, A. M. *J. Microbiol. Biol. Educ.* **2011**, *12* (1), 51-53

5. Crystal Analysis

Single crystal of $C_{17}H_{19}N_3O_2S_3$ Ulbactin diastereomer were recrystallized from pentane and dichloromethane as supplied. A suitable crystal was selected and the crystal was mounted on a loop with paratone oil on a XtaLAB Synergy, Duaflex, HyPix diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [1], the structure was solved with the She1XT [2] structure solution program using Intrinsic Phasing and refined with the She1XL [3] refinement package using Least Squares mimization.

[1] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
[2] Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
[3] Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal structure determination of [Ulbactin_diastereomer]

Crystal Data for $C_{17}H_{19}N_3O_2S_3$ (M =393.53 g/mol): monoclinic, space group I2 (no. 5), a = 11.9054(5) Å, b = 7.9651(3) Å, c = 19.2708(9) Å, β = 103.596(4)°, V = 1776.20(13) Å^3, Z = 4, T = 100(2) K, μ(MoKα) = 0.434 mm^{-1}, $Dcalc$ = 1.472 g/cm^3, 13787 reflections measured (3.676° ≤ 2Θ ≤ 58.246°), 4765 unique (R_{int} = 0.0478, R_{sigma} = 0.0487) which were used in all calculations. The final R_1 was 0.0327 (I > 2σ(I)) and wR_2 was 0.0784 (all data).

Refinement model description

Number of restraints - 1, number of constraints - unknown.

Details:

1. Fixed Uiso
   At 1.2 times of:
   All C(H) groups, All C(H,H) groups
   At 1.5 times of:
   All C(H,H,H) groups, All O(H) groups

2.a Ternary CH refined with riding coordinates:
   C13(H13), C8(H8), C6(H6), C3(H3), C5(H5)

2.b Secondary CH2 refined with riding coordinates:
   C2(H2A,H2B), C17(H17A,H17B), C10(H10A,H10B)

2.c Aromatic/amide H refined with riding coordinates:
   C23(H23), C22(H22), C24(H24), C21(H21)

2.d Idealised Me refined as rotating group:
   C12(H12A,H12B,H12C)

2.e Idealised tetrahedral OH refined as rotating group:
   O25(H25)

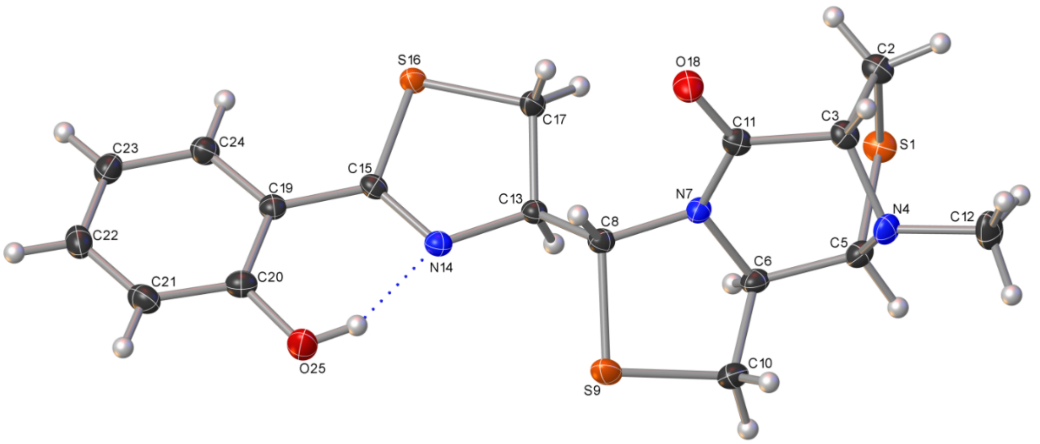


Table 1 Crystal data and structure refinement for Ulbactin_diastereomer.

Identification code	Ulbactin_diastereomer
Empirical formula	$C_{17}H_{19}N_3O_2S_3$
Formula weight	393.53
Temperature/K	100(2)
Crystal system	monoclinic
Space group	I2
a/Å	11.9054(5)
b/Å	7.9651(3)
c/Å	19.2708(9)
α/°	90
β/°	103.596(4)
γ/°	90
Volume/Å^3	1776.20(13)
Z	4
ρ_{calc}g/cm^3	1.472
μ/mm^{-1}	0.434
F(000)	824.0
Crystal size/mm^3	0.196 × 0.157 × 0.028
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.676 to 58.246
Index ranges	$-16 \le h \le 15$, $-10 \le k \le 10$, $-26 \le l \le 26$
Reflections collected	13787
Independent reflections	4765 [R_{int} = 0.0478, R_{sigma} = 0.0487]
Data/restraints/parameters	4765/1/228
Goodness-of-fit on F^2	1.006
Final R indexes [I>=2σ (I)]	R_1 = 0.0327, wR_2 = 0.0769
Final R indexes [all data]	R_1 = 0.0361, wR_2 = 0.0784
Largest diff. peak/hole / e Å^{-3}	0.30/-0.21
Flack parameter	-0.04(4)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Ulbactin_diastereomer. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S16	4757.9(5)	3401.1(7)	5928.5(3)	16.07(13)
S1	10099.5(6)	787.4(8)	7337.9(4)	19.58(15)
S9	8526.9(5)	7141.0(7)	6827.3(4)	22.19(16)
O18	8639.4(15)	3153(2)	5319.9(9)	21.4(4)
O25	5168.2(16)	9185(2)	5886.8(11)	24.0(4)
N14	5972.3(18)	6143(2)	6218.2(11)	15.2(4)
N4	11128.0(16)	3202(3)	6747.6(11)	17.9(4)
N7	8840.7(17)	4018(3)	6465.8(11)	14.1(4)
C19	3947(2)	6724(3)	5778.8(13)	14.8(5)
C13	6804(2)	4778(3)	6451.2(13)	13.7(5)
C8	7947(2)	5289(3)	6288.4(14)	15.0(5)
C15	4937(2)	5601(3)	5987.1(13)	14.1(4)
C23	1869(2)	7149(4)	5428.5(14)	21.3(5)
C2	10168(2)	511(3)	6412.7(13)	18.0(5)
C11	9211.9(19)	3211(3)	5937.7(13)	15.8(4)
C22	2047(2)	8849(3)	5341.0(15)	22.1(5)
C6	9530(2)	4185(3)	7202.0(13)	16.4(5)
C17	6310.9(19)	3154(3)	6078.4(14)	17.5(5)
C3	10366(2)	2304(3)	6159.4(13)	15.8(5)
C24	2818(2)	6096(3)	5633.8(14)	18.2(5)
C20	4109(2)	8474(3)	5719.8(13)	18.4(5)
C12	12311(2)	2556(3)	6914.3(17)	25.5(6)
C21	3151(2)	9510(3)	5482.3(14)	22.4(5)
C5	10569(2)	3027(3)	7330.2(13)	17.0(5)
C10	9833(2)	6055(3)	7285.7(16)	23.1(6)

Table 3 Anisotropic Displacement Parameters (Å^2×10^3) for Ulbactin_diastereomer. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S16	14.2(3)	13.2(3)	20.9(3)	-1.6(2)	4.5(2)	-1.4(2)
S1	24.3(3)	20.0(3)	15.8(3)	3.5(2)	7.5(2)	-1.1(2)
S9	19.2(3)	14.5(3)	32.7(4)	-5.6(3)	5.5(3)	-3.0(2)
O18	23.8(9)	26.8(10)	13.4(8)	-2.3(8)	3.7(7)	5.2(8)
O25	20.3(9)	14.9(8)	34.6(11)	1.1(8)	2.3(8)	-1.2(7)
N14	16.3(9)	15.0(10)	14.5(10)	-1.7(8)	3.9(8)	-0.2(7)
N4	11.5(8)	20.6(10)	21.8(11)	0.2(9)	4.4(8)	-1.8(8)
N7	12.8(9)	16.9(9)	12.6(10)	-1.1(8)	3.0(7)	0.1(7)
C19	16.3(11)	16.4(12)	11.7(11)	-1.5(8)	3.5(9)	0.6(8)
C13	14.8(10)	13.8(10)	12.7(11)	-1.4(9)	3.5(9)	0.1(9)
C8	14.6(10)	15.6(11)	15.3(11)	-2.2(9)	4.7(9)	-1.1(8)
C15	17.2(10)	13.0(10)	13.5(11)	-0.7(9)	6.4(9)	0.7(9)
C23	16.6(11)	24.9(13)	21.1(13)	-2.8(11)	1.8(10)	0.6(10)
C2	23.0(11)	18.5(11)	14.3(12)	1.0(9)	8.3(10)	0.3(10)
C11	16.0(10)	15.6(11)	17.3(11)	0.3(9)	7.0(9)	-2.8(9)
C22	20.6(12)	26.2(13)	18.4(13)	-1.8(10)	2.6(10)	7.1(10)
C6	15.8(11)	19.2(11)	14.1(11)	-4.5(9)	3.3(9)	-1.6(9)
C17	12.4(10)	14.9(11)	25.2(13)	-2.9(10)	4.7(9)	-0.6(9)
C3	17.4(11)	17.7(11)	14.5(11)	0.5(9)	8.0(9)	0.0(9)
C24	18.2(11)	17.0(12)	19.7(13)	-1.2(9)	5.2(10)	-0.3(9)
C20	21.2(11)	17.6(11)	16.5(12)	-1.8(10)	5.0(9)	-2.0(10)
C12	14.2(12)	24.6(14)	38.4(17)	3.7(12)	7.5(11)	1.0(9)
C21	27.4(13)	17.1(12)	21.8(13)	-1.2(10)	3.7(11)	2.9(10)
C5	15.4(11)	19.3(12)	15.3(11)	-1.1(9)	1.5(9)	-1.5(9)
C10	17.9(12)	22.0(13)	27.4(15)	-8.8(11)	1.3(11)	-2.3(10)

Table 4 Bond Lengths for Ulbactin_diastereomer.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S16	C15	1.766(3)	C23	H23	0.9500
S16	C17	1.814(2)	C23	C22	1.387(4)
S1	C2	1.818(3)	C23	C24	1.388(4)
S1	C5	1.871(3)	C2	H2A	0.9900
S9	C8	1.842(2)	C2	H2B	0.9900
S9	C10	1.816(3)	C2	C3	1.545(3)
O18	C11	1.226(3)	C11	C3	1.522(3)
O25	H25	0.8400	C22	H22	0.9500
O25	C20	1.350(3)	C22	C21	1.382(4)
N14	C13	1.468(3)	C6	H6	1.0000
N14	C15	1.283(3)	C6	C5	1.517(3)
N4	C3	1.461(3)	C6	C10	1.532(4)
N4	C12	1.462(3)	C17	H17A	0.9900
N4	C5	1.440(3)	C17	H17B	0.9900
N7	C8	1.450(3)	C3	H3	1.0000
N7	C11	1.362(3)	C24	H24	0.9500
N7	C6	1.468(3)	C20	C21	1.395(4)
C19	C15	1.459(3)	C12	H12A	0.9800
C19	C24	1.400(3)	C12	H12B	0.9800
C19	C20	1.415(4)	C12	H12C	0.9800
C13	H13	1.0000	C21	H21	0.9500
C13	C8	1.522(3)	C5	H5	1.0000
C13	C17	1.528(3)	C10	H10A	0.9900
C8	H8	1.0000	C10	H10B	0.9900

Table 5 Bond Angles for Ulbactin_diastereomer.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C15	S16	C17	89.67(11)	N7	C6	C5	110.6(2)
C2	S1	C5	91.45(12)	N7	C6	C10	104.7(2)
C10	S9	C8	93.31(11)	C5	C6	H6	109.0
C20	O25	H25	109.5	C5	C6	C10	114.3(2)
C15	N14	C13	112.4(2)	C10	C6	H6	109.0
C3	N4	C12	112.8(2)	S16	C17	H17A	110.9
C5	N4	C3	103.98(18)	S16	C17	H17B	110.9
C5	N4	C12	113.1(2)	C13	C17	S16	104.32(16)
C8	N7	C6	112.14(19)	C13	C17	H17A	110.9
C11	N7	C8	120.2(2)	C13	C17	H17B	110.9
C11	N7	C6	123.97(19)	H17A	C17	H17B	108.9
C24	C19	C15	120.8(2)	N4	C3	C2	108.7(2)
C24	C19	C20	118.6(2)	N4	C3	C11	109.9(2)
C20	C19	C15	120.6(2)	N4	C3	H3	109.6
N14	C13	H13	108.8	C2	C3	H3	109.6
N14	C13	C8	108.05(19)	C11	C3	C2	109.41(19)
N14	C13	C17	109.05(19)	C11	C3	H3	109.6
C8	C13	H13	108.8	C19	C24	H24	119.3
C8	C13	C17	113.12(19)	C23	C24	C19	121.3(2)
C17	C13	H13	108.8	C23	C24	H24	119.3
S9	C8	H8	109.2	O25	C20	C19	122.1(2)
N7	C8	S9	105.59(16)	O25	C20	C21	118.4(2)
N7	C8	C13	114.00(19)	C21	C20	C19	119.5(2)
N7	C8	H8	109.2	N4	C12	H12A	109.5
C13	C8	S9	109.45(16)	N4	C12	H12B	109.5
C13	C8	H8	109.2	N4	C12	H12C	109.5
N14	C15	S16	116.62(19)	H12A	C12	H12B	109.5
N14	C15	C19	122.5(2)	H12A	C12	H12C	109.5
C19	C15	S16	120.86(17)	H12B	C12	H12C	109.5
C22	C23	H23	120.4	C22	C21	C20	120.4(3)
C22	C23	C24	119.2(2)	C22	C21	H21	119.8
C24	C23	H23	120.4	C20	C21	H21	119.8
S1	C2	H2A	110.9	S1	C5	H5	110.2
S1	C2	H2B	110.9	N4	C5	S1	106.98(16)
H2A	C2	H2B	109.0	N4	C5	C6	108.8(2)
C3	C2	S1	104.07(17)	N4	C5	H5	110.2
C3	C2	H2A	110.9	C6	C5	S1	110.30(16)
C3	C2	H2B	110.9	C6	C5	H5	110.2
O18	C11	N7	122.6(2)	S9	C10	H10A	110.8
O18	C11	C3	120.9(2)	S9	C10	H10B	110.8
N7	C11	C3	116.4(2)	C6	C10	S9	104.96(17)

C23	C22	H22	119.6	C6	C10	H10A	110.8
C21	C22	C23	120.9(2)	C6	C10	H10B	110.8
C21	C22	H22	119.6	H10A	C10	H10B	108.8
N7	C6	H6	109.0				

Table 6 Torsion Angles for Ulbactin_diastereomer.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
S1	C2	C3	N4	36.8(2)	C11	N7	C6	C5	-12.7(3)
S1	C2	C3	C11	-83.2(2)	C11	N7	C6	C10	110.9(2)
O18	C11	C3	N4	150.0(2)	C22	C23	C24	C19	2.3(4)
O18	C11	C3	C2	-90.7(3)	C6	N7	C8	S9	30.5(2)
O25	C20	C21	C22	-176.6(2)	C6	N7	C8	C13	-89.7(2)
N14	C13	C8	S9	64.4(2)	C6	N7	C11	O18	-176.7(2)
N14	C13	C8	N7	-177.62(19)	C6	N7	C11	C3	5.9(3)
N14	C13	C17	S16	-29.3(2)	C17	S16	C15	N14	-11.4(2)
N7	C11	C3	N4	-32.5(3)	C17	S16	C15	C19	168.5(2)
N7	C11	C3	C2	86.8(3)	C17	C13	C8	S9	-174.77(16)
N7	C6	C5	S1	-70.0(2)	C17	C13	C8	N7	-56.8(3)
N7	C6	C5	N4	47.1(3)	C3	N4	C5	S1	44.4(2)
N7	C6	C10	S9	40.3(2)	C3	N4	C5	C6	-74.8(2)
C19	C20	C21	C22	3.4(4)	C24	C19	C15	S16	10.0(3)
C13	N14	C15	S16	-5.1(3)	C24	C19	C15	N14	-170.2(2)
C13	N14	C15	C19	175.0(2)	C24	C19	C20	O25	176.5(2)
C8	S9	C10	C6	-21.0(2)	C24	C19	C20	C21	-3.5(4)
C8	N7	C11	O18	-20.2(4)	C24	C23	C22	C21	-2.6(4)
C8	N7	C11	C3	162.4(2)	C20	C19	C15	S16	-170.06(19)
C8	N7	C6	C5	-170.8(2)	C20	C19	C15	N14	9.8(4)
C8	N7	C6	C10	-47.3(3)	C20	C19	C24	C23	0.7(4)
C8	C13	C17	S16	-149.56(17)	C12	N4	C3	C2	69.3(3)
C15	S16	C17	C13	22.39(17)	C12	N4	C3	C11	-171.0(2)
C15	N14	C13	C8	146.5(2)	C12	N4	C5	S1	-78.4(2)
C15	N14	C13	C17	23.2(3)	C12	N4	C5	C6	162.4(2)
C15	C19	C24	C23	-179.4(2)	C5	S1	C2	C3	-8.82(17)
C15	C19	C20	O25	-3.5(4)	C5	N4	C3	C2	-53.6(2)
C15	C19	C20	C21	176.5(2)	C5	N4	C3	C11	66.1(2)
C23	C22	C21	C20	-0.3(4)	C5	C6	C10	S9	161.48(18)
C2	S1	C5	N4	-20.37(17)	C10	S9	C8	N7	-4.03(19)
C2	S1	C5	C6	97.87(18)	C10	S9	C8	C13	119.08(19)
C11	N7	C8	S9	-128.60(19)	C10	C6	C5	S1	172.20(19)
C11	N7	C8	C13	111.2(2)	C10	C6	C5	N4	-70.7(3)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Ulbactin_diastereomer.

Atom	*x*	*y*	*z*	U(eq)
H25	5674.02	8429.76	5980.72	36
H13	6921.52	4627.29	6978.63	16
H8	7815.13	5576.86	5770.37	18
H23	1107.3	6711.68	5348.97	26
H2A	10814.8	-240.12	6376.49	22
H2B	9437.62	34.46	6126.02	22
H22	1401.83	9569.13	5181.77	26
H6	9038.72	3881.19	7538.82	20
H17A	6580.52	2167.38	6384.75	21
H17B	6541.92	3016.03	5620.56	21
H3	10734.95	2242.97	5744.26	19
H24	2698.05	4925.11	5676.71	22
H12A	12323.6	1429.97	7120.56	38
H12B	12809.09	3304.32	7257.92	38
H12C	12592.79	2502.33	6476.25	38
H21	3257.94	10676.44	5417.43	27
H5	11120.32	3314.26	7792.1	20
H10A	10483.02	6325.27	7065.51	28
H10B	10049.47	6374.86	7796.32	28

6. Computational

Computational Details. The presented calculations were carried out using the Gaussian 09 suite of programs.[1] Geometry of all reported structures were optimized without symmetry constraint at the B3LYP level of density functional theory (DFT) [2,3] in conjunction with Lanl2dz basis set and corresponding Hay-Wadt effective core potential (ECP) for Fe.[4,5] Standard 6-31G(d,p) basis sets were used for all remaining atoms. The nature of each stationary point was characterized by the presence of zero imaginary frequencies. The relative enthalpies (ΔH) and Gibbs energies (ΔG) are presented as ΔH/ΔG, and calculated under standard conditions (1 atm and 298.15 K). Cartesian coordinates of all reported structures are given in the Supporting Information.

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Cartesian Coordinates (in Å)

HCl

H	0.00000000	0.00000000	0.15708900
Cl	0.00000000	0.00000000	1.44291100

FeCl$_3$ (Sixtet electronic state)

Fe	-6.58924000	-3.62556400	2.58518100
Cl	-6.07605900	-2.00331300	1.25209100
Cl	-5.45715800	-5.46472000	2.52963900
Cl	-8.22453000	-3.40047200	3.98055600

Ligand

C	-3.08776600	-2.76263800	3.09316000
C	-2.33589500	-0.86748400	4.13466400
N	-1.89955000	-2.18129600	3.65854300
S	-3.88796600	-1.43045000	1.98999900
C	-3.04888000	-0.11595000	2.96692800
H	-2.32371100	0.40826200	2.33961600
H	-3.77319200	0.60854600	3.34420500
H	-2.85892900	-3.62516100	2.46425900
H	-1.48930800	-0.29086700	4.51308600
C	-3.28948600	-1.04897100	5.31891800
O	-3.30420700	-0.25018300	6.24906300
C	-4.04041200	-3.17817000	4.21916700
N	-4.14220400	-2.12551600	5.24573800
C	-4.83075000	-2.56718000	6.45179400
S	-4.49393900	-4.40390100	6.57122700
C	-3.58917900	-4.44253300	4.97039900
H	-2.51094400	-4.42173700	5.14514400
H	-3.86342400	-5.35140800	4.42980400
H	-5.03556500	-3.34571400	3.80067900
C	-6.34272000	-2.25698000	6.47801000
C	-6.60161000	-0.73484200	6.66979200
N	-7.02637400	-2.71641400	5.27963600
S	-8.11643000	-0.35677900	5.70193100
H	-6.77342500	-0.48678200	7.71821500
C	-7.92030900	-1.90843800	4.82132500
C	-8.74791100	-2.23895300	3.66415700
C	-9.69560600	-1.33459000	3.14818400
C	-8.59550300	-3.50771300	3.03506000
C	-10.47919000	-1.65783100	2.05099500
H	-9.80588200	-0.36196100	3.61909700
C	-9.39383600	-3.82401200	1.92374300
O	-7.71282400	-4.42523100	3.46093100

C	-10.32070000	-2.91097800	1.44108600
H	-11.20347200	-0.94670300	1.66791700
H	-9.26014400	-4.79694400	1.46279700
H	-10.92860400	-3.17376600	0.57975800
H	-7.27091800	-4.05153200	4.27440700
H	-5.77067500	-0.13173000	6.30021400
H	-4.36490000	-2.06381800	7.30112600
H	-6.76288000	-2.80749200	7.33308100
C	-0.73906500	-2.14620600	2.76775900
H	0.09778000	-1.67829900	3.29315600
H	-0.45042900	-3.17094400	2.51821700
H	-0.92303600	-1.60077800	1.83000900

Complex (Sixtet Electronic State)

C	-1.76507900	-2.57086100	3.62683500
C	-2.61145900	-0.46836500	3.92170100
N	-1.50001600	-1.33849200	4.32454600
S	-2.13919000	-2.12544300	1.82889600
C	-2.75223300	-0.47716000	2.36909500
H	-2.13713400	0.30767900	1.92266900
H	-3.78885600	-0.34259500	2.05589900
H	-0.89529500	-3.23168600	3.63171800
H	-2.45717500	0.54705200	4.29244400
C	-3.85418400	-0.97916900	4.65114400
O	-4.63439800	-0.20787800	5.19826500
C	-2.95122100	-3.29950100	4.28459600
N	-4.01279600	-2.34997300	4.73166500
C	-4.79061400	-2.80938000	5.90069800
S	-4.13988900	-4.47986200	6.33717200
C	-2.54634700	-4.09449600	5.52987800
H	-1.90164800	-3.50503300	6.18859100
H	-2.05338000	-5.03295800	5.26710200
H	-3.38813300	-3.98769700	3.55931400
C	-6.35459200	-2.82681200	5.84020300
C	-6.90603400	-1.71775300	6.75413600
N	-7.01019300	-2.67985500	4.51994100
S	-8.62061400	-1.45833400	6.18876700
H	-6.90743500	-2.02332500	7.80163800
C	-8.18303600	-2.09472800	4.59270300
C	-9.17858500	-1.99869500	3.53126100
C	-10.19885800	-1.02436500	3.60643300
C	-9.21396800	-2.94494700	2.45861300
C	-11.22311000	-0.97893900	2.67595700
H	-10.16139000	-0.28222100	4.39730300
C	-10.28504500	-2.90262100	1.54018200
O	-8.29119700	-3.87965200	2.32377800
C	-11.26688800	-1.93251900	1.64492800

H	-11.98458500	-0.20937600	2.74409300
H	-10.29374900	-3.64236000	0.74722400
H	-12.07289100	-1.90565600	0.91729300
Fe	-6.50446100	-3.49255100	2.69134100
H	-6.33789600	-0.79606100	6.61837400
H	-4.54149400	-2.12605700	6.71863100
H	-6.68750200	-3.80211000	6.22222600
Cl	-5.97470700	-1.82279400	1.31182200
Cl	-5.34141300	-5.37353400	2.57655900
C	-0.17230100	-0.76670300	4.09518500
H	-0.08595900	0.16610200	4.65890700
H	0.58449300	-1.46044000	4.47222100
H	0.03981400	-0.56662000	3.03457100

Fe(acac)$_3$ (Sixtet electronic state)

O	-6.69847400	-3.57454600	4.55100200
C	-7.77428800	-3.46043000	5.22471900
C	-9.06009100	-3.35637800	4.66859800
O	-8.40289600	-3.44375700	2.38846200
C	-9.30449700	-3.35926600	3.28525200
H	-9.90549600	-3.27179000	5.33998900
Fe	-6.39861900	-3.61574500	2.55458700
O	-6.23339700	-3.49669600	0.54780400
O	-6.07369800	-1.62423000	2.56547000
C	-6.03590800	-2.48971400	-0.20811900
C	-5.87844200	-0.81274600	1.60221100
C	-5.85512200	-1.17219600	0.24435000
H	-5.68651500	-0.39492200	-0.49048500
O	-6.56134300	-5.62233100	2.41681500
O	-4.43293600	-3.93211700	2.87051900
C	-5.68027500	-6.53450300	2.54210900
C	-3.77333300	-5.01881400	2.96443100
C	-4.32165000	-6.30325900	2.81480000
H	-3.66300500	-7.15775100	2.90735000
C	-7.60088200	-3.44344800	6.72802000
H	-8.54983100	-3.34997600	7.25997600
H	-7.09808100	-4.36345800	7.04374400
H	-6.94692200	-2.60975200	7.00402600
C	-10.72426100	-3.25517300	2.77176000
H	-10.94778200	-4.13236000	2.15575700
H	-11.45835500	-3.18218800	3.57674400
H	-10.81013500	-2.37737400	2.12290400
C	-5.66235200	0.63062900	2.00242500
H	-5.50463100	1.28643100	1.14374400
H	-6.53003800	0.98118100	2.57086800
H	-4.79603500	0.69204600	2.66920700
C	-5.99949800	-2.78821700	-1.69123400

H	-6.94752800	-3.24903500	-1.98741000
H	-5.82670500	-1.89576600	-2.29615300
H	-5.21046500	-3.52019000	-1.89269500
C	-2.29663100	-4.85941900	3.25428600
H	-1.77586400	-5.81653400	3.32449900
H	-1.83737500	-4.25476400	2.46533400
H	-2.17295100	-4.30927800	4.19282000
C	-6.18397700	-7.95189900	2.37608800
H	-5.39356000	-8.69591400	2.49407900
H	-6.97329900	-8.14274000	3.11057200
H	-6.63628500	-8.05766700	1.38458600

L-Fe(acac)2 (Sixtet Electonic State)

C	-3.28480200	0.36201200	3.60717600
C	-2.90064500	0.40154000	5.86654300
N	-2.25757100	0.64822000	4.57386800
S	-4.86268300	1.24620400	4.20189600
C	-4.23987800	1.20227200	5.93284300
H	-4.06962100	2.22004700	6.29244900
H	-4.96118300	0.71048100	6.58855500
H	-3.03390700	0.75362700	2.61947700
H	-2.23675900	0.67901500	6.68787000
C	-3.16357700	-1.09808000	6.01799100
O	-3.07378600	-1.65384700	7.10774800
C	-3.50468700	-1.15377200	3.52635800
N	-3.53478800	-1.75464300	4.87070400
C	-3.49043600	-3.20633100	4.84234200
S	-2.45789500	-3.63580500	3.35261200
C	-2.39835400	-1.89795100	2.75673300
H	-1.41875200	-1.46393600	2.97045400
H	-2.59713100	-1.88714000	1.68323800
H	-4.46293600	-1.35304900	3.04023100
C	-4.87470600	-3.91162200	4.88692000
C	-5.46722200	-3.84089800	6.31782000
N	-5.85413700	-3.35517400	3.94221100
S	-6.67998400	-2.47461300	6.27931800
H	-5.98608100	-4.76504400	6.58325700
C	-6.74671800	-2.57941300	4.49088100
C	-7.76012200	-1.80203200	3.79048900
C	-8.62846000	-0.95520800	4.51449700
C	-7.86707400	-1.83138700	2.36317400
C	-9.55422100	-0.14321900	3.88327600
H	-8.56916900	-0.93743300	5.59828700
C	-8.81069900	-0.97866700	1.73729000
O	-7.12987400	-2.60689800	1.61074600
C	-9.63683500	-0.15604400	2.48036200
H	-10.20597200	0.49742100	4.46818400

H	-8.86600500	-1.01371800	0.65428700
H	-10.35844000	0.48006400	1.97454000
Fe	-6.34372100	-4.30009000	1.96564700
H	-4.70797900	-3.60998600	7.06652000
H	-2.94455400	-3.53345400	5.72898900
H	-4.70313500	-4.95536100	4.61031100
C	-1.63692900	1.96702200	4.44978100
H	-0.88664000	2.08189600	5.23677500
H	-1.12607800	2.03129900	3.48489100
H	-2.35502000	2.79839100	4.51576100
O	-7.02146200	-5.29924500	0.30980300
O	-4.70297400	-3.92096500	0.88084000
C	-6.40405000	-5.61254800	-0.75709000
C	-4.31661000	-4.39518200	-0.23995400
C	-5.08455900	-5.23146500	-1.06216800
H	-4.65745300	-5.56043100	-2.00132900
O	-8.09692000	-4.95792200	2.82162700
O	-5.53952600	-6.02364000	2.70607400
C	-8.42721400	-6.15366900	3.09593900
C	-6.14727300	-7.11586500	2.98028200
C	-7.53213100	-7.24154300	3.15533500
H	-7.93025500	-8.21819700	3.40166200
C	-5.25687400	-8.33025500	3.13839500
H	-4.50393500	-8.13371100	3.90904300
H	-5.81533700	-9.23073100	3.40213000
H	-4.71518900	-8.50304500	2.20240200
C	-9.89563200	-6.37753900	3.38872100
H	-10.48018900	-6.10259300	2.50444300
H	-10.11916300	-7.41094200	3.66191100
H	-10.20834300	-5.71140900	4.19918000
C	-7.19212400	-6.44313700	-1.74827000
H	-6.60603000	-6.71826700	-2.62759000
H	-7.55299900	-7.35025800	-1.25301600
H	-8.07449400	-5.87809200	-2.06693200
C	-2.92982600	-3.98121600	-0.68222700
H	-2.20623900	-4.27521900	0.08483900
H	-2.64508800	-4.42681900	-1.63743900
H	-2.88778800	-2.89024200	-0.77244600

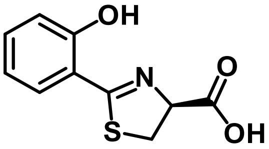
H-ACAC, (protonated acac)

O	-0.02909600	0.24719500	0.00038800
C	0.54101800	1.44244600	0.00080400
C	-0.20067600	2.59971600	0.00040000
C	-1.64110800	2.53095000	-0.00050900
O	-2.24578400	1.43381800	-0.00090700
H	0.29975500	3.56012700	0.00075000
H	-1.02689500	0.42950400	-0.00024300

C	-2.43725100	3.81818900	-0.00122300
H	-2.18993100	4.42179800	0.87928200
H	-2.19157700	4.41951200	-0.88377500
H	-3.50390700	3.59072900	-0.00005700
C	2.03812800	1.40415600	0.00175700
H	2.39382600	0.85892900	0.88256900
H	2.39494200	0.85879500	-0.87851900
H	2.46707400	2.40745800	0.00196500

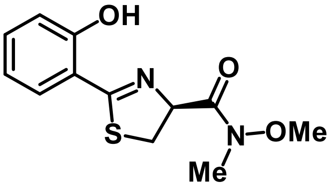
7. Synthesis

7.1 Experimental Procedures



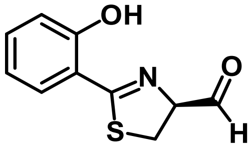
(*S*)-2-(2-hydroxyphenyl)-4,5-dihydrothiazole-4-carboxylic acid Synthesized as described previously by Mislin[9]. Briefly, commercially available 2-hydroxy-benzonitrile (2.44 g, 20.5 mmol) was dissolved in methanol (15 mL). D-cysteine hydrochloride monohydrate (3.0 g, 17.1 mmol) was added to the solution and stirred to dissolve. Phosphate buffer (0.1 M, pH 6.4, 15 mL) was added and the pH of the reaction mixture was adjusted to 6.4 by addition of solid K_2CO_3 and solid citric acid. The reaction was stirred at 60 °C overnight. The reaction mixture was then concentrated and the crude material was dissolved in 100 mL water. The aqueous solution was brought to pH 2 by addition of solid citric acid. The aqueous solution was extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to a yellow solid (3.22 g, 14.54 mmol, 85% yield).

^{1}H NMR: (600 MHz, $(CD_3)_2CO$) (Rotamers) δ 7.47 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 6.98 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.95 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 1H), 5.54 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.77 (qd, *J* = 11.3, 8.6 Hz, 2H).

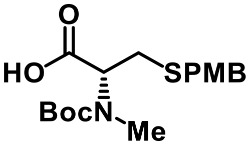


(*S*)-2-(20hydroxyphenyl)-*N*-methoxy-*N*-methyl-4,5-duhydrothiazole-4-carboxamide (13) Synthesized as described previously by Mislin[9]. To a base-washed, flamed dried reaction flask charged with argon, phenol-thiazoline acid (1.73 g, 7.8 mmol) was added and dissolved in DMF (40 mL). Then, EDC (5.94 g, 31 mmol), HOBt (4.18 g, 31 mmol), N,0-dimethyl hydroxylamine hydrochloride (1.51 g, 15.5 mmol) were added. Dry trimethylamine was added dropwise by syringe until the reaction mixture was basic (pH 9) by pH paper (soak indicator in DMF solution and then spray with water). The reaction mixture was stirred overnight at room temperature. The reaction was then diluted with 5 volumes of water. The aqueous mixture was brought to pH 2 by addition of 1 M HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by silica gel chromatography (10% to 100% EtOAc in hexanes) to give a white solid (1.16 g, 4.34 mmol, 56% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 7.43 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.36 (ddd, *J* = 8.8, 7.4, 1.6 Hz, 1H), 6.98 (dd, 1H), 6.88 (ddd, *J* = 8.4, 7.6, 1.1 Hz, 1H), 5.70 (t, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 3.78 (dd, *J* = 16.2, 16.0 Hz, 1H), 3.48 (dd, *J* = 10.9, 9.3 Hz, 1H), 3.29 (s, 3H)

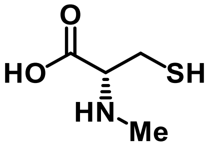


(*S*)-2-(2-hydroxyphenyl)-4,5-dihydrothiazole-4-carbaldehyde (14) Synthesized as described previously by Mislin[9]. Briefly, Weinreb amide **13** (172 mg, 0.644 mmol) was added to a flame-dried, base-washed flask under argon and dissolved in dry THF (13 mL). The reaction mixture was brought to -40 °C in a bath of dry ice and acetone. Lithium aluminum hydride (27 mg, 0.71 mmol) was put under argon and suspended in 0.71 mL dry THF (1 M solution). The suspension was cooled in the bath and added dropwise by syringe down the side of the reaction flask into the reaction mixture. The reaction was stirred at between -50 and -30 °C and monitored by TLC. After 2 hours, the reaction was quenched by addition of 8 mL saturated NH_4Cl and 3 mL 10% $NaHSO_4$ (alternating additions of 1-2 mL each). The reaction was allowed to warm to room temperature while stirring vigorously until two phases formed. The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude aldehyde was unstable and thus quickly carried on to the synthesis of **1** and **15** without further purification.



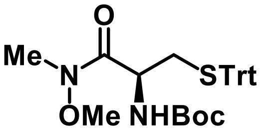
***N*-(*tert*-butoxycarbonyl)-*S*-w(4-methoxybenzyl)-*N*-methyl-*L*-cysteine** Commercially available N-Boc-S-PMB-L-Cysteine (**5**) (5 g, 14.6 mmol) was added to a flame-dried, base-washed flask under argon and dissolved in dry THF (40 mL). Methyl iodide (2.73 mL, 43.8 mmol) was added by syringe and the reaction mixture was brought to 0 °C. Sodium hydride (60% dispersion in oil, 1.76 g, 43.8 mmol) was weighed and transferred to a capped vial. Small portions of sodium hydride were added as solid under argon. Bubbling was given time to subside before next addition. The reaction was allowed to come to room temperature and stirred overnight. Then, the reaction was quenched by dropwise addition of isopropanol (2 mL) and water (2 mL) and then concentrated by rotary evaporation to approximately 1/5 initial volume. The mixture was then diluted with 100 mL water. The aqueous mixture was extracted with diethyl ether (3 x 50 mL) to remove oil from sodium hydride. The aqueous mixture was then acidified to pH 2 by addition of 1 M HCl. The acidic aqueous mixture was extracted with ethyl acetate (3 x 50 mL). Combined organic layers were washed with acidic (pH 2) brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by two rounds of silica gel chromatography (gradient of ethyl acetate in hexanes, 0.5% acetic acid) to give a white solid (3.9 g, 11.1 mmol, 76% yield).

^{1}H NMR (600 MHz, $CDCl_3$) (Rotamers) δ 7.22 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 7.9 Hz, 3H), 4.66 (dd, *J* = 10.3, 5.3 Hz, 1H), 4.30 (m, 1H), 3.78 (m, 3H), 3.69 (s, 3H), 2.99 – 2.91 (m, 1H), 2.82 (s, 3H), 2.69 – 2.79 (m, 1H) 1.42 (s, 9H).
^{13}C NMR (150 MHz, $CDCl_3$) δ 171.11, 155.20, 144.50, 129.59, 127.93, 126.74, 79.73, 77.24, 77.03, 76.82, 66.69, 61.56, 49.75, 34.14, 32.16, 28.36.
IR ($CHCl_3$) 832 (w), 1034 (w), 1161 (s), 1248 (s), 1302 (s), 1324 (w), 1368 (w), 1393 (w), 1456 (w), 1481 (w), 1512 (s), 1610 (w), 1685 (s), 1734 (s), 2976 (w), 3474 (b)
$[\alpha]^{25}_D$ -459
HRMS: (ES$^+$) Found: 356.1527 (+0.31), $C_{17}H_{26}NO_5S$ (M^+) requires: 356.1526

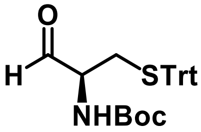


Methyl-*L*-cysteine (6) N-Boc-N-methyl-S-PMB-L-cysteine (1.73 g, 4.8 mmol) was dissolved in ice-cold neat TFA (4 mL). To this, mercury acetate (1.71 g, 5.38 mmol) was added as a solid and the mixture was allowed to sit at room temperature under argon for 30 minutes. The reaction was quenched with water (36 mL), followed by addition of dithiothreitol (5 w/v%, 2.00 g). Which resulted in a thick white/gray precipitate. The reaction was stirred for an additional 30 minutes. Then, the mixture was centrifuged (20 minutes, 3900 RPM) and the clarified aqueous mixture was decanted and extracted with chloroform (10 x 20 mL). The aqueous layer was concentrated by rotary evaporation and lyophilization to give a white solid (1.04 g, 4.08 mmol, 85% yield).

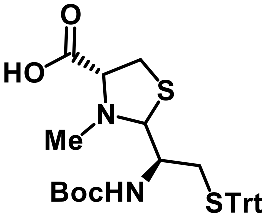
^{1}H NMR: (400 MHz, D_2O) δ 4.14 (t, *J* = 4.4 Hz, 1H), 3.21 (dd, *J* = 15.4, 4.2 Hz, 1H), 3.07 (dd, *J* = 15.4, 4.5 Hz, 1H), 2.73 (s, 3H)
^{13}C NMR: (100 MHz, D_2O) δ 169.90, 73.46, 69.78, 62.19, 42.30, 31.21, 29.32, 26.89, 26.59, 23.37, 22.43
IR (neat): 721 (s), 797 (w), 1048 (w), 1131 (s), 1192 (s), 1422 (w), 1662 (s), 1729 (w), 3034 (b)
$[\alpha]^{25}_D$ +42 (in water)
HRMS: (ES$^+$): Found: 136.0421 (-3.79 ppm), $C_4H_{10}NO_2S$ (M^+) requires: 136.0426



***tert*-butyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate (8)** A flame dried flask was charged with argon, to which *N*-(*tert*-butoxycarbonyl)-*S*-trityl-*D*-cysteine (1 g, 2.16 mmol) was added and dissolved in DMF (8.6 mL). *N,O*-dimthylhydroxylamine hydrochloride (442 mg, 4.53 mmol) was added to the reaction mixture, followed by the addition of EDCI (1.7 g, 8.63 mmol) and DMAP (1.1 g, 8.63 mmol). The reaction was allowed to stir under argon overnight. Once it was determined complete by TLC, the reaction was condensed. The resulting solid was redissolved in EtOAc (30 mL) and washed with 10% $NaHSO_4$ (1 x 30 mL), 10% $NaHCO_3$ (1 x 30 mL), and brine (1 x 30 mL). The organic layer was dried over soldium sulfate, filtered and concentrated. Flash column purification (10% to 70% EtOAc in hexanes) afforded the product as a white solid (946 mg, 86%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 6H), 7.31 – 7.26 (m, 6H), 7.25 – 7.20 (m, 3H), 5.13 (d, *J* = 8.8 Hz, 1H), 4.77 (s, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.57 (dd, *J* = 12.2, 4.6 Hz, 1H), 2.40 (dd, *J* = 12.0, 7.9 Hz, 1H), 1.64 (s, 2H), 1.45 (s, 9H)
^{13}C NMR (150 MHz, $CDCl_3$) δ 171.11, 155.20, 144.50, 129.59, 127.93, 126.74, 79.73, 77.24, 77.03, 76.82, 66.69, 61.56, 49.75, 34.14, 32.16, 28.36.
IR (neat): 700 (s), 743 (s), 1168 (s), 1250 (w), 1366 (w), 1390 (w), 1444(w), 1490 (s), 1490 (s), 1663 (s), 1714 (s), 2939 (w), 2976 (w), 3063 (w), 3322 (b), 3427 (b)
$[\alpha]^{25}_D$ 112
HRMS (ES$^+$): Found: 507.2297 (-2.93 ppm), $C_{29}H_{33}O_4N_2S$ (M^-) requires: 507.2312



***tert*-butyl (*S*)-(1-oxo-3-(tritylthio)propan-2-yl)carbamate** To a flame dried flask under argon, protected weinreb (**8**) (451 mg, 0.890 mmol) was added in THF (1.8 mL). The solution was then cooled to -40°C with a few pieces of dry ice in isopropanol. Meanwhile, to a flame dried vial under argon, a suspension of lithium aluminum hydride (40.5 mg, 1.068 mmol) in THF (1 mL) was prepared and also cooled to -40°C. Once a stable temperature was reached, the LAH/THF suspension was added to the reaction flask slowly over several minutes. The reaction was allowed to gradually warm to -20°C and stirred for 2.5 hours. The reaction was warmed to 0°C and quenched with alternating addition of saturated NH_4Cl (11.1 mL) and 10% $NaHSO_4$ (4.0 mL). This was allowed to stir for 30 minutes. The reaction mixture was then transferred to a separatory funnel and the aqueous layer was extracted. This layer was then washed with EtOAC (3 x 20 mL). The organic layers were combined and washed with brine, dried with Na_2SO_4, filtered and concentrated. The crude oil was then carried through immediately to the next reaction.



(4*R*)-2-((*R*)-1-((*tert*-butoxycarbonyl)amino)-2-(tritylthio)ethyl)-3-ehtylthiazolidine-4-carboxylic acid (9) N-methyl cysteine salt (**6**) (244 mg, 0.979 mmol) was added to a solution of Boc-Trt-aldehyde (398 mg, 0.890 mmol) in ethanol (30 mL) and water (13 mL). To this reaction sodium acetate (358 mg, 3.649 mmol) was added and allowed to stir under argon for 18 hours. Once the reaction was complete, the solvents were concentrated and the resulting solids were suspended in water (20 mL). Citric acid was added until a pH of 2 was achieved. At this point, EtOAc was added (20 mL) and used to extract (3 x 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated. The resulting oil was purified by flash chromatography (10% to 70% EtOAc in hexanes) afforded a clear oil (340 mg, 68%) as a mixture of diastereomers.

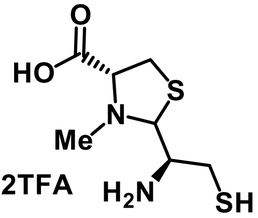
^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (d, *J* = 7.4 Hz, 8H), 7.29 (t, *J* = 7.5 Hz, 8H), 7.21 (t, *J* = 7.2 Hz, 4H), 3.87 (d, *J* = 6.3 Hz, 1H), 3.53 (dt, *J* = 13.7, 7.3 Hz, 3H), 3.03 (dd, *J* = 11.2, 6.0 Hz, 2H), 2.97 – 2.89 (m, 1H), 2.46 (d, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 2.16 (s, 2H), 1.46 (s, 10H)

^{13}C NMR (100 MHz, CD_3OD) δ 220.90, 188.27, 172.64, 144.09, 129.65, 128.27, 127.18, 99.49, 77.37, 77.16, 76.95, 70.10, 44.14, 34.42, 28.45

IR (neat) 698 (s), 7226 (s), 906 (s), 1159 (w), 1492 (w), 1689 (w), 2980 (w), 3066(w), 3408 (b)

$[\alpha]^{25}_D$ -693

HRMS (ES^+): Found: 565.2187 (-0.42 ppm), $C_{31}H_{37}N_2O_4S_2$ (M^+) requires: 565.2189



(4*R*)-2-((*R*)-1-ammonio-2-mercaptoethyl)-4-carboxy-3-methylthiazolidin-3-ium (10) A 10 mL solution of 50% trifluoroacetic acid in DCM was made, to which 3% v/v triisopropyl silane was added. The protected thiazolidine (**9**) (100 mg, 0.177 mmol) was charged to a reaction flask and then dissolved in the freshly made solution (2 mL). This reaction was stirred for 30 minutes at which point only product mass was observed on LCMS. The reaction was condensed. To this water (5 mL) was added to dissolve the product. Insoluble impurities were filtered out and washed with water (5 mL). The resulting water solution was concentrated to about 2 mL, frozen in dry ice and isopropanol bath and lyophilize to a white solid. This was carried through without further purification.

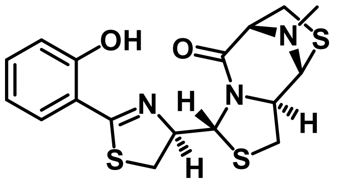
^{1}H NMR (400 MHz, D_2O) δ 4.32 (d, *J* = 10.1 Hz, 1H), 4.11 (dt, *J* = 14.9, 7.4 Hz, 1H), 3.61 (s, 1H), 3.48 (dd, *J* = 11.8, 7.9 Hz, 1H), 3.33 (dd, *J* = 11.9, 5.3 Hz, 1H), 3.20 (ddd, *J* = 10.8, 7.4, 3.6 Hz, 1H), 3.01 (dd, *J* = 15.2, 3.6 Hz, 1H), 2.72 (dd, *J* = 15.1, 7.4 Hz, 1H), 2.55 (s, 3H)

^{1}C NMR (100 MHz, D_2O) δ 176.30, 75.97, 72.65, 57.16, 44.50, 33.88, 23.72

IR (neat) 1136 (s), 1199 (s), 1668 (s), 2819 (w), 2913 (w), 2958 (w), 3370 (b)

$[\alpha]^{25}_D$ -127 (in water)

HRMS (ES^+): Found: 223.0569 (+0.20 ppm), $C_7H_{15}N_2O_2S_2$ (M^+) requires: 223.0569



(3*R*,6*R*,9*R*,9a*R*)-3-((*R*)-2-(2-hydroxyphenyl)-4,5-dihydrothiazol-4-yl-10-methyltetrahydro-1*H*,3*H*,5*H*-6,9-epiminothiazolo[4,3-*c*][1,4]thiazepin-5-one (1)

Deprotected thiazolidine 2 x TFA salt (**10**) (136 mg, 0.302 mmol) was dissolved in 3:1 ethanol:water and added to a flask containing freshly prepared thiazoline aldehyde **14** (38 mg, 0.187 mmol). Sodium acetate trihydrate was added until the reaction measured pH=7 (1.41 g, 10.7 mmol) and the reaction was stirred under argon for 16 hours (overnight). The reaction was concentrated and resuspended in water (50 mL). The reaction was brought to pH=3 with solid citric acid. The acidic aqueous layer was extracted with 3 x 100 mL EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was then dissolved in EtOAc/Methanol and gently heated (50 °C) while stirring until the reaction was complete by LC-MS. The reaction was concentrated, and the resulting oil was purified by silica gel flash chromatography (100% DCM) to afford a yellow oil (340 mg, 68%) as a mixture of diastereomers (**1** and **15**), which were purified by preparative HPLC (45% to 95% acetonitrile in water, 0.1% formic acid) to afford the product as a white solid (17.6 mg, 24% yield).

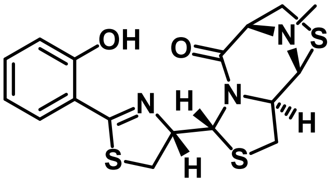
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 – 7.32 (m, 1H), 6.98 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.87 (td, *J* = 7.8, 1.1 Hz, 1H), 5.75 (d, *J* = 6.0 Hz, 1H), 4.86 (ddd, *J* = 8.5, 7.2, 6.0 Hz, 1H), 4.61 (s, 1H), 4.03 (d, *J* = 6.9 Hz, 1H), 3.83 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.45 – 3.39 (m, 2H), 3.32 (d, *J* = 10.7 Hz, 1H), 3.22 (dd, *J* = 10.8, 6.4 Hz, 1H), 2.99 (ddd, *J* = 14.6, 10.2, 7.3 Hz, 2H), 2.28 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 173.93, 167.89, 159.35, 133.43, 130.88, 118.99, 117.37, 116.35, 80.79, 77.37, 77.16, 76.95, 73.21, 71.29, 69.53, 60.71, 40.22, 35.16, 34.66, 33.84

IR ($CHCl_3$) 752 (w), 1029 (s), 1423 (w), 1668 (w), 2851 (w), 2923 (w), 3374 (b)

$[\alpha]^{25}_D$ +131

HRMS: (ES$^+$): Found: 394.0715 (+0.92 ppm), $C_{17}H_{20}O_2N_2S_3$ (M$^+$) requires: 394.0712



(3*R*,6*R*,9*R*,9a*R*)-3-((*S*)-2-(2-hydroxyphenyl)-4,5-dihydrothiazol-4-yl)-10-methyltetrahydro-1*H*,2*H*,5*H*-6,9-epiminothiazolo[4,3-*c*][1,4]thiazepin-5-one (15)

See procedure for **1**. The product was isolated as a white solid (11.5 mg, 16% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.38 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.03 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.90 (td, *J* = 7.8, 1.1 Hz, 1H), 5.65 (d, *J* = 7.7 Hz, 1H), 4.92 (dd, *J* = 16.2, 8.2 Hz, 1H), 4.74 (s, 1H), 4.11 (td, *J* = 3.5, 1.4 Hz, 1H), 3.99 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.39 (dd, *J* = 11.2, 8.6 Hz, 1H), 3.34 – 3.30 (m, 3H), 3.06 (dd, *J* = 11.2, 9.6 Hz, 1H), 2.93 (dd, *J* = 9.5, 4.8 Hz, 1H), 2.35 (s, 3H)

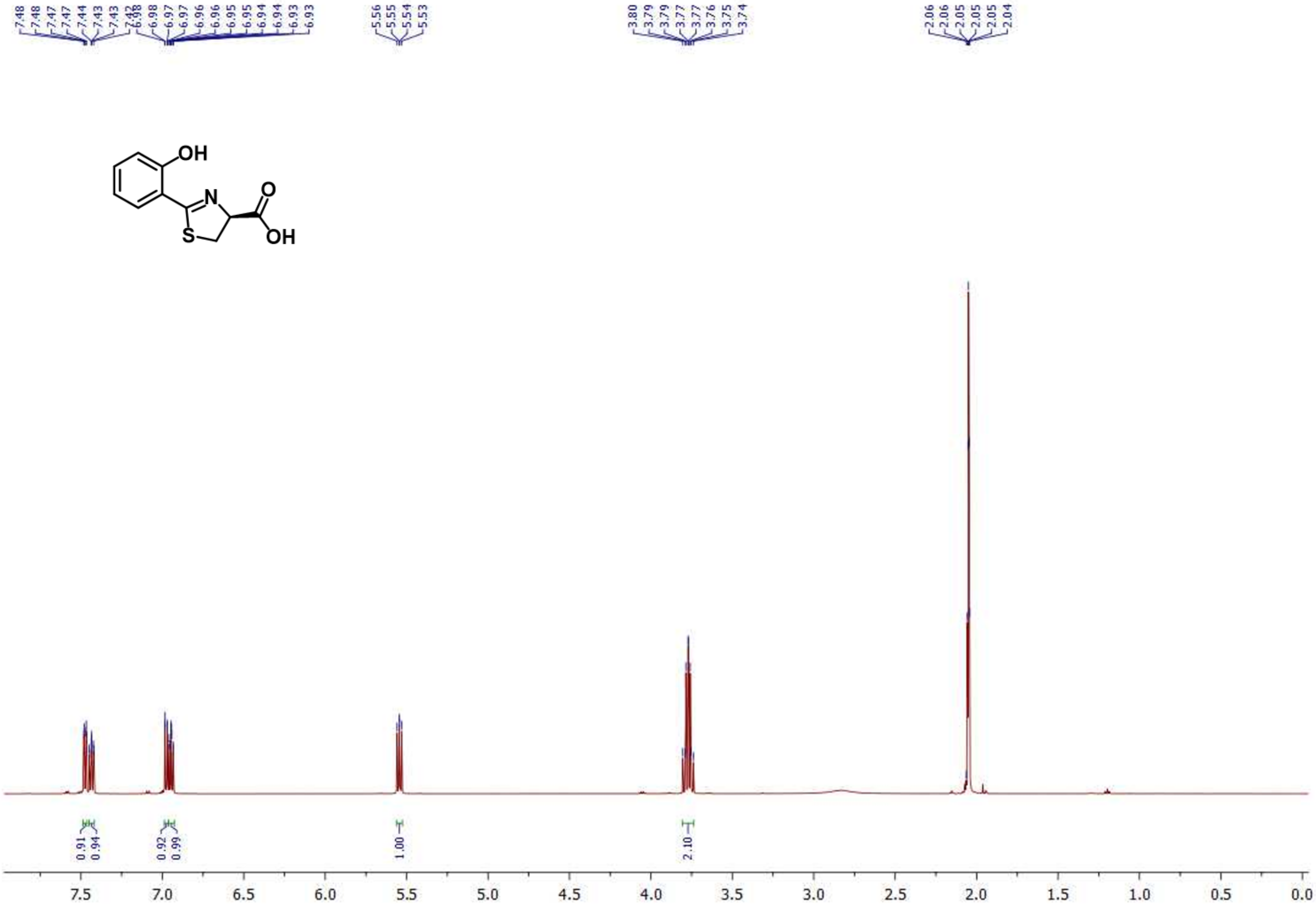
^{13}C NMR (150 MHz, $CDCl_3$) δ 174.38, 168.31, 159.27, 133.53, 130.88, 119.09, 117.36, 116.31, 81.10, 77.37, 77.16, 76.95, 73.39, 71.43, 69.53, 61.27, 40.13, 35.41, 34.46, 34.18

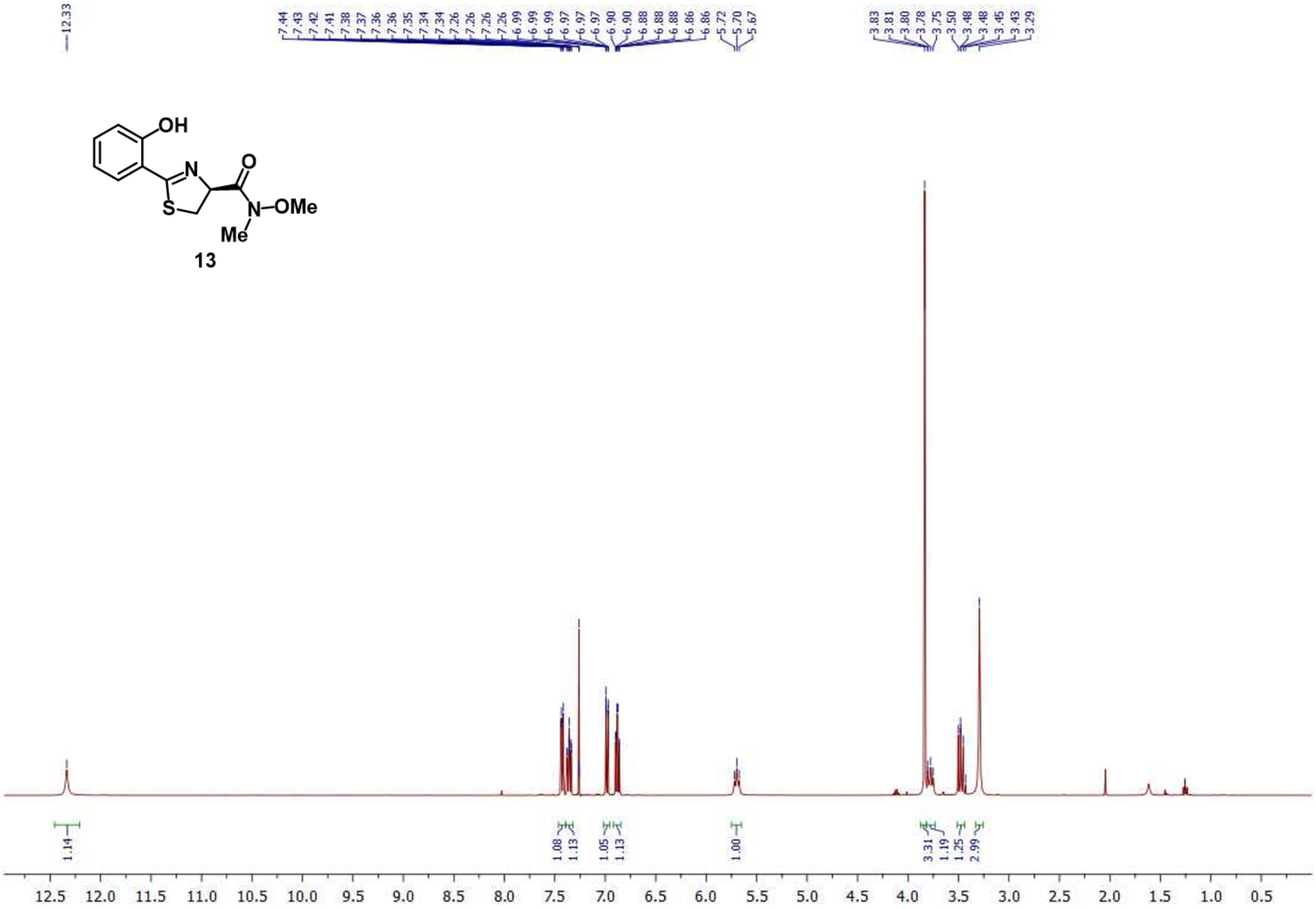
IR ($CHCl_3$) 754 (w), 1029 (s), 1466 (w), 1646 (w), 2850 (w), 2944 (w), 3397 (b)

$[\alpha]^{25}_D$ +135

HRMS: (ES$^+$): Found: 394.0714 (+0.70 ppm), $C_{17}H_{20}O_2N_2S_3$ (M$^+$) requires: 394.0712

7.2 Experimental Spectra





12.33
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7.42
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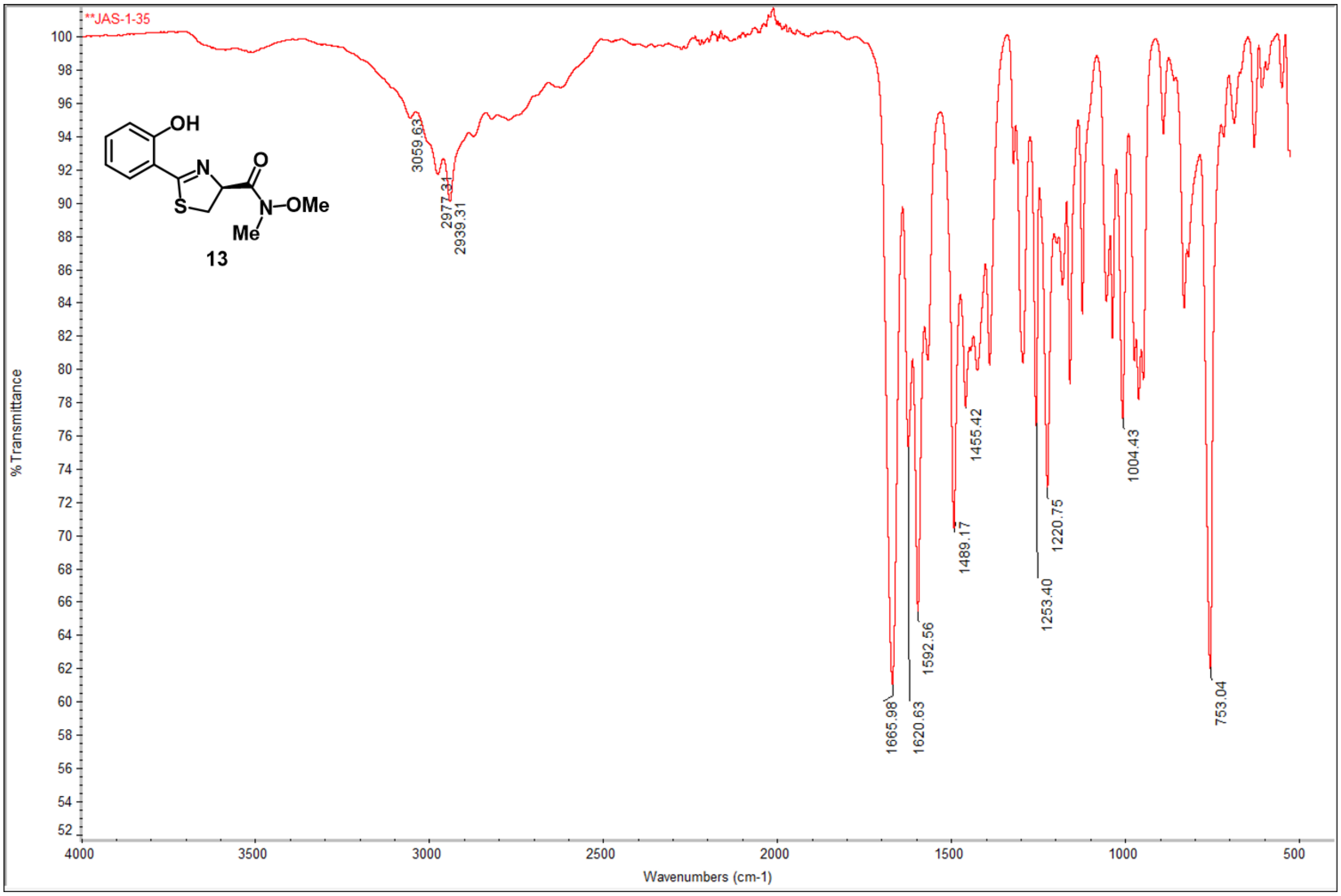
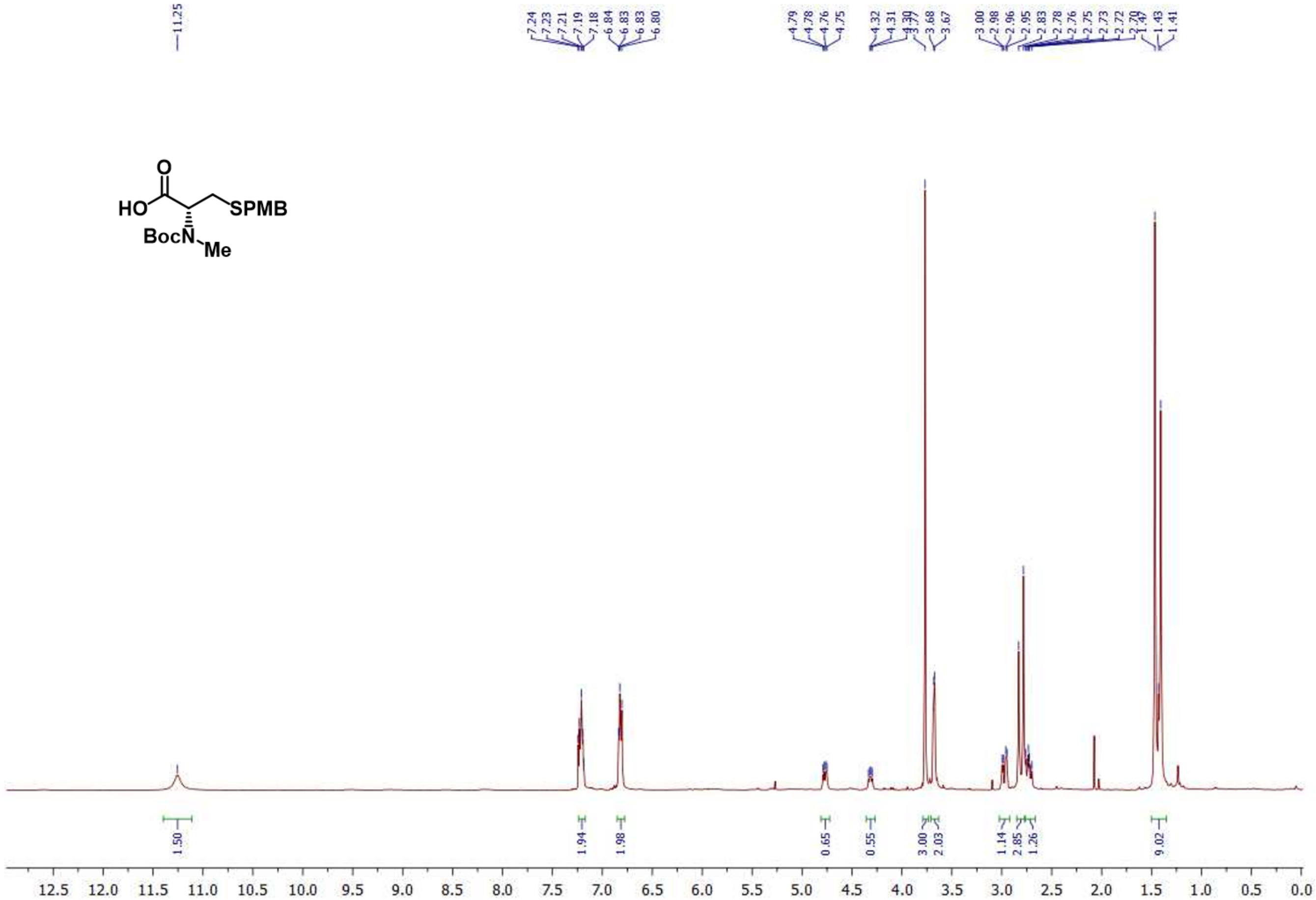
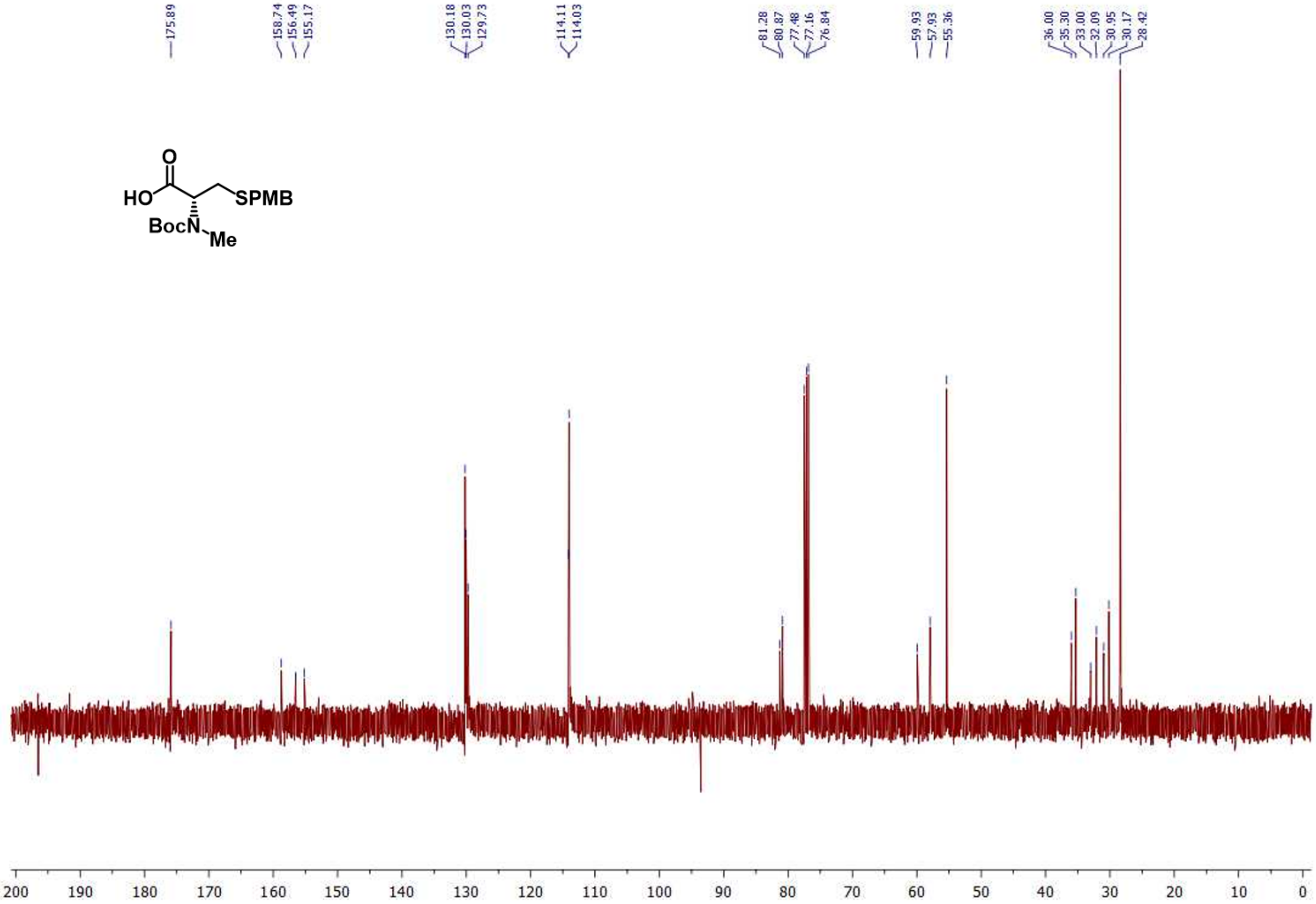
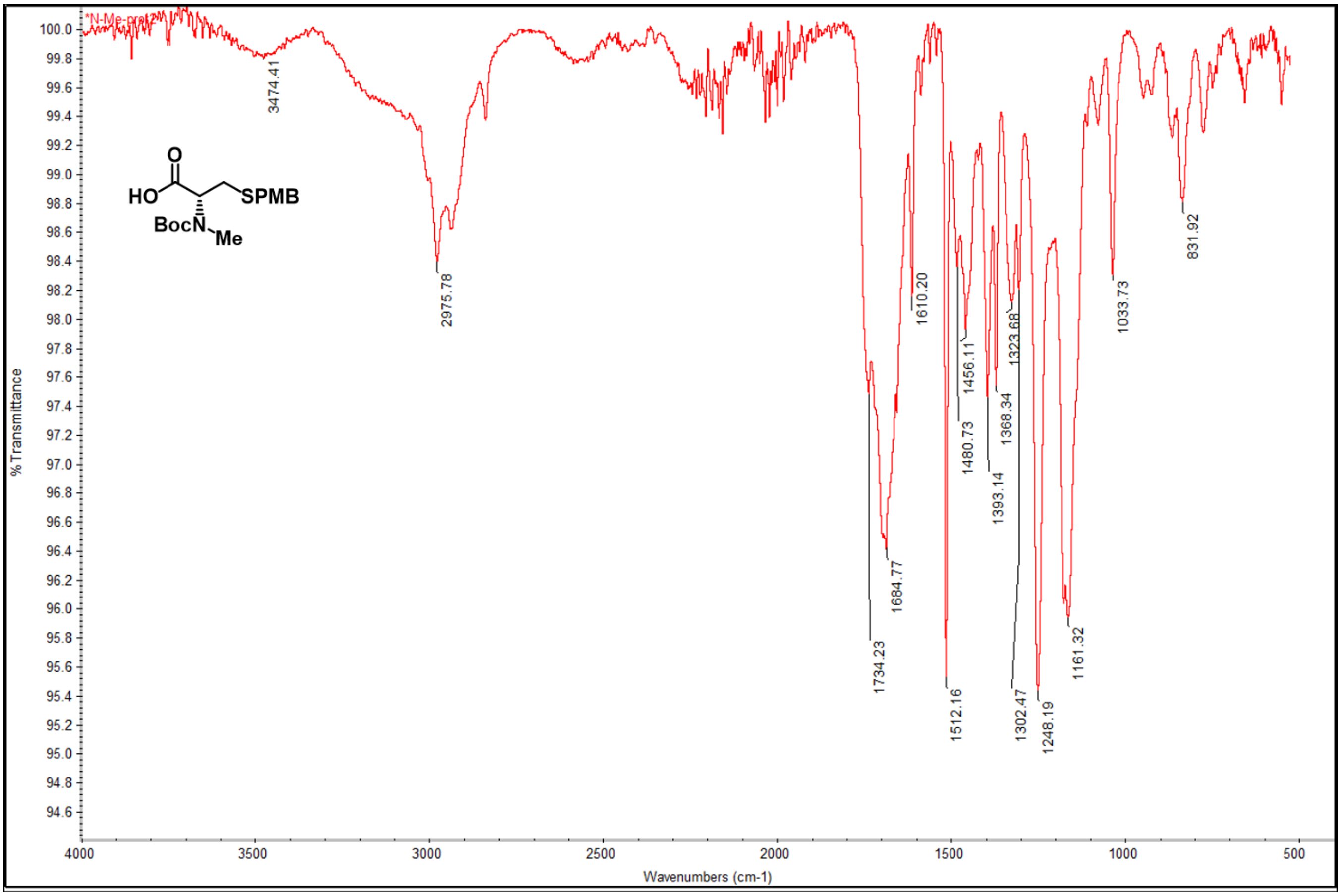
6.88
6.88
6.86
6.86
5.72
5.70
5.67
3.83
3.81
3.80
3.78
3.75
3.50
3.48
3.48
3.45
3.43
3.29
OH
N
O
S
N
OMe
Me
13
1.14
1.08
1.13
1.05
1.13
1.00
3.31
1.19
1.25
2.99
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

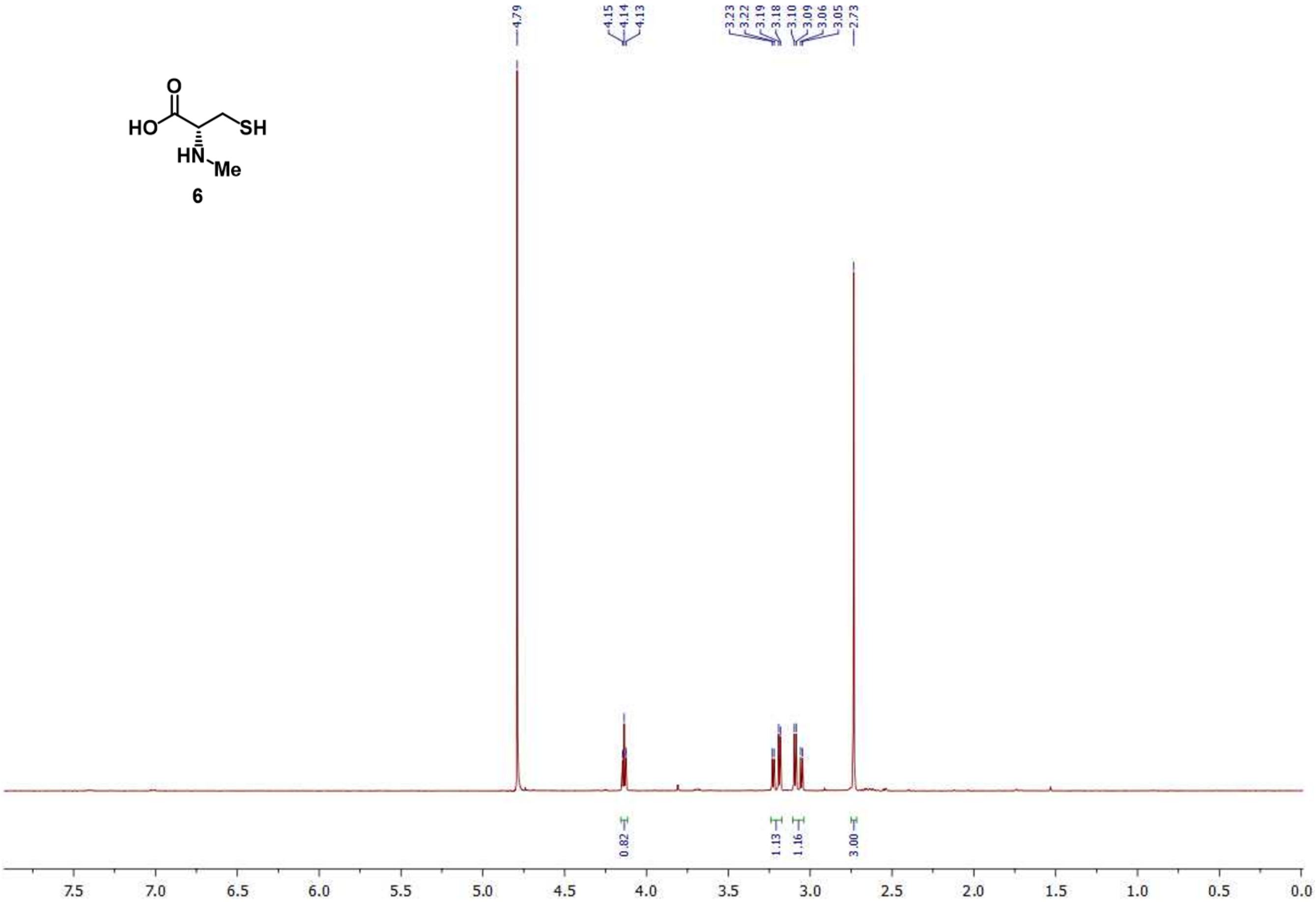


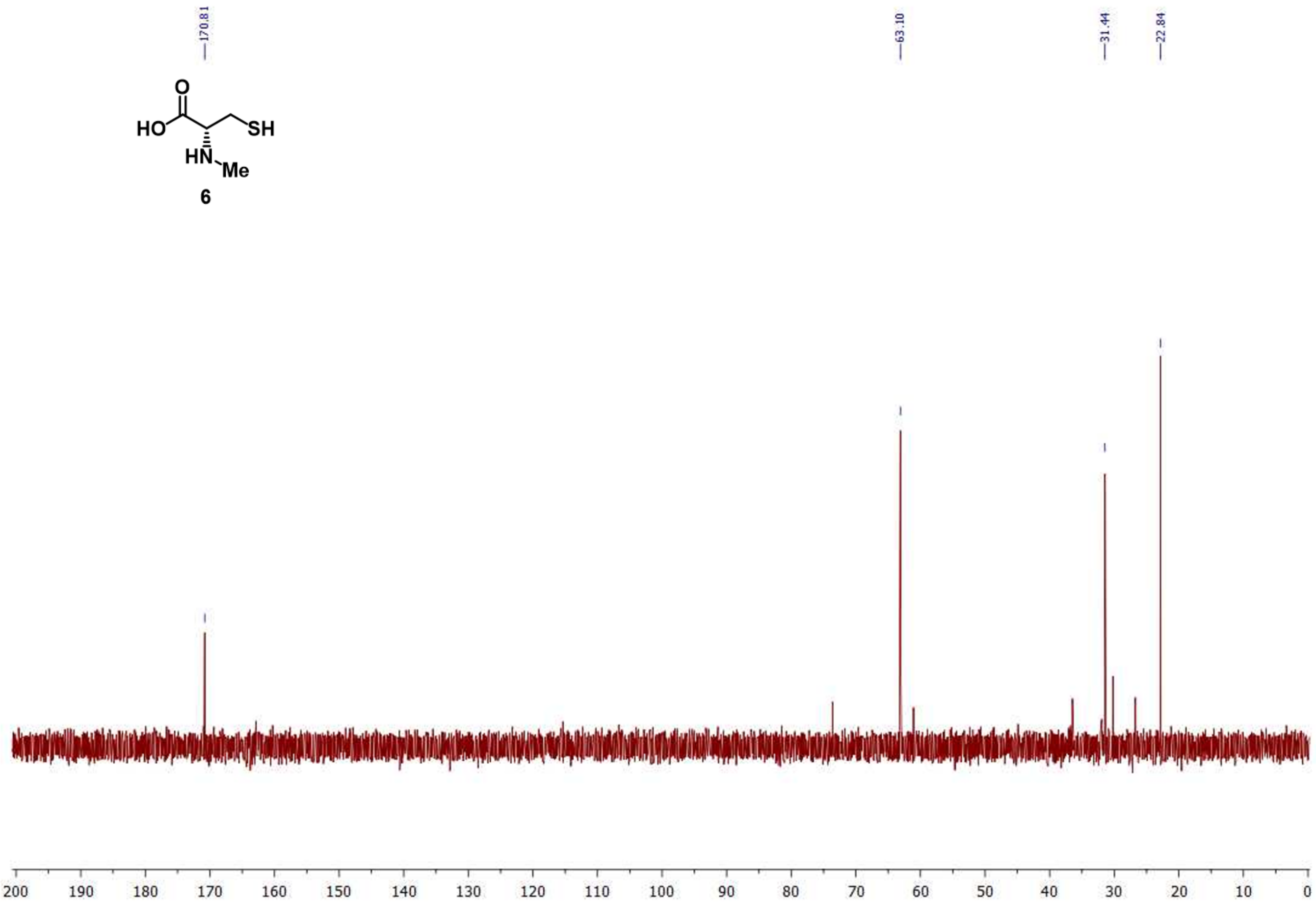
**JAS-1-35
OH
N
O
S
N
OMe
Me
13
% Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
3059.63
2977.31
2939.31
1665.98
1620.63
1592.56
1489.17
1455.42
1253.40
1220.75
1004.43
753.04
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

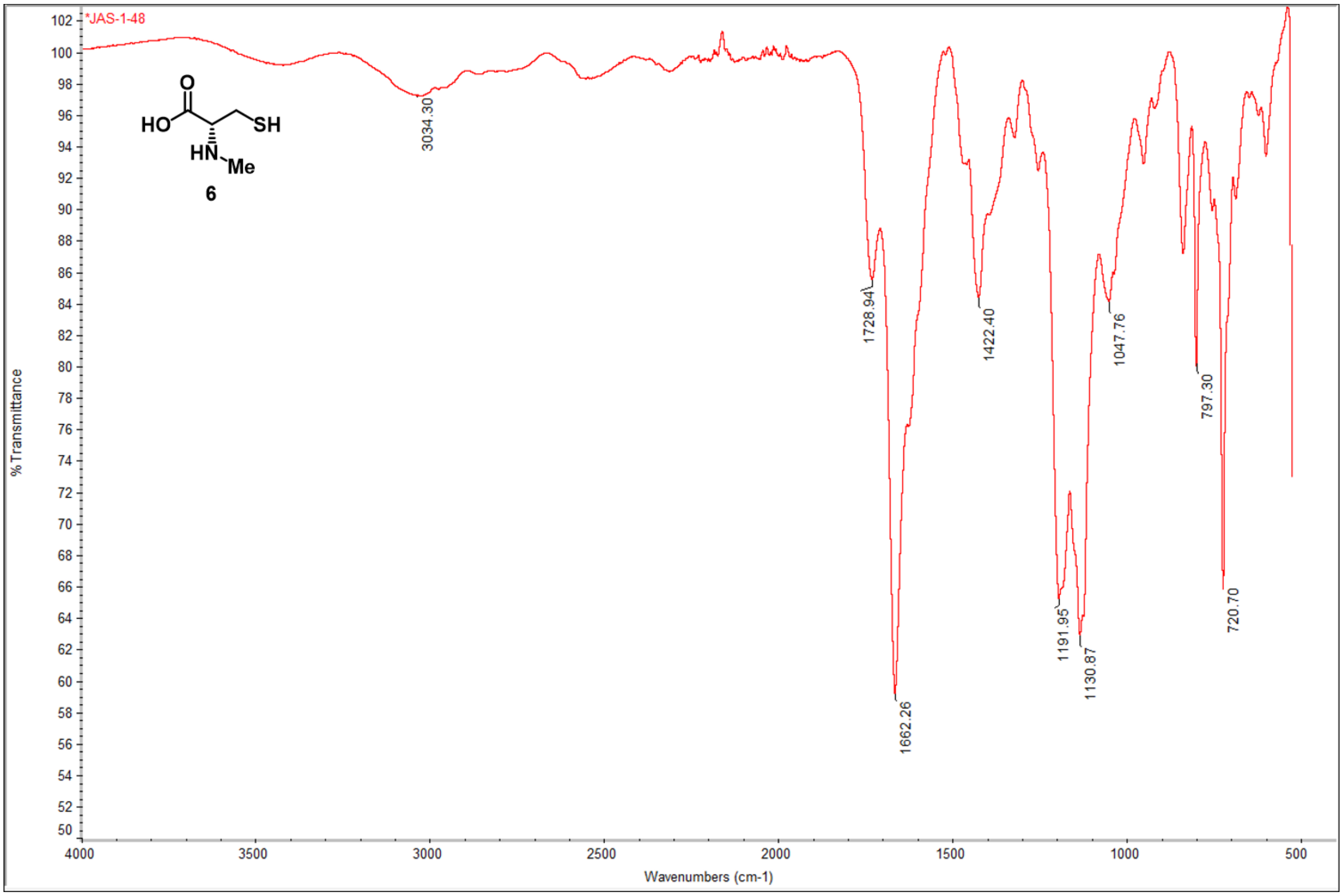

11.25
7.24
7.23
7.21
7.19
7.18
6.84
6.83
6.83
6.80
4.79
4.78
4.76
4.75
4.32
4.31
4.30
3.77
3.68
3.67
3.00
2.98
2.96
2.95
2.83
2.78
2.76
2.75
2.73
2.72
2.70
1.47
1.43
1.41
O
HO
SPMB
BocN
Me
1.50
1.94
1.98
0.65
0.55
3.00
2.03
1.14
2.85
1.26
9.02
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

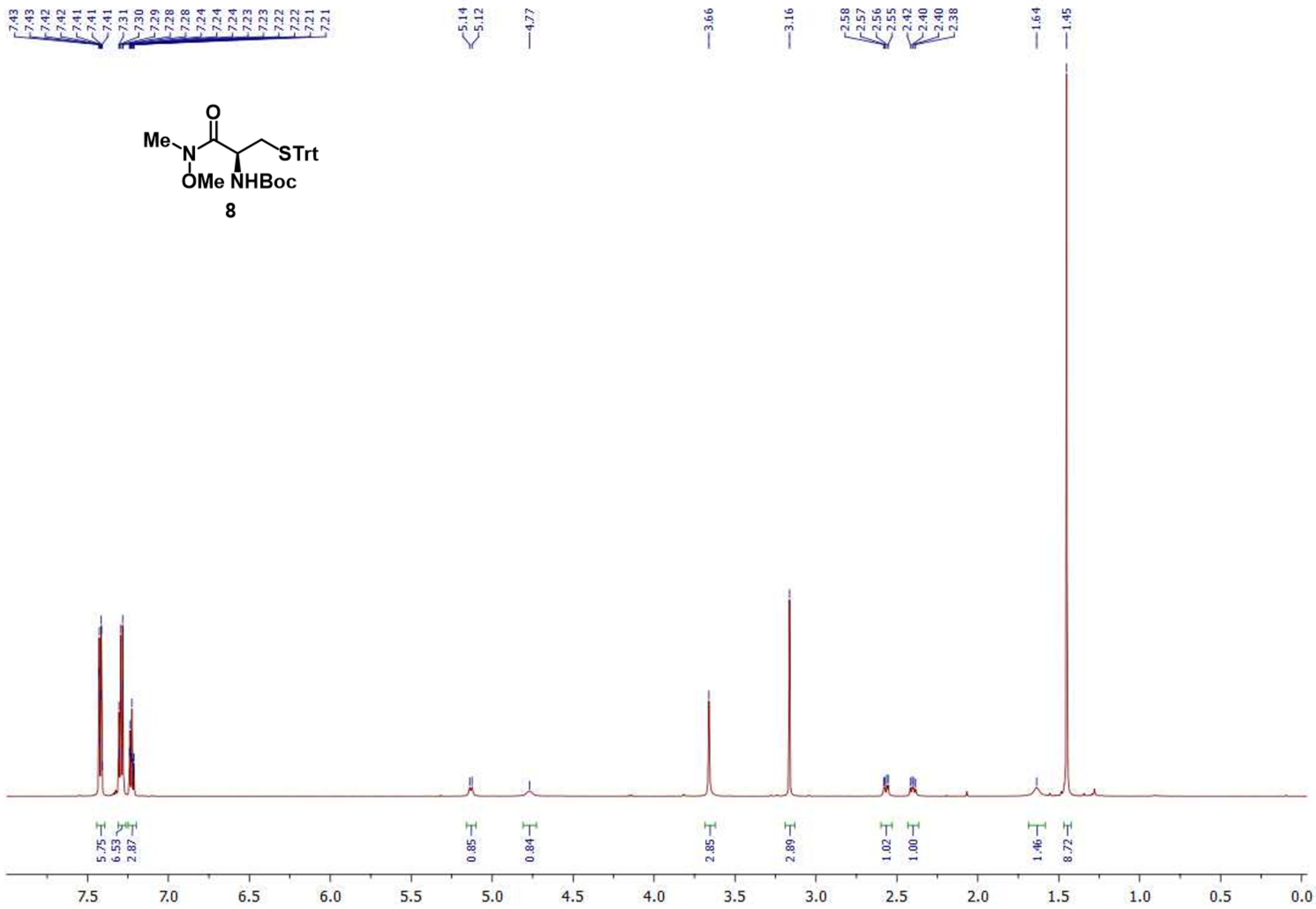

175.89
158.74
156.49
155.17
130.18
130.03
129.73
114.11
114.03
81.28
80.87
77.48
77.16
76.84
59.93
57.93
55.36
36.00
35.30
33.00
32.09
30.95
30.17
28.42
O
HO
SPMB
BocN
Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

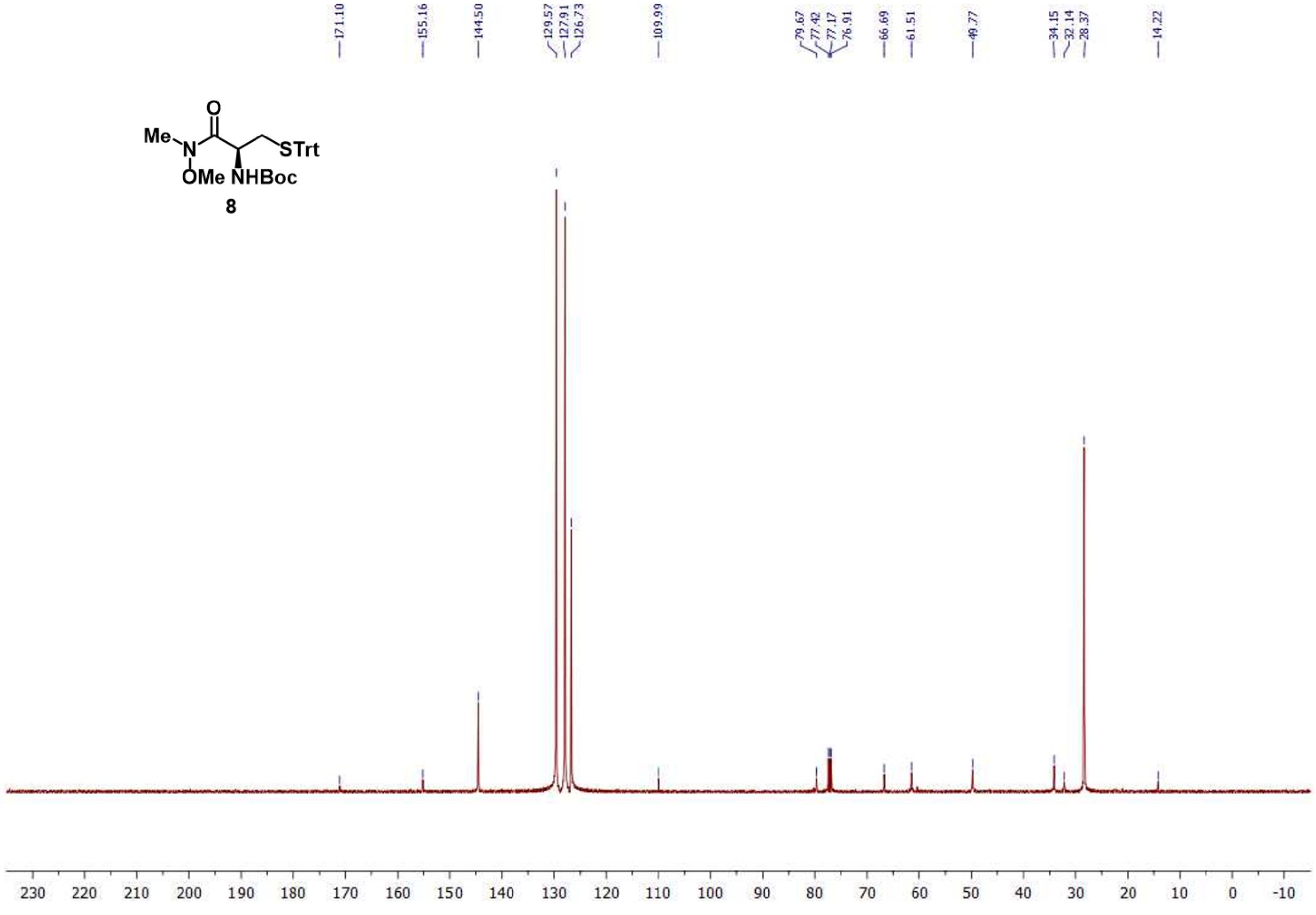

HO
O
SPMB
BocN
Me
% Transmittance
Wavenumbers (cm-1)
3474.41
2975.78
1734.23
1684.77
1610.20
1512.16
1480.73
1456.11
1393.14
1368.34
1323.68
1302.47
1248.19
1161.32
1033.73
831.92
4000
3500
3000
2500
2000
1500
1000
500

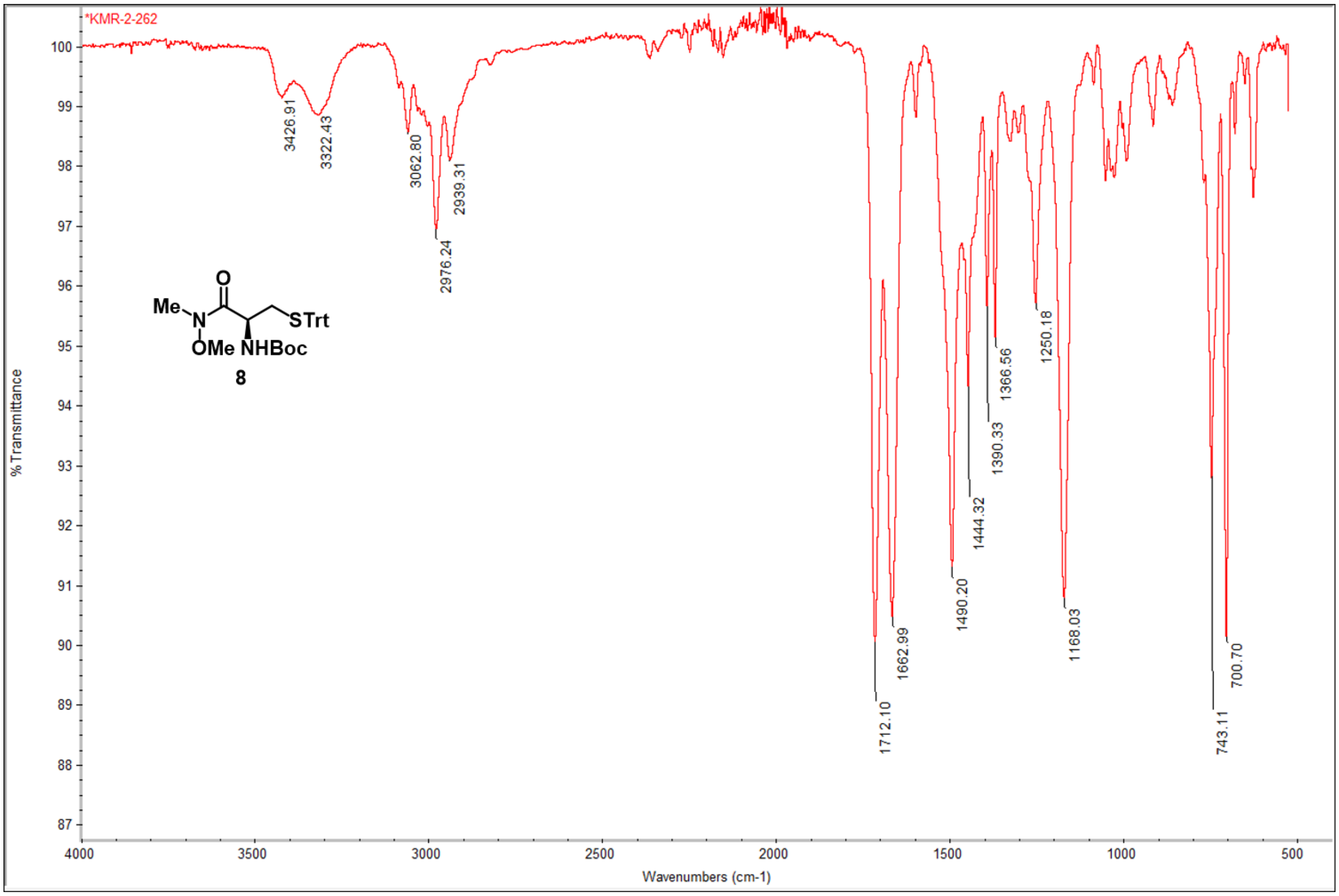

HO
O
SH
HN
Me
6
4.79
4.15
4.14
4.13
3.23
3.22
3.19
3.18
3.10
3.09
3.06
3.05
2.73
0.82
1.13
1.16
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


170.81
63.10
31.44
22.84
HO
O
SH
HN
Me
6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

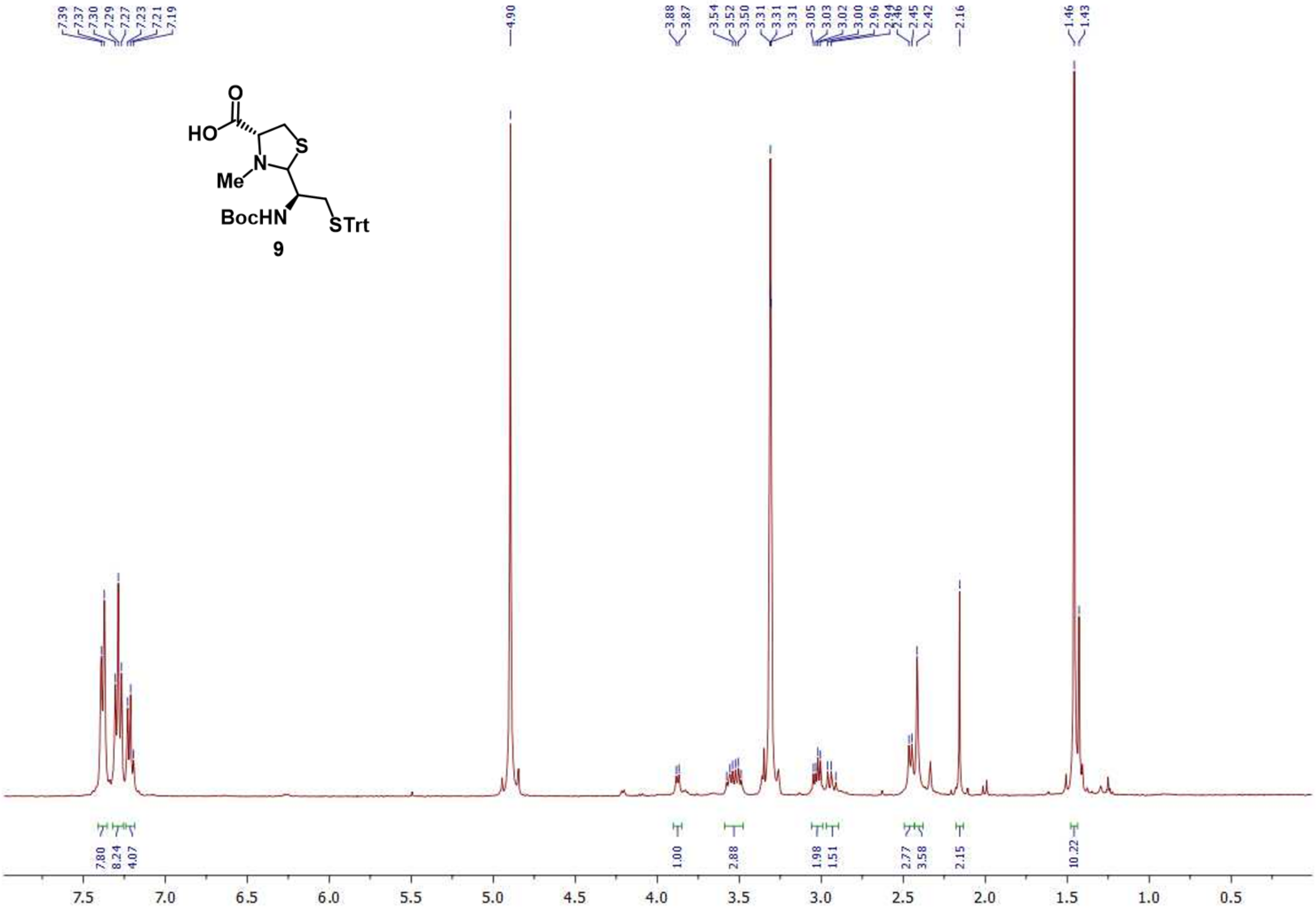

*JAS-1-48
HO
O
SH
HN
Me
6
% Transmittance
102
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
3034.30
1728.94
1662.26
1422.40
1191.95
1130.87
1047.76
797.30
720.70
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)


7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.31
7.30
7.29
7.28
7.28
7.24
7.24
7.24
7.23
7.23
7.22
7.22
7.21
7.21
5.14
5.12
4.77
3.66
3.16
2.58
2.57
2.56
2.55
2.42
2.40
2.40
2.38
1.64
1.45
Me
N
O
OMe
NHBoc
STrt
8
5.75
6.53
2.87
0.85
0.84
2.85
2.89
1.02
1.00
1.46
8.72
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

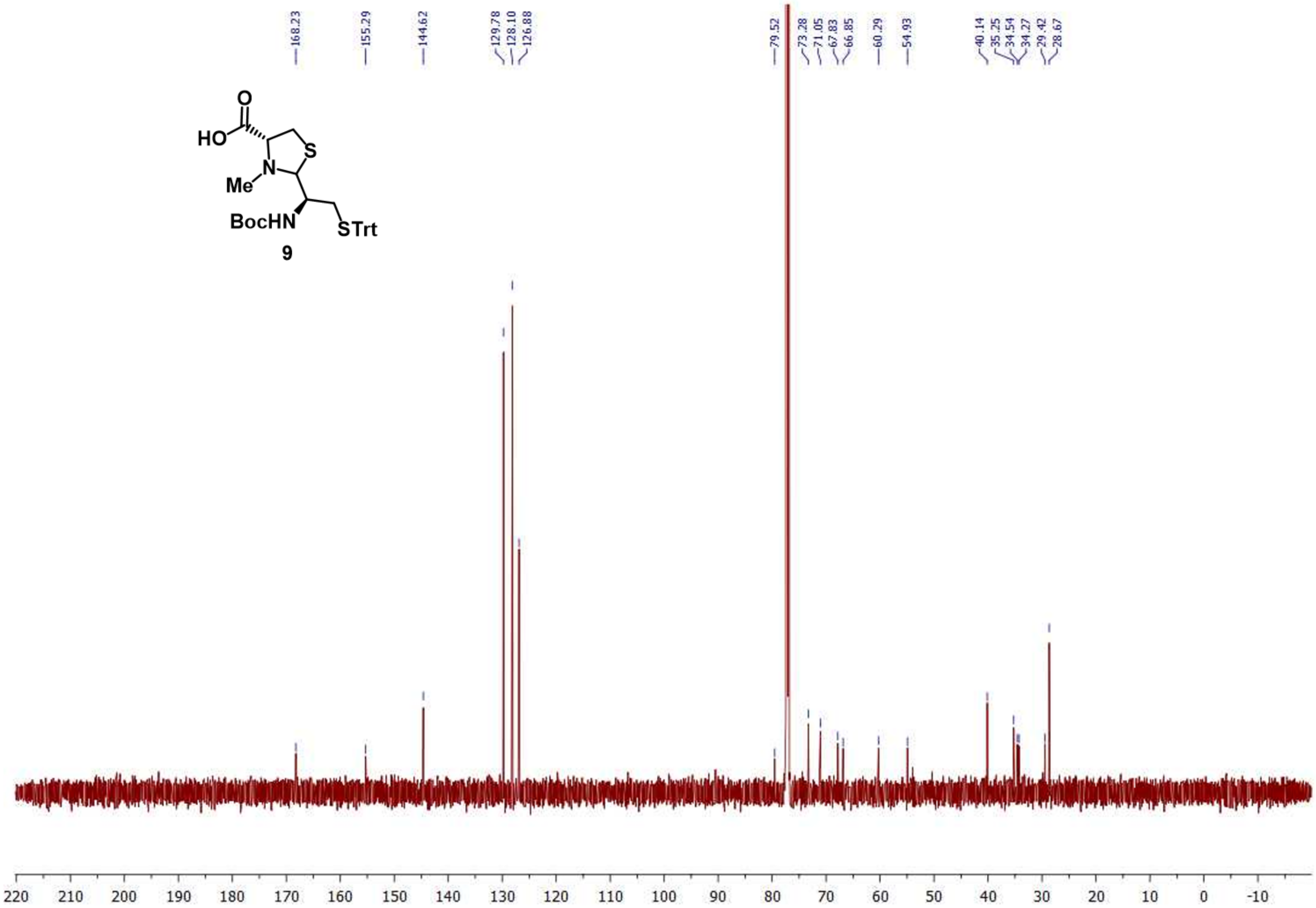

171.10
155.16
144.50
129.57
127.91
126.73
109.99
79.67
77.42
77.17
76.91
66.69
61.51
49.77
34.15
32.14
28.37
14.22
Me
N
O
OMe
NHBoc
STrt
8
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

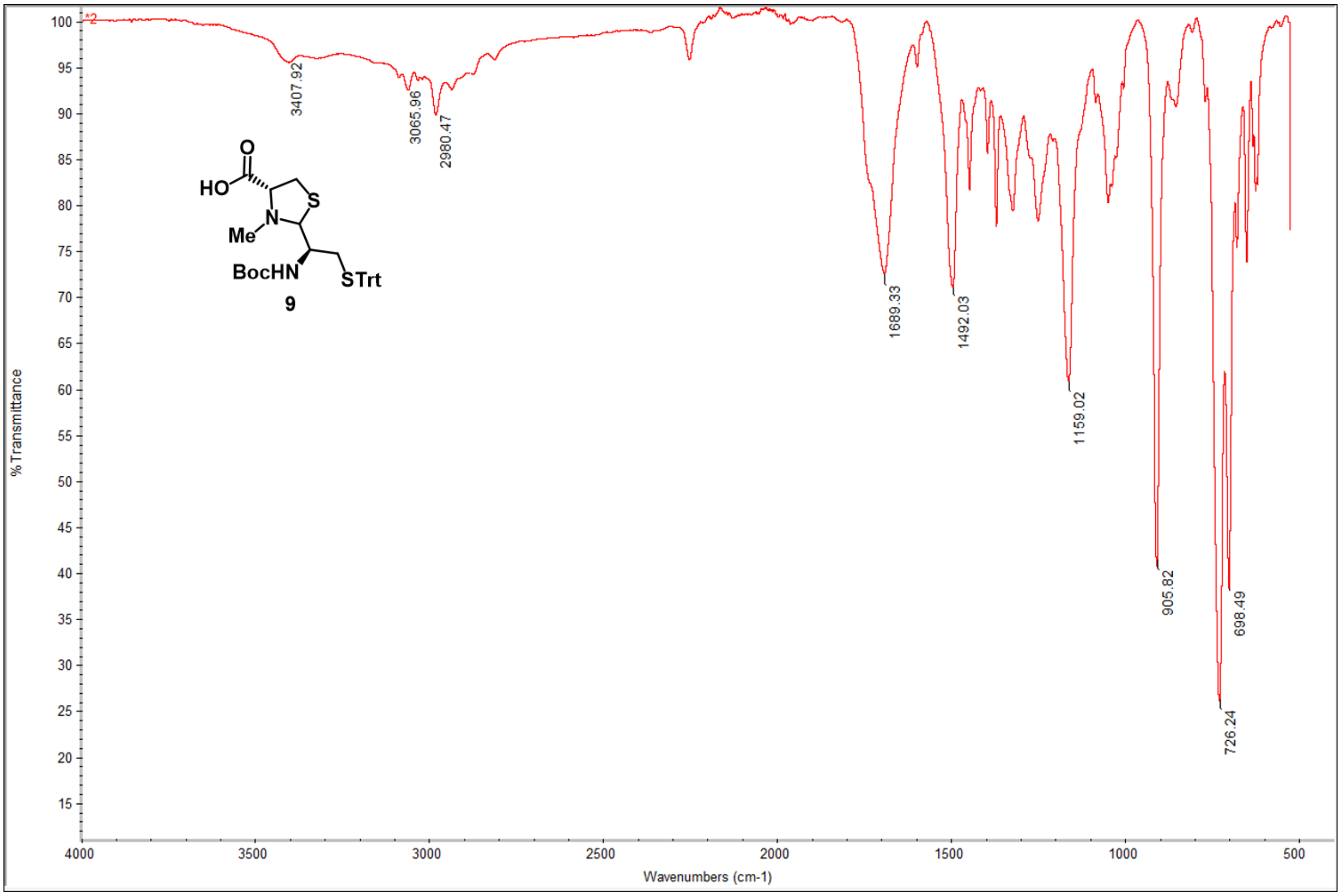

*KMR-2-262
% Transmittance
Wavenumbers (cm-1)
3426.91
3322.43
3062.80
2976.24
2939.31
1712.10
1662.99
1490.20
1444.32
1390.33
1366.56
1250.18
1168.03
743.11
700.70
Me
N
OMe
O
NHBoc
STrt

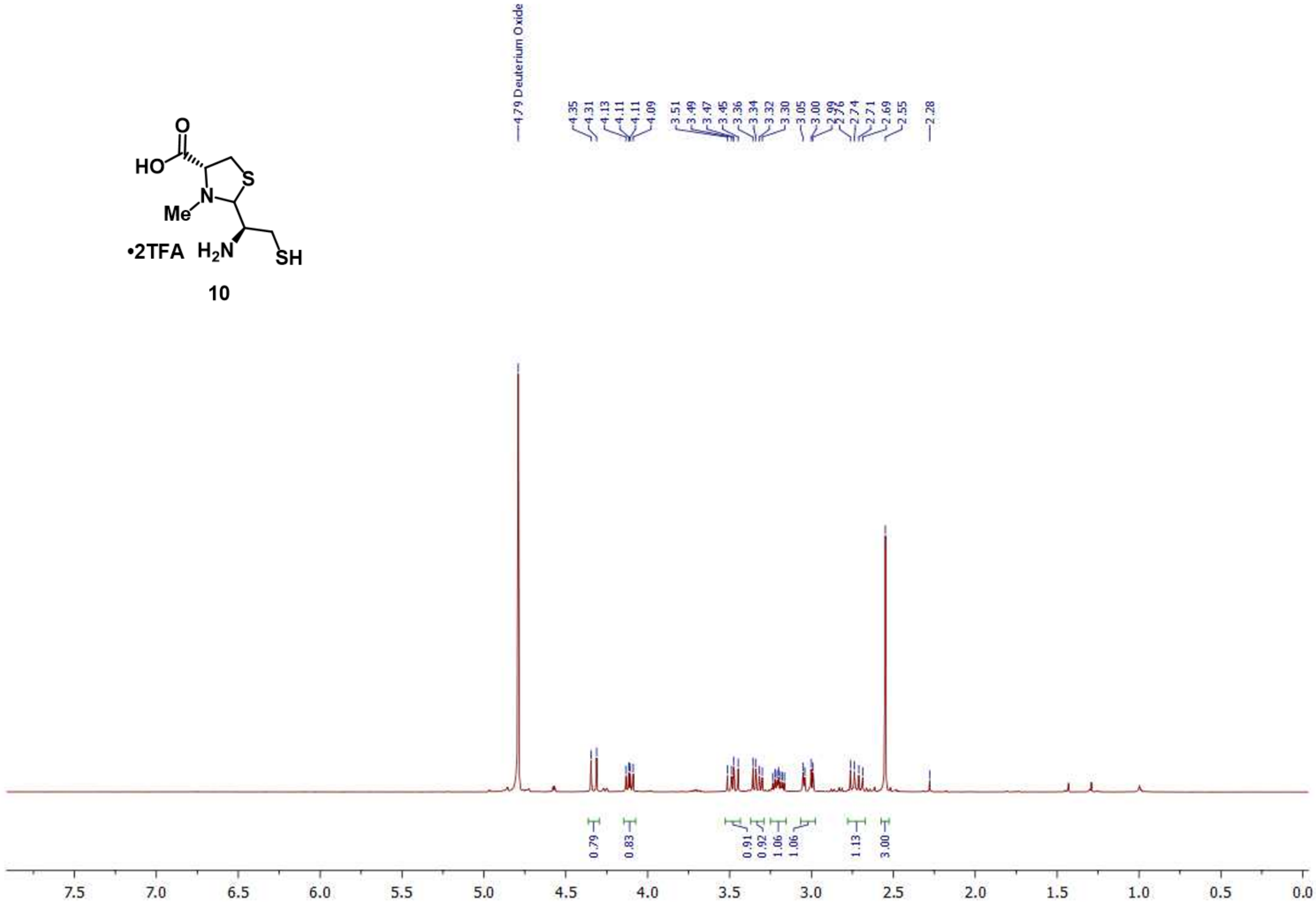
8

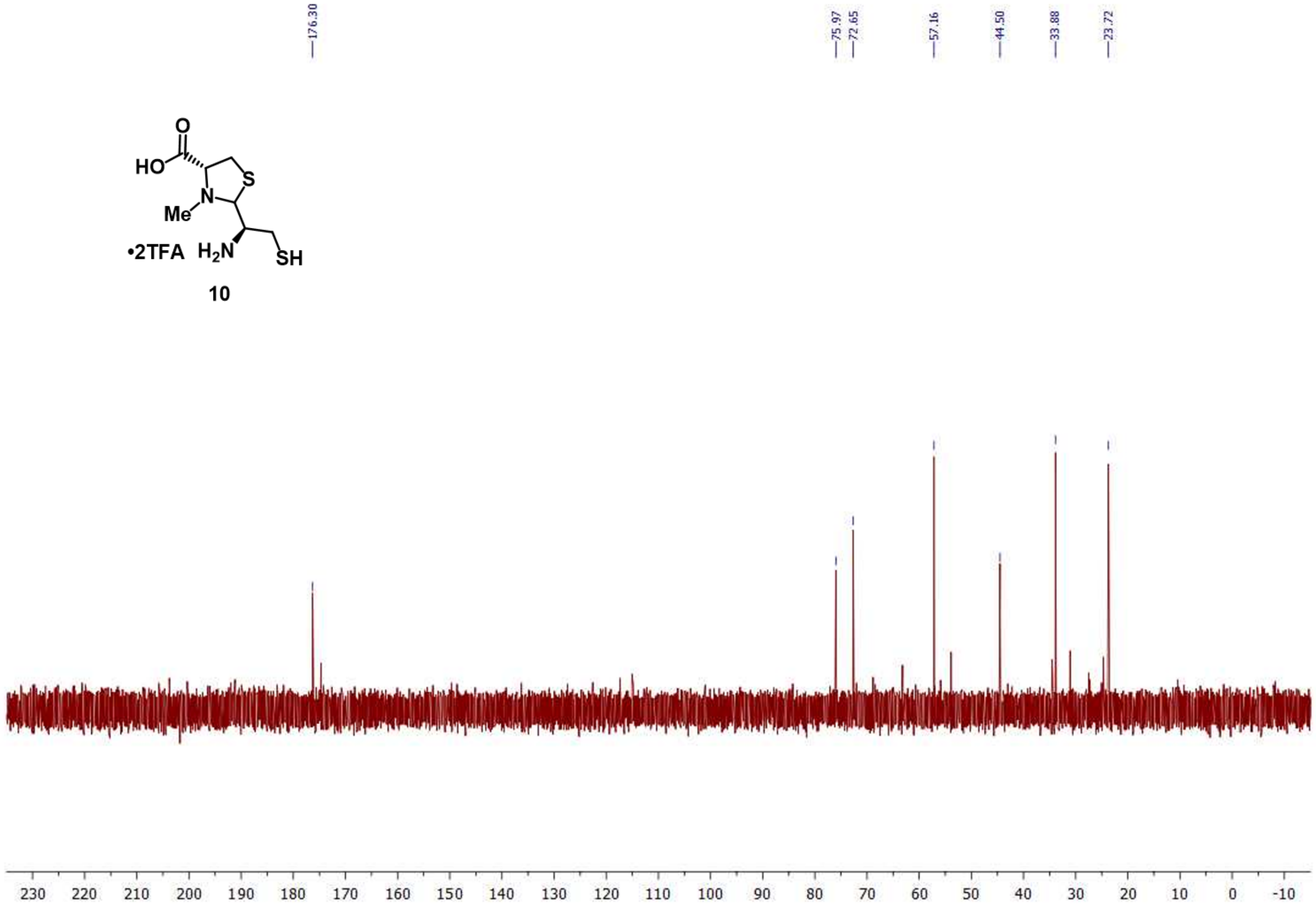

7.39
7.37
7.30
7.29
7.27
7.23
7.21
7.19
4.90
3.88
3.87
3.54
3.52
3.50
3.31
3.31
3.31
3.05
3.03
3.02
3.00
2.96
2.94
2.46
2.45
2.42
2.16
1.46
1.43
7.80
8.24
4.07
1.00
2.88
1.98
1.51
2.77
3.58
2.15
10.22
HO
O
S
N
Me
BocHN
STrt

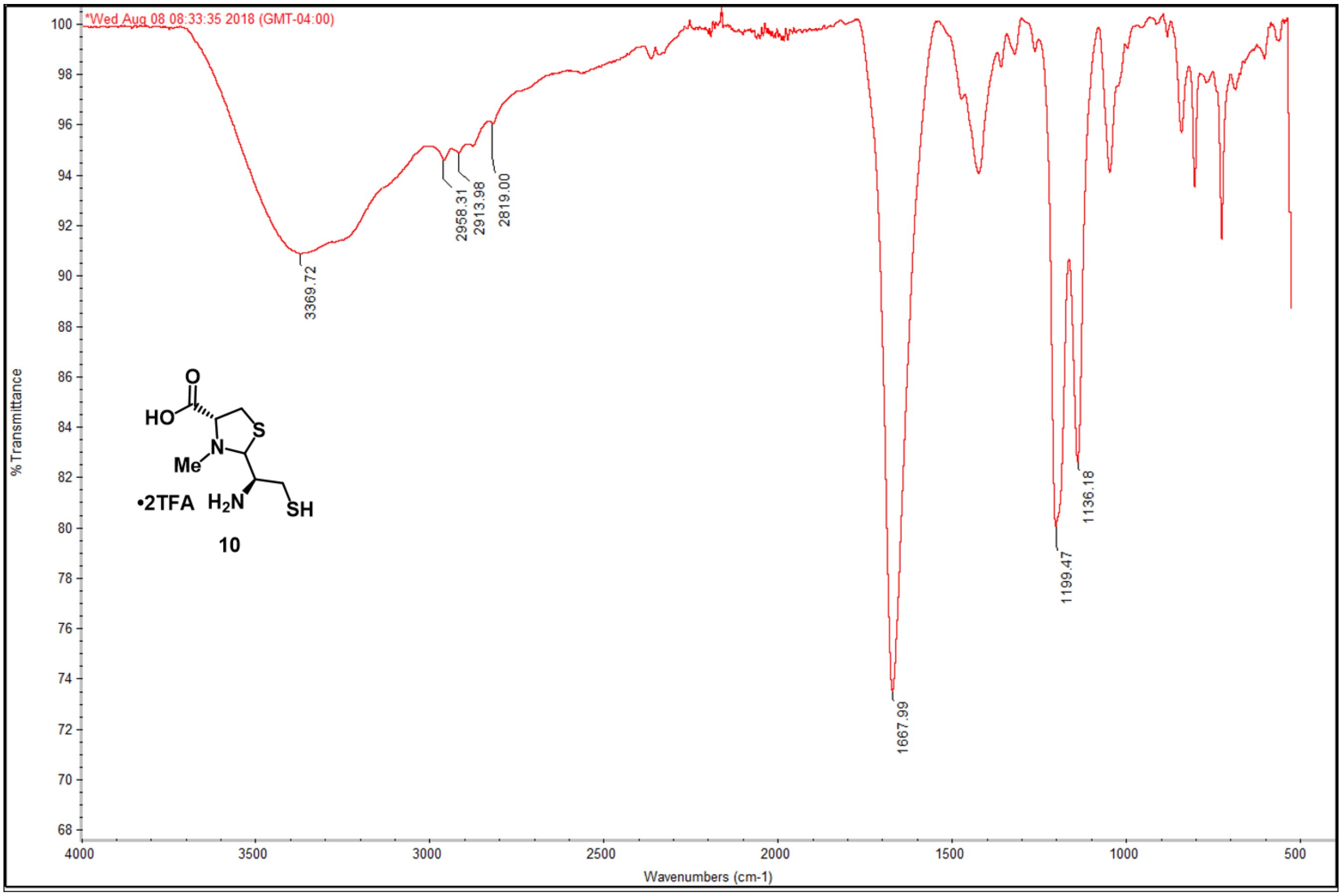
9

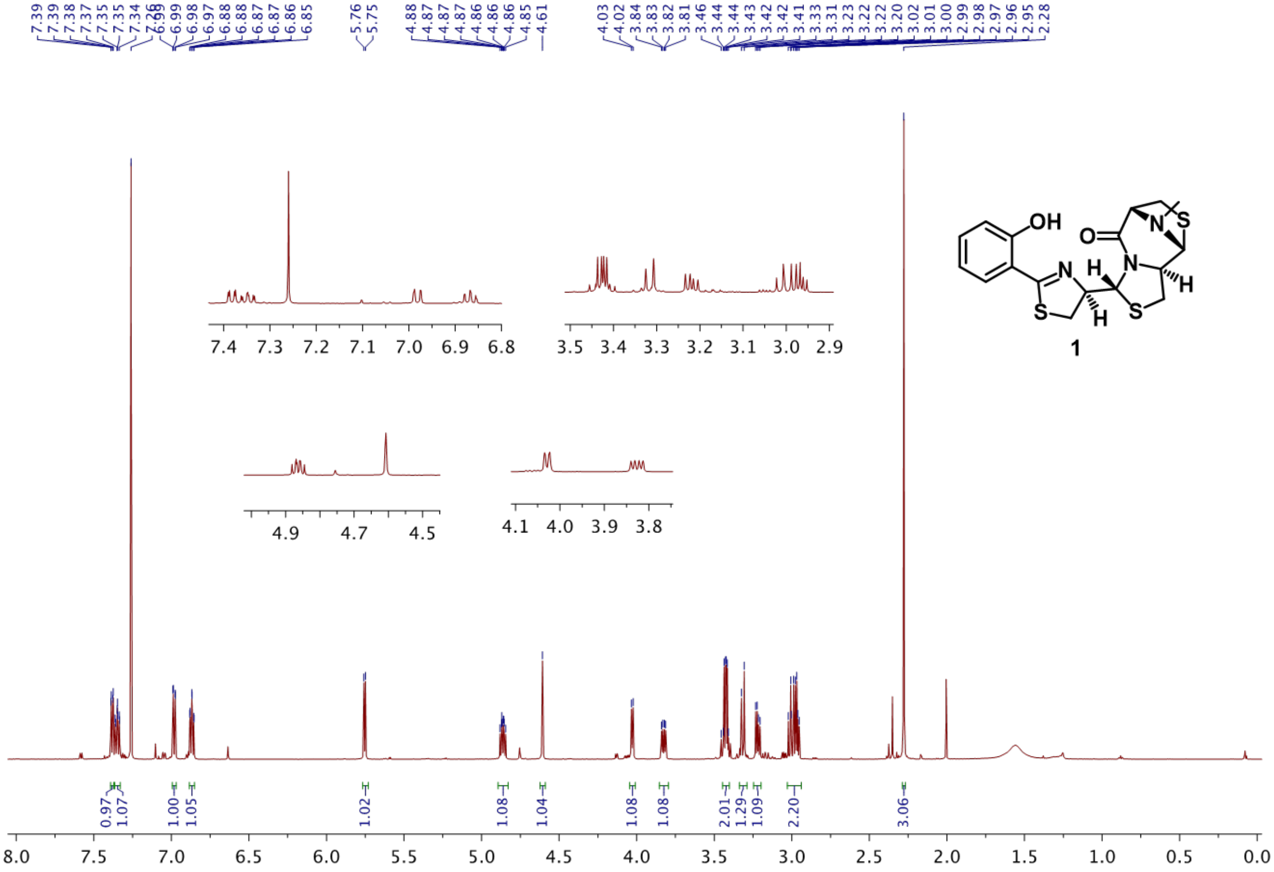

168.23
155.29
144.62
129.78
128.10
126.88
79.52
73.28
71.05
67.83
66.85
60.29
54.93
40.14
35.25
34.54
34.27
29.42
28.67
HO
O
S
N
Me
BocHN
STrt
9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

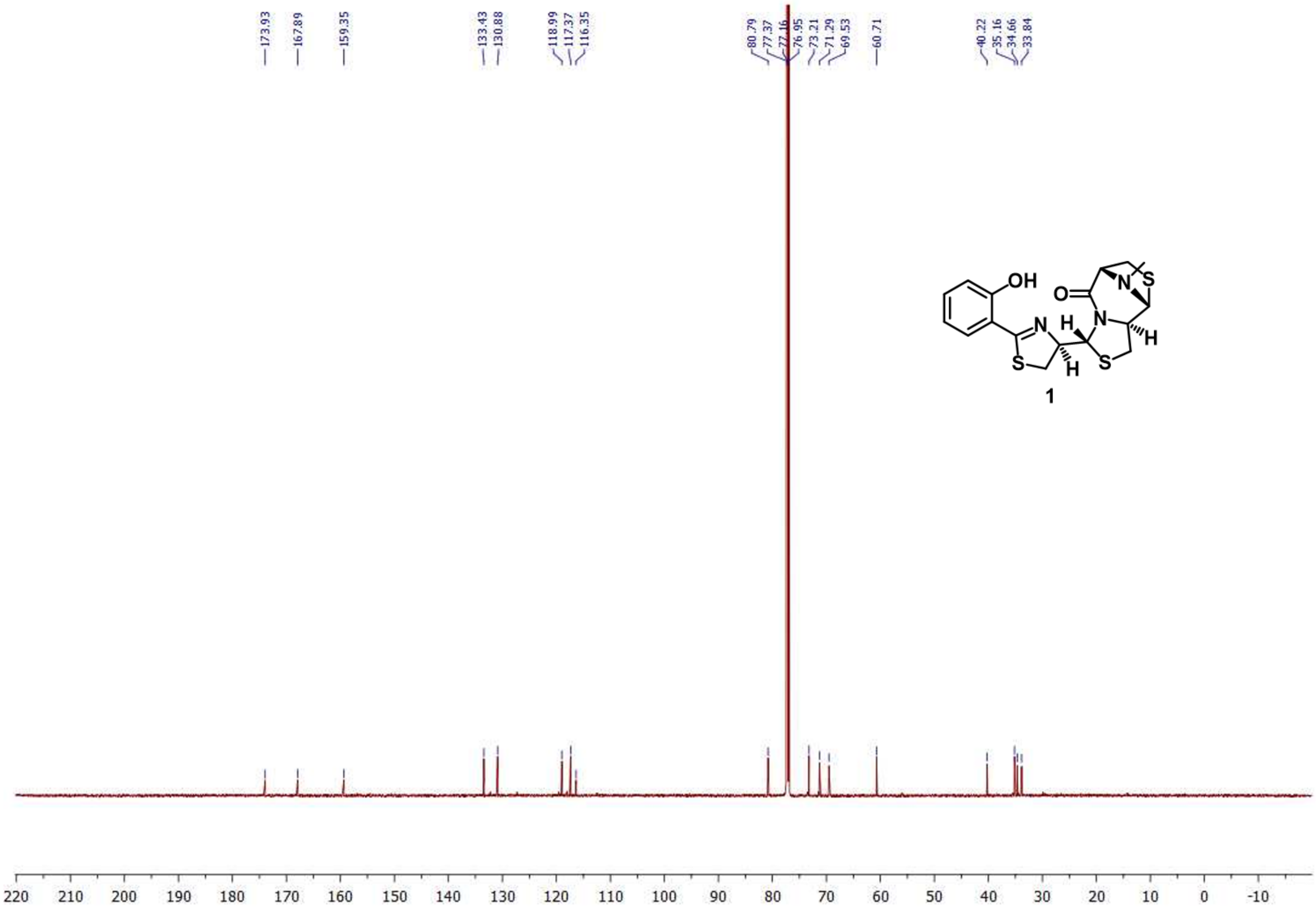

*2
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
% Transmittance
3407.92
3065.96
2980.47
1689.33
1492.03
1159.02
905.82
726.24
698.49
HO
O
S
N
Me
BocHN
STrt
9
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)


HO
O
S
N
Me
•2TFA
H2N
SH
10
4.79 Deuterium Oxide
4.35
4.31
4.13
4.11
4.11
4.09
3.51
3.49
3.47
3.45
3.36
3.34
3.32
3.30
3.05
3.00
2.99
2.76
2.74
2.71
2.69
2.55
2.28
0.79
0.83
0.91
0.92
1.06
1.06
1.13
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

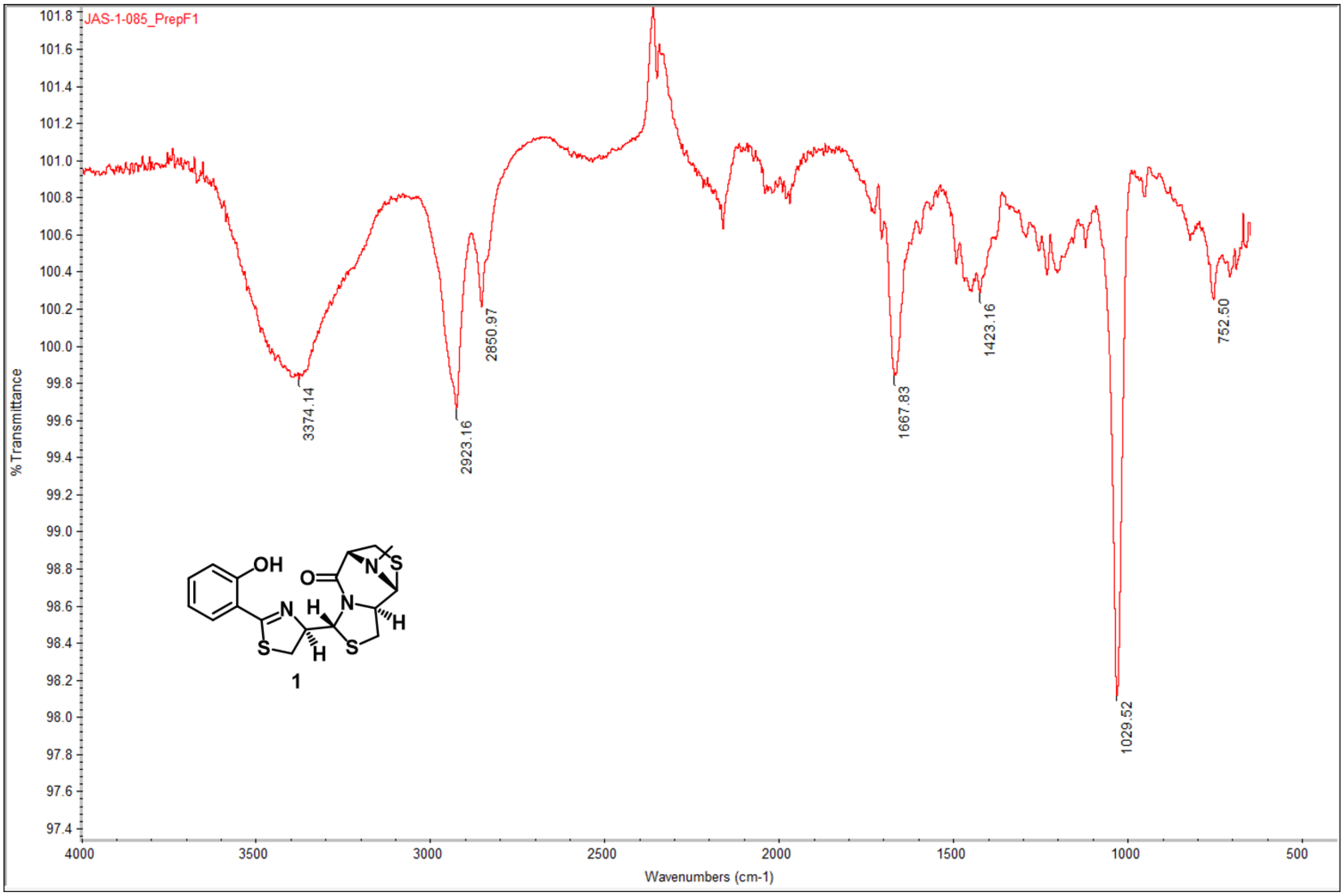

176.30
75.97
72.65
57.16
44.50
33.88
23.72
HO
O
S
N
Me
•2TFA
H2N
SH
10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


*Wed Aug 08 08:33:35 2018 (GMT-04:00)
% Transmittance
Wavenumbers (cm-1)
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
4000
3500
3000
2500
2000
1500
1000
500
3369.72
2958.31
2913.98
2819.00
1667.99
1199.47
1136.18
HO
O
N
S
Me
•2TFA
H2N
SH
10

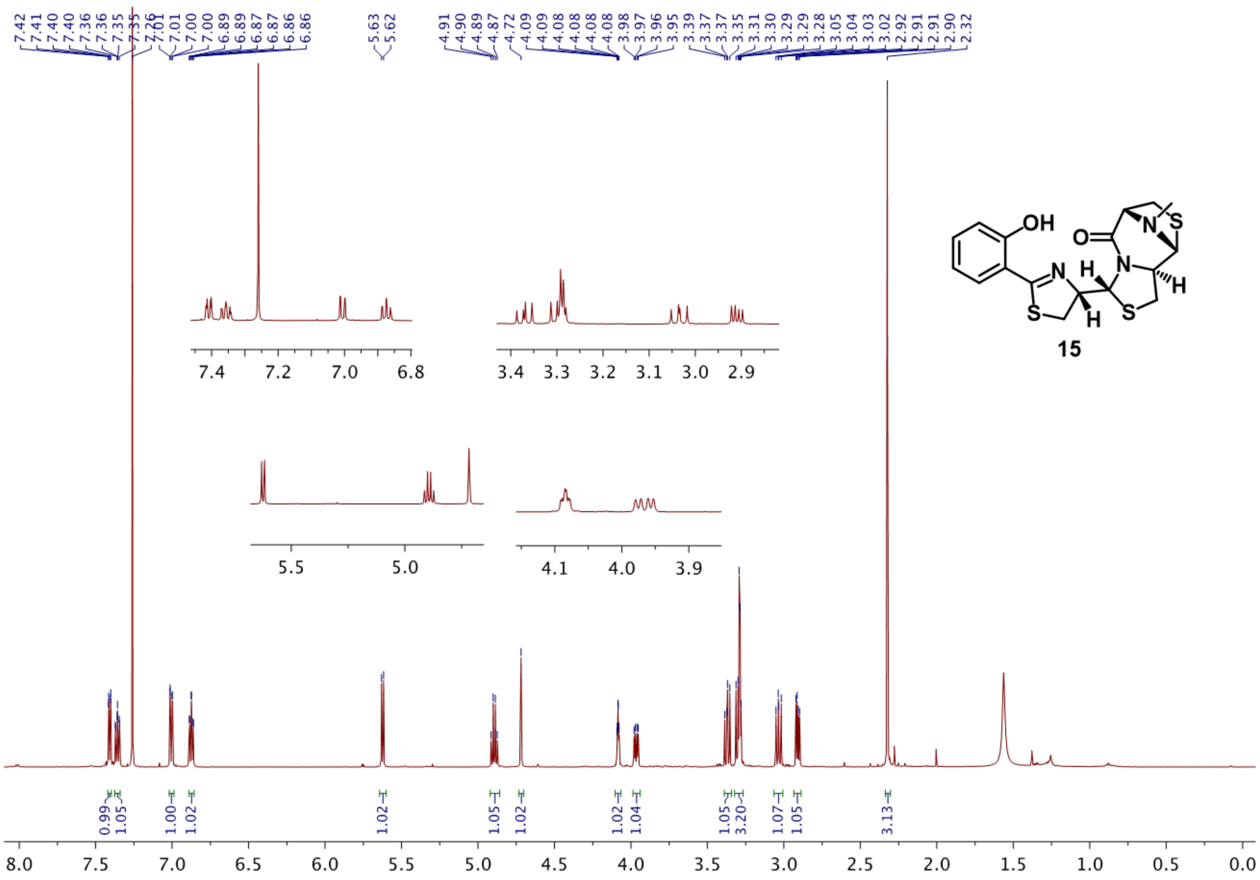

7.39
7.39
7.38
7.37
7.35
7.35
7.34
7.26
6.99
6.99
6.98
6.97
6.88
6.88
6.87
6.87
6.86
6.85
5.76
5.75
4.88
4.87
4.87
4.87
4.86
4.86
4.86
4.85
4.61
4.03
4.02
3.84
3.83
3.82
3.81
3.46
3.44
3.44
3.43
3.42
3.42
3.41
3.41
3.33
3.31
3.23
3.22
3.22
3.20
3.02
3.01
3.00
2.99
2.98
2.97
2.96
2.95
2.28
7.4
7.3
7.2
7.1
7.0
6.9
6.8
3.5
3.4
3.3
3.2
3.1
3.0
2.9
4.9
4.7
4.5
4.1
4.0
3.9
3.8
OH
O
N
S
N
H
N
S
H
S
H
1
0.97
1.07
1.00
1.05
1.02
1.08
1.04
1.08
1.08
2.01
1.29
1.09
2.20
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

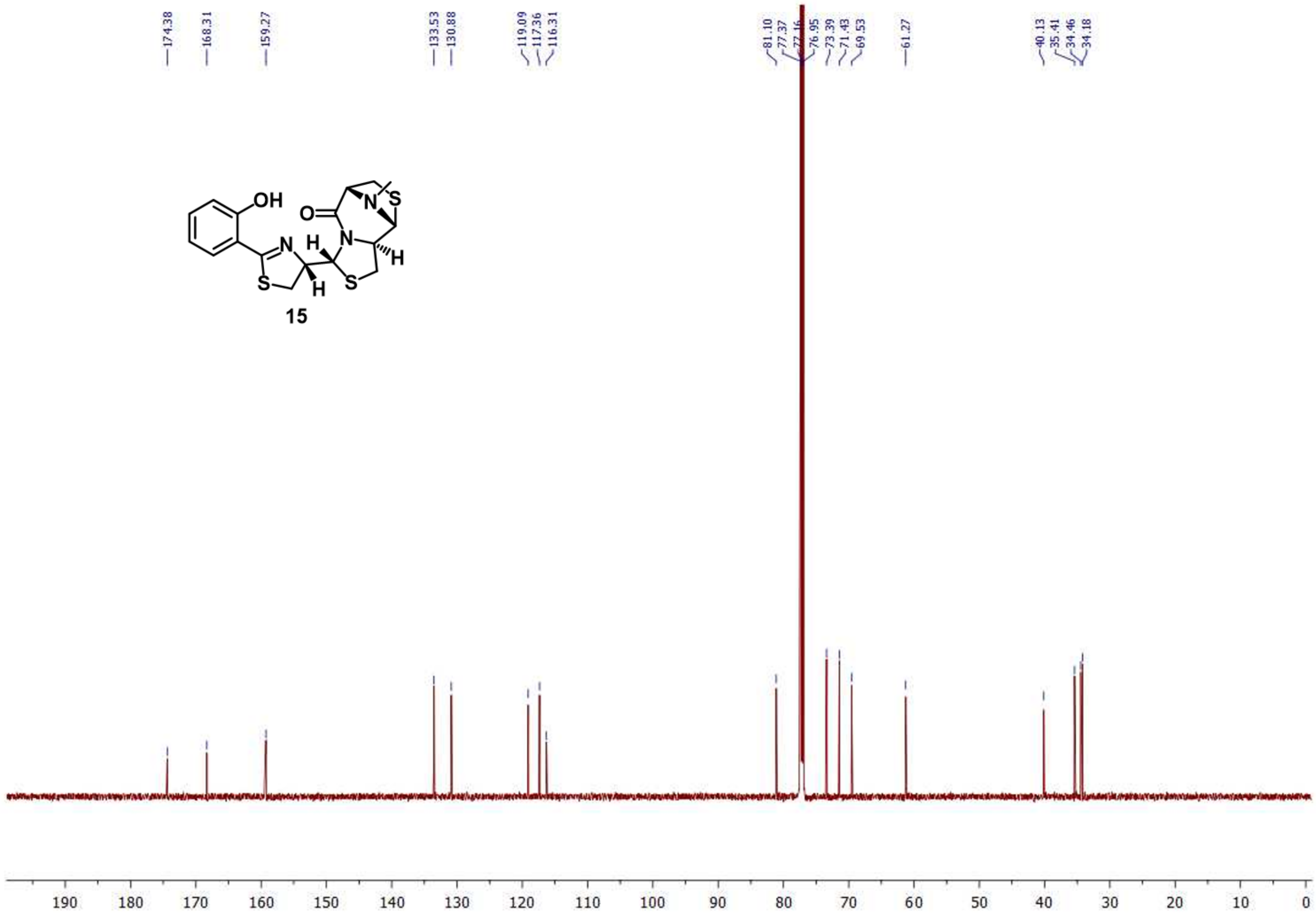


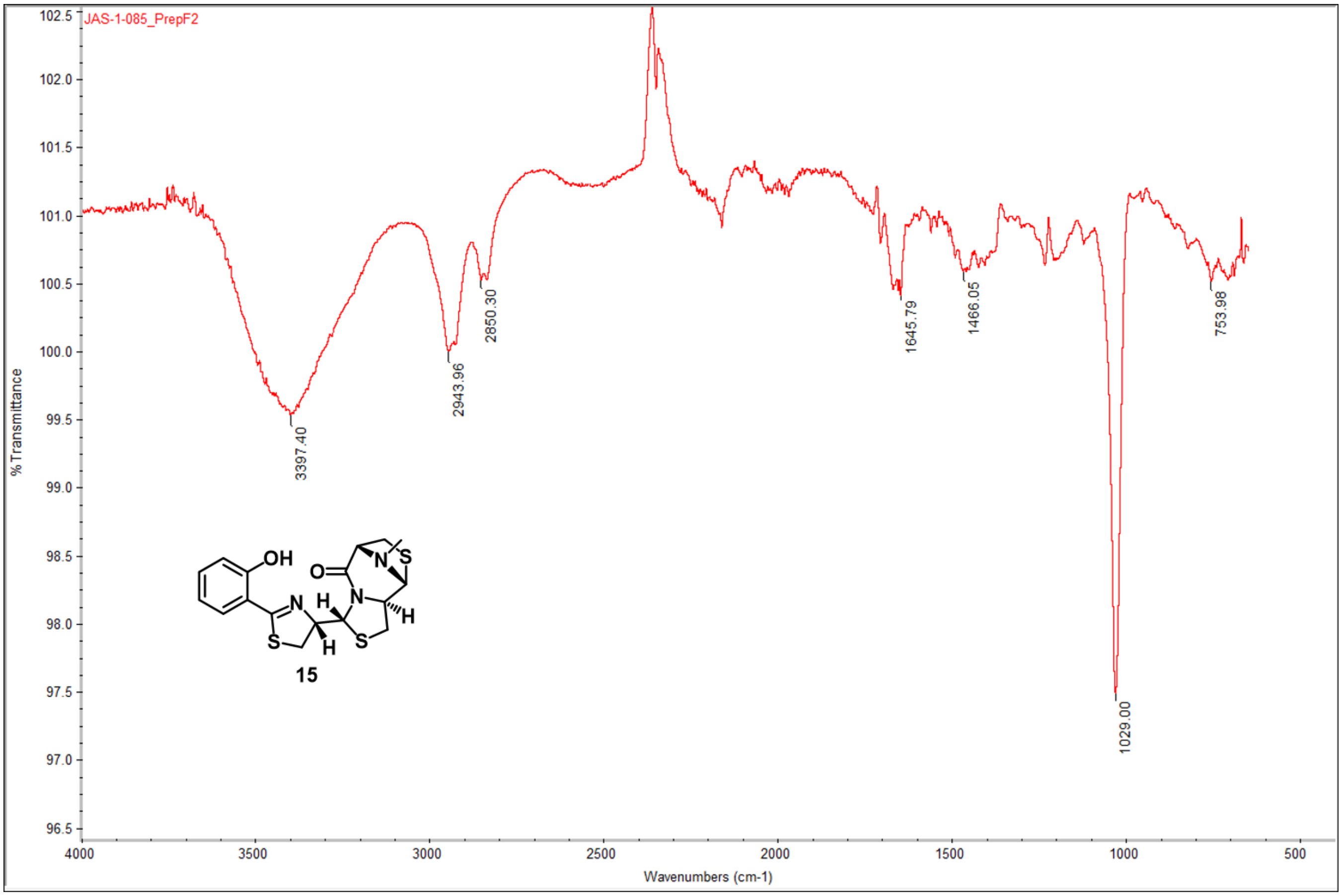
173.93
167.89
159.35
133.43
130.88
118.99
117.37
116.35
80.79
77.37
77.16
76.95
73.21
71.29
69.53
60.71
40.22
35.16
34.66
33.84
OH
O
N
S
H
1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



JAS-1-085_PrepF1
% Transmittance
Wavenumbers (cm-1)
3374.14
2923.16
2850.97
1667.83
1423.16
1029.52
752.50
101.8
101.6
101.4
101.2
101.0
100.8
100.6
100.4
100.2
100.0
99.8
99.6
99.4
99.2
99.0
98.8
98.6
98.4
98.2
98.0
97.8
97.6
97.4
4000
3500
3000
2500
2000
1500
1000
500
OH
O
N
S
H
1


7.42
7.41
7.40
7.40
7.36
7.36
7.35
7.35
7.26
7.01
7.01
7.00
7.00
6.89
6.89
6.87
6.87
6.86
6.86
5.63
5.62
4.91
4.90
4.89
4.87
4.72
4.09
4.09
4.08
4.08
4.08
4.08
3.98
3.97
3.96
3.95
3.39
3.37
3.37
3.35
3.31
3.30
3.29
3.29
3.28
3.05
3.04
3.03
3.02
2.92
2.91
2.91
2.90
2.32
OH
O
N
S
N
H
N
H
S
S
H
15
7.4
7.2
7.0
6.8
3.4
3.3
3.2
3.1
3.0
2.9
5.5
5.0
4.1
4.0
3.9
0.99
1.05
1.00
1.02
1.02
1.05
1.02
1.02
1.04
1.05
3.20
1.07
1.05
3.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


174.38
168.31
159.27
133.53
130.88
119.09
117.36
116.31
81.10
77.37
77.16
76.95
73.39
71.43
69.53
61.27
40.13
35.41
34.46
34.18
OH
O
N
S
N
H
N
H
S
S
H
15
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


JAS-1-085_PrepF2
% Transmittance
102.5
102.0
101.5
101.0
100.5
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
3397.40
2943.96
2850.30
1645.79
1466.05
1029.00
753.98
OH
O
N
H
N
S
S
H
H
S
15
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)