Electronic Supplementary

Complete Amide Cis-Trans Switching Synchronized with Disulfide Bond Formation and Cleavage in a Proline-Mimicking System

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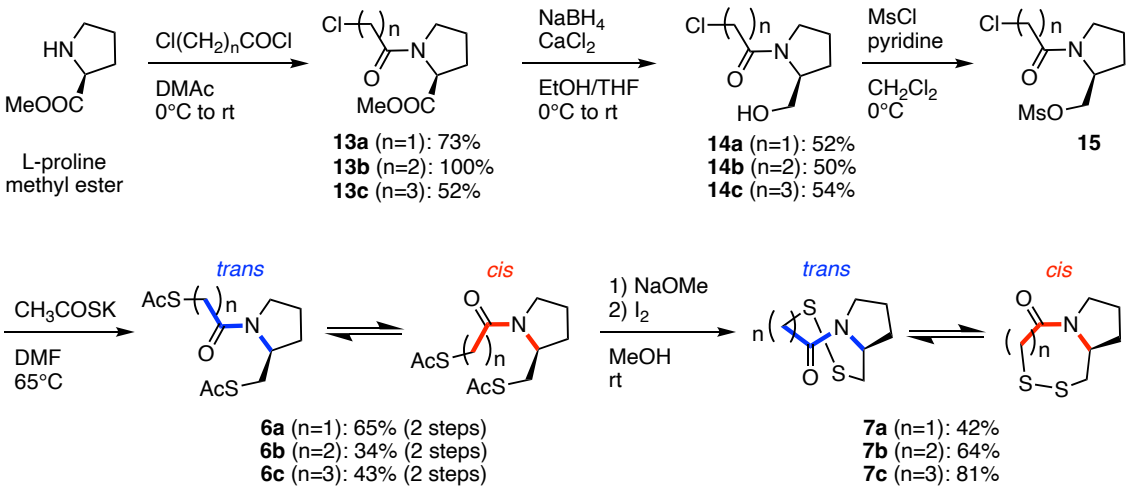


Figure S1. Synthesis of compounds fused with a monocyclic ring.

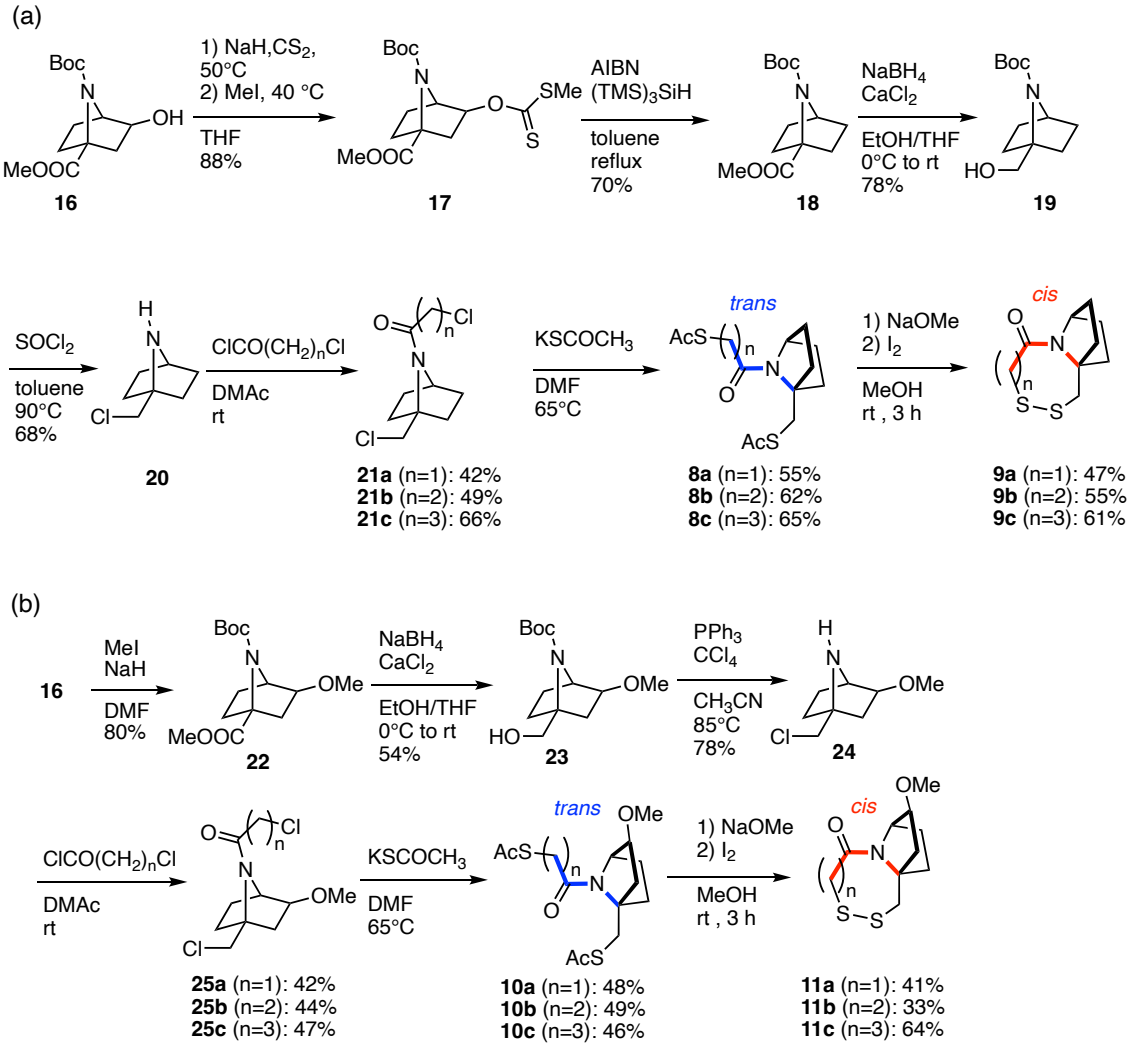


Figure S2. Synthesis of compounds fused with a bicyclic ring.

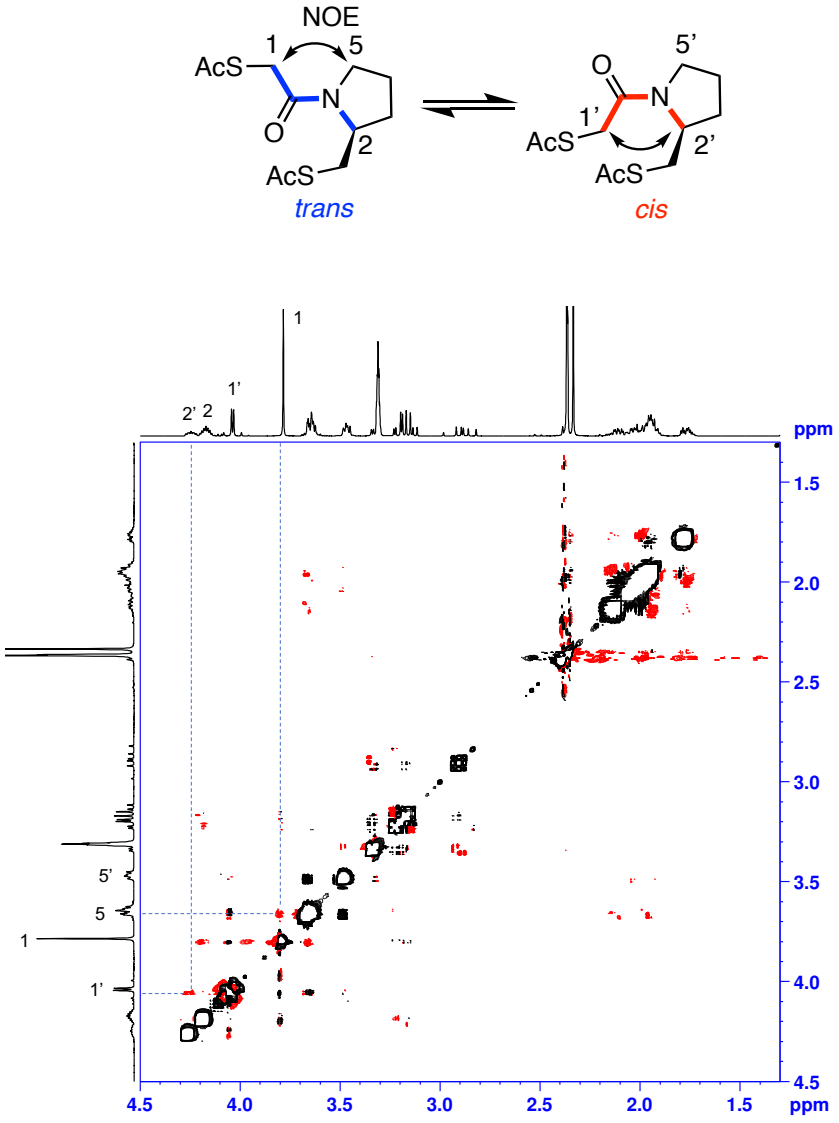
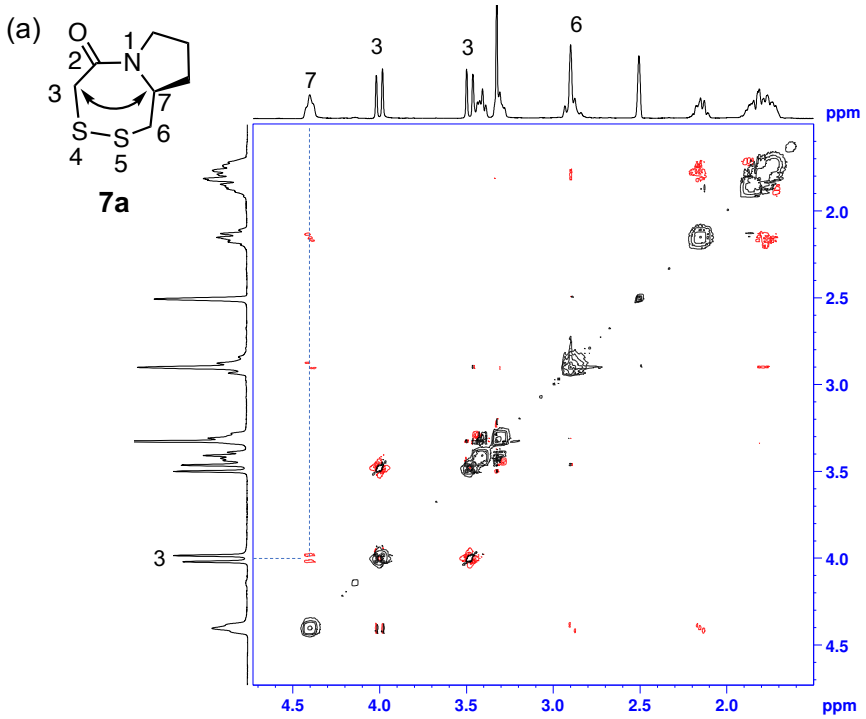


Figure S3. NOESY spectrum of **6a** in MeOD (mixing time = 800 msec).



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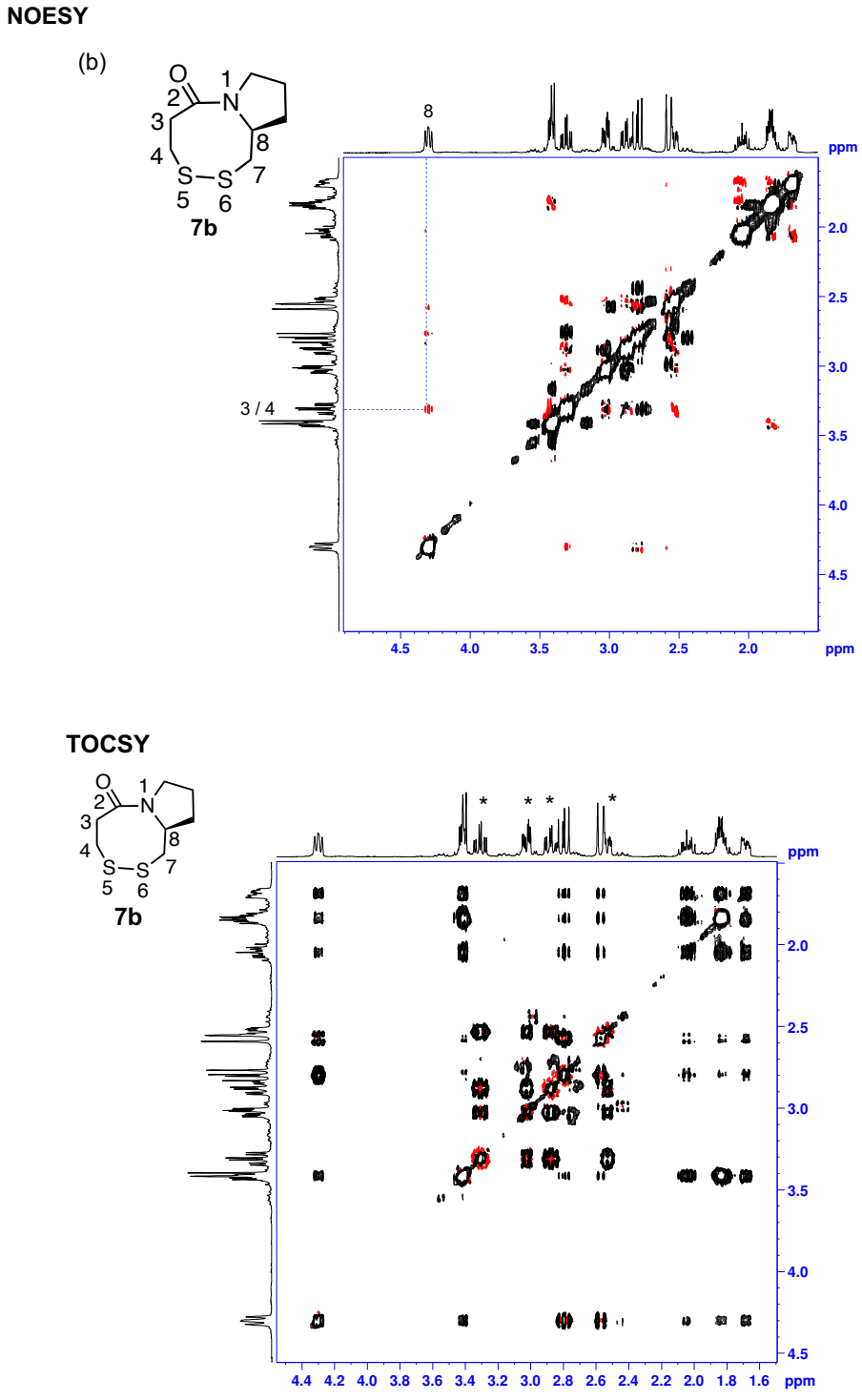

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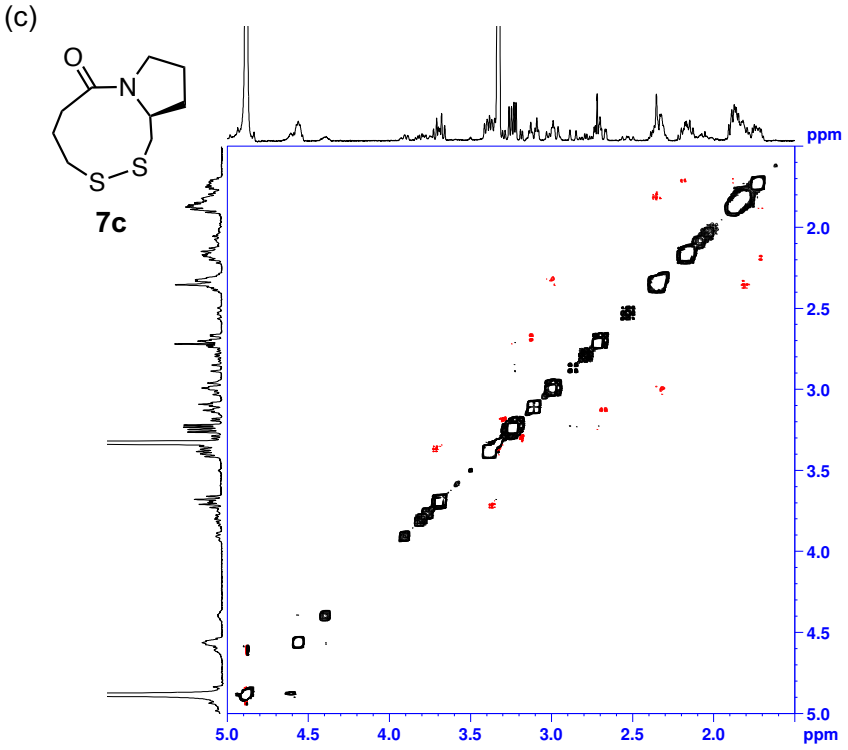


Figure S4. (continued) (c) NOESY spectrum of **7c** in MeOD (mixing time = 800 msec).

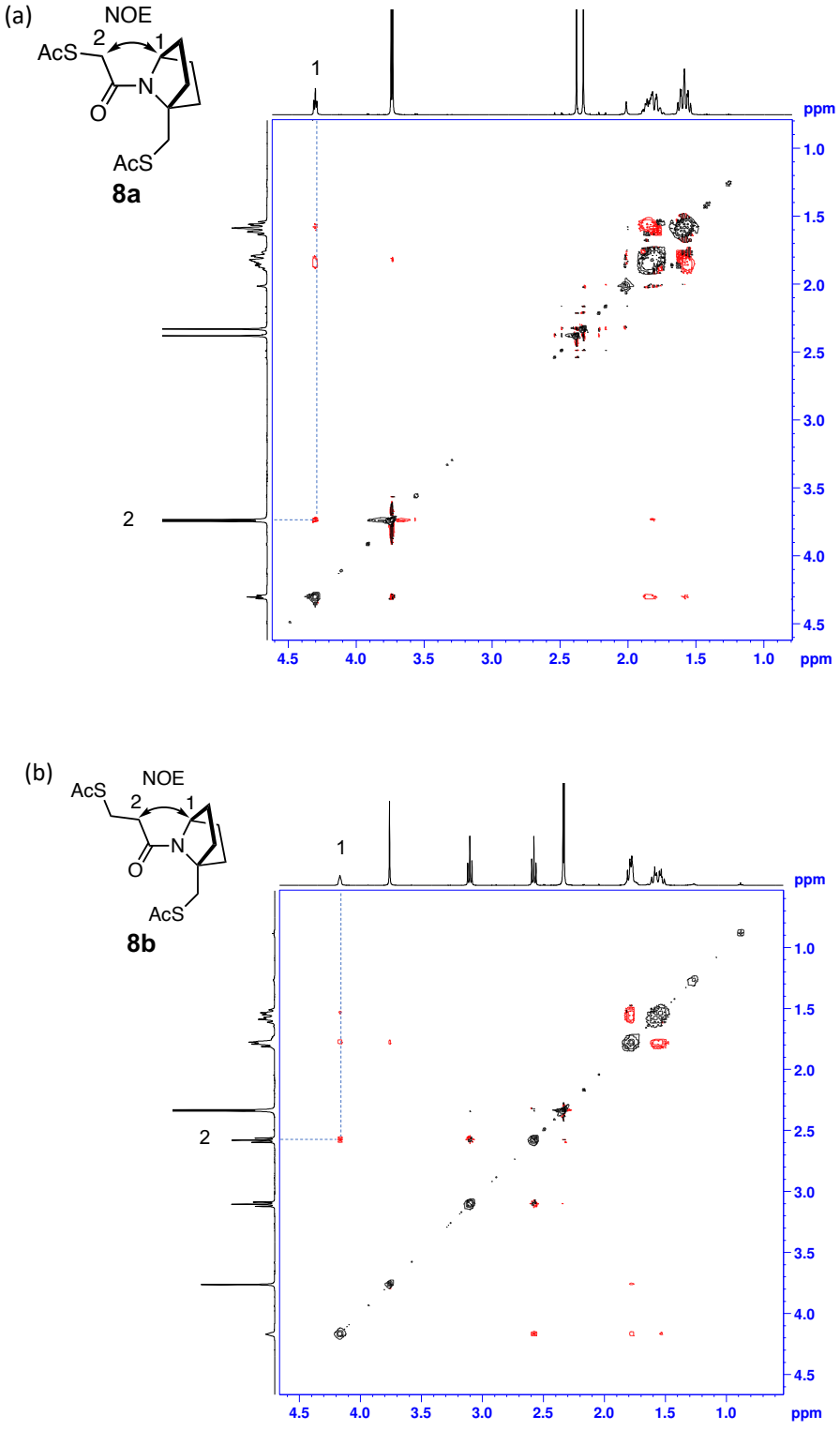


Figure S5. (a) NOESY spectrum of **8a** in $CDCl_3$ (mixing time = 800 msec). (b) NOESY spectrum of **8b** in $CDCl_3$ (mixing time = 800 msec).

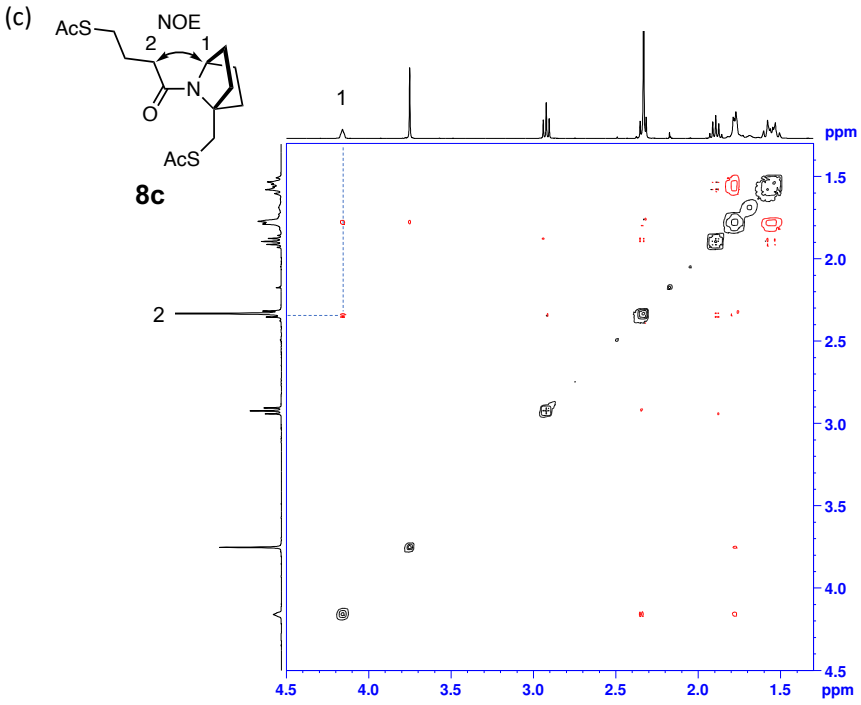


Figure S5. (continued) (c) NOESY spectrum of **8c** in $CDCl_3$ (mixing time = 800 msec).

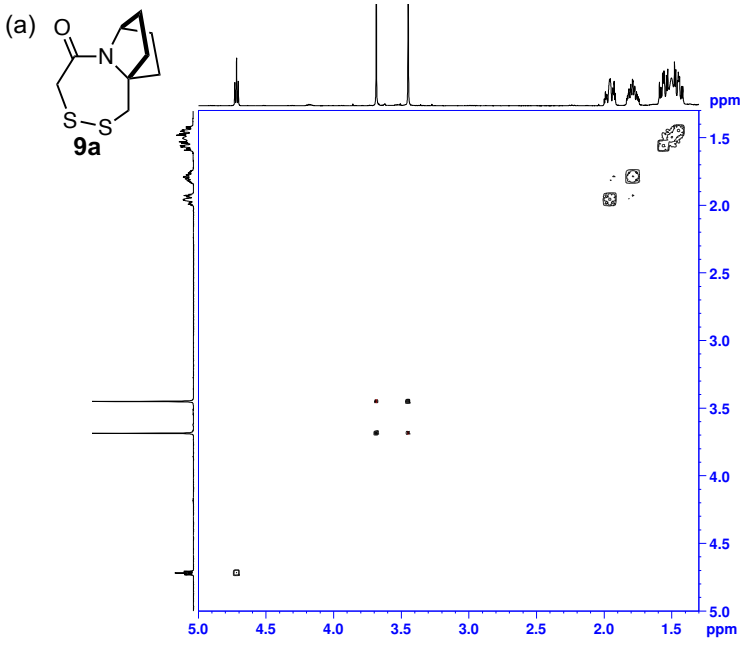
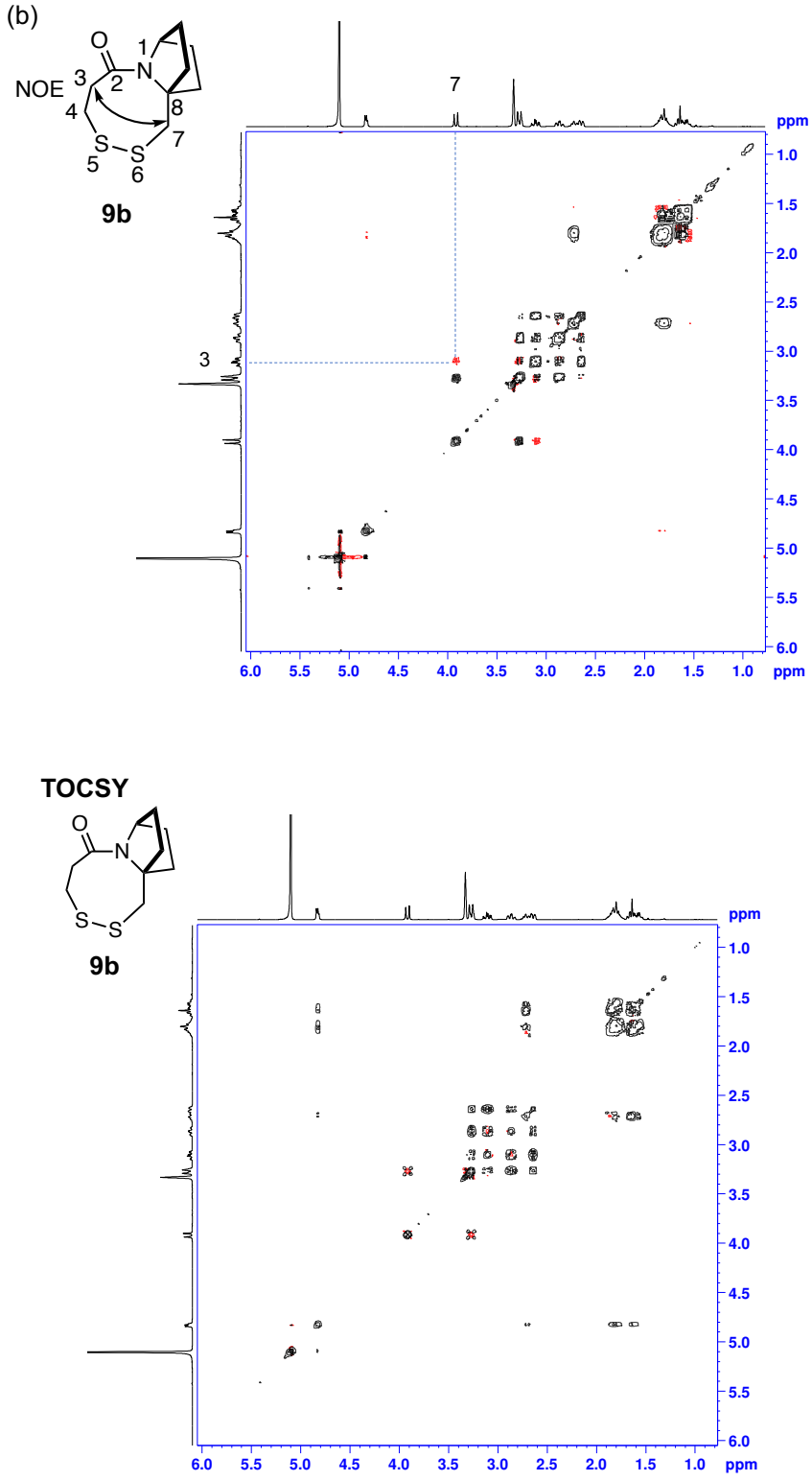


Figure S6. (a) NOESY spectrum of **9a** in CD_2Cl_2 (mixing time = 800 msec).



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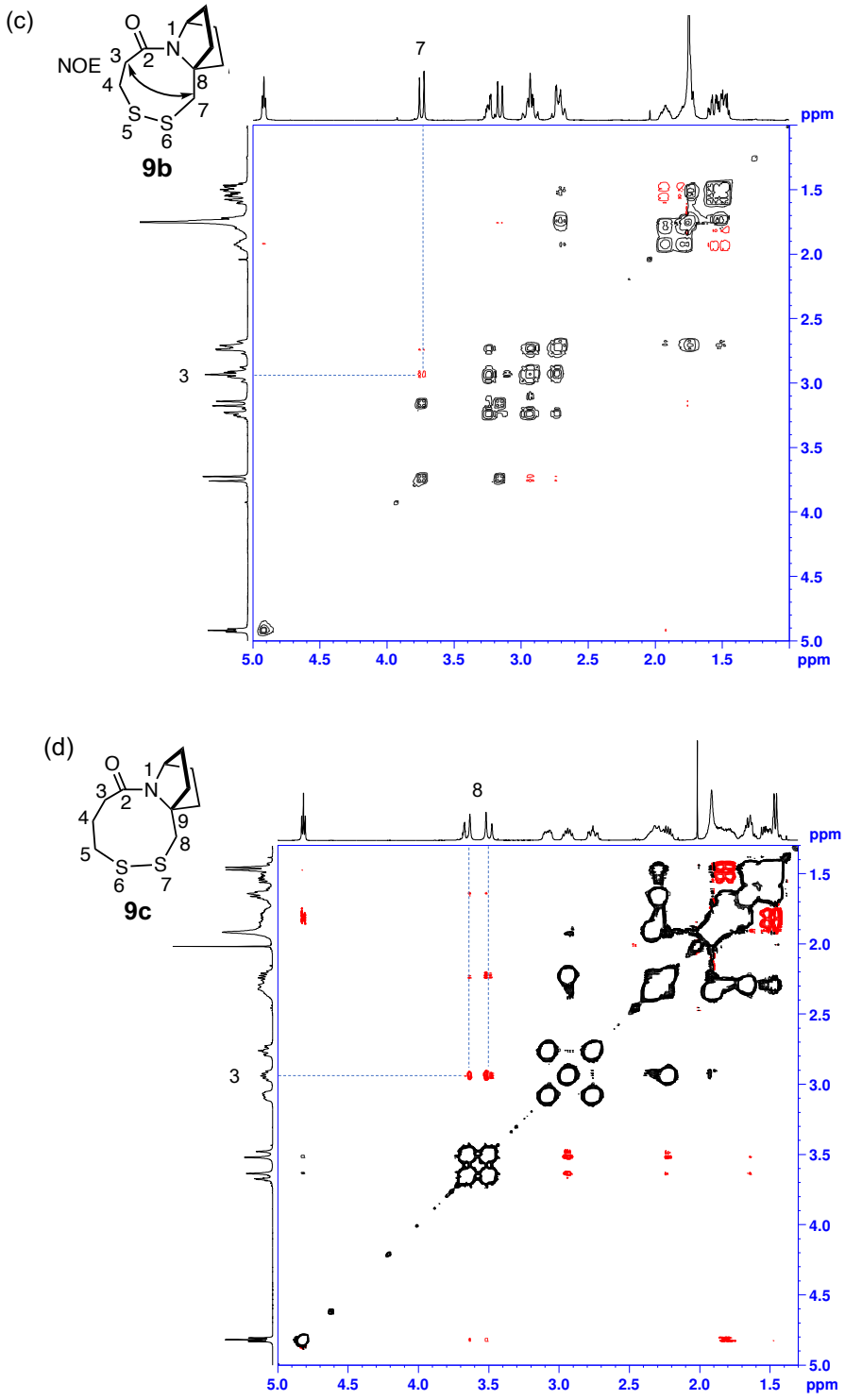

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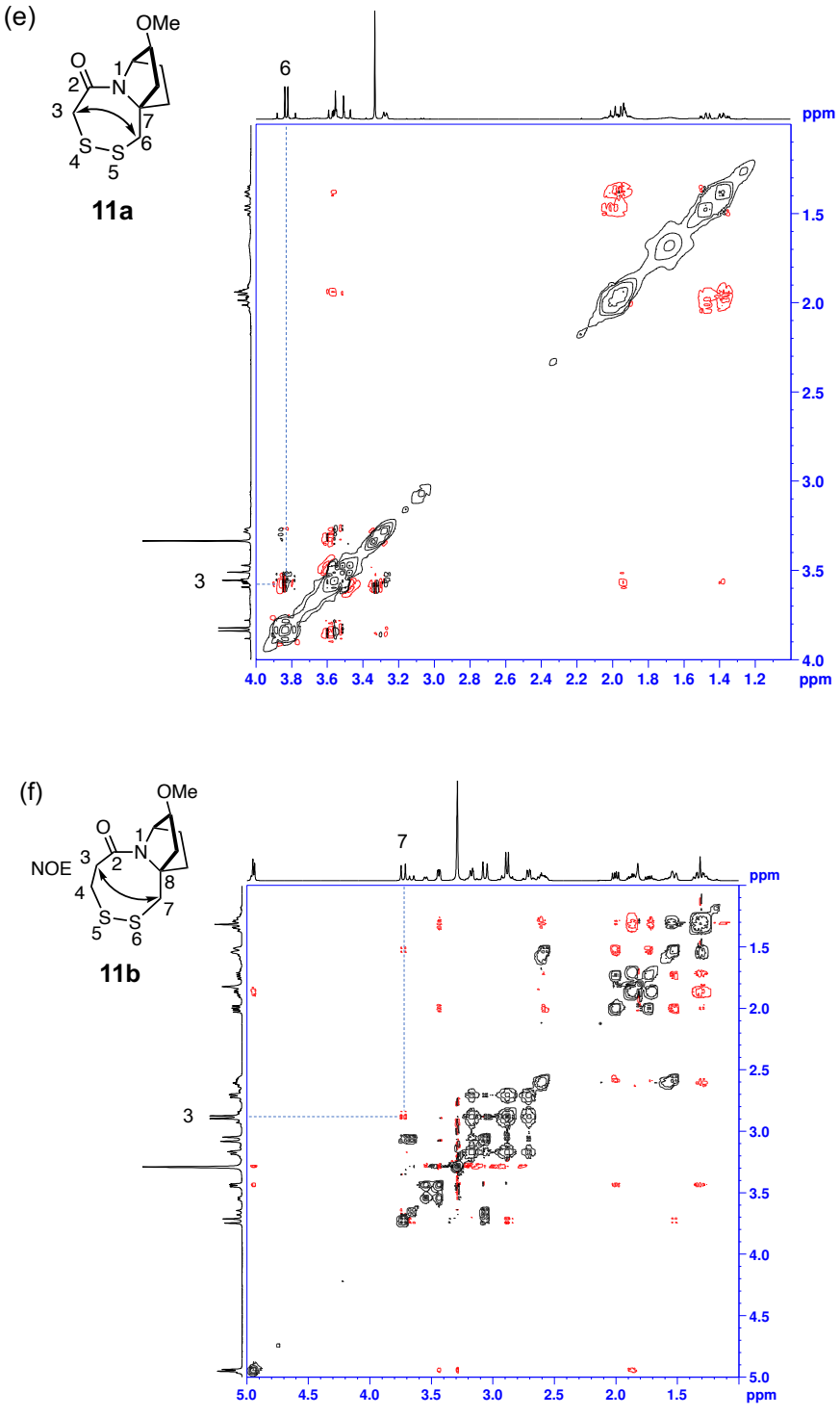

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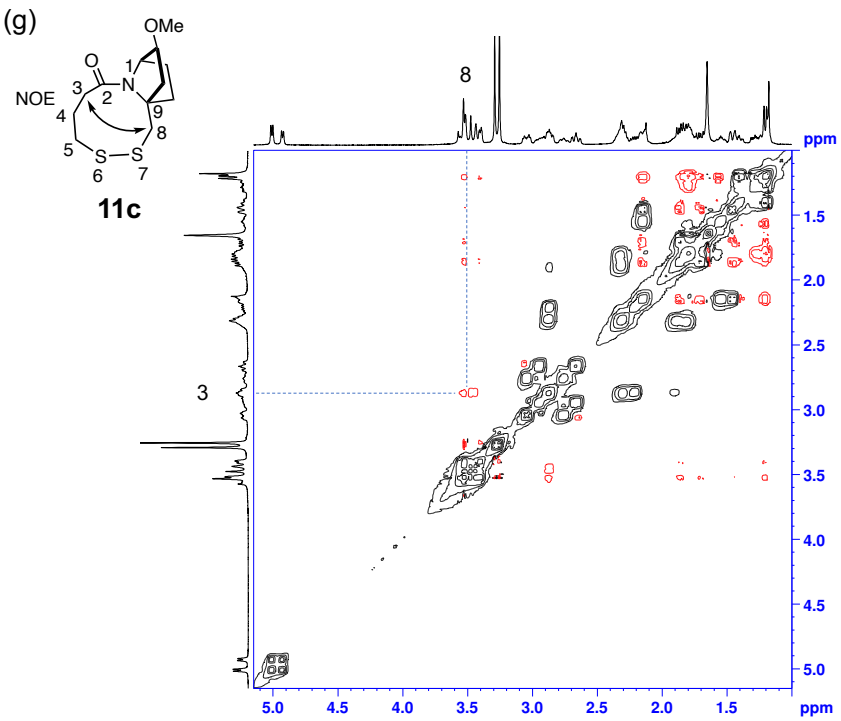


Figure S6. (continued) (g) NOESY spectrum of **11c** in $CDCl_3$ at 276.5 K (mixing time = 800 msec).

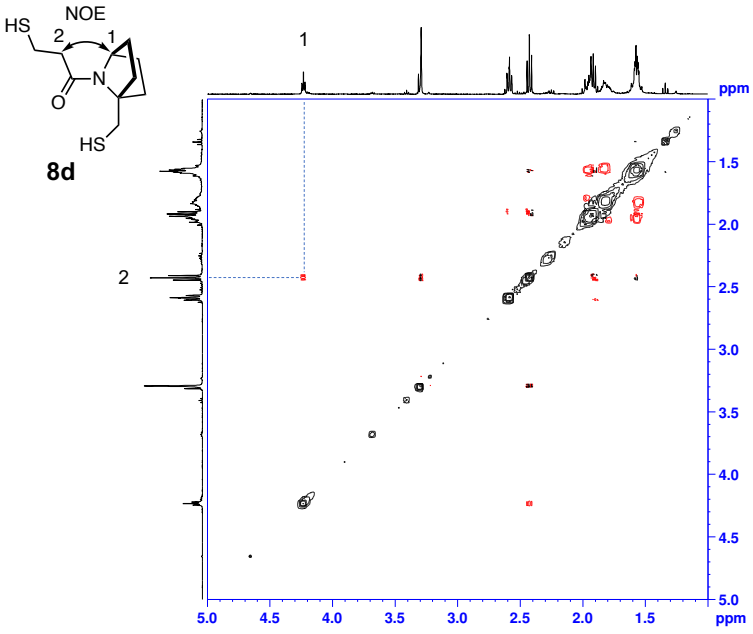


Figure S7. NOESY spectrum of **8d** in $CDCl_3$ (mixing time = 800 msec).

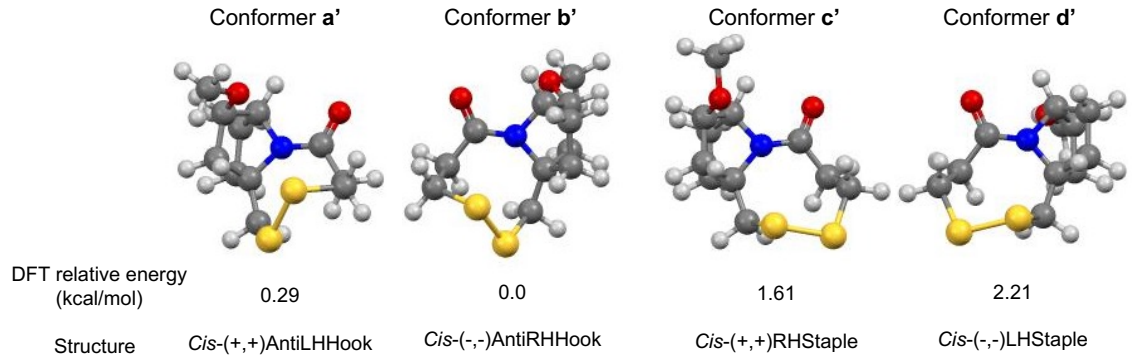
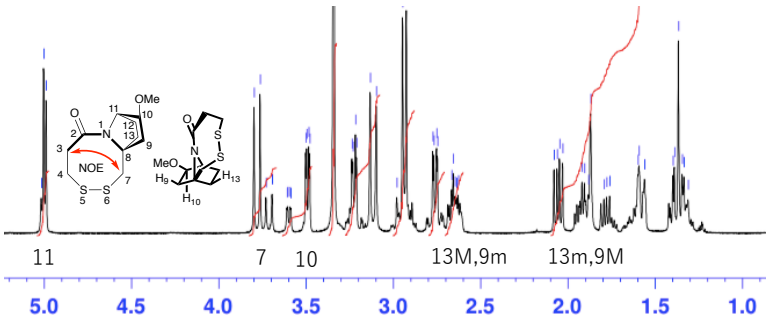


Figure S8. DFT-optimized structures of **11b** at the level of APFD/6-311+G(2d,p) (SCRF=IEFPCM, solvent = $CHCl_3$).

(a)

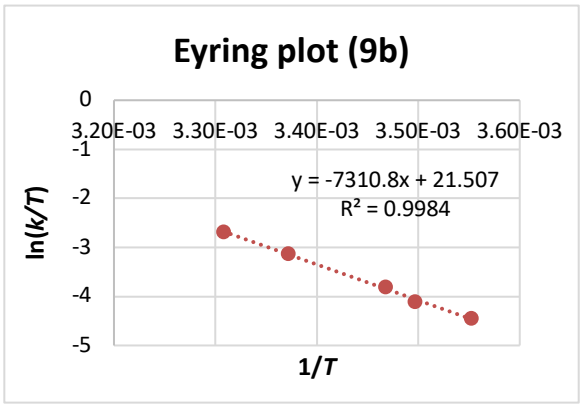


(b)

	Experiment (^{1}H-NMR)		Calculation (GIAO method)	
	major	minor	Conformer **b'**	Conformer **a'**
H11	4.95	4.96	4.95	5.01
H10	3.46	3.55	3.63	3.75
H9	1.52	2.64-2.57	1.64	2.97
H13	2.64-2.57	1.60-1.57	2.88	1.67
H7	3.73	3.66	3.96	3.86

Figure S9. (a) ^{1}H-NMR spectrum of **11b** in $CDCl_3$ at 273 K. "M" shows the signal of the major conformer and "m" shows the signal of the minor conformer. (b) Prediction of chemical shifts of **11b** by GIAO simulation at the reference of TMS at the level of B3LYP/6-311+G (2d,p).

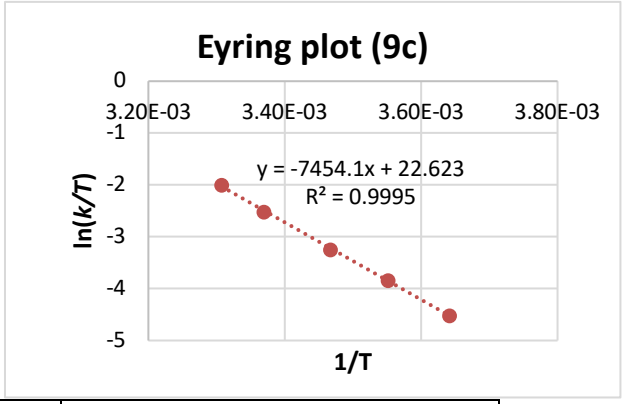
Temp (K)	*k*
281.5	3.29
286.0	4.73
288.4	6.40
296.6	13.0
302.3	20.7



	conformer **a** ⇄ conformer **b**
$\Delta G^{\ddagger}$ (300 K)	15.9 ± 0.7 kcal·mol^{-1}
$\Delta H^{\ddagger}$	14.5 ± 0.3 kcal·mol^{-1}
$\Delta S^{\ddagger}$	-4.5 ± 1.2 cal·mol^{-1}·K^{-1}

Figure S10. The rate (*k*) of disulfide ring isomerization, Eyring plot, and activation parameters for **9b** ($CDCl_3$).

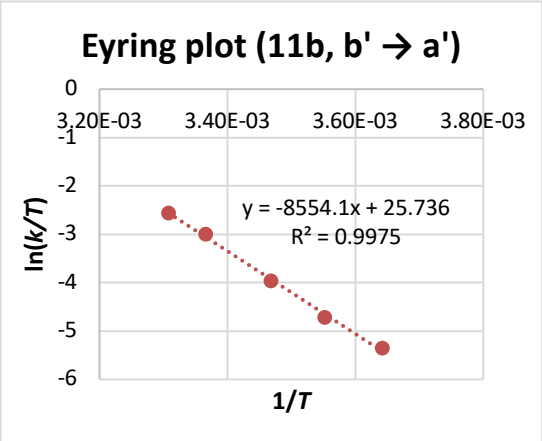
Temp (K)	*k*
274.6	2.98
281.5	6.07
288.4	11.2
296.8	23.8
302.3	40.7

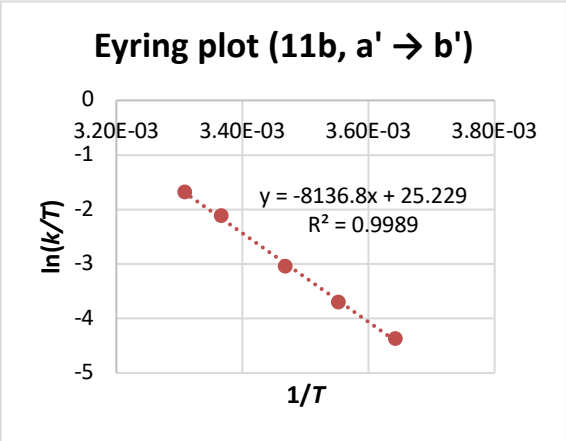


	conformer **a** ⇄ conformer **b**
$\Delta G^{\ddagger}$ (300 K)	15.5 ± 0.4 kcal·mol^{-1}
$\Delta H^{\ddagger}$	14.8 ± 0.2 kcal·mol^{-1}
$\Delta S^{\ddagger}$	-2.3 ± 0.7 cal·mol^{-1}·K^{-1}

Figure S11. The rate (*k*) of disulfide ring isomerization, Eyring plot, and activation parameters for **9c** ($CDCl_3$).

Temp (K)	$k_{b' \rightarrow a'}$	$k_{a' \rightarrow b'}$
274.6	1.29	3.47
281.5	2.52	7.01
288.4	5.47	13.9
297.1	14.8	35.8
302.3	23.3	56.1

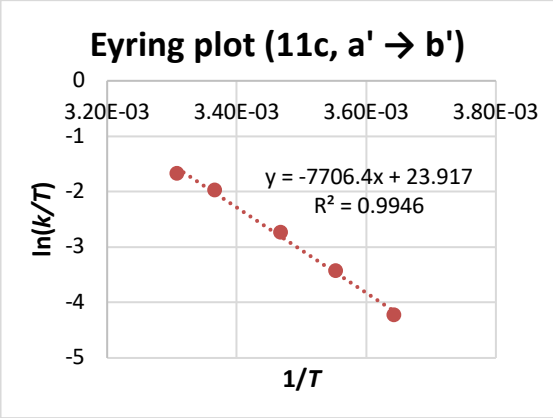


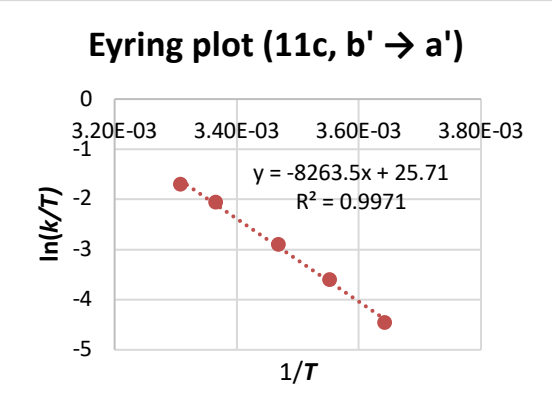


	conformer **b'** → conformer **a'**	conformer **a'** → conformer **b'**
$\Delta G^{\ddagger}$ (300 K)	15.8 ± 1.0 kcal·mol^{-1}	15.3 ± 0.6 kcal·mol^{-1}
$\Delta H^{\ddagger}$	17.0 ± 0.5 kcal·mol^{-1}	16.2 ± 0.3 kcal·mol^{-1}
$\Delta S^{\ddagger}$	3.9 ± 1.7 cal·mol^{-1}·K^{-1}	2.9 ± 1.1 cal·mol^{-1}·K^{-1}

Figure S12. The rate (k) of disulfide ring isomerization, Eyring plot, and activation parameters for **11b** ($CDCl_3$).

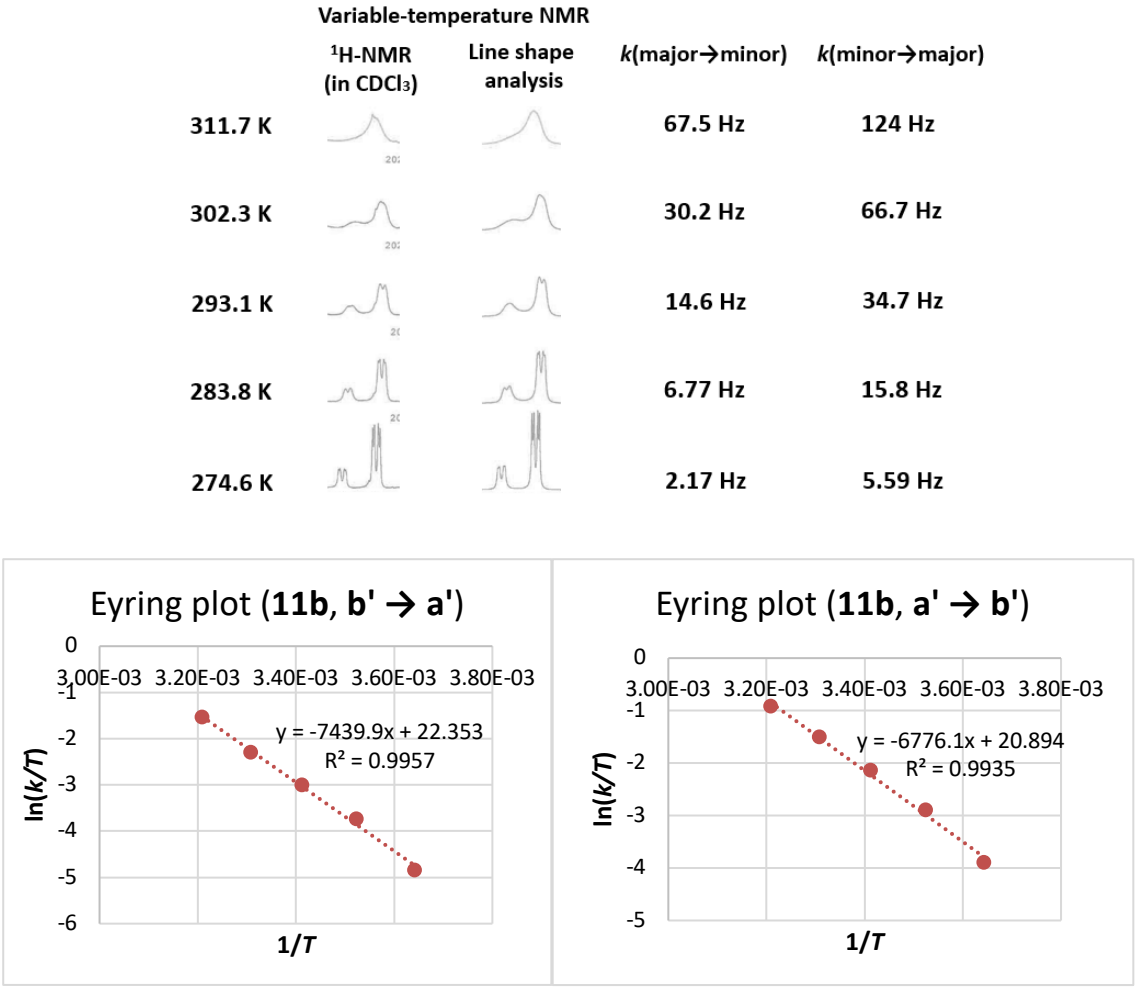
Temp (K)	$k_{b' \rightarrow a'}$	$k_{a' \rightarrow b'}$
274.6	4.0	3.2
281.5	9.2	7.7
288.4	18.9	15.9
297.1	41.4	38.0
302.3	57.2	55.6





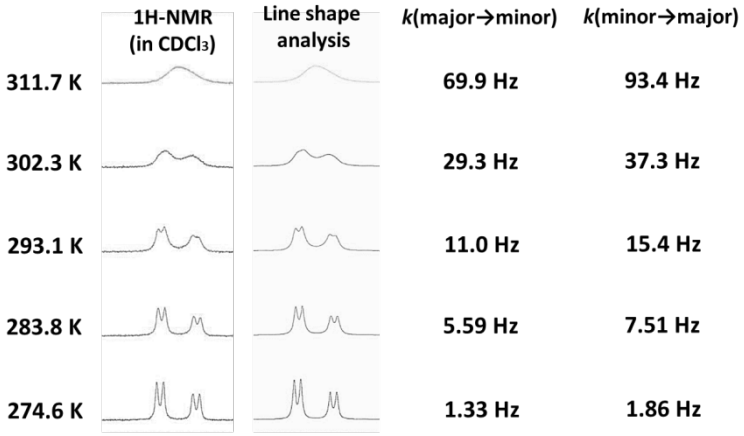
	conformer **b'** → conformer **a'**	conformer **a'** → conformer **b'**
$\Delta G^{\ddagger}$ (300 K)	15.5 ± 1.3 kcal·mol^{-1}	15.5 ± 1.0 kcal·mol^{-1}
$\Delta H^{\ddagger}$	14.8 ± 0.7 kcal·mol^{-1}	14.4 ± 0.5 kcal·mol^{-1}
$\Delta S^{\ddagger}$	-2.3 ± 2.3 cal·mol^{-1}·K^{-1}	-3.5 ± 1.8 cal·mol^{-1}·K^{-1}

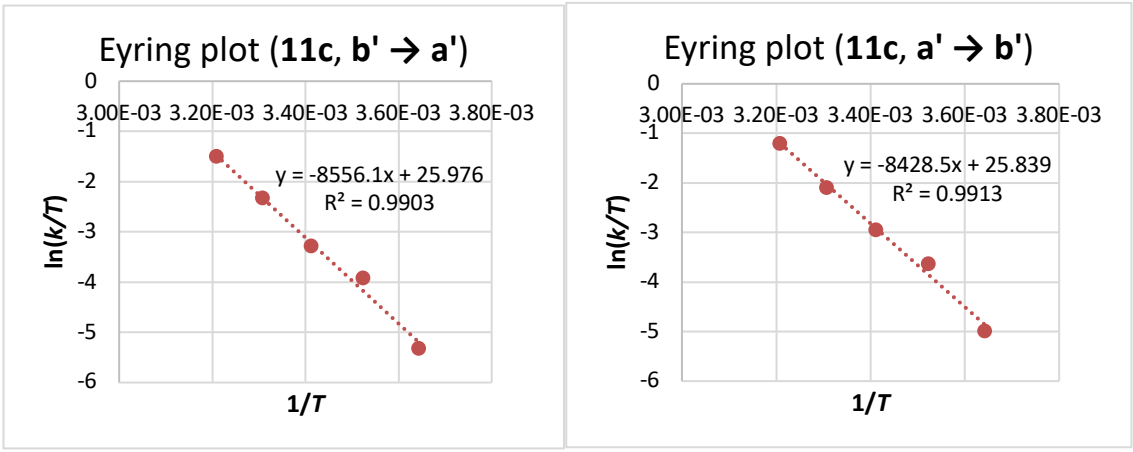
Figure S13. The rate (k) of disulfide ring isomerization, Eyring plot, and activation parameters for **11c** ($CDCl_3$).



	conformer **b'** → conformer **a'**	conformer **a'** → conformer **b'**
$\Delta G^{\ddagger}$ (300 K)	15.6 ± 1.1 kcal·mol^{-1}	15.2 ± 1.3 kcal·mol^{-1}
$\Delta H^{\ddagger}$	14.8 ± 0.6 kcal·mol^{-1}	13.5 ± 0.6 kcal·mol^{-1}
$\Delta S^{\ddagger}$	-2.8 ± 1.9 cal·mol^{-1}·K^{-1}	-5.7 ± 2.1 cal·mol^{-1}·K^{-1}

Figure S14. Line-shape analysis. The rate (k) of disulfide ring isomerization, Eyring plot, and activation parameters (**11b**).





	conformer **b'** → conformer **a'**	conformer **a'** → conformer **b'**
$\Delta G^{\ddagger}$ (300 K)	15.7 ± 2.0 kcal·mol^{-1}	15.5 ± 1.8 kcal·mol^{-1}
$\Delta H^{\ddagger}$	17.0 ± 1.0 kcal·mol^{-1}	16.6 ± 0.9 kcal·mol^{-1}
$\Delta S^{\ddagger}$	4.4 ± 3.3 cal·mol^{-1}·K^{-1}	4.1 ± 3.1 cal·mol^{-1}·K^{-1}

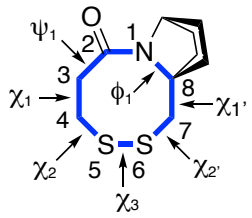
Figure S15. Line-shape analysis. The rate (k) of disulfide ring isomerization, Eyring plot, and activation parameters (**11c**).

Table S1. Experimental and calculated coupling constants of **9b** based on DFT-optimized structures.

^3J coupling constants	Experimental CD_3OD, 273.2 K	Calculated[a] conformer **a** / **b**	conformer **c** / **d**
J_1	13.2	12.4	8.2
J_2	5.2	3.7	2.1

[a] The coupling constants were calculated based on the DFT-optimized structures at the level of APFD/6-311+G(2d,p) (SCRF = IEFPCM, solvent = $CHCl_3$), according to the following Karplus equation[S1]: $J = 9.4\cos^2\theta - 1.4\cos\theta + 1.6$ (θ is the torsion angle between hydrogens)

Table S2. Dihedral angles of stable conformers **a** and **b** of **9b**.



	Conformer	
Dihedral angle	**a**	**b**
χ_3 (CV1)	-73	+73
$\chi_{1'}$ (CV2)	+72	-72
$\chi_{2'}$	-28	+28
χ_1	+59	-59
χ_2	+57	-57
ϕ_2	-6	+6
ψ_1	-96	+96
Conformation	*Cis*-(+,+)AntiLHHook	*Cis*-(-,-)AntiRHHook

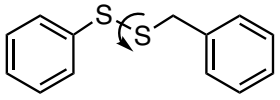
Table S3 Disulfide torsion angle calculated at the APFD/6-311+G(2d,p) level (IEFPCM, solvent = $CHCl_3$).

	Disulfide ring size	Torsion angle of disulfide
12	-	79.94°
9a	7	80.19°
11a	7	-79.81°
9b	8	72.74°
11b	8	72.58°
7b	8	93.84°
4	8	92.41°

9c	9	82.39° (Xray: 89.40°)
11c	9	90.55°

Table S4. Rotational barriers of the disulfide bond (**TS1**) calculated at the APFD/6-311+G(2d,p) level (IEFPCM, solvent = $CHCl_3$).

		$\Delta G^{\ddagger}_{300\,K}$ (kcal/mol) (**TS1**)	
	Disulfide ring size	major conformer → minor conformer	minor conformer → major conformer
7b	8	14.78	14.13
9b	8	16.14	13.79
9c	9	16.48	15.64
12	-	9.04	
4	8	15.95	15.07
CC_9b	- (8)	11.89	9.96



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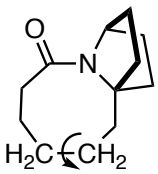


CC_9b

Cyclic Voltammetry Studies

Procedure for cyclic voltammetry measurement

Cyclic voltammetry measurements were carried out using ECstat-301. A 3 mM solution of the substrate in 2 mL 0.1 M $TBAPF_6/CH_3CN$ was placed in a beaker-type glass cell. Cyclic voltammogram was measured with a scan rate of 100 mV s^{-1} using a grassy carbon as a working electrode (WE), a Pt wire as a counter electrode (CE), and Ag/Ag^+ (in 3.33 M KCl aq.) as a reference electrode (RE).[S2][S3]

Instrument settings: Dimensions: WE to RE: 8.0 mm, WE to RE: 6.0 mm, CE to RE: 6.0 mm, Surface area of WE: 7.07 mm^2.

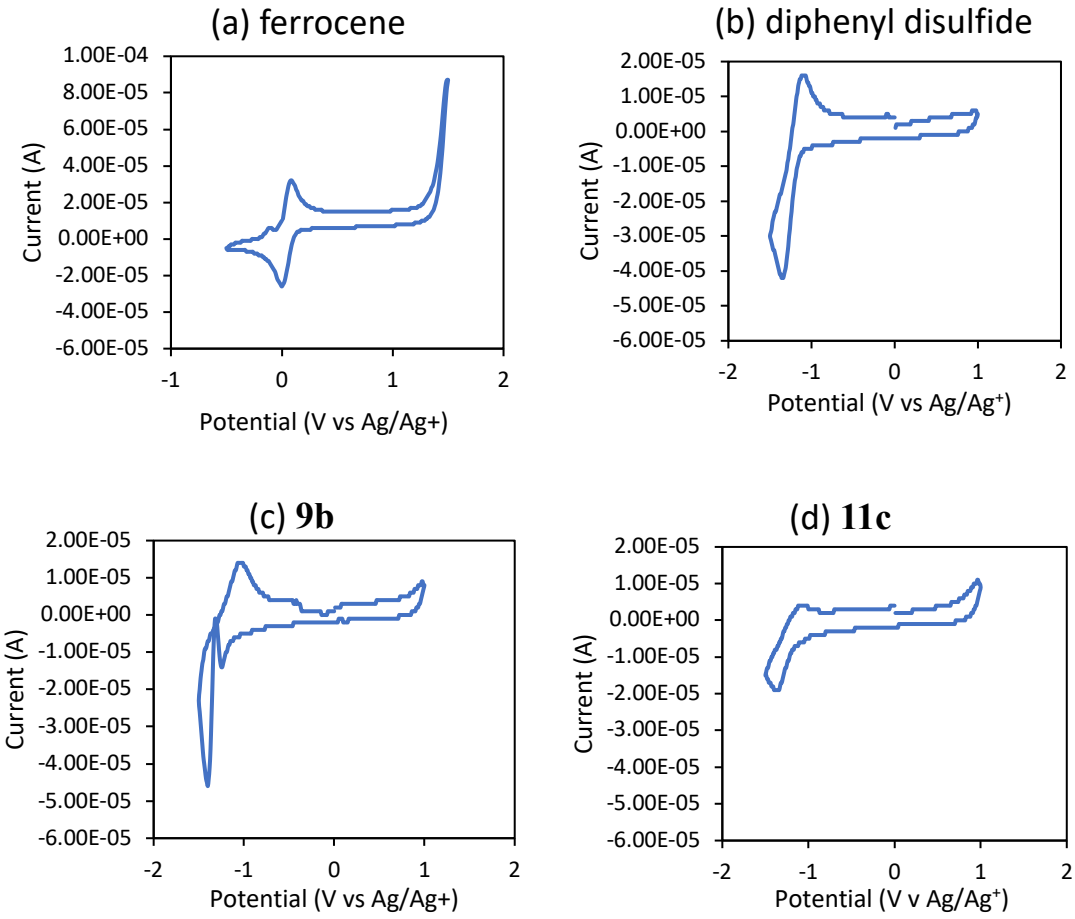


Figure S16. Cyclic voltammograms measured in 0.1 M $TBAPF_6/CH_3CN$ at a scan rate of 100 mV s^{-1}: (a) ferrocene (E^{pc} = +0.38 V (vs SCE)), (b) diphenyl disulfide (E^{pc} = -1.0V (vs SCE)), (c) **9b** (E^{pc} = -1.06V (vs SCE)), and (d) **11c** (E^{pc} = -1.02V (vs SCE)).

2. Experimental Section

General Methods

Unless stated otherwise, commercial grade reagents were used without further purification. Open column chromatography was carried out using Kanto chemical silica gel (silica gel 60 N (100-210 μm)). ^{1}H-NMR (400 MHz) spectra, ^{13}C-NMR (100 MHz) spectra and 2D (COSY, TOCSY, HSQC, and NOESY) were recorded on a Bruker Avance 400 NMR spectrometer running Topspin. The spectra were recorded at 22 °C, unless otherwise noted. ^{1}H-NMR and ^{13}C-NMR chemical shifts (δ) are given in parts per million (ppm) and coupling constants are given in hertz (Hz). s = singlet, brs = broad singlet, d = doublet, t = triplet, m = multiplet.Data for ^{1}H NMR spectra are reported in terms of chemical shift (ppm) relative to residual solvent signals ($CDCl_3$: 7.26 ppm, CD_3OD: 3.31 ppm, DMSO-d_6: 2.50 ppm). Data for ^{13}C{^{1}H} NMR spectra are reported in terms of chemical shift (ppm) relative to residual solvent peak ($CDCl_3$: 77.0 ppm, CD_3OD: 49.0 ppm). All ^{1}H-NMR signals are assigned by 2D-NMR.

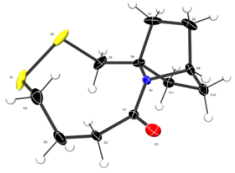
The EXSY spectra were recorded with 6 mixing times (T_m) of 20, 40, 60, 100, 200, and 300 ms at 274.6 K, 281.5 K, 288.4 K, 297.1 K, and 302.3 K. The 90° pulse widths were estimated by a standard method. The temperature was calibrated with methanol as a reference by using a standard method. Parameters were obtained from unbiased estimates of the standard deviations of least-squares parameters and are reported at the 95% confidence level. Line shape analysis was carried out with DNMR software (Bruker Biospin) and was performed by iterative matching of simulated spectra with the experimental spectra.

Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05. The combustion analysis was carried out in the microanalytical laboratory of the University of Tokyo. All melting points were measured with a Yanaco Micro Melting Point Apparatus without correction.

HPLC data were obtained with the following conditions: HPLC Column: Cosmosil 5C_{18}-AR-II, Waters, 10 mm ID x 250 mm, CH_3CN/H_2O=9:1 or 7:3, flow rate 2.0 ml/min, UV detection at 210 nm.

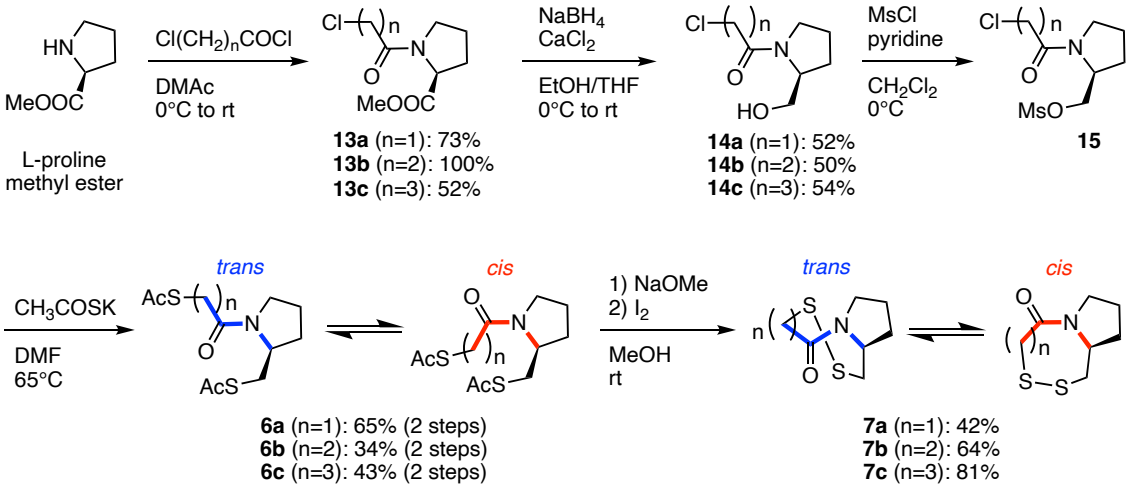
X-ray Crystallographic analysis

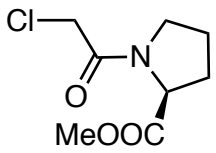
X-ray Crystallographic data of 9c (CCDS No. 2332996)



Empirical formula	C11 H17 N O S2	
Formula weight	243.37	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.8974(17) Å	α= 90°.
	b = 7.8350(8) Å	β= 100.6820(10)°.
	c = 9.4791(10) Å	γ = 90°.
Volume	1160.2(2) $Å^3$	
Z	4	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	0.432 mm^{-1}	
F(000)	520	
Crystal size	0.300 x 0.200 x 0.200 mm^3	
Theta range for data collection	1.303 to 26.120°.	
Index ranges	-19<=h<=18, -9<=k<=9, -11<=l<=11	
Reflections collected	10161	
Independent reflections	2150 [R(int) = 0.0333]	
Completeness to theta = 25.242°	98.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9281 and 0.8477	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2150 / 0 / 136	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1043	
R indices (all data)	R1 = 0.0505, wR2 = 0.1078	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.468 and -0.933 $e.Å^{-3}$	

Synthesis



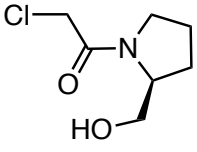


13a

To a solution of proline methyl ester hydrochloride (443.6 mg, 2.68 mmol) in dimethylacetamide (DMAc) (20 mL) was added chloroacetyl chloride (0.26 mL, 3.22 mmol) at 0°C for 20 min and the mixture was stirred at rt for 18 h. Water (40 mL) was added to the mixture, and the mixture was extracted with AcOEt (50 mL × 3). The organic layer was combined, dried over Na_2SO_4, and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt = 1: 2) to give **14a** (401.1 mg, 73%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers): δ 4.56-4.45 (1H, m), 4.08-3.87 (2H, m), 3.73-3.69 (3H, m), 3.67-3.56 (2H, m), 2.23-1.95 (4H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 172.2, 172.1, 165.4, 165.1, 59.4, 59.2, 52.9, 52.4, 47.10, 47.07, 41.9, 41.8, 31.3, 29.1, 24.9, 22.3.



14a

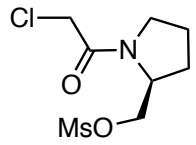
To a solution of **13a** (974.3 mg, 4.74 mmol) in ethanol (EtOH) (18 mL) and tetrahydrofuran (THF) (12 mL) were added calcium chloride ($CaCl_2$) (1.18 g, 10.62

mmol) and sodium borohydride ($NaBH_4$) (653.8 mg, 17.28 mmol) at 0°C. The reaction mixture was stirred at rt for 50 min. A 5% solution of $KHSO_4$ (25 mL) was added at 0°C and the mixture was filtered through Celite and the solid was washed with AcOEt (40 mL × 3) and with water (30 mL). The whole was extracted with AcOEt (50 mL × 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 1: 2 - 1: 5) to give **14a** (435.2 mg, 2.45 mmol, 52%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers): δ 4.25-4.18 (1H, m), 4.07 (2H, s), 3.74-3.51 (4H, m), 2.17-1.63 (4H, m).

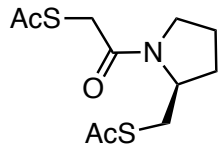
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 167.2, 65.9, 61.7, 59.4, 48.0, 46.1, 42.5, 28.2, 28.0, 24.4, 21.9.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_7H_{13}ClNO_2^+$ ([M+H]$^+$): 178.0629. Found: 178.0603.



15a

To a solution of **14a** (435.2 mg, 2.45 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Et_3N (640 μL) at 0°C. Methanesulfonyl chloride (330 μL, 4.22 mmol) was added slowly to the mixture and the reaction mixture was stirred at 0°C for 50 min. CH_2Cl_2 (50 mL) was added in the mixture and the whole was washed with water (30 mL × 2), saturated aqueous solution of NH_4Cl (30 mL × 2), saturated aqueous solution of $NaHCO_3$ (30 mL × 2) and brine (20 mL), dried over Na_2SO_4 and evaporated to give **15a** (398.8 mg, 1.53 mmol, 62%) as a deep brown oil, which was used for the next reaction without further purification.



6a

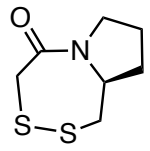
To a solution of **14a** (398.8 mg, 1.53 mmol) in anhydrous N, N-dimethylformamide (DMF) (16 mL) was added potassium thioacetate (664.8 mg, 5.82 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 1 h. Et_2O (30 mL) was added to the mixture and the whole was washed with water (30 mL) and brine (20 mL). The combined

aqueous layer was extracted with Et_2O five times. The combined organic layer was dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 1: 1) to give **6a** (279.2 mg, 1.01 mmol, 65%) as deep brown oil.

^{1}H-NMR (400 MHz, MeOD) (a mixture of rotamers): δ 4.24-4.16 (1H, m), 4.04-3.78 (2H, m), 3.67-3.45 (2H, m), 3.23-2.82 (2H, m), 2.37-2.33 (6H, m), 2.13-1.74 (4H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD) (a mixture of rotamers): δ 196.9, 196.5, 196.4, 195.9, 169.1, 168.7, 59.2, 58.8, 33.5, 33.2, 33.0, 31.2, 30.9, 30.44, 30.41, 30.0, 29.9, 29.5, 24.8, 22.2.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{11}H_{17}NNaO_3S_2^+$ ([M+Na]$^+$): 298.0542. Found: 298.0547.



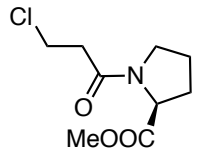
7a

A solution of **6a** (99.2 mg, 0.36 mmol) in anhydrous MeOH (20 mL) was bubbled with N_2 for 20 min, and 28% sodium methoxide (NaOMe) in MeOH (150 μL, 0.77 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 20 min. A solution of I_2 (213.6 mg, 1.68 mmol) in Et_2O (3 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 30 min. Aqueous 10% $Na_2S_2O_3$ (10 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (30 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3: 1) to give **7a** (43.7 mg, 0.23 mmol, 64%) as a brown oil.

^{1}H-NMR (400 MHz, DMSO-d_6) (a mixture of rotamers): δ 4.40 (1H, m), 4.00 (1H, d, J=14.4 Hz), 3.48 (1H, d, J=14.4 Hz) 3.46-3.31 (2H, m), 2.93-2.88 (2H, m), 2.18-1.76 (4H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): (a mixture of rotamers) δ 169.4, 61.2, 46.7, 43.6, 38.5, 33.4, 21.8.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_8H_{15}NNaOS_2^+$ ([M+Na]$^+$): 228.0487. Found: 228.0496.



13b

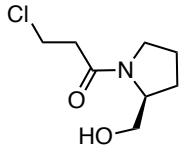
To a solution of proline methyl ester hydrochloride (3.7217 g, 22.6 mmol) in DMAc (40 mL) was added 3-chloropropionyl chloride (2.5 mL) at 0°C for 20 min and at rt for 18 h. Water (40 mL) was added to the mixture, which was extracted with AcOEt (50 mL × 3). The organic layer was combined, dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt=1:2) to give **13b** (4.01 g, 18.56 mmol, 82%) as a colorless oil.

^{1}H (400 MHz, $CDCl_3$) (a mixture of rotamers): δ 4.51-4.42 (1H, m), 3.76-3.71 (3H, m), 3.68-3.49 (4H, m), 2.98-2.75 (2H, m), 2.21-2.00 (4H, m)

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 172.7, 168.6, 60.5, 58.7, 52.4, 47.1, 46.5, 39.5, 37.6, 37.5, 31.5, 29.3, 24.8, 22.7, 14.3.

HRMS (ESI$^+$, *m/z*) Calcd. for $C_9H_{14}ClNO_3Na^+$ ([M+Na]$^+$) 242.0554. Found:242.0558.

Anal.Calcd. for $C_9H_{14}ClNO_3$: C, 49.21; H, 6.42; N, 6.38. Found: C, 48.84; H, 6.25; N, 6.31.



14b

To a solution of **13b** (5.1432 g, 23.48 mmol) in EtOH (90 mL) and THF (60 mL) were added $CaCl_2$ (5.4152 g, 48.79 mmol) and $NaBH_4$ (3.8158 g, 100.87 mmol) at 0°C. The reaction mixture was stirred at rt for 50 min. A 5% solution of $KHSO_4$ (25 mL) was added at 0°C and the mixture was filtered through Celite and the solid was washed with AcOEt (50 mL × 5) and with water (100 mL). The whole was extracted with AcOEt (200 mL× 5). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: hexane: AcOEt = 1:3- AcOEt) to give **14b** (2.2228 g, 11.64 mmol, 50%) as a colorless oil.

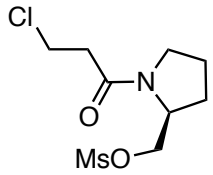
^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers): δ 4.69 (1H, br), 4.25-4.18 (1H, m), 3.70-3.45 (6H, m), 2.92-2.78 (2H, m), 2.09-1.823 (4H, m)

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 171.2, 67.1, 67.1, 61.4, 60.5,

48.3, 48.2, 38.2, 28.3, 26.9, 24.1, 21.1, 14.3.

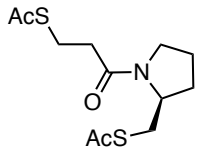
HRMS (ESI$^+$, *m/z*) Calcd. for $C_8H_{15}ClNO_2^+$ ([M+H]$^+$) 192.0786. Found:192.0774.

Anal. Calcd. for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; N, 7.31. Found: C, 50.27; H, 7.86; N, 7.57.



15b

To a solution of **14b** (2.223 g, 11.63 mmol) in anhydrous CH_2Cl_2 (70 mL) was added pyridine (1.8 mL, 22.75 mmol) at 0°C. A solution of methanesulfonyl chloride (1.8 mL, 23.2 mmol) was added dropwise to the mixture and the reaction mixture was stirred at 0°C for 50 min. CH_2Cl_2 (20 mL) was added in the mixture and the whole was washed with water (60mL× 2), saturated aqueous solution of saturated aqueous solution of NH_4Cl (80 mL × 3) and brine (50 mL), dried over Na_2SO_4 and evaporated to give **15b** (3.7539 g, >100%) as a yellow oil, which was used for the next reaction without further purification.



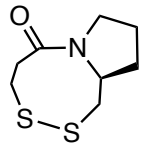
6b

To a solution of **15b** (3.7539 g) in anhydrous DMF (100 mL) was added potassium thioacetate (5.6027 g, 49.06 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 2 h. Et_2O (40 mL) was added to mixture and the whole was washed with water (30 mL) and brine (20 mL). The combined aqueous layer was extracted with Et_2O five times. The combined organic layer was dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **6b** (1.1162 g, 3.86 mmol, 34% from **14b)** as deep brown oil.

^{1}H NMR (400 MHz, MeOD) (a mixture of rotamers): δ 4.19-4.09 (1H, m), 3.52-3.44 (2H, m), 3.20-3.09 (4H, m), 2.90-2.82 (1H, m), 2.61 (1H, m), 2.35-2.31 (6H, m), 2.01-1.73 (4H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 197.4, 197.3, 196.59, 196.57, 172.3, 172.0, 59.5, 58.8, 58.3, 45.2, 35.8, 35.2, 32.9, 31.4, 30.9, 30.5, 30.5, 30.1, 29.5, 28.8, 28.8, 25.7, 25.2, 24.7, 22.3.

HRMS(ESI$^+$, *m/z*) Calcd. for $C_{12}H_{20}NO_3S_2^+$ ([M+H]$^+$) 290.0829. Found: 290.0889.
Anal. Calcd. for $C_{12}H_{19}NO_3S_2$: C, 49.80; H, 6.62; N, 4.84. Found: C, 49.83; H, 6.79; N, 5.09.



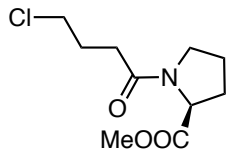
7b

A solution of **6b** (278.6 mg, 0.96 mmol) in anhydrous MeOH (160 mL) was bubbled with N_2 for 1 h, and 28% sodium methoxide (NaOMe) in MeOH (450 μL, 2.32 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (766.1 mg, 6.04 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 30 min. Aqueous 10% $Na_2S_2O_3$ (20 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3:1) to give **7b** (81.9 mg, 0.403 mmol, 42%) as a pale-yellow oil.

^{1}H NMR (400 MHz, MeOD) (a mixture of rotamers): δ 4.52-4.48 (m, 1H), 3.59-3.54 (m, 1H), 3.49-3.08 (m, 3H), 2.97-2.88 (m, 2H), 2.86-2.60 (m, 2H), 2.20-2.13 (m, 1H), 1.99-1.95 (m, 2H), 1.85-1.79 (m, 1H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 173.7, 171.89, 171.86, 171.6, 63.6, 59.1, 58.1, 57.9, 56.8, 47.4, 46.4, 45.0, 42.2, 37.4, 37.0, 36.5, 35.3, 34.5, 34.4, 33.6, 30.5, 30.2, 30.2, 25.5, 25.0, 22.9, 22.6, 22.5.

HRMS (ESI$^+$, *m/z*) Calcd. for $C_8H_{14}NOS_2^+$ ([M+H]$^+$) 204.0511. Found: 204.0527.
Anal. Calcd. for $C_8H_{13}NOS_2$: C, 47.26; H, 6.45; N, 6.89. Found: C, 47.26; H, 6.47; N, 6.83.



13c

To a solution of proline methyl ester hydrochloride (2.1886 g, 13.2 mmol) in DMAc (40

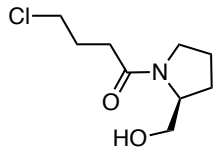
mL) was added 4-chloropropionyl chloride at 0°C for 20 min and at rt for 18 h. Water (40 mL) was added to the mixture, which was extracted with AcOEt (50 mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (50 mL × 2) and saturated aqueous solution of NH_4Cl (50 mL × 2), dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt = 1:2) to give **13c** (1.5894 g, 52%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers): δ 4.48-4.45 (m, 1H), 3.75-3.71 (d, 3H, J=17.2 Hz), 3.68-5.59 (m, 2H), 3.55-3.51 (m, 2H), 2.52-2.47 (m, 2H), 2.21-1.99 (m, 6H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 172.78, 172.77, 172.6, 170.64, 170.57, 59.3, 58.6, 52.3, 52.14, 52.13, 47.0, 46.3, 44.8, 44.7, 31.4, 30.9, 30.7, 29.2, 27.6, 27.4, 24.7, 22.5.

HRMS (ESI$^+$, *m/z*) Calcd. for $C_{10}H_{16}ClNO_3Na^+$ ($[M+Na]^+$) 256.0711. Found:256.0710.

Anal. Calcd. for $C_{10}H_{16}ClNO_3$: C, 51.40; H, 6.90; N, 5.99. Found: C, 51.22; H, 6.77; N, 6.08.



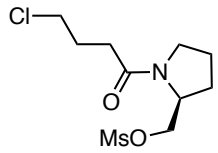
14c

To a solution of **13c** (1.4894 g, 6.36 mmol) in THF/EtOH (20 mL/ 30 mL) were added $NaBH_4$ (523.6 mg, 13.84 mmol) at 0°C. The reaction mixture was stirred for 50 min, rt for 1 h. Then a 5% solution of $KHSO_4$ (25 mL) was added at 0°C and the mixture was extracted with AcOEt (50 mL × 5). The combined organic layer was washed with saturated aqueous solution of $NaHCO_3$ (50 mL), saturated aqueous solution of NH_4Cl (20 mL) and brine (30 mL), dried over Na_2SO_4 and evaporated to give crude mixture, which was purified by column-chromatography (eluent: hexane: AcOEt = 1:2 – AcOEt) to give **14c** (704.5 mg, 54%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers): d 5.04-4.56 (1H, m), 4.37-4.01 (1H, m), 3.67-3.47 (6H, m), 2.52-2.49 (2H, m), 2.17-1.88 (6H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ173.1, 67.20, 67.18, 61.2, 48.1, 44.8, 31.6, 28.3, 27.5, 24.4.

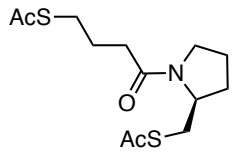
HRMS (ESI$^+$, *m/z*) Calcd. for $C_9H_{16}ClNO_2Na^+$ ($[M+Na]^+$) 228.0762. Found: 228.0733.



15c

To a solution of **14c** (189.5 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (20 mL) was added pyridine (0.12 mL, 1.52 mmol) at 0°C. Methanesulfonyl chloride (85 μL, 1.10 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 50 min. CH_2Cl_2 (20 mL) was added to the mixture and the whole was washed with water (60 mL × 2), saturated aqueous solution of NH_4Cl (80 mL × 3) and brine (50 mL), dried over Na_2SO_4 and evaporated to give **4c** (170.3 mg, 65%) as oil, which was used for the next reaction without further purification.

HRMS (ESI$^+$, *m/z*) Calcd. for $C_{10}H_{19}ClNO_4S^+$ ([M+H]$^+$) 284.0718. Found: 284.0723.

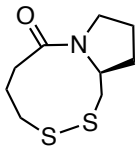


6c

To a solution of **15c** (170.3 mg, 0.61 mmol) in anhydrous DMF (15 mL) was added potassium thioacetate (306.1 mg, 2.17 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 4 h. AcOEt (40 mL) was added to the mixture and the whole was washed with water (30 mL), saturated aqueous solution of $NaHCO_3$ (20 mL × 2), saturated aqueous solution of NH_4Cl (20 mL × 2) and brine (20 mL). The combined aqueous layer was extracted with AcOEt 5 times. The combined organic layer was dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: AcOEt=1:1) to give **6c** (120.4 mg, 0.40 mmol, 43%) as a deep brown oil.

^{1}H NMR (400 MHz, MeOD) (a mixture of rotamers): δ 4.22-4.02 (1H, m), 3.55-3.47 (2H, m), 3.22-3.19 (2H, m), 2.99-2.93 (2H, m), 2.39-2.34 (6H, m), 2.01-1.78 (6H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) (a mixture of rotamers): δ 197.1, 196.5, 173.6, 173.2, 58.8, 58.0, 46.9, 34.1, 33.5, 32.8, 31.3, 30.7, 30.34, 30.30, 30.25, 30.2, 29.4, 29.2, 29.1, 26.5, 25.8, 24.6, 22.1.



7c

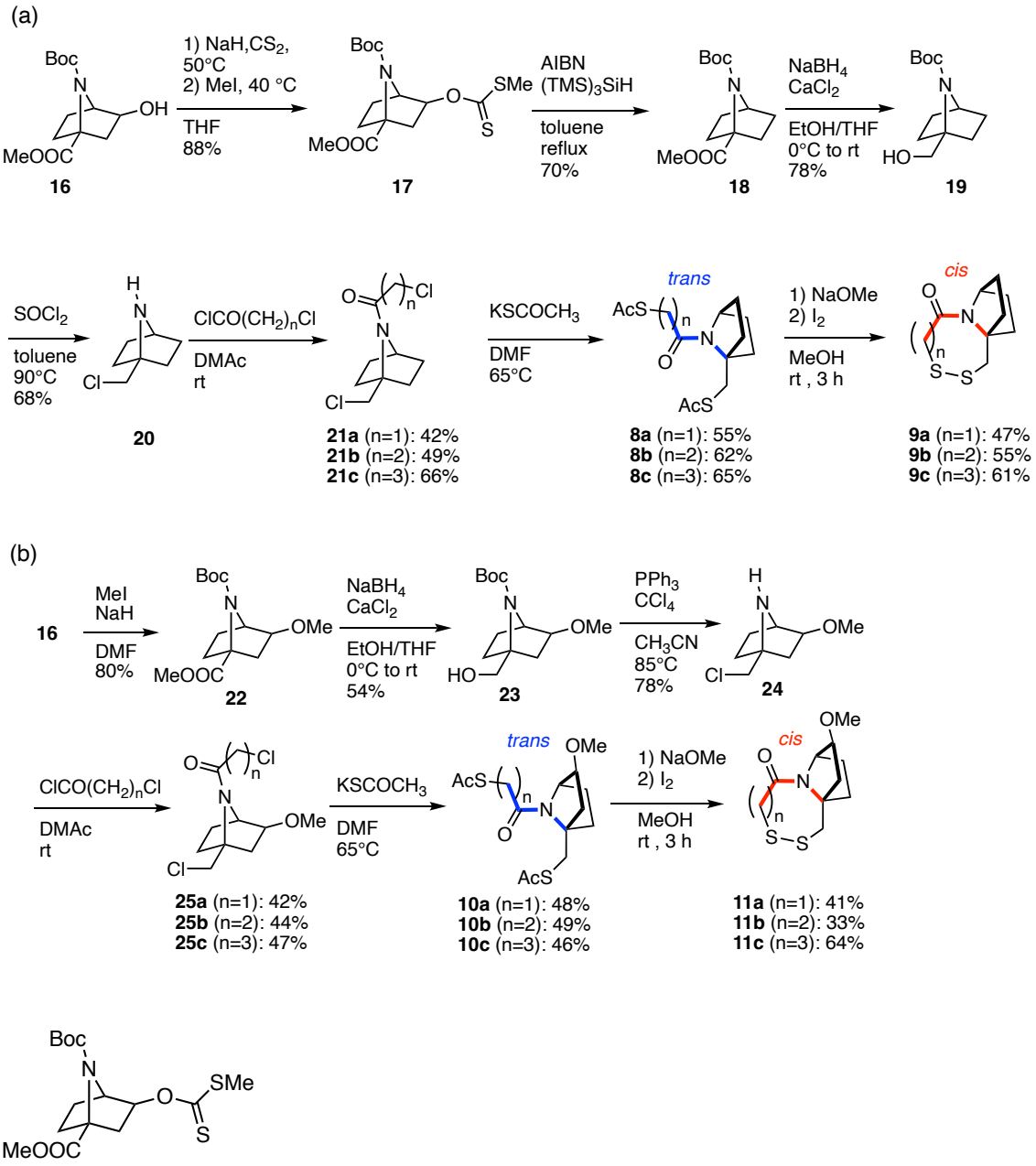
A solution of **6c** (42.6 mg, 0.14 mmol) in anhydrous MeOH (140 mL) was bubbled with N_2 for 30 min, and 28% sodium methoxide (NaOMe) in MeOH (120 μL, 0.62 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 35min. A solution of I_2 (128.8 mg, 1.01mmol) in Et_2O (5 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. Aqueous 10% $Na_2S_2O_3$ (10 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3:1) to give **7c** as a pale yellow oil (11.5 mg, 0.054 mmol, 39%).

^{1}H NMR (400 MHz, MeOD) (a mixture of rotamers): δ 4.59-4.38 (1H, m), 3.81-3.65 (1H, m), 3.25-2.65 (5H, m), 2.55-1.68 (6H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD) (a mixture of rotamers): δ 174.1, 58.2, 44.6, 42.8, 35.5, 31.8, 31.4, 27.2, 22.7.

HRMS(ESI$^+$, *m/z*) Calcd. for $C_9H_{16}NOS_2^+$ ([M+H]$^+$) 218.0668. Found:218.0637.

HPLC (210 nm, CH_3CN: H_2O= 8:2): t_R 8.63 min, 88%.



17

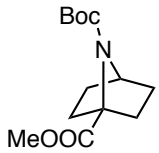
To a solution of **16** (2.26 g, 8.34 mmol) and 60% sodium hydride (NaH) (1.42 g, 35.5 mmol) in anhydrous THF (60 mL) was added carbon disulfide (CS_2) (15 mL, 233.9 mmol) at 0°C. The reaction mixture was stirred at 30°C for 2 h. Iodomethane (MeI) (5.2 mL, 83.53 mmol) was added and the mixture was stirred at 40°C for 2 h. The reaction mixture was poured into ice-water and saturated aqueous solution of NH_4Cl (20 mL), and the mixture was extracted with AcOEt (50 mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (80 mL × 2) and saturated aqueous solution of

NH_4Cl (80 mL × 2), dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 5:1) to give **17** (2.53 g, 7.0 mmol, 84%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 5.27 (1H, dd，J= 4.8, 4.4 Hz), 4.42 (1H, d, J=6.4 Hz), 3.63 (3H, s), 2.39 (3H, s), 2.16 (2H, d, J =6.4 Hz), 2.00-1.91 (1H, m), 1.84-1.76 (1H, m), 1.53-1.49 (2H, m), 1.26 (9H, s), 1.16-1.06 (1H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 214.8, 169.6, 155.1, 84.7, 80.6, 67.32, 62.6, 59.9, 51.9, 41.1, 32.4, 31.2, 27.7, 23.5, 20.6, 18.9.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{15}H_{23}S_2NNaO_5^+$ ([M+Na]$^+$): 384.0910. Found: 384.0904.



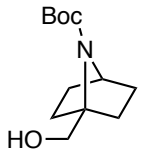
18

To a solution of **17** (2.53 g, 7.0 mmol) and tris(trimethylsilyl)silane ($(TMS)_3SiH$) (3.2 mL, 10.5 mmol) in anhydrous toluene (30 mL) was added AIBN (114.9 mg, 0.7 mmol) at 75°C. The reaction mixture was stirred at 90°C for 30 min and quenched by evaporation of the solvent under reduced pressure. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 7:1) to give **18** (1.47 g, 5.75 mmol, 82%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 4.18 (1H, m), 3.66 (3H, s), 2.07-2.01 (2H, m) 1.82-1.77 (2H, m), 1.65-1.59 (2H, m), 1.41-1.36 (2H, m), 1.29 (9H, s).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 156.3, 80.4, 68.5, 59.5, 51.9, 33.2, 29.1, 27.8.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{13}H_{21}NNaO_4^+$ ([M+Na]$^+$): 278.1363. Found: 278.1346.



19

To a solution of **18** (1.26 g, 4.93 mmol) in EtOH (18 mL) and THF (12 mL) were added $CaCl_2$ (1.09 g, 9.86 mmol) and $NaBH_4$ (746.0 mg, 19.72 mmol) at 0°C. The reaction mixture was stirred at rt for 2 h. A 5% solution of $KHSO_4$ (10 mL) was added at 0°C and the mixture was filtered through Celite and the solid was washed with AcOEt (40 mL ×

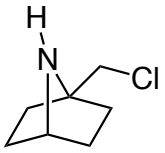
3) and with water (50 mL). The whole was extracted with AcOEt (50 mL × 3). The combined organic layer was washed with brine (80 mL), dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt = 3: 2) to give **19** (814.9 mg, 3.59 mmol, 73%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (1H, brs) 4.23 (1H, t, J= 6.4 Hz), 3.89 (2H, d, J=7.2 Hz), 1.88-1.73 (4H, m), 1.43-1.34 (13H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 80.2, 69.2, 62.1, 58.4, 31.9, 29.3, 28.5.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{12}H_{21}NNaO_3^+$ ([M+Na]$^+$): 250.1414. Found: 250.1394

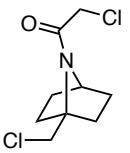
HPLC (210 nm, CH_3CN: H_2O= 9:1): t_R 10.65 min, 96%.



20

To a solution of **19** (814.9 mg, 3.59 mmol) in toluene (35 mL) was added $SOCl_2$ (2.5 mL, 34.7 mmol). The reaction mixture was stirred at 85°C for 8 h. The solution was evaporated to give a crude mixture, which was purified by column-chromatography (eluent: from $CHCl_3$: Acetone= 9:1 to $CHCl_3$: MeOH= 19:1) to give **20** (28.6 mg, 0.16 mmol, 78%) as a colorless oil. The reaction mixture was stirred at rt. under Ar atmosphere for 5 h and quenched by evaporation of the solvent under reduced pressure. Compound **20** was obtained as pale-yellow liquid, which was used in the next step without further purification.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_7H_{13}NCl^+$ ([M+H]$^+$): 146.0731. Found: 146.0748.



21a

To a solution of **20** (162.5 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (30 mL) were added chloroacetyl chloride (150 μL, 1.56 mmol) and Et_3N (300 μL, 2.16 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20min and rt for 18 h, saturated aqueous solution

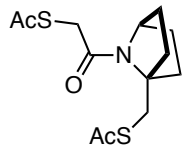
of NH_4Cl (20 mL) was added to quench the reaction, which was extracted with AcOEt (50 mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (20 mL × 2) and saturated aqueous solution of NH_4Cl (20 mL × 2), dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **21a** (131.6 mg, 0.52 mmol, 57%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers): δ 4.34 (2H, s), 4.30 (1H, t, J= 4.8Hz), 4.95(2H, s), 1.92-1.84 (6H, m), 1.60-1.55 (2H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.8, 69.2, 59.4, 47.2, 42.9, 33.7, 29.6.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_9H_{13}Cl_2NONa^+$ ($[M+Na]^+$): 244.0266. Found: 244.0515.

HPLC (210 nm, CH_3CN: H_2O= 9:1): t_R 8.20 min, 99%.



8a

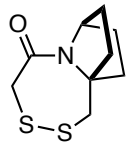
To a solution of **21a** (131.6 mg, 0.52 mmol) in DMF (20 mL) was added potassium thioacetate (788 mg, 6.9 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 24 h. AcOEt (100 mL) was added to the mixture and the whole was washed with water (80 mL × 5) and brine (40 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 3:2) to give **8a** (86.4 mg, 0.29 mmol, 55%) as a deep brown oil.

^1H NMR (400 MHz, $CDCl_3$): δ 4.30 (1H, t J=7.2 Hz), 3.74 (2H, d, J=4.4 Hz), 2.38 (3H, s), 2.33 (3H, s), 1.87-1.53 (8H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.9, 194.6, 165.0, 68.5, 58.6, 33.9, 33.4, 32.2, 30.19, 30.15, 29.8.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{13}H_{19}NaNO_3S_2^+$ ($[M+Na]^+$): 324.0699. Found: 324.0715.

HPLC (210 nm, CH_3CN: H_2O= 9:1): t_R 7.92 min, 100%.



9a

A solution of **8a** (86.4 mg, 0.29 mmol) in anhydrous MeOH (60 mL) was bubbled with

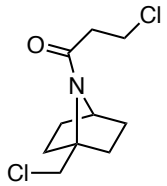
N_2 for 1h, and 28% sodium methoxide (NaOMe) in MeOH (200 μL, 1.03 mmol) was added. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (102.9 mg, 0.81 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. Aqueous 10% $Na_2S_2O_3$ (10 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3:1) to give **9a** as a pale-yellow oil (29.3 mg, 0.14 mmol, 47%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.79 (1H, t, J= 4.8 Hz), 3.75 (2H, s), 3.52 (2H, s), 2.06-1.50 (8H, m).

^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 172.6, 69.4, 59.8, 45.7, 44.6, 37.3, 28.5.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_9H_{14}NOS_2^+$ ([M+H]$^+$): 216.0511. Found: 216.0499.

HPLC (210 nm, CH_3CN: H_2O= 9:1): t_R 8.77 min, 97%.



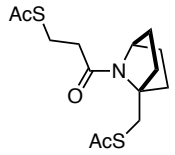
21b

To a solution of **20** (3.21 mmol) in anhydrous CH_2Cl_2 (30 mL) were added 3-chloropropionyl chloride (0.5 mL, 5 mmol) and Et_3N (0.6 mL, 4.32 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min and rt for 18 h, saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction, which was extracted with AcOEt (50 mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (50 mL × 2) and saturated aqueous solution of NH_4Cl (50 mL × 2), dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **21b** (377.3 mg, 1.6 mmol, 49%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (2H, s), 4.25(1H, s), 3.79-3.76 (2H, m), 1.85-1.55 (8H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.9, 68.7, 58.9, 47.6, 39.8, 38.0, 33.8, 29.7.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{10}H_{16}Cl_2NO^+$ ([M+H]$^+$): 236.0603. Found: 236.0605.



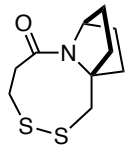
8b

To a solution of **21b** (377.3 mg, 1.6 mmol) in DMF (20 mL) was added potassium thioacetate (78.8 mg, 0.69 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 24 h. AcOEt (100 mL) was added to the mixture and the whole was washed with water (80 mL × 5) and brine (40 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 3:2) to give **8b** (312.7 mg, 0.99 mmol, 62%) as a deep brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (1H, s), 3.76 (2H, s), 3.10 (2H, t, J=7.2Hz), 2.58 (H, t, J=7.2Hz), 2.34 (3H, s), 2.33 (3H, s), 1.81-1.53 (8H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 196.9, 196.5, 168.9, 67.9, 57.9, 35.3, 34.2, 32.5, 30.7, 30.4, 29.9, 24.6.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{14}H_{21}NaNO_3S_2^+$ ([M+Na]$^+$): 338.0855. Found: 338.0854.



9b

To a solution of **8b** (97.1 mg, 0.31 mmol) in anhydrous MeOH (150 mL), dissolved for 1 h under N_2 flow, 28% sodium methoxide (NaOMe) in MeOH (200 μL, 1.03 mmol) was added. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (358.1 mg, 2.82 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. T Aqueous 10% $Na_2S_2O_3$ (20 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3:1) to give **9b** as a pale yellow oil (39.0 mg, 0.17 mmol, 55%).

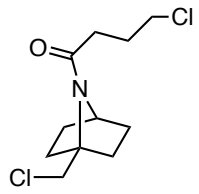
^{1}HNMR (400 MHz, MeOD): δ 4.792 (1H, t, 6.4 Hz), 3.897 (1H, d, J=2.4 Hz), 3.258-3.208 (2H, m), 3.057 (1H, ddd, J=5.2, 13.2, 13.2 Hz), 2.847 (1H, ddd, J=4.4, 13.2, 13.2

Hz), 2.633-2.584 (2H, m), 1.837-1.525 (7H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.03, 67.19, 54.81, 41.11, 37.13, 37.09, 35.51, 32.66, 28.33, 26.75.

HRMS (ESI^+, *m/z*): Calcd. for $C_{10}H_{15}NONaS_2^+$ ($[M+Na]^+$): 252.0487. Found: 252.0478.

HPLC (210 nm, CH_3CN: H_2O= 7:3): t_R 9.72 min, 89%.



21c

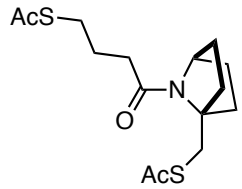
To a solution of **20** (3.21 mmol) in anhydrous CH_2Cl_2 (30 mL) were added 4-chloropropionyl chloride (0.5 mL, 5 mmol) and Et_3N (0.6 mL, 4.32 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min and rt for 18 h, saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction, which was extracted with AcOEt (50 mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (50 mL × 2) and saturated aqueous solution of NH_4Cl (50 mL × 2), dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **21c** (438.2 mg, 1.6 mmol, 55%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (2H, s), 4.26 (1H, s), 3.58 (2H, t, J= 6.4 Hz), 2.43 (2H, t, J= 7.2 Hz), 2.06-2.03 (2H, m), 1.81-1.51 (10H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 68.4, 58.7, 47.8, 44.8, 33.8, 31.6, 29.57, 27.6.

HRMS (ESI^+, *m/z*): Calcd. for $C_{11}H_{18}Cl_2NO^+$ ($[M+H]^+$): 250.0760. Found: 250.0760.

HPLC (210 nm, CH_3CN: H_2O=9:1): t_R 9.06 min, 91%.



8c

To a solution of **21c** (220.6 mg, 0.8 mmol) in DMF (20 mL) was added potassium thioacetate (78.8 mg, 0.69 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 24 h. AcOEt (100 mL) was added to the mixture and the whole was washed with water (80 mL × 5) and brine (40 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-

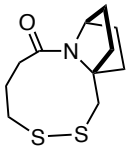
chromatography (eluent: n-hexane: AcOEt=3:2) to give **8c** (157.9 mg, 0.48 mmol, 62%) as a deep brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (1H, s), 3.75 (2H, s), 2.92 (2H, t, J=7.2 Hz), 2.33 (3H, s), 2.32 (3H, s), 1.89 (2H, t, J=7.2 Hz), 1.79-1.53 (8H, m).

^{13}C{^{1}H} NMR (100M Hz, $CDCl_3$): δ 196.9, 195.8, 170.1, 67.6, 57.8, 34.1, 33.7, 32.5, 30.6, 30.2, 29.8, 28.6, 24.9.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{15}H_{23}NNaO_3S_2^+$ ([M+Na]$^+$): 352.1012. Found: 352.1006.

HPLC (210 nm, CH_3CN: H_2O= 7:3): t_R 9.58 min, 97%.



9c

A solution of **8c** (157.9 mg, 0.48 mmol) in anhydrous MeOH (160 mL) was bubbled with N_2 for 1 h, and 28% sodium methoxide (NaOMe) in MeOH (400 μL, 2.06 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (700.2 mg, 5.52 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. Aqueous 10% $Na_2S_2O_3$ (20 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3:1) to give **9c** as white solid (71.2 mg, 0.29 mmol, 60%).

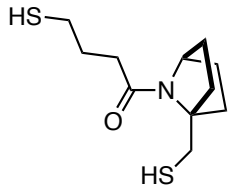
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (1H, t, 5.2 Hz), 3.63-3.43 (2H, m), 3.21-2.74 (3H, m), 2.36-2.23 (3H, m), 1.94-1.52 (8H, m).

^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 172.0, 69.0, 57.3, 47.0, 41.6, 38.3, 36.8, 32.3, 29.5, 27.5, 26.4.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{11}H_{17}NOS_2Na^+$ ([M+Na]$^+$): 266.0644. Found: 266.0652.

HPLC (210 nm, CH_3CN: H_2O= 7:3): t_R 8.56 min, 98%.

Mp: 87-89.5°C.



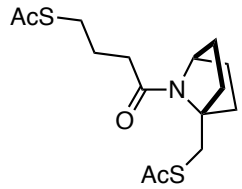
8d

To a solution of **9c** (4.6 mg, 0.02 mmol) in anhydrous MeOH (0.75 mL) was added tris(2-carboxyethyl)phosphine (TCEP) (36.0 mg, 0.1 mmol) at 0°C. 2M $NaHCO_3$ (0.06 mL) was added to the mixture and the reaction mixture was stirred under Ar atmosphere at rt for 5 h. The reaction mixture was evaporated. The residue was washed with $CHCl_3$ and the solution was evaporated to give **8d** (3.5 mg, 0.014 mmol, 72%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21(1H, t, J= 4.8 Hz), 3.27 (2H, s), 2.57 (2H, t, J= 6.8 Hz, J=1.2 Hz), 2.41 (2H, t, J=7.2 Hz), 1.99-1.86 (4H, m), 1.83-1.76 (2H, m), 1.59-1.51 (5H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD): δ 170.7, 69.5, 58.2, 33.9, 33.5, 29.9, 29.1, 29.0, 28.9, 24.3, 24.2.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{11}H_{19}NNaOS_2^+$ ([M+Na]$^+$): 268.0800. Found: 268.0817.



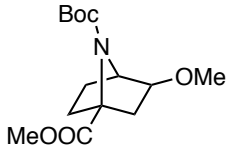
8c (synthesized from **8d)**

To a solution of **8d** (3.5 mg, 0.014 mmol) in pyridine (1 mL), Ac_2O (7 mg, 0.06 mmol) was added. The reaction mixture was stirred at 0°C for 1 h and then at rt for 16 h under Ar atmosphere. AcOEt (30 mL) was added to the mixture and the whole was washed with water (30 mL), saturated aqueous solution of NH_4Cl (30 mL), saturated aqueous solution of $NaHCO_3$ (30 mL) and brine (20 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 2:1) to give **8c** (2.3 mg, 49%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.14(1H, s), 3.74(2H, s), 2.91(2H, t, J=7.2 Hz), 2.318 (3H, s), 2.17 (3H, s), 1.88 (2H, t, J=7.8 Hz), 1.77-1.76 (4H, m), 1.56-1.52 (6H, m).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (1H, s), 3.75 (2H, s), 2.92 (1H t, J=7.2 Hz), 2.33-2.32 (8H, m), 1.91-1.53 (10H, m).

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{15}H_{23}NNaO_3S_2^+$ ([M+Na]$^+$): 352.1012. Found: 352.1006.



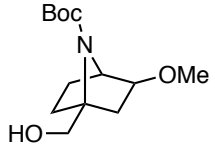
22

To a solution of **16** (896.6 mg, 3.3 mmol) and NaH (400.2 mg, 9.9 mmol) in anhydrous DMF (30 mL) was added MeI (1.32 mL) at 0°C. The reaction mixture was stirred at 0°C for 20 min and rt for 18 h, saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction, which was extracted with AcOEt (50 mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (20 mL × 2) and saturated aqueous solution of NH_4Cl (20 mL × 2) then combined, dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **22** (758.0 mg, 2.66 mmol, 82%) as a colorless oil.

1H NMR (400 MHz, $CDCl_3$): δ 4.41 (1H, d, J=5.2 Hz), 3.80 (3H, s), 3.55-3.53 (1H, m), 3.30 (3H, s), 2.09-1.89 (4H, m), 1.59-1.58 (1H, m), 1.42 (9H, s), 1.32-1.24 (1H, m).

$^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ 171.0, 156.5, 83.4, 80.6, 67.5, 61.4, 60.3, 56.1, 52.1, 33.0, 28.0, 23.8, 21.0, 14.2.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{14}H_{23}NNaO_5^+$ ([M+Na]$^+$): 308.1468. Found: 308.1486.



23

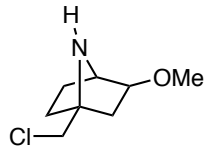
To a solution of **22** (1.4026 g, 4.91 mmol) in EtOH (30 mL) and THF (20 mL) were added $CaCl_2$ (1.2214 g,11.2 mmol) and $NaBH_4$ (982.6 mg 25.8 mmol) at 0°C. The reaction mixture was stirred at rt for 4 h. A 5% solution of $KHSO_4$ (10 mL) was added at 0°C and the mixture was filtered through Celite and the solid was washed with AcOEt (40 mL × 3) and with water (10 mL). The whole was extracted with AcOEt (50 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **23** (834.6 mg, 3.25 mmol, 66%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 5.08(1H, s), 4.34 (1H, d, J=5.6 Hz), 3.97-3.81 (2H, m), 3.51 (1H, dd, J=6.8, 2.4 Hz), 3.29 (3H, d, J=0.4 Hz), 1.83-1.66 (4H, m), 1.44 (9H, s),

1.28-1.20 (6H, m).

$^{13}C\{^{1}H\}$ NMR (100MHz, $CDCl_3$): δ 156.1, 83.2, 80.3, 68.5, 61.5, 60.2, 56.1, 40.0, 31.7, 28.3, 23.7.

HRMS (ESI^+, *m/z*): Calcd. for $C_{13}H_{23}NNaO_4^+$ ($[M+Na]^+$): 280.1519. Found: 280.1526.

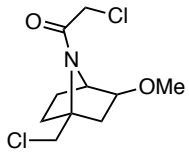


24

To a solution of **23** (53.6 mg, 0.21 mmol) in CH_3CN (10 mL) was added triphenylphosphine (PPh_3) (162.4 mg, 0.62 mmol) and carbon tetrachloride (CCl_4) (150 μL). The reaction mixture was stirred at 85°C for 18 h. The solution was evaporated to give a crude mixture, which was purified by column-chromatography (eluent: from $CHCl_3$: Acetone= 9:1 to $CHCl_3$: MeOH=19:1) to give **24** (28.6 mg, 0.16 mmol, 78%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (1H, d, J=11.6 Hz), 3.79 (1H, d, J=11.2 Hz), 3.58 (1H, dd, J=10.8, 6.0 Hz), 3.28 (3H, s), 2.12 (1H, s), 1.84-1.78 (1H, m), 1.53-1.24 (4H, m).

HRMS (ESI^+, *m/z*): Calcd. for $C_8H_{15}ClNO_4^+$ ($[M+H]^+$): 176.0837. Found: 176.0833.



25a

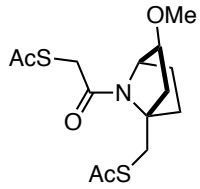
To a solution of **24** (162.5 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (30 mL) were added chloroacetyl chloride (150 μL, 1.56 mmol) and Et_3N (300 μL, 2.16 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min and rt for 18 h, saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction, which was extracted with AcOEt (50mL × 3). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (20 mL × 2) and saturated aqueous solution of NH_4Cl (20 mL × 2) then combined, dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **25a** (131.6 mg, 0.52 mmol, 57%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 (1H, d, J=11.4 Hz), 4.32 (1H, d, J=11.4 Hz), 4.25 (1H, d, J=5.6 Hz), 4.07 (1H, d, J=13.0 Hz), 3.95 (1H, d, J=13.0 Hz), 3.54 (1H, dd,

J=6.8, 2.0 Hz), 3.23 (3H, s), 2.13-1.33 (6H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 82.4, 68.7, 62.7, 55.9, 46.9, 43.1, 42.3, 32.9, 23.7.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{12}H_{19}ClNO_4^+$ ([M+H]$^+$): 252.0553. Found: 252.0561.



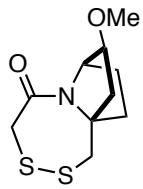
10a

To a solution of **25a** (131.6 mg, 0.52 mmol) in DMF (20 mL) was added potassium thioacetate (699.8 mg, 6.13 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 24 h. Water was added to quench the reaction, which was extracted with AcOEt (50 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$(20 mL) and saturated aqueous solution of NH_4Cl (20 mL × 2) then combined, dried over Na_2SO_4 and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 3:2) to give **10a** (94.2 mg, 0.28 mmol, 49%) as a deep brown oil.

^{1}H-NMR (400MHz, MeOD): δ 4.45 (1H, d, J=5.6 Hz), 3.93 (1H, d, J=15.2 Hz), 3.71 (1H, d, J=4 Hz), 3.67 (1H, d, J=15.2 Hz), 3.6 (1H, dd, J=6.8, 4.8 Hz), 3.32 (3H, s), 2.37 (3H, s), 2.32 (3H, s), 2.02-1.22 (6H, m).

$^{13}C\{^{1}H\}$ NMR (100MHz, MeOD): δ 197.8, 195.9, 169.0, 83.8, 69.4, 63.1, 56.5, 44.1, 34.0, 33.8, 33.0, 30.1, 30.0, 24.5.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{14}H_{21}NNaO_4S_2^+$ ([M+Na]$^+$): 354.0804. Found: 354.0776



11a

A solution of **10a** (94.2 mg, 0.28 mmol) in anhydrous MeOH (150 mL) was bubbled with N_2 for 1 h, and 28% sodium methoxide (NaOMe) in MeOH (200 μL, 1.04 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (280.6 mg, 2.21 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. Aqueous 10% $Na_2S_2O_3$ (20 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL ×

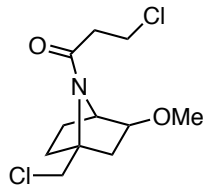
3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH=3:1) to give **11a** as a colorless oil (34.8 mg, 0.14 mmol, 50%).

^1H NMR (400 MHz, CD_2Cl_2): δ 4.91(1H, d, J=6.0 Hz), 3.77(1H, d, J=3.2 Hz), 3.58-3.43 (3H, m), 3.27 (3H, s), 1.97-1.84 (4H, m), 1.46-1.37 (2H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 82.1, 68.5, 62.2, 56.5, 46.0, 45.4, 45.1, 36.1, 23.7.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{10}H_{15}S_2NNaO_2^+$ ([M+Na]$^+$): 268.0436. Found: 268.0426

HPLC (210 nm, CH_3CN: H_2O=7:3): t_R 8.76 min, 94%.



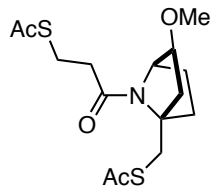
25b

To a solution of **24** (120.6 mg, 0.69 mmol) in DMAc (30 mL) were added 3-chloropropionyl chloride (100 μL, 1.04 mmol) and pyridine (150 μL, 1.88 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min and rt for 18 h, saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction, which was extracted with AcOEt (50 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$(20 mL) and saturated aqueous solution of NH_4Cl (20 mL), dried over Na_2SO_4 and evaporated. The crude was purified by column-chromatography (eluent: n-hexane: AcOEt= 1:1) to give **25b** (131.6 mg, 0.52 mmol, 57%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 4.40 (1H, d, J=11.2 Hz), 4.35 (1H, d, J=11.2 Hz), 4.20 (1H, d, J=5.2 Hz), 3.78-3.67 (2H, m), 3.52 (1H, dd, J=6.8, 2.0 Hz), 3.24 (3H, s), 2.82-2.66 (2H, m), 2.14-1.32 (1H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.5, 82.6, 68.1, 62.1, 56.0, 47.3, 42.5, 39.7, 38.3, 33.0, 23.8.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{12}H_{19}ClNO_4^+$ ([M+H]$^+$): 266.0709. Found: 266.0679.



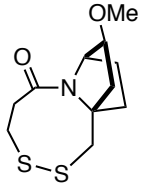
10b

To a solution of **25b** (70.1 mg, 0.21 mmol) in DMF (10 mL) was added potassium thioacetate (78.8 mg, 0.69 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 24 h. AcOEt (30 mL) was added to the mixture and the whole was washed with water (30 mL) and brine (20 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 3:2) to give **10b** (34.3 mg, 0.1 mmol, 49%) as deep brown oil.

^{1}H NMR (400 MHz, MeOD): δ 4.14 (1H, t, J=5.2 Hz), 3.760 (2H, s), 3.61 (1H, d, J=6.8 Hz), 3.30 (3H, s), 3.10-3.04 (2H, m), 2.64-2.62 (2H, m), 2.344-2.337 (6H, m), 1.82-1.41 (6H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD): δ 197.9, 197.6, 84.0, 68.8, 62.4, 56.6, 44.3, 36.5, 34.0, 33.2, 30.5, 30.2, 25.7, 24.6.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{15}H_{23}NNaO_4S_2^+$ ([M+Na]$^+$): 368.0961. Found: 368.0966.



11b

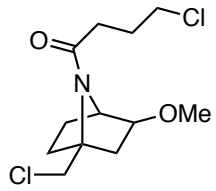
A solution of **10b** (34.3 mg, 0.10 mmol) in anhydrous MeOH (90 mL) was bubbled with N_2 for 1 h, and 28% sodium methoxide (NaOMe) in MeOH (200 μL, 1.03 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (103.3 mg, 0.81 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. Aqueous 10% $Na_2S_2O_3$ (20 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH= 3:1) to give **11b** as a pale yellow oil (13.2 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.951-4.937 (1H, m), 3.745-3.642 (1H, m), 3.553-3.432 (1H, m), 3.287 (3H, s), 3.184-2.576 (6H, m), 2.027-1.282 (5H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.30, 80.24, 66.69, 57.00, 56.74, 50.13, 37.11, 35.89, 32.18, 23.10.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{11}H_{17}NO_2S_2Na^+$ ([M+Na]$^+$): 282.0593. Found: 282.0604.

HPLC (210 nm, CH_3CN: H_2O=7:3): t_R 8.17 min, 98%.

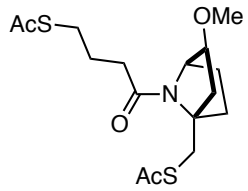


25c

To a solution of **24** (189.2 mg, 0.72 mmol) in anhydrous CH_2Cl_2 (8 mL) was added pyridine (1 mL, 12.5 mmol) at 0°C. A solution of methanesulfonyl chloride (0.9 mL, 11.6 mmol) was added dropwise to the mixture and the reaction mixture was stirred at rt for 48 h. CH_2Cl_2 (20 mL) was added to the mixture and the whole was washed with water (10 mL × 2), saturated aqueous solution of NH_4Cl (30 mL × 10), saturated aqueous solution of $NaHCO_3$ (30 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated to give **25c** (106.8 mg, 0.38 mmol, 53%) as a colorless oil, which was used for the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (2H, d, J= 2.4 Hz), 4.29 (1H, d, J= 5.2 Hz), 3.70-3.59 (2H, m), 3.57 (1H, dd, J=6.8 Hz, 2.4 Hz), 3.29 (1H, s), 2.52-1.70 (6H, m).

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{12}H_{20}Cl_2NO_2^+$ ([M+H]$^+$): 280.0860. Found: 280.0859.



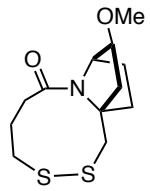
10c

To a solution of **25c** (106.8 mg, 0.38 mmol) in DMF (20 mL) was added potassium thioacetate (236.4 mg, 2.07 mmol). The reaction mixture was stirred at 65°C under Ar atmosphere for 24 h. AcOEt (100 mL) was added to the mixture and the whole was washed with water (200 mL) and brine (40 mL). The combined organic layer was dried over Na_2SO_4, and evaporated to give a crude mixture, which was purified by column-chromatography (eluent: n-hexane: AcOEt= 3:2) to give **10c** (62.5 mg, 0.17 mmol, 46%) as deep brown oil.

^{1}H NMR (400 MHz, MeOD): δ 4.34 (1H, d, J=5.6 Hz), 3.74 (2H, s), 3.59 (1H, dd, J=7.2, 2.4 Hz), 3.29 (3H, s), 2.92-2.90 (2H, m), 2.40-2.36 (2H, m), 2.32 (6H, s), 2.01-1.64 (8H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD): δ 197.6, 196.9, 173.2. 83.7, 68.2, 62.1, 56.2, 43.9, 34.8, 33.6, 32.9, 30.2, 29.8, 29.0, 26.3, 24.3.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{16}H_{25}S_2NNaO_4^+$ ([M+Na]$^+$): 382.1117. Found: 382.1115.



11c

A solution of **10c** (62.5 mg, 0.18 mmol) in anhydrous MeOH (150 mL) was bubbled with N_2 for 1 h, and 28% sodium methoxide (NaOMe) in MeOH (200 μL, 1.03 mmol) was added to the solution. The reaction mixture was stirred at rt under N_2 flow for 35 min. A solution of I_2 (215.8mg, 1.70 mmol) in Et_2O (9 mL) was added to the reaction mixture dropwise until the color became pale. The reaction mixture was stirred at rt under N_2 flow for 2 h. Aqueous 10% $Na_2S_2O_3$ (20 mL) was added to the solution and the mixture was evaporated to remove MeOH solvent. The solution was extracted with AcOEt (50 mL × 3), and the organic layer was washed with washed with saturated aqueous solution of NH_4Cl (30 mL), dried over Na_2SO_4 and evaporated to give a crude, which was purified by column-chromatography (eluent: n-hexane: EtOH=3:1) to give **11c** as a pale yellow oil (31.6 mg, 0.12 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02-4.92 (1H, m), 3.57-3.43 (3H, m), 3.29-3.25 (3H, m), 3.06-2.66 (6H, m), 2.31-1.18 (6H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD):

δ 174.6, 84.3, 81.2, 69.5, 60.5, 56.6, 46.7, 42.7, 37.6, 32.6, 24.7, 22.5.

HRMS (ESI$^+$, *m/z*): Calcd. for $C_{12}H_{19}NO_2S_2Na^+$ ([M+Na]$^+$): 296.0749. Found: 296.0742.

HPLC (210 nm, CH_3CN: H_2O=7:3): t_R 9.12 min, 99%.

3. ^{1}H and ^{13}C-NMR Charts of synthesized compounds

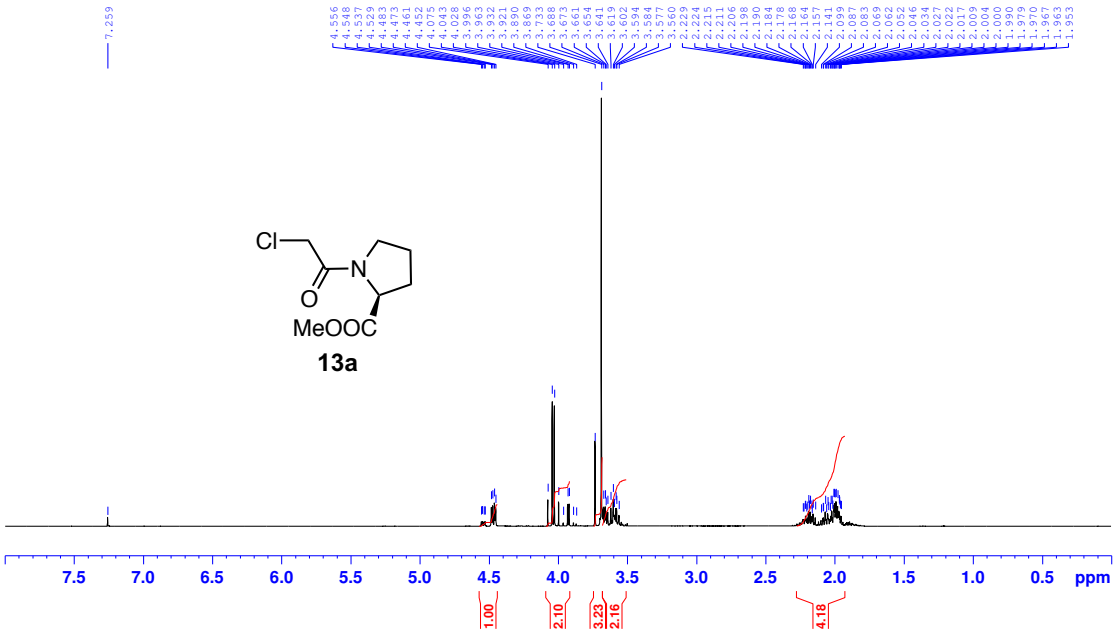


Figure S17. ^{1}H NMR spectrum of **13a** in $CDCl_3$.

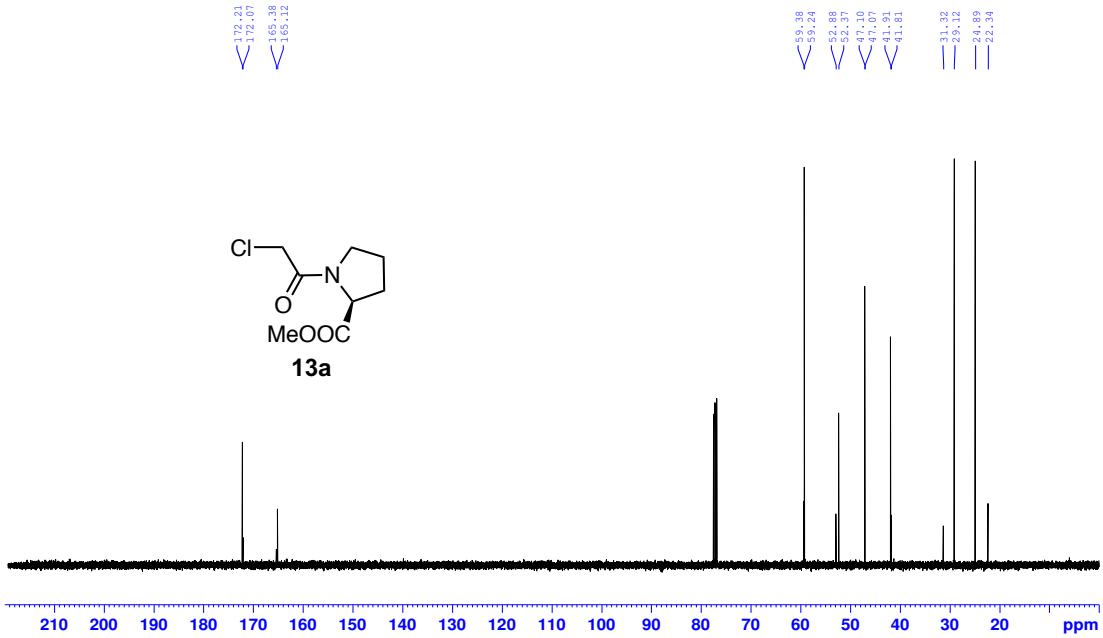


Figure S18. ^{13}C NMR spectrum of **13a** in $CDCl_3$.

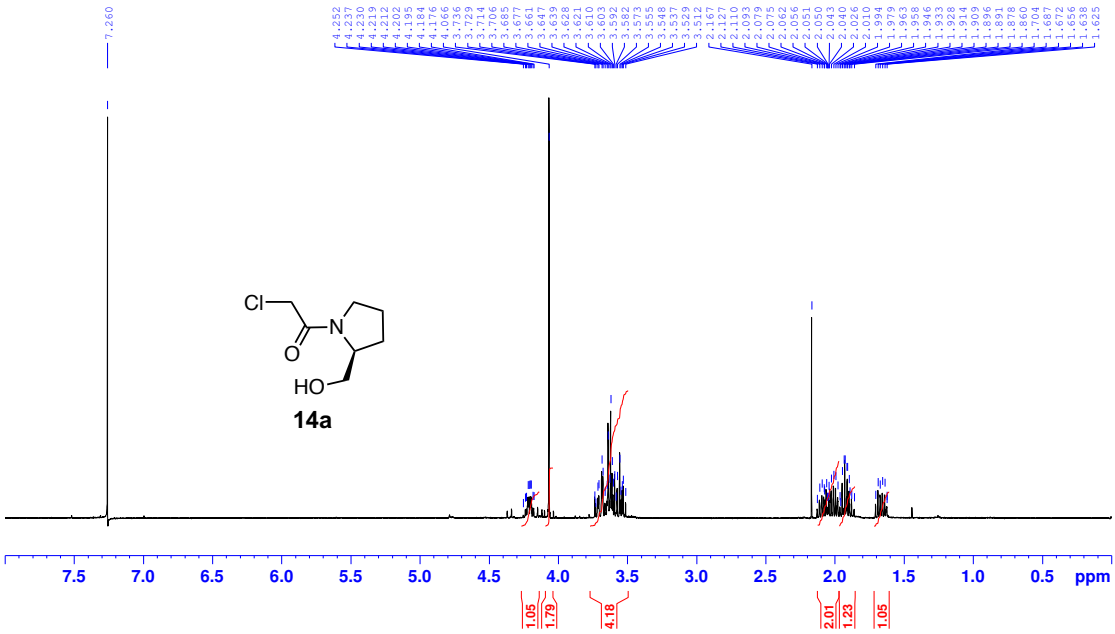


Figure S19. ^{1}H NMR spectrum of **14a** in $CDCl_3$.

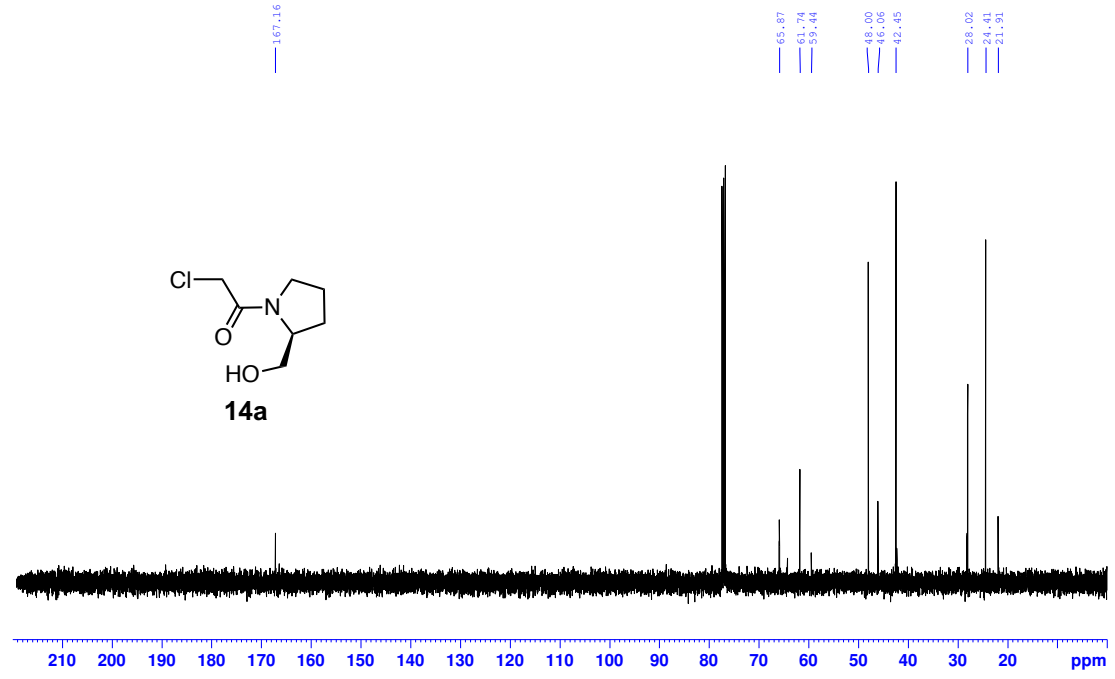


Figure S20. ^{13}C NMR spectrum of **14a** in $CDCl_3$.

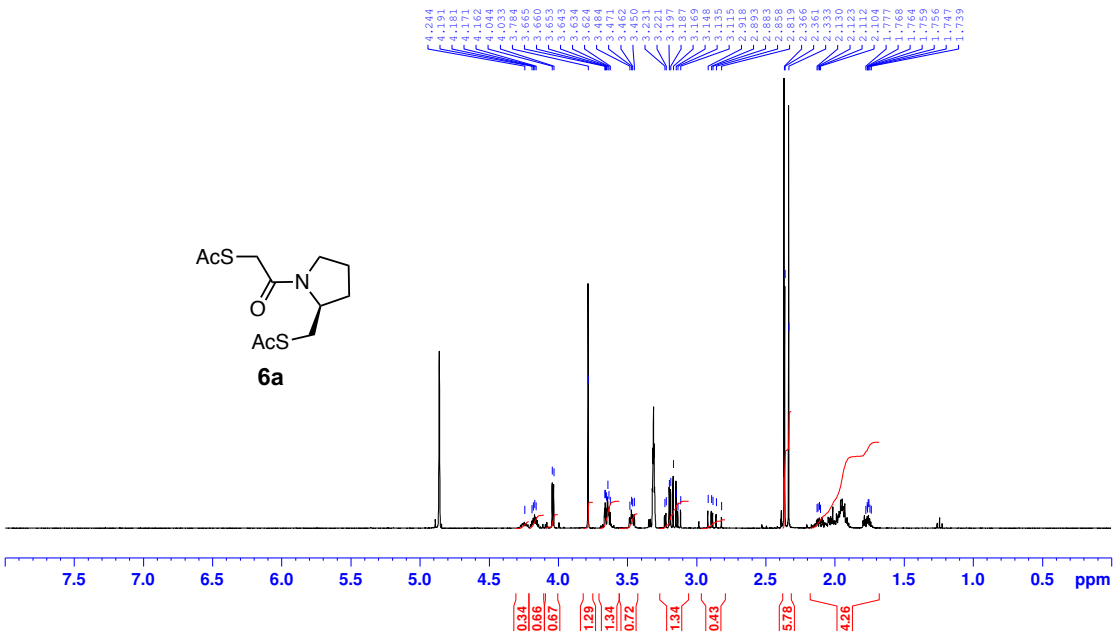


Figure S21. ^{1}H NMR spectrum of **6a** in MeOD.

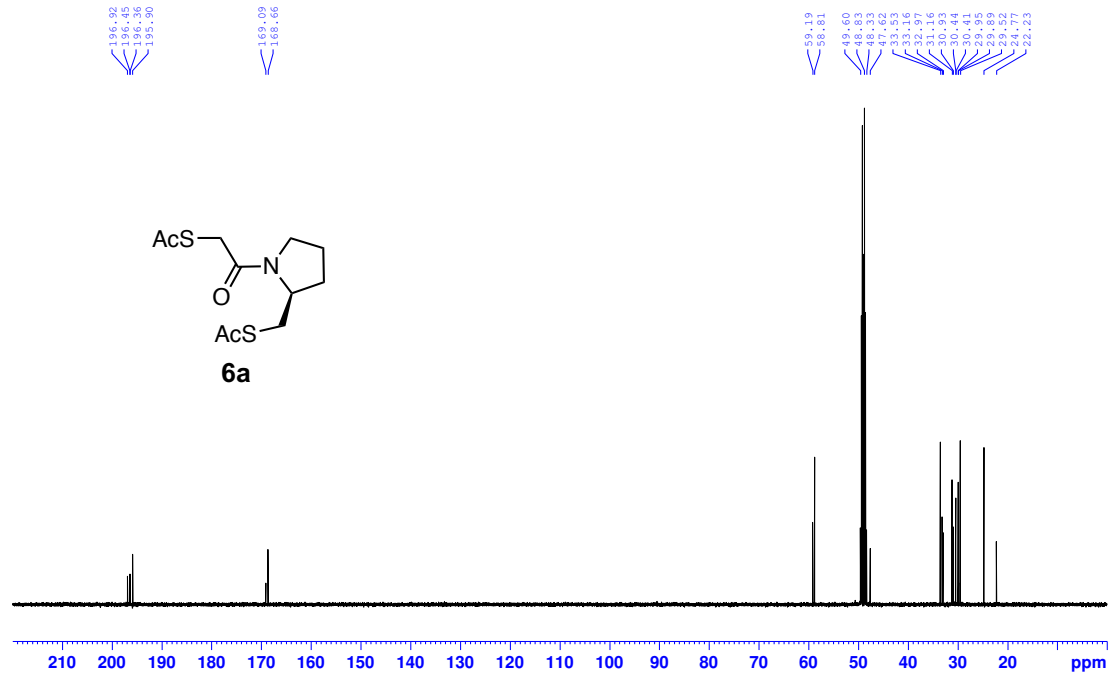


Figure S22. ^{13}C NMR spectrum of **6a** in MeOD.

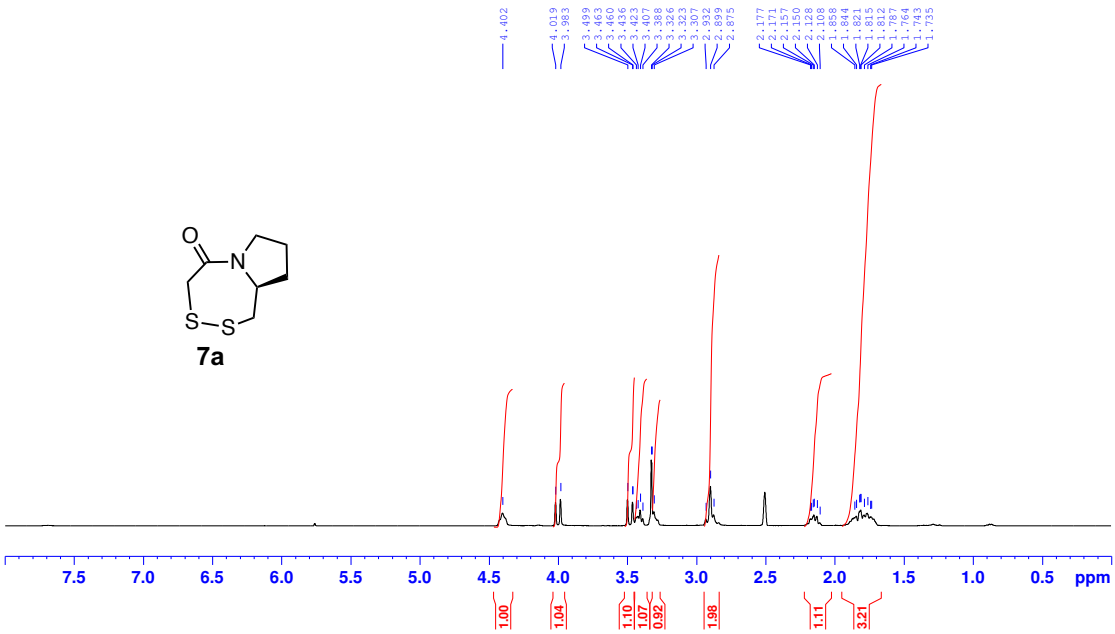


Figure S23. [1]H NMR spectrum of **7a** in DMSO-d_6.

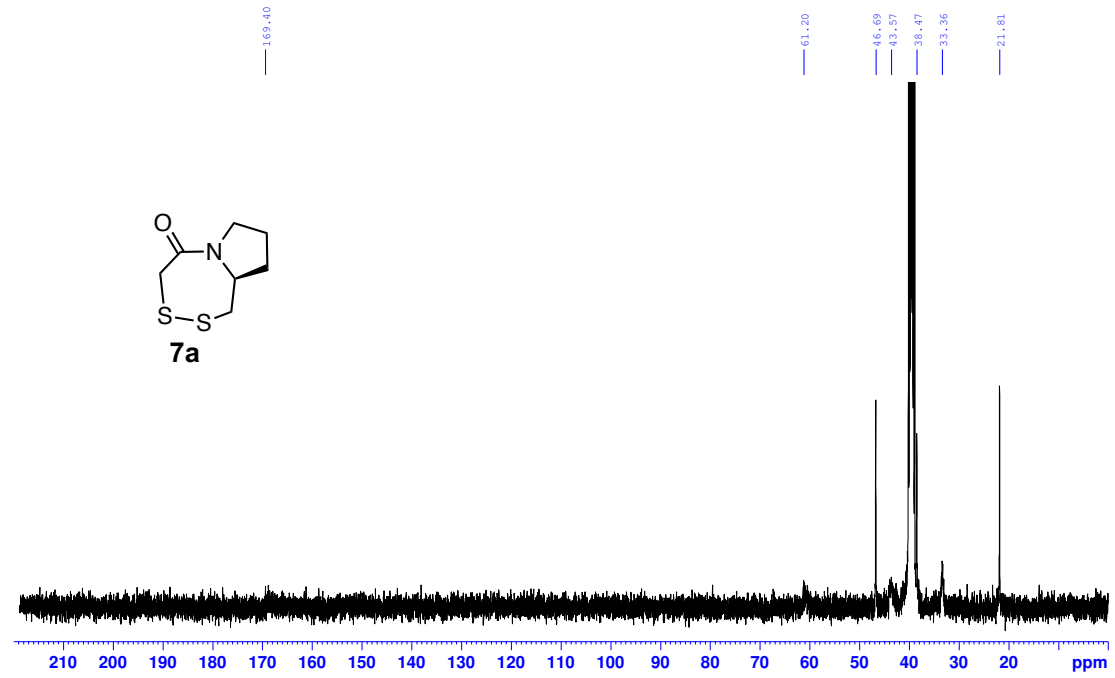


Figure S24. [13]C NMR spectrum of **7a** in DMSO-d_6.

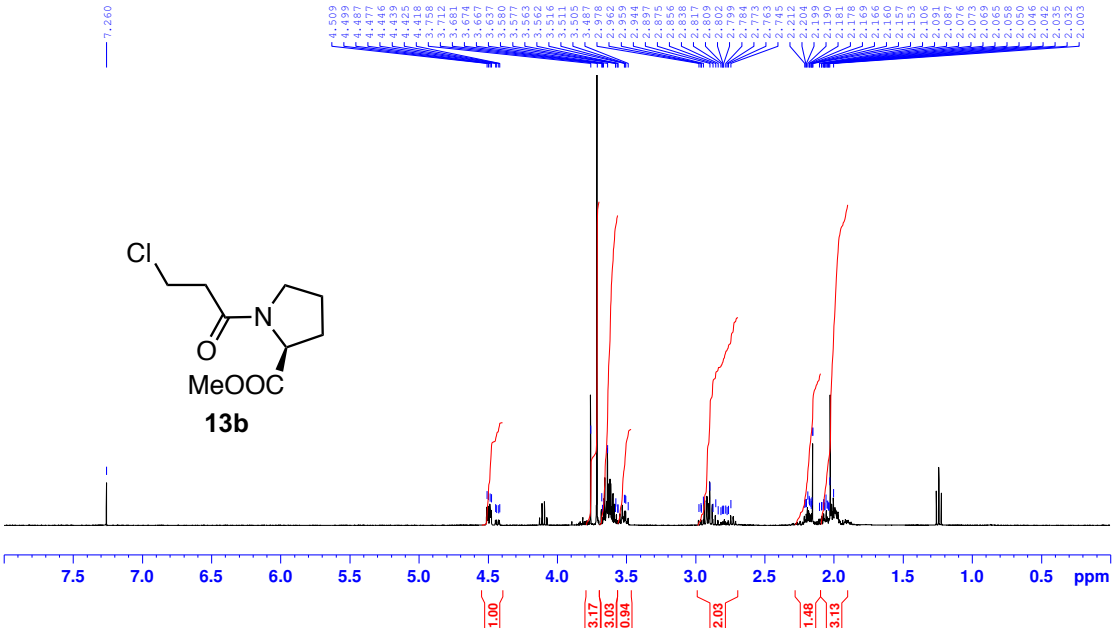


Figure S25. ^{1}H NMR spectrum of **13b** in $CDCl_3$.

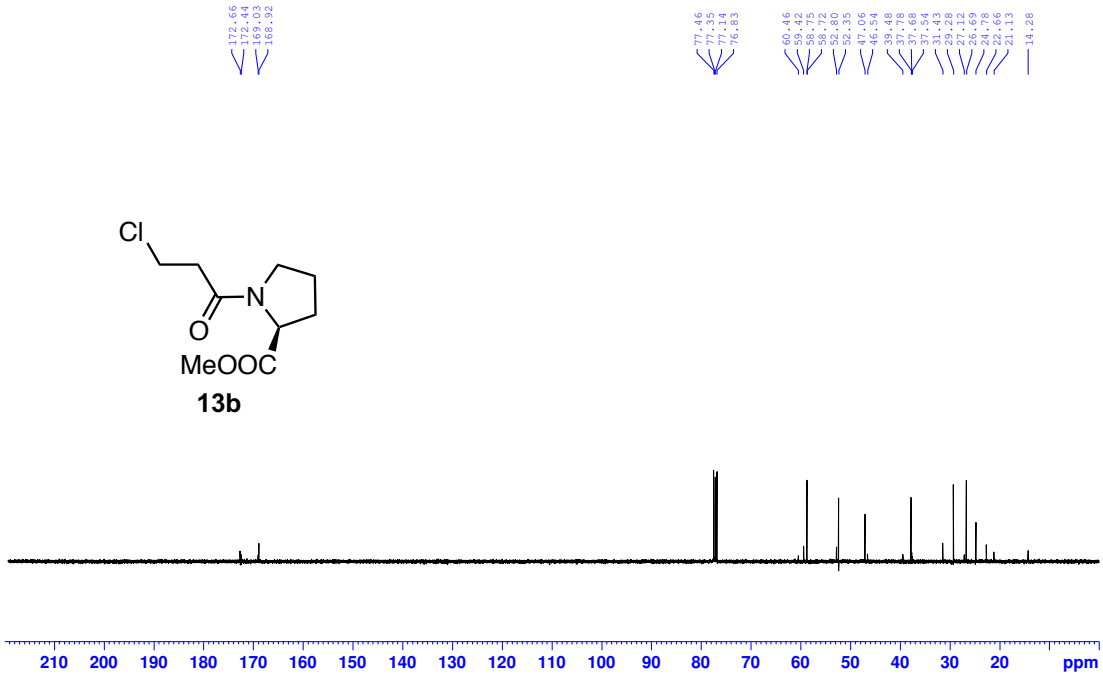


Figure S26. ^{13}C NMR spectrum of **13b** in $CDCl_3$.

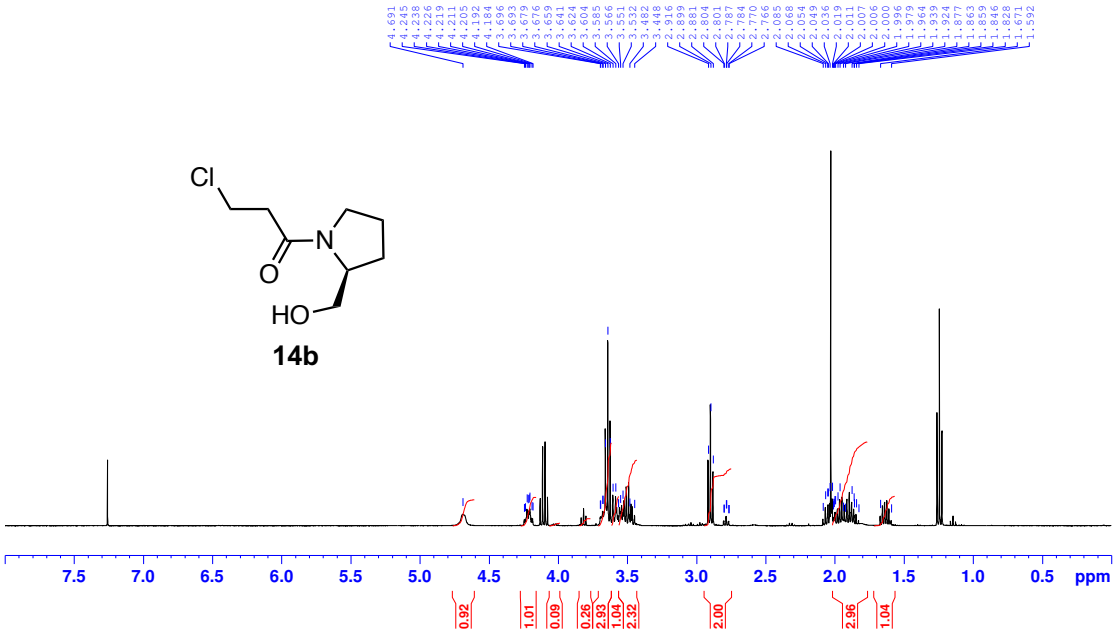


Figure S27. ^{1}H NMR spectrum of **14b** in $CDCl_3$.

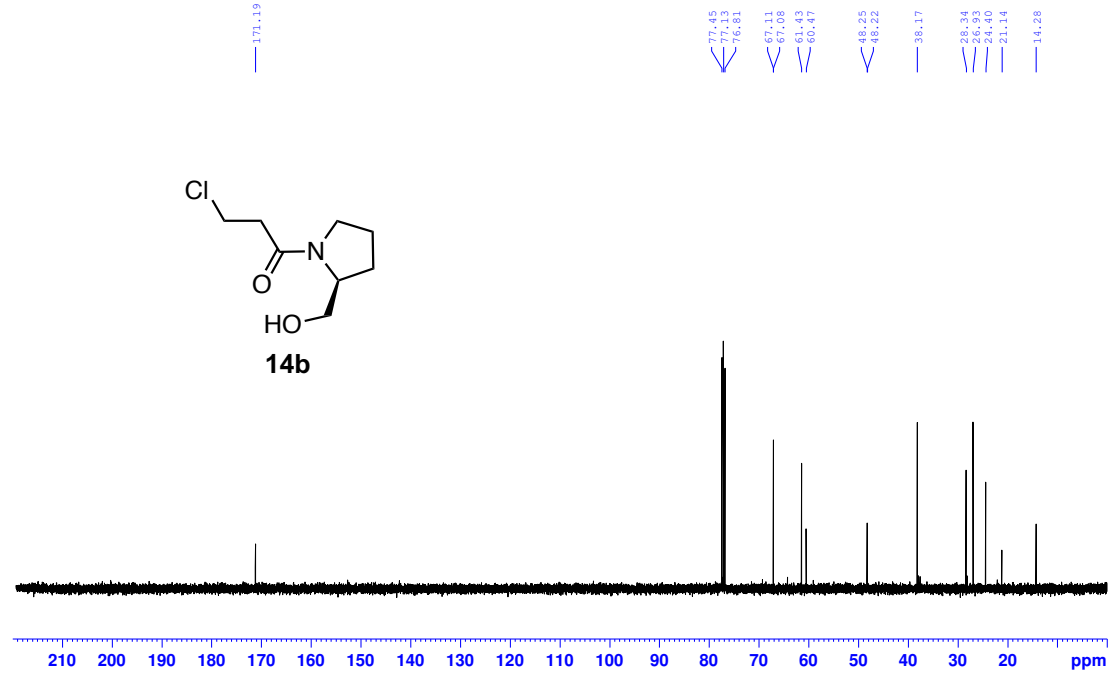


Figure S28. ^{13}C NMR spectrum of **14b** in $CDCl_3$.

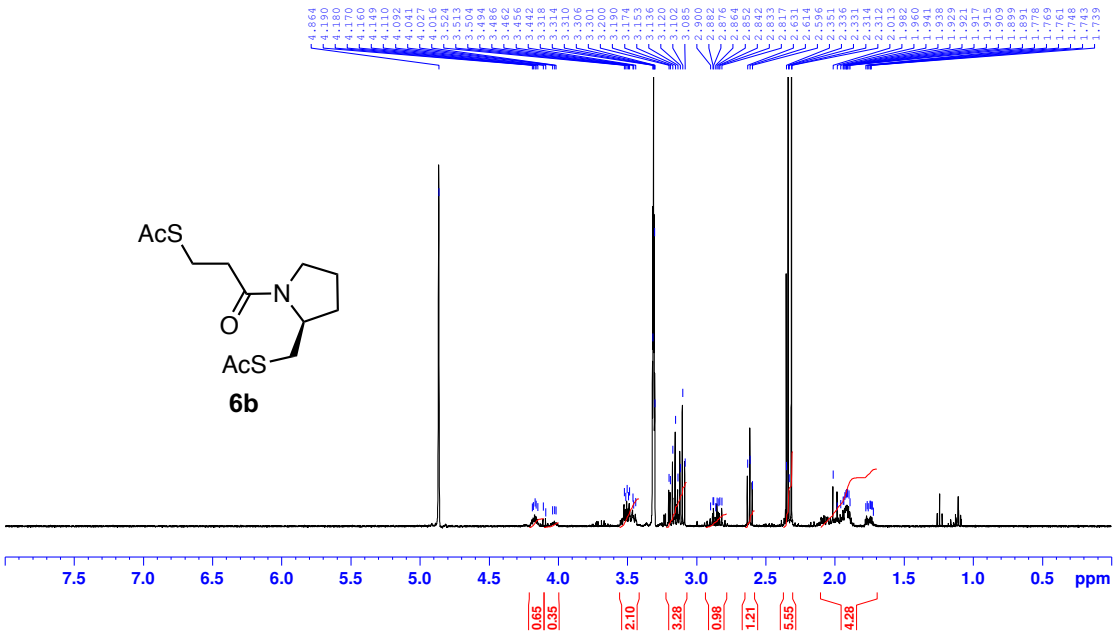


Figure S29. [1]H NMR spectrum of **6b** in MeOD.

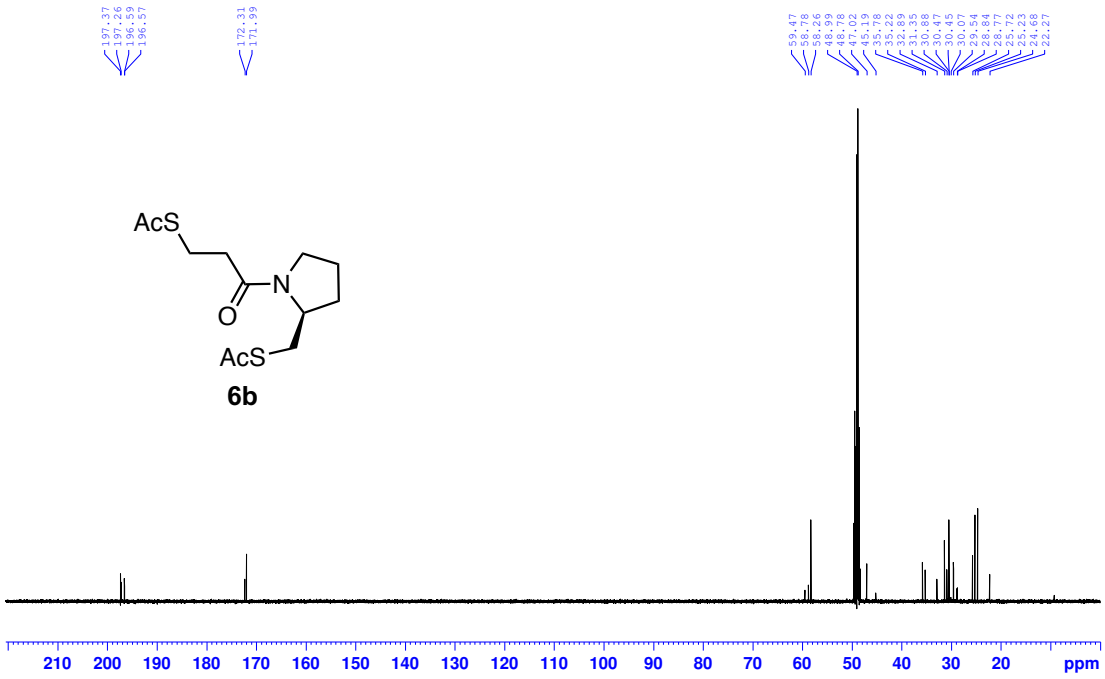


Figure S30. [13]C NMR spectrum of **6b** in MeOD.

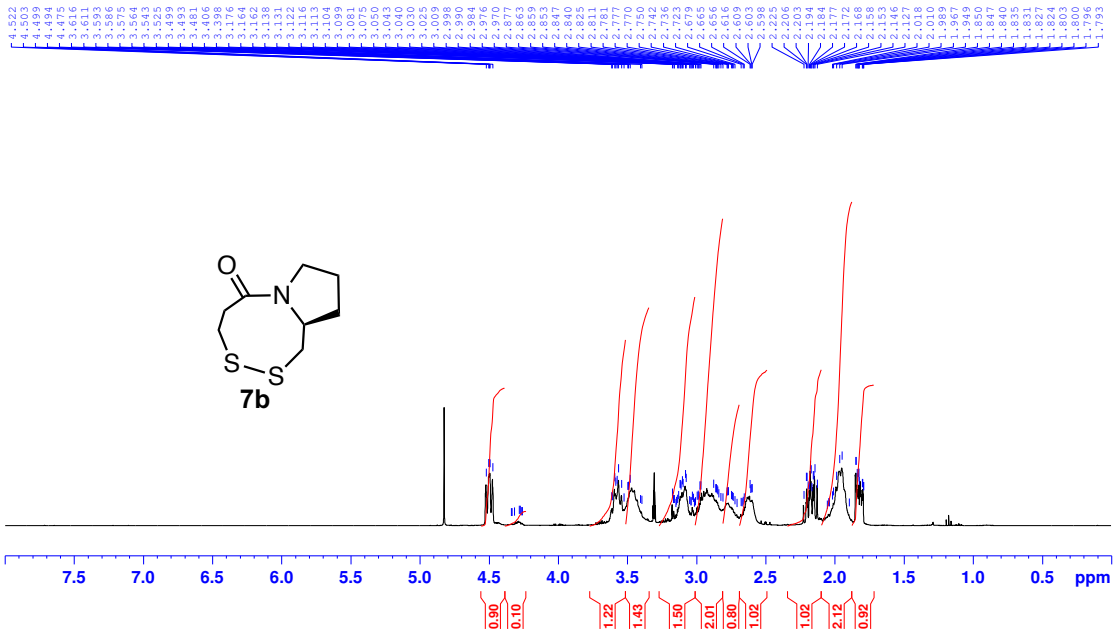


Figure S31. [1]H NMR spectrum of **7b** in MeOD.

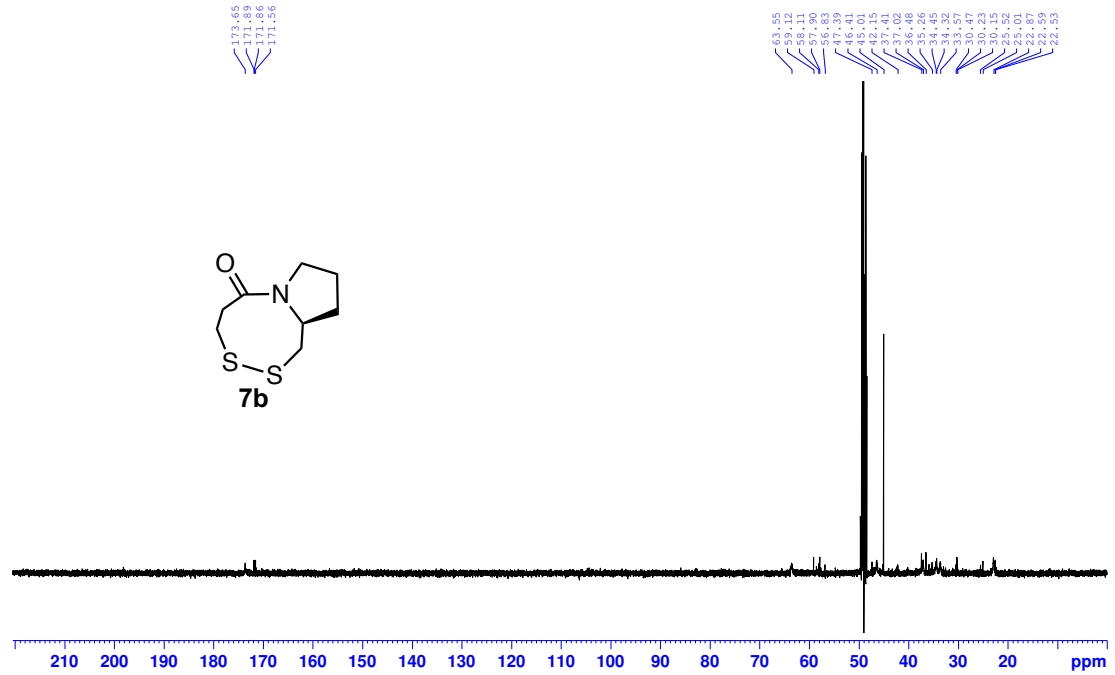


Figure S32. [13]C NMR spectrum of **7b** in MeOD.

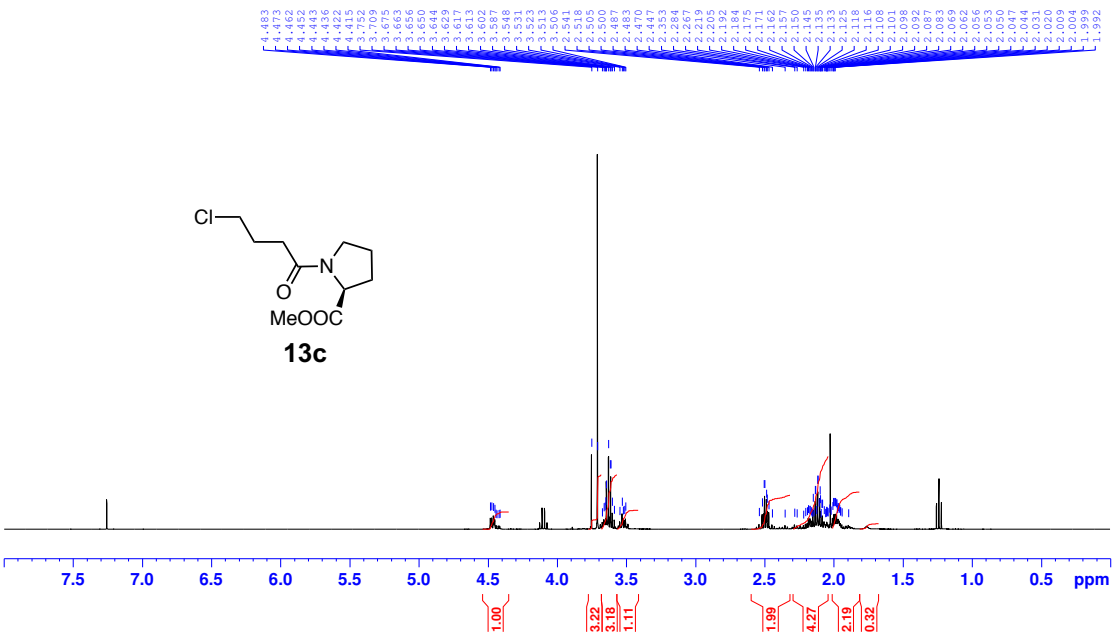


Figure S33. ^{1}H NMR spectrum of **13c** in $CDCl_3$.

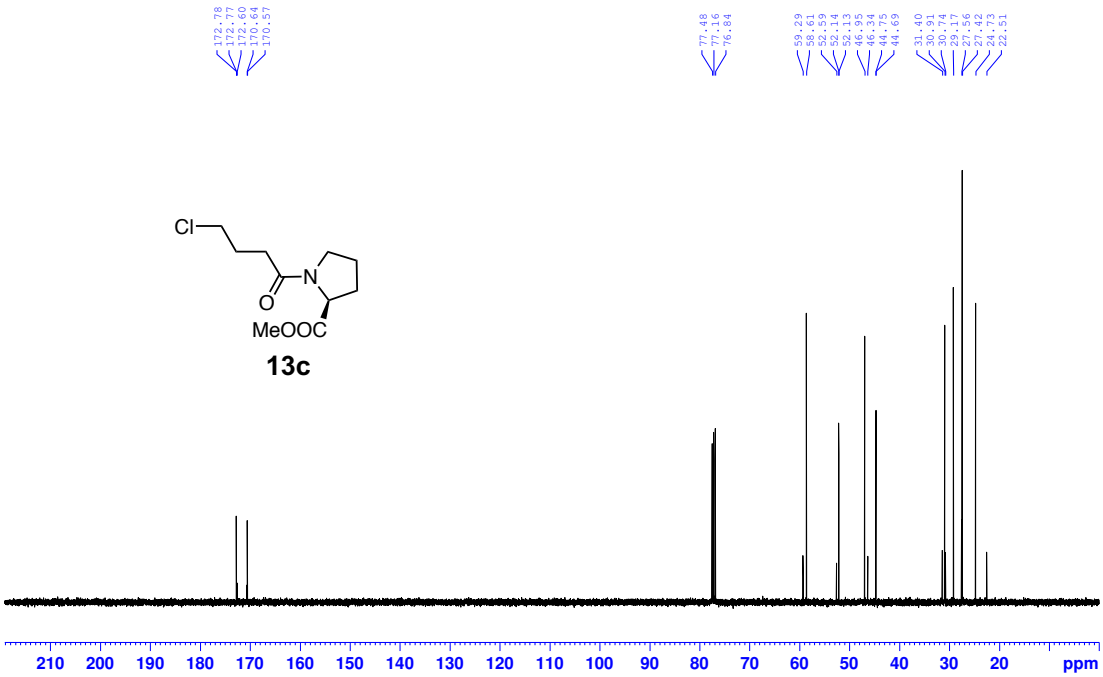


Figure S34. ^{13}C NMR spectrum of **13c** in $CDCl_3$.

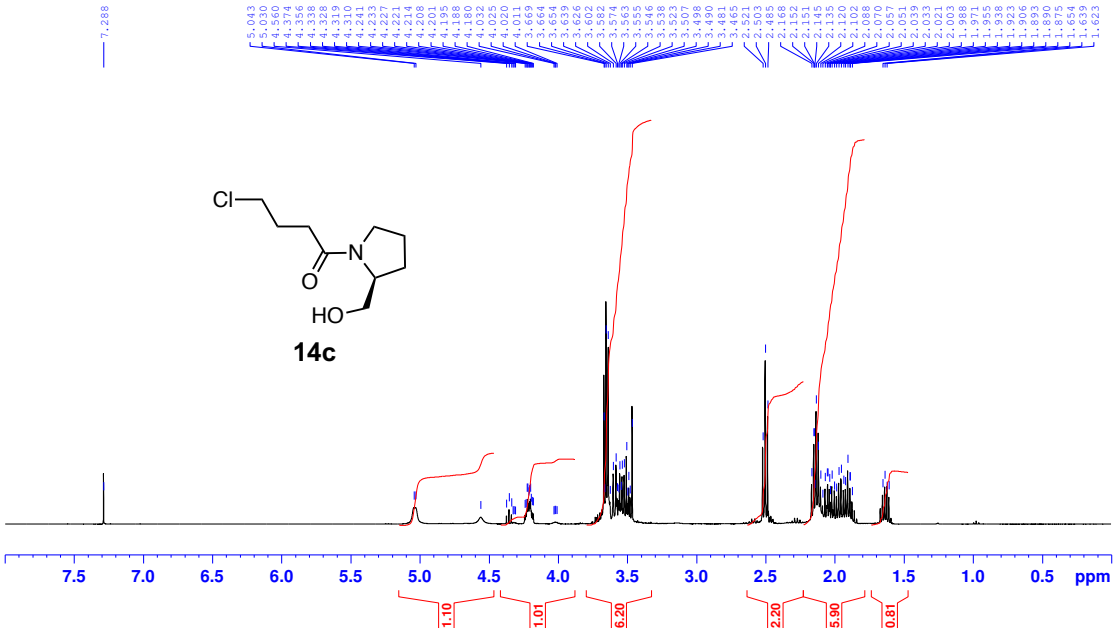


Figure S35. ^{1}H NMR spectrum of **14c** in $CDCl_3$.

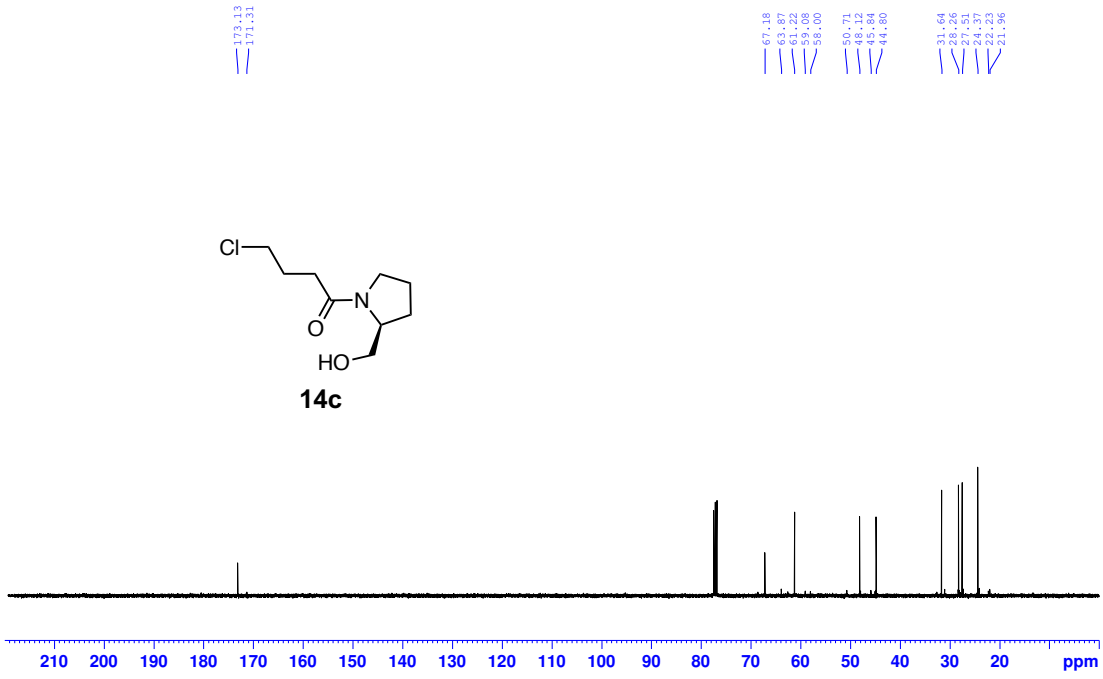


Figure S36. ^{13}C NMR spectrum of **14c** in $CDCl_3$.

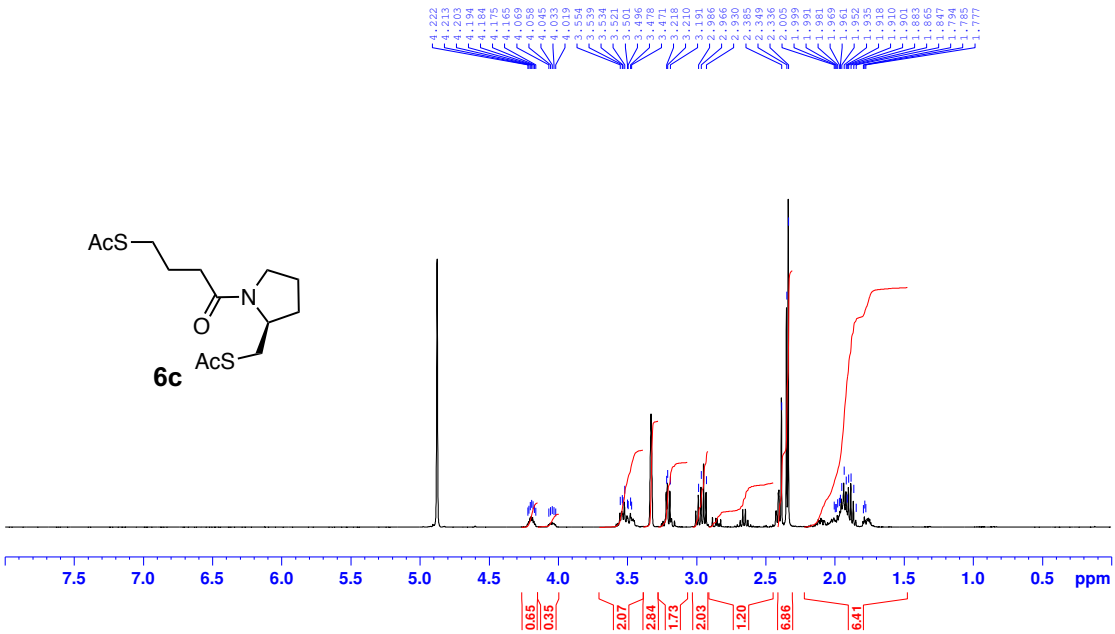


Figure S37. ^{1}H NMR spectrum of **6c** in $CDCl_3$.

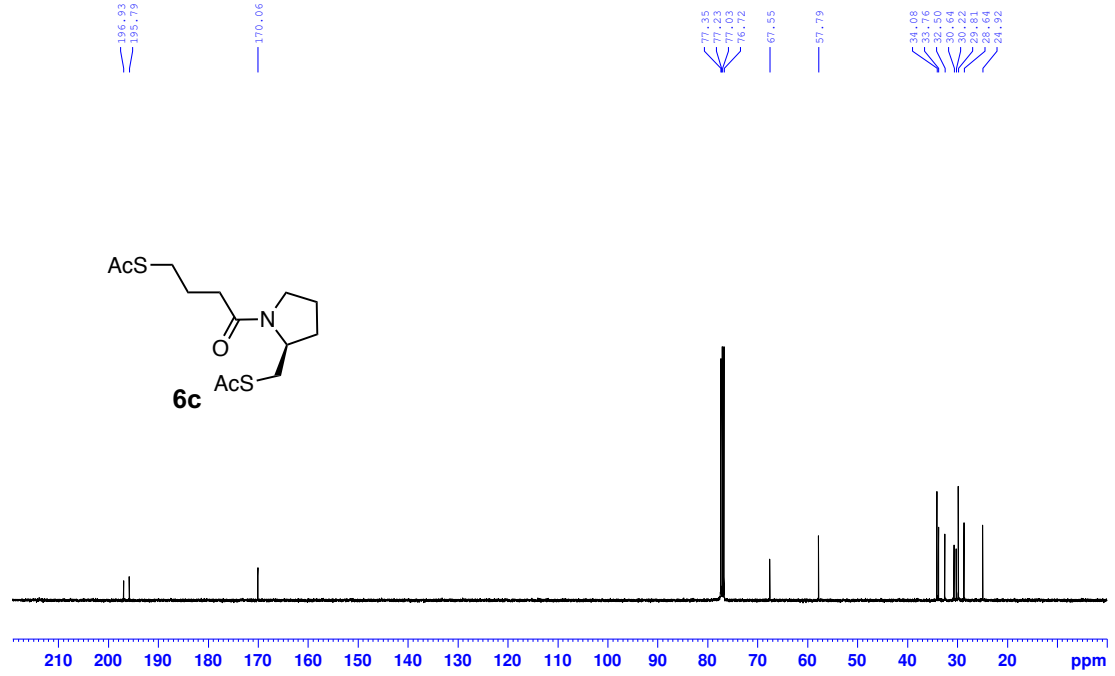


Figure S38. ^{13}C NMR spectrum of **6c** in $CDCl_3$.

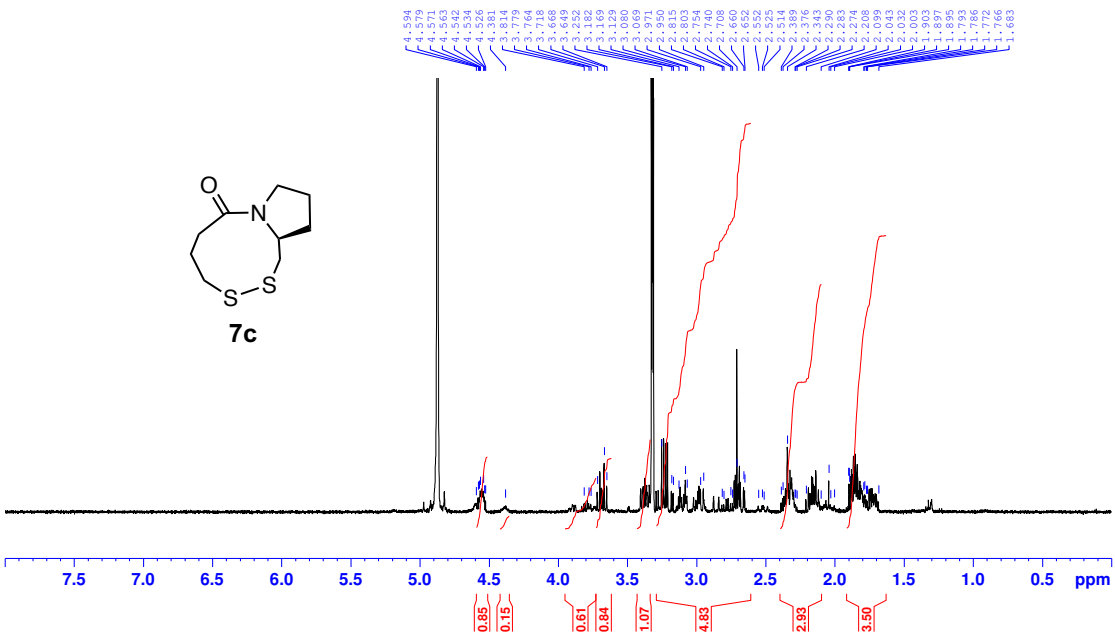


Figure S39. [1]H NMR spectrum of **7c** in MeOD at 274.6 K.

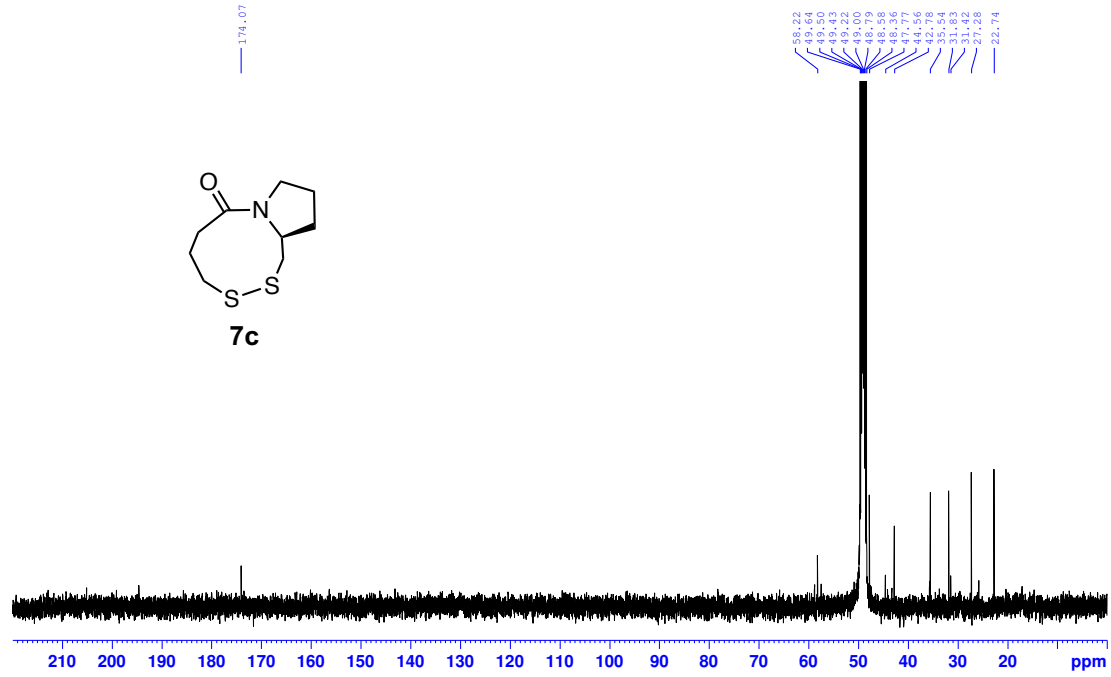


Figure S40. [13]C NMR spectrum of **7c** in MeOD at 274.6 K.

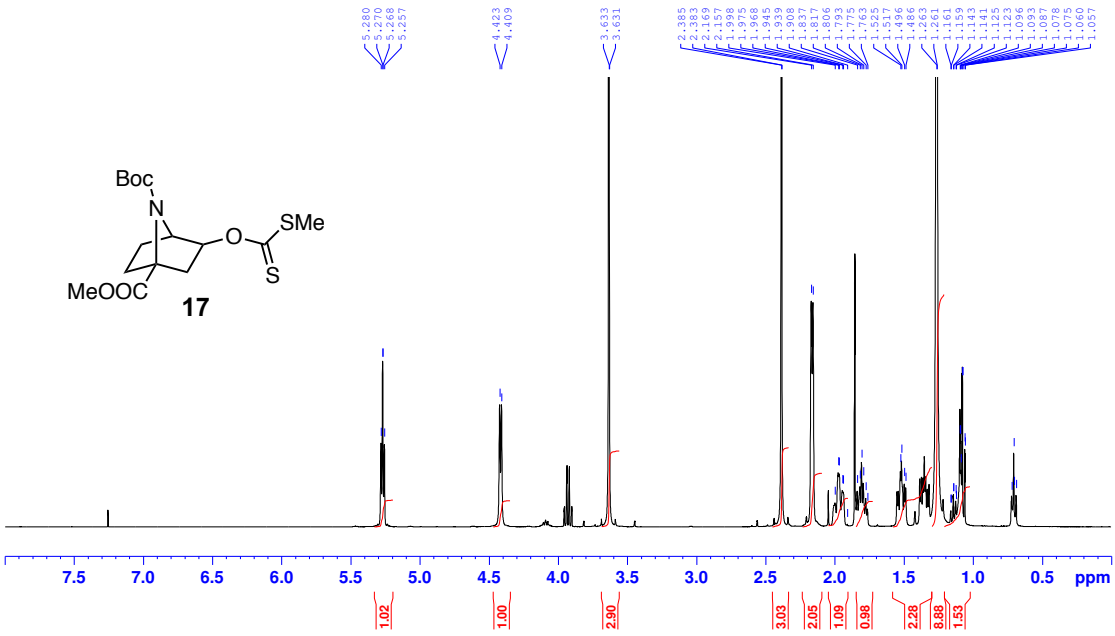


Figure S41. ^{1}H NMR spectrum of **17** in $CDCl_3$.

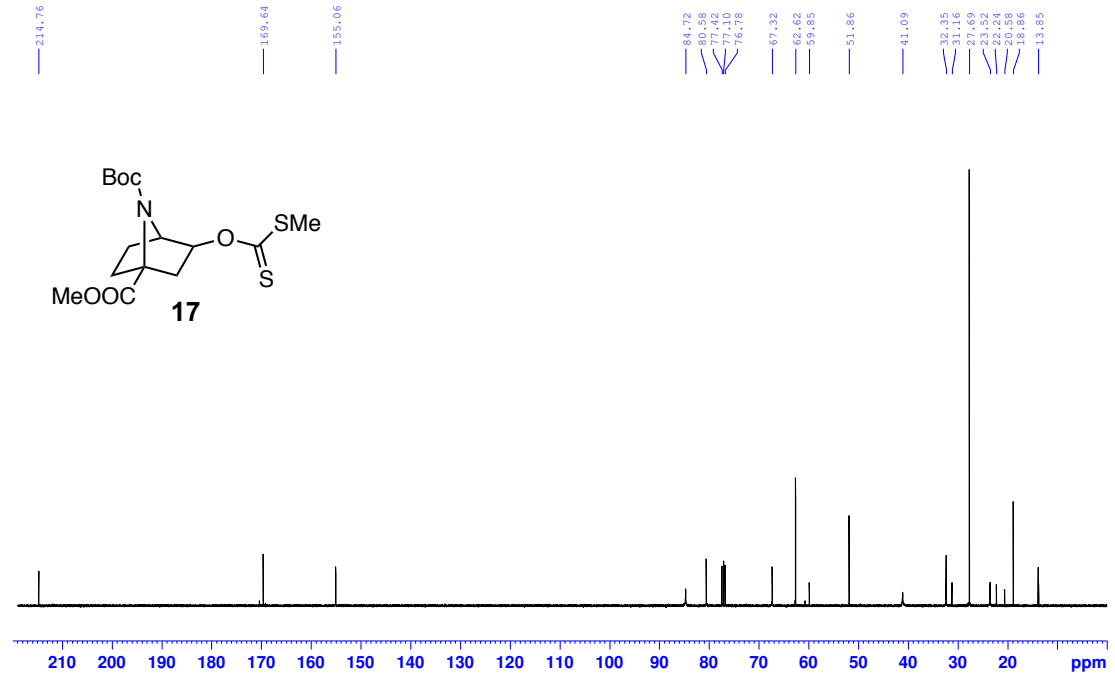


Figure S42. ^{13}C NMR spectrum of **17** in $CDCl_3$.

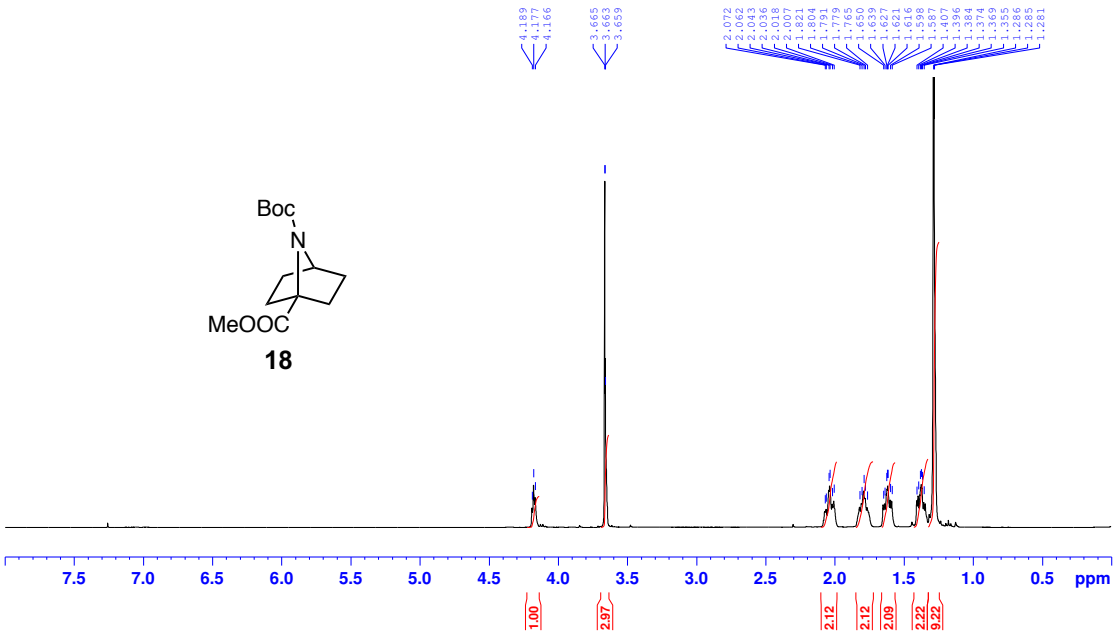


Figure S43. ^{1}H NMR spectrum of **18** in $CDCl_3$.

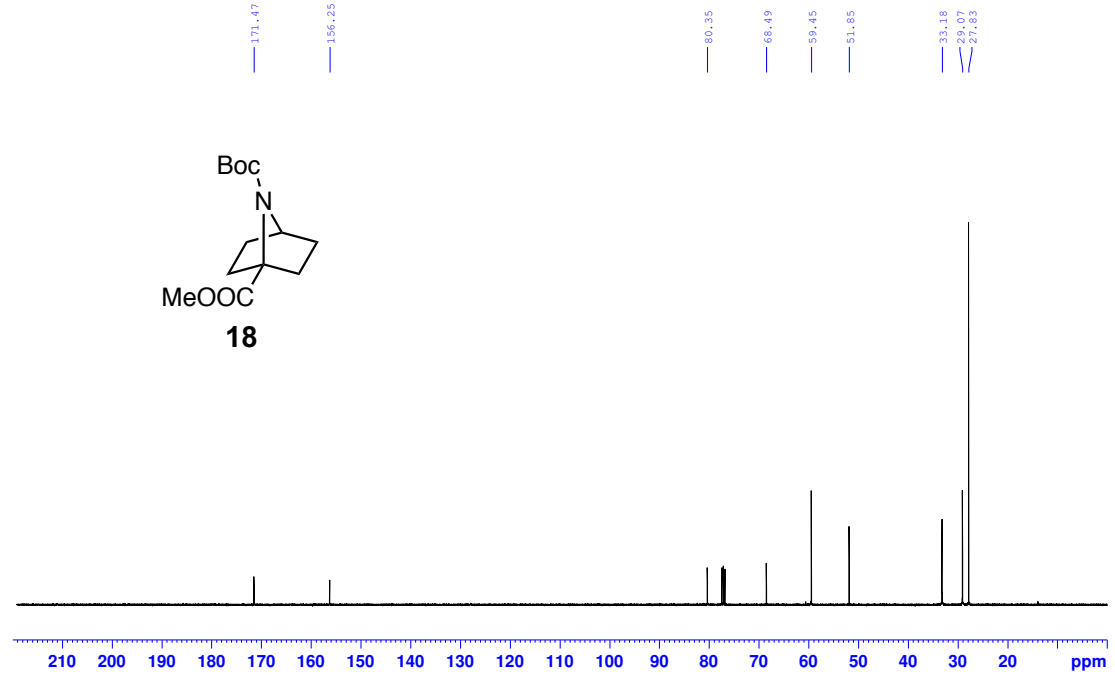


Figure S44. ^{13}C NMR spectrum of **18** in $CDCl_3$.

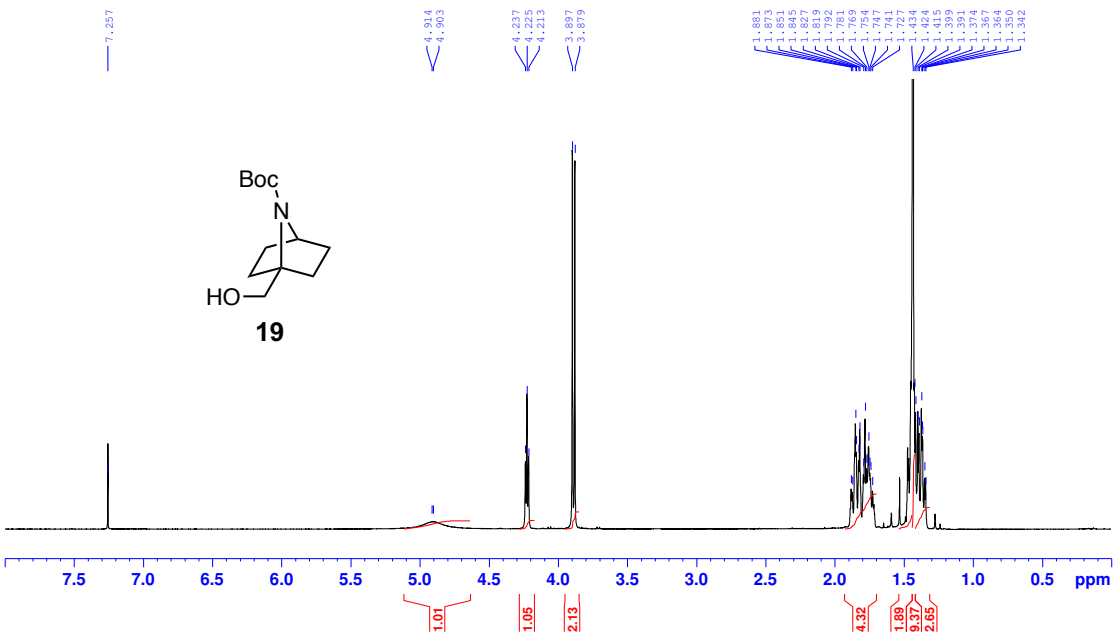


Figure S45. ^{1}H NMR spectrum of **19** in $CDCl_3$.

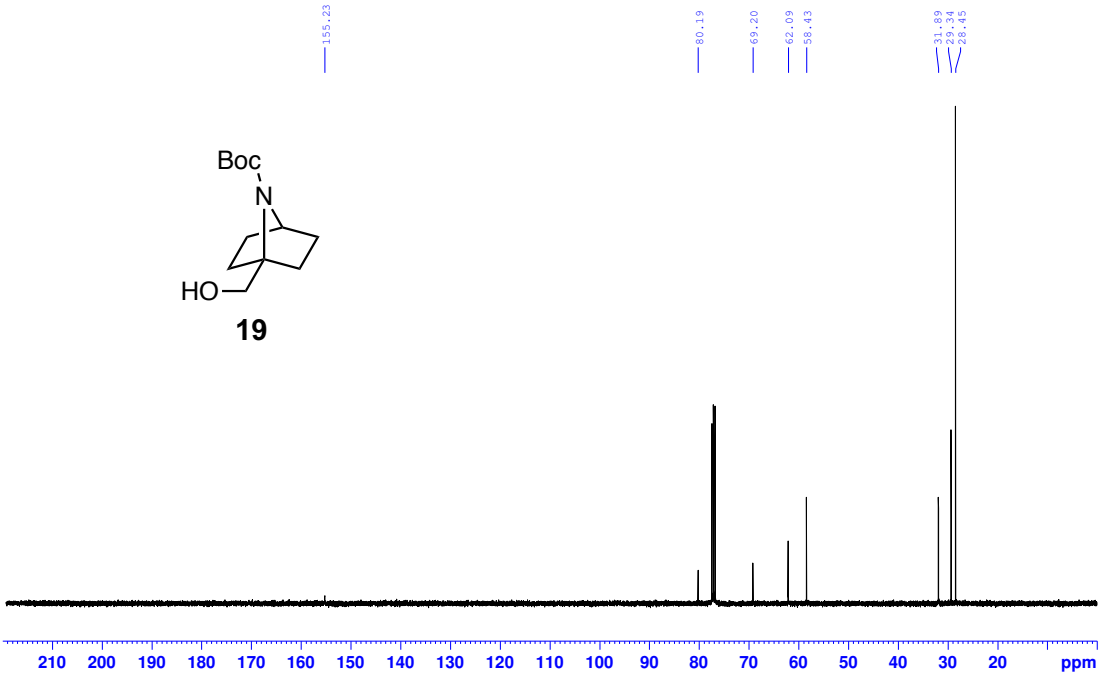


Figure S46. ^{13}C NMR spectrum of **19** in $CDCl_3$.

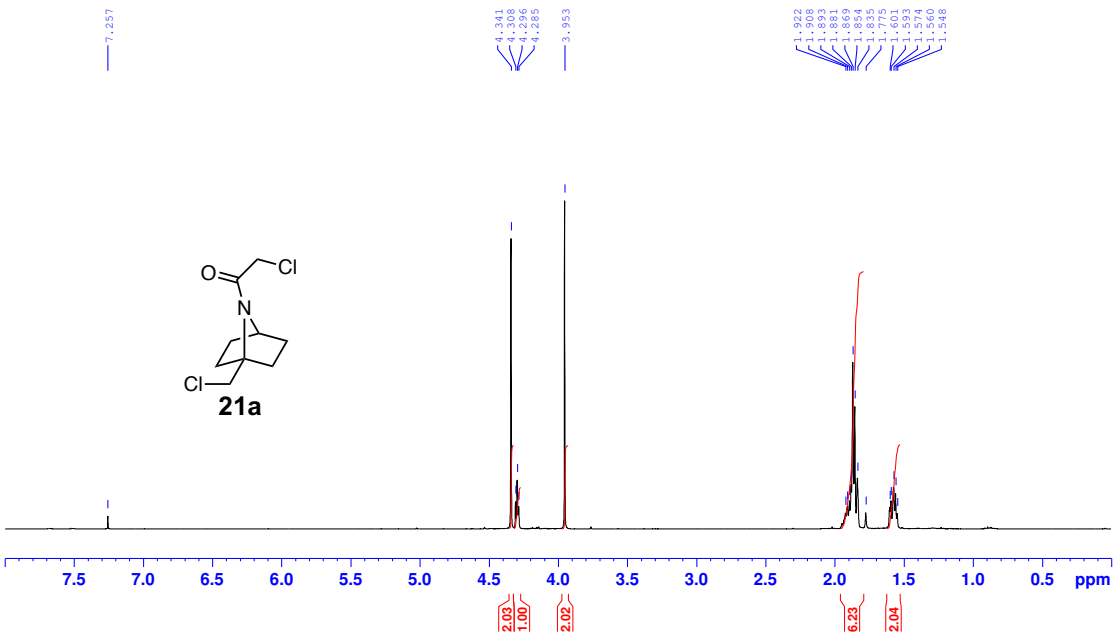


Figure S47. ^{1}H NMR spectrum of **21a** in $CDCl_3$.

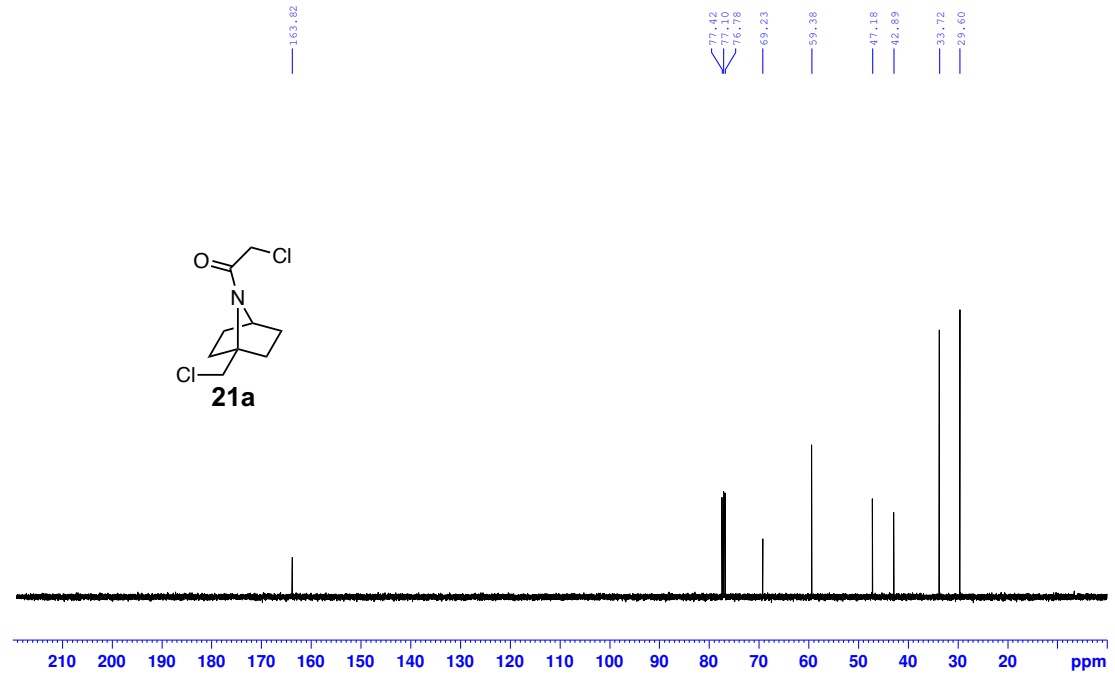


Figure S48. ^{13}C NMR spectrum of **21a** in $CDCl_3$.

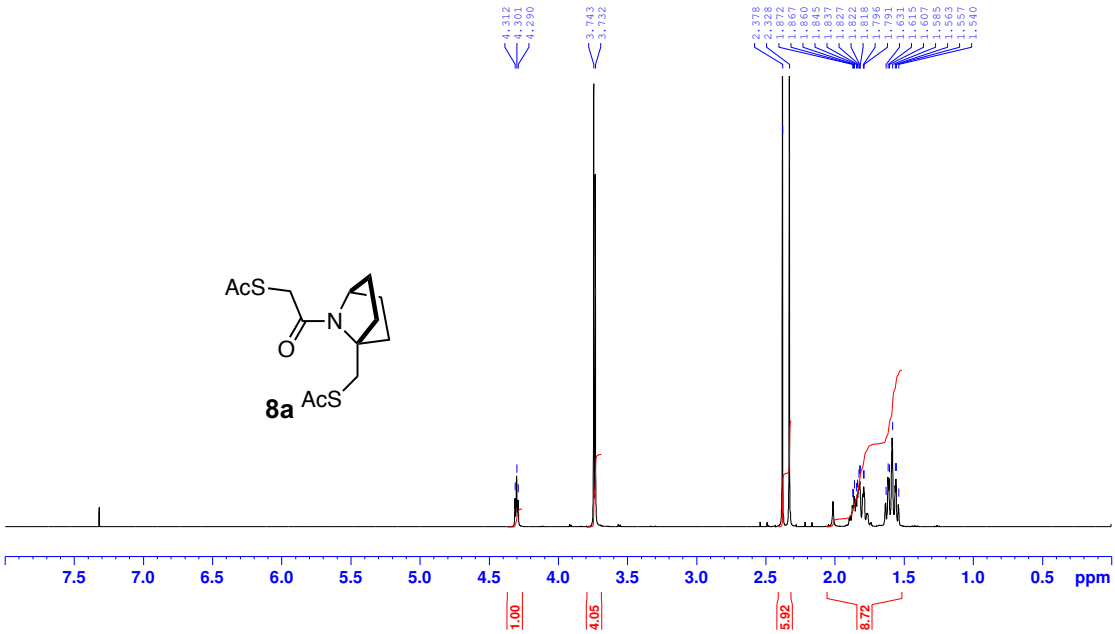


Figure S49. ^{1}H NMR spectrum of **8a** in $CDCl_3$.

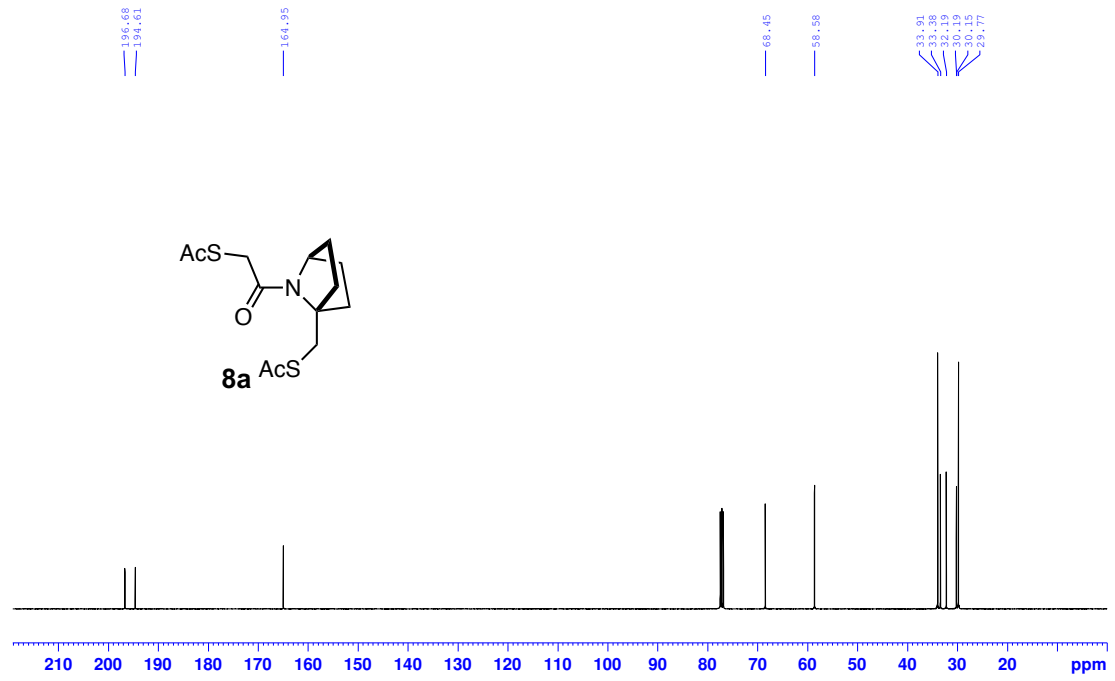


Figure S50. ^{13}C NMR spectrum of **8a** in $CDCl_3$.

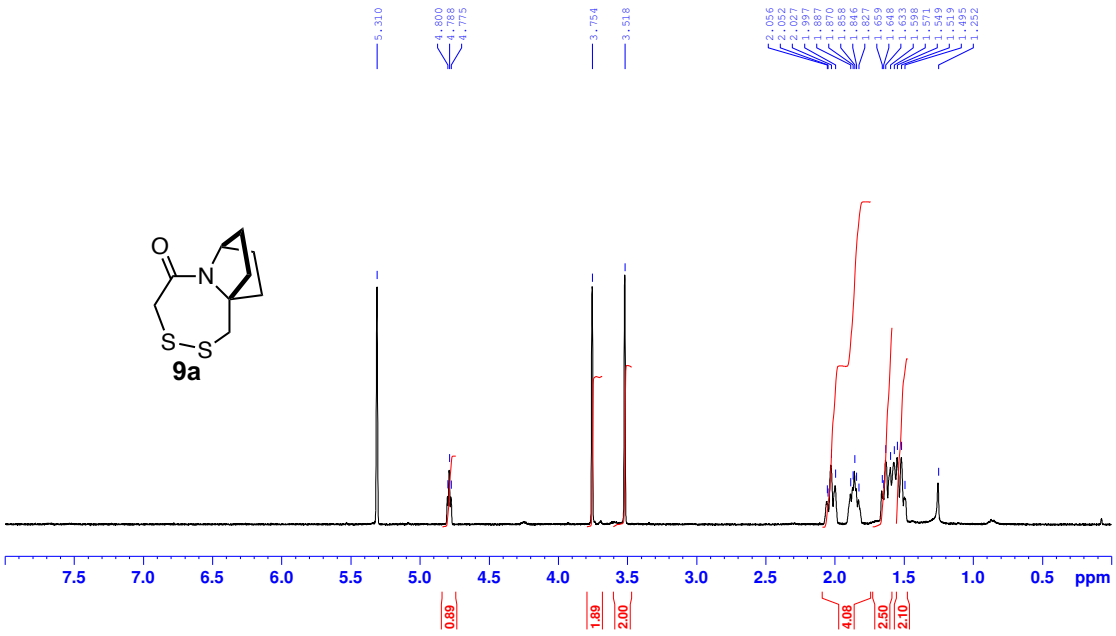


Figure S51. ^{1}H NMR spectrum of **9a** in CD_2Cl_2.

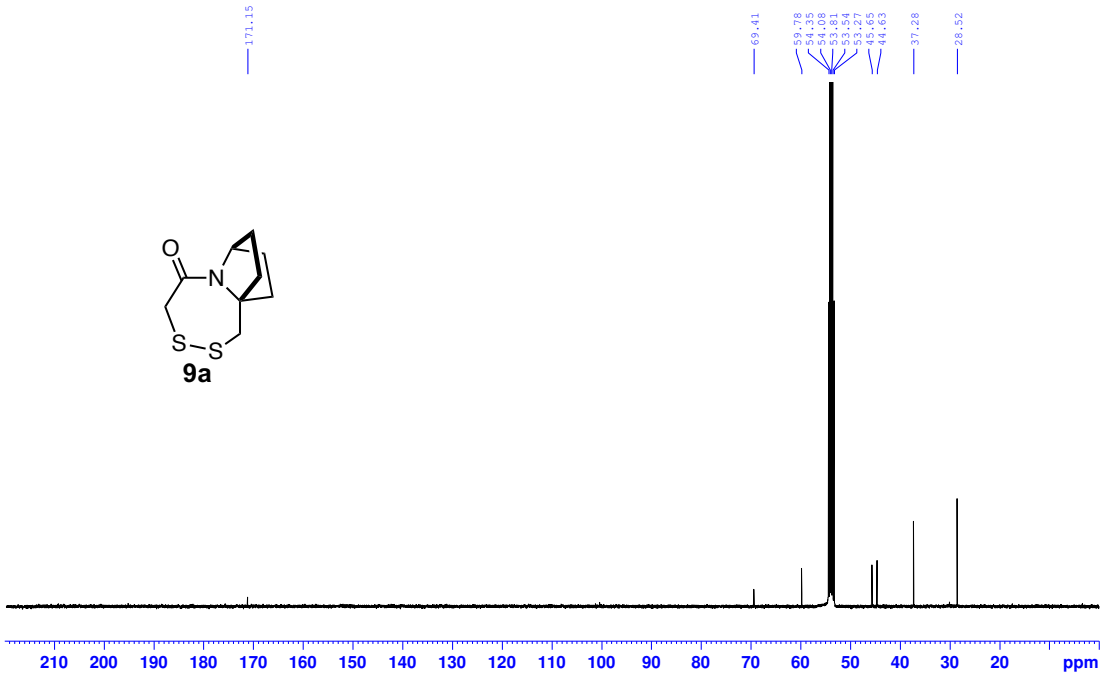


Figure S52. ^{13}C NMR spectrum of **9a** in CD_2Cl_2.

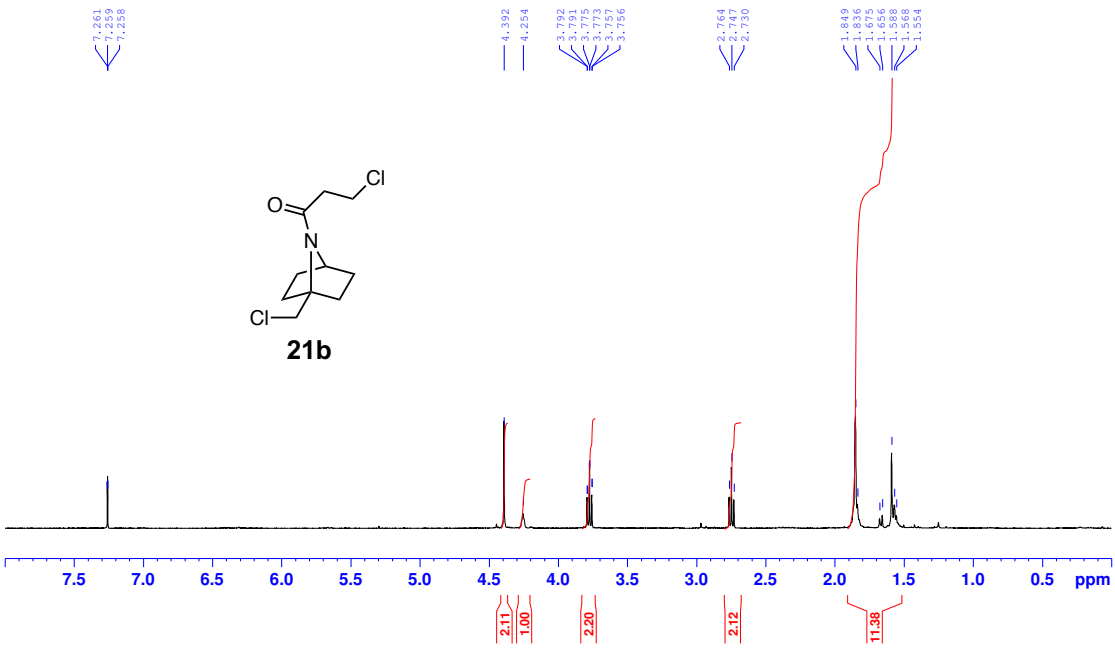


Figure S53. ^{1}H NMR spectrum of **21b** in $CDCl_3$.

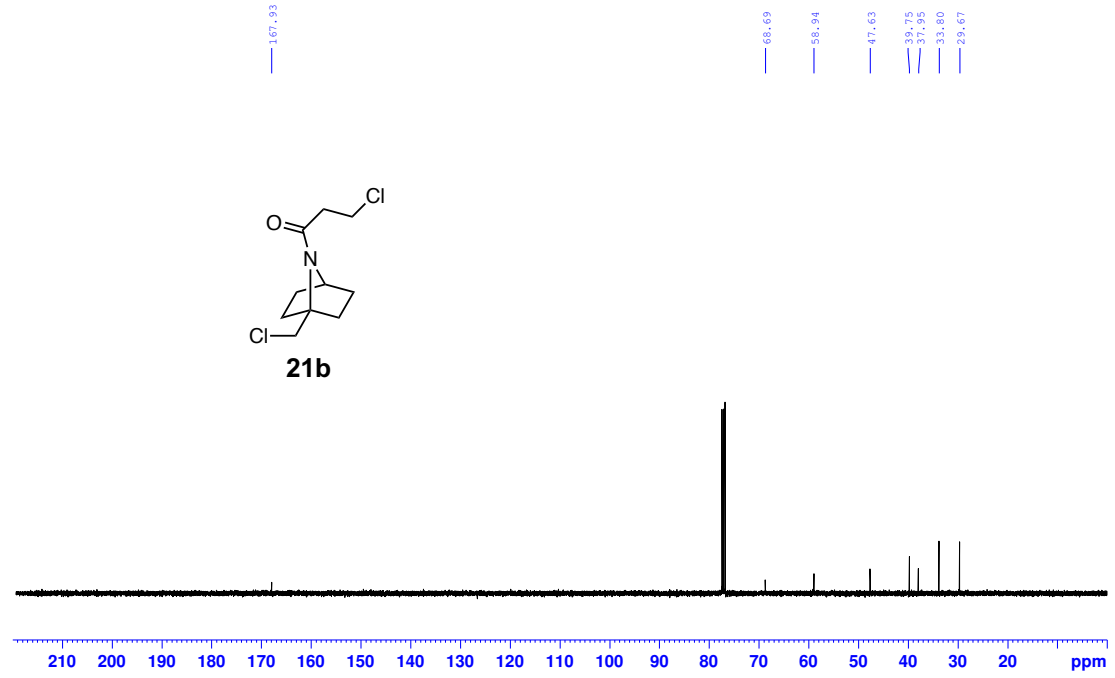


Figure S54. ^{13}C NMR spectrum of **21b** in $CDCl_3$.

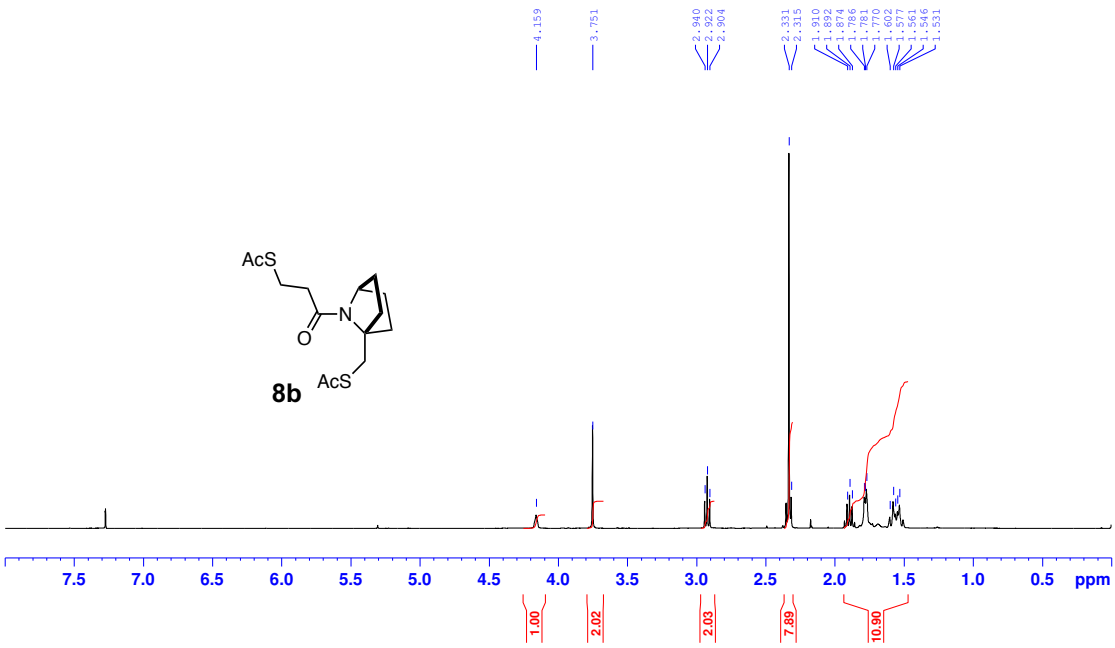


Figure S55. ^{1}H NMR spectrum of **8b** in $CDCl_3$.

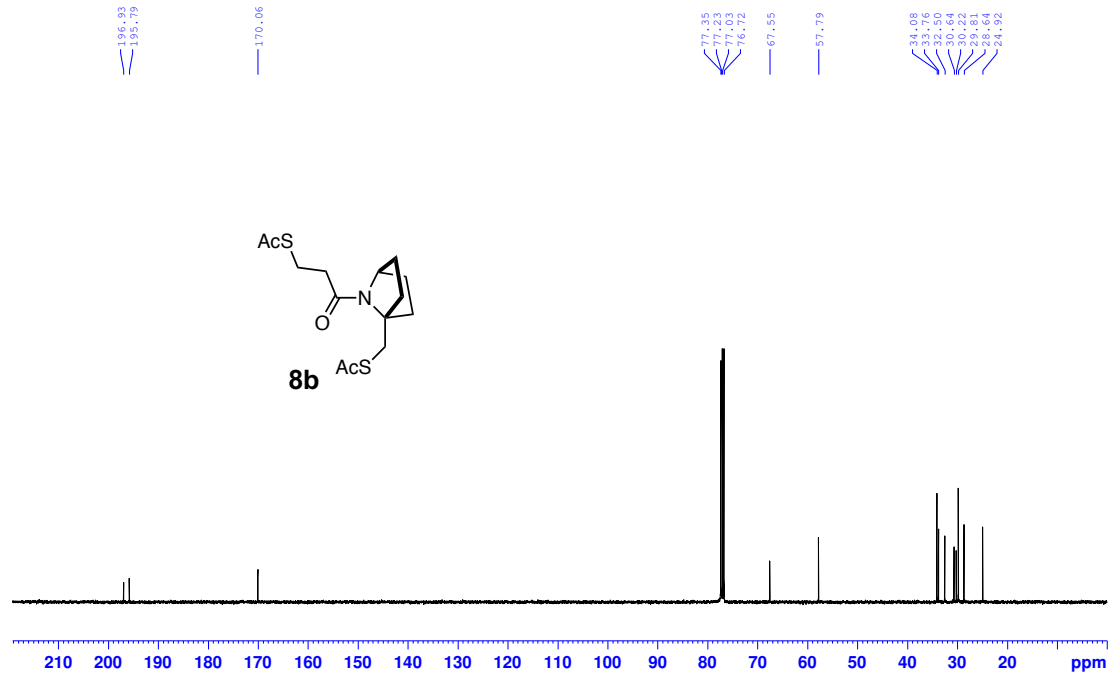


Figure S56. ^{13}C NMR spectrum of **8b** in $CDCl_3$.

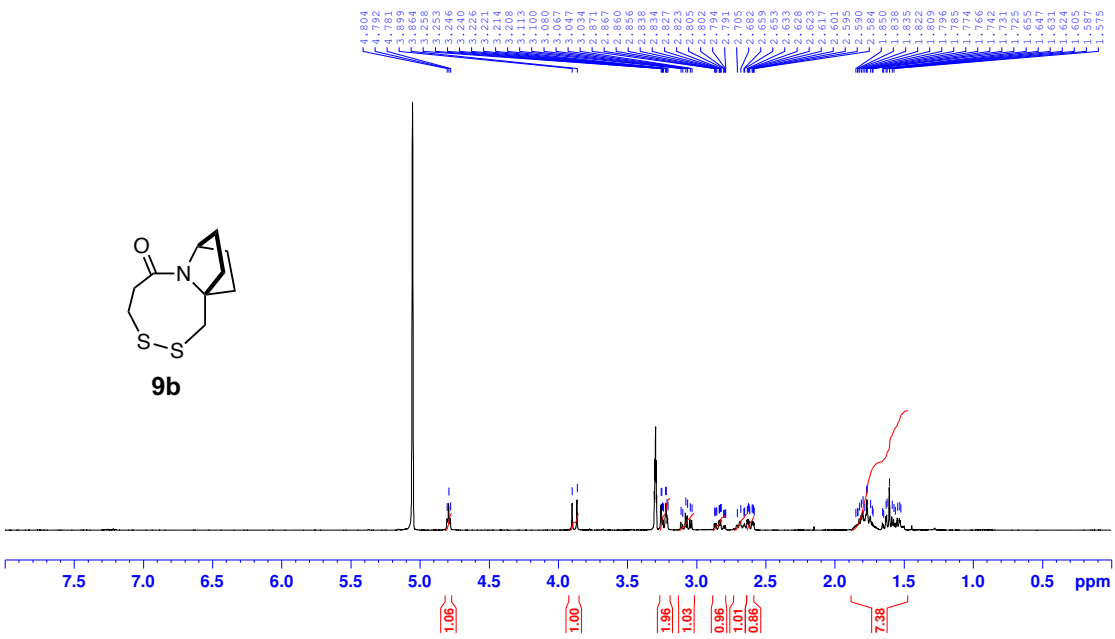


Figure S57. [1]H NMR spectrum of **21b** in MeOD at 274.4 K.

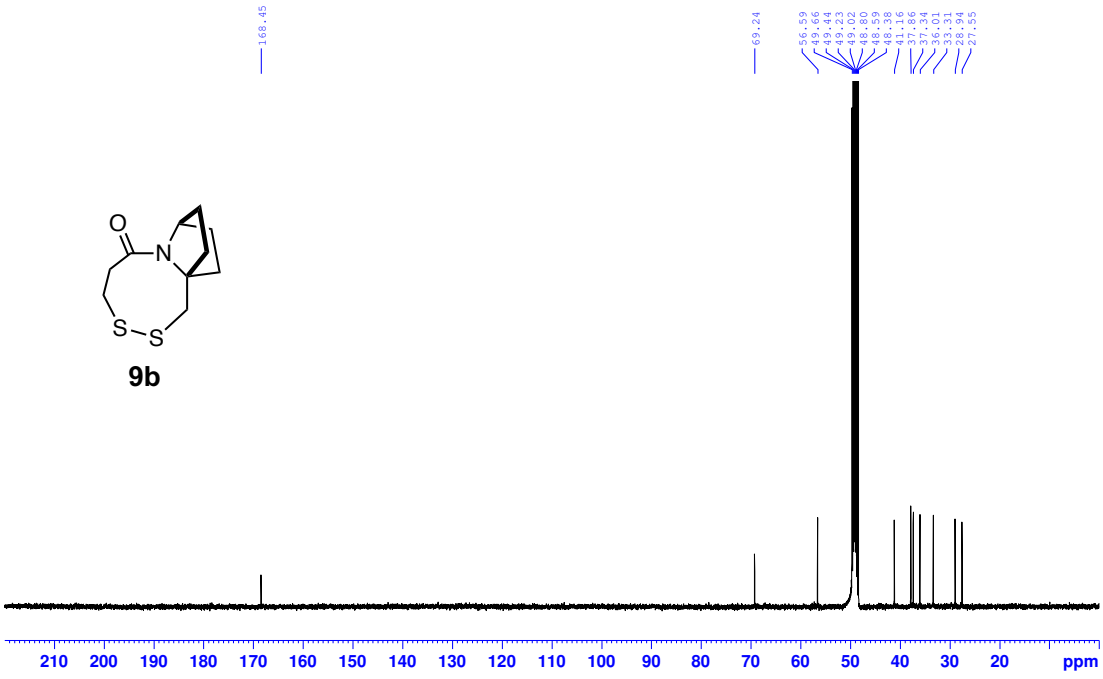


Figure S58. [13]C NMR spectrum of **9b** in MeOD at 274.4 K.

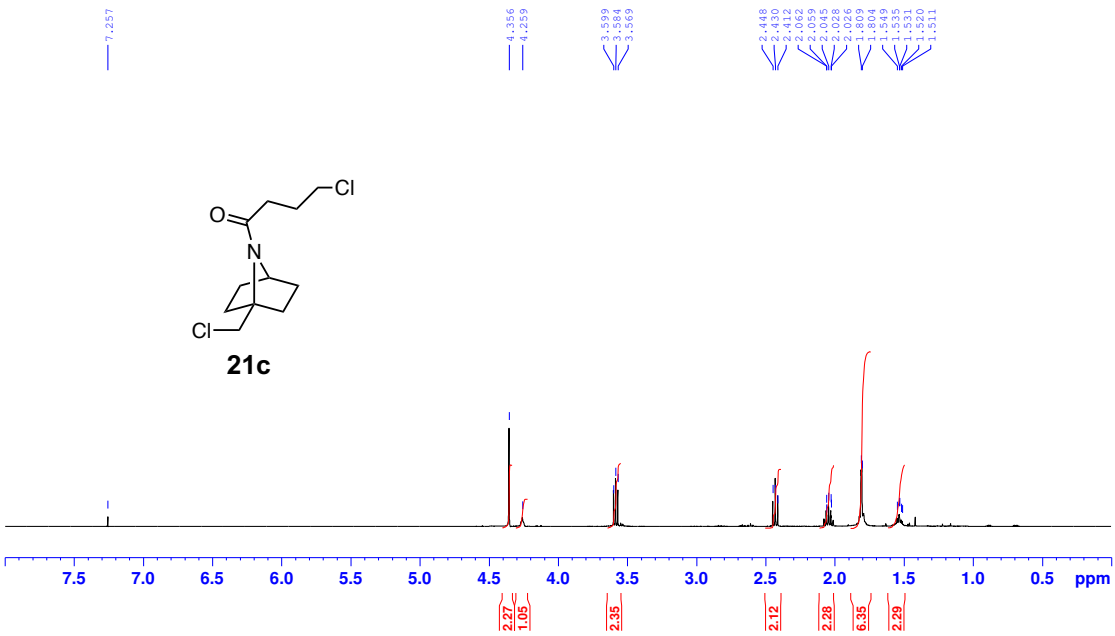


Figure S59. ^{1}H NMR spectrum of **21c** in $CDCl_3$.

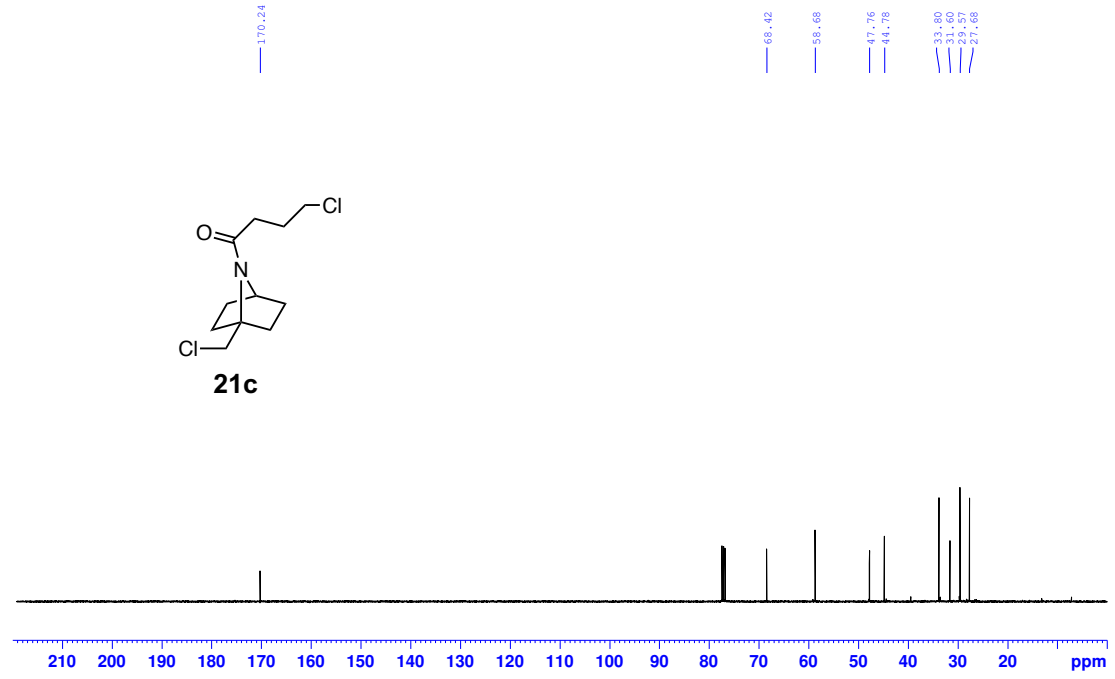


Figure S60. ^{13}C NMR spectrum of **21c** in $CDCl_3$.

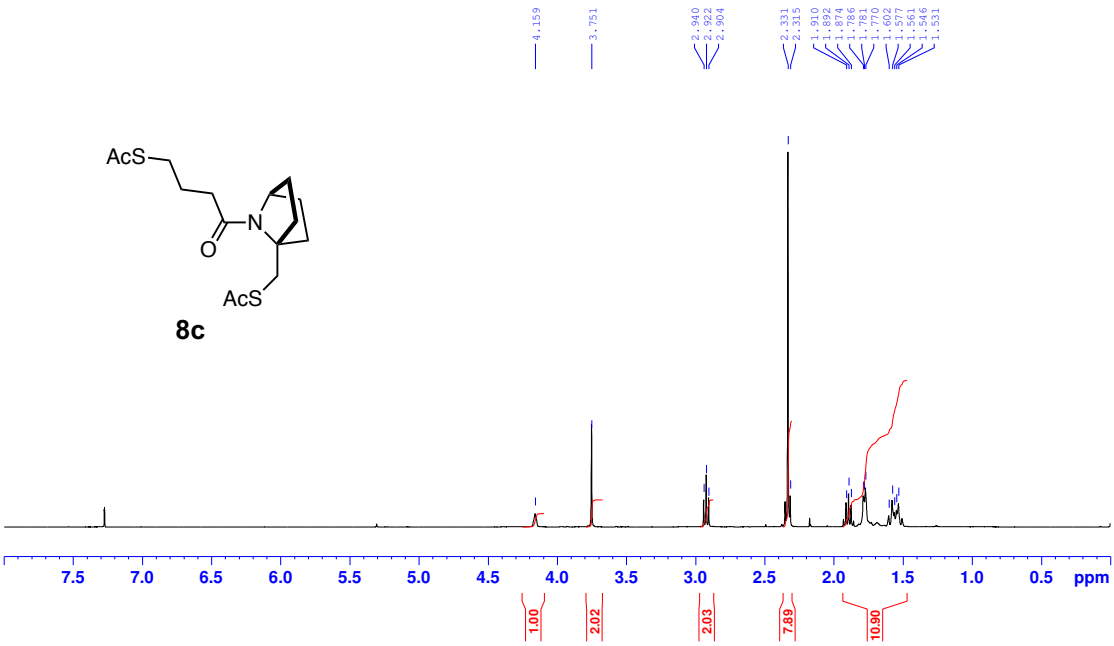


Figure S61. ^{1}H NMR spectrum of **8c** in $CDCl_3$.

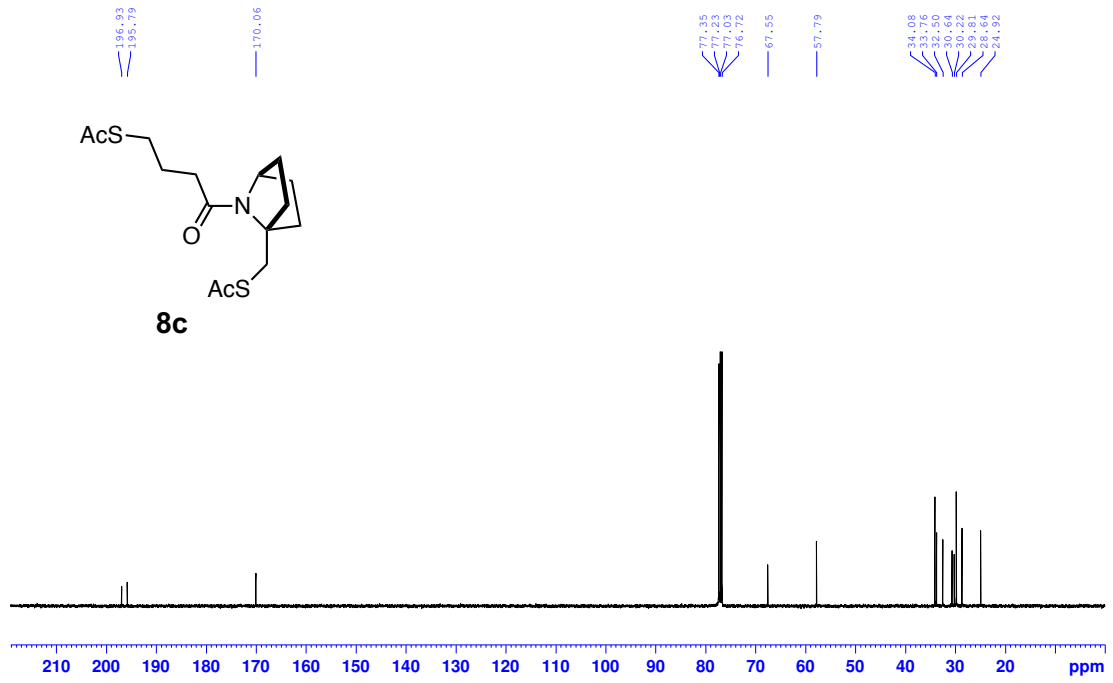


Figure S62. ^{13}C NMR spectrum of **8c** in $CDCl_3$.

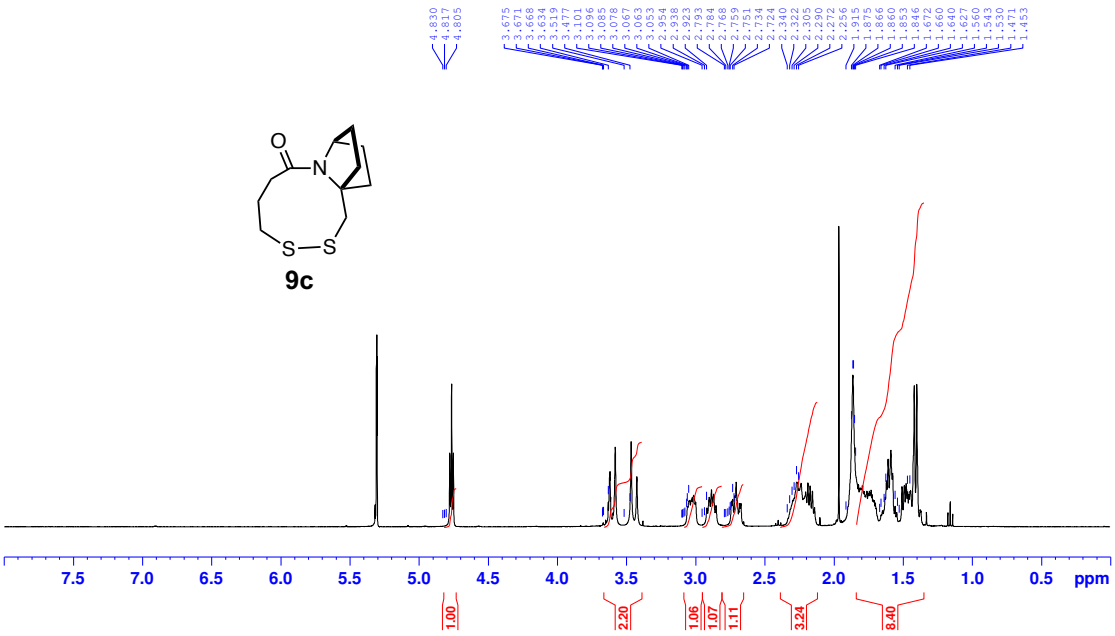


Figure S63. ^{1}H NMR spectrum of **9c** in CD_2Cl_2 at 274.6 K.

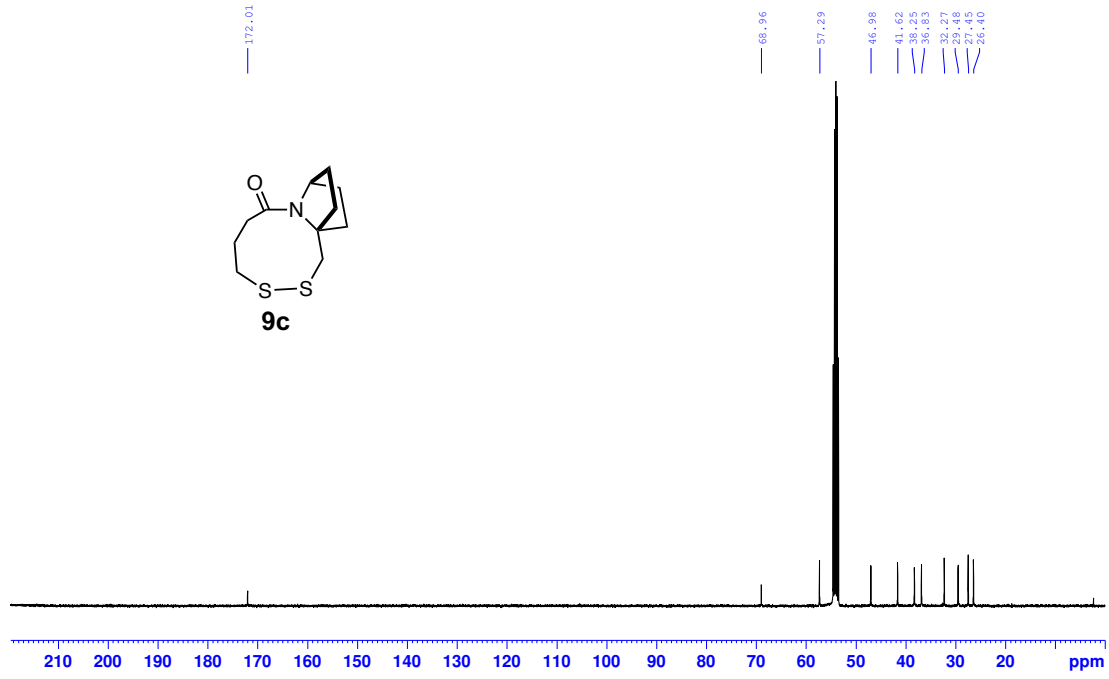


Figure S64. ^{13}C NMR spectrum of **9c** in CD_2Cl_2 at 274.6 K.

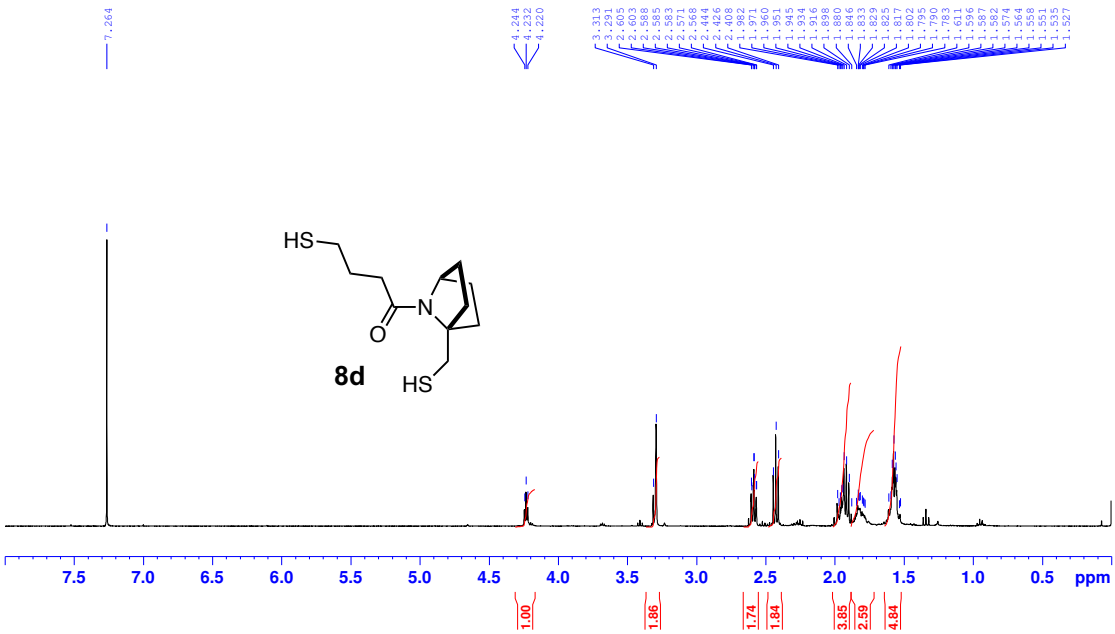


Figure S65. ^{1}H NMR spectrum of **8d** in $CDCl_3$.

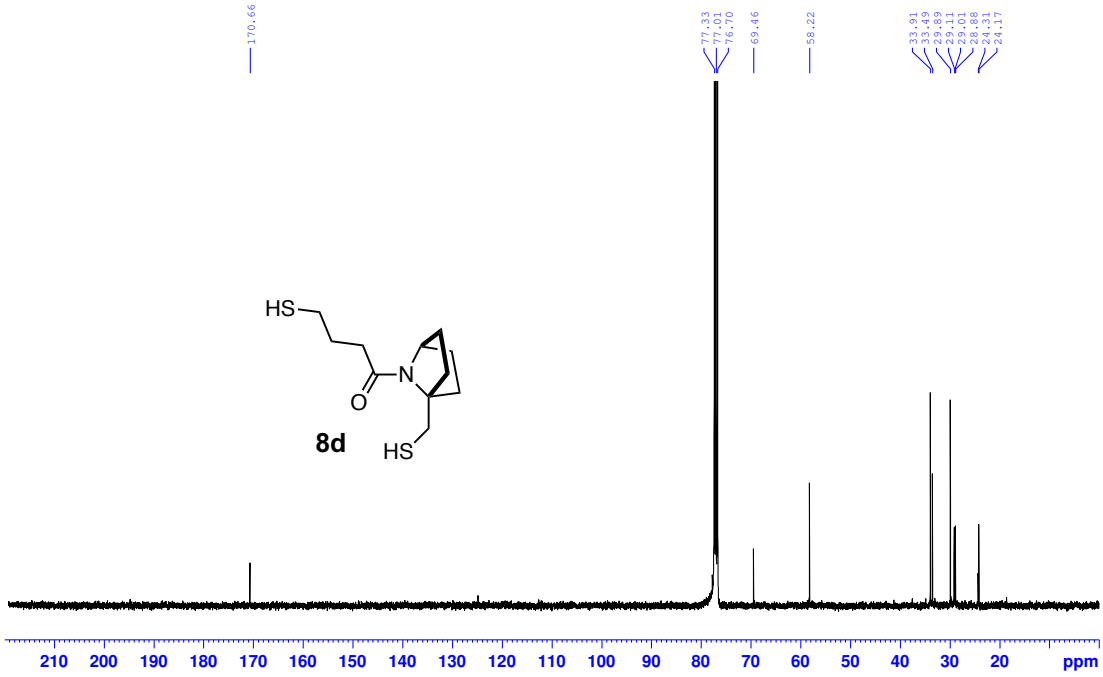


Figure S66. ^{13}C NMR spectrum of **8d** in $CDCl_3$.

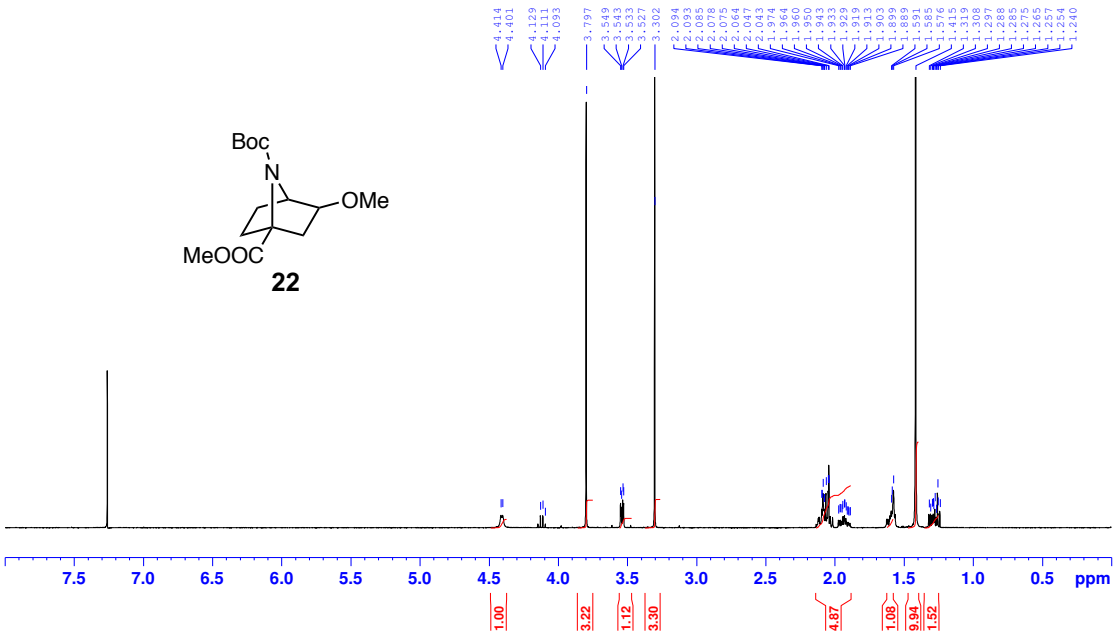


Figure S67. ^{1}H NMR spectrum of **22** in $CDCl_3$.

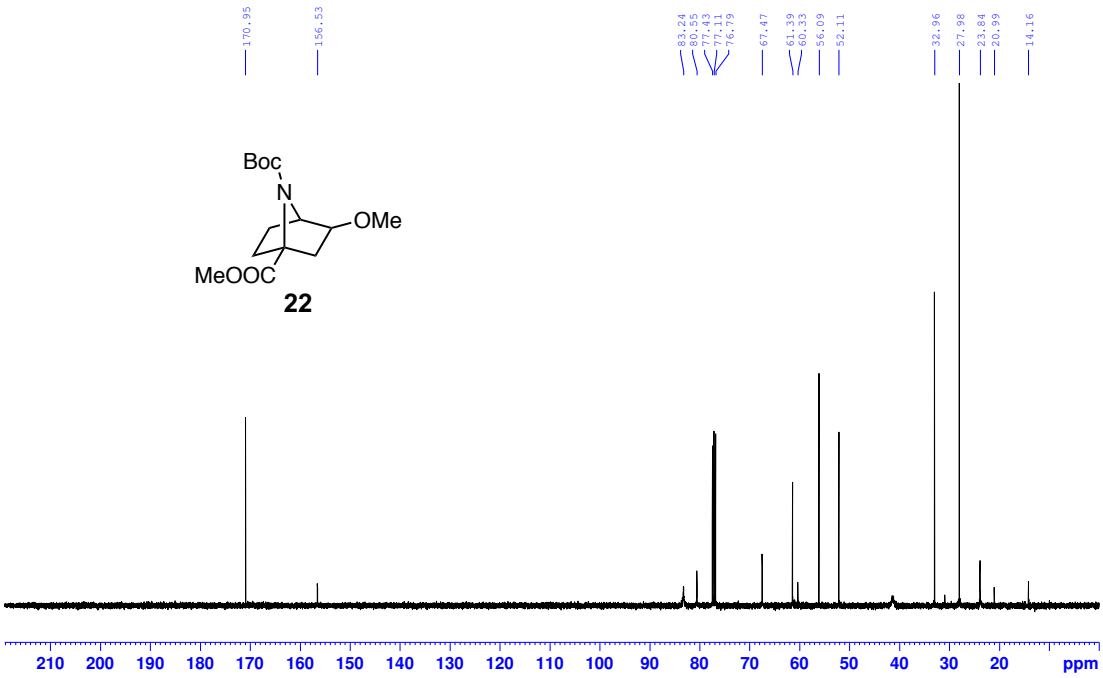


Figure S68. ^{13}C NMR spectrum of **22** in $CDCl_3$.

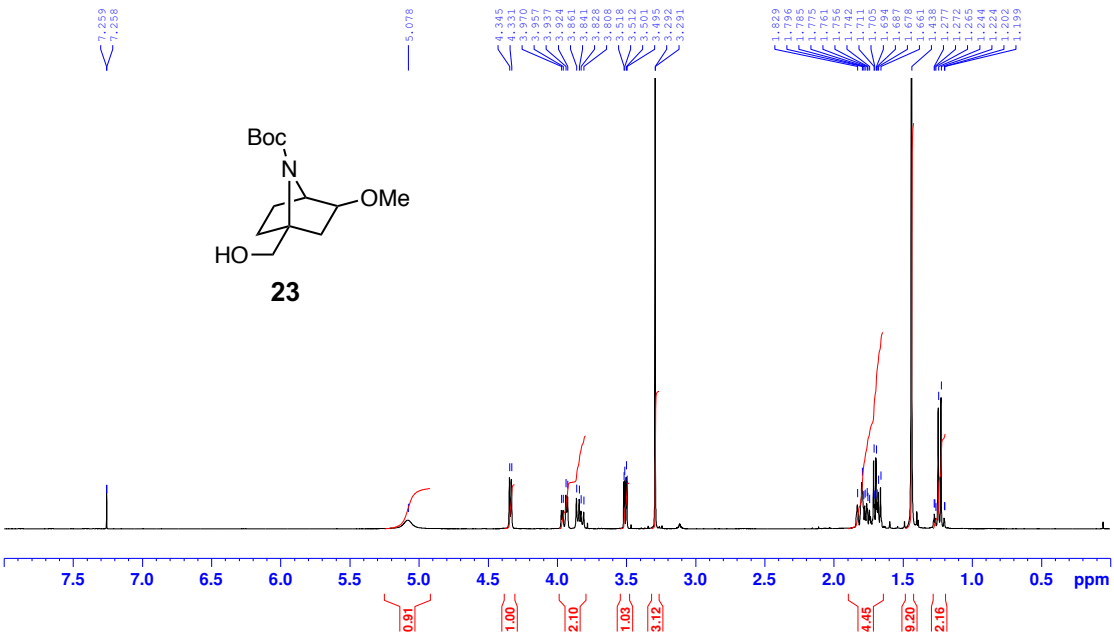


Figure S69. ^{1}H NMR spectrum of **23** in $CDCl_3$.

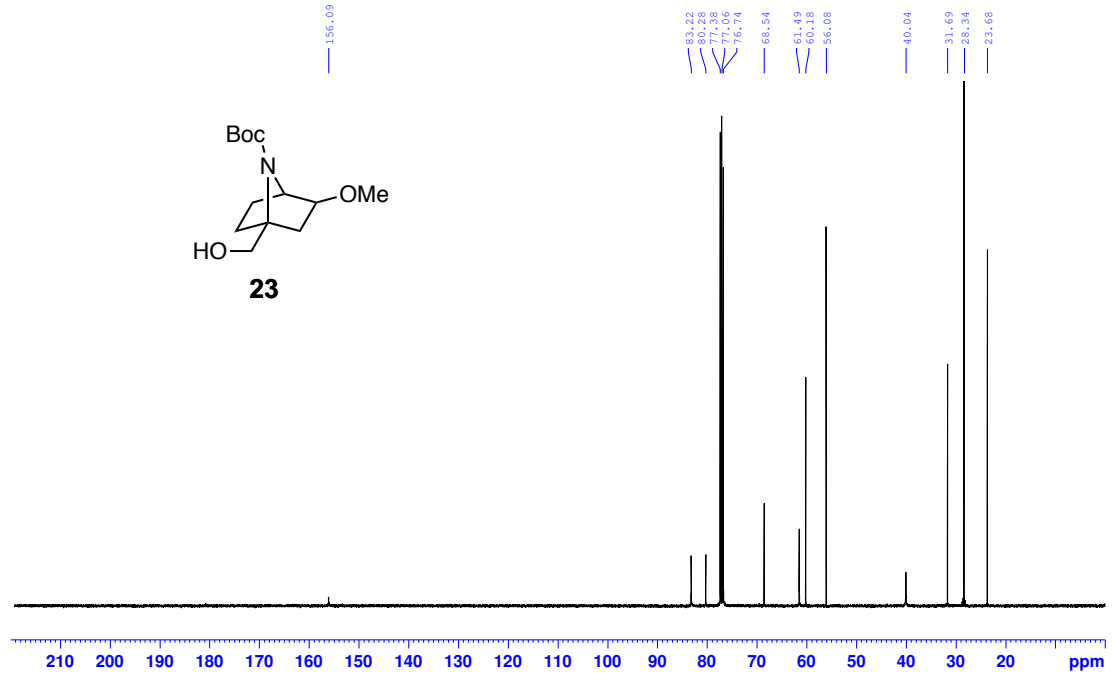


Figure S70. ^{13}C NMR spectrum of **23** in $CDCl_3$.

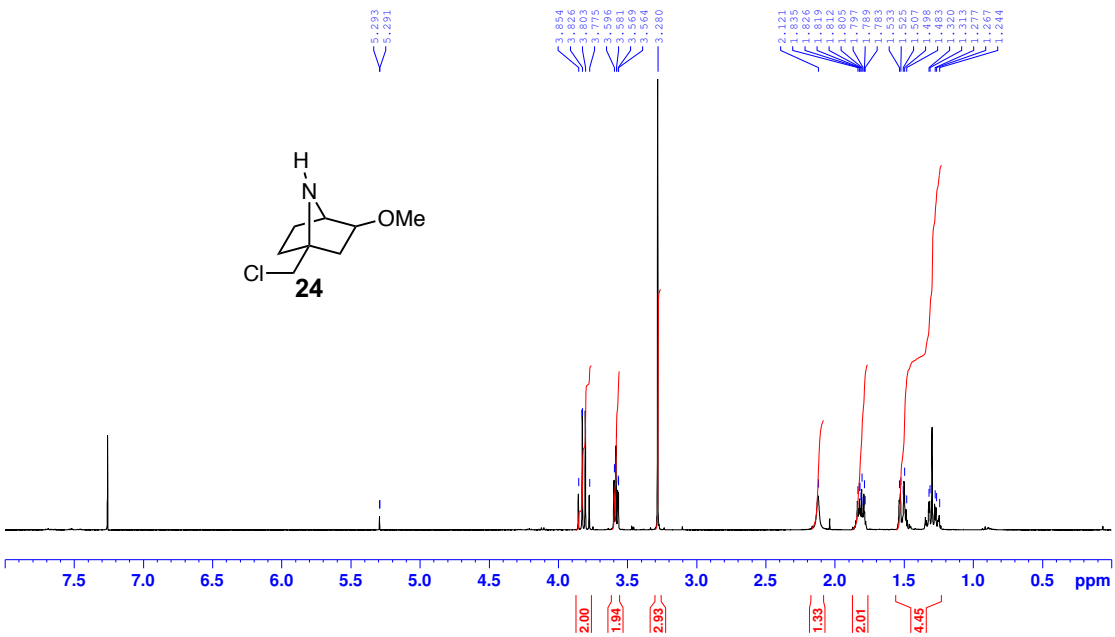


Figure S71. ^{1}H NMR spectrum of **24** in $CDCl_3$.

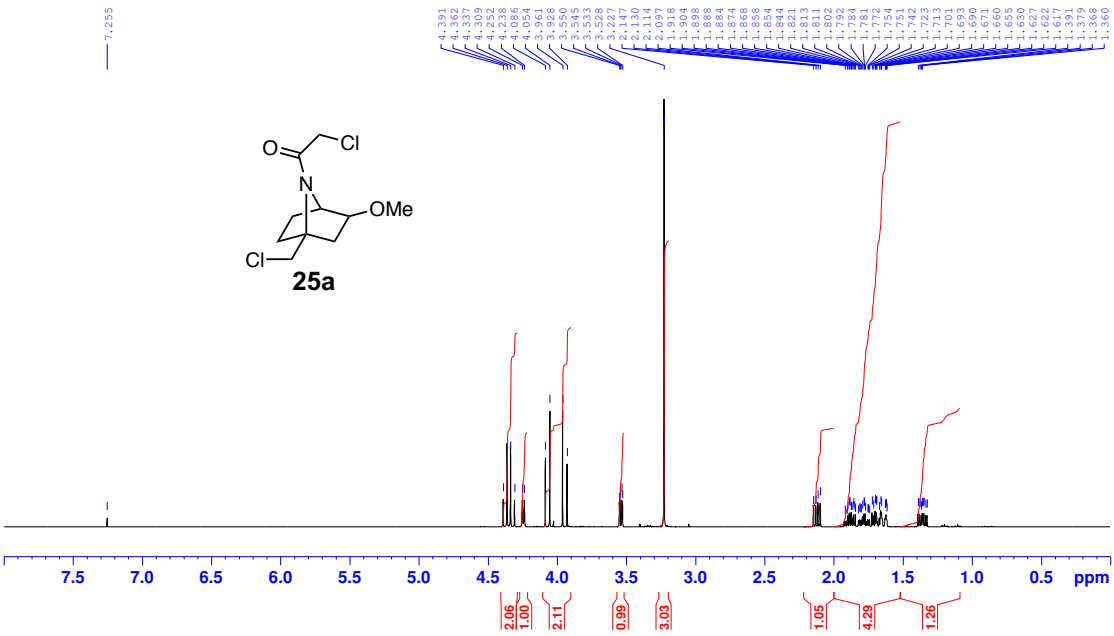


Figure S72. ^{1}H NMR spectrum of **25a** in $CDCl_3$.

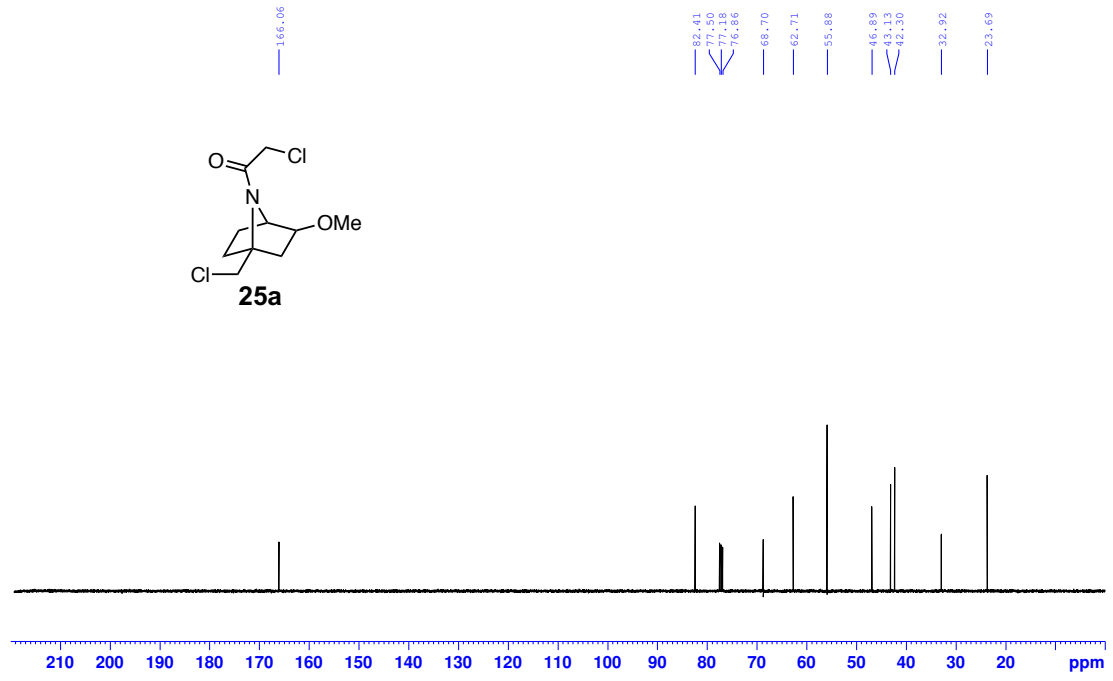


Figure S73. ^{13}C NMR spectrum of **25a** in $CDCl_3$.

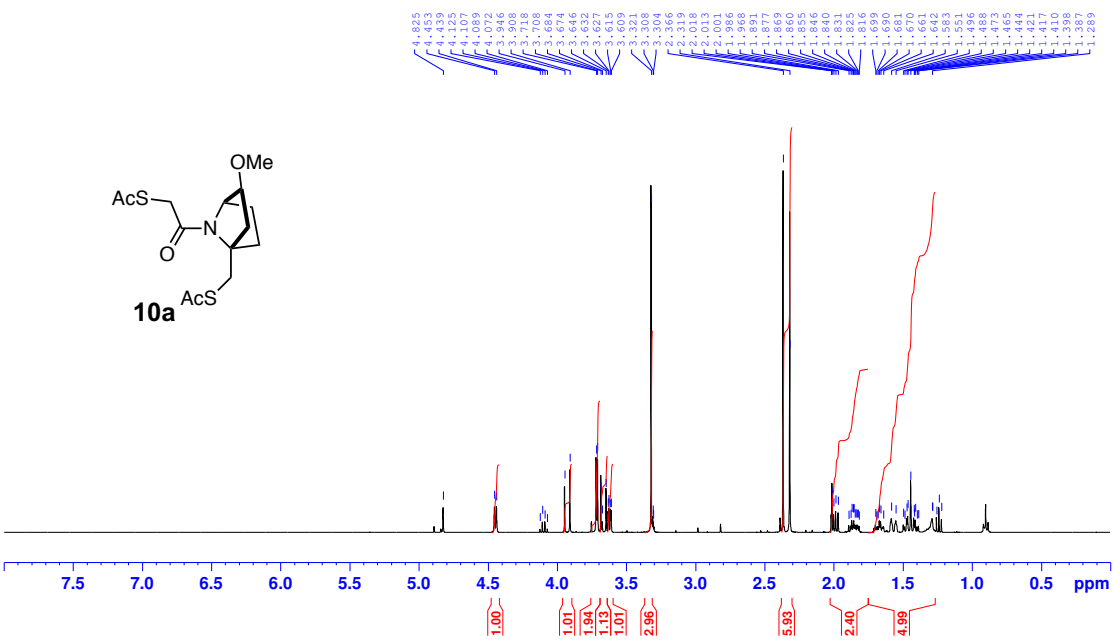


Figure S74. [1]H NMR spectrum of **10a** in MeOD.

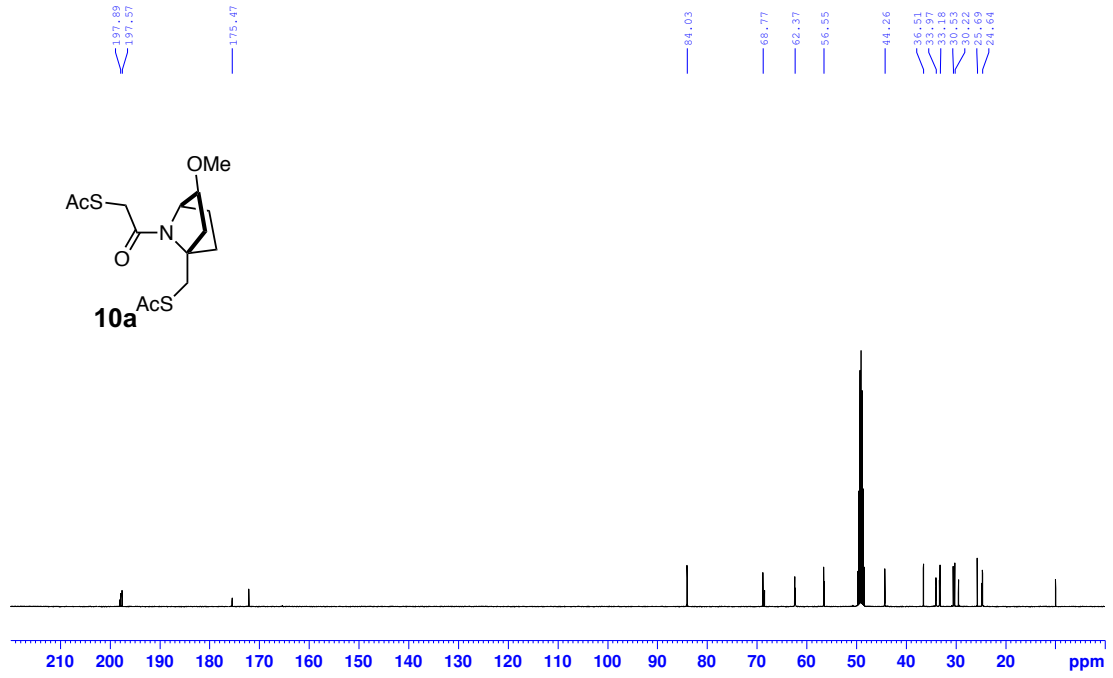


Figure S75. [13]C NMR spectrum of **10a** in MeOD.

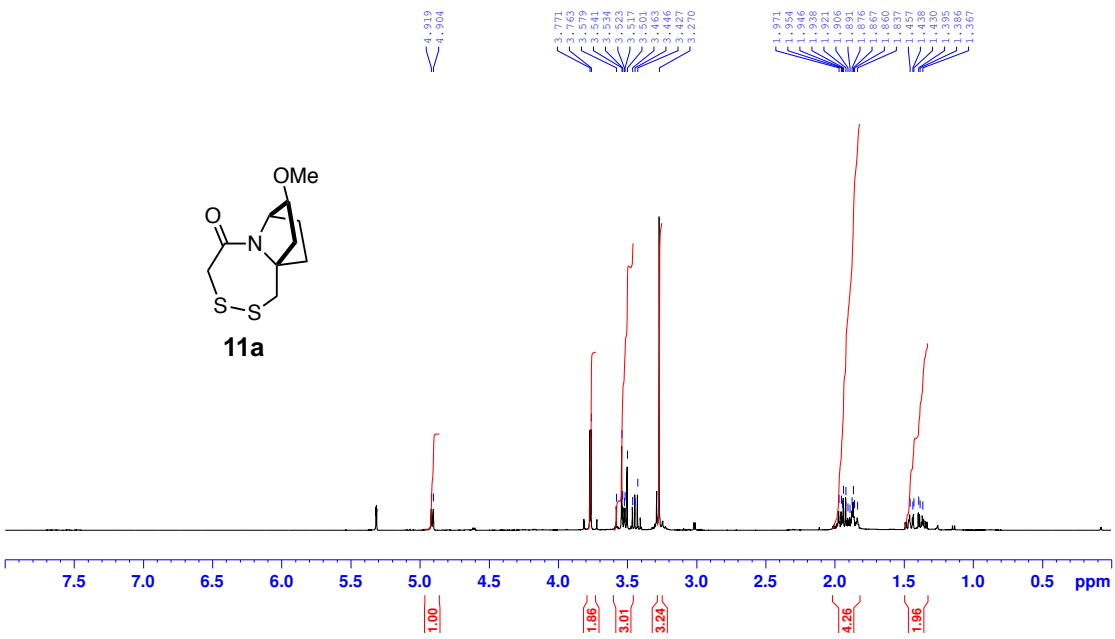


Figure S76. ^{1}H NMR spectrum of **11a** in CD_2Cl_2.

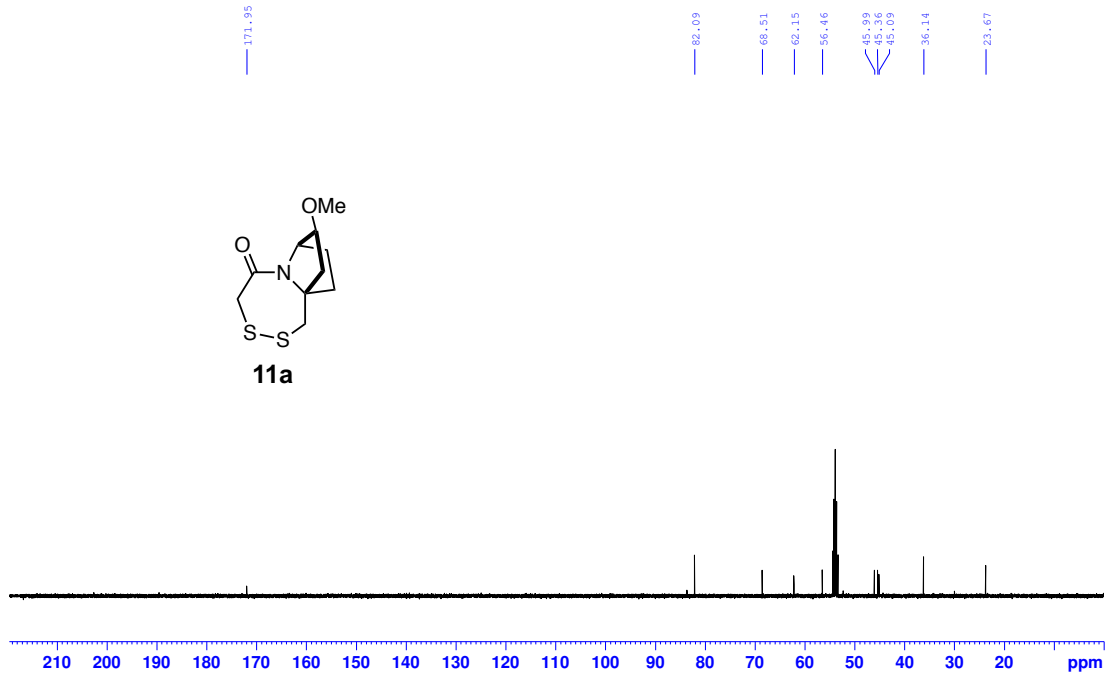


Figure S77. ^{13}C NMR spectrum of **11a** in CD_2Cl_2.

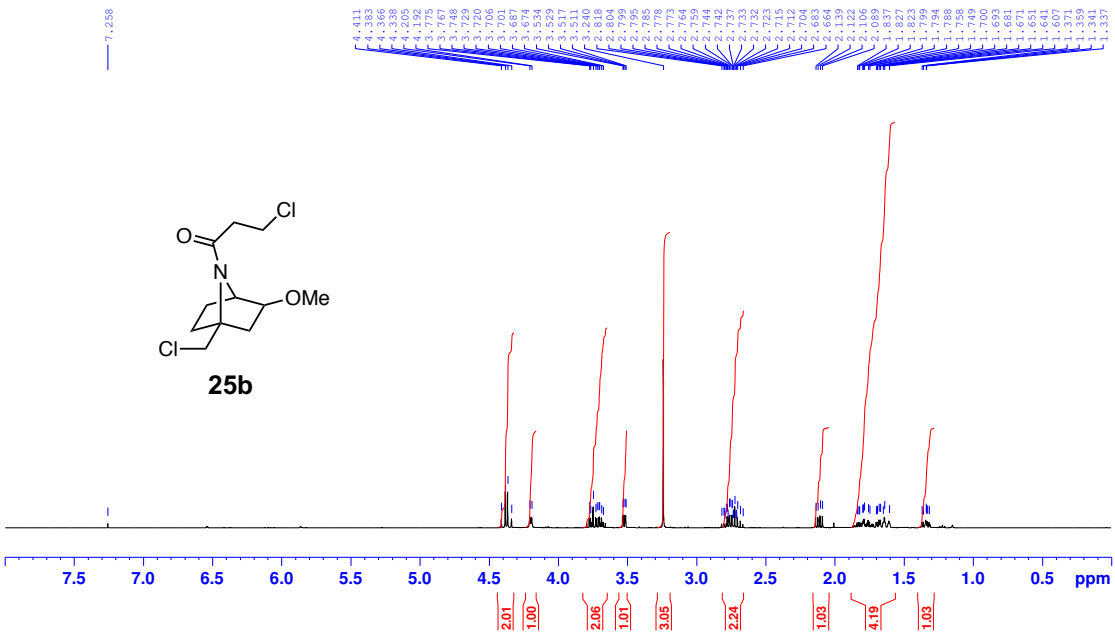


Figure S78. ^{1}H NMR spectrum of **25b** in $CDCl_3$.

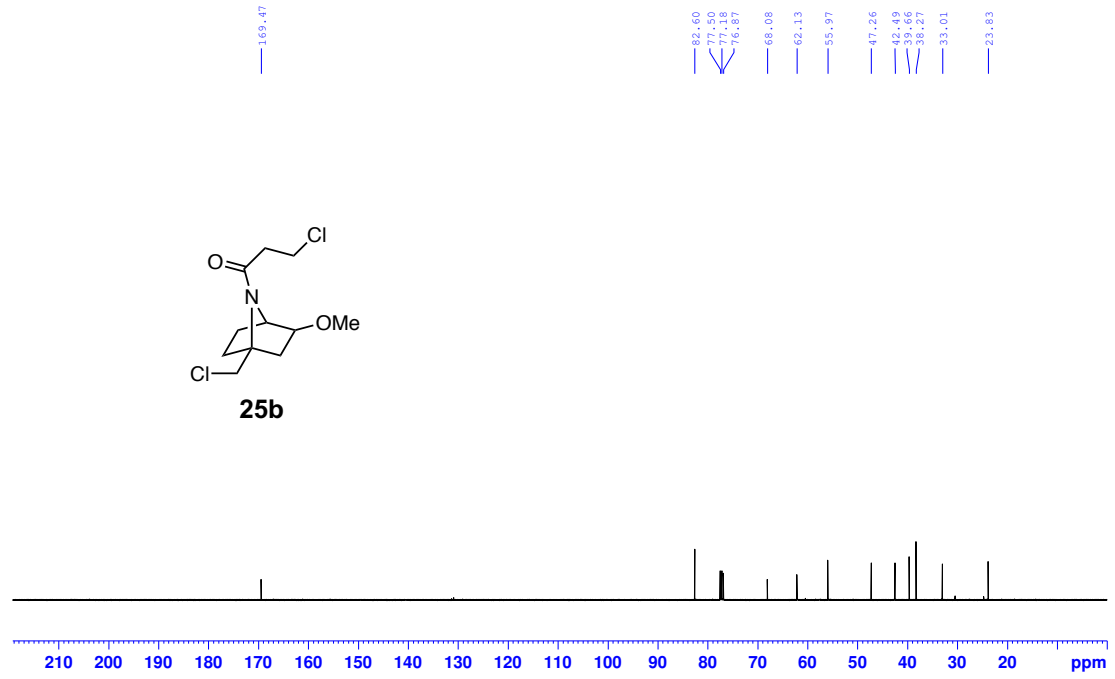


Figure S79. ^{13}C NMR spectrum of **25b** in $CDCl_3$.

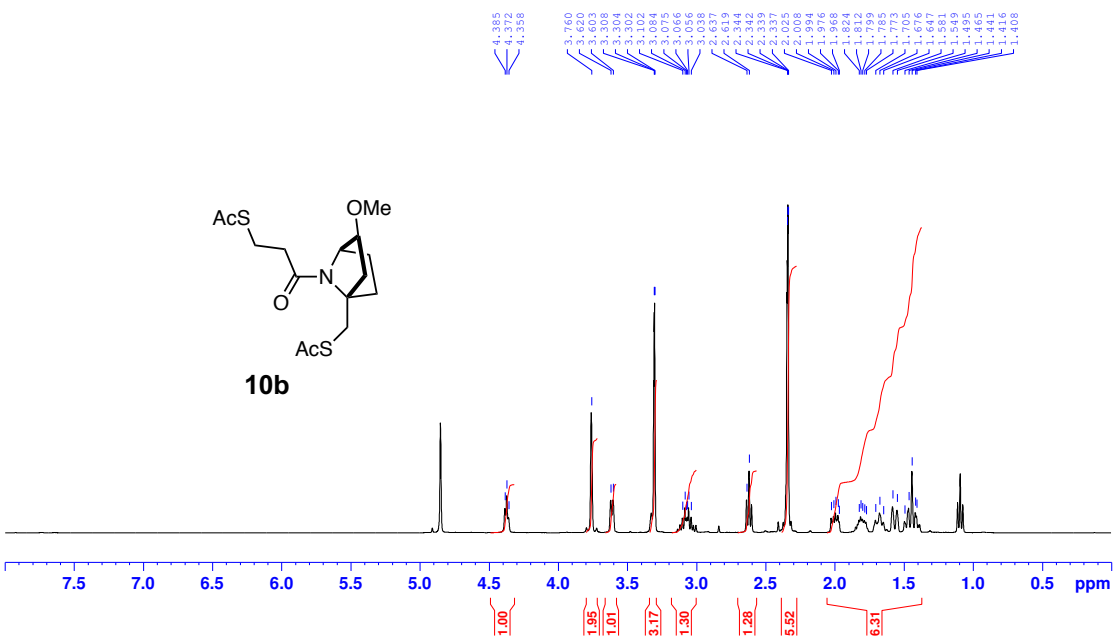


Figure S80. [1]H NMR spectrum of **10b** in MeOD.

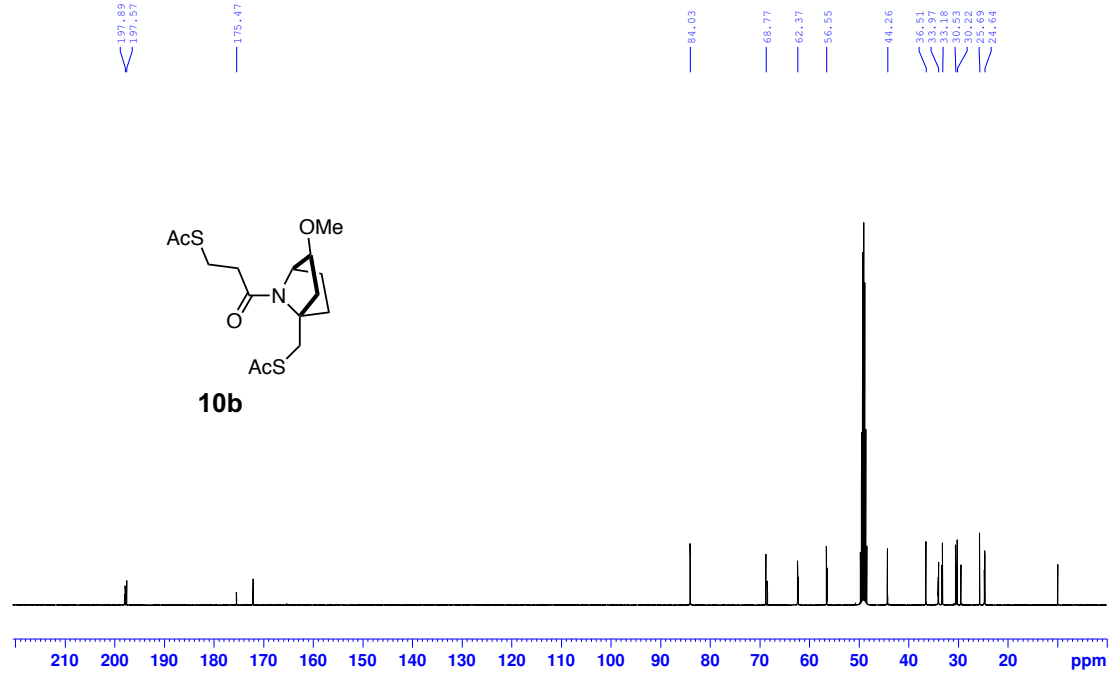


Figure S81. [13]C NMR spectrum of **10b** in MeOD.

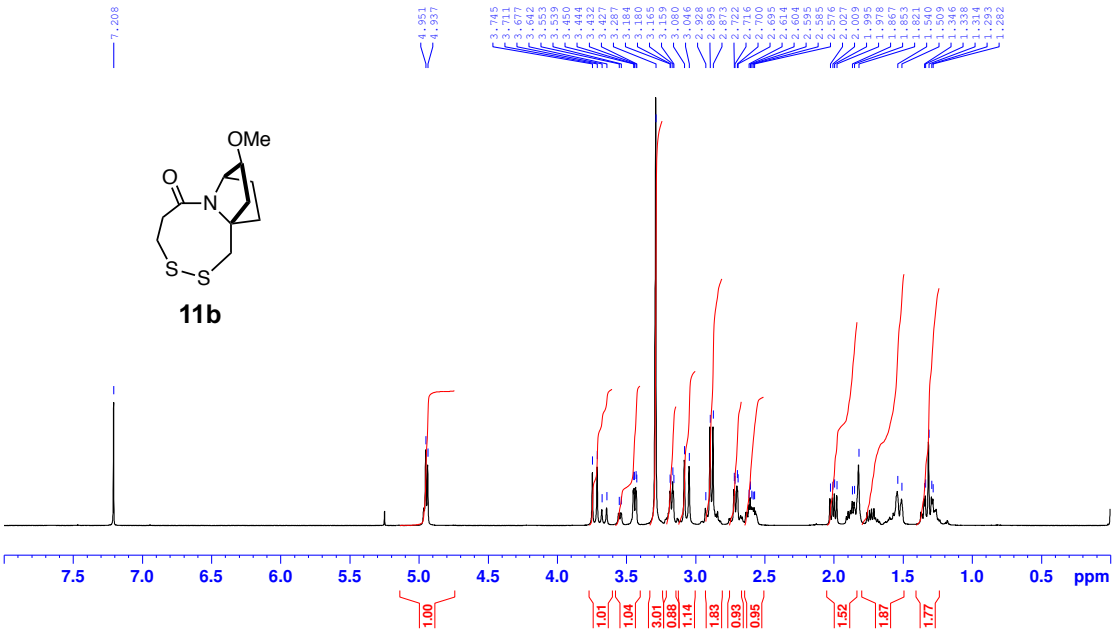


Figure S82. ^{1}H NMR spectrum of **11b** in $CDCl_3$ at 274.6 K.

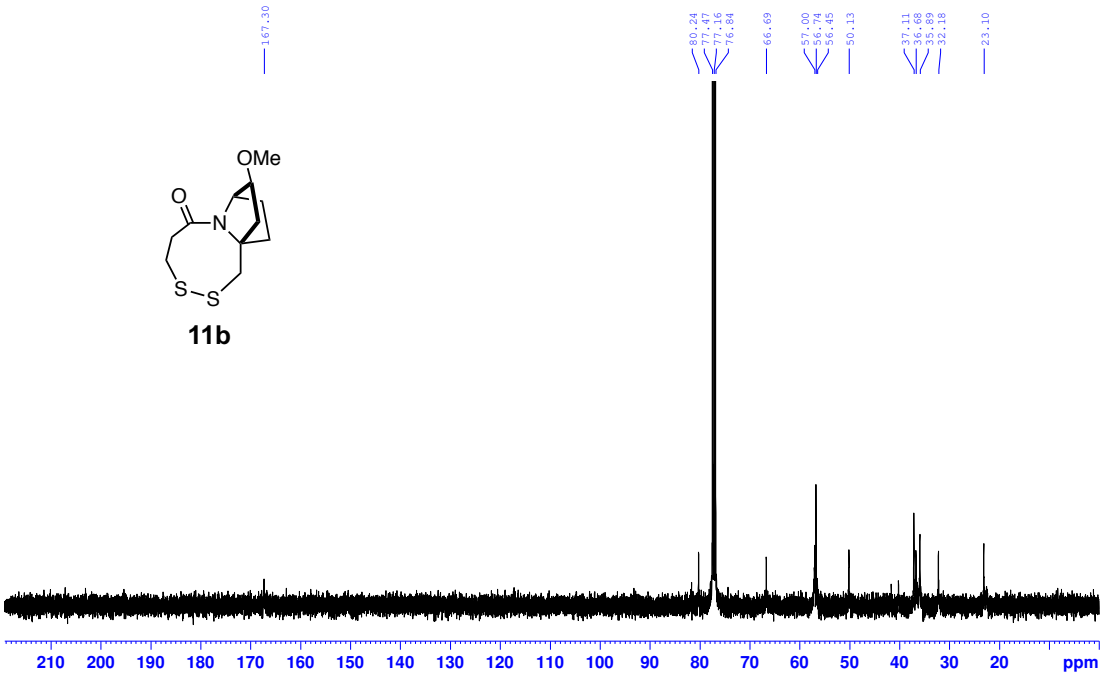


Figure S83. ^{13}C NMR spectrum of **11b** in $CDCl_3$ at 274.6 K.

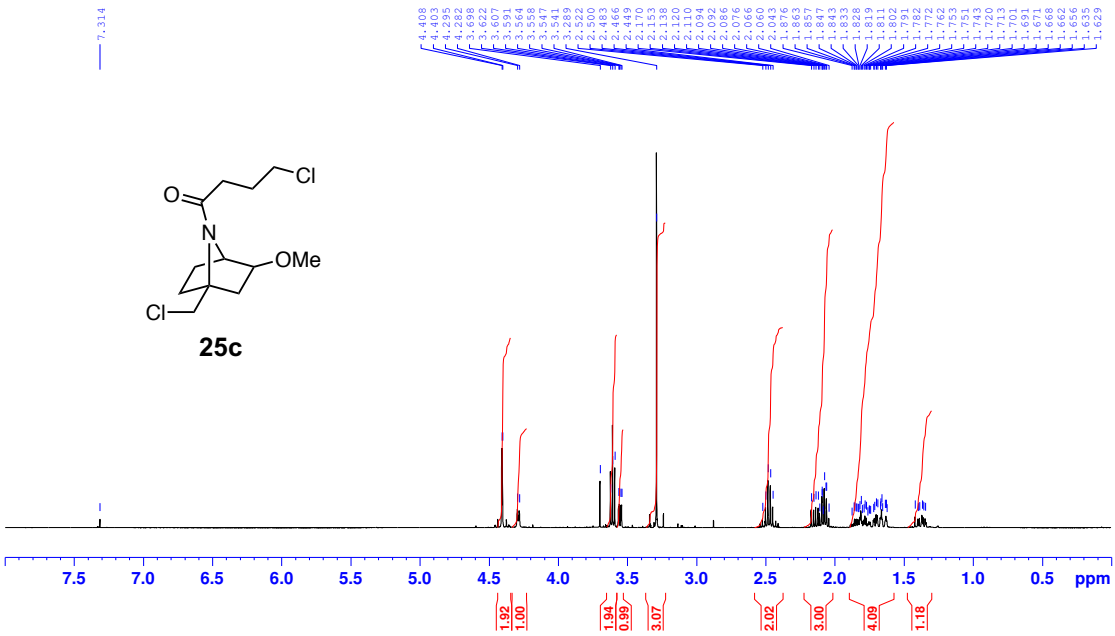


Figure S84. ^{1}H NMR spectrum of **25c** in $CDCl_3$.

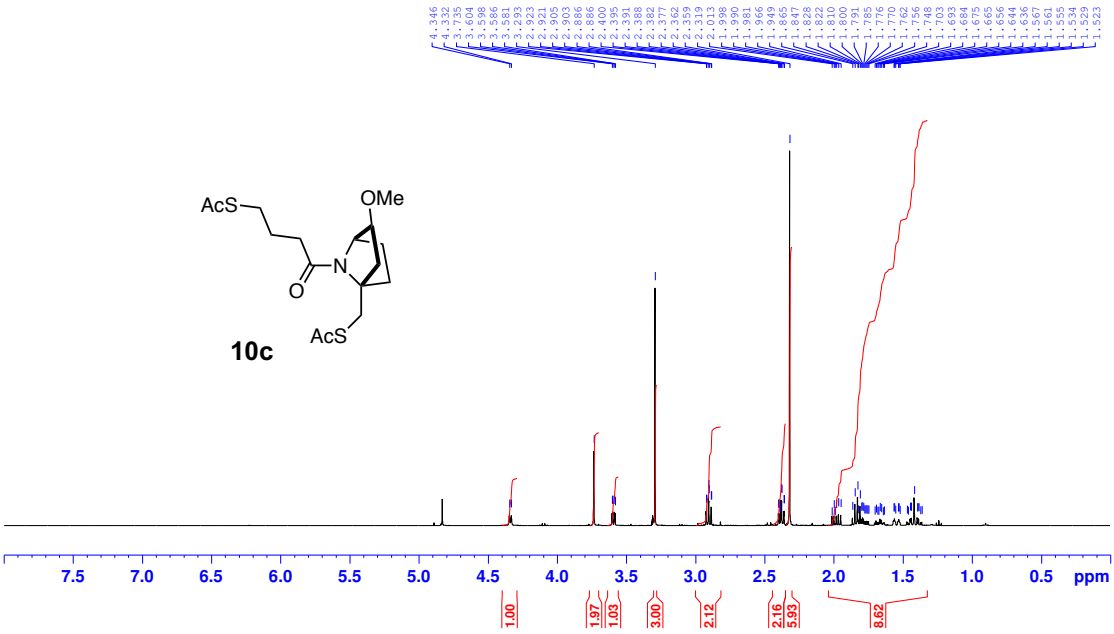


Figure S85. [1]H NMR spectrum of **10c** in MeOD.

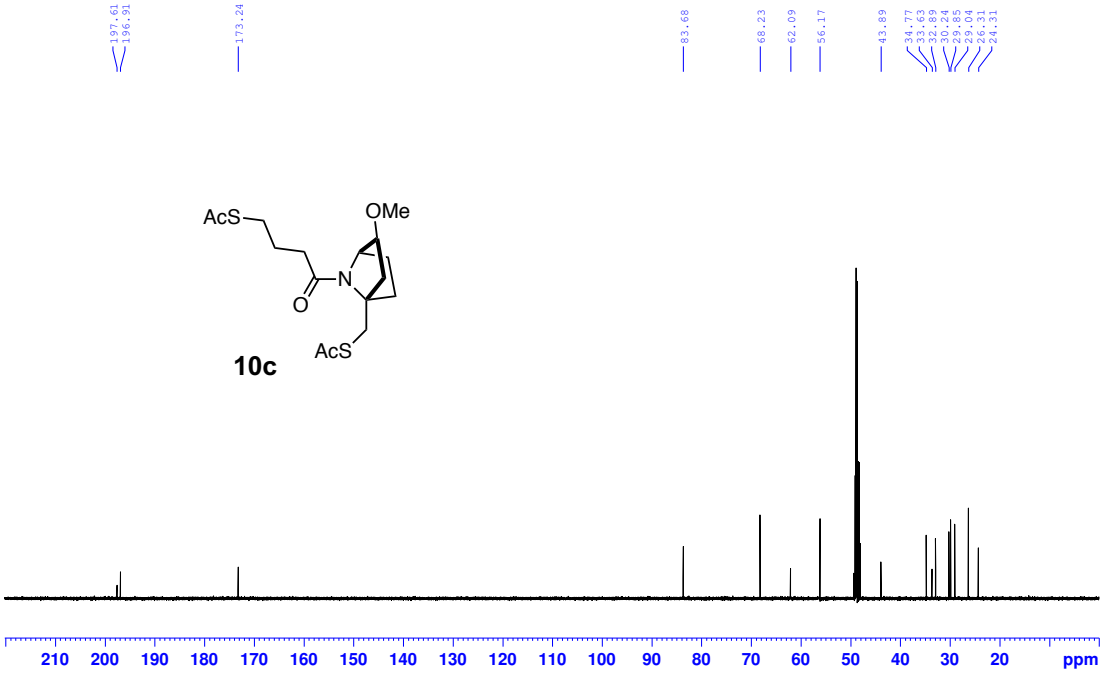


Figure S86. [13]C NMR spectrum of **10c** in MeOD.

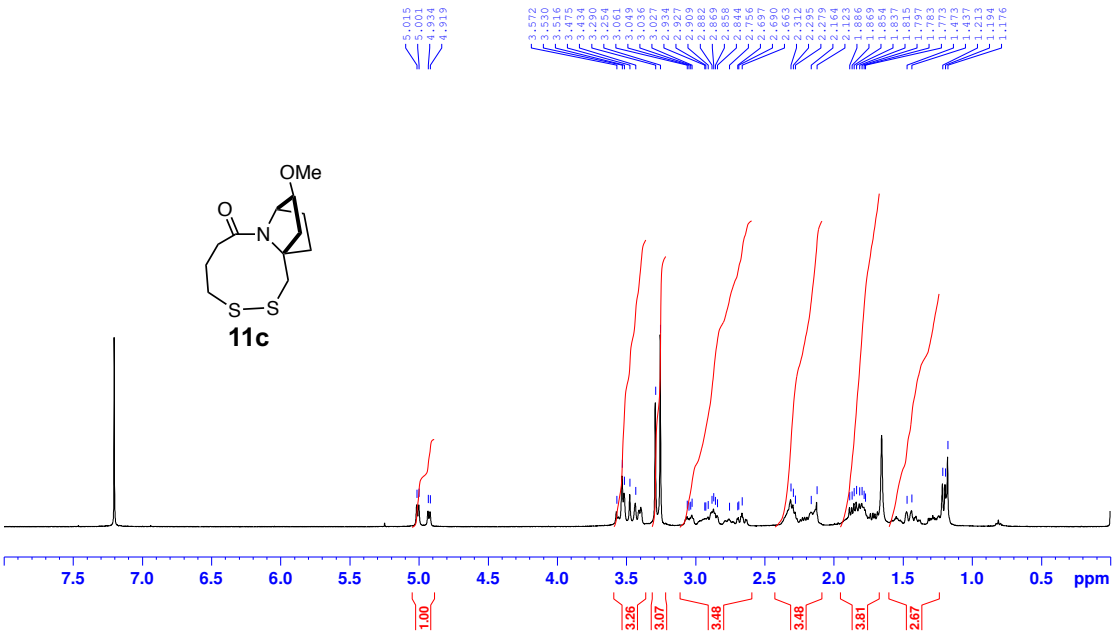


Figure S87. ^{1}H NMR spectrum of **11c** in $CDCl_3$ at 274.6K.

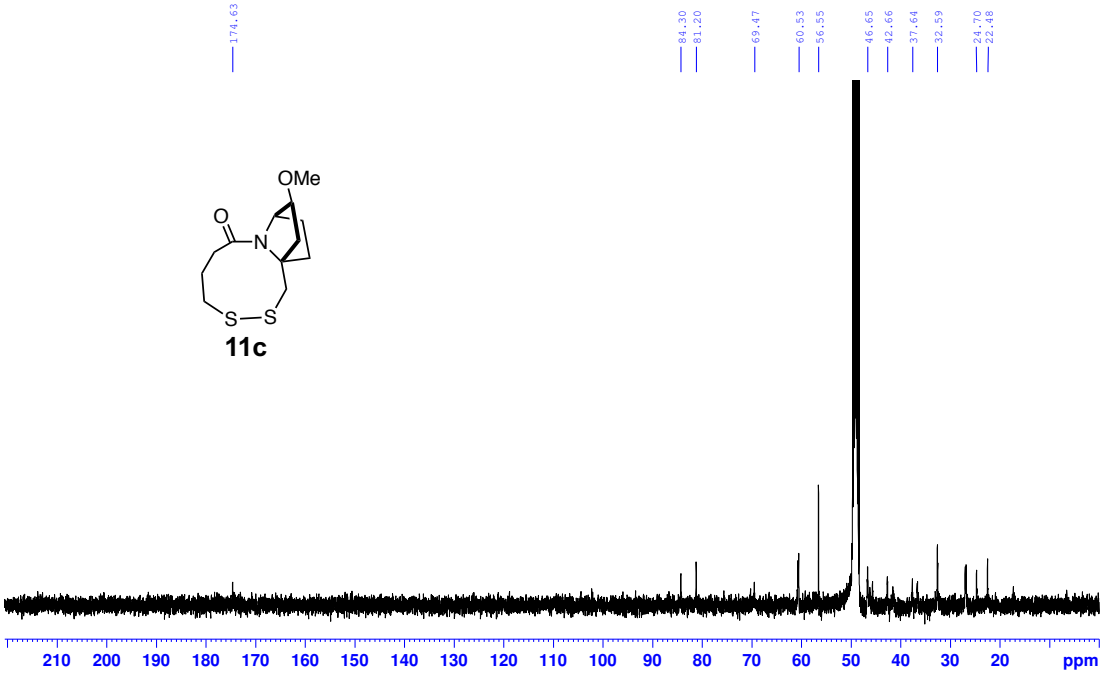


Figure S88. ^{13}C NMR spectrum of **11c** in MeOD.

4. HPLC Charts

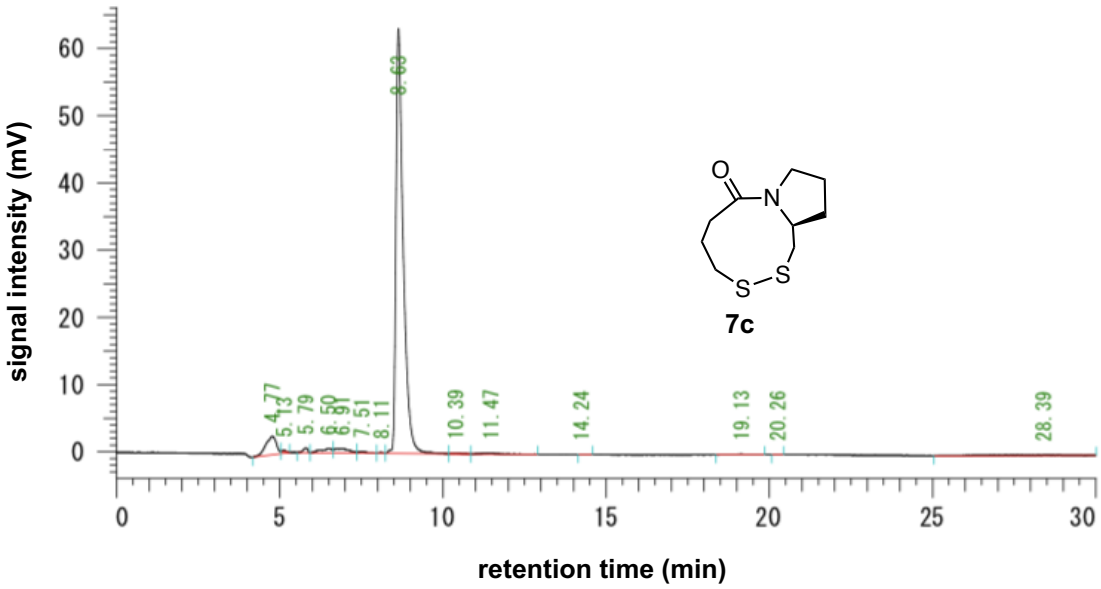


Figure S89. HPLC chart of **7c**.

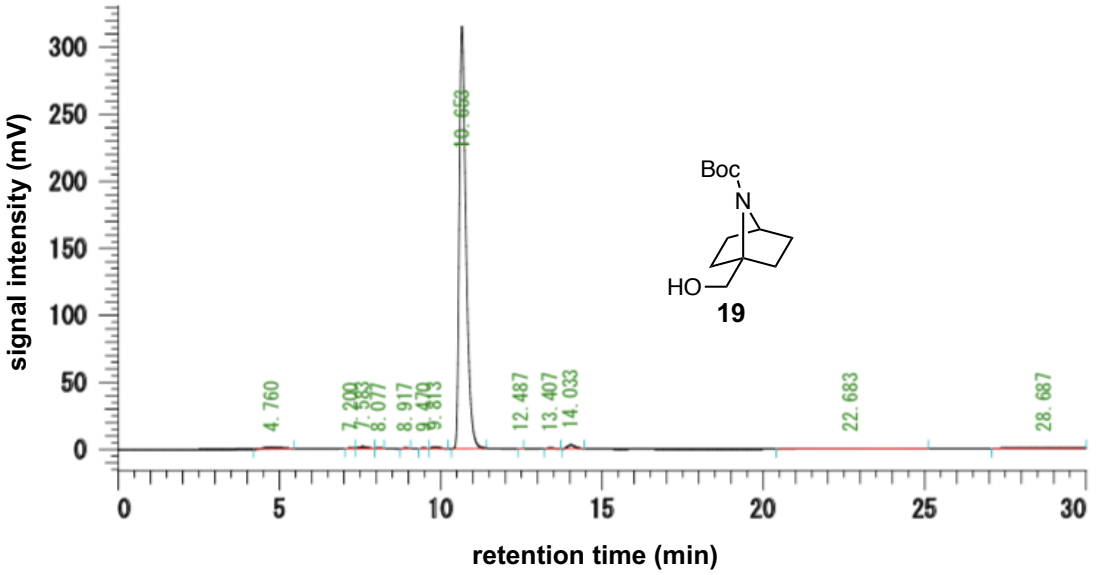


Figure S90. HPLC chart of **19**.

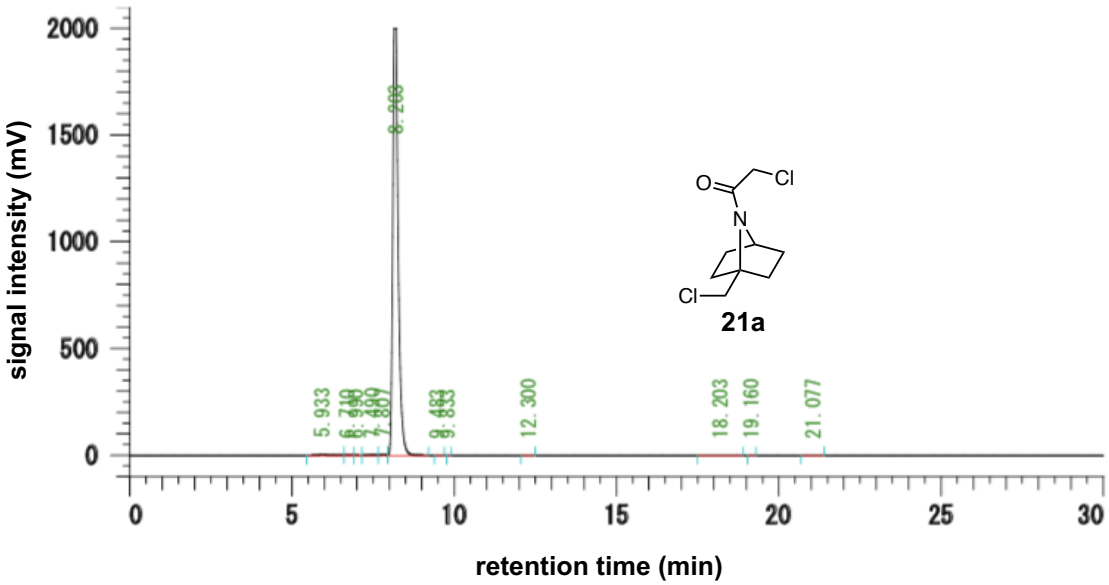


Figure S91. HPLC chart of **21a**.

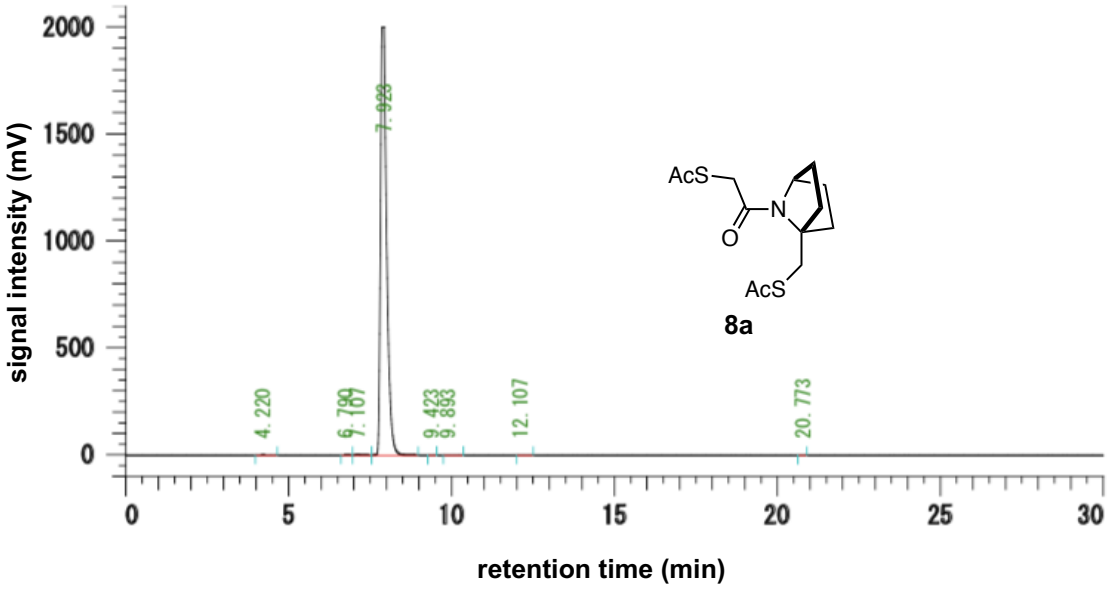


Figure S92. HPLC chart of **8a**.

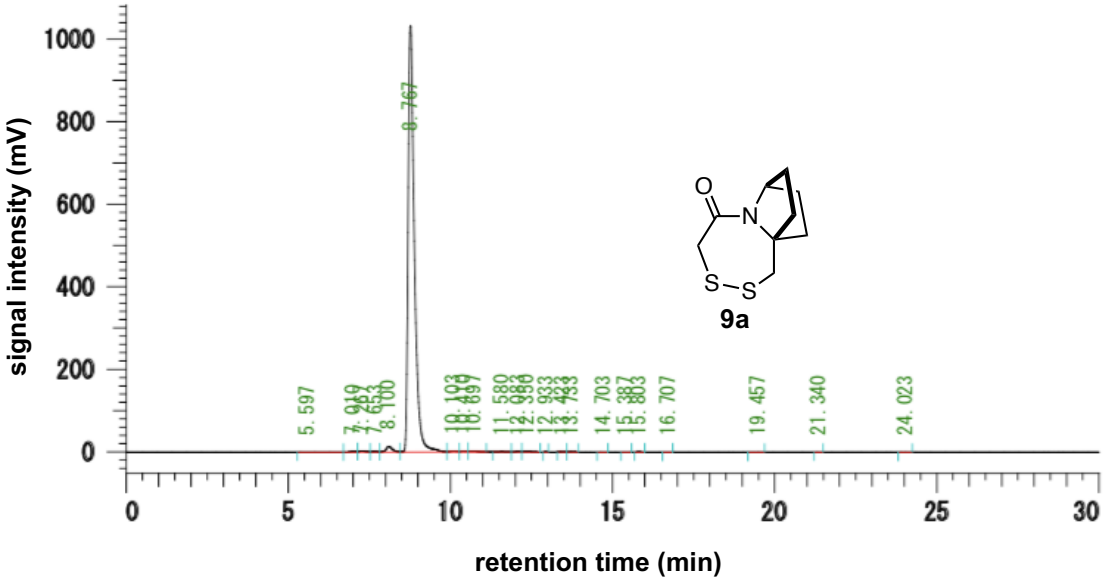


Figure S93. HPLC chart of **9a**.

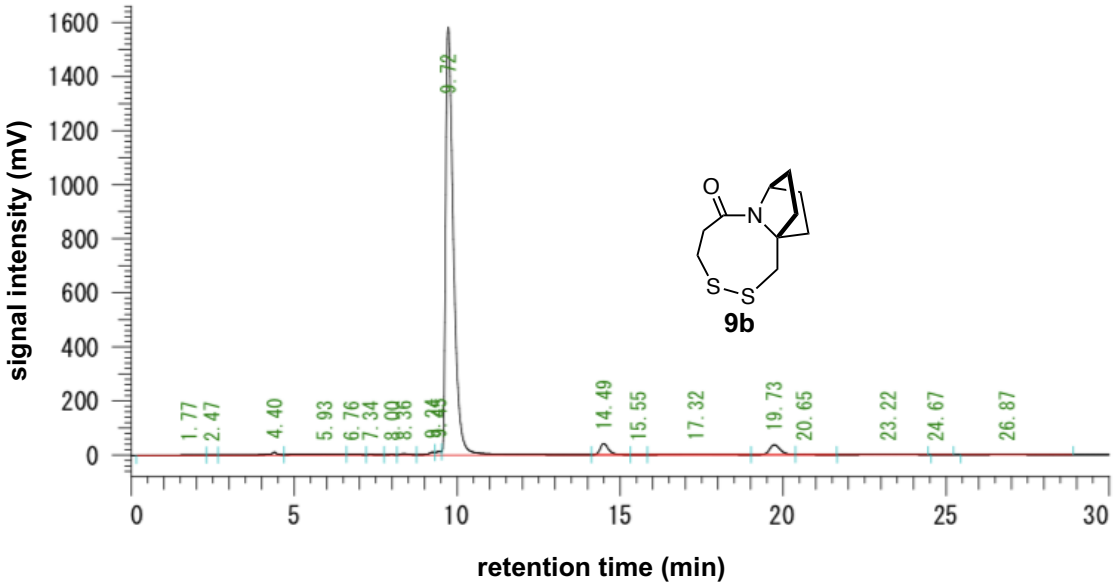


Figure S94. HPLC chart of **9b**.

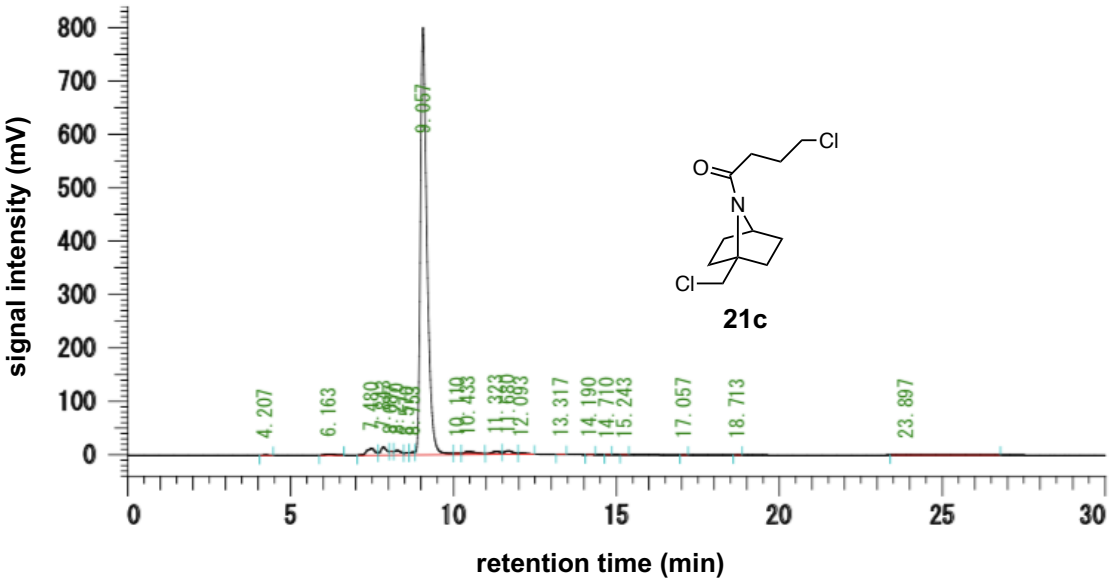


Figure S95. HPLC chart of **21c**.

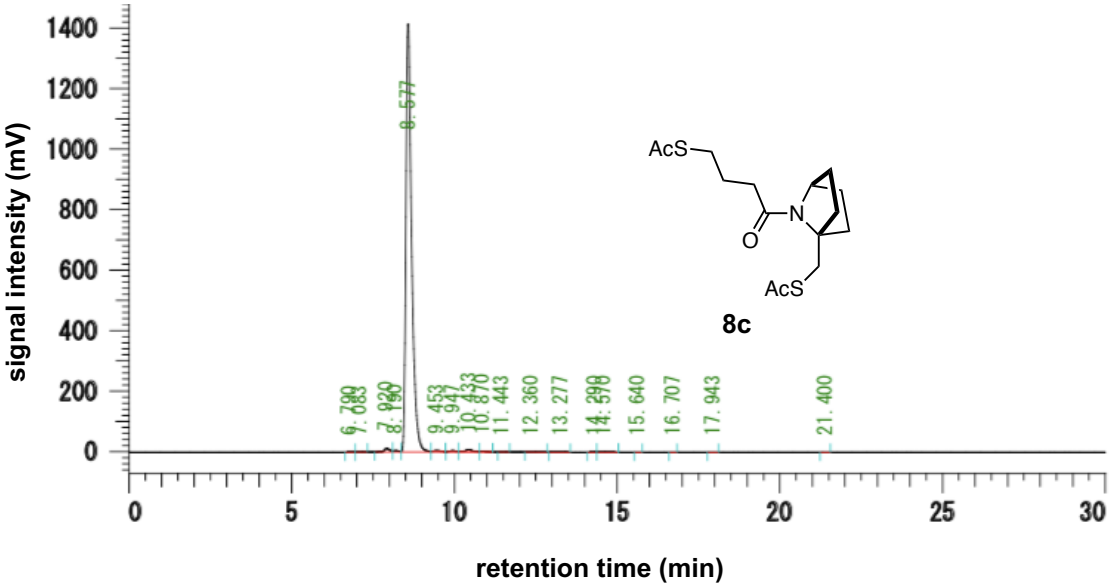


Figure S96. HPLC chart of **8c**.

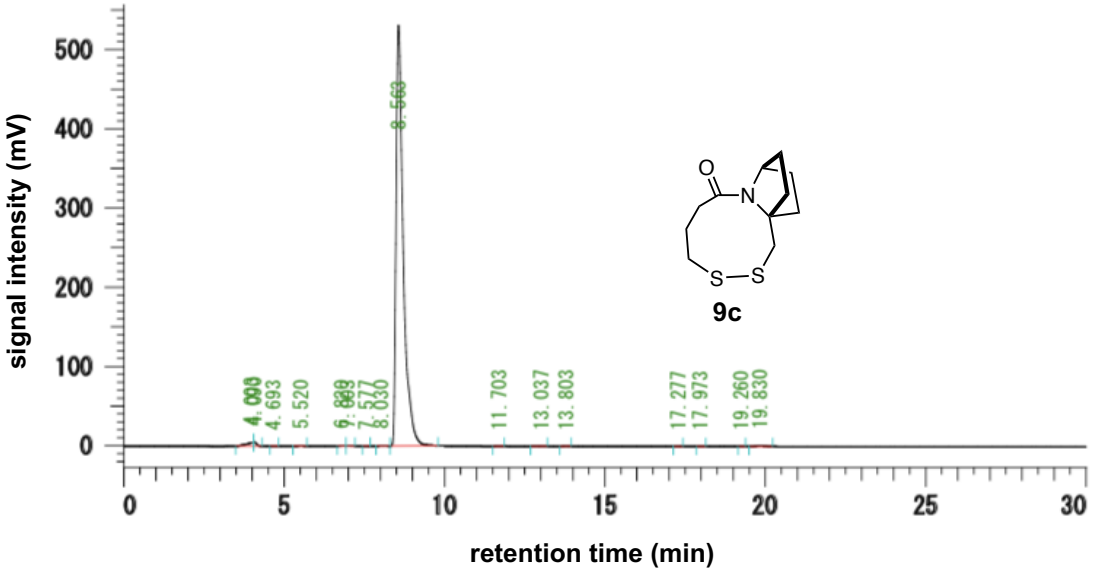


Figure S97. HPLC chart of **9c**.

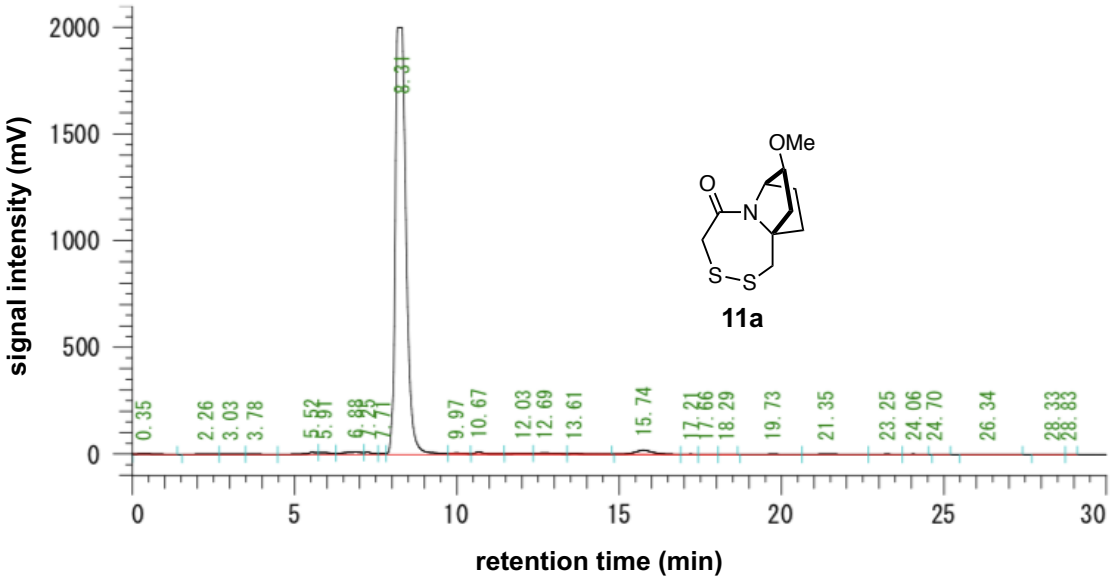


Figure S98. HPLC chart of **11a**.

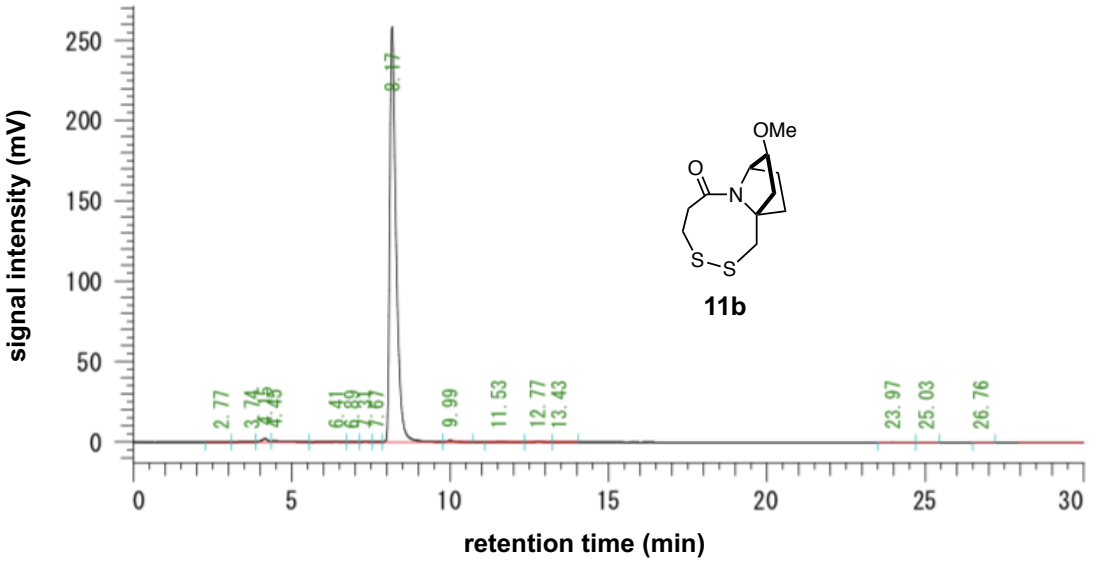


Figure S99. HPLC chart of **11b**.

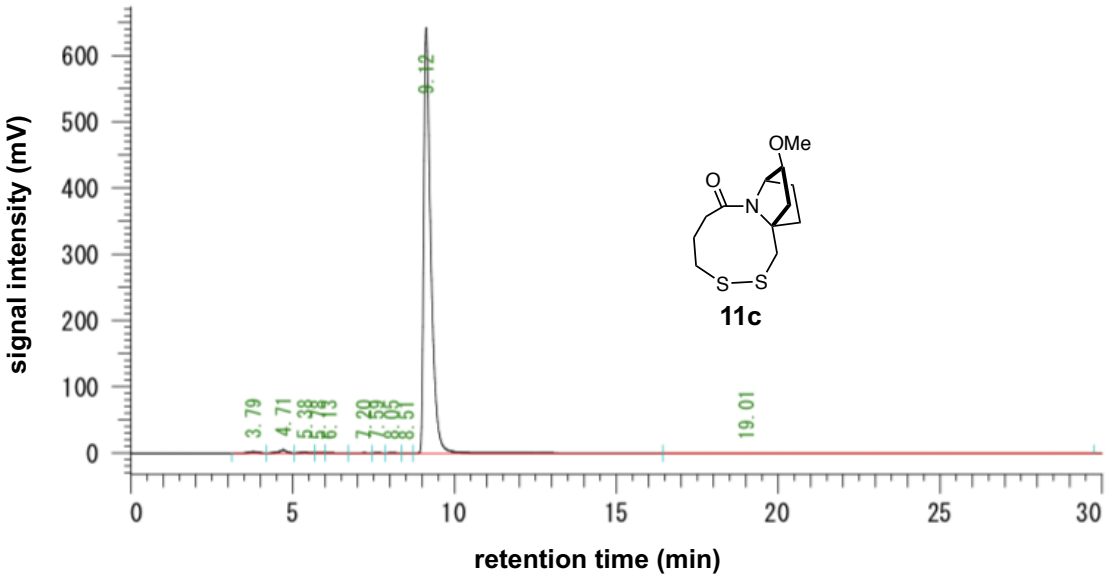


Figure S100. HPLC chart of **11c**.

5. Computational Study

Metadynamics Simulations

Metadynamics calculations were performed with Desmond using the OPSL3e force field (Scrhödinger Inc., U.S.A.). The simulation conditions are as follows:

Temperature = 300.0 K, Pressure = 1.01325 bar, Ensemble = NPT, Solvent = $CHCl_3$, Simulation time = 20 ns.

DFT calculation

The energy minimum structures and transition state (TS) structures of isomerization were fully optimized at the APFD/6-311+G(2d,p) level using the Gaussian 16 program.[S4] Bulk solvation effects (self-consistent reaction field, SCRF) were simulated in chloroform by the IEFPCM method (SCRF = IEFPCM, solvent = $CHCl_3$). Harmonic frequency calculations characterized the optimized structures. Intrinsic reaction coordinate (IRC) calculations of the transition structures verified reactants, intermediates, and products on the potential energy surface.

Optimized structures for conformers **a** – **d** in **9b** and conformers **a'** – **d'** in **11b** were obtained by further DFT optimization of the energy-minimum conformers obtained from metadynamics simulation. Transition state structures were predicted either by using the intermediate structures from the metadynamics simulations as initial structures or from scans of the dihedral angles χ_3 and $\chi_{1'}$ of the energy minimum conformers.

Calculated energies and coordinates

Conformer a

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.204645 Hartree

EE + Thermal Free Energy Correction = -1315.85 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.174453	0.717690	0.513458
2	6	0	-3.093331	0.037660	-0.511610
3	6	0	-2.163805	-1.036320	-1.127110
4	6	0	-0.843973	-0.847064	-0.340681

5	6	0	-1.096495	-1.340308	1.101400
6	6	0	-1.963624	-0.214844	1.710778
7	7	0	-0.877655	0.624968	-0.160195
8	6	0	-0.085142	1.688490	-0.379103
9	8	0	-0.403583	2.815776	0.000760
10	6	0	1.237503	1.507144	-1.091135
11	6	0	2.386311	1.364904	-0.100581
12	16	0	2.161288	-0.053496	1.019445
13	16	0	1.961091	-1.642715	-0.269765
14	6	0	0.299842	-1.517933	-1.061238
15	1	0	-2.425160	1.744740	0.759289
16	1	0	-3.424851	0.753822	-1.265891
17	1	0	-3.980339	-0.387713	-0.038352
18	1	0	-1.992039	-0.853004	-2.190959
19	1	0	-2.542627	-2.054370	-1.018140
20	1	0	-0.157799	-1.459696	1.640479
21	1	0	-1.598606	-2.309964	1.084310
22	1	0	-2.909726	-0.572573	2.121427
23	1	0	-1.424859	0.307704	2.504021
24	1	0	1.393373	2.413027	-1.682475
25	1	0	1.239899	0.664665	-1.780116
26	1	0	2.433366	2.227905	0.570365
27	1	0	3.342459	1.273311	-0.618840
28	1	0	0.427517	-1.098995	-2.060565
29	1	0	0.016585	-2.566972	-1.189229

Conformer b

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.204662 Hartree

EE + Thermal Free Energy Correction = -1315.85 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.173046	0.711568	0.520690
2	6	0	1.964079	-0.230094	1.711117
3	6	0	1.095771	-1.350839	1.094688
4	6	0	0.841477	-0.846917	-0.343364
5	6	0	2.160260	-1.030013	-1.133116
6	6	0	3.090542	0.039553	-0.510979
7	7	0	0.874870	0.623526	-0.150957
8	6	0	0.089453	1.690649	-0.376870
9	8	0	0.413755	2.817817	-0.001216
10	6	0	-1.235218	1.512901	-1.085959
11	6	0	-2.382276	1.368669	-0.093326
12	16	0	-2.159942	-0.054694	1.021082
13	16	0	-1.964341	-1.638826	-0.274862
14	6	0	-0.303318	-1.513155	-1.066625
15	1	0	2.424004	1.736798	0.773775
16	1	0	1.426680	0.286531	2.509173

17	1	0	2.910820	-0.590983	2.117521
18	1	0	0.157556	-1.473760	1.633922
19	1	0	1.597455	-2.320575	1.069852
20	1	0	1.986726	-0.838616	-2.195274
21	1	0	2.539517	-2.048778	-1.032630
22	1	0	3.978399	-0.389143	-0.042264
23	1	0	3.420769	0.761523	-1.260287
24	1	0	-1.240321	0.672585	-1.777671
25	1	0	-1.391753	2.420821	-1.673892
26	1	0	-3.339448	1.281380	-0.610486
27	1	0	-2.426530	2.229197	0.581028
28	1	0	-0.021248	-2.561950	-1.199284
29	1	0	-0.431124	-1.089855	-2.064117

Conformer c

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.203727 Hartree

EE + Thermal Free Energy Correction = -1315.8463 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.359311	0.538506	-0.552605
2	6	0	2.951239	0.329863	0.854960
3	6	0	1.905300	-0.595517	1.530841
4	6	0	0.869933	-0.803378	0.406554
5	6	0	1.525395	-1.684149	-0.682509
6	6	0	2.527539	-0.736548	-1.371567
7	7	0	0.914409	0.520688	-0.263860
8	6	0	0.256497	1.693129	-0.085852
9	8	0	0.712253	2.742658	-0.535028
10	6	0	-1.078699	1.736691	0.624467
11	6	0	-2.275942	1.423514	-0.291694
12	16	0	-3.113751	-0.149825	0.074011
13	16	0	-1.714719	-1.567483	-0.431095
14	6	0	-0.437218	-1.401954	0.879718
15	1	0	2.658523	1.458082	-1.044746
16	1	0	3.029198	1.284555	1.379206
17	1	0	3.948904	-0.111591	0.813059
18	1	0	1.433887	-0.107408	2.388476
19	1	0	2.322054	-1.544356	1.874573
20	1	0	0.769270	-2.037495	-1.387058
21	1	0	1.992973	-2.559722	-0.227140
22	1	0	3.555465	-1.102628	-1.346199
23	1	0	2.256016	-0.562201	-2.414614
24	1	0	-1.163018	2.765853	0.975897
25	1	0	-1.093440	1.098030	1.507391
26	1	0	-1.999959	1.446276	-1.347216
27	1	0	-3.071279	2.159675	-0.145646
28	1	0	-0.886478	-0.879226	1.723268

29	1	0	-0.215622	-2.417926	1.217465

Conformer d

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.203723 Hartree

EE + Thermal Free Energy Correction = -1315.8463 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.359248	0.538240	-0.552833
2	6	0	-2.527637	-0.737112	-1.371296
3	6	0	-1.525141	-1.684400	-0.682292
4	6	0	-0.869788	-0.803342	0.406646
5	6	0	-1.905297	-0.595433	1.530803
6	6	0	-2.951068	0.330104	0.854870
7	7	0	-0.914354	0.520499	-0.264247
8	6	0	-0.256711	1.693100	-0.085995
9	8	0	-0.712867	2.742570	-0.534812
10	6	0	1.078575	1.736879	0.624232
11	6	0	2.275846	1.423650	-0.291845
12	16	0	3.113743	-0.149671	0.073961
13	16	0	1.714844	-1.567465	-0.430961
14	6	0	0.437400	-1.401742	0.879881
15	1	0	-2.658508	1.457664	-1.045247
16	1	0	-2.256622	-0.563124	-2.414532
17	1	0	-3.555550	-1.103164	-1.345255
18	1	0	-0.768921	-2.037396	-1.386900
19	1	0	-1.992365	-2.560106	-0.226837
20	1	0	-1.434003	-0.107534	2.388615
21	1	0	-2.322208	-1.544293	1.874307
22	1	0	-3.948905	-0.110987	0.813318
23	1	0	-3.028526	1.285004	1.378814
24	1	0	1.093455	1.098435	1.507319
25	1	0	1.162795	2.766126	0.975412
26	1	0	3.071213	2.159762	-0.145657
27	1	0	1.999977	1.446449	-1.347390
28	1	0	0.215847	-2.417604	1.217998
29	1	0	0.886771	-0.878784	1.723234

TS1

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 1

Thermal Correction to Free Energy = 0.203664 Hartree

EE + Thermal Free Energy Correction = -1315.8252 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.987164	-0.712990	1.742960
2	6	0	2.254289	0.404680	0.726093
3	6	0	3.086749	-0.147853	-0.437554
4	6	0	2.059682	-1.046658	-1.163653
5	6	0	0.765326	-0.861313	-0.325067
6	6	0	0.949212	-1.597610	1.008144
7	7	0	0.925055	0.540492	0.121699
8	6	0	0.475117	1.721962	-0.365050
9	8	0	1.141665	2.749159	-0.288087
10	6	0	-0.977044	1.800554	-0.793544
11	6	0	-1.855290	1.629857	0.453452
12	16	0	-2.846066	0.105093	0.660446
13	6	0	-0.433557	-1.252000	-1.152642
14	16	0	-2.057913	-1.557914	-0.399893
15	1	0	1.570195	-0.301630	2.664189
16	1	0	2.902897	-1.249085	1.998628
17	1	0	2.605718	1.344400	1.142529
18	1	0	3.965128	-0.694700	-0.089673
19	1	0	3.426823	0.665548	-1.081363
20	1	0	2.349525	-2.098827	-1.200238
21	1	0	1.890255	-0.711729	-2.190660
22	1	0	-0.000489	-1.637247	1.544464
23	1	0	1.287079	-2.623348	0.847801
24	1	0	-1.248208	1.094138	-1.574665
25	1	0	-1.116360	2.800348	-1.205056
26	1	0	-2.633997	2.395368	0.478862
27	1	0	-1.250018	1.739243	1.353537
28	1	0	-0.237688	-2.264228	-1.526289
29	1	0	-0.525776	-0.621590	-2.036953

TS2

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 1

Thermal Correction to Free Energy = 0.204929 Hartree

EE + Thermal Free Energy Correction = -1315.8309 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.813045	0.232459	-0.964844
2	6	0	-2.299721	0.668928	0.419731
3	6	0	-2.614539	-0.406250	1.446252
4	6	0	-1.615519	-1.502984	1.046947
5	6	0	-0.839318	-0.914884	-0.160240
6	6	0	-1.797093	-0.862524	-1.368235
7	7	0	-0.834881	0.529677	0.243326
8	6	0	-0.175804	1.648129	-0.173218
9	8	0	-0.639888	2.764503	0.050055

10	6	0	1.150723	1.556785	-0.875430
11	6	0	2.329085	1.513935	0.083112
12	16	0	2.502459	-0.089356	0.961668
13	6	0	0.372827	-1.849617	-0.385719
14	16	0	2.126629	-1.394351	-0.573114
15	1	0	-2.786426	1.074316	-1.660048
16	1	0	-3.841318	-0.131746	-0.920019
17	1	0	-2.565485	1.680962	0.704224
18	1	0	-3.656830	-0.725206	1.389572
19	1	0	-2.425569	-0.046469	2.459651
20	1	0	-2.084359	-2.448885	0.765829
21	1	0	-0.911237	-1.709036	1.855710
22	1	0	-1.240834	-0.587671	-2.268973
23	1	0	-2.257803	-1.836903	-1.548162
24	1	0	1.229882	2.465575	-1.475809
25	1	0	1.198985	0.701788	-1.553531
26	1	0	2.226978	2.257569	0.877708
27	1	0	3.259555	1.709123	-0.452599
28	1	0	0.199180	-2.400718	-1.316039
29	1	0	0.367556	-2.591015	0.411753

Conformer a'

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.233756 Hartree

EE + Thermal Free Energy Correction = -1430.2885 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.504571	-1.782282	0.186593
2	6	0	-1.961494	-0.598985	-0.627520
3	6	0	-2.141836	0.683458	0.180053
4	6	0	-1.117129	0.485747	1.324896
5	6	0	-0.414295	-0.834613	0.948223
6	6	0	-1.405278	-1.982940	1.255946
7	7	0	-0.518544	-0.805882	-0.529264
8	8	0	-1.838063	1.772936	-0.660590
9	6	0	-2.083092	3.020755	-0.057388
10	6	0	0.283136	-0.925773	-1.603367
11	8	0	-0.162878	-0.853384	-2.747373
12	6	0	1.770842	-1.120971	-1.409437
13	6	0	2.517711	0.208355	-1.413267
14	16	0	1.969832	1.330621	-0.087047
15	6	0	0.906554	-1.079120	1.636069
16	16	0	2.225354	0.209684	1.616503
17	1	0	-2.606886	-2.662420	-0.449644
18	1	0	-3.483698	-1.565049	0.618224
19	1	0	-2.297374	-0.525474	-1.656791
20	1	0	-3.170960	0.783246	0.549706
21	1	0	-1.575690	0.419365	2.313111

22	1	0	-0.404773	1.309670	1.329697
23	1	0	-0.904623	-2.947169	1.138351
24	1	0	-1.776325	-1.918766	2.280586
25	1	0	-1.849971	3.787047	-0.796368
26	1	0	-3.135904	3.117011	0.240797
27	1	0	-1.454160	3.183707	0.826800
28	1	0	2.113420	-1.716302	-2.259252
29	1	0	2.015463	-1.675062	-0.504912
30	1	0	2.314824	0.767647	-2.331526
31	1	0	3.594522	0.048440	-1.334235
32	1	0	1.344844	-2.021815	1.305207
33	1	0	0.688354	-1.185981	2.702703

Conformer b'

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.233148 Hartree

EE + Thermal Free Energy Correction = -1430.2889 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.008206	-0.588802	2.185049
2	6	0	1.549947	0.396614	1.142915
3	6	0	2.605303	-0.307430	0.290456
4	6	0	1.737029	-1.260685	-0.571246
5	6	0	0.297093	-0.957691	-0.093426
6	6	0	0.157651	-1.550859	1.325129
7	7	0	0.437042	0.487740	0.201023
8	8	0	3.287791	0.662863	-0.472442
9	6	0	4.390665	0.131956	-1.170046
10	6	0	-0.208771	1.639349	-0.061777
11	8	0	0.088022	2.686079	0.510975
12	6	0	-1.328285	1.655668	-1.079456
13	6	0	-2.690554	1.577721	-0.403504
14	16	0	-2.864802	0.077128	0.613385
15	6	0	-0.705909	-1.451732	-1.107643
16	16	0	-2.509645	-1.444136	-0.723646
17	1	0	0.387948	-0.056079	2.907594
18	1	0	1.808822	-1.090351	2.732192
19	1	0	1.856249	1.369117	1.514152
20	1	0	3.325069	-0.850129	0.916783
21	1	0	1.988743	-2.315849	-0.453668
22	1	0	1.843556	-0.992537	-1.625692
23	1	0	-0.883985	-1.555012	1.641737
24	1	0	0.518818	-2.581278	1.342314
25	1	0	4.855514	0.954515	-1.713039
26	1	0	5.124364	-0.302386	-0.478105
27	1	0	4.090829	-0.640608	-1.889598
28	1	0	-1.239936	0.867364	-1.824529
29	1	0	-1.248449	2.610882	-1.604820

30	1	0	-3.498292	1.620248	-1.136175
31	1	0	-2.820352	2.396937	0.309945
32	1	0	-0.500323	-2.515450	-1.260035
33	1	0	-0.557481	-0.957628	-2.069017

Conformer c'

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.231945 Hartree

EE + Thermal Free Energy Correction = -1430.2864 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.192654	0.424945	-1.921313
2	6	0	-2.003280	0.594458	-0.400968
3	6	0	-2.396126	-0.714512	0.286984
4	6	0	-1.248696	-1.635246	-0.145649
5	6	0	-0.306935	-0.722217	-0.960518
6	6	0	-0.978851	-0.451274	-2.321783
7	7	0	-0.541990	0.569791	-0.270864
8	8	0	-2.397318	-0.639781	1.695785
9	6	0	-3.514939	0.042716	2.218572
10	6	0	0.139499	1.737193	-0.169592
11	8	0	-0.433877	2.769647	0.170166
12	6	0	1.629017	1.786717	-0.424406
13	6	0	2.477012	1.368861	0.791550
14	16	0	3.399611	-0.182994	0.566349
15	6	0	1.077911	-1.322297	-1.075353
16	16	0	1.924147	-1.612397	0.528413
17	1	0	-2.161570	1.397233	-2.415507
18	1	0	-3.151248	-0.040207	-2.161741
19	1	0	-2.433615	1.496038	0.020881
20	1	0	-3.378602	-1.059676	-0.060845
21	1	0	-1.575215	-2.492547	-0.736294
22	1	0	-0.746205	-2.001208	0.752272
23	1	0	-0.290761	0.091282	-2.975732
24	1	0	-1.259041	-1.378655	-2.825089
25	1	0	-4.452999	-0.421855	1.887008
26	1	0	-3.449779	-0.022895	3.304451
27	1	0	-3.525904	1.100735	1.932233
28	1	0	1.831315	2.833198	-0.655480
29	1	0	1.908460	1.207960	-1.304740
30	1	0	1.880500	1.298356	1.702441
31	1	0	3.269207	2.099982	0.974172
32	1	0	1.752144	-0.757281	-1.718035
33	1	0	0.954949	-2.307746	-1.532891

Conformer d'

APFD/6-311+G(2d,p), SCRF = IEFPCM, solvent = $CHCl_3$

Number of Imaginary Frequency = 0

Thermal Correction to Free Energy = 0.232114 Hartree

EE + Thermal Free Energy Correction = -1430.2854 Hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.613499	-1.694000	1.646608
2	6	0	1.804225	-0.256824	1.167906
3	6	0	2.625855	-0.268902	-0.129637
4	6	0	1.610065	-0.837798	-1.160588
5	6	0	0.339585	-1.028060	-0.309918
6	6	0	0.584341	-2.230836	0.631508
7	7	0	0.473258	0.083415	0.655675
8	8	0	3.013425	1.055875	-0.419423
9	6	0	3.907872	1.140168	-1.504875
10	6	0	-0.023052	1.336620	0.779077
11	8	0	0.356516	2.073252	1.684828
12	6	0	-1.058932	1.865119	-0.190038
13	6	0	-2.504647	1.710967	0.305900
14	16	0	-3.459943	0.417155	-0.547896
15	6	0	-0.926727	-1.208518	-1.117915
16	16	0	-2.454541	-1.316679	-0.098631
17	1	0	1.215351	-1.704488	2.662121
18	1	0	2.551021	-2.253366	1.646664
19	1	0	2.159208	0.458692	1.902642
20	1	0	3.520124	-0.898043	-0.030189
21	1	0	1.936136	-1.765128	-1.634340
22	1	0	1.431188	-0.094441	-1.942170
23	1	0	-0.347007	-2.511601	1.128205
24	1	0	0.935979	-3.094454	0.063320
25	1	0	4.154625	2.193149	-1.638232
26	1	0	4.828576	0.577427	-1.302271
27	1	0	3.465620	0.760896	-2.434858
28	1	0	-0.945324	1.449927	-1.190855
29	1	0	-0.827161	2.929633	-0.259936
30	1	0	-3.084564	2.612221	0.086768
31	1	0	-2.546337	1.549089	1.384341
32	1	0	-0.837608	-2.162306	-1.644735
33	1	0	-1.082917	-0.439363	-1.873166

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