Electronic Supplementary Information (ESI)

An anti-tetraamination of a 1,3-diene unit via cascade annulations of the azulenone scaffold with dicarbonyl azo-compounds

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S1-S5: Experimental Section

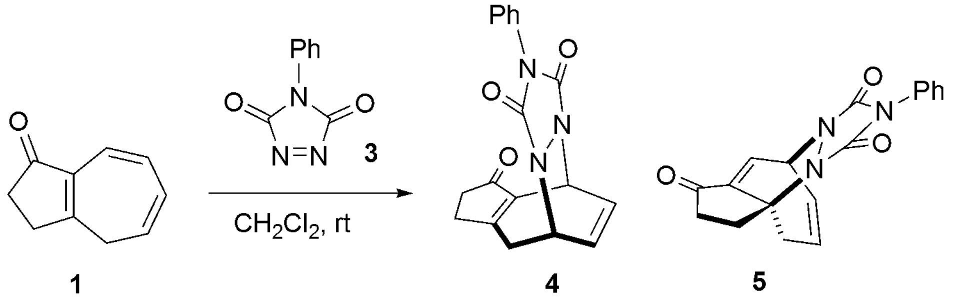
S6-S17: ^{1}H and ^{13}C-NMR Spectra

S18-S29: X-ray Structure of compound 10b (CCDC-759029)

General: NMR spectra were recorded on JEOL JNM-ECX 400 (^{1}H/400 MHz, ^{13}C/100 MHz) and JNM-ECX 600 (^{1}H/600 MHz, ^{13}C/150 MHz) spectrometers. Chemical Shifts are reported in δ (ppm) and are referenced to proton and carbon resonances of the NMR solvent ($CHCl_3$: δ 7.26, and δ 77.16, DMSO: δ 2.50 and δ 39.52). Mass spectra were recorded on JEOL JMS-T100CS (ESI) spectrometer. The medium pressure liquid chromatography (MPLC) purifications using a silica-gel column were performed on a YAMAZEN YFLC-AI-580.

Materials: The azulenone **1** was prepared from 3-phenylpropanoylchloride according to Scott's procedure [Scott, L. T.; Sumpter, C. A. *Org. Synth.*, **1990**, *69*, 180]. The diallyl azodicaboxylate **6c** was prepared from allylchloroformate by treatment with hydrazine hydrate followed by oxidation with iodobenzene diacetate.

*Synthesis of **4** and **5**.*



To a solution of azulenone **1** (250 mg, 1.71 mmol) in dichloromethane (4 mL, 0.42 M) was added PTAD **3** (600 mg, 3.42 mmol, 2 eq). After stirring for 3 h at room temperature, the resulting mixture was concentrated. The residue was purified by silica-gel column chromatography to afford **4** (346 mg, 1.08 mmol, 63%) and **5** (39 mg, 0.21 mmol, 7%) as white powders.

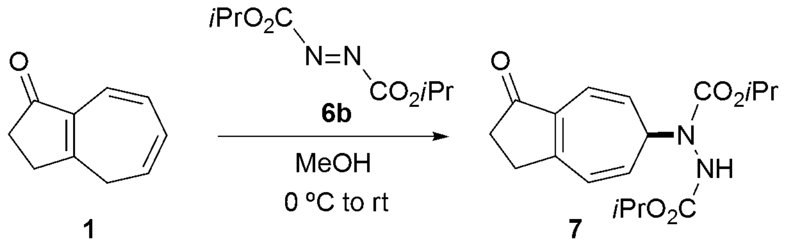
4:^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.48-7.40 (4H, m), 7.34 (1H, m), 6.61 (1H, dd, *J* = 8.8, 6.6 Hz), 6.28 (1H, m), 5.62 (1H, dd, *J* = 6.6, 1.1 Hz), 5.18 (1H, m), 3.16 (1H, dd, *J* = 19.9, 4.4 Hz), 2.74 (1H, dd, *J* = 19.9, 1.9 Hz), 2.60 (1H, m), 2.52-2.39 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.76, 172.67, 152.55, 150.69, 138.28, 133.67, 131.29, 128.88, 127.96, 126.30, 125.26, 49.97, 43.95, 36.36, 33.58, 29.98; HR-MS (ESI) calcd for $C_{18}H_{15}N_3NaO_3$ $[M+Na]^+$ 344.0998, found 344.0963.

The ^{1}H and ^{13}C NMR spectra of **4** are shown in Figure S1-S2.

5: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.52-7.49 (2H, m), 7.45 (2H, m), 7.41 (1H, d, *J* = 7.1 Hz), 7.36 (1H, m), 6.07 (1H, m), 5.68 (1H, dt, *J* = 7.1, 3.8 Hz), 5.25 (1H, t, *J* = 7.1 Hz), 3.26-3.18 (1H, ddd, *J* = 19.7, 3.8, 2.2 Hz), 2.82-2.70 (2H, m), 2.69-2.61 (1H, ddd, *J* = 18.7, 8.8, 2.2 Hz), 2.56-2.46 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.82, 152.23, 150.66, 138.85, 132.92, 131.38, 131.32, 129.06, 128.19, 125.38, 124.08, 63.30, 49.26, 37.22, 36.06, 32.49; HR-MS (ESI) calcd. for $C_{18}H_{15}N_3NaO_3$ $[M+Na]^+$ 344.0998, found 344.0992.

The ^{1}H and ^{13}C NMR spectra of **5** are shown in Figure S3-S4.

*Ene reaction of **1** with **6b** to form **7**.*

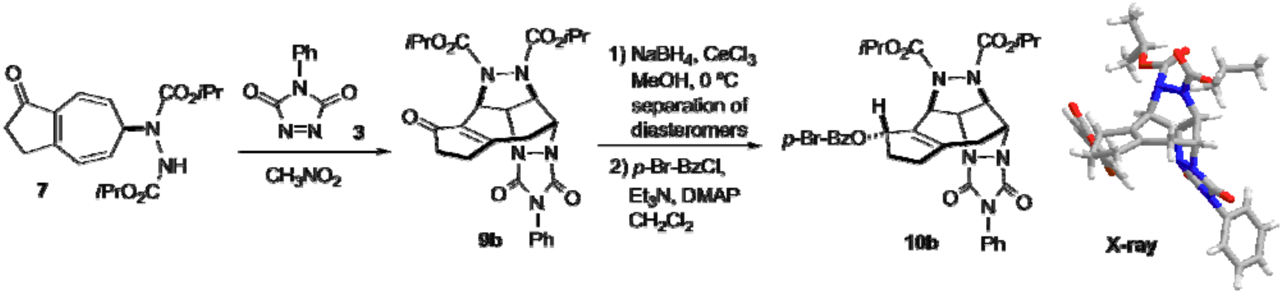


To a solution of azulenone **1** (50 mg, 0.342 mmol) in methanol (1 mL, 0.34 M) at 0 °C was added **6b** (diisopropyl azodicarboxylate, 204 μL, 1.03 mmol, 3 eq). The mixture was gradually warmed to room temperature. After stirring for overnight at room temperature, the reaction mixture was concentrated and purified by silica-gel column chromatography to afford **7** (107 mg, 0.307 mmol, 90%) as a white amorphous.

7: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.45 (1H, s), 6.50 (1H, d, J =10.2 Hz), 6.34 (1H, d, J = 10.0 Hz), 5.85 (1H, m), 5.58 (1H, m), 4.86 (1H, m), 4.79 (1H, m), 4.36 (1H, brs), 2.94-2.78 (2H, m), 2.48-2.40 (2H, m), 1.32-1.10 (12H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.74, 166.23, 156.84, 155.09, 139.03, 131.28, 124.56, 119.25, 70.86, 70.27, 34.17, 31.66, 29.46, 22.73, 22.10, 22.06, 14.22; HR-MS (ESI) calcd. for $C_{18}H_{24}N_2NaO_5$ $[M+Na]^+$ 371.1598, found 371.1578.

The ^{1}H and ^{13}C NMR spectra of **7** are shown in Figure S5-S6.

*Sequential annulations of **7** with **3** to form **9b** and subsequent conversions into crystalline **10b**.*



To a solution of **7** (50.0 mg, 0.144 mmol) in nitromethane (5 mL, 0.03 M) at 0 °C was added PTAD **3** (50.3 mg, 0.285 mmol, 2 eq). The mixture was gradually warmed to room temperature and stirred for 30 min. The resulting mixture was concentrated and purified by silica-gel column chromatography to afford **9b** (65.0 mg, 0.124 mmol, 86%) as a white powder.

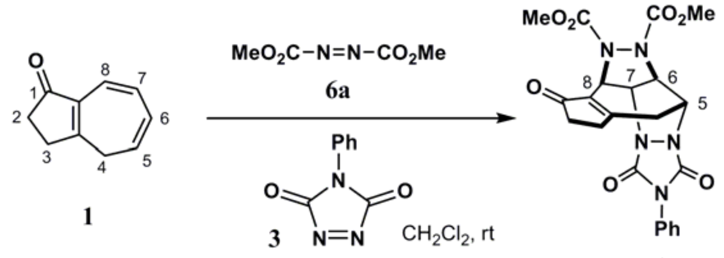
9b: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.52-7.43 (4H, m), 7.40 (1H, m), 5.40 (1H, t, J = 8.0 Hz), 5.10 (1H, d, J = 6.5 Hz), 5.02 (1H, m), 4.96-4.84 (2H, m), 4.81 (1H, m), 2.98 (1H, dd, J = 19.4, 4.0 Hz), 2.74 (1H, d, J = 19.4 Hz), 2.64 (2H, m), 2.43 (2H, t, J = 4.8 Hz), 1.34-1.16 (12H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 205.01, 173.00, 155.55, 153.69, 152.62, 131.31, 128.29, 127.60, 125.50, 70.75, 69.55, 61.32, 60.80, 55.23, 52.84, 33.70, 33.30, 31.35, 21.30, 21.11, 20.97; HR-MS (ESI) calcd. for $C_{26}H_{29}N_5NaO_7$ $[M+Na]^+$ 546.1998, found 546.1986.

The ^{1}H and ^{13}C NMR spectra of **9b** are shown in Figure S7-S8.

To a solution of **9b** (100 mg, 0.191 mmol) and $CeCl_3 \cdot 7H_2O$ (213 mg, 0.573 mmol, 3 eq) in methanol (10 mL, 0.019 M) was added $NaBH_4$ (8.70 mg, 0.23 mmol, 1.2 eq) portionwise at 0 °C. The mixture was stirred at 0 °C for 1 h and then warmed to room temperature. The reaction mixture was treated with water (10 mL) and concentrated to remove methanol. The residue was extracted with ethylacetate (3 x 20 mL), and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration, the resulting mixture was separated by silica-gel column chromatography to afford a separable 1:3 diastereomeric mixture of the secondary alcohols: less polar (17 mg, 17%) and polar (52 mg, 52%). The crystalline derivative **10b** were synthesized from the less polar diastereomer of the alcohol as follows.

To a solution of the less polar (60 mg, 0.114 mmol), triethylamine (96 μL, 0.685 mmol, 6 eq) and DMAP (1.4 mg, 10 mol%) in dichloromethane (2 mL, 0.06 M) was added 4-bromobenzoyl chloride (75.2 mg, 0.342 mmol, 3 eq). After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ethylacetate (3 x 20 ml). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica-gel column chromatography to afford **10b** (65.0 mg, 80%). Recrystallization of **10b** in 2-propanol and subsequent X-ray analysis allowed structural determination of **10b**.

*One-pot synthesis of **9a***



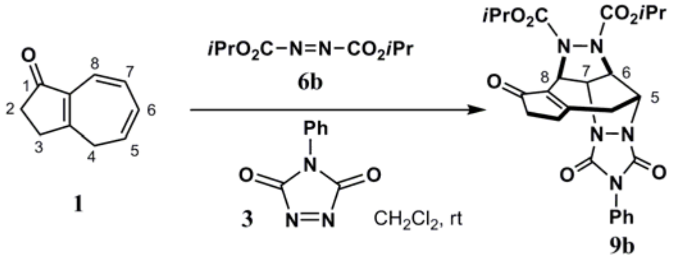
9a

To a solution of azulenone **1** (146.2 mg, 1.0 mmol) in dichloromethane (2 mL, 0.5 M) was added **6a** (dimethyl azodicarboxylate: 434 μL, 3.0 mmol, 3 eq). After being stirred for 5 h at room temperature, complete consumption of **1** was monitored by TLC analysis. PTAD **3** (263 mg, 1.5 mmol, 1.5 eq) was then added in one portion, and the resulting mixture was stirred for additional 1 h at room temperature. Concentration and purification by silica-gel column chromatography afforded **9a** (285 mg, 62%) as a white powder.

9a: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.52-7.43 (4H, m), 7.43-7.37 (1H, m), 5.42 (1H, t, J = 7.8 Hz), 5.32 (1H, d, J = 6.5 Hz), 5.16 (1H, m), 4.85 (1H, m), 3.76 (3H, s), 3.74 (3H, s), 2.97 (1H, dd, J = 19.4, 4.1 Hz), 2.74 (1H, d, J = 19.4 Hz), 2.73-2.56 (2H, m) 2.43 (2H, t, J = 4.9 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 205.20, 173.37, 156.45, 153.77, 152.69, 131.34, 128.36, 127.66, 125.56, 61.31, 60.83, 55.17, 53.65, 53.02, 52.83, 33.77, 33.32, 31.42; HR-MS (ESI) calcd. for $C_{22}H_{21}N_5NaO_7$ $[M+Na]^+$ 490.1298, found 490.1333.

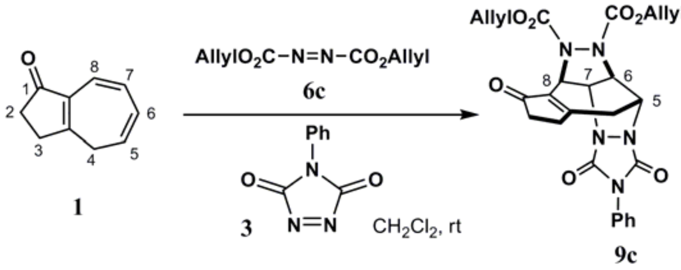
The ^{1}H and ^{13}C NMR spectra of **9a** are shown in Figure S9-S10.

*One-pot synthesis of **9b***



To a solution of azulenone **1** (146.2 mg, 1.0 mmol) in dichloromethane (2 mL, 0.5 M) was added **6b** (diisopropyl azodicarboxylate 595 μL, 3.0 mmol, 3 eq). After being stirred for 16 h at room temperature, complete consumption of **1** was monitored by TLC analysis. PTAD **3** (263 mg, 1.5 mmol, 1.5 eq) was then added in one portion, and the resulting mixture was stirred for additional 1 h at room temperature. Concentration and purification by silica-gel column chromatography afforded **9b** (365 mg, 70%) as a white powder.

*One-pot synthesis of **9c***



To a solution of azulenone **1** (146.2 mg, 1.0 mmol) in dichloromethane (2 mL, 0.5 M) was added **6c** (diallyl azodicarboxylate, 594 mg, 3.0 mmol, 3 eq). After being stirred for 10 h at room temperature, complete consumption of **1** was monitored by TLC analysis. PTAD **3** (263 mg, 1.5 mmol, 1.5 eq) was then added in one portion, and the resulting mixture was stirred for additional 1 h at room temperature. Concentration and purification by silica-gel column chromatography afforded **9c** (340 mg, 0.65 mmol, 66%) as a white powder.

9c: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.52-7.43 (4H, m), 7.41 (1H, m), 6.04-5.87 (2H, m), 5.46 (1H, t, J = 8.0 Hz), 5.42-5.22 (4H, m), 5.36 (1H, d, J = 6.5 Hz), 5.32-5.21 (2H, m), 5.14 (1H, dd, J = 8.4, 6.5 Hz), 4.84 (1H, m), 4.72-4.60 (4H, m), 2.98 (1H, dd, J = 19.6, 4.0 Hz), 2.75 (1H, d, J = 19.6 Hz), 2.71-2.57 (2H, m), 2.44 (2H, t, J = 4.8 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 205.69, 173.85, 154.23, 153.07, 132.34, 131.88, 131.40, 128.63, 128.61, 127.95, 125.91, 117.46, 66.92, 66.82, 66.12, 61.31, 61.08, 55.29, 53.26, 52.98, 34.14, 33.50, 31.64; HR-MS (ESI) calcd. for

$C_{26}H_{25}N_5NaO_7$ $[M+Na]^+$ 542.1698, found 542.1674.

The ^1H and ^{13}C NMR spectra of **9c** are shown in Figure S11-S12.

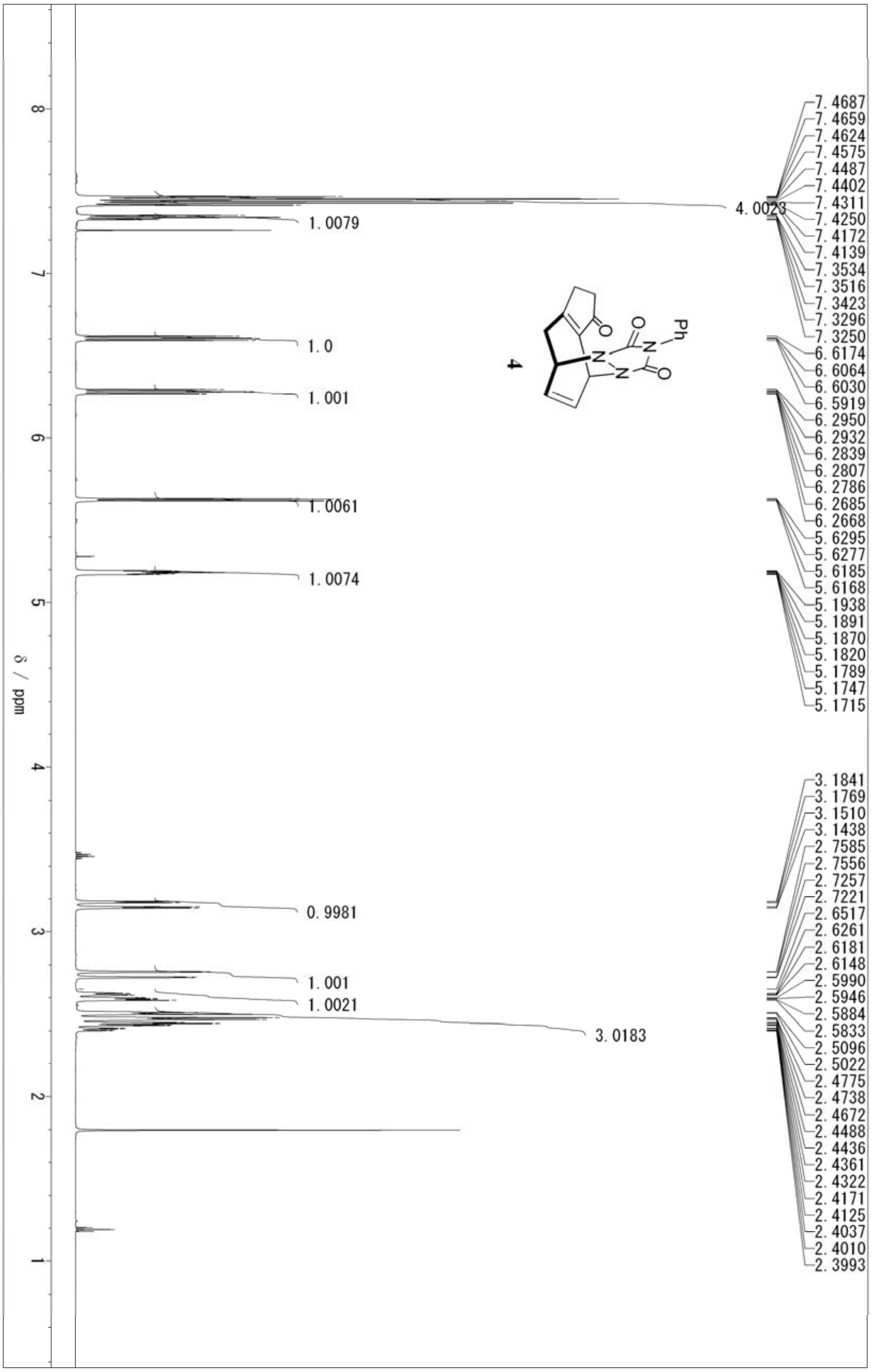


Figure S1. ^{1}H NMR spectra of 4 in $CDCl_3$

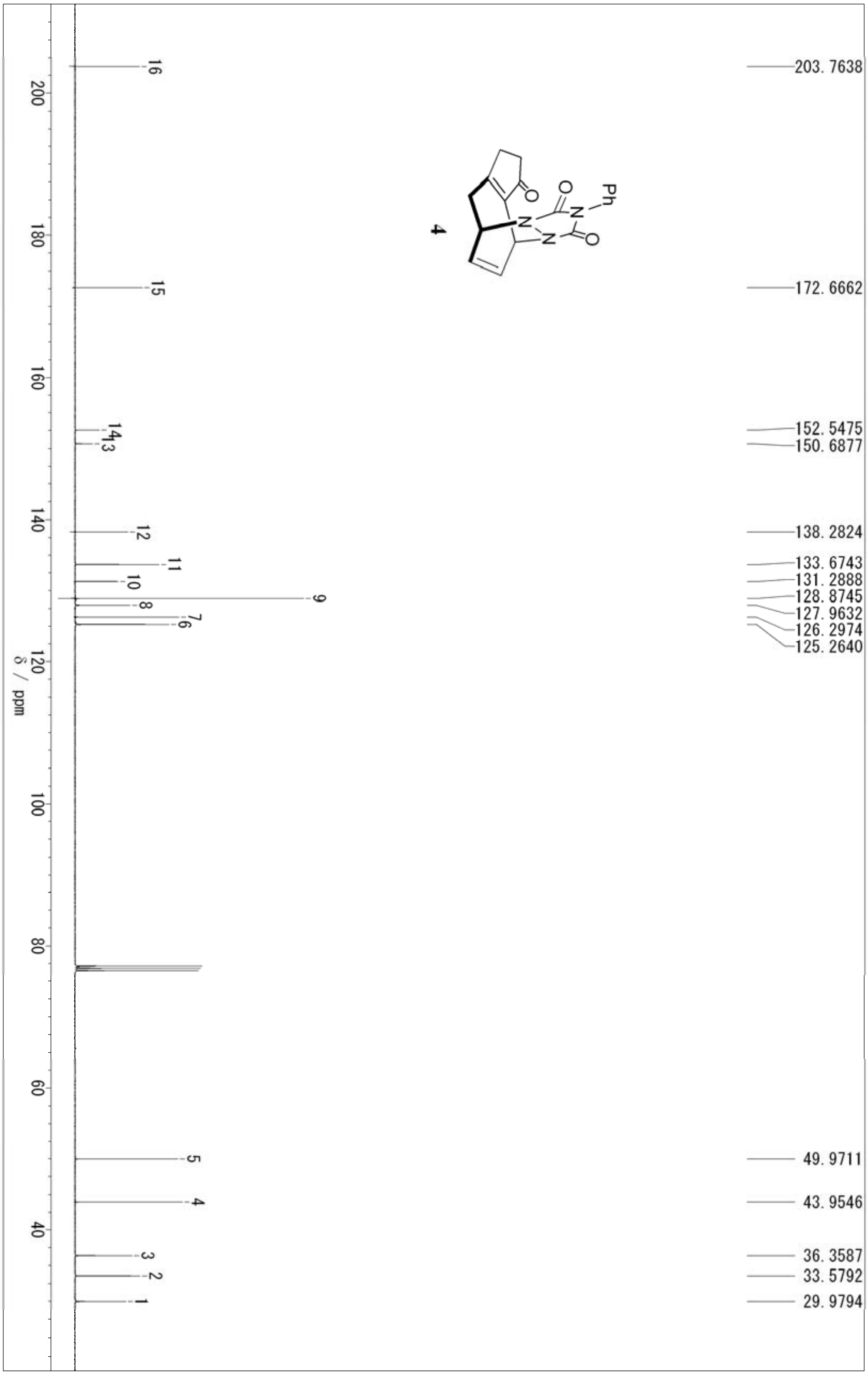


Figure S2. ^{13}C NMR spectra of 4 in $CDCl_3$

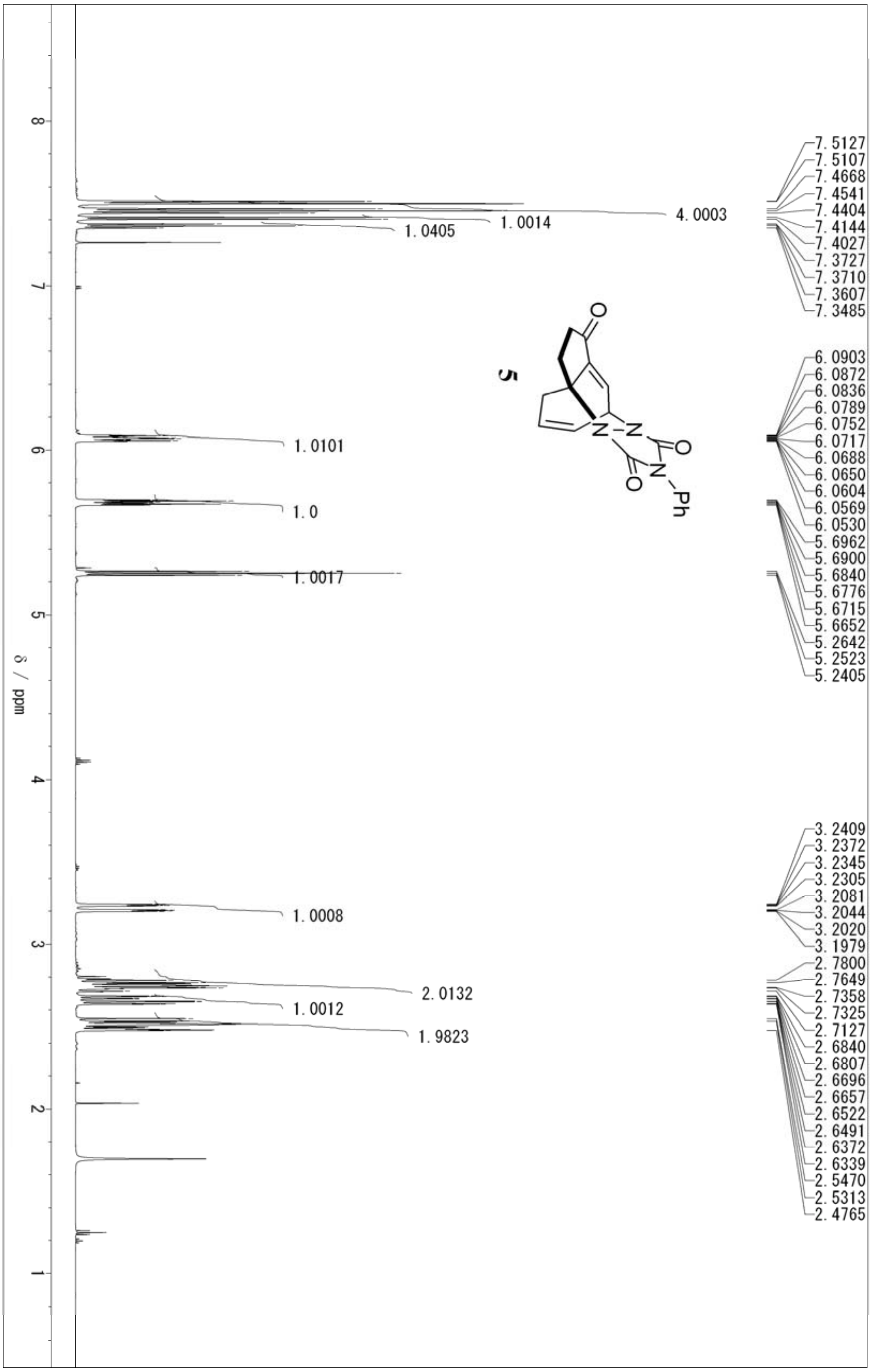


Figure S3. ^{1}H NMR spectra of 5 in $CDCl_3$

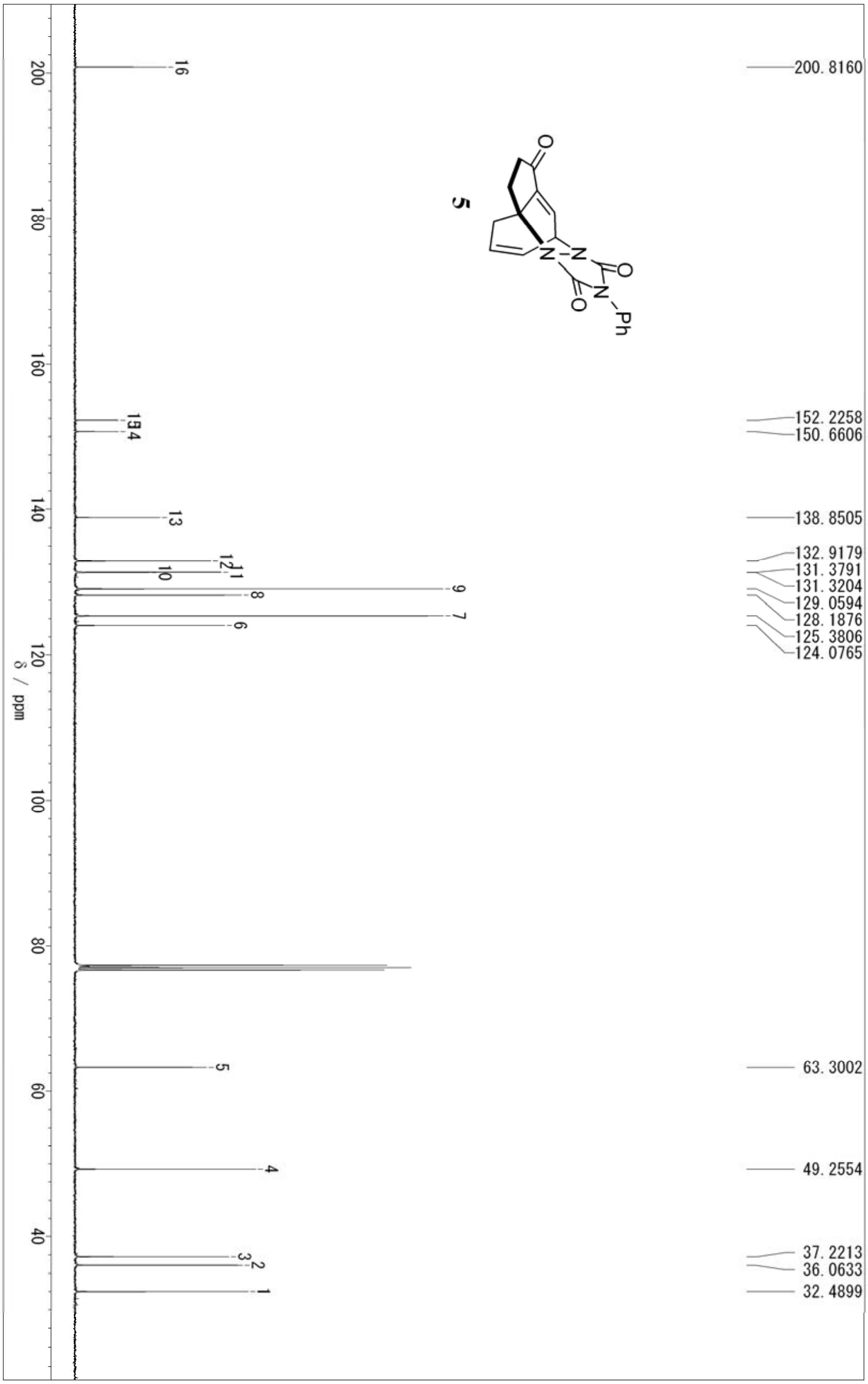


Figure S4. ^{13}C NMR spectra of 5 in $CDCl_3$

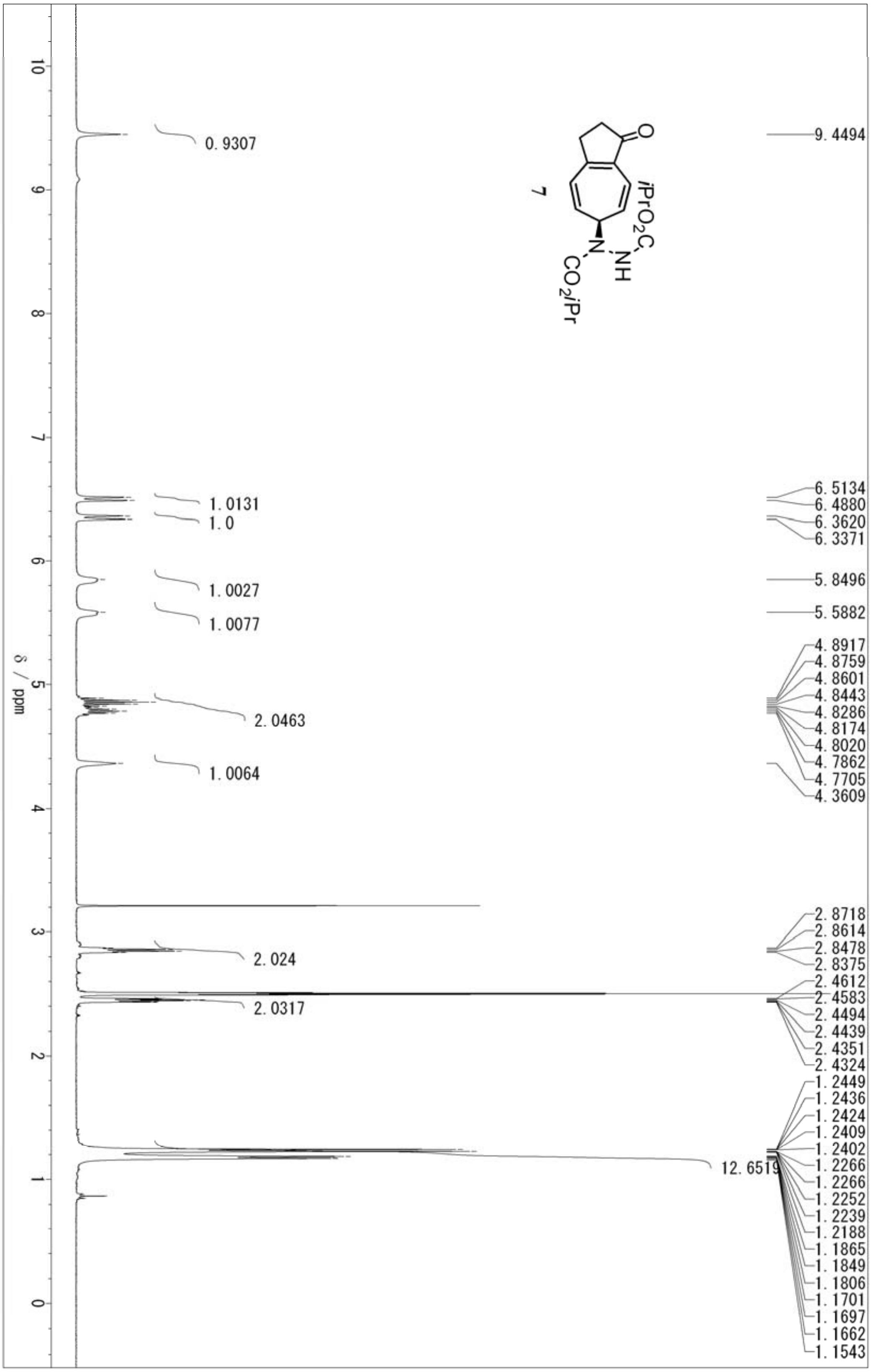


Figure S5. ^{1}H NMR spectra of 7 in DMSO-d_6

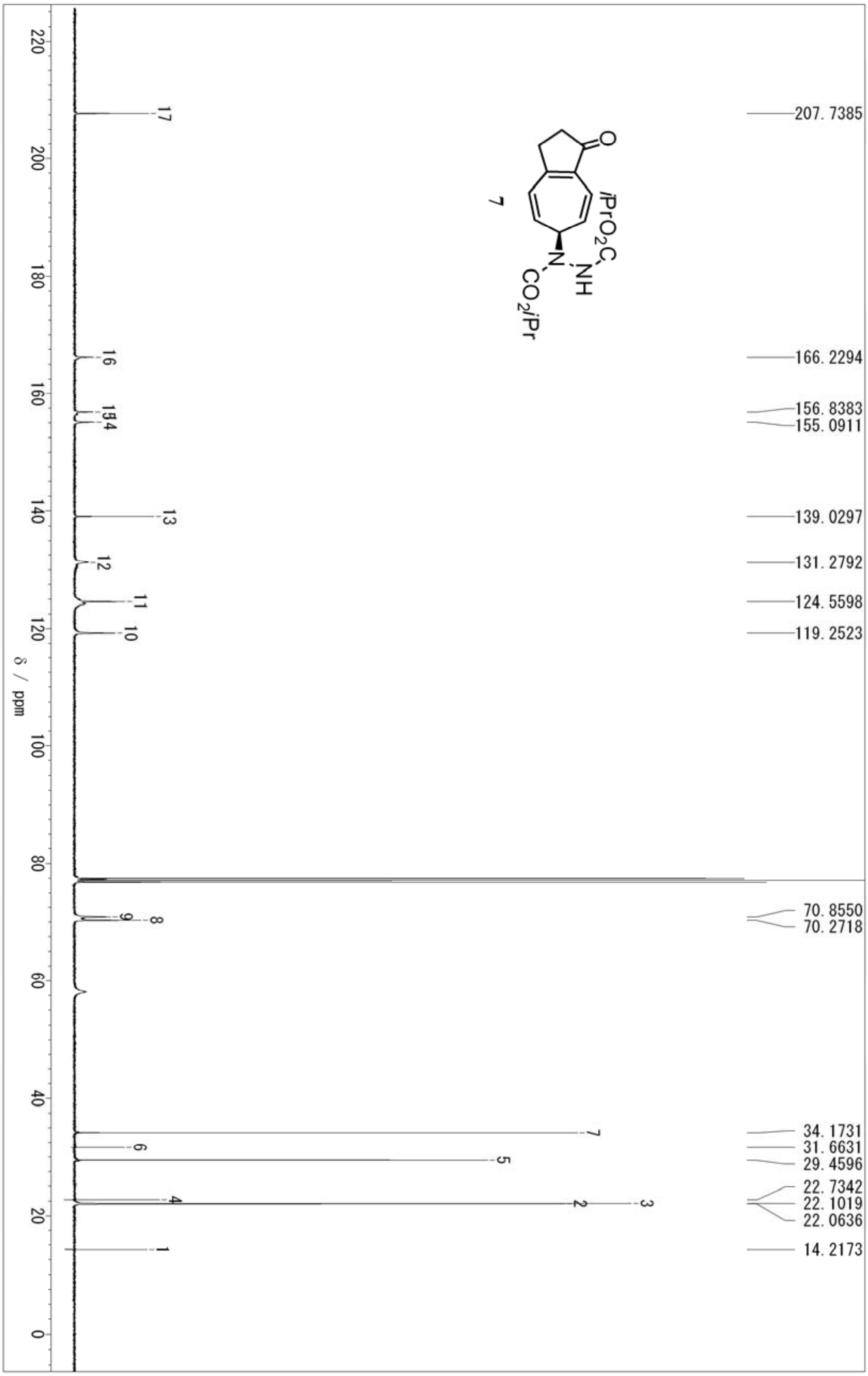


Figure S6. ^{13}C NMR spectra of 7 in CDCl$_3$

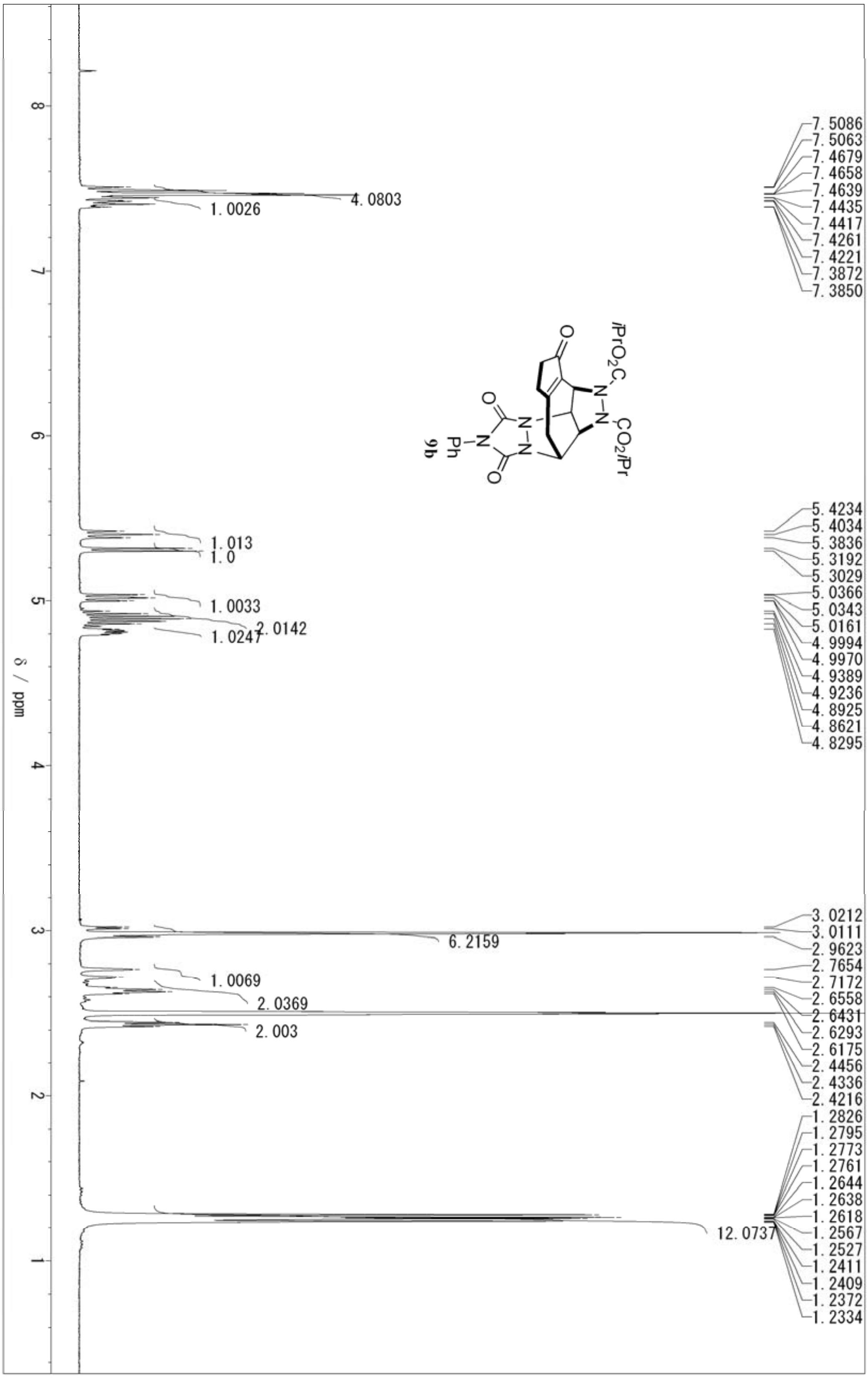


Figure S7. ^{1}H NMR spectra of 9b in DMSO-d_6

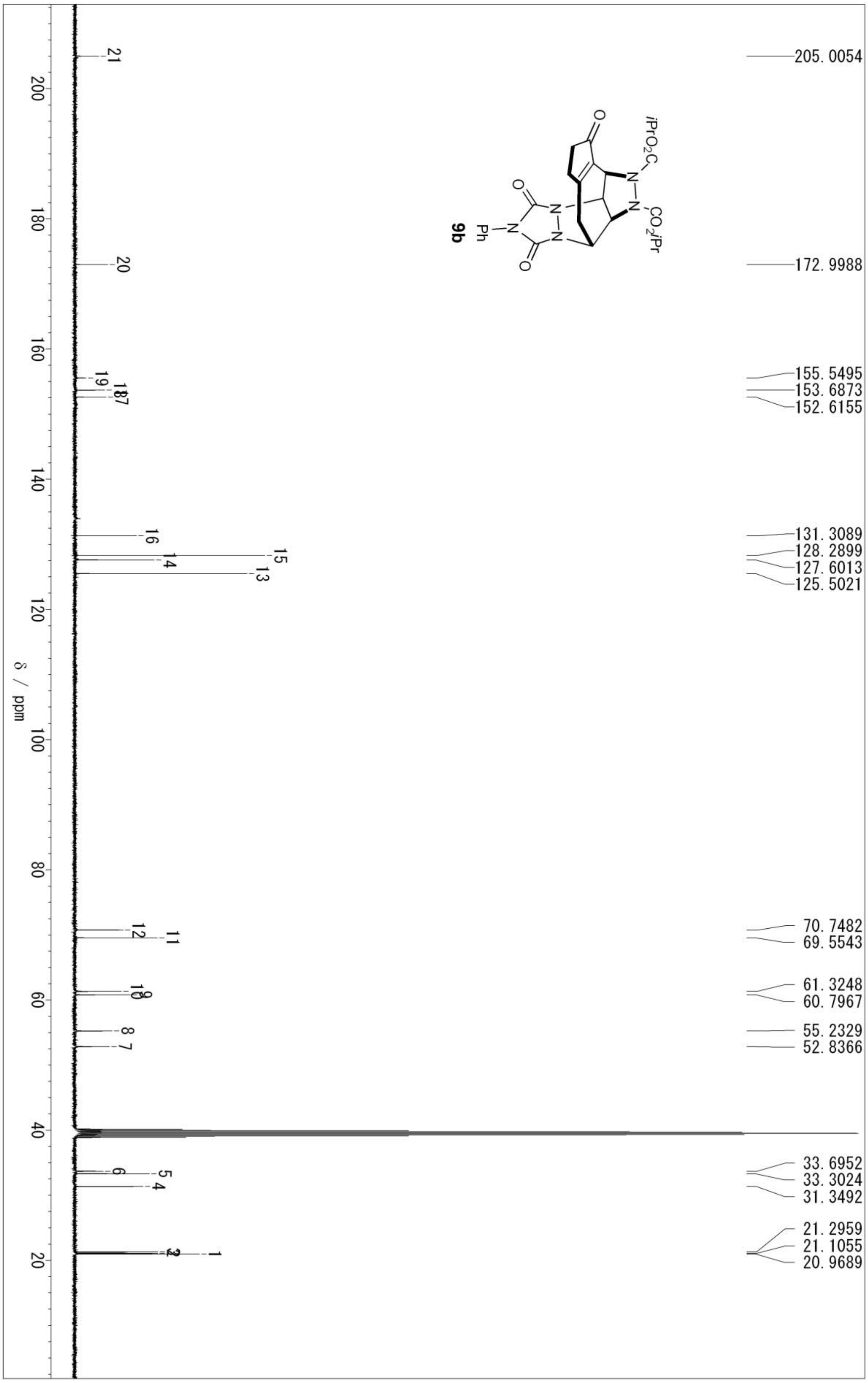


Figure S8. ^{13}C NMR spectra of 9b in DMSO-d_6

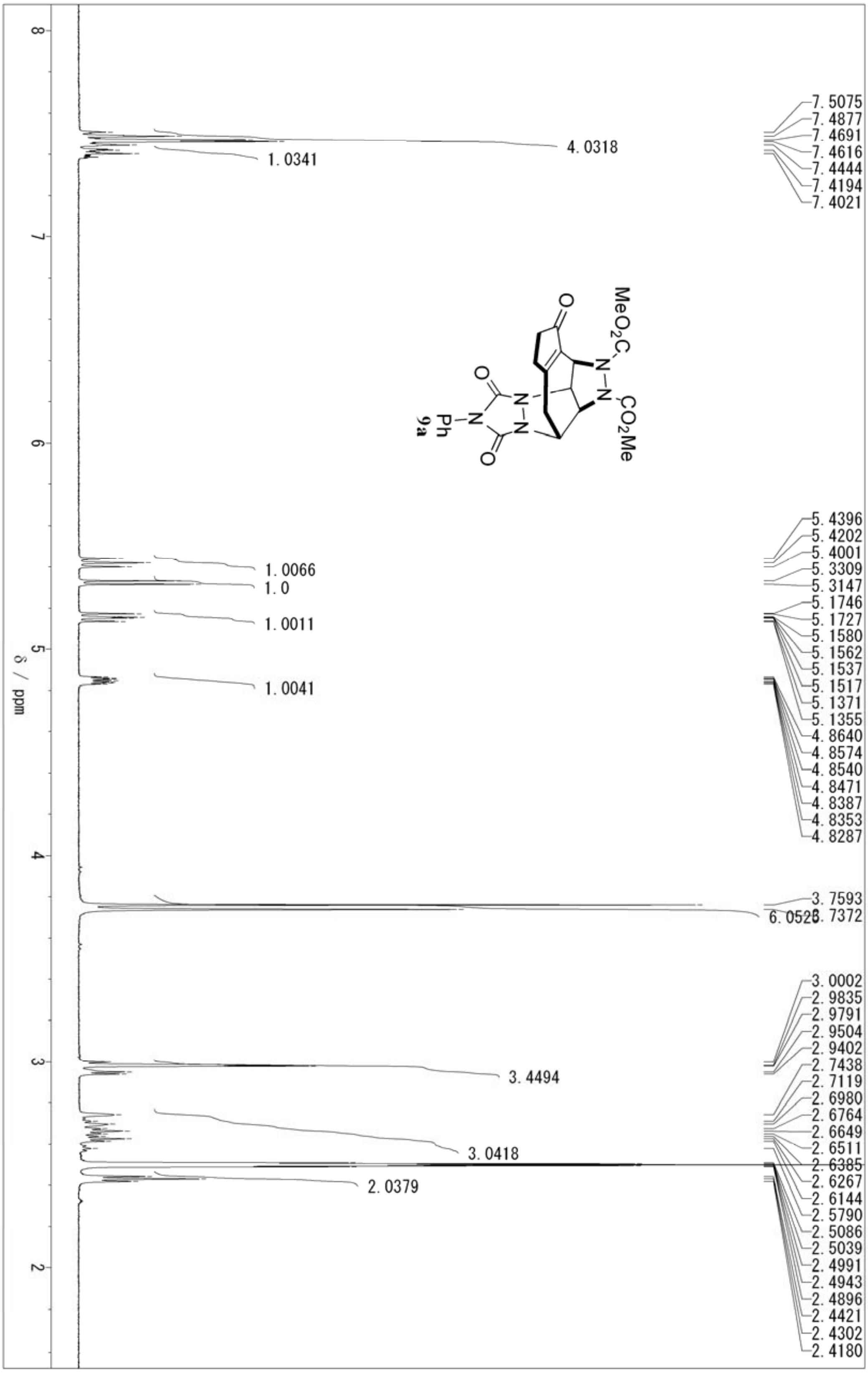


Figure S9. ^{1}H NMR spectra of 9a in DMSO-d_6

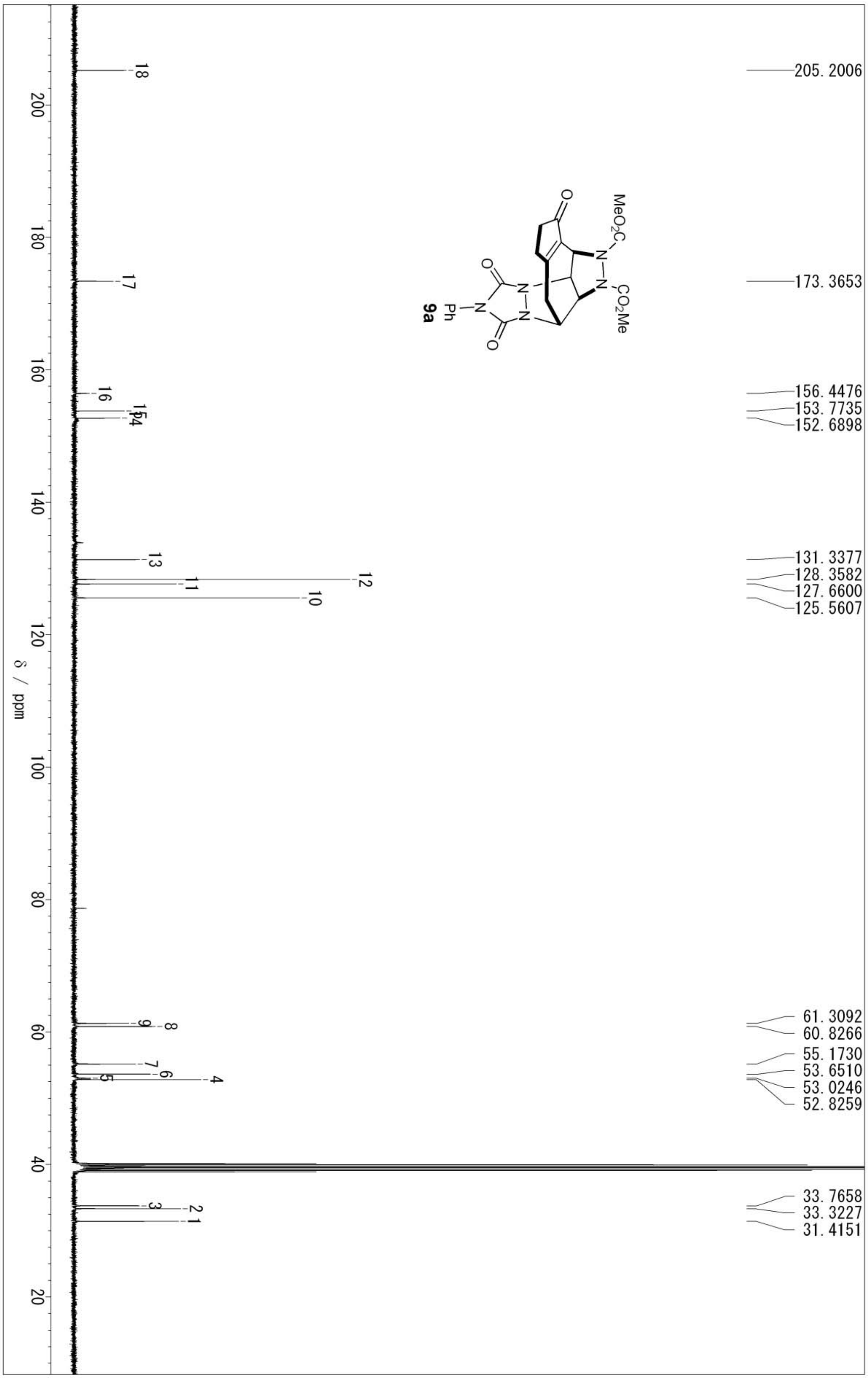


Figure S10. ^{13}C NMR spectra of 9a in DMSO-d_6

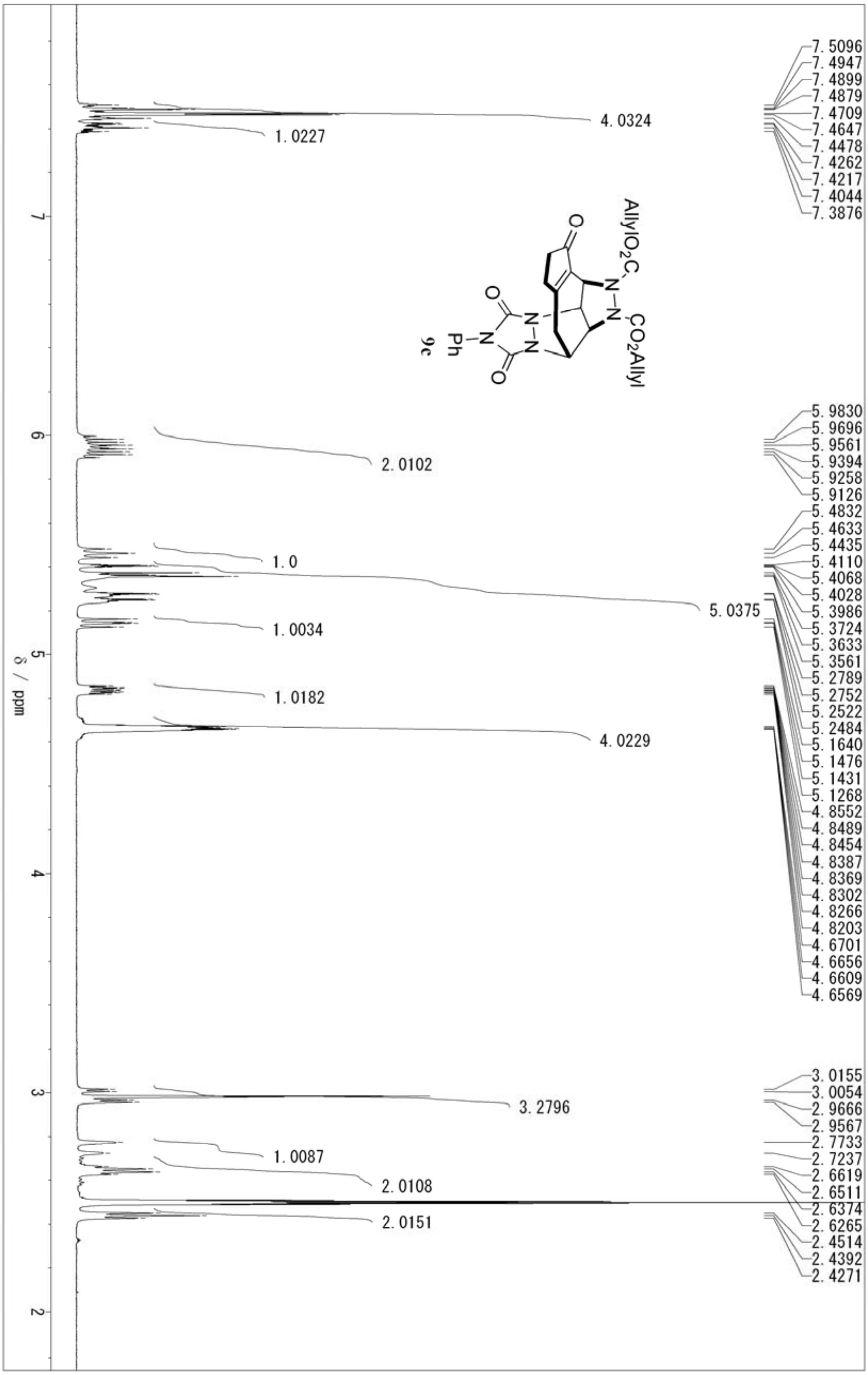


Figure S11. ^{1}H NMR spectra of 9c in DMSO-d_6

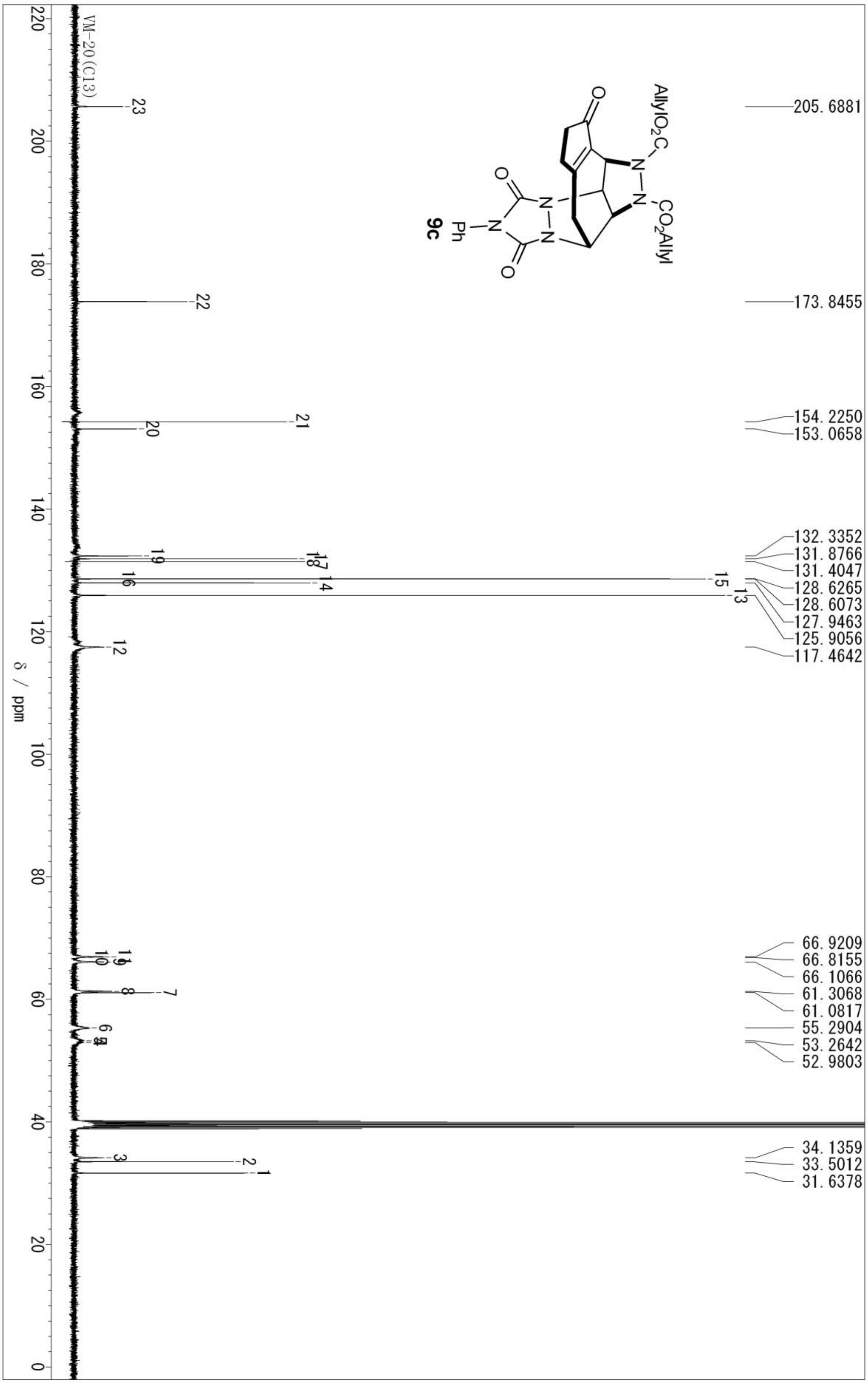
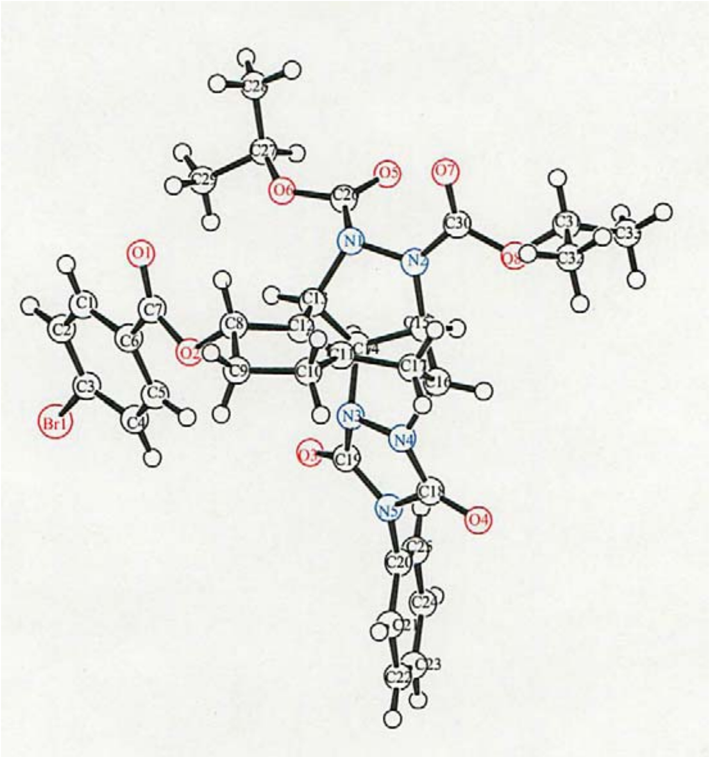
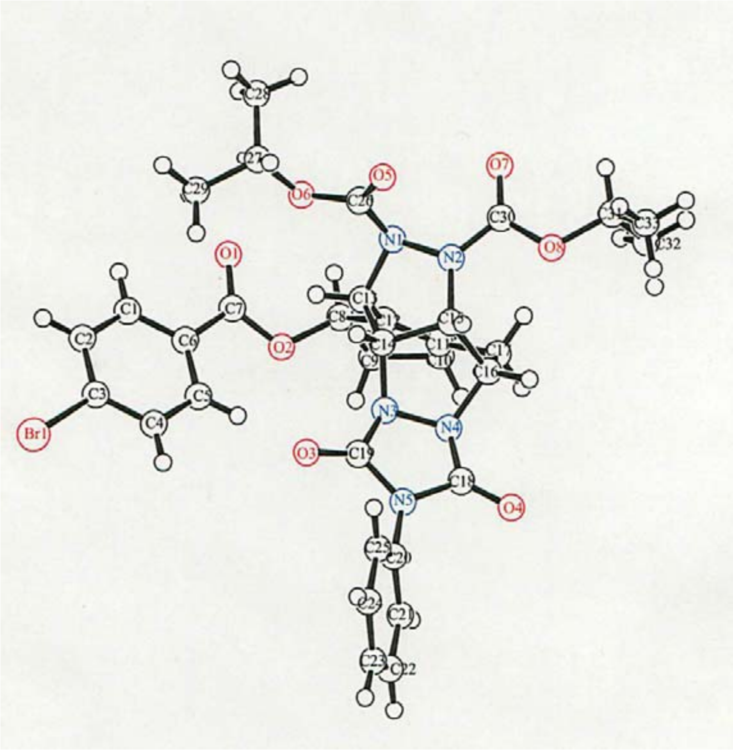


Figure S12. ^{13}C NMR spectra of 9c in DMSO-d_6

X-ray Structure Report for CCDC-759029

ORTEP drawings of X-ray crystal structure of compound **10b**





Data Collection

A colorless block crystal of $C_{33}H_{34}BrO_8N_5$ having approximate dimensions of 0.15 x 0.11 x 0.03 mm was mounted in a loop. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu-Kα radiation.

Indexing was performed from 3 oscillations that were exposed for 180 seconds. The crystal-to-detector distance was 127.40 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

a = 12.0539(2) Å
b = 23.6403(4) Å β = 108.9507(7)$^{\circ}$
c = 12.1023(2) Å
V = 3261.70(10) Å^3

For Z = 4 and F.W. = 708.56, the calculated density is 1.443 g/cm^3. The systematic absences of:

h0l: l ± 2n
0k0: k ± 2n

uniquely determine the space group to be:

$P2_1/c$ (#14)

The data were collected at a temperature of -50 $\pm$ 1°C to a maximum 2θ value of 136.5°. A total of 96 oscillation images were collected. A sweep of data was done using ω scans from 80.0 to 260.0° in 15.0° step, at χ=54.0° and ϕ = 0.0°. The exposure rate was 60.0 [sec./$^{\circ}$]. A second sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=54.0° and ϕ = 60.0°. The exposure rate was 60.0 [sec./$^{\circ}$]. Another sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=54.0° and ϕ = 120.0°. The exposure rate was 60.0 [sec./$^{\circ}$]. Another sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=54.0° and ϕ = 180.0°. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=54.0° and ϕ = 240.0°. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=54.0° and ϕ = 320.0°. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=20.0° and ϕ = 0.0°. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 15.0° step, at χ=20.0° and ϕ = 140.0°. The exposure rate was 60.0 [sec./°]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Data Reduction

Of the 57974 reflections that were collected, 5962 were unique (R_{int} = 0.032); equivalent reflections were merged.

The linear absorption coefficient, μ, for Cu-Kα radiation is 22.206 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.865 to 0.936. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[3] on F^2 was based on 5962 observed reflections and 425 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.0649$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2)/ \Sigma w(Fo^2)^2]^{1/2} = 0.2151$$

The standard deviation of an observation of unit weight[4] was 1.13. A Sheldrick weighting scheme was used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.75 and -0.75 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[8]. All calculations were performed using the CrystalStructure[9] crystallographic software package except for refinement, which was performed using SHELXL-97[10].

References

(1) SHELX97: Sheldrick, G.M. (1997).

(2) DIRDIF99: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1999). The DIRDIF-99 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least Squares function minimized: (SHELXL97)

$$\Sigma w(F_o^2-F_c^2)^2 \qquad \text{where w = Least Squares weights.}$$

(4) Standard deviation of an observation of unit weight:

$$[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$$

where: N_o = number of observations
N_v = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) CrystalStructure 3.8: Crystal Structure Analysis Package, Rigaku and Rigaku Americas (2000-2007). 9009 New Trails Dr. The Woodlands TX 77381 USA.

(10) SHELX97: Sheldrick, G.M. (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{33}H_{34}BrO_8N_5$
Formula Weight	708.56
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.15 X 0.11 X 0.03 mm
Crystal System	monoclinic
Lattice Type	Primitive
Indexing Images	3 oscillations @ 180.0 seconds
Detector Position	127.40 mm
Pixel Size	0.100 mm
Lattice Parameters	a = 12.0539(2) Å b = 23.6403(4) Å c = 12.1023(2) Å β = 108.9507(7) ^{o} V = 3261.70(10) Å^3

Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.443 g/cm^3
F_{000}	1464.00
μ(CuKα)	22.206 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku RAXIS-RAPID
Radiation	CuKα (λ = 1.54187 Å) graphite monochromated
Detector Aperture	460 mm x 256 mm
Data Images	96 exposures
ω oscillation Range (χ=54.0, ϕ=0.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
ω oscillation Range (χ=54.0, ϕ=60.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
ω oscillation Range (χ=54.0, ϕ=120.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
ω oscillation Range (χ=54.0, ϕ=180.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
ω oscillation Range (χ=54.0, ϕ=240.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°

ω oscillation Range (χ=54.0, ϕ=320.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
ω oscillation Range (χ=20.0, ϕ=0.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
ω oscillation Range (χ=20.0, ϕ=140.0)	80.0 - 260.0°
Exposure Rate	60.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	136.5°
No. of Reflections Measured	Total: 57974 Unique: 5962 (R_{int} = 0.032)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.865 - 0.936)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w (Fo^2 - Fc^2)^2
Least Squares Weights	w = 1/ [$\sigma^2(Fo^2) + (0.0831 \cdot P)^2$ $+ 5.8952 \cdot P$] where P = (Max(Fo^2,0) + 2Fc^2)/3
$2\theta_{max}$ cutoff	136.5°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	5962
No. Variables	425
Reflection/Parameter Ratio	14.03
Residuals: R1 (I>2.00σ(I))	0.0649
Residuals: R (All reflections)	0.1067
Residuals: wR2 (All reflections)	0.2151
Goodness of Fit Indicator	1.133
Max Shift/Error in Final Cycle	0.000

Maximum peak in Final Diff. Map	0.75 $e^{-}/Å^{3}$
Minimum peak in Final Diff. Map	-0.75 $e^{-}/Å^{3}$