Synthesis of a Benzodiazepine-derived Rhodium (Amino)(aryl)carbene Complex by C-H Bond Activation

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Supporting Information

I. Experimental Section

General Experimental. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. All reactions were performed in glassware that had been oven-dried overnight or flame-dried under high vacuum immediately prior to use. Air- and water-sensitive complexes were stored and manipulated in either a Braun or Vac Atmospheres nitrogen glove box unless otherwise noted. Tricyclohexylphosphine was purchased from Strem and stored in a nitrogen glovebox. THF-d_8 was vacuum transferred from sodium/benzophenone ketyl, degassed by three freeze-pump-thaw cycles, and stored under an atmosphere of nitrogen in a sealed vessel. $CDCl_3$ was treated with potassium carbonate and magnesium sulfate, then passed through glass-fiber filter paper prior to use. Non-deuterated reaction solvents were passed through a column of activated alumina under nitrogen pressure, and ether and THF were subsequently sparged with nitrogen prior to use.[1] Triethylamine was distilled from calcium hydride and stored under nitrogen prior to use. Ethereal solutions of methyllithium were titrated with 3,5-di(*t*-butyl)-4-hydroxytoluene(BHT)/fluorene in dry THF immediately prior to use. $ZnCl_2$ was fused under high vacuum and stored under nitrogen. [RhCl(coe)$_2$]$_2$ (coe = *cis*-cyclooctene) was prepared according to literature methods[2] and stored at -30 °C under nitrogen. Thin-layer chromatography was performed on 60 Å F254 250-μm silica gel plates. Flash column chromatography was performed using silica gel (60 Å 230-240 mesh). NMR spectra were obtained on Bruker AVQ-400 and AVB-400 instruments. For ^{1}H and ^{13}C spectra, chemical shifts (δ) are reported relative to a residual solvent peak (3.58 ppm for ^{1}H NMR spectra in THF-d_8, 7.26 ppm for ^{1}H spectra in $CDCl_3$, 77.23 ppm for ^{13}C spectra in $CDCl_3$, 2.05 ppm for ^{1}H in acetone-d_6, 28.99 ppm for ^{13}C spectra in acetone-d_6), whereas ^{31}P NMR resonances are reported with respect to a trimethyl phosphate external standard. All NMR chemical shifts are reported in units of parts per million (ppm). IR spectra were recorded using thin films with Thermo Electron Nicolet Avatar 360 and Avatar 370 FT-IR instruments equipped with attenuated total reflectance accessories. Only partial IR data are reported. Elemental analyses and mass spectrometry were performed by the UC Berkeley Mass Spectrometry Facility. Elemental analyses were performed using a Perkin Elmer 2400 Series II combustion analyzer. High-resolution EI mass spectra were obtained using a Micromass Prospec (magnetic sector) instrument. High-resolution FAB mass spectra were obtained using a Micromass ZAB2-EQ (magnetic sector) instrument. X-Ray crystallography was performed by Dr. Alan Oliver at the UC Berkeley CHEXRAY facility.

2-Methylamino-benzaldehyde (4). In a modification of the procedure described by Baum et al.,[3] an oven-dried 1L 3-necked round-bottom flask containing a magnetic stir bar was charged with anhydrous zinc chloride (18.6 g, 136 mmol) and THF (400 mL) inside an inert-atmosphere glove-box. One arm of the flask was sealed with a glass stopcock, and another sealed with a gas inlet adapter. Methyllithium (45.5 mL, 2.4 M in diethyl ether, 110 mmol) was added via syringe to the zinc chloride slurry with vigorous stirring to generate the organozinc reagent mixture, which was stirred at ambient temperature for an additional 40 min. A solution of anthranil (benzo[*c*]isoxazole, 5.50 mL, 54.6 mmol) in THF (55 mL) and a solution of anhydrous nickel(acac)$_2$ (acac = acetylacetonate, 1.40 g, 5.46 mmol) in THF (55 mL) were then successively added to the stirred organozinc reagent slurry. The third arm of the flask was sealed with a glass stopcock, and the reaction vessel was removed from the glovebox and placed under positive nitrogen pressure on a dual gas manifold. The reaction mixture was stirred at ambient

temperature for 3 h and 20 min, and the reaction was then quenched by addition of 18 mL of 6 N HCl. The resulting mixture was adjusted to pH 6 by addition of saturated sodium bicarbonate with vigorous stirring, and was decanted away from the green solids, which were triturated with diethyl ether (2 x 50 mL). The combined solutions were concentrated *in vacuo* until precipitation occurred, and the resulting mixture was partitioned between diethyl ether (200 mL) and water (50 mL) in a separatory funnel, adding a mixture of anhydrous magnesium sulfate (24.2 g) in water (200 mL) to expedite phase separation. The turbid aqueous phase was separated from the orange organic phase and flocculent purple solid and was back-extracted with two additional 100 mL aliquots of ether. The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield the crude product, which was chromatographed on silica gel, eluting with 9:1 petroleum ether:ethyl acetate. Fractions containing the desired product were concentrated to a yellow oil containing a residual white impurity that was distilled under reduced pressure (ca. 0.1 torr, bp = 51 ºC) to give **1** (4.70 g, 64% yield), as a yellow oil that exhibited spectroscopic properties consistent with literature data.[3] ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.82 (s, 1H, aldehyde C-*H*), 8.25 (br s, 1H, N-*H*), 7.40-7.65 (m, 2H, Ar-*H*), 6.66-6.71 (m, 2H, Ar-*H*) 2.93 (s, 3H, methyl C-*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 193.9 (*C*HO), 151.6 (*C$_{Ar}$*), 136.6 (*C$_{Ar}$*), 135.9 (*C$_{Ar}$*), 118.4 (*C$_{Ar}$*), 114.7 (*C$_{Ar}$*), 110.4 (*C$_{Ar}$*), 29.12 (N-*Me*).

1-Methyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (6). An oven-dried 100 mL round-bottom Schlenk flask containing a magnetic stir bar was sealed with a rubber septum and placed under positive nitrogen pressure on a dual gas manifold. Aminobenzaldehyde **1** (1.56 g, 11.5 mmol) was added to the flask via syringe, followed by a 30 mL aliquot of dry dichloromethane. The resulting solution was stirred while being allowed to cool in an ice-water bath. Triethylamine (1.70 mL, 12.2 mmol) was added via syringe to the stirred solution. The Schlenk sidearm valve was closed and a syringe fitted with a nitrogen balloon was inserted into the rubber septum. Bromoacetyl bromide (1.51 mL, 17.3 mmol) was added via syringe to the reaction mixture with vigorous stirring. The reaction vessel was removed from the ice-water bath 15 min after the addition was complete, and the reaction mixture was stirred at ambient temperature while the reaction progress was monitored by thin-layer chromatography. After 4 h, the reaction mixture was poured into 100 mL of ice water, and the resulting mixture transferred to a separatory funnel. The crude product was extracted into dichloromethane (100 mL). The aqueous phase was separated and back-extracted with dichloromethane (2 x 25 mL). The combined organic fractions were washed with saturated sodium bicarbonate (2 x 60 mL), 0.5 M sulfuric acid (2 x 60 mL), water (80 mL), and saturated potassium bromide (80 mL). The potassium bromide solution was back-extracted with dichloromethane (40 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield the crude α-bromoamide intermediate **5** as a viscous brown oil that was chromatographed on silica gel using 1:2 to 1:1 ethyl acetate:hexanes solvent gradient. Fractions containing only the desired material were combined and concentrated *in vacuo* to give **5** as a yellow-green solid (2.01 g, 68 % yield). By proton NMR, **5** appeared to be composed of a 9:1 mixture of amide bond rotamers, and we have been unable to identify conditions to effect separation of these species. ^{1}H NMR (CDCl$_3$, 400 MHz); major species: δ 10.2 (s, 1H, aldehyde C-*H*), 8.01 (dd, 1H, *J* = 7.6,1.6 Hz, Ar-*H*), 7.74 (ddd, 1H, *J* = 7.6, 7.6, 1.6 Hz, Ar-*H*), 7.61 (apparent t, 1H, *J* = 7.6 Hz, Ar-*H*), 7.39 (apparent d, 1H, *J* = 7.8 Hz, Ar-*H*), 3.58 (AB q, 2H, *J* = 10.8 Hz, methylene C-*H*), 3.33 ppm (s, 3H, N-*Me*); minor species: δ 10.0 (s, 1H, aldehyde C-*H*),

7.93 (dd, 1H, J = 7.8,1.3 Hz, Ar-H), 7.68 (ddd, 1H, J = 7.7, 7.7, 1.4 Hz, Ar-H), 7.50 (apparent t, 1H, J = 7.4 Hz, Ar-H), 7.27 (apparent d, 1H, partially obscured by residual CHCl$_3$ signal, Ar-H), 4.06 (s, 2H, methylene C-H), 3.50 (s, 3H, N-Me). ^{13}C NMR (100 MHz, CDCl$_3$, major species): δ 189.1 (aldehyde C), 166.6 (amide C), 144.1 (C_{Ar}), 135.8 (C_{Ar}), 132.4 (C_{Ar}), 131.2 (C_{Ar}), 129.8 (C_{Ar}), 129.4 (C_{Ar}), 38.75 (CH_2Br), 26.12 (N-Me).

An oven dried 100 mL 3-neck round-bottom flask containing a magnetic stir bar was equipped with an oven-dried cold-finger gas condenser. The other necks of the flask were fitted respectively with a rubber septum and a gas inlet adapter, and the apparatus was flushed with nitrogen on a dual gas manifold for several minutes prior to sealing the sidearm of the gas condenser with a rubber septum. The reaction vessel was immersed in a dry ice/isopropanol slurry, and the cold finger was also charged with dry ice/isopropanol. A stream of anhydrous ammonia was passed through the condenser inlet until the flask was charged with ca. 50 mL of ammonia. A solution of **5** (1.97 g) in THF (15 mL) was added to the reaction vessel via syringe. The cooling bath was removed and the reaction mixture was warmed to reflux while stirring for 1 h. The ammonia was then allowed to evaporate. The crude product was partitioned between dichloromethane (100 mL) and water (100 mL). The organic phase was separated, washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to an orange residue that was transferred to a column of silica gel using a minimal volume of dichloromethane and eluted with ethyl acetate. Fractions containing only pure material were concentrated *in vacuo* to give the benzodiazepine **6** as an off-white solid (1.20 g, 89% yield, 61% overall yield based on **5**). ^{1}H NMR (400 MHz, acetone-d$_6$): δ 8.59 (s, 1H, imine C-H), 7.55-7.63 (m, 2 H, Ar-H), 7.47 (d, J = 8.4, 1 H, Ar-H), 7.30 (apparent t, J = 7.2, 1 H, Ar-H), 4.11 (s, 2 H, methylene C-H), 3.34 (s, 3 H, N-Me). ^{13}C NMR (100 MHz, acetone-d$_6$): δ 168.0, 163.5, 142.9, 131.6, 129.2, 127.9, 123.9, 121.2, 56.6, 34.1. IR (film): 1697, 1655, 1629, 1598, 1574, 547, 775, 762 cm^{-1}. HR-MS (EI+) Calcd. for C$_{10}$H$_{10}$N$_2$O: 174.0793. Found: 174.0793. Anal. Calcd. for C$_{10}$H$_{10}$N$_2$O: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.80; H, 5.92; N, 16.12.

II. Computational Methodology. The B3LYP/LACVP** level of theory with 'medium' grid density was employed for initial optimizations. The resulting optimized structures were resubmitted using the same method with 'fine' grid density. The Jaguar 6.5 quantum chemistry package was used throughout this study.[4] For N, C, P, Cl, and H, the 6-31G basis set of Pople and co-workers was used.[5] A Hay-Wadt effective core potential was used for Rh.[6] The symbol * indicates addition of polarization functions to atoms H through Ar. Full geometry optimizations and analytical vibrational frequency calculations were performed for all simplified model systems. Ground state structures were characterized by exactly 0 imaginary vibrational frequencies. Gibbs free energies ΔG for 298.15 K and 1 atm are based on unscaled molecular vibrations.

Table S-1. Energies for minimized structures (Figures S-2 and S-3).

| Structure	ΔG[a] (Hartrees)	relative ΔG (Kcal/mol)	ΔH (Hartrees)	relative ΔH (Kcal/mol)
7'	-2063.473439	0.00	-2063.389840	0.00
8'	-2063.480089	-4.17	-2063.396527	-4.19

a) At 298.15 K
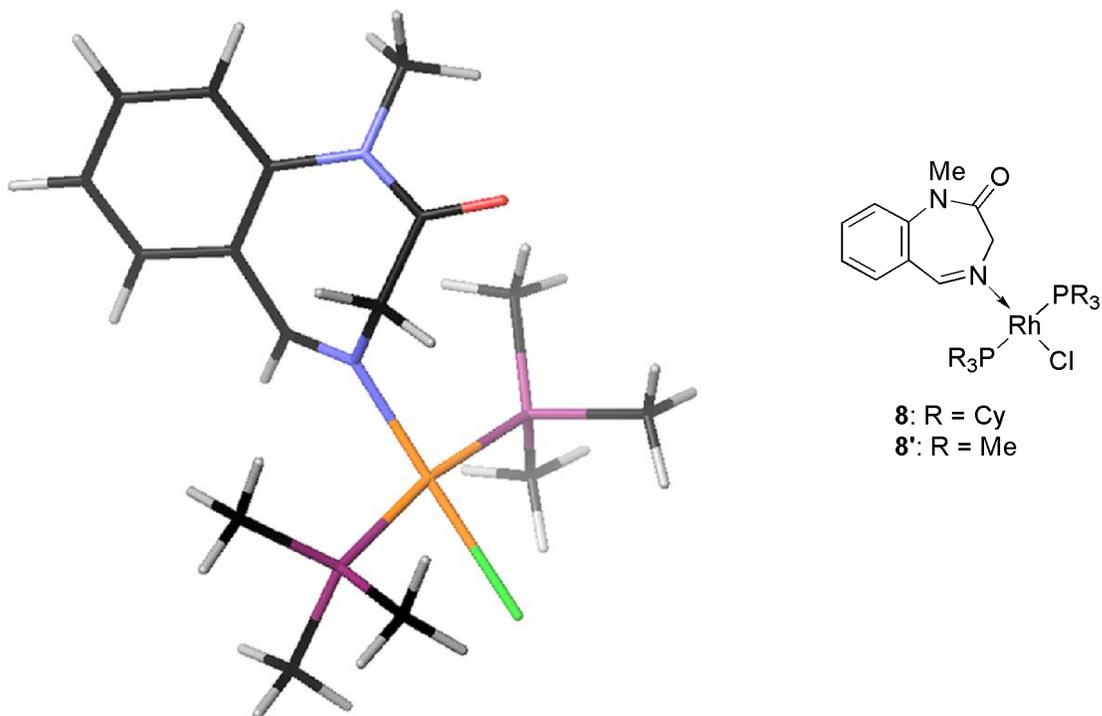
Figure S-2. DFT Geometry-optimized Structure for **8'**.
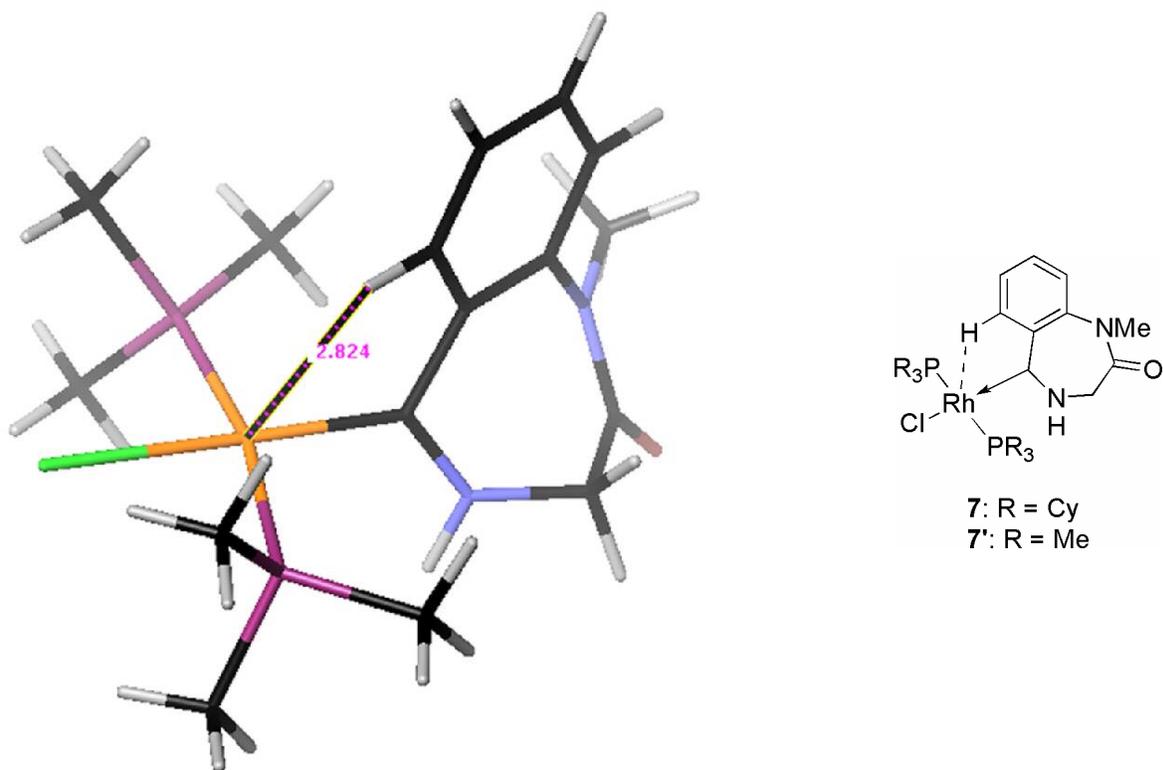

Figure S-3. DFT geometry-optimized Structure of **7'** Illustrating the Pre-agostic Interaction between the C6-H Bond and the Rhodium Center.

III. Structural Solution for **7•2THF-d₈**.

      X-ray crystallography was performed by Dr. Allen Oliver at the UC Berkeley X-ray diffraction facility (CHEXRAY). X-ray data were collected using a fragment of a bladelike crystal of **7•2THF-d₈** with a Bruker SMART[7] CCD area detector employing Mo-Kα radiation at -150 ±1 °C. Data were integrated by the program SAINT,[8] corrected for Lorentz and polarization efects, analyzed for agreement and possible absorptions using XPREP,[9] and an empirical absorption correction was applied using SADABS.[10] The structure was solved by direct methods[11] and expanded using Fourier techniques[12] Neutral atom scattering factors were taken from Cromer and Waber.[13] Anomolous dispersion effects were included in Fcalc[14] and the values for Δf' and Δf'' were those of Creagh and McAuley.[15] Values for the mass attenuation coefficents are those of Creagh and Hubbell.[16] All calculations were performed using the teXsan[17] crystallographic software package. Experimental details are summarized in the tables below.

Table S-4a. Crystal Data

Empirical Formula	$RhClP_2O_3N_2C_{54}H_{92}$
Formula Weight	1017.6
Crystal Color, Habit	Dark red, blade
Crystal Dimensions	0.27 x 0.19 x 0.10 mm
Crystal System	Triclinic
Lattice Type	Primitive
Lattice Parameters	a = 12.793(3) Å
	b = 13.340(3) Å
	c = 15.940(4) Å
	α = 84.821(3)°
	β = 82.535(3)°
	γ = 82.274(3)°
	V = 2665(1) Å³
Space Group	P 1̄(#2)
Z Value	2
D_{calc}	1.268 g/cm³
F_{000}	1092.00
μ (Mo-K$_α$)	4.72 cm⁻¹

Table S-4b. Intensity Measurements.

Diffractometer	Bruker SMART CCD
Radiation	MoKα (λ = 0.71069 Å)
	Graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame
Scan Type	ω (0.3 degrees per frame)
$2θ_{max}$	52.8°
No. of Reflections Measured	Total: 18723
	Unique: 9961 (R_{int} = 0.027)
Corrections	Lorentz-polarization
	Absorption (Tmax = 1.00 Tmin = 0.88)

Table S-4c. Structure Solution and Refinement.

Structure Solution	Direct methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma \, w(\, \mid Fo \mid - \mid Fc \mid \,)^2$
Least Squares Weights	$w = 1/\sigma^2(Fo) =$
	$\sigma^2{}_c(Fo) + [(p^2/4)Fo^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	7177
No. Variables	571
Relfection/Parameter Ratio	12.57
Residuals: R; Rw; Rall	0.037; 0.042; 0.061
Goodness of Fit Indicator	1.57
Max Shift/Effor in Final Cycle	0.03
Maximum Peak in Final Diff. Map	0.54 e^-/ Å^3
Minimum Peak in Final Diff. Map	-0.47 e^-/ Å^3

**IV.** NMR Spectra for New Compounds.
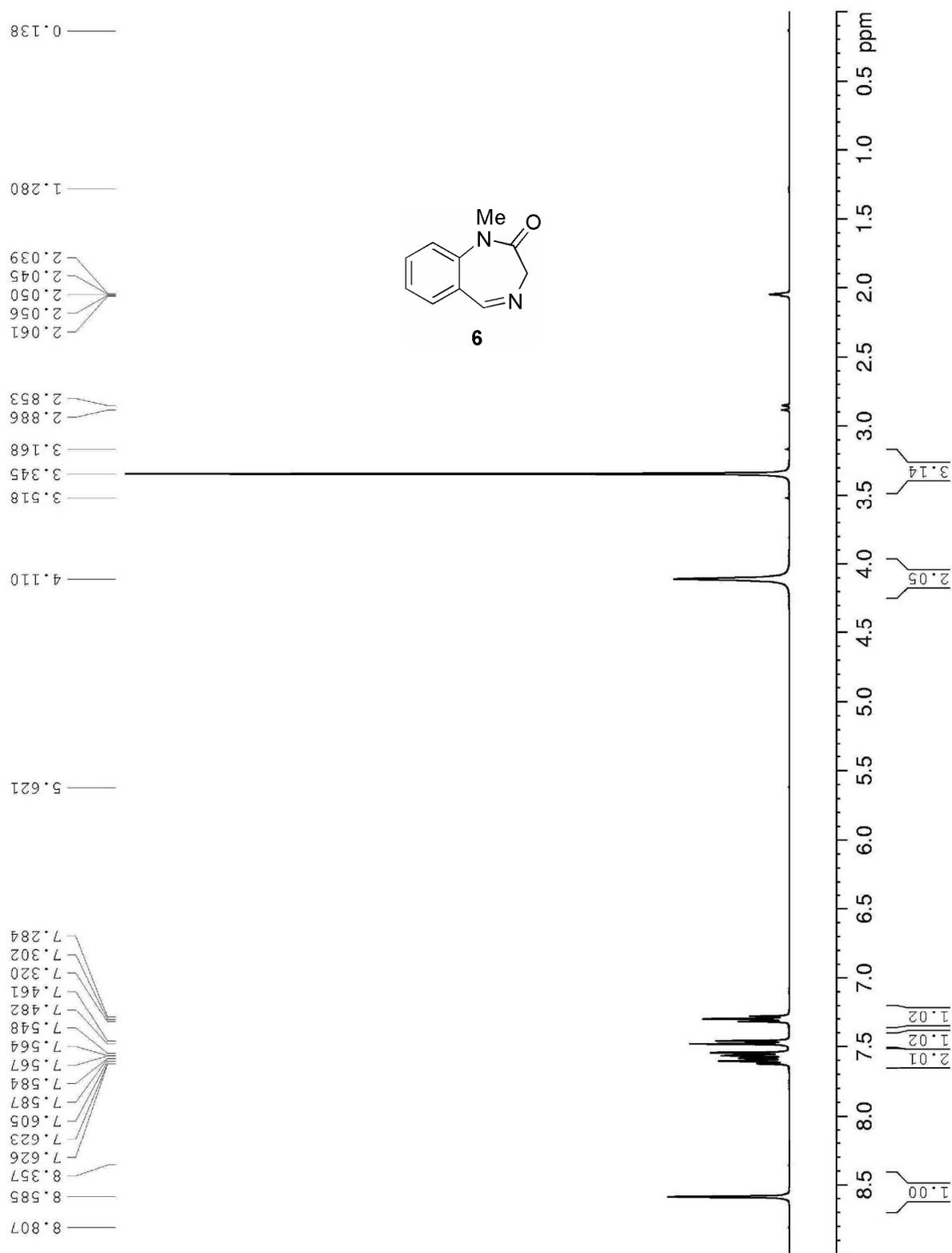
Figure S-5a. ^{1}H NMR spectrum of **6**.
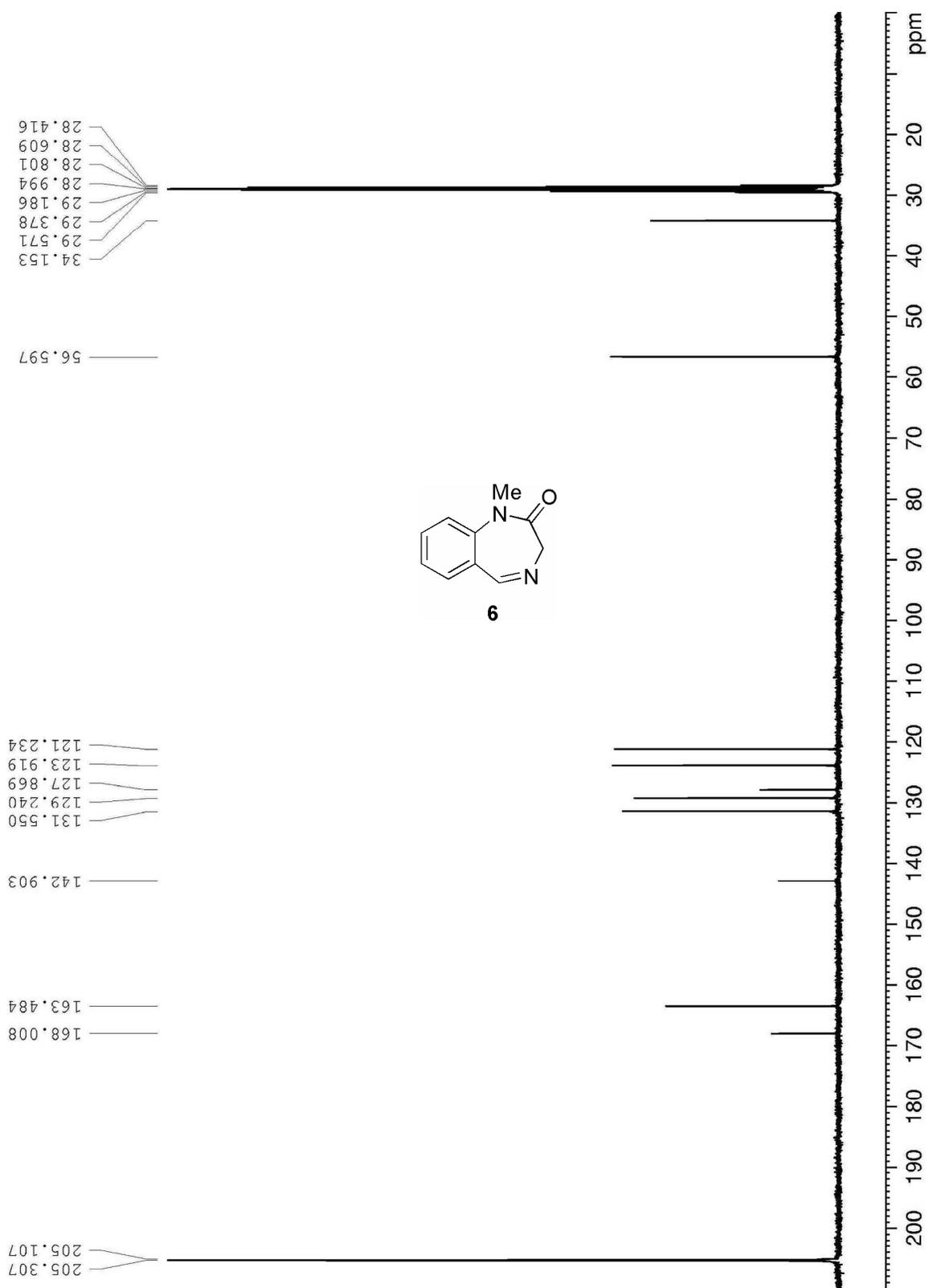
Figure S-5b. ^{13}C NMR spectrum of **6**.
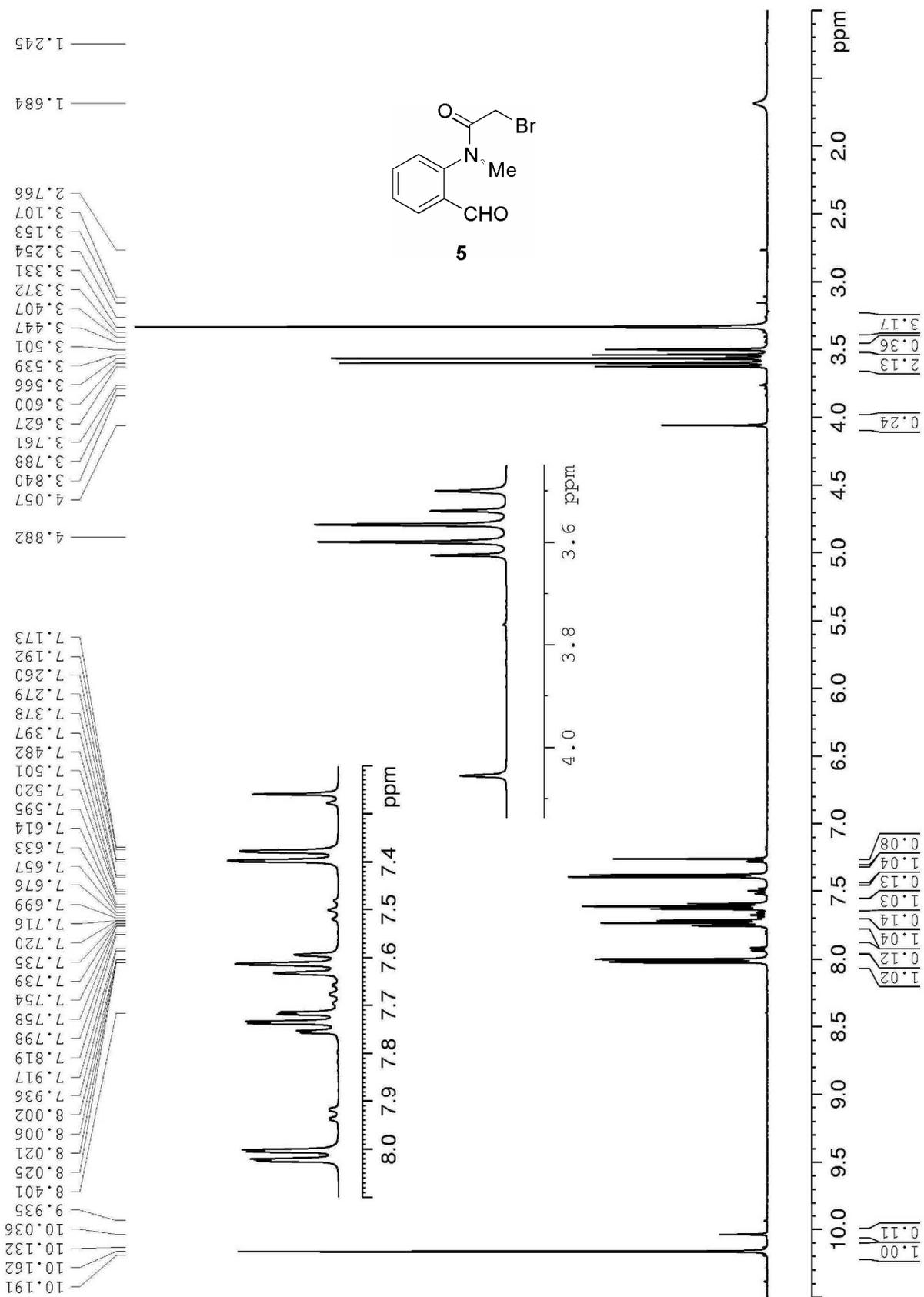
Figure S-6a. ^{1}H NMR spectrum of **5**.
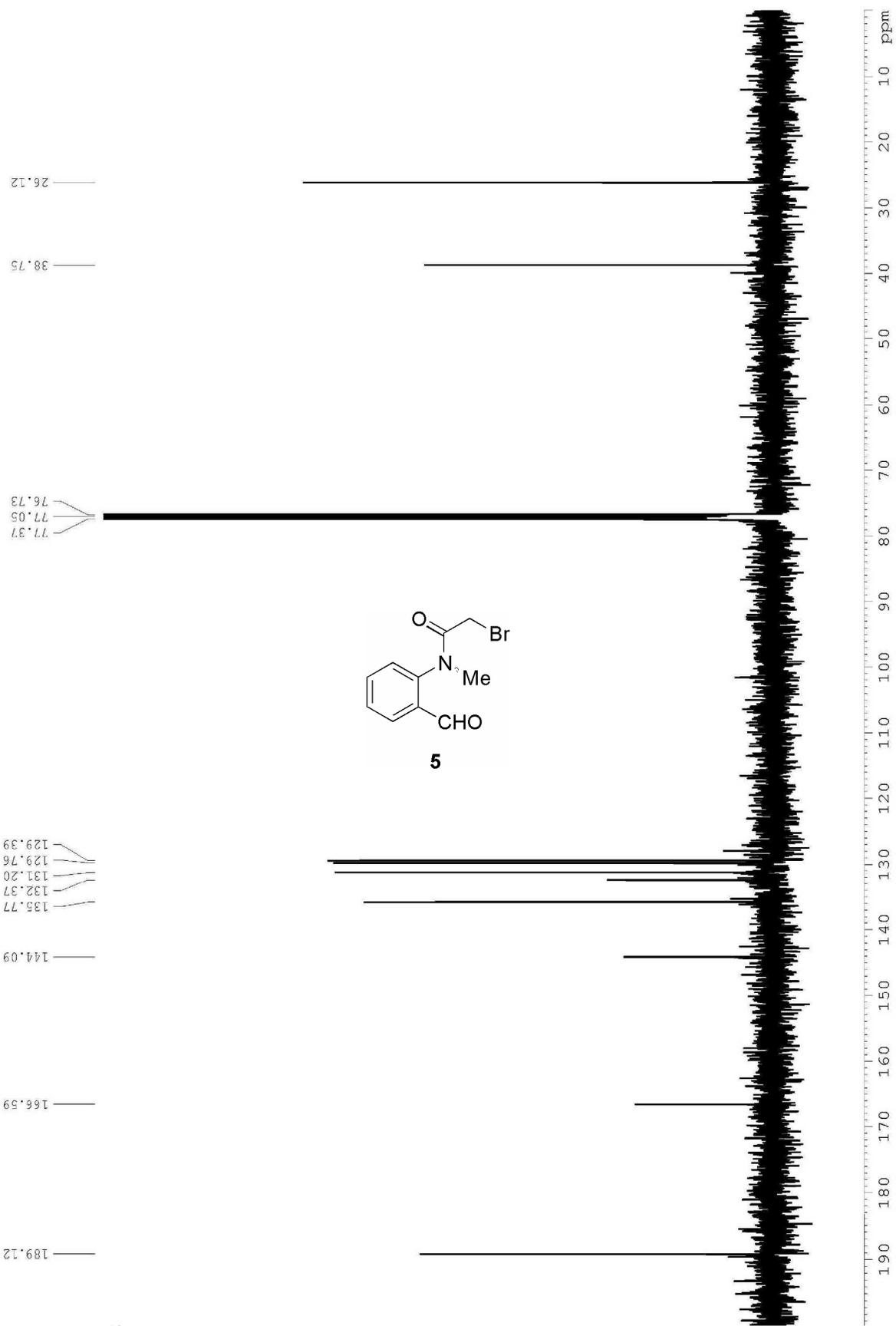
Figure S-6b. ^{13}C NMR spectrum of **5**.

26.12
38.75
76.73
77.05
77.37
129.39
129.76
131.20
132.37
135.77
144.09
166.59
189.12

5
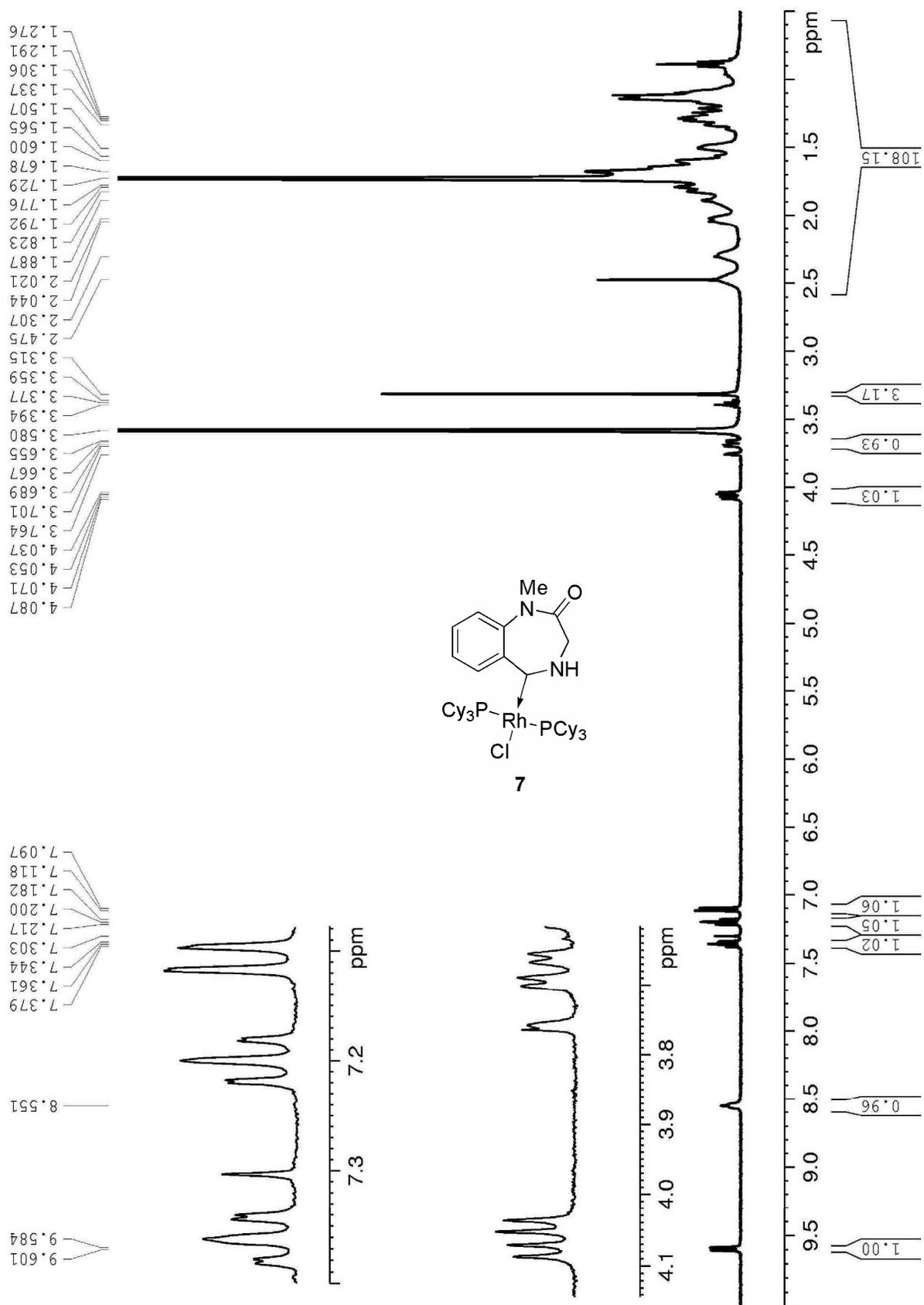
**Figure S-7a.** ^{1}H NMR Spectrum of **7**·2THF-d$_8$.
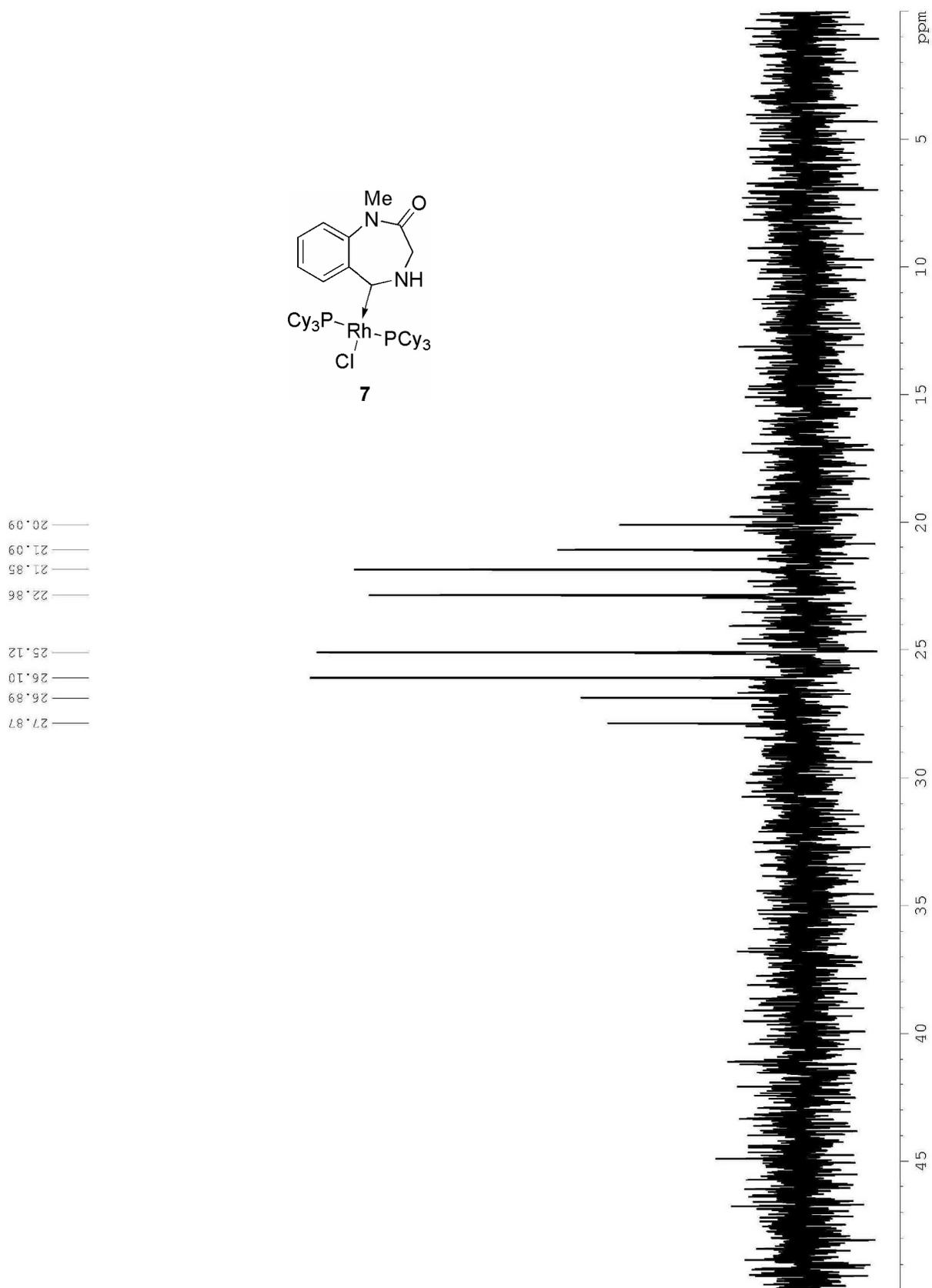
Figure S-7b. ^{31}P NMR spectrum of **7**·2THF.

V. References and Notes.

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