

Asymmetric *Morita-Baylis-Hillman* Reaction Catalyzed By Isophoronediamine-Derived Bis-(thio)urea Organocatalysts

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Supporting Information

Materials. Commercial reagents were purchased from Sigma Aldrich, Fluka, Acros, Lancaster or NovaBioChem, and used as received. Solvents were distilled and dried prior to use following standard procedures.^[1] Air- and/or moisture-sensitive reactions were carried out in a *mbraun* Unilab glove box under argon atmosphere or in the fume hood using Schlenk technique. Chromatographic separations were performed using silica gel 60 (230-400 mesh) from MN GmbH & Co.

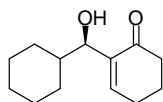
Instrumentation. Nuclear magnetic resonance (¹H and ¹³C) spectra were recorded on a Bruker AC250 (250 MHz), Bruker AC300 (300 MHz) or Bruker DPX300 (300 MHz) NMR spectrometer. FT-IR spectra were recorded on a Perkin-Elmer Paragon 1000. HPLC analyses were performed using Agilent 1100 Series or Merck Hitachi LaChrom HPLC instrument. GC analyses were performed using HP 6890 Series or HP 6890N instrument and N₂ as carrier gas. HRMS analyses were performed on a *Finnigan* MAT 900S spectrometer.

(I) Catalysis experiments

General procedure for catalysis experiments

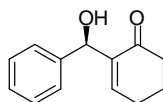
DABCO (5.61 mg, 50.0 μmol) and catalyst **1d** (35.6 mg, 50.0 μmol) were dissolved in 2-cyclohexen-1-one (**3**) (96.5 μL, 96.1 mg, 1.00 mmol), and tridecane (15.2 μL, 11.5 mg, 62.5 μmol) was added as internal standard. The mixture was cooled to 10 °C on a coolable shaker plate and cyclohexanecarbaldehyde (**2**) (30.1 μL, 28.0 mg, 250 μmol) was added. The mixture was shaken for 72 h at 10 °C and 400 rpm. Aliquots of 10.0 μL were taken at intervals and analyzed by GC on chiral stationary phase. In case of HPLC analysis, the reaction was stopped after 72 h and the product isolated by column chromatography (*n*-hexane : ethyl acetate 3 : 1).

2-(Cyclohexyl-hydroxy-methyl)-cyclohex-2-en-1-one (Table 4, entry 1)



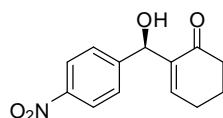
The racemic product was obtained following a literature procedure.^[2] GC (*Varian* CP-Chirasil-Dex, 160 °C (33 min)): τ_R = 2.16 min (tridecane), 23.28 min ((*S*)-product, minor), 25.04 min ((*R*)-product, major). Absolute configuration was assigned by comparison of the retention times with those reported by *Nagasawa* et al.^[3]

2-(Hydroxy-phenyl-methyl)-cyclohex-2-en-1-one (Table 4, entry 2)



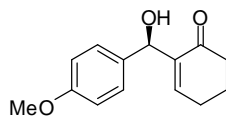
The racemic product was prepared following a literature procedure.^[2] GC (*Varian* CP-Chirasil-Dex, 160 °C (40 min)): τ_R = 2.16 min (tridecane), 30.13 min ((*S*)-product, minor), 31.96 min ((*R*)-product, major). Absolute configuration was assigned by comparison of the retention times with those reported by *Nagasawa* et al.^[3]

2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohex-2-en-1-one (Table 4, entry 3)



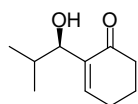
The racemic product was prepared following a literature procedure.^[4] HPLC (*Merck* (*R,R*)-Whelk O1, *n*-hexane/2-propanol 9 : 1, flow: 1.00 ml/min, 50 min): τ_R = 27.66 min ((*S*)-product, minor), 37.15 min ((*R*)-product, major). Absolute configuration was assigned by comparison of the retention times with those reported by *Schaus* et al.^[5]

2-[Hydroxy-(4-methoxy-phenyl)-methyl]-cyclohex-2-en-1-one (Table 4, entry 4)



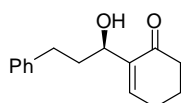
The general procedure for the catalysis experiments was followed and the product isolated by column chromatography. The product was obtained as a highly viscous yellow liquid in 79 % yield (46 mg, 198 μ mol). Analytical data were in agreement with the literature.^[6] HPLC (*Merck* (*R,R*)-Whelk O1, *n*-hexane/2-propanol 9 : 1, flow: 1.00 ml/min, 50 min): τ_R = 29.41 min (minor), 33.12 min (major). Absolute configuration was not assigned.

2-(1-Hydroxy-2-methyl-propyl)-cyclohex-2-en-1-one (Table 4, entry 5)



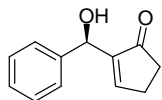
The racemic product was prepared following a literature procedure.^[4] GC (*Varian* CP-Chirasil-Dex, 130 °C (22 min)): τ_R = 4.91 min (tridecane), 17.95 min ((*S*)-product, minor), 19.52 min ((*R*)-product, major). Absolute configuration was assigned by comparison of the retention times with those reported by *Nagasawa et al.*^[3]

2-(1-Hydroxy-3-phenyl-propyl)-cyclohex-2-en-1-one (Table 4, entry 6)



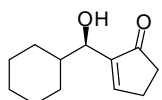
The general procedure for the catalysis experiments was followed and the product isolated by column chromatography. The product was obtained as a highly viscous yellow liquid in 52 % yield (30 mg, 130 μ mol). Analytical data were in agreement with the literature.^[7] HPLC (*Daicel* CHIRALCEL, OD-H, *n*-hexane/2-propanol 9 : 1, flow: 0.50 ml/min, 35 min): τ_R = 18.76 min ((*S*)-product, minor), 37.15 min ((*R*)-product, major). Absolute configuration was assigned by comparison of the retention times with those reported by *Schaus et al.*^[5]

2-(Hydroxy-phenyl-methyl)-cyclopent-2-en-1-one (Table 4, entry 7)



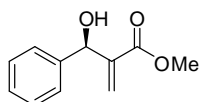
The racemic product was prepared following a literature procedure.^[4] GC (*Varian* CP-Chirasil-Dex, 160 °C (29 min)): τ_R = 2.17 min (tridecane), 23.33 min, 25.20 min. Absolute configuration was not assigned.

2-(Cyclohexyl-hydroxy-methyl)-cyclopent-2-en-1-one (Table 4, entry 8)



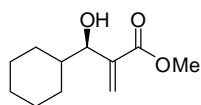
To a mixture of cyclohexanecarbaldehyde (60.2 μ L, 500 μ mol, 1.00 eq), imidazole (34.0 mg, 500 μ mol, 1.00 eq) in aqueous NaHCO₃ solution (1M, 2.00 mL) and THF (500 μ L) was added 2-cyclopenten-1-one (62.9 μ L, 750 μ mol, 1.50 eq), and the solution was stirred for 60 h at rt. HCl (1M, 3.00 mL) was added and the aqueous phase extracted with ethyl acetate (3 \times 3.00 mL). The organic phase was dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The racemic product was obtained as a highly viscous yellow liquid in 41 % yield (40.0 mg, 206 μ mol). Analytical data were in agreement with the literature.^[8] GC (*Varian* CP-Chirasil-Dex, 160 °C (22 min)): τ_R = 2.17 min (tridecane), 17.53 min (minor), 18.59 min (major). Absolute configuration was not assigned.

2-(Hydroxy-phenyl-methyl)-acrylic acid methyl ester (Table 4, entry 9)



The racemic product was prepared following a literature procedure.^[2] GC (*Varian* CP-Chirasil-Dex, 135 °C (35 min)): τ_R = 4.14 min (tridecane), 28.15 min, 29.50 min. Absolute configuration was not assigned.

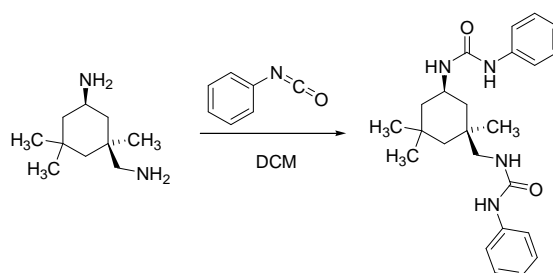
2-(Cyclohexyl-hydroxy-methyl)-acrylic acid methyl ester (Table 4, entry 10)



The racemic product was prepared following a literature procedure.^[9] GC (Varian CP-Chirasil-Dex, 130 °C (35 min)): τ_R = 4.91 min (tridecane), 25.97 min (minor), 26.83 min (major). Absolute configuration was not assigned.

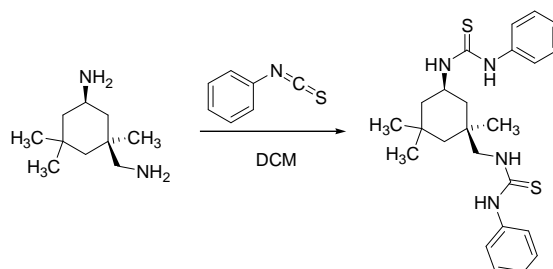
(II) Preparation of the bis-(thio)urea catalysts 1a, 1c, 1e and 1f.

Preparation of N-Phenyl-N'-[(1R,3S)-3-[[[(phenylamino)oxomethyl]amino]methyl]-3,5,5-trimethyl-cyclohexyl]urea (1a)



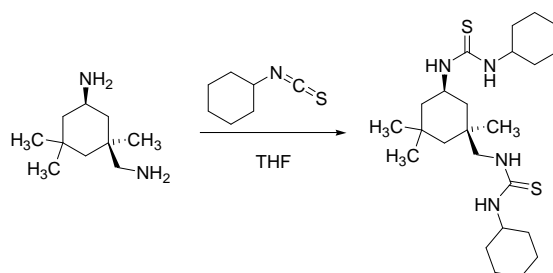
(1R,3S)-3-(Aminomethyl)-3,5,5-trimethyl-cyclohexylamine (860 μ L, 4.65 mmol, 1.00 eq) was dissolved in dry DCM (8.00 mL), and phenylisocyanate (1.02 mL, 9.34 mmol, 2.01 eq) was added. A colorless precipitate formed immediately which was filtered off. It was recrystallized from $\text{CHCl}_3/\text{MeOH}$ to yield the desired bis-urea quantitatively (1.90 g, 4.65 mmol) as colorless crystals suitable for x-ray crystallography. $[\alpha]_{589}^{20} = -38.5^\circ$ ($c = 1.09$, MeOH). mp 190-193°C. $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ = 0.82-1.11 (m; 12H), 1.12-1.25 (m; 1H), 1.52-1.70 (m; 2H), 2.87 (dq; $J = 11.7$ Hz, 5.85 Hz, 6.43 Hz, 2H), 3.71-3.89 (m; 1H), 5.96 (d; $J = 7.60$ Hz, 1H), 6.21 (t; $J = 5.85$ Hz, 1H), 6.82-6.92 (m; 2H), 7.13-7.26 (m; 4H), 7.32-7.42 (m; 4H), 8.25 (s; 1H), 8.37 (s; 1H). $^{13}\text{C-NMR}$ (75 MHz, DMSO-d_6): δ = 23.2, 27.5, 31.5, 34.9, 36.0, 41.8, 42.3, 46.1, 46.8, 52.7, 117.3, 117.4, 120.8, 128.5, 128.6, 140.4, 140.5, 154.4, 155.3. FT-IR (CsI): $\tilde{\nu}$ [cm^{-1}] = 3334 (m(br)), 2959 (w), 1646, 1603, 1560 (all s), 1500, 1444, 1314, 1237 (all m), 758, 692 (both w). HRMS (ESI): Calcd. for $[\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_2\text{Na}]$ ($[\text{M}+\text{Na}]^+$): 431.242, Found: 431.242 (± 0.002 u). Anal. Calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_2$: C 70.56, H 7.90, N 13.71 Found: C 70.54, H 8.04, N 13.71.

Preparation of *N*-Phenyl-*N'*-[(1*R*,3*S*)-3-[[[(phenylamino)thioxomethyl]amino]methyl]-3,5,5-trimethylcyclohexyl]thiourea (**1c**)



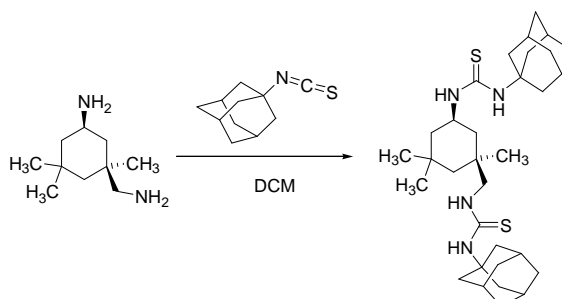
(1*R*,3*S*)-3-(Aminomethyl)-3,5,5-trimethylcyclohexylamine (200 μ L, 1.08 mmol, 1.00 eq) was dissolved in dry DCM (10.0 mL), and phenylisothiocyanate (262 μ L, 2.21 mmol, 2.05 eq) was slowly added. The mixture was stirred for two hours at rt, the solvent removed under reduced pressure, and the resulting solid recrystallized from acetone. The desired bis-thiourea was obtained quantitatively (476 mg, 1.08 mmol) as colorless crystals suitable for x-ray crystallography. $[\alpha]_{589}^{20} = -33.2^\circ$ ($c = 0.69$, MeOH). mp 181-183°C. $^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 0.78$ -1.13 (m; 12H), 1.14-1.24 (m; 1H), 1.77-2.01 (m; 2H), 3.45 (dq; $J = 5.55$ Hz, 13.3 Hz, 29.4 Hz, 2H), 4.44-4.64 (m; 1H), 5.70 (d; $J = 7.97$ Hz, 1H), 6.04 (t; $J = 5.55$ Hz, 1H), 7.02-7.48 (m; 10H), 7.91 (s; 1H), 8.01 (s; 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta = 23.5$, 27.7, 32.1, 35.0, 36.8, 41.2, 45.3, 47.8, 49.1, 59.1, 125.0, 125.4, 127.2, 127.5, 130.3, 130.4, 135.9, 136.0, 179.4, 181.2. FT-IR (ATR, film): $\tilde{\nu}$ [cm^{-1}] = 3242 (m(br)), 2951, 2951 (both m), 2088 (w(br)), 1705 (w), 1593 (m), 1528, 1490 (both s), 1446 (m), 1350, 1312, 1238, 1177 (all s), 907 (m), 729, 693 (both s). HRMS (ESI): Calcd. for $[\text{C}_{24}\text{H}_{32}\text{N}_4\text{S}_2\text{Na}]$ ($[\text{M}+\text{Na}]^+$): 463.197, Found: 463.197 (± 0.002 u). Anal. Calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{S}_2$: C 65.41, H 7.32, N 12.71 Found: C 65.06, H 7.42, N 12.57.

Preparation of *N*-Cyclohexyl-*N'*-[(1*R*,3*S*)-3-[[[(cyclohexylamino)thioxomethyl]amino]methyl]-3,5,5-trimethylcyclohexyl]thiourea (**1e**)



(1*R*,3*S*)-3-(Aminomethyl)-3,5,5-trimethyl-cyclohexylamine (1.00 mL, 5.40 mmol, 1.00 eq) was dissolved in dry THF (1.00 mL), and cyclohexylisothiocyanate (1.55 mL, 11.3 mmol, 2.10 eq) was slowly added under argon atmosphere whereupon a yellow gel formed immediately. The solvent was removed under reduced pressure, and the resulting solid purified by column chromatography (CHCl₃/MeOH 100 : 5). The desired bis-thiourea was obtained in 65 % yield (1.60 g, 3.53 mmol) as a pale yellow solid. mp 139-141°C. ¹H-NMR (300 MHz, CDCl₃): δ = 0.85-1.48 (m; 25H), 1.55-1.83 (m; 5H), 1.83-2.12 (m; 5H), 3.25 (s; 2H), 3.75-4.08 (m; 2H), 4.38-4.64 (m; 1H), 5.76-6.37 (m; 4H). ¹³C-NMR (75 MHz, CDCl₃): δ = 24.2, 24.7, 24.8, 25.4, 27.8, 32.1, 32.9, 33.0, 33.2, 35.0, 36.5, 41.3, 45.7, 47.5, 48.0, 52.6, 57.7, 179.5. FT-IR (ATR, film): $\tilde{\nu}$ [cm⁻¹] = 3253 (w(br)), 2927 (m), 2851 (w), 2099 (w(br)), 1536 (s), 1448, 1359, 1255 (all m), 1062, 973, 889 (all w), 733 (s), 700 (m). HRMS (ESI): Calcd. for [C₂₄H₄₄N₄S₂Na] ([M+Na]⁺): 475.291, Found: 475.291 (± 0.002 u).

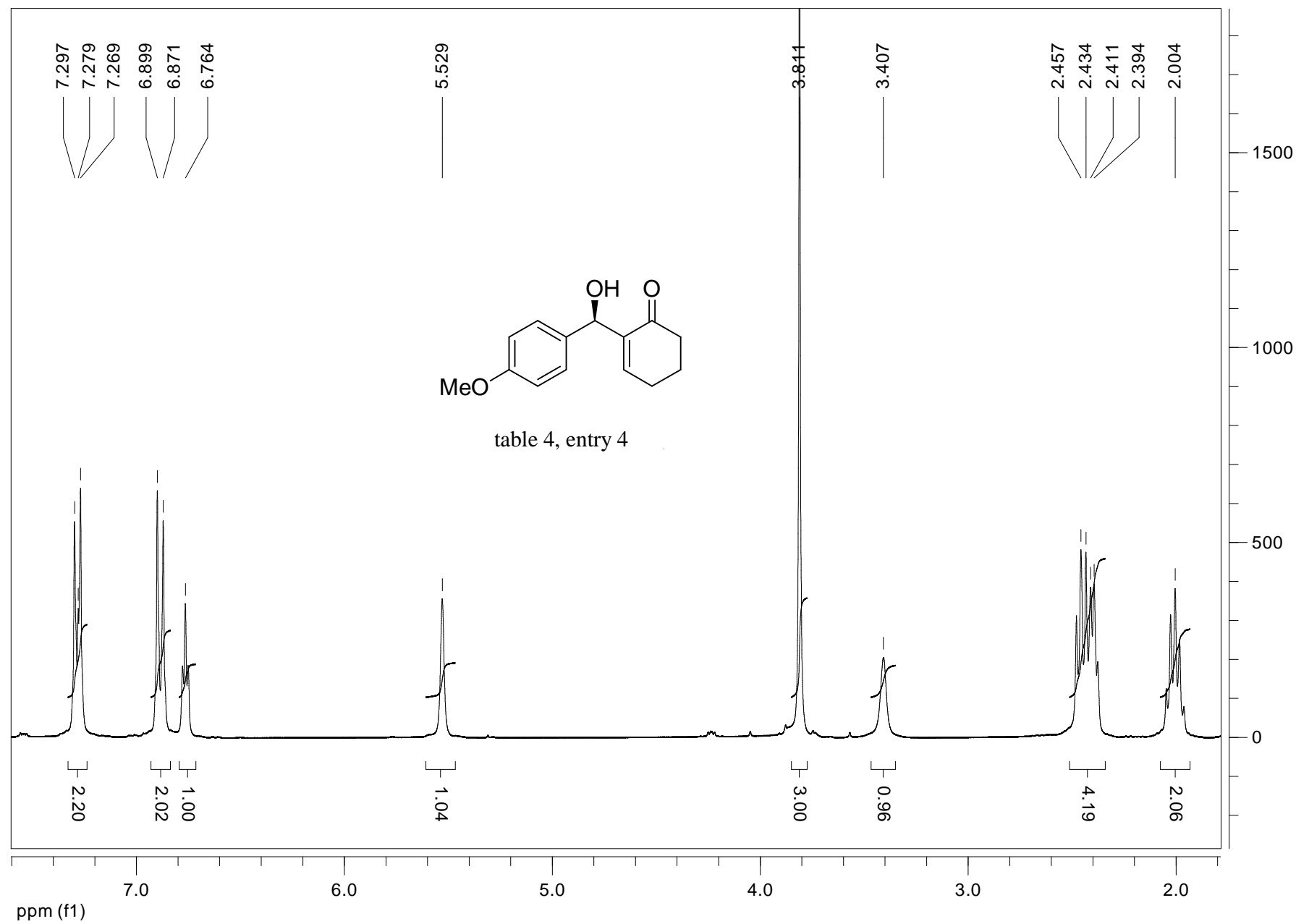
Preparation of *N*-Tricyclo[3.3.1.1^{3,7}]dec-1-yl-*N'*-[[(1*S*,5*R*)-1,3,3-trimethyl-5-[[[(tricyclo[3.3.1.1^{3,7}]dec-1-yl)amino]thioxomethyl]amino]cyclohexyl]methyl]thiourea (**1f**)

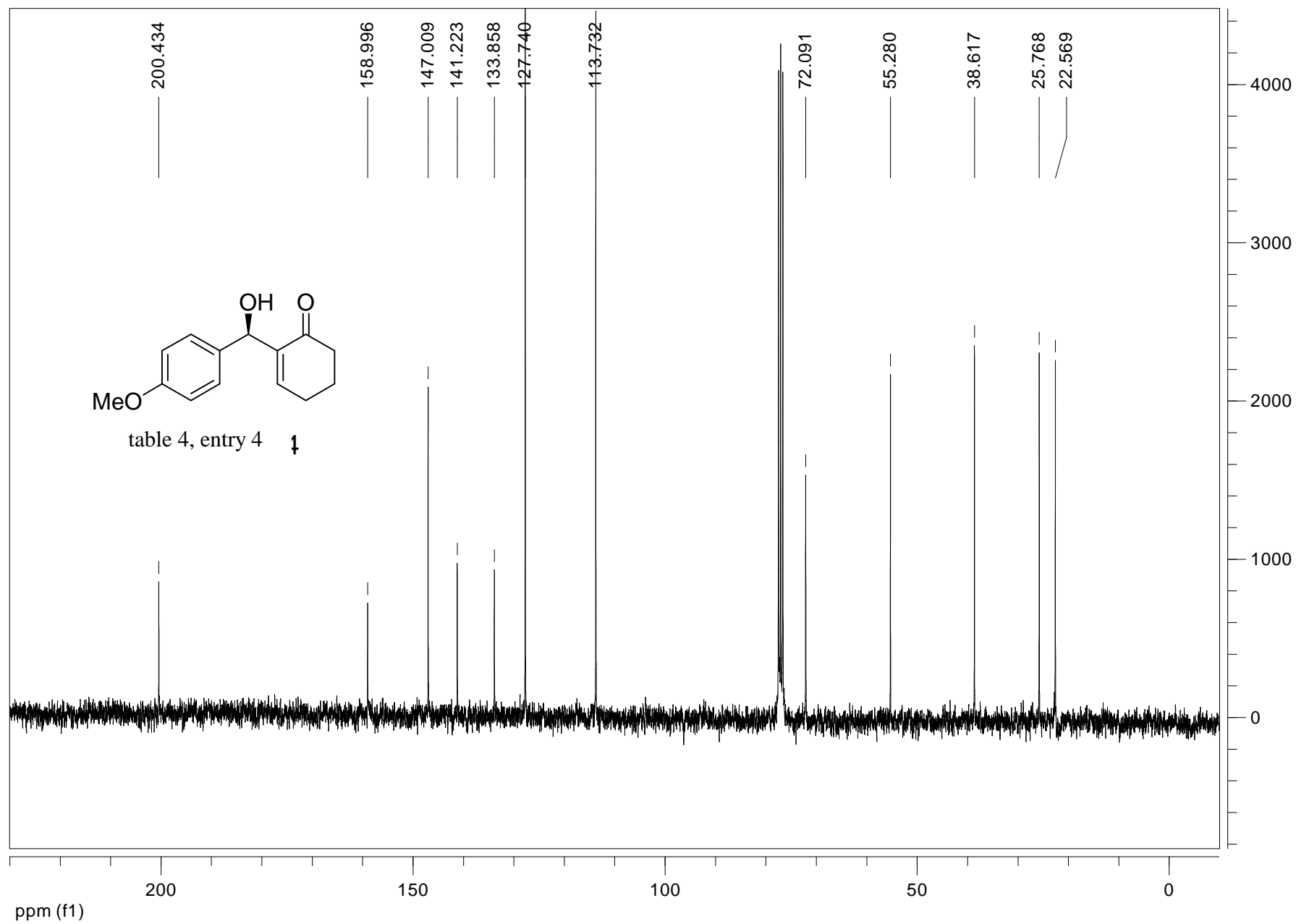


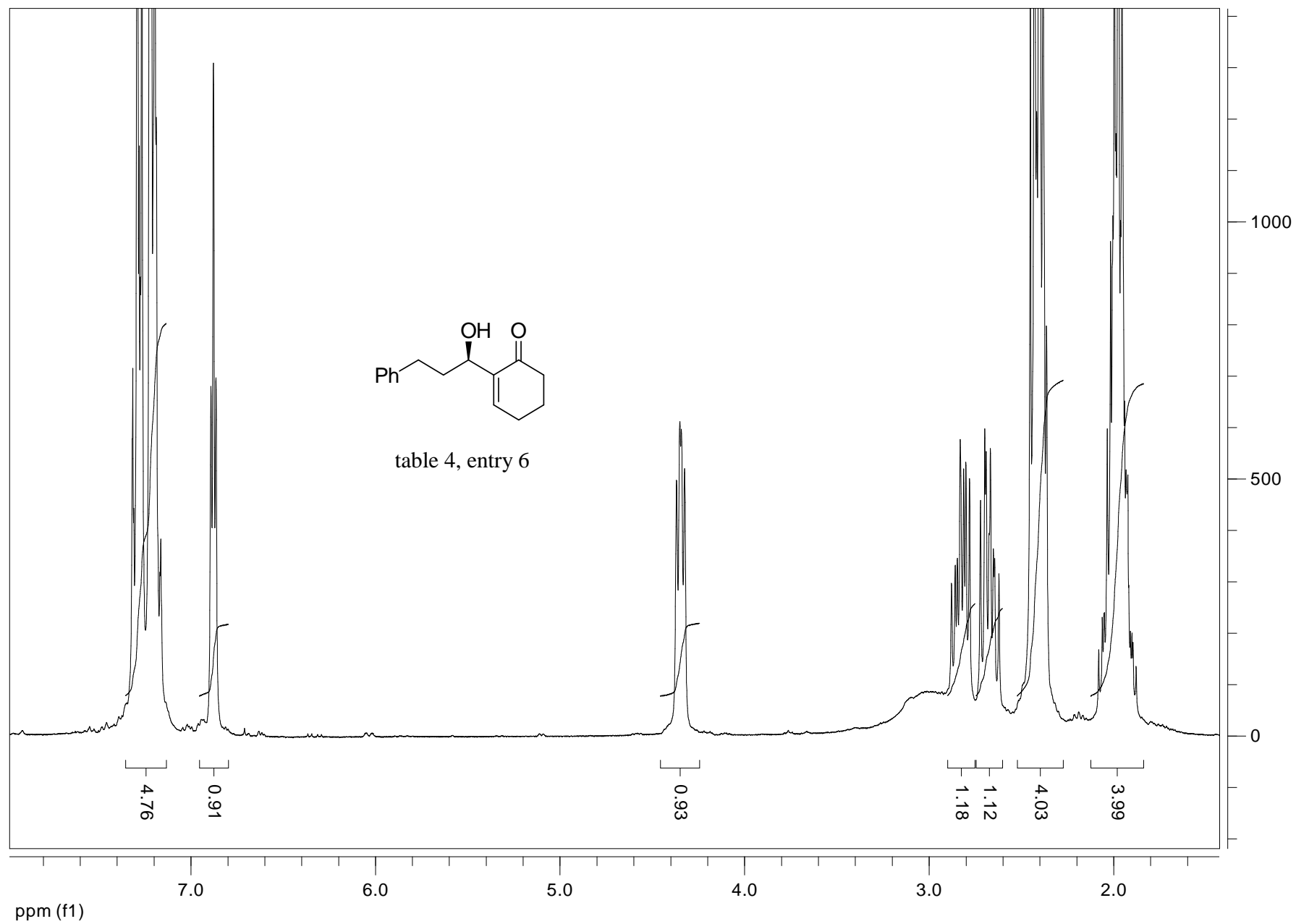
(1*R*,3*S*)-3-(Aminomethyl)-3,5,5-trimethyl-cyclohexylamine (100 μL, 540 μmol, 1.00 eq) was dissolved in dry DCM (1.00 mL), and 1-adamantylisothiocyanate (209 mg, 1.08 mmol, 2.00 eq) was slowly added under argon atmosphere. The mixture was stirred for two hours at rt, then the solvent removed under reduced pressure and the resulting solid purified by column chromatography (CHCl₃/MeOH 100 : 5). The desired bis-thiourea was obtained quantitatively (307 mg, 540 μmol) as a colorless solid. mp 180-182°C. ¹H-NMR (300 MHz, CDCl₃): δ = 0.92-1.33 (m; 12H), 1.58-1.79 (m; 12H), 1.92-2.07 (m; 13H), 2.07-2.19 (m; 6H), 3.40 (s; 2H), 4.41-4.62 (m; 1H), 5.47 (d(br); 1H), 5.70-5.94 (m; 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 23.9, 27.8, 29.4, 32.1, 35.0, 36.1, 36.5, 41.8, 42.5, 45.8, 47.9, 49.1, 54.0, 179.9. FT-IR (ATR, film): $\tilde{\nu}$ [cm⁻¹] = 3267 (w(br)), 2907 (s), 2847 (m), 2208 (w(br)), 1529 (s), 1452 (m), 1355, 1340, 1300, 1234 (all s), 1101, 1075 (both m), 977 (w), 906, 727 (both s), 693, 643 (both m). HRMS (ESI): Calcd. for [C₃₂H₅₃N₄S₂] ([M+H]⁺): 557.371, Found: 557.371 (± 0.002 u).

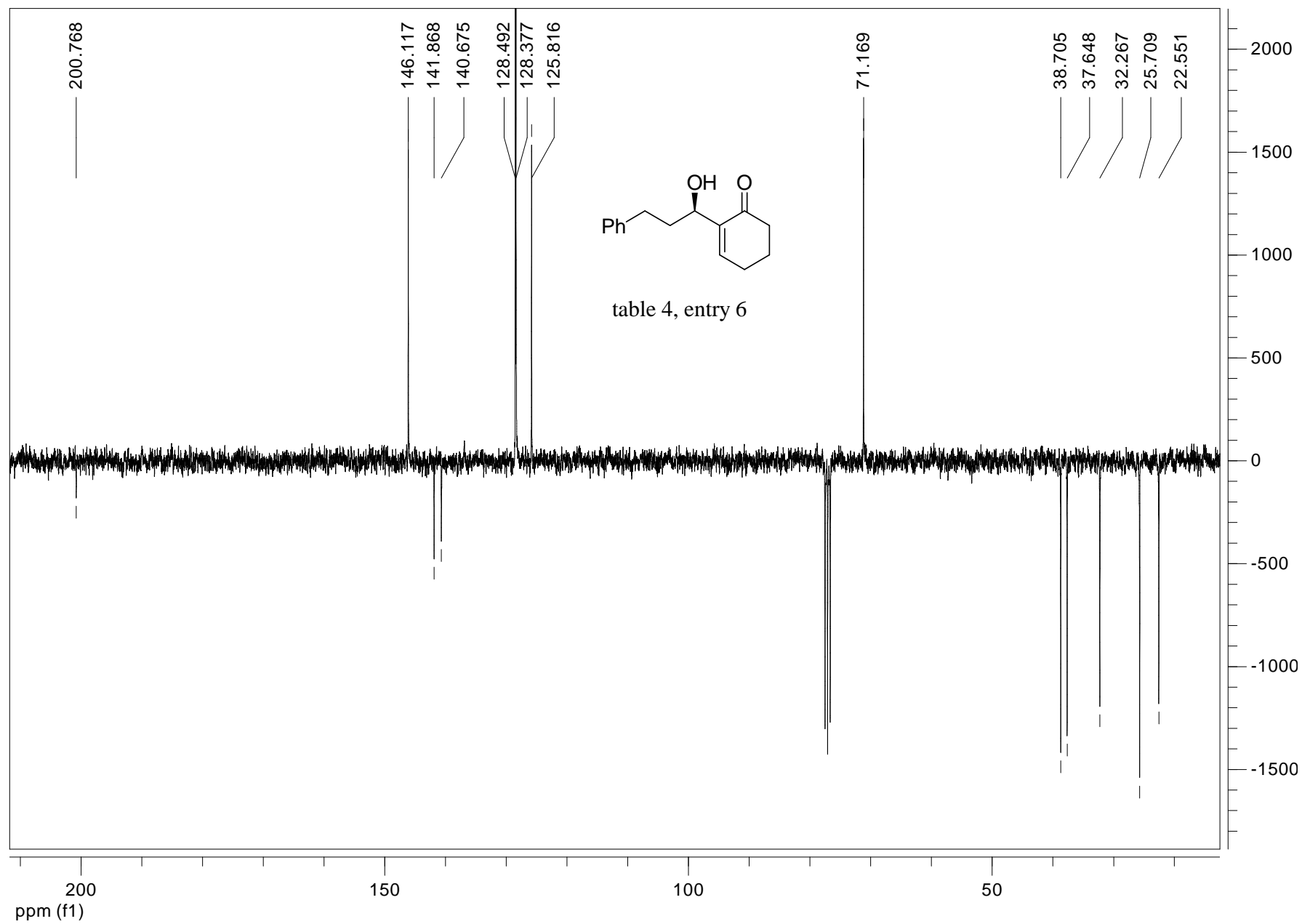
X-ray crystallographic data for 1a and 1c

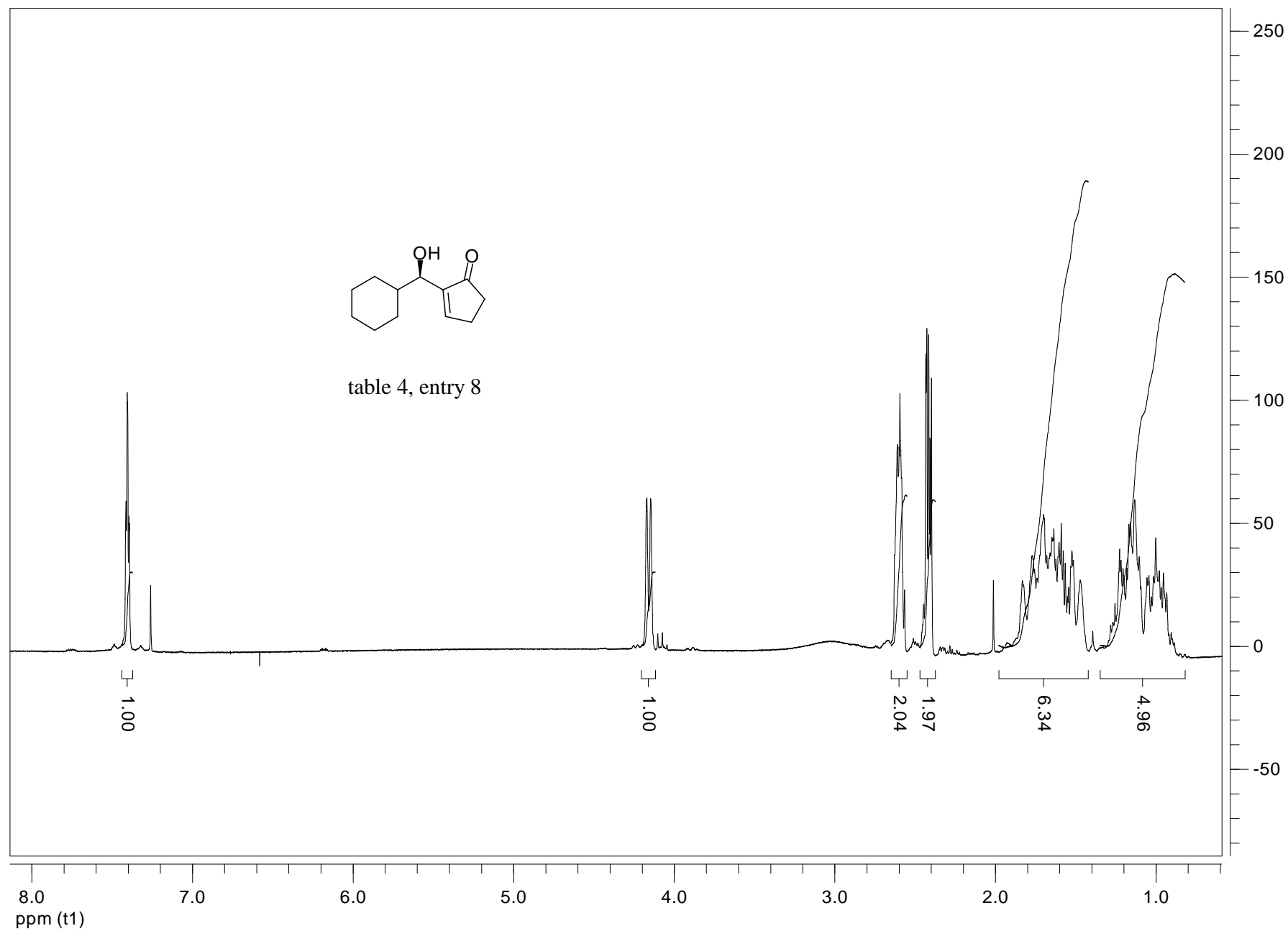
	1a	1c
formula	$\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_2$	$\text{C}_{24}\text{H}_{32}\text{N}_4\text{S}_2$
M_r	408.54	440.66
crystal dimensions [mm]	0.3x0.2x0.2	0.3x0.1x0.05
crystal system	monoclinic	orthorhombic
space group	$P2_1$ (no. 4)	$P2_12_12_1$ (no. 19)
a [Å]	9.244 (7)	7.5688 (3)
b [Å]	9.5634 (10)	9.5287 (4)
c [Å]	13.502 (2)	33.9726 (14)
α [°]	90	90
β [°]	106.642 (6)	90
γ [°]	90	90
V [Å ³]	1143.6 (2)	2450.1 (2)
ρ_{calcd} [g·cm ⁻³]	1.186	1.195
Z	4	4
radiation	Mo- K_α	Mo- K_α
scan mode	ϕ/ω	ϕ/ω
$2\ \Theta_{\text{max}}$ [°]	54	54
unique reflections	2565	5183
observed reflections	1812	3529
$R1$	0.0803	0.040
$wR2$	0.1063	0.071
$\rho_{\text{fin}}(\text{max})$ [e·Å ⁻³]	0.242	0.248
CCDC depository no.	605967	605968

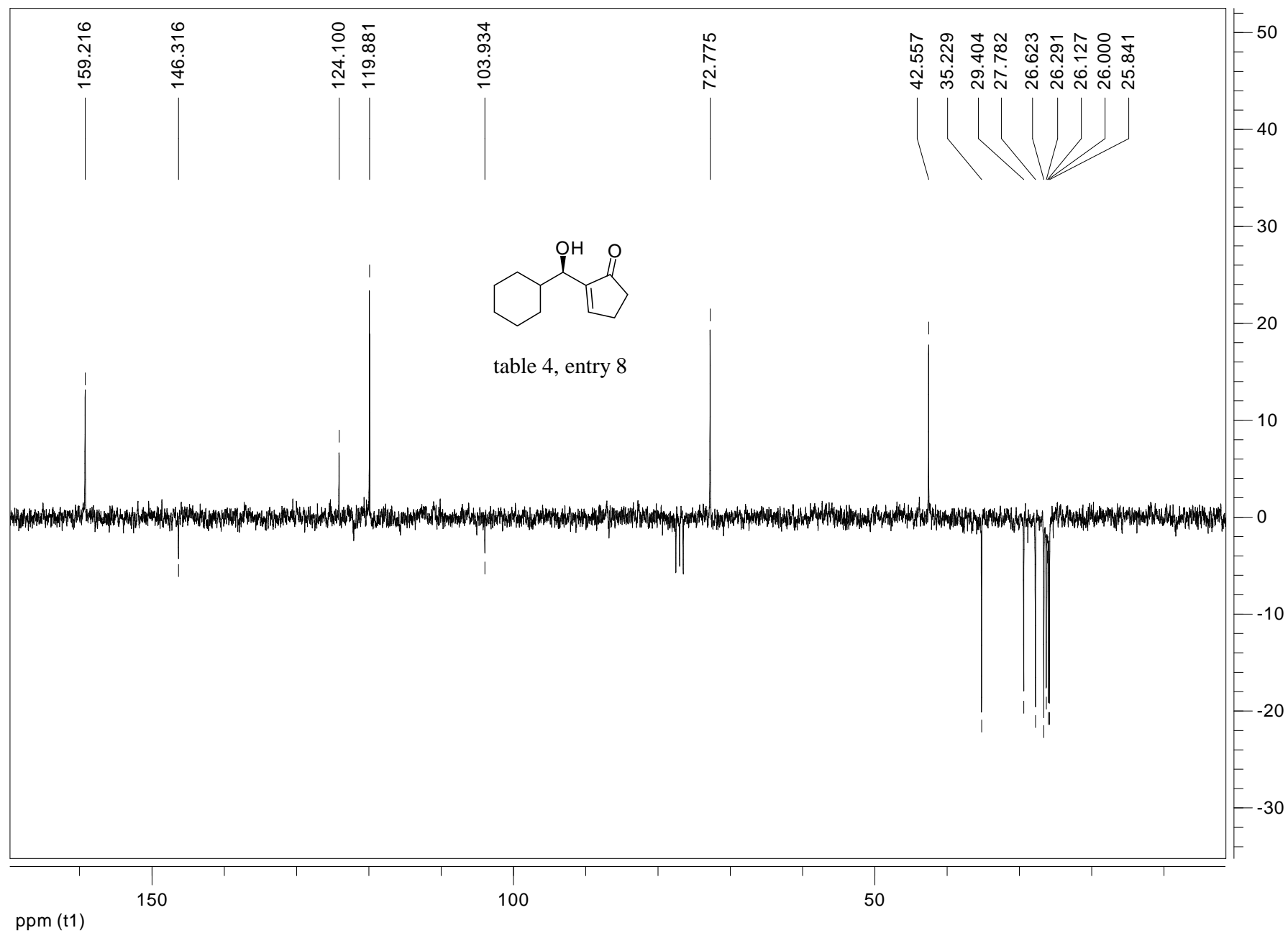


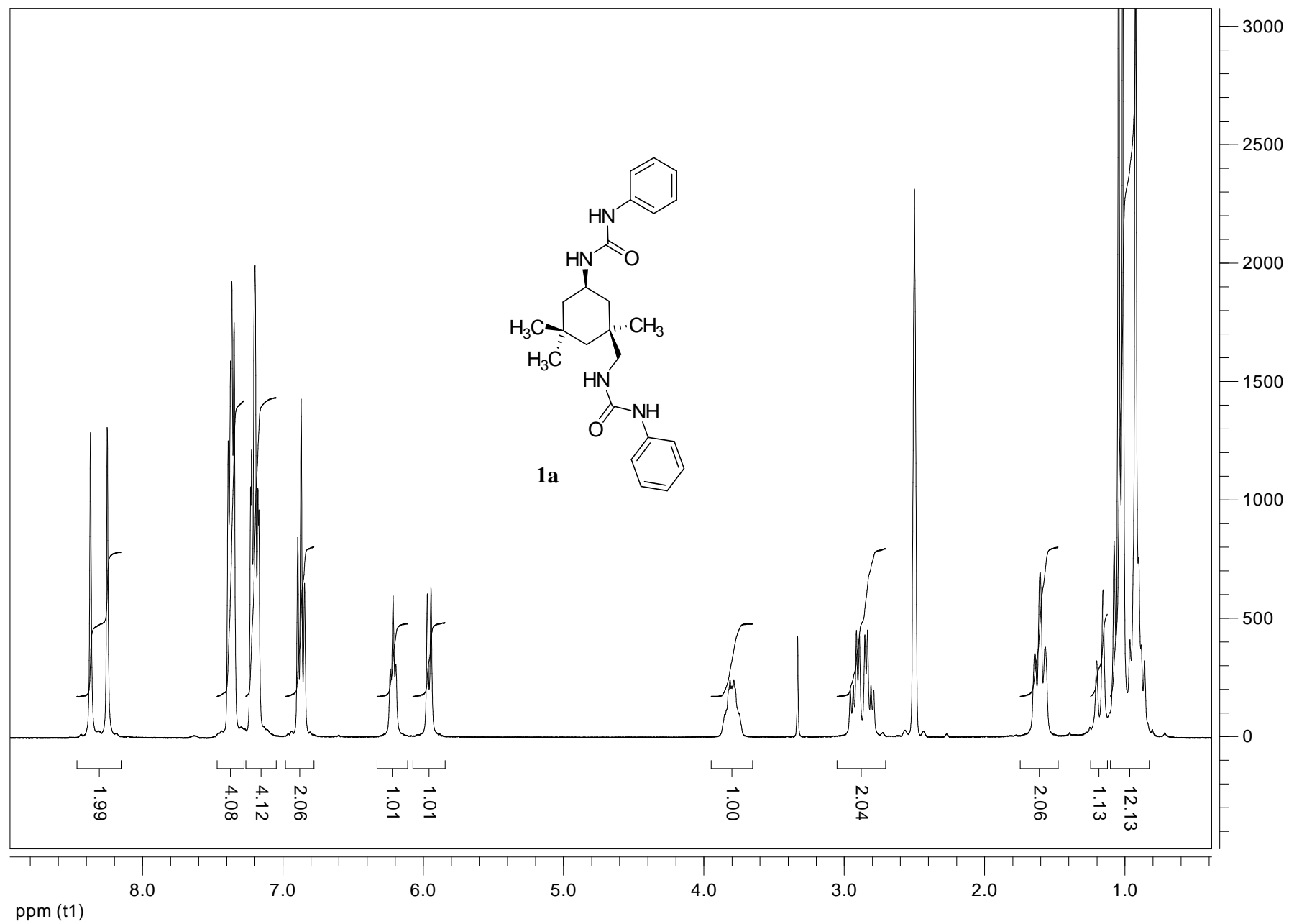


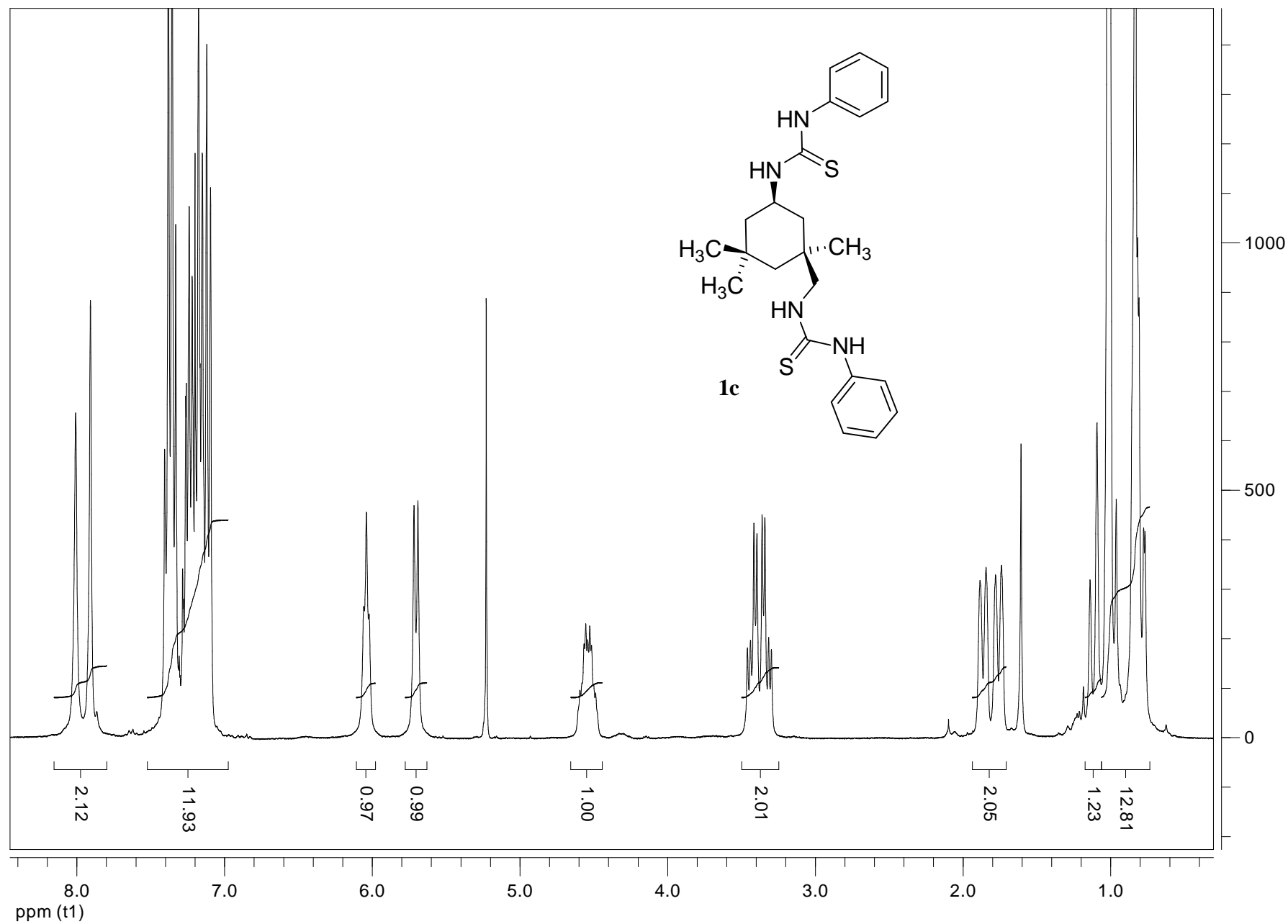


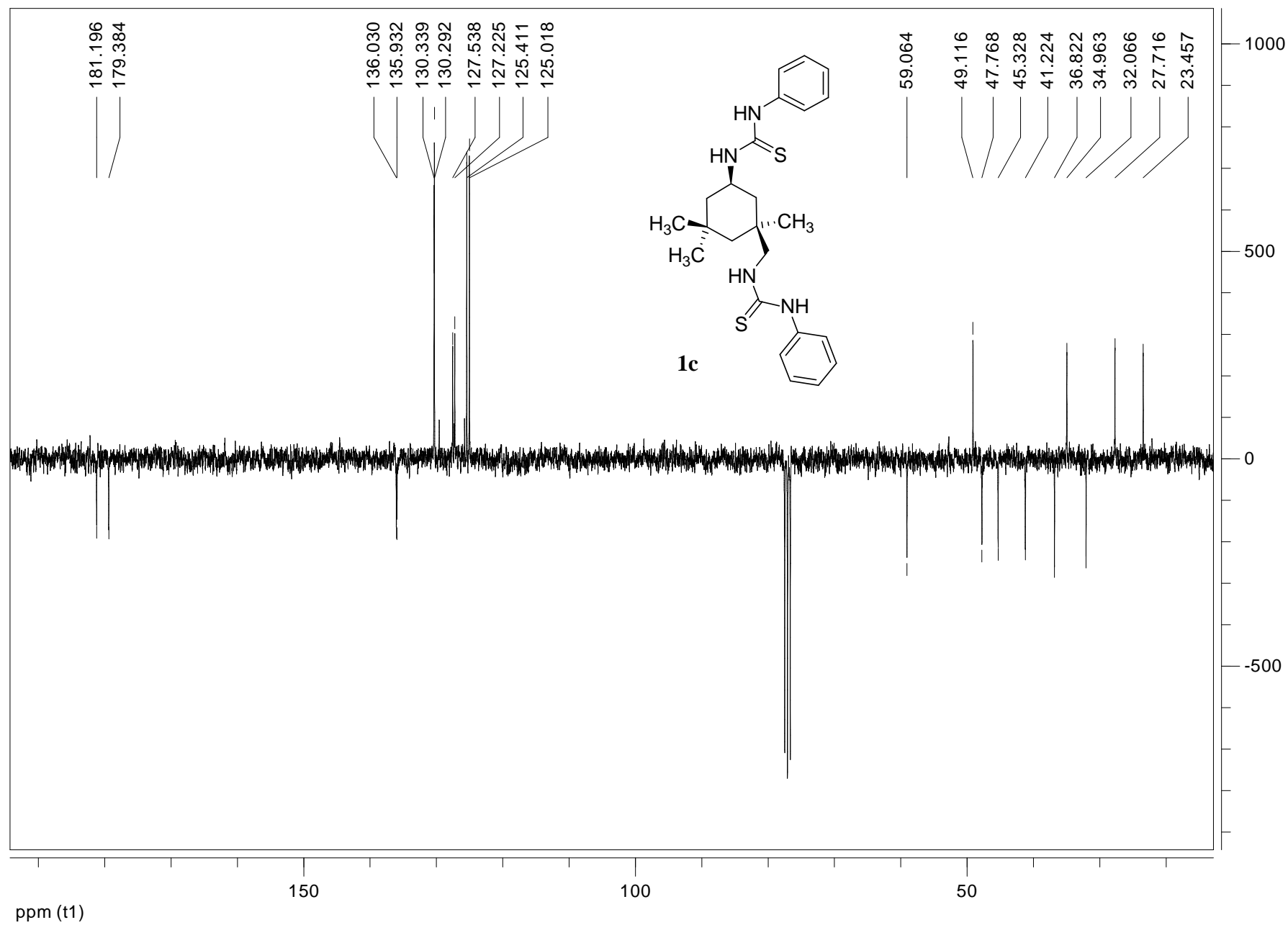


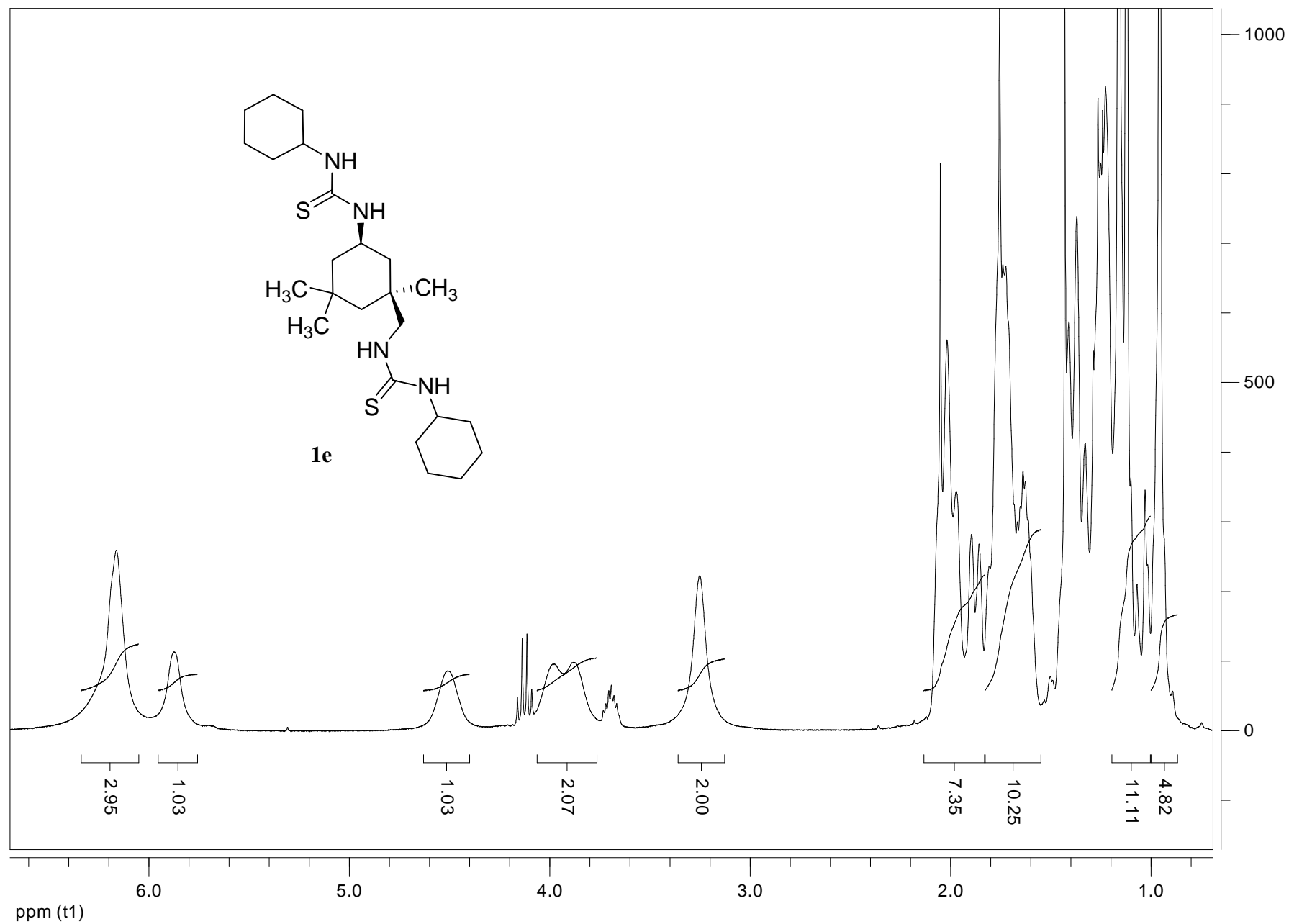


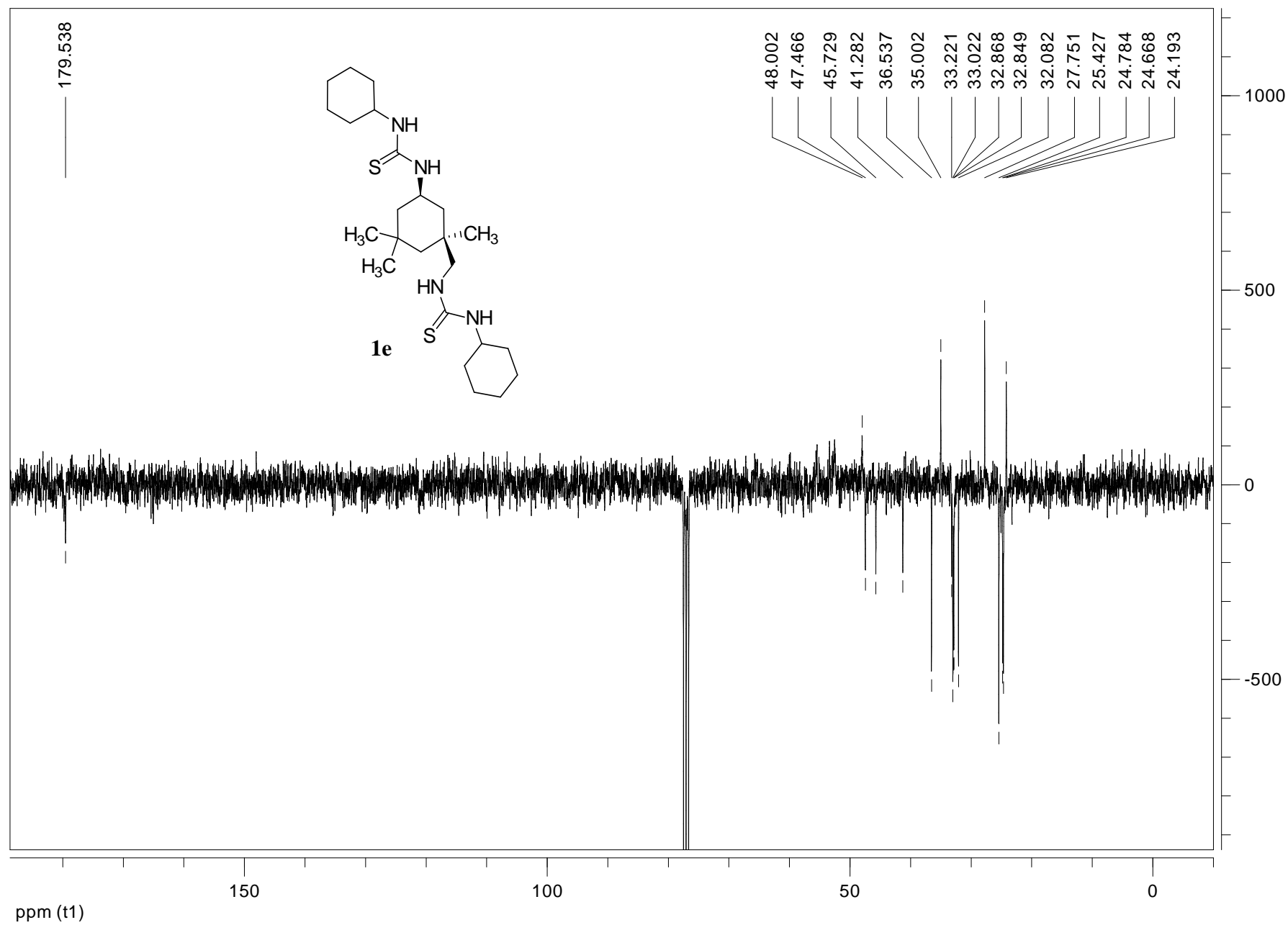


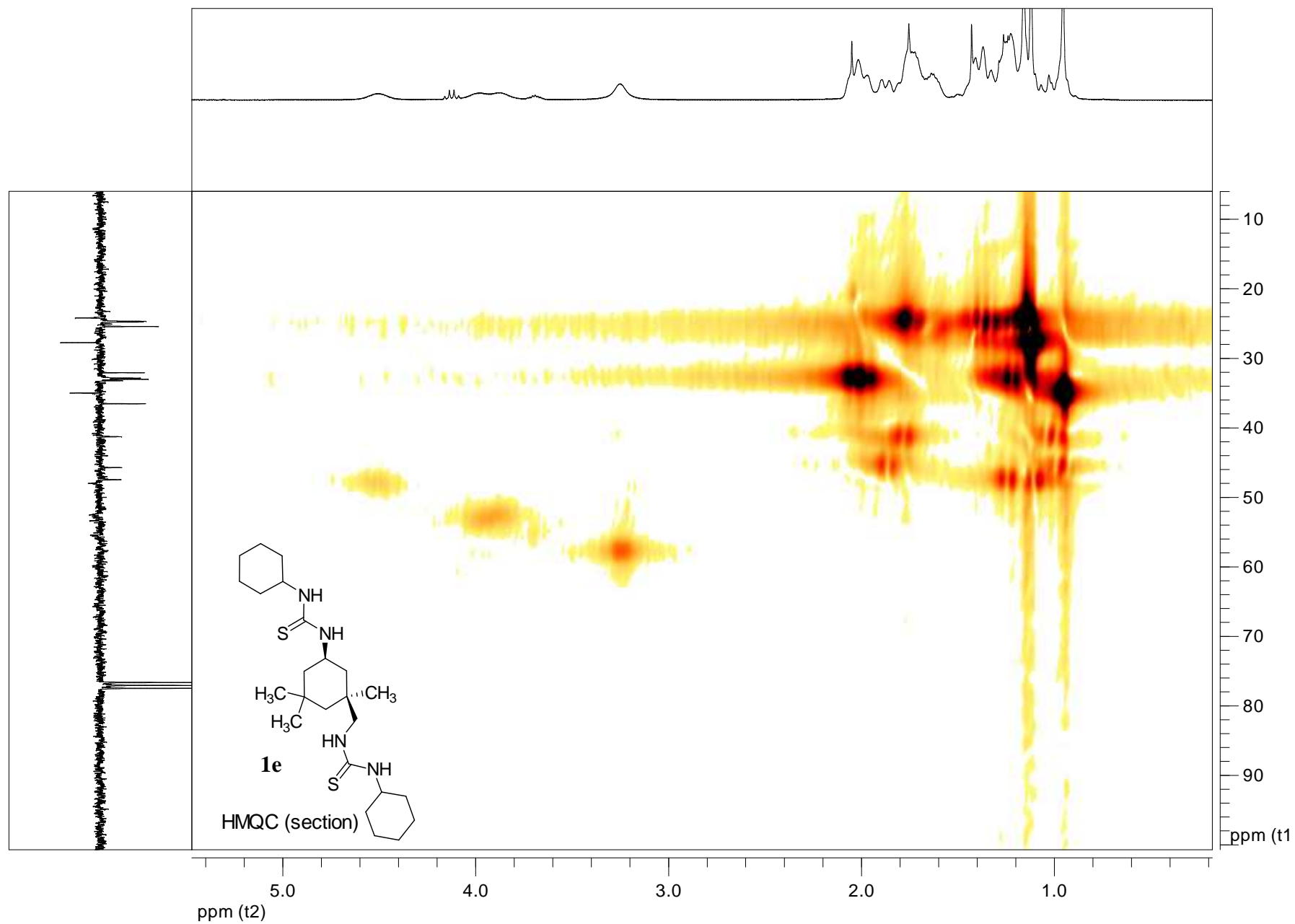


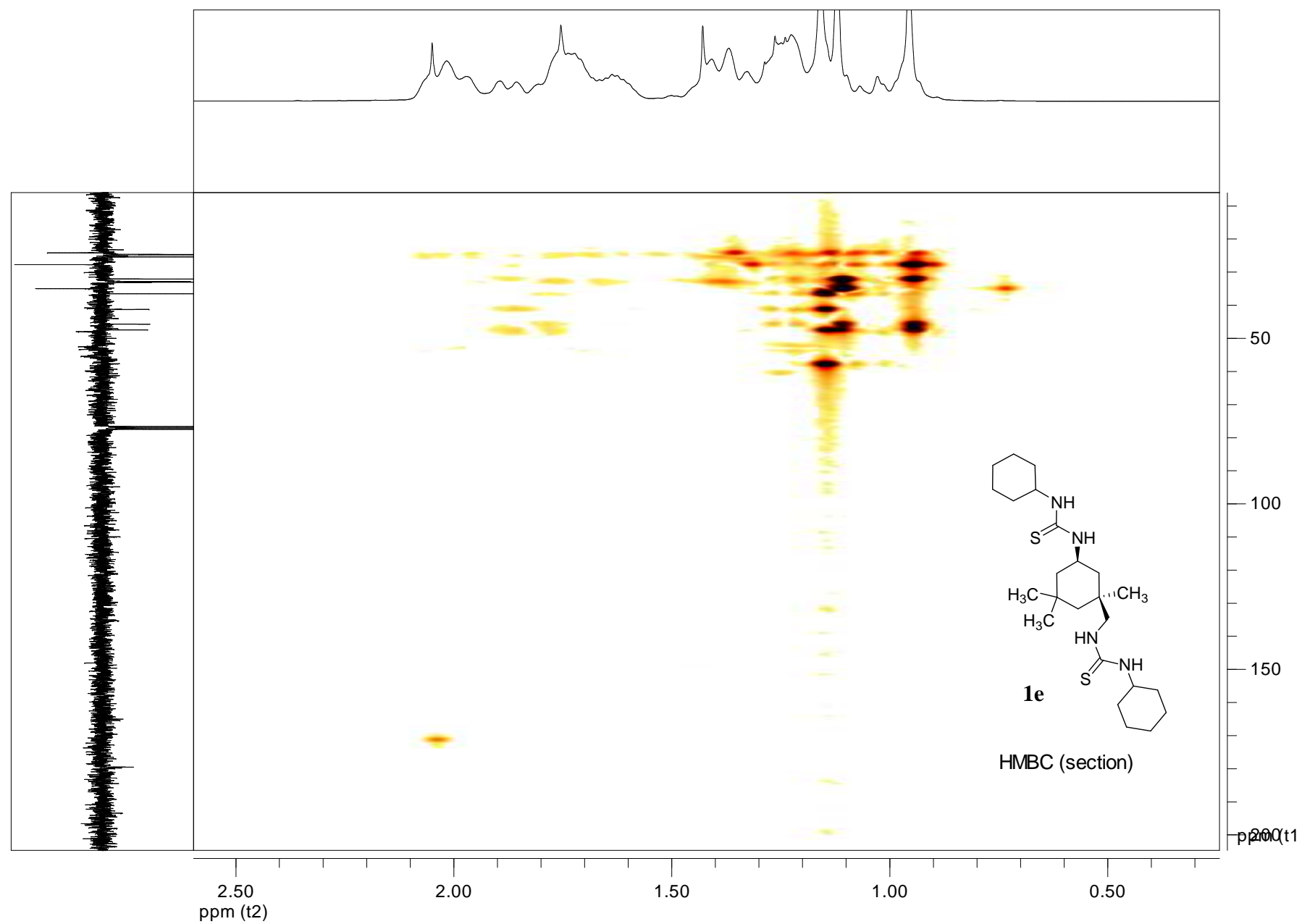


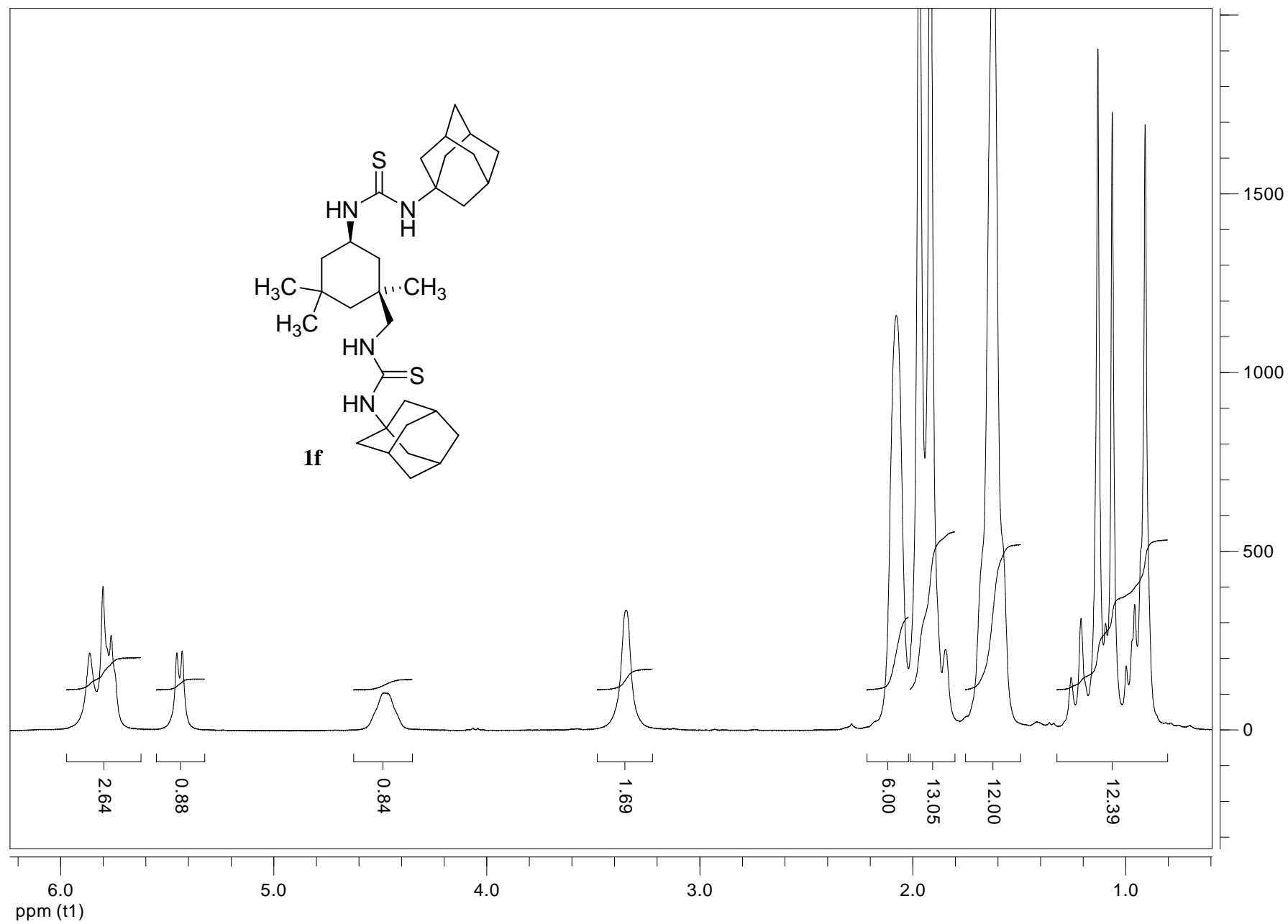


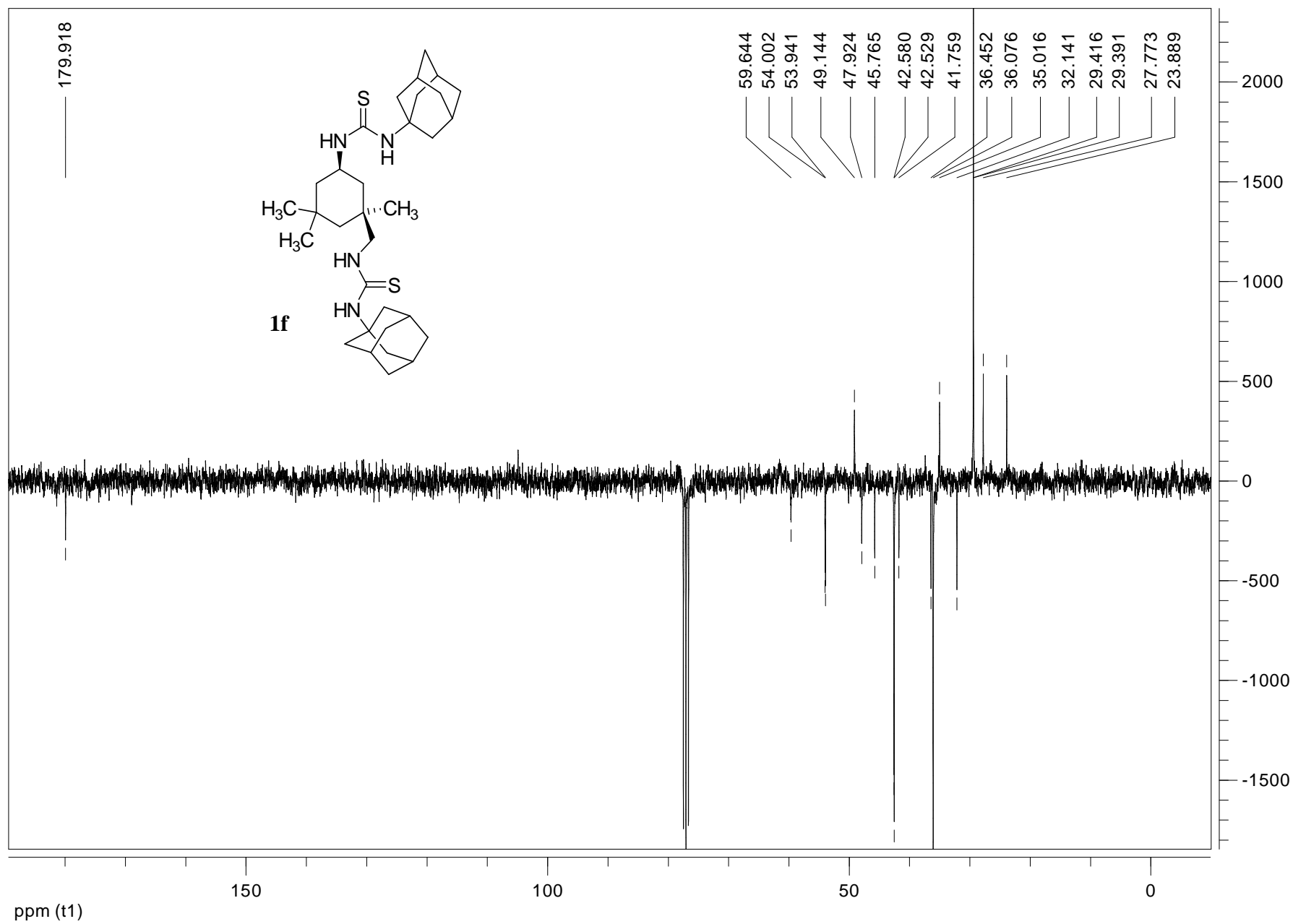












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