Catalytic Enantioselctive Synthesis of Carbocyclic and Heterocyclic Spiranes via a Decarboxylative Aldol Cyclization

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Table of Contents

Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[1] Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz and 600 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), C_6D_6 (δ 7.16 ppm) or CD_3OD (δ 3.31 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), C_6D_6 (δ 128.06 ppm) or CD_3OD (δ 49.01 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Analytical SFC was performed with a Mettler SFC supercritical chromatography system utilizing Chiralpak (AD-H, IB or IC) or Chiracel (OD-H, OJ-H or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed with an Agilent 6850 GC utilizing a CP-CHIRASIL-DEX CB column (25 m x 0.25 mm). Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, TCI or Alfa Aesar and used as received unless otherwise stated. (*S*)-*t*-BuPHOX was prepared by known methods.[2]

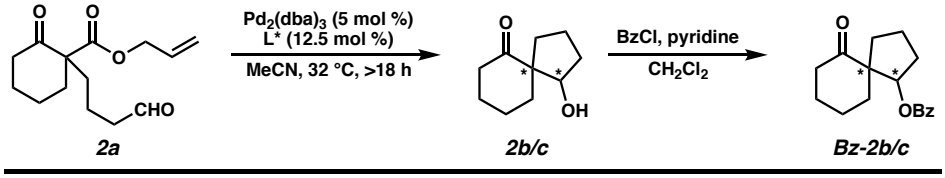
List of Abbreviations:

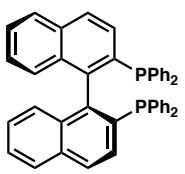
Ac – acetyl, BINAP – 2,2'–Bis(diphenylphosphino)–1,1'–binaphthyl, Bz – benzoyl, DIBAL – diisobutylaluminium hydride, *dr* – diastereomeric ratio, *ee* – enantiomeric excess, EtOAc – Ethyl acetate, IPA – isopropyl alcohol, MeOH – methanol, SFC – supercritical fluid chromatography, THF – tetrahydrofuran, TLC – thin-layer chromatography.

Optimization of Reaction Conditions

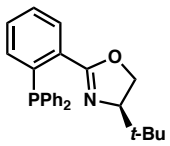
Optimization reactions were performed according to representative procedure A. After column chromatography, the purified fraction was concentrated and conversion and diastereomeric ratio were determined by GC analysis and ^{1}HNMR. The *ee* value was determined by SFC using a chiral stationary phase, after transformation to the benzoyl ester, according to representative procedure B.

Table S1. Chiral ligand screen in MeCN; conversion determined by GC-FID, dr of **2b/c** determined by ^{1}H NMR, ee of **Bz-2b/c** determined by SFC.

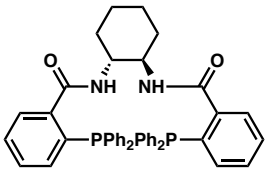




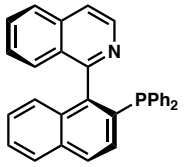
(*S*)-BINAP
conversion: 43%
dr (b:c): 53:47
ee (b/c): <5%/<5%



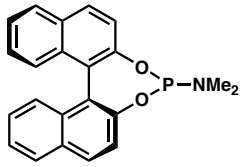
(*R*)-*t*-Bu-PHOX
conversion: 32%
dr (b:c): 47:53
ee (b/c): <5%/<5%



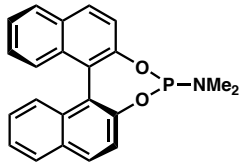
(*R,R*)-DACH-phenyl Trost ligand
conversion: 25%
dr (b:c): 41:59
ee (b/c): <5%/<5%



(*S*)-QUINAP
conversion: 53%
dr (b:c): 54:46
ee (b/c): <5%/<5%

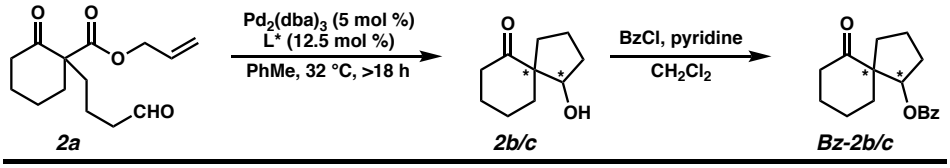


(*S*)-BINOL-P-NMe_2 (20 mol %)
conversion: 57%
dr (b:c): 52:48
ee (b/c): <5%/<5%

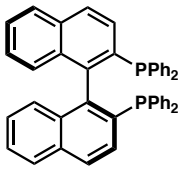


(*S*)-BINOL-P- (NMe_2 (20 mol %)
conversion: 57%
dr (b:c): 52:48
ee (b/c): <5%/<5%

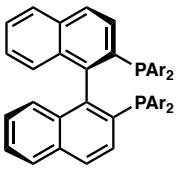
Table S2. Chiral ligand screen in PhMe; conversion determined by GC-FID, dr of **2b/c** determined by ^{1}H NMR, ee of **Bz-2b/c** determined by SFC.



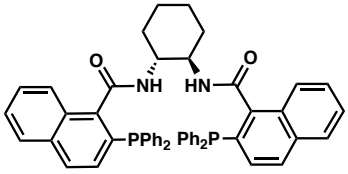
2a *2b/c* *Bz-2b/c*



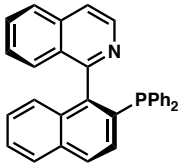
(*S*)-BINAP
conversion: 100%
dr (b:c): 59:41
ee (b/c): 10%/9%



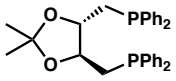
(*R*)-DM-BINAP
(Ar = 3,5-Me-C_6H_3)
conversion: 100%
dr (b:c): 38:62
ee (b/c): 6%/>5%



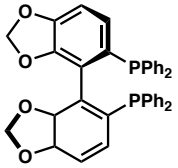
(*R,R*)-DACH-napthyl Trost ligand
conversion: 35%
dr (b:c): 80:20
ee (b/c): <5%/<5%



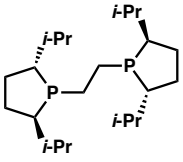
(*S*)-QUINAP
conversion: 100%
dr (b:c): 72:28
ee (b/c): 15%/7%



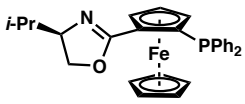
(*S,S*)-DIOP
conversion: 100%
dr (b:c): 71:29
ee (b/c): >5%/>5%



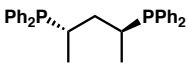
(*R*)-SEGPHOS
conversion: 97%
dr (b:c): 38:62
ee (b/c): 6%/6%



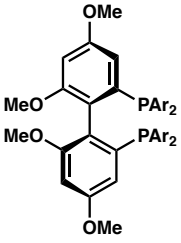
(*2R, 5R*)-*i*-Pr-BPE
conversion: 42%
dr (b:c): 42:58
ee (b/c): <5%/<5%



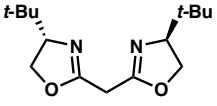
(*S,S*)-Cp-Fe(4-*i*-Pr-oxazolinyl)$C_5H_3PPh_2$
conversion: 95%
dr (b:c): 43:57
ee (b/c): 11%/5%



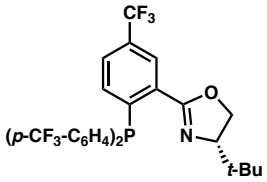
(*S,S*)-BDPP
conversion: 86%
dr (b:c): 41:59
ee (b/c): 11%/5%



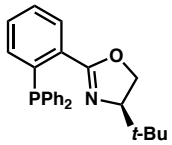
(*R*)-BTFM-GARPHOS
(Ar = 3,5-$(CF_3)_2$-C_6H_3)
conversion: 14%
dr (b:c): 49:51
ee (b/c): ND



(*S*)-*t*-Bu-H_2BOX
conversion: 11%
dr (b:c): ND
ee (b/c): ND

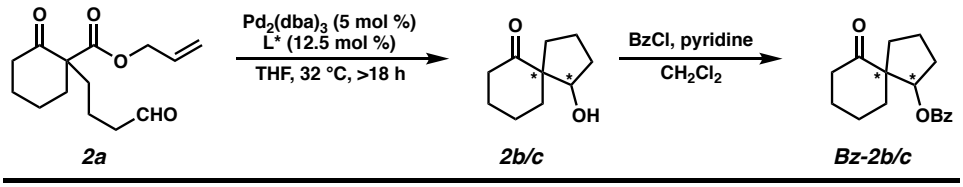


(*S*)-$(CF_3)_3$-*t*-Bu-PHOX
conversion: 98%
dr (b:c): 79:21
ee (b/c): 13/41

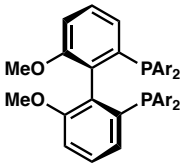


(*R*)-*t*-Bu-PHOX
conversion: 100%
d.r. (b:c): 35:18
ee (b/c): 37/63

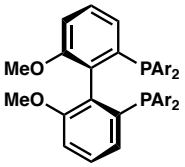
Table S3. Chiral ligand screen in THF; conversion determined by GC-FID, dr of **2b/c** determined by ^{1}H NMR, ee of **Bz-2b/c** determined by SFC.



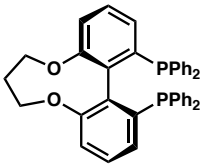
2a ***2b/c*** ***Bz-2b/c***



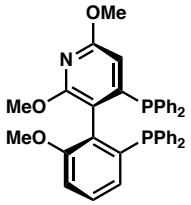
(*S*)-3,5-Xyl-MeOBIPHEP
(Ar = 3,5-Me-C_6H_3)
conversion:100%
dr (b:c): 31:69
ee (b/c): 3%/–1%



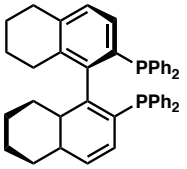
(*S*)-3,5-*t*-Bu-MeOBIPHEP
(Ar = 3,5-*t*-Bu-C_6H_3)
conversion:100%
dr (b:c): 24:76
ee (b/c): –1%/–1%



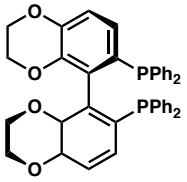
(*S*)-C3-TunePhos
conversion:100%
dr (b:c): 36:64
ee (b/c): 10%/–1%



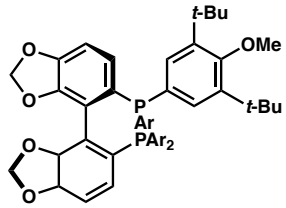
(*R*)-P-Phos
conversion:100%
dr (b:c): 40:60
ee (b/c): –6%/–6%



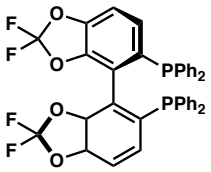
(*R*)-H_8-BINAP
conversion: 100%
dr (b:c): 35:65
ee (b/c): –5%/–1%



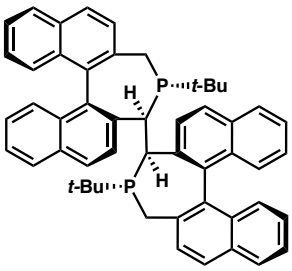
(*R*)-SynPhos
conversion: 100%
dr (b:c): 36:64
ee (b/c): –6%/–2%



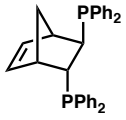
(*R*)-DTBM-SEGPHOS
conversion: 100%
dr (b:c): 25:75
ee (b/c): 4%/–2%



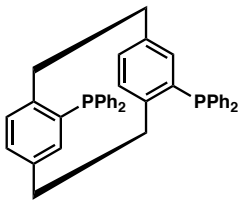
(*R*)-DifluoroPhos
conversion: 97%
dr (b:c): 25/75
ee (b/c): 4%/–2%



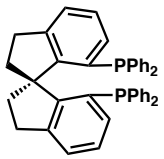
(*S*)-BINAPINE
conversion: 7%
dr (b:c): 47:53
ee (b/c): ND



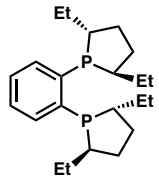
(*R,R*)-NorPhos
conversion: 100%
dr (b:c): 32:68
ee (b/c): 3%/0%



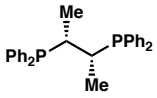
(*R*)-PhanePhos
conversion: 100%
dr (b:c): 42:58
ee (b/c): 5%/–3%



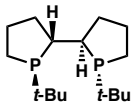
(*R*)-SDP
conversion: 100%
d.r. (a/b): 40:60
ee (a/b): 3%/2%



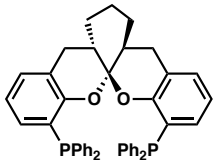
(*2R,5R*)-Et-DUPHOS
conversion: 54%
dr (b:c): 45:55
ee (b/c): 1%/0%



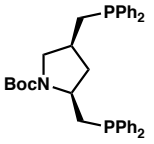
(*S,S,R,R*)-ChiraPhos
conversion: 46%
dr (b:c): 47:53
ee (b/c): 1%/–6%



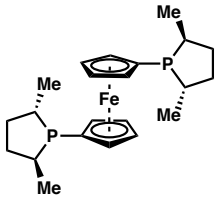
(*S,S',R,R'*)-TangPhos
conversion: 94%
dr (b:c): 45:55
ee (b/c): –1%/0%



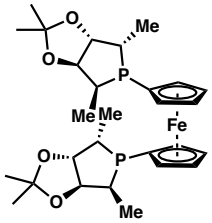
(*S,S,S*)-(–)-Ph-SKP
conversion: 100%
dr (b:c): 40:60
ee (b/c): 6%/1%



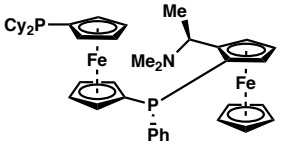
(*S,S*)-BPPM
conversion: 100%
dr (b:c): 58:42
ee (b/c): –10%/0%



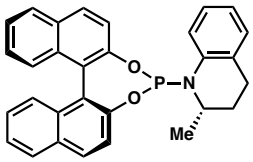
(*2S,5S*)-Me-Ferrocelane
conversion: 86%
dr (b:c): 56:44
ee (b/c): 0%/0%



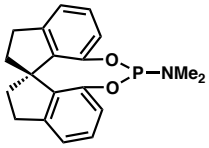
(*S*)-Me-f-KetalPhos
conversion: 100%
dr (b:c): 62:38
ee (b/c): 3%/–1%



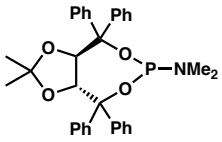
ChenPhos
conversion: 100%
d.r. (a/b): 28:72
ee (a/b): 2%/0%



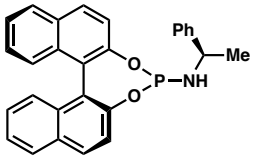
(S,S_a)-THQPhos (20 mol %)
conversion: 38%
dr (b:c): 85:15
ee (b/c): 2%/0%



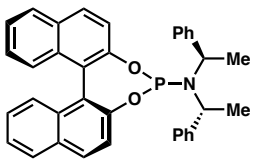
(*R*)-SIPHOS (20 mol %)
conversion: 45%
dr (b:c): 75:25
ee (b/c): 7%/0%



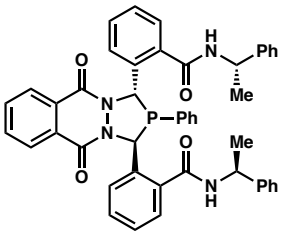
(*R,R*)-TADDOL-P-NMe_2
conversion: 97%
dr (b:c): 93:7
ee (b/c): 4%/0%



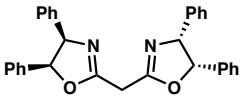
(*S*)-BINOL-P-(*R*)-NHCH(Me)Ph
(20 mol %)
conversion: 3%
dr (b:c): ND
ee (b/c): ND



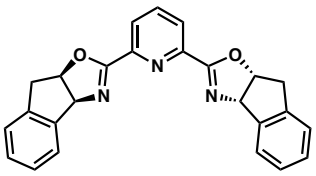
(*S*)-BINOL-P-(*R,R*)-$N[CH(Me)Ph]_2$
(20 mol %)
conversion: 96%
dr (b:c): 60:40
ee (b/c): 4%/0%



(*S,S,S*)-DiazaPhos-PPE
(20 mol %)
conversion: 17%
dr (b:c): 79:21
ee (b/c): 11%/0%

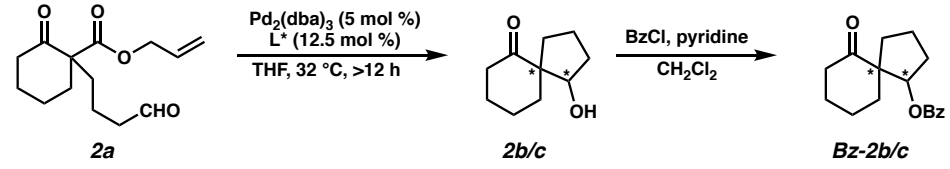


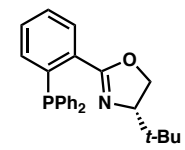
(*4R,5S*)-Ph_2-H_2BOX
conversion: 3%
dr (b:c): ND
ee (b/c): ND



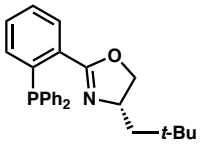
(3a*S*,8a*R*)-in-pyBOX
conversion: 5%
dr (b:c): ND
ee (b/c): ND

Table S4. PHOX-type ligand screen in THF; conversion determined by GC-FID, dr of **2b/c** determined by ^{1}H NMR, ee of **Bz-2b/c** determined by SFC.

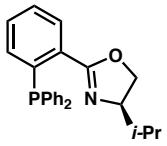




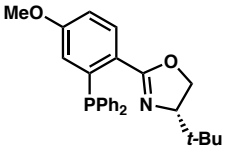
conversion: 100%
dr (b:c): 55:45
ee (b/c): 45%/15%



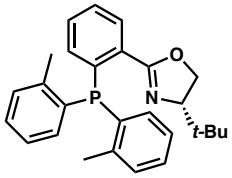
conversion: 100%
dr (b:c): 48:52
ee (b/c): 25%/10%



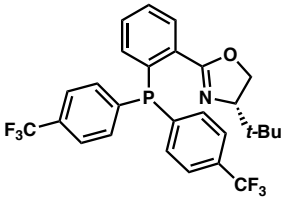
conversion: 100%
dr (b:c): 55:45
ee (b/c): 45%/15%



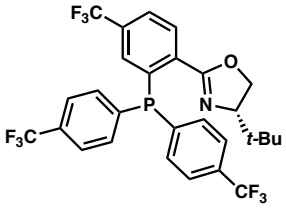
conversion: 67%
dr (b:c): 53:47
ee (b/c): 50%/8%



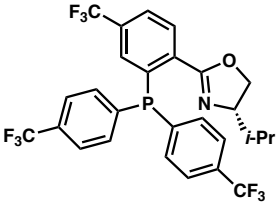
conversion: 7%
dr (b:c): ND
ee (b/c): ND



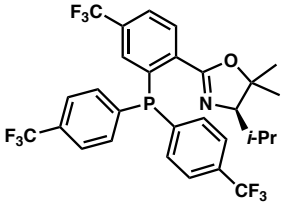
conversion: 100%
dr (b:c): 60:40
ee (b/c): 14%/18%



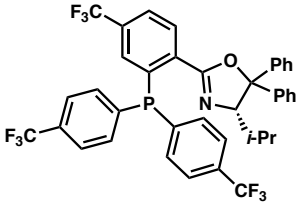
(in PhMe)
conversion: 98%
dr (b:c): 79:21
ee (b/c): 13%/41%



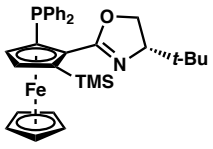
conversion: 100%
dr (b:c): 66:34
ee (b/c): 8%/17%



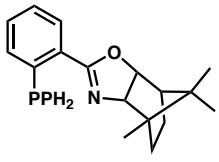
conversion: 96%
dr (b:c): 66:34
ee (b/c): 1%/4%



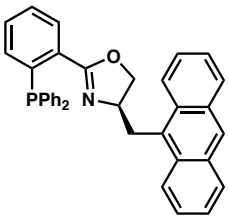
conversion: 100%
dr (b:c): 67:33
ee (b/c): 11%/10%



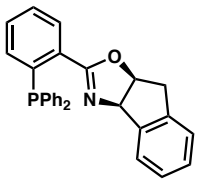
conversion: 100%
dr (b:c): 64:36
ee (b/c): 18%/10%



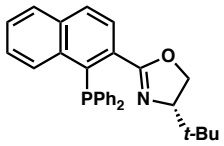
conversion: 88%
dr (b:c): 48:52
ee (b/c): 29%/12%



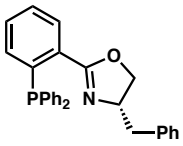
conversion: 93%
dr (b:c): 57:43
ee (b/c): 30%/14%



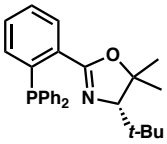
conversion: 82%
dr (b:c): 67:33
ee (b/c): 50%/17%



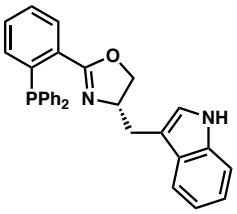
conversion: 91%
dr (b:c): 52:48
ee (b/c): 33%/11%



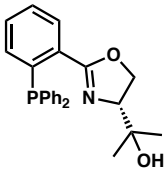
conversion: 99%
dr (b:c): 54:46
ee (b/c): 34%/11%



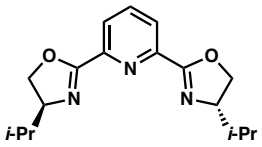
conversion: 99%
dr (b:c): 50:40
ee (b/c): 11%/–6%



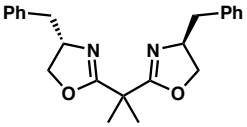
conversion: 30%
dr (b:c): 71:29
ee (b/c): 18%/–2%



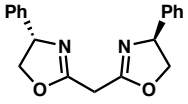
conversion: 33%
dr (b:c): 65:35
ee (b/c): 18%/–1%



conversion: 58%
dr (b:c): 62:38
ee (b/c): 6%/17%

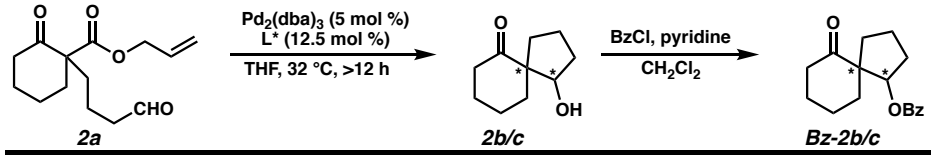


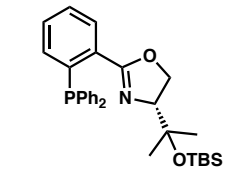
conversion: 34%
dr (b:c): 60:40
ee (b/c): 1%/2%



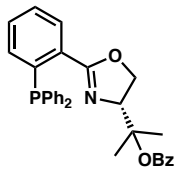
conversion: 5%
dr (b:c): ND
ee (b/c): ND

Table S5. Serine-derived PHOX ligand screen in THF; conversion determined by GC-FID, dr of **2b/c** determined by ^{1}H NMR, ee of **Bz-2b/c** determined by SFC.

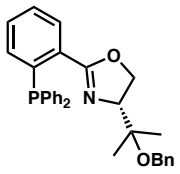




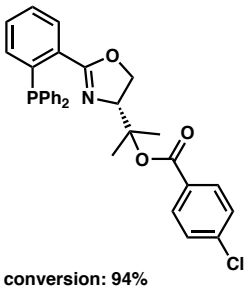
conversion: 55%
dr (b:c): 71:29
ee (b/c): 55%/18%



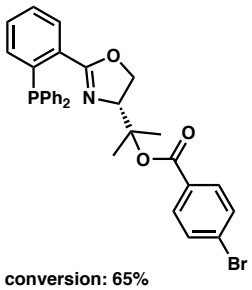
conversion: 89%
dr (b:c): 76:24
ee (b/c): 60%/22%



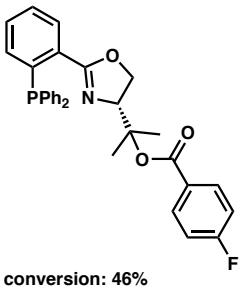
conversion: 100%
dr (b:c): 62:38
ee (b/c): 48%/15%



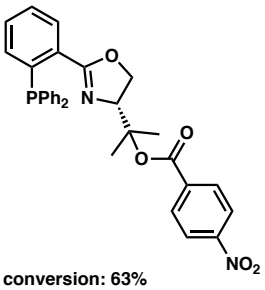
conversion: 94%
dr (b:c): 74:26
ee (b/c): 64%/43%



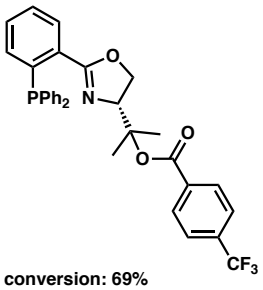
conversion: 65%
dr (b:c): 75:25
ee (b/c): 62%/24%



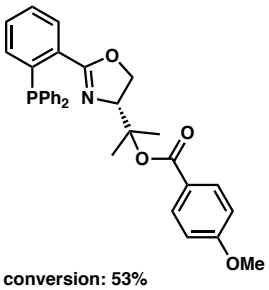
conversion: 46%
dr (b:c): 78:22
ee (b/c): 60%/31%



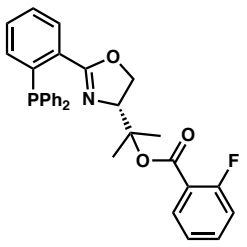
conversion: 63%
dr (b:c): 72:28
ee (b/c): 45%/12%



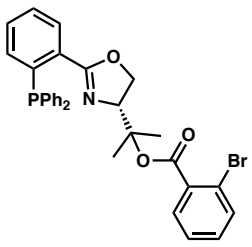
conversion: 69%
dr (b:c): 75:25
ee (b/c): 60%/31%



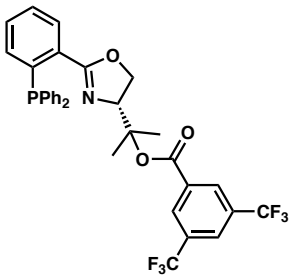
conversion: 53%
dr (b:c): 73:27
ee (b/c): 54%/22%



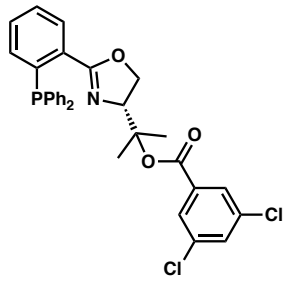
conversion: 36%
dr (b:c): 74:26
ee (b/c): 55%/24%



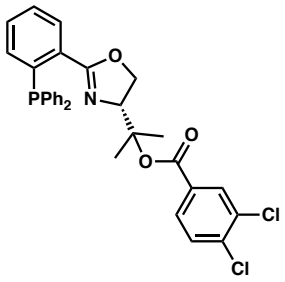
conversion: 42%
dr (b:c): 75:25
ee (b/c): 56%/24%



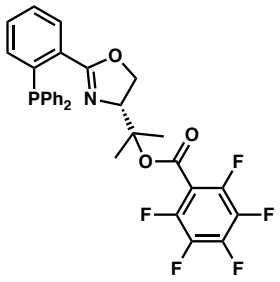
conversion: 37%
dr (b:c): 79:21
ee (b/c): 50%/18%



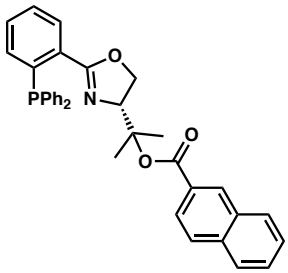
conversion: 100%
dr (b:c): 74:26
ee (b/c): 61%/20%



conversion: 100%
dr (b:c): 75:25
ee (b/c): 65%/25%

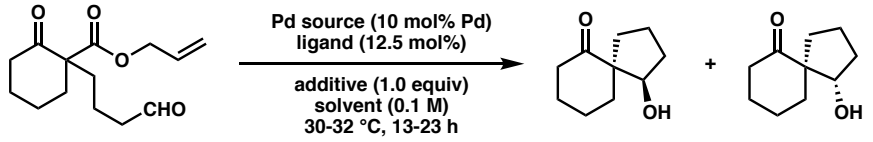


conversion: 21%
dr (b:c): 79:21
ee (b/c): 52%/21%



conversion: 100%
dr (b:c): 72:28
ee (b/c): 60%/21%

Table S6. Optimization of additional reaction parameters.



2a **2b** **2c**

entry	Pd source	ligand	additive	solvent	conv (%)[a, b]	*dr* (a:b)[a]	*ee* (%)[c]
1	$Pd_2(dba)_3$	L5	none	toluene	-[d]	63:37[e]	–35(–15)
2	$Pd(dmdba)_2$	L5	none	toluene	94	53:47	–42(–19)
3	$Pd_2(dba)_3$	L2	none	toluene	99	79:21	12(27)
4	$Pd_2(dba)_3$	L5	none	THF	>99	57:43	–45(–14)
5	$Pd_2(dba)_3$	L5	none	*p*-dioxane	-[d]	-	–28(–21)
6	$Pd_2(dba)_3$	L3	none	THF	>99	56:44	34(11)
7	$Pd_2(dba)_3$	L4	none	THF	>99	48:52	26(10)
8	$Pd_2(dba)_3$	L6	none	THF	97	49:51	–10(–13)
9	$Pd_2(dba)_3$	L7	none	THF	55	71:29	–55(–18)
10	$Pd_2(dba)_3$	L8	none	THF	89	53:47	33(11)
11	$Pd_2(dba)_3$	L9	none	THF	>99	52:48	11(–6)
12	$Pd_2(dba)_3$	L10	none	THF	69	66:34	–51(–16)
13[f]	$Pd(OAc)_2$	L5	none	THF	76	44:56	–71(–51)
14	$Pd_2(dba)_3$	L5	phenol	THF	>99	40:60	–75(–16)
15	$Pd(OAc)_2$	L1	phenol	THF	71	74:26	81(30)
16[f]	$Pd(OAc)_2$	L1	acetic acid	THF	-[d](77)	60:40	74(45)
17	$Pd(OAc)_2$	L1	meldrum's acid	THF	>99	72:28	9(13)
18	$Pd(OAc)_2$	L1	barbituric acid	THF	trace	-	-
19	$Pd(OAc)_2$	L1	aniline	THF	>99	69:31	58(23)
20	$Pd(OAc)_2$	L1	2-methoxyphenol	THF	>99	67:33	82(29)
21	$Pd(OAc)_2$	L10	2-methoxyphenol	THF	>99	62:38	–75(–29)
22	$Pd(OAc)_2$	L1	thymol	THF	>99	76:24	81(31)
23	$Pd(OAc)_2$	L1	2,6-dimethoxyphenol	THF	>99	41:59	84(44)
24	$Pd(OAc)_2$	L1	3,5-dimethoxyphenol	THF	76	63:37	83(24)
25	$Pd(OAc)_2$	L1	3,5-dimethylphenol	THF	68	74:26	81(42)
26[g]	$Pd(OAc)_2$	L1	3,5-dimethylphenol	THF	-[d](91)	75:25[e]	83(47)
27[h]	$Pd(OAc)_2$	L1	3,5-dimethylphenol	*p*-dioxane	-[d](87)	85:15[e]	86(72)

[a]Determined by GC. [b]Parenthetical value is isolated yield. [c]Determined by SFC after transformation to benzoyl ester; Parenthetical value is the *ee* of the minor diastereomer. [d]Disappearance of **2a** was checked by TLC. [e]Determined by ^{1}H NMR. [f]Reaction performed for 37 h. [g]Reaction performed at 40 °C. [h]Reaction temperature performed for 28 h at 35 °C after 16 h at 30 °C.

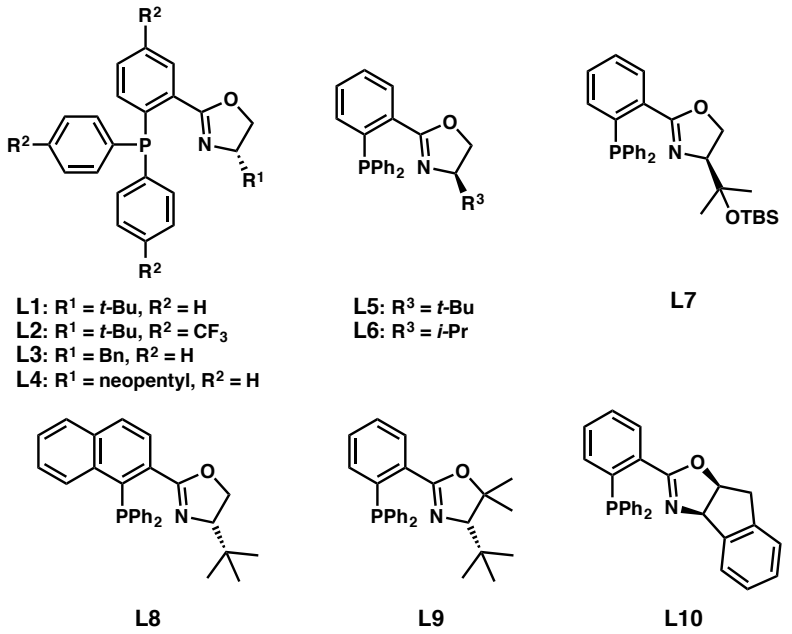
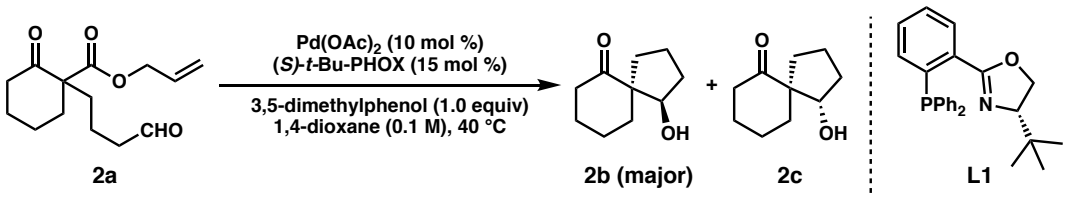


Figure S1. PHOX-Ligands for the Optimization of Reaction Conditions (Table S6).

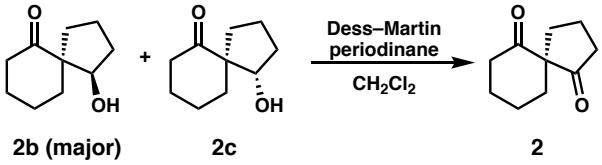
Experimental Procedures

Representative Procedure A: Intramolecular Aldol Cyclization



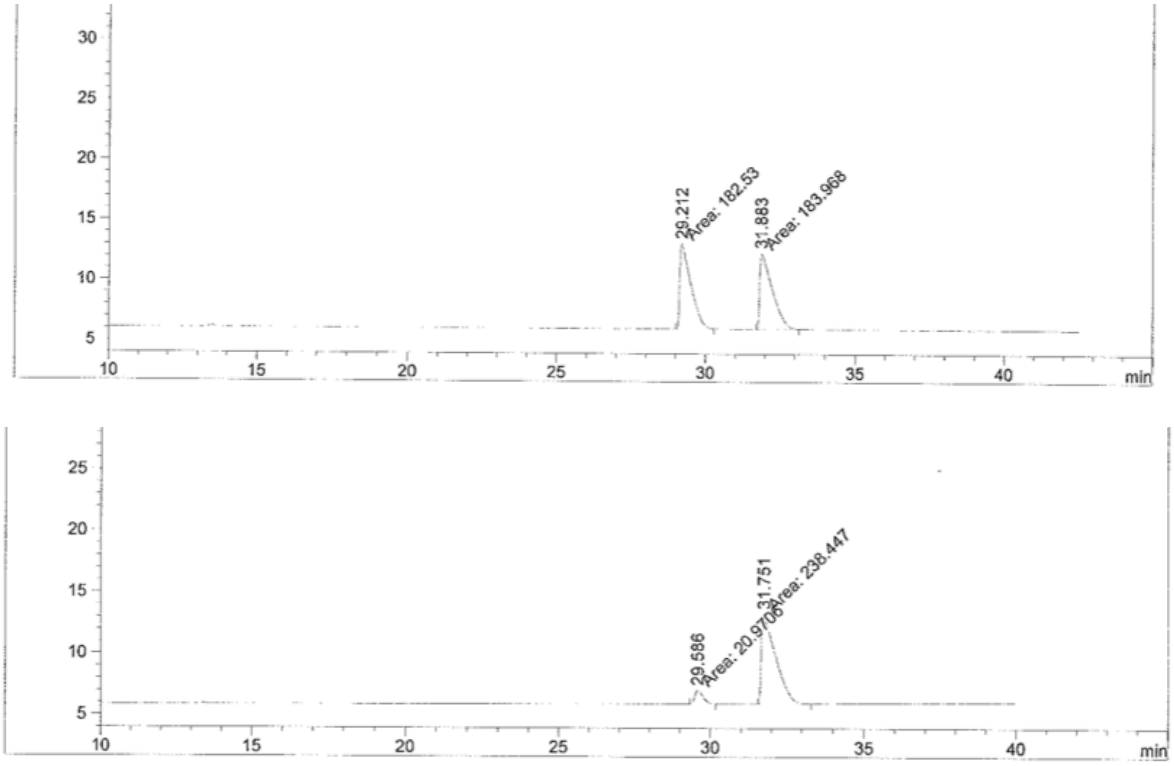
(1*R*,5*S*)-1-hydroxyspiro[4.5]decan-6-one (2b) and **(1*S*,5*S*)-1-hydroxyspiro[4.5]decan-6-one (2c)**: A solution of aldehyde **2a** (50 mg, 0.198 mmol, 1.0 equiv) in 1,4-dioxane (2.0 mL) was added to $Pd(OAc)_2$ (4.4 mg, 0.0196 mmol, 0.1 equiv), (*S*)-*t*-BuPHOX **L1** (11.5 mg, 0.0297 mmol, 0.15 equiv) and 3,5-dimethylphenol (24.2 mg, 0.198 mmol, 1.0 equiv) in a 4 mL scintillation vial equipped with a magnetic stirring bar. After sealing the vial, the mixture was stirred at 40 °C until the full consumption of aldehyde **2a** was observed by TLC analysis. The solvent was removed under reduced pressure. Flash column chromatography (SiO_2, 14%→33% EtOAc/Hexanes) afforded β-hydroxy ketones **2b/c** (30.1 mg, 0.179 mmol, 90% yield, colorless oil) as a mixture of diastereomers (**2b**/**2c** = 85/15, determined by ^{1}H NMR analysis); R_f = 0.39 (33% EtOAc in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$, 85:15 mixture of diastereomers) δ 4.49 (t, *J* = 6.5 Hz, 1H, C*H*-OH, minor), 3.98 (q, *J* = 5.3 Hz, 1H, C*H*-OH, major), 3.58 (d, *J* = 5.7 Hz, 1H, O*H*, major), 2.49 – 2.38 (m, 1H), 2.37 – 2.28 (m, 1H), 2.15 – 2.04 (m, 1H), 1.99 – 1.87 (m, 2H), 1.86 – 1.51 (m, 10H): characterization data match known values.[3]

Representative Procedure B: Oxidation of Aldol Products



(*R*)-Spiro[4.5]decane-1,6-dione (2): Dess-Martin periodinane (64.6 mg, 0.152 mmol, 2.0 equiv) was slowly added to a mixture of β-hydroxy ketones **2b/c** (12.8 mg, 0.076 mmol, 1.0 equiv) in CH_2Cl_2 (0.51 mL) at room temperature. The reaction mixture was stirred for 3.5 h and the crude reaction mixture was purified directly by flash column chromatography (SiO_2, 11% EtOAc/Hexanes). Purification afforded diketone **2** (11.8 mg, 0.071 mmol, 93% yield) as a colorless oil. 84% *ee*, $[\alpha]_D^{25}$ +155.3 (*c* 0.57, $CHCl_3$); R_f = 0.47 (20% EtOAc in hexanes): ^{1}H NMR

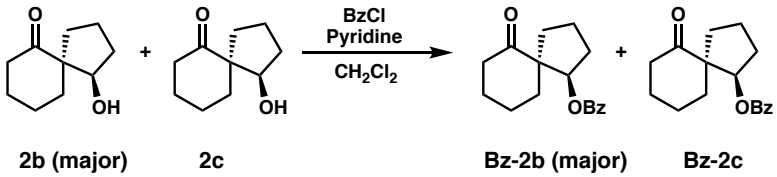
(500 MHz, $CDCl_3$) δ 2.74 – 2.61 (m, 2H), 2.43 (dt, J = 14.2, 5.5 Hz, 1H), 2.30 (td, J = 7.9, 2.5 Hz, 2H), 2.16 – 2.09 (m, 1H), 2.09 – 1.95 (m, 2H), 1.95 – 1.82 (m, 2H), 1.80 – 1.70 (m, 1H), 1.68 – 1.53 (m, 3H); characterization data match known values;[4] Chiral GC assay (CP-CHIRASIL-DEX CB column): 90 °C isothermal method over 40 min. t_R: minor 29.6 min, major 31.8 min.



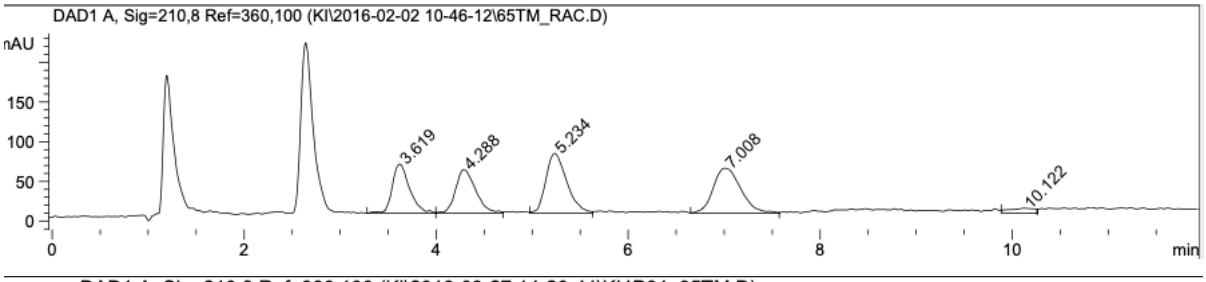
Signal 1: FID1 A,

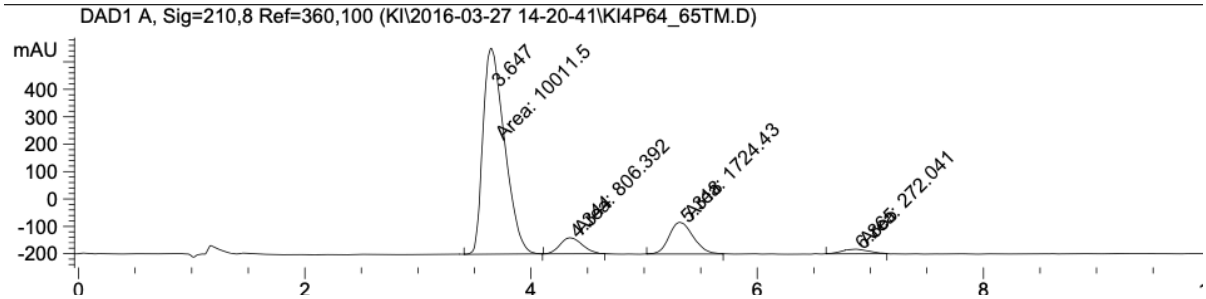
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	29.586	MM	0.3144	20.97059	1.11150	8.08373
2	31.751	MM	0.5432	238.44659	7.31653	91.91627

Representative Procedure C: Benzoylation of Aldol Products



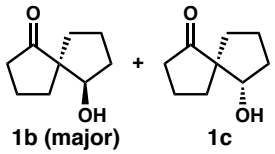
(1*R*,5*S*)-6-Oxospiro[4.5]decan-1-yl benzoate (Bz-2b) and **(1*S*,5*S*)-6-oxospiro[4.5]decan-1-yl benzoate (Bz-2c)**: To a mixture of β-hydroxy ketones **2b/c** (6.4 mg, 0.038 mmol, 1.0 equiv) in CH_2Cl_2 (0.15 mL) was added benzoyl chloride (17.5 mL, 0.151 mmol, 4.0 equiv) and pyridine (24 mL, 0.30 mmol, 7.9 equiv). The mixture was stirred until full consumption of spiro ketone **2b/c** was observed (generally, overnight). Flash column chromatography (SiO_2, 9% diethyl ether in hexanes eluent→9% EtOAc in hexanes eluent) afforded spiro ketone **Bz-2b/c** (10.4 mg, 0.038 mmol, >99% yield) as a mixture of diastereomers (**1e/f** = 85/15, determined by ^{1}H NMR analysis); 85% *ee* (major isomer), 73% *ee* (minor isomer); ^{1}H NMR (500 MHz, $CDCl_3$, 85:15 mixture of diastereomers) δ 8.11 – 8.07 (m, 1H, minor), 8.04 – 7.99 (m, 2H, minor), 7.95 – 7.87 (m, 2H, major), 7.58 – 7.51 (m, 1H, major), 7.47 – 7.44 (m, 2H, minor), 7.43 – 7.38 (m, 2H, major), 5.79 (dd, *J* = 5.7, 2.9 Hz, 1H, C*H*-OBz, minor), 5.63 (dd, *J* = 5.3, 1.5 Hz, 1H, C*H*-OBz, major), 2.77 (ddd, *J* = 13.3, 9.3, 7.4 Hz, 1H), 2.54 – 2.42 (m, 1H), 2.41 – 2.35 (m, 1H), 2.31 (td, *J* = 13.6, 5.9 Hz, 1H), 2.24 – 2.09 (m, 1H), 2.08 – 2.01 (m, 1H), 2.00 – 1.60 (m, 8H), 1.54 (td, *J* = 13.6, 4.2 Hz, 1H), 1.30 (ddd, *J* = 13.3, 8.0, 5.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, 85:15 mixture of diastereomers) δ 210.7, 166.0, 133.3, 133.1, 130.1, 129.7, 129.7, 128.6, 128.5, 80.5, 78.2, 60.7, 60.7, 41.5, 39.4, 38.0, 34.4, 33.7, 32.5, 31.0, 27.8, 27.3, 22.6, 22.5, 21.7, 21.5; IR (Neat Film, NaCl) 2938, 2864, 1716, 1450, 1314, 1274, 1176, 1111, 1070, 1026, 712; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{21}O_3$ $[M+H]^+$: 273.1491, found 273.1490; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OB-H, λ = 210 or 235 nm, t_R: **Bz-2b** (major) 3.6 min, **Bz-2b** (minor) 4.3 min, **Bz-2c** (major) 5.3 min, **Bz-2c** (minor) 6.8 min.





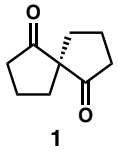
Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.647	MM	0.2217	1.00115e4	752.64709	78.1271
2	4.344	MM	0.2256	806.39166	59.56629	6.2929
3	5.318	MM	0.2465	1724.43494	116.59898	13.4570
4	6.865	MM	0.2699	272.04147	16.79893	2.1229



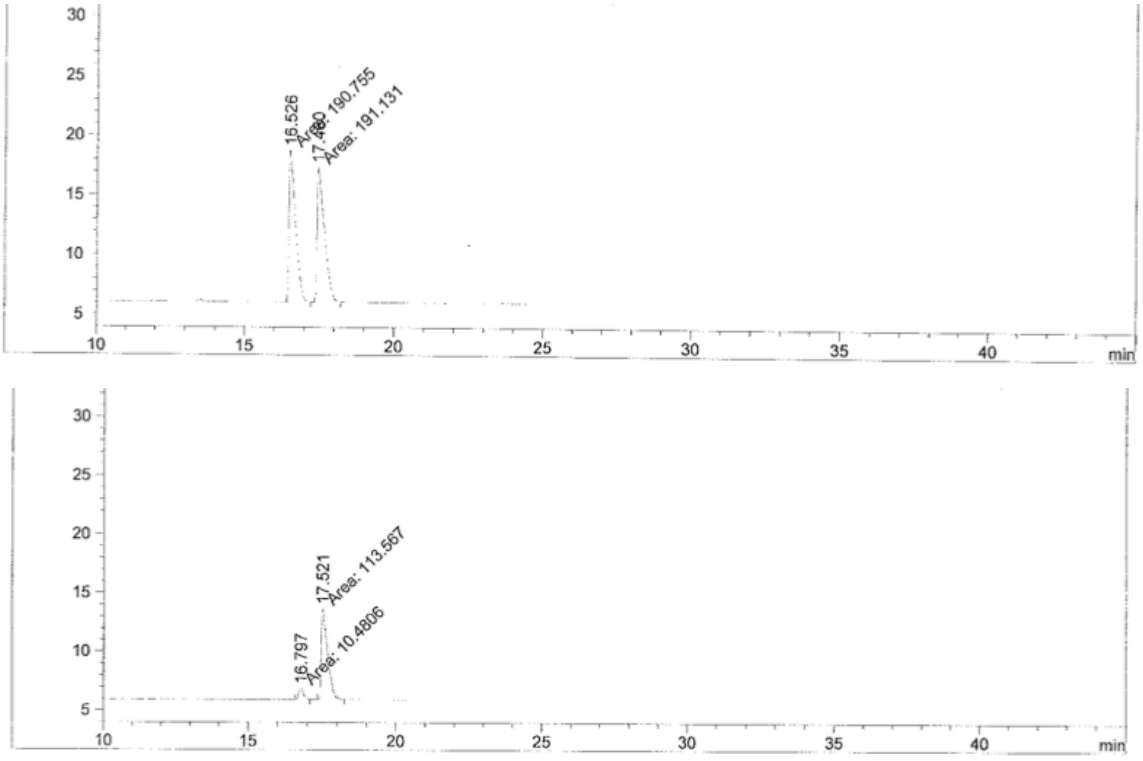
1b (major) 1c

(5*R*,6*R*)-6-Hydroxyspiro[4.4]nonan-1-one (1b) and **(5*R*,6*S*)-6-hydroxyspiro[4.4]nonan-1-one (1c):** Prepared according to representative procedure A: aldehyde **2a** (90 mg, 0.378 mmol); stirred at 40 °C for 15 h; Flash column chromatography (SiO_2, 17–33% EtOAc/Hexanes) afforded β-hydroxy ketones **1b**/**c** (44.8 mg, 0.291 mmol, 77% yield, 72:28 mixture of diastereomers as determined by ^{1}H NMR analysis); R_f = 0.27 (33% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 72:28 mixture of diastereomers) δ 4.22 (t, *J* = 6.7 Hz, 1H, C*H*-OH, minor), 4.01 (s, 1H, C*H*-OH, major), 3.46 (br s, 1H, O*H*, major), 2.40 – 2.15 (m, 3H), 2.14 – 2.05 (m, 1H), 2.04 – 1.53 (m, 13H); characterization data match known values.[5] ^{1}H NMR (500 MHz, $CDCl_3$, 72:28 mixture of diastereomers) δ 4.22 (t, *J* = 6.7 Hz, 1H, C*H*-OH, minor), 4.01 (s, 1H, C*H*-OH, major), 3.46 (br s, 1H, O*H*, major), 2.40 – 2.15 (m, 3H), 2.14 – 2.05 (m, 1H), 2.04 – 1.53 (m, 13H); characterization data match known values.[4]



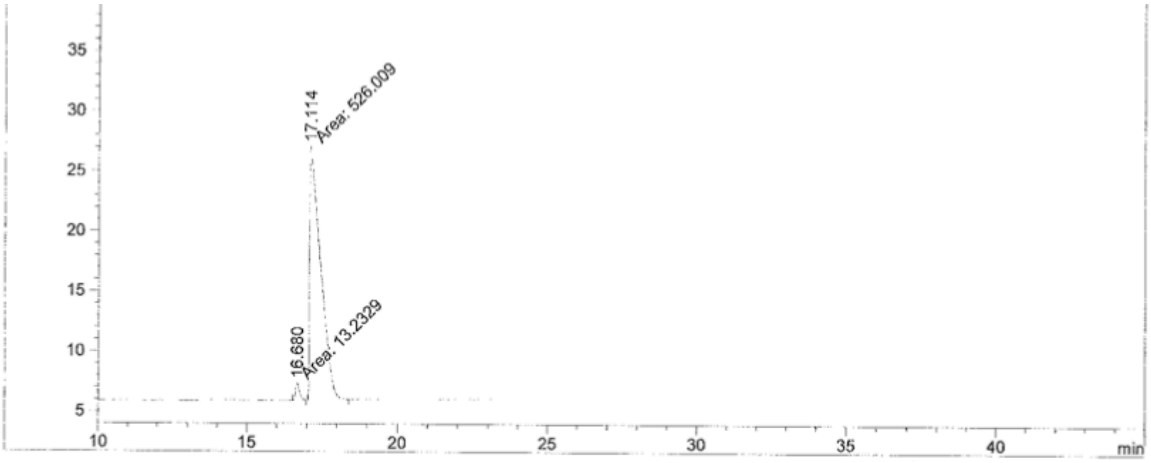
1

(*R*)-Spiro[4.4]nonane-1,6-dione (1): Prepared according to representative procedure B: Mixture of β-hydroxy ketones **1b/c** (35.5 mg, 0.230 mmol); stirred for 26 h at room temperature; flash column chromatography (SiO_2, 11% EtOAc/Hexanes) afforded diketone **1** (30.8 mg, 0.202 mmol, 88% yield) as a white solid (83% *ee*). Diketone **1** (20.1 mg, 0.132 mmol) and hexanes (0.163 mL) were added to a scintillation vial. The vial was sealed and the residue dissolved by slight warming. The solution was gradually cooled to ambient temperature and was allowed to stand over 3 h. Recrystallization afforded diketone **1** (16.5 mg, 0.108 mmol, 82% yield) as a white solid; 95% *ee*, $[a]_D^{25}$ +175.1 (*c* 0.25, $CHCl_3$); R_f = 0.39 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 – 2.24 (m, 6H), 2.23 – 2.12 (m, 2H), 1.95 – 1.85 (m, 2H), 1.85 – 1.76 (m, 2H); characterization data match known values;[4] Chiral GC assay (CP-CHIRASIL-DEX CB column): 90 °C isothermal method over 20 min. t_R: minor 16.8 min, major 17.5 min.



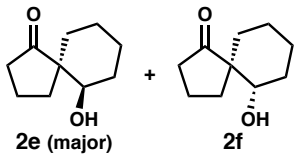
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	16.797	MM	0.1833	10.48062	9.53132e-1	8.44889
2	17.521	MM	0.2448	113.56670	7.73273	91.55111



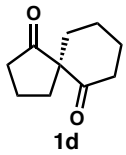
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	16.680	MM	0.1549	13.23288	1.42413	2.45398
2	17.114	MM	0.4150	526.00916	21.12304	97.54602



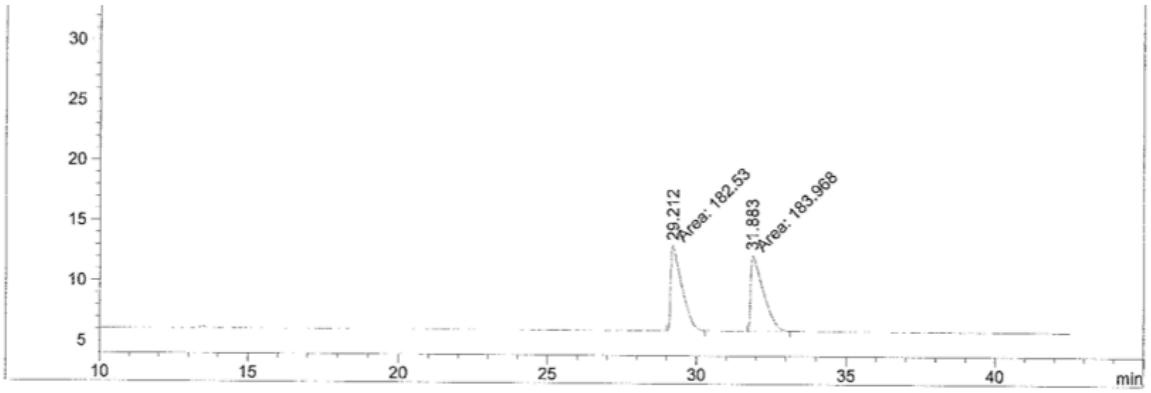
(5*R*,6*R*)-6-Hydroxyspiro[4.5]decan-1-one (2e) and **(5*R*,6*S*)-6-hydroxyspiro[4.5]decan-1-one (2f):** Prepared according to representative procedure A: aldehyde **2d** (50 mg, 0.198 mmol); stirred at 40 °C for 20 h; Flash column chromatography (SiO_2, 17%→33% EtOAc/hexanes) afforded β-hydroxy ketones **2e** (18.9 mg, 0.112 mmol, 57% yield) and **2f** (9.1 mg, 0.054 mmol, 27% yield) as colorless oils (**2e**/**2f** = 67/33, determined by mass of isolated products). β-hydroxy ketone **2e** (major): R_f = 0.52 (33% EtOAc in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (br s, 1H, O*H*), 3.66 (m, 1H, C*H*-OH), 2.47 – 2.32 (m, 1H), 2.31 – 2.21 (m, 1H), 2.08 – 1.99 (m, 1H), 1.98 – 1.73 (m, 6H), 1.65 – 1.54 (m, 1H), 1.50 – 1.33 (m, 3H), 1.31 – 1.20 (m, 1H). β-hydroxy ketone **2f** (minor): R_f = 0.33 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (dd, *J* = 10.6, 4.2 Hz, 1H, C*H*-OH), 2.40 – 2.27 (m, 1H), 2.26 – 2.12 (m, 1H), 2.07 – 1.92 (m, 1H), 1.89

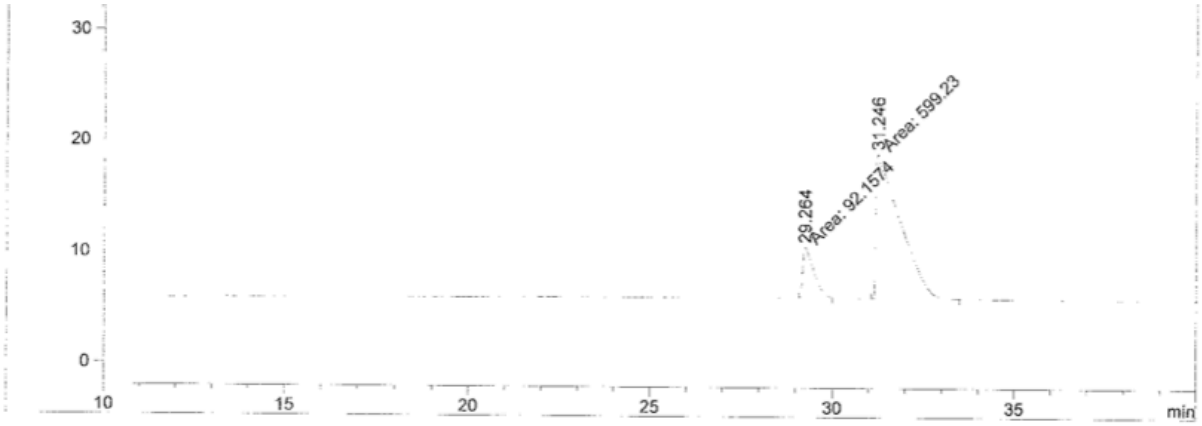
– 1.69 (m, 4H), 1.67 – 1.44 (m, 4H), 1.41 – 1.16 (m, 4H); characterization data match known values.[6]



1d

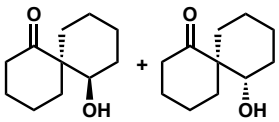
(*R*)-Spiro[4.5]decane-1,6-dione (2): Prepared according to representative procedure B: Mixture of β-hydroxy ketones **2e/f** (8.8 mg, 0.052 mmol); stirred at ambient temperature for 12 h; flash column chromatography (SiO_2, 11% EtOAc in hexanes eluent) afforded diketone **2** (7.7 mg, 0.046 mmol, 88% yield) as a colorless oil: 73% *ee*, $[\alpha]_D^{25}$ +144.3 (*c* 0.3, $CHCl_3$); R_f = 0.47 (20% EtOAc in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.77 – 2.58 (m, 2H), 2.48 – 2.39 (m, 1H), 2.30 (td, *J* = 7.9, 2.4 Hz, 2H), 2.17 – 2.10 (m, 1H), 2.10 – 1.96 (m, 2H), 1.95 – 1.82 (m, 2H), 1.80 – 1.69 (m, 1H), 1.69 – 1.53 (m, 3H); characterization data match known values;[3] Chiral GC assay (CP-CHIRASIL-DEX CB column): 90 °C isothermal method over 40 min. t_R: minor 29.6 min, major 31.8 min.





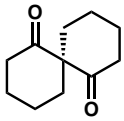
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	29.264	MM	0.3432	92.15742	4.47507	13.32935
2	31.246	MM	0.7705	599.22968	12.96203	86.67065



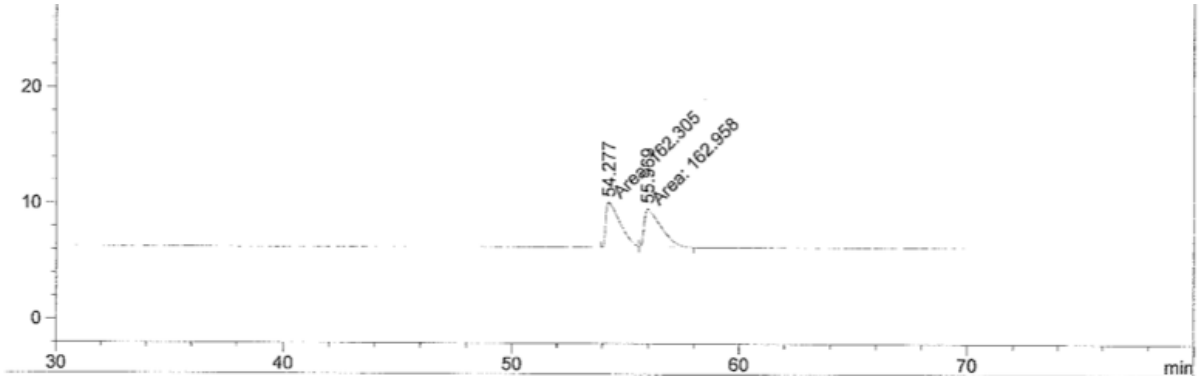
3b (major) **3c**

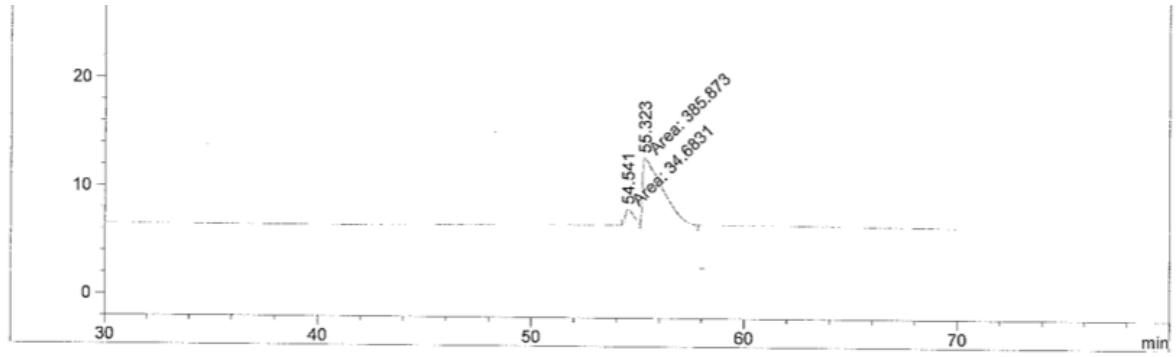
(6*R*,7*R*)-7-Hydroxyspiro[5.5]undecan-1-one (3b) and **(6*R*,7*S*)-7-hydroxyspiro[5.5]undecan-1-one (3c):** Prepared according to representative procedure A: Aldeyde **3a** (237.5 mg, 0.892 mmol); stirred at 40 °C for 15 h; flash column chromatography (SiO_2, 14%→33% EtOAc/Hexanes) afforded β-hydroxy ketones **3b/c** (133 mg, 0.730 mmol, 82% yield, 76:24 mixture of diastereomers as determined by ^{1}H NMR analysis) as a colorless oil; R_f = 0.50 (33% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 76:24 mixture of diastereomers) δ 4.09 (dt, *J* = 11.6, 3.5 Hz, 1H, C*H*-OH, minor), 3.41 (q, *J* = 7.5 Hz, 1H, C*H*-OH, major), 3.20 (d, *J* = 7.6 Hz, 1H, O*H*, major), 2.62 – 2.49 (m, 1H), 2.31 – 2.15 (m, 2H), 2.13 – 1.92 (m, 2H), 1.89 – 1.59 (m, 8H), 1.58 – 1.10 (m, 5H); characterization data match known values.[4]



3

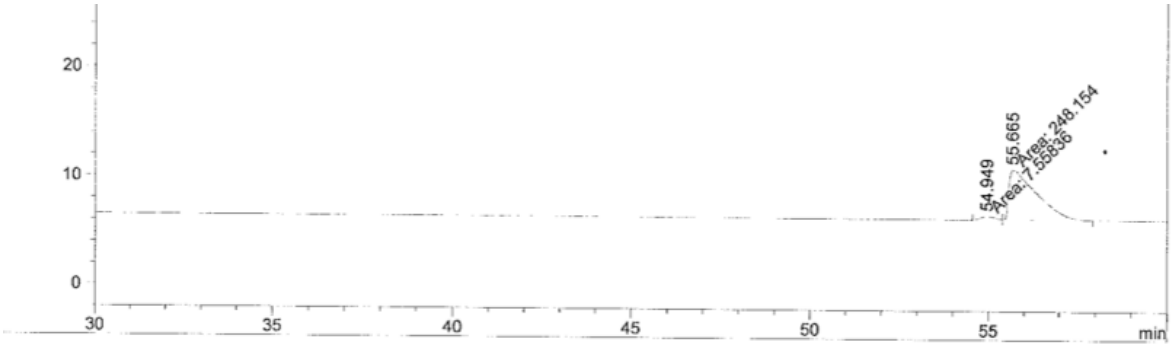
(*R*)-Spiro[5.5]undecane-1,7-dione (3): Prepared according to representative procedure B: Mixture of β-hydroxy ketones **3b/c**; stirred at ambient temperature for 34 h; flash column chromatography (SiO_2, 11% EtOAc/Hexanes) afforded diketone **3** (70.0 mg, 0.388 mmol, 82% yield) as a white solid (84% *ee*). Diketone **3** (67.0 mg, 0.372 mmol) and hexanes (0.315 mL) were added to a scintillation vial equipped with a magnetic stirring bar. The vial was sealed and the contents dissolved at 45 °C. The solution was gradually cooled to 23 °C and was allowed to stand for 12 h. Filtration afforded diketone **3** (52.3 mg, 0.290 mmol, 78% yield) as a white solid; 94% *ee*, $[\alpha]_D^{25}$ +125.5 (*c* 0.26, $CHCl_3$); R_f = 0.52 (11% EtOAc/Hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 – 2.33 (m, 6H), 1.97 – 1.86 (m, 2H), 1.74 (m, 6H), 1.54 – 1.42 (m, 2H); characterization data match known values;[4] Chiral GC assay (CP-CHIRASIL-DEX CB column): 90 °C isothermal method over 60 min. t_R: minor 54.9 min, major 55.7 min.





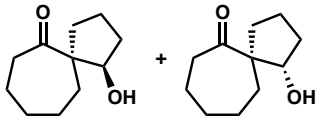
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	54.541	MM	0.4199	34.68313	1.37669	8.24697
2	55.323	MM	1.0632	385.87289	6.04893	91.75303



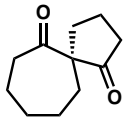
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	54.949	MM	0.4150	7.55836	3.03514e-1	2.95581
2	55.665	MM	0.9044	248.15375	4.57319	97.04419



4b (major) **4c**

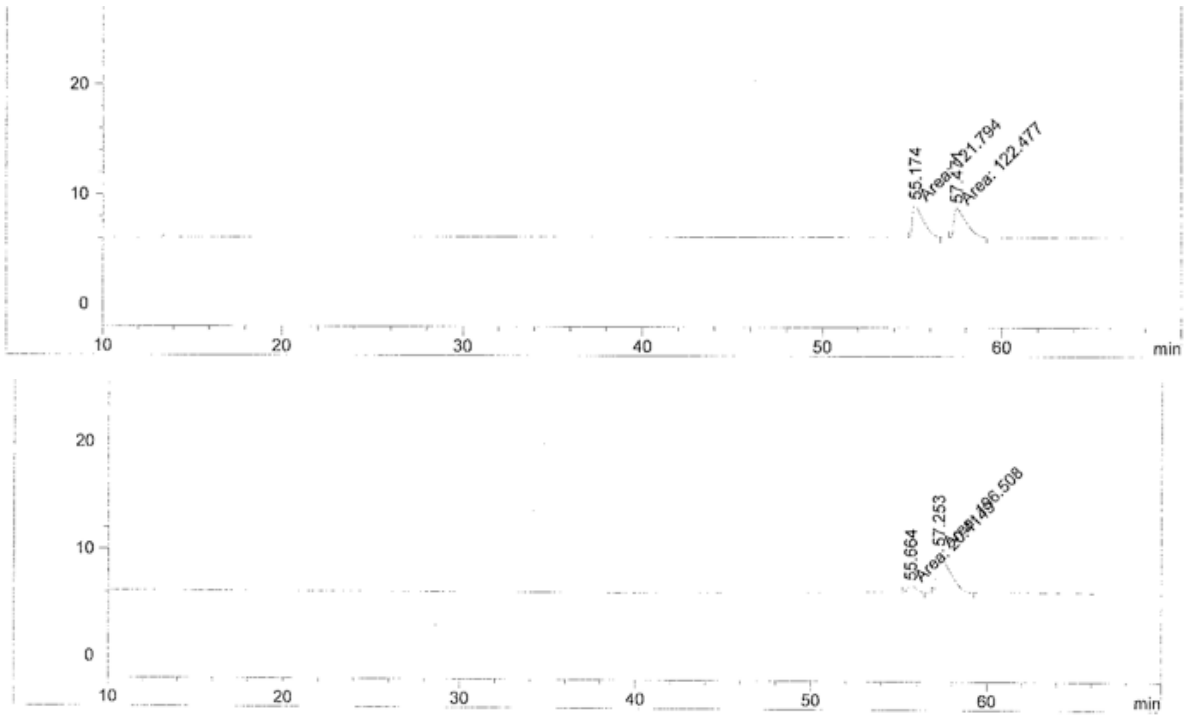
(1*R*,5*S*)-1-Hydroxyspiro[4.6]undecan-6-one (4b) and **(1*S*,5*S*)-1-hydroxyspiro[4.6]undecan-6-one (4c):** Prepared according to representative procedure A: Aldehyde **4a** (76.2 mg, 0.286 mmol); stirred at 35 °C for 48 h; flash column chromatography (SiO_2, 17%→20%→33% EtOAc/Hexanes) afforded β-hydroxy ketones **4b/c** (47.7 mg, 0.262 mmol, 92% yield, 66:34 mixture of diastereomers as determined by ^{1}H NMR analysis) as a colorless oil. The relative stereochemistry was determined by analogy compared with the ^{1}H NMR spectrum of similar known carbocyclic compounds. Specifically, the peak corresponding to the hydroxyl group shows specific characteristics in the ^{1}H NMR;[5] R_f = 0.35 (33% EtOAc/Hexanes): ^{1}H NMR (500 MHz, $CDCl_3$, 66:34 mixture of diastereomers) δ 4.30 (t, *J* = 6.8 Hz, 1H, C*H*-OH, minor), 3.99 (q, *J* = 4.7 Hz, 1H, C*H*-OH, major), 3.09 (d, *J* = 5.3 Hz, 1H, O*H*, major), 2.64 – 2.47 (m, 2H), 2.22 – 2.11 (m, 1H), 2.10 – 1.90 (m, 2H), 1.90 – 1.78 (m, 1H), 1.78 – 1.43 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$, 66:34 mixture of diastereomers) δ 219.1, 217.5, 81.8, 77.0, 62.5, 62.0, 42.9, 41.9, 36.2, 34.2, 33.8, 33.5, 32.8, 30.5, 30.4, 30.0, 26.3, 26.2, 25.7, 25.4, 21.0, 19.9; IR (Neat Film, NaCl) 3437, 2930, 2858, 1693, 1444, 1348, 1316, 1193, 1154, 1082, 938, 888; HRMS (ESI/APCI) *m/z* calc'd for $C_{11}H_{19}O_2$ $[M+H]^+$: 183.1385, found 183.1377.



4

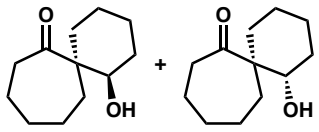
(*R*)-Spiro[4.6]undecane-1,6-dione (4): Prepared according to representative procedure B: Mixture of β-hydroxy ketones **4b/c** (40 mg, 0.222 mmol); stirred at ambient temperature for 13 h; flash column chromatography (SiO_2, 11% EtOAc/Hexanes) afforded diketone **4d** (37.2 mg, 0.206 mmol, 93% yield) as a colorless oil. The absolute configuration was determined by analogy compared with similar known carbocyclic spiro compounds;[5] 81% *ee*, $[\alpha]_D^{25}$ +230.7 (*c* 0.28, $CHCl_3$); R_f = 0.54 (20% EtOAc/Hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88 (td, *J* = 11.6, 2.6 Hz, 1H), 2.67 (p, *J* = 6.5 Hz, 1H), 2.42 (ddd, *J* = 10.5, 7.7, 2.2 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.30 – 2.20 (m, 1H), 2.09 (dd, *J* = 14.7, 10.8 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.93 – 1.82 (m, 3H), 1.82 – 1.74 (m, 1H), 1.73 – 1.63 (m, 2H), 1.60 – 1.40 (m, 2H), 1.30 – 1.20 (m, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 216.6, 210.8, 68.0, 42.0, 38.6, 34.2, 33.6, 30.6, 26.5, 25.7, 19.4; IR (Neat Film, NaCl) 2930, 2859, 1737, 1694, 1454, 1445, 1405, 1340, 1324, 1154, 950, 887 843, 818 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $C_{11}H_{16}O_2$ $[M]^+$: 180.1150, found 180.1158. Chiral GC assay (CP-CHIRASIL-DEX CB column): 90 °C isothermal method over 60 min. t_R: minor 55.7 min, major 57.3 min.



Signal 1: FID1 A,

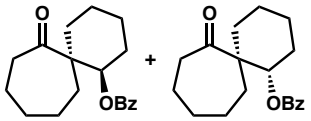
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	55.664	MM	0.5352	20.41489	6.35689e-1	9.41113
2	57.253	MM	0.8472	196.50795	3.86603	90.58887



5b (major) **5c**

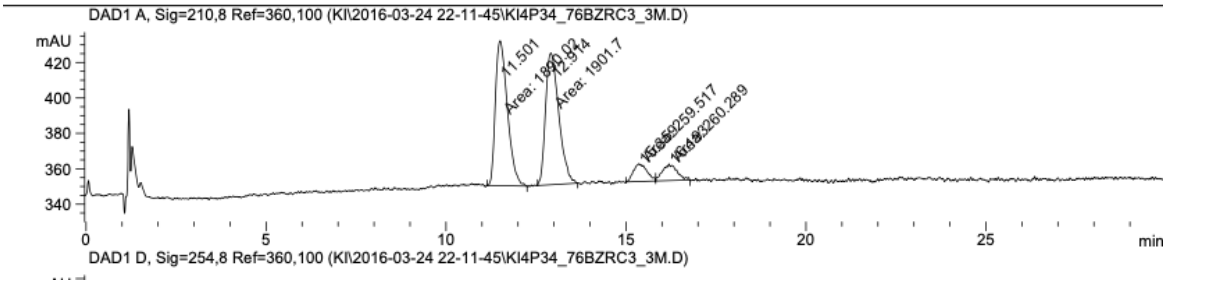
(1*R*,6*S*)-1-Hydroxyspiro[5.6]dodecan-7-one (5b) and **(1*S*,6*S*)-1-hydroxyspiro[5.6]dodecan-7-one (5c):** Prepared according to representative procedure A: Aldehyde **5a** (40 mg, 0.143 mmol); stirred at 40 °C for 40 h; flash column chromatography (SiO_2, 14%→33% EtOAc in hexanes eluent) afforded β-hydroxy ketones **5b/c** (21.2 mg, 0.108 mmol, 76% yield, 67:33 mixture of diastereomers as determined by ^1H NMR analysis) as a colorless oil; R_f = 0.46 (33% EtOAc/Hexanes): ^1H NMR (500 MHz, $CDCl_3$, 67:33 mixture of diastereomers) δ 3.99 (dt, *J* =

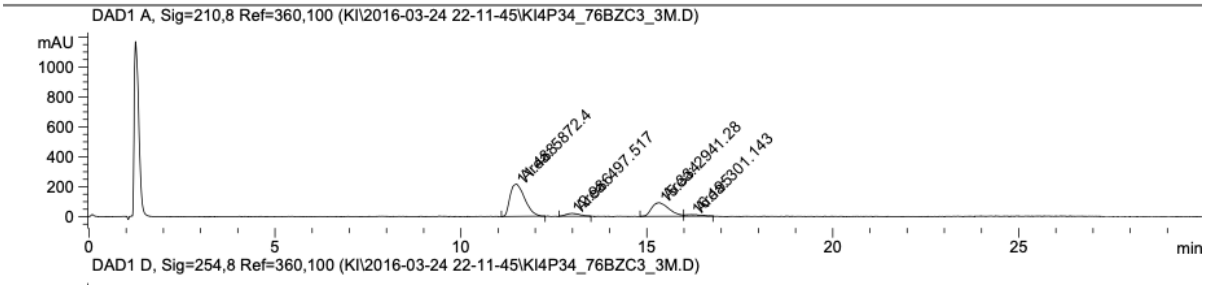
11.4, 3.8 Hz, 1H, C*H*-OH, minor), 3.64 (q, *J* = 5.6 Hz, 1H, C*H*-OH, major), 3.15 (d, *J* = 6.6 Hz, 1H, O*H*, major), 2.73 – 2.54 (m, 1H), 2.50 – 2.28 (m, 1H), 2.25 – 2.11 (m, 1H), 2.08 – 1.97 (m, 1H), 1.92 – 1.83 (m, 1H), 1.81 – 1.13 (m, 15H); characterization data match known values.[7]



Bz-5b (major) **Bz-5c**

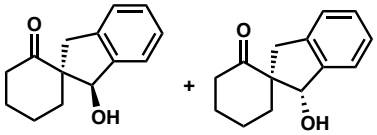
(1*R*,6*S*)-7-Oxospiro[5.6]dodecan-1-yl benzoate (Bz-5b) and **(1*S*,6*S*)-7-oxospiro[5.6]dodecan-1-yl benzoate (Bz-5c):** Prepared according to representative procedure C: Mixture of β-hydroxy ketones **5b/c** (5.0 mg, 0.025 mmol); stirred at ambient temperature for 12 h; flash column chromatography (SiO_2, 9% diethyl ether in hexanes eluent→9% EtOAc/Hexanes) afforded benzoyl esters **Bz-5b/c** (7.7 mg, 0.025 mmol, >99% yield, 67:33 mixture of diastereomers as determined by ^{1}H NMR analysis) as a colorless oil. The absolute configuration was determined by analogy compared with similar known carbocyclic spiro compounds;[5] 84% *ee* (major isomer), 81% *ee* (minor isomer); R_f = 0.67 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 67:33 mixture of diastereomers) δ 8.19 – 8.14 (m, 2H, minor), 8.05 – 8.00 (m, 2H, minor), 8.00 – 7.94 (m, 2H, major), 7.68 (t, *J* = 7.5 Hz, 1H, minor), 7.59 – 7.50 (m, 2H, major), 7.47 – 7.38 (m, 2H, major), 5.42 (dd, *J* = 8.4, 3.8 Hz, 1H, C*H*-OBz, minor), 5.34 – 5.28 (m, 1H, C*H*-OBz, major), 2.78 (td, *J* = 11.7, 2.9 Hz, 1H), 2.60 – 2.48 (m, 1H), 2.29 – 2.19 (m, 1H), 2.12 (dd, *J* = 14.6, 9.8 Hz, 1H), 2.07 – 1.90 (m, 2H), 1.89 – 1.33 (m, 13H), 1.31 – 1.20 (m, 1H), 1.16 – 1.05 (m, 1H), 0.93 – 0.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, 67:33 mixture of diastereomers) δ 215.8, 214.6, 165.8, 165.5, 134.7, 133.1, 133.0, 130.7, 130.7, 130.4, 129.8, 129.7, 129.0, 128.5, 77.4, 76.1, 75.3, 54.8, 53.9, 41.7, 39.8, 32.2, 30.9, 30.7, 27.6, 27.3, 26.5, 26.5, 24.3, 24.2, 22.8, 21.2, 21.0, 20.5; IR (Neat Film, NaCl) 3063, 2931, 2861, 1788, 1716, 1600, 1584, 1450, 1337, 1314, 1269, 1213, 1174, 1109, 1070, 1015, 711 cm^{-1}; HRMS **(**ESI/APCI**)** *m/z* calc'd for $C_{19}H_{25}O_3$ $[M+H]^+$: 301.1804, found 301.1797. SFC conditions: 3% IPA, 2.5 mL/min, Chiralcel OD-H, λ = 210 nm, t_R: **Bz-5b** (major) 11.5 min, **Bz-5b** (minor) 13.0 min, **Bz-5c** (major) 15.3 min, **Bz-5c** (minor) 16.2 min.





Signal 1: DAD1 A, Sig=210,8 Ref=360,100

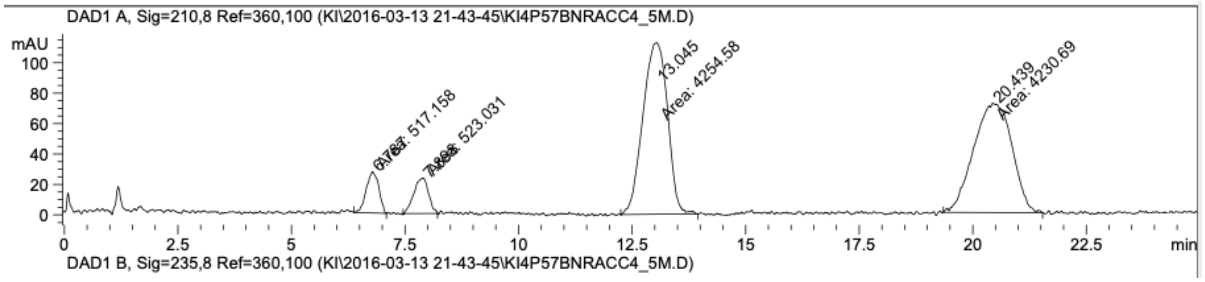
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.488	MM	0.4559	5872.40283	214.70224	61.0923
2	12.986	MM	0.4278	497.51663	19.38089	5.1758
3	15.334	MF	0.5398	2941.28418	90.81655	30.5990
4	16.195	FM	0.4752	301.14267	10.56220	3.1329

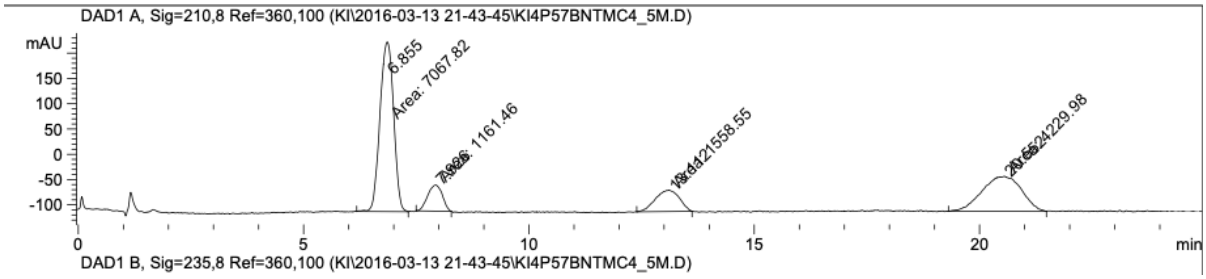


6b (major) **6c**

(1*S*,1'*R*)-1'-Hydroxy-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-2-one (7b) and **(1*S*,1'*S*)-1'-hydroxy-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-2-one (7c):** Prepared according to representative procedure A: Aldehyde **6a** (20 mg, 0.067 mmol); stirred at 35 °C for 19 h; flash column chromatography (SiO_2, 17%→33% EtOAc/Hexanes) afforded β-hydroxy ketones **6b/c** (13.6 mg, 0.063 mmol, 94% yield, 62:38 mixture of diastereomers as determined by ^{1}H NMR analysis) as a colorless oil. The relative and absolute stereochemistry was determined by analogy compared with the ^{1}H NMR spectrum of similar known carbocyclic spiro compounds. Specifically, the peak corresponding to the hydroxyl group shows specific characteristics in the ^{1}H NMR;[5] 72% *ee* (major diastereomer), 46% *ee* (minor diastereomer); R_f = 0.39 (33% EtOAc in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$, 62/38 mixture of diastereomers) δ 7.44 – 7.34 (m, 1H), 7.27 – 7.16 (m, 3H), 5.68 (s, 1H, C*H*-OH, minor), 5.01 (s, 1H, C*H*-OH, major), 3.71 (d, *J* = 16.4

Hz, 1H, O*H*, major), 3.03 (q, *J* = 15.6 Hz, 1H), 2.95 – 2.86 (m, 1H), 2.72 – 2.56 (m, 1H), 2.56 – 2.45 (m, 1H), 2.13 – 1.56 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$, 62/38 mixture of diastereomers) δ 214.2, 213.4, 143.0, 143.0, 140.3, 138.7, 128.8, 128.5, 127.4, 127.3, 125.3, 125.0, 124.8, 124.5, 81.7, 76.8, 62.4, 61.7, 40.6, 40.3, 39.6, 38.7, 37.5, 30.9, 27.6, 27.5, 22.4, 22.0; IR (Neat Film, NaCl) 3417, 2936, 2862, 1702, 1481, 1460, 1442, 1338, 1311, 1225, 1128, 1054, 1020, 751, 722 cm^{-1}; HRMS **(**ESI/APCI**)** *m/z* calc'd for $C_{14}H_{16}O_2$ $[M]^+$: 216.1150, found 216.1130. SFC conditions: 3% IPA, 2.5 mL/min, Chiralcel OJ-H, λ = 210 nm, t_R: **7b** (major) 6.9 min, **7b** (minor) 7.9 min, **7c** (minor) 13.1 min, **7c** (major) 20.6 min.

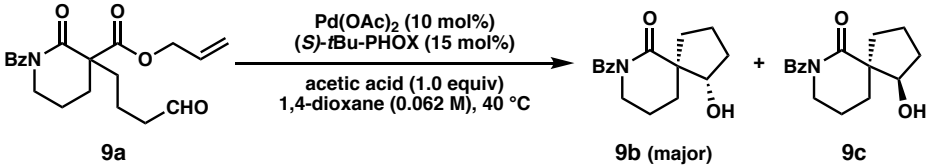




Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.855	MM	0.3511	7067.81738	335.50436	50.4203
2	7.926	MM	0.3732	1161.45557	51.86626	8.2856
3	13.112	MM	0.6165	1558.55212	42.13146	11.1184
4	20.552	MM	1.0153	4229.98242	69.43938	30.1758

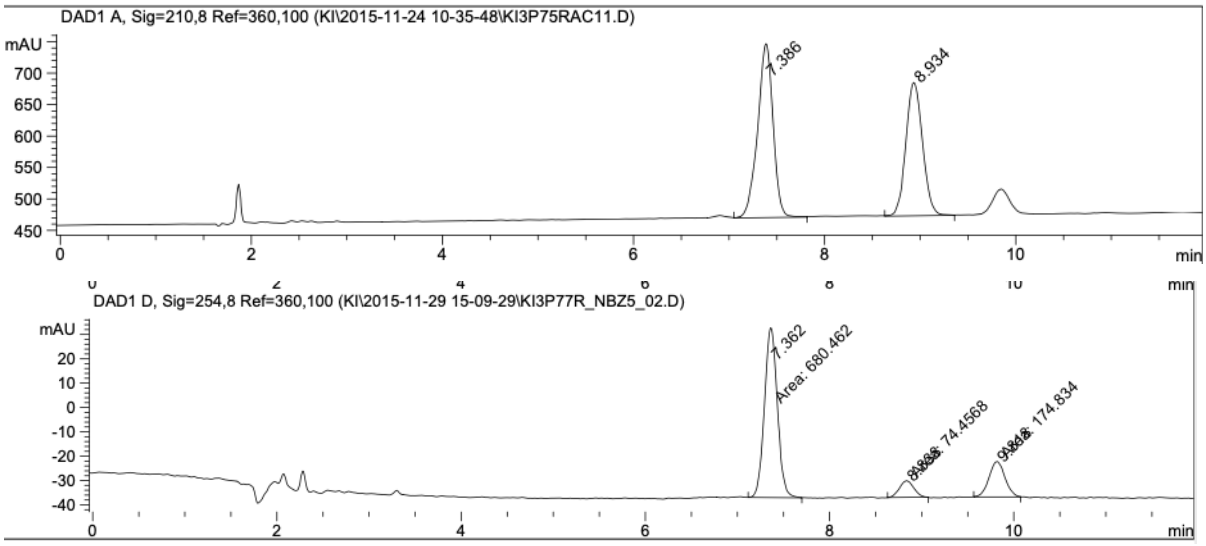
Representative Procedure D: Intramolecular Aldol Cyclization of Lactam Substrates



9a **9b** (major) **9c**

(1*S*,5*R*)-7-Benzoyl-1-hydroxy-7-azaspiro[4.5]decan-6-one (9b) and **(1*R*,5*R*)-7-benzoyl-1-hydroxy-7-azaspiro[4.5]decan-6-one (9c):** A solution of aldehyde **9a** (50 mg, 0.140 mmol, 1.0 equiv) in 1,4-dioxane (2.25 mL) was added to $Pd(OAc)_2$ (3.1 mg, 0.0138 mmol, 0.1 equiv), (*S*)-*t*-BuPHOX **L1** (8.1 mg, 0.0209 mmol, 0.15 equiv) and acetic acid (8.0 μL, 0.140 mmol) in a 4 mL scintillation vial equipped with a magnetic stirring bar. The vial was sealed and stirred at 40 °C until the full consumption of aldehyde **9a** was observed by TLC analysis (40 h). The reaction mixture was concentrated under reduced pressure. Flash column chromatography (SiO_2, 20%→33% EtOAc/Hexanes) afforded lactam **9b** (27.3 mg, 0.10 mmol, 71% yield) and lactam **9c** (7.5 mg, 0.027 mmol, 20% yield) as white solids (**9b**/**9c** = 78/22, determined by mass of isolated products).

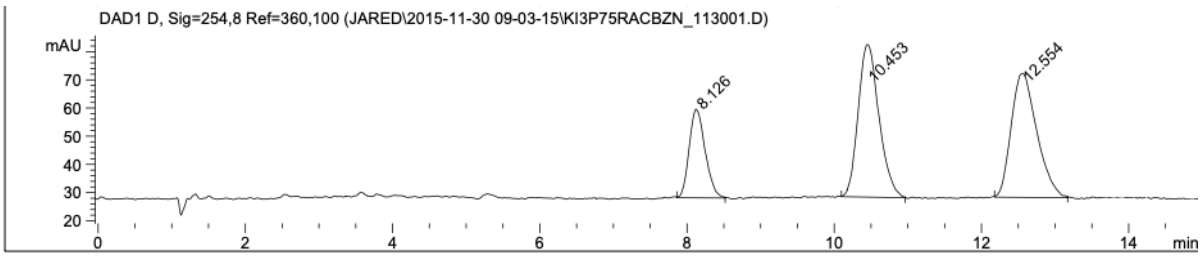
lactam **9b**: 89% *ee*, $[\alpha]_D^{25}$ +83.9 (*c* 0.23, $CHCl_3$); R_f = 0.40 (50% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.48 – 7.44 (m, 1H), 7.40 – 7.35 (m, 2H), 4.61 (t, *J* = 7.3 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.78 – 3.67 (m, 1H), 2.21 – 1.94 (m, 5H), 1.90 – 1.54 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.9, 175.2, 136.6, 131.5, 128.3, 127.5, 77.3, 55.3, 46.7, 35.6, 32.4, 26.6, 20.2; One aliphatic ^{13}C-signal does overlap and could not be identified; IR (Neat Film, NaCl) 3463, 2953, 2876, 2362, 1675, 1449, 1388, 1278, 1153, 1061, 724, 695. HRMS (EI^+) *m/z* calc'd for $C_{16}H_{19}O_3N$ $[M]^+$: 273.1365, found 273.1351; SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IB, λ = 254 nm, t_R: major 7.4 min, minor 8.9 min.

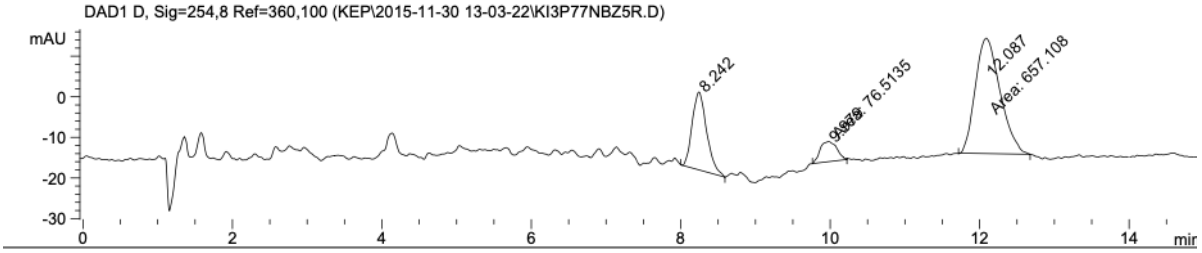


Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.362	MM	0.1626	680.46173	69.75076	73.1874
2	8.838	MM	0.1795	74.45676	6.91275	8.0082
3	9.818	MM	0.2003	174.83411	14.54606	18.8044

lactam **9c**: 79% *ee*, $[\alpha]_D^{25}$ +28.1 (*c* 0.36, $CHCl_3$); R_f = 0.60 (50% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 3.99 (q, J = 6.2 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.81 – 3.72 (m, 1H), 3.25 (d, *J* = 7.8 Hz, 1H), 2.40 – 2.26 (m, 1H), 2.11 – 1.83 (m, 5H), 1.81 – 1.54 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 175.2, 136.1, 131.9, 128.4, 127.9, 82.0, 54.4, 46.7, 36.5, 34.6, 33.3, 21.2, 20.4; IR (Neat Film, NaCl) 3479, 2955, 2870, 1674, 1448, 1392, 1281, 1152, 1078, 919, 797, 749, 726, 696, 660. HRMS (EI^+) *m/z* calc'd for $C_{16}H_{19}O_3N$ $[M]^+$: 273.1365, found 273.1337; SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD–H, λ = 254nm, t_R: minor 10.5 min, major 12.6 min.

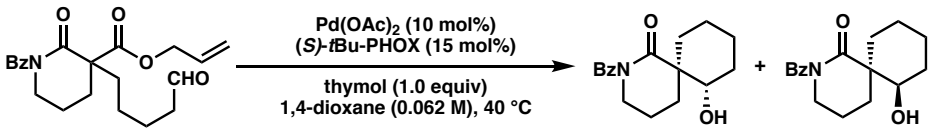




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.242	BB	0.2071	258.40625	19.19525	26.0483
2	9.979	MM	0.2578	76.51351	4.94630	7.7128
3	12.087	MM	0.3847	657.10754	28.46713	66.2389

The relative stereochemistry was determined by analogy compared with the ^{1}H NMR spectrum of **10b/c** and similar known carbocyclic spiro compounds. The peak of the hydroxy group shows specific character in the ^{1}H NMR.[5] The absolute configuration was determined by analogy compared with **10b/c** and similar known carbocyclic spiro compounds.[8]

Representative Procedure E: Intramolecular Aldol Cyclization of Lactam Substrates

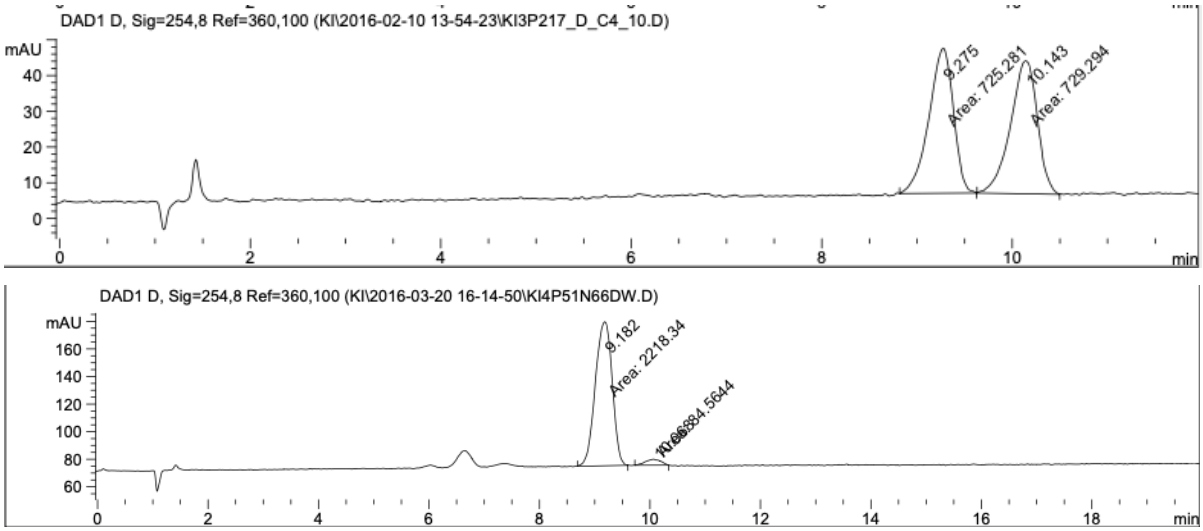


10a **10b** (major) **10c**

(6*R*,7*S*)-2-Benzoyl-7-hydroxy-2-azaspiro[5.5]undecan-1-one (11b) and **(6*R*,7*R*)-2-benzoyl-7-hydroxy-2-azaspiro[5.5]undecan-1-one (11c):** A solution of a lactam **10a** (80 mg, 0.215 mmol, 1.0 equiv) in 1,4-dioxane (3.47 mL) was added to $Pd(OAc)_2$ (4.8 mg, 0.0214 mmol, 0.1 equiv), (*S*)-*t*-BuPHOX (12.5 mg, 0.032 mmol, 0.15 equiv) and thymol (32.3 mg, 0.215 mmol) in a 20 mL scintillation vial equipped with a magnetic stirring bar. The vial was sealed and stirred at 40 °C until the full consumption of aldehyde **10a** was observed by TLC analysis (25 h). The reaction mixture was concentrated under reduced pressure. Flash column chromatography (SiO_2, 20% EtOAc/Hexanes) afforded lactam **10b** (33.2 mg, 0.116 mmol, 54% yield) and lactam **10c** (24.2 mg, 0.084 mmol, 39% yield) as white solids (**10b/10c** = 58/42, determined by mass of isolated products).

lactam **10b**: 93% *ee*, $[\alpha]_D^{25}$ +55.4 (*c* 0.31, $CHCl_3$); R_f = 0.46 (50% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.49 – 7.43 (m, 1H), 7.42 – 7.35 (m, 2H), 4.16 (dd, *J* = 11.8, 4.1 Hz, 1H), 3.94 – 3.87 (m, 1H), 3.76 – 3.68 (m, 1H), 2.15 – 1.92 (m, 5H), 1.89 – 1.81 (m, 1H), 1.79 – 1.69 (m, 2H), 1.66 – 1.54 (m, 2H), 1.49 – 1.22 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$)

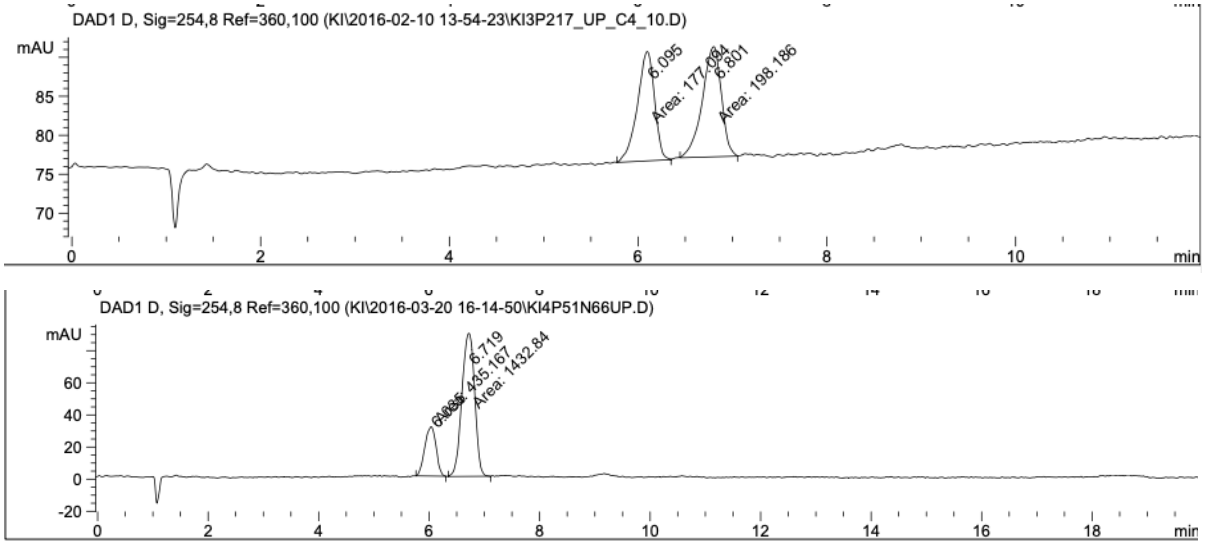
δ 179.9, 175.1, 136.6, 131.5, 128.3, 127.6, 72.8, 51.0, 46.3, 33.0, 29.0, 24.3, 22.3, 20.0, 19.6; IR (Neat Film, NaCl) 3478, 3061, 2937, 2864, 1675, 1600, 1448, 1391, 1284, 1168, 1150, 1053, 944, 195, 733, 722, 695 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{21}O_3N$ $[M+H]^+$: 288.1599, found 288.1594; SFC conditions: 10% IPA, 2.5 mL/min, Chiralcel OJ-H, λ = 254nm, t_R: major 9.2 min, minor 10.0 min. The relative stereochemistry and the absolute configuration were determined by transformation to known compound **13**.



Signal 4: DAD1 D, Sig=254,8 Ref=360,100

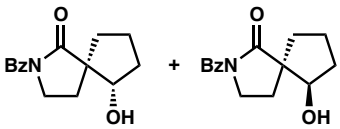
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.182	MM	0.3540	2218.34155	104.44615	96.3279
2	10.068	MM	0.3236	84.56437	4.35561	3.6721

Spiro δ-lactam **10c**: 69% *ee*, $[\alpha]_D^{25}$ +22.5 (*c* 0.29, $CHCl_3$); R_f = 0.57 (hexanes:EtOAc = 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.51 – 7.47 (m, 1H), 7.43 – 7.37 (m, 2H), 3.91 – 3.84 (m, 1H), 3.76 – 3.68 (m, 1H), 3.63 (s, 1H), 3.50 (br s, 1H), 2.39 – 2.28 (m, 1H), 2.13 – 1.92 (m, 4H), 1.88 – 1.66 (m, 3H), 1.64 – 1.50 (m, 3H), 1.42 – 1.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.0, 175.3, 136.1, 131.8, 128.5, 127.7, 73.2, 48.2, 47.0, 31.3, 30.9, 29.2, 20.9, 20.5, 19.0; IR (Neat Film, NaCl) 3436, 2932, 2861, 1674, 1448, 1390, 1285, 1147, 1071, 795, 726, 696 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{21}O_3N$ $[M+H]^+$: 288.1599, found 288.1594; SFC conditions: 10% IPA, 2.5 mL/min, Chiralcel OJ-H, λ = 254nm, t_R: minor 6.0 min, major 6.7 min.



Signal 4: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.035	MM	0.2360	435.16730	30.73179	23.2958
2	6.719	MM	0.2677	1432.84375	89.20397	76.7042

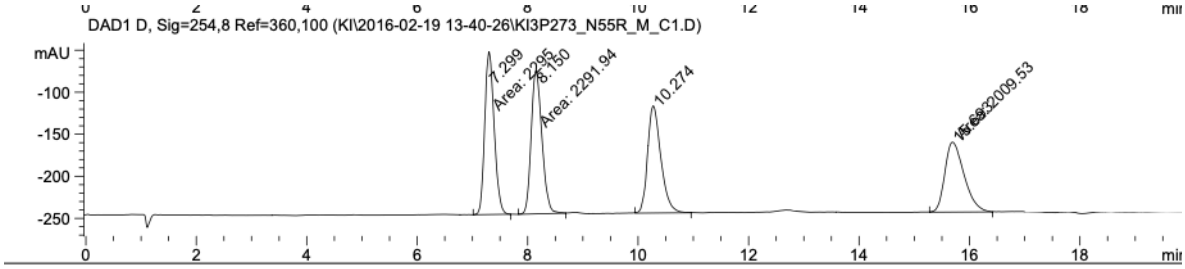


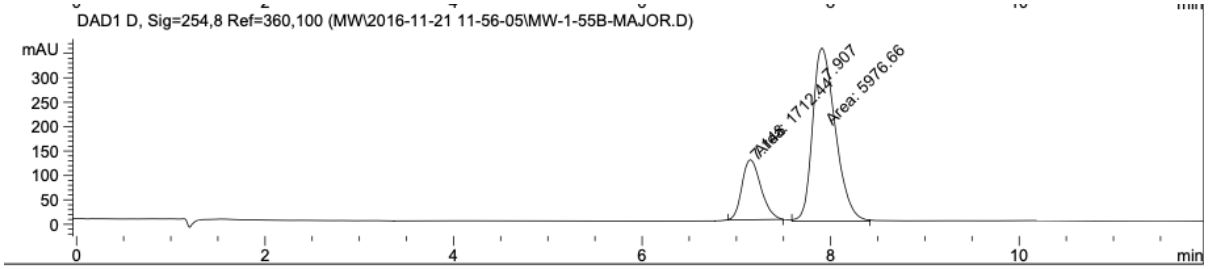
7b (major) **7c**

(5R,6S)-2-Benzoyl-6-hydroxy-2-azaspiro[4.4]nonan-1-one (7b) and **(5R,6R)-2-benzoyl-6-hydroxy-2-azaspiro[4.4]nonan-1-one (7c):** Prepared according to representative procedure E: Aldehyde **7a** (70 mg, 0.20 mmol, 1.0 equiv); stirred at 40 °C for 43 h; flash column chromatography (SiO_2, 10% EtOAc/Hexanes) afforded lactam **7b** (24.9 mg, 0.096 mmol, 47% yield) and lactam **8c** (24.9 mg, 0.096 mmol, 47% yield) as white solids (**7b/7c** = 50/50, determined by mass of isolated products).

lactam **7b**: 55% *ee*, $[\alpha]_D^{25}$ +16.8 (*c* 0.19, $CHCl_3$); R_f = 0.13 (10% EtOAc/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.50 (tt, *J* = 6.9, 1.3 Hz, 1H), 7.44 – 7.35 (m, 2H), 4.33 (t, *J* = 7.5 Hz, 1H), 4.01 – 3.90 (m, 1H), 3.89 – 3.79 (m, 1H), 2.58 – 2.47 (m, 1H), 2.15 – 2.01 (m, 2H), 2.00 – 1.88 (m, 1H), 1.88 – 1.67 (m, 4H), 1.66 – 1.53 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 170.9, 134.5, 132.0, 128.9, 127.9, 77.3, 57.2, 44.0, 34.4, 33.1, 24.8, 20.4; IR (Neat Film, NaCl) 3446, 2961, 2877, 2363, 2340, 1738, 1674, 1448, 1358, 1320, 1242, 1177, 1164, 1083,

1026, 857, 800, 728, 696, 657 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{15}H_{18}O_3N$ $[M+H]^+$: 260.1287, found 260.1282; SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IC, λ = 254 nm, t_R: minor 7.1 min, major 7.9 min.





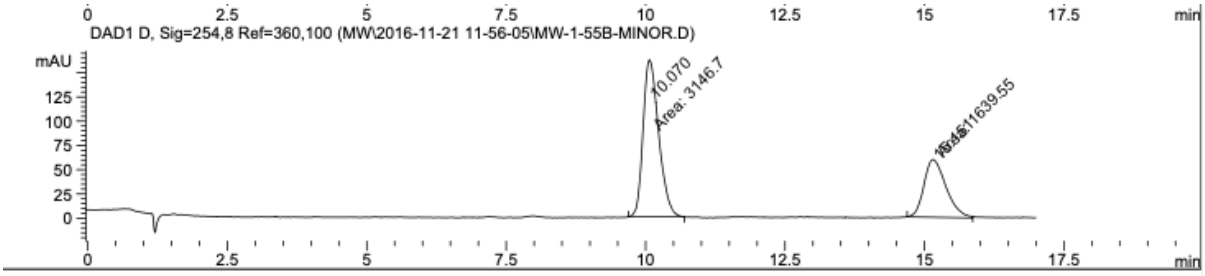
Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.148	MM	0.2317	1712.43604	123.19031	22.2710
2	7.907	MM	0.2806	5976.65869	355.03192	77.7290

Spiro γ-lactam **7c**: 31% *ee*, $[\alpha]_D^{25}$ –22.4 (*c* 0.21, $CHCl_3$); R_f = 0.30 (10% EtOAc/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.53 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.46 – 7.39 (m, 2H), 4.13 (q, *J* = 4.3 Hz, 1H), 4.02 – 3.91 (m, 1H), 3.87 (dt, *J* = 11.5, 7.7 Hz, 1H), 3.39 (d, *J* = 3.9 Hz, 1H), 2.24 – 2.10 (m, 1H), 2.07 – 1.82 (m, 5H), 1.81 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 170.5, 134.3, 132.2, 129.0, 128.0, 80.5, 55.8, 43.5, 34.0, 33.5, 30.0, 21.2; IR (Neat Film, NaCl) 3480, 2959, 2870, 2359, 2333, 1740, 1670, 1448, 1359, 1308, 1245, 1166, 1077, 859, 796, 728, 698, 656 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{15}H_{18}O_3N$ $[M+H]^+$: 260.1287, found 260.1283; SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak IC, λ = 254 nm, t_R: major 10.1 min, minor 15.2 min.

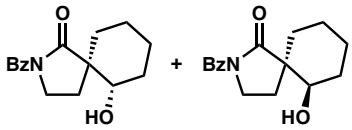
The relative stereochemistry was determined by analogy compared with the ^1H NMR spectrum of **10b/c** and similar known carbocyclic spiro compounds. The peak of the hydroxy group

shows specific character in the ^{1}H NMR.[5] The absolute configuration was determined by analogy compared with **10b/c** and similar known carbocyclic spiro compounds.[8]



Signal 4: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.070	MM	0.3239	3146.70459	161.90285	65.7446
2	15.151	MM	0.4580	1639.55444	59.66026	34.2554

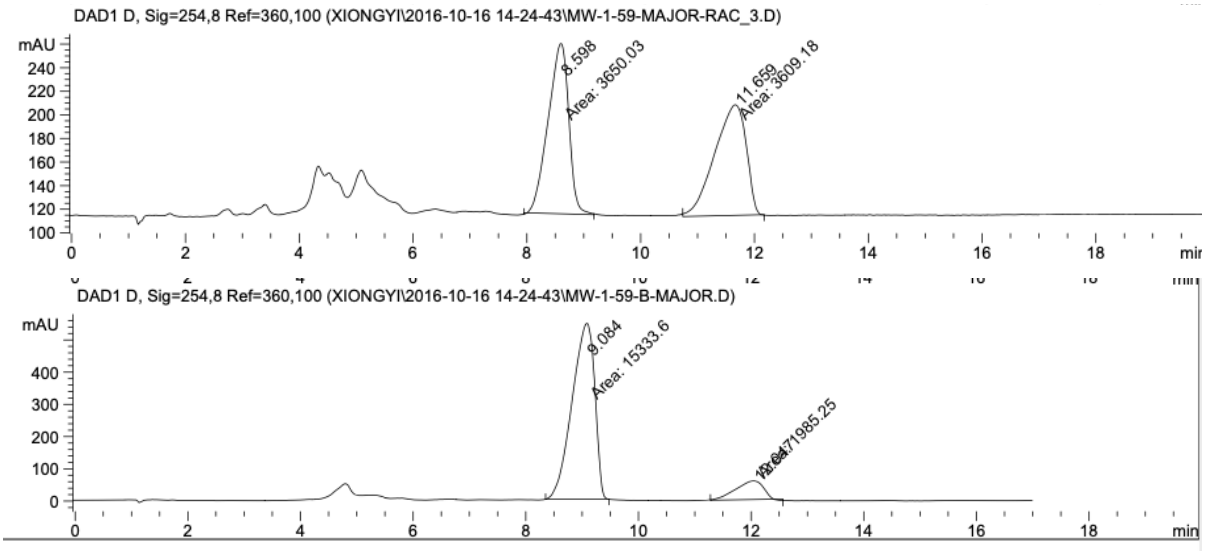


8b (major) **8c**

(5*R*,6*S*)-2-Benzoyl-6-hydroxy-2-azaspiro[4.5]decan-1-one (9b) and **(5*R*,6*R*)-2-benzoyl-6-hydroxy-2-azaspiro[4.5]decan-1-one (9c):** Prepared according to representative procedure E: Aldehyde **8a** (71.5 mg, 0.20 mmol, 1.0 equiv); stirred 15 h at 40 °C; flash column chromatography (SiO_2, 10% EtOAc in dichloromethane eluent) afforded lactam **8b** (29.9 mg, 0.109 mmol, 55% yield) and lactam **8c** (17.6 mg, 0.064 mmol, 32% yield) as white solids (**8b/9c** = 63/37, determined by mass of isolated products).

Spiro γ-lactam **8b**: 77% *ee*, $[\alpha]_D^{25}$ –42.7 (*c* 0.21, $CHCl_3$); R_f = 0.22 (10% EtOAc/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H), 7.50 (tt, *J* = 7.5, 1.9 Hz, 1H), 7.44 – 7.36 (m, 2H), 4.00 – 3.92 (m, 1H), 3.92 – 3.85 (m, 1H), 3.85 – 3.78 (m, 1H), 2.48 – 2.34 (m, 1H), 1.96 – 1.79 (m, 3H), 1.78 – 1.59 (m, 3H), 1.57 – 1.44 (m, 1H), 1.42 – 1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 170.9, 134.6, 131.9, 129.0, 127.9, 72.4, 53.7, 43.7, 32.2, 31.2, 24.3, 21.5, 21.2; IR (Neat Film, NaCl) 3470, 2933, 2860, 1736, 1673, 1449, 1364, 1309, 1248, 1152, 1066, 987, 916, 873, 844, 797, 730, 703, 657 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{16}H_{20}O_3N$ $[M+H]^+$: 274.1443, found 274.1439; SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OJ-H, λ = 254 nm,

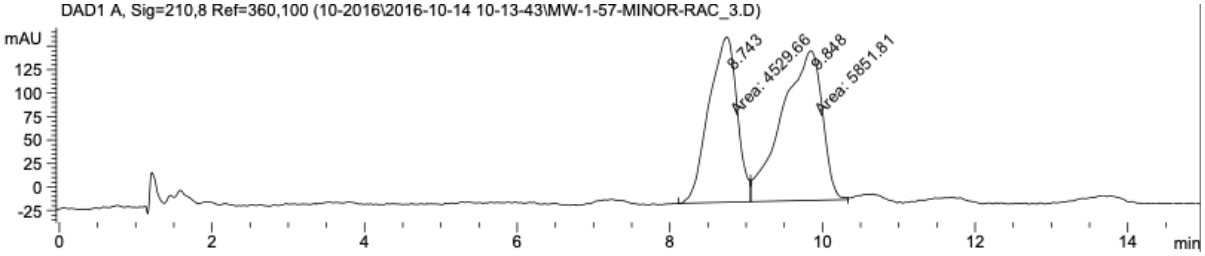
t_R: major 9.1 min, minor 12.0 min. The absolute stereochemistry was determined by x-ray crystallographic analysis.

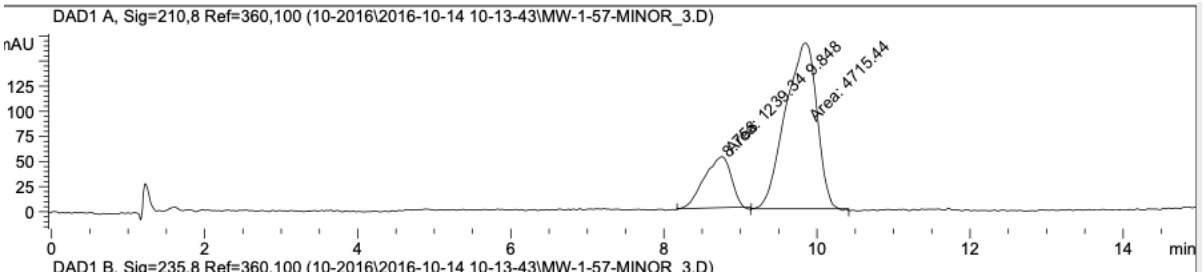


Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.084	MM	0.4678	1.53336e4	546.31305	88.5371
2	12.047	MM	0.5672	1985.24841	58.33852	11.4629

Spiro γ-lactam **8c**: 62% *ee*, $[\alpha]_D^{25}$ –62.0 (*c* 0.21, $CHCl_3$); R_f = 0.39 (10% EtOAc/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 2H), 7.56 – 7.50 (m, 1H), 7.47 – 7.38 (m, 2H), 4.02 – 3.93 (m, 1H), 3.88 – 3.76 (m, 2H), 3.61 (br s, 1H), 2.18 – 1.97 (m, 3H), 1.95 – 1.64 (m, 3H), 1.57 – 1.34 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 170.7, 134.4, 132.2, 128.9, 128.0, 71.8, 49.6, 43.1, 28.9, 28.1, 27.6, 21.0, 20.0; IR (Neat Film, NaCl) 3480, 2933, 2858, 1732, 1668, 1448, 1362, 1307, 1248, 1179, 1142, 1047, 856, 794, 729, 699, 656 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{16}H_{20}O_3N$ $[M+H]^+$: 274.1443, found 274.1438; SFC conditions: 8% IPA, 2.5 mL/min, Chiralcel OJ-H, λ = 254 nm, t_R: minor 15.5 min, major 17.6 min. The relative stereochemistry and the absolute configuration were inferred from the x-ray strure of **8b**.



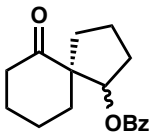
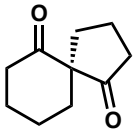
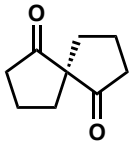
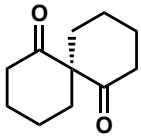
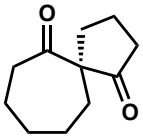
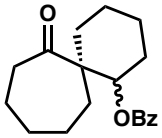
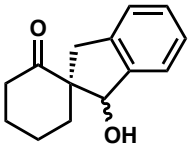


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.758	MM	0.4069	1239.33752	50.76529	20.8125
2	9.848	MM	0.4765	4715.44238	164.92177	79.1875

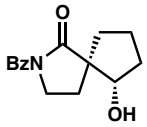
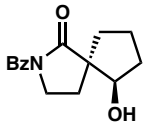
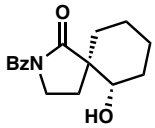
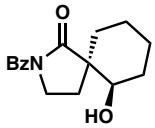
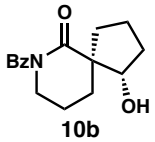
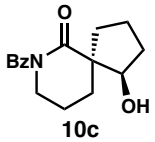
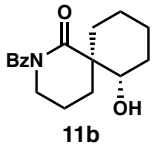
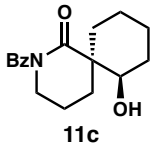
Determination of Enantiomeric Excess and Optical Rotation

Table S7. Separation Conditions for Ketones.

entry	compound	analytical conditions	*ee* (%)	polarimetry
1	 **Bz-2b/c**	SFC: 3% IPA, 2.5 mL/min, Chiralpak OB-H, l = 210 or 235 nm, t_R: **Bz-2b** (major) 3.6 min, (minor) 4.3 min, **Bz-2c** (major) 5.3 min, (minor) 6.8 min.	85 (**1e**) 73 (**1f**)	–
2	 **2**	Chiral GC: CP-CHIRASIL-DEX CB column, 90 °C isothermal method over 40 min, t_R: minor 29.6 min, major 31.8 min.	84	$[a]_D^{25}$ = +155.3 (*c* 0.57, $CHCl_3$)
3	 **1**	Chiral GC: CP-CHIRASIL-DEX CB column, 90 °C isothermal method over 20 min, t_R: minor 16.8 min, major 17.5 min.	95	$[a]_D^{25}$ = +175.1 (*c* 0.25, $CHCl_3$)
4	 **3**	Chiral GC: CP-CHIRASIL-DEX CB column, 90 °C isothermal method over 60 min, t_R: minor 54.9 min, major 55.7 min.	94	$[a]_D^{25}$ = +125.5 (*c* 0.26, $CHCl_3$)
5	 **4**	Chiral GC: CP-CHIRASIL-DEX CB column, 90 °C isothermal method over 65 min, t_R: minor 55.7 min, major 57.3 min.	81	$[a]_D^{25}$ = +230.7 (*c* 0.28, $CHCl_3$)
6	 **Bz-5b/c**	SFC: 3% IPA, 2.5 mL/min, Chiralcel OD-H, l = 210 nm, t_R: **Bz-5b** (major) 11.5 min, (minor) 13.0 min, **Bz-5c** (major) 15.3 min, (minor) 16.2 min.	84 (**6d**) 81 (**6e**)	–
7	 **6b/c**	SFC: 5% IPA, 2.5 mL/min, Chiralcel OJ-H, l = 210 nm, t_R: **6b** (major) 6.9 min, (minor) 7.9 min, **6c** (minor) 13.1 min, (major) 20.6 min.	72 (**7b**) 46 (**7c**)	–

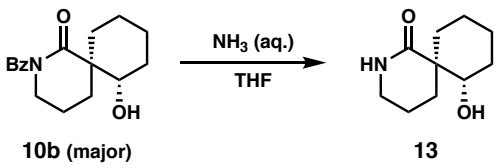
Racemic compounds were prepared using *rac*-BINAP instead of the chiral PHOX ligand with the same procedure for the separation of enantiomers.

Table S8. Separation Conditions for Lactams.

entry	compound	analytical conditions	*ee* (%)	polarimetry
1	 **8b**	SFC: 20% IPA, 2.5 mL/min, Chiralpak IC, l = 254 nm, t_R: minor 7.1 min, major 7.9 min.	55	$[a]_D^{25}$ = +16.8 (*c* 0.19, $CHCl_3$)
2	 **8c**	SFC: 20% IPA, 2.5 mL/min, Chiralpak IC, l = 254 nm, t_R: major 10.1 min, minor 15.2 min.	31	$[a]_D^{25}$ = –22.4 (*c* 0.21, $CHCl_3$)
3	 **9b**	SFC: 20% IPA, 2.5 mL/min, Chiralcel OJ-H, l = 254 nm, t_R: major 9.1 min, minor 12.0 min.	77	$[a]_D^{25}$ = –42.7 (*c* 0.21, $CHCl_3$)
4	 **9c**	SFC: 20% IPA, 2.5 mL/min, Chiralcel OJ-H, l = 254 nm, t_R: minor 15.5 min, major 17.6 min.	62	$[a]_D^{25}$ = –62.0 (*c* 0.21, $CHCl_3$)
5	 **10b**	SFC: 20% IPA, 2.5 mL/min, Chiralpak IB, l = 254 nm, t_R: major 7.5 min, minor 9.1 min.	92	$[a]_D^{25}$ = +83.9 (*c* 0.23, $CHCl_3$)
6	 **10c**	SFC: 15% IPA, 2.5 mL/min, Chiralpak AD-H, l = 254 nm, t_R: major 10.5 min, minor 12.6 min.	72	$[a]_D^{25}$ = +28.1 (*c* 0.36, $CHCl_3$)
7	 **11b**	SFC: 10% IPA, 2.5 mL/min, Chiralcel OJ-H, l = 254 nm, t_R: major 9.2 min, minor 10.0 min.	93	$[a]_D^{25}$ = +55.4 (*c* 0.31, $CHCl_3$)
8	 **11c**	SFC: 10% IPA, 2.5 mL/min, Chiralcel OJ-H, l = 254 nm, t_R: minor 6.0 min, major 6.7 min.	69	$[a]_D^{25}$ = +22.5 (*c* 0.28, $CHCl_3$)

Racemic compounds were prepared using *rac*-BINAP instead of the chiral PHOX ligand with the same procedure for the separation of enantiomers.

Formal Synthesis of (–)-Isonitramine:

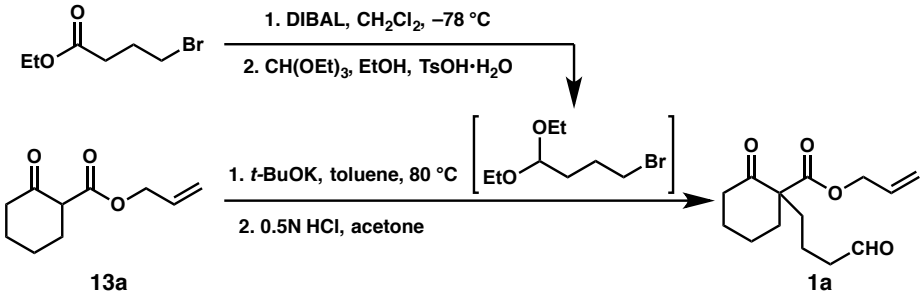


10b (major) **13**

(6*R*,7*S*)-7-Hydroxy-2-azaspiro[5.5]undecan-1-one (13): Ammonium hydroxide (28.0–30.0% as NH_3) (0.165 mL) was added to a stirred solution lactam **10b** (38 mg, 0.132 mmol, 1.0 equiv, 93% *ee*) in THF (0.76 mL) at 0 °C. After warming to ambient temperature, the reaction mixture was stirred for 3 h. To the mixture was added water (0.76 mL) and $CHCl_3$/MeOH = 4/1 (0.76 mL). After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$/MeOH = 4/1 (0.76 mL) six times. The combined organic layers were dried over $MgSO_4$ and charged to flash column chromatography (SiO_2, EtOAc→$CHCl_3$/MeOH = 10/1). Purification afforded spiro amide **13** (23.1 mg, 0.126 mmol, 95% yield) as a white solid; $[\alpha]_D^{25}$ +70.5 (*c* 0.25, $CHCl_3$); R_f = 0.16 (9% MeOH in $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (br s, 1H), 4.30 – 4.19 (m, 1H), 3.36 – 3.20 (m, 2H), 2.30 (s, 1H), 2.03 – 1.90 (m, 1H), 1.89 – 1.68 (m, 6H), 1.68 – 1.57 (m, 1H), 1.52 – 1.27 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 73.1, 48.2, 42.4, 32.6, 28.8, 24.5, 21.3, 19.8, 19.3. Characterization data match known values.[8]

Preparation of Substrates:

Representative Procedure F:

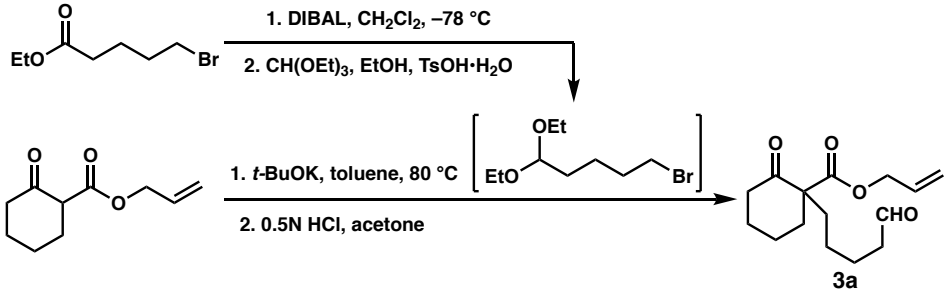


Allyl 2-oxo-1-(4-oxobutyl)cyclohexane-1-carboxylate (1a): To a stirred solution of ethyl 4-bromobutyrate (3.0 g, 15.38 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) was added DIBAL (2.88 mL, 16.16 mmol, 1.05 equiv) dropwise at –78 °C. The reaction mixture was stirred for 1 h at –78 °C. After addition of 1M HCl (30 mL), the mixture was gradually warmed to ambient temperature and stirred for 1.5 h. Separation of the organic layer, was followed by extraction of the aqueous layer with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. To the obtained crude residue was added EtOH (45 mL), triethyl orthoformate (12 mL, 72.15 mmol, 4.70 equiv) and *p*TsOH·H_2O (146 mg, 0.77 mmol, 0.05 equiv). The mixture was stirred for 12 h, then concentrated. Saturated aqueous sodium bicarbonate (24 mL) and toluene (30 mL) were added, and the biphasic mixture was stirred and separated. The obtained organic layer was washed with saturated aqueous sodium bicarbonate (2 x 15 mL) and water (2 x 15 mL). The organic layer was dried over $MgSO_4$, filtrated and concentrated *in vacuo*. After toluene was added, the organic layer was concentrated again to afford crude 4-bromo-1,1-diethoxybutane (3.2 g).

To a solution of β-keto ester **13a**[9] (500 mg, 2.74 mmol, 1.0 equiv) and 4-bromo-1,1-diethoxybutane (709 mg, 3.15 mmol, 1.15 equiv) in toluene (4.5 mL) was added *t*-BuOK (353 mg, 3.15 mmol, 1.15 equiv). After warming to 80 °C, the reaction mixture was stirred for 15 h at 80 °C. After cooling to ambient temperature, saturated aqueous ammonium chloride (3.5 mL) and EtOAc were added to the reaction mixture. After separation of the organic layer, the aqueous layer was extracted by EtOAc (2 x 2.5 mL). The combined organic layers were concentrated under reduced pressure. To the obtained crude residue in acetone (5 mL) was added 0.5M HCl (3.5 mL) dropwise at 0 °C. After warming to ambient temperature, the reaction mixture was stirred for 4 h. To the reaction mixture was added EtOAc (5 mL) and the organic layer was separated. The aqueous layer was extracted by EtOAc (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$ and

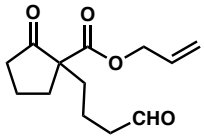
concentrated *in vacuo*. Flash column chromatography (SiO_2, 11% EtOAc in hexanes eluent) afforded aldehyde **1a** (392 mg, 1.55 mmol, 57% yield) as a colorless oil: R_f = 0.15 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.1 Hz, 1H), 6.03 – 5.75 (m, 1H), 5.40 – 5.17 (m, 2H), 4.74 – 4.54 (m, 2H), 2.55 – 2.49 (m, 1H), 2.49 – 2.38 (m, 4H), 2.05 – 1.94 (m, 1H), 1.90 – 1.81 (m, 1H), 1.80 – 1.73 (m, 1H), 1.70 – 1.52 (m, 5H), 1.52 – 1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 202.2, 171.7, 131.5, 119.4, 66.0, 60.9, 44.1, 41.2, 36.2, 34.2, 27.7, 22.7, 17.3; IR (Neat Film, NaCl) 2944, 2867, 2725, 1713, 1452, 1310, 1208, 1181, 1137, 1099, 987, 938; HRMS (ESI$^+$) *m/z* calc'd for $C_{14}H_{21}O_4$ $[M+H]^+$: 253.1440, found 253.1436.

Representative Procedure G:



Allyl 2-oxo-1-(5-oxopentyl)cyclohexane-1-carboxylate (3a): To a stirred solution of ethyl 5-bromovalerate (3.0 g, 14.3 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) was added DIBAL (2.67 mL, 15.0 mmol, 1.05 equiv) dropwise at –78 °C. The reaction mixture was stirred for 1.5 h at –78 °C. To the reaction mixture was added 1M HCl (30 mL) and the mixture was gradually warmed to ambient temperature and stirred for 80 min. After separating the organic layer, the aqueous layer was extracted by CH_2Cl_2 (2 x 15 mL). Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. To the obtained crude residue was added EtOH (45 mL), triethyl orthoformate (12 mL, 72.15 mmol, 5.05 equiv) and *p*-TsOH·H_2O (136 mg, 0.71 mmol, 0.05 equiv). The mixture was stirred for 12 h and concentrated. Saturated aqueous sodium bicarbonate (24 mL) and toluene (30 mL) were added, and the biphasic mixture was stirred and separated. The obtained organic layer was washed with saturated aqueous sodium bicarbonate (2 x 15 mL) and water (2 x 15 mL). The organic layer was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. After adding toluene, the organic layer was concentrated again to afford crude 5-bromo-1,1-diethoxypentane (3.6 g).

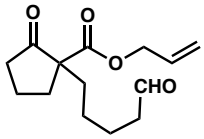
To a solution of allyl 2-oxocyclohexane-1-carboxylate (β-keto ester)[9] (1.37 g, 7.51 mmol, 1.0 equiv) and 5-bromo-1,1-diethoxypentane (2.07 g, 8.64 mmol, 1.15 equiv) in acetone (14 mL) was added K_2CO_3 (5.19 g, 37.6 mmol, 5.0 equiv) and KI (249 mg, 1.5 mmol, 0.2 equiv). The reaction mixture was refluxed for 39 h. After cooling to ambient temperature, saturated aqueous ammonium chloride (20 mL) and EtOAc (14 mL) were added to the reaction mixture. After separating the organic layer, the aqueous layer was extracted by EtOAc (2 x 11 mL). Combined organic layers were concentrated under reduced pressure. To the obtained crude residue in acetone (13.7 mL) was added 0.5M HCl (9.6 mL) dropwise at 0 °C. After warming to ambient temperature, the reaction mixture was stirred for 4 h. To the reaction mixture was added EtOAc (20 mL) and the organic layer was separated, followed by extraction of the aqueous layer by EtOAc (2 x 11 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography (SiO_2, 11% EtOAc/Hexanes) afforded aldehyde **3a** (1.05 g, 3.92 mmol, 52% yield) as a colorless oil: R_f = 0.37 (20% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.7 Hz, 1H), 5.88 (ddt, *J* = 16.3, 10.4, 5.9 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.62 (dq, *J* = 5.9, 1.2 Hz, 2H), 2.53 – 2.46 (m, 1H), 2.46 – 2.39 (m, 3H), 2.04 – 1.95 (m, 1H), 1.87 (ddd, *J* = 13.5, 12.3, 4.7 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.70 – 1.52 (m, 6H), 1.44 (ddd, *J* = 13.7, 12.0, 4.2 Hz, 1H), 1.33 – 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9, 202.6, 171.8, 131.6, 119.3, 65.9, 60.9, 43.7, 41.2, 36.2, 34.5, 27.7, 24.0, 22.7, 22.5; IR (Neat Film, NaCl) 3426, 2943, 2866, 2721, 1713, 1649, 1452, 1310, 1240, 1204, 1175, 1136, 1099, 990, 937, 816 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{15}H_{23}O_4$ $[M+H]^+$: 267.1596, found 267.1595.



1a

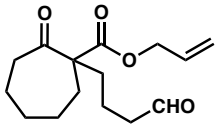
Allyl 2-oxo-1-(4-oxobutyl)cyclopentane-1-carboxylate (1a): Prepared according to representative procedure F. β-keto ester[10] (219 mg, 1.30 mmol, 1.0 equiv), 4-bromo-1,1-diethoxybutane (381 mg, 1.69 mmol, 1.3 equiv) and *t*BuOK (190 mg, 1.69 mmol, 1.3 equiv). The reaction mixture for alkylation was stirred at 80 °C for 16 h. Flash column chromatography (SiO_2, 11% EtOAc/Hexanes) afforded aldehyde **1a** (136 mg, 0.57 mmol, 44% yield) as a colorless oil: R_f

= 0.2 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.4 Hz, 1H), 5.95 – 5.81 (m, 1H), 5.34 – 5.19 (m, 2H), 4.60 (dt, *J* = 5.6, 1.4 Hz, 2H), 2.60 – 2.49 (m, 1H), 2.49 – 2.39 (m, 2H), 2.32 – 2.22 (m, 1H), 2.10 – 1.88 (m, 4H), 1.75 – 1.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 201.5, 170.4, 131.5, 118.7, 66.1, 60.4, 44.1, 38.2, 33.3, 33.0, 19.9, 17.7; IR (Neat Film, NaCl) 3456, 3087, 2959, 2890, 2829, 2727, 1749, 1727, 1648, 1458, 1407, 1319, 1258, 1227, 1182, 1161, 1128, 1084, 1030, 991, 936, 842. HRMS (EI$^+$) *m/z* calc'd for $C_{13}H_{18}O_4$ $[M]^+$: 238.1205, found 238.1198.



2d

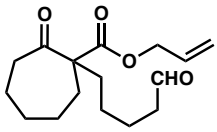
Allyl 2-oxo-1-(4-oxobutyl)cyclopentane-1-carboxylate (2d): Prepared according to representative procedure F: β-keto ester[10] (400 mg, 2.38 mmol, 1.0 equiv) and 5-bromo-1,1-diethoxypentane (683 mg, 2.86 mmol, 1.20 equiv) and *t*-BuOK (320 mg, 2.85 mmol, 1.20 equiv). The reaction mixture was stirred at 80 °C for 22 h. Flash column chromatography (SiO_2, 11% EtOAc in hexanes eluent) afforded aldehyde **2d** (278 mg, 1.10 mmol, 46% yield) as a colorless oil: R_f = 0.24 (20% EtOAc in hexanes); 1H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.5 Hz, 1H), 5.87 (ddt, *J* = 16.2, 10.7, 5.7 Hz, 1H), 5.38 – 5.14 (m, 2H), 4.59 (dt, J = 5.6, 1.3 Hz, 2H), 2.58 – 2.47 (m, 1H), 2.47 – 2.34 (m, 3H), 2.31 – 2.20 (m, 1H), 2.08 – 1.83 (m, 4H), 1.68 – 1.52 (m, 3H), 1.46 – 1.31 (m, 1H), 1.31 – 1.17 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.8, 202.4, 170.8, 131.7, 118.7, 66.0, 60.5, 43.6, 38.1, 33.6, 33.0, 24.5, 22.3, 19.8; IR (Neat Film, NaCl) 3456, 3087, 2952, 2724, 1748, 1724, 1649, 1462, 1407, 1317, 1272, 1225, 1160, 1089, 992, 937. HRMS (EI$^+$) *m/z* calc'd for $C_{14}H_{20}O_4$ $[M]^+$: 252.1362, found 252.1386.



4a

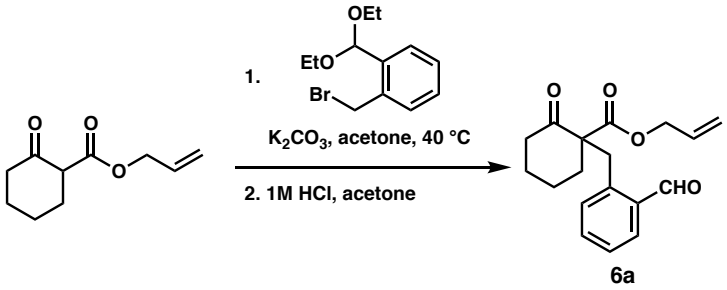
Allyl 2-oxo-1-(4-oxobutyl)cycloheptane-1-carboxylate (4a): Prepared according to representative procedure F. β-keto ester[11] (303 mg, 1.54 mmol, 1.0 equiv), 4-bromo-1,1-diethoxybutane (416 mg, 1.85 mmol, 1.20 equiv) and *t*-BuOK (207 mg, 1.84 mmol, 1.20 equiv). The reaction mixture was stirred at 80 °C for 22 h. Flash column chromatography (SiO_2, 11%

EtOAc/Hexanes) afforded aldehyde **4a** (236 mg, 0.886 mmol, 58% yield) as a colorless oil; R_f = 0.25 (20% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.5 Hz, 1H), 5.95 – 5.84 (m, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.68 – 4.58 (m, 2H), 2.69 – 2.61 (m, 1H), 2.51 – 2.41 (m, 3H), 2.20 – 2.12 (m, 1H), 2.01 – 1.92 (m, 1H), 1.82 – 1.72 (m, 2H), 1.72 – 1.52 (m, 7H), 1.49 – 1.40 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 202.1, 172.1, 131.7, 119.1, 65.9, 62.9, 44.2, 42.3, 34.9, 33.0, 30.0, 25.7, 25.0, 17.5; IR (Neat Film, NaCl) 3426, 2936, 2862, 2724, 1725, 1709, 1456, 1222, 1173, 1151, 989, 940; HRMS (EI$^+$) *m/z* calc'd for $C_{15}H_{22}O_4$ $[M]^+$: 266.1518, found 266.1502.

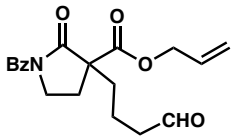


5a

Allyl 2-oxo-1-(5-oxopentyl)cycloheptane-1-carboxylate (6a): Prepared according to representative procedure F. β-keto ester[11] (325 mg, 1.66 mmol, 1.0 equiv), 5-bromo-1,1-diethoxypentane (476 mg, 1.99 mmol, 1.20 equiv) and *t*-BuOK (223 mg, 1.99 mmol, 1.20 equiv). The reaction mixture was stirred at 80 °C for 9 h. Flash column chromatography (SiO_2, 11% EtOAc in hexanes eluent) afforded aldehyde **5a** (226 mg, 0.806 mmol, 49% yield) as a colorless oil; R_f = 0.24 (20% EtOAc in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (q, *J* = 1.0 Hz, 1H), 5.98 – 5.79 (m, 1H), 5.38 – 5.17 (m, 2H), 4.69 – 4.53 (m, 2H), 2.68 – 2.56 (m, 1H), 2.52 – 2.39 (m, 2H), 2.20 – 2.07 (m, 1H), 2.04 – 1.92 (m, 1H), 1.80 – 1.49 (m, 10H), 1.49 – 1.36 (m, 1H), 1.32 – 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6, 202.6, 172.3, 131.7, 119.0, 65.8, 62.9, 43.7, 42.3, 35.3, 33.0, 30.0, 25.7, 25.0, 24.3, 22.5; IR (Neat Film, NaCl) 2935, 2862, 2720, 1725, 1711, 1453, 1220, 1168, 990, 940; HRMS (ESI$^+$) *m/z* calc'd for $C_{16}H_{25}O_4$ $[M+H]^+$: 281.1753, found 281.1736.

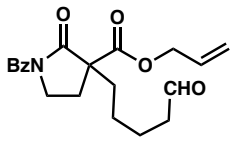


Allyl 1-(2-formylbenzyl)-2-oxocyclohexane-1-carboxylate (6a): To a solution of allyl 2-oxocyclohexane-carboxylate (β-keto ester)[8] (107 mg, 0.587 mmol, 2.0 equiv) and 1-(bromomethyl)-2-(diethoxymethyl)benzene[12] (80 mg, 0.293 mmol, 1.0 equiv) in acetone (1.2 mL) was added K_2CO_3 (810 mg, 5.86 mmol, 20.0 equiv). The reaction mixture was stirred at 40 °C for 13 h. After cooling to ambient temperature, to the reaction mixture was added saturated aqueous ammonium chloride and EtOAc. After separating the organic layer, the aqueous layer was extracted by EtOAc (2 x 11 mL) and the combined organic layers were concentrated under reduced pressure. To the obtained crude residue in acetone (1.6 mL) was added 1M HCl (1.6 mL) dropwise at ambient temperature and the reaction mixture was stirred for 4 h. To the reaction mixture was added EtOAc and organic layer was separated. After extracting the aqueous layer by EtOAc twice, the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2, 9%→11% EtOAc/Hexanes) afforded aldehyde **6a** (56 mg, 0.186 mmol, 64 % yield) as a colorless oil; R_f = 0.36 (20% EtOAc in hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.83 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.84 – 5.73 (m, 1H), 5.30 – 5.19 (m, 2H), 4.52 (ddq, *J* = 13.3, 6.0, 1.1 Hz, 1H), 4.43 (ddq, *J* = 13.1, 6.0, 1.1 Hz, 1H), 3.81 (d, *J* = 14.1 Hz, 1H), 3.44 (d, *J* = 14.1 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.33 (dq, *J* = 12.8, 2.6 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.76 – 1.68 (m, 1H), 1.67 – 1.56 (m, 2H), 1.56 – 1.47 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.8, 192.1, 170.5, 139.3, 135.3, 133.3, 132.9, 131.3, 131.2, 127.5, 119.7, 66.2, 62.2, 41.4, 36.1, 34.6, 27.6, 22.7; IR (Neat Film, NaCl) 3346, 3074, 2944, 2867, 1714, 1698, 1600, 1574, 1451, 1309, 1292, 1263, 1248, 1205, 1133, 1093, 991, 940, 758 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $C_{18}H_{21}O_4$ $[M+H]^+$: 301.1440, found 301.1425.



7a

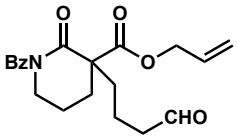
Allyl 1-benzoyl-2-oxo-3-(4-oxobutyl)pyrrolidine-3-carboxylate (7a): Prepared according to representative procedure G. Lactam[13] (1.0 g, 3.66 mmol, 1.0 equiv.) and 4-bromo-1,1-diethoxybutane (948 mg, 4.21 mmol, 1.15 equiv). The reaction mixture for alkylation was refluxed for 39 h. Flash column chromatography (SiO_2, 10→20% EtOAc in hexanes eluent) afforded aldehyde **7a** (659 mg, 1.92 mmol, 52% yield) as a colorless oil; R_f = 0.26 (35% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.0 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.52 (tt, *J* = 7.5, 1.7 Hz, 1H), 7.44 – 7.37 (m, 2H), 5.91 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.38 – 5.25 (m, 2H), 4.67 (dt, *J* = 5.7, 1.3 Hz, 2H), 4.08 – 3.99 (m, 1H), 3.99 – 3.90 (m, 1H), 2.63 (ddd, *J* = 13.3, 7.6, 3.6 Hz, 1H), 2.51 (td, *J* = 6.8, 1.0 Hz, 2H), 2.18 (dt, *J* = 13.3, 8.6 Hz, 1H), 2.11 – 1.97 (m, 1H), 1.89 – 1.72 (m, 2H), 1.67 – 1.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 172.0, 170.6, 170.1, 134.0, 132.3, 131.3, 129.0, 128.0, 119.5, 66.7, 58.0, 43.8, 43.8, 33.4, 27.4, 17.2; IR (Neat Film, NaCl) 2956, 2730, 1751, 1727, 1681, 1600, 1449, 1362, 1306, 1296, 1247, 1192, 1125, 980, 936, 860, 796, 730, 698, 656 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{22}NO_5$ $[M+H]^+$: 344.1498, found 344.1497.



8a

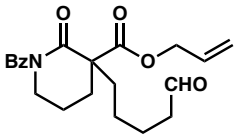
Allyl 1-benzoyl-2-oxo-3-(5-oxopentyl)pyrrolidine-3-carboxylate (8a): Prepared according to representative procedure G: Lactam[13] (700 mg, 2.56 mmol, 1.0 equiv) and 5-bromo-1,1-diethoxypentane (705 mg, 2.95 mmol, 1.15 equiv). The reaction mixture for alkylation was refluxed for 19 h. Flash column chromatography (SiO_2, 10→20% EtOAc in hexanes eluent) afforded aldehyde **8a** (582 mg, 1.63 mmol, 64% yield) as a colorless oil: R_f = 0.30 (35% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.4 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.55 – 7.47 (m, 1H), 7.45 – 7.35 (m, 2H), 5.98 – 5.83 (m, 1H), 5.40 – 5.23 (m, 2H), 4.66 (dt, *J* = 5.7, 1.3 Hz, 2H), 4.05 – 3.96 (m, 1H), 3.96 – 3.86 (m, 1H), 2.65 – 2.55 (m, 1H), 2.45 (td, *J* = 7.2, 1.4 Hz, 2H), 2.17 – 1.98 (m, 2H), 1.88 – 1.75 (m, 1H), 1.65 (p, *J* = 7.3 Hz, 2H), 1.53 – 1.40 (m, 1H), 1.39 – 1.22 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 172.1, 170.6, 170.2, 134.0, 132.2,

131.3, 129.0, 128.0, 119.4, 66.6, 57.9, 43.7, 43.5, 33.7, 27.5, 24.1, 22.2; IR (Neat Film, NaCl) 2940, 2862, 2726, 1751, 1725, 1679, 1602, 1449, 1363, 1306, 1294, 1245, 1196, 1179,1126, 983, 938, 861, 796, 729, 698, 656 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{20}H_{24}NO_5$ $[M+H]^+$: 358.1654, found 358.1646.



9a

Allyl 1-benzoyl-2-oxo-3-(4-oxobutyl)piperidine-3-carboxylate (9a): Prepared according to representative procedure G: Lactam[13] (332 mg, 1.16 mmol, 1.0 equiv) and 4-bromo-1,1-diethoxybutane (334 mg, 1.48 mmol, 1.3 equiv). The reaction mixture for alkylation was refluxed for 19 h. Flash column chromatography (SiO_2, 14% EtOAc/Hexanes) afforded lactam aldehyde **9a** (300 mg, 0.84 mmol, 72% yield) as a colorless oil: R_f = 0.32 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.3 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.48 (tt, *J* = 7.2, 2.3 Hz, 1H), 7.41 – 7.34 (m, 2H), 5.99 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.47 – 5.31 (m, 2H), 4.74 (dt, *J* = 5.9, 1.2 Hz, 2H), 3.89 – 3.72 (m, 2H), 2.52 – 2.35 (m, 3H), 2.07 – 1.83 (m, 5H), 1.83 – 1.66 (m, 1H), 1.63 – 1.45 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 175.1, 171.9, 171.8, 135.9, 131.9, 131.4, 128.2, 128.2, 120.0, 66.8, 56.7, 46.7, 44.0, 35.0, 30.6, 20.4, 17.5; IR (Neat Film, NaCl) 2950, 2887, 2727, 1725, 1702, 1680, 1600, 1449, 1390, 1348, 1273, 1191, 1171, 1150, 1067, 990, 941, 726, 695 660 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{20}H_{24}NO_5$ $[M+H]^+$: 358.1654, found 358.1647.



10a

Allyl 1-benzoyl-2-oxo-3-(5-oxopentyl)piperidine-3-carboxylate (10a): Prepared according to representative procedure G: Lactam[13] (336 mg, 1.17 mmol, 1.0 equiv) and 5-bromo-1,1-diethoxypentane (321 mg, 1.34 mmol, 1.15 equiv). The reaction mixture for alkylation was refluxed for 19 h. Flash column chromatography (SiO_2, 14% EtOAc/Hexanes) afforded aldehyde **10a** (302 mg, 0.81 mmol, 69% yield) as a colorless oil: R_f = 0.35 (33% EtOAc/Hexanes); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.5 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.48 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 5.99 (ddt, *J* = 16.5, 10.4, 6.0 Hz, 1H), 5.45 – 5.32 (m, 2H), 4.73 (d, *J* = 6.0 Hz, 2H), 3.85 – 3.73 (m, 2H), 2.47 – 2.37 (m, 3H), 2.06 – 1.80 (m, 5H), 1.64 – 1.52 (m, 2H), 1.47 – 1.34 (m, 1H), 1.30 – 1.19 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 175.2, 172.0, 171.9, 135.9, 131.9, 131.4, 128.2, 120.0, 66.7, 56.7, 46.7, 43.7, 35.4, 30.6, 24.3, 22.4, 20.5; One aromatic or olefinic ^{13}C-Signal does overlap and could not be identified; IR (Neat Film, NaCl) 2943, 2870, 2723, 1724, 1680, 1449, 1390, 1276, 1149, 1170, 1191, 990, 942, 725, 695, 661 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1811, found 372.1813.

References

[1] A. M. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

[2] Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth*. **2009**, *86*, 181–193.

[3] Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126–4127.

[4] Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron* **2003**, *59*, 8989–8999.

[5] Suemune, H.; Maeda, K.; Kato, K.; Sakai, K. *J. Chem. Soc*., *Perkin Trans. 1*, **1994**, 3441–3447.

[6] Dake, G. R.; Fenster, M. D. B.; Fleury, M.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5676–5683.

[7] Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. M. *J. Org. Chem.* **1993**, *58*, 5944–5951.

[8] Keppens, M.; Kimpe, N. D. *J. Org. Chem.* **1995**, *60*, 3916–3918.

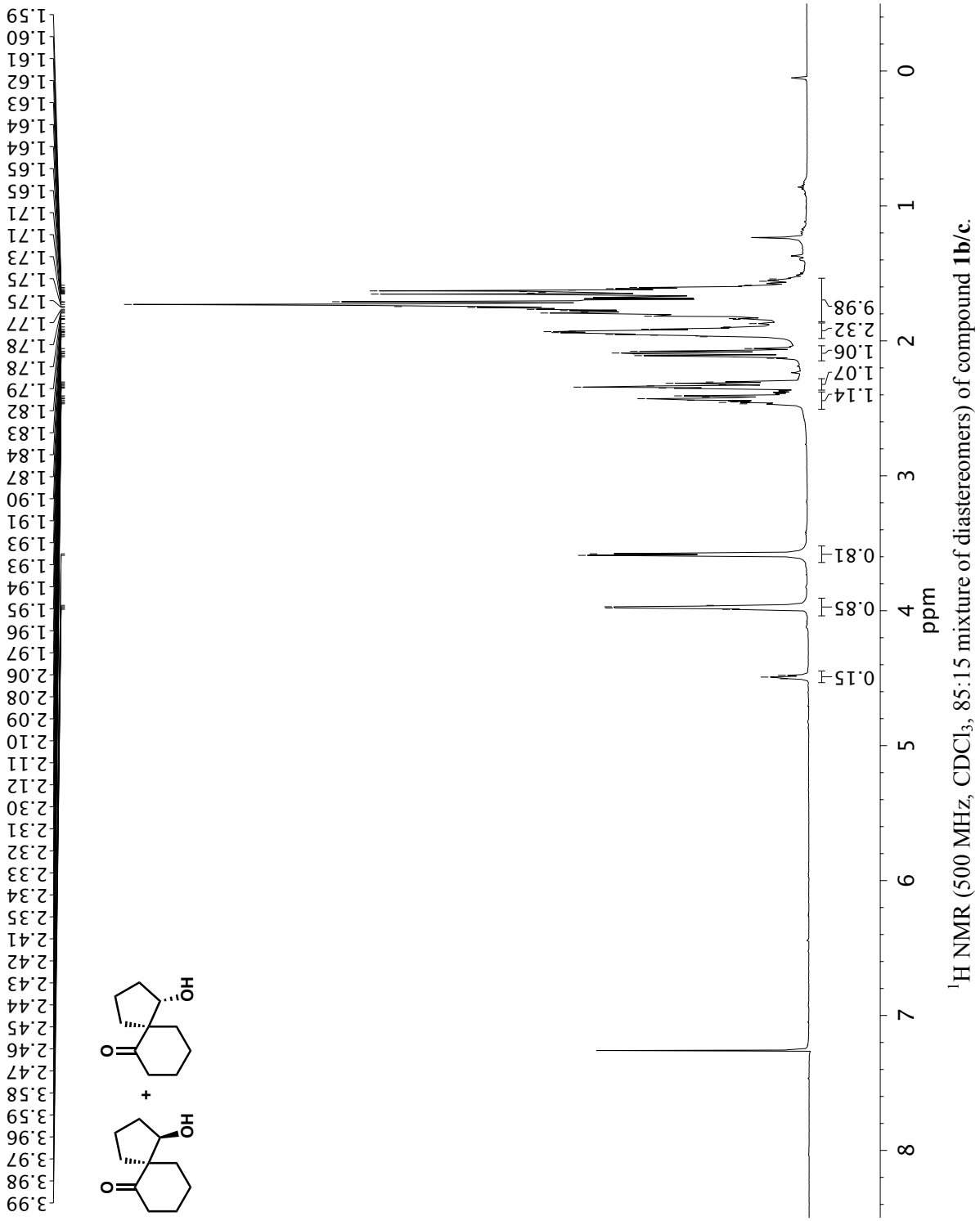
[9] Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist Jr., J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223.

[10] Doran, R.; Guiry, P. J. *J. Org. Chem.* **2014**, *79*, 9112–9124.

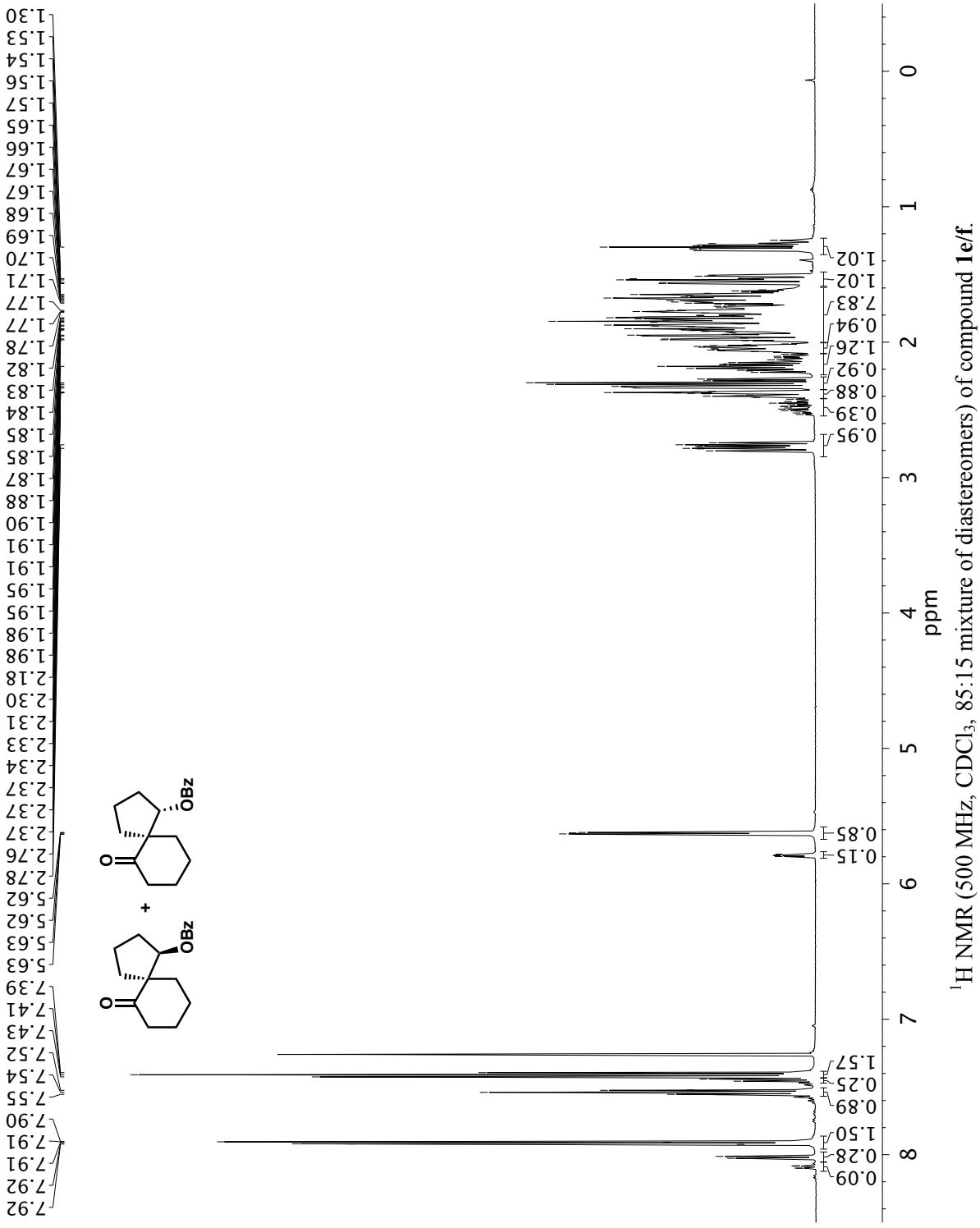
[11] Rambla, M.; Duroure, L.; Chabaud, L.; Guillou, C. *Eur. J. Org. Chem.* **2014**, 7716–7720.

[12] Parvatkar, P.; Kato, N.; Uesugi, M.; Sato, S.; Ohkanda, J. *J. Am. Chem. Soc.* **2015**, *137*, 15624–15627.

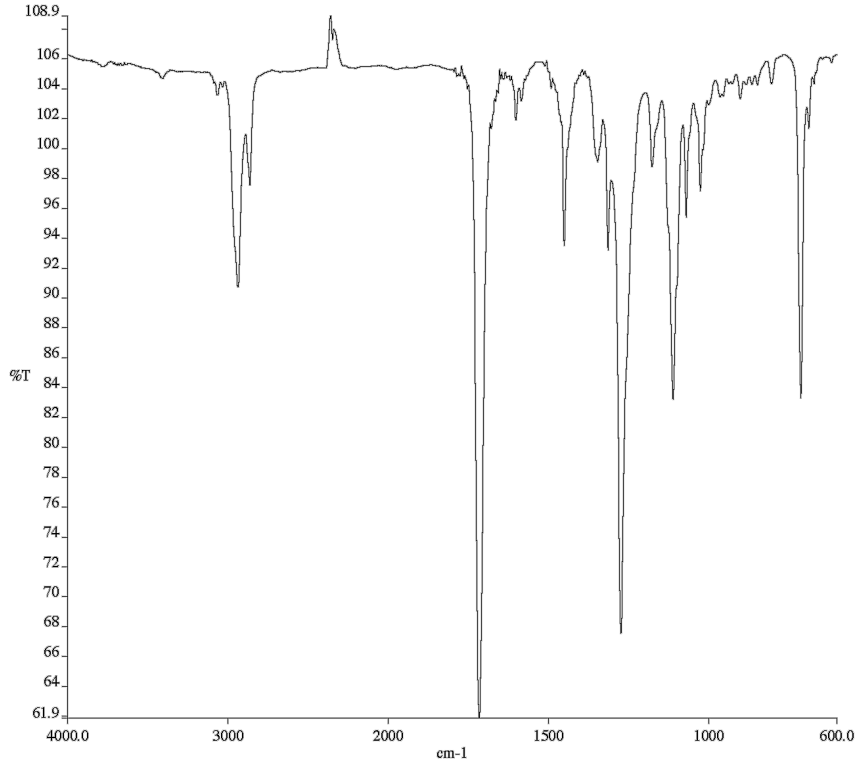
[13] Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133.



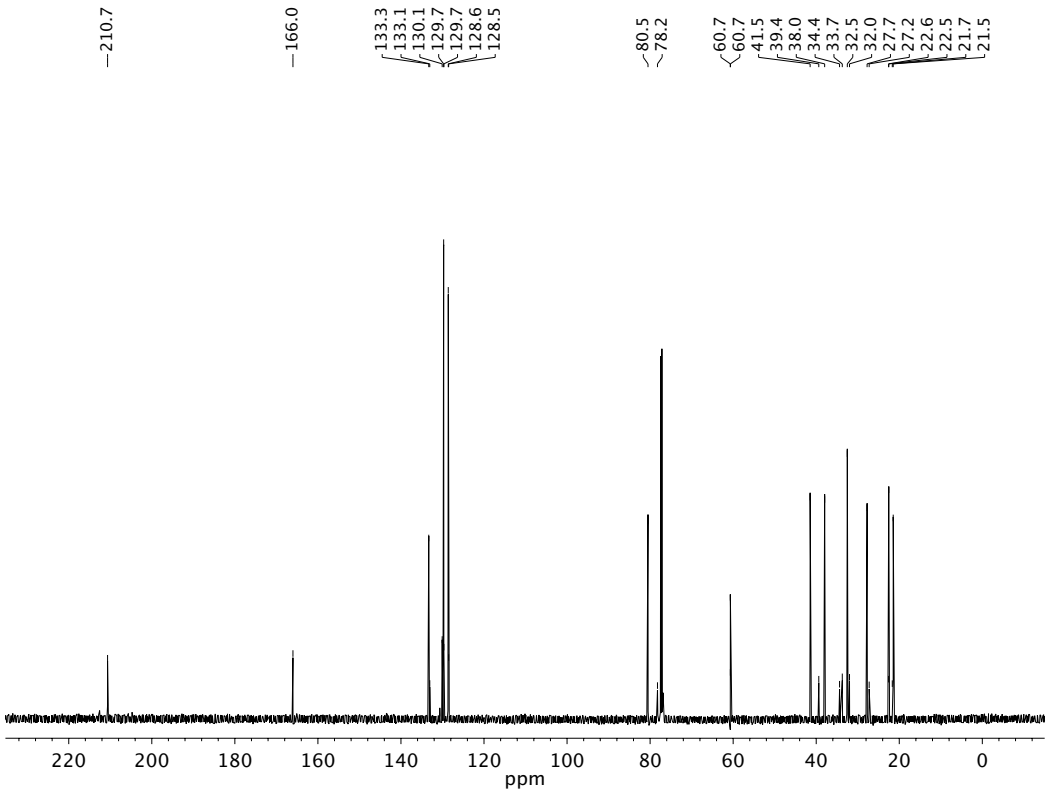
^{1}H NMR (500 MHz, $CDCl_3$, 85:15 mixture of diastereomers) of compound **1b/c**.



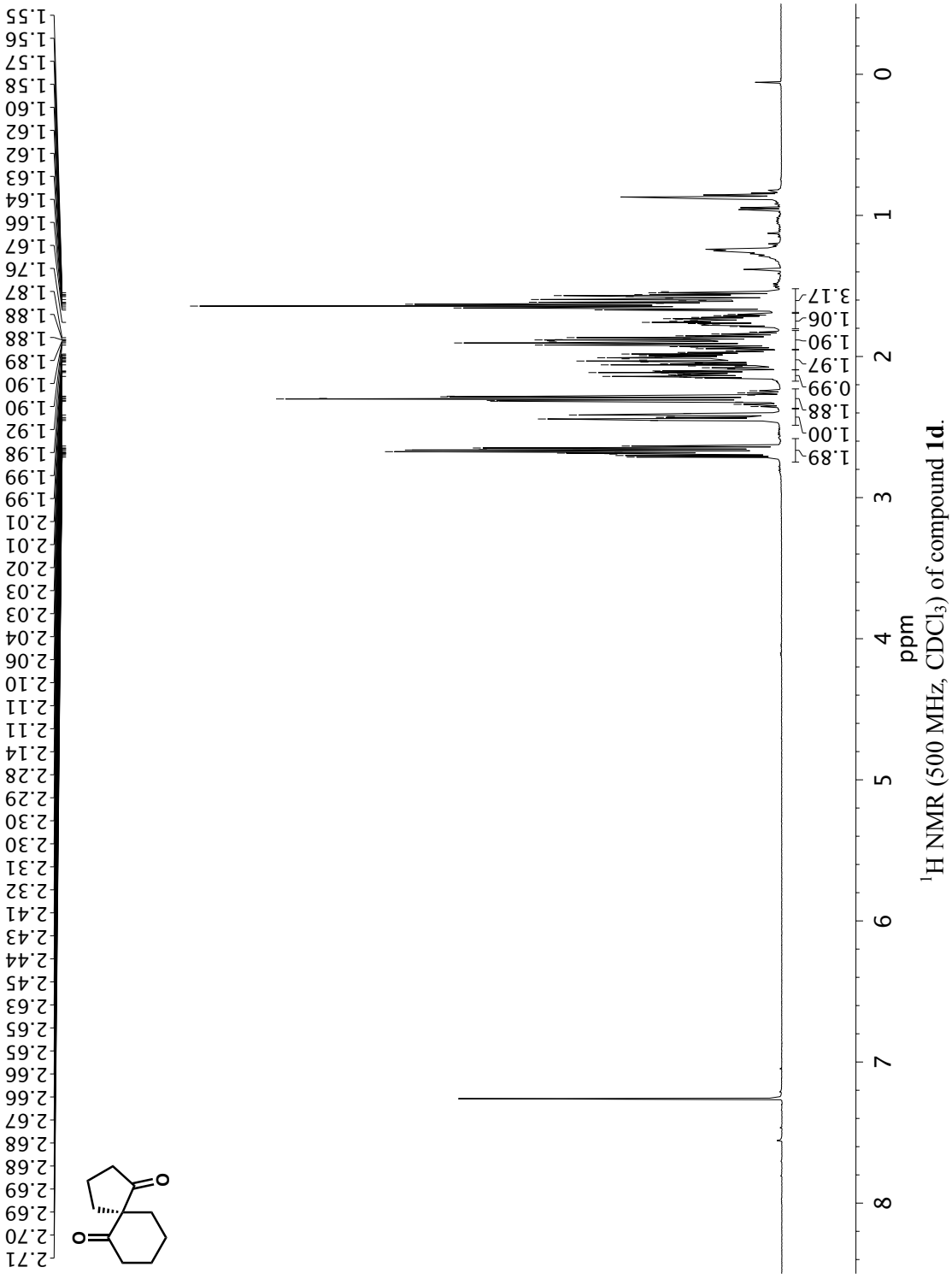
^{1}H NMR (500 MHz, $CDCl_3$, 85:15 mixture of diastereomers) of compound **1e/f**.



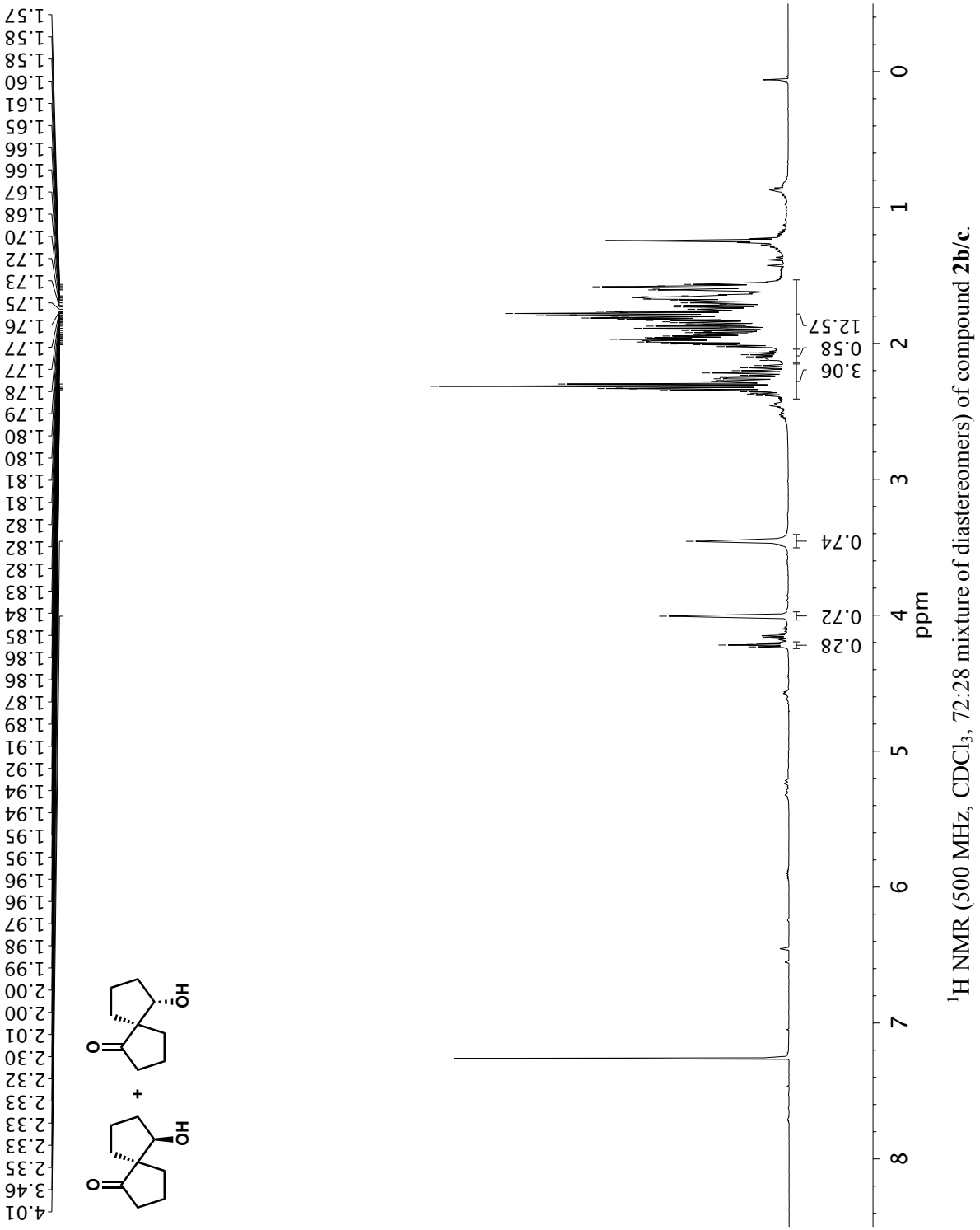
Infrared spectrum (Thin Film, NaCl) of compound **1e/f**.



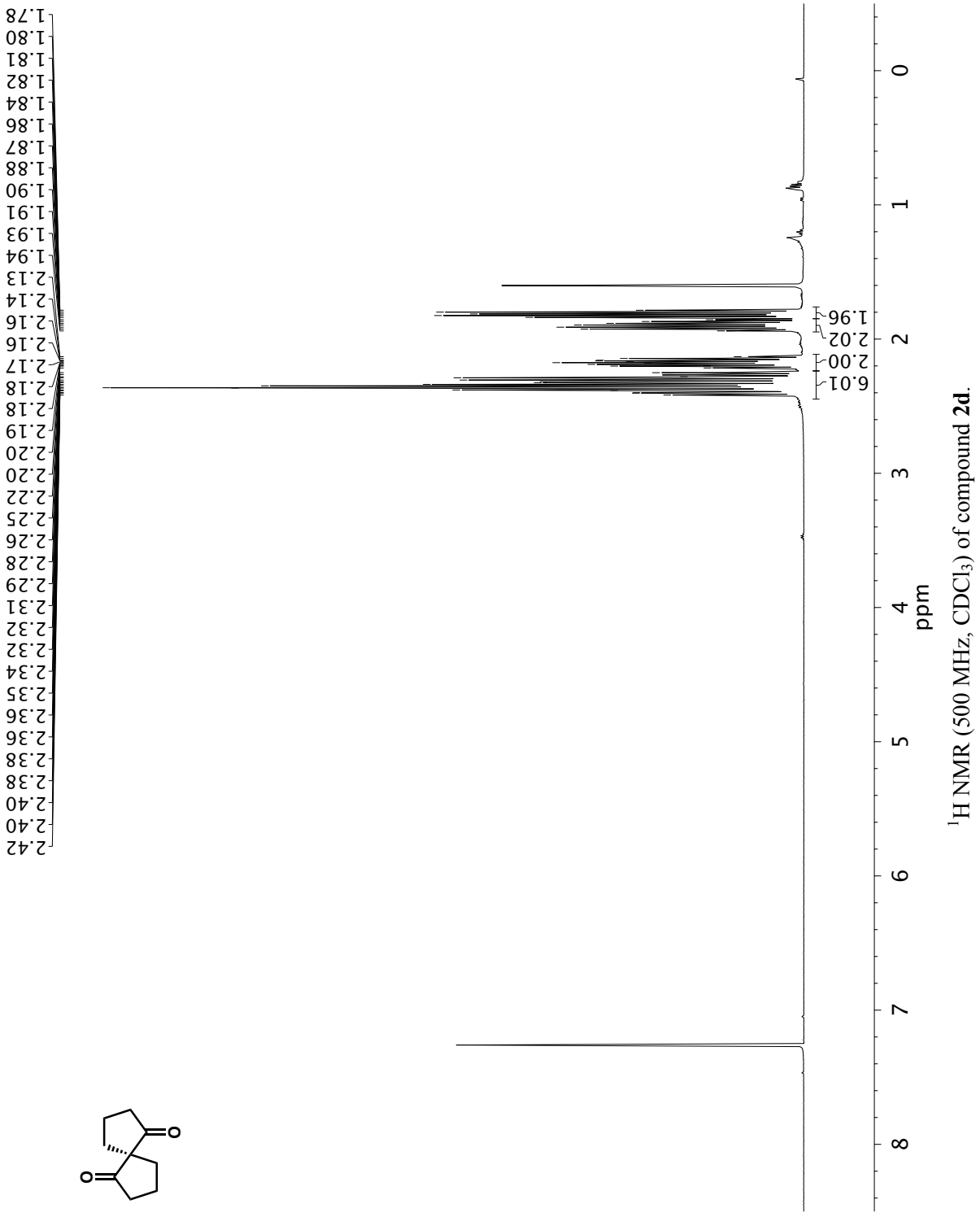
^{13}C NMR (125 MHz, $CDCl_3$, 85:15 mixture of diastereomers) of compound **1e/f**.



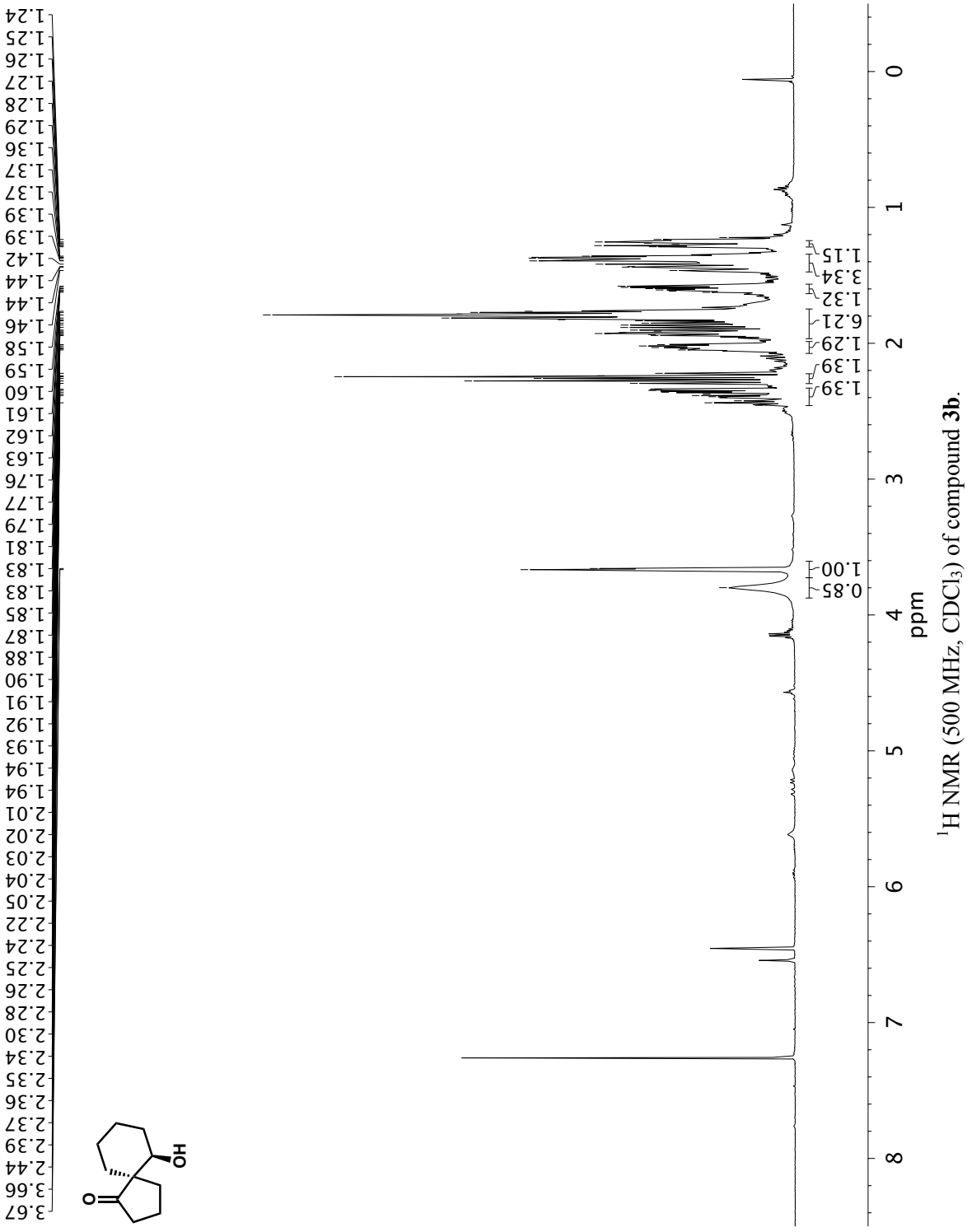
^{1}H NMR (500 MHz, $CDCl_3$) of compound **1d**.



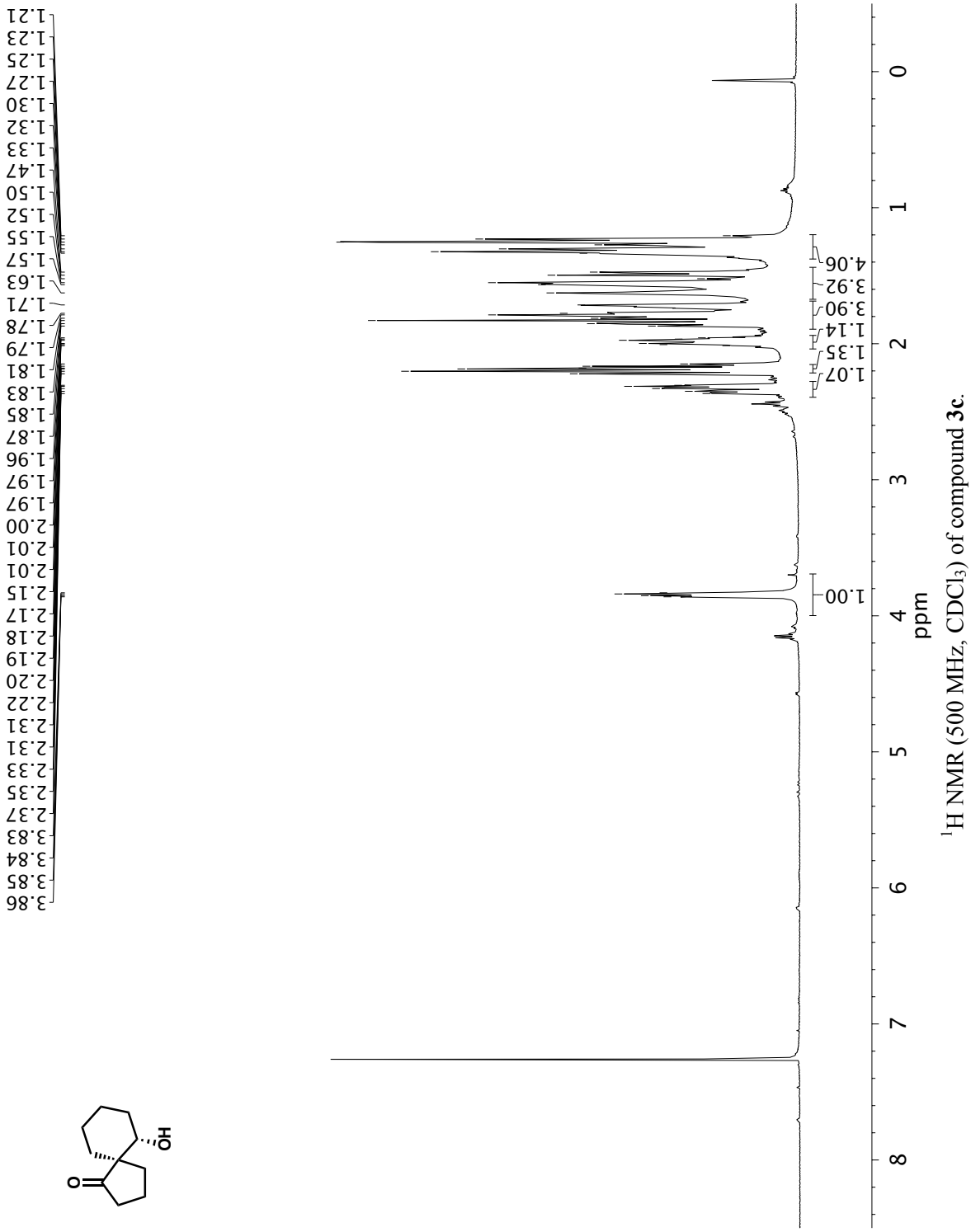
^{1}H NMR (500 MHz, $CDCl_3$, 72:28 mixture of diastereomers) of compound **2b/c**.



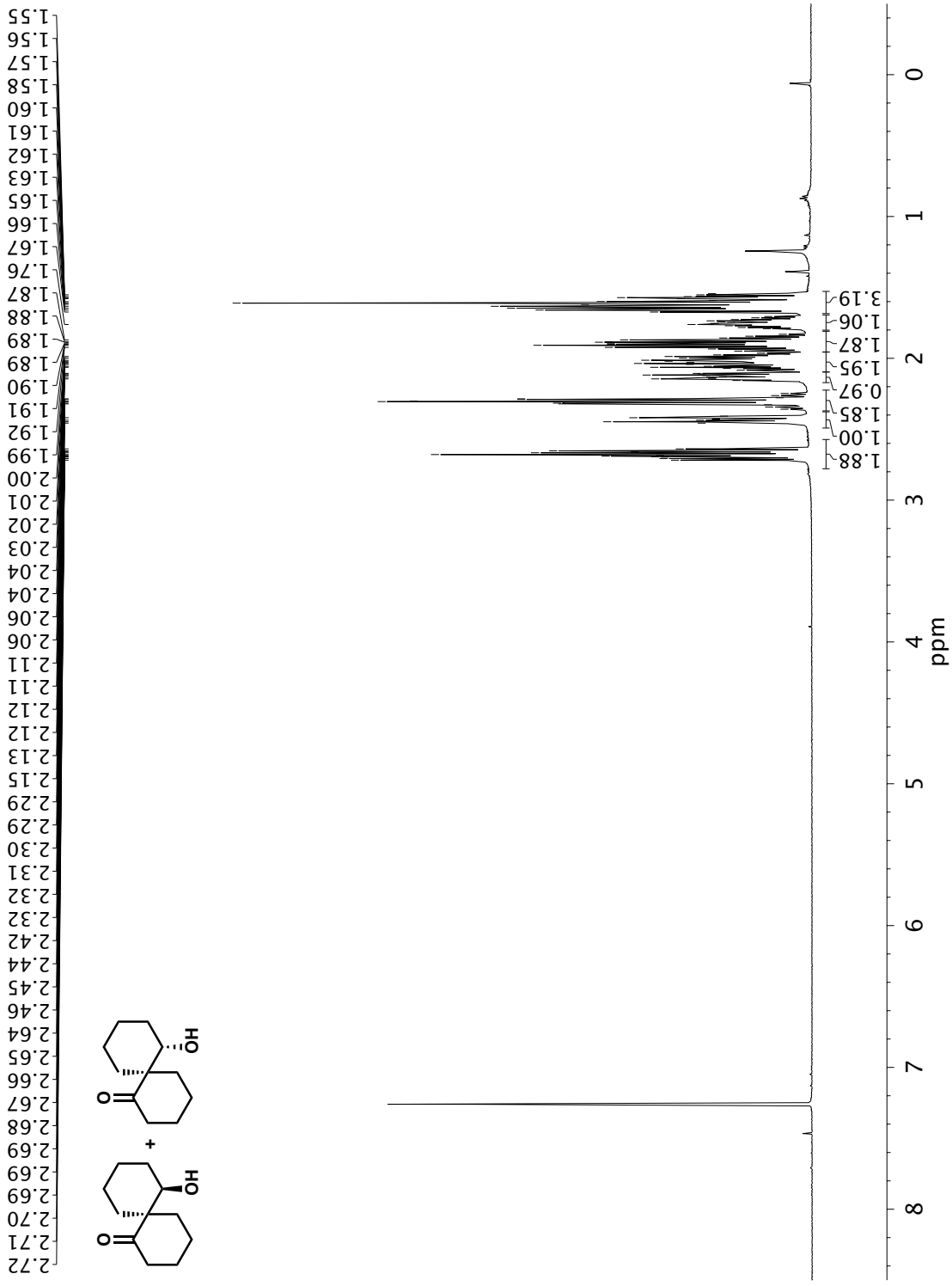
^{1}H NMR (500 MHz, $CDCl_3$) of compound **2d**.



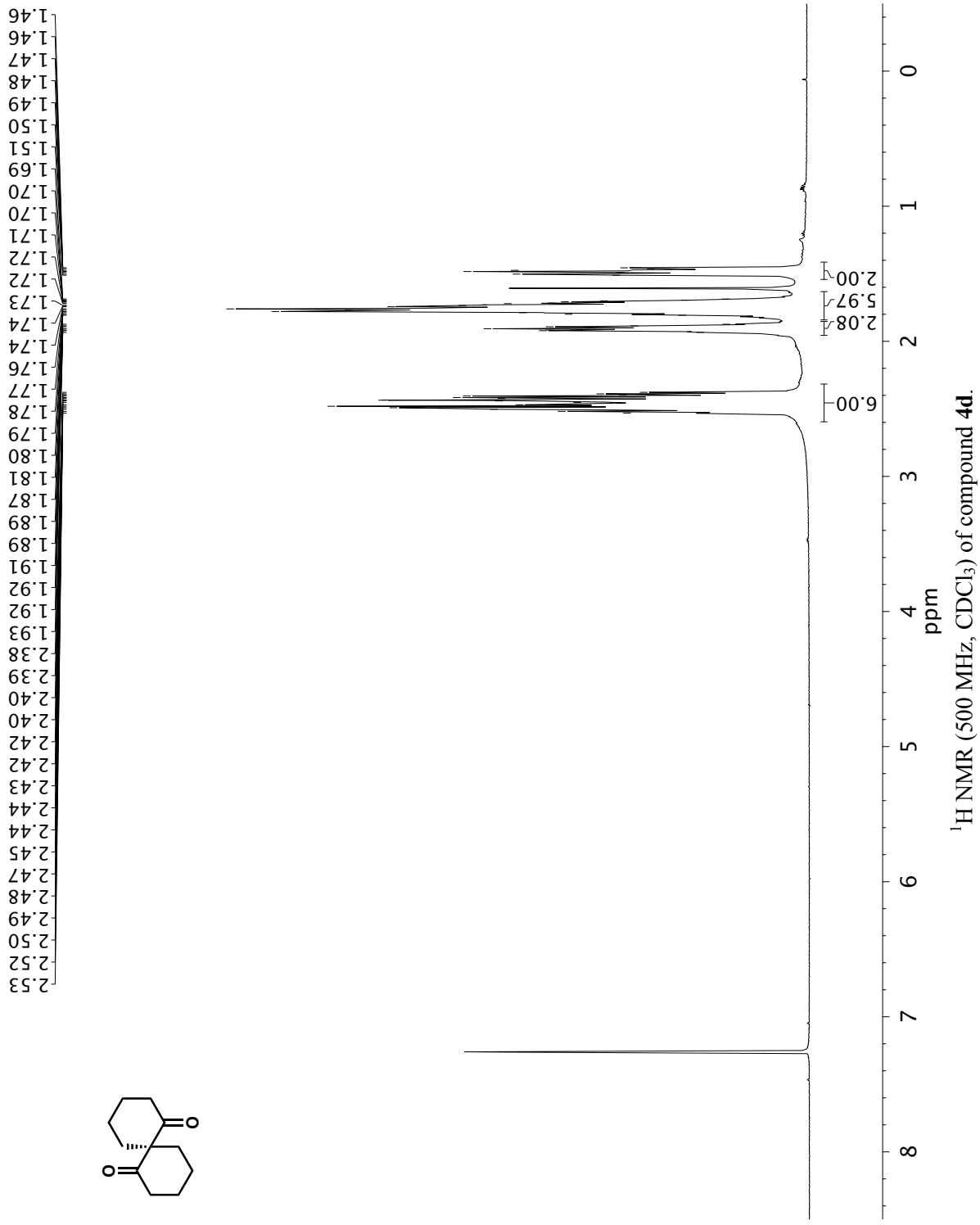
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3b**.



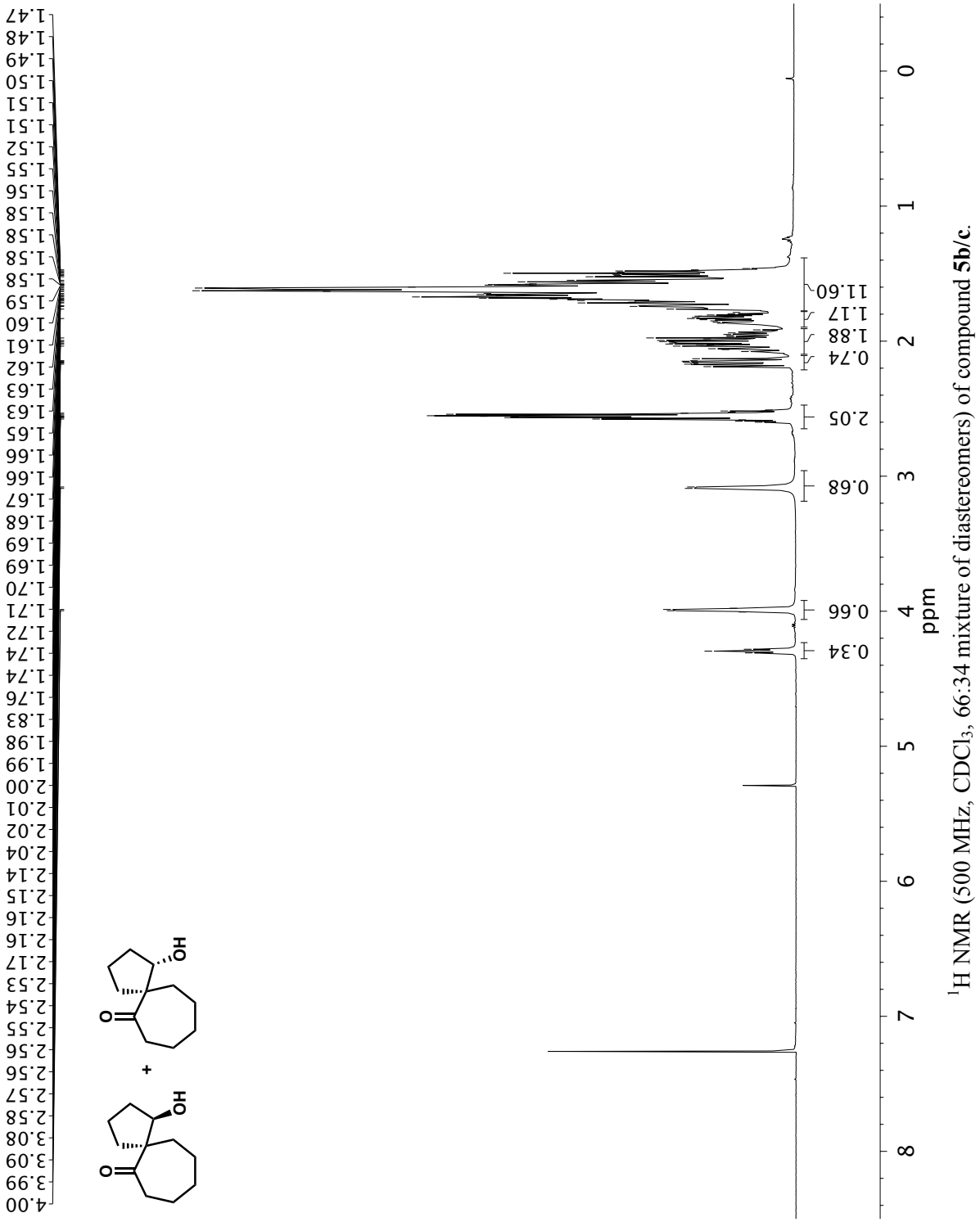
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3c**.



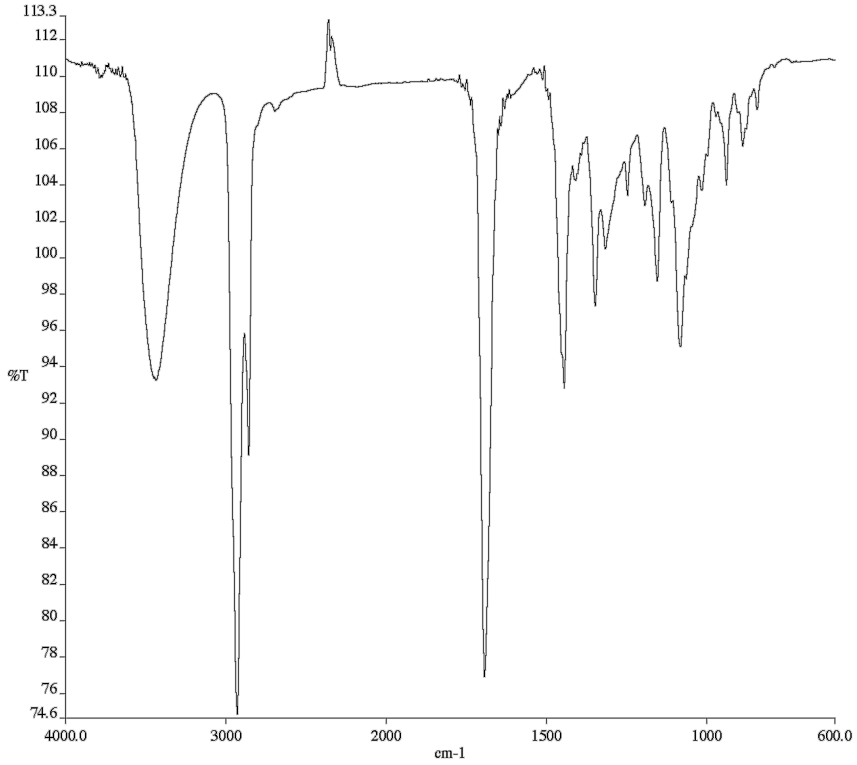
^{1}H NMR (500 MHz, $CDCl_3$, 76:24 mixture of diastereomers) of compound **4b/c**.



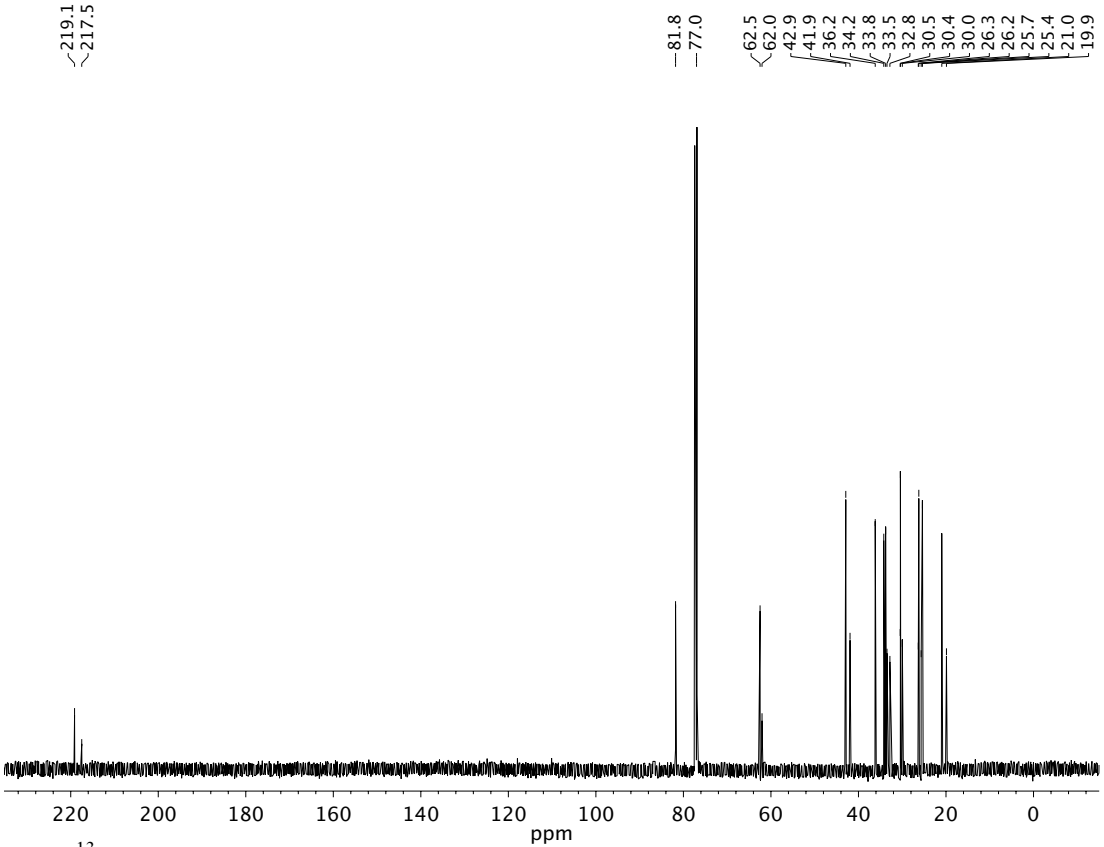
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4d**.



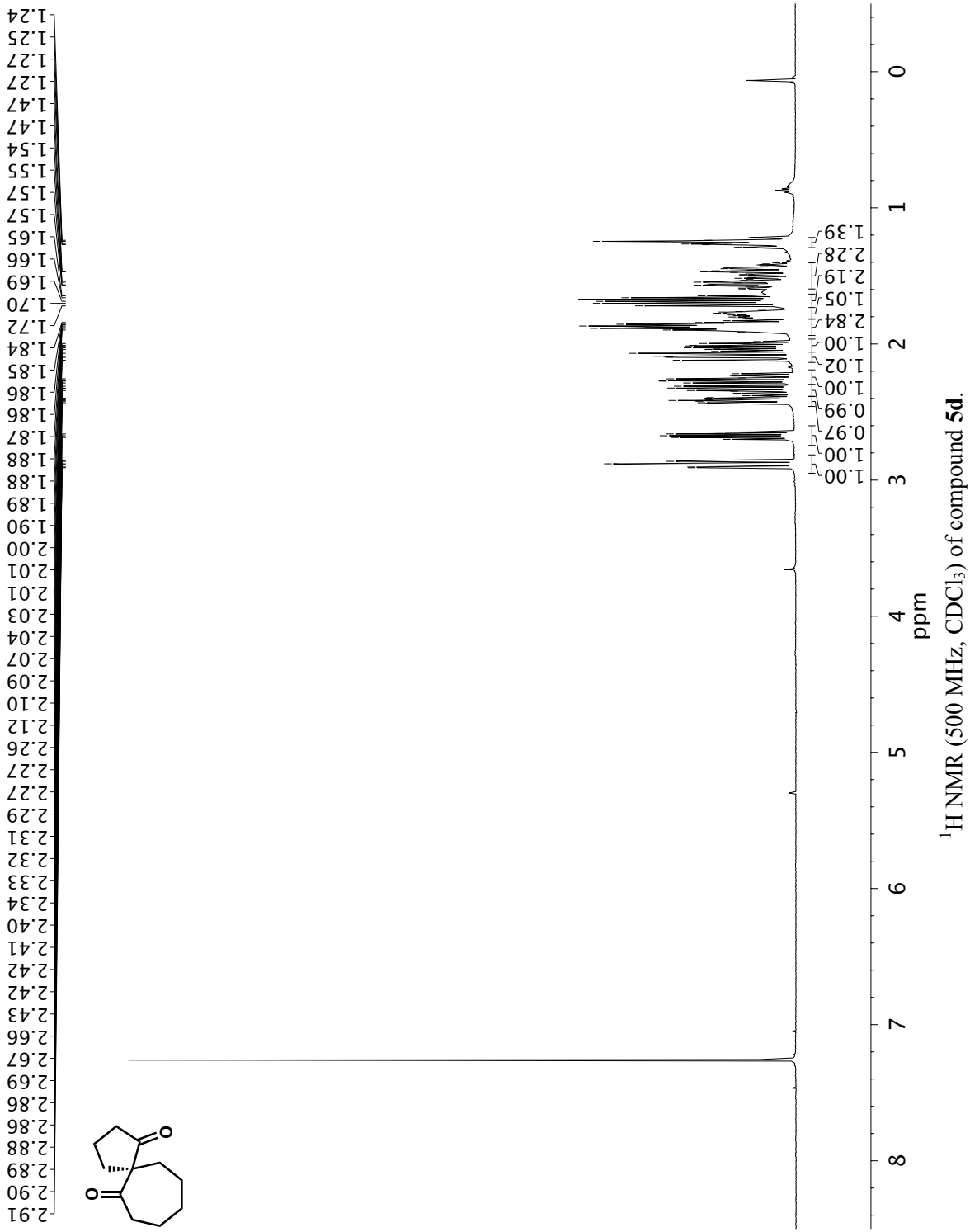
^{1}H NMR (500 MHz, $CDCl_3$, 66:34 mixture of diastereomers) of compound **5b/c**.



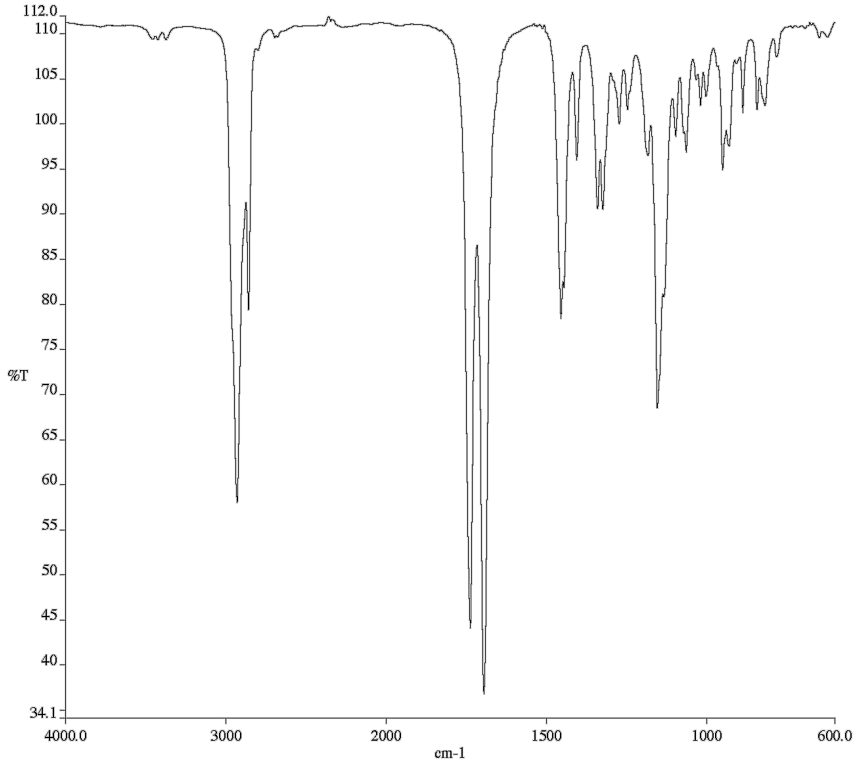
Infrared spectrum (Thin Film, NaCl) of compound **5b/c**.



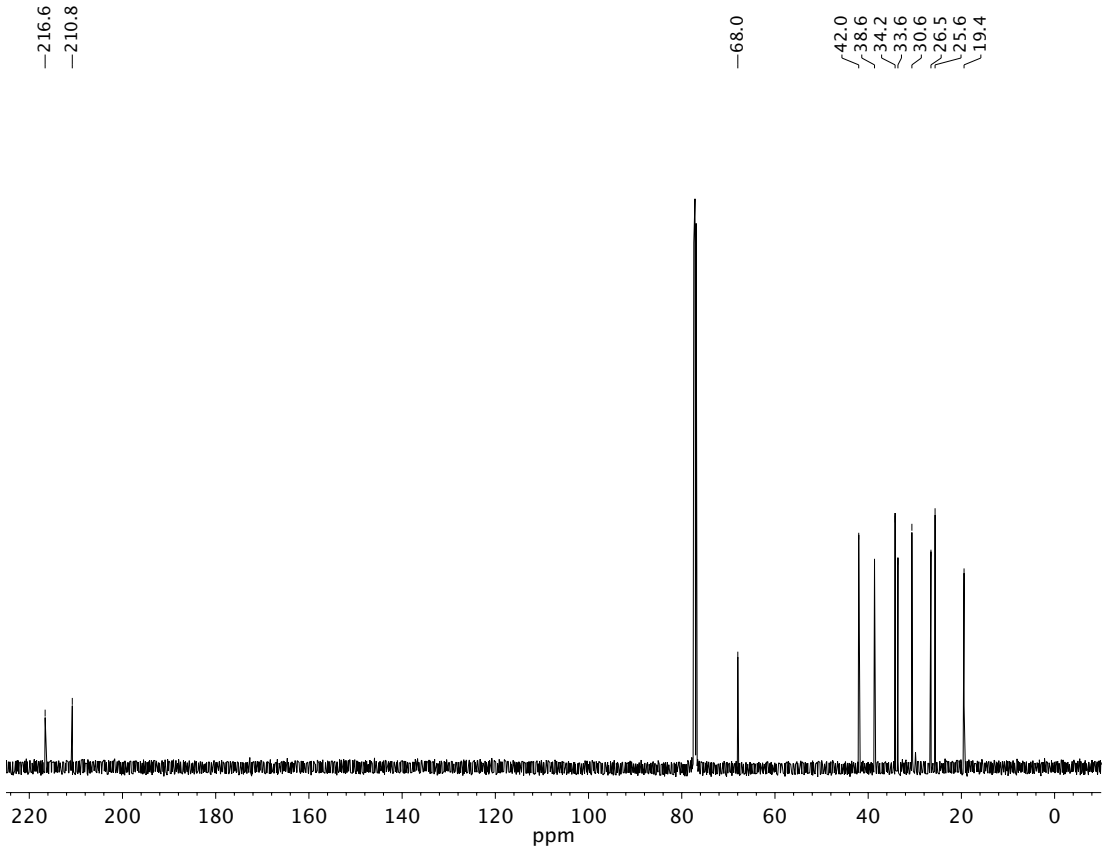
^{13}C NMR (125 MHz, $CDCl_3$, 66:34 mixture of diastereomers) of compound **5b/c**.



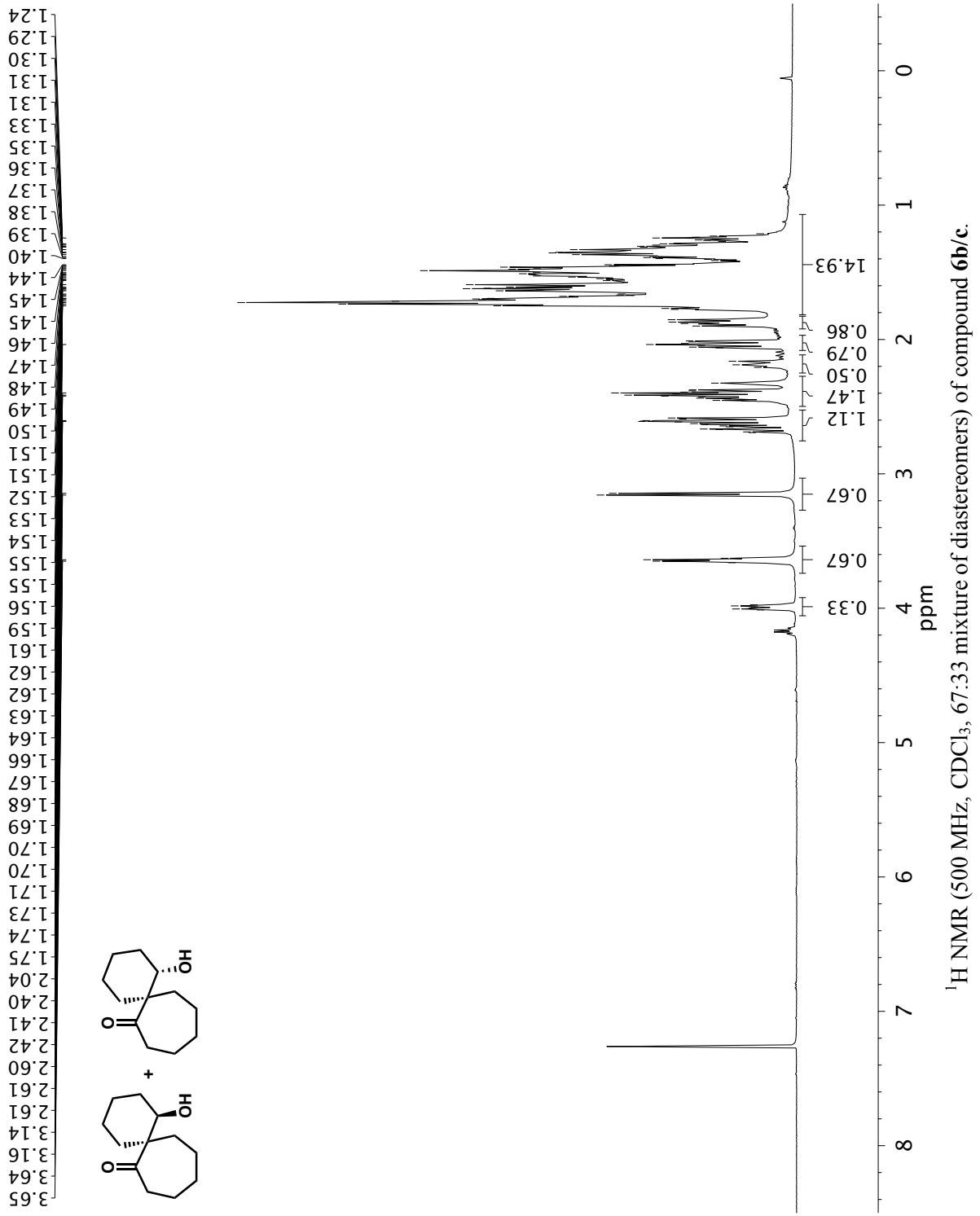
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5d**.



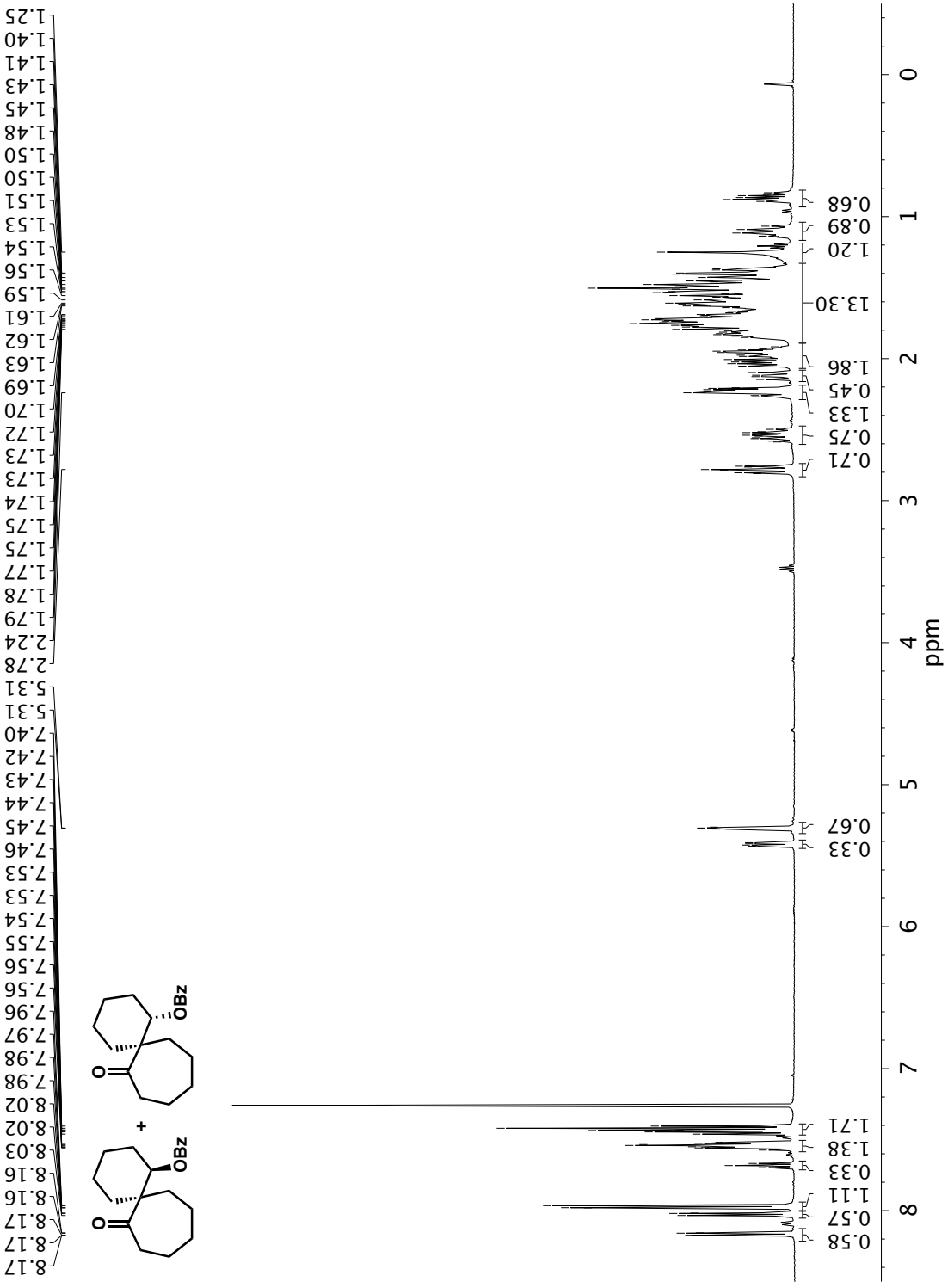
Infrared spectrum (Thin Film, NaCl) of compound **5d**.



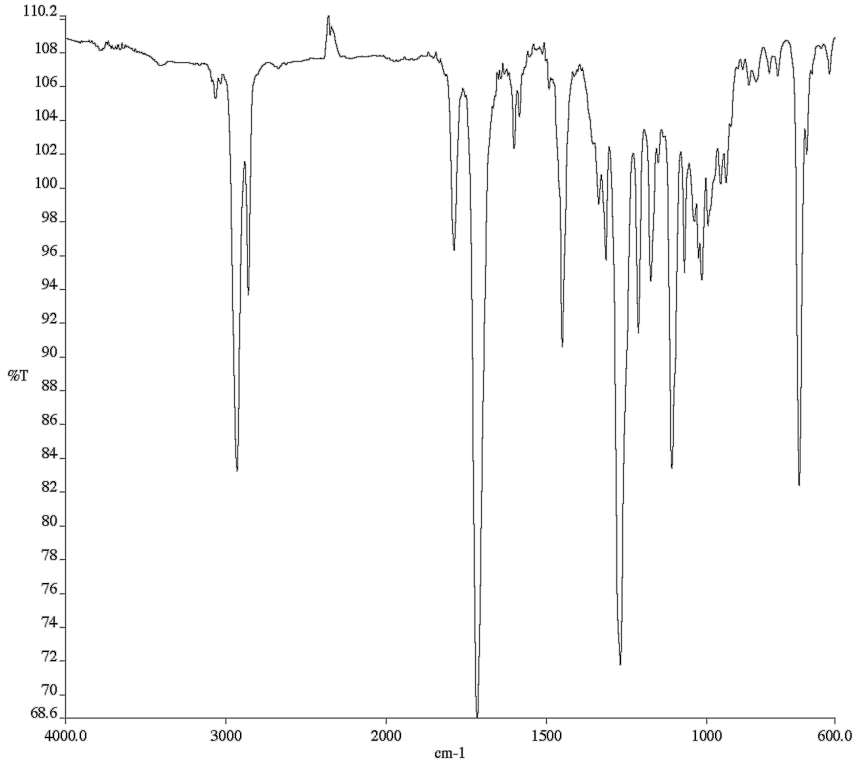
^{13}C NMR (126 MHz, $CDCl_3$) of compound **5d**.



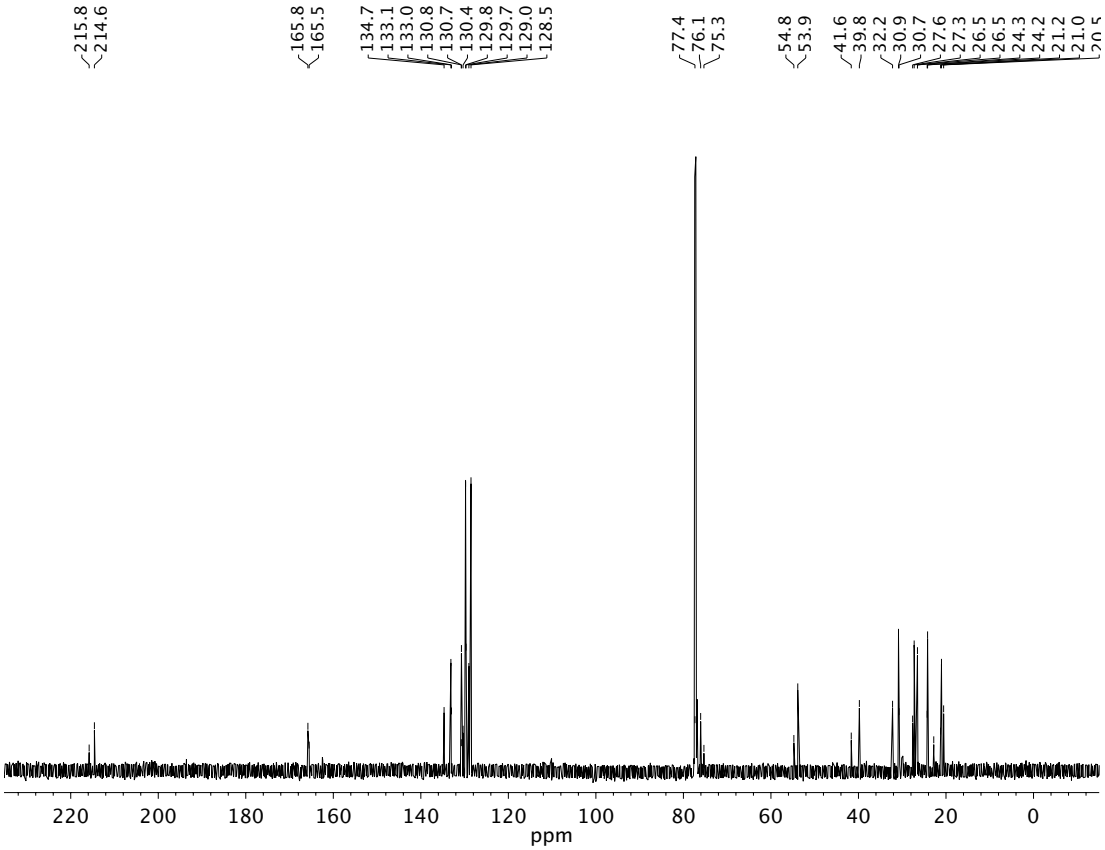
^{1}H NMR (500 MHz, $CDCl_3$, 67:33 mixture of diastereomers) of compound **6b/c**.



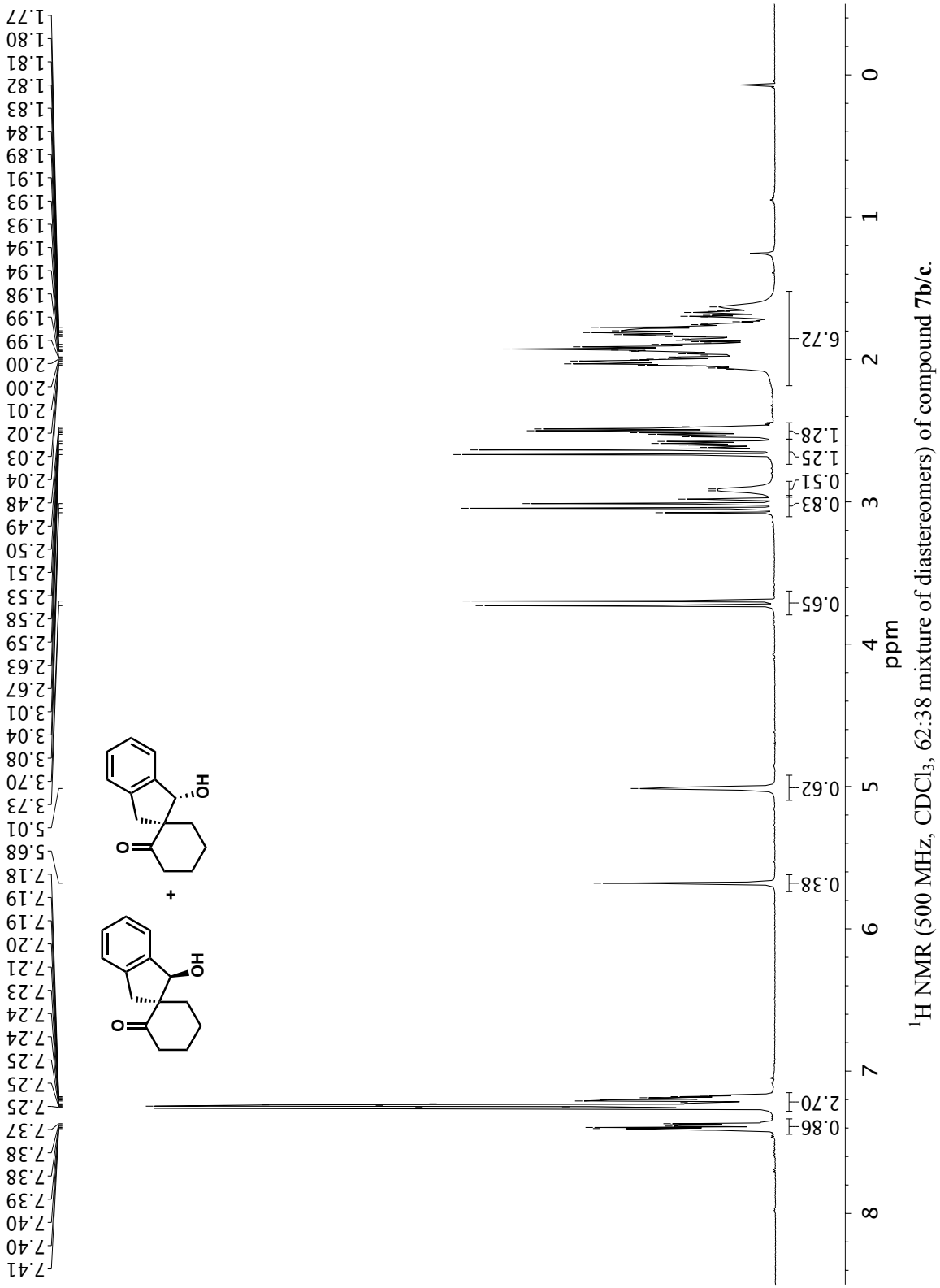
^{1}H NMR (500 MHz, $CDCl_3$, 67:33 mixture of diastereomers) of compound **6d/e**.



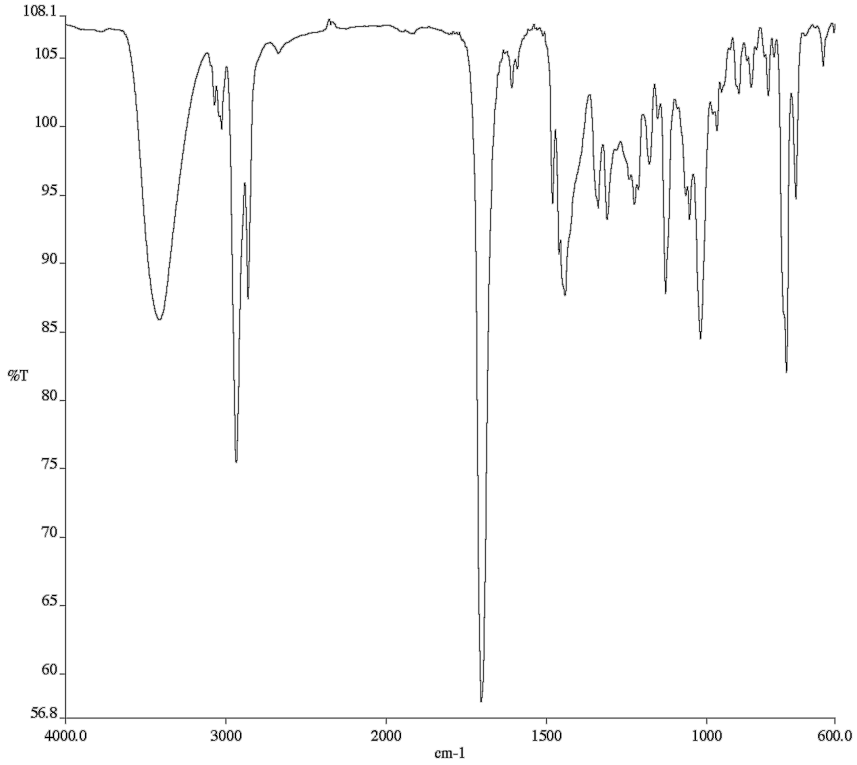
Infrared spectrum (Thin Film, NaCl) of compound **6d/e**.



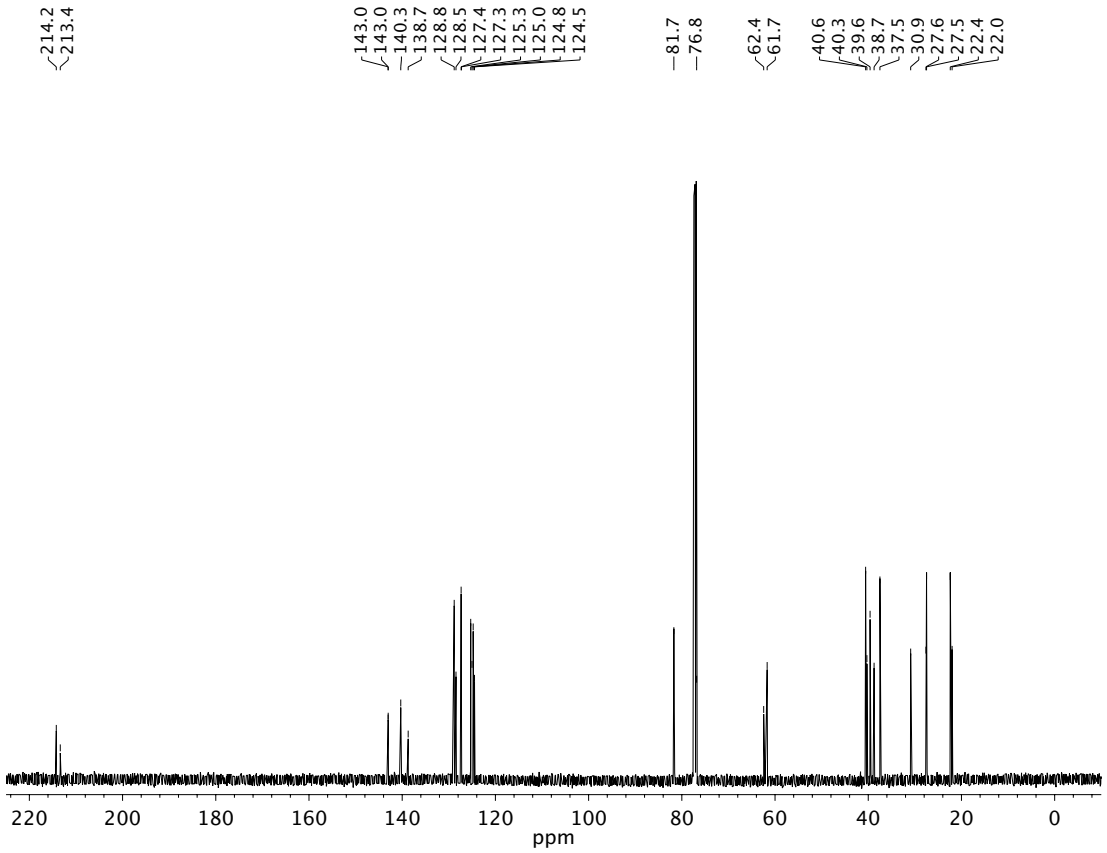
^{13}C NMR (125 MHz, $CDCl_3$, 67:34 mixture of diastereomers) of compound **6d/e**.



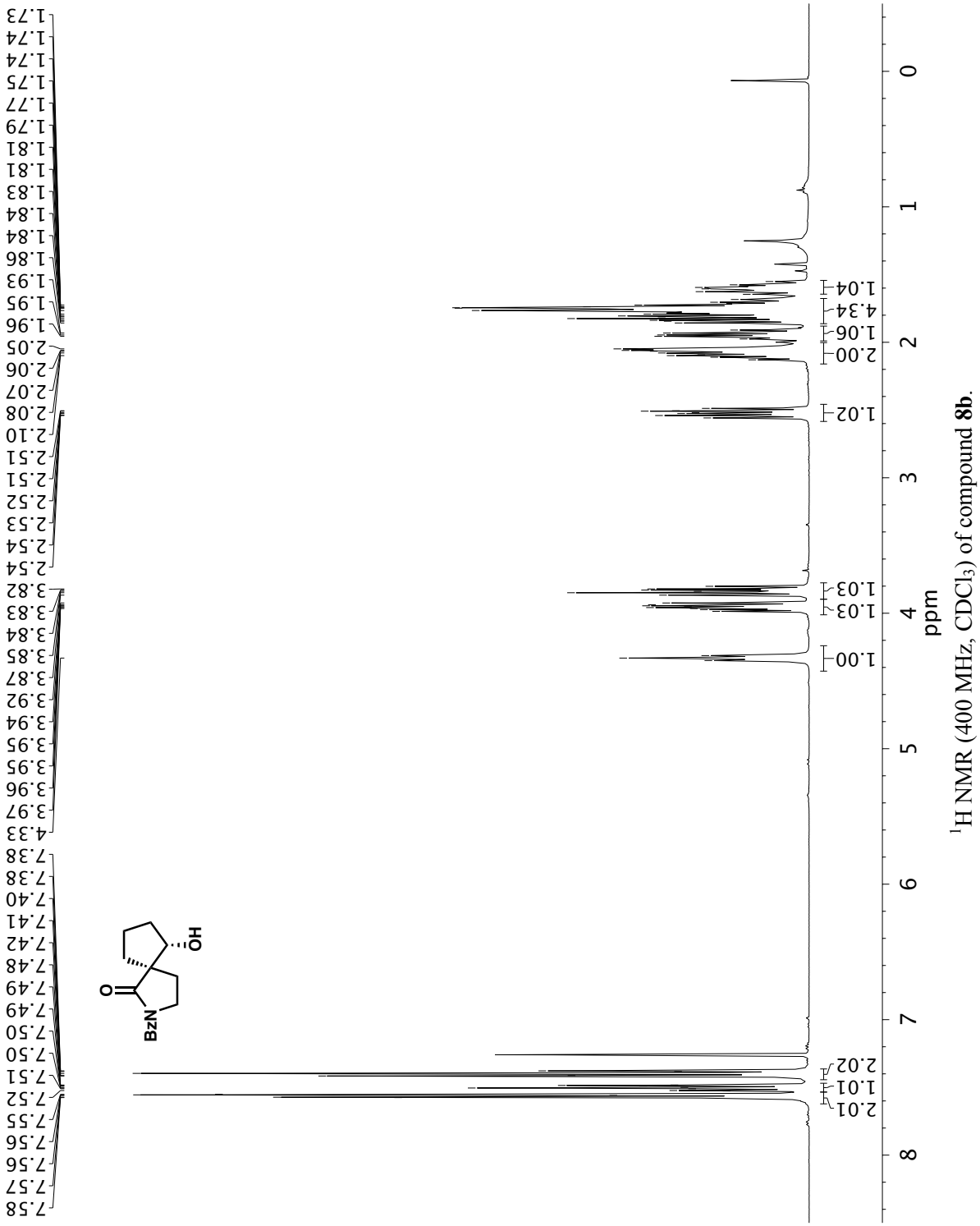
^{1}H NMR (500 MHz, $CDCl_3$, 62:38 mixture of diastereomers) of compound **7b/c**.



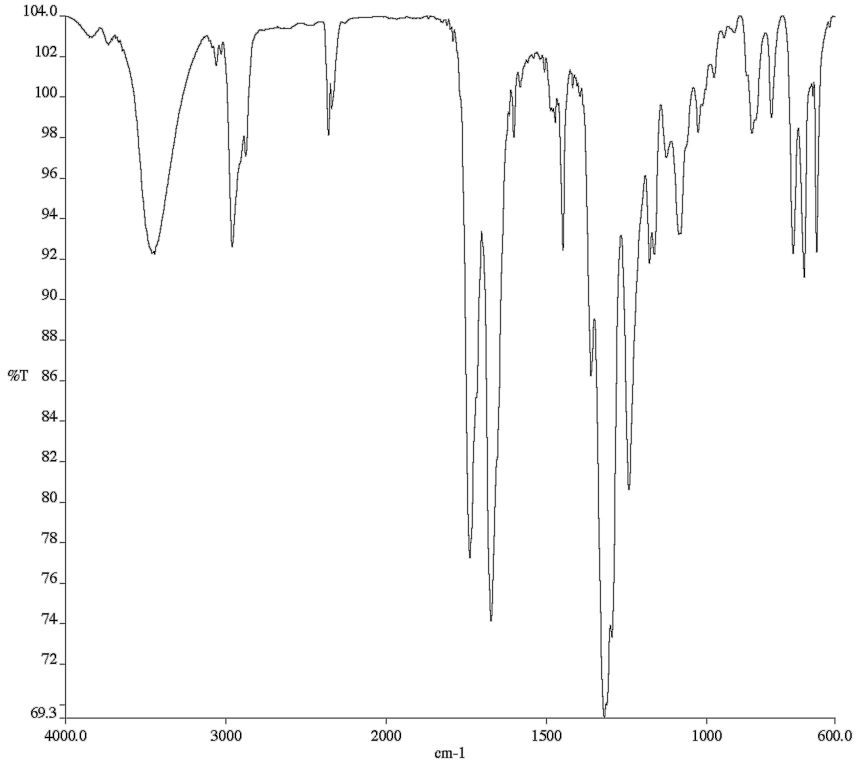
Infrared spectrum (Thin Film, NaCl) of compound **7b/c**.



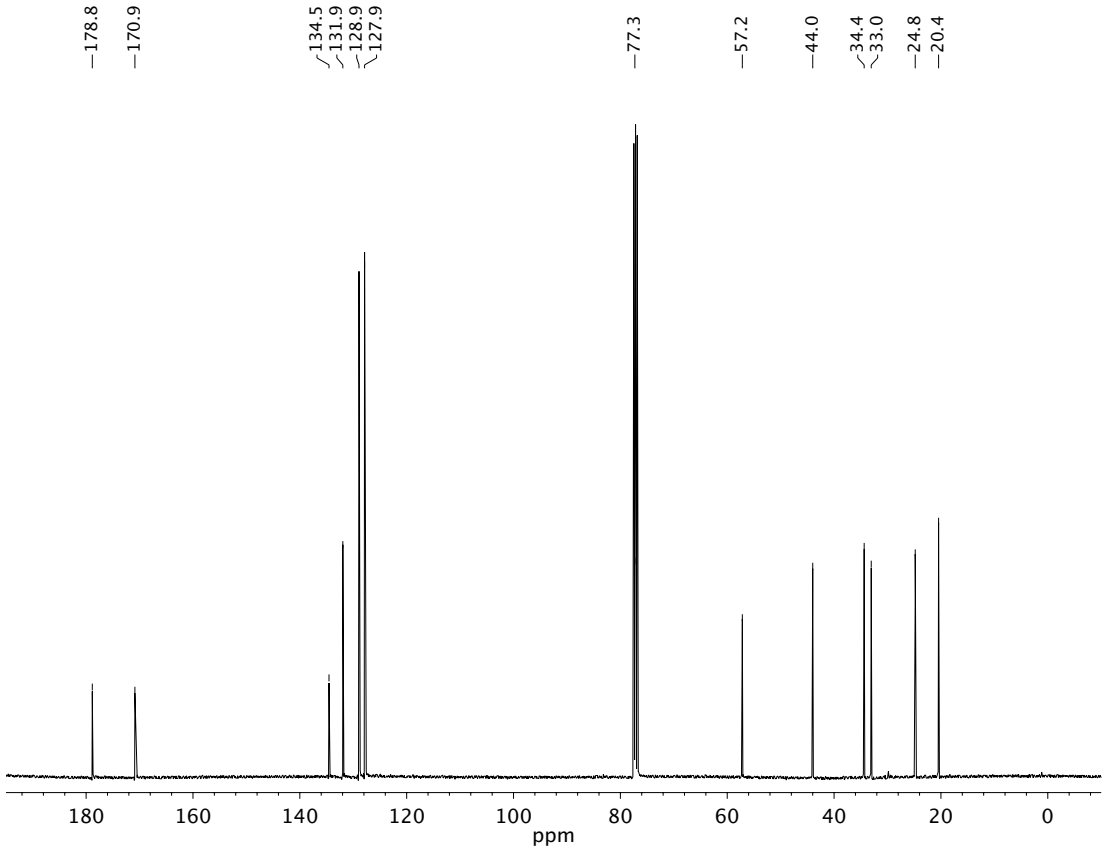
^{13}C NMR (125 MHz, $CDCl_3$, 62:38 mixture of diastereomers) of compound **7b/c**.



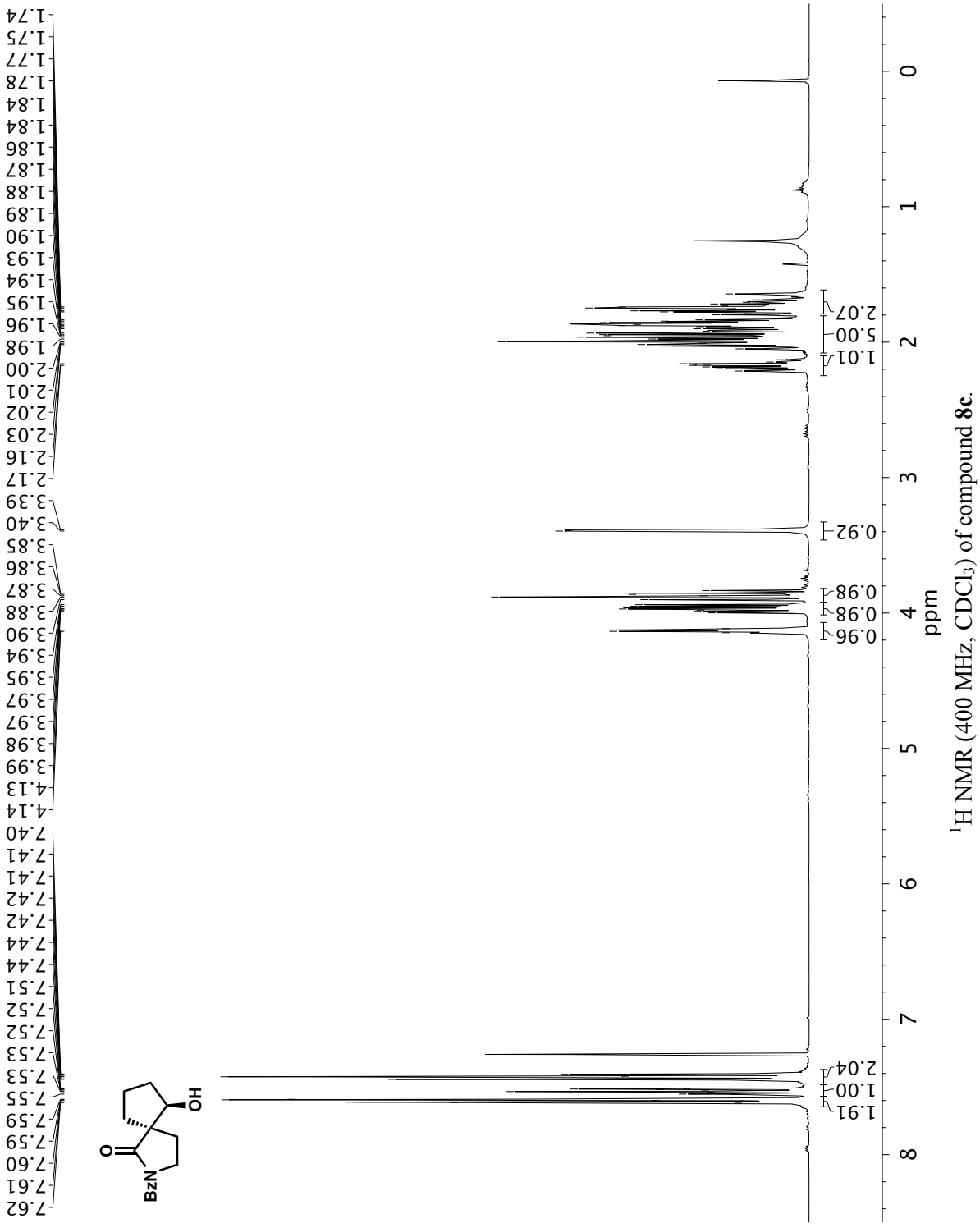
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8b**.



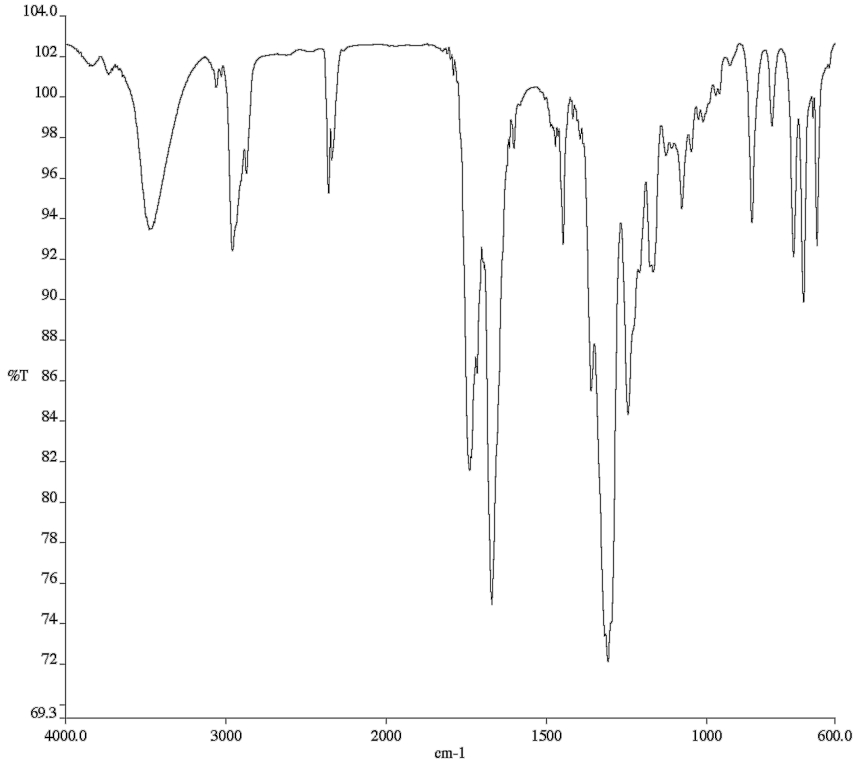
Infrared spectrum (Thin Film, NaCl) of compound **8b**.



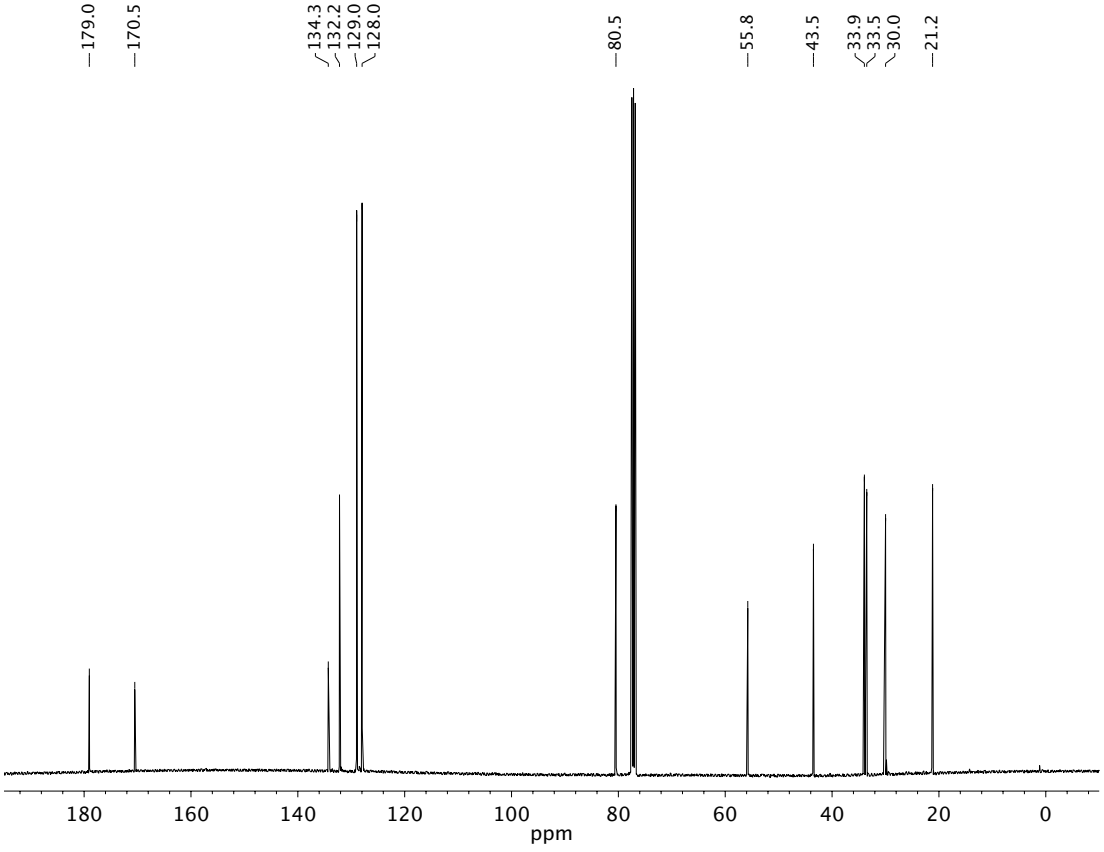
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8b**.



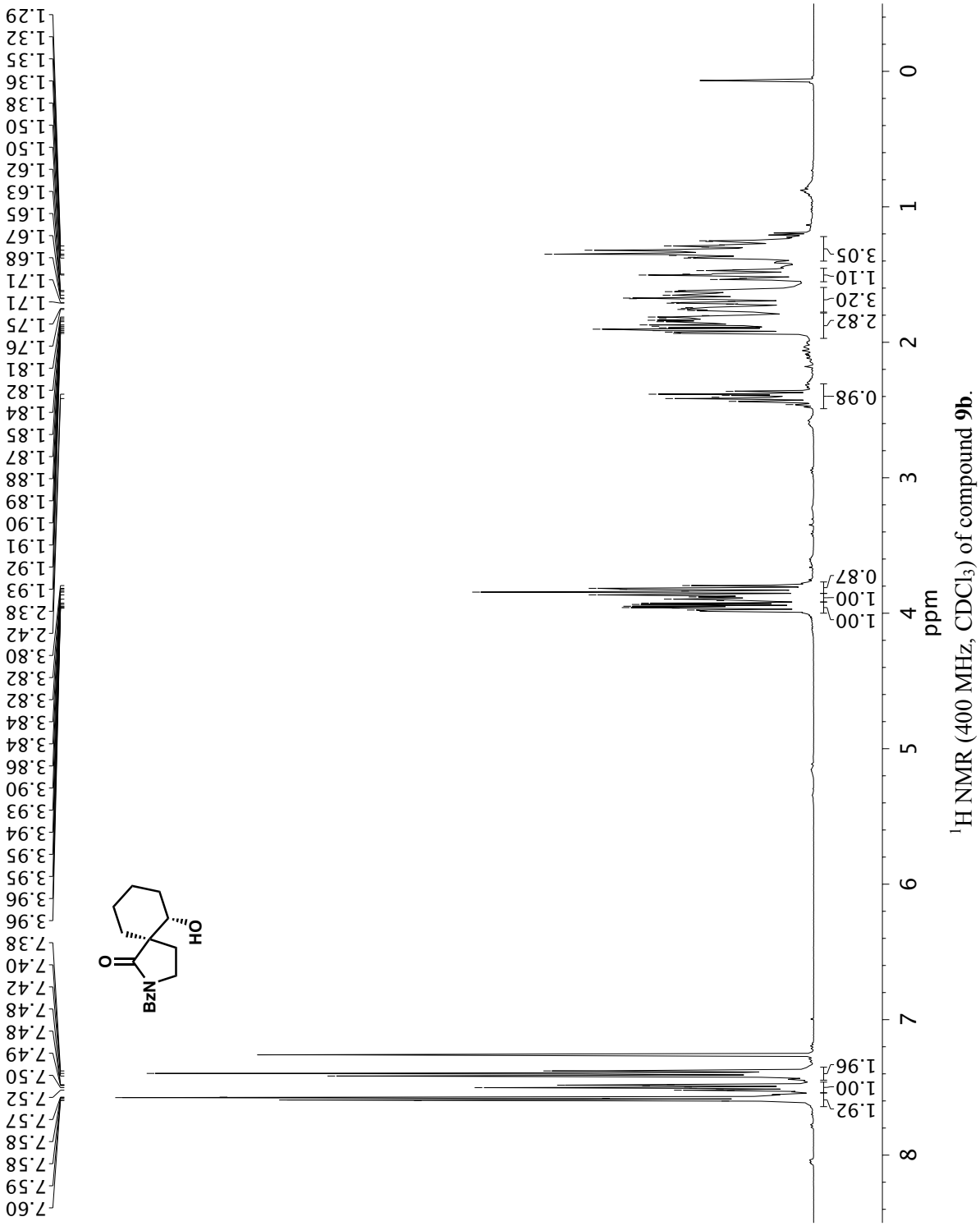
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8c**.



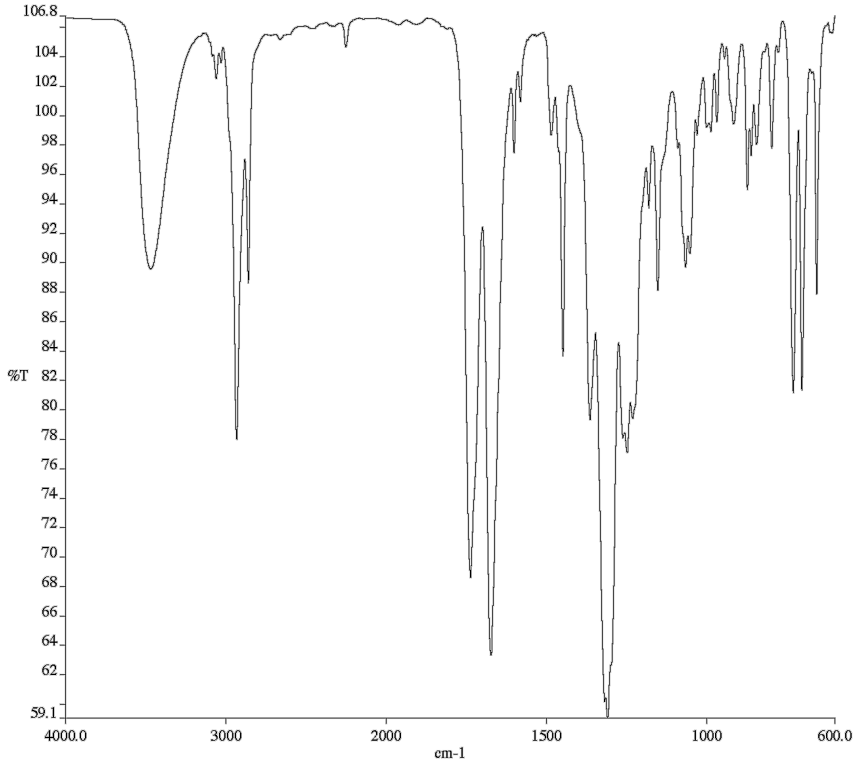
Infrared spectrum (Thin Film, NaCl) of compound **8c**.



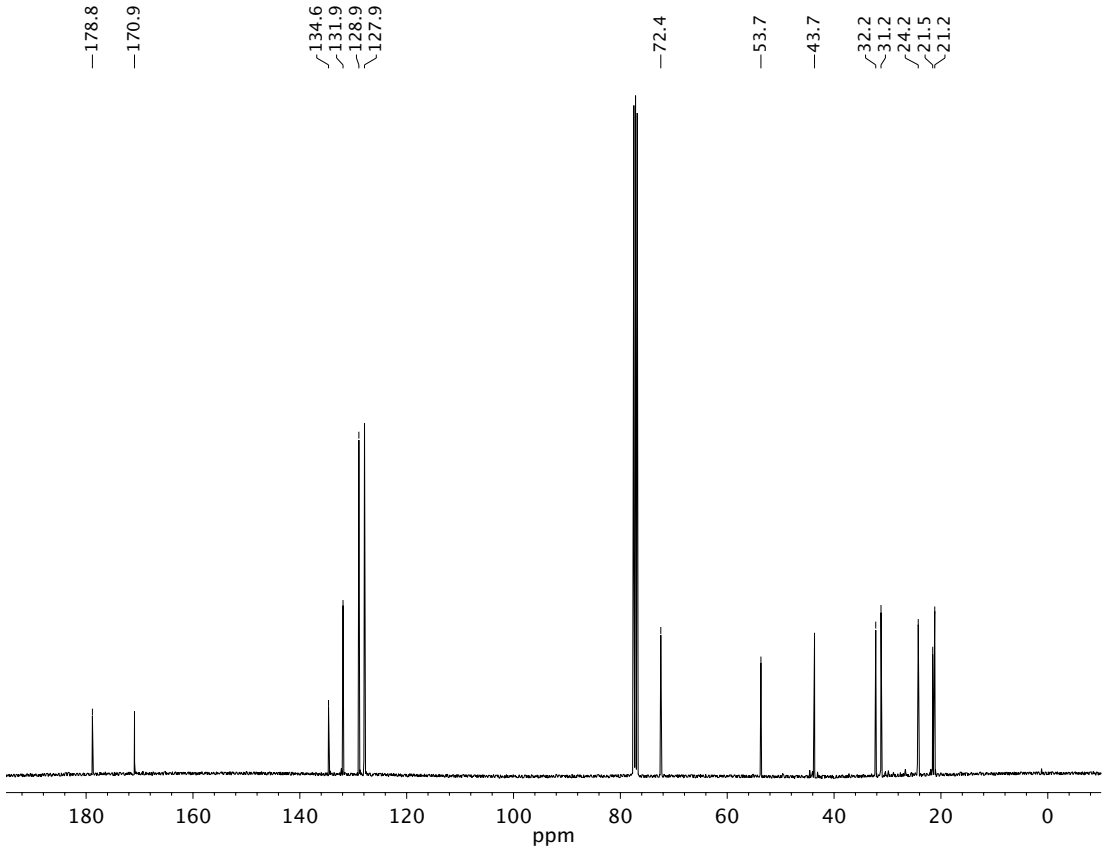
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8c**.



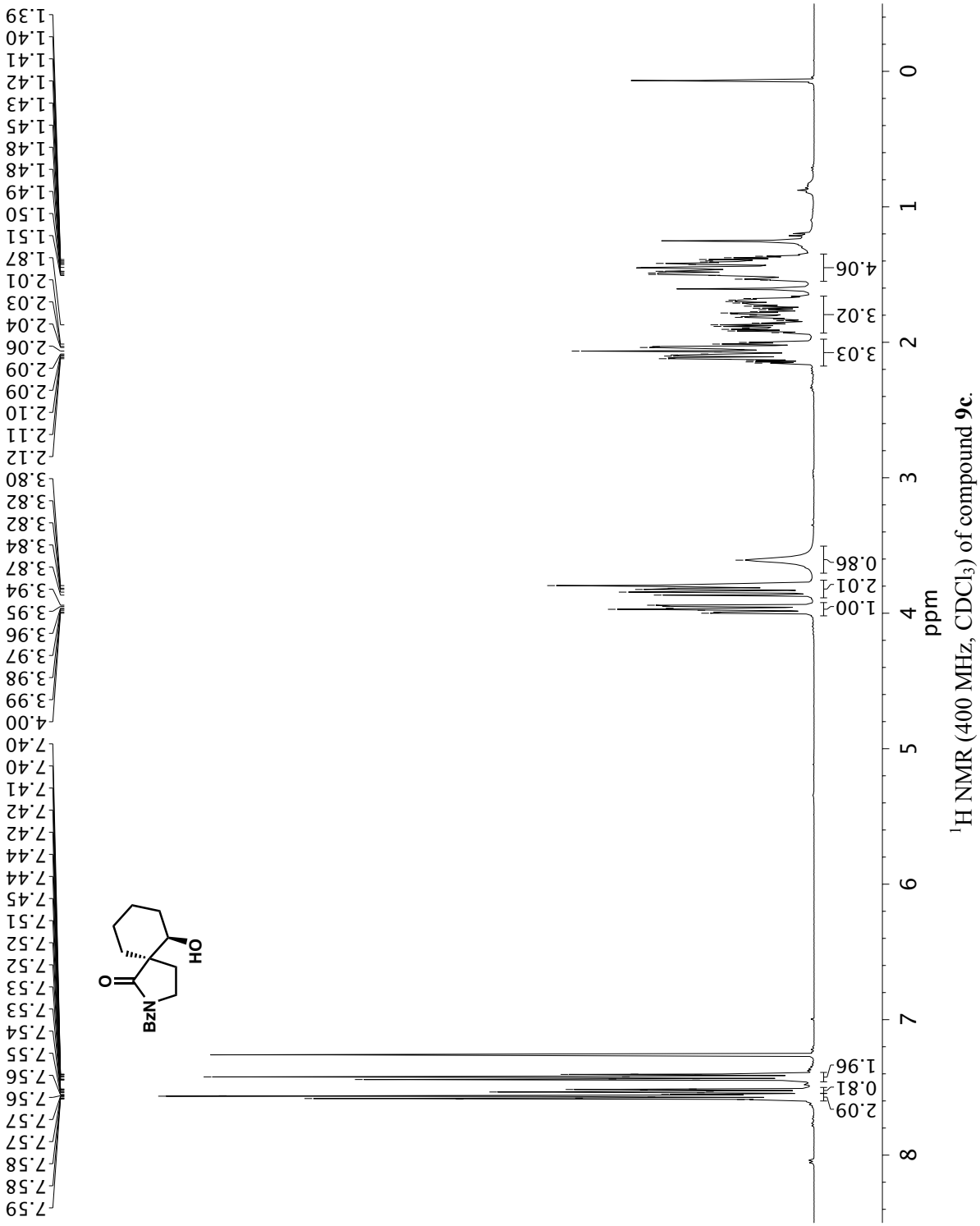
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9b**.



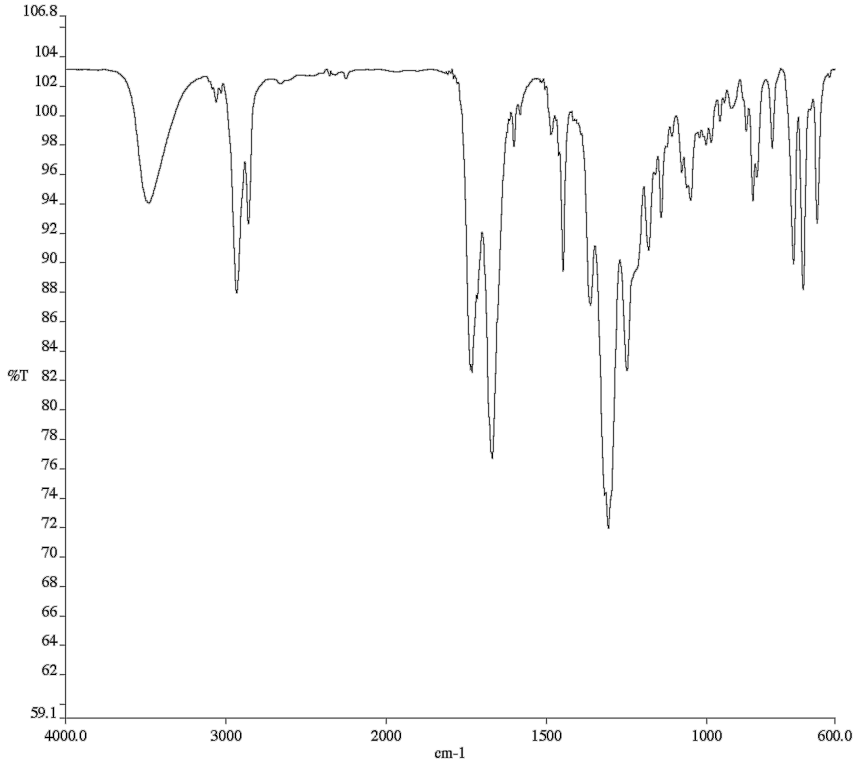
Infrared spectrum (Thin Film, NaCl) of compound **9b**.



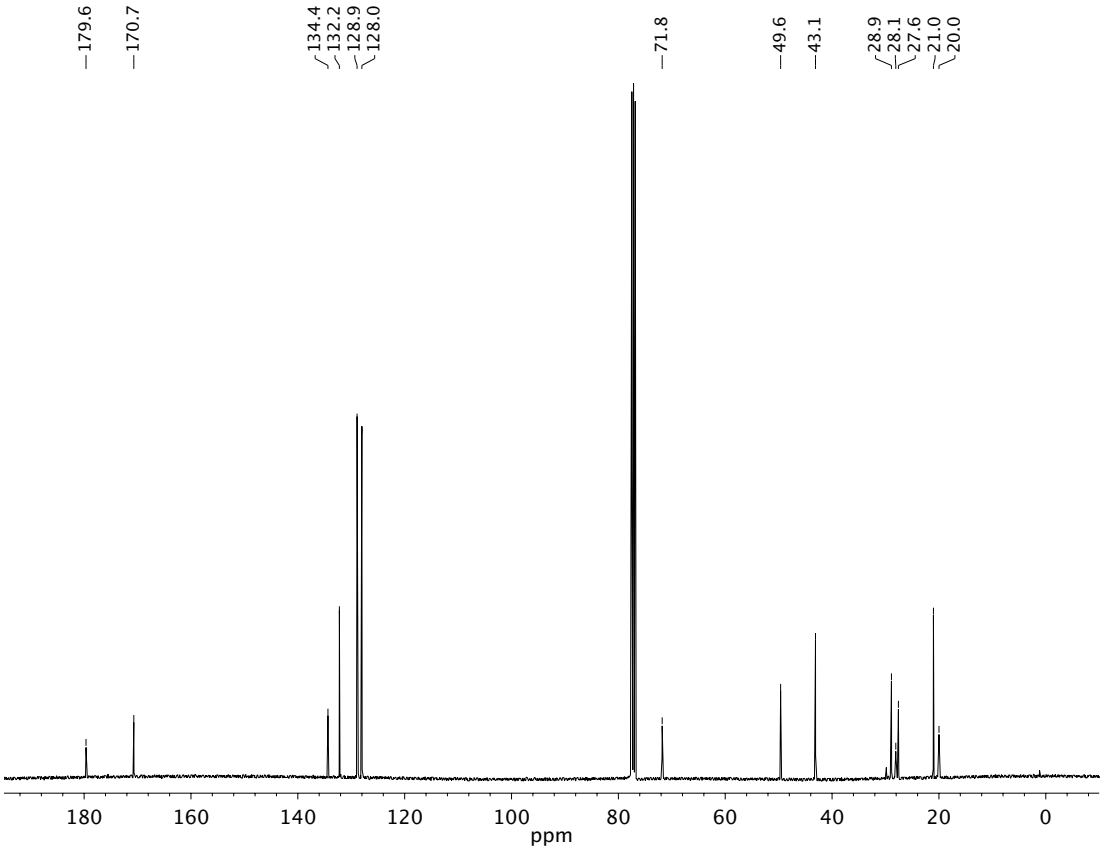
^{13}C NMR (100 MHz, $CDCl_3$) of compound **9b**.



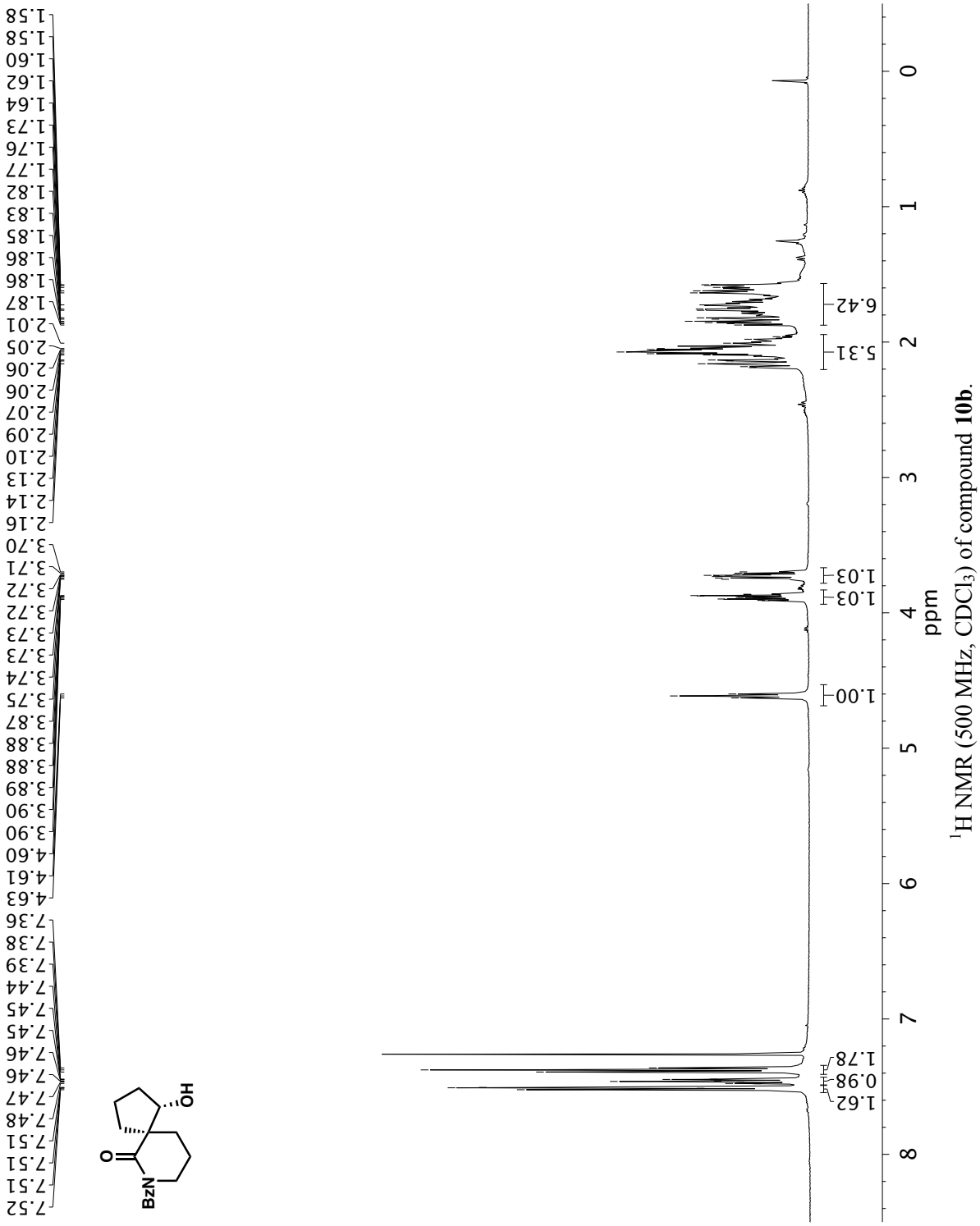
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9c**.



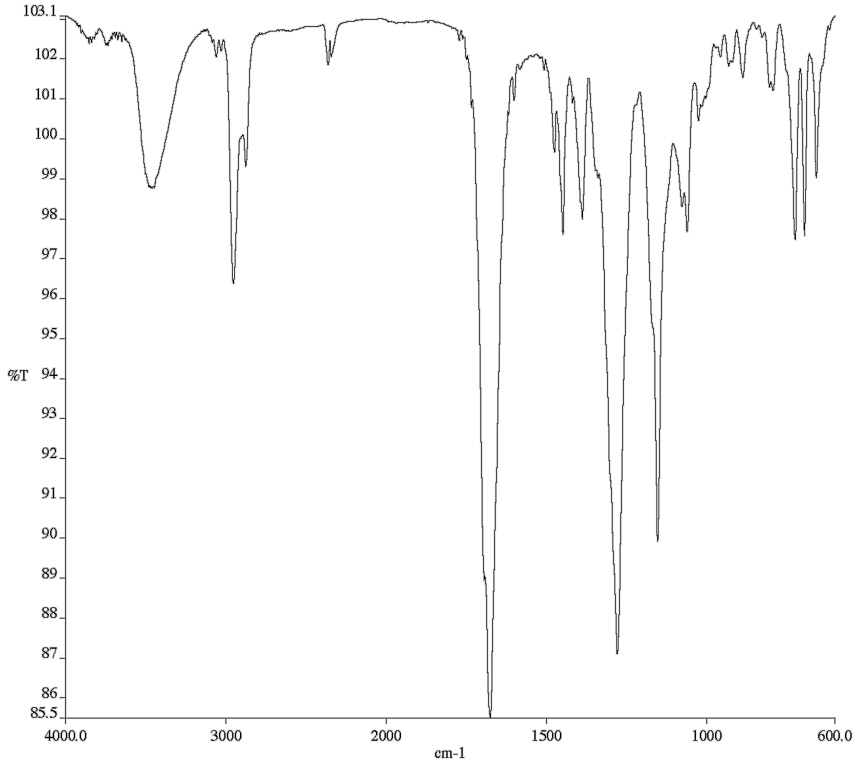
Infrared spectrum (Thin Film, NaCl) of compound **9c**.



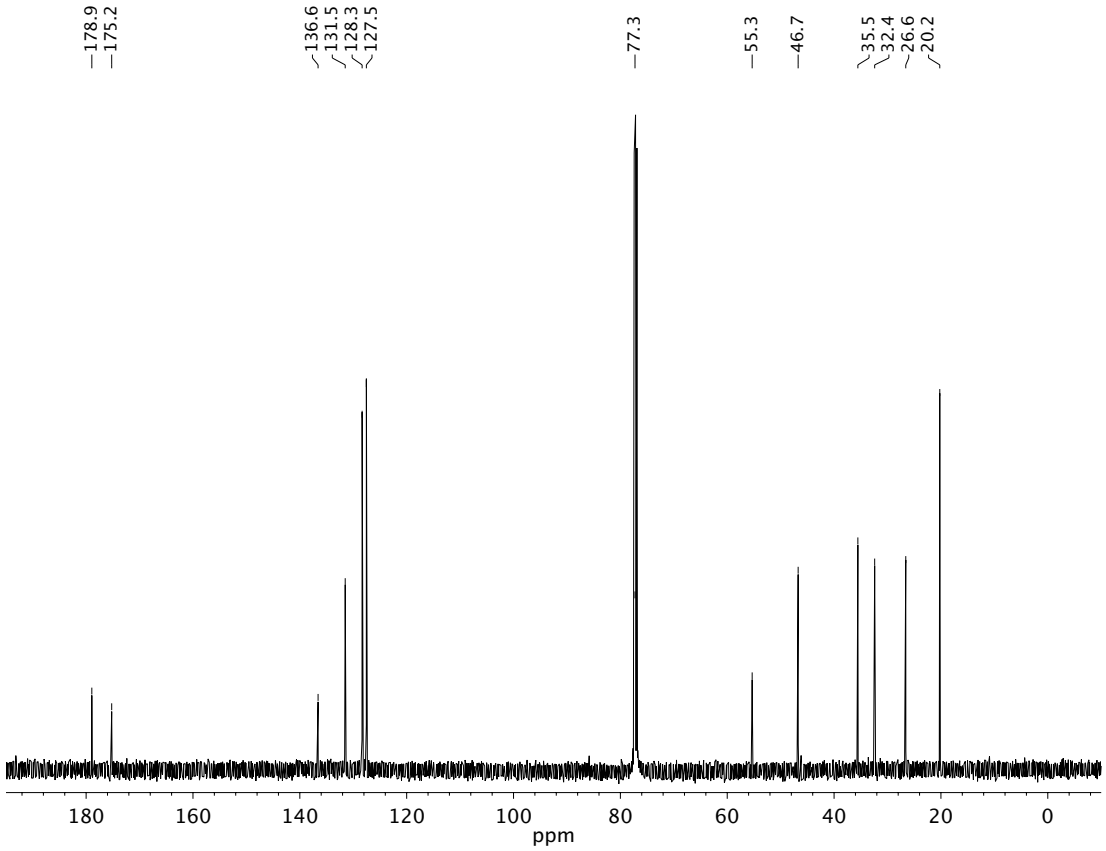
^{13}C NMR (100 MHz, $CDCl_3$) of compound **9c**.



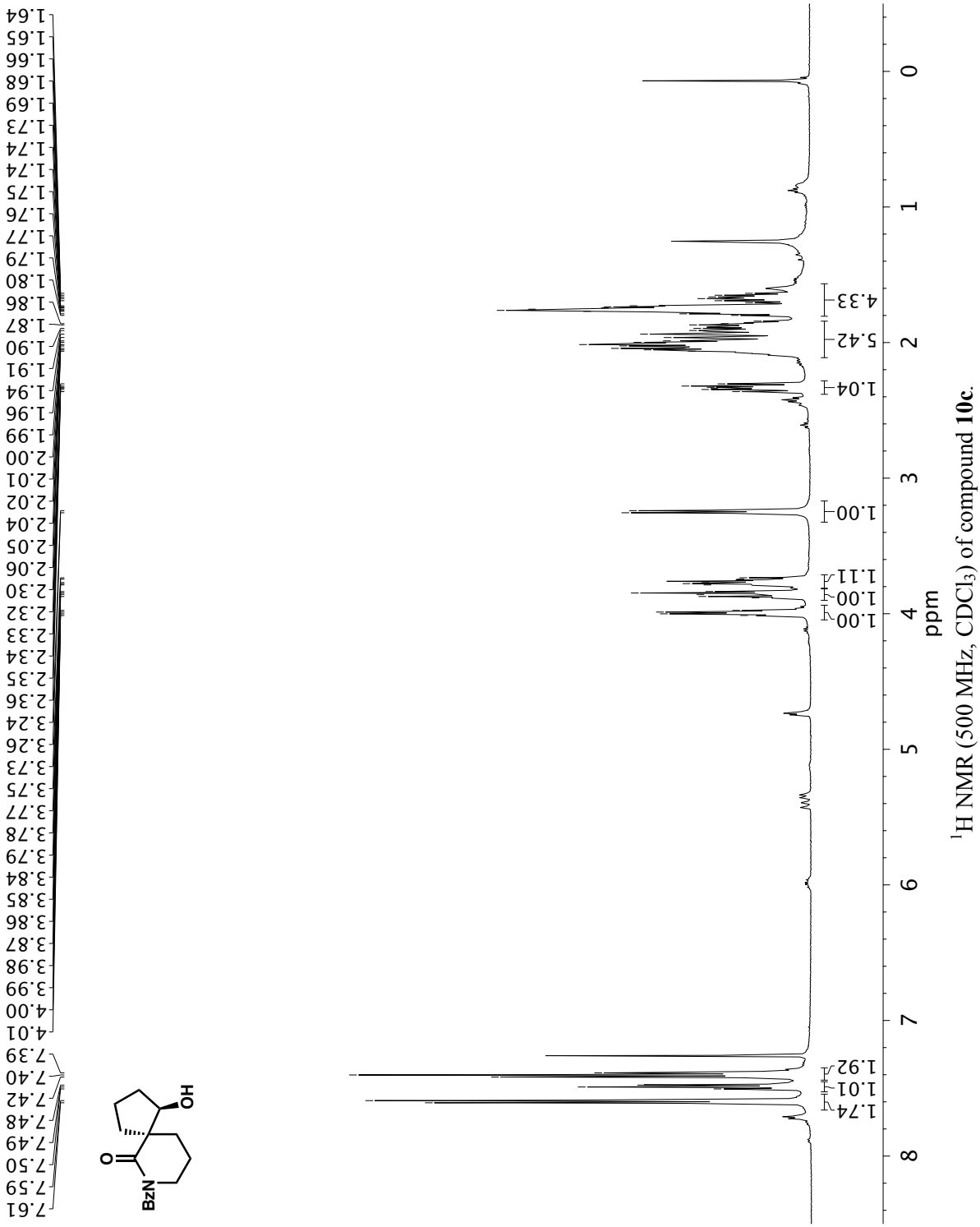
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10b**.



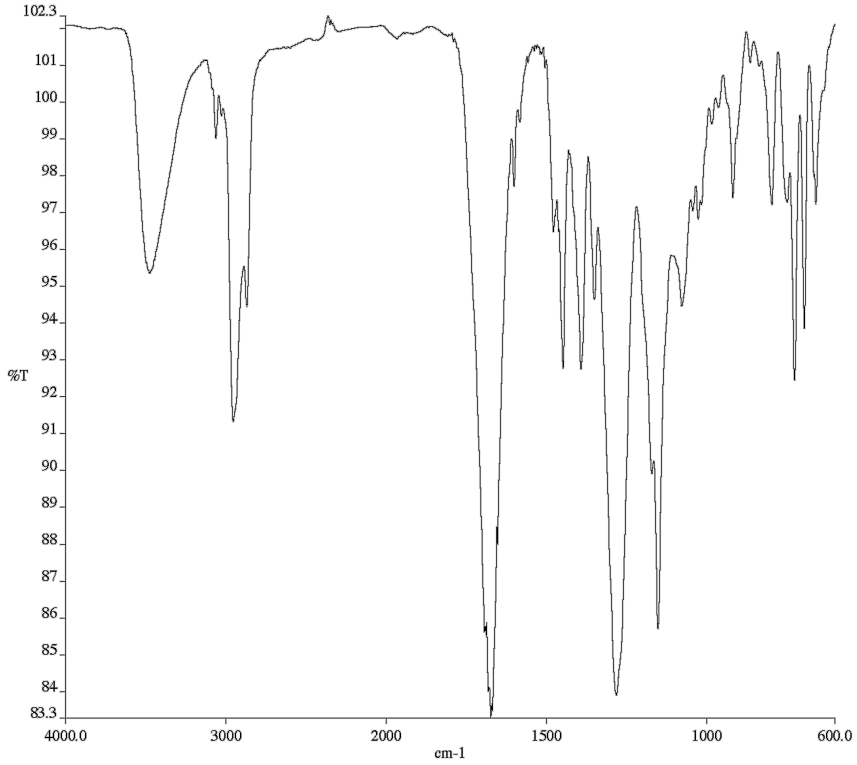
Infrared spectrum (Thin Film, NaCl) of compound **10b**.



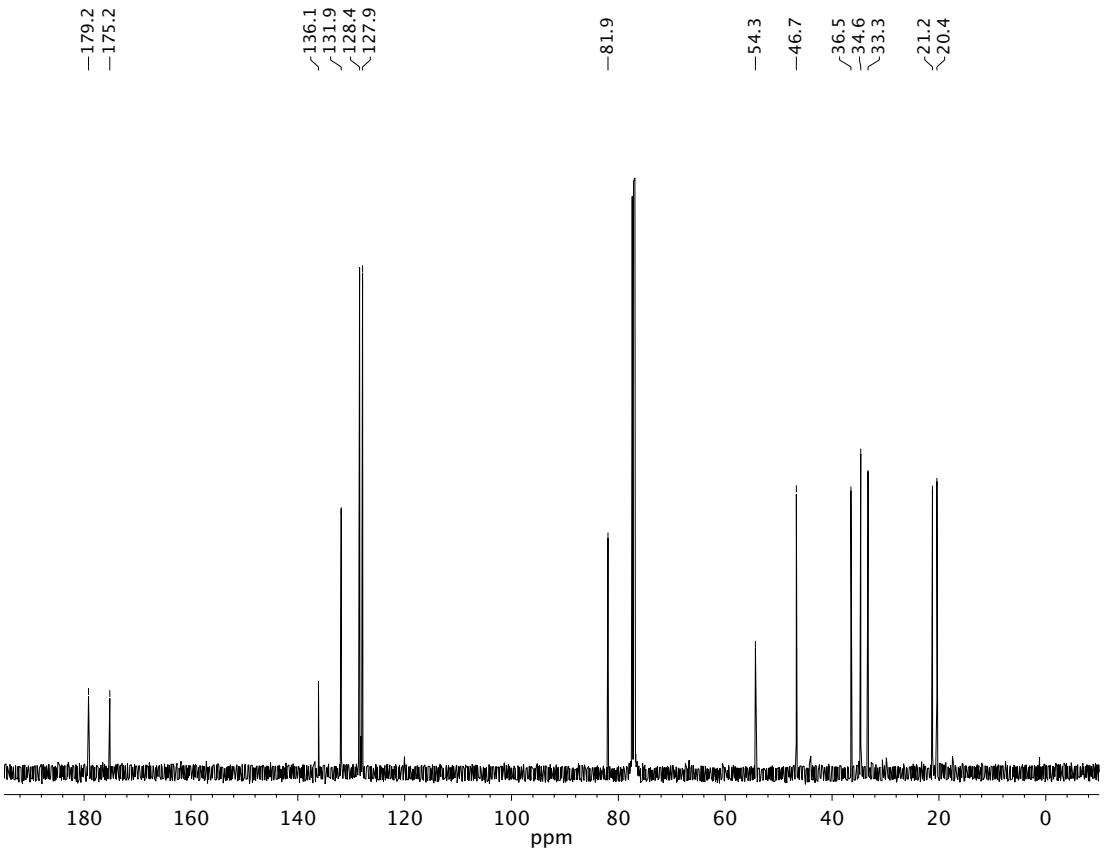
^{13}C NMR (125 MHz, $CDCl_3$) of compound **10b**.



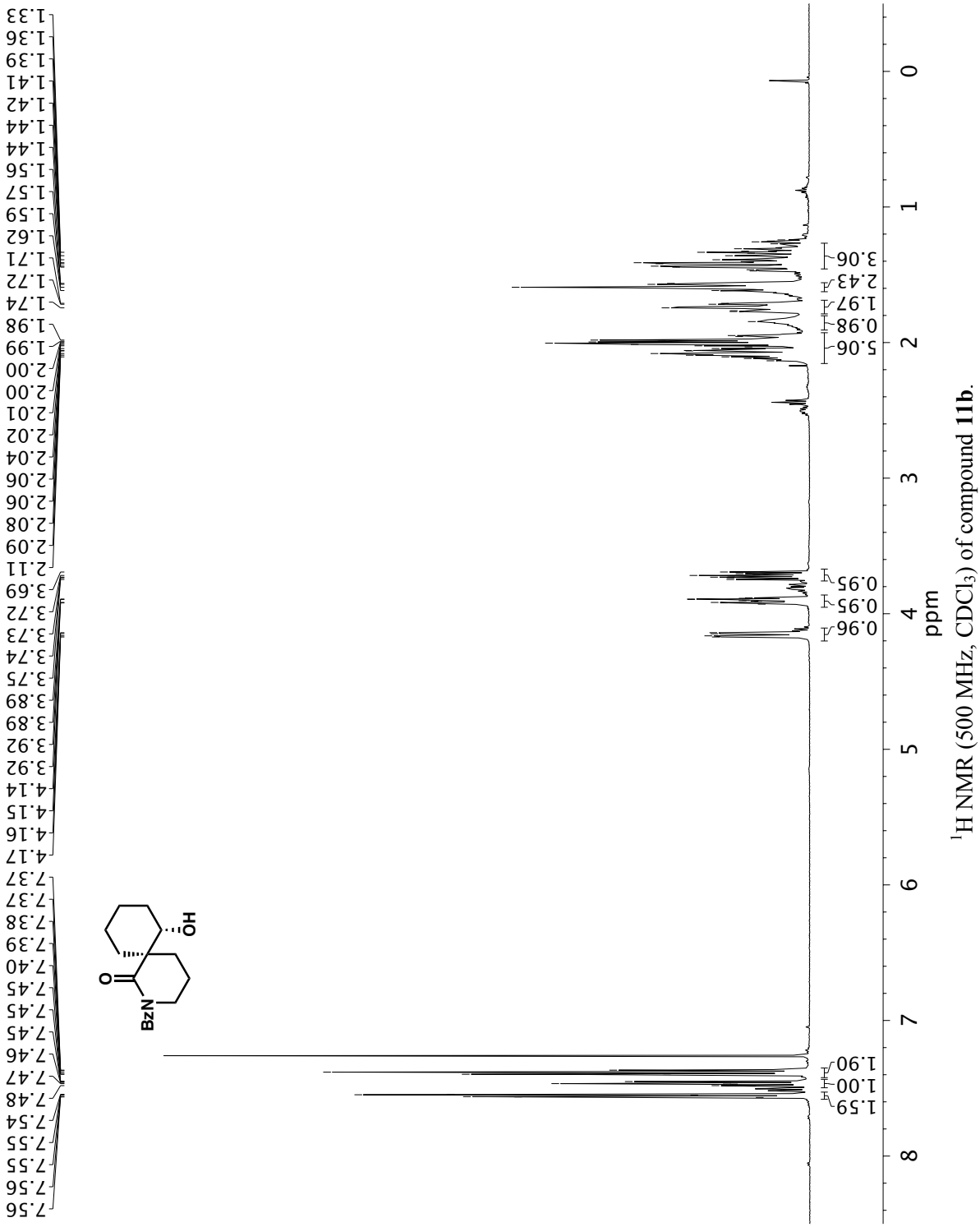
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10c**.



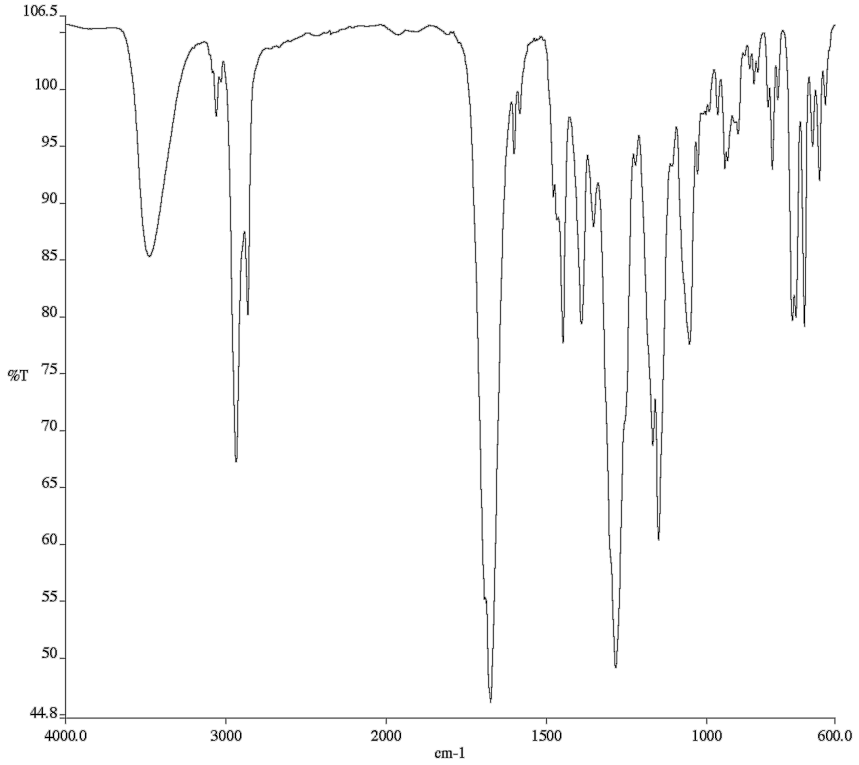
Infrared spectrum (Thin Film, NaCl) of compound **10c**.



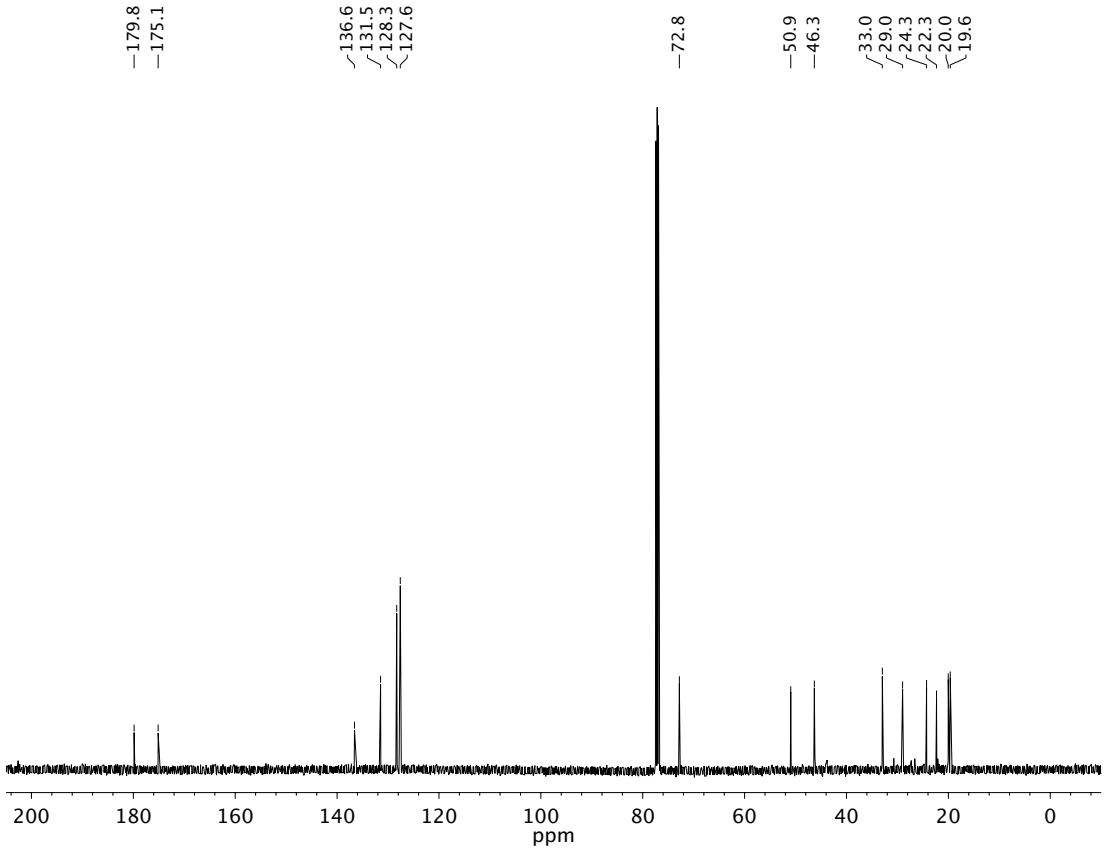
^{13}C NMR (125 MHz, $CDCl_3$) of compound **10c**.



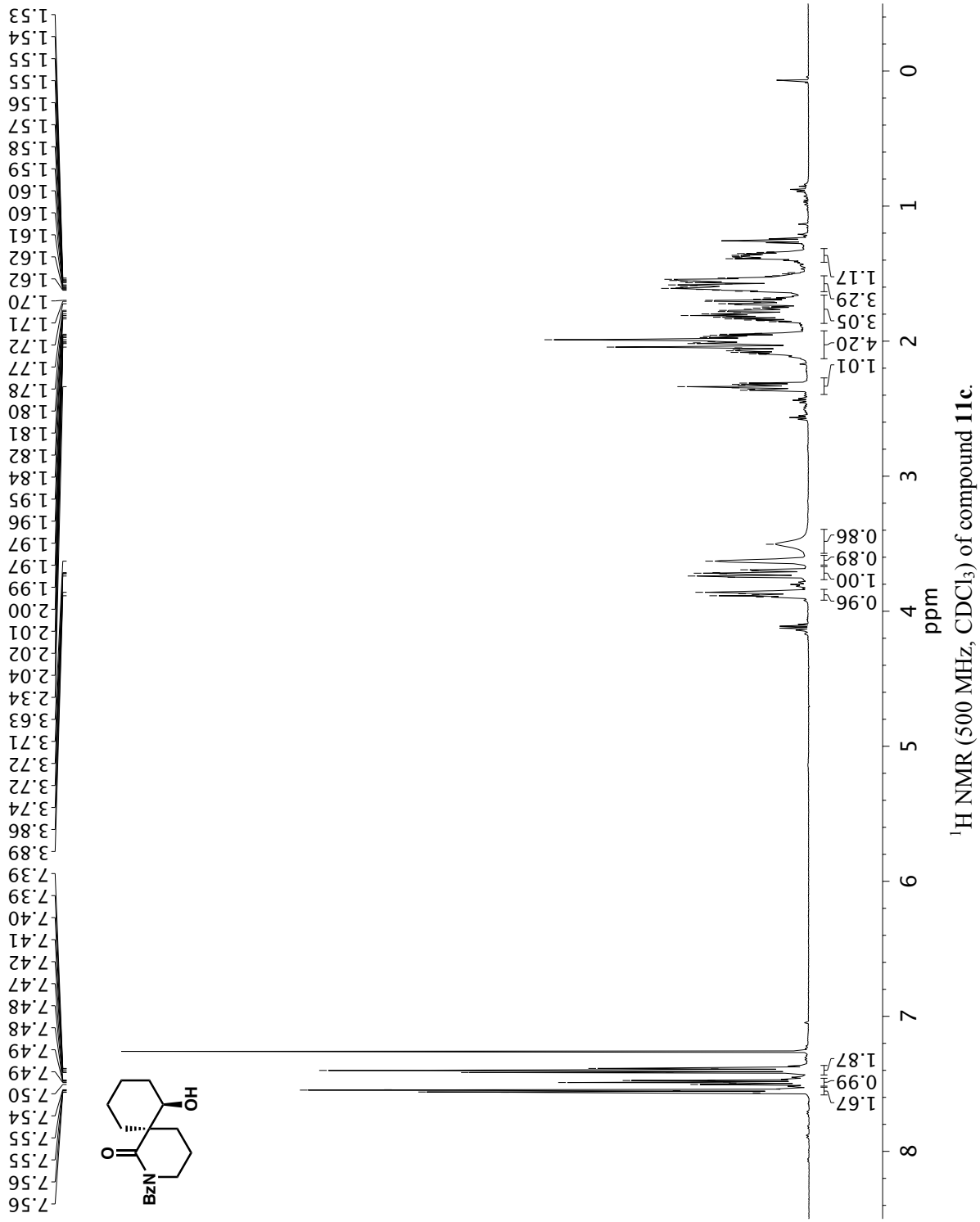
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11b**.



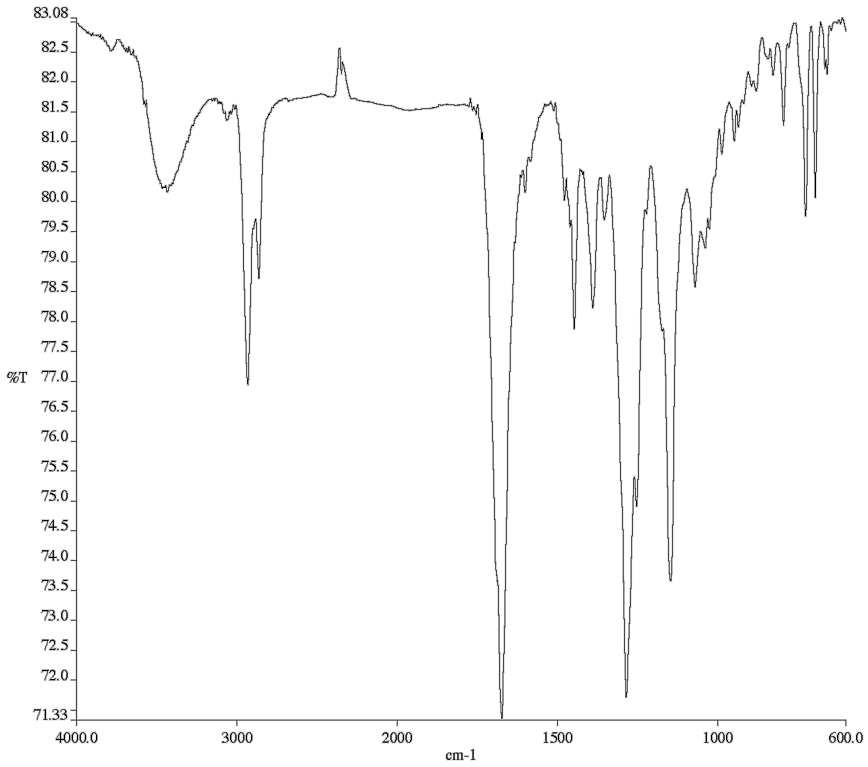
Infrared spectrum (Thin Film, NaCl) of compound **11b**.



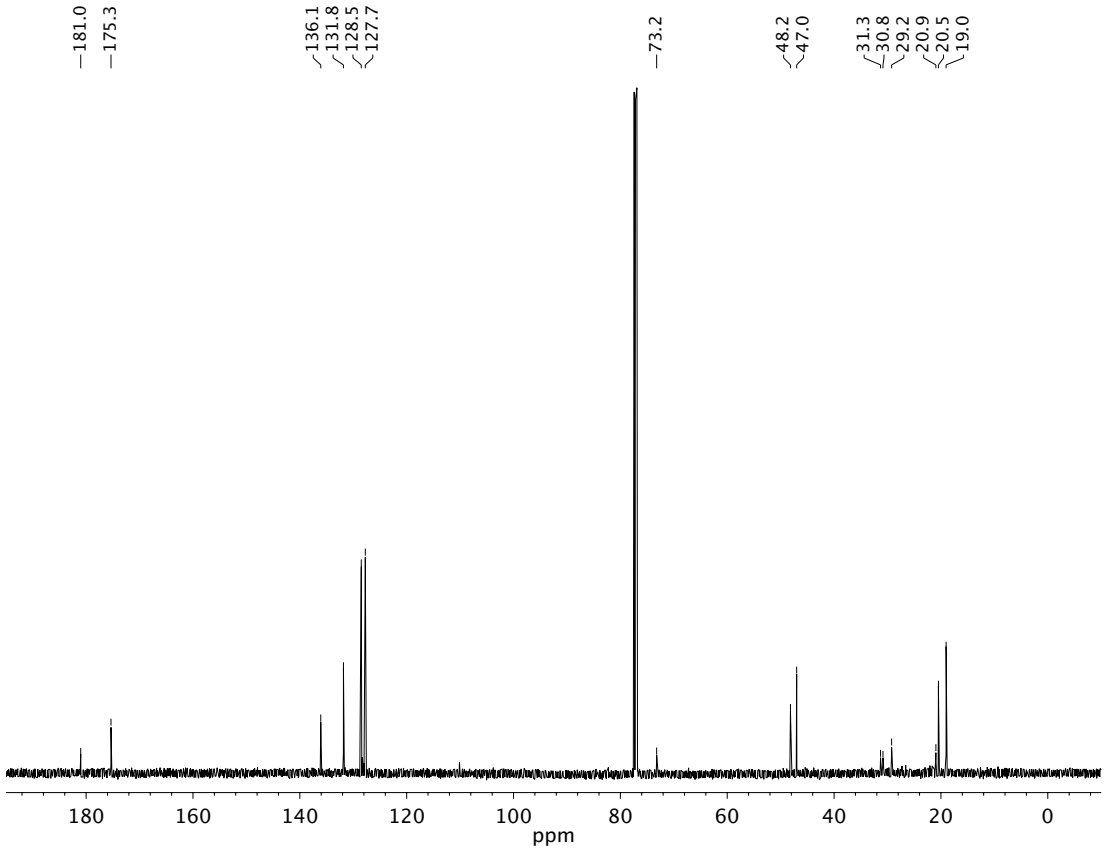
^{13}C NMR (125 MHz, $CDCl_3$) of compound **11b**.



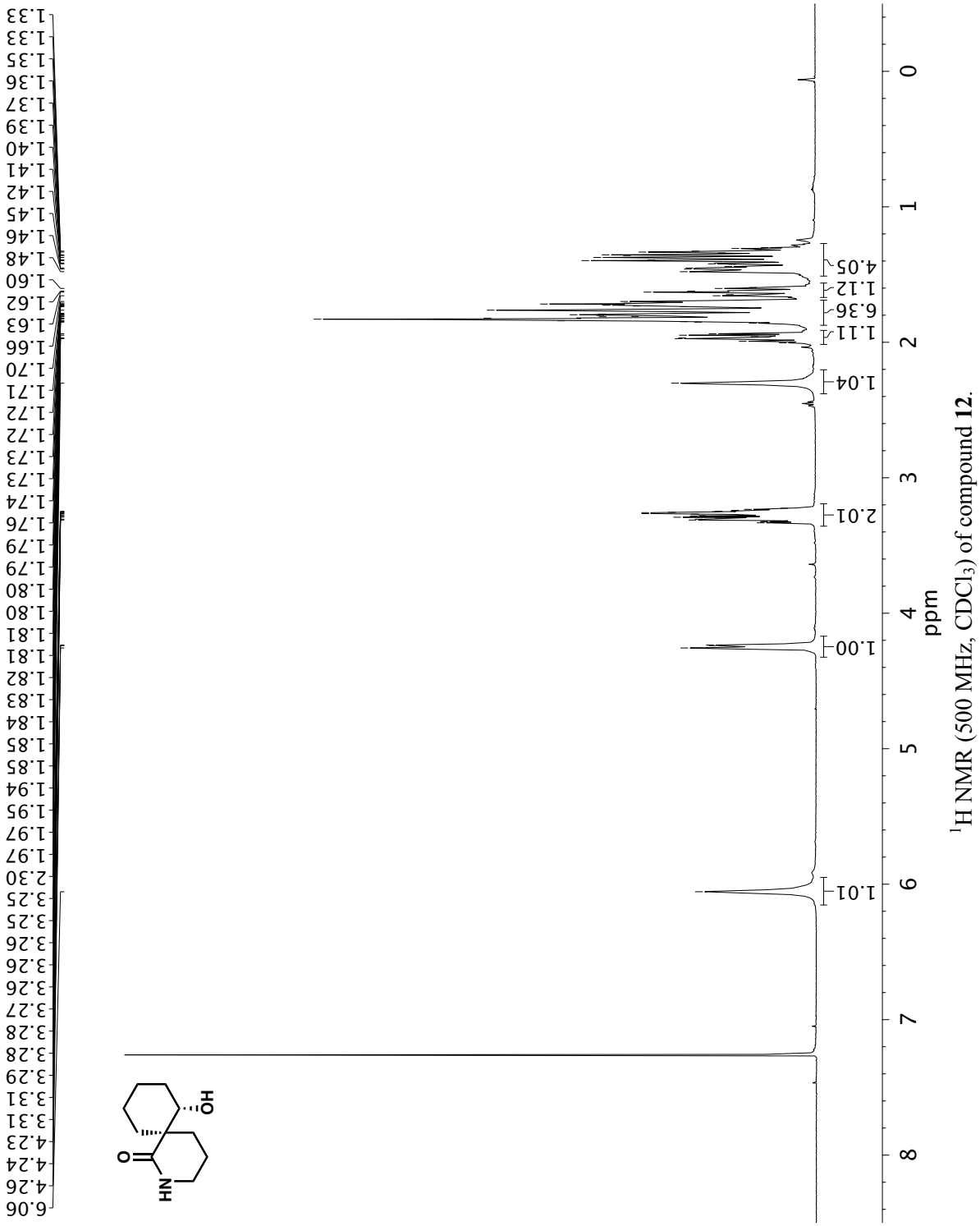
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11c**.



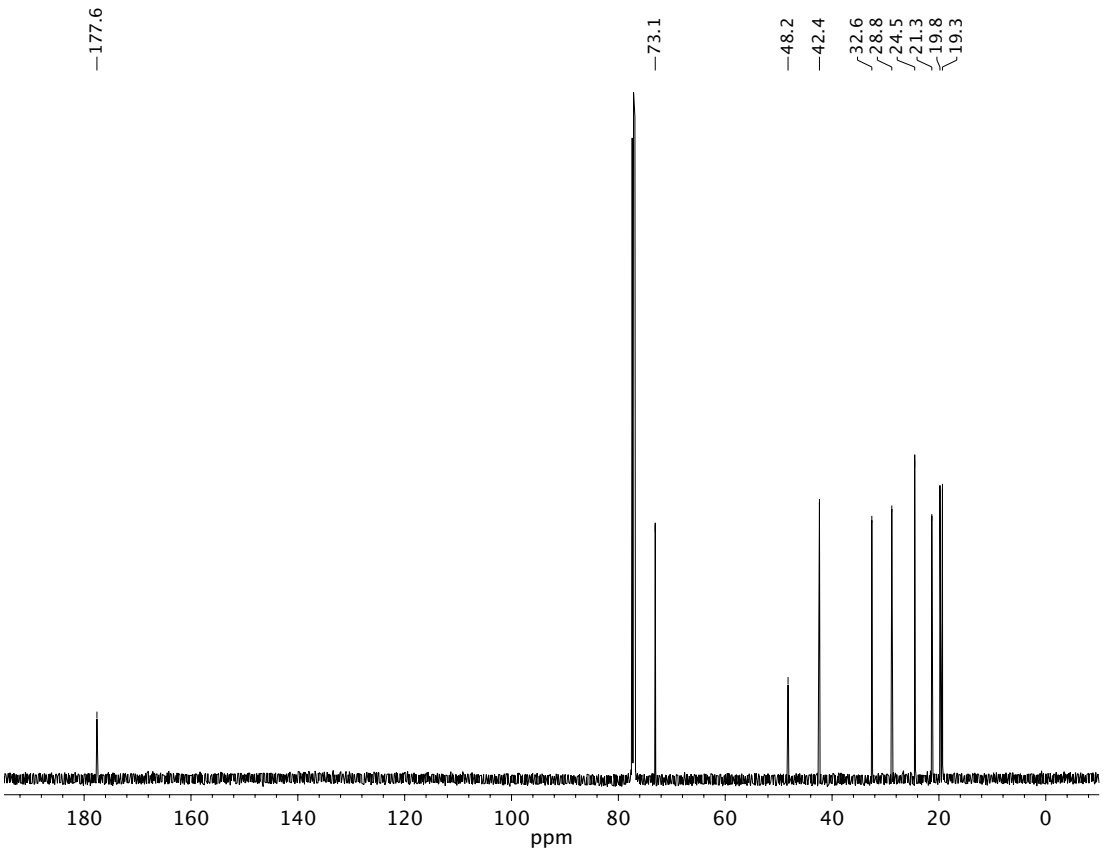
Infrared spectrum (Thin Film, NaCl) of compound **11c**.



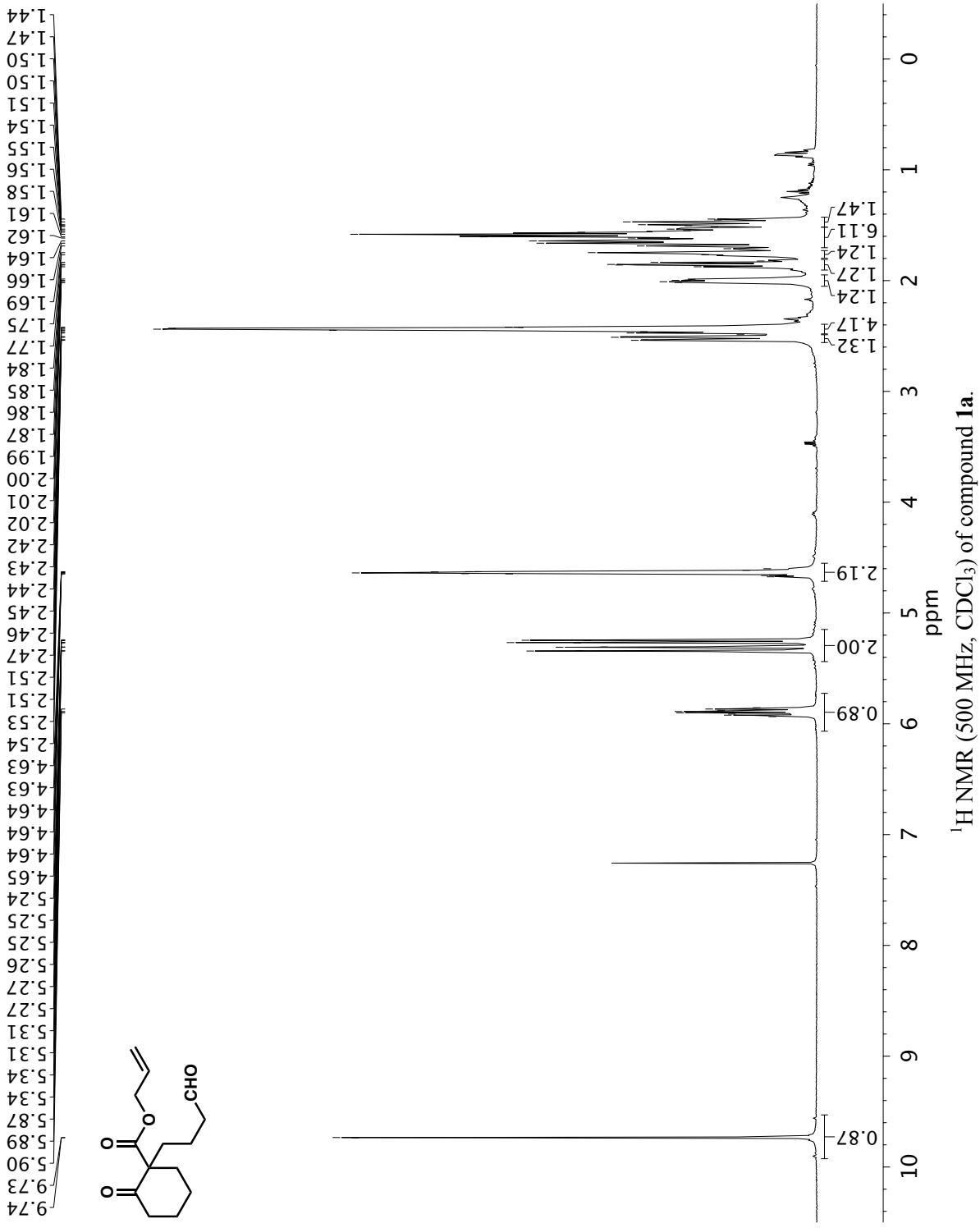
^{13}C NMR (125 MHz, $CDCl_3$) of compound **11c**.



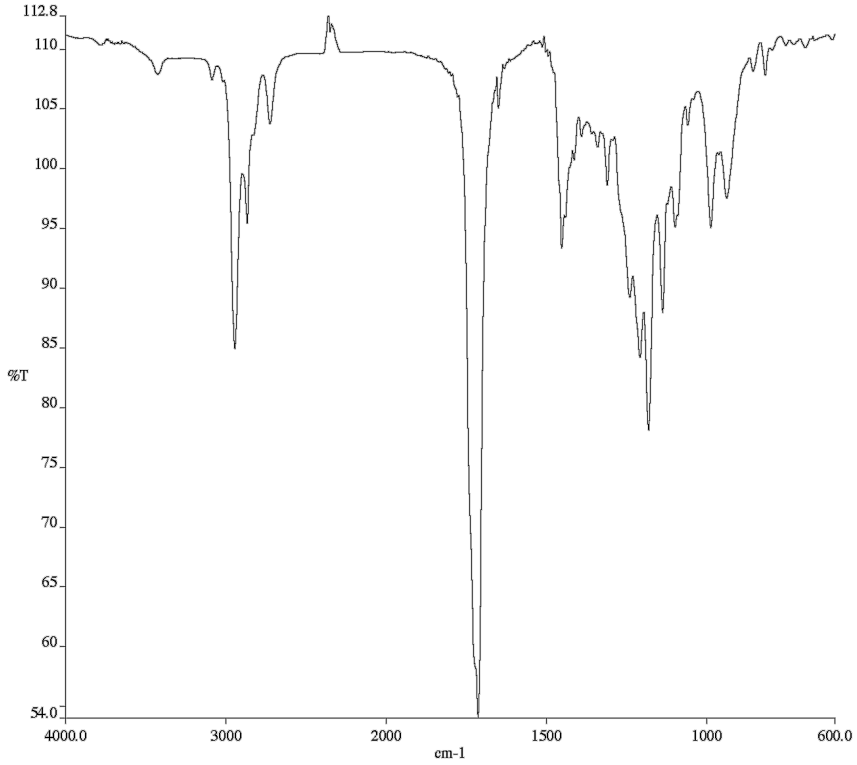
^{1}H NMR (500 MHz, $CDCl_3$) of compound **12**.



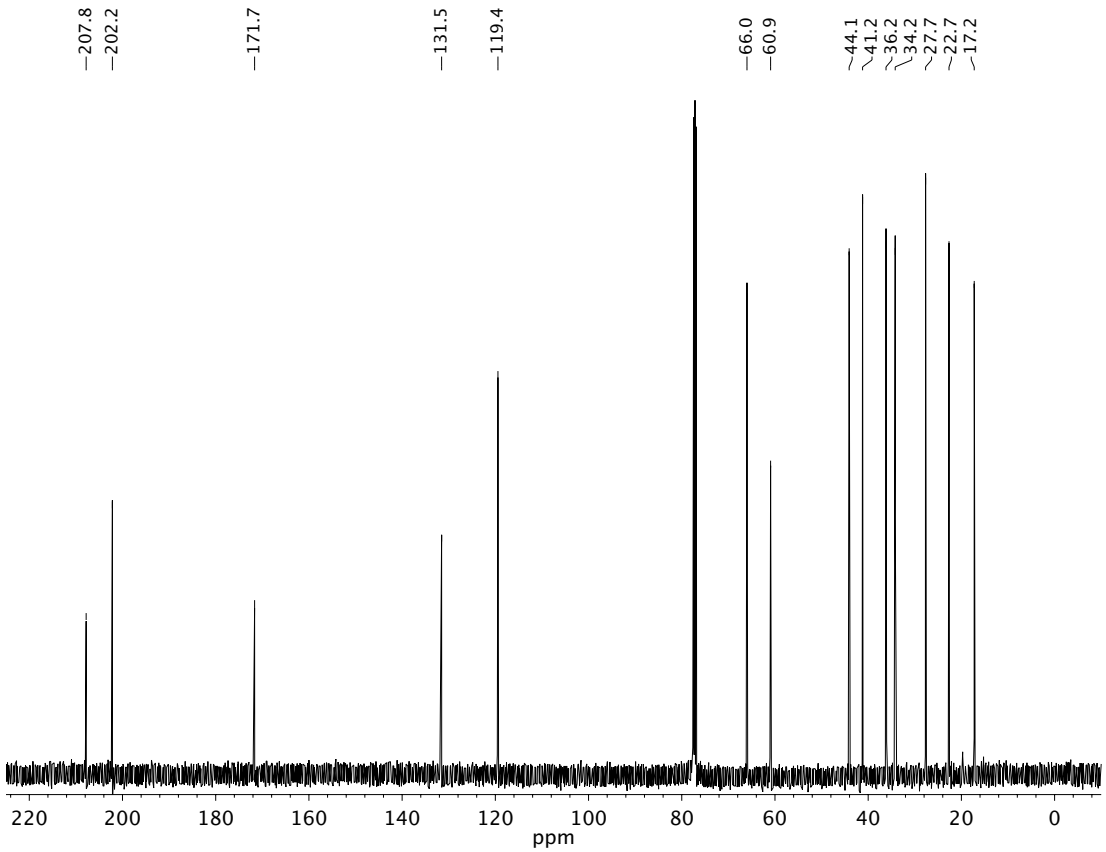
^{13}C NMR (125 MHz, $CDCl_3$) of compound **12**.



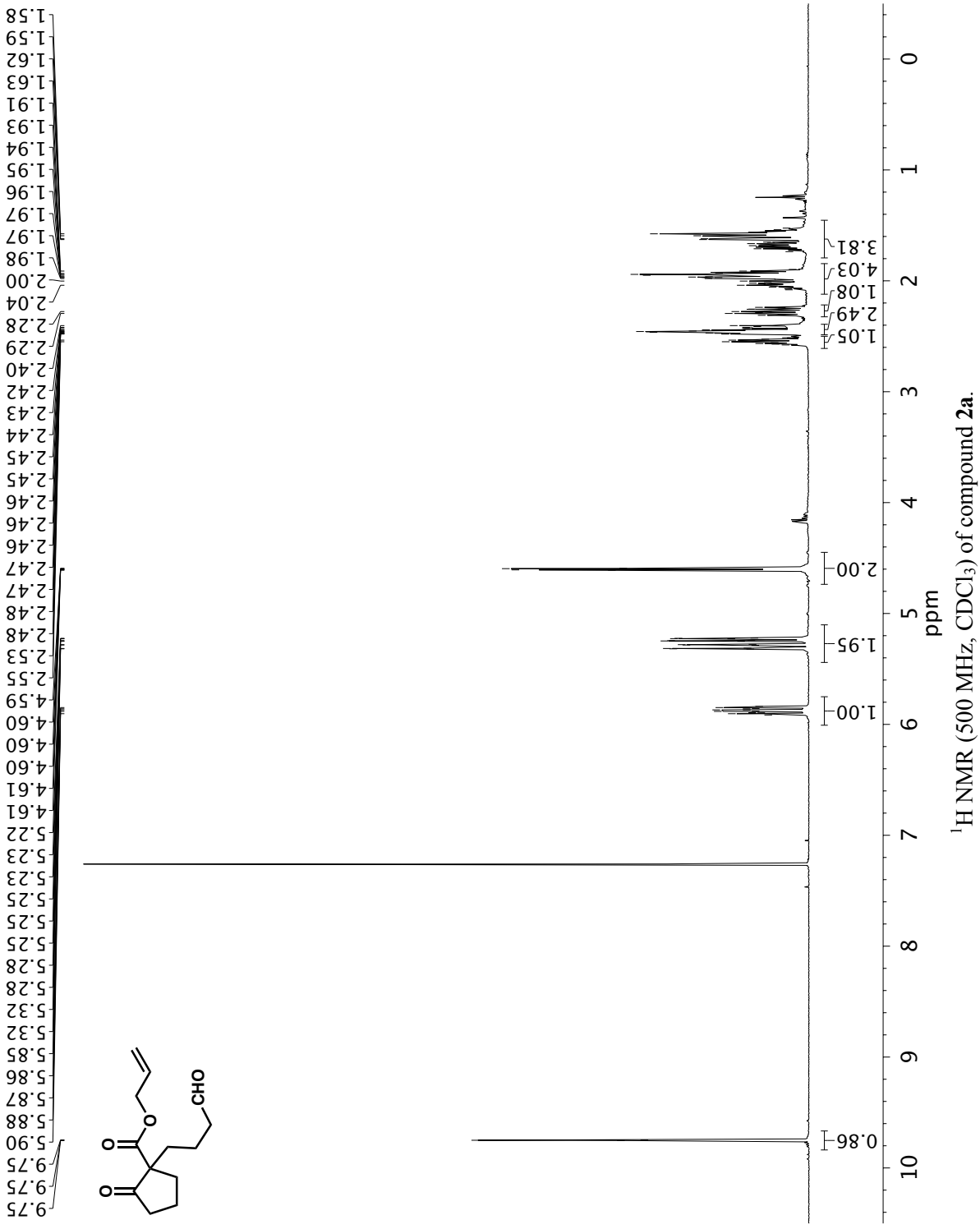
^{1}H NMR (500 MHz, $CDCl_3$) of compound **1a**.



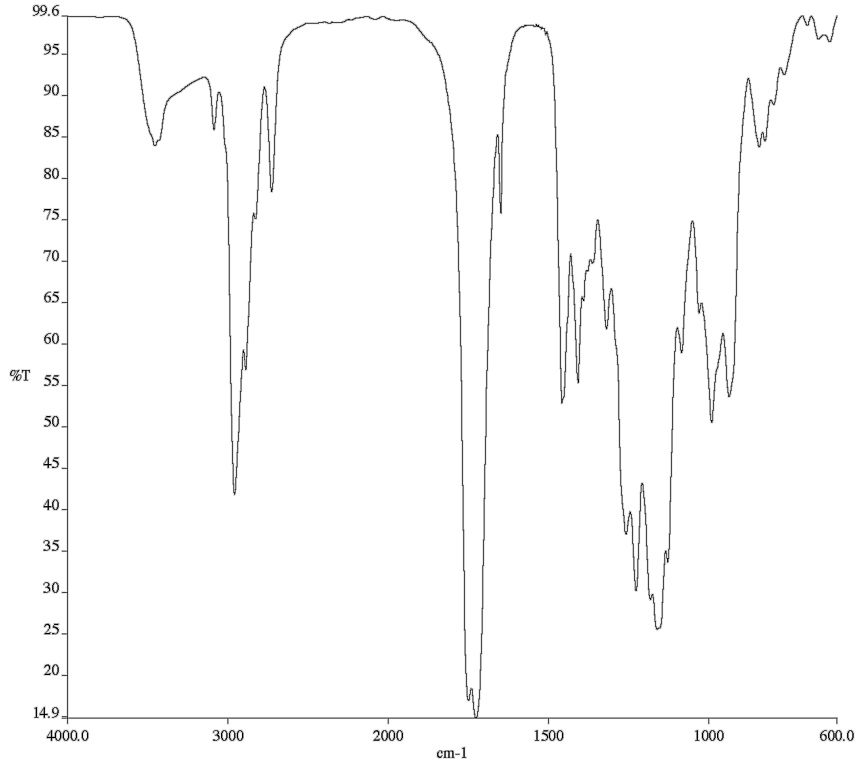
Infrared spectrum (Thin Film, NaCl) of compound **1a**.



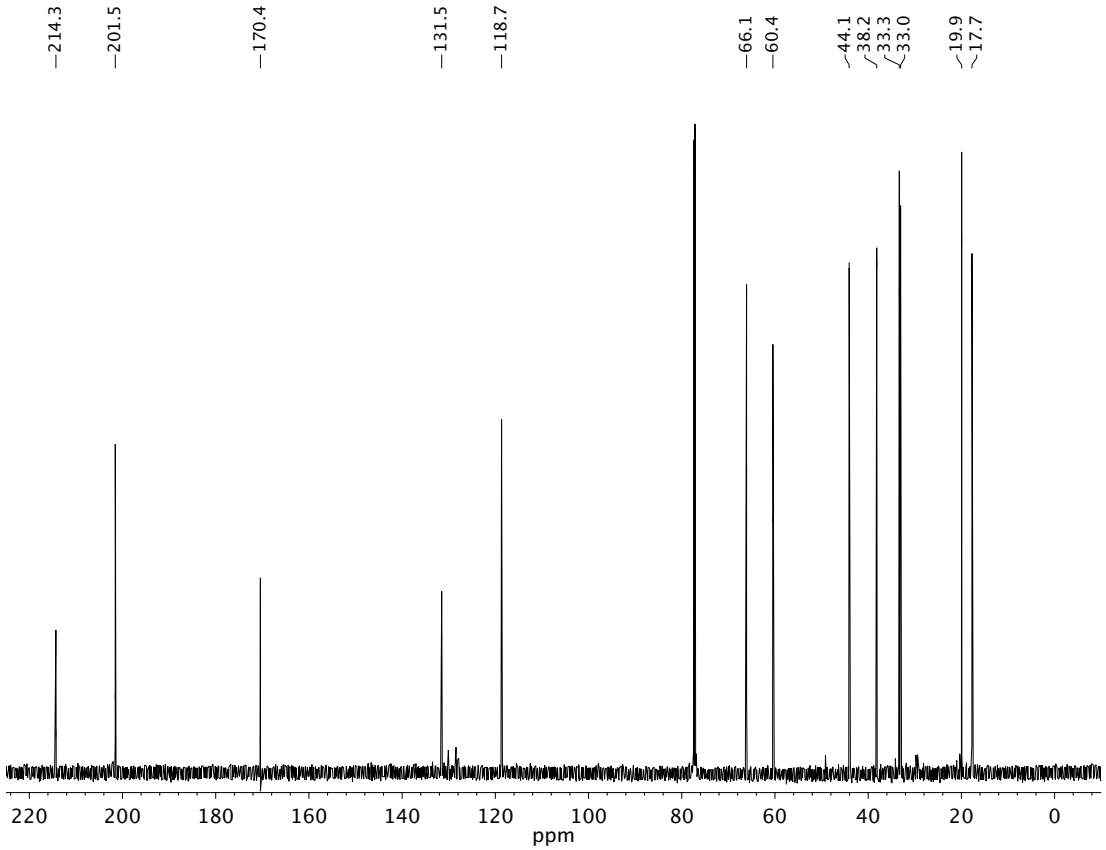
^{13}C NMR (125 MHz, $CDCl_3$) of compound **1a**.



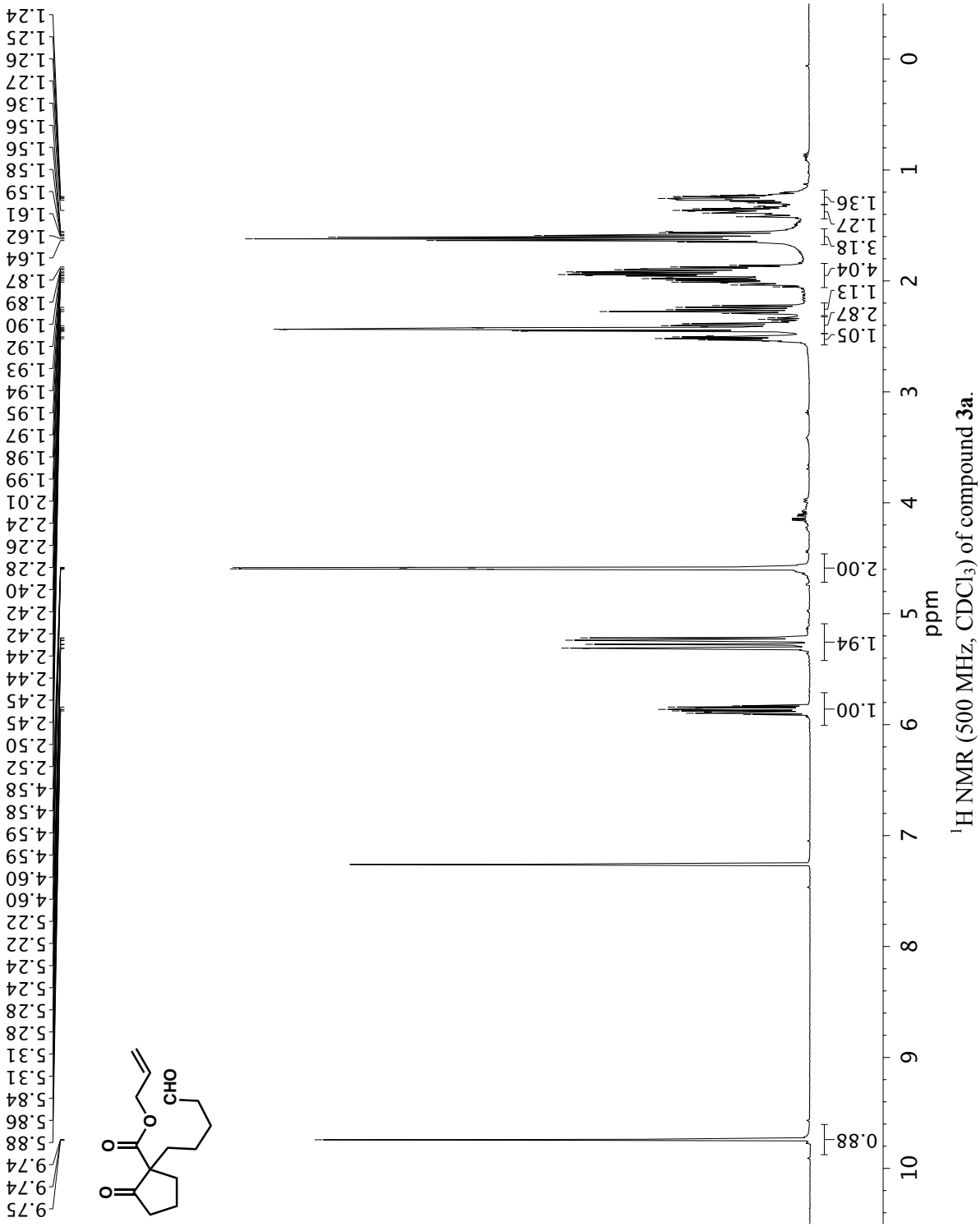
^{1}H NMR (500 MHz, $CDCl_3$) of compound **2a**.



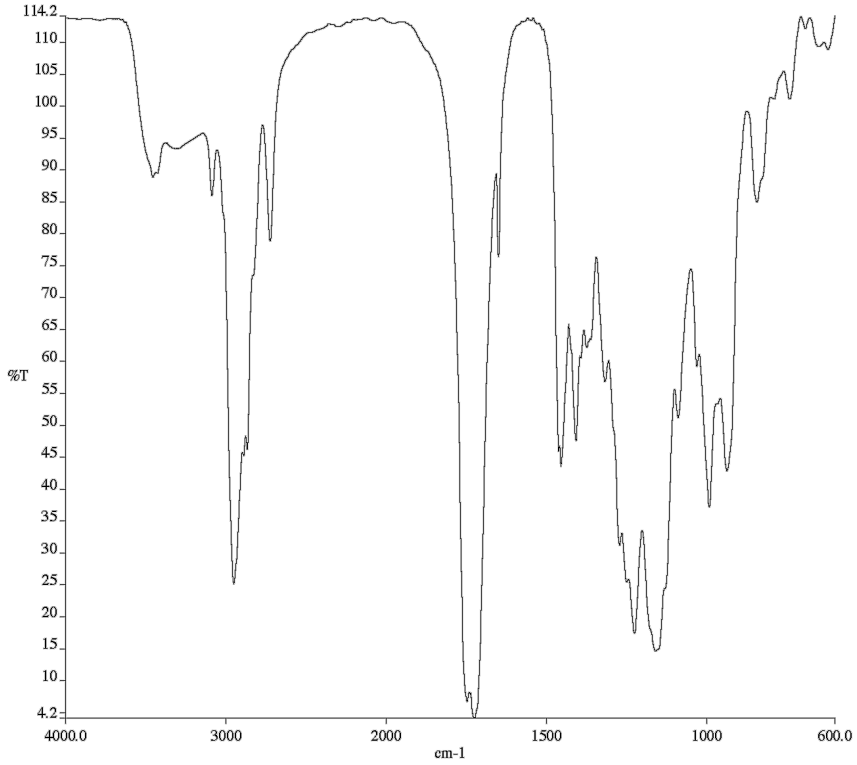
Infrared spectrum (Thin Film, NaCl) of compound **2a**.



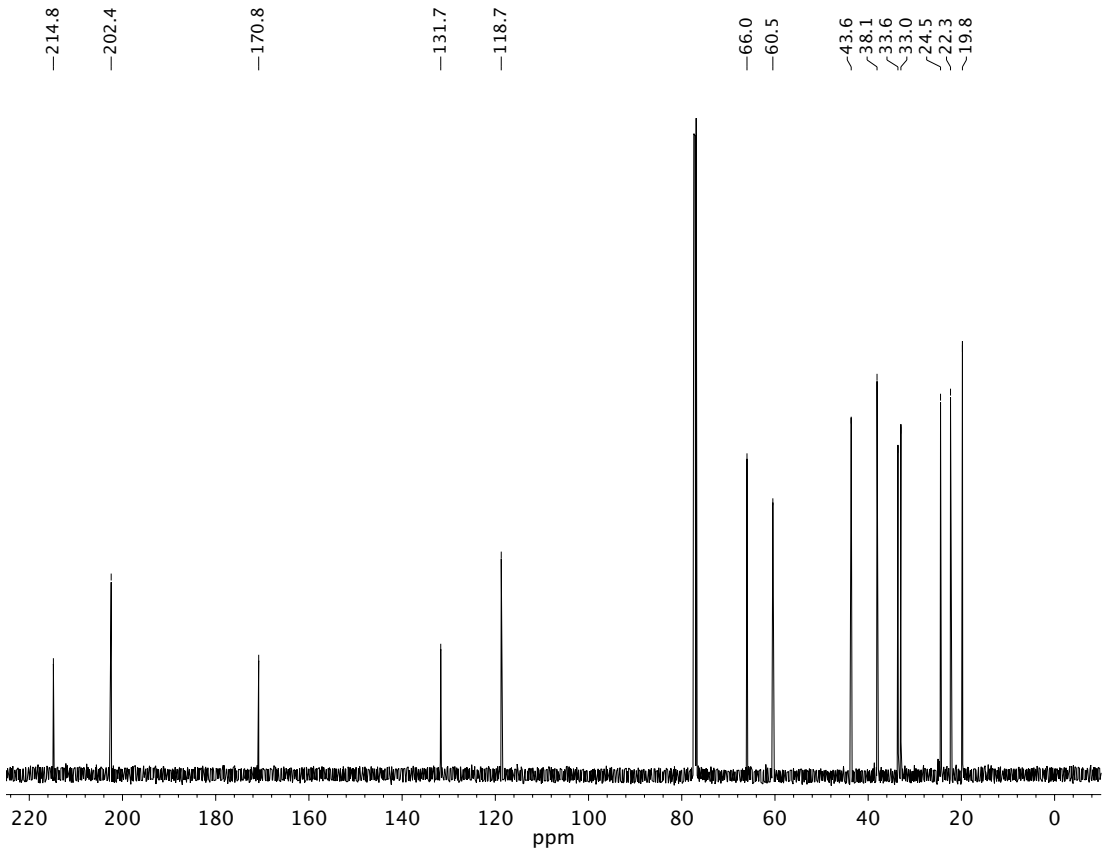
^{13}C NMR (125 MHz, $CDCl_3$) of compound **2a**.



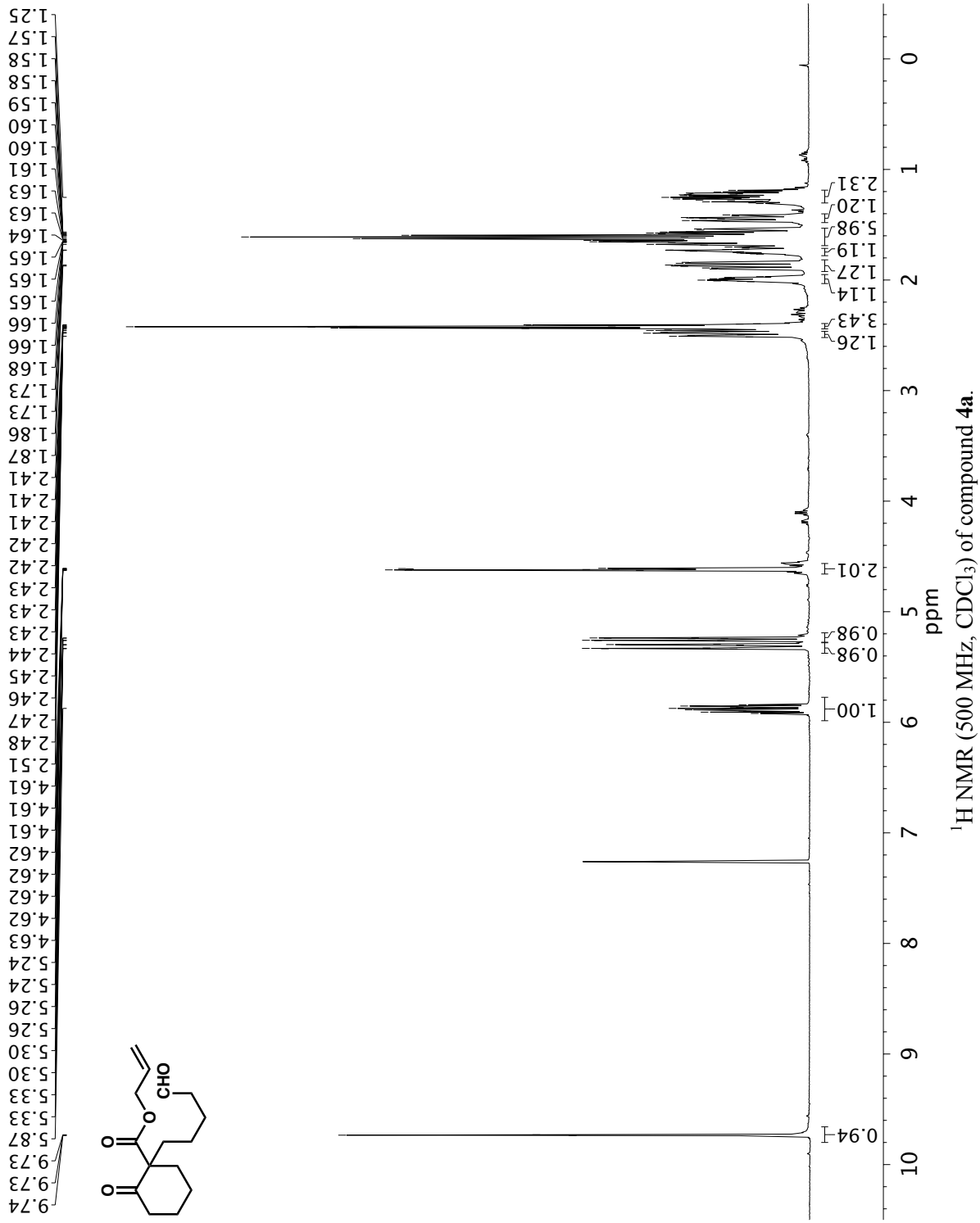
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3a**.



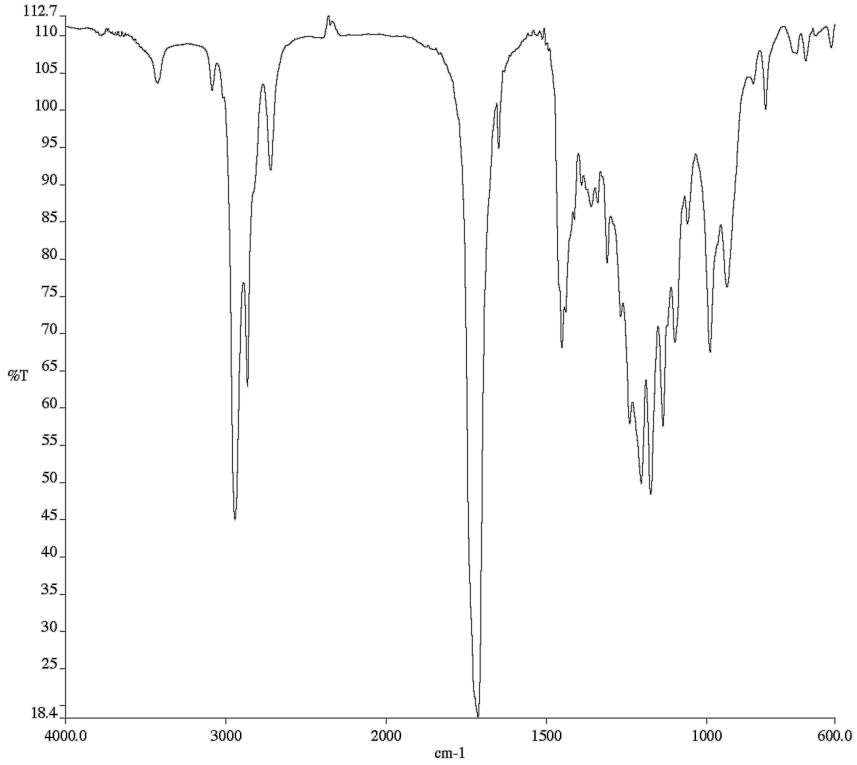
Infrared spectrum (Thin Film, NaCl) of compound **3a**.



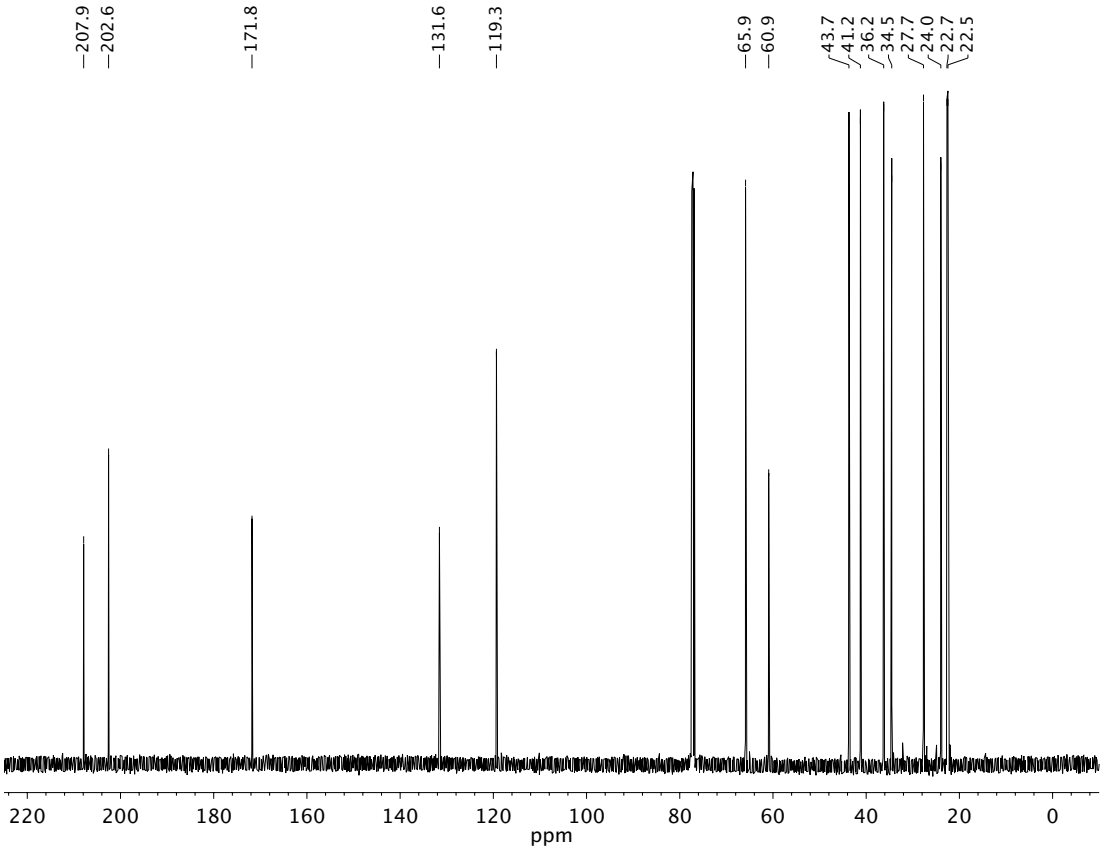
^{13}C NMR (125 MHz, $CDCl_3$) of compound **3a**.



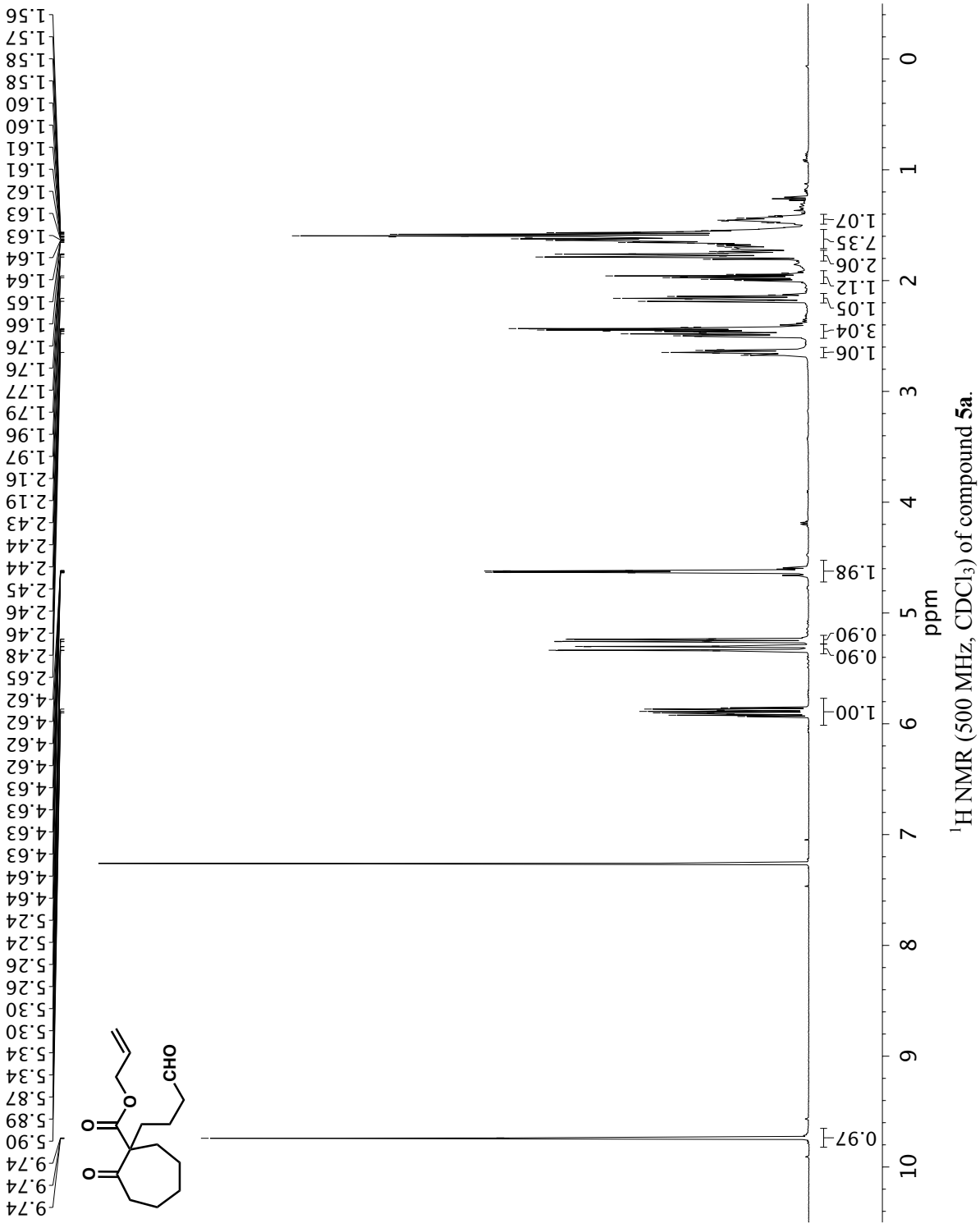
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4a**.



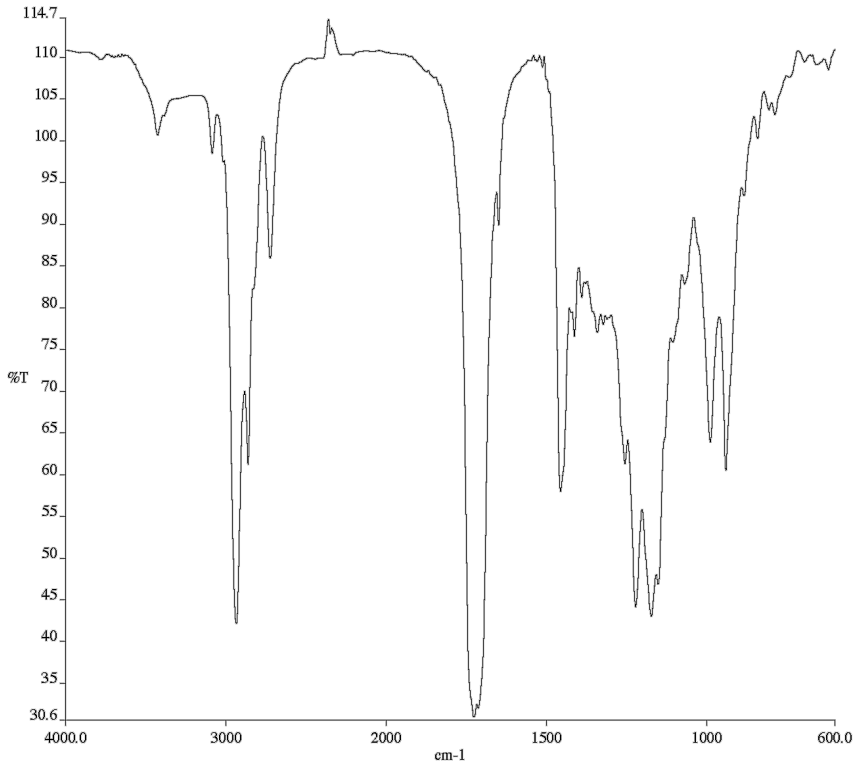
Infrared spectrum (Thin Film, NaCl) of compound **4a**.



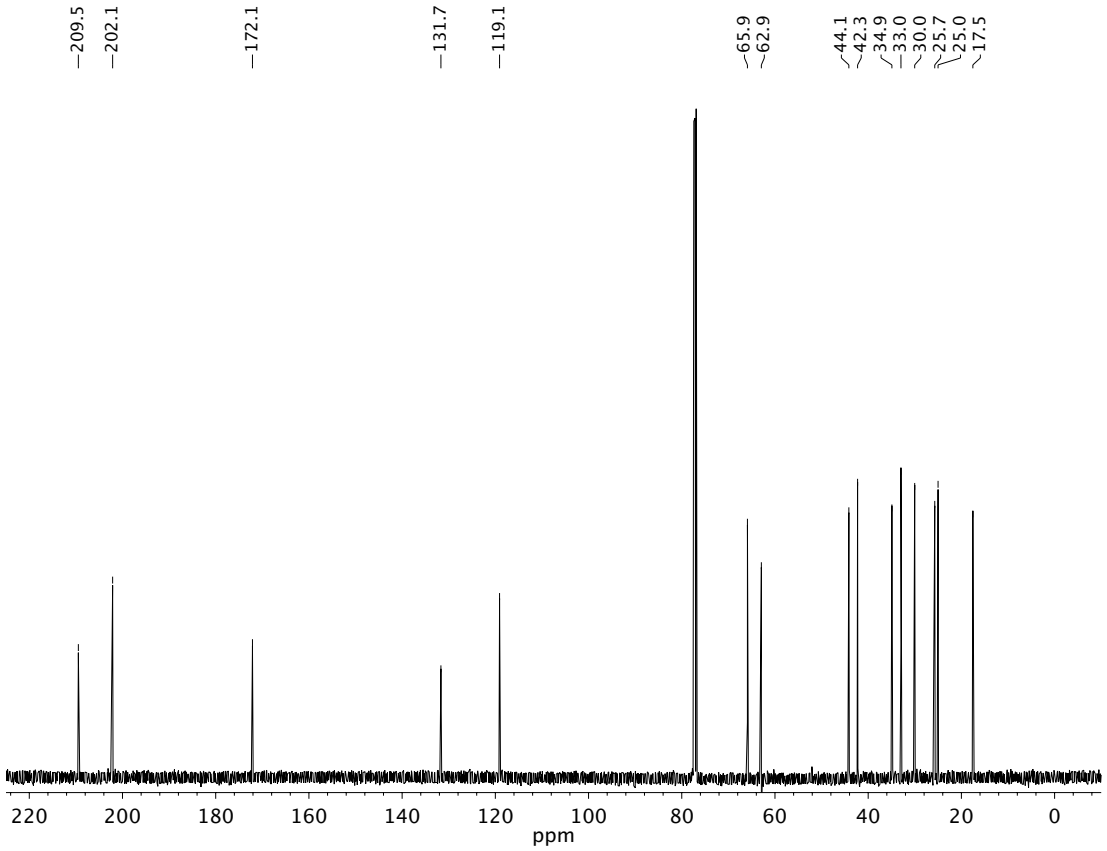
^{13}C NMR (125 MHz, $CDCl_3$) of compound **4a**.



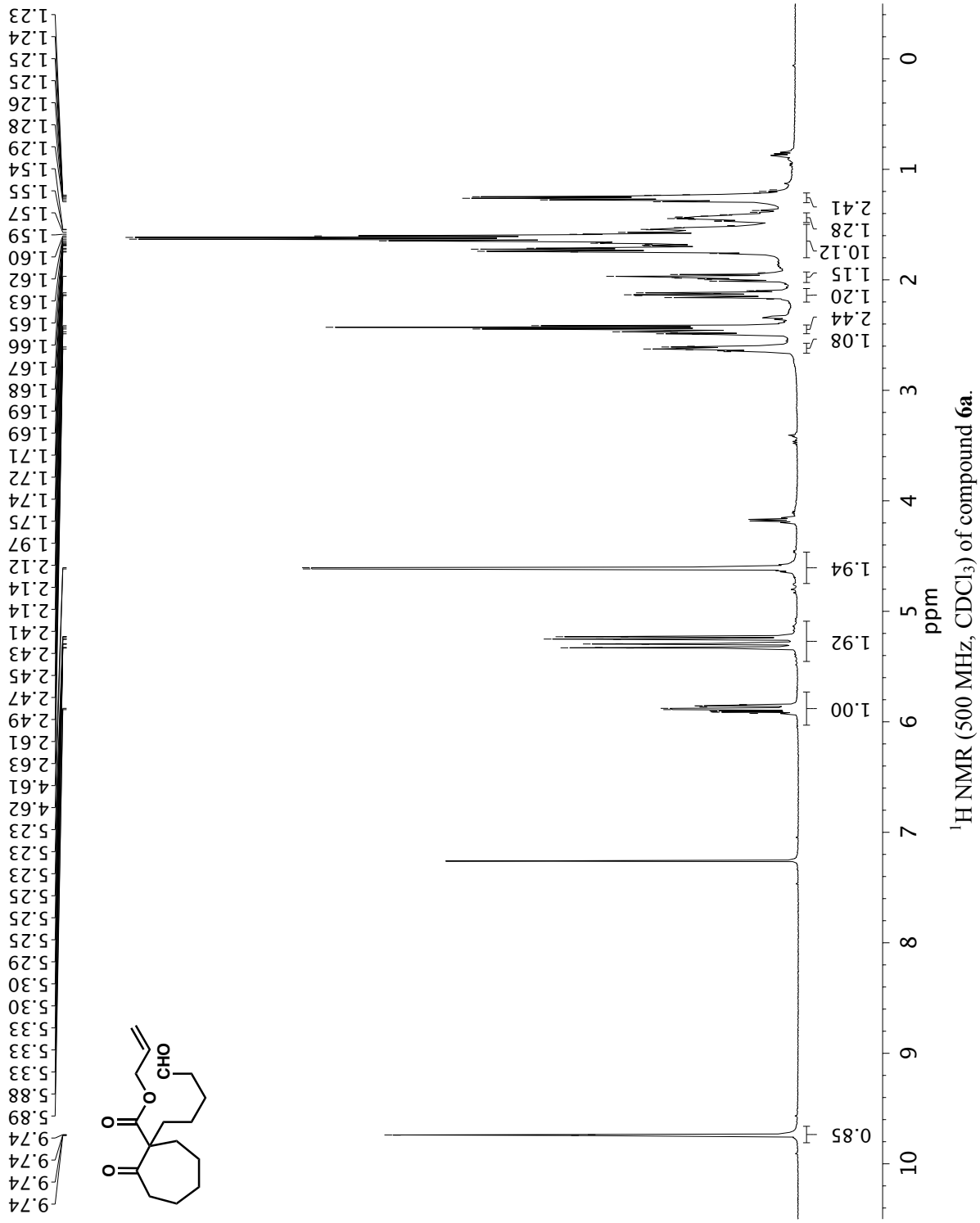
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5a**.



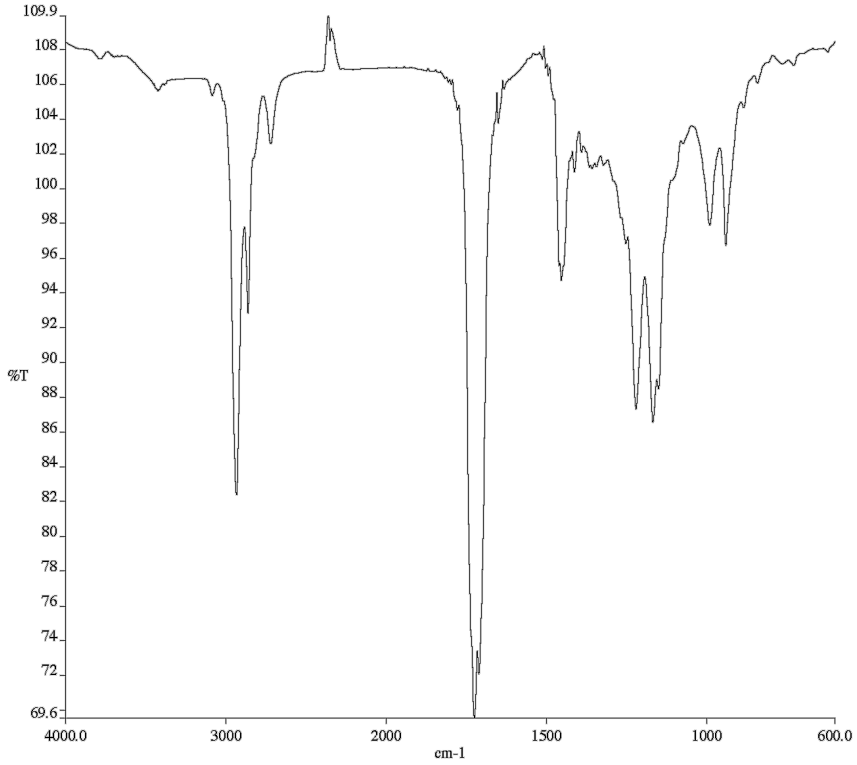
Infrared spectrum (Thin Film, NaCl) of compound **5a**.



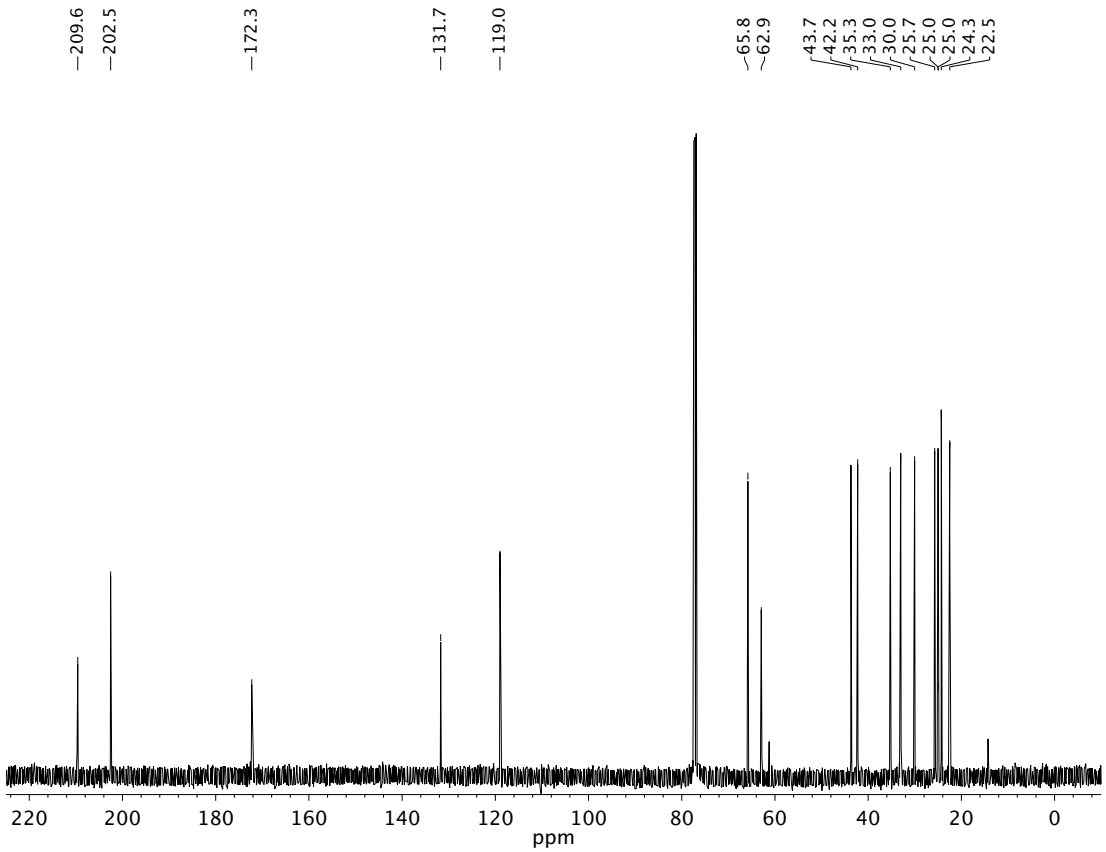
^{13}C NMR (125 MHz, $CDCl_3$) of compound **5a**.



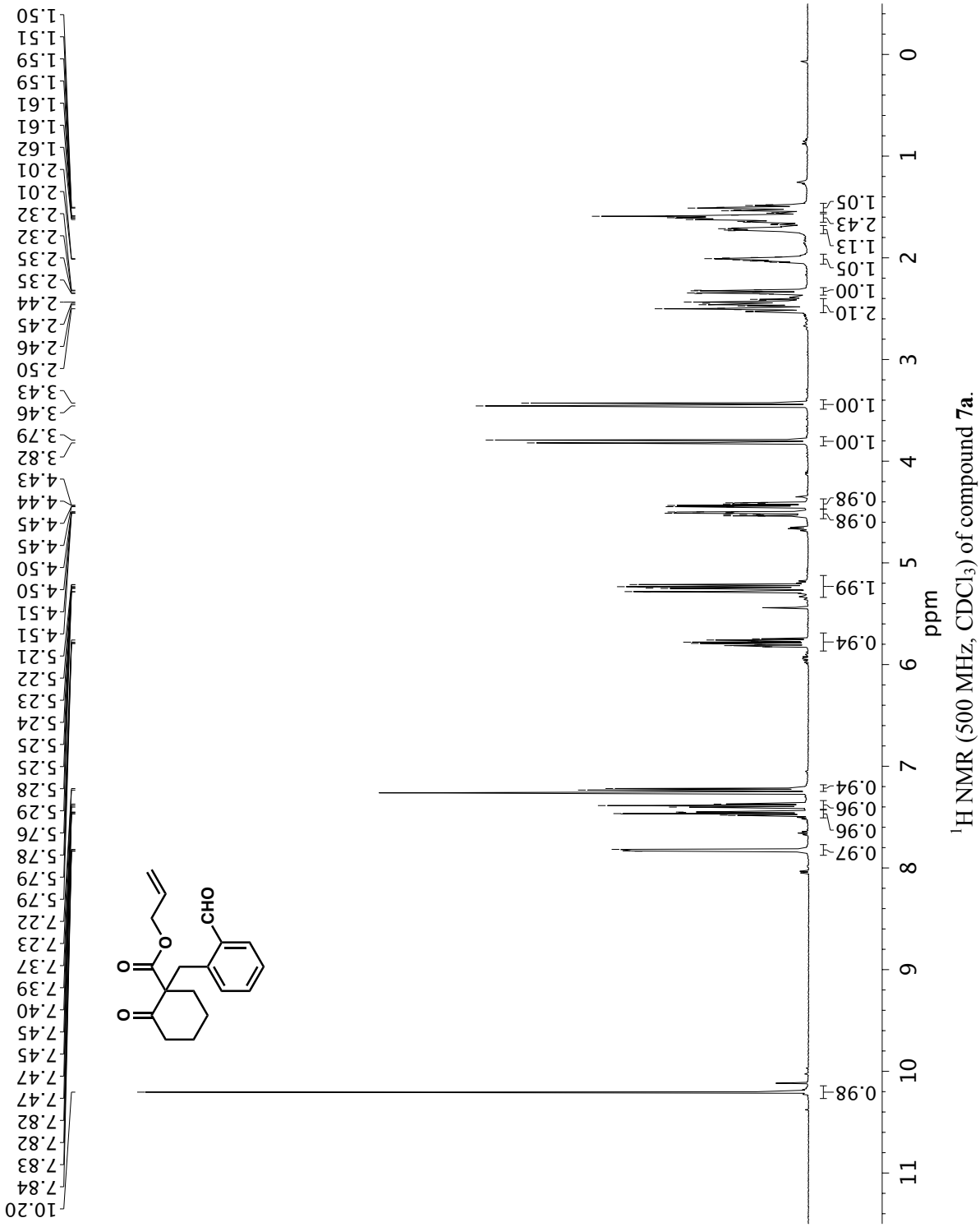
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6a**.



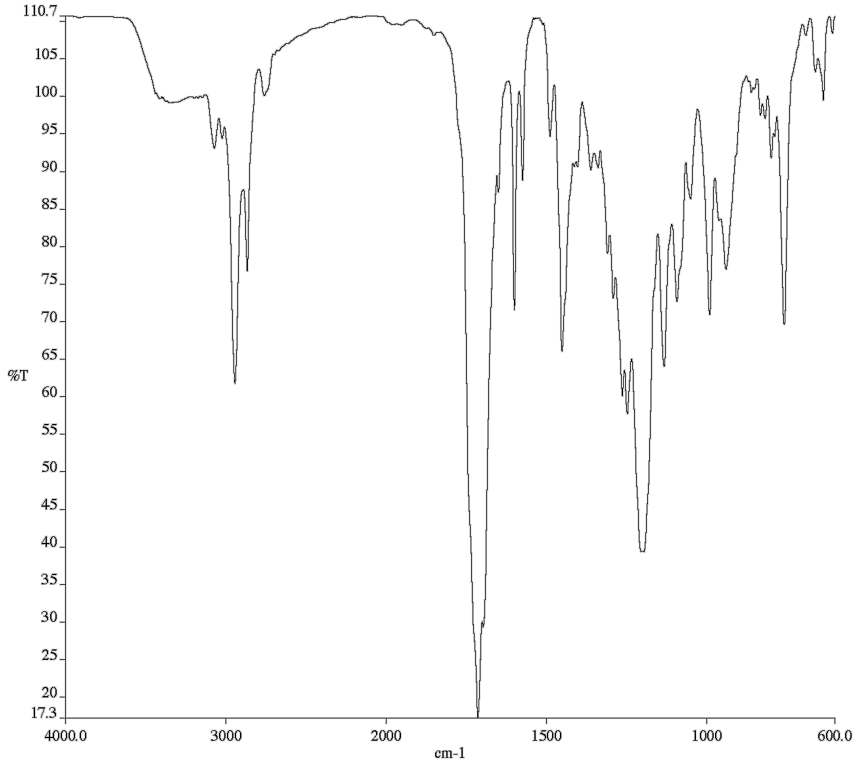
Infrared spectrum (Thin Film, NaCl) of compound **6a**.



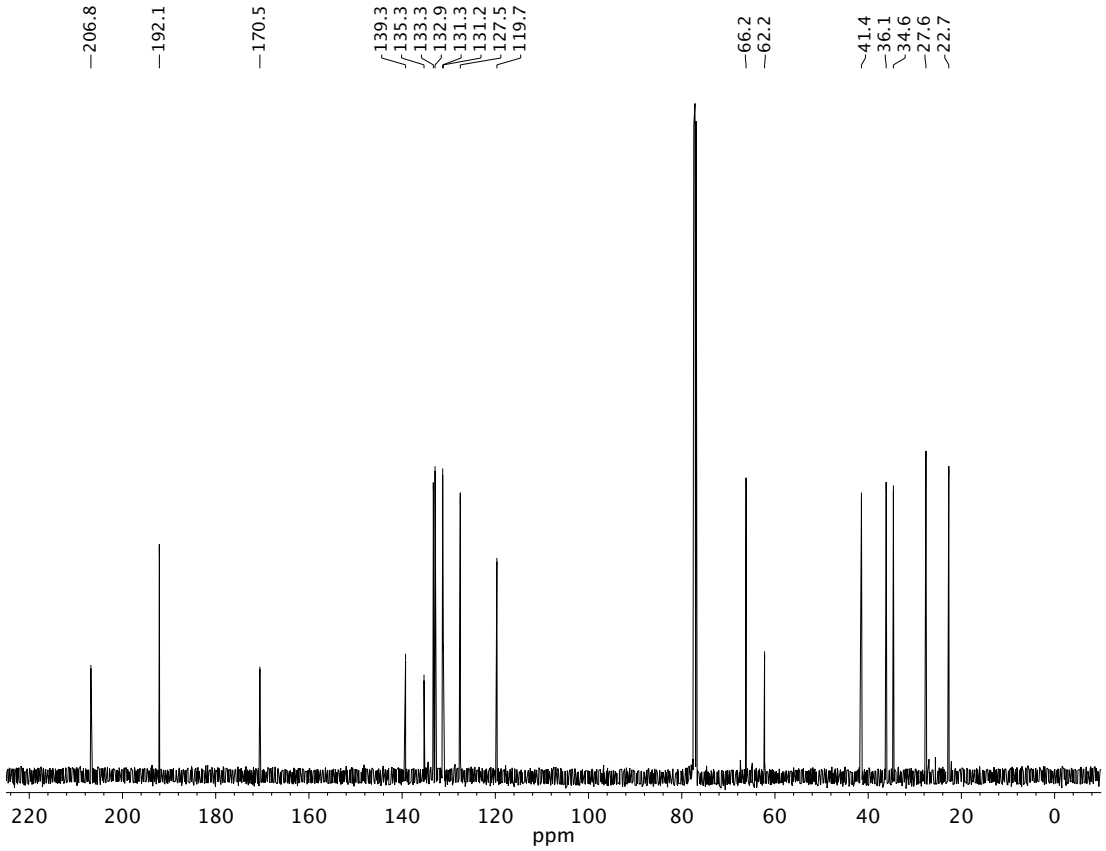
^{13}C NMR (125 MHz, $CDCl_3$) of compound **6a**.



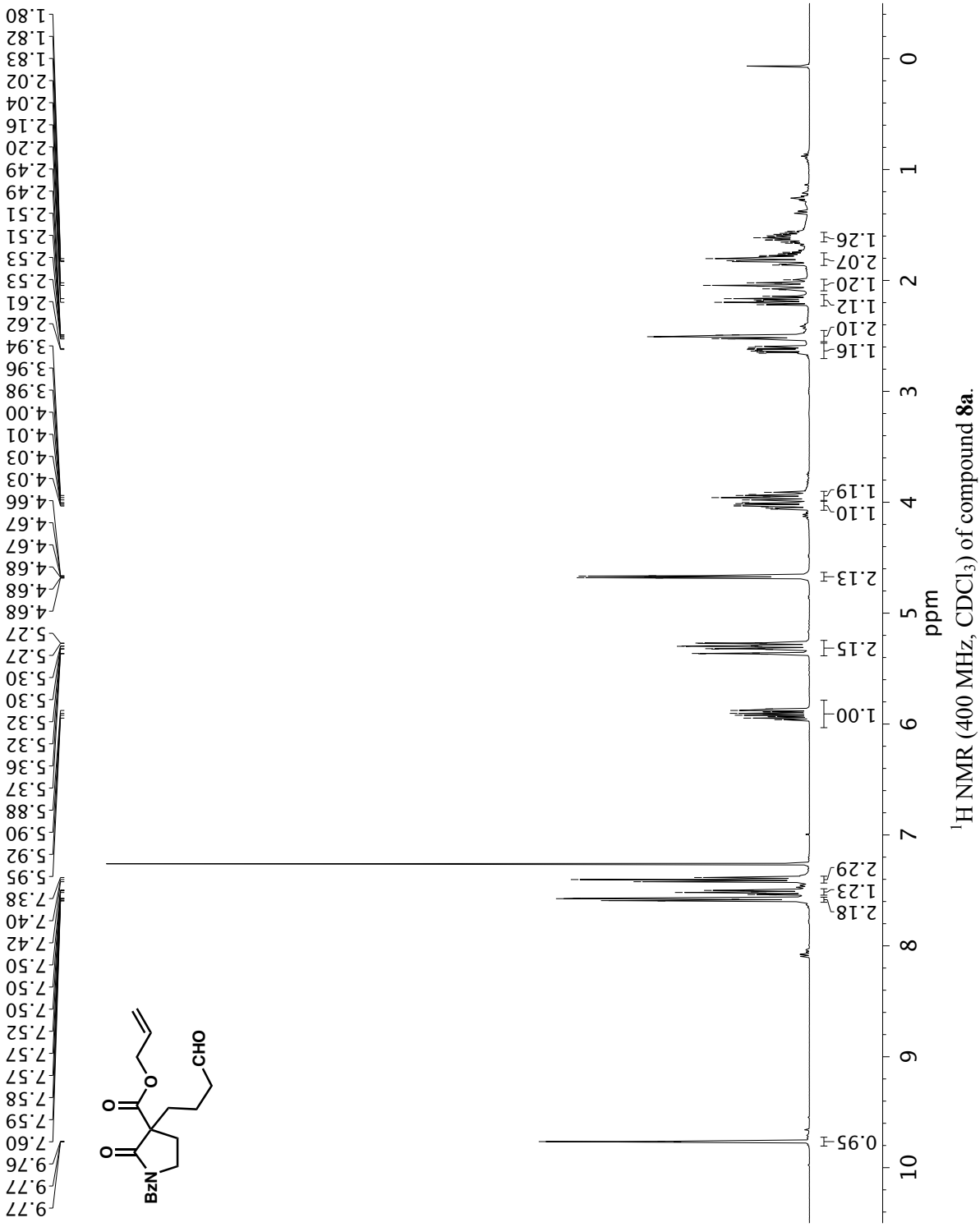
^{1}H NMR (500 MHz, $CDCl_3$) of compound **7a**.



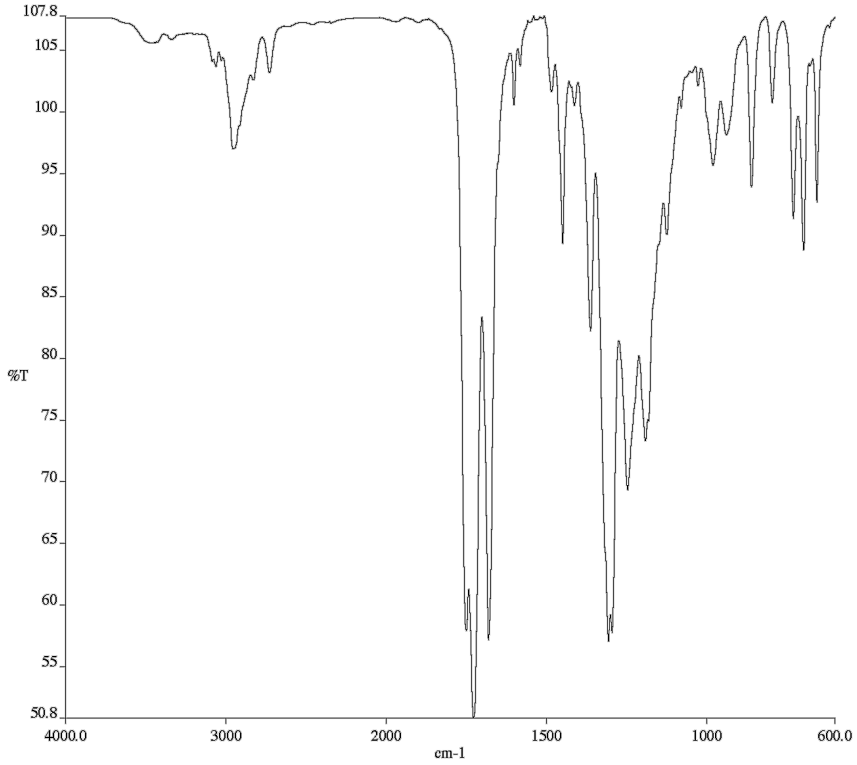
Infrared spectrum (Thin Film, NaCl) of compound **7a**.



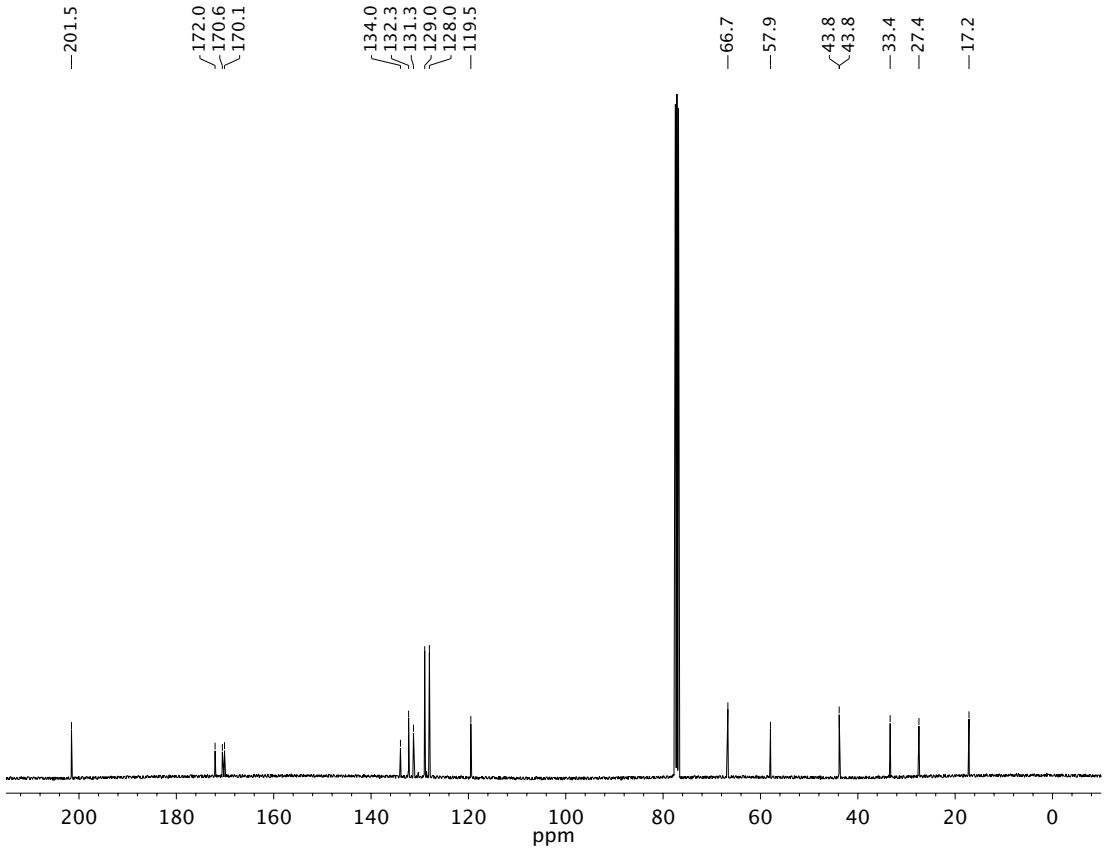
^{13}C NMR (125 MHz, $CDCl_3$) of compound **7a**.



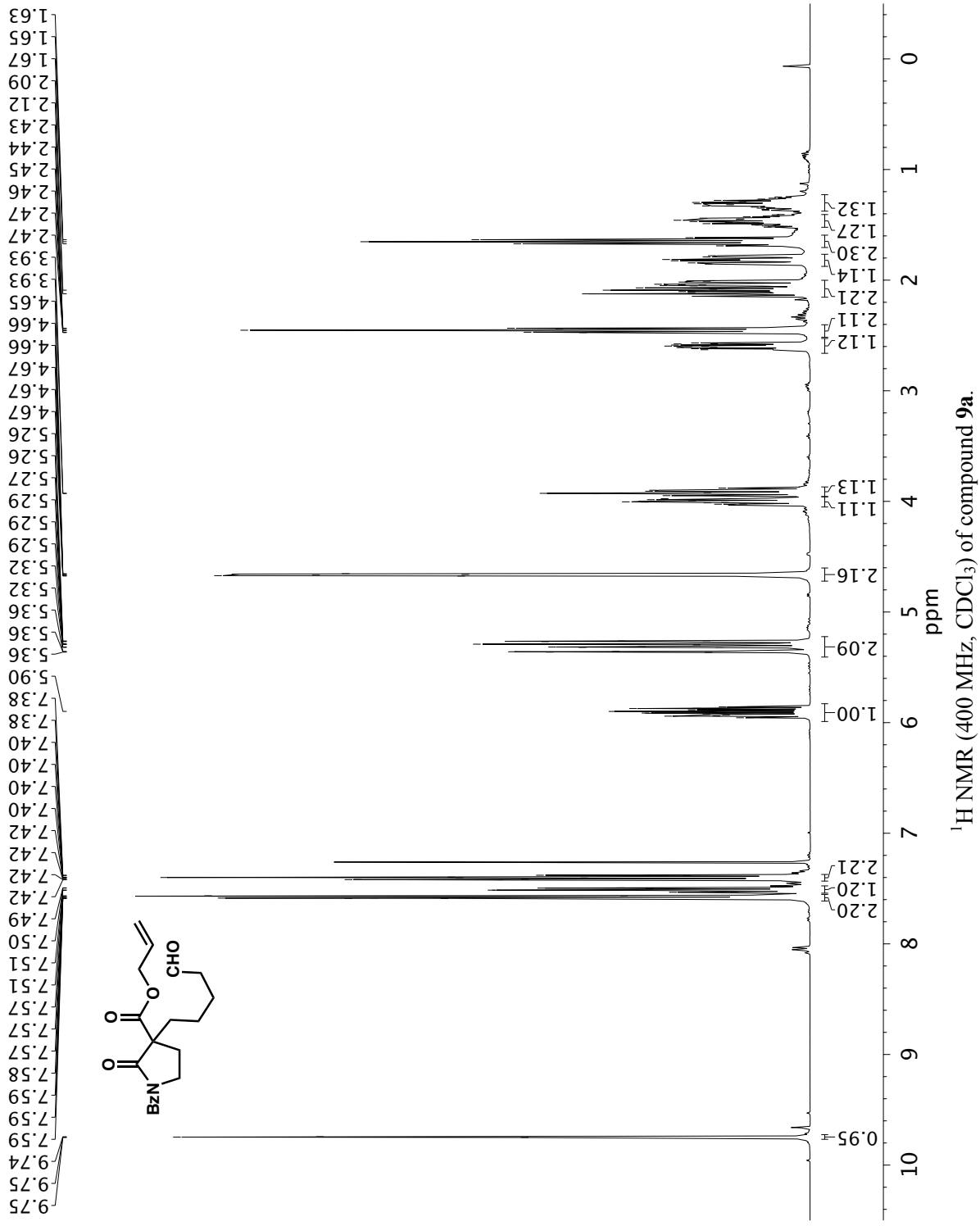
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8a**.



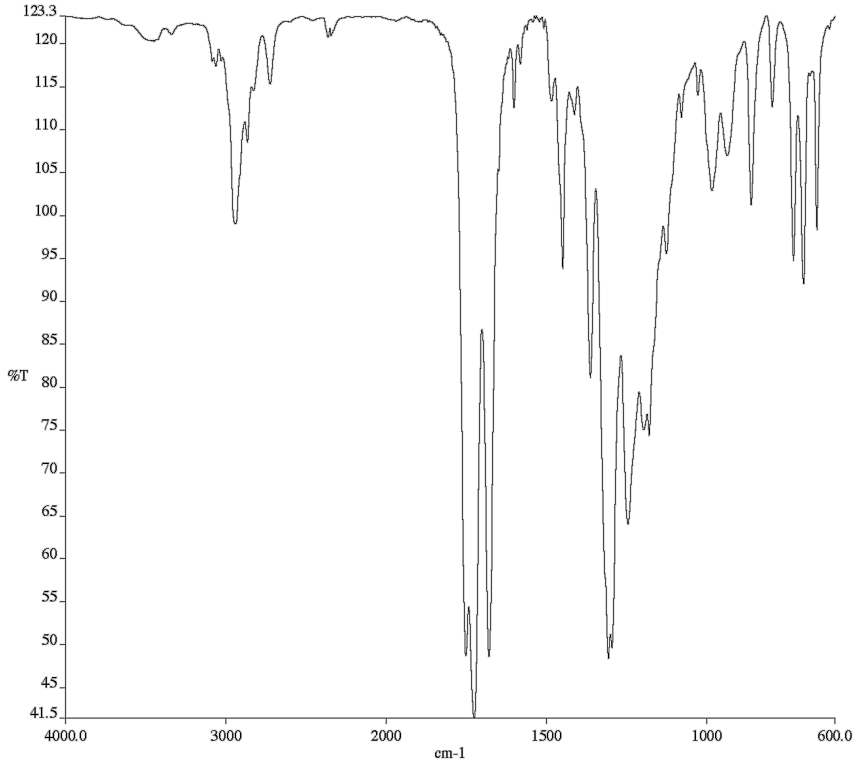
Infrared spectrum (Thin Film, NaCl) of compound **8a**.



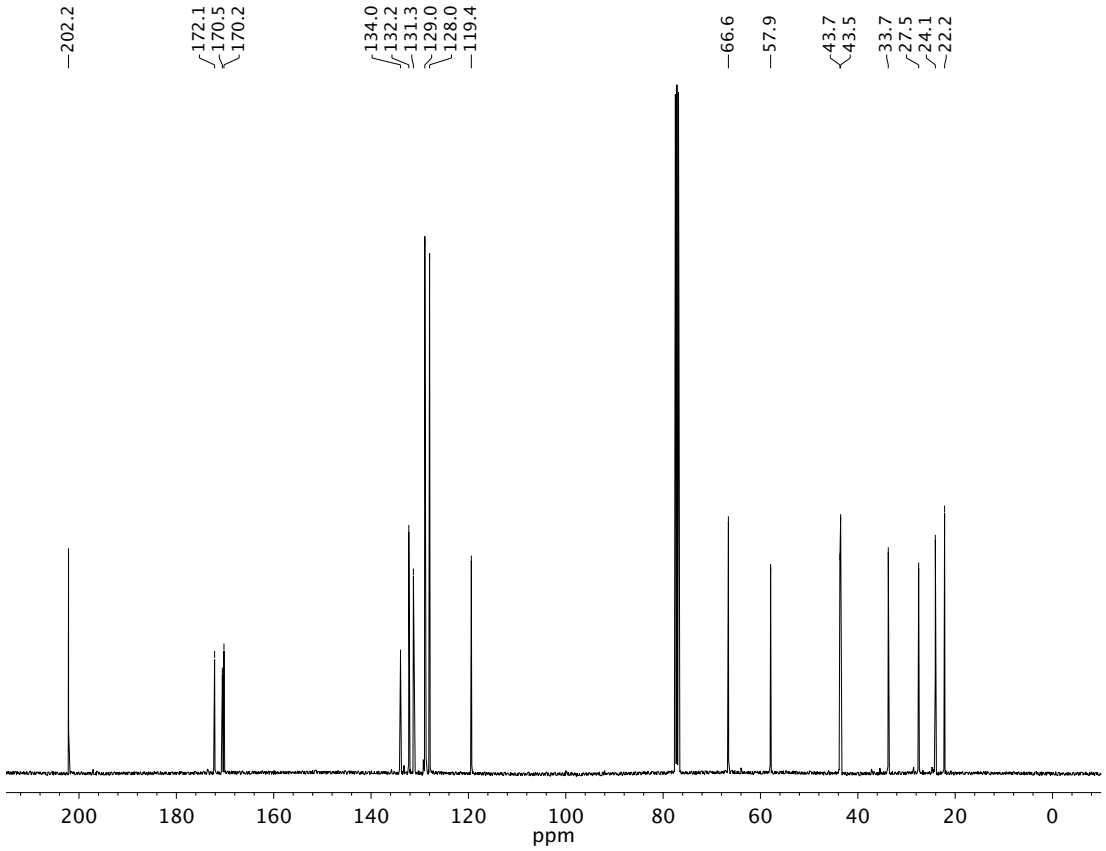
^{13}C NMR (100 MHz, $CDCl_3$) of compound **8a**.



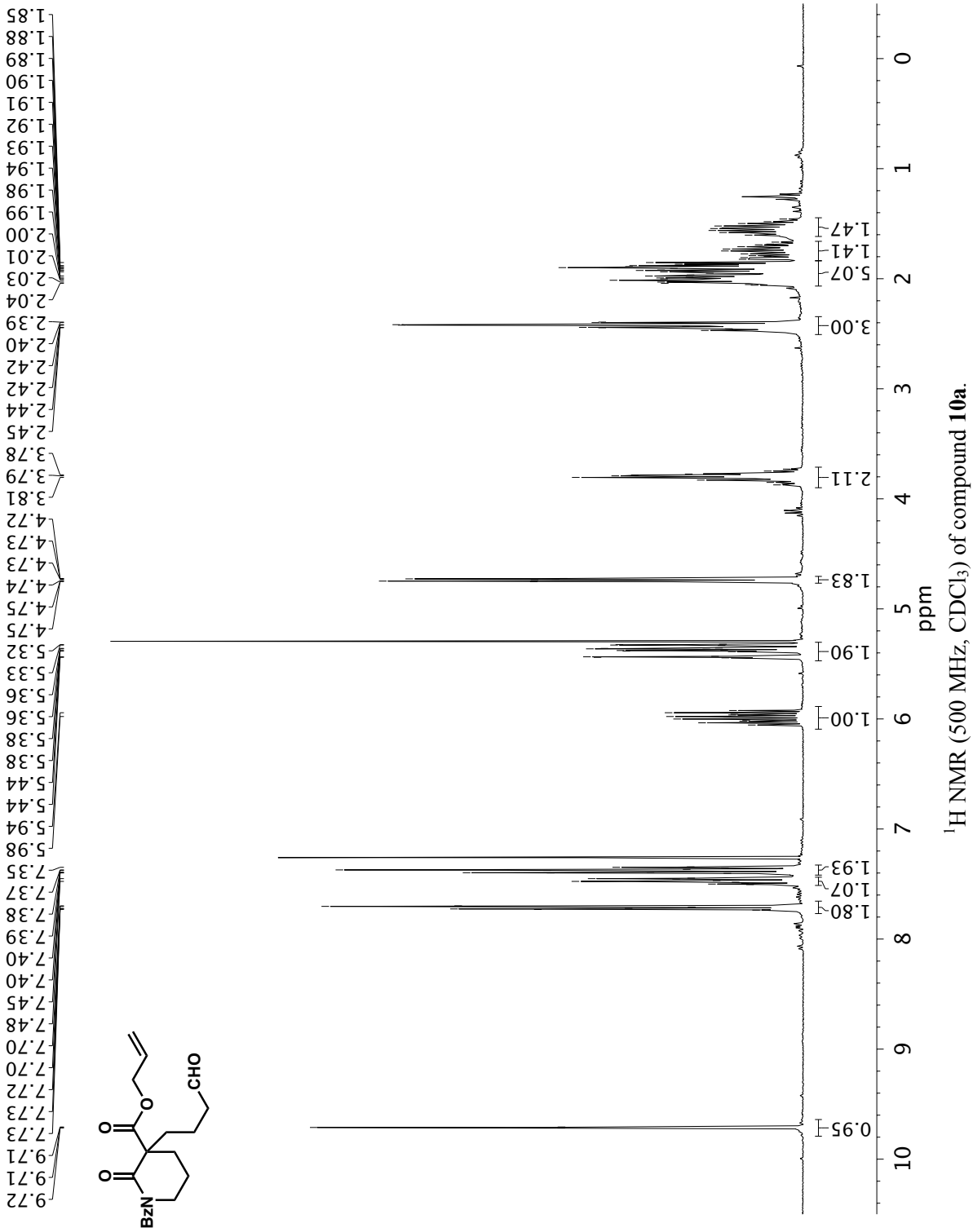
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9a**.



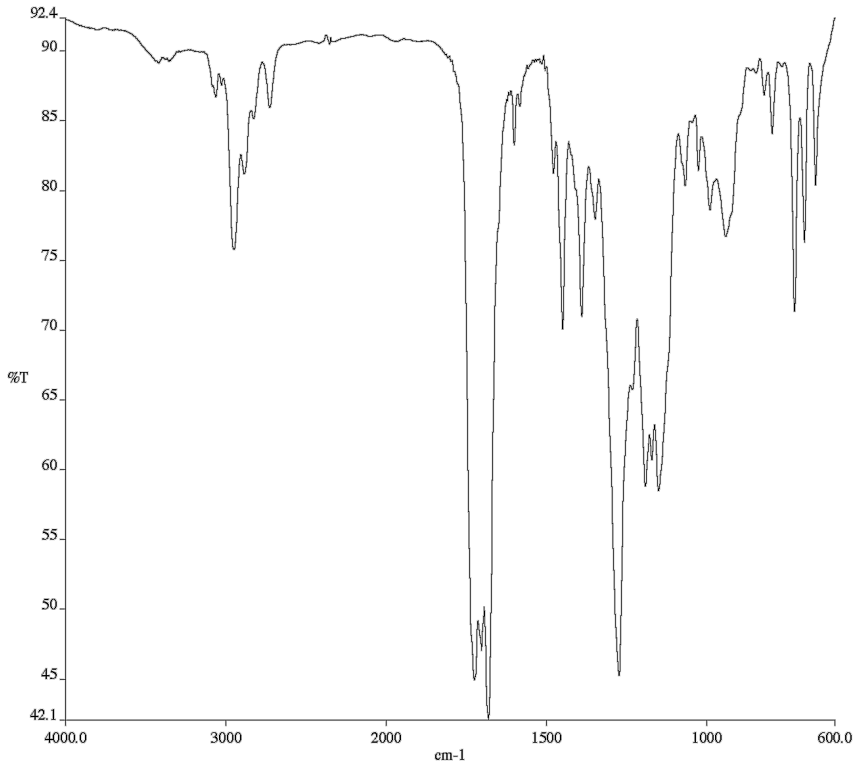
Infrared spectrum (Thin Film, NaCl) of compound **9a**.



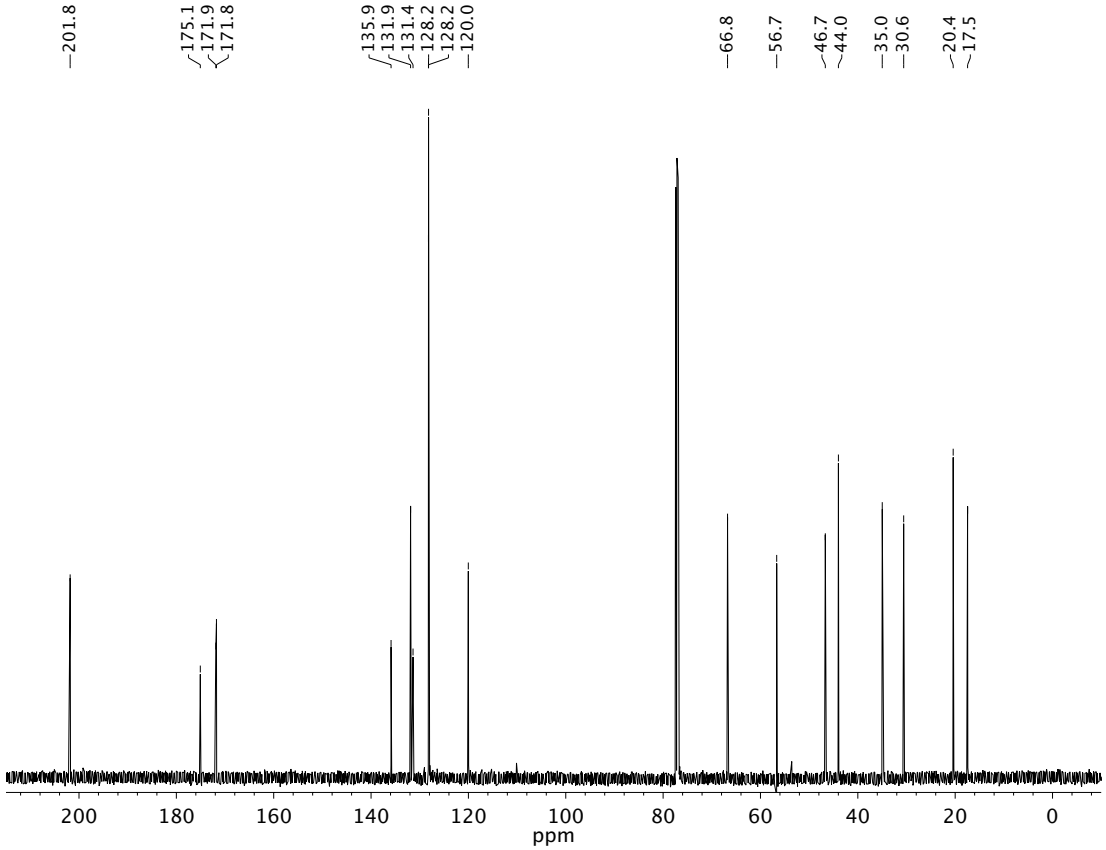
^{13}C NMR (100 MHz, $CDCl_3$) of compound **9a**.



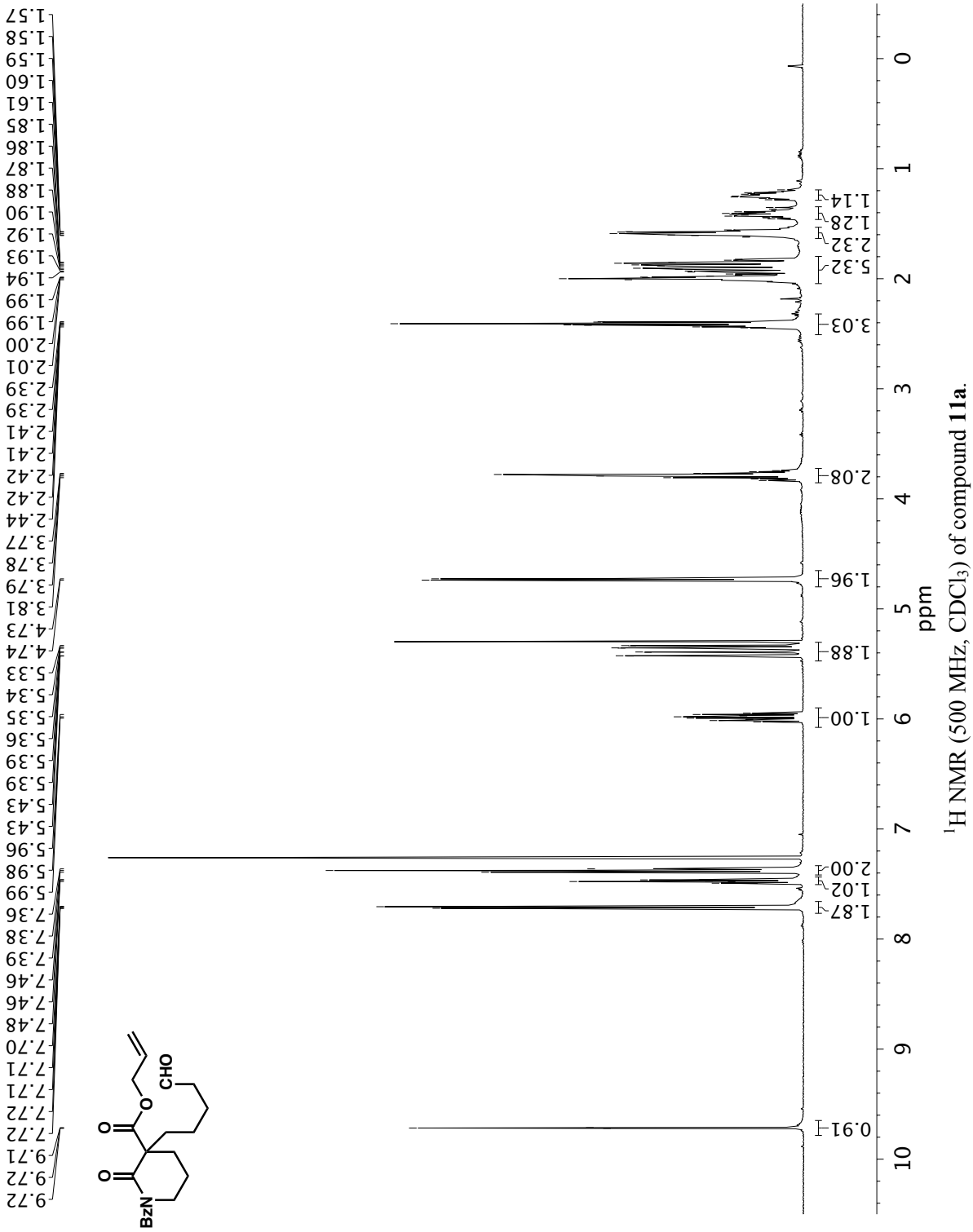
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10a**.



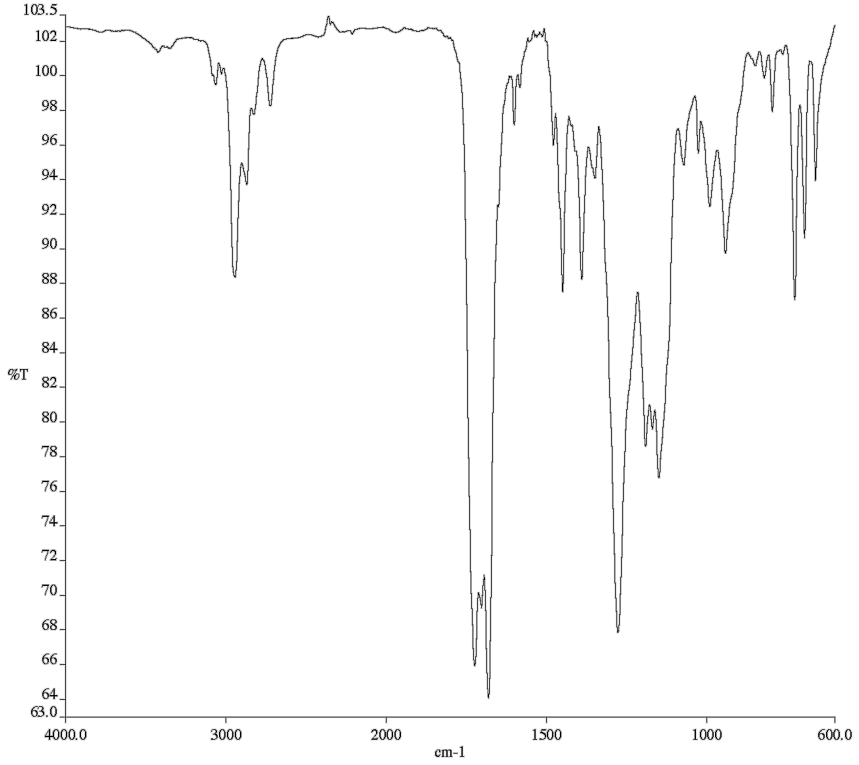
Infrared spectrum (Thin Film, NaCl) of compound **10a**.



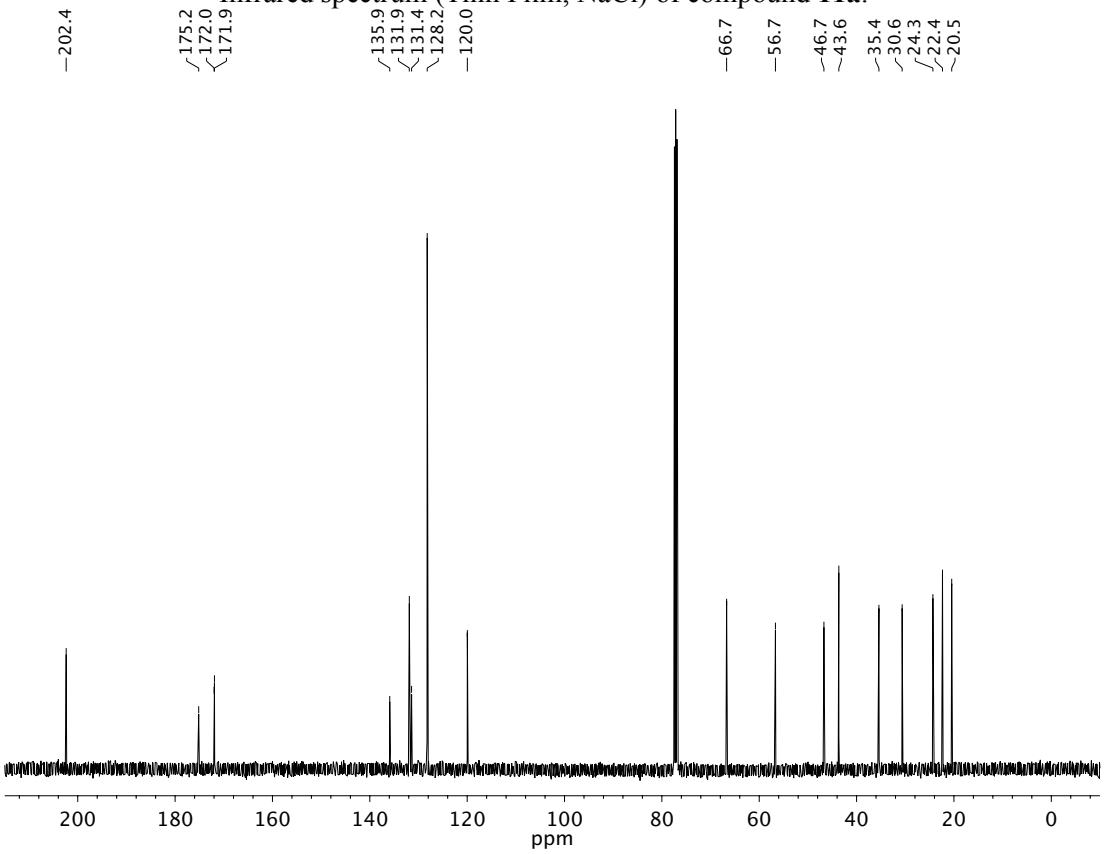
^{13}C NMR (125 MHz, $CDCl_3$) of compound **10a**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **11a**.



Infrared spectrum (Thin Film, NaCl) of compound **11a**.



^{13}C NMR (125 MHz, $CDCl_3$) of compound **11a**.

Crystal Structure Data for Aldol Product 8b

Aldol product **8b** was recrystallized in a chloroform/hexane mixture to provide crystals suitable for X-ray analysis.

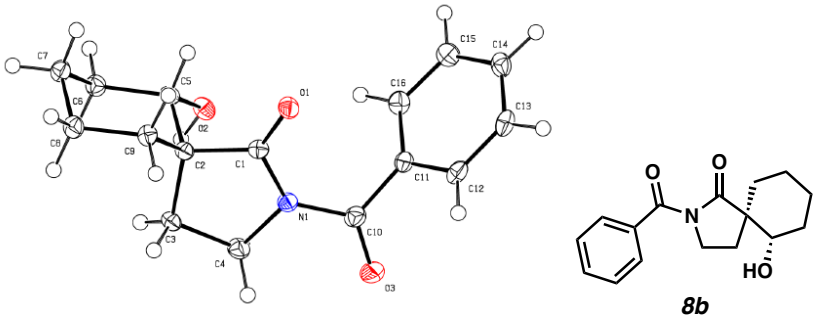


Figure S2. Crystal Structure of compound **8b**. (Thermal ellipsoids are shown with 50% probability)

Table S9. Crystal data and structure refinement for **8b**.

Empirical formula	C16 H19 N O3	
Formula weight	273.32	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 2_1 1	
Unit cell dimensions	a = 6.0356(4) Å	α = 90°.
	b = 10.8751(9) Å	β = 97.925(3)°.
	c = 10.5262(7) Å	γ = 90°.
Volume	684.32(8) $Å^3$	
Z	2	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.741 mm^{-1}	
F(000)	292	
Crystal size	0.23 x 0.18 x 0.13 mm^3	
Theta range for data collection	4.240 to 78.780°.	
Index ranges	-7<=h<=7, -13<=k<=13, -13<=l<=13	
Reflections collected	34337	
Independent reflections	2909 [R(int) = 0.0404]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9848 and 0.8741	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2909 / 1 / 257
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0287, wR2 = 0.0730
R indices (all data)	R1 = 0.0292, wR2 = 0.0736
Absolute structure parameter	0.13(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.191 and -0.203 e.$Å^{-3}$

Table S10. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **8b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4857(2)	6150(1)	6117(1)	20(1)
O(2)	6609(2)	3556(1)	4446(1)	19(1)
O(3)	5125(3)	3545(2)	8945(1)	32(1)
N(1)	4456(2)	4189(1)	6889(1)	17(1)
C(1)	4223(3)	5089(2)	5954(2)	15(1)
C(2)	3074(3)	4554(2)	4705(2)	15(1)
C(3)	2088(3)	3332(2)	5111(2)	17(1)
C(4)	3292(3)	3043(2)	6462(2)	21(1)
C(5)	4948(3)	4373(2)	3843(2)	16(1)
C(6)	4003(3)	3971(2)	2491(2)	19(1)
C(7)	2230(3)	4878(2)	1870(2)	20(1)
C(8)	363(3)	5014(2)	2704(2)	20(1)
C(9)	1301(3)	5454(2)	4049(2)	17(1)
C(10)	5527(3)	4293(2)	8153(2)	20(1)
C(11)	7218(3)	5287(2)	8471(2)	18(1)
C(12)	7088(3)	6031(2)	9535(2)	21(1)
C(13)	8724(3)	6913(2)	9883(2)	22(1)
C(14)	10521(3)	7032(2)	9202(2)	21(1)
C(15)	10660(3)	6282(2)	8144(2)	22(1)
C(16)	9002(3)	5418(2)	7768(2)	20(1)

Table S11. Bond lengths [Å] and angles [°] for **8b**.

O(1)-C(1)	1.221(2)
O(2)-H(2)	0.91(4)
O(2)-C(5)	1.422(2)
O(3)-C(10)	1.212(2)
N(1)-C(1)	1.381(2)
N(1)-C(4)	1.471(2)
N(1)-C(10)	1.401(2)
C(1)-C(2)	1.515(2)
C(2)-C(3)	1.541(2)
C(2)-C(5)	1.557(2)
C(2)-C(9)	1.541(2)
C(3)-H(3A)	0.99(2)
C(3)-H(3B)	0.94(2)
C(3)-C(4)	1.538(2)
C(4)-H(4A)	1.00(3)
C(4)-H(4B)	0.99(3)
C(5)-H(5)	1.02(2)
C(5)-C(6)	1.522(2)
C(6)-H(6A)	0.98(3)
C(6)-H(6B)	0.99(2)
C(6)-C(7)	1.534(2)
C(7)-H(7A)	0.96(3)
C(7)-H(7B)	0.98(3)
C(7)-C(8)	1.529(2)
C(8)-H(8A)	1.01(2)
C(8)-H(8B)	1.01(2)
C(8)-C(9)	1.527(2)
C(9)-H(9A)	1.020(19)
C(9)-H(9B)	0.99(3)
C(10)-C(11)	1.493(2)
C(11)-C(12)	1.392(3)
C(11)-C(16)	1.395(2)
C(12)-H(12)	0.96(3)
C(12)-C(13)	1.389(3)
C(13)-H(13)	0.97(3)
C(13)-C(14)	1.386(3)

C(14)-H(14)	0.96(3)
C(14)-C(15)	1.392(3)
C(15)-H(15)	0.99(2)
C(15)-C(16)	1.390(3)
C(16)-H(16)	1.01(3)

C(5)-O(2)-H(2)	108.9(19)
C(1)-N(1)-C(4)	112.62(14)
C(1)-N(1)-C(10)	127.47(16)
C(10)-N(1)-C(4)	119.80(14)
O(1)-C(1)-N(1)	124.74(16)
O(1)-C(1)-C(2)	125.60(15)
N(1)-C(1)-C(2)	109.66(15)
C(1)-C(2)-C(3)	103.79(13)
C(1)-C(2)-C(5)	105.78(13)
C(1)-C(2)-C(9)	110.59(13)
C(3)-C(2)-C(5)	113.05(14)
C(3)-C(2)-C(9)	113.64(13)
C(9)-C(2)-C(5)	109.56(13)
C(2)-C(3)-H(3A)	110.4(14)
C(2)-C(3)-H(3B)	113.5(15)
H(3A)-C(3)-H(3B)	106.9(19)
C(4)-C(3)-C(2)	106.35(14)
C(4)-C(3)-H(3A)	108.9(12)
C(4)-C(3)-H(3B)	110.8(14)
N(1)-C(4)-C(3)	104.75(14)
N(1)-C(4)-H(4A)	109.8(15)
N(1)-C(4)-H(4B)	107.4(14)
C(3)-C(4)-H(4A)	113.3(14)
C(3)-C(4)-H(4B)	111.4(14)
H(4A)-C(4)-H(4B)	110(2)
O(2)-C(5)-C(2)	110.05(13)
O(2)-C(5)-H(5)	108.8(12)
O(2)-C(5)-C(6)	112.88(14)
C(2)-C(5)-H(5)	105.8(12)
C(6)-C(5)-C(2)	111.85(13)
C(6)-C(5)-H(5)	107.2(12)
C(5)-C(6)-H(6A)	109.8(15)

C(5)-C(6)-H(6B)	108.3(13)
C(5)-C(6)-C(7)	111.34(14)
H(6A)-C(6)-H(6B)	108(2)
C(7)-C(6)-H(6A)	109.0(15)
C(7)-C(6)-H(6B)	110.7(13)
C(6)-C(7)-H(7A)	110.0(14)
C(6)-C(7)-H(7B)	109.7(15)
H(7A)-C(7)-H(7B)	107(2)
C(8)-C(7)-C(6)	110.05(14)
C(8)-C(7)-H(7A)	108.6(13)
C(8)-C(7)-H(7B)	111.1(15)
C(7)-C(8)-H(8A)	109.8(13)
C(7)-C(8)-H(8B)	110.0(12)
H(8A)-C(8)-H(8B)	107.1(17)
C(9)-C(8)-C(7)	110.78(13)
C(9)-C(8)-H(8A)	108.9(13)
C(9)-C(8)-H(8B)	110.2(12)
C(2)-C(9)-H(9A)	108.6(11)
C(2)-C(9)-H(9B)	107.7(14)
C(8)-C(9)-C(2)	111.22(14)
C(8)-C(9)-H(9A)	110.0(10)
C(8)-C(9)-H(9B)	112.7(14)
H(9A)-C(9)-H(9B)	106.4(18)
O(3)-C(10)-N(1)	119.27(17)
O(3)-C(10)-C(11)	121.84(17)
N(1)-C(10)-C(11)	118.82(15)
C(12)-C(11)-C(10)	119.22(16)
C(12)-C(11)-C(16)	120.00(17)
C(16)-C(11)-C(10)	120.62(16)
C(11)-C(12)-H(12)	117.5(16)
C(13)-C(12)-C(11)	119.77(17)
C(13)-C(12)-H(12)	122.7(16)
C(12)-C(13)-H(13)	122.3(16)
C(14)-C(13)-C(12)	120.43(17)
C(14)-C(13)-H(13)	117.2(16)
C(13)-C(14)-H(14)	120.1(16)
C(13)-C(14)-C(15)	119.81(17)
C(15)-C(14)-H(14)	120.0(17)

C(14)-C(15)-H(15)	120.5(13)
C(16)-C(15)-C(14)	120.19(17)
C(16)-C(15)-H(15)	119.3(13)
C(11)-C(16)-H(16)	120.5(15)
C(15)-C(16)-C(11)	119.77(16)
C(15)-C(16)-H(16)	119.7(15)

Table S12. Anisotropic displacement parameters ($Å^2$ x 10^3) for **8b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2} U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	14(1)	20(1)	1(1)	-1(1)	-2(1)
O(2)	14(1)	18(1)	25(1)	0(1)	1(1)	2(1)
O(3)	32(1)	37(1)	24(1)	14(1)	-4(1)	-11(1)
N(1)	18(1)	15(1)	17(1)	3(1)	1(1)	-1(1)
C(1)	15(1)	14(1)	18(1)	2(1)	3(1)	2(1)
C(2)	13(1)	14(1)	16(1)	1(1)	1(1)	0(1)
C(3)	15(1)	14(1)	20(1)	1(1)	1(1)	-2(1)
C(4)	23(1)	15(1)	23(1)	4(1)	0(1)	-2(1)
C(5)	13(1)	15(1)	19(1)	0(1)	3(1)	0(1)
C(6)	18(1)	20(1)	18(1)	-2(1)	3(1)	-1(1)
C(7)	22(1)	20(1)	17(1)	1(1)	1(1)	-1(1)
C(8)	17(1)	20(1)	20(1)	2(1)	-2(1)	2(1)
C(9)	17(1)	15(1)	18(1)	1(1)	0(1)	2(1)
C(10)	18(1)	22(1)	19(1)	4(1)	2(1)	1(1)
C(11)	17(1)	20(1)	15(1)	4(1)	-1(1)	1(1)
C(12)	21(1)	28(1)	14(1)	3(1)	2(1)	4(1)
C(13)	27(1)	22(1)	14(1)	0(1)	-2(1)	6(1)
C(14)	20(1)	20(1)	22(1)	2(1)	-5(1)	1(1)
C(15)	17(1)	25(1)	24(1)	1(1)	3(1)	2(1)
C(16)	19(1)	22(1)	20(1)	-2(1)	3(1)	2(1)

Table S13. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **8b**.

	x	y	z	U(eq)
H(2)	6120(50)	2770(30)	4310(30)	38(7)
H(3A)	470(40)	3420(20)	5150(20)	14(5)
H(3B)	2250(40)	2680(20)	4540(20)	17(5)
H(4A)	2240(40)	2800(30)	7080(20)	27(6)
H(4B)	4440(40)	2400(20)	6440(20)	21(6)
H(5)	5650(30)	5210(20)	3770(20)	13(5)
H(6A)	3320(40)	3150(20)	2520(20)	23(6)
H(6B)	5250(40)	3910(20)	1980(20)	17(5)
H(7A)	2890(40)	5670(20)	1780(20)	18(5)
H(7B)	1630(40)	4590(20)	1000(20)	25(6)
H(8A)	-780(40)	5630(20)	2300(20)	16(5)
H(8B)	-440(40)	4200(20)	2750(20)	14(5)
H(9A)	40(30)	5526(19)	4600(17)	5(4)
H(9B)	2000(40)	6280(20)	4050(20)	22(6)
H(12)	5820(40)	5930(30)	9980(30)	27(6)
H(13)	8700(40)	7450(30)	10620(20)	26(6)
H(14)	11700(50)	7610(30)	9480(30)	34(7)
H(15)	11940(40)	6360(20)	7640(20)	16(5)
H(16)	9100(40)	4890(30)	6990(20)	29(7)

Table S14. Torsion angles [°] for **8b**.

O(1)-C(1)-C(2)-C(3)	-165.21(17)
O(1)-C(1)-C(2)-C(5)	75.6(2)
O(1)-C(1)-C(2)-C(9)	-43.0(2)
O(2)-C(5)-C(6)-C(7)	-179.66(14)
O(3)-C(10)-C(11)-C(12)	-51.7(3)
O(3)-C(10)-C(11)-C(16)	123.8(2)
N(1)-C(1)-C(2)-C(3)	14.98(17)
N(1)-C(1)-C(2)-C(5)	-104.25(15)
N(1)-C(1)-C(2)-C(9)	137.20(14)
N(1)-C(10)-C(11)-C(12)	131.41(18)
N(1)-C(10)-C(11)-C(16)	-53.1(2)
C(1)-N(1)-C(4)-C(3)	-3.70(19)
C(1)-N(1)-C(10)-O(3)	161.61(18)
C(1)-N(1)-C(10)-C(11)	-21.4(3)
C(1)-C(2)-C(3)-C(4)	-16.70(17)
C(1)-C(2)-C(5)-O(2)	60.06(17)
C(1)-C(2)-C(5)-C(6)	-173.63(14)
C(1)-C(2)-C(9)-C(8)	171.94(14)
C(2)-C(3)-C(4)-N(1)	12.86(18)
C(2)-C(5)-C(6)-C(7)	55.58(18)
C(3)-C(2)-C(5)-O(2)	-52.86(18)
C(3)-C(2)-C(5)-C(6)	73.45(18)
C(3)-C(2)-C(9)-C(8)	-71.81(17)
C(4)-N(1)-C(1)-O(1)	172.87(17)
C(4)-N(1)-C(1)-C(2)	-7.32(18)
C(4)-N(1)-C(10)-O(3)	-14.3(3)
C(4)-N(1)-C(10)-C(11)	162.72(16)
C(5)-C(2)-C(3)-C(4)	97.43(16)
C(5)-C(2)-C(9)-C(8)	55.72(17)
C(5)-C(6)-C(7)-C(8)	-56.81(19)
C(6)-C(7)-C(8)-C(9)	58.18(19)
C(7)-C(8)-C(9)-C(2)	-58.66(18)
C(9)-C(2)-C(3)-C(4)	-136.87(15)
C(9)-C(2)-C(5)-O(2)	179.28(13)
C(9)-C(2)-C(5)-C(6)	-54.41(18)
C(10)-N(1)-C(1)-O(1)	-3.3(3)

C(10)-N(1)-C(1)-C(2)	176.56(15)
C(10)-N(1)-C(4)-C(3)	172.76(15)
C(10)-C(11)-C(12)-C(13)	176.38(16)
C(10)-C(11)-C(16)-C(15)	-174.62(17)
C(11)-C(12)-C(13)-C(14)	-2.1(3)
C(12)-C(11)-C(16)-C(15)	0.8(3)
C(12)-C(13)-C(14)-C(15)	1.6(3)
C(13)-C(14)-C(15)-C(16)	0.1(3)
C(14)-C(15)-C(16)-C(11)	-1.3(3)
C(16)-C(11)-C(12)-C(13)	0.9(3)

Table S15. Hydrogen bonds for **8b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(1)#1	0.91(4)	1.89(4)	2.7986(19)	175(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+1