

Supporting Information

Stereoselective Synthesis of P-Chiral Phosphorus Compounds From *N*-*t*-Butoxycarbonyl Amino Acids

William H. Hersh,^{*†} Lauren Klein,[†] and Louis J. Todaro[§]

[†]Department of Chemistry and Biochemistry, Queens College and the Graduate Center of the City University of New York, Flushing, NY 11367-1597, and [§]Department of Chemistry, Hunter College, New York, NY 10021

william_hersh@qc.edu

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General . All manipulations of air-sensitive compounds were carried out in an inert atmosphere glovebox under recirculating nitrogen. ¹H, ¹³C, and ³¹P NMR spectra were recorded at 400, 100, and 160 MHz, respectively; chemical shifts are reported relative to TMS for ¹H and ¹³C NMR, and to external 85% H₃PO₄ at 0 ppm (positive values downfield) for ³¹P NMR. Infrared spectra were obtained in 0.1 mm NaCl solution cells on a computer-controlled FT-IR spectrometer. Optical rotations were measured at room temperature in a 1.0 dm cell.

All solvents were treated under nitrogen. Benzene and tetrahydrofuran were distilled from sodium benzophenone ketyl. Hexane was purified by washing successively with 5% nitric acid in sulfuric acid, water, sodium bicarbonate solution, and water, and then dried over calcium chloride and distilled from *n*-butyllithium in hexane. CDCl₃ was vacuum-transferred from phosphorus pentoxide. Silica gel (200-400 mesh) was dried for several hours under vacuum while heating with a heat gun and was transferred under vacuum into the glovebox. PhPCl₂ was degassed prior to use, NEt₃ was distilled from CaH₂, and *t*-Boc amino acids were used as received.

(2R, 4S)-3-*tert*-butyloxycarbonyl-5-oxo-2-phenyl-1,3,2-oxazaphospholidine (7). In the glovebox, *t*-Boc glycine (2.00g, 11.2 mmol) was dissolved in 3 mL of THF, and the solvent was removed under vacuum in order to remove any water that might be present. It was then redissolved in 40 mL of THF, NEt₃ (2.36 g, 24.4 mmol) was added in ~1 mL of THF, and then a solution of 2.18 g (12.2 mmol) of PhPCl₂ in 10 mL of THF was added dropwise over 5 min to the stirred solution, immediately giving a white precipitate. An aliquot taken for ³¹P NMR showed complete conversion to product, but stirring was still allowed to continue overnight. The mixture was filtered through a short column of silica gel (filling 30 mL of a 60 mL fritted funnel), washed with THF, and the solvent removed to give 2.12 g crude product (66% yield) that was close to spectroscopically pure. This was crystallized by dissolving in 2 mL of CH₂Cl₂, cooling at –30 °C, layering on an equal volume of hexanes, and cooling overnight to give 0.78 g of fine white crystals; a second crop of 0.55 g was obtained in the same way (41% total yield). IR (CHCl₃): 1797 (s), 1713 (s) cm⁻¹; ¹H NMR (CDCl₃): δ 7.50 (m, 5H), 4.23 (br dd, ³J_{PH} = 4.9 Hz, ²J_{HH} = 17.8 Hz, 1H), 3.95 (dd, ³J_{PH} = 1.4 Hz, ²J_{HH} = 17.8 Hz, 1H) 1.45 (s, 9H). ³¹P NMR (CDCl₃): 135.2 ppm. ¹³C NMR (CDCl₃): 170.8 (br s), 152.4 (br s), 139.37 (d, J_{PC} = 43.3 Hz), 132.2, 129.2 (d, J_{PC} = 23.8 Hz), 129.0 (d, J_{PC} = 6.3 Hz), 83.1, 42.8 (br s), 28.2 ppm. Anal. Calcd for C₁₃H₁₆NO₄P: C, 55.52; H, 5.73; N, 4.98. Found: C, 55.79; H, 5.91; N, 4.78.

(2R, 4S)-3-*tert*-butyloxycarbonyl-4-methyl-5-oxo-2-phenyl-1,3,2-oxazaphospholidine (8). In the glovebox, *t*-Boc alanine (2.00g, 10.6 mmol) was dissolved in 3 mL of THF, and the solvent was removed under vacuum in order to remove any water that might be present. It was then redissolved in 40 mL of THF, NEt₃ (2.11 g, 20.8 mmol) was added in ~1 mL of THF, and then a solution of 1.89 g (10.6 mmol) of PhPCl₂ in 10 mL of THF was added dropwise over 5 min to the stirred solution, immediately giving a white precipitate. The mixture was filtered through a short column of silica gel (filling 30 mL of a 60 mL fritted funnel), washed with THF, and the solvent removed to give 2.66 g of spectroscopically pure crude product (85% yield). This was dissolved in ~2 mL of ether, cooled to –30 °C, and then 2 ml of hexanes was layed on and the mixture allowed to stand at –30 °C overnight to give 0.68 g of fine white crystals; a second crop of 0.45 g was obtained in the same way (36% total yield). [α]_D²⁶ = 372.8 (c = 2.485, C₆H₆); IR (CHCl₃): 1787 (s), 1712 (s), 1678 (m) cm⁻¹; ¹H NMR (CDCl₃): δ 7.55 (m, 3H), 7.47 (m, 2H), 4.43 (br s, 1H), 1.70 (d, ³J_{HH} = 6.8 Hz, 3H), 1.29 (s, 9H). ³¹P NMR (CDCl₃): 134.6 ppm. ¹³C NMR (CDCl₃): 173.5 (br s), 152.1 (br s), 139.8 (d, J_{PC} = 49.1 Hz), 132.6, 130.1 (d, J_{PC} = 26.1 Hz), 128.9 (d, J_{PC} = 7.1 Hz), 82.9, 50.4, 28.0, 18.3 ppm. Anal. Calcd for C₁₄H₁₈NO₄P: C, 56.95; H, 6.14; N, 4.74. Found: C, 56.84; H, 6.19; N, 4.79.

(2R, 4S)-3-*tert*-butyloxycarbonyl-4-isopropyl-5-oxo-2-phenyl-1,3,2-oxazaphospholidine (9). The synthetic details may be found in the published Note. Details of the structure determination may be found in the cif file, and comparison of selected bond lengths and angles to *cis*-3-toluenesulfonyl-5-oxo-2-phenyl-1,3,2-oxazaphospholidine (**2**) may be found in Table 1.

Variable temperature NMR spectra. Data collected as described in the published Note may be found in Table 2.

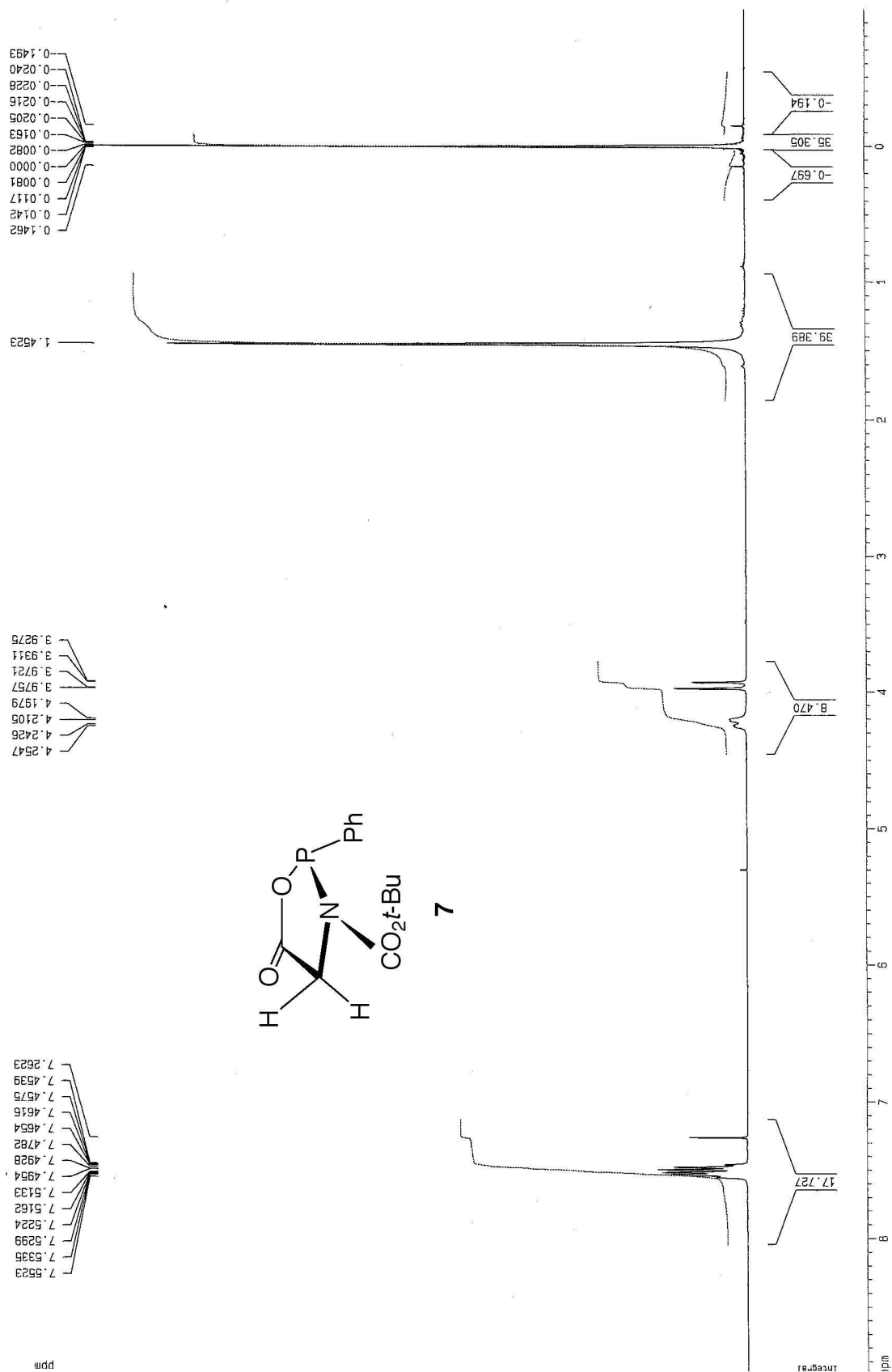
Table 1. Comparison of Bond Lengths (Å) and Angles (°) in **2** and **9**.

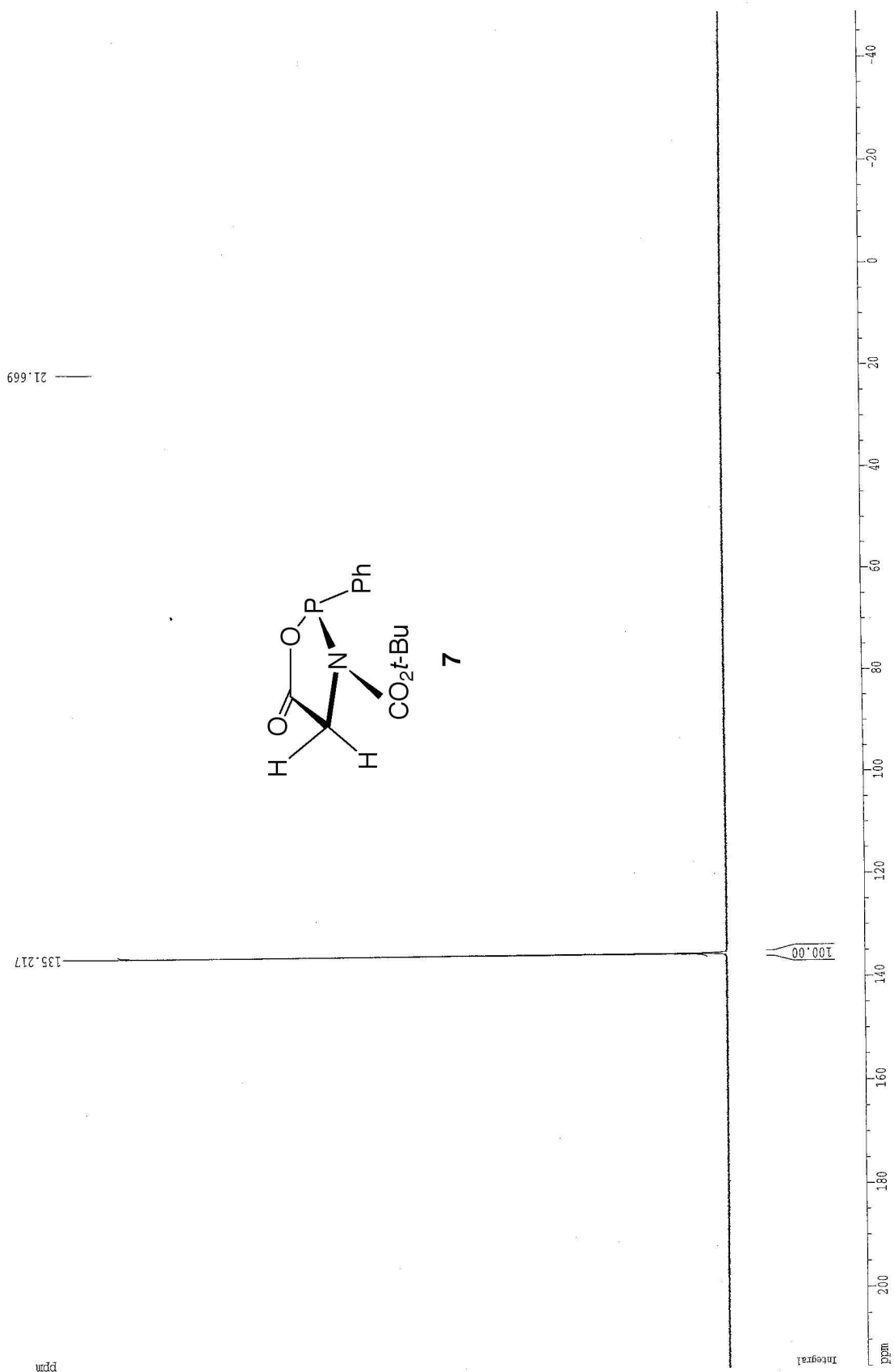
	2	9
P-O _{ring}	1.678 (3)	1.643 (6)
P-N	1.744 (4)	1.753 (6)
P-Ph	1.824 (5)	1.831 (8)
O _{ring} -C	1.367 (6)	1.372 (9)
N-C _{ring}	1.475 (6)	1.439 (9)
O _{ring} -P-N	90.9 (2)	88.7 (3)
O _{ring} -P-Ph	101.1 (2)	100.5 (3)
N-P-Ph	99.9 (2)	102.0 (3)
P-N-C _{ring}	112.5 (3)	116.1 (4)
P-N-R ^a	118.4 (2)	120.1 (5)
C _{ring} -N-R ^a	120.0 (3)	122.7 (6)
ΣN ^b	350.9	358.9

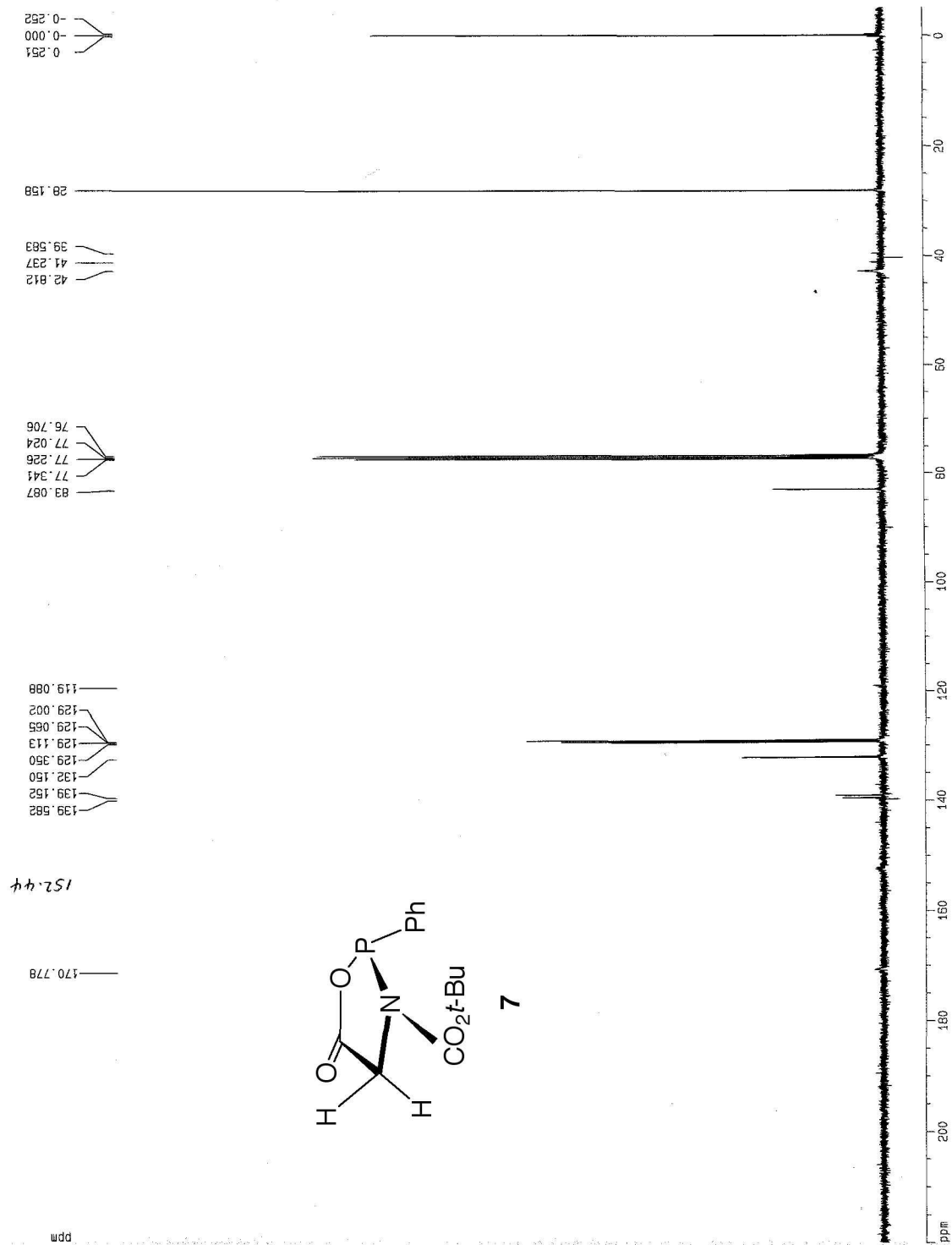
^aR' = non-ring substituent on nitrogen. ^bsum of the three angles at nitrogen.

Table 2. Variable temperature NMR data

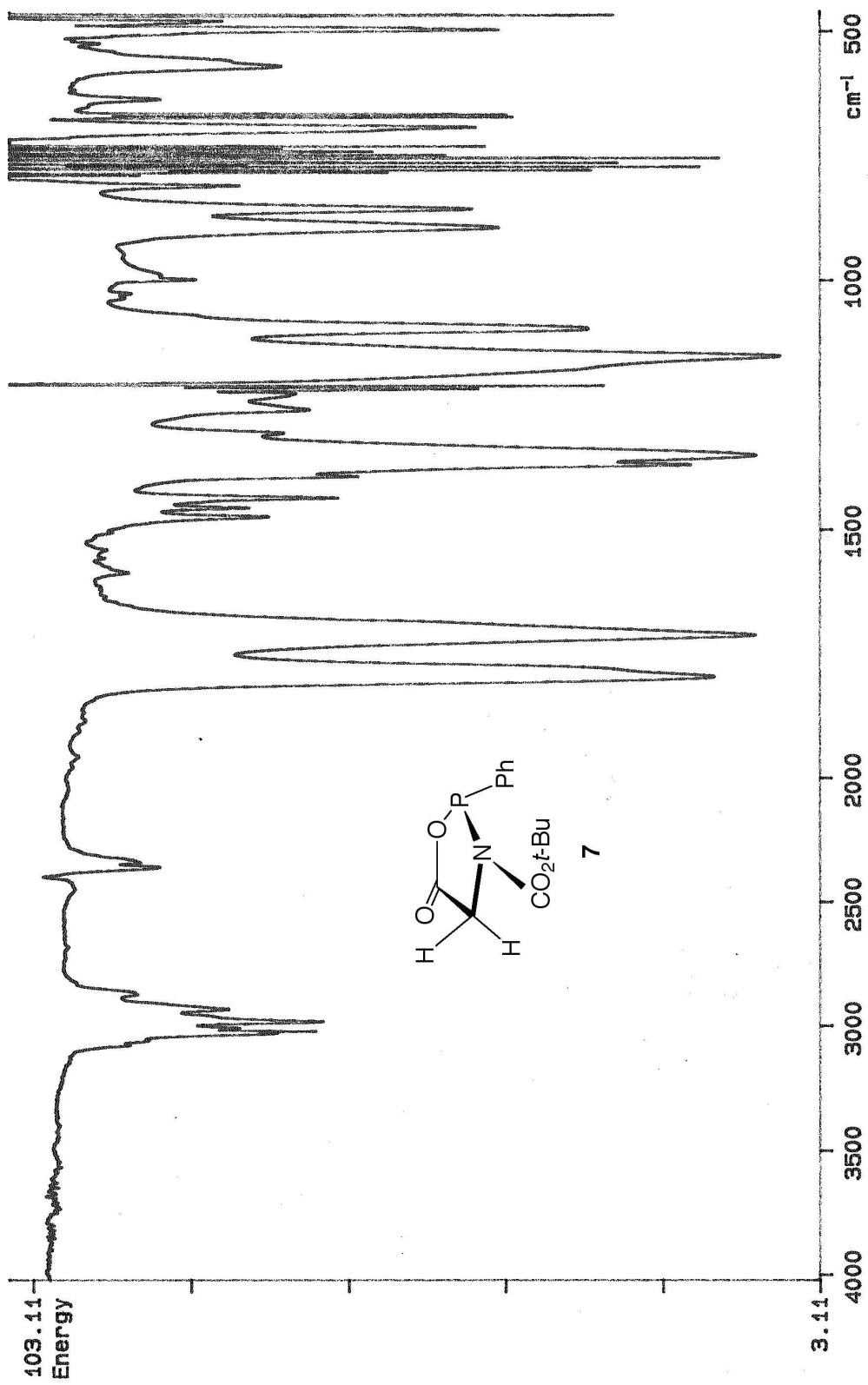
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Compound 7																
2	T	31P integral	t-Bu integral	calcd 1/K	all chem. shift differences in ppm				cis-CHN	TMS	k(t-Bu) (s-1)	k(CHN) (s-1)					
3		K(31P)	K(t-Bu)	for gNMR	t-Bu chem	extrapolated	shift diff	extrapolated	shift diff	v(1/2) (Hz)							
4	-30	4.3524	9.2424	0.2358	0.05689	0.05792	0.050965	0.05097	1.624	0.1 ± 0.1	0.05 ± 0.05						
5	-20	3.6333	3.9745	0.2561	0.0581	0.05705	0.056475	0.05648	1.867	0.7 ± 0.1	0.4 ± 0.2						
6	-10		3.7230	0.2763	0.05717	0.05618		0.05199	1.218	4 ± 1	4 ± 1						
7	0			0.2866	0.0543	0.05531		0.06750	1.508	7 ± 1	7 ± 1						
8	10			0.3167	0.0544	0.05357		0.07301	1.276	21 ± 1	22 ± 2						
9	20			0.3366	0.0537	0.05277		0.07852	1.508	55 ± 5	70 ± 20						
10	30			0.3564	0.0527	0.05183		0.08403	1.16	150 ± 10							
11	40			0.3760	0.05183	0.050954		0.08954	1.043	300 ± 20							
12	50			0.3954	0.05096	0.05009		0.09505	0.966	600 ± 20							
13	60			0.4144	0.05009			0.10056	1.218	1100 ± 100							
14	K = [major]/[minor]																
15				For chem. shift extrapolation:							k for major to minor						
16				slope =			-8.700E-05		5.510E-04								
17				int. =			0.05531		0.06750								
18	Compound 8																
19	T	31P integral	t-Bu integral	CHN integral	average K	calcd 1/K	all chem. shift differences in ppm				CHN	TMS	k(t-Bu) (s-1)	k(CHN) (s-1)			
20		K(31P)	K(t-Bu)	K(CHN)	for gNMR	shift diff	t-Bu chem	extrapolated	shift diff	extrapolated	v(1/2) (Hz)						
21	-60	8.0588	7.5000	7.4706	7.6684	0.1341	0.2427	0.2426	0.1143	0.11555	2.4874						
22	-40	5.9294	6.3158	6.0476	6.0940	0.1544	0.2305	0.2311	0.137	0.1345	1.7339	0.1 ± 0.1	0.5 ± 0.25				
23	-20		6.1257	5.7767	5.9468	0.1738	0.2210	0.2195	0.1522	0.15345	1.7339	1.5 ± 0.5	1 ± 0.25				
24	-10					0.1832	0.2128	0.2138		0.162925	1.3338	5 ± 2	5 ± 1				
25	22					0.2116		0.1953		0.193245	1.2758	90 ± 20	160 ± 20				
26	K = [major]/[minor]																
27						For chem. shift extrapolation:					k for major to minor						
28						slope =			-5.776E-04		9.475E-04						
29						int. =			0.2080		0.1724						
30	Compound 9																
31	T	31P integral	t-Bu integral	CHN integral	average K	calcd 1/K	all chem. shift differences in ppm				CHN	31P chem	31P	TMS	Ph3	k(t-Bu) (s-1)	k(CHN) (s-1)
32		K(31P)	K(t-Bu)	K(CHN)	for gNMR	shift diff	t-Bu chem	extrapolated	shift diff	extrapolated	shift diff	extrapolated	v(1/2) (Hz)	v(1/2) (Hz)			
33	-40	10.5612	11.3750	11.6667	11.1826	0.0913	0.2779	0.2780	0.1231	0.1243	0.9080	0.9045	2.21	2.78			
34	-20	9.1304	9.5758	9.4904	9.3953	0.1045	0.2633	0.2633	0.1408	0.1392	0.8760	0.8800	1.07	3.05	0.05 ± 0.05	0.2 ± 0.1	0.1 ± 0.1
35	0	7.1066	8.4870	8.6235	8.0178	0.1172	0.2488	0.2486	0.1553	0.1540	0.8500	0.8554	1.18	2.46	0.5 ± 0.4	0.7 ± 0.1	1 ± 0.5
36	10	7.8108	9.6942	8.5030	8.6054	0.1294	0.2412	0.2413	0.1598	0.1615	0.8490	0.8431	0.93	2.73	1.5 ± 0.2	2 ± 0.5	1.5 ± 0.5
37	23					0.1312		0.2338		0.1711		0.8271	0.88	3.16	7 ± 1	7 ± 1	5 ± 1
38	30					0.1353		0.2267		0.1763		0.8185	0.88	1.65	13 ± 1	12 ± 1	9 ± 1
39	40					0.1411		0.2193		0.1837		0.8062	0.92	1.54		50 ± 10	35 ± 5
40	50					0.1468		0.2120		0.1912		0.7940	0.82	1.54		50 ± 10	50 ± 10
41	K = [major]/[minor]																
42						For chem. shift extrapolation:					k for major to minor						
43						slope =			-7.328E-04		7.427E-04		-1.229E-03		(line-width used for calculations)		
44						int. =			0.2486		0.1540		0.8554		is shown above, each is 1 Hz lower		
45	Compound 10																
46	T	CH2	CH2	calcd 1/K	chem. shift differences in ppm				CH2 chem	TMS	k(CH2) (s-1)						
47		K(CH2)	K(t-Bu)	for gNMR	CH2 chem	extrapolated	shift diff	extrapolated	shift diff	v(1/2) (Hz)							
48	-20	0.11	9.0909	0.1100	0.0845	0.0847			1.98								
49	-10	0.12	8.3333	0.1212	0.0845	0.0843			1.65	0.2 ± 0.1							
50	0	0.13	7.6923	0.1326	0.0840	0.0839			1.88	0.6 ± 0.1							
51	5	0.14	7.1429	0.1384	0.0835	0.0837			1.65	1 ± 0.1							
52	15	0.15	6.6667	0.1500	0.0833	0.0833			1.53	2.8 ± 0.2							
53	25			0.1617	0.0829	0.0829			1.06	7 ± 1							
54	30			0.1676	0.0827	0.0827			1.00	13 ± 1							
55	K = [major]/[minor]																
56				For chem. shift extrapolation:							k for major to minor						
57				slope =			-3.8983E-05										
58				int. =			0.08388										



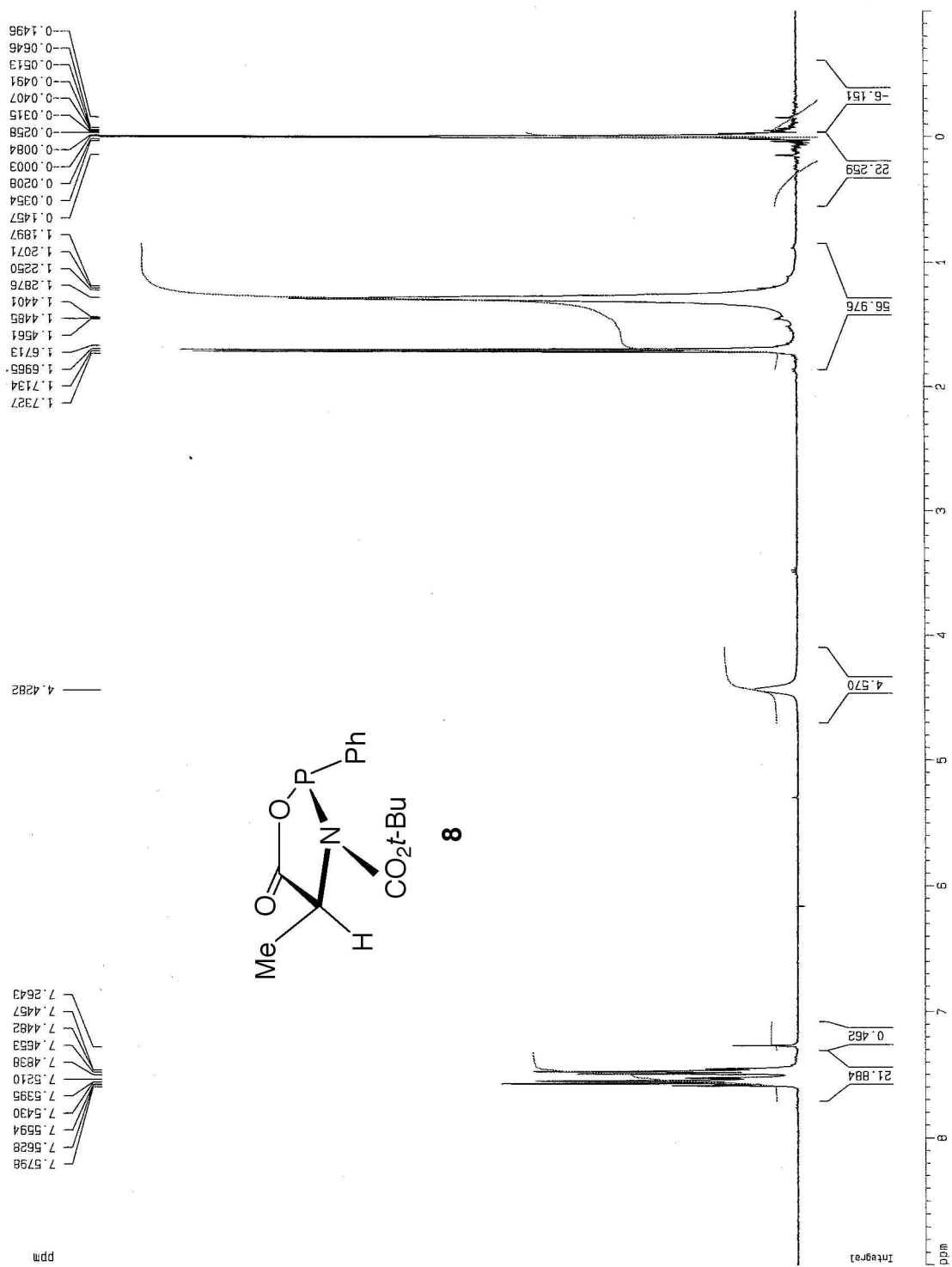


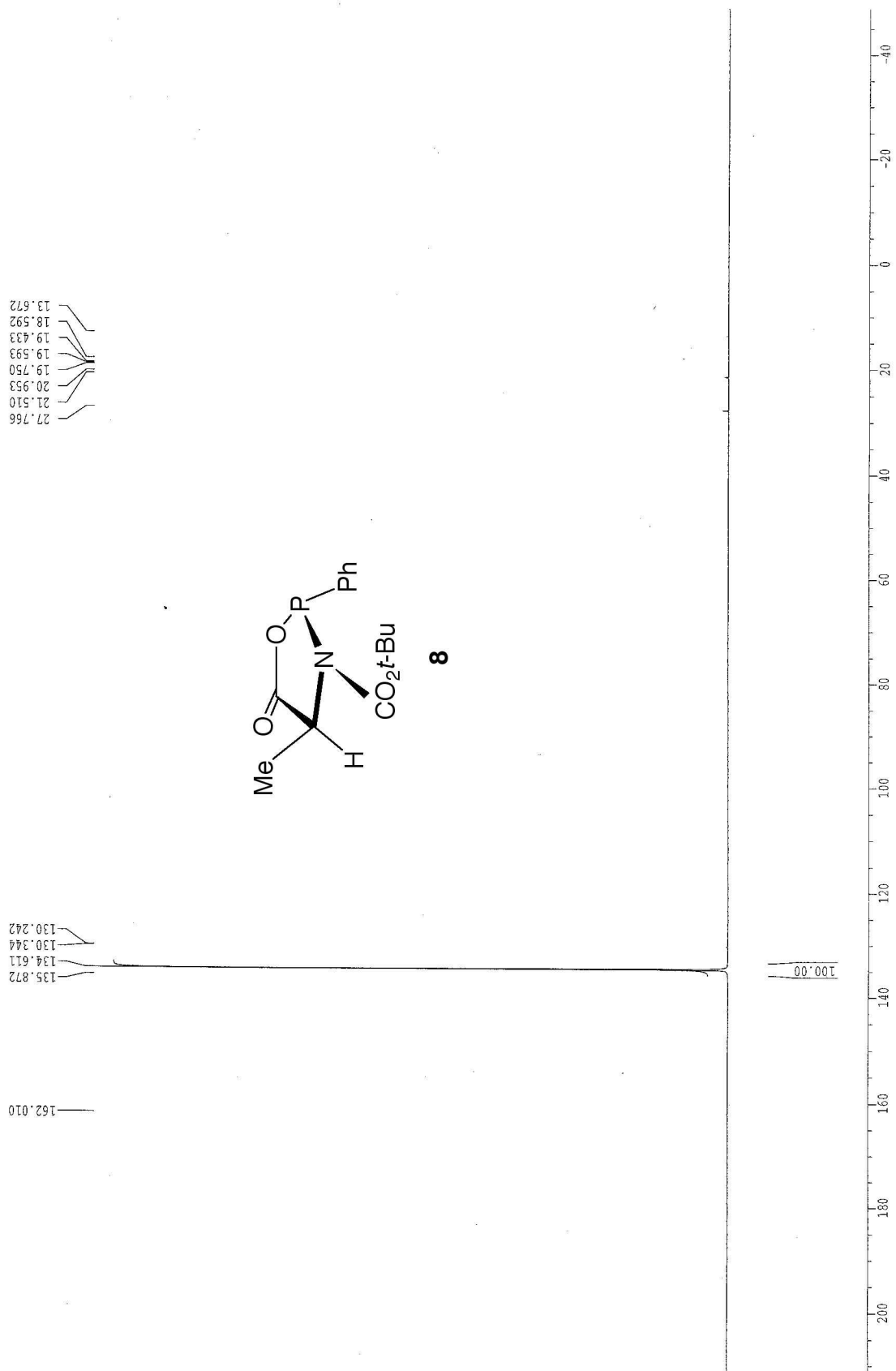


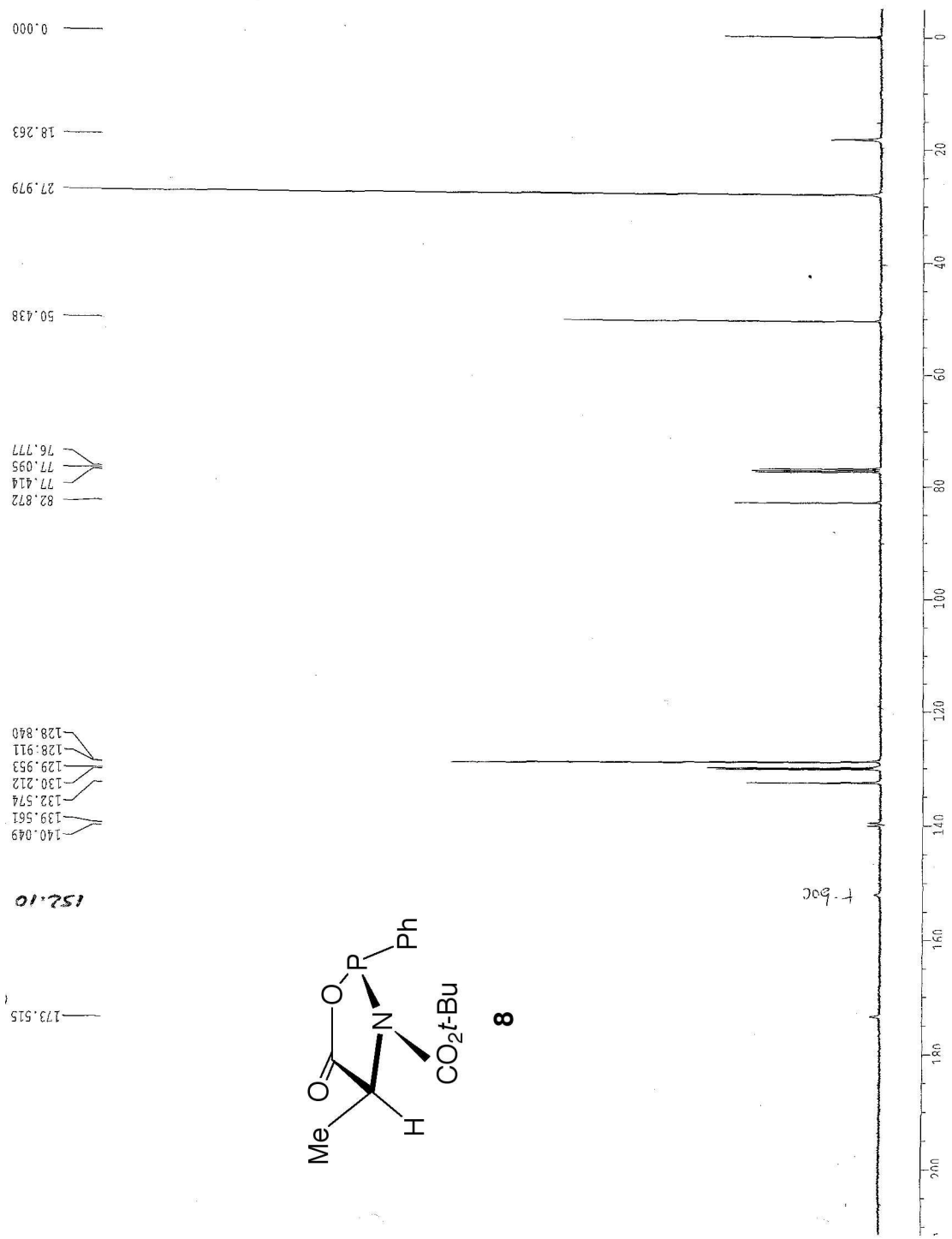
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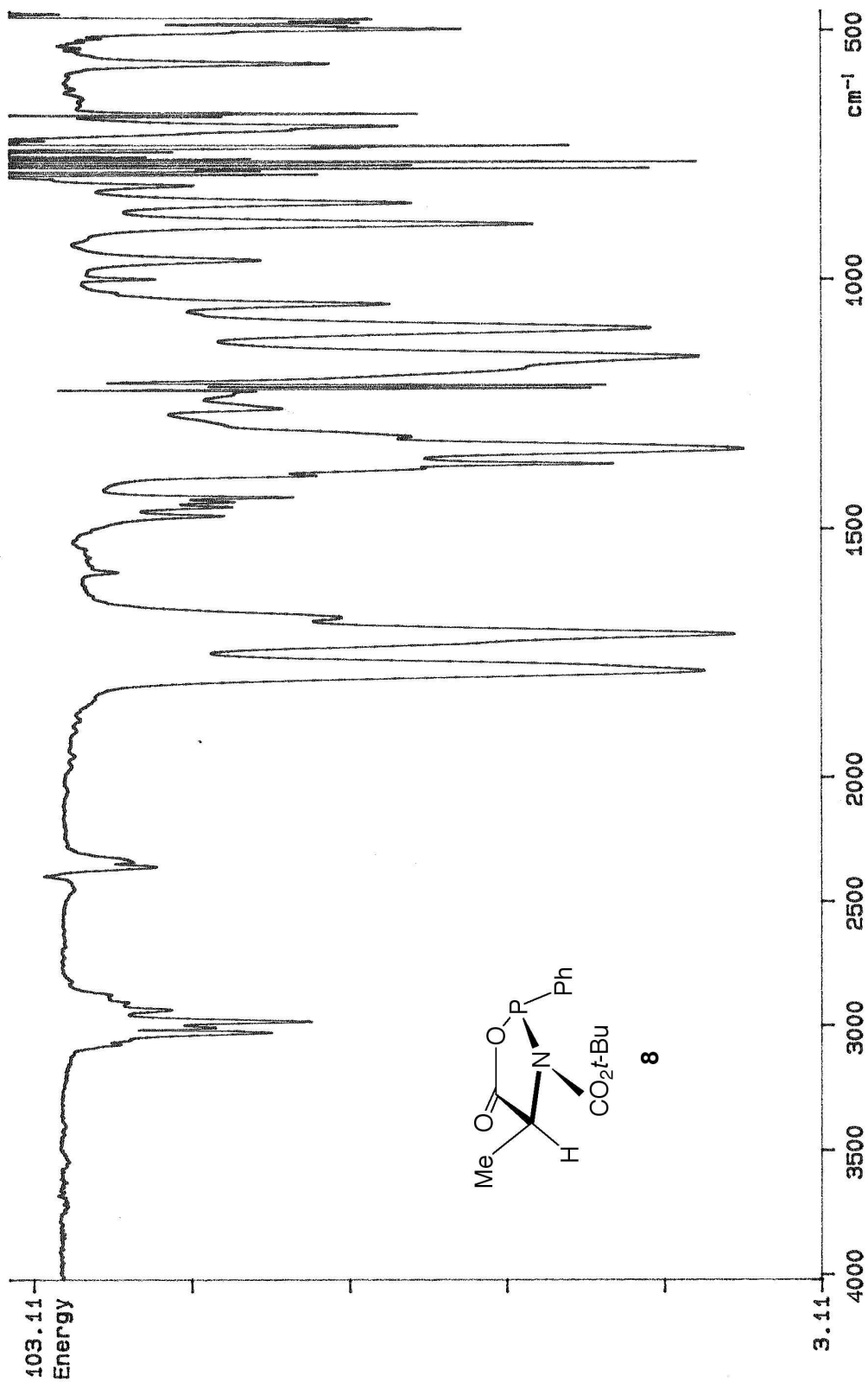




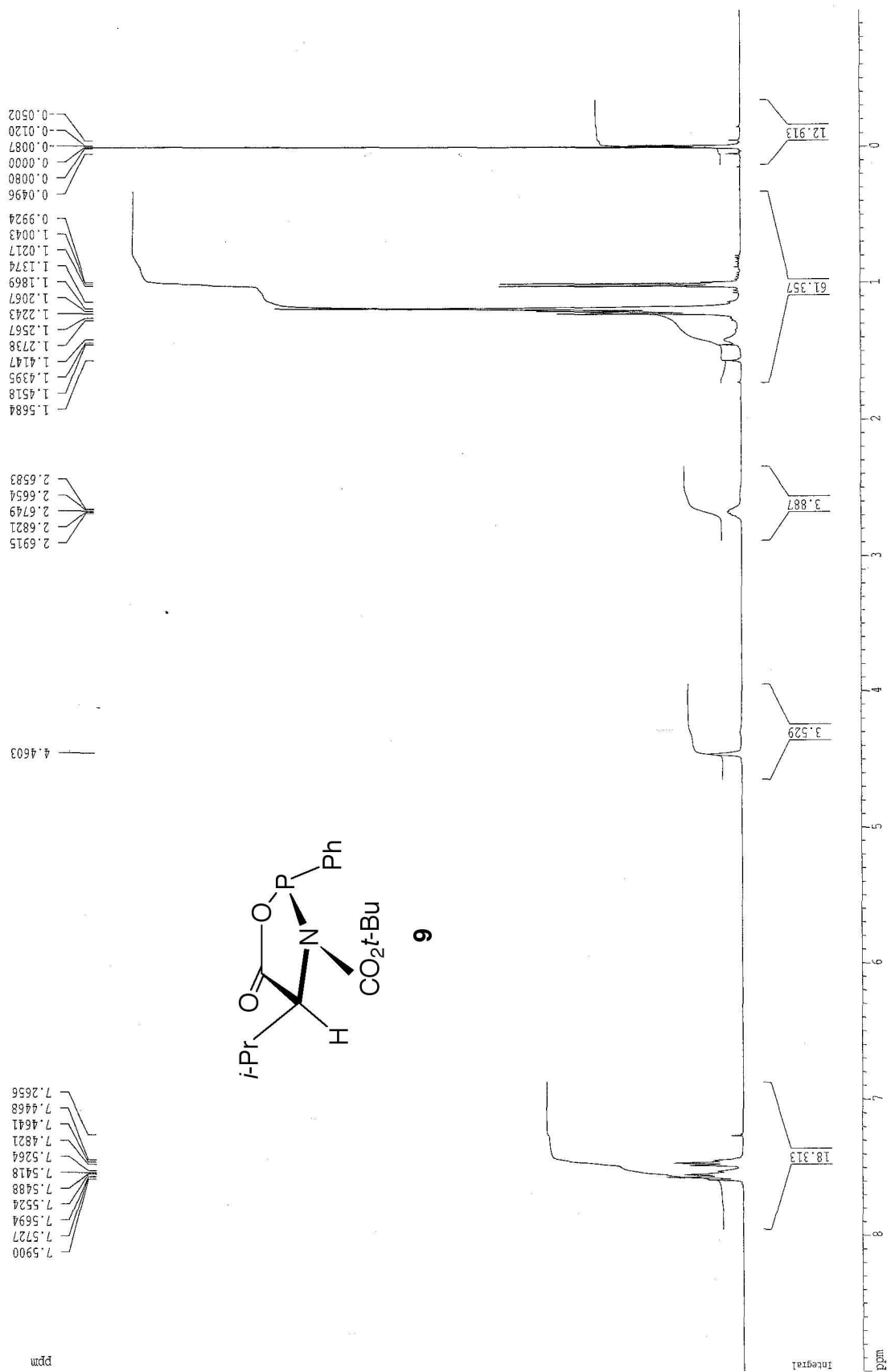


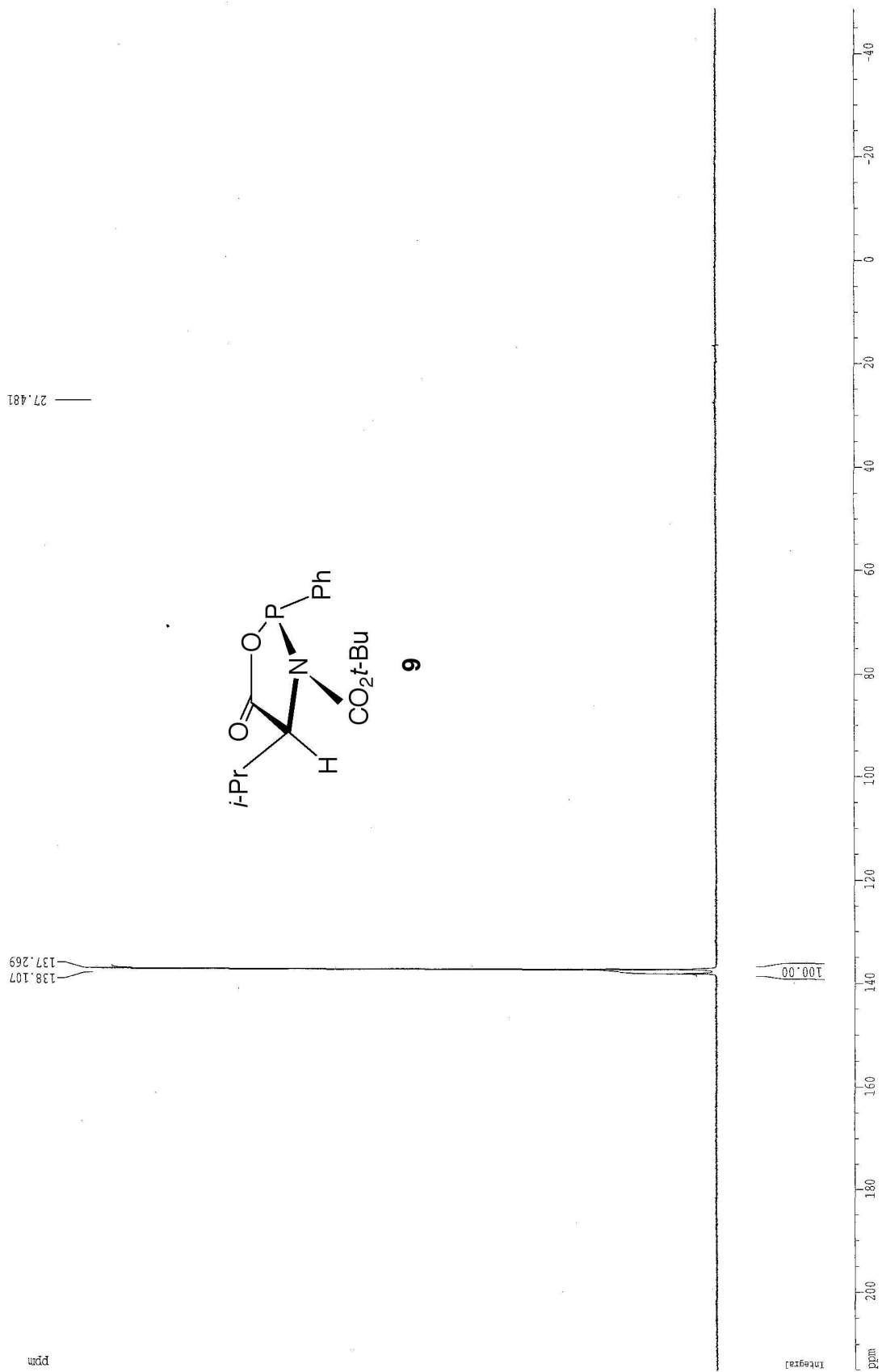
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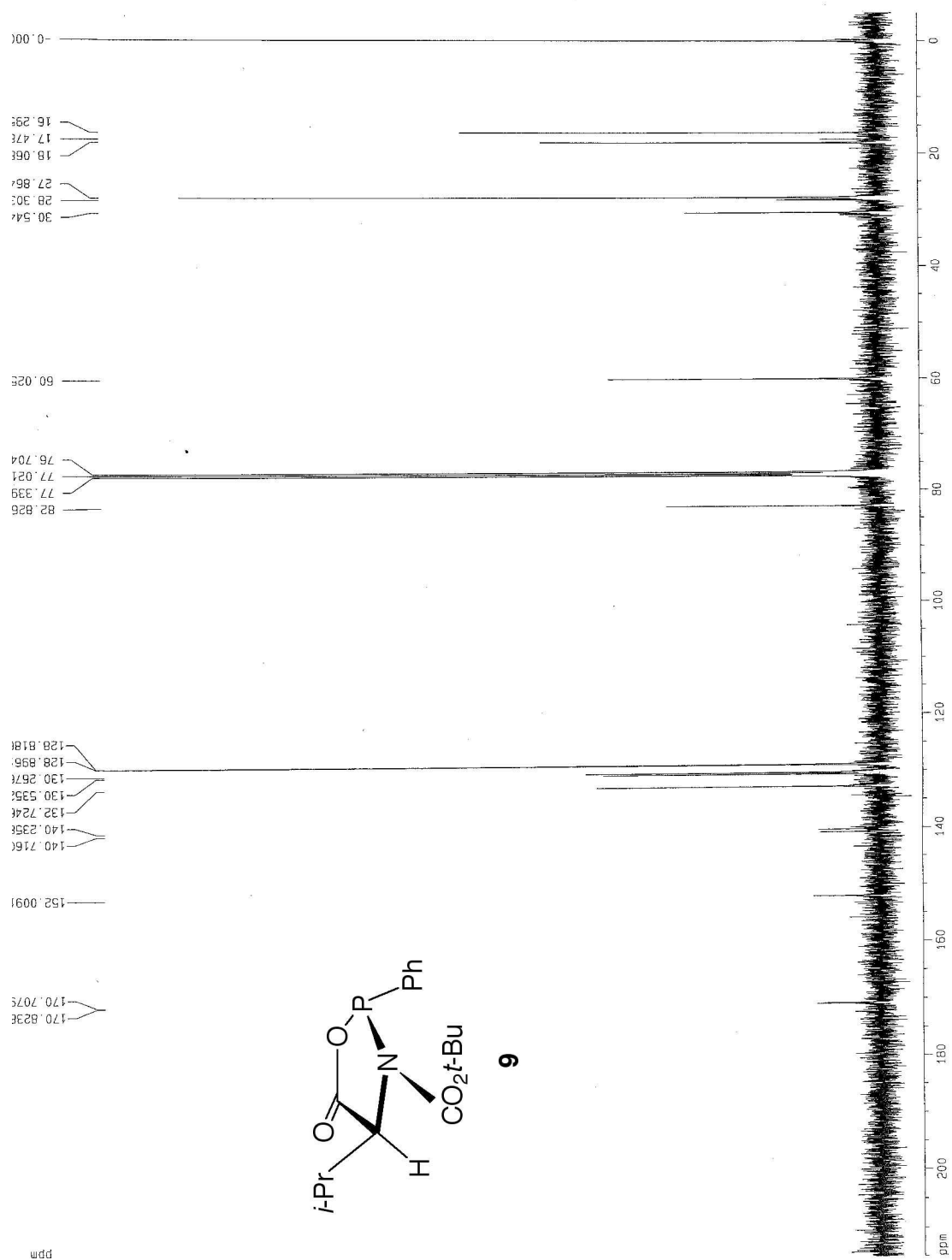
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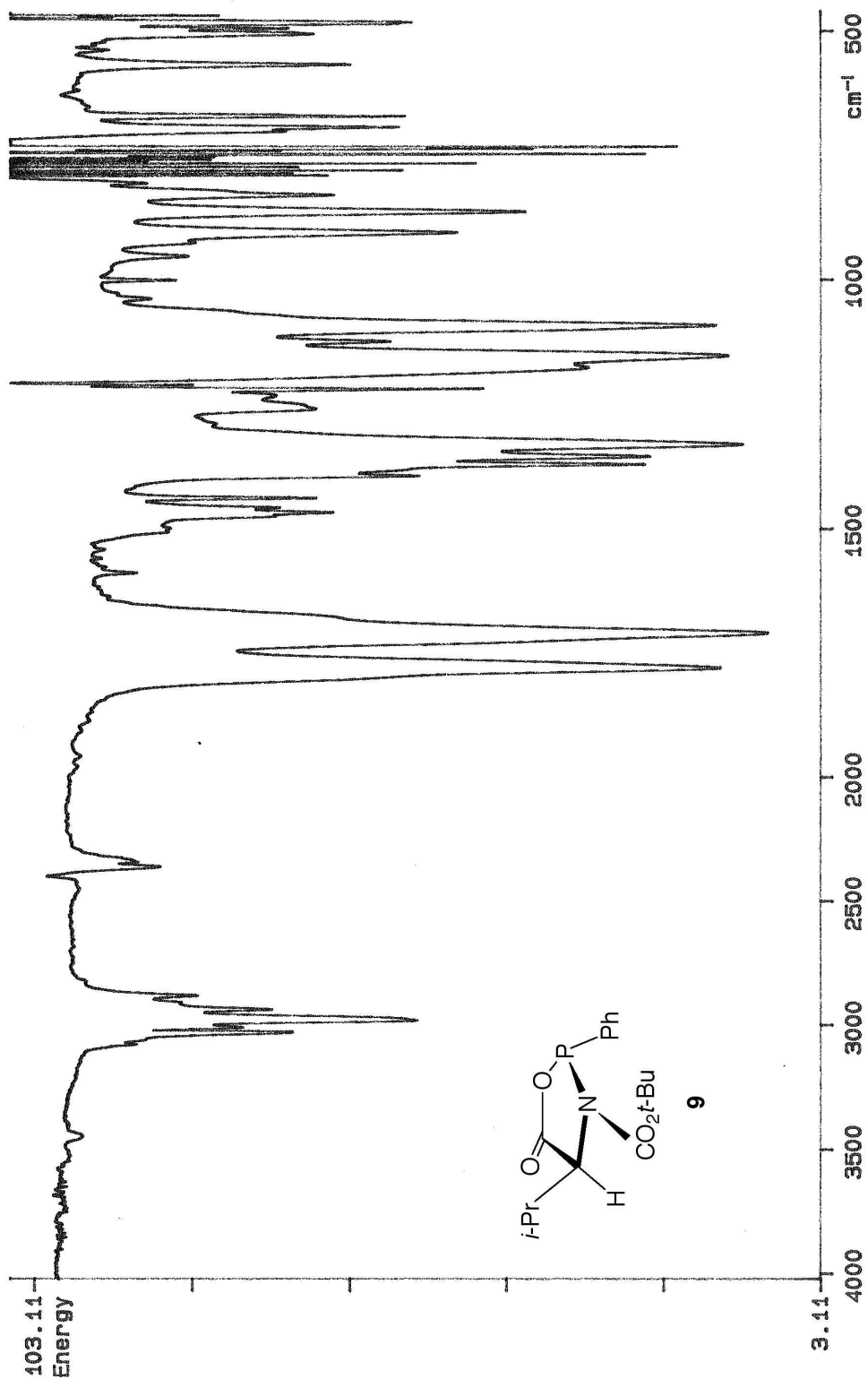
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P-E



1/2/04
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