Metal-Catalyzed Rearrangement of Enantiomerically Pure Alkylidenecyclopropane Derivatives as a New Access to Cyclobutenes Possessing Quaternary Stereocenters

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1. General Procedures

General procedure for the preparation of cyclobutene derivatives with Pt-catalyst (procedure A):

$PtCl_2$ (53.2 mg, 0.2 mmol) was added to a solution of alkylidenecyclopropane **1** (1 mmol) in 1,2-dichloroethane (10 mL) under Argon atmosphere. The resulting mixture was then stirred at 80 °C for 12 hours (monitored by TLC). The mixture was then filtered through a short pad of silica and the filtrate was evaporated. The crude product was purified by column chromatography on silica gel (hexane as eluent) to give products **2** and/ or **3.**

General procedure for the preparation of cyclobutene derivatives 2a-b with Pt-catalyst under CO atmosphere (procedure C):

$PtCl_2$ (53.2 mg, 0.2 mmol) was added to a solution of alkylidenecyclopropane **1** (1 mmol) in toluene (10 mL). The resulting mixture was then stirred at 80 °C under CO atmosphere (1 atm). The mixture was then filtered through a short pad of silica and the filtrate was evaporated. The crude product was purified by column chromatography on silica gel (hexane as eluent) to give products **2** and/ or **3.**

General procedure for the preparation of cyclobutene derivatives with Pd-catalyst (procedure B):

To a solution of alkylidenecyclopropane **1** (1 mmol) in 1, 2-dichloroethane (10 mL) was added palladium acetate (22.45 mg, 0.1 mmol) and copper(II) bromide (44.67 mg, 0.2 mmol). The mixture was stirred under Ar atmosphere for 6-10 hours at 80 °C (monitored by TLC). Then the mixture was filtered through a short pad of silica, the solvent was removed under reduced pressure and the crude was subjected to a flash column chromatography on silica gel (hexane as eluent) to give the products **2** and/ or **3.**

General procedure for the preparation of dicarbonyl derivatives 11-12 from cyclobutenes (procedure D):

RuO_2 (13.31 mg, 0.1 mmol) was added to a solution of cyclobutene **2** (0.5 mmol) and $NaIO_4$ (3 mmol) in $CDCl_3$ (4 mL) and H_2O (2 mL). The resulting mixture was then stirred at room temperature for 10 h (monitored by TLC). The aqueous layer was then extracted with ether (3×3 mL), the organic phases were combined and washed with brine (1×3 mL), separated, dried and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane / ethyl acetate 10:1) to give products **11** or **12.**

2. Characterization Data

(3-ethyl-3-methylcyclobut-1-enyl)benzene **(2a)**. Was prepared from the general procedure C. Pale yellow oil isolated in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 8.6 Hz, 3H), 1.13 (s, 3H), 1.47 (dq, J_1 = 1.7 Hz, J_2 = 8.0 Hz, 2H), 2.37 (dd, J_1 = 12.5 Hz, J_2 = 36.5 Hz, 2H), 6.42 (s, 1H), 7.24-7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 23.9, 32.9, 40.7, 43.6, 124.7, 127.7, 128.6, 135.6, 136.0, 142.9.

1-(3-ethyl-3-methylcyclobut-1-enyl)-4-methylbenzene **(2b)**. Was prepared from the general procedure C. Pale yellow oil isolated in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H), 1.16 (s, 3H), 1.50 (dq, J_1 = 1.6 Hz, J_2 = 7.9 Hz, 2H), 2.29 (s, 3H), 2.39 (dd, J_1 = 12.5 Hz, J_2 = 36.2 Hz, 2H), 6.31 (s, 1H), 7.07 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 21.6, 23.9, 32.9, 40.7, 43.5, 124.6, 129.2, 132.9, 134.8, 137.5, 142.7.

1,3-dibromo-5-(3-ethyl-3-methylcyclobut-1-enyl)benzene **(2c)**. Was prepared from the general procedure A. Pale yellow oil isolated in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 1.14 (s, 3H), 1.48 (dq, J_1 = 1.9 Hz, J_2 = 8.1 Hz, 2H), 2.34 (dd, J_1 = 12.6 Hz, J_2 = 37.5 Hz, 2H), 6.44 (s, 1H), 7.31 (d, J = 1.8 Hz, 2H), 7.44 (t, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 23.6, 32.6, 40.6, 44.1, 123.2, 126.5, 132.8, 138.9, 139.6, 140.4.

1,3-dibromo-5-(3-ethyl-3-methylcyclobut-1-enyl)benzene **(2d)**. Was prepared from the general procedure A. Pale yellow solid isolated in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3H), 1.2 (s, 3H), 1.54 (dq, J_1 = 1.8 Hz, J_2 = 8.0 Hz, 2H), 2.42 (dd, J_1 = 12.3 Hz, J_2 = 35.7 Hz, 2H), 3.76 (s, 3H), 6.70 (s, 1H), 6.84 (d, J = 9.3

Hz, 2H), 7.27 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 23.2, 32.3, 40.1, 42.6, 54.8, 113.2, 125.3, 128.0, 132.6, 141.6, 158.7.

1-(benzyloxy)-2-(3-ethyl-3-methylcyclobut-1-enyl)benzene **(2e)**. Was prepared from the general procedure B. Pale yellow oil isolated in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.18 (s, 3H), 1.53 (dq, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 2H), 2.49 (dd, J_1 = 12.3 Hz, J_2 = 35.4 Hz, 2H), 5.11 (s, 2H), 6.45 (s, 1H), 6.88-6.94 (m, 2H), 7.13-7.19 (m, 2H), 7.28-7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 23.1, 32.2, 41.1, 43.5, 69.6, 111.2, 120.1, 123.8, 126.6, 127.1, 127.4, 127.9, 128.1, 136.7, 138.4, 140.5, 156.9.

((2-(3-ethyl-3-methylcyclobut-1-enyl)ethyl)benzene **(2f)**. Was prepared from the general procedure A. Pale yellow oil isolated in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J = 7.4 Hz, 3H), 1.03 (s, 3H), 1.37 (dq, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 2H), 2.01 (dd, J_1 = 12.8 Hz, J_2 = 35.3 Hz, 2H), 2.24 (dt, J_1 = 1.1 Hz, J_2 = 8.0 Hz, 2H), 2.68 (t, J = 8.0 Hz, 2H), 5.76 (t, J = 1.4 Hz, 1H), 7.09-7.24 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 23.9, 32.7, 32.9, 33.5, 39.1, 43.3, 123.1, 128.5, 128.6, 136.2, 142.6, 146.2.

(3-butyl-3-methylcyclobut-1-enyl)benzene **(2g)**. Was prepared from the general procedure B. Pale yellow oil isolated in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 5.6 Hz, 3H), 1.19 (s, 3H), 1.23-1.33 (m, 4H), 1.43-1.50 (m, 2H), 2.40 (dd, J_1 = 12.5 Hz, J_2 = 34.7 Hz, 2H), 6.37 (s, 1H), 7.14-7.19 (m, 2H), 7.23-7.31 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 23.7, 24.4, 28.4, 40.1, 41.2, 43.1, 124.6, 127.7, 128.5, 135.5, 136.3, 142.6.

(3-allyl-3-methylcyclobut-1-enyl)benzene **(2h)**. Was prepared from the general procedure B. Pale yellow oil isolated in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H), 2.23 (t, J = 6.2 Hz, 2H), 2.46 (dd, J_1 = 12.6 Hz, J_2 = 45.8 Hz, 2H), 4.95-5.03 (m, 2H), 5.74-5.88 (m, 1H) 6.36 (s, 1H), 7.17-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 39.8, 41.8, 44.0, 115.9, 123.7, 124.6, 126.8, 128.2, 134.7, 135.7, 141.9.

1-bromo-4-(3-ethyl-3-methylcyclobut-1-enyl)benzene **(2i)**. Was prepared from the general procedure B. Pale yellow oil isolated in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 8.9 Hz, 3H), 1.16 (s, 3H), 1.50 (dq, J_1 = 1.5 Hz, J_2 = 7.9 Hz, 2H), 2.40 (dd, J_1 = 12.6 Hz, J_2 = 36.3 Hz, 2H), 6.38 (s, 1H), 7.14-7.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 23.0, 32.1, 39.9, 42.8, 123.8, 126.9, 127.8, 134.7, 135.2, 142.1.

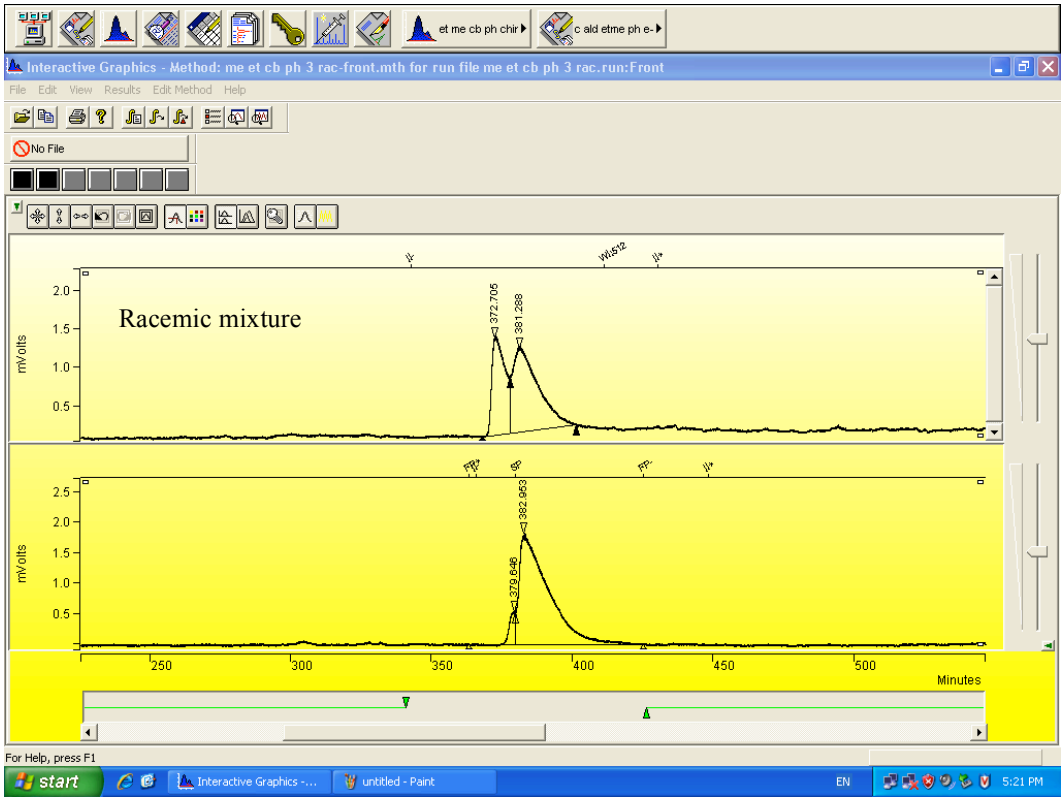
1-(3-butyl-3-methylcyclobut-1-enyl)-4-methylbenzene **(2j)**. Was prepared from the general procedure B. Pale yellow oil isolated in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H), 1.15 (s, 3H), 1.23-1.31 (m, 4H), 1.43-1.50 (m, 2H), 2.28 (s, 3H), 2.39 (dd, J_1 = 12.5 Hz, J_2 = 34.7 Hz, 2H), 6.30 (s, 1H), 7.06 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.9, 23.0, 23.7, 27.7, 39.4, 40.5, 42.2, 123.8, 128.5, 132.1, 134.3, 136.7, 141.8.

2-ethyl-2-methyl-4-oxo-6-phenylhexanal **(11)**. Was prepared from the general procedure D. Pale yellow oil isolated in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (t, J = 7.4 Hz, 3H), 1.05 (s, 3H), 1.44-1.52 (m, 2H), 2.47-2.71 (m, 4H), 2.81 (t, J = 10.1 Hz, 2H), 7.10-7.24 (m, 5H), 9.48 (s, 1H),. ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 18.2, 28.1, 29.2, 44.4, 48.1, 49.7, 125.7, 127.8, 128.0, 140.3, 204.9, 207.4.

2-ethyl-2-methyl-4-oxo-4-phenylbutanal **(12)**. Was prepared from the general procedure D. Pale yellow oil isolated in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J = 9.0 Hz, 3H), 1.15 (s, 3H), 1.56-1.71 (m, 2H), 3.22 (dd, J_1 = 17.7 Hz, J_2 = 28.5 Hz, 2H), 7.38-7.43 (m, 2H), 7.43-7.54 (m, 1H), 7.87-7.90 (m, 2H), 9.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.3, 19.2, 29.1, 32.6, 45.1, 128.3, 128.9, 133.4, 133.7, 198.2, 205.8.

Determination of enantiomeric excesses.

(S)-(3-ethyl-3-methylcyclobut-1-enyl)benzene **(2a)**. $[\alpha]_D^{25}$ -22.76 (*c* 0.018, diethyl ether). Determination of the ee of **2a** by GC (column: TFA-β-Cyclodextrin; 50 °C ;



600 min).

Racemic mixture

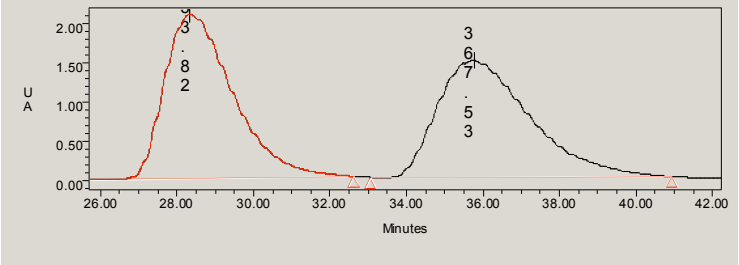
Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		48.4878	372.705	0.000	488704	BV	191.6	U
2		51.5122	381.288	0.000	625165	VB	784.6	U
	Totals:	100.0000		0.000	1113869			

Enantioenriched mixture

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		5.3276	379.646	0.000	73103	BV	0.0	
2		94.6724	382.953	0.000	1299054	VB	447.3	
	Totals:	100.0000		0.000	1372157			

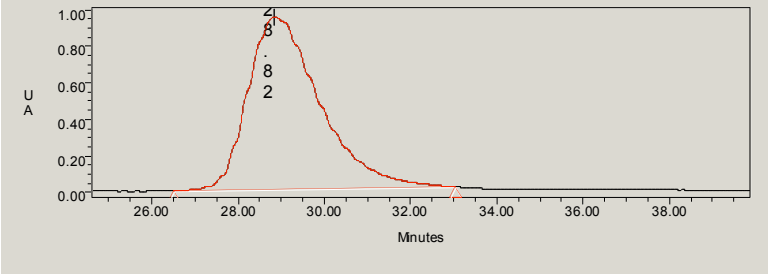
(S)-2-ethyl-2-methyl-4-oxo-6-phenylhexanal **(11).** The enantiomeric ratio was determined by HPLC using a 0.46 x 25 cm Chiralcell-AD-H column; flow rate: 0.3 mL.min^{-1}; eluent: (hexane: 2-propanol, 98:2).

Racemic mixture



	Retention Time	Area	% Area	Height	Int Type	Width
1	28.337	258328764	50.94	2087301	bb	456.000
2	35.763	248833898	49.06	1492222	bb	472.500

Enantioenriched mixture



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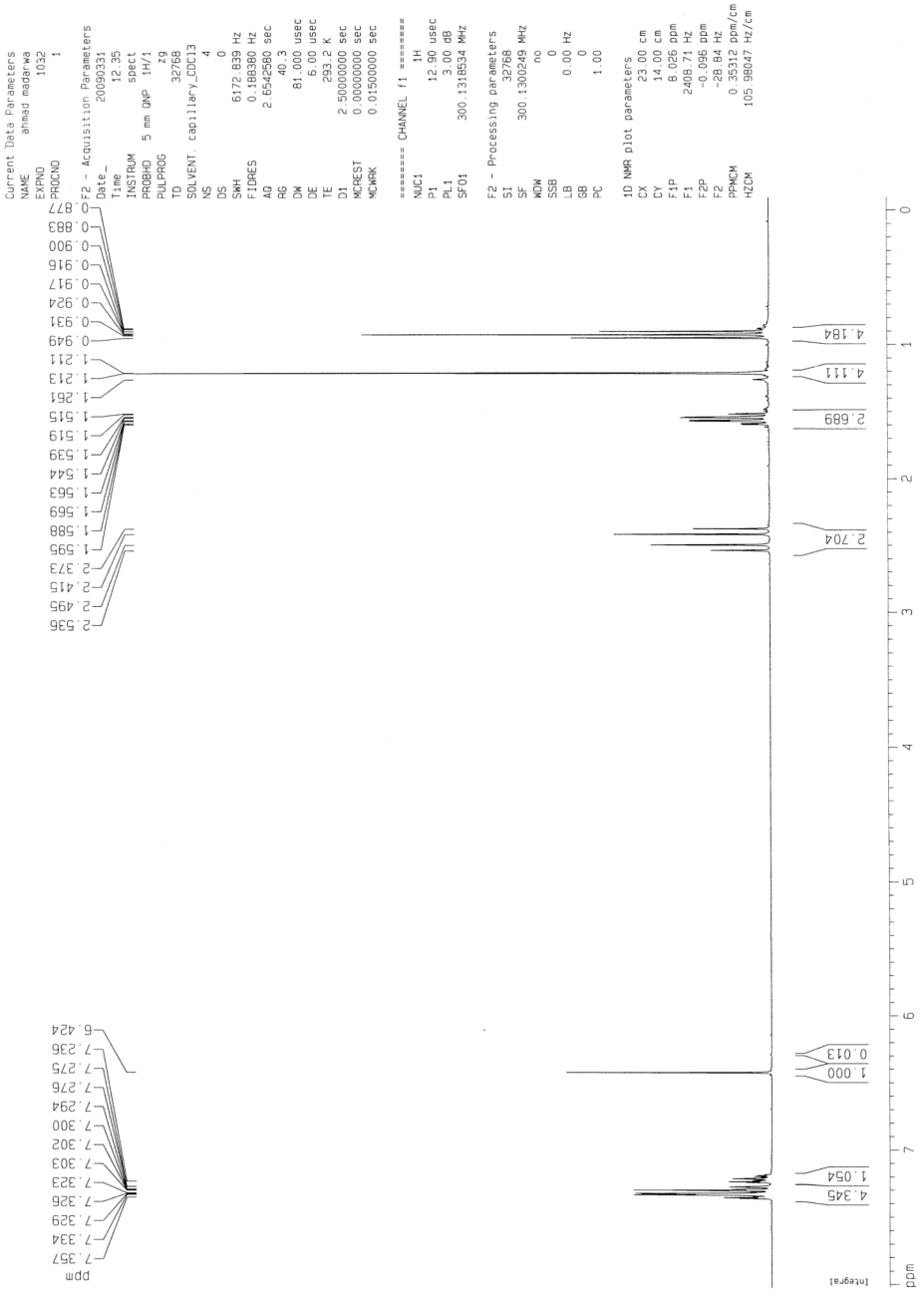
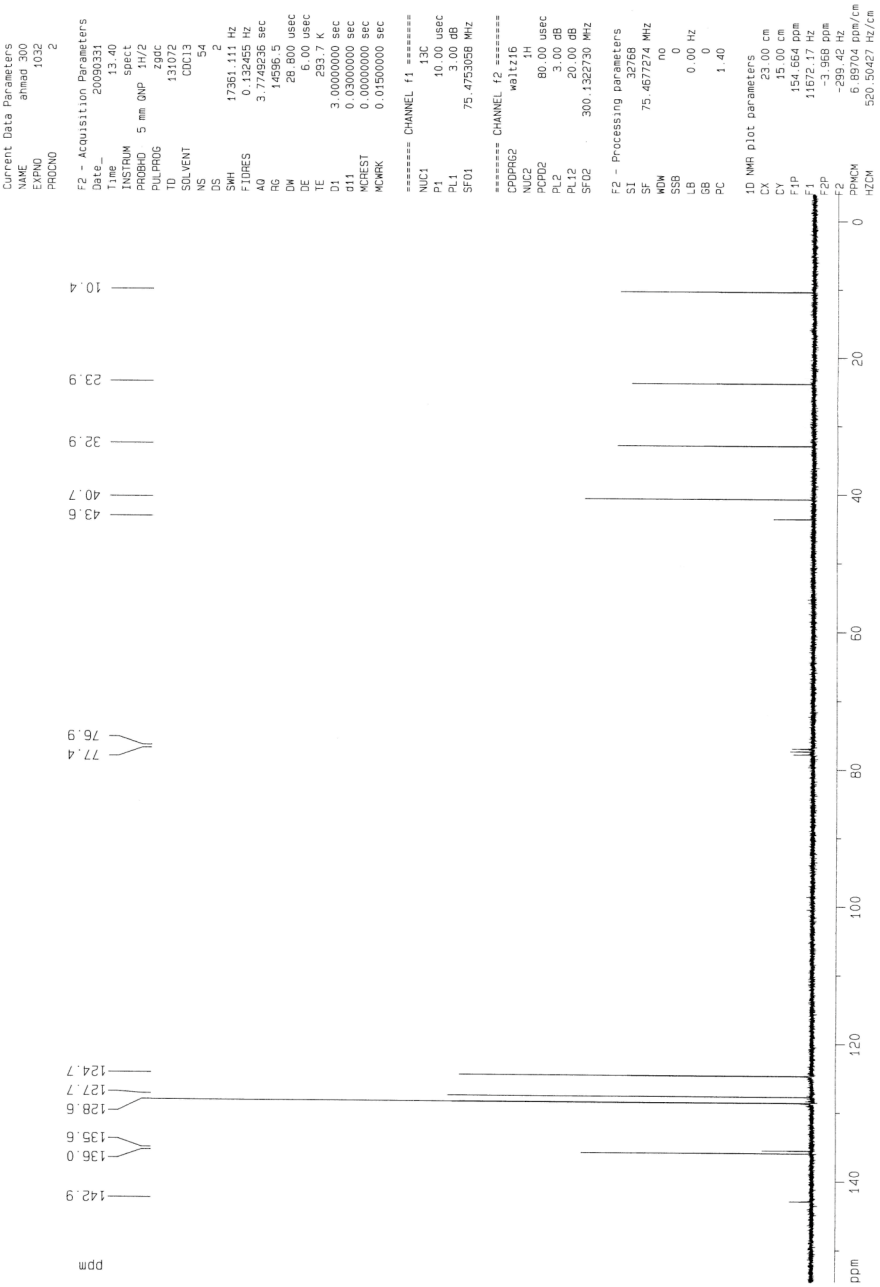
	Retention Time	Area	% Area	Height	Int Type	Width
1	28.826	109804009	100.00	945764	bb	391.500

NMR and NOE analyses

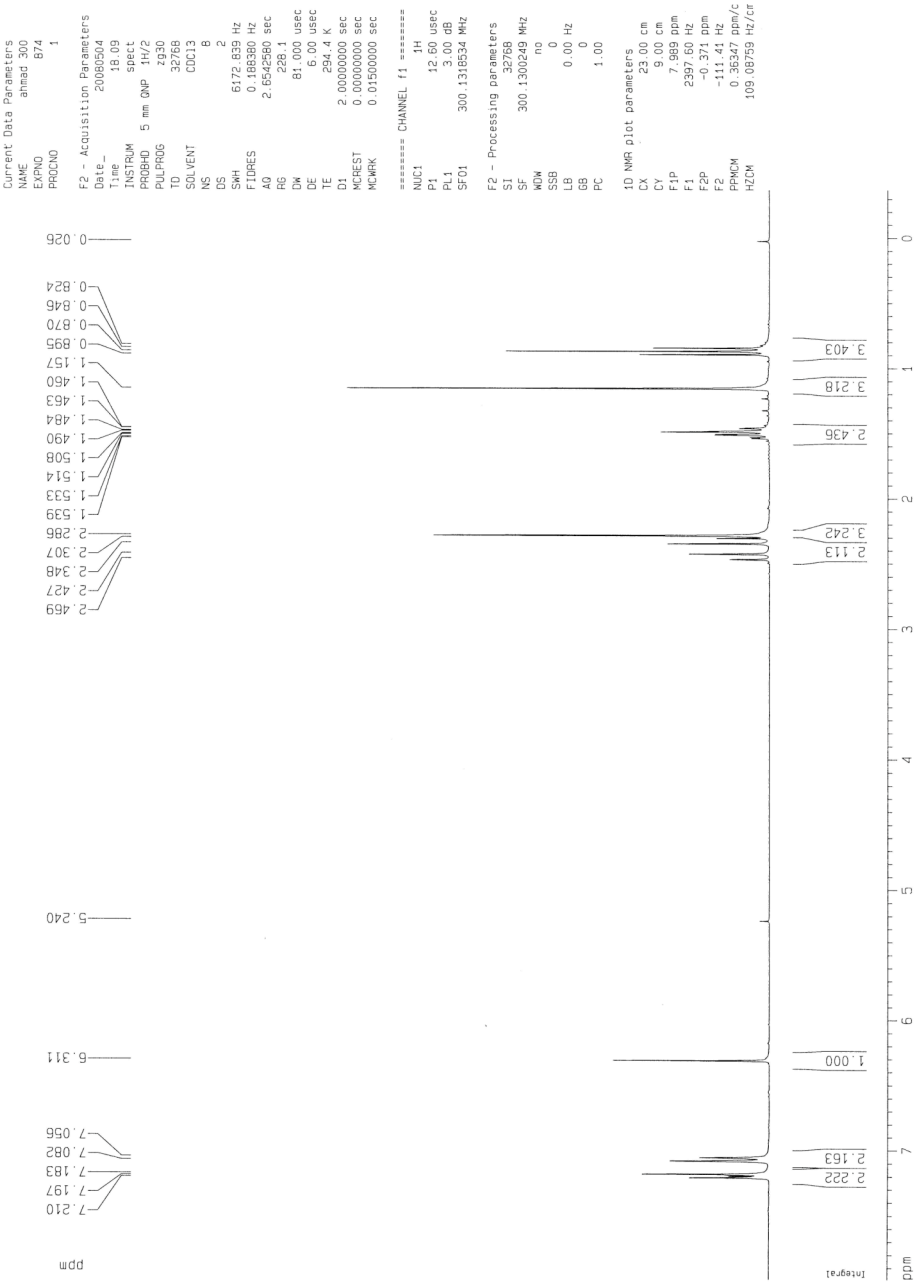
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2a**



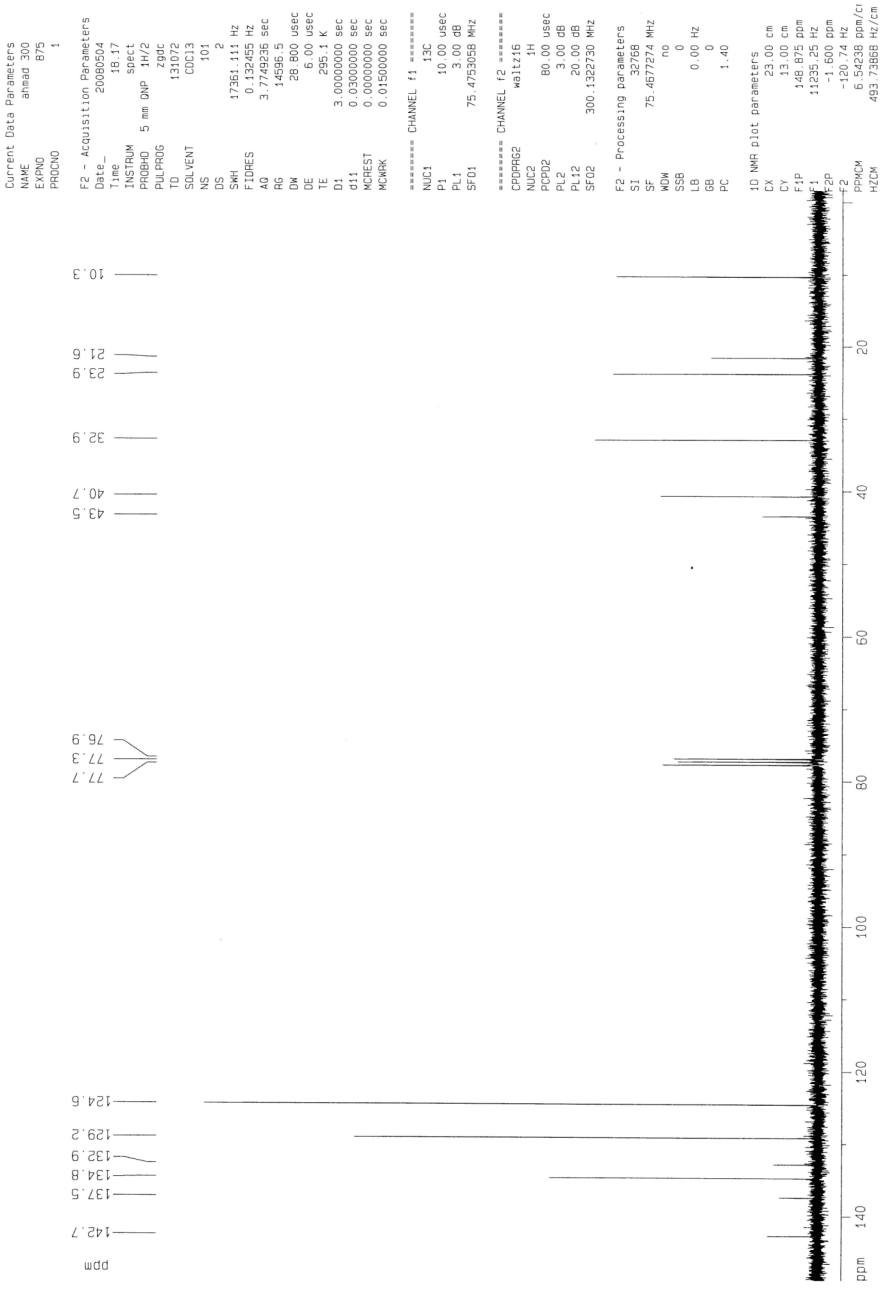
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2a**



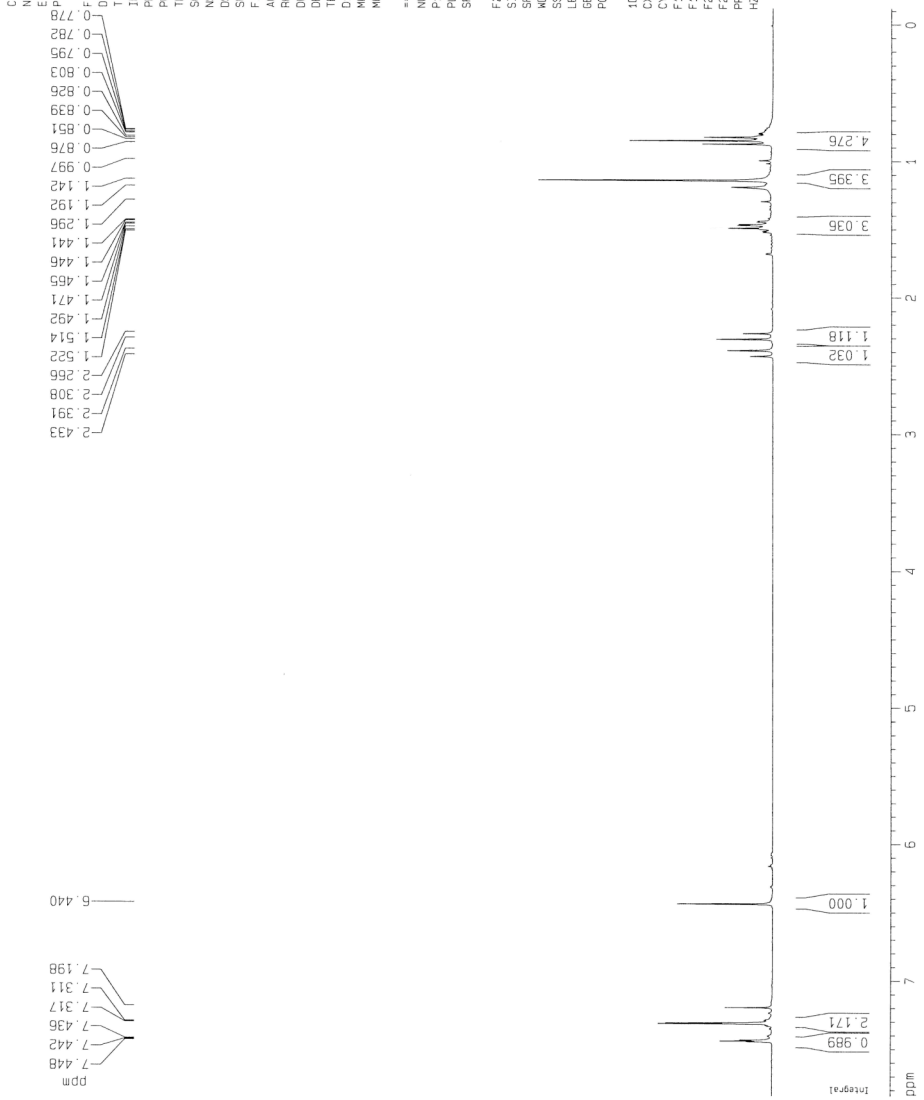
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2b**



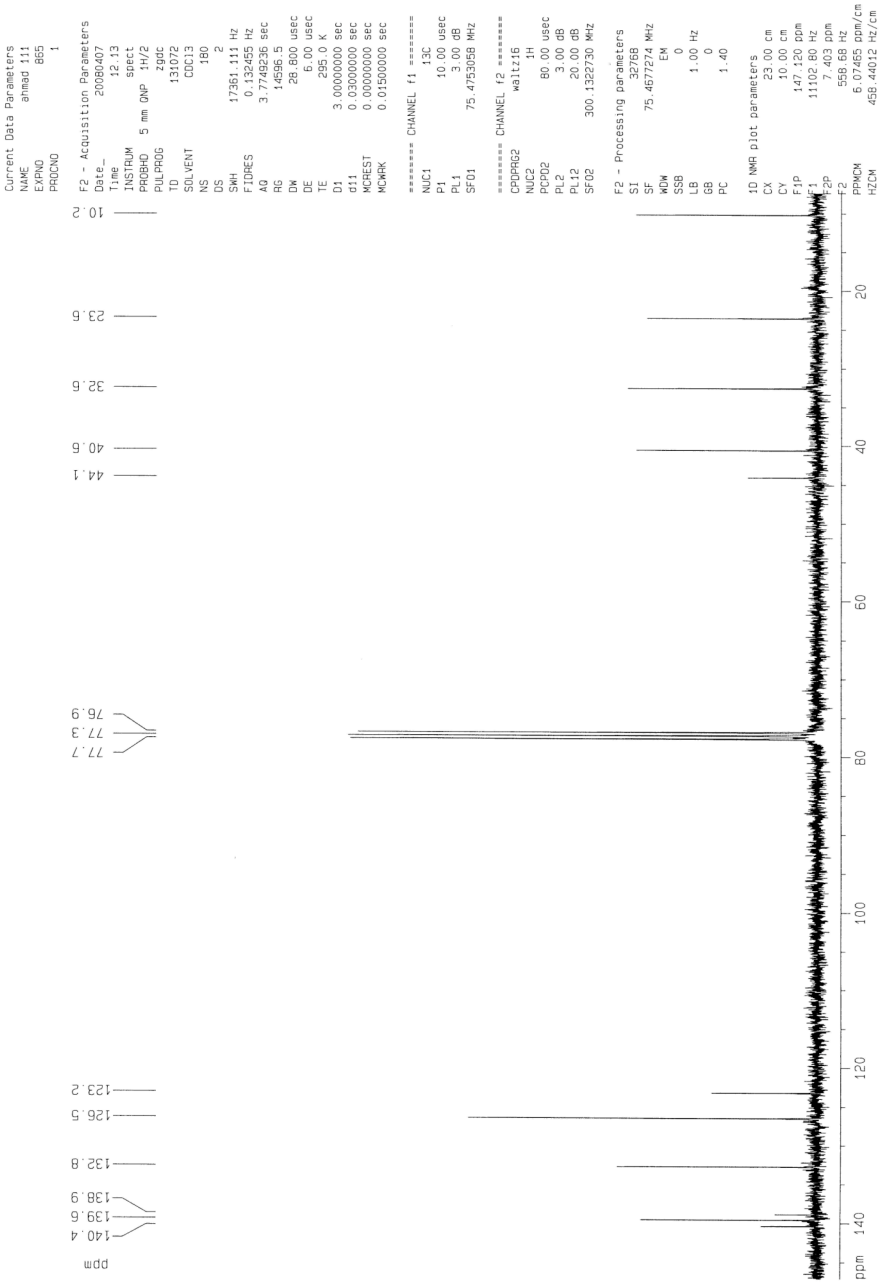
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2b**



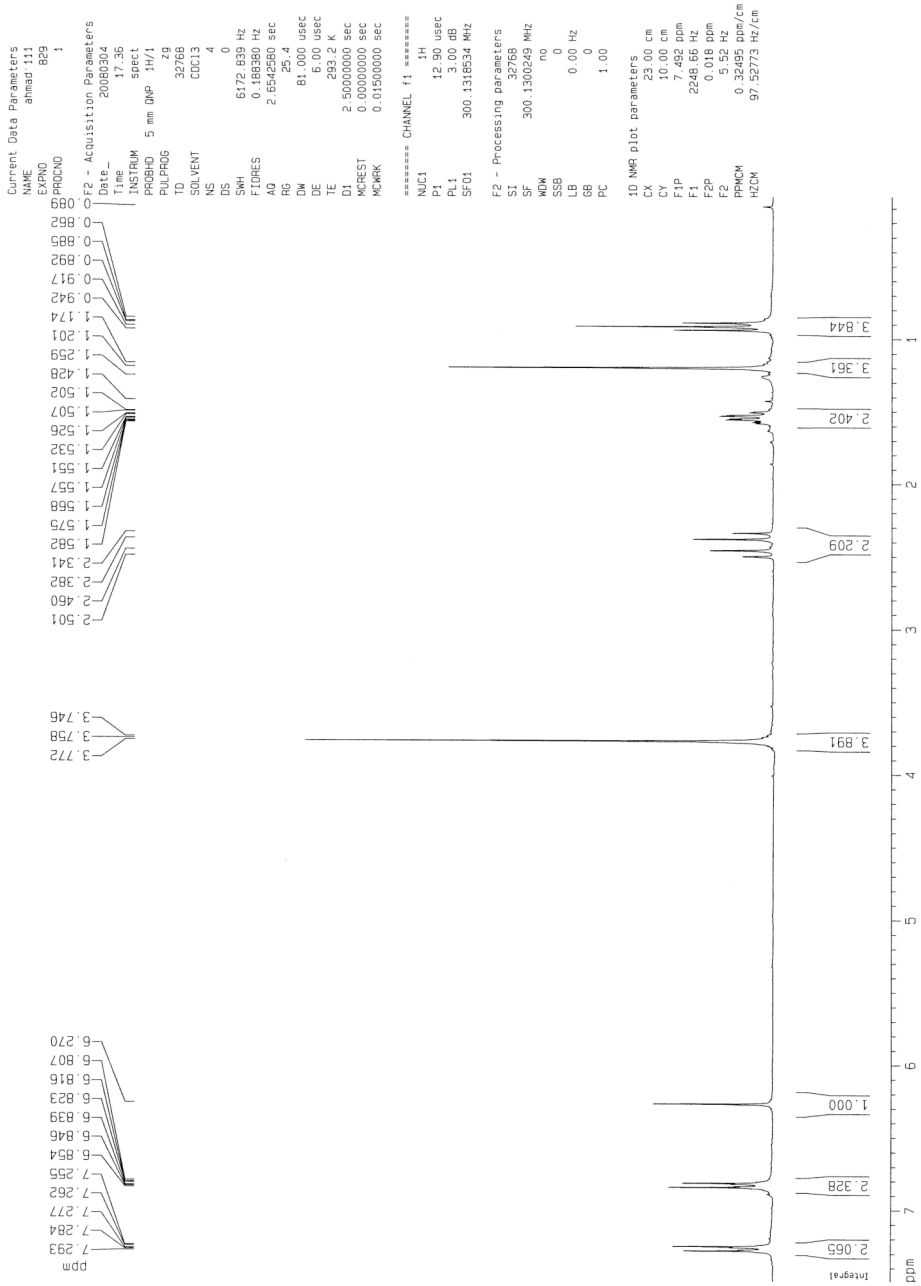
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2c**



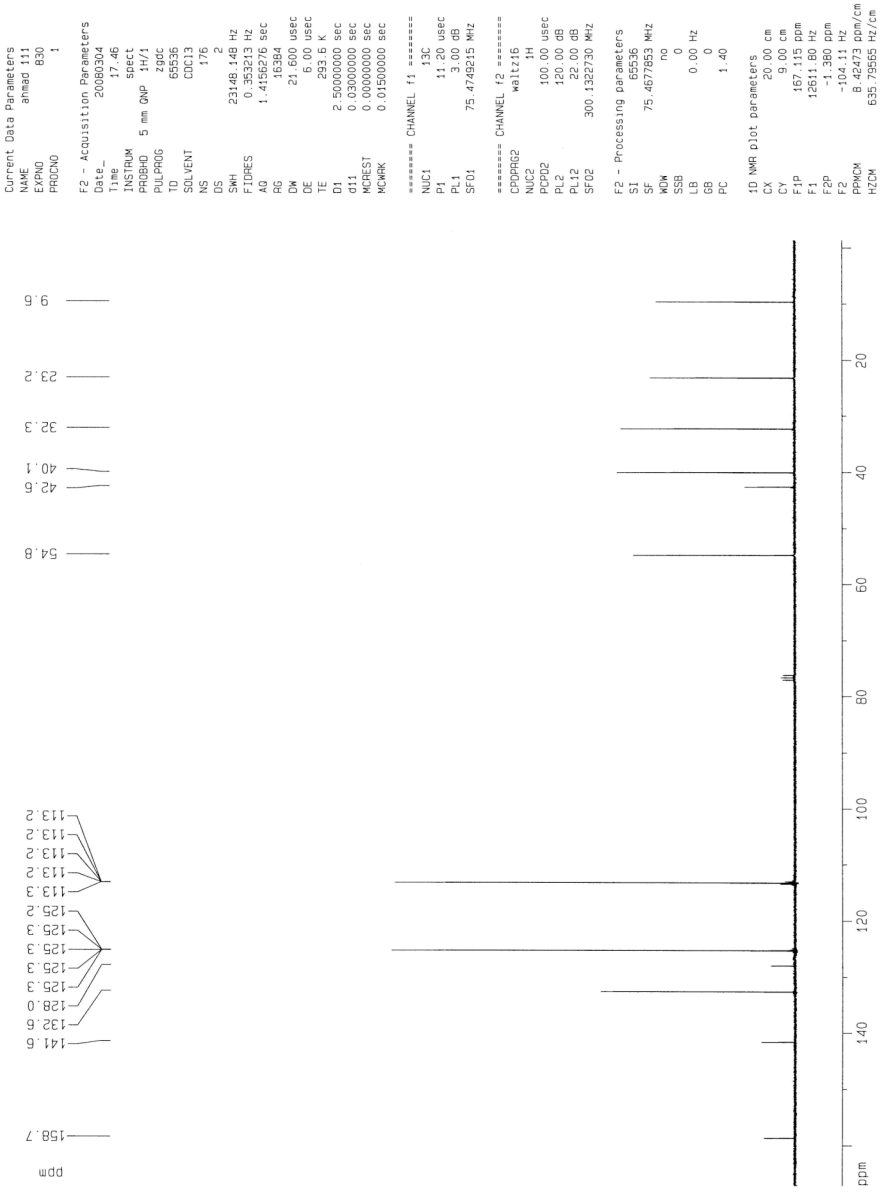
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2c**



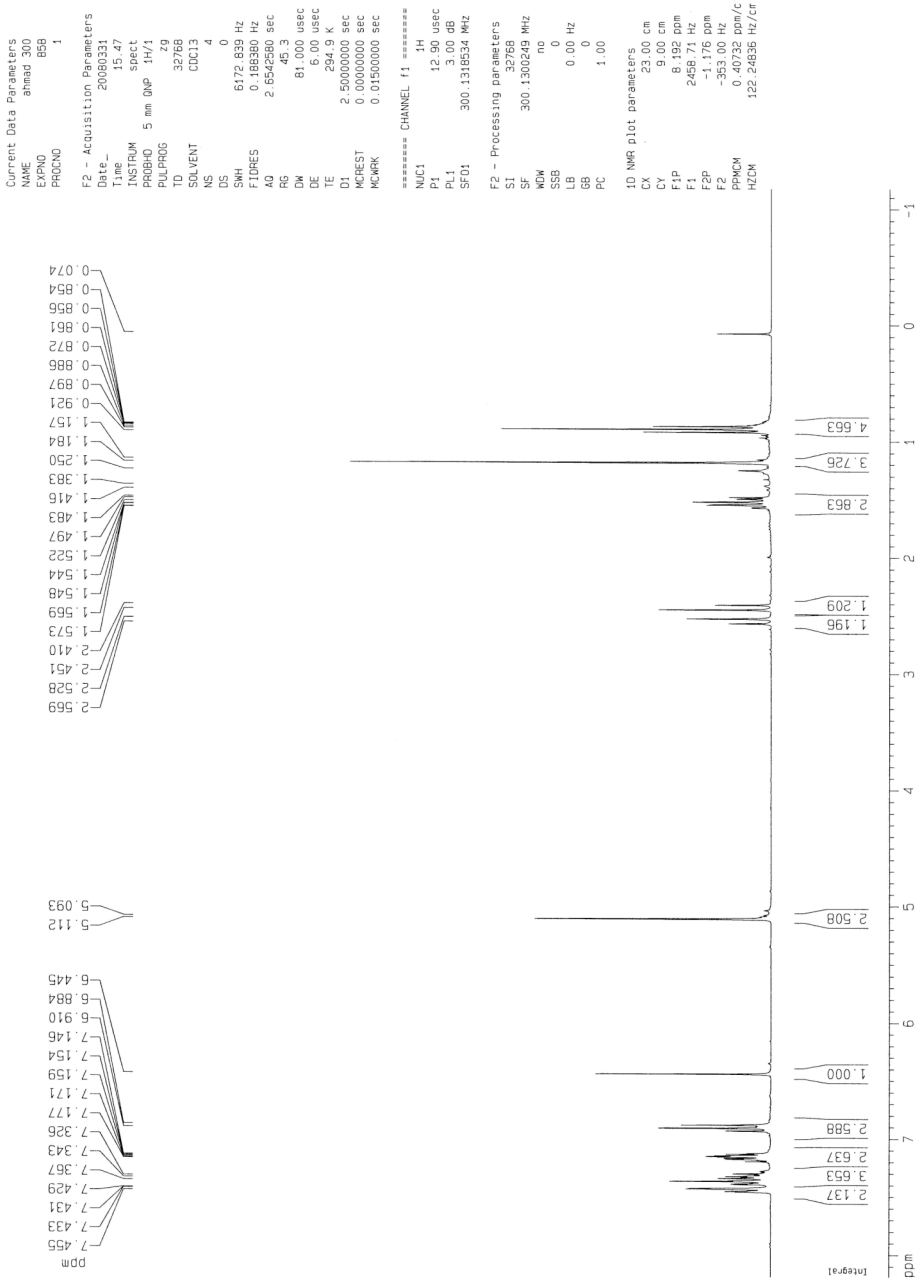
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2d**



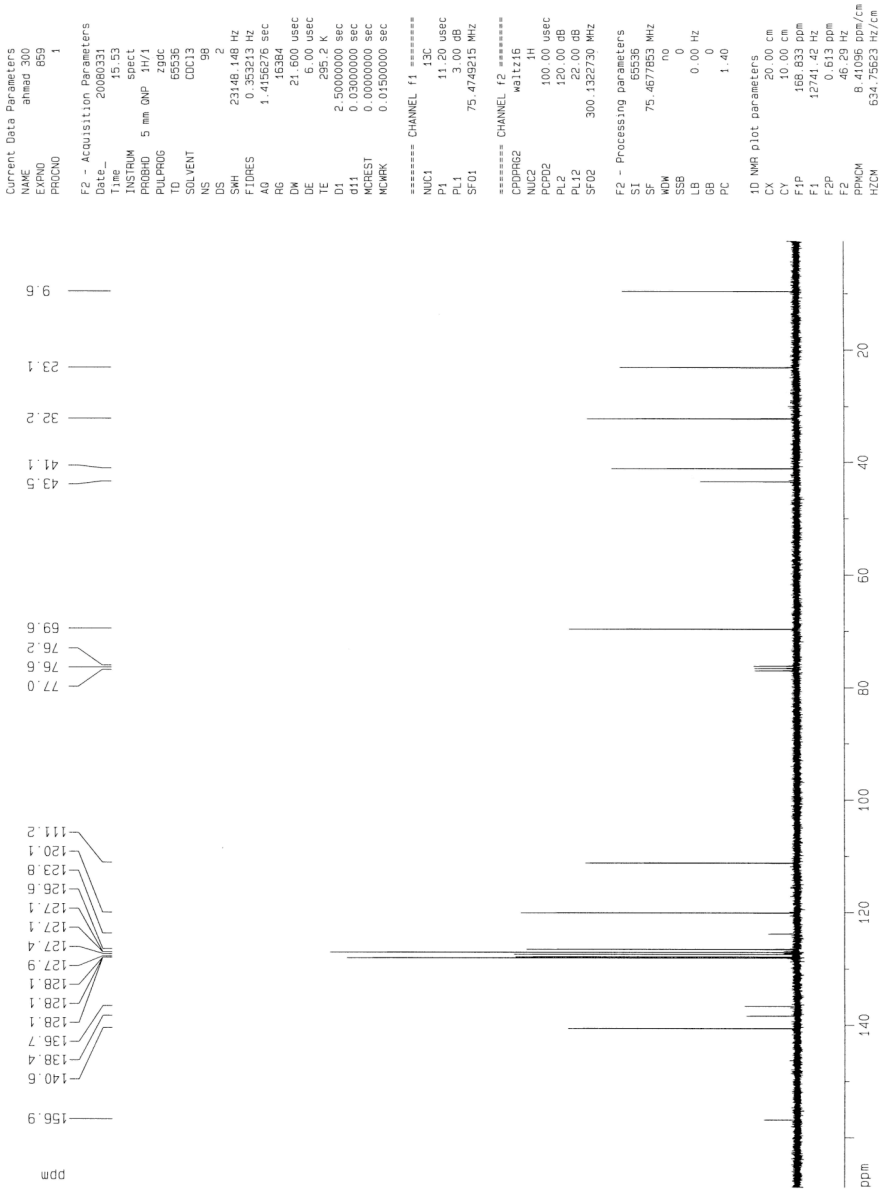
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2d**



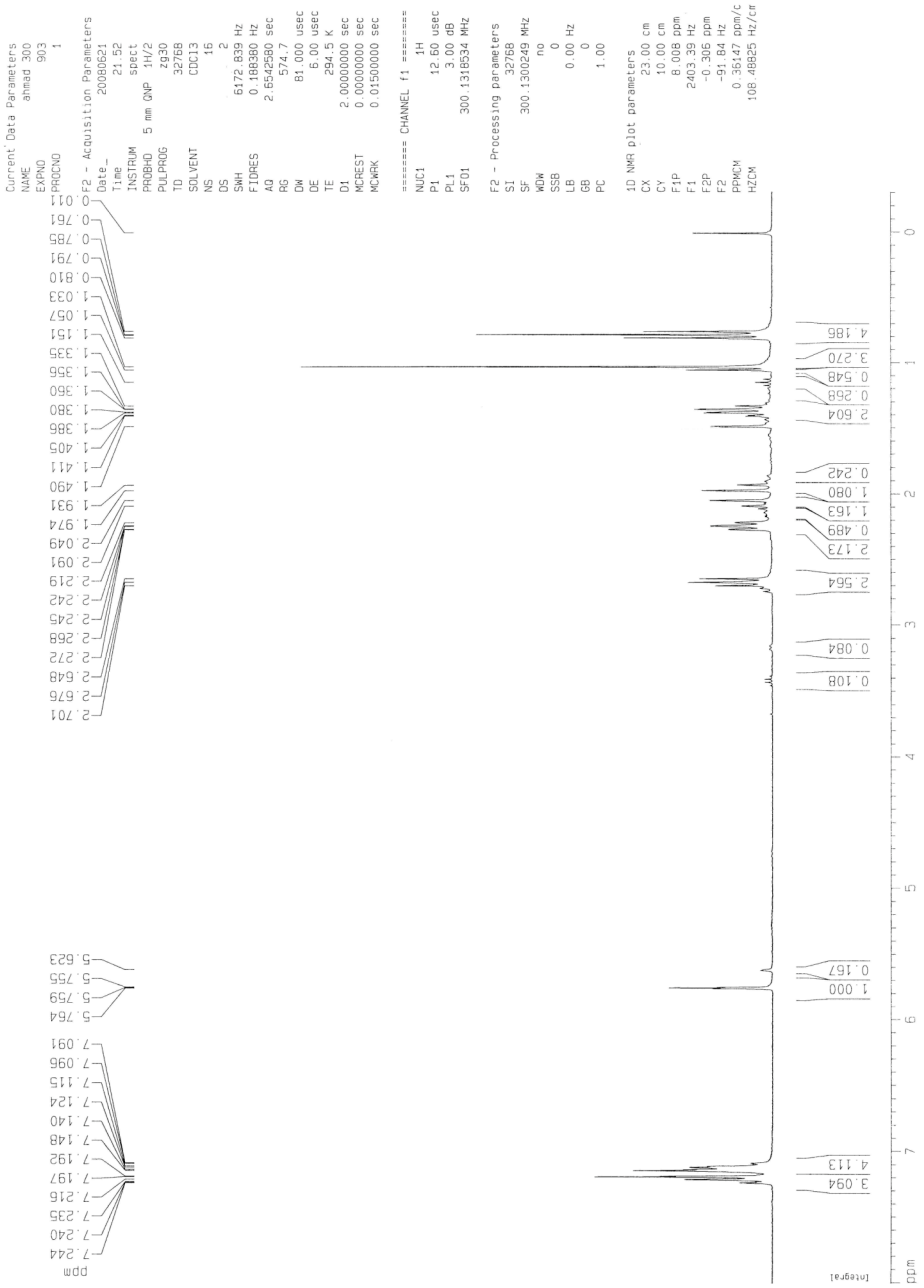
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2e**



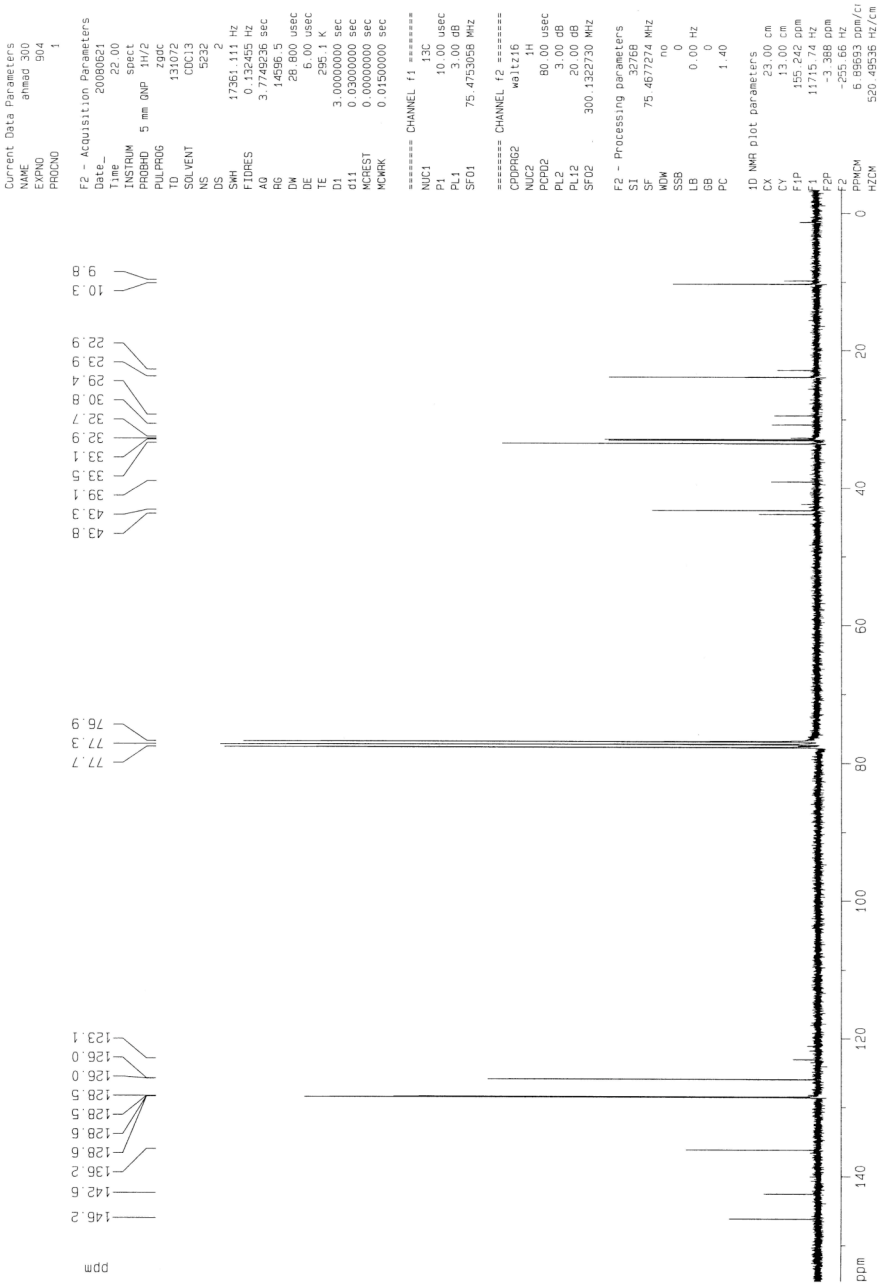
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2e**



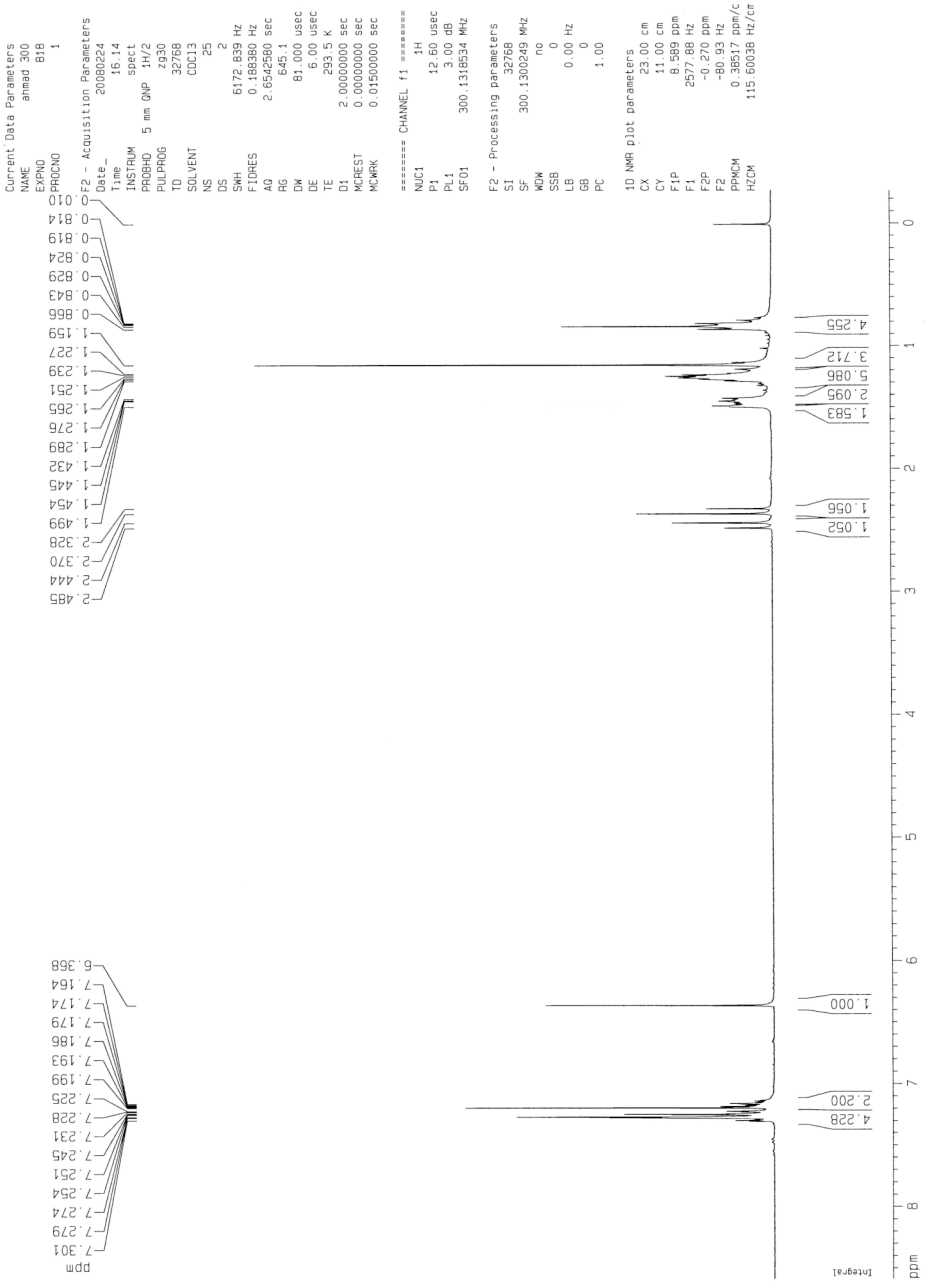
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2f**



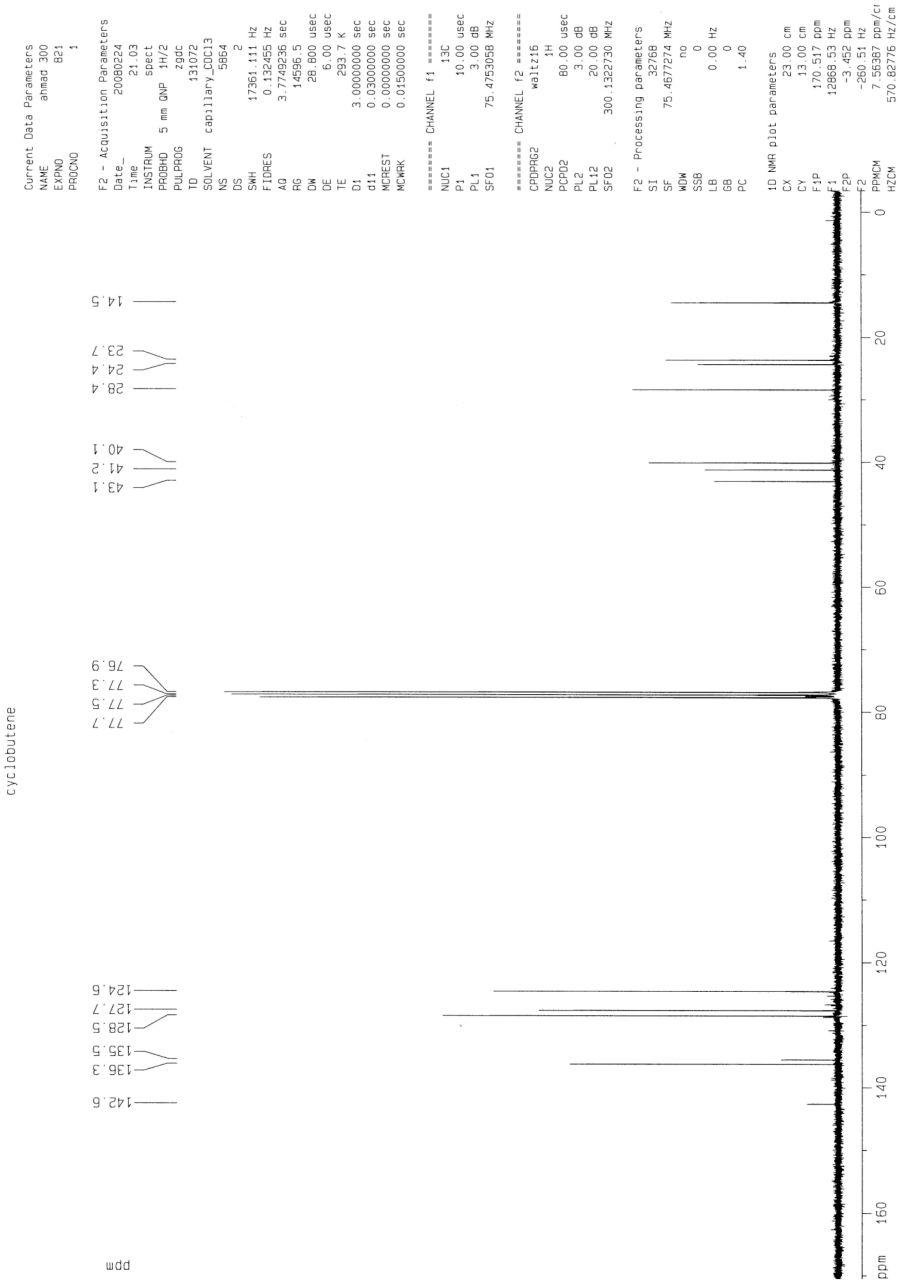
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2f**



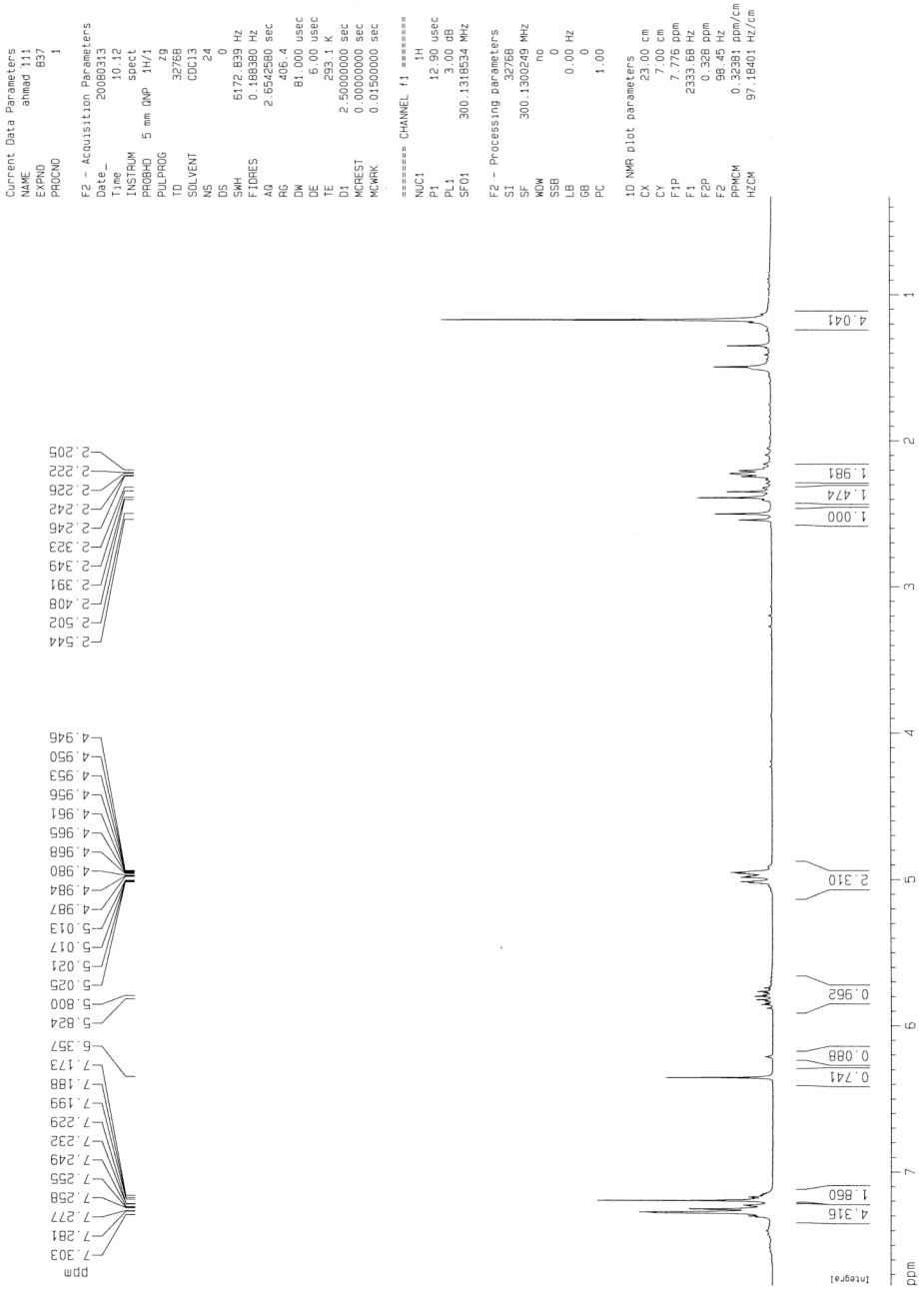
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2g**



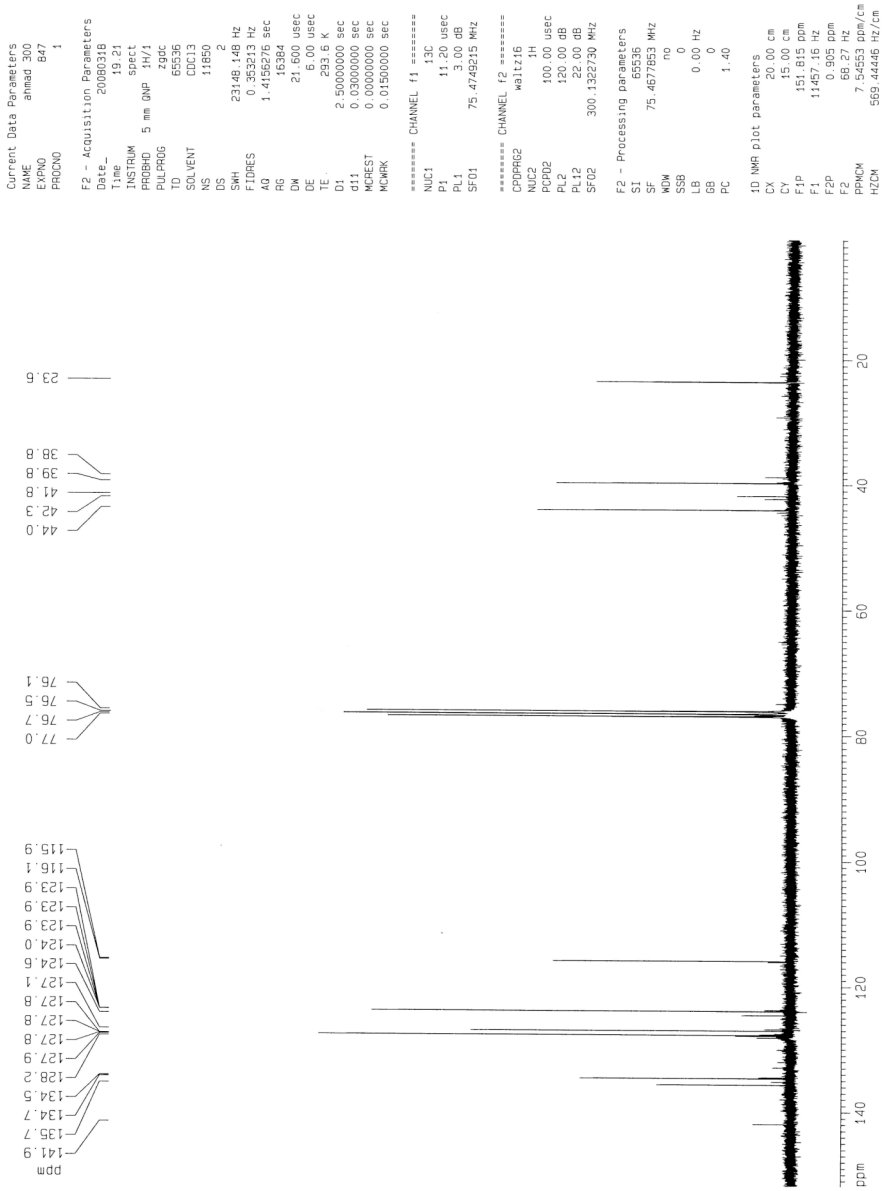
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2g**



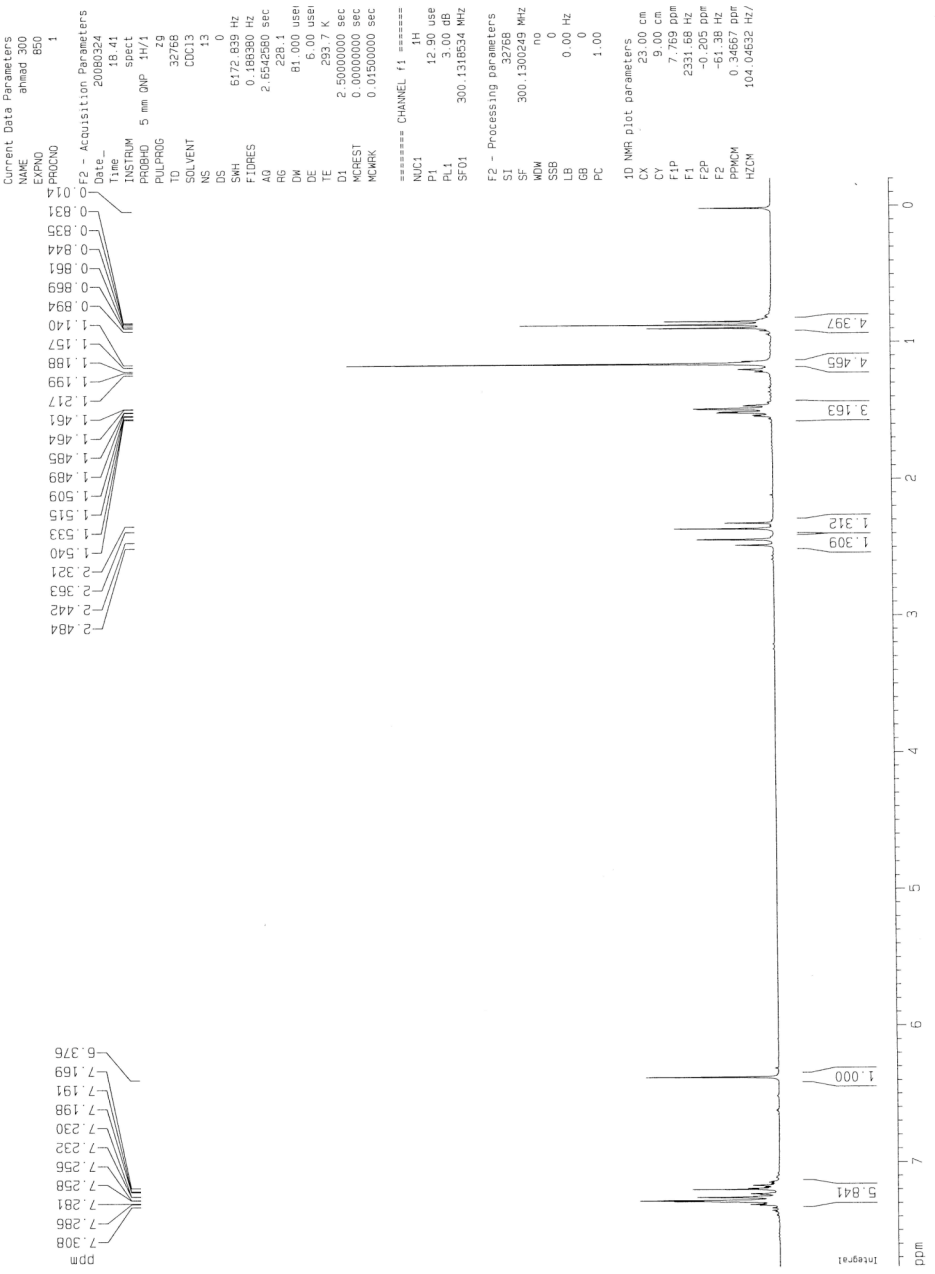
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2h**



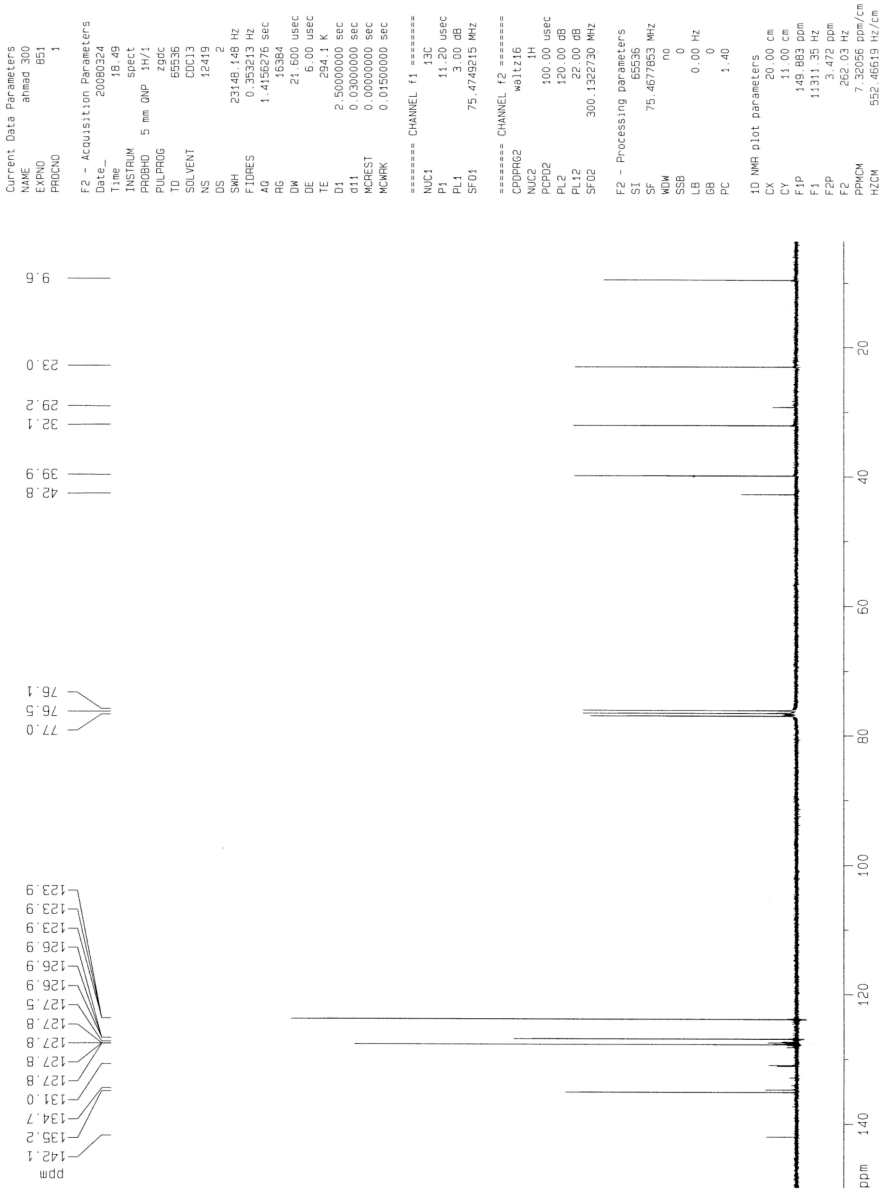
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2h**



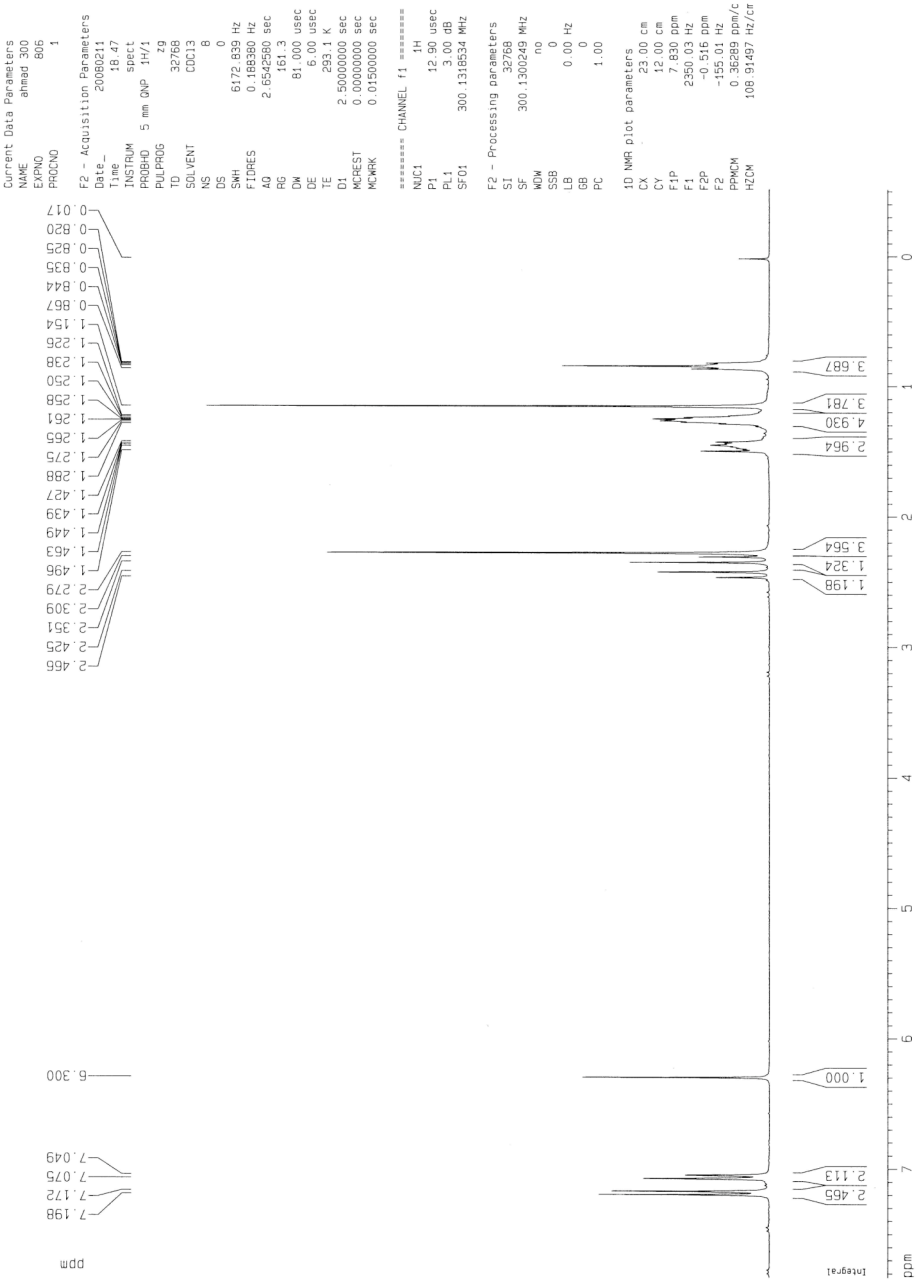
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2i**



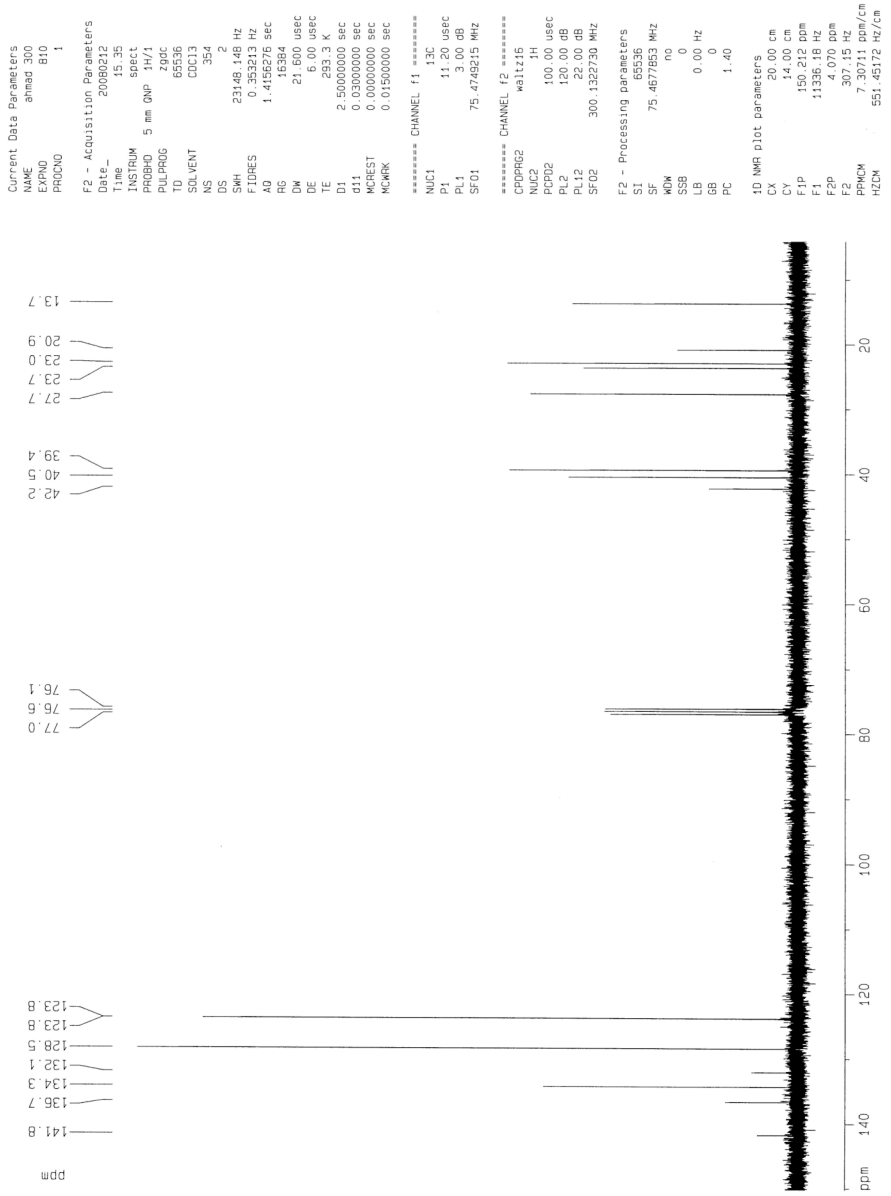
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2i**



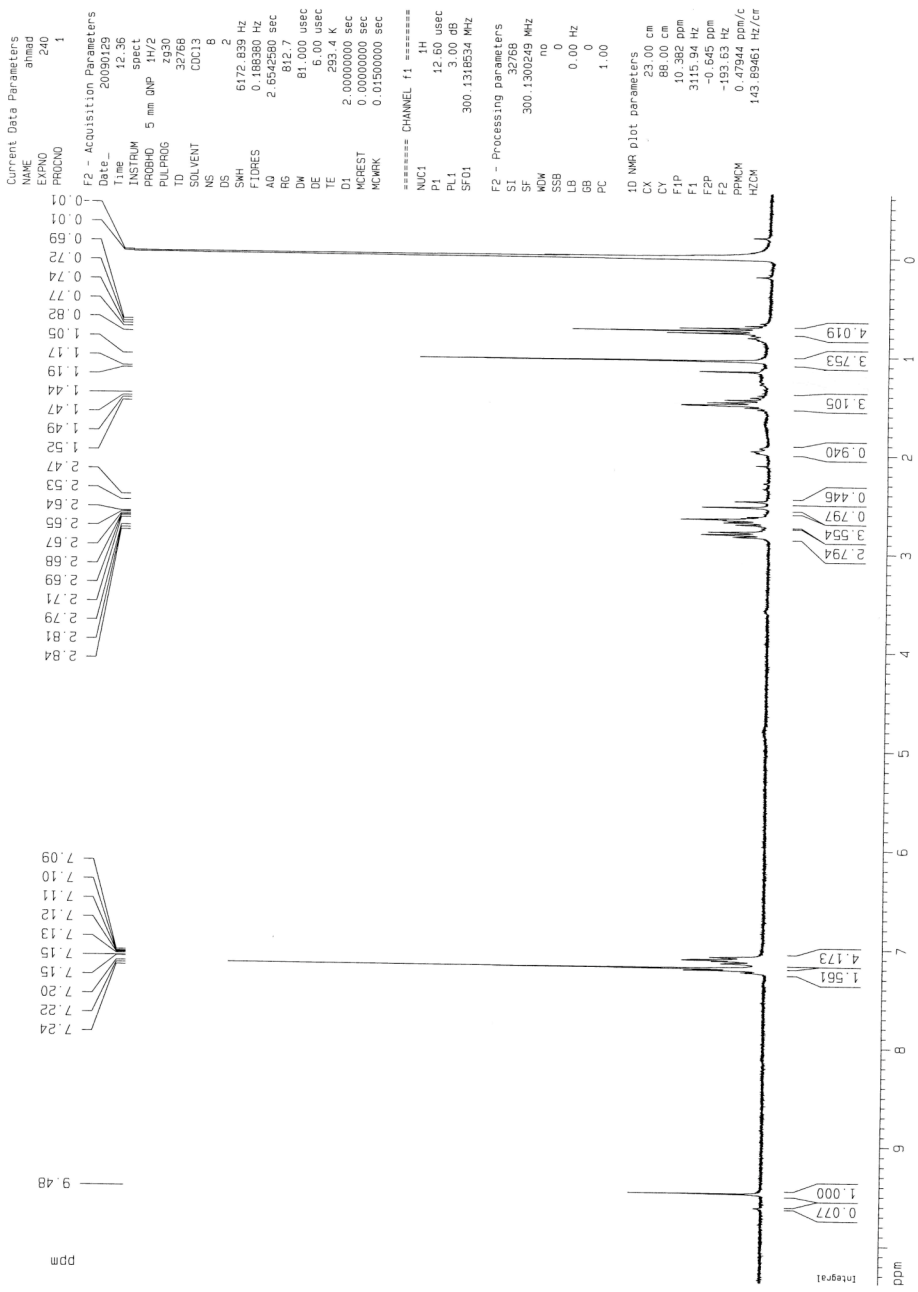
. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2j**



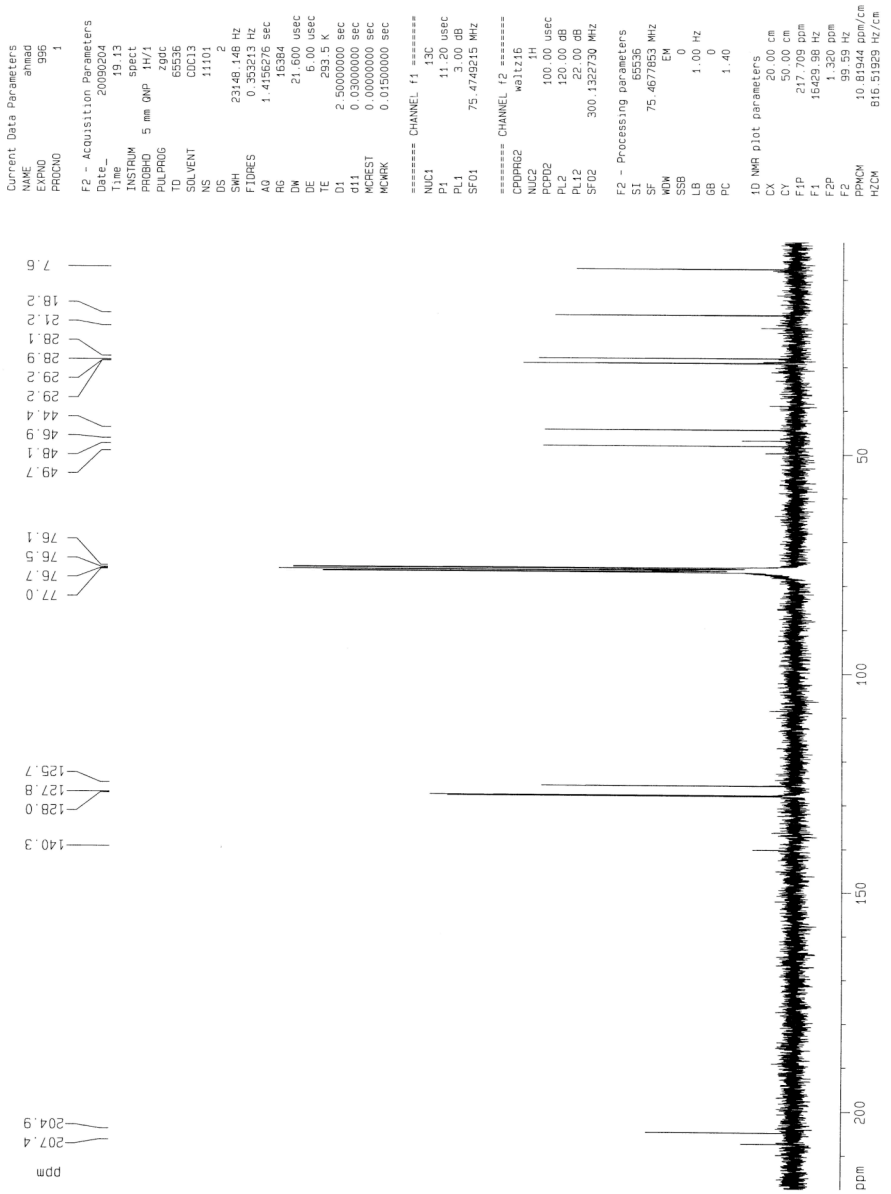
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **2j**



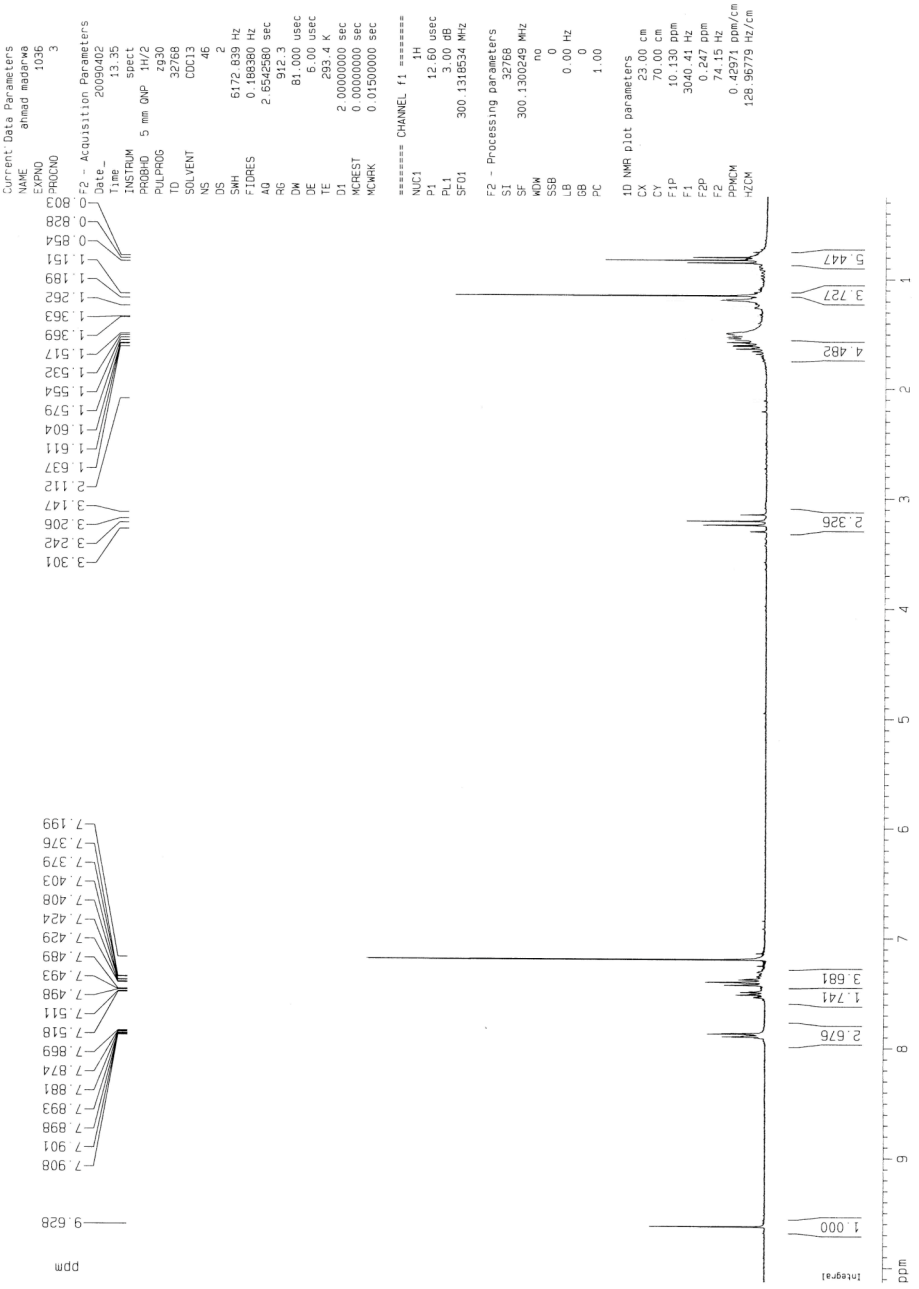
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **11**



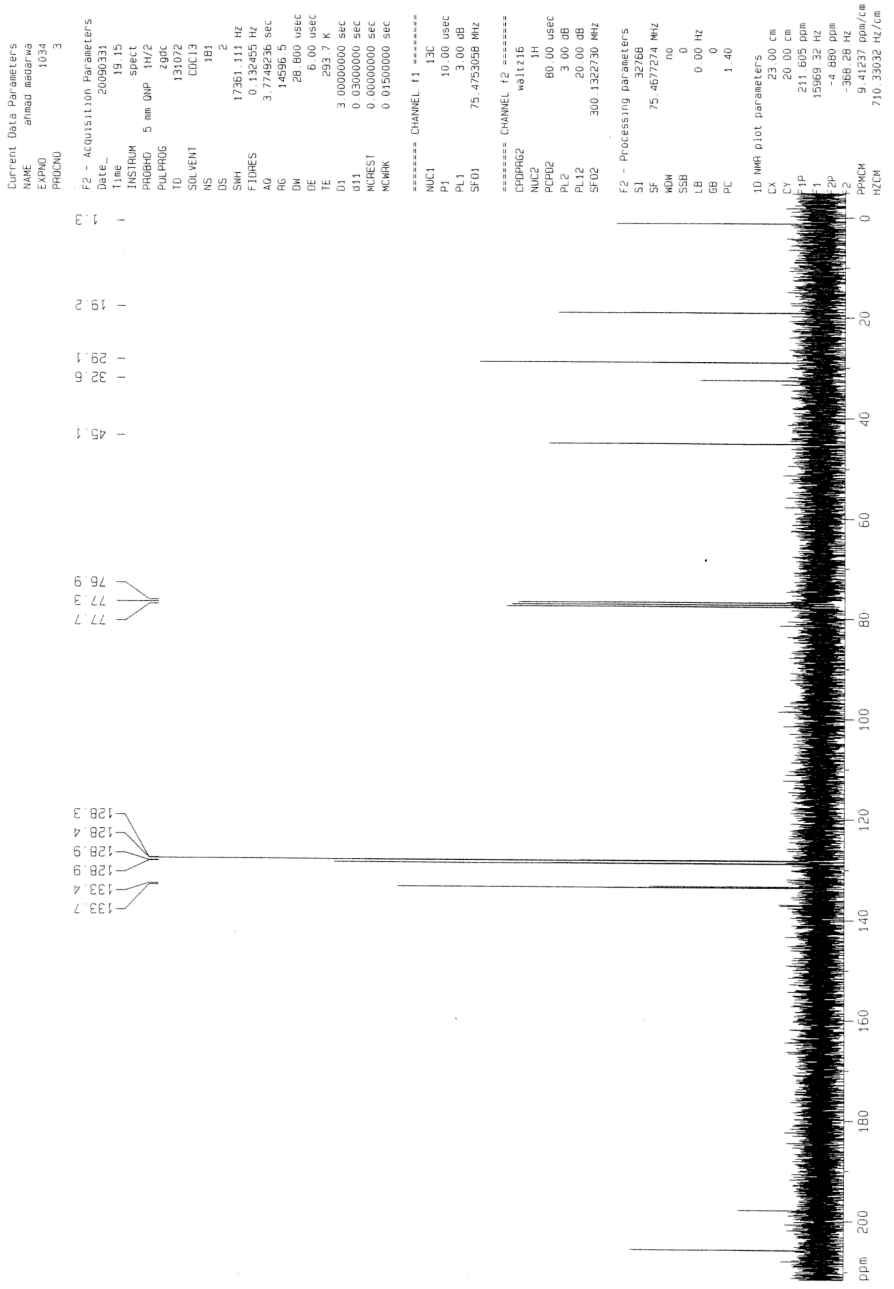
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **11**



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **12**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **12**



NOE data of **2d**