Enantiomerically Pure Synthesis of β-Substituted γ-Butyrolactones: A Key Intermediate to Concise Synthesis of Pregabalin

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Supporting Information

Contents

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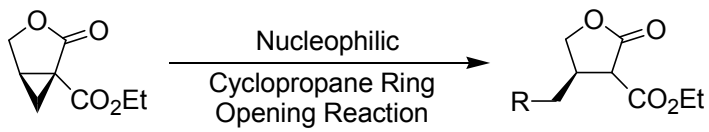
Experimental Section

Melting points were determined on a capillary melting point apparatus and were uncorrected. Optical rotations were measured using sodium light (D line, 589.3 nm). NMR spectra were obtained (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) and measured in $CDCl_3$ or CD_3OD. Chemical shifts were recorded in ppm relative to internal standard $CDCl_3$, and coupling constants were reported in Hz. The enantiomeric excess was determined by with CHIRALDEX β-DM column. All reactions were carried out in oven-dried glassware under a N_2 atmosphere. All solvents were distilled from the indicated drying reagents right before use: THF (Na, benzophenone), CH_2Cl_2 (P_2O_5) and MeCN (CaH_2). The normal work-up included extraction, drying over Na_2SO_4 or $MgSO_4$ and evaporation of volatile materials *in vacuo*. Purifications by column chromatography were performed using silica gel 60 (230 ~ 400 mesh).

Nucleophilic Cyclopropane Ring Opening Reaction (Table 2)



S_1 (R = isopropyl)
S_2 (R = cyclohexyl)
S_3 (R = phenyl)
S_4 (R = vinyl)
S_5 (R = phthalimidyl)
S_6 (R = azido)

S_1: To a stirred suspension of CuI (1.12 g, 5.88 mmol) in anhydrous THF (36 mL) at -45 ^{o}C was added isopropylmagnesium chloride in THF (2.0 M, 14.69 mL, 29.38 mmol) dropwise. The organocuprate formation was typically complete within 30 min. (*1S,5R*)-Bicyclic lactone (2.00 g, 11.75 mmol) in anhydrous THF (36 mL) was added to the solution via cannular at -45 ^{o}C. The resulting solution was stirred for 30 min warming to -15 ^{o}C, which was quenched with saturated ammonium chloride solution, then stirred overnight with diethyl ether at room temperature. The ethereal layer was separated and the aqueous layer was extracted with ethylacetate (×2). The

combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane to afford 9:1 diastereomeric mixture **S1** (2.32 g, 92.1%) as a colorless oil.: ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ4.47 (1H, t, *J* = 8.83 Hz), 4.21 (2H, q, *J* = 7.56 Hz), 3.84 (1H, t, *J* = 8.72 Hz), 3.17 (1H, d, *J* = 9.51 Hz), 3.01 (1H, m), 1.52 (1H, m), 1.41 (1H, m), 1.36 (1H, m), 1.27 (3H, t, *J* = 7.11 Hz), 0.88 (6H, t, *J* = 7.27 Hz); ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ172.1, 167.8, 72.2, 62.1, 52.9, 41.6, 38.3, 26.0, 22.5, 22.3, 14.0; HRMS (EI) calcd. for $C_{11}H_{18}O_4$: 214.1205, found: 214.1208.

S_2: To a stirred suspension of CuI (112 mg, 0.59 mmol) in anhydrous THF (5 mL) at -45 ^{o}C was added cyclohexylmagnesium chloride in THF (2.0 M, 1.47 mL, 2.94 mmol) dropwise. The organocuprate formation was complete after 1 h. (*1S,5R*)-Bicyclic lactone (200 mg, 1.18 mmol) in anhydrous THF (5 mL) was added to the solution via cannular at -45 ^{o}C. The solution was stirred for about 30 min warming to -15 ^{o}C, which was quenched with saturated ammonium chloride solution, then stirred overnight with diethyl ether at room temperature. The ethereal layer was separated and the aqueous layer was extracted with ethylacetate (×2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane to afford 18:1 diastereomeric mixture **S2** (281 mg, 94.1%) as a colorless oil.: ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ4.47 (1H, t, *J* = 8.78 Hz), 4.22 (2H, q, *J* = 7.22 Hz), 3.84 (1H, t, *J* = 8.65 Hz), 3.16 (1H, d, *J* = 9.46 Hz), 3.07(1H, m), 1.66 (5H, m), 1.38 (2H, m), 1.28 (3H, t, *J* = 7.09 Hz), 1.16 (5H, m), 0.85 (1H, m); ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ172.2, 167.8, 72.3, 62.1, 53.0, 40.2, 37.7, 35.4, 33.3, 33.1, 26.3, 26.01, 26.00, 14.0; HRMS (EI) calcd. for $C_{14}H_{22}O_4$: 254.1518, found: 254.1518.

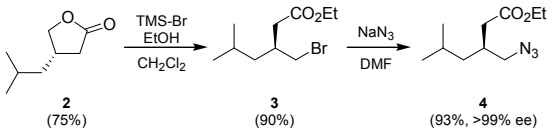
S_4: To a stirred solution of CuBr-Me_2S (362mg, 1.76 mmol) in anhydrous THF (3.5 mL) and Me_2S (1.0 mL) was added vinyl magnesium bromide in THF (1.0M, 3.53 mL, 3.53 mmol) at -40^{o}C. The solution was stirred for 20 min warming to -20 ^{o}C. (*1S,5R*)-Bicyclic lactone (200 mg, 1.18 mmol) in THF (3 mL) was added slowly over 1 h to the reaction mixture via cannular. After 1.5 h stirring at room temperature, the reaction mixture was quenched with saturated ammonium chloride solution. The organic layer was seperated and the aqueous layer was extracted with ethyl acetate (×2). The combined organic layer was washed with 17% aqueous NH_4OH solution and brine, and then was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane to afford a 11:1 diastereomeric mixture **S4** (108 mg, 46.4%) as a colorless oil.: ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ5.67 (1H, m), 5.11 (2H, m), 4.46 (1H, dd, *J* = 9.01 Hz and 7.60 Hz), 4.21 (2H, q, *J* = 7.12 Hz), 3.92 (1H, dd, *J* = 8.99 Hz and 7.52 Hz), 3.22 (1H, d, 8.40 Hz), 3.01 (1H, m), 2.26 (2H, m), 1.26 (3H, t, *J* = 7.16 Hz); ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ171.8, 167.4, 133.3, 118.5, 71.4, 62.1, 51.8, 39.3, 36.2, 14.0; HRMS (EI) calcd. for $C_{10}H_{14}O_4$: 198.0892, found: 198.0893.

S_5: A solution of (*1S,5R*)-bicyclic lactone (200 mg, 1.18 mmol), potassium phthalimide (435.4 mg, 2.35 mmol) and 18-crown-6 (621.4 mg, 2.35 mmol) in anhydrous DMF (3 mL) was heated for 2 h at 70^{o}C. After removal of DMF under reduced pressure, distilled water was added to the residue. The solution was extracted with methylene chloride (×3). The combined organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure, during which excess potassium phthalimide was precipitated. After removal of the precipitates by filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using 30% ethyl acetate/hexane to afford **S5** (247.0 mg, 66.3%) as a

colorless oil.: ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ7.84 (2H, m), 7.74 (2H, m), 4.51 (1H, t, *J* = 9.32 Hz), 4.12 (2H+1H, m), 3.85 (2H, m), 3.48 (1H, d, *J* = 9.23 Hz), 3.42 (1H, m), 1.18 (3H, t, *J* = 7.08 Hz); ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ170.8, 168.1, 166.7, 134.4, 131.6, 123.6, 69.8, 62.4, 50.2, 39.6, 38.3, 13.9; HRMS (EI) calcd. for $C_{16}H_{15}NO_6$: 317.0899, found: 317.0899.

S_6: A solution of (*1S,5R*)-bicyclic lactone (54.6 mg, 0.32 mmol), sodium azide (83.4 mg, 1.28 mmol), glacial acetic acid (74 μl, 1.29 mmol), and triethylamine (0.9 μl, 6.46 μmol) in anhydrous DMF (1 mL) was heated for 4 h at 70^{o}C. After removal of DMF under reduced pressure, saturated ammonium chloride solution was added. The solution was extracted with methylene chloride (×3), and then the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 30% ethyl acetate/hexane to afford 15:1 diastereomeric mixture **S6** (43.7mg, 68.3%) as a colorless oil.; ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ4.47 (1H, dd, *J* = 9.08 Hz and 7.86 Hz), 4.25 (2H, q, *J* = 7.14 Hz), 4.05 (1H, dd, *J* = 9.09 Hz and 7.45 Hz), 3.53 (2H, dd, *J* = 6.15 Hz and 2.16Hz), 3.40 (1H, d, *J* = 8.30 Hz), 3.18 (1H, m), 1.30 (3H, t, *J* = 7.23 Hz) ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ170.7, 166.7, 68.9, 62.6, 51.2, 49.2, 39.3, 14.0; HRMS (EI) calcd. for $C_8H_{11}N_3O_4$: 213.0750, found: 213.0750.

Synthesis of the Intermediates for Pregabalin (Scheme 2)



2 (75%) **3** (90%) **4** (93%, >99% ee)

(*S*)-3-Bromomethyl-5-methyl-hexanoic acid ethyl ester (3): To a stirred solution of **2** (1.11g, 7.81 mmol) and ethanol (2.28 mL, 39.0 mmol) in anhydrous methylene chloride (40 mL) at 0 ^{o}C was added bromotrimethylsilane (3.03 mL, 23.4 mmol) dropwise. The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with distilled water and then stirred for 5 min. The organic layer was separated and washed with 5% sodium thiosulfate solution (×1), then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate/hexane to afford **3** (1.77 g, 90.3%) as a colorless oil.: ^{1}H NMR (400 MHz, $CDCl_3$) δ4.11 (2H, q, *J* = 7.12 Hz), 3.54 (1H, dd, *J* = 10.22 Hz and 3.72 Hz), 3.44 (1H, dd, *J* = 10.20 Hz and 4.97 Hz), 2.45 (1H, dd, *J* = 15.81 Hz and 7.19 Hz), 2.29 (1H, dd, *J* = 15.76 Hz and 5.72 Hz), 2.22 (1H, m), 1.60 (1H, m), 1.32 (1H, m), 1.24 (3H, t, *J* = 7.12 Hz), 1.15 (1H, m), 0.88 (6H, d, J=6.58 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.3, 60.4, 41.8, 38.98, 37.7, 34.1, 25.0, 22.9, 22.2, 14.2; HRMS (EI) calcd. for $C_{10}H_{19}BrO_2$: 250.0568, found: 250.0565.

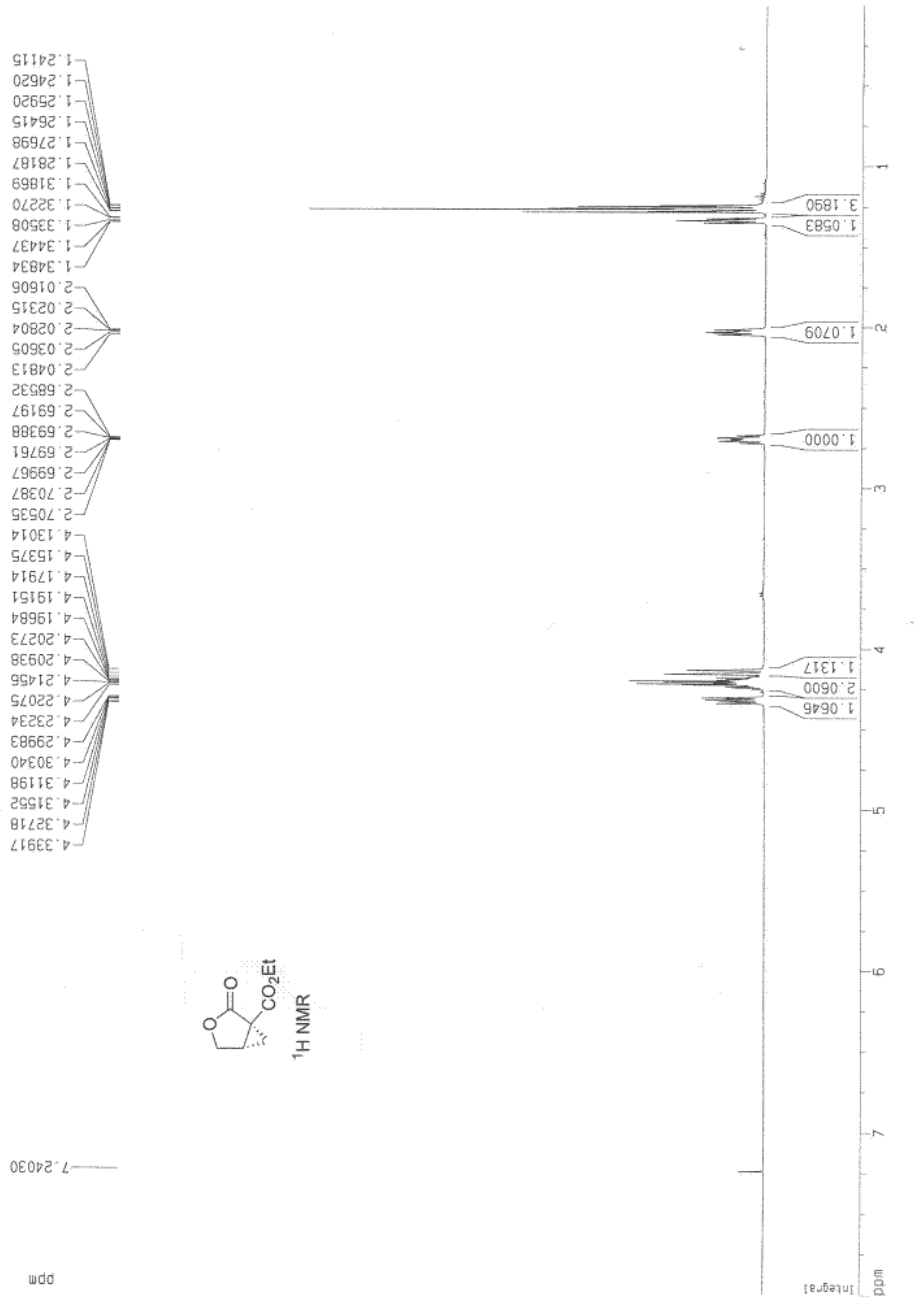
(*S*)-3-Azidomethyl-5-methyl-hexanoic acid ethyl ester (4): A solution of **3** (876 mg, 3.49 mmol) and sodium azide (907 mg, 13.95 mmol) in anhydrous DMF (10 mL) was stirred at room temperature for 4 h. DMF was removed under reduced pressure. Distilled water and methylene chloride was added to the residue, and the aqueous layer was extracted by methylene chloride (×3). The combined organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% ethyl acetate/hexane to afford **4** (691 mg, 92.9%) as a colorless oil.: ^{1}H NMR (400 MHz, $CDCl_3$) δ4.11 (2H, q, *J* = 7.16 Hz), 3.34 (1H, dd, *J* = 12.18 Hz and 4.97 Hz), 3.26 (1H, dd, *J* = 12.12 Hz and 6.14 Hz), 2.29 (2H, m), 2.14 (1H, m), 1.60 (1H, m), 1.24 (3H+1H, m), 1.13 (1H, m), 0.87 (6H, dd, *J* =

6.56 Hz and 2.44 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.4, 60.4, 55.0, 41.1, 37.0, 33.3, 25.1, 22.6, 22.5, 14.2; HRMS (EI) calcd. for $C_{10}H_{19}N_3O_2$: 213.1477, found: 213.1475.

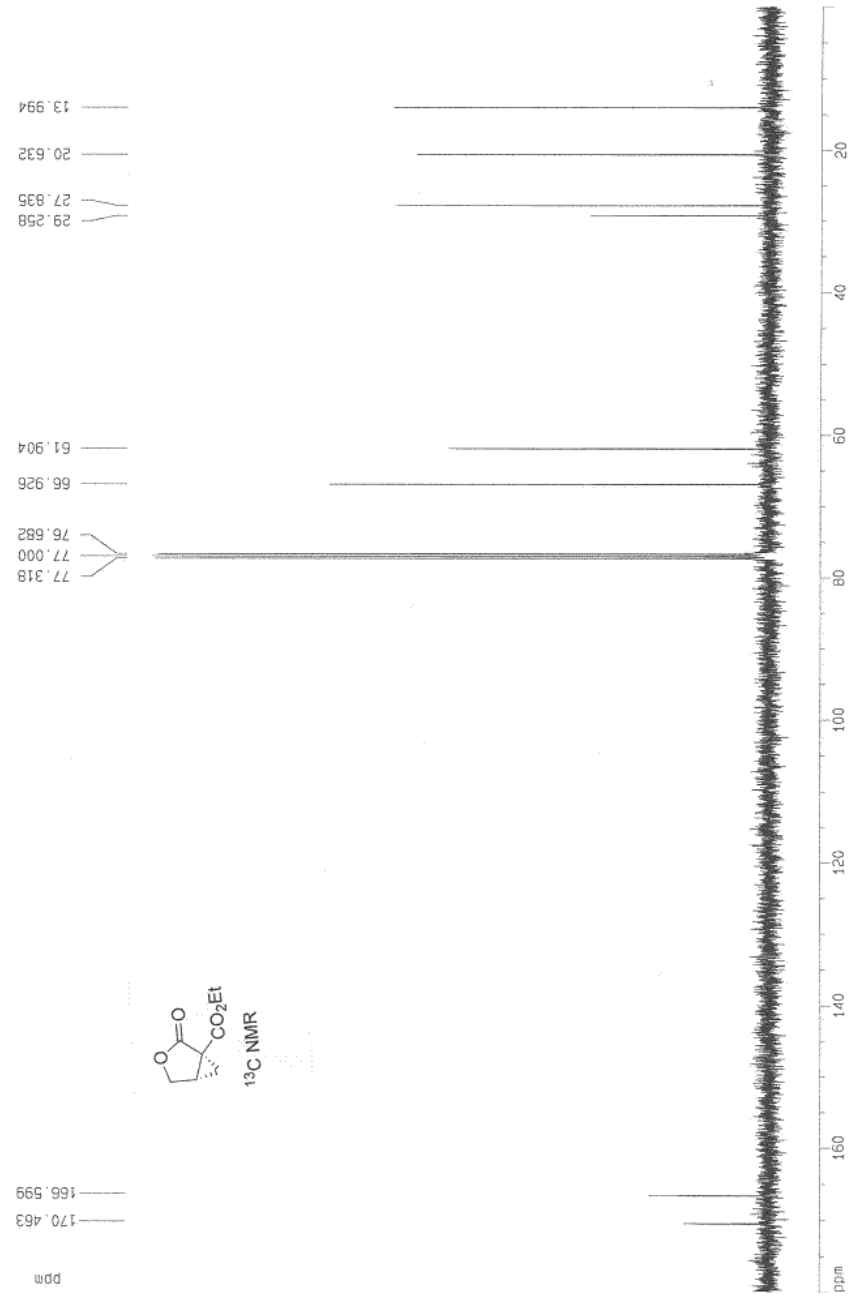
For the measurement of enantiomeric excess, **4** (10 mg) was stirred with 10% Pd/C (10 mg) in ethyl acetate (1 mL) in the presence of triflouroacetic anhydride (0.5 mL) under hydrogen balloon for 3 h. The resulting solution was filtered through celite, and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 40% ethyl acetate/hexane to obtain the corresponding trifluoroacetamide as a colorless oil in a quantitative yield. The ee of the trifluoroacetamide was >99% by chiral GC analysis using a CHIRALDEX β-DM column (130 ^{o}C, 1.4 kgf/cm^3) with a retention time of 51.17 min, whereas its enantiomer had a retention time of 52.30 min.

1) Characterizations of (*1R,5S*)- and (*1S,5R*)-[3.1.0]-bicyclic lactones

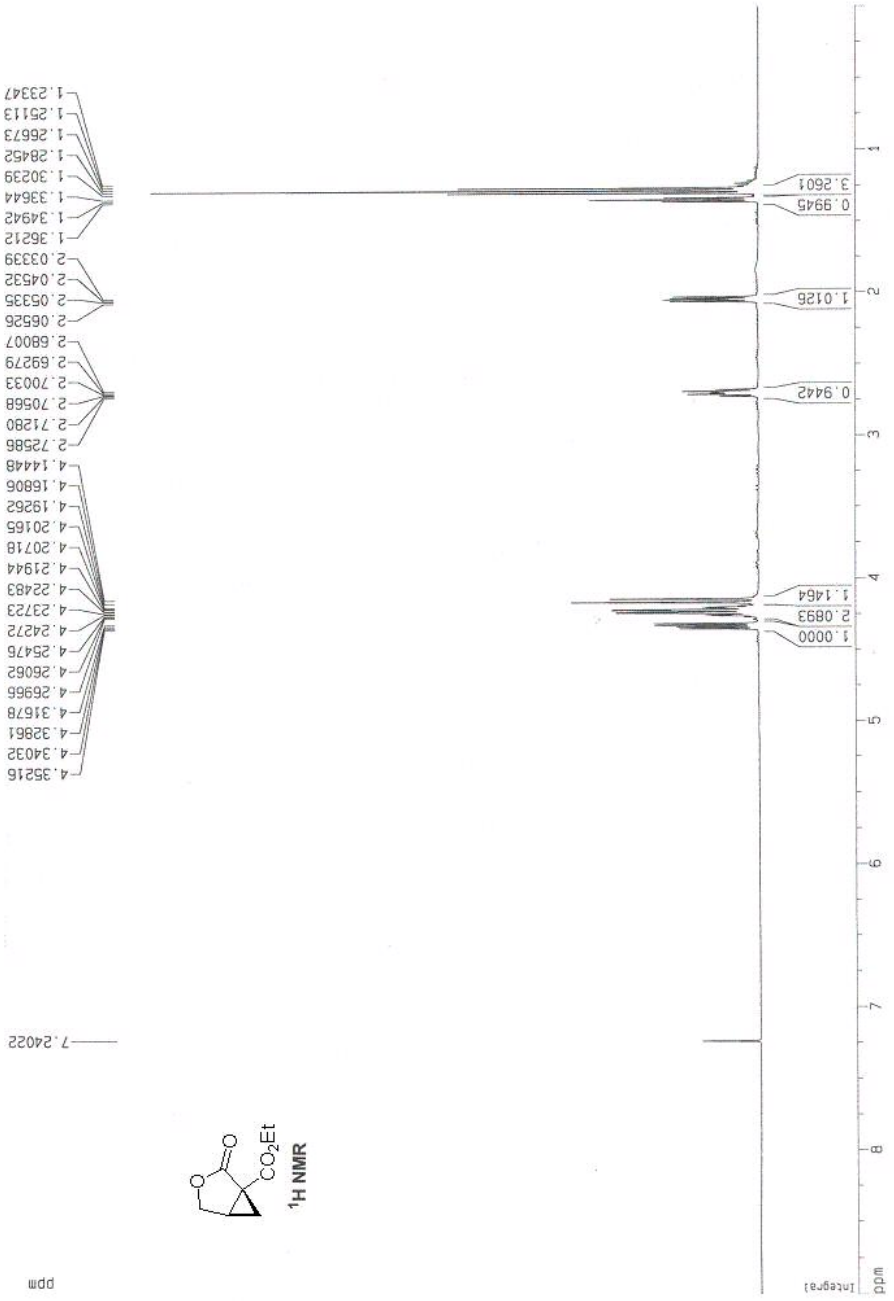
^{1}H NMR (400 MHz, $CDCl_3$) of (*1R,5S*)-Bicyclic Lactone (1)



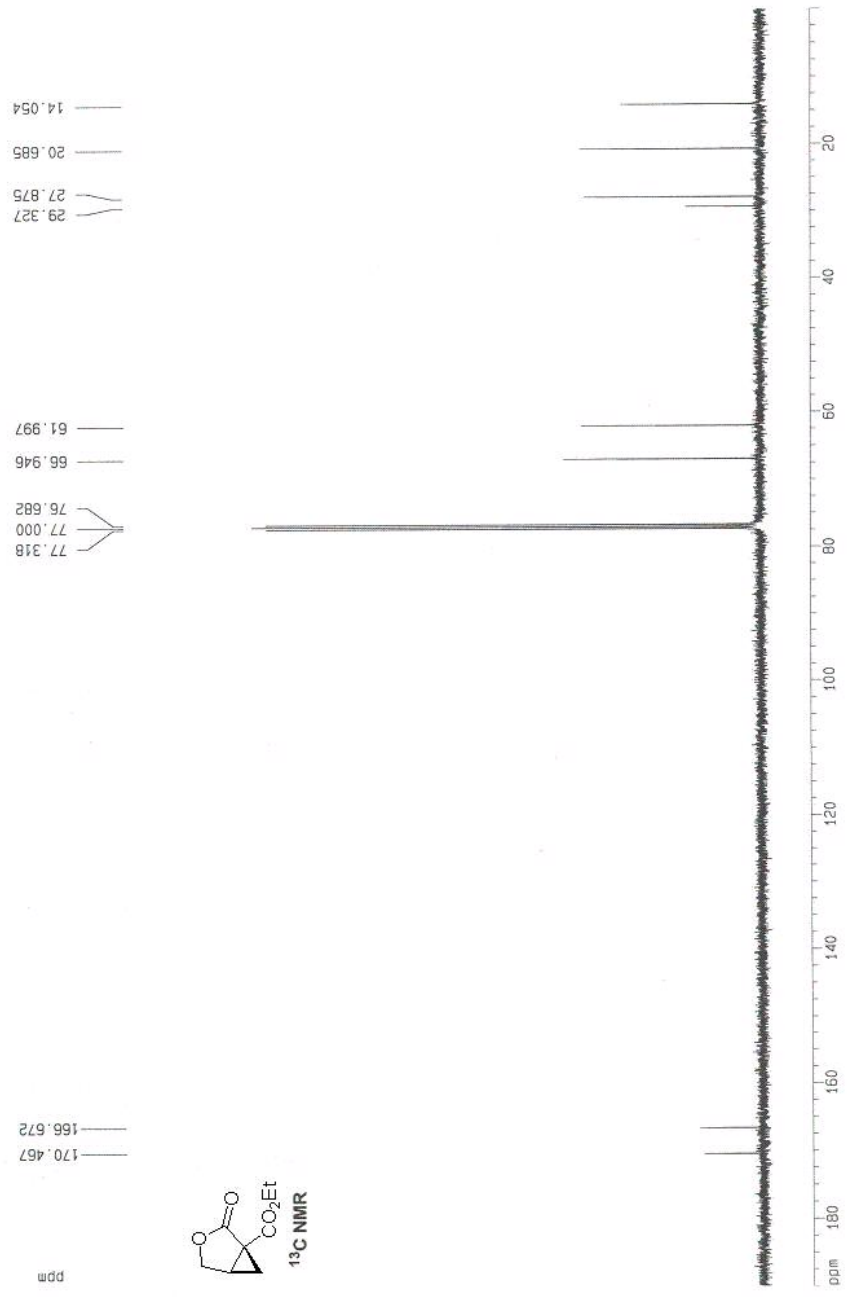
^{13}C NMR (100 MHz, $CDCl_3$) of (*1R,5S*)-Bicyclic Lactone (1)



^{1}H NMR (400 MHz, $CDCl_3$) of (*1S,5R*)-Bicyclic Lactone (ent-1)

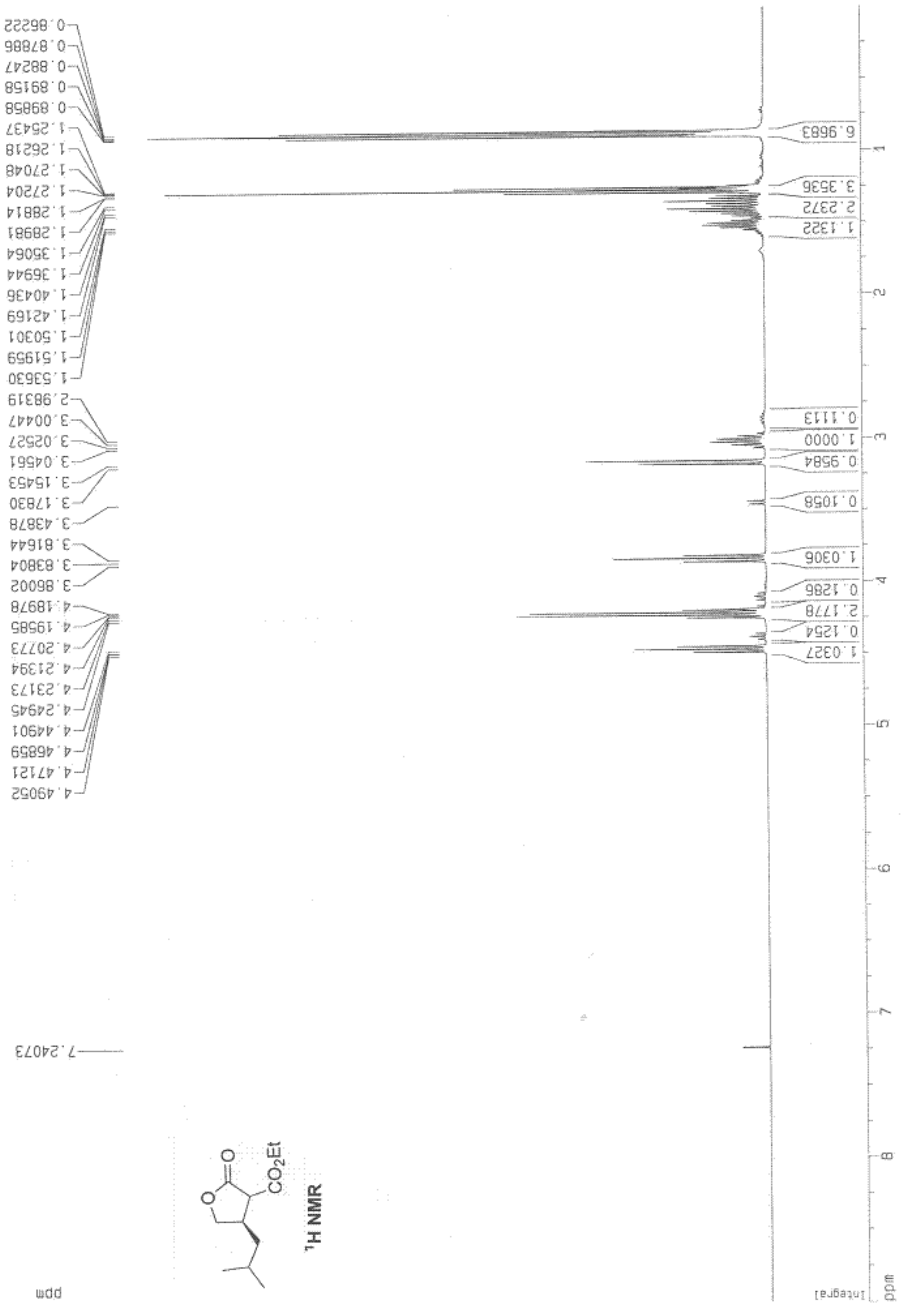


^{13}C NMR (100 MHz, $CDCl_3$) of (*1S,5R*)-Bicyclic Lactone (ent-1)

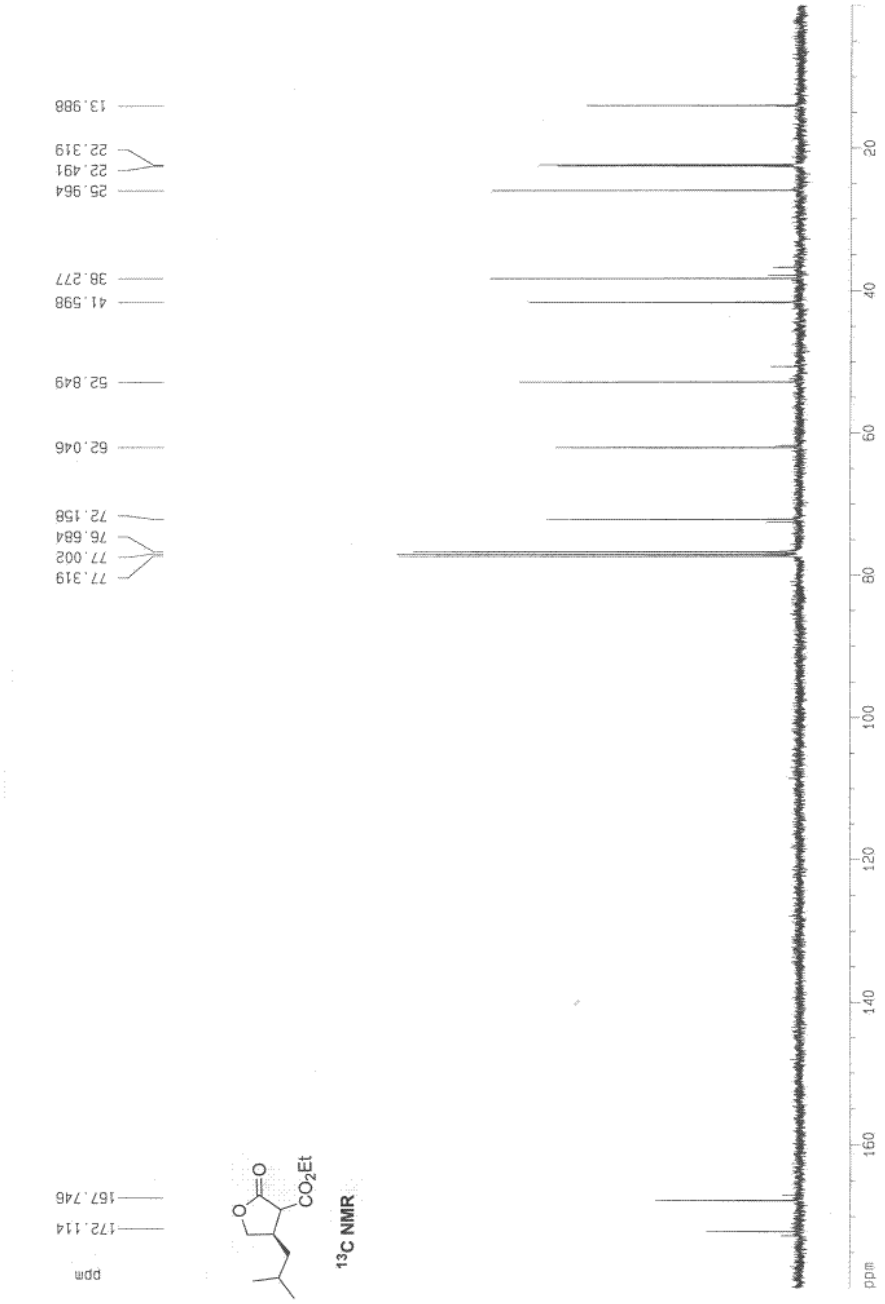


2) Characterizations of nucleophilic cyclopropane ring opening reaction products (Table 2)

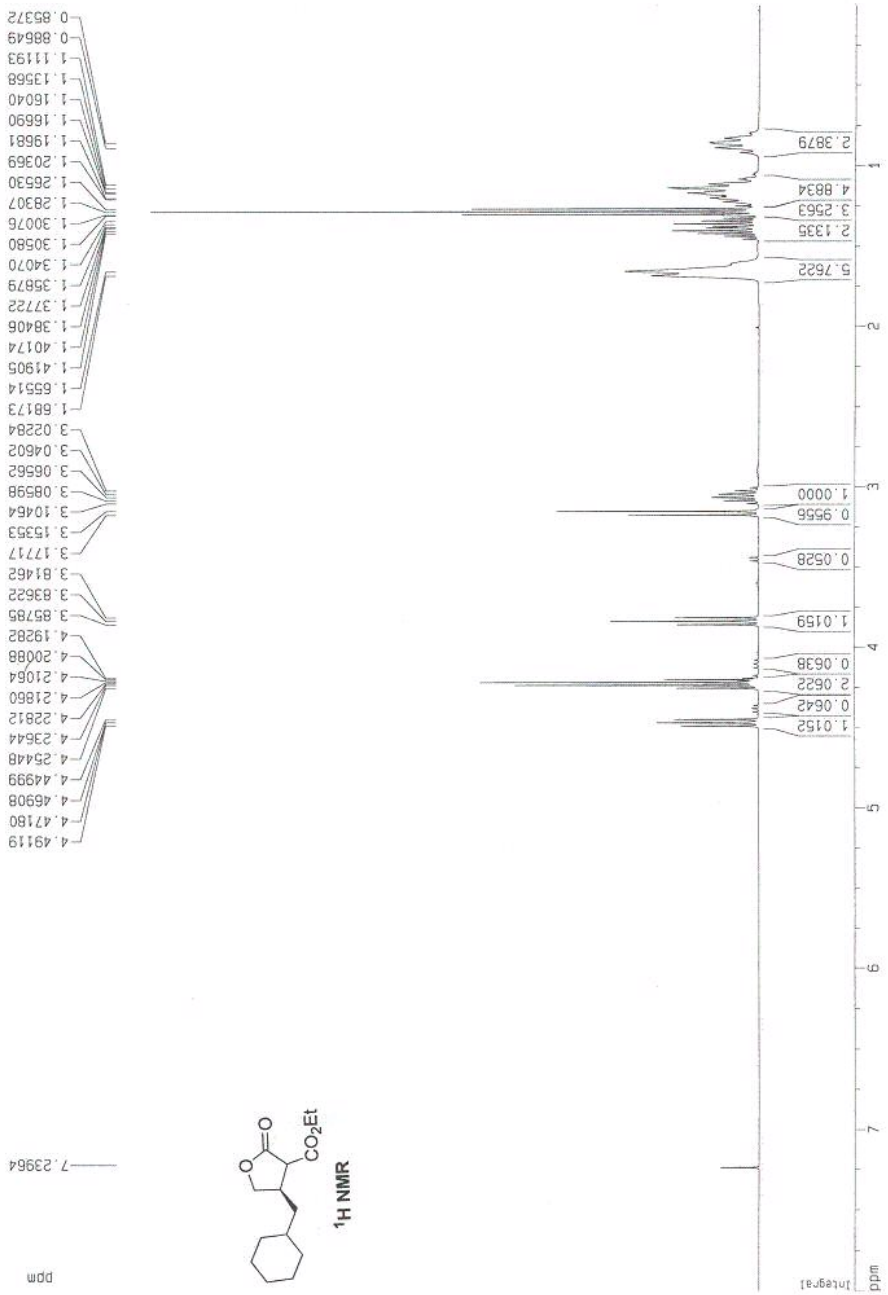
^{1}H NMR (400 MHz, $CDCl_3$) of S_1



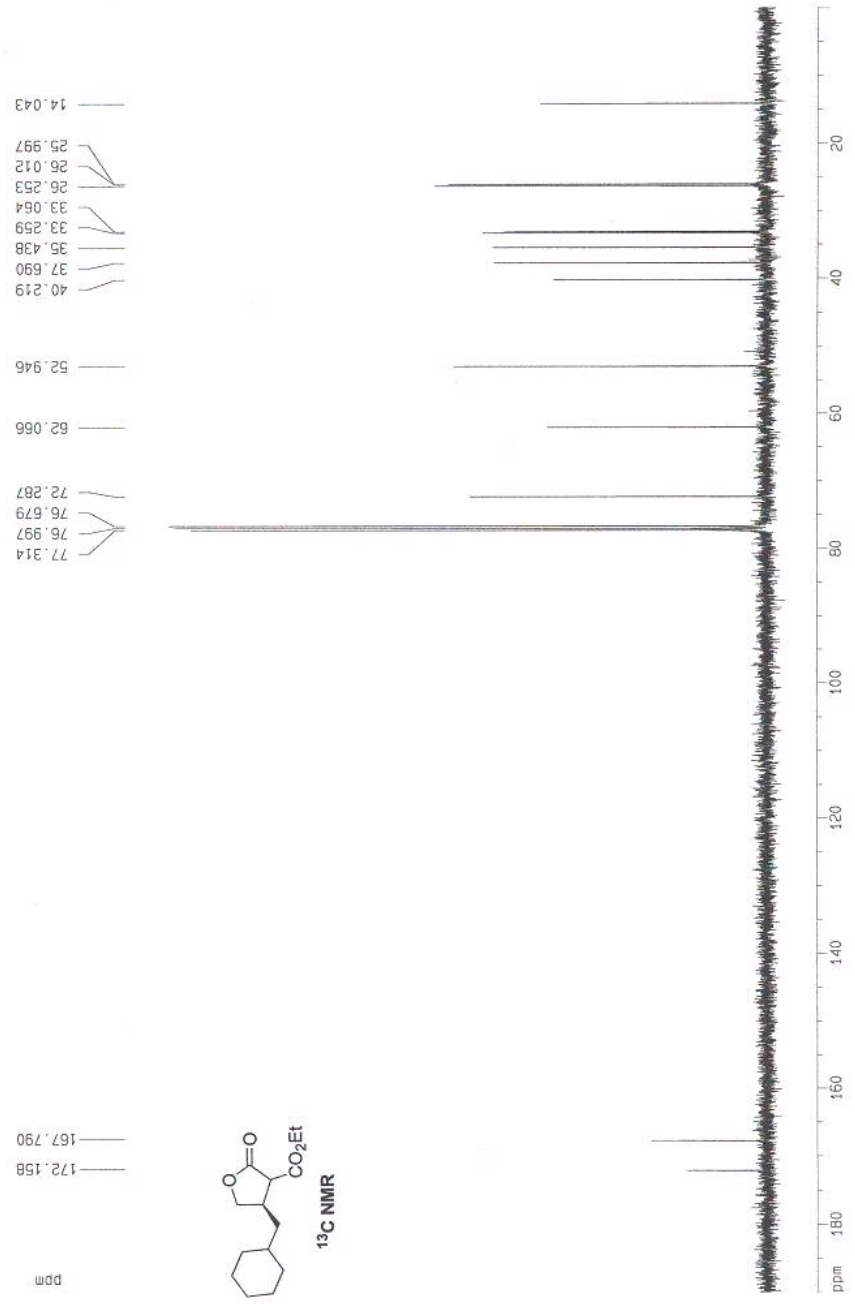
^{13}C NMR (100 MHz, $CDCl_3$) of of S_1



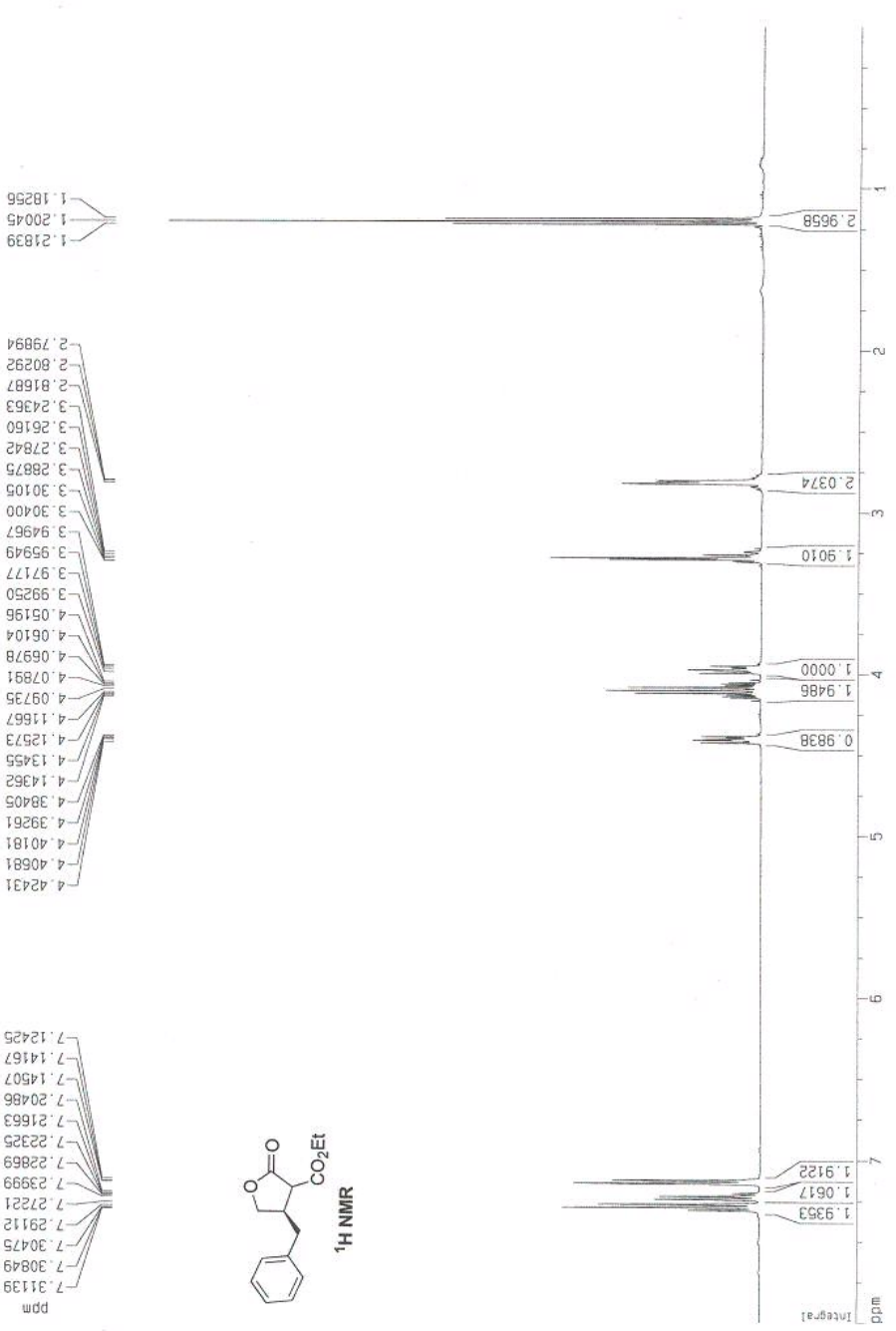
^{1}H NMR (400 MHz, $CDCl_3$) of S_2



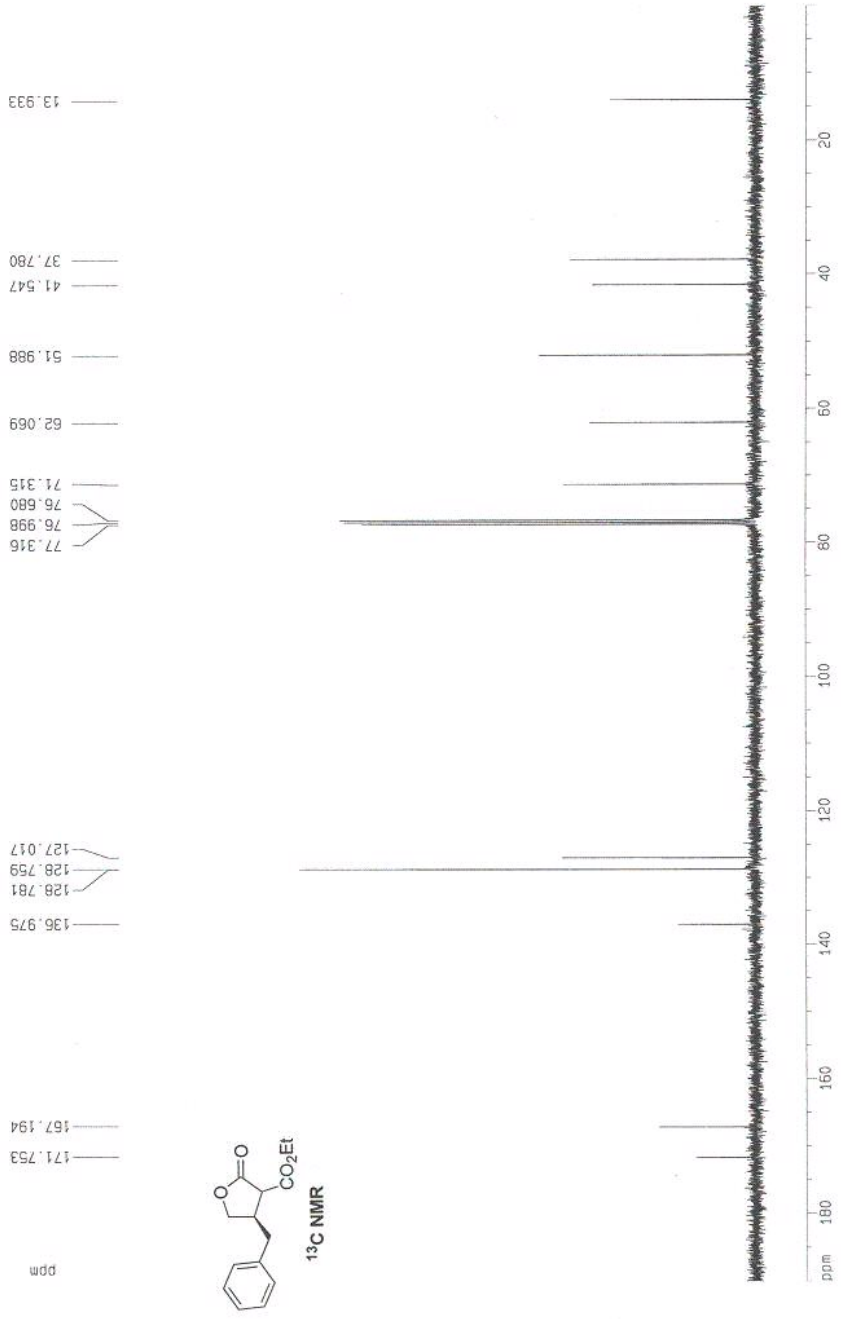
^{13}C NMR (100 MHz, $CDCl_3$) of S_2



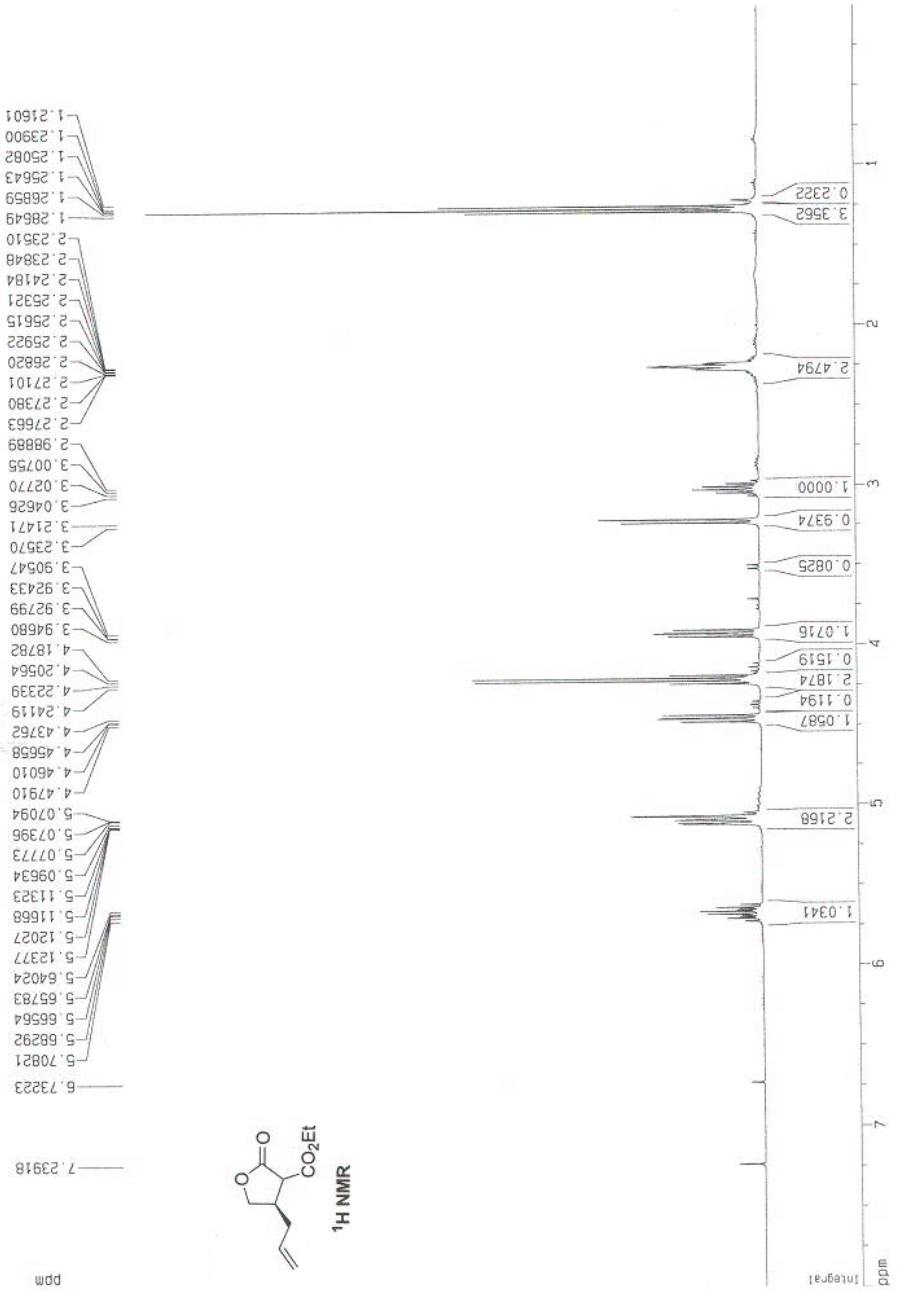
^{1}H NMR (400 MHz, $CDCl_3$) of S_3



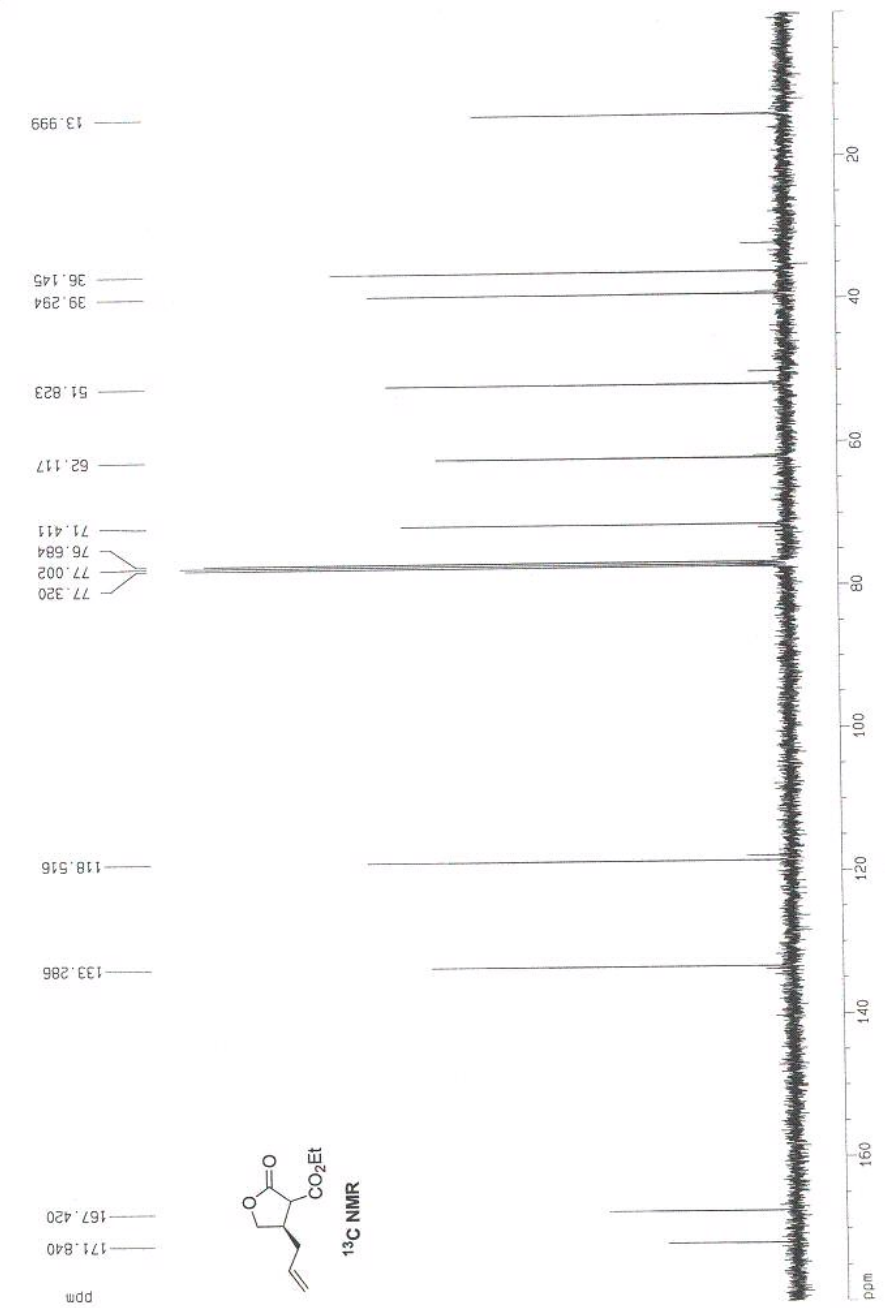
^{13}C NMR (100 MHz, $CDCl_3$) of S_3



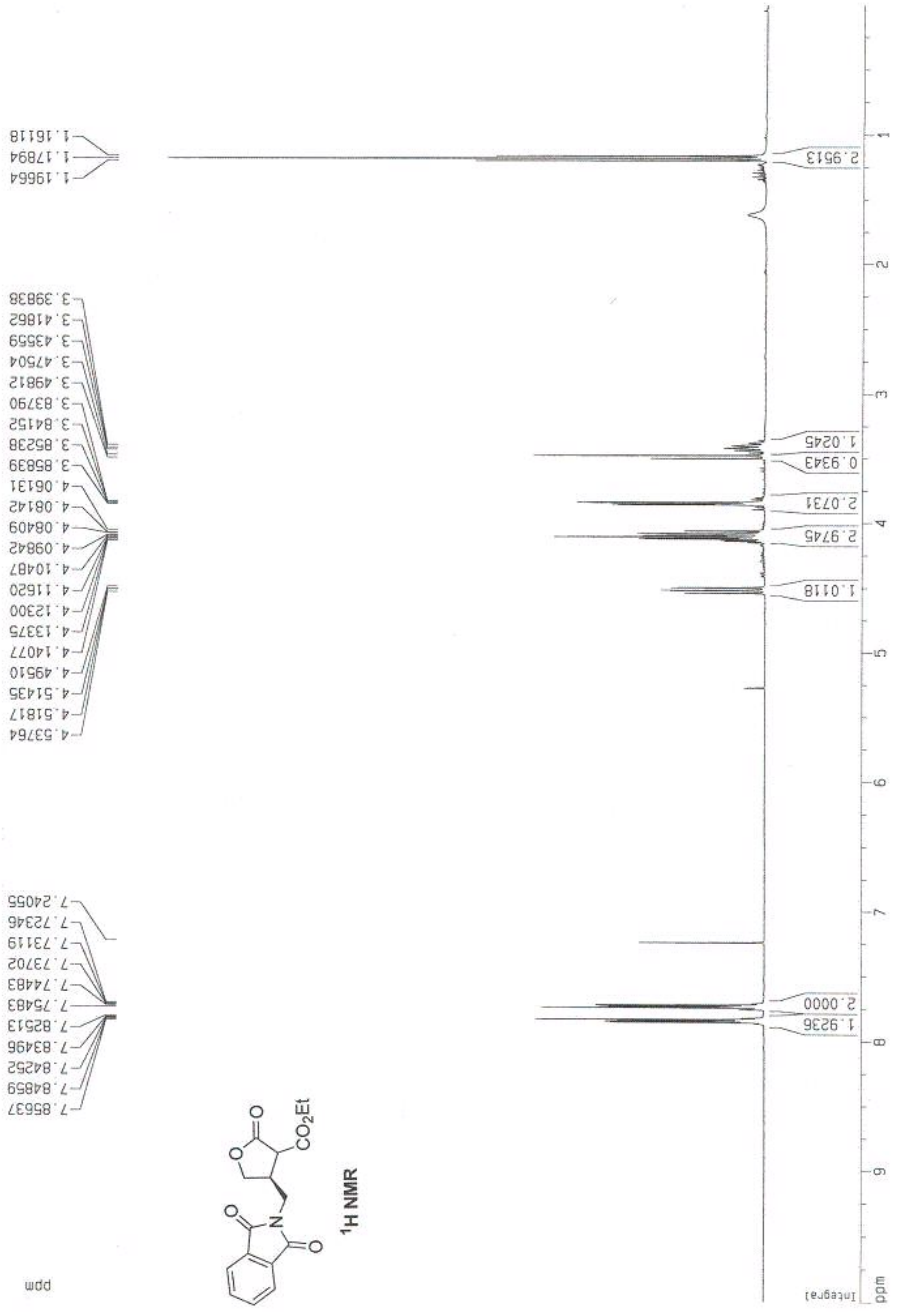
^{1}H NMR (400 MHz, $CDCl_3$) of S_4



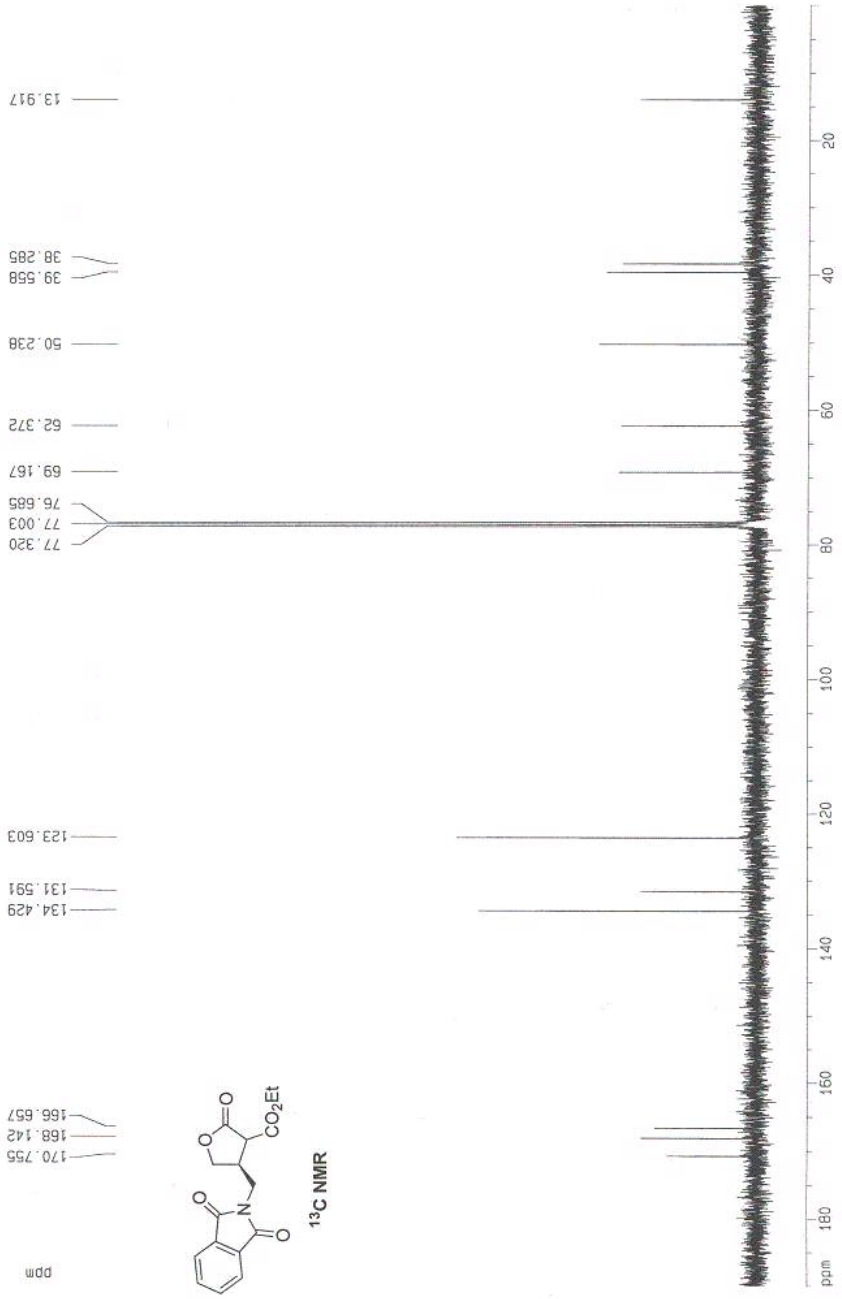
^{13}C NMR (100 MHz, $CDCl_3$) of S_4



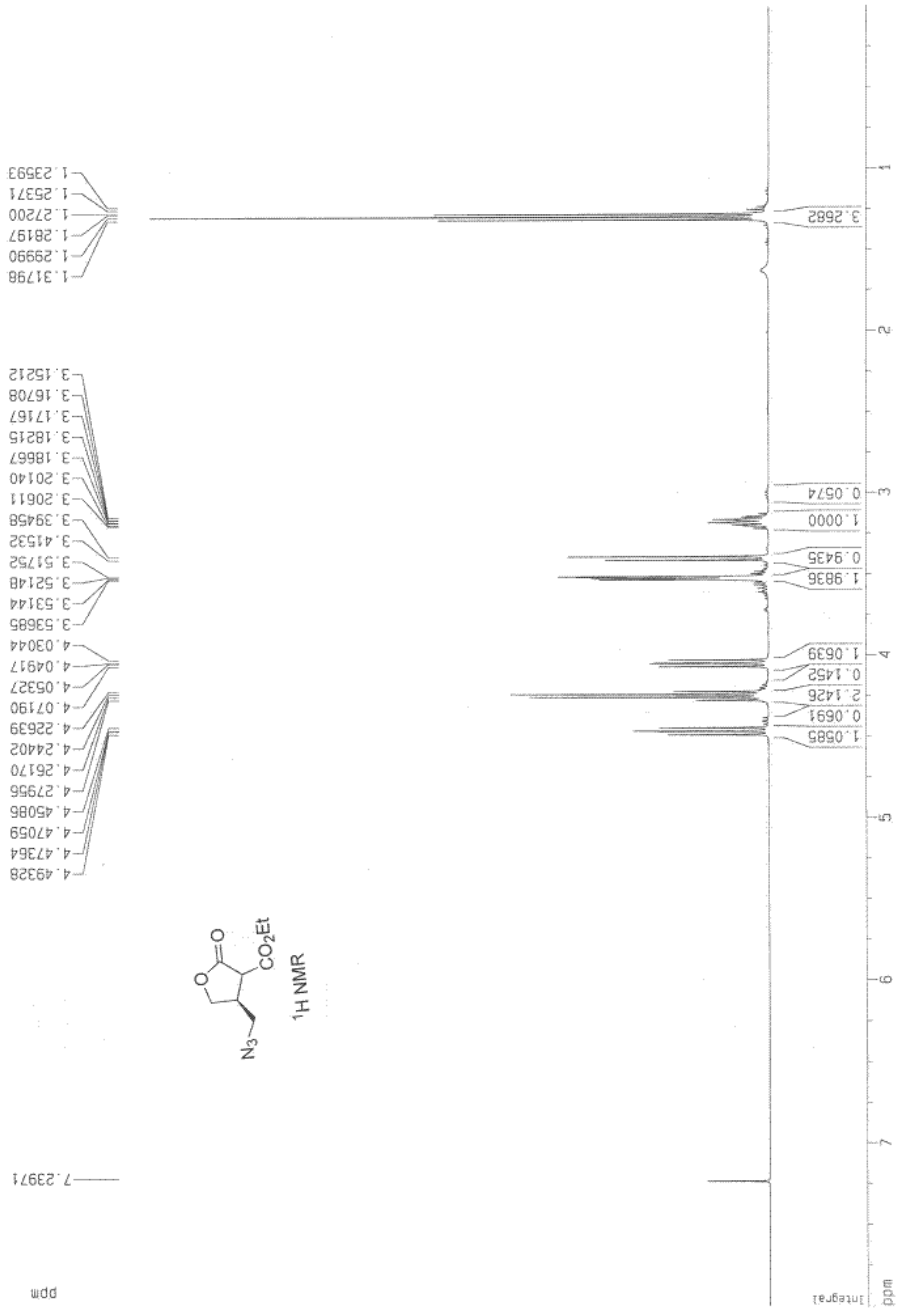
^{1}H NMR (400 MHz, $CDCl_3$) of S_5



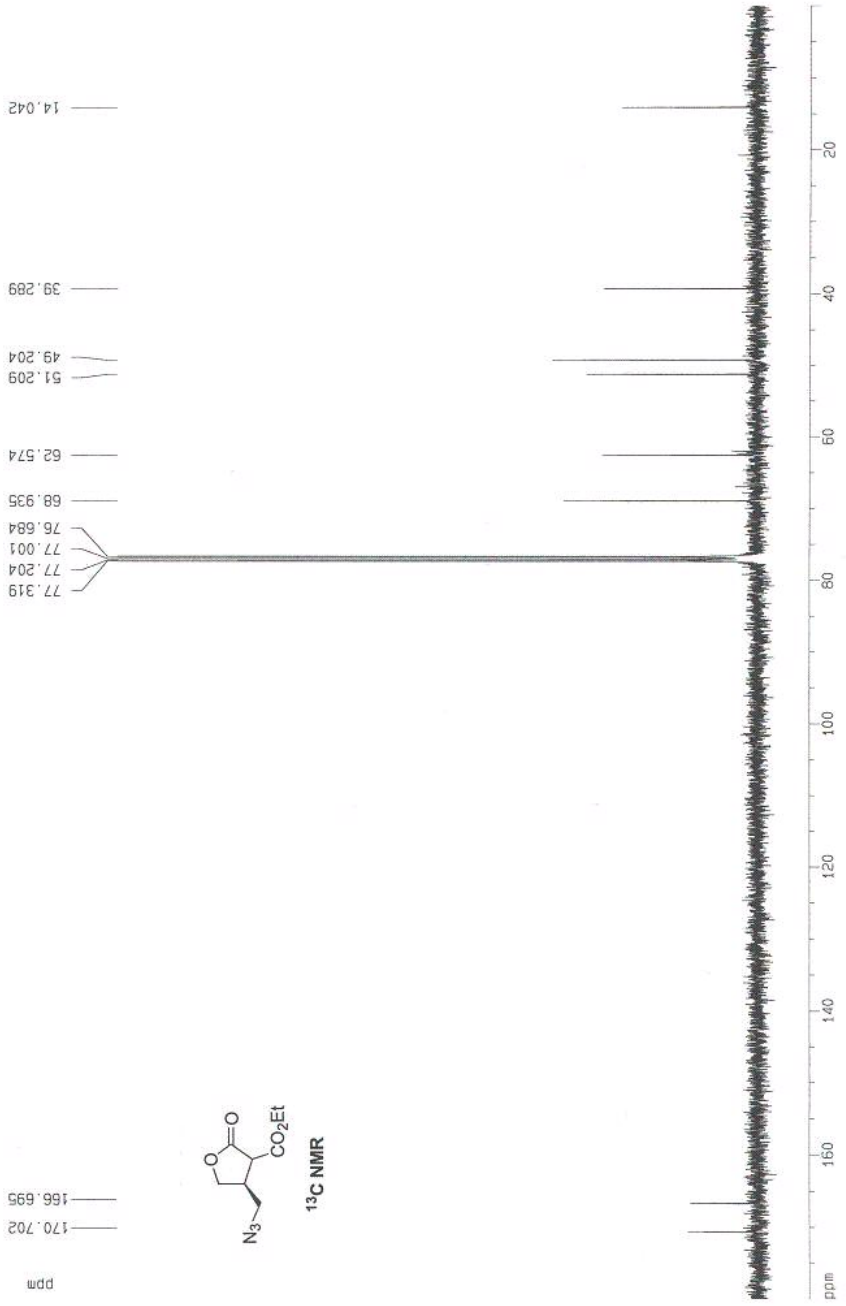
^{13}C NMR (100 MHz, $CDCl_3$) of S_5



^{1}H NMR (400 MHz, $CDCl_3$) of S_6

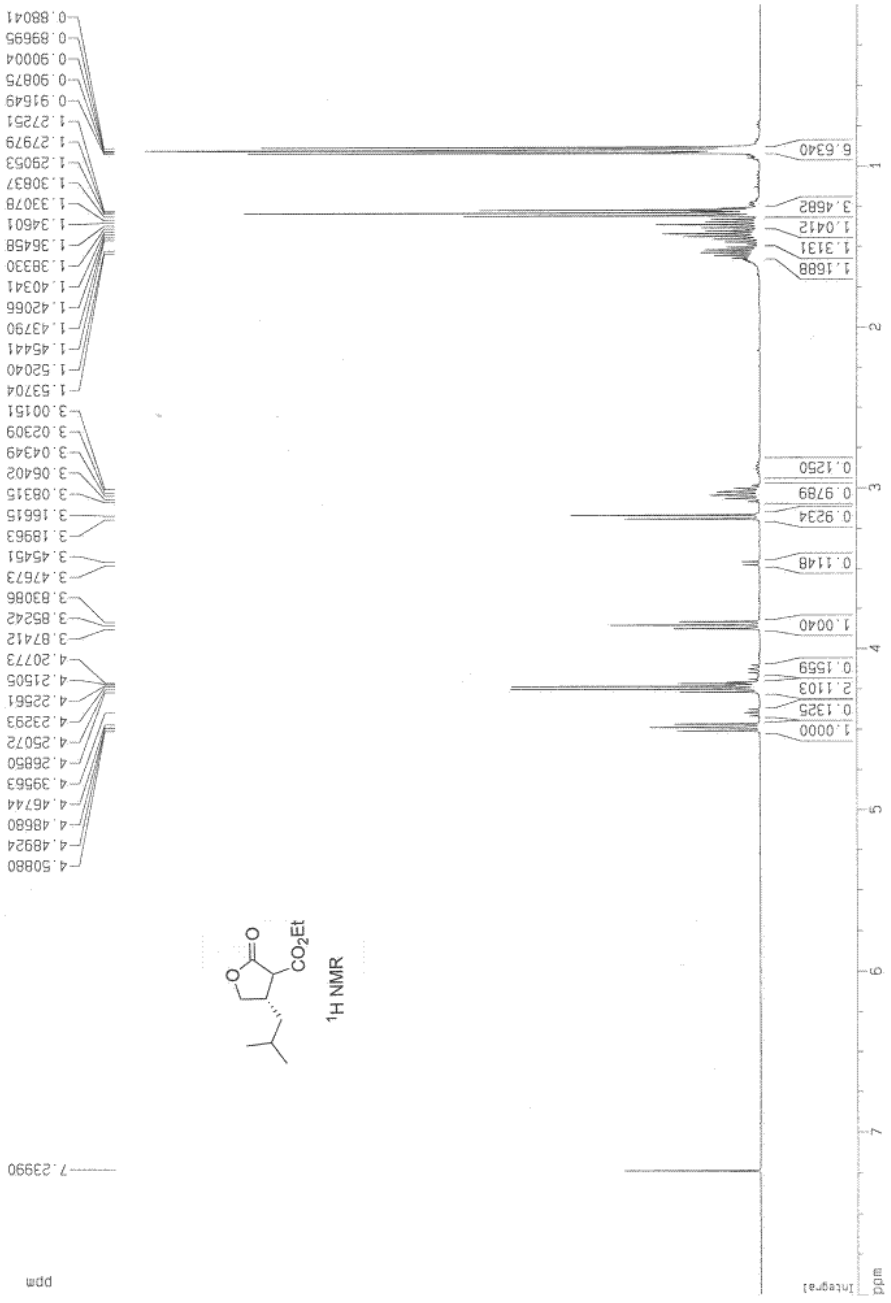


^{13}C NMR (100 MHz, $CDCl_3$) of S_6

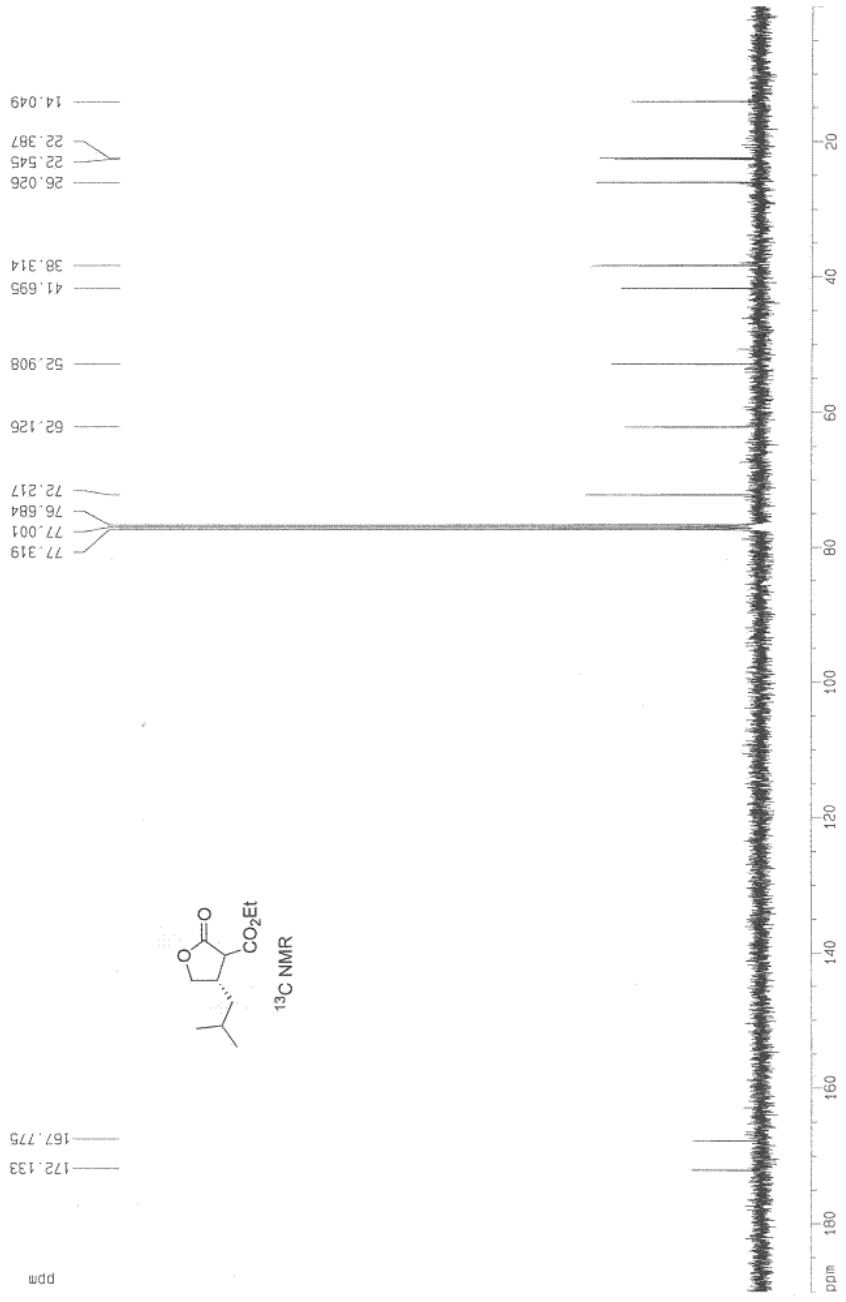


3) Characterizations of the products in Pregabalin synthesis (Scheme 2)

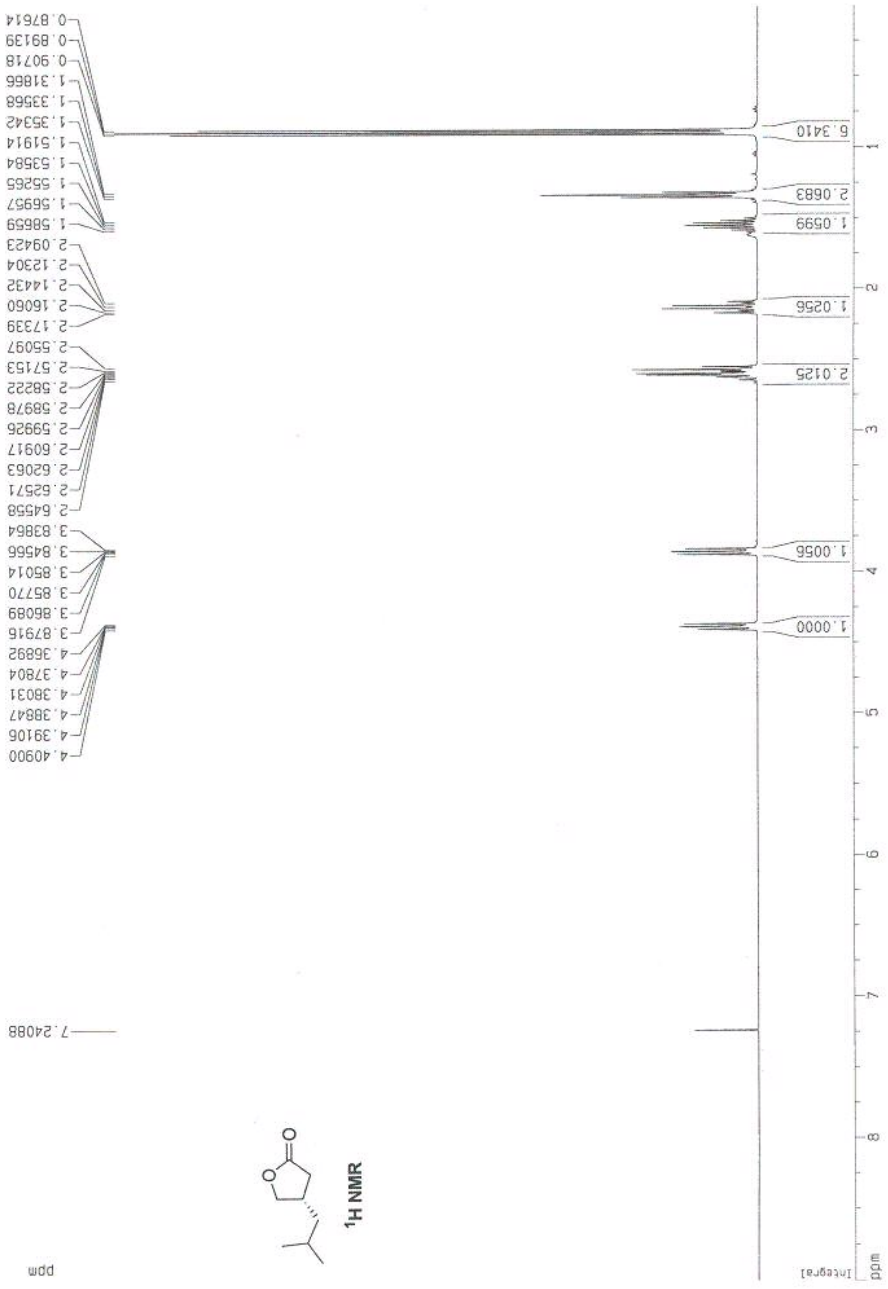
^{1}H NMR (400 MHz, $CDCl_3$) of the Lactones



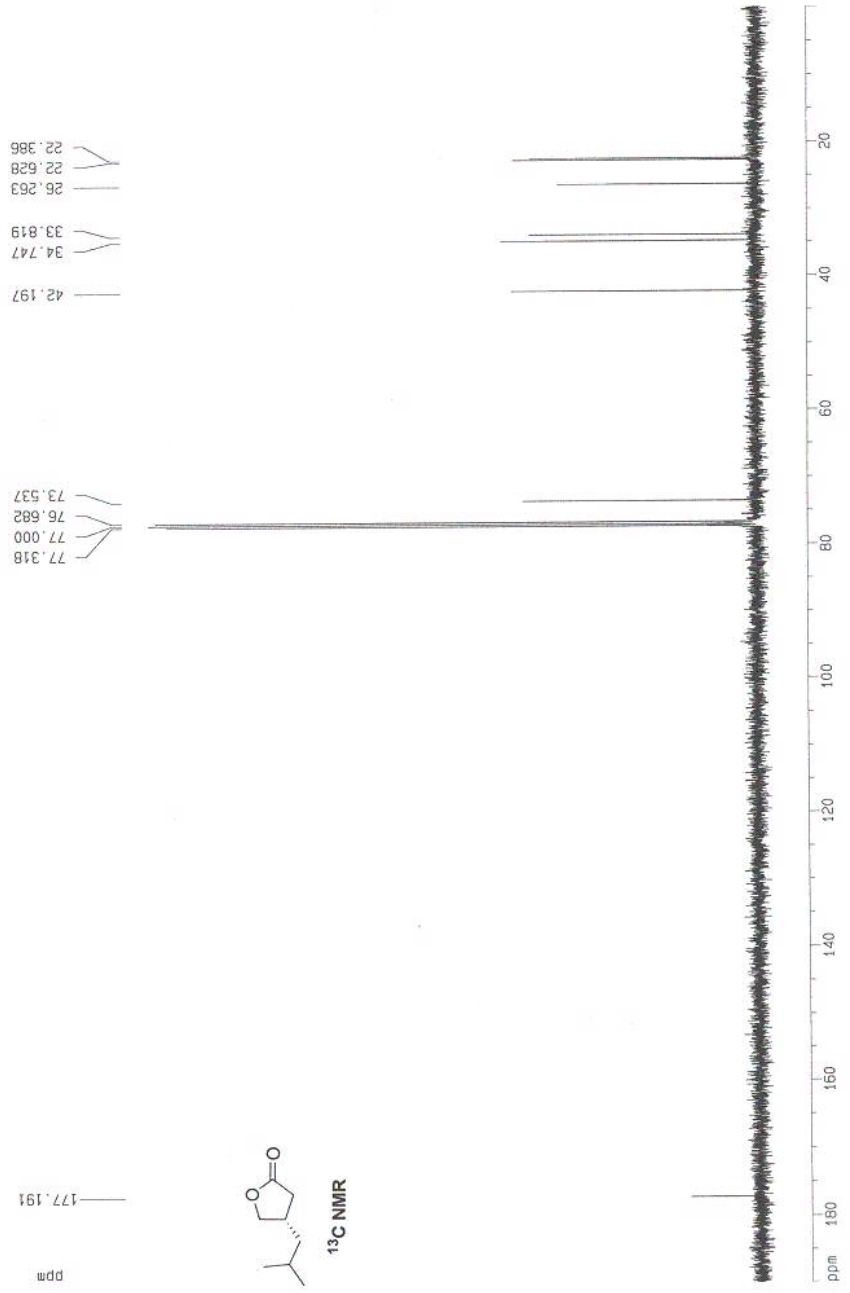
^{13}C NMR (100 MHz, $CDCl_3$) of the Lactones



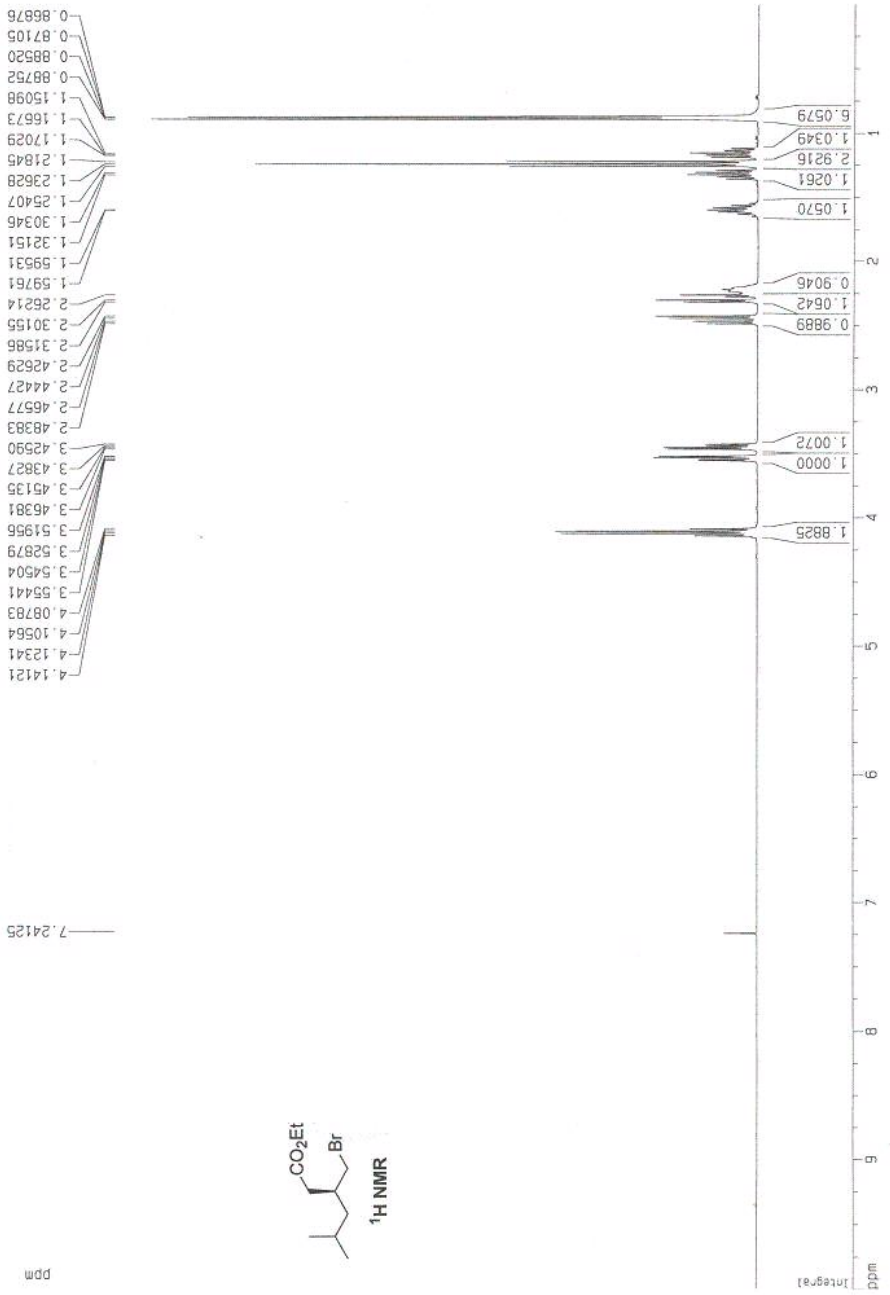
^{1}H NMR (400 MHz, $CDCl_3$) of 2



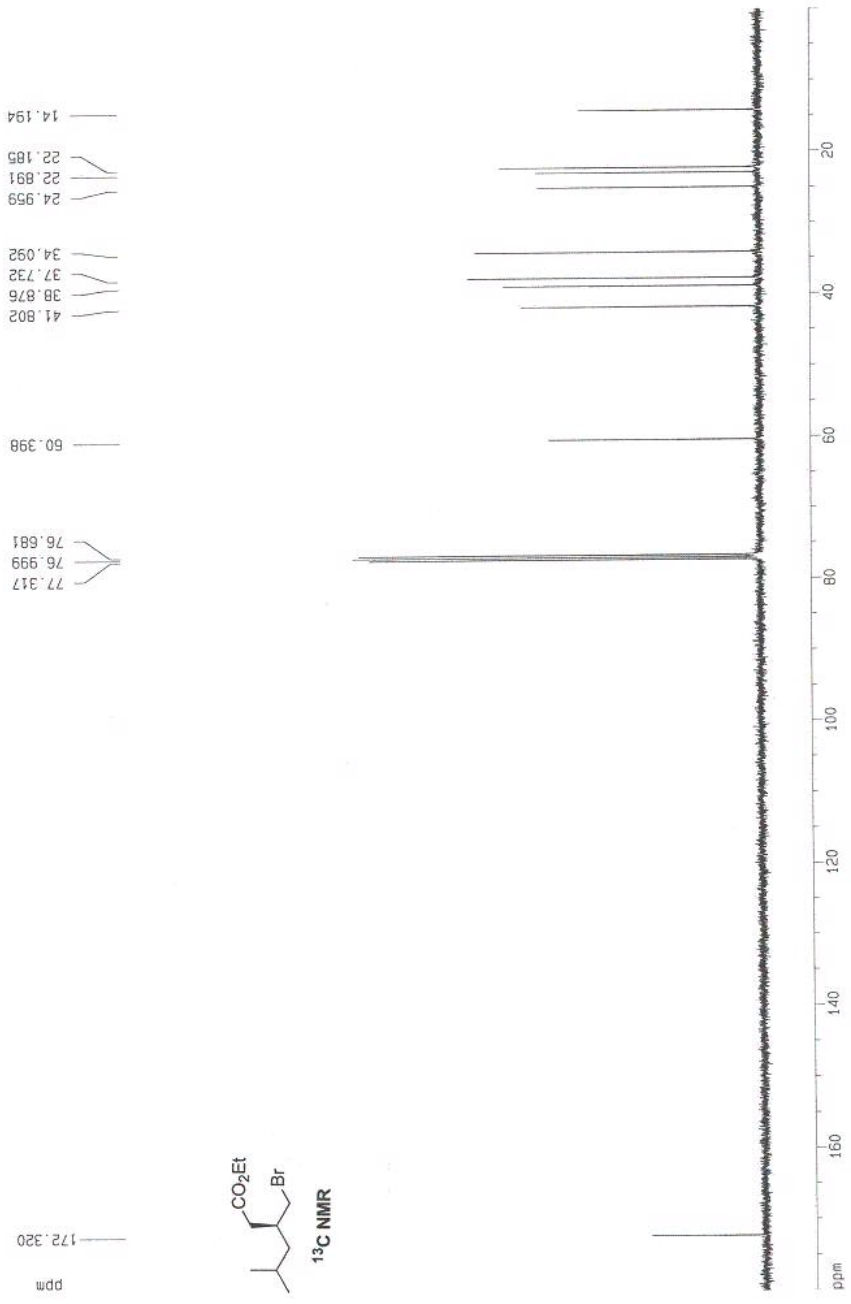
^{13}C NMR (100 MHz, $CDCl_3$) of 2



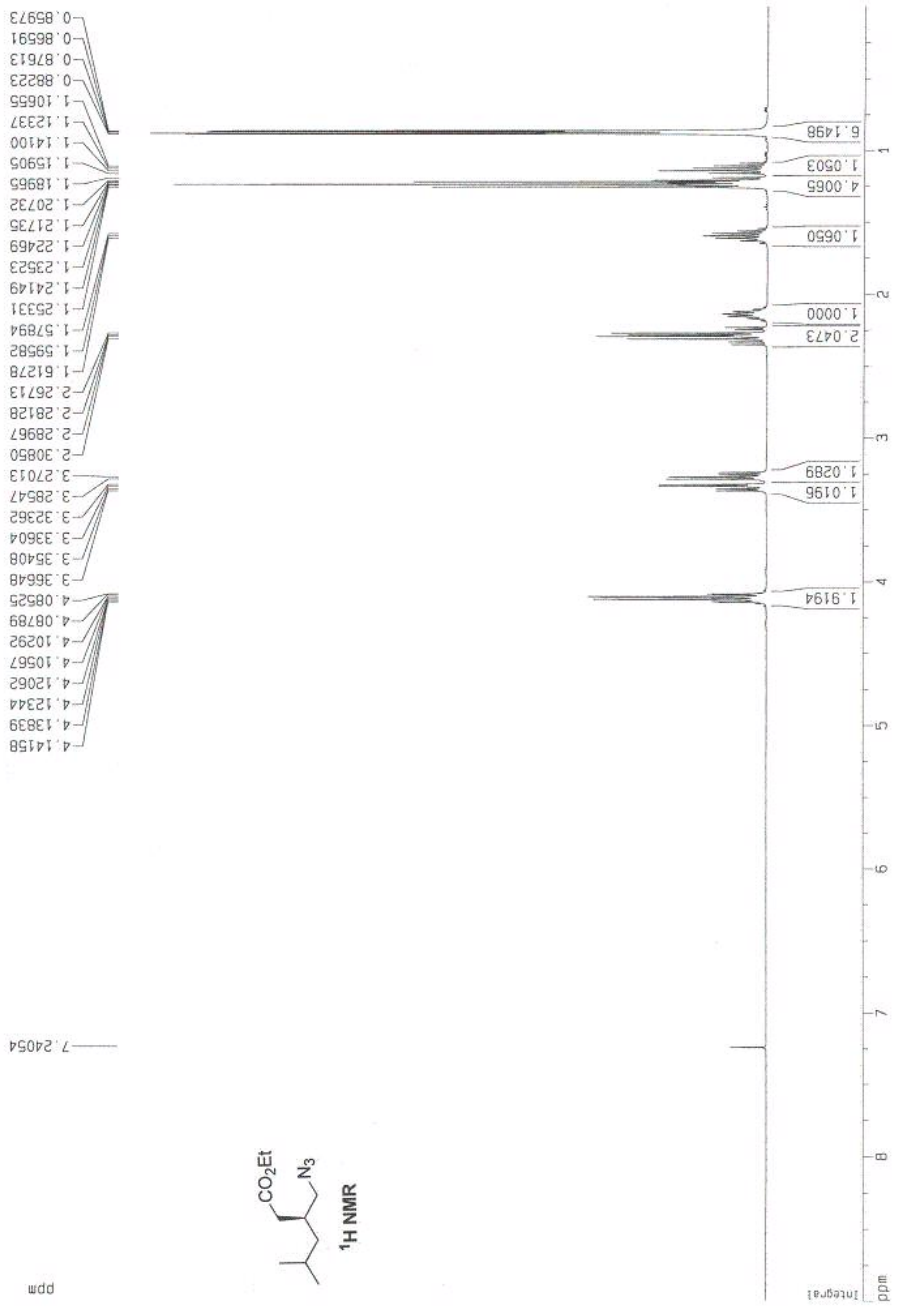
^{1}H NMR (400 MHz, $CDCl_3$) of 3



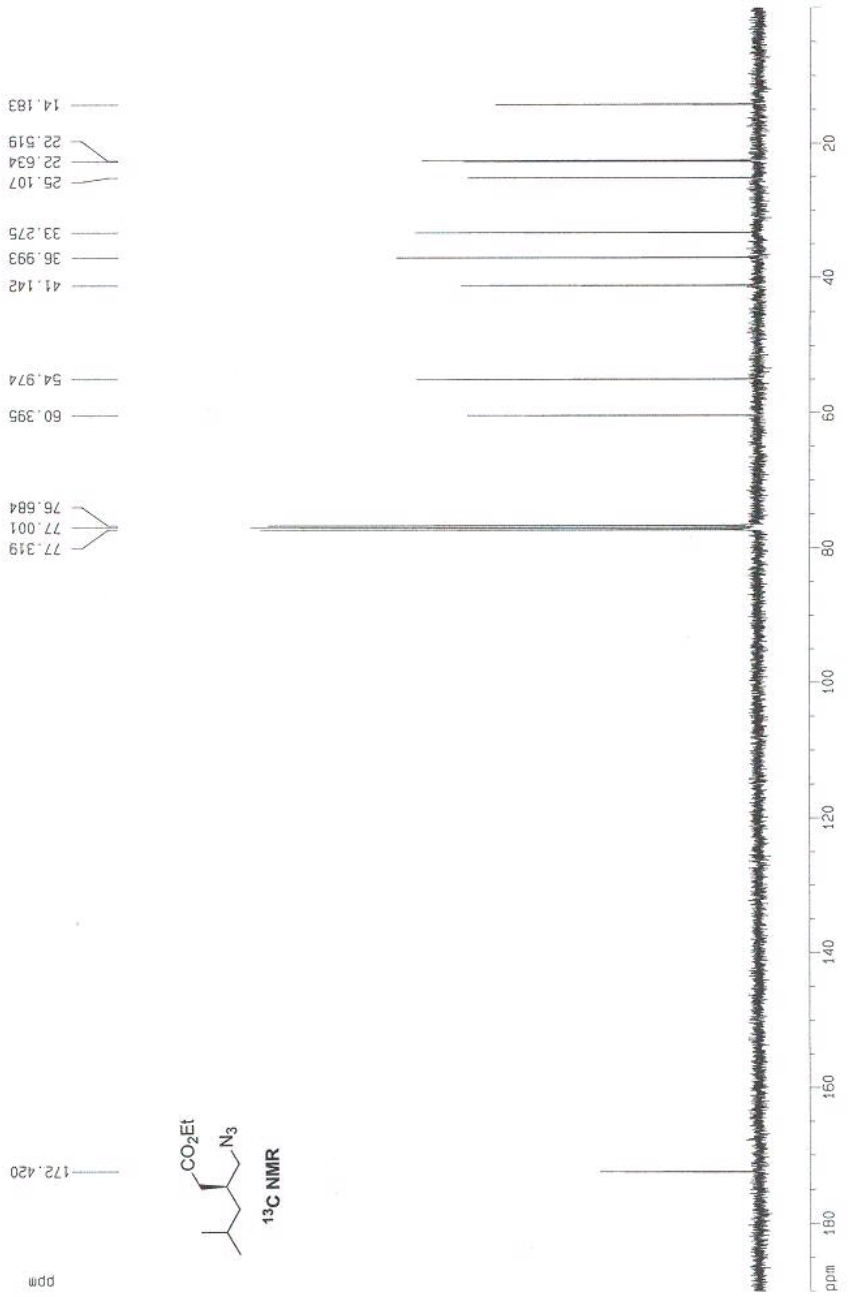
^{13}C NMR (100 MHz, $CDCl_3$) of 3



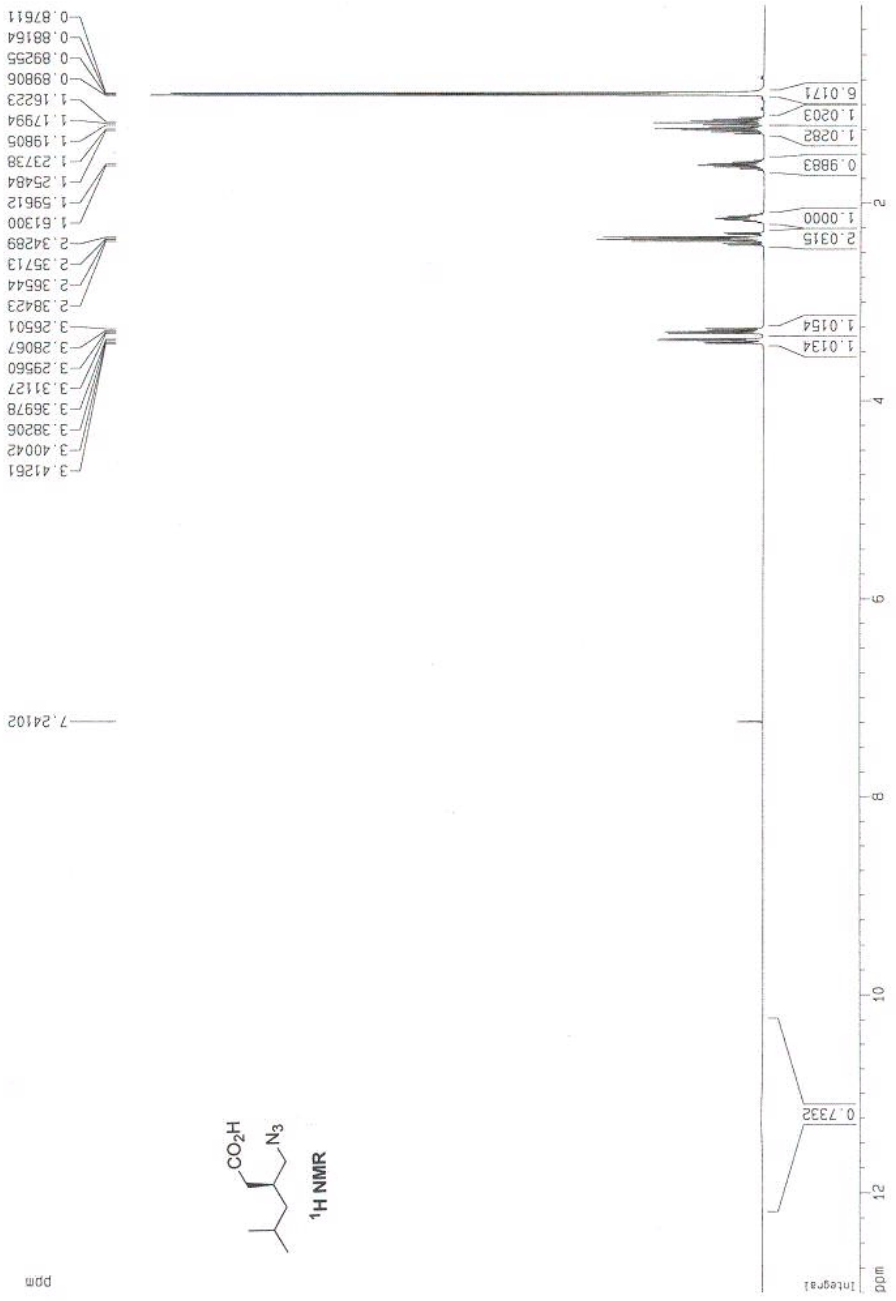
^{1}H NMR (400 MHz, $CDCl_3$) of 4



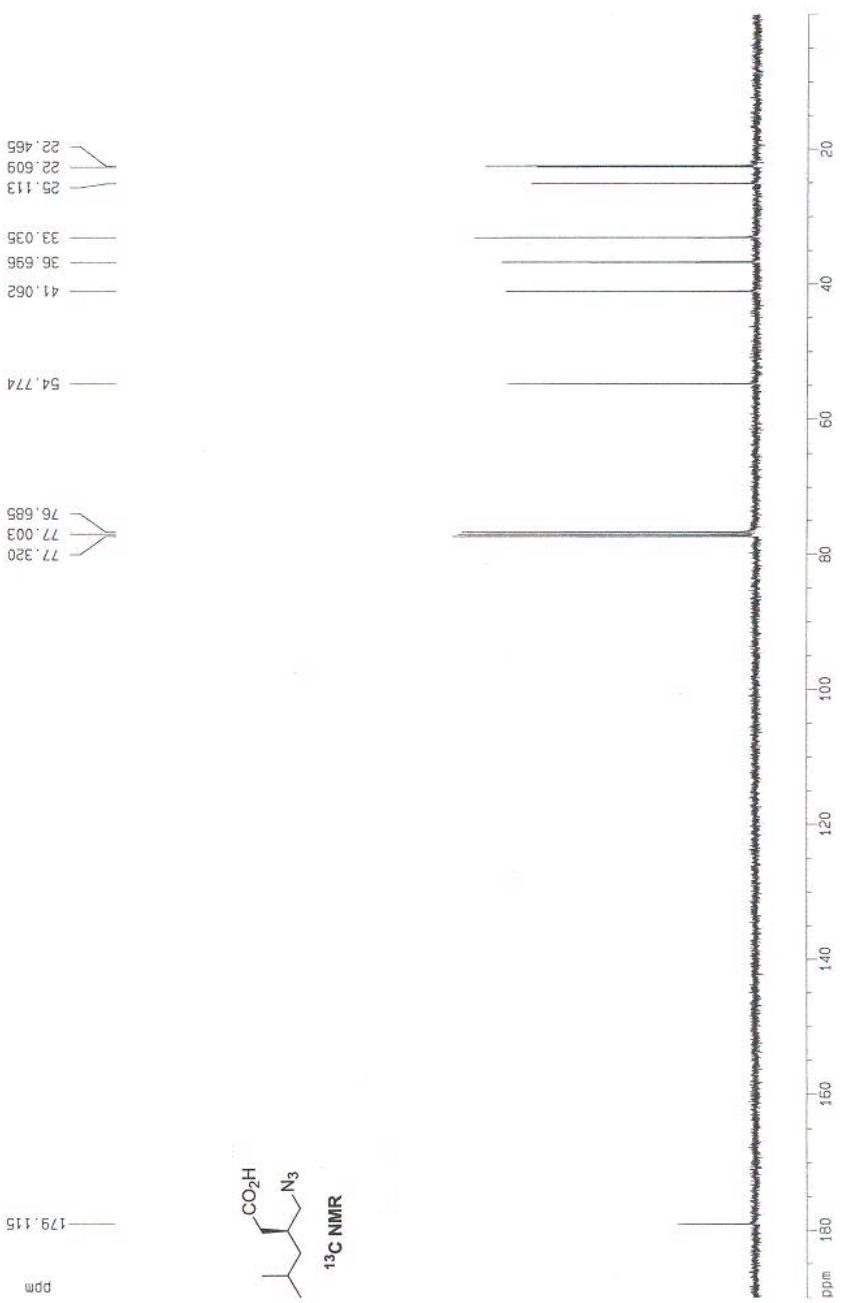
^{13}C NMR (100 MHz, $CDCl_3$) of 4



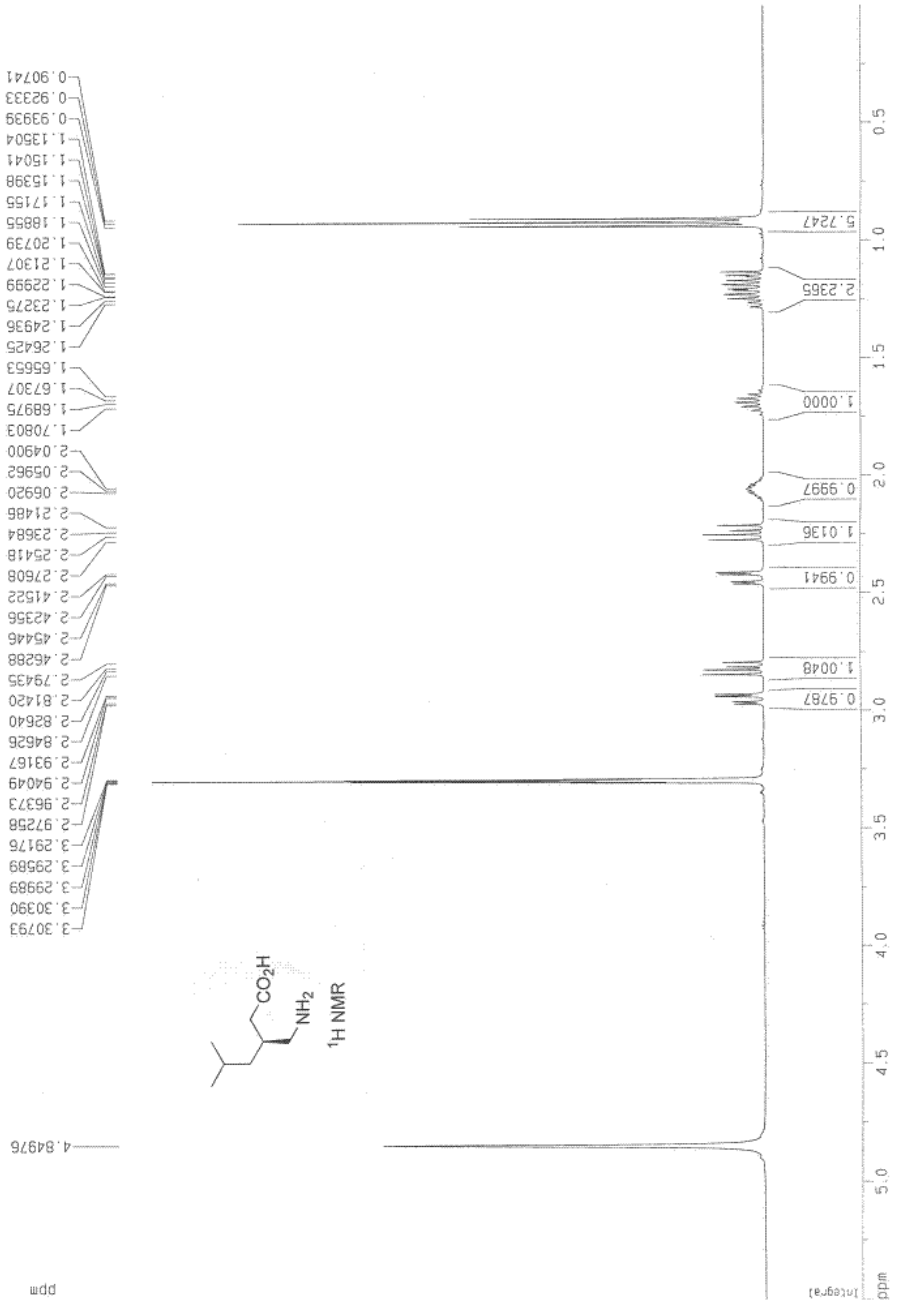
^{1}H NMR (400 MHz, $CDCl_3$) of (*S*)-3-azidomethyl-5-methyl-hexanoic acid



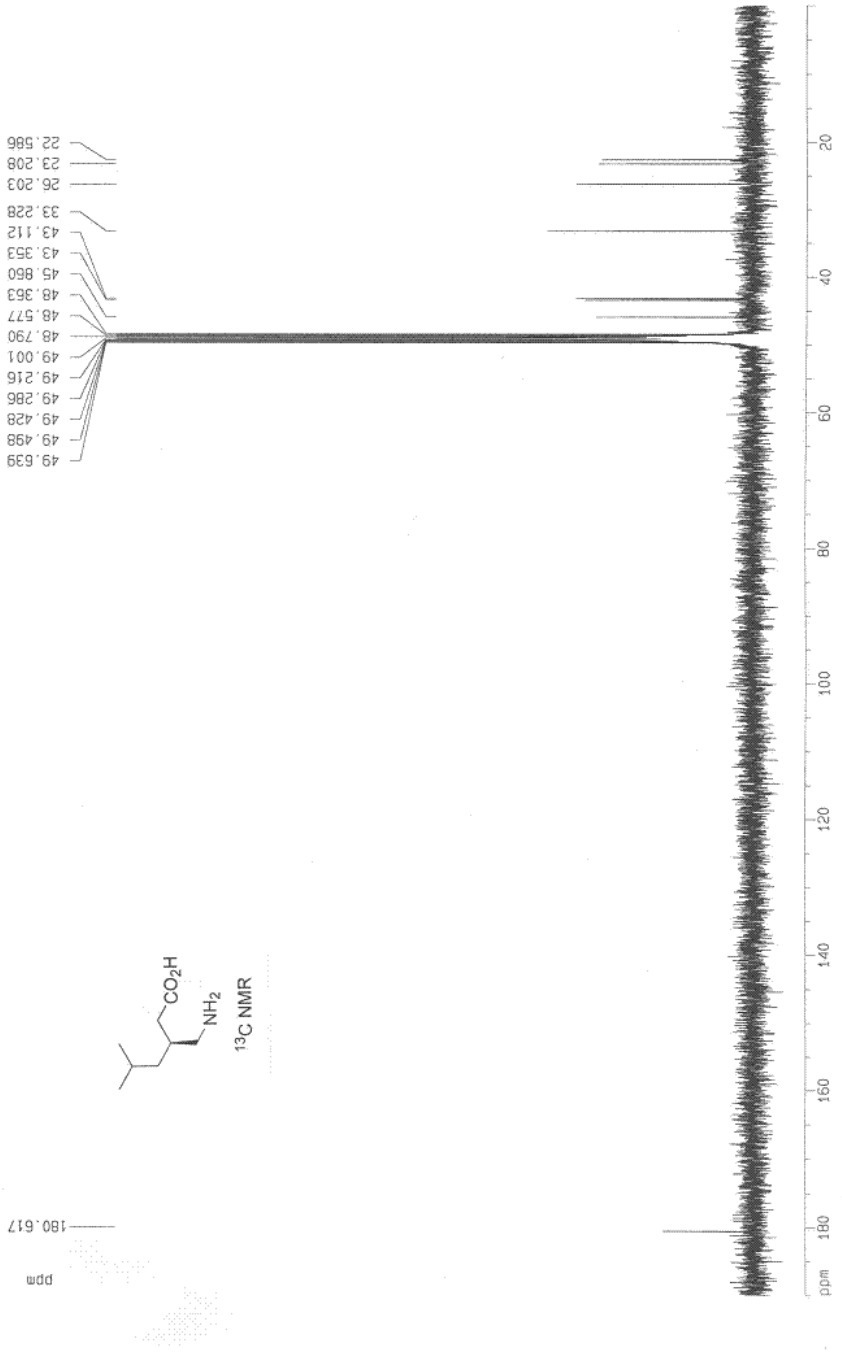
^{13}C NMR (100 MHz, $CDCl_3$) of (*S*)-3-azidomethyl-5-methyl-hexanoic acid



^{1}H NMR (400 MHz, CD_3OD) of Pregabalin (5)

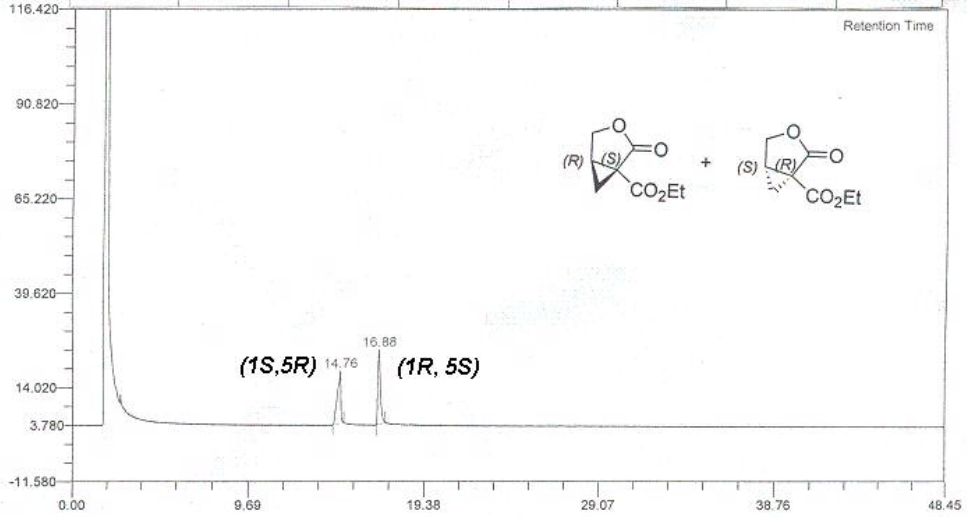


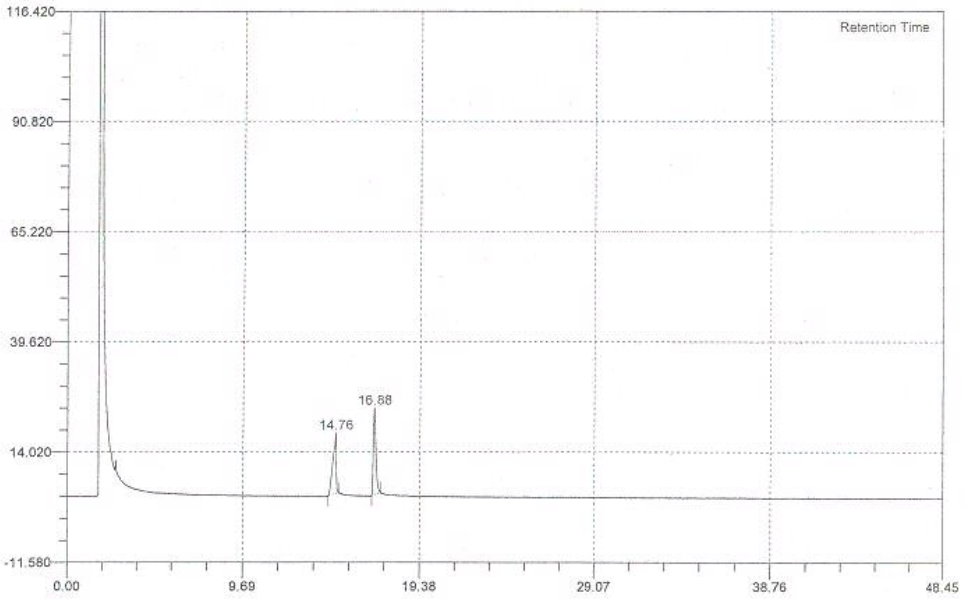
^{13}C NMR (100 MHz, CD_3OD) of Pregabalin (5)



4) GC chromatogram for %ee in Table 1:

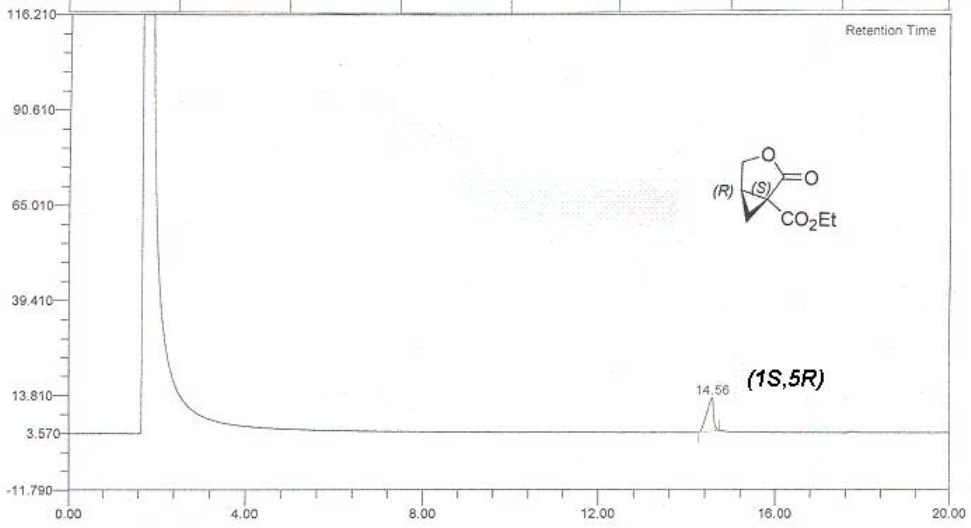
PK No.	RT	Peak Width	Area	Height	Area %	Height %	Code
1	14.765	12.253	3360132	14248	48.13439	41.23162	BB
2	16.885	8.736	3620598	20308	51.86561	58.76838	BB
Total		10.5(+/-)0.497	6980730	34556	100.00000	100.00000	

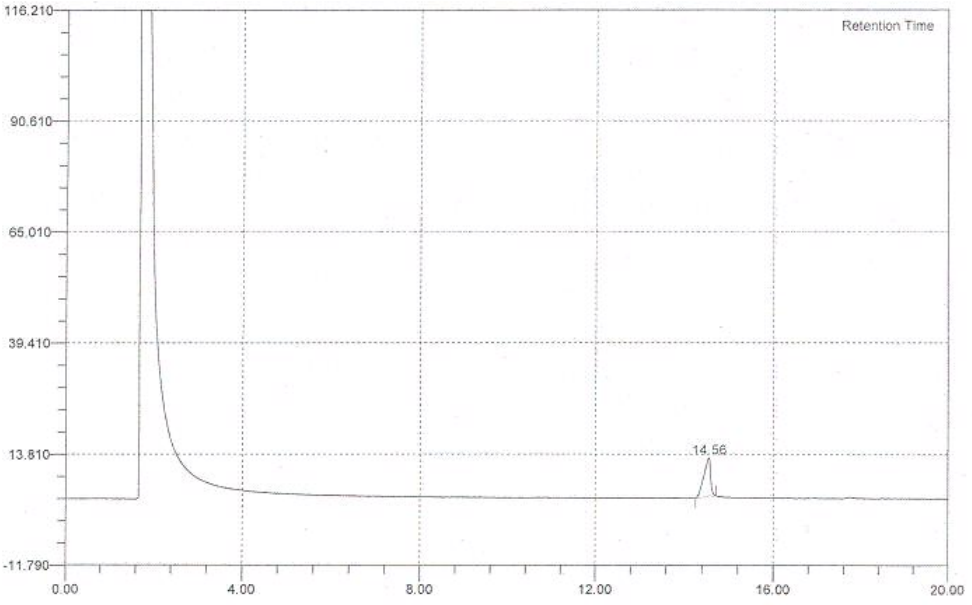




(주)도남 인스트루먼트
-1-

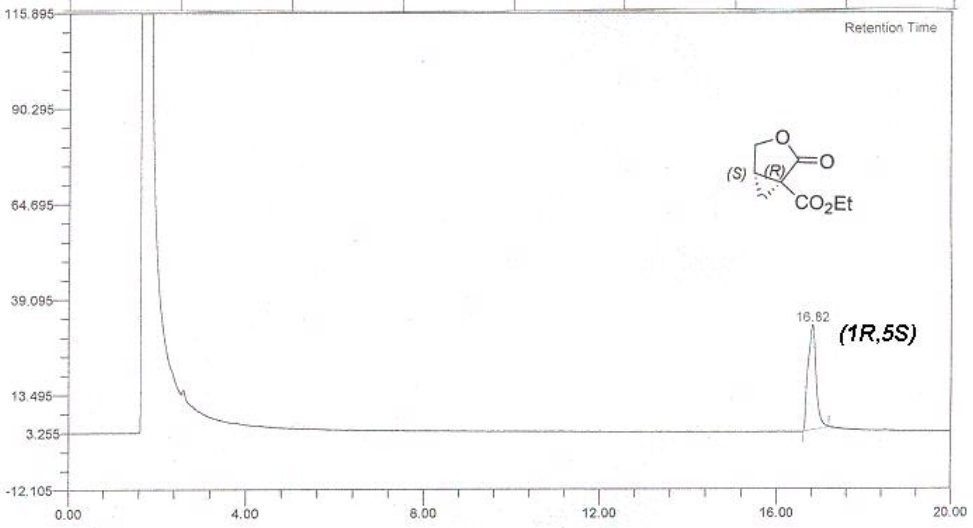
PK No.	RT	Peak Width	Area	Height	Area %	Height %	Code
1	14.561	9.451	1724434	9009	100.00000	100.00000	BB
Total		9.5(+/-)0.000	1724434	9009	100.00000	100.00000	

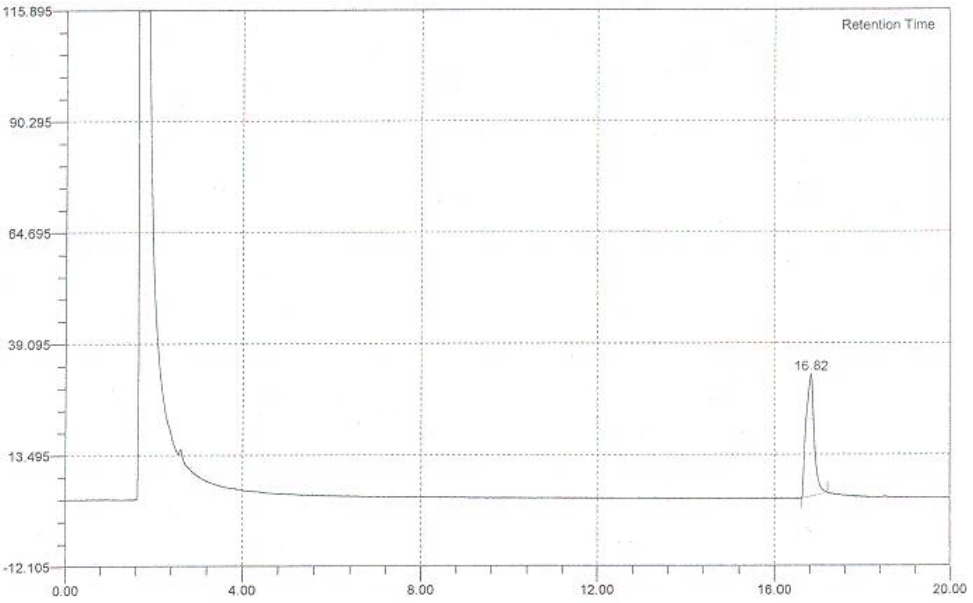




(주)도남 인스트루먼트
-1-

PK No.	RT	Peak Width	Area	Height	Area %	Height %	Code
1	16.820	11.758	6385776	28219	100.00000	100.00000	BB
Total		11.8(+/-)0.000	6385776	28219	100.00000	100.00000	

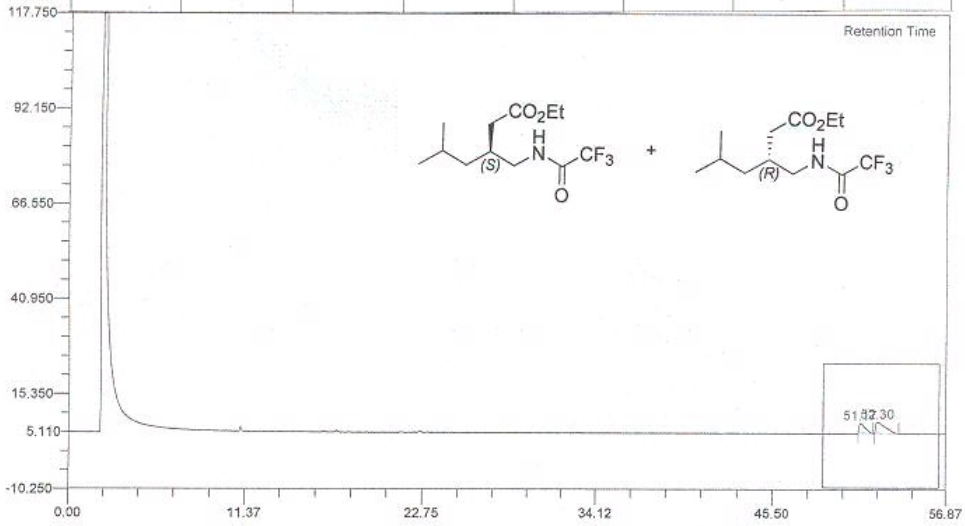


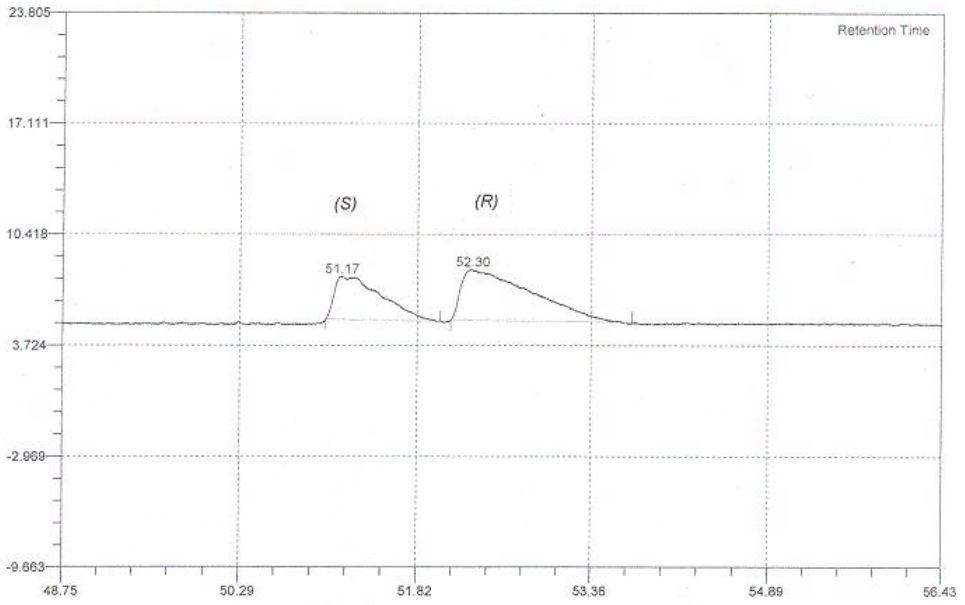


(주)도남 인스트루먼트
-1-

5) GC chromatogram for %ee in Figure 4:

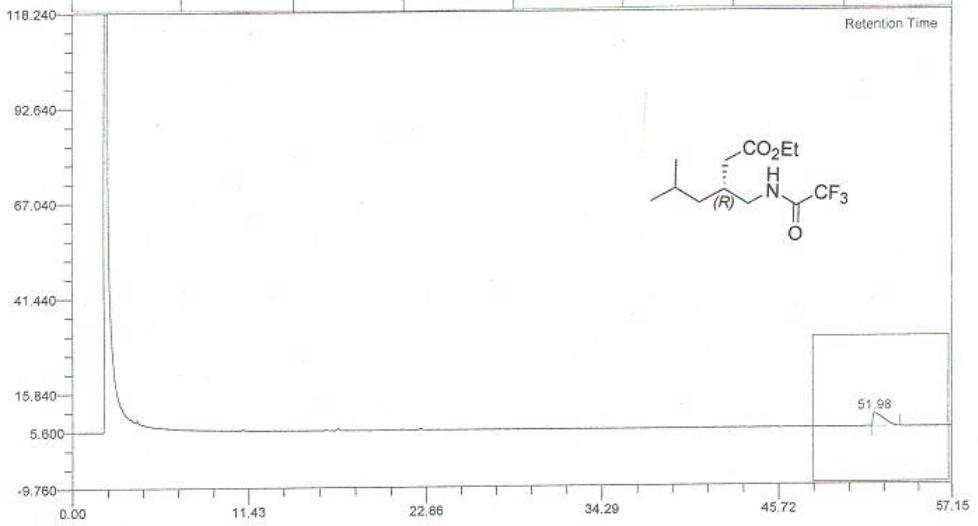
PK No.	RT	Peak Width	Area	Height	Area %	Height %	Code
1	51.172	27.363	1350870	2594	35.94194	46.01739	tep-BB
2	52.303	42.802	2407608	3043	64.05806	53.98261	tep-BB
Total		35.1(+/-)2.183	3758478	5637	100.00000	100.00000	

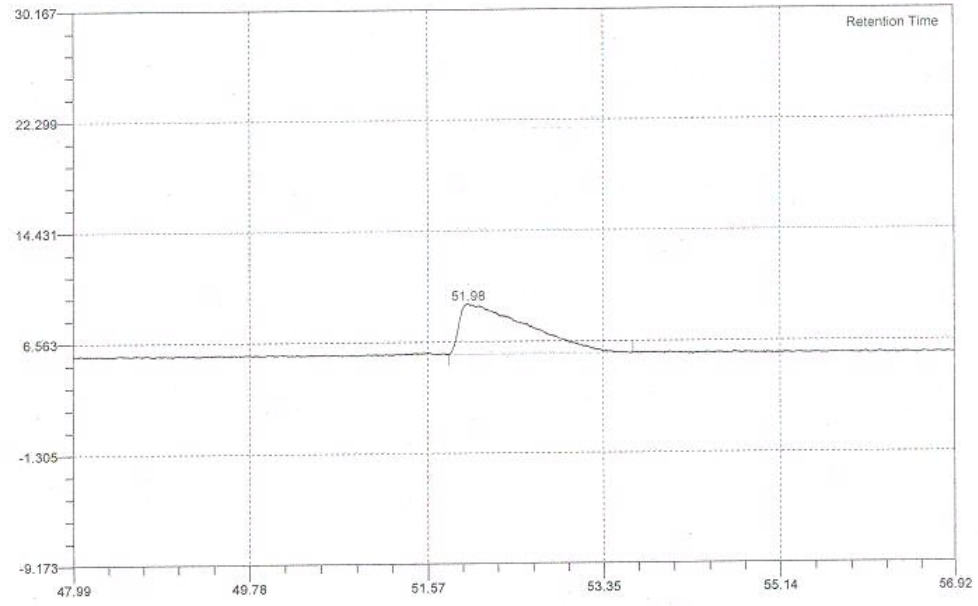




(주)도남 인스트루먼트
-1-

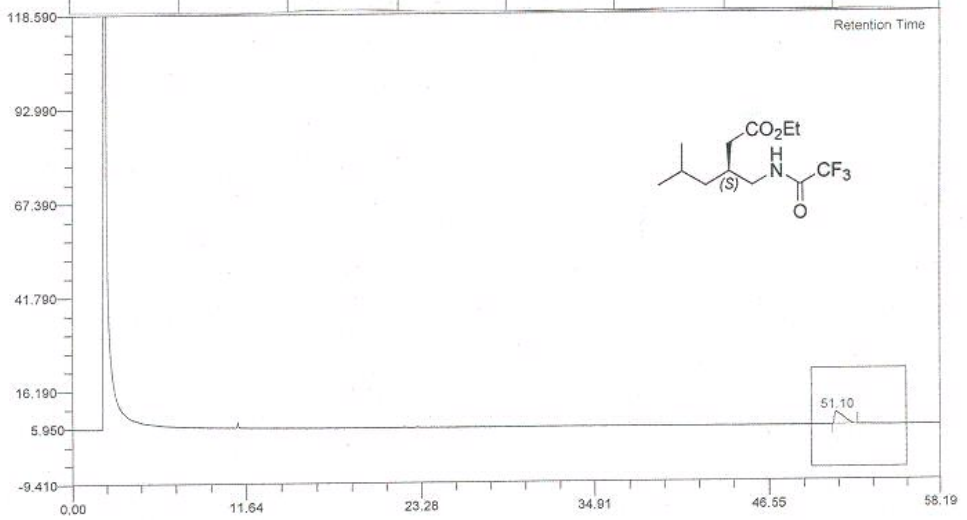
PK No.	RT	Peak Width	Area	Height	Area %	Height %	Code
1	51.979	45.495	3128145	3579	100.00000	100.00000	tep-BB
Total		45.5(+/-)0.000	3128145	3579	100.00000	100.00000	

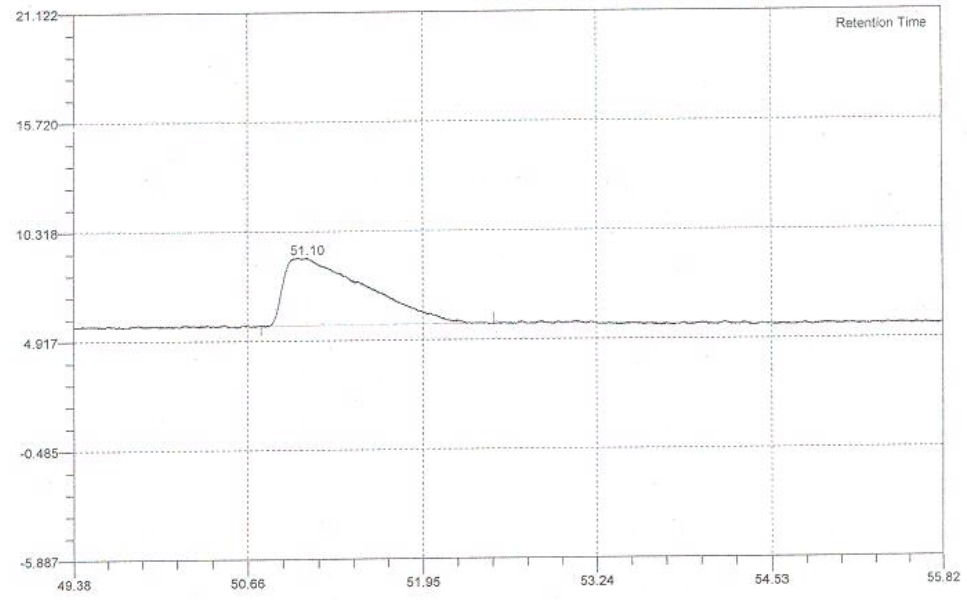




(주)도남 인스트루먼트
-1-

PK No.	RT	Peak Width	Area	Height	Area %	Height %	Code
1	51.102	40.989	2574759	3347	100.00000	100.00000	tep-BB
Total		41.0(+/-)0.000	2574759	3347	100.00000	100.00000	





(주)도남 인스트루먼트
-1-