

Construction of *N*-1H, 1H-perfluoroalkylated peptide bonds

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1. Experimental procedure for the synthesis of **2** (n = 0)

(L)Phenylalanine methyl ester hydrochloride (4.314 g, 20.00 mmol) was suspended in CH₂Cl₂ (100 mL). Water (100 mL) and Na₂CO₃ (14.0 g) were added. The mixture was stirred for 30 min. The clear organic layer was separated. NaHCO₃ (2.016 g, 24.00 mmol), water (100 mL) and trifluoroethylating agent CF₃CH₂I(C₆H₅)N(SO₂CF₃)₂ (12.48 g, 22.00 mmol) were added with stirring at room temperature. After 4 h, the CH₂Cl₂ layer was again separated and washed with 3×100 mL of water. The organic solvent was evaporated. The obtained residue was subjected to column chromatography using 10-40% acetone in n-hexanes. After evaporation of organic solvents, the obtained ester intermediate was stirred in 80 mL of 1.0 M NaOH aqueous solution for 16 h. The aqueous solution was then cooled in an ice bath and acidified with conc. HCl to pH 4.5. The formed white precipitate was filtered and lyophilized to yield 4.390 g (17.76 mmol, 88.8 %) of compound **1** (n = 0).

Compound **1** (n = 0) (2.472 g, 10.00 mmol), (L)leucine methyl ester hydrochloride (1.854 g, 10.00 mmol), HOBt (1.486 g, 11.00 mmol), and EDAC•HCl (2.109 g, 11.00 mmol) were suspended in CH₂Cl₂ (100 mL). The reaction mixture was stirred and cooled at 0 °C. DIEA (3.48 mL, 20.0 mmol) was added in one portion through a syringe. The reaction was continued at 0 °C for 2 h and at room temperature for 14 h. The reaction mixture was then washed with 100 mL of 0.5 M HCl, 100 mL of 0.1 M NaHCO₃, and 100 mL of H₂O respectively. The organic layer was separated, and the solvent was evaporated. The obtained crude product was subjected to column chromatography with 10–30% acetone in n-hexanes to yield 3.418 g (9.129 mmol, 91.3%) of compound **2** (n = 0).

2. Experimental procedure for the synthesis of **3**

N^α-phthaloyl glycine acid chloride (2.683 g, 12.00 mmol) was dissolved in 20 mL of dry CH₃CN. Pyridine (2.5 mL) was added through a syringe. Compound **2** (n = 0) (3.744 g, 10.00 mmol) dissolved in 20 mL of dry CH₃CN was added to above solution with stirring. The reaction mixture was refluxed for 4 h. The solvent was then evaporated. The obtained residue was dissolved in ethyl acetate (40 mL) and washed with H₂O (40 mL) for 3 times. The organic layer was separated and the solvent was evaporated. The obtained residue was subjected to column chromatography with 10-40% acetone in n-hexanes. The desired product compound **3** was obtained (4.897 g, 8.720 mmol, 87.2%).

3. Experimental procedure for the synthesis of **4** (n = 0)

N^α-Fmoc-glycine acid chloride (1.579 g, 5.00 mmol) was dissolved in 15 mL of dry CH₃CN. Compound **2** (n = 0) (3.744 g, 10.00 mmol) dissolved in 20 mL of dry CH₃CN was added to above solution with stirring. The reaction mixture was refluxed for 4 h. The solvent was then evaporated. The obtained residue was dissolved in ethyl acetate (40 mL) and washed with 0.5 M NaHCO₃ (40 mL) twice and H₂O (40 mL) once. The organic layer was separated and the solvent was evaporated. The obtained residue was subjected to column chromatography with 10-40% acetone in n-hexanes. The desired product compound **4** (n = 0) was obtained (2.717 g, 4.157 mmol, 83.1%).

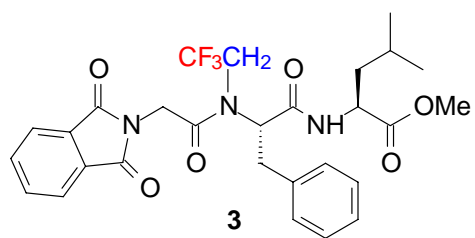
4. Experimental procedure for the synthesis of **5**

Compound **4** (n = 0) (1.550 g, 2.375 mmol) was dissolved in 20 mL of 20% 4-(aminomethyl) piperidine in CHCl₃. The solution was stirred at room temperature for 3 h, then washed with H₂O (20 mL) twice and extracted with a phosphate buffer of pH 5.4 (20 mL) twice. The organic layer was separated and dried using anhydrous Na₂SO₄, and the solvent was evaporated. The obtained residue was dissolved in 30 mL of dry CH₃CN. *N*^α-Fmoc-glycine acid chloride (0.750 g, 2.375 mmol) was then added. The reaction mixture was refluxed for 4 h. The solvent was then evaporated. The obtained residue was dissolved in ethyl acetate (40 mL) and washed with 0.5 M NaHCO₃ (40 mL) twice and H₂O (40 mL) once. The organic layer was separated and the solvent was evaporated. The obtained residue was subjected to column chromatography with 10-40%

acetone in n-hexanes. The intermediate product FmocGlyGlyCF₃CH₂(L)Phe(L)LeuOMe was obtained (0.925 g, 1.301 mmol, 54.8%).

The intermediate product FmocGlyGlyCF₃CH₂(L)Phe(L)LeuOMe (0.397 g, 0.559 mmol) was dissolved in 15 mL of 20% 4-(aminomethyl)piperidine in CHCl₃. The solution was stirred at room temperature for 3 h, then washed with H₂O (20 mL) twice and extracted with a phosphate buffer of pH 5.4 (20 mL) twice. The organic layer was separated and dried using anhydrous Na₂SO₄, and the solvent was evaporated. The obtained residue was dissolved in 25 mL of CH₂Cl₂. Then *N*^α-Boc-(L)tyrosine (0.157 g, 0.559 mmol), HOBt (0.080 g, 0.590 mmol), and EDC·HCl (0.113 g, 0.590 mmol) were added. The reaction mixture was stirred and cooled in an ice bath. DIEA (1.50 mL, 8.61 mmol) was added in one portion through a syringe. The reaction was continued at 0 °C for 2 h and at room temperature for 24 h. The reaction mixture was then washed with 30 mL of 0.5 M HCl, 30 mL of 0.1 M NaHCO₃, and 30 mL of H₂O respectively. The organic layer was separated, and the solvent was evaporated. The obtained crude product was subjected to column chromatography with 20–50% acetone in n-hexanes to yield 0.211 g (0.281 mmol, 50.3%) of compound **5**.

5. HRMS and NMR spectra of **3**



Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

94 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)

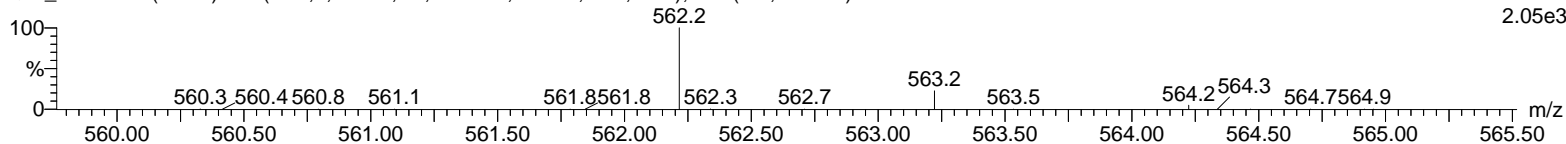
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Changqing Lu, Lu_01

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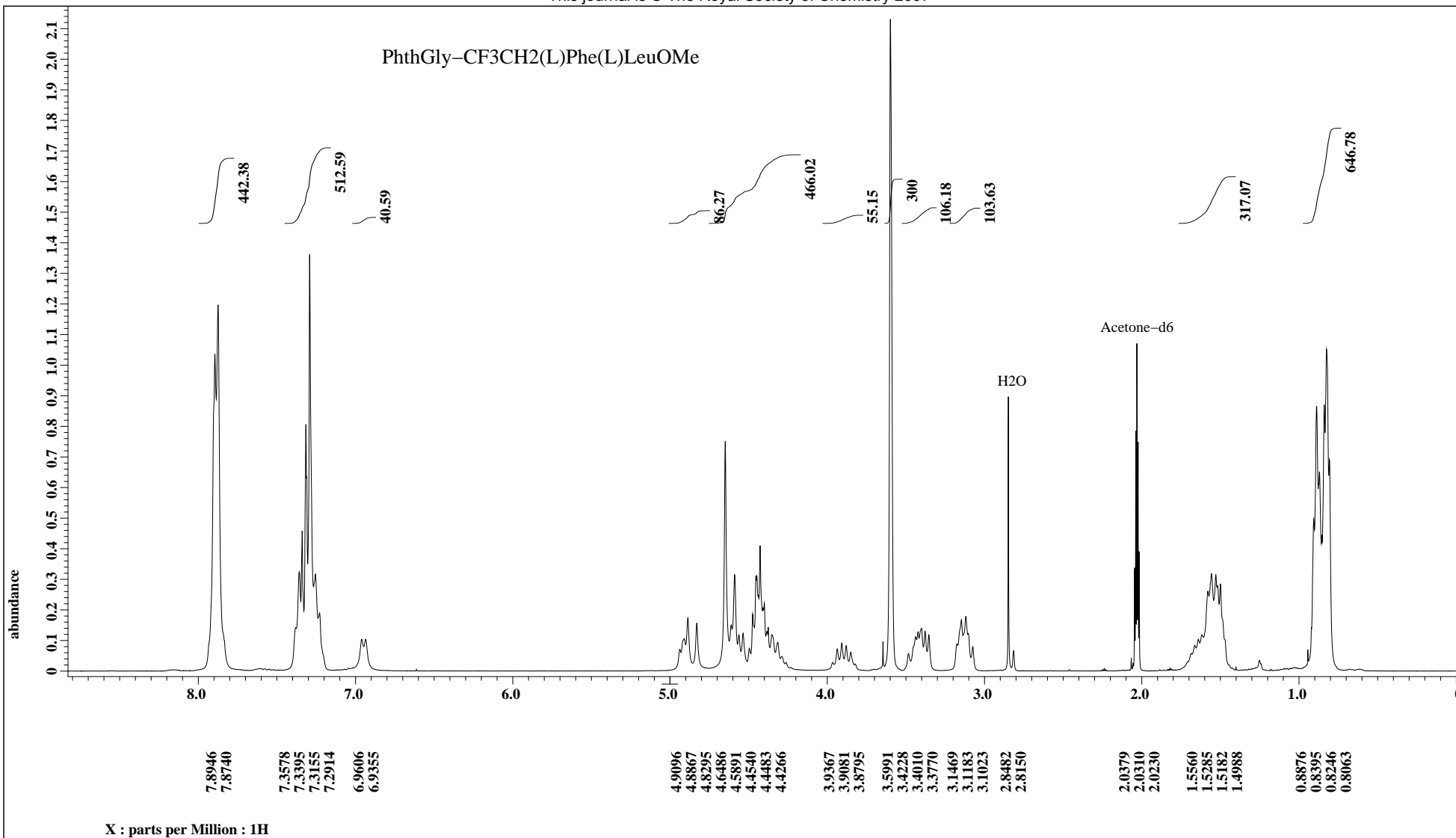
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2.05e3

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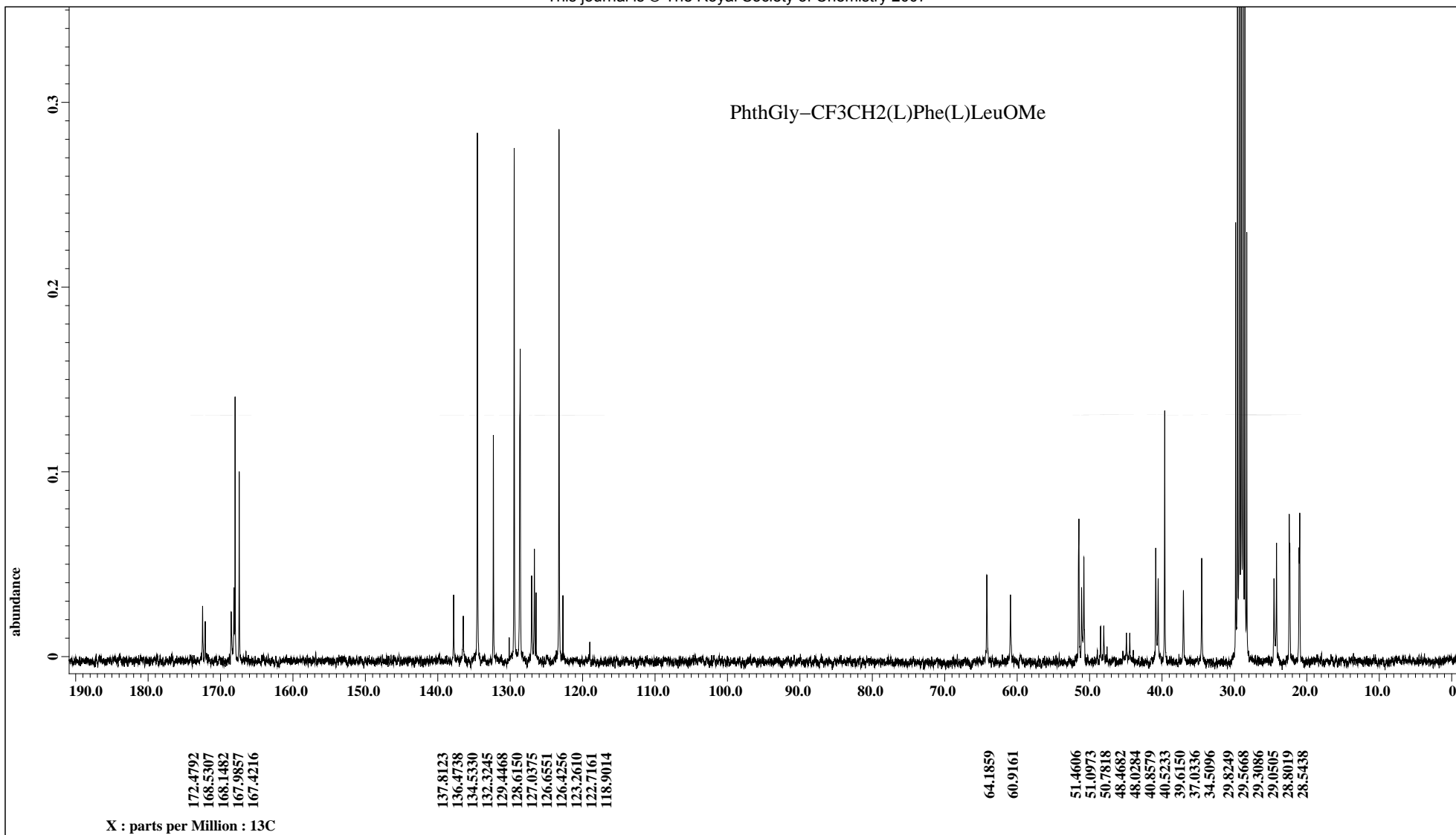
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PhthGly-CF₃CH₂(L)Phe(L)LeuOMe



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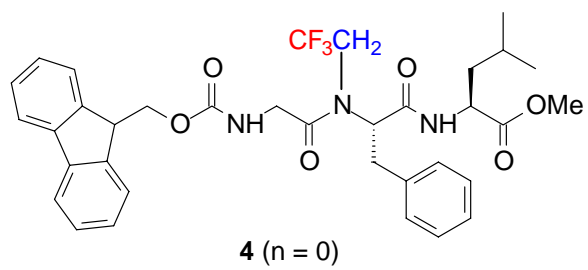
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6. HRMS and NMR spectra of **4** (n = 0)



Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

113 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)

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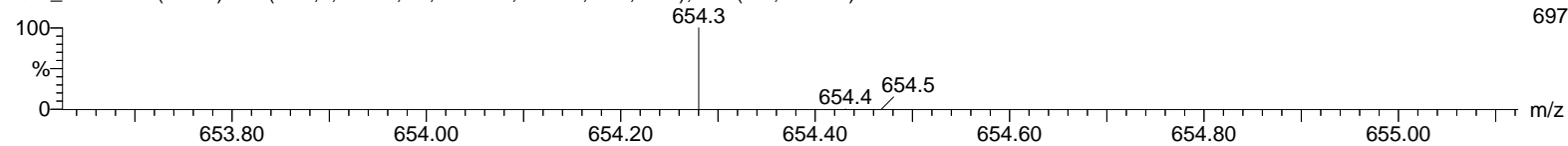
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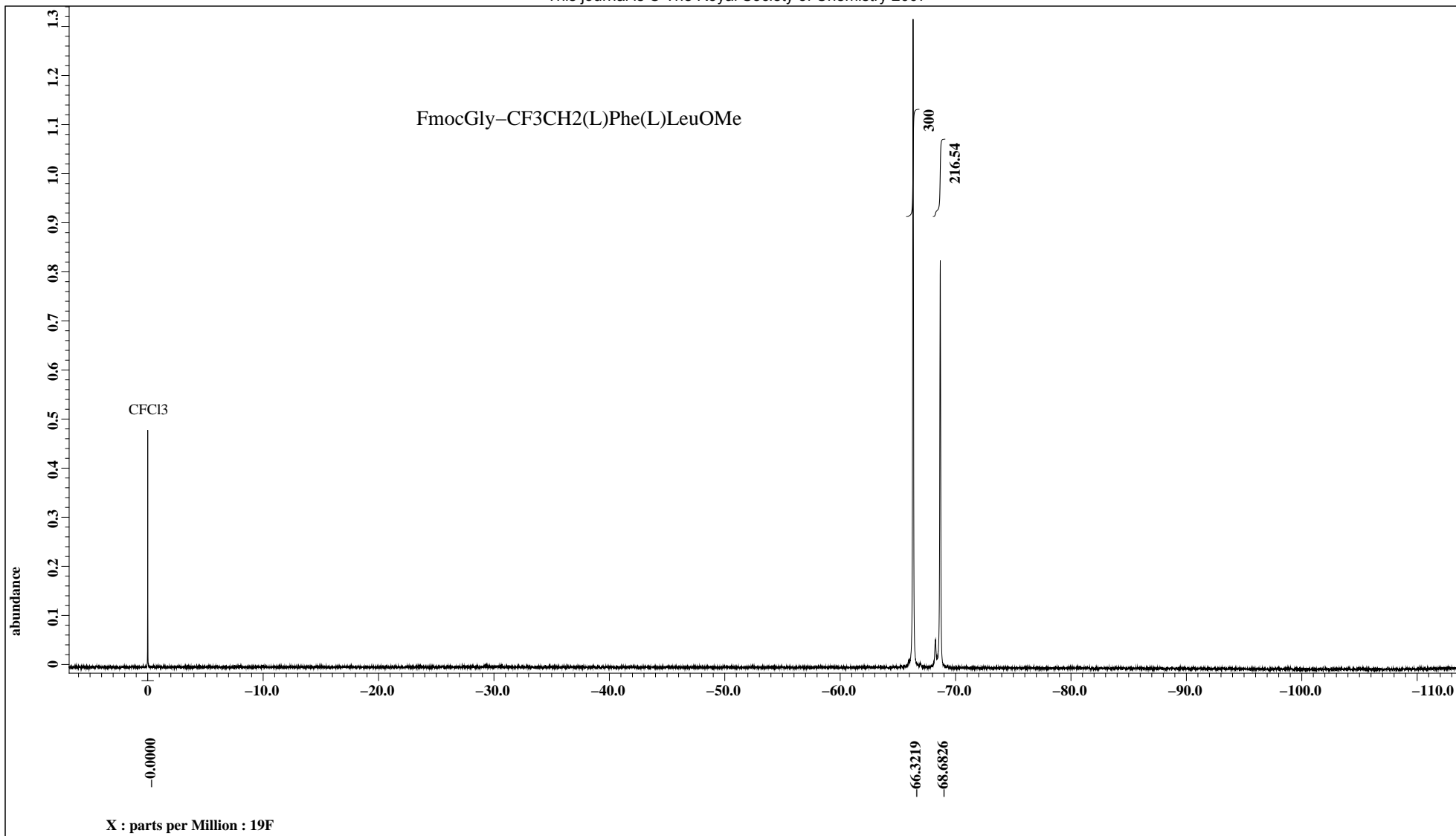
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Q-tof
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697



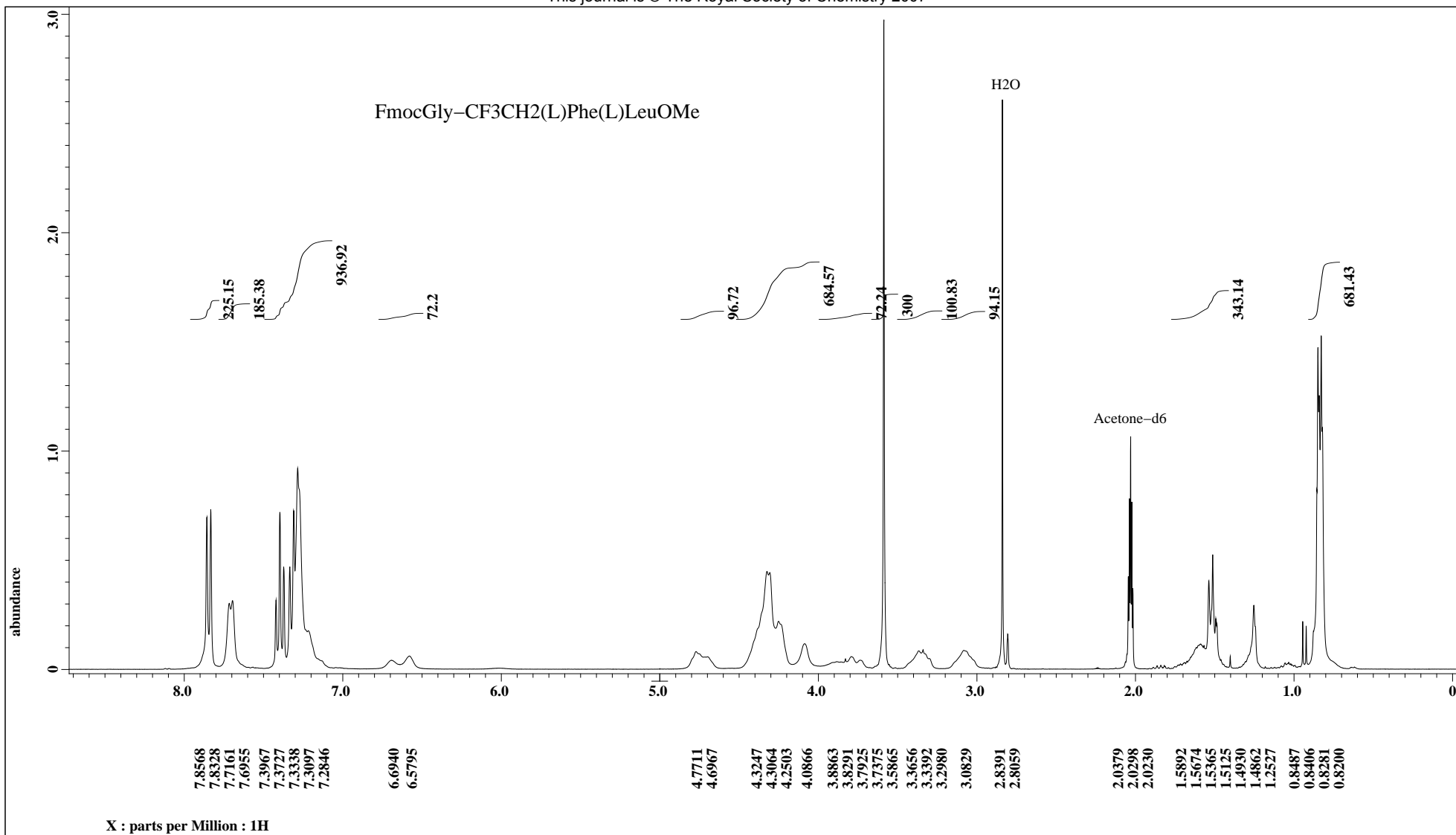
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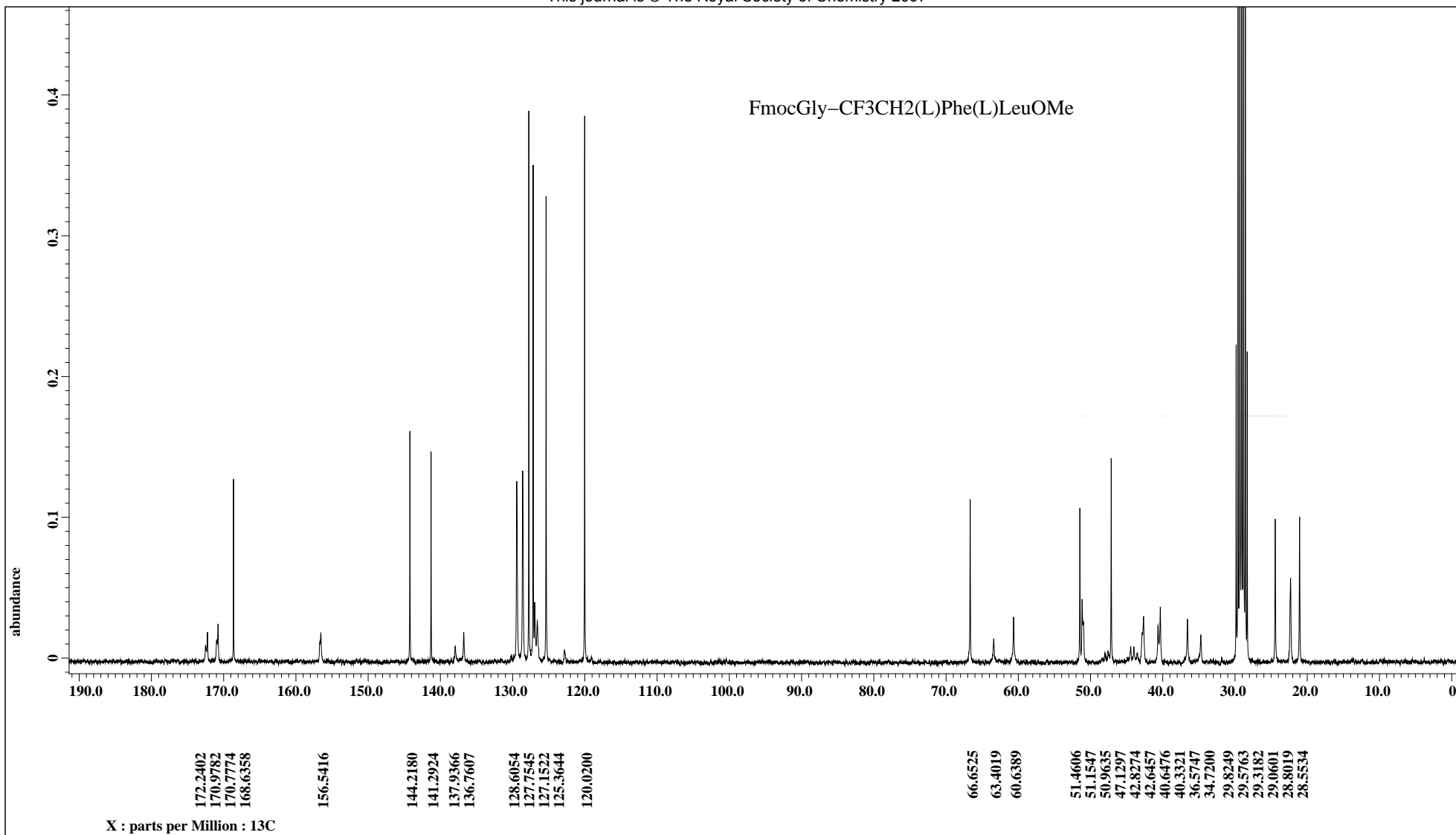
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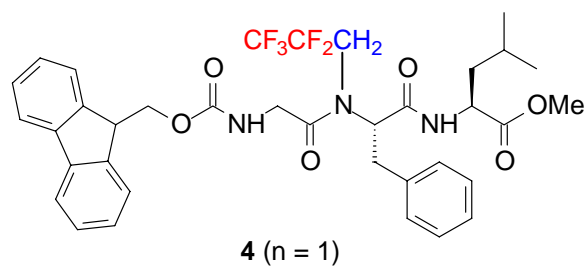
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7. HRMS and NMR spectra of **4** (n = 1)



Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

113 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)

Elements Used:

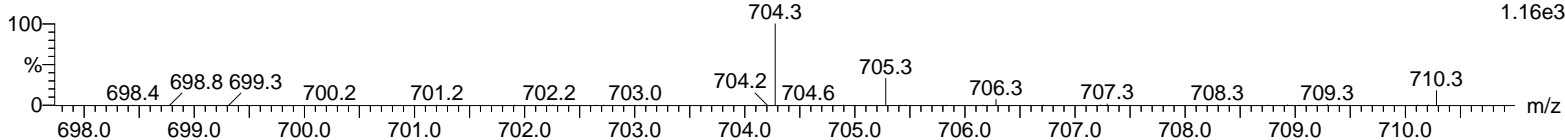
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Changqing Lu, Lu_03

Mass Spec Lab, SCS, University of Illinois

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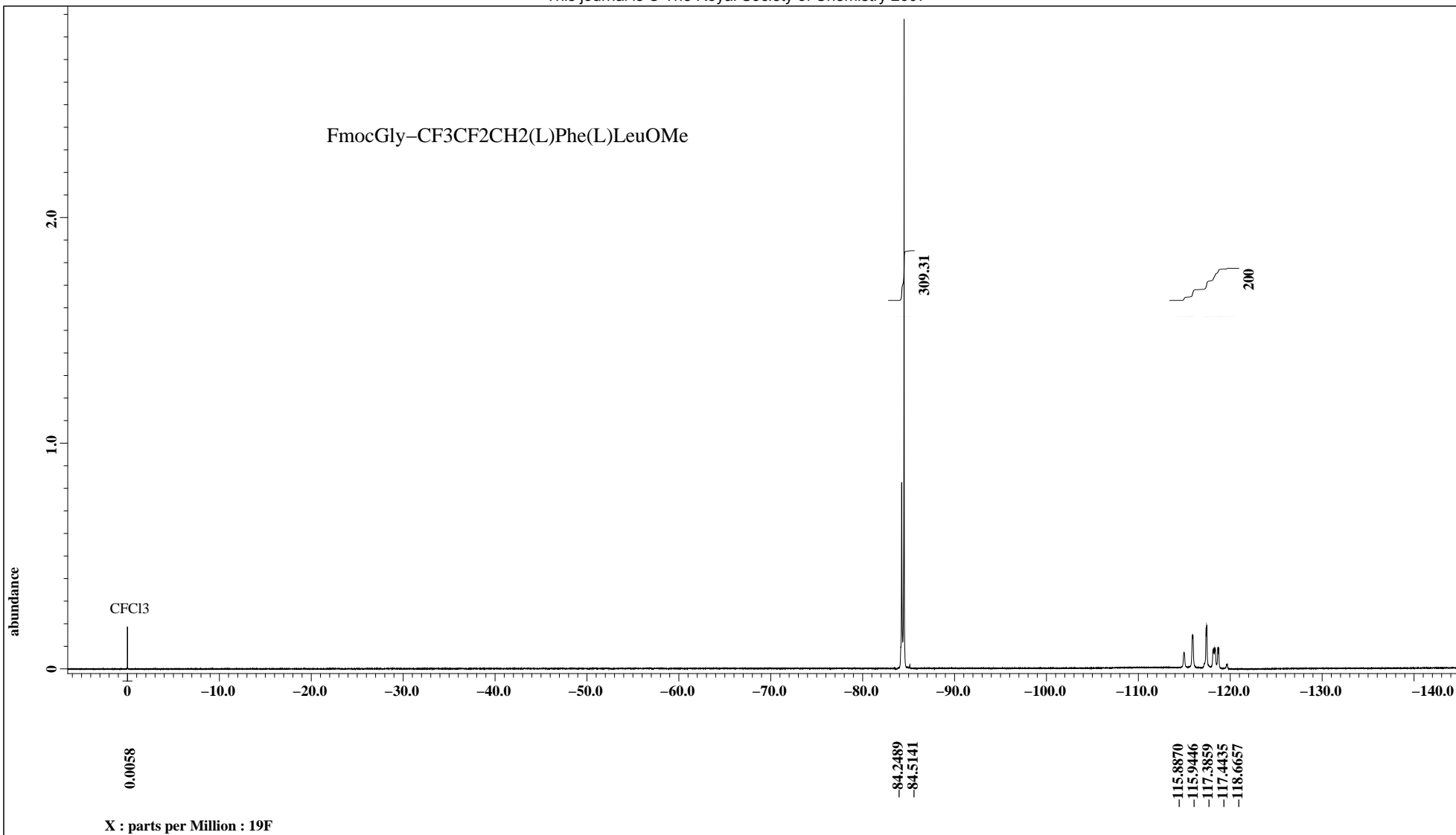
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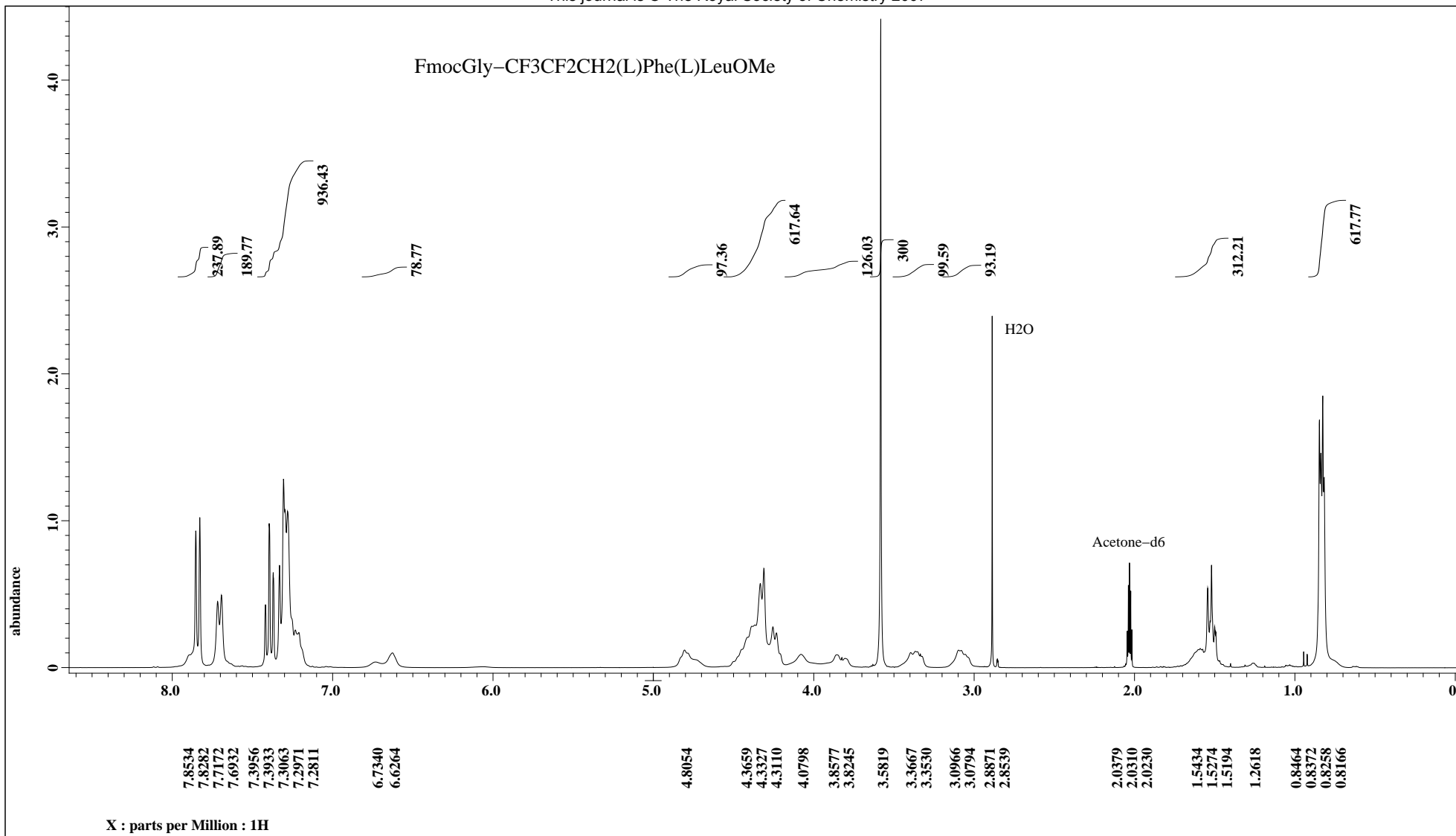
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FmocGly-CF₃CF₂CH₂(L)Phe(L)LeuOMe



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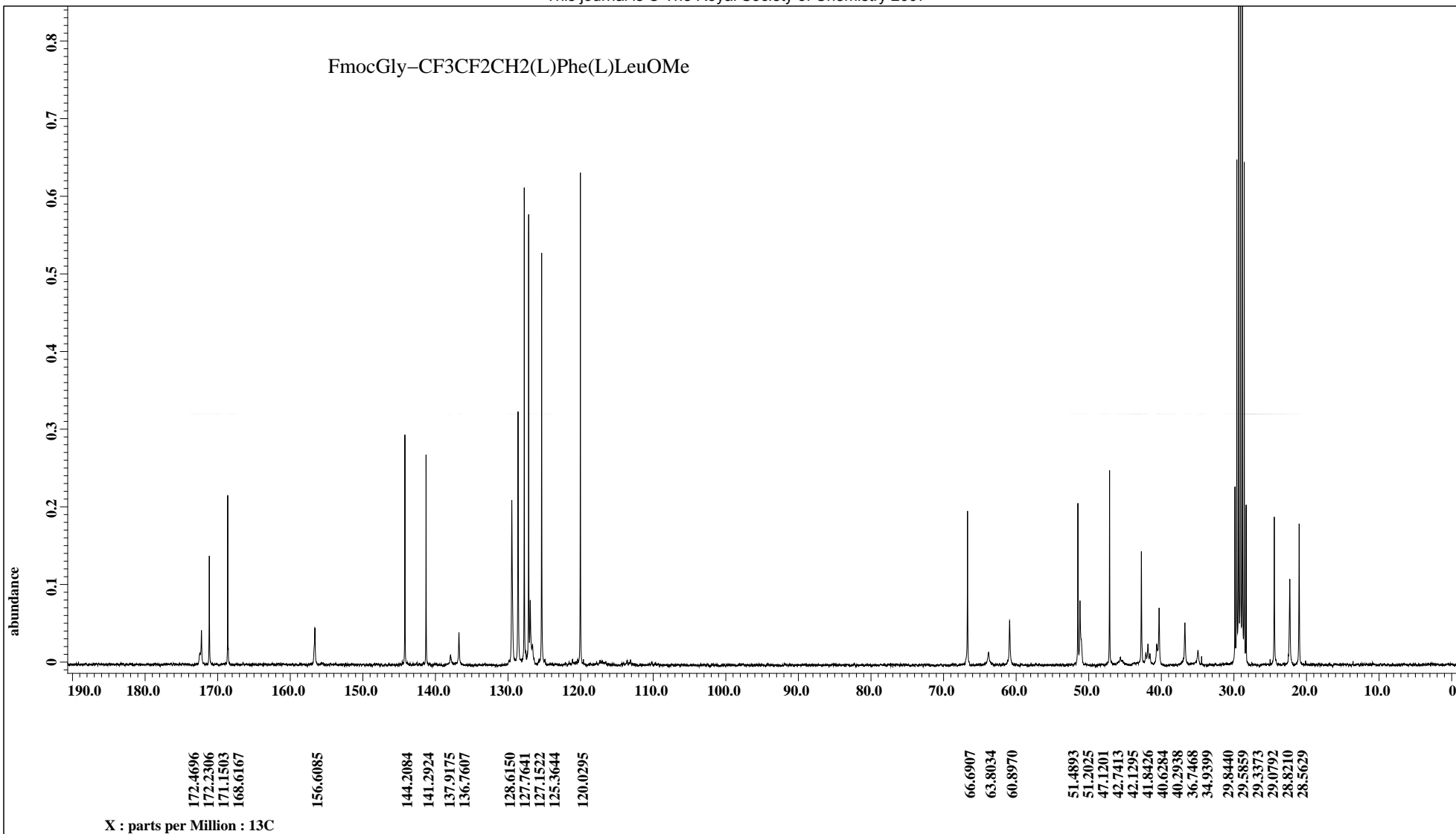
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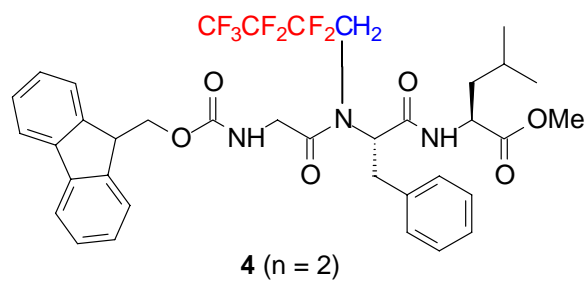
FmocGly-CF₃CF₂CH₂(L)Phe(L)LeuOMe



Filename	= Lu_FmocGly-CF3CF2CH2(Field strength	= 7.0586013[T] (300[MHz]	X_acq_time	= 1.38412032[s]
Author	= Delta	X_acq_duration	= 1.38412032[s]	X_angle	= 30[deg]
Experiment	= single_pulse_dec	X_domain	= 13C	X_atn	= 6[dB]
Sample_id	= 1	X_freq	= 75.56823426[MHz]	X_pulse	= 4.68333333[us]
Solvent	= ACETONE-D6	X_offset	= 100[ppm]	Irr_atn_dec	= 22[dB]
Creation_time	= 9-JUL-2007 08:58:23	X_points	= 32768	Irr_atn_noe	= 22[dB]
Revision_time	= 6-AUG-2007 16:47:36	X_prescans	= 4	Irr_noise	= WALTZ
Current_time	= 6-AUG-2007 16:48:11	X_resolution	= 0.72248054[Hz]	Decoupling	= TRUE
Comment	= single_pulse decouple	X_sweep	= 23.67424242[kHz]	Initial_wait	= 1[s]
Data_format	= 1D_COMPLEX	Irr_domain	= 1H	Noe	= TRUE
Dim_size	= 26214	Irr_freq	= 300.52965592[MHz]	Noe_time	= 2[s]
Dim_title	= 13C	Irr_offset	= 5[ppm]	Recvr_gain	= 60
Dim_units	= [ppm]	Clipped	= TRUE	Relaxation_delay	= 2[s]
Dimensions	= X	Mod_return	= 1	Repetition_time	= 3.38412032[s]
Site	= ECX 300	Scans	= 8708	Temp_get	= 21.7[dc]
Spectrometer	= DELTA2_NMR	Total_scans	= 8708		
		x_90_width	= 14.05[us]		



8. HRMS and NMR spectra of **4** (n = 2)



Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

113 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)

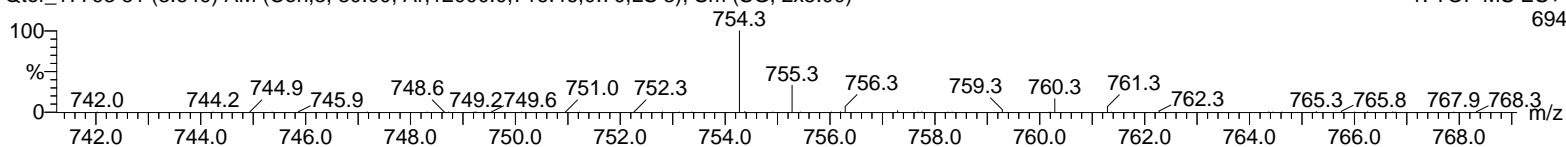
Elements Used:

C: 0-50 H: 0-80 N: 2-4 O: 5-7 F: 7-7 Na: 0-1

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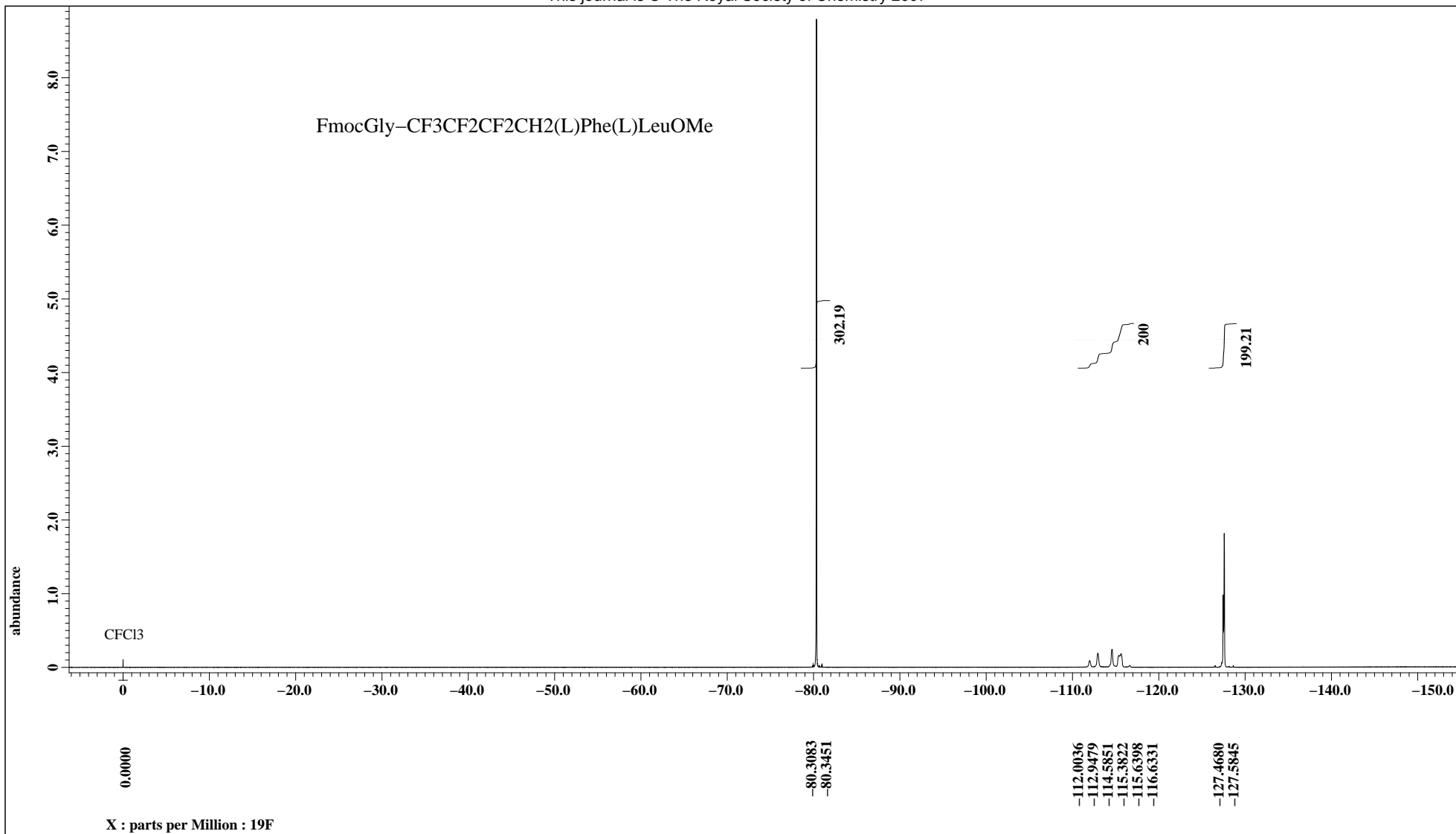
Mass Spec Lab, SCS, University of Illinois

Qtof_17793 51 (3.649) AM (Cen,3, 80.00, Ar,12000.0,716.46,0.70,LS 3); Sm (SG, 2x5.00)

Q-tof
1: TOF MS ES+
694

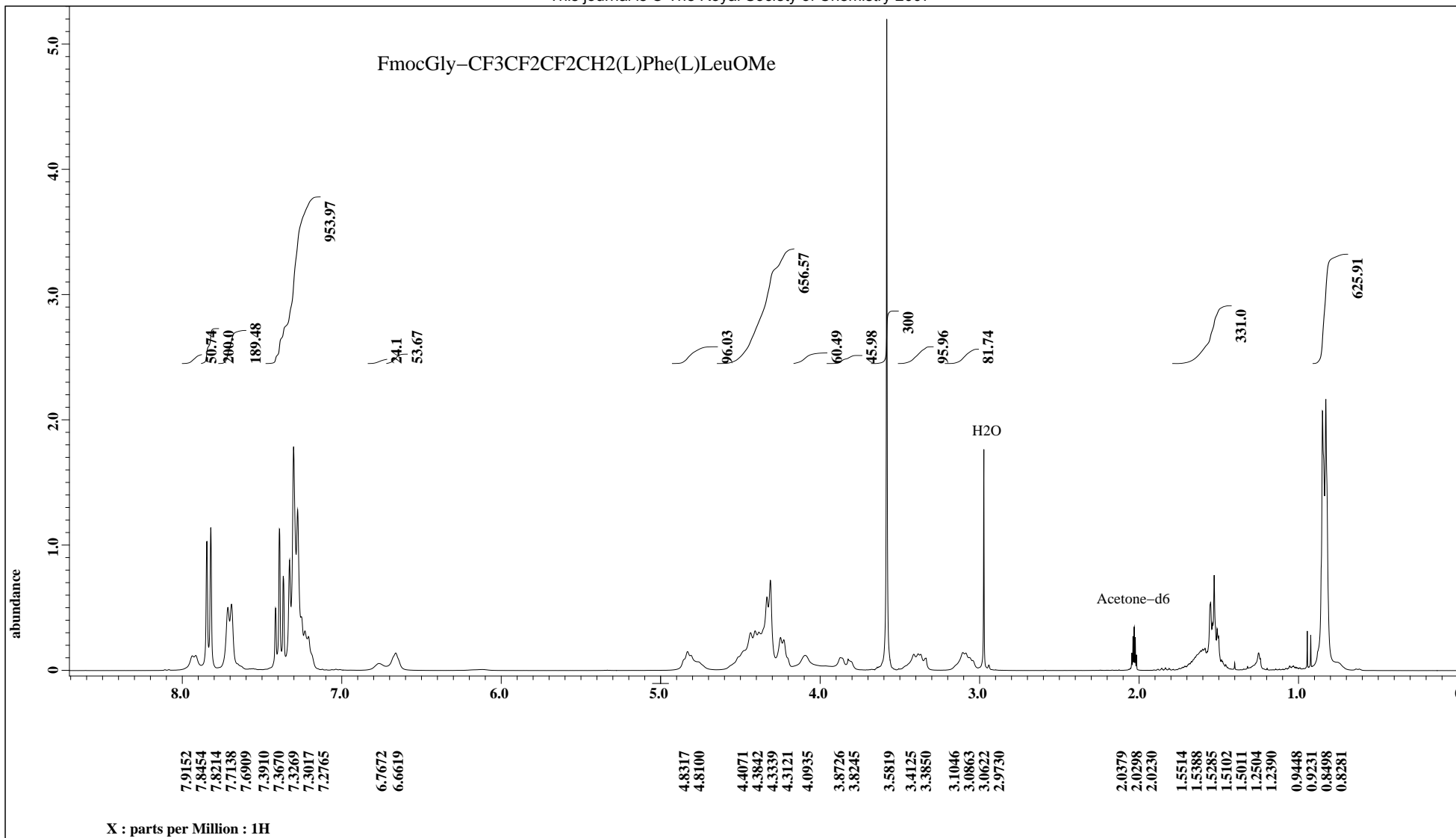
Minimum: -1.5
Maximum: 5.0 10.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
754.2725	754.2727	-0.2	-0.3	16.5	9.9	C37 H39 N3 O6 F7
	754.2703	2.2	2.9	13.5	6.1	C35 H40 N3 O6 F7 Na



Filename	= Lu_FmocGly-CF3CF2CF2C	Field_strength	= 7.0586013[T] (300[MHz]	Total_scans	= 32
Author	= Delta	X_acq_duration	= 0.5767168[s]	X_90_width	= 12.2[us]
Experiment	= single_pulse.ex2	X_domain	= 19F	X_acq_time	= 0.5767168[s]
Sample_id	= 1	X_freq	= 282.78036857[MHz]	X_angle	= 45[deg]
Solvent	= ACETONE-D6	X_offset	= -75[ppm]	X_atn	= 3[dB]
Creation_time	= 2-JUL-2007 16:13:20	X_points	= 32768	X_pulse	= 6.1[us]
Revision_time	= 6-AUG-2007 16:30:50	X_prescans	= 1	Irr_mode	= Off
Current_time	= 6-AUG-2007 16:31:29	X_resolution	= 1.7339533[Hz]	Tri_mode	= Off
Comment	= single_pulse	X_sweep	= 56.81818182[kHz]	Dante_presat	= FALSE
Data_format	= 1D_COMPLEX	Irr_domain	= 19F	Initial_wait	= 1[s]
Dim_size	= 26214	Irr_freq	= 282.78036857[MHz]	Recvr_gain	= 36
Dim_title	= 19F	Irr_offset	= 5[ppm]	Relaxation_delay	= 2[s]
Dim_units	= [ppm]	Tri_domain	= 19F	Repetition_time	= 2.5767168[s]
Dimensions	= X	Tri_freq	= 282.78036857[MHz]	Temp_get	= 20.9[dC]
Site	= ECX 300	Tri_offset	= 5[ppm]		
Spectrometer	= DELTA2_NMR	Clipped	= FALSE		
		Mod_return	= 1		
		Scans	= 32		



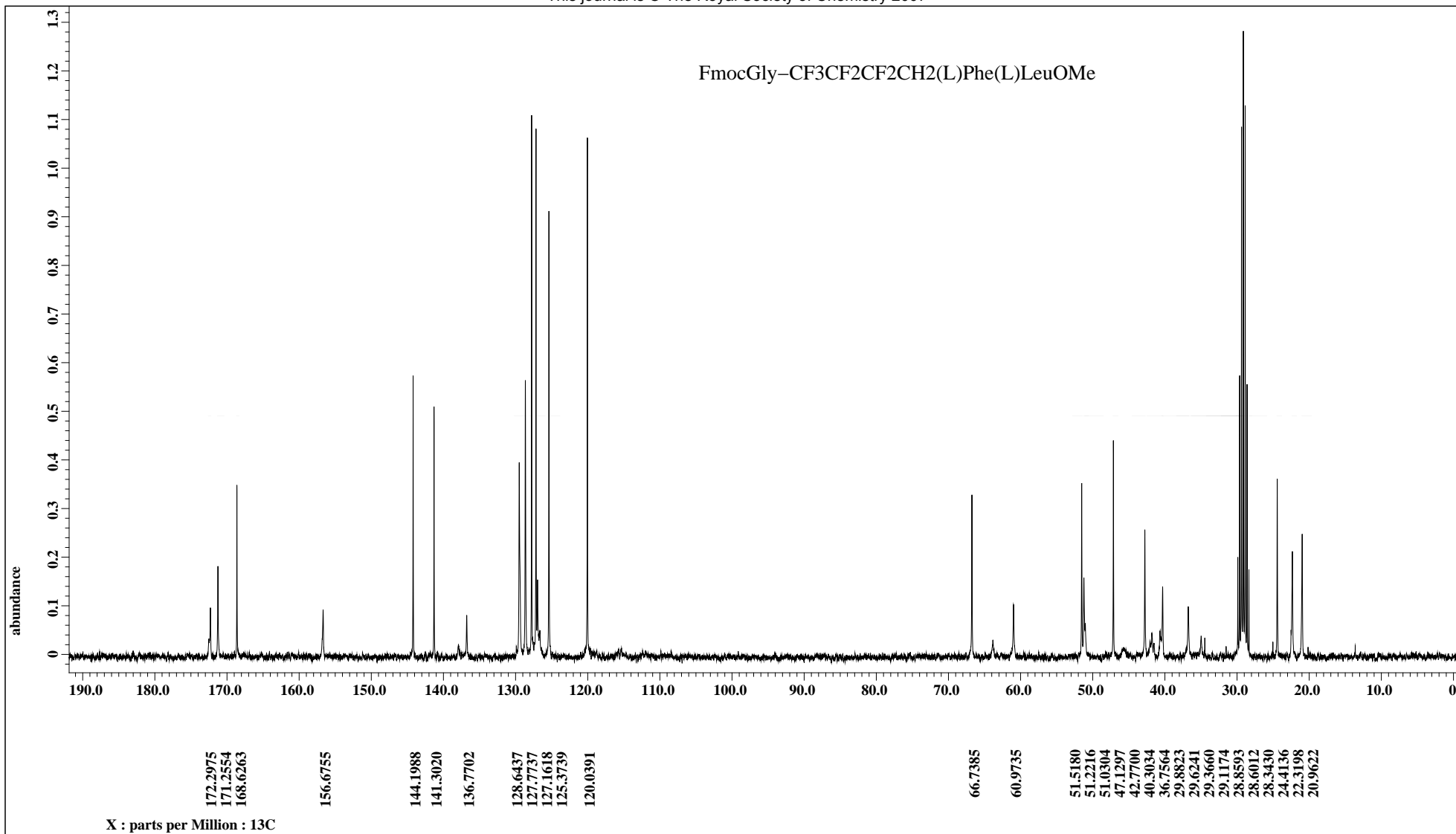


Filename = Lu_FmocGly-CF₃CF₂CF₂C
 Author = Delta
 Experiment = single_pulse.ex2
 Sample_id = 1
 Solvent = ACETONE-D6
 Creation_time = 2-JUL-2007 16:18:08
 Revision_time = 6-AUG-2007 16:24:44
 Current_time = 6-AUG-2007 16:25:16
 Comment = single_pulse
 Data_format = 1D_COMPLEX
 Dim_size = 13107
 Dim_title = 1H
 Dim_units = [ppm]
 Dimensions = X
 Site = ECX 300
 Spectrometer = DELTA2_NMR

Field_strength = 7.0586013[T] (300[MHz]
 X_acq_duration = 2.90717696[s]
 X_domain = 1H
 X_freq = 300.52965592[MHz]
 X_offset = 5[ppm]
 X_points = 16384
 X_prescans = 1
 X_resolution = 0.34397631[Hz]
 X_sweep = 5.63570784[kHz]
 Irr_domain = 1H
 Irr_freq = 300.52965592[MHz]
 Irr_offset = 5[ppm]
 Tri_domain = 1H
 Tri_freq = 300.52965592[MHz]
 Tri_offset = 5[ppm]
 Clipped = FALSE
 Mod_return = 1
 Scans = 32

Total_scans = 32
 X_90_width = 13.3[us]
 X_acq_time = 2.90717696[s]
 X_angle = 45[deg]
 X_atn = 3[dB]
 X_pulse = 6.65[us]
 Irr_mode = Off
 Tri_mode = Off
 Dante_presat = FALSE
 Initial_wait = 1[s]
 Recvr_gain = 30
 Relaxation_delay = 2[s]
 Repetition_time = 4.90717696[s]
 Temp_get = 20.9[dC]





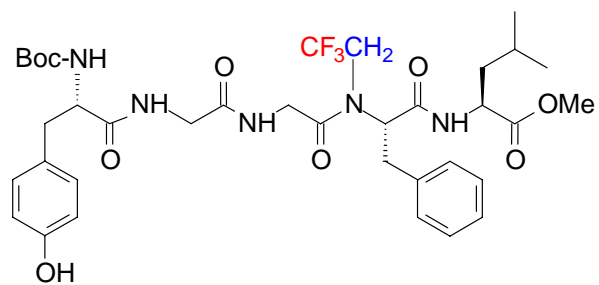
Filename = Lu_FmocGly-CF₃CF₂CF₂C
 Author = Delta
 Experiment = single_pulse_dec
 Sample_id = 1
 Solvent = ACETONE-D₆
 Creation_time = 10-JUL-2007 18:53:52
 Revision_time = 6-AUG-2007 16:51:09
 Current_time = 6-AUG-2007 16:51:38
 Comment = single pulse decouple
 Data_format = 1D_COMPLEX
 Dim_size = 26214
 Dim_title = 13C
 Dim_units = [ppm]
 Dimensions = X
 Site = ECX 300
 Spectrometer = DELTA2_NMR

Field_strength = 7.0586013[T] (300[MHz]
 X_acq_duration = 1.38412032[s]
 X_domain = 13C
 X_freq = 75.56823426[MHz]
 X_offset = 100[ppm]
 X_points = 32768
 X_prescans = 4
 X_resolution = 0.72248054[Hz]
 X_sweep = 23.67424242[kHz]
 Irr_domain = 1H
 Irr_freq = 300.52965592[MHz]
 Irr_offset = 5[ppm]
 Mod_return = 1
 Scans = 454
 Total_scans = 454
 X_90_width = 14.05[us]

X_acq_time = 1.38412032[s]
 X_angle = 30[deg]
 X_atn = 6[dB]
 X_pulse = 4.68333333[us]
 Irr_atn_dec = 22[dB]
 Irr_atn_noe = 22[dB]
 Irr_noise = WALTZ
 Decoupling = TRUE
 Initial_wait = 1[s]
 Noe = TRUE
 Noe_time = 2[s]
 Recvr_gain = 60
 Relaxation_delay = 2[s]
 Repetition_time = 3.38412032[s]
 Temp_get = 20.9[dC]



9. HRMS and NMR spectra of **5**



5

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

410 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)

Elements Used:

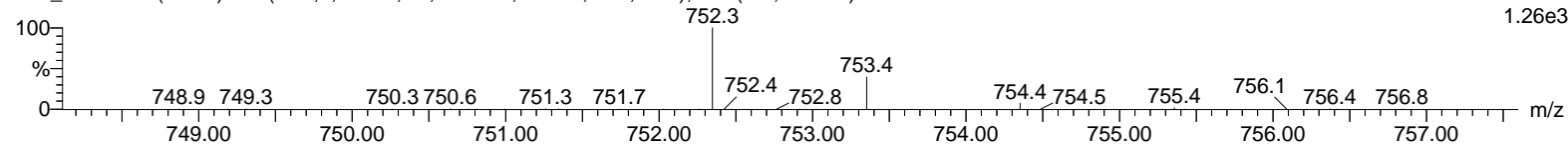
C: 0-50 H: 0-80 N: 2-6 O: 5-10 F: 3-3 Na: 0-1

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Mass Spec Lab, SCS, University of Illinois

Qtof_17795 19 (1.364) AM (Cen,3, 80.00, Ar,12000.0,716.46,0.70,LS 3); Sm (SG, 2x5.00)

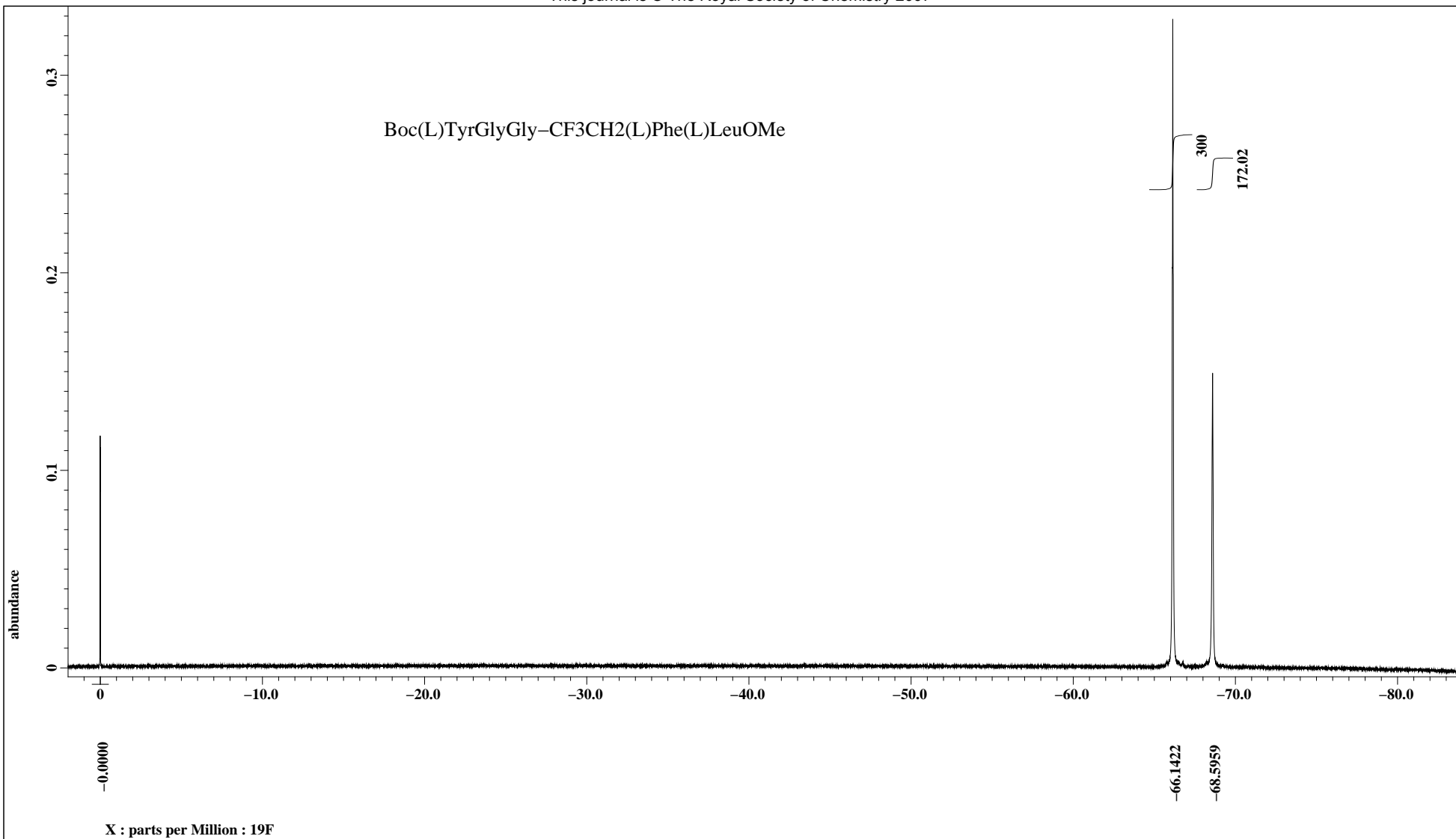
Q-tof
1: TOF MS ES+
1.26e3



Minimum: -1.5
Maximum: 5.0 10.0 100.0

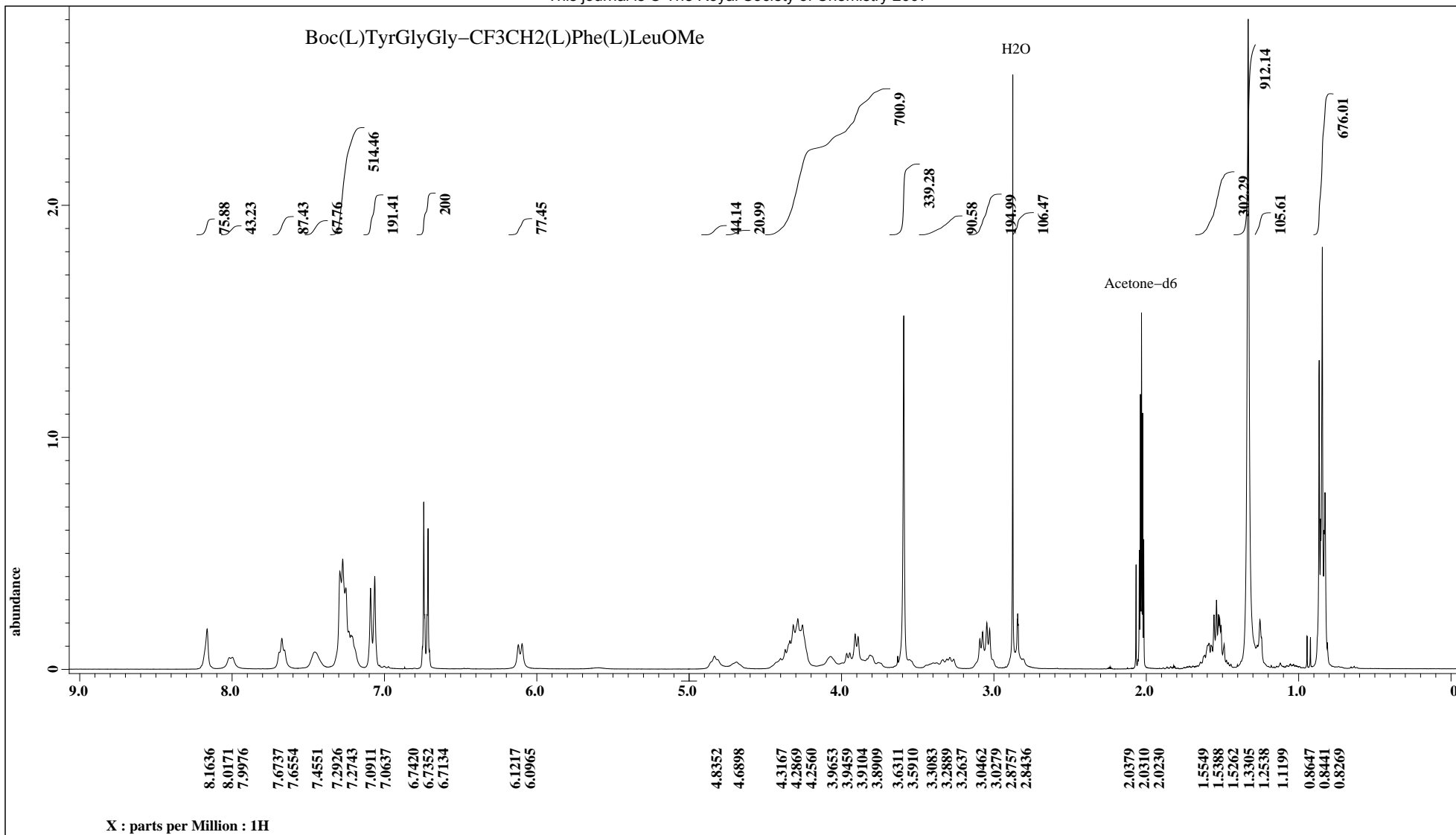
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
752.3472	752.3482	-1.0	-1.3	13.5	10.7	C36 H49 N5 O9 F3
	752.3458	1.4	1.9	10.5	6.1	C34 H50 N5 O9 F3 Na
	752.3499	-2.7	-3.6	14.5	15.9	C39 H50 N3 O7 F3 Na
	752.3523	-5.1	-6.8	17.5	24.0	C41 H49 N3 O7 F3

Boc(L)TyrGlyGly-CF₃CH₂(L)Phe(L)LeuOMe



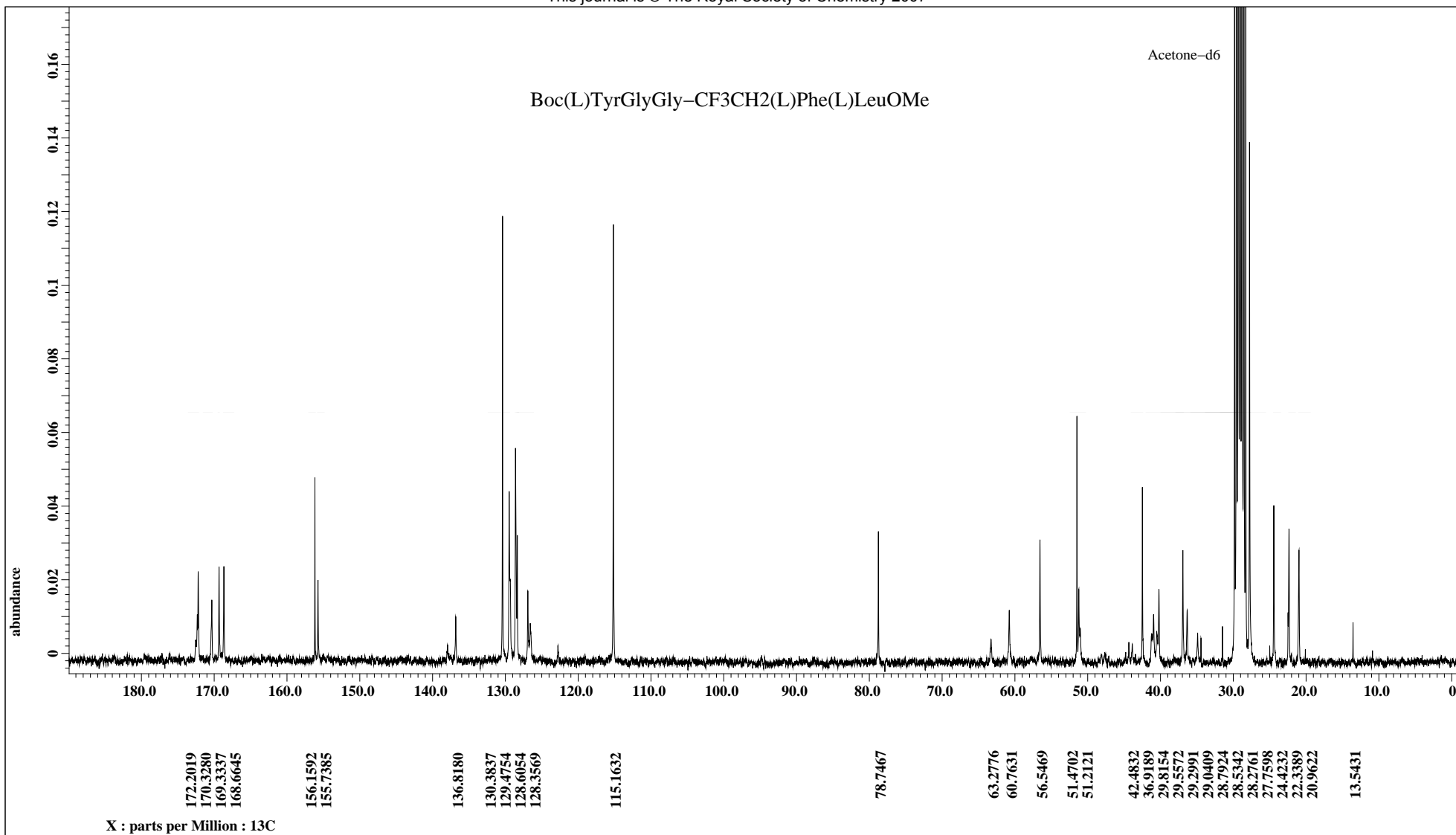
Filename	= Lu_Boc(L)TyrGlyGly-CF	Field_strength	= 7.0586013[T] (300[MHz]	Total_scans	= 64
Author	= Delta	X_acq_duration	= 1.02760448[s]	X_90_width	= 12.2[us]
Experiment	= single_pulse.ex2	X_domain	= 19F	X_acq_time	= 1.02760448[s]
Sample_id	= 1	X_freq	= 282.78036857[MHz]	X_angle	= 45[deg]
Solvent	= ACETONE-D6	X_offset	= -40[ppm]	X_atn	= 3[dB]
Creation_time	= 1-JUL-2007 20:43:57	X_points	= 32768	X_pulse	= 6.1[us]
Revision_time	= 6-AUG-2007 14:48:22	X_prescans	= 1	Irr_mode	= Off
Current_time	= 6-AUG-2007 14:49:46	X_resolution	= 0.97313706[Hz]	Tri_mode	= Off
Comment	= single_pulse	X_sweep	= 31.8877551[kHz]	Dante_presat	= FALSE
Data_format	= 1D_COMPLEX	Irr_domain	= 19F	Initial_wait	= 1[s]
Dim_size	= 26214	Irr_freq	= 282.78036857[MHz]	Recvr_gain	= 40
Dim_title	= 19F	Irr_offset	= 5[ppm]	Relaxation_delay	= 2[s]
Dim_units	= [ppm]	Tri_domain	= 19F	Repetition_time	= 3.02760448[s]
Dimensions	= X	Tri_freq	= 282.78036857[MHz]	Temp_get	= 21.3[dC]
Site	= ECX 300	Tri_offset	= 5[ppm]		
Spectrometer	= DELTA2_NMR	Clipped	= FALSE		
		Mod_return	= 1		
		Scans	= 64		





Filename	= Lu_Boc(L)TyrGlyGly-CF	Field strength	= 7.0586013[T] (300[MHz]	Total_scans	= 32
Author	= Delta	X_acq_duration	= 2.90717696[s]	X_90_width	= 13.3[us]
Experiment	= single_pulse.ex2	X_domain	= 1H	X_acq_time	= 2.90717696[s]
Sample_id	= 1	X_freq	= 300.52965592[MHz]	X_angle	= 45[deg]
Solvent	= ACETONE-D6	X_offset	= 5[ppm]	X_atn	= 3[dB]
Creation_time	= 1-JUL-2007 20:36:12	X_points	= 16384	X_pulse	= 6.65[us]
Revision_time	= 6-AUG-2007 15:02:21	X_prescans	= 1	Irr_mode	= Off
Current_time	= 6-AUG-2007 15:03:01	X_resolution	= 0.34397631[Hz]	Tri_mode	= Off
Comment	= single_pulse	X_sweep	= 5.63570784[kHz]	Dante_presat	= FALSE
Data_format	= 1D_COMPLEX	Irr_domain	= 1H	Initial_wait	= 1[s]
Dim_size	= 13107	Irr_freq	= 300.52965592[MHz]	Recvr_gain	= 40
Dim_title	= 1H	Irr_offset	= 5[ppm]	Relaxation_delay	= 2[s]
Dim_units	= [ppm]	Tri_domain	= 1H	Repetition_time	= 4.90717696[s]
Dimensions	= X	Tri_freq	= 300.52965592[MHz]	Temp_get	= 21.2[dC]
Site	= ECX 300	Tri_offset	= 5[ppm]		
Spectrometer	= DELTA2_NMR	Clipped	= FALSE		
		Mod_return	= 1		
		Scans	= 32		





Filename = Lu_Boc(L)TyrGlyGlyCF3
 Author = Delta
 Experiment = single_pulse_dec
 Sample_id = 1
 Solvent = ACETONE-D6
 Creation_time = 7-JUL-2007 11:57:29
 Revision_time = 6-AUG-2007 15:14:30
 Current_time = 6-AUG-2007 15:15:08
 Comment = single pulse decouple
 Data_format = 1D_COMPLEX
 Dim_size = 26214
 Dim_title = 13C
 Dim_units = [ppm]
 Dimensions = X
 Site = ECX 300
 Spectrometer = DELTA2_NMR

Field_strength = 7.0586013[T] (300[MHz]
 X_acq_duration = 1.38412032[s]
 X_domain = 13C
 X_freq = 75.56823426[MHz]
 X_offset = 100[ppm]
 X_points = 32768
 X_prescans = 4
 X_resolution = 0.72248054[Hz]
 X_sweep = 23.67424242[kHz]
 Irr_domain = 1H
 Irr_freq = 300.52965592[MHz]
 Irr_offset = 5[ppm]
 Clipped = TRUE
 Mod_return = 1
 Scans = 16405
 Total_scans = 16405
 X_90_width = 14.05[us]

X_acq_time = 1.38412032[s]
 X_angle = 30[deg]
 X_atn = 6[dB]
 X_pulse = 4.68333333[us]
 Irr_atn_dec = 22[dB]
 Irr_atn_noe = 22[dB]
 Irr_noise = WALTZ
 Decoupling = TRUE
 Initial_wait = 1[s]
 Noe = TRUE
 Noe_time = 2[s]
 Recvr_gain = 60
 Relaxation_delay = 2[s]
 Repetition_time = 3.38412032[s]
 Temp_get = 21.7[°C]



