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SYNTHESIS OF 2,2-DIFLUORINATED-[6]-GINGEROL USING SELECTIVE C-C BOND CLEAVAGE

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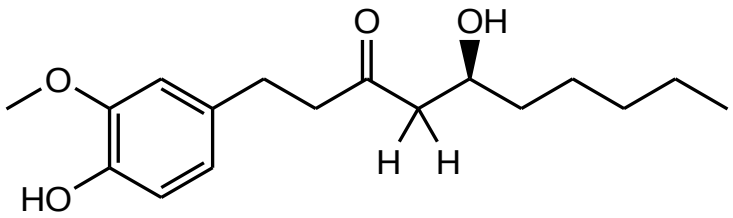
Undergraduate Research Symposium

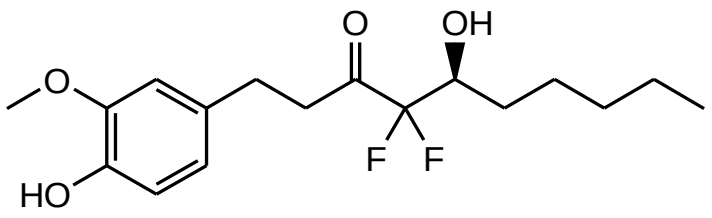
Methodist University JOURNEY UNDERGRADUATE RESEARCH AND CREATIVITY

PURPOSE/HYPOTHESIS

- **Purpose**: The purpose of this research is to synthesize 2,2-difluorinated-[6]-gingerol



6-gingerol



2,2-difluorinated-[6]-gingerol

Target Molecule

Figure 1. [6]-gingerol and its fluorinated analogue.
(Structure Produced from ChemDraw Ultra 8.0)

INTRODUCTION

- [6]-gingerol is the most biologically active constituent of ginger[1]
- Rhizome of Ginger[2]
- Anti-inflammatory[3]
- Anti-cancer[3]
- Anti-oxidant[3]
- Anti-obesity[3]
- Heart Disease[4]

Figure 2. Fresh Ginger.(Picture Retrieved from Shutterstock Images)

INTRODUCTION

Fluorine Effects on [6]-gingerol

1. C-F more stable than C-H by about 14kcal/mol[5]

2. High reactivity[6]

3. Difficult synthesis (not naturally occurring)

INTRODUCTION

Previous Attempts to synthesize 2,2-difluorinated-[6]-gingerol

I. Fukuda and his colleagues (1996) [7]

- 12 Step Synthesis
- 10% Total Yield

II. Dr. Han, Dr. Kim and Dr. Colby (2011) [8]

III. Former Methodist University students (Anita Djonlic, Christopher West, and Emir Nazdrajic)

METHODOLOGY

Reaction Overview

1. Addition of Protecting Group to Vanillylacetone
2. Fluorination Using 2,2,2-trifluoroethyl-2,2,2-trifluoroacetate
3. Further Fluorination Using Selecfluor
4. Aldol reaction using hexanal
5. Deprotection using TBAF

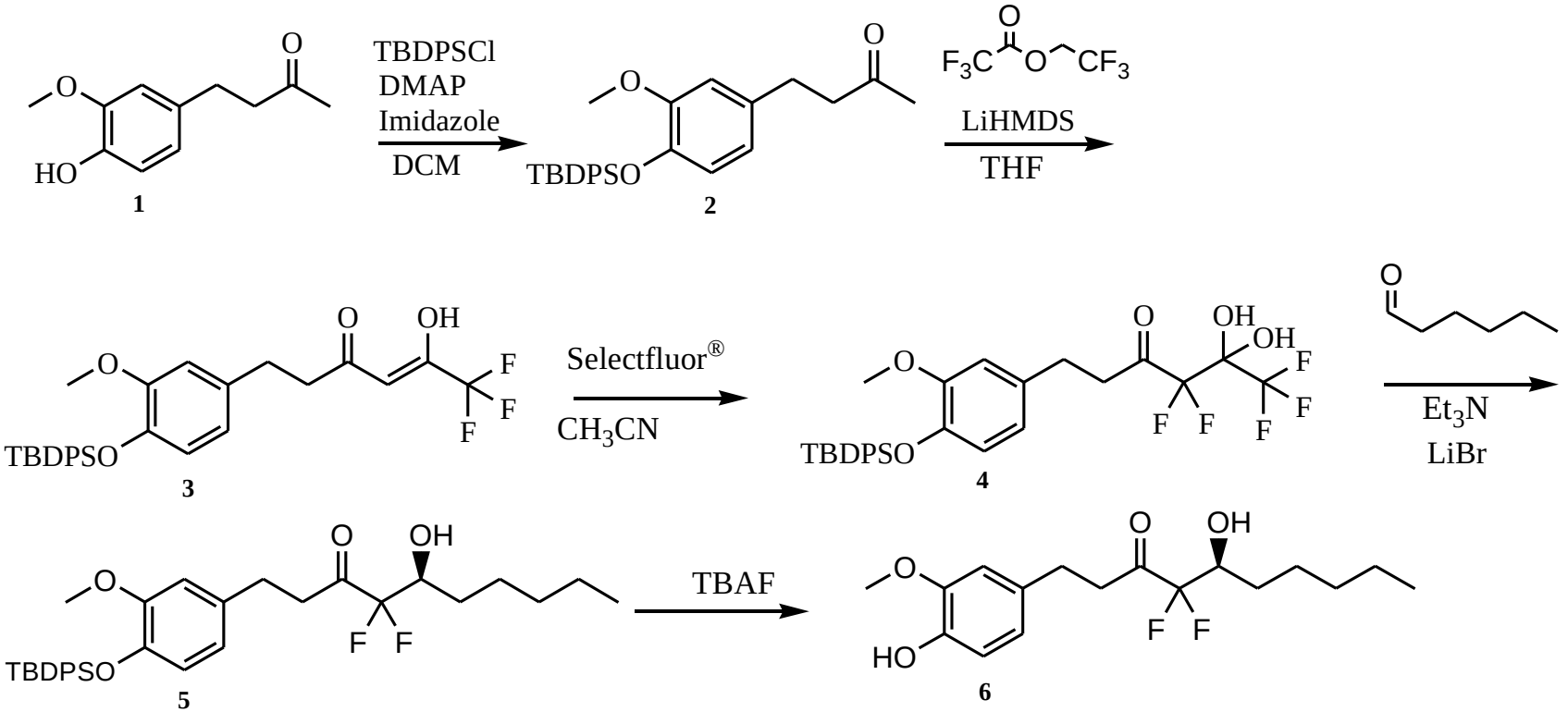


Figure 4. Total-Step Synthesis from Vanillylacetone **1** to 2,2-difluorinated-[6]-Gingerol **6**.

DATA

STEP 1: Addition of Protecting Group (TBDPSCl)

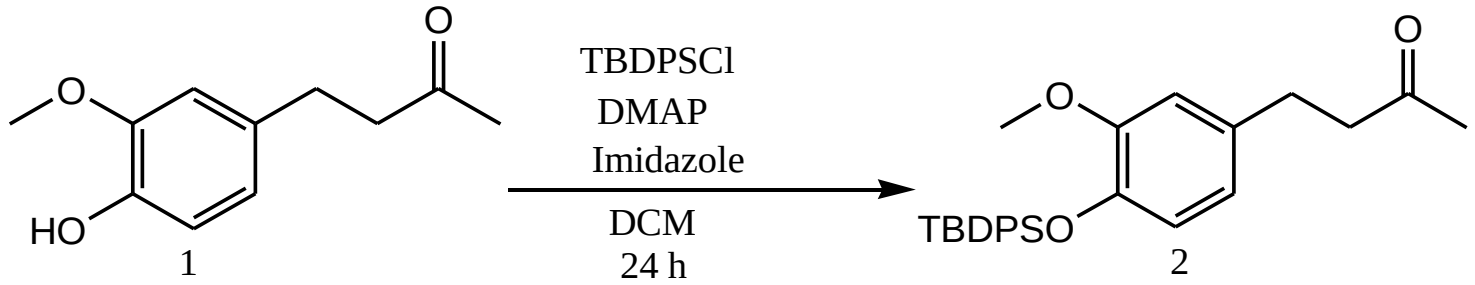


Figure 5. First-step Reaction, Protection of Alcohol.

Reactants	Molar Mass (g/mol)	Equivalence	Mole (mmol)	Volume (mL)	Density (g/mL)	Mass (mg)
1	194.22	1	0.51	N/A	N/A	100.00
Imidazole	68.07	3	1.53	N/A	N/A	104.15
DMAP	122.17	1	0.51	N/A	N/A	62.31
TBDPSCl	274.86	3	1.53	N/A	1.06	420.53
DCM	N/A			5.15	N/A	N/A

Table 1. First-step Reaction Data.

DATA

STEP 2: Fluorination using 2,2,2-trifluoroethyl-2,2,2-trifluoroacetate

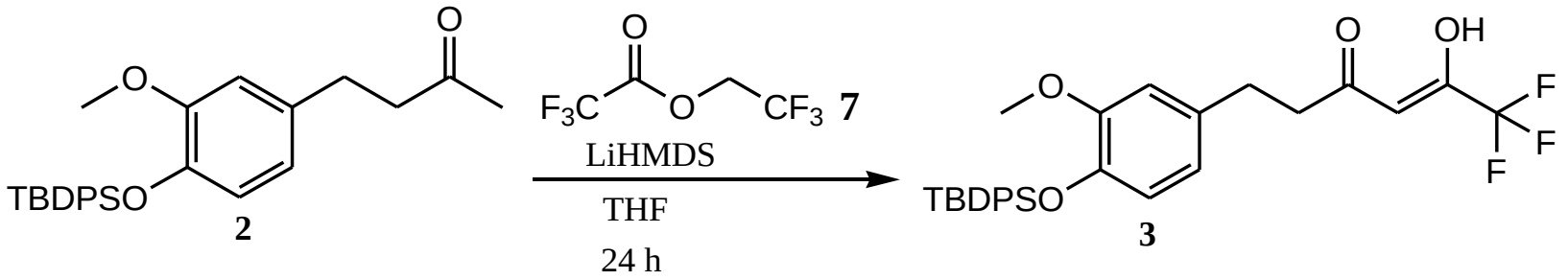


Figure 6. Second-step Reaction.

Reactants	Molar Mass (g/mol)	Equivalence	Mole (mmol)	Volume (mL)	Density (g/mL)	Mass (mg)
2	432.70	1	0.23	N/A	N/A	100.00
7	196.48	2	0.46	0.06	1.64	90.38
LiHMDS	167.32	2	0.46	0.09	0.86	76.97
THF	N/A			3.00	N/A	N/A

Table 2. Second-step Reaction Data.

DATA

STEP 3: Further Fluorination Using Selectfluor®

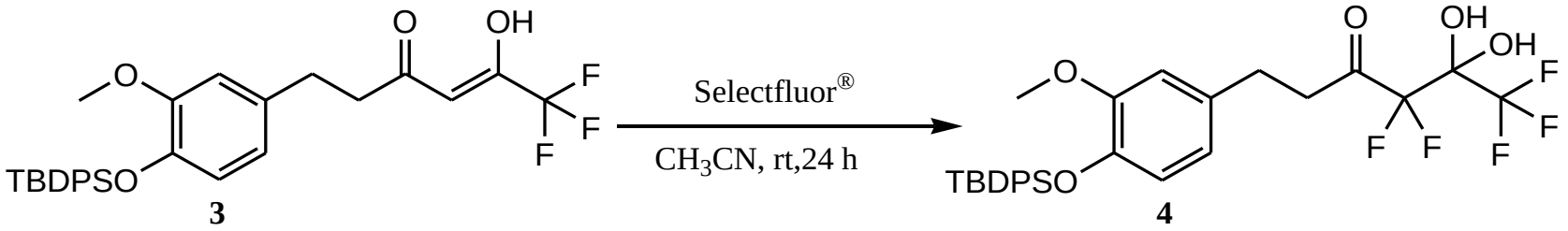


Figure 7. Third-step Reaction.

Reactants	Molar Mass (g/mol)	Equivalence	Mole (mmol)	Volume (mL)	Density (g/mL)	Mass (mg)
3	528.00	1	0.57	N/A	N/A	300.00
Selectfluor®	354.26	2.5	1.43	N/A	N/A	503.05
CH_3CN	N/A			6.00	N/A	N/A

Table 3. Third-step Reaction Data.

DATA

Trial Reaction for 2nd Step: Fluorination of Acetophenone

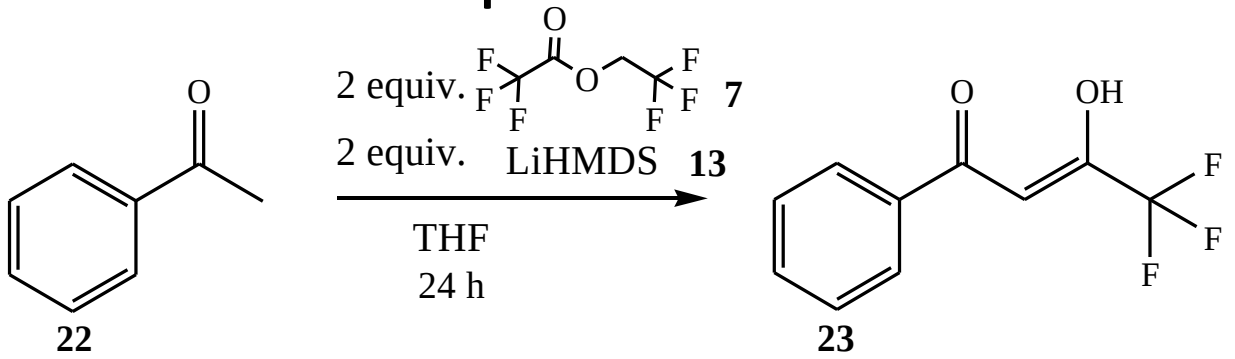


Figure 8. Fluorination of Acetophenone.

Reactants	Molar Mass (g/mol)	Equivalence	Mole (mmol)	Volume (mL)	Density (g/mL)	Mass (mg)
Acetophenone	120.15	1	4.16	0.49	1.03	500.00
7	196.48	2	8.32	1.00	1.64	1635.10
LiHMDS	167.32	2	8.32	1.62	0.86	1392.40
THF	N/A			41.61	N/A	N/A

Table 4. Fluorination of Acetophenone Data.

DATA

Trial Reaction for 3rd Step: Further Fluorination Using Selectfluor®

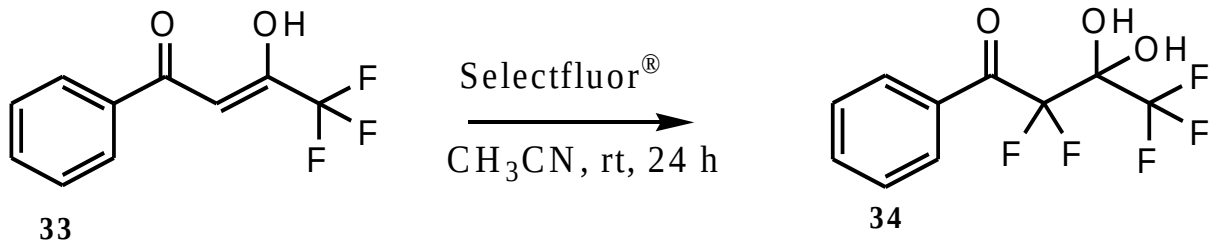


Figure 7. Third-step Reaction.

Reactants	Molar Mass (g/mol)	Equivalence	Mole (mmol)	Volume (mL)	Density (g/mL)	Mass (mg)
33	216.00	1	4.629	N/A	N/A	1000.00
Selectfluor®	354.26	2.5	11.573	N/A	N/A	4099.67
CH_3CN	N/A			46.00	N/A	N/A

Table 3. Further Fluorination of Trial Reaction Data.

RESULTS/DISCUSSION

- Step 1
  - Expected Mass = 0.223 g
  - Experimental Mass= 0.340 g
  - Quantitative Yield
  - Leftover Starting Material (TBDPSCl)
  - Successful Reaction Overall

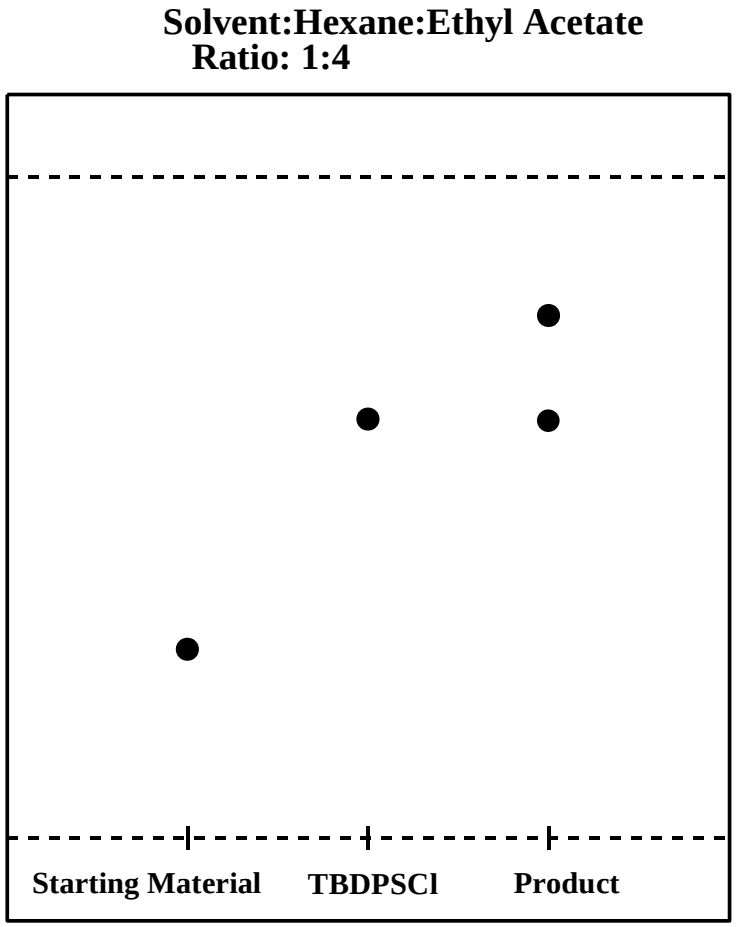


Figure 9. First reaction thin-layer chromatography (TLC). (Spectrum Drawn from ChemDraw Ultra 8.0)

RESULTS/DISCUSSION

Step 1: Predicted ^{1}H NMR of Protected Vanillylacetone

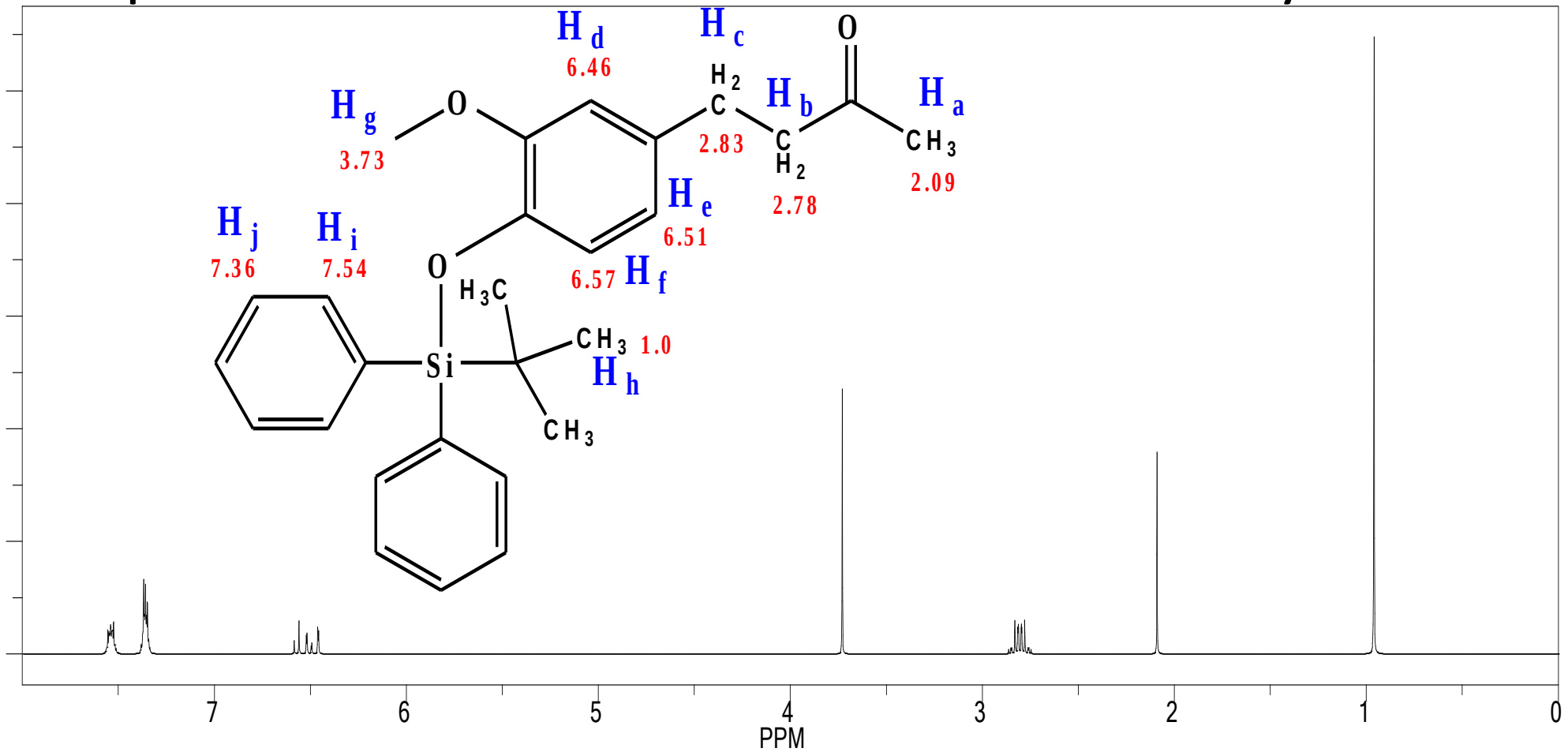


Figure 10. Predicted ^{1}H NMR of Protected Vanillylacetone **2.**
(Structure Produced and Spectrum Drawn from ChemDraw Ultra 8.0)

RESULTS/DISCUSSION

STEP 1. Addition of Protecting Group (TBDPSCl)

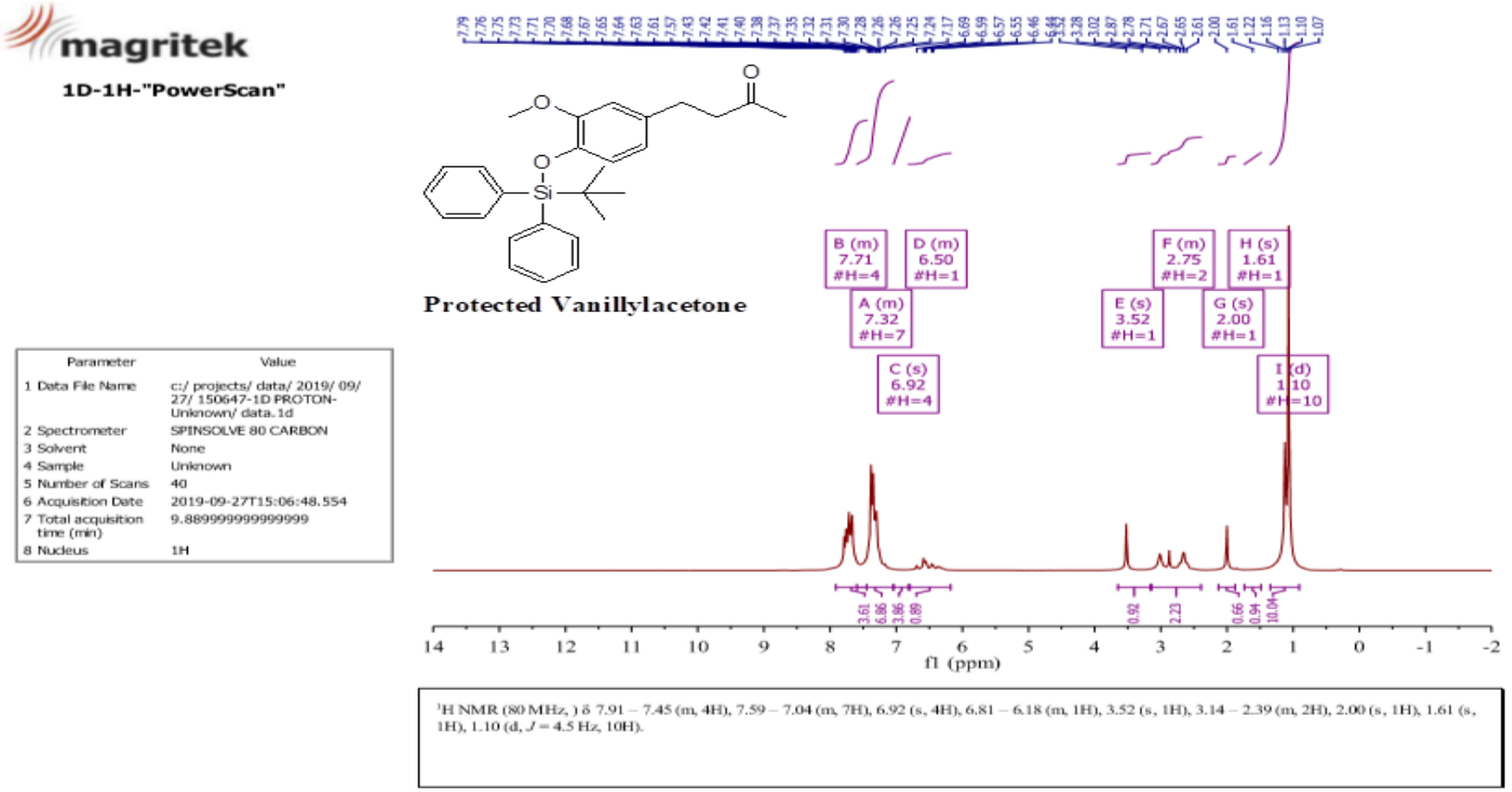


Figure 11. Experimental ^{1}H NMR of Protected Vanillylacetone.
(Spectrum Produced by Magritek, Spin Solve 80)

RESULTS/DISCUSSION

- Step 2: Fluorination

- Expected Mass = 0.121 g
- Experimental Mass= 0.351 g
- Quantitative Yield
- Leftover Starting Material (TBDPSCl and LiHDMS)
- Successful Reaction Overall

RESULTS/DISCUSSION

STEP 2. Fluorination

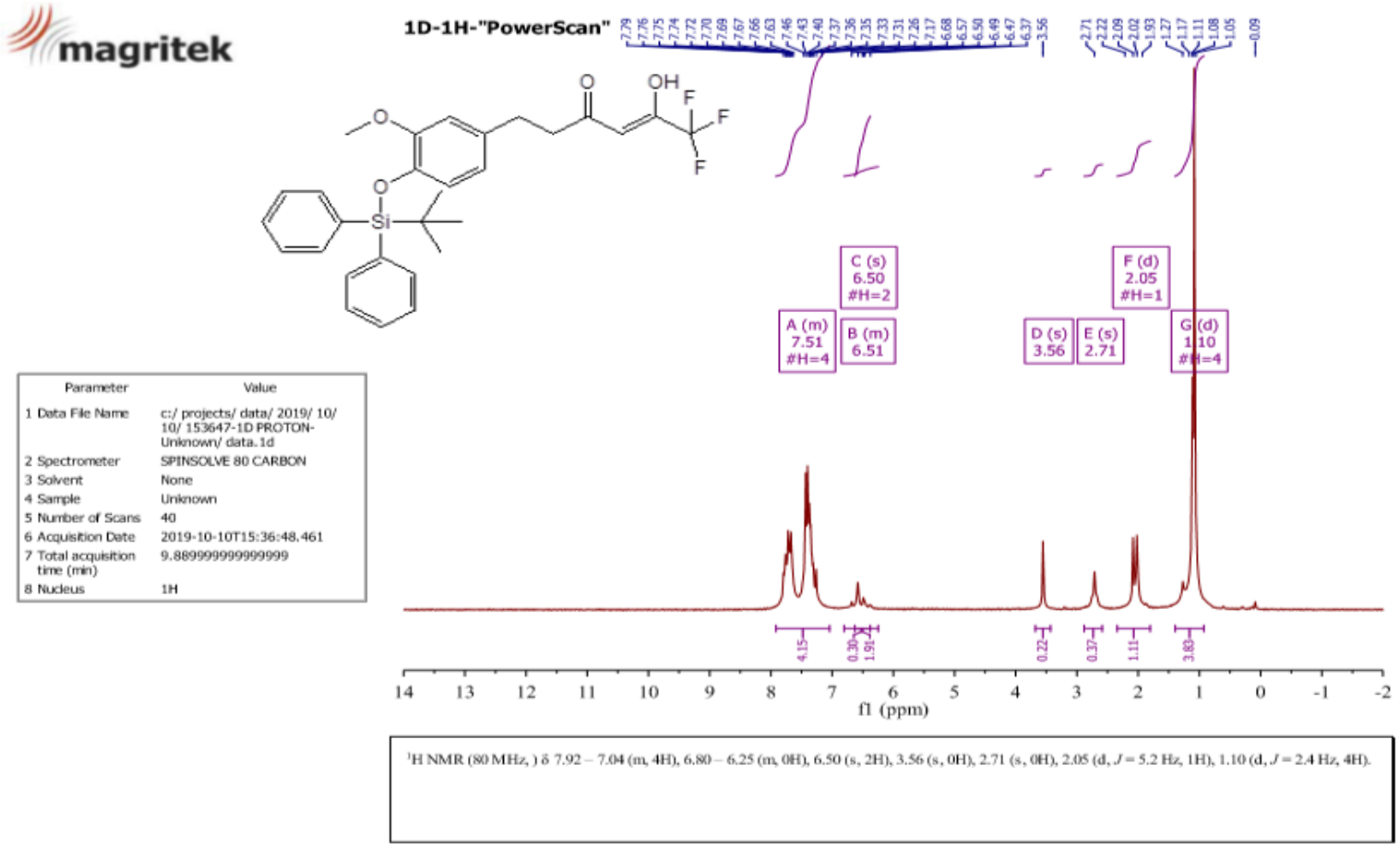


Figure 12. Experimental ^{1}H NMR of protected 6,6,6-trifluro-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hex-4-en-3-one.

RESULTS/DISCUSSION

STEP 2. Fluorination

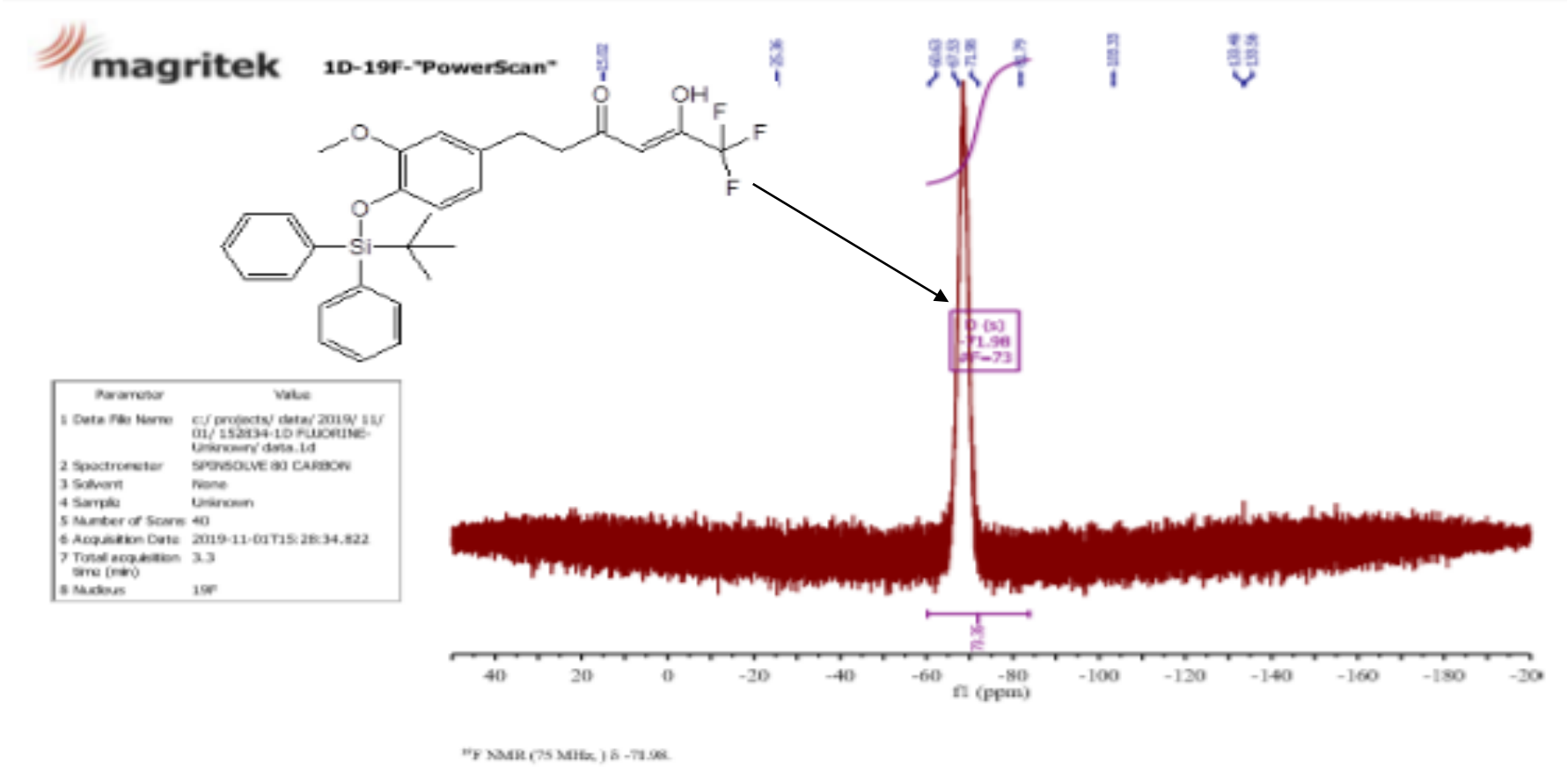


Figure 13. Experimental ^{19}F NMR of protected 6,6,6-trifluro-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hex-4-en-3-one.

RESULTS/DISCUSSION

- Step 3: Further Fluorination

- Expected Mass = 0.332 g
- Experimental Mass = 0.029 g
- Extremely Low Percent Yield
- Lost of reaction Product Through Celite Filtration
- Reaction Nearly Completed
- Needed More Reaction Time

RESULTS/DISCUSSION

STEP 3. Further Fluorination

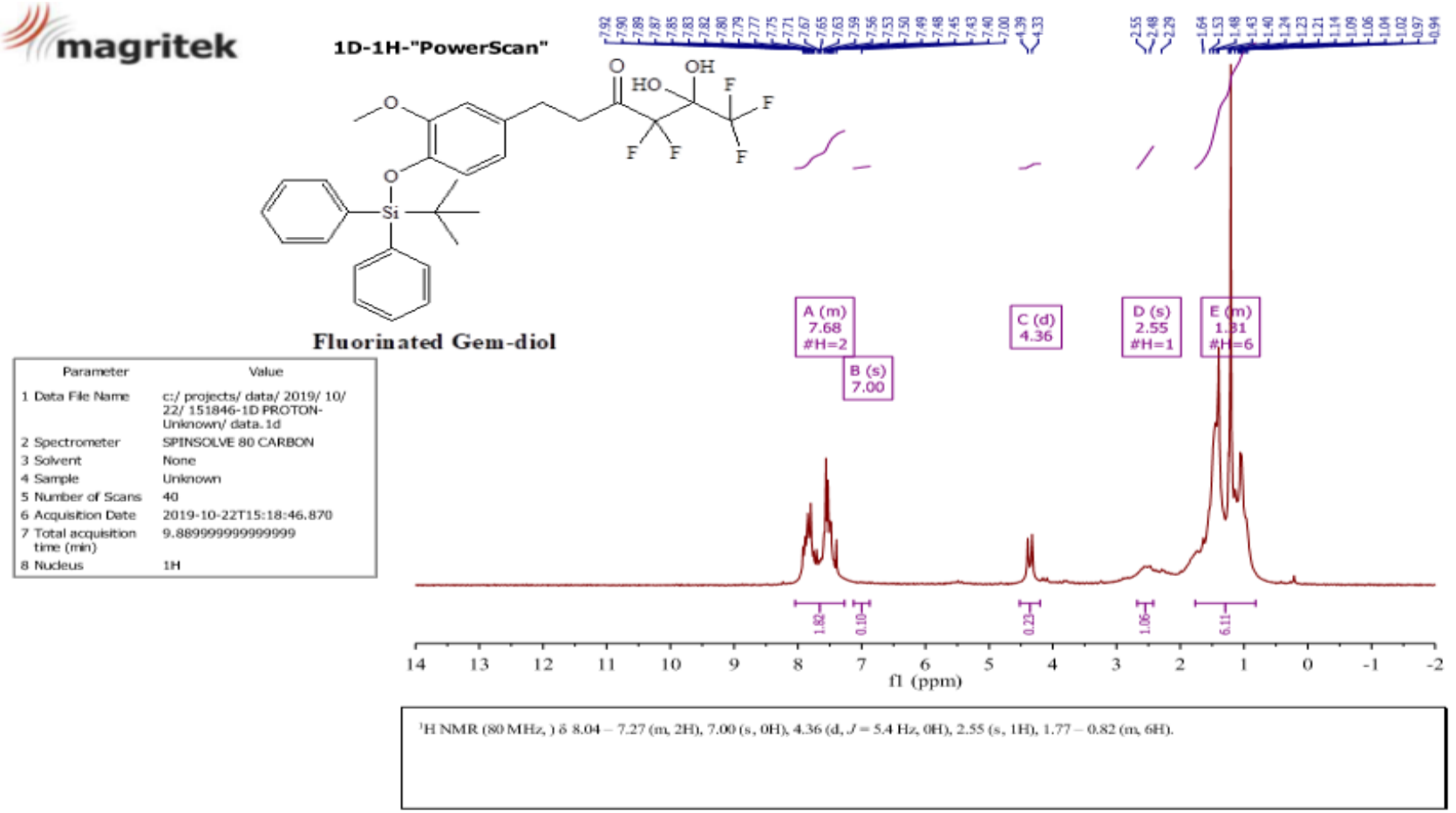


Figure 14. Experimental ^{1}H NMR of Pentafluoro Gem-diol.

RESULTS/DISCUSSION

STEP 3. Further Fluorination

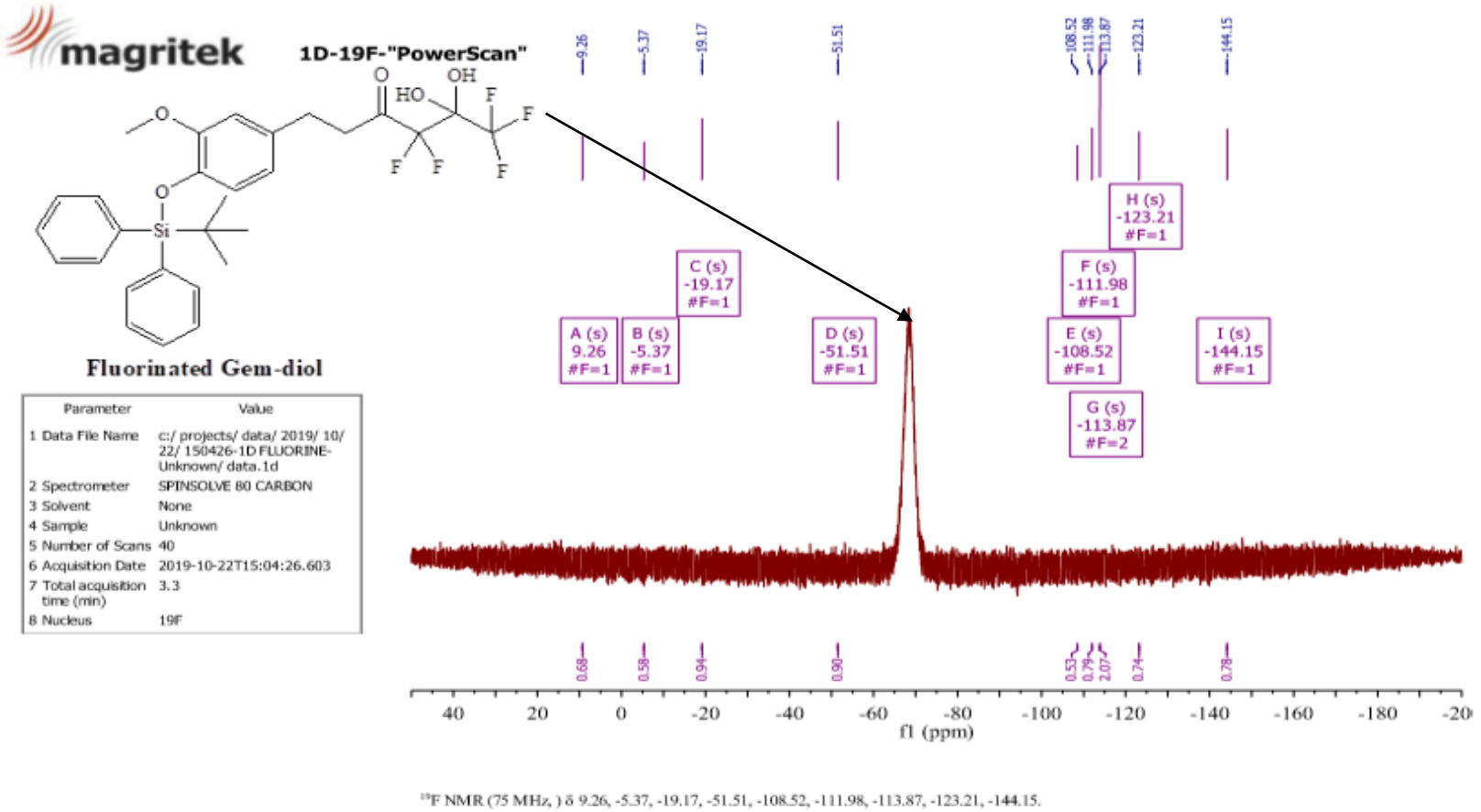


Figure 15. Experimental ^{19}F NMR of Pentafluoro Gem-diol.

RESULTS/DISCUSSION

- Trial Reaction for 2nd Step: Fluorination of Acetophenone

- 78 % Percent Yield
- Successful Reaction
- ^{1}H NMR and ^{19}F NMR Spectra Showed Expected Results

RESULTS/DISCUSSION

Trial Reaction for 2nd Step: Fluorination of Acetophenone

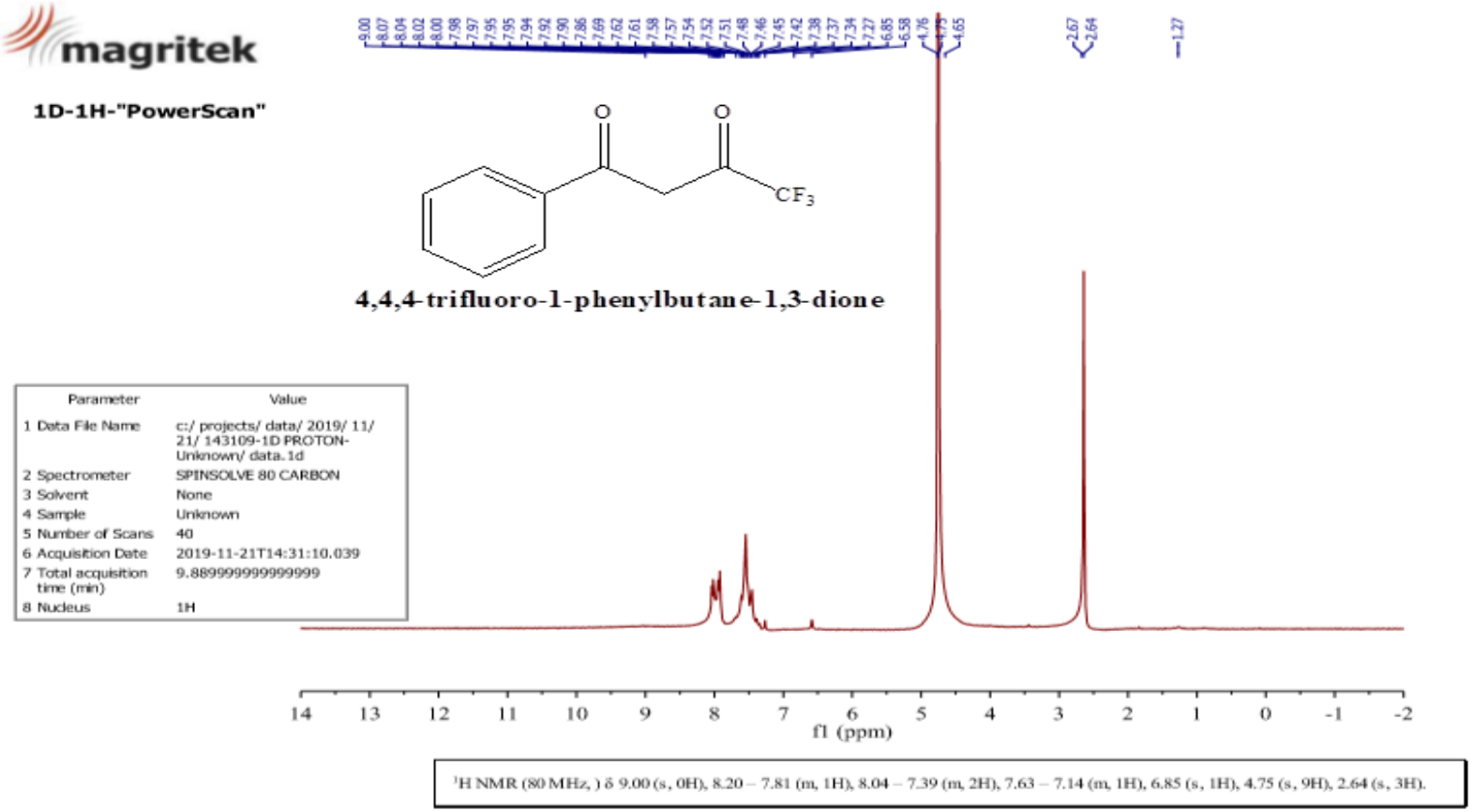


Figure 16. Experimental ^{1}H NMR of 4,4,4-trifluorinated-1-phenylbutane-1,3-dione.

RESULTS/DISCUSSION

Trial Reaction for 2nd Step: Fluorination of Acetophenone

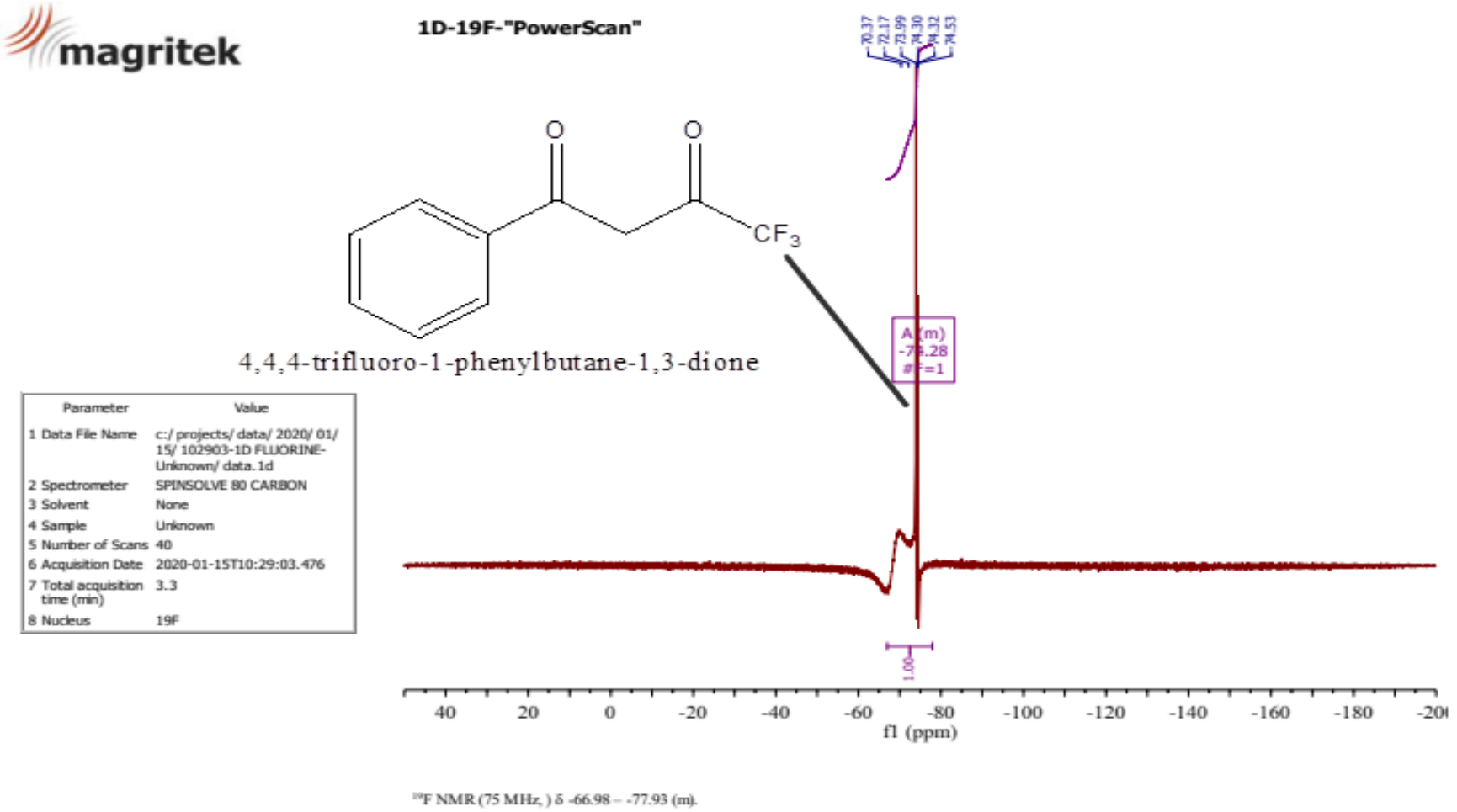


Figure 17. Experimental ^{19}F NMR of 4,4,4-trifluorinated-1-phenylbutane-1,3-dione.

RESULTS/DISCUSSION

- Trial Reaction for 3rd Step: Further Fluorination
  - 83.96 % Percent Yield
  - Successful Reaction
  - ^{19}F NMR Spectra Showed Expected Results

RESULTS/DISCUSSION

Trial Reaction for 3rd Step : Further Fluorination

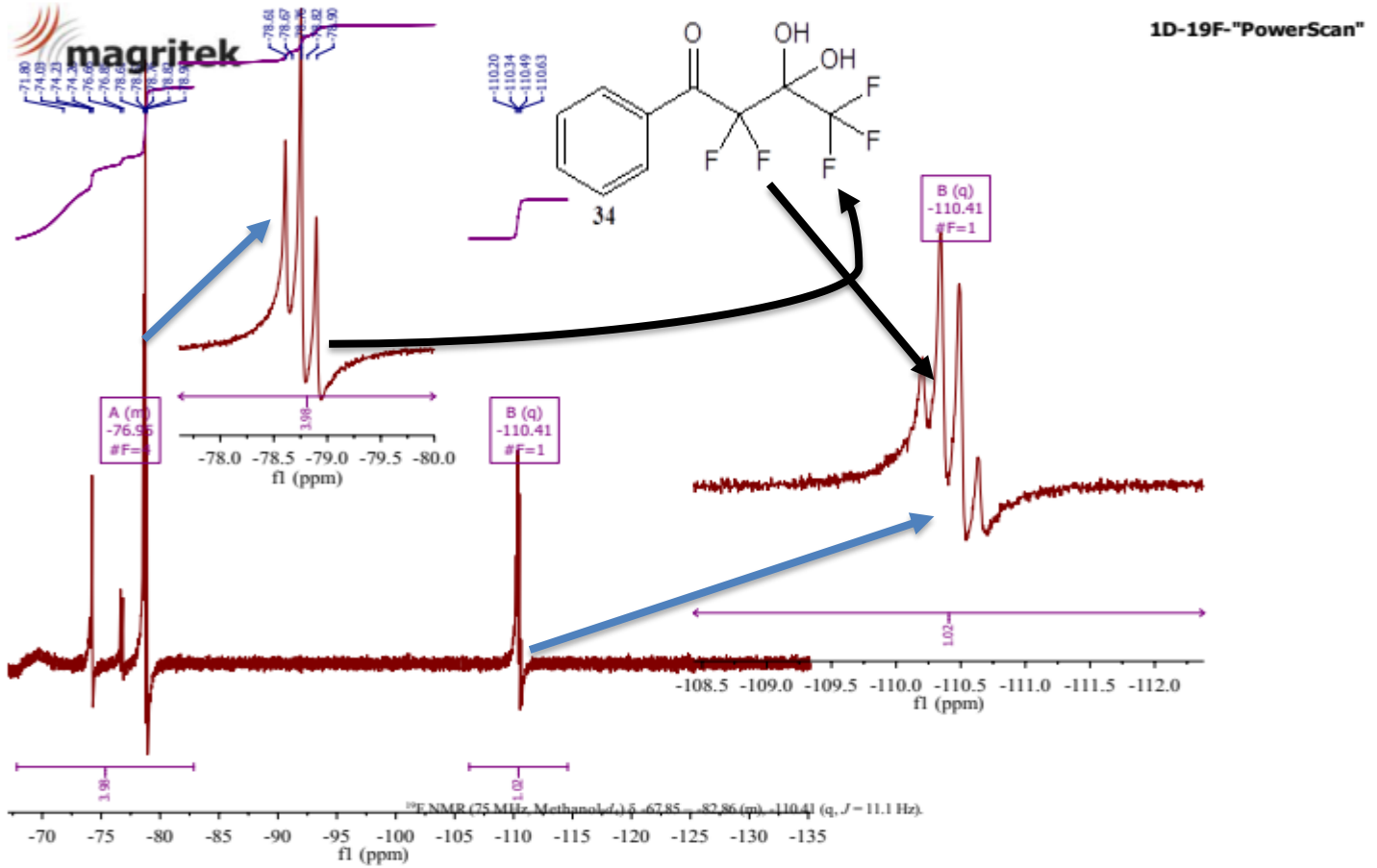


Figure 17. Experimental ^{19}F NMR of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one.

CONCLUSION

- This research attempted to synthesize 2,2-difluorinated-[6]-gingerol by five-step Synthesis.
- Only three steps were conducted.
- ^{1}H NMR and ^{19}F NMR :
  - Step 1: Successful reaction with the presence of some TBDPSCl leftover.
  - Step 2: Successful reaction with of solvent such has THF and DCM.
  - Step 3: Incomplete reaction, no presence of fluorine peak on the ^{19}F NMR.
  - Trial reaction of 2^{nd} and 3^{rd} steps: Successfully synthesized the desired products.
- This new route of synthesis was very efficient.

Future Work:

- Since the trial reactions of the steps 2 and 3 led to the generation of gem-diol from acetophenone as the original starting material, the future work is to apply the same conditions used during the trial reactions to the steps 2 and 3 reactions of the main research project by having protected vanillylacetone as the original starting material.
- After a successful third step, the fourth and fifth steps reactions will lead to the production of the target compound, which is 2,2 difluorinated-[6]-gingerol.

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- Dr. Cu Phung, Professor of Chemistry
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