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Progress towards the Total synthesis of Frondosin D lab report

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Admirabilis Kalolella

Organic synthesis lab report

01/04/2023

Progress toward the Total synthesis of Frondosin D

Introduction:

Organic synthesis has allowed humans to synthesize molecules beneficial to their existence. Over the years, more complex methods have been developed. This includes the Diels-Alder Reactions that was recognized with the Nobel Prize in Chemistry in 1950[1]. The increase in the complexity of Organic Chemistry provided more tools for synthesizing natural compounds with important medicinal properties but whose isolation was complicated and, in some cases, even unfeasible.[2] Natural products are the basis of the pharmaceutical industry.

Marine sponges are a source of various biologically active compounds with interesting medicinal applications. In 1997, the Frondosin family of marine-derived meroterpenoid natural products was first isolated from the marine sponge from Micronesia, *Dysidea frondos*[3]. The extracts showed an affinity towards the receptor CX-CLR1/2 of the cytokine interleukin-8 (IL-8). This inhibits the binding of the cytokine interleukin-8 (IL-8) to its receptor. Studies of the extract revealed a family of five sesquiterpene hydroquinones was responsible for the observed inhibitory activity[3]. Based on their bicyclo[5.4.0]undecene core, Frondosins are a fascinating group of chemical compounds. In addition to their affinity to IL-8, the frondosins have been shown to inhibit protein kinase C (PKC).[4]

Many chronic and acute illnesses have been linked to the IL-8 signaling pathway. These include sepsis syndrome, psoriasis, rheumatoid arthritis, gout, and asthma[5]. Further experiments studying inflammation in animals have shown that IL-8 is the key leukocyte chemotactic factor[5]. It directs neutrophil recruitment, and activation at the inflammatory focus. As a result of this, Frondosins have increasingly attracted attention as potential IL8 receptor antagonists. This has lead to a possibility of new pharmacological agents against autoimmune hyperactivity. Also, neutrophil activation plays a key role in malignant tumor progression and metastasis in certain cancers. This has further made Frondonsins a promising candidate for oncology studies[6-7]. Furthermore, preliminary anti-HIV assays have revealed that Frondosins A and D exhibit HIV-inhibitory activity at the low micromolar level[8].With a host of biological implications for IL-8 inhibition, Frondosins became a popular target for total synthesis

Frondosins B, C, D, and E have a common structural feature:: a bicyclo[5.4.0]undecane sesquiterpene core structure. The difference is in the structure C and D rings (Figure 1). All the members of the Frondosin family except Frondosin A have a tetracyclic core structure. Frondosin A has a tricyclic structure rather than a tetracyclic structure[9]. Synthesis of Frondosin A, B, and C has been achieved via 5-Exo cyclization-Claisen rearrangements[10](Figure 2). Despite these achievements in synthesizing Frondosin A to C, Frondosins have proven to have a difficult synthetic route, with the synthesis of Frondosin D yet to happen[10]. Overall, the above-mentioned facts make Frondosin D an exciting synthetic target. The cyclization/Claisen rearrangement sequence will be applied for the synthesis of Frondosin D through a strategy that allows the simultaneous assembly of three of the requisite rings with the seven-membered ring at the core. The sequence would also generate a ketone carbonyl group in the seven-membered ring, for further functionalization of the advanced intermediate.

In this paper, we report the approach used by the Ovaska research group to synthesize the molecular scaffold of frondosins D.The studied synthetic approach for the synthesis of Frondosin D designed by the Ovaska group involves the cyclization/Claisen rearrangement sequence that allows the assembly of the seven-membered ring in the Frondosin D core structure.

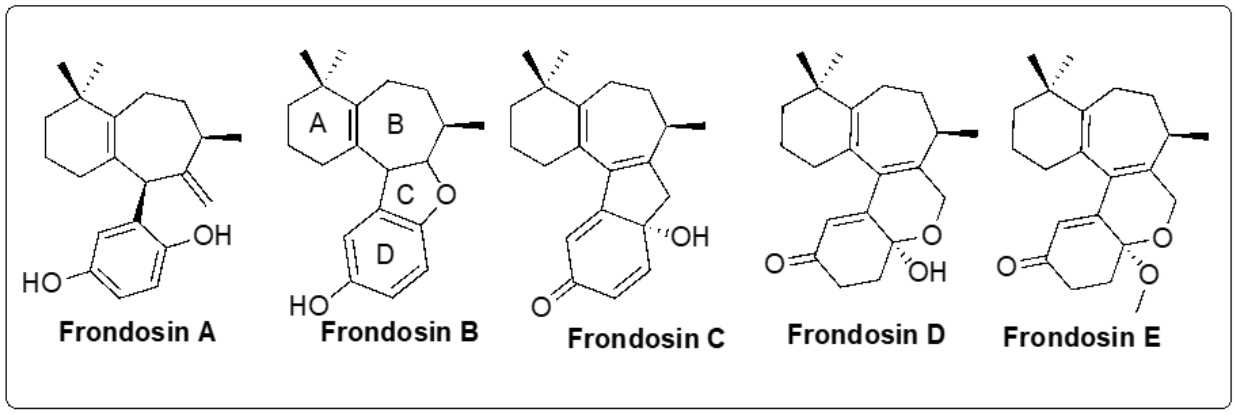


Figure 1. Structure of Frondosins A-E

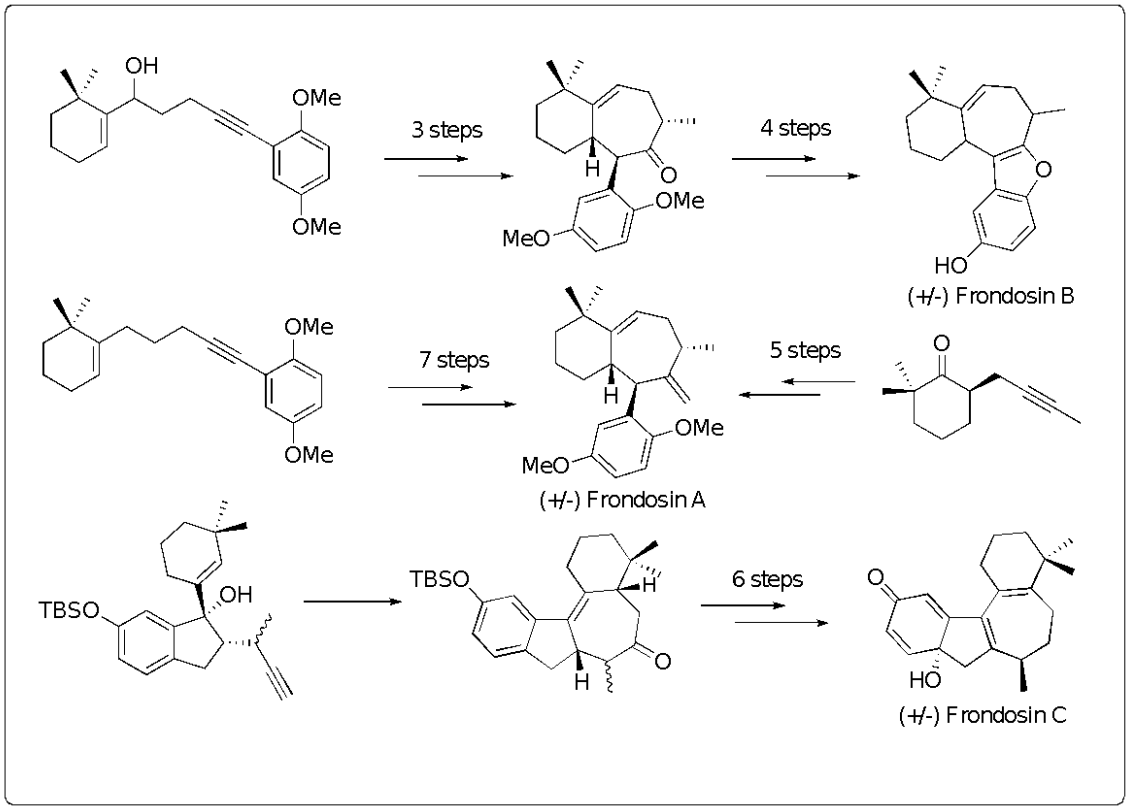


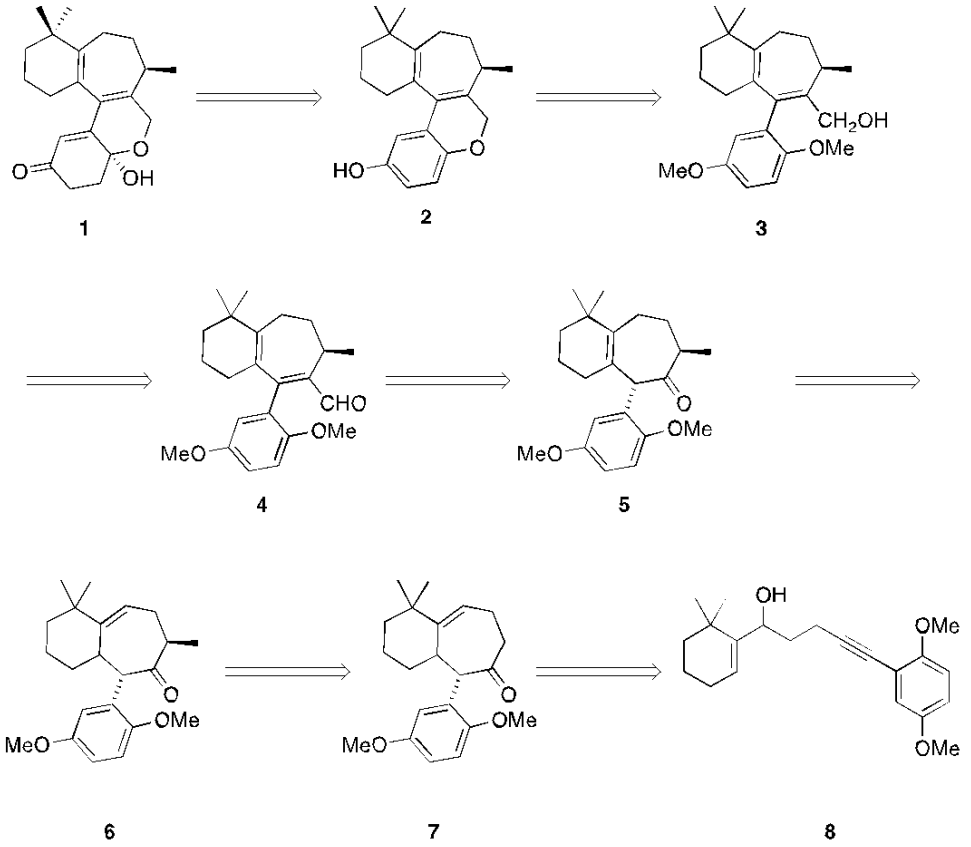
Figure 2: Applications of the 5-exo cyclization-Claisen rearrangements in the total synthesis of Frondosin B, A, and C.[11,12,13]

Results and discussion:

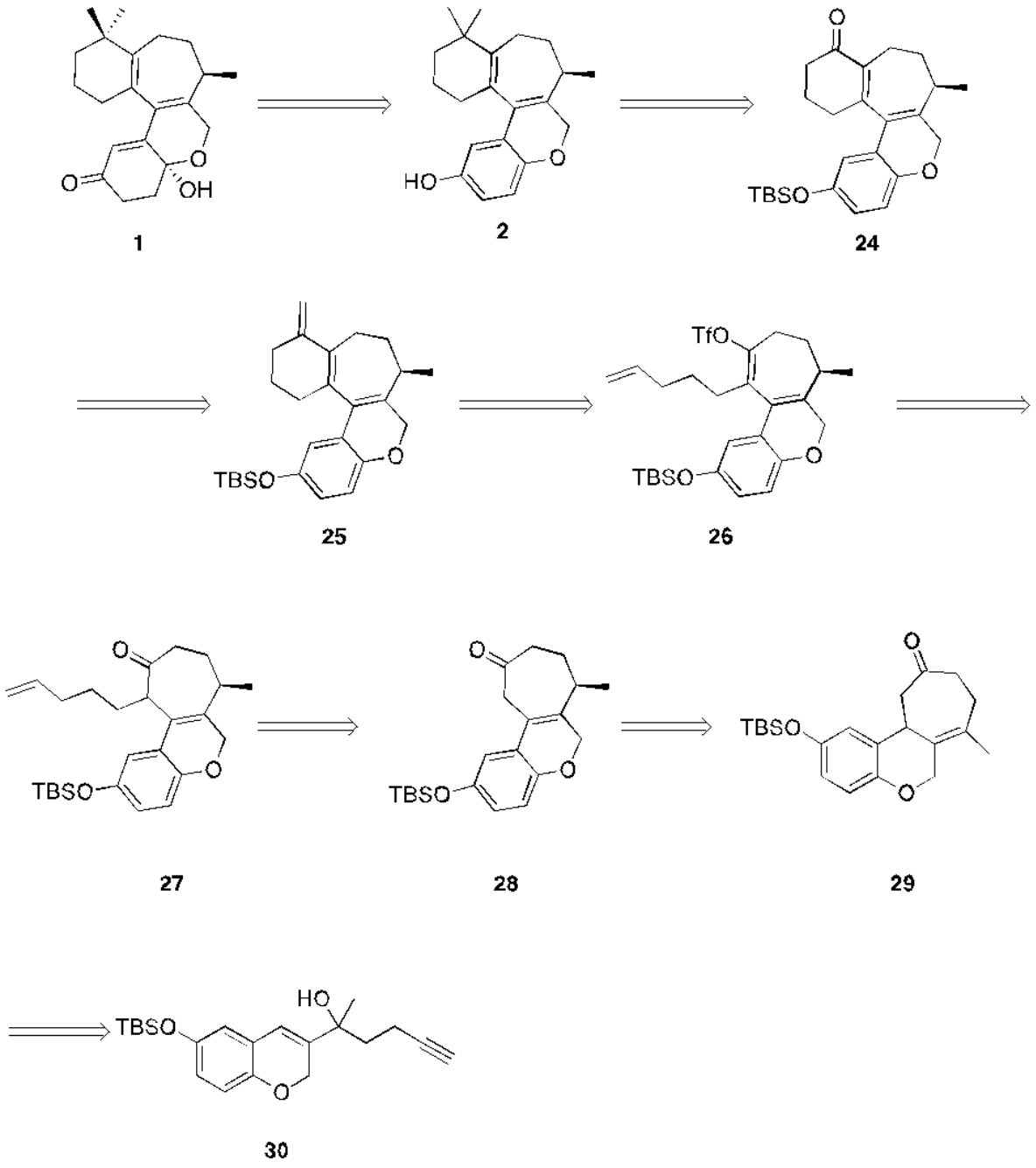
The Ovaska lab has explored two different approaches towards the synthesis of Frondosin D in the past. These are A-D-B-C and D-C-A-B approach. The approaches differ from one another in the order that each ring of the core structure of frondosin D is assembled. The first approach, A-D-B-C approach(Scheme 1), the ring C is synthesized in the last step, after the seven-membered ring B which is constructed through tandem cyclization/ Claisen rearrangement. The second approach, called D-C-B-A approach(scheme 2), ring D is present in the starting material and ring A is synthesized last, after rings C and B are assembled. Here, retrosynthesis starts with a tertiary alcohol **30.** This is then cyclized through cyclization/Claisen rearrangement sequence to yield the tricyclic cycloheptanoid intermediate **29**. Then, the double bond in ring B is isomerized into the same position as seen in the frondosin D ring system. This yields ketone **28**. Specifically, the synthetic route for the synthesis of the tricyclic intermediate was explored. The resulting ketone can then be alkylated with methyl lithium and the appropriate alkyl iodide to form ketone **27** that can undergo a triflation in the alpha position to the carbonyl to yield triflate **26**. The Heck reaction can then be applied for the assembling of the last ring in the system to form **25**. The terminal double bond attached to ring A can be selectively dehydroxylated and then ketone **24** can be formed through the 1,2-diol oxidative cleavage protocol. The gem-dimethylated intermediate can be synthesized from **24** by the utilization of a variation of the Reetz conditions that has been designed by Trauner et al.[14] At this point, the TBS

group can be removed with TBAF to form intermediate **2**, which can be subsequently oxidized by hypervalent iodide oxidation to yield frondosin D.

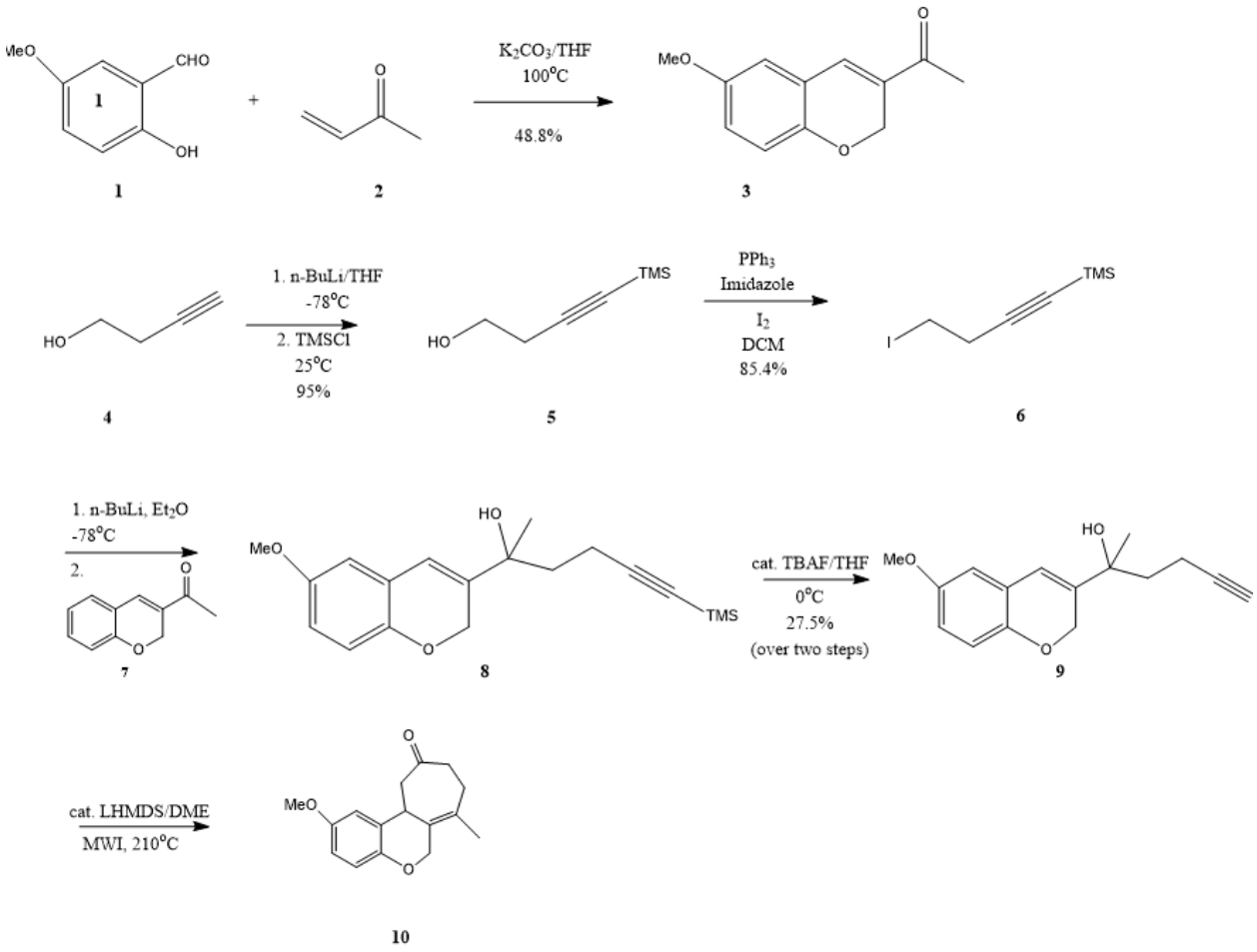
In this independent study we explored the synthetic route for the synthesis of the tricyclic intermediate presented in Scheme 3.



Scheme 1: A-D-B-C Retrosynthetic Approach for frondosin D



Scheme 2: D-C-B-A Retrosynthetic Approach for frondosin D



Scheme 3: Synthesis of tricyclic intermediate 9

The synthesis begins with the synthesis of ketone **3** from commercially available 2-hydroxy-5-methoxy benzaldehyde **1** and methyl vinyl ketone **2** through an intermolecular Baylis-Hillman reaction. The triple bond in 4-pentyn-1-ol is then protected with a -TMS group to yield

alcohol **5** that can be converted to iodide an **6** in an Appel reaction. Iodide **6** is coupled with ketone **3** through n-BuLi coupling to yield compound **8** as a crude product. The crude product from the coupling reaction was then used for direct TBAF deprotection. According to previous studies in the Ovaska lab, this resulted in higher yields and reduced time and material input in the synthesis of cyclization precursor **9**. This precursor then has to undergo a tandem cyclization/Claisen rearrangement sequence to yield the tricyclic intermediate **10**. The reaction to obtain product **10** was not done in this independent study due to time constraints and challenges observed in synthesizing precursor **6**. Precursor **6** had to be redistilled to purify it. When this proved to be challenging redistillation was done on precursor **5**, the alcohol to purify it and proceed with the synthesis.

Conclusion:

The synthesis of Frondosin D has not yet been achieved. In the independent study, we explored the synthesis tricyclic intermediate that is the part of the core of the Frondosin D. Though there were challenges observed in this synthesis, specifically during the synthesis of precursor **6**.The Ovaska group, through future studies, hopes to explore this work further to fully synthesize the tricyclic intermediate of the Frondosin D.

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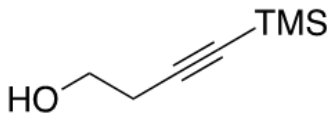
Experimental Details:

General Experimental

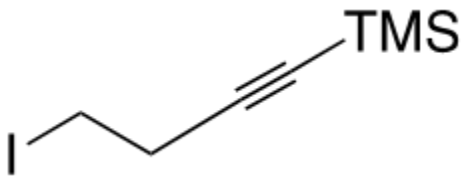
The synthesized compounds were analyzed using ^{1}H and ^{13}C NMR acquired with a Varian INOVA NMR 500 MHz spectrophotometer and with deuterated chloroform as solvent. The chemical shifts observed are reported as parts per million (ppm), with tetramethylsilane as the primary reference at $\delta = 0.00$ ppm. Moreover, the coupling constants J are reported in hertz (Hz). The synthesized compounds were purified by column chromatography, flash chromatography in Biotage Isolera One purification system, simple distillation, or fractional distillation. All the starting materials used were purchased from Aldrich, Acros or Strem. Diethyl ether, dichloromethane, tetrahydrofuran, and dimethylformamide were purchased from Fisher and VWR and were dried and deoxygenated via a *PureSolv* solvent purification system. Trimethylsilyl chloride, phenetole, acetonitrile and triethylamine were freshly distilled from calcium hydride. Furthermore, all glassware was flame-dried under nitrogen atmosphere and all reactions were performed under dry nitrogen atmosphere conditions.

Experimental Details



[35] 4-(trimethylsilyl)but-3-yn-1-ol

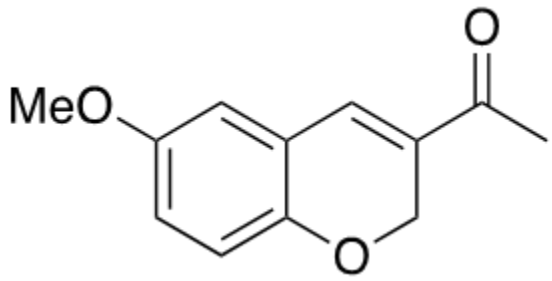
n-Butyllithium (1.6 M in hexane, 91.6ml, 146.6 mmol) was added dropwise to a stirring solution of but-3-yn-1-ol (6.02g, 70.57mmol) in tetrahydrofuran (70 ml) at -78°C, and the resulting mixture was stirred for 1 h. Trimethylsilyl chloride (19.9 ml, 157.05 mmol) was then added dropwise and the reaction was warmed to 0°C and stirred for 1 h. Then, 10% hydrochloric acid (15 ml) was added and the reaction was stirred for 30 min at 0°C. At this point, tetrahydrofuran was removed under reduced pressure, and diethyl ether (35 ml) and water (20 ml) were added to the mixture. The layers were separated, and the aqueous layer was rinsed with diethyl ether (3x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was filtered through a pad of silica using hexane and compound **1** was obtained as a colorless liquid (9.32g, 93.6 %). Compound **1** was previously reported.[6]



[36] (4-iodobut-1-yn-1-yl)trimethylsilane

To a stirring solution of **35** (3.955 g, 27.8mmol) with triphenylphosphine (8.76g, 33.36 mmol) and imidazole (2.84g g, 41.68 mmol) in dichloromethane (100 ml) at 0°C, I_2 (8.47 g, 33.36

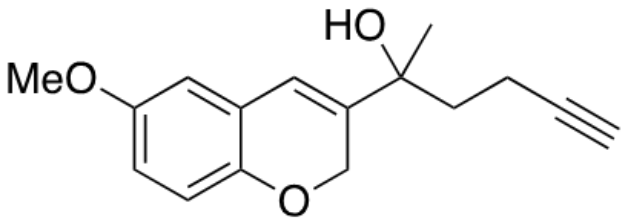
mmol) was added. Then, the reaction mixture was allowed to stir at room temperature for 14 h before being quenched with saturated ammonium chloride (25 ml). At this point, the reaction mixture was diluted with dichloromethane (20 ml) and layers were separated. The aqueous layer was extracted with dichloromethane (2x 30 ml) and the resulting combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Crude product was filtered through a pad of silica using hexane to yield **2** as a colorless liquid (5.983g, 85.4%). **1H NMR** ($CDCl_3$, 500 MHz): δ 3.22 (t, J = 7.6 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 0.16 (s, 9H) ppm. **13C NMR** ($CDCl_3$, 126 MHz): δ 105.2, 86.9, 25.2, 1.18, 0.08 ppm.



[33] 1-(6-methoxy-2H-chromen-3-yl)ethenone

Methyl vinyl ketone (1.99, 28.32 mmol) was added to a stirring mixture of 2-Hydroxy-5-methoxybenzaldehyde (3.92g, 28.32 mmol) and potassium carbonate (4.31g, 28.32 mmol) in methyl ethyl ketone (45 ml). The mixture was heated at 100°C for 10 h and then it was allowed to cool down to room temperature before being diluted with ethyl acetate (70 ml). The resulting mixture solution was filtered over celite and then mixed with water (50 ml). The aqueous layer was rinsed with ethyl acetate (4x 30 ml), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (SNAP Ultra, 25g, 2 to 20%, 10CV, ethyl acetate in hexane) to obtain **33** as a yellow solid (1.878g, 48.8 %). **1H NMR** (500 MHz, $CDCl_3$): δ 7.27 (s, 1H),

6.86–6.78 (m, 2H), 6.72 (d, J = 2.7 Hz, 1H), 4.95 (s, 2H), 3.78 (s, 3H), 2.41 (s, 3H) ppm; **13CNMR** (126 MHz, $CDCl_3$): δ 196.1, 154.4, 149.7, 134.1, 131.7, 121.5, 118.4, 117.1, 113.3, 64.3, 55.9, 25.2 ppm.

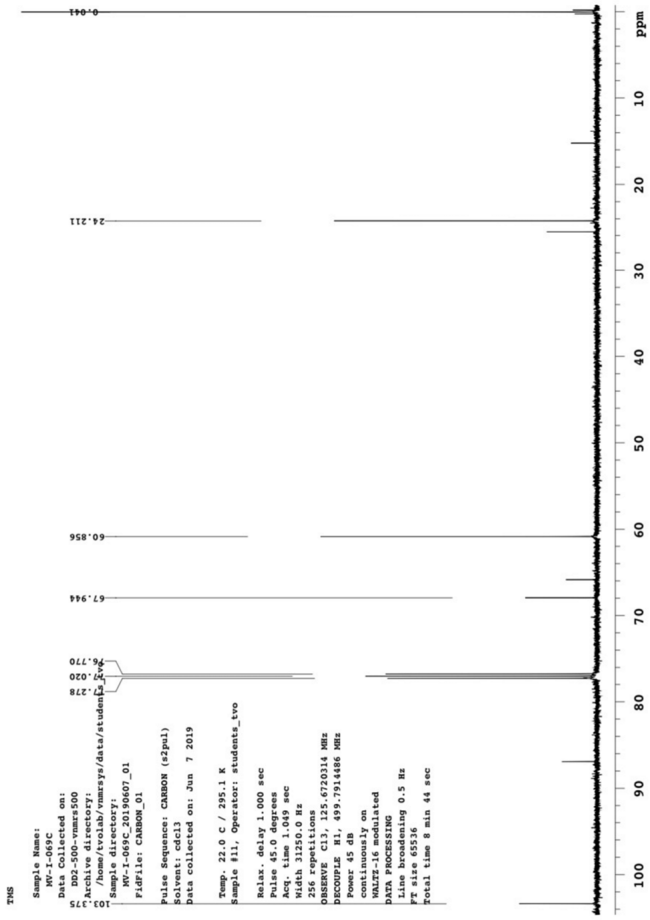


amount to a stirring solution of the resulting crude product in tetrahydrofuran (18 ml) at 0°C. The reaction was allowed to stir for 1.5 h before being quenched with water (1 ml). Them, tetrahydrofuran was removed under reduced pressure, and the resulting mixture was diluted with diethyl ether (40 ml) and water (15 ml), and layers were separated. The aqueous layer was extracted with diethyl ether (2x 25 ml), and the resulting combined organic layers were dried over magnesium sulfate and concentrated ***[38] 2-(6-methoxy-2H-chromen-3-yl)hex-5-yn-2-ol***

t-Butyllithium (1.9M in hexane, 5.31 mL, 12.87 mmol) was added dropwise to a stirring solution of iodide **36** (2.47g, 9.91 mmol) in diethyl ether (75 ml) at -78°C. Then, the ketone **33** (1.012g, 4.95 mmol) was dissolved in diethyl ether (40 ml) and slowly transferred via cannula to the reaction mixture. Then, the reaction mixture was stirred at -78°C for 1 h before being quenched with methanol (2 ml) and allowed to warm to room temperature. Water (40 ml) was added to the mixture and the aqueous layer was separated from the organic layer. The aqueous layer was then washed with diethyl ether (2x 30 ml), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. At this point, *tetra-n*-butylammonium fluoride (1M in tetrahydrofuran, 0.2 mL) was added in catalytic under

reduced pressure. Crude product was purified by Biotage Isolera™ (SNAP Ultra, 25g, 5 to 40%, 10CV, ethyl acetate in hexane) to obtain **38** as a yellow liquid (0.357g, 27.5 %). **1HNMR** (500 MHz, $CDCl_3$): δ 6.76 (d, J = 8.8 Hz, 1H), 6.67 (dd, J = 8.8, 3.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 6.44 (s, 1H), 4.64-4.67 (m, 2H), 3.76 (s, 3H), 2.20-2.35 (m, 2H), 2.07 (s, 1H), 1.98-2.00 (m, 1H), 1.89-1.90 (t, J = 7.6 Hz, 2H), 1.41 (s, 3H) ppm. **13CNMR** (500 MHz, $CDCl_3$): δ 154.4, 147.2, 139.7, 123.6, 118.8, 116.1, 114.2, 112.1, 84.3, 73.8, 69.3, 65.5, 55.9, 38.8, 27.3, 13.7 ppm.

NMR SPECTRA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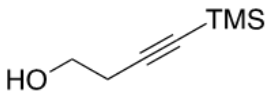
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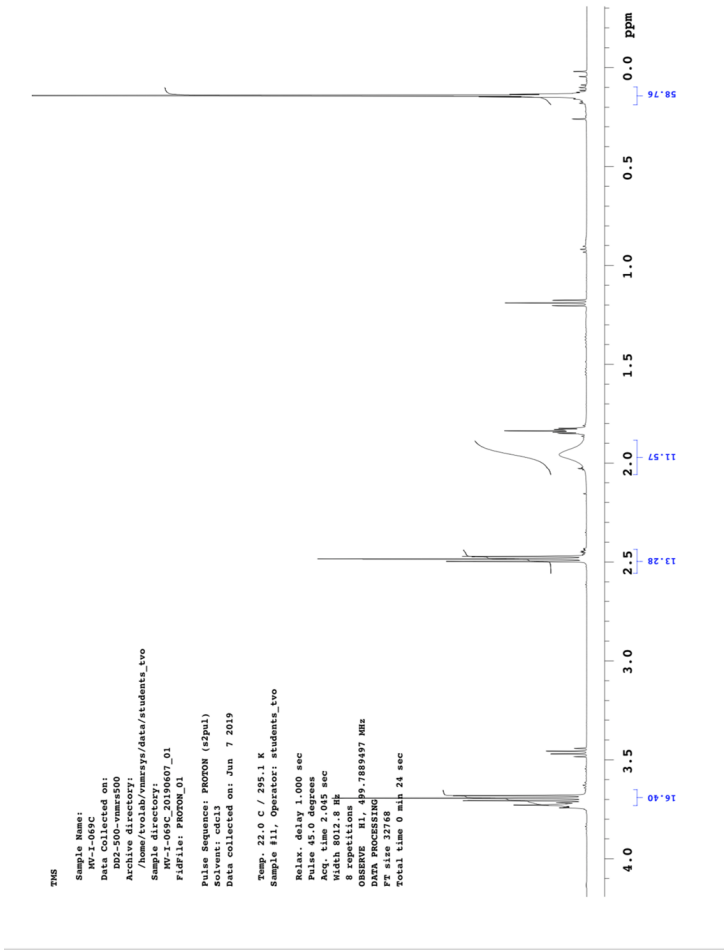
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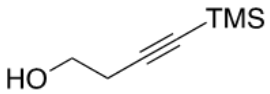
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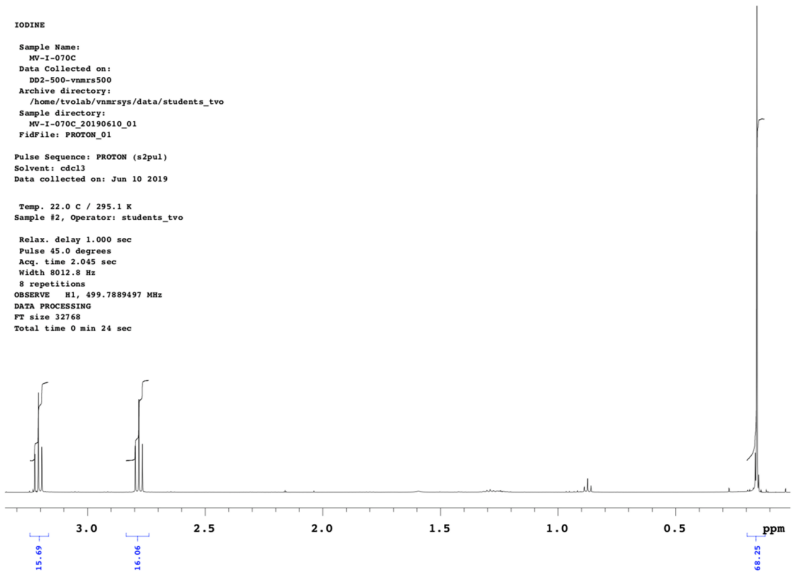
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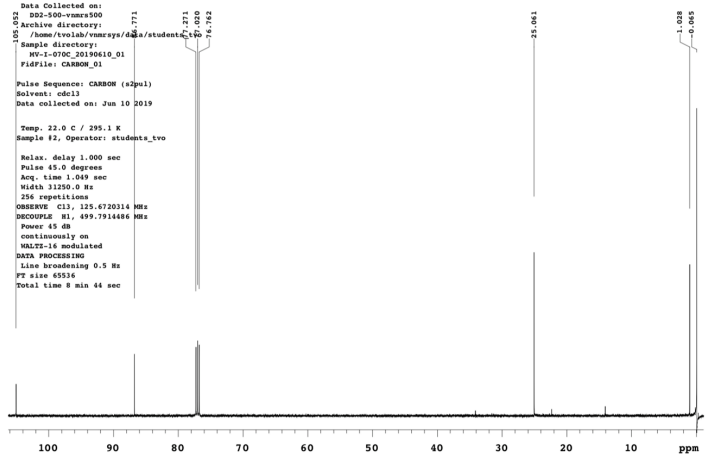
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ppm


I
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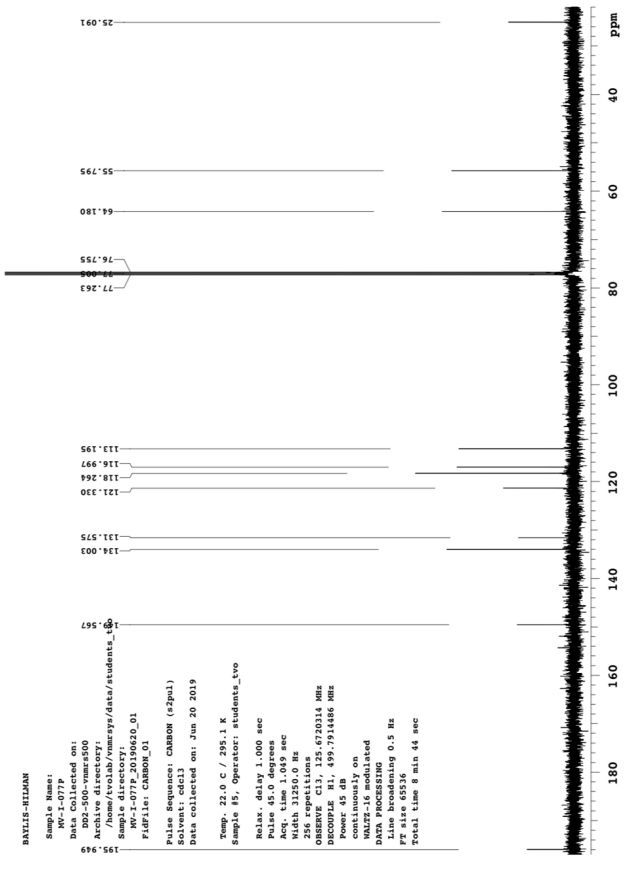
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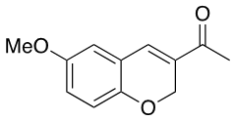
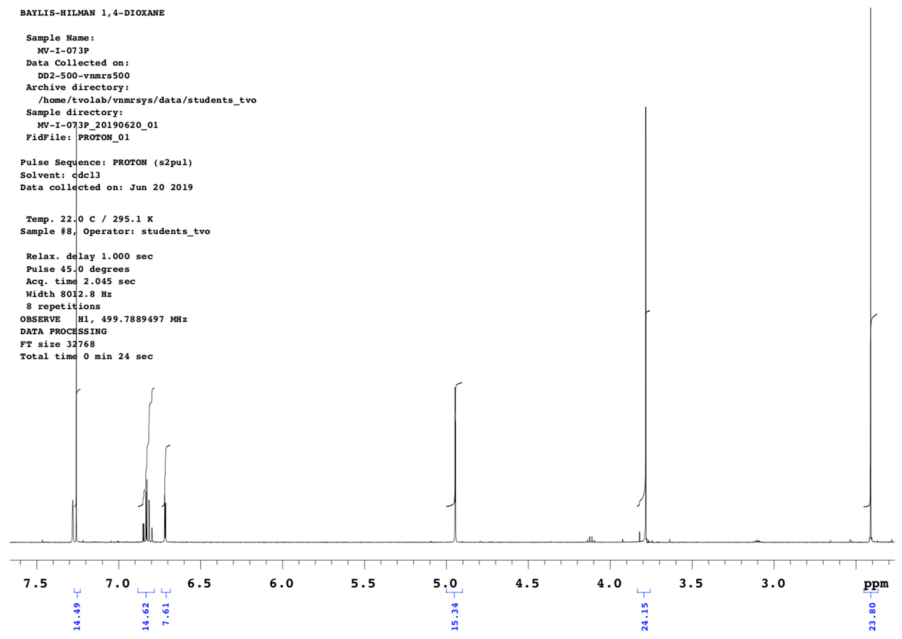
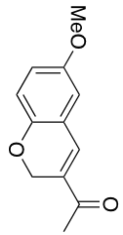
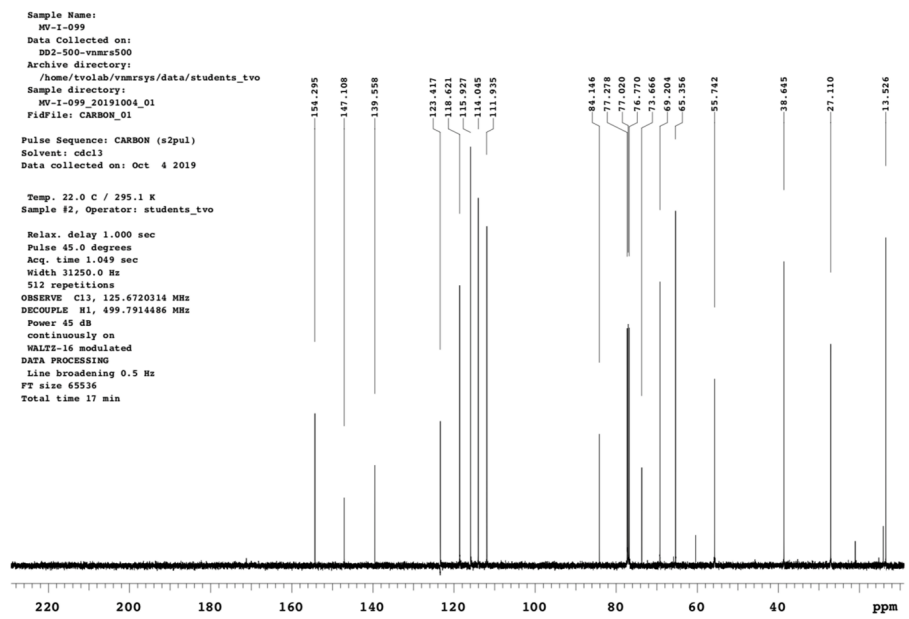
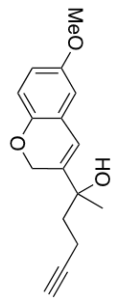
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.049 sec
Width 31250.0 Hz
256 repetitions
OBSERVE C13, 125.6720314 MHz
DECOUPLE H1, 499.7914486 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 8 min 44 sec
195.949
197.567
134.003
131.575
121.330
118.264
116.997
113.195
77.263
76.755
64.180
55.795
25.091
ppm

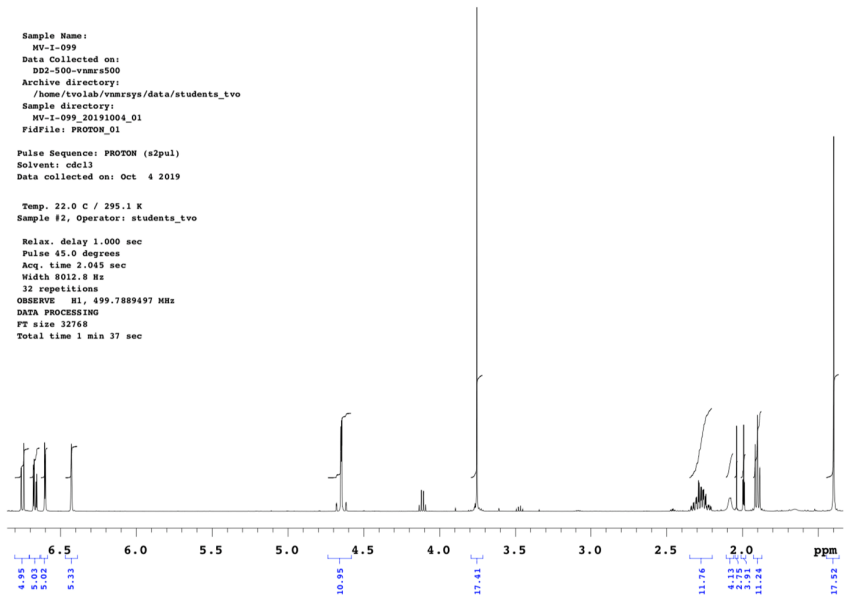

MeO
O
O

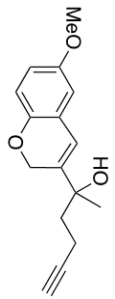

BAYLIS-HILMAN 1,4-DIOXANE
Sample Name:
MV-I-073P
Data Collected on:
DD2-500-vnmrs500
Archive directory:
/home/tvolab/vnmrsys/data/students_tvo
Sample directory:
MV-I-073P_20190620_01
FidFile: PROTON_01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 20 2019
Temp. 22.0 C / 295.1 K
Sample #8, Operator: students_tvo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.045 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.7889497 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 24 sec
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
14.49
14.62
7.61
15.34
24.15
23.80


MeO
O
O


Sample Name:
MV-I-099
Data Collected on:
DD2-500-vnmrs500
Archive directory:
/home/tvolab/vnmrsys/data/students_tvo
Sample directory:
MV-I-099_20191004_01
FidFile: CARBON_01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 4 2019
Temp. 22.0 C / 295.1 K
Sample #2, Operator: students_tvo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.049 sec
Width 31250.0 Hz
512 repetitions
OBSERVE C13, 125.6720314 MHz
DECOUPLE H1, 499.7914486 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
154.295
147.108
139.558
123.417
118.621
115.927
114.045
111.935
84.166
77.278
77.020
76.770
73.666
69.204
65.356
55.742
38.645
27.110
13.526
220
200
180
160
140
120
100
80
60
40
ppm


MeO
O
HO


Sample Name:
MV-I-099
Data Collected on:
DD2-500-vnmrs500
Archive directory:
/home/tvolab/vnmrsys/data/students_tvo
Sample directory:
MV-I-099_20191004_01
FidFile: PROTON_01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 4 2019
Temp. 22.0 C / 295.1 K
Sample #2, Operator: students_tvo
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.045 sec
Width 8012.8 Hz
32 repetitions
OBSERVE H1, 499.7889497 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 37 sec
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
4.95
5.03
5.02
5.33
10.95
17.41
11.76
4.13
2.75
3.91
11.24
17.52


MeO
O
HO