# Synthesis of Gallicynoic Acids

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# Overview

- Background
- Previous Work
- Retrosynthetic Scheme
- Proposed Synthetic Scheme
- In the lab
- Future Work
- Acknowledgements

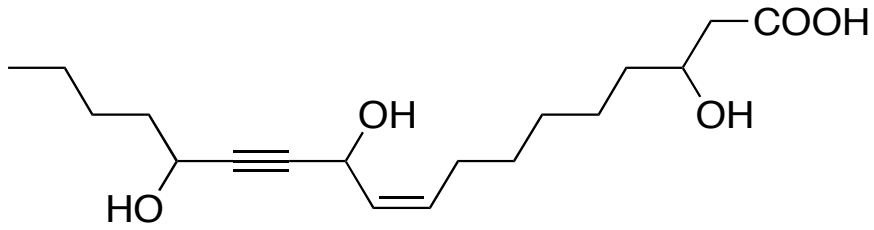
# Background

Recently, a series of nine structurally related acetylenic carboxylic acids, gallicynoic acids, have been isolated from a fungus, basidiomycete *Coriolopsis gallica,* a fungus belonging to the family Polyporaceae. Some of these acetylenic metabolites exhibit diverse bioactivities, including cytotoxic, antimicrobial, enzyme-inhibitory, and anti-HIV activities. By modifying a previous synthetic scheme, the synthesis of these acetylenic acids in a racemic fashion is attempted. The new, revamped synthetic scheme pursuing the desired racemic products will be presented. This scheme is set up accordingly such that all the acids will be prepared with the same synthetic scheme. Currently, an enantioselective acetylide/aldehyde process leading to non-racemic gallicynoic acids with the desired stereochemistry is devised.

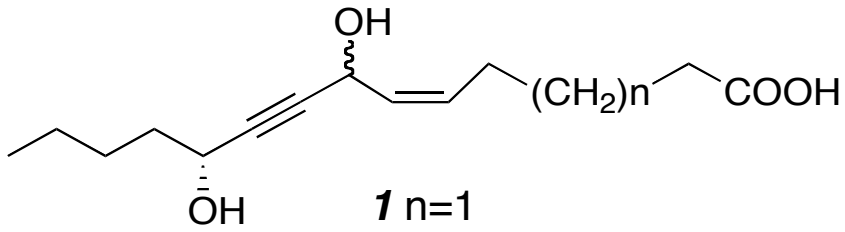
Zhong-Yu Zhou, Fei Wang, Jian-Guo Tang, Li-Zhen Fang, Ze-Jun Dong and Ji-Kai Liu "Gallicynoic Acids A-I, Acetylenic Acids from the Basidiomycete Coriolopsis gallica." *J. Nat. Prod.* **2008**, *71,* 223-226.

# Background

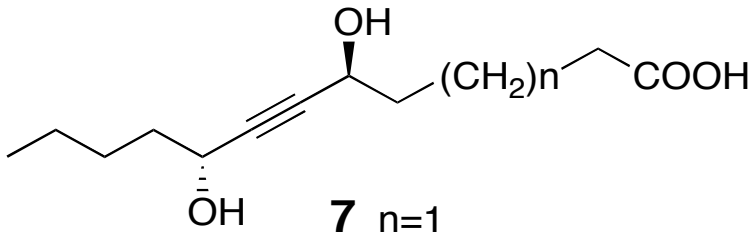
The compounds below were isolated from a sample collected in July of 2005. In this project, the focus was on ***1*** & ***4***.



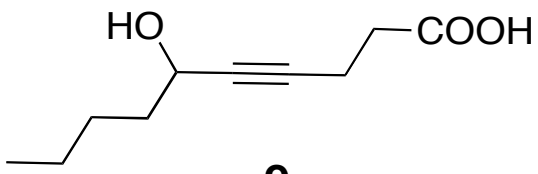

**5**




***1*** n=1
***2*** n=2
***3*** n=3
***4*** n=5




**7** n=1
**8** n=5

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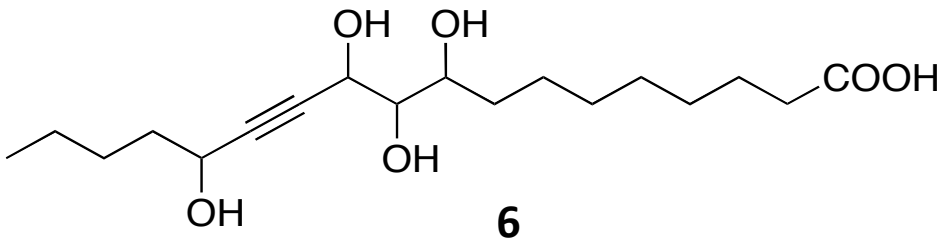
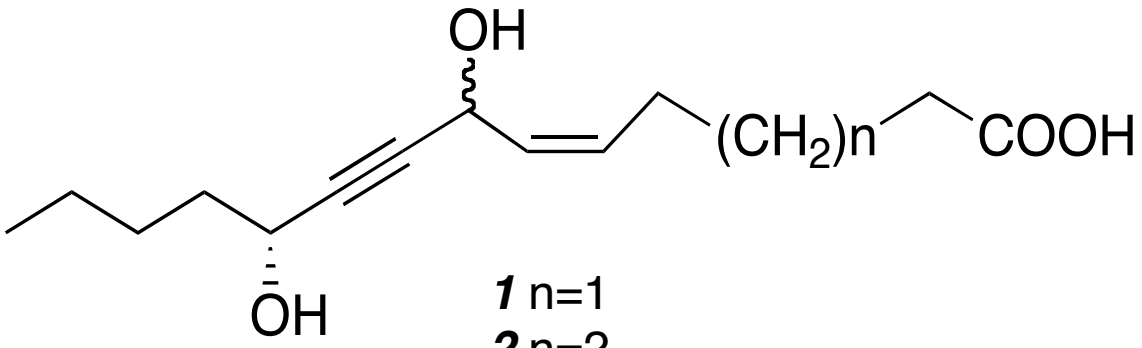



**6**

Zhong-Yu Zhou, Fei Wang, Jian-Guo Tang, Li-Zhen Fang, Ze-Jun Dong and Ji-Kai Liu "Gallicynoic Acids A-I, Acetylenic Acids from the Basidiomycete Coriolopsis gallica." *J. Nat. Prod.* **2008**, *71*, 223-226.

# Gallicynoic Acids *1-4*



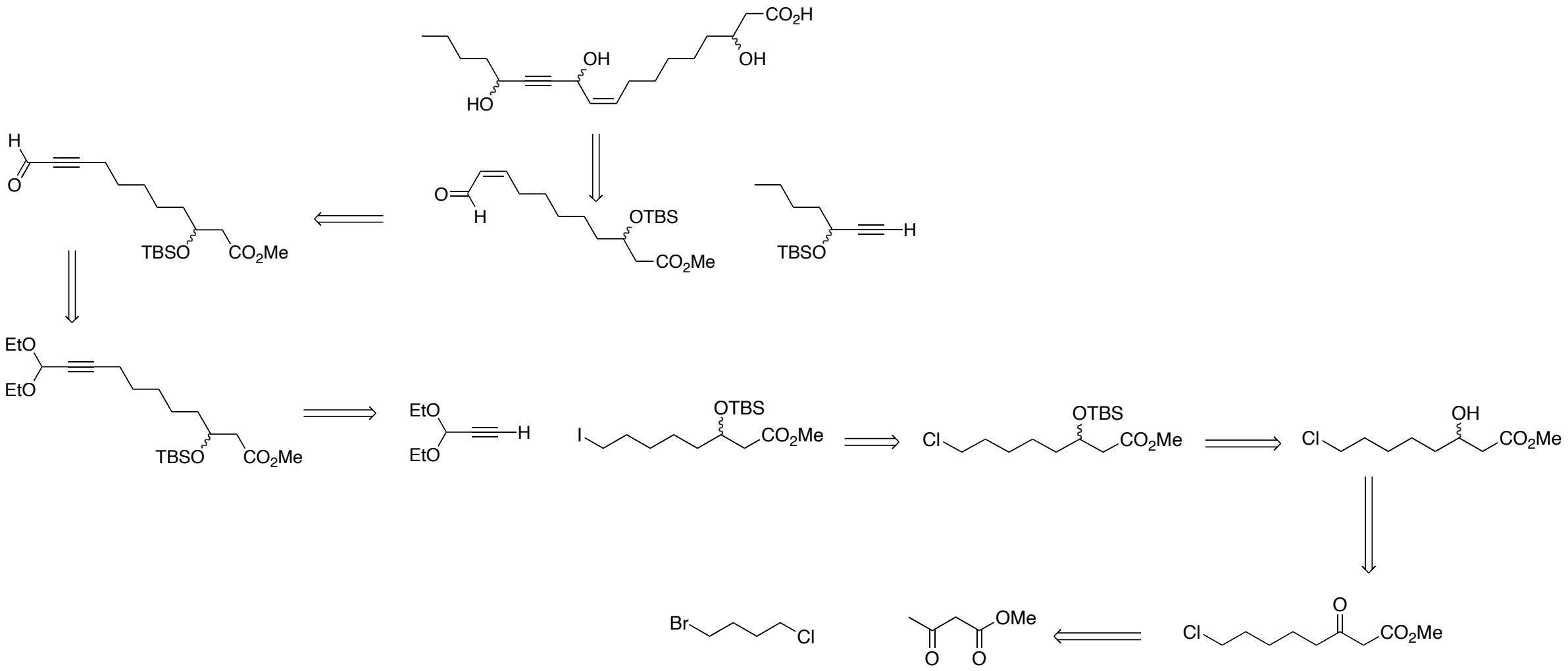

***1*** n=1
***2*** n=2
***3*** n=3
***4*** n=5

- All nine Gallicynoic acids were collected as colorless oils isolated from a culture of *Coriolopsis gallica*
- The structures of the nine acetylenic acids have been elucidated by NMR and FABMS analyses
- Compounds ***1-4*** were identified as cytotoxic

Zhong-Yu Zhou, Fei Wang, Jian-Guo Tang, Li-Zhen Fang, Ze-Jun Dong and Ji-Kai Liu "Gallicynoic Acids A-I, Acetylenic Acids from the Basidiomycete Coriolopsis gallica." *J. Nat. Prod.* **2008**, *71*, 223-226.

# Synopsis of Previous Work

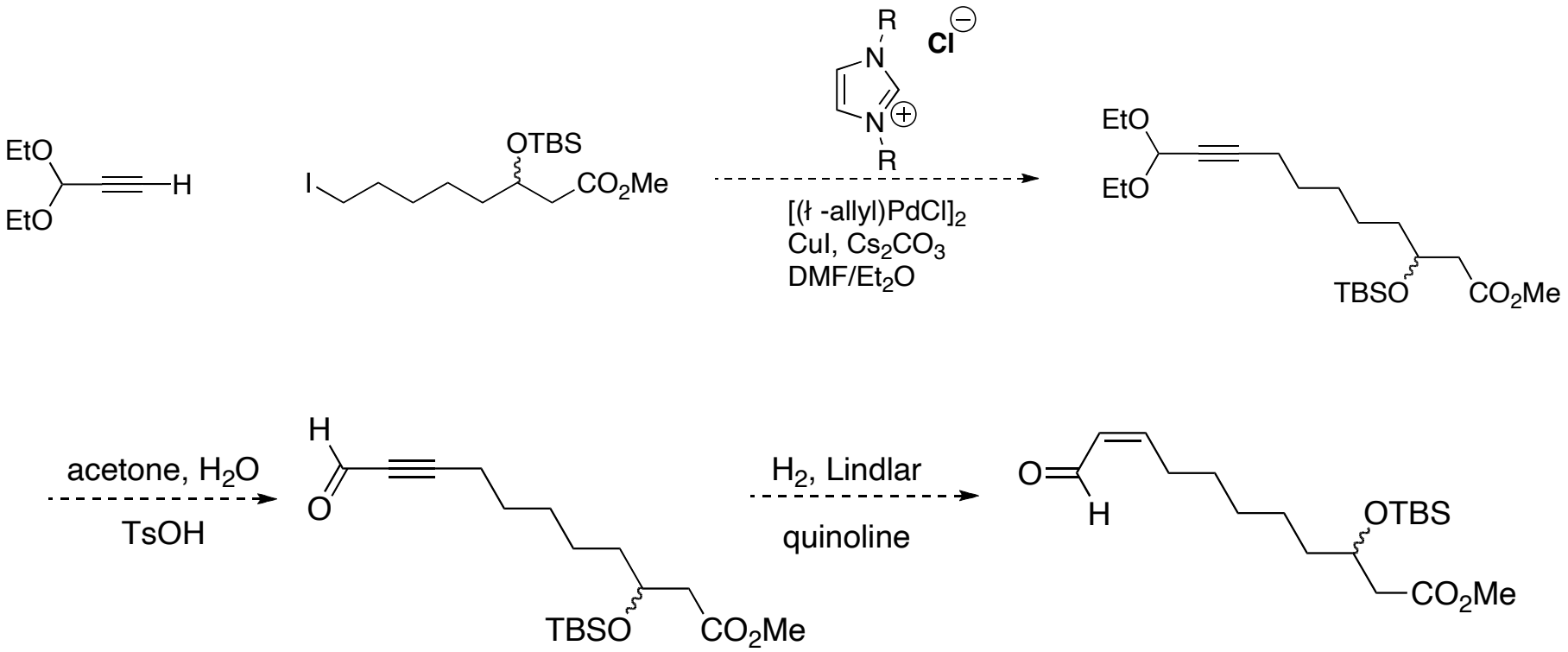
Nina McCulley's synthesis of Gallicynoic Acid 5



# Synopsis of Previous Work

Future work of Galllicynoic Acid 5

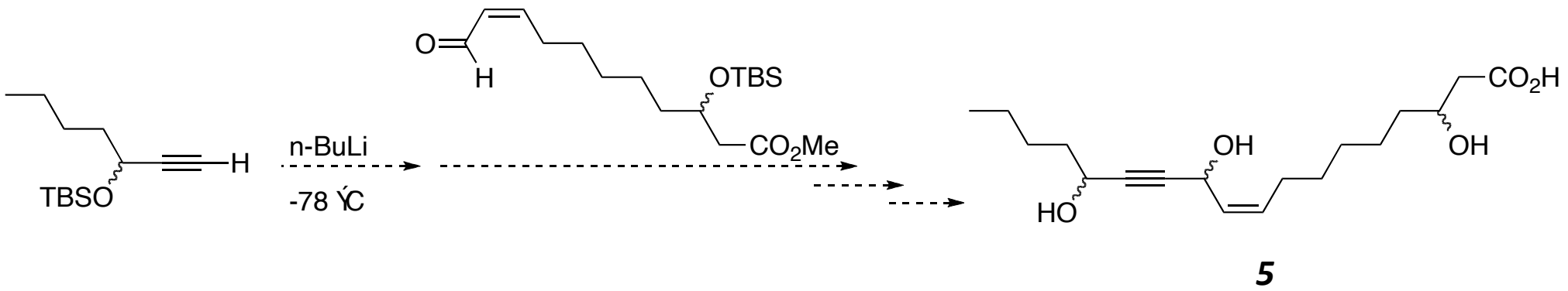
- Foreseen problems with the last step, which is similar to a step in my synthesis
- From the alkyne to the cis-alkene, there are problems with the alkene isomerizing



# Synopsis of Previous Work

Future work of Galllicynoic Acid 5

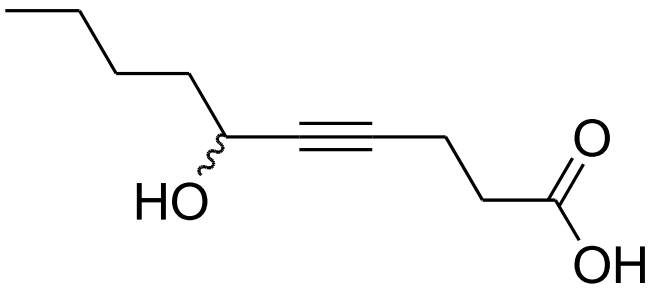
- If the problem of the alkene isomerizing is overcome, then the last step to get to ***5*** would be attempted



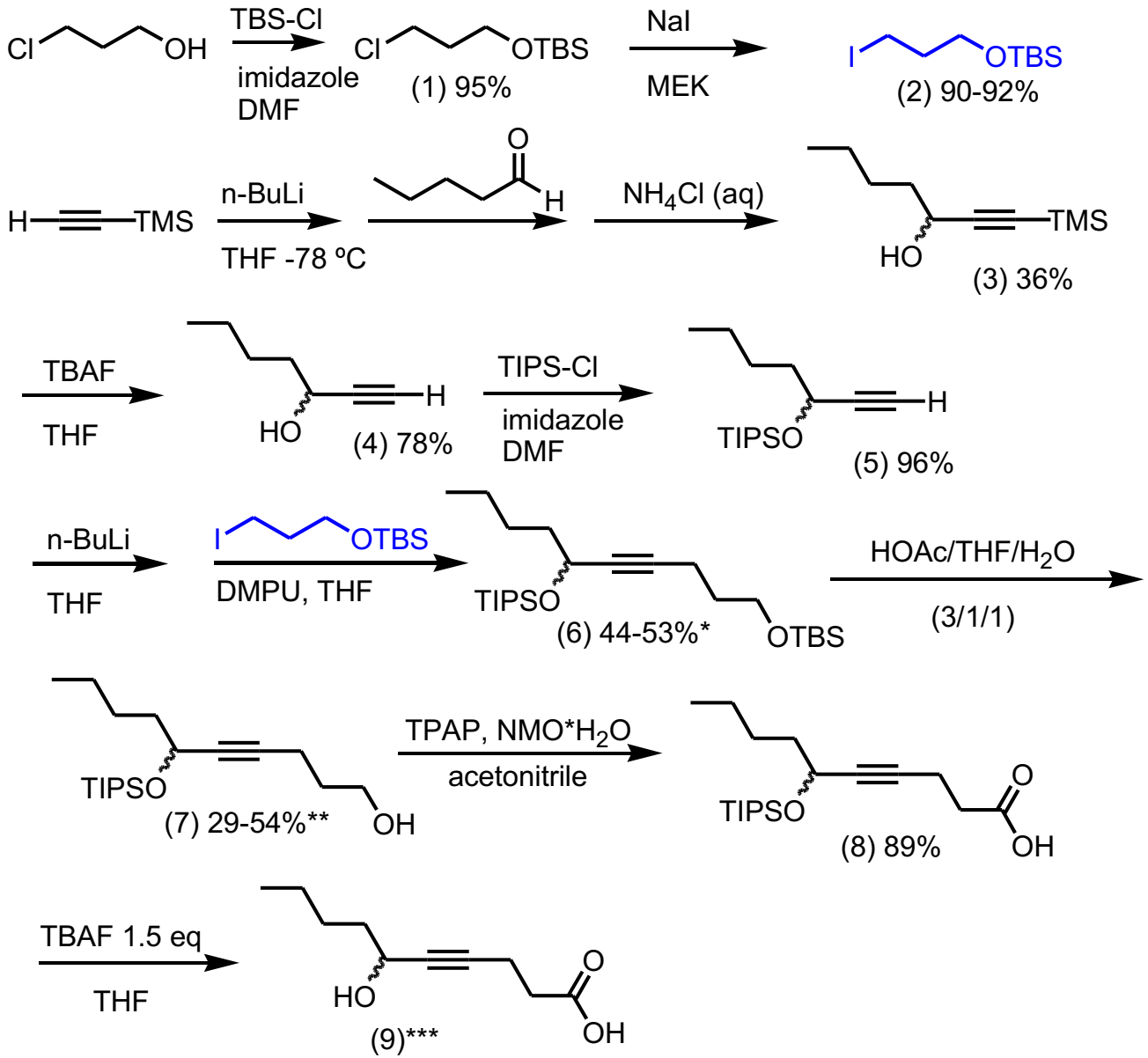

***5***

# Synopsis of Previous Work

Mary West's synthesis of Gallicynoic Acid 9

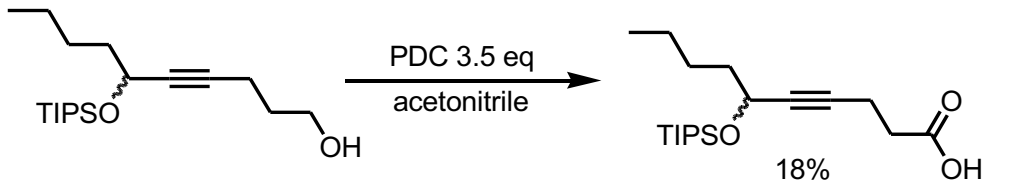


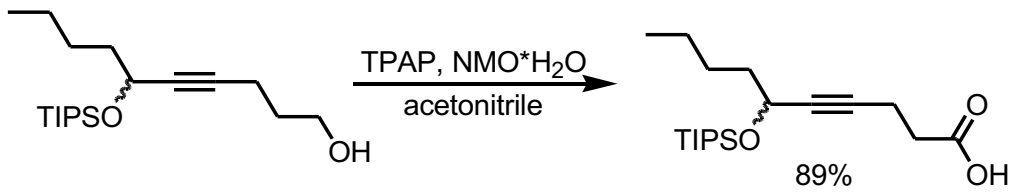

***9***



# Synopsis of Previous Work

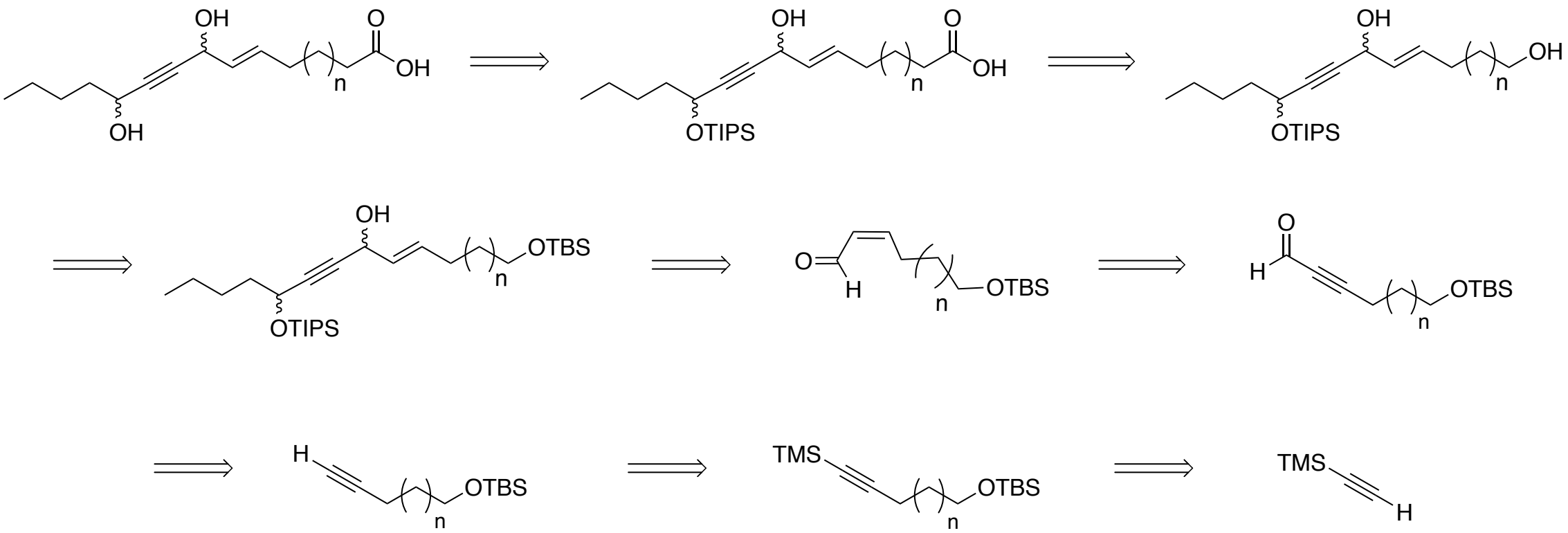
- Focused on the oxidation of the primary alcohol and optimizing this step within the synthesis



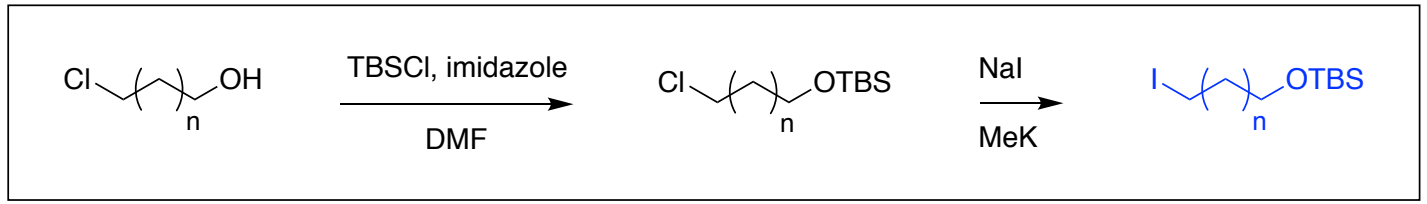



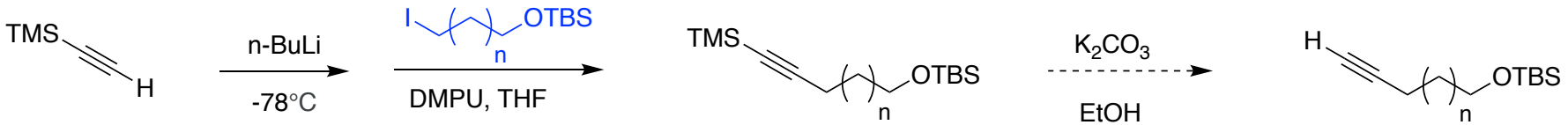

- Pure product of Gallicynoic Acid 9 was never isolated
- Crude NMR showed evidence of product, but very little product led to difficulty with purification

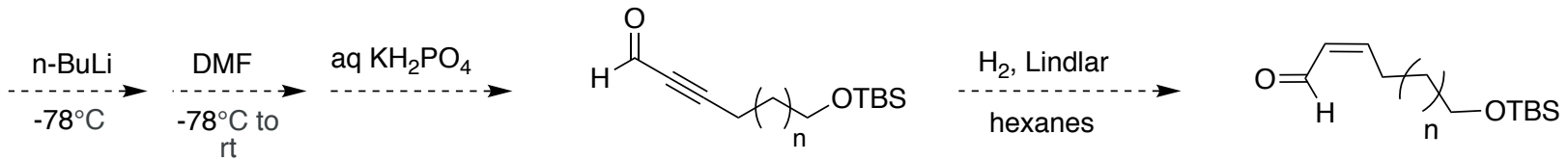
# Retrosynthetic Scheme

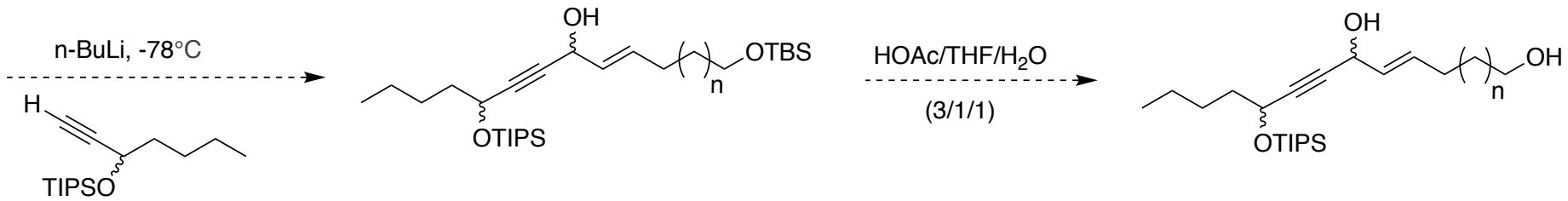


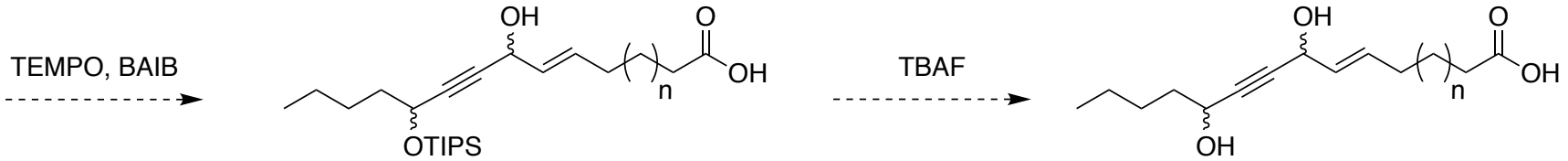
# Proposed Synthesis



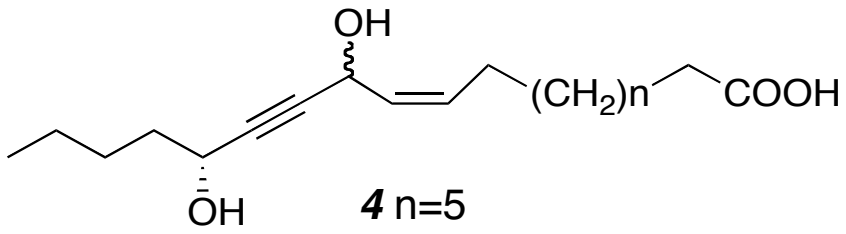



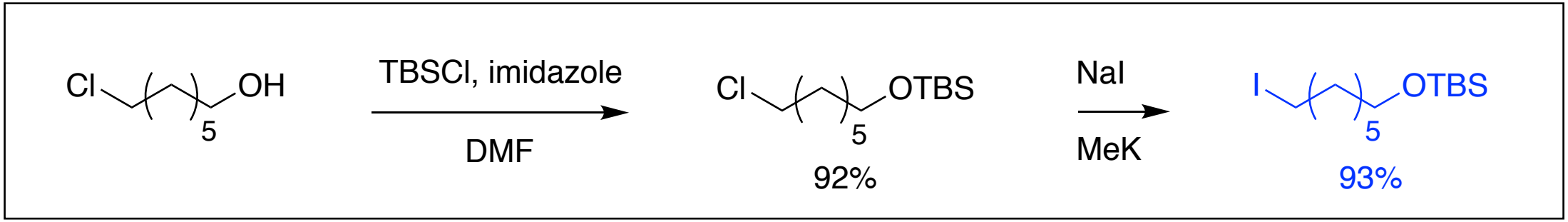

***1*** n=1
***2*** n=2
***3*** n=3
***4*** n=5

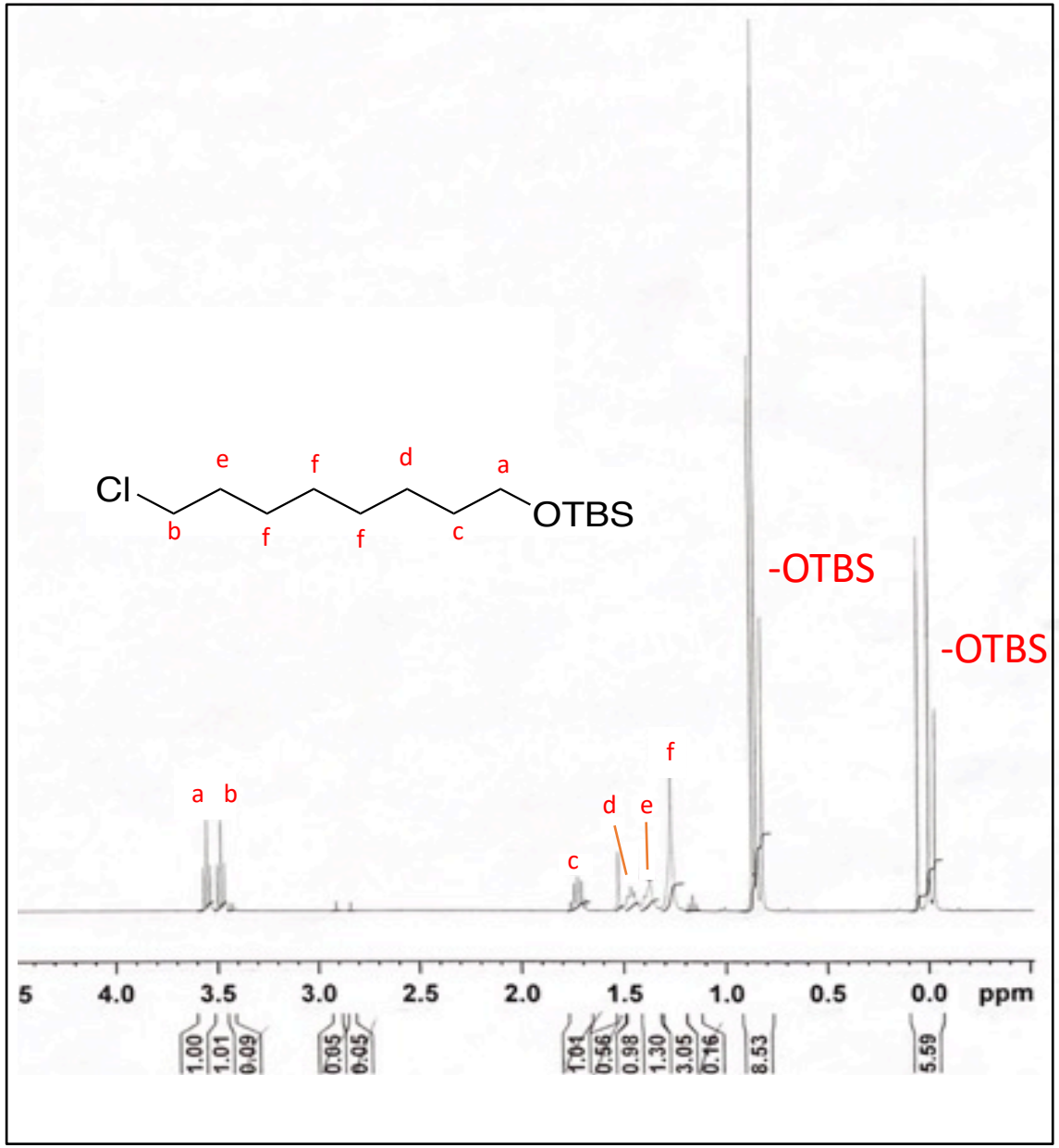
# Formation of Iodide Intermediate

Target molecule:




***4*** n=5




Cl
e
f
d
a
b
f
f
c
OTBS
-OTBS
-OTBS
a b
c
d
e
f
5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.01
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0.05
0.05
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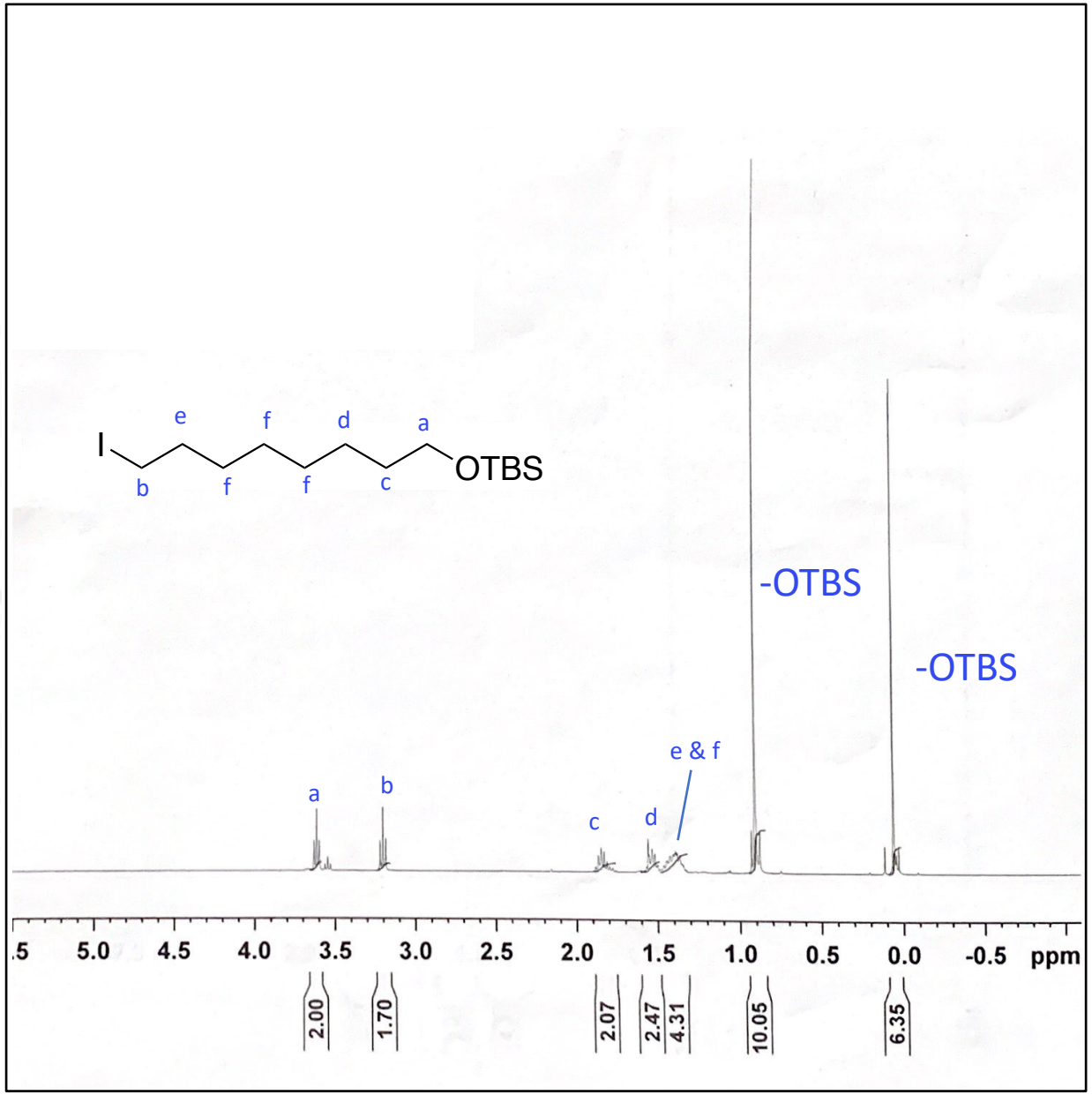
1.30
3.05
0.16
8.53
5.59


I
e
f
d
a
b
f
f
c
OTBS
-OTBS
-OTBS
a
b
c
d
e & f
.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
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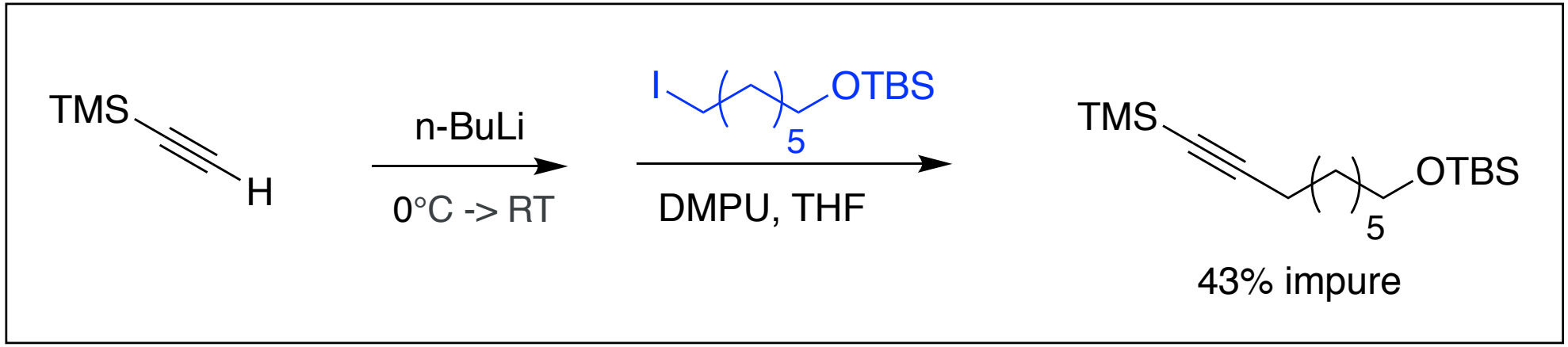
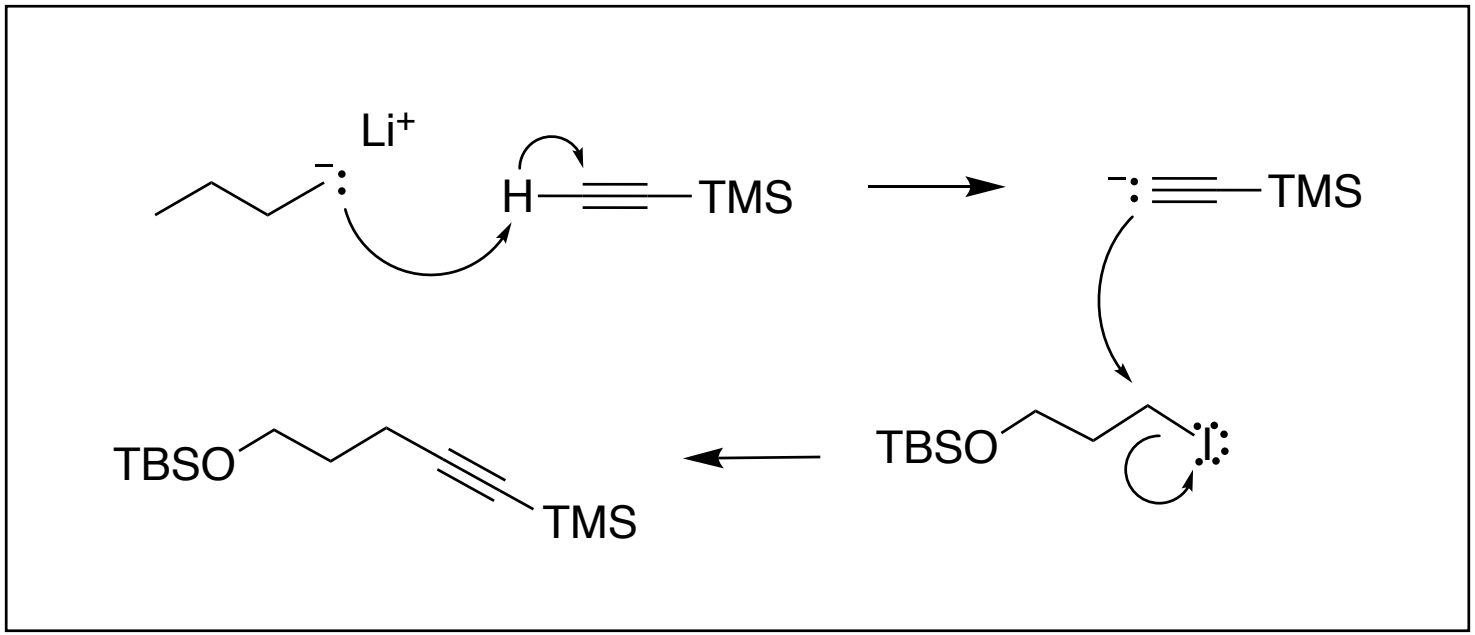
2.07
2.47
4.31
10.05
6.35

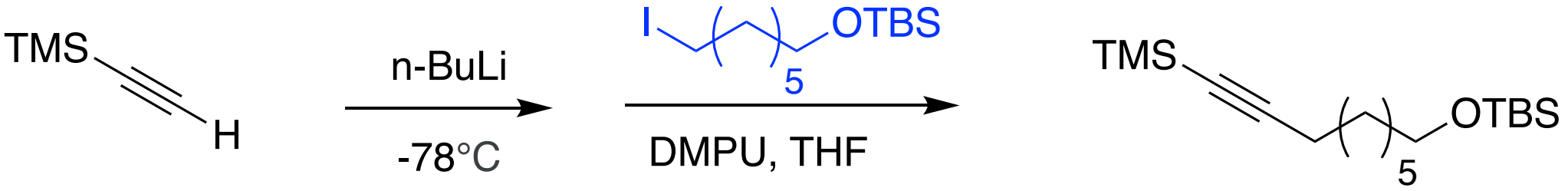
# Alkylation Step



# *n*-BuLi Mechanism

- This alkylation step is significant and was the most problematic step
- In literature, a straightforward $S_N2$ reaction
- Basic acetylides lead to E2 side products

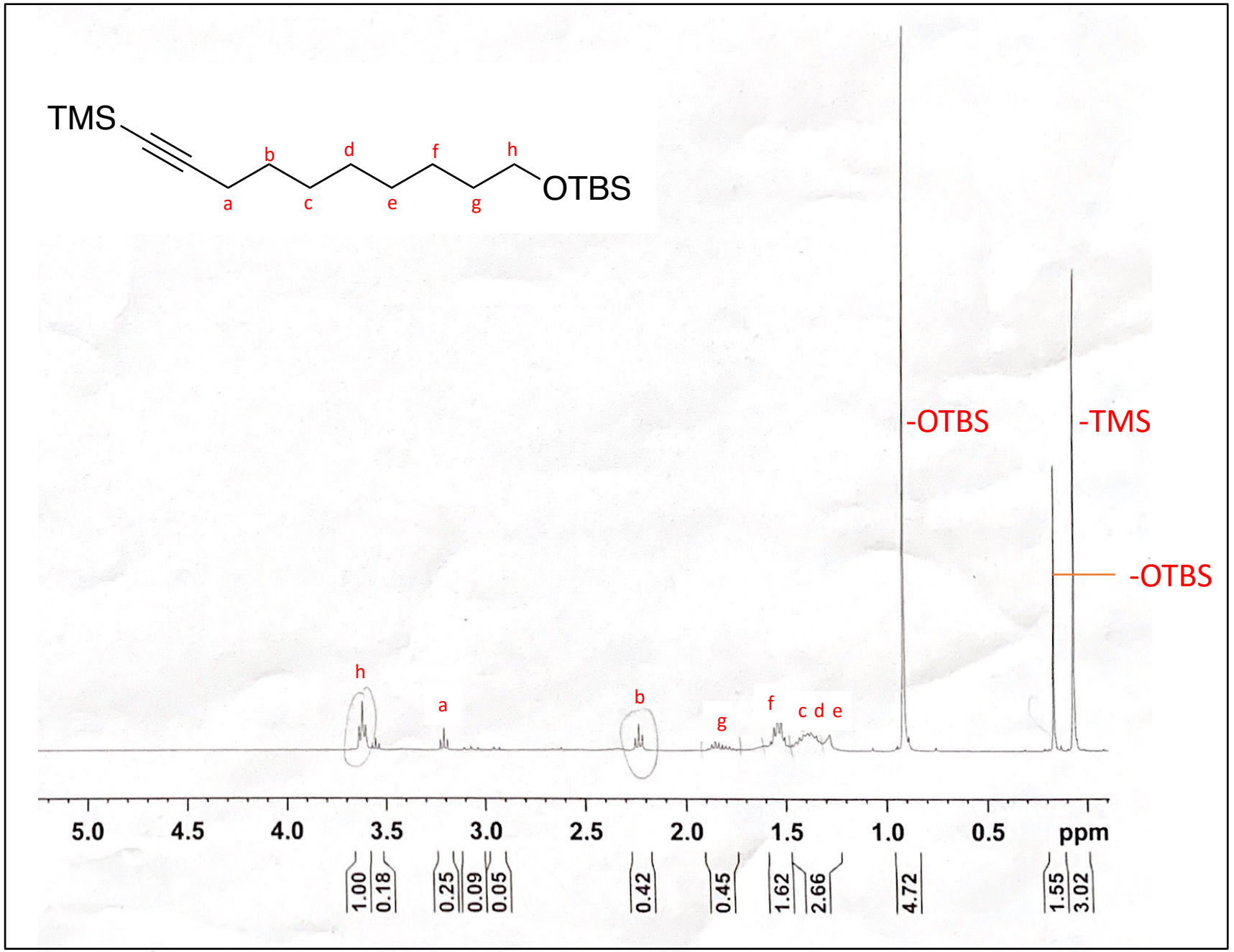





| Aprotic Solvent | Temperature | Yield |
|---|---|---|
| DMPU | -78°C | - |
| DMPU | 0°C → RT | 43% impure |

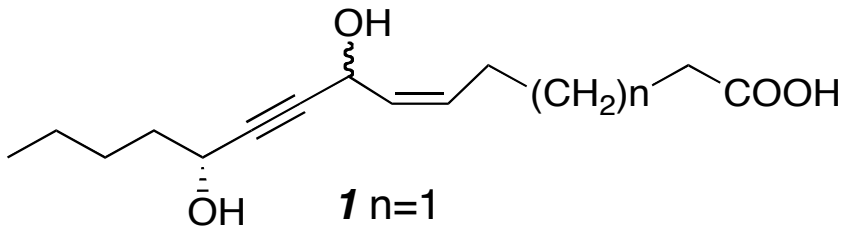
- Product desilylated on the column during the purification process
- Need to dope column with $Et_3N$

Crude $^{1}$H NMR


TMS
a
b
c
d
e
f
g
h
OTBS
-OTBS
-TMS
-OTBS
h
a
b
g
f
c d e
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.18
0.25
0.09
0.05
0.42
0.45
1.62
2.66
4.72
1.55
3.02

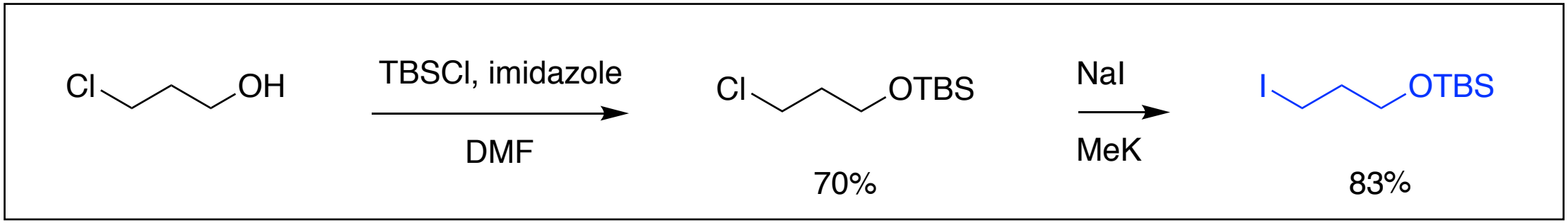
# Formation of Iodide Intermediate

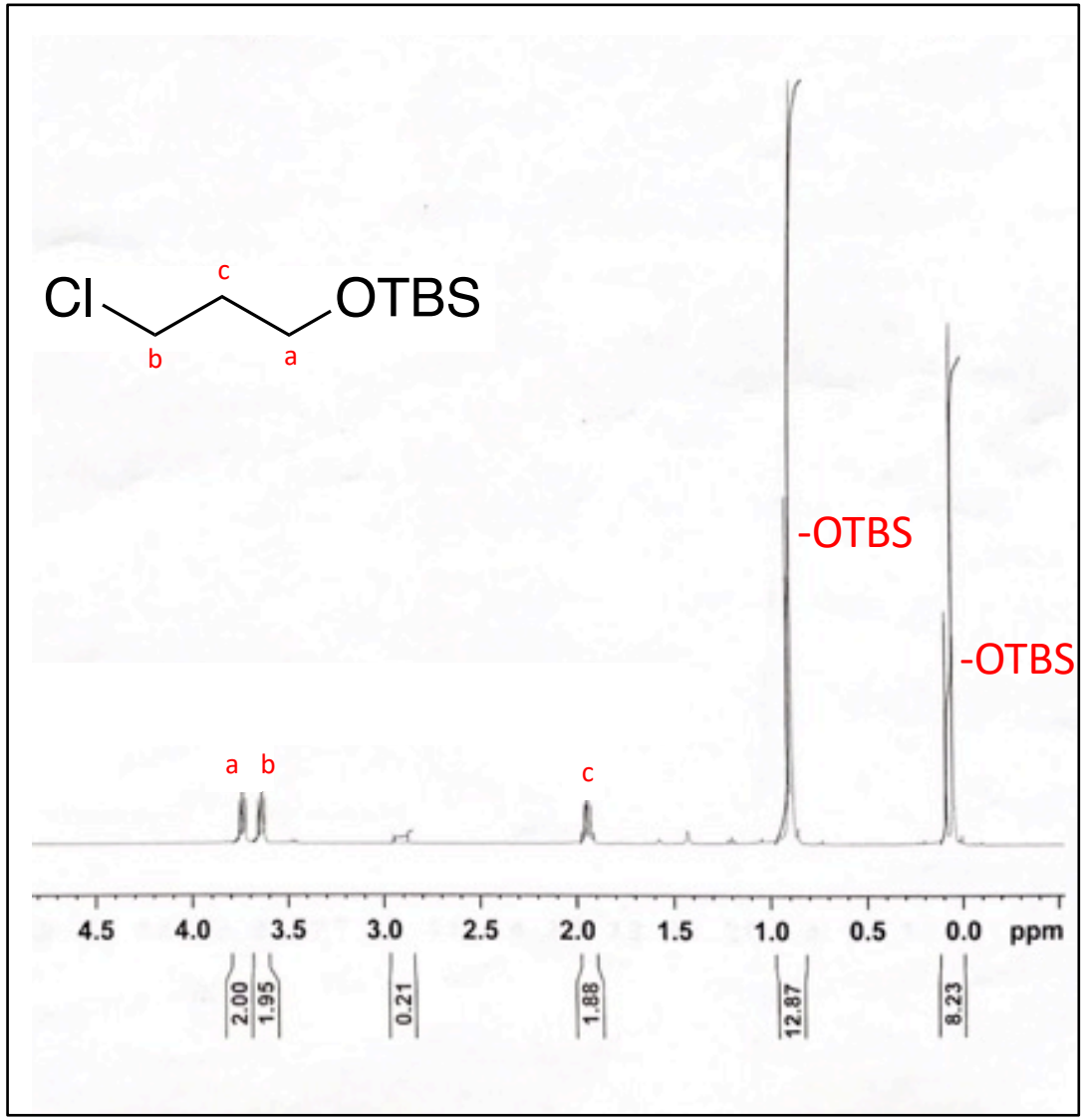
Target molecule:




***1*** n=1

*Changed the original target molecule to a smaller carbon chain to begin with




Cl
c
b
a
OTBS
-OTBS
-OTBS
a
b
c
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3.5
3.0
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0.0
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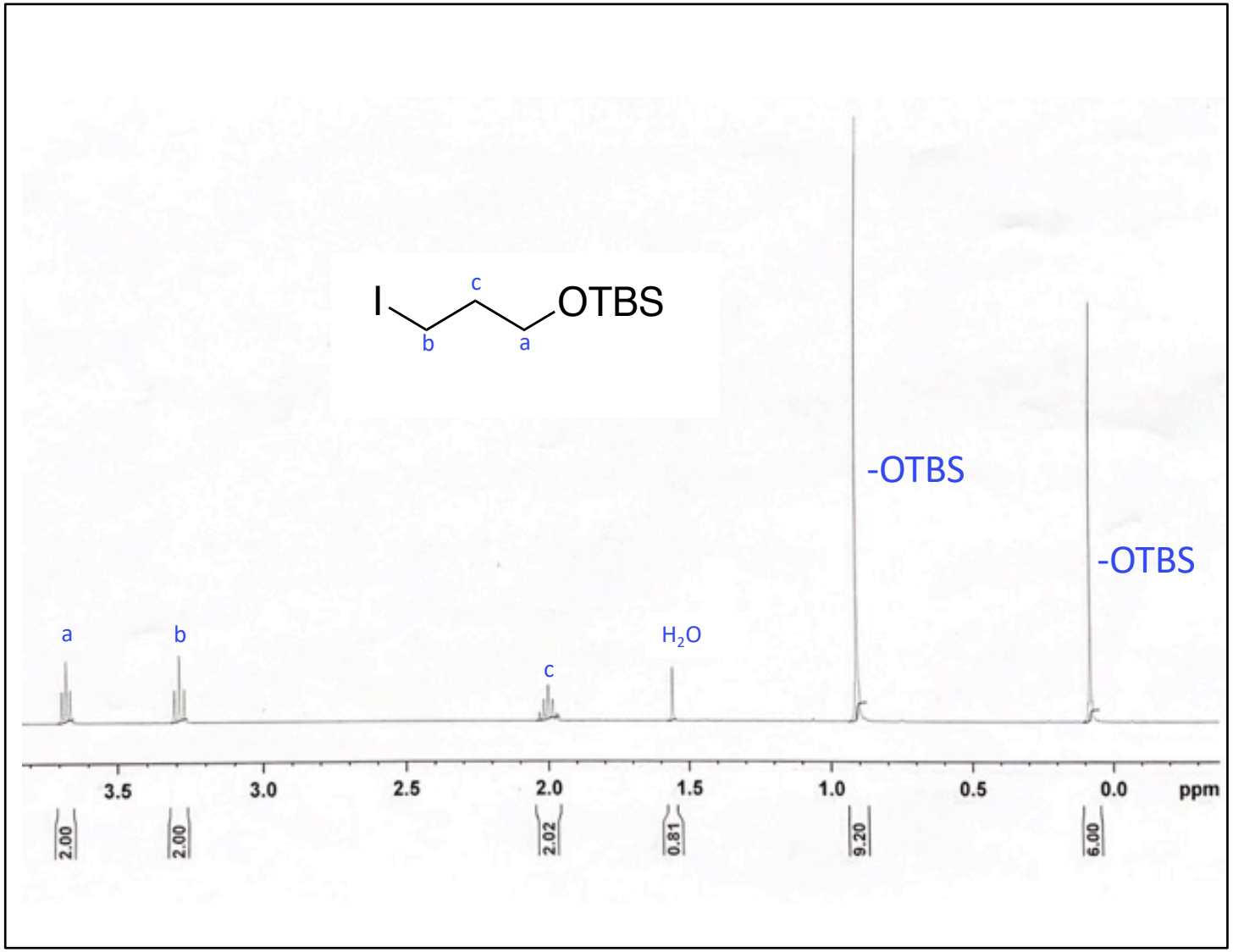
1.88
12.87
8.23


I
c
b
a
OTBS
-OTBS
-OTBS
a
b
c
$H_2O$
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3.0
2.5
2.0
1.5
1.0
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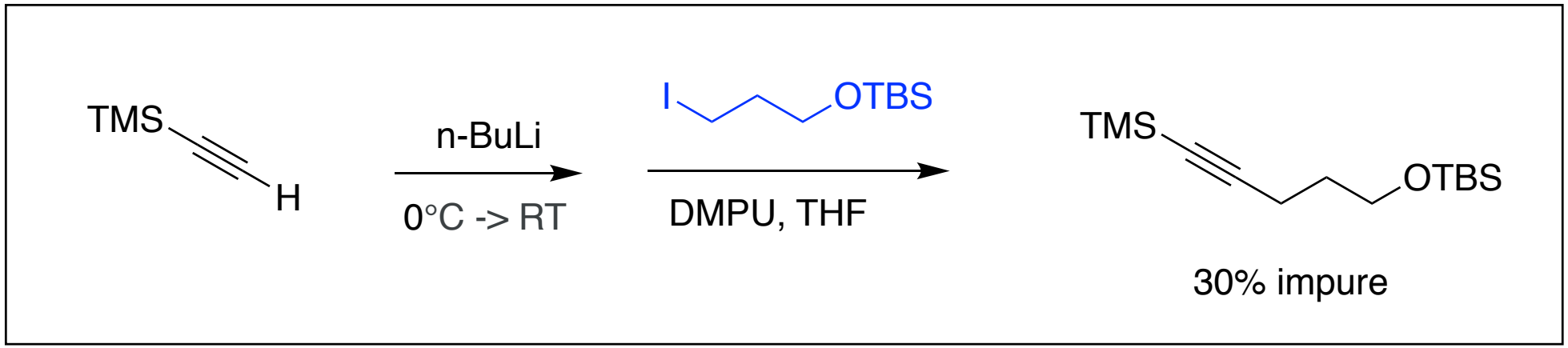
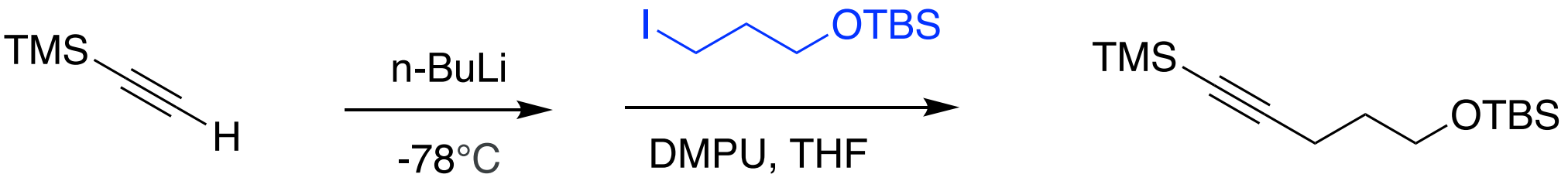
0.0
ppm
2.00
2.00
2.02
0.81
9.20
6.00

# Alkylation Step



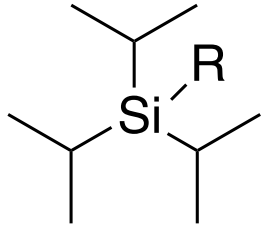



| Aprotic Solvent | Temperature | Yield |
|---|---|---|
| DMPU | 0°C → RT | 30% impure |
| TMEDA | 0°C → -20°C | - |
| HMPA | 0°C → RT | 14% impure |

- Encountered the same problems as before during the purification process

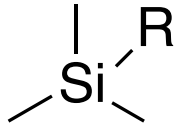
# Alternate alkyne

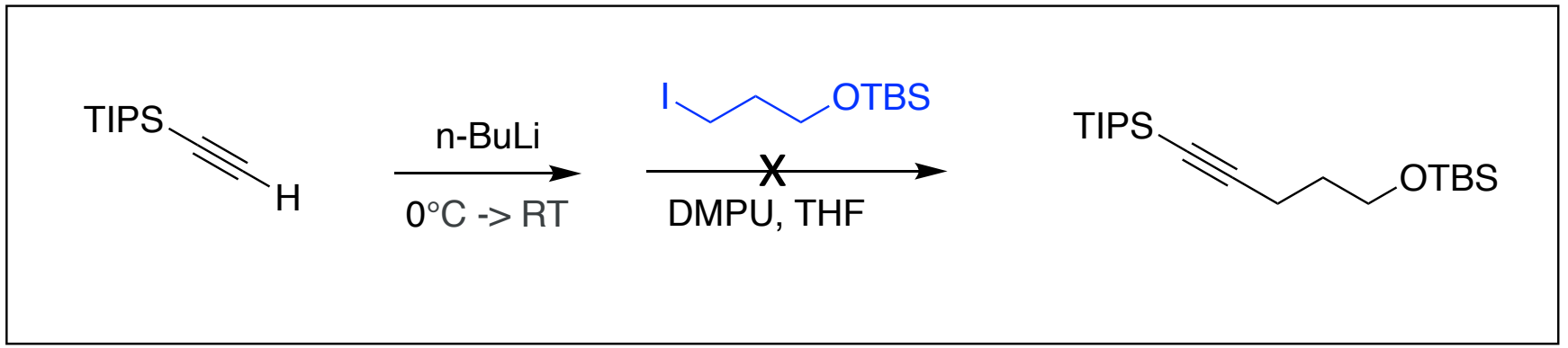
Triisopropylsilyl, TIPS




Vs.

Trimethylsilyl, TMS

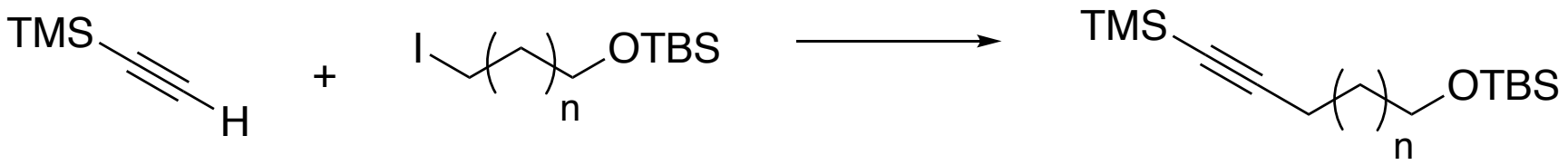


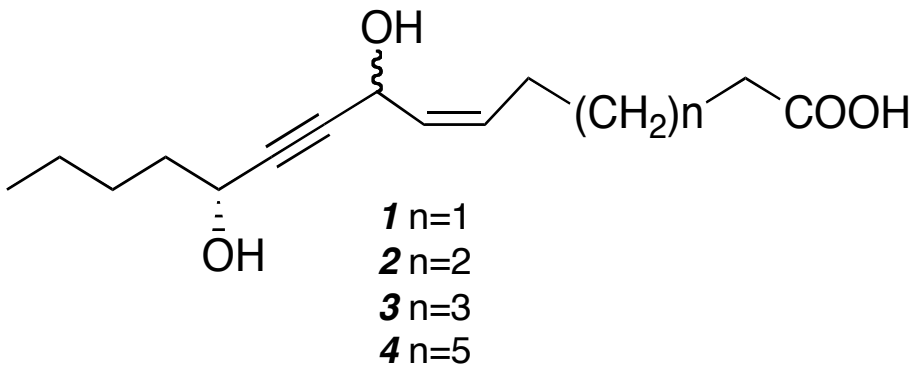

- Recovered some starting material from reaction

# Future Work

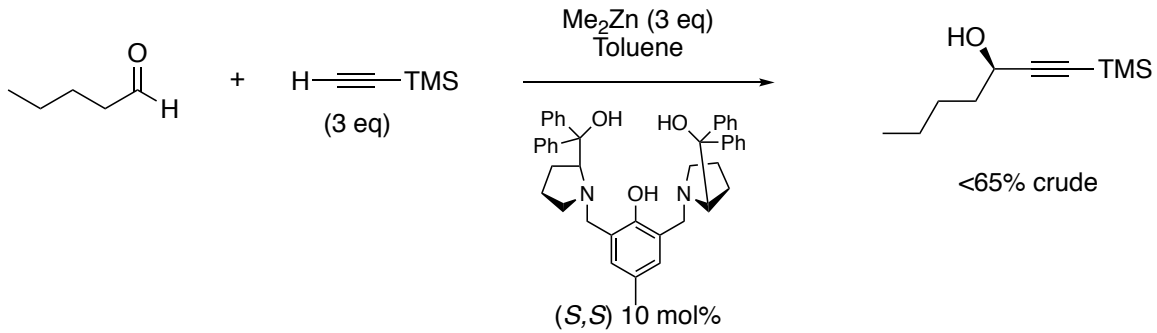
- Optimization of the alkylation step in the synthesis: crude NMR shows evidence of product, however not pure

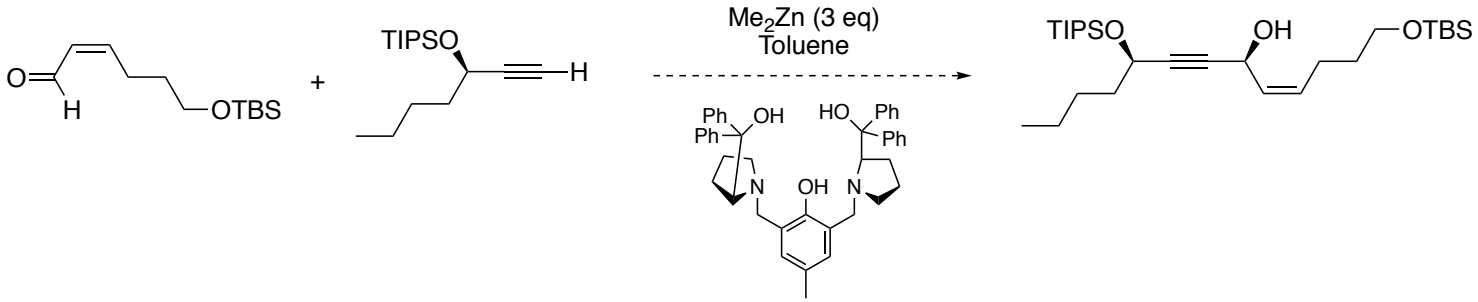



- Once the optimization of this alkylation step is achieved, the rest of the steps of the total synthesis of ***1*** & ***4*** will be pursued

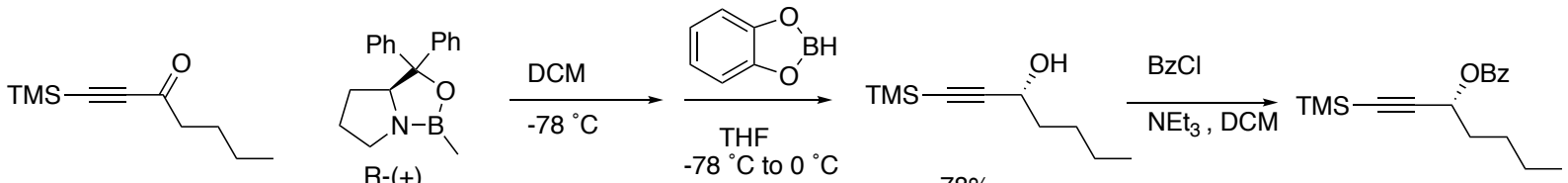


# Corey-Bakshi-Shibata (CBS) Reduction




Trost et al. *J. Am. Chem. Soc.* **2006**, *128*, 8-9




CBS Reduction

# My Future


I will be attending UCSB for graduate school this fall and will be joining Dr. Bruce Lipshutz's lab

# Acknowledgements


- Dr. David Ball
- Lab mate, Juan Caravez
- Stockroom Staff
- CSU, Chico Department of Chemistry & Biochemistry


Chico

*Today Decides Tomorrow*