# A Three-Step Synthesis of an Alkyne Containing Farnesyl Derivative

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# Three Step Synthesis of an Alkyne Containing Farnesyl Derivative

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## Abstract

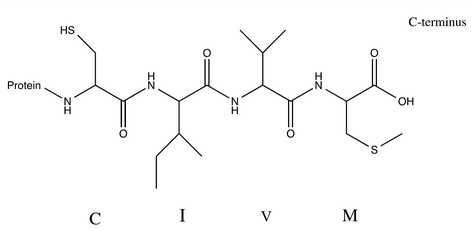
Farnesylation is a key protein modification for cellular signaling that is unregulated in cancer patients. The goal here is to synthesize an alkyne-containing farnesyl mimic that will allow for the targeting of farnesylated proteins. First, farnesol was THP protected using dihydropyran and PPTs. The THP protected farnesol was then oxidized using $SeO_2$ and t-Bu-OOH and purified using column chromatography. The resulting alcohol was then converted to an alkyne containing ether upon treatment with NaH and $BrCH_2CH_2CCH$. The resulting alkyne has more carbons than previously synthesized alkyne substrates. This will allow for further study of the relationship between farnesylation and length of isoprenoids.

## Introduction

Farnesylation is a type of protein prenylation, which is a posttranslational modification involving covalent addition of farnesyl isoprenoids to cysteine residues at or near the C-terminus of proteins. These farnesylated proteins (ex. Ras proteins) possess a CaaX motif, which is more often prenylated in cancer patients. The attachment of the hydrophobic prenyl groups can anchor proteins to the intracellular domain creating protein-protein interactions and signaling pathways. We are creating a non-natural farnesyl mimic to study the process of farnesylation.

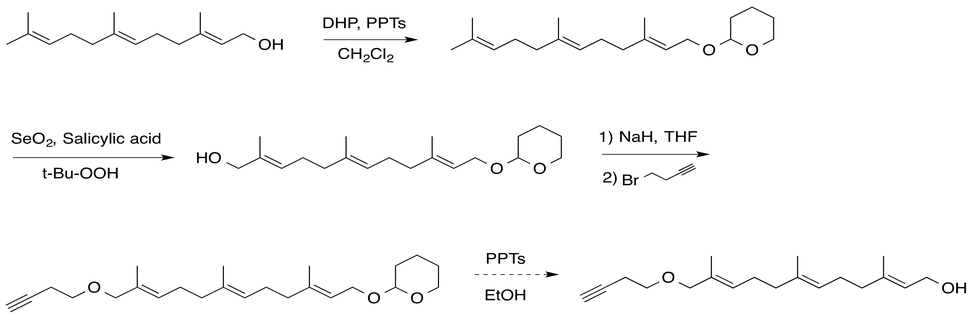
In order to produce an alkyne-containing farnesyl mimic that will allow for the targeting of farnesylated proteins, a three step synthesis was followed. First, a protecting group was added to farnesol. Farnesol was protected with THP using dihydropyran and PPTs, so that the alcohol would not react during the next step. If the alcohol had not been protected, then two different alcohols with the same reactivity would have been produced in the second step. Second, the THP protected farnesol was oxidized using $SeO_2$ and t-Bu-OOH and purified using column chromatography. Third, the resulting alcohol was then converted, using the common method of Williamson-Ether Synthesis, to an alkyne containing an ether with NaH and $BrCH_2CH_2CCH$. Through NMR analysis, it was verified that the three step synthesis was successful in synthesizing an alkyne-containing farnesyl mimic.

## Background




Farnesyl isoprenoids prenylate to proteins ending with specific amino acid sequences known as CaaX box. C represents Cysteine, A represents an aliphatic amino acid, and X represents a specific amino acid that controls the length of the isoprenoid. Shown above is the CaaX box of a Ras protein which is often prenylated and associated with cancer. The amino acids in this sequence are cysteine, isoleucine, valine, and methionine.

## Synthetic Scheme




## TLC Plates and NMR Data

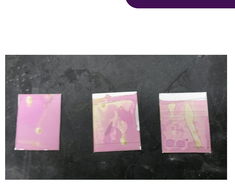


Figure 1. TLC of step 1 run in three different solvents

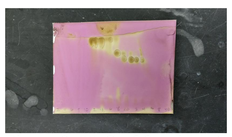


Figure 2. TLC of fractions 1-30 after synthesis of alcohol

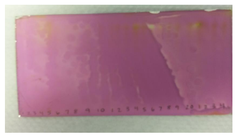


Figure 3. TLC of fractions 1-24 of ether separation

Figure 4. TLC of vials 25-48 of ether separation

Figure 5. TLC of reaction progress from alcohol to ether

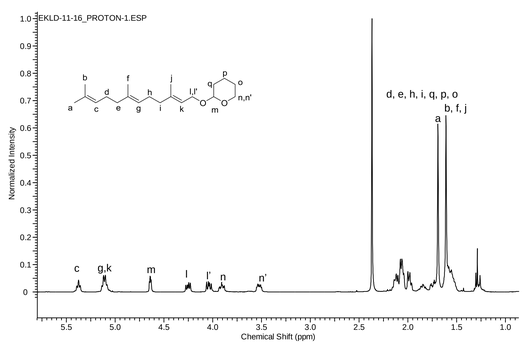



Figure 6. NMR of THP-protected farnesol

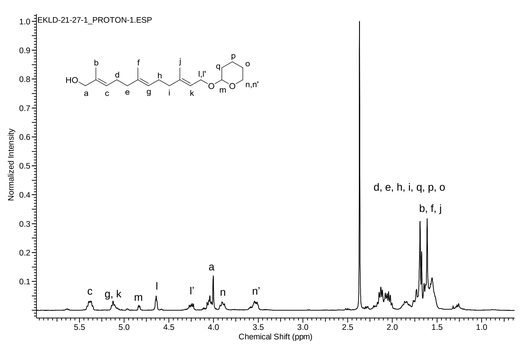



Figure 7. NMR of alcohol

## Green Chemistry

Green chemistry is a method in making chemical reactions safer, by using different reaction schemes or using safer, less harmful chemicals. Green chemistry can also be used to make a reaction less expensive. In the synthesis of farnesyl transferase mimics, t-Bu-OOH is used. t-Bu-OOH can cause genetic defects, alongside being flammable, toxic, and an environmental hazard. t-Bu-OOH could possibly be replaced with solvents that are similar in chemical makeup, such as Hydroperoxide 1,1-dimethylethyl, or, Hydroperoxide.

| Comparison Parameters | Hazards | Cost |
|---|---|---|
| 70% t-Bu-OOH | Flammable, harmful, toxic, environmental hazard, can cause genetic defects | $1.23/mL |
| Hydroperoxide 1,1-dimethylethyl | Flammable, acute toxicity, corrosive | $1.23/mL |
| Hydroperoxide-*d* | Acute toxicity, corrosive, flammable | $7.62/mL |

## Results/Discussion/Conclusion

An alkyne containing a farnesyl derivative was created in a three-step synthesis to help understand the process of farnesylation. At the end of each step of synthesis, the product was analyzed by TLC to monitor completion. For step two the oxidized product was successfully purified by column chromatography. Only vials containing purified alcohol were combined and analyzed. NMR was used to verify final product purity. Through labeling NMR peaks, it can be concluded that this farnesyl derivative was successfully created. Future research will lead to the synthesis of longer, more complex farnesyl derivatives and their role in cancer growth and progression.

## Future Directions

- Improve purity of product
- Green reaction with t-Bu-OOH replacements
- Farnesylation in living cells

## References

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## Acknowledgements

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