Synthesis and Evaluation of Alkyne Contaning Isoprenoid Analogue

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Abstract

Protein prenylation is a lipid post-translational modification in which either a 15-carbon farnesyl or a 20-carbon geranylgeranyl isoprenoid moiety is linked to a specific cysteine residue within a protein. Two enzymes, farnesyltransferase or geranylgeranyltransferase facilitates prenylation. Two percent of proteins in the human genome are prenylated, among which include Ras and Rho proteins that affect cellular growth and regulation. Overexpression of prenylated proteins have been related to diseases including cancer, Alzheimer's, fungal infections and malaria. Moreover, 30% of all reported cancers are related to mutation within K-Ras proteins (Bos et. al, 1991). Due to the fact that many prenylated proteins gain their active function after being post-transnationally modified, the study of controlling these modifications remains important. There have been improvements on this subject over the last two-decades, however, there is still a need to investigate how prenylation regulates the cellular function and how it's catalytic activity can be used as a tool to explore other cellular functions.

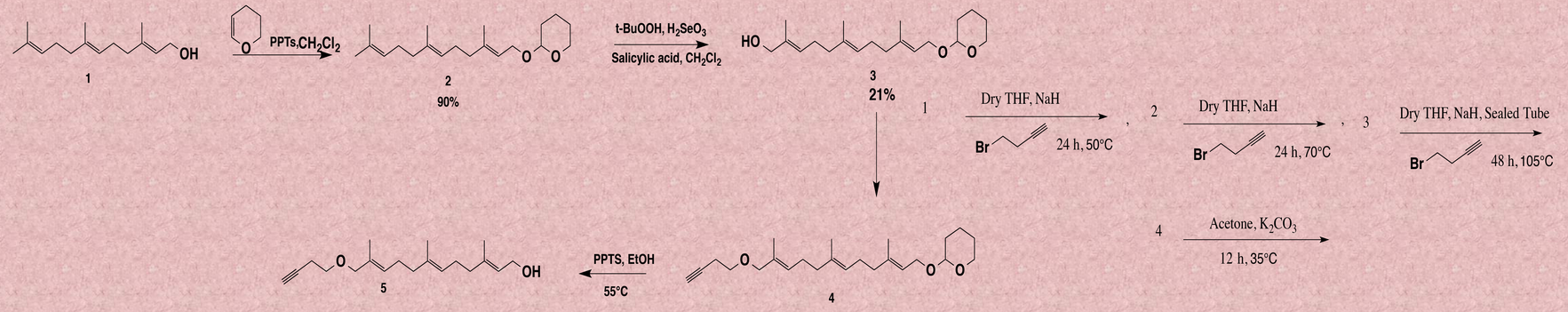
As to date, the Distefano lab has described several different analogues that act as substrates for farnesyltransferase. Using farnesyltransferase as a tool, their lab has been able to append different functionalities to proteins through their isoprenoid linkage including alkyne, azide, hydrazines, benzophenone, DTAFP, diazirine. With these functionalized proteins, they study isoprenoid-binding sites through photo-crosslinking and append chemical reporters to the prenylome through orthogonal chemistry unique to the click reaction and oxime chemistry.

To examine the effectiveness of alkyne containing isoprenoid analogues, Hela cells were treated with them. In 2007, Distefeno group reported the synthesis of **6**, and it was used the labeling of specific proteins. It was incorporated with proteins. It was the first example of successful alkyne containing analogue to be incorporated into living cells. When **6** was used for labeling, the reaction of interest went ahead successfully, however other side reaction followed, and the source remains unknown.

Goal of the Project

A new idea comes to address the source of the side reaction. Instead of using **6**, using **5** was proposed. The difference between **5** & **6** is that, propargyl bromide was used in the synthesis of **5**, while 4-bromobut-1-yne will be used for the synthesis of **6** as shown in scheme 1. This paper reports the attempt synthesis of **5** as shown in scheme 2.

Scheme 1: Alkyne containing Isoprenoid analogues**:**



Scheme 2: Proposed synthesis route for 5

Results and Berief Discussion

Compounds **2** & **3** has been successfully been synthesis using those reagents and staring materials shown in scheme 2. TLC plate, ^{1}H-NMR, and Mass Spec have been utilized to confirm the formation of these compounds. Several attempts has been made to synthesis compound **4**, unfortunately they have not been successful. Discussion, and experimental section for both compounds **2** & **3** have been reported in a written report. Discussion for the several attempts to make compound **4** is also including into the written report. Below is a link for the report.

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References

(1) L. V. R. Bonaga; H. C. Zhang and B. E. Maryanoff, Chem. Commun., 2004, 2394–2395
(2) Ayako Hosokawa; James W. Wollack; George Barany★ Mark D. Distefan★
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