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A Theoretical Synthesis of Manool

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Abstract

Manool is a type of compound matter which can be observed in the extract from the surface of the aerial parts of Salvia tingitana. Manool presents the most active character when it is resisting against Gram-positive bacteria. So, the synthesis of manool is necessary. Also, according to the structure, of retrosynthesis, the synthesis of Manool is feasible. A way is developed by breaking the structure into three pieces and using Diels-Alder reaction and Grignard reaction to reconnect these pieces. Here is a brief introduction of manool and the way to conduct the retrosynthesis analysis.

Keywords

Manool; Retrosynthesis; Synthesis.

1. Introduction

(4aR)-trans-5-(1,5,5,8aS-Tetramethyl-2-methylenedecahydro-1-naphththalenyl)-(3R)-methyl-1-penten-3-ol, also named as manool, is a natural product which exist in Salvia tingitana. It presents activity in the resistance against Gram-positive bacteria, and it shows inhibition character of the production and hydrolysis of ATP [1]. It could aslo modulate the oxidative stress in the rod outer segment [2]. In addition to that, manool can also be considered as the raw material for many compounds, including sclareol [3], g-bicyclohomofarnesal [4], and trans-totarol [5], etc. However, one of the natural sources of manool namely tingitana maybe extinct in North Africa [6], and the only known collection recently is from Saudi Arabia [7]. So, to artificially synthesized manool is essential. In this work, a way of synthesis of manool is developed by using retrosynthesis.

2. The retrosynthesis analysis

The structure can be broken up into three pieces. First, the carbon chain can be removed from the hexatomic ring. And the left parallel hexatomic rings can be synthesized by using Diels-Alder reaction twice. The train of thought is as the figure.1.

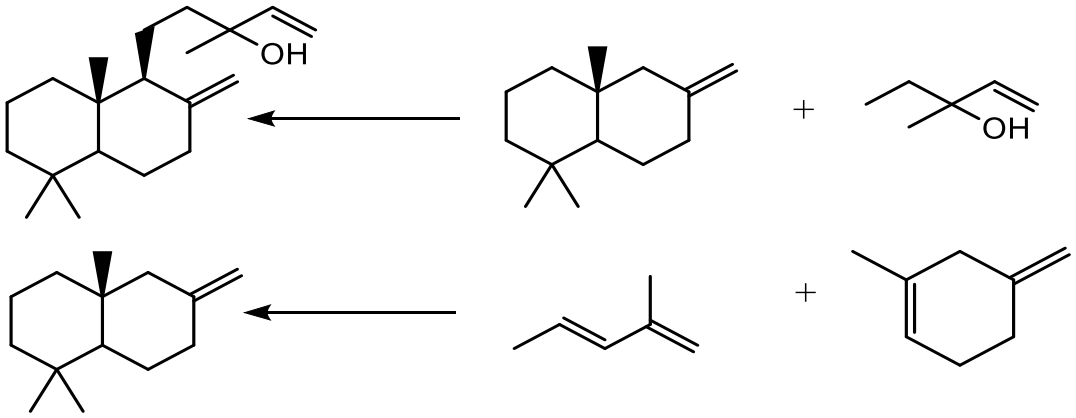

Figure.1 Retrosynthesis of Manool

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Hence, it becomes clear that if the manool needs to be successfully synthesized, one should start to work on these three carbon skeletons.

3. Synthesis of manool

Figure.2 presents the synthetic route of manool.

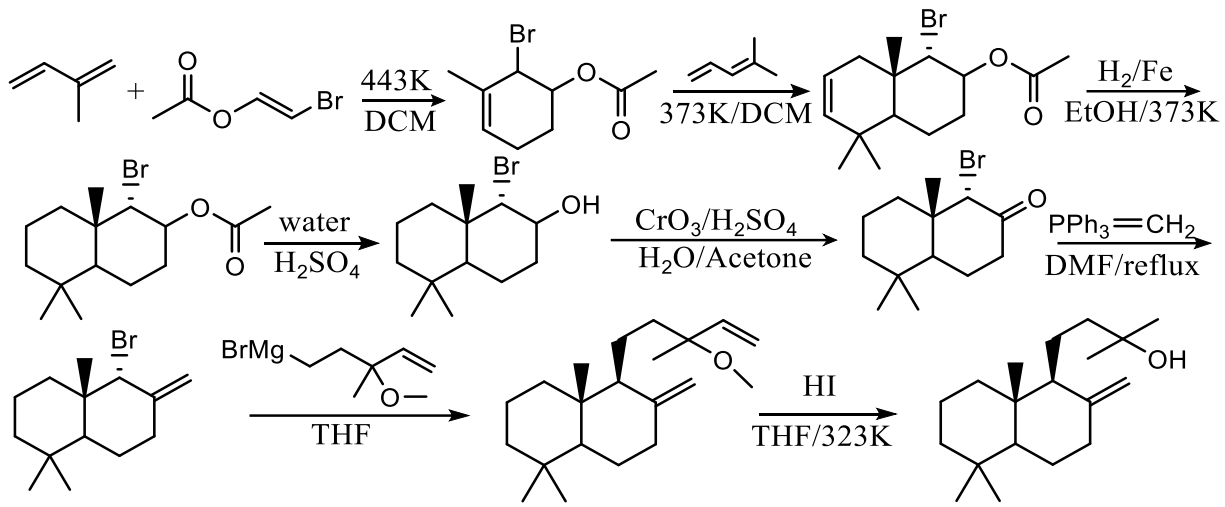

Figure.2 Synthesis of Manool

During the second application of Diels-Alder reaction, the methyl tends to connect with the side which has smaller volume. So, the methyl will react in a way that figure 2 shows. In addition to that, the bromine and the methyl will each appear in the different side of the paper thanks to the volume issue. Such spatial structure could make contributions in forming the structure when it reacts with the Grignard reagent. Since the Grignard reagent is a kind of nucleophilic substitution, and it's reactant is primary haloalkanes. Due to the Grignard reagent is a strong nucleophile, the reaction would be performed as a SN2 reaction. Therefore, the spatial configuration will change. When the replacement of bromine by the Grignard reagent happens, the Grignard reagent will be at the same side of the methyl on the alpha carbon atom.

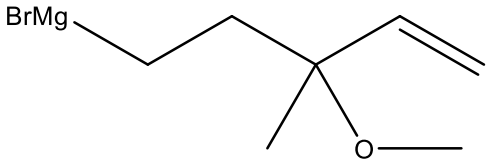

Figure.3 The Grignard reagent to be synthetized

Figure.3 shows the structure of the Grignard reagent used. And the synthesis of the Grignard reagent used is as follows.

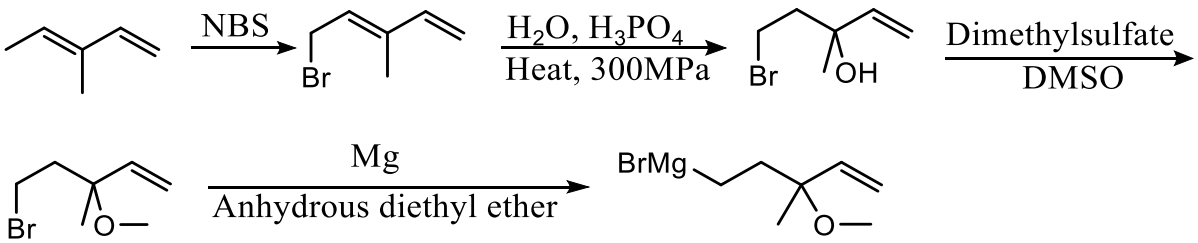

Figure.4 The synthesis of the Grignard reagent

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After the replacement of the bromine, when the reactant begin to react with water, please control the quantity of reactant so that there will be only one hydroxyl exist. When it comes to the selectivity, the 3' carbon atom can better disperse the positive charge. So, the water will connect with the 3' carbon atom, lose it's hydrogen ions and form hydroxyl.

4. Conclusion

In this work, a way of synthesis of manool is developed by using the retrosynthesis analysis. This way mainly contains Diels-Alder reaction and Grignard reaction. The SN2 and volume issue are used to control the spatial configuration. Through the synthesis, it shows high atom economy and the organic reagents are of low toxicity. Hence, the synthesis meets the requirement of green chemistry.

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