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Brief Analysis of Synthesis of Tepuazine A Based on Simple Retrosynthesis

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Abstract. Dimeric phenazine glycosides tepuazine A is a new microbial natural product found in the soil samples collected from deep Venezuelan quartz-rich caves as a kind of metabolits of 24 actinomycetes and 25 fungi, which are discovered in this soil sample. This paper provides some ideas on the chemical synthesis of dimeric phenazine glycosides tepuazine A based on simple analysis using retrosynthesis, in which suggest some possible ways to artificially synthesis the compound. With these, two ways to form an essential bond between two sub-units of the molecule is discussed. When there are more relative research about tepuazine A, this paper may help the further research on dimeric phenazine glycosides tepuazine A or practical synthesis of it.

Keywords: Tepuazine A, Retrosynthesis

1. Introduction

Dimeric phenazine glycosides tepuazine A (1 in fig 1) is a rare metabolite which is hard to interpret its structure, which is isolated from Streptomyces sp. CMB-CA091 along with nine other natural products in the picture below [1].

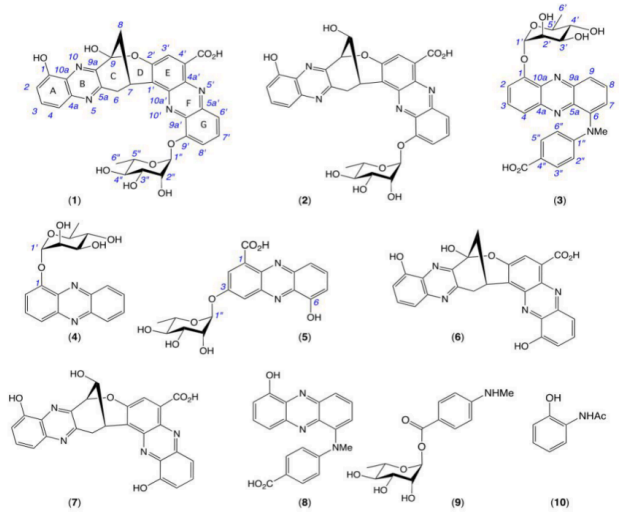

Figure 1. Natural products isolated from streptomyces sp. CMB-CA091 [1]

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Dimeric phenazine glycosides tepuazine A can be recognized as a compound which is made of two phenazine derivatives connecting with each other. This kind of dimeric structures appears in many metabolits of some natural organisms. For those metabolits which have a dimeric structure, this structure may be the proper and rapid assembly in the cellular milieu [2]. Also, as scientists investigate more of the phenazine compounds, they were found to exhibit a broad range of biological activities, such as antibacterial, antimalarial, antitumor and antiparasitic activities [3]. Therefore, dimeric phenazine glycosides tepuazine A might also participate in some of these activities, which is valuable for further research. In this work, I tried to analyze the possible ways to synthesize Tepuazine A artificially using retrosynthesis.

2. Possible synthesize path

Dimeric phenazine glycosides tepuazine A has a complex and rare dimeric phenazine structure, as the figure 2 shows. It is formed by connecting two phenazine derivatives and a five-carbon sugar in some unknown conditions inside to bodies of these small organisms.

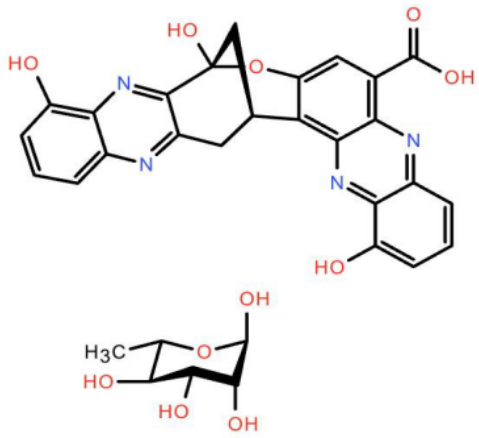

Figure 2. Tepuazine A without glycoside

2.1. Divide tepuazine A

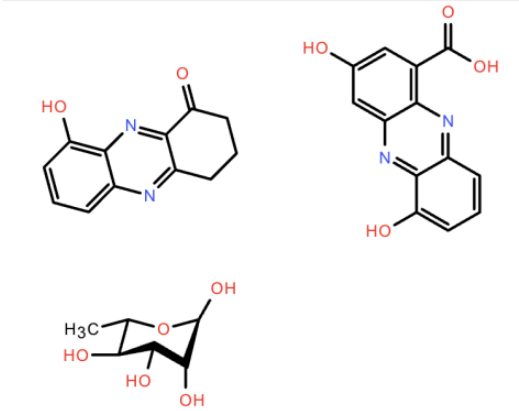

Figure 3. Retrosynthesis of tepuazine A

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To start with, the structure of Tepuazine A should be divided into different parts in order to decrement its complexity. Using retrosynthesis, the three intermediates that can be found without considering the possibility of synthesize and ways of connecting the bonds between is shown in the figure 3. These three intermediates are consist of two kinds of phenazine derivatives and a five carbon sugar.

2.2. Connecting phenazine derivatives

In the chemical synthesis of tepuazine A, the dehydration with alcohol group is probably the easiest step, which can be rule out at first.

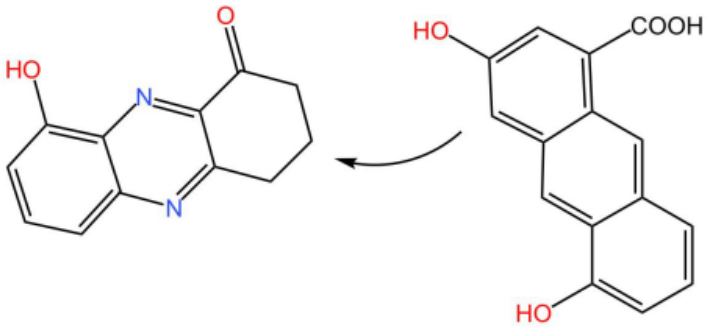

Figure 4. Phenazine derivatives bonding site

To think about the process, the last few steps before the formation of tepuazine A can be bonding the two phenazine derivatives together. This seems to be reasonable because the small organisms that synthesize tepauzine A possibly synthesized these dimeric phenazine molecules in this way [3].

Since phenazine is available, it is reasonable to start with phenazine and edit it to these phenazine derivatives following some certian steps. However, this leads to the most crucial problem about the chemical synthesis of tepuazine A - how to connect the carbon carbon bond of the two phenazine derivatives.

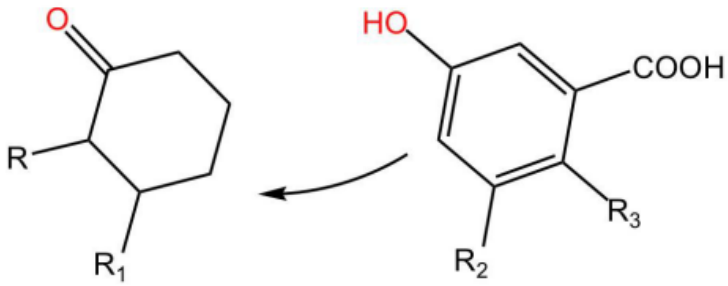

Figure 5. Aromatic bonding site

As it is shown in the figure 5, the structure becomes clearer when excluding the further parts of the molecules. Now they look like two aromatic derivatives and the goal is biphenyl structure at the accurate site. In an artificial synthesis, there are many to acquire biphenyl, such as Friedel-Crafts reaction, Suzuki reaction, Ullmann reaction, e.g. For this situation, Ullmann reaction might be a good choice, considering that the bond is possibly directly connected in this reaction, and might not

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trigger other unrealized reactions to happen. Still, the true mechanism of this reaction remains unclear about which form of the Cu catalyzes these kinds of reactions [4].

2.3. Ullmann reaction

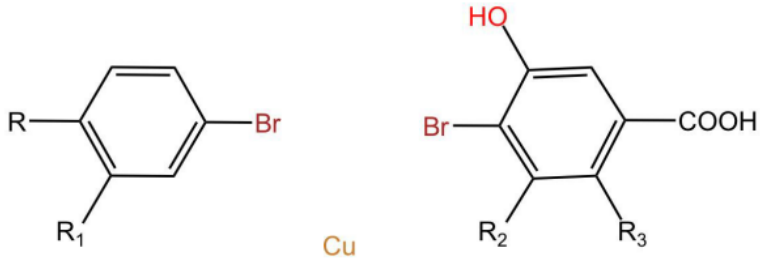

Figure 6. Using ullmann reaction

In order to use Ullmann reaction, the two sub-parts need to add on two bromines on the reaction sites and use overdosed quantity of Cu powder and heat the reagent to a high temperature. However, these two phenazine derivatives have many functional groups, and one even has the five-carbon sugar connecting with. It will make the products more random and unpredictable when they are heated. The adding of bromine on the phenazine derivatives can also connect on some places other than the target sites, which made the situation even worse. These can be solved partially in another approach to the final product.

3. Another approach

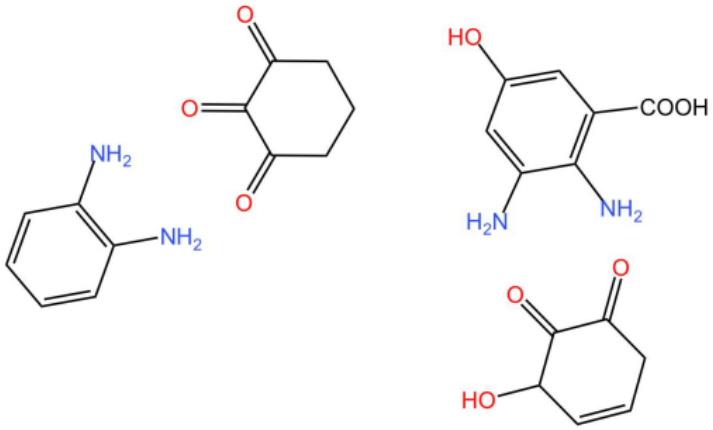

Figure 7. Another approach

Thinking about how the small organisms form these molecules agian, the way of connecting the two phenazine derivatives may be restricted by the physical or chemical conditions in their body. Therefore, the artificial synthesize of tepuazine A can have a different approach. In this approach, the bond between the two aromatic derivatives formed many steps before tepuazine A appear. The two phenazine derivatives are not acquired by directly editing a finished product of phenazine, but synthesized as one of the steps. The 1,2-diaminobenzene can react with these adjacent carbon oxygen double bonds in high temperature to form phenazine. This might avoid the problem caused by heating the products. On the other hand, these aromatic compounds are available. As in the figure

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16 shows, the reaction can then be changed to use Ullmann reaction to connect two aromatic rings first. The other two rings can be connected one by one. By allowing them to have their connecting sites have different functional groups, this also reduced the chance that the two rings connect in the wrong place to form phenazines [5].

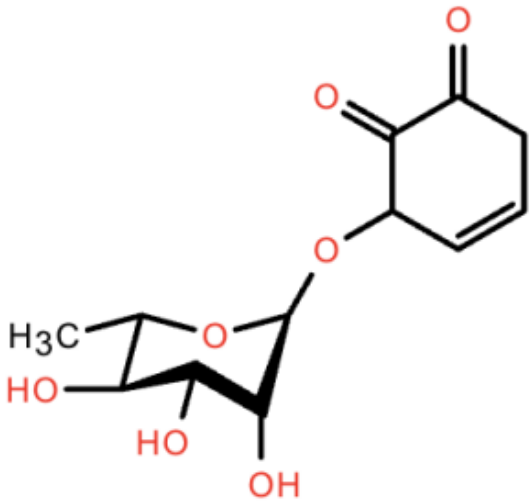

Figure 8. Connect sugar beforehand

What's more, this approach can also cease another disadvantage of the previous one. As we can see in Figure 2,3, there are three alcohol groups and a carboxyl group distributed around the two separate phenazines. In order to connect the five-carbon sugar directly at the lowest one alcohol group, however, the sugar might then dehydrate with these other groups because one alcohol group is similar to the target one and the carboxyl group is even more attracting then these two alcohol groups. Now, the dehydration can be made long before forming the dimeric phenazine, and be connected as the figure 7 shows.

4. Conclusion

Dimeric phenazine glycosides tepuazine A is a rare kind of molecule which was found from some microorganisms in the quartz cave. By using retrosynthesis, this paper suggests some possible ways to synthesize the molecule tepuazine A. Since these dimeric phenazine molecules were rare to find in nature and phenazines were possible to bring beneficial effect to human kinds in a vast aspect, tepuazine A might have make some use in the future. The approaches of synthesizing Tepuazine A can then be useful in a sense.

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