Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/44/20240956

The total synthesis of Wulfenioidin F

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Abstract. Zika virus, an RNA virus that can cause severe damage to the human body, has long lacked an effective drug. Scientists have discovered recently that Wulfenioidin, a plant distributed in southern China, contains a compound in its root that holds the potential to become an anti-Zika drug. Through extraction, multiple kinds of Wulfenioidin were discovered and their structures were characterized through various spectroscopic methods. However, there isn't a total synthesis pathway for Wulfenioidin. This essay focuses on Wulfenioidin F and provides a full synthesis pathway for the molecule. The route begins with the synthesis of two fragments 6-(2-bromo-6-methylphenyl)-6-methoxy-2-methylhexan-2-ol and 5-(propan-2-yl)-3-(I^5-diazynylidene)-3,4-dihydro-2H-pyran-2,4-dione, which then undergo a convergent coupling to form an eight-carbon ring. An intermolecular Diels-Alder reaction combines the benzyne and pyrone together, forming the final product and completing the total synthesis.

Keywords: Wulfenioidin F, Zika virus, synthesis

1. Introduction

Zika virus (ZIKV) is a positive-strand RNA flavivirus mainly transmitted through mosquitoes that inflicts damage upon human organs, notably affecting the nervous, cardiovascular, and reproductive systems [1]. Despite the widespread of ZIKV infection and its severeness, there are currently no appropriate drugs or preventive vaccines to cure the disease.

In recent years, however, a breakthrough in the scientific exploration of indigenous Chinese plants has uncovered a species possessing anti-Zika properties, including compounds called *Wulfenioidin* [2]. This plant, previously utilized for alleviating symptoms like coughing, edema, and arthritis, concealed an undiscovered facet of its capabilities [2].

The roots of *Wulfenioidin* plant were extracted for analysis. The structures and absolute configurations were characterized by spectroscopic methods, single crystal X-ray diffraction, and electronic circular dichroism analyses. According to the research conducted by Wen-Chao Tu, Yong-Xiang Huang and others, *Wulfenioidin F* was isolated as a colourless, oily substance and its formula is $C_{21}H_{28}O_3$ [3]. The IR spectrum exhibited typical absorptions of a hydroxyl and a benzene ring. As the five double bonds accounted for five indices of hydrogen deficiency, *Wulfenioidin F* was tricyclic.

Upon further scrutiny by scientists, *Wulfenioidin F* underwent extensive biological testing. Abundant data, including EC_{50} values, demonstrated the compound's proficiency in inhibiting viral replication,

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thereby inhibiting them from replication and protecting the host from further defection. In conclusion, *Wulfenioidin F* is qualified as one of the candidates for future research as antiviral drugs against ZIKV infection.

2. Synthesis Pathway Description

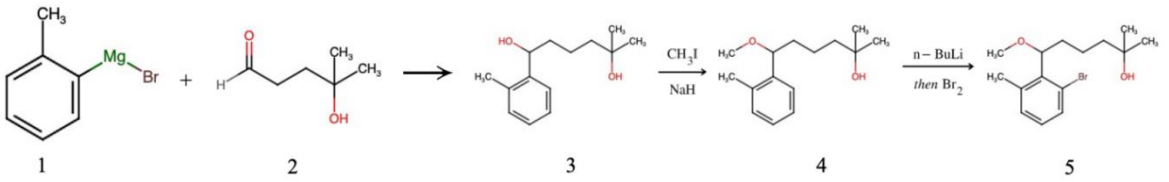

Figure 1. Preparation of 6-(2-bromo-6-methylphenyl)-6-methoxy-2-methylhexan-2-ol

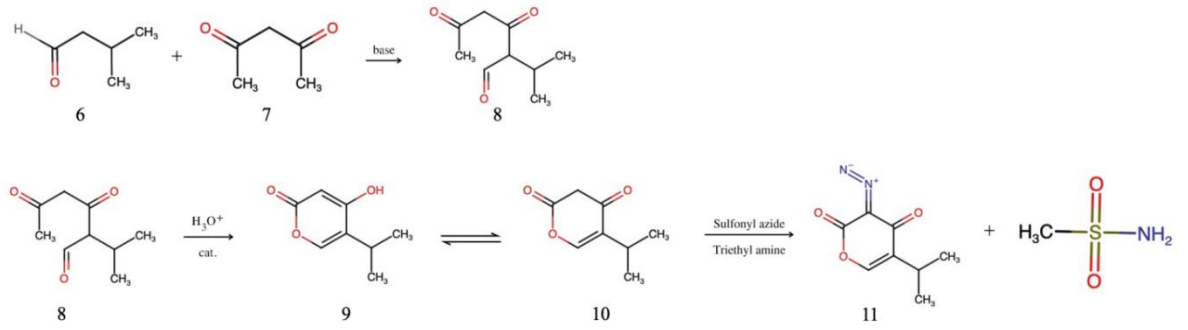

Figure 2. Preparation of 5-(propan-2-yl)-3-(I^5-diazynylidene)-3,4-dihydro-2H-pyran-2,4-dione

To synthesize the desired compound, we begin with two raw materials to prepare: bromo(2-methylphenyl) magnesium and 5-hydroxy-5-methylhexan-2-one. Figure 1 shows the process of synthesizing 6-(2-bromo-6-methylphenyl)-6-methoxy-2-methylhexan-2-ol. Initially, they undergo a Grignard reaction, leading to product 2. Subsequently, upon the addition of NaH and CH3I, an ether is formed, leading to product 3. Since the bond linking the benzene ring and the carbon chain can rotate freely, through rotation, product 4 will react with the strong base n-BuLi, resulting in an intermediate reactive substance, from which one hydrogen is removed. Finally, the addition of Br2 leads to an addition of Br functional group on the benzene ring, which serves as a “handle” for the ultimate connection of two subparts. This process yields our first target molecule, product 5.

The second stage of the whole synthetic pathway is the preparation of 5-(propan-2-yl)-3-(I^5-diazynylidene)-3,4-dihydro-2H-pyran-2,4-dione, as shown in figure 2. To start with, use isovaleraldehyde and acetylacetone as starting material. Both compounds are commonly used and can be bought at a relatively low price. First, add excessive base into the mixture, and both compounds will form enolates due to the deprotonation of carbonyls. The acetylacetone enolate is more stable because it can resonate and form a symmetrical structure. Thus, the isovaleraldehyde enolate, being more reactive, will add on to the carbon linked to the ketone functional group of the acetylacetone, forming product 8. Afterwards, add acid and catalyst into the mixture. The oxygen on the ketone functional group in product 8 is partially negative. Hence, they combine with the excessive protons in the environment, and the bonds rearrange to form product 9. Product 9 then resonates in the form of structure 10, which is the needed molecule for diazo transfer to occur. Add sulfonyl azide and triethyl amine, serving as reagents for diazo transfer reaction, into the mixture. Compound 10 reacts with the two reagents, forming compound 11 and byproduct methane sulfonamide.

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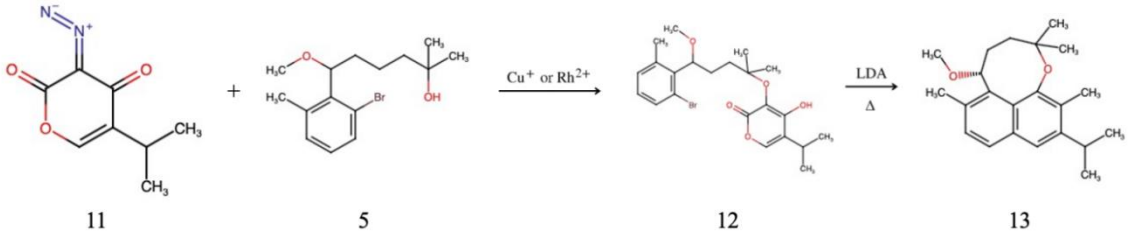

Figure 3. Scheme 2. Combination of two subparts and advancement to *Wulfenioidin F*

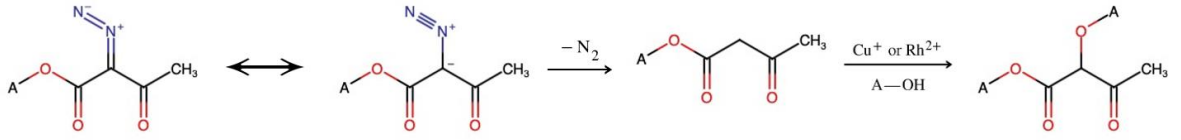

Figure 4. Schematic view of the reaction mechanism for Diazo carbonyl and alcohol

The ultimate step entails the amalgamation of the two entities previously synthesized. Nevertheless, prior to initiating this connection, it is necessary to ascertain whether there will be a reaction in the wrong orientation, leading to the production of unwanted byproducts. To prevent this from happening, we must first form the eight-carbon ring through the linkage of two subparts, which ends up in the formation of ether. Referring to Figure 3 above, which offers an outline of how to combine the subparts, the N_2 exhibits a strong stability under natural conditions, thus the bond connecting N and C isn't stable and can easily break. This results in the formation of carbene, which easily reacts with alcohol under the presence of catalysts such as Cu^+ or Ru^{2+}, as the catalyst can stabilize the carbene and facilitate the interaction of the two molecules, resulting in the addition of an alcohol to the central carbon. This catalytic process contributes to the production of ether. Figure 4. indicates an effective schematic pathway for Diazo transfer.

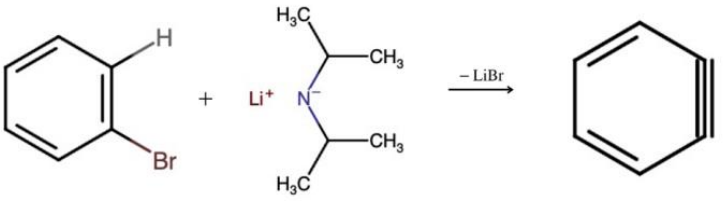

Figure 5. Schematic view of the reaction mechanism for Benzyne

Then, we need to synthesize benzyne as it serves as an intermediate compound that allows the Diels-Alders reaction to happen, which is crucial for the entire process. Referring to Figure 5, which provides a method of synthesizing benzyne that will be utilized to further process, we use a benzene ring with a Bromine functional group to react with strong base, in this case, LDA. Because the Nitrogen from the strong base has an affinity for hydrogen, it forms a bond with the hydrogen. The bond between the hydrogen and the benzene breaks, forming a new bond on the benzene, and the Bromine leaves the benzene ring. According to the Pka data [4], it is evident that the hydrogen-nitrogen bond is low in acidity, indicating that it is stable. Consequently, this reaction yields benzyne along with two by-products. Thus, this is why LDA is used in the final step of scheme 2.

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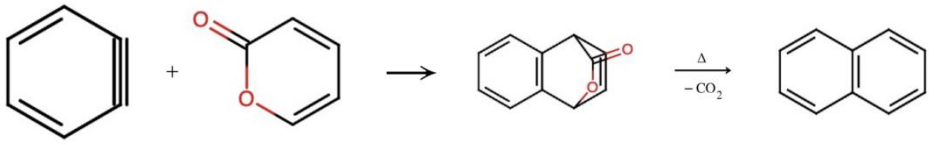

Figure 6. Schematic view of Diels-Alder reaction between benzyne and pyrone that forms a naphthalene

Finally, we establish a connection between benzyne (an intermediate form of product 5 in Scheme 2, with the benzene converted into benzyne) and pyrone (product 11 in Scheme 2) using the Diels-Alder reaction. During this reaction, the benzyne and the pyrone are connected, and part of the pyrone is folded upwards, creating an angle. Under a heating condition, the CO_2 component dissociates, breaking the bonds and yielding the object, naphthalene. Thus, this is why heating is required in the final step of scheme 2. This leads us to the final product, *Wulfenioidin F.* Figure 6 refers to the connection of lower two parts, which is the merge of naphthalene [5].

3. Conclusion

This paper presents a synthesis pathway that leads to the production of *Wulfenioidin F*, which can be adopted as a drug defending against ZIKA virus. This work segregates the intended substance to two subparts and offers details of synthesis procedure. Also, the order of combining two subparts mentioned in the final step is emphasized. The whole work enables researchers to approach the final compound, *Wulfenioidin F*, thus helping them to produce it more efficiently.

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