Retrosynthesis of Wulfenioidins L with Potential Anti-Zika Virus Activity

Tanghe Wang[1*], Yuning Gu[2,a]

[1]School of Life Science, University of Nottingham, Nottingham NG7 2UH, United Kingdom
[2]School of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin 150040, China

Abstract. The paper discusses the retrosynthesis of Wulfenioidin L, a compound showing potential anti-Zika virus activity. Wulfenioidins were isolated from Orthosiphon wulfenioides, with some demonstrating virus entry inhibition. The paper focuses on Wulfenioidin L due to its relative potency and fewer pharmacokinetic challenges compared to others. It presents significant synthesis challenges, including its polycyclic structure with chiral centers and multiple substituents. The study proposes two retrosynthetic pathways for Wulfenioidin L, involving complex reactions like Diels-Alder and oxidation. The synthesis approach also addresses issues like regioselectivity, yield optimization, and environmentally friendly practices.

1. Introduction

In a study published this year, Tu et al. isolated eleven wulfenioidins from Orthosiphon wulfenioides [1]. Among these compounds, five demonstrated anti-Zika virus (ZIKV) activity. They inhibit the entry of the virus into cells by suppressing the expression of the ZIKV envelope (E) protein [1,2]. Compared to ribavirin, a ZIKV treatment known for causing damage to red blood cells, wulfenioidins show potential for a new treatment approach with lower toxicity [3].

Among these compounds, wulfenioidin L (Figure 1) is less potent compared to wulfenioidins F and H, and even to ZIKV ribavirin [1]. However, when wulfenioidins F and H face pharmacokinetic challenges, wulfenioidin L emerges as the best alternative. Therefore, conducting a retrosynthesis analysis of its structure is essential.

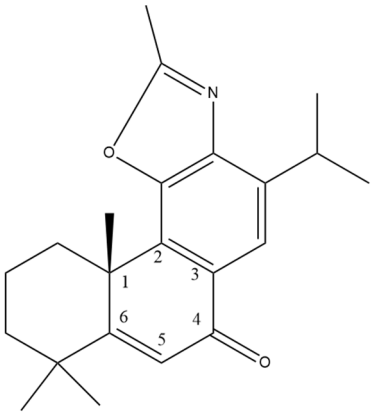

Figure 1. Structure of Wulfenioidins L. Six carbon atoms in centre cyclohexene are labeled with number 1-6.

Some aspects of its structure present significant synthetic challenges. Firstly, it comprises four rings: two cyclohexanes, one benzene, and one oxazole. The synthesis of such polycyclic compounds often entails complex ring-closure steps. The conditions required for forming each ring may differ, and some ring-closure reactions can lead to low yields or unwanted by-products. Secondly, there is a chiral center located between the two cyclohexanes. A major challenge in synthesizing chiral molecules lies in achieving enantioselectivity, meaning the selective synthesis of a specific enantiomer over its mirror isomer. As the two enantiomers of a chiral molecule can have vastly different biological and pharmacological properties, precise control over the synthesis of enantiomer products is crucial. Finally, the numerous substituents on these rings add to the complexity, making it challenging to ensure the selectivity of the reaction.

In our study on the synthesis of Wulfenioidin L, the challenges posed by its polycyclic structure, multiple chiral centers, and various substituents are meticulously addressed through a series of sophisticated strategies. For the polycyclic structure, our approach includes template-directed synthesis to pre-organize reactants, reducing entropy and facilitating complex ring formations, and sequential ring formation, enabling precise control over the final polycyclic system. To tackle the chiral centers, we employed enantioselective catalysis, leveraging chiral catalysts to ensure the correct spatial arrangement of atoms, and chiral pool synthesis, using naturally occurring chiral molecules as starting points. For managing multiple substituents, our study emphasizes regioselective reactions to add substituents accurately, coupled with protection and

* Corresponding author: mbytw6@nottingham.ac.uk
[a]guyuning2002@g mail.com

deprotection strategies to prevent side reactions and orderly introduce various functional groups. These methods collectively demonstrate a deep understanding of organic synthesis complexities, showcasing our ability to efficiently construct a molecule as intricate as Wulfenioidin L with the desired stereochemistry and functional group arrangement, all while maintaining high yield and purity.

2. Main (I)

In this study, we proposed two distinct retrosynthetic pathways for the target molecule. The first pathway involves the sequential disconnection of the 1-2 and 3-4 carbon bonds in the central cyclohexene, following the removal of a functional group. Conversely, the second pathway commences with the cleavage of the 1-2 carbon bond, subsequent to which a functional group is removed, prior to severing the 4-5 carbon bonds.

Regarding the initial pathway, our approach begins with the reduction of the double bond at the fourth carbon atom, followed by the concurrent cleavage of the 1-2 and 3-4 carbon bonds. This strategic sequence paves the way for the potential application of forward synthesis techniques, namely the Diels-Alder reaction and specific oxidation reactions, to efficiently construct the desired molecular structure (see Figure 2).

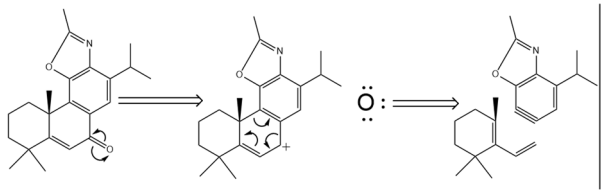

Figure 2. Disconnecting the centre cyclohexene in route 1.

Our further retrosynthesis analysis begins with 1,3, 3-trimethyl-2-Vinylcyclohexame-1-ene. First, we once again use 4+2 cyclo-addition to break two bonds of cyclohexene to obtain a carbon chain with two double bonds and two hydrocarbon groups. An olefin is then oxidized by functional group interconnection. This gives us the opportunity to disconnect the hydroxyl carbon and the α carbon. Finally, the synthetic equivalent of synthon we obtain by reducing the principal carbon chain is 4-methyl-1,3-pentadiene. However, we cannot get it from the market, so it is necessary to start the preparation with 3-Methyl-2-butenal [4] (see Figure 3).

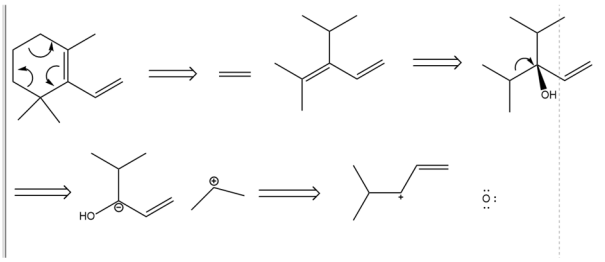

Figure 3. Retrosynthesis of 1,3,3-trimethyl-2-vinylcyclohex-1-ene.

In the retrosynthesis of 4-isopropyl-2-methylbenzyne[d]oxazole, a pivotal initial step is the hydrogenation of the benzyne moiety to yield a benzene ring. This fundamental transformation is crucial, as it establishes the core structure essential for further chemical modifications. Subsequent to this, the strategic disconnection of the isopropyl group from the benzene ring is undertaken. Given that cis synthesis typically incorporates halogenation and Friedel-Crafts alkylation processes, the synthetic equivalent identified for this synthon is 4-bromo-2-methylbenzo [d]oxazole. Proceeding with the cleavage of the carbon bond linking the benzene and oxazole rings results in the formation of a synthetic equivalent, 2-amino-3-bromophenol. The final step involves the breaking of the bromine-carbon bond, leading to the production of 2-aminophenol (see Figure 4).

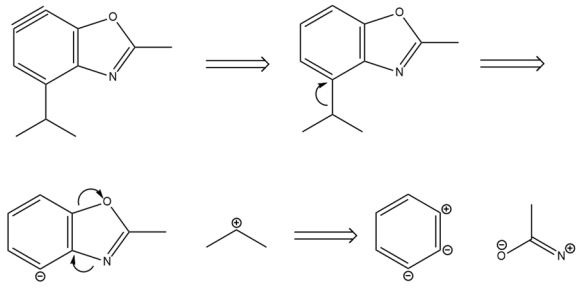

Figure 4. Retrosynthesis of 4-isopropyl-2-methylbenzyne[d]oxazole.

Our forward synthesis strategy start on the preparation of 4-isopropyl-2- methylbenzo[d]oxazole (Figure 5). This process necessitates a critical decision-making step when handling 2-aminophenol. The key consideration here is whether to prioritize the synthesis of the benzoxazole moiety first or to introduce a halide functional group initially. The latter approach, involving the initial introduction of a halide, is advantageous for the subsequent incorporation of the isopropyl group. Given that the ortho-amino group acts as an electron-donating group, and the intermediate hydroxyl group functions as an electron-withdrawing group, electrophilic aromatic substitution at the sixth carbon atom exhibits high selectivity [5]. On the other hand, as a neutral functional group, oxazole does not contribute to the regioselectivity of the reaction. Consequently, implementing halogenation and Corey-Posner reaction prior to the construction of the oxazole rings could significantly enhance the overall yield of the synthesis.

Furthermore, the fluorination reaction presents significant challenges in terms of control, often leading to difficulty in obtaining the desired product. Iodination, while less reactive, tends to result in aliphatic hydrocarbon substitution rather than halogenation. Chlorination, despite its high reactivity, is less feasible due to chlorine being a gas, which complicates the control over its quantity [6]. Consequently, we opt for bromination using Br_2 for the free radical reaction, as it

offers a more controllable and effective approach for our synthesis process.

The synthesis of benzoxazole from 2-aminophenol typically involves the use of carboxylic acids or their derivatives as an additional synthon. There are principally two methods available for this synthesis. The first method involves the reaction of 2-aminophenol with carboxylic acid, employing polyphosphate as both solvent and catalyst [7]. While this method is cost-effective, the use of strong acid polyphosphate can lead to undesirable side effects such as equipment corrosion and typically results in lower yields. The alternative method utilizes a nanoporous material, MCM-41, in place of the strong acid [8]. This approach not only yields higher efficiency but also aligns with environmentally friendly practices. Therefore, we opted for this method in our synthesis.

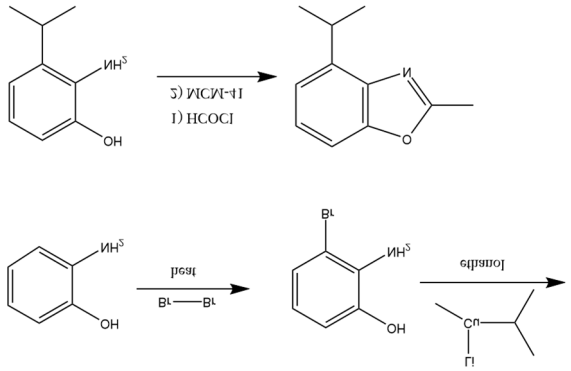

Figure 5. Preparation of 4-isopropyl-2- methylbenzo[d]oxazole

The final step in our synthesis involves the dehydrogenation of a substituted benzene ring back to benzene. This step is deliberately reserved for the end because it disrupts the aromaticity of the benzene ring, complicating the addition of substituents. Various methods exist for generating benzyne, but the most economical and convenient involves the conversion of anthranilic acid to diazo salt (i), which, upon heating, decomposes into carbon dioxide, nitrogen, and benzene [9]. However, the presence of the isopropyl group, being a strong electron-donating moiety, predominantly directs the reaction to occur at the ortho and para positions. Our objective is to target the reaction exclusively at the para position. Therefore, it is imperative to employ appropriate protective groups to shield the adjacent carbon atoms prior to this reaction [10].

We opted to employ the nitration reaction as the initial step in generating the nitrate substituent, followed by the reduction reaction to yield 4-isopropyl-2-methyl-7-nitrobenzo[d]oxazole. Subsequently, halogenation and the Corey-Posner Reaction were employed to introduce a carboxyl group. Finally, the protective group will be removed (see Figure 6).

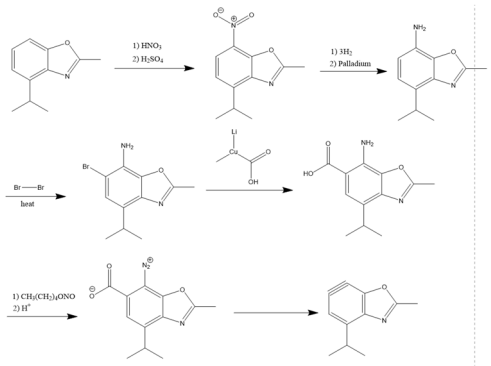

Figure 6. Preparation of 4-isopropyl-2-methylbenzyne[d]oxazole from 4-isopropyl-2-methylbenzo[d]oxazole

In the initial step, we planed to synthesis 1,3,3-trimethyl-2-ene vinylcyclohexane using 3-Methyl-2-butenal and methyltriphenylphosphonium bromide, yielding 4-methyl- 1,3-pentadiene (Figure 7) [4]. Then, an acid-catalyzed hydration reaction was employed to introduce a hydroxyl group to the less substituted carbon atom on the double bond. To enhance the selectivity of the reaction between the two double bonds, a protective group can be added during this process. The next step involves utilizing the collins oxidation, which is considered an effective method for oxidizing the hydroxyl group into a ketone group [11]. Subsequently, we opted to introduce an isopropyl group using Grignard reagent, followed by the removal of the hydroxyl group through burgess dehydration. Finally, the Diels-Alder reaction will assist us in synthesizing 1,3,3-trimethyl-2-ene vinylcyclohexane.

This reaction is a [4+2] cycloaddition, where a diene (4-electron component) reacts with a dienophile (2-electron component) to form a six-membered ring. The reaction proceeds through a concerted mechanism, meaning it occurs in a single step without any intermediate formation. Under general conditions, the highest occupied molecular orbital (HOMO) of the diene interacts with the lowest unoccupied molecular orbital (LUMO) of the dienophile to form a bond. The diene component should have conjugated double bonds, while the dienophile typically contains electron-withdrawing groups to enhance its reactivity. Solvent and temperature choices are crucial; typically, a non-polar solvent and elevated temperatures are used to accelerate the reaction. No additional catalyst is usually required unless one seeks to influence the stereochemistry of the product [12].

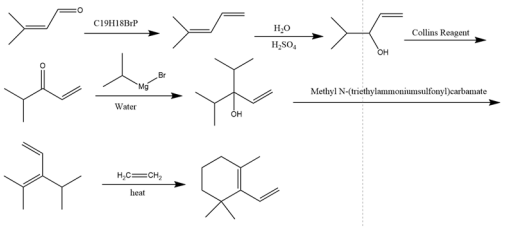

Figure 7. Forward synthesis of 1,3,3-trimethyl-2-ene vinylcyclohexane.

In the final step, we will once again utilize the Diels-Alder reaction to combine the two compounds. Subsequently, we intend to allow this compound to react with air in the presence of cobalt to introduce a hydroxy substituent [13]. Following this, the Collins reaction will be employed once more to oxidize the hydroxy substituent and generate our target product(see Figure 8).

The Collins reaction is an oxidation process primarily used to convert primary and secondary alcohols into aldehydes and ketones, respectively. The mechanism involves the use of the Collins reagent, which is a complex of chromium (VI) oxide with pyridine in dichloromethane (CrO3·2Py·2Cl2). In this reaction, the alcohol undergoes a two-step oxidation process. Initially, the alcohol is coordinated with the chromium atom of the reagent, facilitating the transfer of a hydride ion from the alcohol to the chromium, thereby oxidizing the alcohol to a carbonyl compound. The chromium, in turn, is reduced from the +6 to the +4 oxidation state. This reaction is particularly noted for its mild conditions and ability to provide high selectivity and yields, often over 90%, especially when converting sensitive alcohols to aldehydes without further oxidation to carboxylic acids. The high yields and selectivity make the Collins reaction a valuable method in organic synthesis, especially for complex molecule construction where maintaining functional group integrity is crucial.

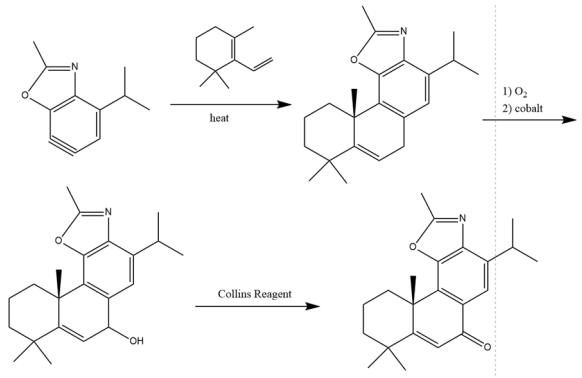

Figure 8. Forward synthesis of Wulfenioidins L.

3. Main (II)

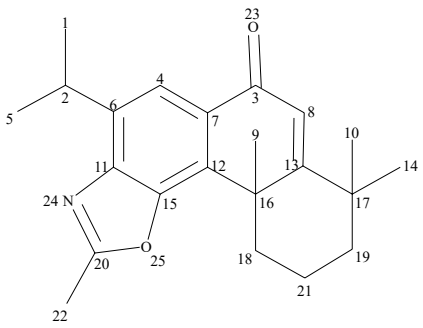

Figure 9. Structure of Wulfenioidins L.

Figure 9 shows the Structure of Wulfenioidins L.

3.1. Generalization

In the synthesis of this compound, we can roughly cut the compound into two major parts by the organic synthesis cut-off method.

Cutting the 3-7 carbon-carbon bond and cutting the 12-16 carbon-carbon bond to get the compounds compound 1 and compound 2 as shown in Figure 10 below:

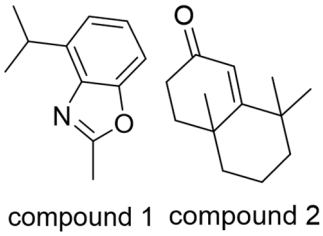

Figure 10. The two major parts of Wulfenioidins L.

3.2. Synthetic pathway analysis

Regarding the synthetic pathway of compound 1, we can get the following general route through the reverse analysis of organic synthesis:

The synthetic idea of this route is shown in Figure 11:

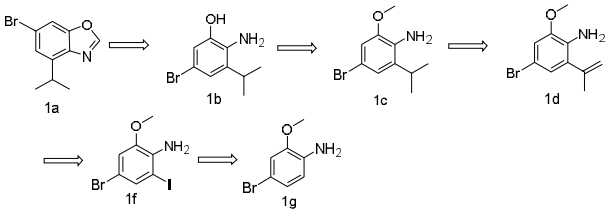

Figure 11. Synthesis ideas for the reverse synthetic route of compound 1.

Firstly, the carbon atom linking O-N in the N-C-O of the oxazole ring in compound 1 is opened to obtain the phenolic hydroxyl group and amino group-containing compound 1b in the neighboring position.

Then the structure of phenolic hydroxyl group of 1b can be hydrolyzed by the structure of anisole to obtain phenolic hydroxyl group, so the previous compound of 1b is anisole structure 1c.

Next, the isopropyl group adjacent to the amino group of compounds 1c can be made from isobutylene by performing a hydrogen reduction reaction, so that its previous step compound can be made from isobutylene adjacent to the amino group (1d).

The isobutene in the 1d compound can be made by the Suzuki-Miyaura reaction [14], which builds carbon-carbon bonds through a coupling reaction. And in the coupling reaction, among the raw material halogenated benzene, the iodine substituent has the highest activity, so the raw material of this coupling reaction is the iodine substituent compound 1f.

And the iodinated compound 1f can be made from the iodine-free benzene ring structure by electrophilic substitution reaction [9], and its iodine element can be

made from the reaction of NIS (N-iodosuccinimide) and the initiator BPO (dibenzoyl peroxide).

3.3. Implementation method

At this point, the reverse synthesis of the synthetic route of compound 1 has been analyzed and the route of the compound is shown in Figure 12:

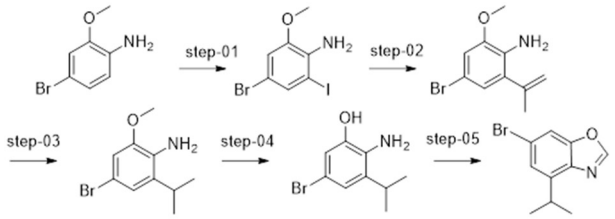

Figure 12. Synthetic route to compound compound 1.

The compound 1 was synthesized from the starting material 4-bromo-2-methoxyaniline by a 5-step reaction including Iodination, Suzuki-Miyaura reaction, Hydrogenation reduction reaction, Demethyl ether reaction, and oxazole ring closure reaction.

The first step of the reaction can be made by stirring and heating with DMSO as solvent, NIS as iodination reagent and BPO as initiator to make Iodination compound. The mechanism is as follows:

Firstly, the electrophilic reagent is dissociated into the positive ion E+ with electrophilicity under certain conditions. Then E+ attacks the benzene ring and forms a π-complex (which can be interpreted as a carbon positive ion) with the π-electrons of the benzene ring very quickly, and the π-complex still maintains the structure of the benzene ring. Immediately after the π complex, the electrophilic reagent E+ further connects directly with one of the carbon atoms of the benzene ring to form the σ complex. σ complex formation is the result of the electron-deficient electrophilic reagent E+ obtaining two electrons from the benzene ring and combining with the carbon atom on the benzene ring to form a σ bond. At this time, and electrophilic reagent E + form σ-bond carbon atom from sp2 hybridization into sp3 hybridization, carbon ring on the π-electrons only four, that is, four π-electrons distributed in five carbon atoms to form a p - π conjugate system. So the carbon ring is no longer the original stable conjugated system, but the electron-deficient conjugated system. This electron-deficient conjugated system has a tendency to lose hydrogen protons and restore the original stable conjugated system. Therefore, the σ complex quickly loses hydrogen protons, and the carbon atom that forms the σ bond with the electrophilic reagent E+ changes from sp3 hybridization to sp2 hybridization, and returns to the original stable conjugated system.

The second step of the reaction is the Suzuki-Miyaura reaction. It is a relatively new organic coupling reaction in which aryl or alkenyl boronic acids or boronic esters are cross-coupled with chloro, bromo, and iodo-substituted aromatics or olefins catalyzed by a zero-valent palladium complex.The Suzuki reaction is very tolerant to functional groups [15], and is very compatible with functional groups such as -CHO, -COCH3, -CO2C2H5, -OCH3, -CN, -NO2, -F, etc. The reaction is selective, and different halogen groups are compatible. The reaction is selective, and the activity of different halogens, as well as the same halogen in different positions for the reaction may vary, and trifluoromethanesulfonate, diazonium salts, iodonium salts, or arylsulfonium salts and arylboronic acids can also be reacted in the following order of activity:

R-I＞R-OTf＞R-Br＞＞R-Cl

The other substrate is typically arylboronic acid, prepared by reacting aryl lithium or Grignard reagents with alkylboronic esters. These compounds are stable in the presence of air and water vapor and are easily stored. The Suzuki reaction is catalyzed by a four-coordinated palladium catalyst, widely used as tetrakis(triphenylphosphine)palladium, with other ligands such as AsPh3, n-Bu3P, and (MeO)3P, as well as the bidentate ligands, dppe, and dppp, among others.

As shown in Figure 13, first the halogenated hydrocarbons undergo oxidative addition with zero-valent palladium, which interacts with a base to produce a strongly electrophilic organopalladium intermediate. At the same time arylboronic acid interacts with base to generate the acid radical type complex tetravalent borate intermediate, then trans metalation occurs to obtain the bidentate ligand Pd(II) intermediate, and finally the target product is obtained by reduction and elimination and regeneration of the Pd(0) catalyst. The oxidative addition step produces conformationally maintained products when reacted with vinyl halides, but conformationally flipped products when reacted with allyl and benzyl halides. This step first produces the cis-palladium complex, which immediately transforms to the trans-isomer. Reductive elimination yields a conformationally maintained product.

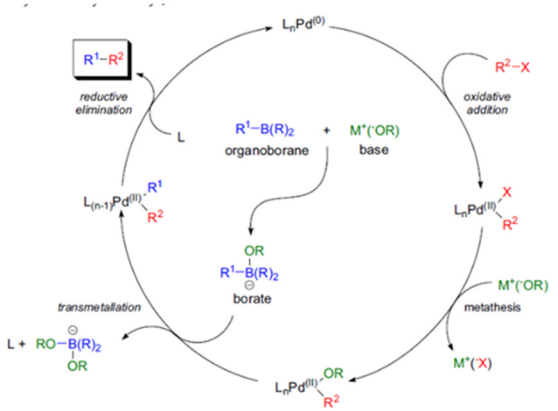

Figure 13. Fundamentals of the Suzuki-Miyaura reaction.

The third step of the reaction is a palladium-catalyzed hydrogenation reduction reaction. The reduction of a double-bonded olefin to a single bond catalyzed by metallic palladium is based on the

following mechanism: the first step is the activation of the catalyst palladium, where the reaction solvent (or catalyst additive) activates the palladium atoms prior to the reaction in order to facilitate the subsequent steps. The second step is the formation of free radicals. The catalyst palladium crystallizes in the reaction solvent to form a palladium carbide, in which a carbon atom has four electrons involved in the reaction, thus forming an intermediate free radical. The third step is the reaction of the radical reactive species, which is isolated from the double or triple bond in the reactant, and which combines with the radical to form a temporary palladium carbide reactive intermediate, which then undergoes a rearrangement reaction to ultimately produce a single bond consisting of the palladium carbide and the reactant.

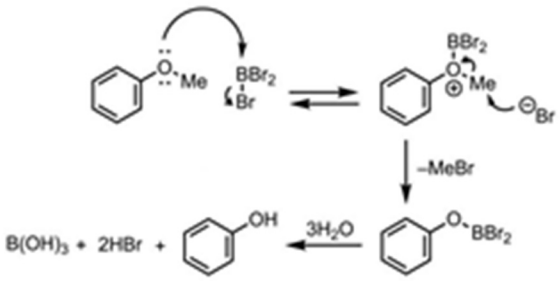

Figure 14. Reactions of demethyl ether when using boron tribromide as a reagent

The fourth step of the reaction for the reaction of demethyl ether, organic synthesis of most cases using Lewis's acid, in this case, considering the green environment and the conditions of the reaction situation, we reagent to use boron tribromide. The reaction mechanism is boron tribromide is a very acidic Lewis's acid, the lone pair of electrons on the O atom into the empty orbitals of the B atom to form a complex, the O atom also becomes positively charged. Next, the bromine negative ion removed from BBr3 in the previous step attacks the methyl group, producing methyl bromide and alkoxydibromoborane. The alkoxydibromoborane is then hydrolyzed to boric acid, hydrogen bromide and the corresponding hydroxyl compound. The reaction process is shown in the figure 14.

The fifth step of the reaction is the reaction between the neighboring phenolic hydroxyl group and the amino group to generate the oxazole ring. There are many ways to generate the oxazole ring, here p-toluenesulfonic acid is used as the acid catalyst, trimethyl orthoformate is used as the ring-closing reagent and raw materials to generate the oxazole ring. The reaction mechanism is as follows Figure 15: TosMIC deprotonates the aldehyde for nucleophilic addition, and the oxygen negative ion formed bonds with the carbon atom of isonitrile to form the oxazoline intermediate:

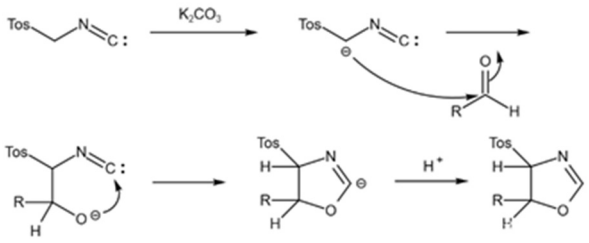

Figure 15. Reaction routes for the generation of oxazole rings from neighboring phenolic hydroxyl and amino groups

At this point, the synthesis method and mechanism of compound 1 are described.

Regarding the synthetic pathway of the end product, we can get the following general route (see Figure 16) by reverse organic synthesis analysis:

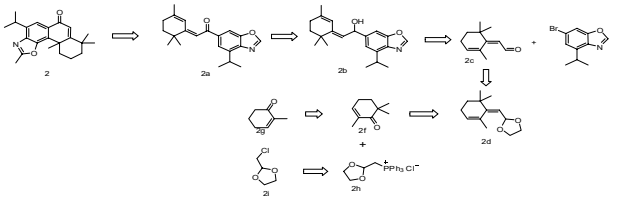

Figure 16. Approximate synthetic pathway of the end product.

The synthetic idea of the route is as follows:

The product is made by carbon coupling between the carbon neighboring carbon of the oxygen atom on the oxazole ring and compound 2, and its feedstock is 2a. the ketone carbonyl group of 2a is oxidized from alcohol, so its feedstock is 2b. 2b is synthesized again by the reaction of feedstock of aldehyde, 2c, with compound 1. the aldehyde group of 2c is synthesized by the hydrolysis of acetal, so its feedstock is 2d. the presence of an olefin in 2d can be associated by observing the wittig reaction [15], so the synthesis of 2d can be made from the raw material 2f of ketone and the raw material 2h of phosphorylidene by wittig reaction. The two methyl groups located in the α-position of the carbonyl group in 2f can be made from iodomethane by substitution reaction. Therefore, the synthetic route of the product is shown in Figure 17:

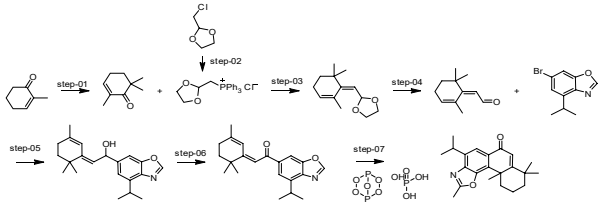

Figure 17. Synthesis pathway of the end product.

Its raw materials are synthesized into final products by substitution reaction, Wittig reaction, hydrolysis reaction, oxidation reaction and coupling reaction.

The first step is the substitution reaction, first NaH attacks the carbon of carbonyl α, generating hydrogen and a complex of Na with the raw material, and then a nucleophilic substitution reaction with two molecules of iodomethane generates the product.

The second and third steps are combined to form the Wittig reaction, a nucleophilic addition of an aldehyde or ketone to phosphoribosyl (Wittig's reagent) to produce an olefin. Figure 18 shows the first step in the Wittig reaction is the addition of phosphoribosyl to the carbonyl group, and the amphoteric intermediate that is formed is cyclized to form an oxaphosphoributane intermediate. Ring fragmentation produces an olefin and a trisubstituted phosphine oxide. The very strong forces of the phosphorus and oxygen atoms drive this reaction.

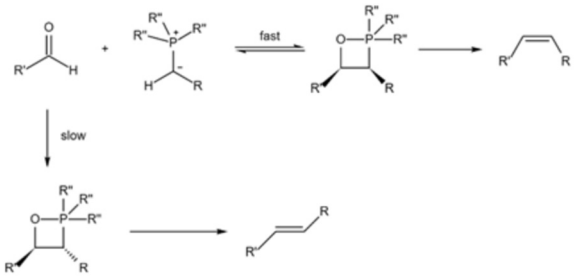

Figure 18. Wittig reaction.

The fourth step is the hydrolysis reaction, i.e. the hydrolysis of the acetal to an aldehyde under acidic conditions. Acetal reaction, the carbonyl group is a strong polar group, its carbon shows a strong positive charge, and thus easy to react with nucleophilic reagents. The oxygen on the hydroxyl group in alcohols has a lone pair of electrons and is strongly nucleophilic, and the oxygen attacks the carbonyl carbon with its lone pair of electrons to form a hemiacetal. The reaction is acid-catalyzed and reversible. The -OH of the hemiacetal is unstable, and it is very easy to form an acetal by dehydration condensation with another molecule of alcohol. Acetal formation reaction with concentrated sulfuric acid water absorption to make into an acetal reaction forward completely, while dilute sulfuric acid to promote the hydrolysis of acetal to the original aldehyde and alcohol.

The fifth step is the substitution reaction, the reaction requires the use of organic strong base n-butyllithium, n-butyllithium first attack aldehyde hydrogen to generate a lithium complex, and then and the bromine substituent nucleophilic substitution reaction to generate products.

The sixth step of the reaction is an oxidation reaction, that is, the alcohol hydroxyl group is oxidized to ketone. Considering the rate of reaction, oxidation was carried out using Dess-Martin oxidant (see Figure 19). Dess-Martin oxidation reaction refers to the oxidation of primary or secondary alcohols to aldehydes or ketones using Dess-Martin reagent [DMP; 1,1,1,-triacetoxy-1,1-dihydro-1,2-phenyliodono-3-(1H)-one]. This method is characterized by shorter reaction time, milder conditions, and less oxidizing agent than other oxidation methods.

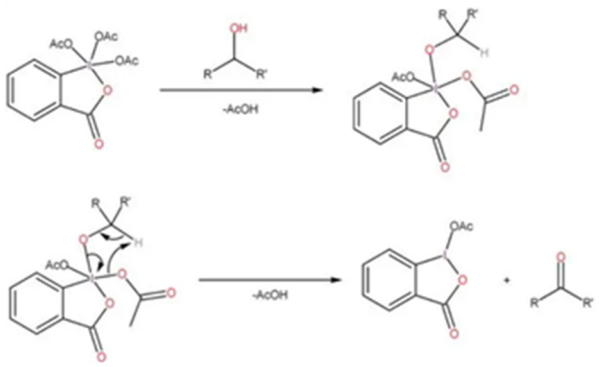

Figure 19. Dess-Martin oxidation reaction.

The seventh step of the reaction is to build a carbon-carbon coupling reaction, which uses a phosphorus reagent to build a carbon-carbon coupling, and the carbon on the raw material of the reaction is first attacked by the phosphorus reagent to form a Phosphiranium Salt of the carbon positive ion, and then the final product is obtained by coupling.

In comparing the two synthetic pathways for Wulfenioidin L proposed in your study, Pathway A appears more straightforward, utilizing well-understood reactions such as the Diels-Alder reaction, while Pathway B involves more complex steps, including strategic disconnections and functional group manipulations. Regarding yield and efficiency, Pathway A might offer a more streamlined approach potentially leading to higher yields. In contrast, Pathway B, with its meticulous functional group handling, could provide better control over the final product's structure, potentially enhancing overall yield despite its complexity. Scalability-wise, Pathway A could be more scalable due to its reliance on more conventional reactions. However, Pathway B's complexity and the need for precise control over multiple steps might pose scalability challenges. Overall, Pathway A's effectiveness lies in its simplicity and potential for higher yields, making it suitable for large-scale synthesis. Pathway B, though potentially less scalable, might offer a more precise synthesis of Wulfenioidin L, especially in terms of maintaining the integrity of its complex structure.

4. Conclusion

The study successfully proposes a synthetic pathway for Wulfenioidin L, a compound with promising anti-Zika virus properties. The paper highlights the complexities of synthesizing such a molecule, including managing its intricate polycyclic structure and chiral centers. The proposed methods, notably the Diels-Alder reaction, offer a viable approach while emphasizing regioselectivity and yield optimization. Furthermore, the study underscores the importance of environmentally friendly practices in pharmaceutical synthesis, demonstrating a responsible approach to drug development. This research not only contributes to

the field of medicinal chemistry but also sets a precedent for sustainable practices in complex molecule synthesis.

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Tanghe Wang, and Yuning Gu contributed equally to this work and should be considered co-first authors.

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