New Approaches for the Synthesis of Cleistanthol

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Abstract

An article published on 15 April 2022 isolated cleistanthol from Sauropus spatulifolius. This report will present one of the first few new approaches for synthesizing cleistanthol and how the approach is derived by retrosynthetic analysis, along with discussions on the weaknesses of this approach and suggestions for possible improvements. Sauropus spatulifolius, often used in traditional Chinese medicine, is expected to play a role in treating some diseases of the respiratory system. To make the medicine more efficient and targeted, this work is committed to excogitate a convenient approach to synthesize an abstract of sauropus spatulifolius, cleistanthol, in high yield. The approach takes stereostructure into account so as to be utilized in pharmacy.

Keywords: Cleistanthol, sauropus spatulifolius, diterpenoids, synthesis, retrosynthesis

1.Introduction

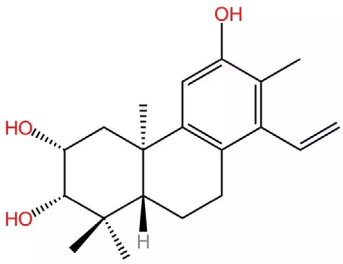

Figure 1. The Structure of Cleistanthol [Owner-draw]

Cleistanthol is a known type of diterpenoid that is isolated from Sauropus spatulifolius, namely 'Long-Li-Ye' in Chinese. The plant is commonly used as an ingredient for cooking, as well as a herbal medicine for cough, asthma, bronchitis, etc. Cleistanthol, according to the article 'Diterpenoids from Sauropus spatulifolius Leaves with Antimicrobial Activities', demonstrates antibacterial activity and a strong antiviral effect [1]. To be specific, cleistanthol has moderate inhibitory activity against Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis, Shigella flexneri, as well as vesicular stomatitis virus, and influenza A virus. As a result, cleistanthol might become an important component in medicines for the above diseases. The structure of the abstracted cleistanthol is shown in Figure 1.

Although currently, researchers are able to isolate the compound from Sauropus spatulifolius, a pathway allowing people to artificially synthesize cleistanthol is essential to be developed so as to produce it in bulk quantity. In this report, we will present a possible pathway for the synthesis of cleistanthol, explain the mechanisms behind the series of reactions, and discuss its drawback and potential improvements to increase the final yield of the compound.

The Retrosynthesis method is used for deriving the process, meaning to work backward from the desired product. This approach was formalized by E.J. Corey (Harvard University; Nobel Prize, 1990). The target molecule is first dissociated (meaning the breaking of certain bonds) into two fragments named 'synthons'. Finally, after finding the suitable reagents called 'synthetic equivalents' which perform the same function as synthons, the forward reaction needs to be checked to make sure of its correctness.

2. Method

The direct synthesis process is first presented to explain the reaction mechanisms step by step.

2.1 *Fusing the Middle Six-Membered Ring with the Benzene Ring*

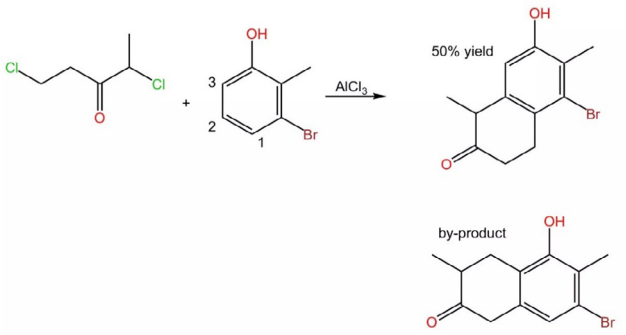

Figure 2. Fusing the Middle Six-Membered Ring with the Benzene Ring [Owner-draw]

Possible products of cyclization are presented in Figure 2. The reactants at the beginning are 1,4-dichloropentan-3-one and 3-bromo-2-methyl phenol (both purchasable

according to PubChem), with AlCl3 as the catalyst [2,3]. 1,4-dichloropentan-3-one reacts with AlCl3 and then generates AlCl4- hence carbocations at both ends of the carbon chain. The benzene ring, which is rich in electrons, attacks the carbocation. 1,4-dichloropentan-3-one substitutes the Hydrogen atoms on carbons 1,2 or 2,3(a by-product will thus form).

As a result, cyclohexane with a methyl and a carbonyl group is added to the benzene. The yield is about 50% because a by-product will be formed, and the preference of each product is almost the same.

2.2 *Robinson Annulation for the Addition of a Six-Membered Ring*

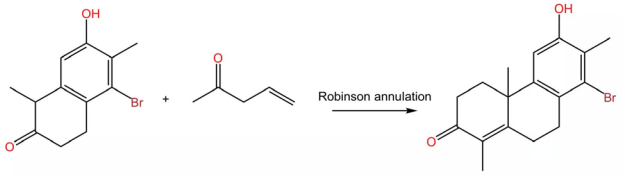

Figure 3. Robinson Annulation for the Addition of a Six-Membered Ring [Owner-draw]

Figure 3 presents the product of Robinson annulation. 4-Penten-2-one(purchasable according to PubChem) and the previous product can undergo the Robinson annulation, which can form three new carbon-carbon bonds to create a six-membered ring[4,5].

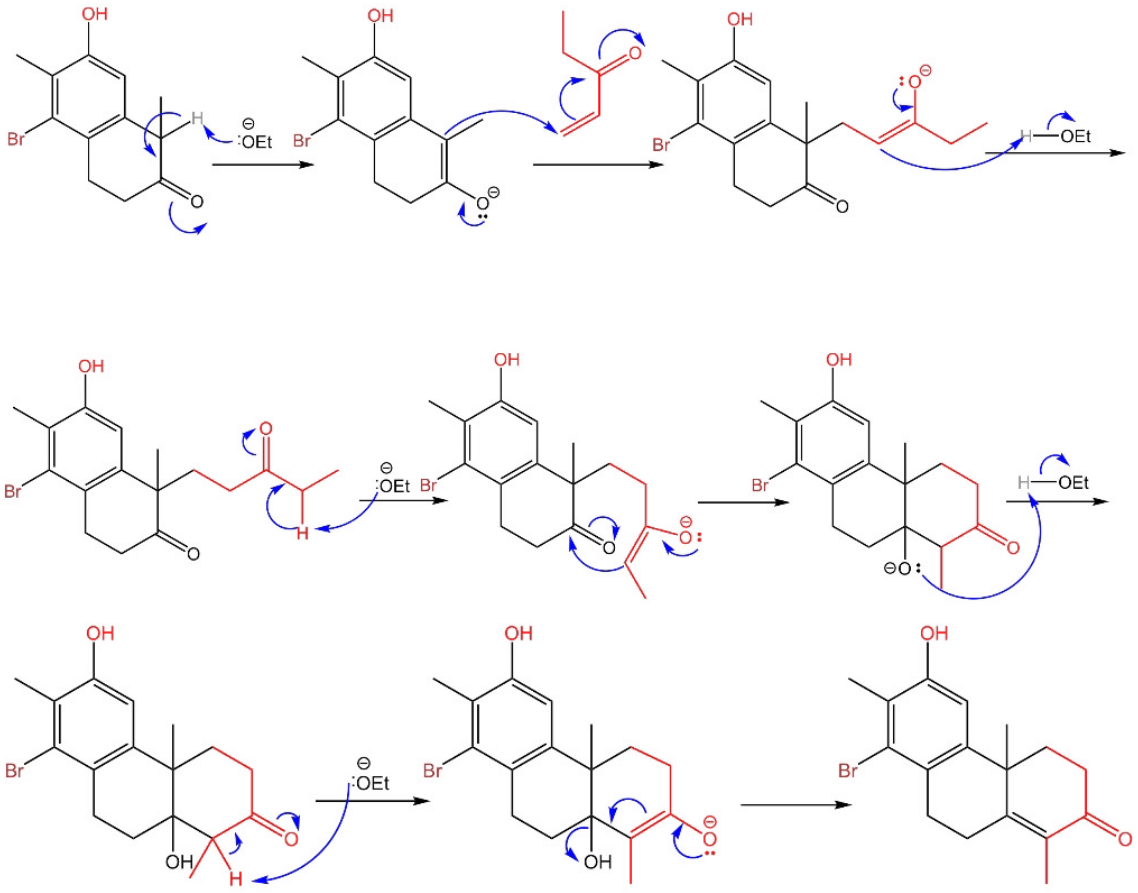

Figure 4. The Mechanism of Robinson Annulation [Owner-draw]

The mechanism is shown in Figure 4. First, a vinyl ketone is attacked by a nucleophilic ketone in a Michael Reaction, producing the intermediate Michael adduct. The aldol type ring closure follows to generate the keto alcohol. Then the dehydration produces the annulation product. In the Michael Reaction, an enolate nucleophile which is formed by the ketone deprotonated by a base attacks the electron acceptor. The α,β-unsaturated ketone is the electron acceptor in the general case.

In the examples above, regioselectivity is determined by the formation of the thermodynamic enolate. In addition, regioselectivity is often controlled by using β-diketones or β-ketoesters as the enolate component, for deprotonation on the carbon of the carbonyl side is highly favored. Then, the intramolecular aldol condensation reaction proceeds in the form of the installation of a six-membered ring. Eventually, the three carbon atoms of the α, β-unsaturated system, and the carbon α to its carbonyl group form the

four-carbon bridge of the new ring. To avoid reactions between the original enolate and cyclohexenone products, the initial Michael adduct is usually first isolated and then cyclized in another step to give the desired octane.

2.3 *Methylation*

Lithium, ammonia, and iodomethane react and generate CH3LiI which works as an electrophilic reagent. Because Lithium is positive, the carbon becomes partially negatively charged. Then the carbon-carbon double bond attacks the carbon of CH3LiI, so the methyl group and LiI are added to the carbon-carbon bond. The hydronium ion in the water can take place of LiI. It should be noted that the reaction needs to be done in steps. CH3LiI is an extremely strong Lewis base, which can seize protons from water and other Lewis acids, so it should not come into contact with water and carbon dioxide. The product of the methylation is shown in Figure 5[6].

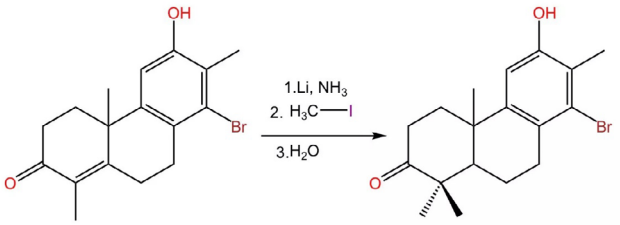

Figure 5. Methylation [Owner-draw]

2.4 *Reduction from Ketone Functional Group to Alcohol Functional Group by Sodium Borohydride*

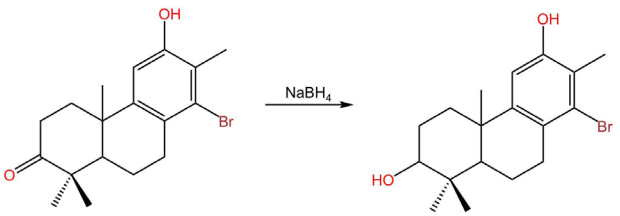

Figure 6. Reduction from Ketone Functional Group to Alcohol Functional Group by Sodium Borohydride [Owner-draw]

The product of the reduction is shown in Figure 6. NaBH4 can be used to reduce the carbonyl group to the alcohol group. The mechanism of this step is to use the nucleophilic addition of the hydrogen dissociated from NaBH4 to the carbon in the carbonyl group, the positively charged center.

2.5 *Elimination of Alcohol Functional Group to Alkene by Concentrated Sulfuric Acid*

Concentrated sulfuric acid is used for dehydration and the formation of the double bond. The secondary alcohol will follow the E1 elimination mechanism. The oxygen atom of OH which has the Highest Occupied Molecular Orbital (HOMO) is protonated by acid. A good leaving group H2O+ is formed, giving a secondary carbocation H2O is removed and thus allowing the double bond to form.

Take note that concentrated sulfuric acid is also a strong oxidizing agent, which oxidizes some alcohol to form carbon dioxide as well as sulfur dioxide [7]. Gases, along with the carbon mess formed by sulfuric acid reacting with alcohol, need to be removed before the next step of synthesis takes place.

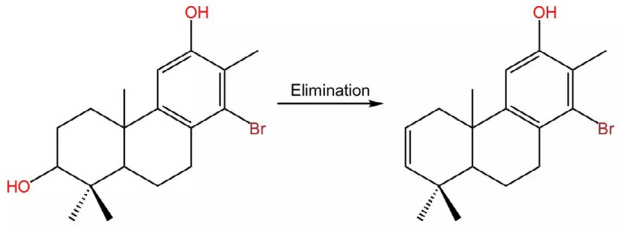

Figure 7. Elimination of Alcohol Functional Group to Alkene by Concentrated Sulfuric Acid [Owner-draw]

Figure 7 shows the product of the elimination. We deliberately place the step of adding an alkyl group to the ring before the elimination, so that the double bond will not form at the undesirable position, as shown by the image above. The by-product will reduce the yield of the target molecule. Figure 8 shows the unfavorable product in elimination if alkyl group is not added in the beginning.

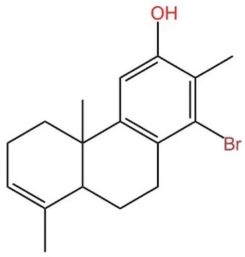

Figure 8. Undesired Elimination By-product If Alkyl Group Is Not First Added [Owner-draw]

2.6 *Upjohn dihydroxylation*

Osmium tetroxide reacts with the π electrons of the alkene by syn addition so that a cis-diol is formed instead of a trans-diol. As OsO4 is expensive and also very toxic, in practice it is used in small amounts as a catalyst [8]. Hydrogen peroxide or NMO(4-Methylmorpholine N-oxide) is often used to regenerate OsO4. The product of Upjohn dihydroxylation is shown in the Figure 9. A detailed reaction mechanism is presented in Figure 10 [9].

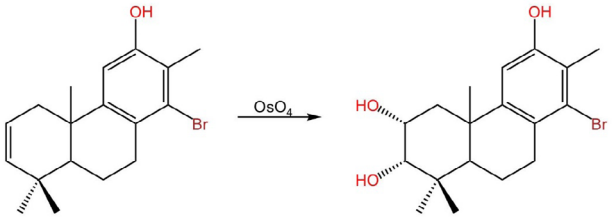

Figure 9. Upjohn Dihydroxylation [Owner-draw]

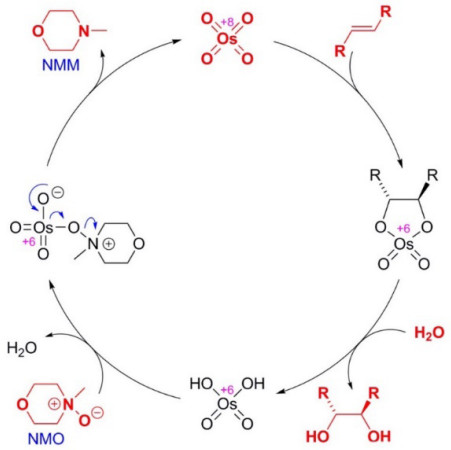

Figure 10. Mechanism of Upjohn Dihydroxylation [9]

2.7 ***Suzuki Coupling Reaction***

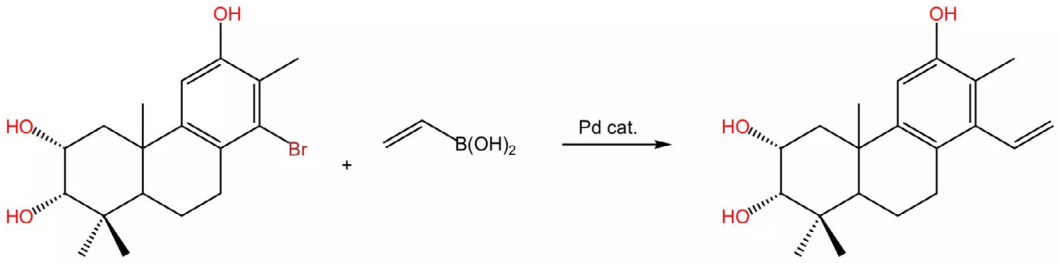

Figure 11. Suzuki Coupling Reaction [Owner-draw]

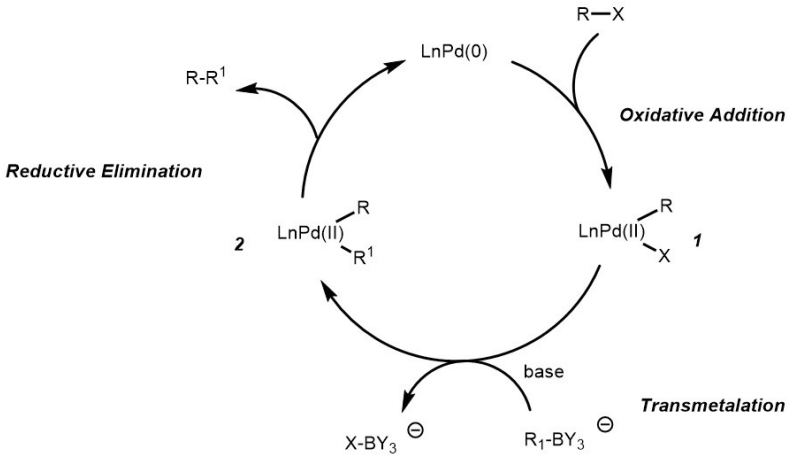

Figure 12. Mechanism of Suzuki Coupling Reaction [10]

The product of Suzuki Coupling reaction is presented in Figure 11. Figure 12 shows the mechanism for the Suzuki Coupling Reaction [10].

There are mainly three steps:

1) Oxidative Addition

R-Br reacts with the Pd catalyst to form R-Pd-Br organopalladium complex as Pd inserts itself between the alkyl group and the halogen.

2) Transmetalation

R'-B(OH)3 has a polar, where R' (in this case ethene) is partially negative. R-Pd-Br also had a polar where Pd is partially positive. An organometallic reaction is performed and forms R-Pd-R' (in this case R-Pd-Ethene).

3) Reductive Elimination

The palladium complex goes to eliminate to form the desired product R-R' and regenerate Pd metal. As a result,

alkyl group coupling is achieved by Suzuki Reaction, and Pd acts as a catalyst in the reaction.

In this case, Suzuki Reaction helps to convert the substituent (a Bromine atom) on the benzene ring to an ethyl group. The whole synthesis is shown in Figure 13.

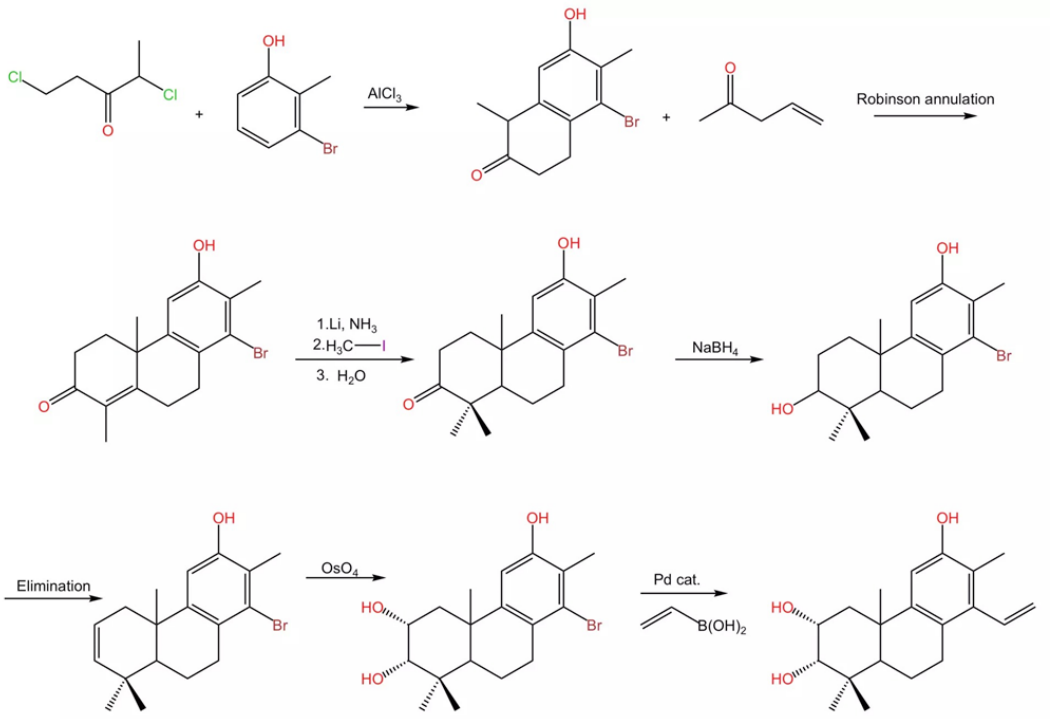

Figure 13. The Complete Synthesis [Owner-draw]

3. Retrosynthetic Analysis

The retrosynthesis idea will be presented in this section, showing the thinking process by using retrosynthesis to design a synthesis pathway. Figure 14,15,16,17 show each step of the retrosynthesis.

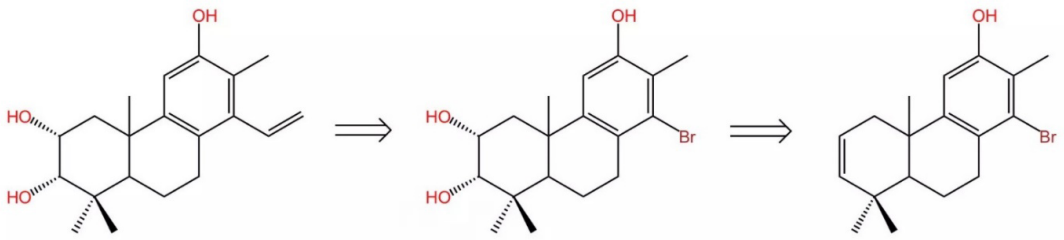

Figure 14. Retrosynthesis I [Owner-draw]

A carbon-carbon double bond is difficult to be added to the benzene ring in general, so the Suzuki coupling reaction is turned to which can replace the bromine with the carbon-carbon double bond.

When adding the OH group to the ring, the stereo structure needs to be considered as it is a cis-diol in cleistanthol. Upjohn dihydroxylation can add two alcohol groups simultaneously and form the cis-diol.

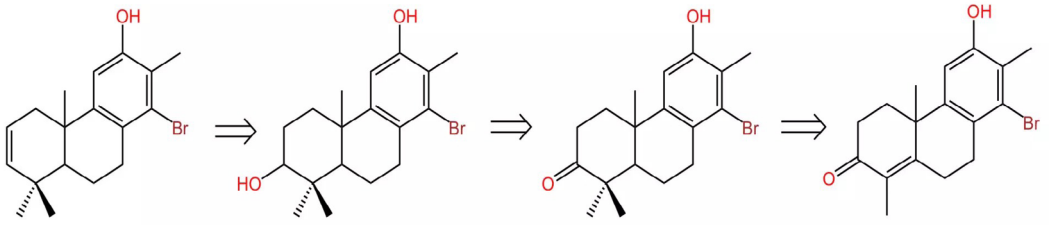

Figure 15. Retrosynthesis II [Owner-draw]

When come to this step, Robinson annulation has been already decided to form the leftmost ring. In order to prepare conditions for the annulation, a carbonyl and a carbon-carbon double bond need to be in the accurate position (shown in the figure above). As there can't have double methyl groups, one has to be added after the Robinson annulation.

The benzene ring is determined not to be broken (dissociate the bonds) because it's more arduous to form. The dissociation of bonds thus takes place between the other two six-membered rings. As a result, the Robinson annulation is used to perform a '4+2' cycloaddition. A methyl group is also added to the reactant, 4-Penten-2-one, which is near the carbonyl. This will make the addition of alkyl groups easier, as it's unattainable to add two methyl groups to one carbon simultaneously.

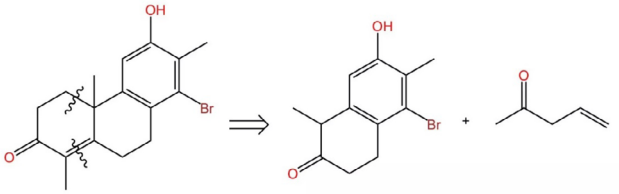

Figure 16. Retrosynthesis III [Owner-draw]

For the compound formed by a benzene ring and cyclohexane fused together, the dissociation of bonds between the two rings gives the final, simplest starting materials. To add the ketone with a five-carbon chain to the benzene ring, electrophilic aromatic substitution is used by adding two chlorine atoms to the ketone. It creates two partially positive sites (the carbon atoms) on the ketone which will be attacked by the electron-rich benzene ring.

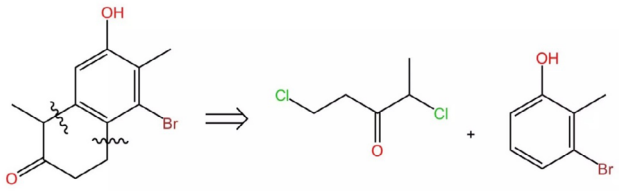

Figure 17. Retrosynthesis of the Six-Membered Ring [Owner-draw]

4. Discussion

4.1 *Fusing the Middle Six-Membered Ring with the Benzene Ring*

The formation of the by-product reduces the yield by almost 50%, which undermines the practicability of the synthesis process. Subsequent synthesis might work on modifying the reactant to avoid the formation of the by-product.

4.2 *Methylation*

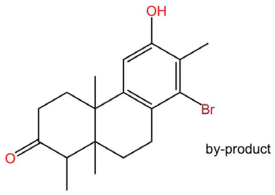

Figure 18. By-product of Methylation [Owner-draw]

Figure 18 shows the by-product of methylation. The methyl group can be added to either carbon of the original carbon-carbon double bond without significant bias, so the yield is about 50%. Although the alkyl group is successfully added, the yield might be improved by using more advanced methods in future research.

4.3 *Reduction from Ketone Functional Group to Alcohol Functional Group by Sodium Borohydride*

Sodium Borohydride is flammable, toxic, and corrosive [11]. It will decompose in water to form sodium hydroxide which is corrosive and dangerous to human health, as well as hydrogen which is flammable. Moreover, the heat produced by this reaction might be enough to ignite the hydrogen gas. NaBH4 should be preserved in a dry and cool environment. During the synthesis, try to keep it from moisture (H2O) for safety.

4.4 *Upjohn dihydroxylation*

Considering cis-diol in the target molecule, osmium tetroxide is used because of the addition it provides to the alkene functional group. OsO4 may have residues in the synthesis. Since this compound will most likely be used in pharmaceuticals, and OsO4 is highly toxic, it can be considered to be replaced by other reagents. KMnO4 might be an alternative. Although KMnO4 should not be taken orally, it's not toxic and much cheaper. But the alcohol might be further oxidized in KMnO4, so the yield will be lower. To obtain the cis-diol, a cold, dilute medium KMnO4 solution is generally used as the oxidizing agent.

4.5 *Stereochemistry*

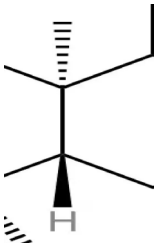

Figure 19. Stereochemistry of the Hydrogen Atom [Owner-draw]

The special stereochemistry of a hydrogen atom that is hard to obtain is shown in Figure19. For this current synthesis process, the positions of the hydrogen atom and the alkyl group in the figure shown are unable to be controlled. More time and effort will be needed to sort out four (two chiral centers hence the number is square of two) types of different stereoisomers, which will reduce the yield of the target molecule. Future studies on the synthesis of cleistanthol could improve in controlling stereochemistry more precisely. Besides, experiments should be done to further check the validity of this synthesis process.

5. Conclusion

In the synthesis, the yield is tried to be controlled to the greatest extent, and only a few reactions are presented with by-products. The cleistanthol is synthesized mainly for medicinal use. For this reason, reagents used for preparation should be non-toxic or less toxic since there may be residues in the process. However, in the above synthesis pathway, both NaBH4 and OsO4 are acute toxic. Subsequent studies are expected to search for other cheap, non-toxic, environmental friendly reagents.

Pharmacy has high requirements for the stereo structure of the compound, otherwise the drug may not work or even have negative effects. To avoid side effects of the drug made from cleistanthol, we will conduct further studies of the stereochemistry of the final product. The results provide researchers with a new synthesis approach of the cleistanthol, and it is hoped to be optimized by other researchers to be really involved in medical use.

Reference

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