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The Retrosynthesis of Centratherolides A

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Abstract. Centratherolide A is a furanoheliangolide isolated from Centratherum punctatum. It possesses a complicated structure with a furan-3(2H)-one ring, and α, β-unsaturated lactone ring, and a flexible chiral 3-chloro-2-hydroxy-2-methylpropanoyl side chain on carbon 8 and demonstrats selective cytotoxicity to colon cancer HCT116. This brings potential medical use to Centratherolide A, yet this compound is largely dependent on extraction from Centraterum punctatum. The complex structure and functional side chain introduce difficult to chemical synthesis. This research project focuses on the unique structure on Centratherolide A, and the construction of a new retrosynthetic pathway. By focusing on the key functional and characteristic structure, the retrosynthetic process will break the furan ring, α, β-unsaturated lactone ring and chiral side change individually. Each step has the potential to be reversed and use to synthesis Centratherolide A. This research project provides the first retrosynthesis for this molecule filling up the blank. Moreover, the logic used in this retrosynthesis can be used as reference for centratherolides B-G's synthesis, providing the corner stone for furanoheliangolides' potential medical use.

Keywords: Centratherolide, Furanoheliangolide, Centratherum, retrosynthetic process

1. Introduction

1.1. Centratherolides' research background and value

Sesquiterpene Lactone contains a core structure of 15-carbon terpenoid skeleton plus a lactone ring. Such compound is mainly distributed in compositae plants. Centratherolide A is selectively cytotoxicity against HCT116 cells, which is a type of colon cancer [1]. This provides Centratherolides A the potential to be developed as a new treatment for colon cancer. Moreover, as the mechanism of Centratherolide A involves influencing the function of TOP3B (a DNA topoisomerase, an enzyme that controls and alters the topologic states of DNA during transcription), causing it to fail cleaning up the R-loos, which leads to the accumulation of RNA toxicity, the specific function of TOP3B could be reveal [2]. Mipsagargin, a structurally similar sesquiterpene lactone, has advanced to Phase II clinical trials.

1.2. Centratherolide A's discovery and structure

Centratherolide A is extracted from Bolivian-produced Centratherum punctatum. The core structure includes Furan-3 (2H)-one ring, α,β-Unsaturated lactone ring and the Chiral side chain connected

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from carbon 8 are the important structure of this compound [1].

The furan-3(2H)-one ring is a characteristic structure of furanoheliangolides as shown in Figure 1. It helps construct a rigid ring system to fix the molecular conformation, ensuring that the α,β-unsaturated lactone ring can specifically bind to target proteins and avoiding the loss of activity caused by conformational disorder [1].



Figure 1. Furan-3 (2H)-one ring in Centratherolide A

The α,β-unsaturated lactone ring serves as the core toxic site shown in Figure 2. It inhibits protein function by covalently binding to the thiol groups (-SH) of target proteins [1]. It is a very typical Michael acceptor [3].



Figure 2. α,β-unsaturated lactone ring in Centratherolide A

The chiral side chain (at C-8 of centratherolide A) ensures stereo-matching between the side chain, shown in Figure 3, and the binding pocket of target proteins, improving binding specificity. The hydroxyl group in the side chain can form hydrogen bonds to further stabilize the molecule-protein complex, and these features collectively regulate the selective cytotoxicity against TOP3B-KO (TOP3B-knockout) cells [1].

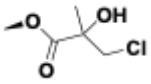


Figure 3. 3-chloro-2-hydroxy-2-methylpropanoyl moiety in Centratherolide A

1.3. Synthesis on the current stage

So far, the chemical synthesis of this molecule has made very little progress, and the research on this molecule has only reached the stage of isolation and identification. In the absence of chemical synthesis, it will be difficult to obtain large-scale production and meet the needs of subsequent pharmacological studies for this molecule.

1.4. The core and value of this research project

This project is tailored for creating a retrosynthetic process for Centratherolide A. Through this development, more possibilities for the synthesis of Centratherolide A will be explored. Moreover, this retrosynthesis act as a reference for further development.

2. Retrosynthetic strategy analyses

2.1. Reverse synthetic design principle

According to the potential bond enthalpy and reactivity of functional group, either strategical bond or polarcovalent bond will be considered to be broken first. This retrosynthesis is for a reference

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tool, with the ultimate goal being commercial reactants that can be produced within two steps.

2.2. Stepwise decomposition of the reverse reaction of molecule A

2.2.1. Elimination unimolecular reaction

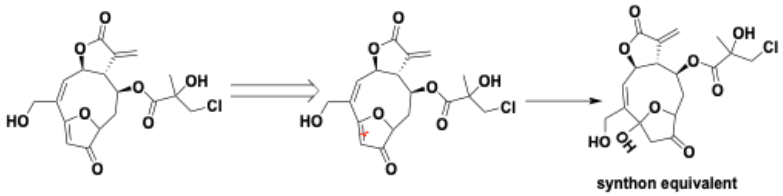


Figure 4. First step, unimolecular elimination reaction

In this step, the π bond is broken to provide a suitable environment for the base-catalysed aldol addition reaction. The combination of these conditions will pull apart one of the key structures of Centratherolide A (furan-3(2H)-one ring) [1]. As shown in Figure 4, the red line shows where bond is broken.

2.2.2. Base-catalysed Aldol addition reaction

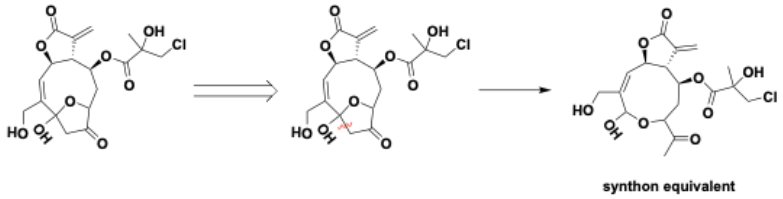


Figure 5. Second step base-catalysed aldol addition reaction

With base catalyst add, this step will pull apart the furan-3(2H)-one ring, greatly influencing the structure as shown in Figure 5 [4]. This mean that this is a very strategical bond break.

2.2.3. Hemiacetal cyclization-reduction

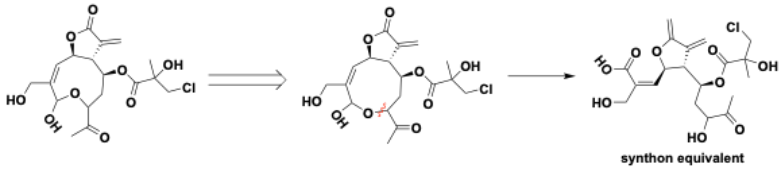


Figure 6. Third step, hemiacetal cyclization-reduction

Through the Hemiacetal cyclization-reduction, as shown in Figure 6, a complex heterocyclic ring will be pulled apart, and the result will be a linear like structure [5]. This further simplifies the structure with a suitable mechanism.

The first three steps are very much unchangeable in terms of their order. They must follow this order because if E_1 is not carried out, the Base catalysed Aldol addition reaction does not have the correct condition to occur. If the Hemiacetal cyclization-reduction happens before the other two, a larger size ring will be produced leading to a highly unstable molecule which is most likely impossible.

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2.2.4. Fischer esterification

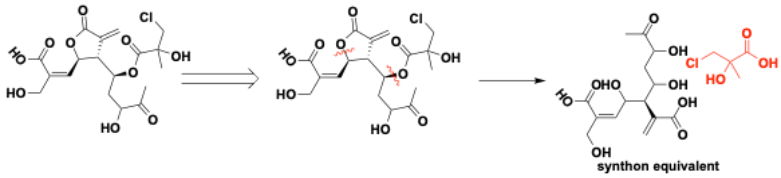


Figure 7. Fourth step. fischer esterification

Fischer esterification disconnects both esters as shown in Figure 7. This frees the side chain as a whole. The molecule highlighted in red will be taken out. In other words, in the synthesis, it will be added in as a reactant at this stage [6].

2.2.5. Wittig reaction

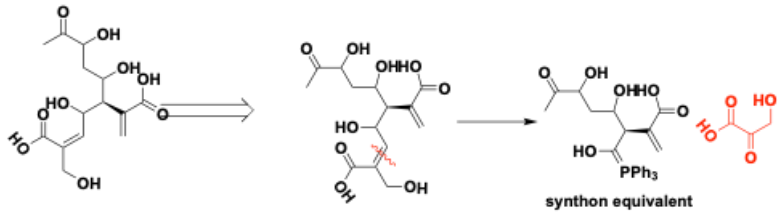


Figure 8. Fifth step, wittig reaction

Through Wittig reaction, another molecule will be separated simplifying the structure. Similar to the last step, the molecule is highlighted in red for the same reason [7]. This is shown through Figure 8. 2.2.6 Grignard reagent

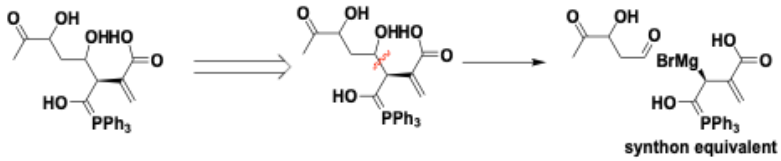


Figure 9. Sixth step, grignard reagent

At last, the whole structed is broken from the middle providing two different molecules with a linear shape. Grignard reagent is chosen because it is one of the most commonly used carbon-carbon bond-forming addition mechanisms displayed in Figure 9. Also is this scenario, the product seems to have a high possibility to be directly applied in a forward synthesis.

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2.3. Overall retrosynthesis

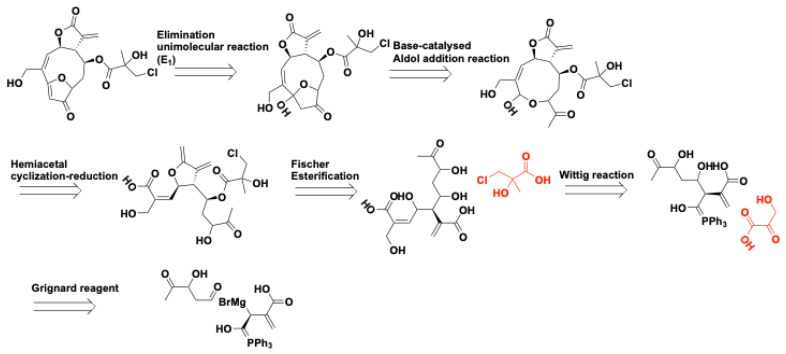


Figure 10. Overall step wise retrosynthesis

3. Result and discussion

3.1. Verification of the rationality of the reverse reaction decomposition steps

3.1.1. The rationality of the ring-opening of α, β-unsaturated lactone rings and C-8 side chain cleavage

The Fischer esterification is a possible mechanism to break α, β-unsaturated lactone ring [4]. There are no basic reagents that will possibly cause acid and base reaction due to the strong acidic catalyst this mechanism require. Because this process is reversable, the condition must be tailor for forward reaction. The Williamson ether synthesis is not considered as it will generate organic salt further complicating the structure.

3.1.2. The rationality of the disassembling the bridging bond of the furan ring

The base catalysed Aldol addition is not an inherently difficult mechanism to occur [1]. This is a fundamental yet well-established mechanism in organic chemistry. It will require a relatively lower room temperature of 0−5°C to prevent dehydration and excess water should be avoided if the reaction is intended to be an addition rather than a condensation [1]. Although risks like side reaction or selectivity might occur, but it is a suitable mechanism to cleavage the bond and break the furan ring.

3.2. Potential problems and solutions

In the final step, the Grignard reagent has two distinct potential reaction sites. This may result in a certain difference between the actual product obtained after the reaction and the expected one. However, the Grignard reagent is more likely to react with aldehyde, so the overall product should be able to allow the experiment to proceed to the next step. Therefore, in general, this step is reasonable and practical.

The solution could be to use another reaction mechanism to help separate this large molecule, or to wait until more common raw materials can be produced in large quantities in the future, allowing the final step to be improved.

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4. Conclusion

In this research project, a completely new analytical approach for the reverse reaction of centratherolide was presented. Through six key reverse reaction mechanisms, four molecular fragments with potential for synthesis were obtained. The reverse reaction analysis conducted in this investigation project divided the molecule into smaller fragments in the shortest possible steps, reducing costs and allowing for subsequent commercial development.

This project enriched the reverse reaction analysis of Furanoheliangolide and provided reference materials for synthetic chemistry. The reverse reaction analysis offered a potential synthetic pathway for A in the laboratory, helping to advance subsequent pharmacological research. Moreover, similar Furanoheliangolide molecules (Centratherolides B-G) can also be used as a reference for this reverse reaction molecule because the difference lies in the side chain at C-8. The experimental steps can be changed in terms of sequence to some extent, but the rationality of the molecules needs to be taken into account.

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