Synthetic Route Proposal for Cleistanthol Based on Retrosynthesis Approach

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Abstract: Cleistanthol of the diterpenoid group is a newly isolated naturally-occuring molecule of biological and pharmaceutical significance. The molecule contians three ring structures, only one of them aromatic, and hydroxy- and hydrocarbon- substitution groups modifying these rings. However, for this compound, a synthetic method has not yet been proposed for it and similar structures sharing the common ring structure but different sites and contents of modifying groups. This paper focuses on the construction of this molecule based on a reverse analysis from a retrosynthetic approach, and analyzed the advantages, shortcomings, and probable future advancements and improvements possibly being made to the route. This study also investigates its synthesis from a biological oriented approach given the target molecule's likely medical application, and discussed certain aspects during the synthetic pathway possibly hindering its use and possible circumvention to be introduced.

1 Introduction

Cleistanthol, a chemical extracted from Sauropus spatulifolius, a culinary ingredient and herbal medicine [1], is the center of investigation of this paper. In this paper, a possible synthetic route for the complex polycyclic compound using retrosynthetic methods is being explored (see Figure 1).

Fig. 1. Leaves of Sauropus spatulifolius Beille [2].

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The retrosynthetic method, first developed by E. J. Corey in the 1960s, provided a pathway for finding possible bond-breaking sites and organizing reactions so that a reasonable combination of reagents can be found to compose the target molecule by reverting the bond-breaking order devised in the retrosynthetic pathway. Using this method to break down complex molecules can often yield promising results, as shown in this paper by J. M. Smith et al. introducing such method of retrosynthesis [3]. Herbal tea and dried leaves made from the cleistanthol containing plant Sauropus spatulifolius Beille had been considered a effective treatment to upper respiration pathway inflammation in East and Southeast Asian herbal medicines [4], and research had also shown that the molecule of interest possesses potential antimicrobial, antivirus, and anticancer values [1,5], indicating potential commercial values of the synthesis of this molecule. This paper examines a possible retrosynthetic mechanism of the molecule's decomposition, and a synthetic pathway inspired by the retrosynthetic mechanism.

2 Synthetic Elaboration

2.1 Synthetic Pathway Overview

Figure 2 demonstrated the full intended synthetic route full synthesis route, with the explanation elaborated below:

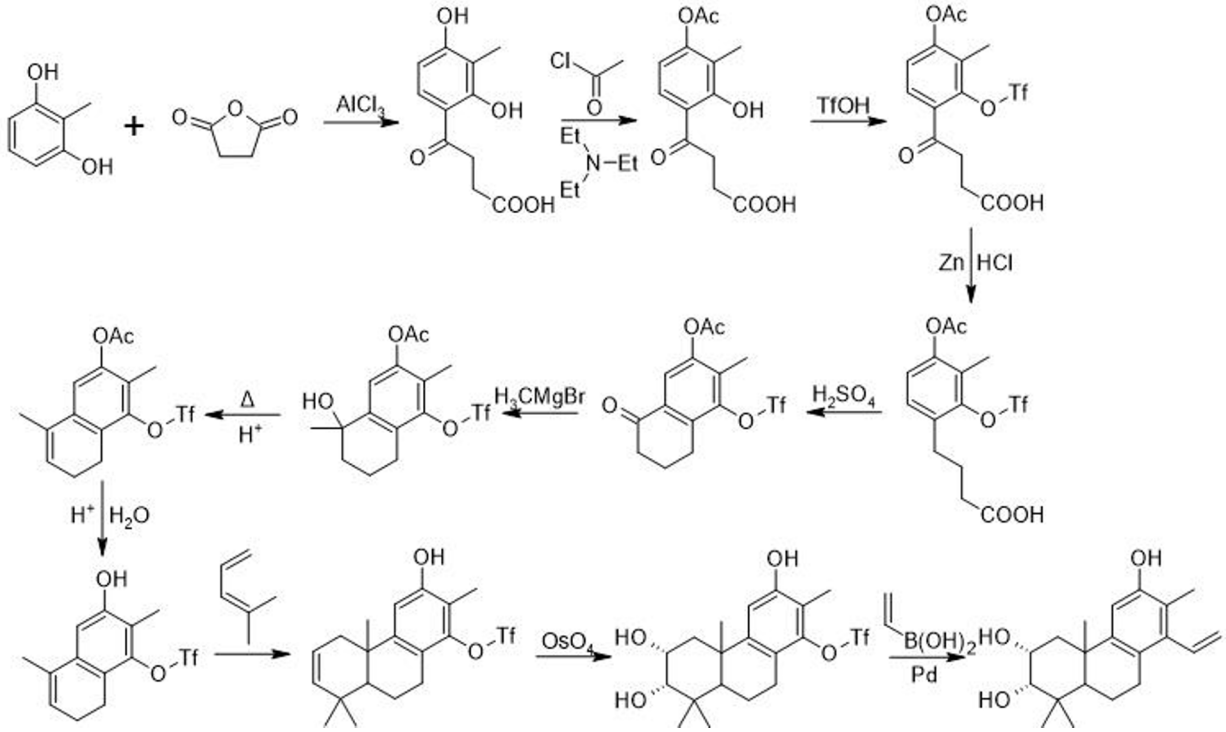

Fig. 2. Full Synthetic Pathway (Owner-drawn).

The synthesis features a step-by-step edition of the original molecule. The route can be divided into four main phases: pre-treatment of the reagents, Haworth synthesis to construct the second ring [6], Diels-Alders reaction to construct the third ring, and post-treatment to carry out final modifications [7].

2.2 Reagents and Experimental Conditions

The reagents used in this synthetic method, apart from common solvents, ions, and acids, are listed below, along with their CAS number:

2-Methylresorcinol 608-25-3;
Succinic anhydride 108-30-5;
Acetyl chloride 75-36-5;
Triethylamine 121-44-8;
Trifluoromethanesulfonic acid 1493-13-6;
Methylmagnesium bromide 75-16-1;
3-methylpenta-1,3-diene 926-56-7;
4-Osmium tetroxide 20816-12-0;

All of the compounds listed above can be purchased on Sigma-Aldrich.

Vinylboronic acid 4363-34-2

The compound above can be purchased on Ambinter.

Among those, except the two initial reagents and the Diels-Alders reagent applied to compose the third ring, all are fairly common organic chemical reagents easily purchasable without need for great expenses. However, according to information provided by MSDS, many of the chemical substances listed above are shown to possess toxicity or are known to cause environmental harm [8-10]. All steps in the synthesis can occur without extreme external circumstances, and are conductible in laboratory circumstances without the need of specific apparatus [11].

2.3 Stepwise Synthesis Description

Firstly, to prevent unfavorable regioselective preferences caused by the replacement groups on the benzene ring, which will cause the second ring to form at 5- and 6- positions, the ingredient is changed to be symmetrical. Then,

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the 1- hydroxyl is protected and 3- hydroxyl is altered in order to facilitate further reaction on a favorable reaction site.

Secondly, the Haworth synthesis, but a slightly altered version using a base to remove hydrochloric acid and a Grignard reagent add a methyl group to its 7- position, is continued to construct the second ring to form a substituted dihydronaphthalene. This phase requires the most number of synthetic steps among the four and is also prone to the production of by-products, the only phase among the four where a considerable amount of by-products can be possibly yielded. The cyclo-addition may occur in the reverse direction, which, though electrically unfavorable, can still happen to a certain extent. The modification of trifluoromethanesulfonic acid and its later modification during the Suzuki coupling shall also decrease the overall yield, as at least two more purification steps are introduced. A possible prevention is to alter the starting reagent or use an reaction other than Suzuki coupling, but so far no noteworthy, or even comparable, possibility have been found.

Thirdly, a simple Diels-Alder reaction is used to add a third ring to the structure as there is no other possible site for the cyclo-addition to occur other than the desired site on the second ring. A single-step process can be used because the two methyl groups on the 1- position of the diene and the aforementioned methyl group can hinder the combination of the molecules at an undesirable reversed position, and the methyl groups' electron-giving effect can promote the reaction in the forward direction.

Lastly, osmium tetroxide is used to construct a diol in syn stereographic position. A Suzuki coupling reaction, using the triflate group incorporated in the first phase, finishes the synthetic route by coupling the product with a vinyl group.

2.4 Retrosynthetic Analyses

Elaborated below is the retrosynthesis bond breaking route for the target molecule, as shown in Figure 3.

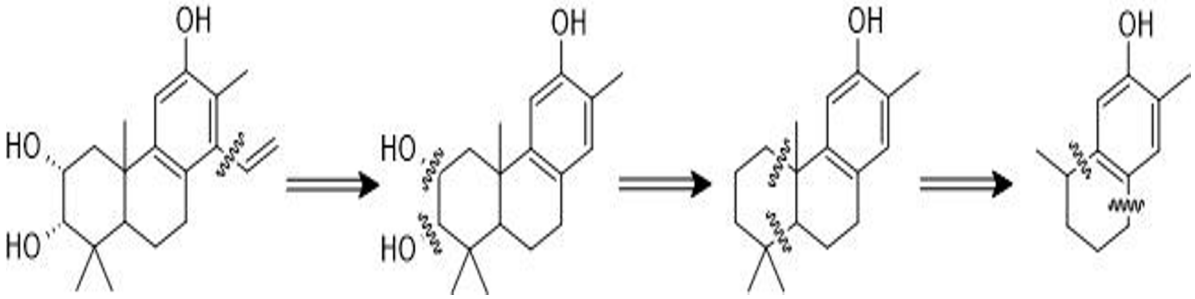

Fig. 3. Retrosynthetic Mechanisms (Owner-drawn)

The design, exceedingly simple in essence, progresses the synthesis as each structural complex is removed from the structure one by one. The corresponding synthesis adds the ring structures and the modification groups onto deliberately set reaction sites, as shown in four phases of the synthesis, each representing one bondbreaking step in the retrosynthesis. The relative complexity of its synthetic realization is the result of interactions between different functional groups that demanded the adding and removing of protection groups and modification of groups that is later reverted or further modified. Many other pathways for bond breaking is also possible, including a single step coordinated decomposition that cleaves both non-aromatic ring structures.

The retrosynthetic mechanic proposed is a complete guide to the procedure of the synthesis stated above, with each bond-breaking step roughly corresponding to one of the phases of the synthesis. The first phase prepares for the reactions to occur; then the second and third phase corresponds with the last and second-to-last step of the retrosynthesis, and the last phase finishes the first and second step of bond-breaking at once.

Alternative bond-breaking structures are also possible, namely an method to deconstruct the lower two rings in one single series of reaction by breaking the bond between the shared carbon molecule in advance. But due to ability and time restrictions, this possible pathway is not further investigated.

3 Discussion

The full synthesis contains eleven steps, and each of them require purification of its product. Moreover, the second step may produce undesirable side-products with unwanted placement of the ring. In terms of yield, efficiency, and atom economy, this synthetic proposal is far from ideal. If better substitutes of the ring formation reactions were applied, it is very possible for the route to be further simplified. Some of the reagents in our approach is toxic, corrosive, or can deal bodily harm. If the molecule is to be synthesized for medical or clinical purposes, these reagents, including triflate and osmium tetroxide, is to be replaced, and spatial orientation becomes of critical concern.

In addition, Due to restrictions on our knowledge and equipment, we did not consider the stereochemistry of the compound during the synthesis and did not conduct an experiment to prove the actual feasibility of our proposed route, which might become a hindrance for further research as experimental data is not available. To tackle the problem of different spatial construction within the product, a possible approach of asymmetrical synthesis is discussed, but confinements on the choice of possible reactions to enable such a pathway aborted its effort. The ringed nature of the chiral centers also increased the difficulty of creating such a method. The most feasible approach to distinguish between stereoisomers so far is still

chemical separation after production rather than production processes favoring specific products.

4 Conclusions

The proposed synthesis route enables the reproducible manufacture of cleistanthol in adequate laboratory settings, with acceptable levels of by-product generation (mainly in the two ring formation steps). This may serve as an aid during the process of transforming a herbal treatment into a modern medicine tested by scientific methods. Future research of the molecule can possibly focus on the pharmaceutical values of this molecule and its derivatives, as well as possible methods to improve the synthetic route, including:

1. Asymmetric synthesis or introduction of separation of different stereoisomers.

2. The elimination of the need for certain steps of protection group addition and removal.

3. Overall simplification of the synthetic route by altering the retrosynthetic mechanic or adopting shorter reactions. Increasing the overall atomic efficiency is also viable.

4. Transition from bodily toxic and environmentally damaging reagent to more biologically friendly ones.

5. Larger scale adoption of the synthetic route, and possibly feasible industrial-scale production.

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All authors contributed equally to this work and should be considered co-first authors.

References

1 P. Wu, Y. Cui, X. Han, C. Wang, P. An et al., Diterpenoids from Sauropus spatulifolius Leaves with Antimicrobial Activities, *J. Nat. Prod.* **85** 1304-1314 (2022) https://doi.org/10.1021/acs.jnatprod.2c00020

2 G. Mazza, Sauropus spatulifolius is a small 40 cm shrub native to Vietnam. Decorative leaves and medicinal virtues [Photograph], https://www.monaconatureencyclopedia.com/sauropus-spatulifolius-2/?lang=en, Retrieved November 5, 2022

3 J. M. Smith, S. J. Harwood, P. S. Baran, Radical retrosynthesis. *Accounts of Chemical Research* **51**(8) 1807-1817 (2018)

4 P. Puccio, *Sauropus spatulifolius, Monaco Nature Encyclopedia,* https://www.monaconatureencyclopedia.com/sauropus-spatulifolius-2/?lang=en, Retrieved November 5, 2022

5 L. A. Maslovskaya, A. I. Savchenko, V. A. Gordon, P. W. Reddell, C. J. Pierce et al., Isolation and Confirmation of the Proposed Cleistanthol Biogentic Link from Croton insularis, *Org. Lett* **13** 1032-1035 (2011) https://doi.org/10.1021/ol103083m

6 D. Z. Wang, Comprehensive organic name reactions and reagents (John Wiley2009), pp. 1342-1346

7 D. Z. Wang, Comprehensive organic name reactions and reagents (John Wiley2009), pp. 2733-2743

8 Sigma-Aldrich, Safety Data Sheet, Triethylamine, April 23, 2020, https://www.msds.com/view/4905977/16564599, Retrieved November 5, 2022

9 Combi-Blocks, Safety Data Sheet, Osmium Tetraoxide, December 13, 2019, https://www.msds.com/view/5365559/17570282, Retrieved November 5, 2022

10 Sigma-Aldrich Sweden AB, Säkerhetsdatablad, Trifluoromethanesulfonic acid, June 6, 2019, https://www.msds.com/view/4872726/15873971, Retrieved November 5, 2022

11 Combi-Blocks, Safety Data Sheet, Osmium Tetraoxide, December 13, 2019, https://www.msds.com/view/5437175/17586279, Retrieved November 5, 2022