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Step-by-Step Retrosynthetic Analysis of Norcyclocitrinoic acid A

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Abstract:

Norcyclocitrinoic acid A is a tetracyclic steroid with a bicyclic system, known for its potential as an anti-osteoporosis agent. This research focuses on the theoretical analysis of its retrosynthetic pathway, aiming to simplify the complex structure into manageable intermediates. By applying established organic chemistry principles, such as hydration reactions, Michael addition, and functional group interconversion, key disconnection points were strategically identified to break down the molecule step by step. The retrosynthetic approach was grounded in theoretical frameworks to ensure the proposed pathway's feasibility for practical synthesis. Through this process, a complete and theoretically sound retrosynthetic pathway was developed, providing a potential blueprint for future experimental synthesis. This research not only suggests a viable synthetic route for Norcyclocitrinoic acid A but also offers valuable insights into the retrosynthesis of other complex polycyclic molecules, demonstrating the utility of retrosynthetic analysis in addressing the challenges posed by structurally intricate compounds in synthetic organic chemistry.

Keywords:-component: Norcyclocitrinoic acid A, tetracyclic steroid, hydration reaction.

1. Introduction

Norcyclocitrinoic acid A, a recently discovered compound from the deep-sea-derived fungus Rhizopus sp. W23, has garnered significant attention for its highly effective anti-osteoporosis properties. Osteoporosis, a chronic metabolic bone disease, is characterized by decreased bone density resulting from an imbalance in bone homeostasis, where osteoclasts resorb bone and osteoblasts form bone. Its 2D structure is shown in Figure1. However, most anti-osteoporosis drugs are limited to inhibiting the function and differentiation of osteoclasts, with few drugs acting directly on osteoblasts. Additionally, there are few natural small molecules that target osteoblasts [1]. Existing treatments for osteoporosis include bisphosphonates, selective estrogen receptor modulators (SERMs), denosumab, and teriparatide. Bisphosphonates, such as alendronate and risedronate, inhibit osteoclast-mediated bone resorption but can cause gastrointestinal side effects and, in rare cases, osteonecrosis of the jaw [2]. SERMs, such as ralox-

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ifene, mimic estrogen's beneficial effects on bone density without some of the associated risks of estrogen therapy but carry an increased risk of blood clots and stroke [3]. Denosumab, a monoclonal antibody that inhibits RANKL, prevents osteoclast formation but may increase the risk of infections and dermatological reactions [4]. Teriparatide, a recombinant form of parathyroid hormone, stimulates osteoblast activity but poses a risk of osteosarcoma with long-term use and is costly [5].

Norcyclocitrinoic acid A stands out as a promising alternative due to its potent activity in promoting bone density and strength, potentially with fewer side effects. Nonetheless, because of its very complex polycyclic structure, the synthesis of norcyclocitrinoic acid A represents a great challenge and no efficient practical synthetic route for that compound has ever been reported. To address this gap, a thorough theoretical investigation of a retrosynthetic pathway leading to norcyclocitrinoic acid A is presented, offering a foundation for future practical synthetic approaches. Several key reactions were included in the analysis, such as hydration, the Diels-Alder reaction, and Michael addition, along with functional group interconversions (FGI). Based on these reactions, a complete theoretical retrosynthetic analysis of norcyclocitrinoic acid A was developed. The complete process of the designed retrosynthetic pathway is illustrated in the Figure2. This investigation provides an effective and theoretically sound strategy for the synthesis of norcyclocitrinoic acid A, offering valuable insights derived from first principles to guide practical synthetic efforts.

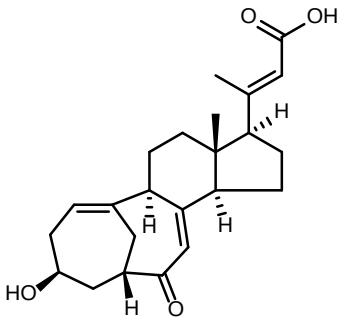

Figure 1. 2-dimensional structure of Norcyclocitrinoic acid A.

2. Overall retrosynthesis and multi-step analysis

In theory, under the retrosynthetic analysis, it is possible to disconnect norcyclocitrinoic acid A through a series of rational disconnections into simpler precursor molecules. This strategy targets strategic intermediates and transformations to facilitate the synthetic procedure. This work shows the overall retrosynthetic strategy for norcyclocitrinoic acid A that encompasses identifying key intermediates, hydration (H), Diels-Alder reaction (DA), Michael addition and functional-group interconversion steps. The overall strategy is to identify each oxidation level and functional group to determine strategic bonds. The next step is to identify the disconnection of the most important ring, utilizing hydration reactions to break the olefin on the ring. The target product will be divided into two synthons, using various reactions to break the bonds on each synthon. This division will result in the following precursor molecules: hexane-2,5-dione, methyl prop-2-enoate, 1-hydroxypropan-2-one, and 3-methylbut-3-en-2-one.

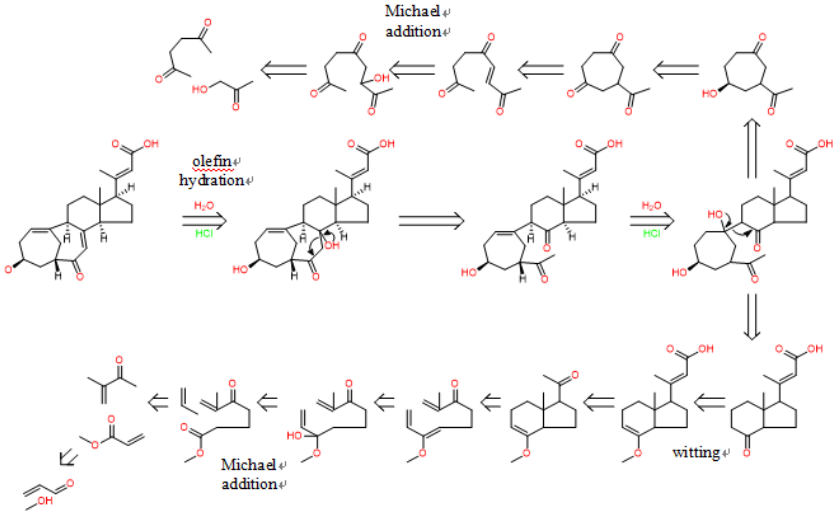

Figure 2. Overall complete retrosynthesis process.

First, water is added to norcyclocitrinoic acid A. The hydration reaction occurs in the presence of an HCl catalyst. This reaction targets the double bonds on the bridge-ring and the seven-membered ring, transforming norcyclocitrinoic acid A into (2E)-3-(7a-methyl-4-oxo-octahydro-1H-inden-1-yl) but-2-enoic acid and (5S)-3-acetyl-5-hydroxycycloheptan-1-one. As shown in Figure 3, the decomposition process results in the formation of these two key intermediates.

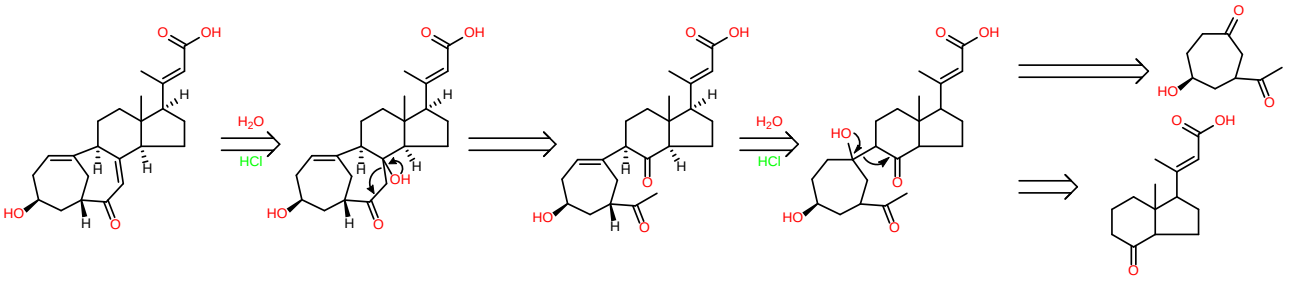

Figure 3. The process of hydration resolution of olefins.

The carbonyl group of (2E)-3-(7a-methyl-4-oxo-octahydro-1H-inden-1-yl) but-2-enoic acid can be transformed into a hydroxy group through the Wittig reaction with the addition of phosphorus ylides. Subsequently, the side chain can be converted into a carbonyl group by adding alcohol and water through esterification and hydrolysis reactions. Using a retro-Diels-Alder reaction, the six-membered ring will break into a straight chain containing three olefin groups, one carbonyl group, and one hydroxy group. Same as the step-by-step process shown in Figure 4, a hydration reaction is then employed to transform the olefin groups into ketone groups. The retro-Michael addition reaction is used to break the bond on the straight chain, resulting in the formation of methyl prop-2-enoate and 3-methylbut-3-en-2-one.

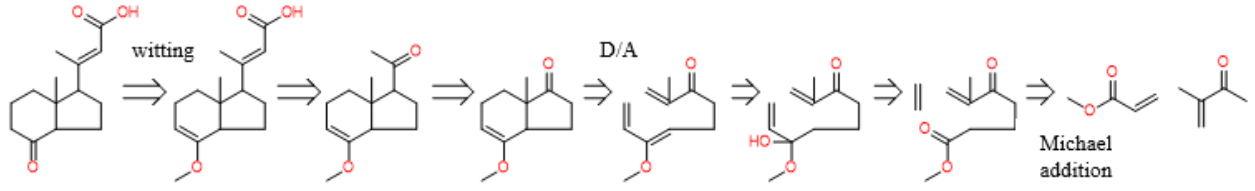

Figure 4. The process of breakdown (2E)-3-(7a-methyl-4-oxo-octahydro-1H-inden-1 yl) but-2-enoic acid.

The hydroxy group of (5S)-3-acetyl-5-hydroxycycloheptan-1-one is first transformed into a carbonyl group through an oxidation reaction. Using the retro-Michael addition reaction, one of the bonds on the seven-membered ring is broken, resulting in a straight chain with three carbonyl groups and one olefin group. Through a hydration reaction, the carbon-carbon double bond is converted into a carbon-carbon single bond, adding an additional hydroxy group. With the continued addition of water, (5S)-3-acetyl-5-hydroxycycloheptan-1-one is ultimately broken down into hexane-2,5-dione and 1-hydroxypropan-2-one. Figure 5 shows the last part of the entire retrosynthesis step.

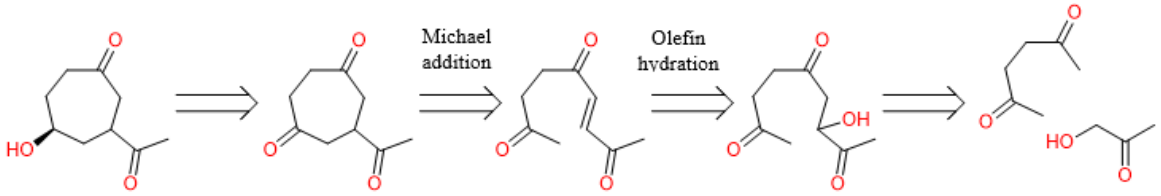

Figure 5. The process of breakdown of (5S)-3-acetyl-5-hydroxycycloheptan-1-one.

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3. Conclusion

This research provides a detailed theoretical analysis of the retrosynthetic pathway of norcyclocitrinoic acid A, a complex polycyclic molecule with significant therapeutic potential as an anti-osteoporosis agent. By employing key reactions such as hydration, Diels-Alder reaction, Michael addition, and functional group interconversion (FGI), The research developed a comprehensive retrosynthetic pathway that offers valuable insights into the efficient construction of norcyclocitrinoic acid A and contributes to the broader field of synthetic organic chemistry.Despite these advances, several challenges were encountered during this study. The structural complexity of norcyclocitrinoic acid A complicates the identification of direct disconnections, necessitating extensive theoretical analysis to propose feasible intermediates. Moreover, theoretically feasible and reasonable retrosynthetic pathways and operations may encounter difficulties during practical synthesis. Future studies should focus on the experimental validation of the proposed retrosynthetic pathway to confirm its feasibility and efficiency. Optimization of reaction conditions, including temperature, solvent, and catalyst, is essential to improve the practical application of the synthesis. Additionally, exploring analogs of norcyclocitrinoic acid A could lead to the discovery of compounds with higher efficacy and fewer side effects.

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