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Total Synthesis of Anti-osteoporosis Natural Product Peniditerpenoid A

Zicheng Wang[1], Chengyuan Li[1], Yuheng Wang[1*]

[1]College of Pharmacy, China Pharmaceutical University, Nanjing, China
**Corresponding Author. Email: 2020242655@stu.cpu.edu.cn*

Abstract. Peniditerpenoid A is an unprecedentedly isolated indole diterpenoid natural product that displays potential in inhibiting rankly induced osteoclast differentiation, make it a competitor for relevant treatment. We report a retrosynthesis analysis and total synthesis route of Peniditerpenoid A, and completed the construction of complex multi-membered ring systems including heterocycles by nucleophilic addition and intramolecular condensation. The highlight of the synthesis is that we use multicomponent reaction to control the product configuration and use DABCO as catalyst to improve the yield of the target product. Our study provides a new way for large-scale synthesis of Peniditerpenoid A and related drug development.

Keywords: Osteoporosis, Peniditerpenoid A, Total synthesis, Natural product

1. Introduction

Osteoporosis is a systemic bone disease primarily characterized by increased bone fragility, decreased bone mass, and heightened susceptibility to fractures [1]. Associated with serious morbidity and mortality, osteoporosis is a common condition among middle-aged and elderly individuals. The symptoms of osteoporosis include pain and spinal deformity, which leads to functional impairment and thoracic deformity, thereby affecting cardiopulmonary function [1].

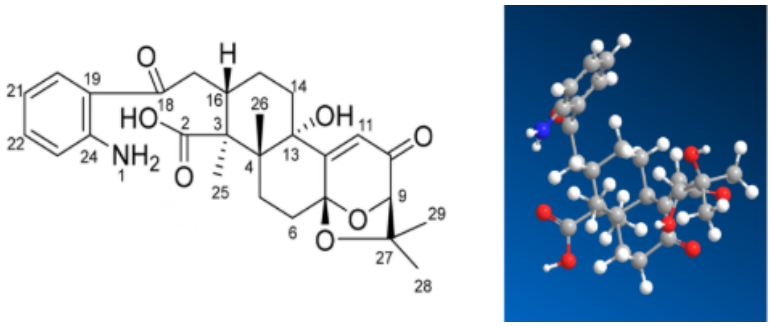

Figure 1. Structure of Peniditerpenoid A

Due to its chronic nature, osteoporosis necessitates decades of treatment and therapy. Given the rising concerns regarding side effects and the potential for rebound phenomena, there is an urgent

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need for improvements in long-term bone-specific pharmacological treatment strategies [2]. In 2024, Jian Cai, Min Li, and their colleagues isolated an unprecedented dicyclophosphoryl indole diterpenoid, Peniditerpenoid A (1), from Penicillium sp. SCSIO 41411, a fungus derived from mangrove sediments [3].

Inhibiting lipopolysaccharide-induced NF-κB and further preventing RANKL-induced osteoclast differentiation in bone marrow macrophages, compound 1 effectively reduces the activation level of NFATc1, leading to diminished osteoclast differentiation [4]. These findings indicate that compound 1 holds significant potential as an inhibitor in the treatment of osteoporosis-related diseases. As an indole diterpenoid (IDT), compound 1 features a complex ring system. Although it exhibits an overall planar structure, the molecule contains multiple chiral centers, along with an unsaturated carbonyl group and an amino group. Additionally, compound 1 has a tendency to undergo intramolecular reactions.

2. Result and method

After analyzing all the possible bond cleavage of Peniditerpenoid A, a step-by-step decomposition strategy comes out, which is better than other reverse synthesis routes by comparing the reaction efficiency, raw material availability and step complexity of different routes. Systematically analyzing the oxidation level and functional group distribution characteristics of each ring system of this compound, we focused our attention on the relatively complex D ring, hoping to find the optimal strategy for reverse synthesis by disassembling this heterocyclic structure (Figure 1). The presence of these two characteristic functional groups indicates that the reactive properties of these two classical organic structures were leveraged for efficient and precise bond cleavage. Considering the harsh conditions of [2+2] Diels-Alder reaction and the possible side reactions associated with C-C bond cleavage of other rings, we did not choose [2+2] cycloaddition or C-C bond cleavage at other ring positions as the primary strategy. Ketal reaction conditions are mild, high selectivity, accurate construction of the target ring (Figure 2). Additionally, the ketone group and diol as intermediates are both easily synthesized functional groups, which greatly reduces the difficulty of subsequent synthesis [5]. Therefore, we finally confirmed that the formation of ketal is a key step in the synthesis of this heterocycle.

Completing the inverse synthesis analysis of ketal structure, we turned to the carbon-carbon double bond of D ring and try to break it through appropriate reaction strategy. Due to the unique electron cloud distribution and functional group proximity effect of α, β-unsaturated ketone, its structural characteristics provide us with a clear reaction direction (Figure 2). We can achieve the forward synthesis of this part by highly efficient C-C linkage of the multi-membered ring fragments obtained after disassembly with oxopentanal 11 through classical aldol condensation reaction (Figure 2). After completing the preliminary decomposition of D ring, we turn our attention to the remaining multicyclic system. The structural characteristics of the polycarbonyl group contained, high reactivity of α-H at the carbonyl ortho position leads to the carbon chain cleavage and further decomposition of the remaining ring system through nucleophilic addition and other common organic reactions [6].

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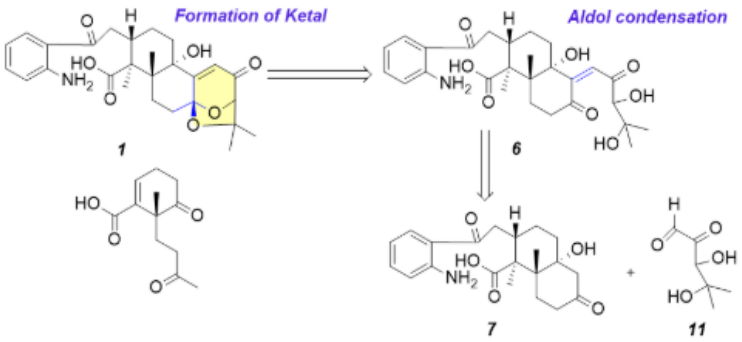

Figure 2. Retrosynthesis analysis 1

The polycarbonyl structure, containing carbonyl carbon, directly connected to the benzene ring and the carbonyl group on the lower carboxyl carbon formed a typical 1,5-dicarbonyl structure in the molecular skeleton, a critical active site for subsequent bond cleavage. While a methyl group attached to C3 (Figure 1), the steric effect and electronic effect of methyl group combine to make C3 a chiral carbon with S configuration. Based on above analysis, the target compound is reasonably resolved into three core components from the perspective of forward synthesis, including o-formanilide, which is easy to prepare industrially and has low cost, and decalin 8 in Figure 3. Retrosynthetically, multi-component reaction contains successive steps with high region selectivity [7]. Decalin 8 is relatively simple in structure and easy to be disassembled by conventional reactions.

It is worth mentioning that in the decalin system obtained by disassembly, the bridge carbon C13 (Figure 1) of the bridge ring system of [4.4.0] connects a hydroxyl group. A carbonyl functional group exists at C7 in decalin 8 (Figure 3), one carbon away from the bridgehead carbon C13, and both of them form β-hydroxyketone structure in space structure. This special structure combination provides us with a new approach of bond cleavage. Thus, we designed a targeted C-C bond cleavage reaction based on the structural characteristics of 3β-hydroxyketone, the decalin system is successfully resolved into a structurally stable six-membered ring segment and a linear carbon chain connected to it (Figure 3). Surprisingly, in the previous step, we took advantage of aldol condensation to form conjugated system and specific carbon chain length to obtain one of the intermediates of this compound, then formed 1,5-dicarbonyl structure in the molecular structure again (Figure 3). This repeated structural feature suggests that we can take advantage of the regioselectivity of Michael nucleophilic addition reactions to synthesize the key intermediate 9 (Figure 3). After a series of precise bond-breaking operations and structural derivations, we finally obtained two easily accessible critical synthetics, including a six-membered ring intermediate 10 containing α, β-unsaturated carboxylic acids and an industrially common unsaturated butanone (Figure 3).

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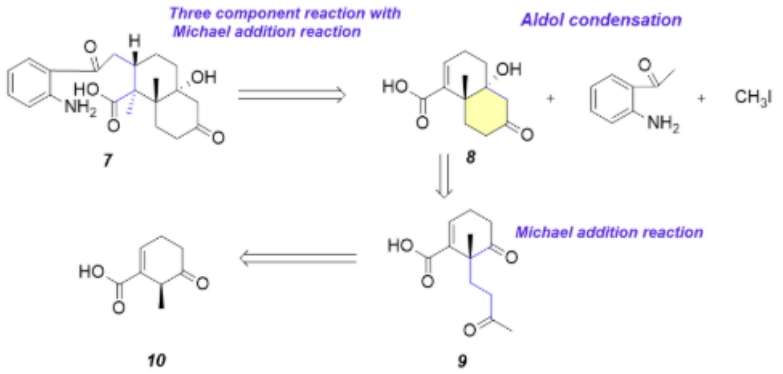

Figure 3. Retrosynthesis analysis 2

The synthesis of acid 10 begins with bromination of butanone as shown in Figure 4. Bromine is easy to react with α-H of butanone under the catalysis of iron. In order to complete the bromination reaction of two H atoms, we appropriately raised the reaction temperature and reaction time. Bromide ion, as a good leaving group, provides active sites for carbon chain growth in dibromobutan 16 (Figure 4) [8]. Considering the substitution of terminal carbon, the steric hindrance of electrophile is smaller, and the yield of intermediate 17 can be improved by extending carbon chain from above.Pyrrolidine as electron donor can enhance the reactivity of α-H. Therefore, we innovatively propose to use the catalytic effect of this electron donor to promote the substitution reaction of α-H of aldehyde with bromobutanone 16, thus increasing the yield, as is shown in Figure 4. Aldehyde groups have higher reactivity than ketone carbonyl groups. With this property, acetic acid can condense with aldehyde groups generated from the previous step and has high selectivity. It should be noted that lowering the temperature and increasing the acid concentration can not only improve the selectivity, but also ensure the formation of α, β-unsaturated acid 18 conjugate system (Figure 4) [9]. This key structure plays an important role in the formation of C-C bonds and the subsequent construction of six-membered rings. In the synthesis of target compound acid 10, bromine departs to form carbocation, and the transfer of unorbital electron pairs leads to the formation of C-C bond, thus completing the construction of six-membered rings. However, we soon encountered difficulties, and the yield of this compound in the actual reaction was too low. Thus, we introduced DABCO. As a nucleophile, DABCO promotes the coordinated transfer of electron pairs, resulting in the efficient formation of C-C bonds at α position, as shown in Figure 4 [10]. Through a series of reactions mentioned, we obtained the important intermediate acid 10.

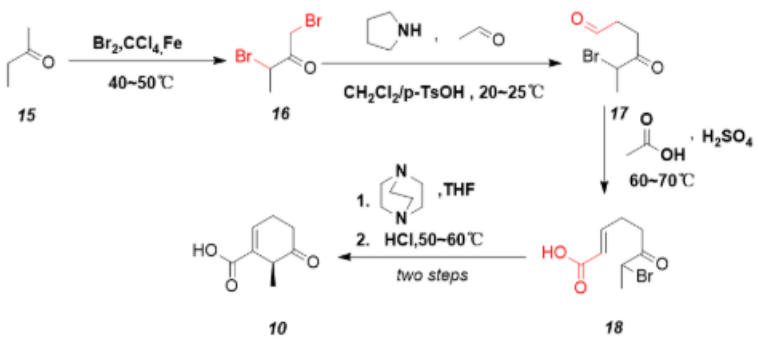

Figure 4. Synthesis of Carboxylic Acid 10

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The synthesis of oxopentanal 16 begins with the addition of propylene to o-dihydroxypropane 20 (Figure 5), leveraging phosphotungstic acid as catalyst [11]. Subsequent oxidation of o-dihydroxypropane 20 provides oxidized propionaldehyde. CuO-CeO_2 plays a key role in overcoming the excessive oxidation of hydroxyl groups on terminal carbons [12]. The precise oxidation of cupric oxide-ceria ensures both the yield of oxopropionaldehyde 21, shown in Figure 5 and the avoidance of excessive oxidation to oxopropionic acid. The α-H of oxopropionaldehyde 21 has good reactivity. Since intermediate 22 has only one α-H site and its H activity is much higher than that of acetone, α-bromination and hydrolysis led to intermediate 22 (Figure 5) [13]. Condensation of intermediate 22 with acetone under acidic conditions thus affords oxopentanal 11 in relatively high yields despite the presence of other condensation byproducts. Oxopentanal 11 contains the structure of o-dicarbonyl and o-diol with poor stability. Therefore, the linkage of oxopentanal 11 and carbocyclic ring 8 and subsequent synthesis are extremely challenging (Figure 6).

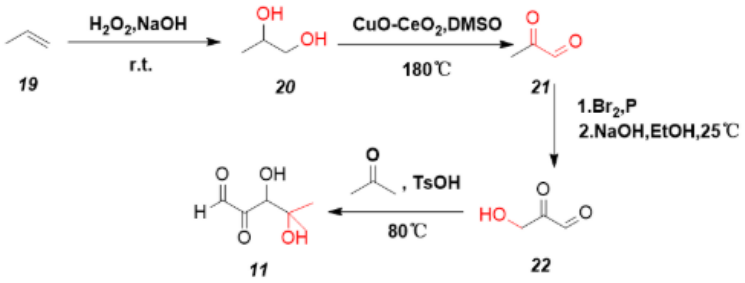

Figure 5. Synthesis of Oxopentanal 11

Then intermediate acid 10 undergoes a subjection to Michael addition and condensation to construct Decalin system (Figure 6). In alkaline environment, the carboxyl group of intermediate 10 easily reacts with other reagents. We esterify the carboxyl group, thereby protecting it from conversion of the functional group [14]. In order to avoid hydrolysis of ester group, we adopt alkaline environment and lower temperature in the process of intramolecular condensation of carboxylate 23 to form intermediate 9, which avoids deprotection and elimination of hydroxyl group (Figure 6). Then the intermediate 8 reacts with o-formylaniline and methyl iodide through multi-component synergistic reaction [15]. The target chiral carbon C3 in S configuration was generated by the directed attack of nucleophile. This step is highly stereoselective, which is essential for the stereosynthesis of Peniditerpenoid A (Figure 6). The steric hindrance effect of carbonyl group and multiple reactive sites of intermediate 7 greatly reduced the yield of intermediate 6 (Figure 6). In order to overcome this difficulty, we innovatively used Ti organic complex as a site-selective catalyst (Figure 6) [16]. The functionalization of this site achieved highly selective condensation and improved the yield of intermediate 6 to a certain extent. Finally, the intermediate 6 was placed in an acidic environment, a deprotection reaction occurred, and a stable ketal heterocycle was formed, resulting in the final target product, as is shown in Figure 6.

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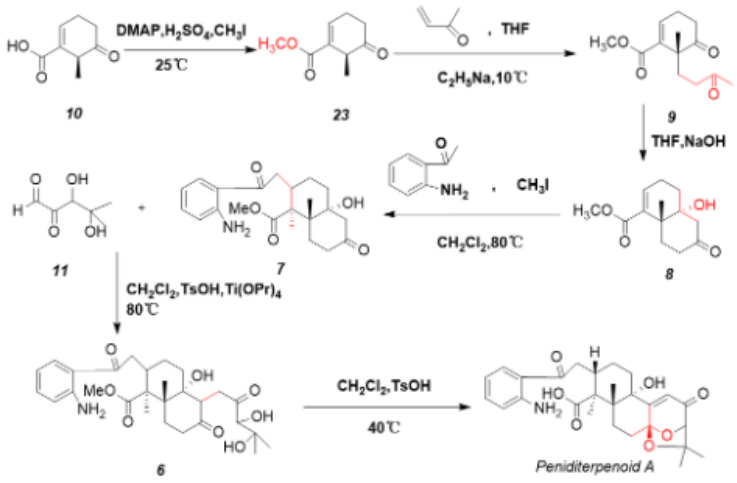

Figure 6. Total synthesis of Peniditerpenoid A

3. Discussion

We innovatively applied multi-component synergistic reaction to asymmetric synthesis by taking advantage of the directed attack of nucleophils. This effectively ensures the biological activity of natural products and improves the yield of target products, providing ideas for asymmetric synthesis of other chiral carbon sites containing methyl or other group modifications. In the construction of six-membered rings, we use nucleophile DABCO as catalyst to activate the reaction sites of substrates. The electron pushing effect of DABCO effectively promoted the electron pair cooperative transfer, leading to the formation of C-C bond, thus successfully completing the construction of six-membered rings and successfully improving the yield. The application of DABCO plays an important role in ring formation. However, problems still exist, which have not been completely solved in the research. The structural instability of oxopentanal is a major difficulty in the subsequent synthesis. While the steric hindrance effect and multiple reactive sites of polycyclic ring greatly reduce the selectivity of oxopentanal linking to specific sites of carbocyclic ring. Although we tried to improve the selectivity and yield by using new metal catalysts, the yield did not increase significantly. Redesigning the synthetic route of D ring and searching for suitable catalyst become the main direction of our follow-up research.

4. Conclusion

We firstly analyzed the retrosynthesis of the Peniditerpenoid A reasonably, and completed the design of its total synthetic route. The synthetic route enables the construction of its complex polycyclic system with precise stereo control via a series of reactions including nucleophilic addition, intramolecular condensation, multicomponent reactions catalyzed by DABCO, aldol condensation, Michael addition, targeted C-C bond cleavage, bromination, oxidation, esterification, and deprotection, a total of 14 reactions.

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