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The Synthesis of Peniditerpenoid A

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Abstract. Peniditerpenoid A, a di-seco-indole diterpenoid, which was obtained from the mangrove-sediment-derived fungus Penicillium sp. SCSIO 41411, may act as an inhibitor with significant potential for the treatment of diseases related to osteoporosis. Based on retrosynthetic analysis, a 15-step forward synthetic route was proposed, in which 1-alkenyl-3-butyne was used as the starting material, and the target molecular structure was constructed through carbon chain extension, the Diels-Alder reaction, functional group transformation (e.g., hydroxylation, introduction of cyano group, etc.) and Michael addition. Despite the poor stereoselectivity of some steps, low yields, and lack of literature support for the interconversion of 1,2-cyclohexanediones, the present study provides a basis for the synthesis of Peniditerpenoid A, which is expected to be widely used in the treatment of osteoporosis-related diseases.

Keywords: Peniditerpenoid A, Di-seco-indole diterpenoid, Synthesis analysis

1. Introduction

Terpenes are natural organic compounds commonly found in nature, with isoprene as the basic unit, which takes different linkages and different oxidation levels. Many representative drugs in current clinical use such as Paclitaxel (for breast and ovarian cancer treatment), artemisinin (for malaria), and etoposide (for small cell lung cancer and lymphoma) are all based on this scaffold development. Researchers have also modified natural terpenoids to enhance efficacy and reduce side effects: glycyrrhizic acid derivatives showed encouraging anti-inflammatory activity; and several other types of monoterpene derivatives displayed potential in alleviating anxiety and inducing sleep onset latency.

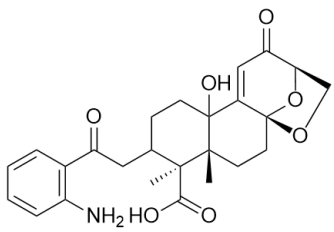

Figure 1. Peniditerpenoid A

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Peniditerpenoid A (Figure 1) is a di-seco-indole diterpenoid which was obtained from the mangrove-sediment-derived fungus Penicillium sp. SCSIO 41411. Peniditerpenoid A can inhibit lipopolysaccharide-induced NF-κB and further prevent RANKL-induced osteoclast differentiation in bone marrow macrophages. It can also exert significant inhibition of NF-κB activation in the classical pathway by preventing TAK1 activation, IκBα phosphorylation, and p65 translocation. Furthermore, Peniditerpenoid A effectively reduced the level of NFATc1 activation, resulting in the attenuation of osteoclast differentiation. The physical properties of this molecule have been characterized using techniques including mass spectrometry, polarimetry, UV absorption spectroscopy, IR spectroscopy, NMR, and X-ray diffraction. It has a molecular formula of $C_{27}H_{33}NO_7$and a molecular weight of 483.55. At room temperature, it presents as white needle-like crystals with a melting point of 245–247 °C. Its chiral carbons exhibit the configuration (3S, 4R, 7S, 9R, 13S, 16S) [1]. After retrosynthetic analysis of this molecule, we have successfully devised a pathway for the total synthesis of Peniditerpenoid A in a total of fifteen steps, hoping to give theoretical guidance on the synthesis of this molecule.

2. An overview of di-seco-indole diterpenoids

Di-seco-indole diterpenoids are a series of compounds based on a terpene skeleton and containing an indole ring. The core of these compounds is a diterpene skeleton with two chemical bond cleavages, and this skeleton is combined with an indole ring. Di-seco-indole diterpenoids are mainly found in certain fungi, especially in some strains of Fusarium and Penicillium [2, 3]. Some di-seco-indole diterpenoids can act on the nervous system, interfering with the transmission of nerve signals [4]; some di-seco-indole diterpenoids can also inhibit cell proliferation and induce apoptosis, etc [5]; there are also some di-seco-indole diterpenoids with a certain degree of antimicrobial activity, which can inhibit the growth and reproduction of certain bacteria or fungi [6].

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3. The retrosynthesis analysis and the proposed synthesis route

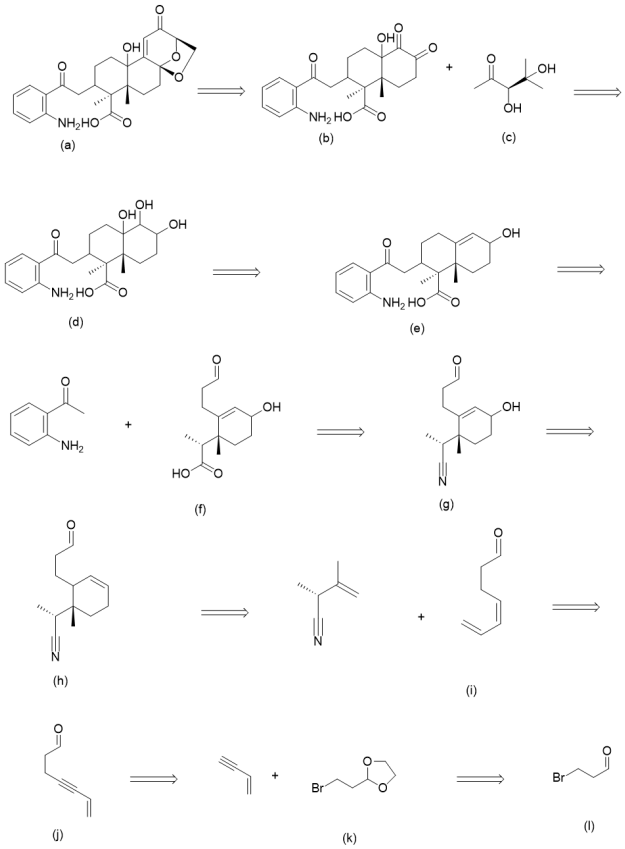

Figure 2. Retrosynthetic analysis of Peniditerpenoid A

Although the structure seems to be very complicated, we can still find some hints to complete our retrosynthesis analysis. As shown in Figure 2, because target molecule (a) has an acetal structure, it can be synthesized from a ketone. Moreover, alpha-beta unsaturated ketones can be synthesized through an aldol reaction. The 1,2-diketone structure in (b) can be derived from the 1,2-dihydroxyl structure in (c) without affecting the other hydroxyl group. Two of the hydroxyl groups in (c) could be derived from the carbon-carbon double bond in (d). Because (e) contains a 1,5-dicarbonyl structure, we can use a cascade reaction (a Wittig reaction followed by a Michael addition) to synthesize it using (f) and 1-(2-aminophenyl) ethan-1-one. The α, β-unsaturated alcohol structure in (f) can be derived from the propylene structure in (h) using singlet oxygen as an oxidant. The six-membered ring in (h) can be formed via a Diels-Alder reaction. One of the carbon-carbon double bonds in molecule (i) could be derived from a carbon-carbon triple bond, and molecule (j) can be formed by an SN2 reaction, which can extend the carbon chain. At this point, we have completed the retrosynthetic analysis.

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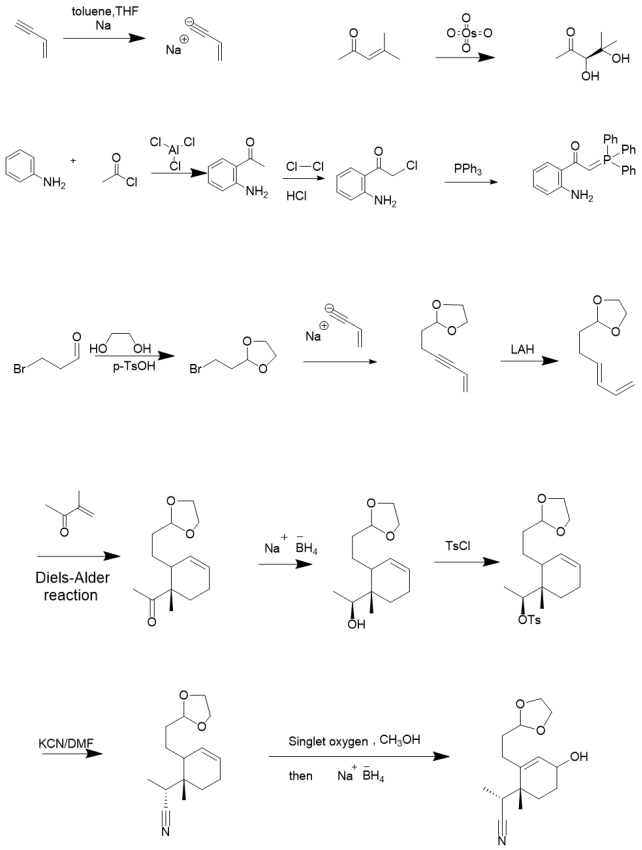

Figure 3. The first part of the synthesis route

Once we finalized our retrosynthesis pathway, we could then figure out the forward synthesis route. As shown in Figure 3, sodium but-1-en-3-yne can be prepared from but-1-en-3-yne. Subsequently, we protected the carbonyl group in 3-bromopropanal. Afterwards, we extended the carbon chain through a nucleophilic substitution, and used LAH to selectively reduce the C-C triple bond into a trans C-C double bond. Then, it is easy to perform the Diels–Alder reaction with 3-methylbut-3-en-2-one and the previous product, which introduces another carbonyl. The carbonyl is then reduced to a hydroxyl group. TsCl is then used to turn the hydroxyl group into OTs, a good leaving group, which allows the introduction of the cyan group by a nucleophilic substitution. By adding singlet oxygen, methanol, and the reductant $NaBH_4$, the cyclic olefin performs a Schenck Reaction and got an allylic alcohol [7].

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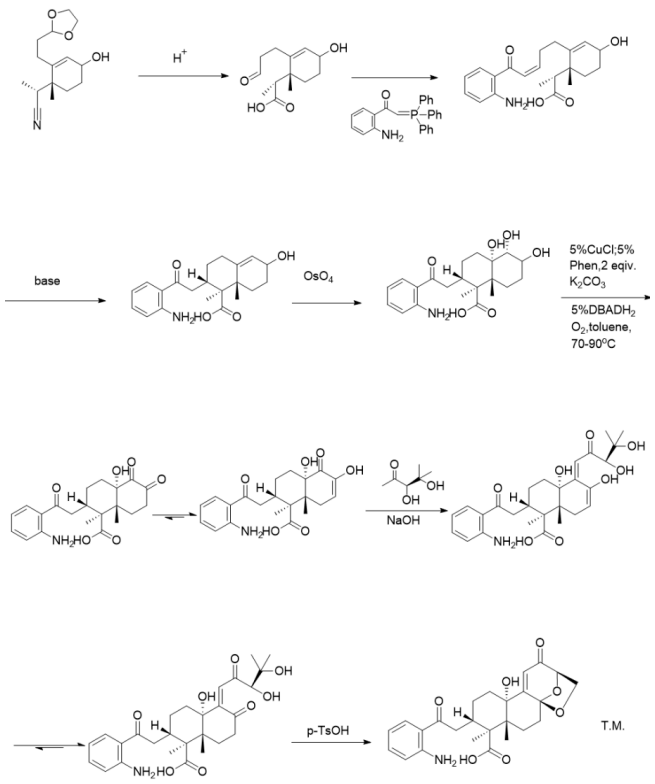

Figure 4. The second part of synthesis route

As Figure 4 shows, the acetal structure is then changed into ketone under acidic conditions. The Phosphorus ylide prepared from aniline and acetyl chloride was then used to perform a Wittig reaction, which was better than a simple aldol condensation reaction because the existing carboxyl group in the substrate may lead to the occurrence of another aldol condensation reaction (Figure 5). Then, under alkaline condition, a Michael addition is performed to form a six-membered ring. Subsequently, using Osmium tetraoxide, we formed a cis-vicinal diol, which was further oxidized by oxygen with a copper catalyst, and two of the hydroxyl groups were oxidized into a carbonyl group [8]. The other hydroxyl group is unaffected because there is no hydrogen on the carbon connected to that hydroxyl group. This 1,2-Cyclohexanedione structure would be unstable; therefore, one of the carbonyl groups would exist as an enol (Figure 6). The other carbonyl group is left unchanged, because neither of the two carbons attached to it has a hydrogen atom on it. As a result, the unchanged carbonyl group can selectively perform aldol condensation with (R)-3,4-dihydroxy-4-methylpentan-2-one. After that, the enol will revert to the ketone. Finally, in acid condition, the carbonyl group can react with the two hydroxyl groups and form an acetal structure, completing the final step of synthesis.

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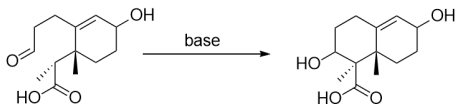

Figure 5. The other aldol condensation

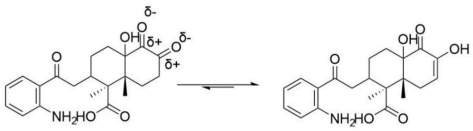

Figure 6. The keto enol tautomerization

4. Conclusion

After 15 steps of operation, we successfully synthesized Peniditerpenoid A. However, this synthetic pathway has some drawbacks. In step eleven, the stereoselectivity may be relatively poor, and in step seven, the yield is also relatively low. Besides, there is no relevant literature to support the mutual transformation of the 1, 2-cyclohexanedione structure described in the article. Despite these limitations, we still hope that our study will enable the wider application of this substance in the treatment of osteoporosis-related diseases.

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