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Total Synthesis Analysis of Pseuboyenes D

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Abstract:

In this work, we propose a total synthesis route for the antifungal agent Pseuboyenes D, a compound derived from Pseudallescheria boydii CS-793. Pseuboyenes D exhibits antifungal activity comparable to Amphotericin B while offering the advantage of a simpler structure, making it a promising candidate for clinical applications. The system became the focus of this analysis due to its regioselectivity, and after exploration, a [2+2] photocycloaddition and ring expansion strategy was adopted to construct the key bridged ring system. The route employs readily available substrates and mild reaction conditions, making it scalable and suitable for large-scale production. Computational analysis of the regioselectivity of the photocycloaddition revealed that the bridged adduct was thermodynamically favored over the fused system. The synthetic route was further diversified by incorporating functional group modifications using TMS derivatives, enhancing the potential for pharmacological applications. Overall, this work establishes an efficient and scalable synthetic pathway for Pseuboyenes D, paving the way for future applications in antifungal drug development.

Keywords: Total Synthesis Analysis; Pseuboyenes D; Antifungal; [2+2] Photocycloaddition.

1. Introduction

Fungal infections, which often lead to severe symptoms and even fatal results, pose a significant challenge to global health. Amphotericin B has long been the first-line medication for systemic fungal infections due to its potent antifungal activity. However, its complex structure, high production costs, and associated toxicity necessitate the search for alternative antifungal agents. Recently, a natural product named Pseuboyenes D was derived from the cold-seep-sediment fungus Pseudallescheria boydii CS-793 [1]. This compound not only exhibits antifungal activity comparable to that of amphotericin B but also features a simpler chemical structure, making it easier to synthesize. This simplicity makes Pseuboyenes D an attractive candidate as a clinical replacement for Amphotericin B. In this study, which propose a total synthesis route for Pseuboyenes D and E.The synthetic route employs a [2+2] photocycloaddition and ring expansion strategy to obtain the desired skeleton. The substrates can be synthesized through a simple linear synthesis, implying that inexpensive and readily available starting materials and mild synthetic steps can be used(see Figure 1).

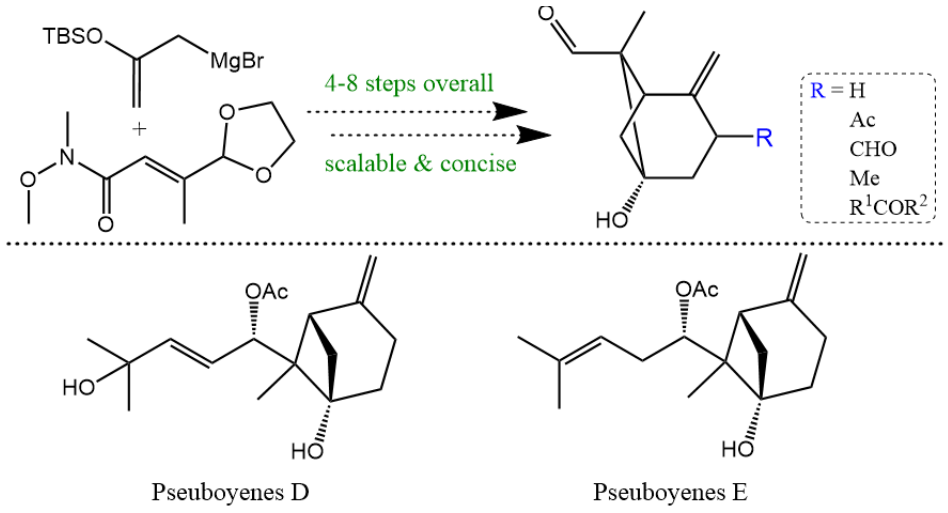

Figure 1. The graphical abstract of this work.

2. Retrosynthetic analysis

The inspiration for our initial retrosynthetic analysis was largely drawn from the direct 2+2 photocycloaddition. Because the formation of the bridged ring system represents the primary synthetic challenge in the synthesis of Pseuboyenes D. Bridged ring systems are typically harder to construct than fused ring systems due to the associated ring strain, utilizing an irreversible addition might be advantageous for the cyclization reaction.

Firstly, the disassembly of Pseuboyenes D (6) leads to the alkyne 8 and aldehyde 5. Subsequent examination of the bridged ring system 5 revealed that direct construction of the bridge ring system via [2+2] photocycloaddition might preferentially yield the straight product [2], which is the fused system (7). Generally, photobicyclisation tends to favor the formation of five-membered ring systems (rule of five) [3,4]. To ensure the prevalence of the crossed adduct, the reacting olefinic units need only two atoms [5].

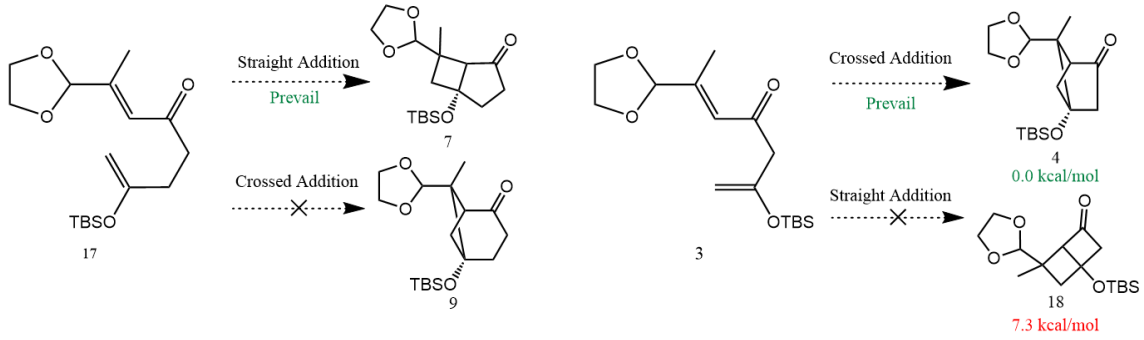

Figure 2. Regioselectivity of photocycloaddition of diolefins 17 and 3.

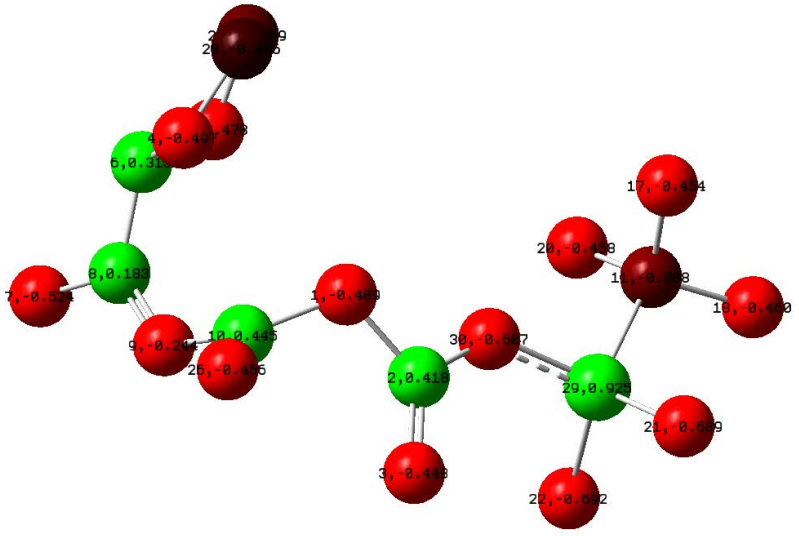

Figure 3. Mulliken charges of diolefins 3.

The energetics of the straight and crossed adducts of 3 and 17 as well as the Mulliken charges of Diolefins 17 were studied computationally using the B3LYP/6-31G(d) method [6]. The charges on carbons 8 and 2 are 0.183 and 0.418, while those on carbons 9 and 3 are -0.244 and -0.448, respectively. The computed energy for the crossed adduct (-1216.958544 Hartree) was lower than that for the straight adduct (-1216.946951 Hartree) (Details are available in the supporting information). That revealed the Mulliken charges are matched and the bridged ring system (4) is thermodynamically preferred which as shown in Figure 2 and 3[7].

Leveraging this principle, I explored a skeletal editing strategy: initially, a substrate with one less carbon was subjected to photocycloaddition, yielding the bridged ring system (4), followed by the insertion of one carbon to achieve the desired structure (5). Furthermore, the insertion of TMS group during this ring expansion process offers additional possibilities for structural diversification. By reacting with various electrophiles, it enables the

conversion of silane into different organic functionalities, such as acetyl, aldehyde, methyl, and ether groups. This is highly advantageous for structural modifications in pharmacology. Finally, the necessary carbon chain was constructed using Grignard reagent for carbonyl addition. The overall retrosynthetic route is shown in Figure 4.

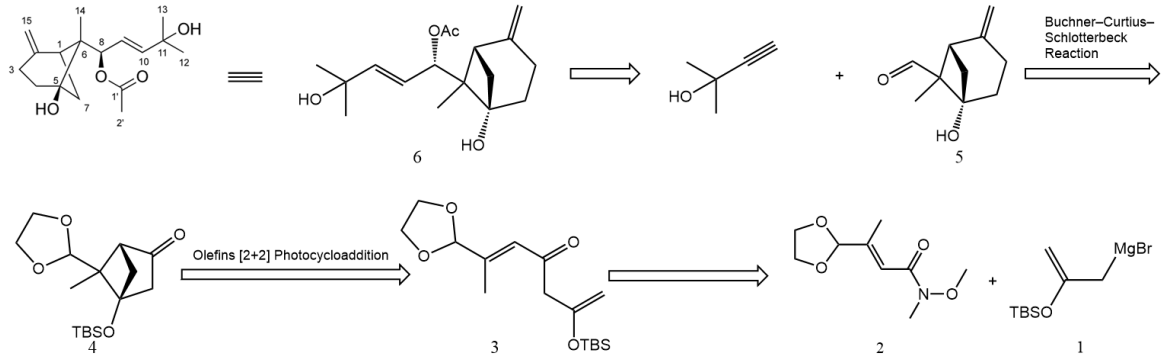

Figure 4. Provides a retrosynthetic overview of the strategy employed in the current total synthesis.

3. Forward synthesis

The forward synthesis begins with the simple treatment of commercially available reagents. Hydrolysis [8], protection, enolization, and amidation are carried out to prepare Grignard reagent 1 and Weinreb amide 2. Subsequently, carbonyl addition-elimination is performed to obtain the carbon chain 3 required for cyclization.

Then, [2+2] photocycloaddition was performed under irradiation, leading to the bridged ring system 4.

Next, compound 4 was treated with $TMSCHN_2$ and MeOH in the presence of catalytic amounts of $Rh_2(TFA)_4$ to afford the ring-expanded product 19. If MeOH treatment is not applied [9], but instead acetic anhydride, Vilsmeier-Haack conditions, iodomethane, and aldehyde with bismuth triflate are used, the silane can be respectively converted to the acetyl 9b, aldehyde 9c, methyl 9d, and ether 9e, as shown in Figure 8 [10].

Subsequently, Ketone 9a was converted to the olefin using the Wittig reaction, and the acetal was hydrolyzed in the subsequent workup to afford aldehyde 5.

Following this, the enantioselective addition reaction of alkyne 8 directly to aldehyde 5 in the presence of (-)-N-methylephedrine to furnish propargylic alcohol 10 [11]. For alcohol 15, the reaction of Grignard reagents 13 and aldehyde 5 with chiral diamine 14 can afford it [12].

Thereafter, alkyne 10 was then reduced to trans-alkene 11 upon exposure to sodium dissolved in ammonia.

Finally, alcohols 11 and 15 were each treated with acetic anhydride and TBAF to afford Pseuboyenes D (6) and E (16). The overall synthetic routes are shown in Figures 5, 6, and 7.

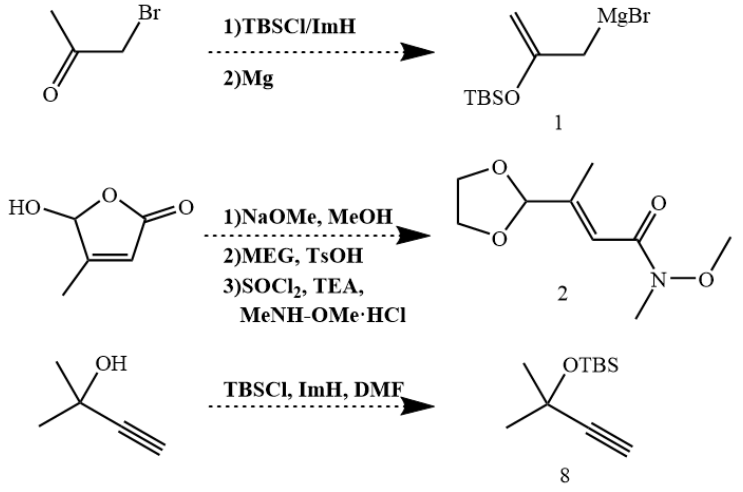

Figure 5. Preparation of Substrates.

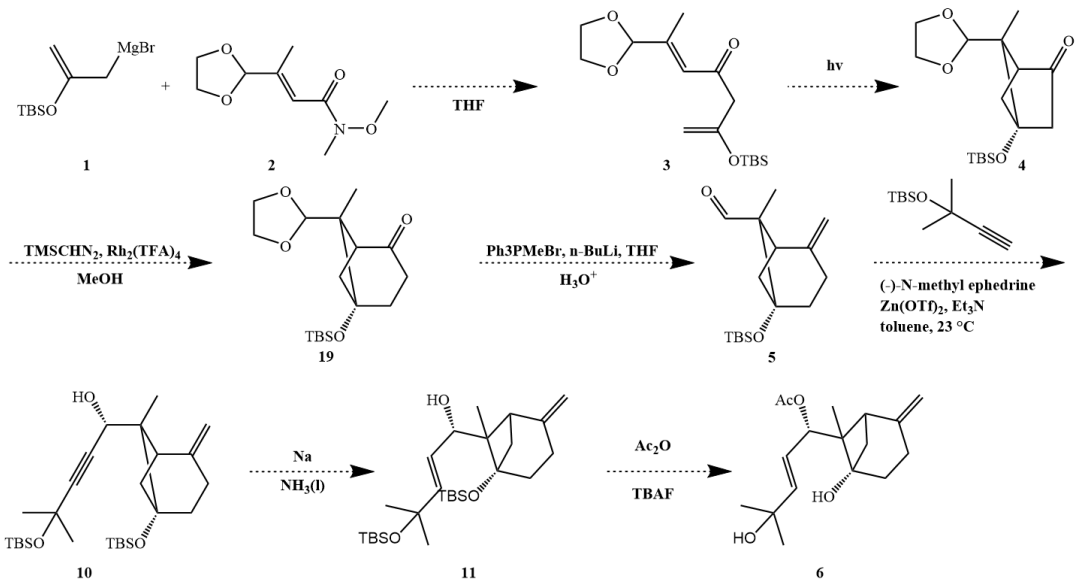

Figure 6. Total synthesis route of Pseuboyenes D.

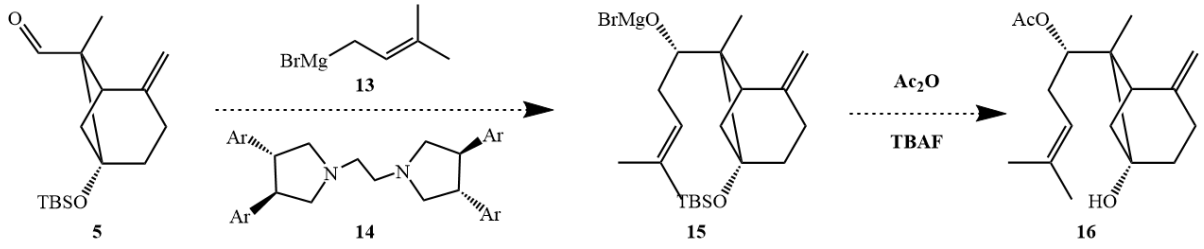

Figure 7. Synthesis route of Pseuboyenes E.

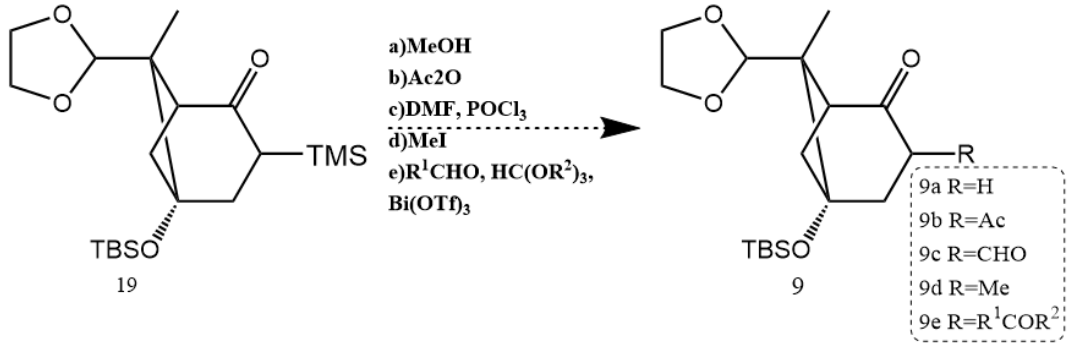

Figure 8. Scalable synthesis of intermediate 19.

4. Conclusion

The chemistry described herein laid the foundation for the eventual total synthesis of Pseuboyenes D (6) and E (16). Efficient synthetic routes to the key bridged ring system are detailed. Our initial analysis revealed that directly constructing the bridged ring system was not feasible due to the steric hindrance of the substrate, which would lead to the predominance of fused adduct 7. Attempts to use hydrogen bonding to fix the conformation were found to be cumbersome and ineffective. Further exploration surprisingly revealed that using a substrate with one less carbon could successfully construct the desired bridged ring system 4, followed by a ring expansion leading to the target skeleton 9. Subsequent enantioselective addition and simple conversions afforded the target molecule. This route is highly scalable, providing possibilities for molecular diversity construction relevant to chemical biology and medicinal chemistry studies. Additionally, the use of

inexpensive starting materials makes it suitable for large-scale production, demonstrating promising prospects for application. Overall, this work has established a novel and efficient synthetic pathway for Pseuboyenes D (6) and E (16).

5. Appendix

Optimization and frequency computational data for diolefins 3 (si_001.LOG)

Optimization and frequency computational data for crossed adduct 4 (si_002.out)

Optimization and frequency computational data for straight adduct 18 (si_003.out)

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