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Total synthesis of (±)-Simonsol C using acid-induced dearomatization as key reaction

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Abstract

Total synthesis of (±)-simonsol C was accomplished using a dearomatization under acidic condition as key step to construct aryl containing quaternary center. The 6/5/6 benzofuran unit was formed through reductive elimination with Zn/AcOH and a spontaneous oxy-Michael addition. This synthesis consists of 8 steps and achieves an overall yield of 13%, making it the shortest known route.

Keywords

(±)- simonsol C • acidic dearomazation •benzofuran• total synthesis

Introduction

Star anise, derived from *Illicium* species cultivated in southeastern China [1]. possesses significant economic, culinary, and medicinal value [2]. Particularly noteworthy are its medicinal properties, including insecticidal, antibacterial, anti-inflammatory, analgesic, and neurotrophic activities [3] .In 2013, Wang group isolated (±)-simonsol C from star anise, which features a unique 6/5/6 tricyclic benzofuran structure [4] .They found that it exhibits biological activity that promotes neuronal synapse growth and inhibits acetylcholinesterase.

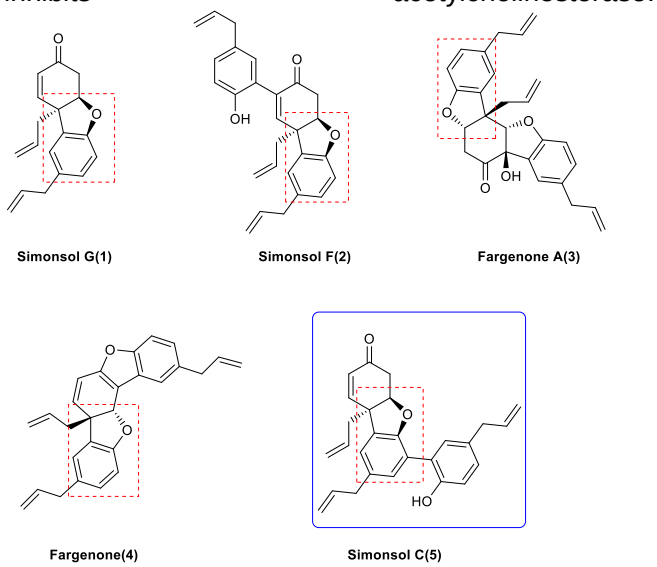
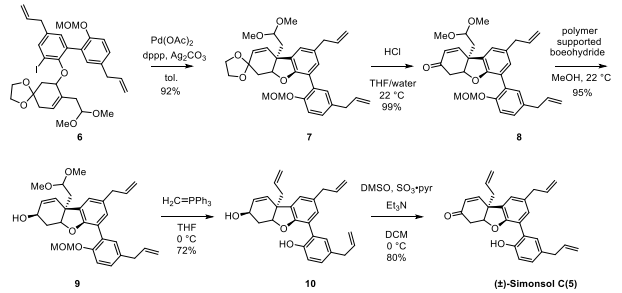


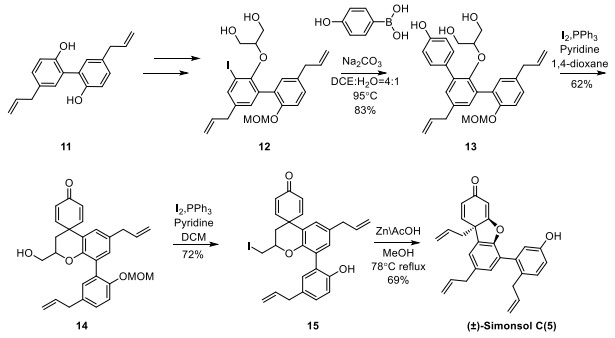
Figure 1. Representative sesquineolignan compounds.

(±)-simonsol C has received considerable attention due to the presence of an aryl- and allyl- containing quaternary carbon, which is common in natural products such as galanthamine and morphine. To construct the quaternary carbon in simonsol C, two reports have utilized alkaline dearomatization strategies and another report used intramolecular Heck reaction as the key reaction [5]. However, there have been no reports or studies utilizing acidic dearomatization, which is also effective, to synthesize aryl quaternary carbon.



Scheme 1. The first total synthesis of (±)-simonsol C by Banwell group.

In the first report of total synthesis of simonsol C in 2016 (Figure 2), Banwell group employed an intramolecular Heck reaction as key step to furnish the aryl containing quaternary center and simultaneously afford benzofuran skeleton[6]. This synthesis involved a total of 12 steps and achieved 12% overall yield.



Scheme 2. The second total synthesis of (±)-simonsol C by our group.

In May 2024, Qin group reported the second total synthesis of (±)-simonsol C (Scheme 2) [5b]. An effective strategy to form 6/5/6 benzofuran scaffold was developed. Specifically, a basic dearomatization and reductive elimination with Zn/AcOH to construct an aryl and allyl containing quaternary center, a simultaneous phenol initiated oxy-Michael addition to afford benzofuran unit. This synthesis took 9 steps and achieved an overall yield of 13%. Also in 2024, Nugent reported another efficient way to access the 6/5/6 benzofuran scaffold of simonsol C, utilizing a alkaline dearomitization as the key reaction, followed by a functional-group-selective Wittig and concurrent oxy-Michael addition [5a]. The bromo phenol acetal was used in intramolecular alkylative dearomitization, which was first reported by Magnus [7] and has been used in synthesizing natural products containing aryl quaternary carbon [8].

Unlike the intramolecular alkylation strategy of a phenol derivative, which can only be applied in basic dearomatization, our approach using an α-iodo phenol ether as precursor of dearomitization offers considerable versatility. Not only can it be employed under basic dearomatization conditions, but it is also effective under Lewis acid conditions. Combined with a reductive elimination using Zn/AcOH, benzofuran skeleton can be easily synthesized. This dual applicability of our new approach will be demonstrated next in the synthesis of simonsol C.

Results and Discussion

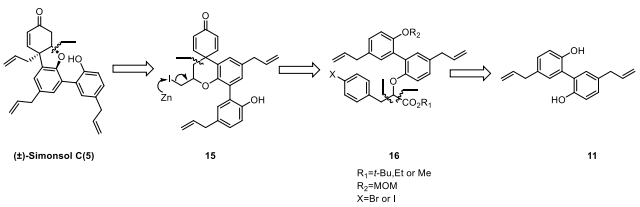
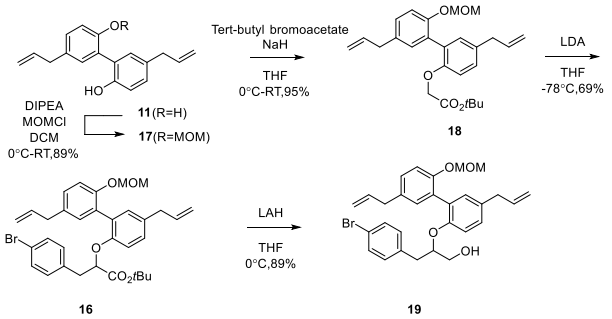


Figure 2. Retrosynthetic analysis of (±)-simonsol C.

Based on extensive literature investigations, our retrosynthetic analysis strategy for (±)-simonsol C is as follows （Figure 2）: The 6/5/6 benzofuran skeleton of (±)-simonsol C can be accessed via an oxy-Michael addition from dienone **15**. The 6/6/6 tricyclic structure in **15** can be constructed through dearomatization of compound **16**, which can be rapidly formed through consecutive alkylation step starting from magnolol (**11**). Additionally, using magnolol as the starting material brings two allyl groups into the product, avoiding the challenges associated with tedious allyl formation reaction.

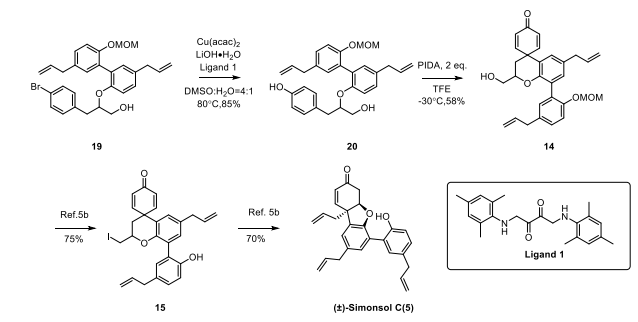


Scheme 3. Rapid access of the basic skeleton of (±)- simonsol C.

The synthetic route for (±)-simonsol C is shown in Figure 4. Starting with magnolol, one of the phenol groups was selectively protected by controlling the equivalents of MOMCl and DIPEA, affording compound **17** with an 89% yield [9].

During this process of alkylation with bromo ethyl acetate, three bases were tested: potassium carbonate, cesium carbonate, and sodium hydride. Considering the kPa requirements for the reaction, since the alkylation targeted the phenolic hydroxyl group, weaker bases like potassium carbonate and cesium carbonate should theoretically suffice. However, the reaction outcomes with these two bases did not meet the desired expectations, as some starting material remained after 5 hours. Extending the reaction time did not fully consume the starting material. Subsequently, when the base was changed to the stronger sodium hydride, the reaction proceeded much better. Within 2 hours, all the starting material was completely reacted, yielding compound **18** with a 95% isolation yield[10].

Using LDA to deprotonate α-Hydrogen atom of the carbonyl group in compound **18**, followed by the addition of 4-bromobenzyl bromide for alkylation, compound **16** was isolated in 69% yield[11]. It was then reduced to alcohol **19** with 2 equiv. LAH at 0 °C. The reaction was completed within 10 minutes and **19** was isolated in 89% yield[12].



Scheme 4. Synthetic details to (±)-simonsol C.

The Ullmann reaction was subsequently employed to replace the bromine atom on the benzene ring with a hydroxyl group, using a catalytic amount of oxalamide ligand. This transformation is critical for enabling further functionalization, and the reaction conditions were optimized to achieve an 85% yield, minimizing potential side reactions [13]. The dearomatization step is crucial for constructing the cyclohexadienone unit. Oxidation with PIDA in trifluoro ethanol, the original phenol was converted into a quinone moiety, successfully forming aryl containing quaternary center. However, in this step, the reaction was too rapid to control. After optimizing the reaction time and temperature, the reaction was carried out at -30 °C for 15 minutes, **14** was isolated as high as 58% yield [14]. Iodination of compound **14** and subsequent reductive elimination were performed according to our previous report and similar results were obtained. [15] In detail, a Zn/AcOH reductive elimination was utilized to liberate allyl group and simultaneously, an oxy-Michael addition occurred to construct the 6/5/6 tricyclic skeleton, affording the final product (±)-simonsol C in 70% yield. The spectral data are in agreement with those previously reported.[4]

Conclusion

Total synthesis of (±)-simonsol C was accomplished using a dearomatization under acidic condition as key step to construct aryl containing quaternary center. The 6/5/6 benzofuran unit was formed through reductive elimination with Zn/AcOH and a spontaneous oxy-Michael addition. This largely enhances our synthetic efficiency and shortens the number of synthetic steps. The whole synthesis route has 8 steps and a total yield of 13%, which could be the shortest synthesis route to date.

The structural motif of an all-carbon quaternary center containing an aryl group is common in many natural products, such as galanthamine and morphine. Our current strategy provides an alternative approach for the synthesis of aryl-containing quaternary carbon centers, which could be valuable for the synthesis of related natural products and their derivatives.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data of new compounds.

Acknowledgements

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

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