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First total synthesis of rhuscholide A, glabralide B and denudalide

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ABSTRACT

The first total synthesis of rhuscholide A, a benzofuran lactone possessing anti-HIV-1 activity, had been accomplished in 14 linear steps with 10.6% overall yield. In this synthesis, base-mediated phenol *ortho*-alkylation and piperidine promoted aldol condensation were exploited as key steps. The synthesis was flexible and allowed for the convenient preparation of two analogous natural products glabralide B and denudalide.

Introduction

Benzofuran-2(3H)-ones is an important structural motif present in many biologically active natural products [1] and pharmaceutical compounds [2]. Over the years, several synthetic strategies had been developed for the construction of such framework, including the lactonization of 2-hydroxyphenylacetic acid derivatives [3], tandem Friedel–Crafts/lactonization [4], Reppe-type cyclocarbonylation of alkenyl- or allylphenols [5], Palladium-catalyzed C—H activation of phenylacetic acid followed by lactonization [6], transition-metal-catalyzed coupling reaction [7]. In our search for potent anti-HIV-1 agents from natural products [8], two benzofuranone-type compounds, rhuscholide A and compound **2,** had been isolated from *Rhus chinensi* [8b]. Rhuscholide A showed anti-HIV-1 activity with EC_{50} and CC_{50} values of 1.62 and 68.69 μM, respectively, and a therapeutic index of 42.31. Compound **2**, which shares the same skeleton with **1** but lacks substituent at C-3, exhibited moderate activity with an EC_{50} value of 3.70 μM (TI > 3.28). This finding suggested propan-2-ylidene group is important for anti-HIV-1 activity. Action mechanisms study indicated **1** might target on late-steps of HIV-1 life cycle [9]. Analogous natural products glabralide B (**3**) and denudalide (**4**) with variations in the side chain had been isolated from *Sarcandra glabra* [10] and *Magnolia denudate* [11], respectively. Denudalide had also been found in the extracts of *Lettowianthus stellates* [12], and this compound exhibited cytotoxic activities against the SFME and r/mHM-SFME-1 cell lines. The biological activity of glabralide B has not been investigated due to its limited availability from natural source.

Given the promising bioactivity of **1**, it is highly desirable to establish an efficient access to **1** and its analogues to fulfill further pharmacological investigation. No synthetic studies on rhuscholide A and **2**–**4** have been reported so far. Herein, we describe the first total synthesis of **1**–**4**.

Results and discussion

General structural features of **1**–**4** include a benzofuran-2-one motif and a C_{20} or C_{10} side chain. We envisioned that rhuscholide A and glabralide B could be obtained from **2** and **4**, respectively, via an aldol condensation with acetone. The requisite γ-lactone motif was envisioned to arise from advanced intermediates **5** or **6**, both of them could be divided in half via phenol *ortho*-alkylation to deliver phenol **7** and bromides. The desired geranylgeranyl bromide could be prepared from related alcohol [13], while geranyl bromide was commercially available (Scheme 1).

The known compound **7** was readily prepared from hydroquinone via a three-step sequence (benzylation/allylation/Claisen rearrangement) [14]. For the synthesis of rhuscholide A, the treatment of **7** with allylic bromine **8** and NaH in toluene afforded phenol *ortho*-alkylation product **5** in 68% yield [15]. Increase the NaH loading from 1 to 1.2 equivalent led to a slightly decrease in the yield (64%). It was planned to generate the requisite γ-lactone motif from **5** by employing the sequence: oxidative terminal double bond cleavage [16], oxidation and lactonization. Unfortunately,

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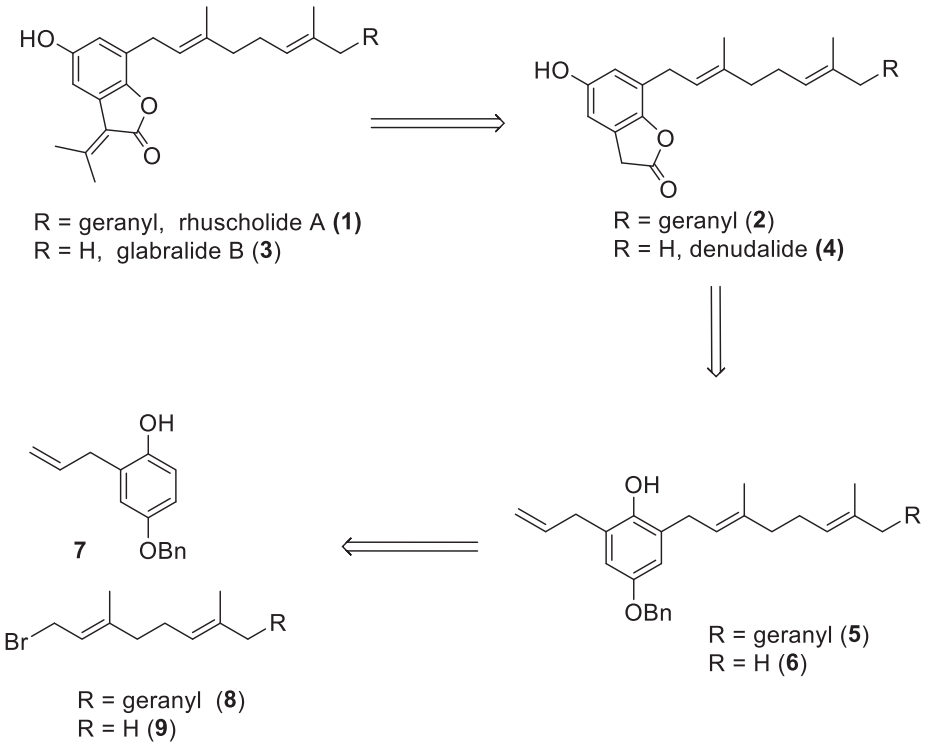
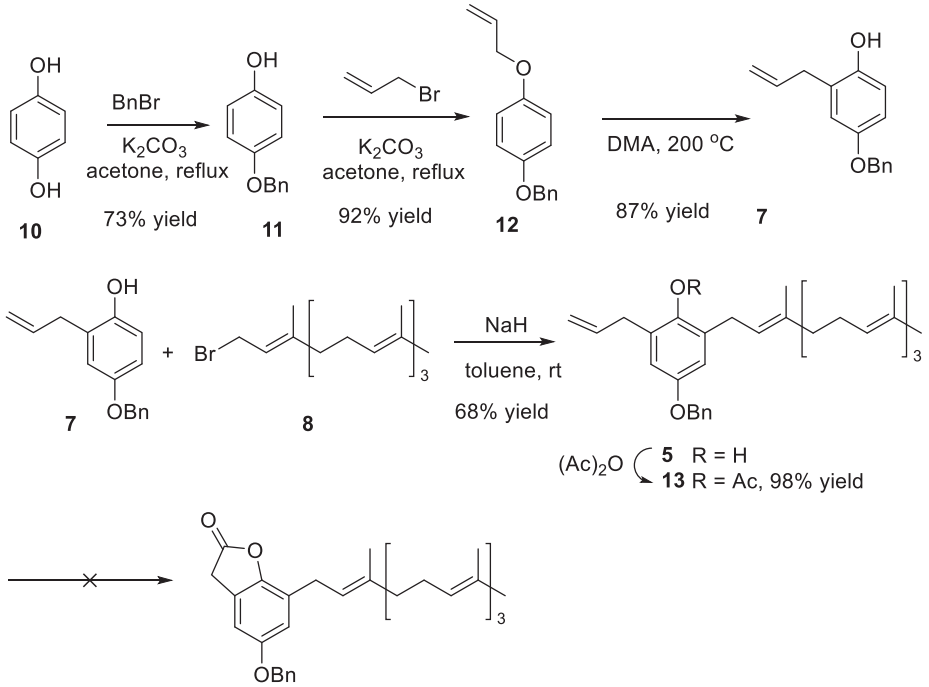


Scheme 1. Retrosynthetic analysis of **1**–**4**.

the first dihydroxylation step proved unexpectedly challenging. The treatment of **5** with a variety of standard oxidants (e.g., OsO_4, RuO_4) routinely used for alkene cleavage gave complicated products. Extensive attempts to optimize the reaction conditions (such as using acetyl group to protect hydroxyl group) did not improve the outcome (Scheme 2). With this setback, we revised our approach to initially prepare the γ-lactone precursor before the C20 side chain installation.

Protection of the phenol in **7** with acetate was achieved under a standard acetylization protocol to give compound **14**. Osmium-catalyzed dihydroxylation followed by cleavage of the diol with $NaIO_4$ [17] and acid catalyzed acetalization delivered **15** in 68% yield over 3 steps. Subsequent deacetylization using NaOH led to the formation of phenol **16** in nearly quantitative yield. Notably, these steps were readily scalable and allowed for the production of multigram quantities of phenol **16** (Scheme 3).



Scheme 2. Tentative approach toward rhuscholide A.

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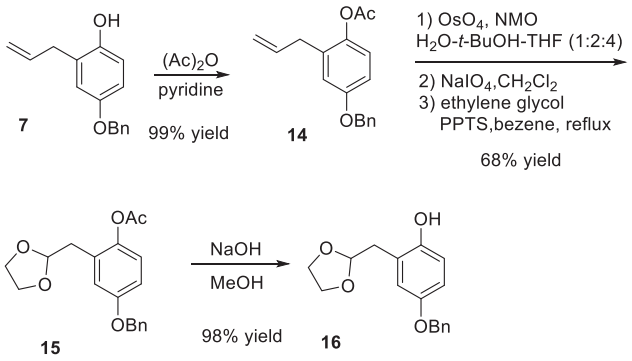
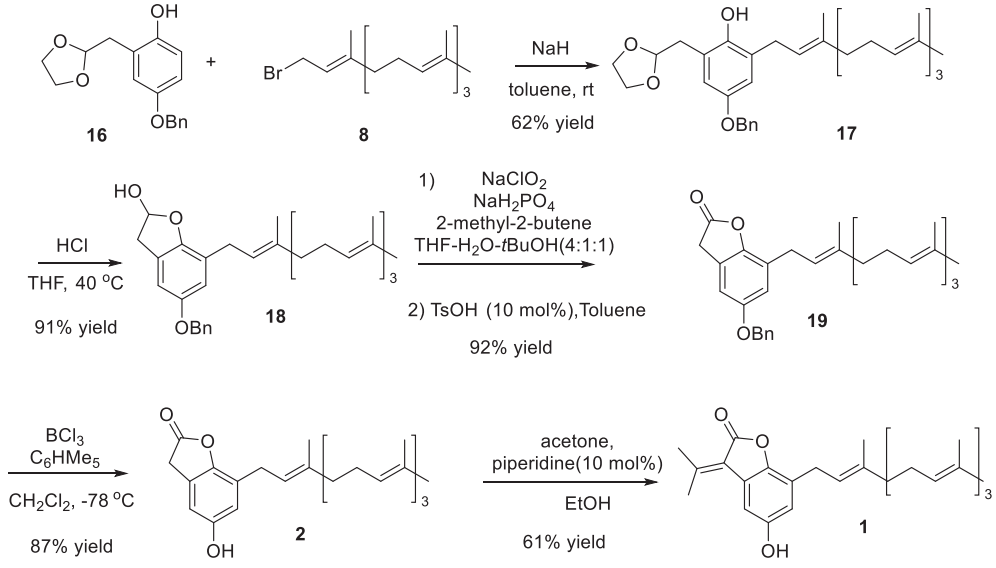


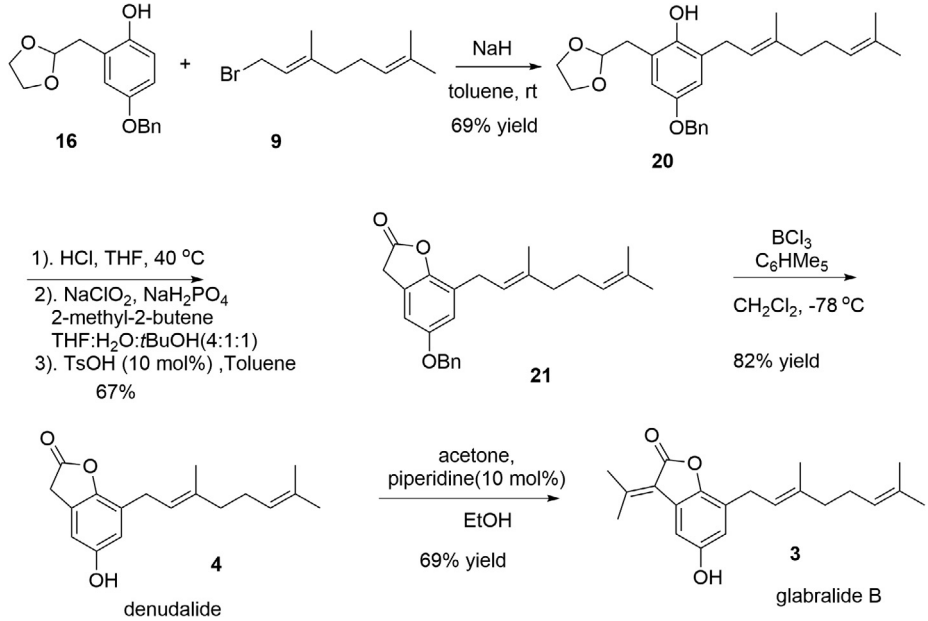
Scheme 3. Preparation of phenol **16**.

In the forward synthesis, the C_{20} side chain was introduced via NaH-mediated phenol *ortho*-alkylation as previously demonstrated in the synthesis of **5** (Scheme 4). Deprotection of the acetal protecting group followed by concomitant cyclization afforded hemiacetal **18** in 91% yield. For the conversion of lactol to lactone, the traditional pyridinium dichromate (PDC) mediated oxidation resulted in low yield. A two-step process of Pinnick oxidation followed by lactonization afforded benzofuran-2-one **19** in a high yield (92%). Removal of the benzyl group with BCl_3 [18] led to the first total synthesis of **2**. Conversion of **2** to rhuscholide A was conveniently achieved upon the treatment of **2** with piperidine in a 1:1 acetone-ethanol mixture [19].

The availability of this synthesis was further demonstrated in the synthesis of glabralide B and denudalide. **16** was cleanly alky-



Scheme 4. Final steps leading to rhuscholide A.



Scheme 5. Total synthesis of glabralide B and denudalide.

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lated with geranyl bromide affording **20** in 69% yield. Finally, benzofuran lactones **4** and **3** were obtained successively from **20** following the route and conditions already established in the synthesis of **1** (Scheme 5). Our NMR data of synthetic compounds **1**–**4** are in agreement with the reported values of the natural products.

Conclusion

In conclusion, we have performed an efficient route for the first total synthesis of rhuscholide A (**1**) from commercially available hydroquinone and geranyllinalool. This synthesis utilized base-mediated phenol *ortho*-alkylation and piperidine promoted aldol condensation as key steps and furnished rhuscholide A in 10.6% overall yield in 14 linear steps. Two analogous natural products glabralide B (**3**) and denudalide (**4**) were also synthesized, which should facilitate the investigation of structure-activity relationships for anti-HIV-1 activity.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151059.

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