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Biomimetic total syntheses of renifolin F and antiarone K†

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The first biomimetic and concise racemic total syntheses of renifolin F and antiarone K, accomplished in 8 and 7 linear steps, respectively, are presented in this article. Our synthetic approach commences with substituted aldehydes to produce prenylated aldol products followed by ene-type intramolecular cyclization affording a five-member core ring. This key step mediated by $InCl_3 \cdot 4H_2O$ is a novel procedure first utilized in prenylated systems which directly culminates mainly into tertiary alcohols.

Introduction

For synthetic chemists, the goal of synthetic efficiency typically quantified by step count and overall yields provides a wealth of incentive and inspiration for developing novel tactics and techniques. Many of the pharmaceutical chemicals used today are derived from natural sources, once a major medication source. Flavonoids' fascinating biological and therapeutic properties, along with their intricate structure, have attracted the attention of the synthetic organic community. Flavonoids are abundant in the kingdom of plants and are precious natural resources. Chalcone has been acknowledged as a preferred scaffold in medicinal chemistry.[1] Naturally occurring Chalcones are categorized as phenolic compounds within the flavonoid class and have a five-membered ring assembled from β-carbon of chalcone and dimethylallyl carbon. They exhibit numerous pharmacological and biological properties such as antiparasitic, antitumor, cytotoxic, antifungal, anti-inflammatory, antiallergic, antiviral, and antibacterial. Some of these compounds have the potential to treat neurodegenerative and vasodilatory disorders.[2–4]

Renifolin D–F were isolated from entire *Desmodium Renifolium* plants by Yan-Ping Li *et al.* in 2014 (Fig. 1).[5] Utilizing five tumor cell lines, the cytotoxicity of each isolate was assessed. Compared to the positive control drug paclitaxel renifolin E and F were 100 times less potent and showed only little cytotoxicity (IC_{50} values of 2.8 and 2.2 μM, respectively) against A549 human lung carcinoma cells.[1] Furthermore, Feng Huang and co-workers isolated renifolin F (**2**) from another medicinal plant *Shuteria Involucrate* in 2022 and mentioned the therapeutic effect on allergic asthma. Approximately 300 million people worldwide suffer from allergic asthma, a chronic and diverse illness. Currently, corticosteroids, β-agonists, and leukotriene receptor antagonists are the major treatments for asthma. However, for 5–10% of individuals with severe asthma, the benefits of these therapies are insufficient, and long-term use of these medications might result in major side effects. Therefore, finding a safe anti-asthma medicine is essential.[6] Given the biological significance and natural scarcity of renifolin F (**2**), it is imperative to establish a succinct strategy for its total synthesis. This would facilitate additional biological assessments and evaluations. Taro Nomura and co-workers extracted antiarone K (**1**) from the root bark of *Antiaris*

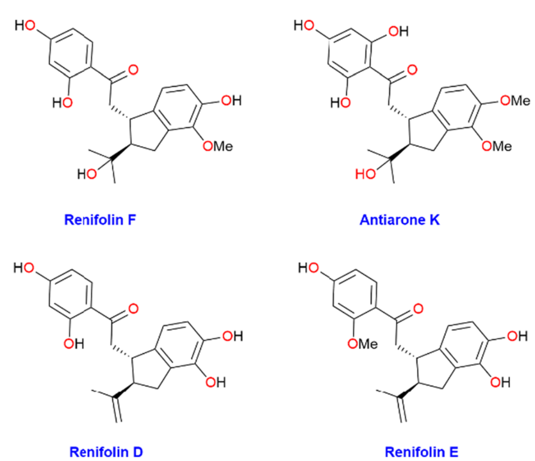

Fig. 1 Structure of few chalcone natural products.

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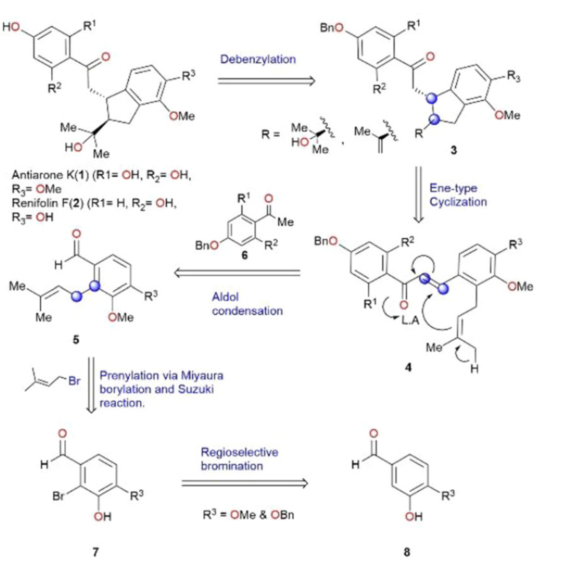
Toxicaria in 1991, collected from Indonesia.[7] Antiarone K (**1**) and renifolin F (**2**) are recognized as chalcone derivatives that possess an isoprenoid moiety.

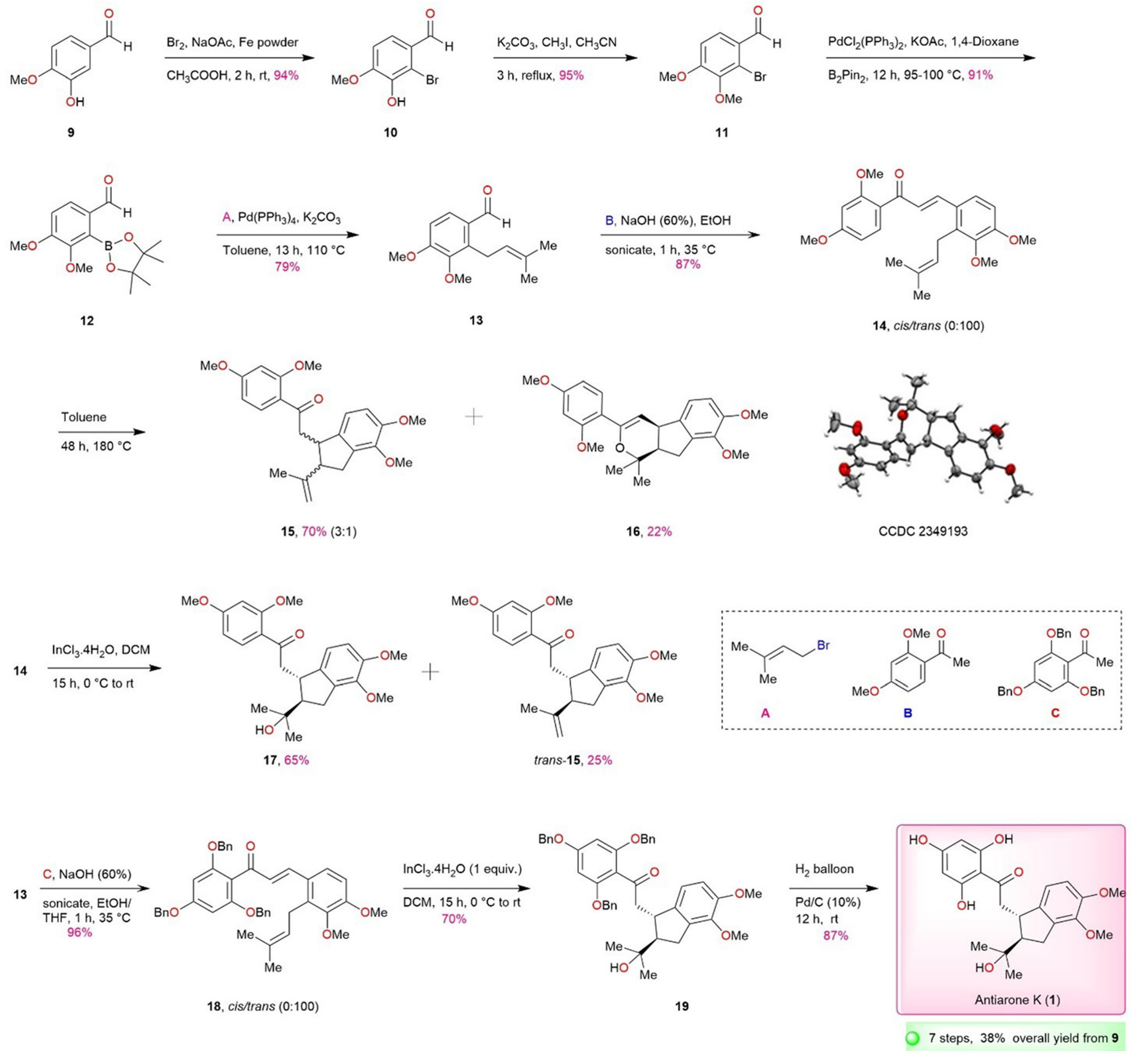
We conceived a biomimetic synthesis as illustrated in retrosynthetic Scheme 1. The key step in this strategy is an ene-type cyclization based on proposed biosynthesis.[5] Renifolin F (**2**) and antiarone K (**1**) could be synthesized from the deprotection of benzylated cyclized compound **3**. Intermediate **3** was envisaged to be obtained by an intramolecular ene-type cyclization of compound **4** which in turn could be derived from prenylated aldehyde **5** through an aldol condensation reaction. Different substituted prenylated aldehydes **5** could be accessed from **7** *via* prenylation. Compound **7** was synthesized using readily accessible and cost-effective starting material **8** *via* regioselective bromination. (The blue circles in Scheme 1 serve as an indicator for the formation of a new C–C bond.)

Herein we disclose an effective and flexible approach for the total synthesis of renifolin F (**2**) and antiarone K (**1**) from commercially available starting materials. With a strong emphasis on our retrosynthetic plan, we aim to produce substituted prenylated aldehyde **13**, a crucial intermediate in our synthesis process. The synthesis of compound **13** has been previously established through the direct prenylation of veratraldehyde **28**, resulting only in 12% of the desired product, as well as other isomers by Irinel and co-authors.[8] In order to achieve better results, we have implemented an alternative approach based on oxazoline directed metalation to attain the required regiochemistry and to avoid unwanted isomers (Scheme S1, ESI†).[9–14] This approach has furnished an improved overall yield of 35%. The yield was further enhanced finally to an impressive overall 64% by a novel approach (Scheme 2). In this method for the synthesis of precursor **13**, we began with commercially procurable and inexpensive isovanillin **9**. Bromination[15] of **9** in the presence of Br_2 and iron powder furnished **10** in 94% yield and subsequent methylation[15] of the **10** produced **11** in 95% yield. Bromo compound **11** was subjected to Miyaura borylation[16] using a palladium catalyst, resulting in the formation of borylated product **12** in very good yield. Suzuki[17] reaction was carried out with **12**, resulting in the smooth formation of compound **13** in a satisfactory yield using tetrakis(triphenylphosphine) $[Pd(PPh_3)_4]$ and prenyl bromide.



Scheme 1 Retrosynthetic analysis.

Following the acquisition of requisite **13** through our improved prenylation strategy, an aldol condensation reaction was conducted using **13** and benzylated acetophenone derivative **B** under sonication.[18] The outcome was the generation of prenylated aldol condensation product **14** in 87% yield. Subsequently, our attention is directed towards forming the five-membered core ring *via* intramolecular ene-type cyclization. Based on literature precedents of closely related systems,[19,20] we initially subjected **14** to thermal conditions at high temperature (toluene, 180 °C) in a sealed tube. The reaction was non-selective and furnished an inseparable 3 : 1 *trans*/*cis* mixture (^{1}H and ^{13}C NMR, see ESI†) along with a further cyclized product **16**, originating from *cis*-**15**. The unambiguous confirmation of structure **16** was done by X-ray crystallography. Several standard demethylation protocols were attempted on **15** but none were successful (Table S1, ESI†). We first thought of addressing non-selective ene-type cyclization that gave *trans*/*cis* mixture under thermal conditions. It was planned to explore the intramolecular cyclization of the **14** in the presence of Lewis acids. To start our investigation, we conducted experiments under various reaction conditions using **14** as a model substrate and the results are depicted in Table 1. The best results were observed when 1 equiv. of $InCl_3·4H_2O$ was used in the presence of DCM at 0 °C (Table 1, entry 11) which furnished the desired product 17 stereoselectively in 65% yield along with 25% of *trans*-**15**. Reducing the amount of Lewis acid to 0.5 equiv. gave diminished yields (Table 1, entry 15). This is a significant achievement as this type of cyclization is novel and not reported earlier with $InCl_3·4H_2O$ to the best of our knowledge. The structural assignments of **17** and *trans*-**15** were based on ^{1}H and ^{13}C NMR analysis. The presence of a tertiary alcohol moiety (2-hydroxy-2-propanyl group) in **17** was supported by the presence of a peak at 72.8 ppm (carbinol carbon) in the ^{13}C NMR spectrum, consistent with the findings in the isolation report. The structure of **17** was further corroborated with 2D NMR (HMBC and HMQC) techniques. Demethylation of **17** also proved to be problematic as for **15**. Therefore, it was imperative to opt for a protecting group that could be readily removed at the end after the cyclization. In this context, antiarone K (**1**) possessing a tertiary alcohol unit and two methyl ether moieties on the fused aromatic ring appeared to be a straightforward target. So, we commenced the total synthesis of antiarone K (**1**) (Scheme 2) starting with differentially protected precursor *via* this novel cyclization method utilizing $InCl_3·4H_2O$, which is expected to directly furnish the required tertiary alcohol derivative as the major product. With precursor **13** as the key component, differentially protected **18** was synthesized using aldol reaction of acetophenone derivative **C** under sonication[15] employing NaOH



Scheme 2 Total synthesis of antiarone K (**1**).

(aq.) and EtOH as a solvent in 96% yield. The key intramolecular cyclization of **18** mediated by $InCl_3{\cdot}4H_2O$ gratifyingly produced tertiary alcohol derivative **19** stereoselectively in 70% yield. Alkene product, similar to **15**, was not detected in this case. The final step for the completion involves debenzylation using 10% Pd/C under hydrogen atmosphere (balloon)[21] leading to the successful production of 87% antiarone K (**1**) from **19**. The overall yield achieved was 38%, and the entire process involved 7 consecutive steps. The NMR data pertaining to the synthetic antiarone K (**1**) aligns with the results documented in the isolation report.

With the successful completion of total synthesis of antiarone K (**1**), we turned our attention to undertaking the total synthesis of renifolin F (**2**) (Scheme 3). Our objective was to synthesize prenylated aldehyde **25**, a vital intermediate for this synthesis while considering the structure of renifolin F (**2**). In compound **25**, the *para* and *meta* hydroxy are protected by the benzyl and methoxy groups respectively. This protective strategy is implemented to achieve the desired positioning of the hydroxy and methoxy groups following a targeted debenzylation step. The synthesis of Intermediate **23** was initially carried out in 5 steps using known protocols (Scheme S2, ESI†), yielding 36% overall.[22–25] Through the adoption of an alternative route, we successfully produced **23** in just 3 steps (Scheme 3), with a remarkable overall yield of 77% – surpassing the previous route by more than double and reducing the number of steps required. To achieve this objective, established methods like benzylation,[25] bromination, and methylation were

Table 1 Optimization of the reaction condition for the ene-type cyclization of **14** [a]

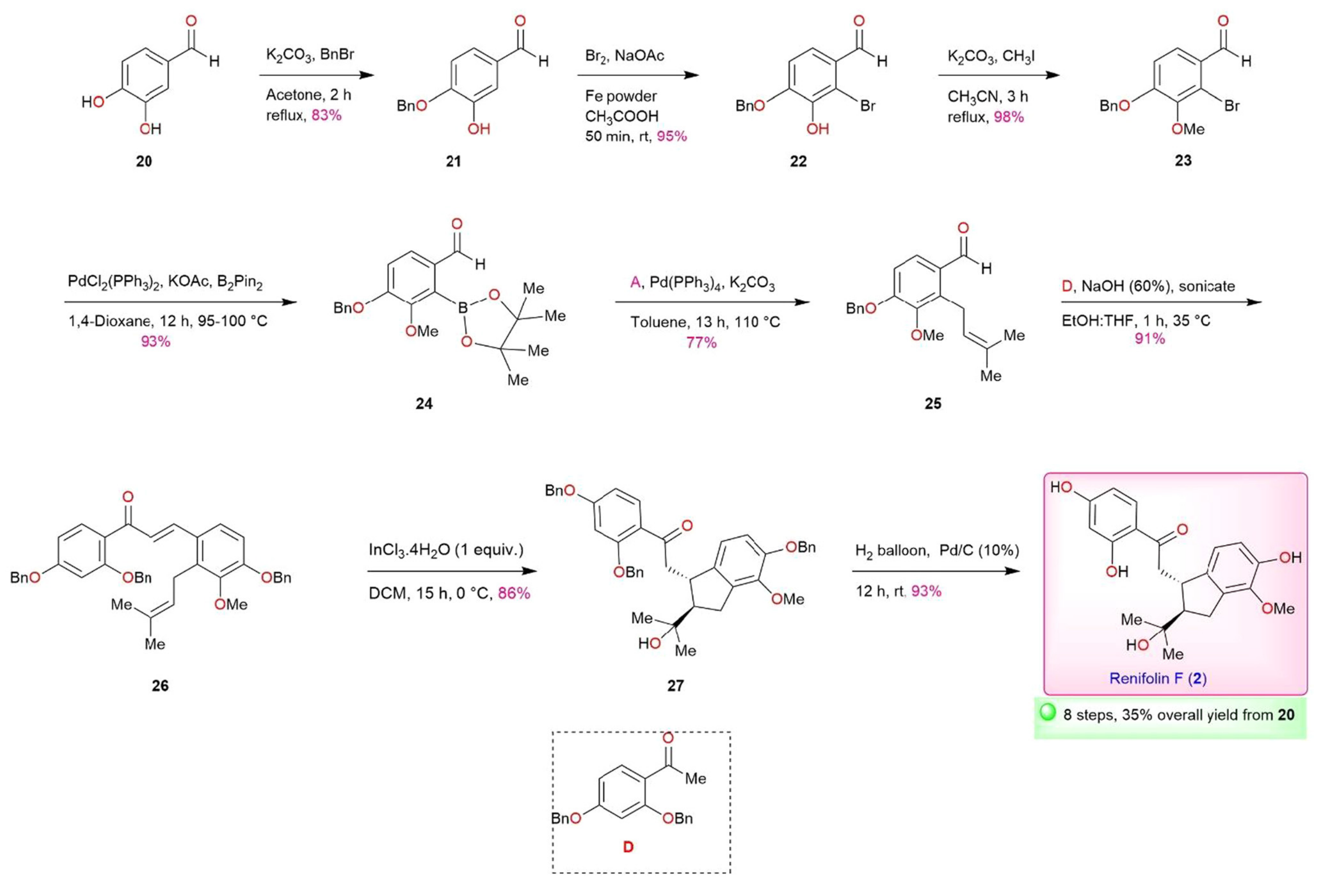
Entry	Lewis acid (equiv.)	Solvent	Time (h)	Yield[d] (%) (**15**)	Yield[d] (%) (**17**)
1[b]	None	Toluene	48	70[e]	ND
2	$In(OTf)_3$ (1)	DCM	18	35[e]	ND
3	$Bi(OTf)_3$ (1.6)	THF	8	51[e]	25
4	$Yb(OTf)_3$ (1)	THF	20	ND	ND
5	$ZnCl_2$ (1)	DCM	11	20[f]	55
6	$ZnCl_2$ (1)	CH_3CN	15	ND	ND
7[c]	$ZnBr_2$ (1)	Toluene	22	33[e]	ND
8	$BF_3 \cdot Et_2O$ (5)	THF	18	22[e]	50
9	$B(C_6F_5)_3$ (1)	CH_3CN	15	ND	ND
10	$Zn(OTf)_2$	CH_3CN	48	ND	ND
11	**$InCl_3 \cdot 4H_2O$ (1)**	**DCM**	**20**	**25[f]**	**65**
12	$InCl_3 \cdot 4H_2O$ (1)	THF	24	Trace	Trace
13	$InCl_3 \cdot 4H_2O$ (1)	CH_3CN	24	ND	ND
14	$InCl_3 \cdot 4H_2O$ (1)	DMF	24	ND	ND
15	$InCl_3 \cdot 4H_2O$ (0.5)	DCM	30	10[f]	30
16	$InCl_3 \cdot 4H_2O$ (1)	DCE	15	20[f]	60
17	$InCl_3 \cdot 4H_2O$ (1)	Dioxane	24	ND	ND

[a] Reaction conditions: the reaction was carried out with **14** (0.1 mmol, 1 equiv.), reagents in different solvent (3 ml), temp (0 °C to r.t [b] 180 °C, [c] 80 °C), [d] isolated yield, [e] *trans*/*cis* (3 : 1), [f] *trans*, ND = not detected, compound **16** (entry 1, 22%).

employed on protocatechualdehyde **20** to obtain **23** through intermediates **21** and **22** in excellent yields. Compound **23** was further converted into key intermediate **25** *via* **24** using Miyaura borylation (93%) and Suzuki reaction (77%). The synthesis of renifolin F (**2**) was successfully achieved by utilizing key intermediate **25** in aldol condensation, $InCl_3 \cdot 4H_2O$ ene-type intramolecular cyclization, and selective debenzylation *via* **26** and **27**, yielding 91%, 86%, and 93% respectively (Scheme 3). We have accomplished the total synthesis of renifolin F (**2**) in 8 linear steps with an overall yield of 35%. The spectral data of synthetic renifolin F (**2**) corresponds with the findings outlined in the isolation report.

Conclusions

To summarize, we have accomplished a concise and scalable first total synthesis of antiarone K (**1**) and renifolin F (**2**) in 7 and 8 steps with an overall yield of 38% and 35% respectively. The four crucial transformations facilitated the successful completion of the synthesis. These transformations include the synthesis of prenylated aldehyde, aldol condensation, In(III)-mediated cyclization to construct the five-member core ring, and finally palladium-catalyzed debenzylation to deliver phenolic compounds.



Scheme 3 Total synthesis of renifolin F (**2**).

Data availability

Data is available in the ESI.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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