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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 InCl₃·4H₂O 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. 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

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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 (IC50 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 coworkers extracted antiarone K (1) from the root bark of Antiaris

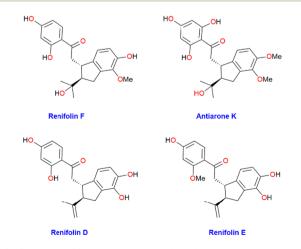


Fig. 1 Structure of few chalcone natural products.

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†). 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. Bromination¹⁵ of 9 in the presence of Br₂ and iron powder furnished 10 in 94% yield and subsequent methyl-

Scheme 1 Retrosynthetic analysis.

ation¹⁵ of the **10** produced **11** in 95% yield. Bromo compound 11 was subjected to Miyaura borylation¹⁶ using a palladium catalyst, resulting in the formation of borylated product 12 in very good yield. Suzuki¹⁷ reaction was carried out with 12, resulting in the smooth formation of compound 13 in a satisfactory yield using tetrakis(triphenylphosphine) [Pd(PPh₂)₄] and prenyl bromide.

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% vield. 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 (1H and 13C 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 InCl₃·4H₂O 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 InCl3·4H2O to the best of our knowledge. The structural assignments of 17 and trans-15 were based on ¹H and ¹³C 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 ¹³C 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 InCl₃·4H₂O, 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 sonication15 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 InCl₃·4H₂O 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 syn-

thesize 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

7 steps, 38% overall yield from 9

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

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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Entry	Lewis acid (equiv.)	Solvent	Time (h)	$\begin{array}{c} {\rm Yield}^d \\ {\rm (\%)(15)} \end{array}$	Yield ^d (%) (17)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\overline{1^b}$	None	Toluene	48	70 ^e	ND
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2	$In(OTf)_3(1)$	DCM	18	35^e	ND
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3	$Bi(OTf)_3$ (1.6)	THF	8	51^e	25
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4		THF	20	ND	ND
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	5	$ZnCl_2(1)$	DCM	11	20^f	55
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6	$ZnCl_{2}(1)$	CH_3CN	15	ND	ND
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	7^c	$ZnBr_{2}(1)$	Toluene	22	33^e	ND
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	8		THF	18	22^e	50
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	9		CH ₃ CN	15	ND	ND
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	10	$Zn(OTf)_2$	CH_3CN	48	ND	ND
13 InCl ₃ ·4H ₂ O (1) CH ₃ CN 24 ND ND 14 InCl ₃ ·4H ₂ O (1) DMF 24 ND ND 15 InCl ₃ ·4H ₂ O (0.5) DCM 30 10 ^f 30	11	InCl ₃ ·4H ₂ O (1)	DCM	20	25^f	65
14 InCl ₃ ·4H ₂ O (1) DMF 24 ND ND 15 InCl ₃ ·4H ₂ O (0.5) DCM 30 10 ^f 30	12	$InCl_3 \cdot 4H_2O(1)$	THF	24	Trace	Trace
15 $InCl_3 \cdot 4H_2O(0.5)$ DCM 30 10^f 30	13	$InCl_3 \cdot 4H_2O(1)$	CH_3CN	24	ND	ND
3 2 ()	14	$InCl_3 \cdot 4H_2O(1)$	DMF	24	ND	ND
16 $InCl_2 \cdot 4H_2O(1)$ DCE 15 20^f 60	15	$InCl_{3}\cdot 4H_{2}O(0.5)$	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	17		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, InCl₂·4H₂O enetype 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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