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The Biomimetic Total Syntheses of the Antiplasmodial Tomentosones A and B

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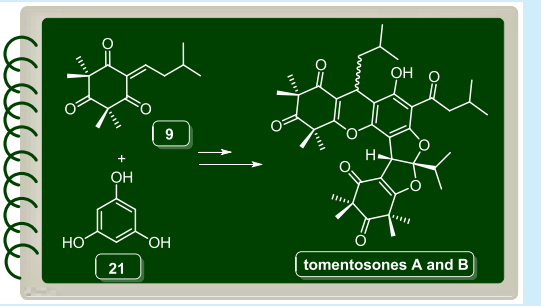
ABSTRACT: The first biomimetic total syntheses of natural phloroglucinols tomentosones A and B and their analogues have been accomplished. The synthetic strategy primarily referred to the potential biosynthetic precursors and their possible sequence of segments assembly by chemological evolution of the structural entities and enabled rapid access of the titled compounds in a practical fashion.



Polycyclic polymethylated phloroglucinols (PPPs) bearing a fascinating tetramethylcyclohexenedione or acylphloroglucinol scaffold represent the most characteristic family of secondary metabolites that are mainly encountered from the Myrtaceae and Guttiferae plants.[1] Because of their architectural complexity as well as diverse structure features, the chemistry of PPPs have recently become one of hotspots in natural product research and generated considerable attention among natural product chemists.[1,2] Moreover, the emerging significant biological activities, such as potent antibacterial,[3] immunosuppressive effect,[4] anti-inflammatory,[5] and antiplasmodial[6] activities have sparked remarkable efforts toward the development of pharmaceuticals and agrochemicals by employing PPPs as attractive lead compounds or popular synthetic targets in recent years.[1,7,8]

Rhodomyrtone (**1**), rhodomyrtosone A (**2**), rhodomyrtosone G (**3**), and rhodomyrtosone C (**4**) are examples representing this class of compounds, whose structural motifs are situated on a tetramethylcyclohexenedione or acylphloroglucinol scaffold. Tomentosones A (**5**) and B (**6**) were isolated from the *Rhodomyrtus tomentosa* (Aiton) Hassk,[9] which is a perennial Myrtaceae shrub native to southern and southeastern Asia, particularly in south China.[10] The key structural features of the two unique PPPs **5** and **6** are an unprecedented continuous 6/6/6/5/5/6 fused rings system, which is constituted by fusing an intriguing bisfuran-β-triketone acylphloroglucinol scaffold with β-triketone-pyran skeleton. Notably, the main difference of structural feature between tomentosones A and B is the orientation of the isobutyl side chain attached at C-7‴ position as shown in Figure 1.

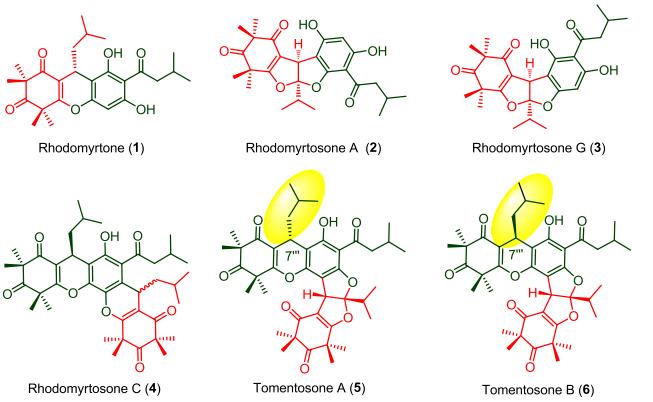


Figure 1. Structures of representative acylphloroglucinols.

Tomentosone A exhibit significant antimalarial properties by inhibition the growth of chloroquine-sensitive (3D7) and resistant (Dd2) strains of the malaria parasite *Plasmodium falciparum*, displaying IC_{50} values of 1.00 and 1.49 μM, respectively. However, tomentosone B was found to be significantly less active against both strains with IC_{50} over 40 μM, strongly indicating that the orientation of the isobutyl side chain attached at C-7‴ plays a critical role for their

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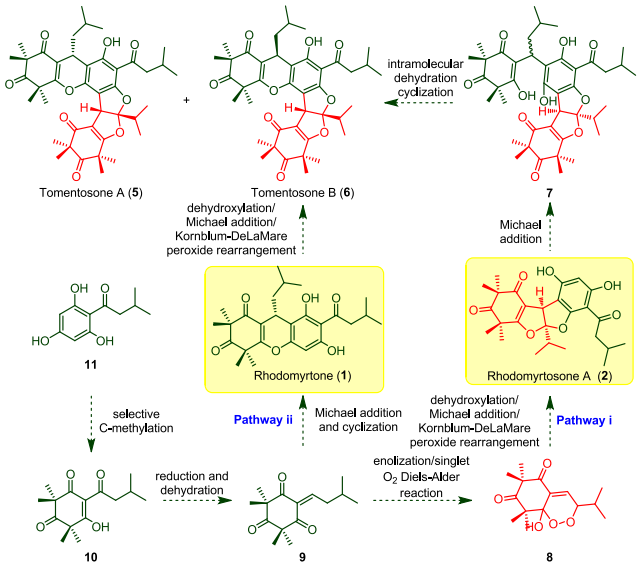
antiplasmodial activity. Moreover, tomentosone A was suggested to be a promising antiplasmodial drug candidate with no obvious toxicity observed even up to 40 μM. Accordingly, their remarkable pharmaceutical activities and novel structures make them appealing synthetic targets. In this communication, we report the first total syntheses of tomentosones A and B featuring potential biosynthetic precursors and their possible sequence of segments assembly by chemological analysis of their structural bioconstruction and enabled to rapid access of the target molecules.

On the basis of our ongoing research efforts on efficiently accessing natural polycyclic phloroglucinols via biomimetic pathways,[11] we are intrigued by the possibility of forging the first total syntheses of tomentosones A (**5**) and B (**6**) via a biomimetic strategy. As outlined in Scheme 1, we tentatively

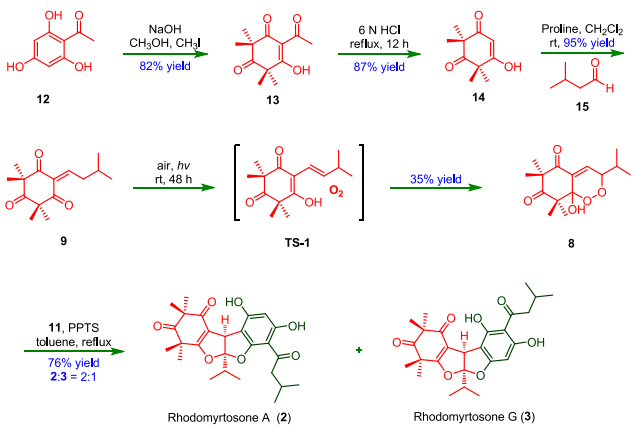
Scheme 1. Proposed Biosynthetic Pathways for Tomentosones A (5) and B (6)



proposed that the biogenetic synthesis pathways of tomentosones A and B might be originated from the critical precursor rhodomyrtone (**1**) or rhodomyrtosone A (**2**) through two potentially alternative biosynthesis pathways. In the pathway **i**, after the spontaneous enolization, the intermediate **9** could further undergo a singlet O_2 induced Diels–Alder reaction, furnishing the key biosynthetic peroxide **8**. Subsequently, the dehydroxylation/Michael addition/Kornblum–DeLaMare peroxide rearrangement cascade sequence, which was previously established by Porco and modified by our group,[11f,12] would be able to transform **8** to the natural product rhodomyrtosone A (**2**).[13,14] The further introduction of the β-triketone unit to the phloroglucinol core, followed by intramolecular dehydration cyclization, would finish the construction of tomentosones A and B scaffold through the potential intermediate **7**. Similarly, the alternative pathway **ii** also shared these key biosynthetic transformations, whereas the major difference was the priority to construction of the β-triketone-pyran skeleton than bisfuran-β-triketone architecture.[15]

With these scenarios in mind, the realization of biomimetic total syntheses of tomentosones A and B first focused on pathway **i** and commenced with the synthesis of critical precursor rhodomyrtosone A (**2**) as shown in Scheme 2. Following our previously established procedure,[11a] the α,β-

Scheme 2. Synthetic Routine for the Critical Precursors 2 and 3



unsaturated ketone **9** was readily prepared from acylphloroglucinol **12** in multigram quantities via the selective C-methylation, retro-Friedel–Crafts acylation, and proline-catalyzed Knoevenagel condensation reactions. The singlet O_2 Diels–Alder reaction of α,β-unsaturated ketone **9** was further modified to generate the diastereoisomeric peroxide **8** in 35% yield through the spontaneous enolization/air oxidation cascade reaction under room-light conditions.[11f] Then, the dehydroxylation/Michael addition/Kornblum–DeLaMare peroxide rearrangement cascade reaction was well performed to transform peroxide **8** and acylphloroglucinol **11** into a pair of readily separated isomers **2** and **3** in good combined yield with a ratio about 2:1.[11f,12]

With the synthesis of rhodomyrtosone A (**2**) secured, the next task was to explore the key biosynthetic Michael addition with the aim to install the isopentyl β-triketone fragment. As expected, the base-mediated Michael addition processed smoothly under room temperature to afford the critical intermediate **7** in 92% yield. The further PTSA-mediated intramolecular cyclization of **7** generated a pair of diastereoisomers **16** and **17** with excellent yield. However, we were surprised to find that compounds **16** and **17** shared distinctive differences with those of tomentosones A and B (**5** and **6**) in most cases of ^{1}H and ^{13}C NMR profiles. The further extensive NMR spectroscopic analyses successfully established them as a pair of regioisomers of tomentosones A and B (**5** and **6**), thus giving trivial names as *iso*-tomentosones A and B (**16** and **17**) as depicted in Scheme 3. Notably, the planar structure of *iso*-tomentosone A (**16**) was fortunately further confirmed by single-crystal X-ray diffraction. The generation of **16** and **17** could chemologically attribute to the superior nucleophilicity of *ortho*-phenolic hydroxyl functionality of **7** because of the strong intramolecular 1,3-hydrogen bonding effect with aryl ketone moiety, which makes it much more electron rich than that of the para-hydroxyl group.[16]

To further understand the regioselectivities between the hydroxyl functionalities for these phenolic compounds, the further accesses of the analogues **19** and **20** of the tomentosones A and B through rhodomyrtosone G (**3**) were then conducted. **3** was subjected to the NaH-mediated Michael addition reaction condition, expectedly generating the desired product **18** in 87% yield with the successful installation of the isopentyl β-triketone fragment. The subsequently cationic catalyzed intramolecular dehydrated cyclization resulted in a pair of separable diastereoisomers **19**

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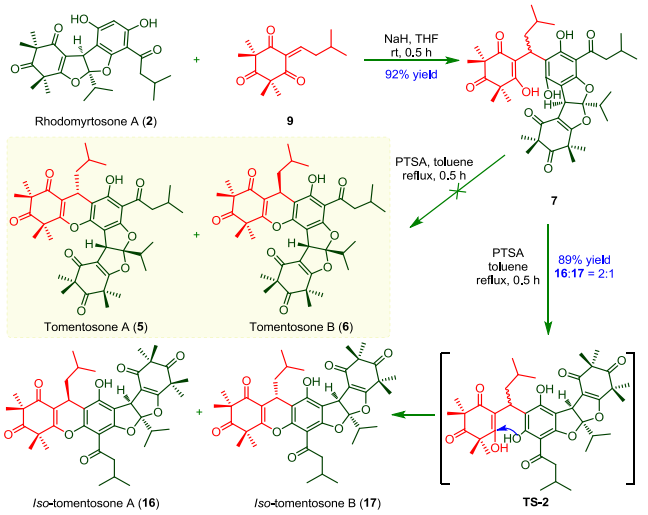
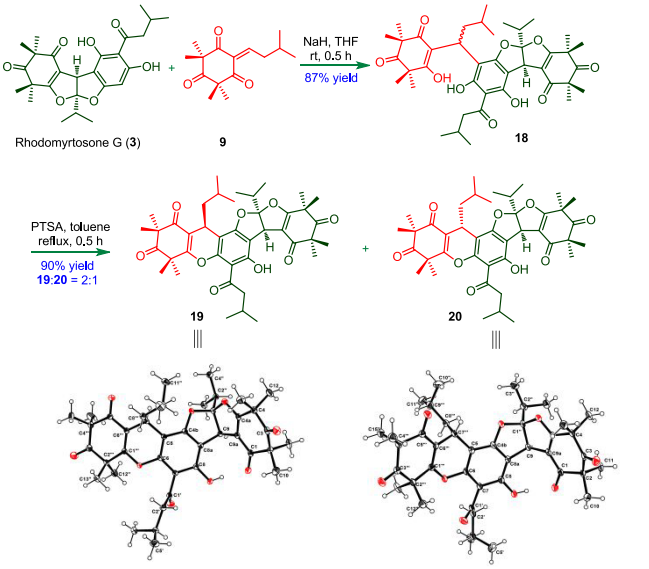
Scheme 3. Biomimetic Total Syntheses of *iso*-Tomentosones A and B (16 and 17)



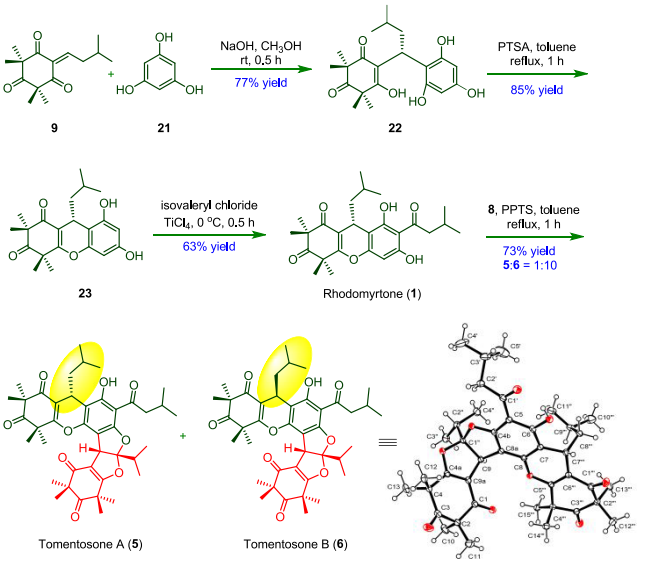
and **20** with 90% combined yield. Interestingly, the formation of **19** and **20** smoothly took placed as expected without cleavage or rearrangement of ketal moiety, although the bisfuran-β-triketone ring system[14] was sensitive to strong acidic reaction condition. Fortunately, both of the single crystals of the complex products **19** and **20** suitable for X-ray diffraction analyses (Scheme 4) were successfully obtained from ethyl acetate solvent system, which provided conclusive evidence for the intractable establishments of their relative configurations.

Scheme 4. Biomimetic Total Syntheses of the Analogues 19 and 20



The aforementioned disappointing results strongly indicated that tomentosones A and B might be produced from natural product rhodomyrtone (**1**)[15,17] through the late stage functionalization as depicted in Scheme 5. To further clarify the possible deduction and finish the first biomimetic total synthesis, another synthetic pathway was performed with commercially available phloroglucinol **21**. First, **23** could be efficiently accessed through Michael addition and intra-

Scheme 5. Biomimetic Total Syntheses of Tomentosones A and B

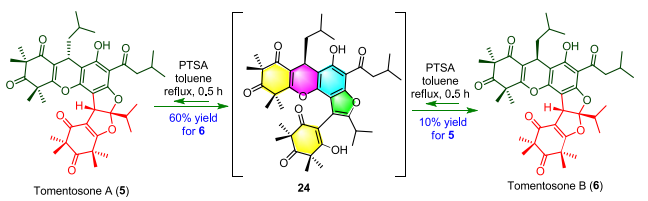


molecular dehydration cyclization in two steps with 65% total yield. With the efficient synthesis of **23** established, the titanium tetrachloride-mediated selective Friedel–Crafts acylation could readily introduce the desired isovaleryl side chain to offer the targeted rhodomyrtone (**1**) in 63% yield.

Rhodomyrtone (**1**) then underwent the critical dehydroxylation/Michael addition/Kornblum–DeLaMare peroxide rearrangement cascade reaction with peroxide **8** to rapidly accomplish the establishment of hexacyclic fused rings scaffold, generating the expected tomentosones A and B in 73% total yield with a ratio about 1:10. To our delight, the NMR and HRESIMS spectra of the synthetic tomentosones A and B are in complete agreement with those reported in the literature. Moreover, the X-ray diffraction (XRD) analysis experiment was also conducted for the readily crystallized synthetic tomentosone B (**6**), thus unambiguously confirming its structure and restrengthened our successful first total syntheses of tomentosones A (**5**) and B (**6**). Their successful syntheses also strongly suggested that the aforementioned synthetic transformation might be probably proceeded by mimicking their biosynthetic generations, although strong acid was applied.

Considering the little amount of the tomentosone A (**5**) generated in the synthetic process, the intertransformation between tomentosones A (**5**) and B (**6**) through the possible benzofuran intermediate **24** was subsequently investigated as shown in Scheme 6. Treating tomentosone B (**6**) with PTSA could convert tomentosone B (**6**) into tomentosone A (**5**) in nearly 10% yield (70% brsm). However, with the same

Scheme 6. Intertransformation of Tomentosones A and B (5 and 6)



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reaction condition, **5** could be rapidly converted into **6** in 60% yield. The aforementioned informative results collectively pointed to that tomentosone B (**6**) should be a thermodynamically favorable product in the equilibrium under the acidic condition, which was also responsive for the ratio of 1:10 (**5**:**6**) detected during the aforementioned synthetic dehydration cyclization. The favorable generation of **6** in the equilibration might be due to its more steric hindrance, which made it hard to be hydrolyzed, thus resulting it as a more stable product under the acidic condition.

In summary, the first biomimetic total syntheses of tomentosones A and B have been achieved by chemological analysis of their structural bioconstruction inspired by their possible biosynthetic pathway. Our synthetic strategy primarily relied on their potential biosynthetic precursors and the possible sequence of segments assembly, which not only highlighted the possible biogenetic pathways of these natural products but also paved the way to rapidly access tomentosones A and B and their analogues in a practical fashion. Taking the advantage of its simplicity and efficiency, the wide potential utility of this study would be reflected in terms of the studies for biosynthesis, total synthesis, structure−activity relationship, and drug development of these kinds of natural products. The further investigations directed toward these goals are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02943.

Experimental section, detailed experimental procedures, and full spectroscopic data for all related compounds (PDF)

Accession Codes

CCDC 2025991, 2025993, and 2025996−2025997 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

⊥X.Z. and C.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(17) Rhodomyrtone (**1**) was previously synthesized by Maier (ref 16), and we have modified its synthetic process to be more concise and practical.

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