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The First Racemic Total Syntheses of the Antiplasmodials Watsonianones A and B and Corymbone B

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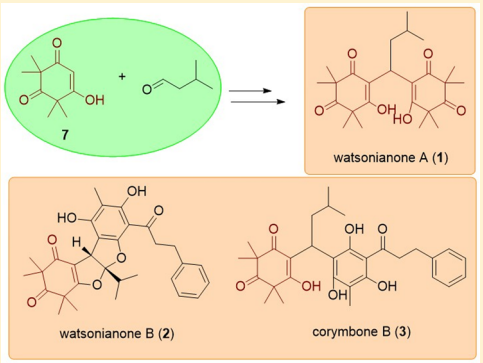
Supporting Information

ABSTRACT: The first biomimetic total syntheses of three biologically meaningful acylphloroglucinols, watsonianones A and B and corymbone B, with potent antiplasmodial activity, were performed. Their total syntheses were carried out through a diversity-oriented synthetic strategy from congener 2,2,4,4-tetramethyl-6-(3-methylbutylidene)cyclohexane-1,3,5-trione with high step efficiency. The spontaneous enolization/air oxidation of the precursor 2,2,4,4-tetramethyl-6-(3-methylbutylidene)cyclohexane-1,3,5-trione through a singlet O_2-induced Diels−Alder reaction pathway to assemble the key biosynthetic peroxide intermediate is also discussed.



Polycyclic polymethylated phloroglucinols (PPPs) containing a tetramethylcyclohexenedione moiety have emerged as attractive targets for total synthesis in recent years due to their structural diversity, architectural complexity, and wide-ranging biological activities.[1−5] Among them, watsonianones A and B (**1** and **2**) possess the first naturally occurring bis-tetramethylcyclohexatrione skeleton and an intriguing fused bisfurano β-triketone scaffold, respectively. Corymbone B (**3**) has been disclosed to be a novel acyclic acylphloroglucinol (Figure 1).[4] All of these compounds exhibited highly significant antiplasmodial activity against chloroquine-resistant (Dd2) and chloroquine-sensitive strains (3D7) of *Plasmodium falciparum*, which are responsible for serious malarial infections.[4,5] Specifically, watsonianone B showed the most potent inhibitory effect with an IC_{50} value as low as 0.3 μM against *P. falciparum* 3D7, and it demonstrated significant selectivity versus the human cell line HEK 293 (>400-fold).[4a] The remarkable biological activities and novel structural features of the synthesized compounds render them appealing targets for total synthesis and structure−activity relationship studies.

In our ongoing research to discover biologically meaningful and structurally diverse acylphloroglucinols from Chinese medicinal plants and their chemical syntheses,[6] the bioactivities and novel structures of compounds **1**−**3** captured our attention. Their structures prompted the exploration of the full potential of a diversity-oriented synthetic strategy, which would permit efficient access to the biomimetic total syntheses of watsonianones A and B and corymbone B (**1**−**3**), respectively, with the aim of revealing their potential in drug discovery and biosynthesis. Herein, we report experimental details for the first racemic total syntheses of compounds **1**−**3** with the use of a bioinspired synthetic strategy, using 2,2,4,4-tetramethyl-6-(3-methylbutylidene)cyclohexane-1,3,5-trione (**9**) as the mutual synthetic precursor.

Regarding their characteristic structures, it could be speculated that these novel natural products might biosynthetically originate from the precursors syncarpic acid (**7**) and isovaleraldehyde (**8**) through a series of intriguing biotransformations. Therefore, the retrosynthetic analysis of watsonianones A and B and corymbone B (**1**−**3**) is summarized in Scheme 1. Watsonianone A (**1**) and corymbone B (**3**) could be formed through a Michael addition from intermediate **9**. Intermediate **9** could be formed from the common intermediates syncarpic acid (**7**) and isovaleraldehyde (**8**) by an organocatalyzed Knoevenagel condensation. Watsonianone B (**2**) could be formed by incorporation of intermediate **10** and 2,4,6-trihydroxy-4-methydihydrochalcone via a sequential dehydroxylation/Michael addition/Kornblum−DeLaMare per-

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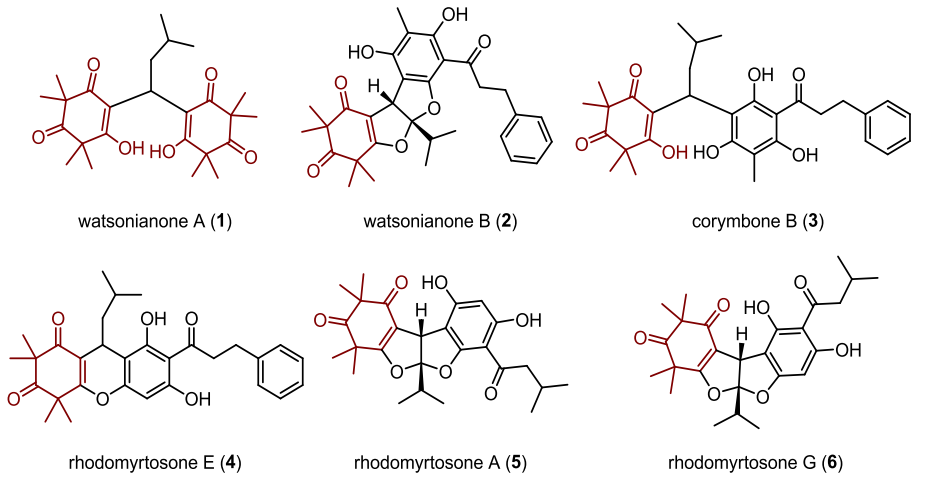
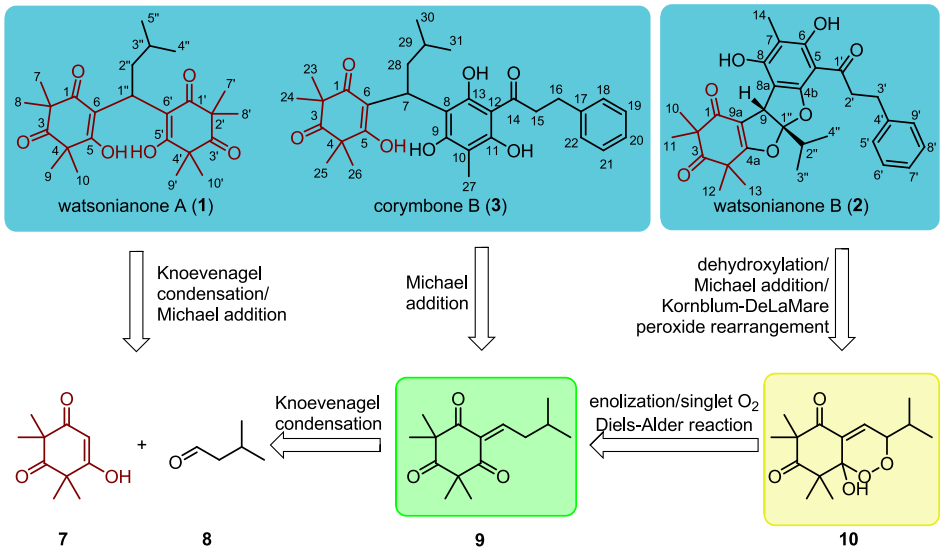
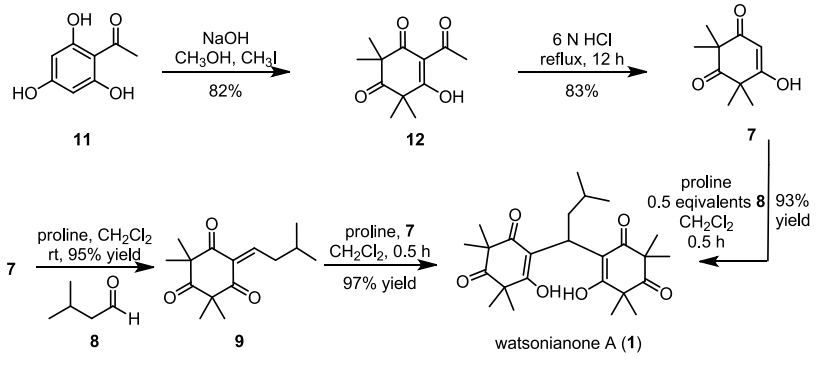


Figure 1. Representative Polycyclic Polymethylated Phloroglucinols.

Scheme 1. Retrosynthetic Analysis of Watsonianones A and B (1 and 2) and Corymbone B (3)



Scheme 2. Synthetic Route to Watsonianone A



oxide rearrangement cascade reaction.[7] Chemically, intermediate **10** could be envisioned from compound **9** through a putative sequential transformation, which could include a spontaneous enolization/singlet O_2 Diels–Alder cycloaddition as the key reaction.[7,8]

The total synthesis of watsonianone A (**1**), as shown in Scheme 2, began with the commercially available phloroacetophenone (**11**). Compound **11** was converted into the precursor syncarpic acid (**7**) by our previously established two-step protocol involving the selective C-methylation and thermally promoted retro-Friedel–Crafts acylation reactions.[9] Proline-catalyzed Knoevenagel condensation[10] with excess isovaleraldehyde (**8**) was applied to directly install the isopentyl chain to afford precursor **9** in 95% yield. Compound

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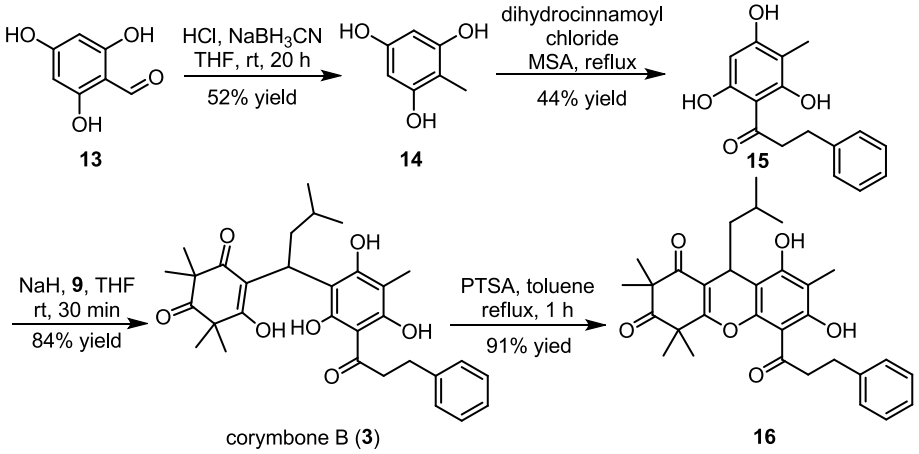
Scheme 3. Synthesis of Corymbone B (3) and Derivative 16



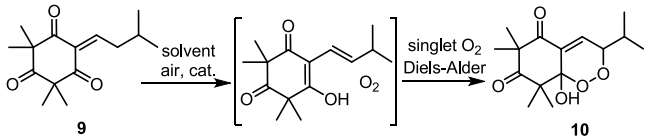
9 was transformed into the target watsonianone A (**1**) in 97% yield by a proline-mediated Michael addition. Moreover, the exploration of different catalytic condensation conditions with the aim of directly transforming syncarpic acid (**7**) and isovaleraldehyde (**8**) into watsonianone A (**1**) in one step was also performed. Satisfyingly, when 2.0 equiv of syncarpic acid (**7**) was used, the Knoevenagel condensation/Michael addition cascade reaction[11] proceeded smoothly and afforded product watsonianone A (**1**) in one step in 93% yield. Therefore, the first racemic total synthesis of watsonianone A (**1**) was successfully established, and it provided a concise synthetic route to rapidly access this bioactive molecule and its structural derivatives.

With the synthesis of precursor **9** in place, the total syntheses of watsonianone B (**2**) and corymbone B (**3**) were attempted. The requisite acylphloroglucinol **15** was synthesized from the commercially available aldehyde **13** in two steps. The selective reduction of **13** with $NaBH_3CN$ under acidic conditions afforded methylphloroglucinol (**14**).[12] Compound **14** afforded key intermediate **15** in moderate yield via the treatment with dihydrocinnamoyl chloride in the presence of MSA (methylsulfonic acid) through an acid-catalyzed Friedel–Crafts acylation. When precursor **9** was subjected to a NaH/tetrahydrofuran (THF) solution of dihydrochalcone **15**, the Michael addition reaction afforded corymbone B (**3**) in 91% yield.

The ^1H NMR spectrum of corymbone B (**3**) in $CDCl_3$ showed the presence of a pair of keto/enol tautomers.[4b] Although its NMR and HRESIMS data (for details, see Supporting Information) matched those of the natural isolate, its spectroscopic assignments were difficult. Hence, corymbone B (**3**) was cyclized with *p*-toluenesulfonic acid (PTSA) to afford the racemic product **16**, which could be readily characterized via NMR data to confirm its structure. Compound **16** closely resembled the known compound 6,8-dihydroxy-9-isobutyl-2,2,4,4-tetramethyl-5-(3-phenylpropanoyl)-4,9-dihydro-1*H*-xanthene-1,3(2H)-dione[13] and was successfully produced in 91% yield. The NMR spectra of compound **16** shared close similarity (except for the lack of a methyl moiety) with those of the aforementioned known compound, thus confirming the structure of corymbone B (**3**).

The total synthesis of watsonianone B (**2**) commenced with the preparation of racemic peroxide intermediate **10** according to the previously reported protocol,[7] in which the photocatalyzed peroxidation seemed to be incompatible with substrate **9** under the conditions of a 300 W medium-pressure mercury lamp, providing peroxide **10** in 29% yield (entry 1 in Table 1). Serendipitously, the treatment of substrate **9** under ambient light conditions in an air atmosphere for 6 h led to peroxide **10** in 13% yield (entry 2). Although the yield was unsatisfactory, it showed promising potential because of the mild reaction conditions. In an attempt to improve the yield of this spontaneous enolization/air oxidation cascade sequence under similar conditions, variables such as solvent, catalyst, and lighting sources were screened.

Table 1. Partial Optimization of the Reaction Conditions for the Synthesis of Peroxide 10[a]



entry	solvent	catalyst	photo condition	*t* (°C)	time (h)	yield (%)[b]
1	DCM	–	*hν*[c]	rt	6	29
2	DCM	–	*hν*	rt	6	13
3	DCM	TFA	*hν*	rt	12	10
4	DCM	HOAc	*hν*	rt	12	13
5	DCM	PTSA	*hν*	rt	12	<10
6	DCM	ET_3N	*hν*	rt	12	<10
7	$CHCl_3$	–	*hν*	rt	12	13
8	THF	–	*hν*	rt	12	12
9	MeCN	–	*hν*	rt	12	18
10	MeOH	–	*hν*	rt	12	<10
11	toluene	–	*hν*	rt	12	13
12	toluene	–	*hν*	60	12	<10
13	–[d]	–	*hν*	rt	24	35
14	–[e]	–		rt	24	<10
15	–[d]	–	*hν*	60	12	11

[a]Reaction conditions: compound **9** (0.5 mmol), solvent (3 mL), *hν* (house light), rt, 6–12 h. [b]Combined yield of the isolated product. [c]*hν* (300 W medium-pressure mercury lamp). [d]Neat (solvent free). [e]Neat (solvent free), in the dark. DCM: dichloromethane; TFA: trifluoroacetic acid; PTSA: *p*-toluenesulfonic acid.

The addition of catalytic Bronsted acid or base failed to promote the transformation, whereas the solvents did influence

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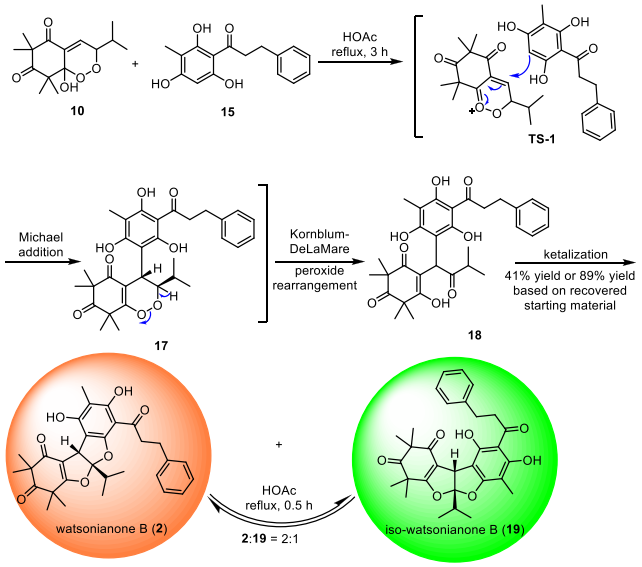
the reaction efficiency (entries 7−12). In this way, the product was obtained in 18% yield in MeCN. The exposure of neat **9** in thin-film form proved to be the most effective conditions, yielding product **10** in a 35% yield, as shown in entry 13. As expected, no reaction occurred in the absence of light (entry 14), which strongly suggested that the reaction should take place through a singlet O_2 Diels−Alder reaction pathway.[14] Normally, the singlet O_2-induced Diels−Alder reaction would require the presence of a photosensitizer; thus, these results also indicated that the α,β-unsaturated intermediate **9** might act as a self-photosensitizer because of its extensive conjugated system.[14,15] Elevated temperatures seemed to be detrimental for spontaneous transformation (entry 15). Notably, the spontaneous oxidation process coupled with the mild reaction conditions present in the wild plant suggests a strong possibility for the process to be biomimetic in nature, and it may in fact mimic the actual biosynthetic generation of **10** and its derivatives downstream.[4,16]

Having established the optimal conditions to access the key intermediate **10**, our efforts were focused on constructing the bisfurano β-triketone scaffold of watsonianone B (**2**) through the sequential dehydroxylation/Michael addition/Kornblum−DeLaMare peroxide rearrangement cascade sequence.[7] As shown in Scheme 4, the acid-promoted elimination of the

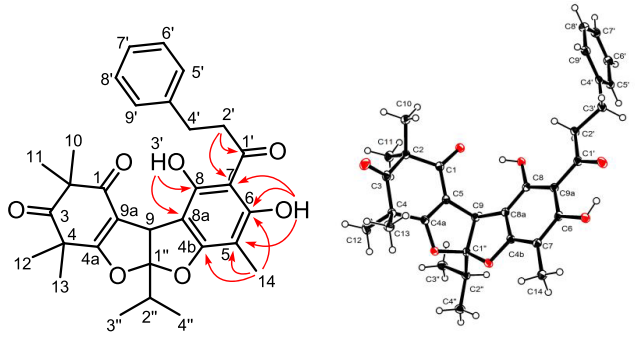
Scheme 4. Biomimetic Total Syntheses of Watsonianone B (2) and *iso*-Watsonianone B (19)



hydroxy group of **10** would lead to the *in situ* generated α,β-unsaturated oxonium ion. Trapping of this active electrophile with 2,4,6-trihydroxy-4-methydihydrochalcone (**15**) via a Michael addition reaction afforded intermediate **17**. The subsequent Kornblum−DeLaMare peroxide rearrangement of **17** would afford the bisfurano-β-triketone scaffold via intermediate **18**. Gratifyingly, this cascade proceeded in an efficient manner in refluxing HOAc, leading to the formation of watsonianone B (**2**) in 27% yield. The ^{1}H and ^{13}C NMR spectra as well as the HRESIMS data of synthetic watsonianone B (**2**) fully matched those of the isolate reported by Carroll and his co-workers (for details, see the Supporting Information).[4a]

The formation of compound **19** accounted for the remaining 14% yield, and **19** showed close similarity with the product watsonianone B (**2**) in both the structural skeleton and spectroscopic data. Compound **19** was purified as a solid and possessed the same molecular formula as **2**. The ^{1}H and ^{13}C NMR spectroscopic data (Supporting Information) of **19** were similar to those of **2**, suggesting that the two compounds were regioisomers. This conclusion was confirmed by the HMBC correlations from H_3-14 to C-4b, C-5, and C-6; HO-6 to C-5, C-6, and C-7; and HO-8 to C-8 and C-8a, as well as the correlations from H_2-2′ to C-1′ and C-7, which indicated that the phenylpropanoyl group in **19** was located at C-7. A single crystal of **19** suitable for X-ray crystallography analysis (Cu Kα radiation) was obtained from a $CDCl_3$ solution, which unequivocally confirmed the structure of **19** (Supporting Information). Based on the aforementioned results, the structure of compound **19** was defined and given the trivial name *iso*-watsonianone B.

Scheme 5. HMBC Correlations and ORTEP Drawing of *iso*-Watsonianone B (19)



Compounds **2** and **19** were thus shown to be regioisomers, as expected from the two phenolic groups that may participate in the cyclization process. A similar regioisomeric cyclization has been reported in rhodomyrtone and rhodomyrtosone B natural products.[17] Compound **19** was stable at room temperature and could be separated by silica gel column chromatography. *iso*-Watsonianone B (**19**) and watsonianone B (**2**) could be tautomerized in refluxing HOAc. The equilibrium between *iso*-watsonianone B (**19**) and watsonianone B (**2**) could be attributed to the reversibility of ketal formation under acidic conditions. In this regard, it is possible that the series of natural products belonging to the bisfurano β-triketone family might also exist as complex mixtures of regioisomers, although compelling evidence from a naturally occurring source has not been confirmed.

In summary, the biosynthetic hypothesis of these natural products inspired us to explore a diversity-oriented synthetic strategy, subsequently leading to the first biomimetic total syntheses of antiplasmodial watsonianones A (**1**) and B (**2**) and corymbone B (**3**). The results revealed the spontaneous enolization/air oxidation of precursor **9** through a singlet O_2-induced Diels−Alder reaction pathway for the generation of peroxide **10**. The mild reaction conditions strongly suggests the possibility of a biomimetic process in nature and may in fact mimic the actual biosynthetic processes for the related downstream natural products. Complementing the efficiency and simplicity of the developed synthetic route, this methodology also provides a route for the rapid assembly of similar phloroglucinol-derived products in a practical fashion and sufficient quantities to facilitate drug discovery. Further

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investigations on the SAR study and antiplasmodial mechanism of these compounds will be directed toward this goal and reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b01077.

Experiment procedures, NMR spectra, MS data for new compounds, and X-ray crystallography data for compound **19** (PDF)

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Notes

The authors declare no competing financial interest.

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