A Bio-Inspired Synthesis of Peshawaraquinone

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ABSTRACT: A ten-step bio-inspired enantioselective synthesis of peshawaraquinone, an uncommon and complex naphthoquinone meroterpenoid is described. Key to the success of this synthetic pathway is a well-tuned HFIP-promoted metal-free allylation was developed to coupling lawsone with allylic alcohols, together with an usual organo-catalyzed [3+2] cycloaddition for constructing the bicyclo[3.2.1]octane core structure. Further investigation disclosed peshawaraquione is a racemic mixture.

Natural products continue as a major source of inspiration for synthetic chemists in terms of their bioactivities and fascinating structures, which also challenge synthetic community to provide efficient strategy for total synthesis.[1] In some cases, biomimetic synthesis provide an expedient synthetic pathway for preparing complex natural product.[2] In the case of naphthoquinone meroterpenoid natural products with intricate structure,[3] the structural features demonstrate their mixed biosynthetic origin which nature combines the terpenoid motif with polyketide building block, and the structural diversity was mainly derived from the reactivity mode of the naphthoquinones, naphthalene or 2-hydroxy-1,4-naphthoquinone (lawsone) as nucleophiles and electrophiles.[4] Several impressive total syntheses of these natural products have been reported (Figure 1),[5] such as isomarinone (**2**), napyradiomycin A1 (**3**), furaquinocin C (**4**), pinnatal (**5**) and merochlorins (**6** and **7**), and they continue inspire the synthetic community to develop ever efficient synthetic strategies. In this regard, we started a project toward peshawaraquinone (**1**), which was isolated from the stem heartwood of *Heterophragma adenophyllum* from Pakistan.[6] More recently, the anti-inflammatory activity of peshawaraquinone was reported.[7] Herein we delineate the evolution of our synthetic strategy which culminating in a concise, bio-inspired enantioselective synthesis of peshawaraquinone.[8]

Peshawaraquinone (**1**) is an unusual natural product containing a characteristic naphthoquinone dimeric moiety, however, its structure which belong to the meroterpenoids demonstrate its mixed biosynthetic origin. One of its structure features is the distinguished, an unprecedent bicyclo[3.2.1]octane moiety derived from 2-hydroxy-1,4-naphthoquinone (lawsone), and is the only known natural product containing such a structural motif.[9] Meanwhile, its cage-like structure with seven rings and six continuous stereocenters including one all-carbon quaternary centers, making it an attractive, but challenging synthetic target. In Scheme 1, we propose a biosynthetic pathway to peshawaraquinone. Upon close inspection of its molecular architecture, 3-geranyllawsone (**8**), which itself is also a natural product,[10] and previously proposed as the biosynthesis intermediate to pyranokunthone B (**9**) and pinnatal (**5**) through allylic oxidation and intramolecular Diels-Alder reaction[5c] was defined as possible starting material. Through oxidation of the activated allylic position at C11 followed by desaturation would afford hypothetical intermediate **11**, which would then undergo 6π electrocyclization to pyrone **12**. A Schenck ene reaction[11] mediated by singlet oxygen ($^1O_2$) could then provide allylic alcohol **13**, primed for an S_N1' reaction with lawsone to provide **14**, followed by [3+2] cycloaddition would then give the natur-

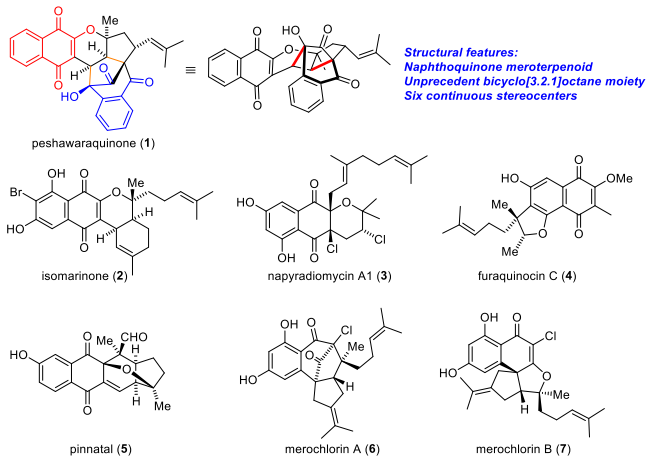
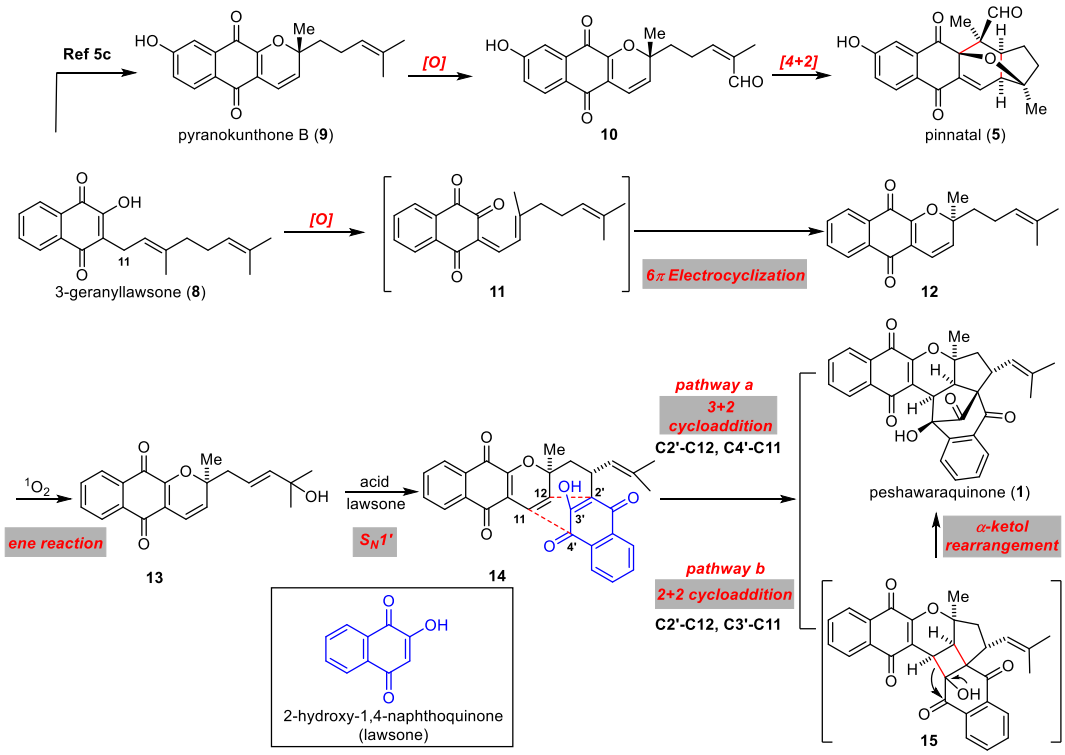


Figure 1. Selected polycyclic naphthoquinone meroterpenoids.

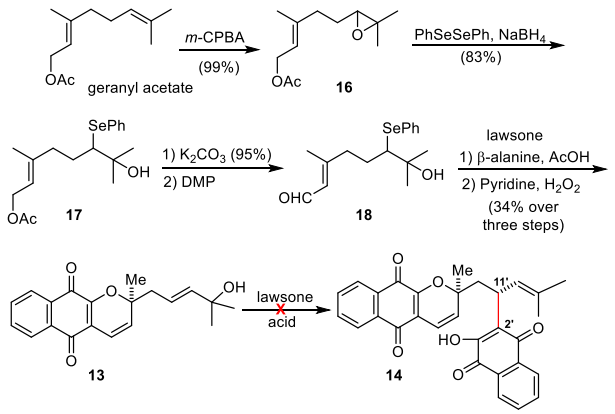
Scheme 1. Proposed biosynthetic pathway of peshawaraquinone



al product. An alternative pathway through [2+2] photocycloaddition[12] followed by acyloin rearrangement[13] of intermediate **15** would also give peshawaraquinone.

Initially, our synthetic studies commenced with the known selective epoxidation from commercially available geranyl acetate (Scheme 2), then the epoxide **16** was opened by the in-situ generated sodium phenylselenide.[14] It is worth to note that mono-phenylselenation **17** was formed in 10 minutes, and the allylic acetate would also be phenylselenated when extending the reaction time. Removal of the acetate followed by Dess-Martin oxidation afforded enal **18**. Condensation with lawsone followed by mild oxidative elimination delivered the tertiary alcohol **13**. Schenck ene reaction was also tried from compound **12** to synthesis **13,** but only substrate decomposition was observed. From **13**, several Lewis acids were screened

Scheme 2. Attempted synthesis peshawaraquinone through S_N1' reaction.



with lawsone and three other aromatic compounds (furan, 1,2,4-benzenetriol and 1,2,4- naphthalenetriol), however no expected product was formed (For details, see Supporting Information).

These results necessitated that the C2'-C11' bond be formed by a different method. and we decided to explore a sequence in which C2'-C11' bond formation preceded naphthoquinone formation from lawsone. Ultimately, this decision allowed completion of peshawaraquinone and the successful synthetic route starting from geranyl acetate is shown in Scheme 3. Although $^1O_2$-mediated ene reaction was not successful in our hands, through the reported condition by Sharpless[15] involving oxyselenation and oxidative elimination, tertiary alcohol **19** containing a skip diene moiety was prepared efficiently in one step. Several Lewis acids were screened for performing this challenging S_N1' displacement with lawsone, but with no success. As we reasoned the alcohol group can be activated by Lewis acid, reaction failure was presumably due to the performance of lawsone acting as a nucleophile. We subsequently found that by solely using HFIP as the reaction solvent, the desired product **20** could be formed in 95% yield without Lewis acid! Notably, when the reaction was conducted in TFE, no product formation was observed. The plausible reason for the success of this reaction utilizing HFIP[16,17] might be ascribed to: 1) the acidity and reduced nucleophilicity of HFIP to stabilize the formed allylic carbocation; 2) HFIP enhance the nucleophilicity of lawsone. Under this powerful solvent effect, the C2'-C11' bond was constructed efficiently in only two steps, and this developed HFIP-promoted allylation was further tested the substrate scope. As show in table 1. This reaction proved to be tolerant with aromatic and aliphatic allylic alcohols and provided the products (**21**-**26**) in an efficient manner.

Scheme 3. Bio-Inspired Synthesis of Peshawaraquinone.

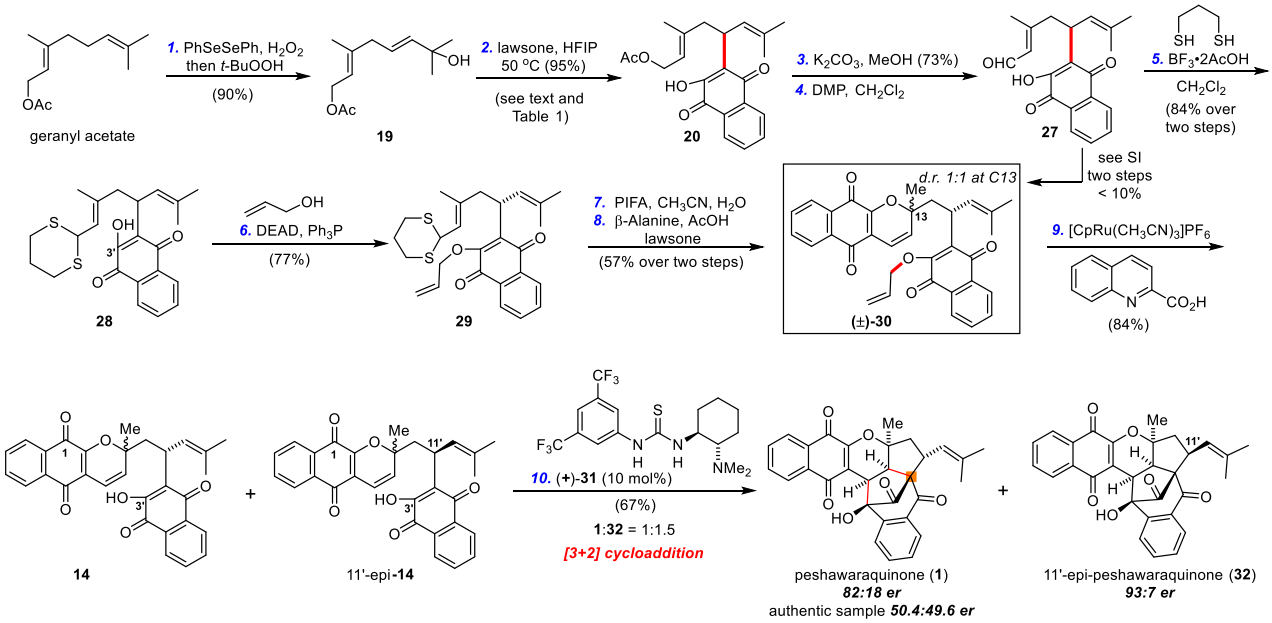
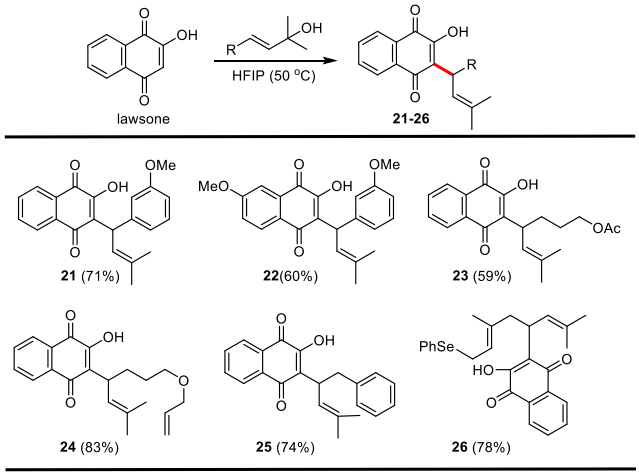


Table 1. Scope of HFIP promoted allylation.[a,b]



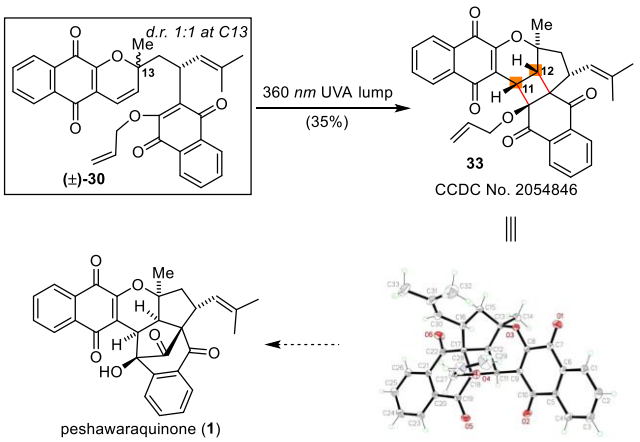
[a] Reaction conditions: alcohol (1 equiv), naphthoquinone (2 equiv) in HFIP (1 mmol/mL for alcohol), 50 °C. [b] Yields of isolated products are given.

Moving forward from **20**, removal of the acetate and Dess-Martin oxidation afforded the unstable α,β-unsaturated aldehyde **27,** which was first protected as 1,3-dithiane, then protected the C3' hydroxy group as allyl ether through Mitsunobu reaction followed by Stork-Zhao dethioacetalization[18] and the formed aldehyde was submitted under catalytic amount of AcOH and β-alanine, pyran **30**, the protected form of the biosynthetic precursor **14** was generated through Knoevenagel condensation and oxa 6π electrocyclization. Worth to mention, protection of the hydroxy group of **28** as an allyl ether is especially important, as direct condensation **27** with lawsone was unsuccessful and transform corresponding allyl ether of **27** to **30** suffer low yield (compound **30** could be prepared from **27** in two steps, however, the yield is less than 10%). The methoxy group as protection group was also used for preparing the pyran, but demethylation to **14** failed albeit with exploration of a series of reaction conditions (For details, see Supporting Information). Deprotection of the allyl ether under mild reaction conditions reported by Kitamura,[19] the precursor for the last key step was prepared. With the inseparable penultimate intermediate **14** and 11-epi-**14** in hand, NEt_3 was first used for the cascade reaction,[20] however, only substrate decomposition was observed. Inspired by the thiourea catalyzed Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes originally reported by one of us (Zhou) with Du,[21] the Takemoto catalyst **31** was used for the proposed cascade reaction. To our delight, the [3+2] cycloaddition delivered the natural product efficiently with its diastereomer **32** in a ratio of 1:1.5, and the result of this successful last step was ever better with both products are enantiopure, 82:18 er for natural product peshawaraquione and 93:7 er for 11'-epi-peshawaraquione (For screened catalyst, see Supporting Information). The success of this cascade reaction is plausible rely on the hydroxy group of C3' is deprotonated by the tertiary amine segment of the catalyst which act as nucleophile as well as the carbonyl group of C1 was activated through form hydrogen bonds with the thiourea segment of the catalyst. And this stereodivergent step stand as a kinetic resolution of **11** and 11'-epi-**11** simply mediated by Takemoto catalyst. As the optical rotation of peshawaraquinone was not reported in the isolation paper,[6] and based on our proposal, biosynthetic pathway of peshawaraquinone involved non-enzymes pathway, so we re-isolated natural product and chiral HPLC measurement further supporting natural product is a racemic mixture[22] and the synthetic 11-epi-peshawaraquione could also be a natural product still await to found.[23]

Moreover, we also found **30** could undergo [2+2] cycloaddition in neat or under photo-irradiated condition, and the structure of **33** was further confirmed by X-ray crystallography analysis (Scheme 4). From **33**, the proposed sequence of deprotection followed by α-ketol rear-

rangement was halted due to the stereochemistry of C11 and C12 was not matched for natural product. Collectively, both the [2+2] photocycloaddition and the [3+2] cycloaddition occurred smoothly indicated the close proximity of pyran and naphthoquinone ring.

Scheme 4. Attempted [2+2] photocycloaddition approach to peshawaraquinone (1).



In summary, a bio-inspired enantioselective synthesis of peshawaraquinone has been accomplished concisely via the well-tuned HFIP-promoted allylation and Takemoto catalyst elicited formal [3+2] cycloaddition. We anticipate that adaptations to the general strategy described herein will facilitate the total synthesis of other naphthoquinone natural products.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org." Experimental details, spectroscopic data, and crystallographic data.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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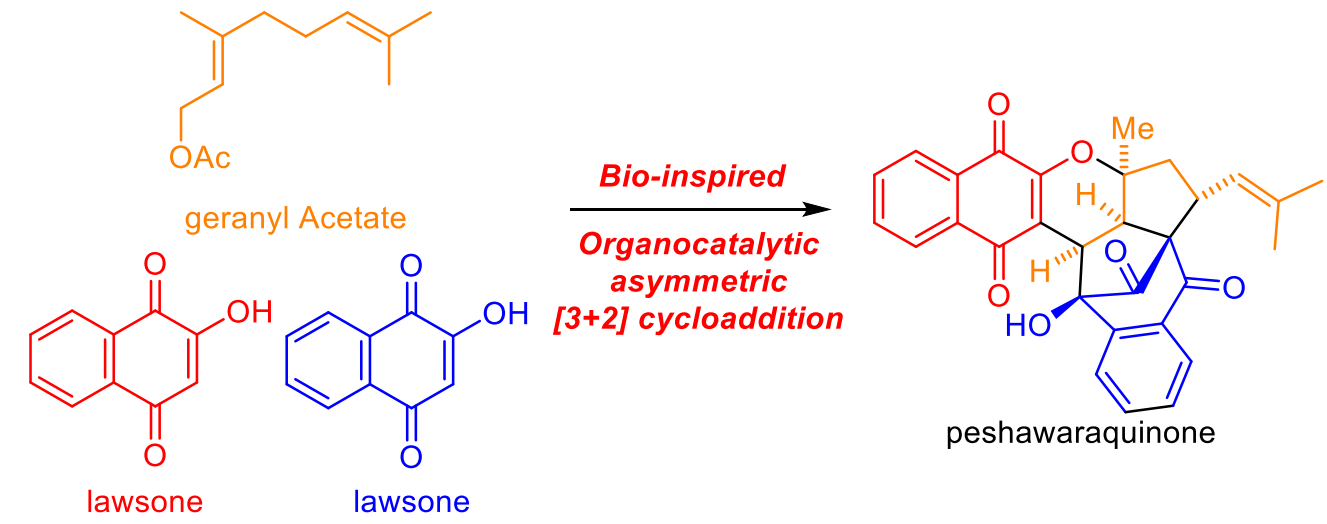
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