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Expediently Scalable Synthesis and Antifungal Exploration of (+)-Yahazunol and Related Meroterpenoids

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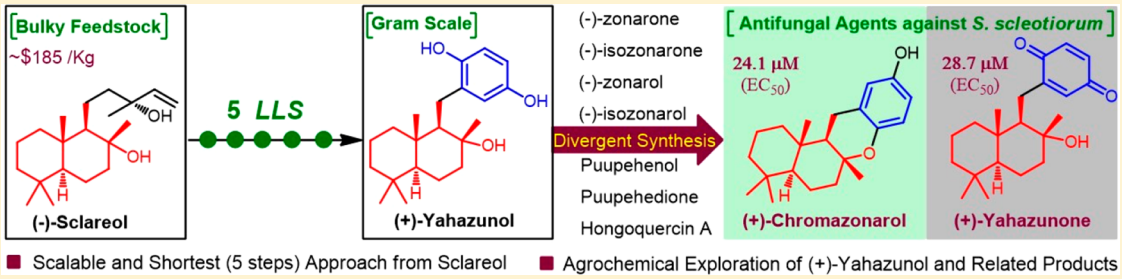
Supporting Information



ABSTRACT: The efficient synthesis and antifungal exploration of (+)-yahazunol and related natural products are described. Central to this strategy is the Barton decarboxylative coupling, comprising a one-pot radical decarboxylation and quinone addition cascade. The scalable synthesis of (+)-yahazunol was accomplished in five longest linear sequences (LLS) starting from commercially available and inexpensive (−)-sclareol. The divergent translational potential of (+)-yahazunol was demonstrated by the expedient preparation of (−)-zonarone, (−)-isozonarone, (−)-zonarol, (−)-isozonarol, (+)-chromazonarol, and (+)-yahazunone. This approach also enables the formal synthesis of puupehenol, puupehedione, and hongoquercin A. Antifungal evaluation was performed, and this represents the first biological profiles for (+)-yahazunone, (+)-8-*O*-acetylyahazunone, and (+)-8-*O*-acetylyahazunol. (+)-Chromazonarol and (+)-yahazunone are promising candidates against *Sclerotinia scleotiorum*, with EC_{50} values of 24.1 and 28.7 μM, respectively, demonstrating advantages over the original model (DM) and synthesized heterocyclic mimic (**3a**) of meroterpenoids. This will favor the establishment of a chemical repertoire in the management of different plant diseases.

Co-evolving with biological systems for millions of years, natural products often feature biologically relevant pharmacophores that have resulted in preferred ligand−protein binding motifs.[1] A range of uncharted chemotypes were discovered and developed as chemical probes and drugs from natural products or their intricate frameworks.[2] Natural products also occupy a privileged space in novel agrochemical discovery, with up to 50% of pesticide sales (in 2012) and >60% of all action mechanisms of pesticides inspired by them.[3] Biologically important natural products have been serving as powerful weapons for human beings in the competition with various pests. Meroterpenoids are an assembly of sesquiterpene and phenolic or quinone moieties. They possess versatile bioactivities ranging from anticancer and anti-HIV to antifungal potentials.[4] In continuing efforts to discover novel agrochemicals based on natural products,[5−8] we are interested in hydroquinone sesquiterpenes with a drimane skeleton among different meroterpenoids not only for their versatile biological activities but also for the diverse structures with a constant scaffold as shown in Figure 1A serving as potential respiration regulators.

Minor modifications of the decoration on either the hydroquinone or the drimane subunits will lead to a number of meroterpenoid natural products. More interestingly, some related enantiomers exist naturally or can be produced artificially, exemplified by (−)-yahazunol and (+)-yahazunol (Figure 1B), which were isolated from the brown seaweed *Dictyopteris undulata* Okamura in 1979[9] and a sponge of the genus *Dysidea* in 2005,[10] respectively. (−)-Yahazunol showed a strong antimicrobial activity against some yeasts, and (+)-yahazunol demonstrated modest inhibition against human tumor cell lines MDA-MB-231 and A-549. (−)-Yahazunol-related natural products, including zonarol, isozonarol, zonarone, and isozonarone, were isolated,[11,12] some of which are fungitoxic toward *Phytophthora cinnamomic*, *Rhizoctonia solani*, and *Sclerotinia sclerotiorum*. Feeding-deterrent activity was reported for cyclozonarone.[13] There are no reports documenting the agrochemically antifungal potential of (+)-yahazunol and related enantiomers of natural products

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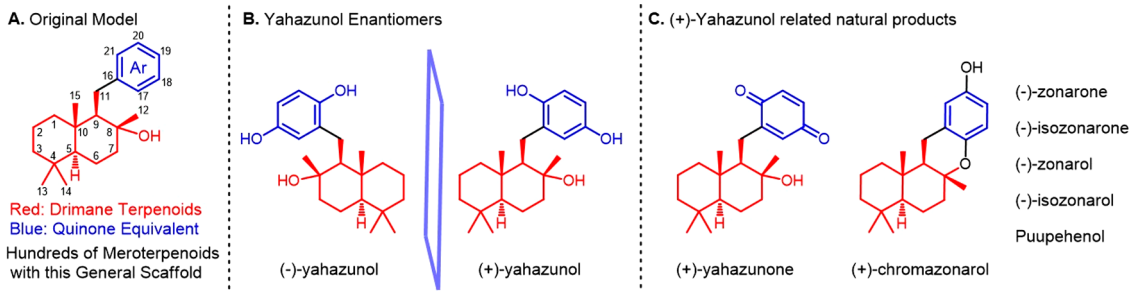
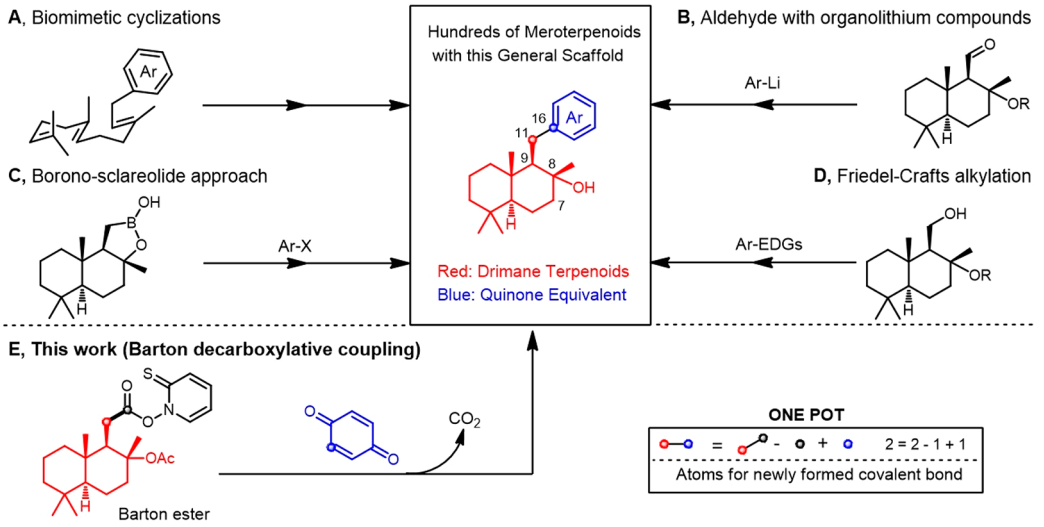
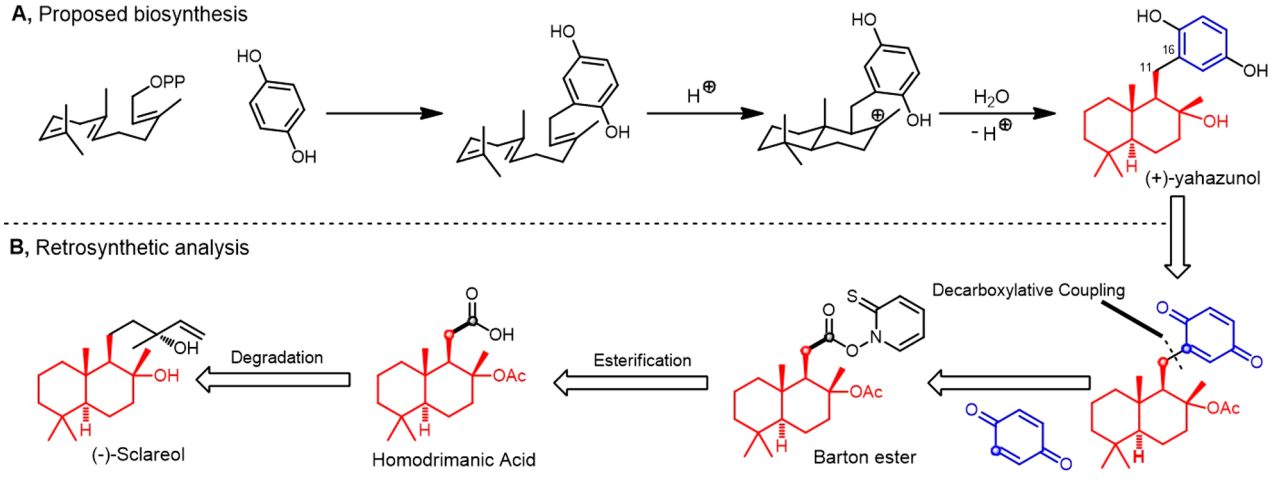


Figure 1. Drimane meroterpenoid model and yahazunol-related products.

Scheme 1. Versatile Protocols for the Synthesis of Drimane Meroterpenoids



Scheme 2. Retrosynthetic Analysis of (+)-Yahazunol



(Figure 1C), including (+)-chromazonarol, (−)-zonarone, and (−)-isozonarone. Considering the importance of chirality in agrochemical exploration and medicinal chemistry,[14] we previously conceived "carbon assimilation" and applied it for the rapid and divergent construction of (+)-yahazunol mimics from readily available materials, whereby drimanyl isoxazoline and drimanyl pyrimidine mimics are presented as potent antifungal leads.[8] Herein, we document the efficient synthesis and antifungal exploration of (+)-yahazunol and related natural products and analogues.

RESULTS AND DISCUSSION

Retrosynthetic Analysis and Tactic Development. Besides biomimetic cyclizations of polyprenoids[15] and catalyzed epoxypolyene cyclization[16,17] for the construction of drimanyl meroterpenoids (Scheme 1A), applying a semisynthesis protocol is powerful when starting from the readily available labdane-type diterpenes,[18] including sclareol, sclareolide, labdanolic acid, abietic acid, larixol, and ozic acid. This protocol is well developed for the efficient synthesis of drimane meroterpenoids by the coupling of a drimanyl or drimenyl

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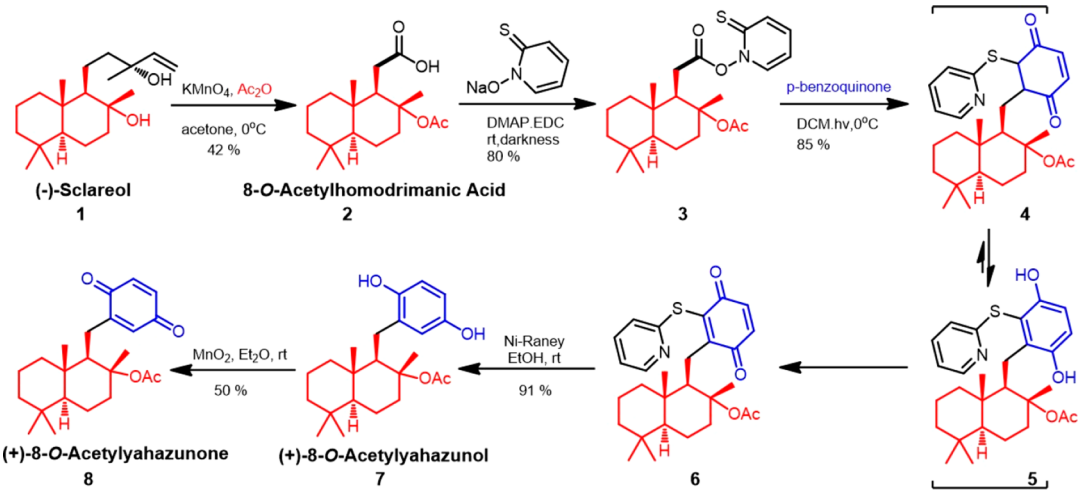
Scheme 3. Synthesis of 8-*O*-Acetyl Derivatives of (+)-Yahazunol and (+)-Yahazunone



aldehyde with an organolithium compound derived from arenes[19−22] (Scheme 1B). Recently, a seminal and divergent synthesis of bioactive meroterpenoids has been developed by the Baran group through the invention of "borono-sclareolide"[23] (Scheme 1C). This allowed the synthesis of (+)-chromazonarol in six steps from (+)-sclareolide, which also served as a node for (+)-yahazunol and related natural products. Dethe and co-workers utilized Lewis-acid-catalyzed Friedel−Crafts alkylations for the establishment of (+)-chromazonarol (Scheme 1D).[24,25]

Biosynthetically, the generation of (+)-yahazunol presumably involves the coupling of farnesyl pyrophosphate and hydroquinone followed by stereoselective polyene cyclization. The generated tertiary carbocation is captured by H_2O enantioselectively to afford (+)-yahazunol (Scheme 2A). Inspired by this biosynthetic pathway and the elegant synthesis of rearranged drimane meroterpenoids,[26−28] we envisioned that the Barton ester of homodrimanic acid might be an ideal synthon or equivalent to replace farnesyl pyrophosphate for coupling.

From a structural standpoint and proposed biosynthesis, the relatively "simple" (+)-yahazunol or its derivative was chosen as the starting point for potential divergent transformations to other related drimane meroterpenoids. The global retrosynthetic analysis is depicted in Scheme 2B featuring the connection of the drimane unit with a hydroquinone by the establishment of the C-11−C-16 bond, through a radical decarboxylative coupling. The starting materials for this approach may be traced back to (−)-sclareol and quinone, which are both commercially available and inexpensive.

Synthesis of Precursors or Analogues of (+)-Yahazunol. As shown in Scheme 3, the synthetic approach started from optically pure and bulk feedstock, (−)-sclareol (**1**), which is a well-known fragrance diterpenoid isolated mainly from the plant *Salvia sclarea*. This diterpenoid is used in the perfume industry and can be purchased even in kilogram quantities.[29] Oxidative degradation of (−)-sclareol (**1**)[30] with potassium permanganate in the presence of Ac_2O gave the 8-*O*-acetylhomodrimanic acid (**2**) directly in moderate yield (42%), with sclareolide as the other major product (yield 35%). The latter can be used as a starting material in the synthesis of complex natural products[18] or be hydrolyzed to homodrimanic acid.

The synthesis of the required photolabile and redox-active thiohydroxamic ester **3** (Barton ester)[26,28] was efficiently obtained from the condensation of 8-*O*-acetylhomodrimanic acid (**2**) with 2-mercaptopyridine *N*-oxide applying Steglich-esterification conditions. Shielding the reaction is necessary in the case of the decomposition of the photosensitive intermediate **3**. Light-induced (250 W) decarboxylative coupling of **3** with the electron-deficient benzoquinone was achieved at 0 °C in a tandem one-pot reaction. A drimanic radical was produced in the presence of light and trapped by the quinone through a radical-chain process to yield semiquinone **4**. This sequence constructs the C-11−C-16 bond in only three steps from sclareol. In contrast, there are usually more than six steps required for the coupling of a drimanyl aldehyde with an organolithium compound or in the Suzuki coupling approach with "borono-sclareolide". In addition, the former approach often suffers from an ensuing post-deoxygenation of 11-hydroxymeroterpenoids under the rather harsh conditions. Compound **4** tautomerizes to the pyridylthio hydroquinone meroterpenoid **5**, preventing further attack by a drimanyl radical to the second dienone moiety of **4**. The pyridylthioquinone meroterpenoid **6** was obtained in good yield (85%) by in situ oxidation of **5** with an excess of the quinone. ESIMS analysis showed two ions at m/z 482.22 $[M + H]^+$ and 504.19 $[M + Na]^+$. The ^{13}C NMR and DEPT spectra showed the presence of 28 carbons, including five methyls, six methylenes, eight methines, and nine nonprotonated carbons. Two carbonyl resonances at δ_C 182.0 and 185.5 corroborated the presence of a 1,4-benzoquinone moiety. The resonance at δ_C 169.5 represented the acetate carbonyl carbon. The ^1H NMR spectrum indicated the presence of four protons in the pyridine ring (δ_H 7.02, 7.34, 7.55, and 8.26), two quinone hydrogens (δ_H 6.82), and five methyl singlets (δ_H 0.80, 0.87, 0.92, 1.60, and 1.75).

Treatment of compound **6** with Raney-nickel in EtOH at room temperature for a few minutes (5−10 min) afforded the acetate of (+)-yahazunol (**7**) in excellent yield (91%), which is otherwise hard to achieve by regioselective esterification of (+)-yahazunol. The ESIMS data correlated well with the (+)-8-*O*-acetylyahazunol by showing two ions at m/z 397.29 $[M + Na]^+$ and 315.31 $[M - HOAc + H]^+$. The ^{13}C NMR and DEPT spectra showed the presence of 23 carbons, including seven nonprotonated carbons, five methines, six methylenes,

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and five methyls. The carbonyl resonance at δ_C 170.1 verified the preservation of the ester moiety during Raney-nickel reduction. The ^{1}H NMR spectrum showed three aromatic hydrogens (δ_H 6.58, 6.65, and 6.67), two phenolic protons (δ_H 5.71 and 6.56), and five methyls (δ_H 0.78, 0.84, 0.98, 1.60, and 1.93). Heterogeneous oxidation of (+)-8-*O*-acetylyahazunol (**7**) with MnO_2 produced (+)-8-*O*-acetylyahazunone (**8**) in practical yield (50%). Other oxidation systems were also explored for this transformation, and no improvements could be achieved (see Supporting Information for more details).

Thus, the successful preparation of (+)-8-*O*-acetylyahazunol (**7**) was established, representing the core scaffold of the drimane meroterpenoids in Figure 1. This method served as a good alternative to the aforementioned available protocols (Scheme 1) by avoiding the air/moisture-sensitive organometallic reagents, ensuing manipulation for dehydroxylation, stoichiometric transition metal reagent mediation, isomerization, etc.

Synthesis of (+)-Yahazunol and Related Meroterpenoids. Attempted hydrolysis of (+)-8-*O*-acetylyahazunol (**7**) with LiOH or NaOH did not provide the target (+)-yahazunol (**9**), although full conversion was observed. Adding $LiAlH_4$ to a solution of acetate **7** in anhydrous THF at 0 °C afforded (+)-yahazunol (**9**) in 93% yield. The ion at *m*/*z* 315.47 $[M - H_2O + H]^+$ was observed in the ESIMS spectrum. Resonances for the ester group were absent in the ^{13}C NMR spectrum, and the resonance at δ_C 75.1 was consistent with the presence of an oxygenated tertiary carbon. With the assistance of DEPT spectra, we speculated compound **9** comprised six nonprotonated carbons, five methines, six methylenes, and four methyls. The ^{1}H NMR spectrum verified the presence of three aromatic hydrogens (δ_H 6.49, 6.53, and 6.63), two phenolic protons (δ_H 7.45 and 8.76), a tertiary hydroxy group (δ_H 4.89), and four methyl singlets (δ_H 0.82, 0.86, 0.97, and 1.30). The structure of (+)-yahazunol (**9**) was confirmed by X-ray diffraction (Figure 2) and was deposited at the CCDC with the number 1827163.

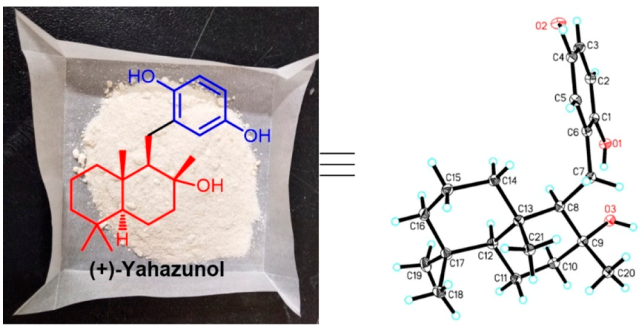

Figure 2. Scalable synthesis and crystal structure of (+)-yahazunol (**9**).

As shown in Scheme 4, a scalable synthesis of (+)-yahazunol (**9**) can be conducted successfully (4 g prepared), and this route constitutes the shortest sequences (5 LLS) to date starting from sclareol. The novel acetate **7** was obtained successfully as a precursor for (+)-yahazunol (**9**). Acetate **7** is not readily available through the regioselective esterification of the tertiary hydroxy group of **9**. (+)-Yahazunol (**9**) was enlisted in the preparation of other drimane meroterpenoid-derived natural products (Scheme 4). Treatment of (+)-yahazunol (**9**) with trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature (rt) afforded (+)-chromazonarol (**13**) in up to 94% yield. The structure was confirmed by ESIMS, ^{1}H and ^{13}C NMR, and DEPT data (vide infra).[23] Other acid-mediated cyclizations with BF_3—Et_2O, ion-exchange resin (Amberlyst15), *p*-TsOH, and Eaton reagent (7.7 wt % P_2O_5 solution in methanesulfonic acid) afforded unwanted by-products or led to decomposition.

Oxidation of diphenol **9** with MnO_2 afforded (+)-yahazunone (**10**) in 83% yield. Notably, (+)-yahazunone (**10**) is supposed to be a new natural product along with (+)-yahazunol. Treatment of (+)-yahazunone (**10**) with $SOCl_2/Et_3N$ gave the inseparable *exo*- and *endo*-cyclic olefins **11a** and **11b** in 86% combined yield. The reaction temperature definitively influenced the ratio of (−)-zonarone (**11a**) to (−)-isozonarone (**11b**) (Scheme 4). Increased temperature favored the formation of isomer **11b**, which may be more stable than the disubstituted alkene **11a**. Decomposition of (+)-yahazunone (**10**) was also detectable when the temperature was increased.

Reduction of (−)-zonarone (**11a**) and its isomer **11b** with sodium dithionite in CH_2Cl_2 afforded (−)-zonarol (**12a**) and (−)-isozonarol (**12b**) in 50% combined yield, but avoided the formation of the tetrasubstituted cyclic olefin isomer of (−)-zonarol from the direct treatment of (+)-chromazonarol (**13**) by BCl_3.[23] Usage of $LiAlH_4$ is to be avoided, since its usage invariably led to the decomposition of (−)-zonarone (**11a**) and (−)-isozonarone (**11b**).

Formal Synthesis of (+)-Chromazonarol-Related Meroterpenoids. With (+)-chromazonarol (**13**) in hand, attention turned to the synthesis of other bioactive meroterpenoids (Scheme 5). Synthesis of puupehenol (**14**) and (+)-8-*epi*-puupehedione (**15**) was accomplished via oxidation by IBX, followed by redox manipulation.[23] Formal synthesis of antibacterial (+)-hongoquercin A (**16**) was realized through a C—H functionalization over four steps.[31]

Antifungal Exploration of (+)-Yahazunol (9) and Related Meroterpenoids. Keeping in mind the importance of natural products in medicinal and agrochemical exploration, the diverse bioactivities of (−)-yahazunol and related natural products prompted us to explore the agrochemical potential of the synthesized naturally occurring meroterpenoids [(+)-yahazunol,[10] (+)-yahazunone,[23] (+)-chromazonarol,[20] and (−)-isozonarol[10,32]] and enantiomers [(−)-zonarone,[33] (−)-isozonarone,[12,19] and (−)-zonarol[23]] or analogues [(+)-8-*O*-acetylyahazunol, (+)-8-*O*-acetylyahazunone] as antifungal agents.

Synthetic (+)-yahazunol (**9**) and (+)-chromazonarol (**13**) were initially evaluated against seven agriculturally important plant pathogens (see Supporting Information for more details). (+)-Yahazunol (**9**) showed modest activity against all the tested fungi, while the antifungal activities were enhanced when the structure comprised the tetracyclic counterpart (+)-chromazonarol (**13**). This structure features decalin-fused dihydrobenzopyran, displaying excellent activity against *Sclerotinia scleotiorum*. The enhancement in the effect against *Rhizoctonia solani* is also impressive. Oxidation of (+)-yahazunol (**9**) to the quinone **10** can lead to an increased antifungal effect, likely due to the formation of a Michael acceptor, which may interact with amino acid residues in the active site. It is noteworthy that the location of the olefinic bond (**11a** vs **11b**) is crucial for antifungal effect against *R. solani*. (+)-Chromazonarol (**13**) was recognized as the most potent compound against *S. scleotiorum*, with an EC_{50} value of 24.1 μM in vitro

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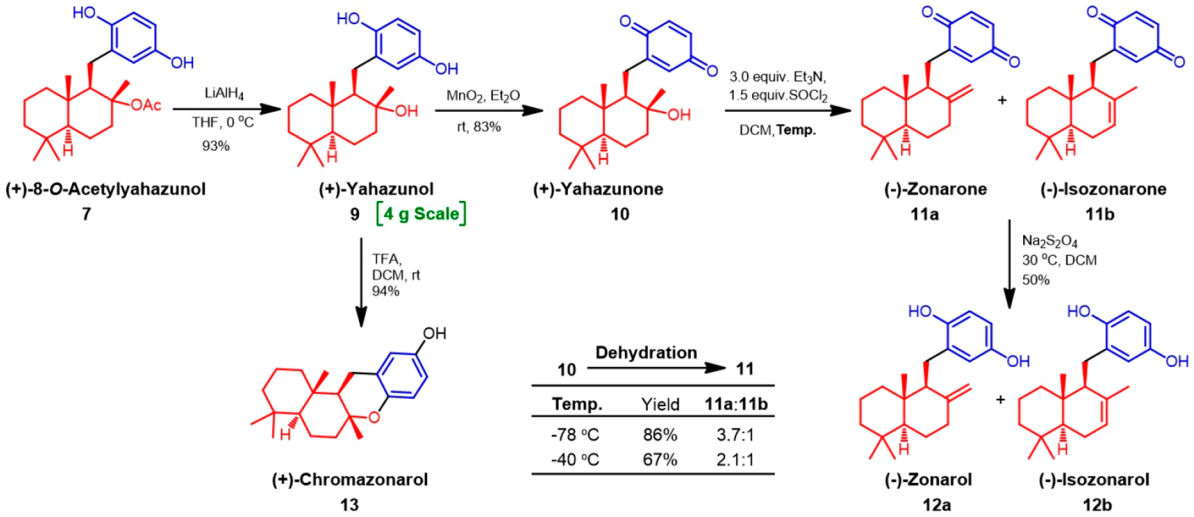
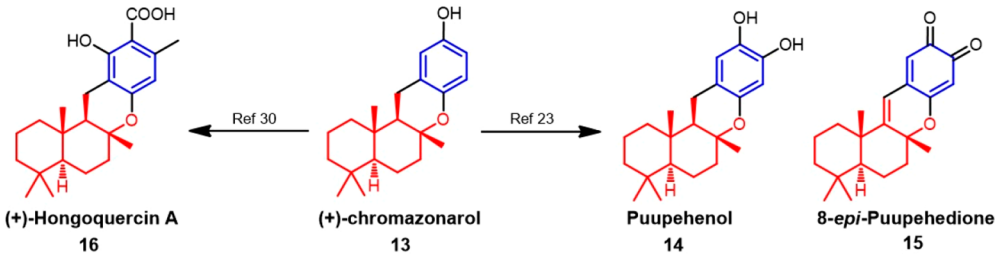
Scheme 4. Synthesis of (+)-Yahazunol (9) and Its Transformation into Related Analogues



Scheme 5. Formal Synthesis of (+)-Chromazonarol (13)-Related Meroterpenoids



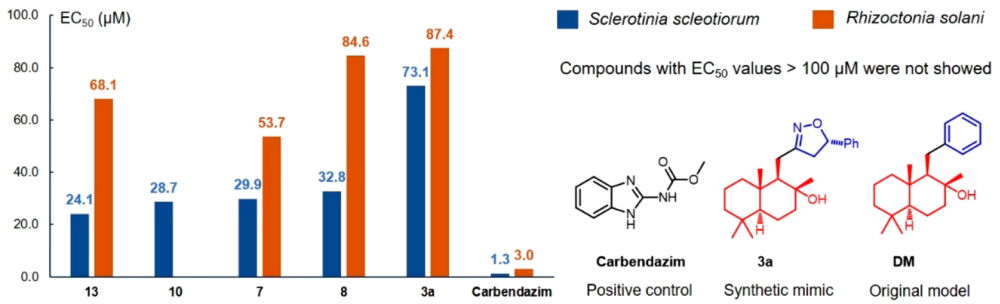


Figure 3. Antifungal activity of (+)-yahazunol (**9**) and related compounds.

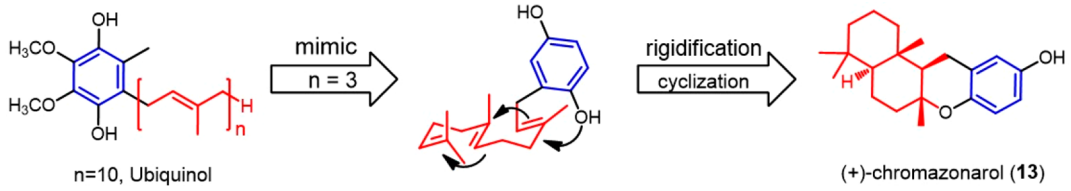


Figure 4. Relationship between ubiquinol and (+)-chromazonarol (**13**).

(Figure 3). Notably, the in vivo assessment of **13** on rape leaves (*Brassica napus*) showed both curative and preventative effects. Furthermore, the presumed natural product, yahazunone (**10**), also showed prominent activity in vitro against *S. scleotiorum* with an EC_{50} value of 28.7 μM. Both (+)-yahazunone (**10**) and (+)-chromazonarol (**13**) showed advantages in the inhibition of *S. scleotiorum* compared to the original model, (1*R*,2*R*,4a*S*,8a*S*)-1-benzyl-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (DM), and one of the previously reported heterocyclic mimics, **3a** (Figure 3).[8] This biologically complementary effect against different plant pathogens will favor the establishment of the chemical repertoire in the management of different plant diseases. This represents the first biological profiles reported for (+)-yahazunone (**10**), (+)-8-*O*-acetylyahazunone (**8**), and (+)-8-*O*-acetylyahazunol (**7**).

On the other hand, coenzyme Q*n* are present in respiring eukaryotic cells and participate in aerobic cellular respiration

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and energy generation in the form of ATP. The precursor of (+)-yahazunol (**9**) was proposed as one kind of analogue of coenzyme Q*n* (n = 3), and the synthesized natural products can be regarded as conformational restricted congeners of ubiquinol (Figure 4). The preferred conformation may be forged and adopted to minimize the entropic loss in the binding interaction with the pharmacological target, leading to enhanced potency and improved selectivity.

In summary, the scalable and efficient synthesis of (+)-yahazunol (**9**) was accomplished in five longest linear sequences (LLS) starting from commercially available and inexpensive (−)-sclareol (**1**), with a Barton decarboxylative coupling as the key step. This is the shortest approach to (+)-yahazunol (**9**) employing (−)-sclareol (**1**) as starting material. The divergent translational potential of (+)-yahazunol (**9**) was demonstrated by the expedient preparation of (+)-yahazunone (**10**), (−)-zonarone (**11a**), (−)-isozonarone (**11b**), (−)-zonarol (**12a**), (−)-isozonarol (**12b**), and (+)-chromazonarol (**13**). This radical decarboxylation and quinone addition cascade should also enable the formal synthesis of puupehenol (**14**), 8-*epi*-puupehedione (**15**), and (+)-hongoquercin A (**16**). The antifungal screening of the synthesized natural products and analogues showed (+)-chromazonarol (**13**) and (+)-yahazunone (**10**) as promising candidates against *S. scleotiorum* with EC_{50} values of 24.1 and 28.7 μM, respectively. This is beneficial to the structure optimization for the discovery of novel agrochemicals. Further exploration of the mechanism of action will also be facilitated by the scalable synthesis of (+)-yahazunol (**9**) and analogues reported herein.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise stated, all solvents and reagents were purchased from commercial sources (Energy or Meryer Chemicals etc.); they were analytically pure and used without further purification. Anhydrous solvents were dried and distilled by standard techniques before use. Silica gel GF_{254} and column chromatography silica gel for isolation (200−300 mesh) were both purchased from Qingdao Broadchem Industrial Co., Ltd. Reaction progress was monitored by TLC on silica gel GF_{254} with phosphomolybdic acid and ultraviolet (UV_{254} nm) detection. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 or 600 spectrometer with $CDCl_3$ or acetone-d_6 as solvent and tetramethylsilane as the internal standard. The chemical shifts (δ) were recorded in parts per million (ppm). ESIMS data were obtained with a Waters Xevo TQ-S micro-spectrometer. The single-crystal X-ray diffraction study was carried out on a Bruker SMART APEX CCD diffractometer. The fungi were provided by the College of Plant Protection, Nanjing Agricultural University (Nanjing, China).

Antifungal Assay. The in vitro and in vivo antifungal activities of the synthesized natural products and analogues were carried out according to the published method.[5] All the tested compounds were dissolved in DMSO at a given concentration, and the in vitro activity against the plant pathogens was tested by virtue of the mycelium growth rate. The in vivo biotest was conducted on rape leaves (*Brassica napus*). All experiments were replicated three times, and the statistical analyses of the antifungal bioassay were performed using SPSS software version 20.0.

Synthesis of Pyridylthioquinone Meroterpenoid (Intermediate 6). *Synthesis of Homodrimanic Acid through Oxidative Degradation of (−)-Sclareol (1).* Homodrimanic acid (**2**) was synthesized in a one-pot reaction following the procedure of Alvarez-Manzaneda.[30] To a solution of (−)-sclareol (5.00 g, 16.23 mmol) in acetone (120 mL) and Ac_2O (30 mL) was added slowly $KMnO_4$ (16.00 g, 101.27 mmol) in portions in an ice bath. The reaction mixture was stirred at 0 °C and monitored by TLC until the reaction was complete. A solution of Na_2CO_3 (10 g) in H_2O (150 mL) was added to quench the reaction, and the mixture was stirred for 15 min. The resulting mixture was extracted with EtOAc (3 × 100 mL) and combined. The organic phases were washed sequentially with a saturated aqueous solution of $Na_2S_2O_3$ (2 × 50 mL) and brine (50 mL) and then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, affording homodrimanic acid (**2**) as a white solid (42% yield). Note: Sclareolide was isolated in 35% yield from this residue. ^{1}H NMR (400 MHz, $CDCl_3$) for homodrimanic acid, δ 0.79 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.03−1.12 (m, 2H), 1.17 (m, 1H), 1.26 (m, 1H), 1.36−1.47 (m, 2H), 1.51 (s, 3H, CH_3), 1.53 (m, 1H), 1.59 (m, 1H), 1.66−1.77 (m, 2H), 1.88 (s, 3H, CH_3), 2.21 (m, 1H), 2.34−2.44 (m, 2H), 2.77 (m, 1H), 3.50 (s, br, 1H).

Synthesis of Barton Ester of Homodrimanic Acid (3).[26,28] To a solution of homodrimanic acid (**2**) (143 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 2-mercaptopyridine *N*-oxide (60 mg, 0.47 mmol), followed by the addition of 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl) (115 mg, 0.6 mmol) and dimethylaminopyridine (12 mg, 0.10 mmol) in an ice bath. The mixture was stirred in the dark and allowed to warm to ambient temperature until it was complete as monitored by TLC. The mixture was diluted with CH_2Cl_2 (30 mL), and the combined organic phases were washed with water (3 × 15 mL) and brine (15 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude products. The resultant residue was purified by flash chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (4:1, v/v) as eluent to give the Barton ester **3** in 80% yield, which was used without any further purification for the next step.

Synthesis of the Pyridylthioquinone Meroterpenoid (6). To a solution of Barton ester **3** (122 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (5 mL) was added *p*-benzoquinone (94 mg, 0.87 mmol), and the reaction mixture was cooled at 0 °C followed by irradiation with a high-pressure mercury lamp (250 W). The reaction process was monitored by TLC until full conversion of compound **3** was observed. The concentrated mixture was subjected to chromatography on silica gel (200−300 mesh) with petroleum ether/EtOAc (5:1, v/v) to afford compound **6** in 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.04 (dd, J = 12.2, 2.0 Hz, 1H), 1.16−1.26 (m, 2H), 1.35−1.44 (m, 2H), 1.48 (m, 1H), 1.51−1.57 (m, 2H), 1.58−1.63 (m, 1H), 1.60 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.86 (ddd, J = 12.6, 3.1, 3.1 Hz, 1H), 2.21 (dd, J = 10.7, 2.9 Hz, 1H), 2.72 (ddd, J = 12.4, 3.3, 2.9 Hz, 1H), 2.87 (dd, J = 13.8, 2.9 Hz, 1H), 3.14 (dd, J = 13.8, 10.7 Hz, 1H), 6.82 (d, J = 1.3 Hz, 2H), 7.02 (dd, J = 4.92, 4.92 Hz, 1H), 7.34 (m, 1H), 7.55 (m 1H), 8.26 (dd, J = 4.9, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 18.7, 19.7, 20.10, 21.6, 23.3, 26.4, 33.4, 33.5, 39.4, 39.8, 40.0, 41.6, 55.7, 57.8, 87.6, 120.7, 122.8, 136.7, 137.1, 137.4, 139.2, 149.8, 155.1, 157.3, 169.5, 182.0, 185.5; ESIMS calcd for $C_{28}H_{36}NO_4S$ $[M + H]^+$ 482.24, found 482.22; $C_{28}H_{35}NNaO_4S$ $[M + Na]^+$ 504.22; found 504.19.

Synthesis of (+)-8-*O*-Acetylyahazunol (7). To a solution of pyridylthioquinone meroterpenoid **6** (192 mg, 0.40 mmol) in anhydrous EtOH was added Raney-nickel (1.40 g, excess). The reaction mixture was stirred for 5 min at ambient temperature for full conversion. The heterogeneous system was filtered, and the solvent was removed under reduced pressure to give the crude products, which were purified by flash column chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (4:1, v/v) to afford (+)-8-*O*-acetylyahazunol (**7**) in 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (td, J = 13.0, 3.7 Hz, 1H), 0.78 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.04 (dd, J = 14.3, 4.8 Hz, 1H), 1.25−1.35 (m, 4H), 1.51 (m, 1H), 1.60 (s, 3H, CH_3), 1.64−1.70 (m, 2H), 1.77 (m, 1H), 1.93 (s, 3H, CH_3), 2.03 (dd, J = 7.1, 2.9 Hz, 1H), 2.56 (dd, J = 15.4, 7.0 Hz, 1H), 2.74−2.82 (m, 2H), 5.71 (s, br, 1H, *OH*), 6.56 (s, br, 1H, OH), 6.58 (dd, J = 8.5, 3.1 Hz, 1H, *aromatic H*), 6.65 (d, J = 3.1 Hz, 1H, *aromatic H*), 6.67 (d, J = 8.5 Hz, 1H, *aromatic H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 18.2, 19. 9, 20.0, 21.5, 22.6,

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27.1, 33.0, 33.4, 38.9, 40.3, 40.3, 41.4, 55.5, 58.1, 90.1, 113.9, 116.3, 118.4, 129.5, 148.1, 148.8, 170.1; ESIMS calcd for $C_{23}H_{34}NaO_4$ $[M + Na]^+$ 397.24, found 397.29; $C_{21}H_{31}O_2$ $[M - HOAc + H]^+$ 315.23, found 315.31.

Synthesis of (+)-8-*O*-Acetylyahazunone (8). To a solution of (+)-8-*O*-acetylyahazunol (**7**) (374 mg, 1.00 mmol) in Et_2O (20 mL) was added MnO_2 (348 mg, 4.00 mmol). The reaction mixture was stirred at ambient temperature until the full conversion of **7** as monitored by TLC. The mixture was filtered through Celite and rinsed by Et_2O (2 × 10 mL). The filtrate was concentrated and subjected to flash column chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (5:1, v/v) to afford (+)-8-*O*-acetylyahazunone (**8**) in 50% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H, *CH*$_3$), 0.88 (s, 3H, *CH*$_3$), 0.91 (s, 3H, *CH*$_3$), 0.98−1.04 (m, 2H), 1.15 (td, *J* = 12.9, 3.9 Hz, 1H), 1.27 (dd, *J* = 12.5, 3.1 Hz, 1H), 1.37−1.45 (m, 2H), 1.55 (m, 1H), 1.57 (s, 3H, *CH*$_3$), 1.61 (m, 1H), 1.64−1.71 (m, 2H), 1.74 (s, 3H, *CH*$_3$), 1.94 (dd, *J* = 6.9, 4.2 Hz, 1H), 2.48 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.63 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.76 (m, 1H), 6.68 (d, *J* = 2.4 Hz, 1H, quinone *H*), 6.71 (d, *J* = 10.1, 2.4 Hz, 1H, quinone *H*), 6.78 (d, *J* = 10.1 Hz, 1H, quinone *H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 18. 5, 19.7, 20.2, 21.5, 22.9, 23.8, 33.2, 33.4, 39.2, 39.5, 39.9, 41.6, 55.7, 59.0, 87.3, 132.7, 136.1, 136.9, 152.0, 169.5, 187.3, 187.8; ESIMS calcd for $C_{23}H_{33}O_4$ $[M + H]^+$ 373.24, found 373.20; $C_{23}H_{32}NaO_4$ $[M + Na]^+$ 395.22; found 395.18.

Synthesis of (+)-Yahazunol (9). To a solution of (+)-8-*O*-acetylyahazunol (**7**) (375 mg, 1.00 mmol) in anhydrous tetrahydrofuran (THF) (10 mL) was added $LiAlH_4$ (40 mg, 1.00 mmol) at 0 °C. The reaction mixture was stirred at this temperature until the full conversion of (+)-8-*O*-acetylyahazunol (**7**) monitored by TLC. An aqueous solution of HCl (1 M, 5 mL) was added at 0 °C to quench the reaction, and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layers were collected and washed sequentially with 5% $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The resultant residue was purified by chromatography on silica gel (200−300 m) to afford (+)-yahazunol (**9**) in 93% yield: ^{1}H NMR (600 MHz, acetone-d_6) δ 0.72 (td, *J* = 13.2, 3.8 Hz, 1 H), 0.82 (s, 3 H, *CH*$_3$), 0.86 (s, 3 H, *CH*$_3$), 0.95 (m, 1 H), 0.97 (s, 3 H, *CH*$_3$), 1.10 (td, *J* = 13.4, 4.4 Hz, 1 H), 1.30 (s, 3H, *CH*$_3$), 1.31−1.38 (m, 3H), 1.55−1.65 (m, 4H), 1.83 (m, 1H), 1.92 (ddd, *J* = 12.7, 3.3, 3.3 Hz, 1H), 2.39 (dd, *J* = 15.0, 6.2 Hz, 1H, Ph-*CH*), 2.85 (dd, *J* = 15.0, 2.2 Hz, 1H, Ph-*CH*), 4.89 (s, br, *OH*), 6.49 (dd, *J* = 8.5, 2.9 Hz, 1H, *aromatic H*), 6.53 (d, *J* = 8.5 Hz, 1H, *aromatic H*), 6.63 (d, *J* = 2.9 Hz, 1H, *aromatic H*), 7.45 (s, br, 1H, *OH*), 8.76 (s, br, 1H, *OH*); ^{13}C NMR (150 MHz, acetone-d_6) δ 15.8, 19.0, 21.1, 21.8, 24.5, 27.9, 33.7, 33.7, 40.5, 41.3, 42.4, 44.4, 56.8, 62.2, 75.1, 114.2, 117.4, 118.8, 131.1, 149.6, 150.3; ESIMS calcd for $C_{21}H_{31}O_2$ $[M - H_2O + H]^+$ 315.23, found 315.47. The pale yellow solid was redissolved in EtOAc, and the crystals obtained from this solution were subjected to X-ray single-crystal diffraction analysis (CCDC: 1569963).

Synthesis of (+)-Yahazunone (10). A solution of (+)-yahazunol (**9**) (332 mg, 1.00 mmol) in anhydrous Et_2O (10 mL) was treated with MnO_2 (348 mg, 4.00 mmol) at 25 °C. The reaction mixture was stirred until full conversion of (+)-yahazunol (**9**). The heterogeneous system was filtered through Celite and rinsed with Et_2O (2 × 10 mL). The filtrate was concentrated and subjected to flash column chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (4:1, v/v) to afford (+)-yahazunone (**10**) as a yellow wax in 83% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H, *CH*$_3$), 0.87 (s, 3H, *CH*$_3$), 0.88 (s, 3H, *CH*$_3$), 0.93 (dd, *J* = 11.9, 2.3 Hz, 1H), 1.12 (td, *J* = 13.3, 4.3 Hz, 1H), 1.21 (s, 3H, *CH*$_3$), 1.26 (m, 1H), 1.45−1.31 (m, 2H), 1.61−1.53 (m, 3H), 1.72−1.62 (m, 2H), 1.81−1.73 (m, 1H), 1.89 (dt, *J* = 12.2 Hz, J_2 = 3.2 Hz, 1H), 2.48 (ddd, *J* = 15.2, 5.2, 1.3 Hz, 1H, Ph-*CH*), 2.63 (ddd, *J* = 15.2, 6.0, 1.5 Hz, 1H, Ph-*CH*), 6.6 (d, *J* = 1.4 Hz, 1H), 6.7 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.75 (d, *J* = 10.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 18.5, 20.4, 21.5, 23.7, 24.6, 33.3, 33.4, 39.4, 40.4, 41.6, 44.7, 56.1, 61.6, 73.9, 132.9, 136.2, 137.0, 152.6, 187.8, 188.1; ESIMS calcd for $C_{21}H_{29}O_2$ $[M - H_2O + H]^+$ 313.22, found 313.24; $C_{21}H_{30}NaO_3$ $[M + Na]^+$ 353.21, found 353.25.

Synthesis of (−)-Zonarone (11a) and (−)-Isozonarone (11b). To a stirred solution of (+)-yahazunone (**10**) (330 mg, 1.00 mmol) and Et_3N (417 μL, 3.00 mmol) in anhydrous CH_2Cl_2 (8 mL) was added a solution of $SOCl_2$ (106 μL, 1.50 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The reaction mixture was stirred for full conversion before it was quenched by the addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The resulting mixture was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (8:1, v/v) to afford (−)-zonarone (**11a**) and (−)-isozonarone (**11b**) in the ratio of 3.7:1 as a yellow solid, in 86% combined yield. Zonarone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3H, *CH*$_3$), 0.83 (s, 3H, *CH*$_3$), 0.90 (s, 3H, *CH*$_3$), 1.11−1.22 (m, 2H), 1.31−1.37 (m, 2H), 1.41 (m, 1H), 1.44 (m, 1H), 1.46 (m, 1H), 1.54 (m, 1H), 1.75 (m, 1H), 1.79 (m, 1H), 2.04 (m, 1H), 2.38 (m, 1H), 2.63−2.55 (m, 2H, quinone-*CH*$_2$), 4.33 (s, 1H, =*CH*$_2$), 4.78 (s, 1H, =*CH*$_2$), 6.47 (d, *J* = 2.1 Hz, 1H), 6.68 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.75 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.4, 21.7, 23.1, 24.2, 33.6 (2 × C), 37.9, 39.2, 39.9, 42.0, 54.1, 55.6, 108.0, 132.9, 136.0, 136.9, 147.2, 149.4, 187.7, 187.8. Selected signals for (−)-isozonarone (**11b**): ^{1}H NMR (400 MHz, CDCl3) δ 0.85 (s, 3H, *CH*$_3$), 0.87 (s, 3H, *CH*$_3$), 0.90 (s, 3H, *CH*$_3$), 5.43 (s, br, 1H, =*CH*−), 6.79 (d, *J* = 9.5 Hz, 1 H), 6.68 (d, *J* = 9.5 Hz, 1H, *H* in quinone ring). The other signals overlap with the (−)-zonarone signals): ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 21.9, 22.7, 23.7, 25.7, 33.0, 33.2, 36.8, 39.7, 42.1, 50.1, 52.9, 123.4, 132.7, 133.5, 136.1, 137.0, 151.5, 187.4, 187.6; ESIMS calcd for $C_{21}H_{29}O_2$ $[M + H]^+$ 313.22, found 313.32; $C_{21}H_{28}NaO_2$ $[M + Na]^+$ 335.20, found 335.29; $C_{42}H_{56}NaO_4$ $[2M + Na]^+$ 647.41, found 647.55.

Synthesis of (−)-Zonarol (12a) and (−)-Isozonarol (12b). To a solution of the mixture of (−)-zonarone (**11a**) and (−)-isozonarone (**11b**) (63 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added sodium dithionite (208 mg, 1.20 mmol). The resulting suspension was stirred for 24 h at 30 °C, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (6:1, v/v) to afford a mixture of (−)-zonarol (**12a**) and (−)-isozonarol (**12b**) as a white solid in 50% combined yield. (−)-Zonarol (**12a**) signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H, *CH*$_3$), 0.83 (s, 3H, *CH*$_3$), 0.89 (s, 3H, *CH*$_3$), 1.38−1.44 (m, 4H), 1.56−1.67 (m, 4H), 1.73−1.78 (m, 2H), 2.16 (dd, *J* = 5.5, 5.5 Hz, 1H), 2.40 (m, 1H), 2.70 (d, *J* = 6.3 Hz, 2H), 4.42 (s, br, 1H, *OH*), 4.54 (s, br, 1H, *OH*), 4.69 (d, *J* = 1.6 Hz, 1H, =*CH*$_2$), 4.81 (d, *J* = 1.6 Hz, 1H, =*CH*$_2$), 6.52 (d, *J* = 3.1 Hz, 1H), 6.59−6.61 (m, 2H, *H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 19.7, 21.9, 23.8, 24.6, 33.8 (2 × C), 38.3, 39.5, 40.4, 42.2, 55.7, 56.3, 107.7, 113.2, 116.1, 116.7, 130.2, 147.6, 148.9, 149.3. (−)-Isozonarol (**12b**) signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 6H, 2 × *CH*$_3$), 0.91 (s, 3H, *CH*$_3$), 1.12 (m, 1H), 1.32−1.36 (m, 3H), 1.34−1.40 (m, 2H), 1.47 (s, 3H, *CH*$_3$), 1.53 (m, 1H), 1.85−1.94 (m, 2H), 2.40 (m, 1H), 2.57−2.61 (m, 2H), 4.32 (s, br, 1H, *OH*), 4.40 (s, br, 1H, *OH*), 5.39 (s, br, 1H, =*CH*), 6.49 (d, *J* = 2.8 Hz, 1H, *aromatic H*), 6.59 (m, 1H, *aromatic H*), 6.74 (d, *J* = 2.8 Hz, 1H, *aromatic H*); ESIMS calcd for $C_{21}H_{30}KO_2$ $[M + K]^+$ 353.19, found 353.22.

Synthesis of (+)-Chromazonarol (13). To a solution of (+)-yahazunol (**9**) (332 mg, 1.00 mmol) in anhydrous CH_2Cl_2 (10 mL) was added TFA (75.00 μL, 1.00 mmol) at ambient temperature. The reaction mixture was stirred until full conversion as monitored by TLC. A saturated $NaHCO_3$ aqueous solution (15 mL) was added to quench the reaction. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with H_2O (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product. The resultant residue was purified by chromatography on silica gel (200−300 m) with petroleum ether/EtOAc (8:1, v/v) to yield (+)-chromazonarol (**13**) as a white solid in 94% yield: ^{1}H NMR

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(600 MHz, $CDCl_3$) δ 0.84 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.96 (dd, J = 12.4, 3.2 Hz, 1H), 1.02 (dd, J = 12.0, 2.1 Hz, 1H), 1.16 (m, 1H), 1.17 (s, 3H, CH_3), 1.33−1.50 (m, 3H), 1.61−1.70 (m, 4H), 1.75 (m, 1H), 2.04 (m, 1H), 2.55−2.57 (m, 2H, Ph-CH_2), 4.60 (s, br, 1H, *OH*), 6.54−6.58 (m, 2H, *aromatic H*), 6.62 (d, J = 8.4 Hz, 1H, *aromatic H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.8, 18.5, 19.7, 20.7, 21.6, 22.5, 33.2, 33.4, 36.8, 39.2, 41.1, 41.8, 52.0, 56.1, 76.7, 114.2, 115.8, 117.5, 123.3, 147.1, 148.5; ESIMS calcd for $C_{21}H_{31}O_2$ $[M + H]^+$ 315.23, found 315.26.

The reader is referred to the Supporting Information for the comparison of observed and reported data of (+)-yahazunol, (+)-yahazunone, (−)-zonarone, (−)-zonarol, and (+)-chromazonarol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00310.

X-ray crystallographic data (CIF)

Synthetic details, comparison of observed and reported data, antifungal data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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