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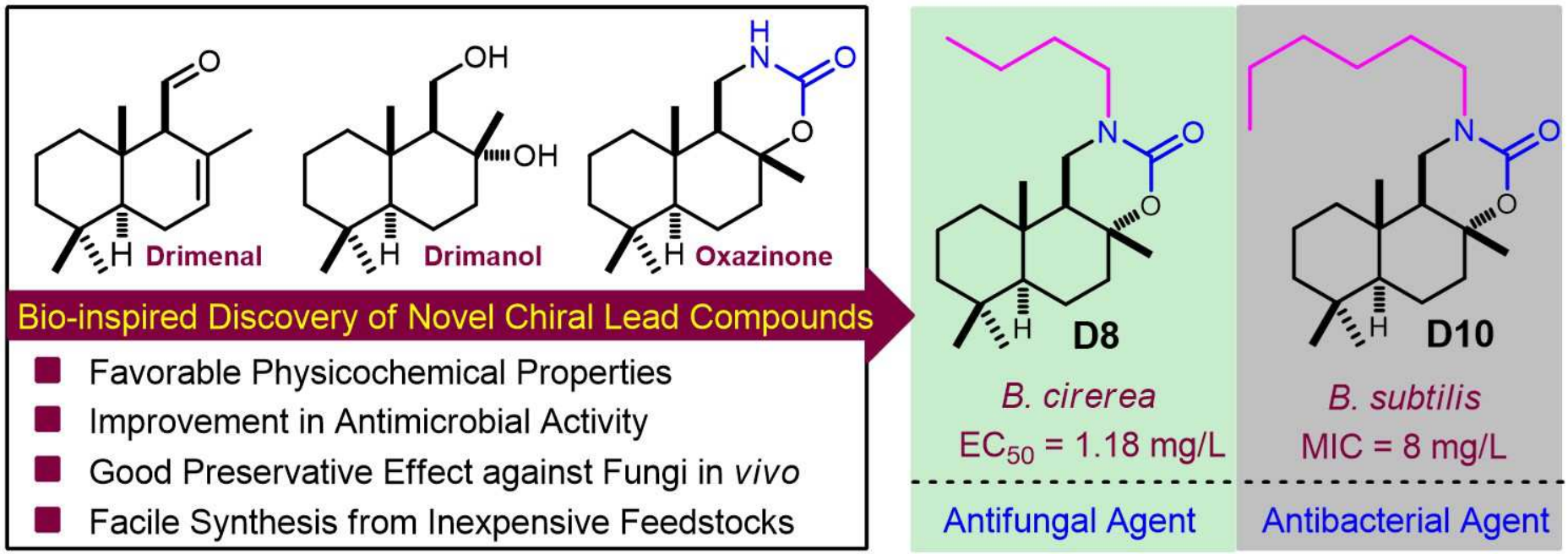
Graphical Abstract



Synthesis and Bio-inspired Optimization of Drimenal: Discovery of Chiral Drimane Fused Oxazinones as Promising Antifungal and Antibacterial Candidates

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Abstract: The synthesis of antifungal natural product drimenal was accomplished. Bio-inspired optimization protruded chiral 8-(*R*)-drimane fused oxazinone **D** as a lead, considering favorable physicochemical profiles for novel pesticides. The improved scalable synthesis of scaffold **D** was implemented by Hofmann rearrangment under mild conditions. Detailed structural optimization was discussed for both antifungal and antibacterial exploration. Substituted groups (SGs) with C_3~C_5 hydrocarbon chain are recommended for exploration of antifungal agents, while substituents with C_4~C_6 carbon length are preferred for antibacterial ingredients. The chiral drimane fused oxazinone **D8** was selected as a promising antifungal candidate against *Botrytis cirerea*, with an EC_{50} value of 1.18 mg/L, with the enhancement of up to >25 folds and >80 folds than the mother compound **D**, and acyclic counterpart **AB5**, respectively. The in *vivo* bioassay confirmed much better preservative effect of **D8** than that of Carbendazim. The chiral oxazinone variant **D10** possessed prominent antibacterial activity, with MIC values of 8 mg/L against both *Bacillus subtilis* and *Ralstonia solanacearum*, showing advantages over the positive control streptomycin sulfate.

Keywords: Chiral Pesticide, Lead Optimization, Drimane, Oxazinone, Structure-activity Relationship

1. Introduction

The ever increasing population coupled with changing dietary habits throughout the world, required continued improvements in food supplement from limited available farmland [1, 2]. With an evolving array of agrochemical tools, the agrochemical industry is a driving force in the green revolution to control a myriad of agricultural pests. It is desirable for the discovery of new agrochemicals with favorable environmental and toxicological profiles, which has been playing an undoubtedly important role in the management of resistance and shifting pest spectra and other agricultural practices. One of the most important issues and the biggest challenges is the discovery of novel structures with high potency for a specific target.

The combinatorial chemistry and high-throughput screening (HTS) generated hope for revolutionizing drug discovery. Structure-based drug design or biotational design emerged as powerful tools and have been attracting remarkable attention in both medicines and agrochemicals[3]. Beside the target-oriented tactics, the ligand-optimization is anastrophic but also powerful and easily operable wepeaon to address biological problems. Alongside the fruitful achievements in the discovery of a new drug[4] or pesticides[5] with the old ones as models, natural products are attracting starting points, not only in the novel scaffold but also can act as a probe for novel target [6, 7]. Unfortunately, many “hit” compounds were unsuccessfully converted to “lead” compounds, or unsuitable for further optimization due to the inherently unfavorable properties, i.e., size, permeability, and conformation. So we

envisage that simulation of the bioactively important natural products is a good choice for lead discovery, in which physicochemical profiles should be attached and compared as important metrics before structure optimization.

Drimane and related meroterpenoids attracted wide attention from synthetic chemists because of various bioactivities, ranging from medicinal importance to agrochemical interests[8, 9]. Our interest in drimane related natural products was triggered by the special structural properties with the enrichments in sp3 fraction, which is important for improving druggablity[10, 11]. Consistent with that of other bioactive terpenoids (e.g. artemisinin), the biologically important drimane also featured specific mono or multi-oxidation, or rigid conformation (fused ring or chirality) of its core structure[8], such as the antifungal natural products drimenal[12], polygodial, isotadeonal and marasmal B[13] (Fig.1). Our continuous efforts[14, 15] in the discovery of novel chiral fungicides candidates based on natural products encourage us to explore the drimane related natural agents, and the antifungal drimenal gave us an impetus. Herein, we would like to document the synthesis, bioactivity and bioinspired optimization of drimenal and drimenol, in which the chiral drimane fused oxazinones were discovered as promising antifungal and antibacterial candidates.

2. Results and discussion

2.1. Molecular Design and Chemical Synthesis

2.1.1 Synthesis of Drimenal and Drimenol

Degradation of abundant diterpenoids will be a good choice for the semi-synthesis of drimane related sesquiterpenoids. As shown in Fig. 2, the

commercially inexpensive (-)-sclareol was chosen as a starting material for the scalable preparation of (+)-sclareolide in good yield [16]. The 8-OH drimanol was synthesized in three steps using only one SiO_2 column chromatography according to the previous procedure in a moderate yield [17],[18], with the Baeyer-Villiger rearrangement as the key translation. The *p*-TsOH mediated one-step regioselective dehydration of the tertiary hydroxyl group provided a more facile access to drimenol than the previous Mitsunobu conditions (DEAD/PPh_3)[19], in view of both high yield and operational simplicity. It can also be achieved effectively through a 3-step approach reported by Hayakawa and Kigoshi [20]. Oxidation of drimenol with P_2O_5 afforded the drimenal in good yield, whose ^{1}HNMR and ^{13}CNMR spectra were identical to those previously reported [12].

2.1.2 Divergent synthesis of drimane mimics

As shown in Fig. 3, divergent synthesis was conducted for Drimenol and 8-hydroxyl Drimanol, including different ethers, esters, and carbamates. The previously founded bioactivity-guided mixture synthesis[14] was applied for the discovery of the promsing orientation of structural optimization. A number of halogenated hydrocarbons, acids, and amines were selected to get more precise insight into the effect of different substituents on bioactivity, and typical derivatives were listed in Fig. 3. Exposure of these alcohols to halogenated hydrocarbons in refluxing anhydrous THF with KOH as base furnished different ethers (**A**, **AB**). The alcohol esters of drimenol and 8-hydroxyl drimanol were prepared efficiently with different organic acids through Steglich-type reaction (**B**, **BB**). The carbamates (**C**, **CB**) were prepared easily from the condensation of alcohols and isocyanates with toluene as media. The 8-hydroxyl drimanol was further oxidized by Jone's reagent to produce the drimanic acid, from which the esters (**AC**) were achieved after the nucleophilic

attack of carboxylic anion to halogenated hydrocarbons.

2.1.3. Design and synthesis of rigid drimane fused dioxanone

The conformation restricted counterpart 8-(*R*)-dioxanone (**E**), was synthesized by trapping of 8-hydroxyl drimanol with triphosgene under -78 □ in 87% yield. The aza-bioisostere **D** was prepared from sclareolide, through hydrazinolysis followed by curtius rearrangement, and the 8-*epi* stereoisomer 8-(*S*)-Oxazinone (8-*epi* **D**) was constructed based on 8-*epi*-(+)-sclareolide, which can be prepared efficiently *via* the exposure of (+)-sclareolide to a mixture of sulfuric and formic acids [21]. Both 8-(*R*)-oxazinone and 8-(*S*)-oxazinone were confirmed by single crystal diffraction, with the CCDC numbers 1569963 and 1569964 respectively (Fig. 4).

The poor yield of chiral 8-(*R*)-oxazinone **D** from curtius rearrangement was due to the reverse reaction to the corresponding sclareolide and the formation of the 8-formyl drimanyl amine as a byproduct. Fortunately, the improvement in the synthesis of **D** was realized by switching the Curtius reaction to Hofmann rearrangement [22], in which the basic system of PIDA can translate the homodrimanyl amide to intra-carbamate in up to 92% yield under relatively mild condition (Fig. 5). The optimization of 8-(*R*)-oxazinone was initiated with the decoration of the “NH” in amide subunit, through nucleophilic substitution under basic conditions. Gratifyingly, the structure and stereochemistry of the oxazinone derivatives were further determined by acquiring single crystal X-ray structure of the **D12** (CCDC 1569965), other than the MASS, HNMR, and CNMR spectra.

2.2. Antifungal Activity and SAR Discussion

2.2.1. SAR of Drimenal, Drimenol, and Related Derivatives

As shown in Fig. 2, the antifungal activity of drimenal is more promising than that of its reduced counterpart drimenol, and we envisaged that the antifungal

bioactivity may be improved with the increment in the oxidative states of drimane scaffold, examplified by the aforementioned drimanes related natural products. The drimenal usually served as a starting material to establish many biologically important drimane quinones, while the instablitiy of drimenal and drivatives thereof made us explore the more stable and easily accessible precursors, i.e. Drimenol and 8-hydroxyl-drimanol, for structural optimization, biological evaluation, and SAR to get more promising agrochemical candidates.

The homodirmanyl amides were protruded as promising antifungal agents[14], showing similar antifungal spectrum to that of Drimenol and Drimenal. The frequently used substituted groups (SGs) from the commercially available source were decorated to the core structure of drimane, including saturated and unsaturated halogenated hydrocarbons, aicds, and isocyanate. After intitial bioactivity- guided mixed synthesis and antifungal assessment, all the compounds from 8-OH-Drimanol listed in Fig.3 were synthesized specifically and evaluated against *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, *Fusarium graminearum*, and *Botrytis cirerea* (supporting information). The derivative mixture of 8-OH-drimanol was more active than that of drimenol, which confirm the crucial role of the hydroxyl group on the antifungal effect (**AB** vs **A**, **BB** vs **B**, **CB** vs **C**). It is noteworthy that the etherification of drimenol did not show advantages either in stability and bioactivities. The hydrophobic and sterically bulky sbustituents were baleful for the inhibtition of all the tested plant pathogens. As shown in Table 1, all the compounds were prepared and EC_{50} values were tested specifically for derivatives of 8-hydroxyl drimanol, and substituted groups (SGs) were recommended to be shorter than 5-carbon-length.

The oxidation at 9-position (**AC**) is more beneficial for the improvement in the antifungal activity against both *Sclerotinia sclerotiorum* and *Botrytis cirerea*. The

formal NH insertion of **BB3** or amide insertion of **AB5** to get **CB2** led to blossom in antifungal bioactivity, which can be synthesized easily from the condensation of isocyanate and drimanol. Though both the esters of drimanic acid and carbamates of 8-hydroxyl drimanol showed a comparable antifungal effect against *Sclerotinia sclerotiorum* and *Botrytis cirerea*, utilization of 8-hydroxyl-drimanol as scaffold has advantages over both drimenol and drimanic acid in synthetic manipulation or/and antifungal potential.

2.2.2. Discovery of chiral drimane fused oxazinones as potential lead compounds

Flexible molecules may require more energy to adopt a needed binding conformation, reducing the biological potency. The rigidification or conformational restriction of ligands has attracted remarkable attention and been widely applied in both drug [23]and pesticide [24] design, which can minimize the entropic loss for the ligands in binding with pharmacological target through adopting a preferred conformation, which leads to enhanced potency and improved selectivity, and reduces the possibility of undesired metabolism.

Inspection of 8-OH-drimanol showed that it has potential in conformational restriction *via* the tether of the free teminal hydroxyl groups to reduce the number of free rotatable bonds (Fig. 4). Considering the Clog P is an important metric to distinguish fungicides from herbicides and insecticides, the calculated analysis of the aforementioned scaffolds was conducted before lead optimization, and the results rationalize our design, with the Clog P values of 2.974 and 2.834 for 8-(*R*) -oxazinone (scaffold **D**) and cyclic carbonate ester (scaffold **E**), respectively. The synthesized compounds **D**, 8-*epi*-**D** and **E** were evaluated against up to 11 kinds of plant pathogens (see supporting information), to find the valuable one and explore the effects of chirality, conformational restriction and substitution of “O” by “NH”. The

198 conformation constrained variations showed good activity against *R. solani*, *S.*
199 *sclerotiorum*, *F. graminearum* and *B. Cirerea*. The 8-(*R*)-Oxazinone (**D**) possessed
200 much better acitivtity than its diastereoisomer 8-(*S*)-Oxazinone against most of the
201 tested fungi, which is a little different from the case our previously reported about
202 homodrimanyl amides[14]. The importance of the introduction of "NH" was
203 confirmed by the dramatic decline in the activity when "NH" was replaced by
204 "O"(scaffold **D** vs **E**). With easy preparation, good activity, novel scaffold, favorable
205 physicochemical profiles and optimizable potential, the chiral drimane fused
206 oxazinone **D** can be chosen as a lead compound. The improved synthesis of **D** via
207 Hofmann rearrangement laid a solid foundation for scalability and optimization.

208 The antifungal activity was enhanced with the expansion of hydrocarbon chain
209 (**D1** ~ **D8**), while the reverse phenomenon was detected when the carbon chain longer
210 than the *n*-butyl group (**D9** and **D10**), the antifungal activity was almost lost when
211 *n*-dodecyl group was imported (**D11**), this may be due to the excessive increment in
212 the Clog P values. Substituted groups (SGs) with C_3 ~ C_5 hydrocarbon chain are
213 recommended for detailed exploration, and C_3 substituents were chosen as a model
214 (**D3** ~ **D6**). Sterically hindered isomer is unfavorable in view of reduced yield and
215 activities (**D3** vs **D4**), desaturation of **D3** didn't produce fruitful improvement either
216 (**D5** and **D6**). Interestingly, decoration of prenyl (**D7**), formally dimethylation of **D5**,
217 reinforced the activity by more than 2 and 3 folds against *Fusarium graminearum* and
218 *Botrytis cirerea*, respectively. Patulous allyl systems, including benzyl and substituted
219 benzyl groups, were also brought to the drimane fused oxazinone (**D12** ~ **D19**), and
220 the activities were strengthened with the simplest benzyl group. It is noteworthy that
221 the biological activities are very sensitive to the position and electronic properties of
222 substituted groups on the phenyl ring. Though the *para*-methyl candidate (**D14**) can

provide comparable results, the antifungal activities dropped sharply when it was switched to *meta*-position (**D13**) or replaced by the electron-withdrawing groups, including fluorine (**D15**) and chlorine (**D18**). Gratifyingly, elaborate tuning protrudes the *n*-butyl substituted variant **D8** as a promising antifungal candidate, possessing pronounced activities against *Sclerotinia sclerotiorum* and *Botrytis cirerea*, with EC_{50} values of 7.70 mg/L and 1.18 mg/L, respectively (Fig. 5, Table 2). It is worth noting that the activity against *Botrytis cirerea* was enhanced >25 folds, >10 folds, and >80 folds than mother compound **D**, acyclic counterparts **CB2** and **AB5**, respectively. With the widely used commercial fungicide Carbendazim as a positive control, the in *vivo* antifungal effect of the promising oxazinone **D8** was conducted against *Botrytis cinerea* on cucumber leaf. As shown in Fig. 6, compound **D8** showed much better preventative effect (＞ 4.5 fold) than that of Carbendazim, with preventative rate of up to 58% at 100 mg/L, verifying the original molecular design and the potential of drimane fused oxazinone as a lead for the discovery of novel agrichemicals.

Considering the importance of oxazolidinone in the antibiotic market [25], the synthesized drimane fused oxazinones, formally with an expanded oxazolidinone ring, were further explored for the antibacterial possibility against both Gram negative bacteria and Gram positive bacteria, including *Xanthomonas oryzae* (-), *Erwinia carotovora* (-), *Xanthomonas oryzae pv.oryzicola* (-), *Ralstonia solanacearum* (-), *Pseudomonas syringae pv. Lachrymans* (-), *Bacillus subtilis* (+), and *Clavibacter michiganensis subsp. Sepedonicus* (+). To our delight, most of the oxazinones demonstrated moderate to good antibacterial activities against agriculturally important *Bacillus subtilis* and *Ralstonia solanacearum*. There are 19 entries much more active than the positive control streptomycin sulfate. Similar SAR to that of the antifungal section was detected (Table 3 vs Table 2), substitution on the NH subunit is necessary

for the enhancement of antibacterial activity, while the preferred substituents were extended from C_3-C_5 to C_4-C_6 hydrocarbon chain. As can be seen in Table 3, the three tested bacteria were inhibited by **D7** and **D10** much easier than the positive control streptomycin sulfate. Noteworthily, the benzyl variant (**D16**) also showed much better activity against *Bacillus subtilis* and *Ralstonia solanacearum* than the positive control. The candidate **D10** was most potent and can inhibit efficiently *Bacillus subtilis*, *Xanthomonas oryzae pv.oryzicola* and *Ralstonia solanacearum*, with the MIC values of 8, 12.5 and 8 mg/L respectively (Fig.5, Table 3).

3. Conclusions

In summary, the synthesis and antifungal exploration of drimenol and drimenal were accomplished and followed by bioactivity-guided divergent optimization. Inspired by the bioactive natural drimane sesquiterpenoids and related quinones or hydroquinones, the 8-hydroxyl-drimanol was selected as a potent scaffold and further sublimated to chiral drimane fused oxazinones, considering the favorable physicochemical profiles before structural optimization. The chiral 8-(*R*)-drimane fused oxazinone **D** was protruded as an optimized lead, with good activity, novel chiral scaffold, favorable physicochemical profiles as well as optimizable potential. The improved scalable synthesis of this chiral scaffold was implemented by Hofmann rearrangment under mild conditions, which facilitated the bioactivity-guided optimization. Substituted groups (SGs) with C_3~C_5 hydrocarbon chain are recommended for the exploration of antifungal agents, while substituents with C_4~C_6 carbon length are preferred for antibacterial ingredients. Gratifyingly, the chiral 8-(*R*)-drimane fused oxazinone **D8** possessed prominent antifungal activity against *Botrytis cirerea*, with EC_{50} value of 1.18 mg/L, demonstrating the enhancement of up to > 25 folds, > 10 folds, and > 80 folds than mother compound **D**, acyclic

counterparts **CB2** and **AB5**, respectively. The in *vivo* bioassay demonstrated much better preventative effect of **D8** than that of Carbendazim. The chiral oxazinone variant **D10** was most potent in antibacterial screening, with MIC values of 8 mg/L against both *Bacillus subtilis* and *Ralstonia solanacearum*, showing advantages over the positive control streptomycin sulfate. Further exploration of those chiral alkaloids in solving biological problems and related mechanism is in progress and will be reported in due course.

4. Experimental section

4.1. Chemistry

4.1.1. Instruments, Chemicals and Related Materials.

All solvents and reagents were purchased from commercial sources (Energy or Meryer Chemicals etc.), they were analytically pure and used as received. 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 thin-layer chromatography (TLC) on silica gel GF_{254} with phosphomolybdic acid and ultraviolet (UV_{254}nm) detection. Yields of all the title compounds were not optimized. Melting points (m.p.) were recorded on Shenguang WRS-1B melting point apparatus and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were carried out utilizing a Bruker AV 400 or 500 spectrometers with $CDCl_3$ as solvent and tetramethylsilane as the internal standard. Electrospray ionization mass spectrometry (ESI-MS) data were obtained with Waters Xevo TQ-S Micro-Spectrometer. Elemental analyses were performed on a CHN-O-Rapid

instrument. FTIR data was collected on FTIR Research Spectrometers. The single crystal diffraction was carried out on Bruker SMART APEX CCD diffractometer. The fungi and bacteria were provided by the College of Plant Protection, Nanjing Agricultural University (Nanjing, China).

4.1.2. Synthesis of 8-hydroxyl drimanol

Synthesis of (+)-sclareolide was accomplished through the oxidative degradation of (-)-sclareol [16]. The 8-hydroxyl drimanol was synthesized in three steps according to the previous procedures reported by Kane [17] and George [18] in 54% yield, see supporting information for synthetic details.

4.1.3. Synthesis of Drimenol

To a solution of 8-hydroxyl drimanol (1.20 g, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL), *p*-TsOH·H_2O (0.95 g, 5.0 mmol, 1.0 equiv) was added in portions at 0 °C. The reaction mixture was stirred and allowed to warm to ambient temperature (15 ~ 17 °C), the reaction progress was monitored by TLC until the reaction was complete. The mixture was diluted with CH_2Cl_2 (30 mL), and quenched by the addition of the saturated $NaHCO_3$ aqueous solution (30 mL). The organic phase was washed sequentially with $NaHCO_3$ (30 mL × 2), H_2O (30 mL × 3) and brine (30 mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel by gradient elution with petroleum ether/EtOAc (v/v) = 10:0 to 10:2 to yield Drimenol as a white solid (0.64 g, 58 %). M.p.:70.7 °C. $[\alpha]_D^{28.9}$ = −25.27 (c 0.1, DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (d, J = 5.6 Hz, 1H, C=*CH*-CH_2), 3.85 (dd, J_1 = 11.30 Hz, J_2 = 3.25 Hz, 1H, *CH*$_2$OH), 3.73 (dd, J_1 =

11.30 Hz, J_2 = 4.90 Hz, 1H, *CH*$_2$OH), 1.94~2.02 (m, 2H, H in naphthane ring), 1.82~1.91 (m, 2H, H in naphthane ring), 1.78 (s, 3H, *CH*$_3$C=CH-CH$_2$), 1.57(m, 1H, H in naphthane ring), 1.41~1.47 (m, 2H, H in naphthane ring), 1.32 (s, br, 1H, OH), 1.17 (td, J_1 = 13.65 Hz, J_2 = 4.20 Hz, 2H, *H* in naphthane ring), 1.07 (td, J_1 = 13.65 Hz, J_2 = 3.90 Hz, 1H, *H* in naphthane ring), 0.89 (s, 3H, *CH*$_3$), 0.87 (s, 3H, *CH*$_3$), 0.86 (s, 3H, *CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.88 (*C*), 124.12 (*CH*), 60.93 (*CH*$_2$), 57.28 (*CH*), 49.89 (*CH*), 42.13 (*CH*$_2$), 39.89 (*CH*$_2$), 36.07 (*C*), 33.37 (*CH*$_3$), 32.92 (*C*), 23.58 (*CH*$_2$), 22.06 (*CH*$_3$), 21.95 (*CH*$_3$), 18.76 (*CH*$_2$), 14.94 (*CH*$_3$). Elemental anal. calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; Found: C, 81.11; H, 11.65; LC–MS (ESI$^+$) m/z: Calcd. for $C_{15}H_{27}O$ $[M+H]^+$: 223.21, Found: 223.21; $C_{15}H_{26}ONa$ $[M+Na]^+$: 245.19, Found: 245.34.

4.1.4. Synthesis of Drimenal

To a solution of Drimenol (0.444 g, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL), was added DMSO (1.0 mL, 14.08 mmol, 7.0 equiv) and P_2O_5 (3.0 g, 21.13 mmol, 10.5 equiv) successively at 0 °C. The reaction mixture was stirred at 15 ~ 17 °C for about 0.5 h, and cooled to 0 °C again followed by the addition of the second batch of NEt_3 (1.2 mL, 8.5 mmol, 4.25 equiv). It was stirred at 15~17 °C until the complete consumption of Drimenol, monitored by TLC. The mixture was quenched by the addition of cold saturated NH_4Cl aqueous solution (10 mL). The organic phase was separated and the aqueous phase was extracted by CH_2Cl_2 (10 mL × 2), the combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (200-300m) with PE/EtOAc = 5:1 as eluent to yield drimenal (0.405 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H, *CH*$_3$), 0.92 (s, 3H, *CH*$_3$), 1.07 (s, 3H, *CH*$_3$),

1.15 (dd, J_1 = 11.92 Hz, J_2 = 5.04 Hz, 1H), 1.22 (dd, J_1 = 13.48 Hz, J_2 = 4.04 Hz, 1H), 1.28 (td, J_1 = 12.96 Hz, J_2 = 3.64 Hz, 1H), 1.41~1.48 (m, 2H), 1.54 (m,1H), 1.62 (brs, 3H, *CH*$_3$), 1.66 (dq, J_1 = 12.80 Hz, J_2 = 3.20 Hz, 1H), 1.97 (m, 1H), 2.08 (m, 1H), 2.59 (s, 1H), 5.69 (m, 1H), 9.69 (d, J = 5.12 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.73 (*CH*$_3$), 18.28 (*CH*$_2$), 21.63 (*CH*$_3$), 22.08 (*CH*$_3$), 23.66 (*CH*$_2$), 33.03 (*C*), 33.31 (*CH*$_3$), 37.01 (*C*), 40.36 (*CH*$_2$), 41.99 (*CH*$_2$), 49.05 (*CH*), 67.58 (*CH*), 125.47 (*CH*), 127.78 (*C*), 206.72 (*C*). Elemental anal. calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; Found: C, 81.80; H, 10.91; LC-MS (ESI) m/z: Calcd. for $C_{15}H_{25}O$ $[M+H]^+$: 221.19, Found: 221.21; $C_{15}H_{24}ONa$ $[M+Na]^+$: 243.17, Found: 243.24.

See supporting information for synthetic procedure for ethers (*Series* **A** *and* **AB**), *esters* (*Series* **B** *and* **BB**) *and carbamates* (*Series* **C** *and* **CB**) *of Drimenol and 8-OH-Drimanol; and the synthesis of esters of 8-OH-Drimanic Acid* (*Series* **AC**).

4.1.5. Synthesis of drimane fused oxazinone (scaffolds D and 8-epi-D).

Curtius Rearrangement Approach. To a solution of (+)-sclareolide (2.50 g, 10.0 mmol, 1.0 equiv) in ethanol (20 mL) was added hydrazine hydrate (5 mL, 0.54 mmol, 1.0 equiv) dropwise with an ice-bath. The reaction mixture was then stirred at room temperature for about 60 min until the reaction was complete monitored by TLC. The solvent was removed under reduced pressure to give crude products. The residue was purified by flash chromatography on silica gel (200 ~ 300 m) (EtOAc to MeOH/EtOAc = 1:20, v/v) to give the 8-(*R*)-acylhydrazine intermediate as a white solid (2.62 g, yield 93%), R_f = 0.13 (MeOH/Ethyl Acetate = 1:10), M.p. 150.5-153.5 □. ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.79 (s, 6H, 2×*CH*$_3$), 0.87 (s, 3H, *CH*$_3$), 0.95~0.99 (m, 2H, *H* in naphthane ring), 1.14 (s, 3H, *CH*$_3$), 1.15 (td, J_1 = 13.48 Hz, J_2 = 4.08 Hz, 1H, *H* in naphthane ring), 1.21~1.62 (m, 8H, *H* in naphthane ring and *NH*$_2$), 1.68 (m, 1H, *H* in naphthane ring), 1.77 (dd, J_1 = 5.32 Hz, J_2 = 4.40 Hz, 1H, *H* in

naphthane ring), 1.93 (dt, J_1 = 12.48 Hz, J_2 = 3.28 Hz, 1H, *H* in naphthane ring), 2.14 (dd, J_1 = 15.36 Hz, J_2 = 4.40 Hz, 1H, CH_2-C=O), 2.37 (dd, J_1 = 15.36 Hz, J_2 = 5.32 Hz, 1H, CH_2-C=O), 7.47 (br, s, 1H, *NH*-C=O). LC–MS (ESI^+) m/z: Calcd. for $C_{16}H_{29}N_2O$ $[M\text{-}H_2O+H]^+$ 265.23, Found:265.34; $C_{16}H_{30}N_2O_2Na$ $[M+Na]^+$305.22, Found:305.32.

The 8-*epi*-acylhydrazine counterpart was prepared starting from 8-*epi*-sclareolide through similar manipulation in 92% yield.

To a solution of the synthesized 8-(*R*)-acylhydrazine (564 mg, 2.0 mmol, 1.0 equiv) in THF/H_2O (10 mL/ 10 mL) were added $NaNO_2$ (207 mg, 3.0 mmol, 1.5 equiv). The reaction was cooled to 0 ^oC with ice-bath, then 5.76 mL of 0.5 M aqueous solution of HCl was added, and the reaction mixture was stirred until the full conversion of acylhydrazine monitored by TLC. The reaction mixture was then extracted with DCM (20 mL × 3). The combined organic phase was washed with 5% $NaHCO_3$ (20 mL × 2), water (20 mL × 2) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude products. The resultant residues were purified by chromatography on silica gel (200 ~ 300m) with carefully gradient elution to give the 8-(*R*)-oxazinone **D** in 36 % yield. R_f = 0.58 (MeOH/Ethyl Acetate = 1:10), M.p. 188.2-189.3 □. ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.01~1.07 (m, 2H, *H* in naphthane ring), 1.18 (td, J_1 = 14.80 Hz, J_2 = 3.84 Hz, 1H, *H* in naphthane ring), 1.31 (m, 1H, *H* in naphthane ring), 1.39 (s, 3H, CH_3), 1.42-1.55 (m, 3H, *H* in naphthane ring), 1.60 (m, 1H, *H* in naphthane ring), 1.64-1.71 (m, 2H, *H* in naphthane ring), 1.76 (m, 1H), 2.02 (dt, J_1 = 12.64 Hz, J_2 = 3.16 Hz, 1H), 3.19 (m, 1H), 3.27 (m,1H), 6.28 (br, s, 1H, *NH*). Elemental anal. calcd for $C_{16}H_{27}$ NO_2: C, 72.41; H, 10.25; N, 5.28; Found: C, 72.36; H, 10.19; N, 5.33; LC–MS (ESI^+) m/z: Calcd. for $C_{16}H_{27}NO_2Na$

392 $[M+Na]^+$ 288.19, Found:288.35. The white solid was re-dissolved in CH_2Cl_2 to afford
393 colorless square crystal easily, which was confirmed by X-ray single crystal
394 diffraction (CCDC: 1569963).

395 The 8-(*S*)-oxazinone 8-*epi*-**D** was prepared accordingly in 23% yield. R_f = 0.58
396 (MeOH / Ethyl Acetate = 1:10), M.p. 248.6-249.3 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ
397 0.84 (s, 3H, *CH*$_3$), 0.89 (s, 3H, *CH*$_3$), 1.02 (s, 3H, *CH*$_3$), 1.14 (td, J_1 = 14.32 Hz, J_2 =
398 4.68 Hz, 1H, H in naphthane ring), 1.27 (m, 1H, *H* in naphthane ring), 1.38 (s, 3H,
399 *CH*$_3$), 1.39~1.70 (m, 8H, *H* in naphthane ring), 1.74 (m, 1H), 2.11 (dt, J_1 = 13.80 Hz,
400 J_2 = 2.64 Hz, 1H), 3.38 (dd, J_1 = 12.68 Hz, J_2 = 3.80 Hz, 1H), 3.48 (dd, J_1 = 12.68 Hz,
401 J_2 = 7.08 Hz, 1H), 5.78 (br, s, 1H, *NH*). Elemental anal. calcd for $C_{16}H_{27}NO_2$: C,
402 72.41; H, 10.25; N, 5.28; Found: C, 72.44; H, 10.15; N, 5.25; LC–MS (ESI^+) m/z:
403 Calcd. for $C_{16}H_{27}NO_2Na$ $[M+Na]^+$ 288.19, Found:288.32. This compound was also
404 confirmed by X-ray single crystal diffraction (CCDC: 1569964).

405 ***Hofmann Rearrangement Approach***. The (+)-sclareolide (1.0 g, 4.0 mmol, 1.0
406 equiv) was dissolved in 7 M ammonia in MeOH (4.0 mL, 28 mmol, 7.0 equiv),
407 followed by the addition of $NaOCH_3$ (0.216 g, 4.0 mmol, 1.0 equiv) at ambient
408 temperature, then the flask was immersed into the pre-heated oil bath at 60 □ and
409 stirred for 24 hours until the full conversion of sclareolide tracked by TLC. The
410 solvent was removed under reduced pressure to give crude products, which was
411 purified by flash chromatography on silica gel (200 ~ 300 m) (EtOAc to MeOH /
412 EtOAc = 1:20, as eluent, v/v) to give the 8-(*R*)-homodrimanyl amide intermediate as
413 white solid (0.94 g, yield 88%), R_f = 0.39 (MeOH/Ethyl Acetate = 1:10), M.p.
414 119.0-120.6 □. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 6H, 2 × *CH*$_3$), 0.87 (s, 3H,
415 *CH*$_3$), 0.97~1.03 (m, 2H, *H* in naphthane ring), 1.14 (td, J_1 = 14.24 Hz, J_2 = 4.12 Hz,
416 1H, *H* in naphthane ring), 1.15 (s, 3H, *CH*$_3$), 1.26 (m, 1H, *H* in naphthane ring),

1.35~1.70 (m, 6H, *H* in naphthane ring), 1.76~1.82 (m, 2H, *H* in naphthane ring), 1.93 (dt, J_1 = 12.48 Hz, J_2 = 3.24 Hz, 1H), 2.16 (dd, J_1 = 15.56 Hz, J_2 = 4.28 Hz, 1H), 2.43 (dd, J_1 = 15.56 Hz, J_2 = 5.08 Hz, 1H), 2.44 (br, s, 1H, *OH*), 5.49 (br, s, 1H, *NH*), 5.99(br, s, 1H, *NH*). LC–MS (ESI^+) m/z: Calcd. for $C_{16}H_{28}NO$ $[M\text{-}H_2O+H]^+$ 250.22, Found 250.31; Calcd. for $C_{16}H_{29}NNaO_2$ $[M+Na]^+$ 290.21, found 290.31; Calcd. for $C_{32}H_{58}N_2NaO_4$ $[2M+Na]^+$ 557.43, found 557.51.

To the synthesized 8-(*R*)-homodrimanyl amide (267 mg, 1.0 mmol, 1.0 equiv) in MeOH (10 mL) was added KOH (140 mg, 2.5 mmol, 2.5 equiv) at room temperature. The reaction was cooled to 0^oC, PIDA (354mg,1.1mol, 1.1equiv) was added in portions, and the reaction mixture was then stirred until the reaction was complete tracked by TLC. The volatile solvent was removed under reduced pressure and then extracted with DCM (20 mL × 3). The combined organic phase was washed with saturated aqueous solution of NH_4Cl (15 mL × 3), water (15 mL × 3) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude products, which were purified by flash chromatography on silica gel (200~300 m) to give the 8-(*R*)-oxazinone **D** as a white solid in 96% yield.

The improved synthesis of 8-*epi*-oxazinone (8-*epi*-**D**) was furnished accordingly in 91% yield.

4.1.6. **Synthesis of 8-(*R*)-dioxanone (Compound E) from 8-hydroxyl-Drimanol**

To a solution of 8-OH-Drimanol (240 mg, 1.0 mmol, 1.0 equiv) in DCM (10 mL) was added pyridine slowly (0.50 mL, 6.21 mmol, 6.21 equiv) at room temperature. The reaction was cooled to -78 ^oC, a solution of triphosgene (296 mg, 1.0 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise, then the mixture was allowed to warm gradually to room temperature and stirred for about 4 hours. The reaction was quenched by the addition of 0.5 M HCl (12 mL), the inorganic phase was extracted

with DCM (10 mL ×3). The combined organic phase was washed with water (15 mL × 3) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude products which were purified by flash chromatography on silica gel (200 ~ 300 m) with petroleum ether/EtOAc = 1:2 (V/V) as eluent to give 8-(*R*)- dioxanone **E** as white solid (231 mg, 87% yield). M.p.196.6-196.9 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H, *CH*$_3$), 0.90 (s, 3H, *CH*$_3$), 0.91 (s, 3H, *CH*$_3$), 1.04-1.39 (m, 5H, *H* in naphthane ring), 1.42-1.58 (m, 3H, *H* in naphthane ring), 1.49 (s, 3H, *CH*$_3$), 1.67 (td, J_1 = 13.20 Hz, J_2 = 4.40 Hz, 1H, *H* in naphthane ring), 1.81 (m, 1H, *H* in naphthane ring), 1.89 (m, 1H, *H* in naphthane ring), 2.05 (dt, J_1 = 12.68 Hz, J_2 = 3.48 Hz, 1H, *H* in naphthane ring), 4.33-4.43 (m, 2H, O*CH*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.52, 18.14, 19.52, 21.38, 21.72, 33.08, 33.30, 36.38, 39.01, 39.85, 41.53, 51.24, 55.85, 66.88, 82.15, 149.12. Elemental anal. calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84; Found: C, 72.24; H, 9.91; LC–MS (ESI$^+$) m/z: Calcd. for $C_{16}H_{26}NaO_3$ $[M+Na]^+$ 289.18, Found:289.24.

4.1.7. **General Procedure for the *N*-alkylation of Oxazinone.**

To a solution of 8-(*R*)-oxazinone **D** (265 mg, 1.0 mmol, 1.0equiv) in anhydrous THF (10 mL) was added NaH (60% dispersion in mineral oil, 0.080 g, 2.0 mmol, 2.0 equiv) at 0 ^{o}C. The reaction mixture was then stirred for about 30 min, then benzyl chloride (0.14 mL, 1.2 mmol, 1.2 equiv) was added and the mixture was refluxed until the full consumption of 8-(*R*)-oxazinone monitored by TLC. The reaction was then cooled to room temperature and quenched by careful addition of saturated NH_4Cl aqueous solution (adjusted pH ~7). The volatile solvent was removed under reduced pressure and then extracted with EtOAc (20 mL ×3). The combined organic phase was washed with water (20 mL ×3) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude products which were

purified by flash chromatography on silica gel (200 ~ 300m) (petroleum ether/EtOAc = 2:1, v/v) to give compound **D12** as a colorless square crystal (298 mg, 84% yield). R_f = 0.84 (Petroleum/Ethyl Acetate = 1:1), M.p. 138.6-139.4 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 3H, *CH_3*), 0.80 (s, 3H, *CH_3*), 0.93~1.02 (m, 2H, *H* in naphthane ring), 1.14 (td, J_1 = 14.16 Hz, J_2 = 4.56 Hz, 1H, *H* in naphthane ring), 1.28 (m, 1H, *H* in naphthane ring), 1.33 (s, 3H, *CH_3*), 1.35-1.44 (m, 3H, *H* in naphthane ring), 1.53 (m, 1H, *H* in naphthane ring), 1.65 (td, J_1 = 13.68 Hz, J_2 = 4.44 Hz, 1H, *H* in naphthane ring), 1.71-1.78 (m, 2H, *H* in naphthane ring), 2.02 (dt, J_1 = 12.72 Hz, J_2 = 3.20 Hz, 1H, *H* in naphthane ring), 2.97-3.09 (m, 2H, N*CH_2*CH), 4.48 (dd, *J* = 14.88 Hz, 1H, *CH_2*Ph), 4.66 (dd, *J* = 14.88 Hz, 1H, *CH_2*Ph), 7.22-7.36(m, 5H, *aromatic H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.20 (*CH_3*), 18.22 (*CH_2*), 19.45 (*CH_2*), 21.41 (*CH_3*), 21.45 (*CH_3*), 33.06 (*C*), 33.33 (*CH_3*), 36.27 (*C*), 39.06 (*CH_2*), 40.08 (*CH_2*), 41.59 (*CH_2*), 42.45 (*CH_2*), 51.73 (*CH*), 52.73 (*CH_2*), 55.74 (*CH*), 80.02 (*C*), 127.56 (*CH*), 127.87 (2 × *CH*), 128.69 (2 × *CH*), 136.89 (*C*), 153.82 (*C*). Elemental anal. calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94; Found: C, 77.79; H, 9.51; N, 3.86; LC–MS (ESI^+) m/z: Calcd. for $C_{23}H_{34}NO_2$ $[M+H]^+$ 356.26, Found 356.33; $C_{23}H_{33}NO_2Na$ $[M+Na]^+$ 378.24, Found: 378.31. The compound **D12** was confirmed by X-ray single crystal diffraction (CCDC: 1569965).

All the derivatives in Table 2 were synthesized through similar manipulation.

4.2. Bioassay

4.2.1. General Procedure for Antifungal Bioassay

The antifungal activity of the target compounds was tested in vitro against the eleven plant pathogenic fungi using the mycelium growth rate test, which we used previously[14]. The in vivo biological assay against *Botrytis cinerea* of the **D8** and the positive control (carbendazim) was carried out on the cucumber leaf accordingly. See

supporting information for details.

4.2.2. General Procedure for Antibacterial Bioassay

Antibacterial activities of the target compounds were tested in *vitro* against the seven phytopathogenic bacteria (*Xanthomonas oryzae pv. oryzae*, *Bacillus subtilis*, *Erwinia carotovora*, *Xanthomonas oryzae pv. Oryzicola*, *Ralstonia solanacearum*, *Pseudomonas syringae pv. lachrymans* and *Clavibacter michiganensis subsp. sepedonicus*) using the filter paper dispersion method (K-B method) for initial screening. All the tested compounds were dissolved in DMSO at a concentration of 10 mg/L. Round filter papers with the diameter of 5mm were put on the plating medium containing 108 CFU/mL of the indicator strains, then 2 μL of the stock solution (10mg/L) was added to each filter paper, with sterile water as the blank control. The plating medium was cultured at 28 □ for 16-24 h. Then diameter (mm) of inhibition zone was detected. The average value was calculated to evaluate the antibacterial effects with three repetitions.

The agar diffusion dilution method (ADM)[26] was further applied to confirm the minimum inhibitory concentration (MIC) of the target compounds. Stock solution was diluted to 100, 50, 25, 12.5, 6.25, 3.125, 1.5625 μg/mL or 128, 64, 32, 16, 8, 4μg/mL according to the same ADM adopted to assess MIC. Subsequently, 2 μL of the nutrient broth containing 108 CFU/mL of the indicator strains were inoculated to all plates. Plates were then cultured at 28 □ for 16~24 h. MIC was defined as the lowest concentration that did not result in any visible growth of the microorganism in comparison with the growth in the control plate; the presence of one or two colonies was not taken into account for the final assessment of MIC. Three bacterial strains were chosen for the determination of MICs (μg/mL), which were listed in Table 3. The above experiments were repeated for three times and streptomycin sulfate was

chosen as positive control simultaneously.

The statistical analyses of Antifungal Bioassay and Antibacterial Bioassay were performed by SPSS software version 20.0.

Author Contributions

S. Li conceived and designed this work, D. Li performed the chemical synthesis and biological experiments, S. Zhang helped to perform the derivative synthesis and biological test. D. Li, S. Zhang, Z. Song and W. Li carried out NMR and MASS detection and elemental analysis. F. Zhu and J. Zhang conducted the FTIR test. D. Li and S. Li analyzed the data. S. Li wrote the paper.

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Appendix A. Supplementary data

List of synthesized compounds, antifungal, and antibacterial data, selected antifungal pictures, NMR spectra and X-ray spectra are available.

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Figures

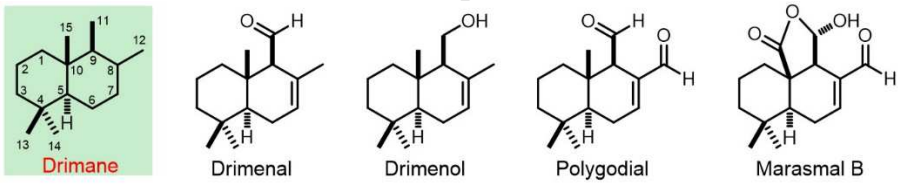
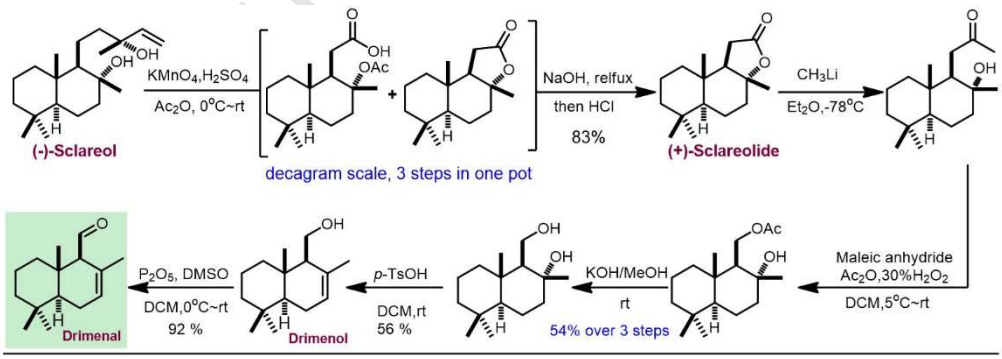


Fig.1. Drimane and typical bioactive natural products with specific oxidation and chirality



Bioactivity (50 mg/L)	*R. S.*	*S. S.*	*F.G.*	*B. C.*	*G. G.*	*F. F.*	*F. S.*	*P. C.*	*C. L.*
Drimenol	43.98	40.12	30.37	55.55	17.19	41.66	21.40	42.03	15.57
Drimenal	62.26	61.37	35.52	65.08	24.47	34.88	23.49	45.57	20.79

Note: All values are means of three replicates. R.S.:*Rhizoctonia solani*; S.S.:*Sclerotinia scleotiorum*; F.G.:*Fusarium graminearum*; B.C.: *Botrytis cinerea*; G.G.: *Gaeumanomyces graminis*; F.F.: *Fusarium fujikuroi*; F.S.: *Fusarium sulphureum*; P.C.: *Phytophthora capsici*; C.L.: *Colletotrichum lagenarium*.

Fig.2. Synthesis and antifungal activity of Drimenol and Drimenal

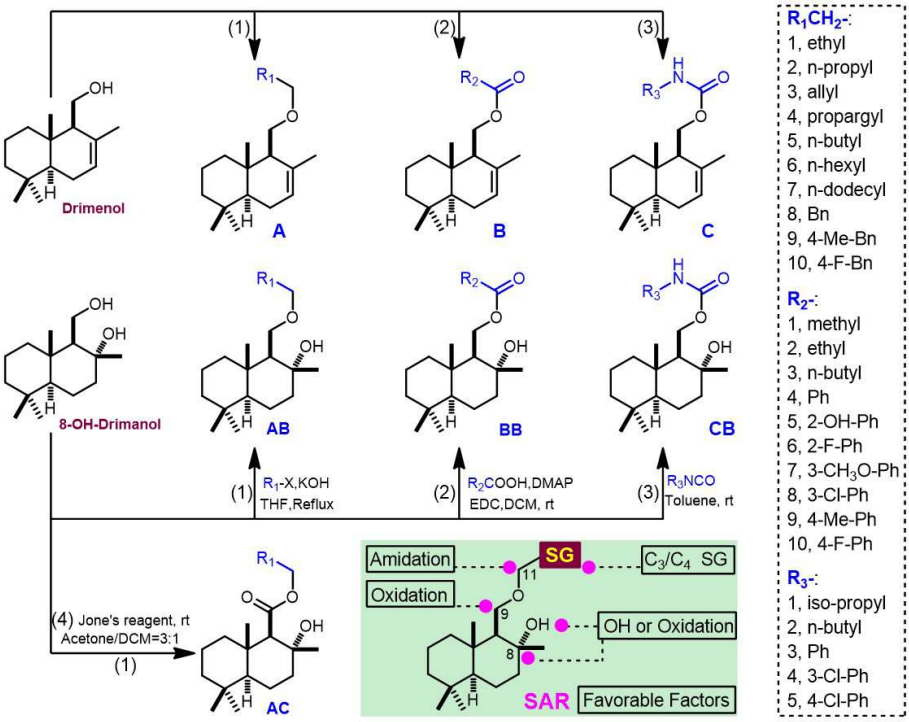
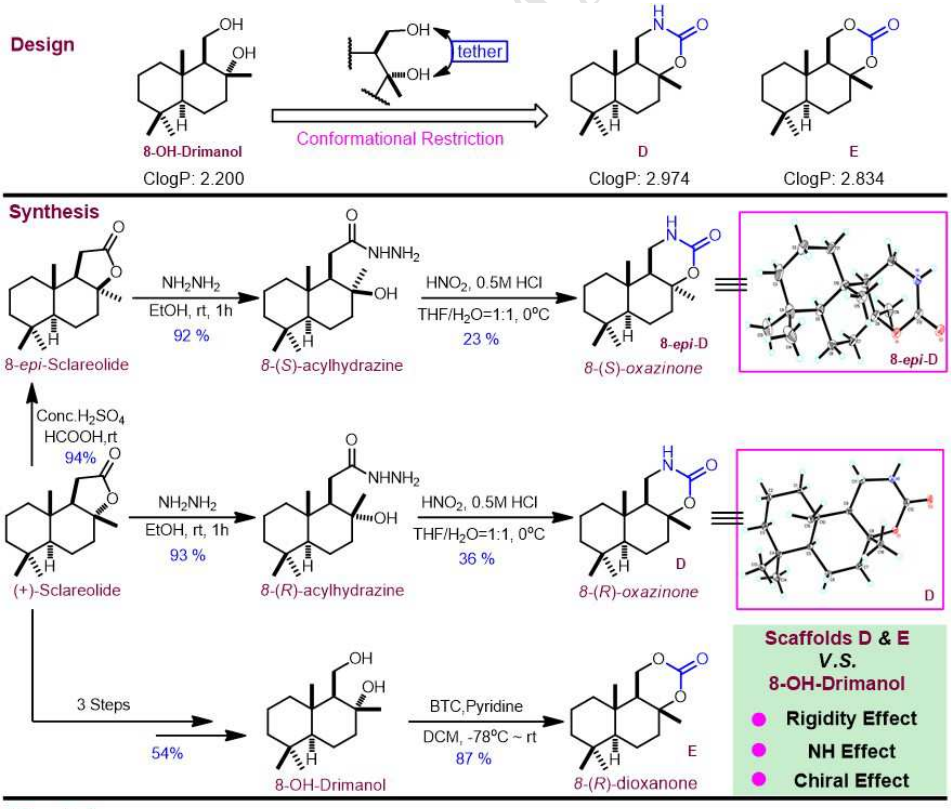


Fig.3. Diverse Synthesis and SAR of Drimenol and 8-OH-Drimanol



Bioactivity (100 mg/L)	*R. solani*	*S. sclerotiorum*	*F. graminearum*	*B. cinerea*	*F. fujikuroi*	*A. solani*
D	73.01	80.57	70.37	74.96	68.62	64.16
8-*epi*-D	54.27	46.31	58.67	79.89	46.67	52.20
E	62.87	41.18	9.20	38.32	20.29	20.23

Fig.4. Design, synthesis and antifungal activity of rigid drimanol analogs

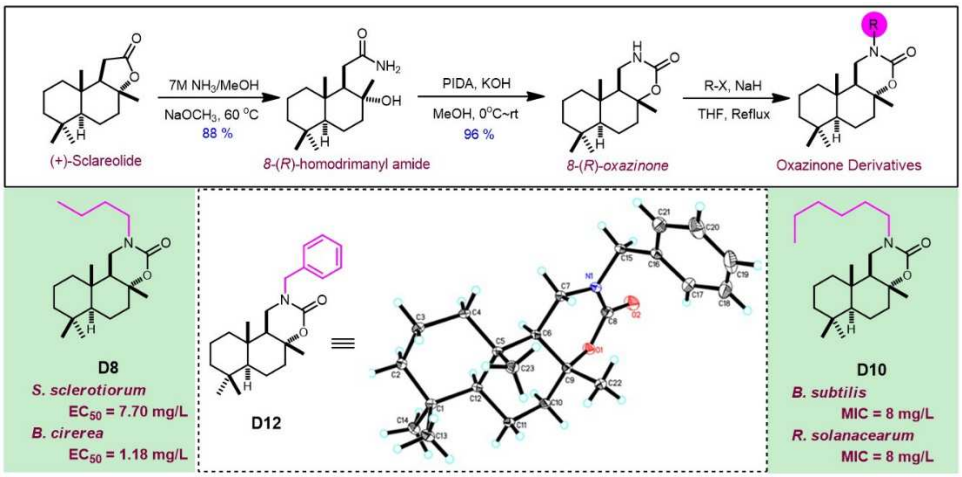


Fig.5. Improved synthesis and optimization of chiral drimane fused oxazinones

Compound (100mg/L)	Preservative Rate (%)
CK	-
D8	57.97
Carbendazim	12.08

Fig.6. In vivo antifungal activity of **D8** against *Botrytis cinerea*

Tables

Table 1. EC_{50} values of the 8-OH-drimenol derivitives *in vitro* (unit: μg/mL)

Compd.	R	*R. solani*	*S. sclerotiorum*	*F. graminearum*	*B. cirerea*
	R1=				
AB1	CH_3	41.06±0.56	74.86±0.04	46.22±1.10	60.80±0.16
AB2	CH_2CH_3	33.69±0.62	33.69±0.62	38.14±0.36	22.54±0.14
AB3	$CH=CH_2$	41.13±0.26	23.77±0.36	66.52±0.22	40.20±0.21
AB4	CH≡CH	20.10±0.20	**18.91±0.06**	25.58±0.37	23.94±0.26
AB5	$(CH_2)_2CH_3$	49.87±0.18	65.98±0.68	>100	>100
AB7	$(CH_2)_4CH_3$	>100	>100	>100	>100
AB8	Ph	>100	>100	>100	>100
AB9	4-CH_3Ph	>100	>100	>100	>100
AB10	4-FPh	>100	>100	>100	>100
AC1	CH_3	>100	68.69±0.03	46.24±0.14	68.69±0.03
AC2	CH_2CH_3	45.35±0.10	20.07±0.08	43.12±0.12	20.07±0.08
AC3	$CH=CH_2$	32.09±0.09	**16.65±0.18**	41.43±0.19	**16.65±0.18**
AC4	CH≡CH	27.66±0.14	**18.4±0.07**	31.8±0.22	**12.76±0.12**
AC5	$(CH_2)_2CH_3$	43.10±0.12	**12.74±0.24**	42.87±0.13	**13.04±0.13**
AC7	$(CH_2)_4CH_3$	>100	>100	>100	>100
AC8	Ph	>100	>100	>100	>100
	R2=				
BB1	CH_3	66.82±1.84	>100	64.86±0.12	61.40±0.05

BB2	CH_2CH_3	77.15±0.13	64.42±0.03	>100	46.97±0.08
BB3	$(CH_2)_3CH_3$	61.20±0.56	59.63±0.05	>100	21.72±0.14
BB4	Ph	>100	>100	>100	>100
BB9	4-CH_3Ph	>100	>100	>100	>100
BB10	4-FPh	>100	>100	>100	50.83±0.38
	R_3=				
CB1	$(CH_3)_2CH$	43.51±0.25	>100	>100	**11.39±0.38**
CB2	$(CH_2)_3CH_3$	>100	**13.90±0.30**	>100	**12.62±0.17**
CB3	Ph	53.09±1.42	>100	>100	59.71±0.96

Table 2 EC_{50} values of the chiral drimane fused oxazinones *in vitro* (unit: μg/mL)

Compd.	*R*	*R. solani*	*S. sclerotiorum*	*F. graminearum*	*B. cirerea*
D	H	19.25±0.58	35.32±0.12	32.00±0.23	33.23±0.03
D1	-CH_3	20.05±0.18	39.88±0.04	73.62±0.04	35.54±0.21
D2	-CH_2CH_3	60.86±0.05	26.04±0.06	56.12±0.04	34.56±0.08
D3	-$CH_2CH_2CH_3$	13.41±0.11	12.49±0.09	38.31±0.06	23.26±0.16
D4	-$CH(CH_3)_2$	25.66±0.21	42.98±0.03	33.31±0.21	19.30±0.12
D5	-$CH_2C{=}CH_2$	35.44±0.10	19.52±0.12	40.99±0.20	33.11±0.04
D6	-$CH_2C{\equiv}CH$	27.42±0.22	13.91±0.07	29.18±0.04	20.72±0.16
D7	-$CH_2CH{=}C(CH_3)_2$	20.45±0.32	35.97±0.04	16.12±0.12	**9.14±0.37**
D8	-$(CH_2)_3CH_3$	11.40±0.39	**7.70±0.15**	11.91±0.12	**1.18±0.70**
D9	-$(CH_2)_4CH_3$	22.05±0.13	**9.08±0.33**	26.93±0.28	**9.37±0.26**
D10	-$(CH_2)_5CH_3$	31.83±0.34	26.28±0.38	26.99±0.39	**5.71±0.56**
D11	-$(CH_2)_{11}CH_3$	>100	>100	>100	>100
D12	Bn-	15.28±0.15	48.16±0.05	13.36±0.36	11.37±0.22
D13	3-CH_3Bn-	>100	>100	>100	>100
D14	4- CH_3Bn-	11.71±0.61	43.98±0.51	19.99±0.48	10.17±0.33
D15	4-FBn-	>100	>100	>100	>100
D16	2-ClBn-	31.43±0.83	>100	67.55±0.40	>100
D17	3-ClBn-	>100	>100	>100	>100
D18	4-ClBn-	14.20±0.26	>100	>100	>100
D19	3,5-FBn-	>100	>100	>100	>100

Note: See supporting information for EC_{90} values.

Table 3 Antibacterial activities (MIC, mg/L) of the chiral drimane fused oxazinones

Compd.	*R*	*Bacillus subtilis*(+)	*Xanthomonas oryzae pv.oryzicola* (-)	*Ralstonia solanacearum* (-)
D	H	100 (0.377)	100 (0.377)	100 (0.377)
D1	$-CH_3$	＞100 (＞0.358)	＞100 (＞0.358)	100 (0.358)
D2	$-CH_2CH_3$	＞100 (＞0.341)	＞100 (＞0.341)	100 (0.341)
D3	$-CH_2CH_2CH_3$	25 (0.081)	25 (0.081)	25 (0.081)
D4	$-CH(CH_3)_2$	25 (0.081)	25 (0.081)	25 (0.081)
D5	$-CH_2C=CH_2$	50 (0.164)	50 (0.164)	50 (0.164)
D6	$-CH_2C\equiv CH$	＞100 (＞0.330)	＞100 (＞0.330)	100 (0.330)
D7	$-CH_2CH=C(CH_3)_2$	**8 (0.024)**	25 (0.075)	**8 (0.024)**
D8	$-(CH_2)_3CH_3$	**12.5 (0.039)**	**12.5 (0.039)**	**12.5 (0.039)**
D9	$-(CH_2)_4CH_3$	25 (0.074)	25 (0.074)	25 (0.074)
D10	$-(CH_2)_5CH_3$	**8 (0.023)**	**12.5 (0.036)**	**8 (0.023)**
D11	$-(CH_2)_{11}CH_3$	＞100 (＞0.230)	＞100 (＞0.230)	＞100 (＞0.230)
D12	Bn-	**12.5 (0.035)**	100 (0.281)	**8 (0.022)**
D13	3-CH_3Bn-	＞100 (＞0.271)	＞100 (＞0.271)	100 (0.271)
D14	4- CH_3Bn-	100 (0.271)	＞100 (＞0.271)	100 (0.271)
D15	4-FBn-	＞100 (＞0.268)	＞100 (＞0.268)	＞100 (＞0.268)
D16	2-ClBn-	**12.5 (0.032)**	25 (0.064)	25 (0.064)
D17	3-ClBn-	＞100 (＞0.256)	＞100 (＞0.256)	＞100 (＞0.256)
D18	4-ClBn-	100 (0.256)	100 (0.256)	100 (0.256)
D19	3,5-2FBn-	100 (0.255)	＞100 (＞0.255)	＞100 (＞0.255)
	streptomycin sulfate	25 **(0.017)**	100 (0.069)	50 **(0.034)**

Note: Data in parentheses was presented in molar concentration (mmol/L); The molecular weight (MW) of streptomycin sulfate is 1457.38, and the **MICs of streptomycin monomer are 0.034, 0.138** and **0.068 mmol/L** against the listed three bacteria respectively.

Highlights

Synthesis and bioassay of natural products drimenal and drimenol was accomplished from sclareol.

Bio-inspired optimization protruded 8-(*R*)-drimane fused oxazinone **D** as a lead for novel agrochemicals.

Practical synthesis and divergent optimization of scaffold **D** were implemented.

Both antifungal and antibacterial candidates with prominent activities were achieved.