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Communication

Divergent synthesis of four isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid, esters and evaluation for the antifungal activity

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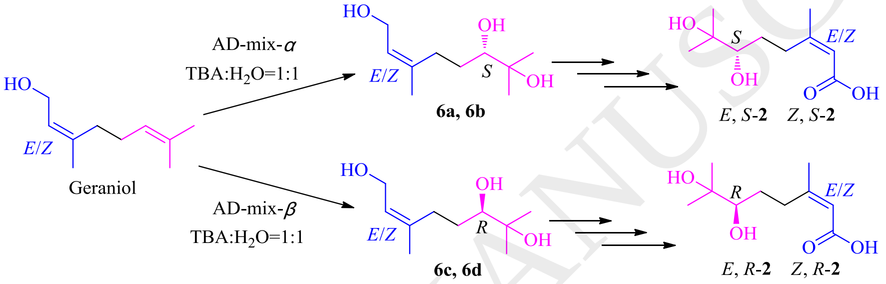
GRAPHICAL ABSTARCT



The four isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid **2** and esters **4** were synthesized and their antifungal activities were evaluated.

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ABSTRACT

The four isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid **2** were synthesized *via* the selective direct Sharpless asymmetry dihydroxylation of geraniol as the key step in 35.0%-48.0% overall yields with 91.9%-97.7% *ee* values for esters **4** and 31.3%-36.4% overall yields with 90.3-97.5% *ee* values for acids **2** using *cis*- and *trans*-geraniol as raw materials. Their structures were characterized by ^{1}H, ^{13}C NMR and HR-ESI-MS data. The *in vivo* bioassay results showed that the chiral acid (*Z*, *S*)-**2** was a good lead compound with 80%-100% inhibitory rates against *P. cubensis*, *E. graminis*, *P. sorghi* and *C. gloeosporioides* at the concentration of 400 μg/mL.

(6*R*)-3,7-Dimethyl-7-hydroxy-2-octen-6-olide (*R*-**1**) (Fig. 1), which has an unique seven-membered lactone, and (2*Z*, 6*R*)-6,7-dihydroxy-3,7-dimethyloct-2-enoic acid (*Z*, *R*-**2**) (Fig. 2) were first isolated from the honey bee fungal entomopathogen *Ascosphaera apis*, as well as the fruit of plant *Litsea cubeba* in Tibet, and they exhibited good antifungal and antioxidant activities [1,2]. This type of seven-membered lactone with *α*-hydroxy side chain was seldom found in nature, and the synthesis of which is unusual in literatures. 6,7-Dihydroxy-3,7-dimethyloct-2-enoic acid has been reported to be used in the treatment of skin lesion, however the olefin configuration, the absolute configuration of chiral center and its source were unknown [3]. 6,7-Dihydroxy-3,7-dimethyloct-2-enoic acid with the unknown olefin configuration, and absolute configuration of chiral center with very small optical rotation was also isolated from the root of *Litsea cubeba* and *Amomum tsao-ko* [4,5]. In the previous paper, the racemic 3,7-dimethyl-7-hydroxy-2-octen-6-olide (**1**), benzo analog 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide (**3**) and (*E*)-6,7-dihydroxy-3,7-dimethyl-oct-2-enoic acid (*E*-

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2) (Fig. 1) were all synthesized *via* the epoxidation-lactonization approaches of olefin acid [6-8]. The (6*R*) and (6*S*) isomers (*R*-**1** and *S*-**1**) were also synthesized with high *ee* values *via* Sharpless asymmetry dihydroxylation as the key steps due to its ability of construction chiral alcohol [9-15]. In order to compare the antifungal activity differences against phytopatho-gens and get insights into the relationship of the structures and antifungal activities between the seven-membered lactones, ring-opening olefin acids and olefin acid esters, the four stereoisomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid (*Z*, *R*-**2,** *Z*, *S*-**2**, *E*, *R*-**2**, *E*, *S*-**2**) and their methyl ester **4** (Fig. 2) were synthesized, and the in *vivo* antifungal activities were assayed in this paper.

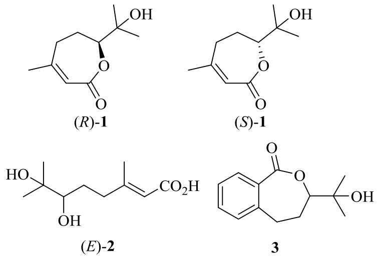


Fig. 1. The structures of seven-membered lactones and relating acid.

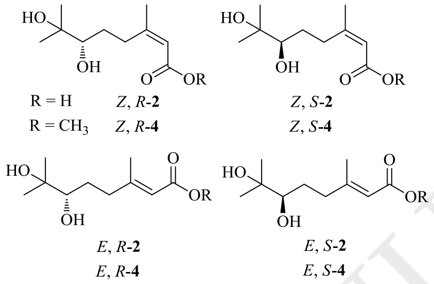
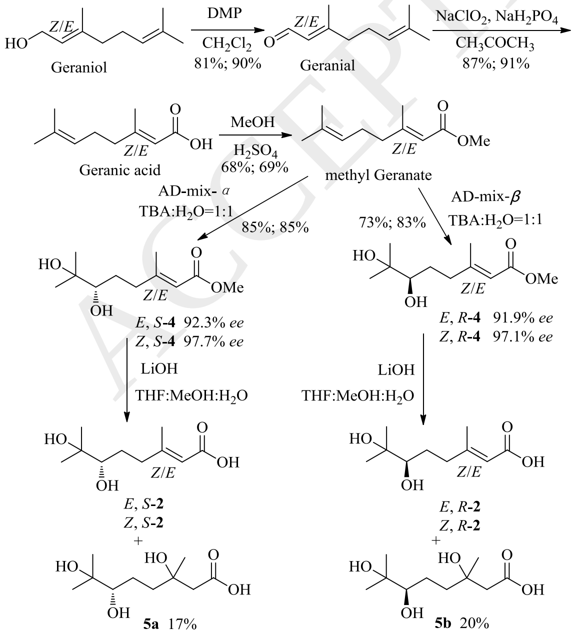


Fig. 2. The isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid and their esters.

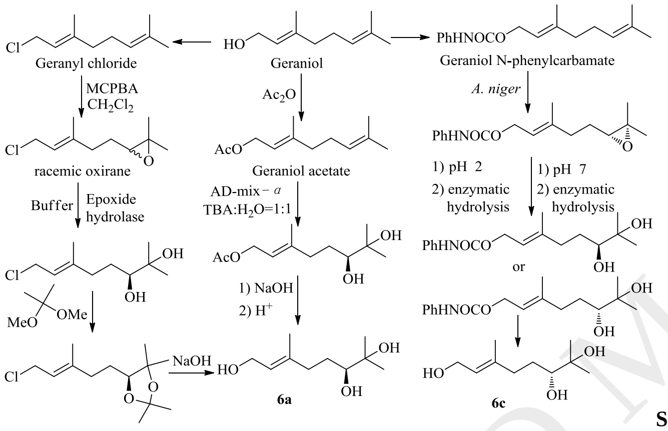
The synthetic strategy (Scheme 1) was initially investigated according to the procedures in the previous report [9]. First, *cis*- /*trans*-geraniols were oxidized to *cis*-/*trans*-geranials by Dess-Martin oxidant reagent (DMP). Then *cis*-/*trans*-geranials were further oxidized to *cis*-/*trans*-geranic acids with $NaClO_2$ [6]. Because the acids could not react with the AD-mix-*α*/ AD-mix-*β* directly, so the esters were prepared *via* the acids and methanol in the presence of concentrated H_2SO_4 at ambient temperature. Then the Sharpless asymmetry dihydroxylation of the esters were conducted with AD-mix-*α* and AD-mix-*β* to successfully give the chiral vicinal diol esters **4** (Fig. S1-8 and S65-70 in Supporting information) in 35.0%-48.0% overall yields with 91.9%-97.7% *ee* values, respectively. However, when they were hydrolyzed by base solution, only the mixtures of **2** and the Michael addition products **5** were afforded under various conditions such as LiOH, NaOH, KOH as the base, the water, water-methanol, water-THF, water-methanol-THF and isopropanol as the solvents. Unfortunately, even repeatedly performing the purification of the mixtures though preparative HPLC and TLC plates, we could not get a pure product **2** from the reaction mixture. Occasionally, the pure byproduct **5a** and **5b** were obtained in very low yield by preparative TLC plates and their structures were characterized by ^{1}H NMR, ^{13}C NMR (Figs. S9-12 in Supporting information) and high resolution mass spectrometry. Nonetheless, the absolute configuration of new chiral center was uncertain.



Scheme 1. The synthetic route of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid by hydrolysis.

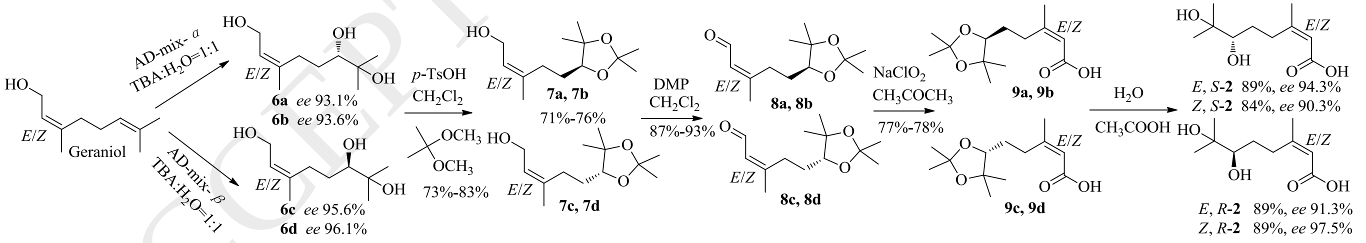
Because of the unsuccessful transformation from chiral esters to acids by hydrolysis, and construction chiral centers *via* Sharpless asymmetry dihydroxylation of *cis*- and *trans*-geranials due to their complexity of products in water media, then we have to change our synthetic strategy and go back to the raw materials (Schemes 2 and 3). To the best of our knowledge, *trans*-geraniol could be transferred to chiral triol mono acetate or *N*-phenylcarbamate, or geranyl chloride *vic*-diol by Sharpless asymmetry dihydroxylation, biological transformation or chemo-enzymatic hydrolysis with high *ee* values [16-21] (Scheme 2), whereas, these conversion approaches from these mono acetate or *N*-phenylcarbamate to chiral triol **6a** and **6c** need further exploration. On the other side, the resolution of chiral triol mono benzoate by formation and chromatographic separation of diastereoisomeric esters and further reduction with $LiAlH_4$ to produce chiral triol **6a** and **6c** has also been reported [22]. All of these methods would take 3-5 steps and the overall yields were not satisfied. Although the selective direct dihydroxylation of geraniol double bond at allylic alcohol position by OsO_4-TMEDA system at -78 °C was disclosed [23], the selective direct transformation at the remote double bond from geraniol to chiral triol **6a**-**6d** was seldom found in references [24].

In this case, the direct transformation from geraniol to chiral triol was explored by repeated experiments in more details, and found that the Sharpless asymmetry dihydroxylation could be directly utilized to transfer both *cis*- and *trans*-geraniol to afford the key chiral triol intermediates **6a**-**6d** in high yields (73%-83%) and high *ee* values (93.1%-96.1% *ee*) (Figs. S13-20 and S53-58 in Supporting information). The key chiral triol **6a**-**6d** were easily protected by converting into the related acetonide derivatives **7a**-**7d** using 2,2-dimethoxypropane (2,2-DMP) [25]. Then compounds **7a**-**7d** were oxidized to aldehyde **8a**-**8d** by DMP. After that, **8a**-**8d** were further oxidized to *cis*-/*trans*-acids **9a**-**9d** with $NaClO_2$ [6]. All of these processes did not change the absolute configuration of the chiral centers. Finally, deprotection of **9a**-**9d** by AcOH-H_2O successfully gave the four isomers of the chiral hydroxyl olefin acids **2** in 32.6%-36.4% overall yields and 90.3%-97.5% *ee* values (Figs. S45-52, S59-64 and S73-76 in Supporting Information) [26].



Scheme 2. The possible synthetic routes of chiral triols **6a** and **6c** [16-21].

In the literatures, 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid was isolated from the root of *Litsea cubeba*, and the configuration of its double bond was determined to *E* by the synthesis and comparison of its NMR data with the *Z* isomer [1, 4, 8]. However, the natural *E* isomer only had a $[\alpha]^{20}_{D}$-0.8 (*c* 0.35, MeOH) optical rotation [4], we deduced that it was almost the racemic compound compared with the $[\alpha]^{20}_{D}$-30.1 (*c* 1.2, MeOH) for the (*E*, *S*)-**2**, and $[\alpha]^{20}_{D}$ +26.3 (*c* 1.5, MeOH) for the (*E*, *R*)-**2** synthesized in this paper**.**



Scheme 3. The synthetic route of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid isomers by Sharpless asymmetric dihydroxylation.

Table 1.
The *in vivo* antifungal activity (inhibitory rate, %) of chiral acids **2** and esters **4** against several phytopathagens at 400 μg/mL.

Compd.	*P. cubensis*	*E. graminis*	*P. sorghi*	*C. gloeosporioides*
(*E*, *R*)-**4**	0	0	0	0
(*E*, *S*)-**4**	50	0	0	0
(*Z*, *R*)-**4**	80	0	0	0
(*Z*, *S*)-**4**	90	0	50	30
(*E*, *R*)-**2**	60	0	0	0
(*E*, *S*)-**2**	100	0	0	0
(*Z*, *R*)-**2**	100	100	60	65
(*Z*, *S*)-**2**	100	100	80	100
Flumorph	95	-	-	-
Enestroburin	-	100	-	-

Azoxystrobin	-	-	100	-
Prochloraz	-	-		95

P. cubensis: *Pseudoperonospora cubensis*; *E. graminis*: *Erysiphe graminis*; *C. gloeosporioides: Colletotrichum gloeosporioides*; *P. sorghi*: *Puccinia sorghi*. -: not detected.

The *in vivo* fungicidal activity was evaluated according to the procedures (Section 1.2 in Supporting information) [27-29] and presented in Table 1. These data indicated that the chiral acids (*Z*, *R*)-**2** and (*Z*, *S*)-**2** and their esters have much higher activities with the inhibitory rates of 80%-100% than the chiral acid (*E*, *R*)-**2** and itsester **4**, the ester (*E*, *S*)-**4** with the control rates of 0-60% against *P. cubensis* except (*E*, *S*)-**2** with 100% inhibitory rate; the chiral acids (*Z*, *R*)-**2** and (*Z*, *S*)-**2** have much higher activities with the inhibitory rates of 60%-100% than the chiral acid (*E*, *R*)-**2**, (*E*, *S*)-**2** and all four ester **4** with the inhibitory rates of 0-50% against *E. graminis*, *P. sorghi* and *C. gloeosporioides*. These data also showed that the chiral acids have better activities than their esters. The activities of the chiral acids with *Z*-configuration of double bond are better than those with *E*-configuration, and the activities of the chiral acids with *S*-configuration of chiral alcohol are better than those with *R*-configuration. Except against *P. sorghi*, the chiral acids (*Z*, *S*)-**2** showed the same or even better activities against *P. cubensis*, *E. graminis* and *C. gloeosporioides* as that of the positive control. Based on the above data, the chiral acid (*Z*, *S*)-**2** is a good lead compound with a broad spectrum of fungicidal activities, the configurations of the olefin's double bond and the chiral alcohol play a crucial rule for the fungicidal activities.

In conclusion, the four isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid and their esters were synthesized *via* Sharpless asymmetry dihydroxylation as the key step in 35.0%-48.0% overall yields with 91.9%-97.7% *ee* values for esters **4** and 31.3%-36.4% overall yields with 90.3-97.5% *ee* values for acids **2**, respectively, using *cis*- and *trans*-geraniol as the raw materials. Their structures were characterized by ^{1}H NMR, ^{13}C NMR and HR-ESI-MS data. The *in vivo* bioassay results showed that the chiral acids (*Z, S*)-**2** is a good lead compound with 80%-100% inhibitory rates against *P. cubensis*, *E. graminis, P. sorghi* and *C. gloeosporioides* at 400 μg/mL.

Acknowledgments

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