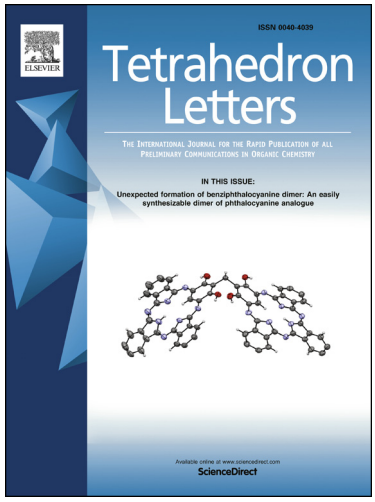

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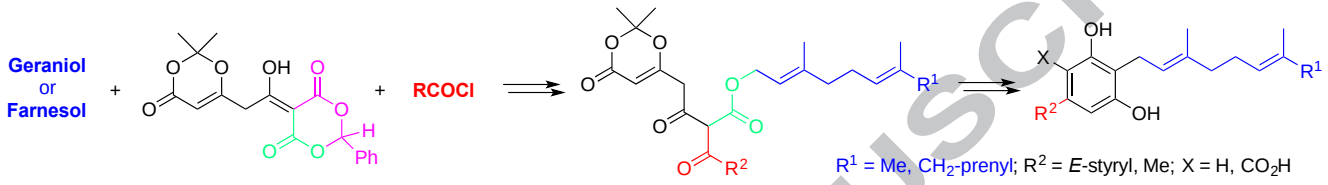

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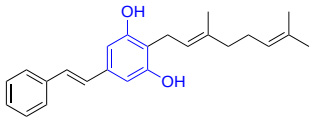
ABSTRACT

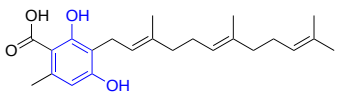
Biomimetic total syntheses of resorcinols amorphastilbol, grifolin and grifolic acid have been completed in four steps starting from geraniol and farnesol without the use of phenolic protection. The key steps involve *C*-acylation of dioxinone-*β*-keto esters, followed by palladium catalyzed decarboxylative allylic rearrangement and biomimetic aromatization.

Introduction

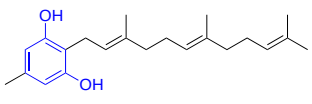
Meroterpenoids are hybrid natural products with mixed biosynthetic origin.[1] Amorphastilbol (**1**), grifolic acid (**2**) and grifolin (**3**) are bioactive resorcinol meroterpenoids containing tetraketide-terpenoid moieties that are biosynthesized via polyketide and terpenoid pathways (Figure 1). Amorphastilbol (**1**) was first isolated from extracts of *Amorpha fruticose*, *Amorpha nanna* and *Amorpha canescens* in 1979.[2] Further studies revealed its antimicrobial and anti-diabetic activities.[3] Grifolic acid (**2**) and grifolin (**3**) are structurally related resorcinols found in extracts of plant *Peperomia galioides* and the inedible mushroom *Albatrellus dispansus* and possess antibiotic and anti-tumor properties, respectively.[4]



Amorphastilbol (**1**)



Grifolic Acid (**2**)



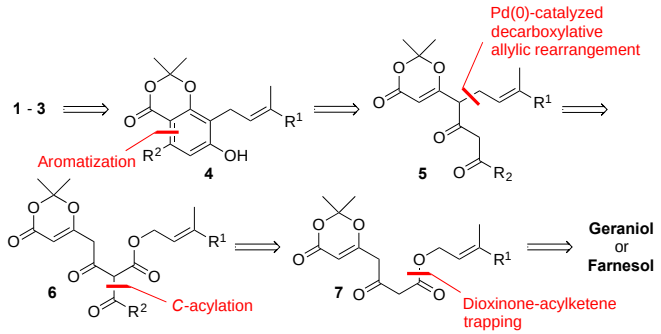
Grifolin (**3**)

Figure 1. Bioactive resorcinols amorphastilbol (**1**), grifolic acid (**2**) and grifolin (**3**).

Due to the fact that these natural products are hit molecules for infectious diseases and cancer, total syntheses and related studies of these resorcinols have been reported by various groups.[5] A common synthetic strategy in this prior chemistry involves stepwise derivatization of aromatic component such as orcinol. A major drawback of this approach is the need for phenol protecting groups and the need to introduce structural diversity early. Inspired by the pioneering work of Harris, Harris and Hyatt, our group has developed a general approach over the past decade to access diverse resorcylate natural products using diketo-dioxinones as a masked triketo-ketenes.[6-8] During the synthesis of aigialomycin D, a highly regioselective decarboxylative allylic rearrangement catalyzed by palladium(0) was observed.[9] Application of this fortuitous side reaction led to the development of a general approach to access meroterpenoids with diverse substitution patterns. More recently, we developed an improved protocol for the synthesis of dioxinone *β*-keto esters based on the reaction of allylic alcohols with dioxinone-acyl-ketenes generated from the selective mono-retro-Diels Alder reactions of dioxane-4,6-dione-keto-dioxinones.[10] This methodology was applied to the biomimetic total syntheses of the antibiotic (±)-cannabiorcichromenic acid and the anti-HIV agent (±)-daurichromenic acid.[10] Herein, we report very concise total syntheses of such bioactive geranyl- and farnesyl-substituted resorcinols from non-aromatic precursors without the need of phenol protection and which are appropriate for structure activity optimization.

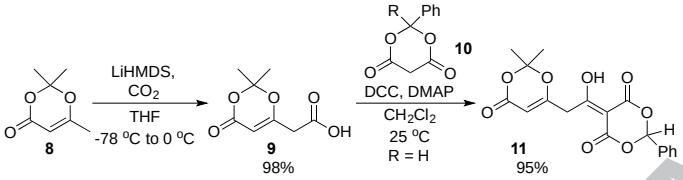
Results and Discussion

Amorphastilbol (**1**), grifolic acid (**2**) and grifolin (**3**) share the same substitution pattern on the aromatic unit and we considered that they should be available in four steps via a common reaction



Scheme 1. Projected retrosynthesis.

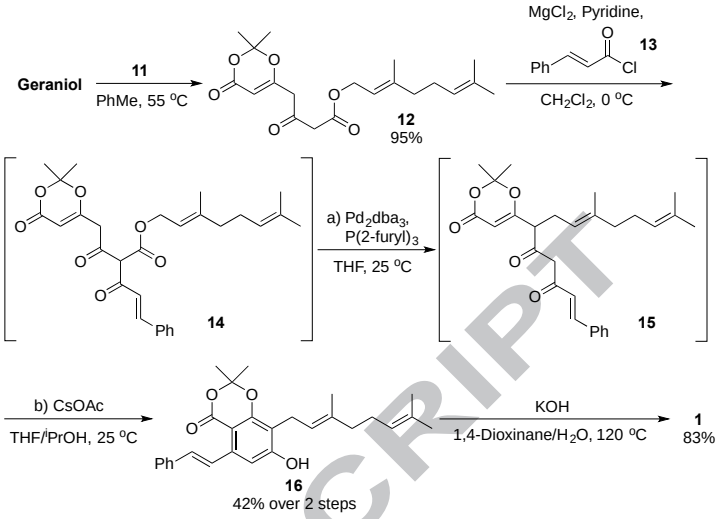
pathway (Scheme 1). The required diol or carboxylic acid moieties the targets could be formed by selective manipulation of the 2,2-dimethyl-1,3-benzodioxan-4-one of resorcylates **4** via hydrolytic decarboxylation or saponification. Resorcylates **4** should be available via the cycloaromatization of *β*,*δ*-diketo dioxinones **5**, which could be synthesized via palladium(0)-catalyzed decarboxylative allylic rearrangement of dioxinone *β*,*δ*-diketo esters **6**.[11] Dioxinone *β*,*δ*-diketo esters **6** are available via *C*-acylation of dioxinone *β*-keto esters **7**, which in turn should be easily synthesized from geraniol or farnesol.



Scheme 2. Synthesis of dioxane-4,6-dione-keto-dioxinone **11**.

The key *C*-acylating reagent **11** was synthesized in two steps from dioxinone **8** by reaction of the derived enolate at -78 °C with carbon dioxide to provide dioxinone acid **9** (98%) and subsequent DCC-mediated coupling with malonate **10** (R = H, 95%) (Scheme 2).[12] In our earlier report, malonate **10** (R = Me) was employed in related chemistry.[10] However, the use of malonate **10** (R = H) was found to be superior since it is more readily synthesized from malonic acid and benzaldehyde and more easily purified by simple crystallization than malonate **10** (R = Me) from malonic acid and acetophenone. Additionally, with heating at 55 °C, the thermally induced retro-Diels-Alder reaction of malonate **10** (R = H) occurred at a similar rate to that of malonate **10** (R = Me) and selectively gave the key derived dioxinone-acyl ketene reactive intermediate, presumably due to the phenyl ring π-delocalization into the O-CO σ* orbital during fragmentation.[13]

Firstly, we examined the synthesis of amorphastilbol (**1**) (Scheme 3). Geraniol was trapped with the dioxinone-acyl ketene, generated from dioxane-4,6-dione-keto-dioxinone **11**, at 55 °C to yield dioxinone *β*-keto ester **12** in 95% yield. Subsequent acylation with *trans*-cinnamoyl chloride **13** in the presence of magnesium chloride and pyridine provided the



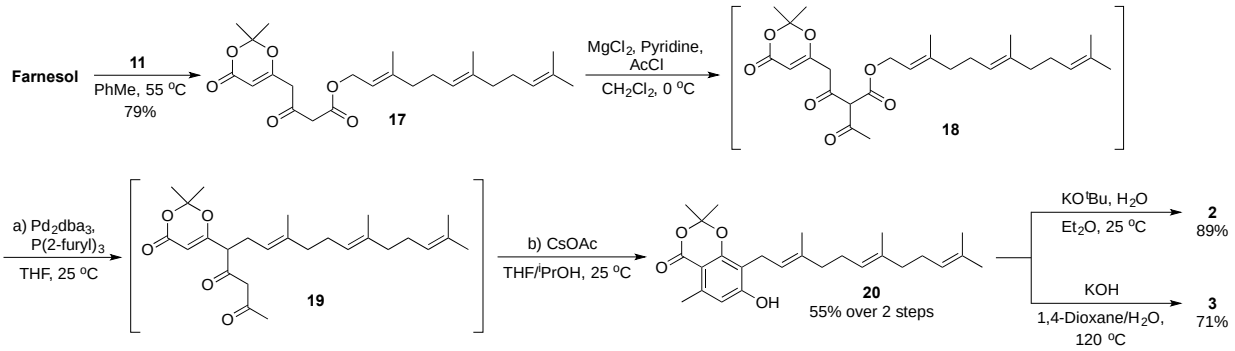
Scheme 3. Total synthesis of Amorphastilbol (**1**).

dioxinone *β*,*δ*-diketo ester **14**. Direct reaction with Pd_2dba_3 and $P(2\text{-furyl})_3$ resulted in decarboxylative allylic rearrangement to give *β*,*δ*-diketo dioxinone **15**, which aromatized readily in the presence of cesium acetate to afford resorcylate **16** in 42% yield over two steps. The expected regioselectivity of the palladium(0) catalyzed allylic rearrangement reaction was confirmed by a single crystal X-ray structural determination of the resorcylate **16**. Subsequent hydrolytic decarboxylation under basic conditions at 120 °C gave amorphastilbol (**1**) (83%) with an overall yield of 33% over four steps from geraniol. The spectroscopic data were in full agreement with those reported for the isolated natural product.[2]

Encouraged by the results, we next applied the method for the syntheses of grifolic acid (**2**) and grifolin (**3**) (Scheme 4). Fragmentation of dioxane-4,6-dione-keto-dioxinone **11** at 55 °C and ketene trapping with farnesol gave the *β*-keto ester **17** (79%). This was directly converted into resorcylate **20** via Claisen condensation, palladium(0)-catalyzed decarboxylative allylic rearrangement and base-mediated aromatization. Finally, saponification[14] of resorcylate **20** gave grifolic acid (**2**) (89%) with an overall yield of 39% while hydrolytic decarboxylation gave grifolin (**3**) (71%) with an overall yield of 30%. The analytical data of the synthetic products were compared with data reported for the isolated natural products and were found to be in complete agreement.[4b]

Conclusion

The total syntheses of amorphastilbol (**1**), grifolic acid (**2**) and grifolin (**3**) were accomplished in four linear steps using a common reaction sequence starting from commercially available geraniol or farnesol. The key resorcylate intermediates were biomimetically synthesized via a highly regioselective decarboxylative allylic rearrangement catalyzed by palladium(0). Further studies on the biomimetic total syntheses of



Scheme 4. Total syntheses of grifolic acid (**2**) and grifolin (**3**).

meroterpenoids and related medicinal chemistry are ongoing in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxx.

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11. Dioxinone *β,δ*-diketo esters exist as mixtures of keto-enol tautomers. They have been drawn as the keto-tautomer throughout the article for simplicity.
12. Dioxane-4,6-dione-keto-dioxinone **11** could not be purified by column chromatography, the yield of the DCC-mediated coupling reaction of dioxinone acid **9** with malonate **10** (R = H) was determined by ^{1}H NMR spectroscopy with the use of pentachloroethane as internal standard. It was observed that dioxane-4,6-dione-keto-dioxinone **11** decomposed slowly to dioxinone-acyl ketene at 25 ^{o}C and reacted with moisture to form *β*-keto-dioxinone. Storage of dioxane-4,6-dione-keto-dioxinone **11** is possible at -20 ^{o}C for 24 h.
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Highlights

- Ketene generation from dioxanedione **11** by retro-Diels Alder reaction
- Keto-dioxinone esters syntheses by ketene-trapping with terpene alcohols
- Mild Claisen *C*-acylation of keto-dioxinone esters
- Biomimetic conversion into terpene-resorcylates by palladium catalysis
- Total synthesis of the meroterpenoids amorphastilbol, grifolin and grifolic acid