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Total Synthesis of Grifolin, Grifolic Acid, LL-Z1272α, LL-Z1272β, and Ilicicolinic Acid A

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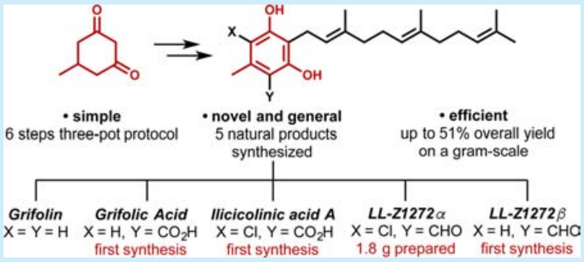
Supporting Information

ABSTRACT: A novel synthetic approach for the synthesis of bioactive phenolic natural products is reported. This strategy highlights the power of halogenative aromatization reactions recently developed in our group for preparing densely functionalized arenes in a controlled fashion. Five natural products related by an aromatic core and a farnesyl side chain are synthesized. In contrast to prior methods, this synthesis features high efficiency and generality that permits preparation of targets in gram-scale quantities.



Polysubstituted aromatics are a common structural element in a variety of natural products.[1−3] Among them, polysubstituted resorcinols, often classified as "phenolic compounds",[2] occupy a special place as they share structural similarity (a resorcinol moiety connected to terpenoid side chain[3]) and possess prominent biological profiles.[4−8] For example, popular synthetic targets ascochlorin,[3a] ascofuranone,[3b] and colletochlorin B[3c] demonstrate a variety of significant biological behaviors, including antibacterial,[3a,b,4a,b,5b] antifungal,[4b,6b] anticancer,[4c,d,5a,6a] and anti-inflamatory[5d] activities. Another family of bioactive phenolic compounds that features a polysubstituted resorcinol core fused with farnesyl side chain have garnered less attention.[3] Among numerous representatives, the most promising biological properties among this group are displayed by grifolin (**1**),[3d] grifolic acid (**2**),[3e] LL-Z1272α (**3**),[3f] LL-Z1272β (**4**),[3f] and ilicicolinic acid A (**5**),[3g,h] which exhibit anti-inflammatory,[7a] antifungal,[7b] antibacterial,[3h,7b,8a,b] cytotoxicic,[7b−e] antiviral,[7b] and antioxidant[7d] effects (Figure 1). Herein, we report the results of our efforts to develop a general approach to these natural products.

Considering the rich biological profile and diversity of natural products in this class one would expect general synthetic approaches to be in high demand. Indeed, over the past decades several approaches were developed.[9] Despite the relatively simple construction comprising a polysubstituted aromatic core fused to a terpenoid side chain, synthesis has proven challenging. For instance, a classical aromatic substitution approach[9a−d] forges the key C−C bond, but yields are often very low (Scheme 1, 1a). The efficiency of this connection can be improved by modifying the aromatic substrate,[9e,f] but protection of multiple functional groups is required (Scheme 1, 1b). The first general method was developed by Mori[9b,g] and features *tert*-butyllithium-based alkylation of a pentadienyl anion (Scheme 1, 2a). This method proved successful for a number of natural products, but harsh conditions are needed and overall yields did not exceed 15%. A

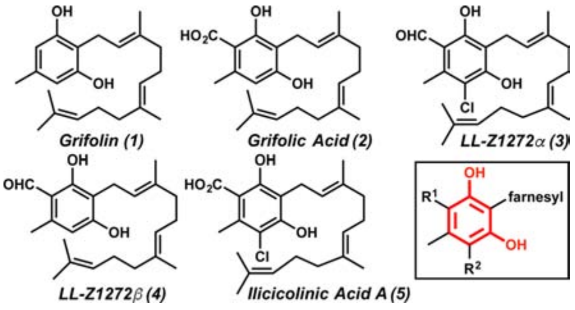
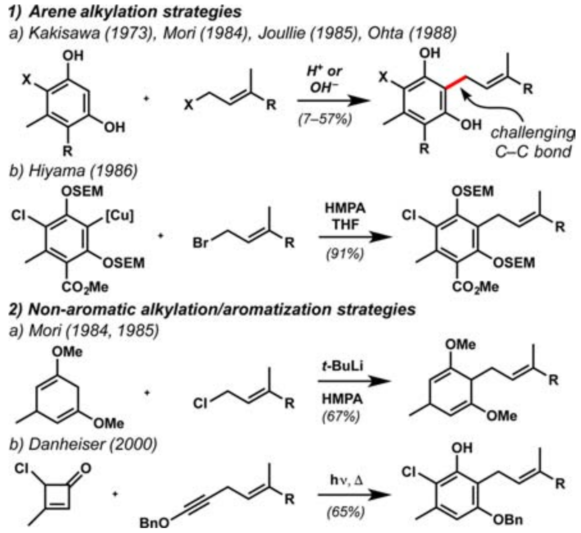


Figure 1. Examples of bioactive phenolic compounds.

Scheme 1. Different Approaches to Phenolic Compounds



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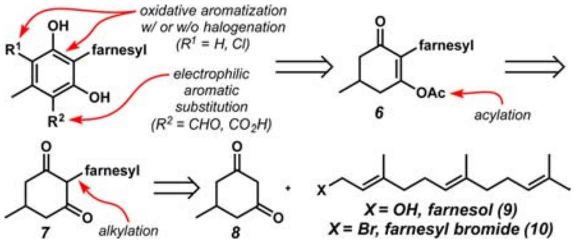
Scheme 2. Retrosynthetic Analysis



beautiful synthesis described by Danheiser[9h] introduced cyclobutenone-based benzannulation as a tool for assembling the aromatic core although a specifically designed alkynyl ether is required (Scheme 1, 2b). Collectively, none of the described approaches offers both generality and efficiency, and thus, new synthetic routes to phenolic natural products are necessary.

We recently reported an efficient method for the regiodivergent synthesis of halogenated resorcinols using readily available vinylogous esters and sulfonyl halides as halenium sources.[10] In the course of our studies, we found that by changing the nature and amount of halogen source one may direct the reaction to produce either halogenated or *des*-halo resorcinols with high selectivity. We envisioned taking advantage of both outcomes to develop a unified synthetic route to the family of farnesylated resorcinol natural products.

Given the evident challenge in forging the C−C linkage between the arene and side chain, our retrosynthetic analysis focused on identifying an efficient solution to this problem that would be applicable to the entire family (Scheme 2). We hypothesized that functionalized natural products could be accessed through a combination of electrophilic aromatic substitution and our novel oxidative aromatization methodology.[10] Thus, vinylogous ester **6** would serve as a common precursor already containing the challenging C−C bond. Intermediate **6** would be generated from functionalized 1,3-cyclohexanedione derivative **7**, which would, in turn, be prepared by alkylation of commercially available 5-methylcyclohexa-1,3-dione (**8**) and a simple derivative of farnesol (**9**).

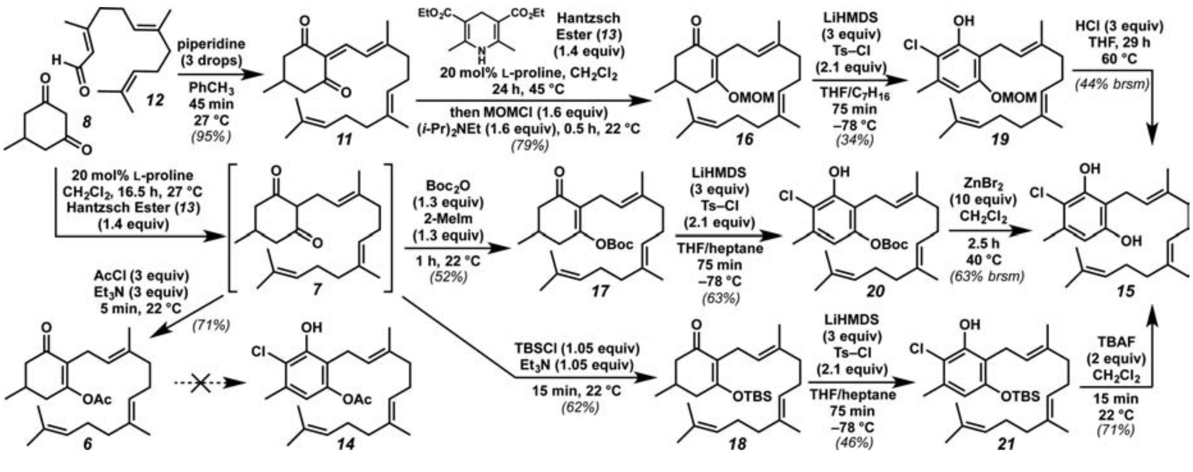
Our synthetic studies commenced with the attempted alkylation of dione **8**.[11] We initially aimed to install the side chain directly with farnesol as an electrophile via bismuth(III) catalysis.[11a] Unfortunately, we observed no reaction with dione **8**, although farnesol (**9**) was consumed. As an alternative, we attempted alkylation of dione **8** with farnesyl bromide (**10**)[12] using various basic conditions.[11b,c] After intensive screening, the best conversion was observed when K_2CO_3 was used as a base, but even in the presence of an excess of dione **8** the reaction produces a mixture of four products among which the undesired C,C-dialkylated product predominates.

To circumvent the overalkylation problem, we modified our strategy to target unsaturated dione **11** as an intermediate. To our delight, aldol condensation between dione **8** and farnesal (**12**)[13] occurred rapidly in the presence of catalytic amounts of piperidine to produce the desired conjugated dione **11** in excellent yield (Scheme 3). Inspired by this discovery, we next searched for a reduction process to convert dione **11** into the requisite intermediate **7**. Numerous conjugate reduction conditions were tested, including Cu(I) hydride,[14a,b] catecholborane,[14c] Zn/AcOH,[14d] or Mg/MeOH,[14e,f] but these methods failed to produce the desired diketone **7** in significant yield. A literature search identified Ramachary's proline-catalyzed direct aldol condensation/conjugate reduction method using the Hantzsch ester (**13**) as a potential solution.[15] In our hands, the first attempted cascade reaction between diketone **8** and aldehyde **12** resulted in isolation of dione **7** in 73% yield on 50 mg scale. We noticed, however, that ketone **7** is sensitive to the nature of the solid phase during chromatographic purification, and multiple purifications on SiO_2 decreased yield dramatically. The reaction scale was also a significant factor in purification, and an increase to a 600 mg scale led to isolation of product **7** in only 29% yield after SiO_2 chromatography. The same reaction conditions using isolated condensation product **11** as a starting material furnished the reduction product **7** in 72% isolated yield using neutral alumina as a solid phase for column chromatography.

Since the one-step aldol/reduction protocol requires no workup, we considered telescoping the intermediate (**7**) into the vinylogous ester-forming step to avoid the problematic isolation of the diketone. Indeed, treatment of the crude reaction mixture with AcCl and base allowed access to vinylogous acetate **6**, which can be easily isolated by SiO_2 chromatography in 71% overall yield (Scheme 3). This three step, one-pot protocol also did not suffer any decrease in efficiency on a larger scale.

In our previous studies, we reported that vinylogous acetates similar to intermediate **6** are transformed into unprotected resorcinols upon treatment with LiHMDS and TsCl as an electrophilic Cl source.[10] Unfortunately, substrate **6** did not behave similarly, and neither aryl acetate **14** nor the hydrolyzed

Scheme 3. Search of the Optimal Aromatization Intermediate



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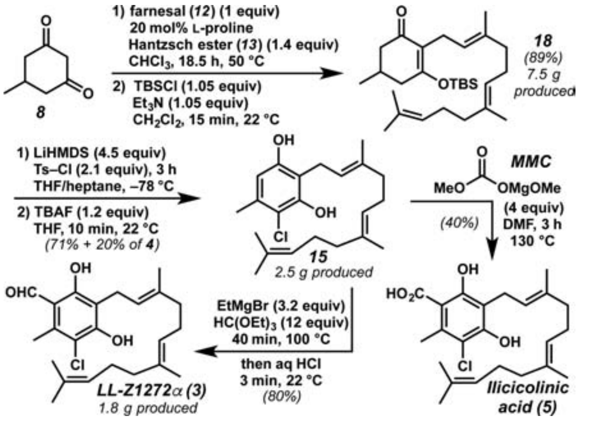
analogue **15** were observed. Confronted with this obstacle, we searched for an alternative intermediate suitable for the aromatization step (Scheme 3). Since we require a removable O substituent, we prepared several derivatives using our reductive alkylation/esterification sequence with electrophiles typically employed for protecting group installation. Use of MOM-Cl, Boc_2O, or TBS-Cl as electrophile furnished analogues **16**−**18**. To our delight, all three of these substrates could be converted to the corresponding chlororesorcinols (**19**−**21**) through our aromatization method, but subsequent O−E group cleavage proved to be an unexpectedly difficult task. Different acidic and basic conditions were examined, and the desired free resorcinol **15** was obtained from **19**−**21** using HCl, $ZnBr_2$,[16] or TBAF, respectively. In the course of this study, we also learned that the target resorcinol **15** is highly sensitive to both Lewis and Brønsted acids as well as strong basic conditions. For example, acetal **19** can be converted to resorcinol **15** using HCl with only moderate conversion. Increasing temperature or concentration resulted in product decomposition. The hydrolysis of carbonate **20** required quenching the reaction at only ∼50% conversion or the accumulated resorcinol product slowly converted into new products (four to five new spots on TLC). Silyl ether **21** (obtained from vinylogous ester **18**) behaved more predictably, however, and upon treatment with TBAF resorcinol **15** was the sole product. Another advantage of the silyl derivative (**21**) is that it can be transformed into resorcinol **15** using the crude residue from the aromatization step after simple aqueous workup, thus simplifying overall synthetic picture.

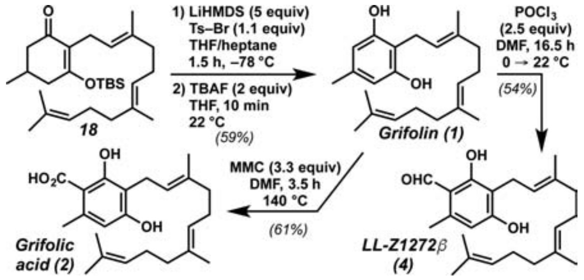
After further refinement, we successfully transformed commercially available dione **8** into vinylogous silyl ester **18** on a multigram scale in excellent yield with a single chromatographic purification (Scheme 4). Our halogenative aromatization protocol was also optimized using silyl ester **18** and functions reliably on a multigram scale as well. Under optimized conditions, this substrate produces a small quantity of the *des*-chlororesorcinol **1** as a side product, which is identical to the natural product grifolin. Having established a sound, scalable route to chlororesorcinol **15**, we next attempted functional group addition reactions to access natural products **3** and **5**. Our investigation of various formylation conditions[9b,17] found the best results using a combination of EtMgBr and triethyl orthoformate.[9b,h] Under optimized conditions, bioactive aldehyde LL-Z1272*α* (**3**) formed in 80% yield on >1 gram scale (51% overall yield from diketone **8**). Next, we examined oxidation of aldehyde LL-Z1272*α* (**3**) to access ilicicolinic acid A (**5**). Various oxidation protocols (e.g., peroxide-based oxidations[19a−d] and hypochlorite-promoted oxidation[19e]) were tested, but none of the methods delivered the desired carboxylic acid functionality in an acceptable yield. Attempted direct carboxylation found that the Mechoulam procedure utilizing magnesium methyl carbonate (MMC) in DMF[20] furnished ilicicolinic acid A (**5**) in 40% yield (with 40% of recovered resorcinol **15**), constituting the first total synthesis of this natural product.

Scheme 4. Total Synthesis of Natural Products 3 and 5



Our previous studies on aromatizing halogenation had indicated that the *des*-halo resorcinols are major products when *N*-iodosuccinimide (NIS) is used as the oxidant instead of TsCl.[10] Under these conditions, key vinylogous ester **18** produces grifolin (**1**) in 36% yield (along with 10% of the iodinated analogue). Optimization of reaction conditions revealed that the reaction pathway leading to grifolin (**1**) can be favored when 1.1 equiv of *p*-toluenesulfonyl bromide (TsBr) is used as a halogen source (Scheme 5), providing a platform to access metabolites **2** and **4**.

Scheme 5. Total Synthesis of Natural Products 1, 2, and 4



An attempt to use the orthoester-based formylation protocol[9b,h] with grifolin (**1**) to access natural product LL-Z1272*β* (**4**) did not generate the needed aldehyde functionality but instead resulted in formation of an undesired compound.[18] Further investigation revealed that Vilsmeier−Haack formylation[17d] (which failed with chlororesorcinol **15**) readily converted grifolin (**1**) into the desired natural product LL-Z1272*β* (**4**) in 54% yield (along with 19% of recovered grifolin), thus completing the first total synthesis of this compound. Aldehyde oxidation using LL-Z1272*β* (**4**) to access grifolic acid (**2**) proved unsuccessful. Fortunately, the direct carboxylation protocol[20] with MMC in DMF[19a] again proved effective, furnishing grifolic acid (**2**) in 61% yield (along with 20% of recovered grifolin) and completing the first total syntheses of this target molecule. The collective syntheses of grifolin (**1**), grifolic acid (**2**), LL-Z1272*α* (**3**), LL-Z1272*β* (**4**), and ilicicolinic acid A (**5**) demonstrate the generality of our approach to resorcinol-based natural products.

In conclusion, we have developed a novel synthetic route to the family of polysubstituted phenolic natural products featuring farnesyl side chains. This approach features high efficiency and generality, thus enabling total syntheses of five different natural products in a controlled fashion. The proven simplicity and efficiency of the synthesis on greater than gram scale requires only 3 days for reaction completion and suggests that our route is amenable to the construction of a variety of synthetic analogous and natural products with related polysubstituted aromatic cores. Studies toward these objectives are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02469.

Experimental procedures and characterization data (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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