

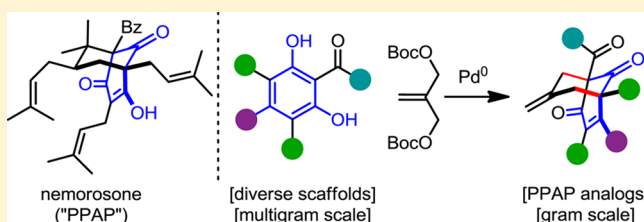
# Rapid Synthesis of Polyprenylated Acylphloroglucinol Analogs via Dearomative Conjunctive Allylic Annulation

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## Supporting Information

**ABSTRACT:** Polyprenylated acylphloroglucinols (PPAPs) are structurally complex natural products with promising biological activities. Herein, we present a biosynthesis-inspired, diversity-oriented synthesis approach for rapid construction of PPAP analogs via double decarboxylative allylation (DcA) of acylphloroglucinol scaffolds to access allyl-desoxyhumulones followed by dearomative conjunctive allylic alkylation (DCAA).



## INTRODUCTION

Polyprenylated acylphloroglucinol (PPAP) natural products including nemorosone, clusianone, and hyperforin are structurally complex molecules having promising chemotherapeutic properties (Figure 1).<sup>1,2</sup> As such, their laboratory syntheses

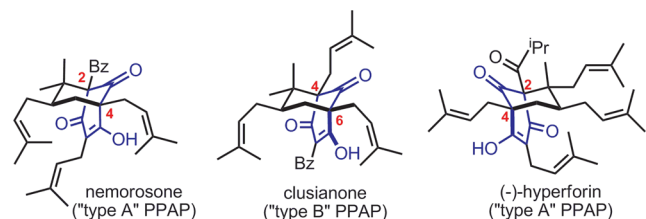


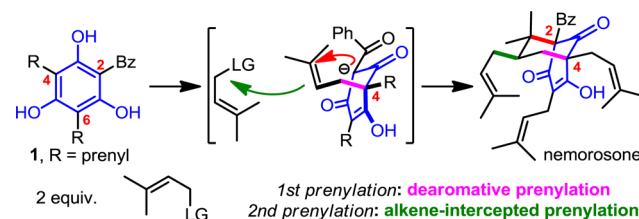
Figure 1. Representative PPAP natural products.

have received considerable attention.<sup>3</sup> PPAPs are highly regarded for their biological activities<sup>1</sup> which include anticancer,<sup>2b–e,g,h</sup> antiviral,<sup>2f</sup> and antibacterial<sup>2i</sup> properties. Bottlenecks toward their applications in disease treatment are stability issues,<sup>4</sup> synthetic challenges,<sup>3</sup> and promiscuous biological activity.<sup>1e</sup> Thus, medicinal chemistry and biological evaluation of novel analogs within the PPAP family are of high interest but have been underdeveloped.<sup>3m,5</sup> With these challenges in mind, we sought to develop a route that was both chemically efficient and applicable to diversity-oriented synthesis (DOS).<sup>6</sup>

As expertly penned by Mulzer in a recent review,<sup>7</sup> there are numerous tactics to render a given synthesis efficient including biosynthetic considerations. By considering a biosynthetic hypothesis for a natural product, often innate reactivity can be exploited, ideally resulting in an efficient synthetic strategy. In the case of PPAPs, the molecules are presumed to be derived from three building blocks: a desoxyhumulone substrate such as **1** and two additional prenyl cation equivalents which react distinctly to assemble the bicyclo[3.3.1]nonane core via (a)

dearomative prenylation and (b) alkene-intercepted prenylation (Scheme 1).<sup>1</sup> Union of the prenyl fragments with the

## Scheme 1. Biosynthetic Hypothesis for PPAP's



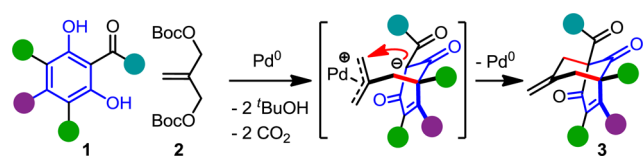
phloroglucinol at either the 2- and 4-positions or the 4- and 6-positions yields nemorosone (arbitrary absolute configuration shown) or clusianone, respectively. Generally speaking, this isomeric difference is referred to as “type A” and “type B” throughout this family. Thus, hyperforin is a “type A” PPAP through union of the phloroglucinol core to a geranyl fragment (dearomatization) and a prenyl cation (cascade bicyclo[3.3.1]nonane assembly). Although the biosynthesis is efficient and complexity generating, it has yet to be realized in a laboratory setting.<sup>3</sup>

We hypothesized that Pd-catalyzed dearomative conjunctive allylic annulation (DCAA) of desoxyhumulones **1** and 2-methylene-1,3-propanediol derivative **2** would serve as an efficient biosynthesis-inspired, diversity-oriented strategy to access a plethora of PPAP analogs **3** possessing many of the essential structural features for bioactivity (Scheme 2).<sup>2</sup> Such an approach to PPAP core structures would take advantage of biosynthetic, innate reactivity<sup>8,9</sup> (phloroglucinol dearomatization, allylic alkylation) and utilize the predictably reactive reagent **2** which has been utilized extensively in conjunctive

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### Scheme 2. A Biosynthesis-Inspired DOS Approach to PPAP Analogs

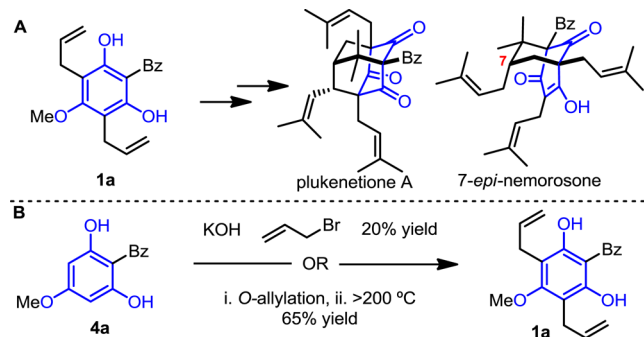


bond-forming processes.<sup>10</sup> Herein, we report our initial discoveries enabling the rapid construction of diverse PPAP analogs for biological evaluation through this modular and step-economic sequence.

### ■ ALLYL-DESOXYHUMULONE SCAFFOLD SYNTHESIS VIA DOUBLE DECARBOXYLATIVE ALLYLATION

In order to realize a diversity-oriented approach to PPAP-type structures, it was necessary to establish a modular, scalable, and robust route to allyl-desoxyhumulone scaffolds **1**. The synthesis of allyl desoxyhumulone **1a**, a common intermediate en route to the natural products plukenetione A, 7-*epi*-nemorosone, and (–)-clusianone (Scheme 3A),<sup>3g,i,p</sup> has been achieved by direct

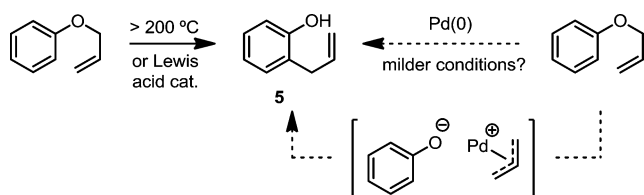
### Scheme 3. Utility and Challenges Associated with Allyl-Desoxyhumulone **1a**



C-allylation of 2-acylphloroglucinol **4a** with allyl bromide in low yield due to overallylation<sup>11</sup> or by selective O-allylation then Claisen rearrangement requiring temperatures exceeding 200 °C (Scheme 3B).

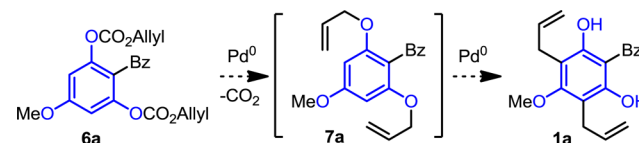
Generally speaking, allylated phenols **5** can be accessed through high-temperature (>200 °C) or Lewis acid promoted [3,3]-allyl phenyl ether Claisen rearrangements (Scheme 4).<sup>12</sup>

### Scheme 4. Alternative Approaches to C-allylated phenols



Due to the sensitivity of acylphloroglucinols and desoxyhumulones, we wondered if a relatively low-temperature and neutral formal allyl phenyl ether Claisen rearrangement could be achieved via Pd(0)-catalysis. As shown in Scheme 5, we envisioned access to desoxyhumulones via Pd-catalyzed decarboxylative allylation (DcA)<sup>13</sup> which should controllably generate diallyl phenyl ether<sup>14</sup> **7a** in accord with the site-

### Scheme 5. Double DcA/Formal Claisen Rearrangement



specificity of the DcA process.<sup>15,16</sup> The Pd-catalyst could then trigger a “formal” Claisen rearrangement under mild conditions via allyl phenyl ether ionization<sup>17</sup> and concomitant C-allylation to provide product **1a** (Scheme 5).

To examine the possibility for a mild Pd-catalyzed double decarboxylative allylation/Claisen rearrangement sequence yielding desoxyhumulones **1**, we prepared the requisite starting material **6a** in >95% yield from 2-benzoylphloroglucinol **4a** and allyl chloroformate.<sup>18</sup> Excitingly, we found that a highly efficient reaction of **6a** to the desired product **1a** occurred using 1 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> in cyclohexane (CyH) at 75 °C for 2 h (Table 1,

**Table 1. Development of Double DcA/Formal Claisen Rearrangement**

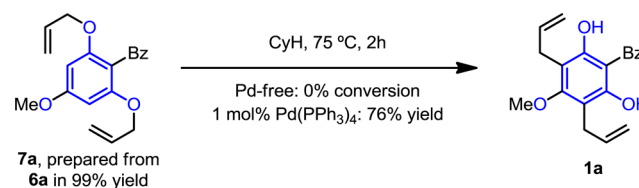
entry	solvent	temp (°C)	time (h)	product	yield (%)	[conv. (%)]
1	CyH	75	2	<b>1a</b>	87 <sup>a</sup>	
2	CyH	75	5 min	<b>7a</b>		[100] <sup>b</sup>
3	CH <sub>2</sub> Cl <sub>2</sub>	40	1	<b>7a</b>		[100] <sup>b</sup>
4	THF	66	1	<b>7a</b>		[100] <sup>b</sup>
5	toluene	110	1	<b>1a</b>	64 <sup>a</sup>	

<sup>a</sup>Isolated yields after silica gel chromatography. <sup>b</sup>Percent conversion as determined by <sup>1</sup>H NMR analysis.

entry 1). Of note, reaction for 5 min under the same conditions resulted in complete conversion to the O-allylated byproduct **7a** confirming its intermediacy en route to product **1a**. Regarding other solvents, CH<sub>2</sub>Cl<sub>2</sub> and THF yielded only O-allylated products (Table 1, entries 3 and 4), whereas toluene was also found to be a competent solvent for desoxyhumulone scaffold synthesis (Table 1, entry 5).

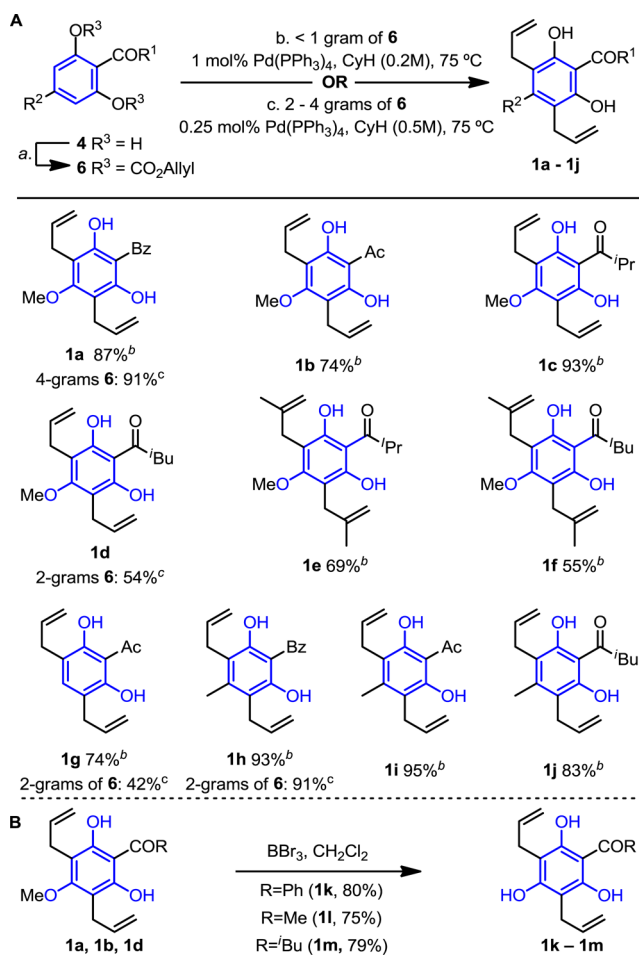
To confirm that Pd(PPh<sub>3</sub>)<sub>4</sub> is involved in the mild allyl aryl ether Claisen rearrangement, we prepared **7a** via DcA of **6a** and resubjected it to the reaction conditions sans the palladium catalyst. Not surprisingly, no conversion was observed. Upon addition of the palladium catalyst under the optimized conditions (cyclohexane, 75 °C), conversion to **1a** commences (Scheme 6).

### Scheme 6. Requirement of Pd(0) for [3,3]-Allyl Aryl Ether Claisen Rearrangement



Regarding the scope of allyl-desoxyhumulone synthesis via double DcA/formal Claisen rearrangement, phloroglucinols with a variety of 2-acyl groups were found to be compatible coupling partners (Scheme 7A). For example, desoxyhumu-

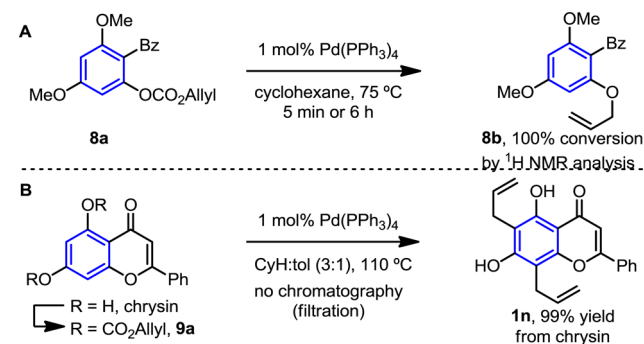
### Scheme 7. Scope of Allyl-Desoxyhumulone Synthesis



lones **1a–1d** having 2-benzoyl-, acetyl-, isobutyryl-, and isovaleryl groups were prepared. Internal allylic substitution proceeded as desired to afford products **1e** and **1f**; however, terminally substituted allylic coupling partners (e.g., cinnamyl and prenyl) afforded complex mixtures.<sup>19</sup> Excitingly, the reaction could be extended to related aromatic starting materials such as resorcinol **1g** and orcinols **1h–1j**. Importantly, a variety of large-scale (gram–multigram scale) reactions were performed for each of the compatible scaffolds identified (phloroglucinols **1a/d**, resorcinol **1g**, and orcinol **1h**). All multigram scale reactions were successful with reduced catalyst loading (0.25 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>) at an increased concentration (0.5 M in cyclohexane). To broaden substrate scope and further enhance the diversity of PPAP analogs for our investigation, we also removed the *O*-methyl group on **1a**, **1b**, and **1d** with BBr<sub>3</sub> to access the unprotected variants **1k–1m** (Scheme 7B).

In addition to the synthesis of desoxyhumulones **1a–1m** via DcA/formal Claisen rearrangement, we also investigated the synthesis of related scaffolds (Scheme 8). Interestingly, we found that the *mono*-allyl phenyl carbonate **8a** only underwent DcA to provide allyl phenyl ether **8b** under the optimized conditions and did not undergo formal allyl phenyl ether [3,3]-

### Scheme 8. Related Scaffolds for Pd-Catalyzed DcA



Claisen rearrangement regardless of the reaction duration (Scheme 8A). In addition, the double DcA/Claisen rearrangement was extended to the chrysin-derived flavone scaffold **9a** under slightly modified conditions (Scheme 8B). From the commercially available flavone chrysin, we prepared 6,8-diallylchrysin<sup>20</sup> **1n** without silica gel chromatography in 99% yield over the two-step sequence via intermediate **9a**.

### BIOSYNTHESIS-INSPIRED, DIVERSITY-ORIENTED SYNTHESIS OF PPAP ANALOGS

With a variety of desoxyhumulone scaffolds **1a–1j** in hand, many of which were prepared in multigram quantities, we next turned to the development of the key dearomative conjunctive allylic annulation (DCAA) to provide a diversified set of PPAP analogs. Using the model coupling reaction between **1a** and **2**, we began our quest for the optimal Pd catalyst, solvent, and reaction conditions (Table 2). *Mono*-methyl allyl desoxyhumu-

Table 2. Development of DCAA

entry	solvent	temp (°C)	time (h)	catalyst	yield (%)
1 <sup>a</sup>	CyH	75	0.5	Pd(PPh <sub>3</sub> ) <sub>4</sub> <sup>c</sup>	87
2 <sup>b</sup>	toluene	100	1	Pd/BINAP <sup>d</sup>	81
3	DCE	80	0.5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	trace <sup>e</sup>
4	toluene	80	0.5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	trace <sup>e</sup>
5	THF	65	0.5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	trace <sup>e</sup>
6	CyH	75	24	Pd/BINAP	68
7	THF	65	24	Pd/BINAP	80

<sup>a</sup>Standard conditions A. <sup>b</sup>Standard conditions B. <sup>c</sup>2.5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>. <sup>d</sup>2 mol % Pd<sub>2</sub>dba<sub>3</sub>, 4 mol % *rac*-BINAP, premixed in reaction solvent for 10 min. <sup>e</sup>Determined by <sup>1</sup>H NMR of the crude reaction mixture.

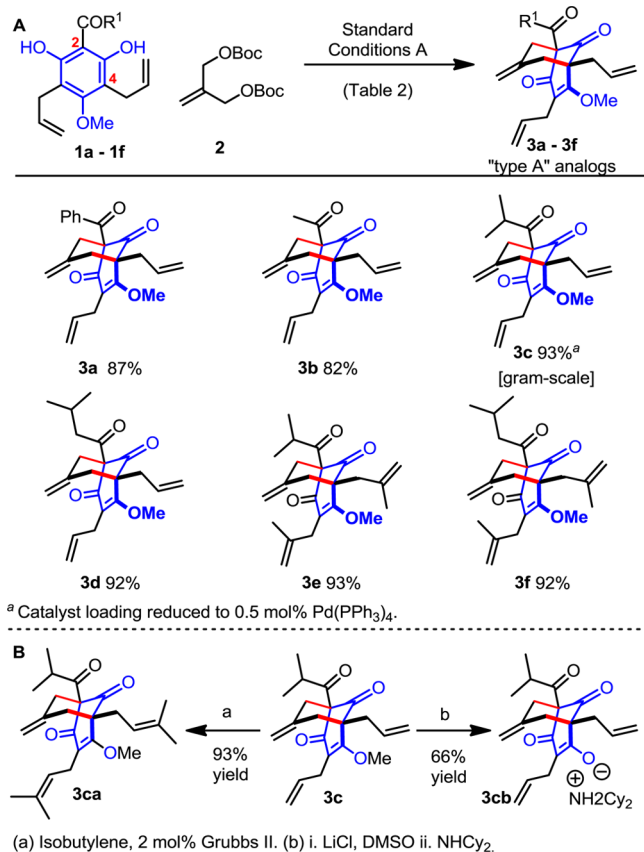
lone **1a** was chosen as an initial scaffold as it was thought, based on our previous studies,<sup>3g</sup> that the methyl ether would direct the annulation to the 2- and 4-positions of the substrate ("type A" annulation).

We ultimately identified two standard conditions (A and B, Table 2, entries 1 and 2) that were utilized throughout our studies to construct PPAP analogs. Standard conditions A (Pd(PPh<sub>3</sub>)<sub>4</sub>, cyclohexane) were found to be highly solvent dependent as related conditions in DCE, toluene, and THF did not produce the desired product (Table 2, entries 3–5).

Standard conditions B (Pd/BINAP) appeared to be more tolerant to solvent choice, though reaction times were found to be significantly longer in lower boiling solvents such as cyclohexane and THF (Table 2, entries 6 and 7).

Interestingly, using either the methylated (**1a–1f**, Scheme 7A) or the nonmethylated (**1k–1m**, Scheme 7B) desoxyhumulone scaffolds, either “type A” or “type B” PPAP structures could be selectively prepared (Schemes 9 and 10,

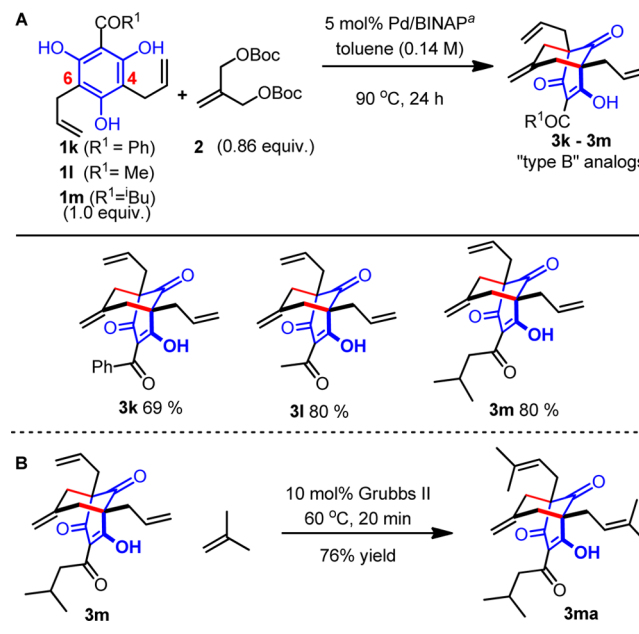
**Scheme 9. “Type A” PPAP Analogs via DCAA**



respectively). *O*-Methyl-desoxyhumulones **1a–1f** reacted under standard conditions A (Table 2, entry 1) to yield “type A” PPAP analogs **3a–3f** in excellent yields (Scheme 9A). The reaction tolerated both allyl (**3a–3d**) and  $\beta$ -methylallyl (**3e** and **3f**) substitution at C4 and C6. Pleasingly, the nonmethylated desoxyhumulones **1k–1m** exclusively provided “type B” annulation adducts **3k–3m** under modified conditions via regioselective cyclization at the more nucleophilic C4 and C6 positions (Scheme 10A).<sup>3c</sup> We discovered that increased reaction times, lower temperatures, and larger catalyst (Pd<sub>2</sub>dba<sub>3</sub>/BINAP) loadings were required for successful cyclization to the “type B” core as low yields were obtained using standard conditions A or B. As one possible explanation, the nucleophilic phenolate moiety at C5 may bind to binary palladium(0) more effectively than BINAP resulting in loss of catalytic activity.<sup>21</sup> Pleasingly, our general purification procedure developed for dearomatized phloroglucinols and PPAP derivatives<sup>3p,18</sup> allowed access to bicyclo[3.3.1]nonanes **3k–3m** along with their potassium salts<sup>18</sup> in high yields without the use of silica gel chromatography (Scheme 10A).

Moreover, using the Grubbs second-generation catalyst, we could also conveniently access prenylated analogs of both “type

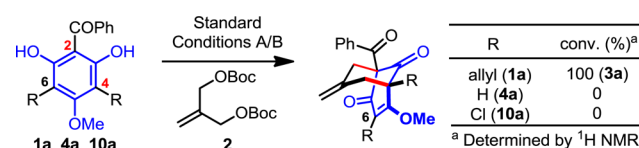
**Scheme 10. “Type B” PPAP Analogs via DCAA**



A and B” PPAPs **3** as shown for prenylated variants **3ca** (Scheme 9B) and **3ma** (Scheme 10B) in excellent yields. All products **3** led to selective prenylation of the monosubstituted allyl groups leaving the *exo*-methylene intact.<sup>22</sup> Removal of the methyl enol ether could be accomplished in good yield revealing the vinylogous acid functionality commonly found in PPAP natural products (Scheme 9B). We opted to store the vinylogous acid **3ca** as its dicyclohexyl ammonium salt, and the “type B” scaffolds **3k–3m** were stored as potassium salts<sup>18,3p</sup> due to their enhanced stability and shelf life.<sup>4</sup>

We also found that alkyl substitution at C4 and C6 was important for success of the DCAA reaction (Scheme 11).

**Scheme 11. Importance of Alkyl Substitution at Both C4 and C6**



While the standard allyl-desoxyhumulone **1a** underwent clean reaction under the optimized conditions to afford **3a**, neither the proteo-(**4a**) or the chlorinated (**10a**) variants reacted with conjunctive reagent **2** under standard conditions A or B, likely due to a combination of steric and electronic influences.

From the successful studies on allyl-desoxyhumulones **1a–1f** (Scheme 9) and **1k–1m** (Scheme 10), we reasoned that other scaffolds bearing at least a resorcinol oxygenation pattern, an acyl group, and alkyl substituents at C4 and C6 should also undergo the desired DCAA process. We proceeded to test our hypothesis by further broadening our investigation to construct a diverse set of resorcinol- and orcinol-derived PPAP analogs via DCAA (Scheme 12). Excitingly, we discovered that resorcinol derivative **1g** and orcinol derivatives **1h–1j** yielded “type A” PPAP analogs **3g–3j** lacking a vinylogous acid moiety (Scheme 12, eqs 1 and 2). Moreover, the structure of DCAA product **3h** was unequivocally determined by X-ray crystallography (Figure 2).<sup>18</sup> Diallyl-chrysin **1n** exclusively afforded “type



## Scheme 12. Other Scaffolds That Undergo DCAA

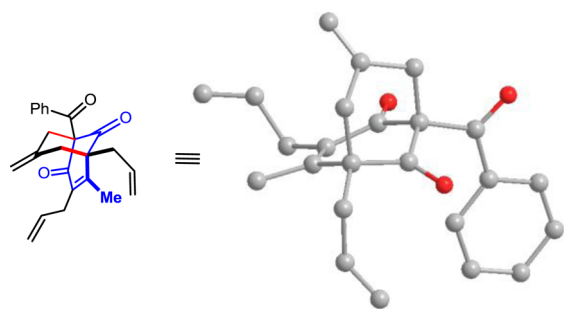
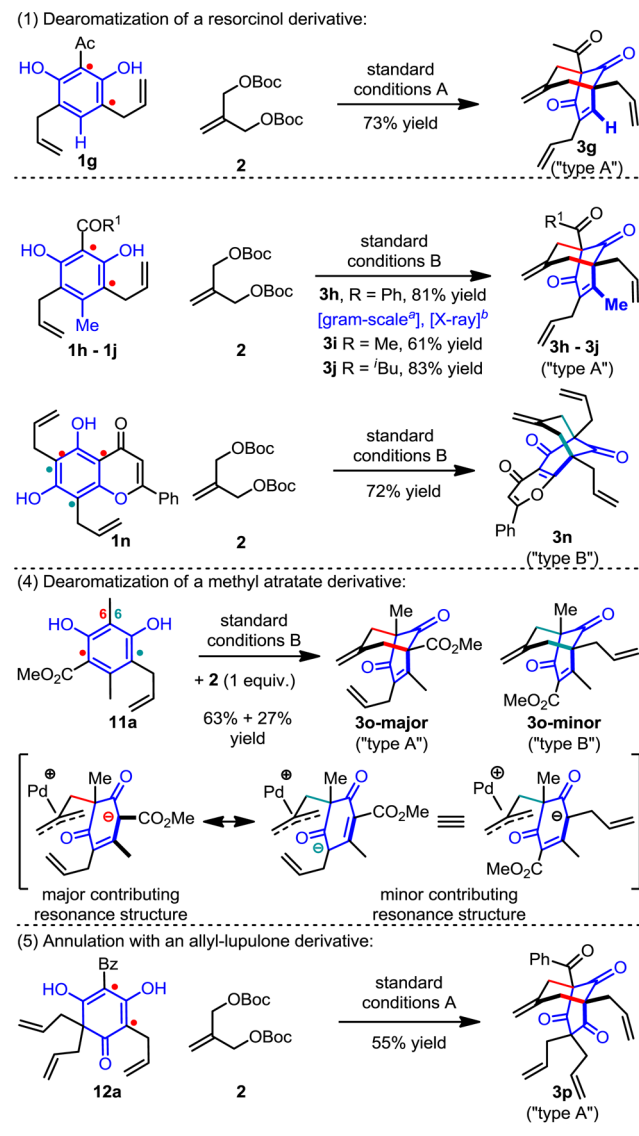


Figure 2. X-ray crystal structure of analog 3h.

B" pyranone heterocycle **3n** (Scheme 12, eq 3), likely resulting from enhanced nucleophilicity of the unprotected phenol moiety positioned *para* to the acyl group in **1n** (cf. Scheme 10). DCAA adduct **3n** is structurally similar to the anticancer PPAP natural products oblongifolins F and G.<sup>22</sup> Next, starting from allylated methyl atrate (**11a**), available in 1-step from methyl atrate, an inexpensive flavoring molecule (~\$0.25/g),<sup>24</sup> DCAA yielded two-separable products having "type A" (**3o-major**, 63% yield) and "type B" (**3o-minor**, 27% yield) fusion

patterns. The mixture likely arises from the intermediate anion reacting through either major- or minor-contributing resonance structures, which can be reasoned by the fact that keto-stabilized allyl anions prefer to react at the most-stabilized position.<sup>25</sup> Finally, lupulone derivative **12a** yielded a PPAP analog bearing *gem*-diallyl substitution (Scheme 12, eq 5).<sup>26</sup>

In conclusion, we have achieved a biosynthesis-inspired, diversity-oriented synthesis approach to both "type A and B" PPAP analogs. Through the use of two consecutive Pd-catalyzed reactions, double DcA/Claisen rearrangement and a DCAA, we can rapidly prepare PPAP molecules for biological evaluation. The reaction is applicable to a number of electron-rich aromatic substrates bearing a resorcinol or phloroglucinol substitution pattern. Further studies including construction of highly diverse PPAP-inspired chemical libraries for biological studies and development of asymmetric DCAA are currently in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

## S Supporting Information

Experimental details and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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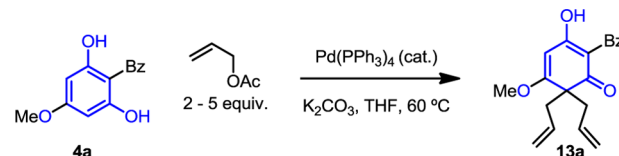
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