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Letter

Regiodivergent 1,3-Annulation of Valylene with 4-Hydroxycoumarins

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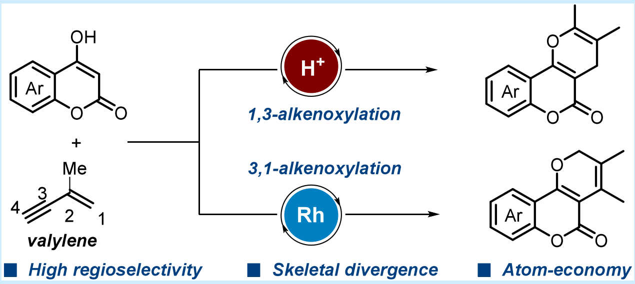
ABSTRACT: Pyranocoumarins are widely distributed in natural products and exhibit intriguing biological activities, making their efficient synthesis highly desirable. Herein, we developed an efficient method for synthesizing two new types dimethylallyl-decorated pyranocoumarins in efficiency through catalytic formal [3 + 3] annulation of 4-hydroxycoumarins with valylene. Under acid catalysis, exclusive 1,3-alkenoxylation afforded natural product-like angular pyranocoumarins, while Rh catalysis switched regioselectivity to 3,1-alkenoxylation. The protocol features high atom-economy, readily available substrates, and excellent regio- and chemo-selectivity. Mechanistic studies indicated the reaction proceeds via regioselective hydroalkoxylation to form diene or allene intermediates, followed by intramolecular cyclization. This work not only represents a good paradigm in addressing selectivity challenges in reactions involving substrates with multireactive-site but also offers a robust platform for rapid construction of skeletal variants beyond naturally occurring structures.



Coumarin is an important class of organic heterocyclic compounds with a benzopyrone skeleton. It is widely distributed in plants of the Apiaceae, Rutaceae, and Leguminosae families,[1] and was first isolated from *Dipteryx odorata* (coumarou) in 1820.[2] Owing to their unique biological activities[3] and fluorescent properties,[4] coumarins have become favored star molecules for medicinal and material chemists. Among them, pyranocoumarins serve as key intermediates in the synthesis of various pharmaceuticals and are well-known for their broad-spectrum bioactivity. In particular, the Bothrioclinin family of compounds, isolated from *Ekebergia pterophylla* and *Bothriocline laxa*,[5] represents a class of structurally unique angular pyranocoumarins (Figure 1). The presence of dimethylallyl units, such as 3-methyl-2-butenyl (prenyl), can enhance the lipophilicity of molecules and facilitate their permeation across cellular membranes.[6] Therefore, the development of efficient synthetic methods for pyranocoumarins bearing a dimethylallyl motif has attracted continuous attention in organic and medicinal chemistry research.

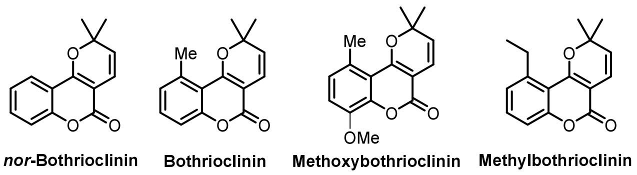


Figure 1. Natural Bothrioclinin family compounds.

4-Hydroxycoumarin, which can be biosynthesized via *Escherichia coli*,[7] serves as a well-known versatile synthon and an important reagent in the field of heterocyclic synthesis.[8] In this context, several protocols for the synthesis of the Bothrioclinin-type skeleton from commercially available 4-hydroxycoumarin have been developed (Figure 2A). For instance, 4-hydroxycoumarin can undergo Friedel–Crafts-type alkylation and cyclization with propargyl reagents under the catalysis of Lewis acids or Brønsted acids,[9] which represents one of the most representative methods for the construction of pyranocoumarin derivatives.[10] In addition, pyranocoumarins can also be obtained via acid-catalyzed cyclization of 4-hydroxycoumarin with α, β-unsaturated ketones or aldehydes.[11] Moreover, annulation of 4-hydroxycoumarin with prenyl bromide or isoprene,[12] followed by oxidative dehydrogenation, provides an alternative approach. Although these methods are practical, the development of a reliable methodology that enables the rapid construction of skeletal variants beyond naturally occurring structures still remains underexplored to date.

Over the past decade, the catalytic sequential hydrofunctionalization of 1,3-enynes has been developed as an

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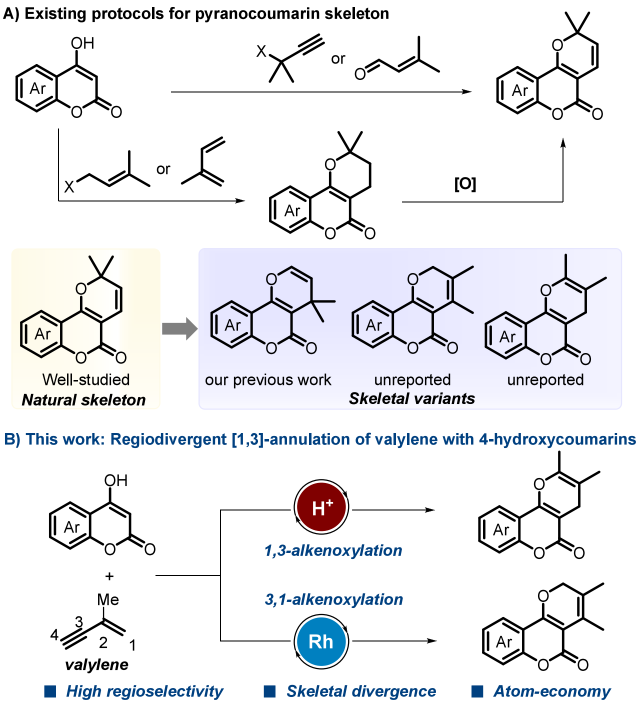
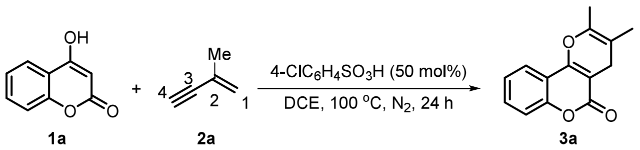


Figure 2. Synthesis of Bothrioclinin and its analogues.

emerging strategy for the rapid assembly of heterocyclic molecules.[13] However, the smallest substituted 1,3-enyne, valylene (2-methyl-1-butene-3-yne), a potential feedstock for the installation of biologically relevant dimethylallyl group, is seriously overlooked. Previously, we have adopted a dual-ligand controlled strategy for 2,4-/4,2-alkenoxylation of valylene with 4-hydroxycoumarins under rhodium catalysis,[14] selectively producing natural pyranocoumarin skeleton and its reverse-prenylated isomers. To further expand the molecular diversity and on our continuous studies of selective prenylation,[15] herein we report a regio-divergent 1,3-annulation of valylene with 4-hydroxycoumarins under either Brønsted acid or Rh catalysis, producing two new types of dimethylallyl-decorated coumarins with excellent atom economy (Figure 2B).

Initially, 4-hydroxycoumarin (**1a**) and valylene (**2a**) were employed as model substrates under various conditions (Table 1 and Tables S1−S6, pages S3−S6). Pleasingly, the desired 1,3-alkenoxylation product **3a** could be obtained in 73% yield under the optimized conditions (entry 1). Notably, the 2,4-annulated products obtained under previous Rh/dual-ligand catalysis were not observed under current conditions. In the absence of acid, control experiment revealed that no product was formed under thermal conditions (entry 2). 4-$ClC_6H_4SO_3H$ was found to be the optimal acid catalyst for this transformation. In comparison, sulfonic acids such as TsOH, 4-$NO_2C_6H_4SO_3H$, and 4-$MeOC_6H_4SO_3H$ were less effective (entry 3). Additionally, other Brønsted acids ($PhCO_2H$, $Ph_2P(O)OH$, HCl) and Lewis acids ($AlCl_3$, $ZnCl_2$, or $Sc(OTf)_3$) were also evaluated. Nevertheless, they all exhibited no catalytic activity (entries 4 and 5). Decreasing or increasing the catalytic dosage of 4-$ClC_6H_4SO_3H$ significantly impaired the reaction efficiency (entry 6). A survey of solvents demonstrated that DCE was crucial for promoting the reaction. Replacing DCE with PhCl or MeCN only delivered pyranocoumarin **3a** in 52% or 3% yield, respectively (entry 7). Other polar solvents, such as 1,4-dioxane, MeOH, DMF, or DMSO, were all not applicable (entry 8). An evaluation of the reaction temperature showed that 100 °C was the optimal choice (entry 9).

Table 1. Optimization under Acid Conditions[a]



Entry	Variation from standard conditions	Yield of **3a** (%)
1	none	73
2	no acid	n.d.
3	4-$NO_2C_6H_4SO_3H$, 4-$MeOC_6H_4SO_3H$ or TsOH as catalyst	16, 49, 33
4	$PhCO_2H$, $Ph_2P(O)OH$, or HCl as catalyst	n.d.
5	$AlCl_3$, $ZnCl_2$, or $Sc(OTf)_3$ as catalyst	n.d.
6	20 mol % or 100 mol % of 4-$ClC_6H_4SO_3H$ was used	10, 33
7	PhCl or MeCN instead of DCE	52, 3
8	1,4-dioxane, MeOH, DMF, or DMSO instead of DCE	n.d.
9	80 or 120 °C instead of 100 °C	66, 44

[a] Conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), 4-$ClC_6H_4SO_3H$ (50 mol %), DCE (0.5 mL), 100 °C, 24 h, N_2 atmosphere.

With the optimized conditions in hand, the generality of 4-hydroxycoumarins was explored to demonstrate the feasibility and practicality of this protocol (Figure 3). Using 4-$ClC_6H_4SO_3H$ as the acid, a series of 4-hydroxycoumarins were successfully converted via 1,3-hydroalkenoxylation. Under the optimal conditions, the desired product **3a** was isolated in 64% yield from the reaction of 4-hydroxycoumarin **1a** and valylene **2a**. Due to solubility issue, incomplete conversions of the 4-hydroxycoumarin substrates were observed. Prolonging the reaction time could increase the isolated yields (72% yield for **3a**). The electronic properties and positions of the substituents on the phenyl ring had a negligible effect on this reaction. For example, a variety of functional groups, including electron-withdrawing groups (-F, -Cl, and -Br), underwent the annulation smoothly to afford the corresponding products (**3b**−**d**) in 36−63% yields. In addition, electron-donating groups (-OMe and -Me) were also compatible with the process in moderate yields (**3e**−**g**). Satisfactorily, the introduction of substituents at the 7- or 8-position of the coumarin phenyl ring was amenable to the current conditions, delivering **3h**−**m** in decent yields. Additionally, benzocoumarins were accessible under the standard conditions (**3n**−**o**). Although 4-aminocoumarin was not compatible with the current conditions (**3p**), the annulation of hydroxypyranone **1q** with valylene proceeded smoothly, yielding **3q** in 44% yield. Among these products, the structures of **3a**, **3e**, and **3m** were confirmed by single-crystal X-ray crystallography. The 4-hydroxycoumarin substrates with other fragile substituents were also evaluated under the current acid catalysis (see page S30 in the Supporting Information for details). While an ester group at the C6-position was compatible with the current annulations and afforded the corresponding product **3s** in 66% yield (page S14, Supporting Information), amino or cyano group was not tolerated under the current conditions. Unfortunately, 1,3-dicarbonyl compounds were not compatible under the current conditions. In addition to valylene, 2-methyldec-1-en-3-yne was converted

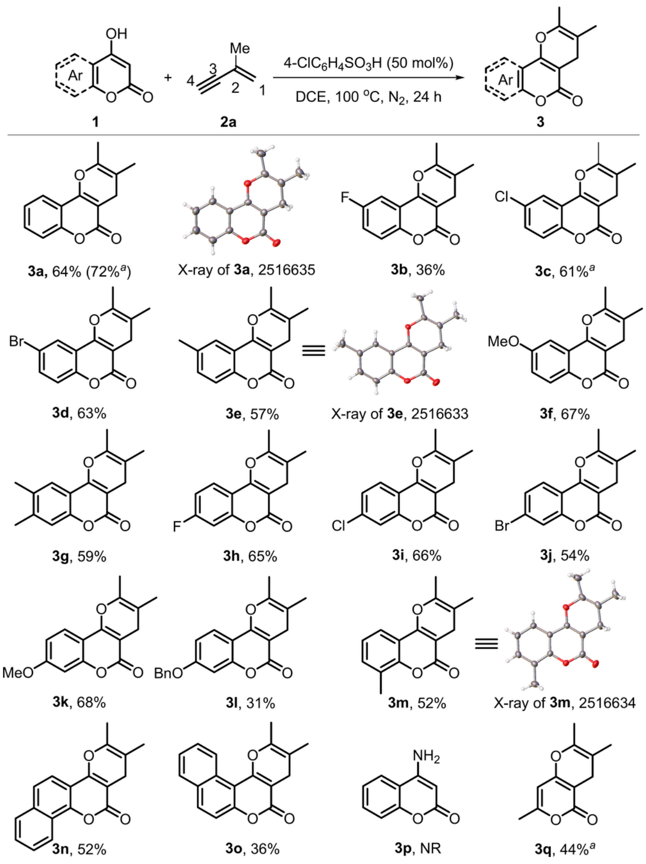


Figure 3. Substrate scope for acid-catalyzed 1,3-alkenoxylation. **1** (0.10 mmol), **2a** (0.20 mmol), 4-ClC$_6$H$_4$SO$_3$H (50 mol %), DCE (0.5 mL), 100 °C, 24 h, N$_2$ atmosphere. Isolated yields were given. Legend: ^{a}36 h.

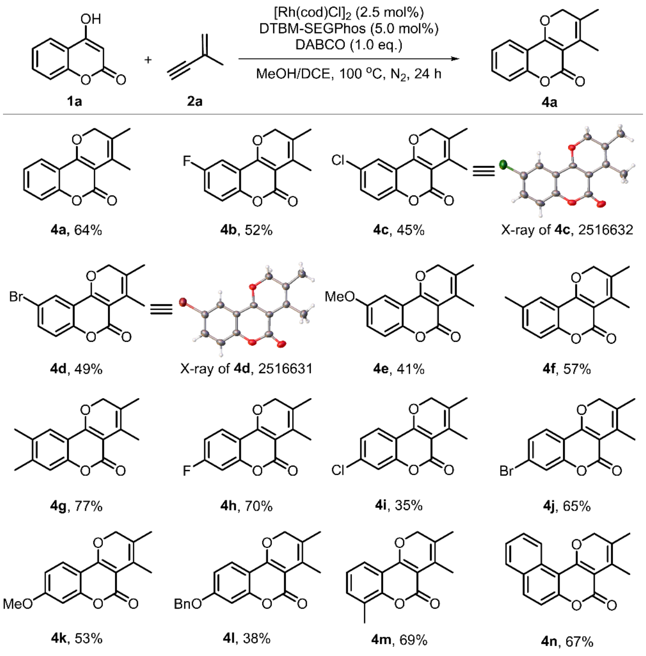


Figure 4. Substrate scope for Rh-catalyzed 3,1-alkenoxylation. Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), [Rh(cod)Cl]$_2$ (2.5 mol %), DTBM-SEGPhos (5 mol %), DABCO (1.0 equiv.), MeOH (0.3 mL), DCE (0.2 mL), N$_2$ atmosphere. Isolated yields were were given.

into the furanocoumarin in 56% yield, whereas the reaction with 1,4-diphenyl-1,3-enyne yielded a complex mixture of inseparable isomers (page S30).

To exploit the structural diversity of the pyranocoumarin skeleton, we then turned our attention to the 3,1-hydro-alkenoxylation reaction. Our previous work has shown that the [Rh(cod)Cl]$_2$/BINAP/P(4-ClC$_6$H$_4$)$_3$/DABCO catalyst combination could promote the 2,4-hydro-alkenoxylation of valylene in excellent regioselectivity, while moderate selectivity toward the 3,1-alkenoxylation product was observed under the catalysis of [Rh(cod)Cl]$_2$/BINAP/DABCO.[14] Inspired by these promising results and to further improve the selectivity, we continued to systematically optimize the reaction parameters, including ligands, additives, and solvents (see Tables S7–S11, pages S6–S9). Delightfully, excellent selectivity (>95%) for the 3,1-alkenoxylation product **4a** could be obtained when the reaction was conducted with DTBM-SEGPhos as the ligand in DCE/MeOH mixed solvents at 100 °C. Under these optimized conditions, the substrate scope of 4-hydroxycoumarins was subsequently examined (Figure 4). Under the optimized conditions, 4-hydroxycoumarin **1a** was exclusively converted to **4a** in 64% yield. This annulation was found to be amenable to 4-hydroxycoumarins bearing electron-withdrawing groups, such as −F, −Cl, and −Br groups (**4b**–**d**). The structures of **4c** and **4d** were confirmed by single-crystal X-ray crystallography. In addition, the electron-donating groups (−OMe and −Me) had a slight influence on this transformation, affording **4e**–**g** in 41–77% yields. Notably, the functional groups attached at other positions of the phenyl ring were compatible with this protocol, giving **4h**–**m** in 35–70% yields. Remarkably, benzocoumarins exhibited good reactivity, providing **4n** in 67% yield. The reaction of 4-hydroxycoumarin with an ester group at the C6-position could also lead to a 34% yield of the corresponding product **4o** (page S19, Supporting Information). But substrates with an amino or cyano group were not applicable under the current conditions (see page S30 in the Supporting Information for details). Additionally, 1,3-dicarbonyl compounds, whether acyclic or cyclic, were all unsuitable substrates under the current rhodium-catalyzed conditions (page S30). For other 1,3-enynes, such as 2-methyldec-1-en-3-yne and 1,4-diphenyl-1,3-enyne, all showed no reactivity under the current rhodium catalysis (page S30).

To elucidate the mechanism and probe the possible intermediates, a series of mechanistic experiments were carried out (Figure 5). First, the isolated compound **5a** was smoothly converted to product **3a** in 54% yield under acidic conditions. In comparison, no annulated product was obtained in the absence of acid (Figure 5A). In addition, a crossover reaction between **5a** and **1b** could yield a mixture of **3a** and **3b** (Figure 5B). These results suggest that the 1,3-alkenoxylation reaction may proceed through a reversible 4,3-hydroalkoxylation first to deliver diene intermediate **5a**, followed by acid-promoted intramolecular annulation. A higher acid catalyst amount led to a decreased yield of annulated product, probably by promoting the reverse reaction of diene intermediate **5a** (Table 1, entry 6). Besides, this tandem acid-catalyzed process requires a good balance of appropriate catalyst acidity, explaining why either excessively strong or excessively weak acid catalysts are unfavorable for this annulation reaction (Table S2). Next, homopropargyl coumarin **9** was also synthesized and subjected to Rh-catalyzed conditions (Figure 5C). However, the desired

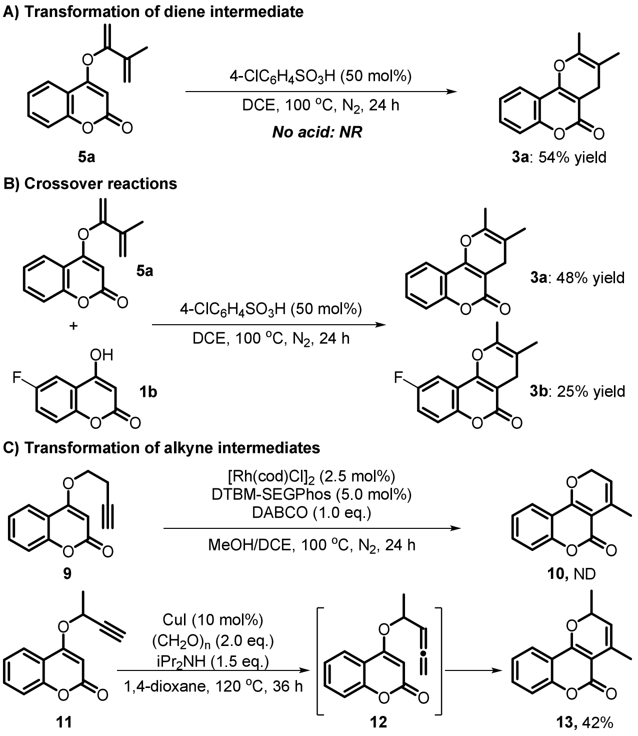


Figure 5. Mechanistic studies.

annulation product **10** was not detected, indicating that the reaction pathway may proceed through an alternative intermediate. As a result, we sought to test the allene intermediate **12** through its in situ formation in the Cu-catalyzed reaction of propargyl coumarin **11** with paraformaldehyde.[16] To our delight, cyclic product **13** was successfully afforded in 42% yield (Figure 5C), suggesting that the 3,1-alkenoxylation reaction may start with the Rh-catalyzed 1,4-hydroalkoxylation between 4-hydroxycoumarin and valylene, delivering the allene intermediate.[13c,g] Then an intramolecular annulation occurs rapidly with the aid of base, giving the 3,1-alkenoxylation product **4** with good selectivity.

Based on the aforementioned mechanistic investigations, plausible reaction mechanisms are proposed (Figure 6). Under Brønsted acid catalysis, the acid facilitates the nucleophilic addition between valylene **2a** and 4-hydroxycoumarin **1a**, leading to the formation of intermediate **A**. This intermediate then undergoes deprotonation to yield intermediate **5a**. Subsequently, the acid activates the conjugated diene moiety, triggering an intramolecular cyclization process that generates intermediate **C**. A final deprotonation step completes the reaction, affording the 1,3-hydroalkenoxylation product **3a**. In contrast, under Rh catalysis, oxidative addition of 4-hydroxycoumarin **1a** to the Rh(I) complex generates the Rh(III)-hydride intermediate **D**. This is followed by migratory insertion with valylene **2a**, which affords the allenylated Rh(III) intermediate **E**. A subsequent reductive elimination event constructs the C−O bond, yielding the pivotal O-allenyl intermediate **F**. Finally, base-promoted intramolecular cyclization proceeds to furnish the corresponding 3,1-hydroalkenoxylation product **4a**.

The synthetic potential of this protocol was also demonstrated by diverse transformations. As shown in Figure 7, the lactone moiety of **3d** could be smoothly reduced by LiAlH$_4$ to afford alcohol **15** in 51% yield. In addition, oxidation

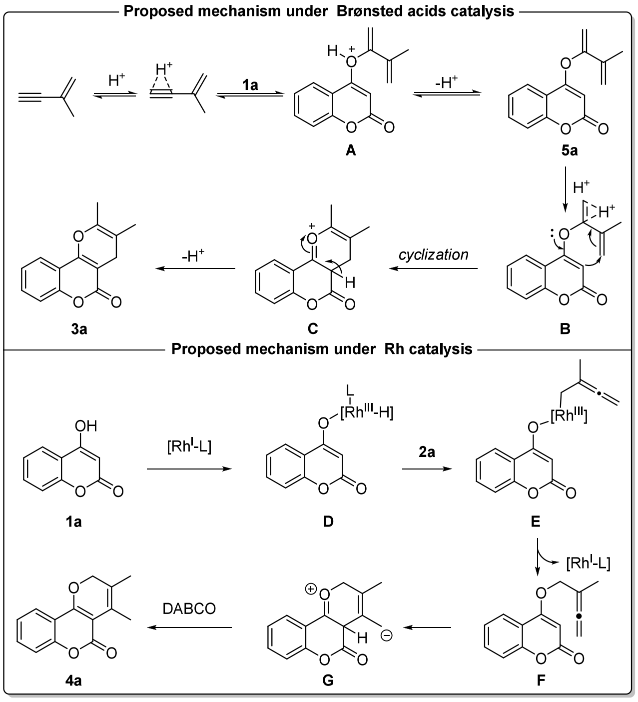


Figure 6. Proposed mechanisms.

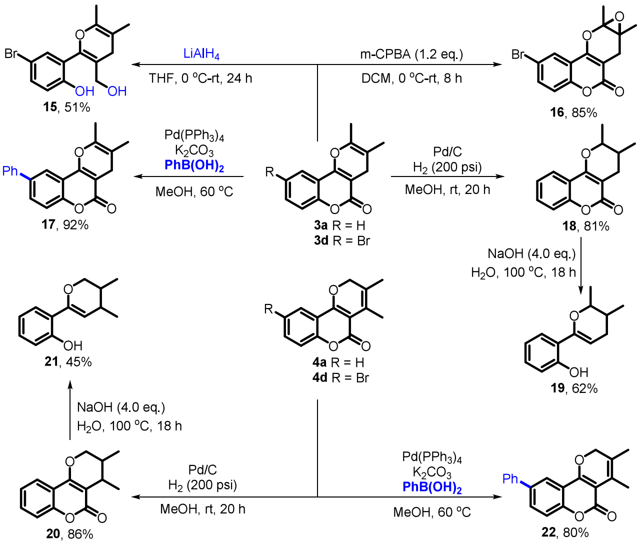


Figure 7. Synthetic utilization.

of **3d** with *m*-CPBA delivered epoxide **16** in good yield. Pd-catalyzed Suzuki coupling of **3d** provided arylated product **17** in a 92% yield. Notably, the tetrasubstituted alkenyl group of **3a** was selectively hydrogenated with Pd/C under mild conditions, affording desired product **18** in 81% yield. Subsequently, treatment of **18** with NaOH at 100 °C delivered ring-opening product **19** in moderate yield. Similarly, selective hydrogenation of **4a** furnished pyranocoumarin analogue **20** in 86% yield, and subsequent treatment with base gave phenol **21** in acceptable yield. Finally, skeleton-divergent product **4d** could be arylated with arylboronic acid to give **22** in 80% yield, thus remedying the limitations of our substrate synthesis.

In summary, we have developed an efficient method to construct skeletal-divergent pyranocoumarins through a regio-controllable 1,3-annulation of valylene with 4-hydroxycoumarins. Under acid catalysis, 1,3-alkenoxylation occurred exclusively to deliver dimethylallyl-decorated pyranocoumarins, while the adoption of Rh catalysis efficiently switched the regioselectivity to 3,1-alkenoxylation. Mechanistic studies implied that the reaction initially proceeds through a regioselective hydroalkoxylation of valylene with 4-hydroxycoumarins to form O-alkenylated or O-allenylated intermediates, followed by an intramolecular cyclization reaction. This work offers a generalizable platform for addressing selectivity challenges in reactions involving substrates with multiple reactive sites.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.6c01546.

> Experimental procedures, characterization data, NMR spectra, and X-ray crystallography data (PDF)

Accession Codes

Deposition Numbers 2516631−2516635 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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