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# Lewis acid-promoted intramolecular cyclization of *ortho*-prenylated chalcones: application to first total synthesis of ( $\pm$ ) involucrasin C and its novel analogues†

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This study presents a refinement of a synthetic protocol for the diastereoselective intramolecular ene-type cyclization of *ortho*-prenylated chalcones using ZnCl<sub>2</sub>, leading to the corresponding tertiary alcohols sans the undesired alkene by-product. While InCl<sub>3</sub>·4H<sub>2</sub>O offers the best yield, ZnCl<sub>2</sub> with slightly diminished yield provides a cheaper alternative. To assess diastereoselectivity, the prenyl group was replaced with a cinnamyl moiety, forming a third consecutive chiral center as a single diastereomer. Additionally, total synthesis of ( $\pm$ ) involucrasin C, along with the synthesis of several structurally related novel analogues, is presented in this work.

## Introduction

Natural products and their derivatives have been a pivotal source of therapeutic agents throughout history, providing a wealth of structurally diverse and biologically active compounds.<sup>1</sup> These naturally occurring substances, derived from plants, animals, and microorganisms, have played a critical role in the development of pharmaceuticals.<sup>2</sup> Their inherent biological activity and complex structures offer unique templates for the synthesis of derivatives with enhanced pharmacological properties.

The natural product featuring an indane-based scaffold is recognized for its potential as an anti-cancer agent.<sup>3–6</sup> Scaffolds with tertiary alcohol groups present in pharmaceuticals led to better metabolic stability to treat rheumatoid arthritis, influenza and spinal muscular atrophy.<sup>7</sup> Some of the compounds exhibited anti-inflammatory activity, suggesting their potential utility in modulating inflammatory pathways and contributing to therapeutic effects observed in relevant models.<sup>8</sup>

Indane-based scaffolds are often found in several classes of secondary metabolites such as polyketides, terpenes and alkaloids.<sup>9</sup> Fig. 1 displays the chemical structures of indane-based natural products, highlighting the indane scaffold, a distinguishing feature frequently observed in a wide range of secondary metabolites.<sup>10</sup> The molecules depicted include derivatives such as ( $\pm$ ) indidene A, ( $\pm$ ) involucrasin C, renifolin F, G, and H, as well as antiarones J and K. Indidene A and

involucrasin C are known to exhibit mild *in vitro* cytotoxicity towards cancer cells and anti-inflammatory properties.<sup>11–14</sup>

In 2022, Z. Yang *et al.* isolated racemic involucrasin C with a trans relative configuration from the whole plant of *Shutteria involucrata*.<sup>15</sup> Involucrasin C significantly suppressed the secretion of pro-inflammatory cytokines IL-6, TNF- $\alpha$ , and IL-1 $\beta$ , implicating these natural 2,3-dihydro-1*H*-indene derivatives as potential bioactive constituents of *S. involucrata* with early-stage anti-inflammatory effects.

For the intramolecular cyclization of *o*-cinnamyl-substituted chalcones, S. Ogoshi *et al.* reported the first example of a direct

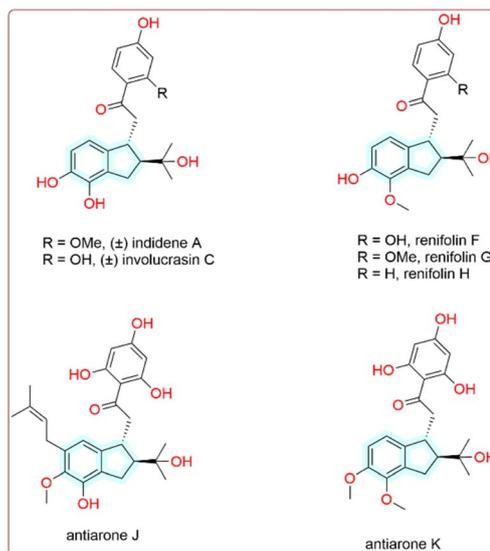


Fig. 1 Indane-based natural products.

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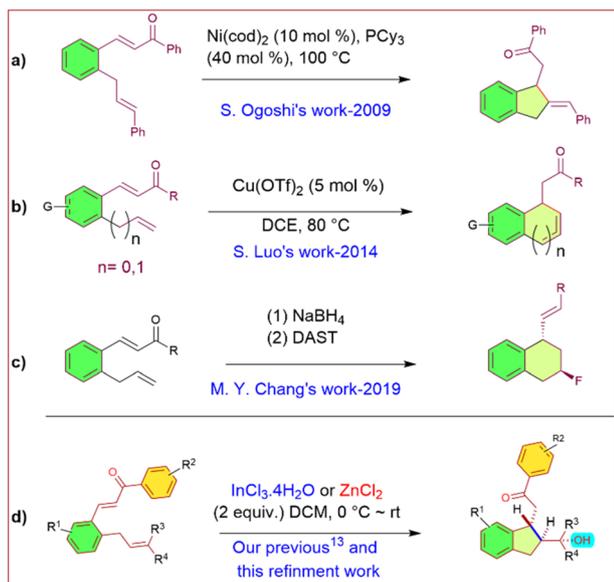


Fig. 2 Reported work (a–c) vs. current work (d).

conjugate addition of simple alkenes to enones catalyzed by a nickel(0) complex, enabling the introduction of an alkenyl group at the  $\beta$ -position of enones (Fig. 2a).<sup>16</sup> S. Luo *et al.* explored the copper(II) triflate-catalyzed intramolecular conjugate addition of simple alkenes to  $\alpha,\beta$ -unsaturated carbonyl compounds, facilitating the synthesis of five- and six-membered cyclic products (Fig. 2b).<sup>17</sup> Further advancing the field, M.-Y. Chang *et al.* developed a concise two-step protocol for the regio- and stereoselective synthesis of 3-fluorotetralines bearing two stereocenters and an E-configured styryl group, employing  $\text{NaBH}_4$ -mediated reduction of oxygenated *o*-allylchalcones followed by DAST-induced intramolecular annulation of the resulting alkenols (Fig. 2c).<sup>18</sup>

Our recent study focused on the total syntheses of renifolin F and antiarone K.<sup>13</sup> We employed *ortho*-prenylated chalcones as substrates and treated them with Lewis acids to achieve intramolecular cyclization. Among the various Lewis acids tested,  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  (1 equiv.) proved particularly effective, directly yielding the core scaffolds of these natural products along with the byproduct **2a'**. This study presents efforts to optimize the methodology for selectively obtaining the target tertiary alcohol while minimizing the formation of the alkene byproduct. We focused on the reaction parameters such as Lewis acid loading, alternative Lewis acid and solvent system to suppress competing side reaction and minimize the formation of undesired byproduct.

## Results and discussion

To optimize the reaction conditions, we selected **1a** as a model substrate, and the outcomes of the optimization experiments are illustrated in Table 1. Initially, we attempted to obtain the desired product **2a** using  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  (1 equiv.) and DCM as the

Table 1 Optimization of the reaction conditions<sup>a</sup>

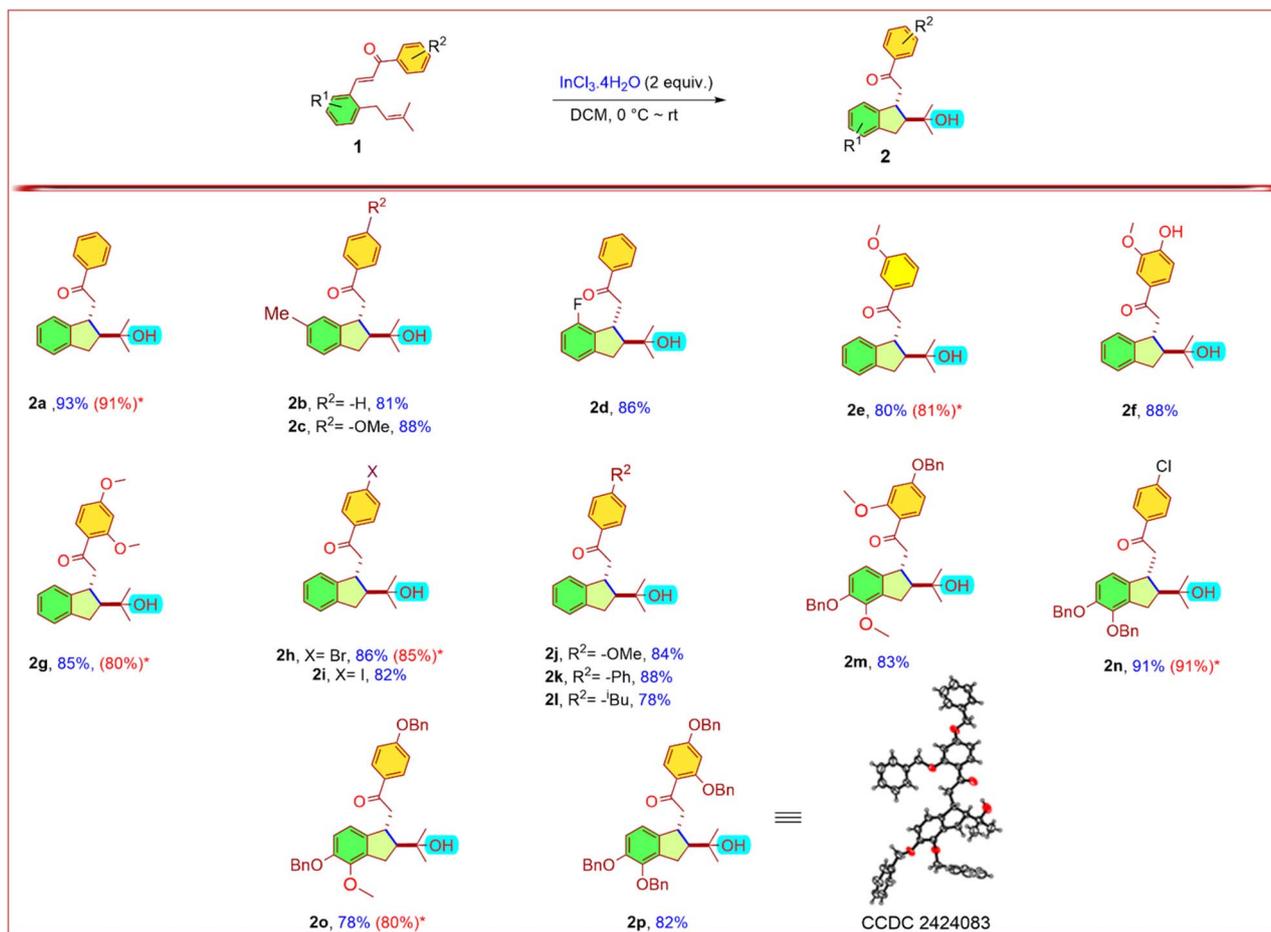
Entry	Lewis acid (equiv.)	Solvent	<b>2a</b> <sup>b</sup> (Yield %)
1	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (1)	DCM	66 & 25 <sup>c</sup>
2	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (2)	DCM	93
3	$\text{ZnCl}_2$ (2)	DCM	75
4	$\text{ZnCl}_2$ (2)	DCM : $\text{H}_2\text{O}$ (99 : 1)	90
5	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (2)	THF	Trace
6	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (2)	$\text{CH}_3\text{CN}$	ND
7	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (2)	DMF	ND
8	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (2)	Dioxane	ND
9	$\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ (2)	DCE	90
10	$\text{ZnCl}_2$ (2)	DCE : $\text{H}_2\text{O}$ (99 : 1)	82
11	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2)	THF	50 & 20 <sup>c</sup>
12	$\text{Zn}(\text{OTf})_2$ (2)	$\text{CH}_3\text{CN}$	ND
13	$\text{B}(\text{C}_6\text{F}_5)_3$ (2)	$\text{CH}_3\text{CN}$	ND

<sup>a</sup> Reaction condition: the reaction was carried out with **1a** (0.1 mmol, 1 equiv.), reagents in different solvent (3 ml), 15–24 h. <sup>b</sup> Isolated yield. <sup>c</sup> product **2a'**, ND = not detected, 0 °C ~ rt.

solvent at 0 °C to room temperature, which resulted in 66% yield of **2a**, along with 25% of **2a'** (Table 1, entry 1) in 24 h. To further enhance the yield of **2a**, we increased the Lewis acid to 2 equiv. in the same reaction conditions as before used,<sup>13</sup> we obtained our desired diastereomer **2a** in 93% yield after 15 h with no detectable **2a'** by-product. Subsequent reaction optimization involved screening various solvents, with DCM emerging as the most suitable for this reaction (Table 1, entries 1–8). We then explored alternative catalysts, replacing  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  with  $\text{ZnCl}_2$ ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{Zn}(\text{OTf})_2$ , and  $\text{B}(\text{C}_6\text{F}_5)_3$  (Table 1, entries 3, 11–13). Among them, only  $\text{ZnCl}_2$  in DCM gave the desired product with a 75% yield (Table 1, entry 3). Surprisingly, the addition of water (1 : 99) with DCM and DCE increased the yield of the desired product to 90% and 82%, respectively (Table 1, entries 4 & 10). In contrast,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (2 equiv.) in THF produced **2a** in a lower yield of 50%, along with 20% of byproduct **2a'** (Table 1, entry 11). Both  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  and  $\text{ZnCl}_2$  show comparable effectiveness in this methodology; therefore, we explored the substrate scope with both Lewis acid and synthesized several examples with each.

With the optimized reaction conditions established (Table 1, entry 2), we turned our attention to exploring the synthesis of involucrasin C derivatives by varying the substrate scope on the aromatic ring. As illustrated in Scheme 1, a variety of  $\text{R}^1$  substituents on the aromatic ring, including electron-rich (**2b**, **2c**, **2m–2p**), electron-deficient (**2d**), and electron-neutral (**2a**, **2e–2l**) groups, were efficiently converted into the desired products (**2**) under the standard conditions, achieving good to excellent yields. The reaction demonstrated broad tolerance for various

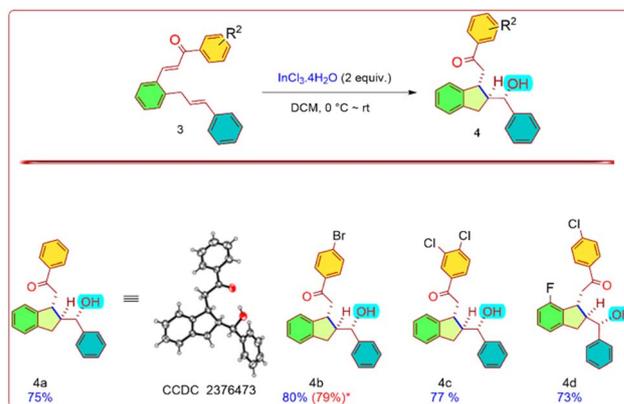




Scheme 1 Substrate scope for the synthesis of involucrasin C derivatives. Reaction conditions: the reaction was carried out with **1** (0.2 mmol, 1 equiv.),  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  (2 equiv.), DCM (6 ml) at 0 °C ~ rt for 15–24 h. \*  $\text{ZnCl}_2$  (2 equiv.), DCM :  $\text{H}_2\text{O}$  (99 : 1).

functional groups  $\text{R}^2$  on the other aromatic benzene ring. For example, methoxy-substituted derivatives (**2c**, **2e**, **2f**, **2g**, **2j**) showed high yields, indicating that electron-donating groups are well accommodated. Similarly, benzyloxy-substituted derivatives (**2m**, **2o–2p**) were produced efficiently, further underscoring the reaction's versatility. Hydroxy (**2f**) and halogen (**2h–2i**, **2n**) substituents were also well tolerated, highlighting the reliability of the reaction conditions. Additionally,  $\text{R}^2$  substituents such as phenyl and isobutyl (**2k–2l**) also afforded good to excellent yields.

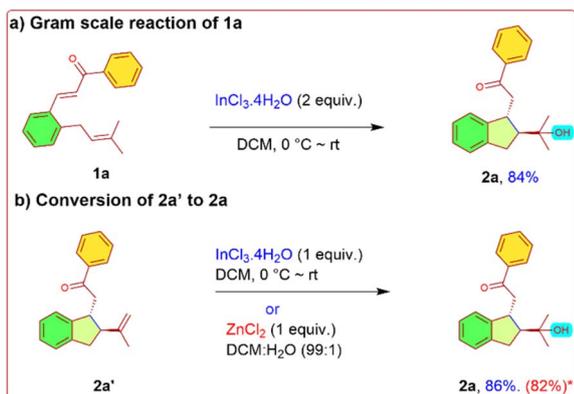
To further investigate the diastereoselectivity of our methodology, we evaluated the reaction conditions using substrate **3a**, where the two methyl groups were replaced by hydrogen and a phenyl group. Remarkably, the transformation proceeded with excellent diastereoselectivity, affording a single diastereomer under the optimized conditions. The relative configuration of compound **4a** was unambiguously determined by X-ray crystallography (Scheme 2), confirming the selective outcome. This high level of diastereocontrol suggests that the steric effects of the phenyl substituents play a crucial role in directing the reaction pathway. Notably, the methodology proved to be



Scheme 2 Substrate scope of **4**. Reaction conditions: the reaction was carried out with **3** (0.2 mmol, 1 equiv.),  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  (2 equiv.), DCM (6 ml) at 0 °C ~ rt \*  $\text{ZnCl}_2$  (2 equiv.), DCM :  $\text{H}_2\text{O}$  (99 : 1).

reliable across various substrates, delivering **4a** (75%), **4b** (80%), **4c** (77%), and **4d** (73%) in good yields while maintaining complete diastereoselectivity.

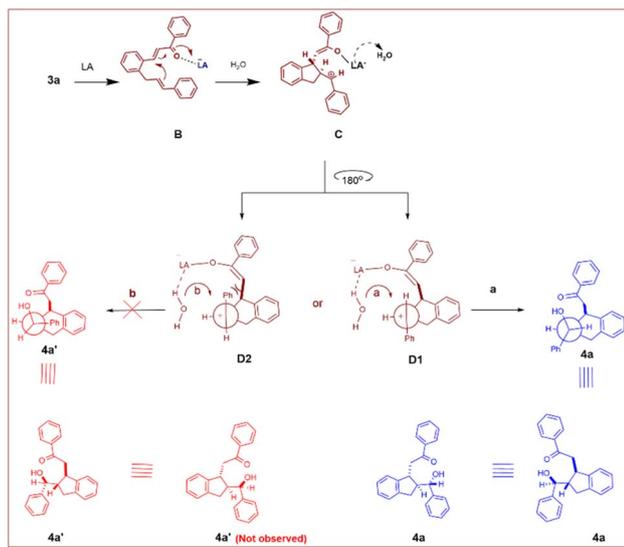




Scheme 3 Gram scale reaction, conversion of 2a' to 2a.

To demonstrate the practical applicability and significance of the established protocol, a gram-scale experiment was performed utilizing substrate **1a** (1.0 g, 3.6231 mmol) following standard reaction conditions (Scheme 3a). The desired product **2a** was isolated with a good yield of 84%. To investigate the conversion of **2a'** to **2a**, we used 1 equiv. of  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  under the same reaction conditions. The study demonstrated that the reaction progressed efficiently, leading to the formation of the expected product **2a** with an 86% yield (\*  $\text{ZnCl}_2$  (1 equiv.),  $\text{DCM} : \text{H}_2\text{O}$  (99 : 1)). This result indicates that the minor alkene product **2a'** of reaction **1a** was converted into the desired tertiary alcohol (Scheme 3b).

A plausible mechanism for intramolecular cyclization has been proposed to account for the formation of a tertiary alcohol, as depicted in Scheme 4. Initially, Lewis acid coordinates with the oxygen atom of the carbonyl group of **3a** (intermediate **B**), thereby enhancing the electrophilicity of the conjugate double

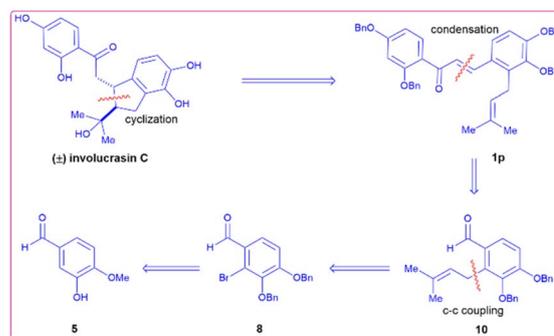
Scheme 4 Possible reaction mechanism for diastereoselective formation of **4a**.

bond to promote the attack by nucleophilic double bond and furnish intermediate **C**. Between two possible orientations of **C**, *i.e.*, **D1** and **D2**, the hydroxy group is then delivered from the less hindered side of **D1** (path a), leading to the formation of product **4a** as a single diastereomer.

## Application to first total synthesis of ( $\pm$ ) involucrasin C

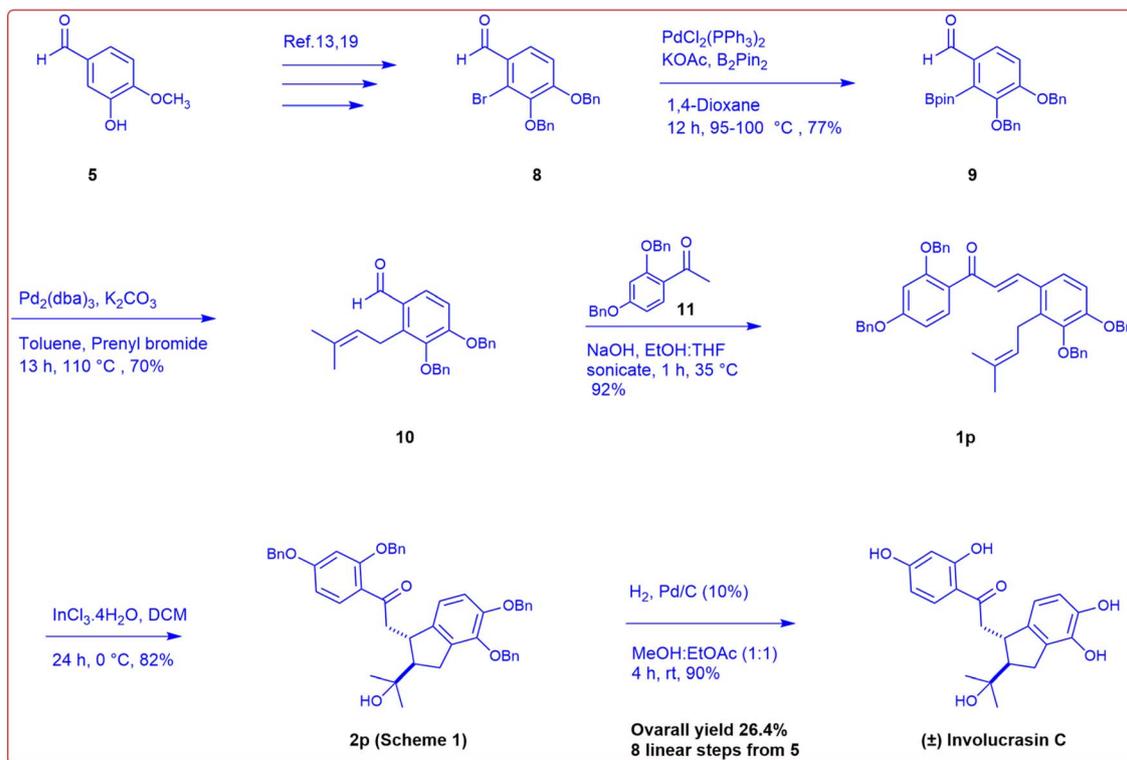
Scheme 5 outlines our retrosynthetic approach toward the total synthesis of ( $\pm$ ) involucrasin C. We envisioned that the stereoselective construction of the five-membered carbon framework bearing a tertiary alcohol (carbinol carbon) and phenolic groups could be achieved *via* an intramolecular cyclization, followed by debenzoylation of the intermediate **1p**. The key intermediate **1p** is accessible through an aldol condensation of prenylated aldehyde **10**. The latter, in turn, is derived from commercially available isovanillin **5** by a sequence of regioselective bromination, demethylation, Miyaura borylation, and Suzuki cross-coupling to install the prenyl moiety.

The first total synthesis of ( $\pm$ ) involucrasin C was accomplished in eight linear steps with an overall yield of 26%, as outlined in Scheme 6. The synthesis commenced with commercially available and inexpensive isovanillin (**5**), which underwent regioselective bromination, followed by demethylation and benzylation to afford aryl bromide **8** *via* a previously reported protocol. This intermediate set the stage for further elaboration. Pd-catalyzed Miyaura borylation of **8** furnished boronic ester **9**, which underwent Suzuki cross-coupling with prenyl bromide to deliver prenylated aldehyde **10** in 70% yield.<sup>13,19</sup> An aldol condensation between **10** and acetophenone derivative **11** proceeded efficiently under mild basic conditions to afford chalcone **1p** in 92% yield. Subsequent Lewis acid-promoted intramolecular cyclization of **1p** using  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  provided tertiary alcohol **2p** with high diastereoselectivity in 82% yield. Finally, debenzoylation of **2p** *via* catalytic hydrogenation ( $\text{H}_2$  balloon, Pd/C) furnished the natural product ( $\pm$ ) involucrasin C in 90% yield.<sup>13</sup> This concise and efficient synthetic route highlights regioselective functionalization, cross-coupling, and stereoselective cyclization to access the complex polyphenolic core of the target molecule.



Scheme 5 Retrosynthetic analysis of involucrasin C.





Scheme 6 First total synthesis of (±) involucrasin C.

## Conclusions

We have developed an  $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$  or  $\text{ZnCl}_2$ -mediated intramolecular cyclization of prenylated chalcones, enabling the efficient synthesis of natural product derivatives bearing tertiary alcohols through a practical approach. This methodology exhibits broad substrate scope, delivering moderate to high yields with excellent diastereoselectivity under mild reaction conditions. Notably, the protocol demonstrates strong functional group tolerance and is scalable to gram quantities, underscoring its synthetic utility. Furthermore, this strategy was successfully employed in the first total synthesis of (±) involucrasin C, highlighting its versatility and applicability in complex molecule construction.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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