

# Six-Step Total Synthesis of Isohirsut-4-ene through [5+2+1] Cycloaddition and Transannular Epoxide–Alkene Cyclization

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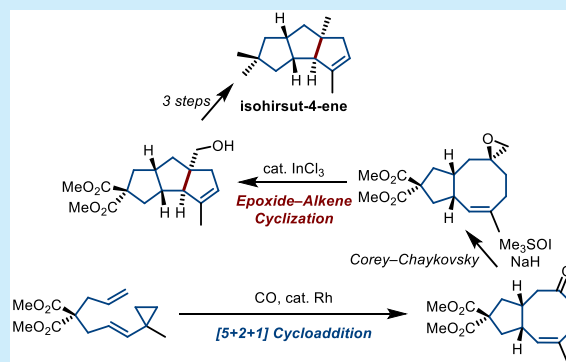


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**ABSTRACT:** A six-step total synthesis of isohirsut-4-ene with a 5/5/5 tricyclic core has been achieved. The synthesis features a Rh(I)-catalyzed [5+2+1] cycloaddition, a Corey–Chaykovsky reaction, and a transannular epoxide–alkene cyclization that afford the skeleton of the target molecule. This three-step strategy was further utilized to synthesize more 5/5/5 tricyclic analogues with one or two bridgehead quaternary centers.



Natural products of triquinanes, including linear, angular, and propellane triquinanes (Figure 1a), have been the targets of organic synthesis since the past century.<sup>1</sup> One reason is that many triquinanes (especially linear triquinanes) have significant biological activities, and the synthesis of these molecules and their analogues can pave the way for downstream biological and medicinal investigations. The second reason for this might be the compact and challenging tricyclic skeletons and different substitutions in these molecules, which promote chemists to create either new reactions or strategies for synthesis.<sup>2</sup>

Two natural products, isohirsut-1-ene and isohirsut-4-ene in Figure 1a, were isolated from engineered bacteria by the Ikeda group.<sup>3</sup> Their structures have not been confirmed by either X-ray or total synthesis, even though Tantillo<sup>4</sup> and Kutateladze<sup>5</sup> have used computational NMR data to predict their relative configuration. Therefore, total synthesis could be used to confirm their structures. Here, we report the first total synthesis of isohirsut-4-ene, which confirms the originally proposed structure of this natural product.

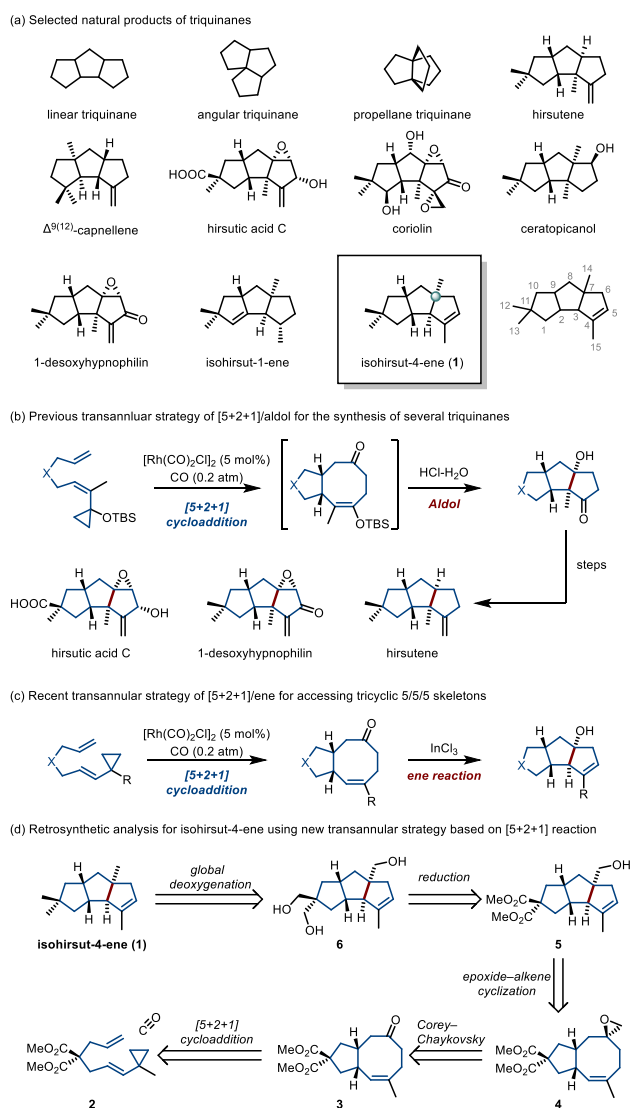
In addition to the aim described above, we were also interested in developing a general [5+2+1] reaction-based<sup>6</sup> transannular strategy for linear triquinanes with a bridgehead quaternary carbon at position C-7, like that in the natural product of isohirsut-4-ene. Previously, we have developed a [5+2+1] cycloaddition/aldol reaction strategy to achieve a linearly fused 5/5/5 tricyclic skeleton with a quaternary carbon at position C-3 (Figure 1b).<sup>7,8</sup> Several linear triquinanes such as hirsutene, hirsutic acid C, and 1-desoxyhypnophilin have been produced using this strategy.<sup>7</sup> Recently, we have also developed a [5+2+1]/ene strategy to construct linear 5/5/5 and 6/5/5 tricyclic skeletons (Figure 1c).<sup>9</sup> Unfortunately,

these two strategies are not efficient for the synthesis of isohirsut-4-ene.

Figure 1d outlines our retrosynthetic analysis of isohirsut-4-ene in racemic fashion using a new transannular strategy based on the [5+2+1] reaction. We envisioned that the product of the [5+2+1] reaction can be converted to an epoxide by the Corey–Chaykovsky reaction.<sup>10</sup> Then, Lewis acid-catalyzed epoxide–alkene cyclization, which is regarded as an ene-like or Prins-like reaction, can introduce a -CH<sub>2</sub>OH group into position C-7 of the corresponding triquinane. This -CH<sub>2</sub>OH group can then be converted to a methyl group by deoxygenation. In this synthesis, we proposed to use a gem-diester-substituted carbon (DEC) tether instead of a gem-dimethyl-substituted carbon (DMC) tether because DEC could reduce the volatility of all of the corresponding starting materials and intermediates in the synthesis, which is helpful for the purification and separation processes involved. The DEC tether can finally be converted to the DMC tether by global deoxygenation of three hydroxyl groups in **6**.

Following the retrosynthetic plan, we started our process by synthesizing the known compound **2** (Scheme 1), DEC tethered ene-vinylcyclopropane (ene-VCP),<sup>11</sup> in one step from the commercial compounds on a gram scale (7.35 g, 35% yield). Then we carried out the [5+2+1] reaction<sup>6</sup> on a 5

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**Figure 1.** (a) Selected natural products of triquinanes, two of which were obtained from engineered bacteria. (b) Previous transannular strategy for the total synthesis of several linear triquinanes. (c) Recent transannular strategy for accessing tricyclic skeletons. (d) Retrosynthetic analysis of isohirsut-4-ene.

mmol scale using the previously optimized conditions {0.2 atm of CO, 80 °C, dioxane as the solvent, 5 mol % catalyst [Rh(CO)<sub>2</sub>Cl]<sub>2</sub>}. The desired 5/8 bicyclic product **3** was obtained in 64% yield as a single diastereomer. Then, we carried out the Corey–Chaykovsky reaction under standard

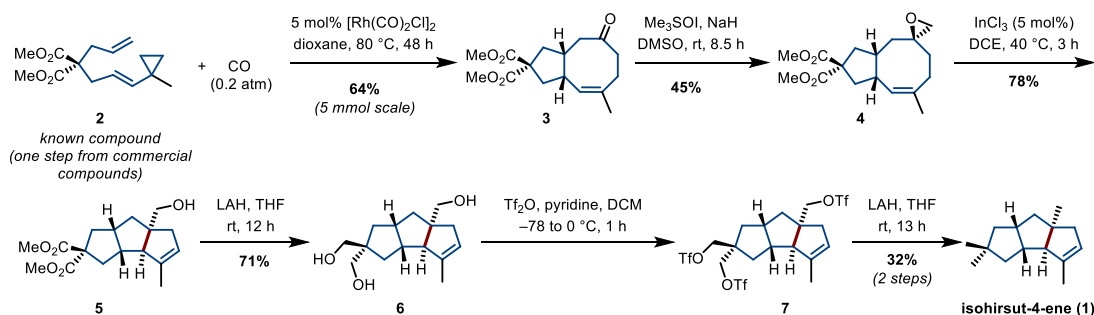
conditions (trimethylsulfoxide iodide, NaH as the base, and DMSO as the solvent), to convert **3** to epoxide **4** in 45% yield. The relative configuration of **4** was proposed on the basis of the structure of its analogue, **9a**, as confirmed by X-ray determination (see [Scheme 2](#)).

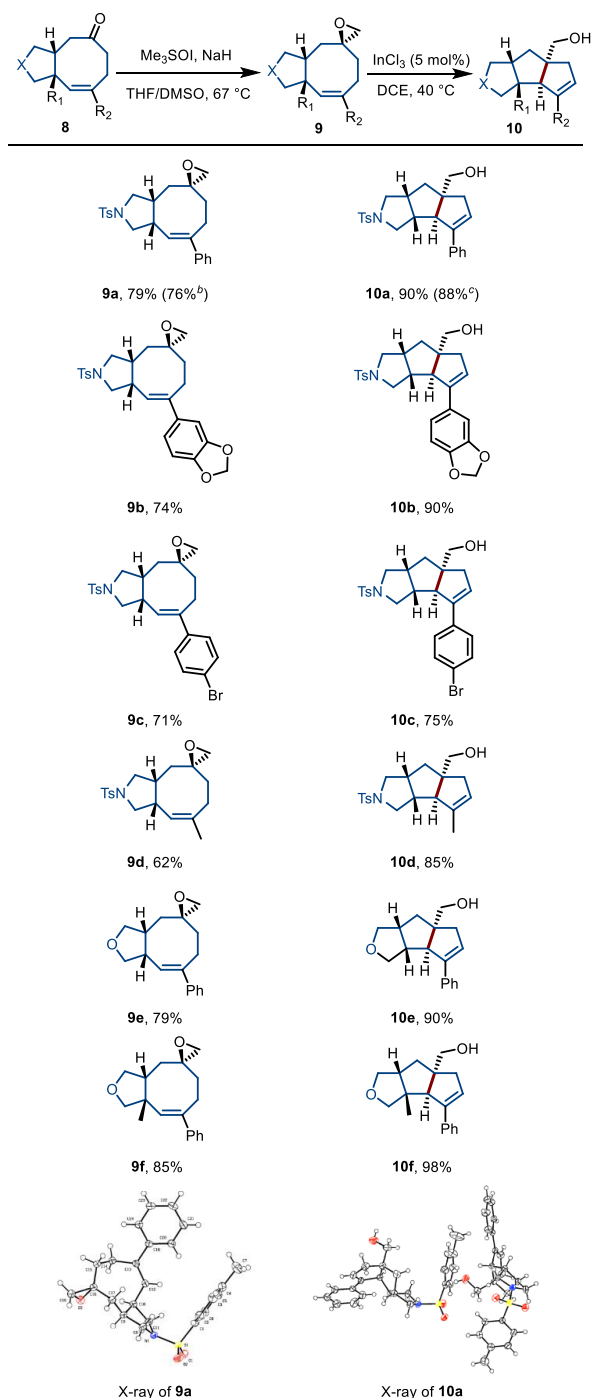
The intramolecular epoxide–alkene cyclization (including epoxide–arene reaction) dates to 1962.<sup>12</sup> To date, many Brønsted acids and Lewis acids such as *p*-toluenesulfonic acid, hydrochloric acid, BF<sub>3</sub>·Et<sub>2</sub>O, SnCl<sub>4</sub>, Bi(OTf)<sub>3</sub>, and TiCl<sub>4</sub> have been used to catalyze the intramolecular epoxide–alkene cyclization.<sup>13</sup> Most reported examples of this reaction were applied to convert chain substrates to build six-membered rings (some reactions gave [3+2] products instead).<sup>14</sup> However, to the best of our knowledge, the transannular epoxide–alkene cyclization catalyzed by a Lewis acid has never been developed. In this work, to our delight, a transannular epoxide–alkene cyclization using InCl<sub>3</sub> as the catalyst can afford 5/5/5-fused tricyclic product **5** in 78% yield (the details of the screening of the catalysts for this reaction are available in the [Supporting Information](#)). The relative configuration of **5** was proposed on the basis of its analogue, **10a**, as confirmed by X-ray diffraction (XRD) analysis (see this in [Scheme 2](#) and DFT rationalization in the [Supporting Information](#)).

Compound **5** can be reduced by LiAlH<sub>4</sub> (LAH) to deliver a triol product **6** in 71% yield. Then, we turned our attention to the deoxygenation of triol. Because deoxygenation through radical processes<sup>15</sup> is difficult for primary alcohols, nucleophilic deoxygenations, which typically employ a metal hydride reagent, such as lithium aluminum hydride, to reduce an activated derivative of the alcohol (halide or sulfonate ester), are expected to be more practical.<sup>16</sup> Initially, we converted the triol into methanesulfonate esters using MsCl and pyridine as the base. Then, we treated the resulting oil with LAH. To our disappointment, no desired product but the triol was reproduced, indicating that LAH attacked sulfur atoms of the reactant.<sup>17</sup> Considering that trifluoro-methanesulfonate ester is a better leaving group than methanesulfonate ester, we decided to convert the triol compound into trifluoro-methanesulfonate ester **7** for further investigation.<sup>18</sup> Gratifyingly, with LAH, all three hydroxyl groups in **7** were reduced and the desired product **1** (isohirsut-4-ene) was obtained in an overall yield of 32% in two steps. Synthetic compound **1** had NMR spectral data that were fully consistent with those reported in the literature<sup>3</sup> (see the [Supporting Information](#) for comparison). Therefore, we achieved a six-step total synthesis of isohirsut-4-ene in racemic fashion from the known compound **2**.

Encouraged by the success described above, we further extended this strategy to synthesize other analogues of linear triquinane ([Scheme 2](#)). The [5+2+1] products used were

### Scheme 1. Total Synthesis of Isohirsut-4-ene



Scheme 2. Synthesis of 5/5/5 Tricyclic Molecules<sup>a</sup>

<sup>a</sup>See the Supporting Information for the detailed reaction conditions. Substrate amounts were 0.05–0.2 mmol, and the reported yields represent an average of the yields of the isolated products from two runs. The XRD experiments demonstrated the relative configurations of **9a** and **10a**. <sup>b</sup>On a 1.8 mmol scale. <sup>c</sup>On a 1.2 mmol scale.

those we previously reported.<sup>9</sup> To our delight, the Corey–Chaykovsky reaction worked well for all of these [5+2+1] products, affording the desired epoxides **9** in moderate to good yields (62–85%). The high diastereoselectivity of this reaction is attributed to the smaller ring strain of the eight-membered ring in the corresponding transition states (detailed DFT discussions are given in the Supporting Information). We then tested the  $\text{InCl}_3$ -catalyzed epoxide–alkene cyclization for these

epoxides (Scheme 2). We found that all substituted alkenes with an *N*-tosyl group as the tether gave the corresponding products in good yields (75–98%). The relative configuration of **10a** was proven by the XRD experiment. It is important to point out that substrate **9f** can give **10f** in 98% yield, which has a crucial methyl group at position C-2. These syntheses here further demonstrate the generality of this three-step strategy for constructing a 5/5/5 tricyclic core with one or two quaternary carbons at the bridgehead positions. DFT calculations showed that the transannular epoxide–alkene cyclization occurs through a stepwise mechanism, but the transition state of cyclization, which leads to the *cis*–*ant**cis* configuration of triquinanes, is much preferred; thus, this epoxide–alkene cyclization achieves high stereoselectivity (see the Supporting Information for a discussion). In addition, epoxidation and epoxide–alkene cyclization can be carried out on a >1 mmol scale (see Scheme 2).

In conclusion, the first total synthesis of isohirsut-4-ene has been accomplished by us in six steps from the known ene-VCP substrate **4**. Rh(I)-catalyzed [5+2+1] cycloaddition, Corey–Chaykovsky reaction, and intramolecular epoxide–alkene cyclization were utilized as key reactions. This transannular strategy provides a new way to synthesize linear triquinanes with a bridgehead quaternary center at position C-7. Constructing 5/5/5 tricyclic systems in such a way would have great potential in the synthesis of other natural products and analogues, and this work is ongoing in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c04383>.

DFT study, experimental procedures, characterization data, and crystallographic data for all new compounds (PDF)

### Accession Codes

CCDC 2130262–2130263 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Author Contributions

§J.L. and Y.Z. contributed equally to this work.

## Notes

The authors declare no competing financial interest.

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