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Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization

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ABSTRACT: A gold-catalyzed cyclization of 1-propargyl-1,2,3,4-tetrahydro-β-carboline led to formation the D-ring of strictamine. Functional group modifications of the resulting tetracyclic indolenine led to the formal total synthesis of (±)-strictamine.

Akuammiline alkaloids (Figure 1) are monoterpene indole alkaloids bearing a cage-like structure and a broad range of biological activities, including anticancer, antibacterial, anti-inflammatory, and antimalarial inhibitory activities.1 Strictamine (1) was first isolated by Ganguli et al. in 1966 from Rhazya stricta, used as a folk medicine in India,2 and was seen as a pharmaceutical resource due to its potent inhibition of monoamine oxidase(s).1a The unique pentacyclic cage-like structure of strictamine has attracted the attention of many synthetic chemists, and much effort has been expended seeking a total synthesis;3 however, its total synthesis has not been disclosed until quite recently.4,5 This is mainly due to the difficulty of forming the C7–C16 bond for construction of the central D-ring and the construction of the E-ring, which induces a disfavored boat–boat conformation of C/E rings.

Scheme 1. Our Concept for Construction of the D-Ring of Strictamine Based on Gold(I)-Catalyzed Cyclization

Our group is engaged in developing gold-catalyzed cascade cyclizations of alkynes for construction of indole-derived polycyclic heterocycles.8 For example, we have developed a fused carbazole synthesis based on the intramolecular cascade cyclization reaction of aniline bearing a diyne moiety (Scheme 1, eq 1).8ac This reaction proceeds through 5-endo-dig hydroami-
nation to form an indole ring, followed by 6-endo-dig hydroarylation from the C3 position of the indole ring. More recently, we reported construction of a tetracyclic indoline ring through formation of a 3-allenylindole intermediate by migration of a propargyl group on the nitrogen atom of an aniline, followed by second and third cyclizations (eq 2).8d In these reactions, gold-catalysts efficiently promote nucleophilic attack of the indole ring on a carbon–carbon multiple bond to facilitate the second ring closure. On the basis of this chemistry, we expected that gold-catalyzed cyclization at the indole C3 position of 1-propargyl-THBC derivatives would allow efficient construction of the D-ring of akuamidine alkaloids including strictamine (1) (eq 3). It should be noted that a related approach based on a gold catalyzed 6-endo-dig cyclization of 1-homopropargyl-THBC was recently reported by Wang et al.9 This reaction requires N-silylation for selective cyclization at the C3 position of indole. This contribution and the recent achievements by Garg4 and Zhu5 prompted us to report our study on the formal total synthesis of (±)-strictamine by gold-catalyzed cyclization.

Our retrosynthetic analysis of strictamine (1) is outlined in Scheme 2. Strictamine can be obtained from tryptamine (9) by construction of the E-ring using a reductive Heck-type reaction10 according to Zhu’s protocol,5 in addition to formation of the methyl ester moiety. The iodobutenyl group of 6 can be easily introduced to the nitrogen atom of 7, which is the expected product of the aforementioned gold-catalyzed cyclization reaction. The cyclization precursor, 1-propargyl-THBC derivative 8, will be readily prepared from tryptamine (9).

### Scheme 2. Retrosynthetic Analysis of Strictamine (1)

![Diagram](image)

Synthesis of the cyclization precursor of type 8 is shown in Scheme 3. Following the procedure documented in the literature,11 the known 1-propargyl-THBC derivative 12 was prepared from tryptamine (9) via formylation with HCO2Et, cyclization with POCl3, and addition of Grignard reagent 11. Tosylation and desilylation of 12 afforded propargyl-THBC derivative 13. Hydroxymethylation of the terminal alkyne of 13 and protecting group modifications afforded cyclization precursors 8a and 8b, bearing a tosyl or nosyl protecting group, respectively.

We then investigated the gold-catalyzed cyclization of propargyl THBC derivatives. Fortunately, treatment of the tosylmide 8a, having an unprotected hydroxymethyl group with XPhosAuCl (cat. 16)12 possessing a bulky electron-donating ligand in the presence of AgNTf2 in 1,2-dichloroethane (DCE) gave the desired compound 7a in 20% yield (entry 1). Improvement in yield was observed by use of IPrAuCl (cat. 17)13 and JohnPhosAu(MeCN)SbF6 (cat. 18)14 (33–35%, entries 2 and 3). Screening of the reaction solvents revealed that THF (52%, entry 4) and EtOH (50%, entry 5) are more suitable for the reaction. Among the catalysts examined, a combination of SPhosAuCl (cat. 19)15 and AgNTf2 showed the most efficient activity (69%, entry 6). Use of the nosylmide 8b as the substrate slightly improved the yield to 76% (entry 7).

### Scheme 3. Synthesis of the Cyclization Precursors

![Diagram](image)

### Table 1. Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
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<tbody>
<tr>
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<td>cat. 16/AgNTf2</td>
<td>DCE †</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
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<td>8a</td>
<td>cat. 17/AgNTf2</td>
<td>DCE †</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>cat. 18</td>
<td>DCE †</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
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<td>8a</td>
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<td>20</td>
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<tr>
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<td>EtOH</td>
<td>4</td>
<td>50</td>
</tr>
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<td>6</td>
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<td>EtOH</td>
<td>5</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>8b</td>
<td>cat. 19/AgNTf2</td>
<td>EtOH</td>
<td>14</td>
<td>76</td>
</tr>
</tbody>
</table>

†DCE = 1,2-dichloroethane. †Isolated yield.

The formal total synthesis of (±)-strictamine is shown in Scheme 4. An iodobutenyl group was introduced using 21 after protection of the terminal hydroxyl group and removal of the
Ns group to give substrate 6a for the Heck-type reaction. Unfortunately, all our attempts at construction of the E-ring using 6a have been unsuccessful. For example, treatment of 6a with Pd(OAc)2, PPh3, n-Bu4NCl, and K2CO3 in DMF gave a complex mixture of unidentified products without promoting the desired cyclization. Thus, we decided to prepare the enoate-type cyclization precursor 26. Conversion of the N-protecting group17 of 20 from Ns to Boc to give 23, removal of the silyl group, two-step oxidation of the primary alcohol, and esterification of the resulting carboxylic acid gave the enoate 25. Finally, removal of the Boc group and iodobutenylation of the amino group led to the desired enoate 26, which is Zhu's strictamine precursor.5 The spectral data of 26 were in good agreement with those reported.5

Scheme 4. Formal Total Synthesis of (±)-Strictamine

In summary, we succeeded in the formal total synthesis of (±)-strictamine, an akuammiline alkaloid possessing a cage-like structure. Starting from tryptamine, tetracyclic indolenines bearing the A-D ring system were synthesized based on gold-catalyzed cyclization of 1-propargyl-1,2,3,4-tetrahydro-β-carbol ine derivatives. Further studies on asymmetric total synthesis of strictamine including optimization of protecting group strategy are now under way in our laboratory.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and characterization data for all new compounds (PDF)

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Notes
The authors declare no competing financial interest.

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REFERENCES


(17) Conversion of the nitrogen protecting groups (Ts, Ns, and Boc) was necessary because (1) hydroxymethylation of Ns derivative with HCHO was less efficient than that of the Ts derivative 13, (2) deprotection of Ns group was unsuccessful after construction of the enoate moiety, and (3) as our first choice, the replacement of Ns group in 20 with Boc group was safer than direct replacement with an iodobutyl group, considering the later oxidative treatment. For optimization of our synthesis, a Boc-based synthesis or conversion of 6a to 26 should be examined. Fortunately, our preliminary investigation has revealed that the gold-catalyzed cyclization of N-Boc substrate 8c (for Boc-based synthesis) gave the desired product in 41% yield (not optimized, see graphic).