Construction of a fully substituted cyclopentenone as the core skeleton of stemonamide via a Nazarov cyclization

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Graphical Abstract

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Abstract
A synthetic study of the Stemona alkaloid stemonamide is described. The FeCl\(_3\)-promoted fast Nazarov reaction of \(\beta\)-alkoxy divinyl ketones in the presence of \(t\)-BuOH afforded an \(\alpha\)-methylene cyclopentenone, which was subsequently subjected to the Rh-catalyzed C-H amination to provide a fully appropriately substituted \(\alpha\)-methylene cyclopentenone as the core skeleton of stemonamide.

Key Words
Natural Product, Stemona Alkaloid, Nazarov Reaction, C-H amination, Synthetic Study

The Stemona alkaloids are a class of polycyclic alkaloids containing the pyrrolo[1,2-\(a\)]azepine nucleus. Derived from Stemonaaceae plants, they have long been used in traditional Chinese and Japanese folk medicine for cough relief medication and in anthelmintics.\(^1\) Although numerous analogues have been isolated from these plants,\(^2\) difficulty in purifying the crude extracts has prevented more extensive study of the compounds’ individual bioactivities. Stemonamide (1) is one example of this class of alkaloids, isolated from the roots of the Stemona japonica by Xu in 1994.\(^3\) It has a tetracyclic structure with a fully substituted core cyclopentenone bearing two spiro five-membered heterocycles (Figure 1). While several groups have succeeded in achieving the total synthesis of racemic stemonamide (1) using an \(N\)-acyliminium approach\(^4\) and a radical cascade reaction\(^5\) as the key steps, respectively, much larger amounts of these alkaloids in pure form are required for use in medicinal chemistry and drug development. Therefore a more efficient synthetic methodology would be highly desirable.
Recently, we developed the acid-catalyzed fast Nazarov cyclization using β-alkoxy divinyl ketones derived from torquoselective olefination via ynolates (Scheme 1)\textsuperscript{6,7} and have also achieved the enantioselective Nazarov reaction catalyzed by a chiral Lewis acid.\textsuperscript{8} It was anticipated that the cyclization products of this reaction, the α-alkoxy cyclopentenones, would lead to the cyclopentenone core structure in stemonamide (1). Herein, we report the synthesis of a fully appropriately substituted cyclopentenone, which can be regarded as the core structure of stemonamide (1), via a modified Nazarov reaction.

![Stemonamide (1).](image)

**Figure 1.** Stemonamide (1).

As shown in our synthetic strategy (Scheme 2), the target core structure 2 is the fully substituted α-exo-methylene cyclopentenone bearing a quaternary center at C-9a. We envisioned making the carbon-nitrogen bond at the C-9a position (stemonamide numbering) via the intramolecular C-H bond amination of the carbamate 3. The fully substituted cyclopentenone 3 would be constructed by our modified Nazarov reaction.\textsuperscript{9} The precursor, the β-alkoxy divinyl ketone 4, would be prepared by the torquoselective olefination of the ester 7.

**Scheme 1.** Acid-catalyzed fast Nazarov reaction of β-alkoxy divinyl ketones.
Scheme 2. Synthetic strategy of the core structure of stemonamide (2).

The divinyl ketones 4 were prepared as shown in Scheme 3. The ester 7a,10 protected by a TBDPS group at the terminal alcohol, reacted with the ynolate 6,11 prepared from the α,α-dibromo ester and s-BuLi, at room temperature to give the tetrasubstituted olefin 5a with excellent E-selectivity.12 The carboxylic acid in 5a was converted into the Weinreb amide 8a (R = TBDPS),13 and the amides 8b-8e (R = TBS, TMS, MOM, and Me) were prepared from 8a. The next alkenylation was found to be highly dependent on the steric hindrance of the terminal protecting group, even though it is far from the reaction center. The alkenyllithium 9,14 prepared from the corresponding bromide and t-BuLi, reacted with 8a and 8b to afford the divinyl ketones 4a and 4b in low yield. Although 8c gave 4c in better yield, 8d did not work well, possibly due to the steric hindrance of the MOM-lithium complex. The methyl ether 8e (R = Me) provided the corresponding divinyl ketone 4e in satisfactory yield.


With the divinyl ketones 4e and 4c in hand, we next examined the Nazarov reaction with Sc(OTf)3.
as the catalyst. Previously, we have shown that the Nazarov reaction generates a small amount of $\alpha$-exo-methylene products (12) along with the major $\alpha$-alkoxy product (11). In the present case, however, since the $\alpha$-exo-methylene compounds (e.g., 12) are the desired products, an alkoxide (RO') must act as a base, deprotonating the $\beta$-proton (route b in Scheme 4), rather than as a nucleophile, attacking the $\alpha$-cation (route a) in the cyclopentadienyl cation intermediates 10. For the selective synthesis of the $\alpha$-exo-methylene compounds, the nucleophilicity of the alkoxide should be diminished by steric hindrance. Since the intermolecular migration of the alkoxide has been proven by our previous studies, a sterically hindered alcohol as an additive would lead to route b (elimination) rather than route a (addition).

![Scheme 4](image)

**Scheme 4.** Two kinds of products via the Nazarov reaction.

Based on this concept, the Nazarov reaction of 4e was attempted using Sc(OTf)$_3$ and t-BuOH as additives (Table 1). As expected, the $\alpha$-exo-methylene product 13e was generated in the presence of 1.0 equiv of t-BuOH and 0.1 equiv of Sc(OTf)$_3$ albeit in low yield (entry 1). While increasing the equivalents of t-BuOH enhanced the yield of 13e, up to 70%, the catalyst also had to be increased to complete the reaction (entries 2 and 3).

![Table 1](image)

**Table 1** Nazarov cyclization of the $\beta$-alkoxy divinyl ketone (4e).

<table>
<thead>
<tr>
<th>entry</th>
<th>Sc(OTf)$_3$</th>
<th>t-BuOH</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1</td>
<td>1.0</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>3.0</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>10</td>
<td>70</td>
</tr>
</tbody>
</table>

$a$ The ratios were determined by the $^1$H-NMR of the mixture of 13e and 14.
For a more selective formation of 13e, the ethoxy group at the β-position in 4e should be less nucleophilic; for preparation on a larger scale, a less expensive Lewis acid should be used. Screening results revealed that a combination of the β-isopropoxy divinyl ketone 18e and the inexpensive FeCl₃ afforded the completely selective formation of 13e in good yield. As shown in Scheme 5, the isopropyl ester 15a was olefinated via the ynolate 6 to give a carboxylate, which was subsequently esterificated to give 16a in good yield. After conversion to the Weinreb amide 17a and replacement of the TBDPS group with a methyl group at the terminal position, alkenylation provided the divinyl ketone 18e, which was subjected to the Nazarov reaction in the presence of 1.0 equiv of FeCl₃ in CH₂Cl₂/t-BuOH (1:1) to furnish the α-exo-methylene compound 13e with excellent selectivity.

Scheme 5. Preparation of the cyclopentenone 13e via the Nazarov cyclization of the β-isopropoxy divinyl ketone 18e.

Next, we examined the C-H amination by a carbamate to form the fully substituted cyclopentenone. The α-exo-methylene moiety was protected by a phenylthio group, before removal of the TBS group by 6 M HCl. Formation of the carbamate with trichloroacetyl isocyanate afforded the precursor 3e after deprotection at the α-exo-methylene moiety with Oxone®. The carbamate 3e, when subjected to
rhodium(II) acetate-catalyzed C-H amination at the β-methine position, proceeded smoothly to afford the desired spirocyclic compound 2e in excellent yield. However, demethylation at the terminal methoxy moiety was unsuccessful (Scheme 6).

Since it was found that the deprotection of the methoxy moiety must be carried out at an earlier stage, the TBS and methoxy groups were successively deprotected in good yield by 6 M HCl and then AlCl₃/Bu₄NI (TBAI), in which the product 19, iodinated at the exo-β-position, was isolated. This primary diol 19 was selectively protected with TIPSCl at the less hindered site to give the alcohol 20 after elimination of iodide with basic alumina. The alcohol 20 was converted into the carbamate 3g (R = TIPS), which was submitted to the rhodium(II) acetate-catalyzed C-H amination; however, it did not work at all, probably due to “remote” steric hindrance. Therefore, we prepared the substrates bearing several kinds of different protecting groups at the terminal position (Scheme 7).
Scheme 7. Preparation of 3.

The results of the C-H amination are summarized in Table 2. Although the TMS- and Ms- protected substrates (3i, 3j) did not give 2 (entries 3 and 4), the amination reactions of 3f (R = H) and 3h (R = Ac) successfully afforded the spirocyclic products 2f and 2h in high yield respectively (entries 2 and 5).

Table 2  Synthesis of the A-ring of stemonamide (1) via C-H amination.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>3</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIPS</td>
<td>3g</td>
<td>125</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>3f</td>
<td>80</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>3i</td>
<td>25</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ms</td>
<td>3j</td>
<td>125</td>
<td>1&lt;5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>3h</td>
<td>125</td>
<td>0.6</td>
<td>80</td>
</tr>
</tbody>
</table>

In conclusion, we have synthesized the core skeleton of stemonamide (1) via the Nazarov reaction, in which a new method for the selective synthesis of the α-exo-methylene cyclopentenones from β-alkoxy divinyl ketones has been developed. The spirocyclic products 2 have a fully substituted
cyclopentenone bearing appropriate functionality for stemonamide (1) and thus would be a potential precursor for its total synthesis. Furthermore, this study demonstrates the synthetic utility of the torquoselective olefination via ynolates as well as the Nazarov reaction.

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References and notes
7 For a review on torquoselective olefination, see: Shindo, M; Mori, S. Synlett, 2008, 2231.
8 Yaji, K.; Shindo, M. Synlett 2009, 2524.
10 The ester 7a was prepared from 1,5-pentanediol by a four-step sequence: (a) NaH, TBDPSCl; THF, room temperature; (b) (COCl)2, DMSO, Et3N; CH2Cl2, -78 °C to room temperature; (c) NaClO2, NaH2PO4; t-BuOH/THF/2-methyl-2-butene (3:1:1), H2O, room temperature; (d) EtBr, K2CO3; DMF, room temperature (78% yield).
11 For a review on ynolates, see: Shindo, M. Tetrahedron 2007, 63, 10.
The alkenyl bromide 9 was prepared from 2-butyn-1-ol in two steps, as follows: (1) Cp₂TiCl₂ (cat.), ℯ-BuMgCl; Et₂O, room temperature; then (BrCF₂)$_2$; THF, room temperature; (2) TBSCl, imidazole, DMAP; CH₂Cl₂, room temperature (57% yield).

An ester having a methoxy group at the terminal position in place of TBDPSO gave the olefinated product in low yield. The reason for this is not clear.


Procedure for the synthesis of 13e: To a solution of 18e (986 mg, 2.47 mmol) in 14 mL of CH₂Cl₂/t-BuOH (1:1), under argon, was added anhydrous FeCl₃ (401 mg, 2.47 mmol). After 3 min at room temperature, the mixture was quenched by saturated aqueous NaHCO₃, and extracted with CH₂Cl₂. The organic extracts were washed with saturated aqueous NaHCO₃ and brine, and dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel (5%-7% EtOAc/hexane) to give 13e (593.9 mg, 71%) as a yellow oil.

1H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.52-1.68 (m, 4H), 1.79 (d, J = 1.6 Hz, 3H), 2.40-2.49 (m, 1H), 2.52-2.61 (m, 1H), 3.30-3.37 (m, 1H), 3.30 (s, 3H), 3.39 (t, J = 6.4 Hz, 2H), 3.70-3.74 (m, 1H), 3.78-3.82 (m, 1H), 5.42 (s, 1H), 6.06 (t, J = 1.6 Hz, 1H); 13C NMR (100 MHz, CDCl₃) δ -5.88, -5.84, 8.10, 17.8, 23.8, 25.5, 28.3, 29.4, 46.6, 58.3, 63.8, 72.0, 114.8, 138.8, 144.0, 168.1, 195.7; IR (neat) 2930, 1697, 1119, 484.2 cm⁻¹; MS (FAB) m/z 339 (M⁺+H); HRMS (FAB) m/z calcd for C₁₉H₃₅O₃Si (M⁺+H): 339.2355, found: 339.2360.


2h. 1H NMR (600 MHz, CDCl₃) δ 1.60-1.77 (m, 4H), 1.87 (s, 3H), 2.06 (s, 3H), 2.40-2.47 (m, 1H), 2.48-2.62 (m, 1H), 4.06-4.15 (m, 2H), 4.37 (dd, J = 13.8 Hz, 9.0 Hz, 2H), 5.71 (bs, 1H), 5.72 (s, 1H), 6.25 (s, 1H); 13C NMR (150 MHz, CDCl₃) δ 8.74, 20.9, 24.9, 25.7, 28.9, 63.5, 64.6, 73.5, 117.5, 142.4, 146.2, 158.6, 163.2, 171.2, 192.4; IR (neat) 3306, 2956, 2926, 1770, 1732, 1715, 1248, 1038, 468.7 cm⁻¹; MS (ESI) m/z 316 (M⁺+Na); HRMS (FAB) m/z calcd for C₁₅H₂₀O₂N (M⁺+H): 294.1341, found: 294.1343.