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

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ABSTRACT

A synthetic study of the *Stemona* alkaloid stemonamide is described. The $FeCl_3$-promoted fast Nazarov reaction of β-alkoxy divinyl ketones in the presence of *t*-BuOH afforded an α-methylene cyclopentenone, which was subsequently subjected to the Rh-catalyzed C–H amination to provide a fully appropriately substituted α-methylene cyclopentenone as the core skeleton of stemonamide.

The *Stemona* alkaloids are a class of polycyclic alkaloids containing the pyrrolo[1,2-*a*]azepine nucleus. Derived from *Stemonaceae* plants, they have long been used in traditional Chinese and Japanese folk medicine for cough relief medication and in anthelmintics.[1] Although numerous analogs have been isolated from these plants,[2] difficulty in purifying the crude extracts has prevented a 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 (Fig. 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)[6,7] and have also achieved the enantioselective Nazarov reaction catalyzed by a chiral Lewis acid.[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.

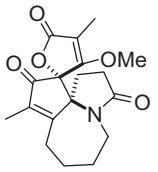

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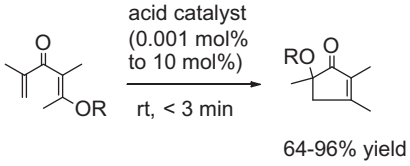
Figure 1. Stemonamide (**1**).



Scheme 1. Acid-catalyzed fast Nazarov reaction of β-alkoxy divinyl ketones.

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

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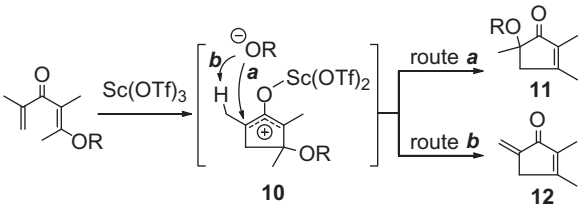
our modified Nazarov reaction.[9] The precursor, the β-alkoxy divinyl ketone **4**, would be prepared by the torquoselective olefination of the ester **7**.

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**–**e** (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 α-*exo*-methylene products (**12**) along with the major α-alkoxy product (**11**).[6,8] In the present case, however, since the α-*exo*-methylene compounds (e.g., **12**) are the desired products, an alkoxide (RO^-) must act as a base, deprotonating the β-proton (route ***b*** in Scheme 4), rather than as a nucleophile, attacking the α-cation (route ***a***) in the cyclopentadienyl cation intermediates **10**. For the selective synthesis of the α-*exo*-methylene compounds, the nucleophilicity of the alkoxide should be diminished by steric hindrance. Since the *inter*molecular migration of the alkoxide has been proven by our previous studies,[6] a sterically hindered alcohol as an additive would lead to route ***b*** (elimination) rather than route ***a*** (addition).

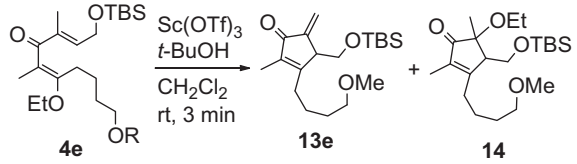
Based on this concept, the Nazarov reaction of **4e** was attempted using $Sc(OTf)_3$ and *t*-BuOH as additives (Table 1). As expected, the α-*exo*-methylene product **13e** was generated in the presence of 1.0 equiv of *t*-BuOH and 0.1 equiv of $Sc(OTf)_3$ albeit in low yield (entry 1). While increasing 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).

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 $FeCl_3$ 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.[15] After conversion to the Wein-



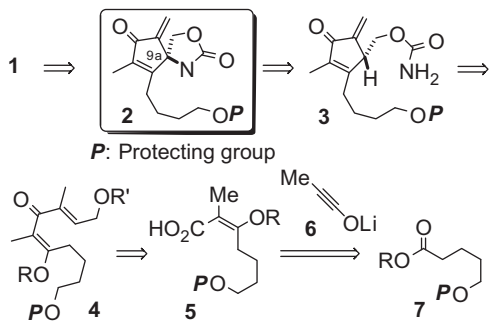
Scheme 4. Two kinds of products via the Nazarov reaction.

Table 1
Nazarov cyclization of the β-alkoxy divinyl ketone (**4e**)

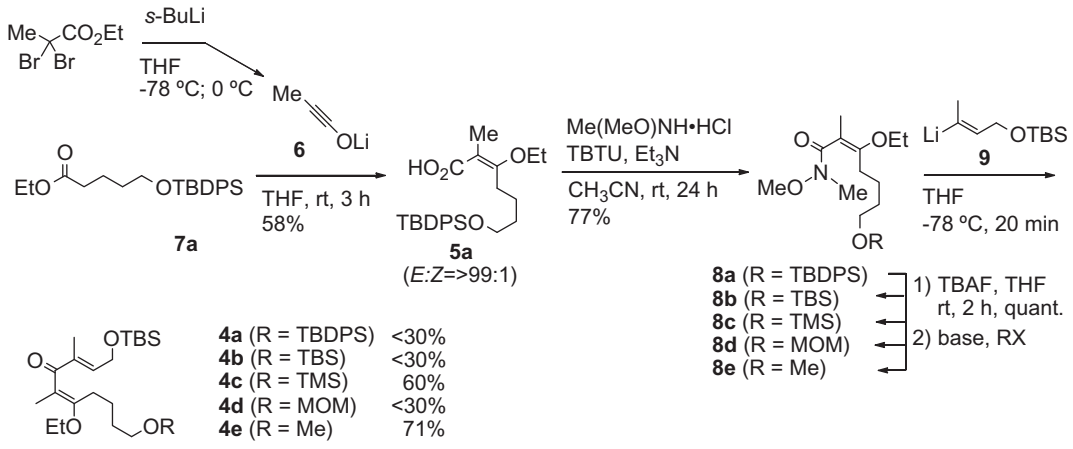


Entry	Equivalents		Yield[a] (%)	
	$Sc(OTf)_3$	*t*-BuOH	**13e**	**14**
1	0.1	1.0	23	37
2	0.5	3.0	48	22
3	1.0	10	70	6

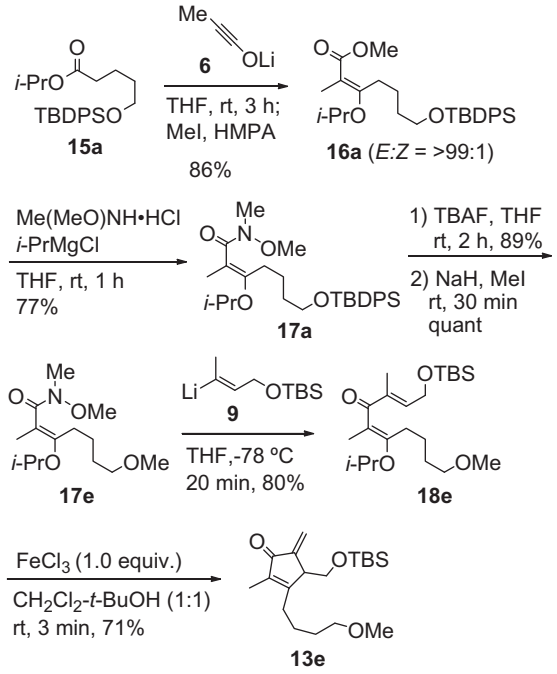
[a] The ratios were determined by the ^1H NMR of the mixture of **13e** and **14**.



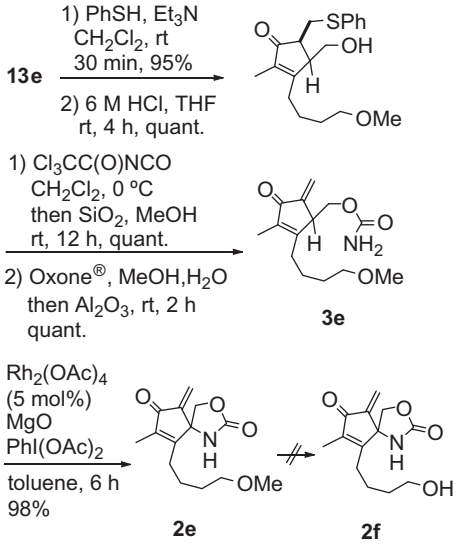
Scheme 2. Synthetic strategy of the core structure of stemonamide (**2**).



Scheme 3. Preparation of the β-alkoxy divinyl ketones **4**.



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



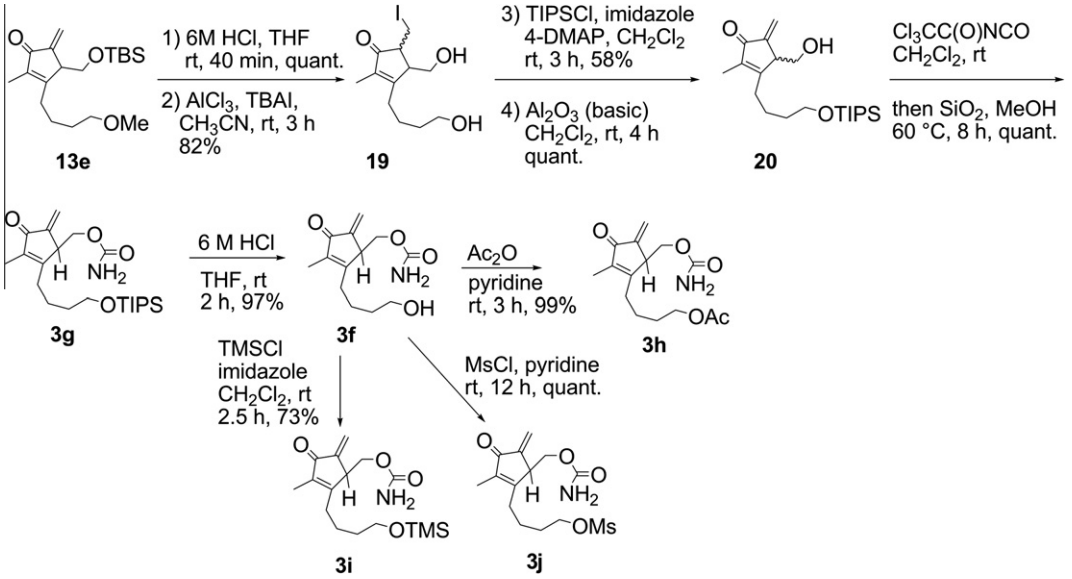
Scheme 6. Preparation of the spirocyclic carbamate **2** via C–H amination.

reb amide **17a**[16] 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 $FeCl_3$ in CH_2Cl_2/*t*-BuOH (1:1) to furnish the α-*exo*-methylene compound **13e** with excellent selectivity.[17]

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 the 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[18] 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).

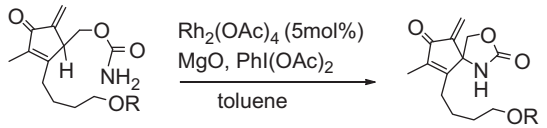
Since it was found that the deprotection of the methoxy moiety must be carried out at an earlier stage, the TBS and methoxy groups were successively deprotected in good yield by 6 M HCl and then $AlCl_3$/Bu_4NI (TBAI),[19] in which the product **19**, iodinated at the *exo*-β-position, was isolated. 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).

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



Scheme 7. Preparation of **3**.

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



3 **2**

Entry	R	**3**	Temp (°C)	Time (h)	Yield (%)
1	TIPS	**3g**	125	6	0
2	H	**3f**	80	3	80
3	TMS	**3i**	25	1	0
4	Ms	**3j**	125	1	<5
5	Ac	**3h**	125	0.6	80

3h (R = Ac) successfully afforded the spirocyclic products **2f** and **2h**[20] in high yields, respectively (entries 2 and 5).

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.

Acknowledgments

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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, Et_3N; CH_2Cl_2, −78 °C to room temperature; (c) $NaClO_2$, NaH_2PO_4; *t*-BuOH/THF/2-methyl-2-butene (3:1:1), H_2O, room temperature; (d) EtBr, K_2CO_3; DMF, room temperature (78% yield).
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14. The alkenyl bromide **9** was prepared from 2-butyn-1-ol in two steps, as follows: (1) Cp_2TiCl_2 (cat.), *i*-BuMgCl; Et_2O, room temperature; then $(BrCF_2)_2$; THF, room temperature; (2) TBSCl, imidazole, DMAP; CH_2Cl_2, room temperature (57% yield).
15. 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.
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17. Procedure for the synthesis of **13e**: To a solution of **18e** (986 mg, 2.47 mmol) in 14 mL of CH_2Cl_2/*t*-BuOH (1:1), under argon, was added anhydrous $FeCl_3$ (401 mg, 2.47 mmol). After 3 min at room temperature, the mixture was quenched by saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$, 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{35}O_3Si$ (M^++H): 339.2355, found: 339.2360.
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20. Compound **2h**: ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{15}H_{20}O_5N$ (M^++H): 294.1341, found: 294.1343.