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COMMUNICATION

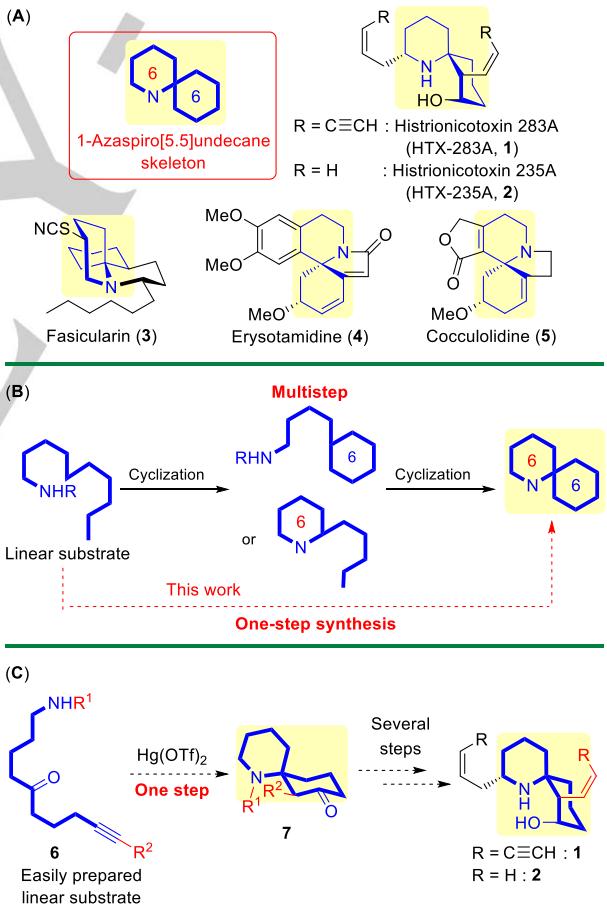
One-Step Synthesis of the 1-Azaspiro[5.5]undecane Skeleton Characteristic of Histrionicotoxin Alkaloids from Linear Substrates via $Hg(OTf)_2$-Catalyzed Cycloisomerization

Kunihiro Matsumura,[a] Keisuke Nishikawa,*[a] Hiroaki Yoshida,[a] Toshiki Niwa,[a] Yuichiro Fushii,[a] Matsumi Doe,[a] and Yoshiki Morimoto*[a]

Abstract: Histrionicotoxin (HTX) alkaloids isolated from the poison arrow frogs possess a unique structure characterized by a 1-azaspiro[5.5]undecane skeleton common to the HTX family. The unique molecular architecture of HTXs and the interest as potential target drugs have prompted synthetic chemists to promote the total synthesis so far. However, all of the synthetic strategies to access the 1-azaspiro[5.5]undecane framework of HTXs take multistep from linear starting materials due to stepwise construction of either six-membered carbo- or azacycle. Herein, we report the direct one-step construction of the 1-azaspiro[5.5]undecane skeleton from linear amino ynone substrates bearing an *N*-methoxycarbonyl group utilizing our mercuric triflate ($Hg(OTf)_2$)-catalyzed cycloisomerization reaction. The utility of this novel methodology was demonstrated by the total and formal syntheses of HTX-235A and HTX-283A, respectively, from the azaspirocycle.

Many spirocyclic natural products have been isolated from a range of organisms, including marine sponges and ascidians, plants, and poison frogs. Owing to their particular functionalities and inherent three dimensional chemical space, spiro rings have attracted increasing interest in targeted drug discovery.[1] Of these natural products, we focused on azaspiro compounds, in particular histrionicotoxin 283A (HTX-283A, **1**, Scheme 1A), which was isolated from the poison arrow frog *Dendrobates histrionicus* and structurally characterized in 1971 by Witkop et al.[2] Compound **1** is a neurotoxin that noncompetitively inhibits the nicotinic acetylcholine receptor. Structurally, **1** is composed of two enyne side chains and a 1-azaspiro[5.5]undecane ring common to the histrionicotoxin alkaloid family consisting of many analogues with different side chains like histrionicotoxin 235A (HTX-235A, **2**).[3] The 1-azaspiro[5.5]undecane framework is the core skeleton not only of histrionicotoxin alkaloids, but also of many other alkaloids such as fasicularin (**3**),[4] erysotamidine (**4**),[5] and cocculolidine (**5**).[6]

The molecular architecture of histrionicotoxins has attracted considerable attention from synthetic chemists, and a number of relevant synthetic studies have been published to date.[7] However, all of the synthetic strategies to access the 1-azaspiro[5.5]undecane framework of histrionicotoxins take multistep from linear starting materials because of stepwise construction of either six-membered carbo- or azacycle (Scheme 1B). Therefore, we tried to challenge a one-step synthesis that involved direct construction of the desired azaspirocycle from a linear substrate. In this contribution, we report the diastereoselective construction of the 1-azaspiro[5.5]undecane skeleton **7** common to histrionicotoxins in one step from linear amino ynone substrate **6** utilizing a $Hg(OTf)_2$-catalyzed cycloisomerization reaction and the total and formal syntheses of HTX-235A (**2**) and HTX-283A (**1**), respectively, from the spirocycle **7** (Scheme 1C).



Scheme 1. (**A**) Chemical structures of some natural products having the 1-azaspiro[5.5]undecane skeleton, (**B**) a one-step synthesis of the spirocycle, and (**C**) our synthetic strategy for histrionicotoxin alkaloids.

Previously, we have reported a $Hg(OTf)_2$-catalyzed cycloisomerization reaction of linear amino ynone substrates into 1-azaspiro[4.5]decane skeletons in one step.[8] For example, the

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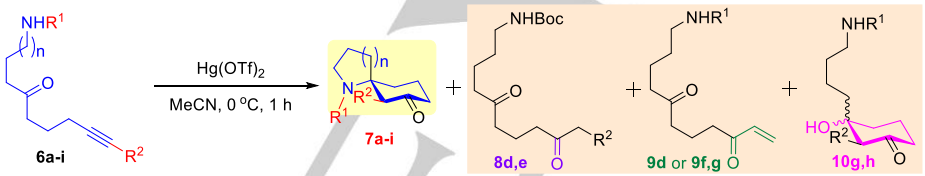
cycloisomerization reaction of linear substrates **6a-c** (n = 1) afforded azaspirocycles **7a-c** in good yield (74–93%) (entries 1–3 in Table 1), respectively, and this cyclization was found to be applicable to the total synthesis of complex natural products such as lepadiformine alkaloids and tetrodotoxin analogues.[8] Therefore, we simply thought that the reaction could also proceed similarly for homologous cyclization precursor **6d** (n = 2).[9] Disappointingly, when the same conditions as those in entries 1–3 were subjected to homologous **6d**, the reaction did not afford any spirocycle **7d** but instead only two by-products, diketone **8d** which was hydrated at the alkyne moiety and α,β-unsaturated ketone **9d**, along with the starting material **6d** (entry 4). Increasing the catalyst loading to 20 mol % prevented the recovery of **6d** but still yielded **8d** and **9d** (entry 5). According to Nishizawa et al., the $Hg(OTf)_2$-*N*,*N*,*N*',*N*'-tetramethylurea (TMU) complex is a highly effective catalyst under very mild conditions.[10] Although TMU was added to the solution, the result was similar to that in entries 4 and 5 (entry 6). The cyclization of **6e** with a sterically less crowded hydrogen in the R^2 group and **6f** with an *N*-tosyl group did not provide the desired azaspirocycles as well (entries 7 and 8).

The mechanism of the cycloisomerization we propose is shown for **6d** in Scheme 2.[8] The aminoketal intermediate **I** is formed via 6-*exo*-dig intramolecular oxymercuration to the π-electrons of the alkyne, followed by the nucleophilic addition of the nitrogen function. Through a Petasis-Ferrier-type reaction, the protonation of **I** to yield the iminium ion intermediate **II** and subsequent nucleophilic addition of a mercuric enolate to the iminium carbon would construct the desired spirocycle **7d** regenerating the catalyst (path a). Why is not the spirocycle **7d** (n = 2) formed, though spirocycles **7a-c** (n = 1) are easily formed? In the similar *N*-acyliminium ion spirocyclization, Kibayashi et al. have suggested that the spirocyclization preferentially occurs via the intermediacy of five-membered ring *N*-acyliminium ions rather than via the six-membered ring analogue such as **II**,[11] because the LUMO energy of five-membered ring *N*-acyliminium ions with exocyclic amide carbonyl groups is lower than that of six-membered ring analogues.[12] Thus, the less electrophilic reactivity of the six-membered ring *N*-acyliminium ion **II** would inhibit the cyclization to **7d**. Therefore, exogeneous H_2O contaminant reacts with the iminium ion moiety in **II**, yielding the diketone intermediate **III** which would be led to the unwanted diketone **8d** and α,β-unsaturated ketone **9d** (path b). The factors of the unsuccessful cycloisomerization to **7d** could be related to steric bulkiness of an *N*-Boc group as well as the aforementioned less electrophilic reactivity of six-membered ring *N*-acyliminium ion **II**. Therefore, we replaced the *N*-protecting group by a sterically smaller methoxycarbonyl group than a Boc group.

Table 1. Cycloisomerization of linear substrates **6a-i**.



Entry	R^1, R^2	$Hg(OTf)_2$ (mol %)	n	Yield (%)[a]				
				7	8	9	10	6
1[b]	R^1 = Boc, R^2 = H (**a**)	5	1	74 (**7a**)	–	–	–	10 (**6a**)
2[c]	R^1 = Boc, R^2 = $CH_2OTBDPS$ (**b**)	3	1	82 (**7b**)	–	–	–	–
3[c]	R^1 = Boc, R^2 = $CH_2CH_2OTBDPS$ (**c**)	3	1	93 (**7c**)	–	–	–	–
4	R^1 = Boc, R^2 = $CH_2OTBDPS$ (**d**)	5	2	–	5 (**8d**)	35 (**9d**)	–	45 (**6d**)
5	R^1 = Boc, R^2 = $CH_2OTBDPS$ (**d**)	20	2	–	15 (**8d**)	62 (**9d**)	–	–
6[d]	R^1 = Boc, R^2 = $CH_2OTBDPS$ (**d**)	20	2	–	34 (**8d**)	13 (**9d**)	–	–
7[e]	R^1 = Boc, R^2 = H (**e**)	20	2	–	36 (**8e**)	–	–	–
8	R^1 = Ts, R^2 = $CH_2OTBDPS$ (**f**)	20	2	–	–	19 (**9f**)	–	–
9	R^1 = CO_2Me, R^2 = $CH_2OTBDPS$ (**g**)	20	2	34 (**7g**)	–	39 (**9g**)	11 (**10g**)[f]	–
10	R^1 = CO_2Me, R^2 = $CH_2CH_2OTBDPS$ (**h**)	20	2	33 (**7h**)	–	–	26 (**10h**)[g]	–
11	R^1 = CO_2Me, R^2 = H (**i**)	20	2	32 (**7i**)	–	–	–	–

[a] Isolated yield. [b] Cited from refs [8a,b]. [c] Cited from ref. [8c]. [d] TMU (0.6 equiv) as the additive was added to the solution. [e] Complex mixture. [f] Equatorial alcohol. For diastereoselectivity to give **10g**, see the Supporting Information (SI). [g] Axial alcohol. For diastereoselectivity to give **10h**, see the SI.

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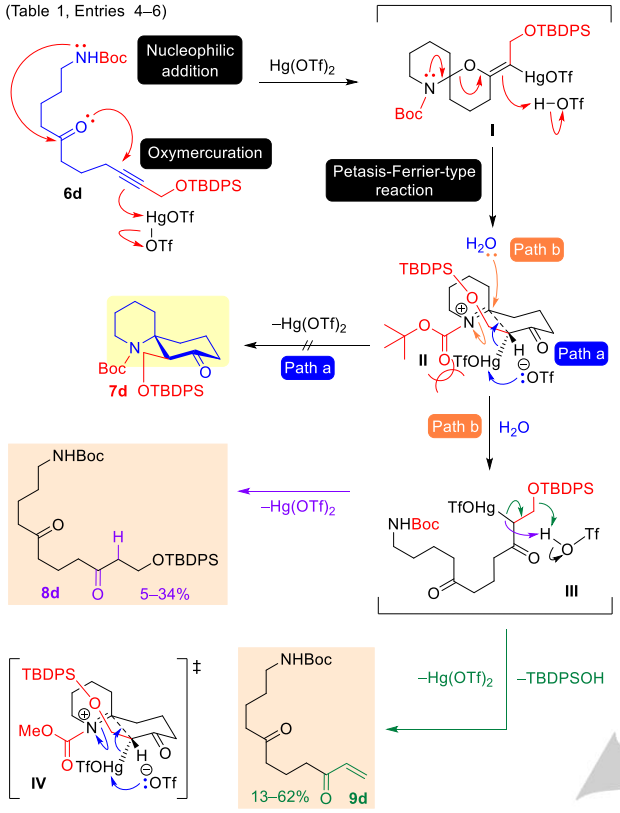
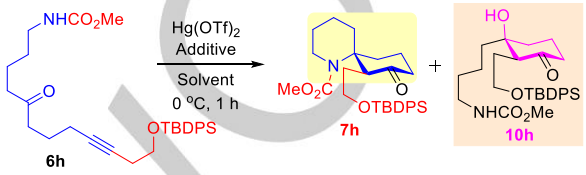


Scheme 2. Proposed mechanism for the cycloisomerization of ynone **6d**.

Fortunately, the cyclization of **6g** led to the desired spirocyclic product **7g** (34%),[9] but also afforded α,β-unsaturated ketone **9g** as the major by-product (39%) as well as cyclohexanol **10g** (11%) (Table 1, entry 9).[9] Considering the chair-like transition states of the iminium ion intermediate, the desired molecule **7g** would be diastereoselectively obtained through the more stable transition state **IV** (Scheme 2) without steric repulsion.[13] To prevent formation of unwanted α,β-unsaturated ketone, we increased the number of methylene units in the R^2 group, obtaining ynone **6h**. Cycloisomerization of **6h** afforded the desired spirocycle **7h**, but did not improve its low yield (33%) (entry 10). Furthermore, ynone **6i** with a hydrogen atom in the R^2 group afforded only the spirocyclic product **7i** (32%) (entry 11).

We then optimized the cycloisomerization reaction of the linear substrate **6h** (Table 2). When the catalyst loading was decreased to 5 mol %, the yield of the desired **7h** decreased to 18% (entries 1 and 2). Among the various solvents examined at 0 °C, MeCN was a solvent of choice (entries 1, 3, and 4). To check its effect, H_2O was added to the reaction solution. As expected, the H_2O-contaminated solution yielded only cyclohexanol **10h** (67%) (entry 5). The $Hg(OTf)_2$-TMU complex also led to **10h** (52%) (entry 6). Thus, to ensure dry conditions, 3Å molecular sieves (MS3A) were added to the reaction mixture, but the reaction gave a complex mixture (entry 7).[14] Encouragingly, adding MS5A significantly improved the **7h** yield to 61% (entry 8).[15] We examined the amount of MS5A, and it was found that approximately 500 wt% is better. When the reaction scales were increased to 82 mg, 235 mg, and 454 mg without additives, the **7h** yield increased to 36%, 54%, and 64%, respectively (Table 3). We presumed that incresing the reaction scale improves the **7h** yield because the effect of exogenous H_2O in the reaction system relatively lowers. Thus, the direct one-step construction of the 1-azaspiro[5.5]undecane skeleton in histrionicotoxins from a linear substrate has been achieved.

Table 2. Cycloisomerization of linear substrate **6h**.



Entry	$Hg(OTf)_2$ (mol %)	Additive	Solvent	Yield (%)[a]	
				7h	**10h**
1	20	–	MeCN	33	26
2	5	–	MeCN	18	52
3	20	–	Toluene	–	56
4	20	–	$MeNO_2$	19	40
5	20	H_2O (100 mol %)	$MeNO_2$	–	67
6	20	TMU (0.6 equiv)	MeCN	Trace	52
7[b]	20	MS3A (100 wt%)	MeCN	–	–
8	20	MS5A (511 wt%)	MeCN	61	10

[a] Isolated yield. [b] Complex mixture.

Table 3. Cycloisomerization of linear substrate **6h**[a]

Entry	$Hg(OTf)_2$ (mol %)	Additive	Scale (mg)	Solvent	Yield (%)[b]	
					7h	**10h**
1	20	–	40	MeCN	33	26
2	20	–	82	MeCN	36	24
3	20	–	235	MeCN	54	13
4	20	–	454	MeCN	64	7

[a] The reaction in Table 3 is the same as that in Table 2. [b] Isolated yield.

Having developed our $Hg(OTf)_2$-catalyzed cycloisomerization, we embarked on the total synthesis of histrionicotoxin alkaloids

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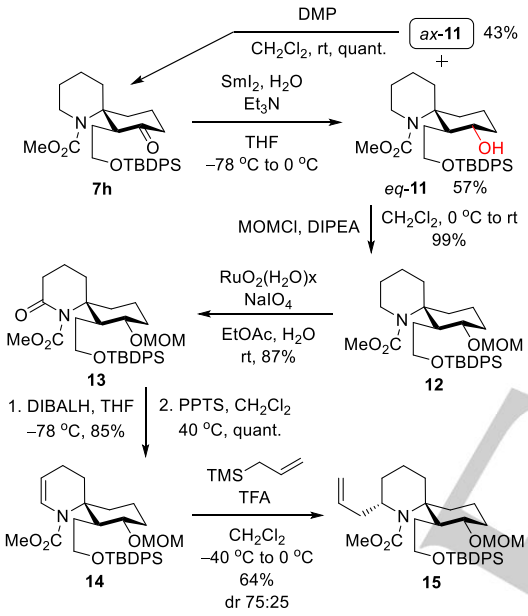
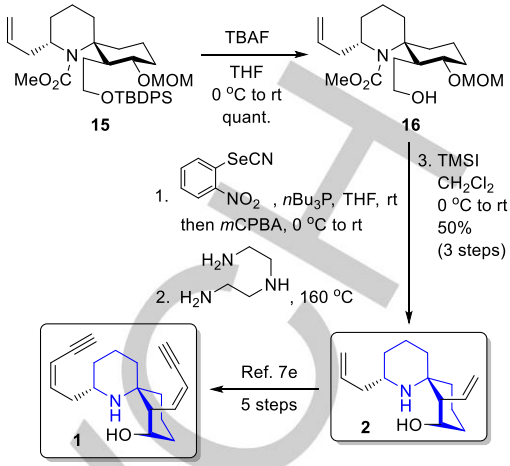
(Scheme 3). The single-electron reduction of **7h** utilizing SmI_2 in the presence of H_2O and triethylamine gave the desired equatorial alcohol *eq*-**11** (57%) as a major diastereomer, along with the axial alcohol *ax*-**11** (43%).[16] Compound *ax*-**11** was returned to **7h** by Dess-Martin periodinane (DMP) oxidation and re-submitted to the SmI_2-mediated reduction.[17] After methoxymethyl (MOM) acetal protection of the hydroxyl group in *eq*-**11**, piperidine **12** was oxidized by ruthenium tetroxide, giving lactam **13**.[18] After reducing the lactam carbonyl moiety in **13** using diisobutylaluminum hydride (DIBALH), the resulting aldehyde was treated under acidic conditions, giving ene-carbamate **14** in quantitative yield. The allylation of **14** with allyltrimethylsilane and trifluoroacetic acid (TFA) afforded allylpiperidine **15** in dr 75:25.[19] The two diastereomers were easily separated by silica gel column chromatography.



Scheme 3. Synthesis of allylpiperidine **15**

Scheme 4 outlines the synthesis of HTX-235A (**2**) from synthesized **15**. The *tert*-butyldiphenylsilyl group in **15** was deprotected with tetrabutylammonium fluoride (TBAF), yielding alcohol **16**. After constructing a vinylic group by Nishizawa-Grieco elimination,[7e,20] the methoxycarbonyl group was removed by the diethylenetriamine-mediated cleavage reaction reported by Ohshima et al.[21] The deprotection of the MOM group provided the natural product **2**. The ^{1}H- and ^{13}C-NMR data for synthetic **2** were consistent with those of the previously synthesized authentic sample.[7e] Tokuyama et al. have reported that compound **2** can be transformed to HTX-283A (**1**);[7e] therefore, this synthesis also means the formal one of **1**.

In conclusion, we have developed a novel methodology for the direct one-step synthesis of the 1-azaspiro[5.5]undecane skeleton common to histrionicotoxin alkaloids from linear substrates bearing an *N*-methoxycarbonyl group. The key reaction proceeds via our $Hg(OTf)_2$-catalyzed cycloisomerization. The utility of the methodology was demonstrated by the total



Scheme 4. Total synthesis of histrionicotoxin alkaloids.

synthesis of HTX-235A. Application of the methodology to other HTX analogues and natural products is under investigation in our laboratory.

Experimental Section

Experimental procedures, spectroscopic data, copies of ^{1}H- and ^{13}C-NMR spectra, and crystallographic data are available in the SI.

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Keywords: alkaloids • cyclization • diastereoselectivity • spiro compounds • total synthesis

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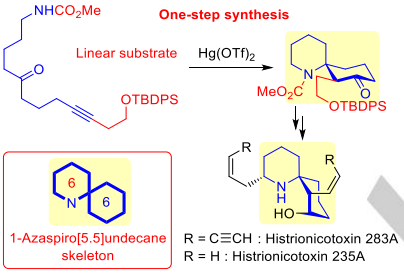
COMMUNICATION

A one-step synthesis of the 1-azaspiro[5.5]undecane skeleton in histrionicotoxin alkaloids from a linear substrate was realized utilizing a $Hg(OTf)_2$-catalyzed cycloisomerization reaction. Histrionicotoxin alkaloids as potential target drugs were successfully synthesized via our developed cyclization.



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