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Synthesis of the Tricyclic Core in Stemonamine Alkaloids via One-Pot Gold(I)-Catalyzed Cyclization and Schmidt Rearrangement: Formal Synthesis of (±)-Stemonamine

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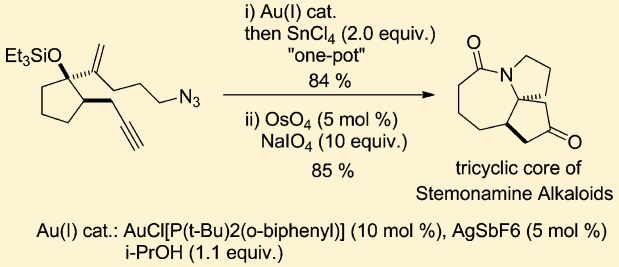
Supporting Information

ABSTRACT: An efficient synthesis of the tricyclic cyclopenta[1,2-*b*]pyrrolo[1,2-*a*]azepine nucleus of stemonamine alkaloids is reported. The key reaction utilizes a one-pot gold(I)-catalyzed cyclization and $SnCl_4$-mediated Schmidt rearrangement. Notably, the phosphine ligand had a crucial effect on the gold(I)-catalyzed cyclization. As an application of this new methodology, the formal synthesis of (±)-stemonamine has been accomplished.



INTRODUCTION

The *Stemona* alkaloids have been used in folk medicine in East Asia for treatment of respiratory diseases. According to the substructures of the pyrrolo[1,2-*a*]azepine nucleus, the *Stemona* alkaloids are structurally divided into eight subgroups.[1] Among them, the stemonamine group alkaloids possessing a tricyclic cyclopenta[1,2-*b*]pyrrolo[1,2-*a*]azepine core represent a significant synthetic challenge (Figure 1).

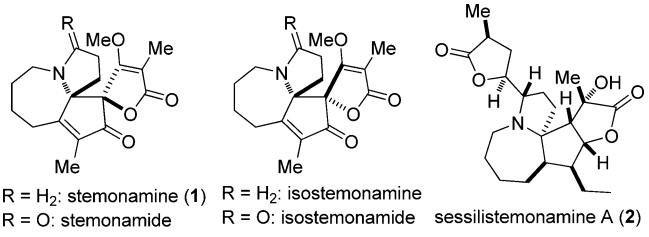


Figure 1. Examples of the stemonamine group alkaloids.

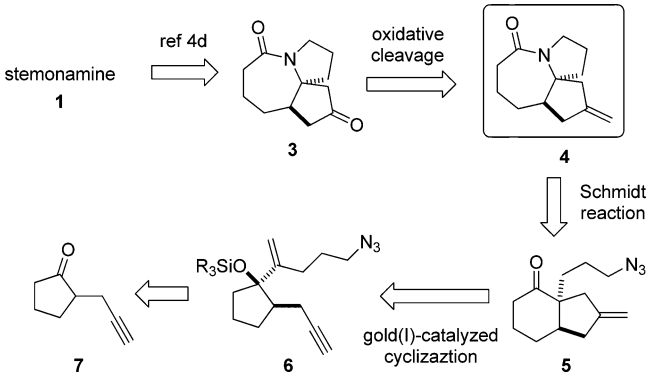
Stemonamine **1**, a representative alkaloid, was isolated from *Stemona japonica* Miq. in 1973.[2] With the discovery of stemonamine **1**, a structural analogue, isostemonamine, was simultaneously discovered,[2] and sessilistemonamine A **2**, a structurally more complicated natural product, was recently isolated.[3]

Because of the unique structure and the potential biological activities, the stemonamine alkaloids have attracted synthetic chemists.[4,5] Over the past decade, several syntheses of (±)-stemonamine **1** have been reported. Many of these reactions rely on the use of the Schmidt rearrangement as a key transformation. For example, Tu and co-workers revealed the first total synthesis of (±)-stemonamine **1** via $TiCl_4$-promoted tandem semipinacol rearrangement/Schmidt reaction.[4a] Later, Taniguchi and Ishibashi reported a total synthesis of (±)-stemonamine **1** via a radical cascade involving two *endo*-selective cyclizations.[4b] Tu and co-workers revised their $TiCl_4$-promoted Schmidt reaction for a formal synthesis of (±)-stemonamine **1** from an azido-dione precursor,[4c] and they newly designed a $TiCl_4$-promoted tandem intramolecular Prins cyclization/Schmidt reaction from azido-acetal toward a formal synthesis of (±)-stemonamine **1**.[4d] Unlike (±)-stemonamine, no successful synthesis of sessilistemonamine A **2** has been reported, to our knowledge.

RESULTS AND DISCUSSION

In this paper, we report a new synthesis of the tricyclic core structure of the stemonamine alkaloid **4** (Scheme 1). We envisioned that this compound could be easily synthesized via the Schmidt rearrangement[6] of keto azide **5**. This compound may be accessed by the gold(I)-catalyzed domino cyclization[7]

Scheme 1. Synthetic Scheme for the Keto-amide 4



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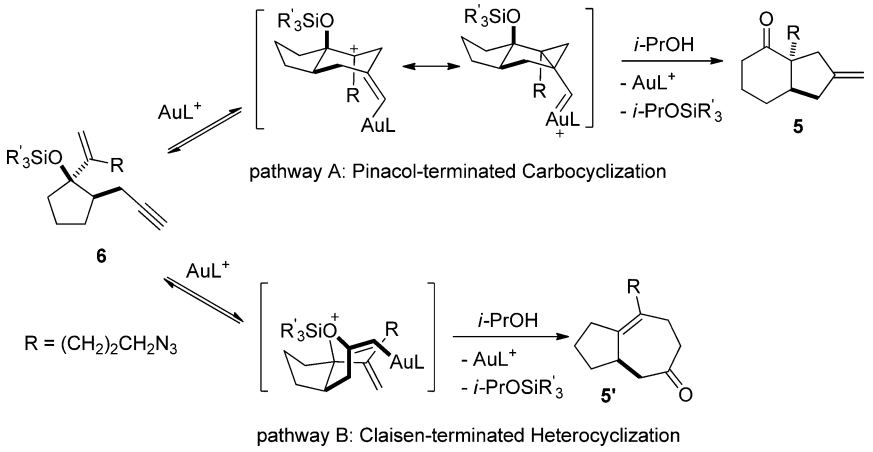
Scheme 2. Divergent Pathways in the Gold(I)-Catalyzed Domino Cyclization of 3-Siloxy-1,6-enyne Substrate 6

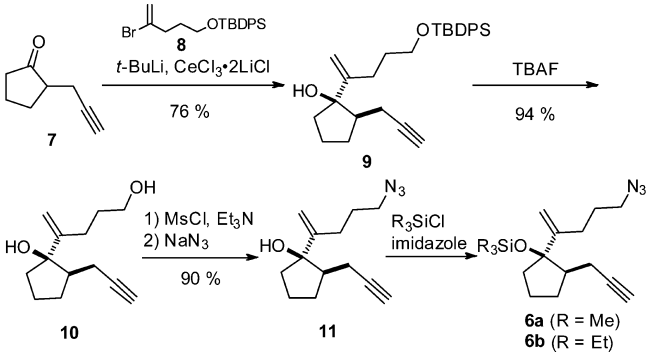


developed by us and Kirsch[8,9] from the 3-siloxy-1,6-enyne **6**, which can be prepared from readily available 2-(prop-2-ynyl)-cyclopentanone **7**.[10] Oxidative cleavage of the exo olefin in **4** would provide the keto amide **3**, which was used as a key intermediate in Tu's synthesis of (±)-stemonamine **1**.[4d] Thus, the current work may represent the formal synthesis of (±)-stemonamine **1**. Moreover, the synthesis will pave the way for the synthesis of sessilistemonamine A **2**.

On the basis of the early reports in the related area,[11,12] we expected competition between the Pinacol-terminated carbocyclization pathway (pathway A in Scheme 2) and the Claisen-terminated heterocyclization pathway (pathway B in Scheme 2) in the gold(I)-catalyzed reaction of **6**. Thus, finding the optimal reaction condition would be of crucial importance in optimizing the formation of compound **5** over **5′** in designing the synthetic strategy shown in Scheme 1.

In order to access the azide precursor **6** in the initial stage of the project, we first investigated the cerium-mediated addition of a vinyllithium reagent generated from readily available vinyl bromide precursor **8**[4d] to the ketone **7** (Scheme 3).

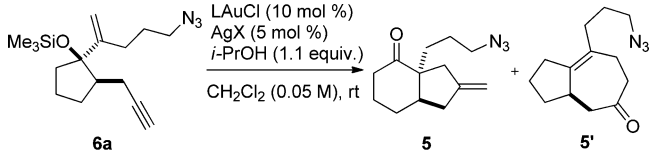
Scheme 3. Preparation of Azido-enynes 6a and 6b



Optimization using anhydrous $CeCl_3$[13] gave the alcohol **9** in low yield. After extensive studies, we discovered that tertiary alcohol **9** could be obtained in 76% yield as a single diastereomer when $CeCl_3$·2LiCl[14] was used. After the subsequent removal of the TBDPS group, the resulting diol **10** could be converted into the 3-siloxy-1,6-enynes **6a** and **6b** (in 51% yield for **6a** and 68% yield for **6b** over three-step yields) via **11** with no particular event.

With the compound **6a** in hand, we explored various reaction conditions for the gold(I)-catalyzed pinacol-terminated carbocyclization pathway. First, we explored the effect of various phosphine ligands (Table 1). As with our previous study,[8] the

Table 1. Optimization of the Gold(I)-Catalyzed Domino Cyclization: Ligand and Counteranion Effect[a]



entry	L	X	yield (%, 5:5′)[b]
1	$P(C_6F_5)_3$	SbF_6	34[c] (20:80)
2	PPh_3	SbF_6	21 (67:33)
3[d]	P(*t*-Bu)$_2$(*o*-biphenyl)	SbF_6	41 (>99:1)
4	P(*t*-Bu)$_2$(*o*-biphenyl)	OTf	34 (>99:1)
5	P(*t*-Bu)$_2$(*o*-biphenyl)	BF_4	7 (>99:1)

[a]See the Experimental Section for a detailed description of the optimization. [b]NMR yield measured by crude ^{1}H NMR using mesitylene as an internal standard. [c]Isolated yield. [d]20 mol % of gold(I) complex and 10 mol % of AgX were used.

selectivity proved to be highly dependent upon the nature of the phosphine ligand. An electron-poor ligand $P(C_6F_5)_3$ directed the reaction toward the Claisen-terminated domino pathway, generating compound **5′** as the major product in low yield (entry 1). Switching to the PPh_3 ligand changed the course of the reaction, showing moderate selectivity toward the pinacol-terminated pathway (entry 2). Notably, using the P(*t*-Bu)$_2$(*o*-biphenyl) ligand showed complete selectivity toward formation of **5**, even though the yield was moderate (entry 3). As demonstrated in our previous study,[8] the improved selectivity can be reasonably explained by the effect of the P(*t*-Bu)$_2$(*o*-biphenyl) ligand that stabilizes the cyclopropyl gold-carbene intermediate shown in Scheme 2. Varying the counteranions little improved the yield of **5** (entries 4 and 5).

The above result indeed confirms that the nature of the phosphine ligand had a crucial effect on the selectivity of the reaction pathway. We then further explored the effect of the solvent and the silyl groups to improve the yield of the desired transformation (Table 2). When the reactions were performed in chlorinated solvents at elevated temperature, the reaction again showed only moderate yields (entries 1 and 2). The use

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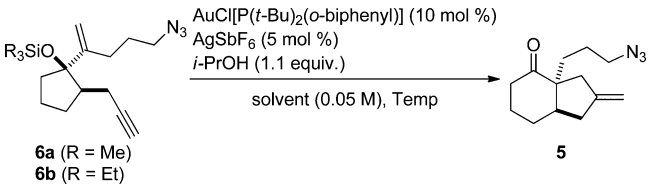
Table 2. Optimization of the Gold(I)-Catalyzed Domino Cyclization: Solvent and Substrate Effect[a]

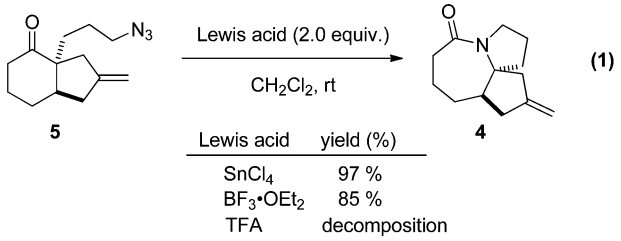


entry	substrate	solvent	temp	yield (%)[b]
1	**6a**	$ClCH_2CH_2Cl$	50 °C	33
2	**6a**	$CHCl_3$	40 °C	36
3	**6a**	toluene	70 °C	15
4	**6a**	CH_3NO_2	rt	47
5	**6a**	CH_3NO_2	70 °C	64
6	**6b**	CH_3NO_2	70 °C	90(85[c])

[a]See the Experimental Section for a detailed description of the optimization. [b]NMR yield measured by crude ^1H NMR using mesitylene as an internal standard. [c]Isolated yield.

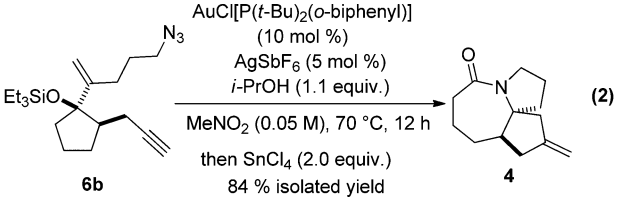
of toluene somewhat dropped the yield (entry 3). Notably, switching to nitromethane significantly increased the yield of **5** to 47% with no detrimental effect on the selectivity when the reaction was performed at rt (entry 4). Increasing the reaction temperature to 70 °C improved the yield of the product in 64% (entry 5). A further increase of the yield was observed when bulkier (and presumably more stable) triethyl silyl ether **6b** was used. Thus, under the optimized condition using **6b** as the substrate, the azidoketone **5** was obtained in 85% isolated yield.

It should be noted that formation of the keto-amide **4** was not observed in the above cases, presumably because cationic gold(I) complexes are not oxophilic enough to induce the intramolecular Schmidt rearrangement. Thus, we explored intramolecular Schmidt rearrangement of the keto azide **5** using various oxophilic Lewis acids. As shown in eq 1, using 2 equiv



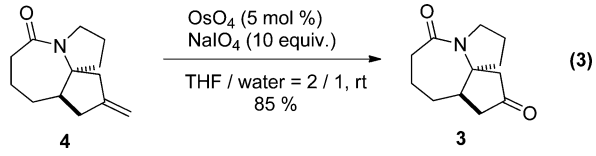
of $SnCl_4$ produced the optimal result, generating compound **4** in 97% yield. Employing $BF_3{\cdot}OEt_2$ somewhat decreased the yield of the desired transformation, whereas using trifluoroacetic acid resulted in extensive decomposition of the starting material.

Having established the sequential two-step method for the synthesis of compound **4** from **6b**, we then investigated the one-pot protocol. As depicted in eq 2, the desired amide **4** was



obtained in 84% yield from **6b** without isolating the intermediate keto azide **5**. The yield of the one-step protocol is comparable to that of the sequential method. Thus, the synthetic efficiency of the key events could be significantly improved.

Our final task was to convert the compound **4** into keto-amide **3** via the oxidative cleavage of the exo olefin. This reaction was accomplished by the use of catalytic OsO_4 with $NaIO_4$[15] in 85% yield (eq 3). The structure of compound **3** agrees well with those reported previously.[4d]



CONCLUSION

In conclusion, we have established a new synthetic method toward the tricyclic core of the stemonamine alkaloids. The key step involves the one-pot gold(I)-catalyzed domino cyclization and intramolecular Schmidt rearrangement. Based on this reaction, the formal synthesis of (±)-stemonamine **1** has been accomplished. Expansion of the methodology established in this study to the total synthesis of more structurally complex sessilistemonamine A **2** is in progress, and the result will be reported in due course.

EXPERIMENTAL SECTION

General Remarks. All solvents were dried and distilled according to the standard methods before use. AuCl[P(*t*-Bu)$_2$(*o*-biphenyl)] and AuCl[P(C$_6$F$_5$)$_3$] were prepared according to the literature procedures.[16] Experiments were performed in flame-dried glassware with rubber septa under a positive pressure of nitrogen. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and acidic *p*-anisaldehyde, and heat as a developing agent. Flash chromatography was carried out on Merck 60 silica gel (230−400 mesh). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. ^1H NMR spectra were referenced to $CDCl_3$ (7.26 ppm), and chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.23 ppm). IR spectra were recorded on an FTIR spectrometer as a thin film on NaCl plates. HRMS spectra were performed by EI or FAB using a magnetic sector-electric sector double focusing mass analyzer.

Preparation of Azido-enynes 6a and 6b. *1-(5-((tert-Butyldiphenylsilyl)oxy)pent-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclopentanol (**9**).* Anhydrous $CeCl_3$ (1.46 g, 5.92 mmol, 1.5 equiv) was mixed with LiCl (507.1 mg, 12.0 mmol, 3.0 equiv) in a flask, and THF (20.0 mL) was added. The slurry was prepared by vigorously stirring for 2 h at room temperature under a N_2 atmosphere. In a separate flask, a pentane solution of *t*-BuLi (7.0 mL, 11.9 mmol, 1.7 M, 3.0 equiv) was added dropwise to a solution of ((4-bromopent-4-en-1-yl)oxy)(*tert*-butyl)diphenylsilane **8**[4d] (2.43 g, 5.99 mmol, 1.5 equiv) in Et_2O (12.0 mL) at −78 °C. After addition, the solution was stirred for 30 min at −78 °C. The slurry was cooled to −78 °C, and then the generated vinyllithium species was cannulated to the $CeCl_3{\cdot}2LiCl$ slurry. After addition, the solution was stirred for 30 min at −78 °C. A solution of 2-(prop-2-ynyl)cyclopentanone **7**[17] (489.2 mg, 4.00 mmol) in THF (12.0 mL) was added to the reaction mixture at −78 °C. The reaction was stirred for 30 min at −78 °C and quenched with water. The reaction mixture was extracted with Et_2O (20 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluted with hexane:EtOAc = 95:5) to give the compound **9** (1.35 g, 3.02 mmol, 76% yield) as a colorless oil.

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R_f = 0.24 (hexane:EtOAc = 95:5); ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.49 (s, 1H), 1.56−1.80 (m, 5H), 1.81−2.00 (m, 3H), 2.00−2.13 (m, 4H), 2.17 (dd, J_1 = 8.3 Hz, J_2 = 2.5 Hz, 1H), 2.20−2.29 (m, 1H), 3.71 (t, J = 6.1 Hz, 2H), 4.91 (d, J = 1.1 Hz, 1H), 5.19 (s, 1H), 7.32−7.47 (m, 6H), 7.62−7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.4, 21.6, 27.1, 27.9, 29.6, 32.3, 40.0, 45.6, 63.8, 69.1, 84.2, 84.9, 109.3, 127.8, 129.8, 134.2, 135.8, 152.1; IR (NaCl) ν 3309, 3071, 2957, 2858, 1472, 1428, 1390, 1112, 701 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{38}O_2Si$ (M^+) 446.2641, found 446.2639.

*1-(5-Hydroxypent-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclopentanol (**10**).* A solution of TBAF (5.0 mL, 5.0 mmol, 1.0 M, 2.0 equiv) in THF was added to a solution of the compound **9** (1.12 g, 2.51 mmol) in THF (20.0 mL). The reaction was stirred for 1 h 30 min at room temperature, and then the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluted with hexane:EtOAc = 50:50) to give the compound **10** (491.6 mg, 2.36 mmol, 94% yield) as a colorless oil. R_f = 0.31 (hexane:EtOAc = 60:40); ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.50 (t, J = 5.3 Hz, 1H), 1.60−1.74 (m, 4H), 1.74−1.89 (m, 3H), 1.90−1.99 (m, 2H), 2.00−2.07 (m, 1H), 2.07−2.19 (m, 4H), 2.19−2.31 (m, 1H), 3.70 (q, J = 6.0 Hz, 2H), 4.96 (d, J = 1.0 Hz, 1H), 5.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 21.5, 27.8, 29.5, 32.2, 40.3, 45.6, 62.7, 69.2, 84.2, 84.9, 109.5, 151.9; IR (NaCl) ν 3303, 2944, 2873, 2116, 1638, 1430, 1157, 1113, 1057, 864, 630 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1465.

*1-(5-Azidopent-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclopentanol (**11**).* To a solution of the compound **10** (489.5 mg, 2.35 mmol) in CH_2Cl_2 (15.0 mL) were added triethylamine (0.66 mL, 4.74 mmol, 2.0 equiv) and methanesulfonyl chloride (0.22 mL, 2.84 mmol, 1.2 equiv) at 0 °C. After being stirred for 10 min at 0 °C, the reaction mixture was quenched with water. The mixture was extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was used without further purification. NaN_3 (466.6 mg, 7.18 mmol) was added to a crude mesylate in DMF (15 mL). After being stirred for 4 h at 40 °C, the reaction mixture was quenched with water. The mixture was extracted with Et_2O (20 mL × 3), and then the combined organic was washed with water (20 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluted with hexane:EtOAc = 90:10) to give the compound **11** (492.3 mg, 2.11 mmol, 90% two-step yield) as a colorless oil. R_f = 0.31 (hexane:EtOAc = 90:10); ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.54 (s, 1H), 1.59−1.74 (m, 3H), 1.75−1.94 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 2.01−2.14 (m, 4H), 2.19 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 2.21−2.31 (m, 1H), 3.34 (t, J = 6.7 Hz, 2H), 4.94 (d, J = 0.8 Hz, 1H), 5.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 21.5, 28.4, 28.7, 29.5, 40.2, 45.6, 51.4, 69.3, 84.0, 84.7, 109.8, 151.2; IR (NaCl) ν 3303, 2944, 2872, 2097, 1638, 1451, 1350, 1254, 1153, 1015, 905, 629 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{20}ON_3$ (MH^+) 234.1606, found 234.1603.

*1-(5-Azidopent-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclopentyl)oxy)-trimethylsilane (**6a**).* To a solution of compound **11** (116.7 mg, 0.500 mmol) in DMF (3.0 mL) was added imidazole (681.2 mg, 10.0 mmol, 20 equiv) and chlorotrimethylsilane (0.64 mL, 5.01 mmol, 10 equiv). The reaction was stirred for 30 min at room temperature, and the reaction was quenched with water. The reaction mixture was extracted with Et_2O (10 mL × 3). The organic layer was combined, washed with water (10 mL × 3), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluted with hexane:Et_2O = 98:2) to give the compound **6a** (151.8 mg, 0.497 mmol, 99% yield) as a colorless oil. R_f = 0.47 (hexane:Et_2O = 98:2); ^{1}H NMR(300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.50−1.66 (m, 2H), 1.66−1.85 (m, 5H), 1.87 (t, J = 2.7 Hz, 1H), 1.94−2.10 (m, 5H), 2.21 (ddd, J_1 = 17.0 Hz, J_2 = 3.7 Hz, J_3 = 2.9 Hz, 1H), 3.32 (td, J_1 = 6.8 Hz, J_2 = 1.5 Hz, 2H), 4.91 (d, J = 1.3 Hz, 1H), 5.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.1, 17.7, 21.7, 28.6, 28.8, 29.4, 36.9, 48.1, 51.4, 68.0, 85.3, 87.2, 110.9, 150.6; IR (NaCl) ν 3310, 2957, 2873, 2097, 1639, 1451, 1349, 1251, 1161, 1123, 1085, 1046, 1007, 961, 908, 840, 753, 627 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{28}ON_3Si$ (MH^+) 306.2002, found 306.2005.

*1-(5-Azidopent-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclopentyl)oxy)-triethylsilane (**6b**).* Using the above procedure for giving **6a**, a mixture of chlorotriethylsilane (1.0 mL, 5.96 mmol, 10 equiv), imidazole (0.80 g, 11.8 mmol, 20 equiv), and substrate **11** (140.5 mg, 0.602 mmol) in DMF (3.0 mL) was reacted for 30 h at 30 °C to give the compound **6b** (157.4 mg, 0.453 mmol, 75% yield) as a colorless oil. R_f = 0.39 (hexane:Et_2O = 98:2); ^{1}H NMR(300 MHz, $CDCl_3$) δ 0.59 (q, J = 7.9 Hz, 6H), 0.94 (t, J = 7.9 Hz, 9H), 1.51−1.68 (m, 2H), 1.69−1.86 (m, 5H), 1.88 (t, J = 2.7 Hz, 1H), 1.96−2.14 (m, 5H), 2.26 (ddd, J_1 = 17.0 Hz, J_2 = 3.6 Hz, J_3 = 2.8 Hz, 1H), 3.33 (td, J_1 = 6.7 Hz, J_2 = 1.5 Hz, 2H), 4.91 (d, J = 1.3 H, 1H), 5.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.8, 7.5, 17.9, 22.1, 28.6, 28.8, 29.7, 37.2, 48.6, 51.5, 68.1, 85.4, 86.8, 110.7, 150.8; IR (NaCl) ν 3311, 2956, 2913, 2876, 2097, 1640, 1458, 1348, 1240, 1160, 1123, 1085, 1046, 1006, 962, 906, 727, 627 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{34}ON_3Si$ (MH^+) 348.2471, found 348.2475.

Optimization of Gold(I)-Catalyzed Cyclization. *General Procedure of Gold(I)-Catalyzed Cyclization.* (Entry 1 in Table 1 is described.) To a solution of $AgSbF_6$ (1.7 mg, 0.0049 mmol, 5 mol %) in CH_2Cl_2 (1.0 mL) was added a solution of $AuCl[P(C_6F_5)_3]$ (7.6 mg, 0.0099 mmol, 10 mol %) in CH_2Cl_2 (1.0 mL), and the mixture was stirred at room temperature for 10 min. The resulting suspension was filtered through Celite and concentrated. The residue was dried under high vacuum for 2 h. To this residue, a solution of substrate **6a** (30.6 mg, 0.100 mmol) and *i*-PrOH (8.4 μL, 0.11 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) was added. The resulting mixture was stirred for 5 h at room temperature. The resulting reaction mixture was passed through a pad of silica and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (eluted with hexane:Et_2O = 98:2 → 80:20) to give the compound **5** (1.6 mg, 0.0069 mmol, 7% yield) and **5′** (6.3 mg, 0.027 mmol, 27%) as colorless oils, and **6a** was recovered in 56% yield (17.2 mg, 0.0563 mmol).

*3a-(3-Azidopropyl)-2-methylenehexahydro-1H-inden-4(2H)-one (**5**).* R_f = 0.35 (hexane:Et_2O = 80:20); ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.27−1.40 (m, 1H), 1.40−1.53 (m, 1H), 1.53−1.69 (m, 2H), 1.81−2.03 (m, 5H), 2.11−2.23 (m, 1H), 2.25−2.52 (m, 4H), 3.11 (dd, J_1 = 16.5 Hz, J_2 = 1.4 Hz, 1H), 3.16−3.35 (m, 2H), 4.89 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 25.1, 25.3, 34.1, 36.5, 38.7, 40.7, 47.3, 51.8, 59.2, 107.4, 148.1, 214.1; IR (NaCl) ν 3072, 2936, 2872, 2096, 1704, 1656, 1454, 1425, 1352, 1312, 1252, 1179, 1121, 947, 879, 714, 522 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{20}ON_3$ (MH^+) 234.1606, found 234.1609.

*8-(3-Azidopropyl)-2,3,3a,4,6,7-hexahydroazulen-5(1H)-one (**5′**).* R_f = 0.22 (hexane:Et_2O = 80:20); ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.27−1.39 (m, 1H), 1.46−1.61 (m, 1H), 1.62−1.84 (m, 3H), 1.91−2.06 (m, 1H), 2.06−2.17 (m, 2H), 2.24−2.45 (m, 6H), 2.56 (dd, J_1 = 14.9 Hz, J_2 = 3.0 Hz, 1H), 2.66−2.90 (m, 2H), 3.28 (t, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 27.2, 29.6, 32.1, 33.3, 35.7, 39.2, 42.7, 49.6, 51.4, 129.8, 142.7, 212.8; IR (NaCl) ν 2950, 2863, 2095, 1706, 1450, 1347, 1256 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{20}ON_3$ (MH^+) 234.1606, found 234.1603.

Optimized Condition of Formation of 5 (Entry 6 in Table 2). Using the general procedure of gold(I)-catalyzed cyclization, a mixture of $AgSbF_6$ (1.8 mg, 0.0052 mmol, 5 mol %), $AuCl[P(t\text{-}Bu)_2(o\text{-}biphenyl)]$ (5.3 mg, 0.010 mmol, 10 mol %), substrate **6b** (34.9 mg, 0.100 mmol), and *i*-PrOH (8.4 μL, 0.11 mmol, 1.1 equiv) in $MeNO_2$ (2.0 mL) was reacted for 7 h at 70 °C to give the compound **5** (19.8 mg, 0.0849 mmol, 85% yield) as a colorless oil.

Optimized Condition for Intramolecular Schmidt Reaction. *10-Methyleneoctahydro-1H-cyclopenta[b]pyrrolo[1,2-a]azepin-5(6H)-one (**4**).* A solution of $SnCl_4$ (0.16 mL, 0.16 mmol, 1.0 M, 2.0 equiv) in CH_2Cl_2 was added to a solution of the compound **5** (18.5 mg, 0.0793 mmol) in CH_2Cl_2 (0.80 mL). After stirring for 4 h at room temperature, the reaction was quenched with triethylamine. The resulting reaction mixture was passed through a pad of Celite and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (eluted with hexane:EtOAc =

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20:80) to give the compound **4** (15.8 mg, 0.0770 mmol, 97% yield) as a colorless oil. R_f = 0.26 (hexane:EtOAc = 20:80); ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.56−1.85 (m, 7H), 1.91−2.01 (m, 1H), 2.08 (ddd, J_1 = 14.8 Hz, J_2 = 7.0 Hz, J_2 = 2.8 Hz, 1H), 2.27 (dd, J_1 = 15.9 Hz, J_2 = 8.9 Hz, 2H), 2.40 (tq, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 2.44−2.54 (m, 2H), 2.71 (d, J = 16.3 Hz, 1H), 3.32−3.49 (m, 1H), 3.71−3.84 (m, 1H), 4.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 21.2, 28.6, 35.7, 37.7, 43.6, 44.3, 45.4, 49.0, 70.2, 108.8, 147.2, 172.6; IR (NaCl) ν 2927, 2857, 1629, 1415, 1345, 1251, 1177, 882 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{20}ON$ (MH^+) 206.1545, found 206.1543.

One-Pot Procedure for Compound (4). To a solution of $AgSbF_6$ (1.2 mg, 0.0035 mmol, 5 mol %) in CH_2Cl_2 (1.0 mL) was added a solution of AuCl[P(*t*-Bu)$_2$(*o*-biphenyl)] (3.8 mg, 0.0072 mmol, 10 mol %) in CH_2Cl_2 (1.0 mL), and the mixture was stirred at room temperature for 10 min. The resulting suspension was filtered through Celite and concentrated. The residue was dried under high vacuum for 2 h. To this residue, a solution of substrate **6b** (25.1 mg, 0.0722 mmol) and *i*-PrOH (6.1 μL, 0.080 mmol, 1.1 equiv) in $MeNO_2$ (1.5 mL) was added. The resulting solution was stirred for 12 h at 70 °C, and then a solution of $SnCl_4$ (0.14 mL, 0.14 mmol, 1.0 M) in CH_2Cl_2 was added. After stirring for 1 h 30 min at room temperature, the reaction mixture was quenched with triethylamine. The resulting reaction mixture was passed through a pad of Celite and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (eluted with hexane:EtOAc = 20:80) to give the compound **4** (12.4 mg, 0.0604 mmol, 84% two-step yield) as a colorless oil.

Hexahydro-1*H*-cyclopenta[*b*]pyrrolo[1,2-*a*]azepine-5,10-(6*H*,11*H*)-dione (3). To a solution of compound **4** (12.3 mg, 0.0599 mmol) in THF (2.0 mL)/water (1.0 mL) was added sodium periodate (127.6 mg, 0.597 mmol, 10 equiv). A water solution of osmium tetroxide (19.2 mg, 0.00302 mmol, 4 wt %, 5 mol %) was added to the reaction mixture. The reaction was stirred for 10 h at room temperature and quenched with saturated $Na_2S_2O_3$ aqueous solution. The reaction mixture was extracted with EtOAc (10 mL × 4). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluted with EtOAc) to give the compound **3** (10.6 mg, 0.0511 mmol, 85% yield) as a white solid. R_f = 0.11 (EtOAc); mp. 157−159 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.47−1.62 (m, 1H), 1.66−1.84 (m, 3H), 1.85−1.98 (m, 2H), 1.98−2.08 (m, 2H), 2.17−2.36 (m, 3H), 2.38−2.50 (m, 1H), 2.51−2.74 (m, 3H), 3.49 (td, J_1 = 11.6 Hz, J_2 = 6.7 Hz, 1H), 3.83 (dd, J_1 = 12.1 Hz, J_2 = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.8, 31.6, 36.7, 43.8, 44.9, 45.9, 47.7, 49.3, 67.3, 172.7, 214.6; IR (NaCl) ν 2927, 2870, 1741, 1626, 1450, 1418, 1347, 1275, 1240, 1178, 1140, 1121, 907 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_2N$ (M^+) 208.1338, found 208.1340.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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