HETEROCYCLES, Vol. 103, No. , 2021, pp. -. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 7th October, 2020, Accepted, 4th November, 2020, Published online, 13th November, 2020
DOI: 10.3987/COM-20-S(K)38

DE NOVO APPROACH TO IZIDINES VIA A GOLD-CATALYZED HYDROAMINATION–*N*-ACYLIMINIUM ION CYCLIZATION OF ACYCLIC YNAMIDES

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This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

Abstract – A gold(I)-catalyzed novel domino reaction of acyclic ynamides yielding nitrogen-fused bicyclic skeletons was described. The reaction with 10 mol% JohnPhosAuNTf$_2$ and stoichiometric amount of PhCO$_2$H enables constructions of quinolizidine and indolizidine skeleton having tetrasubstituted carbon center. Especially in the case of quinolizidine synthesis, the quaternary stereogenic center could be furnished under highly diastereoselective manner.

Alkaloids have been an important source for the development of pharmaceutical sciences.[1] Some alkaloids work as medicines as they are, and the others provide useful structural motifs for biological activities. Thus, in either case, a development of an efficient method for achieving intricately fused polycyclic frameworks of the alkaloids has been believed as a goal for synthetic organic chemists. Among the alkaloids, nitrogen-fused bicycles such as pyrrolizidines, indolizidines, quinolizidines, and lehmizidines are classified in izidines and widely observed as the key structures in fascinating biologically active compounds.[2]

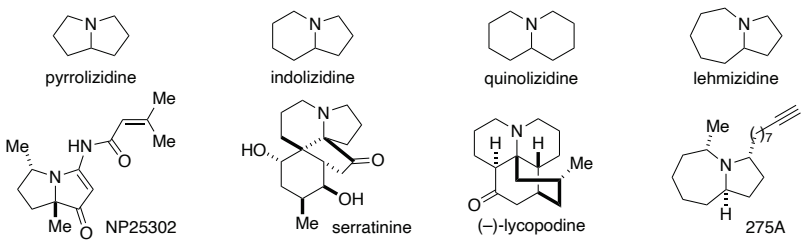
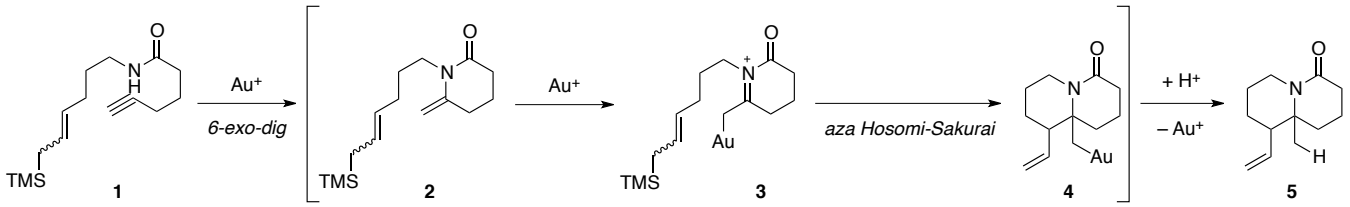


Figure 1. Izidines and related natural alkaloids

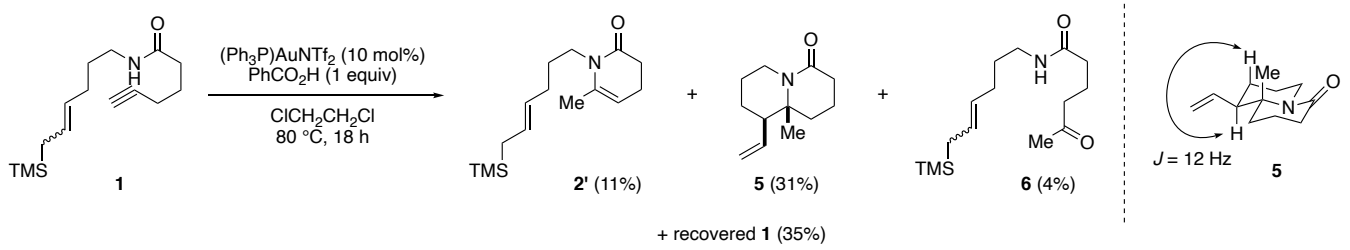
However, these bicyclic skeletons were conventionally constructed through step-by-step transformations despite their pharmaceutical interests and demands. Hence, a concise and common approach via a domino process has been required and several domino reactions were recently applied as key steps for total syntheses of complex alkaloids.[3] Furthermore, since gold-catalyzed domino reactions are highly focused as a useful method since the highly alkyne selective transformation could be induced by the alkynophilicy of the gold catalyst under mild conditions leaving the various functional groups intact.[4] However, a few domino processes leading to izidine skeletons were applied for total synthesis of natural alkaloids.[5] Thus, we planned a gold-catalyzed domino reaction, which consists of a hydroamidation of alkyne and an *N*-acyliminium ion cyclization,[6] for a de novo synthesis of izidines.

As shown in Scheme 1, we envisioned a gold-catalyzed domino procedure leading to quinolizidine skeleton. The first, 6-*exo*-*dig* cyclization could be induced by an activation of triple bond in an acyclic ynamide **1** with gold catalysis to afford enamide **2** in situ. Then a cationic gold this time would activate the enamide moiety to generate an acyliminium intermediate **3**.[7] The cyclization with the pendant allyltrimethylsilyl group and the acyliminium could provide the bicyclic quinolizidine skeleton and the catalyst could be regenerated by a protodeauration.



Scheme 1. Working hypothesis for quinolizidine by gold-catalyzed domino reaction

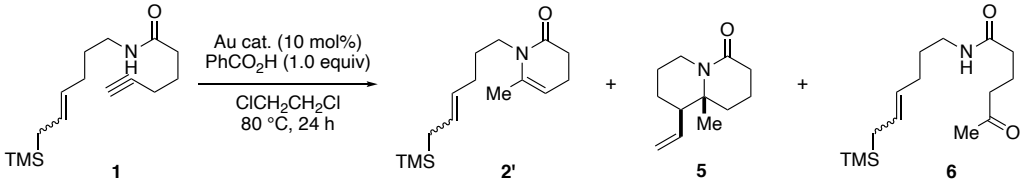
Based on the hypothesis, we examined the double cyclization reaction of acyclic precursor **1** (for preparation, see Experimental section) with catalytic $(Ph_3P)AuNTf_2$[8] in the presence of $PhCO_2H$ as a proton source for the final protodeauration step (Scheme 2). As a result, the substrate was not consumed completely but desired quinolizidine **5** was isolated as a sole diastereomer with a highly labile monocyclic lactam **2´**, which would be caused from **2** via olefin isomerization, and a ketone **6** derived from the hydrolysis of **2´**. The relative stereochemistry of the quinolizidine **5** was determined by the coupling constant of methine proton, which suggested that the methine proton occupies an axial position in stable chair-chair conformation of quinolizidine skeleton.



Scheme 2. Initial attempt of double cyclization

Encouraged with this result, the ligands on the gold were screened as shown in Table 1. Although CyJohnPhosAuNTf$_2$ did not work well in our reaction (entry 1), the catalysts with more bulky ligands afforded the desired **5** in moderate yields (entries 2–4). The bulkiness on phosphine atom improved the yield of **5** to 67% and gave its possible precursor **2′** in 23% (entry 5). Since the further introduction of substituent on the phenyl group was ineffective (entries 6 and 7), we selected JohnPhos as a best ligand for our domino reaction. Then we tried to tune up the catalyst species with acetonitrile ligand[9] (entry 8) or chloride-bridged dimeric catalyst[10] (entries 9 and 10), however, those were found to be inferior to the use of simple JohnPhosAuNTf$_2$.

Table 1. Screening of the ligands



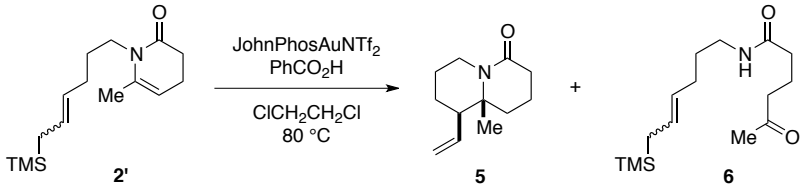
Entry	Au cat.	**2'** (%)	**5** (%)	**6** (%)
1[a]	CyJohnPhosAuNTf$_2$	2	10	11
2	SPhosAuNTf$_2$	6	42	4
3	RuPhosAuNTf$_2$	8	37	0
4	XPhosAuNTf$_2$	23	58	6
5	JohnPhosAuNTf$_2$	23	67	3
6	*t*BuXPhosAuNTf$_2$	12	37	3
7	*t*BuMePhosAuNTf$_2$	14	70	11
8	JohnPhosAu(MeCN)SbF$_6$	23	43	4
9	(JohnPhosAu)$_2$ClBF$_4$	60	0	25
10	(JohnPhosAu)$_2$ClNTf$_2$	35	33	15

[a]Starting material was recovered in 67% yield.

The other counter anions ($^-$OTf, $^-$BF$_4$, $^-$PF$_6$, and $^-$SbF$_6$) or solvents (toluene, 1,4-dioxane, and cyclopentyl methyl ether) were examined, however, the yield of **5** did not improved at all.

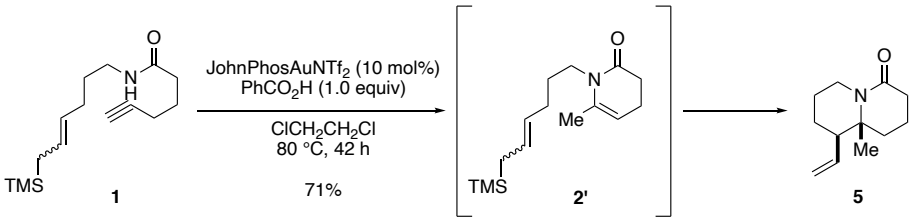
As shown in Table 2, it was proved that the **2´** was a transient precursor of aza Hosomi-Sakurai reaction and a gold catalyst actually triggered the second cyclization by inducing acyl iminium in situ. In the absence of the gold catalyst (entries 1 and 2), benzoic acid by itself did not catalyze the aza Hosomi-Sakurai reaction; instead, **2´** and **6** generated after the work up were recovered. On the other hand, Au catalyst promoted the cyclization to afford **5** in 67% after 24 h (entry 3). Furthermore, Au catalyst with benzoic acid worked cooperatively to enhance the reaction rate to give **5** in 87% within 10 h (entry 4). It was suggested that the $PhCO_2H$ accelerated a protodeauration step of alkyl gold complex resulted by acyliminium formation from the lactam **2´** and assisted a regeneration of a gold catalyst.

Table 2. The role of a gold catalyst in aza Hosomi-Sakurai reaction



Entry	JohnPhosAuNTf$_2$	$PhCO_2H$	Time (h)	**2'** (%)	**5** (%)	**6** (%)
1	–	–	24	51	0	44
2	–	1.0 equiv	24	43	0	55
3	10 mol%	–	24	0	67	0
4	10 mol%	1.0 equiv	10	0	87	0

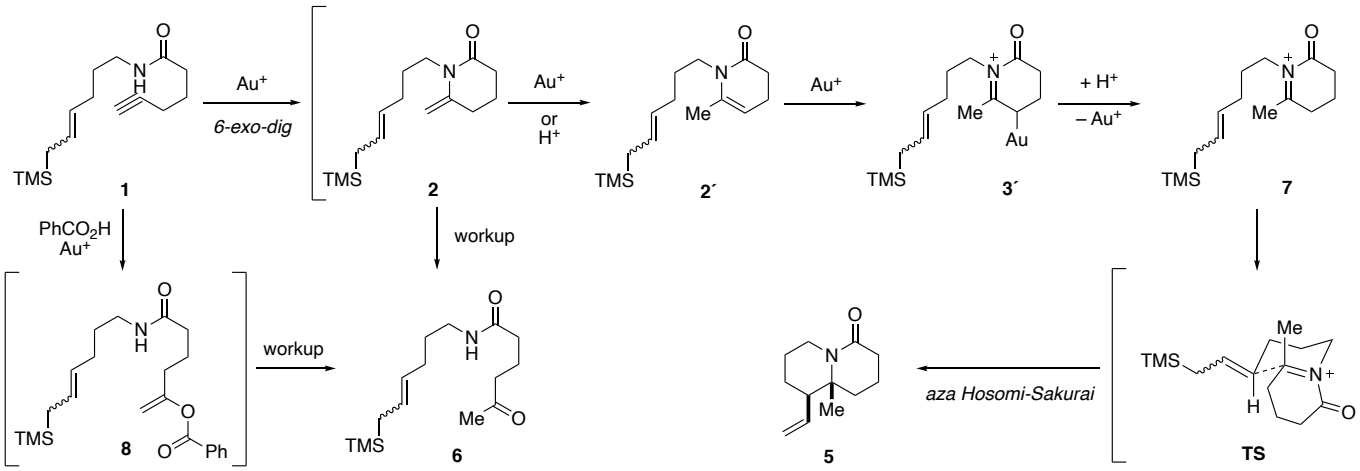
Finally, the desired quinolozidine **5** was obtained in 71% after a complete consumption of the linear ynamide **1** and the transient lactam **2´** under the optimal conditions (Scheme 3).



Scheme 3. Quinolizidine synthesis under optimal conditions

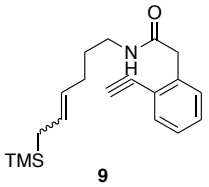
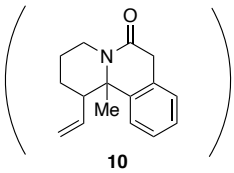
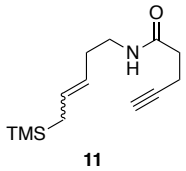
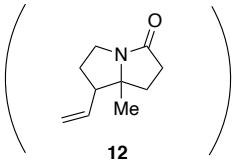
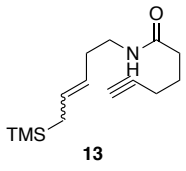
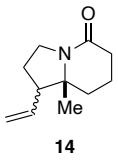
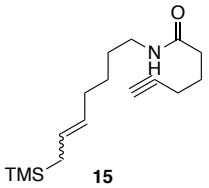
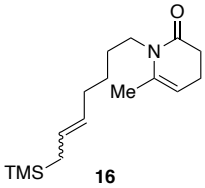
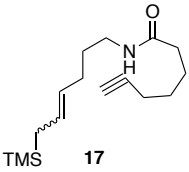
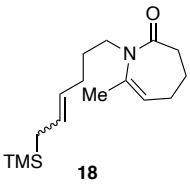
A plausible reaction mechanism was depicted in Scheme 4. The first cyclization was triggered by the activation of the triple bond by gold to give the lactam **2** via hydroamidation reaction, and subsequent isomerization of olefin promoted by gold or $PhCO_2H$ would provide **2´**. The lactam **2´** was further activated by gold catalysis followed by protodeauration provided the acyliminium intermediate **7**. The second, aza Hosomi-Sakurai reaction would proceed via Zimmerman-Traxler transition state leading to a

single, *cis*-diastereomer **5**.[11] The ketone **6** was possibly afforded by a hydrolysis of **2** or enol benzoate **8** caused by a nucleophilic attack of benzoate anion to the activated triple bond.



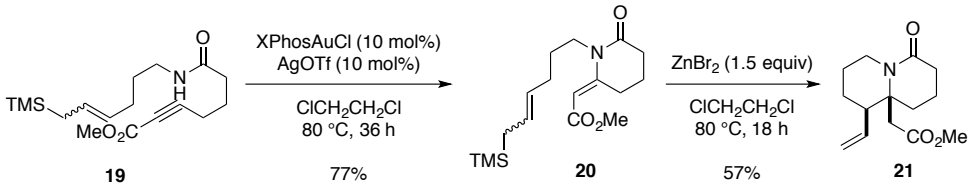
Scheme 4. Plausible reaction mechanism

Table 3. Scope and limitation of the domino reactions[a]

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **9**	 **10**	24	–
2	 **11**	 **12**	24	–
3	 **13**	 **14**	24	69 (dr = 1.2:1)
4	 **15**	 **16**	82	20
5	 **17**	 **18**	24	25

[a]The reactions were conducted with JohnphosAuNTf$_2$ (10 mol%) and PhCO$_2$H (1 equiv) in ClCH$_2$CH$_2$Cl (0.1 M) at 80 °C.

Next, we applied the optimal conditions for the constructions of various fused bicyclic systems (Table 3). Aiming a synthesis of a benzoquinolizidine skeleton **10**, ynamide **9** was prepared and attempted the double cyclization under the optimal conditions (entry 1). Although the substrate was quickly consumed on the TLC analysis to afford a single spot which supposed to be an enaminone intermediate, however, the Hosomi-Sakurai reaction was failed to give a complex mixture possibly due to a highly unstable nature of a benzene-fused enaminone intermediate. A hydroamidation of **11** found to be difficult since a suitable orbital overlap between the nitrogen atom and the activated triple bond would be circumvented by the conformational restriction (entry 2). On the other hand, an indolizidine skeleton **14** could be furnished as an inseparable mixture of diastereomers (the ratio was almost 1.2:1) in 69% yield (entry 3). The reactions of **15** and **17**, which include a 7-membered ring formation, could not provide a 1-aza-bicyclo[5.4.0]undecanes, but unstable lactams **16** and **18** were only observed (entries 4 and 5).
Finally, ynoate **19**, which was anticipated to equip an ester in the quinolizidine for further transformation, was applied in our domino cyclization. Despite the several efforts on the domino cyclization, it was found that the reaction was unfortunately interrupted in first hydroamidation step. However, after the revisions on the catalytic system, a combination of XPhosAuCl and AgOTf proved to be most effective for the first hydroamidation step (77% yield), and the Hosomi-Sakurai reaction of **20** could be induced by the aid of the lactam to $ZnBr_2$ to give the desired quinolizidine skeleton **21** in 57% yield. This result suggested that the mechanism via gold carbene generation from terminal alkyne could be experimentally excluded for the first hydroamidation step in our system and highly congested, electron poor olefin could not be activated by the cationic gold in the second cyclization step. In contrast to the π-philic gold catalyst, $ZnBr_2$ would fortunately be able to activate the sterically less hindered ester carbonyl group as σ-acid to generate the desired acyliminium intermediate.



19 **20** **21**

Scheme 5. Synthesis of a functionalized quinolizidine

In summary, we developed a gold(I)-catalyzed novel domino reaction of linear ynamide yielding nitrogen-fused bicyclic skeleton. The reaction found to be applied to furnish quinolizidine and indolizidine skeleton having tetrasubstituted carbon. Especially in the case of quinolizidine synthesis, a quaternary stereogenic center could be afforded under highly diastereoselective manner. Since the ester functional group could be introduced adjacent to the quaternary center by the aid of additional Lewis acid, an application of this strategy to natural alkaloid synthesis is ongoing in our laboratory.

EXPERIMENTAL

General: All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial suppliers and used as received. Anhydrous solvents were prepared by distillation over CaH_2, or purchased from commercial suppliers. ^1H and ^{13}C NMR spectra were measured on a JEOL ECA 500, JEOL ECX 400 or a Varian GEMINI 300 instrument, using $CHCl_3$ (7.26 ppm for ^1H) and $CDCl_3$ (77.0 ppm for ^{13}C) as an internal reference. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. *J* values were in hertz. Mass spectra were measured on a JEOL JMS-GCmate II or a JEOL JMS-AX 505 HAD mass spectrometer, and the ionization method was electron impact (EI, 70 eV) and fast atom bombardment (FAB). IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica Silica Gel 60N (spherical, neutral, 40–50 μm). Thin layer chromatography was performed on precoated silica gel 60 F_{254} plates (Merck).

6-Bromo-1-(trimethylsilyl)-2-hexene (S-1)[12]: A solution of 5-bromo-1-pentene (0.8 mL, 6.76 mmol), allyltrimethylsilane (5.4 mL, 34.0 mmol), and Grubbs' 2nd generation catalyst (55.8 mg, 0.0657 mmol) was heated in refluxing CH_2Cl_2 (33.5 mL). After 15 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: *n*-pentane) to give the bromide **S-1** (1.29 g, 82%, (*E*):(*Z*) = 83:17) as a colorless oil. The ^1H NMR spectrum was identical with that previously reported.[12] R_f 0.55 (*n*-pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.52–5.41 (1H, m), 5.23–5.10 (1H, m), 3.45–3.33 (2H, m), 2.25–2.20 (2H, m), 1.98–1.84 (2H, m), 1.54–1.40 (2H, m), 0.00 (1.5H, s), –0.01 (7.5H, s).

6-Azide-1-(trimethylsilyl)-2-hexene (S-2) [12]: To a stirred solution of the bromide **S-1** (2.04 g, 8.66 mmol) in DMF (108 mL) was added NaN_3 (1.70 g, 26.1 mmol) at room temperature. After stirred at 70 °C for 5 h, the reaction was quenched with water. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue (1.41 g, 83%), which proved to be pure by ^1H NMR, was conducted to the next reaction without further purification. The ^1H NMR spectrum was identical with that previously reported.[12] R_f 0.25 (*n*-pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.49–5.38 (1H, m), 5.24–5.15 (1H, m), 3.30–3.22 (2H, m), 2.11–2.04 (2H, m), 1.70–1.59 (2H, m), 1.49–1.40 (2H, m), 0.00 (1.5H, s), –0.01 (7.5H, s).

6-(Trimethylsilyl)-4-hexen-1-amine (S-3) [12]: To a stirred suspension of LAH (272 mg, 7.18 mmol) in Et_2O (17.5 mL) was added a solution of the azide (668 mg, 3.38 mmol) in Et_2O (5 mL) at 0 °C. After stirred for 3 h at room temperature, the mixture was diluted with Et_2O (22 mL) at 0 °C and the reaction was quenched with 15% aqueous NaOH (0.3 mL) and water (0.9 mL). After stirred for 1 h at room temperature, the solution was filtered through a Celite pad, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue (540 mg, 93%), which proved to be pure by ^1H NMR, was conducted to the next

reaction without further purification. The ^{1}H NMR spectrum was identical with that previously reported.[12] R_f 0.08 ($CHCl_3$/MeOH = 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45–5.34 (1H, m), 5.30–5.18 (1H, m), 2.74–2.66 (2H, m), 2.15–1.98 (2H, m), 1.54–1.38 (4H, m), –0.01 (1.5H, s), –0.2 (7.5H, s).

***N*-[6-(Trimethylsilyl)-4-hexen-1-yl]-5-hexynamide (1):** To a stirred solution of 5-hexynoic acid (0.29 mL, 2.63 mmol), EDCI (644 mg, 3.36 mmol), and DMAP (388 mg, 3.18 mmol) in CH_2Cl_2 (20.0 mL) was added a solution of the amine (540 mg, 3.15 mmol) in CH_2Cl_2 (14.5 mL). After stirred for 2.5 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/ EtOAc = 70:30) to give the amide **1** (574 mg, 82%) as a pale yellow oil. R_f 0.55 (*n*-hexane/ EtOAc = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48–5.30 (2H, m), 5.30–5.17 (1H, m), 3.30–3.22 (2H, m), 2.33–2.20 (4H, m), 2.06–1.93 (3H, m), 1.91–1.81 (2H, m), 1.60–1.39 (4H, m), 0.00 (1.5H, s), –0.02 (7.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 127.4, 127.1, 83.6, 69.1, 39.2, 35.2, 30.2, 30.0, 24.3, 22.8, 17.9, –1.84; IR (neat) 3446, 1646, 1248 cm^{-1}; MS (EI) *m/z* 265 (M^+); HRMS (EI) calcd for $C_{15}H_{27}NOSi$ (M^+) 265.1862, found 265.1883.

Gold-catalyzed domino reaction of ynamide (Table 1, General Procedure): To a stirred solution of the amide **1** (1 equiv) in $ClCH_2CH_2Cl$ (0.1 M) were added $PhCO_2H$ (1 equiv) and JohnPhosAuNTf$_2$ (0.10 equiv) at room temperature. After stirred for 24 h at 80 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 80:20; *n*-hexane/ EtOAc = 50:50; EtOAc only) to give the lactam **2´** (unstable), the quinolizidine **5**, and the ketone **6**.

Lactam 2´: R_f 0.50 (*n*-hexane/EtOAc = 75:25 with AcOH (3% v/v)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43–5.36 (1H, m), 5.28–5.20 (1H, m), 5.02–4.96 (1H, m), 3.59–3.54 (2H, m), 2.47–2.42 (2H, m), 2.16–2.14 (2H, m), 2.04–1.97 (2H, m), 1.92 (3H, s), 1.44–1.38 (4H, m), 0.00 (1.5H, s), –0.02 (7.5H, s).

Quinolizidine 5: R_f 0.15 (*n*-hexane/EtOAc = 75:25 with AcOH (3% v/v)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (1H, ddd, *J* = 17.0, 10.0, 8.5 Hz), 5.08 (1H, d, *J* = 17.0 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 4.68–4.62 (1H, m), 2.60–2.52 (1H, m), 2.39–2.24 (2H, m), 2.06 (1H, ddd, *J* = 12.5, 8.5, 4.0 Hz), 1.78–1.74 (1H, m), 1.69–1.53 (6H, m), 1.45–1.36 (1H, m), 1.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 138.5, 116.8, 58.4, 52.5, 36.8, 36.7, 33.1, 27.0, 25.0, 19.1, 16.5; IR (neat) 2948, 1637, 1400 cm^{-1}; MS (EI) *m/z* 193 (M^+); HRMS (EI) calcd for $C_{12}H_{19}NO$ (M^+) 193.1467, found 193.1470.

Ketone 6: R_f 0.05 (*n*-hexane/EtOAc = 75:25 with AcOH (3% v/v)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49–5.38 (2H, m), 5.24–5.18 (1H, m), 3.27–3.20 (2H, m), 2.54–2.50 (2H, m), 2.21–2.14 (5H, m), 2.02–1.88 (4H, m), 1.60–1.39 (4H, m), 0.09 (1.5H, s), –0.02 (7.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 172.0,

127.3, 127.1, 42.5, 39.1, 35.5, 30.2, 30.03, 29.97, 22.7, 19.8, –1.86; IR (neat) 3437, 1645, 839 cm^{-1}; MS (EI) *m/z* 283 (M^+); HRMS (EI) calcd for $C_{15}H_{29}NO_2Si$ (M^+) 283.1968, found 283.1977.

(2-Iodophenyl)methanol (S-4)[13]: To the vigorously stirred solution of 2-iodobenzoic acid (5.00 g, 19.8 mmol) in THF (100 mL), $NaBH_4$ (1.97 g, 4.94 mmol) was added portionwise (with 5 min intervals during 15 min) at 0 °C. After stirred for 15 min, $BF_3 \cdot OEt_2$ (3.7 mL, 30 mmol) was added at the same temperature. After stirred at room temperature for 3.5 h, the reaction was quenched with aqueous HCl (10%, 5 mL) at 0 °C. Then, to the resulting suspension was added aqueous NaOH (5%, 15 mL). After removal of THF under reduced pressure, the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$, filetered, and concentrated in vacuo. The residue (4.54 g, 98%), which proved to be pure by ^1H NMR, was conducted to the next reaction without further purification. The ^1H NMR spectrum was identical with that previously reported.[13] R_f 0.47 (*n*-hexane/EtOAc = 70:30); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 8.0 Hz), 7.46 (1H, d, *J* = 8.0 Hz), 7.37 (1H, t, *J* = 8.0 Hz), 7.01 (1H, t, *J* = 8.0 Hz), 4.68 (2H, d, *J* = 6.5 Hz), 1.98 (1H, t, *J* = 6.5 Hz).

2-Iodobenzyl chloride (S-5)[14]: To a stirred solution of the alcohol **S-4** (2.00 g, 8.55 mmol) in CH_2Cl_2 (16.6 mL) were added Et_3N (1.6 mL, 11.5 mmol), DMAP (88.0 mg, 0.72 mmol), and TsCl (2.44 g, 12.8 mmol) at room temperature. After stirred for 10 h, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and combined organic phase were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane) to give the chloride **S-5** (1.91 g, 88%) as a yellow oil. The ^1H NMR spectrum was identical with that previously reported.[14] R_f 0.73 (*n*-hexane/EtOAc = 80:20); ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 8.0 Hz), 7.46 (1H, d, *J* = 7.7 Hz), 7.35 (1H, t, *J* = 8.0 Hz), 7.00 (1H, t, *J* = 7.7 H), 4.68 (2H, s).

(2-Iodophenyl)acetonitrile (S-6)[15]: To a stirred solution of the benzyl chloride **S-5** (1.70 g, 6.73 mmol) in EtOH (17 mL) was added NaCN (660 mg, 13.5 mmol) at room temperature. After stirred for 6 h at 80 °C, the reaction was quenched with water. The aqueous phase was extracted with Et_2O and combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/Et_2O = 80:20) to give the nitrile **S-6** (1.51 g, 92%) as a yellow oil. The ^1H NMR spectrum was identical with that previously reported.[15] R_f 0.35 (*n*-hexane/EtOAc = 90:10); ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 7.8 Hz), 7.53 (1H, d, *J* = 7.8 Hz), 7.35 (1H, t, *J* = 7.8 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 3.82 (2H, s).

2-(2-Ethynylphenyl)acetic acid (S-7)[16]: To a stirred solution of the iodide **S-6** (985 mg, 4.05 mmol) in DMF (1.5 mL) were added TMS acetylene (0.72 mL, 5.1 mmol), Et_3N (2.0 mL, 15 mmol), $Pd(PPh_3)_2Cl_2$ (44.6 mg, 0.0635 mmol), and CuI (38.6 mg, 0.203 mmol) at room temperature. After stirred for 12 h at 50 °C, the reaction was quenched with water. The aqueous phase was extracted with EtOAc and the

combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified through a silica gel pad (eluent: *n*-hexane/EtOAc = 90:10) to give the crude acetylene (854 mg) as a brown oil. The above crude oil was dissolved in 15% aqueous NaOH (2.4 mL) and stirred under reflux for 2.5 h. The mixture was washed with Et_2O and the aqueous phase was acidified (pH 1) with 15% aqueous HCl. The aqueous phase was extracted with Et_2O and the combined organic phase were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 3:1 with formic acid (3% v/v)) to give the carboxylic acid **S-7** (243 mg, 38%) as orange powder. The ^{1}H NMR spectrum was identical with that previously reported.[16] R_f 0.61 (*n*-hexane/EtOAc = 75:25 with formic acid (1 drop)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 7.3 Hz), 7.35–7.24 (3H, m), 3.90 (2H, s), 3.29 (1H, s).

***N*-6-Trimethylsilyl-4-hexenyl-2-(2-ethynylphenyl)acetamide (9):** To a stirred solution of the carboxylic acid **S-7** (56.5 mg, 0.353 mmol) in CH_2Cl_2 (6.5 mL) were added the amine **S-3** (72.4 mg, 0.423 mmol) in CH_2Cl_2 (2.0 mL), EDCI·HCl (81.1 mg, 0.423 mmol), HOBt (52.5 mg, 0.388 mmol), and DMAP (1.8 mg, 0.084 mmol) at room temperature. After stirred for 4 h, the reaction was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 80:20) to give the amide **9** (76.8 mg, 58%) as a yellow oil. R_f 0.42 (*n*-hexane/EtOAc = 67:33 with formic acid (1 drop)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (1H, m), 7.36–7.34 (2H, m), 7.29–7.24 (1H, m), 5.50 (1H, br s), 5.39–5.26 (1H, m), 5.20–5.10 (1H, m), 3.75 (2H, s), 3.32 (1H, s), 3.25–3.17 (2H, m), 1.95–1.90 (2H, m), 1.57–1.43 (2H, m), 1.39–1.33 (2H, m), 0.07 (1.5H, s), –0.02 (7.5H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 137.8, 133.1, 130.1, 129.6, 127.3, 127.2, 126.1, 122.0, 81.98, 81.94, 42.5, 39.1, 29.9, 24.4, 22.6, –1.81; IR (neat) 3300, 1647, 1556, 1248, 1157, 839, 757 cm^{-1}; MS (EI) *m/z* 313 (M^+); HRMS (EI) calcd for $C_{19}H_{27}NOSi$ (M^+) 313.1862, found 313.1888.

5-(Trimethylsilyl)-3-penten-1-ol (S-8)[17]: A solution of 3-buten-1-ol (0.17 mL, 1.99 mmol), allyltrimethylsilane (0.9 mL, 5.99 mmol), and Grubbs' 2nd generation catalyst (50.0 mg, 0.059 mmol) was heated in refluxing CH_2Cl_2 (6.0 mL). After 24 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 90:10) to give the alcohol **S-8** (256 mg, 81%, (*E*):(*Z*) = *ca*. 67:33) as a colorless oil. The ^{1}H NMR spectrum was identical with that previously reported.[17] R_f 0.54 (*n*-hexane/EtOAc = 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67–5.51 (1H, m), 5.36–5.19 (1H, m), 3.71–3.60 (2H, m), 2.38–2.26 (2H, m), 1.54 (0.67H, d, J = 7.5 Hz), 1.51 (1.33H, d, J = 7.5 Hz), 0.20 (3H, s), –0.01 (6H, s).

5-(Trimethylsilyl)-3-penten-1-amine (S-9) [18]**:** To a stirred solution of the alcohol **S-8** (500 mg, 3.16 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (0.7 mL, 4.68 mmol), DMAP (15.0 mg, 0.123 mmol), and TsCl (903 mg, 4.74 mmol) at room temperature. After stirred for 11 h, the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 and combined organic phase were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by Florisil pad (eluent: *n*-hexane/EtOAc = 95:5) to give the crude tosylate as an orange oil. The residue (922 mg), which proved to be pure by ^{1}H NMR, was conducted immediately to the next reaction. R_f 0.78 (*n*-hexane/AcOEt = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (0.67H, d, J = 8.5 Hz), 7.99 (1.33H, d, J = 8.5 Hz), 7.61 (0.67H, d, J = 8.5 Hz), 7.54 (1.33H, d, J = 8.5 Hz), 5.73–5.61 (1H, m), 5.33–5.24 (1H, m), 4.28 (0.67H, t, J = 6.9 Hz), 4.19 (1.33H, t, J = 6.9 Hz), 2.70 (0.99H, s), 2.65 (2.01H, s), 2.59–2.49 (2H, m), 1.62 (0.67H, d, J = 9.3 Hz), 1.59 (1.33H, d, J = 7.8 Hz), 0.17 (2.97H, s), 0.16 (6.03H, s). To a solution of the above crude tosylate in DMSO (13 mL) was added NaN_3 (0.31 g, 4.8 mmol) at room temperature. After stirred for 6 h at the same temperature, the reaction was quenched with water and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue (587 mg) was conducted immediately to the next reaction without further purification. R_f 0.82 (*n*-hexane/AcOEt = 70:30). To a stirred suspension of LAH (240 mg, 6.4 mmol) in Et_2O (9.0 mL) was added a solution of the azide (668 mg, 3.38 mmol) in Et_2O (3.0 mL) at 0 °C. After stirred for 7 h at room temperature, the mixture was diluted with Et_2O (12 mL) at 0 °C and the reaction was quenched with water (0.24 mL), 15% aqueous NaOH (0.24 mL), and water (0.72 mL). After stirred for 1 h at room temperature, the solution was filtered through a Celite pad, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: $CHCl_3$/EtOH = 20:10) to give the amine **S-9** (280 mg, 56% for 3 steps, (*E*):(*Z*) = *ca*. 67:33) as a colorless oil. The ^{1}H NMR spectrum was identical with that previously reported.[18] R_f 0.08 ($CHCl_3$/EtOH = 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57–5.42 (1H, m), 5.29–5.14 (1H, m), 2.79–2.62 (2H, m), 2.16–2.10 (2H, m), 1.53–1.43 (4H, m), –0.01 (2.97H, s), –0.02 (6.03H, s).

***N*-[5-(Trimethylsilyl)-3-penten-1-yl]-4-pentynamide (11):** According to the procedure for **9**, the amide was obtained in 83% (168 mg) as a colorless oil starting from **S-9** (167 mg, 1.02 mmol) and 4-pentynoic acid (83.0 mL, 0.846 mmol). R_f 0.31 (*n*-hexane/ EtOAc = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (1H, br s), 5.57–5.44 (1H, m), 5.24–5.14 (1H, m), 3.38–3.24 (2H, m), 2.53–2.49 (2H, m), 2.39–2.34 (2H, m), 2.23–2.16 (2H, m), 1.98 (1H, s), 1.44 (0.73H, d, J = 8.8 Hz), 1.42 (1.27H, d, J = 8.8 Hz), –0.02 (3.3H, s), –0.04 (5.7H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 129.5, 124.7, 83.0, 69.2, 39.3, 35.4, 32.7, 22.8, 14.9, –1.83; IR (neat) 3310, 2955, 1649, 1551, 1249, 855, 756 cm^{-1}; MS (EI) *m/z* 237 (M^+); HRMS (FAB) calcd for $C_{13}H_{24}NOSi$ (M^++H) 238.1627, found 238.1660.

***N*-[5-(Trimethylsilyl)-3-penten-1-yl]-5-hexynamide (13):** According to the procedure for **9**, the amide was obtained in 67% (133 mg) as a colorless oil starting from **S-9** (150 mg, 0.953 mmol) and 5-hexynoic acid (0.087 mL, 0.795 mmol). R_f 0.25 (*n*-hexane/ EtOAc = 67:33); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58–5. 44 (2H, m), 5.24–5.12 (1H, m), 3.30–3.23 (2H, m), 2.33–2.17 (6H, m), 1.96 (1H, s), 1.46 (0.69H, d, J = 9.8 Hz), 1.41 (1.31H, d, J = 9.8 Hz), 0.00 (3.1H, s), –0.02 (5.9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 129.6, 124.8, 83.6, 69.1, 39.2, 35.1, 32.7, 24.2, 22.8, 17.8, –2.0 ; IR (neat) 3310, 2954, 1645, 1556, 1248 cm^{-1}; MS (EI) *m/z* 251 (M^+); HRMS (EI) calcd for $C_{14}H_{25}NOSi$ (M^+) 251.1706, found 251.1704.

Indolizidine 14: According to the General procedure, indolizidine **14** (1.2:1 mixture of *cis*- and *trans*-diastereomers) was obtained in 69% (14.0 mg) as a colorless oil starting from **11** (28.2 mg, 0.112 mmol). R_f 0.58 ($CHCl_3$/ MeOH = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (0.44H, ddd, J = 18.6, 8.9, 8.0 Hz), 5.58 (0.56H, ddd, J = 16.4, 8.9, 8.9 Hz), 5.17–5.00 (2H, m), 3.82–3.73 (0.56H, m), 3.71–3.62 (0.44H, m), 3.44–3.36 (1H, m), 2.59–2.22 (3H, m), 2.03–1.68 (4H, m), 1.61–1.56 (0.88H, m), 1.42–1.33 (1.12H, m), 1.24 (1.68H, s), 1.02 (1.32H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.35, 168.99, 137.71, 135.70, 117.56, 115.75, 63.53, 63.19, 55.40, 53.56, 42.83, 42.73, 34.42, 31.22, 30.51, 31.41, 27.13, 26.05, 25.92, 19.67, 17.67, 17.47; IR (neat) 3430, 3078, 1598, 1465, 919, 752 cm^{-1}; MS (EI) *m/z* 179 (M^+); HRMS (EI) calcd for $C_{11}H_{17}NO$ (M^+) 179.1310, found 179.1305.

7-(Trimethylsilyl)-5-hepten-1-ol (S-10)[19]: To a stirred solution of $[Ph_3PCH_2CH_2TMS]I$ (2.37 g, 4.83 mmol) in THF (40 mL) was added BuLi (1.6 M in *n*-hexane, 3.2 mL, 5.12 mmol) at –78 °C. After stirred for 1.5 h at room temperature, a dark red solution of ylide was caused. To this ylide solution was added dropwise tetrahydro-2*H*-pyran-2-ol[20] (235 mg, 2.30 mmol) in THF (10 mL) at –78 °C and stirred for 0.5 h at the same temperature. After stirred for 16 h, the reaction was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 80:20) to give the alcohol **S-10** (227 mg, 53%, (*E*):(*Z*) = *ca*. 85:15) as a colorless oil. The ^{1}H NMR spectrum was identical with that previously reported.[19] R_f 0.49 (*n*-hexane/EtOAc = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46–5.37 (1H, m), 5.29–5.20 (1H, m), 3.69–3.63 (2H, m), 2.04–2.00 (2H, m), 1.62–1.55 (2H, m), 1.47–1.39 (4H, m), 1.24 (1H, br s), 0.00 (7.7H, s), –0.02 (1.3H, s).

7-(Trimethylsilyl)-5-hepten-1-yl tosylate (S-11)[21]: To a stirred solution of the alcohol **S-10** (279 mg, 1.50 mmol) in CH_2Cl_2 (150 mL) were added Et_3N (0.34 mL, 2.27 mmol), DMAP (7.3 mg, 0.060 mmol), and TsCl (428 mg, 2.24 mmol) at room temperature. After stirred for 24 h the same temperature, the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 and combined organic phase were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by Florisil pad (eluent: *n*-hexane/EtOAc = 80:20) to give the tosylate **S-11** (316 mg, 72%) as an

orange oil. The ^{1}H NMR was identical with that of previously reported,[21] and was conducted immediately to the next reaction. R_f 0.68 (*n*-hexane/EtOAc = 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 5.43–5.34 (1H, m), 5.19–5.11 (1H, m), 4.05–3.99 (2H, m), 3.77–3.72 (4H, m), 2.45 (3H, s), 1.97–1.83 (4H, m), 1.70–1.58 (2H, m), 1.41–1.33 (4H, m), –0.02 (2.97H, s), –0.03 (6.03H, s)

7-(Trimethylsilyl)-5-hepten-1-amine (S-12)[19]: To a solution of the tosylate **S-11** (205 mg, 0.701 mmol) in DMSO (3.5 mL) was added NaN_3 (59.3 mg, 0.912 mmol) at room temperature. After stirred for 6 h at the same temperature, the reaction was quenched with water and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue (350 mg) was conducted immediately to the next reaction without further purification. R_f 0.90 (*n*-hexane/EtOAc = 90:10). To a stirred suspension of LAH (53.2 mg, 1.40 mmol) in Et_2O (1.0 mL) was added a solution of the azide (350 mg) in Et_2O (5.0 mL) at 0 °C. After stirred for 7 h at room temperature, the mixture was diluted with THF (7.0 mL) at 0 °C and the reaction was quenched with water (0.15 mL), 15% aqueous NaOH (0.15 mL), and water (0.45 mL). After stirred for 1 h at room temperature, the solution was filtered through a Celite pad, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue (119 mg, 91%), which proved to be pure by ^{1}H NMR, was conducted immediately to the next reaction. The ^{1}H NMR spectrum was identical with that previously reported.[19] R_f 0.1 ($CHCl_3$/MeOH = 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46–5.37 (1H, m), 5.29–5.20 (1H, m), 2.63 (2H, br s), 2.04–1.97 (2H, m), 1.65–1.37 (8H, m), 0.00 (6.03H, s), –0.02 (2.97H, s).

***N*-[7-(Trimethylsilyl)-5-hepten-1-yl]-5-hexynamide (15):** According to the procedure for the amide **9**, amide **15** was obtained in 56% (78.5 mg) as a colorless oil starting from **S-12** (95.9 mg, 0.517 mmol) and 5-hexynoic acid (56.6 mg, 0.505 mmol). R_f 0.27 (*n*-hexane/EtOAc = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, br s), 5.44–5.34 (1H, m), 5.26–5.17 (1H, m), 3.27–3.22 (2H, m), 2.32–2.23 (4H, m), 2.03–1.95 (3H, m), 1.89–1.82 (2H, m), 1.55–1.33 (6H, m), 0.01 (2.97H, s), –0.01 (6.03H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 126.8, 126.0, 83.6, 69.1, 39.4, 35.1, 29.3, 27.0, 26.6, 24.2, 18.5, 17.8, –1.80; IR (neat) 3310, 3087, 1645, 1556, 1248, 1153, 855 cm^{-1}; MS (EI) *m/z* 279 (M^+); HRMS (EI) calcd for $C_{16}H_{29}NOSi$ (M^+) 279.2019, found 279.2048.

Lactam 16: According to the General procedure, lactam **16** was obtained in 20% (3.2 mg) as a colorless oil starting from **15** (15.7 mg, 0.0562 mmol). R_f 0.66 (*n*-hexane/EtOAc = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50–5.43 (1H, m), 5.37–5.30 (1H, m), 4.60 (1H, t, J = 4.4 Hz), 3.53 (2H, t, J = 7.2 Hz), 2.30 (2H, t, J = 7.6 Hz), 2.01 (2H, dt, J = 7.2 and 7.2 Hz), 1.80–1.73 (2H, m), 1.61–1.45 (5H, m), 1.37–1.28 (2H, m), 0.02 (7.5H, s), –0.07 (1.5H, s).

***N*-[6-(Trimethylsilyl)-4-hexen-1-yl]-6-heptynamide (17):** According to the procedure for the amide **9**, amide **17** was obtained in 77% (57.6 mg) as a colorless oil starting from **S-3** (45.9 mg, 0.268 mmol) and

6-heptynoic acid (33.7 mg, 0.267 mmol). R_f 0.30 (*n*-hexane/EtOAc = 70:30 with formic acid (1 drop)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (1H, br s), 5.47–5.33 (1H, m), 5.26–5.14 (1H, m), 3.27–3.21 (2H, m), 2.22–2.16 (4H, m), 2.03–1.98 (2H, m), 1.94 (1H, s), 1.78–1.70 (2H, m), 1.62–1.49 (4H, m), 1.44 (0.68H, d, J = 8.8 Hz), 1.23 (1.32H, d, J = 8.8 Hz), –0.01 (3.06H, s), –0.03 (5.94H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 127.3, 126.9, 84.1, 68.6, 39.1, 36.2, 30.5, 29.8, 27.9, 24.8, 22.6, 18.1, –2.0; IR (neat) 3310, 2952, 1644, 1556 cm^{-1}; MS (EI) *m/z* 279 (M^+); HRMS (EI) calcd for $C_{16}H_{29}NOSi$ (M^+) 279.2019, found 279.2013.

Lactam 18: According to the General procedure, lactam **18** was obtained in 25% (3.0 mg) as a colorless oil starting from **17** (12.0 mg, 0.0429 mmol). R_f 0.78 ($CHCl_3$/ MeOH = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, t, J = 6.6 Hz), 5.41–5.32 (1H, m), 5.25–5.18 (1H, m), 3.53–3.45 (2H, m), 2.41 (t, J = 6.8 Hz) 2.17–1.98 (6H, m), 1.87 (3H, s), 1.58–1.49 (2H, m), 1.45 (0.68H, d, J = 6.8 Hz), 1.39 (1.32H, d, J = 6.8 Hz), –0.10 (3.06H, s), –0.30 (5.94H, s).

2-(5-Hexynyloxy)tetrahydro-2*H*-pyran (S-13)[22]: To a stirred solution of 5-hexyn-1-ol (2.25 g, 22.9 mmol) and DHP (6.19 mL, 68.7 mmol) in CH_2Cl_2 (114 mL) was added PPTS (1.14 g, 0.458 mmol) at room temperature. After stirred for 2 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 80:20) to give the ether **S-13** (4.02 g, 96%) as a colorless oil. ^{1}H NMR spectrum was identical with that previously reported.[22] R_f 0.85 (*n*-hexane/AcOEt = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, t, J = 3.3 Hz), 3.90–3.80 (1H, m), 3.80–3.70 (1H, m), 3.54–3.46 (1H, m), 3.44–3.36 (1H, m), 2.23 (2H, td, J = 7.2 and 2.4 Hz), 1.94 (1H, t, J = 2.4 Hz), 1.86–1.46 (10H, m).

Methyl 7-(tetrahydro-2*H*-pyran-2-yloxy)-2-heptynoate (S-14)[22]: To a stirred solution of the acetylene **S-13** (0.497 mg, 2.73 mmol) in THF (2.72 mL) was added dropwise BuLi (1.60 M in hexane, 2.71 mL, 4.10 mmol) at –78 °C. After stirred for 2 h at –78 °C, to this solution was added dropwise methyl chloroformate (0.624 mL, 8.19 mmol) at 0 °C. After stirring at room temperature for 22 h, the reaction was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 90:10) to afford the ester **S-14** (551 mg, 84%) as a colorless oil; ^{1}H NMR spectrum was identical with that previously reported.[22] R_f 0.55 (*n*-hexane/AcOEt = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (1H, t, J = 3.9 Hz), 3.90–3.80 (1H, m), 3.80–3.70 (4H, m), 3.54–3.46 (1H, m), 3.44–3.36 (1H, m), 2.38 (2H, t, J = 6.0 Hz), 1.86–1.46 (10H, m).

Methyl 7-hydroxy-2-heptynoate (S-15)[22]: To a stirred solution of the ester **S-14** (1.4 g, 5.82 mmol) in EtOH (31.3 mL) was added PPTS (167 mg, 0.64 mmol) at room temperature. After stirred for 10 h at 55 °C, the reaction was quenched with aqueous $NaHCO_3$ and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 80:20) to give the alcohol **S-15** (940 mg, 89%) as a yellow oil. ^{1}H NMR spectrum of this alcohol was identical with that previously reported.[22] R_f 0.23 (*n*-hexane/AcOEt = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (3H, s), 3.68 (2H, t, J = 5.7 Hz), 2.40 (2H, t, J = 2.4 Hz), 1.74–1.66 (4H, m).

6-Methoxycarbonyl-5-hexynoic acid (S-16)[22]: To a stirred solution of the alcohol **S-15** (290 mg, 1.82 mmol) in DMF (12.2 mL) were added Celite (2.39 g) and PDC (2.36 g, 6.27 mmol) at room temperature. After stirred for 6 h at the same temperature, silica gel was added to this stirred mixture and then filtered through a Celite pad. The solution was acidified (pH 1) by the addition of 1 M aqueous HCl and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 50:50) to give the carboxylic acid **S-16** (223 mg, 72%) as a yellow oil; ^{1}H NMR spectrum was identical with that previously reported.[22] R_f 0.33 (*n*-hexane/ EtOAc = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (3H, s), 2.51 (2H, t, J = 6.9 Hz), 2.49 (2H, t, J = 6.9 Hz), 1.93 (2H, tt, J = 6.9 and 6.9 Hz).

***N*-[6-(Trimethylsilyl)-4-hexen-1-yl]-6-methoxycarbonyl-5-hexynamide (19):** According to the procedure for the amide **9**, amide **19** was obtained in 81% (509 mg) as a colorless oil starting from the amine **S-3** (405 mg, 2.36 mmol) and the carboxylic acid **S-16** (335 mg, 1.97 mmol). R_f 0.56 (*n*-hexane/ EtOAc = 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (1H, br), 5.46–5.34 (1H, m), 5.32–5.12 (1H, m), 3.75 (3H, s), 3.25 (2H, t, J = 3.6 Hz), 2.44 (2H, t, J = 6.9 Hz), 2.30 (2H, t, J = 4.8 Hz), 2.08–1.98 (2H, m), 1.98–1.86 (2H, m), 1.60–1.50 (2H, m), 1.48–1.38 (2H, m), 0.00 (1.5H, s), –0.02 (7.5H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 154.0, 127.3, 127.1, 126.4, 126.0, 88.7, 73.5, 52.6, 39.4, 39.2, 34.9, 30.2, 29.9, 29.6, 24.5, 23.3, 22.7, 18.6, 18.1, –1.9; IR (neat) 3297, 3086, 2237, 1717, 1647 cm^{-1}; MS (EI) *m/z* 323 (M^+); HRMS (EI) *m/z* calcd for $C_{17}H_{29}NO_3Si$ (M^+) 323.1922, found 323.1917.

Enamide 20: To a stirred solution of the amide **19** (43.1 mg, 0.132 mmol) in $ClCH_2CH_2Cl$ (1.32 mL) were added XPhosAuCl (9.38 mg, 0.0132 mmol) and AgOTf (3.40 mg, 0.0132 mmol) at room temperature. After stirred for 36 h at 80 °C, the reaction was quenched with aqueous $NaHCO_3$ and the mixture was filtered through a Celite pad. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 90:10) to give the enamide **20** (33.0 mg, 77%) as a colorless oil. R_f 0.58 (*n*-hexane/ EtOAc = 70:30); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 5.46–5.40 (1H, m), 5.30–5.20 (2H, m), 3.74–3.68 (5H, m), 3.23 (2H, t, J = 3.6 Hz), 2.58–2.54 (2H, m), 2.02–1.98 (2H, m), 1.84–1.80 (2H, m), 1.62–1.58 (2H, m), 1.42–1.40 (2H, m), 0.00 (1.5H, s), –0.02 (7.5H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 167.8, 155.7, 127.3, 127.0, 126.6, 125.7, 95.9, 51.0, 42.5, 33.5, 30.3, 26.6, 26.5, 26.1, 24.5, 22.7, 18.6, –1.8; IR (neat) 3630, 2952, 2361, 1717, 1695 cm^{-1}; MS (EI) *m/z* 323 (M^+); HRMS (EI) *m/z* calcd for $C_{17}H_{29}NO_3Si$ (M^+) 323.1950, found 323.1917.

Quinolizidine 21: To a stirred solution of enamide **20** (17.8 mg, 0.055 mmol) in $ClCH_2CH_2Cl$ (0.1 M, 0.55 mL) was added $ZnBr_2$ (18.5 mg, 0.082 mmol) at room temperature. After stirred for 18 h at 80 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was filtered through a Celite pad. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 85:15 to 30:70) to give the quinolizidine **21** (7.8 mg, 57%) as a yellow oil. R_f 0.17 (*n*-hexane/ EtOAc = 30:70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64–5.50 (1H, m), 5.14–5.06 (2H, m), 4.78–4.68 (1H, m), 3.62 (3H, s), 3.17 (1H, d, J = 15.0 Hz), 2.78–2.60 (1H, m), 2.40–2.28 (2H, m), 2.28–2.18 (2H, m), 2.00–1.90 (1H, m), 1.74–1.60 (6H, m), 1.60–1.36 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.5, 137.6, 118.2, 60.3, 51.8, 50.4, 37.1, 37.1, 36.7, 32.8, 31.8, 26.9, 24.6, 16.5; IR (neat) 3440, 2926, 1733, 1625 cm^{-1}; MS (EI) *m/z* 251 (M^+); HRMS (EI) *m/z* calcd for $C_{14}H_{21}NO_3$ (M^+) 251.1521, found 251.1535.

ACKNOWLEDGEMENTS

This work was partly supported by The Naito Foundation (for K.S.).

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