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Development of a Brønsted Acid-Promoted Arene−Ynamide Cyclization toward the Total Syntheses of Marinoquinolines A and C and Aplidiopsamine A

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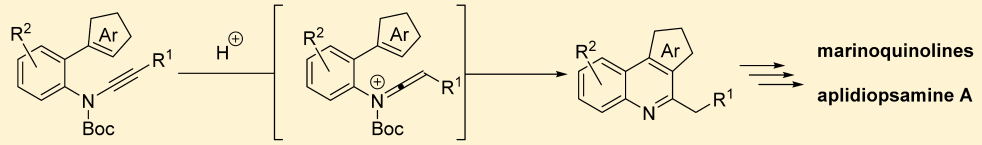
Supporting Information



ABSTRACT: A Brønsted acid-promoted arene−ynamide cyclization has been developed to construct the 3*H*-pyrrolo[2,3-*c*]quinolines. This reaction consists of the generation of a highly reactive keteniminium intermediate from arene−ynamide activated by a Brønsted acid and electrophilic aromatic substitution reaction to give arene-fused quinolines in high yields. This methodology enabled facile access to marinoquinolines A and C and aplidiopsamine A.

INTRODUCTION

Heterocycles are an important and attractive class of compounds for medicinal and material chemistries. Of these, the quinoline skeleton is an important nucleus that is frequently found as a component in pharmaceutical agents and biologically active natural products.[1] Recently, the 3*H*-pyrrolo[2,3-*c*]-quinoline ring system was found in marine natural products. Marinoquinolines A−F were isolated from the marine bacteria and found to possess weak antibacterial and antifungal activities and moderate cytotoxicity against growing mammalian cell lines.[2] Furthermore, as the structurally related binuclear alkaloid, aplidiopsamine A was isolated from the temperate Australian ascidian, *Aplidiopsis confluata*, and exhibited significant growth inhibition of chloroquine-resistant strains of the malaria parasite, *Plasmodium falciparum* (Figure 1).[3] Although the efficient synthesis of these natural products was reported, there is no report of the synthesis of these analogues that have other fused aromatic rings, instead of a pyrrole ring.[4,5] Recently, ynamides have received much attention as fascinating building blocks for the synthesis of nitrogen-containing compounds.[6] A wide range of nucleophiles have been shown to react at the α position of ynamides, which is activated as keteniminium ions by the action of a Brønsted acid.[7] We recently reported a domino reaction of ynamides with aldimines or ketimines in the presence of a catalytic amount of triflic imide to afford α,β-unsaturated amidines or dihydroquinolines in good yields.[8] In this paper, we report a Brønsted acid-promoted cyclization of arene−ynamides to afford the arene-fused quinoline derivatives and the total syntheses of marinoquinolines A and C and aplidiopsamine A as an application of this methodology.

The retrosynthetic analysis of 3*H*-pyrrolo[2,3-*c*]quinolines is shown in Scheme 1. We anticipated that the tricyclic heterocycle could be synthesized by electrophilic aromatic substitution reaction with the keteniminium intermediate of arene−ynamide,[7,9] which could be easily prepared by the

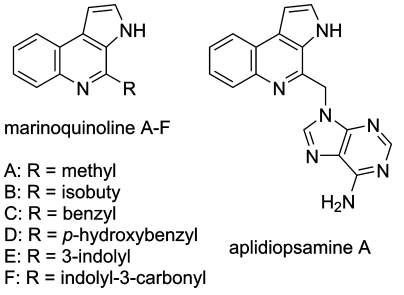
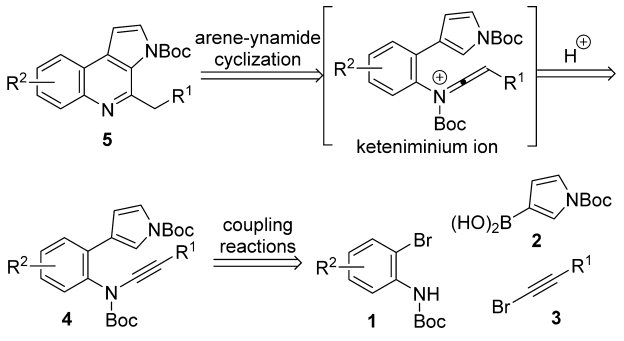


Figure 1. Natural products possessing a 3*H*-pyrrolo[2,3-*c*]quinoline ring system.

Scheme 1. Retrosynthetic Analysis of 3*H*-Pyrrolo[2,3-*c*]quinoline Ring Construction



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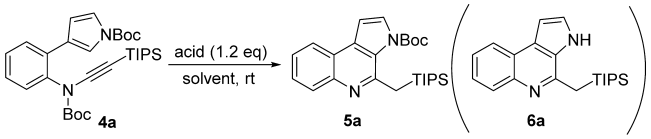
coupling reactions of *N*-(*tert*-butoxycarbonyl)-2-bromoaniline with the corresponding boronic acid and bromoacetylene.

RESULTS AND DISCUSSION

We examined the cyclization reaction of arene−ynamide **4a** under several conditions (Table 1). Initially, we investigated several Brønsted acids for a cyclization reaction with **4a** in dichloromethane at room temperature. Gratifyingly, the use of 1.2 equiv of triflic imide (Tf_2NH) as a strong acid gave the desired tricyclic quinoline derivative **5a** in 85% yield in 5 min (entry 1). It is noteworthy that the acidity of acids is very important in this cyclization reaction. The yields were lower, and some starting material was recovered, as the acidity of acids was weaker (entries 2−5). Interestingly, the cyclization reaction with triflic acid (TfOH) was accompanied by removal of the *tert*-butoxycarbonyl group on the pyrrole moiety to afford the product **6a** in 86% yield (entry 6). Moreover, we investigated the reaction with π-acidic transition metal salts, such as Au, Ag, and Cu salts, for the cyclization reaction; however, the reaction did not proceed well, and the recovery of starting material **4a** was mainly observed (entries 7−9). The reaction in other solvents, such as toluene and hexane, gave moderate yields (entries 10 and 11). The reaction was carried out with a catalytic amount of triflic imide (20 mol %) to provide low yield (entry 12).

Table 1. Optimization of Reaction Conditions[a]

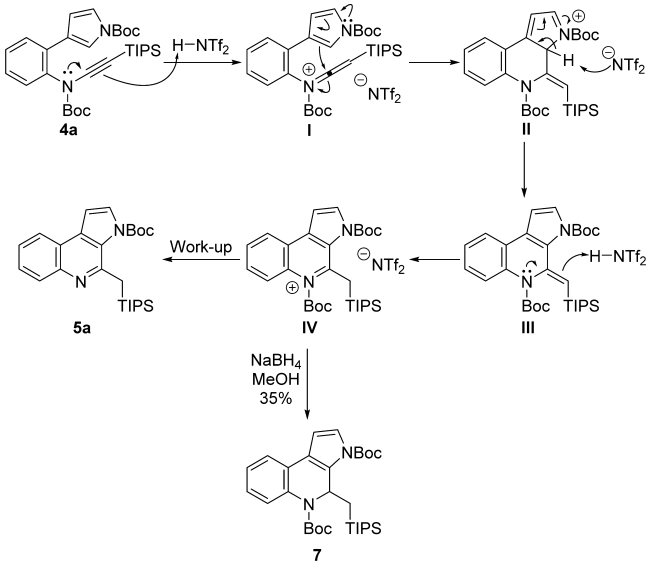


entry	acid	time	solvent	yield (%)[b]
1	Tf_2NH	5 min	CH_2Cl_2	85
2	TFA	12 h	CH_2Cl_2	26
3	*p*-TsOH	12 h	CH_2Cl_2	59
4	CSA	12 h	CH_2Cl_2	58
5	HBF_4	5 min	CH_2Cl_2	72
6	TfOH	5 min	CH_2Cl_2	86 (**6a**)
7	AgOTf	12 h	CH_2Cl_2	11
8	$Cu(OTf)_2$	12 h	CH_2Cl_2	26
9	$AuCl(PPh_3)$	12 h	CH_2Cl_2	0
10	TfOH	5 min	toluene	76
11	TfOH	5 min	hexane	73
12[c]	Tf_2NH	12 h	CH_2Cl_2	18

[a]Unless otherwise noted, reactions were performed with **4a** (0.2 mmol) and acid (0.24 mmol) in solvent (0.1 M) at rt. [b]Isolated yields. [c]Using 20 mol % of Tf_2NH.

Based on these results, a plausible mechanism is shown in Scheme 2. First, the reaction of ynamide **4a** would be initiated by an addition of triflic imide to generate the highly reactive keteniminium intermediate **I**. Electrophilic aromatic substitution reaction would occur to yield the intermediate **III** along with a regeneration of a Brønsted acid. Probably, intermediate **III** would react further with a Brønsted acid to afford quinolinium **IV**, which was then hydrolyzed during an aqueous workup to give the desired product **5a**.[10] The formation of **IV** as an initial product is supported by the following results: (1) The reaction could not be promoted by a catalytic amount of an acid (Table 1, entry 12). (2) The reaction with the *N*-methoxycarbonyl analogue of **4a** also gave **5a** in 65% yield. (3)

Scheme 2. Proposed Mechanism for Arene−Ynamide Cyclization Reaction



When the reaction was quenched by $NaBH_4$ in methanol, the 1,2-dihydroquinoline **7** was obtained in a moderate yield.

Under the optimized reaction conditions (1.2 equiv of TfOH in CH_2Cl_2 at rt), the arene−ynamide cyclization reaction of various ynamides **4** was achieved, and the results are summarized in Scheme 3. The reaction with substrates **4b−d** bearing other heteroaromatic groups, such as 3-furyl, 3-thenyl, and 3-indolyl, afforded the desired products **6b−d** in high yields. Substrate **4e**, with a simple phenyl ring, afforded phenanthridine **6e** in a moderate yield. Substrates bearing electron-donating (**4f**) or electron-withdrawing (**4g**) groups at the *para* position on the phenyl ring are well-tolerated, giving products **6f** and **6g** in high yields, respectively. Finally, the substituents on a terminal position of ynamide were investigated. Not only a silyl group but also a hydrogen atom (**4h**) and phenyl (**4i**) and ester (**4j**) groups are applicable under this reaction to give the desired cyclized products **6h−j** in good yields. As a consequence, we accomplished the total syntheses of marinoquinolines A (**6h**) and C (**6i**). Overall, our methodology represents the divergent synthesis of analogues of 3*H*-pyrrolo[2,3-*c*]quinolines.

Finally, the total synthesis of aplidiopsamine A was pursued. First, halogenation of the *N*-Boc-protected derivative of marinoquinoline A (**6h**) was investigated. However, all attempts of radical or ionic bromination of the quinolinylmethyl moiety failed.[11] Thus, we examined the synthesis of 2-(halomethyl)quinolines **8** or **9** from ynamides **4k,l** (Table 2). The acid treatment of halogenated ynamides **4k** and **4l** afforded complex mixtures containing a small amount of the desired products (entries 1 and 2). Gratifyingly, the acid treatment of ynamide **4a** and desilylation with tetra-*n*-butylammonium fluoride (TBAF), followed by bromination with *N*-bromosuccinimide (NBS) at −78 °C in one pot, gave the desired bromide **8** in 43% yield (entry 3). After several modifications, we found that an addition of TBAF was not required when **4a** was treated with the acid for 60 min at −78 °C prior to the addition of NBS to give the desired product in 64% yield (entry 4). We presumed that the bromodesilylation reaction promoted by NBS would occur after the acid treatment of ynamide **4a**: the cyclic bromonium ion **V** was generated from the vinylsilane

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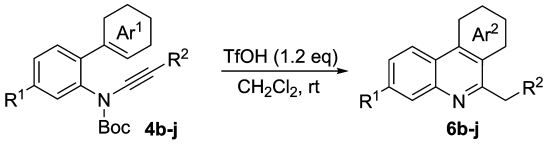
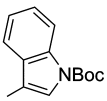
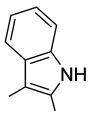
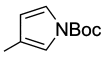
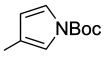
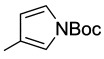
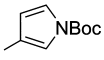
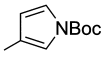
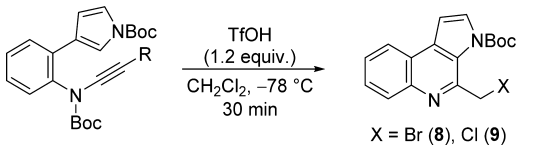
Scheme 3. Substrate Scope[a]



entry	4b-j	Ar^1	R^1	R^2	Product	Ar^2	yield (%)
1	**4b**		H	TIPS	**6b**		92
2	**4c**		H	TIPS	**6c**		88
3	**4d**		H	TIPS	**6d**		77
4	**4e**		H	TIPS	**6e**		52
5	**4f**		Me	TIPS	**6f**		79
6	**4g**		F	TIPS	**6g**		90
7	**4h**		H	H	**6h**		73
8	**4i**		H	Ph	**6i**		74
9	**4j**		H	CO_2Et	**6j**		79

[a]Reactions were performed with **4** (0.2 mmol) and TfOH (0.24 mmol) in CH_2Cl_2 (0.1 M) at rt. Isolated yields.

Table 2. Preparation of 2-(Halomethyl)quinoline[a]



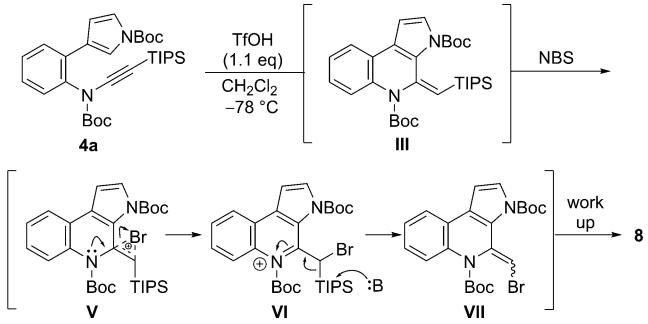
entry	R	conditions	yield (%)[b]
1	Br (**4k**)	TfOH, CH_2Cl_2	trace
2	Cl (**4l**)	TfOH, CH_2Cl_2	trace
3	TIPS (**4a**)	TfOH, CH_2Cl_2; TBAF; NBS	43
4	TIPS (**4a**)	TfOH, CH_2Cl_2; NBS	64
5	TIPS (**4a**)	TfOH, CH_2Cl_2; Br_2	32

[a]Reactions were performed with **4** (0.2 mmol). [b]Isolated yields.

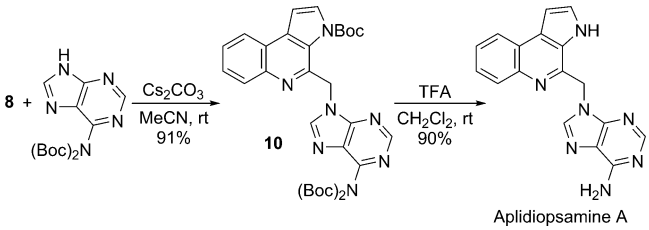
intermediate **III**, followed by the ring opening of the cyclic brominium ion to give the intermediate **VI**. Then, the basic species, such as succinimide and triflate anion, attached to the silicon atom to give vinyl bromide **VII**, which after workup afforded the desired product **8** (Scheme 4).[12] The use of bromine in place of NBS resulted in no improvement (entry 5).

The total synthesis of aplidiopsamine A was accomplished as shown in Scheme 5. The reaction of bromide **8** and di-Boc-

Scheme 4. Plausible Mechanism for the Synthesis of Bromide 8 from Ynamide 4a



Scheme 5. Total Synthesis of Aplidiopsamine A



protected adenine[13] with Cs_2CO_3 in CH_3CN, followed by the acidic deprotection of all three *tert*-butoxycarbonyl groups in **10**, afforded aplidiopsamine A in a high yield. Overall, the total synthesis of aplidiopsamine A was accomplished in 46% yield over five steps from *tert*-butyl (2-bromophenyl)carbamate.

■ CONCLUSION

We have developed a Brønsted acid-promoted arene−ynamide cyclization to provide arene-fused quinolines in high yields. The arene−ynamide could be easily prepared from commercially available *N*-(*tert*-butoxycarbonyl)-2-bromoaniline in two steps. The key reaction of arene−ynamide relied on the generation of the highly reactive keteniminium intermediate by the activation with a strong Brønsted acid and electrophilic aromatic substitution reaction. Furthermore, the total syntheses of marinoquinolines A and C as well as aplidiopsamine A clearly demonstrated a utility of this methodology. Further applications and biological evaluation of their analogues are ongoing in our laboratory.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out in flame-dried glassware under argon atmosphere and stirred via magnetic stir plates. All reactions were monitored by analytical thin-layer chromatography. Visualization was accomplished by UV light (254 nm), phosphomolybdic acid, or anisaldehyde. Flash column chromatography was performed using silica gel 60 (mesh 230−400). All reactions were carried out with anhydrous solvents unless otherwise noted. All reagents and starting materials, unless otherwise noted, were purchased from commercial vendors. Quadrupole, double-focusing magnetic sector, and TOF mass spectrometers were used for EI-, FAB-, and ESI-MS, respectively. Infrared spectra were recorded as thin films on sodium chloride plates. NMR spectra (500 MHz for ^1H, 125 MHz for ^{13}C) were measured in $CDCl_3$ unless otherwise mentioned. Chemical shift values (δ) are reported in parts per million (tetramethylsilane was used as an internal standard). The ^1H NMR spectra are reported as follows δ (multiplicity, coupling constant *J*, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The ^{13}C chemical shifts are reported relative to $CDCl_3$ (77.0 ppm),

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DMSO-d_6 (39.5 ppm), and acetone-d_6 (206.7 and 30.4 ppm). Bromoacetylenes **3** were prepared according to previous procedures.[14]

General Procedure for *N*-(*tert*-Butoxycarbonyl) *o*-Bromoanilines (1a–c).[15] To a solution of sodium hydride (1.1 equiv) in THF (0.2 M) was added *o*-bromoaniline derivative (10 mmol). The mixture was refluxed for 1 h and then cooled to room temperature. Di-*tert*-butyl dicarbonate (1.2 equiv) was added, and the slurry was stirred for 30 min. To the mixture was added a second portion of sodium hydride (1.1 equiv), and the reaction was brought back to reflux overnight. The reaction was cooled to room temperature and carefully quenched with water. This mixture was extracted with ether, and the organic layers were dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt) to afford N-protected *o*-bromoaniline.

Spectral data of *tert*-butyl (2-bromophenyl)carbamate (**1a**) and *tert*-butyl (2-bromo-5-fluorophenyl)carbamate (**1b**) are identical to those reported in ref 15.

***tert*-Butyl (2-Bromo-5-methylphenyl)carbamate (1c).** **1c** was obtained following the general procedure as a yellow oil (2.81 g, 98%) after purification by column chromatography: R_f = 0.21 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.99 (br s, 1H), 7.36 (d, J = 8.3 Hz, 1H), 6.96 (br s, 1H), 6.72 (dd, J = 8.0, 2.0 Hz, 1H), 2.31 (s, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.4, 138.5, 135.8, 131.8, 124.7, 120.5, 109.0, 81.0, 28.3, 21.3; IR (neat) 3412, 3019, 2641, 1726, 1584, 1520, 1445, 1217 cm^{-1}; MS m/z 287 (M$^+$), 230 (M − *t*-Bu), 186 (M − Boc); HRMS (m/z) calcd for $C_{12}H_{16}BrNNaO_2$ [M + Na]$^+$ 308.0262, found 308.0262.

(1-(*tert*-Butoxycarbonyl)-1*H*-pyrrol-3-yl)boronic Acid (2a). To a THF (200 mL) solution of 3-bromo-*N*-(*tert*-butoxycarbonyl)-pyrrole[16] (5.0 g, 20.3 mmol) was added dropwise *n*-butyllithium in hexane (1.6 M hexane solution, 15.2 mL, 24.4 mmol) at −78 °C. After being stirred for 20 min, a THF (10 mL) solution of trimethylborate (6.8 mL, 60.9 mmol) was added to the reaction mixture. After being stirred for 5 min, 50% aq MeOH (20 mL) was added to the reaction mixture. The reaction mixture was diluted with Et_2O (300 mL), and the organic layer was washed with water (200 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. To the crude product was added hexane to give a pale brown solid. Filtration gave the titled compound (1.97g, 47%): ^{1}H NMR (acetone-d_6) δ 7.65 (m, 1H), 7.20 (dd, J = 3.2, 2.0 Hz, 1H), 6.51 (dd, J = 3.2, 1.4 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (acetone-d_6) δ 149.5, 128.6, 121.0, 117.3, 84.3, 28.0 (one carbon overlapped).

General Procedure for *N*-Boc-Protected *o*-Aryl Anilines. A mixture of *N*-Boc-protected *o*-bromoaniline **1** (1 equiv), the corresponding boronic acid (1.6 equiv), tetrakis(triphenylphosphine)-palladium (5 mol %), and potassium carbonate (2.5 equiv) in toluene/EtOH (4/1) (0.1 M) was stirred at 80 °C under an argon atmosphere for 2–4 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt) to afford the desired product.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)amino)phenyl)-1*H*-pyrrole-1-carboxylate.** The product was obtained following the general procedure (1.8 mmol scale) as pale yellow solids (606 mg, 94%) after purification by column chromatography: mp 94–98 °C (hexanes/EtOAc); R_f = 0.32 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.39–7.31 (m, 2H), 7.31–7.23 (m, 2H), 7.05 (ddd, J = 7.5, 7.5, 1.3 Hz, 1H), 6.77 (br s, 1H), 6.36 (dd, J = 3.2 Hz, 1.7 Hz, 1H), 1.62 (s, 9H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.9, 148.5, 135.6, 129.6, 128.0, 124.5, 124.0, 123.0, 121.0, 119.8, 118.1, 112.6, 84.1, 80.3, 28.3, 28.0; IR (KBr) ν_{max} 3414, 2326, 1744, 1721, 1585, 1512, 1485, 1447, 1381, 1346 cm^{-1}; MS (FAB) m/z 358 (M$^+$), 303 (M − *t*-Bu + 2H), 246 (M − 2*t*-Bu + 2H); HRMS-ESI (m/z) calcd for $C_{20}H_{27}N_2O_4$ [M + H]$^+$ 359.1965, found 359.1954. Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.84; H, 7.39; N, 7.78.

***tert*-Butyl (2-(Furan-3-yl)phenyl)carbamate.** The product was obtained following the general procedure (1.8 mmol scale) as yellow solids (444 mg, 95%) after purification by column chromatography: mp 62–64 °C (hexanes/EtOAc); R_f = 0.32 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 7.7 Hz, 1H), 7.59–7.57 (m, 1H), 7.56 (dd, J = 1.6, 1.6 Hz, 1H), 7.31 (ddd, J = 8.2, 8.2, 1.5 Hz, 1H), 7.27–7.23 (m, 1H), 7.07 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 6.62 (br s, 1H), 6.56 (dd, J = 1.7, 0.9 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.9, 143.8, 140.1, 135.7, 129.7, 129.0, 128.4, 123.2, 122.5, 120.1, 111.1, 80.5, 28.3; IR (KBr) ν_{max} 3422, 3348, 2978, 2920, 1728, 1589, 1516, 1501, 1447, 1366 cm^{-1}; MS (FAB) m/z 259 (M$^+$), 203 (M − *t*-Bu + H), 186 (M − *t*-BuO), 159 (M − Boc); HRMS-ESI (m/z) calcd for $C_{15}H_{18}NO_3$ [M + H]$^+$ 260.1281, found 260.1280. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.26; H, 6.73; N, 5.26.

***tert*-Butyl (2-(Thiophen-3-yl)phenyl)carbamate.** The product was obtained following the general procedure (3.0 mmol scale) as a pale brown oil (586 mg, 71%) after purification by column chromatography: R_f = 0.30 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.48 (dd, J = 4.9, 2.9 Hz, 1H), 7.35–7.30 (m, 2H), 7,28–7.24 (m, 1H), 7.17 (dd, J = 4.9, 1.5 Hz, 1H), 7.10–7.05 (m, 1H), 6.63 (br s, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.8, 138.6, 135.5, 130.0, 128.4, 128.3, 126.7, 126.2, 123.4, 123.0, 119.8, 80.5, 28.3; IR (KBr) ν_{max} 3422, 3102, 3003, 2978, 2930, 1732, 1585, 1533, 1514, 1447, 1393, 1368, 1302 cm^{-1}; MS (FAB) m/z 275 (M$^+$), 220 (M − *t*-Bu + 2H), 219 (M − *t*-Bu + H). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.24; H, 6.20; N, 5.08.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)amino)phenyl)-1*H*-indole-1-carboxylate.** The product was obtained following the general procedure (0.5 mmol scale) as white solids (191 mg, 94%) after purification by column chromatography: mp 123–126 °C (hexanes/EtOAc); R_f = 0.30 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.23 (br d, J = 7.5 Hz, 1H), 8.13 (br d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.43–7.35 (m, 3H), 7.32 (dd, J = 7.6, 1.6 Hz, 1H), 7.28–7.23 (m, 1H), 7.12 (ddd, J = 7.5, 7.5, 1.3 Hz, 1H), 6.54 (s, br, 1H), 1.70 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.9, 149.6, 136.6, 135.5, 130.8, 129.4, 128.7, 125.0, 124.5, 123.1, 122.9, 122.4, 120.2, 120.0, 117.9, 115.4, 84.1, 80.4, 28.3, 28.2; IR (KBr) ν_{max} 3421, 3009, 2980, 2931, 1732, 1578, 1516, 1477, 1450, 1373, 1308 cm^{-1}; MS (FAB) m/z 408 (M$^+$), 352 (M − *t*-Bu + H), 308 (M − Boc + 2H). Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.78; H, 7.00; N, 6.82.

***tert*-Butyl [1,1′-Biphenyl]-2-ylcarbamate.**[17] The product was obtained following the general procedure (4.0 mmol scale) as yellow solids (916 mg, 85%) after purification by column chromatography: R_f = 0.29 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 7.8 Hz, 1H), 7.49 (dd, J = 7.5, 7.5 Hz, 2H), 7.45–7.31 (m, 4H), 7.20 (dd, J = 7.5, 1.4 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.57–6.45 (br s, 1H), 1.46 (s, 9H).

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)amino)-4-methylphenyl)-1*H*-pyrrole-1-carboxylate.** The product was obtained following the general procedure (3.0 mmol scale) as an amorphous solid (805 mg, 72%) after purification by column chromatography: R_f = 0.35 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.91 (br s, 1H), 7.35 (br s, 1H), 7.30 (br s, 1H), 7.14 (d, J = 7.7 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.75 (br s, 1H), 6.33 (dd, J = 3.2, 1.7 Hz, 1H), 2.37 (s, 3H), 1.62 (s, 9H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 153.0, 148.6, 138.1, 135.4, 129.5, 124.0, 123.8, 121.5, 121.0, 120.2, 117.9, 112.7, 84.1, 80.3, 28.3, 28.0, 21.5; IR (neat) 3418, 2980, 1728, 1522, 1387, 1344 cm^{-1}; MS (FAB) m/z 372 (M$^+$), 316 (M − *t*-Bu), 260 (M − 2*t*-Bu), 173 (M − 2Boc); HRMS-ESI (m/z) calcd for $C_{21}H_{28}KN_2O_4$ 411.1686, found 411.1692.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)amino)-4-fluorophenyl)-1*H*-pyrrole-1-carboxylate.** The product was obtained following the general procedure (3.0 mmol scale) as an amorphous solid (915 mg, 81%) after purification by column chromatography: R_f = 0.33 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 11.7 Hz, 1H), 7.39–7.35 (m, 1H), 7.31–7.27 (m, 1H), 7.17 (dd, J = 8.5, 6.4 Hz, 1H), 6.86 (br s, 1H), 6.72 (ddd, J = 8.2, 8.2, 2.7 Hz, 1H), 6.31 (dd, J = 3.2, 1.7 Hz, 1H), 1.63 (s, 9H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.4 (d, J = 225 Hz), 152.4, 148.5, 137.2 (d, J = 10.8 Hz), 130.7 (d, J = 9.6 Hz), 123.1, 121.2, 119.6 (d, J = 2.4 Hz), 118.1, 112.5, 109.3 (d, J = 21.6 Hz), 106.3 (d, J = 27.6 Hz), 84.3, 80.8, 28.2, 27.9; IR (neat)

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3414, 2980, 1732, 1522, 1489, 1473, 1458, 1385, 1369 cm^{-1}; MS (FAB) m/z 376 (M^+), 320 (M − *t*-Bu), 264 (M − 2*t*-Bu + H); HRMS-ESI (m/z) calcd for $C_{20}H_{25}FN_2NaO_4$ 399.1696, found 399.1703.

General Procedure for Ynamides 4a–l.[18d] To a solution of *N*-Boc-protected *o*-aryl aniline (1.0 equiv), the corresponding bromoacetylene (1.5 equiv), copper iodide (0.30 equiv), and 1,10-phenanthroline (0.36 equiv) in toluene (0.1 M) was added a 0.5 M toluene solution of potassium bis(trimethylsilyl)amide (KHMDS, 1.5 equiv) at 90 °C over 1 h under an argon atmosphere. After being stirred at 90 °C for 2 h, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt) to afford the desired product.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)((triisopropylsilyl)-ethynyl)amino)phenyl)-1*H*-pyrrole-1-carboxylate (4a).** The product was obtained following the general procedure (2.5 mmol scale, *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)phenyl)-1*H*-pyrrole-1-carboxylate and (bromoethynyl)triisopropylsilane as starting materials) as a yellow oil (1.27 g, 94%) after purification by column chromatography: R_f = 0.33 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, J = 7.6, 1.3 Hz, 1H) 7.44−7.40 (m, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.36−7.31 (m, 1H), 7.31−7.26 (m, 2H), 6.51−6.47 (m, 1H), 1.60 (s, 9H), 1.39 (br s, 9H), 1.01(s, 21H); ^{13}C NMR ($CDCl_3$) δ 153.2, 148.8, 137.0, 132.7, 129.4, 128.4, 128.2, 127.6, 124.6, 120.4, 117.9, 112.2, 98.1, 83.6, 82.6, 67.3, 28.0, 27.9, 18.6, 11.5; MS (ESI) m/z 539 ([M + H]$^+$), 483 (M − *t*-Bu + 2H), 439 (M − Boc + 2H), 383, 295; IR (KBr) ν_{max} 2941, 2891, 2864, 2176, 1748, 1732, 1501, 1477, 1458, 1393, 1369, 1346, 1327 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{31}H_{47}N_2O_4Si$ 539.3300, found 539.3293.

***tert*-Butyl (2-(Furan-3-yl)phenyl)((triisopropylsilyl)ethynyl)-carbamate (4b).** The product was obtained following the general procedure (2.3 mmol scale, *tert*-butyl (2-(furan-3-yl)phenyl)carbamate and (bromoethynyl)triisopropylsilane as starting materials) as white solids (850 mg, 84%) after purification by column chromatography: mp 56−59 °C (hexanes/EtOAc); R_f = 0.32 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 50 °C) δ 7.71 (d, J = 0.96 Hz, 1H), 7.48−7.43 (m, 2H), 7.40 (m, 1H), 7.37−7.27 (m, 2H), 6.70−6.65 (m, 1H), 1.35 (s, 9H), 1.03 (s, 21H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 153.0, 143.0, 140.3, 137.2, 130.9, 129.3, 128.6, 128.3, 128.0, 123.0, 110.3, 98.1, 82.8, 67.6, 27.8, 18.6, 11.5; IR (KBr) ν_{max} 2943, 2924, 2893, 2866, 2176, 1736, 1462, 1393, 1369 cm^{-1}; MS m/z 440 ([M + H]$^+$), 384 (M − *t*-Bu + 2H), 340 (M − Boc + 2H), 296 (M − Boc + 2H − *i*-Pr), 254; HRMS-ESI (m/z) calcd for $C_{26}H_{38}NO_3Si$ 440.2615, found 440.2614.

***tert*-Butyl (2-(Thiophen-3-yl)phenyl)((triisopropylsilyl)-ethynyl)carbamate (4c).** The product was obtained following the general procedure (1.8 mmol scale, *tert*-butyl (2-(thiophen-3-yl)-phenyl)carbamate and (bromoethynyl)triisopropylsilane as starting materials) as a yellow oil (714 mg, 87%) after purification by column chromatography: R_f = 0.36 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 50 °C) δ 7.48−7.45 (m, 1H), 7.45−7.43 (m, 1H), 7.43−7.40 (m, 1H), 7.36−7.32 (m, 3H), 7.31−7.28 (m, 1H), 1.27(br s, 9H), 1.04 (s, 21H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 152.8, 139.1, 137.3, 134.6, 130.1, 128.4, 128.2, 128.0, 125.3, 122.7, 98.5, 82.5, 67.6, 27.7, 18.6, 11.5 (one carbon is overlapped); IR (KBr) ν_{max} 3102, 2943, 2893, 2866, 2176, 1736, 1462, 1393, 1369 cm^{-1}; MS (FAB) m/z 456 ([M + H]$^+$), 400 (M − *t*-Bu + 2H), 356 (M − Boc + 2H), 312; HRMS-ESI (m/z) calcd for $C_{26}H_{38}NO_2SSi$ 456.2387, found 456.2393. Anal. Calcd for $C_{26}H_{37}NO_2SSi$: C, 68.52; H, 8.18; N, 3.07. Found: C, 68.35; H, 8.31; N, 3.08.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)((triisopropylsilyl)-ethynyl)amino)phenyl)-1*H*-indole-1-carboxylate (4d).** The product was obtained following the general procedure (1.5 mmol scale, *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)phenyl)-1*H*-indole-1-carboxylate and (bromoethynyl)triisopropylsilane as starting materials) as a yellow oil (627 mg, 71%) after purification by column chromatography: R_f = 0.44 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 1H), 7.65 (s, 1H), 7.59−7.49 (m, 3H), 7.45−7.37 (m, 2H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.20 (dd, J = 7.3, 7.3 Hz, 1H), 1.67 (s, 9H), 1.27 (br s, 9H), 0.99−0.78 (m, 21H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 153.3, 149.6, 138.2, 135.7, 131.34, 131.25, 129.6, 128.2, 128.1, 128.0, 124.4, 124.0, 122.8, 120.1, 118.8, 115.2, 97.8, 83.6, 82.6, 67.4, 28.3, 27.8, 18.6, 11.4; IR (KBr) ν_{max} 2978, 2941, 2891, 2864, 2176, 1732, 1454, 1373, 1308 cm^{-1}; MS (FAB) m/z 589 ([M + H]$^+$), 532 (M − *t*-Bu + H), 489 (M − Boc + 2H), 433 (M − *t*-Bu − Boc + 3H), 389 (M − 2Boc + 3H), 345, 301, 259, 231; HRMS-ESI (m/z) calcd for $C_{35}H_{49}N_2O_4Si$ 589.3456, found 589.3454. Anal. Calcd for $C_{35}H_{48}N_2O_4Si$: C, 71.39; H, 8.22; N, 4.76. Found: C, 71.21; H, 8.38; N, 4.76.

***tert*-Butyl [1,1′-Biphenyl]-2-yl((triisopropylsilyl)ethynyl)-carbamate (4e).** The product was obtained following the general procedure (1.5 mmol scale, *tert*-butyl [1,1′-biphenyl]-2-ylcarbamate and (bromoethynyl)triisopropylsilane as starting materials) as a brown oil (303 mg, 45%) after purification by column chromatography: R_f = 0.23 (2.5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 55 °C) δ 7.50−7.40 (m, 3H), 7.40−7.34 (m, 5H), 7.32−7.27 (m, 1H), 1.22 (s, 9H), 1.07−1.01 (m, 21H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 152.9, 140.1, 139.1, 137.5, 130.7, 128.8, 128.5, 128.32, 128.25, 127.9, 127.3, 98.7, 82.5, 67.6, 27.7, 18.7, 11.5; IR (KBr) ν_{max} 2957, 2941, 2891, 2864, 2178, 1734, 1481, 1458, 1437, 1383, 1369, 1304 cm^{-1}; MS (ESI) m/z 449 (M^+), 406 (M − *i*-Pr), 349 (M − Boc + H), 324, 306 (M − *i*-Pr − Boc + H), 264, 220. Anal. Calcd for $C_{28}H_{39}NO_2Si$: C, 74.78; H, 8.74; N, 3.11. Found: C, 74.54; H, 8.81; N, 3.10.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)((triisopropylsilyl)-ethynyl)amino)-4-methylphenyl)-1*H*-pyrrole-1-carboxylate (4f).** The product was obtained following the general procedure (1.0 mmol scale, *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)-4-methylphenyl)-1*H*-pyrrole-1-carboxylate and (bromoethynyl)triisopropylsilane as starting materials) as a yellow oil (415 mg, 75%) after purification by column chromatography: R_f = 0.33 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.40−7.34 (m, 2H), 7.29−7.23 (m, 1H), 7.20 (br s, 1H), 7.14 (br d, J = 8.0 Hz, 1H), 6.46 (dd, J = 2.7, 1.6 Hz, 1H), 2.36 (s, 3H), 1.60 (s, 9H), 1.41 (br s, 9H), 1.00 (s, 21H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 153.3, 148.8, 137.6, 136.6, 129.6, 129.24, 129.17, 128.7, 124.6, 120.3, 117.6, 112.3, 98.2, 83.5, 82.5, 67.1, 28.0, 27.9, 20.8, 18.6, 11.5; IR (neat) 2940, 2893, 2862, 2171, 1736, 1508, 1458, 1389, 1346 cm^{-1}; MS (FAB) m/z 553 (M + H$^+$), 496 (M − *t*-Bu), 441 (M − 2*t*-Bu), 353 (M − 2Boc), 309 (M − 2Boc − *i*-Pr); HRMS-ESI (m/z) calcd for $C_{32}H_{48}N_2NaO_4Si$ 575.3281, found 575.3298.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)((triisopropylsilyl)-ethynyl)amino)-4-fluorophenyl)-1*H*-pyrrole-1-carboxylate (4g).** The product was obtained following the general procedure (1.0 mmol scale, *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)-4-fluorophenyl)-1*H*-pyrrole-1-carboxylate and (bromoethynyl)triisopropylsilane as starting materials) as a yellow oil (362 mg, 65%) after purification by column chromatography: R_f = 0.31 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 50 °C) δ 7.43 (dd, J = 8.7, 6.2 Hz, 1H), 7.37 (dd, J = 1.7, 1.7 Hz, 1H), 7.25 (dd, J = 3.6, 1.3 Hz, 1H), 7.12 (dd, J = 8.9, 2.6 Hz, 1H), 7.04 (ddd, J = 8.3, 8.3, 2.6 Hz, 1H), 6.43 (dd, J = 3.2, 1.7 Hz, 1H), 1.60 (s, 9H), 1.37 (br s, 9H), 1.01 (m, 21H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 161.5 (d, J = 248 Hz), 152.8, 148.7, 137.9 (d, J = 10.8 Hz), 130.6 (d, J = 8.4 Hz), 129.0 (d, J = 4.8 Hz), 123.8, 120.5, 117.7, 115.6 (d, J = 20.4 Hz), 105.4 (d, J = 24.0 Hz), 112.1, 97.4, 83.7, 83.0, 67.9, 28.0, 27.8, 18.6, 11.4; IR (neat) 2959, 2866, 2360, 2175, 1744, 1508, 1458, 1389, 1346 cm^{-1}; MS (FAB) m/z 557 (M + H$^+$), 550 (M − *t*-Bu), 444 (M − 2*t*-Bu), 357 (M − 2Boc), 314 (M − 2Boc − *i*-Pr); HRMS-ESI (m/z) calcd for $C_{31}H_{45}FN_2NaO_4Si$ 579.3030, found 579.3035.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)(ethynyl)amino)-phenyl)-1*H*-pyrrole-1-carboxylate (4h).** To a solution of **4a** (1.49 g, 2.8 mmol) in THF (28 mL) was added tetra-*n*-butylammonium fluoride (3.3 mL, 1 M in THF) at room temperature under an argon atmosphere. After being stirred for 30 min, the reaction mixture was diluted with Et_2O (30 mL), washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt 50:1 to 20:1) to afford the desired product (890 mg, 84%) as a yellow oil: R_f = 0.28 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 55 °C) δ 7.50−7.46 (m, 2H), 7.38−7.35 (m, 1H), 7.33 (ddd,

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J = 7.5, 7.5, 1.4 Hz, 1H), 7.30−7.26 (m, 2H), 6.49 (dd, J = 3.3, 1.9 Hz, 1H), 2.79 (s, 1H), 1.61 (s, 9H), 1.30 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 153.0, 148.6, 136.2, 132.7, 129.3, 128.7, 128.0, 127.7, 124.3, 120.4, 117.8, 112.0, 83.8, 82.9, 57.6, 27.9, 27.5; IR (KBr) ν_{max} 3310, 2980, 2934, 2918, 2145, 1734, 1749, 1458, 1449, 1393, 1369, 1346, 1314 cm^{-1}; MS (FAB) m/z 383 (M + H)$^+$, 326 (M − t-Bu + H). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.13; H, 7.03; N, 7.30.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)(phenylethynyl)-amino)phenyl)-1*H*-pyrrole-1-carboxylate (4i).** The product was obtained following the general procedure (1.0 mmol scale, *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)phenyl)-1*H*-pyrrole-1-carboxylate and (bromoethynyl)benzene as starting materials) as a brown oil (330 mg, 72%) after purification by column chromatography: R_f = 0.21 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 50 °C) δ 7.53−7.48 (m, 2H), 7.43 (dd, J = 7.7, 1.4 Hz, 1H), 7.37−7.27 (m, 5H), 7.27−7.18 (m, 3H), 6.53 (dd, J = 3.4, 1.7 Hz, 1H), 1.58 (s, 9H), 1.34 (br s, 9H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 152.9, 148.7, 137.0, 133.0, 131.1, 129.4, 128.6, 128.3, 128.1, 127.7, 127.2, 124.5, 123.7, 120.5, 118.1, 112.2, 84.6, 83.8, 82.7, 69.7, 28.0, 27.7; IR (KBr) ν_{max} 2980, 2931, 2918, 2253, 1734, 1499, 1477, 1449, 1389, 1369, 1346 cm^{-1}; MS (FAB) m/z 459 (M + H)$^+$, 403 (M − t-Bu + 2H), 402 (M − t-Bu + H), 347 (M − 2t-Bu + 3H), 346 (M − 2t-Bu + 2H), 301, 259 (M − 2Boc + 3H); HRMS-ESI (m/z) calcd for $C_{28}H_{31}N_2O_4$ 459.2278, found 459.2272.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)(3-ethoxy-3-oxoprop-1-yn-1-yl)amino)phenyl)-1*H*-pyrrole-1-carboxylate (4j).** To a solution of ynamide (**4h**) (716 mg, 1.87 mmol) in THF (9.0 mL) was added 1.0 M THF solution of LiHMDS (2.1 mL, 2.06 mmol) at −78 °C under an argon atmosphere. After being stirred at the same temperature for 30 min, to the mixture was added ethyl chloroformate (215 μL, 2.25 mmol) and stirred for 30 min at −78 °C. The reaction mixture was quenched by saturated aq NH_4Cl (3.0 mL) and diluted with Et_2O (15 mL), washed with water (15 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt = 10:1) to afford the desired product (748 mg, 88%) as amorphous: R_f = 0.15 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 35 °C) δ 7.48 (dd, J = 7.7, 1.4 Hz, 1H), 7.40 (dd, J = 1.9, 1.9 Hz, 1H), 7.39−7.26 (m, 4H), 6.42 (dd, J = 3.2, 1.7 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.61 (s, 9H), 1.34 (br s, 9H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 48 °C) δ 154.5, 151.9, 148.6, 135.3, 133.0, 129.7, 129.2, 128.0, 127.9, 124.0, 120.6, 118.0, 112.1, 84.3, 83.9, 83.5, 65.5, 61.3, 27.9, 27.5, 14.1; IR (KBr) ν_{max} 2982, 2229, 1744, 1701, 1501, 1477, 1458, 1388, 1346 cm^{-1}; MS (FAB) m/z 455 (M + H$^+$), 255 (M − 2Boc), 209 (M − 2Boc − EtO); HRMS-ESI (m/z) calcd for $C_{25}H_{30}N_2NaO_6$ 477.1996, found 477.1991.

***tert*-Butyl 3-(2-((Bromoethynyl)(*tert*-butoxycarbonyl)-amino)phenyl)-1*H*-pyrrole-1-carboxylate (4k).** To a solution of ynamide (**4h**) (99.3 mg, 0.26 mmol) in THF (1.5 mL) was added 1.0 M THF solution of LiHMDS (0.34 mL, 0.34 mmol) at −78 °C under an argon atmosphere. After being stirred at the same temperature for 30 min, to the mixture was added *N*-bromosuccinimide (60 mg, 0.34 mmol). The mixture was warmed to the ambient temperature and stirred for 30 min. The reaction mixture was quenched by saturated aq NH_4Cl (2 mL) and diluted with Et_2O (10 mL), washed with water (2 mL) and brine (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt = 20:1) to afford the desired product (102 mg, 85%) as an amorphous solid: R_f = 0.22 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.36−7.31 (m, 2H), 7.24−7.19 (m, 2H), 7.18−7.13 (m, 2H), 6.33 (dd, J = 3.2, 1.7 Hz, 1H), 1.47 (s, 9H), 1.22 (br s, 9H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 152.9, 148.7, 136.2, 132.9, 129.4, 128.8, 128.1, 127.7, 124.3, 120.5, 118.0, 112.1, 83.9, 83.1, 73.9, 28.0, 27.6; IR (KBr) ν_{max} 2978, 2931, 2900, 1732, 1501, 1477 cm^{-1}; MS (FAB) m/z 461 (M + H$^+$), 348 (M − 2Boc); HRMS-ESI (m/z) calcd for $C_{22}H_{26}BrN_2O_4$ 461.1070, found 461.1043.

***tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)(chloroethynyl)amino)-phenyl)-1*H*-pyrrole-1-carboxylate (4l).** To a solution of ynamide (**4h**) (268 mg, 0.7 mmol) in THF (7.0 mL) was added 1.0 M THF solution of LiHMDS (0.91 mL, 0.91 mmol) at −78 °C under an argon atmosphere. After being stirred at the same temperature for 30 min, to the mixture was added *N*-chlorosuccinimide (122 mg, 0.91 mmol). The mixture was warmed to the ambient temperature and stirred for 30 min. The reaction mixture was quenched by saturated aq NH_4Cl (5 mL), diluted with Et_2O (15 mL), washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt = 20:1) to afford the desired product (249 mg, 85%) as an amorphous solid: R_f = 0.22 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.52−7.48 (m, 1H), 7.47−7.44 (m, 1H), 7.38−7.34 (m, 2H), 7.32−7.28 (2H, m), 6.47 (dd, J = 3.4, 1.7 Hz, 1H), 1.62 (s, 9H), 1.37 (br s, 9H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 153.0, 148.6, 136.2, 132.8, 129.3, 128.7, 128.0, 127.7, 124.2, 120.4, 117.8, 111.9, 83.8, 83.0, 77.2, 27.9, 27.5; IR (KBr) ν_{max} 2978, 2931, 2900, 1732, 1500, 1454 cm^{-1}; MS (FAB) m/z 416 (M$^+$), 361 (M − Boc), 305 (M − 2Boc); HRMS-ESI (m/z) calcd for $C_{22}H_{26}ClN_2O_4$ 417.1576, found 417.1588.

General Procedure for the Cyclization Reaction with Ynamide 4a−j. To a solution of ynamide (0.20 mmol) in dichloromethane (2.0 mL) was added TfOH (0.24 mmol) at room temperature under an argon atmosphere. After being stirred at the ambient temperature for 5 min, the reaction was quenched by triethylamine, and the mixture was diluted with $CHCl_3$ (5 mL), washed with water (2 × 5 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt) to afford the desired product.

4-((Triisopropylsilyl)methyl)-3*H*-pyrrolo[2,3-*c*]quinoline (6a). The product **6a** (58.3 mg, 86%) was obtained following the general procedure using **4a** with TfOH as a yellow amorphous solid: R_f = 0.26 (20% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.82 (br s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.54−7.50 (m, 1H), 7.49−7.44 (m, 1H), 7.35 (d, J = 3.2 Hz, 1H), 7.03 (d, J = 2.9 Hz, 1H), 2.66 (s, 2H), 1.22−1.08 (m, 3H), 0.99 (d, J = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 149.1, 142.9, 128.6, 128.5, 127.5, 125.7, 124.8, 124.5, 122.7, 122.4, 102.2, 18.6, 18.4, 11.7; IR (KBr) ν_{max} 2943, 2862, 1581, 1562, 1528, 1458, 1389, 1362, 1339, 1315 cm^{-1}; MS (FAB) m/z 339 (M + H$^+$), 295 (M − i-Pr); HRMS-ESI (m/z) calcd for $C_{21}H_{31}N_2Si$ 339.2251, found 339.2268.

***tert*-Butyl 4-((Triisopropylsilyl)methyl)-3*H*-pyrrolo[2,3-*c*]-quinoline-3-carboxylate (5a).** The product **5a** (74.6 mg, 85%) was obtained following the general procedure using **4a** with Tf_2NH as a yellow oil: R_f = 0.28 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.10−8.04 (m, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 3.7 Hz, 1H), 7.59 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.50−7.43 (m, 1H), 7.03 (d, J = 3.5 Hz, 1H), 3.21 (s, 2H), 1.67 (s, 9H), 1.12−1.00 (m, 3H), 0.93 (d, J = 7.2 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 151.9, 149.0, 143.9, 133.6, 130.0, 128.4, 128.1, 127.1, 124.7, 122.8, 121.0, 104.7, 84.6, 28.0, 21.6, 18.7, 11.6; IR (KBr) ν_{max} 2928, 2862, 1744, 1501, 1458, 1354 cm^{-1}; MS (FAB) m/z 439 (M + H$^+$), 395 (M − i-Pr); HRMS-ESI (m/z) calcd for $C_{26}H_{39}N_2O_2Si$ 439.2775, found 439.2783.

4-((Triisopropylsilyl)methyl)furo[2,3-*c*]quinoline (6b). The product **6b** (62.5 mg, 92%) was obtained following the general procedure using **4b** as a colorless solids: mp 48−50 °C (hexanes); R_f = 0.30 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 7.6, 7.6 Hz, 1H), 7.50 (dd, J = 7.5, 7.5 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 2.86 (s, 2H), 1.19−1.10 (m, 3H), 1.02 (d, J = 7.2 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 150.0, 148.1, 145.9, 144.3, 128.9, 128.1, 127.0, 125.0, 123.2, 122.1, 105.6, 18.5, 17.7, 11.5; IR (neat) ν_{max} 2940, 2889, 2866, 1593, 1520, 1462, 1358 cm^{-1}; MS (EI) m/z 339 (M$^+$), 296 (M − i-Pr), 254, 210; HRMS-ESI (m/z) calcd for $C_{21}H_{30}NOSi$ 340.2091 [M + H]$^+$, found 340.2090. Anal. Calcd for $C_{21}H_{29}NOSi$: C, 74.28; H, 8.61; N, 4.13. Found: C, 74.19; H, 8.84; N, 4.06.

4-((Triisopropylsilyl)methyl)thieno[2,3-*c*]quinoline (6c). The product **6c** (62.6 mg, 88%) was obtained following the general procedure using **4c** as a pale yellow oil: R_f = 0.38 (5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.20 (ddd, J = 8.2, 0.6, 0.6 Hz, 1H), 8.06 (ddd, J = 8.3, 0.6, 0.6 Hz, 1H), 7.96 (dd, J = 5.4, 0.9 Hz, 1H), 7.76 (dd, J = 5.5, 1.2 Hz, 1H), 7.64 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.53 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 2.79 (s, 2H), 1.33−1.16 (m, 3H), 1.03

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(d, J = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 156.9, 145.1, 141.2, 133.7, 129.8, 128.9, 127.7, 125.1, 123.1, 122.7, 122.2, 22.5, 18.6, 11.7; IR (KBr) ν_{max} 3061, 2941, 2889, 2864, 1614, 1555, 1495, 1464, 1412, 1381, 1346, 1321 cm^{-1}; MS (FAB) m/z 356 (M + H), 312 (M − i-Pr); HRMS-ESI (m/z) calcd for $C_{21}H_{30}NSSi$ 356.1863, found 356.1854. Anal. Calcd for $C_{21}H_{29}NSSi$: C, 70.93; H, 8.22; N, 3.94. Found: C, 70.86; H, 8.44; N, 3.93.

6-((Triisopropylsilyl)methyl)-7*H*-indolo[2,3-*c*]quinoline (6d). The product **6d** (59.8 mg, 77%) was obtained following the general procedure using **4d** as a yellow amorphous solid: R_f = 0.16 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.66 (d, J = 7.5 Hz, 1H), 8.56 (d, J = 8.6 Hz, 1H), 8.43 (br s, 1H), 8.17−8.10 (m, 1H), 7.71−7.52 (m, 4H), 7.47−7.37 (m, 1H), 2.79 (s, 2H), 1.32−1.19 (m, 3H), 1.05 (d, J = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 149.4, 143.1, 138.5, 131.7, 129.3, 126.4, 125.50, 125.45, 123.5, 123.3, 123.2, 122.9, 120.8, 120.5, 112.0, 18.7, 18.4, 11.7; IR (KBr) ν_{max} 2940, 2862, 1620, 1566, 1524, 1497, 1462, 1389, 1362, 1335 cm^{-1}; MS (EI) m/z 388 (M$^+$), 345 (M − i-Pr). Anal. Calcd for $C_{25}H_{32}N_2Si$: C, 77.27; H, 8.30; N, 7.21. Found: C, 77.04; H, 8.37; N, 7.13.

6-((Triisopropylsilyl)methyl)phenanthridine (6e). The product **6e** (36.4 mg, 52%) was obtained following the general procedure using **4e** as a yellow oil: R_f = 0.23 (2.5% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$, 50 °C) δ 8.61 (d, J = 8.3 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 7.6 Hz, 1H), 7.70−7.61 (m, 2H), 7.54 (dd, J = 7.6 Hz, 1H), 2.98 (s, 2H), 1.29−1.18 (m, 3H), 1.03 (d, J = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 162.4, 143.9, 132.7, 130.0, 129.1, 128.4, 126.83, 126.76, 126.0, 125.5, 122.9, 122.4, 121.8, 19.6, 18.7, 11.8; IR (neat) 2959, 2865, 1734, 1582, 1522, 1458, 1350, 1317 cm^{-1}; MS (FAB) m/z 350 (M + H$^+$), 306 (M − i-Pr), 220 (M − 3i-Pr); HRMS-ESI (m/z) calcd for $C_{23}H_{32}NSi$ 350.2299, found 350.2292.

7-Methyl-4-((triisopropylsilyl)methyl)-3*H*-pyrrolo[2,3-*c*]quinoline (6f). The product **6f** (55.7 mg, 79%) was obtained following the general procedure using **4f** as an amorphous solid: R_f = 0.20 (12% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.55 (br s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.81 (s, 1H), 7.34 (d, J = 2.9 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 2.6 Hz, 1H), 2.66 (s, 2H), 2.54 (s, 3H), 1.23−1.14 (m, 3H), 1.01 (d, J = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 148.8, 135.4, 133.5, 128.4, 128.1, 127.7, 126.5, 124.7, 122.5, 120.2, 102.0, 21.6, 18.7, 18.3, 11.8; IR (neat) 3012, 2943, 2866, 1581, 1523, 1462, 1361, 1315 cm^{-1}; MS (FAB) m/z 353 (M + H$^+$), 309 (M − i-Pr), 223 (M − 3i-Pr); HRMS-ESI (m/z) calcd for $C_{22}H_{33}N_2Si$ 353.2408, found 353.2401.

7-Fluoro-4-((triisopropylsilyl)methyl)-3*H*-pyrrolo[2,3-*c*]quinoline (6g). The product **6g** (64.2 mg, 90%) was obtained following the general procedure using **4g** as colorless solids: mp 85−87 °C (hexanes/AcOEt); R_f = 0.20 (12% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.71 (br s, 1H), 8.07 (dd, J = 8.7, 6.2 Hz, 1H), 7.66 (dd, J = 10.9, 2.6 Hz, 1H), 7.37 (d, J = 2.9 Hz, 1H), 7.24 (ddd, J = 8.5, 8.5, 2.4 Hz, 1H), 6.99 (d, J = 2.9 Hz, 1H), 2.65 (s, 2H), 1.23−1.12 (m, 3H), 1.00 (d, J = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 161.2 (J = 243.5 Hz), 150.3, 143.9 (J = 12.0 Hz), 128.3, 127.7, 125.1, 124.2 (J = 9.6 Hz), 119.2, 113.9 (J = 24.0 Hz), 112.8 (J = 20.4 Hz), 102.1, 18.6, 18.4, 11.8; IR (neat) 2943, 2866, 2360, 1627, 1581, 1531, 1462, 1438, 1381, 1358 cm^{-1}; MS (FAB) m/z 357 (M + H$^+$), 313 (M − i-Pr), 227 (M − 3i-Pr); HRMS-ESI (m/z) calcd for $C_{21}H_{30}FN_2Si$ 357.2157, found 357.2166.

4-Methyl-3*H*-pyrrolo[2,3-*c*]quinoline (Marinoquinoline A) (6h).[4c] The product **6h** (26.6 mg, 73%) was obtained following the general procedure using **4h** as white solids: R_f = 0.10 (AcOEt); ^{1}H NMR (acetone-d_6) δ 11.2 (br s, 1H), 8.24−8.18 (m, 1H), 8.02−7.96 (m, 1H), 7.57 (d, J = 2.9 Hz, 1H), 7.53−7.45 (m, 2H), 7.11 (d, J = 3.2 Hz, 1H), 2.82 (s, 3H).

4-Benzyl-3*H*-pyrrolo[2,3-*c*]quinoline (Marinoquinoline C) (6i).[4c] The product **6i** (38.2 mg, 74%) was obtained following the general procedure using **4i** as white solids: R_f = 0.34 (50% AcOEt/hexanes); ^{1}H NMR (acetone-d_6) δ 11.1 (br s, 1H), 8.28−8.17 (m, 1H), 8.10−7.99 (m, 1H), 7.57−7.47 (m, 3H), 7.41 (d, J = 7.7 Hz, 1H), 7.22 (t, J = 7.6 Hz, 2H), 7.17−7.08 (m, 2H), 4.55 (s, 2H).

Ethyl 2-(3*H*-Pyrrolo[2,3-*c*]quinolin-4-yl)acetate (6j). The product **6j** (40.2 mg, 79%) was obtained following the general procedure using **4j** as an amorphous solid: R_f = 0.23 (30% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 9.85 (br s, 1H), 8.22−8.17 (m, 1H), 8.16−8.12 (m, 1H), 7.62−7.53 (m, 2H), 7.46 (dd, J = 2.7 Hz, 1H), 7.09−7.06 (m, 1H), 4.28 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 142.5, 141.1, 129.2, 129.1, 128.4, 126.5, 126.1, 126.0, 123.4, 122.9, 101.6, 61.8, 43.7, 14.0; IR (neat) 3329, 2981, 2931, 1732, 1635, 1589, 1527, 1462, 1442, 1365 cm^{-1}; MS (FAB) m/z 255 (M + H$^+$); HRMS-ESI (m/z) calcd for $C_{15}H_{15}N_2O_2$ 255.1128, found 255.1124.

Di-*tert*-butyl 4-((Triisopropylsilyl)methyl)-3*H*-pyrrolo[2,3-*c*]-quinoline-3,5(4*H*)-dicarboxylate (7). To a solution of ynamide **4a** (107.8 mg, 0.20 mmol) in dichloromethane (2.0 mL) was added Tf_2NH (0.24 mL of 1.0 M CH_2Cl_2 solution, 0.24 mmol) at room temperature under an argon atmosphere. After being stirred at the ambient temperature for 15 min, a solution of $NaBH_4$ (37.8 mg, 1.0 mmol) in MeOH (1.0 mL) was added to the reaction mixture. After 30 min, the mixture was washed with water (5 mL) and brine (3 mL), dried over Mg_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt = 50:1) to afford the desired product **7** (37.9 mg, 35%) as an amorphous solid: R_f = 0.30 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.52 (br s, 1H), 7.43−7.37 (m, 1H), 7.20−7.13 (m, 2H), 7.10 (d, J = 3.4 Hz, 1H), 6.60 (br d, J = 9.5 Hz, 1H), 6.42 (d, J = 3.4 Hz, 1H), 1.60 (s, 9H), 1.46 (s, 9H), 1.17−1.08 (m, 3H), 1.07 (d, J = 6.9 Hz, 9H), 1.02 (d, J = 6.9 Hz, 9H), 0.93−0.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.6, 148.2, 135.6, 132.8, 128.0, 126.0, 124.9, 124.7, 122.1, 120.4, 118.1, 105.8, 83.7, 81.0, 48.7, 28.2, 28.0, 19.0, 18.8, 11.4; IR (KBr) ν_{max} 2939, 2866, 1744, 1697, 1505, 1454 cm^{-1}; MS (FAB) m/z 541 (M + H$^+$), 485 (M − 2t-Bu), 429 (M − 2t-Bu); HRMS-ESI (m/z) calcd for $C_{31}H_{49}N_2O_4Si$ 541.3456, found 541.3475.

Total Synthesis of Aplidiopsamine A. *tert*-Butyl 4-(bromomethyl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (8). To a solution of ynamide **4a** (107.8 mg, 0.20 mmol) in dichloromethane (2.0 mL) was added TfOH (19.5 μL, 0.22 mmol) at −78 °C under an argon atmosphere. After being stirred at the same temperature for 60 min, N-bromosuccinimide (42.8 mg, 0.24 mmol) was added to the reaction mixture. After 1 h, the reaction mixture was diluted with AcOEt (10 mL), washed with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried over Mg_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt) to afford the desired product **8** (46.2 mg, 64% yield) as colorless solids: mp 127−129 °C (hexanes/AcOEt); R_f = 0.19 (10% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.18−8.11 (m, 2H), 7.79 (d, J = 3.4 Hz, 1H), 7.68 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.61 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.11 (d, J = 3.4 Hz, 1H), 5.43 (s, 2H), 1.72 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 148.7, 145.5, 134.7, 130.3, 129.3, 127.8, 127.0, 126.0, 122.9, 122.6, 104.5, 85.3, 37.1, 28.0 (one carbon overlapped); IR (KBr) ν_{max} 2980, 2932, 1748, 1576, 1518, 1501, 1476, 1458, 1414, 1396, 1360, 1312 cm^{-1}; MS (EI) m/z 362 [(M + 2)$^+$], 360 (M$^+$), 306 [(M + 2) − t-Bu + H], 304 (M − t-Bu + H), 262 [(M + 2) − Boc + H], 260 (M − Boc + H); HRMS-ESI (m/z) calcd for $C_{17}H_{18}N_2O_2Br$ 361.0546, found 361.0529.

***N*-Boc-Protected Aplidiopsamine A (10).** To a solution of N,N-di(*tert*-butoxycarbonyl)adenine (67.1 mg, 0.2 mmol) in acetonitrile (2.0 mL) was added Cs_2CO_3 (71.7 mg, 0.22 mmol) under an argon atmosphere. After being stirred at the same temperature for 30 min, compound **8** (86.7 mg, 0.22 mmol) was added and stirred for 2 h. The reaction mixture was diluted with AcOEt (5.0 mL), washed with water (2.0 mL) and brine (2.0 mL), dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography (hexanes/AcOEt = 2:1) to afford the desired product **10** (111.4 mg, 91%) as a yellow oil: R_f = 0.19 (33% AcOEt/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.35 (s, 1H), 8.14−8.04 (m, 1H), 7.86−7.78 (m, 1H), 7.78−7.70 (m, 1H), 7.59−7.48 (m, 2H), 7.16−7.06 (m, 1H), 6.29 (s, 2H), 1.70 (s, 9H), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 154.0, 151.6, 150.2, 149.8, 149.1, 147.1, 142.8, 142.2, 134.4, 130.0, 129.3, 128.6, 127.5, 126.7, 126.0, 122.7, 122.0, 105.2, 85.5, 83.3, 49.1, 28.0, 27.7; IR (KBr) ν_{max} 2980, 2916, 2849, 1786, 1751, 1603, 1578, 1449,

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1382, 1369, 1356, 1341, 1306 cm^{-1}; MS (FAB) m/z 616 ($[M + H]^+$), 516 (M − Boc + 2H), 442, 386, 342; HRMS-ESI (m/z) calcd for $C_{32}H_{38}N_7O_6$ 616.2878, found 616.2870.

Aplidiopsamine A.[3] To a solution of **10** (49.5 mg, 0.080 mmol) in CH_2Cl_2 (2.0 mL) was added trifluoroacetic acid (1.7 mL) at room temperature under an argon atmosphere. After being stirred at the same temperature for 7 h, the solvent was removed under reduced pressure and $CHCl_3$ (10 mL) was added to the residue. The mixture was alkalized by saturated aq $NaHCO_3$ and extracted with $CHCl_3$ (10 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by column chromatography ($CHCl_3$/MeOH = 20:1) to afford aplidiopsamine A (22.8 mg, 90%) as a white powder: R_f = 0.22 (5% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 12.37 (br s, 1H), 8.33 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 7.79−7.73 (m, 2H), 7.55−7.43 (m, 2H), 7.26 (br s, 2H), 7.20 (m, 1H), 5.94 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 156.0, 152.4, 149.8, 143.3, 142.2, 141.5, 129.0, 128.2, 127.9, 126.7, 125.64, 125.61, 123.2, 118.5, 101.3, 44.5.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR 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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