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Total Synthesis of Ascididemin-Type Alkaloids Using Alkyne Building Blocks

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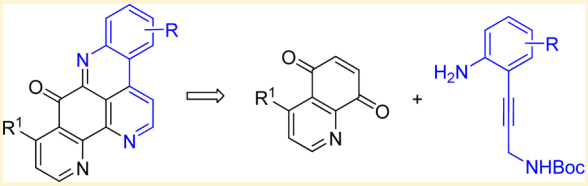
Supporting Information

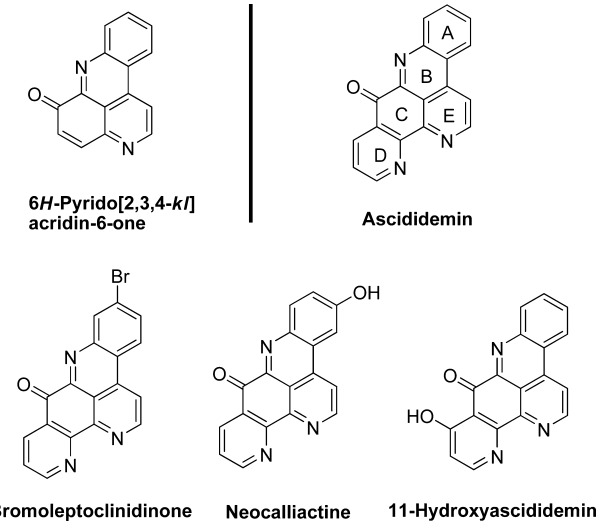
ABSTRACT: A common approach to ascididemin-type alkaloids, including ascididemin, bromoleptoclinidinone, neocalliactine acetate, and 11-hydroxyascididemin, based on a Brønsted acid-promoted tandem annulation has been developed. Alkyne building blocks were first designed and then employed in alkaloid synthesis; these building blocks can be accessed by a Sonogashira coupling reaction on a multigram scale.



INTRODUCTION

Ascididemin-type alkaloids, consisting of ascididemin,[1] bromoleptoclinidinone,[2] neocalliactine,[3] and 11-hydroxyascididemin,[4] belong to a subclass of pyridoacridine alkaloids that were isolated from marine tunicates and sponges.[5] These pentacyclic alkaloids share a common *6H*-pyrido[2,3,4-*kl*]acridin-6-one skeleton and differ in substituent pattern and distribution (Scheme 1). Because of their significant cytotoxic properties, especially in vitro antitumor activity, the ascididemin-type alkaloids have attracted considerable attention as potential drug candidates for the treatment of cancers.[6] Recent studies of structure−activity relationships have revealed that some ascididemin analogues even display stronger cytotoxity than natural ascididemin alkaloid.[7] Consequently, for further screening and biological evaluation, it still remains an urgent need to rapidly access diverse ascididemin-type alkaloids and their analogues by means of chemical synthesis.

Scheme 1. Ascididemin-Type Alkaloids



Among the known strategies to synthesize ascididemin-type alkaloids, the classic methodology of Bracher starting from *o*-aminoacetophenone (**I**) proved applicable (Scheme 2). This approach consists of an oxidative amination followed by stepwise construction of rings B and E of ascididemin.[8] To implement biomimetic synthesis as well as to improve Bracher's protocol with "pot economy", Kashman[9] and Echavarren[10] independently synthesized *N*-trifluoroacetamidokynuramine (**II**) and cinnamaldehyde-*N*,*N*-dimethylhydrazone (**III**) as surrogates for **I**. Although aminoquinone precursors derived from building blocks **II** and **III** introduce all of the requisite atoms for the assembly of the final ascididemin alkaloid, inherent limitations such as reaction efficiency and substituent flexibility still remain. Following our continuing studies on aminoquinones,[11] as well as aiming at developing a more common and efficient approach to ascididemin-type alkaloids, we designed **IV**, a new type of alkyne building block. As outlined in Scheme 3, aminoquinones **V** derived from alkyne building blocks **IV** were envisioned to be transformed to ascididemin alkaloids through a tandem [(6 + 0) + (4 + 2)] annulation, in which two six-membered nitrogen-containing rings might be constructed in a one-pot manner.

RESULTS AND DISCUSSION

Alkyne building blocks **IV** were prepared from *N*-Boc-protected propargylamine and a variety of 2-iodoanilines by a Sonogashira coupling reaction. As shown in Table 1, the reaction gave excellent results in terms of yield and functional group tolerance. Both bromine and hydroxy groups on the benzene moiety were kept intact. Furthermore, the synthesis of alkyne **IV-1** could be scaled to decagram quantities without any loss of yield.

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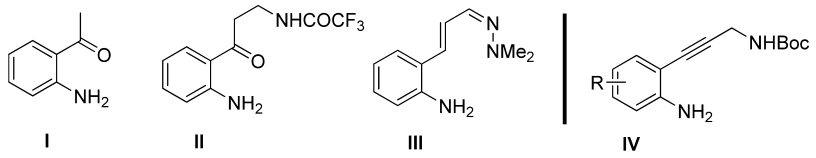
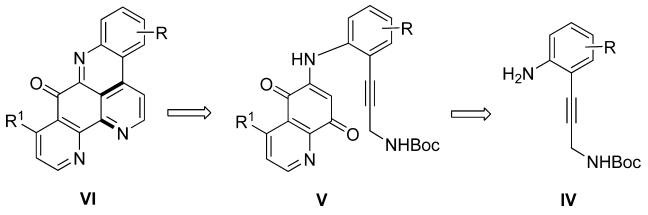
Scheme 2. Different Building Blocks



Scheme 3. Our Synthetic Plan

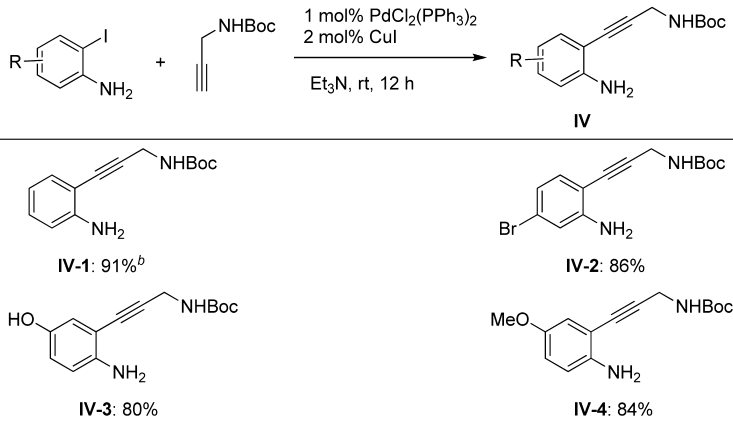


With significant amounts of the alkyne building blocks in hand, we next attempted to perform the oxidative amination between **IV** and quinones (Table 2). Because of the relatively low nucleophilicity of the aniline functionality, metallic Lewis acids such as $CeCl_3{\cdot}7H_2O$,[10] $NaAuCl_4{\cdot}2H_2O$,[11a] and $Cu(OAc)_2$[12] were employed as promoters for the transformation. After careful experimental comparisons, we eventually fixed the conditions by using a catalytic amount of the cerium salt in combination with alcoholic solvent. According to the optimized conditions, the oxidative amination of quinoline-5,8-dione and **IV-1**−**4** proceeded smoothly to afford aminoquinones **V-1**−**4** in yields ranging from 65% to 75%. However, in the case of 4-chloroquinoline-5,8-dione, the yield of aminoquinone **V-5** dropped to 50%, even though it was isolated as a major product. Additionally, as a precursor of deazaascididemin alkaloid, aminoquinone **V-6** could be accessed smoothly from naphthalene-1,4-dione and alkyne building block **IV-1**.

To test the feasibility of the postulated tandem [(6 + 0) + (4 + 2)] annulation, aminoquinone **V-1** was initially chosen as a model substrate (Table 3). At the beginning, a gold(I) catalyst with benign carbophilicity was regarded as an ideal catalyst,[13] since its selective activation of the triple bond was expected to induce an intramolecular attack by the aminoquinone functionality that in turn would trigger the whole domino process. However, to our disappointment, when 5 mol % $Ph_3PAuNTf_2$ was employed, a messy reaction mixture was obtained at 100 °C using acetic acid as the solvent. Only a trace amount of the anticipated product ascididemin (**VI-1**) was detected (Table 3, entry 1). When acidic additives such as H_2SO_4, *p*-toluenesulfonic acid (*p*-TSA), and (+)-camphor-10-sulfonic acid [(+)-CSA] were used, a moderate yield was observed in the case of concentrated H_2SO_4 (Table 3, entries 2−4). It was demonstrated that H_2SO_4 is superior to the two sulfonic acids. A control experiment excluding the gold(I) catalyst gave ascididemin in a comparable yield (Table 3, entry 5), which led us to recognize that Brønsted acids play a crucial role in the domino cyclization. Attempts to increase the amount of H_2SO_4 from 10 to 50 equiv resulted in a slight improvement in the yield (Table 3, entry 6). Further screening revealed that a mixture of H_2SO_4 and HOAc in a 1:1 (v/v) ratio improved the transformation, and the yield was enhanced to 66% (Table 3, entry 7). To accelerate the transient aromatization process, copper(II) and iron(III) salts containing acetate and sulfate counteranions were employed. The experimental results demonstrated that iron(III) sulfate is more advantageous than copper(II) acetate (Table 3, entries 8 and 9). Accordingly, the optimized conditions were defined as a combination of iron(III) sulfate and H_2SO_4 (Table 3, entry 9).

As well as aminoquinone **V-1**, brominated aminoquinone **V-2** underwent the domino cyclization to afford alkaloid bromoleptoclinidinone (**VI-2**) in good yield (Table 4, entries 1 and 2). For ease of isolation, neocalliactine derived from **V-3** was converted to its acetate derivative by in situ acetylation, and neocalliactine acetate (**VI-3**) was isolated in 44% yield over two steps (Table 4, entry 3). The solubility of neocalliactine methyl ether (**VI-4**) is different from that of neocalliactine, and it could be prepared straightforwardly from aminoquinone **V-4** in a very high yield (Table 4, entry 4). However, aminoquinone **V-5** containing a chlorine atom located at the *para* position of the pyridine ring was converted to 11-chloroascididemin (**VI-5**) in

Table 1. Preparation of Alkyne Building Blocks via Sonogashira Reaction[a]



[a]Unless otherwise mentioned, the reaction was performed on a 10 mmol scale. [b]The yield was calculated when the scale of the reaction was increased to 50 mmol.

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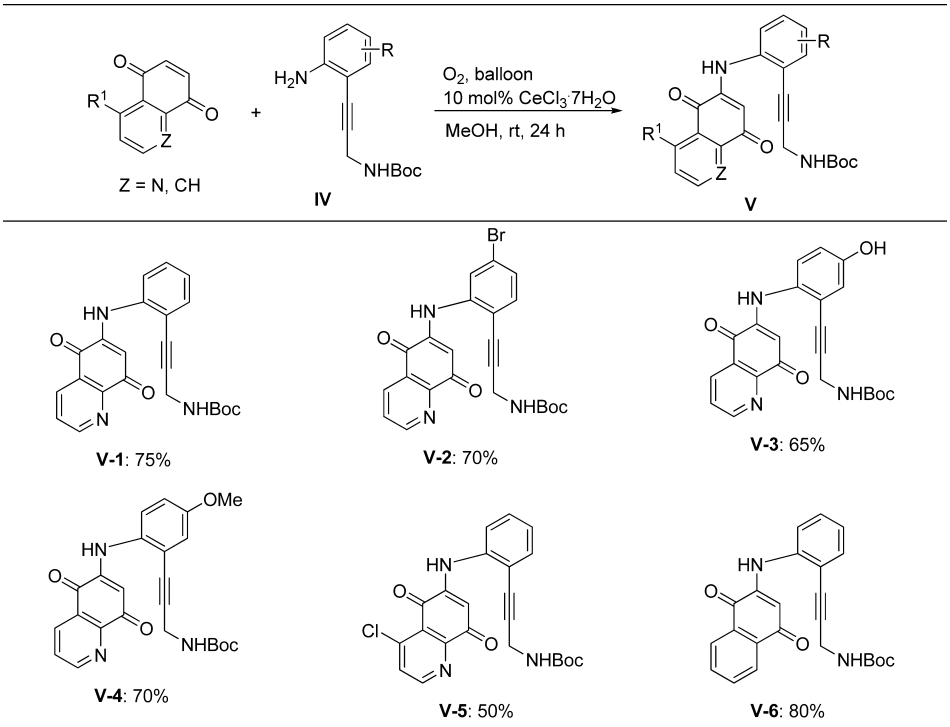
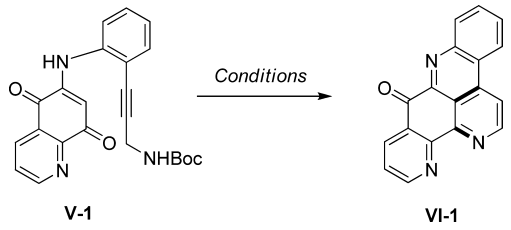
Table 2. Preparation of Aminoquinones via Oxidative Amination[a,b]



[a]Reaction conditions: a mixture of quinone (5.0 mmol), **IV** (5.0 mmol), $CeCl_3 \cdot 7H_2O$ (180 mg), and 50 mL of MeOH was stirred at rt for 24 h under an oxygen atmosphere. [b]Isolated yields after column chromatography are shown.

Table 3. Optimization of the Tandem Annulation



entry	conditions[a]	yield (%)[b]
1	5 mol % $Ph_3PAuNTf_2$, HOAc, 100 °C, 1 h	<5
2	5 mol % $Ph_3PAuNTf_2$, 10 equiv of H_2SO_4, HOAc, 100 °C, 1 h	40
3	5 mol % $Ph_3PAuNTf_2$, 10 equiv of *p*-TSA, HOAc, 100 °C, 1 h	<5
4	5 mol % $Ph_3PAuNTf_2$, 10 equiv of (+)-CSA, HOAc, 100 °C, 1 h	<5
5	10 equiv H_2SO_4, HOAc, 100 °C, 1 h	45
6	50 equiv of H_2SO_4, HOAc, 100 °C, 1 h	50
7	H_2SO_4/HOAc (1:1 v/v), 100 °C, 2 h	66
8	10 mol % $Cu(OAc)_2$, H_2SO_4/HOAc (1:1 v/v), 100 °C, 2 h	51
9	10 mol % $Fe_2(SO_4)_3$, H_2SO_4/HOAc (1:1 v/v), 100 °C, 2 h	75

[a]The reaction was performed under an oxygen atmosphere; the concentration of **V-1** was 0.1 M. [b]Isolated yields after column chromatography.

an inferior yield (Table 4, entry 5). The chorine atom in **VI-5** can be further replaced by a hydroxyl group, delivering 11-hydroxyascididemin in 82% yield (Scheme 4). Under identical conditions, the synthesis of **VI-6**, an isomer of deazaascididemin, was achieved in 80% yield from aminoquinone **V-6** in a similar manner (Table 4, entry 6). The NMR spectral data for the synthetic alkaloids ascididemin, bromoleptoclinidinone, and 11-hydroxyascididemin were in agreement with the reported ones.[1,2,4]

CONCLUSION

An array of ascididemin-type alkaloids were successively prepared by means of a Brønsted acid-promoted tandem annulation. A new class of alkyne building blocks that can be generated on a multigram scale were first designed and employed. Further details on the tandem annulation as well as applications of the alkyne building blocks in alkaloid synthesis will be pursued in the future.

EXPERIMENTAL SECTION

General Information. All melting points were determined without correction. ^1H NMR spectra were obtained at 300, 400, or 600 MHz, and ^{13}C NMR spectra were obtained at 75, 100, or 125 MHz. Spectra were recorded in $CDCl_3$, CD_3COD, DMSO-d_6, or CF_3CO_2D solution using the residual protonated solvent as the internal standard; *J* values are given in hertz. High-resolution mass spectrometry measurements were carried out on a Q-TOF micromass apparatus.

General Procedure for the Preparation of Alkyne Building Blocks IV by a Sonogashira Coupling Reaction. Under the protection of nitrogen, triethylamine (40 mL) was added to a flask containing substituted 2-iodoaniline (10.0 mmol), *tert*-butyl prop-2-ynylcarbamate (1.55 g, 10 mmol), *trans*-dichlorobis(triphenylphosphine)palladium(II) (70.4 mg, 0.1 mmol), and copper(I) iodide (38.1 mg, 0.2 mmol). The mixture was stirred overnight at room temperature (monitored by TLC). After completion of the reaction, the solvent was removed under vacuum. The obtained residue was treated with a mixture of chloroform (60 mL) and water (60 mL). The separated organic layer was washed with brine (60 mL) and dried with anhydrous $MgSO_4$. After filtration, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/PE = 1:4 for **IV-1**, **IV-2**, and **IV-4**; EtOAc/PE = 1:2 for **IV-3**) to give alkyne building block **IV**.

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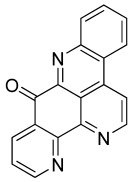
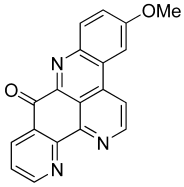
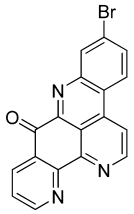
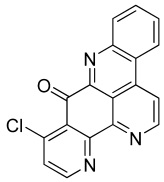
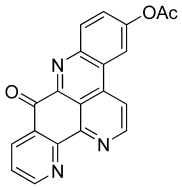
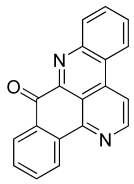
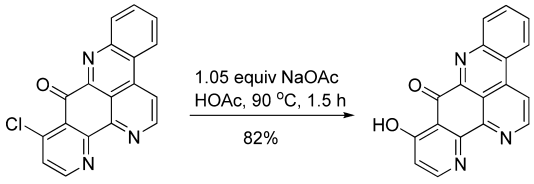
Table 4. Synthesis of Ascididemin-Type Alkaloids via Tandem Annulation[a,b]

Entry	Ascididemin-type alkaloid	Entry	Ascididemin-type alkaloid
1	 **VI-1:** 75%	4	 **VI-4:** 86%
2	 **VI-2:** 79%	5	 **VI-5:** 45%
3	 **VI-3:** 44%[c]	6	 **VI-6:** 80%

[a]Reaction conditions: a mixture of aminoquinone (0.3 mmol), $Fe_2(SO_4)_3$ (0.03 mmol), 1.5 mL of H_2SO_4 (c) and 1.5 mL of HOAc was stirred at 100 °C for 2 h under an oxygen atmosphere. [b]Isolated yields after column chromatography are shown. [c]2.0 equiv of Ac_2O was used to acylate the free phenol group.

Scheme 4. Synthesis of 11-Hydroxyascididemin



VI-5 **11-Hydroxyascididemin**

*tert-Butyl [3-(2-Aminophenyl)prop-2-yn-1-yl]carbamate (**IV-1**).* White solid, 2.24 g, 91% yield; mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H), 7.13–7.09 (m, 1H), 6.68–6.63 (m, 2H), 4.83 (s, 1H), 4.22 (s, 2H), 4.18 (d, J = 5.4 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 148.1, 132.0, 129.6, 117.7, 114.2, 107.1, 90.8, 79.9, 79.7, 31.3, 28.3; IR (KBr) ν_{max} 3451, 3367, 1681, 1517, 1449, 1249, 1167, 865, 745 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2NaO_2$ 269.1266 [M + Na]$^+$, found 269.1263.

*tert-Butyl [3-(2-Amino-4-bromophenyl)prop-2-yn-1-yl]carbamate (**IV-2**).* Light-yellow solid, 2.78 g, 86% yield; mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 6.76 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.85 (s, 1H), 4.31 (s, 2H), 4.15 (d, J = 5.6 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 149.2, 133.1, 123.4, 120.5, 116.8, 106.1, 91.8, 80.1, 78.9, 31.3, 28.3; IR (KBr) ν_{max} 3451, 3361, 1667, 1504, 1366, 1247, 1164, 882, 792 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{17}BrN_2NaO_2$ 347.0371 [M + Na]$^+$, found 347.0367.

*tert-Butyl [3-(2-Amino-5-hydroxyphenyl)prop-2-yn-1-yl]carbamate (**IV-3**).* Brown solid, 2.10 g, 80% yield; mp 144–147 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.36 (t, J = 5.2 Hz, 1H), 6.56–6.49 (m, 3H), 4.76 (s, 2H), 3.96 (d, J = 5.2 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.4, 147.6, 142.7, 117.6, 116.6, 115.1, 106.3, 91.4, 79.4, 78.3, 30.5, 28.2; IR (KBr) ν_{max} 3420, 3385, 3291, 2971, 1699, 1509, 1456, 1283, 1155, 852, 783 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2NaO_3$ 285.1215 [M + Na]$^+$, found 285.1212.

*tert-Butyl [3-(2-Amino-5-methoxyphenyl)prop-2-yn-1-yl]carbamate (**IV-4**).* Brown oil, 2.32 g, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 2.8 Hz, 1H), 6.75 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 4.18 (d, J = 5.2 Hz, 2H), 3.94 (s, 2H), 3.72 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 151.6, 142.3, 117.2, 115.9, 115.8, 107.9, 90.7, 79.9, 79.7, 55.7, 31.2, 28.3; IR (KBr) ν_{max} 3358, 2977, 2223, 1670, 1503, 1367, 1170, 1039, 856 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{20}N_2NaO_3$ 299.1372 [M + Na]$^+$, found 299.1370.

General Procedure for the Oxidative Amination of Quinones and Alkyne Building Blocks IV. A solution of quinoline-5,8-dione or naphthoquinone (5.0 mmol), alkyne building block **IV** (5.0 mmol), cerium chloride heptahydrate ($CeCl_3{\cdot}7H_2O$, 180.0 mg), and methanol (50 mL) was stirred under an oxygen atmosphere at room temperature for 24 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (EtOAc/PE = 1:1 for **V-1–5**; EtOAc/PE = 1:4 for **V-6**) to give aminoquinone **V**.

*tert-Butyl [3-(2-((5,8-Dioxo-5,8-dihydroquinolin-6-yl)amino)-phenyl)prop-2-yn-1-yl]carbamate (**V-1**).* Red needle solid, 1.51 g, 75% yield; mp 147–149 °C (EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (dd, J_1 = 4.6 Hz, J_2 = 1.4 Hz, 1H), 8.45 (dd, J_1 = 7.8 Hz, J_2 = 1.4

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Hz, 1H), 8.23 (s, 1H), 7.64 (dd, J_1 = 7.9 Hz, J_2 = 4.7 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.14 (t, J = 7.0 Hz, 1H), 6.73 (s, 1H), 4.95 (s, 1H), 4.26 (d, J = 5.1 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 181.6, 155.2, 148.6, 143.0, 138.4, 134.4, 132.9, 129.5, 127.3, 126.5, 124.6, 119.9, 115.8, 105.2, 94.1, 80.0, 78.0, 31.2, 28.3; IR (KBr) ν_{max} 3329, 3301, 1711, 1615, 1571, 1307, 751 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_3NaO_4$ 426.1430 [M + Na]$^+$, found 426.1430.

*tert-Butyl [3-(4-Bromo-2-((5,8-dioxo-5,8-dihydroquinolin-6-yl)-amino)phenyl)prop-2-yn-1-yl]carbamate (**V-2**).* Red needle solid, 1.68 g, 70% yield; mp 109−111 °C (EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, J_1 = 4.7 Hz, J_2 = 1.7 Hz, 1H), 8.45 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 1H), 8.25 (s, 1H), 7.66 (dd, J_1 = 7.9 Hz, J_2 = 4.7 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.26 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 6.75 (s, 1H), 4.96 (s, 1H), 4.26 (d, J = 5.4 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.2, 181.4, 155.4, 148.4, 142.4, 139.6, 134.5, 133.7, 127.6, 127.2, 126.7, 123.4, 122.3, 114.4, 106.0, 95.4, 80.2, 77.2, 31.3, 28.4; IR (KBr) ν_{max} 3347, 3280, 1713, 1682, 1615, 1565, 1325, 795 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{20}BrN_3NaO_4$ 504.0535 [M + Na]$^+$, found 504.0532.

*tert-Butyl [3-(2-((5,8-Dioxo-5,8-dihydroquinolin-6-yl)amino)-5-hydroxyphenyl)prop-2-yn-1-yl]carbamate (**V-3**).* Red needle solid, 1.36 g, 65% yield; mp 192−194 °C ($CHCl_3$/MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.92 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 8.48 (dd, J_1 = 7.9 Hz, J_2 = 1.6 Hz, 1H), 7.75 (dd, J_1 = 7.9 Hz, J_2 = 4.8 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 6.88 (dd, J_1 = 8.6 Hz, J_2 = 2.8 Hz, 1H), 5.98 (s, 1H), 4.00 (s, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 183.5, 182.4, 157.5, 156.5, 150.1, 148.5, 136.0, 131.4, 129.3, 128.4, 127.3, 123.5, 121.8, 120.4, 118.1, 103.8, 93.8, 80.7, 79.0, 31.5, 28.8; IR (KBr) ν_{max} 3326, 3272, 1723, 1697, 1603, 1570, 1536, 1302, 987 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_3NaO_5$ 442.1379 [M + Na]$^+$, found 442.1382.

*tert-Butyl [3-(2-((5,8-Dioxo-5,8-dihydroquinolin-6-yl)amino)-5-methoxyphenyl)prop-2-yn-1-yl]carbamate (**V-4**).* Red needle solid, 1.51 g, 70% yield; mp 188−190 °C (EA/cyclohexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (dd, J_1 = 4.7 Hz, J_2 = 1.7 Hz, 1H), 8.43 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 1H), 7.96 (s, 1H), 7.62 (dd, J_1 = 7.8 Hz, J_2 = 4.7 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.01 (d, J = 2.9 Hz, 1H), 6.93 (dd, J_1 = 8.9 Hz, J_2 = 2.9 Hz, 1H), 6.54 (s, 1H), 4.92 (s, 1H), 4.22 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.0, 181.7, 156.6, 155.2, 148.8, 143.7, 134.3, 131.4, 127.3, 126.4, 122.4, 117.8, 117.5, 115.7, 104.1, 93.7, 80.0, 78.1, 55.6, 31.1, 28.3; IR (KBr) ν_{max} 3403, 3247, 1720, 1618, 1577, 1495, 1309, 722 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_3NaO_5$ 456.1535 [M + Na]$^+$, found 456.1535.

*tert-Butyl [3-(2-((4-Chloro-5,8-dioxo-5,8-dihydroquinolin-6-yl)-amino)phenyl)prop-2-yn-1-yl]carbamate (**V-5**).* Red needle solid, 1.09 g, 50% yield; mp 161−162 °C (EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, J = 5.2 Hz, 1H), 8.30 (s, 1H), 7.64 (d, J = 5.2 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.45−7.36 (m, 2H), 7.15 (t, J = 6.9 Hz, 1H), 6.71 (s, 1H), 4.99 (s, 1H), 4.27 (d, J = 2H, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 179.7, 155.2, 154.0, 150.6, 145.0, 143.7, 138.2, 132.9, 129.5, 124.9, 124.1, 120.2, 116.1, 104.1, 94.2, 80.2, 78.0, 31.2, 28.3; IR (KBr) ν_{max} 3385, 1715, 1627, 1555, 1506, 1301, 750 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_3NaO_4$ 460.1040 [M + Na]$^+$, found 460.1043.

*tert-Butyl [3-(2-((1,4-Dioxo-1,4-dihydronaphthalen-2-yl)amino)-phenyl)prop-2-yn-1-yl]carbamate (**V-6**).* Red needle solid, 1.60 g, 80% yield; mp 148−150 °C (EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.12 (d, J = 6.5 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.49−7.35 (m, 3H), 7.10 (t, J = 7.5 Hz, 1H), 6.55 (s, 1H), 5.04 (s, 1H), 4.27 (d, J = 5.4 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 181.8, 143.2, 139.0, 134.8, 133.0, 132.7, 132.4, 130.2, 129.4, 126.5, 126.1, 124.1, 119.4, 115.5, 104.4, 94.0, 79.9, 78.2, 31.2, 28.3; IR (KBr) ν_{max} 3358, 3284, 1687, 1670, 1613, 1521, 1295, 1268, 720 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_4$ 425.1477 [M + Na]$^+$, found 425.1478.

General Procedure for the Preparation of Ascididemin-Type Alkaloids through Brønsted Acid-Promoted Domino Cyclization. Under an oxygen atmosphere, ferric sulfate (12.0 mg, 0.03 mmol) and aminoquinone **V** (0.3 mmol) were added successively to a flask containing sulfuric acid (1.5 mL) and acetic acid (1.5 mL). The reaction mixture was heated at 100 °C for 2 h and then cooled to 0 °C. After the pH was adjusted to 9.0 with saturated Na_2CO_3 solution (30 mL), chloroform (60 mL) was added. The separated organic layer was washed with brine (30 mL) and water (30 mL) and dried with anhydrous $MgSO_4$. After filtration, the filtrate was concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/PE = 3:1 for **VI-1** and **VI-5**; $CHCl_3$/MeOH = 100:1 for **VI-2**−**4** and **VI-6**) to give ascididemin alkaloid **VI**.

*Ascididemin (**VI-1**).* Yellow solid, 63.6 mg, 75% yield; mp >300 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, J = 5.6 Hz, 1H), 9.17 (d, J = 3.2 Hz, 1H), 8.79 (d, J = 7.9 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.54 (d, J = 5.7 Hz, 1H), 8.01 (t, J = 7.1 Hz, 1H), 7.94 (t, J = 7.7 Hz, 1H), 7.67 (dd, J_1 = 7.5 Hz, J_2 = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, CF_3CO_2D) δ 175.6, 154.7, 151.4, 148.2, 147.3, 147.1, 144.9, 141.4, 139.5, 138.7, 138.1, 132.7, 131.4, 128.9, 127.6, 127.5, 123.3; IR (KBr) ν_{max} 3061, 2973, 1674, 1579, 1411, 1266, 767, 738, 725 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_9N_3NaO$ 306.0643 [M + Na]$^+$, found 306.0640.

*Bromoleptoclinidinone (**VI-2**).* Yellow solid, 85.6 mg, 79% yield; mp >300 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, J = 5.7 Hz, 1H), 9.17 (dd, J_1 = 4.6 Hz, J_2 = 1.7 Hz, 1H), 8.79−8.76 (m, 2H), 8.52 (d, J = 8.8 Hz, 1H), 8.48 (d, J = 5.7 Hz, 1H), 8.01 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.68 (dd, J_1 = 7.9 Hz, J_2 = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 155.6, 152.0, 150.1, 149.8, 146.7, 146.2, 137.6, 136.6, 135.2, 134.0, 128.8, 126.1, 125.7, 124.2, 122.1, 117.8, 116.5; IR (KBr) ν_{max} 3070, 2954, 1678, 1598, 1580, 1409, 1263, 950, 738 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_8BrN_3O$ 360.9851 [M]$^+$, found 360.9850.

*Neocalliactine Acetate (**VI-3**).* Yellow solid, 45.0 mg, 44% yield; mp >300 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, J = 5.5 Hz, 1H), 9.17 (d, J = 3.3 Hz, 1H), 8.70 (d, J = 7.7 Hz, 1H), 8.62 (d, J = 9.0 Hz, 1H), 8.43−8.41 (m, 2H), 7.74 (d, J = 8.5 Hz, 1H), 7.67 (dd, J_1 = 7.4 Hz, J_2 = 4.7 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD) δ 181.3, 169.0, 155.1, 152.1, 151.7, 149.3, 149.2, 145.1, 143.0, 137.5, 136.4, 133.8, 128.7, 126.6, 125.7, 124.4, 117.6, 117.1, 115.0, 20.7; IR (KBr) ν_{max} 2961, 2928, 1759, 1717, 1701, 1580, 1511, 1209, 807, 739 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{11}N_3NaO_3$ 364.0698 [M + Na]$^+$, found 364.0699.

*5-Methoxyascididemin (**VI-4**).* Yellow solid, 80.8 mg, 86% yield; mp >300 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (d, J = 5.7 Hz, 1H), 9.16 (dd, J_1 = 4.6 Hz, J_2 = 1.7 Hz, 1H), 8.80 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1H), 8.50 (d, J = 9.2 Hz, 1H), 8.44 (d, J = 5.7 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.67 (dd, J_1 = 7.9 Hz, J_2 = 4.6 Hz, 1H), 7.59 (dd, J_1 = 9.2 Hz, J_2 = 2.7 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (75 MHz, CF_3CO_2D) δ 175.0, 169.3, 154.4, 150.7, 148.4, 147.2, 146.3, 142.4, 136.0, 133.6, 132.6, 132.4, 131.6, 131.4, 129.0, 123.4, 107.9, 58.9; IR (KBr) ν_{max} 2973, 1666, 1611, 1400, 1243, 852, 743 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{11}N_3NaO_2$ 336.0749 [M + Na]$^+$, found 336.0745.

*11-Chloroascididemin (**VI-5**).* Yellow solid, 42.8 mg, 45% yield; mp >300 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, J = 5.5 Hz, 1H), 8.96 (d, J = 5.0 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.00 (t, J = 7.1 Hz, 1H), 7.92 (t, J = 7.5 Hz, 1H), 7.69 (d, J = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, CF_3CO_2D) δ 174.7, 159.8, 152.4, 150.5, 149.1, 146.9, 146.1, 142.0, 139.9, 137.8, 135.6, 128.3, 128.0, 127.6, 123.8, 118.3; IR (KBr) ν_{max} 2955, 1682, 1600, 1558, 1419, 1287, 762 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_8ClN_3NaO$ 340.0254 [M + Na]$^+$, found 340.0252.

*9H-Benzo[b]pyrido[4,3,2-mn]acridin-9-one (**VI-6**).* Yellow solid, 67.6 mg, 80% yield; mp >300 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, J = 5.7 Hz, 1H), 8.85 (dd, J_1 = 8.0 Hz, J_2 = 0.9 Hz, 1H), 8.62−8.58 (m, 2H), 8.48 (dd, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 7.99−7.94 (m, 1H), 7.90−7.80 (m, 2H), 7.68 (td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H); ^{13}C NMR (75 MHz, CF_3CO_2D) δ 177.5, 153.6, 148.1, 144.6, 143.6, 141.1, 140.6, 140.0, 137.9, 134.1, 132.9, 129.2, 128.8, 128.5, 128.3, 127.2, 122.2; IR (KBr) ν_{max} 2986, 1676, 1593, 1572, 1412, 1262, 735 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{10}N_2NaO$ 305.0691 [M + Na]$^+$, found 305.0687.

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11-Hydroxyascididemin. A mixture of **VI-5** (104 mg, 0.33 mmol), acetic acid (6.8 mL), and sodium acetate (340 mg) was heated at 90 °C for 1.5 h. The reaction mixture was cooled and diluted with water. The precipitated solid was filtered, washed with water (10 mL), and dried to give 11-hydroxyascididemin. Yellow solid, 73.6 mg, 82% yield; mp >260 °C (MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.06 (s, 1H), 9.31 (d, J = 5.6 Hz, 1H), 8.89 (d, J = 5.5 Hz, 1H), 8.73 (d, J = 7.8 Hz, 1H), 8.64 (dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz, 1H), 8.58 (d, J = 5.6 Hz, 1H), 8.06 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.00 (td, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1H), 7.16 (d, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 169.4, 156.6, 154.0, 150.0, 149.2, 145.7, 145.6, 137.8, 133.3, 132.1, 131.4, 123.7, 123.0, 117.7, 117.1, 115.5, 114.8; IR (KBr) ν_{max} 3486, 1668, 1604, 1561, 1494, 1179, 842, 773 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_9N_3NaO_2$ 322.0592 $[M + Na]^+$, found 322.0589.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all 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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■ REFERENCES

(1) Kobayashi, J.; Cheng, J. F.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoa, S. *Tetrahedron Lett.* **1988**, *29*, 1177−1180.

(2) For the isolation, structure elucidation, and structure revision of 2-bromoleptoclinidinone, see: (a) Bloor, S. J.; Schmitz, F. J. *J. Am. Chem. Soc.* **1987**, *109*, 6134−6136. (b) de Guzman, F. S.; Schmitz, F. J. *Tetrahedron Lett.* **1989**, *30*, 1069−1070.

(3) Cimino, G.; Crispino, A.; De Rosa, S.; De Stefano, S.; Gavagnin, M.; Sodano, G. *Tetrahedron* **1987**, *43*, 4023−4030.

(4) Schmitz, F. J.; de Guzman, F. S.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.* **1991**, *56*, 804−808.

(5) For reviews of pyridoacridine alkaloids, see: (a) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825−1838. (b) Skyler, D.; Heathcock, C. H. *J. Nat. Prod.* **2002**, *65*, 1573−1581.

(6) (a) Marshall, K. M.; Barrows, L. R. *Nat. Prod. Rep.* **2004**, *21*, 731−751. (b) Matsumoto, S. S.; Biggs, J.; Copp, B. R.; Holden, J. A.; Barrows, L. R. *Chem. Res. Toxicol.* **2003**, *16*, 113−122. (c) Morvan, D. *Mar. Drugs* **2013**, *11*, 3846−3860. (d) von Schwarzenberg, K.; Vollmar, A. M. *Cancer Lett.* **2013**, *332*, 295−303.

(7) (a) Delfourne, E.; Bastide, J. *Med. Res. Rev.* **2003**, *23*, 234−252. (b) Delfourne, E.; Darro, F.; Portefaix, P.; Galaup, C.; Bayssade, S.; Bouteille, A.; Le Corre, L.; Bastide, J.; Collignon, F.; Lesur, B.; Frydman, A.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 3765−3771. (c) Delfourne, E.; Kiss, R.; Le Corre, L.; Dujols, F.; Bastide, J.; Collignon, F.; Lesur, B.; Frydman, A.; Darro, F. *J. Med. Chem.* **2003**, *46*, 3536−3545. (d) Delfourne, E.; Kiss, R.; Le Corre, L.; Merza, J.; Bastide, J.; Frydman, A.; Darros, F. *Bioorg. Med. Chem.* **2003**, *11*, 4351−4356. (e) Delfourne, E.; Kiss, R.; Le Corre, L.; Dujols, F.; Bastide, J.; Collignon, F.; Lesur, B.; Frydman, A.; Darro, F. *Bioorg. Med. Chem.* **2004**, *12*, 3987−3994.

(8) (a) Bracher, F. *Heterocycles* **1989**, *29*, 2093−2095. (b) Bracher, F. *Liebigs Ann. Chem.* **1992**, 1205−1207.

(9) Gellerman, G.; Rudi, A.; Kashman, Y. *Synthesis* **1993**, 239−241.

(10) (a) Cuerva, J. M.; Cardenas, D. J.; Echavarren, A. M. *Chem. Commun.* **1999**, 1721−1722. (b) Cuerva, J. M.; Cardenas, D. J.; Echavarren, A. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1360−1365.

(11) (a) Jiang, C.; Wang, S. *Synlett* **2009**, 1099−1102. (b) Jiang, C.; Xu, M.; Wang, S.; Wang, H.; Yao, Z.-J. *J. Org. Chem.* **2010**, *75*, 4323−4325. (c) Fei, N.; Hou, Q.; Wang, S.; Wang, H.; Yao, Z.-J. *Org. Biomol. Chem.* **2010**, *8*, 4096−4103. (d) Fei, N.; Yin, H.; Wang, S.; Wang, H.; Yao, Z.-J. *Org. Lett.* **2011**, *13*, 4208−4211. (e) Yin, H.; Kong, F.; Wang, S.; Yao, Z.-J. *Tetrahedron Lett.* **2012**, *53*, 7078−7082.

(12) Lisboa, C. d. S.; Santos, V. G.; Vaz, B. G.; de Lucas, N. C.; Eberlin, M. N.; Garden, S. J. *J. Org. Chem.* **2011**, *76*, 5264−5273.

(13) For selected reviews of homogeneous gold catalysis, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211. (b) Li, Z.; He, C. *Chem. Rev.* **2008**, *108*, 3239−3265. (c) Acradi, A. *Chem. Rev.* **2008**, *108*, 3266−3325. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351−3378. (e) Corma, A.; Leyva-Perez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657−1712. (f) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994−2009.