HETEROCYCLES, Vol. 97, No. 1, 2018, pp. 365 - 382. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 23rd January, 2018, Accepted, 8th February, 2018, Published online, 21st February, 2018
DOI: 10.3987/COM-18-S(T)24

FORMAL TOTAL SYNTHESIS OF (±)-STRICTAMINE

Keigo Sato, Noriyuki Takanashi, Noriyuki Kogure, Mariko Kitajima, and Hiromitsu Takayama*

Laboratory of Biofunctional Molecular Chemistry, Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan; E-mail: takayamah@faculty.chiba-u.jp

Abstract – A formal total synthesis of an akuammiline-type indole alkaloid, (±)-strictamine, which features ozonolysis, the Staudinger reaction, and the aza-Wittig reaction to construct its D-ring, is reported.

INTRODUCTION

Akuammiline (**1**)[1]-type indole alkaloids are constituents of genera *Alstonia* and *Hunteria* in family Apocynaceae.[2] After the isolation of echitamine (**3**) by Gorup-Besanez in 1875,[3] more than sixty congeners of akuammiline-type alkaloids were found. These alkaloids have highly rigid cage-like skeletons consisting of a "methanoquinolizidine" fused to an indolenine or indoline ring (Figure 1).

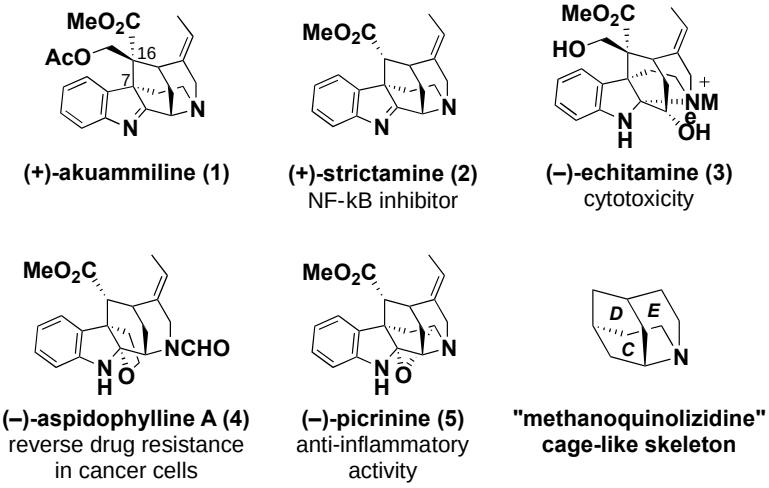


Figure 1. Representative akuammiline indole alkaloids **1**-**5**

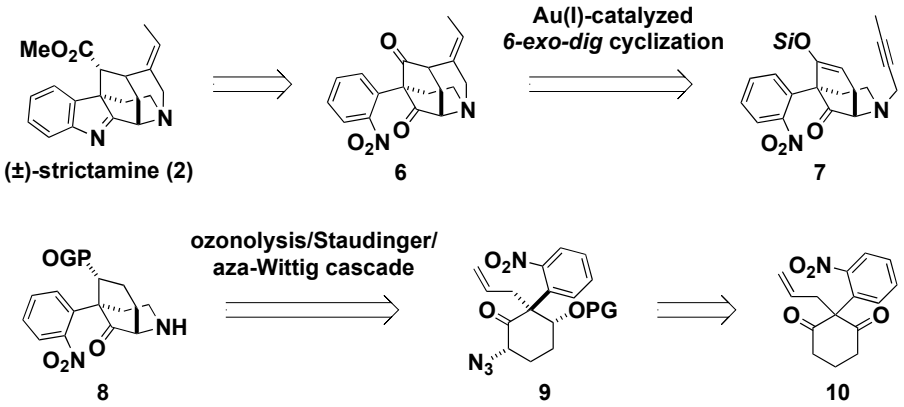
In addition, they exhibit various biological activities, such as anticancer, anti-inflammatory, antibacterial, and antimalarial activities,[4] depending on the substituents on their skeletons. Synthetic studies of these

alkaloids have been carried out enthusiastically for many decades[5,6] due to their exciting chemical and biological properties. Among them, the first total synthesis of strictamine (**2**)[7] in chiral form by Garg[5r] and that in racemic form by Zhu[5s] were independently reported in 2016. The former group applied Au(I)-catalyzed cyclization of alkynyl silyl enol ether and Fischer indolization as key reactions. The latter group accomplished the preparation of the methanoquinolizidine skeleton by a Ni(0)-promoted intramolecular 1,4-addition of alkenyl iodide. Thereafter, Ohno and co-workers[5t] succeeded in the construction of the D-ring by a Au(I)-catalyzed *6-endo-dig* cyclization of 1-propargyl-1,2,3,4-tetrahydro-β-carboline derivative, which was transformed into Zhu's strictamine precursor *via* a few steps. Gaich's group[5u] completed a formal total synthesis of (±)-strictamine (**2**) using [2,3]-Stevens rearrangement twice. Snyder[5w] achieved the shortest asymmetric total synthesis of strictamine (**2**) by adopting an approach similar to Ohno's synthesis. After that, a novel strategy that included the SmI_2-mediated ring migration for the construction of strictamine (**2**) was developed by Zu.[5x] Quite recently, Qin's group[5y] disclosed an asymmetric formal total synthesis of strictamine (**2**) that featured Friedel-Crafts cyclization and intramolecular aza-1,6-conjugate addition.

On the other hand, we have developed a stereoselective Au(I)-catalyzed *6-exo-dig* cyclization reaction of silyl enol ether having an internal alkyne, which produced a piperidine derivative with an exocyclic (*E*)-ethylidene side chain,[8] and applied it to the total synthesis of conolidine and apparicine[8a] as well as some sarpagine-related indole alkaloids.[8b] In our continuous studies on the synthesis of bioactive alkaloids,[9] we planned to apply the reaction for the total synthesis of strictamine (**2**), which is also equipped with an (*E*)-ethylidene-piperidine moiety in its molecule. Herein, we report our attempts at the construction of the methanoquinolizidine skeleton in strictamine (**2**) by utilizing the above-mentioned Au(I)-catalyzed reaction and a formal total synthesis of (±)-strictamine (**2**) using a synthetic intermediate in the first half of the study.

RESULTS AND DISCUSSION

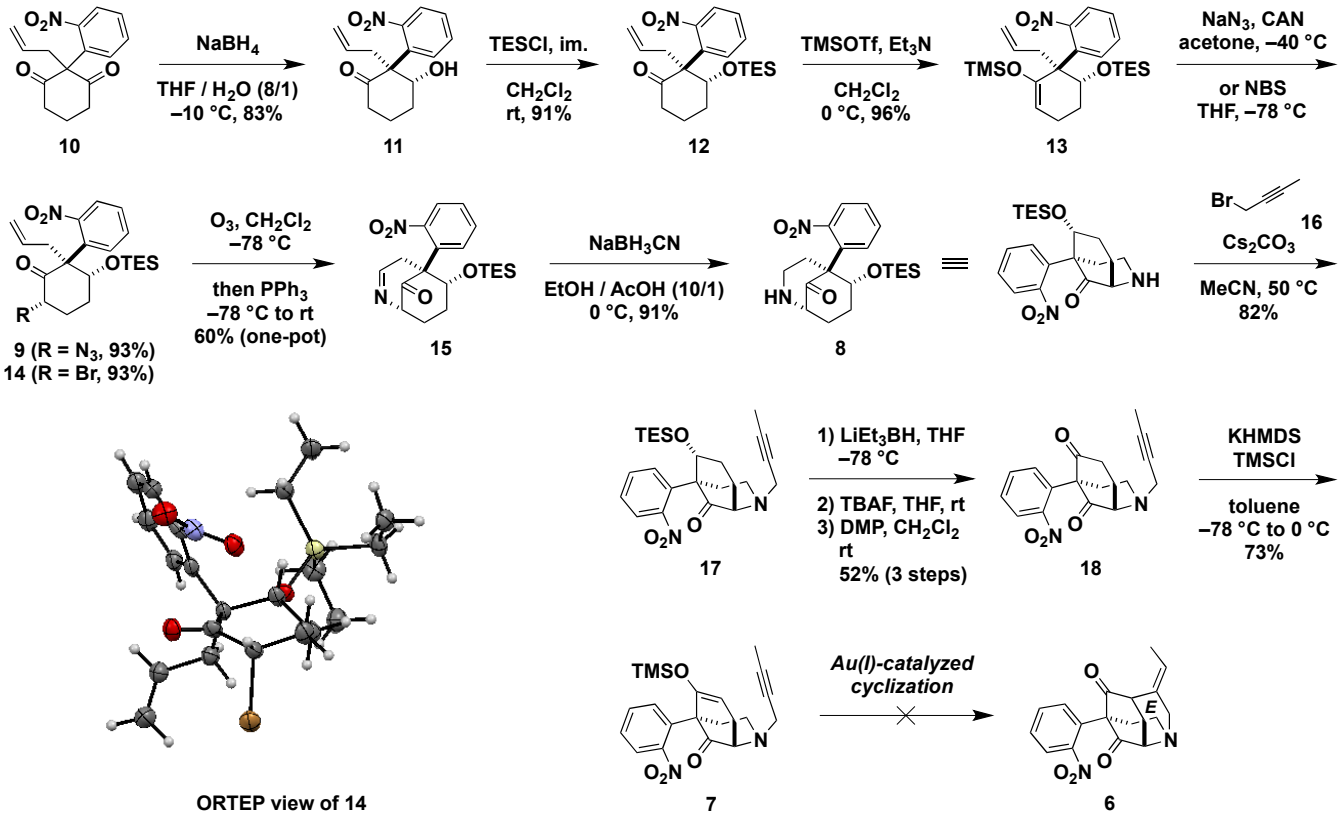
Our retrosynthetic analysis of (±)-**2** is shown in Scheme 1. The formation of an indolenine ring and the installation of an ester moiety were planned in late stage of the synthesis. We had expected that the Au(I)-catalyzed cyclization reaction of alkynyl silyl enol ether **7** would give the (*E*)-ethylidene moiety embedded in the six-membered ring of diketone **6**. Cyclization precursor **7** would be prepared from secondary amine **8** in a few steps. For the transformation of enazide **9** into secondary amine **8**, we had chosen a sequence of steps that included ozonolysis, the Staudinger reaction,[10] and the aza-Wittig reaction[11] in a one-pot operation. Enazide **9** would be prepared through the diastereoselective reduction and the oxidative α-azidation[12] of dicarbonyl compound **10**, a known Bonjoch's intermediate for the syntheses of 3a-(*o*-nitrophenyl)octahydroindol-4-ones.[13]



Scheme 1. Retrosynthetic analysis of (±)-**2**

Initially, we prepared silyl enol ether **7** from known diketone **10**,[13] as shown in Scheme 2. Attempts at the partial reduction of diketone in **10** under the reported conditions[14] afforded significant quantities of diol. After investigation of the reaction conditions, we found that treatment of **10** with sodium borohydride in a mixture of THF and water (8/1) at −10 °C gave β-hydroxyketone **11** in 83% yield as a single diastereomer. After protection of the hydroxy group in **11** with a TES group, resulting silyl ether **12** was converted into silyl enol ether **13**, which was immediately treated with sodium azide in the presence of CAN to afford enazide **9** in excellent yield as a single isomer. The relative stereochemistry at the three chiral centers in enazide **9** was elucidated by comparison of the spectral data of **9** with those of α-bromo adduct **14**, which was obtained by treatment of **13** with NBS, and its structure was confirmed by X-ray crystallographic analysis. Ozonolysis of the terminal olefin in **9** followed by treatment with PPh_3 produced fused bicyclic imine **15** in 60% yield *via* the intramolecular Staudinger/aza-Wittig reaction. Treatment of resulting imine **15** with sodium cyanoborohydride in the acidic condition gave amine **8** in 91% yield. Alkylation of secondary amine **8** using alkynyl bromide **16** in the presence of cesium carbonate afforded **17** in 82% yield. Subsequent attempts at the direct conversion of **17** into diketone **18** *via* removal of the silyl group and the oxidation of the resulting alcohol were unsuccessful due to a retro-aldol reaction of the β-hydroxy ketone intermediate. In this context, diketone **18** was obtained in three steps, as follows: Reduction of **17** with super hydride at −78 °C provided the corresponding alcohol, which was exposed to TBAF to give diol. Oxidation of the resulting diol with Dess-Martin periodinane[15] gave diketone **18** in 52% overall yield. To perform the initially intended Au(I)-catalyzed cyclization reaction, a silyl enol ether derivative was prepared. Regioselective enolate formation with KHMDS and trapping with chlorotrimethylsilane afforded silyl enol ether **7** in 73% yield.

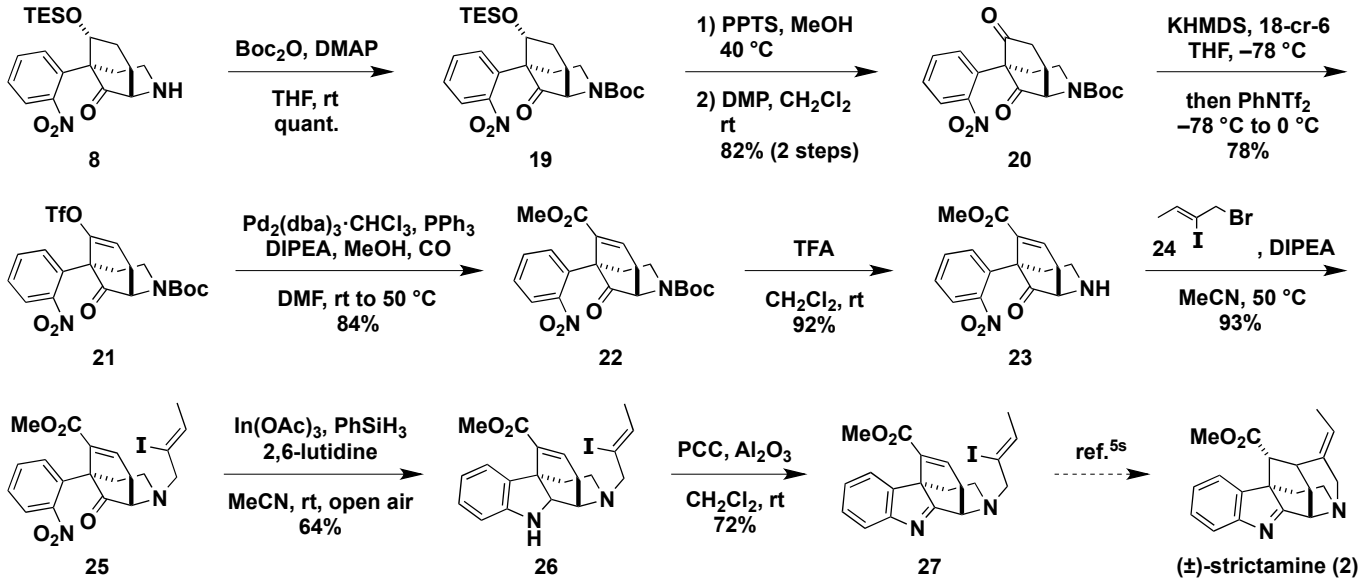
With silyl enol ether **7** in hand, we next investigated the Au(I)-catalyzed *6-exo-dig* cyclization. However, despite massive efforts, such as using IPrAuCl or Et_3PAuCl in the presence of $AgBF_4$ or (C-dtbm)$AuBF_4$[16] for the construction of the E-ring, cyclization product **6** was not obtained at all.



Scheme 2. Synthesis of silyl enol ether **7**

We then altered the synthetic route that utilized synthetic intermediate **8**. Protection of secondary amine **8** with Boc_2O in the presence of DMAP gave corresponding carbamate **19** quantitatively, which was further converted into diketone **20** in 82% overall yield from **19** *via* deprotection of the hydroxy group and successive oxidation with Dess-Martin periodinane. Deprotonation of diketone **20** with KHMDS and treatment of the resulting enolate with *N*-phenyl triflimide (McMurry reagent)[17] provided triflate **21** in 78% yield. Triflate **21** was converted into α,β-unsaturated ester **22** by Pd(0)-catalyzed homologation under CO atmosphere in 84% yield. Removal of Boc group with TFA afforded corresponding amine **23** in 92% yield. Resulting secondary amine **23** was alkylated with allyl bromide **24**[18] to provide key intermediate **25** in 93% yield.

Just while conducting the study on the intramolecular 1,4-addition of alkenyl iodide **25**, Zhu's total synthesis of (±)-**2** was reported.[5s] We then decided to accomplish the research as a formal total synthesis of (±)-**2** by providing indolenine-ring-fused alkenyl iodide **27**, which was Zhu's strictamine precursor.[5s] Reduction of the nitro and carbonyl groups of **25** with phenylsilane in the presence of $In(OAc)_3$ in air gave only indoline-ring-fused alkenyl iodide **26** in 64% yield, which was converted into cyclization precursor **27** by PCC oxidation in 72% yield. The spectral data of indolenine **27** were in good agreement with Zhu's report.[5s]



Scheme 3. Synthesis of (±)-**2**

In conclusion we have accomplished the formal total synthesis of (±)-strictamine (**2**). The key transformation in our approach includes a) a highly diastereoselective α-azidation of ketone and b) a sequence of steps that include ozonolysis, the Staudinger reaction, and the aza-Wittig reaction to form the 2-azabicyclo[3.3.1]nonane skeleton. Further synthetic study of akuammiline-related alkaloids is under way in our laboratory.

EXPERIMENTAL

UV spectra were recorded in MeOH on a JASCO V-560 instrument. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using TMS as the internal standard with JEOL JNM ECZ-400, JNM ECP-400, and JNM ECS-400 at 400 MHz (^{1}H) or 100 MHz (^{13}C), and JNM ECZ-600, JNM ECP-600, and JNM ECA-600 at 600 MHz (^{1}H) or 150 MHz (^{13}C), respectively. J values are given in Hz. Mass spectra were recorded on a JEOL AccuTOF LC-plus JMS-T100LP. Melting points were measured with a Yanaco MP-500P. TLC was carried out on Merck precoated silica gel 60 F254 plates (0.25 mm thick) and Fuji Silysia Chemical precoated amino-silica gel plates. Column chromatography was performed using Kanto Chemical silica gel 60N [40–50 mm (for flash column chromatography)] and Fuji Silysia Chemical Chromatorex NH [100–200 mesh (for amino-silica gel column chromatography)]. Medium pressure liquid chromatography (MPLC) was performed using Kusano Kagakukikai C.I.G. prepacked column CPS-HS-221-05 (SiO_2), JASCO UV-2075 Plus (pump), and UV-2080 Plus (UV detector). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

2-Allyl-3-hydroxy-2-(2-nitrophenyl)cyclohexan-1-one (11). To a stirred solution of **10** (6.36 g, 23.3 mmol) in a mixed solvent of THF/H_2O (8/1, 117 mL) was added in small portions $NaBH_4$ (529 mg, 14.0 mmol) at −10 °C under Ar atmosphere. After stirring for 7.5 h at the same temperature, an additional amount of $NaBH_4$ (529 mg, 14.0 mmol) was introduced to the reaction mixture in small portions. After stirring for another 21 h at the same temperature, the reaction was quenched by adding 1 M aqueous HCl and then diluted with $CHCl_3$. After separation of the two layers, the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 2/5 to 1/1) to afford an inseparable mixture of **11** and corresponding diol (5.72 g) as a pale yellow oil. The ratio of **11** (83%) and the diol (6%) was determined by ^{1}H NMR analysis. Spectral and physical properties of **11** are consistent with previously reported data.[14] **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.91 (1H, dd, *J* = 8.1, 1.5 Hz), 7.60 (1H, ddd, *J* = 8.1, 8.1, 1.5 Hz), 7.52 (1H, dd, *J* = 8.1, 1.5 Hz), 7.43 (1H, ddd, *J* = 8.1, 8.1, 1.5 Hz), 5.35 (1H, dddd, *J* = 17.2, 10.2, 7.3, 6.2 Hz), 5.08 (1H, ddd, *J* = 17.2, 1.5, 1.5 Hz), 4.97 (1H, ddd, *J* = 10.2, 1.5, 1.5 Hz), 4.69 (1H, m), 3.51 (1H, dd, *J* = 16.3, 6.2 Hz), 2.61 (1H, ddd, *J* = 16.3, 7.3, 1.5 Hz), 2.45-2.37 (2H, overlapped), 2.19-1.92 (4H, overlapped). diol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 8.04 (1H, br-d, *J* = 8.1 Hz), 7.55 (1H, ddd, *J* = 8.1, 6.6, 2.2 Hz), 7.41 (1H, ddd, *J* = 8.1, 6.6, 2.2 Hz), 7.38 (1H, dd, *J* = 8.1, 2.2 Hz), 5.68 (1H, dddd, *J* = 17.2, 10.4, 9.2, 4.4 Hz), 5.19 (1H, br-d, *J* = 17.2 Hz), 4.96 (1H, ddd, *J* = 10.4, 1.7, 1.7 Hz), 4.68 (1H, m), 4.34 (1H, br-s), 2.91 (1H, dd, *J* = 16.1, 9.2 Hz), 2.48 (1H, br-d, *J* = 16.1 Hz), 2.02 (1H, m), 1.93-1.60 (5H, overlapped); ESI-MS: 300 $[M+Na]^+$.

2-Allyl-2-(2-nitrophenyl)-3-((triethylsilyl)oxy)cyclohexan-1-one (12). To a stirred solution of the above mixture of **11** and the diol (83:6, 5.72 g) in dry CH_2Cl_2 (100 mL) were added imidazole (2.25 g, 33.0 mmol) and TESCl (5.56 mL, 33.2 mmol) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 20 h at the same temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and then diluted with $CHCl_3$. After separation of the two layers, the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/20) to afford **12** (6.86 g, 91% based on **11**) as a pale yellow solid; mp (plate): 80-85 °C; IR (ATR) ν_{max} cm^{-1}: 2952, 2910, 2875, 1705, 1526, 1355, 1083, 1003; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.89 (1H, dd, *J* = 8.0, 1.4 Hz), 7.54 (1H, ddd, *J* = 8.2, 7.4, 1.4 Hz), 7.47 (1H, dd, *J* = 8.2, 1.4 Hz), 7.40 (1H, ddd, *J* = 8.0, 7.4, 1.4 Hz), 5.36 (1H, dddd, *J* = 17.1, 10.2, 7.7, 5.6 Hz), 5.06 (1H, dd, *J* = 17.1, 1.6 Hz), 4.95 (1H, dd, *J* = 10.2, 1.5 Hz), 4.68 (1H, dd, *J* = 10.9, 4.8 Hz), 3.54 (1H, dd, *J* = 16.6, 5.6 Hz), 2.58 (1H, dd, *J* = 16.6, 7.7 Hz), 2.39 (2H, m), 2.09-1.89 (4H, overlapped), 0.76 (9H, t, *J* = 7.8

Hz), 0.33 (3H, dq, *J* = 15.5, 7.8 Hz), 0.25 (3H, dq, *J* = 15.5, 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 206.8, 150.0, 134.4, 132.64, 132.62, 131.8, 127.6, 125.5, 118.0, 75.2, 63.6, 37.5, 32.7, 30.4, 18.7, 6.6, 4.6; HRESI-MS: calcd. for $C_{21}H_{31}NO_4SiNa$ $[M+Na]^+$ 412.1920; found 412.1911.

{[1-Allyl-2'-nitro-6-(triethylsilyl)oxy-1,4,5,6-tetrahydro-(1,1'-biphenyl)-2-yl]oxy}trimethylsilane (13). To a stirred solution of **12** (957 mg, 2.45 mmol) in dry CH_2Cl_2 (12.2 mL) were added Et_3N (2.04 mL, 14.7 mmol) and TMSOTf (1.55 mL, 8.59 mmol) at 0 °C under Ar atmosphere, and the reaction mixture was stirred for 5 h at the same temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and then diluted with $CHCl_3$. After separation of the two layers, the aqueous layer was extracted two times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/30) to afford **13** (1.08 g, 96%) as a yellow amorphous solid; IR (ATR) ν_{max} cm^{-1}: 2954, 2911, 2876, 1529, 1361, 1251, 1198, 1090, 845, 745; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.55 (1H, dd, *J* = 8.1, 1.5 Hz), 7.54 (1H, dd, *J* = 8.2, 1.5 Hz), 7.42 (1H, ddd, *J* = 8.2, 7.3, 1.5 Hz), 7.29 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz), 5.67 (1H, dddd, *J* = 17.2, 10.3, 7.9, 5.5 Hz), 5.02 (1H, dd, *J* = 17.2, 1.5 Hz), 4.86 (1H, dd, *J* = 10.3, 0.7 Hz), 4.67 (1H, dd, *J* = 5.1, 2.6 Hz), 4.51 (1H, dd, *J* = 11.7, 4.4 Hz), 3.26 (1H, dd, *J* = 15.3, 5.5 Hz), 2.72 (1H, dd, *J* = 15.3, 7.9 Hz), 2.22 (1H, m), 2.09 (1H, m), 1.88 (1H, ddd, *J* = 11.7, 11.7, 0.7 Hz), 1.72 (1H, m), 0.78 (9H, t, *J* = 7.9 Hz), 0.33 (3H, dq, *J* = 15.8, 7.9 Hz), 0.26 (3H, dq, *J* = 15.8, 7.9 Hz), 0.08 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.9, 150.0, 136.5, 135.6, 133.1, 129.8, 126.6, 124.2, 115.4, 100.4, 73.8, 53.1, 38.5, 27.8, 21.2, 6.7, 4.7, −0.1; HRESI-MS: calcd. for $C_{24}H_{39}NO_4Si_2Na$ $[M+Na]^+$ 484.2315; found 484.2344.

2-Allyl-6-azido-2-(2-nitrophenyl)-3-[(triethylsilyl)oxy]cyclohexan-1-one (9). To a stirred solution of **13** (7.25 g, 15.7 mmol) in dry acetone (314 mL) were added NaN_3 (4.59 g, 70.6 mmol) and CAN (8.60 g, 15.7 mmol) at −40 °C under Ar atmosphere, and the reaction mixture was stirred at the same temperature. The mixture was treated twice (i.e., after 1 and 2 h) with an additional amount of CAN (8.60 g, 15.7 mmol). After stirring for another 3 h, the reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted two times with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (ether/*n*-hexane = 1/15) to afford **9** (6.27 g, 93%) as a colorless oil; IR (ATR) ν_{max} cm^{-1}: 2954, 2913, 2877, 2092, 1698, 1521, 1354, 1233, 1088, 998; ^{1}H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ ppm: 7.77 (1H, d, *J* = 7.3 Hz), 7.53 (1H, ddd, *J* = 7.3, 7.3, 1.3 Hz), 7.40 (1H, ddd, *J* = 7.3, 7.3, 1.3 Hz), 7.35 (1H, br-d, *J* = 7.3 Hz), 5.47 (1H, dddd, *J* = 16.9, 10.3, 6.9, 6.9 Hz), 5.04 (1H, dd, *J* = 16.9, 1.4 Hz), 4.97 (1H, dd, *J* = 10.3, 1.1 Hz), 4.61

(1H, dd, *J* = 8.9, 3.4 Hz), 3.90 (1H, dd, *J* = 5.3, 5.3 Hz), 3.30 (1H, br-d, *J* = 11.4 Hz), 2.96 (1H, dd, *J* = 15.8, 7.1 Hz), 2.18 (1H, m), 2.07-1.94 (2H, overlapped), 1.88 (1H, m), 0.84 (9H, t, *J* = 7.8 Hz), 0.42 (6H, overlapped); ^{13}C NMR ($CDCl_3$, 100 MHz, at 55 °C) δ ppm: 202.3, 149.9, 133.5, 132.9, 132.5, 131.7, 128.1, 125.4, 118.8, 74.5, 63.3, 62.0, 34.3, 26.6, 25.7, 6.6, 4.9; HRESI-MS: calcd. for $C_{21}H_{30}N_4O_4SiNa$ $[M+Na]^+$ 453.1934; found 453.1913.

2-Allyl-6-bromo-2-(2-nitrophenyl)-3-[(triethylsilyl)oxy]cyclohexan-1-one (14). To a stirred solution of **13** (16.5 mg, 35.6 μmol) in dry THF (0.6 mL) was added a solution of NBS (9.5 mg, 53.5 μmol) in dry THF (0.4 mL) at −78 °C under Ar atmosphere, and the reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted two times with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (Et_2O/*n*-hexane = 1/15) to afford **14** (15.5 mg, 93%) as a pale yellow crystal; mp (plate): 93-94 °C. (Recrystalyzed from *n*-hexane.); IR (ATR) ν_{max} cm^{-1}: 3020, 2955, 2912, 2876, 1702, 1525, 1353, 1216, 1105, 1086, 1004, 818, 749, 665; ^{1}H NMR (C_6D_6, 400 MHz, at 65 °C) δ ppm: 7.43 (1H, d, *J* = 7.3 Hz), 7.29 (1H, d, *J* = 7.3 Hz), 6.94 (1H, ddd, *J* = 8.0, 7.3, 1.4 Hz), 6.68 (1H, ddd, *J* = 8.0, 7.3, 1.4 Hz), 5.60 (1H, dddd, *J* = 17.0, 10.3, 7.0, 6.6 Hz), 5.13 (1H, ddd, *J* = 17.0, 1.7, 1.7 Hz), 4.97 (1H, ddd, *J* = 10.3, 1.5, 1.5 Hz), 4.64 (1H, dd, *J* = 10.8, 4.2 Hz), 4.26 (1H, dd, *J* = 4.0, 4.0 Hz), 3.58 (1H, dd, *J* = 16.3, 7.0 Hz), 3.32 (1H, dd, *J* = 16.3, 6.6 Hz), 2.47-2.31 (1H, m), 2.28-2.11 (1H, m), 2.01-1.87 (1H, m), 1.73-1.61 (1H, m), 0.77 (9H, t, *J* = 7.7 Hz), 0.31 (3H, dq, *J* = 15.4, 7.7 Hz) , 0.25 (3H, dq, *J* = 15.4, 7.7 Hz); ^{13}C NMR (C_6D_6, 100 MHz, at 65 °C) δ ppm: 199.6, 150.7, 133.7, 132.4, 132.1, 128.9, 128.4, 126.2, 119.3, 76.1, 64.4, 48.6, 35.9, 30.2, 26.9, 6.8, 5.2; HRESI-MS: calcd. for $C_{21}H_{30}BrNO_4SiNa$ $[M+Na]^+$ 490.1025; found 490.1039.
Deposition number CCDC-1820067 for compound **14**. Free copies of the data can be obtained *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail:deposit@ccdc.cam.ac.uk).

5-(2-Nitrophenyl)-6-[(triethylsilyl)oxy]-2-azabicyclo[3.3.1]non-2-en-9-one (15). A solution of **9** (5.83 g, 13.5 mmol) in CH_2Cl_2 (500 mL) was cooled to −78 °C and ozone was gently bubbled through the reaction mixture for 90 min at the same temperature. To the stirred solution was added PPh_3 (14.2 g, 54.0 mmol) at the same temperature under Ar atmosphere. The reaction mixture was warmed to room temperature and stirred for 18.5 h at the same temperature. The resultant mixture was evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/4 to 3/7) to afford **15** (3.14 g, 60%) as a yellow solid; IR (ATR) ν_{max} cm^{-1}: 2952, 2876, 1720, 1528,

1355, 1097, r g 1075; ^{1}H NMR ($CDCl_3$, 600 MHz) δ ppm: 7.92 (1H, dd, *J* = 8.0, 1.4 Hz), 7.88 (1H, br-s), 7.55 (1H, ddd, *J* = 8.0, 7.4, 1.4 Hz), 7.45 (1H, ddd, *J* = 8.0, 7.4, 1.4 Hz), 7.16 (1H, dd, *J* = 8.0, 1.4 Hz), 4.88 (1H, dd, *J* = 10.3, 5.6 Hz), 4.26 (1H, br-s), 4.22 (1H, dd, *J* = 18.3, 2.6 Hz), 2.78 (1H, d, *J* = 18.3 Hz), 2.18-1.99 (3H, overlapped), 1.78 (1H, m), 0.75 (9H, t, *J* = 7.7 Hz), 0.31 (3H, dq, *J* = 15.1, 7.7 Hz), 0.21 (3H, dq, *J* = 15.1, 7.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ ppm: 209.4, 162.7, 149.9, 133.2, 132.1, 130.7, 128.2, 125.4, 74.9, 64.8, 59.2, 47.2, 26.5, 24.5, 6.6, 4.5; HRESI-MS: calcd. for $C_{20}H_{29}N_2O_4Si$ $[M+H]^+$ 389.1897; found 389.1906.

5-(2-Nitrophenyl)-6-[(triethylsilyl)oxy]-2-azabicyclo[3.3.1]nonan-9-one (8). To a stirred solution of **15** (26.3 mg, 67.6 μmol) in a mixed solvent of EtOH/AcOH (10/1, 0.66 mL) was added $NaBH_3CN$ (6.7 mg, 101 μmol) at 0 °C under Ar atmosphere, and the reaction mixture was stirred for 3.5 h at the same temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted once with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/1 to MeOH/$CHCl_3$ = 1/10) to afford **8** (23.9 mg, 91%) as a yellow oil; IR (ATR) ν_{max} cm^{-1}: 2952, 2875, 1715, 1528, 1355, 1076, 1008, 811, 739; ^{1}H NMR ($CDCl_3$, 600 MHz) δ ppm: 7.94 (1H, dd, *J* = 8.0, 1.4 Hz), 7.56 (1H, ddd, *J* = 8.0, 7.4, 1.4 Hz), 7.43 (1H, ddd, *J* = 8.0, 7.4, 1.4 Hz), 7.36 (1H, dd, *J* = 8.0, 1.4 Hz), 4.96 (1H, dd, *J* = 8.8, 8.8 Hz), 3.71 (1H, ddd, *J* = 15.0, 12.0, 4.8 Hz), 3.53 (1H, ddd, *J* = 12.0, 4.8, 1.8 Hz), 3.23 (1H, dd, *J* = 3.3, 3.3 Hz), 2.93 (1H, ddd, *J* = 15.0, 6.8, 1.8 Hz), 2.39 (1H, ddd, *J* = 14.4, 10.2, 6.8 Hz), 2.29 (1H, m), 2.24-2.07 (3H, overlapped), 0.75 (9H, t, *J* = 7.8 Hz), 0.32 (3H, dq, *J* = 15.0, 7.8 Hz), 0.24 (3H, dq, *J* = 15.0, 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ ppm: 214.5, 149.7, 135.5, 132.2, 130.1, 127.9, 125.5, 75.3, 59.5, 58.9, 43.3, 42.0, 31.5, 26.6, 6.7, 4.6; HRESI-MS: calcd. for $C_{20}H_{31}N_2O_4Si$ $[M+H]^+$ 391.2053; found 391.2052.

2-(But-2-yn-1-yl)-5-(2-nitrophenyl)-6-[(triethylsilyl)oxy]-2-azabicyclo[3.3.1]nonan-9-one (17). To a stirred solution of **8** (80.8 mg, 0.206 mmol) in dry MeCN (1.0 mL) were added Cs_2CO_3 (101 mg, 0.310 mmol) and **16** (28.8 mg, 0.217 mmol) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 2.5 h at 50 °C. After cooling to room temperature, water was added to the reaction mixture and the resultant mixture was diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted once with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/5) to afford **17** (75.1 mg, 82%) as a colorless oil; IR (ATR) ν_{max} cm^{-1}: 3026, 2971, 1740, 1529, 1374, 1215, 1175, 940; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.88 (1H, dd,

J = 7.8, 1.4 Hz), 7.54 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.41 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.38 (1H, dd, *J* = 7.8, 1.4 Hz), 4.86 (1H, dd, *J* = 9.2, 7.8 Hz), 3.39 (1H, ddd, *J* = 6.9, 4.6, 2.3 Hz), 3.34 (1H, m), 3.33-3.26 (2H, m), 2.79 (1H, m), 2.32-2.22 (2H, overlapped), 2.20-2.08 (1H, m), 2.06-1.96 (1H, m), 1.94 (1H, d, *J* = 2.3 Hz), 1.90-1.81 (1H, m), 1.81 (3H, t, *J* = 2.3 Hz), 0.74 (9H, t, *J* = 7.8 Hz), 0.30 (3H, dq, *J* = 15.6, 7.8 Hz), 0.22 (3H, dq, *J* = 15.6, 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 206.5, 150.1, 135.2, 131.9, 131.2, 127.8, 125.3, 80.6, 75.4, 74.6, 64.1, 58.8, 46.9, 44.8, 33.4, 30.1, 23.8, 6.7, 4.7, 3.5; HRESI-MS: calcd. for $C_{24}H_{35}N_2O_4Si$ $[M+H]^+$ 443.2366; found 443.2359.

2-(But-2-yn-1-yl)-5-(2-nitrophenyl)-2-azabicyclo[3.3.1]nonane-6,9-dione (18). To a stirred solution of **17** (308 mg, 0.695 mmol) in dry THF (7.0 mL) was added $LiEt_3BH$ (1.0 M in THF, 1.39 mL, 1.39 mmol) at −78 °C under Ar atmosphere, and the reaction mixture was stirred for 4.5 h at the same temperature. The reaction was quenched by adding 1 M aqueous NaOH and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted two times with AcOEt. The combined organic layers were dried over K_2CO_3, filtered, and evaporated under reduced pressure to afford a crude product that was used in the next reaction without purification. To a stirred solution of the above crude product in dry THF (3.5 mL) was added TBAF (1.0 M in THF, 0.835 mL, 0.835 mmol) at 0 °C under Ar atmosphere, and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched by adding water and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted two times with AcOEt. The combined organic layers were dried over K_2CO_3, filtered, and evaporated under reduced pressure to afford the crude diol (204 mg), a portion of which was used in the next reaction without purification. To a stirred solution of the above crude diol (151 mg, 0.457 mmol) in dry CH_2Cl_2 (9.1 mL) was added Dess-Martin periodinane (581 mg, 1.37 mmol) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 6 h at the same temperature. The reaction was quenched by adding 1 M aqueous NaOH and saturated aqueous $Na_2S_2O_3$, and then diluted with $CHCl_3$. After separation of the two layers, the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/1 to 1/3) to afford **18** (86.6 mg, 52% from **17**) as a white amorphous solid; IR (ATR) ν_{max} cm^{-1}: 2919, 2860, 1738, 1692, 1523, 1442, 1348, 1146, 1034, 1011, 904, 856, 790, 722, 649; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 8.19 (1H, dd, *J* = 8.3, 1.4 Hz), 7.72 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.53 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.51 (1H, d, *J* = 8.3 Hz), 3.76 (1H, dd, *J* = 3.1, 3.1 Hz), 3.57 (1H, dq, *J* = 16.5, 2.4 Hz), 3.50 (1H, dq, *J* = 16.5, 2.4 Hz), 3.28 (1H, ddd, *J* = 12.4, 12.4, 4.1 Hz), 3.12 (1H, ddd, *J* = 13.1, 5.5, 2.8 Hz), 3.06 (1H, dd, *J* = 20.0, 9.6 Hz), 2.80 (1H, ddd, *J* = 20.0, 11.0, 9.6 Hz), 2.73-2.66 (2H, overlapped), 2.60 (1H, ddd, *J* = 12.4, 12.4, 6.2 Hz), 2.17 (1H, m), 1.85 (3H, t, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ ppm: 207.6, 202.3, 147.3, 134.1,

132.1, 129.4, 128.8, 125.8, 81.5, 74.1, 68.6, 64.4, 45.7, 43.7, 38.0, 36.9, 20.0, 3.5; HRESI-MS: calcd. for $C_{18}H_{18}N_2O_4Na$ $[M+Na]^+$ 349.1164; found 349.1168.

2-(But-2-yn-1-yl)-5-(2-nitrophenyl)-6-[(trimethylsilyl)oxy]-2-azabicyclo[3.3.1]non-6-en-9-one (7). To a stirred solution of **18** (28.9 mg, 88.5 μmol) in dry toluene (1.25 mL) was added KHMDS (0.5 M in toluene, 442 μL, 221 μmol) at −78 °C under Ar atmosphere. After stirring for 20 min at the same temperature, TMSCl (33.5 μL, 265 μmol) was added to the mixture. After stirring for 5.5 h at 0 °C, the reaction was quenched by adding saturated aqueous $NaHCO_3$ and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted once with AcOEt. The combined organic layers were dried over K_2CO_3, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 2/5 to 1/1) to afford **7** (25.6 mg, 73%) as a pale yellow amorphous solid, together with recovered **18** (5.2 mg, 18%); IR (ATR) ν_{max} cm^{-1}: 3051, 2955, 2920, 2835, 1735, 1668, 1526, 1354, 1267, 1252, 1209, 1173, 869, 840; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.97 (1H, dd, *J* = 8.3, 1.4 Hz), 7.60 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.47-7.42 (2H, overlapped), 5.11 (1H, dd, *J* = 5.2, 2.4 Hz), 3.50 (1H, d, *J* = 5.2 Hz), 3.46 (1H, ddd, *J* = 12.9, 12.4, 4.4 Hz), 3.37 (1H, dq, *J* = 16.2, 2.2 Hz), 3.33 (1H, dq, *J* = 16.2, 2.2 Hz), 3.07 (1H, ddd, *J* = 12.9, 1.8, 1.8 Hz), 2.69 (1H, dd, *J* = 18.1, 5.2 Hz), 2.58 (1H, ddd, *J* = 18.1, 2.4, 2.4 Hz), 2.49 (1H, ddd, *J* = 12.4, 12.4, 4.4 Hz), 2.44 (1H, ddd, *J* = 12.4, 1.8, 1.8 Hz), 1.83 (3H, t, *J* = 2.2 Hz), −0.05 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ ppm: 204.6, 150.0, 145.8, 133.1, 132.3, 129.6, 127.9, 125.1, 100.9, 80.8, 74.7, 63.3, 59.1, 44.7, 43.3, 36.0, 24.1, 3.6, −0.2; HRESI-MS: calcd. for $C_{21}H_{27}N_2O_4Si$ $[M+H]^+$ 399.1740; found 399.1747.

***tert*-Butyl 5-(2-nitrophenyl)-9-oxo-6-[(triethylsilyl)oxy]-2-azabicyclo[3.3.1]nonane-2-carboxylate (19).** To a stirred solution of **8** (70.8 mg, 181 μmol) in dry THF (3.6 mL) were added DMAP (2.2 mg, 18.1 μmol) and Boc_2O (47.0 μL, 218 μmol) at 0 °C under Ar atmosphere, and the reaction mixture was stirred for 21.5 h at room temperature. The reaction was quenched by adding water and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/9) to afford **19** (88.7 mg, quant.) as a white amorphous solid; IR (ATR) ν_{max} cm^{-1}: 3020, 2958, 2933, 2877, 1726, 1684, 1528, 1396, 1366, 1356, 1259, 1215, 1159, 1100, 1066, 1018, 856, 805, 748, 665; ^1H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ ppm: 7.93 (1H, d, *J* = 8.2 Hz), 7.55 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.43 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.40 (1H, d, *J* = 8.2 Hz), 4.89 (1H, dd, *J* = 8.5, 8.5 Hz), 4.34 (1H, br-s), 3.87 (1H, ddd, *J* = 13.7, 9.1, 6.4 Hz), 3.66 (1H, br-s), 3.32 (1H, br-s), 2.37-1.86 (5H, m), 1.47 (9H, s), 0.76 (9H, t, *J* = 7.7 Hz), 0.35 (3H, dq, *J* = 15.4, 7.7 Hz), 0.27 (3H, dq, *J* = 15.4, 7.7 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz, at 55 °C) δ ppm: 204.8, 154.5, 150.1, 134.7, 132.1, 130.6, 128.1, 125.6, 80.5, 75.5, 59.4, 58.6, 41.0, 32.4, 31.5, 28.4, 25.7, 6.6, 4.8; HRESI-MS: calcd. for $C_{25}H_{38}N_2O_6SiK$ $[M+K]^+$ 529.2136; found 529.2143.

***tert*-Butyl 5-(2-nitrophenyl)-6,9-dioxo-2-azabicyclo[3.3.1]nonane-2-carboxylate (20).** To a stirred solution of **19** (1.10 g, 2.24 mmol) in dry MeOH (23.0 mL) was added PPTS (1.13 g, 4.49 mmol) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 18 h at 40 °C. The resultant mixture was evaporated under reduced pressure to afford the crude alcohol, which was used in the next reaction without purification. To a stirred solution of the above crude alcohol in dry CH_2Cl_2 (23.0 mL) was added Dess-Martin periodinane (1.90 g, 4.49 mmol) at 0 °C under Ar atmosphere, and the reaction mixture was stirred for 14.5 h at room temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, and then diluted with $CHCl_3$. After separation of the two layers, the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/4 to 2/3) to afford **20** (0.69 g, 82% from **19**) as a white amorphous solid; IR (ATR) ν_{max} cm^{-1}: 2976, 2935, 1743, 1699, 1526, 1393, 1366, 1346, 1322, 1300, 1240, 1156, 1123, 1031, 1007, 912, 857, 759, 735; ^{1}H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ ppm: 8.22 (1H, dd, *J* = 8.2, 1.4 Hz), 7.71 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.54 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 7.46 (1H, d, *J* = 8.2 Hz), 4.80 (1H, br-s), 4.28 (1H, br-d, *J* = 7.3 Hz), 3.50 (1H, ddd, *J* = 13.7, 13.7, 4.4 Hz), 3.07 (1H, dd, *J* = 19.9, 9.4 Hz), 2.76 (1H, dd, *J* = 19.9, 10.1 Hz), 2.71 (1H, d, *J* = 10.1 Hz), 2.49 (1H, ddd, *J* = 13.7, 6.5, 6.5 Hz), 2.40-2.15 (2H, m), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz, at 55 °C) δ ppm: 206.0, 200.9, 154.1, 147.5, 134.1, 131.8, 129.2, 129.1, 126.1, 81.4, 68.5, 58.5, 40.3, 37.4, 35.9, 28.4, 23.7; HRESI-MS: calcd. for $C_{19}H_{22}N_2O_6Na$ $[M+Na]^+$ 397.1376; found 397.1380.

***tert*-Butyl 5-(2-nitrophenyl)-9-oxo-6-{[(trifluoromethyl)sulfonyl]oxy}-2-azabicyclo[3.3.1]non-6-ene-2-carboxylate (21).** To a stirred solution of **20** (1.33 g, 3.55 mmol) in dry THF (3.55 mL) were added sequentially 18-crown-6 (3.76 g, 14.2 mmol) and KHMDS (0.5 M in toluene, 7.11 mL, 3.55 mmol) at −78 °C under Ar atmosphere. After stirring for 30 min at the same temperature, McMurry reagent (3.81 g, 10.7 mmol) in dry THF (12.8 mL) was added to the mixture. After stirring for 12.5 h at 0 °C, the reaction was quenched by adding saturated aqueous NH_4Cl and then diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/6 to 2/3) to afford **21** (1.40 g, 78%) as a white amorphous solid; IR (ATR) ν_{max} cm^{-1}: 2980, 2936, 1746, 1694, 1531, 1396, 1367, 1355,

1306, 1285, 1211, 1138, 1056, 1005, 976, 926, 853, 837, 814, 733; ^{1}H NMR ($CDCl_3$, 600 MHz, at 55 °C) δ ppm: 8.14 (1H, d, *J* = 8.2 Hz), 7.70 (1H, ddd, *J* = 8.2, 7.3, 0.9 Hz), 7.57 (1H, ddd, *J* = 8.2, 8.2, 0.9 Hz), 7.48 (1H, d, *J* = 7.3 Hz), 6.24 (1H, dd, *J* = 5.7, 2.5 Hz), 4.74 (1H, br-s), 4.27 (1H, br-d, *J* = 11.4 Hz), 3.68 (1H, ddd, *J* = 13.2, 13.2, 3.4 Hz), 2.96 (1H, ddd, *J* = 18.8, 5.0, 2.7 Hz), 2.83 (1H, dd, *J* = 13.0, 2.5 Hz), 2.66 (1H, dd, *J* = 18.8, 5.3 Hz), 2.34 (1H, ddd, *J* = 12.7, 12.7, 5.3 Hz), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz, at 55 °C) δ ppm: 199.2, 153.8, 149.7, 142.6, 133.5, 129.7, 129.6, 129.0, 126.2, 118.2 (q, *J* = 320 Hz), 117.5, 81.5, 57.4, 56.7, 38.4, 36.0, 28.9, 28.3; HRESI-MS: calcd. for $C_{20}H_{21}F_3N_2O_8SNa$ $[M+Na]^+$ 529.0868; found 529.0873.

2-(*tert*-Butyl) 6-methyl 5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]non-6-ene-2,6-dicarboxylate (22). To a stirred solution of **21** (562 mg, 1.11 mmol) in dry DMF (15.0 mL) were added $Pd_2(dba)_3{\cdot}CHCl_3$ (115 mg, 111 μmol), PPh_3 (58.2 mg, 222 μmol), DIPEA (0.41 mL, 4.44 mmol), and dry MeOH (1.80 mL, 44.4 mmol) at room temperature, and CO was gently bubbled through the reaction mixture for 5 min at the same temperature. After stirring for 6 h at 50 °C under CO atmosphere, the resultant mixture was filtered through Celite® and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/4) to afford **22** (386 mg, 84%) as a pale yellow amorphous solid; IR (ATR) ν_{max} cm^{-1}: 2978, 2888, 1739, 1690, 1526, 1437, 1391, 1364, 1308, 1281, 1231, 1163, 1137, 1058, 1008, 982, 853, 747; ^{1}H NMR ($CDCl_3$, 600 MHz, at 55 °C) δ ppm: 7.90 (1H, d, *J* = 8.2 Hz), 7.64 (1H, dd, *J* = 7.6, 7.6 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 7.45 (1H, dd, *J* = 8.2, 7.6 Hz), 7.31 (1H, d, *J* = 4.1 Hz), 4.67 (1H, br-s), 4.19 (1H, br-s), 3.50 (3H, s), 3.49-3.42 (1H, m), 3.02 (1H, d, *J* = 18.6 Hz), 2.88 (1H, d, *J* = 12.5 Hz), 2.80 (1H, br-d, *J* = 18.6 Hz), 2.47 (1H, ddd, *J* = 12.5, 12.5, 5.3 Hz), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz, at 55 °C) δ ppm: 202.3, 164.6, 153.9, 149.4, 139.8, 133.4, 132.6, 131.1, 129.8, 128.3, 125.5, 81.1, 57.5, 55.3, 51.7, 39.0, 36.2, 33.5, 28.4; HRESI-MS: calcd. for $C_{21}H_{24}N_2O_7Na$ $[M+Na]^+$ 439.1481; found 439.1487.

Methyl 5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (23). To a stirred solution of **22** (66.0 mg, 159 μmol) in dry CH_2Cl_2 (3.0 mL) was added dry TFA (240 μL, 3.17 mmol) at 0 °C under Ar atmosphere, and the reaction mixture was stirred for 2.5 h at room temperature. The resultant mixture was evaporated under reduced pressure. The residue was purified by amino-silica gel column chromatography (MeOH/$CHCl_3$ = 1/19) to afford **23** (46.3 mg, 92%) as a white amorphous solid; IR (ATR) ν_{max} cm^{-1}: 3315, 3024, 2951, 2879, 1711, 1523, 1437, 1408, 1351, 1281, 1256, 1227, 1194, 1172, 1123, 1073, 1038, 991, 916, 852, 664; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.93 (1H, dd, *J* = 7.8, 1.4 Hz), 7.67 (1H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.60 (1H, dd, *J* = 8.2, 1.4 Hz), 7.46 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.40 (1H, dd, *J* = 5.0, 2.8 Hz), 3.51 (3H, s), 3.50-3.43 (1H, m), 3.39 (1H, ddd, *J* = 14.6, 12.0, 2.8 Hz),

3.15-3.04 (2H, overlapped), 2.95 (1H, br-d, *J* = 12.4 Hz), 2.83 (1H, ddd, *J* = 21.9, 5.3, 1.2 Hz), 2.64 (1H, ddd, *J* = 12.4, 12.4, 5.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 210.0, 164.8, 148.8, 140.4, 134.6, 132.5, 130.4, 129.8, 128.0, 125.3, 58.1, 55.8, 51.6, 44.4, 39.2, 33.5; HRESI-MS: calcd. for $C_{16}H_{17}N_2O_5$ $[M+H]^+$ 317.1138; found 317.1125.

Methyl 2-((*Z*)-2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (25). To a stirred solution of **23** (83.7 mg, 0.265 mmol) in dry MeCN (5.5 mL) were added DIPEA (70.4 µL, 0.398 mmol) and **24**[18] (63.7 µL, 0.530 mmol) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 26.5 h at 50 °C. After cooling to room temperature, water was added to the reaction mixture and the resultant mixture was diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/3) to afford **25** (122 mg, 93%) as a white solid; IR (ATR) ν_{max} cm^{-1}: 3019, 2995, 2947, 2871, 1706, 1641, 1523, 1435, 1352, 1296, 1236, 1215, 1124, 1090, 1067, 1005, 950, 915, 850, 812, 751, 665, 632; ^{1}H NMR ($CDCl_3$, 400 MHz, at 55 °C) δ ppm: 7.91 (1H, d, *J* = 8.2 Hz), 7.62 (1H, dd, *J* = 7.3, 7.3 Hz), 7.59 (1H, d, *J* = 7.3 Hz), 7.42 (1H, dd, *J* = 8.2, 7.3 Hz), 7.31 (1H, t-like, *J* = 3.9 Hz), 5.87 (1H, q, *J* = 6.4 Hz), 3.48 (3H, s), 3.40-3.25 (4H, m), 2.92-2.81 (3H, m), 2.69 (2H, dd, *J* = 8.2, 3.2 Hz), 1.78 (3H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, at 55 °C) δ ppm: 204.9, 165.0, 149.4, 139.3 (*J* = 6.7 Hz), 134.5, 133.3, 132.4, 131.1, 130.1, 128.0, 125.3, 107.7, 65.4, 61.7, 55.7, 51.5, 44.3, 38.2, 30.7, 21.6; HRESI-MS: calcd. for $C_{20}H_{22}IN_2O_5$ $[M+H]^+$ 497.0573; found 497.0595.

Methyl 12-((*Z*)-2-iodobut-2-en-1-yl)-1,2,9,9a-tetrahydro-1,4a-(epiminoethano)carbazole-4-carboxylate (26). To a stirred solution of **25** (516 mg, 1.04 mmol) in dry MeCN (21.0 mL) were added $In(OAc)_3$ (304 mg, 1.04 mmol), $PhSiH_3$ (0.40 mL, 3.13 mmol), and 2,6-lutidine (0.12 mL, 1.04 mmol) at room temperature in air, and the reaction mixture was stirred at the same temperature. The mixture was treated three times (i.e., after 24, 48, and 72 h) with an additional amount of $PhSiH_3$ (0.40 mL, 3.13 mmol). After stirring for another 8 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$, and the mixture was diluted with AcOEt. After separation of the two layers, the aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/3) to afford **26** (300 mg, 64%) as a white amorphous solid; UV (MeOH) λ_{max} nm: 277.0, 238.5, 204.5; IR (ATR) ν_{max} cm^{-1}: 3405, 3015, 2947, 2910, 2813, 1713, 1637, 1458, 1432, 1296, 1252, 1133, 1033, 858, 810, 795, 749, 698; ^{1}H NMR ($CDCl_3$, 600 MHz) δ ppm: 7.65 (1H, d, *J* = 7.6 Hz), 7.23 (1H, dd, *J* = 7.6, 7.6 Hz), 7.13 (1H, d, *J* = 7.6 Hz), 6.98 (1H, t-like, *J* = 3.8 Hz), 6.95 (1H, dd, *J* = 7.6,

7.6 Hz), 5.97 (1H, q, *J* = 6.2 Hz), 5.95 (1H, br-s), 3.83 (3H, s), 3.58 (1H, dd, *J* = 5.7, 2.1 Hz), 3.42 (1H, d, *J* = 13.8 Hz), 3.37 (1H, d, *J* = 13.8 Hz), 3.13 (1H, d, *J* = 2.1 Hz), 2.59 (1H, dd, *J* = 12.3, 4.5 Hz), 2.52 (1H, dd, *J* = 20.3, 4.5 Hz), 2.46 (1H, ddd, *J* = 12.3, 12.3, 3.0 Hz), 2.26 (1H, ddd, *J* = 20.3, 5.7, 3.0 Hz), 1.96 (1H, br-d, *J* = 13.1 Hz), 1.84 (1H, ddd, *J* = 13.1, 13.1, 4.5 Hz), 1.82 (3H, d, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ ppm: 166.8, 153.2, 140.7, 134.2, 133.6, 132.1, 127.7, 124.4, 122.4, 114.3, 109.3, 75.7, 65.7, 51.6, 48.3, 43.4, 42.1, 32.2, 27.0, 21.7; HRESI-MS: calcd. for $C_{20}H_{24}IN_2O_2$ $[M+H]^+$ 451.0882; found 451.0887.

Methyl 12-((*Z*)-2-iodobut-2-en-1-yl)-1,2-dihydro-1,4a-(epiminoethano)carbazole-4-carboxylate (27). To a stirred solution of **26** (10.1 mg, 22.4 μmol) in dry CH_2Cl_2 (0.90 mL) were added PCC (9.7 mg, 44.8 μmol) and neutral aluminum oxide silica gel (35.2 mg) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 27 h at the same temperature. The resultant mixture was filtered through Celite® and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel MPLC (AcOEt/*n*-hexane = 1/3) to afford **27** (7.2 mg, 72%) as a pale yellow solid. The spectral and physical properties of **27** are consistent with previously reported data.[5s] UV (MeOH) λ_{max} nm: 247.5, 203.0; IR (ATR) ν_{max} cm^{-1}: 2950, 2922, 2853, 2813, 1714, 1630, 1598, 1436, 1344, 1282, 1259, 1228, 1196, 1115, 1091, 1063, 1019, 1000, 912, 804, 745, 664; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.91 (1H, dd, *J* = 7.8, 0.9 Hz), 7.67 (1H, d, *J* = 7.3 Hz), 7.38 (1H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.23 (1H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.06 (1H, dd, *J* = 3.2, 3.2 Hz), 5.89 (1H, q, *J* = 6.4 Hz), 3.95 (1H, d, *J* = 6.0 Hz), 3.76 (3H, s), 3.39 (1H, d, *J* = 14.2 Hz), 3.23 (1H, d, *J* = 14.2 Hz), 3.06 (1H, ddd, *J* = 14.2, 12.8, 3.2 Hz), 2.93 (1H, dd, *J* = 20.6, 4.1 Hz), 2.78 (1H, ddd, *J* = 20.6, 6.4, 3.2 Hz), 2.72-2.62 (2H, overlapped), 1.79 (3H, d, *J* = 6.4 Hz), 1.57 (1H, ddd, *J* = 12.8, 12.8, 4.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 183.1, 165.8, 156.0, 141.2, 140.1, 132.9, 129.7, 128.4, 126.3, 125.5, 120.8, 108.5, 65.1, 55.2, 54.7, 51.7, 43.1, 35.8, 33.9, 21.7; HRESI-MS: calcd. for $C_{20}H_{22}IN_2O_2$ $[M+H]^+$ 449.0726; found 449.0719.

ACKNOWLEDGEMENTS

This work was supported by JSPS (Japan Society for the Promotion of Science) KAKENHI Grant Numbers 16H05094, 17H03993, and 16K08155.

REFERENCES AND NOTES

1. T. A. Henry, *J. Chem. Soc.*, 1932, 2759.
2. For selected reviews of akuammiline alkaloids, see: (a) A. Ramirez and S. Garcia-Rubio, *Curr. Med. Chem.*, 2003, **10**, 1891; (b) D. Zhang, H. Song, and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447; (c) R. Eckermann and T. Gaich, *Synthesis*, 2013, **45**, 2813; (d) J. M. Smith, J. Moreno, B. W. Boal, and N.

K. Garg, *Angew. Chem. Int. Ed.*, 2015, **54**, 400; (e) W. Zi, Z. Zuo, and D. Ma, *Acc. Chem. Res.*, 2015, **48**, 702; (f) G. L. Adams and A. B. Smith III, 'The Alkaloids: The Chemistry of the Akuammiline Alkaloids', Vol. 76, ed. by H.-J. Knölker, Academic Press, Inc., Amsterdam, 2016, pp. 171-257; (g) R. B. Susick, L. A. Morrill, E. Picazo, and N. K. Garg, *Synlett*, 2017, **28**, 1.

3. E. F. von Gorup-Besanez, *Justus Liebigs Ann. Chem.*, 1875, **176**, 88.
4. For selected biological activities, see: (a) S. C. Dutta, S. K. Bhattacharya, and A. B. Ray, *Planta Med.*, 1976, **30**, 86; (b) S. K. Bhattacharya, R. Bose, S. C. Dutta, A. B. Ray, and S. R. Guha, *Indian J. Exp. Biol.*, 1979, **17**, 598; (c) P. Leewanich, M. Tohda, K. Matsumoto, S. Subhadhirasakul, H. Takayama, N. Aimi, and H. Watanabe, *Eur. J. Pharmacol.*, 1997, **332**, 321; (d) G. Hugel, D. Royer, L. L. Men-Olivier, B. Richard, M. J. Jacquier, and J. Levy, *J. Org. Chem.*, 1997, **62**, 578; (e) G. C. Jagetia, M. S. Baliga, P. Venkatesh, J. N. Ulloor, S. K. Mantena, J. Genebriera, and V. Mathuram, *J. Pharm. Pharmacol.*, 2005, **57**, 1213; (f) G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama, and T.-S. Kam, *J. Nat. Prod.*, 2007, **70**, 1783; (g) H. Arai, Y. Hirasawa, A. Rahman, I. Kusumawati, N. C. Zaini, S. Sato, C. Aoyama, J. Takeo, and H. Morita, *Bioorg. Med. Chem.*, 2010, **18**, 2152; (h) Y. Hou, X. Cao, L. Wang, B. Cheng, L. Dong, X. Luo, G. Bai, and W. Gao, *J. Chromatogr. B*, 2012, **908**, 98; (i) K. Zaima, I. Koga, N. Iwasawa, T. Hosoya, Y. Hirasawa, T. Kaneda, I. S. Ismail, N. H. Lajis, and H. Morita, *J. Nat. Med.*, 2013, **67**, 9; (j) L. Zhang, C.-J. Zhang, D.-B. Zhang, J. Wen, X.-W. Zhao, Y. Li, and K. Gao, *Tetrahedron Lett.*, 2014, **55**, 1815.
5. For the representative total synthesis of akuammiline alkaloids, see vincorine: (a) M. Zhang, X. Huang, L. Shen, and Y. Qin, *J. Am. Chem. Soc.*, 2009, **131**, 6013; (b) W. Zi, W. Xie, and D. Ma, *J. Am. Chem. Soc.*, 2012, **134**, 9126; (c) B. D. Horning and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2013, **135**, 6442; aspidophylline A: (d) L. Zu, B. W. Boal, and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 8877; (e) M. Teng, W. Zi, and D. Ma, *Angew. Chem. Int. Ed.*, 2014, **53**, 1814; (f) W. Ren, Q. Wang, and J. Zhu, *Angew. Chem. Int. Ed.*, 2014, **53**, 1818; (g) S.-Z. Jiang, X.-Y. Zeng, X. Liang, T. Lei, K. Wei, and Y.-R. Yang, *Angew. Chem. Int. Ed.*, 2016, **55**, 4044; (h) T. Wang, X. Duan, H. Zhao, S. Zhai, C. Tao, H. Wang, Y. Li, B. Cheng, and H. Zhai, *Org. Lett.*, 2017, **19**, 1650; scholarisine A: (i) G. L. Adams, P. J. Carroll, and A. B. Smith III, *J. Am. Chem. Soc.*, 2012, **134**, 4037; (j) G. L. Adams, P. J. Carroll, and A. B. Smith III, *J. Am. Chem. Soc.*, 2013, **135**, 519; (k) M. W. Smith and S. A. Snyder, *J. Am. Chem. Soc.*, 2013, **135**, 12964; picrinine: (l) J. M. Smith, J. Moreno, B. W. Boal, and N. K. Garg, *J. Am. Chem. Soc.*, 2014, **136**, 4504; (m) J. M. Smith, J. Moreno, B. W. Boal, and N. K. Garg, *J. Org. Chem.*, 2015, **80**, 8954; aspidodasycarpine, lonicerine, and lanciferine: (n) Y. Li, S. Zhu, J. Li, and A. Li, *J. Am. Chem. Soc.*, 2016, **138**, 3982; calophyline A: (o) G. Li, X. Xie, and L. Zu, *Angew. Chem. Int. Ed.*, 2016, **55**, 10483; corymine: (p) B. Zhang, X. Wang, C. Cheng, D. Sun, and C. Li, *Angew. Chem. Int. Ed.*, 2017, **56**, 7484; scholarisine K and

alstolactine A: (q) D. Wang, M. Hou, Y. Ji, and S. Gao, *Org. Lett.*, 2017, **19**, 1922; strictamine: (r) J. Moreno, E. Picazo, L. A. Morrill, J. M. Smith, and N. K. Garg, *J. Am. Chem. Soc.*, 2016, **138**, 1162; (s) W. Ren, Q. Wang, and J. Zhu, *Angew. Chem. Int. Ed.*, 2016, **55**, 3500; (t) D. Nishiyama, A. Ohara, H. Chiba, H. Kumagai, S. Oishi, N. Fujii, and H. Ohno, *Org. Lett.*, 2016, **18**, 1670; (u) R. Eckermann, M. Breunig, and T. Gaich, *Chem. Commun.*, 2016, **52**, 11363; (v) R. Eckermann, M. Breunig, and T. Gaich, *Chem. Eur. J.*, 2017, **23**, 3938; (w) M. W. Smith, Z. Zhou, A. X. Gao, T. Shimbayashi, and S. A. Snyder, *Org. Lett.*, 2017, **19**, 1004; (x) X. Xie, B. Wei, G. Li, and L. Zu, *Org. Lett.*, 2017, **19**, 5430; (y) T. Xiao, Z.-T. Chen, L.-F. Deng, D. Zhang, X.-Y. Liu, H. Song, and Y. Qin, *Chem. Commun.*, 2017, **53**, 12665.

6. For previous synthetic studies on strictamine or related methanoquinolizidine akuammilines, see: (a) L. J. Dolby and Z. Esfandiari, *J. Org. Chem.*, 1972, **37**, 43; (b) L. J. Dolby and S. J. Nelson, *J. Org. Chem.*, 1973, **38**, 2882; (c) M.-L. Bennasar, E. Zulaica, M. Lopez, and J. Bosch, *Tetrahedron Lett.*, 1988, **29**, 2361; (d) T. Koike, H. Takayama, and S. Sakai, *Chem. Pharm. Bull.*, 1991, **39**, 1677; (e) J. Levy, J. Sapi, J. Y. Laronze, D. Royer, and L. Toupet, *Synlett*, 1992, **1992**, 601; (f) M.-L. Bennasar, E. Zulaica, A. Ramírez, and J. Bosch, *J. Org. Chem.*, 1996, **61**, 1239; (g) C. C. Llopart and J. A. Joule, *ARKIVOC*, 2004, **x**, 20; (h) Y. Yasui, T. Kinugawa, and Y. Takemoto, *Chem. Commun.*, 2009, **45**, 4275; (i) R. V. Edwankar, C. R. Edwankar, O. A. Namjoshi, J. R. Deschamps, and J. M. Cook, *J. Nat. Prod.*, 2012, **75**, 181; (j) T. Watanabe, N. Umezawa, N. Kato, and T. Higuchi, *Chem. Eur. J.*, 2013, **19**, 4255; (k) Y. Komatsu, K. Yoshida, H. Ueda, and H. Tokuyama, *Tetrahedron Lett.*, 2013, **54**, 377; (l) M. Kawano, T. Kiuchi, S. Negishi, H. Tanaka, T. Hoshikawa, J. Matsuo, and H. Ishibashi, *Angew. Chem. Int. Ed.*, 2013, **52**, 906; (m) Q. Li, G. Li, S. Ma, P. Feng, and Y. Shi, *Org. Lett.*, 2013, **15**, 2601; (n) W. Ren, N. Tappin, Q. Wang, and J. Zhu, *Synlett*, 2013, **24**, 1941; (o) E. S. Andreansky and S. B. Blakey, *Org. Lett.*, 2016, **18**, 6492.
7. H. K. Schnoes, K. Biemann, J. Mokry, I. Kompis, A. Chatterjee, and G. Ganguli, *J. Org. Chem.*, 1966, **31**, 1641.
8. (a) N. Takanashi, K. Suzuki, M. Kitajima, and H. Takayama, *Tetrahedron Lett.*, 2016, **57**, 375; (b) M. Kitajima, K. Watanabe, H. Maeda, N. Kogure, and H. Takayama, *Org. Lett.*, 2016, **18**, 1912.
9. For recent total synthesis of bioactive alkaloids in our laboratory, see: (a) M. Kitajima, Y. Murakami, N. Takahashi, Y. Wu, N. Kogure, R.-P. Zhang, and H. Takayama, *Org. Lett.*, 2014, **16**, 5000; (b) M. Azuma, T. Yoshikawa, N. Kogure, M. Kitajima, and H. Takayama, *J. Am. Chem. Soc.*, 2014, **136**, 11618; (c) H. Ishida, S. Kimura, N. Kogure, M. Kitajima, and H. Takayama, *Tetrahedron*, 2015, **71**, 51; (d) H. Ishida, S. Kimura, N. Kogure, M. Kitajima, and H. Takayama, *Org. Biomol. Chem.*, 2015, **13**, 7762; (e) R. Tokuda, Y. Okamoto, T. Koyama, N. Kogure, M. Kitajima, and H. Takayama, *Org. Lett.*, 2016, **18**, 3490; (f) T. Hirama, T. Umemura, N. Kogure, M. Kitajima, and H. Takayama,

Tetrahedron Lett., 2017, **58**, 223; (g) S. Tooriyama, Y. Mimori, Y. Wu, N. Kogure, M. Kitajima, and H. Takayama, *Org. Lett.*, 2017, **19**, 2722.

10. H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635.
11. S. Shah and J. D. Protasiewicz, *Coord. Chem. Rev.*, 2000, **210**, 181.
12. P. Magnus and L Barth, *Tetrahedron*, 1995, **51**, 11075.
13. D. Solé, J. Bosch, and J. Bonjoch, *Tetrahedron*, 1996, **52**, 4013.
14. J. Bonjoch, D. Solé, and X. Cuesta, *Heterocycles*, 1997, **45**, 315.
15. D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.
16. T. Iwai, H. Okochi, H. Ito, and M. Sawamura, *Angew. Chem. Int. Ed.*, 2013, **52**, 4239.
17. J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.
18. W. Yin, M. S. Kabir, Z. Wang, S. K. Rallapalli, J. Ma, and J. M. Cook, *J. Org. Chem.*, 2010, **75**, 3339.