FORMAL TOTAL SYNTHESIS OF (±)-STRIC TAMINE

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).

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 due to their exciting chemical and biological properties. Among them, the first total synthesis of strictamine \( (\mathbf{2}) \) in chiral form by Garg and that in racemic form by Zhu 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 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-\( \beta \)-carboline derivative, which was transformed into Zhu’s strictamine precursor via a few steps. Gaich’s group completed a formal total synthesis of (\( \pm \))-strictamine \( (\mathbf{2}) \) using [2,3]-Stevens rearrangement twice. Snyder achieved the shortest asymmetric total synthesis of strictamine \( (\mathbf{2}) \) 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 \( (\mathbf{2}) \) was developed by Zu. Quite recently, Qin’s group disclosed an asymmetric formal total synthesis of strictamine \( (\mathbf{2}) \) 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, and applied it to the total synthesis of conolidine and apparicine as well as some sarpagine-related indole alkaloids. In our continuous studies on the synthesis of bioactive alkaloids, we planned to apply the reaction for the total synthesis of strictamine \( (\mathbf{2}) \), 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 \( (\mathbf{2}) \) by utilizing the above-mentioned Au(I)-catalyzed reaction and a formal total synthesis of (\( \pm \))-strictamine \( (\mathbf{2}) \) using a synthetic intermediate in the first half of the study.

**RESULTS AND DISCUSSION**

Our retrosynthetic analysis of \( (\pm)\)-\( \mathbf{2} \) 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 \( \mathbf{7} \) would give the \( (E) \)-ethylidene moiety embedded in the six-membered ring of diketone \( \mathbf{6} \). Cyclization precursor \( \mathbf{7} \) would be prepared from secondary amine \( \mathbf{8} \) in a few steps. For the transformation of enazide \( \mathbf{9} \) into secondary amine \( \mathbf{8} \), we had chosen a sequence of steps that included ozonolysis, the Staudinger reaction, and the aza-Wittig reaction in a one-pot operation. Enazide \( \mathbf{9} \) would be prepared through the diastereoselective reduction and the oxidative \( \alpha \)-azidation of dicarbonyl compound \( \mathbf{10} \), a known Bonjoch’s intermediate for the syntheses of \( 3\alpha-\left(\alpha\text{-nitrophenyl}\right)\)octahydroindol-4-ones.
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 conditions14 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 PPh3 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 periodinane15 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 Et3PAuCl in the presence of AgBF4 or (C-dtbm)AuBF4,15 for the construction of the E-ring, cyclization product 6 was not obtained at all.
We then altered the synthetic route that utilized synthetic intermediate 8. Protection of secondary amine 8 with Boc$_2$O 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) 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 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. 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. 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.
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. ¹H and ¹³C 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 (¹H) or 100 MHz (¹³C), and JNM ECZ-600, JNM ECP-600, and JNM ECA-600 at 600 MHz (¹H) or 150 MHz (¹³C), 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 (SiO₂), 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$_2$O (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, 1.5, 1.5 Hz), 7.52 (1H, dd, J = 8.1, 1.5 Hz), 7.43 (1H, ddd, J = 8.1, 1.5, 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), 7.24 (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$_2$Cl$_2$ (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) $\nu_{\text{max}}$ 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$_4$SiNa [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$_2$Cl$_2$ (12.2 mL) were added Et$_3$N (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) $\nu_{\text{max}}$ 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$_4$Si$_2$Na [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$_2$S$_2$O$_3$ 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) $\nu_{\text{max}}$ 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); ¹³C NMR (CDCl₃, 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 C₂₁H₃₀N₄O₄SiNa [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 Na₂S₂O₃ 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 MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (Et₂O/n-hexane = 1/15) to afford 14 (15.5 mg, 93%) as a pale yellow crystal; mp (plate): 93-94 °C. (Recrystallized from n-hexane.); IR (ATR) νmax cm⁻¹: 3020, 2955, 2912, 2876, 1702, 1525, 1353, 1216, 1105, 1086, 1004, 818, 749, 665; ¹H NMR (C₆D₆, 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, d, dd, J = 8.0, 7.3, 1.4 Hz), 6.68 (1H, d, dd, J = 8.0, 7.3, 1.4 Hz), 5.60 (1H, d, dd, J = 17.0, 10.3, 7.0, 6.6 Hz), 5.13 (1H, d, dd, J = 17.0, 1.7, 1.7 Hz), 4.97 (1H, d, dd, J = 10.3, 1.5, 1.5 Hz), 4.64 (1H, d, dd, J = 10.8, 4.2 Hz), 4.26 (1H, d, dd, J = 4.0, 4.0 Hz), 3.58 (1H, d, dd, J = 16.3, 7.0 Hz), 3.32 (1H, d, 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); ¹³C NMR (C₆D₆, 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 C₂₁H₃₀BrN₂O₄SiNa [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 CH₂Cl₂ (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 PPh₃ (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) νmax cm⁻¹: 2952, 2876, 1720, 1528,
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 NaBH₃CN (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 NaHCO₃ 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 MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/n-hexane = 1/10) to afford 8 (23.9 mg, 91%) as a yellow oil; IR (ATR) νmax cm⁻¹: 2952, 2875, 1715, 1528, 1355, 1076, 1008, 739; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₀H₃₁N₂O₄Si [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 Cs₂CO₃ (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 MgSO₄, 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) νmax cm⁻¹: 3026, 2971, 1740, 1529, 1374, 1215, 1175, 940; ¹H NMR (CDCl₃, 400 MHz) δ ppm: 7.88 (1H, dd,
\( J = 7.8, 1.4 \text{ Hz} \), 7.54 (1H, ddd, \( J = 7.8, 7.8, 1.4 \text{ Hz} \)), 7.41 (1H, ddd, \( J = 7.8, 7.8, 1.4 \text{ Hz} \)), 7.38 (1H, dd, \( J = 7.8, 1.4 \text{ Hz} \)), 7.86 (1H, ddd, \( J = 7.8, 7.8, 1.4 \text{ Hz} \)), 7.41 (1H, ddd, \( J = 7.8, 7.8, 1.4 \text{ Hz} \)), 7.38 (1H, dd, \( J = 7.8, 1.4 \text{ Hz} \)), 7.29 (1H, m), 2.32-2.22 (2H, overlapped), 2.20-2.08 (1H, m), 1.94 (1H, d, \( J = 2.3 \text{ Hz} \)), 1.90-1.81 (1H, m), 1.81 (3H, t, \( J = 2.3 \text{ Hz} \)), 0.74 (9H, t, \( J = 2.3 \text{ Hz} \)); \(^{13}\text{C NMR (CDCl}_3, 100 MHz) \delta 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\(_2\)O\(_4\)Si [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\(_3\)BH (1.0 M in THF, 1.39 mL, 1.39 mmol) at \(-78^\circ\text{C}\) 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\(_2\)CO\(_3\), 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 \text{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\(_2\)CO\(_3\), 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\(_2\)Cl\(_2\) (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\(_2\)S\(_2\)O\(_3\), 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) \( \nu_{\text{max}} \text{ cm}^{-1}: 2919, 2860, 1738, 1692, 1523, 1442, 1348, 1146, 1034, 1011, 904, 856, 790, 722, 649; ^1\text{H NMR (CDCl}_3, 400 MHz) \delta ppm: 8.19 (1H, dd, } J = 8.3, 1.4 \text{ Hz}), 7.72 (1H, ddd, } J = 7.6, 7.6, 1.4 \text{ Hz}), 7.53 (1H, ddd, } J = 7.6, 7.6, 1.4 \text{ Hz}), 7.51 (1H, d, } J = 8.3 \text{ Hz}), 3.76 (1H, dd, } J = 3.1, 3.1 \text{ Hz}), 3.57 (1H, dq, } J = 16.5, 2.4 \text{ Hz}), 3.50 (1H, dq, } J = 16.5, 2.4 \text{ Hz}), 3.28 (1H, dd, } J = 12.4, 12.4, 4.1 \text{ Hz}), 3.12 (1H, ddd, } J = 13.1, 5.5, 2.8 \text{ Hz}), 3.06 (1H, dd, } J = 20.0, 9.6 \text{ Hz}), 2.80 (1H, dd, } J = 20.0, 11.0, 9.6 \text{ Hz}), 2.73-2.66 (2H, overlapped), 2.60 (1H, ddd, } J = 12.4, 12.4, 6.2 \text{ Hz}), 2.17 (1H, m), 1.85 (3H, t, } J = 2.4 \text{ Hz}); ^{13}\text{C NMR (CDCl}_3, 150 MHz) \delta ppm: 207.6, 202.3, 147.3, 134.1,
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 NaHCO₃ 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 K₂CO₃, 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) νmax cm⁻¹: 3051, 2955, 2920, 2835, 1735, 1668, 1526, 1354, 1267, 1252, 1209, 1173, 869, 840; ¹H NMR (CDCl₃, 400 MHz) δ ppm: 7.97 (1H, dd, J = 8.3, 1.4 Hz), 7.60 (1H, dddd, 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, dddd, 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, dddd, J = 12.9, 1.8, 1.8 Hz), 2.69 (1H, dd, J = 18.1, 5.2 Hz), 2.58 (1H, dddd, J = 18.1, 2.4, 2.4 Hz), 2.49 (1H, dddd, J = 12.4, 12.4, 4.4 Hz), 2.44 (1H, dddd, J = 12.4, 1.8, 1.8 Hz), 1.83 (3H, t, J = 2.2 Hz), −0.05 (9H, s); ¹³C NMR (CDCl₃, 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 C₁₁₈H₁₈N₂O₄Na [M+Na]⁺ 349.1164; found 349.1168.

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 Boc₂O (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 MgSO₄, 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) νmax cm⁻¹: 3020, 2958, 2933, 2877, 1726, 1684, 1528, 1396, 1366, 1356, 1259, 1215, 1159, 1100, 1066, 1018, 856, 805, 748, 665; ¹H NMR (CDCl₃, 400 MHz, at 55 °C) δ ppm: 7.93 (1H, d, J = 8.2 Hz), 7.55 (1H, dddd, J = 7.8, 7.8, 1.4 Hz), 7.43 (1H, dddd, J = 7.8, 7.8, 1.4 Hz), 7.40 (1H, d, J = 8.2 Hz), 4.89 (1H, ddd, J = 8.5, 8.5 Hz), 4.34 (1H, br-s), 3.87 (1H, dddd, 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$_2$O$_6$SiK [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$_2$Cl$_2$ (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$_2$S$_2$O$_3$, 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) $\nu_{\text{max}}$ 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$_2$O$_6$Na [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$_4$Cl 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) $\nu_{\text{max}}$ 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, $J = 13.2$, 13.2, 3.4 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, 33.5, 28.4, 28.3; HRESI-MS: calcd. for C$_{20}$H$_{21}$F$_3$N$_2$O$_8$SNa $[M+Na]^+$ 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)$_3$·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) $\nu_{\text{max}}$ 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, ddd, $J = 7.6$, 7.6 Hz), 7.59 (1H, d, $J = 7.6$ Hz), 7.45 (1H, ddd, $J = 8.2$, 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), 3.49-3.42 (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, 57.4, 55.3, 51.7, 39.0, 36.2, 33.5, 28.4; HRESI-MS: calcd. for C$_{21}$H$_{24}$N$_2$O$_7$Na $[M+Na]^+$ 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$_2$Cl$_2$ (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) $\nu_{\text{max}}$ 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, ddd, $J = 5.0$, 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) \( \delta \) 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\(_2\)O\(_5\) [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 \( \mu \)L, 0.398 mmol) and 24 (63.7 \( \mu \)L, 0.530 mmol) at room temperature under Ar atmosphere, and the reaction mixture was stirred for 26.5 h at 50 \( ^\circ \)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) \( \nu_{\text{max}} \) cm\(^{-1}\): 3019, 2995, 2947, 2871, 1706, 1641, 1523, 1435, 1352, 1296, 1236, 1215, 1124, 1090, 1067, 1050, 950, 850, 812, 751, 665, 632; \(^1\)H NMR (CDCl\(_3\), 400 MHz, at 55 \( ^\circ \)C) \( \delta \) 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 \( ^\circ \)C) \( \delta \) 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\(_{22}\)N\(_2\)O\(_5\) [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) \( \lambda_{\text{max}} \) nm: 277.0, 238.5, 204.5; IR (ATR) \( \nu_{\text{max}} \) 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) \( \delta \) 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, \( J = 7.6, \)
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 CH₂Cl₂ (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.⁵

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REFERENCES AND NOTES


