A Concise Formal Total Synthesis of Mappicine and Nothapodytine B via an Intramolecular Hetero Diels−Alder Reaction

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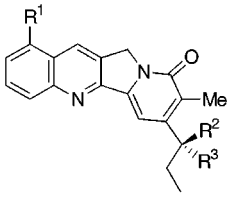
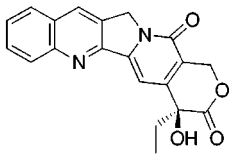
A six-step formal total synthesis of a natural alkaloid, mappicine (**3**), has been achieved. The highlight of our synthetic strategy is an intramolecular hetero Diels−Alder reaction that was used for the construction of the CD ring system of mappicine (**3**). In addition, it was demonstrated that the Sonogashira coupling reaction of 2-chloro-3-hydroxymethylquinoline (**8c**) with trimethylsilylacetylene proceeded at room temperature in excellent yield.

Introduction

The E ring decarboxylated camptothecin analogues, nothapodytines A (**1**) and B (**2**), have been recently isolated from *Nothapodytes foetida*.[1] Nothapodytine B (mappicine ketone) (**2**) is an oxidized derivative of natural alkaloid mappicine (**3**),[2] and both **1** and **2** show significant cytotoxicity in the human KB cell line.[3] Since nothapodytine B (**2**) has been identified as an antiviral agent with selective activities against herpes simplex virus-1 (HSV-1) and HSV-2,[4] this family of alkaloids has received considerable attention by organic chemists.[5] Although the synthesis of nothapodytine B (**2**) was initially accomplished by thermolysis of camptothecin (**4**)[6] and several other methods for the construction of these types of alkaloids have also been reported,[7] limited supplies of **2** made it necessary to develop novel synthetic methodologies for nothapodytine B (**2**). Herein we present a novel synthetic approach to mappicine (**3**) employing the intramolecular hetero Diels−Alder reaction as a key step.[8]



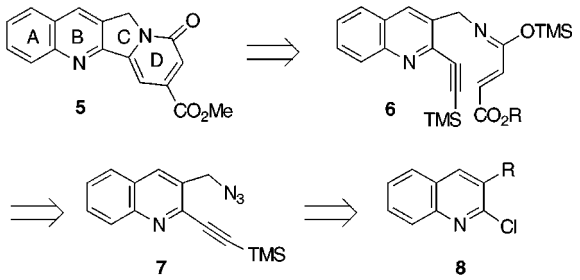
Nothapodytine A (**1**): R^1=OMe, R^2, R^3=O
Nothapodytine B (**2**): R^1=H, R^2, R^3=O
(Mappicine ketone)
Mappicine (**3**): R^1=H, R^2=OH, R^3=H



Camptothecin (**4**)

The retrosynthetic analysis for mappicine (**3**) is shown in Scheme 1. Since the transformation of the ester **5** into

Scheme 1



mappicine (**3**) has been achieved by Kametani et al.,[9] the synthesis of **5** completes the task. The pivotal step of the synthesis is an intramolecular hetero Diels−Alder reaction of the 1-azadienyne **6**. Though a large number of natural products have been synthesized by using the hetero Diels−Alder reaction have been reported,[10] little is known about the practical applications of hetero Diels−Alder reactions of 1-azabutadiene derivatives for the construction of polycyclic natural alkaloids. The tetracyclic ester **5** could be generated by the intramolecular hetero Diels−Alder reaction of the 1-azadienyne **6**, which might be formed in situ from the corresponding amide derivative. The acetylene **7**, convertible to **6**, would be synthesized using palladium-catalyzed Sonogashira coupling of the 2-chloroquinoline derivative **8** with trimethylsilylacetylene.

Results and Discussion

To introduce an acetylene moiety into the C-2 position of the 2-chloroquinoline derivatives, palladium-catalyzed

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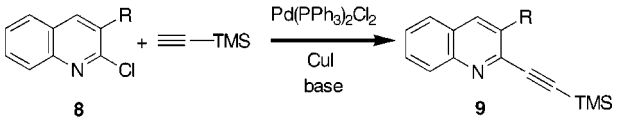

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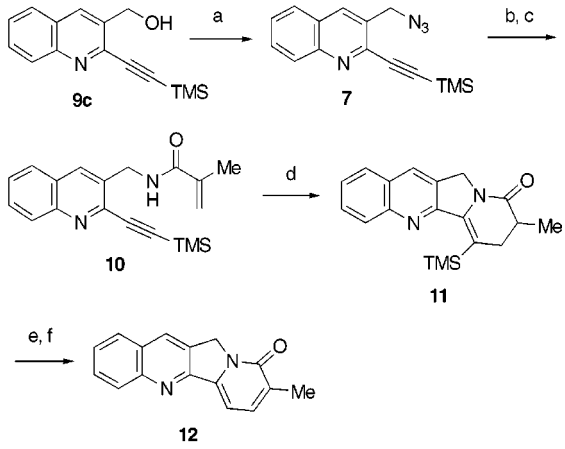
Sonogashira Coupling Reaction of the 2-Chloroquinoline Derivatives

entry	compound	R	base / solvent	time (h)	yield (%)
1	**8a**	CHNOH	Et_3N / DMF	1.0	72
2	**8b**	CHO	Et_3N / DMF	1.5	92
3	**8c**	CH_2OH	Et_3N / DMF	1.0	98
4	**8d**	CH_2NPht	Et_3N / DMF	2.0	28

All reactions were carried out by using $Pd(PPh_3)_2Cl_2$ (5 mol %) and CuI (5 mol %) under argon atmosphere.

Figure 1.

Scheme 2

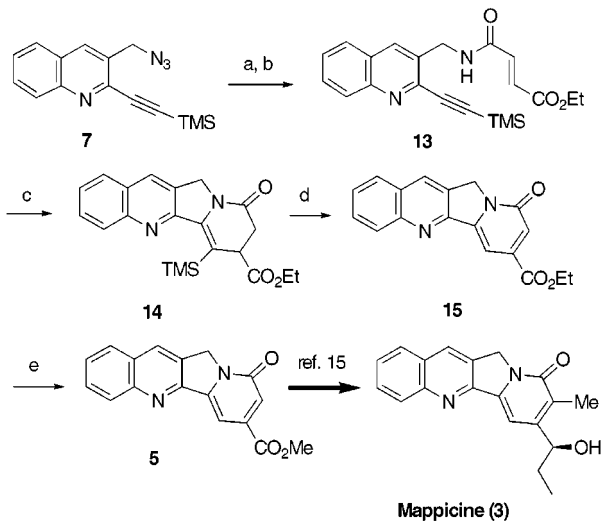


Reagents and Conditions : a; NaN_3, CBr_4, PPh_3, DMF (97%). PPh_3, H_2O, 45 °C. c; BOP, methacrylic acid, Et_3N, DMF (55% for 2 steps). d; TMSCl, Et_3N, $ZnCl_2$, toluene, 180 °C, sealed tube (79%). e; 47% HBr, AcOEt (83%). f; DDQ, benzene (78%).

Sonogashira coupling reactions[11] were investigated as depicted in Figure 1. The reactions proceeded smoothly in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 5 mol % of CuI, producing the (trimethylsilyl)acetylene derivative. It was found that the *N*-phthalimide moiety in **8d** was not suitable for the Sonogashira coupling process (entry 4).

Having established the efficient synthesis of the acetylene derivative **9c**, we next examined the transformation of the primary hydroxyl group of **9c** into an azide group. Treatment of the alcohol **9c** with sodium azide, carbon tetrabromide, and triphenylphosphine afforded the corresponding azide (Scheme 2), which was subjected to reduction[12] with triphenylphosphine followed by a condensation reaction with methacrylic acid in the presence of benzotriazolyl-*N*-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP)[13] to give rise to the amide **10** in 55% overall yield for two steps. It is worthwhile to notice that Schotten−Baumann reaction of the corresponding amine and methacryloyl chloride furnished **10**

Scheme 3



Reagents and Conditions : a; PPh_3, H_2O, THF, 55 °C. b; BOP, Fumaric acid monoethyl ester, *i*-Pr_2NEt, MeCN (67% for 2 steps). c; TMSCl, *i*-Pr_2NEt, $ZnCl_2$, Toluene, 180 °C, sealed tube (76%). d; 47% HBr, AcOEt, reflux (93%). e; concd. H_2SO_4, MeOH, reflux (67%).

in 30% overall yield. Heating of the amide **10** with chlorotrimethylsilane and triethylamine at 180 °C in the presence of zinc chloride[14] produced the desired tetracyclic compound **11** in 79% yield. Desilylation[15] of the vinylsilane **11** with 47% aqueous hydrogen bromide solution followed by DDQ oxidation[16] produced **12** in good yield.

With the efficient synthesis of the basic carbon framework of mappicine (**3**) established, our attention was next focused on the application of this synthetic methodology to natural alkaloid synthesis. A formal synthesis of mappicine (**3**) commenced with compound **7**. The amide formation reaction was carried out in a manner similar to that described above. Thus, reduction of **7** with wet triphenylphosphine followed by the condensation with fumaric acid monoethyl ester in the presence of BOP and Hünig's base gave the unsaturated amide **13** in 67% overall yield (Scheme 3). Intramolecular hetero Diels−Alder reaction of **13** led to the cycloadduct **14** (76%), which was treated with aqueous hydrogen bromide to provide the ester **15** (93% yield) in a single step. As it turned out, the electron-withdrawing substituent group (ethyl ester in **13**) did not impede the cycloaddition; on the contrary, it promoted the autoxidation of the corresponding cycloadduct. Finally, compound **15** was subjected to transesterification reaction with methanol in the presence of concd H_2SO_4 to afford methyl ester **5**. The structure of **5** was confirmed by HMBC experiments. Compound **5** had already been transformed into nothapodytine B (**2**) and mappicine (**3**) by Kametani and coworkers.[9]

In conclusion, we have developed a novel synthetic route to nothapodytine B (**2**) and mappicine (**3**) by using intramolecular hetero Diels−Alder reaction as a key step.

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This methodology could be adaptable for the synthesis of their analogues and camptothecin (**4**).

Experimental Section

General. Unless otherwise noted, all reactions were performed in oven-dried glassware, sealed with a rubber septum under an atmosphere of argon. Anhydrous tetrahydrofuran (THF) and acetonitrile (MeCN) were purchased from Kanto Chemical Co., Inc. Toluene and diisopropylethylamine (*i*-Pr_2-NH) were distilled from CaH_2. Triethylamine (Et_3N) was distilled from KOH immediately before use. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 and used immediately. Benzene (C_6H_6), ethyl acetate (EtOAc), and methanol (MeOH) were distilled under argon immediately prior to use. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried by being stirred over anhydrous Na_2SO_4, filtered through Celite, and concentrated under reduced pressure with the aid of a rotary evaporator. Flash chromatography was carried out using Merck 60 (230−400 mesh) or Cica 60 (spherical/40−100 μm) silica gel. Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). Compounds were visualized using a ultraviolet lamp (254 nm) and/or by staining with *p*-anisaldehyde (in EtOH), phosphomolybdic acid (in EtOH), or ammonium molybdate (in 10% H_2SO_4). IR spectra were recorded as KBr pellets unless otherwise noted. Until otherwise noted, ^{1}H NMR spectra were measured as $CDCl_3$ solutions at 300 MHz, and ^{13}C NMR spectra were recorded as $CDCl_3$ solution at 75 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$. *J* values are in hertz.

2-Chloro-3-(hydroxyiminomethyl)quinoline (8a). To a stirred solution of the aldehyde **8b**[17] (1.0 g, 5.24 mmol) in pyridine (5 mL) was added hydroxylamine hydrochloride (372 mg, 5.76 mmol) at room temperature, and then the mixture was stirred at room temperature for 1 h. After removal of the solvent, the crude oxime was recrystallized from EtOH to give **8a** (946 mg, 88%) as yellow needles, mp 151−152 °C. IR (KBr) cm^{-1}: 3500, 1615. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.67 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.84 (1H, ddd, J = 6.0, 6.0, 1.5 Hz), 7.95 (1H, d, J = 7.0 Hz), 8.08 (1H, d, J = 9.0 Hz), 8.54 (1H, s), 8.73 (1H, s), 11.0 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 125.1, 126.9, 127.8, 127.9, 128.8, 131.7, 135.8, 144.2, 147.1, 148.1. HRMS (EI) *m*/*z*: Calcd for $C_{10}H_7ClN_2O$ (M^+): 206.0246. Found: 206.0249.

2-Chloro-3-(phthalimidomethyl)quinoline (8d). To a stirred solution of the alcohol **8c**[18] (50.0 mg, 0.28 mmol) in anhydrous THF (3.0 mL) were added phthalimide (41.8 mg, 0.28 mmol), triphenylphosphine (74.5 mg, 0.28 mmol), and diethyl azodicarboxylate (0.05 mL, 0.28 mmol) at −10 °C, and then the mixture was allowed to warm to room temperature and stirred for 5 h. After removal of the solvent, the crude phthalimide was chromatographed. Elution with a 95:5 mixture of $CHCl_3$-MeOH afforded **8d** (153. 4 mg, 75%) as a white powder, mp 164−166 °C. IR (KBr) cm^{-1}: 1775, 1735. ^{1}H NMR δ: 5.14 (1H, s), 7.53 (1H, dd, J = 7.0, 1.0 Hz), 7.68−8.05 (8H, m). ^{13}C NMR δ: 39.3, 123.8, 127.1 127.4, 127.5, 128.3, 130.6, 132.0, 134.5, 137.1, 147.2, 149.4, 167.9. HRMS (EI) *m*/*z*: Calcd for $C_{18}H_{11}ClN_2O_2$ (M^+): 322.0508. Found: 322.0479.

Representative Procedure for the Sonogashira Coupling Reaction.

3-Hydroxymethyl-2-[(trimethylsilyl)ethynyl]quinoline (9c). To a stirred solution of the alcohol **8c** (1.00 g, 5.18 mmol) in anhydrous DMF (5.0 mL) were added $Pd(PPh_3)_2Cl_2$ (180 mg, 0.26 mmol), CuI (50.0 mg, 0.26 mmol), Et_3N (3.0 mL, 21.5 mmol), and (trimethylsilyl)acetylene (0.81 mL, 5.73 mmol) at room temperature, and the mixture was stirred at the same temperature for 1 h. After filtration through Celite, the filtrate was concentrated to the crude product, which was chromatographed. Elution with a 3:1 mixture of hexanes−EtOAc afforded the alcohol **9c** (1.30 g, 98%) as yellow scales, mp 137−138 °C. IR (KBr) cm^{-1}: 3225, 2140.^{1}H NMR δ: 0.32 (9H, s), 2.33 (1H, t, J = 6.0 Hz), 4.99 (2H, d, J = 6.0 Hz), 7.53 (1H, dd, J = 7.0, 1.0 Hz), 7.68 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.79 (1H, d, J = 8.0 Hz), 8.08 (1H, d, J = 8.0 Hz), 8.19 (1H, s). MS (EI) *m*/*z*: 255 (M^+). Anal. Calcd for $C_{15}H_{17}NOSi$: C, 70.54; H, 6.74; N, 5.48. Found: C, 70.45; H, 6.80; N, 5.52.

3-Azidomethyl-2-[(trimethylsilyl)ethynyl]quinoline (7). A mixture of the acetylene alcohol **9c** (1.0 g, 3.92 mmol), sodium azide (382 mg, 5.88 mmol), triphenylphosphine (1.54 g, 5.88 mmol), and carbon tetrabromide (1.95 g, 5.88 mmol) in anhydrous DMF (10 mL) was vigorously stirred at room temperature for 15 min. After removal of the solvent under reduced pressure, the residue was chromatographed. Elution with a 10:1 mixture of hexanes−EtOAc yielded the azide **7** (1.06 g, 97%) as colorless prisms, mp 94−95 °C. IR (neat) cm^{-1}: 2100. ^{1}H NMR δ: 0.34 (9H, s), 4.75 (2H, s), 7.56(1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.74 (1H, ddd, J = 7.0, 7.0, 1.4 Hz), 7.81-(1H, d, J = 7.0 Hz), 8.12 (1H, d, J = 7.0 Hz), 8.15 (1H, s). ^{13}C NMR δ: 0.47, 52.1, 100.9, 101.5, 127.1, 127.6, 127.8, 129.3, 130.3, 130.5, 135.0, 142.5, 147.6. HRMS (EI) *m*/*z*: Calcd for $C_{15}H_{16}N_4Si$ (M^+): 280.1144. Found: 280.1142.

3-Methacrylamidomethyl-2-[(trimethylsilyl)ethynyl]-quinoline (10). To a solution of the azide **7** (406 mg, 1.45 mmol) in THF (15 mL) were added triphenylphosphine (572 mg, 2.18 mmol) and water (0.33 mL) at room temperature, and then the resulting mixture was heated at 45 °C for 1 h. After removal of the solvent under reduced pressure, the residue was diluted with EtOAc (10 mL). The organic layer was dried over Na_2SO_4, and then the solvent was evaporated to furnish the crude amine, which was used in the next step without purification.

To a stirred solution of the crude amine in anhydrous DMF (14 mL) were added benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (641 mg,1.45 mmol), methacrylic acid (0.13 mL, 1.53 mmol), and Et_3N (0.40 mL, 2.90 mmol) at room temperature, and then the resulting mixture was stirred at the same temperature for 6 h. After removal of the solvent under reduced pressure, the residue was chromatographed. Elution with a 4:1 mixture of hexanes−EtOAc gave rise to the amide **10** (256 mg, 55% overall yield for two steps) as colorless prisms, mp 142−143 °C. IR (neat) cm^{-1}: 3350, 1670, 1627. ^{1}H NMR δ: 0.33 (9H, s), 1.98 (3H, s), 4.77 (2H, d, J = 6.0 Hz), 5.38 (1H, s), 5.76 (1H, s), 6.64 (1H, br s), 7.54 (1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.70 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.77 (1H, d, J = 7.0 Hz), 8.08 (1H, d, J = 7.0 Hz), 8.12 (1H, s). MS (EI) *m*/*z*: 322 (M^+). Anal. Calcd for $C_{19}H_{22}N_2$-OSi: C, 70.77; H, 6.88; N, 8.69. Found: C, 70.49; H, 6.91; N, 8.47.

11*H*-7,8-Dihydro-8-methyl-6-trimethylsilyl-9-oxoindolizino[1,2-*b*]quinoline (11). A mixture of the amide **10** (62 mg, 0.19 mmol), $ZnCl_2$ (51.8 mg, 0.38 mmol), TMSCl (0.48 mL, 3.8 mmol), and Et_3N (0.53 mL, 3.8 mmol) in anhydrous toluene (3.0 mL) was heated in a sealed tube at 180 °C for 5 h. After removal of the solvent under reduced pressure, saturated aqueous NH_4Cl solution was added. The resulting mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated to leave the crude product, which was chromatographed. Elution with a 3:1 mixture of hexanes−EtOAc afforded the cycloadduct **11** (48.4 mg, 79%), as orange needles, mp 222−224 °C. IR (neat) cm^{-1}: 1675.^{1}H NMR δ: 0.39 (9H, s), 1.30 (3H, d, J = 6.0 Hz), 2.40 (1H, dd, J = 16.0, 11.0 Hz), 2.58 (1H, m), 2.75 (1H, dd, J = 16.0, 6.0 Hz), 5.00 (2H, d, J = 5.0 Hz), 7.54 (1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.71 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.82 (1H, d, J = 7.0 Hz), 8.08 (1H, s), 8.09 (1H, d, J = 7.0 Hz). MS (EI) *m*/*z*: 322 (M^+). Anal. Calcd for $C_{19}H_{22}N_2OSi$: C, 70.77; H, 6.88; N, 8.69. Found: C, 70.72; H, 6.93; N, 8.67.

11*H*-8-Methyl-9-oxoindolizino[1,2-*b*]quinoline (12) To a stirred solution of the compound **11** (10.0 mg, 0.03 mmol) in EtOAc (1.5 mL) was added dropwise 47% aqueous HBr solution (0.3 mL, 2.60 mmol) at room temperature, and then the resulting mixture was stirred at the same temperature

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for 5 min. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried and evaporated to leave the crude product, which was chromatographed. Elution with a 1:1 mixture of hexanes−EtOAc gave the desilylated compound (6.2 mg, 83%), as light yellow needles, mp 243−245 °C.

IR (KBr) cm^{-1}: 1653. ^1H NMR δ: 1.34 (3H, d, J = 6.0 Hz), 2.42 (1H, m), 2.73 (2H, m), 5.00 (2H, s), 6.24 (1H, s), 7.56 (1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.73 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.82 (1H, d, J = 7.0 Hz), 8.10 (1H, d, J = 7.0 Hz), 8.11(1H, s). MS (EI) m/z: 250 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.59; H, 5.72; N, 11.05.

To a stirred solution of the above product (62.3 mg, 0.25 mmol) in C_6H_6 (5.0 mL) was added DDQ (86.3 mg, 0.38 mmol) at room temperature, and the mixture was stirred at room temperature for 15 min. After addition of saturated aqueous $NaHCO_3$ solution, the organic layer was separated. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated to leave the crude product, which was chromatographed. Elution with a 95:5 mixture of $CHCl_3$−MeOH gave rise to **12** (48.4 mg, 78%) as light yellow prisms, mp 230−232 °C. IR (KBr) cm^{-1}: 1654, 1594.^1H NMR δ: 2.31 (3H, s), 5.24 (2H, s), 7.22 (1H, d, J = 7.0 Hz), 7.53 (1H, d, J = 7.0 Hz), 7.60 (1H, d, J =7.0 Hz), 7.78 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.87 (1H, d, J = 7.0 Hz), 8.17 (1H, d, J = 8.0 Hz), 8.28 (1H, s). ^{13}C NMR δ: 17.0, 49.9, 100.9, 127.5, 128.0, 128.2, 128.8, 129.6, 130.3, 130.6, 130.9, 137.8, 143.7, 148.9, 153.6, 161.9. HRMS (EI) m/z: Calcd for $C_{16}H_{12}N_2O$ (M^+): 248.0949. Found: 248.0941.

3-[2(*E*)-3-Ethoxycarbonylacrylamidomethyl]-2-[(trimethylsilyl)ethynyl]quinoline (13). To a stirred solution of the azide **7** (549 mg, 1.96 mmol) were added triphenylphosphine (514 mg, 1.96 mmol) and H_2O (0.40 mL) at room temperature, and the resulting mixture was heated at 55 °C for 1 h. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc (10 mL). The organic layer was dried and evaporated to leave the amine, which was used in the next step without purification.

To a stirred solution of the above product in anhydrous MeCN (10 mL) were added BOP (867 mg, 1.96 mmol), fumaric acid monoethyl ester (283 mg, 1.96 mmol), and *i*-Pr_2NEt (0.68 mL, 3.92 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 3 h. Evaporation of the solvent yielded the crude product, which was chromatographed. Elution with a 3:1 mixture of hexanes−EtOAc provided the amide **13** (501 mg, 67% overall yield for two steps), as an orange oil. IR (neat) cm^{-1}: 3260, 1718, 1660. ^1H NMR δ: 0.33 (9H, s), 1.28 (3H, t, J = 6.0 Hz), 4.25 (2H, q, J = 7.0 Hz), 4.85 (2H, d, J = 6.0 Hz), 6.40 (1H, br s), 6.87 (1H, d, J =15.0 Hz), 6.96 (1H, d, 15.0 Hz), 7.54 (1H, dd, J = 7.0, 7.0 Hz), 7.70 (1H, ddd, J =7.0, 7.0, 1.5 Hz), 7.76 (1H, d, J = 7.0 Hz), 8.08 (1H, d, J = 7.0 Hz), 8.12(1H, s). MS (EI) m/z: 380 (M^+). Anal. Calcd for $C_{21}H_{24}N_2O_3Si$: C, 66.29; H, 6.36; N, 7.36. Found: C, 66.41; H, 6.39; N, 7.28.

11*H*-7,8-Dihydro-7-ethoxycarbonyl-6-trimethylsilyl-9-oxoindolizino[1,2-*b*]quinoline (14) A mixture of the amide **13** (31.4 mg, 0.08 mmol), $ZnCl_2$ (23.2 mg, 0.17 mmol), TMSCl (0.21 mL, 1.66 mmol), and *i*-Pr_2NEt (0.29 mL, 1.66 mmol) in anhydrous toluene (3.0 mL) was heated in a sealed tube at 180 °C for 5 h. After removal of the solvent under reduced pressure, saturated aqueous NH_4Cl solution was added. The resulting mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated to give the crude product, which was chromatographed. Elution with a 3:1 mixture of hexanes−EtOAc provided the cycloadduct **14** (24.0 mg, 76%), as a colorless powder, mp 155−157 °C. IR (neat) cm^{-1}: 1720, 1680. ^1H NMR δ: 0.46 (9H, s), 1.25 (3H, t, J =7.0 Hz), 2.66 (1H, dd, J = 16.0, 7.0 Hz), 3.05 (1H, dd, J = 16.0, 1.5 Hz), 3.72 (1H, dd, J = 7.0, 1.5 Hz), 4.13 (2H, m), 4.90 (1H, d, J = 15.0 Hz), 5.08 (1H, d, J = 15.0 Hz), 7.56 (1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.72 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.82 (1H, d, J = 7.0 Hz), 8.08 (1H, s), 8.10 (1H, d, J = 7.0 Hz). ^{13}C NMR δ: 0.39, 13.9, 33.0, 41.4, 47.7, 61.1, 109.6, 127.1, 127.5, 127.8, 129.3, 129.4, 129.7, 129.9, 135.8, 145.1, 148.3, 168.1, 172.5. HRMS (EI) m/z: Calcd for $C_{21}H_{24}N_2O_3Si$ (M^+): 380.1555. Found: 380.1537.

11*H*-7-Ethoxycarbonyl-9-oxoindolizino[1,2-*b*]quinoline (15). To a stirred solution of the compound **14** (41.9 mg, 0.11 mmol) in EtOAc (5.0 mL) was added dropwise 47% aqueous HBr solution at room temperature, and then the resulting mixture was refluxed for 1 h. The solution was neutralized with saturated aqueous $NaHCO_3$ solution at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated to leave the crude product, which was chromatographed. Elution with a 95:5 mixture of $CHCl_3$−MeOH gave **15** (31.4 mg, 93%), as a colorless powder, mp 215−217 °C. IR (KBr) cm^{-1}: 1725, 1670, 1610, 1604. ^1H NMR δ: 1.45 (3H, t, J = 7.0 Hz), 4.45 (2H, q, J = 6.0 Hz), 5.31 (2H, s), 7.40 (1H, d, J = 1.5 Hz), 7.68 (1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.83 (1H, d, J =1.5 Hz), 7.84 (1H, ddd, J = 7.0, 7.0, 1.5 Hz), 7.94 (1H, d, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.41 (1H, s). ^{13}C NMR δ: 14.1, 50.1, 62.1, 95.2, 99.7, 122.2, 128.0, 128.2, 128.7, 129.9, 130.7, 131.1, 142.4, 149.1, 161.3, 164.8, 174.2, 212.5. HRMS (EI) m/z: Calcd for $C_{18}H_{14}N_2O_3$ (M^+): 306.1004. Found: 306.0966.

11*H*-7-Methoxycarbonyl-9-oxoindolizino[1,2-*b*]quinoline (5). To a stirred solution of **15** (31.4 mg, 0.10 mmol) in MeOH (3.0 mL) was added concd H_2SO_4 (0.1 mL, 1.82 mmol) at room temperature, and then the resulting mixture was refluxed for 5 h. The solution was neutralized with saturated aqueous $NaHCO_3$ solution at 0 °C, and the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated to furnish the crude product, which was chromatographed. Elution with a 95:5 mixture of $CHCl_3$−MeOH gave rise to **5** (19.6 mg, 67%), as a colorless powder, mp 185−187 °C. IR (KBr) cm^{-1}: 1725, 1669, 1610, 1605. ^1H NMR δ: 3.97 (3H, s), 5.29 (2H, s), 7.36 (1H, d, J = 1.5 Hz), 7.65 (1H, ddd, J = 7.0, 7.0, 1.0 Hz), 7.79 (1H, d, J = 1.5 Hz), 7.81 (1H, ddd, J =7.0, 7.0, 1.5 Hz), 7.93 (1H, d, J = 8.0 Hz), 8.23 (1H, d, J = 8.0 Hz), 8.37 (1H, s). ^{13}C NMR δ: 50.2, 53.0, 99.6, 122.1, 128.0, 128.1, 128.2, 128.6, 129.9, 130.6, 131.0. 142.0, 146.7, 149.0, 152.6, 161.1, 165.1. HRMS (EI) m/z: Calcd for $C_{17}H_{12}N_2O_3$ (M^+): 292,-0848. Found: 292.0815.

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Supporting Information Available: Supporting Information Available: ^1H and ^{13}C NMR spectral data for **8a, 8d, 7**, **12**, **14**, **15**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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