SYNTHESIS OF PYRROLO[2,3-c]QUINOLINE ALKALOID MARINOQUINOLINES

Takashi Nishiyama, a Mari Murakami, a Kimiko Taninaka, a Erina Hamada, a Mai Endo, a Daiki Kinou, a Noriyuki Hatae, b and Tominari Choshi*a

*aFaculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan
bFaculty of Pharmaceutical Sciences, Yokohama University of Pharmacy, 601 Matano, Totsuka-ku, Yokohama 245-0066, Japan E-mail: choshi@fukuyama-u.ac.jp

We dedicate this paper to Professor Dr. Yasuyuki Kita on the celebration of his 77th birthday.

Abstract – In this study, the synthesis of pyrrolo[2,3-c]quinoline as a common skeleton, is described. The process is based on the thermal electrocyclization of 3-phenylpyrrole containing isocyanate as 2-azahexatriene. Using this approach, the total synthesis of three natural marinoquinolines A, B, and E can be successfully achieved.

INTRODUCTION

Quinoline is an important nitrogen-containing heterocycle; it is a common component in pharmaceutical agents and biologically active natural products. 1 Among them, marinoquinolines A-F, 2 aplidiopsamine A, 3 and trigonoine B 4 have been reported as marine natural products possessing the pyrrolo[2,3-c]quinoline skeleton (Figure 1).

Figure 1
Marinoquinoline A has been isolated from *Rapidithrix thailandica* by Srisukchayakul et al. in 2007. In addition, marinoquinolines B–F have been isolated from *Ohtaekwangia kribbensis* by Okanya et al. in 2013. Marinoquinolines A–F exhibit antibacterial, antifungal, and acetylcholinesterase inhibiting activities.\(^2\) Aplidiopsamine A is a potent antimalarial agent.\(^3\) Trigonoine B has been reported to exhibit anti-HIV activity.\(^4\) Furthermore, some 4-substituted pyrroloquinoline derivatives have been reported to exhibit antitubercular activity.\(^5\) The development of a convenient and efficient synthetic method to construct the pyrrolo[2,3-c]quinoline skeleton has attracted considerable attention from organic and medicinal chemists owing to their unique structures, characteristics, and biological activities. Therefore, the total synthesis of marinoquinolines and aplidiopsamine A has been achieved via various synthetic strategies using the pyridine ring formation from 3-arylpyrroles via the Morgen–Walls reaction,\(^6\) Pictet–Spengler reaction,\(^7\) tandem reductive cyclization,\(^8\) Pd-catalyzed imine cyclization,\(^9\) Bishler–Napieralski reaction,\(^10\) and arene–ynamide cyclization.\(^11\) Furthermore, the total synthesis of marinoquinolines C and E has been reported via synthetic strategy using the pyrrole ring formation from 2-chloro-3-nitroquinoline by Bartoli indolization.\(^12\)

We are interested in the synthesis of heterocyclic compounds by constructing fused pyridine ring systems using the thermal electrocyclization of an azahexatriene system.\(^13\) Furthermore, we have been searching for stronger biologically active compounds using these natural compounds and their derivatives.\(^14\) We have recently reported a one-pot reaction wherein carboxylic acid 4 was converted to isocyanate 5 as 2-azahexatriene using Curtius rearrangement followed by a microwave-assisted electrocyclization to construct a fused pyridone ring (Scheme 1).\(^15\) In fact, a convenient total synthesis of isocryptolepine (8) has been achieved using this method.\(^16\)

![Scheme 1](image-url)
RESULTS AND DISCUSSION

In this paper, we disclose the total synthesis of marinoquinolines by constructing a pyrrolo[2,3-c]quinoline framework via the electrocyclization of 2-(pyrrol-3-yl)phenyl isocyanate as the 2-azahexatiriene system.

Our retrosynthetic analysis of marinoquinolines is depicted in Scheme 2. We planned to introduce a side chain via a coupling reaction to the C4-position of marinoquinolines 9 in the final step. We anticipated the formation of a common pyrrolo[3,2-c]quinoline nucleus 10 using the thermal electrocyclization of 2-(pyrrol-3-yl)phenyl isocyanate 11 as the 2-azahexatriene system, which is derived from the cleavage at the C3a–C4 bond position of 10. Isocyanate 11 will be prepared by the Curtius rearrangement of 2-(pyrrol-3-yl)benzoic acid (12), which is easily obtained from methyl 2-(pyrrol-3-yl)benzoate.

As shown in Scheme 3, methyl 2-(pyrrol-3-yl)benzoate 15 was synthesized using the Suzuki–Miyaura coupling reaction of methyl 2-bromobenzoate (13) and 1-(triisopropylsilyl)-1H-pyrrole-3-boronic acid pinacol ester (14) using Guido’s conditions. Subsequently, the TIPS group of 15 was removed with TBAF to obtain methyl 2-(pyrrol-3-yl)benzoate (16) with 99% yield. The hydrolysis of the obtained ester 16 with 1 M NaOH produced benzoic acid 12 in 84% yield.
Next, the synthesis of a pyrrolo[2,3-c]quinoline skeleton via electrocyclization was examined (Scheme 4). Carboxylic acid 12 was reacted with DPPA and Et₃N in 1,2-dichlorobenzene (1,2-DCB) at 60 °C for 30 min to obtain isocyanate 11 via the Curtius rearrangement. The reactant was purified to obtain pyrrolo[3,2-c]quinolin-4-one 10 instead of isocyanate 11 in 99% yield. Surprisingly, this result showed that electrocyclization proceeded immediately at the same temperature after the rearrangement reaction to form isocyanate. In addition, electrocyclization under microwave irradiation was performed; however, this approach was not more effective than the conventional one for substrate 12. As described above, pyrroloquinolinone 10 was efficiently synthesized in a four-step sequence.

Next, to investigate substituent introduction at the C4 position of the obtained pyrroloquinolinone 10 (Scheme 5), treatment of 10 with trifluoromethanesulfonic anhydride (Tf₂O) and pyridine afforded triflate 17 in 61% yield. Sperry et al. have reported the synthesis of marinoquinolines C and E using the Suzuki–Miyaura reaction between 4-chloropyrrolo[2,3-c]quinoline and boronic acid MIDA esters (benzyl and indol-3-yl). Therefore, we attempted to synthesize marinoquinoline E via the Suzuki–Miyaura reaction between triflate 17 and \(N\)-SEM-indol-3-ylboric acid pinacol ester 18. The treatment of triflate 17
with 18 in the presence of Pd(PPh₃)₄ produced 4-(indol-3-yl)pyrrolo[2,3-c]quinoline 19 in 85% yield. Finally, the SEM group of 19 was removed with TBAF to obtain marinoquinoline E (1e) in 56% yield.

Table 1. Synthesis of Marinoquinolines A, B, and C

<table>
<thead>
<tr>
<th>run</th>
<th>reagents (eq)</th>
<th>conditions (eq)</th>
<th>No.</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeB(OH)₂ (1.5)</td>
<td>K₂CO₃ (3), Pd(PPh₃)₄ (0.01), 1,4-dioxane, reflux, 12 h</td>
<td>1a</td>
<td>Me</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>trimethylboroxine (2)</td>
<td>K₂CO₃ (2), Pd(PPh₃)₄ (0.01), 1,4-dioxane, reflux, 12 h</td>
<td>1a</td>
<td>Me</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Me₃Al (7)</td>
<td>Pd(PPh₃)₄ (0.01), THF, reflux, 12 h</td>
<td>1a</td>
<td>Me</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>iBuB(OH)₂ (1.5)</td>
<td>K₂CO₃ (2), Pd(PPh₃)₄ (0.01), 1,4-dioxane/H₂O, 80 °C, 1.5 h</td>
<td>1b</td>
<td>iBu</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>iBu₂Al (7)</td>
<td>Pd(PPh₃)₄ (0.01), THF, reflux, 15 h</td>
<td>1b</td>
<td>iBu</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Bn-Bpin (1.5)</td>
<td>K₂CO₃ (2), Pd(PPh₃)₄ (0.01), 1,4-dioxane, reflux, 12 h</td>
<td>1c</td>
<td>Bn</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Bn₂Al (7)</td>
<td>Pd(PPh₃)₄ (0.01), THF, reflux, 15 h</td>
<td>1c</td>
<td>Bn</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>MeOH (20), CO (1 atm), Et₃N (2), Pd(OAc)₂ (0.05), dpf (0.1), DMF, 80 °C, 12 h</td>
<td>20</td>
<td>CO₂Me</td>
<td>67</td>
</tr>
</tbody>
</table>

Next, we attempted to synthesize marinoquinolines A, B, and C by introducing an alkyl group at the C4 position of 17. As shown in Table 1, the synthesis of marinoquinolines was examined using the Suzuki–Miyaura reaction between triflate 17 with commercial boric acid derivatives; however, desired marinoquinolines could not be obtained (runs 1, 2, 4, and 6). The abovementioned results showed that the borane reagent has low reactivity with substrate 17. Therefore, we decided to examine the coupling reaction using trialkylaluminums reported by Hirota et al. The coupling reaction of 17 with trimethylaluminum in the presence of Pd(PPh₃)₄ produced marinoquinoline A (1a) in 96% yield (run 3). Subsequently, the treatment of 17 with triisobutylaluminum under the same condition produced marinoquinoline B (1b) in 59% yield (run 5). Next, the introduction of a benzyl group was examined using tribenzylaluminum; however, marinoquinoline C (1c) was not obtained because the triflate moiety of 17 was hydrolyzed (run 7). The introduction of an alkyl group into 17 was determined to be optimal with an aluminum reagent. Furthermore, we performed the three-component cross-coupling reaction of
triflate 17 with CO and MeOH in the presence of Pd catalyst and obtained methyl ester 20 in 67% yield (run 8). If compound 20 is used, the synthesis of other marinoquinolines and aplidiopsamine A is thought to be possible. The physical and spectroscopic data of our synthesized marinoquinolines A, B, and E are identical to those of natural and synthetic compounds.

**CONCLUSION**

This paper describes the synthesis of a common pyrrolo[2,3-c]quinoline skeleton using the thermal electrocyclization of 3-phenylpyrrole containing isocyanate as 2-azahexatriene. Using this approach, the total synthesis of three natural marinoquinolines was successfully achieved. Marinoquinoline E was synthesized by performing a coupling reaction with triflate and a borane reagent via a seven-step sequence with 18% overall yield. In addition, marinoquinolines A and B were synthesized using trialkylaluminum as a coupling reagent via a six-step sequence with 37% and 23% overall yields, respectively. Further applications and biological evaluation of their analogues are ongoing in our laboratory.

**EXPERIMENTAL**

General Methods: All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel 60PF$_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Kanto Co. Lit.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me$_4$Si (δ 0.00). NMR spectra were measured with CDCl$_3$ unless otherwise noted. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance ($^{13}$C-NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to CDCl$_3$ (δ 77.0) and DMSO-d$_6$ (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and high-resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system.

**Methyl 2-(N-triisopropylsilylpyrrol-3-yl)benzoate (15)**

A mixture of methyl 2-bromobenzoate (13) (483 μL, 3.44 mmol), 1-(triisopropylsilyl)-1H-pyrrole-3-boronic acid pinacol ester (14) (1 g, 2.87 mmol), K$_3$PO$_4$ (973 mg, 4.59 mmol), Pd(OAc)$_2$ (19 mg, 0.09 mmol), and SPhos (71 mg, 0.17 mmol) in n-BuOH/H$_2$O (20 mL/10 mL) was stirred at 80 °C for 1.5 h under N$_2$ atmosphere. The reaction mixture was quenched with water, and then the mixture was extracted
with EtOAc. The EtOAc layer was washed with water and brine, dried over Na$_2$SO$_4$, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc–hexane (1:99 v/v) to give methyl 2-(pyrrol-3-yl)benzoate 15 (800 mg, 77%) as colorless oil. IR (ATR) $\nu = 1720$ cm$^{-1}$. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 1.12 (18H, d, $J = 2.8$ Hz), 1.46 (3H, sept, $J = 7.7$ Hz), 3.73 (3H, s), 6.39 (1H, dd, $J = 1.5$, 2.8 Hz), 6.77 (1H, dd, $J = 1.8$, 2.8 Hz), 6.86 (1H, dd, $J = 1.5$, 2.8 Hz), 7.23 (1H, t, $J = 7.8$ Hz), 7.42 (1H, t, $J = 7.8$ Hz), 7.47 (1H, d, $J = 7.8$ Hz), 7.56 (1H, d, $J = 7.8$ Hz). $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 11.7, 17.8, 52.0, 110.9, 122.4, 124.4, 125.3, 125.4, 128.6, 129.7, 130.5, 131.1, 135.5, 170.9. MS m/z: 357 (M$^+$).

HRMS (EI): calcd for C$_{21}$H$_{31}$NO$_2$Si 357.2124; found 357.2134.

Methyl 2-(pyrrol-3-yl)benzoate (16)
A solution of TBAF (1.0 M in THF, 3.4 mL, 3.43 mmol) was added dropwise to a solution of methyl 2-(pyrrol-3-yl)benzoate 15 (818 mg, 2.29 mmol) in THF (30 mL) at 0 °C under N$_2$ atmosphere. After stirring at rt for 0.5 h, the reaction mixture was quenched with water, and then was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane (1:4, v/v) as an eluent to give methyl 2-(pyrrol-3-yl)benzoate (16) (455 mg, 99%) as yellow solid. Mp 68–70 °C (EtOAc–hexane). IR (ATR) $\nu = 1712$ cm$^{-1}$. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 3.79 (3H, s), 6.32 (1H, dd, $J = 2.7$, 4.8 Hz), 6.82 (1H, dd, $J = 2.4$, 4.3 Hz), 6.94 (1H, t, $J = 2.4$, 2.7 Hz), 7.24–7.29 (1H, m), 7.43–7.45 (2H, m), 7.60 (1H, d, $J = 7.7$ Hz), 8.28 (1H, br s). $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 52.0, 108.7, 116.3, 118.2, 123.1, 125.6, 128.7, 129.9, 130.7, 130.8, 135.5, 170.6. MS m/z: 201 (M$^+$). HRMS (EI): calcd for C$_{12}$H$_{11}$NO$_2$ 201.0790; found 201.0783.

2-(Pyrrol-3-yl)benzoic acid (12)
To an ester 16 (250 mg, 1.24 mmol) in EtOH (12 mL) was added 1 M NaOH aqueous solution (12 mL), and then was stirred at 60 °C for 24 h. The reaction mixture was diluted with water, and then was acidified with 10% HCl aqueous solution to precipitate the carboxylic acid. The precipitation was filtrated off to give the crude benzoic acid 12 (194 mg, 84%) as white solid. Mp 125–127 °C (EtOAc–hexane). IR (ATR) $\nu = 1666$ cm$^{-1}$. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 6.39 (1H, dd, $J = 1.9$, 4.8 Hz), 6.87 (1H, dd, $J = 2.4$, 4.8 Hz), 6.98 (1H, dd, $J = 1.9$, 2.4 Hz), 7.32 (1H, t, $J = 7.7$ Hz), 7.44 (1H, t, $J = 7.7$ Hz), 7.50 (1H, d, $J = 7.7$ Hz), 7.89 (1H, d, $J = 7.7$ Hz), 8.39 (1H, br s). $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$: 109.4, 116.9, 118.4, 122.7, 126.0, 129.2, 130.3, 130.8, 131.8, 136.5, 173.1. MS m/z: 187 (M$^+$). HRMS (EI): calcd for C$_{11}$H$_{9}$NO$_2$ 187.0633; found 187.0645.

Pyrrolo[2,3-c]quinolin-4-one (10)
A solution of benzoic acid 12 (338 mg, 1.81 mmol), DPPA (1.2 mL, 5.42 mmol), and Et$_3$N (0.75 mL, 5.42 mmol) in 1,2-dichlorobenzene (3 mL) were stirred at 60 °C for 30 min. After cooling to an ambient temperature, the solvent was removed, and the residue was purified by column chromatography using
EtOAc–hexane (1:3 v/v) as an eluent to give the pyrroloquinolinone 10 (398 mg, 99%) as white solid. Mp 146–148 °C (EtOAc–hexane). IR (ATR) ν = 1635 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ: 6.87–6.89 (1H, m), 7.18 (1H, t, J = 7.8 Hz), 7.32 (1H, t, J = 7.8 Hz), 7.36–7.38 (2H, m), 7.93 (1H, d, J = 7.8 Hz), 11.34 (1H, br s), 12.21 (1H, br s). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 102.3, 115.8, 117.4, 121.6, 122.5, 122.9, 126.2, 126.5, 127.2, 135.4, 155.1. MS m/z: 184 (M⁺). HRMS (EI): calcd for C₁₁H₈N₂O 184.0637; found 184.0652.

4-(Trifluoromethylsulfonyloxy)pyrrolo[2,3-c]quinoline (17)

Tf₂O (71 μL, 0.43 mmol) was added to a stirred solution of the pyrroloquinolinone 10 (61 mg, 0.29 mmol) and pyridine (69 μL, 0.86 mmol) in CH₂Cl₂ under cooling with ice. After stirring at rt for 30 min, the solution was treated with water. The mixture was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with water and brine and then dried over Na₂SO₄. The solvent was removed, and the residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:4, v/v) as an eluent to give the triflate 17 (55 mg, 61%) as white solid. Mp 135–137 °C (EtOAc–hexane). IR (ATR) ν = 1041, 1481 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) δ: 7.13–7.15 (1H, m), 7.52 (1H, t, J = 2.8 Hz), 7.61–7.67 (2H, m), 8.06–8.09 (1H, m), 9.10 (1H, br s). ¹³C-NMR (75 MHz, CDCl₃) δ: 103.4, 116.6, 118.4, 120.8, 123.0, 123.7, 127.1, 127.4, 128.2, 128.9, 130.1, 134.5, 139.9, 141.2 MS m/z: 316 (M⁺). HRMS (EI): calcd for C₁₂H₇F₃N₂O₃S 316.0129; found 316.0129.

4-[N-(Trimethylsilylethoxymethyl)indol-3-yl]pyrrolo[2,3-c]quinoline (19)

A mixture of triflate 17 (71 mg, 0.23 mmol), N-SEM-indol-3-ylboronic acid 18 (168 mg, 0.45 mmol), 2 M K₂CO₃ aqueous solution (0.23 mL, 0.45 mmol), LiCl (19 mg, 0.45 mmol), and Pd(PPh₃)₄ (12 mg, 1 μmol) in dioxane (3 mL) was refluxed for 12 h under N₂ atmosphere. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc–hexane (3:7 v/v) as an eluent to give the 4-(indol-3-yl)pyrroloquinoline 19 (79 mg, 85%) as white solid. Mp 130–132 °C (EtOAc–hexane). ¹H-NMR (300 MHz, CDCl₃) δ: –0.06 (9H, s), 0.89 (2H, t, J = 8.3 Hz), 3.53 (2H, t, J = 8.3 Hz), 5.51 (2H, s), 7.14 (1H, d, J = 3.0 Hz), 7.27 (1H, t, J = 7.5 Hz), 7.35 (1H, t, J = 7.5 Hz), 7.42 (1H, d, J = 3.0 Hz), 7.54–7.65 (3H, m), 7.79 (1H, s), 8.05 (1H, d, J = 7.5 Hz), 8.22–8.27 (2H, m), 9.10 (1H, br s). ¹³C-NMR (75 MHz, CDCl₃) δ: –1.41, 17.7, 66.3, 76.0, 102.1, 110.6, 114.8, 120.9, 121.5, 122.8, 122.9, 123.1, 125.3, 125.7, 126.1, 127.2, 127.9, 128.3, 128.7, 129.4, 137.1, 142.3, 143.1. MS m/z: 413 (M⁺). HRMS (EI): calcd for C₂₅H₂₇N₃O₅Si; 413.1923; found 413.1938.

Marinoquinoline E (1e)

TBAF (1.0 M in THF, 0.3 mL, 0.32 mmol) was added dropwise to a solution of 4-(indol-3-yl)pyrroloquinoline 19 (44 mg, 0.11 mmol) and ethylenediamine (21 μL, 0.32 mmol) in THF (2 mL) under N₂ atmosphere. After refluxing for 12 h, the reaction mixture was quenched with water, and
then was extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc–hexane (1:1, v/v) as an eluent to give marinoquinoline E (1e) (17 mg, 56%) as yellow solid. Mp 263–264 °C (EtOAc–hexane). ¹H-NMR (300 MHz, CDCl₃) δ: 7.15 (1H, d, J = 2.7 Hz), 7.23–7.34 (2H, m), 7.44 (1H, d, J = 2.9 Hz), 7.51 (1H, d, J = 7.4 Hz), 7.57–7.65 (2H, m), 7.84 (1H, s), 8.03 (1H, d, J = 7.4 Hz), 8.23–8.27 (2H, m), 8.47 (1H, br s), 8.94 (1H, br s). ¹H-NMR (300 MHz, acetone–d₆) δ: 7.18–7.26 (3H, m), 7.47–7.57 (3H, m), 7.61 (1H, d, J = 7.1 Hz), 8.18 (1H, d, J = 7.8 Hz), 8.22–8.28 (2H, m), 8.72 (1H, d, J = 7.8 Hz), 10.88 (1H, br s), 11.06 (1H, br s). ¹³C-NMR (75 MHz, acetone–d₆) δ: 102.2, 112.3, 114.7, 121.1, 123.3, 123.46, 123.52, 123.6, 125.6, 126.5, 127.1, 127.7, 127.8, 128.0, 129.6, 129.7, 137.9, 143.5, 144.3. MS m/z: 283 (M⁺). HRMS (EI): calcd for C₁₉H₁₃N₂ 283.1109; found 283.1113.

Marinoquinoline A (1a)
A mixture of triflate 17 (20 mg, 0.063 mmol), trimethylaluminum (28 μL, 0.43 mmol) and Pd(PPh₃)₄ (7 mg, 6.3 μmol) in THF (2 mL) was refluxed for 12 h under N₂ atmosphere. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc–hexane (1:3 v/v) as an eluent to give marinoquinoline A (1a) (11 mg, 96%) as white solid. Mp 231–233 °C (EtOAc–hexane). ¹H-NMR (300 MHz, CDCl₃) δ: 2.88 (3H, s), 7.09 (1H, d, J = 3.0 Hz), 7.43 (1H, d, J = 3.0 Hz), 7.51–7.61 (2H, m), 8.10–8.13 (1H, m), 8.16–8.19 (1H, m), 9.01 (1H, br s). ¹H-NMR (300 MHz, acetone–d₆) δ: 2.82 (3H, s) 7.12 (1H, d, J = 2.9 Hz), 7.46–7.53 (2H, m), 7.58 (1H, d, J = 2.9 Hz), 7.98–8.01 (1H, m), 8.20–8.23 (1H, m), 11.15 (1H, br s). ¹³C-NMR (75 MHz, acetone–d₆) δ: 21.1, 102.0, 123.7, 124.1, 125.7, 126.1, 127.2, 128.3, 128.4, 129.7, 143.6, 146.8. MS m/z: 182 (M⁺). HRMS (EI): calcd for C₁₂H₁₀N₂ 182.0844; found 182.0845.

Marinoquinoline B (1b)
Marinoquinoline B (1b) (yield 59%) was prepared according to a synthetic method for 1a as white solid. Mp 182–183 °C (EtOAc–hexane). ¹H-NMR (300 MHz, CDCl₃) δ: 1.03 (6H, d, J = 7.1 Hz), 2.41 (1H, sept, J = 7.1 Hz), 3.04 (2H, d, J = 7.3 Hz), 7.09 (1H, d, J = 3.0 Hz), 7.43 (1H, d, J = 3.0 Hz), 7.51–7.61 (2H, m), 8.10–8.13 (1H, m), 8.16–8.19 (1H, m), 9.01 (1H, br s). ¹H-NMR (300 MHz, acetone–d₆) δ: 0.99 (6H, d, J = 6.6 Hz), 2.43 (1H, sept, J = 6.6 Hz), 3.06 (2H, d, J = 7.3 Hz), 7.12 (1H, d, J = 2.7 Hz), 7.47–7.52 (2H, m), 7.55 (1H, d, J = 2.7 Hz), 7.79–8.02 (1H, m), 8.21–8.24 (1H, m), 11.13 (1H, br s). ¹³C-NMR (75 MHz, acetone–d₆) δ: 23.0, 29.0, 44.0, 101.9, 123.7, 124.0, 125.6, 126.0, 127.0, 128.6, 129.8, 130.0, 143.7, 150.0. MS m/z: 224 (M⁺). HRMS (EI): calcd for C₁₅H₁₆N₂ 224.1313; found 224.1322.

Methyl pyrrolo[2,3-c]quinoline-4-carboxylate (20)
Carbon monoxide was bubbled for 5 min to a mixture of the triflate 17 (102 mg, 0.33 mmol), MeOH (0.27 mL, 6.58 mmol), Et₃N (0.09 mL, 0.66 mmol), dpff (18 mg, 0.033 mmol), and Pd(OAc)₂ (13 mg,
0.017 mmol) in DMF (7 mL) at rt. The resulting mixture was stirred at 80 °C for 12 h under a CO atmosphere. After cooling to an ambient temperature, the mixture was quenched with water and then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc–hexane (3:7, v/v) as an eluent to give the methyl ester 20 (50 mg, 67%) as yellow solid. Mp 151–153 °C (EtOAc–hexane).

IR (ATR) ν = 1701 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) δ: 4.16 (3H, s), 7.12–7.14 (1H, m), 7.58 (1H, t, J = 2.7 Hz), 7.66–7.70 (2H, m), 8.24–8.27 (1H, m), 8.34–8.38 (1H, m), 10.33 (1H, br s). ¹³C-NMR (75 MHz, CDCl₃) δ: 53.3, 101.5, 123.1, 125.1, 126.8, 127.8, 128.2, 128.8, 130.8, 130.9, 133.4, 141.7, 166.9. MS m/z: 226 (M⁺). HRMS (EI): C₁₃H₁₀N₂O₂ calcld for 226.0742; found 226.0752.

ACKNOWLEDGEMENTS
This work was supported in part by a Grant-in-Aid for Scientific Research (C) of the Japan Society for the Promotion of Science (grant number 15K07880 for T. C.).

REFERENCES