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STUDIES TOWARD THE SYNTHESIS OF TODDAQUINOLINE BY INTRAMOLECULAR CYCLIZATION

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Abstract – In connection with studies on the total synthesis of toddaquinoline (**1**), the synthesis of [1,3]dioxolo[4',5':4,5]benzo[*h*]quinoline (**1a**), which is the tetracyclic core of **1**, was investigated. Intramolecular benzene-pyridine coupling reactions of the monobromide (**9**) and dibromide (**10**), using a Pd reagent and Cu reagent, were evaluated to produce **1a** in poor to moderate yields.

INTRODUCTION

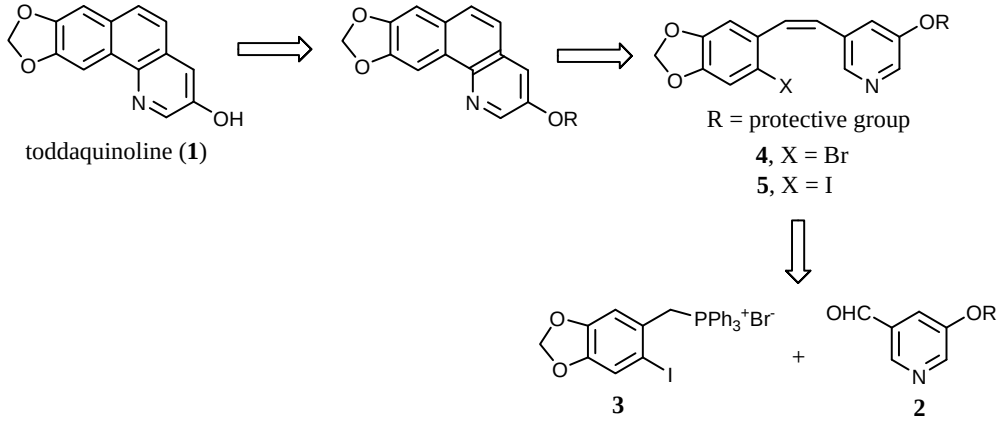
Toddaquinoline (**1**) is a benzo[*h*]quinoline alkaloid isolated in 1993 from the root bark of *Toddalia asiatica*, a constituent of many Asian folk medicines.[1,2] Soon thereafter its unique tetracyclic skeleton attracted the researchers' attention for its total synthesis. There are only a few references about the synthetic studies of toddaquinoline involving photocyclizations, intramolecular additions or radical cyclizations.[3-5]

Palladium-assisted aryl-aryl coupling reactions have been used to synthesize many condensed aromatic compounds. Given the interesting structure of toddaquinoline, its intriguing biological activity and our interest in biaryl coupling reactions by Pd reagent, we engaged in the total synthesis of toddaquinoline. Our synthetic strategy contains a unique coupling reaction between the arene and pyridine rings using Pd reagent. Additionally, we were very interested to find if an intramolecular Ullmann coupling, the copper-mediated coupling of aryl halide, is effective for the synthesis of benzo[*h*]quinoline skeleton.

RESULTS AND DISCUSSION

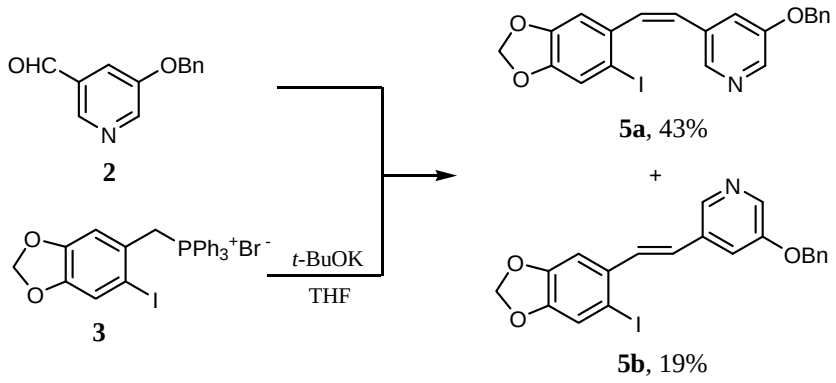
Harrowven *et al.* were the first to produce the total synthesis of toddaquinoline[4] using a radical approach.

Although the radical cyclization of Harrowven's bromo-intermediate (**4**) produced **1** in 61% yield, we planned to apply the Pd method to the more reactive iodo-alkene (**5**) than the bromo-alkene (**4**) to investigate the utility of the aryl-aryl coupling reaction using the Pd reagent.



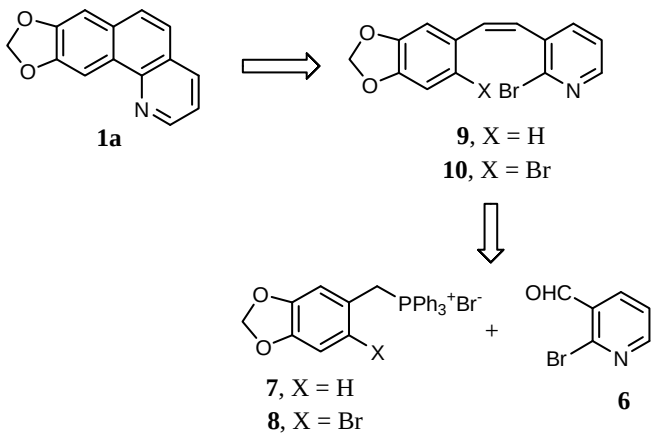
Scheme 1. Retrosynthesis of Toddaquinoline (**1**) (plan A).

In plan A (Scheme 1), the synthesis of the iodo-alkene (**5**), the key intermediate for the synthesis of toddaquinoline (**1**), was achieved according to method for the bromo-intermediate (**4**) synthesis[3-6] from the aldehyde **2** and the triphenylphosphonium salt **3** prepared from 3,5-dibromopyridine and the piperonyl alcohol, respectively. The triphenylphosphonium salt **3** after the Wittig reaction with the aldehyde **2** produced a mixture of the *cis*-**5a** and *trans*-iodoalkene **5b** (~2:1) separable by column chromatography (Scheme 2).



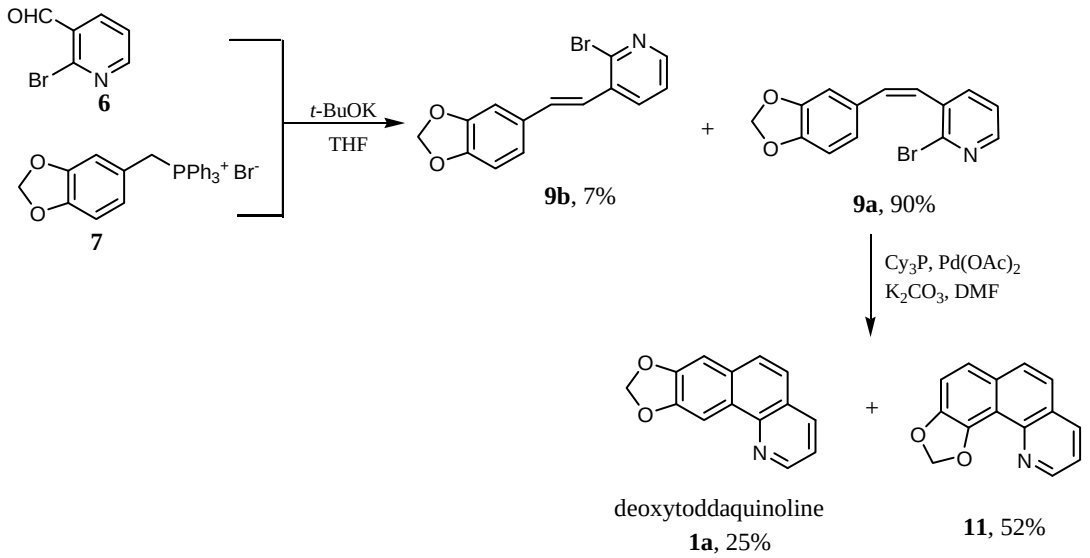
Scheme 2. Synthesis of Compound **5**.

Unfortunately, the intramolecular benzene-pyridine coupling reaction by Pd reagent of the *cis*-alkene **5a** possessing a leaving group on the benzene ring was not successful. Therefore, we envisioned plan B, which contains the coupling reaction of compounds **9** and **10** possessing a leaving group on the pyridine ring, as preliminary experiments for the synthesis of toddaquinoline (**1**) (Scheme 3).



Scheme 3. Retrosynthesis of Deoxytoddaquinoline (**1a**) (plan B).

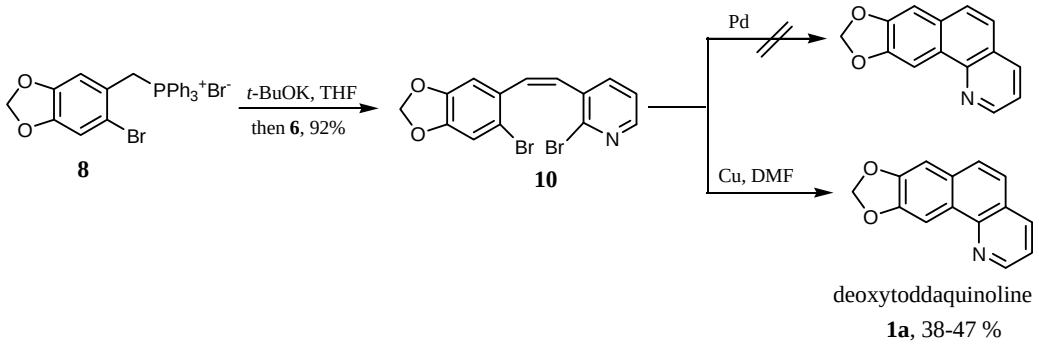
The synthesis of deoxytoddaquinoline (**1a**) was realized from the 2-bromo-aldehyde (**6)** and phosphonium salt **7**. The *ortho*-lithiation of 2-bromopyridine with LDA followed by electrophilic substitution with DMF provided the aldehyde **6**,[7-9] since the piperonyl alcohol was transformed into the triphenylphosphonium salt **7**.[5, 10-11] The phosphonium salt **7** was coupled with the aldehyde **6** using standard Wittig conditions giving a mixture of the *cis*- **9a** and *trans*-bromoalkene **9b** (~15:1) separable by column chromatography. Although the biaryl coupling reaction of the *cis*-compound **9a** using Pd occurred, two of the postulated products **1a** (deoxytoddaquinoline, 25%) and **11** (52%) were obtained favoring the undesired compound **11**, which showed that a coupling reaction mainly took place at the more hindered position (Scheme 4).[12]



Scheme 4. Synthesis of Deoxytoddaquinoline (**1a**) by Pd-mediated Intramolecular Cyclization.

The biaryl coupling reaction of the dibromide **10**, which would be expected to produce only **1a**, was then carried out. In order to achieve this reaction, we synthesized the dibromide **10** in a manner similar to that used for compounds **5** and **9**. Although the Pd-mediated coupling reaction of the dibromide **10** did not

give any cyclization product, the Ullmann reaction[13] of **10** gave the desired compound **1a** in a moderate yield (Scheme 5).



Scheme 5. Synthesis of Deoxytoddaquinoline (**1a**) by Cu-mediated Intramolecular Cyclization.

EXPERIMENTAL

General: Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The ^{1}H-NMR spectra in deuteriochloroform were recorded by a Varian Gemini-200, Mercury-300 or VXR-500 spectrometer. The NMR spectra data are reported in parts per million downfield from the internal standard (tetramethylsilane, δ 0.0). The FAB-MS were obtained using a VG AutoSpec spectrometer with *m*-nitrobenzyl alcohol as the matrix. The elemental analysis was performed using a Yanaco MT-5 analyzer. Column chromatography was carried out with Merck silica gel (230-400 mesh). The TLC analysis was performed on Kieselgel 60 F_{254} (Merck) plates. All the experiments were carried out in an argon atmosphere, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene, and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give the purified $Pd(OAc)_2$. The copper was purified by a published method.[14]

Substrates: 3-Formyl-5-benzyloxypyridine (**2**),[3-5] [(6-iodo-1,3-benzodioxol-5-yl)methyl]triphenyl-phosphonium bromide (**3**),[6,15] 2-bromo-3-formylpyridine (**6**),[7-9] [(1,3-benzodioxol-5-yl)methyl]triphenyl-phosphonium bromide (**7**),[5,10-11] [(6-bromo-1,3-benzodioxol-5-yl)methyl]triphenylphosphonium bromide (**8**),[5,11]and [1,3]dioxolo[4',5':4,5]benzo[*h*]quinoline (deoxytoddaquinoline) (**1a**)[15] are known compounds.

The Wittig procedure of compounds 2 and 3. Phosphonium bromide **3** (8.481 g, 14.06 mmol) was suspended in dry THF (40 mL) and cooled to 0 °C, then *t*-BuOK (1.631 g, 14.53 mmol) was added and the mixture was stirred for 10 min at 0 °C. A solution of 3-formyl-5-benzyloxypyridine **2** (1.00 g, 2.21 mmol) in THF (5 mL) was then dropwise added and the mixture was stirred at rt for 2h. When the reaction was finished, water was added and the mixture extracted with Et_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The yellow oily residue was dissolved in CH_2Cl_2 and subjected to column chromatography (silica gel, hexane:AcOEt = 10:1 ~ 4:1) to yield the *cis*-isomer **5a** (hexane:AcOEt = 10:1, 923 mg, 43%) and the *trans*-isomer **5b** (hexane:AcOEt = 4:1, 397 mg, 19%).

3-[(1*Z*)-2-(6-Iodo-1,3-benzodioxol-5-yl)ethenyl]-5-benzyloxypyridine (5a) pale yellow prisms, mp 77-79 °C (AcOEt/hexane). IR ($CHCl_3$) cm^{-1}: 1227, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 8.19 (d, 1H, Py-H, *J* = 2.8 Hz), 8.01 (m, 1H, Py-H), 7.32-7.42 (m, 5H, Ar-H), 7.26 (s, 1H, Ar-H), 6.99 (t, 1H, Py-H, *J* = 2.2 Hz), 6.58 (s, 1H, Ar-H), 6.57 (d, 1H, =CH, *J* = 12.0 Hz), 6.49 (d, 1H, =CH, *J* = 12.0 Hz), 5.93 (s, 2H, OCH_2O), 4.94 (s, 2H, Ar-CH_2). MS (FAB, positive ion mode) *m/z*: 458 [$M+1^+$]. *Anal*. Calcd for $C_{21}H_{16}NO_3I$: C, 55.16; H, 3.52; N, 3.06. Found C, 55.34; H, 3.59; N, 3.07.

3-[(1*E*)-2-(6-Iodo-1,3-benzodioxol-5-yl)ethenyl]-5-benzyloxypyridine (5b) pale yellow needles, mp 140-141 °C (AcOEt). IR (KBr) cm^{-1}: 1256, 1036. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.32 (d, 1H, Py-H, *J* = 1.8 Hz), 8.28 (d, 1H, Py-H, *J* = 2.7 Hz), 7.35-7.48 (m, 7H, Py-H, Ar-H), 7.27 (d, 1H, =CH, *J* = 16.2 Hz), 7.12 (s, 1H, Ar-H), 6.76 (d, 1H, =CH, *J* = 16.2 Hz), 6.00 (s, 2H, O-CH_2-O), 5.17 (s, 2H, Ar-CH_2). MS (FAB, positive ion mode) *m/z*: 458 [$M+1^+$]. *Anal*. Calcd for $C_{21}H_{16}NO_3I$: C, 55.16; H, 3.52; N, 3.06. Found C, 54.82; H, 3.72; N, 3.01.

The Wittig procedure of compounds 6 and 7. Phosphonium bromide **7** (3.5 g, 7.33 mmol) was suspended in dry THF (25 mL) and cooled to 0 °C, then *t*-BuOK (0.85 g, 7.58 mmol) was added, and the mixture was stirred for 10 min at 0 °C. A solution of 2-bromo-3-formylpyridine **6** (0.45 g, 2.44 mmol) in THF (5 mL) was then dropwise added and the mixture was stirred at rt for 3h. When reaction was finished, water was added and the mixture extracted with Et_2O. The combined organic layers were dried with K_2CO_3 and concentrated *in vacu*o. The yellow residue (3.57 g) was dissolved in CH_2Cl_2 and subjected to column chromatography (silica gel, hexane:AcOEt = 10:1) to yield the *cis*-isomer **9a** (0.671 g, 90%) and the *trans*-isomer **9b** (0.049 g, 7%).

(*Z*)-3-[2"-(1',3'-Benzodioxol-5'-yl)]-1"-ethenyl-2-bromopyridine (9a) white powder, mp 48-50 °C (crude). IR (NaCl) cm^{-1}: 2780, 1620, 1430, 1210, 1030. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.24 (dd, 1H, Py-H, *J* = 1.5 Hz; 4.8 Hz), 7.49 (dd, 1H, Py-H, *J* = 1.5 Hz; 7.8 Hz), 7.09 (dd, 1H, Py-H, *J* = 4.8 Hz; 7.8 Hz), 6.68 (d, 1H, =CH, *J* = 12.0 Hz), 6.67 (d, 1H, Ar-H, *J* = 7.5 Hz), 6.64 (dd, 1H, Ar-H, *J* = 1.5 Hz; 7.5 Hz), 6.57 (d, 1H, Ar-H, *J* = 1.5 Hz), 6.45 (d, 1H, =CH, *J* = 12.0 Hz), 5.91 (s, 2H, O-CH_2-O). MS (FAB, positive ion mode) *m/z*: 303, 305 [M^+]. HRMS (FAB) calcd for $C_{14}H_{10}NO_2{}^+Br$: 302.9894 found 302.9919.

(*E*)-3-[2"-(1',3'-Benzodioxol-5'-yl)]-1"-ethenyl-2-bromopyridine (9b) white powder, mp 144-146 °C ($CHCl_3$/Et_2O). IR (KBr) cm^{-1}: 2780, 1615, 1440, 1230, 1040. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.23 (dd, 1H, Py-H, *J* = 1.8 Hz; 4.8 Hz), 7.88 (dd, 1H, Py-H, *J* = 1.8 Hz; 7.2 Hz), 7.25 (dd, 1H, Py-H, *J* = 4.8 Hz; 7.2 Hz), 7.18 (d, 1H, =CH, *J* = 16.2 Hz), 7.10 (d, 1H, Ar-H, *J* = 1.5 Hz), 6.97 (dd, 1H, Ar-H, *J* = 1.5 Hz; *J* = 7.9 Hz), 6.96 (d, 1H, =CH, *J* = 16.2 Hz), 6.81 (d, 1H, Ar-H, *J* = 7.9 Hz), 6.00 (s, 2H, O-CH_2-O). MS (FAB, positive ion mode) *m/z*: 303, 305 [M^+]. HRMS (FAB) calcd for $C_{14}H_{10}NO_2{}^+Br$: 302.9894, found 302.9930.

General procedure for the coupling reaction by Pd of (*Z*)-3-[2”-(1’,3’-benzodioxol-5’-yl)]-1”-ethenyl-2-bromopyridine (9a). The bromopyridine **9a** (50 mg, 0.16 mmol) was dissolved in dry DMF (2 mL) and the solution was placed in an argon atmosphere at 120 °C for a few minutes. $Pd(OAc)_2$ (7.36 mg, 0.03 mmol), Cy_3P (18.44 mg, 0.06 mmol) and K_2CO_3 (45.46 mg, 0.32 mmol) were then added and the mixture was carried out under reflux for 4h. The reaction mixture was extracted with AcOEt, the combined organic layers were washed with brine, dried with K_2CO_3 and evaporated. The brown residue (48 mg) was dissolved in CH_2Cl_2 and subjected to column chromatography on silica gel. Elution with hexane-AcOEt (10:1) gave the desired product **1a** (8.9 mg, 25%) and successive elution with hexane-AcOEt (3:1) produced **11** (19.2 mg, 52%).

[1,3]Dioxolo[4’,5’:4,5]benzo[*h*]quinoline (deoxy-toddaquinoline) (1a) colorless needles, mp 124-125 °C ($Et_2O/CHCl_3$) [lit.,[15] 121-122 °C]. IR (KBr) cm^{-1}: 2780, 1500, 1250, 1040. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.93 (dd, 1H, Py-H, *J* = 1.5; 4.2 Hz), 8.65 (s, 1H, Ar-H), 8.14 (dd, 1H, Py-H, *J* = 1.5; 8.1 Hz), 7.68 (d, 1H, Ar-H, *J* = 9.0 Hz), 7.57 (d, 1H, Ar-H, *J* = 9.0 Hz), 7.46 (dd, 1H, Py-H, *J* = 4.2; 8.1 Hz), 7.23 (s, 1H, Ar-H), 6.13 (s, 2H, O-CH_2-O). MS (FAB, positive ion mode) *m/z*: 224 [M+1$^+$]. HRMS (FAB) calcd for $C_{14}H_{10}NO_2^+$: 224.0711, found 224.0750.

[1,3]Dioxolo[4’,5’:3,4]benzo[*h*]quinoline (11) yellow needles, mp 152-154 °C (Et_2O). IR (KBr) cm^{-1}: 2820, 1530, 1280, 1040. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.09 (dd, 1H, Py-H, *J* = 1.5; 4.5 Hz), 8.15 (dd, 1H, Py-H, *J* = 1.5; 8.1 Hz), 7.71 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.52 (dd, 1H, Py-H, *J* = 4.5; 8.1 Hz), 7.50 (d, 1H, Ar-H, *J* = 2.1 Hz), 7.47 (d, 1H, Ar-H, *J* = 2.1 Hz), 7.31 (d, 1H, Ar-H, *J* = 8.5 Hz), 6.38 (s, 2H, O-CH_2-O). MS (FAB, positive ion mode) *m/z*: 224 [M+1$^+$]. Anal. Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 74.83; H, 4.18; N, 6.39.

(*Z*)-3-[2”-(1’,3’-Benzodioxol-6’-bromo-5’-yl)]-1”-ethenyl-2-bromopyridine (10). The phosphonium bromide **8** (1.84 g, 3.31 mmol) was suspended in dry THF (10 mL) and cooled to 0 °C, then *t*-BuOK (0.38 g, 3.42 mmol) was added and the mixture was stirred for 15 min at 0 °C then for 15 min at rt. A solution of 2-bromo-3-formylpyridine **6** (0.22 g, 1.1 mmol) in THF (5 mL) was then dropwise added (20 min, 0 °C) and the mixture was stirred at rt for 2h. The reaction mixture was diluted with water and extracted with Et_2O. The combined organic layers were dried with K_2CO_3 and concentrated in vacuo. The yellow residue (1.72 g) was dissolved in CH_2Cl_2 and subjected to column chromatography (silica gel, hexane:AcOEt = 15:1) to yield the *cis*-isomer **10** (0.415 g, 92%) as colorless needles, mp 131.5-133.5 °C ($Et_2O/CHCl_3$). IR (KBr) cm^{-1}: 2780, 1617, 1210, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.21 (dd, 1H, Py-H, *J* = 1.8 Hz; 4.8 Hz), 7.30 (dd, 1H, Py-H, *J* = 1.8 Hz; 7.8 Hz), 7.05 (dd, 1H, Py-H, *J* = 4.8 Hz; 7.8 Hz), 7.03 (s, 1H, Ar-H), 6.77 (d, 1H, =CH, *J* = 12.0 Hz), 6.62 (d, 1H, =CH, *J* = 12.0 Hz), 6.40 (s, 1H, Ar-H), 5.91 (s, 2H, O-CH_2-O). MS (FAB, positive ion mode) *m/z* 382, 384, 386 [M+1$^+$]. Anal. Calcd for $C_{14}H_{92}NO_2$ Br: C, 43.90; H, 2.37; N, 3.66. Found: C, 43.85; H, 2.46; N, 3.52.

General procedure for the coupling reaction by Cu of (*Z*)-3-[2”-(1’,3’-benzodioxol-6’-bromo-5’-yl)]-1”-ethenyl-2-bromopyridine (10). The dibromopyridine **10** (70 mg, 0.18 mmol) was dissolved in dry DMF (2 mL) and the solution was heated at 100 °C in an argon atmosphere for a few minutes. The activated copper (46.44 mg, 0.73 mmol) was added and the mixture was heated for 2h at 100 °C, for 1.5h at 150 °C and then for 4.5h at 200 °C. The mixture was cooled to rt, diluted with water and then was extracted with AcOEt. The combined organic layers were washed with saturated NaCl solution, dried with K_2CO_3 and concentrated. The residue (59.8 mg) dissolved in CH_2Cl_2 was purified via column chromatography on silica gel. Elution with hexane-AcOEt (15:1) gave the cyclization product, deoxytoddaquinoline **1a** (19.1 mg, 47%), and successive elution with hexane-AcOEt (10:1) gave the unreacted starting material **10** (34.2 mg, 48%). The compound **1a** was identified with the synthetic sample obtained from the reaction using the Pd-reagent.

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