

A Convenient Synthetic Method of a 5,7-Diarylcyclopenteno-[1,2-*b*]pyridine-6-carboxylate: A Key Intermediate for Potent Endothelin Receptor Antagonists

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Abstract—A convenient method for the synthesis of the title intermediate **4** was described. The key steps of this synthesis involved: (1) regioselective addition reaction of arylzinc reagent to quinolic anhydride in 42% isolated yield, (2) conversion of a ketoacid **7** to an enone **14**, which was achieved in 65% yield by intramolecular Knoevenagel reaction of β -ketoester generated by condensation of an acid imidazolidine **11** with an ester enolate, followed by dehydration assisted with silica gel, and (3) stereoselective reduction of an allyl alcohol **15** in 75% yield with zinc under acidic conditions. This synthesis enabled us to provide hundreds of grams of **4** without chromatographic purification.

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Introduction

Endothelin-1 (ET-1),¹ and its closely related isopeptides (ET-2, ET-3) were identified in 1988 as potent vasoconstrictor peptides consisting of 21 amino acids. Since peptide endothelin receptor antagonists such as BQ-123² exhibited their clinical potential in endothelin-mediated disorders, many pharmaceutical companies have extensively pursued studies directed toward the development of non-peptide endothelin antagonists as therapeutic agents.³

We discovered a 6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine derivative **1** to be a novel lead structure for a potent endothelin receptor antagonist (Fig. 1). Through the derivatization of **1**, we discovered that introduction of functional groups into the α -position of the 4-methoxyphenyl group changed biological properties without losing the binding affinities. Actually, we identified compound **2** and **3** with highly potent in vivo efficacy in a mouse model.⁴ However, extensive derivatization of **1**

was limited by difficulty on the supply of the key intermediate **4** in a facile manner. Therefore, establishment of a convenient and practical synthetic method of **4** was essential.⁴ In this paper, we describe a feasible approach by improving regio- and stereo-selectivity at key reaction steps shown in Scheme 1.

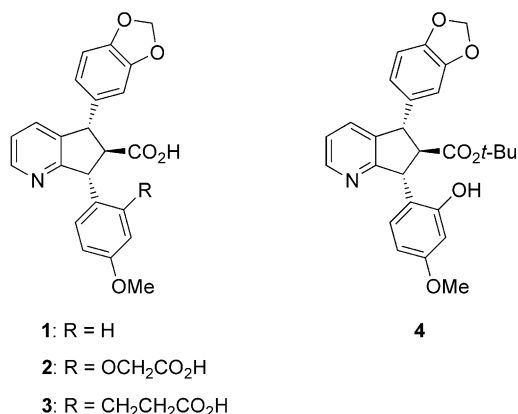
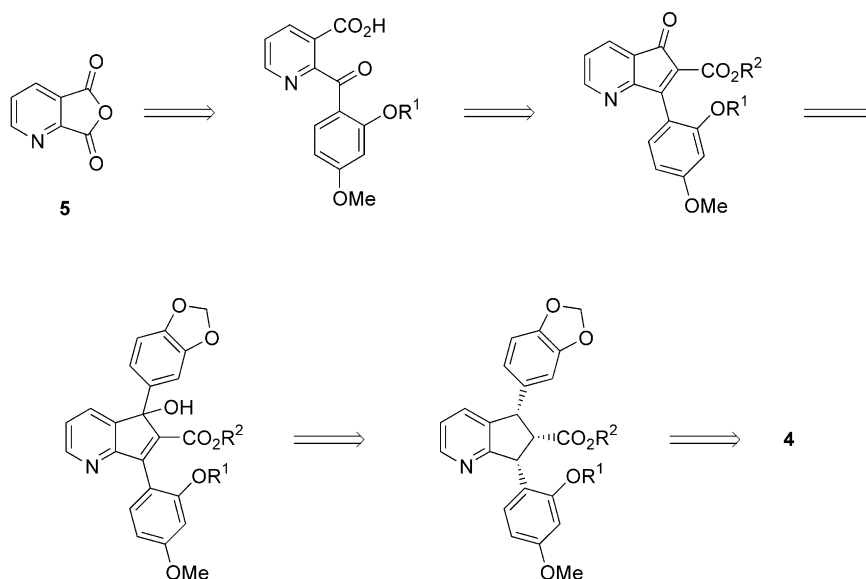


Figure 1. 6-Carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine derivatives.

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Scheme 1. Retrosynthetic analysis of **4**.

Results and Discussion

Retrosynthetic analysis of **4** suggested a potentially feasible approach for the diastereoselective synthesis (Scheme 1). This approach needed optimization and improvement of: (1) regioselectivity of the addition reaction of an arylmetal reagent to quinolinic anhydride **5**, (2) reaction conditions of the conversion of the ketoacid **7** into the enone **14**, and (3) stereoselectivity of the hydrogenation of the allyl alcohol system in **15**. In addition, we also considered to use no chromatography in the process for the preparation of a large amount of the intermediate.

To begin with, the regioselective addition of the aryl moiety to the anhydride **5** was investigated. The addition reaction of 2-benzyloxy-4-methoxyphenyl magnesium bromide or the corresponding lithium reagent to **5** gave a mixture of regioisomer **7** and **8** in 65% (**7/8**=4:3) and 36% yield (**7/8**=3:2), respectively (Table 1).^{5,6} Since

the loss of the regioselectivity in the reaction was considered to be due to the high nucleophilicity of these arylmetal reagents, we examined the reaction with the corresponding arylzinc reagent that is known to have lower nucleophilicity. As expected, the zinc reagent, prepared in situ from the corresponding lithium reagent with zinc chloride, improved the regioselectivity (**7/8**=6:1). The desired isomer **7** was exclusively obtained as a crystalline solid in 42% yield, and the yield was reproducible (40–50% yield) even in a kilogram-scale preparation.

For the conversion of the ketoacid **7** to the enone **14**, we adopted a strategy via a β -keto ester **12**.⁷ The reaction of the corresponding acid chloride or acid imidazolid **11** with a magnesium salt of malonic acid monoester under Masamune's condition⁸ did not produce the desired β -keto ester **12**, probably due to the low reactivity of the acid chloride or the acid imidazolid. Since the acid imidazolid **11** was obtained as a crystalline solid in high yield, further investigation was carried out using **11**. Treatment of the imidazolid **11** with 1.2 equivalents of an enolate of *tert*-butyl acetate unexpectedly provided a cyclized product **13** in good yield. Purification of the product **13** by column chromatography on silica gel or alumina was unsuccessful because of its instability of the product under both weak acidic and basic conditions. When the crude material obtained via a usual work up was treated with silica gel in chloroform, the dehydration occurred smoothly to provide the desired enone **14** in good yield. As a result, treatment of the acid imidazolid **11** with 1.5 equivalents of the lithium enolate of *tert*-butyl acetate at -70 to -60 °C followed by dehydration assisted with silica gel reproducibly produced the enone **14** in 65% yield as a crystalline solid. The proposed mechanism of the reaction is shown in Figure 2; (1) the acid imidazolid moiety of **11** reacted with the enolate of *tert*-butyl acetate to produce the β -keto ester **12**, (2) an acidic proton of **12** was abstracted by an excess amount of the enolate anion to

Table 1. Regioselective addition of arylmetal reagents to quinolinic anhydride **5**

X	Yield (%)	Ratio (7/8)
Li	65	4:3
MgBr	36	3:2
ZnCl ^a	40	6:1
Ti(<i>Oi</i> -Pr) ₃ ^b	No reaction	—

^aPrepared from the corresponding lithium reagent with ZnCl₂.

^bPrepared from the corresponding lithium reagent with TiCl(*Oi*-Pr)₃.

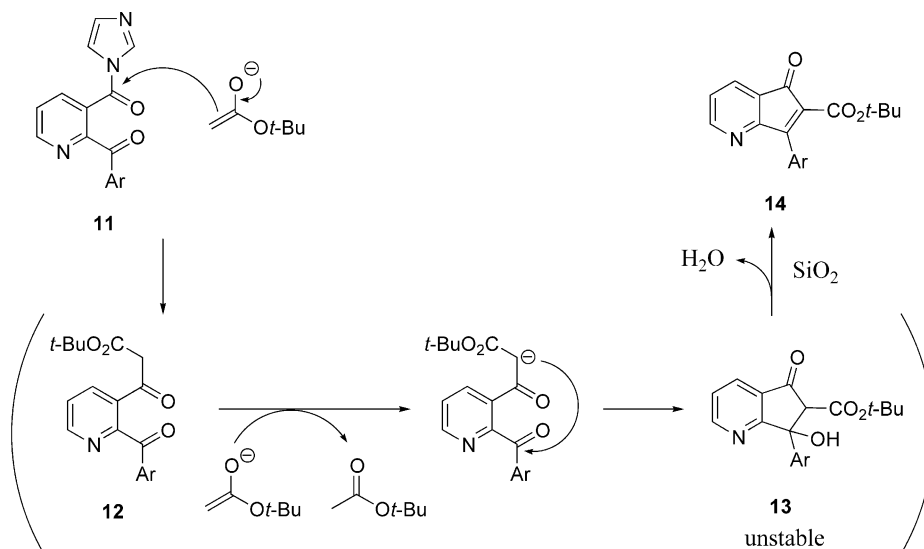


Figure 2. Mechanism of the formation of **14**.

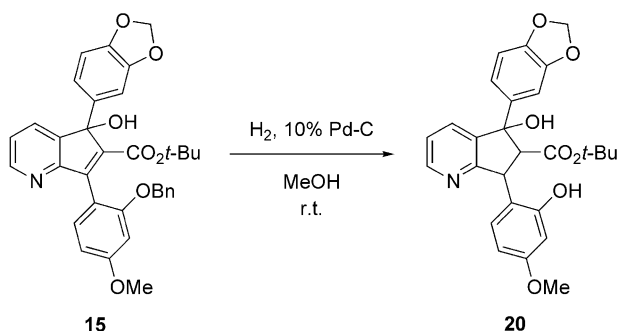


Figure 3. Catalytic hydrogenation of the intermediate **15**.

generate the α -anion of **12**, (3) the anion intramolecularly attacked the carbonyl group to provide the labile β' -hydroxy- β -ketoester **13**, and (4) **13** was dehydrated in the presence of silica gel to give **14**. The addition of a

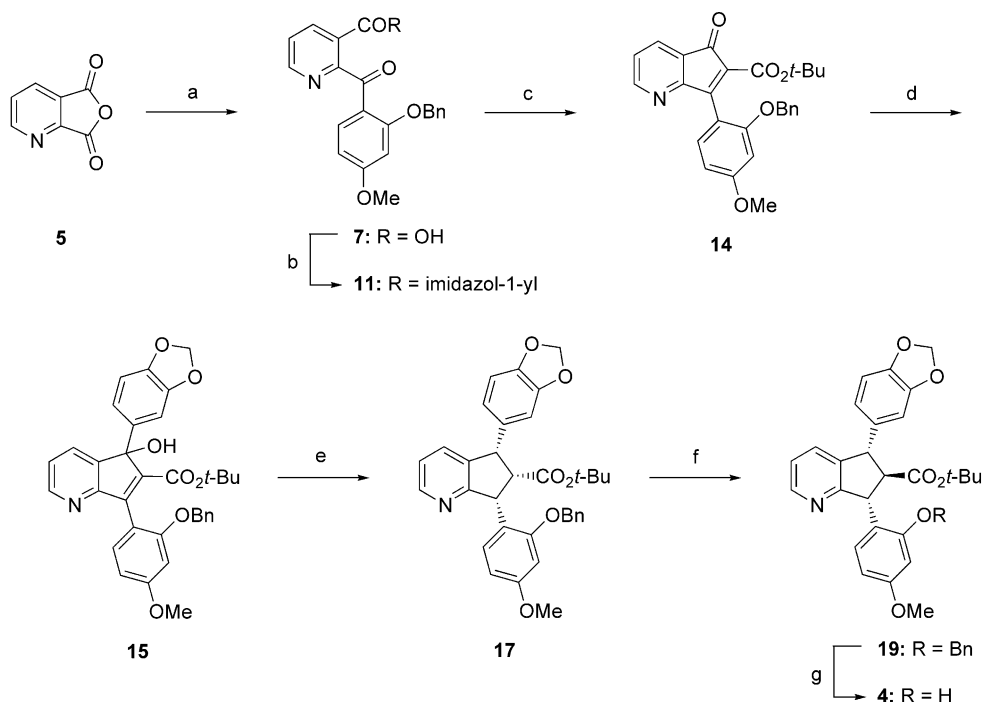
3,4-methylenedioxyphenylmagnesium bromide to the enone **14** successfully produced an allyl alcohol **15** in 91% yield.

Stereoselective reduction of the allyl alcohol system in **15** was also crucial in this synthesis. In fact, the catalytic hydrogenation of **15** in the presence of 10% Pd on carbon gave a saturated alcohol **20** in 82% yield as shown in Figure 3. Since it was known that the deoxygenation of a simple allyl alcohol system was achieved by using zinc,⁹ we applied the procedure to the more complex system of **15**. The results are summarized in Table 2. Reduction with 3 equivalents of zinc in the presence of 5 equivalents of acetic acid resulted in the production of a deoxygenated compound **16** in 10% yield, while 64% of the starting material **15** was recovered. In contrast, the use of other reducing agents such as SnCl_2 and Fe did

Table 2. Results on the reduction of **15** with various reducing agents

Reagent	Solvent	Additive	Temperature (°C)	Results
Zn (3 equiv)	THF	AcOH (5 equiv)	0 to rt	15 : 64%, 16 : 10%
SnCl_2 (3 equiv)	THF–MeOH (1:1)	None	rt to reflux	No reaction
SnCl_2 (3 equiv)	MeOH	1 N HCl (5 equiv)	rt	No reaction
Fe (3 equiv)	MeOH	1 N HCl (5 equiv)	70	No reaction
Mg (3 equiv)	THF–MeOH (1:1)	None	70	No reaction
Zn (3 equiv)	THF	4 N HCl (5 equiv)	0	17 : 33%, 16 + 18 : 24%
Zn (7.5 equiv)	THF	4 N HCl (9 equiv)	0	16 : 0%, 17 : 56%, 18 : 24%
Zn (7.5 equiv)	THF–EtOH (1:1)	4 N HCl (9 equiv)	0	16 : 0%, 17 : 79%, 18 : 14%

^aA mixture of *trans*–*trans* isomer **19** and *cis*–*trans* isomers.



Scheme 2. Synthesis of the key intermediate **4**. Reagents and conditions: (a) *n*-BuLi, 4-bromo-3-benzyloxyanisole **6**, THF, -60°C , ZnCl_2 , 40°C ; (b) CDI, DMF, rt; (c) (1) $\text{CH}_3\text{CO}_2t\text{-Bu}$, LDA, -70°C , (2) SiO_2 , CHCl_3 , rt; (d); 3,4-(methylenedioxy)phenylmagnesium bromide, THF, -78°C ; (e) Zn, 4N HCl in dioxane, THF, EtOH, 10°C ; (f) *tert*-BuOK, *tert*-BuOH, 60°C ; (g) H_2 , Pd/C, THF, MeOH, rt.

not lead to the deoxygenated products. In addition, it was revealed that the acid used with zinc was crucial to the course of the reaction. When **15** was treated with 3 equivalents of zinc in the presence of 5 equivalents of hydrogen chloride, the deoxygenation and reduction of the double bond occurred simultaneously to produce the *cis-cis* isomer **17** in 33% yield accompanied by **16**, a *trans-trans* isomer **19** and *cis-trans* isomers. Although the hydrogenation of **15** was completed with an increased amount of zinc (7.5 equiv) and hydrogen chloride (9 equiv), the ratio of the *cis-cis* isomer **17** to the other isomers was not satisfactory (5:2). Optimization of the reaction solvent revealed that using a mixture of THF and EtOH (1:1) as a solvent resulted in improvement in the ratio of **17** to **18** up to 5:1 as well as the yield (79%). When the deoxygenated intermediate **16** was treated with zinc powder (5 equiv) in the presence of hydrogen chloride (5 equiv), a mixture of the hydrogenated compound **17** and **18** was obtained in 98% yield in a ratio of 5:1. It is interesting to note that the thermodynamically less stable isomer **17** was obtained as a major product. Although the detailed mechanism of the reaction is not clear, the results suggested that the deoxygenation occurred at first to give **16**, in which the double bond may migrate via a 1,3 hydride shift, and then the double bond was reduced with the residual zinc. As a result, deoxygenation and hydrogenation of **15** were simultaneously achieved under mild conditions and the desired isomer **17** was exclusively isolated by crystallization of the crude mixture in 75% yield.

17 was completely epimerized to a thermodynamically more stable *trans-trans* isomer **19** in 93% yield by the

treatment with *tert*-BuOK in dioxane–*tert*-BuOH (1:1) at 60°C . Finally, the catalytic hydrogenation of **19** in the presence of 10% Pd on charcoal at 3 kg/cm² of pressure provided the key intermediate **4** in 89% yield.

In summary, we successfully developed a convenient method for the synthesis of the intermediate **4**. The key points of the method are as follows: (1) regioselectivity of the addition reaction of the aryl moiety to quinolic anhydride was improved by using arylzinc reagent generated in situ to provide the desired ketoacid **7** in 42% yield, (2) cyclization of **7** was achieved in 65% yield to give the enone **14** by the treatment of the corresponding acid imidazolidine **11** with the ester enolate followed by dehydration assisted with silica gel and (3) stereoselective hydrogenation of the allyl alcohol system in **15** was accomplished by using zinc in the presence of hydrogen chloride to afford the *cis-cis* isomer **17** in 75% yield. Through the method we developed, **4** was obtained in six steps with 13.4% overall yield from quinolic anhydride **5** without chromatographic purification (Scheme 2). This synthetic method enables us to do extensive derivatization of this class of compounds for potent endothelin receptor antagonists. The results of the derivatization will be reported in the near future.

Experimental

General

All reagents and solvents were of commercial quality and were used without further purification unless otherwise noted. Melting points were determined with a

Yanaco MP micromelting point apparatus and were not corrected. ^1H NMR spectra were recorded on a Varian Gemini-300 instrument at 300 MHz. Chemical shifts were reported in parts per million as δ units relative to tetramethylsilane as an internal standard. Mass spectra were recorded with fast atom bombardment (FAB) ionization on a JEOL JMS-SX 102A spectrometer. Thin layer chromatography was performed with E. Merck Kieselgel 60 F₂₅₄ plates (0.25 mm) and visualized with UV light or phosphomolybdic acid. Column chromatography was performed on Wako gel C-300.

3-Benzylloxy-4-bromoanisole (6). To a solution of 2-bromo-5-methoxyphenol⁷ (2330 g, 11.5 mol) in acetone (12.0 L) were added anhydrous K_2CO_3 (1590 g, 11.5 mol) and benzyl bromide (1970 g, 11.5 mol), and the mixture was stirred at 60 °C for 12 h. After the reaction mixture was cooled to room temperature, the insoluble material was removed by filtration. The filtrate was concentrated and the residual oil was distilled under reduced pressure (1–2 mmHg, 160–170 °C) to provide **6** (2100 g, 62% yield). ^1H NMR (CDCl_3): δ 3.75 (s, 3H), 5.12 (s, 2H), 6.40 (dd, $J=2.7$, 8.7 Hz, 1H), 6.52 (d, $J=2.7$ Hz, 1H), 7.22–7.53 (m, 5H), 7.42 (d, $J=8.7$ Hz, 1H); MS m/z 293 ($\text{M}+\text{H}$)⁺.

3-(2-Benzylloxy-4-methoxybenzoyl)-2-(methoxycarbonyl)pyridine (9) and 2-(2-Benzylloxy-4-methoxybenzoyl)-3-(methoxycarbonyl)pyridine (10). To a solution of **5** (12.37 g, 42.2 mmol) in THF (80 mL) was added a 1.66 M solution of *n*-butyllithium in hexane (25.4 mL, 42.2 mmol) at –78 °C, and the mixture was stirred at the same temperature for 1 h. To a solution of quinolinic anhydride (6.29 g, 42.2 mmol) in THF (210 mL) was added the solution described above at –78 °C. After being stirred for 30 min, the mixture was quenched with 1 N HCl (200 mL), and was extracted with EtOAc (2×300 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. To a solution of the residue in CH_2Cl_2 (17 mL) and MeOH (83 mL) were added 4-(dimethylamino)pyridine (733 mg, 6.00 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (9.71 g, 50.7 mmol) at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was washed with saturated NaHCO_3 solution, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated. The regioisomers were separated by column chromatography on silica gel to give the methyl ester **9** (5.74 g, 36%) and **10** (4.66 g, 29%). **9**: ^1H NMR (CDCl_3) δ 3.76 (s, 3H), 3.86 (s, 3H), 4.67 (s, 2H), 6.43 (d, $J=2.3$ Hz, 1H), 6.65 (dd, $J=2.3$, 8.8 Hz, 1H), 6.90–6.93 (m, 2H), 6.97 (dd, $J=4.9$, 7.9 Hz, 1H), 7.19–7.28 (m, 3H), 7.80 (dd, $J=1.6$, 7.9 Hz, 1H), 8.17 (d, $J=8.8$ Hz, 1H), 8.47 (dd, $J=1.6$, 4.9 Hz, 1H); HRMS calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_5$ ($\text{M}+\text{H}$)⁺: 378.1341. Found 378.1349. **10**: ^1H NMR (CDCl_3) δ 3.79 (3H, s), 3.86 (3H, s), 4.74 (2H, s), 6.44 (1H, d, $J=2.3$ Hz), 6.64 (dd, $J=2.3$, 8.8 Hz, 1H), 6.926.95 (m, 2H), 7.20 (dd, $J=4.8$, 7.8 Hz, 1H), 7.23–7.29 (m, 3H), 7.57 (dd, $J=1.7$, 7.8 Hz, 1H), 8.04 (d, $J=8.8$ Hz, 1H), 8.41 (dd, $J=1.7$, 4.8 Hz, 1H); HRMS calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_5$ ($\text{M}+\text{H}$)⁺: 378.1341. Found 378.1335.

3-(2-Benzylloxy-4-methoxybenzoyl)-2-pyridinecarboxylic acid (8). To a solution of the methyl ester **10** (4.66 g, mmol) in MeOH (90 mL) and dioxane (10 mL) was added 6 N NaOH (9.0 mL), and the mixture was stirred at room temperature overnight. After removal of MeOH under reduced pressure, the residual solution was neutralized with 2 N HCl (30 mL). The resulting precipitate was collected by filtration, washed with acetone followed by Et_2O , and dried under reduced pressure to give the corresponding carboxylic acid **8** (5.27 g, 95% yield). mp: 165–166 °C (dec.); MS m/z 364 ($\text{M}+\text{H}$)⁺. Anal. calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.76; H, 4.59; N, 3.82.

2-(2-Benzylloxy-4-methoxybenzoyl)-3-pyridinecarboxylic acid (7). To a solution of 4-bromo-3-benzylloxylanisole **6** (1050 g, 3.58 mol) in THF (10 L) was added a 1.58 M solution of *n*-butyllithium in hexane (3.0 L, 4.74 mol) at –60 to –65 °C, and the mixture was stirred at –65 °C for 1 h. To that solution was added ZnCl_2 (683 g, 5.01 mol) at –65 °C, and the resulting mixture was warmed to 30 °C over 1 h. To the mixture was added quinolinic anhydride (534 g, 3.58 mol), and the mixture was stirred at 40 °C overnight. The mixture was quenched with 2 N HCl (5.0 L), and was stirred at room temperature for 2 days. The resulting precipitate was collected by filtration, washed with 2 N HCl (2.0 L) followed by acetone (2.0 L) and Et_2O (2.0 L), and dried under reduced pressure to give **7** (546 g, 42% yield). mp: 213–214 °C (dec.); ^1H NMR (CD_3OD) δ 3.88 (s, 3H), 4.73 (s, 2H), 6.61 (d, $J=2.3$ Hz, 1H), 6.72 (dd, $J=2.3$ and 8.9 Hz, 1H), 6.92–7.00 (m, 2H), 7.12 (dd, $J=4.9$, 7.8 Hz, 1H), 7.21–7.30 (m, 3H), 7.95 (dd, $J=1.7$, 7.8 Hz, 1H), 8.07 (d, $J=8.9$ Hz, 1H), 8.38 (dd, $J=1.7$, 4.9 Hz, 1H), MS m/z 364 ($\text{M}+\text{H}$)⁺. Anal. calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.15; H, 4.61; N, 3.78.

2-(2-Benzylloxy-4-methoxybenzoyl)-3-(1-imidazolyl)carbonylpyridine (11). To an ice-cooled solution of **7** (2160 g, 5.94 mol) in DMF (3.0 L) was added carbonyldiimidazole (1200 g, 7.40 mol), and the mixture was stirred at room temperature for 2.5 h. The mixture was poured into ice-cooled water (20.0 L), and the resulting precipitate was collected by filtration, washed with water (2.0 L) followed by diethyl ether (2.0 L), and dried at 50 °C under reduced pressure (3–5 mmHg) to give **11** (2140 g, 87% yield). mp: 167–169 °C (dec.); ^1H NMR (CDCl_3) δ 3.78 (s, 3H), 4.46 (d, $J=10.2$ Hz, 1H), 4.76 (d, $J=10.2$ Hz, 1H), 6.36 (d, $J=8.5$ Hz, 1H), 6.41 (dd, $J=2.2$, 8.5 Hz, 1H), 6.45 (d, $J=2.2$ Hz, 1H), 6.93–6.97 (m, 2H), 7.14 (brs, 1H), 7.19 (dd, $J=4.8$, 7.8 Hz, 1H), 7.277.34 (m, 3H), 7.46 (br s, 1H), 7.53 (dd, $J=1.5$, 7.8 Hz, 1H), 8.03 (br s, 1H), 8.73 (dd, $J=1.5$, 4.8 Hz, 1H); MS m/z 426 ($\text{M}+\text{H}$)⁺. Anal. calcd for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_4 \cdot 0.15\text{H}_2\text{O}$: C, 69.27; H, 4.67; N, 10.10. Found: C, 69.11; H, 4.59; N, 10.08.

7-(2-Benzylloxy-4-methoxyphenyl)-6-tert-butoxycarbonyl-7-hydroxy-5-oxocyclopenteno[1,2-*b*]pyridine (13). To a solution of diisopropylamine (0.103 mL, 0.73 mmol) in THF (1.0 mL) was added a 1.59 M solution of *n*-butyllithium in hexane (0.46 mL, 0.73 mmol) at –78 °C, and the mixture was stirred at 0 °C for 15 min. To that

solution was added *tert*-butyl acetate (0.104 mL, 0.77 mmol) at -78°C , and the mixture was stirred at the same temperature for 30 min. To that solution was added a solution of **11** (202 mg, 0.49 mmol) in THF (2.4 mL) at -78°C , and the mixture was stirred at the same temperature for additional 30 min. The mixture was quenched with saturated NH_4Cl solution, and was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , and concentrated to give the fused alcohol **13** (220 mg). ^1H NMR (CDCl_3) δ 1.47 (s, 9H), 3.80 (s, 3H), 4.13 (s, 1H), 4.52 (d, $J=10.8$ Hz, 1H), 4.76 (d, $J=10.8$ Hz, 1H), 6.44 (d, $J=2.3$ Hz, 1H), 6.62 (dd, $J=2.3, 8.6$ Hz, 1H), 6.78 (dd, $J=1.2, 7.8$ Hz, 1H), 7.17–7.25 (m, 5H), 7.67 (dd, $J=1.5, 7.8$ Hz, 1H), 7.85 (d, $J=8.7$ Hz, 1H), 8.71 (dd, $J=1.2, 1.5$ Hz, 1H); MS m/z 462 ($\text{M}+\text{H}$) $^+$.

The resulting crude material described above was dissolved in CHCl_3 (5 mL), and SiO_2 (5 mL) was added to the solution. After being vigorously stirred at room temperature overnight, the SiO_2 was filtered off, and washed with EtOAc (30 mL). The filtrate and washings were combined and concentrated. The residue was washed with hexane–EtOAc (10:1, 10 mL) to yield enone **14** as an orange solid (184 mg, 85% yield).

7-(2-Benzoyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-oxocyclopenta-1,3-dienol[2,1-*b*]pyridine (14). To a solution of diisopropylamine (586 mL, 4.18 mol) in THF (3.8 L) was added a 1.54 M solution of *n*-butyllithium in hexane (2.71 L, 4.17 mol) at -70°C , and the mixture was stirred at the same temperature for 1 h. To that solution was added *tert*-butyl acetate (580 mL, 4.30 mol) at -70°C , and the mixture was stirred at the same temperature for 1 h. To a solution of **11** (1150 g, 2.78 mol) in THF (10.0 L) was added the enolate solution described above via canula at -70 to -60°C . After being stirred at -70°C for 30 min, the mixture was quenched with saturated NH_4Cl solution (500 mL). After being warmed to room temperature, the mixture was extracted with EtOAc (12 L). The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated. To a solution of the residue in CHCl_3 (5.0 L) was added silica gel (Merck 7734, 2.0 L), and the mixture was stirred at room temperature overnight. The silica gel was filtered off, and washed with EtOAc (5.0 L). The filtrate and washings were combined and concentrated. The residue was crystallized from MeOH to give **14** (800 g, 65% yield). mp: $147\text{--}148^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.35 (s, 9H), 3.84 (s, 3H), 5.09 (s, 2H), 6.62 (d, $J=2.3$ Hz, 1H), 6.67 (dd, $J=2.3, 8.6$ Hz, 1H), 7.22 (dd, $J=5.3, 7.4$ Hz, 1H), 7.24 (brs, 5H), 7.56 (d, $J=8.6$ Hz, 1H), 7.78 (dd, $J=1.5, 7.4$ Hz, 1H), 8.55 (dd, $J=1.5, 5.3$ Hz, 1H); MS m/z 444 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{27}\text{H}_{25}\text{NO}_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.19; H, 5.71; N, 3.18.

7-(2-Benzoyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-5-hydroxycyclopenta-1,3-dienol[2,1-*b*]pyridine (15). To a solution of the enone **14** (467 g, 1.05 mol) in THF (3.0 L) was added a 2.34 M solution of (3,4-methylenedioxyphenyl)magnesium bromide in

THF (650 mL, 1.52 mol) prepared from 4-bromo-1,2-(methylenedioxy)benzene (382 g, 1.90 mol) and magnesium turnings (48.6 g, 2.00 mol) at -78°C , and the mixture was stirred at the same temperature for 15 min. The mixture was quenched with saturated NH_4Cl solution (4 L), and was extracted with EtOAc (3×5.0 L). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was crystallized from hexane–EtOAc (5:1) to give **15** (542 g, 91% yield). mp: $151\text{--}152^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.17 (s, 9H), 3.85 (s, 3H), 4.40 (br s, 1H), 5.06 (s, 2H), 5.89 (s, 2H), 6.37–6.49 (br s, 1H), 6.65–6.67 (m, 2H), 6.86–6.93 (br s, 1H), 7.09 (dd, $J=4.9, 7.6$ Hz, 1H), 7.11 (br s, 1H), 7.21–7.27 (m, 5H), 7.32–7.42 (br s, 1H), 7.51 (dd, $J=1.8, 7.6$ Hz, 1H), 8.47 (dd, $J=1.8, 7.9$ Hz, 1H); MS m/z 566 ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{27}\text{H}_{25}\text{NO}_7\cdot 0.25$ hexane: C, 72.62; H, 5.92; N, 2.39. Found: C, 72.89; H, 5.62; N, 2.46.

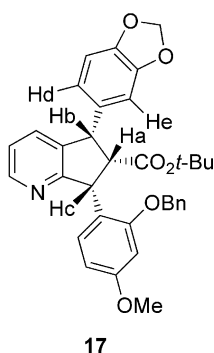
Reduction of 15 with zinc in the presence of 9 equivalents of hydrogen chloride. To a suspension of **15** (3.34 g, 5.91 mmol) and zinc powder (2.90 g, 44.4 mmol) in THF (30 mL) and EtOH (30 mL) was added dropwise a 4 N solution of HCl in dioxane (13.3 mL) at 0°C . After being stirred at 0°C for 1 h, the mixture was neutralized with saturated NaHCO_3 solution. The insoluble material was removed by filtration and the filtrate was extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over MgSO_4 , and concentrated. The residue was crystallized from hexane–EtOAc (1:1) to give **17** (2.48 g, 76% yield). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to provide the second crop of **17** (0.10 g, 3% yield) and an inseparable mixture **18** (0.45 g, 14% yield) containing the *cis*–*trans* isomers and the *trans*–*trans* isomer **19** in a ratio of 7:3 by ^1H NMR.

Reduction of 15 with zinc via an intermediate 16. To a suspension of **15** (730 mg, 1.29 mmol) and zinc powder (253 mg, 3.87 mmol) in THF (10 mL) was added AcOH (0.390 mL, 6.81 mmol) at 0°C . After being stirred at the same temperature for 1 h, the mixture was neutralized with saturated NaHCO_3 solution, and was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , and concentrated. The residue was purified by column chromatography on silica gel eluting with 33% EtOAc/hexane to give the deoxy product **16** (73 mg, 10% yield) and the starting material **15** (465 mg, 64% recovery). **16**: MS m/z 550 ($\text{M}+\text{H}$) $^+$.

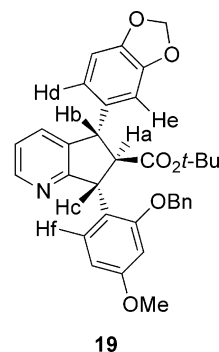
To a suspension of **16** (73 mg, 0.13 mmol) and zinc powder (43 mg, 0.65 mmol) in THF (2.0 mL) was added 4 N HCl in dioxane (0.17 mL, 0.68 mmol) at 0°C , and the mixture was stirred at the same temperature for 30 min. The mixture was neutralized with saturated NaHCO_3 solution, and was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , and concentrated. The residue (69 mg) was elucidated to be a mixture of **17** and **18** in a ratio of 5:1 by ^1H NMR.

(5*RS*,6*RS*,7*SR*)-7-(2-Benzoyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (17). To a stirred suspension of **15** (377g,

667 mmol) and zinc powder (327 g, 5.00 mol) in THF (2.0 L) and EtOH (2.0 L) was added 4 N HCl in dioxane (1.5 L) below 10 °C over 1.5 h. After the addition was completed, the mixture was neutralized with saturated Na₂CO₃ solution (1.5 L) and NaHCO₃ powder. The resulting mixture was filtered through a pad of Celite, and the filtrate was extracted with CHCl₃ (10 L). The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was crystallized from hexane–EtOAc (2:1) to give **17** as a colorless solid (276 g, 75% yield). mp: 169–170 °C; ¹H NMR (CDCl₃) δ 0.82 (s, 9H), 3.74 (s, 3H), 3.98 (t, *J* = 7.8 Hz, 1H), 4.67 (d, *J* = 7.8 Hz, 1H), 5.11 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 2H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 6.46–6.50 (m, 2H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.86–6.88 (m, 2H), 7.12–7.17 (m, 1H), 7.32–7.54 (m, 7H), 8.49–8.52 (m, 1H); The NOEs were observed between δ 3.98 (Ha) and δ 4.67 (Hb), δ 3.98 (Ha) and δ 5.11 (Hc), δ 4.67 (Hb) and δ 5.11 (Hc), δ 4.67 (Hb) and δ 6.87 (Hd), δ 4.67 (Hb) and δ 6.86 (He). MS *m/z* 552 (M + H)⁺. Anal. calcd for C₃₄H₃₃NO₆: C, 74.03; H, 6.03; N, 2.54. Found: C, 74.40; H, 6.18; N, 2.57.



(5S,6SR,7SR)-7-(2-Benzyloxy-4-methoxyphenyl)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (19). To a solution of **17** (540 g, 979 mmol) in dioxane (2.5 L) and *tert*-BuOH (2.5 L) was added *tert*-BuOK (11.0 g, 98.0 mmol), and the mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture was partitioned between EtOAc (2.5 L) and H₂O (2.5 L). The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was crystallized from hexane–EtOAc (4:1) to give **19** (501 g, 93% yield). mp: 160–161 °C; ¹H NMR (CDCl₃) δ 1.30 (s, 9H), 3.47 (t, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 4.42 (d, *J* = 10.5 Hz, 1H), 4.62 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 10.6 Hz, 1H), 4.85 (d, *J* = 10.6 Hz, 1H), 5.90 (s, 2H), 6.22 (dd, *J* = 1.7, 8.0 Hz, 1H), 6.29 (d, *J* = 1.7 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 6.52 (dd, *J* = 2.4, 7.9 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.82–6.88 (m, 2H), 7.09–7.11 (m, 2H), 7.16–7.26 (m, 4H), 8.45–8.48 (m, 1H); The NOEs were observed between δ 3.47 (Ha) and δ 6.22 (Hd), δ 3.47 (Ha) and δ 6.29 (He), δ 4.42 (Hb) and δ 4.62 (Hc), δ 4.42 (Hb) and δ 6.22 (Hd), δ 4.42 (Hb) and δ 6.29 (He), δ 4.62 (Hc) and δ 7.19 (Hf). MS *m/z* 552 (M + H)⁺. Anal. calcd for C₃₄H₃₃NO₆·0.3 hexane: C, 74.46; H, 6.49; N, 2.42. Found: C, 74.69; H, 6.19; N, 2.54.



(5S,6SR,7SR)-6-tert-butoxycarbonyl-7-(2-Hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (4). To a suspension of **19** (345 g, 625 mmol) in THF (2.0 L) and MeOH (2.0 L) was added 10% Pd/C (50 wt% H₂O, 345 g), and the mixture was hydrogenated at 3 atm of pressure at room temperature overnight. The mixture was filtered through a pad of Celite, washed with THF, and the filtrate was concentrated. The residue was crystallized from EtOAc–hexane, and the crystalline solid was collected by filtration, and dried in vacuo at 40 °C to give **4** as a pale brown solid (258 g, 89% yield). mp: 167–168 °C; ¹H NMR (CDCl₃) δ 1.39 (s, 9H), 3.55 (dd, *J* = 9.8, 10.2 Hz, 1H), 3.77 (s, 3H), 4.56 (d, *J* = 9.8 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 5.97 (s, 2H), 6.44 (dd, *J* = 2.6, 8.6 Hz, 1H), 6.61 (d, *J* = 2.6 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.72 (dd, *J* = 1.7, 7.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 7.16 (dd, *J* = 5.0, 7.7 Hz, 1H), 7.35 (dd, *J* = 1.4, 7.7 Hz, 1H), 8.37 (dd, *J* = 5.0, 7.7 Hz, 1H); MS *m/z* 462 (M + H)⁺. Anal. calcd for C₂₇H₂₇NO₆·0.2 hexane: C, 70.75; H, 6.27; N, 2.93. Found: C, 70.97; H, 5.95; N, 3.12.

6-tert-Butoxycarbonyl-5-hydroxy-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (20). To a solution of **15** (1.00 g, 1.77 mmol) in THF (20 mL) and MeOH (20 mL) was added 10% Pd on carbon (300 mg), and the mixture was hydrogenated at atmospheric pressure at room temperature overnight. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to give **20** as a pale yellow solid (697 mg, 83% yield). ¹H NMR (CDCl₃) δ 0.88 (s, 9H), 3.74 (s, 3H), 3.90 (d, *J* = 6.3 Hz, 1H), 5.34 (d, *J* = 6.3 Hz, 1H), 5.97 (s, 2H), 6.35 (dd, *J* = 2.7, 8.6 Hz, 1H), 6.46 (d, *J* = 2.7 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.29 (m, 1H), 7.68 (dd, *J* = 1.5, 7.6 Hz, 1H), 8.51 (dd, *J* = 1.5, 5.1 Hz, 1H); MS *m/z* 478 (M + H)⁺.

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6. In order to identify each structure of the product **7** and **8**, they were converted to the corresponding methyl ester **9** and **10** and separated by column chromatography on silica gel to determine the ratio of the isomers via the reaction.
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