Studies on Quinoline and Isoquinoline Derivatives. IX.¹
Synthesis of Pyrrolo[1,2-β]isoquinolines from
3-Bromoisoquinoline Derivatives

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The reaction of 3-bromo-1-methoxyisoquinoline with propargyl alcohol in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide gave 3-(1-methoxy-3-isoquinolyl)propargyl alcohol in good yield. Cyclization of 3-(1-methoxy-3-isoquinolyl)propanol obtained by the catalytic reduction of the propargyl alcohol, afforded a 1,2,3,5-tetrahydropyrrolo[1,2-β]isoquinoline derivative. The synthesis of a pyrrolo[3,2,1-de]phenanthridine derivative was accomplished by the introduction of an acrylic acid moiety into the pyrrolo[1,2-β]isoquinoline and subsequent reduction and cyclization of the resulting ethyl pyrrolo[1,2-β]isoquinoline-10-acrylate.

Keywords—palladium-catalyzed reaction; dichlorobis(triphenylphosphine)palladium; carbon–carbon bond formation; cyclization reaction; bromination; intramolecular Grignard reaction; pyrrolo[1,2-β]isoquinoline; pyrrolo[3,2,1-de]phenanthridine; 1,3-dibromoisoquinoline

During our investigation on the palladium-catalyzed reaction of haloisoquinolines with terminal olefins or acetylenes,²,³ this type of reaction was found to be a practical method for the synthesis of isoquinoline derivatives having a carbon substituent at the 3-position. As an application of the above-mentioned findings, this paper deals with the synthesis of pyrrolo[1,2-β]isoquinoline and pyrrolo[3,2,1-de]phenanthridine derivatives from 3-bromoisoquinolines using such palladium-catalyzed reactions and subsequent cyclizations.

First, the synthesis of 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-β]isoquinoline (10) was investigated. When 1,3-dibromoisoquinoline (1)⁴ was treated with propargyl alcohol in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine,⁵ colorless needles (2) of mp 134—135 °C were obtained in good yield. The spectral data and elemental analysis of the product showed the compound to contain a 3-hydroxypropynyl group and a bromine atom. Catalytic reduction of the product (2) gave 3-(1-isooquinolyl)propanol (3), which was identical with an authentic specimen prepared from 3-(1-isooquinolyl)propargyl alcohol.²

Similarly, 1 reacted with ethyl acrylate in the presence of palladium acetate and triphenylphosphine in triethylamine⁶ to give colorless needles of mp 112—113.5 °C, although in this case a considerable amount (63%) of the starting material was recovered. Catalytic reduction of ethyl 3-bromo-1-isooquinolyl-trans-acyrate (4) thus obtained afforded ethyl 1-isooquinolylpropanonate (5), whose structure was determined by proton nuclear magnetic resonance (¹H-NMR) spectroscopy. These results demonstrated that in the 1,3-dibromoisoquinoline system, the reaction occurred at the 1-position rather than the 3-position.

Thus, in order to introduce the necessary substituent into the 3-position, 1 was transformed into 3-bromo-1-methoxyisoquinoline (6) prior to the palladium-catalyzed reaction with propargyl alcohol. The reaction of 6 and propargyl alcohol under similar conditions to the above gave 3-(1-methoxy-3-isooquinolyl)propargyl alcohol (7), as expected. On treatment with phosphorus tribromide in chloroform, 3-(1-methoxy-3-isooquinolyl)-
propanol (9), which was obtained by the catalytic reduction of 7 over palladium charcoal, was readily cyclized to the pyrrolo[1,2-b]isoquinoline (10), together with a small amount of 3-(3-bromopropyl)-1-isoquinolone (11). Compound 11 was dehydrobrominated with sodium amide in benzene to give 10 in good yield. In addition, the reaction of 6 with ethyl acrylate in the presence of palladium (II) acetate and triphenylphosphine gave the ethyl 1-methoxy-3-isoquinolino-trans-acrylate (8), in which the geometry of the side chain was determined by $^1$H-NMR spectrometry.

Next, the transformation of 10 into a derivative of pyrrolo[3,2,1-de]phenanthridine (22) was examined as follows. When 10 was brominated with a limited amount of N-bromosuccinimide (NBS) in carbon tetrachloride, a monobromide (12) was obtained as a sole product. The subsequent bromination of 12 with the same reagent gave the dibromide (13). On the other hand, the oxidation of 10 with selenium dioxide gave the 1-hydroxypyrrolo[1,2-b]isoquinoline (14), which on treatment with phosphorus tribromide was converted to the positional isomer (15) of the bromide (12).

Then, the reaction of these bromides (12, 13, and 15) with ethyl acrylate were tested to find a suitable route for the construction of the pyrrolo[3,2,1-de]phenanthridine ring. Although the reaction of 13 and that of 15 both failed to give the desired products, the reaction of 12 with ethyl acrylate was successfully achieved to give compound 16 under similar conditions to the case of 6. In order to synthesize 18 by intramolecular condensation, 16 was reduced to the saturated compound (17), but 17 was unchanged by treatment with sodium amide, and 18 was not obtained. Thus, before the reduction of the acrylate moiety in 16, compound 16 was oxidized with selenium dioxide to give the hydroxy-ester (19). The hydroxyester (19) was reduced to the saturated hydroxy-ester (20) by catalytic reduction over palladium-charcoal catalyst.
Finally, the synthesis of the pyrrolo[3,2,1-de]phenanthridine (21) was accomplished by intramolecular Grignard reaction. Namely, 20 was brominated by treatment with phosphorus tribromide, and the resultant bromo-ester (21) was allowed to react with magnesium foil in tetrahydrofuran. The usual work-up of the reaction mixture afforded 3-ethoxy-7-oxo-2,4,5,7-tetrahydro-1H-pyrrolo[3,2,1-de]phenanthridine (22) as a main product, together with a small amount of 17.

The structures of all the products described above were supported by the spectral data and the satisfactory elemental analyses.

**Experimental**

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. $^1$H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in $\delta$ value. The following abbreviations are used: $s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, quint = quintet, $m$ = multiplet, $br$ = broad, and $bs$ = broad singlet. Mass spectra (MS) were taken on a Hitachi M-52G spectrometer.

3-(3-Bromo-1-isouinoly)propargyl Alcohol (2)—A mixture of 1,3-dibromoisoquinoline (I) (800 mg, 2.8 mmol), propargyl alcohol (170 mg, 3 mmol), Pd(PP$_3$)$_2$Cl$_2$ (50 mg), Cul (25 mg), and Et$_3$N (20 ml) was stirred for 13.5 h at room temperature. After removal of the resulting precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO$_2$ column chromatography using CHCl$_3$ as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 134–135 °C. Yield 650 mg (89%). IR $\nu_{\text{max}}$ cm$^{-1}$: 3620, 2240. $^1$H-NMR (CDCl$_3$): 3.97 (1H, s), 4.45 (2H, s), 7.35–8.00 (4H, m), 8.15–8.40 (1H, m). Anal. Calcd for C$_{12}$H$_8$BrNO: C, 54.99; H, 3.08; Br, 30.49; N, 5.35. Found: C, 54.88; H, 3.07; Br, 30.14; N, 5.31.

3-(1-Isouinoly)propanol (3)—Catalytic Reduction of 2: A mixture of 2 (120 mg, 0.46 mmol), 10% Pd-C (400 mg), and MeOH (20 ml) was shaken in an H$_2$ stream at room temperature. After absorption of H$_2$ had ceased (44 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short Al$_2$O$_3$ column using CHCl$_3$ as an eluent. The residual oil was distilled under reduced pressure to give a colorless liquid, bp 191–198 °C (1 mmHg). Yield 65 mg (76%). IR $\nu_{\text{max}}$ cm$^{-1}$: 3640.
i) Catalytic Reduction of 3-(1-Isoquinolyl)propargyl Alcohol: A mixture of 3-(1-isooquinolyl)propargyl alcohol (900 mg, 5 mmol), 10% Pd-C (2.0 g), and MeOH (20 ml) was shaken in an H₂ stream at room temperature. After absorption of H₂ had ceased (230 ml), the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to give a colorless liquid, which was distilled under reduced pressure. Yield 650 mg (71%).

Ethyl 3-Bromo-1-isooquinoline-trans-acrylate (4) —— A mixture of 1 (800 mg, 2.8 mmol), ethyl acrylate (330 mg, 3.3 mmol), Pd(OAc)₂ (25 mg), PPh₃ (50 mg), and Et₃N (5 ml) was heated in a sealed tube at 120 °C for 20 h. After removal of the resulting precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO₂ column chromatography using C₆H₆ as an eluent. The first fraction gave the starting material (500 mg, 63%), and the second fraction afforded colorless needles (4) (110 mg, 13%), which were recrystallized from acetone–hexane. mp 112—113.5 °C. IR ν(C=O) cm⁻¹: 1720, 970. ¹H-NMR (CDCl₃): 1.25 (3H, t, J = 7.0 Hz), 4.66 (2H, q, J = 7.0 Hz), 7.13 (1H, d, J = 16.0 Hz), 7.30—7.90 (4H, m), 7.90—8.30 (1H, m), 8.20 (1H, d, J = 16 Hz). Anal. Calcd for C₁₂H₁₂BrNO: C, 54.92; H, 3.95; Br, 26.10; N, 4.58. Found: C, 54.76; H, 4.00; Br, 26.05; N, 4.63.

Ethyl 1-Isoquinolinepropanoate (5) —— A mixture of 4 (70 mg, 0.23 mmol), 10% Pd-C (0.2 g), and MeOH (10 ml) was shaken in an H₂ stream at room temperature. After absorption of H₂ had ceased (20 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short Al₂O₃ column using CHCl₃ as an eluent. The residual oil was distilled under reduced pressure to give a colorless liquid, bp 145—150 °C (2 mmHg). Yield 30 mg (57%). IR ν(C=O) cm⁻¹: 1725. ¹H-NMR (CDCl₃): 1.23 (3H, t, J = 7.0 Hz), 2.70—3.13 (2H, m), 3.34—3.80 (2H, m), 4.12 (2H, q, J = 7.0 Hz), 7.40—8.00 (4H, m), 8.80—8.40 (1H, m), 8.45 (1H, d, J = 6.0 Hz). Anal. Calcd for C₁₄H₁₄NO₂: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.34; H, 6.62; N, 6.01.

3-Bromo-1-methoxyisoquinoline (6) —— A solution of 1 (10.5 g, 36 mmol) in dioxane (70 ml) was added to a solution of NaOme–MeOH [prepared from Na (1.2 g, 50 mmol) and dry MeOH (60 ml)] and the mixture was refluxed for 1.5 h. After absorption of H₂ had ceased (20 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was washed with a small amount of CHCl₃ and the mixture was filtered. The residue was recrystallized from acetone–hexane to give colorless needles, mp 73—74 °C. Yield 8.0 g (92%). ¹H-NMR (CDCl₃): 4.06 (3H, s), 7.20—7.88 (4H, m), 7.97—8.30 (1H, m). Anal. Calcd for C₁₀H₇BrNO: C, 50.44; H, 3.39; Br, 33.56; N, 5.88. Found: C, 50.64; H, 3.33; Br, 33.22; N, 5.87.

3-(1-Methoxy-3-isooquinolyl)propargyl Alcohol (7) —— A mixture of 6 (4.92 g, 20 mmol), propargyl alcohol (1.80 g, 34 mmol), Pd(PPh₃)₄Cl₂ (300 mg), Cu (150 mg), and Et₃N (80 ml) was refluxed for 16 h. After removal of the precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al₂O₃ column chromatography using CHCl₃ as an eluent. Recrystallization from hexane–acetone gave pale yellow needles, mp 94—95 °C. Yield 3.9 g (89%). IR ν(C=O) cm⁻¹: 3635. ¹H-NMR (CDCl₃): 3.00—3.56 (1H, br), 4.12 (3H, s), 4.60 (2H, s), 7.06—7.85 (4H, m), 7.85—8.28 (1H, m). Anal. Calcd for C₁₃H₁₁NO₂: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.93; H, 5.19; N, 6.39.

Ethyl 1-Methoxy-3-isooquinoline-trans-acrylate (8) —— A mixture of 6 (450 mg, 1.9 mmol), ethyl acrylate (380 mg, 3.8 mmol), Pd(OAc)₂ (30 mg), PPh₃ (60 mg), and Et₃N (3.0 ml) was heated in a sealed tube at 120 °C for 22 h. The precipitate was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO₂ column chromatography using CHCl₃ as an eluent. Recrystallization from hexane–ether gave colorless needles, mp 84—85 °C. Yield 410 mg (84%). IR ν(C=O) cm⁻¹: 1710, 985. ¹H-NMR (CDCl₃): 1.37 (3H, t, J = 7.0 Hz), 4.06 (3H, s), 4.21 (2H, q, J = 7.0 Hz), 6.98 (1H, d, J = 17.0 Hz), 7.12 (1H, s), 7.20—7.90 (4H, m), 7.90—8.30 (1H, m). Anal. Calcd for C₁₄H₁₂NO₂: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.07; H, 6.12; N, 5.49.

3-(1-Methoxy-3-isooquinolyl)propanol (9) —— A mixture of 7 (5.60 g, 26.3 mmol), 10% Pd-C, and MeOH (60 ml) was shaken in a stream of H₂ at room temperature. After absorption of H₂ (1400 ml) had ceased the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al₂O₃ column chromatography using CHCl₃ as an eluent. The residual oil was distilled under reduced pressure to give a colorless viscous liquid, bp 170—172 °C (1 mmHg). Yield 5.18 g (92%). IR ν(C=O) cm⁻¹: 3600. ¹H-NMR (CDCl₃): 2.00 (2H, quint, J = 6.0 Hz), 2.90 (2H, t, J = 6.0 Hz), 3.73 (2H, t, J = 6.0 Hz), 3.70—4.05 (1H, br), 4.07 (3H, s), 6.96 (1H, s), 7.23—7.70 (3H, m), 7.96—8.35 (1H, m). Anal. Calcd for C₁₃H₁₂NO₂: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.11; H, 6.88; N, 6.44.

Reaction of 9 with Phosphorus Tribromide —— Phosphorus tribromide (5.2 g, 19 mmol) was slowly added to a solution of 9 (3.40 g, 16 mmol) in CHCl₃ (40 ml) with stirring at 0—5 °C, and the mixture was refluxed for 20 h. After concentration to dryness under reduced pressure, a small amount of ice was added to the residue. The aqueous layer was made alkaline with K₂CO₃ and extracted with CHCl₃. Removal of the CHCl₃ gave the crude product, which was purified by Al₂O₃ column chromatography using C₆H₆ and C₆H₆-CHCl₃ (10:1). The C₆H₆ fraction gave 5-oxo-1,2,3,5-tetrahydropyrrol[1,2-b]isoquinoline (10) as colorless needles, which were recrystallized from hexane–acetone. mp 123—124 °C. Yield 1.98 g (68%). IR ν(C=O) cm⁻¹: 1670. ¹H-NMR (CDCl₃): 2.15 (2H, quint, J = 7.0 Hz), 3.03 (2H, t, J = 7.0 Hz), 4.12 (2H, t, J = 7.0 Hz), 6.31 (1H, s), 7.20—7.80 (3H, m), 8.25—8.53 (1H, m). Anal. Calcd for

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C₅H₁₁NO: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.59; H, 5.95; N, 7.65. The C₅H₆-CHCl₃ (10:1) fraction afforded colorless needles, 3-(3-bromopropyl)isoquinolin-1-(2H)-one (11), which were recrystallized from hexane-acetone. mp 184.5—185°C. Yield 0.32 g (80%). IR ν(CHCl) cm⁻¹: 3400, 1660. ¹H-NMR (CDCl₃): 2.20—2.67 (2H, m), 2.89 (2H, t, J = 7.0 Hz), 3.15 (2H, t, J = 7.0 Hz), 6.40 (1H, s), 7.05—8.08 (3H, m), 8.40 (1H, d, J = 8.0 Hz), 12.00—12.85 (1H, br). Anal. Calcd for C₁₅H₁₁BrNO: C, 54.15; H, 4.51; N, 5.26; Br, 30.02. Found: C, 54.62; H, 4.57; N, 5.28; Br, 29.62.

5-Oxo-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinoline from 11 — A solution of 11 (1.5 g, 5.6 mmol) in C₅H₆ (10 ml) was added to a suspension of NaN₃ (0.65 g, 17 mmol) in CCl₄ (20 ml) with stirring at room temperature and the mixture was stirred for 24 h, then concentrated to dryness under reduced pressure. A small amount of ice was added to the residue, and the aqueous layer was extracted with CHCl₃. Removal of the CHCl₃ gave the crude product, which was purified by Al₂O₃ column chromatography using C₅H₆-CHCl₃ (2:1) as an eluent. Recrystallization from acetone–hexane gave colorless needles. mp 123—124°C. Yield 0.96 g (92%).

10-Bromo-5-oxo-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinoline (12) — N-Bromosuccinimide (0.95 g, 5.3 mmol) was added to a solution of 10 (0.9 g, 5 mmol) in CCl₄ (15 ml) during 2 h under refluxing, and the mixture was refluxed for 1 h, then concentrated to dryness under reduced pressure. H₂O (20 ml) was added to the residue, and the aqueous layer was extracted with CHCl₃. The CHCl₃ extract was obtained through a short column of Al₂O₃ using CHCl₃ as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 141—142°C. Yield 1.15 g (90%). IR ν(CHCl) cm⁻¹: 1650. ¹H-NMR (CDCl₃): 2.17 (2H, quint, J = 7.0 Hz), 3.12 (2H, t, J = 7.0 Hz), 4.21 (2H, t, J = 7.0 Hz), 7.05—7.90 (3H, m), 8.06—8.50 (1H, m). Anal. Calcd for C₁₅H₁₁BrNO: C, 54.57; H, 3.78; Br, 30.25; N, 5.30. Found: C, 54.56; H, 3.73; Br, 30.06; N, 5.29.

1,10-Dibromo-5-oxo-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinoline (13) — N-Bromosuccinimide (660 mg, 3.7 mmol) was added to a solution of 12 (900 mg, 3.4 mmol) in CCl₄ (15 ml), and the mixture was refluxed for 2 h. After removal of the solvent under reduced pressure, H₂O (20 ml) was added to the residue, and the aqueous layer was extracted with CHCl₃. The CHCl₃ extract was obtained through a short column of Al₂O₃ using CHCl₃ as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 170°C (dec.). Yield 1.53 g (92%). IR ν(CHCl) cm⁻¹: 1650. ¹H-NMR (CDCl₃): 2.30—2.88 (2H, m), 3.97—4.83 (2H, m), 5.35—5.70 (1H, m), 7.28—8.07 (3H, m), 8.15—8.57 (1H, m). Anal. Calcd for C₁₅H₁₁Br₂NO: C, 42.01; H, 2.64; Br, 46.59; N, 4.08. Found: C, 42.23; H, 2.64; Br, 46.76; N, 4.14.

1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinoline (14) — Selenium dioxide (124 mg, 1 mmol) was added to a solution of 10 (400 mg, 2 mmol) in dioxane (20 ml), and the mixture was refluxed for 1 h. After filtration of the precipitated Se, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO₂ column chromatography using ether as an eluent. The etheral fraction gave pale yellow needles, mp 170—171°C, which were used without further purification in the next experiment. Yield 360 mg (38%). IR ν(CHCl) cm⁻¹: 3300, 1660. ¹H-NMR (CDCl₃): 1.80—2.97 (2H, m), 3.50—4.50 (2H, m), 4.80—5.53 (1H, m), 5.05 (1H, br s), 6.50 (1H, s), 7.07—7.87 (3H, m), 8.02—8.46 (1H, m).

5-Bromo-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinoline-10-trans-acrylate (16) — A mixture of 12 (250 mg, 0.7 mmol), ethyl acrylate (250 mg, 2.5 mmol), Pd(OAc)₂ (20 mg), PPh₃ (40 mg), and Et₄N (10 ml) was heated in a sealed tube at 130°C for 16 h. After removal of the precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short column of Al₂O₃ using CHCl₃ as an eluent. Recrystallization from acetone–hexane gave pale yellow needles, mp 215—216°C. Yield 220 mg (82%). IR ν(CHCl) cm⁻¹: 1730, 1660, 985. ¹H-NMR (CDCl₃): 1.35 (3H, t, J = 7.0 Hz), 2.19 (2H, quint, J = 7.0 Hz), 3.23 (2H, t, J = 7.0 Hz), 4.20 (2H, t, J = 7.0 Hz), 4.28 (2H, q, J = 7.0 Hz), 6.13 (1H, d, J = 16.0 Hz), 7.13—8.00 (3H, m), 7.85 (1H, d, J = 16.0 Hz), 8.25—8.63 (1H, m). Anal. Calcd for C₁₅H₁₂NO₂C: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.02; N, 4.93.

5-Benzyl-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinolinolinoepropanoate (17) — A mixture of 16 (170 mg, 0.6 mmol) and 10% Pd-C (0.68 g) in MeOH (10 ml) was shaken in a shaker at room temperature. After absorption of H₂ (21 ml) had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short column of Al₂O₃ using CHCl₃ as an eluent. The CHCl₃ fraction gave a colorless viscous liquid which was used without further purification in the next step. Yield 150 mg (88%). IR ν(CHCl) cm⁻¹: 1730, 1660. ¹H-NMR (CDCl₃): 1.22 (3H, t, J = 7.0 Hz), 1.83—2.78 (4H, m), 2.78—3.55 (4H, m), 4.10 (2H, q, J = 7.0 Hz), 4.17 (2H, t, J = 7.0 Hz), 7.18—7.86 (3H, m), 8.15—8.60 (1H, m).

Ethyl 1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrole[1,2-b]isoquinolinolino-10-trans-acrylate (19) — Selenium dioxide (210 mg, 1.6 mmol) was added to a solution of 16 (800 mg, 2.8 mmol) in dioxane (30 ml) and the mixture was refluxed

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for 44 h. After removal of the precipitated Se by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al₂O₃ column chromatography using CHCl₃ as an eluent. The crude product obtained from the CHCl₃ fraction was treated with active charcoal in MeOH. Recrystallization from acetone–hexane gave pale yellow needles, mp > 230 °C. Yield 0.80 g (94%). IR ν(CHCl₃) cm⁻¹: 3310, 1710. ¹H-NMR (CDCl₃): 1.35 (3H, t, J = 7.0 Hz), 2.00–2.73 (2H, m), 4.06–4.70 (2H, m), 4.28 (2H, q, J = 7.0 Hz), 4.76–5.50 (2H, m), 6.62 (1H, d, J = 16.0 Hz), 7.03–7.53 (3H, m), 7.68 (1H, d, J = 16.0 Hz), 7.85–8.33 (1H, m). Anal. Caled for C₁₇H₁₄NO₄: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.02; H, 5.50; N, 4.45.

Ethyl 1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-b]isoquinoline-10-propanoate (20)—A mixture of 19 (800 mg, 2.7 mmol) and 10% Pd-C (2.0 g) in MeOH (20 ml) was shaken in a stream of H₂ at room temperature. After absorption of H₂ (88 ml) had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure to give a residue, which was passed through a short column of Al₂O₃ using CHCl₃ as an eluent. Removal of the solvent gave a colorless viscous liquid which was used without further purification in the next step. Yield 620 mg (77%). IR ν(CHCl₃) cm⁻¹: 3300, 1710. ¹H-NMR (CDCl₃): 1.16 (3H, t, J = 7.0 Hz), 1.80–2.47 (2H, m), 2.47–2.92 (2H, m), 2.92–3.50 (2H, m), 3.85–4.50 (2H, m), 4.08 (2H, q, J = 7.0 Hz), 4.70–5.23 (1H, br), 5.38 (1H, t, J = 4.0 Hz), 7.10–7.90 (3H, m), 8.07–8.54 (1H, m).

Ethyl 1-Bromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-b]isoquinoline-10-propanoate (21)—Phosphorus tribromide (560 mg, 2 mmol) was slowly added to a solution of 20 (270 mg, 0.9 mmol) in CHCl₃ with stirring at 0–5 °C, and the mixture was refluxed for 4 h. After removal of the solvent, a small amount of ice was added to the residue. The aqueous layer was made alkaline with K₂CO₃ and extracted with CHCl₃. The CHCl₃ extract was passed through a short column of SiO₂ using CHCl₃ as an eluent. Removal of the solvent gave a colorless viscous liquid, which was used without further purification in the next step. Yield 310 mg (95%). IR ν(CHCl₃) cm⁻¹: 1720. ¹H-NMR (CDCl₃): 1.21 (3H, t, J = 7.0 Hz), 2.34–2.90 (4H, m), 2.90–3.47 (2H, m), 3.80–4.80 (2H, m), 4.11 (2H, q, J = 7.0 Hz), 5.77 (1H, t, J = 2.0 Hz), 7.20–7.88 (3H, m), 8.27–8.60 (1H, m).

3-Ethoxy-7-oxo-2,4,5,7-tetrahydro-1H-pyrrrolo[3,2,1-de]phenanthridine (22)—Magnesium (40 mg, 1.7 mmol) and a small amount of I₂ were added to a solution of 21 (300 mg, 0.83 mmol) in tetrahydrofuran (THF) (20 ml), and the mixture was refluxed for 7 h with stirring. After removal of the solvent under reduced pressure, H₂O (30 ml) was added to the residue. The aqueous layer was treated with NH₄Cl made alkaline with K₂CO₃ and extracted with CHCl₃. The crude product was purified by SiO₂ column chromatography using ether and acetone as eluents. The ether fraction gave a colorless viscous liquid (20 mg, 9%) which was identical with 17 obtained in the above experiment. The acetone fraction afforded pale yellow needles, which were recrystallized from acetone–hexane after treatment with active charcoal in MeOH. mp 216–218 °C. Yield 110 mg (50%). IR ν(CHCl₃) cm⁻¹: 1670. MS m/z: 267 (M⁺). ¹H-NMR (CDCl₃): 1.15 (3H, t, J = 7.0 Hz), 1.85–3.05 (6H, m), 4.05 (2H, q, J = 7.0 Hz), 3.45–4.75 (2H, m), 7.15–7.90 (3H, m), 8.25–8.70 (1H, m). Anal. Caled for C₁₇H₁₇NO₂: C, 76.32; H, 6.41; N, 5.24. Found: C, 76.13; H, 6.22; N, 5.03.

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References