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Condensed Heteroaromatic Ring Systems. V.[1] Formal Synthesis of Matrine and Related Compounds Using Palladium-Catalyzed Carbon–Carbon Bond Formations as Key Reactions

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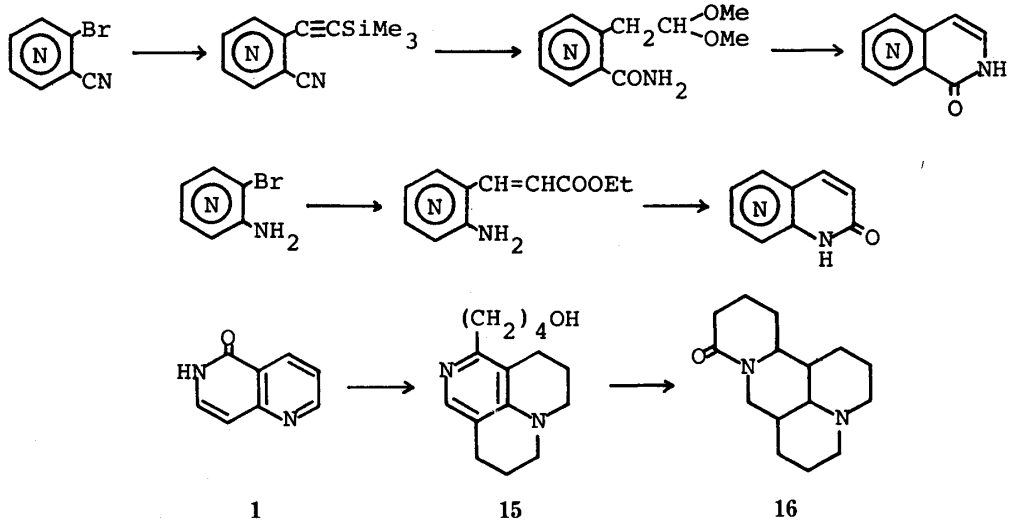
The iodination and subsequent dehydroxychlorination of 1,6-naphthyridin-5(6*H*)-one gave 5-chloro-8-iodo-1,6-naphthyridine, which was converted to the 5-methoxy derivative. Starting from this compound, didehydromatrine was synthesized by using palladium-catalyzed cross-coupling reactions with ethyl acrylate and 3-butyn-1-ol, as key reactions. Similarly, nordehydro-α-matrinidine was synthesized through four steps from 8-bromo-1,6-naphthyridine, obtained by the bromination of unsubstituted 1,6-naphthyridine.

Keywords——synthesis; matrine; didehydromatrine; nordehydro-α-matrinidine; palladium-catalyzed reaction; 1,6-naphthyridine; ethyl acrylate; 3-butyn-1-ol

As a part of our investigations on the synthesis of condensed heteroaromatic ring systems, we developed[1,2] two methods for the general synthesis of various naphthyridinones from halopyridines using palladium-catalyzed reactions. In order to utilize these methods in the field of natural product syntheses, extensive studies have been carried out. The present paper deals with a synthesis of didehydromatrine (**15**), which has already been transformed to matrine (**16**).[3]



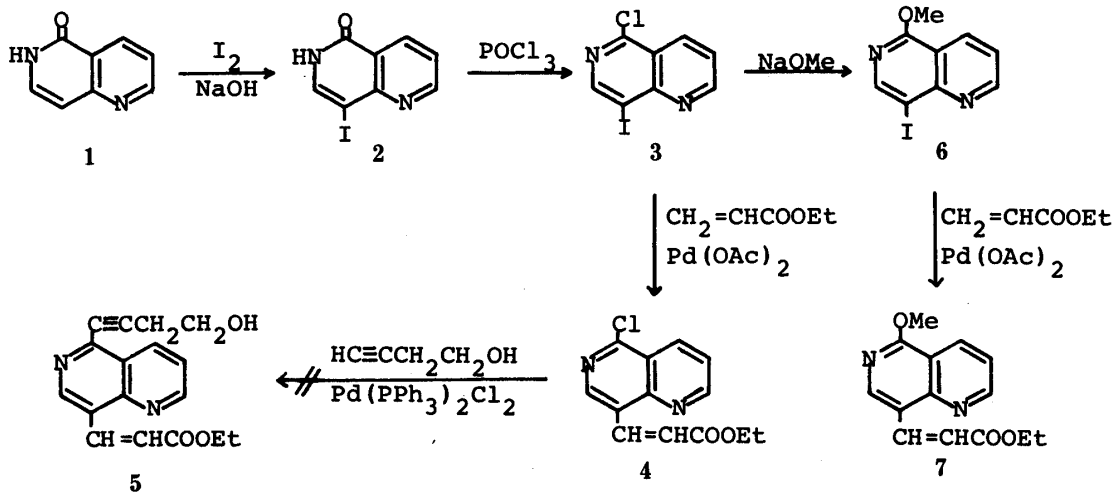
1 **15** **16**

Chart 1

Firstly, 1,6-naphthyridine derivatives, having favorable substituents for the synthesis of didehydromatrine (**15**) were prepared in the following manner. The reaction of 1,6-naphthyridin-5(6*H*)-one (**1**)[2] with iodine under alkaline conditions gave 8-iodo-1,6-

naphthyridin-5(6*H*)-one (**2**), which was converted to 5-chloro-8-iodo-1,6-naphthyridine (**3**) by the conventional phosphoryl chloride treatment. Although **3** reacted with ethyl acrylate in the presence of palladium acetate in triethylamine to give the desired ethyl 5-chloro-1,6-naphthyridine-8-acrylate (**4**) selectively, further condensation of **4** with 3-butyn-1-ol in the presence of dichlorobis(triphenylphosphine)palladium in triethylamine failed to give the desired ethyl 5-(4-hydroxybut-1-yn-1-yl)-1,6-naphthyridine-8-acrylate (**5**). It is likely that the chloro substituent at the 5-position of **4** is removed during the transformation of the unsaturated side-chain of **4** to a saturated one by catalytic hydrogenation.

Thus, in order to protect the 5-position from catalytic hydrogenation, **3** was converted to 8-iodo-5-methoxy-1,6-naphthyridine (**6**) by treatment with sodium methoxide, palladium-catalyzed reaction of which with ethyl acrylate gave ethyl 5-methoxy-1,6-naphthyridine-8-acrylate (**7**) in 88% yield. The structure of the 1,6-naphthyridine-8-acrylates (**4** and **7**), including the *trans* side-chain geometry, was supported by the spectral data.



1 2 3 6 5 4 7

Chart 2

Then, the skeleton of **15** was constructed by intramolecular amide formation. The catalytic hydrogenation of **7** over platinum dioxide gave selectively ethyl 5-methoxy-1,2,3,4-tetrahydro-1,6-naphthyridine-8-propionate (**8**). On treatment with sodium methoxide, **8** underwent cyclization to give the desired tricyclic lactam (**9**) in good yield. Demethylation of **9** with hydroiodic acid yielded the tricyclic α-pyridone (**10**). When **10** was heated with phosphoryl bromide, dehydroxybromination accompanied with oxidation resulted in the formation of the bromonaphthyridinone (**11**), whose spectral data clearly demonstrated the presence of an olefinic linkage.

Subsequently, another side-chain with four carbon atoms was introduced into **11** by the palladium-catalyzed reaction of **11** with 3-butyn-1-ol, and the butynyl compound (**12**) was obtained in 70% yield, as expected. The butynyl compound (**12**) was hydrogenated to the butanol (**13**) by catalytic hydrogenation over palladium carbon under atmospheric pressure. The catalytic hydrogenation of **13** with Raney nickel under moderate hydrogen pressure (6 atm), yielded the dihydropyridonebutanol (**14**). Compound **12** was directly hydrogenated to **14** with Raney nickel under the same hydrogen pressure (6 atm) in 79% yield. Finally, the carbonyl group of **14** was removed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®) in toluene at 100°C. The didehydromatrine (**15**) thus obtained has already been derived to matrine (**16**) in three steps by Okuda *et al.*[3]

In addition to the investigation described above, the synthesis of nordehydro-α-matrinidine (**22**), the skeleton of didehydromatrine (**15**), was accomplished in a similar

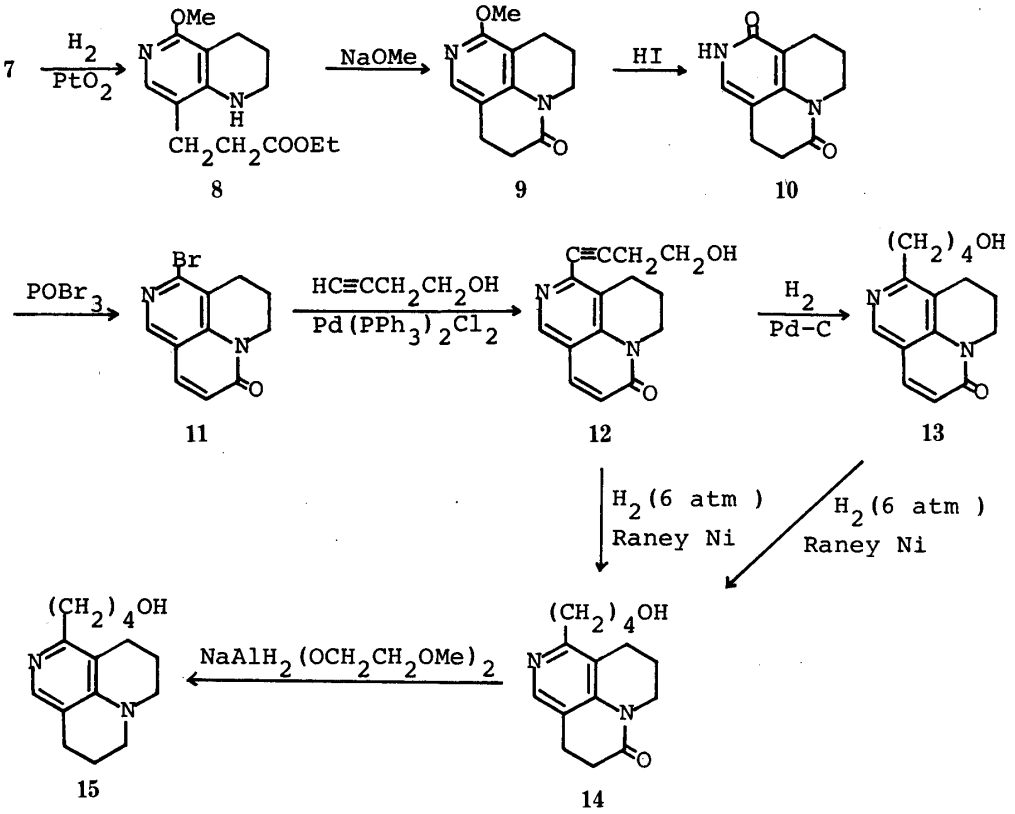
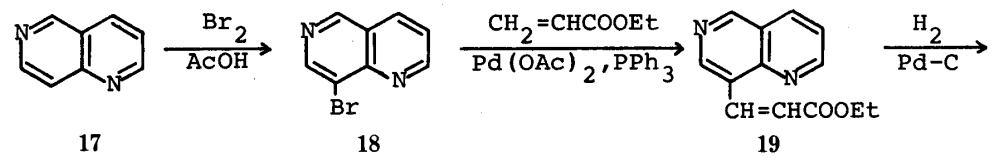


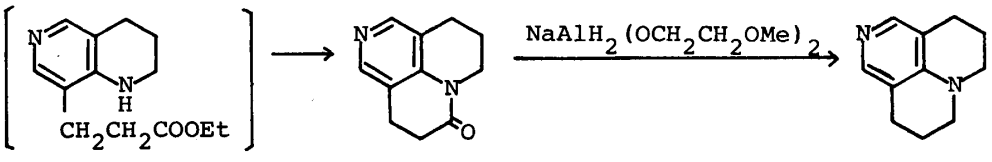
Chart 3

manner.

The bromination of 1,6-naphthyridine (**17**) in carbon tetrachloride was reported[4] to give a mixture of 8-bromo- (**18**) (23%), 3-bromo- (18%), and 3,8-dibromo-1,6-naphthyridine (11%). When **17** was brominated with bromine in acetic acid, however, **18** was obtained as the main product.



17 18 19



20 21 22

Chart 4

The palladium-catalyzed cross-coupling reaction of **18** with ethyl acrylate smoothly proceeded to give ethyl 1,6-naphthyridine-8-acrylate (**19**). When **19** was hydrogenated over palladium carbon under atmospheric pressure, the tetrahydro intermediate (**20**), in contrast to the case of the similar compound (**8**), cyclized to the tricyclic lactam (**21**) during the hydrogenation. Although **21** was resistant to lithium aluminum hydride reduction, the amide group was successfully removed by treatment with Vitride® to give the desired product (**22**).

The hydrobromide of **22** was identical with an authentic specimen of nordehydro-α-matrinidine hydrobromide.

The present results demonstrate that the palladium-catalyzed carbon–carbon bond formation is efficient for the construction of hetero-polycyclic ring systems.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer, and chemical shifts are expressed in δ (ppm) values relative to Me_4Si and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, and br=broad.

8-Iodo-1,6-naphthyridin-5(6*H*)-one (2)——A mixture of 1,6-naphthyridin-5(6*H*)-one (**1**)[2] (1.46 g, 10 mmol), I_2 (2.52 g, 10 mmol), and 0.4 N NaOH (50 ml) was heated at 80 °C for 3 h. The mixture was diluted with H_2O, then the precipitate was collected and recrystallized from MeOH to give pale yellow needles, mp 274—277 °C. Yield 1.90 g (70%). IR (KBr) cm^{-1}: 3160, 1660. ^{1}H-NMR (DMSO-d_6): 7.62 (1H, dd, J=4.0, 8.0 Hz), 7.95 (1H, s), 8.55 (1H, dd, J=2.0, 8.0 Hz), 9.05 (1H, dd, J=2.0, 4.0 Hz), 11.7—12.0 (1H, br s). *Anal.* Calcd for $C_8H_5IN_2O$: C, 35.32; H, 1.85; N, 10.30. Found: C, 35.33; H, 1.63; N, 9.89.

5-Chloro-8-iodo-1,6-naphthyridine (3)——A mixture of **2** (1.76 g, 6.5 mmol) and $POCl_3$ (30 ml) was refluxed for 1.5 h. After evaporation of the excess $POCl_3$, the residue was poured into ice-water. The resulting mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract, was recrystallized from cyclohexane to give colorless needles, mp 127—129 °C. Yield 1.20 g (64%). ^{1}H-NMR ($CDCl_3$): 7.68 (1H, dd, J=4.0, 8.0 Hz), 8.58 (1H, dd, J=2.0, 8.0 Hz), 8.96 (1H, s), 9.20 (1H, dd, J=2.0, 4.0 Hz). *Anal.* Calcd for $C_8H_4ClIN_2$: C, 33.08; H, 1.39; N, 9.64. Found: C, 33.09; H, 1.24; N, 9.26.

Ethyl 5-Chloro-1,6-naphthyridine-8-acrylate (4)——A mixture of **3** (1.26 g, 4.3 mmol), ethyl acrylate (0.60 g, 6.0 mmol), $Pd(OAc)_2$ (30 mg), and Et_3N (2 ml) was heated in a sealed tube at 100 °C for 14 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The C_6H_6 eluate gave colorless needles, which were recrystallized from cyclohexane, mp 129.5—131 °C. Yield 0.53 g (47%). IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$): 1.38 (3H, t, J=7.0 Hz), 4.37 (2H, q, J=7.0 Hz), 7.06 (1H, d, J=16.0 Hz), 7.69 (1H, dd, J=4.0, 8.0 Hz), 8.55 (1H, d, J=16.0 Hz), 8.65 (1H, dd, J=2.0, 8.0 Hz), 8.73 (1H, s), 9.22 (1H, dd, J=2.0, 4.0 Hz). *Anal.* Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.28; H, 3.97; N, 10.33.

8-Iodo-5-methoxy-1,6-naphthyridine (6)——A solution of **3** (2.90 g, 10 mmol) in MeONa–MeOH, prepared from Na (0.25 g, 10 mmol) and dry MeOH (20 ml), was refluxed for 1 h. After removal of the MeOH, the residue was diluted with H_2O, and the mixture was extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from CH_2Cl_2–hexane to give pale yellow needles, mp 120—121 °C. Yield 2.80 g (98%). ^{1}H-NMR ($CDCl_3$): 4.13 (3H, s), 7.51 (1H, dd, J=4.0, 8.0 Hz), 8.50 (1H, dd, J=2.0, 8.0 Hz), 8.65 (1H, s), 9.12 (1H, dd, J=2.0, 4.0 Hz). *Anal.* Calcd for $C_9H_7IN_2O$: C, 37.78; H, 2.46; N, 9.79. Found: C, 37.70; H, 2.19; N, 9.62.

Ethyl 5-Methoxy-1,6-naphthyridine-8-acrylate (7)——A mixture of **6** (4.20 g, 15 mmol), ethyl acrylate (2.50 g, 25 mmol), $Pd(OAc)_2$ (50 mg), Et_3N (2.50 g, 25 mmol), and MeCN (50 ml) was heated at 85 °C in a sealed tube for 24 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave colorless needles, which were recrystallized from hexane, mp 101—104 °C. Yield 3.33 g (88%). IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR ($CDCl_3$): 1.37 (3H, t, J=7.0 Hz), 4.17 (3H, s), 4.33 (2H, q, J=7.0 Hz), 7.13 (1H, d, J=16.0 Hz), 7.50 (1H, dd, J=4.0, 8.0 Hz), 8.40 (1H, d, J=16.0 Hz), 8.47 (1H, s), 8.57 (1H, dd, J=2.0, 8.0 Hz), 9.12 (1H, dd, J=2.0, 4.0 Hz). *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.09; H, 5.22; N, 10.60.

Ethyl 5-Methoxy-1,2,3,4-tetrahydro-1,6-naphthyridine-8-propionate (8)——A solution of **7** (3.00 g, 12 mmol) in MeOH (200 ml) was hydrogenated over PtO_2 (200 mg) under atmospheric pressure at room temperature. The reaction was stopped after 3 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was distilled under reduced pressure to give a colorless liquid, bp 150 °C (3 mmHg). Yield 2.56 g (83%). IR ($CHCl_3$) cm^{-1}: 3460, 1725. ^{1}H-NMR ($CDCl_3$): 1.25 (3H, t, J=7.0 Hz), 1.6—2.3 (2H, m), 2.4—2.9 (6H, m), 3.0—3.6 (2H, m), 3.90 (3H, s), 4.16 (2H, q, J=7.0 Hz), 4.54 (1H, br s), 7.57 (1H, s). Monopicrate: yellow needles (CH_2Cl_2–hexane), mp 130—134 °C (dec.). *Anal.* Calcd for $C_{14}H_{20}N_2O_3$ (monopicrate): C, 48.68; H, 4.70; N, 14.19. Found: C, 48.72; H, 4.60; N, 13.90.

1-Methoxy-6-oxo-4,5,9,10-tetrahydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine (9)——A solution of **8** (2.56 g, 9.7 mmol) in MeONa–MeOH, prepared from Na (0.27 g, 12 mmol) and dry MeOH (70 ml), was refluxed for 0.5 h. After removal of the MeOH, the residue was diluted with H_2O, and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from hexane to give colorless needles, mp 102—103 °C. Yield 2.00 g (95%). IR ($CHCl_3$) cm^{-1}: 1675. ^{1}H-NMR ($CDCl_3$): 1.7—2.2 (2H, m), 2.4—3.2 (6H, m), 3.7—4.1 (2H, m), 3.92

(3H, s), 7.70 (1H, s). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.29; H, 6.50; N, 12.94.

1,6-Dioxo-1,2,4,5,9,10-hexahydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine (10)——A solution of **9** (2.44 g, 11 mmol) in 57% HI (30 ml) was heated at 80 °C for 4.5 h. The mixture was poured into ice-water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from MeOH–AcOEt to give colorless needles, mp 265—270 °C (dec.). Yield 1.93 g (85%). IR ($CHCl_3$) cm^{-1}: 1640. ^1H-NMR ($CDCl_3$): 1.6—2.3 (2H, m), 2.4—3.0 (6H, m), 3.7—4.1 (2H, m), 7.14 (1H, s), 12.7—13.5 (1H, br s). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.42; H, 5.95; N, 13.57.

1-Bromo-6-oxo-9,10-dihydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine (11)——A mixture of **10** (3.00 g, 15 mmol) and $POBr_3$ (30 g) was heated at 120 °C for 5 h. The mixture was poured into ice-water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using C_6H_6–AcOEt (3 : 1) and AcOEt as eluents. The AcOEt eluate gave colorless needles, mp 215—218 °C, which were recrystallized from CH_2Cl_2–hexane. Yield 2.49 g (64%). IR ($CHCl_3$) cm^{-1}: 1660. ^1H-NMR ($CDCl_3$): 1.8—2.6 (2H, m), 2.8—3.3 (2H, m), 4.0—4.4 (2H, m), 6.75 (1H, d, J=10.0 Hz), 7.72 (1H, d, J=10.0 Hz), 8.43 (1H, s). *Anal.* Calcd for $C_{11}H_9BrN_2O$: C, 49.83; H, 3.42; N, 10.56. Found: C, 49.84; H, 3.21; N, 10.41.

4-(6-Oxo-9,10-dihydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-3-butyn-1-ol (12)——A mixture of **11** (1.50 g, 5.7 mmol), 3-butyn-1-ol (0.60 g, 8.6 mmol), $Pd(PPh_3)_2Cl_2$ (200 mg), CuI (100 mg), Et_3N (1.00 g, 10 mmol), and dimethylformamide (DMF) (20 ml) was heated at 65°C for 5 h. After removal of the DMF under reduced pressure, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using $CHCl_3$–Et_3N (9 : 1) as an eluent. The $CHCl_3$–Et_3N (9 : 1) eluate gave colorless needles, mp 189—191 °C, which were recrystallized from C_6H_6. Yield 1.01 g (70%). IR ($CHCl_3$) cm^{-1}: 3300, 2240, 1660. ^1H-NMR ($CDCl_3$): 1.8—2.6 (2H, m), 2.7—3.4 (4H, m), 3.5—4.5 (5H, m), 6.72 (1H, d, J=10.0 Hz), 7.68 (1H, d, J=10.0 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.54; N, 11.01. Found: C, 70.53; H, 5.48; N, 10.73.

6-Oxo-9,10-dihydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine-1-butanol (13)——A solution of **12** (0.50 g, 20 mmol) in MeOH (30 ml) was hydrogenated over 10% Pd–C (150 mg) under atmospheric pressure at room temperature. The reaction was stopped after 2 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was recrystallized from C_6H_6–hexane to give colorless needles, mp 135—137 °C. Yield 0.47 g (93%). IR ($CHCl_3$) cm^{-1}: 3640, 1660. ^1H-NMR ($CDCl_3$): 1.3—2.6 (6H, m), 2.7—3.2 (4H, m), 3.13 (1H, s), 3.6—4.0 (2H, m), 4.0—4.3 (2H, m), 6.68 (1H, d, J=10.0 Hz), 7.38 (1H, d, J=10.0 Hz), 8.59 (1H, s). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.80; H, 7.03; N, 10.58.

6-Oxo-4,5,9,10-tetrahydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine-1-butanol (14)——i) A solution of **13** (0.60 g, 2.3 mmol) in MeOH (30 ml) was hydrogenated over Raney Ni, prepared from Ni–Al alloy (3.0 g), under a pressure of 6 atm at room temperature. The reaction was stopped after 1 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was recrystallized from CH_2Cl_2–hexane to give colorless needles, mp 136.5—137 °C. Yield 0.51 g (83%). IR ($CHCl_3$) cm^{-1}: 3640, 1680. ^1H-NMR ($CDCl_3$): 1.2—2.3 (6H, m), 2.3—3.1 (8H, m), 3.1—4.0 (5H, m), 8.10 (1H, s). *Anal.* Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.95; H, 7.92; N, 10.51.

ii) A solution of **12** (1.32 g, 5.2 mmol) in MeOH (40 ml) was hydrogenated over Raney Ni, prepared from Ni–Al alloy (6.0 g), under a pressure of 6 atm at room temperature. The reaction was stopped after 3 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was recrystallized from CH_2Cl_2–hexane to give **14**. Yield 1.07 g (79%).

Didehydromatrine (15)——Vitride® (70% in toluene) (3 ml, 10 mmol) was added to a solution of **14** (0.69 g, 2.7 mmol) in dry toluene (15 ml), and the mixture was heated at 100 °C for 1 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from CH_2Cl_2–hexane to give colorless prisms, mp 101—103 °C (lit.[5] mp 105—106 °C). Yield 0.48 g (74%). IR ($CHCl_3$) cm^{-1}: 3640. ^1H-NMR ($CDCl_3$): 1.3—2.3 (8H, m), 2.3—3.0 (6H, m), 3.0—3.5 (4H, m), 3.5—3.9 (2H, m), 4.66 (1H, br s), 7.70 (1H, s).

8-Bromo-1,6-naphthyridine (18)——Bromine (14.0 g, 85 mmol) was added to a solution of 1,6-naphthyridine (**17**) (10.0 g, 77 mmol) in AcOH (100 ml), and the mixture was heated at 80 °C for 12 h. After removal of the AcOH under reduced pressure, the residue was poured into ice-water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave colorless needles, mp 82—84 °C (lit.[4] mp 84—86 °C), which were recrystallized from cyclohexane. Yield 8.80 g (55%). ^1H-NMR ($CDCl_3$): 7.63 (1H, dd, J=4.0, 8.0 Hz), 8.31 (1H, dd, J=2.0, 8.0 Hz), 9.00 (1H, s), 9.18 (1H, s), 9.1—9.4 (1H, m).

Ethyl 1,6-Naphthyridine-8-acrylate (19)——A mixture of **18** (0.80 g, 3.9 mmol), ethyl acrylate (0.80 g, 7.8 mmol), $Pd(OAc)_2$ (20 mg), PPh_3 (40 mg), Et_3N (0.50 g, 4.7 mmol), and MeCN (4 ml) was heated at 120 °C in a sealed tube for 24 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$, and the $CHCl_3$ layer was extracted with 3 N HCl. The 3 N HCl layer was made alkaline with K_2CO_3 and extracted with ether. The crude product, obtained from the ethereal extract, was recrystallized from ether–hexane to give pale yellow needles, mp 90—92 °C. Yield 0.60 g

(69%). IR ($CHCl_3$) cm^{-1}: 1720. ^1H-NMR ($CDCl_3$): 1.38 (3H, t, $J=7.0$ Hz), 4.35 (2H, q, $J=7.0$ Hz), 7.14 (1H, d, $J=16.0$ Hz), 7.62 (1H, dd, $J=4.0$, 8.0 Hz), 8.37 (1H, dd, $J=2.0$, 8.0 Hz), 8.62 (1H, d, $J=16.0$ Hz), 9.00 (1H, s), 9.20 (1H, dd, $J=2.0$, 4.0 Hz), 9.30 (1H, s). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.18; H, 5.44; N, 12.00.

6-Oxo-4,5,9,10-tetrahydro-6*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine (21)——A solution of **19** (4.15 g, 18 mmol) in EtOH (100 ml) was hydrogenated over 10% Pd–C (1.0 g) under atmospheric pressure at room temperature. The reaction was stopped after 3 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the EtOH, the residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave colorless needles, mp 109.5—111.5 °C, which were recrystallized from cyclohexane. Yield 2.62 g (76%). IR ($CHCl_3$) cm^{-1}: 1660. ^1H-NMR ($CDCl_3$): 1.7—2.2 (2H, m), 2.3—3.1 (6H, m), 3.7—4.1 (2H, m), 8.25 (2H, s). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.07; H, 6.35; N, 14.80.

Nordehydro-α-matrinidine (22)——Vitride® (70% in toluene) (9 ml, 30 mmol) was added to a solution of **21** (2.00 g, 11 mmol) in dry toluene (30 ml), and the mixture was refluxed for 48 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was distilled under reduced pressure to give a pale yellow solid, bp 145 °C (3 mmHg). Yield 1.20 g (64%). ^1H-NMR ($CDCl_3$):1.7—2.2 (4H, m), 2.4—2.9 (4H, m), 3.0—3.4 (4H, m), 7.79 (2H, s). Hydrobromide: colorless needles (MeOH–AcOEt), mp 272 °C (lit.[6] mp 275 °C).

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