[Chem. Pharm. Bull. 34(7)2760—2765(1986)]

Condensed Heteroaromatic Ring Systems. IX.[1] Total Synthesis of Aaptamine

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(Received December 26, 1985)

A five-step synthesis of aaptamine, a marine alkaloid containing a benzo[*d,e*][1,6]naphthyridine ring, from 6,7-dimethoxy-8-nitro-1(2*H*)-isoquinolone was accomplished in satisfactory yield. As a basis for the above synthesis, a facile preparation of 6,7-dimethoxy-1(2*H*)-isoquinolones from 3,4-dimethoxybenzaldehydes was developed using the palladium-catalyzed reaction of *o*-bromobenzaldehyde derivatives with trimethylsilylacetylene as a key reaction.

Keywords——synthesis; aaptamine; palladium-catalyzed reaction; trimethylsilylacetylene; 6,7-dimethoxy-1(2*H*)-isoquinolone

Total synthesis of aaptamine (**21**), a marine alkaloid isolated from the Okinawan sea sponge *Aaptos aaptos*,[2] was previously reported by Pelletier and Cava[3a] and by Kelly and Maguire.[3b] As a part of our investigation on the synthesis of condensed heteroaromatics by means of palladium-catalyzed reactions, we became interested in the total synthesis of aaptamine, because of the presence of a benzo[*d,e*][1,6]naphthyridine nucleus in its structure. We have already reported a facile method for the construction of the isoquinolone skeleton from *o*-bromobenzamide derivatives.[4] The method is applicable to the synthesis of some naphthyridinones from pyridinecarboxamide derivatives with an adjacent halo-substituent.[4]

From these points of view, the synthesis of isoquinolone derivatives containing the necessary substituents for the next cyclization to aaptamine (**21**) was firstly investigated. 6-Bromo-3,4-dimethoxy-2-nitrobenzaldehyde (**1**), prepared by the methylation of 6-bromo-4-hydroxy-3-methoxy-2-nitrobenzaldehyde with methyl iodide in the presence of potassium carbonate, was converted to 6-bromo-3,4-dimethoxy-2-nitrobenzonitrile (**2**) *via* the corresponding aldoxime. The condensation of **2** and trimethylsilylacetylene (TMSA) in the presence of dichlorobis(triphenylphosphine)palladium at 40—45 °C proceeded smoothly to give 3,4-dimethoxy-2-nitro-6-(trimethylsilylethynyl)benzonitrile (**3**). In this case, a narrow range of reaction temperature is required to obtain the desired product in satisfactory yield. When **3** was treated with sodium methoxide in methanol–dimethylformamide (DMF), 6-(2,2-dimethoxyethyl)-3,4-dimethoxy-2-nitrobenzonitrile (**4**) was obtained together with 6-ethynyl-2,3,4-trimethoxybenzonitrile (**5**), as a by-product. The partial hydrolysis of the cyano group of **4** with hydrogen peroxide under alkaline conditions gave 6-(2,2-dimethoxyethyl)-3,4-dimethoxy-2-nitrobenzamide (**6**). On heating with *p*-toluenesulfonic acid (TsOH) in methanol–benzene, **6** cyclized smoothly to give 6,7-dimethoxy-8-nitro-1(2*H*)-isoquinolone (**7**), as expected.

During the investigation on the synthesis of **7**, described above, an alternative synthesis of **7** was attempted, but without success. Namely, the palladium-catalyzed reaction of **1** and TMSA afforded 3,4-dimethoxy-2-nitro-6-(trimethylsilylethynyl)benzaldehyde (**8**), but on treatment of **8** with sodium methoxide, a resinous substance was obtained instead of the

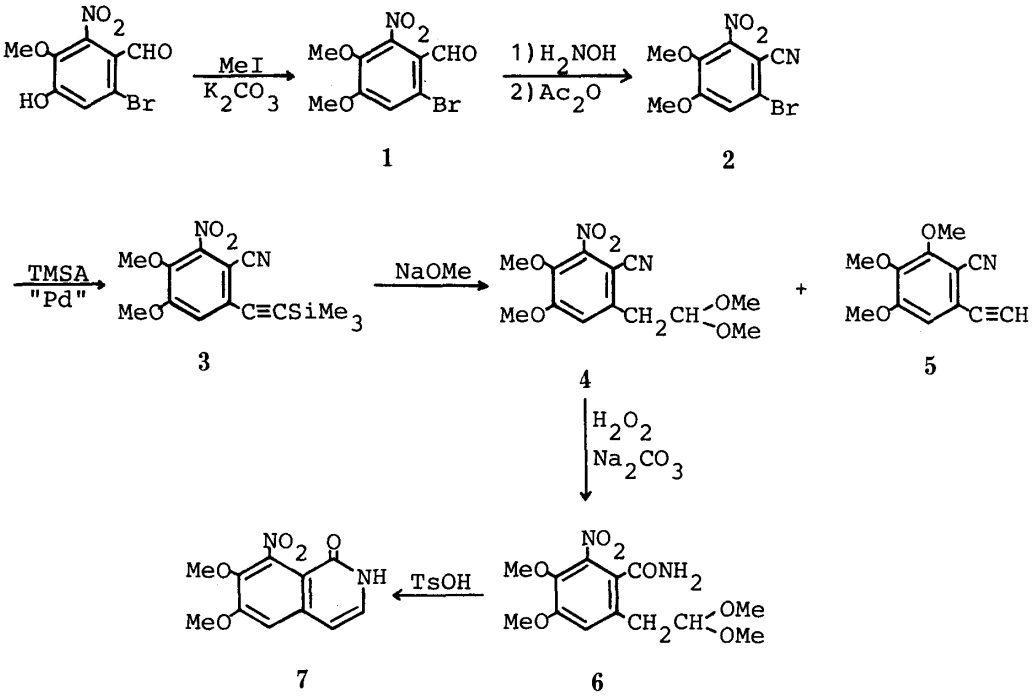

Chart 1

desired 6-(2,2-dimethoxyethyl)-3,4-dimethoxy-2-nitrobenzaldehyde (**9**). When the cyano group of **2** was hydrolyzed in advance of the reaction with TMSA, the resulting 6-bromo-3,4-dimethoxy-2-nitrobenzamide (**10**) was unreactive toward TMSA, so the desired compound was not formed. The cyclization of 6-ethynyl-3,4-dimethoxy-2-nitrobenzamide (**11**), easily obtained from **3** by the action of cuprous iodide in DMF, did not give **7**.

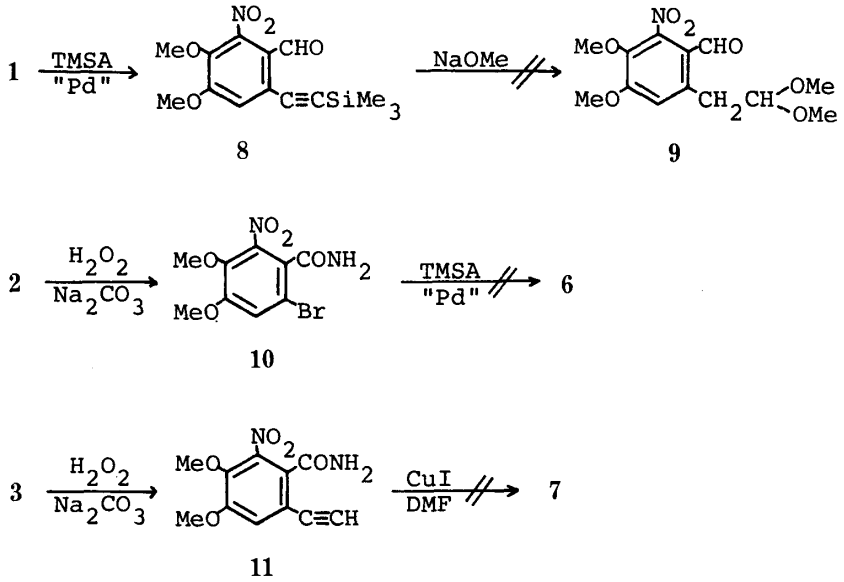

Chart 2

In addition to the above trials, synthesis and nitration of 6,7-dimethoxy-1(2*H*)-isoquinolone (**16**) was investigated. Namely, 2-bromo-4,5-dimethoxybenzonitrile (**12**) was obtained from 2-bromo-4,5-dimethoxybenzaldehyde according to the reported method.[5] The palladium-catalyzed reaction of the benzonitrile (**12**) with TMSA followed by treatment with sodium ethoxide gave 2-(2-ethoxyethenyl)-4,5-dimethoxybenzonitrile (**14**). The cyclization of

2-(2-ethoxyethenyl)-4,5-dimethoxybenzamide (**15**) prepared by the alkaline hydrolysis of **14** with hydrogen peroxide, proceeded smoothly to give **16**. The nitration of **16** with nitric acid, however, resulted in the formation of many products, and the presence of **7** in the crude products was not detected by thin-layer chromatographic analysis.

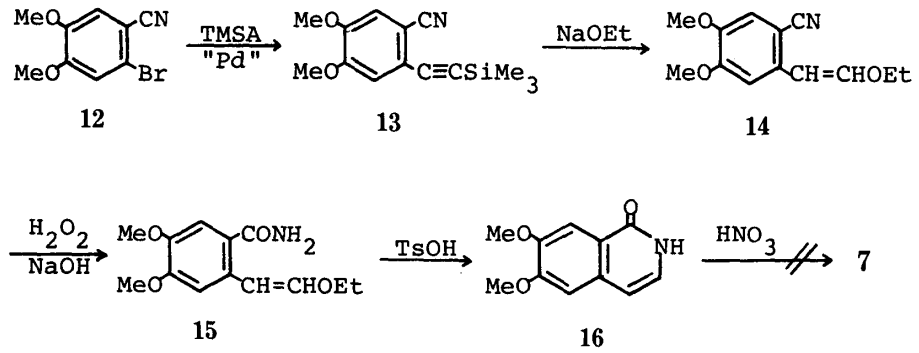

Chart 3

Based upon these results, the route shown in Chart 1 is concluded to be practical for the synthesis of **7**. Finally, the synthesis of aaptamine (**21**) from **7** was attempted according to our previous naphthyridine cyclization method.[4] The dehydroxy-chlorination of **7** with phosphoryl chloride under conventional conditions afforded 1-chloro-6,7-dimethoxy-8-nitroisoquinoline (**17**), which was allowed to react with TMSA in the presence of palladium catalyst. 6,7-Dimethoxy-8-nitro-1-(trimethylsilylethynyl)isoquinoline (**18**) thus obtained was treated with sodium methoxide to give 1-(2,2-dimethoxyethyl)-6,7-dimethoxy-8-nitroisoquinoline (**19**), which was readily hydrogenated to the corresponding amino compound (**20**) in the presence of palladium carbon. When **20** was treated with hydrogen chloride in methanol at room temperature, aaptamine hydrochloride (**21**) was obtained. It was confirmed to be identical with an authentic sample provided by Dr. Y. Ohizumi.

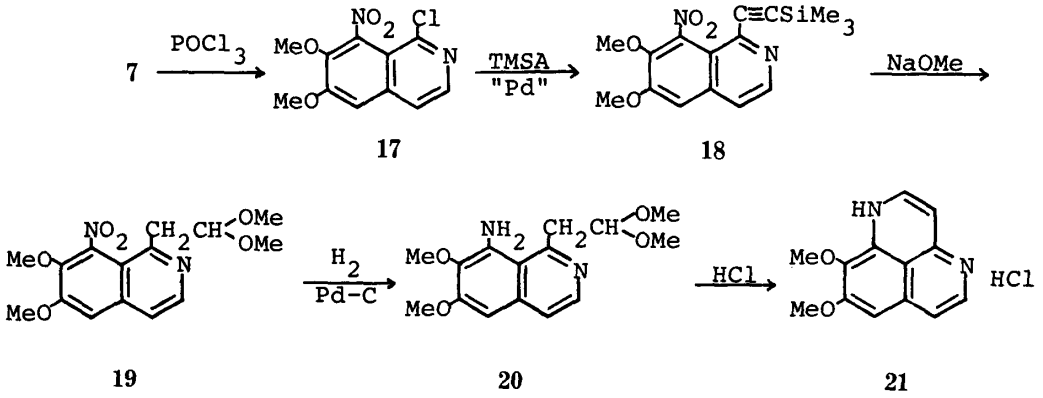

Chart 4

Experimental

All melting 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 JMN-PMX 60 spectrometer. Mass spectra (MS) were determined with Hitachi M-52 and JEOL JMS-01SG-2 spectrometers. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and br = broad.

6-Bromo-3,4-dimethoxy-2-nitrobenzaldehyde (1)——A mixture of 6-bromo-4-hydroxy-3-methoxy-2-nitrobenzaldehyde[6] (37.6 g, 0.14 mol), K_2CO_3 (22.6 g, 0.16 mol), MeI (58.0 g, 0.41 mol), and DMF (150 ml) was heated at 50 °C for 5 h. After dilution with H_2O, the mixture was extracted with ether, and the ethereal extract was

washed with H_2O three times. The crude product obtained from the ethereal extract was recrystallized from CH_2Cl_2–hexane to give pale yellow scales, mp 114.5—115.5 °C. Yield 34.8 g (88%). IR ($CHCl_3$) cm^{-1}: 1695. ^1H-NMR ($CDCl_3$): 3.90 (3H, s), 4.01 (3H, s), 7.26 (1H, s), 10.13 (1H, s). *Anal.* Calcd for $C_9H_8BrNO_5$: C, 37.26; H, 2.77; N, 4.82. Found: C, 37.39; H, 2.75; N, 4.53.

6-Bromo-3,4-dimethoxy-2-nitrobenzonitrile (2)——A mixture of **1** (38.2 g, 0.13 mol), $NH_2OH \cdot HCl$ (18.3 g, 0.26 mol), AcONa (21.6 g, 0.26 mol), and EtOH (200 ml) was refluxed for 12 h. After removal of the EtOH, H_2O was added to the residue. The resulting solid was filtered off, washed with H_2O, and dried under reduced pressure. A mixture of the solid and Ac_2O (200 ml) was refluxed for 20 h. After removal of the excess Ac_2O, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The crude product obtained from the C_6H_6 eluate was recrystallized from CH_2Cl_2–hexane to give colorless needles, mp 134—135 °C. Yield 36.2 g (96%). IR ($CHCl_3$) cm^{-1}: 2230. ^1H-NMR ($CDCl_3$): 3.95 (3H, s), 4.01 (3H, s), 7.28 (1H, s). *Anal.* Calcd for $C_9H_7BrN_2O_4$: C, 37.65; H, 2.45; N, 9.75. Found: C, 37.81; H, 2.44; N, 9.59.

3,4-Dimethoxy-2-nitro-6-(trimethylsilylethynyl)benzonitrile (3)——A mixture of **2** (2.87 g, 10 mmol), TMSA (2.00 g, 20 mmol), $Pd(PPh_3)_2Cl_2$ (300 mg), CuI (150 mg), Et_3N (1.50 g, 15 mmol), and DMF (9 ml) was stirred at room temperature. After *ca.* 5 min, the reaction temperature started to rise and was kept at 40—45 °C with external cooling. When the exothermic reaction stopped, the mixture was stirred without cooling for 1 h, diluted with H_2O, and extracted with ether. The ethereal extract was washed with H_2O three times, dried over $MgSO_4$, and purified by SiO_2 column chromatography using C_6H_6–hexane (1 : 1) as an eluent. The crude product obtained from the C_6H_6–hexane (1 : 1) eluate was recrystallized from CH_2Cl_2–hexane to give colorless scales, mp 126—127 °C. Yield 2.54 g (83%). IR ($CHCl_3$) cm^{-1}: 2230, 2160. ^1H-NMR ($CDCl_3$): 0.29 (9H, s), 3.99 (3H, s), 4.02 (3H, s), 7.16 (1H, s). *Anal.* Calcd for $C_{14}H_{16}N_2O_4Si$: C, 55.24; H, 5.29; N, 9.20. Found: C, 55.05; H, 5.21; N, 9.09.

6-(2,2-Dimethoxyethyl)-3,4-dimethoxy-2-nitrobenzonitrile (4)——An MeONa–MeOH solution, prepared from Na (1.06 g, 46 mmol) and dry MeOH (70 ml), was added to a solution of **3** (7.00 g, 23 mmol) in DMF (70 ml). After being heated at 45 °C for 3 h, the mixture was diluted with H_2O and extracted with ether. The ethereal extract was washed with H_2O, dried over $MgSO_4$, and purified by SiO_2 column chromatography using C_6H_6 and C_6H_6–AcOEt (10 : 1) as eluents. The crude product obtained from the C_6H_6 eluate was recrystallized from CH_2Cl_2–hexane to afford 6-ethynyl-2,3,4-trimethoxybenzonitrile (**5**) as pale yellow needles, mp 88—90 °C. Yield 930 mg (19%). IR ($CHCl_3$) cm^{-1}: 3300, 2230. ^1H-NMR ($CDCl_3$): 3.43 (1H, s), 3.90(3H, s), 3.93 (3H, s), 4.06 (3H, s), 6.88 (1H, s). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.08; H, 4.98; N, 6.23.

The C_6H_6–AcOEt (10 : 1) eluate gave a brown liquid (**4**), which was used in the next step without further purification or elemental analysis. Yield 4.54 g (67%). IR ($CHCl_3$) cm^{-1}: 2230. ^1H-NMR (CCl_4): 3.02 (2H, d, J=5.0 Hz), 3.34 (6H, s), 3.90 (3H, s), 4.00 (3H, s), 4.49 (1H, t, J=5.0 Hz), 7.07 (1H, s). MS *m/z*: 296 (M^+). High-resolution MS Calcd for $C_{13}H_{16}N_2O_6$: 296.1007. Found: 296.1013.

6-(2,2-Dimethoxyethyl)-3,4-dimethoxy-2-nitrobenzamide (6)——A mixture of **4** (4.54 g, 15 mmol), 30% H_2O_2 (18 ml), 3 N Na_2CO_3 (5 ml), and MeOH (50 ml) was heated at 50 °C for 2 h. Then, 30% H_2O_2 (18 ml) and 3 N Na_2CO_3 (5 ml) were added to the mixture, and the reaction was continued at 50 °C for 4 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from MeOH–AcOEt to give colorless prisms, mp 160—161.5 °C. Yield 3.61 g (75%). IR (KBr) cm^{-1}: 3380, 3220, 1670. ^1H-NMR (DMSO-d_6): 2.98 (2H, d, J=5.0 Hz), 3.28 (6H, s), 3.85 (3H, s), 3.93 (3H, s), 4.66 (1H, t, J=5.0 Hz), 7.26 (1H, s), 7.8 (1H, br s), 7.9 (1H, br s). *Anal.* Calcd for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.57; H, 5.75; N, 8.81.

6,7-Dimethoxy-8-nitro-1(2*H*)-isoquinolone (7)——A mixture of **6** (4.11 g, 13 mmol), TsOH (400 mg), MeOH (50 ml), and C_6H_6 (50 ml) was refluxed for 12 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from MeOH–AcOEt to give yellow prisms, mp 255—260 °C (dec.). Yield 2.96 g (90%). IR (KBr) cm^{-1}: 3350, 1665. ^1H-NMR (DMSO-d_6): 3.88 (3H, s), 4.05 (3H, s), 6.63 (1H, d, J=7.0 Hz), 7.27 (1H, d, J=7.0 Hz), 7.50 (1H, s), 11.2—11.8 (1H, br). *Anal.* Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.82; H, 4.01; N, 10.97.

3,4-Dimethoxy-2-nitro-6-(trimethylsilylethynyl)benzaldehyde (8)——A mixture of **1** (1.38 g, 4.8 mmol), TMSA (1.00 g, 10 mmol), $Pd(PPh_3)_2Cl_2$ (150 mg), CuI (75 mg), Et_3N (0.75 g, 7.5 mmol), and DMF (7 ml) was stirred at room temperature for 1 h. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was washed with H_2O, dried over $MgSO_4$, and purified by SiO_2 column chromatography using C_6H_6 as an eluent. The crude product obtained from the C_6H_6 eluate was recrystallized from ether–hexane to give yellow needles, mp 144—146 °C, which were used in the next step without elemental analysis. Yield 1.07 g (73%). IR ($CHCl_3$) cm^{-1}: 2150, 1700. ^1H-NMR ($CDCl_3$): 0.27 (9H, s), 3.90 (3H, s), 4.00 (3H, s), 7.08 (1H, s), 10.30 (1H, s). MS *m/z*: 367 (M^+). High-resolution MS Calcd for $C_{14}H_{17}NO_5Si$: 307.0875. Found: 307.0872.

6-Bromo-3,4-dimethoxy-2-nitrobenzamide (10)——A mixture of **2** (2.87 g, 10 mmol), 30% H_2O_2 (15 ml), 3 N Na_2CO_3 (15 ml), and MeOH (40 ml) was heated at 50 °C for 15 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from acetone–hexane to give colorless needles, mp 217—218.5 °C. Yield 960 mg (31%). IR (KBr) cm^{-1}: 3360, 3180, 1650.

^{1}H-NMR (DMSO-d_6): 3.87 (3H, s), 3.97 (3H, s), 7.60 (1H, s), 7.9 (1H, br s), 8.1 (1H, br s). *Anal.* Calcd for $C_9H_9BrN_2O_5$: C, 35.43; H, 2.97; N, 9.18. Found: C, 35.69; H, 2.83; N, 9.11.

6-Ethynyl-3,4-dimethoxy-2-nitrobenzamide (11)——A mixture of **3** (1.00 g, 3.3 mmol), 30% H_2O_2 (5 ml), 3 N Na_2CO_3 (5 ml), and MeOH (40 ml) was stirred at room temperature for 3 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from MeOH–AcOEt to give pale yellow needles, mp 208—210 °C. Yield 550 mg (67%). IR (KBr) cm^{-1}: 3360, 3280, 3170, 1650, 1630. ^{1}H-NMR (CF_3CO_2H): 3.05 (1H, s), 3.59 (3H, s), 3.62 (3H, s), 6.91 (1H, s). *Anal.* Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.70; H, 3.99; N, 10.92.

4,5-Dimethoxy-2-(trimethylsilylethynyl)benzonitrile (13)——A mixture of 2-bromo-4,5-dimethoxybenzonitrile[5] (1.50 g, 6.2 mmol), TMSA (1.24 g, 12 mmol), $Pd(PPh_3)_2Cl_2$ (150 mg), CuI (75 mg), Et_3N (930 mg, 9.3 mmol), and DMF (8 ml) was heated in a sealed tube at 100 °C for 18 h. The reaction mixture was diluted with H_2O and extracted with ether. The residue obtained from the ethereal extract was purified by SiO_2 column chromatography using C_6H_6–hexane (2 : 1) as an eluent. The crude product obtained from the C_6H_6–hexane (2 : 1) eluate was recrystallized from CH_2Cl_2–hexane to give colorless needles, mp 122.5—123.5 °C, which were used in the next step without elemental analysis. Yield 1.04 g (64%). IR ($CHCl_3$) cm^{-1}: 2230, 2160. ^{1}H-NMR ($CDCl_3$): 0.29 (9H, s), 3.89 (3H, s),3.92 (3H, s), 6.99 (1H, s), 7.04 (1H, s). MS *m/z*: 259 (M^+). High-resolution MS Calcd for $C_{14}H_{17}NO_2Si$: 259.1028. Found: 259.1026.

2-(2-Ethoxyethenyl)-4,5-dimethoxybenzonitrile (14)——Compound **13** (1.40 g, 5.4 mmol) was added to an EtONa–EtOH solution [prepared from Na (500 mg, 22 mmol) and dry EtOH (30 ml)], and the mixture was refluxed for 12 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The crude product obtained from the C_6H_6 eluate, was recrystallized from CH_2Cl_2–hexane to give colorless prisms, mp 95—97 °C. Yield 840 mg (67%). IR ($CHCl_3$) cm^{-1}: 2210. ^{1}H-NMR ($CDCl_3$): 1.38 (3H, t, J=7.0 Hz), 3.87 (3H, s), 3.91 (3H, s), 4.02 (2H, q, J=7.0 Hz), 5.56 (1H, d, J=7.0 Hz), 6.35 (1H, d, J=7.0 Hz), 6.96 (1H, s), 7.80 (1H, s). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.65; H, 6.46; N, 5.97.

2-(2-Ethoxyethenyl)-4,5-dimethoxybenzamide (15)——A mixture of **14** (760 mg, 3.3 mmol), 30% H_2O_2 (8 ml), 3 N NaOH (2 ml), and MeOH (20 ml) was heated at 70 °C for 3 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from CH_2Cl_2–hexane to give colorless needles, mp 158—160 °C. Yield 310 mg (38%). IR ($CHCl_3$) cm^{-1}: 3360, 3190, 1640. ^{1}H-NMR ($CDCl_3$): 1.34 (3H, t, J=7.0 Hz), 3.88 (3H, s), 3.90 (3H, s), 4.00 (2H, q, J=7.0 Hz), 5.68 (1H, d, J=7.0 Hz), 5.8—7.0 (2H, br), 6.29 (1H, d, J=7.0 Hz), 7.17 (1H, s), 7.66 (1H, s). *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.93; H, 6.86; N, 5.55.

6,7-Dimethoxy-1(2*H*)-isoquinolone (16)——A mixture of **15** (630 mg, 2.5 mmol), TsOH (60 mg), and C_6H_6 (30 ml) was refluxed for 6 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from $CHCl_3$–C_6H_6 to give colorless needles, mp 227—230 °C (lit.[7] mp 244—245 °C). Yield 400 mg (78%). IR (KBr) cm^{-1}: 3400, 1650, 1630. ^{1}H-NMR (DMSO-d_6): 3.89 (3H, s), 3.91 (3H, s), 6.51 (1H, d, J=7.0 Hz), 7.15 (1H, d, J=7.0 Hz), 7.19 (1H, s), 7.63 (1H, s), 10.8—11.5 (1H, br). *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.56; H, 5.25; N, 6.80.

1-Chloro-6,7-dimethoxy-8-nitroisoquinoline (17)——A mixture of **7** (2.96 g, 12 mmol) and $POCl_3$ (50 ml) was refluxed for 0.5 h. After removal of the excess $POCl_3$, the residue was poured into ice-water. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The crude product obtained from the $CHCl_3$ eluate was recrystallized from CH_2Cl_2–hexane to give colorless needles, mp 184—185.5 °C. Yield 2.93 g (92%). ^{1}H-NMR ($CDCl_3$): 4.01 (3H, s), 4.08 (3H, s), 7.21 (1H, s), 7.49 (1H, d, J=6.0 Hz), 8.22 (1H, d, J=6.0 Hz). *Anal.* Calcd for $C_{11}H_9ClN_2O_4$: C, 49.17; H, 3.37; N, 10.42. Found: C, 49.28; H, 3.30; N, 10.20.

6,7-Dimethoxy-8-nitro-1-(trimethylsilylethynyl)isoquinoline (18)——A mixture of **17** (1.34 g, 5.0 mmol), TMSA (1.00 g, 10 mmol), $Pd(PPh_3)_2Cl_2$ (150 mg), CuI (75 mg), Et_3N (750 mg, 7.5 mmol), and DMF (7 ml) was heated in a sealed tube at 65 °C for 2 h. The mixture was diluted with H_2O, extracted with ether, and dried over $MgSO_4$. The residue obtained from the ethereal extract was purified by SiO_2 column chromatography using C_6H_6 and C_6H_6–AcOEt (20 : 1) as eluents. The crude product obtained from the C_6H_6–AcOEt (20 : 1) eluate was used in the next step without further purification or elemental analysis. A part of the crude product was recrystallized from CH_2Cl_2–hexane to give brown needles, mp 145—148 °C. Yield 1.40 g, (85%). ^{1}H-NMR ($CDCl_3$): 0.33 (9H, s), 4.00 (3H, s), 4.05 (3H, s), 7.12 (1H, s), 7.46 (1H, d, J=6.0 Hz), 8.43 (1H, d, J=6.0 Hz). MS *m/z*: 330 (M^+). High-resolution MS Calcd for $C_{16}H_{18}N_2O_4Si$: 330.1035. Found: 330.1042.

1-(2,2-Dimethoxyethyl)-6,7-dimethoxy-8-nitroisoquinoline (19)——An MeONa–MeOH solution [prepared from Na (390 mg, 17 mmol) and dry MeOH (15 ml)] was added to a solution of **18** (1.40 g, 4.2 mmol) in DMF (15 ml). The mixture was heated at 60 °C for 1.5 h, diluted with H_2O, and extracted with ether. The ethereal extract was washed with H_2O three times, then evaporated, and the residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave a brown liquid, which was used in the next step without further purification. Yield 1.01 g (63%). Picrate: yellow needles (ether–CH_2Cl_2), mp 114—115 °C. ^{1}H-NMR ($CDCl_3$): 3.30 (2H, d, J=6.0 Hz),

3.37 (6H, s), 3.98 (3H, s), 4.03 (3H, s), 5.20 (1H, t, J=6.0 Hz), 7.17 (1H, s), 7.40 (1H, d, J=6.0 Hz), 8.42 (1H, d, J=6.0 Hz). MS m/z: 322 (M^+). High-resolution MS Calcd for $C_{15}H_{18}N_2O_6$: 322.1164. Found: 322.1210. *Anal.* Calcd for $C_{21}H_{21}N_5O_{13}$ (picrate): C, 45.74; H, 3.84; N, 12.70. Found: C, 45.81; H, 3.61; N, 12.76.

8-Amino-1-(2,2-dimethoxyethyl)-6,7-dimethoxyisoquinoline (20)——A solution of **18** (1.28 g, 4.0 mmol) in MeOH (250 ml) was hydrogenated over 10% Pd–C (300 mg) at atmospheric pressure. After removal of the catalyst by filtration, the MeOH was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using $CHCl_3$ and $CHCl_3$–MeOH (100 : 1) as eluents. The $CHCl_3$–MeOH (100 : 1) eluate gave a brown liquid which was used in the next step without further purification or elemental analysis. Yield 1.09 g (94%). IR ($CHCl_3$) cm^{-1}: 3420, 3330. ^{1}H-NMR ($CDCl_3$): 3.44 (6H, s), 3.84 (2H, d, J=6.0 Hz), 3.88 (3H, s), 3.95 (3H, s), 5.03 (1H, t, J=6.0 Hz), 5.2—5.7 (2H, br), 6.58 (1H, s), 7.26 (1H, d, J=6.0 Hz), 8.23 (1H, d, J=6.0 Hz). MS m/z: 292 (M^+). High-resolution MS Calcd for $C_{15}H_{20}N_2O_4$: 292.1421. Found: 292.1438.

Aaptamine Hydrochloride (21)——A solution of **19** (1.09 g, 3.7 mmol) in dry MeOH (30 ml) containing HCl (0.41 g, 11 mmol) was stirred at room temperature for 1.5 h. After removal of the solvent, the residue was purified by SiO_2 column chromatography using $CHCl_3$ and $CHCl_3$–MeOH (20 : 1) as eluents. The crude product obtained from the $CHCl_3$–MeOH (20 : 1) eluate was recrystallized from MeOH–acetone to give yellow needles, mp 105—107 °C (lit.[2] mp 110—113 °C), undepressed on admixture with an authentic sample. Yield 440 mg (45%). ^{1}H-NMR (DMSO-d_6): 3.83 (3H, s), 4.00 (3H, s), 6.57 (1H, d, J=7.0 Hz), 6.85 (1H, d, J=7.0 Hz), 7.11 (1H, s), 7.38 (1H, d, J=7.0 Hz), 7.88 (1H, d, J=7.0 Hz).

Acknowledgement The authors are grateful to Dr. Yasushi Ohizumi, Mitsubishi-Kasei Institute of Life Sciences, for providing an authentic specimen of aaptamine hydrochloride.

References and Notes

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