Synthesis of 8-Methoxy-1-methyl-1*H*-benzo[*de*][1,6]naphthyridin-9-ol (Isoaaptamine) and Analogues

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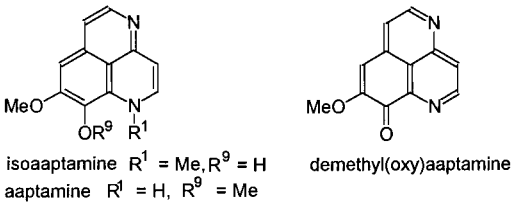
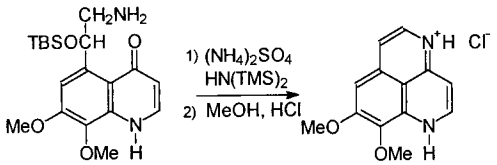
Received July 17, 2000

8-Methoxy-1-methyl-1*H*-benzo[*de*][1,6]naphthyridin-9-ol, isoaaptamine, a PKC inhibitor isolated from sponge was synthesized. The synthesis parallels a synthesis of 8,9-dimethoxybenzo[*de*][1,6]-naphthyridine, aaptamine, but uses a nitromethyl substituent as a precursor of the key 5-(2-aminoethyl)-1*H*-quinolin-4-one intermediate. The quinolone intermediates were prepared by thermolysis (220−240 °C) of anilinomethylene derivatives of Meldrum's acid. The quinolone intermediates were N-methylated prior to cyclization to the benzo[*de*][1,6]naphthyridine derivatives. Aaptamine and several analogues of aaptamine and isoaaptamine were prepared including 9-demethylaaptamine, 1-methyl-8-demethylaaptamine, 1-methylaaptamine, and the 8,9-methylenedioxy analogues of aaptamine and 1-methylaaptamine.

The isolation of 8-methoxy-1-methyl-1*H*-benzo[*de*][1,6]-naphthyridin-9-ol, referred to herein as isoaaptamine, was first reported in 1988 by Fedoreev and co-workers, who isolated the compound from a Suberitidae sponge.[1] The compound was isolated again in 1990 from the Red Sea sponge, *Aaptos aaptos*.[2] A natural product drug discovery program at SmithKline Beecham led to isolation of isoaaptamine on the basis of anti-cancer screening.[3] The purified compound showed activity as a PKC inhibitor, but was inactive against PKA. The isolation of the compound has again been reported recently, and it shows cytotoxicity toward several tumor cell lines.[4] The goal of the present work was to develop a method for synthesis of isoaaptamine and analogues in order to explore the structural range of PKC inhibitory and antitumor activity. Isoaaptamine is closely related structurally to aaptamine[5] and is also related to demethyl(oxy)aaptamine, which has shown cytotoxicity[5] and activity in a cell adherence assay related to PKC inhibition.[6]

There have been several syntheses of aaptamine,[7] and demethyl(oxy)aaptamine has also been synthesized.[8] There has been no report of the synthesis of isoaaptamine. The existing aaptamine syntheses use either the quinoline or isoquinoline components of the benzo[*de*][1,6]-naphthyridine ring as the nucleus on to which the third ring is constructed. The former group includes the routes developed by Cava,[8] Yamanaka,[9] Tollari,[10] and Joule.[11] The syntheses of Kelly,[12] Raphael,[13] and Sato[14] proceed through quinoline intermediates. After consideration and brief exploration of some of the other routes, we decided to adapt the Andrew−Raphael route to the synthesis of isoaaptamine. The key step in this synthesis is the cyclization of a 5-(2-aminoethyl)-4-quinolone to the benzo[*de*][1,6]naphthyridine ring by heating with hexamethyldisilazane and ammonium sulfate.





Adaptation of this synthesis to isoaaptamine required a selective protection of the 9-oxygen and, more importantly, the introduction of the *N*-methyl group at an appropriate point. The construction of the quinolone intermediate proceeds by the well-known Conrad−Lim-

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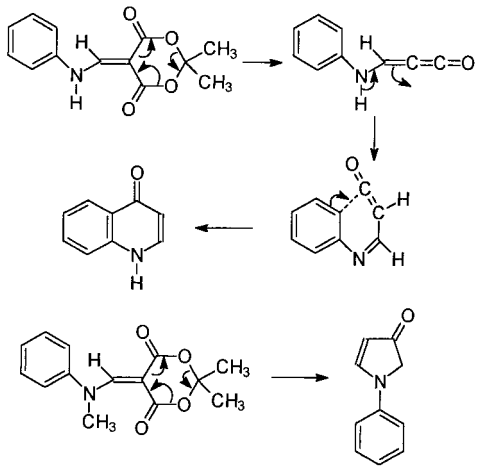
10.1021/jo001080s CCC: $19.00
Published on Web 10/13/2000

pach synthesis,[15] using an anilinomethylene Meldrum's acid intermediate, as developed by Cassis, Tapai, and Valderarrama.[16] 5-Nitrovanillin was benzylated and converted to the TBS-protected cyanohydrin **5b**.[13] Selective reduction of the nitro group was achieved using $TiCl_3$ near neutral pH.[17] Condensation with the methoxymethylene derivative of Meldrum's acid (**8**) provided **7b**, which was cyclized to the quinolone **9b** in 56% yield. A similar route, with the 8-hydroxy protected by a TBS group, provided quinolone **9c**. A good yield of **10b** was obtained by N-methylation of **9b**, but several efforts to reduce the cyano group to the primary amine failed, probably because of competing debenzylation. Efforts to N-methylate **9c** were foiled by concomitant loss of the TBS protecting group. An alternate approach using Katritzky's *N*-hydroxymethylbenzotriazole method[16] succeeded for methylation of the protected cyanohydrin **6c** to give **6d**. This compound was successfully condensed with **8** to give **7d**. However, **7d** was recovered unchanged from the cyclization conditions (240 °C, 1 h). This result indicates a requirement for an unsubstituted nitrogen in the cyclization. It appears that the *N*-H must play a role in determining the rate of decomposition of the dioxane-4,6-dione ring. Mechanistic studies of the thermal decomposition of anilinomethylene Meldrum's acid derivatives have mainly been carried out under flash vacuum pyrrolysis (FVP) conditions and have emphasized the role of a 1,3-hydrogen shift.[19] Under FVP conditions the *N*-methylanilinomethylene derivative gives 1-phenyl-2*H*-pyrrol-3-one, not *N*-methylquinolone.[20]



An isomer of isoaaptamine, compound **2e**, 1-methyl-8-demethylaaptamine, was successfully synthesized following a similar route. The aldehyde **3e** with reversed placement of the methoxy and benzyloxy substituents was prepared from 5-nitrovanillin. Conversion to the TBS-protected cyanohydrin and the condensation with **8** proceeded smoothly to give **7e**. Thermal cyclization to quinolone **9e** occurred in good yield. N-Methylation with methyl iodide gave **10e**. The reduction of the cyano group again proved troublesome, however. The best conditions found involved use of $CoCl_2$ and $NaBH_4$.[21] When followed by selective protection of the primary aminomethyl group by carboxybenzylation, **11e** was obtained in 34% yield. The reduction was hard to reproduce, however. Application of modified Andrew−Raphael cyclization conditions[13] to **11e** provided **2e**. Andrew and Raphael used sonication to accelerate the reaction. We found inclusion of triethylamine in the reaction made sonication unnecessary (Scheme 1). A more efficient synthesis of **2e** was eventually developed.

Because the difficulties with the previous approaches resulted mainly from the reaction conditions required for reduction of the cyano group, a revised route using a nitromethyl group was developed. Condensation of nitromethane with **3b** catalyzed by Amberlyst A21 ion-exchange resin,[22] followed by protection with TBS triflate gave **12b**. Both nitro groups were reduced using $NiCl_2$−$NaBH_4$[23] and the primary alkylamine was selectively protected by CBZ-Cl by reaction at −78 °C → −30 °C. The primary arylamine **14b** reacted with **8** to give **15b**. The cyclization of **15b** was successful, although the yield of **16b** was somewhat lower (35%) than had been achieved with the nitrile intermediate. Good regioselectivity for *N* versus *O* alkylation of the quinolone **16b** was achieved with methyl iodide and K_2CO_3 in DMF. After removal of the CBZ protecting group by transfer hydrogenolysis,[24] cyclization and aromatization gave isoaaptamine **2b** in 73% yield. The overall yield of **2b** was 15% (Scheme 2). HRMS confirmed the composition of the synthetic material, and ^{1}H and ^{13}C NMR comparison of synthetic isoaaptamine with a sample of natural origin confirmed their identity.

Cyclization of **16b** gave **1b**, 9-demethylaaptamine **1b**. Air oxidation gave demethyl(oxy) aaptamine **18**, which has previously been isolated as a natural product[5] and synthesized.[8]

Modification of the O- and N-alkylation pattern of the isoaaptamine synthesis permitted synthesis of aaptamine and several new analogues. Aaptamine **1f** and *N*-methylaaptamine, **2f**, were prepared starting with 5-nitroveratraldehyde.[13] Modification of the conditions of the nitromethane addition were needed because of failure of the anionic resin to produce good yields. Conditions reported by Fernandez et al. involving TBS-chloride and TBAF, followed by TBS-triflate,[25] gave an 86% yield of the silylated adduct **12f**. Reduction of **12f** was done by transfer hydrogenation[24] to give **13f**. Carboxybenzylation, condensation with **8**, and cyclization to **15f** proceeded in excellent yield. After removal of the CBZ group, cyclization proceeded to give aaptamine hydrochloride in 83% yield. The overall yield of 42% represents a modest improvement on the 26% overall yield reported by Andrew and Raphael using the cyano intermediate.[13] Comparison of the ^{1}H-spectrum with the published data for the natural compound, and spectra of synthetic material provided by Cava,[8] Joule,[11] and Kelly[12] confirmed the identity of the product. We observed a significantly higher melting point, 176−177 °C, than

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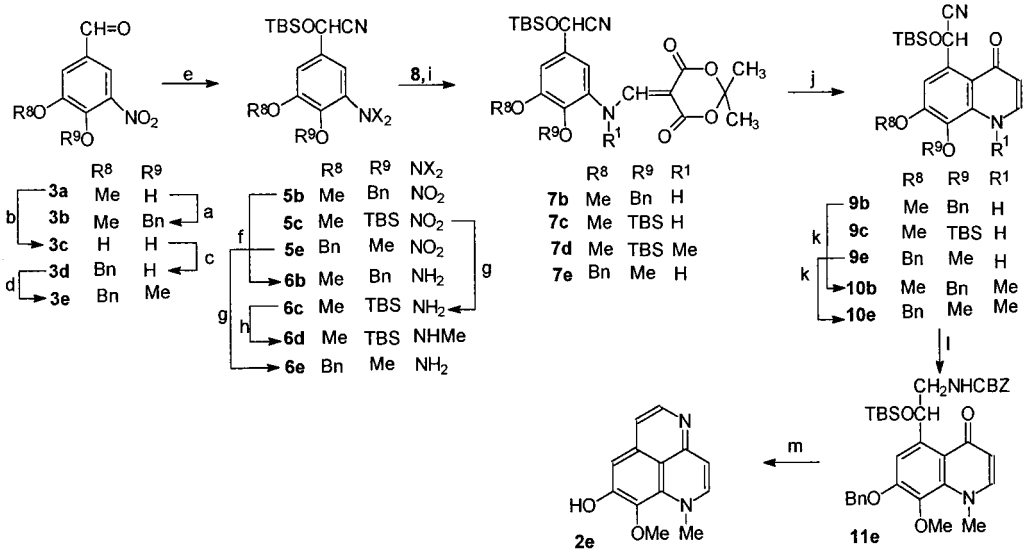
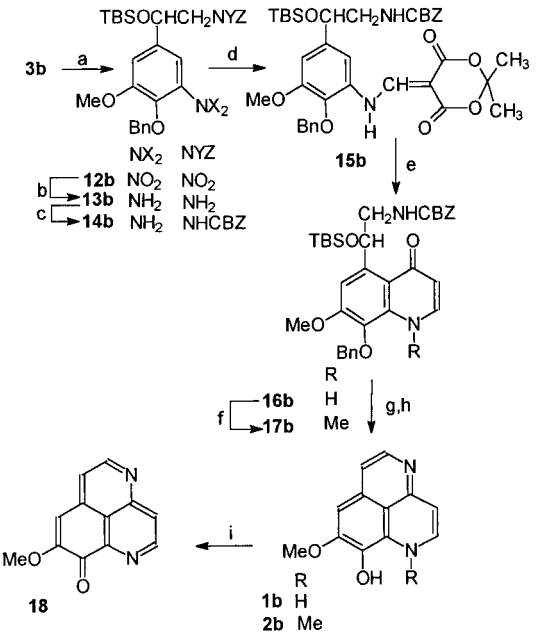
Scheme 1[a]



[a] Key: (a) KOH, $BnN^+(Bu)_3Br^-$, BnBr, CH_2Cl_2, H_2O, rt, 24 h; **3b** (92%); (b) $AlCl_3$, pyridine, $CHCl_3$, 0 °C to reflux, 24 h; **3c** (98%); (c) KF, BnBr, DMF, 140 °C, 48 h; **3d** (93%); (d) KOH, $BnN^+(Bu)_3Br^-$, Me_2SO_4, $CHCl_3$, H_2O, rt, 36 h; **3e** (92%); (e) KCN, ZnI_2, TBS-Cl, 18-crown-6, acetonitrile, 70 °C; 3 h, **5b** (92%); 48 h, **5c** (82%); 5h, **5e** (81%); (f) $TiCl_3$ in 20% HCl, 4 M NH_4OAc, acetone, rt, 12 h; **6b** (86%); (g) $TiCl_4$, $HgCl_2$, Mg, *t*-BuOH, THF, 15 min; **5c**, 0 °C, 1.5 h; **6c** (85%); (h) 1-$HOCH_2Bt$, EtOH, rt, 24 h, $NaBH_4$, THF, reflux, **6d** (77%); (i) **8**, reflux 12 h; **7b** (85%); **7c** (83%); **7e** (88%); (j) diphenyl ether; 220 °C, 20 min, **9b** (56%); 240 °C, 15 min, **9c** (52%); 240 °C, min, **9e** (78%); (k) K_2CO_3, MeI, DMF, 70 °C, 2 h, **10e** (96%); (l) $CoCl_2$, $NaBH_4$, MeOH, 0 °C, 2 h; CBZ-Cl, Et_3N, DMAP, DMF, 0 °C, 3 h, **10e** (34%); (m) $(NH_4)_2SO_4$, Et_3N, HMDSA, MeOH, HCl, rt, 20 h; **2e** (68%).

Scheme 2[a]



[a] Key: (a) CH_3NO_2, Amberlyst A-21, rt, 3 h, TBSOTf, 2,6-lutidine, 0 °C to rt, 1 h; **12b** (92%); (b) $NiCl_2$, $NaBH_4$, 25 °C, 25 min; **13b** (86%); (c) CBZ-Cl, DMAP, K_2CO_3, −78 °C to −30 °C, 8 h, **14b** (97%); (d) **8**, reflux 4 h; **15b** (87%); (e) diphenyl ether; 240 °C, 20 min, **16b** (35%); (f) K_2CO_3, MeI, DMF; 100 °C, 2 h, **17b** (79%); (g) 10% Pd−C, NH_4OAc, MeOH, 40 °C, 20 min; (h) $(NH_4)_2SO_4$, Et_3N, HMDSA, reflux, 20 h; MeOH, HCl, rt, 20 h; **1b** (83%), **2b** (73%); (i) MeOH, O_2, 0.2 M $NaHCO_3$, 1 h, **18** (73%).

previously reported. It is not clear if this represents a different crystal form or a different state of hydration.

N-Methylation of **16f** prior to the cyclization gave **17f**, which was converted to *N*-methylaaptamine **2f** in 73% yield. This compound was previously prepared by Hibino et al. by a process involving N-methylation during a thermal cyclization.[14]

The analogues in which the O(8)−O(9) methylation pattern was reversed from that in isoaaptamine were prepared using **3e** as the starting aldehyde. The nitromethane addition was successful using the Amberlyst A-21 procedure.[22] The other steps parallel the isoaaptamine synthesis. The final cyclization and aromatization gave *N*-methyl-8-demethylaaptamine **2e** in 76% yield. The unmethylated quinolone **16e** was converted to 8-demethylaaptamine **1e** in 68% yield.

The final analogues targeted for synthesis were 8,9-methylenedioxy derivatives. The nitration of 1,3-benzodioxole-5-carboxaldehyde gives the 6-nitro product.[26] It was therefore necessary to find an alternate means for introduction of nitrogen at C5. The bromoaldehyde **3d**[27] was chosen as the starting material and was protected as the dioxolane. Buchwald's Pd-catalyzed amination conditions[28] gave **4i** in 96% yield after removal of the dioxolane protecting group. Addition of nitromethane (Amberlyst A-21) and O-silylation proceeded efficiently to give **12g** (86%). The *N*-CBZ protecting group was removed cleanly at the same time as the reduction of the nitro group by use of transfer hydrogeneration with 10% Pd−C and $NH_4^+HCO_2^-$ (95%).[24] The remainder of the synthesis followed the previous method (Scheme 3). Both the *N*-methyl, **2g**, and unsubstituted, **1g**, methylenedioxy analogues were obtained.

Biological Activity

Compounds **1b**, **1e**, **2e**, **1g**, and **2g** were submitted for evaluation in the NCI tumor cell line panel.[29] Compounds **2b**, **1g**, and **2g** showed sufficient initial response for

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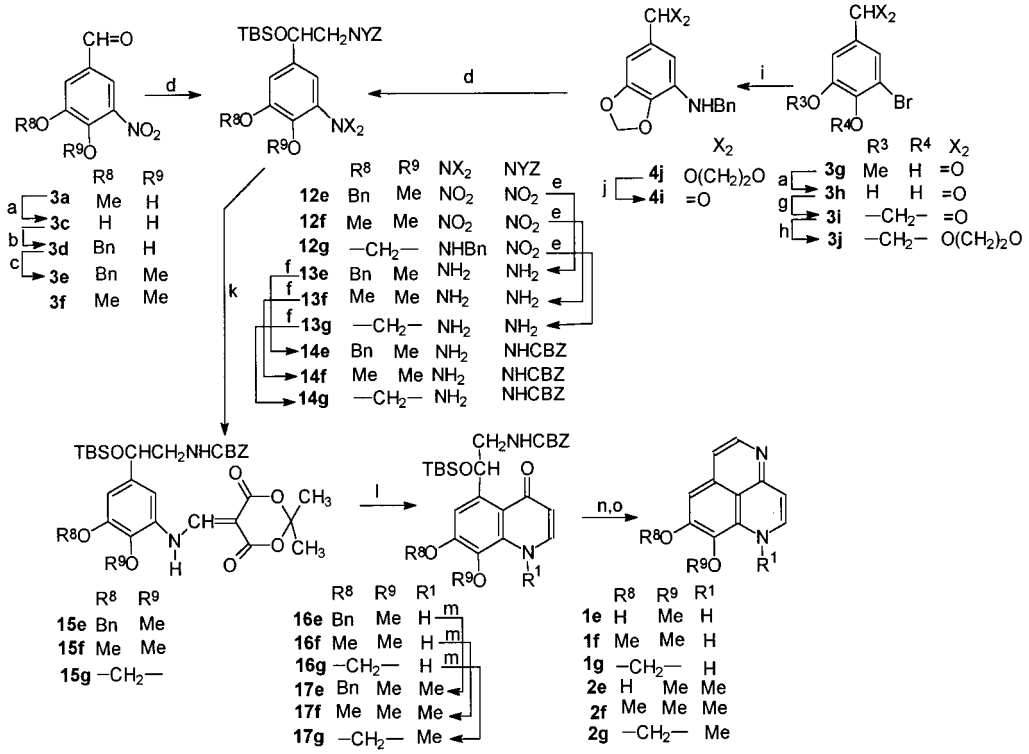
Scheme 3[a]



[a] Key: (a) $AlCl_3$, pyridine, $CHCl_3$, 0 °C to reflux, 24 h; **3c** (98%); 36 h, **3h** (92%); (b) KF, BnBr, DMF, 140 °C, 48 h; **3d** (93%); (c) KOH, $BnN^+(Bu)_3Br^-$, Me_2SO_4, $CHCl_3$, H_2O, rt, 36 h; **3e** (92%); **12g** (86%); (d) CH_3NO_2, Amberlyst A-21, rt 3 h; TBSOTf, 2,6-lutidine, 0 °C to rt, 2 h, **3f** (93%), CH_3NO_2, TBAF, Et_3N, TBS-Cl, 0 °C to rt, 3 h; TBSOTf, 2,6-lutidine, 0 °C to rt, 2 h, **10e** (93%); (e) $NiCl_2$, $NaBH_4$, 0 °C, 25 min; **13e** (76%), 10% Pd−C, NH_4O_2CH, reflux, 2 h; **13f** (100%); **13g** (98%); (f) CBZ-Cl, DMAP, K_2CO_3, −78 to −30 °C, 8 h, **14e** (97%); **14f** (84%); **14g** (91%); (g) KF, CH_2Br_2, DMF, 140 °C, 4 h, **3i** (85%); (h) $HOCH_2CH_2OH$, PTSA, benzene, reflux 24 h; **4c** (98%); (i) $BnNH_2$, $Pd_2(dba)_3$, *S*-Binap, NaO-*t*-Bu, toulene, 90 °C, 3 h, **4j** (96%); (j) PPTS, acetone, H_2O, reflux, 30 min; **4i** (100%); (k) **8**, reflux 4 h; **15e** (82%); **15f** (86%); **15g** (84%); (l) diphenyl ether; 240 °C, 20 min, **16e** (82%); **16f** (68%); **16g** (67%); (m) K_2CO_3, MeI, DMF, 100 °C, 2 h, **17e** (96%); **17f** (68%); **17g** (86%); (n) 10% Pd−C, NH_4O_2CH, MeOH, 40 min; (o) $(NH_4)_2SO_4$, Et_3N, HMDSA, reflux, 20 h; MeOH, HCl, rt, 20 h; **1e** (76%); **1f** (85%); **1g** (68%); **2e** (68%); **2f** (73%); **2g** (91%).

repeat testing in the primary screen but none met the criteria for further evaluation.

Experimental Section

General Procedures. Starting materials were obtained from commercial sources and used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Triethylamine (TEA), pyridine, acetonitrile, and toluene were distilled from calcium hydride and stored under nitrogen. Reactions under anhydrous conditions were performed using oven-dried and/or flame-dried glassware and dry solvents under an inert atmosphere. Melting points were determined on a Thomas-Hoover capillary melting point apparatus in an open capillary tube and are uncorrected. EM Science aluminum TLC plates coated with silica gel 60 F_{254} were visualized with UV light, vanillin stain, and/or Dragendorff stain. Flash chromatography was performed under medium pressure using either ICN Silica 60, 32−63 Å, or EM Science silica gel 60 Geduran, 35−75 μM. Solvent removal was normally done using a rotary evaporator under aspirator pressure. High boiling solvents were removed using a vacuum pump. NMR spectra were recorded at 300 MHz for proton and 75 MHz for carbon. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

4-Benzyloxy-3-methoxy-5-nitrobenzaldehyde (3b) A mixture of 5-nitrovanillin **3a** (5.00 g, 25.36 mmol), benzyl bromide (21.70 g, 126.80 mmol), KOH (2.33 g, 56.72 mmol), and benzyltriethylammonium chloride (2.90 g, 12.68 mmol) in 60 mL of CH_2Cl_2 and 60 mL of distilled water was stirred at room temperature for 24 h under nitrogen. The aqueous layer was extracted with CH_2Cl_2 and combined with the organic layer of the reaction mixture. The CH_2Cl_2 solution was washed with 10% aqueous NaOH and brine. The organic layer was dried with $MgSO_4$ and filtered, and solvents were removed in vacuo. The residue was flash chromatographed (hexanes to CH_2Cl_2) to give 6.82 g of **3b** as a pale yellow oil (92% yield): lit.[30] mp 57−58 °C; ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H), 7.83 (d, 1H, J = 1.83 Hz), 7.64 (d, 1H, J = 1.83 Hz), 7.48−7.35 (m, 5H), 5.30 (s, 2H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.5, 155.4, 146.9, 145.8, 136.2, 132.1, 129.2, 129.14, 129.08, 120.2, 113.4, 76.8, 57.2; MS *m*/*z* 288 (M + 1).

2-(*tert*-Butyldimethylsilyloxy)-2-(4-benzyloxy-3-methoxy-5-nitrophenyl)ethanonitrile (5b). To 20 mL of freshly distilled acetonitrile were added, in order, the aldehyde **3b** (1.00 g, 3.48 mmol), KCN (1.13 g, 17.40 mmol), 50 mg of 18-crown-6, and 50 mg of ZnI_2. A positive pressure of nitrogen was established, and the solution was stirred at room temperature for 15 min. *tert*-Butyldimethylsilyl chloride (TBS−Cl) (630 mg, 4.18 mmol) was added, and the solution was heated at 70 °C for 3 h. The solvent was removed and the residue suspended in 50 mL of EtOAc and filtered. The filtrate was washed several times with distilled water. The organic layer was dried with $MgSO_4$ and filtered and the solvent removed in vacuo. Flash chromatography (2:1 EtOAc/hexanes) gave 1.37 g of **5b** as a pale yellow solid in 92% yield: ^{1}H NMR ($CDCl_3$) δ 7.50−7.33 (m, 5H), 7.25 (s, 1H), 7.24 (s,1H), 5.50 (s, 1H), 5.19 (s, 2H), 3.97 (s, 3H), 0.96 (s, 9H), 0.27 (s, 3H), 0.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.5, 144.8, 141.7, 135.7, 132.3, 128.3, 128.18, 128.15, 118.0, 113.1, 112.7, 75.7, 62.5, 56.3, 25.1, 17.8, −5.4, −5.6; MS *m*/*z* 428 (M^+).

2-(5-Amino-4-benzyloxy-3-methoxyphenyl)-2-(*tert*-butyldimethoxysilyloxy)ethanonitrile (6b) The silylated cyanohydrin **5b** (1.00 g, 2.33 mmol) was dissolved in 30 mL of

(30) Martin, P. *Helv. Chim. Acta* **1989**, *72*, 1554.

acetone, and 60 mL of 4 M $NH_4O_2CCH_3$ solution was added. $TiCl_3$ (3.31 g, 21.4 mmol) was added as a 19% solution in 20% aqueous HCl (14.6 mL). The solution was stirred at room temperature for 12 h. The solution was extracted with CH_2Cl_2. The combined organic layers were washed with water. The organic layer was dried with $MgSO_4$ and filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography (CH_2Cl_2) to give 848 mg of **6b** as a tan amorphous solid in 86% yield: ^{1}H NMR ($CDCl_3$) δ 7.48−7.31 (m, 5H), 6.46 (d, 1H, J = 1.47 Hz), 6.44 (d, 1H, J = 1.95 Hz), 5.37 (s, 1H), 5.00 (s, 2H), 3.88 (s, 3H), 0.95 (s, 9H), 0.22 (s, 3H), 0.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.9, 140.8, 137.3, 134.7, 132.1, 128.1, 128.0, 127.8, 119.1, 106.0, 99.6, 74.1, 63.6, 55.5, 25.2, 17.9, −5.4, −5.5; MS m/z 399 (M^+).

5-[5-[1-(*tert*-Butyldimethylsilyloxy)-1-cyanomethyl]-2-benzyloxy-3-methoxyphenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (7b). Meldrum's acid (456 mg, 3.16 mmol) was refluxed under nitrogen in 40 mL of trimethyl orthoformate for 3 h to give **8**. The aniline **6b** (840 mg, 2.11 mmol) in 5 mL of trimethyl orthoformate was added and the solution refluxed for 12 h. The solvent was removed and the residue was flash chromatographed (1:1 EtOAc/hexanes) to give 995 mg of **7b** as a white solid (85% yield): ^{1}H NMR ($CDCl_3$) δ 8.43 (d, 1H, J = 14.65 Hz.), 7.43−7.39 (m, 2H), 7.33−7.29 (m, 3H), 6.95 (br. s, 1H), 6.93 (br. s, 1H), 5.44 (s, 1H), 5.18 (s, 2H), 3.98 (s, 3H), 1.75 (s, 6H), 0.96 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 163.2, 153.4, 150.5, 137.1, 135.2, 133.3, 132.3, 129.0, 128.4, 128.1, 118.4, 106.9, 104.7, 87.6, 74.9, 63.1, 55.9, 26.7, 25.2, 17.8, −5.4, −5.5; MS m/z 552 (M^+).

2-(*tert*-Butyldimethylsilyloxy)-2-[8-benzyloxy-7-methoxy-4(1*H*)-quinolinon-5-yl]ethanonitrile (9b). The Meldrum's acid derivative **7b** (200 mg, 0.361 mmol) was added to 10 mL of diphenyl ether. A stream of nitrogen was passed through the solution for 20 min, and the flask was then lowered into a large preheated silicone oil bath at 240 °C. The temperature of the bath dropped to approximately 225 °C and rose again to 240 °C in 5−7 min. The solution was stirred in the bath for a total of 20 min and was then removed and allowed to cool. The solvent was removed under vacuum (0.1 mmHg, 110 °C). The residue was purified by flash chromatography (3:1 EtOAc/hexanes to EtOAc) to give 91 mg of **9b** (56% yield): ^{1}H NMR ($CDCl_3$) δ 8.51 (br s, 1H), 7.59 (s, 1H), 7.42−7.34 (m, 6H), 7.12 (s, 1H), 6.11 (dd, 1H, J = 1.53, 7.64 Hz), 5.21 (dd, 2H, J = 11.30, 23.50 Hz), 4.04 (s, 3H), 0.99 (s, 9H), 0.31 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.3, 151.9, 137.7, 136.2, 135.8, 133.68, 133.66, 128.3, 119.6, 116.6, 110.5, 106.6, 75.1, 61.1, 55.7, 25.3, 17.8, 17.8, −5.5, −5.6; MS m/z 451 (M + 1).

2-(*tert*-Butyldimethylsilyloxy)-2-[-8-benzyloxy-7-methoxy-1-methyl-4(1*H*)-quinolinon-5-yl]ethanonitrile (10b). K_2CO_3 (550 mg, 3.97 mmol) was flame dried in a flask and allowed to cool. Compound **9b** (600 mg, 1.32 mmol) and 20 mL of DMF were added, followed by methyl iodide (559 mg, 3.97 mmol). The solution was stirred under nitrogen for 3 h at 100 °C. The solution was allowed to cool and poured into water and extracted with EtOAc. The combined organic layers were washed with water. The organic layer was dried with $MgSO_4$, filtered and solvents were removed in vacuo. The crude material was purified by flash chromatography (EtOAc) to give 600 mg of **10b** in 97% yield: ^{1}H NMR ($CDCl_3$) δ 7.71 (br s, 1H), 7.44−7.35 (m, 5H), 7.23 (d, 1H, J = 7.81 Hz), 7.13 (s, 1H), 6.12 (d, 1H, J = 7.81 Hz), 4.99 (dd, 2H, J = 11.23, 23.43 Hz), 4.02 (s, 3H), 3.90 (s, 3H), 0.99 (s, 9H),, 0.31 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.7, 154.6, 145.5, 137.6, 136.6, 135.9, 135.2, 128.3, 128.1, 127.9, 119.6, 119.0, 110.4, 107.1, 76.1, 61.5, 55.8, 45.9, 25.3, 17.9, −5.5, −5.6; MS m/z 465 (M + 1).

2-(*tert*-Butyldimethylsilyloxy)-2-(3-*tert*-butyldimethylsilyloxy-4-methoxy-5-nitrophenyl)ethanonitrile (5c). KCN (11.56 g, 172.5 mmol) was flame dried in a flask and allowed to cool. 5-Nitrovanillin **3a** (5.00 g, 25.4 mmol), DMAP (1.55 g, 12.7 mmol), ZnI_2 (200 mg), and 18-crown-6 (200 mg) were dissolved in 100 mL of freshly distilled acetonitrile, and a positive pressure of nitrogen was established. The solution was then heated at 80 °C for 5 min. TBS-Cl (11.47 g, 76.1 mmol) was then added and maintained at 80 °C for 48 h. The solution was allowed to cool and the solvent removed in vacuo. The residue was mixed with EtOAc and filtered through Celite. The bed of Celite was rinsed with copious amounts of EtOAc. The solvent was removed in vacuo to a volume of approximately 300 mL. This solution was washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried with $MgSO_4$ and filtered and the solvent removed in vacuo. The crude material was purified by flash chromatography (2:1 CH_2Cl_2/hexanes) to give 9.40 g of **5c** (82% yield): ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 1H), 7.04 (s, 1H), 5.37 (s, 1H), 3.79 (s, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H).

2-(5-Amino-3-*tert*-butyldimethlsilyloxy-4-methoxyphenyl)-2-(*tert*-butyldimethlysilyloxy)ethanonitrile (6c). $HgCl_2$ (1.89 g, 9.94 mmol) and 20 mL of THF were added to a flame-dried flask, and a nitrogen atmosphere was established. Magnesium metal (967 mg, 39.77 mmol) was added, and the mixture was stirred at room temperature for 10 min. The supernatant was removed with a syringe, and the residue was washed three times with 20 mL of THF using a syringe. The solution was cooled to 0 °C, and 9.94 mL of a 1 M solution of $TiCl_4$ in toluene (1.89 g, 9.94 mmol) was added dropwise and stirred for 5 min. A solution of the nitro compound **5c** (1.50 g, 3.32 mmol), 8 mL of *t*-BuOH, and 15 mL of THF was added dropwise. The resulting mixture was stirred for 1.5 h at room temperature. 50 mL of saturated $NaHCO_3$ solution was added, along with 100 mL of EtOAc. The mixture was then filtered through Celite and the Celite bed was washed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic solutions were dried with $MgSO_4$, filtered, and the solvents were removed in vacuo. The crude material was subjected to flash chromatography (1:1 EtOAc/hexanes) to give of the amine **6c** (1.22 g) in 85% yield: ^{1}H NMR ($CDCl_3$) δ 6.37 (d, 1H, J = 1.83 Hz), 6.33 (d, 1H, J = 2.44 Hz), 5.27 (s, 1H), 3.69 (s, 3H), 0.92 (s, 9H), 0.84 (s, 9H), 0.103 (s, 9H), 0.04 (s, 3H).

5-[5-[1-(*tert*-Butyldimethylsilyloxy)-1-cyanomethyl]-3-*tert*-butyldimethylsilyloxy-2-methoxyphenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (7c). Using the general procedure for Meldrum's acid adduct formation described for **7b**, compound **7c** (1.81 g, 3.08 mmol) was obtained as a white solid in 83% yield: ^{1}H NMR ($CDCl_3$) δ 11.19 (d, 1H, J = 14.65 Hz), 8.49 (d, 1H, J = 14.65 Hz), 6.90 (s, 1H), 6.80 (s, 1H), 5.35 (s, 1H), 3.77 (s, 3H), 1.66 (s, 6H), 0.90 (s, 9H), 0.87 (s, 9H), 0.16 (s, 3H), 0.15 (s, 6H), 0.09 (s, 3H).

2-(*tert*-Butyldimethylsilyloxy)-2-[-7-*tert*-butyldimethylsilyloxy-8-methoxy-4(1*H*)-quinolinon-5-yl]ethanonitrile (9c). Using the general procedure for thermal cyclization to a quinolone described for **9b**, compound **9c** (266 mg, 0.551 mmol) was obtained as a tan solid in 52% yield: ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1H), 7.29 (dd, 1H, J = 5.49, 7.32 Hz), 7.00 (s, 1H), 6.86 (s, 1H), 5.92 (dd, 1H, J = 1.83, 7.32 Hz), 3.67 (s, 3H), 0.79 (s, 9H), 0.71 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H).

2-(3-*tert*-Butyldimethoxysilyloxy-4-methoxyphenyl-5-methylamino)-2-(*tert*-butyldimethlsilyloxy)ethanonitrile (6d). The amine **6c** (500 mg, 0.580 mmol) and 1-hydroxymethylbenzotriazole (173 mg, 0.580 mmol) were dissolved in a minimum amount of refluxing absolute ethanol. The solution was allowed to cool and kept at room temperature for 24 h with occasional mixing. The flask was cooled to 0 °C for several hours. The precipitated solid was filtered and washed with ice-cold ethanol. This solid was then dissolved in 25 mL of THF, $NaBH_4$ (138 mg, 3.55 mmol) was added, and the solution was refluxed under nitrogen until the starting material was no longer was detected by TLC. The solution was poured into water and extracted with diethyl ether. The organic layers were washed with both saturated $NaHCO_3$ and water. The combined organic solutions were dried with $MgSO_4$ and filtered, and the solvents were removed in vacuo. The crude material was purified by flash chromatography (2:1 CH_2Cl_2/hexanes) to give 382 mg of **6d** (77% yield): ^{1}H NMR

($CDCl_3$) δ 6.41 (d, 1H, J = 2.44 Hz), 6.35 (d, 1H, J = 1.83 Hz), 5.42 (s, 1H), 3.78 (s, 3H), 2.86 (s, 3H), 1.00 (s, 9H), 0.94 (s, 9H), 0.20 (s, 3H), 0.18 (s, 6H), 0.13 (s, 3H).

5-[5-[5-[1-(*tert*-Butyldimethylsilyloxy)-1-cyanomethyl]-3-*tert*-butyldimethylsilyloxy-2-methoxyphenyl]-*N*-methylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (7d) Using the general procedure for Meldrum's acid adduct formation, product **7d** (485 mg, 0.820 mmol) was obtained in 94% yield: ^{1}H NMR ($CDCl_3$) δ (This compound exhibits rotational isomerism. The peaks listed correspond to the primary rotamer) 8.17 (s, 1H), 7.03 (d, 1H, J = 2.44 Hz), 6.91 (d, 1H, J = 2.44 Hz), 5.43 (s, 1H), 5.30 (s, 1H), 3.87 (s, 3H), 3.62 (s, 3H), 1.76 (s, 6H), 0.95 (s, 9H), 0.93 (s, 9H), 0.25 (s, 3H), 0.20−0.14 (m, 9H).

2-(4-Benzyloxy-3-methoxy-5-nitrophenyl)-2-(*tert*-butyldimethylsilyloxy)nitroethane (12b). The aldehyde **3b** (4.00 g, 13.92 mmol) was dissolved in 13 mL of dry THF. Amberlyst A-21 ion-exchange resin (9.60 g) was added, followed by nitromethane (10.30 g, 167.04 mmol). The solution was stirred at room temperature for 3 h. The solution was diluted with 100 mL of EtOAc and filtered, and the resin was washed with copious amounts of EtOAc. The filtrate was concentrated in vacuo and the residue was recystallized from CH_2Cl_2/hexanes. The nitroaldol product **5b** (4.13 g) containing less than 5% aldehyde was obtained. The adduct was dissolved in 120 mL THF containing 2,6-lutidine (2.64 g, 24.6 mmol) under nitrogen. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (TBSOTf) (5.70 g, 21.6 mmol) was added dropwise with a syringe. The solution was stirred for 2 h while coming to room temperature. The solution was diluted with 200 mL of EtOAc and organic layer was washed with $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$, filtered, and the solvent removed in vacuo. The residue was subjected to flash chromatography (3:1 CH_2Cl_2/hexanes) and 5.19 g of the silyl derivative **12b** was obtained as a white solid in 81% overall yield. An analytical sample was obtained by recrystallization from CH_2Cl_2/hexanes: mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 7.48−7.33 (m, 6H), 7.18 (d, 1H, J = 1.83 Hz), 5.42 (dd, 1H, J = 3.05, 9.16 Hz), 5.19 (s, 2H), 4.52 (dd, 1H, J = 9.16, 12.21 Hz), 4.41 (dd, 1H, J = 3.66, 12.20 Hz), 3.96 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2, 145.7, 141.9, 136.7, 136.2,129.1, 128.9, 114.0, 113.7, 82.8, 76.5, 72.1, 57.1, 26.0, 18.5, −4.3, −5.1; MS m/z 462 (M^+). Anal. Calcd for $C_{22}H_{30}N_2O_7Si$: C, 57.12; H, 6.54; N, 6.05. Found: C, 57.14; H, 6.56; N, 5.99.

2-(5-Amino-4-benzyloxy-3-methoxyphenyl)-2-(*tert*-butyldimethylsilyloxy)ethylamine (13b). The dinitro derivative **12b** (3.60 g, 8.43 mmol) and $NiCl_2$−$6H_2O$ (8.02 g, 33.7 mmol) were added to 90 mL of MeOH and 45 mL of THF and cooled to 0 °C. $NaBH_4$ (2.96 g, 77.8 mmol) was added portionwise over 15 min, and the mixture was stirred at 0 °C for 10 min. The solvents were removed in vacuo, and 150 mL of $CHCl_3$ and 20 mL of water were added. The mixture was filtered through Celite, and the inorganic residue was removed from the Celite pad, triturated with 50 mL of $CHCl_3$, and filtered through Celite again. This procedure was repeated until no product was detected by TLC in the $CHCl_3$ after trituration. The $CHCl_3$ was concentrated in vacuo to approximately 150 mL, and the organic layer was washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$ and filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (96.5:3:1.5 $CHCl_3$/MeOH/TEA). The diamine **13b** (2.68 g) was obtained as a brown oil in 86% yield: ^{1}H NMR ($CDCl_3$) δ 7.47−7.32 (m, 5H), 6.35 (br s, 1H), 6.29 (br s, 1H), 4.99 (d, 2H, J = 1.22 Hz), 4.55 (br t, 1H, J = 5.50 Hz), 3.84 (s, 3H), 3.73 (br s, 2H), 2.84 (br d, 2H, J = 5.49 Hz), 2.05 (br s, 2H), 0.92 (s, 9H), 0.07 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.3, 140.9, 139.3, 138.5, 134.4, 128.88, 128.85, 128.5, 107.6, 100. 7, 76.3, 74.8, 56.2, 50.8, 26.4, 18.7, −4.1, −4.4; MS m/z 403 (M + 1).

***O*-Benzyl *N*-2-(5-Amino-4-benzyloxy-3-methoxyphenyl)-2-(*tert*-butyldimethylsilyloxy)ethyl carbamate (14b).** The bis-amine **13b** (646 mg, 1.61 mmol), DMAP (196 mg, 1.61 mmol), and K_2CO_3 (440 mg, 3.21 mmol) in 35 mL of dry THF were cooled to −78 °C under nitrogen. CBZ-Cl (274 mg, 1.61 mmol) in 10 mL of dry THF was added dropwise via an addition funnel over 15 min. The solution was stirred at −78 °C for 6 h and then allowed to warm to −30 °C and was stirred until the starting material was no longer detected by TLC. The solution was poured into 100 mL of water and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. Flash chromatography (2:1 hexanes/EtOAc) gave 832 mg (97% yield) of the carbamate **14b** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.47−7.29 (m, 10H), 6.34 (br s, 1H), 6.31 (br s, 1H), 5.11 (s, 2H), 4.99 (s, 2H), 4.63 (dd, 1H, J = 3.66, 7.32 Hz), 3.82 (s, 3H), 3.71 (br s, 2H), 3.50−3.39 (m, 1H), 3.22−3.10 (m, 1H), 0.89 (s, 9H), 0.02 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.9, 153.4, 141.0, 138.9, 138.5, 137.2, 134.5, 129.0, 128.9, 128.9, 128.6, 128.5, 106.9, 100.6, 74.8, 74.2, 67.2, 56.2, 49.9, 26.4, 18.7, −4.2, −4.5; MS m/z 536 (M^+).

5-[5-[2-(Benzyloxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-benzyloxy-3-methoxyphenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (15b). Meldrum's acid (0.413 g, 2.87 mmol) was refluxed under nitrogen in 35 mL of trimethyl orthoformate for 2 h. The arylamine **14b** (1.14 g, 2.39 mmol) was dissolved in 15 mL of trimethyl orthoformate and added to the above solution and refluxed for 4 h. The solvent was removed in vacuo and the residue subjected to flash chromatography (2:1 hexanes/EtOAc) to give 1.00 g of **15b** as a white solid (87% yield): mp 110−111 °C after recrystallization from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 11.40 (d, 1H, J = 14.65 Hz), 8.41 (d, 1H, J = 14.65 Hz), 7.40−7.27 (m, 10H), 6.82−6.80 (m, 2H), 5.14 (s, 2H), 5.10 (s, 2H), 4.99 (br t, 1H, J = 6.41 Hz), 4.72 (br dd, 1H, J = 3.97, 7.63 Hz), 3.91 (s, 3H), 3.50−3.39 (m, 1H), 3.23−3.12 (m, 1H), 1.75 (s, 6H), 0.89 (s, 9H), 0.04 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 65.3, 164.1, 156.8, 153.8, 151.4, 140.2, 136.9, 136.6, 136.3, 132.7, 129.9, 129.1, 129.0, 128.8, 128.6, 107.9, 105.4, 105.2, 87.9, 75.6, 73.9, 67.3, 56.6, 49.8, 27.5, 26.3, 18.7, −4.2, −4.5; MS m/z 691 (M^+).

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[8-benzyloxy-7-methoxy-4(1*H*)-quinolinon-5-yl]ethyl Carbamate (16b).** To a solution of 100 mL of diphenyl ether was added **15b** (1.09 g, 1.57 mmol). A stream of nitrogen was passed through the solution for 20 min and the flask was then lowered into a large silicone oil bath preheated to 240 °C. The temperature of the bath dropped to approximately 225 °C and rose again to 240 °C in 5−7 min. The solution was stirred in the bath for a total of 18 min, then removed and allowed to cool. The solvent was removed under vacuum (0.1 mmHg, 110 °C). Flash chromatography (1:2 to 6:1 hexanes/EtOAc) gave 0.326 g of the quinolone **16b** as a tan solid (35% yield). An analytical sample, mp 63−65 °C, was obtained by recrystallization from EtOAc/hexanes: ^{1}H NMR (acetone-d_6) δ 10.19 (br s, 1H), 7.55 (d, 1H, J = 7.33 Hz), 7.42 (s, 1H), 7.39−7.06 (m, 10H), 6.54 (br t, 1H, J = 4.58 Hz), 6.07 (br s, 1H), 5.84 (d, 1H, J = 7.33 Hz), 5.08 (dd, 2H, J = 10.99, 18.01 Hz), 4.86 (s, 2H), 3.90 (s, 3H), 3.50−3.40 (m, 1H), 3.37−3.29 (m, 1H), 0.83 (s, 9H), −0.02 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (acetone-d_6) δ 180.3, 156.8, 152.7, 141.6, 138.1, 137.9, 137.6, 136.9, 136.4, 129.1, 128.7, 128.6, 128.5, 128.1, 128.0, 118.0, 110.9, 107.8, 74.8, 70.7, 65.9, 56.0, 49.9, 26.0, 18.4, −4.8, −5.0; MS m/z 589 (M^+). Anal. Calcd for $C_{33}H_{40}N_2O_6Si$: C, 67.32; H, 6.85; N, 4.75. Found: C, 67.35; H, 6.80; N, 4.69.

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[8-benzyloxy-7-methoxy-1-methyl)-4(1*H*)-quinolinon-5-yl]ethyl Carbamate (17b).** The quinolone carbamate **16b** (0.480 g, 0.82 mmol), K_2CO_3 (0.338 g, 2.45 mmol), and CH_3I (0.346 g, 2.45 mmol) were dissolved in 20 mL of DMF under nitrogen and heated to 90−100 °C for 2 h. The solution was poured into 100 mL of water and extracted with EtOAc. The extracts were washed with water and brine. The extract was dried with $MgSO_4$, filtered and the solvent removed in vacuo. The material was purified by flash chromatography (20:1 to 4:1 CH_2Cl_2/acetone) to give 0.390 g of the *N*-methyl quinolone **17b** as a tan solid in 79% yield. An analytical sample was recrystallized from EtOAc/hexanes: mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.44−7.23 (m, 10H), 7.17 (d, 1H, J =

7.32 Hz), 6.57 (br t, 1H, J = 4.57 Hz), 6.05 (d, 1H, J = 7.33 Hz), 5.43 (dd, 1H, J = 4.88, 6.10 Hz), 5.05−4.88 (m, 4H), 3.94 (s, 3H), 3.88 (s, 3H), 3.61−3.41 (m, 2H), 0.91 (s, 9H), −0.077 (s, 3H), −0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.2, 156.9, 155.1, 145.8, 143.1, 138.4, 137.5, 137.3, 136.9, 135.8, 129.0, 128.8, 128.7, 128.4, 120.1, 111.4, 108.5, 76.7, 71.0, 66.7, 56.5, 50.3, 46.7, 20.4, 18.7, −4.3, −4.4; MS m/z 603 (M^+). Anal. Calcd for $C_{34}H_{42}N_2O_6Si$: C, 67.74; H, 7.02; N, 4.64. Found: C, 67.57; H, 6.94; N, 4.56.

8-Methoxy-1-methyl-1*H*-benzo[*de*][1,6]naphthyridin-9-ol (Isoaaptamine, 2b). To a flask containing *N*-methyl quinolone **17b** (0.260 g, 0.430 mmol) and 0.130 g of 10% Pd−C in 8 mL of methanol was added NH_4O_2CH (0.217 g, 3.45 mmol). The solution was lowered into a 40 °C oil bath and stirred for 20 min. The mixture was filtered through Celite and washed with copious amounts of MeOH. The solvent was removed under reduced pressure and the residue kept under a vacuum for 24 h. The free amine (0.089 g, 0.2363 mmol) and $(NH_4)_2SO_4$ (0.013 g, 0.0984 mmol) were placed in a flask with 12 mL of HMDSA and 6 mL of TEA. The flask was flushed with nitrogen for 20 min and then heated in an oil bath for 20 h at 130 °C. The solution was allowed to cool, and the solvents were removed in vacuo. The residue was dissolved in 25 mL of MeOH and filtered, 1.5 mL of concd HCl was added, and a nitrogen atmosphere was established. The solution was stirred at room temperature for 1.5 h. The solvents were removed under reduced pressure, and the residual water removed by repetitive evaporation of added MeOH under reduced pressure. The residue was kept under vacuum for 20 min and then dissolved in 25 mL of anhydrous MeOH. HCl gas was passed through the solution for 1.5 h. The flask was stoppered and kept at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography. (5:3:2 $CHCl_3$/MeOH/EtOAc) to give 0.087 g of isoaaptamine (**2b**) as a yellow solid in 73% yield as the hydrochloride salt. A pure sample was prepared by recrystallization from MeOH/acetone: mp 237 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.41 (br s, 1H), 7.68 (d, 1H, J = 7.32 Hz), 7.21 (d, 1H, J = 6.94 Hz), 7.10 (s, 1H), 6.75 (d, 1H, J = 6.94 Hz), 6.10 (d, 1H, 7.31 Hz), 3.99 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 153.6, 149.3, 149.2, 132.3, 129.3, 127.9, 118.1, 113.2, 101.6, 97.5, 56.6, 46.1; UV (95% EtOH) λ_{max} 203 nM (ϵ 33 509), 236 nM (ϵ 19 155), 263 nM (ϵ 26 554), 323 nM (ϵ 7366), 393 nM (ϵ 7464); EI$^+$HRMS calcd for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0896.

8-Methoxy-1*H*-benzo[*de*][1,6]naphthyridin-9-ol (9-Demethylaaptamine, 1b). Using the same procedure for HMDSA-mediated cyclization and methanolic HCL elimination, 9-demethylaaptamine hydrochloride salt **1b** (66 mg, 0.263 mmol) was obtained in 83% yield as a yellow/green solid. A pure sample was obtained by recrystallization from MeOH/acetone: mp 205 °C dec; ^{1}H NMR (DMSO-d_6) δ 12.12 (br s, 1H), 11.90 (br d, 1H, J = 4.89 Hz), 10.04 (s, 1H), 7.68 (t, 1H, J = 6.45 Hz), 7.20−7.17 (m, 1H), 7.05 (s, 1H), 6.75 (d, 1H, J = 7.33 Hz), 6.17 (d, 1H, J = 7.33 Hz), 3.93 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 152.1, 150.1, 142.3, 129.8, 129.1, 128.3, 128.0, 116.7, 112.9, 100.6, 97.5, 56.5; UV (95% EtOH) λ_{max} 208 nM (ϵ 35 786), 242 nM (ϵ 20 184), 268 nM (ϵ 12 740), 278 nM (ϵ 11 051), 318 nM (ϵ 4174), 356 nM (ϵ 3611); EI$^+$HRMS calcd for $C_{13}H_{10}N_2O_2$ 214.0742, found 214.0745.

8-Methoxy-1*H*-benzo[de][1,6]naphthyridin-9-one (Demethyloxy(oxy)aaptamine, 18). 9-Demethylaaptamine **1b** (75 mg, 0.296 mmol) was dissolved in 5 mL of MeOH and 3 mL of 0.2 M $NaHCO_3$ and was stirred under an atmosphere of oxygen at room temperature and pressure for 1 h. The MeOH was removed in vacuo and the aqueous solution extracted with $CHCl_3$. The organic layer was dried with $MgSO_4$ and filtered and the solvent removed in vacuo. The material was purified by flash chromatography (19:1 $CHCl_3$/MeOH) to give 47 mg of **18** as a green solid (73% yield). An analytical sample was prepared by recrystallization from $CHCl_3$/hexanes: mp 220 °C dec (lit.[8] mp 210−212 °C); ^{1}H NMR (DMSO-d_6) δ 9.09 (d, 1H, J = 4.27 Hz), 9.06 (d, 1H, J = 6.11 Hz), 8.17 (d, 1H, J = 5.49 Hz), 7.70 (d, 1H, J = 4.27 Hz), 7.12 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (D_6-DMSO) δ 177.1, 157.4, 155.7, 148.9, 148.9, 147.5, 136.5, 126.5, 122.3, 117.8, 108.9, 5612; UV (95% EtOH) λ_{max} 203 nM (ϵ 28 005), 233 nM (ϵ 22 251), 304 nM (ϵ 3471), 371 nM (ϵ 8901); EI$^+$HRMS calcd for $C_{13}H_8N_2O_2$ 212.0586, found 212.0584.

3,4-Dihydroxy-5-nitrobenzaldehyde (3c). To 5-nitrovanillin **3a** (5.00 g, 25.4 mmol) and $AlCl_3$ (3.72 g, 27.9 mmol) was added 50 mL of $CHCl_3$, and the mixture was cooled to 0 °C with an ice bath. Pyridine (8.83 g, 111.6 mmol) was added dropwise with a syringe. The ice bath was removed and the solution refluxed under nitrogen for 24 h. The solvent was removed in vacuo, 300 mL of 20% HCl solution was added to the residue, and the mixture was stirred for 30 min. The solution was extracted with EtOAc. The extracts were combined and washed with brine. The combined organic solutions were dried with $MgSO_4$ and filtered, and the solvents were removed in vacuo. The crude material was filtered hot with EtOAc. The solution was concentrated and the product precipitated using hexanes and filtered. **3c** (4.53 g) was obtained as a gray solid in 98% yield and recrystallized from EtOAc/hexanes: mp 148−150 °C (lit.[31] mp 145−148 °C); ^{1}H NMR (DMSO-d_6) δ 9.76 (s, 1H), 7.92 (d, 1H, J = 1.83 Hz), 7.42 (d, 1H, J = 1.83 Hz); ^{13}C NMR (DMSO-d_6) δ 190.49, 148.33, 147.33, 137.12, 126.96, 119.66, 115.81; MS m/z 184 (M + 1).

3-Benzyloxy-4-hydroxy-5-nitrobenzaldehyde (3d). KF (7.69 g, 132.4 mmol) was flame dried in a flask and allowed to cool. The aldehyde **3c** (4.85 g, 18.6 mmol) was added with 70 mL of DMF. Benzyl bromide (13.61 g, 79.6 mmol) was added, and the mixture was heated under nitrogen at 140 °C for 48 h. To the cooled solution was added 300 mL of 10% HCl, and the mixture was extracted with EtOAc. The extract was washed with water and brine. The solution was dried with $MgSO_4$ and filtered, and the solvents were removed in vacuo. Flash chromatography (CH_2Cl_2) gave 6.70 g of **3d** as an orange solid in 93% yield that was recrystallized from EtOAc/hexanes: mp 149−150 °C; ^{1}H NMR (DMSO-d_6) δ 9.79 (s, 1H), 8.06 (d, 1H, J = 1.83 Hz), 7.66 (d, 1H, J = 1.22 Hz), 7.49−7.44 (m, 2H), 7.39−7.26 (m, 3H), 5.29 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 190.34, 149.0, 148.1, 137.2, 135.9, 128.5, 128.2, 127.9, 126.8, 121.1, 114.2, 70.8; MS m/z 274 (M + 1).

3-Benzyloxy-4-methoxy-5-nitrobenzaldehyde (3e). The aldehyde **3d** (4.00 g, 14.6 mmol), dimethyl sulfate (18.47 g, 146.4 mmol), KOH (3.28 g, 58.52 mmol), and benzyltriethylammonium chloride (1.67 g, 7.32 mmol) were added to 60 mL of $CHCl_3$ and 60 mL of distilled water, and the mixture was stirred at room temperature for 36 h under a nitrogen atmosphere. The aqueous layer was separated and extracted with $CHCl_3$. The combined organic layers were concentrated in vacuo. The residue was taken up in diethyl ether and was washed with 2 N NH_4OH, 10% aqueous NaOH, and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography (3:1 CH_2Cl_2/hexanes) to yield 6.82 g of **3e** as a pale yellow solid (92% yield) that was recrystallized from CH_2Cl_2/hexanes: mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H), 7.84 (d, 1H, 1.84 Hz), 7.69 (d, 1H, J = 1.83 Hz), 7.48−7.37 (m, 5H), 5.23 (s, 2H), 4.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 188.6, 153.3, 147.8, 134.8, 130.9, 128.5, 128.4, 128.3, 127.2, 119.2, 114.7, 71.3, 61.9; MS m/z 288 (M + 1).

2-(3-Benzyloxy-4-methoxy-5-nitrophenyl)-2-(*tert*-butyldimethylsilyloxy)nitroethane (12e). Using the general procedure for Amberlyst A-21-mediated Henry reaction described for **12b**, followed by *tert*-butyldimethylsilyl ether formation, compound **12e** (1.86 g, 93% yield) was obtained from the aldehyde **3e**, mp 98−99 °C, after recrystallization from CH_2Cl_2/hexanes: ^{1}H NMR ($CDCl_3$) δ 7.45−7.33 (m, 5H), 7.19−7.17 (m, 2H), 5.33 (dd, 1H, J = 3.36, 9.46 Hz), 5.18 (dd, 2H, J = 15.20, 11.60 Hz), 4.44 (dd, 1H, J = 9.46, 11.90 Hz), 4.33 (dd, 1H, J = 3.36, 11.90 Hz), 4.03 (s, 3H), 0.85 (s, 9H), 0.03 (s, 3H), −0.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1, 144.6, 142.9, 135.1, 134.9, 128.5, 128.2, 126.9, 114.7, 113.4, 81.9, 71.1, 61.7, 25.1, 17.6, −5.2, −5.9; MS 462 (M^+). Anal. Calcd for $C_{22}H_{30}N_2O_7Si$: C, 57.12; H, 6.54; N, 6.05. Found: C, 57.16; H, 6.58; N, 5.99.

(31) Lange, R. G. *J. Org. Chem.* **1962**, *27*, 2037.

2-(5-Amino-3-benzyloxy-4-methoxyphenyl)-2-(*tert*-butyldimethylsilyloxy)ethylamine (13e). Using the general procedure for nitro group reduction with $NiCl_2$-$6H_2O$/$NaBH_4$ described for **13b**, compound **13e** (970 mg, 76% yield) was obtained as a brown oil: ^{1}H NMR ($CDCl_3$) δ 7.46−7.27 (m, 5H), 6.35 (d, 1H, J = 1.22 Hz), 6.31 (d, 1H, J = 1.22 Hz), 5.09 (s, 2H), 4.46 (br t, 1H, J = 5.19 Hz), 3.86 (s, 3H), 3.84 (br s, 2H), 2.76−2.72 (m, 2H), 1.18 (br s, 2H), 0.91 (s, 9H), 0.03 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.2, 139.8, 138.7, 136.8, 134.9, 128.1, 127.4, 126.8, 106.2, 101.7, 76.1, 70.1, 59.6, 50.6, 25.5, 17.9, −4.9, −5.3; MS m/z 403 (M^+).

***O*-Benzyl *N*-2-(5-Amino-4-benzyloxy-3-methoxyphenyl)-2-(*t*-butyldimethylsilyloxy)ethyl carbamate (14e).** Using the general procedure for selective protection of the primary amine described for **14b**, compound **14e** (1.00 g, 97% yield) was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.45−7.27 (m, 10H), 6.38 (br s, 1H), 6.34 (br s, 1H), 5.11 (s, 2H), 5.07 (s, 2H), 4.96 (m, 1H), 4.61 (dd, 1H, J = 3.97, 7.03 Hz), 3.85 (s, 3H), 3.84 (s, 2H), 3.46−3.36 (m, 1H), 3.18−3.08 (m, 1H), 0.88 (s, 9H), 0.50 (s, 3H), −0.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.1, 140.70, 139.6, 137.8, 135.9, 128.9, 128.3, 127.7, 107.1, 102.7, 92.0, 86.7, 81.2, 76.9, 71.0, 60.5, 51.4, 26.4, 18.7, −4.1, −4.4; MS m/z 536 (M^+).

5-[5-[2-(Benzyloxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3-benzyloxy-2-methoxyphenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (15e). Using the general procedure for Meldrum's acid adduct formation described for **7c**, compound **15e** (1.12 g, 1.79 mmol) was obtained in 90% yield, mp 108−109 °C,after recrystallization from EtOAc/hexanes: ^{1}H NMR ($CDCl_3$) δ 11.66 (d, 1H, J = 14.65 Hz), 8.64 (d, 1H, J = 14.65 Hz), 7.46−7.26 (m, 10H), 6.95 (s, 1H), 6.84 (s, 2H), 5.11 (br s, 4H), 4.98 (m, 1H), 4.73 (m, 1H), 4.00 (s, 3H), 3.48−3.36 (m, 1H), 3.24−3.11 (m, 1H), 1.76 (s, 6H), 0.88 (s, 9H), 0.02 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.7, 164.1, 156.8, 152.6, 151.4, 139.8, 139.2, 136.9, 136.6, 131.9, 129.2, 129.0, 129.0, 128.7, 128.7, 127.9, 109.8, 105.5, 105.3, 81.2, 73.9, 71.5, 67.3, 61.8, 49.9, 27.6, 26.3, 18.7, −4.2, −4.5; MS m/z 691 (M^+).

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[7-benzyloxy-8-methoxy-4(1*H*)-quinolinon-5-yl]ethyl Carbamate (16e).** Using the general procedure for thermal cyclization in diphenyl ether, **16e** was obtained as an off white solid (850 mg, 82% yield). An analytical sample was prepared by recrystallization from EtOAc/hexanes: mp 139−141 °C; ^{1}H NMR (acetone-d_6) δ 10.38 (br s, 1H), 7.62 (br t, 1H, J = 6.41 Hz), 7.49 (s, 1H), 7.45−7.11 (m, 10H), 6.57 (br t, 1H, J = 4.88 Hz), 6.09−6.03 (m, 1H), 5.90 (d, 1H, J = 7.32 Hz), 5.20 (dd, 2H, J = 12.11, 20.76 Hz), 4.85 (s, 2H), 3.85 (s, 3H), 3.48−3.28 (m, 2H), 0.80 (s, 9H), −0.03 (s, 3H), −0.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.1, 157.2, 151.9, 141.4, 137.9, 137.4, 136.8, 136.7, 135.4, 129.2, 128.9, 128.7, 128.4, 128.1, 127.9, 118.3, 111.5, 109.4, 71.4, 70.6, 66.9, 61.5, 50.2, 26.4, 18.7, −4.2, −4.5; MS m/z 589 (M^+). Anal. Calcd for $C_{33}H_{40}N_2O_6Si$: C, 67.32; H, 6.85; N, 4.75. Found: C, 67.14; H, 6.79; N, 4.77.

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[7-benzyloxy-8-methoxy-1-methyl-4(1*H*)-quinolinon-5-yl]ethyl Carbamate (17e).** Using the general procedure for *N*-methylation of quinolones, **17e** (128 mg, 96% yield) was obtained as an off-white solid. An analytical sample was recrystallized from EtOAc/hexanes: mp 156−158 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.49−7.22 (m, 11H), 6.58 (br t, 1H, J = 4.89 Hz), 6.07 (d, 1H, J = 7.32 Hz), 5.42 (br t, 1H, J = 5.20 Hz), 5.20 (dd, 2H, J = 11.60, 17.09 Hz), 5.01 (s, 2H), 4.00 (s, 3H), 3.85 (s, 3H), 3.58−3.41 (m, 2H), 0.88 (s, 9H), −0.05 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.2, 156.9, 154.5, 145.9, 142.9, 137.9, 137.7, 137.5, 136.8, 129.2, 128.9, 128.7, 128.4, 127.9, 120.4, 111.4, 109.8, 71.4, 70.9, 66.7, 62.2, 50.3, 46.5, 26.4, 18.7, −4.3, −4.4; MS m/z 603 (M^+). Anal. Calcd for $C_{34}H_{42}N_2O_6Si$: C, 67.74; H, 7.02; N, 4.64. Found: C, 67.75; H, 6.99; N, 4.67.

9-Methoxy-1-methyl-1*H*-benzo[*de*][1,6]naphthyridin-8-ol (1-Methyl-8-demethylaaptamine, 2e). To a flask containing the *N*-methylquinolone **17e** (318 mg, 0.527 mmol) and 156 mg of 10% Pd−C in 10 mL of methanol was added NH_4O_2CH (267 mg, 3.45 mmol). The solution was placed in a 40 °C oil bath and stirred for 20 min. The mixture was filtered through Celite and washed with copious amounts of MeOH. The solvent was removed in vacuo and the residue kept under vacuum for 24 h. The free amine and $(NH_4)_2SO_4$ (28 mg, 0.212 mmol) were placed in a flask containing 30 mL of HMDSA and 15 mL of TEA. The reaction was carried out as described for **2b**. The crude product was purified by flash chromatography (85:15 $CHCl_3$/MeOH). The residue was recrystallized from MeOH/acetone. 1-Methyl-8-demethylaaptamine hydrochloride salt **(2e)** (97 mg, 68% yield) was obtained as yellow crystals: mp 194−196 °C; ^{1}H NMR (DMSO-d_6) δ 7.80 (d, 1H, J = 7.32 Hz), 7.29 (d, 1H, J = 7.32 Hz), 6.89 (s, 1H), 6.75 (d, 1H, J = 7.33 Hz), 6.34 (d, 1H, 7.33 Hz), 3.93 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 157.9, 148.6, 148.4, 135.2, 133.2, 133.1, 129.3, 116.8, 112.3, 105.7, 93.4, 61.9, 45.4; UV (95% EtOH) λ_{max} 202 nM (ϵ 24 372), 231 nM (ϵ 14 786), 261 nM (ϵ 20 326), 273 nM (ϵ 19 183), 316 nM (ϵ 3413), 387 nM (ϵ 5973); EI$^+$HRMS calcd for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0898.

8-Demethylaaptamine (1e). Using the general procedure for HMDSA-mediated cyclization and methanolic HCl elimination as described for **2b**, 8-demethylaaptamine, **1e**, was obtained was obtained from **16e** in 76% overall yield as a hydrochloride salt (110 mg) and was recrystallized from MeOH/acetone: mp 227−229 °C dec; ^{1}H NMR (CD_3OD) δ 7.69 (d, 1H, J = 7.32 Hz), 7.09 (d, 1H, J = 7.33 Hz), 6.72 (s, 1H), 6.66 (d, 1H, J = 7.32 Hz), 6.26 (d, 1H, J = 6.71 Hz), 3.87 (s, 3H); ^{13}C NMR (CD_3OD) δ 155.9, 149.5, 140.27, 133.9, 131.9, 130.8, 127.9, 115.5, 111.8, 104.6, 97.3, 59.1; UV (95% EtOH) λ_{max} 201 nM (ϵ 21, 482), 234 nM (ϵ 20, 482), 268 nM (ϵ 24, 120), 312 nM (ϵ 4, 329), 361 nM (ϵ 5, 428); EI$^+$HRMS calcd for $C_{13}H_{10}N_2O_2$ 214.0742, found 214.0749.

2-(3,4-Dimethoxy-5-nitrophenyl)-2-(*tert*-butyldimethylsilyloxy)nitroethane (12f). TBAF($3H_2O$) (3.44 g, 10.92 mmol) was dissolved in 75 mL of THF and cooled to 0 °C. Nitromethane (2.67 g, 43.7 mmol), 3,4-dimethoxy-5-nitrobenzaldehyde[13] (5.00 g, 21.8 mmol), TEA (3.31 g, 32.8 mmol), and TBS chloride (6.58 g, 43.7 mmol) were added sequentially. The reaction was stirred for 2 h while coming to room temperature. The solution was filtered, and the residue was washed with EtOAc. The filtrate was washed with water and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was subjected to flash chromatography (1.5:1 hexane/EtOAc) to yield 6.07 g of the impure nitroaldol adduct. The adduct was dissolved in 125 mL dry THF containing 2,6-lutidine (5.60 g, 52.3 mmol) under nitrogen. The solution was cooled to 0 °C, and TBSOTf (8.29 g, 31.38 mmol) was added dropwise using a dry syringe. The solution was stirred for 2 h and was poured into 100 mL of EtOAc. The organic layers were washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. Flash chromatography (6.5:3.5 CH_2Cl_2/hexanes) gave 7.20 g of the silyl derivative **12f** as a white solid in 86% yield that was recrystallized from hexanes: mp 92−94 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 1H, J = 1.83 Hz), 7.16 (d, 1H, J = 1.22 Hz), 5.42 (dd, 1H, J = 3.36, 9.47 Hz), 4.50 (dd, 1H,J = 9.46, 11.90 Hz), 4.40 (dd, 1H,J = 3.05, 12.10 Hz), 3.99 (s, 3H), 3.94 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1, 145.3, 143.4, 136.1, 113.8, 113.7, 82.8, 72.1, 65.5, 57.0, 26.0, 18.5, −4.3, −5.1; MS m/z 387 (M + 1). Anal. Calcd for $C_{16}H_{26}N_2O_7Si$: C, 49.73; H, 6.78; N, 7.24. Found: C, 49.80; H, 6.80; N, 7.20.

2-(5-Amino-3,4-dimethoxyphenyl)-2-(*tert*-butyldimethylsilyloxy)ethylamine (13f). The dinitro compound **12f** (1.50 g, 3.71 mmol) and 400 mg of 10% Pd−C were stirred in 20 mL of MeOH and 10 mL of THF. NH_4O_2CH (2.39 g, 37.8 mmol) was added, and the flask was refluxed in a preheated oil bath for 1 h, after which an additional 2 equiv of NH_4O_2CH was added. The solution was refluxed for another 1 h and allowed to cool. The solution was filtered though Celite, and the Celite pad was washed with 100 mL of MeOH. The solvent was evaporated and the residue taken up in $CHCl_3$ and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried with $MgSO_4$ and filtered and the solvent removed in vacuo. The diamine **13f** (1.30 g) was obtained as a clear oil in 100% yield: ^{1}H NMR ($CDCl_3$) δ 6.31

(d, 1H, J = 1.84 Hz), 6.29 (d, 1H, J = 1.22 Hz), 5.49 (br t, 1H, J = 5.19 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 2.77 (br d, 2H, J = 5.49 Hz), 0.91 (s, 9H), 0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1, 140.5, 139.6, 135.3, 106.8, 100.5, 76.9, 60.2, 56.0, 51.4, 26.3, 18.7, −4.1, −4.5; MS m/z 327 (M + 1).

***O*-Benzyl *N*-2-(5-Amino-3,4-dimethoxyphenyl)-2-(*tert*-butyldimethylsilyloxy)ethyl Carbamate (14f).** Using the general procedure for selective benzyloxycarbonyl protection, **14f** was obtained as a pale yellow oil (1.14 g, 2.12 mmol) in 84% yield: ^{1}H NMR ($CDCl_3$) δ 7.37−7.31 (m, 5H), 6.32 (br s, 2H), 5.11 (br s, 2H), 5.02−4.94 (m, 1H), 4.63 (dd, 1H, J = 3.66, 7.32 Hz), 3.81 (br s, 6H), 3.49−3.39 (m, 1H), 3.19−3.09 (m, 1H), 0.89 (s, 9H), 0.02 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.9, 153.2, 140.8, 138.9, 137.2, 135.5, 128.9, 128.6, 106.8, 100.4, 74.2, 67.1, 60.3, 56.1, 49.9, 26.3, 18.7, −4.2, −4.6; MS 460 (M + 1).

5-[5-[2-(Benzyloxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,3-dimethoxyphenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (15f). Using the general procedure for Meldrum's acid adduct formation, **15f** was obtained as a white solid (2.82 g, 4.44 mmol) in 86% yield and recrystallized from EtOAc/hexanes: mp 134−137 °C; ^{1}H NMR ($CDCl_3$) δ 11.63 (d, 1H, J = 14.03 Hz), 8.63 (d, 1H, J = 14.65 Hz), 7.38−7.29 (m, 5H), 6.93 (br s, 1H), 6.78 (br s, 1H), 5.10 (s, 2H), 4.99 (br t, 1H, J = 6.13 Hz), 4.76 (dd, 1H, J = 3.36, 7.02 Hz), 3.96 (s, 3H), 3.86 (s, 3H), 3.50−3.40 (m, 1H), 3.23−3.12 (m, 1H), 1.75 (s, 6H), 0.90 (s, 9H), 0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.7, 164.1, 156.8, 153.5, 151.4, 139.9, 138.7, 136.9, 131.8, 128.9, 128.6, 107.9, 105.5, 104.9, 88.1, 73.8, 67.2, 61.6, 56.5, 48.9, 27.6, 26.3, 18.6, −4.3, −4.5; MS m/z 614 (M^+).

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[7,8-dimethoxy-4(1*H*)-quinolinon-5-yl]ethyl Carbamate (16f)** Using the general procedure for thermal cyclization, **16f** was obtained as an off-white solid (771 mg, 1.48 mmol) in 89% yield and was recrystallized from acetone/hexanes: mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 8.98 (br s, 1H), 7.47 (t, 1H, J = 6.41 Hz), 7.42 (s, 1H), 7.36−7.25 (m, 5H), 6.51 (br t, 1H, J = 4.57 Hz), 6.11 (d, 1H, J = 7.33 Hz), 5.47−5.41 (m, 1H), 5.01 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.63−3.42 (m, 2H), 0.91 (s, 9H), 0.07 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.1, 157.1, 152.6, 141.5, 137.8, 137.4, 136.6, 134.9, 128.9, 128.3, 118.0, 111.3, 107.9, 70.7, 66.8, 61.4, 56.4, 50.2, 26.4, 18.6, −4.3, −4.5; MS m/z 513 (M + 1). Anal. Calcd for $C_{27}H_{36}N_2O_6Si$: C, 63.25; H, 7.08; N, 5.46. Found: C, 63.06; H, 7.06; N, 5.44.

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[7,8-dimethoxy-1-methyl-4(1*H*)-quinolinon-5-yl]ethyl Carbamate (17f).** Using the general procedure for *N*-methylation of quinolones, **17f** was obtained as an off white solid (280 mg, 0.531 mmol) in 68% yield and recrystallized from EtOAc/hexanes: mp 73−75 °C; ^{1}H NMR (acetone-d_6) δ 7.49 (s, 1H), 7.45 (d, 1H, J = 7.33 Hz), 7.25−7.16 (m, 5H), 6.57 (br t, 1H, J = 4.58 Hz), 6.07 (br s, 1H), 5.81 (d, 1H, J = 7.94 Hz), 4.85 (s, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 3.72 (s, 3H), 3.48−3.27 (m, 2H), 0.82 (s, 9H), −0.03 (s, 3H), −0.18 (s, 3H); ^{13}C NMR (d_6−Acetone) δ 178.6, 155.8, 154.4, 145.7, 141.5, 137.3, 136.9, 136.64, 127.9, 127.3, 127.2, 119.3, 109.6, 107.7, 70.1, 64.9, 60.6, 55.1, 49.0, 45.1, 25.1, 17.5, −5.8, −5.9; MS m/z 527 (M + 1). Anal. Calcd for $C_{28}H_{38}N_2O_6Si$: C, 63.85; H, 7.27; N, 5.32. Found: C, 63.57; H, 7.33; N, 5.23.

8,9-Dimethoxy-1-methyl-1*H*-benzo[*de*][1,6]-naphthyridine (*N*-Methylaaptamine, 2f). The *N*-methylquinolone **17f** (430 mg, 0.815 mmol) and 95 mg of 20% $Pd(OH)_2$−C in 20 mL of methanol were stirred under an atmosphere of hydrogen at room temperature and pressure for 45 min. The mixture was filtered through Celite and was washed with copious amounts of methanol. The solvent was removed under reduced pressure and the residue put under a vacuum pump for 24 h. The free amine and $(NH_4)_2SO_4$ (0.013 g, 0.0984 mmol) were placed in a flask with 15 mL of HMDSA and 8 mL of TEA and fitted with a condenser. The reaction and workup was carried out as for **2b**. The product was purified by flash chromatography (85:15 chloroform/MeOH) and recrystallized from methanol and EtOAc. *N*-Methylaaptamine **(2f)** was obtained as a hydrochloride salt (189 mg, 83% yield) as a yellow solid and recrystallized from MeOH/acetone: mp 198−199 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.83 (d, 1H, J = 7.32 Hz), 7.40 (d, 1H, J = 7.32 Hz), 7.16 (s, 1H), 6.87 (d, 1H, J = 7.33 Hz), 6.30 (d, 1H, 7.32 Hz), 3.94 (s, 6H), 3.72 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.7, 158.8, 148.9, 148.8, 134.5, 133.7, 129.8, 117.5, 113.0, 102.2, 98.4, 62.2, 56.7, 45.5; UV (95% EtOH) λ_{max} 205 nM (ϵ 25, 924), 240 nM (ϵ 20, 229), 260 nM (ϵ 20, 739), 273 nM (ϵ 19, 183), 317 nM (ϵ 3, 831), 386 nM (ϵ 5, 625); EI$^+$HRMS calcd for $C_{14}H_{14}N_2O_2$ 242.1055, found 242.1052.

8,9-Dimethoxy-1*H*-benzo[*de*][1,6]naphthiridine (Aaptamine, 1f). Using the general procedure for HMDSA-mediated cyclization and methanolic HCL elimination, aaptamine hydrochloride **1f** (104 mg, 0.392 mmol) was obtained in 73% yield. The yellow solid was recrystallized from MeOH/acetone to give yellow crystals: mp 176−177 °C; ^{1}H NMR (DMSO-d_6) δ 12.26 (br s, 1H), 7.79 (d, 1H, J = 7.33 Hz), 7.37 (d, 1H, J = 7.32 Hz), 7.08 (s, 1H), 6.84 (d, 1H, J = 7.32 Hz), 6.31 (d, 1H, 6.71 Hz), 3.93 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (D_6-DMSO) δ 156.9, 149.8, 142.1, 133.8, 132.7, 131.4, 129.9, 116.4, 112.8, 101.0, 98.2, 60.4, 56.6; UV (95% EtOH) λ_{max} 202 nM (ϵ 24, 372), 238 nM (ϵ 20, 703), 257 nM (ϵ 21, 775), 313 nM (ϵ 4, 740), 374 nM (ϵ 5, 479); EI$^+$HRMS calcd for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0903.

7-Bromo-1,3-benzodioxde-5-carboxaldehyde (3i). KF (9.72 g, 167.30 mmol) was flame dried in a flask and allowed to cool. 5-Bromo-3,4-dihydroxybenzaldehyde[31] (4.00 g, 18.4 mmol) was added with 50 mL of DMF. Dibromomethane (3.12 g, 18.40 mmol) was added, and the mixture was heated at 140 °C for 4 h. The cooled solution was mixed with water and extracted three times with diethyl ether. The combined organic extracts were washed once with a 10% NaOH. The organic solution was dried with $MgSO_4$, filtered, and solvents were removed in vacuo. The crude material was purified by flash chromatography (CH_2Cl_2) to yield 3.26 g of **3i** as a white solid (85% yield) that was recrystallized from CH_2Cl_2/hexanes: mp 130−131 °C (lit.[27] mp 125−127 °C); ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.54 (s, 1H), 7.26 (s, 1H), 6.16 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 189.5, 151.7, 149.4, 133.3, 131.4, 106.7, 103.1, 101.3; MS m/z 231 (M + 2), 229 (M^+).

7-Bromo-5-(1,3-dioxolan-2-yl)-1,3-benzodioxole (3j). The aldehyde **3i** (2.89 g, 12.62 mmol), ethylene glycol (3.45 g, 55.72 mmol). and 50 mg of PTSA in 60 mL of benzene were refluxed for 24 h under nitrogen using a Dean-Stark apparatus for azeotropic removal of water. The cooled reaction solution was washed with 10% aqueous KOH, water, and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude material was purified by flash chromatography (2:1 hexane/EtOAc) to give 3.38 g of the acetal **3j** as a yellow oil in 98% yield: ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 1H), 6.89 (s, 1H), 6.04 (s, 2H), 5.69 (s, 1H), 4.13−3.97 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 148.6, 146.9, 134.1, 124.1, 106.5, 103.2, 102.2, 100.8, 65.8; MS m/z 275 (M + 2), 273 (M^+). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.25; H, 5.72; N, 4.68. Found: C, 68.05; H, 5.74; N, 4.60.

7-Benzylamino-5-(1,3-dioxolan-2-yl)-1,3-benzodioxole (4j). To the dioxalane **3j** (2.38 g, 8.72 mmol) under nitrogen were added benzylamine (1.12 g, 10.5 mmol), $Pd_2(dba)_3$ (80 mg, 0.87 mmol), (*S*)-BINAP (150 mg, 0.24 mmol), and *t*-BuONa (1.17 g, 12.20 mmol). A 100 mL portion of degassed toluene was added, and nitrogen was flushed above the solution for 15 min. The flask was sealed and placed in an oil bath preheated to 90 °C and stirred at that temperature for 3 h. The cooled solution was diluted with 200 mL of diethyl ether and filtered through Celite. The solvents were removed in vacuo, and the residue was purified by flash chromatography (2:1 hexane/EtOAc) to give 2.50 g of **4j** as a pale yellow oil in 96% yield: ^{1}H NMR ($CDCl_3$) δ 7.40−7.27 (m, 5H), 6.49 (s, 1H), 6.46 (s, 1H), 5.93 (s, 2H), 5.68 (s, 1H), 4.40 (d, 2H, J = 5.49 Hz), 4.11−3.95 (m, 4H), 3.92 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.9, 139.8, 134.9, 133.3, 132.9, 129.2, 128.1, 127.9, 105.8, 104.4, 101.6, 98.0, 65.7, 48.8; MS m/z 300 (M + 1).

7-Benzylamino-1,3-benzodioxole-5-carboxaldehyde (4i). The amino acetal **4j** (1.00 g, 3.34 mmol) and PPTS (250 mg, 1.00 mmol) in 19 mL of acetone and 1 mL of water were refluxed for 30 min. The acetone was removed in vacuo, and

50 mL of EtOAc was added. The organic layer was washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (2:1 hexane/EtOAc) to give 860 mg of the aldehyde **4i** as a pale yellow oil in 100% yield: ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 1H), 7.39−7.28 (m, 5H), 6.88 (s, 1H), 6.86 (s, 1H), 6.05 (s, 2H), 4.44 (d, 2H, J = 5.49 Hz), 4.09 (t, 1H, J = 5.49 Hz); ^{13}C NMR ($CDCl_3$) δ 191.4, 148.4, 139.7, 139.0, 133.3, 132.8, 129.3, 128.1, 127.9, 110.3, 102.5, 100.8, 48.5; MS m/z 256 (M + 1).

7-(Benzylamino)-5-(1-*tert*-butyldimethylsilyloxy-2-nitroethyl)-1,3-benzodioxole (12g). Using the general procedure for Amberlyst A-21-mediated Henry reaction followed by *tert*-butyldimethylsilyl ether formation, compound **12g** (1.15 g, 2.66 mmol) was obtained in 86% overall yield (based on recovered aldehyde **4i**): mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 5H), 6.34 (s, 1H), 6.29 (s, 1H), 5.94 (s, 2H), 5.22 (dd, 1H, J = 3.06, 9.77 Hz), 4.45 (dd, 1H, J = 9.77, 11.60 Hz), 4.39 (d, 2H, J = 5.49 Hz), 4.29 (dd, 1H, J = 3.05, 12.20 Hz), 4.01 (t, 1H, J = 5.80), 0.82 (s, 9H), −0.02 (s, 3H), −0.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1, 138.4, 133.8, 133.40, 132.1, 128.3, 127.1, 127.0, 104.0, 100.8, 96.7, 82.6, 72.5, 47.7, 25.2, 17.7, −5.1, −6.0; MS m/z 431 (M + 1). Anal. Calcd for $C_{22}H_{30}N_2O_5Si$: C, 61.37; H, 7.02; N, 6.50. Found: C, 61.38; H, 6.98; N, 6.45.

7-Amino-5-(1-*tert*-butyldimethylsilyloxy)2-aminoethyl)1,3-benzodioxole (13g). To a stirred solution of the silylated nitroaldol adduct **12g** (1.02 g, 2.37 mmol) and 650 mg of 10% Pd−C in 45 mL of methanol and 15 mL of THF was added NH_4O_2CH (1.50 g, 23.70 mmol), and the flask was placed in a preheated oil bath at °C. The solution refluxed for 1 h and was allowed to cool. The solution was filtered though Celite, and the Celite pad was washed with 100 mL of EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was flash chromatographed (98:2 $CHCl_3$/TEA to 88:10:2 $CHCl_3$/MeOH/TEA) to give 700 mg of **13g** as an amorphous solid in 95% yield: ^{1}H NMR ($CDCl_3$) δ 6.32 (s, 1H), 6.26 (s, 1H), 5.91 (s, 2H), 4.47 (t, 1H, J = 5.49 Hz), 3.55 (br s, 2H), 2.75 (d, 2H, J = 5.50 Hz), 1.28, (br s, 2H), 0.90 (s, 9H), 0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.2, 138.5, 133.9, 129.9, 108.7, 101.3, 98.3, 77.1, 51.6, 26.4, 18.7, −4.1, −4.5; MS m/z 311 (M + 1).

***O*-Benzyl *N*-[2-(7-Amino-1,3-benzodioxol-5-yl)-2-(*tert*-butyldimethylsilyloxy)ethyl] Carbamate (14 g)** Using the general procedure for selective CBZ protection of the primary alkylamine, compound **14g** (285 mg, 0.639 mmol) was obtained as a pale yellow oil in 91% yield: ^{1}H NMR ($CDCl_3$) δ 7.38−7.30 (m, 5H), 6.34 (s, 1H), 6.26 (s, 1H), 5.92 (s, 2H), 5.10 (s, 2H), 4.98−4.92 (m, 1H), 4.60 (dd, 1H, J = 4.27, 6.72 Hz), 3.54 (br s, 2H), 3.54 (m, 2H), 3.43−3.34 (m, 1H), 3.19−3.09 (m, 1H), 0.88 (s, 9H), 0.01 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.9, 148.4, 137.6, 137.2, 134.2, 130.1, 129.1, 128.6, 127.4, 108.8, 101.4, 98.3, 74.2, 67.1, 50.1, 26.3, 18.7, −4.2, −4.6; MS m/z 444 (M^+).

5-[2-(Benzyloxycarbonylamino)-1-(*tert*-butyldimethyl-silyloxy)ethyl]-1,3-dioxolan-7-ylaminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (15g). The general procedure for Meldrum's acid adduct formation provided compound **15g** (927 mg, 1.54 mmol) as white solid in 84% yield which was recrystallized from EtOAc/hexanes: mp 159−162 °C; ^{1}H NMR ($CDCl_3$) δ 11.19 (d, 1H, J = 14.65 Hz), 8.81 (d, 1H, J = 14.04 Hz), 7.37−7.30 (m, 5H), 6.73 (s,1H), 6.70 (s, 1H), 6.08 (d, 1H, J = 1.22 Hz), 5.09 (s, 2H), 4.98 (br t, 1H, 5.80 Hz), 4.73−4.68 (m, 1H), 3.45−3.33 (m, 1H), 3.22−3.11 (m, 1H), 1.75 (s, 6H), 0.88 (s, 9H), 0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.9, 163.7, 156.8, 154.4, 149.9, 138.9, 137.2, 136.9, 128.9, 128.6, 121.4, 109.8, 105.7, 104.9, 102.9, 88.2, 73.6, 67.2, 48.9, 27.5, 26.3, 18.6, −4.2, −4.5; MS m/z 598 (M^+).

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[1,3-dioxolo[4,5-*h*]-6(9*H*)-quinolinon-6-yl]ethyl Carbamate (16g).** Using the general procedure for thermal cyclization to a quinolone derivative, compound **16g** (616 mg, 1.23 mmol) was obtained as an off-white solid in 67% yield and was recrystallized from EtOAc/hexanes: mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 9.03 (br s, 1H), 7.37−7.21 (m, 6H), 7.17 (br t, 1H, J = 6.41 Hz), 6.58−6.53 (m, 1H), 5.96 (d, 1H, J = 7.93 Hz), 5.90 (d, 2H, J = 24.42 Hz), 5.49−5.41 (m, 1H), 5.02 (s, 2H), 3.86 (br t, 1H, J = 10.38 Hz), 3.49 (br d, 1H, J = 11.59 Hz), 0.90 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.5, 157.7, 148.6, 140.9, 137.4, 137.1, 133.8, 129.0, 128.6, 128.2, 127.0, 118.7, 111.3, 105.0, 103.0, 70.0, 67.0, 49.3, 26.4, 18.7, −4.4, −4.5; MS m/z 497 (M + 1). Anal. Calcd for $C_{26}H_{32}N_2O_6Si$: C, 62.88; H, 6.49; N, 5.64. Found: C, 62.88; H, 6.50; N, 5.58.

***O*-Benzyl *N*-2-(*tert*-Butyldimethylsilyloxy)-2-[9-methyl-1,3-dioxolo[4,5-*h*]-6(9*H*)quinolinon-6-yl]ethyl Carbamate (17g).** Using the general procedure for N-methylation of quinolones, **17g** was obtained as an off-white solid (390 mg, 76% yield) and recrystallized from from EtOAc/hexanes: mp 197−199 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1H), 7.36−7.25 (m, 5H), 7.17 (d, 1H, J = 7.32 Hz), 6.60 (t, 1H, J = 4.56 Hz), 6.04 (d, 2H, J = 17.70 Hz), 6.03 (d, 1H, J = 7.93 Hz), 5.41−5.35 (m, 1H), 5.00 (s, 2H), 3.94 (s, 3H), 3.59−3.40 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.7, 156.9, 149.9, 143.8, 142.8, 137.5, 134.5, 129.4, 128.8, 128.4, 128.1, 120.2, 111.3, 106.0, 101.7, 70.5, 66.7, 50.1, 44.4, 24.4, 18.7, −4.4, −4.5; MS m/z 511 (M + 1). Anal. Calcd for $C_{27}H_{34}N_2O_6Si$: C, 63.50; H, 6.71; N, 5.48. Found: C, 63.49; H, 6.70; N, 5.51.

6-Methyl-1,3-dioxolo[4,5-*d*]benzo[*de*][1,6]naphthyridine (*N*-Methylmethylenedioxyaaptamine, 2g). Using the general procedure for HMDSA-mediated cyclization and methanolic HCl elimination, **17g** was converted to *N*-methylmethylenedioxyaaptamine hydrochloride salt **(2g)** (134 mg, 0.504 mmol), obtained as a green/yellow solid (91% yield) that was recrystallized from MeOH/acetone to give light green crystals: mp 260 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.69 (d, 1H, J = 7.32 Hz), 7.37 (d, 1H, J = 6.71 Hz), 7.03 (s, 1H), 6.84 (d, 1H, J = 6.71 Hz), 6.16 (d, 1H, J = 7.33 Hz), 6.15 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (D_2O) 152.6, 147.9, 145.8, 132.69, 130.5, 127.8, 124.5, 117.6, 113.3, 102.3, 98.6, 97.3, 42.7; UV (95% EtOH) λ_{max} 205 nM (ϵ 33 509), 236 nM (ϵ 19 155), 263 nM (ϵ 26 554), 323 nM (ϵ 7366), 393 nM (ϵ 7464); EI$^+$HRMS calcd for $C_{13}H_{10}N_2O_2$ 226.0742, found 226.0740.

1,3-Dioxlo[4,5-*d*]benzo[*de*][1,6]naphthyridine (Methylenedioxyaaptamine, 1g). Using the general procedure for HMDSA-mediated cyclization and methanolic HCl elimination, **16g** gave methylenedioxyaaptamine hydrochloride salt **1g** (67 mg, 0.269 mmol) as a green/yellow solid (68% yield) that was recrystallized from MeOH/acetone: mp 254 °C dec; ^{1}H NMR (DMSO-d_6) δ 12.23 (br s, 1H), 7.70 (d, 1H, J = 6.71 Hz), 7.31 (d, 1H, J = 6.71 Hz), 6.97 (s, 1H), 6.81 (d, 1H, J = 7.33 Hz), 6.25 (s, 2H); ^{13}C NMR (D_3O) δ 151.8, 148.6, 139.9, 131.7, 129.6, 127.4, 122.0, 116.7, 113.4, 103.3, 97.7, 96.8; UV (95% EtOH) λ_{max} 204 nM (ϵ 32 358), 232 nM (ϵ 20 870), 260 nM (ϵ 26 172), 319 nM (ϵ 6053), 400 nM (ϵ 5692); EI$^+$HRMS Calcd for $C_{13}H_8N_2O_2$ 212.0586, Found 212.0587.

Acknowledgment. We thank Dr. Randall Johnson and Dr. Alan J. Freyer of Smith Kline Beecham for providing ^{1}H- and ^{13}C-spectrostopic data for natural isoaaptamine. We thank Professors Ross Kelly, John Joule, and Michael Cava for spectroscopic data for synthetic aaptamine.

Supporting Information Available: ^{1}H and ^{13}C NMR data for intermediates and target compounds **1b**,**e**−**g**, **2b**,**e**−**g**, and **18**. National Cancer Institute screening data in the COMPARE format for compounds **1g** and **2b**,**e**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001080S