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Synthesis of the Marine Alkaloids Aaptamine and Demethyloxyaaptamine and of the Parent Structure Didemethoxyaaptamine

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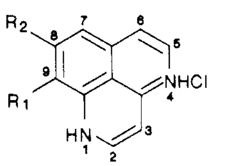
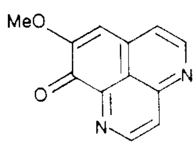
The first synthesis of the novel marine alkaloids aaptamine and demethyloxyaaptamine is described, as well as the first synthesis of the parent heterocycle 1*H*-benzo[*de*][1,6]naphthyridine (didemethoxyaaptamine).

In recent years, interest in the chemistry of marine natural products has increased dramatically. Many of these substances have been shown to have unusual structures, and they often have potentially useful biological properties.[2] Recently Nakamura and co-workers collected and investigated the Okinawan sea sponge *Aaptos aaptos*. The 70% ethanol extracts of *A. aaptos* were shown to possess antitumor, antimicrobial, and α-adrenoceptor blocking capabilities. Chromatographic isolation and spectral characterization of the active components showed the α-blocking properties to be attributed to aaptamine (**1**) and the antitumor and antimicrobial properties to be associated with demethylaaptamine (**2**) and demethyloxyaaptamine (**3**).[3] This novel group of bases represents the only known derivatives of 1*H*-benzo[*de*][1,6]naphthyridine (didemethoxyaaptamine, **4**), an unknown heterocycle that has been previously studied only theoretically.[4] We now disclose the details of our successful synthetic approaches to the natural products aaptamine (**1**) and demethyloxyaaptamine (**3**), as well as the parent structure **4**.[5,6]



1: R_1, R_2 = OMe
2: R_1 = OH, R_2 = OMe
4: R_1, R_2 = H



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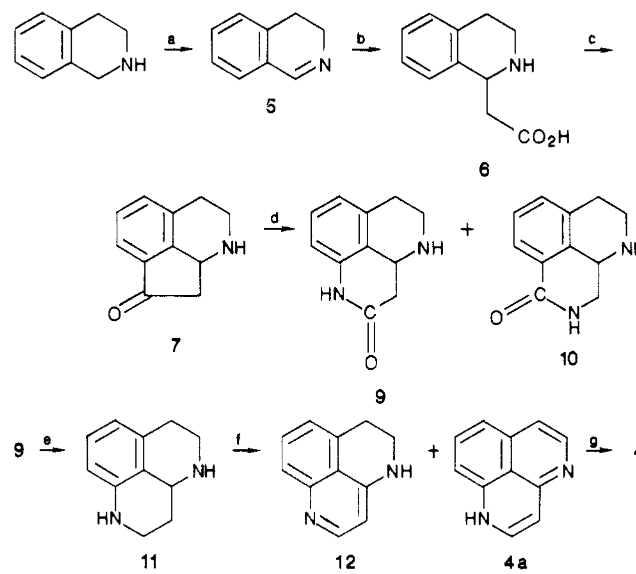
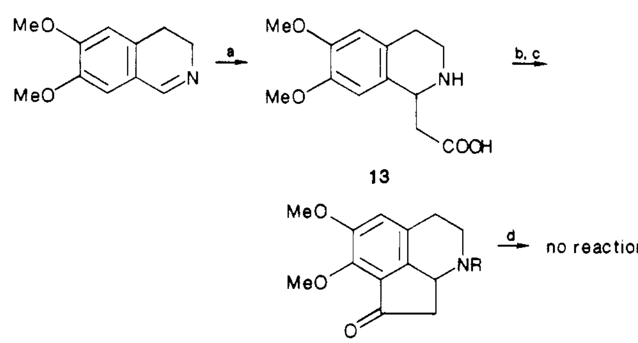
We began with an approach to didemethoxyaaptamine (**4**), since a successful synthesis of this compound not only would provide a model study for the preparation of **1** and **3** but would also provide a deoxygenated analogue of the natural products for possible biological studies. The synthesis of **4** is shown in Scheme I. The readily available 1,2,3,4-tetrahydroisoquinoline was oxidized with NBS–NaOH[7] to 3,4-dihydroisoquinoline (**5**) (94%). This product was reacted with 1 equiv of malonic acid at 120 °C (neat) to give the amino acid **6** in 88% yield.[8] Cyclodehydration of **6** in PPA afforded the tricyclic amino ketone **7**[9] in good yield (79%). As expected, compound **7** underwent a Schmidt reaction to give a separable 5:1 mixture (92%) of desired lactam **9** and its isomer **10**.[10] Amino lactam **9** was reduced cleanly with LAH (90%), and the hexahydro

Scheme I[a]



[a] Reagents: (a) NBS, NaOH, CH_2Cl_2, H_2O (94%); (b) $HO_2CCH_2CO_2H$, 120 °C (88%); (c) PPA, 150 °C (79%); (d) NaN_3, H_2SO_4, **9** (76%), **10** (16%); (e) LAH, THF (90%); (f) 5% Pd–C, xylene, reflux, alumina separation, **4a** (48%), **12** (45%); (g) HCl.

Scheme II[a]



14, R = H
15, R = Ts

[a] Reagents: (a) $HO_2CCH_2CO_2H$, 120 °C (92%); (b) PPA, 100 °C (66%); (c) TsCl, pyridine (66%); (d) NaN_3, H_2SO_4.

(1) (a) University of Pennsylvania. (b) University of Alabama.
(2) Scheuer, P. J., Ed. *Marine Natural Products*; Academic: New York, 1979–1981; Vols. I–IV.
(3) (a) Nakamura, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y. *Tetrahedron Lett.* **1982**, 5555. (b) Ninth International Congress on Heterocyclic Chemistry, Tokyo, 1983; Abstract G-66. (c) *Chem. Abstr. 100*, 83029y **1984**. (d) *J. Pharm. Pharmacol.* **1984**, *36*, 785. (e) *Chem. Abstr.* 1984, *101*, 110892d.
(4) Efros, L. S.; Ezhova, L. A.; Zukhs, E. R.; Treiger, V. M. *Khim. Geterotsikl. Soed.* **1980**, 180.
(5) Preliminary work in this area has been reported: (a) Pelletier, J. C.; Cava, M. P. *Abstracts of Papers*, 188th Meeting of the American Chemical Society, Philadelphia, American Chemical Society: Washington, DC, 1984; Abstract ORGN 63; (b) *Tetrahedron Lett.* **1985**, 1259.
(6) For another synthesis of aaptamine see: Kelly, T. R.; Maguire, M. P. *Tetrahedron* **1985**, *41*, 3033.
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(10) (a) Lansbury, P. T. Mancuso, N. R. *Tetrahedron Lett.* 2445, **1965**. (b) Fikes, L. E.; Shechter, H. *J. Org. Chem.* **1979**, *44*, 741.

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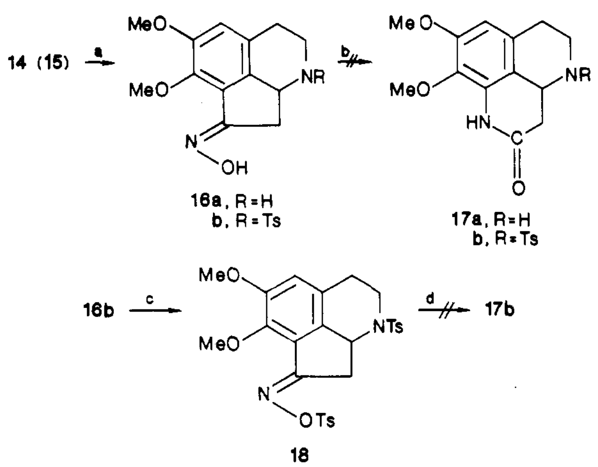
Scheme III[a]



[a] Reagents: (a) $H_2NOH{\cdot}HCl$, py-EtOH (100%); (b) various acid treatment; (c) NaOH, TsCl, acetone–H_2O (80%); (d) various acid and solvolysis treatment.

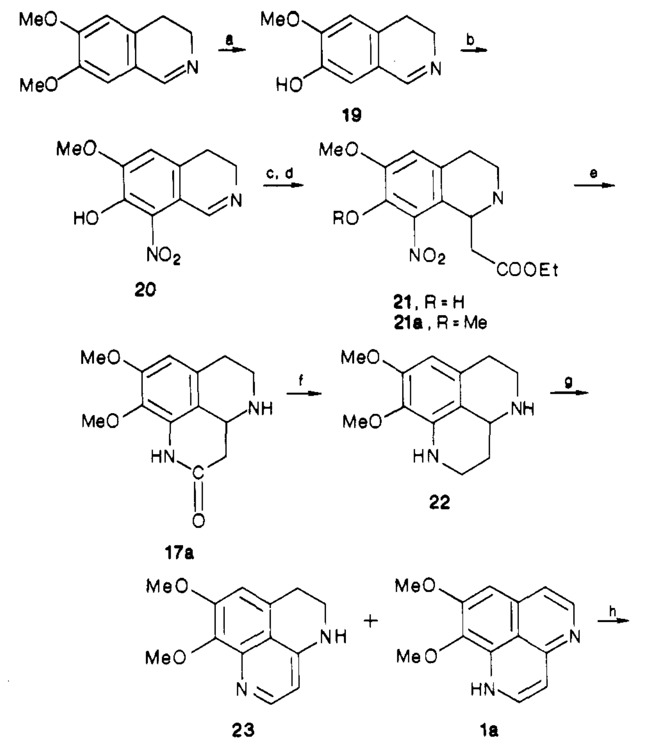
product **11** was dehydrogenated to afford a mixture of the free base of didemethoxyaaptamine (**4a**) (48%) and the dihydro compound **12** (45%), which were separated by alumina chromatography. Free base **4a** was treated with HCl to afford didemethoxyaaptamine (**4**) as the crystalline chloride.

Attention was now turned toward utilizing an analogous route to the natural product aaptamine (Scheme II). 6,7-Dimethoxy-3,4-dihydroisoquinoline[11] was reacted with 1 equiv of malonic acid (120 °C, neat mixture) to afford the amino acid **13** in 92% yield.[8] This product cleanly cyclodehydrated in warm PPA to afford the amino ketone **14** (66%).[12] Further transformation of **14** to the sulfonamide **15** went without difficulty (91%). Treatment of either **14** or **15** with NaN_3 in H_2SO_4, however, resulted in complete recovery of starting material. These results were surprising after observing the ease with which amino ketone **8** underwent lactam formation under identical conditions. It has been documented, however, that aromatic alkyl ketones that possess a moderate or strong electron-donating group in the ortho and/or para position are sluggish or unreactive when subjected to Schmidt conditions.[13] The reasons for this have not been rigorously defined, but they are assumed to be electronic in nature.

We then envisioned another possible pathway from **14** and **15** to the desired lactam system **17** via Beckmann rearrangement of the corresponding oximes of these ketones (Scheme III). Treatment of amino ketone **14** with $H_2NOH{\cdot}HCl$ gave a quantitative yield of a single oxime (^1H NMR). Darling model inspection of the two possible isomers indicated severe steric strain between the oxime hydroxyl and the methoxyl group in the 7-position (isoquinoline numbering) when the oxime is syn to the aromatic group. Steric repulsion is not observed when the oxime is situated anti to the aromatic ring. On the basis of these observations the oxime from ketone **14** was assigned structure **16a**. Analogous results were obtained for conversion of keto sulfonamide **15** to the oxime **16b** (single oxime, quantitative yield).

Exposure of **16a(b)** to various Lewis and mineral acid conditions conducive to Beckman rearrangement[14] afforded only starting materials, hydrolyzed products or decomposition to complex mixtures. It seemed possible

Scheme IV[a]



[a] Reagents: (a) 48% HBr, 95 °C (67%); (b) 40% $NaNO_3$, $NaNO_2$, 0 °C (60%); (c) $HO_2CCH_2CO_2Et$, 120 °C (74%); (d) CH_2N_2, Et_2O, CH_2Cl_2 (95%); (e) 10% Pd–C, H_2 AcOH (77%); (f) B_2H_6, THF, reflux (95%); (g) 5% Pd–C, xylene, reflux, alumina separation, **1a** (38%), **23** (45%); (h) HCl.

that the somewhat harsh conditions required for Beckmann rearrangement may have been detrimental, resulting in hydrolysis or decomposition before rearrangement could occur. To explore this possibility, the oxime tosylate of **16b** was prepared by the Cram method[15] and its solvolytic behavior was investigated. It was expected that **18** would be thermally labile, but in reality this compound was remarkably stable. The stability of **18** was also manifest when it was refluxed in a variety of polar solvents ($CHCl_3$, EtOH, pyridine, DMF) to effect solvolysis. No products could be detected, and near quantitative amounts of starting material were recovered. Finally, Lewis and mineral acid treatment resulted in oxime tosylate hydrolysis without lactam formation. Since the mechanism of the Beckmann rearrangement and the mechanism of the Schmidt reaction are similar,[16] it was assumed that the failure to obtain lactams **17a(b)** via the former method was also due to the electron-donating methoxyl function in the 7-position which may inhibit aromatic migration. It was apparent at this point that another route to aaptamine was needed.

The new and successful approach focused on putting the nitrogen in the 8-position of the isoquinoline system at an earlier stage. The synthesis of aaptamine is shown in Scheme IV. Selective demethylation of 6,7-dimethoxy-3,4-dihydroisoquinoline was achieved via the procedure of Brossi to afford the phenolic isoquinoline system **19**.[17] It was forseen that the stronger ortho–para directing power of the 7-hydroxyl would assist in selective nitration of the 8-position. When **19** was treated with 40% nitric acid and a catalytic amount of $NaNO_2$,[18] a 60% yield of the bright

(11) Spath, E. Polgar, N. *Montasch.* **1961**, *51*, 190.
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(13) Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* **1969**, 183.
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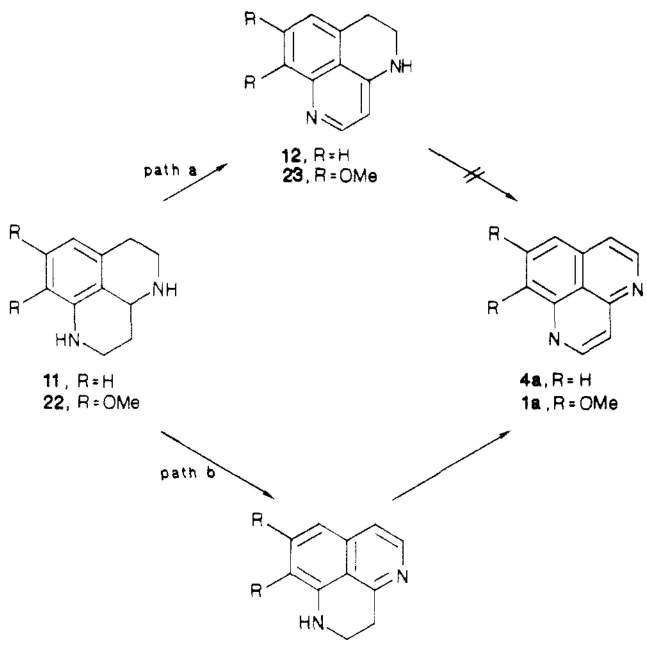
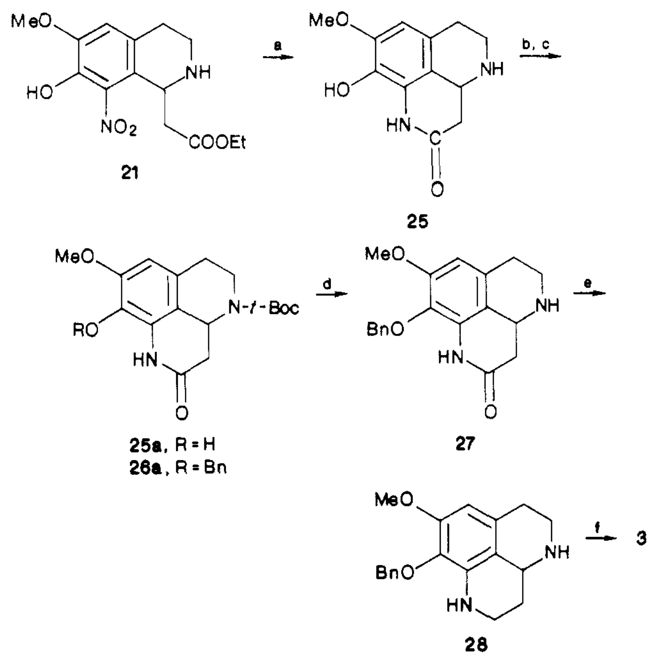
Scheme V

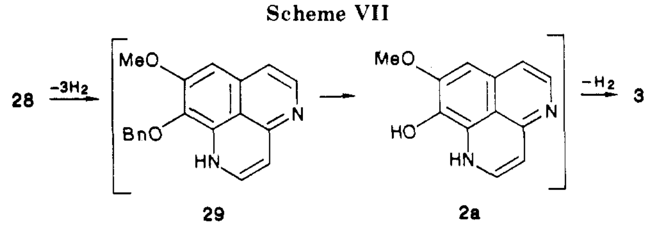


Scheme VI[a]



[a] Reagents: (a) 5% Pd–C, H_2, AcOH (100%); (b) $(Boc)_2O$, $CHCl_3$, reflux (88%); (c) BzlBr, K_2CO_3, acetone, reflux (86%); (d) TFA–H_2O (3:1), 25 °C (96%); (e) B_2H_6, THF, 25 °C (69%); (f) 5% Pd–C, xylene, reflux (35%).

Scheme VII



yellow nitrophenol **20** was obtained as the sole isolable product. This compound was then heated to 120 °C with 2.0 equiv of the monoethyl ester of malonic acid to afford the amino ester **21**,[8] which was subsequently methylated with diazomethane to afford **21a** (70% overall). Hydrogenation of this product in AcOH afforded the desired amino lactam **17a** (77%). Conversion of **17a** to aaptamine was accomplished by (a) reduction with diborane to hexahydroaaptamine (**22**), (b) Pd–C dehydrogenation to a 1:1 separable mixture of aaptamine free base (**1a**) and dihydroaaptamine (**23**), and (c) treatment of **1a** with HCl to obtain **1** (33% overall).

It is interesting to note that neither dihydrodidemethoxyaaptamine **12** nor dihydroaaptamine **23** could be further dehydrogenated by refluxing in xylene with Pd–C. This led us to believe that the dehydrogenation processes (**11** → **4a** + **12**, **22** → **1a** + **23**) were occurring by way of two routes (Scheme V). In the first route (path a), the hexahydro compound loses 2 equiv of hydrogen and appears to be stable at this point to further loss of hydrogen. In the second route (path b) the dihydro isomer **24** may be formed, which proceeds to give the aaptamine structure upon loss of another 1 equiv of hydrogen. Since **24** has not been observed as an intermediate in this step, however, experimental proof for this pathway could not be obtained.

Our attention was now focused on the synthesis of demethyloxyaaptamine **3**. The approach to this compound involved starting with the hydrogenation of the ester **21** (Scheme VI) to afford the amino lactam **25**. Attempts to reduce this compound with LAH or diborane were unsatisfactory. This problem was overcome by protecting the free amine function as an *N*-Boc group[19] and then benzylating the phenol to obtain **26** (76%, two steps). Removal of the *N*-Boc (TFA:H_2O = 3:1)[19] afforded **27** in excellent yield (96%). Diborane reduction of this product was achieved under mild conditions to give the hexahydro compound **28** (69%). When **28** was refluxed in xylene with a catalytic amount of Pd–C, a 35% yield of demethyloxyaaptamine (**3**) was obtained. The remaining reaction products formed a complex mixture from which no other components could be isolated. This dehydrogenation was thought to take place via three steps: (1) loss of 3 mol of hydrogen to provide intermediate **29**, (2) hydrogenolysis of the benzyl group of **29** to give demethylaaptamine free base **2a**, and (3) loss of another 1 equiv of hydrogen from **2a** to afford the product **3** (Scheme VII).

Both synthetic aaptamine and demethyloxyaaptamine were identical in all respects (TLC behavior, UV, IR, MS, ^1H NMR) to authentic samples provided by Professor Nakamura.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus, in open capillary tubes, and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 136 spectrometer. The spectra of solid samples were recorded as KBr pellets, and those of liquid samples were taken neat between NaCl plates. All of the IR spectra are recorded in wavenumbers (cm^{-1}) and br, s, and w stand for broad, strong and weak, respectively.

Proton nuclear resonance spectra (^1H NMR) were measured on a Bruker WM-250 (250 MHz) in deuteriochloroform solutions unless otherwise specified. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (δ = 0) used as the internal standard. Coupling constants, *J*, are given in hertz (Hz) and s, d, t, q, and m indicate singlet, doublet, triplet, quartet, and multiplet, respectively.

Low-resolution mass spectra were recorded on a Perkin-Elmer Model 270B spectrometer. High-resolution mass spectra were recorded on a Hitachi Perkin-Elmer RMH 70 spectrometer.

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(19) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730.

Elemental analyses were carried out by Galbraith Labs, Inc., Knoxville, TN.

Ultraviolet spectra (UV) were obtained on a Perkin-Elmer Model 202 spectrometer using matched 1.0-cm cells.

Thin layer chromatography (TLC) was performed on precoated silica gel TLC plates (unless specified differently), which were developed in the indicated solvent systems. Developed chromatograms were analyzed under ultraviolet irradiation and/or iodine stain.

3,4-Dihydroisoquinoline (5).[20] To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (10.0 g, 75.2 mmol) in CH_2Cl_2 (200 mL) was added *N*-bromosuccinimide (14.7 g, 82.7 mmol) portionwise over 20 min. After the addition was complete, the mixture was stirred until TLC (CH_2Cl_2:MeOH = 9:1) indicated that the starting material was consumed (30 min). Sodium hydroxide (50 mL of a 30% aqueous solution) was added, and stirring was continued for 1 h at 25 °C. The organic layer was separated and washed with water (100 mL), and the product was extracted with 10% HCl (2 × 100 mL). The combined acidic extracts were washed with CH_2Cl_2 (100 mL) and made basic with concentrated ammonia (pH 9). The liberated oil was extracted with CH_2Cl_2 (3 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo to afford a light yellow oil which was distilled [60–65 °C (1 mmHg), [lit.[20] bp 69–72 °C (2 mmHg)]] to give 9.26 g (94%) of colorless oil: IR (NaCl film) 1620 cm^{-1} (ArC=N); ^1H NMR ($CDCl_3$) δ 8.33 (t, J = 2.1 Hz, 1 H, C=N), 7.1–7.4 (m, 4 H, ArH), 3.76 (td, J = 7.8 Hz and J = 2.1 Hz, 2 H, CH_2CH_2N), 2.74 (t, J = 7.8 Hz, 2 H, CH_2CH_2N); MS, *m/e* (M^+) 131 (83%), 130 (100%).

1,2,3,4-Tetrahydroisoquinoline-1-acetic Acid (6). 3,4-Dihydroisoquinoline (4.0 g, 30 mmol) and malonic acid (3.1 g, 30 mmol) were mixed well at 25 °C. The mixture was immersed in an oil bath preheated to 120 °C. After 30–60 min of manual stirring, gas evolution ceased. The solid residue was directly recrystallized from aqueous methanol to afford **6** as colorless, analytically pure needles: 5.0 g (88%); mp 244–245 °C; IR (KBr) 2680 cm^{-1} (NH_2^+), 1575 (CO_2); MS, *m/e* (M^+) 191 (3%), 132 (100%). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.11; H, 6.96; N, 7.20.

1,2,3,8a-Tetrahydrocyclopent[*ij*]isoquinolin-7(8*H*)-one (7).[9] Polyphosphoric acid (80 g) was heated for 20 min in an oil bath at 150 °C. Acetic acid **6** (7.8 g, 41 mmol) was added all at once, and the mixture was stirred manually at 150 °C with a glass rod for 75 min. The dark solution was cooled to room temperature, and ice water (400 mL) was added to destroy the PPA. The aqueous solution was made basic (pH 8–9) with concentrated ammonia, and the liberated base was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to afford a dark solid. Purification by silica gel chromatography (CH_2Cl_2:MeOH = 9:1) gave **7** as a light brown solid: 5.6 g (79%); recrystallized from hexane–ethyl acetate; mp 89–91 °C (lit.[9] mp, 84–87 °C); IR (KBr) 3300 (NH), 1710 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (t, J = 4.5 Hz, 1 H, ArH), 7.34 (Od, J = 4.5 Hz, 2 H, ArH), 4.26 (t, J = 6.4 Hz, 1 H, ArCHN), 3.56–2.46 (m, 6 H, CH_2CO and CH_2CH_2N); MS, *m/e* (M^+) 173 (100%), 172 (65%), 144 (50%), 116 (100%). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.39; H, 6.60; N, 8.17.

3a,4,5,6-Tetrahydro-1*H*-benzo[*de*][1,6]naphthyridin-2-(3*H*)-one (9) and 2,3,9,9a-Tetrahydro-1*H*-benzo[*de*][1,7]-naphthyridin-7(8*H*)-one (10). Amino ketone **7** (4.3 g, 23 mmol) was dissolved in concentrated H_2SO_4 (30 mL) at 0 °C. Sodium azide (2.0 g, 31 mmol) was added cautiously over 5 min. During the addition considerable frothing occurred. After the addition was complete, the mixture was stirred for 15 min at 0 °C and 60 min at 25 °C. Ice water (100 mL) was added, and the solution was made basic (pH 9) with concentrated ammonia. The liberated base was extracted with CH_2Cl_2 (3 × 100 mL), and the combined dried (Na_2SO_4) organic layers were evaporated in vacuo to give a grayish-brown solid: 3.55 g (76%); recrystallized from ethanol–ethyl acetate; mp 170 °C; IR (KBr) 3300 (NH), 1680 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (br s, 1 H, amide NH), 7.12 (t, J = 7.7 Hz, 1 H, ArH), 6.84 (d, J = 7.7 Hz, 1 H, ArH), 6.63 (d, J = 7.7 Hz, 1 H, ArH), 4.19 (dd, J = 14.3 Hz and J = 5.2 Hz, 1 H, ArCHN), 3.46–2.47 (m, 6 H, $CH_2CO$and $ArCH_2CH_2N$); MS, *m/e* (M^+) 188 (55%), 187 (100%), 159 (60%). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.89. Found: C, 69.86; H, 6.68; N, 14.62. The second chromatography fraction afforded lactam **10**: 0.75 g; brown solid; recrystallized from ethanol–ethyl acetate; mp 114–116 °C; IR (KBr) 3500 (NH), 1670 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (m, 1 H, ArH), 7.30 (m, 2 H, ArH), 6.25 (br s, 1 H, amide NH), 4.25 (dd, J = 12.4 Hz and J = 6.0 Hz, 1 H, ArCHN), 2.75–3.60 (m, 6 H, $ArCH_2CH_2N$ and CH_2CO); MS, *m/e* (M^+) 188 (15%), 159 (45%), 131 (100%). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.89. Found: C, 69.87; H, 6.71; N, 14.64.

2,3,3a,4,5,6-Hexahydro-1*H*-benzo[*de*][1,6]naphthyridine (11). To a stirred suspension of lithium aluminum hydride (610 mg) in ice-cold THF (100 mL) under a nitrogen atmosphere was added the lactam **9** (1.37 g, 7.29 mmol) portionwise over 10 min. After the addition was complete, the mixture was refluxed an additional 30 min, cooled to room temperature, and filtered. The residue was broken up with a spatula and washed with CH_2Cl_2 (2 × 50 mL). The product was obtained as a beige powder that was recrystallized from hexane: mp 120–122 °C; IR (KBr) 3300 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (t, J = 7.7 Hz, ArH), 6.39 (d, J = 7.7 Hz, 1 H, ArH), 6.27 (d, J = 7.7 Hz, 1 H, ArH) 3.88 (dd, J = 11.5 Hz, $ArNCH_2CH_2$); MS, *m/e* (M^+) 174 (55%), 173 (100%). Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.18; H, 8.20; N, 15.94.

1*H*-Benzo[*de*][1,6]naphthyridine Hydrochloride (4) and 5,6-Dihydro-4*H*-benzo[*de*][1,6]naphthyridine (12). The diamine **11** (1.00 g, 5.75 mmol) and 5% Pd–C (100 mg) in degassed xylene (20 mL) were refluxed under a nitrogen atmosphere for 2 h. The mixture was cooled to 25 °C, 10% HCl (40 mL) was added, and the mixture was stirred an additional 10 min. The catalyst was filtered and washed with 10% HCl (2 × 10 mL). The aqueous layer was separated, washed with CH_2Cl_2 (20 mL), and made basic (pH 9) with concentrated ammonia. The liberated based was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The resulting yellow-green oil was chromatographed on neutral alumina (CH_2Cl_2:MeOH = 19:1). The first fraction afforded the dihydro compound **12**: 0.52 g (54%); beige solid; recrystallized from ethyl acetate; mp 153–154 °C; IR (KBr) 3200 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.45 (d, J = 5.2 Hz, 1 H, NCH), 7.78 (d, J = 8.6 Hz, 1 H, ArH), 7.54 (dd, J = 8.0 Hz and J = 8.0 Hz, 1 H, CHCHCH), 7.10 (dd, J = 6.9 Hz and J = 2.0 Hz, 2 H, CH_2CH_2N), 3.31 (t, J = 6.1 Hz, 2 H, CH_2CH_2N); MS (CI, isobutane), *m/e* (M^+) 171 (80%), 170 (100%), 169 (60%), 168 (65%). Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.30; H, 5.94; N, 16.13. The second fraction afforded **4a** as a yellow solid that was immediately dissolved in THF and treated with concentrated HCl. Didemethoxyaaptamine **4** [0.30 g (31%)] was obtained as a bright yellow solid: mp >250 °C; IR (KBr) 2700 (NH^+) cm^{-1}; ^1NMR (Me_2SO-d_6) δ 13.45 (br d, J = 6.1 Hz, 1 H, C_2-H), 7.79 (t, J = 7.9 Hz, 1 H, C_8-H) 7.42 (br d, J = 7.1 Hz, 1 H, C_5-H), 7.37 (d, J = 8.3 Hz, 1 H, C_7-H), 7.24 (d, J = 7.7 Hz, 1 H, C_9-H), 6.88 (d, J = 7.2 Hz, 1 H, C_6-H), 6.60 (d, J = 6.9 Hz, 1 H, C_3-H); HRMS *m/e* (M^+) 169.0761, calcd for $C_{11}H_9N_2$ 169.0764, $[(M+1)^+]$ 170.0838, calcd for $C_{11}DH_8N_2$ 170.0842.

6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetic Acid (13). 6,7-Dimethoxy-3,4-dihydroisoquinoline (10.0 g, 52.4 mmol) and malonic acid (5.45 g, 52.4 mmol) were mixed well at 25 °C, and then the mixture was immersed in an oil bath preheated to 120 °C. After 30–60 min of manual stirring, gas evolution ceased. The resultant solid was recrystallized from aqueous methanol to afford **13** as colorless analytically pure needles: 12.1 g (92%); mp 251–252 °C; IR (KBr) 2450 (NH_2^+), 1570 (CO_2) cm^{-1}; MS, *m/e* (M^+) 251 (2%), 192 (100%). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.58. Found: C, 62.00; H, 6.85; N, 5.51.

5,6-Dimethoxy-1,2,3,8a-tetrahydrocyclopent[*ij*]isoquinolin-7(8*H*)-one (14).[12] Polyphosphoric acid (300 g) was heated on the steam bath for 20 min. Amino acid **13** (30 g, 0.12 mol) was added to the PPA and the resultant solution mixed well. The mixture was heated on the steam bath for 1 h while it was manually stirred. The solution was allowed to cool to 25 °C, and the PPA was destroyed with ice water (1 L). Basification with concentrated ammonia (pH 8–9) resulted in the liberation of a base that was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to

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afford 14: 18.5 g (66%); beige solid; recrystallized from hexane–ethyl acetate; mp 107–108 °C (lit.[12] mp 105–108 °C); IR (KBr) 3300 (NH), 1720 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92 (s, 1 H, ArH), 4.19 (t, J = 7.1 Hz, 1 H, ArCHN), 4.06 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.38 (m, 2 H, CH_2CH_2N), 3.01 (AB q, J = 6.7 Hz and J = 5.0 Hz, 1 H, CHCO), 2.85 (m, 2 H, $ArCH_2CH_2N$), 2.53 (AB q, J = 6.7 Hz and J = 5.0 Hz, 1 H, CHCO).

1-(p-Tolylsulfonyl)-5,6-dimethoxy-1,2,3,8a-tetrahydrocyclopent[ij]isoquinolin-7(8H)-one (15). To a solution of the amino ketone 14 (2.44 g, 10.5 mmol) in distilled pyridine (25 mL) at 25 °C was added p-toluenesulfonyl chloride (2.00 g, 10.5 mmol). Stirring was maintained for 1 h, and then water (1 mL) was added. The solution was stirred an additional 5 min and then poured into water (50 mL). The product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 10% HCl (2 × 100 mL) and water (100 mL), dried (Na_2SO_4), and evaporated under reduced pressure to afford a yellow-brown gum that crystallized on treatment with methanol; 3.84 g (94%). Recrystallization from ethanol gave pure 15: mp 158–159 °C; IR (KBr) 1710 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (d, J = 8.3 Hz, 2 H, ArH), 6.89 (s, 1 H, ArH), 4.15 (t, J = 6.5 Hz, 1 H, ArCHN), 4.04 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.66–3.78 (m, 1 H, CHCO), 3.07–3.43 (m, 3 H, CHCO and CH_2CH_2N), 2.58–2.97 (m, 2 H, $ArCH_2CH_2N$), 2.44 (s, 3 H, $ArCH_3$); MS, m/e (M^+) 397 (70%), 372 (40%), 232 (70%), 231 (100%). Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.27. Found: C, 61.75; H, 5.56; N, 3.49; S, 8.44.

5,6-Dimethoxy-1,2,3,8a-tetrahydrocyclopent[ij]isoquinolin-7(8H)-one Oxime (16a). To a solution of the amino ketone 14 (500 mg, 2.15 mmol) in pyridine (5 mL) and ethanol (5 mL) was added hydroxylamine hydrochloride (150 mg, 2.15 mmol). The mixture was refluxed for 30 min during which time a colorless precipitate formed. The mixture was cooled in an ice bath and filtered, and the residue was washed with ethanol (5 mL) and ether (5 mL) and dried to afford 16a [534 mg (100%)] as an analytically pure powder: mp >250 °C; IR (KBr) 3300 (OH), 1630 (C=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.46 (s, 1 H, OH), 9.70 (br s, 1 H, NH), 7.01 (s, 1 H, ArH), 4.54 (t, J = 7.1 Hz, 1 H, ArCHN), 3.81 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 2.70–3.75 (m, 6 H, $ArCH_2CH_2N$ and CH_2CNOH); MS, m/e (M^+) 248 (100%), 233 (80%), 231 (50%), 219 (75%). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.29. Found: C, 62.55; H, 6.62; N, 11.21.

1-(p-Tolylsulfonyl)-5,6-dimethoxy-1,2,3,8a-tetrahydrocyclopent[ij]isoquinolin-7(8H)-one Oxime (16b). To a solution of the keto sulfonamide 15 (500 mg, 1.29 mmol) in pyridine (5 mL) and 955 ethanol (5 mL) was added hydroxylamine hydrochloride (102 mg, 1.48 mmol). The solution was stirred and heated to reflux for 30 min and then cooled in an ice bath. Ether (20 mL) was added, and the colorless precipitate that formed was filtered, washed with ether (10 mL), and dried. The oxime 16b [518 mg (100%)] was obtained as a colorless, analytically pure powder: mp >250 °C; IR (KBr) 3250 (OH), 1590 (C=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.30 (s, 1 H, OH), 7.79 (d, J = 8.1 Hz, 2 H, ArH), 7.46 (d, J = 8.1 Hz, 2 H, ArH), 6.88 (s, 1 H, ArH), 4.12 (t, J = 7.0 Hz, 1 H, ArCHN), 3.76 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 2.21–2.85 (m, 6 H, $ArCH_2CH_2N$ and CH_2CNOH), 2.41 (s, 3 H, $ArCH_3$); MS, m/e (M^+) 402 (100%), 387 (35%), 385 (35%), 371 (40%), 246 (50%), 229 (60%). Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.68; H 5.51; N, 6.96; S, 7.97. Found: C, 59.38; H, 5.45; N, 6.83; S, 8.19.

1-(p-Tolylsulfonyl)-5,6-dimethoxy-1,2,3,8a-tetrahydrocyclopent[ij]isoquinolin-7(8H)-one O-(p-Tolylsulfonyl)oxime (18). To a suspension of the oxime sulfonamide 16b (3.5 g, 8.7 mmol) in 1 N KOH (35 mL) and acetone (350 mL) was added p-toluenesulfonyl chloride (2.3 g, 12 mmol) portionwise over 10 min. The mixture was stirred for 50 min at 25 °C during which time the oxime sulfonamide 16b dissolved and a pale yellow precipitate formed. p-Toluenesulfonyl chloride (2.3 g, 12 mmol) was again added, and the mixture was stirred an additional 35 min. It was then poured into ice water (500 mL), and the precipitate was filtered and washed with water (50 mL). Recrystallization from ethyl acetate afforded the oxime tosylate 18 [4.20 g (86%)] as a pale yellow powder: mp 203–207 °C dec; IR (KBr) 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 4 H, ArH), 6.72 (s, 1 H, ArH), 4.05 (t, J = 5.6 Hz, 1 H, ArCHN), 3.05–3.95 (m, 4 H, $ArCH_2CH_2N$ and CH_2CNOTs), 3.81 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 2.50–2.85 (m, 2 H, $ArCH_2CH_2N$), 2.44 (s, 3 H, $ArCH_3$), 2.43 (s, 3 H, $ArCH_3$); MS, m/e 384 (1%), 346 (60%), 91 (100%). Anal. Calcd for $C_{27}H_{28}N_2O_7S_2$: C, 58.26; H, 5.07; N, 5.03; S, 11.52. Found: C, 58.00; H, 5.15; N, 4.95; S, 11.40.

7-Hydroxy-6-methoxy-3,4-dihydroisoquinoline (19).[17] To 6,7-dimethoxy-3,4-dihydroisoquinoline (30.0 g, 0.157 mmol) was added 48% HBr (210 mL) over 5 min. The warm mixture was inserted into an oil bath preheated to 95 °C and stirred at this temperature for 12–15 h. The solution was then cooled in an ice bath and cautiously made basic with concentrated ammonia until pH 9 was attained. Within minutes a precipitate formed that was collected, washed with water (2 × 100 mL) and ether (2 × 100 mL), and dried. The filtrate was exhaustively extracted with CH_2Cl_2 (8 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo to afford a yellow semisolid. The filtered residue and the semisolid were combined and crystallized from ethanol–ethyl acetate to give 17.8 g (64%) of 19 as colorless rhombs, collected in two crops. The mother liquors were evaporated to afford the starting dihydroisoquinoline: 9.0 g (30%); mp of 19 187–189 °C (lit.[17] mp 189–190 °C); IR (KBr) 2700 (ArOH), 1620 (ArC=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (t, J = 2.3 Hz, 1 H, CH=N), 6.88 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), 6.15 (br s, 1 H, OH), 3.93 (s, 1 H, OCH_3), 3.73 (td, J = 7.3 Hz and J = 2.3 Hz, 2 H, CH_2CH_2N), 2.68 (t, J = 7.3 Hz, 2 H, CH_2CH_2N); MS, m/e (M^+) 177 (100%), 162 (95%).

8-Nitro-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline (20). To an ice-cold vigorously stirred solution of 40% HNO_3 (150 mL) was added 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline (10.0 g, 56.5 mmol) portionwise over 10 min. After the addition was complete, $NaNO_2$ (100 mg) was added along with 5 mL of ethanol. Within minutes a yellow precipitate formed. The mixture was stirred for 30 min at 0 °C. The precipitate was collected and washed with cold ethanol (2 × 50 mL) and ether (2 × 50 mL), affording 20 as the hydronitrate, 9.75 g (61%). The salt was dissolved in the minimum amount of boiling methanol, and the pH was adjusted to 9 with concentrated ammonia. A bright yellow precipitate was liberated which, after chilling in ice, was filtered and washed with cold methanol (2 × 50 mL) to give 7.50 g (60%) of 20 as fine needles in analytically pure form: mp 235–240 °C dec; IR (KBr) 2400 (ArOH), 1630 (C=N), 1540 (NO_2) cm^{-1}; MS, m/e (M^+) 222 (100%). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.12; H, 4.57, N, 12.63.

Ethyl 8-Nitro-7-hydroxy-6-methoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate (21). 8-Nitro-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline (5.00 g, 22.5 mmol) and malonic acid monoethyl ester (5.94 g, 45.0 mmol) were mixed well at room temperature and then immersed into an oil bath preheated to 120 °C. Heating and gas evolution were observed. After 30–60 min of continuous stirring gas evolution ceased and a dark red solid remained. Direct recrystallization of this solid from ethanol afforded 21 as a bright red powder: (5.02 g (72%); mp 159 °C; IR (KBr) 2400 (br s, OH), 1710 (C=0), 1510 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (s, 1 H, ArH), 4.92 (d, J = 7.0 Hz, 1H, ArCHN), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.92 (s, 3 H, OCH_3), 3.25–2.45 (m, 6 H, $ArCH_2CH_2N$ and CH_2CO_2Et), 1.27 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); MS, m/e 223 (100%). Anal. Calcd for $C_{14}H_{18}NO_4$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.15; H, 6.02; N, 8.81.

Ethyl 8-Nitro-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate (21a). A suspension of the nitrophenol 21 (1.60 g, 5.16 mmol) in CH_2Cl_2 (100 mL) was treated with ethereal diazomethane. The mixture was vigorously stirred for 2–4 h during which time a clear yellow solution formed. The excess diazomethane was destroyed by the dropwise addition of acetic acid until gas evolution ceased. The mixture was washed with 10% NaOH (2 × 30 mL) and water (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure to afford a light yellow gum that crystallized on treatment with cold ether. The dimethoxy compound 21 [1.60 g (96%)] was obtained as a tan solid. Recrystallization from hexane–ethyl acetate afforded pure 21a: mp 99–100 °C; IR (KBr) 3350 (w, NH), 1720 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (s, 1 H, ArH), 4.50 (dd, J = 11.0 Hz and J = 2.8 Hz, 1 H, ArCHN), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.88 (s, 6 H, OCH_3); MS, m/e 237 (100%), 190 (20%). Anal. Calcd for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.72, H, 6.25; N, 8.63.

8,9-Dimethoxy-3a,4,5,6-tetrahydro-1H-benzo[de][1,6]naphthyridin-2(3H)-one (17a). A mixture of the nitro amino ester **21a** (1.40 g, 4.32 mmol) and 5% Pd–C (100 mg) in acetic acid (50 mL) was hydrogenated for 1 h at an initial pressure of 45 psi. The catalyst was filtered and washed with acetic acid (2 × 10 mL). The filtrate was condensed under reduced pressure, and the light yellow gummy residue was dissolved in CH_2Cl_2 (60 mL), washed with 10% NaOH (2 × 40 mL) and water (50 mL), and dried (Na_2SO_4). The organic phase was condensed under reduced pressure to afford the lactam **17a** [0.82 g (77%)] as a straw-colored solid: NMR ($CDCl_3$) δ 7.78 (br s, 1 H, lactam NH), 6.37 (s, 1 H, ArH), 4.12 (dd, J = 14.0 Hz and J = 5.0 Hz, 1 H, ArCHN), 3.85 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.44–2.42 (m, 6 H, CH_2CO and $ArCH_2CH_2N$); MS, m/e (M^+) 248 (95%), 247 (60%), 233 (75%), 231 (75%), 217 (100%), 222 (80%). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.29. Found: C, 63.01; H, 6.70; N, 11.03.

8,9-Dimethoxy-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*][1,6]-naphthyridine (22). To a solution of the lactam **17a** (500 mg, 2.00 mmol) in dry THF (40 mL) under a nitrogen atmosphere at 25 °C was added borane (7.0 mL, 0.97 M in THF) dropwise over 5 min with stirring. After the addition was complete, the solution was refluxed for 2 h and then it was cooled to 25 °C. After standard workup, the mixture was partitioned between CH_2Cl_2 (100 mL) and 10% NaOH (50 mL), and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (30 mL), and the combined organic layers were washed with water (50 mL), dried (Na_2SO_4), and evaporated in vacuo to afford the diamine **22** [445 mg (95%)] as a colorless gum. Treatment with ether–hexane produced colorless needles of **22**. Recrystallization from hexane gave pure **22**: mp 106–108 °C; IR (KBr) 3450 (ArNH), 3250 (RNHR) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.97 (s, 1 H, ArH), 4.33 (br s, 1 H, ArNH), 3.85 (t, J = 4.1 Hz, 1 H, ArCHN), 3.80 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.50–3.45 (m, 6 H, $ArNHCH_2$ and $ArCH_2CH_2N$), 1.65–2.10 (m, 2 H, $ArNHCH_2CH_2$); MS, m/e (M^+) 234 (75%), 233 (100%), 205 (40%), 191 (60%), 190 (55%). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.60; H, 7.73; N, 11.84.

Aaptamine (1) and Dihydroaaptamine (23). A mixture of hexahydroaaptamine (**22**; 300 mg, 1.31 mmol) and 5% Pd–C (60 mg) in degassed xylene (12 mL) was refluxed 3.5 h under a nitrogen atmosphere. The mixture was cooled to 25 °C, and 10% HCl (30 mL) was added. Stirring was continued for 10 min, and then the catalyst filtered and washed with 10% HCl (2 × 30 mL). The aqueous layer was separated from the filtrate and washed with CH_2Cl_2 (20 mL). Basification with concentrated ammonia (pH 10) liberated a mixture of bases that was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and condensed under reduced pressure to afford a greenish yellow gum which was chromatographed on neutral alumina (CH_2Cl_2:MeOH = 97:3). The first fraction afforded the free base of aaptamine **1a** [116 mg (39%)] as a yellow gum. It was immediately dissolved in THF (10 mL) and treated with concentrated HCl to give aaptamine as a yellow powder: mp 110–113 °C (lit.[2a] mp 110–113 °C); IR (KBr) 2900 (br s, NH^+) cm^{-1}; (Me_2SO-d_6) δ 13.10 (d, J = 4.5 Hz, 1 H, N_4-H), 12.30 (d, J = 5.3 Hz, 1 H, N_1-H), 7.85 (dd, J = 6.6 Hz and J = 6.6 Hz, 1 H, C_2-H), 7.41 (dd, J = 8.4 Hz and J = 7.0 Hz, 1 H, C_5-H), 7.13 (s, 1 H, C_7-H), 6.88 (d, J = 7.1 Hz, 1 H, C_6-H), 6.47 (d, J = 7.1 Hz, 1 H, C_3-H), 3.98 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3); HRMS, (M^+) m/e 229.0959, calcd for $C_{13}H_{13}N_2O_2$ 229.0974. The second fraction afforded dihydroaaptamine [**23**; 133 mg (45%)] as a faint yellow solid: recrystallization from ethyl acetate; mp 141–142 °C (lit.[2a] mp 137–139 °C); IR (KBr) 3400 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.65 (br s, 1 H, NH), 8.08 (d, J = 7.2 Hz, 1 H, C_7-H), 7.34 (s, 1 H, ArH), 6.63 (d, J = 7.2 Hz, 1 H, C_8-H), 3.10 (t, J = 7.3 Hz, 2 H, C_3-H); MS, m/e (M^+) 230 (100%).

8-Methoxy-9-hydroxy-3a,4,5,6-tetrahydro-1*H*-benzo-[*de*][1,6]naphthyridin-2(3*H*)-one (25). A mixture of the amino ester **21** (1.00 g, 3.22 mmol) and 5% Pd–C (150 mg) in acetic acid (30 mL) was hydrogenated for 1 h at an initial pressure of 45 psi. The catalyst was filtered and washed with acetic acid (2 × 15 mL). The bulk of the acetic acid from the filtrate was removed under reduced pressure, and the residue was dissolved in water (30 mL). The solution was chilled in an ice bath and neutralized with solid $NaHCO_3$. A light gray precipitate formed which was filtered and washed with cold water (3 × 10 mL) and ether (3 × 10 mL). The amino lactam **25** [754 mg (100%)] was obtained as a pale gray powder that was recrystallized from methanol: mp 187–188 °C; IR (KBr) 300 (br s, OH), 1630 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (br s, 1 H, NHCO), 6.38 (s, 1 H, ArH), 4.17 (dd, J = 7.8 Hz and J = 2.5 Hz, 1 H, ArCHN), 3.88 (s, 3 H, OCH_3), 2.42–3.45 (m, 6 H, $ArCH_2N$ and CH_2CO); MS, m/e (M^+) 234 (55%), 233 (100%), 205 (65%). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.30; H, 6.33; N, 11.61.

8-Methoxy-9-hydroxy-4-[(*tert*-butyloxy)carbonyl]-3a,4,5,6-tetrahydro-1*H*-benzo[*de*][1,6]naphthyridin-2-(3*H*)-one (25a). To a suspension of the lactam **25** (4.94 g, 21.1 mmol) in $CHCl_3$ (100 mL) was added di-*tert*-butyl dicarbonate (4.60 g, 21.1 mmol) in one portion. The mixture was refluxed with vigorous stirring for 1.5 h during which time the lactam completely dissolved. The solution was cooled to 25 °C and washed with saturated $NaHCO_3$ (50 mL) and water (50 mL). The brown solution was dried (Na_2SO_4) and evaporated in vacuo to afford a brown gum that was purified by chromatography in silica gel (ethyl acetate:hexane = 3:1). The light tan foamy residue crystallized from hexane–chloroform to afford **25a** [5.77 g (82%)] as colorless needles. The mother liquors were condensed to afford a second crop of **25a**: 0.25 g (4%); total yield 86%. Recrystallization from hexane–ethyl acetate offered pure **25a**: mp 175–176 °C; IR (KBr) 3250 (br s, OH), 1650 (urethane carbonyl), 1690 (amide carbonyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (br s, 1 H, ArCHN), 6.41 (s, 1 H, ArH), 5.74 (br s, 1 H, OH), 4.96 (dd, J = 13.7 Hz and J = 4.6 Hz, 1 H, ArCHN), 4.41 (m, 1 H, CHCO), 3.88 (s, 3 H, OCH_3), 2.42–3.10 (m, 5 H, CHCO and $ArCH_2CH_2N$), 1.51 (s, 9 H, *t*-Bu); MS (Cl, isobutane), m/e (M^+) 335 (15%), 279 (100%), 277 (25%). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.73; H, 6.68; N, 8.38.

8-Methoxy-9-(benzyloxy)-4-[(*tert*-butyloxy)carbonyl]-3a,4,5,6-tetrahydro-1*H*-benzo[*de*][1,6]naphthyridin-2-(3*H*)-one (26). To a refluxing mixture of the lactam phenol **25a** (4.74 g, 14.2 mmol) and K_2CO_3 (5.0 g) in acetone (75 mL) was added benzyl bromide (3.60 g, 21.3 mmol) in one portion. The mixture was refluxed until TLC (ethyl acetate:hexane = 1:1) showed no starting material and a single product had formed (1.5 h). The mixture was allowed to cool to 25 °C, and then water (100 mL) and CH_2Cl_2 (200 mL) were added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residual pale yellow oil crystallized when it was treated with hexane and afforded the *O*-benzyl compound **26** [5.27 g (88%)] as a colorless solid. Recrystallization from hexane–ethyl acetate afforded pure **26**: mp 156–157 °C; IR (KBr) 1680 (urethane carbonyl), 1690 (lactam carbonyl cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (br s, 1 H, NH), 7.37 (m, 5 H, $OCH_2C_6H_5$), 6.45 (s, 1 H, ArH), 5.03 (s, 2 H, $OCH_2C_6H_5$), 4.88 (dd, J = 14.1 Hz and J = 4.9 Hz, 1 H, CHCO), 2.30–2.83 (m, 4 H, $ArCH_2CH_2N$), 1.50 (s, 9 H, *t*-Bu); MS, m/e (M^+) 424 (10%), 368 (30%), 367 (100%), 277 (55%). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.75; H, 6.60; N, 6.48.

8-Methoxy-9-(benzyloxy)-3a,4,5,6-tetrahydro-1*H*-benzo-[*de*][1,6]naphthyridin-2(3*H*)-one (27). To a solution of trifluoroacetic acid (75 mL) and water (25 mL) at 25 °C was added the carbamate **26** (5.27 g, 12.4 mmol) in one portion. The mixture was swirled until the substrate dissolved, and then it was allowed to sit at room temperature for 1 h. Water (250 mL) was added, and a colorless precipitate formed. The mixture was stirred vigorously and made basic with concentrated ammonia (pH 10) with external cooling. Stirring continued for 30 min, and the resulting colorless precipitate was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (100 mL), dried (Na_2SO_4), and evaporated under reduced pressure to afford a colorless solid. Recrystallization from hexane–ethyl acetate afforded **27** [3.85 g (96%)] as colorless needles: mp 120–122 °C; IR (KBr) 3200 (NH), 1650 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (br s, 1 H, amide NH), 7.37 (m, 5 H, $OCH_2C_6H_5$), 6.40 (s, 1 H, ArH), 5.01 (dd, J = 11.1 Hz, ArCHN), 3.88 (s, 3 H, OCH_3), 3.38 (m, 1 H, $ArCH_2CHN$), 2.30–3.12 (m, 5 H, $ArCH_2CHN$ and CH_2CO); MS, m/e (M^+) 324 (60%), 233 (15%), 204 (100%), 91 (60%). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.11; H, 6.35; N, 8.40.

8-Methoxy-9-(benzyloxy)-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*][1,6]naphthyridine (28). To a solution of the lactam **27** (100 mg, 0.309 mmol) in dry THF (5 mL) under a nitrogen atmosphere at 25 °C was added BH_3 (2.00 mL, 0.97 M in THF) dropwise during 5 min. The mixture was stirred for an additional 1 h, and then 10% HCl (3 mL) was cautiously added. The solution was refluxed for 30 min, cooled to 25 °C, diluted with water (30 mL), and washed with ether (2 × 20 mL). The solution was made basic (pH 9) with 10% NaOH, and the liberated base was extracted with hexane (3 × 30 mL). The combined hexane layers were dried (Na_2SO_4) and evaporated under reduced pressure. The colorless residual gum was purified on silica gel (CH_2Cl_2:MeOH = 4:1) to afford the diamine **28** [66 mg (69%)] as a colorless oil. Conversion to the hydrochloride was accomplished by dissolving the gum in THF (5 mL) and adding concentrated HCl (0.25 mL): mp 192–195 °C dec; IR (KBr) 2600 (NH_{2^+}) cm^{-1}; free-base proton NMR ($CDCl_3$) δ 7.26–7.50 (m, 5 H, $OCH_2C_6H_5$), 5.99 (s, 1 H, ArH), 4.91 (s, 2 H, $OCH_2C_6H_5$), 4.19 (br s, 1 H, ArNH), 3.81 (s, 3 H, OCH_3), 3.80 (m, 1 H, ArCHN), 3.32 (m, 3 H, $ArCH_2CHN$ and $ArNHCH_2$), 2.57–3.17 (m, 3 H, $ArCH_2CHN$), 2.00 (m, 1 H, $ArNHCH_2CH$), 1.53–1.70 (m, 1 H, $ArCH_2CH$); MS, m/e (M^+) 311 (100%), 310 (55%), 220 (18%), 219 (50%), 190 (25%). Anal. Calcd for $C_{19}H_{23}N_2O_2Cl$: C, 65.79; H, 6.68; N, 8.08; Cl, 10.22. Found: C, 66.00; H, 6.61; N, 8.19; Cl, 10.01.

Demethyloxyaaptamine (3). A mixture of the diamine **28** (125 mg, 0.403 mmol) and 5% Pd–C (50 mg) in degassed xylene under a nitrogen atmosphere was refluxed for 20 h. The mixture was allowed to cool to 25 °C; the catalyst was filtered and then washed with CH_2Cl_2 (3 × 10 mL). The filtrate was condensed under reduced pressure and the greenish brown residual gum was chromatographed on silica gel (CH_2Cl_2:MeOH = 9:1). The fast-moving yellow product was separated cleanly from the slower moving complex mixture. Demethyloxyaaptamine [**3**; 30 mg (35%)] was obtained as fine bright yellow rods. It was recrystallized from ethyl acetate: mp 210–212 °C (lit.[2b] mp 198–200 °C); IR (KBr) 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.19 (d, J = 5.6 Hz, 1 H, C_3-H), 7.48 (d, J = 4.4 Hz, C_6-H), 6.72 (s, 1 H, C_7-H), 4.02 (s, 3 H, OCH_3); HRMS, m/e (M^+) 212.0631 (30%), calcd for $C_{12}H_8N_2O_2$ 212.0582, $[(M+1)^+]$ 213.0596; calcd for $C_{12}DH_7N_2O_2$ 213.0647. Authentic demethyloxyaaptamine (**3**): mp 212–214 °C; IR (KBr) 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.19 (d, J = 5.7 Hz, 1 H, C_3-H), 9.11 (d, J = 4.4 Hz, 1 H, C_5-H), 8.18 (d, J = 5.7 Hz, 1 H, C_3-H), 7.49 (d, J = 4.4 Hz, 1 H, C_6-H), 6.72 (s, 1 H, C_7-H), 4.02 (s, 3 H, OCH_3); HRMS (Cl, isobutane), m/e (M^+) 213.0655, calcd for $C_{12}H_8N_2O_2$ 213.0662.

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Registry No. 1, 96838-36-7; **1a**, 85547-22-4; **4**, 105400-80-4; **4a**, 36917-96-1; **6**, 105400-81-5; **7**, 53921-72-5; **9**, 105400-82-6; **10**, 105400-83-7; **11**, 105400-84-8; **12**, 105400-85-9; **13**, 68345-67-5; **14**, 5868-19-9; **15**, 105400-86-0; **16a**, 105400-87-1; **16b**, 105400-93-9; **17a**, 96838-34-5; **18**, 105400-88-2; **19**, 4602-73-7; **20**, 96838-32-3; **21**, 96860-72-9; **21a**, 96838-33-4; **22**, 96838-35-6; **23**, 85547-23-5; **25**, 105400-89-3; **25a**, 105400-94-0; **26**, 105400-90-6; **27**, 105400-91-7; **28**, 105400-92-8; **28**·HCl, 105400-95-1; 3,4-dihydroisoquinoline, 3230-65-7; 1,2,3,4-tetrahydroisoquinoline, 91-21-4; malonic acid, 141-82-2; 6,7-dimethoxy-3,4-dihydroisoquinoline, 3382-18-1; malonic acid methyl ester, 1071-46-1.

An Approach to the Synthesis of Bactobolin and the Total Synthesis of N-Acetylactinobolamine: Some Remarkably Stable Hemiacetals

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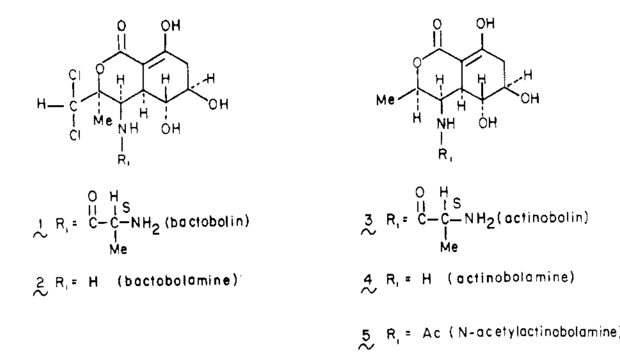
The key steps in the synthesis of N-acetylactinobolamine were the siloxy-Cope rearrangement **17** → **18** and the transformation of pseudoglycal **54**, via its glycosyl azide derivative **55**, to hemiacetal **56**. This hemiacetal, as well as closely related hemiacetals **37** and **48**, proved remarkably unreactive toward processes intended to trap open-chain tautomeric hydroxy aldehydes. In no instance could aldehydo chemistry be realized from these systems.

The Synthetic Plan

Our orienting goal at the inception of this program was that of a total synthesis of the novel antibiotic bactobolin[1,2] (**1**). Since in this exploratory phase we would be working in the racemic series, we defined as our subgoal the desalanyl derivative of **1**, i.e., bactobolamine[3] (**2**). It was assumed that the lessons learned in a synthesis of rac-**2** could be applied to the antipode of the "correct" configuration. Acylation with a suitable derivative of l-alanine would lead, in a straightforward fashion, to **1**.



The novel structural and stereochemical features of bactobolin constitute a formidable challenge to those who would undertake its synthesis. The promising biological properties of this antibiotic (activity against Gram-positive and Gram-negative bacteria via inhibition of protein synthesis, activity against L-1210 mouse leukemia and nonsuppression of immune responses) add to this interest. At the present writing the goal of a total synthesis of bactobolin or bactobolamine has not been accomplished.[4]

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