Synthesis of Heterocyclic Compounds Containing Three Contiguous Hydrogen Bonding Sites in All Possible Arrangements

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Abstract: The synthesis of compounds containing three contiguous hydrogen bond sites is reported. There are six ways of arranging three adjacent hydrogen bond donor (D) and acceptor (A) sites. General synthetic routes to heterocyclic compounds with each arrangement is reported.

Heterocycles with multiple hydrogen bonding sites have gained attention recently for their utility in host-guest systems.1 Many of these heterocyclic hosts were designed with a preorganized array of hydrogen bonding sites that is complementary to that of a guest molecule. Successful heterocyclic hosts were reported for nucleotide bases,1 ureas,2 and several other biologically relevant guest molecules.3

Hydrogen bonding interactions between heterocycles has also found a place in the rapidly expanding area of self-assembling systems.4 These systems incorporate hydrogen bonding sites to control the organization of small components into supramolecular structures, either in solution or the solid state. The most desirable hydrogen bonding partners recognize each other with high selectivity and form tight complexes. Such compounds are said to be well-programmed to self-organize.

We became interested in heterocyclic compounds with three adjacent hydrogen bond donor and acceptor sites as a result of our interest in modular host construction and our interest in self-assembling systems.5 Three adjacent hydrogen bond donor (D) and acceptor (A) sites can be arranged in six different ways: DDD, AAA, AAD, DDA, ADA, and DAD. Reported herein is the synthesis of heterocyclic compounds containing NH donor and N acceptor groups in each of these arrangements. We believe that these convenient syntheses, a few of which followed published procedures, will facilitate a range of studies in the areas of molecular recognition and self-assembly.

Results and Discussion

Hydrogen Bond Donor-Donor-Donor (DDD) Unit. The 1,4-dihydro-2,6-diaminopyridines are one class of compounds reported to date with a hydrogen bond donor-donor-donor (DDD) site.6 The Hantsch synthesis of 1 was reported by Meyer (Scheme I), who studied the substituent effect on the tautomeric equilibrium by 1H NMR.7 It was found that in dimethylformamide-d7 1 (X = 3-nitro) existed exclusively in the 1,4-dihydro tautomeric form. In chloroform-d , a 66:34 mixture of 1,4-dihydro (1a) and 3,4-dihydro (1b) tautomers (slow exchange) were present.8
Hydrogen Bond Donor-Acceptor-Donor (DAD) Unit. Meyer showed that compound 1 (X = 2-nitro) exists exclusively in 3,4-dihydro form 1b in dimethylformamide-d$_7$, presumably to alleviate steric hindrance between the ester and aryl groups.$^7$ Thus, 1 can also serve as a hydrogen bond donor-acceptor-donor (DAD) unit. In chloroform-d, 1 (X = 2-nitro) was found to exist exclusively in 3,4-dihydro form 1b.$^8$ According to $^1$H NMR, compound 1 (X = 2-nitro) is a single diastereoisomer, and this was tentatively assigned as cis on the basis of the very small H$_3$-H$_4$ coupling constant (J$_{3,4}$ = 0 Hz) and the nearly 90° H$_3$-C-C-H$_4$ dihedral angle found for the cis-form by molecular mechanics calculations. Several other heterocyclic hydrogen bond DAD units were used in recognition studies including substituted 2,6-diaminopyridine,$^9$ 2,6-diaminotriazine,$^9$ and 2,6-diaminopurine.$^{10}$

Hydrogen Bond Acceptor-Acceptor-Acceptor (AAA) Unit. 1,9,10-Anthyridines (1,8,9-triazanoranthracenes) contain the hydrogen bond acceptor-acceptor-acceptor (AAA) site.$^{11}$ Caluwe reported$^{12}$ an attractive synthesis of 2,8-diarylanthyridines (e.g., 2a) that used a double Friedländer reaction of 2,6-diamino-3,5-pyridine dicarboxaldehyde (3). Anthyridine 2a was found to be easily reduced, and in binding studies with 1 (X = 3-nitro), was cleanly converted to anthyridan (5,10-dihydroanthyridine) 4a.$^8$ Because of this instability, the synthesis of 5-arylanthyridines was undertaken in an effort to inhibit reduction of the central ring of 2.
Two approaches to the synthesis of 5-arylanthyridines were developed, the first of which was analogous to the Caluwe approach. This route required 4-phenyl-2,6-diamino-3,5-pyridine dicarboxaldehyde (5), which was prepared as outlined in Scheme 3. Thus, trimethylorthobenzoate was heated with two equivalents of malononitrile in pyridine, followed by aqueous hydrochloric acid to afford 6 in 43% yield. A similar procedure was described for the preparation of the analogous 4-methylpyridine. Aminolysis of 6 with concentrated ammonium hydroxide proceeded in quantitative yield and catalytic hydrogenation under acidic conditions afforded 5 in 32% yield.

In the double Friedländer condensations (Scheme 2), pyridine 5 proved to be superior to 3 in several respects. First, 5 was soluble in a wider range of solvents, as were the anthyridine products 2b-2h. Thus, the homogeneous condensation of 5 with ketones was faster and the products were easier to purify. Second, pyridine 5 reacted with a wider range of ketones, including aliphatic ketones that did not react as smoothly with 3. Finally, 5 reacted with ketones to form anthyridines 2b-2h directly, whereas condensations of 6 with ketones resulted in generation of anthyridan (4) in many instances.

The second method used to synthesize 5-arylanthyridines involved the addition of an aryl Grignard reagent to a 5-unsubstituted anthyridine (Scheme 2). Thus, 4-trimethylsilylphenyl magnesium bromide reacted with 2a to form anthyridan 4c in 66% crude yield. Oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) produced anthyridine 2i in quantitative yield. This approach is particularly useful for 5-aryl substituents that cannot tolerate the strong acid or base, or the hydrogenation conditions used in the first approach (Schemes 2 and 3).

Hydrogen Bond Acceptor-Donor-Acceptor (ADA) Unit. There are a number of compounds that can serve as a hydrogen bond ADA unit. These include the uracils, thymines, anthyridans, and anthyridones. Only the anthyridans and anthyridones contain N and NH groups as the hydrogen bond acceptor and donor sites, respectively. 5-Phenylanthridan 4b was prepared in 85% yield by sodium borohydride mediated reduction of the central anthyridine ring of 2b (Scheme 2). The 5-substituted anthyridans exhibited higher chloroform solubility than the corresponding anthyridones, and possessed higher stability than the analogous 5-unsubstituted anthyridans.

Hydrogen Bond Acceptor-Acceptor-Donor (AAD) Unit. Two common heterocyclic compounds that contain contiguous hydrogen bond acceptor-acceptor-donor (AAD) sites are the 4-aminopyrimidin-2-ones (e.g., cytosine) and 2-amino-1,8-naphthyridines. The latter compounds contain all N and NH donor-acceptor sites, and were used by Kelly in a bisubstrate reaction template and by Feibush to produce a chemically bonded stationary phase that selectively
retained guanosine derivatives. Simple 2-amino-1,8-naphthyridines are readily prepared by Knorr cyclization of 2,6-diaminopyridine with 1,3-diketones. Because more elaborate aminonaphthyridines cannot easily be made in this fashion, we recently developed a facile, alternative approach that used the Friedländer condensation.

The AAD site in 2-amidonaphthyridines binds guanosine derivatives and 6-amino-2-pyridones tightly in chloroform \((K_{assoc} > 10^4 \text{ M}^{-1})\). However, a 2-ethoxy-7-amidonaphthyridine was reported to bind a guanosine derivative in chloroform much more weakly \((K_{assoc} \leq 200 \text{ M}^{-1})\). To determine the origin of the detrimental effect caused by the 7-alkoxy substituent, compound 7 was synthesized (Scheme 4). Cyclocondensation of 8 and homophthalic acid in polyphosphoric acid afforded lactone 9 in 97% yield. The mechanism of this reaction is not known, but may proceed through a Friedländer condensation of homophthalic anhydride. To increase the solubility of 9 in chloroform, it was acylated with valeric anhydride to form 7 in 56% yield.

**Scheme 4**

\[
\begin{align*}
\text{CHO} & \quad \text{H}_{2}\text{N} & \quad \text{N} & \quad \text{NH}_{2} \\
\text{HNO} & \quad \text{H}_{2}\text{O} & \quad \text{C} & \quad \text{OH} \\
8 & + & \text{HO}_{2}\text{C} & \quad \text{C} & \quad \text{O}_{2}\text{C} \\
& & \text{PPA} & \rightarrow & \text{R} & \quad \text{N} & \quad \text{HO} \\
& & & & \text{valeric} & \quad \text{anhydride} & \rightarrow \\
& & & & 9: R = H & \quad 7: R = \text{COC}_{4}\text{H}_{9}
\end{align*}
\]

**Hydrogen Bond Donor-Donor-Acceptor (DDA) Unit.** The sixth and final arrangement for three contiguous donor and acceptor sites is found in the DDA motif. Heterocyclic compounds that contain a DDA site are guanosine, deazaguanosine, and 6-amino-2-pyridone. Each of these compounds uses a carbonyl group as a hydrogen bond acceptor, and each suffers from extremely poor solubility in organic solvents. We sought a more soluble DDA unit that would contain only N and NH donor/acceptor groups and could be readily prepared. Shown in Scheme 5 is the synthesis of such a compound (i.e., 10).

**Scheme 5**

\[
\begin{align*}
\text{Ph} & \quad \text{NH} & \quad \text{Ph} & \quad \text{H} & \quad \text{OEt} \\
1) \text{LDA, THF, -78 °C} & \quad \text{Br} & \quad \text{R} & \quad \text{I} & \quad \text{N} & \quad \text{Br} & \quad \text{CO}_{2}\text{Et} & \quad \text{Br} & \quad \text{R} & \quad \text{I} \\
2) \text{PhCHO} & \quad \text{O} & \quad \text{O} \\
11: R = \text{OH} & \quad 12: R = \text{Br}
\end{align*}
\]

Quéguiner reported that 2-bromopyridine is lithiated in the 3-position by lithium diisopropylamide (LDA). Treatment of the resulting anion with benzaldehyde generated alcohol 11 which was reacted with 48% hydrobromic acid to form dibromide 12 in 47% yield for the two steps. The amidine, derived from ethyl cyanoacetate, was found to sequentially displace the bromine atoms of 12 to form 10 in ~15% yield. This route was efficient and DDA unit 10 proved to be very soluble
in chloroform. However, 10 was extremely unstable, undergoing spontaneous oxidation in air to yield the corresponding 2-amino-1,8-naphthyridine.

**Scheme 6**

A stable analog was sought with a quaternary center at C-4 of the 2-amino-1,4-dihydronaphthyridine ring system. Attempts to modify the approach outlined in Scheme 5 by using benzo-phenone instead of benzaldehyde were unsuccessful, so an alternative route was developed. The new route began with 2-pivaloylaminopyridine 13 which was metallated with 2.5 equivalents of n-butyl lithium and treated with N-acetylmorpholine to produce 14 (Scheme 6). Previous routes to 14 required two steps and resulted in low yields. The temperature of the acylation step was critical. At -40 °C, 14 was formed in 60% yield, whereas at higher temperatures only starting material was recovered. Deprotection of 14 proved troublesome. Under basic conditions, the desired o-aminoketone product (15) underwent a Friedländer self-condensation to afford 16. Fortunately, deprotection with hydrochloric acid gave desired o-aminoketone 15 in quantitative yield.

**Scheme 7**

Friedländer condensation of 15 with diethyl malonate required special conditions to avoid the self-condensation of 15. Thus, diethylmalonate was used as solvent with potassium hydroxide as base. In this manner, naphthyridone 17 was formed in 63% yield. Protection at N-1 was achieved by treatment with sodium hydride in dimethylformamide followed by benzyl bromide (74% yield). Conversion of 18 to the corresponding 2-bromoethyl ester was effected by hydrolysis, and sequential treatment with thionyl chloride and 2-bromoethanol. This three-step procedure
afforded 19 in 74% overall yield. Generation of the primary radical with tributyltin hydride and AIBN in refluxing benzene resulted in a 5-exo trig cyclization to produce kinetic product 20.24 None of the desired product, lactone 21, was isolated.

To take advantage of the kinetic 5-exo trig cyclization, the side-chain with the putative radical center was moved to C-4 of the naphthyridine ring. Thus, 13 was again ortho-lithiated, but now acylated with δ-valerolactone at low temperature to produce 22 in 90% yield (Scheme 8). Hydrolysis of 22 with potassium hydroxide produced o-aminoketone 23 in 97% yield. 2-Aminonaphthyridine 24 was generated directly from condensation of 23 with malononitrile (49% yield).25 Alcohol 24 was converted to iodide 25 uneventfully in 78% yield by treatment with iodine, triphenylphosphine, and imidazole. Spiro-cyclization of 25 with tributyltin hydride and AIBN proceeded smoothly to 26 in 58% yield, with recovery of 20% unreacted starting material. This novel reaction leads to the desired hydrogen bond DDA unit, which proved to be stable and chloroform soluble.

Conclusions

Heterocyclic compounds were synthesized containing three adjacent hydrogen bond donor and acceptor groups in all possible arrangements. Each unit contains pyridine-type acceptor and N-H donor sites. A convenient synthesis of stable anthyridine analogs using a double-Friedländer condensation was developed. The synthesis of a hydrogen bond DDA unit, which mimics the hydrogen bond functionality of guanosine, uses a novel radical spiro-cyclization step.

The synthetic routes described are short, and the range of functional groups attached to the heterocycles should allow their incorporation into more elaborate hosts and supramolecular assemblies. Preliminary reports described the relative stability of AAA-DDD, ADD-DAA, and ADA-DAD complexes,5,8 and the now ready availability of the compounds described herein will facilitate a complete analysis of these complexes. Those results will be described elsewhere.26
Experimental

General. All reactions were carried out under a dry nitrogen atmosphere. Tetrahydrofuran (THF), benzene, toluene, dioxane, and diethyl ether (Et₂O) were distilled from sodium benzo-phenone ketyl prior to use. Methanol (CH₃OH) was distilled from magnesium turnings prior to use. N-Acetyl morpholine, triethylamine, methylene chloride, and acetonitrile were distilled from calcium hydride (CaH₂) prior to use. Tributyltin hydride, malononitrile, 2-bromoethanol and δ-valerolactone were freshly distilled prior to use. N,N-Dimethylformamide (DMF) was pre-dried over 4 Å molecular sieves and was distilled from barium oxide prior to use. All other solvents and reagents were of reagent grade quality and used without further purification.

Analytical thin layer chromatography (TLC) was performed on 0.2-mm silica 60 coated plastic or glass plates (EM Science) with F-254 indicator. Flash chromatography was performed on Merck 40-63 μm silica gel.

¹H and ¹³C NMR spectra were recorded on a General Electric QE-300 instrument (300 MHz, ¹H; 75 MHz, ¹³C) in chloroform-d (CDCl₃) unless otherwise stated. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in Hertz (Hz). ¹H NMR spectra were referenced to tetramethylsilane (TMS) at 0.00 ppm in CDCl₃, or to the solvent peak at 2.49 ppm in dimethylsulfoxide-d₆ (DMSO-d₆). ¹³C spectra were referenced to 77.0 ppm in CDCl₃ or to 39.7 ppm in DMSO-d₆. Infrared spectra (IR) were recorded on a Perkin-Elmer 1320 spectrometer, and peaks are reported in cm⁻¹. Mass spectra were obtained on a Finnigan-MAT CH-5 (EI), Finnigan-MAT-731(FD), or ZAB-SE (FAB) spectrometer. Elemental analyses were performed at the University of Illinois School of Chemical Science. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

6-Amino-2-chloro-3,5-dicyano-4-phenylpyridine (6). To a solution of 25 g (0.137 mol) of trimethylorthobenzoate in 11 mL of pyridine was added dropwise 18 g (0.275 mol) of malononitrile. The mixture was heated at 100 °C for 6 h. After cooling in a water bath, 50 mL of concentrated aqueous hydrochloric acid was added slowly (caution! exothermic). The solution was heated at 100 °C for 2 h. After cooling to room temperature, the mixture was diluted with water, and filtered to afford 15 g (43%) of 6 as a yellow solid: mp >250 °C; ¹H NMR (DMSO-d₆) δ 8.40 (br s, 2H, NH₂); 7.65 (s, 5H, Ph-H); MS (EI, 70 eV) m/z 255 (M⁺, 100); Anal. Calcd for C₁₃H₇N₄Cl: C, 61.31; H, 2.77; N, 22.00; Cl, 13.92. Found: C, 61.08; H, 2.67; N, 21.89; Cl, 14.03.

2,6-Diamino-3,5-dicyano-4-phenylpyridine. A mixture of 10 g (39 mmol) of 3, 150 mL of concentrated aqueous hydrochloric acid was added slowly (caution! exothermic). The solution was heated at 100 °C for 2 h. After cooling to room temperature, the mixture was diluted with water, and filtered to afford 15 g (43%) of 6 as a yellow solid: mp >250 °C; ¹H NMR (DMSO-d₆) δ 8.40 (br s, 2H, NH₂); 7.65 (s, 5H, Ph-H); MS (EI, 70 eV) m/z 255 (M⁺, 100); Anal. Calcd for C₁₃H₇N₄Cl: C, 61.31; H, 2.77; N, 22.00; Cl, 13.92. Found: C, 61.08; H, 2.67; N, 21.89; Cl, 14.03.

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2,6-Diamino-3,5-dicyano-4-phenylpyridine. A mixture of 10 g (39 mmol) of 3, 150 mL of concentrated ammonium hydroxide, and 50 mL of acetone was heated to 100 °C in a sealed tube for 12 h. The mixture was cooled to room temperature, the precipitate collected, and washed with water to afford 8.0 g (87%) of the title compound as a yellow solid: mp > 300 °C; ¹H NMR (DMSO-d₆) δ 7.52 (m, 5H, Ph-H); 7.27 (br s, 4H, NH₂); IR (nujol) 3200, 2157; MS (EI, 70 eV) m/z 235 (M⁺, 100); Anal. Calcd for C₁₃H₉N₅: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.01; H, 3.99; N, 29.52.

2,6-Diamino-4-phenylpyridine-3,5-dicarboxaldehyde (5). A solution of 5.4 g (23 mmol) of 2,6-diamino-3,5-dicyano-4-phenylpyridine in 250 mL of methanol and 250 mL of a 2 N aqueous solution of hydrochloric acid was stirred for 0.5 h with 0.25 g of 5% palladium on carbon. An additional 0.25 g of 5% palladium on carbon was added and the resulting mixture stirred under an
atmosphere of hydrogen gas until the absorption of hydrogen was complete. The mixture was filtered through celite. The filtrate evaporated to one half volume and neutralized with a concentrated aqueous ammonium hydroxide solution. The white precipitate was collected and recrystallized from aqueous ethanol to afford 1.8 g (32%) of 5 as a white solid: mp > 300 °C; \( ^1 \text{H} \text{NMR } \delta \) 9.24 (s, 2H, CHO); 9.06 (br s, 2H, NH2); 7.40 (m, 5H, Ph-H); 5.70 (br s, 2H, NH2); \( ^{13} \text{C} \text{NMR } \delta \) 189.7, 164.8, 161.1, 132.3, 129.5, 128.9, 128.3, 106.0; MS (EI, 70 eV) \( m/z \) 241 (M+, 100); HRMS Calcd for C\(_{13}\)H\(_{11}\)N\(_3\)O\(_2\): 241.2495, Found: 241.2490.

**General procedure for the synthesis of 2b-h. 2,5,8-Triphenyl-1,9,10-anthyridine (2b).** To a solution of 0.50 g (2.1 mmol) of 5 and 0.75 g (6.2 mmol) of acetophenone in 20 mL of ethanol was added dropwise 0.5 mL of a 10% solution of potassium hydroxide in ethanol. The mixture was heated at reflux for 3 h, cooled to room temperature, and evaporated under reduced pressure. The residue was purified by flash chromatography (2% MeOH-CH\(_2\)Cl\(_2\)). The crude product was recrystallized from aqueous ethanol to afford 0.73 g (85%) of 2b as a yellow solid: mp > 300 °C; \( ^1 \text{H} \text{NMR } \delta \) 8.48 (m, 4H, Ph-H); 8.18 (d, J = 9.1, 2H, H-4, H-6); 7.97 (d, J = 9.1, 2H, H-3, H-7); 7.50 (m, 11H, Ph-H); \( ^{13} \text{C} \text{NMR } \delta \) 162.5, 156.3, 151.0, 138.2, 136.6, 136.6, 134.2, 130.8, 129.2, 128.9, 128.8, 128.3, 119.4, 119.3; MS (EI, 70 eV) \( m/z \) 409 (M+, 100); Anal. Calcd for C\(_{29}\)H\(_{19}\)N\(_3\): C, 85.06; H, 4.68; N, 10.26. Found: C, 84.94; H, 4.66; N, 10.21.

5,10-Dihydro-2,5,8-triphenyl-1,9,10-anthyridine (4b). To a solution of 0.50 g (2.10 mmol) of 2b in 10 mL of methanol was added 0.2 g (2.1 mmol) of sodium borohydride. The reaction was stirred for 3 h at room temperature, cooled, and quenched with 20 mL of a 2 N aqueous solution of hydrochloric acid. The mixture was heated at reflux for 3 h, cooled to room temperature, and evaporated under reduced pressure. The residue was purified by flash chromatography (2% MeOH-CH\(_2\)Cl\(_2\)) to afford 0.35 g (85%) of 4b as a yellow solid: mp > 300 °C; \( ^1 \text{H} \text{NMR } \delta \) 7.95 (d, J = 6.9, 6H, Ph-H); 7.90 (br s, 1H, NH); 7.70 (m, 6H, H-3, H-7, H-2", H-3"), 7.46-7.30 (m, 14H, Ph-H, H-3, H-7, H-5); MS (EI, 70 eV) \( m/z \) 411 (M+, 100).

2,8-Diphenyl-5-(4-trimethylsilylphenyl)-1,9,10-anthyridine (2i). To a suspension of 200 mg (0.6 mmol) of 2a in 8 mL of THF was added 0.43 g (1.8 mmol) 4-bromo(trimethylsilyl)benzene and 0.5 g (21 mmol) magnesium turnings in 8 mL THF. The mixture was heated at reflux for 1 h at which time it became homogeneous and TLC showed the reaction to be complete. The mixture was cooled to room temperature and poured into 75 mL of water. The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to afford a dark green solid. Flash chromatography (2% MeOH-CHCl\(_3\)) afforded 200 mg (66%) of 4c as a pinkish solid. \( ^1 \text{H} \text{NMR } \delta \) showed this material to be >95% pure. The crude 4c was treated with 200 mg (0.9 mmol) of DDQ in 10 mL of dioxane at 80 °C for 10 min. The solvent was removed under reduced pressure and the black residue was purified by flash chromatography (2% MeOH-CHCl\(_3\)) to afford 200 mg (100%) of 2i as a yellow solid: mp > 300 °C; \( ^1 \text{H} \text{NMR } \delta \) 8.30 (m, 4H, H-2'); 7.97 (d, J = 8.9, 2H, H-4, H-6); 7.70 (m, 6H, H-3, H-7, H-2", H-3"), 7.40 (m, 6H, H-3', H-4'); 0.36 (s, 9H, TMS); \( ^{13} \text{C} \text{NMR } \delta \) 161.8, 155.8, 150.6, 141.5, 137.8, 136.4, 134.0, 133.3, 130.4, 129.7, 128.5, 127.9, 118. 9, 118.6, -1.2. Anal.
Synthesis of heterocyclic compounds

Calcd for C_{32}H_{27}SiN_{3}: C, 79.79; H, 5.65; N, 8.72; Si, 5.83. Found: C, 79.81; H, 5.72; N, 8.73; Si, 5.44.

7-Amino-[2]-benzopyrano-3-oxo-1,8-naphthyridine (9). A mixture of 1.0 g (7.3 mmol) of 8 and 2.0 g (11.1 mmol) of homophthalic acid in 20 g of polyphosphoric acid was heated with stirring to 120 °C for 12 h. The mixture was cooled to room temperature, diluted with 100 mL of water, and neutralized with a 4 N aqueous solution of potassium hydroxide. The resulting precipitate was collected and washed with water until the filtrate was neutral to afford 1.85 g (97%) of crude 9 as a light brown solid: mp > 300 °C; 1H NMR (DMSO-d_6) δ 9.16 (s, 1H, H-5), 8.41 (d, J = 8.6, 1H, H-2'), 8.22 (d, J = 8.6, 1H, H-5'), 8.03 (d, J = 8.7, 1H, H-5), 7.97 (t, J = 7.8, 1H, H-3'), 7.63 (t, J = 7.6, 1H, H-4'), 7.30 (br s, 2H, NH_2), 6.84 (d, J = 8.4, 1H, H-6); MS (EI, 70 eV) m/z 263 (M +, 100); HRMS Calcd for C_{15}H_{9}N_{3}O_{2}: 263.0695, Found: 263.0695.

7-Pentanoylamino-[2]-benzopyrano-3-oxo-1,8-naphthyridine (7). To a suspension of 0.5 g (1.9 mmol) of crude 9 in 20 mL of valeric anhydride was added 1 mL of triethylamine. The suspension was heated at 120 °C for 4 h and cooled to room temperature. The solid was filtered, washed with diethyl ether, and recrystallized from aqueous DMSO to afford 0.4 g (65%) of 7 as a tan solid: mp > 320 °C; 1H NMR (DMSO-d_6) δ 11.21 (br s, 1H, NH), 9.44 (s, 1H, H-5), 8.50 (m, 3H, H-2', H-5', H-5), 8.25 (d, J = 7.9, 1H, H-6), 8.00 (t, J = 8.0, 1H, H-4'), 7.71 (t, J = 8.0, 1H, H-3'); MS (EI, 70 eV) m/z 347 (M^+, 6), 318 (17), 263 (100); IR (nujol) 3300, 1728, 1684; Anal. Calcd for C_{20}H_{17}N_{3}O_{3}: C, 69.15; H, 4.93; N, 12.10; Found: C, 69.22; H, 4.89; N, 12.15.

(2-Bromopyridin-3-yl)phenylmethylbromide (12). To a solution of 0.11 g (0.42 mmol) of 11, prepared according to the Quéguiner protocol, in 4 mL of glacial acetic acid was added 4 mL of a 48% aqueous solution of hydrobromic acid. The mixture was heated at 100 °C for 16 h. The solution was cooled to room temperature, extracted with CH_2Cl_2 (3 x 50 mL), dried over magnesium sulfate, and evaporated to dryness to afford 100 mg (74%) of 12 as a colorless solid. This solid was judged to be >95% pure by 1H NMR and was used without further purification: 1H NMR δ 8.26 (dd, J = 2.9, 1.3, 1H, H-6'), 8.00 (dd, J = 6.0, 2.0, 1H, H-4'), 7.35 (m, 6H, H-5', Ph-H), 6.59 (s, 1H, H-1); MS (EI, 70 eV) m/z 246 (M^+-Br, 52), 248 (52).

1-(2-Pivaloylaminopyridin-3-yl)ethanone (14). To a solution of 2.0 g (11.2 mmol) of 2-pivaloylaminopyridine 13 in 50 mL of THF was added 17.6 mL (28.0 mmol) of a 1.6 M solution of n-butyl lithium in hexane under a dry nitrogen stream at -50 °C. The mixture stood for 2 h at 0 °C during which time a white precipitate formed. The mixture was cooled to -40 °C and a solution of 2.2 g (16.8 mmol) of N-acetylmorpholine in 10 mL of THF was added dropwise. After stirring for 1 h at -40 °C, an aqueous solution of saturated aqueous ammonium chloride solution was added to the mixture. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the organic layer dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by flash chromatography (1% CH_3OH-CH_2Cl_2) to afford 1.1 g (60%) of 14 as an oil. This oil was judged to be >95% pure by 1H NMR and was used without further purification: 1H NMR δ 11.35 (br s, 1H, NH), 8.64 (dd, J = 4.8, 1.9, 1H, H-6), 8.17 (dd, J = 8.0, 1.9, 1H, H-4'), 7.07 (dd, J = 8.0, 4.8, 1H, H-5'), 2.65 (s, 3H, CH_3), 1.35 (s, 9H, CH_3); MS (EI, 70 eV) m/z 220 (M^+, 40), 163 (100).

2-(2-Aminopyridin-3-yl)-4-methyl-1,8-naphthyridine (16). A suspension of 1.0 g (4.3 mmol) of 14 in 50 mL of a 2 N aqueous solution of potassium hydroxide was heated at reflux for 4 h. The
solution was cooled to room temperature, the precipitate collected, and washed with water to give 0.2 g (36%) of 16 as a yellow solid: mp >270 °C; $^1$H NMR δ 9.10 (br dd, 1H, H-7), 8.39 (m, 1H, H-6'), 8.18 (m, 1H, H-5), 8.08 (m, 1H, H-4'), 7.50 (br s, 3H, H-6, NH$_2$), 6.73 (m, 1H, H-5'), 2.78 (s, 3H, CH$_3$); $^{13}$C NMR δ 154.8, 153.4, 153.4, 146.1, 137.2, 133.1, 133.0, 121.5, 121.2, 120.5, 114.6, 112.8, 18.6; MS (EI, 70 eV) m/z 236 (M+, 67), 235 (100); HRMS Calcd for C$_{14}$H$_{12}$N$_4$: 236.1062, Found: 236.1043.

1-(2-Aminopyridin-3-yl)ethanone (15). A suspension of 2.8 g (12.7 mmol) of 14 in 100 mL of a 3 N aqueous solution of hydrochloric acid was heated at reflux for 14 h. The solution was cooled to room temperature, neutralized with a 4 N aqueous solution of potassium hydroxide, and extracted with CH$_2$Cl$_2$ (4 x 50 mL). The combined organic layers were dried over magnesium sulfate, evaporated, and the resulting solid was recrystallized from ethanol to afford 1.8 g (100%) of 15 as a colorless solid: mp 137-139 °C; $^1$H NMR δ 8.20 (br dd, 1H, H-6), 7.97 (br dd, 1H, H-5), 7.00 (br s, 2H, NH$_2$), 6.62 (br dd, 1H, H-5'), 2.54 (s, 3H, CH$_3$); $^{13}$C NMR δ 199.2, 158.7, 154.1, 140.5, 113.1, 112.1, 27.1; MS (EI, 70 eV) m/z 136 (M+, 100); HRMS calcd, for C$_7$H$_8$N$_2$O: 136.0637, found 136.0636; Anal. Calcd for C$_7$H$_8$N$_2$O: C, 61.75; H, 5.92; N, 20.57; Found: C, 61.22; H, 5.93; N, 20.17.

Ethyl 4-methyl-1,8-naphthyridin-(1H)2-one-3-carboxylate (17). To a mixture of 1.8 g (12.8 mmol) of 14 and 20 mL of diethyl malonate was added 0.3 g of crushed potassium hydroxide pellets. The mixture was heated to 110 °C under a constant stream of nitrogen to remove water. After 14 h the mixture was cooled to room temperature, diluted with petroleum ether, and the precipitate collected. The solid was recrystallized from ethanol to afford 1.88 g (63%) of 17 as a colorless solid: mp 226-229 °C; $^1$H NMR (DMSO-d$_6$) δ 12.80 (br s, 1H, NH), 8.56 (dd, J = 4.5, 1.8, 1H, H-7), 8.24 (dd, J = 8.1, 1.8, 1H, H-5), 7.30 (dd, J = 8.1, 4.5, 1H, H-6), 4.30 (q, J = 7.0, 2H, CH$_2$), 2.39 (s, 3H, CH$_3$), 1.28 (t, J = 7.0, 3H, CH$_3$); MS (EI, 70 eV) m/z 232 (M+, 16); Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_3$: C, 62.06; H, 5.21; N, 12.06; Found: C, 62.07; H, 5.22; N, 12.05.

Ethyl 1-benzyl-4-methyl-1,8-naphthyridin-(1H)2-one-3-carboxylate (18). To a solution of 1.5 g (6.5 mmol) of 17 and 0.2 g (7.1 mmol) of sodium hydride in 60 mL of DMF was added dropwise 1.3 g (7.8 mmol) of benzyl bromide at 0 °C. The mixture was stirred for 1 h, diluted with 20 mL of water, and extracted with CH$_2$Cl$_2$ (3 x 75 mL). The combined organic layers were dried over magnesium sulfate, evaporated, and the precipitate collected. The solid was recrystallized from ethanol to afford 1.54 g (74%) of 18 as a colorless solid: mp 125-127 °C; $^1$H NMR δ 8.62 (dd, J = 4.6, 2.0, 1H, H-7), 8.02 (dd, J = 7.9, 2.0, 1H, H-5), 7.51-7.30 (m, 6H, H-6, Ph-H), 5.73 (s, 2H, CH$_2$Ph), 4.44 (q, J = 7.0, 2H, CH$_2$), 2.44 (s, 3H, CH$_3$), 1.40 (t, J = 7.0, 3H, CH$_3$); MS (EI, 70 eV) m/z 322 (M+, 67); Anal. Calcd for C$_{19}$H$_{18}$N$_2$O$_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.78; H, 5.64; N, 8.66.

2-Bromoethyl 1-benzyl-4-methyl-1,8-naphthyridin-(1H)2-one-3-carboxylate (19). A solution of 0.20 g (0.62 mmol) of 18 in 10 mL of a 2 N aqueous solution of potassium hydroxide and 10 mL of ethanol was heated at 90 °C for 14 h. The mixture was neutralized with a 6 N aqueous solution of hydrochloric acid, and extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to give 0.18 g of the crude carboxylic acid. The crude solid was dissolved in 5 mL of THF and 0.08 g (0.80 mmol) of thionyl chloride was added. The mixture was heated to reflux for 2 h, cooled, and 0.12 g (0.80 mmol) of 2-bromoethanol was added. The mixture was stirred at room temperature for 2 h, quenched with water, and
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evaporated to dryness. The solid was recrystallized from ethanol to afford 0.20 g (74%) of 19 as a colorless solid: mp 251-253 °C; 1H NMR δ 8.65 (dd, J = 4.7, 1.3, 1H, H-7), 8.06 (dd, J = 8.0, 1.3, 1H, H-5), 7.6-7.2 (m, 6H, H-6, Ph-H), 5.74 (s, 2H, CH2Ph), 4.70 (t, J = 6.0, 2H, CO2CH2), 3.66 (t, J = 6.0, 2H, CH2Br), 2.50 (s, 3H, CH3); MS (EI, 70 eV) m/z 400 (M+, 24); HRMS Calcd for C19H17N2O3Br: 400.0423, Found: 400.0421.

Spir[2-x-124-tetrahydr-3-furan-13'(4'H)-1'-benzyl-4'-methy-[1'8']-naphthyridin-(1H)2-one] (20). To a refluxing solution of 70 mg (0.12 mmol) of 19 in 10 mL of benzene was added a solution of 80 mg (0.19 mmol) of tributyltin hydride and 5 mg of AIBN in 1 mL of benzene over 7 h via syringe pump. The mixture was cooled to room temperature and evaporated to dryness. The product was purified by radial chromatography (3:1 hexanes-ethyl acetate) to afford the two diastereoisomers of 20 as colorless solids: Isomer A (15 mg, 27%): 1H NMR δ 8.33 (dd, J = 2.5, 1.5, 1H, H-7), 7.55 (dd, J = 6.8, 1.5, 1H, H-5), 7.42 (d, J = 7.0, 2H, Ph-H), 7.25 (m, 3H, Ph-H), 7.06 (dd, J = 6.8, 2.5, 1H, H-6), 5.48 (AB q, J = 14.4, 2H, CH2Ph), 4.38 (m, 2H, CO2CH2), 3.18 (q, J = 6.9, 1H, H-4), 2.78 (m, 1H, CH2), 2.35 (m, 1H, CH2), 1.51 (d, J = 6.9, 3H, CH3); 13C NMR δ 174.1, 167.4, 149.9, 146.4, 137.6, 134.6, 128.3, 127.9, 127.1, 123.2, 119.4, 54.6, 44.4, 35.0, 28.4, 14.7; MS (EI, 70 eV) m/z 322 (M+, 67); HRMS Calcd for C19H18N2O3: 322.1317, Found: 322.1314. Isomer B (14 mg, 25%): 1H NMR δ 8.33 (dd, J = 3.9, 1.1, 1H, H-7), 7.55 (dd, J = 6.8, 1.5, 1H, H-5), 7.42 (d, J = 7.0, 2H, Ph-H), 7.25 (m, 3H, Ph-H), 7.06 (dd, J = 5.1, 2.3, 1H, H-6), 5.48 (d, J = 5.7, 2H, CH2Ph), 4.45 (m, 2H, CO2CH2), 3.43 (q, J = 7.0, 1H, H-4), 2.49 (m, 1H, CH2), 2.46 (m, 1H, CH2), 1.32 (d, J = 7.0, 3H, CH3); MS (EI, 70 eV) m/z 322 (M+, 67); HRMS Calcd for C19H18N2O3: 322.1317, Found: 322.1314.

5-Hydroxy-1-(2-pivaloylaminopyridin-3-yl)pentanone (22). To a solution of 10.0 g (56.0 mmol) of 13 in 200 mL of THF was added 55.0 mL (140 mmol) of a 2.6 M solution n-butyllithium in hexane under a dry nitrogen stream at -80 °C. The mixture was kept at 0 °C for 2 h during which time a white precipitate formed. The mixture was cooled to -70 °C and a solution of 8.4 g (84.0 mmol) of δ-valerolactone in 50 mL of THF was added dropwise. The mixture was stirred for 1 h and allowed to warm to room temperature. An aqueous solution of saturated sodium chloride was added, and the mixture extracted with n-butanol (3 x 300 mL). The combined organic layers were evaporated and the residue purified by flash chromatography (3% CH3OH-CH2Cl2) to afford 14.0 g (90%) of 22 as a yellow solid: mp 100-104 °C; 1H NMR δ 11.42 (br s, 1H, NH), 8.60 (dd, J = 4.8, 1.8, 1H, H-6'), 8.19 (dd, J = 8.0, 1.8, 1H, H-4'), 7.07 (dd, J = 4.8, 8.0, 1H, H-5'), 6.26 (t, J = 6.3, 2H, COCH2), 3.03 (t, J = 6.8, 2H, CH2OH), 2.00 (br s, 1H, OH), 1.79 (m, 2H, CH2), 1.65 (m, 2H, CH2), 1.33 (s, 9H, CH3); 13C NMR δ 202.9, 176.8, 153.2, 151.8, 139.0, 118.1, 118.0, 62.2, 40.5, 39.2, 31.8, 27.4, 20.5; MS (EI, 70 eV) m/z 278 (M+, 14), 121 (100); HRMS Calcd for C15H18N2O3: 278.1630; Found: 278.1634.

5-Hydroxy-1-(2-aminopyridin-3-yl)pentanone (23). A solution of 10.0 g (36.0 mmol) of 22 in 350 mL of a 2 N aqueous potassium hydroxide solution was heated at 100 °C for 5 h. The mixture was cooled to room temperature and extracted with n-butanol (4 x 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent evaporated to afford 6.8 g (97%) of 23 as a colorless solid. This solid was judged to be >95% pure by 1H NMR and was used without further purification: mp 150 °C; 1H NMR δ 8.15 (dd, J = 4.7, 1.8, 1H, H-6'), 7.99 (dd, J = 7.9, 1.8, 1H, H-4'), 6.58 (dd, J = 7.9, 4.7, 1H, H-5'), 6.50 (br s, 2H, NH2), 3.64 (t, J = 6.4, 2H,
2-Amino-3-cyano-4-(4'-hydroxybutyl)-1,8-naphthyridine (24). To a mixture of 2.0 g (16.3 mmol) of 23 and 50 g of malononitrile was added 0.5 g of crushed potassium hydroxide. The mixture was heated to 100 °C under a constant stream of nitrogen to remove water. After 4 h the mixture was cooled to room temperature and purified by flash chromatography (5% CH$_3$OH-CH$_2$Cl$_2$). The crude product was recrystallized from ethyl acetate to afford 1.21 g (49%) of 24 as a yellow solid: mp 245 °C (decomp.); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.82 (dd, $J$ = 4.4, 1.7, 1H, H-7), 8.40 (dd, $J$ = 8.2, 1.7, 1H, H-5), 7.29 (dd, $J$ = 8.2, 4.3, 1H, H-6), 4.44 (br s, 2H, NH$_2$), 3.41 (br m, 3H, CH$_2$OH, OH), 3.16 (t, $J$ = 7.7, 2H, CH$_2$Ar), 1.66 (m, 2H, CH$_2$), 1.52 (m, 2H, CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 160.0, 158.4, 157.3, 155.9, 134.8, 118.9, 115.9, 114.9, 95.8, 60.6, 32.6, 30.8, 27.4; MS (EI, 70 eV) m/z 242 (M$^+$, 46); HRMS Calcd for C$_{13}$H$_{12}$N$_4$O: 242.1168; Found: 242.1166.

2-Amino-3-cyano-4-(4'-iodobutyl)-1,8-naphthyridine (25). To a solution of 0.21 g (0.82 mmol) of triphenylphosphine and 0.06 g (0.90 mmol) of imidazole in 2 mL of acetonitrile and 3 mL of ether was added 0.23 g (0.91 mmol) of iodine at 0 °C. The mixture was stirred for 15 min at room temperature. The mixture was cooled to 0 °C and 0.10 g (0.41 mmol) of 24 was added. The mixture was stirred for 3 h, and diluted with CH$_2$Cl$_2$. The organic layer was separated, dried over magnesium sulfate, and evaporated to dryness. The residue was purified by flash chromatography (3% CH$_3$OH-CH$_2$Cl$_2$) to afford 0.13 g (78%) of 25 as a yellow solid: mp 235 °C (decomp.); $^1$H NMR (DMSO-$d_6$) $\delta$ 8.96 (dd, $J$ = 4.4, 1.9, 1H, H-7), 8.22 (dd, $J$ = 8.2, 1.8, 1H, H-5), 7.31 (dd, $J$ = 8.2, 4.4, 1H, H-6), 6.01 (br s, 2H, NH$_2$), 3.24 (m, 4H, CH$_2$I, ArCH$_2$), 2.1-1.8 (m, 4H, CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 159.4, 158.4, 157.3, 155.9, 134.8, 118.9, 115.8, 114.8, 95.8, 33.1, 31.5, 29.8, 8.4; MS (EI, 70 eV) m/z 352 (M$^+$, 70); HRMS Calcd for C$_{13}$H$_{12}$IN$_4$: 352.0185; Found: 352.0170.

Spiro[cyclopentane-1,4'(1'H)-2'-amino-3'-cyano-1',8'-naphthyridine] (26). To a refluxing solution of 0.60 g (1.70 mmol) of 25 in 100 mL of acetonitrile was added via syringe pump a solution of 0.55 g (1.80 mmol) of tributyltin hydride and 50 mg of AIBN in 2 mL of acetonitrile over 5 h. After the addition was complete, the mixture was cooled to room temperature and evaporated to dryness. The residue was purified by flash chromatography (2% CH$_3$OH-CH$_2$Cl$_2$) and the product recrystallized twice from aqueous ethanol to afford 0.20 g (54%) of 26 as a yellow solid: mp 215 °C (decomp.); $^1$H NMR (DMSO-$d_6$) $\delta$ 9.20 (br s, 1H, NH); 7.99 (br dd, 1H, H-7), 7.51 (br dd, 1H, H-5), 6.92 (br dd, 1H, H-6), 5.62 (br s, 2H, NH$_2$), 2.0-1.6 (m, 8H, CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.6, 148.9, 146.3, 134.6, 125.1, 122.5, 118.8, 60.2, 44.9, 44.3, 25.7; IR (CHCl$_3$) 2245, 2166, 3461, 3403 cm$^{-1}$. MS (EI, 70 eV) m/z 226 (M$^+$, 35); HRMS Calcd for C$_{13}$H$_{14}$N$_4$: 226.1218; found: 226.1215; Anal. Calcd for C$_{13}$H$_{14}$N$_4$: C, 69.00; H, 6.24; N, 24.76; Found: C, 68.97; H, 6.27; N, 24.72.

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