Revised Structure and Convergent Synthesis of Nemertelline, the Neurotoxic Quaterpyridine Isolated from the Hoplonemertine Sea Worm

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The correct structure of the quaterpyridine nemertelline first isolated from hoplonemertine sea worms has been identified as **2** (3,2′:3′,4″:2″,3‴-quaterpyridine). The natural product was synthesized using palladium(0)-catalyzed cross-coupling of 3-(tributylstannyl)-2,3′-bipyridine (**3**) and 4-chloro-2,3′-bipyridine (**4**). The bipyridines were prepared in the presence of the Pd catalyst by cross-coupling 2-bromo-3-(tributylstannyl)pyridine (**5**) and 2,4-dichloropyridine with 3-diethyl-(pyridyl)borane, respectively. X-ray analysis confirmed the structure of **2** and provided its conformation in the solid state. The proton NMR spectrum of **2** identifies it as the natural product first reported in 1976.

Neurotoxic substances have been isolated from the phylum of marine worms called nemertines. Extracts from the hoplonemertine (armed) worm contain a quaterpyridine given the name nemertelline and assigned structure **1** (3,2′:3′,2″:4″,3‴-quaterpyridine). The proof of structure rested in 1976 entirely on the 90 MHz proton NMR spectrum and homonuclear decoupling experiments.[1]

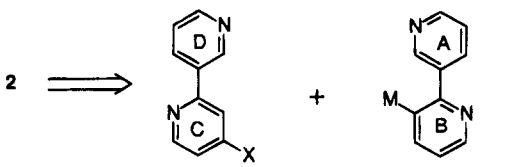
Our successful synthesis of **1**[2] indicates that the proposed structure of the natural product is in fact incorrect. We now present the correct structure **2** (3,2′:3′,4″:2″,3‴-quaterpyridine). Isomers **1** and **2** differ only in the location of the nitrogen atom in the 2,4-disubstituted C ring. Both substances consist of two 3-substituted pyridyl rings along with 2,3- and 2,4-disubstituted pyridine rings. The natural product **2** is an unsymmetrical dimer of 2,3′-bipyridine.

The synthesis of **2** now becomes readily possible given the recent development of palladium catalyzed cross-coupling reactions which allow the easy construction of carbocyclic and heterocyclic polyaromatic substrates from organometallic and halide precursors. Suzuki coupling of boranes or borates[3–7] and Stille coupling of stannanes[8–13] now are the preferred methods of joining such rings.

Results and Discussion

Our retrosynthetic analysis of **2** in Scheme 1 suggests a convergent synthesis in which the B and C rings are disconnected to give the A–B and C–D bipyridyl rings as fragments. We elected to have the A–B fragment **3** serve as the organometallic component, a stannane, and the C–D portion **4** be the halide. In the reversed polarity approach in which the A–B fragment is the halide and the C–D unit contains the organometallic group there is the risk that the desired cross-coupling might fail. Such a cross-coupling is sterically hindered while the homocoupling of the stannane, a common side-reaction in Stille coupling,[14–18] is not hindered and therefore might dominate. In our favored approach homocoupling of the stannane is a more sterically hindered process than cross-coupling.

Scheme 1. Retrosynthetic Analysis



4, X = Cl **3**, M = Bu_3Sn

Synthesis of the A–B Rings. Two approaches were tried, only one being successful. In the successful approach the organometallic group was first added to the B-ring and then the A ring was joined. In unsuccessful attempts this sequence was reversed. The A and B rings were first bonded together and attempts then were made unsuccessfully to add an organometallic group to the B ring of the bipyridine.

Taking advantage of known chemistry,[19–22] directed ortho lithiation of 2-bromopyridine with LDA at −78 °C followed by transmetalation with tributyltin chloride

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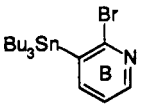
gave 2-bromo-3-(tributylstannyl)pyridine (**5**) (57%). This stannane was easily coupled with diethyl(3-pyridyl)-borane (**6**) in the presence of tetrakis(triphenylphosphine)palladium(0) in THF under the usual aqueous alkaline conditions of the Suzuki reaction to give 86% of 3-(tributylstannyl)-2,3′-bipyridine (**3**, M = Bu_3Sn). Significantly, no destannylation took place under the conditions of the aqueous coupling.



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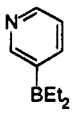

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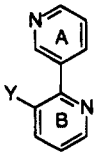

7, Y = Cl
8, Y = Br
9, Y = NH_2

In the alternate route a number of attempts to metalate the A–B ring of 3-halo-2,3′-bipyridine failed. The required 3-chloro-2,3′-bipyridine (**7**) was easily constructed from 2,3-dichloropyridine (92%) and borane **6** under Suzuki conditions. As expected coupling took place at the more reactive 2 position of the dihalide.[23] But all attempts to convert this monochloride to metalated material failed. Thus, attempted transmetalation with n-BuLi at low temperatures (−78 and −100 °C) yielded minimal amounts of lithiated product along with butylated addition product.[24] Attempted Grignard formation from the chloride provided mostly 2,3′-bipyridine reduction product. Tributylstannide ion and the chloride gave only 10% of the 3-stannane. Use of the more reactive 3-bromo-2,3′-bipyridine (**8**) made from the corresponding 3-amine **9** in place of the 3-chloride did not change the outcome significantly.

Cross-coupling of the 2,3-dichloropyridine at the 2 and not the 3 position to afford **7** was easily demonstrated from the proton NMR spectrum by making use of the large deshielding effect of the annular nitrogen atom[25,26] of the B ring on the 2′ and 4′ positions of the 3-pyridyl A ring located at 9.01 and 8.08 ppm, respectively.

Synthesis of the C–D Rings: 2,4-Dichloropyridine made from 4-nitropyridine *N*-oxide[27] was coupled with borane **6** under Suzuki conditions. Coupling took place at the 2- and not the 4-position of the dichloride to give 4-chloro-2,3′-bipyridine (**4**, X = Cl) (57%). There is a clear preference for coupling at the 2- over the 4-position in the 2,4-dichloride. But as the 4-chloro bipyridine product formed in large quantities, this product began to compete with the starting material in the coupling reaction to yield a known terpyridine nicotelline[28] (3,2′:4′,3″-terpyridine). The coupling reaction was readily followed by silica gel TLC and was stopped when the terpyridine started to appear.

The structure of 4-chlorobipyridine **4** was easily established by again making assignments based on the large deshielding effect of an interannular nitrogen atom.[25,26] The singlet of H-2 and the doublet of H-4 of the 3-pyridyl ring of this bipyridine are highly deshielded, being at 9.33 and 8.34 ppm, respectively.

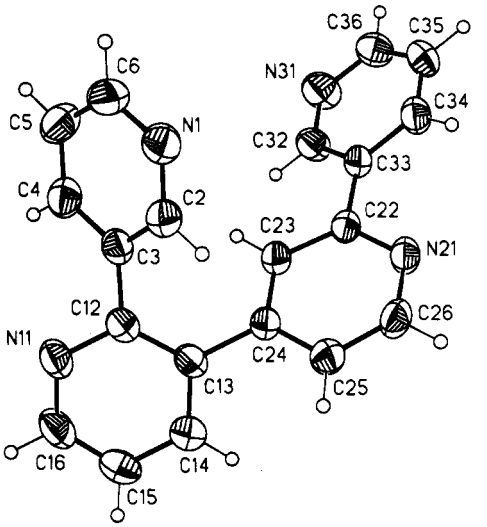

Figure 1. Crystal structure of nemertelline **2** with 50% probability ellipsoids.

Stille Coupling To Give 2. The two bipyridines **3** (M = Bu_3Sn) and **4** (X = Cl) were smoothly cross-coupled with the Pd(0) catalyst in heated toluene to give **2** in 68% yield as demonstrated by both proton NMR and X-ray analysis of the product.

Crystal Structure of 2.[35] An X-ray analysis of the monoclinic crystals, one of just a few such determinations for polypyridines,[29–32] was obtained in order to confirm the structure of the natural product and to obtain information about its correct conformation and thereby aid in the analysis of the NMR spectrum, Figure 1. The molecule is folded into a nonplanar approximate U-shape with, as expected from the structures of related polypyridines,[29–32] the orientation of the annular nitrogen atoms in adjacent rings adopting an s-trans conformation with respect to each other. The A and C rings are approximately parallel to each other and are skewed with respect to the common B ring. The dihedral angle between the rings is 44° for the A and B portion, 53° for the B and C rings, and 23° for the C and D group. The geometry of the A, B, and C rings is similar to that of 1,2-diphenylbenzene.[33]

Proton NMR of 2. Remarkably, none of the 14 aromatic protons overlaps at 300 MHz in CD_3OD where the total shift scale is only 1.7 ppm, Figure 2. However, some signal overlap for three protons does occur in $CDCl_3$ at 8.6 ppm (Experimental Section). The proton NMR spectrum of **2** is unequivocally different from that of **1**.[1]

Comparison of the proton NMR spectrum of our synthetic material with that of the natural quaterpyridine[1] indicates they are identical, thus providing the final proof of structure. The early report used CS_2 as a solvent.[1] We find little difference in the spectra using this solvent or $CDCl_3$.

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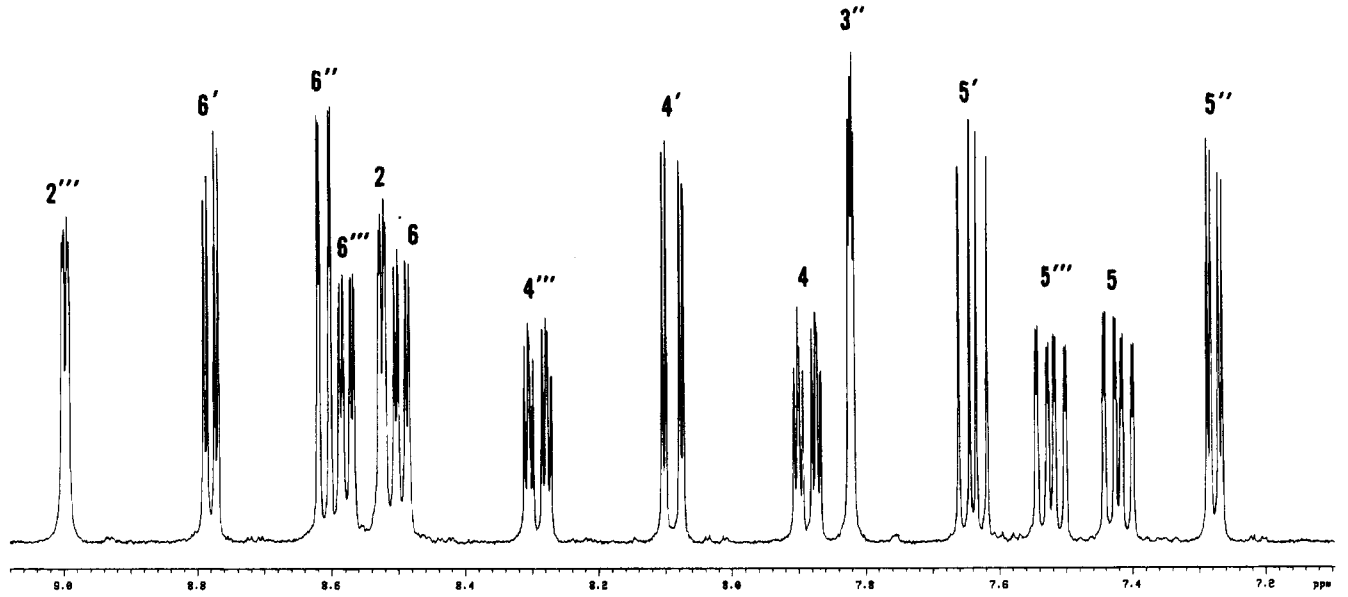


Figure 2. Proton NMR spectrum (300 MHz) of nemertelline **2** in CD_3OD.

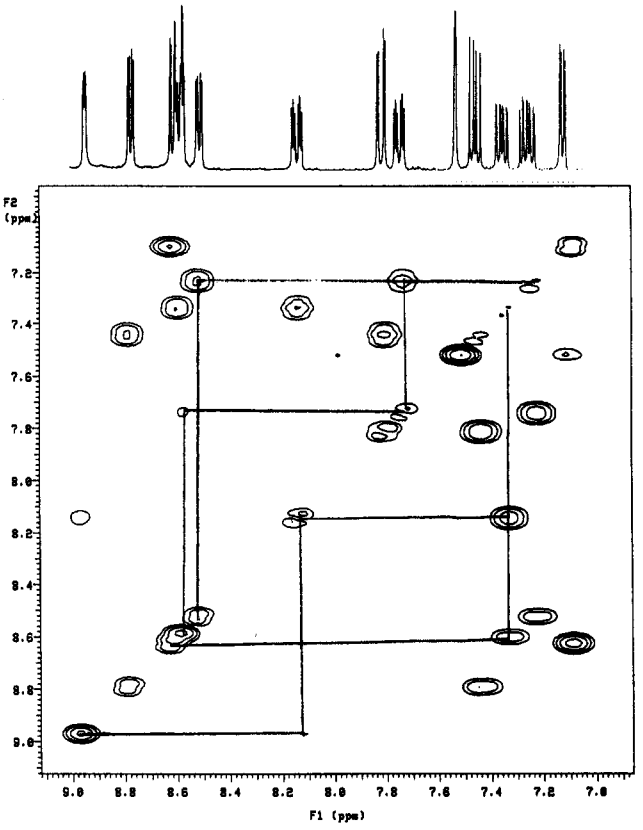
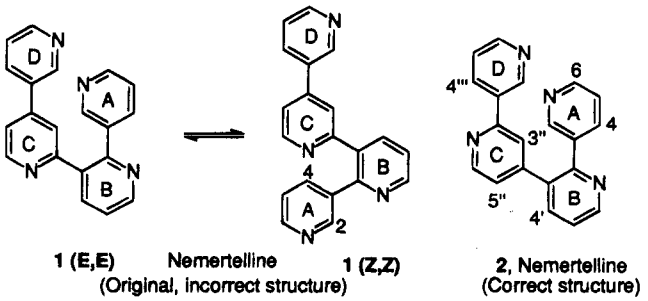


Figure 3. COSY at 300 MHz for nemertelline **2** in $CDCl_3$. The upper set of lines correlates the protons of the A pyridyl ring and the lower set those of the D pyridyl ring.

The COSY of **2** in $CDCl_3$ is given in Figure 3 where the proton assignment of the two important 3-pyridyl rings is emphasized. Significantly, one of these two rings has a pair of signals at lower field than the other; these deshielded protons are easily identified as being α and γ to a nitrogen atom by their spin coupling pattern. Moreover, irradiation of this α proton at 9.00 ppm gave rise to an NOE difference signal for proton 3″ of the C ring at 7.56 ppm while irradiation of this γ signal at 8.19 ppm caused an NOE to appear at the same 3″ proton, easily identified by the absence of large spin couplings and its relatively high field position. Thus, this pair of α and γ signals for the low field 3-pyridyl ring must be associated with the D ring, i.e., they are due to protons 2‴ and 4‴. Because they are located across the ring from the lone electron pair of the nitrogen atom of the C ring they experience the deshielding effect of this electron pair[25,26] causing them to be shifted to such low field. The entire assignment is presented in Figure 2 for a methanolic solution.

This pair of low field signals was assigned by the early workers to 2 and 4 positions of the A ring[1] and not to the D ring as we have done, the crucial error giving rise to an incorrect structure.

We believe the incorrect structural assignment in 1976 is the result of not recognizing that the inter-ring deshielding effect of a nitrogen atom is reduced in stacked rings and a consequence of assuming the wrong conformation for the natural product, shown then as **1(Z,Z)**, where the A, B, and C rings have the *Z* conformation and not the *E* conformation as in the **1(E,E)** arrangement. In the **1(Z,Z)** geometry the 2 and 4 protons of the A ring would be deshielded by the lone electron pair on the nitrogen atoms of the B and C rings. But the magnitude of this deshielding of the A ring by the C ring is reduced when the rings are stacked. These errors marred the successful outcome of an otherwise difficult structure determination.



Experimental Section

Diethyl(3-pyridyl)borane, tributyltin chloride, tetrakis(triphenylphosphine)palladium(0), 2,3-dichloropyridine, 3-amino-2-chloropyridine, 2.5 M n-BuLi, and 2-bromopyridine were purchased from Aldrich Chemical Co. Flash chromatography

made use of Kieselgel 60 230–400 mesh or alumina 80–200 mesh. ^{1}H NMR spectra were recorded at 300 or 500 MHz using $CDCl_3$ (TMS). Solvents were freshly distilled in most cases and degassed by bubbling N_2 through them for 15–30 min. All melting points are uncorrected. The drying agent was either sodium or magnesium sulfate. Thin layer chromatography was carried out with Whatman polyester backed silica gel plates.

2-Bromo-3-(tributylstannyl)pyridine (5). The LDA was freshly made by adding 2.5 M n-butyllithium (4.4 mL, 11 mmol) to a cold (−78 °C) stirred THF (10 mL) solution of i-Pr_2-NH (1.54 mL, 11.0 mmol) under N_2 followed by warming to 0 °C for 0.5 h. This solution was transferred via syringe to a stirred THF (10 mL) solution of 2-bromopyridine (1.0 mL, 10.5 mmol) at −78 °C. The dark orange mixture was stirred for 1 h at −78 °C, and then tributyltin chloride (2.84 mL, 10.5 mmol) was added. The reaction turned pale yellow and was allowed to stir while slowly warming to room temperature. After 10 h the reaction was diluted with 30 mL of diethyl ether and then washed with 30 mL of saturated NH_4Cl. The organic phase was separated, dried, and concentrated to an oil. Column chromatography with Kieselgel 60 and 90/10 hexanes/EtOAc gave 2.66 g (5.95 mmol, 57% yield) of a clear oil that was used directly in the following preparation of the stannane. ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, dd, J = 2 and 5 Hz), 7.60 (1H, dd with Sn side bands, J = 2 and 8 Hz), 7.18 (1H, dd, J = 5 and 8 Hz), 0.87–1.60 (27H, m).

3-(Tributylstannyl)-2,3′-bipyridine (3). 2-Bromo-3-(tributylstannyl)pyridine (**5**) (1.00 g, 2.24 mmol), diethyl(3-pyridyl)-borane (658 mg, 4.47 mmol), and tetrakis(triphenylphosphine)-palladium(0) (129 mg, 0.112 mmol) were dissolved in 20 mL of degassed THF under N_2. The solution was stirred at room temperature for 5 min, and then $NaHCO_3$ (564 mg, 6.71 mmol) dissolved in 10 mL of degassed H_2O was added. The solution was stirred at reflux for 3 h and then cooled to room temperature. The mixture was diluted with 30 mL of EtOAc, and the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel 60 and 100% EtOAc gave 911 mg of a clear oil which was contaminated with a small amount of Ph_3P=O. The Ph_3P=O crystallized on standing and was removed by filtration with hexanes to give 860 mg (1.93 mmol, 86% yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.71 (1H, d, J = 2 Hz), 8.65 (1H, dd, J = 1 and 5 Hz), 8.61 (1H, dd, J = 2 and 5 Hz), 7.87 (2H, m), 7.36 (1H, dd, J = 5 and 9 Hz), 7.24 (1H, dd, J = 5 and 9 Hz), 0.87–1.40 (27H, m). Anal. Calcd for $C_{22}H_{34}N_2Sn$: C, 59.35; H, 7.70; N, 6.29. Found: C, 59.58; H, 7.70; N, 5.98.

3-Chloro-2,3′-bipyridine (7). Diethyl(3-pyridyl)borane (690 mg, 4.69 mmol), 2,3-dichloropyridine (1.41 g, 9.52 mmol), and tetrakis(triphenylphosphine)palladium(0) (578 mg, 0.500 mmol) were placed in degassed THF (25 mL) under N_2. The mixture was stirred for 15 min at room temperature, and then potassium carbonate (1.50 g, 10.9 mmol) in degassed H_2O (10 mL) was added. The mixture was heated at reflux for 72 h and then cooled to 0 °C. After the insoluble catalyst was filtered off, the filtrate was diluted with 25 mL of EtOAc. The organic layer was separated, washed with 20 mL of brine, and then extracted twice with 10 mL portions of 2 M HCl. The two acid washes were combined, neutralized with sodium carbonate, and then extracted twice with 20 mL portions of EtOAc. The organic extracts were combined, dried, and concentrated to an orange oil. Column chromatography with Kieselgel 60 and 1:1 EtOAc:hexanes gave 823 mg (4.32 mmol) of a light yellow solid (mp 66–69 °C, 92% total yield). ^{1}H NMR ($CDCl_3$) δ 9.01 (1H, dd, J = 1 and 2 Hz), 8.68 (1H, dd, J = 2 and 5 Hz), 8.63 (1H, dd, J = 2 and 5 Hz), 8.08 (1H, dt, J = 2, 2 and 8 Hz), 7.84 (1H, dd, J = 2 and 8 Hz), 7.42 (1H, ddd, J = 1, 5 and 8 Hz), 7.29 (1H, dd, J = 5 and 8 Hz). Anal. Calcd for $C_{10}H_7N_2Cl$: C, 63.00; H, 3.70; N, 14.70. Found: C, 62.72; H, 3.61; N, 14.49.

3-Amino-2,3′-bipyridine (9). Diethyl(3-pyridyl)borane (1.14 g, 7.78 mmol), 3-amino-2-chloropyridine (1.00 g, 7.78 mmol), and tetrakis(triphenylphosphine)palladium(0) (578 mg, 0.500 mmol) were added to degassed THF (25 mL) under N_2. The mixture was stirred for 10 min at room temperature, and then K_2CO_3 (5.37 g, 38.9 mmol) in degassed H_2O (10 mL) was added. The mixture was heated at reflux for 72 h and then cooled to 0 °C. After the insoluble catalyst was filtered off, the filtrate was diluted with 25 mL of EtOAc. The organic phase was separated, washed with 20 mL of brine, and then extracted twice with 10 mL portions of 2 M HCl. The acid extracts were combined, neutralized with sodium carbonate, and extracted twice with 20 mL portions of EtOAc. The extracts were combined, dried, and concentrated to a red oil. Column chromatography with Kieselgel 60 and 100% EtOAc gave 580 mg (3.39 mmol) of slightly red crystals (mp 70–74 °C, 44% yield). ^{1}H NMR ($CDCl_3$) δ 8.98 (1H, d, J = 2 Hz), 8.65 (1, dd, J = 2 and 6 Hz), 8.15 (1H, dd, J = 2 and 6 Hz), 8.09 (1H, dt, J = 2, 2 and 9 Hz), 7.45 (1H, dd, J = 6 and 9 Hz), 7.12 (2H, m), 3.2 (NH_2, b, 2H). Anal. Calcd for $C_{10}H_9N_3 \cdot {}^1/_8H_2O$: C, 69.24; H, 5.38; N, 24.22. Found: C, 69.48; H, 5.31; N, 24.32.

3-Bromo-2,3′-bipyridine (8). A cooled (−10 °C) suspension of 3-amino-2,3′-bipyridine (**9**) (365 mg, 1.55 mmol) in 48% HBr (1.5 mL) was stirred for 0.5 h, and Br_2 (0.25 mL, 4.3 mmol) was added. Keeping the reaction below 0 °C, $NaNO_2$ (300 mg, 4.33 mmol) in H_2O (0.4 mL) was added dropwise. After stirring for 0.5 h, NaOH (800 mg, 20.0 mmol) in H_2O (1 mL) was added dropwise making sure the temperature did not exceed 0 °C. The basic aqueous phase was extracted three times with 20 mL of diethyl ether, and the extracts were combined, dried, and concentrated to give 200 mg (0.851 mmol) of an off-white solid (mp 75–77 °C, 55% yield). ^{1}H NMR ($CDCl_3$) δ 8.88 (1H, d, J = 2 Hz), 8.58 (2H, m), 7.93 (2H, m), 7.32 (1H, ddd, J = 1, 5 and 9 Hz), 7.12 (1H, dd, J = 5 and 9 Hz). Anal. Calcd for $C_{10}H_7N_2Br$: C, 51.09; H, 3.00; N, 11.92. Found: C, 51.54; H, 2.96; N, 11.76.

4-Chloro-2,3′-bipyridine (4). 2,4-Dichloropyridine[27] (3.45 g, 23.3 mmol), diethyl(3-pyridyl)borane (3.40 g, 23.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (1.30 g, 11.3 mmol) in degassed THF (80 mL) were stirred at room temperature under N_2. After 5 min, K_2CO_3 (6.44 g, 46.6 mmol) in degassed H_2O (40 mL) was added and the mixture was heated at reflux for 3 h. The mixture was diluted with 50 mL of EtOAc, and the organic layer was dried and concentrated to a red oil. Column chromatography with Kieselgel 60 and 100% EtOAc gave 2.50 g (13.1 mmol) of a slightly yellow oil which crystallized on standing (mp 49–51 °C, 57% yield). ^{1}H NMR ($CDCl_3$) δ 9.33 (1H, d, J = 2 Hz), 9.03 (1H, d, J = 6 Hz), 8.76 (1H, dd, J = 2 and 5 Hz), 8.49 (1H, d, J = 2 Hz), 8.41 (1H, dt, J = 2, 2 and 9 Hz), 8.03 (1H, dd, J = 2 and 6 Hz), 7.49 (1H, ddd, J = 2, 5 and 9 Hz). Anal. Calcd for $C_{10}H_7N_2Cl$: C, 63.00; H, 3.70; N, 14.70. Found: C, 63.05; H, 3.70; N, 14.59.

3,2′:3′,4″:2″,3‴-Quaterpyridine (Nemertelline) (2). A degassed solution of 4-chloro-2,3′-bipyridine (**4**) (132 mg, 0.694 mmol) in toluene and tetrakis(triphenylphosphine)palladium-(0) (80 mg, 0.069 mmol) were stirred at room temperature under N_2 for 15 min. 3-(Tributylstannyl)-2,3′-bipyridine (**3**) (618 mg, 1.39 mmol) was added, and the solution was heated at reflux for 96 h. The mixture was cooled to room temperature, filtered through Celite to remove black catalyst, and concentrated to an oil. Column chromatography with Kieselgel 60 and 80/20 EtOAc/MeOH gave 140 mg (0.451 mmol, 70% yield) of a clear oil. The oil, dissolved in warm diethyl ether, slowly crystallized with scratching (mp 154–156 °C). ^{1}H NMR ($CDCl_3$) δ 9.00 (H2‴, 1H, dd, J = 1 and 3 Hz), 8.84 (H6′, 1H, dd, J = 2 and 5 Hz), 8.67 (H6″, 1H, dd, J = 1 and 6 Hz), 8.65 (H6‴, 1H, dd, J = 2 and 5 Hz), 8.62 (H2, 1H, dd, J = 1 and 3 Hz), 8.57 (H6, 1H, dd, J = 2 and 5 Hz), 8.19 (H4‴, 1H, dt, J = 2, 2 and 9 Hz), 7.85 (H4′, 1H, dd, J = 2 and 9 Hz), 7.78 (H4, 1H, dt, J = 2, 2 and 9 Hz), 7.56 (H3″, 1H, dd, J = 1 and 2 Hz), 7.49 (H5′, 1H, dd, J = 5 and 9 Hz), 7.39 (H5‴, 1H, ddd, J = 1, 5 and 9 Hz), 7.28 (H5, 1H, ddd, J = 1, 5 and 9 Hz), 7.14 (H5″, 1H, dd, J = 2 and 5 Hz). ^{13}C NMR ($CDCl_3$) δ 155.40, 154.24, 150.68, 150.39, 150.18, 150.04, 149.39, 148.24, 148.20, 138.25, 137.05, 135.08, 134.36, 133.80, 123.56, 123.28, 123.08, 122.97, 121.91. HRMS (FAB, m/z) (M + H) calcd 311.1297, found 311.1295. Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.34; H, 4.56; N, 18.13.

Crystal Structure.[35] Colorless crystals of nemertelline **2** were grown in $CHCl_3$. They are monoclinic, space group Cc, M_r = 310.35, a = 18.684(3) Å, b = 8.009(1) Å, c = 11.393(2) Å,

$\beta = 113.92(1)°$, $V = 1558.4(4)$ Å^3, $Z = 4$, $D_{calc} = 1.323$ g cm^{-3}, Mo Kα ($\lambda = 0.71073$ Å), $T = 298$ K. The structure was solved by the direct method and refined in SHELXTL plus[34] using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the positions of the hydrogen atoms were calculated in ideal positons and their isotropic thermal parameters were fixed. The systematic absences could not differentiate between space groups *C*2, *Cc* and *C*2/*c*. All three space groups were tried in the structure solution process but only *Cc* gave a solution. All refinements were carried out in space group *Cc*. In the final cycle of refinement 215 parameters and 1597 reflections [with $I > 2\sigma(I)$] gave R and wR of 0.0373 and 0.0432, respectively.

(34) Sheldrick, G. M. 1990, SHELXTL plus. Nicolet XRD Corp., Madison,WI.

(35) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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