Pergamon

Tetrahedron Vol. 51, No. 42, pp. 11401-11410, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00698-2

Total Synthesis of the Incorrectly Proposed Quaterpyridine Isolated from the Hoplonemertine Sea Worm.

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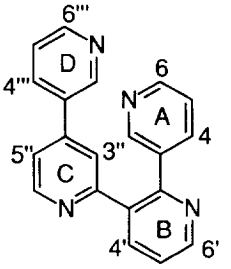
Key words: Quaterpyridine, bipyridine, Pd cross-coupling.

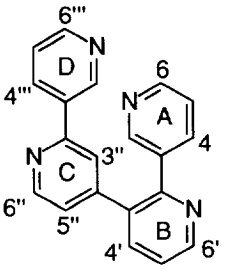
Abstract: Quaterpyridine **1** was synthesized for the first time using palladium-catalyzed cross-coupling reactions. Its proton NMR spectrum shows that is not the natural product called nemertelline isolated from nemertine marine worms as claimed in 1976.

Neurotoxic substances have been isolated from the phylum of marine worms called nemertines. Extracts from the hoplonemertine (armed) *Amphiporus angulatus* (Fabricius) contain anabaseine (3,4,5,6-tetrahydro-2,3'-bipyridine), 2,3'-bipyridine and a quaterpyridine given the name nemertelline (3,2': 3',2'': 4'',3'''-quaterpyridine, **1**).[1] The structure of this first quaterpyridine isolated from a living source rested entirely in 1976 on its 90 MHz proton NMR spectrum and homonuclear decoupling experiments.[1]

We now report the first synthesis of **1** and its correct proton NMR spectrum. Spectral differences between this synthetic quaterpyridine and that of the natural substance clearly indicate that **1** is not the natural product. Our synthesis of the correct isomeric natural material **2** (3,2':3',4'':2'',3'''-quaterpyridine) and its proof of structure by proton NMR and X-ray analysis will be given elsewhere.[2] Isomers **1** and **2** differ only in the location of the nitrogen atom in the C ring. The C ring is a 2,4-disubstituted pyridine in both structures but it is bonded to the D ring at the 4'' position in **1** and the 2'' position in **2**.

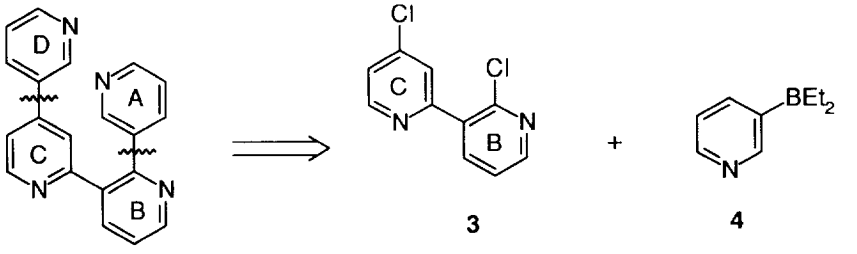


1, Nemertelline
(Original, incorrect structure)

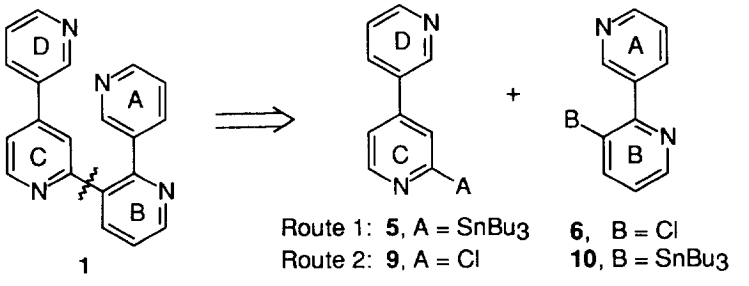


2, Nemertelline
(Correct structure)

Scheme 1: Retrosynthetic Analysis



Scheme 2: Retrosynthetic Analysis



Route 1: **5**, A = $SnBu_3$ **6**, B = Cl
Route 2: **9**, A = Cl **10**, B = $SnBu_3$

RESULTS AND DISCUSSION

Our two retrosynthetic approaches for **1** are given in Schemes 1 and 2. Both are predicated on the use of palladium-catalyzed cross-coupling[3-6] of organometallic and halide hetarenes to form bipyridine (bpy) rings.

According to successful Scheme 1 the two 3-pyridyl rings of **1** are disconnected from the central B-C rings, a 2,3′-bpy, to give its dichloride **3** and a 3-substituted pyridine, here used as its commercially available borane, diethyl(3-pyridyl)borane (**4**).

In Scheme 2 the disconnection is made between the B and C rings to give two different bpy rings, 3,4′-bpy **5** containing the C-D rings and 2,3′-bpy **6** having the A-B rings. The polarity of this disconnection was reversed in our two approaches. In route 1 the C-D rings contain the organometallic stannyl group and the A-B rings the chloride. In route 2 the positions of the stannyl and chloro groups are reversed.

Although both routes in Scheme 2 gave some of the desired quaterpyridine on cross-coupling, the material was contaminated with a homocoupled by-product from the stannane that proved difficult to remove. The synthetic sequence in Scheme 1 therefore is preferred.

In all the approaches the individual bpy rings were constructed by a palladium-catalyzed union of two pyridine rings.

Scheme 1: The preparation of the key dichloro intermediate **3** having the B-C rings is based on our reported synthesis of the 4-chloro-2,3′-bpy precursor (**7**) which was made by selectively coupling borane **4** to the 2-position of 2,4-dichloropyridine.[7]

Monochloro **7** was selectively N-oxidized with MCPBA at the less sterically hindered nitrogen atom to form **8** as expected.[7] Using known chemistry,[8] it was possible to convert this N-oxide to the 4-chloro-2,3′-bipyrid-2′-one with acetic anhydride. This pyridone then was transformed to **3** with $POCl_3$ and DMF. Use of $POCl_3$ directly on the N-oxide gave rise to a mixture of two chlorinated isomers and therefore this approach was avoided. Had chlorination taken place at either the 4′ or the 6′ position and not at the desired 2′ site to give the isomeric dichloride, a low field singlet due to H-2′ would have been present in the proton NMR spectrum. Such was not the case.

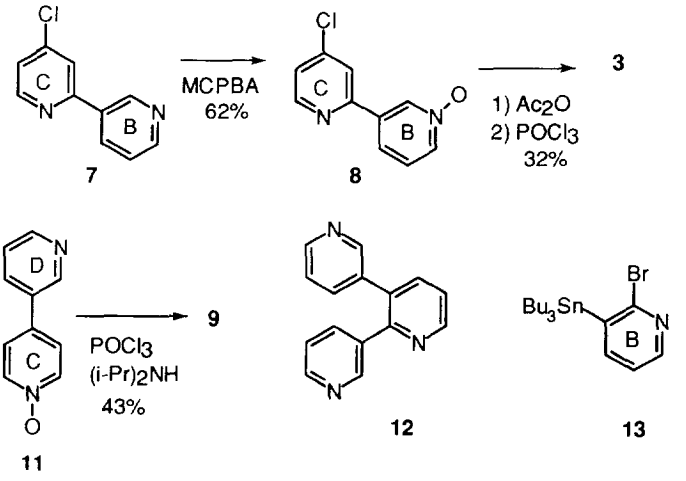
The final Suzuki-type coupling with slightly more than two equivalents of borane **4** and dichloride **3** provided **1** in 64% yield.

Scheme 2, Route 1: The C-D ring system was made quite easily using chemistry recently developed by our group to provide regioselectively N-

functionalized bpy rings.[6,9] Cross-coupling of 4-chloropyridine N-oxide and borane **4** under Suzuki-type conditions gave 3,4'-bipyridine 1'-oxide (**11**) in good yield (75%). This material then was converted to **9** (A = Cl) with $POCl_3$ and diisopropylamine followed by conversion to the Grignard reagent. Trans-metallation with tributyltin chloride afforded 2-tributylstannyl **5** (A = Bu_3Sn) in moderate yield (34%).

The A-B portion, **6** (B = Cl), available from our synthesis of **2**,[2] was easily obtained by coupling borane **4** to 2,3-dichloropyridine at the more reactive 2-chloro position. To verify that it was possible to cross-couple to the sterically hindered 3-chloro position of this bpy, a model coupling with **4** was attempted. The expected, new 3,2': 3',3''-terpyridine **12** was isolated in 62% yield indicating that the coupling reaction with the borane is not especially sensitive toward steric hindrance.

The final coupling to give **1** was carried out under typical Stille conditions using tetrakis(triphenylphosphine)palladium(0) and refluxing toluene. Unfortunately, a mixture of **1** and the homocoupled product from stannane **5** could not be easily separated by silica gel chromatography.



Scheme 2, Route 2: In order to suppress homocoupling, the polarities of the bpy rings were reversed. Again, borrowing from our synthesis of **2**,[2] the organometallic A-B ring was made by ortho lithiation of 2-bromopyridine with LDA (-78 °C) and trans-metallation with tributyltin chloride[10,11] (57%). The resultant known 2-bromo-3-tributylstannylpyridine[2] (**13**) was selectively

coupled to **4** under typical Suzuki conditions to give known bpy[9] **10** (B = Bu_3Sn) in 86% yield. The coupling of chloride **9** (A = Cl) and stannane **10** (B = Bu_3Sn) again gave an inseparable mixture of **1** and a homocoupled product, that from **10**.

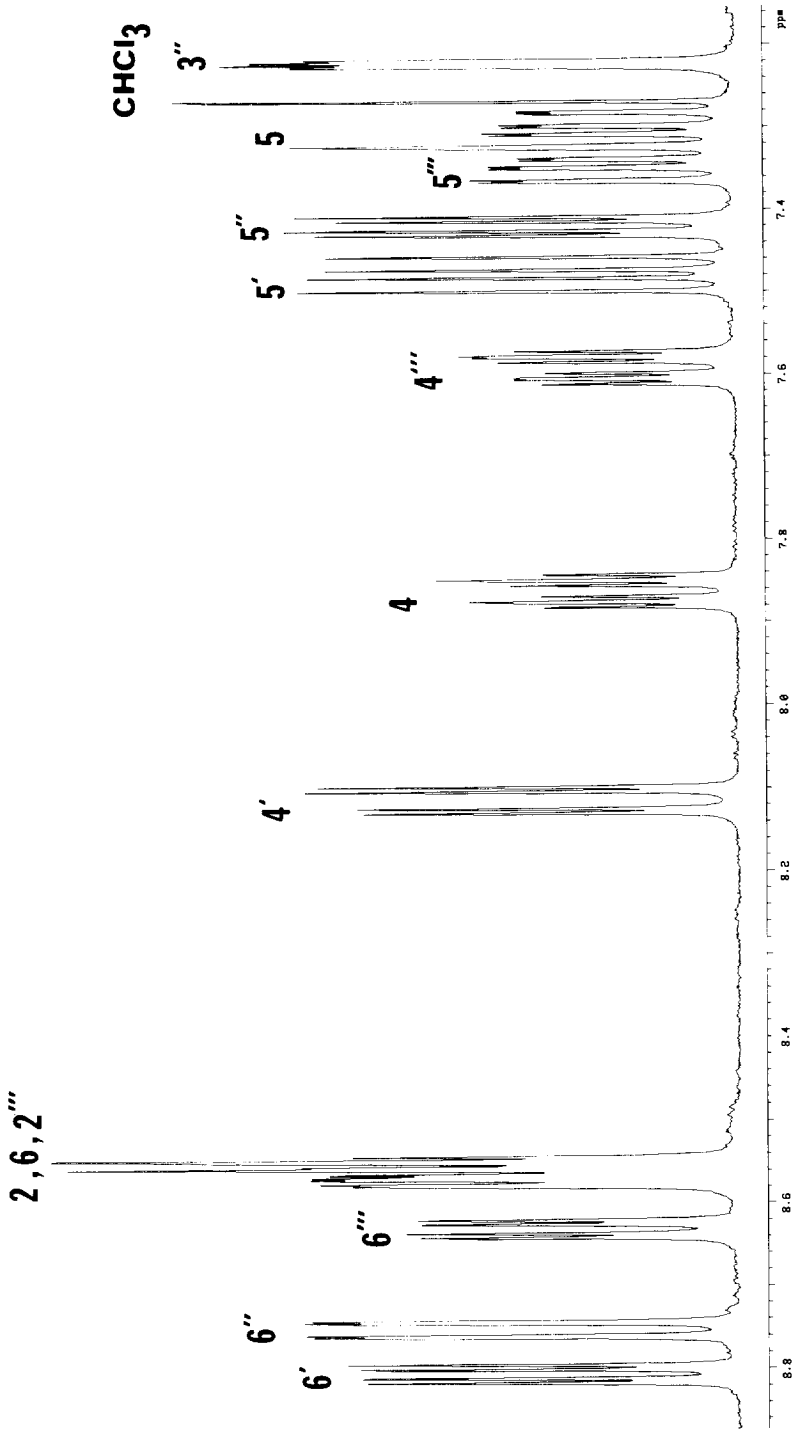
Comparison of Proton NMR Spectra of 1 and 2: The 300 MHz NMR spectrum of **1** in $CDCl_3$ is shown in Figure 1 along with shift assignments for it and **2**[2] in Table 1. Of the 14 aromatic proton signals only three of those in **1** overlap seriously. The assignments are based on COSY and NOE difference spectra as well as the general pattern of chemical shifts and spin couplings observed for polypyridines. Thus, for each ring an α, γ and β dispersion order is usually observed (increasing magnetic field) along with a nitrogen atom lone pair interring deshielding effect[12,13] and a shielding π stacking effect[14] for the A and C rings. Splitting patterns are essential in identifying the degree and position of substitution in each ring.

Only the A ring protons have similar shifts. Five protons have shift differences of at least 0.3 ppm. Three of these (4′, 2‴ and 4‴) are associated with the presence or absence of the interannular nitrogen deshielding effect while the other two (3″ and 5″) may reflect conformational differences.

Nemertelline (**1**) clearly is not the natural product. The material isolated from the marine worm is **2**.

Table 1. Chemical Shifts of **1** and **2** (ppm) in $CDCl_3$.

Cpd	A-Ring	B-Ring	C-Ring	D-Ring
1	8.57 (H2)			8.57(H2‴)
	7.87 (H4)	8.12 (H4′)	7.23 (H3″)	7.61(H4‴)
	7.30 (H5)	7.48 (H5′)	7.43 (H5″)	7.35(H5‴)
	8.57 (H6)	8.82 (H6′)	8.76 (H6″)	8.64(H6‴)
2	8.63 (H2)			9.01(H2‴)
	7.77 (H4)	7.84 (H4′)	7.55 (H3″)	8.19(H4‴)
	7.26 (H5)	7.49 (H5′)	7.13 (H5″)	7.38(H5‴)
	8.56 (H6)	8.83 (H6′)	8.67 (H6″)	8.65(H6‴)


CHCl3
3''
5
5'''
5''
5'
4'''
4
4'
2,6,2'''
6'''
6''
6'
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
ppm

EXPERIMENTAL SECTION

Diethyl(3-pyridyl)borane, 4-chloropyridine N-oxide, tributyltin chloride, tetrakis(triphenylphosphine)palladium(0), phosphorus oxychloride, 2,3-dichloropyridine, 2.5 M n-BuLi, 2-bromopyridine, and 57-80% m-chloroperbenzoic acid (MCPBA) were purchased from Aldrich Chemical Company. Flash chromatography made use of Kieselgel 60 230-400 mesh or alumina 80-200 mesh. ^{1}H NMR spectra were recorded on a Varian Gemini 300 instrument using $CDCl_3$ (TMS) as solvent. Grignard reactions were initiated with I_2 or 1,2-dibromoethane. Solvents often were freshly distilled and degassed by bubbling N_2 through them for 15-30 minutes. All melting points are uncorrected. The drying agent was either sodium or magnesium sulfate.

4-Chloro-2,3′-bipyridine 1′-oxide (8): To a $CHCl_3$ (50 mL) solution of 4-chloro-2,3′-bipyridine (**7**)[2] (2.50 g, 13.1 mmol) was added 57-80% MCPBA (2.83 g, 16.4 mmol). The solution was stirred at room temperature for 24 h and then washed with 10 mL of satd. sodium sulfite, dried, and concentrated to a slightly yellow solid. Column chromatography with Kieselgel and 90/10 EtOAc/MeOH gave 1.67 g (8.08 mmol) of a white solid (mp 109-112 °C, 62% yield). ^{1}H NMR ($CDCl_3$) δ 9.05 (2H, m), 8.45 (1H, d, J = 2 Hz), 8.34 (1H, dt, J = 2, 2 and 8 Hz), 8.10 (1H, dd, J = 2 and 6 Hz), 7.96 (1H, dd, J = 2 and 6 Hz), 7.46 (1H, dd, J = 6 and 8 Hz). Anal. Calcd. for $C_{10}H_7N_2OCl.1/2\ H_2O$: C, 55.69; H, 3.74; N, 12.99. Found: C, 55.76; H, 3.67; N, 13.33.

2′,4-Dichloro-2,3′-bipyridine (3): A suspension of 4-chloro-2,3′-bipyridine 1′-oxide (**8**) (500 mg, 2.42 mmol) and acetic anhydride (20 mL) was heated at reflux for 12 h. The mixture was concentrated to a brown oil, dissolved in 15 mL of MeOH, decolorized with charcoal, and filtered through a bed of Celite. The filtrate was concentrated to a yellow solid which was washed with 20 mL of diethyl ether to give 240 mg (1.16 mmol, 48% yield) of the pyridone. The solid was suspended in $POCl_3$ (5 mL) and DMF (1 mL) and heated at reflux for 18 h. The reaction was concentrated to a brown oil and Na_2CO_3/ice/H_2O was added until the mixture was slightly basic to pH paper. After extraction with 50 mL of EtOAc the organic phase was dried and concentrated to a brown oil. Column chromatography with Kieselgel and 100% EtOAc gave 80 mg (0.36 mmol) of a yellow solid (mp 156-159 °C, 32% yield). ^{1}H NMR ($CDCl_3$) δ 8.68 (1H, d, J = 6 Hz), 8.51 (1H, dd, J = 2 and 6 Hz), 8.02 (1H, dd, J = 2 and 8 Hz), 7.92 (1H, d, J = 2 Hz), 7.51 (2H, m). Anal. Calcd. for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.71; H, 2.62; N, 12.40.

3,4′-Bipyridine 1′-oxide (11): 4-Chloropyridine N-oxide (1.40 g, 10.8 mmol), diethyl(3-pyridyl)borane (1.59 g, 10.8 mmol), tetrakis(triphenylphosphine) palladium(0) (500 mg, 0.430 mmol) in degassed THF (30 mL) were stirred for 5 min at room temperature under N_2. Potassium carbonate (2.98 g, 21.6 mmol) in degassed H_2O (15 mL) was added and the mixture was heated at reflux. After 48 h the mixture was concentrated and MeOH (50 mL) was added. The insoluble K_2CO_3 was filtered off and the filtrate was concentrated onto approx. 5 g of Kieselgel. Column chromatography with 80/20 EtOAc/MeOH gave 1.40 g (8.13 mmol) of an off-white solid (mp 125-127 °C, 75% yield). ^{1}H NMR (DMSO-d_6) δ 8.82 (1H, d, J = 2 Hz), 8.61 (1H, dd, J = 2 and 5 Hz), 8.14 (2H, d, J = 8 Hz), 8.02 (1H, dt, J = 2, 2 and 8 Hz), 7.65 (2H, d, J = 9 Hz), 7.38 (1H, dd, J = 5 and 9 Hz). Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.35; H, 4.67; N, 16.09.

2′-Chloro-3,4′-bipyridine (9): To a cooled (0 °C) suspension of 3,4′-bipyridine 1′-oxide (**11**) (700 mg, 4.07 mmol) in CH_2Cl_2 (5 mL) under N_2 was added $POCl_3$ (2 mL). To this slurry additional $POCl_3$ (2 mL) and $(i\text{-Pr})_2NH$ (2 mL) were added concomitantly over 2 h. The mixture became brown and homogeneous. It was stirred for 1 h while warming to room temperature and was then concentrated to a brown oil. To the oil Na_2CO_3/ice/H_2O was added until the aqueous phase was slightly basic to pH paper. The aqueous phase was extracted with 30 mL of EtOAc and the organic phase was dried and concentrated to a brown solid. Column chromatography with Kieselgel and 100% EtOAc gave 320 mg (1.68 mmol) of a yellow solid (mp 114-115 °C, 41% yield). ^{1}H NMR ($CDCl_3$) δ 8.89 (1H, d, J = 2 Hz), 8.72 (1H, dd, J = 2 and 5 Hz), 8.50 (1H, d, J = 6 Hz), 7.92 (1H, dt, J = 2, 2 and 9 Hz), 7.58 (1H, d, J = 1 Hz), 7.46 (2H, m). Anal. Calcd. for $C_{10}H_7N_2O$: C, 63.00; H, 3.70; N, 14.70. Found: C, 62.96; H, 3.65; N, 14.59.

2′-Tributylstannyl-3,4′-bipyridine (5): 2′-Chloro-3,4′-bipyridine (**9**) (100 mg, 0.522 mmol), freshly distilled THF (10 mL), and Mg (25 mg, 1.04 mmol) were stirred at room temperature under N_2. The reaction was initiated with two drops of 1,2-dibromoethane and then tributyltin chloride (0.500 mL, 1.84 mmol) was added dropwise. After the addition, the mixture was heated at reflux for 4 h and then cooled to room temperature. The reaction was diluted with 30 mL of satd. NH_4Cl and 30 mL of diethyl ether. The organic phase was separated, dried, and concentrated to a yellow oil. Column chromatography with Kieselgel and 60/40 hexanes/EtOAc gave 80 mg (0.18 mmol) of a clear oil (34% yield). ^{1}H NMR ($CDCl_3$) δ 8.86 (1H, d, J = 2 Hz), 8.84 (1H, dd, J = 1 and 6 Hz), 8.66 (1H, dd, J = 2 and 6 Hz), 7.91 (1H, dt, J = 2, 2 and 9 Hz), 7.59 (1H, dd with Sn side bands, J = 1 and 2 Hz), 7.43 (1H, ddd, J = 1, 6 and 9

Hz), 7.33 (1H, dd, J = 2 and 6 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, 59.67; H, 7.74; N, 6.00.

3,2′:3′,3″-Terpyridine Trihydrochloride (12): Diethyl(3-pyridyl)borane (368 mg, 2.50 mmol), 3-chloro-2,3′-bipyridine[2] (448 mg, 2.35 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 10 min at room temperature, and potassium carbonate (685 mg, 4.96 mmol) in degassed H_2O (10 mL) was added. The mixture was heated at reflux for 72 h and then cooled to 0 °C with an ice bath. The insoluble catalyst was filtered off and the filtrate was diluted with 25 mL of EtOAc. The organic phase was separated, washed with 20 mL of brine, and 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 organic extracts were combined, dried, and concentrated to a yellow oil. Column chromatography with Kieselgel and 90/10 EtOAc/MeOH gave 348 mg (1.49 mmol, 62% yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.78 (1H, d, J = 6 Hz), 8.52 (4H, m), 7.80 (1H, d, J = 8 Hz), 7.70 (1H, dd, J = 2 and 9 Hz), 7.45 (2H, m), 7.23 (4H, m). A 100 mg portion of this material was converted to the trihydrochloride salt by dissolving it in 5 mL of EtOAc and adding HCl-ether dropwise. The solid was collected and dried in vacuo to give a white solid. Anal. Calcd. for $C_{15}H_{11}N_3.3HCl$: C, 52.58; H, 4.12; N, 12.26. Found: C, 52.29; H, 4.20; N, 12.28.

3,2′:3′,2″:4″,3‴-Quaterpyridine (1): 2′,4-Dichloro-2,3′-bipyridine (**3**) (80 mg, 0.36 mmol), diethyl(3-pyridyl)borane (**4**) (131 mg, 0.889 mmol), and tetrakis(triphenylphosphine)palladium(0) (41 mg, 0.04 mmol) in degassed THF (80 mL) were stirred at room temperature under N_2. After 5 min, sodium bicarbonate (119 mg, 1.42 mmol) in degassed H_2O (10 mL) was added, and the mixture was heated at reflux for 24 h. The mixture was diluted with 50 mL of EtOAc, and the organic layer was dried and concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 70 mg (0.23 mmol, 64 % yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.82 (H6′, 1H, dd J = 2 and 5 Hz), 8.76 (H6″, 1H, dd, J = 1 and 6 Hz), 8.64 (H6‴, 1H, dd, J = 2 and 6 Hz), 8.57 (H2 and H2‴ and H6, 3H, m), 8.12 (H4′, 1H, dd, J = 2 and 9 Hz), 7.87 (H4, 1H, dt, J = 2, 2 and 9 Hz), 7.61 (H4‴, 1H, dt, J = 2, 2 and 9 Hz), 7.48 (H5′, 1H, dd, J = 5 and 9 Hz), 7.43 (H5″, 1H, dd, J = 2 and 6 Hz), 7.35 (H5‴, 1H, ddd, J = 2, 6 and 9 Hz), 7.30 (H5, 1H, ddd, J = 2, 6 and 9 Hz), 7.23 (H3″, 1H, dd, J = 1 and 2 Hz). Anal. Calcd. for $C_{20}H_{14}N_4 .1/4\ H_2O$: C, 76.26; H, 4.64; N, 17.80. Found: C, 76.40; H, 5.03; N, 17.82.

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(*Received in USA* 1 *June* 1995; *accepted* 28 *August* 1995)