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New syntheses of orelline and analogues via metalation and cross-coupling reactions

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Abstract—New total syntheses of orelline and some analogues are reported. The methodology involves metalation of 3-alkoxy-2-iodopyridines to afford 3,4-dialkoxy-2-iodopyridines, on which cross-coupling reactions are performed to reach the 2,2′-bipyridine skeleton of the alkaloid.

1. Introduction

Orelline (**1a**) is a toxin present in the poisonous mushrooms *Cortinarius Orellanus* and *Speciosissimus*. Its structure has been elucidated by Antkowiak and Gessner.[1]

Numerous studies devoted to this mushroom poisoning[2] need efficient synthesis methods. In the syntheses described by Dehmlow and Schulz (8 steps, 1.4% yield),[3] Tiecco et al. (8 steps, 4.4%),[4] Hasseberg and Gerlach (5 steps, 4.8%)[5] and our group (5 steps, 16.6%),[6] the 2,2′-bipyridine structure was obtained by a homocoupling reaction on 2-halopyridine derivatives.

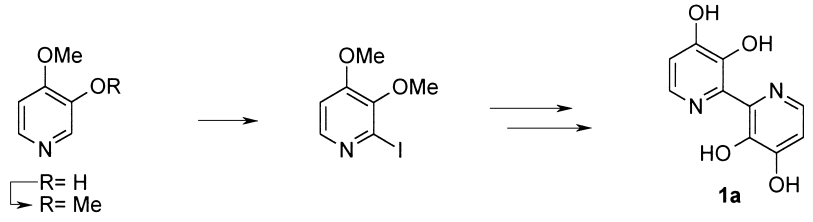
The method described in 1993 by our group involves 3,4-dimethoxypyridine, which was prepared through metalation of 4-methoxypyridine, giving 3-hydroxy-4-methoxypyridine, and subsequent *O*-methylation with diazomethane. The introduction of the halogen at C2, to allow the homocoupling reaction, was then realized in a second metalation step (Scheme 1).[6]

We report here an efficient access to Orelline (**1a**) and its analogues **1b**–**d** (Scheme 2), starting from easily accessible 3-hydroxy-2-iodopyridine; it avoids the use of diazomethane and thus allows to prepare Orelline (**1a**) at a larger scale.

2. Results and discussion

3-Alkoxy-2-iodopyridines **3a**–**b** were first synthesized. To this purpose, 3-hydroxypyridine was easily iodinated at C2, using a procedure described in the literature;[7] *O*-alkylation to afford **3a**–**b** was then effected in good yields using standard procedures (Scheme 3).

The metalation conditions of 3-alkoxy-2-iodopyridines



Scheme 1.

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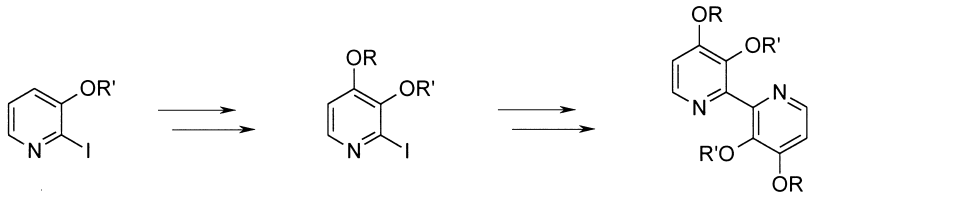
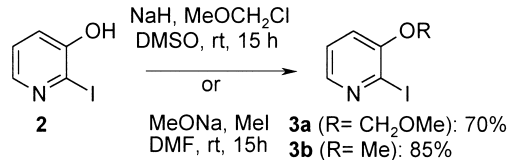
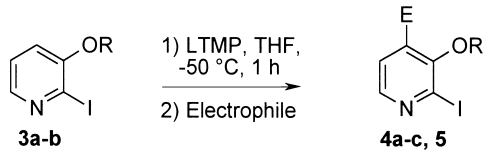


Scheme 2.



Scheme 3.

3a–**b** were then studied. A survey of the literature revealed that alkoxypyridines are generally deprotonated with alkyl- or phenyllithiums.[8] In our case, such bases can't be used in the presence of the iodine atom at C2, so we turned to lithium dialkylamides. We preferred lithium 2,2,6,6-tetramethylpiperidide (LTMP, pKa 37.3) to lithium diisopropylamide (LDA, pKa 35.7). Using LTMP in tetrahydrofuran (THF) at −50°C resulted in clean lithiation of **3a**–**b** at C4, as shown by quenching of the resulting 4-lithio derivatives with electrophiles (Scheme 4, Table 1).



Scheme 4.

Notably, the introduction of a hydroxy group at C4 could be realized in quite good yields (Table, entries 3 and 4) with trimethylborate as an electrophile at low temperature, followed by the in situ reaction of peracetic acid.[9]

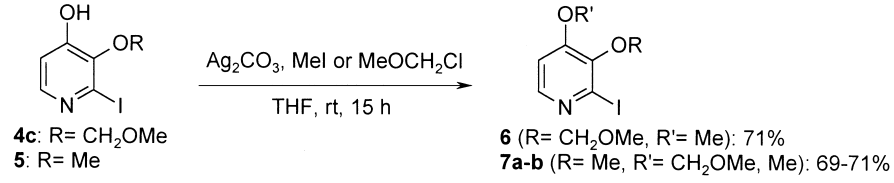
The 4-hydroxy derivatives **4c** and **5** were then protected via their silver salts to give 4-alkoxy derivatives **6** and **7a**–**b** (Scheme 5). Note that the solvent choice was crucial for the regioselectivity of the alkylation.[10]

3,4-Dialkoxy-2-iodopyridines **6**, **7a**–**b** in hands, we had the possibility to involve them in a homocoupling procedure. Nevertheless, cross-coupling was rather chosen because of the possible access to both symmetrical and non-symmetrical bipyridines.

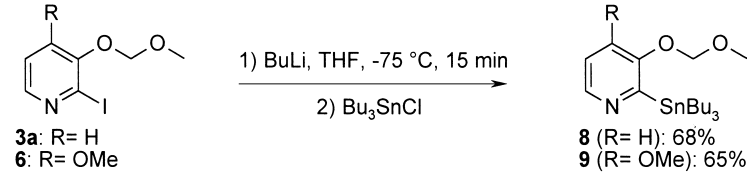
Iodine–lithium exchange was then performed with butyllithium (BuLi) at low temperature. Quenching the 2-lithio derivative with chlorotributylstannane afforded 2-stannylated pyridines **8**–**9** (Scheme 6).

Table 1. Metalation of **3a**–**b**

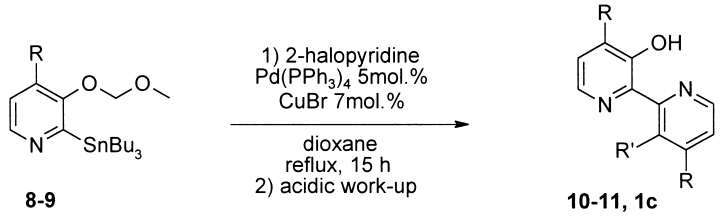
Entry	Starting material	R	Electrophile	Product (E), %yield
1	**3a**	CH_2OMe	D_2O	**4a** (D), 86 (85% *d*)
2	**3a**	CH_2OMe	C_2Cl_6	**4b** (Cl), 75
3	**3a**	CH_2OMe	$B(OMe)_3$/AcOOH	**4c** (OH), 78
4	**3b**	Me	$B(OMe)_3$/AcOOH	**5** (OH), 63



Scheme 5.



Scheme 6.



Scheme 7.

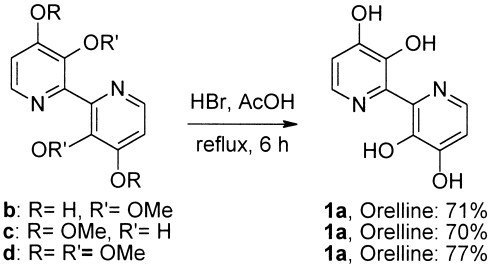
Table 2. Coupling of **8**–**9**

Entry	Starting material	2-Halopyridine	Product (R,R′), yield (%)
1	**8** (R=H)	2-Bromopyridine	**10** (R=R′=H), 74
2	**8** (R=H)	**3a**	**11** (R=H, R′=OH), 91
3	**9** (R=OMe)	**6**	**1c** (R=OMe, R′=OH), 74

Coupling of 2-stannylated pyridines **8**–**9** with 2-halopyridines such as 2-bromopyridine, **3a** and **6**, in the presence of a catalytic amount of $Pd(PPh_3)_4$ and cuprous bromide[13] allowed the synthesis of 2,2′-bipyridines **10**, **11** and **1c** (Scheme 7, Table 2).

Moreover, transmetalation reaction with zinc chloride[11] was also applied to the 2-lithio derivative; the resulting organozinc reagent was coupled with 2-halopyridines such as 2-bromopyridine, **7a** and **7b**, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$),[12] to afford 2,2′-bipyridines **10**, **1b** and **1d** (Scheme 8, Table 3).

Dealkylation of 2,2′-bipyridines **1b**–**d** was achieved at reflux of a mixture of hydrobromic and acetic acids, following the protocole of Dehmlow and Schulz.[3b] In the case of **1d**, the yield to give Orelline (**1a**) could be improved (77 instead of 46%[3b]) (Scheme 9).



Scheme 9.

3. Conclusion

In the previous syntheses, Orelline (**1a**) was prepared in 8 steps from 3-aminopyridine by Dehmlow and Schulz,[3] in 8 steps by Tiecco et al.,[4] in 5 steps by Hasseberg and Gerlach,[5] both from 3-hydroxypyridine, and in 5 steps by our group[6] from 4-methoxypyridine.

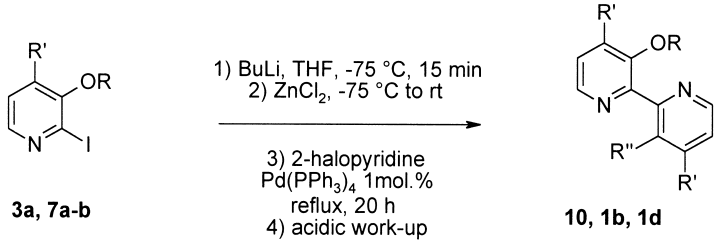
The overall yields of our syntheses are 12.4 (via **1b**), 10.3 (via **1c**) and 13.6% (via **1d**), respectively, in 6, 7 and 6 steps, starting from commercially available 3-hydroxypyridine.

In conclusion, our method allowed syntheses of Orelline (**1a**) and analogues **1b**–**d** through metalation, iodine–lithium exchange and cross-coupling reactions. Note that our methodology is also suitable for the synthesis of non-symmetrical 2,2′-bipyridines (e.g. compound **10**).

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded with a 200 or 300 MHz spectrometer. Melting points are uncorrected.



Scheme 8.

Table 3. Coupling of **3a**, **7a**–**b**

Entry	Starting material	2-Halopyridine	Product (R, R′), yield (%)
1	**3a** (R=CH_2OMe, R′=H)	2-Bromopyridine	**10** (R=R′=R″=H), 32
2	**7a** (R=Me, R′=OCH_2OMe)	**7a**	**1b** (R=Me, R′=OH, R″=OMe), 60
3	**7b** (R=Me, R′=OMe)	**7b**	**1d** (R=Me, R′=R″=OMe), 59

THF and dioxane were distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[14] Commercial solutions of BuLi (2.5 M in hexane) were employed as received. $Pd(PPh_3)_4$ was synthesized by literature method.[12] Metallation and cross-coupling reactions were carried out under dry argon. 3-Hydroxy-2-iodopyridine (**2**) was prepared according to a literature procedure.[7] Deuterium incorporation was determined using ^1H NMR spectra integration.

After the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvents were evaporated under reduced pressure, and unless otherwise noted, the crude compound was chromatographed on a silica gel column (eluent is given in the product description).

4.1.1. 2-Iodo-3-methoxymethoxypyridine (3a). To a stirred suspension of NaH (80% in mineral oil, 2.9 g, 60 mmol) in DMSO (40 mL) was progressively added 3-hydroxy-2-iodopyridine (**2**, 11 g, 50 mmol). After the mixture was stirred for 30 min, $MeOCH_2Cl$ (4.6 mL, 60 mmol) was added at 0°C. The reaction mixture was then warmed to rt and stirred for 15 h. After addition of water (40 mL) and extraction with AcOEt (3×40 mL), the organic phase was washed with water (4×40 mL) to afford 70% of **3a** (eluent: CH_2Cl_2/Et_2O 95:5): mp<50°C (lit.[15] 45°C); ^{13}C NMR ($CDCl_3$) δ 56.7 (OMe), 95.0 (CH_2), 112.6 (C_2), 121.1 (C_4), 123.5 (C_5), 144.0 (C_6), 153.3 (C_3); IR (KBr) ν 2957, 2827, 1557, 1448, 1399, 1266, 1199, 1155, 1042, 968 cm^{-1}. Anal. calcd for $C_7H_8INO_2$ (265.05): C, 31.72; H, 3.04; N, 5.28. Found: C, 31.79; H, 2.94; N, 5.09%.

4.1.2. 2-Iodo-3-methoxypyridine (3b). To a stirred solution of MeONa (3.2 g, 60 mmol) in DMF (50 mL) was progressively added 3-hydroxy-2-iodopyridine (**2**, 11 g, 50 mmol). After the mixture was stirred for 30 min, MeI (3.7 mL, 60 mmol) was added at 0°C. The reaction mixture was then warmed to rt and stirred for 15 h. After addition of water (40 mL) and extraction with AcOEt (3×40 mL), the organic phase was washed with water (4×40 mL) to afford 85% of **3b** (eluent: CH_2Cl_2): mp 55–57°C (lit.[16] 56–57°C); ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe), 6.94 (dd, 1H, J=8.2, 1.5 Hz, H_4), 7.13 (dd, 1H, J=8.2, 4.7 Hz, H_5), 7.94 (dd, 1H, J=4.7, 1.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 56.6 (OMe), 112.0 (C_2), 117.2 (C_4), 123.9 (C_5), 142.9 (C_6), 155.6 (C_3); IR (KBr) ν 2970, 2934, 1559, 1458, 1403, 1288, 1071, 1044, 794, 653 cm^{-1}. Anal. calcd for C_6H_6INO (235.02): C, 30.66; H, 2.57; N, 5.96. Found: C, 30.94; H, 2.87; N, 6.18%.

4.2. General procedure 1: metalation of 2-iodo-3-methoxymethoxy- and 2-iodo-3-methoxypyridines (3a–b)

At −75°C, 2,2,6,6-tetramethylpiperidine (0.40 mL, 2.4 mmol) and, 15 min later, the required 2-iodo-3-alkoxypyridine (2.0 mmol) were added to a solution of BuLi (2.2 mmol) in hexane (0.88 mL) and THF (10 mL). After 1 h at −50°C, the electrophile was added and allowed to react as mentioned in the product description.

4.2.1. 2-Iodo-3-methoxymethoxy(4-D)pyridine (4a). The general procedure 1, starting from **3a** and using D_2O (0.20 mL, 11 mmol) at −50°C, gave **4a** (eluent: CH_2Cl_2/Et_2O 95:5). Yield: 86, 85% *d*. The characteristics of this product were found to be identical to those described for **3a** except for ^1H spectra where the 4-H signal had disappeared.

4.2.2. 4-Chloro-2-iodo-3-methoxymethoxypyridine (4b). The general procedure 1, starting from **3a** and using C_2Cl_6 (0.52 g, 2.2 mmol) at −75°C with subsequent warming at rt, gave **4b** (eluent: CH_2Cl_2). Yield: 75%; colorless oil; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H, OMe), 5.16 (s, 2H, CH_2), 7.24 (d, 1H, J=5.9 Hz, H_5), 8.00 (d, 1H, J=5.9 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 59.4 (OMe), 100.4 (CH_2), 118.3 (C_2), 125.1 (C_5), 134.6 (C_4), 146.7 (C_6), 151.2 (C_3); IR (KBr) ν 2962, 2933, 1534, 1360, 1160, 922, 745 cm^{-1}. Anal. calcd for $C_7H_7ClINO_2$ (299.50): C, 28.07; H, 2.36; N, 4.68. Found: C, 28.27; H, 2.53; N, 4.75%.

4.2.3. 4-Hydroxy-2-iodo-3-methoxymethoxypyridine (4c). The general procedure 1, starting from **3a** and using trimethylborate (0.48 mL, 4.2 mmol) at −75°C, with stirring for 2 h at this temperature, was used. A solution of peracetic acid (0.72 mL of a 32 wt% in dilute acetic acid, 4.2 mmol) was then added, and the mixture was slowly warmed to rt. After the mixture was cooled to −10°C, an aqueous solution (10 mL) of $Na_2S_2O_4$ (0.75 g) was poured dropwise. A 78% yield of **4c** was obtained (eluent: AcOEt): mp 127–129°C; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H, OMe), 4.90 (s, 2H, CH_2), 6.72 (d, 1H, J=5.8 Hz, H_5), 7.5 (s, 1H, OH), 7.72 (d, 1H, J=5.8 Hz, H_6); IR (KBr) ν 2827, 1504, 1380, 1313, 1105, 1150, 1075, 950, 923, 898, 567 cm^{-1}. Anal. calcd for $C_7H_8INO_3$ (281.05): C, 29.92; H, 2.87; N, 4.98. Found: C, 30.18; H, 2.87; N, 4.74%.

4.2.4. 4-Hydroxy-2-iodo-3-methoxypyridine (5). The general procedure 1, starting from **3b** and using trimethylborate (0.48 mL, 4.2 mmol) at −75°C, with stirring for 2 h at this temperature, was used. A solution of peracetic acid (0.72 mL of a 32 wt% in dilute acetic acid, 4.2 mmol) was then added, and the mixture was slowly warmed to rt. After the mixture was cooled to −10°C, an aqueous solution (10 mL) of $Na_2S_2O_4$ (0.75 g) was poured dropwise. A 63% yield of **5** was obtained (eluent: Et_2O): mp 134–136°C; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe), 6.82 (d, 1H, J=5.5 Hz, H_5), 7.5 (s, 1H, OH), 7.91 (d, 1H, J=5.5 Hz, H_6); IR (KBr) ν 2931, 2591, 1523, 1388, 1322, 1261, 1214, 899, 823, 579 cm^{-1}. Anal. calcd for $C_6H_6INO_2$ (251.02): C, 28.71; H, 2.41; N, 5.58. Found: C, 28.95; H, 2.25; N, 5.88%.

4.3. General procedure 2: *O*-methylation of 4-hydroxypyridines (4c, 5)

To the required 4-hydroxypyridine (2.0 mmol) in THF were added at rt Ag_2CO_3 (0.61 g, 2.2 mmol) and, 15 min later, the required halide (2.2 mmol). The mixture was stirred in the dark for 15 h. Silver salts were filtered on Celite® and washed with CH_2Cl_2.

4.3.1. 2-Iodo-4-methoxy-3-methoxymethoxypyridine (6). The general procedure 2, starting from **4c** and using MeI, gave **6** (eluent: CH_2Cl_2/Et_2O 90:10). Yield: 71%; colorless

oil; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H, CH_2OMe), 3.87 (s, 3H, OMe), 5.17 (s, 2H, CH_2), 6.76 (d, 1H, J=5.4 Hz, H_5), 8.00 (d, 1H, J=5.4 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 56.2 (CH_2O*Me*), 58.8 (OMe), 98.9 (CH_2), 108.1 (C_5), 117.2 (C_2), 143.2 (C_3), 147.4 (C_6), 157.9 (C_4); IR (KBr) ν 2918, 2848, 1568, 1477, 1380, 1296, 1158, 1027, 927, 817 cm^{-1}. Anal. calcd for $C_8H_{10}INO_3$ (295.08): C, 32.56; H, 3.42; N, 4.75. Found: C, 32.43; H, 3.38; N, 4.53%.

4.3.2. 2-Iodo-3-methoxy-4-methoxymethoxypyridine (7a). The general procedure 2, starting from **5** and using $MeOCH_2Cl$, gave **7a** (eluent: CH_2Cl_2/Et_2O 80:20). Yield: 69%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.37 (s, 3H, CH_2OMe), 3.76 (s, 3H, OMe), 5.15 (s, 2H, CH_2), 6.88 (d, 1H, J=5.5 Hz, H_5), 7.84 (d, 1H, J=5.5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 57.0 (CH_2O*Me*), 61.1 (OMe), 94.7 (CH_2), 111.1 (C_5), 117.3 (C_2), 146.6 (C_3), 147.4 (C_6), 155.8 (C_4); IR (KBr) ν 2933, 2829, 1566, 1474, 1382, 1281, 1154, 1089, 975 cm^{-1}. Anal. calcd for $C_8H_{10}INO_3$ (295.08): C, 32.56; H, 3.42; N, 4.75. Found: C, 32.77; H, 3.20; N, 4.73%.

4.3.3. 2-Iodo-3,4-dimethoxypyridine (7b). The general procedure 2, starting from **5** and using MeI, gave **7b** (eluent: CH_2Cl_2/Et_2O 80:20). Yield: 71%; mp 89–90°C (lit.[6] 90°C).

4.4. General procedure 3: iodine–lithium exchange of 2-iodopyridines (3a, 6)

At −75°C, the required 2-iodopyridine (2.0 mmol) was added to a solution of BuLi (4.0 mmol) in hexane (1.6 mL) and THF (10 mL). After 15 min at −75°C, Bu_3SnCl (0.60 mL, 2.0 mmol) was added at −75°C with subsequent warming at rt.

4.4.1. Tributyl-3-methoxymethoxypyridine-2-stannane (8). The general procedure 3, starting from **3a**, gave **8** (neutral alumina instead of silica gel, eluent: petroleum ether/CH_2Cl_2 50:50). Yield: 68%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 9H, J=7.2 Hz, Me), 1.06 (m, 6H, CH_2), 1.25 (m, 6H, CH_2), 1.51 (m, 6H, CH_2), 3.39 (s, 3H, OMe), 5.09 (s, 2H, CH_2), 7.00 (dd, 1H, J=7.7, 4.6 Hz, H_5), 7.16 (dd, 1H, J=7.7, 1.2 Hz, H_4), 8.34 (dd, 1H, J=4.6, 1.2 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 10.4 (3Me), 14.1 (3CH_2), 27.7 (3CH_2), 29.6 (3CH_2), 56.4 (OMe), 94.6 (CH_2), 117.7 (C_4), 122.7 (C_5), 144.8 (C_6), 159.0 (C_3), 164.7 (C_2); IR (KBr) ν 3436, 2955, 2928, 1412, 1397, 1252, 1154, 1063, 994, 796 cm^{-1}. Anal. calcd for $C_{19}H_{35}NO_2Sn$ (428.21): C, 53.29; H, 8.24; N, 3.27. Found: C, 52.98; H, 8.15; N, 3.03%.

4.4.2. Tributyl-4-methoxy-3-methoxymethoxypyridine-2-stannane (9). The general procedure 3, starting from **6**, gave **9** (neutral alumina instead of silica gel, eluent: CH_2Cl_2/Et_3N 90:10). Yield: 65%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 9H, J=7.3 Hz, Me), 1.14 (m, 6H, CH_2), 1.32 (m, 6H, CH_2), 1.56 (m, 6H, CH_2), 3.55 (s, 3H, OMe), 3.87 (s, 3H, OMe), 5.10 (s, 2H, CH_2), 6.72 (d, 1H, J=5.4 Hz, H_5), 8.41 (d, 1H, J=5.4 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 10.7 (3Me), 14.1 (3 CH_2), 27.7 (3CH_2), 29.6 (3CH_2), 55.7 (CH_2O*Me*), 58.0 (OMe), 99.2 (CH_2), 106.7 (C_5), 148.1 (C_3), 148.3 (C_6), 156.2 (C_4), 167.4 (C_2); IR (KBr) ν 2956, 2923, 1565, 1462, 1376, 1289, 1154, 1073, 961, 673 cm^{-1}. Anal. calcd for $C_{20}H_{37}NO_3Sn$ (458.23): C, 52.42; H, 8.14; N, 3.06. Found: C, 52.33; H, 8.15; N, 2.91%.

4.5. General procedure 4: cross-coupling from 2-lithiopyridines

After 15 min at −75°C, an anhydrous solution of $ZnCl_2$ (0.82 g, 6.0 mmol) in THF (20 mL) was added to the required 2-lithiopyridine (2.0 mmol) at the same temperature. The reaction mixture was then warmed to rt. After the addition of the required 2-halopyridine (4.0 mmol) and $Pd(PPh_3)_4$ (69 mg, 60 μmol), the mixture was refluxed for 20 h, cooled and evaporated to dryness. The residue was dissolved in conc. NH_4OH (20 mL) and CH_2Cl_2 (50 mL) containing EDTA (3.7 g, 10 mmol). The mixture was refluxed for 1 h.

4.5.1. 3-Hydroxy-2,2′-bipyridine (10). The general procedure 4, starting from **3a** and 2-bromopyridine gave 32% of **10** (eluent: CH_2Cl_2/Et_2O 90:10); mp 91–93°C (lit.[15] 92°C); ^{13}C NMR ($CDCl_3$) δ 121.1 ($C_{5'}$), 123.3 ($C_{3'}$), 125.0 and 126.1 (C_4 and C_5), 137.1 (C_3), 138.2 ($C_{4'}$), 140.2 (C_6), 145.6 ($C_{6'}$), 156.9 (C_2), 158.5 ($C_{2'}$).

4.5.2. 4,4′-Dihydroxy-3,3′-dimethoxy-2,2′-bipyridine (1b). The general procedure 4, starting from **7a** and using **7a** (halopyridine), followed by subsequent treatment of the crude compound (eluent: CH_2Cl_2/MeOH 50:50) in a 50:50 mixture (20 mL) of aqueous 10% HCl and THF at 50°C for 7 h, gave 60% of **1b** (eluent: CH_2Cl_2/MeOH 90:10); mp 151°C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 6H, 2OMe), 6.74 (d, J=5.8 Hz, 2H, $H_{5,5'}$), 7.74 (d, J=5.8 Hz, 2H, $H_{6,6'}$), 8.50 (s, 2H, OH); ^{13}C NMR (DMSO-d_6) δ 60.1 (2OMe), 113.8 ($C_{5,5'}$), 145.6 ($C_{3,3'}$), 146.7 ($C_{6,6'}$), 153.8 ($C_{2,2'}$), 158.0 ($C_{4,4'}$); IR (KBr) ν 2926, 2824, 1609, 1505, 1382, 1318, 1208, 991, 898 cm^{-1}. Anal. calcd for $C_{12}H_{12}N_2O_4$ (248.24): C, 58.06; H, 4.87; N, 11.28. Found: C, 57.82; H, 4.83; N, 11.09%.

4.5.3. 3,3′,4,4′-Tetramethoxy-2,2′-bipyridine (tetramethylorelline) (1d). The general procedure 4, starting from **7b** and using **7b** (halopyridine), gave 59% of **1d** (eluent: $CHCl_3$/MeOH 90:10); mp 186°C (lit.[6] 186–187°C).

4.6. General procedure 5: cross-coupling from tributylpyridine-2-stannanes 8–9

$Pd(PPh_3)_4$ (0.12 g, 0.10 mmol) and CuBr (20 mg, 0.14 mmol) were added to a solution of the required stannane (2.0 mmol) and 2-halopyridine (2.0 mmol) in dioxane (20 mL) at rt. The mixture was refluxed for 15 h, cooled and evaporated to dryness. The residue was dissolved in conc. NH_4OH (20 mL). The compound was then dissolved in Et_2O (50 mL) and treated with aqueous 10% HCl (25 mL). The mixture was stirred at rt for 15 h and neutralized to pH 5 with $NaHCO_3$.

4.6.1. 3-Hydroxy-2,2′-bipyridine (10). The general procedure 5, starting from **8** and 2-bromopyridine, gave crude 3-methoxymethoxy-2,2′-bipyridine (neutral alumina, eluent: CH_2Cl_2/MeOH 95:5); viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 3H, OMe), 5.14 (s, 2H, CH_2), 7.22 (m, 2H, $H_{5,5'}$), 7.52 (dd, J=8.4, 1.3 Hz, 1H, H_4), 7.70 (td, J=7.4,

1.7 Hz, 1H, $H_{4'}$), 7.77 (d, J=7.4 Hz, 1H, $H_{3'}$), 8.37 (dd, J=4.6, 1.2 Hz, 1H, H_6), 8.71 (m, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 56.6 (OMe), 95.4 (CH_2), 123.1 ($C_{5'}$), 123.9 ($C_{3'}$), 124.4 and 125.1 ($C_{4\text{ and }5}$), 136.2 ($C_{4'}$), 143.5 ($C_{6'}$), 148.1 (C_3), 149.9 (C_6), 151.9 (C_2), 155.9 ($C_{2'}$). The subsequent cleavage following the general procedure afforded 74% of **10**.

4.6.2. 3,3′-Dihydroxy-2,2′-bipyridine (11). The general procedure 5, starting from **8** and using **3a** (halopyridine), gave crude 3,3′-bis(methoxymethoxy)-2,2′-bipyridine (neutral alumina, eluent: CH_2Cl_2/MeOH 95:5); viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 6H, 2 OMe), 5.03 (s, 4H, $2CH_2$), 7.22 (dd, J=8.3, 4.5 Hz, 2H, $H_{5,5'}$), 7.50 (dd, J=8.3, 1.1 Hz, 2H, $H_{4,4'}$), 8.31 (dd, J=4.5, 1.1 Hz, 2H, $H_{6,6'}$); ^{13}C NMR ($CDCl_3$) δ 56.2 (2OMe), 95.3 (2 CH_2), 122.9 ($C_{4,4'}$), 124.2 ($C_{5,5'}$), 143.1 ($C_{6,6'}$), 147.6 ($C_{3,3'}$), 152.2 ($C_{2,2'}$). The subsequent cleavage of the crude compound following the general procedure afforded 91% of **11**; mp 188–189°C (lit.[4] 188–190°C).

4.6.3. 3,3′-Dihydroxy-4,4′-dimethoxy-2,2′-bipyridine (1c). The general procedure 5, starting from **9** and using **6** (halopyridine), gave crude 4,4′-dimethoxy-3,3′-bis(methoxymethoxy)-2,2′-bipyridine (neutral alumina, eluent: CH_2Cl_2/MeOH 80:20); viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 6H, 2 CH_2OMe), 3.87 (s, 6H, 2OMe), 4.89 (s, 4H, $2CH_2$), 6.83 (d, J=5.5 Hz, 2H, $H_{5,5'}$), 8.31 (d, J=5.5 Hz, 2H, $H_{6,6'}$); ^{13}C NMR ($CDCl_3$) δ 56.0 ($2CH_2O$*Me*), 56.9 (2OMe), 98.8 ($2CH_2$), 107.6 ($C_{5,5'}$), 141.2 ($C_{3,3'}$), 146.4 ($C_{6,6'}$), 151.4 ($C_{2,2'}$), 159.0 ($C_{4,4'}$). The subsequent cleavage of the crude compound following the general procedure afforded 74% of **1c**; mp 250–252°C (lit.[4] 252–254°C); the NMR data are in accordance with those of the literature for the presumed compound;[4] IR (KBr) ν 2926, 2572, 1457, 1434, 1264, 1242, 1026, 816 cm^{-1}.

4.7. Orelline (1a)

Compound **1b**, **1c** or **1d** (0.50 mmol) was heated at reflux for 5 h in a 33% solution (8 mL) of HBr in AcOH. An additional amount (4 mL) of the 33% solution of HBr in AcOH was added and the mixture was again heated at reflux for 1 h. After evaporation to dryness, addition of water and neutralization to pH 5, the precipitate was collected and washed with water (10 mL). The crude compound was then sublimated at 200°C under 0.1 mbar to afford pure orelline in, respectively, 71, 70 and 77% yield. The physical and spectral data are analogous to those already described in the literature.[4]

References

1. Antkowiak, W. Z.; Gessner, W. P. *Tetrahedron Lett.* **1979**, *21*, 1931–1934.
2. (a) Wurts, M. L.; Torreblanca, R. A. *Arch. Latinoam. Nutr.* **1983**, *33*, 606–619. (b) Antkowiak, W. Z.; Gessner, W. P. *Stud. Org. Chem. (Amsterdam)* **1985**, *20*, 75–83. (c) Antkowiak, W. Z.; Gessner, W. P. *Experientia* **1985**, *41*, 769–771. (d) Rapior, S.; Delpech, N.; Andary, C.; Huchard, G. *Mycopathologia* **1989**, *108*, 155–161. (e) Laatsch, H.; Matthies, L. *Mycologia* **1991**, *83*, 492–500. (f) Matthies, L.; Laatsch, H. *Experientia* **1991**, *47*, 634–640. (g) Delpech, N.; Rapior, S.; Donnadieu, P.; Cozette, A. P. *Nephrologie* **1991**, *12*, 63–66. (h) Antkowiak, W. Z.; Antkowiak, R.; Wyrzykiewicz, E.; Czerwinski, G. *Heterocycles* **1994**, *39*, 477–484. (i) Hoiland, K. *Nord. J. Bot.* **1994**, *14*, 221–228. (j) Oubrahim, H.; Richard, J.-M.; Cantin-Esnault, D.; Seigle-Murandi, F.; Trécourt, F. *J. Chromatogr., A* **1997**, *758*, 145–157. (k) Oubrahim, H.; Richard, J.-M.; Cantin-Esnault, D. *Free Radical Res.* **1998**, *28*, 497–505. (l) Cantin-Esnault, D.; Oubrahim, H.; Richard, J.-M. *Free Radical Res.* **2000**, *33*, 129–137.
3. (a) Dehmlow, E. V.; Schulz, H.-J. *Tetrahedron Lett.* **1985**, *26*, 4903–4906. (b) Dehmlow, E. V.; Schulz, H.-J. *Liebigs Ann. Chem.* **1987**, 857–861.
4. Tiecco, M.; Tingoli, M.; Testaferri, L.; Chianelli, D.; Wenkert, E. *Tetrahedron* **1986**, *42*, 1475–1485.
5. Hasseberg, H.-A.; Gerlach, H. *Helv. Chim. Acta* **1988**, *71*, 957–963.
6. Trécourt, F.; Mallet, M.; Mongin, O.; Gervais, B.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 8373–8380.
7. Koch, V.; Schnatterer, S. *Synthesis* **1990**, 497–498.
8. (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1992**, *52*, 187–304. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090.
9. (a) Green, K. *J. Org. Chem.* **1991**, *56*, 4325–4326. (b) Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1589–1594.
10. As a general paper about reactions of hydroxypyridines and tautomerism, see: Boga, C.; Corradi Bonamartini, A.; Forlani, L.; Modarelli, V.; Righi, L.; Sgarabotto, P.; Todesco, P. E. *Eur. J. Org. Chem.* **2001**, 1175–1182.
11. Trécourt, F.; Gervais, B.; Mallet, M.; Quéguiner, G. *J. Org. Chem.* **1996**, *61*, 1673–1676.
12. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
13. Li, D.; Zhao, B.; LaVoie, E. J. *J. Org. Chem.* **2000**, *65*, 2802–2805.
14. Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, 151.
15. Siemanowski, W.; Witzel, H. *Liebigs Ann. Chem.* **1984**, 1731–1739.
16. Baker, B. R.; McEvoy, F. J. *J. Org. Chem.* **1955**, *20*, 118–135.