Tetrahedron Vol. 49, No. 37, pp. 8373-8380, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

New Synthesis of Orelline by Metalation of Methoxypyridines

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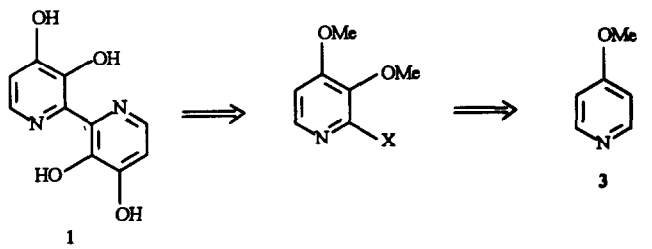
(*Received in Belgium* 23 *April* 1993; *accepted* 1 *July* 1993)

Key Words: Alkaloids; Alkoxypyridines; Coupling; Metalation; Orelline.

Abstract: **A new total synthesis in five steps of the alkaloid Orelline is reported. The methodology involves metalation of methoxypyridines to afford 2-halo-3,4-dimethoxypyridine on which an homocoupling reaction is performed to build the 2,2'-bipyridyl stucture of the alkaloid.**

Orelline (1) is one the main three substances present in the poisonous mushroom *Cortinarius Orellanus* . Its structure has been elucidated by Antkowiak and Gessner.[1] In the previous syntheses, described by Dehmlow and Schulz [2] (8 steps , 1.4 % yield), Tiecco *et al.* [3] (8 steps, 4.4 % yield) and Hasseberg and Gerlach [4] (5 steps, 4.8 % yield) , the 2,2'- bipyridyl structure was obtained by an homocoupling reaction on 2-halo pyridine derivatives (the halogen being introduced by direct halogenation).

We tried to introduce the halogen at C2 by a regioselective metalation [5] of a 3,4-disubstituted pyridine. The 3,4-dimethoxypyridine (**2**) key molecule [6] was prepared by an original metalation of 4-methoxypyridine (**3**).[7] The total yield of the synthesis of Orelline (**1**) was so improved.(scheme 1)



1 3

scheme 1

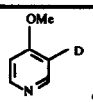
Discussion Section

Our laboratory team know-how in the metalation field [5] allowed us to investigate a new synthesis of Orelline (**1**) using this reaction on substituted pyridines. The retrosynthetic scheme 1 shows that 3,4-dimethoxy-

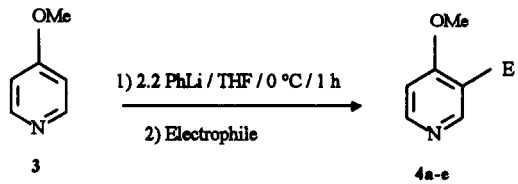
2-substituted pyridines are needed as intermediates. The 2,2'-bipyridyl structure could be obtained using an homocoupling reaction with a bromo or a iodo group at C2, here introduced by metalation.
We first describe the metalation conditions of 4-methoxypyridine, then these of 3,4-dimethoxypyridine (**2**), which was also itself prepared via the metalation of 4-methoxypyridine (**3**).

This new synthetic pathway for the synthesis of 3,4-dimethoxypyridine (**2**) required only 2 steps with an overall yield of 42% starting from 4-methoxypyridine (**3**). [8] In the first step, metalation of **3** occurred at C3 as previously described by Comins *et al.* ;[7] these authors used 1.3 eq. of mesityllithium in THF at - 23°C during 3h. In our laboratory, Mallet [9] proved that the more common phenyllithium was a metalation reagent as efficient as mesityllithium, especially for the metalation of alkoxypyridines. As shown in Table 1, the best metalation conditions were 2.2 eq. of phenyllithium in THF at 0°C during 1 h.; the reaction mixture was hydrolysed by DCl / D_2O in THF.

Table 1 . Metalation Conditions of 4-Methoxypyridine.

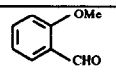
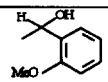
Equivalents of phenyllithium	metalation time (in hours)	 **4a**
1.2	0.5	80%
1.2	1	85%
2.2	1	98%

The 3-lithio-4-methoxypyridine was then quenched by different electrophiles with quite good yields as shown in Table 2.



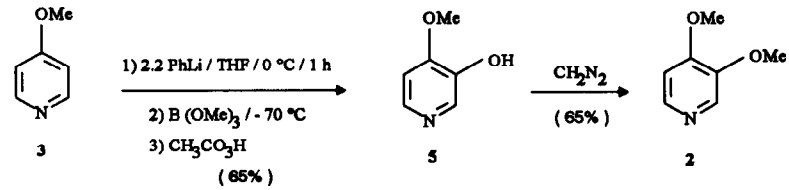
scheme 2

Table 2 . Metalation of 4-Methoxypyridine.

Electrophile	E	Yield (%)
PhCHO	**4b** - CH(OH)Ph	90
I_2	**4c** - I	76
	 **4d**	89
BrCN	**4e** - Br	67

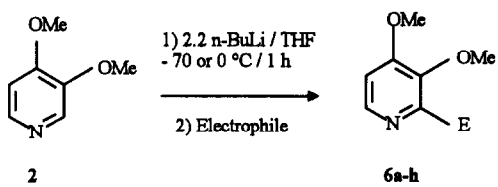
The indroduction of a methoxy group at C3 requires the synthesis of 3-hydroxy-4-methoxypyridine (**5**). Different procedures were tested to prepare this compound starting from 3-lithio-4-methoxypyridine. The use of MoO_5 / pyridine / HMPA complex [10], as well as oxygen [11] gave low yields (respectively 25% and 29%). The best result was obtained with trimethylborate at low temperature followed in situ by the reaction of peracetic acid;[12] 3-hydroxy-4-methoxypyridine (**5**) was thus synthesized with 65% yield.
In the second step the O-methylation of **5** is not easy to realise: the reaction of methyl iodide in basic media failed. Several methylation conditions were tested, but many of these gave only poor yields. The treatment of **5** with diazomethane in presence of a catalytic amount of fluoroboric acid gave successfully 3,4-dimethoxypyridine

(2) with a 65% yield. (scheme 3) It should be noted that 2 could be prepared in a more classical five steps synthesis starting from 3-amino pyridine with 3-fluoro-4-nitro-pyridine N-oxide as an intermediate (overall yield: 22%). [13, 14, 15]



scheme 3

The metalation conditions of 3,4-dimethoxypyridine (2) were then studied. Several attempts with LDA proved us that this base was too weak to perform deprotonation. Very recently, Crowe *et al.* [6] also proved that mesityllithium provided only poor yields. These results clearly showed us that a more stronger metalation reagent was needed. n-Butyllithium was successfully used. A surprisingly single regioselective metalation occurred at C2 without side reactions, such as addition, ring opening... The best metalation conditions required 2.2 equivalents of n-BuLi in THF; unexpectedly the metalation temperature could be either - 70 °C or 0 °C without significant variation of the metalation yield.(Scheme 4 and Table 3)

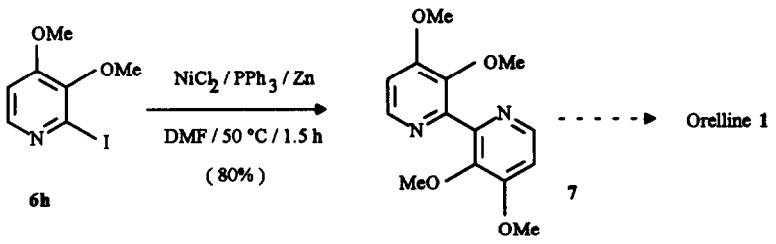


scheme 4

Table 3. Action of Various Electrophiles with 3,4-Dimethoxypyridine.

Electrophile	E	Yield (%)
DCl	**6a** - D	90
$ClSiMe_3$	**6b** - $SiMe_3$	84
CH_3I	**6c** - CH_3	77
	**6d** - CHO	50
HCOOEt	**6d** - CHO	66
DMF	**6d** - CHO	74
PhCHO	**6e** - CH(OH)Ph	45
CH_3CHO	**6f** - $CH(OH)CH_3$	49
$BrCH_2CH_2Br$	**6g** - Br	76
I_2	**6h** - I	82

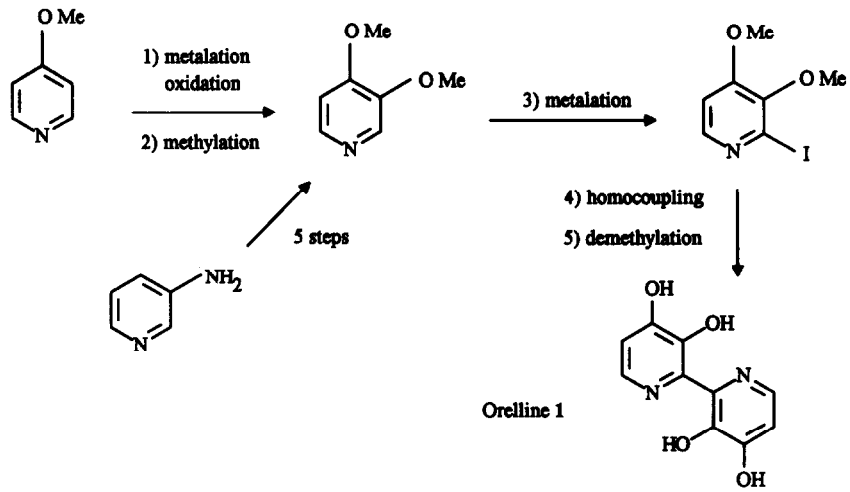
For the synthesis of the target molecule, 2-iodo-3,4-dimethoxypyridine (**6h**) was used. The nickel-phosphine complex-mediated homocoupling of **6h** according to the general procedure described by Tiecco *et al.* [3, 16] gave 3,3',4,4'- tetramethoxy-2,2'- bipyridyl (7) with an excellent yield of 80%. The last step , which is the demethylation of compound 7, was already described by Dehmlow *et al.* [2] (cleavage reagent: HBr / AcOH; yield: 46%) and Tiecco *et al.* [3] (cleavage reagent: HBr in sealed tube; yield: 60%)



scheme 5

In the previous syntheses, Orelline (1) was prepared in 8 steps from 3-amino pyridine with 1.4% yield by Dehmlow and Schulz , [2] in 8 steps with 4.4% yield by Tiecco *et al.* [3] and in 5 steps with 4.8% yield by Hasseberg and Gerlach [4] both from 3-hydroxy pyridine.

In conclusion, we considerably improved the overall yield (16.6 %) of the total synthesis of Orelline 1. Starting from 4-methoxypyridine (5 steps), we successfully used twice the metalation reaction on substituted pyridines together with an homocoupling reaction. (scheme 6) Note that 3,4-dimethoxypyridine could be also prepared from 3-amino pyridine; in this case, the total synthesis of Orelline (1) required 8 steps with an overall yield of 8.4 %.



scheme 6

Experimental Section

IR spectra were recorded on a Beckman IR 4250 or on a Perkin Elmer FT IR 205 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with a 200 MHz Brucker AM 200 spectrometer. Microanalyses were obtained from a Carlo Erba 1106 apparatus. Melting points were obtained on a Kofler apparatus and are uncorrected.

Tetrahydrofuran (THF) was dried over benzophenone-sodium complex and distilled prior to use. Commercial n-butyllithium and phenyllithium were employed as received. Phenyllithium was titrated periodically against 2-butanol. Metalations were carried out under dry argon .

Synthesis of 3-Substituted 4-Methoxypyridines.

General Procedure. Phenyllithium (6.6 mmol) was added to THF (20 mL) at -70°C through a septum inlet. 4-Methoxypyridine (3 mmol, in 5 mL THF) was added slowly at -70°C and the mixture was stirred for 1 h at 0°C, cooled to -70°C, and the electrophilic reagent (7.5 mmol) was added as mentioned in the product description.

General Treatment of the reaction mixture. After the electrophile had reacted, the solution was hydrolysed at -70°C by a large excess of HCl / EtOH / THF, warmed to room temperature, treated with 10 mL of water and with K_2CO_3, and then extracted several times with Et_2O or with CH_2Cl_2. The organic layer was dried over magnesium sulfate ($MgSO_4$) and solvents were removed under reduced pressure to afford the crude product, which was purified by column chromatography (silica gel).

3-Deuterio-4-methoxypyridine (4a). Compound **4a** was prepared by action of DCl / D_2O in THF at -70°C. Eluent: AcOEt. Deuterium incorporation: 98 % (determined from the ^1H NMR integration values). ^1H NMR δ 3.79 (s, 3H, OCH_3), 6.76 (d, 1H, *J= 5.9 Hz*, H5), 8.38 (d, 1H, *J= 5.9 Hz*, H6), 8.38 (s, 1H, H2). ^{13}C NMR δ 54.8,109.7, 150.8, 165.3.

1-(4-Methoxy-3-pyridyl) phenylmethanol (4b). Benzaldehyde in THF was added at -70°C with stirring for 2 h. Eluent: AcOEt / MeOH 95:5. Yield: 90 %; m.p. 174°C, lit (17) 172°C, lit (7a) 169.5-170.5°C. ^1H NMR δ 3.82 (s, 3H, OCH_3), 6.05 (s, 1H, CH), 6.74 (d, 1H, *J= 5.7 Hz*, H5), 7.22-7.41 (m, 5H, phenyl), 8.34 (d, 1H, *J= 5.7 Hz*, H6), 8.45 (s, 1H, H2). ^{13}C NMR δ 55.2, 70.0, 105.9, 126.4, 127.4, 127.6, 128.2, 142.5, 148.4, 150.5, 162.5. IR (KBr): 3082, 2844, 1594, 1494, 1442, 1300, 1190, 1032, 862, 831, 803, 701 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.49; H, 5.96; N, 6.54.

3-Iodo-4-methoxypyridine (4c). [7b] Iodine in THF was introduced slowly at -70°C, with stirring for 1 h. Before extraction, the solution was treated with sodium thiosulfate until bleaching. Eluent: CH_2Cl_2 / AcOEt 90:10. Yield: 76 %; m.p. 71°C. ^1H NMR δ 3.86 (s, 3H, OCH_3), 6.69 (d, 1H, *J= 5.6 Hz*, H5), 8.31 (d, 1H, *J=5.6 Hz*, H6), 8.67 (s, 1H, H2). ^{13}C NMR δ 55.9, 84.8, 106.8, 150.6, 157.6, 163.8. IR (KBr): 3448, 1570, 1474, 1434, 1400, 1294, 1184, 1082, 1016, 824 cm^{-1}. Anal. Calcd for C_6H_6INO: C, 30.66; H, 2.57; N, 5.96. Found: C, 30.70; H, 2.49; N, 5.79.

1-(4-Methoxy-3-pyridyl)-1-(2'-methoxyphenyl) methanol (4d). o-Anisaldehyde in THF was added at -70°C with stirring for 2 h. Eluent: AcOEt / MeOH 95:5. Yield: 89 %; m.p. 155°C. ^1H NMR δ 3.70 (s, 1H, OH), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.28 (s, 1H, CH), 6.78 (d, 1H, *J= 5.7 Hz*, H5), 6.87-6.99 (m, 2H, phenyl), 7.24-7.32 (m, 2H, phenyl), 8.40 (s, 1H, H2), 8.42 (d, 1H, *J=5.7 Hz*, H6). ^{13}C NMR δ 55.3, 55.4, 66.5, 105.9, 110.6, 120.6, 126.5, 127.7, 128.8, 130.0, 149.2, 150.5, 156.7, 162.8. IR (KBr): 3110, 2841, 2721, 1595, 1494, 1303, 1178, 1029, 872, 810, 753 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.79; H, 6.32; N, 5.65.

3-Bromo-4-methoxypyridine (4e). [18] A solution of BrCN in THF was introduced at -70°C, with stirring for 2 h, then the mixture was treated with H_2O / EtOH / THF. Eluent: CH_2Cl_2 / AcOEt 90:10. Yield: 67 %. ^1H NMR δ 3.93 (s, 3H, OCH_3), 6.78 (d, 1H, *J= 6 Hz*, H5), 8.36 (d, 1H, *J= 6 Hz*, H6), 8.53 (s, 1H, H2). Anal. Calcd for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45. Found: C, 38.04; H, 3.01; N, 7.34.

3-Hydroxy-4-methoxypyridine (5). Trimethylborate was added slowly at -70°C with stirring for 3 h. A solution of peracetic acid (32 wt % in dilute acetic acid) was then added and the mixture was warmed to 0°C under stirring for 1 h, and then cooled to -15 °C, whereupon an aqueous solution of sodium dithionite was poured dropwise. Eluent: CH_2Cl_2 / MeOH 90:10. Yield: 65 %; m.p. 143-144°C. ^1H NMR δ 3.88 (s, 3H, OCH_3), 6.80 (d, 1H, *J= 5.4 Hz*, H5), 7.96 (d, 1H, *J= 5.4 Hz*, H6), 8.10 (s, 1H, H2), 10.50 (s, 1H, OH). ^{13}C NMR δ 55.5, 106.7, 135.3, 140.6, 144.9, 154.9. IR (KBr): 3388, 3298, 2441, 2104, 1707, 1597, 1501, 1442, 1383, 1302, 1162, 1072, 1015, 813, 770 cm^{-1}. Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.50; H, 5.71; N, 10.94.

3,4-Dimethoxypyridine (2). [2b, 6, 15] To a stirred solution of solution of **5** (0.225 g, 1.8 mmol) in 50 mL of dichloromethane was added 1 mL of a solution of concentrated HBF_4 in ether (0.15 mL in 25 mL). The mixture was cooled in ice, and an ethereal solution of diazomethane (0.3 g in 30 mL) was added dropwise. After 1 h at room temperature, solvents were removed and the crude product was purified by column chromatography on silica gel (eluent: CH_2Cl_2 / MeOH 95:5) to afford pure **2**. Yield: 65 %. ^1H NMR δ 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.81 (d, 1H, *J= 5.4 Hz*, H5), 8.15 (s, 1H, H2), 8.18 (d, 1H, *J= 5.4 Hz*, H6). ^{13}C NMR δ 54.9, 55.8, 105.7, 132.9, 143.5, 145.0, 154.3. IR (neat): 3000, 2960, 2940, 2840, 1590, 1520, 1460, 1440, 1300, 1240 cm^{-1}. Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.00; H, 6.96; N, 10.25.

Synthesis of 2-Substituted 3,4-Dimethoxypyridines.

General Procedure. n-Butyllithium (4.4 mmol) was added to THF (20 mL) at -70°C through a septum inlet. 3,4-Dimethoxypyridine (2) (2 mmol in 5 mL THF) was added at -70°C. The mixture was stirred for 1 h at this temperature, and the electrophilic reagent (4.4 mmol) was added as mentioned in the product description, and worked up as specified in the general treatment of the reaction mixture of the metalation of the 4-methoxypyridine.

2-Deuterio-3,4-dimethoxypyridine (6a). Compound **6a** was prepared by action of DCl / D_2O in THF at 0°C, and purified by distillation. B.p. 90°C (4 mbar). Yield: 90 %. ^1H NMR δ 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.80 (d, 1H, *J= 5.4 Hz*, H5), 8.18 (d, 1H, *J= 5.4 Hz*, H6).

3,4-Dimethoxy-2-(trimethylsilyl) pyridine (6b). Chlorotrimethylsilane (in THF) was added at 0°C with stirring for 1.5 h. Yield: 84 %. ^1H NMR δ 0.36 (s, 9H, $SiMe_3$), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.86 (d, 1H, J= 5.5 Hz, H5), 8.47 (d, 1H, J= 5.5 Hz, H6). IR (neat): 2960, 2900, 2840, 1570, 1470, 1400, 1300, 1250, 1230, 840 cm^{-1} . Anal. Calcd for $C_{10}H_{17}NO_2Si$: C, 56.83; H, 8.11; N, 6.63. Found: C, 57.28; H, 8.22; N, 7.49.

3,4-Dimethoxy-2-methylpyridine (6c). Methyl iodide was added at -70°C with stirring for 2 h. Eluent: AcOEt / Hexane. Yield: 77 %. ^1H NMR δ 2.41 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.64

(d, 1H, *J= 5.6 Hz*, H5), 8.06 (d, 1H, *J= 5.6 Hz*, H6). ^{13}C NMR δ 18.58, 55.31, 60.04, 105.60, 143.24, 145.16, 152.50, 158.13. IR (neat): 2941, 1588, 1488, 1448, 1421, 1297, 1226, 1118, 1081, 1005, 826, 811cm^{-1}.Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.97; H, 7.32; N, 9.05.

3,4-Dimethoxy-2-formylpyridine (6d). [6] When HCOOEt (a solution in THF) was used (-70°C for 2 h), the yield was 66 %. When N-formylpiperidine (a solution in THF) was used (-40°C for 2 h), the yield was 50 %. When DMF (a solution in THF) was used (-50°C for 2 h), the yield was 74 %. In these three cases, the mixture was hydrolysed at -70°C with a large excess of HCl / EtOH / THF, and the crude product was purified by flash chromatography (eluent: AcOEt / EtOH 98:2). M.p. 62°C. ^1H NMR δ 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.99 (d, 1H, *J= 5.3 Hz*, H5), 8.39 (d, 1H, *J= 5.3 Hz*, H6), 10.31 (s, 1H, CHO). ^{13}C NMR δ 55.60, 61.52, 110.54, 144.45, 146.14, 148.81, 159.41, 189.39. IR (KBr): 2940, 2840, 1710, 1575, 1490, 1440, 1420, 1380, 1310, 1250 cm^{-1}. Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.33; H, 5.64; N, 8.06.

1-(3,4-Dimethoxy-2-pyridyl) phenylmethanol (6e). Benzaldehyde in THF was added at -70°C with stirring for 2 h. The product was purified by recrystallisation from acetone. Yield: 45%; m.p. 75 °C. ^1H NMR δ 3.53 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.90 (s, 1H, OH), 5.90 (s, 1H, CH), 6.80 (d, 1H, *J= 6.0 Hz*, H5), 7.43 (m, 5H, phenyl), 8.20 (d, 1H, *J= 6.0 Hz*, H6). IR (KBr): 3020, 2980, 2840, 1585, 1480, 1300, 1285 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.26; H, 6.17; N, 5.53.

1-(3,4-Dimethoxy-2-pyridyl) ethanol (6f). Acetaldehyde (10 mmol) was added at -70°C with stirring for 2 h. Eluent: Et_2O / EtOH 97:3. Yield: 49 %; m.p. 66°C. ^1H NMR δ 1.39 (d, 3H, *J= 6.4 Hz*, CH_3), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.25 (s, 1H, OH), 5.03 (q, 1H, *J= 6.4 Hz*, CH), 6.76 (d, 1H, *J= 5.5 Hz*, H5), 8.15 (d, 1H, *J= 5.5 Hz*, H6). ^{13}C NMR δ 23.7, 55.4, 60.3, 64.5, 106.7, 141.2, 144.3, 156.0, 158.2. IR (KBr): 3410, 2980, 2960, 2920, 2840, 1590, 1490, 1445, 1420, 1390, 1360, 1300, 1220 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64. Found: C, 59.03; H, 7.51; N, 7.34.

2-Bromo-3,4-dimethoxypyridine (6g). [3] 1,2-Dibromoethane in THF was added at -70°C with stirring for 3 h. Eluent: Et_2O / Hexane 80:20. Yield: 76%; m.p. 70°C. ^1H NMR δ 3.87 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.86 (d, 1H, *J=5.5 Hz*, H5), 7.98 (d, 1H, *J=5.5 Hz*, H6). ^{13}C NMR δ 55.8, 60.1, 107.5, 136.8, 142.4, 145.3, 159.1. IR (KBr): 2950, 2850, 1580, 1560, 1490, 1440, 1390, 1300, 1260 cm^{-1}. Anal. Calcd for $C_7H_8BrNO_2$: C, 38.56; H, 3.70; N, 6.42. Found: C, 38.82; H, 3.83; N, 6.47.

3,4-Dimethoxy-2-iodopyridine (6h). Iodine in THF was introduced slowly at -70°C, with stirring for 0.75 h. Before extraction, the solution was treated with sodium thiosulfate until bleaching. The product was purified by recrystallisation from hexane. Yield: 82 %; m.p. 90°C. ^1H NMR δ 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.76 (d, 1H, *J= 5.5 Hz*, H5), 7.97 (d, 1H, *J=5.5 Hz*, H6). ^{13}C NMR δ 55.8, 60.5, 107.8, 116.5, 145.8, 147.1, 157.8. IR (KBr): 2960, 2920, 2840, 1620, 1480, 1420, 1380, 1300, 1250 cm^{-1}. Anal. Calcd for $C_7H_8INO_2$: C, 31.72; H, 3.04; N, 5.28. Found: C, 31.87; H, 2.94; N, 5.26.

3,3',4,4'-Tetramethoxy-2,2'-bipyridyl (Tetramethylorelline) (7). To a mixture of $NiCl_2$, 6 H_2O (0.595 g, 2.5 mmol) and triphenylphosphine (2.62 g, 10 mmol) in 15 mL of DMF under argon at 50°C, zinc powder (0.165 g, 2.5 mmol) was added, with stirring for 1 h. 2-Iodo-3,4-dimethoxypyridine (0.640 g, 2.4 mmol) was then added with stirring 1.5 h. The mixture is treated with ammonia, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue thus obtained was purified by column chromatography on silica gel (eluent: $CHCl_3$ / MeOH 90:10) to afford 7 (0.268g, 80 %) as a white crystalline powder. M.p. 186-187°C, lit(2b) 187-9°C, lit(3) 186-7°C. ^1H NMR δ 3.65 (s, 6H, 2 OCH_3), 3.87 (s, 6H, 2 OCH_3), 6.83 (d, 2H, *J= 5.52 Hz*, H5+H5'), 8.26 (d, 2H, *J=5.52 Hz*, H6+H6'). ^{13}C NMR δ 55.5 (2 OCH_3), 60.9 (2 OCH_3), 107.3 (C5+C5'), 143.8 (C3+C3'),145.7 (C6+C6'),150.6 (C2+C2'), 158.6 (C4+C4'). IR (KBr) : 3020, 2960, 2940, 2840, 1570, 1485, 1465, 1430, 1400, 1295, 1250, 1230, 1200 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.00; H, 5.86; N, 9.92.

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