Synthesis of Substituted 8-Methoxyquinolines by Regioselective Bromine–Lithium Exchange of 5,7-Dihalo-8-methoxyquinolines and 7-Bromo-8-methoxyquinoline

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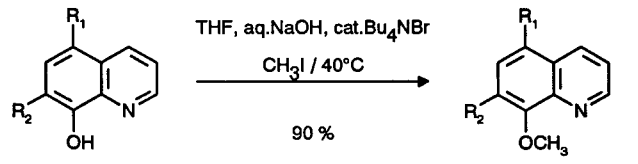
Reaction of phenyllithium with 7-bromo-8-methoxyquinoline, 5,7-dibromo-8-methoxyquinoline and 5,7-diiodo-8-methoxyquinoline has been studied. Thus, bromine–lithium exchange of 7-bromo-8-methoxyquinoline gave the 7-lithio-8-methoxyquinoline which reacted with various electrophiles to afford 7-substituted 8-methoxyquinolines **3a–e**. The same procedure was also applied to 5,7-dibromo-8-methoxyquinoline, which because of the high regioselectivity of the reaction, led to 7-substituted 5-bromo-8-methoxyquinolines **4a–f**; one of them was used for the preparation of a pyridopyranoquinoline.

8-Hydroxyquinoline (oxine) and its halo derivatives on the phenyl ring have found extensive application as analytical reagents, metal extracting agents and corrosion inhibitors because of their ability to form complexes with many metal ions.[1] They are also used as insecticides,[2] bactericides,[3] fungicides,[4] antimalarial agents[5] and more recently as anticancer agents.[6] 8-Alkoxy derivatives have found applications due to their pharmaceutical properties.[7] For these reasons, we have been interested in preparing substituted 8-methoxyquinolines.[8] The 7-bromo-8-hydroxyquinoline **(1a)** and 5,7-dibromo-8-hydroxyquinoline **(1b)** were at first converted to the corresponding methyl ethers.[9,10] Bromine–lithium exchange reaction was first tested with 7-bromo-8-methoxyquinoline **(2a)**. Then, the procedure was extended to 5,7-dibromo-8-methoxyquinoline **(2b)** with a good selectivity and one of the obtained functionalized quinolines was used as key molecule for the synthesis of a pyridopyranoquinoline.

7-Bromo-8-methoxyquinoline **(2a)** and 5,7-dibromo-8-methoxyquinoline **(2b)** were readily prepared from the corresponding substituted 8-hydroxyquinolines **1a, b** by a modification of the Dou's phase-transfer catalyzed *O*-methylation.[11] By this technique, 5,7-diiodo-8-methoxyquinoline **(2c)** could also be prepared from the commercial 5,7-diiodo-8-hydroxyquinoline **(1c)** (Scheme 1).



1a : R_1 = H, R_2 = Br
1b : R_1 = R_2 = Br
1c : R_1 = R_2 = I

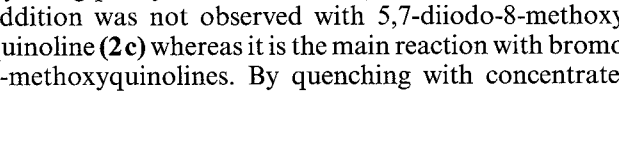
2a : R_1 = H, R_2 = Br
2b : R_1 = R_2 = Br
2c : R_1 = R_2 = I

Scheme 1

The use of alkyllithiums in tetrahydrofuran at −75 °C was not successful with **2a–b** because concurrent nucleophilic addition reaction at the 1–2 bond of the pyridine ring occured.[12] For this reason, the reaction was carried out in diethyl ether with phenyllithium (a two-fold excess was used to improve the yields), which is used either for metalation reactions[13] or halogen–lithium exchanges.[14] Quenching the lithio derivatives with various electrophiles led to 7-substituted 8-methoxyquinolines **3a–e** and regioselectively to 7-substituted 5-bromo-8-methoxyquinolines **4a–f** (Scheme 2). The good regioselectivity observed for **2b** could be due to the good stability of the 7-lithio derivative originating from the *ortho* stabilising effect of the methoxy group.

7-Hydroxy derivatives **3e** and **4d** could also be synthesized by using trimethylborate as an electrophile followed by an in situ oxidation of the boronic intermediate with peracetic acid.[15] Finally, the *O*-methylation[16] of **3e** and **4d** led to the expected 7-methoxy derivatives **3f** and **4g** in excellent yields (Scheme 3).

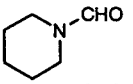
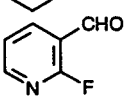
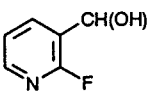
By using phenyllithium in tetrahydrofuran, nucleophilic addition was not observed with 5,7-diiodo-8-methoxyquinoline **(2c)** whereas it is the main reaction with bromo-8-methoxyquinolines. By quenching with concentrated



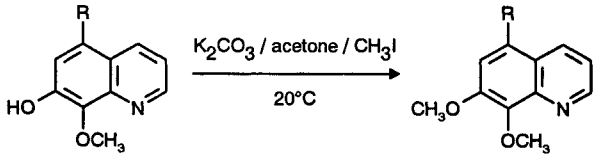
2a : R= H — 63-78 % — **3a-e**
2b : R= Br — 43-56 % — **4a-f**

Scheme 2

Table

Electrophile	E	From 2a (Yield %, Product)	From 2b (Yield %, Product)
HCl / H_2O	H	78, **3a**	56, **4a**
DCl / D_2O	D	76, **3b**	55, **4b**
PhCHO	PhCH(OH)	69, **3c**	54, **4c**
I_2	I	70, **3d**	*a*
$B(OMe)_3/CH_3CO_3H$	OH	63, **3e**	55, **4d**
	CHO	*a*	43, **4e**
		*a*	46, **4f**

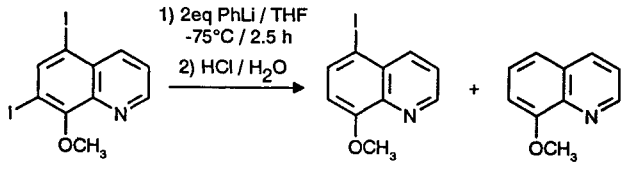
a Compounds have not been synthesized.



3e : R= H 90 % 3f : R= H
4d : R= Br 94 % 4g : R= Br

Scheme 3

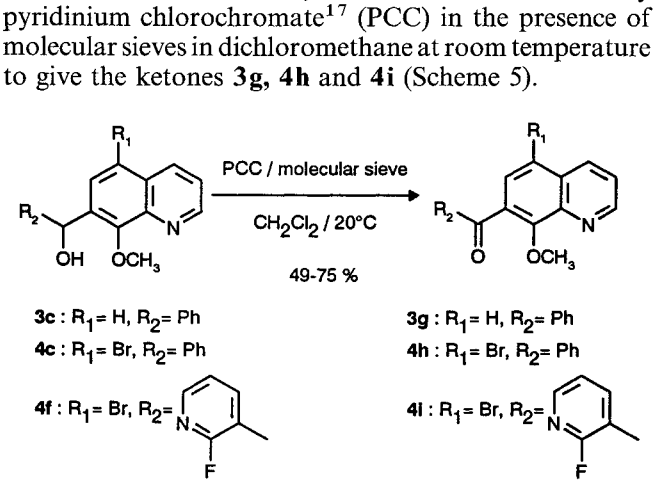
hydrochloric acid, the expected 5-iodo-8-methoxyquinoline (**5**) was obtained along with 8-methoxyquinoline (**3a**). An iodine–lithium exchange faster than the bromine–lithium could explain the formation of **3a** through a 5,7-dilithio intermediate (Scheme 4).



2c 5 3a
27 % 52 %

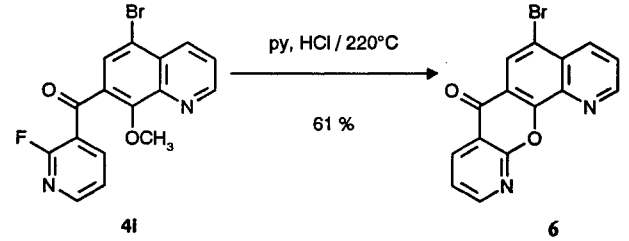
Scheme 4

Oxidation of alcohols **3c, 4c** and **4f** was achieved by pyridinium chlorochromate[17] (PCC) in the presence of molecular sieves in dichloromethane at room temperature to give the ketones **3g, 4h** and **4i** (Scheme 5).



Scheme 5

Xanthone derivatives have potential pharmaceutical properties.[18] Taking advantage of the previously described bromine–lithium exchange of **2b**, cyclization of **4i** with pyridine hydrochloride at its reflux temperature[19] gave 5-bromo-pyrido[3′,2′;8,9]pyrano[3,2-*h*]quinoline (**6**) (Scheme 6).



4i 6

Scheme 6

Melting points were measured on a Kofler apparatus. The NMR spectra were recorded on a Bruker AM 200 spectrometer (^{1}H at 200 MHz and ^{13}C at 50 MHz, with internal standard: TMS in $CDCl_3$ or HMDS in DMSO-d_6). IR spectra were taken on a Beckman IR 4250 spectrometer. Mass spectra were obtained on a JEOL D700 instrument (chemical ionization with ammonia), and elementary analyses were performed on a Carlo Erba apparatus.

Et_2O and THF were distilled from benzophenone/sodium ketyl. The H_2O content of the solvent was estimated to be lower than 45 ppm by the modified Karl Fischer method.[20]

7-Bromo-8-hydroxyquinoline (**1a**)[9] was prepared by the literature method. 2-Fluoro-3-formylpyridine[21] was prepared by metalation of 2-fluoropyridine. Commercial 2 M solution of PhLi in cyclohexane/Et_2O (70:30) was stored and transferred under a dry Ar atmosphere. Other reagents were purchased from Aldrich or Janssen Chemical Companies. Satisfactory microanalyses obtained for all new compounds: C ± 0.31, H ± 0.29, N ± 0.42.

Substituted 8-Methoxyquinolines 2; General Procedure:
The substituted 8-hydroxyquinoline **1** (0.1 mol) was added to a mixture of THF (250 mL), aq NaOH solution (prepared from 15 g NaOH in 30 mL H_2O) and Bu_4NBr (1.5 g). MeI (12.5 mL, 0.2 mol) was added and the resulting mixture was stirred at 40 °C for 20 h. Additional amount of MeI (6.3 mL, 0.1 mol) was added and the red colored mixture was stirred at 40 °C for a further 15 h. Extraction by Et_2O (3 × 200 mL), drying $MgSO_4$ (50 g) and removal of solvent afforded a crude product, which was purified by flash chromatography over silica gel (25 g/1 g).

7-Bromo-8-methoxyquinoline (**2a**); from **1a**; yield: 90% (eluent: CH_2Cl_2/Et_2O, 95:5); mp 79 °C (Lit.[22] mp 80–81 °C; Lit.[23] mp 78 °C).

^{1}H NMR ($CDCl_3$): δ = 4.20 (s, 3 H, OCH_3), 7.41 (d, 1 H, H_5), 7.51 (dd, 1 H, H_3), 7.69 (d, 1 H, H_6), 8.15 (dd, 1 H, H_4), 8.98 (dd, 1 H, H_2); $J_{2,4}$ = 1.8, $J_{2,3}$ = 4.4, $J_{3,4}$ = 8.2, $J_{5,6}$ = 8.4 Hz.

^{13}C NMR ($CDCl_3$): δ = 61.8 (OCH_3), 116.5 (C_7), 121.3 (C_5), 124.0 (C_3), 128.8 (C_b), 130.5 (C_6), 136.0 (C_4), 143.1 (C_a), 150.1 (C_2), 153.3 (C_8).

IR (KBr): ν = 3420, 2930, 1488, 1460, 1360, 1080 cm^{-1}.

5,7-Dibromo-8-methoxyquinoline (**2b**); from **1b**; yield: 90% (eluent: CH_2Cl_2/Et_2O, 80:20); mp 103 °C (Lit.[23] mp 99 °C).

^{1}H NMR ($CDCl_3$): δ = 4.17 (s, 3 H, OCH_3), 7.54 (dd, 1 H, H_3), 8.00 (s, 1 H, H_6), 8.49 (dd, 1 H, H_4), 9.00 (dd, 1 H, H_2); $J_{2,4}$ = 1.6, $J_{2,3}$ = 4.4, $J_{3,4}$ = 8.6 Hz.

^{13}C NMR ($CDCl_3$): δ = 62.3 (OCH_3), 116.4 (C_5), 116.4 (C_7), 122.5 (C_3), 128.1 (C_b), 133.6 (C_6), 136.0 (C_4), 143.7 (C_a), 150.9 (C_2), 153.5 (C_8).

IR (KBr): ν = 2920, 2850, 1735, 1600, 1575, 1490, 1460, 1385, 1370, 1350, 1085 cm^{-1}.

5,7-Diiodo-8-methoxyquinoline (**2c**); from **1c**; yield: 90% (eluent: CH_2Cl_2/Et_2O, 80:20); mp 110 °C (Lit.[24] mp 105–107 °C).

^{1}H NMR ($CDCl_3$): δ = 4.15 (s, 3 H, OCH_3), 7.49 (dd, 1 H, H_3), 8.30 (dd, 1 H, H_4), 8.43 (s, 1 H, H_6), 8.88 (dd, 1 H, H_2); $J_{2,4}$ = 1.5, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.6 Hz.

^{13}C NMR ($CDCl_3$): δ = 62.2 (OCH_3), 91.7–92.3 (C_{5-7}), 123.1 (C_3), 131.2 (C_b), 140.6 (C_4), 142.6 (C_a), 145.0 (C_6), 150.5 (C_2), 157.8 (C_8).

IR (KBr): ν = 3430, 2930, 1560, 1480, 1450, 1360, 1340, 1230, 1080 cm^{-1}.

7-Substituted 8-Methoxyquinolines 3a–e and 5-Bromo-8-Methoxyquinolines 4a–f; General Procedure:
A solution of **2a** or **2b** (3.15 mmol) in Et_2O (20 mL) was added (5 min) to a cold (– 75 °C) solution of PhLi (3.15 mL of a 2 M solution) in Et_2O (30 mL). The resulting mixture was stirred for 2.5 h at – 75 °C before addition of the required electrophile (6.3 mmol) in Et_2O (10 mL). Stirring was continued for 2 h at the same temperature before hydrolysis at – 75 °C by a mixture of conc. HCl (2.5 mL) and THF (7.5 mL) and subsequent addition of H_2O (40 mL) at r.t. Extraction by CH_2Cl_2 (3 × 50 mL), drying ($MgSO_4$)

and removal of solvent afforded a crude product, which was purified by flash chromatography over silica gel (50 g/1 g).

8-Methoxyquinoline (**3a**); from **2a**, electrophile: HCl/H_2O; yield: 78% (eluent: CH_2Cl_2/Et_2O, 95:5); bp 98°C/0.2 mbar (Lit.[25] 167°C/37 mbar).

7-Deuterio-8-methoxyquinoline (**3b**); from **2a**, electrophile: DCl/D_2O; yield: 76% (eluent: CH_2Cl_2/Et_2O, 95:5); bp 98°C/0.2 mbar.

^{1}H NMR ($CDCl_3$): δ = 3.98 (s, 3H, OCH_3), 7.28 (m, 3H, $H_{3,5,6}$), 7.98 (dd, 1H, H_4), 8.85 (dd, 1H, H_2); $J_{2,4}$ = 1.3, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.3 Hz.

^{13}C NMR ($CDCl_3$): δ = 55.3 (OCH_3), 106.7 (t, C_7), 118.6 (C_5), 121.0 (C_3), 126.0 (C_6), 128.7 (C_b), 135.2 (C_4), 139.5 (C_a), 148.5 (C_2), 154.7 (C_8); $J_{7,D}$ = 24 Hz.

1-(8-Methoxy-7-quinolyl)-1-phenylmethanol (**3c**); from **2a**, electrophile: benzaldehyde; yield: 69% (eluent: CH_2Cl_2/Et_2O, 90:10); mp < 50°C.

^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 6.39 (s, 1H, CHOH), 7.3 (m, 8H, $H_{3,5,6}$, Ph), 8.03 (dd, 1H, H_4), 8.81 (dd, 1H, H_2); $J_{2,4}$ = 1.7, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.3, $J_{5,6}$ = 8.5 Hz.

^{13}C NMR ($CDCl_3$): δ = 62.4 (OCH_3), 70.8 (CHOH), 121.0 (C_5), 123.2 (C_3), 125.8 (C_6), 126.3 ($C_{2'}$), 126.3 (C_b), 127.1 ($C_{4'}$), 128.2 ($C_{3'}$), 129.0 (C_7), 136.1 (C_4), 142.3 (C_a), 143.8 ($C_{1'}$), 149.3 (C_2), 152.4 (C_8).

IR (KBr): ν = 3378, 1600, 1499, 1464, 1366, 1310, 1217, 1093, 1037 cm^{-1}.

7-Iodo-8-methoxyquinoline (**3d**); from **2a**, electrophile: iodine; yield: 70% (eluent: CH_2Cl_2/Et_2O, 95:5); mp 95°C (Lit.[22] mp 112–113°C).

^{1}H NMR ($CDCl_3$): δ = 4.12 (s, 3H, OCH_3), 7.25 (d, 1H, H_5), 7.37 (dd, 1H, H_3), 7.58 (d, 1H, H_6), 8.06 (dd, 1H, H_4), 8.87 (dd, 1H, H_2); $J_{2,4}$ = 1.7, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.3, $J_{5,6}$ = 8.7 Hz.

^{13}C NMR ($CDCl_3$): δ = 61.9 (OCH_3), 91.5 (C_7), 121.5 (C_3), 124.5 (C_5), 129.6 (C_b), 135.6–136.1 (C_{4-6}), 142.2 (C_a), 149.8 (C_2), 156.4 (C_8).

IR (KBr): ν = 1581, 1486, 1457, 1356, 1118, 1084, 1038 cm^{-1}.

7-Hydroxy-8-methoxyquinoline (**3e**): The general procedure applied to **2a** using trimethylborate, followed by dropwise addition of 32% peracetic acid in AcOH (1.4 mL), stirring for 30 min at −75°C and for 1 h at 0°C, addition (5 min) of sat. aq $NaHSO_3$ solution (2 mL) and stirring for 30 min at r.t. gave 63% of **3e** (eluent: CH_2Cl_2/Et_2O, 70:30); oil.

^{1}H NMR ($CDCl_3$): δ = 4.11 (s, 3H, OCH_3), 4.4 (s, 1H, OH), 7.20 (dd, 1H, H_3), 7.21 (d, 1H, H_6), 7.44 (d, 1H, H_5), 8.02 (dd, 1H, H_4), 8.81 (dd, 1H, H_2); $J_{2,4}$ = 1.7, $J_{2,3}$ = 4.3, $J_{3,4}$ = 8.2, $J_{5,6}$ = 8.9 Hz.

^{13}C NMR ($CDCl_3$): δ = 62.0 (OCH_3), 118.3–118.6 (C_{5-6}), 123.9 (C_3), 124.0 (C_b), 136.5 (C_4), 139.4 (C_8), 142.3 (C_a), 149.0 (C_7), 149.5 (C_2).

IR (KBr): ν = 2933, 1617, 1501, 1430, 1338, 1199, 1092 cm^{-1}.

5-Bromo-8-methoxyquinoline (**4a**); from **2b**, electrophile: HCl/H_2O; yield: 56% (eluent: CH_2Cl_2/Et_2O, 90:10); mp 86°C (Lit.[26] mp 88°C; Lit.[23] mp 82°C).

^{1}H NMR ($CDCl_3$): δ = 3.93 (s, 3H, OCH_3), 6.71 (d, 1H, H_7), 7.34 (dd, 1H, H_3), 7.51 (d, 1H, H_6), 8.27 (dd, 1H, H_4), 8.81 (dd, 1H, H_2); $J_{2,4}$ = 1.8, $J_{2,3}$ = 4.2, $J_{6,7}$ = 8.5, $J_{3,4}$ = 8.5 Hz.

^{13}C NMR ($CDCl_3$): δ = 55.5 (OCH_3), 107.5 (C_7), 111.1 (C_5), 122.1 (C_3), 127.4 (C_b), 129.4 (C_6), 134.8 (C_4), 140.0 (C_a), 148.9 (C_2), 154.5 (C_8).

IR (KBr): ν = 2920, 2850, 1605, 1585, 1495, 1460, 1355, 1305 cm^{-1}.

5-Bromo-7-deuterio-8-methoxyquinoline (**4b**); from **2b**, electrophile: DCl/D_2O; yield: 55% (eluent: CH_2Cl_2/Et_2O, 90:10); mp 86°C.

^{1}H NMR ($CDCl_3$): δ = 3.93 (s, 3H, OCH_3), 7.34 (dd, 1H, H_3), 7.51 (s, 1H, H_6), 8.27 (dd, 1H, H_4), 8.81 (dd, 1H, H_2); $J_{2,4}$ = 1.8, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.5 Hz.

1-(5-Bromo-8-methoxy-7-quinolyl)-1-phenylmethanol (**4c**); from **2b**, electrophile: benzaldehyde; yield: 54% (eluent: CH_2Cl_2/Et_2O, 92:8); mp 50°C.

^{1}H NMR ($CDCl_3$): δ = 3.7 (s, 1H, OH), 3.97 (s, 3H, OCH_3), 6.40 (s, 1H, CHOH), 7.3 (m, 6H, H_3, Ph), 7.93 (s, 1H, H_6), 8.42 (dd, 1H, H_4), 8.87 (dd, 1H, H_2); $J_{2,4}$ = 1.7, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.6 Hz.

^{13}C NMR ($CDCl_3$): δ = 62.6 (OCH_3), 70.4 (CHOH), 116.2 (C_5), 122.2 (C_3), 126.2 ($C_{2'}$), 127.5 ($C_{4'}$), 128.0 (C_b), 128.4 ($C_{3'}$), 129.1 (C_6), 135.9 (C_4), 137.0 (C_7), 143.0 (C_a), 143.2 ($C_{1'}$), 149.8 (C_2), 152.2 (C_8).

IR (KBr): ν = 3355, 1590, 1491, 1458, 1354, 1247, 1099 cm^{-1}.

5-Bromo-7-hydroxy-8-methoxyquinoline (**4d**): The general procedure applied to **2b** using trimethylborate, followed by dropwise addition of 32% peracetic acid in AcOH (1.4 mL), stirring for 30 min at −75°C and for 1 h at 0°C, addition (5 min) of sat. aq $NaHSO_3$ solution (2 mL) and stirring for 30 min at r.t. gave 55% of **4d** (eluent: CH_2Cl_2/Et_2O, 90:10); mp 183°C.

^{1}H NMR ($CDCl_3$): δ = 4.17 (s, 3H, OCH_3), 7.37 (dd, 1H, H_3), 7.64 (s, 1H, H_6), 8.43 (dd, 1H, H_4), 8.89 (dd, 1H, H_2); $J_{2,4}$ = 1.6, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.5 Hz.

^{13}C NMR ($CDCl_3$): δ = 62.4 (OCH_3), 116.6 (C_5), 119.8 (C_6), 121.9 (C_3), 123.2 (C_b), 136.1 (C_4), 139.6 (C_8), 143.0 (C_a), 148.8 (C_7), 150.4 (C_2).

IR (KBr): ν = 3448, 1560, 1474, 1420, 1340, 1259, 1208, 1150 cm^{-1}.

5-Bromo-7-formyl-8-methoxyquinoline (**4e**); from **2b**, electrophile: *N*-formylpiperidine; yield: 43% (eluent: CH_2Cl_2/Et_2O, 95:5); mp 178°C.

^{1}H NMR ($CDCl_3$): δ = 4.40 (s, 3H, OCH_3), 7.64 (dd, 1H, H_3), 8.19 (s, 1H, H_6), 8.56 (dd, 1H, H_4), 9.02 (dd, 1H, H_2), 10.62 (s, 1H, CHO); $J_{2,4}$ = 1.5, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.6 Hz.

^{13}C NMR ($CDCl_3$): δ = 64.8 (OCH_3), 116.6 (C_5), 124.3 (C_6), 126.6 (C_3), 127.7 (C_7), 132.2 (C_b), 136.1 (C_4), 143.5 (C_a), 150.2 (C_2), 161.0 (C_8), 188.4 (CHO).

IR (KBr): ν = 3448, 1680, 1588, 1498, 1458, 1370, 1256, 1106 cm^{-1}.

1-(5-Bromo-8-methoxy-7-quinolyl)-1-(2-fluoro-3-pyridyl)methanol (**4f**); from **2b**, electrophile: 2-fluoro-3-formylpyridine; yield: 46% (eluent: CH_2Cl_2/EtOAc, 80:20); mp 165°C.

^{1}H NMR ($CDCl_3$): δ = 4.08 (s, 3H, OCH_3), 6.54 (s, 1H, CHOH), 7.23 (m, 1H, $H_{5'}$), 7.50 (dd, 1H, H_3), 7.76 (s, 1H, H_6), 8.05 (m, 2H, $H_{4',6'}$), 8.44 (dd, 1H, H_4), 8.89 (dd, 1H, H_2); $J_{2,3}$ = 4.1, $J_{3,4}$ = 8.5 Hz.

IR (KBr): ν = 3404, 3070, 2938, 1608, 1460, 1437, 1098 cm^{-1}.

5-Substituted 7,8-Dimethoxyquinolines 3f, 4g; General Procedure:
A solution of **3e** or **4d** (1.2 mmol) in acetone (10 mL) was stirred with K_2CO_3 (1.7 g, 12 mmol) and MeI (75 µL, 1.2 mmol) at r.t. for 15 h. Filtration over Celite (10 g), washing with CH_2Cl_2 (50 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product which was purified by flash chromatography over silica gel (25 g/1 g).

7,8-Dimethoxyquinoline (**3f**);[27] from **3e**; yield: 90% (eluent: CH_2Cl_2/Et_2O, 80:20); mp < 50°C.

^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 7.26 (dd, 1H, H_3), 7.33 (d, 1H, H_6), 7.58 (d, 1H, H_5), 8.09 (dd, 1H, H_4), 8.93 (dd, 1H, H_2); $J_{2,4}$ = 1.4, $J_{2,3}$ = 4.0, $J_{3,4}$ = 8.2, $J_{5,6}$ = 8.6 Hz.

^{13}C NMR ($CDCl_3$): δ = 56.6 (OCH_3), 61.5 (OCH_3), 115.2 (C_6), 119.0 (C_3), 123.2 (C_5), 124.1 (C_b), 135.7 (C_4), 142.8 (C_8), 143.0 (C_a), 150.1 (C_2), 151.4 (C_7).

IR (KBr): ν = 3380, 2935, 2840, 1617, 1503, 1475, 1275, 1100 cm^{-1}.

5-Bromo-7,8-dimethoxyquinoline (**4g**); from **4d**; yield: 94% (eluent: CH_2Cl_2/Et_2O, 95:5); mp 103°C.

^{1}H NMR ($CDCl_3$): δ = 3.66 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 7.33 (dd, 1H, H_3), 7.61 (s, 1H, H_6), 8.36 (dd, 1H, H_4), 8.89 (dd, 1H, H_2); $J_{2,4}$ = 1.5, $J_{2,3}$ = 4.2, $J_{3,4}$ = 8.5 Hz.

^{13}C NMR ($CDCl_3$): δ = 57.0 (OCH_3), 61.8 (OCH_3), 115.9 (C_5), 119.4 (C_6), 120.2 (C_3), 123.3 (C_b), 135.5 (C_4), 142.9 (C_a), 143.5 (C_8), 150.8 (C_2), 151.3 (C_7).

IR (KBr): ν = 2920, 1600, 1490, 1475, 1310, 1255, 1150, 1075 cm^{-1}.

5-Iodo-8-methoxyquinoline (5):

A solution of 5,7-diiodo-8-methoxyquinoline (**2c**; 1.29 g, 3.15 mmol) in THF (20 mL) was added (5 min) to a cold (−75 °C) solution of PhLi (3.15 mL of a 2 M solution) in THF (30 mL). The resulting mixture was stirred for 2.5 h at −75 °C before addition of a mixture of conc. HCl (2.5 mL) and THF (7.5 mL) and further addition of H_2O (40 mL) at r.t. Extraction by CH_2Cl_2 (3 × 50 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product, which was purified by flash chromatography on silica gel (80 g) using CH_2Cl_2/Et_2O (95:5) as eluent; mp 109 °C (Lit.[24] mp 95–98 °C).

^{1}H NMR ($CDCl_3$): δ = 4.04 (s, 3 H, OCH_3), 6.79 (d, 1 H, H_7), 7.47 (dd, 1 H, H_3), 7.95 (d, 1 H, H_6), 8.29 (dd, 1 H, H_4), 8.86 (dd, 1 H, H_2); $J_{2,4}$ = 1.3, $J_{2,3}$ = 4.1, $J_{6,7}$ = 8.3, $J_{3,4}$ = 8.5 Hz.

^{13}C NMR ($CDCl_3$): δ = 56.1 (OCH_3), 86.5 (C_5), 109.2 (C_7), 123.1 (C_3), 130.4 (C_b), 137.2 (C_6), 140.1 (C_4), 140.8 (C_a), 149.7 (C_2), 156.1 (C_8).

IR (KBr): ν = 1584, 1496, 1458, 1354, 1304, 1249, 1096 cm^{-1}.

Oxidation of Secondary Alcohols 3c, 4c, 4f to Ketones 3g, 4h, 4i; General Procedure:

A solution of alcohol **3c, 4c, 4f** (0.9 mmol) in CH_2Cl_2 (13 mL) was stirred with molecular sieves (0.6 g) and PCC (0.7 g, 3.2 mmol) at r.t. for 3 h. The mixture was filtered over Celite (10 g) and washed with CH_2Cl_2 (30 mL). The combined CH_2Cl_2 phases were dried ($MgSO_4$) and the solvent removed to afford the crude product which was purified by flash chromatography over silica gel (20 g/1 g).

1-(8-Methoxy-7-quinolyl)-1-phenylmethanone (**3g**); from **3c**; yield: 49% (eluent: CH_2Cl_2/Et_2O, 95:5); oil.

^{1}H NMR ($CDCl_3$): δ = 4.06 (s, 3 H, OCH_3), 7.49 (m, 6 H), 7.89 (m, 2 H), 8.23 (m, 1 H, H_4), 9.00 (m, 1 H, H_2).

^{13}C NMR ($CDCl_3$): δ = 62.3 (OCH_3), 121.1 (C_7), 121.8–124.7 (C_{3-5}), 127.0 ($C_{3'}$), 128.5 ($C_{2'}$), 129.4–129.7 (C_{6-b}), 132.0 ($C_{4'}$), 135.3–135.8 ($C_{4-1'}$), 140.8 (C_a), 149.1 (C_8), 152.8 (C_2), 194.9 (CO).

IR (KBr): ν = 3059, 2938, 1665, 1596, 1462, 1364, 1284, 1094 cm^{-1}.

1-(5-Bromo-8-methoxy-7-quinolyl)-1-phenylmethanone (**4h**); from **4c**; yield: 75% (eluent: CH_2Cl_2/Et_2O, 95:5); oil.

^{1}H NMR ($CDCl_3$): δ = 4.02 (s, 3 H, OCH_3), 7.6 (m, 7 H), 8.54 (m, 1 H, H_4), 9.00 (m, 1 H, H_2).

^{13}C NMR ($CDCl_3$): δ = 61.7 (OCH_3), 113.8 (C_5), 121.7 (C_7), 126.5 ($C_{3'}$), 127.1 (C_3), 127.7 (C_6), 127.8 ($C_{2'}$), 129.5 (C_b), 131.7 ($C_{4'}$), 133.9–134.8 ($C_{4-1'}$), 141.1 (C_a), 148.8 (C_8), 152.0 (C_2), 192.6 (CO).

IR (KBr): ν = 3063, 2936, 1668, 1595, 1457, 1371, 1267, 1101 cm^{-1}.

1-(5-Bromo-8-methoxy-7-quinolyl)-1-(2-fluoro-3-pyridyl)methanone (**4i**); from **4f**; yield: 64% (eluent: CH_2Cl_2/EtOAc, 50:50); mp 120 °C.

^{1}H NMR ($CDCl_3$): δ = 3.93 (s, 3 H, OCH_3), 7.32 (m, 1 H, $H_{5'}$), 7.53 (m, 1 H, H_3), 7.97 (s, 1 H, H_6), 8.14 (m, 1 H, $H_{4'}$), 8.33 (m, 1 H, $H_{6'}$), 8.45 (m, 1 H, H_4), 8.90 (m, 1 H, H_2).

^{13}C NMR ($CDCl_3$): δ = 63.5 (OCH_3), 115.9 (C_5), 121.6 (d, $C_{5'}$), 122.8 (d, $C_{3'}$), 123.8 (C_3), 129.0 (C_6), 130.2 (C_b), 130.9 (C_7), 135.8 (C_4), 141.0 (d, $C_{4'}$), 143.0 (C_a), 150.1 (C_2), 150.5 (d, $C_{6'}$), 156.1 (C_8), 160.2 (d, $C_{2'}$), 190.0 (d, CO); $J_{C4',F}$ = 2.7, $J_{C5',F}$ = 4.4, $J_{CO,F}$ = 5.0, $J_{C6',F}$ = 15.3, $J_{C3',F}$ = 27.5, $J_{C2',F}$ = 244.0 Hz.

IR (KBr): ν = 1656, 1601, 1430, 1355, 1317, 1107 cm^{-1}.

5-Bromopyrido[3',2'; 8,9]pyrano[3,2-*h*]quinoline (6):

A mixture of pyridine (5 mL) and conc. HCl (5.1 mL) was heated to 220 °C for 5 min. Compound **4i** (0.45 mmol) was added to the hot pyridinium chloride. The mixture was refluxed (220 °C) for 15 min and poured onto ice (15 g). Extraction by EtOAc (4 × 30 mL), drying ($MgSO_4$) (10 g) and removal of solvent afforded a crude product which was purified by flash chromatography over silica gel (10 g, eluent: CH_2Cl_2/Et_3N, 90:10); yield: 61%; mp > 250 °C.

^{1}H NMR ($CDCl_3$): δ = 7.59 (dd, 1 H, $H_{5'}$), 7.83 (dd, 1 H, H_3), 8.68 (s, 1 H, H_6), 8.72 (dd, 1 H, H_4), 8.83 (dd, 1 H, $H_{4'}$), 8.90 (dd, 1 H, $H_{6'}$), 9.25 (dd, 1 H, H_2); $J_{2,3}$ = 4.1, $J_{5',6'}$ = 4.6, $J_{4',5'}$ = 7.7, $J_{3,4}$ = 8.5 Hz,

IR (KBr): ν = 1656, 1616, 1599, 1499, 1421, 1380, 1366 cm^{-1}.

MS (CI): m/z (%) = 327/329 ($M^+ + 1$).

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