Rhodium-catalysed nucleophilic ring opening reaction of 1- and 3-ethoxy-5,8-epoxy-5,8-dihydroisoquinolines

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2-Ethoxy-3- and 5-chloropyridines were obtained from 2,3- and 2,5-dichloropyridine. Reaction of 2,3- and 2,5-dichloropyridines with tBuLi in the presence of furan gave 1- and 3-ethoxy-5,8-epoxy-5,8-dihydroisoquinolines. The rhodium-catalysed ring-opening reaction of 1- and 3-ethoxy-5,8-epoxy-5,8-dihydroisoquinolines with 2-bromophenol furnished the isomer 7-(2-bromophenoxy)-1-ethoxy-7,8-dihydroisoquinolin-8-ol, 6-(2-bromophenoxy)-1-ethoxy-5,6-dihydroisoquinolin-5-ol and 7-(2-bromophenoxy)-3-ethoxy-7,8-dihydroisoquinolin-8-ol, 6-(2-bromophenoxy)-3-ethoxy-5,6-dihydroisoquinolin-5-ol respectively.

Keywords: oxabicyclic alkenes, isoquinoline, regioselectivity, ring-opening, rhodium catalysis

The isoquinoline ring system is found in many biologically active alkaloids[1] which have been an important research area for synthetic organic and medicinal[2–5] chemists. Natural products containing the isoquinoline ring have been used as antitumour agents, antimalarial and ionotropic glutamate reseptor antagonists for the central nervous system.[5–7] The synthesis of isoquinolines such as narciclasine **1**, pancratistatin **2** and azapodophyllotoxin **3** as a potential anticancer agents has lead to the investigation of various approaches to novel multifunctional pharmaceutical compounds.[8–13] As a result, there is interest in the synthesis of substituted isoquinolines.

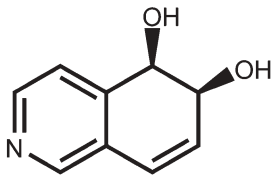
Boyd *et al.*[14] reported the synthesis of *cis*-7,8-dihydroisoquinoline-7,8-diol **4** by the biotransformation of isoquinoline. *Trans*-5,6-dihydroisoquinoline-5,6-diol **5**, a mammalian metabolite, was synthesised by the base-catalysed hydration of the 5,6-epoxy-5,6-dihydroisoquinoline by Boyd *et al.*[15] The oxabicyclic template has become increasingly common as a starting material in the preparation of the cyclic compounds.[16–18]

Recently, Lautens *et al.* has described a new rhodium catalysed ring opening reaction of oxabenzonorbornadienes which have an oxabicyclic skeleton.[19] This reaction produces a new carbon–oxygen bond *via* an intermolecular allylic displacement of the bridgehead oxygen by a wide variety of alcohols and phenols. More recently, Lautens *et al.* reported the regiodivergent nucleophilic ring opening reactions of various racemic heteroaryne-furan Diels–Alder adducts using a chiral cationic Rh(I) catalyst.[20] A regio- and stereoselective rhodium-catalysed ring opening reaction of azaoxabicyclic compounds was designed to form ethoxy-substituted 1,4-dihydroisoquinolines which are useful building blocks.

Results and discussion

1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **10** was prepared starting from 2,3-dichloropyridine **6**. In the preparation of oxabicyclic and azaoxabicyclic compounds, very strong bases (*e.g.*, nBuLi and tBuLi) have generally been used to give benzynes and pyridynes.[21–25] Hegarty showed that the stabilisation of 3,4-pyridines by an alkoxy group adjacent to the ring nitrogen was essential to give the Diels–Alder cycloaddition products in good yields after trapping with furan *in situ*.[23] Thus, treatment of 2,3-dichloropyridine **6** with a metallic sodium–ethanol system gave 2-ethoxy-3-chloropyridine **7** as a sole product (79%).[26] Treatment of 2-ethoxy-3-chloropyridine **7** with tBuLi in THF (–78 °C) resulted in the regioselective lithiation of the C-4 position to give 2-ethoxy-3-chloro-4-lithiopyridine **8**. This was followed by elimination of LiCl and reaction with furan to furnish 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **10** (Scheme 1).

1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **10** was exposed to a rhodium-catalysed ring opening reaction in dioxane at 110 °C with 2-bromophenol as the nucleophile.



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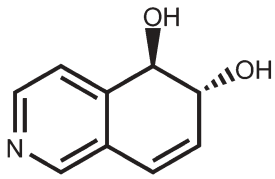

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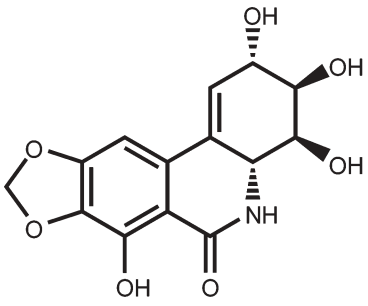

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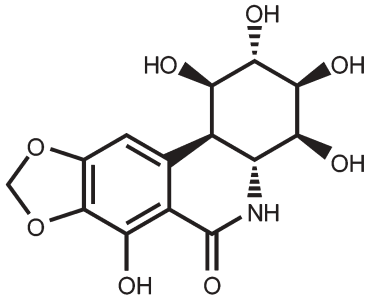

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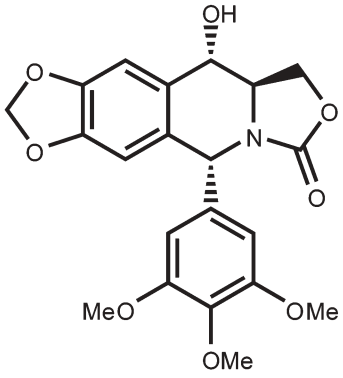

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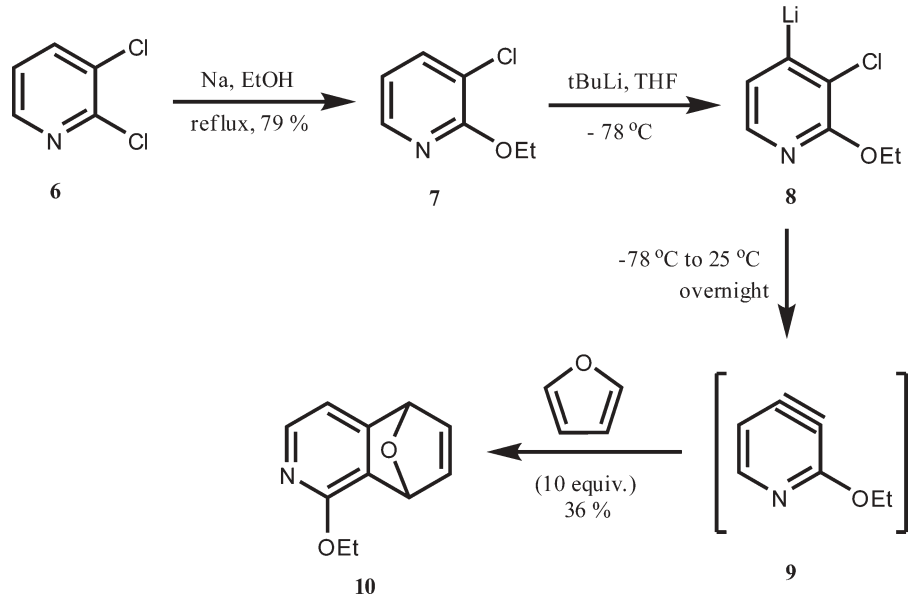


Scheme 1

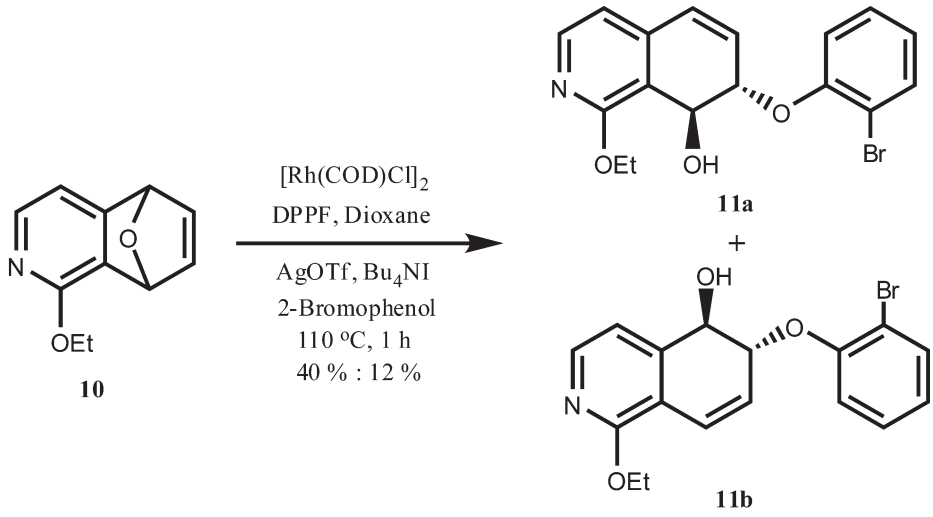
After purification of the product by column chromatography, two ethoxy-substituted 1,4-dihydroisoquinolines (regioisomers) **11a** and **11b** were obtained in good yields (Scheme 2). The structures of ethoxy-substituted 1,4-dihydroisoquinolines were elucidated on the basis of ^{1}H and ^{13}C NMR data. The best condition for this reaction with a $[Rh(COD)Cl]_2$ catalyst were run with bis-(diphenylphosphino)ferrocen (DPPF), AgOTf and Bu_4NI in THF at 110 °C for 1h. However, Lautens *et al.*[20] reported that rhodium-catalysed ring opening of 1,4-dihydroepoxyquinoline failed to react by using $[Rh(COD)Cl]_2$ with or without DPPF or protic additives such as NH_4Cl. In contrast, they successfully performed rhodium-catalysed ring opening of 1,4-dihydroepoxyquinoline by a catalyst prepared by simply combining $Rh(COD)_2OTf$ and (R,S)-PPF-P(t-Bu)$_2$ in THF at 60 °C. Consequently, $[Rh(COD)Cl]_2$ can be used for ring opening reactions of azaoxabicyclic compounds instead of $Rh(COD)_2OTf$.

After the compounds **11a** and **11b** had been synthesised, the same procedure was used in order to obtain further ring-opening products from compound **16**. To this end, the chlorine atom in the 2 position of 2,5-dichloropyridine **12** was substituted with an alkoxy group to obtain 3-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **13**.

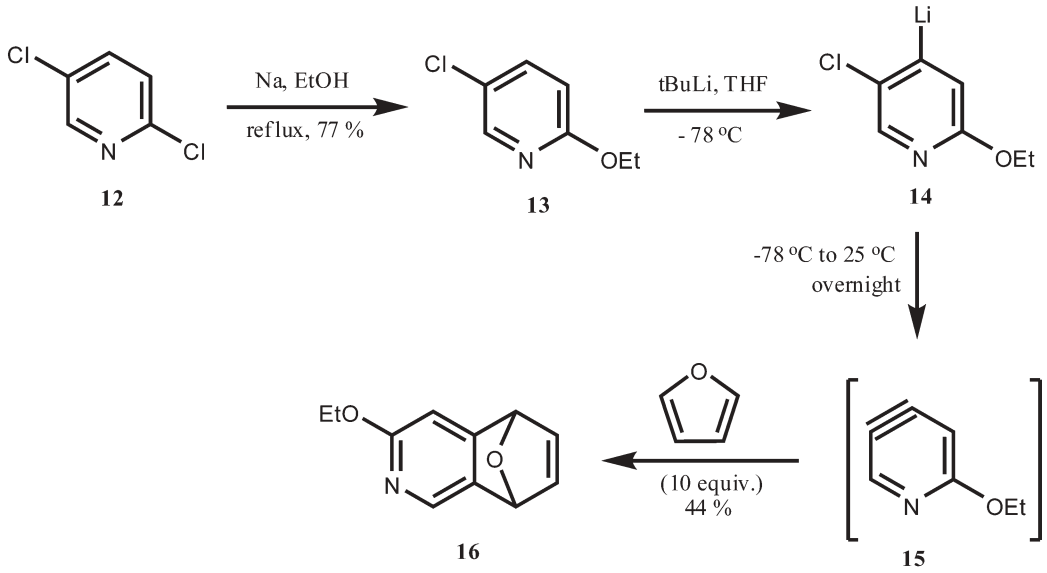
A chlorine atom in the 2 position of a pyridine is easily displaced by an ethoxy group *via* an addition-elimination mechanism. Additionally, α-halopyridines are more reactive than the β-isomers.[27] Thus, treatment of 2,5-dichloropyridine **12** with a metallic sodium-ethanol system afforded 2-ethoxy-5-chloropyridine **13** as a sole product (77%) (Scheme 3).

Treatment of **13** with excess furan in the presence of tBuLi in dry THF under nitrogen and cooling the reaction medium to –78 °C led to the cycloaddition product **16**. The structure of the resultant compound **16** was established by ^{1}H and ^{13}C NMR spectroscopy. The presence of an 11-line ^{13}C NMR spectrum is in full agreement with the proposed asymmetric structure **16** which was obtained as the sole product.

To support the formation of **11a** and **11b** from compound **10**, 2-ethoxy-5-chloropyridine **13** was also submitted to rhodium-catalysed ring opening sequence under the same conditions. Thus, rhodium-catalysed ring opening of 3-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **16** in dioxane at 110 °C with 2-bromophenol as the nucleophile gave the isomeric ethoxy-substituted 1,4-dihydroisoquinolines **17a** and **17b** in good yield (Scheme 4). The structures of regioisomers **17a** and **17b** were elucidated on the basis of ^{1}H and ^{13}C NMR data. The large coupling between the protons H-7 and H-8 (J = 9.3 Hz)



Scheme 2



Scheme 3

in **17a** shows the *trans* relation between those protons. The large coupling between the protons H-5 and H-6 (J = 10.8 Hz) in **17b** also indicated the *trans* configuration of these neighbouring protons. In addition, the presence of a 17-line ^{13}C NMR spectrums for both **17a** and **17b** is in full agreement with the proposed structures. Consequently, these configurational assignments showed that the 1,4-epoxide-ring in **16** underwent a *trans*-ring-opening reaction.

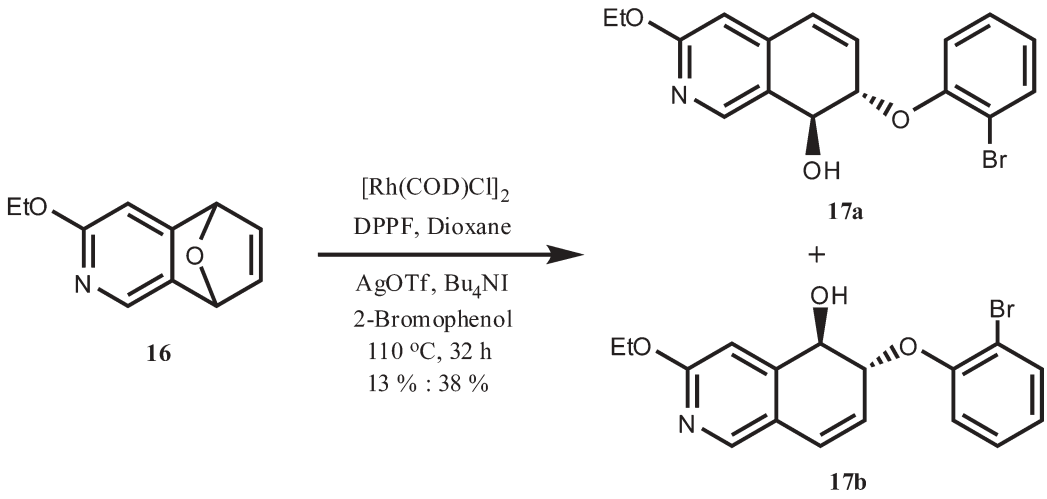
$[Rh(COD)Cl]_2$ can also be used as catalyst in the ring opening reactions of azaoxabicyclic compounds instead of $Rh(COD)_2OTf$. This report describes an effective and concise strategy for a new flexible synthesis of dihydroisoquinoline derivatives.

Experimental

Melting points were determined on a Buchi 539 capillary melting apparatus and are uncorrected. IR spectra were obtained using a Perkin–Elmer Spectrum 1000 FTIR spectrometer as a neat film on a NaCl plate. The ^1H and ^{13}C NMR spectra were recorded on Varian Mercury NMR spectrometer (300 MHz for ^1H, and 75 MHz for ^{13}C) and are reported in δ units with $SiMe_4$ as internal standard. TLC was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). All column chromatography was performed on silica gel (60 mesh, Merck). High resolution mass spectra were obtained from a Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI). Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser.

2-Ethoxy-3-chloropyridine (**7**): Sodium metal (*ca* 1.0 g) was added to dry ethanol (20 mL) in a 100 mL round-bottomed flask fitted with a stirring bar at 0 °C, and the resulting suspension was stirred until the sodium had disappeared and hydrogen evolution ceased. 2,3-Dichloropyridine **6** (2.1 g, 14 mmol) was added and the resulting mixture refluxed overnight. The reaction vessel was allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3x 50 mL). The organic extracts were combined and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a yellow liquid (1.8 g, 79%). (EtOAc: hexane 1:9, R_f 0.75) (2-ethoxy-3-chloropyridine **7** as a colourless liquid). The ^1H NMR spectrum was in agreement with the literature.[26] ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (dd, 1H, J = 4.8, 1.8 Hz), 7.55 (dd, 1H, J = 7.5, 1.8 Hz), 6.75 (dd, 1H, J = 7.5, 4.8 Hz), 4.40 (q, 2H, J = 7.1 Hz, $–CH_2$), 1.39 (t, 3H, J = 7.1 Hz, $–CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 144.8, 138.3, 118.4, 117.2, 62.8, 14.7.

1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline (**10**): An oven-dried 25 mL round-bottomed flask under N_2 fitted with a stirring bar and a septum was charged with a solution of 2-ethoxy-3-chloropyridine **7** (1.2 g, 7.60 mmol) in dry THF (8 mL) under N_2 and cooled to –78 °C. After 30 min at –78 °C, tBuLi (4.88 mL of a 1.7 M solution in hexane, 8.30 mmol), was added slowly with stirring to give a cloudy bright yellow solution. After 60 min at –78 °C, freshly distilled furan (6 mL,



Scheme 4

76 mmol) and THF (8 mL) were added and the mixture was allowed to warm to room temperature overnight. The mixture of the reaction was taken up in CH_2Cl_2 (300 mL) and washed with 10% $NaHCO_3$ (50 mL), water (40 mL), brine (50 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (EtOAc: hexane 1:9, R_f 0.35) to give 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **10** (0.52 g, 36%) as a yellow oil. The ^{1}H NMR spectrum was in agreement with the literature.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, 1H, *J* = 5.0 Hz), 7.10 (dd, A part of AB-system, 1H, *J* = 5.5, 2.1 Hz, –CH=CH), 6.98 (dd, B part of AB-system, 1H, *J* = 5.5, 2.1 Hz, –CH=CH), 6.91 (d, 1H, *J* = 5.0 Hz), 5.89 (m, 1H, –CH–O), 5.69 (m, 1H, –CH–O), 4.38 (q, 2H, *J* = 7.1 Hz, –CH_2), 1.37 (t, 3H, *J* = 7.1 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 157.1, 145.5, 144.0, 142.3, 130.1, 111.0, 82.5, 79.8, 61.8, 15.0.

7-(2-Bromophenoxy)-1-ethoxy-7,8-dihydroisoquinolin-8-ol (**11a**) and *6-(2-bromophenoxy)-1-ethoxy-5,6-dihydroisoquinolin-5-ol* (**11b**): $[Rh(COD)Cl]_2$ (0.0032 g, 0.00065 mmol) and DPPF (0.0072 g, 0.0129 mmol) in 1.5 mL dioxane was added to a flame-dried round-bottomed flask and stirred at room temperature for 10 min to produce a red solution. AgOTf (0.0066 g, 0.0258 mmol) was added followed by sonication for 10 min to produce an orange heterogeneous solution. Bu_4NI (0.0143 g, 0.0387 mmol) was added followed by stirring for another 10 min to give a dark-red solution of the [Rh(COD)I] catalyst. This catalyst solution was treated with 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline (0.100 g, 0.529 mmol) and 2-bromophenol (0.240g, 1.38 mmol), and heated to 110 °C for 1 h. The mixture was poured into NaOH solution (1 M, 50 mL) and extracted with Et_2O (3×100 mL). The combined organic phase was washed with NaOH (1 M, 25 mL), brine (25mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the brown residue was purified by flash chromatography (EtOAc: hexane 1:9) to give (**11a**; 77 mg, 40%, **11b**; 22 mg, 12%).

11a: M.p. 148 °C (recrystallised from hexane/EtOAc), IR (NaCl, cm^{-1}) 3671, 3582, 3435, 2978, 1558, 1474, 1427, 1376, 1243, 1045, 718. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 1H, *J* = 5.1 Hz), 7.58 (br d, 1H, *J* = 7.5 Hz), 7.26 (m, 1H), 7,21 (d, 1H, *J* = 5.1 Hz), 6.90 (m, 2H), 6.77 (dd, A part of AB-system, 1H, *J* = 10.1, 1.9 Hz, –CH=CH), 6.07 (dd, B part of AB-system, 1H, *J* = 10.1, 1.8 Hz, –CH=CH), 5.25 (br d, A part of AB-system, 1H, *J* = 11.7 Hz, –CH–O), 5.16 (td, B part of AB-system, 1H, *J* = 11.7, 2.1 Hz, –CH–OPhBr), 4.40 (q, 2H, *J* = 7.1 Hz, –CH_2), 3.04 (s,1H, –OH), 1.40 (t, 3H, *J* = 7.1 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 154.4, 146.9, 146.5, 133.9, 128.9, 126.4, 123.3, 122.9, 115.7, 114.7, 113.6, 113.3, 82.0, 72.5, 62.2, 14.9. EIMS *m/z* (%): 363 (100), 190 (18), 174 (53), 162 (10), 146 (19); HRMS calcd for $C_{17}H_{16}BrNO_3$ (M+): 361,0314; found: 361.0315.

11b: M.p. 165 °C (recrystallised from hexane/EtOAc), IR (NaCl, cm^{-1}) 3851, 3646, 2926, 2851, 1683, 1652, 1558, 1506, 1539, 1472, 1456, 1435, 1030, 668. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 1H, *J* = 5.1 Hz), 7.56 (br d, 1H, *J* = 7.8), 7.26 (m, 2H), 6.90 (m, 1H), 6.74 (d, 1H, *J* = 5.1 Hz), 6.59 (br d, A part of AB-system, 1H, *J* = 9.7 Hz, –CH=CH), 6.32 (dd, B part of AB-system, 1H, *J* = 9.7, 4.1 Hz, –CH=CH), 5.34 (d, A part of AB-system, 1H, *J* = 4.1 Hz, –CH–O), 5.14 (dt, B part of AB-system, 1H, *J* = 4.1, 0.9 Hz, –CH–OPhBr), 4.46 (q, 2H, *J* = 7.1 Hz, –CH_2), 3.14 (s,1H, –OH), 1.42 (t, 3H, *J* = 7.1 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 154.5, 147.5, 140.3, 133.9, 129.0, 128.7, 128.3, 123.3, 117.0, 115.9 (x2), 114.2, 78.1, 66.6, 62.5, 14.9; HRMS calcd for $C_{17}H_{16}BrNO_3$ (M+): 361,0314; found: 361.0316.

2-Ethoxy-5-chloropyridine (**13**): Sodium metal (*ca* 2.14 g) was added to dry ethanol (100 mL) in a 250 mL round-bottomed flask fitted with a stirring bar at 0 °C. The resulting suspension was stirred until the sodium had disappeared and hydrogen evolution ceased *ca* 1h). 2,5-Dichloropyridine **12** (5 g, 33 mmol) was added and the resulting mixture refluxed for 36 h. The reaction vessel was allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4x 100 mL). The organic extracts were combined and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 2-ethoxy-5-chloropyridine **13** as a yellow liquid (4.09 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 1H, *J* = 2.6 Hz), 7.43 (dd, 1H, *J* = 8.8, 2.6 Hz), 6.60 (dd, 1H, *J* = 8.8, 0.6 Hz), 4.27 (q, 2H, *J* = 7.1 Hz, –CH_2), 1.32 (t, 3H, *J* = 7.1 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 145.3, 138.5, 123.9, 112.2, 62.2, 14.7. Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.28; H, 5.17; N, 8.76%.

3-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline (**16**): An oven-dried 25 mL round-bottomed flask under N_2 fitted with a stirring bar and a septum was charged with a solution of 2-ethoxy-5-chloropyridine **13** (1.1 g, 6.98 mmol) in dry THF (8 mL) under N_2 and cooled to –78 °C. After 30 min at –78 °C, tBuLi (5.41 mL of a 1.7 M solution in hexane, 9.2 mmol), was added slowly with stirring to give a cloudy bright yellow solution. After 60 min at –78 °C, freshly distilled furan (6.6 mL, 69.8 mmol) and THF (5 mL) were added and the mixture allowed to warm to room temperature overnight. The mixture was taken up in CH_2Cl_2 (300 mL) and washed with 10% $NaHCO_3$ (40 mL), water (30 mL), brine (30 mL). The organic phase (Na_2SO_4) was dried and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (Et_2O: hexane 1:1, R_f 0.56) to give 3-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **16** as a yellow oil (0.58 g, 44%). IR (NaCl, cm^{-1}) 3395, 3013, 2978, 2929, 2900, 1633, 1591, 1445, 1403, 1379, 1337, 1282, 1264, 1225, 1092, 1038, 846. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H), 6.99 (dd, A part of AB-system, 1H, *J* = 5.6, 1.8 Hz, –CH=CH), 6.88 (dd, B part of AB-system, 1H, *J* = 5.6, 1.9 Hz, –CH=CH), 6.66 (s, 1H), 5.74 (m, 1H, –CH–O), 5.64 (m, 1H, –CH–O), 4.32 (q, 2H, *J* = 7.1 Hz, –CH_2), 1.36 (t, 3H, *J* = 7.1 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 161.1, 143.5, 140.7, 135.8, 135.5, 105.6, 81.7, 80.4, 62.3, 14.8. EIMS *m/z* (%): 190 (100), 162 (40), 136 (10). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.79; N, 3.35%. HRMS calcd for $C_{11}H_{11}NO_2$ (M+): 189,0790; found: 189.0793.

7-(2-Bromophenoxy)-3-ethoxy-7,8-dihydroisoquinolin-8-ol (**17a**) and *6-(2-bromophenoxy)-3-ethoxy-5,6-dihydroisoquinolin-5-ol* (**17b**): $Rh(COD)Cl]_2$ (0.0027 g, 0.00055 mmol) and DPPF (0.0072 g, 0.0129 mmol) in 1.5 mL dioxane was added to a flame-dried round-bottomed flask and stirred at room temperature for 10 min to produce a red solution. AgOTf (0.0057 g, 0.0222 mmol) was added followed by sonication for 10 min to produce an orange heterogeneous solution. Bu_4NI (0.0122 g, 0.0333 mmol) was added followed by stirring for another 10 min to give a dark-red solution of the [Rh(COD)I] catalyst. 3-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline **16** (0.09 g, 0.476 mmol) and 2-bromophenol (0.206 g, 1.18 mmol), were added to this catalyst solution and heated to 110 °C for 32 h. The mixture was poured into NaOH solution (1 M, 40 mL) and extracted with Et_2O (3×100 mL). The combined organic phase was washed with NaOH (1 M, 20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the brown residue was purified by flash chromatography (EtOAc: hexane 3:7) to give (**17a**; 21 mg, 13%, **17b**; 66 mg, 38%).

17a: Brown liquid, (Rf; 0.57), IR (NaCl, cm^{-1}) 3394, 2975, 2924, 1607, 1557, 1474, 1417, 1326, 1241, 1044, 667. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.58 (dd, 1H, *J* = 7.9, 1.9 Hz), 7.26 (m, 2H), 6.93 (m, 2H), 6.48 (dd, A part of AB-system, 1H, *J* = 9.9, 2.1 Hz, –CH=CH), 6.25 (dd, B part of AB-system, 1H, *J* = 9.9, 2.1 Hz, –CH=CH), 5.26 (dd, A part of AB-system, 1H, *J* = 9.3, 0.9 Hz, –CH–O), 5.05 (dt, B part of AB-system, 1H, *J* = 9.3, 2.1 Hz, –CH–O), 4.37 (q, 2H, *J* = 7.0 Hz, –CH_2), 1.39 (t, 3H, *J* = 7.0 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 154.5, 144.1, 141.8, 134.0, 131.4, 128.9, 127.8, 123.5, 123.0, 116.2, 113.9, 107.8, 81.7, 70.7, 72.0, 14.9; HRMS calcd for $C_{17}H_{16}BrNO_3$ (M+): 361,0314; found: 361.0317.

17b: M.p. 106 °C (recrystallised from hexane/EtOAc), (Rf; 0.74), IR (NaCl, cm^{-1}) 3334, 3063, 2979, 2930, 2900, 1607, 1557, 1488, 1417, 1377, 1336, 1243, 1031, 749. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.57 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.25 (m, 1H), 7.04 (m, 1H), 6.90 (m, 2H), 6.48 (dd, A part of AB-system, 1H, *J* = 9.9, 2.1 Hz, –CH=CH), 5.94 (dd, B part of AB-system, 1H, *J* = 9.9, 1.8 Hz, –CH=CH), 5.21 (dd, A part of AB-system, 1H, *J* = 10.8, 1.3 Hz, –CH–O), 5.07 (dt, B part of AB-system, 1H, *J* = 10.8, 2.1 Hz, –CH–OPhBr), 4.36 (q, 2H, *J* = 7.0 Hz, –CH_2), 1.39 (t, 3H, *J* = 7.0 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 154.4, 147.9, 143.8, 133.9, 128.9, 125.7, 125.0, 123.3, 122.0, 115.9, 113.6, 107.8, 82.0, 72.3, 62.2, 14.8. Anal. Calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.41; H, 4.32; N, 3.68%. HRMS calcd for $C_{17}H_{16}BrNO_3$ (M+): 361,0314; found: 361.0316.

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References

1 K.W. Bentley, *The isoquinoline alkaloids*. Harwood Academic, Amsterdam, 1998, Vol. 1.

2 K.W. Bentley, *Nat. Prod. Rep.*, 2004, **21**, 394.
3 M. Shamma, *The isoquinoline alkaloids*. Academic, London, 1972, pp. 194–228.
4 H.J. Guinaudeau, M. Leboeuf and A. Cave, *J. Nat. Prod*., 1994, **57**, 1033.
5 J.D. Scott and R.M. Williams, *Chem. Rev*., 2002, **102**, 1669.
6 K.H. Kim, I.K. Lee, C.J. Piao, S.U. Choi, J.H. Lee, Y.S. Kim and K.R. Lee, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4487.
7 A. Chimirri, L. De Luca, S. Ferro, G. De Sarro, L. Ciranna and R. Gitto, *Chem. Med. Chem.*, 2009, **4**, 917.
8 M. Matveenko, M.G. Banwell and A.C. Willis, *Tetrahedron*, 2008, **64**, 4817.
9 T. Hudlicky, U. Rinner, D. Gonzalez, H. Akgun, S. Schilling, P. Siengalewicz, T.A. Martinot and G.R. Pettit, *J. Org. Chem.*, 2002, **67**, 8726.
10 G.R. Pettit, R.A. Backhaus and F.E. Boettner, *J. Nat. Prod.*, 1995, **58**, 37.
11 M. Chrzanowska and M.D. Rozwadowska, *Chem. Rev*., 2004, **104**, 3341.
12 K. Tomioka, Y. Kubota and K. Koga, *Tetrahedron Lett*., 1989, **30**, 2953.
13 J.P. Bosmans, J. Van der Eycken, M. Vandewalle, A. Hulkenberg, R. Van Hes and W. Veerman, *Tetrahedron Lett.*, 1989, **30**, 3877.
14 D.R. Boyd, N.D. Sharma, M.R.J. Dorrity, M.V. Hand, R.A.S. McMordie, J.F. Malone, H.P. Porter, H. Dalton, J. Chima and G.N. Sheldrake, *J. Chem.* Soc., *Perkin Trans. I*, 1993, 1065.
15 D.R. Boyd, R.J.H. Davies, L. Hamilton and J.J. McCullough, *J. Chem.* Soc., *Perkin Trans. I*, 1992, 31.
16 B.H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795.
17 L. Kelebekli, *J. Chem. Res.*, 2008, 104.
18 A. Menzek, L. Kelebekli, A. Altundaş, E. Şahin and F. Polat, *Helv. Chim. Acta.*, 2008, **91**, 2367.
19 M. Lautens, K. Fagnou and T. Rovis, *J. Am. Chem. Soc.*, 2000, **122**, 5650.
20 T.D. Nguyen, R. Webster and M. Lautens, *Org. Lett*., 2011, **13**, 1370.
21 G.W. Gribble and M.G. Saulnier, *Tetrahedron Lett.*, 1980, **21**, 4137.
22 G.W. Gribble and M.G. Saulnier, *Heterocycles*, 1993, **35**, 151.
23 S.J. Connon and A.F. Hegarty, *J. Chem. Soc. Perkin Trans 1*, 2000, 1245.
24 S.J. Connon and A.F. Hegarty, *Eur. J. Org. Chem.*, 2004, 3477.
25 W. Lin, L. Chen and P. Knochel, *Tetrahedon*, 2007, **63**, 2787.
26 L. Lai, P. Lin, J. Wang, J. Hwu, M. Shiao and S. Tsay, *J. Chem. Res.* (*S*), 1996, 194.
27 W.S. Yue and J.J. Li, *Org. Lett.*, 2002, **4**, 2201.