Solvent-dependent oxidations of 5- and 6-azaindoles to trioxopyrrolopyridines and functionalised azaindoles†

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A regioselective synthesis of 4,7-dimethoxy 5- and 6-azaindoles **2** has been achieved, based on the appropriate choice of *ortho*-directing or *ortho*-repulsing groups in the formylation of a pyridine ring. Studies on the regioselectivity of the formylation step and on the preparation of azidoacrylate intermediates **4** are described in this paper. The reactivity of the 5- and 6-azaindole structures towards BBr_3-mediated selective monodemethylation and oxidative demethylation reactions were also investigated. The regioselectivity of the deprotection was confirmed using a chemical approach. Oxidation reactions were then carried out on either dimethoxy- or hydroxymethoxyazaindoles, in different solvents, using [bis(trifluoroacetoxy)iodo]benzene. In acetonitrile–water, trioxopyrrolopyridines **12** were obtained, whereas the formation of functionalised azaindoles **17** was observed in acetonitrile–methanol. The tautomeric structure of the trioxopyrrolopyridines was proved by X-ray diffraction analysis.

Introduction

The synthesis and functionalisation of the indole ring continues to interest organic chemists, due to its widespread occurrence in many natural products and biologically active molecules.[1] More recently, azaindoles have proved to be of prime importance to medicinal chemists, and the growing interest of the scientific community and pharmaceuticals firms in this core structure has resulted in a drive to develop new methods for its preparation.[2]

As part of a project directed towards the design of new purine bases,[3] we planned to obtain the 5- and 6-azaquinone indoles **1** (3,7- and 3,9-dideazapurines, respectively) from the di- and monomethoxy 5- and 6-azaindoles **2** and **3** (Fig. 1).[4]

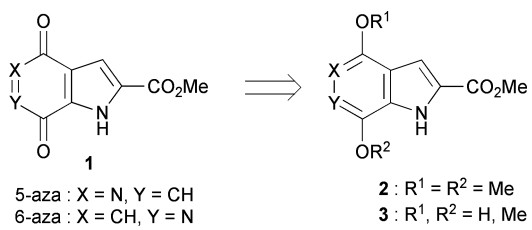

Fig. 1 Strategy to 5- and 6-azaquinone indoles **1**.

Upon searching the literature, we found that preparations of azaquinones are scarce,[5] and that the synthesis of an azaquinone indole had not previously been described. This encouraged us to develop a synthetic route towards such a structure, the results of which are reported herein.

Results and discussion

Synthesis of dimethoxyazaindoles

A synthetic strategy for the regioselective preparation of the 5- and 6-azaindoles **2** has been developed in our group,[6] and is based on an appropriate functionalisation of the pyridine ring followed by the *de novo* pyrrolidine ring formation *via* the Hemetsberger reaction (Fig. 2).[7]

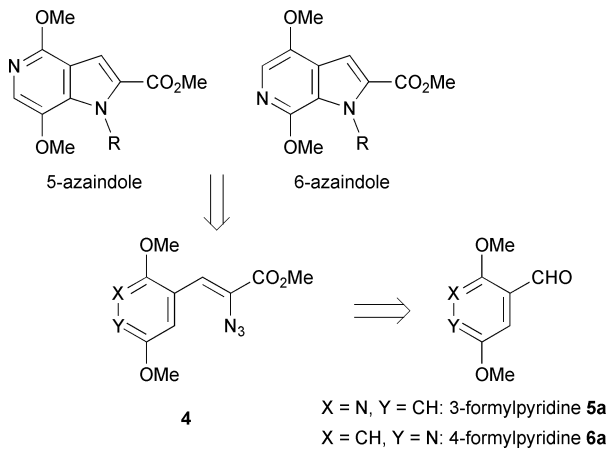

Fig. 2 Access to 5- and 6-aza dimethoxyindoles **2**.

For this selective approach to be possible, we required access to the dimethoxy 3- and 4-formyl pyridines **5a** and **6a**, precursors of the azidoacrylates **4** (Fig. 2). To this end, we envisaged performing a metalation–formylation procedure on 2,5-dimethoxypyridine **8a**, a substrate which was easily obtained in three steps from 2-methoxypyridine (Scheme 1).

Commercially available 2-methoxypyridine was first brominated at the *para* position using *N*-bromosuccinimide (NBS) in a polar solvent.[8] Halogen–lithium exchange followed by an *in situ*

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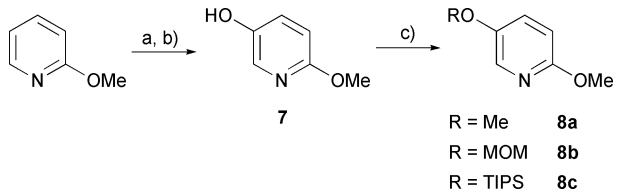


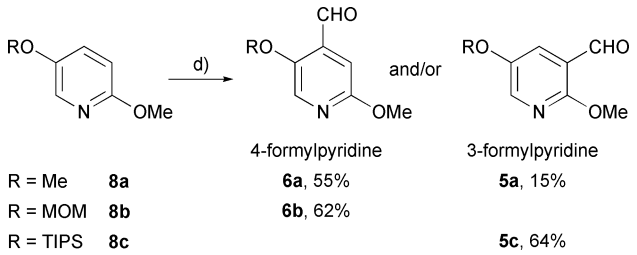
Scheme 1 Synthesis of formylation precursors **8**. *Reagents and conditions*: a) NBS 1.2 equiv, CH_3CN, reflux, 16 h, 81%; b) 1) *n*-BuLi 1.5 equiv, THF, −78 °C, 30 min. 2) $B(OMe)_3$ 1.5 equiv, −78 °C, 2 h. 3) peracetic acid 1.5 equiv, 0 °C, 1 h, **7**, 83%; c) R = Me: K_2CO_3 1.5 equiv, DMF, 50 °C, 10 min then MeI 1.0 equiv, 3 h 30 min, **8a**, 86%. R = MOM: NaH 1.2 equiv, DMF, rt, 45 min then $MeOCH_2Cl$ 1.15 equiv, 3h, **8b**, 92%. R = TIPS: imidazole 2.1 equiv, DMF, $(i\text{-}Pr)_3SiCl$ 1.2 equiv, rt, 24 h, **8c**, quantitative.

trapping with trimethylborate afforded the corresponding borane, which was oxidised to give 5-hydroxy 2-methoxypyridine **7**, after a reductive work-up.[9] Dimethoxypyridine **8a** was then obtained by methylation of pyridinol **7** under basic conditions (Scheme 1).

Although metalation reactions[10] of 2-methoxypyridine have been studied by several research groups,[11] no examples of the metalation/functionalisation of substrate **8a** have been described in the literature. In order to explore this area, we prepared further substrates bearing other groups such as methoxymethoxyl (MOM) (**8b**) and triisopropylsilyl (TIPS) (**8c**) groups (Scheme 1), and studied their behaviour towards the lithiation step.

We then proceeded to investigate on substrates **8** the lithium-based metalation procedure developed by Quéguiner and co-workers.[11b] Lithiation was performed at 0 °C by using methyllithium and a catalytic amount of diisopropylamine (DIPA), followed by an electrophilic quench with *N*-formylpiperidine.

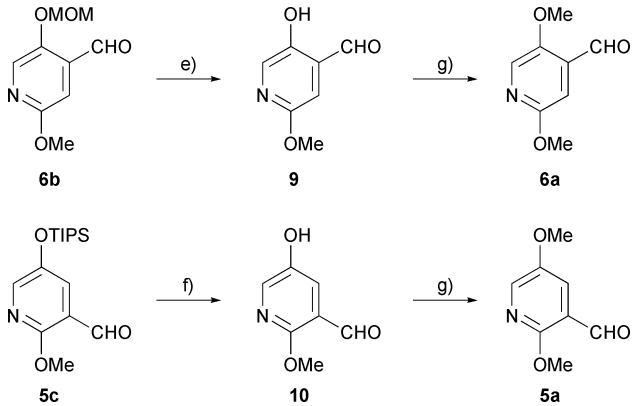
When applied to the dimethoxy substrate **8a**, this method led to an 81:19 mixture (determined from the ^1H NMR of the crude product) of the 4- and 3-formyl derivatives **6a** and **5a**. These were isolated after chromatographic separation in 55% and 15% yields, respectively (Scheme 2). The use of the *ortho*-directing[12] MOM group[13] enhanced the proportion of the 4-isomer, as compound **6b** was obtained from **8b** with a 62% isolated yield.[14] Further investigation of the reaction in the presence of other *ortho*-directing groups such as tetrahydropyranyl ether[15] or *N*,*N*′-diethyl carbamate[12a] were less satisfactory (lower regioselectivity or degradation of starting material without metalation of the pyridine ring, respectively).



Scheme 2 Formylation of 5-substituted 2-methoxypyridines **8**. *Reagents and conditions*: d) 1) MeLi 1.8 equiv, DIPA 2 mol%, THF, 0 °C, 3 h. 2) *N*-formylpiperidine 1.8 equiv, −40 °C, 2 h.

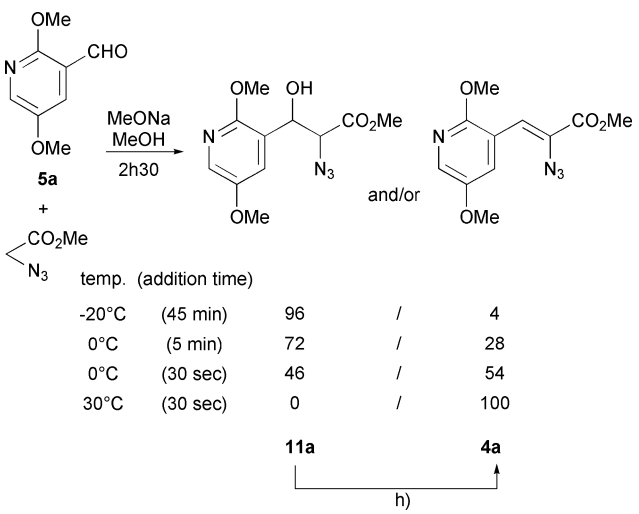
The same metalation–electrophilic quench conditions were then applied to substrate **8c**, which was protected with the sterically hindered triisopropyl group. This resulted in the exclusive formation of compound **5c** with a 64% isolated yield,[16] showing the "*ortho*-repulsing" properties of the TIPS group during metalation reactions (Scheme 2). In this case, a small amount (less than 10%) of the starting material **8c** was detected and separated from the desired product **5c** by flash chromatography.

Deprotections of the MOM and TIPS ethers were carried out under the appropriate conditions (acidic medium for **6b** and a fluoride source for **5c**) to afford the free pyridinols **9** and **10**. These were methylated under basic conditions to give the desired 2,5-dimethoxy-4-formylpyridine **6a** and its 3-formyl regioisomer **5a** in excellent yields (Scheme 3).



Scheme 3 Access to 3- and 4-formyldimethoxypyridines **5a** and **6a**. *Reagents and conditions*: e) 3 N aq HCl, THF, 50 °C, 3 h, 95%; f) TBAF 1.5 equiv, THF, 0 °C to rt, 2 h, 92%; g) K_2CO_3 1.5 equiv, DMF, 50 °C, 10 min then MeI 1.0 equiv, 3 h, **6a**, 89% and **5a**, 96%.

We then turned our attention to the preparation of the azidoacrylates **4**. Our first attempt involved a condensation reaction between 3-formylpyridine **5a** and an excess of methyl azidoacetate, in the presence of sodium methoxide as the base, at 0 °C. These conditions led to the formation of a mixture of the expected azidoacrylate **4a**, together with azidoalcohol **11a** in a 28:72 ratio (Scheme 4).[17]



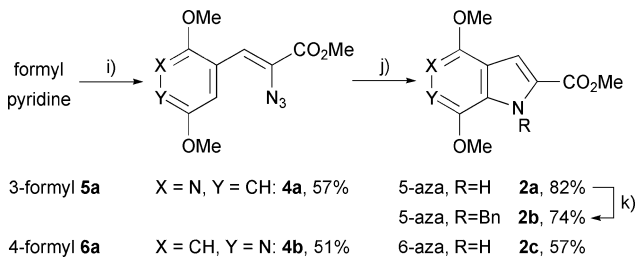
Scheme 4 Azidoalcohol **11a** *versus* azidoacrylate **4a** formation from 3-formylpyridine **5a**. *Reagents and conditions*: h) MsCl 5 equiv, Et_3N 10 equiv, CH_2Cl_2, rt, 15h, 84%.

Azidoacrylate **4a** was easily separated from the azidoalcohol **11a** by flash chromatography, and the latter was converted into **4a** in good yield by reaction with methanesulfonyl chloride in the presence of excess triethylamine (*in situ* basic elimination of the mesylate).

In an attempt to obtain exclusively **4a** from the condensation reaction, we varied the reagent addition time and the reaction temperature. Adding the reagents over 30 seconds (instead of 5 minutes) at the same temperature, a higher proportion of azidoacrylate **4a** was observed (ratio **11a**/**4a** 46:54), showing that exothermicity of the reaction may influence the product distribution.

At a lower temperature (−20 °C), the slow addition (over a 45 min period) of a methanolic solution of **5a** and methyl azidoacetate onto sodium methoxide in methanol resulted in the selective formation of the kinetic product **11a** with a modest 46% isolated yield (Scheme 4).[18] When the reaction was carried out at 30 °C, with a fast addition of the reagents, however, the exclusive formation of the desired acrylate **4a** was observed.

Following this optimised procedure, azidoacrylates **4a** and **4b** were obtained in 57% and 51% isolated yields respectively (Scheme 5). The 5- and 6-azaindoles **2** could then be prepared in moderate to good yield by the Hemetsberger thermolysis reaction. Suspensions of the corresponding acrylates **4** were heated at reflux in xylene for one hour, then the reaction mixture was cooled slowly to crystallise the products. Due to large solubility differences between compounds **2a** and **2c**, complete crystallisation of 5-azaindole occurred at room temperature, whereas only partial crystallisation of the 6-aza isomer was observed at −20 °C. Additional flash chromatography of the supernatant was necessary for complete recovery of compound **2c**. *N*1 functionalisation of the azaindoles is also feasible, as shown by the benzylation of the 5-aza derivative to compound **2b** (Scheme 5).

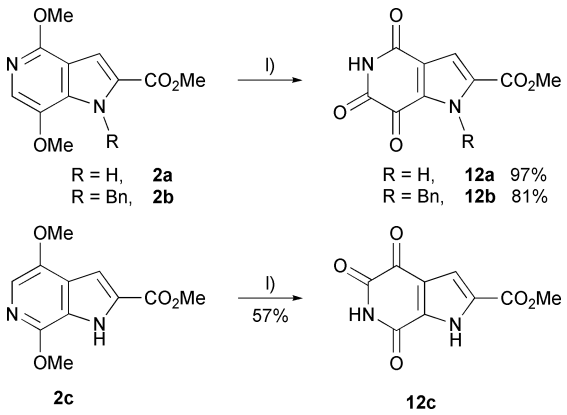


Scheme 5 Synthesis of dimethoxy 5- and 6-azaindoles **2**. *Reagents and conditions:* i) MeONa 4.1 equiv, methyl azidoacetate 3.8 equiv, MeOH, 30 °C, 2 h; j) Xylene, 140 °C, 1 h; k) NaH 1.2 equiv, DMF, 50 °C, 3 h 30 min, then BnBr 1.1 equiv, 50 °C, 2 h.

Oxidation of dimethoxyazaindoles

Continuing our strategy for the preparation of the azaquinone indoles **1**, we then studied their behaviour under oxidising conditions (Fig. 1). We thought it was possible that the behaviour of the dimethoxyazaindoles towards oxidative demethylation conditions may be similar to that of their carbon congeners.[4]

Among the numerous methods of oxidation available to us, we focused our attention on hypervalent iodine reagents. These have proved to be essential in modern organic chemistry, being of great synthetic value as mild and highly chemoselective oxidising reagents.[19] We first attempted the transformation of dimethoxy-5-azaindole **2a** with the commercially available [bis(trifluoroacetoxy)iodo]benzene (PIFA).[20] Four equivalents of the oxidising reagent were necessary for a complete conversion of the starting material. This resulted in the surprising formation of trioxopyrrolopyridine **12a** with an excellent yield of 97% (Scheme 6).[21]



Scheme 6 PIFA-mediated oxidations of dimethoxy-5- and 6-azaindoles **2** to trioxopyrrolopyridines **12**. *Reagents and conditions:* I) PIFA 4 equiv, CH_3CN–water 1:1, rt, 4 h.

This oxidation reaction was also successful when applied to *N*-benzyl-protected 5-azaindoles and in the 6-azaindole series, as the corresponding trioxo compounds **12b** and **12c** were obtained in good yields (Scheme 6).

The identity of the oxidised product was confirmed by high-resolution mass spectroscopy, infrared spectroscopy and NMR, this last technique being essential in determining the tautomeric form of the compound in solution. We observed three peaks at 158.7, 160.0 and 160.7 ppm in the ^{13}C spectrum, similar to those of the amide, rather than the 180–190 ppm usually associated with a quinone (Fig. 3).

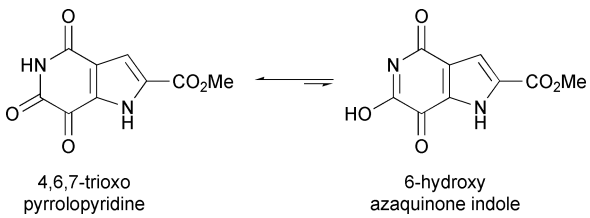


Fig. 3 Tautomeric forms of compound **12a**.

Evaporation of an acetone solution of **12a** provided a single crystal for a X-ray diffraction analysis‡ (Fig. 4). These results supported the spectroscopic data, confirming that the major tautomer form was the 4,6,7-trioxopyrrolopyridine compound rather than the 6-hydroxyazaquinone indole (Fig. 3).

‡ Crystal data for **12a**: $C_9H_6N_2O_3$, $M = 222.16$; triclinic, space group $P\bar{1}$, $a = 5.35$, $b = 8.79$, $c = 10.58$ Å, $\alpha = 111.47$, $\beta = 94.77$, $\gamma = 94.31°$, $V = 458.78(1)$ Å^3, $Z = 2$, $d_x = 1.608$ g cm^{-3}, $\mu = 0.14$ mm^{-1}, $T_{min,max} = 0.991, 0.992$; $T = 293$ K, 3192 measured reflections, 2078 independent reflections ($R_{int} = 0.042$), 1005 reflections with $I > 2.0\sigma(I)$. $R[F^2 > 2\sigma(F^2)] = 0.047$, $\omega R(F^2) = 0.057$, $S = 1.06$. CCDC reference number 641655. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b719776d.

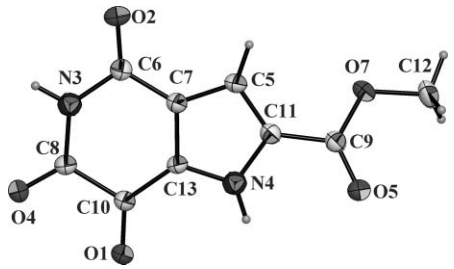


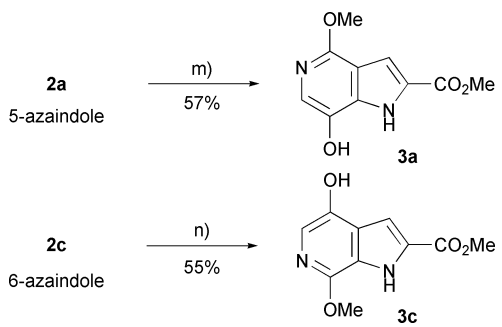
Fig. 4 ORTEP view of the crystal structure of **12a**. Ellipsoids are represented at the 30% probability level.

The bond lengths observed in the X-ray crystal structure[22] allowed us to determine without any doubt that we had isolated the trioxo tautomer. All three carbon–oxygen bond lengths on the pyridine ring were in good agreement with that expected for a carbonyl group C=O; each bond of the pyridine ring, except the junction C(7)–C(13), was a single bond (whereas C(8)–N(3) in the hydroxyquinone form should be a double bond), and the proton H(2) located on N(3) was unambigously detected from the diffraction data (bond length = 0.88 Å) and formed a hydrogen bond with O(4) of another molecule of the cell packing. This last observation provides convincing proof for the trioxo tautomeric form (Fig. 4).[23]

Oxidation of hydroxymethoxyazaindoles

In an attempt to increase the efficiency of the transformation, we then assessed whether we could obtain trioxopyrrolopyridines **12** from monohydroxy azaindoles **3** with a reduced amount of the oxidising agent.[24]

To this end, hydroxymethoxy azaindole substrates were prepared by demethylation of dimethoxy-5- and 6-azaindoles. Dimethoxyazaindoles **2a** and **2c** were treated with optimised equivalents of boron tribromide in dichloromethane to afford the monodemethylated products **3a** and **3c** in 57 and 55% yield, respectively, after optimisation (Scheme 7).[25]

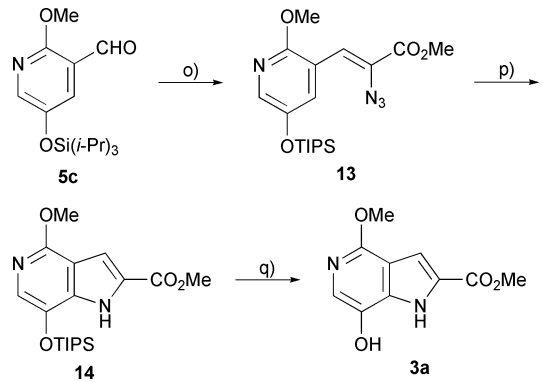


Scheme 7 Selective demethylation of dimethoxy 5- and 6-azaindoles **2** into hydroxymethoxy azaindoles **3**. *Reagents and conditions*: m) BBr_3 5 equiv, CH_2Cl_2, −78°C to rt, 16 h; n) BBr_3 2.5 equiv, CH_2Cl_2, −78 °C to rt, 16 h.

This Lewis acid-promoted demethylation reaction proved to be very substrate-sensitive. When 5-azaindole **2a** was treated with 2.5 equiv of BBr_3, a 70:30 mixture of the starting material and monodemethylated product **3a** (determined by ^{1}H NMR of the crude product) was obtained. With 5 equiv BBr_3, a mixture of **2a**/**3a** in a 16:84 ratio was formed. By comparison, the 6-aza substrate **2c** required only 2.5 equiv of BBr_3 to give a 8:92 mixture of **2c** and monodemethylated product **3c**.

We were not able to obtain a single crystal of a quality suitable for X-ray diffraction analysis of the mono-demethylated products **3a** and **3c**. In order to confirm the regioselectivity of the demethylation, we took advantage of the regioselective synthesis of formyl pyridines that we have previously developed.

Reaction of the TIPS ether of 3-formyl pyridine **5c** with methyl azidoacetate under basic conditions at 0 °C afforded the azido methyl acrylate **13**,[26] which was subsequently submitted to thermolysis conditions. Cleavage of the orthogonal TIPS protecting group on the resulting indole **14** with a fluoride source then provided indirect chemical proof of the selectivity of the demethylation, as 7-hydroxy-4-methoxy-5-azaindole **3a** was obtained (Scheme 8).



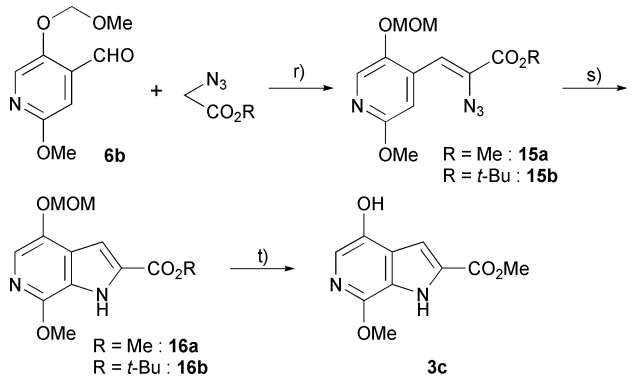
Scheme 8 Access to 7-OTIPS-protected 5-azaindole **7** and TBAF deprotection. *Reagents and conditions*: o) Methyl azidoacetate 3.8 equiv, MeONa 4.1 equiv, MeOH, 0 °C, 2 h, 20%; p) Xylene, 140 °C, 1 h, 77%; q) TBAF, 1.5 equiv, THF, 0 °C to rt, 2 h, 92%.

The same strategy was applied to confirm the regioselectivity of the demethylation of **2c** upon treatment with BBr_3. In this case, however, the three-step sequence, which concluded with an acidic hydrolysis of the methoxymethyl (MOM) ether group, afforded **3c** in a very disappointing 5% overall yield from the 4-formylpyridine **6b** (Scheme 9). The low yield when R = Me is explained by the poor stability of compound **15a** in solution, combined with the unexpectedly low-yielding indole ring formation.

We then attempted to improve the yield of the azidoacrylate formation by using the more stable *tert*-butyl azidoacetate.[27] After the exclusive formation of the azidoalcohol (**11b**) at low temperature, treatment with methanesulfonyl chloride in the presence of excess triethylamine gave the *tert*-butyl azidoacrylate **15b** in 54% yield over the two steps (Scheme 9).

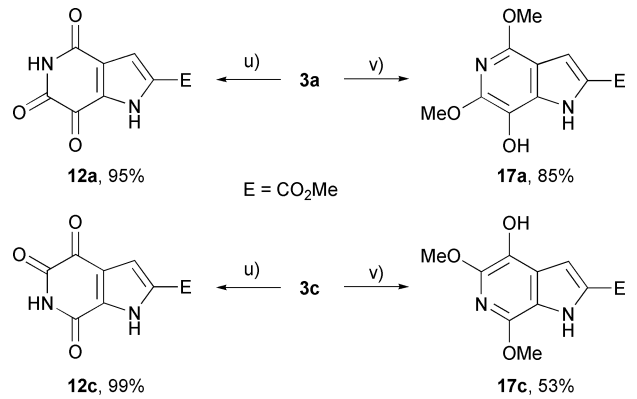
The Hemetsberger reaction then afforded the expected indole **16b** in a good 72% yield. To obtain the monohydroxy compound **3c**, hydrolysis of the MOM ether combined with an *in situ* transesterification (R = *t*-Bu to R = Me) was achieved by a simple treatment of the indole with concentrated hydrochloric acid in methanol. In this way, **3c** was obtained in an improved 19% overall yield from the 4-formylpyridine **6b**.

With the hydroxymethoxy azaindoles **3a** and **3c** in hand, we proceeded to study their behaviour when oxidised by PIFA. In contrast to the dimethoxyazaindole substrates, we found that



Scheme 9 Access to 4-OMOM-protected 6-azaindoles **16** and acidic deprotection. *Reagents and conditions*: R = Me: r) MeONa 4.1 equiv, MeOH, 30 °C, 2 h, 21%; s) Xylene, 140 °C, 2 h, 31%; t) HCl 3M, THF, 50°C, 3 h, 77%. R = *t*-Bu: r) 1) *i*-PrONa 2.0 equiv, *i*-PrOH, −30 °C, 4 h. 2) MsCl 5.0 equiv, Et_3N 10.0 equiv, CH_2Cl_2, 45 °C, 1 h, 54% over 2 steps; s) Xylene, 140 °C, 2 h, 72%; t) Conc. HCl, MeOH, rt, 4.5 h then 50 °C, 20 h, 49%.

the reaction required only one equivalent of oxidising agent for complete conversion of the substrate. When a 1:1 acetonitrile–water solvent mixture was employed, trioxopyrrolopyridines **12a** and **12c** were obtained in excellent 95 and 99% yields, respectively (Scheme 10).



Scheme 10 Solvent-dependent oxidations of hydroxymethoxy-5- and 6-azaindoles **3**. *Reagents and conditions*: u) PIFA 1 equiv, CH_3CN–water 1:1, rt, 1 h; v) PIFA 1 equiv, CH_3CN–methanol 1:1, rt, 1 h.

When water was replaced by methanol, formation of the functionalised 5- and 6-azaindoles **17a** and **17c** was observed, resulting from incorporation of a solvent-derived methoxy group into the 6- and 5-positions, respectively (Scheme 10).

In light of this last result, we can suggest a mechanism for the PIFA-mediated oxidations (figure 5). We propose that the first step consists of the activation of the pyridinol by coordination with a PIFA molecule. This is facilitated by the release of a trifluoroacetate anion. This activation would then favor the attack of a solvent molecule (either water or methanol) on the 4-position, thus forming an (hemi)acetal. The electrophilic character of the 6-position, α to the nitrogen atom, could be the driving force for a second nucleophilic attack by the solvent. There is literature precedence for a similar reaction in an azaquinone structure.[5e]

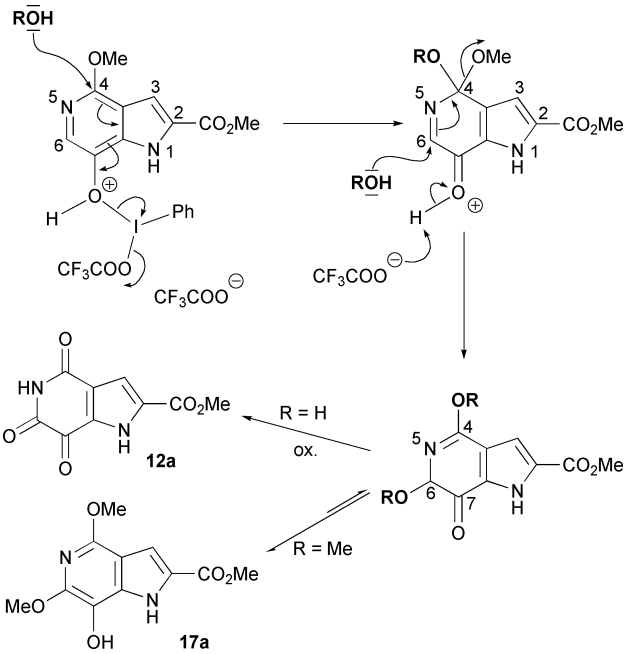


Fig. 5 Plausible mechanism for the PIFA-mediated oxidation of hydroxymethoxy-5- and 6-azaindoles **3**.

The fate of the resulting intermediate would then depend on the nature of the R group: (a) where R = Me, a simple enolisation of the ketone at the 7-position gives the hydroxydimethoxyazaindole **17**; (b) where R = H, an overoxidation occurs[28] that leads, after enolisation at the 4-position, to the trioxopyrrolopyridines **12**.

A similar mechanism could be proposed for the oxidations of dimethoxyazaindoles **2** into pyrrolopyridines **12**,[29] according to Kita's mechanism for the oxidative demethylation of *para*-dimethoxy aromatic rings into *para*-quinones.[20]

Conclusions

In summary, we have described a regioselective synthesis of dimethoxy-5- and 6-azaindoles starting from a common substrate **7**. The reactivity of these nitrogen-containing heterocycles towards Lewis acid-promoted demethylation reactions and PIFA-mediated oxidative demethylations was investigated. The structures of the novel trioxopyrrolopyridine products were proved by crystallographic and spectroscopic means.

We have also demonstrated the utility of these unprecedented oxidation reactions of dimethoxy- and hydroxymethoxyazaindoles as entries to trioxopyrrolopyridines and functionalised azaindoles.

Experimental

Unless otherwise indicated, all reactions were carried out under a positive pressure of argon and with oven-dried glassware. Melting points were measured on a Barnstead Electrothermal 9200 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR SPECTRUM ONE spectrometer (film or 1% in KBr). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker ALS300 and DRX 300 Fourier transform spectrometers, using an internal

deuterium lock, operating at 300 MHz. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, $\delta_H = 0.00$; $CDCl_3$, $\delta_H = 7.26$; acetone-d_6, $\delta_H = 2.05$ and DMSO-d_6, $\delta_H = 2.50$).[30] Data are presented as follows: chemical shift (δ, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad), coupling constant (reported in Hz), assignment. Atom numbering refers to pyridine and indole nomenclatures. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AC200 and DRX 300 Fourier transform spectrometers, using an internal deuterium lock, operating at 50 MHz and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, $\delta_C = 0.00$; $CDCl_3$, $\delta_C = 77.16$; acetone-d_6, $\delta_C = 29.84$ and DMSO-d_6, $\delta_C = 39.52$). Carbon multiplicities (indicated in parentheses) were determined by DEPT experiments. Electron-spray low-resolution mass spectra were recorded on a Thermo ALCQ Advantage spectrometer. Gas chromatography coupled with low-resolution mass spectroscopy (GC-MS) were recorded on a Thermo Focus GC (fused silica column, diameter 0.25 mm, length 15 m, coated with TR5M5, thickness 0.25 μm, initial temperature for 2 min: 70 °C, heating rate 15 °C min^{-1}) DSQ spectrometer operating at 70 eV. High-resolution mass spectra were recorded on a Thermoquest Finnigan MAT 95 XL spectrometer (for chemical ionisations, isobutane was used). Elemental analyses were performed by the Service Central d'Analyses du CNRS, Solaize, France.

Product purification by flash column chromatography was performed using Merck Kieselgel 60 Å (40–63 μm). Analytical thin layer chromatography (TLC) was carried out using Merck commercial aluminium sheets coated (0.2 mm layer thickness) with Kieselgel 60 F254, with visualization by ultraviolet and anisaldehyde stain solution. *N*,*N*-dimethylformamide (HPLC grade) was used as received without purification. THF (anhydrous analytical grade, stored over molecular sieves) was purchased from Carlo Erba Chemicals. Dichloromethane was distilled over calcium hydride prior to use. Diisopropylamine was distilled over sodium hydride prior to use. Methanol and isopropanol were distilled over sodium prior to use. Petroleum ether (PE) refers to the 40–60 °C boiling point fraction. MeLi and *n*-BuLi solutions were titrated using *N*-benzylbenzamide.[31] All other chemical reagents were used as received.

5-Hydroxy-2-methoxypyridine **7** and 2-methoxy-5-(methoxymethoxy)pyridine **8b** were prepared according to known procedures.[9] Methyl- and *tert*-butyl azidoacetate were prepared from methyl- and *tert*-butyl bromoacetate and sodium azide according to a literature procedure.[32]

5-Bromo-2-methoxypyridine

To a solution of 2-methoxypyridine (10.91 g, 100 mmol) in CH_3CN (300 mL) was added *N*-bromosuccinimide (21.36 g, 120 mmol). The mixture was then heated at reflux (90 °C) for 9 h. After cooling down to rt, the mixture was filtered over a pad of silica (3 cm thick, washing with PE–Et_2O 80:20) and, after evaporation of the filtrate under reduced pressure, the crude oil was purified by flash chromatography (PE–Et_2O 95:5) to afford the *title compound* (15.212 g, 81%) as a colorless oil.

Spectral data were identical to those reported in the literature.[8]

General experimental procedure for the methylation of pyridinols: preparation of 2,5-dimethoxypyridine 8a

To a solution of 5-hydroxy-2-methoxypyridine **7** (1.877 g, 15 mmol) in DMF (45 mL) at room temperature was added K_2CO_3 (3.110 g, 22.5 mmol). The mixture was stirred at 50 °C for 10 min, then methyl iodide (935 μL, 15 mmol) was added. The reaction mixture was then stirred for 3 h 30 min at 50 °C. After addition of water (50 mL) and EtOAc (100 mL) and decantation, the aqueous phase was extracted with EtOAc (2 × 100 mL) and the organic phase was dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 70:30) to afford **8a** (1.790 g, 86%) as a yellow liquid.

ν_{max} (film)/cm^{-1} 3583, 2947, 2838, 1738, 1611, 1576, 1493, 1464, 1382, 1253, 1185, 1039, 828 and 742; δ_H (300 MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.69 (1H, d, $J = 9.0$, ArH3), 7.21 (1H, dd, $J = 9.0$ and $J = 3.0$, ArH4) and 7.80 (1H, d, $J = 3.0$, ArH6); δ_C (75 MHz; $CDCl_3$) 53.4 (CH_3), 56.2 (CH_3), 111.0 (CH), 126.7 (CH), 131.0 (CH), 151.1 (C) and 158.7 (C); GC-MS (retention time: 3.97 min) *m*/*z* (EI) 139 ($M^{+\bullet}$, 96%), 138 (100), 96 (48) and 54 (44).

2-Methoxy-5-(triisopropylsilanyloxy)pyridine 8c

To a solution of 5-hydroxy-2-methoxypyridine **7** (2.503 g, 20 mmol) and imidazole (2.859 g, 42 mmol) in DMF (60 mL) at room temperature was added triisopropylsilyl chloride (5.2 mL, 24 mmol). The reaction mixture was stirred for 20 h, after which water (50 mL) and EtOAc (100 mL) were added. After decantation, the aqueous phase was extracted with EtOAc (2 × 100 mL) and the organic phase was dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 90:10) to afford **8c** (6.336 g, quantitative) as a pale yellow liquid.

ν_{max} (film)/cm^{-1} 2945, 2893, 2867, 2727, 1743, 1724, 1607, 1584, 1573, 1488, 1464, 1432, 1378, 1256, 1195, 1115, 1060, 1031, 997, 912, 883, 818 and 688; δ_H (300 MHz; $CDCl_3$) 1.08 (18H, d, $J =$ 6.8, $(CH(CH_3)_2)_3$), 1.16–1.28 (3H, m, $(CH(CH_3)_2)_3$), 3.87 (3H, s, OCH_3), 6.61 (1H, d, $J = 8.9$, ArH3), 7.1((1H, dd, $J = 8.9$ and $J =$ 3.0, ArH4) and 7.79 (1H, d, $J = 3.0$, ArH6); δ_C (75 MHz; $CDCl_3$) 12.6 (CH), 17.8 (CH_3), 53.4 (CH_3), 110.8 (CH), 131.1 (CH), 136.8 (CH), 147.4 (C) and 158.6 (C); GC-MS (retention time: 9.83 min) *m*/*z* (EI) 281 ($M^{+\bullet}$, 22%), 238 (62), 210 (50), 182 (100) and 168 (58).

Typical experimental procedure for the formylation of 5-substituted 2-methoxypyridines 8: preparation of 5a and 6a

To a solution of 2,5-dimethoxypyridine **8a** (417 mg, 3.0 mmol) in anhydrous THF (10 mL) was added diisopropylamine (10 μL, 0.06 mmol). The mixture was then cooled to −40 °C and MeLi (1.6 M solution in Et_2O, 3.4 mL, 5.4 mmol) was slowly added. The resulting mixture was stirred at 0 °C for 3 h, then cooled to −40 °C and *N*-formylpiperidine (600 μL, 5.4 mmol) was added. The mixture was stirred at −40 °C for 2 h then quenched by careful addition of a solution of 37% aqueous HCl (3 mL) in THF (7 mL). The temperature was raised to 20 °C, then water (30 mL) and EtOAc (150 mL) were added. The pH of the resulting mixture was then adjusted to 8–9 with solid K_2CO_3. After decantation,

the aqueous phase was extracted with EtOAc (2 × 20 mL). After drying of the combined organic phases with Na_2SO_4 and filtration, the solvents were removed under reduced pressure. The resulting crude product was purified by flash chromatography (PE–EtOAc 96:4 to 80:20).

The less polar fraction was 2,5-dimethoxypyridine-3-carbaldehyde **5a** (77 mg, 15% yield, colorless solid).

Mp 64–66 °C; Anal. found C, 57.4; H, 5.5; N, 8.35. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4; ν_{max} (KBr)/cm^{-1} 3461, 3055, 2953, 2875, 1679, 1611, 1577, 1488, 1445, 1432, 1411, 1382, 1305, 1290, 1258, 1211, 1172, 1044, 1012, 955, 904, 800, 752 and 737; δ_H (300 MHz; $CDCl_3$) 3.84 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.66 (1H, d, J = 3.3, ArH), 8.10 (1H, d, J = 3.3, ArH) and 10.35 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 53.9 (CH_3), 56.2 (CH_3), 117.9 (C), 121.0 (CH), 140.5 (CH), 151.4 (C), 159.4 (C) and 189.1 (CH).

The more polar fraction was 2,5-dimethoxypyridine-4-carbaldehyde **6a** (279 mg, 56% yield, yellow solid).

Mp 98–100 °C; ν_{max} (KBr)/cm^{-1} 3362, 2976, 2914, 1697, 1616, 1563, 1485, 1456, 1446, 1436, 1396, 1381, 1314, 1277, 1242, 1220, 1190, 1040, 1011, 930, 883, 873 and 742; δ_H (300 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 7.08 (1H, s, ArH), 8.01 (1H, s, ArH) and 10.43 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 53.9 (CH_3), 56.7 (CH_3), 107.8 (CH), 131.5 (CH), 133.3 (C), 151.0 (C), 159.1 (C) and 189.2 (CH); m/z (EI) 167 ($M^{+\bullet}$, 100%), 166 (75) and 44 (88); HRMS (EI) found ($M^{+\bullet}$) 167.0580, $C_8H_9NO_3$ requires 167.0582.

2-Methoxy-5-(methoxymethoxy)pyridine-4-carbaldehyde 6b

Compound **6b** was prepared according to the same procedure as for compounds **5a**/**6a**, scale: 2-methoxy-5-methoxymethoxy-pyridine (1.523 g, 9.0 mmol), THF (30 mL), diisopropylamine (30 μL, 0.18 mmol), MeLi 1.6 M in Et_2O (10.2 mL, 16.2 mmol), *N*-formylpiperidine (1.8 mL, 16.2 mmol). The crude product was purified by flash chromatography (PE–EtOAc 90:10 to 80:20) to afford **6b** (1.083 g, 61%) as a yellow solid.

Mp 39–40 °C; ν_{max} (KBr)/cm^{-1} 3369, 2973, 2930, 1739, 1699, 1609, 1486, 1380, 1235, 1195, 1155, 1083, 1032, 986 and 930; δ_H (300 MHz; $CDCl_3$) 3.53 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.25 (2H, s, CH_2OCH_3), 7.07 (1H, s, ArH), 8.23 (1H, s, ArH), 10.43 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 54.1 (CH_3), 56.7 (CH_3), 96.3 (CH_2), 107.6 (CH), 134.3 (C), 136.0 (CH), 149.0 (C), 159.9 (C) and 189.2 (CH); m/z (CI) 199 (10%), 198 (MH^+, 100) and 89 (15); HRMS (CI) found (MH^+) 198.0766, $C_9H_{12}NO_4$ requires 198.0766.

2-Methoxy-5-(triisopropylsilanyloxy)pyridine-3-carbaldehyde 5c

Compound **5c** was prepared according to the same procedure as for compounds **5a**/**6a**, scale: 2-methoxy-5-triisopropylsilanyloxy-pyridine (2.815 g, 10.0 mmol), THF (35 mL), diisopropylamine (30 μL, 0.2 mmol), MeLi (1.5 M in Et_2O, 12.0 mL, 18.0 mmol), *N*-formylpiperidine (2.0 mL, 18.0 mmol). The crude product was purified by flash chromatography (PE–EtOAc 98:2 to 96:4) to afford **5c** (1.965 g, 64%) as a yellow oil.

ν_{max} (film)/cm^{-1} 2943, 2893, 2868, 2748, 1742, 1691, 1602, 1569, 1474, 1430, 1383, 1286, 1244, 1211, 1048, 1018, 1003, 910, 882, 844, 801, 755, 690, 665 and 587; δ_H (300 MHz; $CDCl_3$) 1.10 (18H, d, J = 6.8, ($CH(CH_3)_2)_3$), 1.18–1.30 (3H, m, ($CH(CH_3)_2)_3$), 4.02 (3H, s, OCH_3), 7.61 (1H, d, J = 3.1, ArH), 8.04 (1H, d, J = 3.1, ArH) and 10.32 (1H, s, CHO); δ_C (50 MHz; $CDCl_3$) 12.5 (CH), 17.8 (CH_3), 53.9 (CH_3), 118.3 (C), 127.6 (CH), 144.2 (CH), 147.9 (C), 159.3 (C) and 189.3 (CH); m/z (CI) 311 (23%) and 310 (MH^+, 100); HRMS (CI) found (MH^+) 310.1838, $C_{16}H_{28}NO_3Si$ requires 310.1838.

Typical experimental procedure for the acidic deprotection of 6b: 5-hydroxy-2-methoxy-pyridine-4-carbaldehyde 9

To a solution of 2-methoxy-5-(methoxymethoxy)pyridine-4-carbaldehyde **6b** (986 mg, 5 mmol) in THF (10 mL) was added 3 N aqueous HCl (15 mL) and the resulting mixture was stirred at 50 °C for 3 h. After this time, the mixture was cooled to room temperature and water (100 mL) was added followed by neutralisation (pH 7–8) with solid K_2CO_3. The aqueous phase was extracted with EtOAc (3 × 100 mL). After drying of the organic phase over Na_2SO_4, filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 70:30) to afford **9** (725 mg, 95%) as a yellow powder.

Mp 136–137 °C; ν_{max} (KBr)/cm^{-1} 3436, 2925, 2616, 1691, 1677, 1472, 1449, 1424, 1394, 1324, 1298, 1229, 1119, 1048, 921, 854, 830 and 733; δ_H (300 MHz; $CDCl_3$) 3.93 (3H, s, OCH_3), 6.93 (1H, d, J = 0.5, ArH3), 8.08 (1H, s, ArH5), 9.46 (1H, s, ArOH) and 9.97 (1H, d, J = 0.5, CHO); δ_C (75 MHz; $CDCl_3$) 54.2 (CH_3), 111.6 (CH), 127.7 (C), 137.3 (CH), 149.0 (C), 158.4 (C) and 196.6 (CH); m/z (ESI^+) 186 (M + CH_3OH + H^+, 100%), 168 (46) and 154 (MH^+, 49); HRMS (EI) found ($M^{+\bullet}$) 153.0421, $C_7H_7NO_3$ requires 153.0426.

Typical experimental procedure for the fluoride-promoted deprotection of 5c: preparation of 5-hydroxy-2-methoxypyridine-3-carbaldehyde 10

Tetra-*n*-butylammonium fluoride (1 M solution in THF, 15 mL, 15 mmol) was added to a stirred solution of 2-methoxy-5-(triisopropylsilanyloxy)pyridine-3-carbaldehyde **5c** (3.095 g, 10 mmol) in anhydrous THF (15 mL) at 0 °C. The temperature was allowed to rise to room temperature and the resulting mixture for stirred for 2 h. After addition of water (15 mL) and EtOAc (50 mL) and decantation, the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with water (2 × 50 mL) and dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 50:50) to afford **10** (1.408 g, 92%) as a white solid.

Mp 104–105 °C; Anal. found C, 54.6; H, 4.6; N, 9.05. $C_7H_7NO_3$ requires C, 54.9; H, 4.6; N, 9.15; ν_{max} (KBr)/cm^{-1} 3466, 3084, 3007, 2962, 2888, 1674, 1312, 1588, 1483, 1460, 1426, 1390, 1323, 1307, 1283, 1226, 1207, 1170, 1132, 1049, 995, 897, 751 and 743; δ_H (300 MHz; $CDCl_3$) 4.03 (3H, s, OCH_3), 5.09 (1H, br s, ArOH), 7.64 (1H, d, J = 3.2, ArH), 8.07 (1H, d, J = 3.2, ArH) and 10.33 (1H, s, CHO); δ_C (50 MHz; $CDCl_3$) 54.1 (CH_3), 118.2 (C), 124.3 (CH), 140.9 (CH), 148.2 (C), 159.3 (C) and 190.2 (CH); m/z (ESI^+) 200 (66%), 186 (M + CH_3OH + H^+, 100) and 154 (MH^+, 59); m/z (ESI^-) 152 (M − H^-, 100%) and 137 (44).

2,5-Dimethoxypyridine-4-carbaldehyde 6a from 5-hydroxy-2-methoxy-pyridine-4-carbaldehyde 9

Compound **6a** was prepared according to the same procedure as for compound **8a**, scale: 5-hydroxy-2-methoxypyridine-4-carbaldehyde **9** (718 mg, 4.7 mmol), DMF (15 mL), K_2CO_3

(971 mg, 7.05 mmol), methyl iodide (295 μL, 4.7 mmol). The crude product was purified by flash chromatography (PE–EtOAc 70:30) to afford **6a** (1.930 g, 96%) as a pale yellow solid.

2,5-Dimethoxypyridine-3-carbaldehyde 5a from 5-hydroxy-2-methoxy-pyridine-3-carbaldehyde 10

Compound **5a** was prepared according to the same procedure as for compound **8a**, scale: 5-hydroxy-2-methoxypyridine-3-carbaldehyde **10** (1.838 g, 12 mmol), DMF (36 mL), K_2CO_3 (2.488 g, 18 mmol). The mixture was stirred at 50 °C for 10 min and then methyl iodide (295 μL, 4.7 mmol). The crude product was purified by flash chromatography (PE–EtOAc 70:30) to afford **5a** (693 mg, 89%) as a pale yellow powder.

Condensation reaction between 3-formyl pyridine 5a and methyl azidoacetate

Sodium metal (226 mg, 9.84 mmol) was added to anhydrous methanol (6 mL) at 0 °C and the resulting mixture stirred until the metal completely dissolved. To this preformed sodium methoxide solution at 0 °C was slowly added (over a 5 min period) a solution in methanol (6 mL) of aldehyde **5a** (401 mg, 2.4 mmol) and methyl azidoacetate (1.055 g, 3.8 mmol). The mixture was stirred at 0 °C for 3 h, then poured onto crushed ice (40 g, in an open beaker) and left for one hour in a refrigerator at 4 °C. The product was recovered by filtration on a sintered glass funnel (no. 4) and dried under vacuum to give a pale yellow solid (315 mg). This product consisted of a 28:72 mixture (determined by ^{1}H NMR) of azidoacrylate **4a** and azidoalcohol **11a**, respectively. The crude product was purified by flash chromatography (PE–AcOEt 70:30, the solid was adsorbed onto silica).

The less polar fraction was 2-azido-3-(2,5-dimethoxypyridin-3-yl)acrylic acid methyl ester **4a** (87 mg, pale yellow powder, 14% yield).

Mp 123–124 °C; ν_{max} (KBr)/cm^{-1} 3088, 2986, 2941, 2853, 2120, 1702, 1611, 1571, 1470, 1440, 1400, 1382, 1347, 1303, 1279, 1261, 1214, 1182, 1146, 1082, 1019 and 962. δ_H (300 MHz; DMSO-d_6) 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 7.03 (1H, s, CH), 7.89 (1H, d, J = 3.0, ArH) and 8.13 (1H, d, J = 3.0, ArH); δ_C (75 MHz; DMSO-d_6) 53.3 (CH_3), 53.8 (CH_3), 56.2 (CH_3), 115.7 (C), 116.0 (CH), 125.3 (CH), 127.3 (C), 132.7 (CH), 150.4 (C), 155.2 (C) and 163.0 (C); m/z (CI) 265 (MH^+, 31%), 238 (14) and 237 (MH^+-N_2, 100); HRMS (CI) found (MH^+) 265.0938, $C_{11}H_{13}N_4O_4$ requires 265.0937.

The more polar fraction was 2-azido-3-(2,5-dimethoxypyridin-3-yl)-3-hydroxypropionic acid methyl ester **11a** (205 mg, white powder, 20% yield).

Mp 145–146 °C; ν_{max} (KBr)/cm^{-1} 3413, 3153, 2965, 2935, 2130, 2098, 1742, 1589, 1484, 1435, 1405, 1351, 1274, 1295, 1214, 1250, 1205, 1068, 1043, 1014, 1008, 947 and 817; δ_H (300 MHz; DMSO-d_6) 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.17 (1H, d, J = 2.3, CHN_3), 5.31 (1H, dd, J = 5.0 and J = 2.3, C*H*OH), 6.23 (1H, d, J = 5.0, disappears after D_2O addition, OH), 7.46 (1H, d, J = 3.0, ArH), 7.80 (1H, d, J = 3.0, ArH); δ_C (75 MHz; DMSO-d_6) 52.7 (CH_3), 53.4 (CH_3), 56.0 (CH_3), 64.0 (CH), 68.5 (CH), 124.1 (CH), 124.3 (C), 129.6 (CH), 151.1 (C), 153.6 (C) and 169.1 (C); m/z (CI) 283 (MH^+, 32%), 265 (MH^+-H_2O, 25), 168 (100) and 88 (37); HRMS (CI) found (MH^+) 283.1044, $C_{11}H_{15}N_4O_5$ requires 283.1042.

Typical experimental procedure for the preparation of azidoacrylates: 2-azido-3-(2,5-dimethoxypyridin-3-yl)acrylic acid methyl ester 4a

Sodium metal (189 mg, 8.2 mmol) was added to anhydrous methanol (4 mL) at 0 °C and the resulting mixture was stirred until the metal completely dissolved. To this preformed sodium methoxide solution at 30 °C was quickly added (within 30 seconds) a solution of aldehyde **5a** (335 mg, 2.0 mmol) and methyl azidoacetate (1.055 g, 7.6 mmol) in methanol (6 mL). The mixture was stirred at 30 °C for 2 h, then poured onto crushed ice (40 g, in an open beaker) and left for one hour in a refrigerator at 4 °C. The product was recovered by filtration on a sintered glass funnel (no. 4) and dried under vacuum to afford **4a** (315 mg, 57%) as an off-white powder.

2-Azido-3-(2,5-dimethoxypyridin-4-yl)acrylic acid methyl ester 4b

Compound **4b** was prepared according to the same procedure as for compound **4a**, scale: sodium metal (189 mg, 8.2 mmol), anhydrous methanol (4 mL), methanol (6 mL), aldehyde (335 mg, 2 mmol), methyl azidoacetate (875 mg, 7.6 mmol), to afford **4b** as a yellow powde (268 mg, 51%).

Mp 117–118 °C (decomposed); ν_{max} (KBr)/cm^{-1} 3439, 3108, 2946, 2925, 2851, 2127, 1716, 1602, 1548, 1487, 1463, 1435, 1384, 1322, 1281, 1254, 1214, 1189, 1082, 1044, 1014, 888 and 739; δ_H (300 MHz; acetone-d_6) 3.84 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.12 (1H, s, CH), 7.50 (1H, s, ArH), 7.89 (1H, s, ArH); δ_C (75 MHz; acetone-d_6) 53.6 (CH_3), 53.6 (CH_3), 57.2 (CH_3), 111.1 (CH), 116.1 (CH), 130.3 (CH), 130.5 (C), 133.3 (C), 149.3 (C), 159.4 (C) and 164.0 (C); m/z (EI) 264 ($M^{+\bullet}$, 53%), 204 (49), 177 (58), 64 (54) and 59 (100); HRMS (EI) found ($M^{+\bullet}$) 264.0856, $C_{11}H_{12}N_4O_4$ requires 264.0859.

4,7-Dimethoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 2a

The reaction was carried out in a 100 mL round-bottomed flask, open to the atmosphere *via* a condenser and an addition funnel. To hot xylene (13 mL) at 140 °C was slowly added with vigorous stirring a suspension of acrylate **4a** (423 mg, 1.6 mmol) in xylene (27 mL). Once the addition was complete, the mixture was stirred for 1 h at 140 °C, then slowly cooled down to room temperature overnight without stirring. After the complete crystallisation of the solid, the supernatant was removed and the solid dried under high vacuum to give 5-azaindole **2a** (310 mg, 82%) as pale pink crystals.

Mp 192–193 °C; Anal. found C, 55.8; H, 5.3; N, 11.65. $C_{11}H_{12}N_2O_4$ requires C, 55.95; H, 5.1; N, 11.85; ν_{max} (KBr)/cm^{-1} 3437, 3300, 2948, 2924, 1702, 1619, 1593, 1537, 1499, 1465, 1446, 1429, 1360, 1307, 1258, 1208, 1157, 1098, 1087, 984, 853 and 754; δ_H (300 MHz; DMSO-d_6) 3.84 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.10 (1H, s, ArH), 7.47 (1H, s, ArH) and 12.57 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 51.9 (CH_3), 52.8 (CH_3), 56.4 (CH_3), 106.5 (CH), 113.0 (C), 120.4 (CH), 127.5 (C), 134.2 (C), 140.0 (C), 152.8 (C) and 160.9 (C); m/z (CI) 238 (12%) and

237 (MH^+, 100); HRMS (CI) found (MH^+) 237.0874, $C_{11}H_{13}N_2O_4$ requires 237.0875.

4,7-Dimethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 2c

The reaction was carried out in a 50 mL round-bottomed flask, open to the atmosphere *via* a condenser and an addition funnel. To hot xylene (8 mL) at 140 °C was slowly added with vigorous stirring a solution of acrylate **4b** (264 mg, 1.0 mmol) in xylene (16 mL). Once the addition was complete, the mixture was stirred for 1 h at 140 °C, then cooled to room temperature over 4 h and kept in a freezer at −20 °C overnight. The supernatant was removed and the solid dried under high vacuum to give 6-azaindole **2c** (73 mg, 31%) as a pale yellow powder. The supernatant was purified by flash chromatography (PE–EtOAc 50:50) to afford **2c** (61 mg, 26%) as a pale yellow powder; overall yield = 57%.

Mp 169–170 °C; ν_{max} (KBr)/cm^{-1} 3306, 2994, 2939, 1713, 1511, 1470, 1448, 1340, 1320, 1288, 1234, 1202, 1097, 992, 827 and 747; δ_H (300 MHz; DMSO-d_6) 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.07 (1H, s, ArH), 7.27 (1H, s, ArH) and 12.62 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 52.0 (CH_3), 52.8 (CH_3), 55.9 (CH_3), 104.9 (CH), 114.7 (CH), 123.0 (C), 124.8 (C), 129.0 (C), 145.7 (C), 146.4 (C) and 161.0 (C); *m*/*z* (EI) 236 ($M^{+\bullet}$, 100%), 221 ($M^{+\bullet} - CH_3^{\bullet}$, 7), 204 ($M^{+\bullet} - CH_3OH$, 53), 189 ($M^{+\bullet} - CH_3OH - CH_3^{\bullet}$, 54); HRMS (EI) found ($M^{+\bullet}$) 236.0798, $C_{11}H_{12}N_2O_4$ requires 236.0797.

1-Benzyl-4,7-dimethoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 2b

To a solution of 5-azaindole **2a** (100 mg, 0.42 mmol) in DMF (3 mL) at room temperature, was added in one portion sodium hydride (60% dispersion in mineral oil, 20 mg, 0.50 mmol). The mixture was heated to 50 °C and stirred for 3 h 30 min. Benzyl bromide (50 µL, 0.42 mmol) was then added and the resulting mixture stirred for an additional 2 h at 50 °C. After cooling to room temperature, water (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 20 mL). The organic phases were dried over Na_2SO_4, filtered and the solvents removed under reduced pressure. The resulting crude product was purified by flash chromatography (PE–EtOAc 70:30) to afford compound **2b** (101 mg, 74%) as a white powder.

Mp 121–122 °C; ν_{max} (KBr)/cm^{-1} 3435, 3028, 3008, 2940, 1712, 1657, 1606, 1520, 1483, 1452, 1437, 1400, 1362, 1312, 1269, 1234, 1203, 1101, 1066, 1011, 985, 857, 749 and 727; δ_H (300 MHz; DMSO-d_6) 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.04 (2H, s, CH_2Ph), 6.93 (2H, d, J = 7.0, CH_2*o*-Ar*H*), 7.17–7.29 (3H, m, CH_2Ar*H*), 7.30 (1H, s, ArH) and 7.54 (1H, s, ArH); δ_C (75 MHz; DMSO-d_6) 49.3 (CH_2), 52.0 (CH_3), 53.0 (CH_3), 56.6 (CH_3), 109.4 (CH), 111.9 (C), 122.0 (CH), 125.9 (CH), 127.0 (CH), 127.0 (C), 128.5 (CH), 134.5 (C), 139.2 (C), 140.5 (C), 153.1 (C) and 160.9 (C); *m*/*z* (ESI$^+$) 328 (19%), 327 (MH^+, 100); HRMS (ESI$^+$) found (MH^+) 327.1347, $C_{18}H_{19}N_2O_4$ requires 327.1345.

Experimental procedure for the oxidation of 4,7-dimethoxy 5-azaindole 2a: 4,6,7-trioxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 12a

To a solution of 5-azaindole **2a** (47 mg, 0.2 mmol) in a 1:1 acetonitrile–water mixture (16 mL) at room temperature was added in one portion [bis(trifluoroacetoxy)iodo]benzene (PIFA) (86 mg, 0.2 mmol). After stirring for one hour, a further portion of PIFA (86 mg, 0.2 mmol) was added. This procedure was repeated two more times, after 2 h and 3 h reaction time, so that a total of four equivalents (344 mg, 0.8 mmol) of PIFA were used. One hour after the last PIFA addition, the mixture was filtered on a sintered glass funnel filled with a pad of silica gel 1 cm thick, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 50:50) to afford a pink solid. This solid was then washed with dichloromethane to give the trioxo compound **12a** (43 mg, 97%) as a pale yellow solid.

Mp 269–270 °C; ν_{max} (KBr)/cm^{-1} 3210, 3137, 2924, 2853, 1690, 1554, 1455, 1432, 1287, 1229, 1138, 1096, 974, 927 and 799; δ_H (300 MHz; DMSO-d_6) 3.85 (3H, s, OCH_3), 7.16 (1H, s, H3), 11.54 (1H, s, H5) and 14.00 (1H, br s, H1); δ_C (75 MHz; DMSO-d_6) 52.4 (CH_3), 113.3 (CH), 123.9 (C), 130.3 (C), 132.8 (C), 158.7 (C), 160.0 (C), 160.7 (C) and 166.5 (C); *m*/*z* (ESI$^+$) 463 (48%), 445 (54), 427.1 (2M + H^+, 29), 222.9 (MH^+, 100), 209 (24); HRMS (ESI$^+$) found (M + Na^+) 245.0174, $C_9H_6N_2O_5Na$ requires 245.0174.

The single crystal for the X-ray diffraction analysis was obtained as follows: a solution of compound **12a** (1 mg) in acetone (0.7 mL) was allowed to stand for three days at room temperature (20 °C) in a test tube (without capping). The resulting colorless needle (0.06 × 0.07 × 0.21 mm) was then analyzed on a Nonius Kappa CCD diffractometer at 293 K. CCDC reference number 641655. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b719776d.†

Experimental procedure for the oxidation of 7-hydroxy 4-methoxy 5-azaindole 3a: preparation of compound 12a

To a solution of 5-azaindole **3a** (22 mg, 0.1 mmol) in a 1:1 acetonitrile–water mixture (8 mL) at room temperature was added in one portion [bis(trifluoroacetoxy)iodo]benzene (PIFA) (44 mg, 0.1 mmol). After stirring for one hour, the resulting mixture was filtered off on a sintered glass funnel filled with a pad of silica gel 1 cm thick, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 50:50) to afford the trioxo compound **12a** (19 mg, 95%) as an orange solid.

Typical experimental procedure for the oxidation of *N*-benzyl-4,7-dimethoxy 5-azaindole 2b: preparation of 1-Benzyl-4,6,7-trioxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 12b

To a solution of *N*-benzyl-5-azaindole **2b** (68 mg, 0.21 mmol) in a 1:1 acetonitrile–water mixture (23 mL) at room temperature was added in one portion [bis(trifluoroacetoxy)iodo]benzene (PIFA) (359 mg, 0.84 mmol). After stirring for 4 h, the resulting mixture was filtered off on a sintered glass funnel filled with a pad of silica gel 1 cm thick, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 70:30) to afford compound **12b** (53 mg, 81%) as a pale brown solid.

Mp 208–209 °C; ν_{max} (KBr)/cm^{-1} 3205, 3120, 2924, 2853, 1728, 1710, 1674, 1526, 1489, 1454, 1425, 1382, 1255, 1186, 1119, 1078, 945, 737 and 707; δ_H (300 MHz; DMSO-d_6) 3.79 (3H, s, OCH_3),

5.99 (2H, s, CH_2Ph), 7.13 (2H, d, $J = 6.4$, CH_2*o*-Ar*H*), 7.25–7.30 (3H, m, CH_2Ar*H*), 7.32 (1H, s, H3) and 11.70 (1H, s, H5); δ_C (75 MHz; DMSO-d_6) 49.7 (CH_2), 52.5 (CH_3), 115.3 (CH), 123.5 (C), 126.7 (CH), 127.4 (CH), 128.5 (CH), 129.5 (C), 132.0 (C), 136.8 (C), 158.5 (C), 159.7 (C), 160.3 (C) and 167.1 (C); *m/z* (ESI$^+$) 648 (32%), 647 (2M + Na^+, 100), 335 (M + Na^+, 11), 313 (MH^+, 8); HRMS (ESI$^+$) found (M + Na^+) 335.0647, $C_{16}H_{12}N_2O_5Na$ requires 335.0644.

Preparation of compound 12c from 4,7-dimethoxy-6-azaindole 2c: 4,5,7-trioxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 12c

Compound **12c** was prepared according to the same procedure as for compound **12b**, scale: 6-azaindole **2c** (50 mg, 0.21 mmol), [bis(trifluoroacetoxy)iodo]benzene (PIFA) (365 mg, 0.85 mmol), 1:1 acetonitrile–water mixture (16 mL). The crude product was purified by flash chromatography (PE–EtOAc 50:50) to afford **12c** (27 mg, 57%) as a yellow powder.

Mp 261–262 °C; ν_{max} (KBr)/cm^{-1} 3436, 3203, 3124, 2925, 2854, 1691, 1561, 1503, 1483, 1425, 1395, 1331, 1276, 1234, 1140, 1101, 990, 932, 809 and 774; δ_H (300 MHz; DMSO-d_6) 3.84 (3H, s, OCH_3), 7.18 (1H, s, H3), 11.73 (1H, br s, H6) and 14.06 (1H, very br s, H1); δ_C (75 MHz; DMSO-d_6) 52.2 (CH_3), 112.5 (CH), 124.3 (C), 129.7 (C), 132.7 (C), 157.3 (C), 159.2 (C), 160.2 (C) and 171.1 (C); *m/z* (ESI$^+$) 468 (22%), 467 (2M + Na^+, 100), 245 (M + Na^+, 15); *m/z* (ESI$^-$) for $C_9H_5N_2O_5$ 221 (M − H^-, 100%); HRMS (ESI$^+$) found (M + Na^+) 245.0177, $C_9H_6N_2O_5Na$ requires 245.0174.

Preparation of compound 12c from 4-hydroxy-7-methoxy 6-azaindole 3c

Compound **12c** was also prepared according to the same procedure as for compound **12a** (from 7-hydroxy 4-methoxy 5-azaindole **3a**), scale: 6-azaindole **3c** (30 mg, 0.134 mmol), [Bis(trifluoroacetoxy)iodo]benzene PIFA (59 mg, 0.137 mmol), 1:1 acetonitrile–water mixture (8 mL). The crude product was purified by flash chromatography (PE–EtOAc 40:60) to afford **12c** (29.5 mg, 99%) as an orange powder.

Typical experimental procedure for the BBr_3 monodemethylation of 4,7-dimethoxyazaindole 2a: preparation of 7-hydroxy-4-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 3a

To a cooled (−78 °C) solution of dimethoxy-5-azaindole **2a** (25 mg, 0.10 mmol) in dichloromethane (2 mL) was added dropwise a 1 M solution of BBr_3 in dichloromethane (535 µL, 0.53 mmol). The mixture was then stirred at room temperature for 16 h. Methanol (2 mL) was added dropwise and the solvent was removed *in vacuuo*. Water (4 mL) was added to the residue and the pH of this solution was carefully adjusted to pH 7 (controlled with a calibrated pH meter) with 0.5 M sodium hydroxide solution. The aqueous phase was extracted with EtOAc (3 × 10 mL) and, after drying over Na_2SO_4, the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (PE–Et_2O 20:80) to afford compound **3a** (13.5 mg, 57%) as a yellow solid.

Mp 183–184 °C (decomposed); ν_{max} (KBr)/cm^{-1} 3315, 2924, 2854, 1711, 1628, 1601, 1541, 1497, 1442, 1389, 1327, 1278, 1208, 1161, 1093, 1071, 989, 936, 829, 749 and 708; δ_H (300 MHz; DMSO-d_6) 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.09 (1H, s, ArH), 7.34 (1H, s, ArH), 9.28 (1H, br s, ArOH) and 12.07 (1H, br s, NH); δ_C (50 MHz; DMSO-d_6) 51.9 (CH_3), 52.6 (CH_3), 106.3 (CH), 113.1 (C), 123.0 (CH), 126.8 (C), 134.0 (C), 136.7 (C), 151.8 (C) and 161.0 (C); *m/z* (CI) 223 (MH^+, 100%), 85 (10), 79 (20); HRMS (CI) found (MH^+) 223.0720, $C_{10}H_{11}N_2O_4$ requires 223.0719.

Preparation of compound 3c from monodemethylation of 4,7-dimethoxyazaindole 2c. 4-Hydroxy-7-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 3c

Compound **3c** was prepared according to the same procedure as for compound **3a**, scale: 6-azaindole **2c** (25 mg, 0.10 mmol), dichloromethane (2 mL), 1 M solution BBr_3 in CH_2Cl_2 (266 µL, 0.26 mmol). The crude product was purified by flash chromatography (PE–Et_2O 30:70) to afford **3c** (13 mg, 55%) as a yellow powder.

Mp 203–204 °C (decomposed); ν_{max} (KBr)/cm^{-1} 3325, 2924, 2852, 1709, 1512, 1449, 1413, 1333, 1262, 1199, 1090, 1063, 820, 776 and 747; δ_H (300 MHz; DMSO-d_6) 3.86 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.16 (1H, s, ArH), 7.17 (1H, s, ArH), 9.41 (1H, s, ArOH) and 12.42 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 52.0 (CH_3), 52.7 (CH_3), 105.5 (CH), 117.6 (CH), 123.2 (C), 124.9 (C), 128.5 (C), 143.1 (C), 145.2 (C) and 161.1 (C); *m/z* (ESI$^+$) 223 (MH^+, 100%), 209 (24), 191 (23); *m/z* (ESI$^-$) 425 (100%), 237 (27), 221 (M − H^-, 30); HRMS (ESI$^+$) found (MH^+) 223.0717, $C_{10}H_{11}N_2O_4$ requires 223.0719.

2-Azido-3-(2-methoxy-5-(triisopropylsilanyloxy)pyridin-3-yl)acrylic acid methyl ester 13

Sodium metal (540 mg, 23.5 mmol) was dissolved in anhydrous methanol (17 mL) at 0 °C under argon. To this preformed sodium methoxide solution at 0 °C was quickly added a solution of aldehyde **5c** (1.77 g, 5.7 mmol) and methyl azidoacetate (2.50 g, 21.7 mmol) in methanol (17 mL). The mixture was stirred at 25 °C for two h, then poured onto crushed ice (120 g) and held for 1 h at 4 °C. After addition of dichloromethane (100 mL) and decantation, the aqueous phase was extracted with dichloromethane (3 × 150 mL). The organic phases were washed with water (2 × 150 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 70:30) to afford acrylate **13** (457 mg, 20%) as an orange solid.

Mp 61–63 °C (decomposed); ν_{max} (KBr)/cm^{-1} 3409, 3093, 2946, 2892, 2867, 2123, 1716, 1612, 1589, 1564, 1468, 1437, 1425, 1403, 1379, 1290, 1277, 1260, 1227, 1141, 1086, 1026, 1009, 901, 883, 864, 834, 748, 740 and 692; δ_H (300 MHz; $CDCl_3$) 1.12 (18H, br d, $J = 6.8$, $(CH(CH_3)_2)_3$), 1.26 (3H, m, $(CH(CH_3)_2)_3$), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 7.18 (1H, s, CH), 7.77 (1H, d, $J = 3.0$, ArH) and 8.15 (1H, d, $J = 3.0$, ArH); δ_C (50 MHz; $CDCl_3$) 12.6 (CH), 17.9 (CH_3), 53.0 (CH_3), 53.8 (CH_3), 116.2 (C), 118.0 (CH), 126.7 (C), 130.3 (CH), 138.2 (CH), 147.1 (C), 156.0 (C) and 163.8 (C); *m/z* (ESI) 407 (MH^+, 12%), 380 (23), 379 (MH^+-N_2, 100).

4-Methoxy-7-triisopropylsilanyloxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 14

A solution of azidoacrylate **13** (369 mg, 0.9 mmol) in dry xylene (32 mL) was added dropwise onto hot (140 °C) xylene (18 mL). After addition, the mixture was heated at 140 °C for 1 h and then cooled down to room temperature. The xylene solution was then chromatographed over silica gel (eluent PE–EtOAc 90:10) to give 5-azaindole **14** (266 mg, 77%) as a pale yellow solid.

Mp 134–135 °C; ν_{max} (KBr)/cm^{-1} 3423, 3114, 2969, 2943, 2866, 1723, 1606, 1546, 1497, 1460, 1432, 1382, 1352, 1309, 1296, 1275, 1239, 1215, 1189, 1178, 1083, 1011, 885, 850 and 833; δ_H (300 MHz; $CDCl_3$) 1.13 (18H, d, $J = 7.2$, $(CH(CH_3)_2)_3$), 1.33 (3H, m, $(CH(CH_3)_2)_3$), 3.95 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.27 (1H, d, $J = 2.3$, H3), 7.50 (1H, s, H6) and 8.91 (1H, br s, NH); δ_C (50 MHz; $CDCl_3$) 12.8 (CH), 18.0 (CH_3), 52.2 (CH_3), 53.3 (CH_3), 108.0 (CH), 114.1 (C), 126.5 (C), 126.8 (CH), 135.6 (C), 135.9 (C), 153.7 (C) and 161.8 (C); *m*/*z* (ESI$^+$) 380 (24%), 379 (MH^+, 100), 365 (13); *m*/*z* (ESI$^-$) 378 (31%), 377 (M-H$^-$, 100); HRMS (ESI$^+$) found (MH^+) 379.2052, $C_{19}H_{31}N_2O_4Si$ requires 379.2053.

Fluoride-promoted deprotection of the TIPS-protected 5-azaindole 14: preparation of 7-hydroxy-4-methoxy 5-azaindole 3a

A 1 M solution of tetra-*n*-butylammonium fluoride in THF (1.15 mL, 1.15 mmol) was added to a stirred solution of 5-azaindole **14** (290 mg, 0.76 mmol) in anhydrous THF (1.2 mL) at 0 °C under argon. The temperature was allowed to rise to room temperature and the resulting mixture for stirred for 35 minutes. After addition of water (1.5 mL) and EtOAc (10 mL), the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with water (2 × 10 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 40:60) to afford **3a** (157 mg, 92%) as an orange solid.

2-Azido-3-(2-methoxy-5-(methoxymethoxy)pyridin-4-yl)acrylic acid methyl ester 15a

Sodium metal (95 mg, 4.1 mmol) was dissolved in anhydrous methanol (3 mL) at 0 °C under argon. To this preformed sodium methoxide solution at 0 °C was quickly added a solution of aldehyde **6b** (199 mg, 1.0 mmol) and methyl azidoacetate (440 mg, 3.8 mmol) in methanol (3 mL). The mixture was stirred at 30 °C for 1 h, then poured onto crushed ice (20 g) and held for 1 h at 4 °C. The product **15a** was recovered by filtration on a sintered glass funnel as a pale yellow solid (60.6 mg, 21%).

Mp 78–79 °C (decomposed); ν_{max} (KBr)/cm^{-1} 3418, 3105, 2956, 2856, 2129, 1716, 1618, 1606, 1546, 1482, 1434, 1381, 1319, 1275, 1260, 1219, 1202, 1155, 1084, 1039, 989 and 962; δ_H (300 MHz; $CDCl_3$) 3.51 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.15 (2H, s, CH_2OCH_3), 7.15 (1H, s, CH), 7.55 (1H, s, ArH), 8.04 (1H, s, ArH); δ_C (50 MHz; $CDCl_3$) 53.4 (CH_3), 53.7 (CH_3), 56.4 (CH_3), 96.4 (CH_2), 110.6 (CH), 116.0 (CH), 129.5 (C), 133.8 (CH), 134.1 (C), 146.5 (C), 159.5 (C) and 163.5 (C); *m*/*z* (ESI) 295 (MH^+, 7%), 267 ($MH^+ - N_2$, 69), 223 (41), 191 (100), 177 (36).

7-Methoxy-4-methoxymethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 16a

Compound **16a** was prepared according to the same procedure as for compound **2a**, scale: azidoacrylate **15a** (36.6 mg, 0.12 mmol), xylene (11 mL). The crude product was purified by flash chromatography (PE–EtOAc 70:30) to afford **16a** as a yellow powder (10.1 mg, 31%).

Mp 119–120 °C; ν_{max} (KBr)/cm^{-1} 3322, 3299, 1716, 1706, 1510, 1443, 1333, 1314, 1299, 1274, 1227, 1206, 1163, 1149, 1092, 1055, 979, 917, 779 and 750; δ_H (300 MHz; $CDCl_3$) 3.55 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 5.26 (2H, s, CH_2OCH_3), 7.25 (1H, d, $J = 2.3$, H3), 7.54 (1H, s, H5) and 9.21 (1H, br s, NH); δ_C (50 MHz; $CDCl_3$) 52.3 (CH_3), 53.3 (CH_3), 56.3 (CH_3), 96.1 (CH_2), 105.8 (CH), 120.9 (CH), 123.1 (C), 126.5 (C), 128.5 (C), 143.7 (C), 147.4 (C) and 161.7 (C); *m*/*z* (ESI$^+$) 268 (13%), 267 (MH^+, 100), 223 (15); HRMS (CI) found (MH^+) 267.0987, $C_{12}H_{15}N_2O_5$ requires 267.0981.

Acidic deprotection of the MOM-protected 6-azaindole 16a: preparation of 4-hydroxy-7-methoxy 6-azaindole 3c

To a solution of 6-azaindole **16a** (80 mg, 0.30 mmol) in THF (1 mL) was added 3 N aqueous HCl (1.1 mL) and the resulting mixture was stirred at 50 °C for 3 h. After this time, the mixture was cooled to room temperature and water (10 mL) was added followed by neutralisation (pH 7–8) with solid K_2CO_3. The aqueous phase was then extracted with EtOAc (3 × 10 mL). After drying of the organic phase over Na_2SO_4, filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 40:60) to afford **3c** (52 mg, 77%) as an orange solid.

2-Azido-3-(2-methoxy-5-(methoxymethoxy)pyridin-4-yl)acrylic acid *tert*-butyl ester 15b

Formation of the azidoalcohol ***11b***: Sodium hydride (60% dispersion in oil, 60 mg, 1.52 mmol) was added portionwise to cold (−30 °C) isopropanol (4.5 mL). To the resulting sodium isopropoxide solution was then added solid aldehyde **6b** (150 mg, 0.76 mmol) until completely dissolved. A solution of *tert*-butyl azidoacetate (477 mg, 3.04 mmol) in isopropanol (0.8 mL) was then added dropwise to the reaction mixture. After stirring for 4 h at −30 °C, water (15 mL) was added. The mixture was allowed to warm to room temperature, then the aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 70:30) to afford azidoalcohol **11b** (170 mg, 63%) as a yellow oil. This compound **11b** was obtained as a 1:1 mixture of two diastereomers: dia1 and dia2.

δ_H (300 MHz; DMSO-d_6) 1.20 (9H, s, *t*-Bu dia1), 1.48 (9H, s, *t*-Bu dia2), 3.39 (3H, s, OCH_3 dia 1), 3.42 (3H, s, OCH_3 dia 2), 3.80 (3H, s, OCH_3 dia 1), 3.81 (3H, s, OCH_3 dia 2), 3.93–3.97 (2H, m, CHN_3 for both dia), 5.14–5.24 (5H, m, CH_2OCH_3 for both dia + CHOH for dia1), 5.39 (dd, $J = 5.3$–2.6, 1H, CHOH for dia2), 6.24 (1H, d, $J = 5.3$, disappears after D_2O addition, OH for dia1), 6.37 (1H, d, $J = 5.3$, disappears after D_2O addition, OH for dia2), 6.83(1H, s, ArH for dia1), 6.90(1H, s, ArH for dia2), 7.88 (1H, s, ArH for dia1) and 7.90 (1H, s, ArH for dia2); δ_C (75 MHz; DMSO-d_6) 27.3 (CH_3), 27.7 (CH_3), 53.2 (CH_3), 53.2 (CH_3), 55.9

(CH_3), 56.0 (CH_3), 63.3 (CH), 64.1 (CH), 68.9 (CH), 69.4 (CH), 82.0 (C), 82.4 (C), 95.1 (CH_2), 95.6 (CH_2), 108.4 (CH), 108.5 (CH), 131.8 (CH), 132.4 (CH), 143.3 (C), 143.9 (C), 144.8 (C), 145.3 (C), 158.7 (C), 158.8 (C), 166.6 (C) and 167.4 (C). (It was impossible to assign with certainty signals for both diastereomers); *m/z* (ESI^+) 731 (2M + Na^+, 14%), 377 (M + Na^+, 54), 355 (MH^+, 100), 299 (MH^+ − isobutene $(CH_3)_2C{=}CH_2$, 36).

*Formation and in situ elimination of the mesylate of compound **11b***: formation of azidoacrylate **15b**: To a solution of **11b** (649 mg, 1.83 mmol) in dichloromethane (50 mL) at 45 °C was added quickly methanesulfonyl chloride (710 µl, 9.19 mmol) and then triethylamine (2.6 ml, 18.30 mmol). The reaction mixture was stirred at 45 °C for 1 h then cooled to room temperature. After addition of a saturated aqueous solution of $NaHCO_3$ (50 mL) and decantation, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were washed with brine (2 × 100 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (PE–EtOAc 80:20) to afford azidoacrylate **15b** (527 mg, 85%) as a yellow solid.

Mp 63–64 °C; ν_{max} (KBr)/cm^{-1} 3435, 2924, 2116, 1712, 1605, 1484, 1384, 1277, 1217, 1200, 1153, 1078, 1037, 995 and 886; δ_H (300 MHz; DMSO-d_6) 1.54 (9H, s, *t*-Bu), 3.43 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.20 (2H, s, CH_2OCH_3), 6.99 (1H, s, CH), 7.44 (1H, s, ArH) and 8.02 (1H, s, ArH); δ_C (75 MHz; DMSO-d_6) 27.6 (CH_3), 53.3 (CH_3), 56.1 (CH_3), 83.8 (C), 96.5 (CH_2), 109.5 (CH), 114.1 (CH), 130.9 (C), 133.8 (C), 134.6 (CH), 145.9 (C), 158.7 (C) and 161.0 (C); *m/z* (ESI^+): 359 (MNa^+, 12%), 337 (MH^+, 26), 309 (MH^+ − N_2, 26), 253 (MH^+ − N_2 − isobutene $(CH_3)_2C{=}CH_2$, 100), 177 (43).

7-Methoxy-4-methoxymethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid *tert*-butyl ester 16b

Compound **16b** was prepared according to the same procedure as for compound **2a**, scale: azidoacrylate **15b** (72 mg, 0.21 mmol), xylene (7.2 mL), reaction time 2 h. The crude product was purified by flash chromatography (PE–EtOAc 70:30) to afford **16b** (47 mg, 72%) as a yellow powder.

Mp 93–94 °C; ν_{max} (KBr)/cm^{-1} 3307, 2979, 2936, 1713, 1620, 1587, 1506, 1445, 1408, 1370, 1336, 1300, 1278, 1227, 1208, 1154, 1093, 1059, 973 and 923; δ_H (300 MHz; DMSO-d_6) 1.56 (9H, s, *t*-Bu), 3.43 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.24 (2H, s, CH_2OCH_3), 7.03 (s, 1H, ArH), 7.40 (1H, s, ArH) and 12.44 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 27.9 (CH_3), 52.9 (CH_3), 55.8 (CH_3), 81.6 (C), 95.4 (CH_2), 104.5 (CH), 119.7 (CH), 122.8 (C), 125.7 (C), 131.0 (C), 142.9 (C), 147.0 (C) and 159.8 (C); *m/z* (ESI^+) 308 (MH^+, 46%), 252 (100), 222 (48); HRMS (EI) found ($M^{+\bullet}$) 308.1370, $C_{15}H_{20}N_2O_5$ requires 308.1372.

Acidic deprotection and *in situ* transesterification of the MOM-protected 6-azaindole 16b: preparation of 4-hydroxy-7-methoxy-6-azaindole 3c

To a solution of 6-azaindole **16b** (48 mg, 0.16 mmol) in methanol (4 mL) was added 3 N aqueous HCl (1 mL) and the resulting mixture stirred at 25 °C for 4 h 30 min: after this time, TLC analysis showed the complete consumption of the starting material. The reaction was then heated to 50 °C for 20 h. A new product was formed whose R_f matched that of compound **3c**. After this time, the mixture was evaporated to dryness. Water (4 mL) was then added to the residue and the pH of this solution was carefully adjusted to pH 7 (controled with a calibrated pH meter) with 0.5 M sodium hydroxide solution. The aqueous phase was then extracted with EtOAc (4 × 15 mL) and, after drying over Na_2SO_4, the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (cyclohexane–EtOAc 60:40) to afford compound **3c** (17 mg, 49%) as a light brown solid.

Typical experimental procedure for the oxidation of 7-hydroxy-4-methoxy 5-azaindole 3a: Preparation of 7-hydroxy-4,6-dimethoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 17a

To a solution of **3a** (26 mg, 0.11 mmol) in a 1:1 acetonitrile–methanol mixture (18 mL) at room temperature was added in one portion [bis(trifluoroacetoxy)iodo]benzene (PIFA) (50 mg, 0.11 mmol). After stirring at room temperature for 4 h, the resulting mixture was filtered off on a sintered glass funnel filled with a pad of silica gel 1 cm thick, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (cyclohexane–EtOAc 70:30) to afford **17a** (25 mg, 85%) as a yellow powder.

Mp 199–200 °C; ν_{max} (KBr)/cm^{-1} 3501, 3373, 2951, 2853, 1702, 1675, 1653, 1612, 1537, 1497, 1470, 1446, 1416, 1377, 1329, 1310, 2289, 2211, 1228, 1042, 977 and 748; δ_H (300 MHz; DMSO-d_6) 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.02 (1H, d, $J = 2.0$, H3), 8.41 (1H, s, ArOH) and 11.63 (1H, s, NH); δ_C (75 MHz; DMSO-d_6) 51.8 (CH_3), 52.8 (CH_3), 53.6 (CH_3), 106.4 (CH), 108.6 (C), 119.5 (C), 126.7 (C), 136.5 (C), 145.53 (C), 148.2 (C) and 161.1 (C); *m/z* (CI) 254 (13%), 253 (MH^+, 100); HRMS (CI) found (MH^+) 253.0820, $C_{11}H_{13}N_2O_5$ requires 253.0824.

Oxidation of 4-hydroxy-7-methoxy 6-azaindole 3c: Preparation of 4-hydroxy-5,7-dimethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 17c

Compound **17c** was prepared according to the same procedure as for compound **17a**, scale: azaindole **3c** (50 mg, 0.22 mmol), PIFA (97 mg, 0.22 mmol), 1:1 acetonitrile–methanol mixture (18 mL). The crude product was purified by flash chromatography (cyclohexane–EtOAc 60:40) to afford **17c** (30 mg, 53%) as a yellow powder.

Mp 176–177 °C; ν_{max} (KBr)/cm^{-1} 3435, 3323, 2951, 1715, 1644, 1598, 1526, 1507, 1451, 1416, 1354, 1328, 1291, 1250, 1210, 1184, 1125, 1095, 1039, 1000, 977, 907 and 770; δ_H (300 MHz; DMSO-d_6) 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.08 (1H, d, $J = 2.0$, H3), 8.63 (1H, s, ArOH) and 12.10 (1H, s, NH); δ_C (75 MHz, DMSO-d_6): 52.0 (CH_3), 52.9 (CH_3), 54.0 (CH_3), 104.7 (CH), 119.1 (C), 125.8 (C), 127.8 (C), 129.9 (C), 140.4 (C), 140.9 (C) and 161.2 (C); *m/z* (ESI^+) 293 (21%), 253 (MH^+, 100), 238 (27), 223 (28), 209 (25); HRMS (ESI^+) found (MH^+) 253.0822, $C_{11}H_{13}N_2O_5$ requires 253.0824.

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