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A Versatile Synthesis of Fully Aromatic Benzo[*c*]phenanthridine Alkaloids

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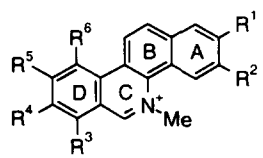
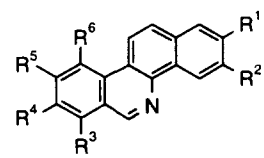
Abstract: A versatile new approach for the synthesis of benzo[*c*]phenanthridine alkaloids is described and is illustrated by the preparation of eight different alkaloids. The key steps are Smiles rearrangements, which allow easy access to 2-bromo-1-naphthylamines from 2-bromo-1-naphthols, and the attachment of the D-ring unit by Suzuki coupling. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The benzo[*c*]phenanthridines are an important group of isoquinoline alkaloids, many of which show a wide range of pharmacological properties including antitumour and antiviral activity.[1-4] They have therefore attracted much synthetic interest in the sixty years since Robinson published the first synthesis.[1-2, 5-13] Most syntheses are linear in nature and involve joining of the components which become the A and D rings early in the sequence. Since most of these alkaloids are differentiated by the sites and nature of oxygenation within these two rings, such a synthetic strategy necessitates an individually tailored sequence for each target molecule.

The aim of the present study was to design a synthesis which included a late stage fusion of the A and D ring components, thereby allowing easy access to a number of benzo[*c*]phenanthridine alkaloids from a few synthetic intermediates.[14] This synthesis should be applicable to the preparation of both the quaternary and *N*-desmethyl analogues of all three main types of the fully aromatic alkaloids, having oxygenation at positions 2,3,7,8-, 2,3,8,9- and 2,3,7,8,10-, examples of which are shown in Figure 1.





chelerythrine	$R^1 + R^2 = OCH_2O$, $R^3 = R^4 = OMe$, $R^5 = R^6 = H$	**norchelerythrine**
nitidine	$R^1 + R^2 = OCH_2O$, $R^4 = R^5 = OMe$, $R^3 = R^6 = H$	**nornitidine**
chelilutine	$R^1 + R^2 = OCH_2O$, $R^3 = R^4 = R^6 = OMe$, $R^5 = H$	**norchelilutine**

Figure 1

Dedicated to Professor A.R. Katritzky on the occasion of his 70th birthday.

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RESULTS AND DISCUSSION

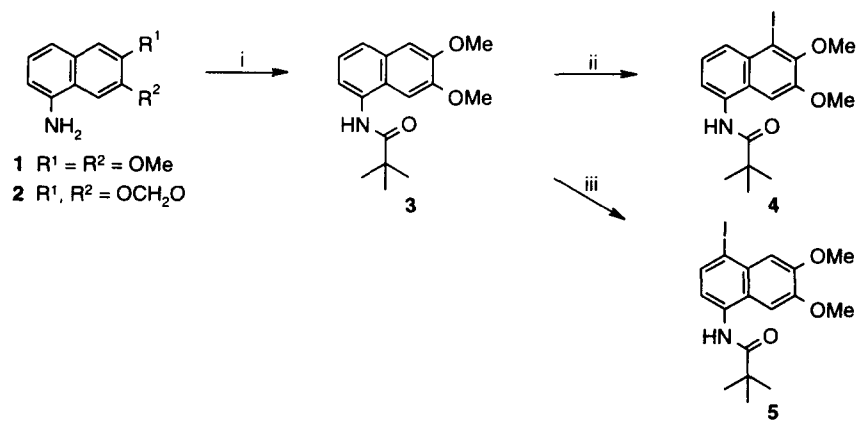
Our general strategy was to perform a Suzuki coupling of an appropriately substituted 2-halogeno-1-naphthylamine with an arylboronic acid followed by a Bischler-Napieralski or similar reaction to complete the synthesis by the formation of ring C. The arylboronic acids were readily prepared by known methods, but the required naphthylamines were undescribed and presented more of a synthetic challenge.

Preparation of 2-halogeno-1-naphthylamines

Ortho-*Lithiation Approach*

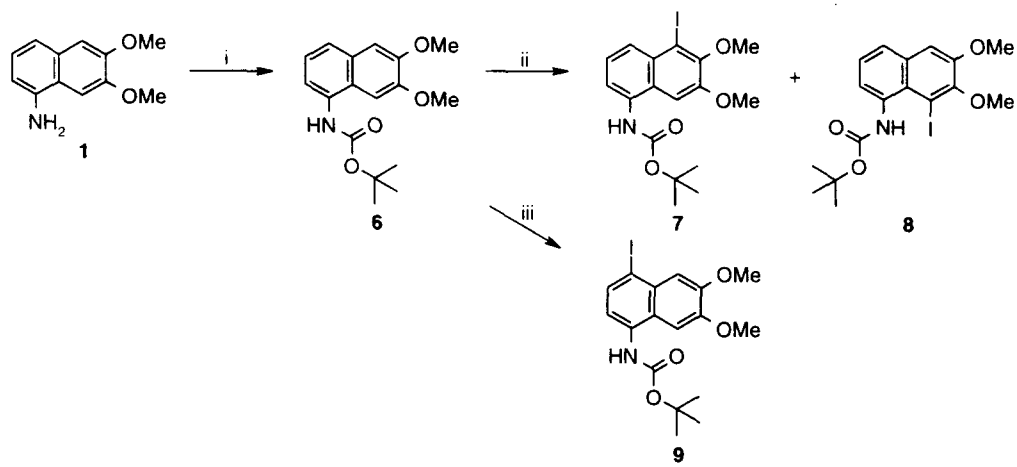
Our first approach to the preparation of the necessary 2-halogeno-1-naphthylamines involved the *ortho* functionalisation of derivatives of the known 6,7-dimethoxy and 6,7-methylenedioxy-1-naphthylamines **1** and **2**.[15-16]

We initially prepared the pivalamide derivative of 6,7-dimethoxy-1-naphthylamine **3**, but lithiation in THF followed by quench with iodine gave the unwanted 5-iodo compound **4** as the only identifiable product. With three *ortho*-directing groups present in **3**, predicting the outcome of this reaction was not easy, but there was previous work to indicate that the pivalamido group is a more powerful *ortho* director than the methoxy group,[17] and the formation of **4** was unexpected. Running the reaction in 1,2-dimethoxyethane (DME), or in THF in the absence of base, gave the 4-iodo compound **5**, presumably *via* electrophilic substitution (Scheme 1).



Scheme 1 Reagents and conditions: i) **1**, Me_3CCOCl, Et_3N, MDC, 0-5°C, 1 h, 87%; ii) 3.0 eq. nBuLi, THF, -20 to 25°C, 5 h, then I_2, -78 to -12°C, 16 h, 17%; iii) 3.0 eq. tBuLi, DME, -60 to 25°C, 3 h, then I_2, -78 to -12°C, 16 h, 40%.

There was literature precedent to suggest that the BOC derivative might be a better *ortho* director than the pivalamide,[18] and the 6,7-dimethoxy compound **6** was therefore prepared and subjected to similar reaction conditions. However, reaction in THF followed by quench with 1,2-diiodoethane afforded a mixture of the 5- and 8-iodo compounds **7** and **8**, and in diethyl ether/DME once again gave the product of electrophilic substitution **9** (Scheme 2). Despite varying the experimental conditions with both pivalamido and BOC derivatives **3** and **6**, no evidence was obtained for the production of any of the desired 2-iodo isomers.

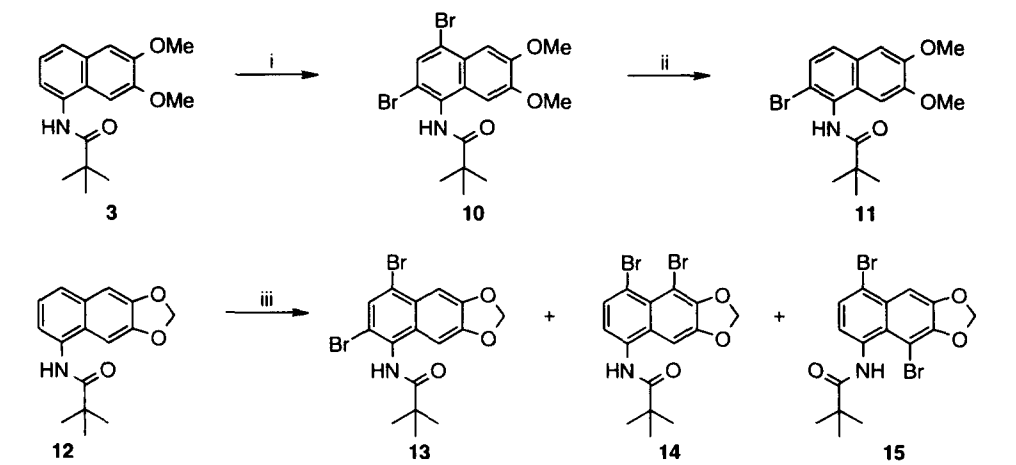


Scheme 2 Reagents and conditions: i) $(Me_3CCO_2)O$, THF, Δ, 2 h, 85%; ii) 2.8 eq. tBuLi, THF, -40 to -20°C, 5 h, then ICH_2CH_2I, -78 to 25°C, 18 h, 30%; iii) 2.8 eq. tBuLi, Et_2O, DME, -40 to -20°C, 5 h, then ICH_2CH_2I, -78 to 25°C, 18 h, 22%.

Electrophilic Bromination Approach

The *ortho*-lithiation work strongly suggested that electrophilic monohalogenation of our 1-naphthylamine derivatives would take place at the 4-position. Having already determined that they were extremely reluctant to form a lithio species at the 2-position, if the 2,4-dihalogeno compounds could be obtained efficiently under electrophilic conditions, a selective bromine/lithium exchange could be possible at the 4-position, which, after proton quench, would furnish the desired 2-halogeno isomers.

Electrophilic dibromination of the dimethoxy pivalamido compound **3** gave exclusively the 2,4-dibromo compound **10**. Selective lithiation/debromination at the 4-position then afforded a fair yield of the desired 2-bromo compound **11**, together with small amounts of the 4-bromo isomer and the desbromo material **3** (Scheme 3). We then attempted to extend this strategy to the 6,7-methylenedioxy compound **12**, but the bromination was particularly unselective, giving similar amounts of the required 2,4-dibromo compound **13** and an inseparable mixture of the 4,5- and 4,8-dibromo isomers **14** and **15**.



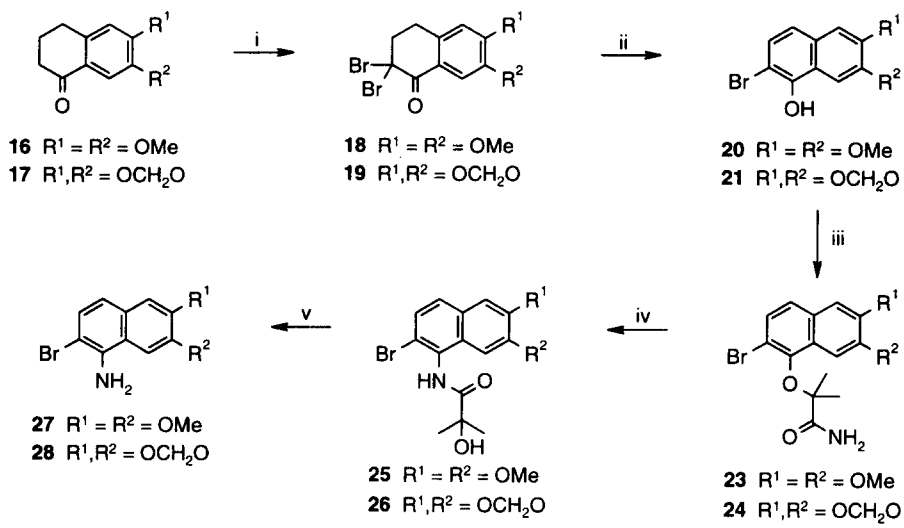
Scheme 3 Reagents and conditions: i) Br_2, NaOAc, AcOH, THF, 45-50°C, 6 h, 70%; ii) 2.0 eq. tBuLi, THF, TMEDA, -78°C, 1 h, then AcOH, -78 to 0°C, 15 min, 48%; iii) Br_2, NaOAc, AcOH, 45-50°C, 2 h, **13** 25%, **14** + **15** 34%.

Since there are considerably more benzo[*c*]phenanthridine alkaloids which have a 2,3-methylenedioxy rather than a 2,3-dimethoxy group, this result was particularly frustrating. Fortunately at this time the more productive approach described below was showing considerable promise, and therefore the electrophilic bromination strategy was abandoned.

Smiles Rearrangement Approach

Having recognised the limitations of synthesis of the required 2-halo-1-naphthylamines by strategies based on the 2-functionalisation of 1-naphthylamines, we reversed the order of introduction and commenced with bromination of the readily available tetralones **16** and **17**[15] (Scheme 4). Both products **18** and **19** were readily prepared, but the dimethoxy compound **18** required purification by trituration with dichloromethane after removal of the reaction solvent. The 2,2-dibromides **18** and **19** were then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in warm acetonitrile to afford the 2-bromo-1-naphthols **20** and **21** in excellent yield.

We now needed to prepare the ether substrates for the Smiles rearrangement, **23** and **24**. However, use of the published conditions[19] for *O*-alkylation with 2-bromo-2-methylpropanamide **22** (sodium hydride, dioxane, reflux) gave poor results when applied to the naphthols **20** and **21**, and yields of the alkylated products were typically below 30%. Increasing the stoichiometry of the sodium hydride, or the use of potassium carbonate in DMF, solid potassium hydroxide in DMSO, or phase transfer conditions all failed to effect an improvement. However, when the alkylation was attempted in aqueous sodium hydroxide in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), a distinct improvement was obtained, (69% yield of **23** after 2 hours at ambient temperature), and when solid sodium hydroxide was substituted for the aqueous reagent the reactions proceeded cleanly to completion in a few hours.



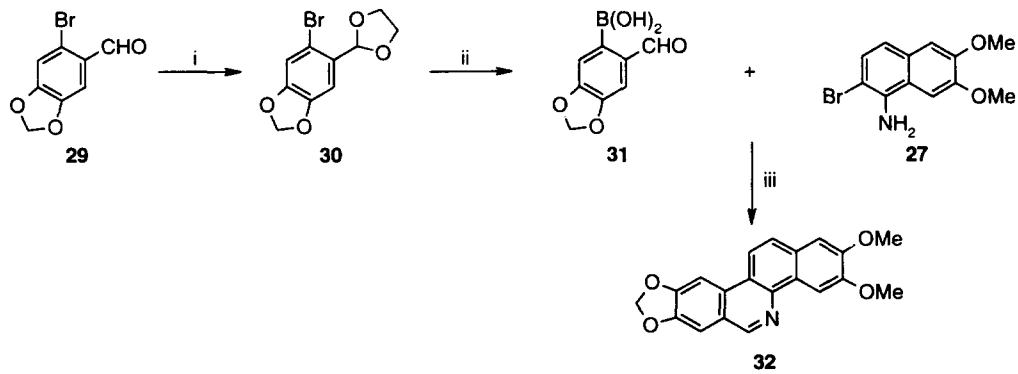
Scheme 4 Reagents and conditions: i) Br_2, $CHCl_3$, 25°C, 18 h, **18** 66%, **19** 97%; ii) DBU, MeCN, 40-45°C, 20 min, **20** 93%, **21** 97%; iii) **22**, granular NaOH, DMPU, 25°C, 2-5 h, **23** 93%, **24** 93%; iv) NaH, 4:1 DMF-DMPU, 100°C, 2 h, **25** 93%, **26** 96%; v) 80% aq. NaOH, MeOH, reflux, 2-4 d, **27** 82%, **28** 74%.

Smiles rearrangement of **23** and **24** using sodium hydride in DMF-DMPU at 100°C gave the hydroxy amides **25** and **26** in high yield. Amide hydrolysis required prolonged heating with an excess of sodium hydroxide in aqueous methanol, but cleanly furnished the desired 2-bromo-1-naphthylamines **27** and **28**. These were purified by recrystallisation from ethanol to give near colourless crystalline solids suitable for storage and use as stock intermediates.

The efficient synthesis of **27** and **28** was a considerable improvement on the Semmler-Wolff reaction which we had used previously to prepare the 1-naphthylamines **1** and **2** from the same tetralone precursors **16** and **17**.[7]

Suzuki Coupling and Final Ring Closure

Having obtained the necessary 2-bromo-1-naphthylamines, our first approach was to attempt a one-pot Suzuki coupling/ring closure with a 2-formylarylboronic acid in order to prepare the normethylbenzo[*c*]-phenanthridines in a single step. Accordingly, 2-formyl-4,5-methylenedioxyphenylboronic acid **31** was prepared in two steps from 2-bromo-4,5-methylenedioxybenzaldehyde **29**[20] (Scheme 5), and coupled with **27** in DME in the presence of palladium acetate/triphenylphosphine. However, the reaction was sluggish and accompanied by extensive deboronation, affording piperonal as a significant side product. The yield of norallonitidine **32** was 35% after careful column chromatography. A synthesis of nornitidine by similar methods furnished the required product in no more than 6% yield. Extensive manipulation of the reaction conditions failed to achieve any yield improvement.



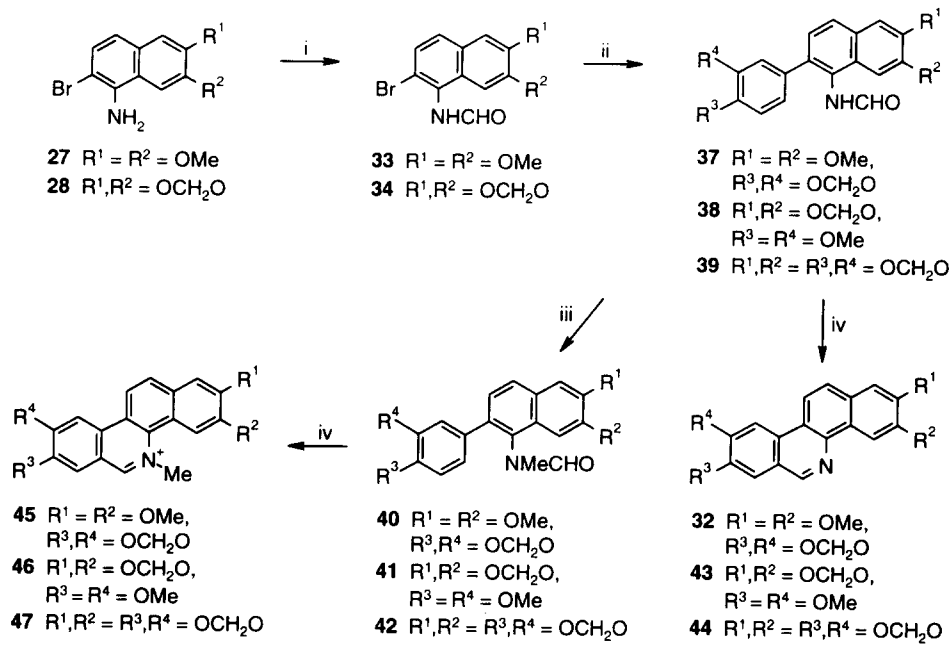
Scheme 5 Reagents and conditions: i) $HOCH_2CH_2OH$, p-TSA, toluene, Δ, 89%; ii) nBuLi, THF, -78°C, then $B(O^iPr)_3$, -78 to 25°C, then dil. HCl, Δ, 61%; iii) $Pd(OAc)_2$, PPh_3, DME, aq. Na_2CO_3, 21 h, 35%.

A number of trial reactions with 1-amido-2-bromonaphthalenes such as **11** or **25** had suggested that much better yields would be obtained in the Suzuki couplings by prior protection of the 1-amino group of **27** or **28**. We therefore decided to formylate in the knowledge that this carbon would be incorporated in the final skeleton as C-6. This was readily achieved with acetic-formic anhydride to give the formamides **33** and **34** (Scheme 6).

2,3,8,9-Tetraoxygenated benzo[c]phenanthridines

Suzuki coupling of the formamides **33** and **34** with 3,4-methylenedioxyphenylboronic acid **35**[21] or 3,4-dimethoxyphenylboronic acid **36**[22] in DME in the presence of palladium(II) acetate and triphenylphosphine gave good to excellent yields of the coupled products **37-39** (Scheme 6). These were then quantitatively methylated using iodomethane and sodium hydride in THF to give *N*-methylformamides **40-42**.

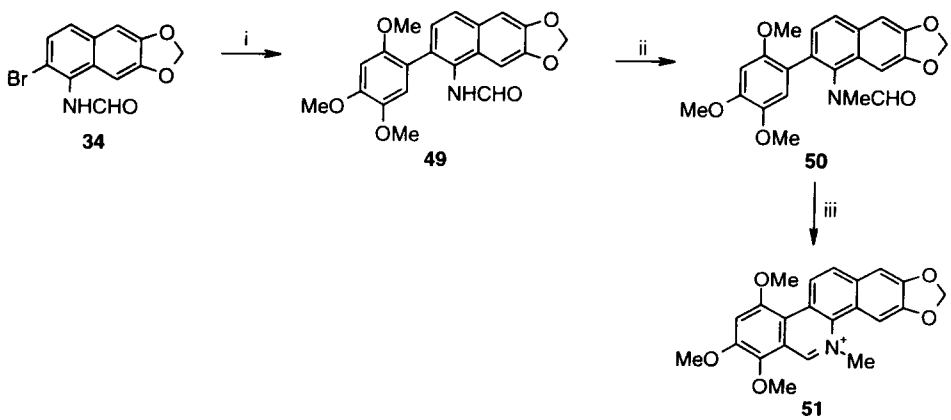
All six 2-aryl-1-formamidonaphthalenes **37-42** were subjected to the Bischler-Napieralski reaction to give the norbases norallonitidine **32**, nornitidine **43** and noravicine **44**, and the quaternised alkaloids allonitidine **45**, nitidine **46** and avicine **47**, all in >90% yield. The final products were obtained directly from the reactions in good purity, but could be further purified by recrystallisation from pyridine/methanol (norbases) or methanol (quaternary compounds).



Scheme 6 Reagents and conditions: i) HCO_2H, Ac_2O, THF, 25°C, 45 min, **33** 91%, **34** 88%; ii) **35** or **36**, $Pd(OAc)_2$, PPh_3, DME, aq. Na_2CO_3, 1.25-4 h, **37** 92%, **38** quant., **39** 74%; iii) MeI, NaH, THF or DMF, 0-25°C, 1.5 h, **40-42** quant.; iv) $POCl_3$, MeCN, reflux 30 min **32** 98%, **43** 99%, **44** 93%, **45** quant., **46** 91%, **47** 96%.

2,3,7,8,10-Pentaoxygenated benzo[c]phenanthridines

Synthesis of chelilutine **51** followed a similar path to the 2,3,8,9-tetraoxygenated quaternary alkaloids described above. Coupling of 2-bromo-1-formamidonaphthalene **34** with 2,4,5-trimethoxyphenylboronic acid **48**, and *N*-methylation of the resulting 2-aryl compound **49** to give the *N*-methylformamide **50** both proceeded in excellent yield (Scheme 7). Cyclisation to chelilutine **51** followed the procedure described by Ishii *et al.*[23] The lack of an alkoxy function *para* to the position of cyclisation can be detrimental to the Bischler-Napieralski reaction, but in this case there is no facile alternative reaction pathway, and the yield was good.

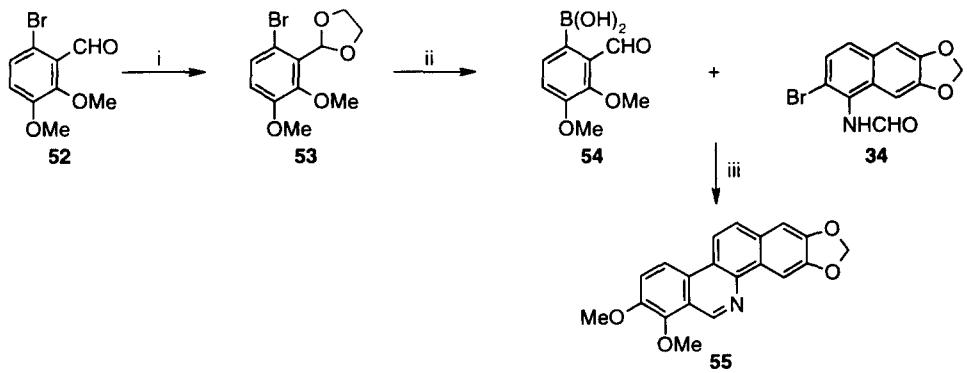


Scheme 7 Reagents and conditions: i) **48**, $Pd(OAc)_2$, PPh_3, DME, aq. Na_2CO_3, 1.25-4 h, 94%; ii) MeI, NaH, THF or DMF, 0-25°C, 1.5 h, 96%; iii) $POCl_3$, MeCN, reflux 3 h, 89%.

2,3,7,8-Tetraoxygenated benzo[c]phenanthridines

For the synthesis of 2,3,7,8-tetraoxygenated alkaloids the strategy employed for the two other alkaloid groups had to be amended, because the required Bischler-Napieralski cyclisation of 2-(3,4-dioxygenated aryl)-1-formamidonaphthalenes gives exclusively the 2,3,8,9-tetraoxygenated isomers. For the necessary cyclisation we therefore employed a modification of the method by which Gronowitz prepared phenanthridine.[24] In this, 2-formylphenylboronic acid and 2-bromoacetanilide were reacted under palladium catalysed coupling conditions, which effected concomitant ring closure to give the *N*-acetyl-5,6-dihydro-6-hydroxyphenanthridine. Treatment with dilute HCl then gave the parent heterocycle.

In our case we required 3,4-dimethoxy-2-formylphenylboronic acid **54**, which was synthesized from 6-bromo-2,3-dimethoxybenzaldehyde **52**[25] in two steps (Scheme 8). Reaction of **54** with 2-bromo-1-formamido-6,7-methylenedioxynaphthalene **34** gave norchelerythrine **55** in 58% yield. Chelerythrine can be prepared by *N*-methylation of norchelerythrine.[26]



Scheme 8 Reagents and conditions: i) $HOCH_2CH_2OH$, p-TSA, toluene, Δ, 89%; ii) nBuLi, THF, -78°C, then $B(O^iPr)_3$, -78 to 25°C, then dil. HCl, Δ, 60%; iii) $Pd(PPh_3)_4$, DME, aq. $NaHCO_3$, 3h, Δ, then dil. HCl, Δ, 58%.

CONCLUSIONS

The above syntheses illustrate a robust and versatile method for the preparation of all three main types of fully aromatic benzo[*c*]phenanthridine alkaloids. The reagents used are readily available and inexpensive, and all the intermediates are stable, crystalline solids. Overall yields for the process vary from 31% for norchelerythrine to 54% for nornitidine, based on the tetralone starting materials.

EXPERIMENTAL

General

Melting points are uncorrected and were determined using either a Mettler FP90 Thermosystem or a Kofler hot-stage melting point apparatus. ^1H NMR spectra were recorded in d^6-DMSO solution (unless otherwise stated) on a Bruker AMX 400 spectrometer at 400 MHz. Signals are quoted as δppm downfield from tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz; chemical shifts were referenced to the deuterated solvent signals. Mass spectra (electron impact unless otherwise stated) were recorded on a Fisons VG Biotic Trio 2 spectrometer. Infrared spectra were recorded as nujol mulls (unless otherwise stated) on a Perkin Elmer 1750 FT-IR photospectrometer. Ultraviolet spectra were recorded on a Perkin Elmer Lambda 19 UV-VIS-NIR photospectrometer. Microanalyses were performed on a Leemans CE440 Elemental Analyser.

N-(6,7-Dimethoxy-1-naphthyl)-2,2-dimethylpropanamide (3)

Triethylamine (3.9 g, 0.038 mol) was added to a solution of 6,7-dimethoxy-1-naphthylamine **1**[15] (6.5 g, 0.032 mol) in dichloromethane (50 mL). The resulting mixture was stirred at ambient temperature for 15 min, then cooled to 0°C and pivaloyl chloride (4.63 g, 0.038 mol) was added over 15 min. The mixture was stirred at 0-5°C for 1 h, then water (250 mL) was added and the phases separated. The organic phase was washed with 1 M HCl (100 mL), then water (2 x 50 mL), dried ($MgSO_4$), filtered and evaporated to leave a purple glass. Crystallisation from toluene/hexane afforded the title compound **3** (8.02 g, 87%) as an off-white solid, mp 118.5-119°C. (Found: C, 70.9; H, 7.2; N, 5.0; $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.4; N, 4.9%); ν_{max} cm^{-1} 3326, 1652, 1536, 1501, 1257, 1219, 1185, 1162 and 860; δ_H 1.33 (9 H, s, 3 x CH_3), 3.84 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.10 (1 H, s, Ar), 7.19 (1 H, d, *J* 8.0, Ar), 7.30 (1 H, t, *J* 8.0, Ar), 7.33 (1 H, s, Ar), 7.64 (1 H, d, *J* 8.0, Ar) and 9.35 (1 H, brs, NH); δ_C 27.4 (3 x q), 55.0 (q), 55.3 (q), 102.0 (d), 106.7 (d), 122.4 (d), 123.4 (d), 124.4 (d), 125.2 (s), 129.6 (s), 132.6 (s), 149.0 (s), 149.1 (s) and 179.6 (s) (quaternary C obscured by solvent peaks); *m/z* 287 (M^+), 203 ($M-C_5H_8O^+$) and 188 ($M-C_5H_9NO^+$).

N-(6,7-Dimethoxy-5-iodo-1-naphthyl)-2,2-dimethylpropanamide (4)

n-Butyllithium (1.83 mL of a 1.43 M solution in hexanes, 2.61 mmol) was added to a solution of *N*-(6,7-dimethoxy-1-naphthyl)-2,2-dimethylpropanamide **3** (0.25 g, 0.87 mmol) in dry THF at -20°C under nitrogen. The resulting mixture was warmed to ambient temperature over 1 h, stirred at this temperature for a further 5 h, then cooled to -78°C and a solution of iodine (0.66 g, 2.61 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at -12°C for 16 h. A saturated solution of sodium metabisulfite (4 mL) was added, the stirred mixture was allowed to warm to ambient temperature, then extracted twice with dichloromethane (30 mL). The combined organic extracts were washed twice with water (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to leave an orange-brown glass. The product was purified by flash column chromatography on silica gel (50 g), eluting with 2:1 hexane/ethyl acetate, to give the title compound **4** (0.57 g, 17%) as a yellow glass. δ_H 1.38 (9 H, s, 3 x CH_3), 3.87 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 7.25 (1 H, s, Ar), 7.36 (1 H, d, *J* 8.0, Ar), 7.41 (1 H, t, *J* 8.0, Ar), 7.92 (1 H, d, *J* 8.0, Ar) and 9.37 (1 H, brs, NH); δ_C 27.5 (3 x q), 39.0 (s), 55.4 (q), 60.0 (q), 95.6 (s), 104.0 (d), 124.4 (d), 124.8 (d), 128.1 (s), 129.7 (d), 130.4 (s), 133.2 (s), 149.8 (s), 151.2 (s) and 177.6 (s); *m/z* 413 (M^+), 329 ($M-C_5H_8O^+$) and 286 ($M-I^+$); high resolution MS *m/z* 413.0523; $C_{17}H_{20}INO_3$ requires 413.0487.

N-(6,7-Dimethoxy-4-iodo-1-naphthyl)-2,2-dimethylpropanamide (5)

t-Butyllithium (3.50 mL of a 1.7 M solution in pentane, 6.00 mmol) was added to a solution of *N*-(6,7-dimethoxy-1-naphthyl)-2,2-dimethylpropanamide **3** (0.57 g, 2.0 mmol) in dry 1,2-dimethoxyethane (DME) (6.0 mL) at -60°C under nitrogen. The resulting mixture was warmed to -10°C, stirred at this temperature for 1 h, then warmed to ambient temperature over 1 h and stirred for a further 1 h. The mixture was cooled to -78°C and a solution of iodine (1.60 g, 6.30 mmol) in dry DME (3 mL) added dropwise. The reaction mixture was stirred at -12°C for 16 h. A saturated solution of sodium thiosulfate (10 mL) was added, the stirred mixture was allowed to warm to ambient temperature, then extracted twice with dichloromethane (40 mL). The combined organic extracts were washed twice with water (25 mL), dried ($MgSO_4$), filtered and evaporated in vacuo to leave a pale brown solid. The product was purified by column chromatography on silica gel (40 g), eluting with 2:1 hexane/ethyl acetate, and gave the title compound **5** (0.33 g, 40%) as a colourless solid. A sample was recrystallised from dichloromethane/hexane to give the title compound as colourless crystals, mp 227-228.5°C. (Found: C, 49.1; H, 4.8; N, 3.2; $C_{17}H_{20}INO_3$ requires C, 49.4; H, 4.9; N, 3.4%); ν_{max} cm^{-1} 3295, 1650, 1592, 1501, 1266 and 1212; δ_H 1.33 (9 H, s, 3 x CH_3), 3.87 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 7.01 (1 H, d, *J* 7.0, Ar), 7.15 (1 H, s, Ar), 7.31 (1 H, s, Ar), 7.93 (1 H, d, *J* 7.0, Ar) and 9.43 (1 H, s, NH); δ_C 27.3 (3 x q), 38.8 (s), 55.2 (q), 55.4 (q), 94.3 (s), 102.7 (d), 110.7 (d), 123.9 (d), 125.6 (s), 130.1 (s), 133.8 (s), 134.6 (d), 149.4 (s), 150.6 (s) and 177.0 (s); *m/z* 413 (M^+), 329 ($M-C_5H_8O^+$) and 286 ($M-I^+$).

1-(*N-tert*-Butoxycarbonylamino)-6,7-dimethoxynaphthalene (6)

Di-*tert*-butyl dicarbonate (3.19 g, 0.15 mol) was added to a solution of 1-amino-6,7-dimethoxynaphthylamine **1** (2.70 g, 0.13 mol) in THF (25 mL) and the resulting solution stirred under reflux for 2 h. The cooled mixture was concentrated *in vacuo*, then dissolved in ethyl acetate and washed twice with 1 M citric acid (25 mL), then with water (40 mL), dried ($MgSO_4$), filtered and evaporated to leave a pink solid. The product was purified by column chromatography on silica gel (100 g), eluting with 1:1 ethyl acetate/hexane. The resulting solid was recrystallised from ethyl acetate/hexane to give the title compound **6** (3.42 g, 85%) as colourless crystals, mp 115.5-116°C. (Found: C, 67.35; H, 6.9; N, 4.6; $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%); ν_{max} cm^{-1} 3344, 1716, 1692, 1632, 1259 and 1238; δ_H 1.51 (9 H, s, 3 x CH_3), 3.88 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 7.26 (1 H, t, *J* 8.0, Ar), 7.29 (1 H, s, Ar), 7.35 (1 H, s, Ar), 7.44 (1 H, d, *J* 8.0, Ar), 7.53 (1 H, d, *J* 8.0, Ar) and 9.13 (1 H, s, NH); δ_C 28.2 (3 x q), 55.4 (2 x q), 78.9 (s), 102.1 (d), 106.8 (d), 118.9 (d), 122.9 (d), 123.1 (s), 123.5 (d), 129.7 (s), 132.9 (s), 149.0 (s), 149.1 (s) and 154.0 (s); *m/z* 303 (M^+), 247 ($M-C_4H_8^+$) and 229 ($M-C_4H_{10}O^+$).

1-(*N-tert*-Butoxycarbonylamino)-6,7-dimethoxy-5-iodonaphthalene (7) and
1-(*N-tert*-butoxycarbonylamino)-6,7-dimethoxy-8-iodonaphthalene (8)

t-Butyllithium (2.7 mL of a 1.7 M solution in pentane, 4.62 mmol) was added to a solution of 1-(*N-tert*-butoxycarbonylamino)-6,7-dimethoxynaphthalene **6** (0.50 g, 1.65 mmol) in dry THF (5.0 mL) at -40°C under nitrogen. The resulting mixture was stirred at -20°C for 5 h, then cooled to -78°C. A solution of 1,2-diiodoethane (1.30 g, 4.61 mmol) in THF (2.0 mL) was added and the resulting solution was stirred and allowed to warm to ambient temperature overnight. Dilute aq. NH_4Cl (15 mL) was added, and the mixture was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (25 mL), dried ($MgSO_4$), filtered and evaporated to leave a brown glass. The product was purified by column chromatography on silica gel (30 g), eluting with 3:1 hexane/ethyl acetate, and gave a mixture of the title compounds (0.21 g, 30%) as an orange oil. 5-isomer **7**; δ_H 1.51 (9 H, s, 3 x CH_3), 3.82 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 7.42 (1 H, t, *J* 8.5, Ar), 7.48 (1 H, s, Ar), 7.57 (1 H, d, *J* 8.5, Ar), 7.79 (1 H, d, *J* 8.5, Ar) and 9.28 (1 H, s, NH); 8-isomer **8**; δ_H 1.47 (9 H, s, 3 x CH_3), 3.78 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 7.22 (1 H, d, *J* 8.5, Ar), 7.40 (1 H, t, *J* 8.5, Ar), 7.49 (1 H, s, Ar), 7.79 (1 H, d, *J* 8.5, Ar) and 8.77 (1 H, s, NH); *m/z* 429 (M^+); high resolution MS m/z 429.0429; $C_{17}H_{20}INO_4$ requires 429.0439.

1-(*N-tert*-Butoxycarbonylamino)-6,7-dimethoxy-4-iodonaphthalene (9)

t-Butyllithium (2.7 mL of a 1.7 M solution in pentane, 4.61 mmol) was added to a solution of 1-(*N-tert*-butoxycarbonylamino)-6,7-dimethoxynaphthalene **6** (0.50 g, 1.65 mmol) in dry diethyl ether (5.0 mL) and dry DME (2.5 mL) at -40°C under nitrogen. The resulting mixture was stirred at -20°C for 5 h and then cooled to -78°C. A solution of 1,2-diiodoethane (1.30 g, 4.61 mmol) in dry DME (5.0 mL) was added and the resulting solution was allowed to warm to ambient temperature over several hours. Aq. NH_4Cl was added, and the mixture was extracted twice with dichloromethane (30 mL). The combined organic extracts were washed with water (30 mL), dried ($MgSO_4$), filtered and evaporated to leave a dark glass. The product was purified by column chromatography on silica gel (30 g), eluting with 15% ethyl acetate in hexane, and gave the title compound **9** (0.16 g, 22%) as a pale yellow solid, mp 140-141°C. (Found: C, 47.4; H, 4.7; N, 3.15; $C_{17}H_{20}INO_4$ requires C, 47.6; H, 4.7; N, 3.3%); ν_{max} cm^{-1} 3338, 1699, 1626 and 1265; δ_H 1.51 (9 H, s, 3 x CH_3), 3.94 (6 H, s, 2 x OCH_3), 7.28 (1 H, d, *J* 8.0, Ar), 7.29 (1 H, s, Ar), 7.41 (1 H, s, Ar), 7.88 (1 H, d, *J* 8.0, Ar) and 9.29 (1 H, s, NH); δ_C 28.1 (3 x q), 55.4 (q), 55.7 (q), 79.2 (s), 92.0 (s), 102.8 (d), 110.8 (d), 120.0 (d), 123.3 (s), 129.9 (s), 134.0 (s), 134.6 (d), 149.3 (s), 150.5 (s) and 153.7 (s); *m/z* 429 (M^+), 373 ($M-C_4H_8^+$) and 329 ($M-C_5H_8O_2^+$).

***N*-(2,4-Dibromo-6,7-dimethoxy-1-naphthyl)-2,2-dimethylpropanamide (10)**

Bromine (11.12 g, 0.070 mol) was added to a solution of *N*-(6,7-dimethoxy-1-naphthyl)-2,2-dimethylpropanamide **3** (8.00 g, 0.028 mol) and sodium acetate (5.85 g, 0.070 mol) in 1:1 acetic acid/THF (80 mL) at

40°C and the mixture stirred at 45-50°C for 6 h. Water (300 mL) and dichloromethane (300 mL) were added, the aqueous layer was basified with 40% aq. NaOH to pH 14, the phases separated, and the aqueous was extracted with further dichloromethane (3 x 300 mL). The combined organic phases were washed with water, dried ($MgSO_4$), filtered and evaporated to leave a dark red glass. Purification by column chromatography on silica gel (300 g), eluting with 2:1 hexane/ethyl acetate gave the title compound **10** (7.70 g, 70%) as a pale orange solid, mp 197-197.5°C. (Found: C, 45.8; H, 4.3; N, 3.0; $C_{17}H_{19}Br_2NO_3$ requires C, 45.9; H, 4.3; N, 3.15%); ν_{max} cm^{-1} 3238, 1660 and 1265; δ_H 1.41 (9 H, s, 3 x CH_3), 3.91 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 7.16 (1 H, s, Ar), 7.44 (1 H, s, Ar), 8.02 (1 H, s, Ar) and 9.57 (1 H, brs, NH); δ_C 27.2 (3 x q), 55.3 (q), 55.5 (q), 102.9 (d), 105.5 (d), 118.2 (s), 118.9 (s), 126.5 (s), 128.4 (s), 130.1 (d), 132.1 (s), 150.5 (s), 150.7 (s) and 176.5 (s) (quaternary C obscured by solvent peaks); *m/z* 443, 445, 447 (M^+), 364, 366 ($M-Br^+$) and 285 ($M-Br_2^+$).

_N_-(2-Bromo-6,7-dimethoxy-1-naphthyl)-2,2-dimethylpropanamide (11)

t-Butyllithium (1.18 mL of a 1.7 M solution in pentane, 2.0 mmol) was added to a solution of *N*-(2,4-dibromo-6,7-dimethoxy-1-naphthyl)-2,2-dimethylpropanamide **10** (0.45 g, 1.0 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (0.30 mL, 2.0 mmol) in dry THF (13 mL) at -78°C and the resulting solution was stirred for 1 h at that temperature under argon. Glacial acetic acid (0.3 mL) was then added, the solution stirred at -78°C for 15 min, then allowed to warm to 0°C. Water (3.0 mL) was added and the mixture was allowed to warm to ambient temperature and stirred for a further 30 min. The phases were separated and the aqueous phase was extracted with diethyl ether (5 mL). The combined organic phases were washed with saturated aq. Na_2CO_3 (15 mL), then with water (2 x 10 mL), dried ($MgSO_4$), filtered and evaporated to leave a red glass. The product was purified by column chromatography on silica gel (25 g), eluting with 4:1 hexane/ethyl acetate to give the title compound **11** (0.18 g, 48%) as a pink solid, mp 128-129°C. (Found: C, 55.75; H, 5.4; N, 3.65; $C_{17}H_{20}BrNO_3$ requires C, 55.75; H, 5.5, N, 3.8%); ν_{max} (KBr) cm^{-1} 3288, 1656 and 1264; δ_H 1.35 (9 H, s, 3 x CH_3), 3.82 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.04 (1 H, s, Ar), 7.38 (1 H, s, Ar), 7.54 (1 H, d, *J* 8.0, Ar), 7.64 (1 H, d, *J* 8.0, Ar) and 9.43 (1 H, brs, NH); δ_C 27.3 (3 x q), 55.0 (q), 55.5 (q), 102.2 (d), 106.8 (d), 118.7 (s), 126.8 (s), 127.3 (d), 127.9 (d), 128.5 (s), 131.7 (s), 149.5 (s), 150.0 (s) and 176.4 (s) (quaternary C obscured by solvent peaks); *m/z* 365, 367 (M^+) and 286 ($M-Br^+$).

2,2-Dimethyl-_N_-(6,7-methylenedioxy-1-naphthyl)propanamide (12)

Prepared from 6,7-methylenedioxy-1-naphthylamine **2**[16] and pivaloyl chloride on a 0.03 mol scale by the same method as for **3**. Purification by filtration of a dichloromethane solution of the crude product through silica gel and crystallisation from ethyl acetate/hexane afforded the title compound **12** (4.93 g, 63%) as a colourless solid, mp 145-146°C. (Found: C, 70.55; H, 6.3; N, 5.2; $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%); ν_{max} cm^{-1} 3271, 1653 and 1247; δ_H 1.31 (9 H, s, 3 x CH_3), 6.12 (2 H, s, CH_2), 7.07 (1 H, s, Ar), 7.19 (1 H, d, *J* 8.0, Ar), 7.30 (1 H, t, *J* 8.0, Ar), 7.33 (1 H, s, Ar), 7.62 (1 H, d, *J* 8.0, Ar) and 9.32 (1 H, brs, NH); δ_C 27.4 (3 x q), 99.3 (d), 101.2 (t), 103.7 (d), 122.9 (d), 123.7 (d), 125.1 (d), 126.7 (s), 130.8 (s), 133.5 (s), 147.1 (s), 147.4 (s) and 177.0 (s) (quaternary C obscured by solvent peaks); *m/z* 271 (M^+) and 187 ($M-C_5H_8O^+$).

_N_-(2,4-Dibromo-6,7-methylenedioxy-1-naphthyl)-2,2-dimethylpropanamide (13),
_N_-(4,5-dibromo-6,7-methylenedioxy-1-naphthyl)-2,2-dimethylpropanamide (14) and
_N_-(4,8-dibromo-6,7-methylenedioxy-1-naphthyl)-2,2-dimethylpropanamide (15)

Bromine (1.81 g, 11.3 mmol) was added to a solution of *N*-(6,7-methylenedioxy-1-naphthyl)-2,2-dimethylpropanamide **12** (1.50 g, 5.53 mmol) and sodium acetate (0.95 g, 11.3 mmol) in glacial acetic acid (15 mL) at 45°C and the mixture stirred at 45-50°C for 2 h. Water (200 mL) and dichloromethane (200 mL) were added, the aqueous layer was basified with 40% aq. NaOH to pH 14, the phases separated, and the aqueous was extracted with further dichloromethane (2 x 100 mL). The combined organic phases were washed with water (2 x 200 mL), dried ($MgSO_4$), filtered and evaporated to leave a reddish-brown glass. Purification by column chromatography on silica gel (60 g), eluting with dichloromethane, gave the 2,4-dibromo compound **13** (0.59 g, 25%) as an orange glass. δ_H 1.33 (9 H, s, 3 x CH_3), 6.24 (2 H, s, CH_2), 7.06 (1 H, s, Ar), 7.46 (1 H,

s, Ar), 7.98 (1 H, s, Ar) and 9.47 (1 H, brs, NH); δ_C 27.2 (3 x q), 39.0 (s), 100.2 (d), 102.4 (t), 102.9 (d), 119.0 (s), 119.5 (s), 128.2 (s), 130.4 (d), 130.6 (s), 132.8 (s), 149.3 (s), 149.3 (s) and 176.7 (s); *m/z* 427, 429, 431 (M^+), 348, 350 ($M-Br^+$); high resolution MS m/z 429.9432; $C_{16}H_{15}Br_2NO_3$ requires 429.9420.

Further elution afforded the 4,5- and 4,8-dibromo compounds **14** and **15** (0.80 g, 34%) as an inseparable mixture. δ_H (major component) 1.27 (9 H, s, 3 x CH_3), 6.30 (2 H, s, CH_2), 7.08 (1 H, d, *J* 8.0, Ar), 7.55 (1 H, s, Ar), 7.76 (1 H, d, *J* 8.0, Ar) and 9.39 (1 H, brs, NH); (minor component) 1.31 (9 H, s, 3 x CH_3), 6.21 (2 H, s, CH_2), 7.11 (1 H, d, *J* 8.0, Ar), 7.46 (1 H, s, Ar), 7.67 (1 H, d, *J* 8.0, Ar) and 9.40 (1 H, brs, NH); *m/z* 428, 430, 432 (MH^+), 348, 350 ($M-Br^+$); high resolution MS m/z 429.9437; $C_{16}H_{15}Br_2NO_3$ requires 429.9420.

General procedure for the preparation of 2,2-dibromo-1-tetralones

A solution of bromine (3.21 g, 20.1 mmol) in chloroform (15 mL) was added over 70 min to a stirred solution of the 1-tetralone **16** or **17** (10.0 mmol) in chloroform (50 mL). The resulting mixture was stirred at ambient temperature overnight. Evaporation of the solvent gave the crude product.

2,2-Dibromo-6,7-dimethoxy-1-tetralone (18)

Purification by trituration with ethyl acetate (10 mL) and filtration of the insoluble material gave the title compound **18** as a yellow solid. The ethyl acetate liquors were concentrated to 2.5 mL, and the solid which separated was collected by filtration and dried at 40°C *in vacuo*, to give a second crop of **18** (combined yield 5.79 g, 66%) as a yellow crystalline solid, mp 166.5°C (decomp.). (Found: C, 39.35; H, 3.3; $C_{12}H_{12}Br_2O_3$ requires C, 39.6; H, 3.3%); ν_{max} cm^{-1} 1666, 1592, 1516, 1345, 1277, 1198, 1141, 1031, 874 and 667; δ_H 2.98 (2 H, t, *J* 5.7, CH_2), 3.07 (2 H, t, *J* 5.7, CH_2), 3.81 (3 H, s, CH_3), 3.87 (3 H, s, CH_3), 6.98 (1 H, s, Ar) and 7.42 (1 H, s, Ar); δ_C 28.5 (t), 45.5 (t), 55.5 (q), 55.9 (q) 68.9 (s), 109.6 (d), 110.8 (d), 119.0 (s), 137.8 (s), 148.3 (s), 154.4 (s) and 182.8 (s); *m/z* (CI) 363, 365, 367 (MH^+), 285, 287 (MH_2-Br^+) and 207 ($MH_3-Br_2^+$).

2,2-Dibromo-6,7-methylenedioxy-1-tetralone (19)

97%, mp 139.5-141°C (from ethanol). (Found: C, 37.8; H, 2.3; $C_{11}H_8Br_2O_3$ requires C, 38.0; H, 2.3%); ν_{max} cm^{-1} 1668, 1618, 1505, 1378, 1263, 1030 and 601; δ_H 2.97 (2 H, t, *J* 5.7, CH_2), 3.04 (2 H, t, *J* 5.7, CH_2), 6.15 (2 H, s, OCH_2O), 6.98 (1 H, s, Ar) and 7.38 (1 H, s, Ar); δ_C 28.9 (t), 45.1 (t), 68.4 (s), 102.4 (t), 106.6 (d), 108.0 (d), 120.6 (s), 140.2 (s), 147.4 (s), 153.1 (s) and 182.5 (s); *m/z* 346, 348, 350 (M^+), 268, 270 ($MH-Br^+$) and 188 ($M-Br_2^+$).

General procedure for the preparation of 2-bromo-1-naphthols

The 2,2-dibromo-1-tetralone **18** or **19** (8.0 mmol) was stirred in acetonitrile (50 mL) at 40°C for 15 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.83 g, 12.0 mmol) was added and the resulting solution stirred at 40-45°C for 20 min. After cooling to room temperature, 1M HCl (50 mL) was added. The mixture was extracted into dichloromethane (2 x 100 mL), and the combined organic phases washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and the solvent evaporated to give the crude product.

2-Bromo-6,7-dimethoxy-1-naphthol (20)

Purification by column chromatography on silica gel (600 g) eluting with 4:1 hexane/ethyl acetate gave the title compound **20** (93%) as an off-white crystalline solid, mp 118-120°C. (Found: C, 50.5; H, 4.1; $C_{12}H_{11}BrO_3$ requires C, 50.9; H, 3.9%); ν_{max} cm^{-1} 3406, 1625, 1588, 1509, 1268, 1204, 1161, 992, 852 and 811; δ_H 3.87 (3 H, s, CH_3), 3.89 (3 H, s, CH_3), 7.22 (1 H, d, *J* 8.7, Ar), 7.27 (1 H, s, Ar), 7.36 (1 H, d, *J* 8.7, Ar), 7.53 (1 H, s, Ar) and 9.62 (1 H, s, OH); δ_C 55.4 (2 x q), 101.2 (d), 103.0 (s), 106.7 (d), 119.5 (d), 121.0 (s), 127.5 (d), 129.2 (s), 148.1 (s), 149.1 (s) and 149.5 (s); *m/z* 282, 284 (M^+) and 204 ($M-HBr^+$).

2-Bromo-6,7-methylenedioxy-1-naphthol (21)

97%, mp 119.5°C (decomp.) (from methanol). (Found: C, 49.4; H, 2.9; $C_{11}H_7BrO_3$ requires C, 49.5; H, 2.6%); ν_{max} cm^{-1} 3383, 1619, 1602, 1499, 1253, 1169, 1041, 950 and 859; δ_H 6.14 (2 H, s, CH_2), 7.20 (1 H,

d, *J* 8.7, Ar), 7.27 (1 H, s, Ar), 7.38 (1 H, d, *J* 8.7, Ar), 7.52 (1 H, s, Ar) and 9.61 (1 H, brs, OH); δ_C 98.4 (d), 101.4 (t), 103.7 (d), 104.0 (s), 120.1 (d), 122.5 (s), 127.9 (d), 130.5 (s), 147.4 (s), 147.6 (s) and 148.6 (s); *m/z* 266, 268 (M^+) and 187 ($M-Br^+$).

General procedure for the O-alkylation of 2-bromo-1-naphthols

Sodium hydroxide (40-60 mesh granules) (0.117 mol) was added to a solution of the 2-bromo-1-naphthol **20** or **21** (19.6 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (45 mL) at room temperature, and the resulting mixture was stirred for 15 min. 2-Bromo-2-methylpropanamide **22** (19.49 g, 0.117 mol) was added and the mixture was stirred vigorously for 2-5 h. Water (100 mL) was then added, together with sufficient 5 M HCl to bring the mixture to pH 0. The resulting suspension was added to water (2.0 L) and allowed to stand overnight. The product was filtered, washed with water (3 x 500 mL), and dried under vacuum at 60°C for 48 h, to give an off-white solid.

2-(2-Bromo-6,7-dimethoxy-1-naphthyloxy)-2-methylpropanamide (23)

93%, mp 177°C (decomp.). (Found: C, 51.9; H, 5.0; N, 3.7; $C_{16}H_{18}BrNO_4$ requires C, 52.2; H, 4.9; N, 3.8%); ν_{max} cm^{-1} 3452, 1684, 1625, 1583, 1513, 1261, 1160, 1138, 910 and 860; δ_H 1.44 (6 H, s, 2 x CH_3), 3.85 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 7.33 (1 H, s, Ar), 7.48 (2 H, s, Ar), 7.53 (1 H, s, Ar), 7.57 (1 H, brs, NH) and 7.95 (1 H, brs, NH); δ_C 25.4 (2 x q), 55.5 (q), 55.6 (q), 84.5 (s), 102.6 (d), 106.9 (d), 113.3 (s), 124.3 (d), 126.9 (s), 127.8 (d), 129.5 (s), 148.0 (s), 149.6 (s), 149.9 (s) and 176.3 (s); *m/z* 367, 369 (M^+) and 282, 284 ($M-C_4H_7NO^+$).

2-(2-Bromo-6,7-methylenedioxy-1-naphthyloxy)-2-methylpropanamide (24)

93%, mp 191°C (decomp.) (from ethanol). (Found: C, 50.9; H, 4.1; N, 4.0; $C_{15}H_{14}BrNO_4$ requires C, 51.2; H, 4.0; N, 4.0%); ν_{max} cm^{-1} 3475, 1686, 1617, 1587, 1251, 1142, 1036, 943 and 848; δ_H 1.41 (6 H, s, 2 x CH_3), 6.14 (2 H, s, CH_2), 7.33 (1 H, s, Ar), 7.46 (1 H, s, Ar), 7.46 (1 H, d, *J* 8.7, Ar), 7.50 (1 H, d, *J* 8.8, Ar) and 7.86 (2 H, brs, NH_2); δ_C 25.4 (2 x q), 84.8 (s), 99.5 (d), 101.8 (t), 104.0 (d), 114.0 (s), 124.9 (d), 128.3 (d), 128.4 (s), 130.9 (s), 147.9 (s), 148.4 (s) and 176.0 (s), (one quaternary C not observed); *m/z* 351, 353 (M^+) and 266, 268 ($M-C_4H_7NO^+$).

General procedure for the Smiles rearrangement

Sodium hydride (9.0 mg, 0.367 mmol) was added to a solution of the 2-(2-bromo-1-naphthyloxy)-2-methylpropanamide **23** or **24** (0.334 mmol) in dry DMF (2.0 mL) and DMPU (0.5 mL). The resulting mixture was stirred at 100°C under argon for 2 h. The solution was then poured into water (40 mL) and extracted with ethyl acetate (40 mL). The organic phase was washed with water (3 x 50 mL), dried ($MgSO_4$), filtered and evaporated to give the product as an off-white solid.

***N*-(2-Bromo-6,7-dimethoxy-1-naphthyl)-2-hydroxy-2-methylpropanamide (25)**

93%, mp 217°C (decomp.). (Found: C, 52.2; H, 4.95; N, 3.9; $C_{16}H_{18}BrNO_4$ requires C, 52.2; H, 4.9; N, 3.8%); ν_{max} cm^{-1} 3320, 1667, 1622, 1584, 1496, 1267, 1222, 1164, 1160 and 856; δ_H 1.47 (6 H, s, 2 x CH_3), 3.84 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 5.73 (1 H, s, OH), 7.09 (1 H, s, Ar), 7.38 (1 H, s, Ar), 7.54 (1 H, d, *J* 8.7, Ar), 7.65 (1 H, d, *J* 8.7, Ar) and 9.57 (1 H, brs, NH); δ_C 27.7 (2 x q), 55.2 (q), 55.5 (q), 72.4 (s), 102.6 (d), 106.7 (d), 118.1 (s), 126.8 (d), 127.2 (d), 127.6 (s), 128.5 (s), 131.4 (s), 149.5 (s), 149.9 (s) and 175.8 (s); *m/z* 367, 369 (M^+), 288 ($M-Br^+$), 282, 284 ($M-C_4H_7NO^+$) and 270 ($M-Br$, H_2O^+).

***N*-(2-Bromo-6,7-methylenedioxy-1-naphthyl)-2-hydroxy-2-methylpropanamide (26)**

94%, mp 212°C (decomp.). (Found: C, 50.8; H, 4.2; N, 3.8; $C_{15}H_{14}BrNO_4$ requires C, 51.2; H, 4.0; N, 4.0%); ν_{max} cm^{-1} 3408, 3366, 3325, 1671, 1617, 1590, 1244, 1040, 942 and 857; δ_H 1.46 (6 H, s, 2 x CH_3), 5.69 (1 H, s, OH), 6.14 (2 H, s, CH_2), 7.19 (1 H, s, Ar), 7.29 (1 H, s, Ar), 7.51 (1 H, d, *J* 8.8, Ar), 7.60 (1 H, d, *J* 8.8, Ar) and 9.50 (1 H, brs, NH); δ_C 27.6 (2 x q), 72.6 (s), 100.2 (d), 101.5 (t), 103.7 (d), 118.9 (s), 127.3 (d),

127.6 (d), 129.4 (s), 130.0 (s), 132.0 (s), 147.7 (s), 148.6 (s) and 176.0 (s); *m/z* 351, 353 (M^+), 272 ($M-Br^+$), 265, 267 ($M-C_4H_7NO^+$) and 254 ($M-Br, H_2O^+$).

General procedure for the preparation of 2-bromo-1-naphthylamines

Sodium hydroxide [40% aq. solution (80 mL, 0.80 mol) and 20-40 mesh beads (32.0 g, 0.80 mol)] was added to a solution of the *N*-(2-bromo-1-naphthyl)-2-hydroxy-2-methylpropanamide **25** or **26** (0.02 mol) in methanol (80 mL), and the resulting mixture was stirred at reflux overnight. Further sodium hydroxide (32.0 g, 0.80 mol) was added, reflux continued for another 1-4 d and the products isolated as described below.

2-Bromo-6,7-dimethoxy-1-naphthylamine (27)

The cooled mixture was added to ice-water (2.0 L). The resulting mixture was allowed to stand for 1 h, filtered, washed with water (2 x 200 mL), and dried in vacuum at 60°C to give the title compound **27** (82%) as a purple solid. A sample was recrystallised from ethanol to give an off-white solid, mp 147.5°C (decomp.). (Found: C, 50.9; H, 4.2; N, 4.9; $C_{12}H_{12}BrNO_2$ requires C, 51.1; H, 4.3; N, 5.0%); ν_{max} cm^{-1} 3442, 3364, 1625, 1587, 1512, 1266, 1231, 1165, 1046 and 859; δ_H 3.84 (3 H, s, CH_3), 3.88 (3 H, s, CH_3), 5.67 (2 H, brs, NH_2), 6.92 (1 H, d, *J* 8.7, Ar), 7.16 (1 H, s, Ar), 7.24 (1 H, d, *J* 8.7, Ar) and 7.48 (1 H, s, Ar); δ_C 55.0 (q), 55.4 (q), 99.8 (s), 102.3 (d), 106.7 (d), 115.6 (d), 117.9 (s), 127.3 (d), 128.6 (s), 139.6 (s), 148.3 (s) and 148.8 (s); *m/z* 281, 283 (M^+), 266, 268 ($M-NH^+$) and 203 ($MH-Br^+$).

2-Bromo-6,7-methylenedioxy-1-naphthylamine (28)

After cooling, water (1.0 L) and ethyl acetate (0.5 L) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 0.5 L). The combined organic layers were washed with water (0.5 L), dried ($MgSO_4$), filtered and evaporated to give a dark brown glass. Column chromatography of this product on silica (150 g), eluting with 25% ethyl acetate in hexane, gave the title compound **28** as an off-white solid (74%), mp 142-142.5°C (from ethanol). (Found: C, 49.3; H, 3.0; N, 5.1; $C_{12}H_{12}BrNO_2$ requires C, 49.65; H, 3.0; N, 5.3%); ν_{max} (KBr) cm^{-1} 3389, 3309, 3207, 1627, 1467, 1450, 1251, 1035, 942 and 849; δ_H 5.61 (2 H, brs, NH_2), 6.11 (2 H, s, CH_2), 6.92 (1 H, d, *J* 8.6, Ar), 7.18 (1 H, s, Ar), 7.27 (1 H, d, *J* 8.6, Ar) and 7.63 (1 H, s, Ar); δ_C 99.4 (d), 100.9 (s), 101.1 (t), 104.0 (d), 116.6 (d), 119.2 (s), 127.9 (d), 130.1 (s), 140.4 (s), 146.9 (s) and 147.1 (s); *m/z* 265, 267 (M^+) and 185 ($MH-Br^+$).

2-(2-Bromo-4,5-methylenedioxyphenyl)-1,3-dioxolane (30)

Ethane-1,2-diol (31.0 mL, 0.50 mol) and p-toluenesulfonic acid monohydrate (0.02 g, 0.1 mmol) were added to a solution of 2-bromo-4,5-methylenedioxybenzaldehyde **29**[20] (11.45 g, 0.50 mL) in toluene (100 mL), and the resulting mixture stirred under reflux for 48 h with Dean and Stark removal of water. Most of the solvent was then evaporated under reduced pressure and the oily residue triturated with aq. $NaHCO_3$ solution. The precipitated solid was collected by filtration, slurried with water (3 x 200 mL), refiltered and dried under vacuum. The title compound **30** was obtained as an off-white solid (12.2 g, 89%), mp 65-67.5°C. (Found: C, 43.65; H, 3.4; $C_{10}H_9BrO_4$ requires C, 44.0; H, 3.3%); ν_{max} cm^{-1} 1414, 1247, 1124, 1084, 1036, 950 and 865; δ_H ($CDCl_3$) 4.03 (2 H, m, CH_2), 4.12 (2 H, m, CH_2), 5.97 (2 H, s, OCH_2O), 6.00 (1 H, s, CH), 6.99 (1 H, s, Ar) and 7.06 (1 H, s, Ar); δ_C ($CDCl_3$) 65.4 (2 x t), 101.9 (t), 102.6 (d), 107.7 (d), 112.8 (d), 113.9 (s), 130.0 (s), 147.5 (s) and 149.0 (s); *m/z* 272, 274 (M^+), 227, 229 ($M-CHO_2^+$), 200, 202 ($M-C_3H_4O_2^+$) and 193 ($M-Br^+$).

2-Formyl-4,5-methylenedioxyphenylboronic acid (31)

n-Butyllithium (1.6 M solution in hexanes, 19.8 mL, 31.6 mmol) was added to a solution of 2-(2-bromo-4,5-methylenedioxyphenyl)-1,3-dioxolane **30** (7.50 g, 27.5 mmol) in dry THF (75 mL) at -78°C. The resulting colourless suspension was stirred at this temperature for 1 h under an atmosphere of argon. Triisopropyl borate (6.72 g, 35.7 mmol) was then added, and stirring continued for 1 h before warming to ambient temperature overnight. The reaction mixture was then cooled to 0°C, 2M HCl (40 mL) was added, and this solution was heated under reflux for 1 h. After cooling the phases were separated and the aqueous layer extracted with ethyl

acetate (100 mL). The combined organic phases were evaporated under reduced pressure to give a pale brown solid which was then dissolved in 2M NaOH (250 mL). The resulting solution was washed with diethyl ether (150 mL), then cooled to 0°C and carefully acidified to pH 1 with conc. HCl. The precipitated solid was filtered off after a further 1 h at 0°C, washed with water (3 x 50 mL) and dried under vacuum at ambient temperature. The title compound **31** was obtained as a colourless solid (3.25 g, 61%), mp 210°C (decomp.). (Found: C, 49.4; H, 3.7; $C_8H_7BO_5$ requires C, 49.5; H, 3.6%); ν_{max} cm^{-1} 3332, 3185, 1661, 1603, 1266, 1091, 1047, 992, 931 and 884; δ_H 6.14 (2 H, s, CH_2), 7.11 (1 H, s, Ar), 7.35 (1 H, s, Ar), 8.34 (2 H, brs, $B[OH]_2$) and 10.03 (1 H, s, CHO); *m/z* 194 (M^+), 150 ($M\text{-}B[OH]_2^+$) and 121 ($M\text{-}B[OH]_2$, CHO^+).

2,3-Dimethoxy-8,9-methylenedioxybenzo[*c*]phenanthridine, (Norallonitidine) (32)

Palladium(II) acetate (7.0 mg, 0.03 mmol), triphenylphosphine (0.16 g, 0.06 mmol) and 2 M aq. Na_2CO_3 (0.75 mL, 1.50 mmol) were added to a solution of 2-bromo-6,7-dimethoxy-1-naphthylamine **27** (0.14 g, 0.50 mmol) in DME (2.5 mL). The resulting mixture was degassed with argon and 2-formyl-4,5-methylenedioxyphenylboronic acid **31** (0.13 g, 0.65 mmol) was added and the mixture was stirred under reflux for 3 h. Further palladium(II) acetate (7.0 mg, 0.03 mmol), triphenylphosphine (0.16 g, 0.06 mmol) and **31** (0.13 g, 0.65 mmol) were then added and stirring was continued overnight under reflux. The cooled mixture was diluted with dichloromethane (5.0 mL) and filtered through Celite. The filter cake was washed with dichloromethane (2 x 5.0 mL) and water (2 x 5.0 mL), and the combined filtrates were separated and the aqueous phase was extracted with dichloromethane (5.0 mL). The combined organic extracts were washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and evaporated to leave a dark brown glass (0.32 g). Purification by column chromatography on silica gel (20 g) eluting with 4:1 to 1:1 hexane/ethyl acetate gave the title compound **32** (57.9 mg, 35%) as a yellow solid. A sample was recrystallised from pyridine/methanol, mp 276-278°C (lit. 278-279°C[27]). (Found: C, 71.7; H, 4.75; N, 4.3; $C_{20}H_{15}NO_4$ requires C, 72.1; H, 4.5; N, 4.2%); UV (EtOH) nm 229 (4.47), 271 (4.82), 282 (4.79), 309 sh (4.38), 330 (3.59), 350 (3.76) and 369 (3.51); ν_{max} (KBr) cm^{-1} 3009, 1617, 1484, 1428, 1252, 1161, 1033, 866, 838 and 801; δ_H 3.96 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 6.28 (2 H, s, CH_2), 7.53 (1 H, s, Ar), 7.68 (1 H, s, Ar), 7.96 (1 H, d, *J* 9.0, Ar), 8.32 (1 H, s, Ar), 8.51 (1 H, d, *J* 9.0, Ar), 8.62 (1 H, s, Ar) and 9.28 (1 H, s, Ar); δ_C 55.6 (q), 55.7 (q), 100.1 (d), 102.2 (t), 103.8 (d), 104.9 (d), 107.6 (d), 118.9 (d), 120.0 (s), 123.2 (s), 126.2 (d), 126.5 (s), 128.1 (s), 130.5 (s), 139.7 (s), 147.8 (s), 149.6 (s), 149.9 (d), 150.0 (s) and 151.6 (s); *m/z* 333 (M^+). Also prepared from compound **37**, as pale yellow crystals (98%), mp 278-279°C.

General procedure for the N*-formylation of 1-naphthylamines*

Acetic-formic anhydride was generated in the reaction flask by dropwise addition of 98% formic acid (1.21 mL, 32 mmol) to acetic anhydride (2.05 mL, 26 mmol) maintained at 0°C, followed by gentle heating (50-60°C, 2 h). The mixture was cooled to room temperature and THF (3.0 mL) was added, followed by a solution of the 1-naphthylamine **27** or **28** (10.0 mmol) in THF (25 mL). The resulting mixture was stirred at room temperature for 45 min. The solvent and other volatiles were removed under high vacuum to give a colourless solid, which was then stirred with ethyl acetate (50 mL), filtered, washed with ethyl acetate and dried to give the product as a colourless solid.

2-Bromo-6,7-dimethoxy-1-formamidonaphthalene (33)

91%, mp 228-229°C. (Found: C, 50.5; H, 4.0; N, 4.5; $C_{13}H_{12}BrNO_3$ requires C, 50.3; H, 3.9; N, 4.5%); ν_{max} (KBr) cm^{-1} 3246, 1659, 1623, 1586, 1508, 1268 and 1046; δ_H (rotamers, major component listed first): 3.87, 3.90 (3 H, s, CH_3), 3.90 (3 H, s, CH_3), 7.16, 7.28 (1 H, s, Ar), 7.40, 7.42 (1 H, s, Ar), 7.59, 7.56 (1 H, d, *J* 8.7, Ar), 7.68, 7.69 (1 H, d, *J* 8.7, Ar), 8.45 (s), 8.19 (d, *J* 8.0) (1H, NH) and 10.05 (s), 9.98 (d, *J* 8.0) (1 H, CHO); δ_C 55.4, 55.5, 55.5, (q), 102.0, 102.4 (d), 106.8, 106.9 (d), 116.9, 117.5 (s), 127.1, 127.1, 127.3, 127.6 (d), 127.0, 128.5, 128.8, 130.0 (s), 149.6, 149.8 (s), 150.2, 150.4 (s) and 159.9, 165.0 (d); *m/z* 309, 311 (M^+), 281, 283 ($M\text{-}CO^+$) and 230 ($M\text{-}Br^+$).

2-Bromo-1-formamido-6,7-methylenedioxynaphthalene (34)

88%, mp 247-249°C (decomp.). (Found: C, 48.8; H, 2.9; N, 4.7; $C_{12}H_8BrNO_3$ requires C, 49.0; H, 2.7; N, 4.8%); ν_{max} cm^{-1} 3210, 3169, 1657, 1524, 1251 and 1038; δ_H (rotamers, major component listed first) 6.17, 6.19 (2 H, s, CH_2), 7.19, 7.26 (1 H, s, Ar), 7.39, 7.42 (1 H, s, Ar), 7.61 7.57 (1H, d, *J* 8.8, Ar), 7.67, 7.68 (1 H, d, *J* 8.8, Ar), 8.42 (s) 8.13 (d, *J* 8.0) (1 H, NH), 10.02 (s) and 9.50 (d, *J* 8.0) (1 H, CHO); δ_C 99.4, 100.0 (d), 101.7, 101.8 (t), 103.8, 104.0 (d), 118.0, 118.2 (s), 127.6, 127.7, 127.8, 127.9 (d), 128.6, 128.9 (s), 129.9, 130.1 (s), 130.6, 130.7 (s), 147.8, 148.0 (s), 148.7, 148.9 (s), and 160.1, 164.9 (d); *m/z* 293, 295 (M^+), 265, 267 ($M\text{-}CO^+$) and 214 ($M\text{-}Br^+$).

General procedure for the Suzuki coupling between 2-bromo-6,7-dioxygenated-1-formamidonaphthalenes and arylboronic acids

Palladium(II) acetate (0.02 mmol) and triphenylphosphine (0.04 mmol) were added to a suspension of the 2-bromo-1-formamidonaphthalene **33** or **34** (0.68 mmol) in DME (3.0 mL). The resulting mixture was degassed and stirred at ambient temperature for 10 min before the addition of 2M aq. Na_2CO_3 solution (1.0 mL). The mixture was again degassed and then stirred in an atmosphere of argon for 1 h. The arylboronic acid **35**, **36** or **48** (1.0 mmol) was then added, and the resulting mixture was heated under reflux with stirring in an atmosphere of argon for 1.25 - 4 h. The cooled mixture was diluted with dichloromethane (40 mL) and water (20 mL), the organic phase was separated, and the aqueous layer was extracted with further dichloromethane (10 mL). The combined organic extracts were washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to leave a pale grey solid. Purification by column chromatography on silica gel (10 g), eluting firstly with 1:1 ethyl acetate/hexane and then with neat ethyl acetate, gave the products.

6,7-Dimethoxy-1-formamido-2-(3,4-methylenedioxyphenyl)naphthalene (37)

92%, mp 246-247°C (from 2-propanol). (Found: C, 66.95; H, 5.0; N, 3.8; $C_{20}H_{17}NO_5$.$0.5H_2O$ requires C, 66.7; H, 5.0; N, 3.9%); ν_{max} cm^{-1} 3224, 1646, 1606, 1497, 1262 and 1037; δ_H (rotamers, major component listed first) 3.91, 3.86 (6 H, s, 2 x CH_3), 6.06, 6.07 (2 H, s, CH_2), 6.88, 6.90 (1 H, dd, *J* 8.0, 1.8, Ar), 6.96 - 7.02 (2 H, m, Ar), 7.20, 7.35 (1 H, s, Ar), 7.29, 7.33 (1 H, d, *J* 8.3, Ar), 7.39, 7.40 (1 H, s, Ar), 8.26, 7.78 (1 H, s, NH), 7.77 (1 H, d, *J* 8.3, Ar) and 9.73, 9.76 (1 H, s, CHO); δ_C 55.1, 55.2, 55.3 (q), 100.7, 100.8 (t), 101.9, 102.4 (d), 106.5, 106.5 (d), 107.8, 108.2 (d), 109.1, 109.9 (d), 122.2, 123.1 (d), 125.2, 125.5, 125.7, 125.9 (d), 125.9 126.0 (s), 127.7 128.0 (s), 128.6, 128.7 (s), 133.0, 133.6, 134.4 (s), 145.9, 146.0 (s), 146.7, 147.0 (s), 149.1, 149.3 (s), 149.7, 149.8 (s) and 160.6, 164.6 (d); *m/z* 351 (M^+) and 323 ($M\text{-}CO^+$).

2-(3,4-Dimethoxyphenyl)-1-formamido-6,7-methylenedioxynaphthalene (38)

Quantitative, mp 251-252°C (from 2-propanol). (Found: C, 66.8; H, 4.9; N, 3.9; $C_{20}H_{17}NO_5$.$0.5H_2O$ requires C, 66.7; H, 5.0; N, 3.9%); ν_{max} (KBr) cm^{-1} 3238, 1649, 1602, 1584, 1248 and 1031; δ_H (rotamers, major component listed first) 3.75, 3.76 (3 H, s, CH_3), 3.79, 3.80 (3 H, s, CH_3), 6.16, 6.17 (2 H, s, CH_2), 6.93, 6.96 (1 H, dd, Ar), 7.01 7.03 (1 H, m, Ar), 7.01 7.20 (1H, s, Ar), 7.33 7.35 (1 H, s, Ar), 7.38, 7.40 (1H, s, Ar), 8.26, (s), 7.73, (d, *J* 11.2), (1 H, NH), 7.75 (1 H, d, *J* 8.3, Ar) and 9.71 (s), 9.75 (d, *J* 11.2), (1 H, CHO); δ_C 55.4, 55.4, 55.5 (q), 100.0, 99.3 (d), 101.3, 101.5 (t), 103.6, 103.7 (d), 111.6, 111.7 (d), 112.8, 113.7 (d), 121.0, 122.0 (d), 126.1, 126.3, 126.7, (d), 127.8, 127.9 (s), 128.5, 128.6 (s), 129.9, 130.1 (s), 131.5, 132.1 (s), 134.3, 135.4 (s), 147.3, 147.5, 147.8, 148.0, 148.1, 148.2, 148.4 (s) and 161.1, 164.7 (d); *m/z* 351 (M^+).

1-Formamido-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)naphthalene (39)

74%, mp 262-263°C. ν_{max} cm^{-1} 3267, 1657, 1247, 1043 and 926; δ_H (rotamers, major component listed first) 6.05, 6.07 (2 H, s, CH_2), 6.16, 6.18 (2 H, s, CH_2), 6.86, 6.89 (1 H, dd, *J* 8.5, 2.0, Ar), 6.8 to 7.0 (2 H, m, 2 x Ar), 7.1 to 7.8 (4 H, m, 4 x Ar), 8.23 (1 H, s, CHO) and 9.72 (1 H, s, NH); δ_C 100.2, 99.5 (d), 101.1, 101.2 (t), 101.5, 101.7 (t), 108.2, 108.5 (d), 109.4, 110.3 (d), 122.5, 123.5 (d), 126.4 (d), 126.4, 126.5 (d), 127.8, 128.1 (s), 128.7, 128.8 (s), 130.2, 130.3 (s), 133.6, 133.1 (s), 135.1, 134.6 (s), 146.5 (s), 147.0, 147.3 (s), 147.5,

147.8 (s), 148.5, 148.6 (s) and 161.1, 164.9 (d); *m/z* (CI) 336 (MH^+); high resolution MS *m/z* 335.0797; $C_{19}H_{13}NO_5$ requires 335.0793.

General procedure for N-*methylation of formamides*

Sodium hydride (80% dispersion in mineral oil), (0.625 mmol) was added to a stirred suspension of the 1-formamido-2-arylnaphthalene **37-39** or **49** (0.50 mmol) in either dry DMF or THF (10 mL) at 0°C under argon. The resulting mixture was warmed to room temperature and stirred for 30 min under argon. Iodomethane (0.75 mmol) was added and the resulting mixture was stirred at room temperature for 1.5 h. 0.25 M HCl was then added to give a mixture having pH 1. The mixture was extracted into dichloromethane (2 x 75 mL), and the organic extract was washed twice with water (2 x 35 mL), dried ($MgSO_4$), filtered and evaporated to give the product as a colourless solid.

6,7-Dimethoxy-2-(3,4-methylenedioxyphenyl)-1-(*N*-methylformamido)naphthalene (40)

Quantitative, mp 193-194°C (from ethyl acetate). (Found: C, 68.9; H, 5.4; N, 4.0; $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%); ν_{max} cm^{-1} 1669, 1466, 1263, 1249 and 1040; δ_H (rotamers, major component listed first) 3.00, 2.94 (3 H, s, NCH_3), 3.88, 3.86 (3 H, s, OCH_3), 3.92, 3.91 (3 H, s, OCH_3), 6.08, 6.07 (2 H, s, CH_2), 6.80, 6.84 (1 H, dd, *J* 8.0, *J* 1.8, Ar) , 6.91, 6.89 (1 H, d, *J* 1.8, Ar), 6.95, 6.98 (1 H, s, Ar), 6.99, 7.00 (1 H, d, *J* 8.0, Ar), 7.33, 7.30 (1 H, d, *J* 8.4, Ar), 7.47, 7.43 (1 H, s, Ar), 7.86, 7.82 (1 H, d, *J* 8.4, Ar) and 8.04, 8.38 (1 H, s, CHO); δ_C 33.3, 35.9 (q) 55.3, 55.5, 55.5, 55.6 (q), 101.0 (t), 101.1, 101.8 (d), 107.0, 107.1 (d), 108.2 (d), 108.7, 109.2 (d), 121.9, 122.3 (d), 124.8, 126.2 (s), 126.2, 126.4, 126.7 (d), 129.2, 129.3 (s), 132.6, 132.8, 132.9, 133.4, 134.8, 135.9 (s), 146.5, 146.6 (s), 147.0, 147.1 (s), 149.5, 149.6 (s), 150.5, 150.6 (s) and 163.6, 163.9 (d); *m/z* 365 (M^+), 350 ($M\text{-}CH_3^+$) and 336 ($M\text{-}CHO^+$).

2-(3,4-Dimethoxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (41)

Quantitative, mp 193.5-195°C (lit. 196-198.5°C[6]) (from ethyl acetate). (Found: C, 68.8; H, 5.5; N, 3.8; $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%); ν_{max} cm^{-1} 1601, 1520, 1501, 1257 and 1026; δ_H (rotamers, major component listed first) 2.95, 2.86 (3 H, s, NCH_3), 3.75, 3.74 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 6.19, 6.17 (2 H, d, *J* 1.5, CH_2), 6.87, 6.91 (1 H, dd, *J* 8.2, 2.0, Ar), 6.90, 6.94 (d, 1 H, d, *J* 2.0, Ar), 7.03, 7.04 (1 H, d, *J* 8.2, Ar), 7.07, 7.14 (1 H, s, Ar), 7.39, 7.35 (1 H, d, *J* 8.3, Ar), 7.47, 7.42 (1 H, s, Ar), 7.86, 7.81 (1 H, d, *J* 8.3, Ar) and 8.05, 8.35 (1 H, s, CHO); δ_C 33.3, 35.8 (q), 55.3, 55.4, 55.4 (q), 98.7, 99.5 (d), 101.4, 101.7 (t), 103.9, 104.1 (d), 111.6 (d), 112.1, 112.5 (d), 120.5, 121.0 (d), 126.5, 126.5, 126.6, 127.0, 127.4 (d), 128.1 (s), 130.4, 130.6 (s), 131.2, 131.3 (s), 133.2, 134.1 (s), 135.4, 136.6 (s), 147.5, 147.8, 148.1, 148.2, 148.3, 148.8, 149.1 (s) and 163.6, 164.2 (d); *m/z* 365 (M^+), 350 ($M\text{-}CH_3^+$) and 336 ($M\text{-}CHO^+$).

6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-1-(*N*-methylformamido)naphthalene (42)

Quantitative, mp 205.5-208°C (lit. 209-211.5°C[6]) (from ethyl acetate). (Found: C, 68.3; H, 4.7; N, 3.8; $C_{20}H_{15}NO_5$ requires C, 68.8; H, 4.3; N, 4.0%); ν_{max} (KBr) cm^{-1} 2908, 1669, 1489, 1454, 1228 and 1039; δ_H (rotamers, major component listed first) 2.95, 2.89 (3 H, s, CH_3), 6.08, 6.06 (2 H, s, CH_2), 6.19, 6.17 (2 H, s, CH_2), 6.78, 6.81 (1 H, dd, *J* 8.5, 2.0, Ar), 6.90, 6.87 (1 H, d, *J* 8.5, Ar), 6.98, 6.99 (1 H, d, *J* 8.5, Ar), 7.03, 7.13 (1 H, s, Ar), 7.33, 7.30 (1 H, d, *J* 8.5, Ar), 7.46, 7.42 (1 H, s, Ar), 7.85, 7.79 (1 H, d, *J* 8.5, Ar) and 8.03, 8.32 (1 H, s, CHO); δ_C 33.5, 36.1 (q), 98.8, 99.7 (d), 101.3, 101.2 (t), 101.8, 101.6 (t), 104.3, 104.1 (d), 108.4 (d), 109.4, 108.8 (d), 122.5, 122.0 (d), 126.7 (d), 127.6, 127.2 (d), 128.3, 126.6 (s), 130.8, 130.7 (s), 132.8, 132.7 (s), 134.3, 133.7 (s), 136.7, 135.4 (s), 146.7, 146.9 (s), 147.3, 147.2 (s), 147.9, 147.7 (s), 149.3, 149.0 (s) and 163.7, 164.2 (d); *m/z* 349 (M^+), 334 ($M\text{-}CH_3^+$) and 320 ($M\text{-}CHO^+$).

General method for Bischler-Napieralski cyclisations

A solution of the formamidonaphthalene **37-39** (0.5 mmol) and phosphorus oxychloride (0.3 mL) in acetonitrile (15 mL) was stirred under reflux for 30 min. The cooled reaction mixture was poured into a

mixture of ice and aq. NH_4OH (or ice-water for *N*-methylated compounds), and the solid which separated was collected by filtration and recrystallised.

8,9-Dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine, (Nornitidine) (43)

Pale yellow crystals (99%) (from pyridine/methanol), mp 281-282°C (lit. 281-282°C[27]). (Found: C, 71.8; H, 4.5; N, 4.5; $C_{20}H_{15}NO_4$ requires C, 72.1; H, 4.5; N, 4.2%); UV (EtOH) nm 229 (4.38), 274 (4.76), 281 (4.76), 315 (4.18), 330 sh (3.88), 348 (3.58) and 367 (3.35); ν_{max} cm^{-1} 1623, 1596, 1521, 1496, 1253, 1159 and 801; δ_H 4.00 (3 H, s, CH_3), 4.09 (3 H, s, CH_3), 6.18 (2 H, s, CH_2), 7.46 (1 H, s, Ar), 7.68 (1 H, s, Ar), 7.93 (1 H, d, *J* 8.8, Ar), 8.14 (1 H, s, Ar), 8.56 (1 H, d, *J* 8.8, Ar), 8.57 (1 H, s, Ar) and 9.29 (1 H, s, Ar); δ_C 56.0 (q), 56.3 (q), 101.3 (d), 101.4 (t), 102.8 (d), 104.5 (d), 108.2 (d), 119.2 (d), 119.8 (s), 122.1 (s), 126.3 (d), 128.4 (s), 128.6 (s), 129.4 (s), 139.9 (s), 148.0 (s), 148.1 (s), 149.9 (d), 150.0 (s) and 153.4 (s); *m/z* 333 (M^+) and 318 ($M\text{-}CH_3^+$).

2,3,8,9-Dimethylenedioxybenzo[*c*]phenanthridine, (Noravicine) (44)

Pale yellow crystals (93%) (from pyridine/methanol), mp 325°C [lit. 325°C (decomp.)[28]]. UV (EtOH) nm 228 (4.47), 273 (4.77), 283 sh (4.73), 327 sh (3.98) and 370 (3.63); ν_{max} cm^{-1} 1595, 1253, 1083 and 943; δ_H 6.21 (2 H, s, CH_2), 6.28 (2 H, s, CH_2), 7.51 (1 H, s, Ar), 7.68 (1 H, s, Ar), 7.93 (1 H, d, *J* 9.0, Ar), 8.32 (1 H, s, Ar), 8.50 (1 H, d, *J* 9.0, Ar), 8.54 (1 H, s, Ar) and 9.28 (1 H, s, Ar); δ_C 100.2 (d), 101.3 (d), 101.6 (t), 102.3 (t), 104.6 (d), 105.0 (d), 119.3 (d), 120.4 (s), 123.3 (s), 126.7 (d), 128.3 (s), 129.5 (s), 130.4 (s), 140.0 (s), 148.0 (s), 148.2 (2 x s), 150.2 (d) and 151.7 (s); *m/z* 317 (M^+); high resolution MS *m/z* 317.0707; $C_{19}H_{11}NO_4$ requires 317.0688.

2,3-Dimethoxy-5-methyl-8,9-methylenedioxybenzo[*c*]phenanthridinium chloride, (Allonitidine chloride) (45)

Yellow needles (quantitative) (from methanol), mp 323-325°C[29]. UV (EtOH) nm 232 (4.37), 274 (4.45), 309 (4.28), 327 (4.26) and 391 (3.53); ν_{max} cm^{-1} 1617, 1505, 1272 and 1037; δ_H 4.03 (3 H, s, OCH_3), 4.08 (3 H, s, OCH_3), 4.99 (3 H, s, NCH_3), 6.49 (2 H, s, CH_2), 7.81 (1 H, s, Ar), 7.89 (1 H, s, Ar), 8.17 (1 H, s, Ar), 8.30 (1 H, d, *J* 8.8, Ar), 8.62 (1 H, s, Ar), 8.76 (1 H, s, *J* 8.8, Ar) and 9.90 (1 H, s, Ar); δ_C 51.3 (q), 56.0 (q), 56.2 (q), 100.6 (d), 104.0 (t), 105.8 (d), 108.0 (d), 109.0 (d), 118.4 (s), 118.6 (d), 121.0 (s), 124.4 (s), 130.2 (d), 131.2 (s), 132.3 (s), 134.8 (s), 149.4 (s), 150.2 (s), 150.7 (s), 150.9 (d) and 157.3 (s); *m/z* 333 ($M\text{-}CH_3^+$); *m/z* (FAB) 348 (M^+); high resolution MS *m/z* 348.1247; $C_{21}H_{18}NO_4$ requires 348.1235.

8,9-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium chloride, (Nitidine chloride) (46)

Yellow needles (91%) (from ethanol), mp 274-275°C (lit. 274-278°C[30]). (Found: C, 57.5; H, 5.1; N, 3.2; $C_{21}H_{18}ClNO_4 .3H_2O$ requires C, 57.6; H, 5.5; N, 3.2%); UV (EtOH) nm 230 (4.50), 272 (4.42), 280 (4.47), 304 (4.25) and 329 (4.16); ν_{max} (KBr) cm^{-1} 3418, 1616, 1503, 1431, 1285 and 1036; δ_H 4.05 (3 H, s, OCH_3), 4.24 (3 H, s, OCH_3), 4.90 (3 H, s, NCH_3), 6.35 (2 H, s, CH_2), 7.78 (1 H, s, Ar), 7.91 (1 H, s, Ar), 8.29 (1 H, d, *J* 9.0, Ar), 8.32 (1 H, s, Ar), 8.37 (1 H, s, Ar), 8.91 (1 H, *J* 9.0, Ar) and 9.88 (1 H, s, Ar); δ_C 51.4 (q), 56.2 (q), 57.2 (q), 102.6 (t), 103.2 (d), 104.5 (d), 105.7 (d), 108.7 (d), 119.2 (d), 119.4 (s), 119.8 (s), 124.0 (s), 129.9 (d), 132.0 (s), 132.4 (s), 132.5 (s), 148.3 (s), 148.8 (s), 151.2 (s), 151.4 (d) and 158.2 (s); *m/z* 333 ($M\text{-}CH_3^+$).

2,3,8,9-Dimethylenedioxy-5-methylbenzo[*c*]phenanthridinium chloride, (Avicine chloride) (47)

Yellow needles (96%) (from methanol), mp 327°C (decomp.), (lit. >300°C[6]). (Found: C, 59.9; H, 4.3; N, 3.5; $C_{20}H_{14}ClNO_4 .2H_2O$ requires C, 59.5; H, 4.5; N, 3.5%); UV (EtOH) nm 231 (4.56), 276 sh (4.43), 280 (4.44), 317 (4.27) and 390 (3.18); ν_{max} (KBr) cm^{-1} 3428, 1619, 1483, 1461, 1293, 1262 and 1036; δ_H 4.89 (3 H, s, NCH_3), 6.35 (2 H, s, CH_2), 6.49 (2 H, s, CH_2), 7.77 (1 H, s, Ar), 7.87 (1 H, s, Ar), 8.26 (1 H, d, *J* 9.0, Ar), 8.31 (1 H, s, Ar), 8.61 (1 H, s, Ar), 8.75 (1 H, d, *J* 9.0, Ar) and 9.87 (1 H, s, Ar); δ_C 51.7 (q), 101.2 (d), 103.3 (t), 104.7 (t), 105.0 (d), 106.1 (d), 106.2 (d), 119.4 (d), 120.4 (s), 121.5 (s), 125.2 (s), 130.8 (d), 133.3 (s), 133.5 (s), 135.3 (s), 149.1 (s), 149.7 (s), 150.8 (s), 151.7 (d) and 157.9 (s); *m/z* 317 ($M\text{-}CH_3^+$).

2,4,5-Trimethoxyphenylboronic acid (48)

A solution of 1-bromo-2,4,5-trimethoxybenzene (2.0 g, 8.1 mmol) in dry THF (7.5 mL) was added dropwise to n-butyllithium (6.3 mL of a 1.6 M solution in hexanes, 10.1 mmol) in dry THF (7.5 mL) at -78°C, and the resulting mixture stirred at that temperature under argon for 1 h. Triisopropyl borate (2.28 g, 12.1 mmol) was added, and the solution stirred at -78°C for 30 min, then allowed to warm to ambient temperature and stirred for an additional 1 h. Water (10.0 mL) and 1 M aq. NaOH (1.0 mL) were added and the phases separated. The organic phase was extracted with water (2 x 25 mL), and the combined aqueous phases were washed with diethyl ether (2 x 20 mL) and then acidified to pH 0-1 with 1 M HCl. A colourless crystalline solid separated on standing overnight; this was collected by filtration, washed with water and dried to give the title compound **48** (1.02 g, 60%) mp 122-124°C (decomp.). (Found: C, 50.9; H, 6.1; $C_9H_{13}BO_5$ requires C, 51.0; H, 6.2%); ν_{max} cm^{-1} 3372, 1606, 1513, 1468 and 1211; δ_H 3.67 (3 H, s, CH_3), 3.79 (3 H, s, CH_3), 3.81 (3 H, s, CH_3), 6.64 (1 H, s, Ar), 7.15 (1 H, s, Ar) and 7.48 (2 H, s, $B[OH]_2$); δ_C 55.5 (q), 56.0 (q), 56.0 (q), 97.0 (d), 118.9 (d), 142.5 (s), 151.9 (s) and 159.3 (s); *m/z* 212 (M^+), 197 ($M-CH_3^+$) and 169 ($M-BHO_2^+$).

1-Formamido-6,7-methylenedioxy-2-(2,4,5-trimethoxyphenyl)naphthalene (49)

Prepared from 2-bromo-1-formamido-6,7-methylenedioxynaphthalene **30** and 2,4,5-trimethoxyphenylboronic acid **48** by the same method as for **37-39**. Yield 94%, mp 186-187°C. (Found: C, 65.6; H, 5.1; N, 3.6; $C_{21}H_{19}NO_6$ requires C, 66.1; H, 5.0; N, 3.7%); ν_{max} cm^{-1} 3161, 1682, 1610, 1527, 1213 and 1030; δ_H (rotamers, major component listed first) 3.67, 3.69 (3 H, s, CH_3), 3.67, 3.70 (3 H, s, CH_3), 3.84, 3.85 (3 H, s, CH_3), 6.15, 6.17 (2 H, s, CH_2), 6.77, 6.77 (1 H, s, Ar), 6.78, 6.79 (1 H, s, Ar), 7.14, 7.32 (1 H, s, Ar), 7.24, 7.25 (1 H, d, *J* 8.4, Ar), 7.36, 7.38, (1 H, s, Ar), 7.69, 7.70 (1 H, d, *J* 8.4, Ar), 8.18, (d, *J* 1.5), 7.75, (d, *J* 7.1), (1 H, NH) and 9.38 (d, *J* 1.5), 9.54 (d, *J* 7.1), (1 H, CHO); δ_C 55.4, 55.4, 55.5 (q), 100.0, 99.3 (d), 101.3, 101.5 (t), 103.6, 103.7 (d), 111.6, 111.7 (d), 112.8, 113.7 (d), 121.0, 122.0 (d), 126.1, 126.3, 126.7, (d), 127.8, 127.9 (s), 128.5, 128.6 (s), 129.9, 130.1 (s), 131.5, 132.1 (s), 134.3, 135.4 (s), 147.3, 147.5, 147.8, 148.0. 148.1, 148.2, 148.4 (s) and 161.1, 164.7 (d); *m/z* 381 (M^+) and 353 ($M-CO^+$).

6,7-Methylenedioxy-1-(*N*-methylformamido)-2-(2,4,5-trimethoxyphenyl)naphthalene (50)

Prepared from 1-formamido-6,7-methylenedioxy-2-(2,4,5-trimethoxyphenyl)naphthalene **49** by the same method as for **40-42**. Yield 96%, mp 212-213°C (lit. 212-214°C[31]) (from ethyl acetate/hexane). (Found: C, 66.5; H, 5.3; N, 3.6; $C_{22}H_{21}NO_6$ requires C, 66.8 ; H, 5.35 ; N, 3.5 %); ν_{max} cm^{-1} 1666, 1611, 1522, 1504, 1216 and 1028; δ_H (rotamers, major component listed first) 2.87 (3 H, s, NCH_3), 3.65, 3.61 (3 H, s, OCH_3), 3.68, 3.70 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 6.18, 6.16 (2 H, AB-system, CH_2), 6.75, 6.70 (1 H, s, Ar), 6.76, 6.81 (1 H, s, Ar), 7.02, 7.11 (1 H, s, Ar), 7.25 (1H, d, *J* 8.4, Ar), 7.45, 7.40 (1H, s, Ar), 7.81, 7.73 (1H, d, *J* 8.4, Ar) and 7.97, 8.25 (1 H, s, CHO); δ_C 32.6, 35.7 (q), 55.7, 55.8, 55.8, 56.2 (q), 97.9, 98.4 (d), 98.5, 99.5 (d), 101.3, 101.6 (t), 103.9, 104.1 (d), 114.4, 114.9 (d), 118.2 (s), 126.1. 126.9 (d), 126.7, 128.0 (s), 127.5, 127.8 (d), 130.3, 130.6 (s), 132.8, 134.0, 134.1, 135.3 (s), 142.0, 142.3 (s), 147.4, 147.6, 148.4, 148.8, 149.1, 149.2, 150.3, 150.4 (s) and 163.2, 163.3 (d); *m/z* 395 (M^+) and 365 ($M-CH_2O^+$).

5-Methyl-2,3-methylenedioxy-7,8,10-trimethoxybenzo[*c*]phenanthridinium chloride, (Chelilutine chloride) (51)

(Prepared according to the method of Ishii *et al.*[23]) A solution of 6,7-methylenedioxy-1-(*N*-methyl formamido)-2-(2,4,5-trimethoxyphenyl) naphthalene **50** (0.080 g, 0.20 mmol) and phosphorus oxychloride (0.40 mL) in acetonitrile (4.0 mL) was stirred under reflux for 3 h. The solvent was removed under reduced pressure and the residue was basified with 10% aq. NaOH, then extracted into chloroform (2 x 30 mL). The chloroform layer was dried (K_2CO_3) and evaporated to dryness. A few drops of 10% HCl were added to an ice-cooled solution of the residue in chloroform (1 mL). The resulting precipitate was collected by filtration, washed with water, and recystallised from aqueous methanol to give the title compound **51** as orange crystals, (0.080 g, 89%), mp 180-182°C (lit. 184-186°C). (Found: C, 54.6; H, 6.3; N, 2.5; $C_{22}H_{20}ClNO_5$.$4H_2O$ requires C, 54.4; H, 5.8; N, 2.9%); UV (EtOH) nm 229 (4.39), 279 (4.42), and 333 (4.10); ν_{max} cm^{-1} 1598,

1358, 1257 and 1034; δ_H 4.08 (3 H, s, CH_3), 4.17 (3 H, s, CH_3), 4.26 (3 H, s, CH_3), 4.93 (3 H, s, NCH_3), 6.34 (2 H, s, CH_2), 7.73 (1 H, s, Ar), 7.76 (1 H, s, Ar), 8.20 (1 H, s, Ar), 8.25 (1 H, d, *J* 9.2, Ar), 9.40 (1 H, d, *J* 9.2, Ar) and 10.02 (1 H, s, Ar); δ_C 52.3 (q), 57.2 (q), 57.4 (q), 62.4 (q), 102.7 (t), 104.3 (d), 105.2 (d), 108.4 (d), 116.6 (s), 119.8 (s), 119.9 (s), 121.9 (d), 125.5 (s), 130.2 (d), 131.4 (s), 131.7 (s), 139.1 (s), 148.4 (s), 148.9 (s), 150.7 (d), 151.3 (s) and 153.7 (s); *m/z* 379 (MH^+), 363 ($M\text{-}CH_3^+$) and 348 (M-2 x CH_3^+).

2-(6-Bromo-2,3-dimethoxyphenyl)-1,3-dioxolane (53)

Prepared from 6-bromo-2,3-dimethoxybenzaldehyde **52**[25] by the same method as for 2-(2-bromo-4,5-methylenedioxyphenyl)-1,3-dioxolane **30**. Yield 89%, mp 79°C. (Found: C, 45.5; H, 4.6; $C_{11}H_{13}BrO_4$ requires C, 45.7; H, 4.5%); ν_{max} cm^{-1} 1476, 1467, 1389, 1300, 1270, 1235, 1056, 1001, 964 and 813; δ_H ($CDCl_3$) 3.84 (3 H, s, CH_3), 3.85 (3 H, s, CH_3), 4.04 (2 H, m, CH_2), 4.27 (2 H, m, CH_2), 6.34 (1 H, s, CH), 6.80 (1 H, d, *J* 8.8, Ar) and 7.28 (1 H, d, *J* 8.8, Ar); δ_C ($CDCl_3$) 56.1 (q), 61.6 (q), 65.9 (2 x t), 101.7 (d), 113.3 (s), 114.4 (d), 129.1 (d), 129.4 (s), 150.2 (s) and 152.8 (s); *m/z* 288, 290 (M^+), 273, 275 ($M\text{-}CH_3^+$) and 255, 257 ($M\text{-}CH_3$, H_2O^+).

3,4-Dimethoxy-2-formylphenylboronic acid (54)

Prepared from 2-(6-bromo-2,3-dimethoxyphenyl)-1,3-dioxolane **53** by the same method as for 2-formyl-4,5-methylenedioxyphenylboronic acid **31**. Yield 60%, mp 141-146°C. ν_{max} cm^{-1} 3370, 3113, 1663, 1269, 1245 and 1003; δ_H (indicated mixture of aldehyde and cyclic acetal forms) aldehyde: 3.85 (3 H, s, CH_3), 3.86 (3 H, s, CH_3), 7.11 (1 H, d, *J* 8.0, Ar), 7.30 (1 H, d, *J* 8.0, Ar), 7.68 (2 H, s, $B[OH]_2$) and 10.30 (1 H, s, CHO); acetal: 3.77 (3 H, s, CH_3), 3.83 (3 H, s, CH_3), 6.23 (1 H, d, *J* 8.0, CH), 6.88 (1 H, d, *J* 8.0, COH), 7.09 (1 H, d, *J* 8.0, Ar), 7.34 (1 H, d, *J* 8.0, Ar) and 9.07 (1 H, s, BOH); δ_C 56.0 (q), 56.1 (q), 60.1 (q), 62.0 (q), 95.6 (d), 114.1 (d), 118.0 (d), 126.0 (d), 127.7 (d), 132.5 (s), 144.1 (s), 146.8 (s), 151.4 (s), 152.3 (s), 154.6 (s) and 191.6 (s); *m/z* 210 (M^+) and 193 ($M\text{-}OH^+$); high resolution MS *m/z* 210.0689; $C_{21}H_{18}NO_4$ requires 210.0700.

7,8-Dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine, (Norchelerythrine) (55)

Tetrakistriphenylphosphinepalladium(0) (0.069 g, 0.06 mmol) was added to a suspension of 2-bromo-1-formamido-6,7-methylenedioxynaphthalene **34** (0.29 g, 1.00 mmol) in DME (3.0 mL). The resulting mixture was degassed and stirred at ambient temperature under argon for 10 min. A solution of $NaHCO_3$ (0.34 g, 4.0 mmol) in water (2.0 mL) was added, and the resulting suspension was degassed and stirred under argon for 1 h. 3,4-Dimethoxy-2-formylphenylboronic acid **54** (0.315 g, 1.50 mmol) was added and the resulting mixture was stirred and heated at reflux under argon for 3 h. 2 M HCl (3.0 mL) was added and the mixture was stirred at reflux for a further 1 h. The cooled mixture was neutralised with 10% aq. NaOH, then extracted into dichloromethane (2 x 30 mL). The combined organic layers were washed with water (2 x 20 mL), dried (Na_2SO_4), filtered and evaporated to leave a dark brown glass (0.54 g). Purification by column chromatography on silica gel (20 g), eluting with 4:1 hexane/ethyl acetate gave the title compound **55** (0.19 g, 58%) as a yellow-brown solid. Recrystallisation from pyridine/methanol gave yellow crystals, mp 215-216°C (lit. 210-212°C[7]). UV (EtOH) nm 243 (4.55), 257 (4.52), 276 (4.66), 324 (4.14) and 384 (3.44); ν_{max} cm^{-1} 1499, 1285, 1272, 1250 and 1080; δ_H 4.03 (3 H, s, CH_3), 4.05 (3 H, s, CH_3), 6.23 (2 H, s, CH_2), 7.53 (1 H, s, Ar), 7.84 (1 H, d, *J* 9.0, Ar), 7.99 (1 H, d, *J* 9.0, Ar), 8.55 (1 H, s, Ar), 8.58 (1 H, d, *J* 9.0, Ar), 8.60 (1 H, d, *J* 9.0, Ar) and 9.63 (1 H, s, Ar); δ_C 56.5 (q), 61.4 (q), 100.8 (d), 101.4 (t), 104.4 (d), 118.6 (d), 118.7 (d), 119.5 (d), 119.6 (s), 121.0 (s), 127.0 (s), 127.1 (d), 128.1 (s), 129.3 (s), 138.8 (s), 144.1 (s), 146.0 (s), 148.0 (s), 148.1 (d) and 149.3 (s); *m/z* 333 (M^+) and 318 ($M\text{-}CH_3^+$); high resolution MS *m/z* 333.1013; $C_{20}H_{15}NO_4$ requires 333.1001.

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