Synthesis of Pyrrolo[4,3,2-*de*]quinolines from 6,7-Dimethoxy-4-methylquinoline. Formal Total Syntheses of Damirones A and B, Batzelline C, Isobatzelline C, Discorhabdin C, and Makaluvamines A−D

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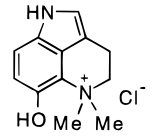
2-Amino-4-nitrophenol and 2-methoxy-5-nitroaniline were converted into the 5-nitroquinolines **6b** and **6d**, respectively, and then the latter into nitro-acetal **6f**. 6,7-Dimethoxy-4-methylquinoline (**6g**) was nitrated at C-5 and then the methyl substituent converted into aldehyde **6j** and then protected giving acetal **6l**. Various means, notably a large excess of $NiCl_2/NaBH_4$, were used to reduce both nitro group and pyridine ring, forming 1,2,3,4-tetrahydroquinolines such as **7b**, **7c**, **7d**, which under acidic conditions closed to give 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolines **9a**, **9d**, **9c**, respectively. In some cases it was unnecessary to protect the aldehyde function, for example quinolinium salt **12c** gave **9j** and nitro-aldehyde **6j** gave **9e** (after BOC protection) directly by reaction with $NiCl_2/NaBH_4$. Substitution of the indole and aniline nitrogens in the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolines was based on a combination of protection, selective deprotection, and the exploitation of the greater acidity of the indole *N*-hydrogen. 8-Chlorination of **6h** and then conversions, as above, gave chloro-diamine-acetal **7e** which on acid treatment produced iminoquinone **11b**; formylation of the nitrogens in **7e** and then acidic treatment allowed formation of the chlorine-substituted 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline **9m** which was then converted into **9p**. De-*O*-methylation and then oxidation of **9b** and **9c** gave *o*-quinones **10b** and **10a**, respectively.

Introduction

The 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system was first recognized as a component of a natural product when the structure of the toad poison, dehydrobufotenine, **1**, was elucidated.[1] Much more recently, several marine alkaloids[2] such as the tricyclic batzellines,[3] isobatzellines,[4] and damirones,[5] and more complex structures such as wakayin,[6] the makaluvamines,[7] the discorhabdines,[8] prianosines,[9] and epinardins,[10] have been described which are also based on a 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus. Many[11] possess potentially valuable biological activity—the makaluvamines and wakayin, for example, exhibit potent *in vitro* cytotoxicity against human colon tumor cell line HCT116; they are topoisomerase II inhibitors.[7,11]



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In most synthetic work relating to these natural products, so far described, including preparations of the unsubstituted[12,13] and 1-methyl[14] tricyclic system, of *O*-methylnordehydrobufotenine,[15] dehydrobufotenine itself,[16] and of batzelline C and isobatzelline C,[17,18] dis-

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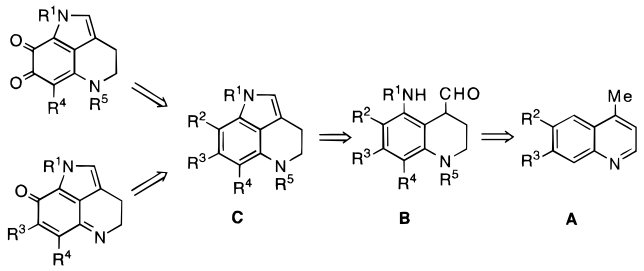
Scheme 1

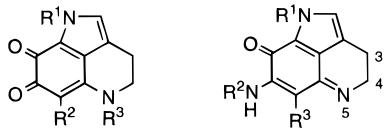


corhabdin C,[18−20] and damirone A[21−23] and B,[21,23] makaluvamine D,[20,24] makaluvamines A−E,[25] and the structurally related mushroom pigment haematopodin,[26] the tricyclic heterocycle has been constructed *from an indole, i.e.* by forming the six-membered nitrogen-containing ring as a late step, by cyclization either of a 4-aminoindole carrying a two-carbon chain at its C-3, or of a tryptamine quinone.

We have been developing[27,28] an alternative strategy, namely the construction of such molecules *starting from a quinoline*; recently two other groups have also described approaches to these tricycles from quinoline or reduced quinoline intermediates[29,30] and one of these was taken through to dehydrobufotenine, damirones A and B, and makaluvamine C.[29] Scheme 1 summarizes our strategy, showing the development of a 4-methylquinoline **A** into a 5-amino-1,2,3,4-tetrahydroquinoline-4-aldehyde **B** in which closure of the pyrrole ring produces target tricycle **C**. We have detailed[27] syntheses of 8-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline starting from a simple quinoline, 6-methoxy-4-methylquinoline. This paper describes our further work in this area, some of which has been published in preliminary form,[28] which constitutes formal total syntheses of damirones A, **2a**, and B, **2b**, batzelline C, **2c**, isobatzelline C, **3a**, makaluvamines A−D, **3b**−**e**, respectively, and discorhabdin C, **4**.

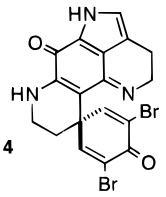
Results and Discussion

Noting the presence and location of a nitrogen substituent on the homocyclic ring in many of these alkaloids, for example, **3**, we planned to extend our earlier work by starting from a quinoline which carried a nitrogen substituent already in place at C-7. 2-Amino-4-nitrophenol was mesylated on both oxygen and nitrogen (→ **5a**) and catalytically reduced and the resulting amine



	R^1	R^2	R^3
2			
a	Me	H	Me
b	H	H	Me
c	Me	Cl	H

	R^1	R^2	R^3
3			
a	Me	H	Cl
b	H	H	H
c	H	H	H 3,4-dehydro-
d	H	H	H N^+5-Me
e	H	4-$HOC_6H_4(CH_2)_2$	H



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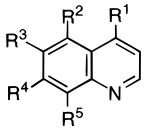
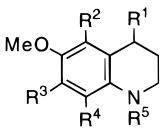
5b converted in 24% yield into quinoline **6a** by reaction with methyl vinyl ketone using sodium 3-nitrobenzenesulfonate[31] as oxidant. Exposure to copper(II) nitrate in acetic anhydride produced the nitroquinoline **6b**. Alternatively, 2-methoxy-5-nitroaniline, following *N*-mesylation (→ **5c**), was reduced and the resulting aniline **5d** comparably converted into a quinoline **6c**, this time accompanied by a minor amount of its 1,2,3,4-tetrahydro derivative **7a**.

	R^1	R^2
5		
a	Ms	NO_2
b	Ms	NH_2
c	Me	NO_2
d	Me	NH_2



	R^1	R^2	R^3	R^4	R^5
6					
a	Me	H	MsO	MsHN	H
b	Me	NO_2	MsO	Ms(Ac)N	H
c	Me	H	MeO	MsHN	H
d	Me	NO_2	MeO	Ms(Ac)N	H
e	CHO	NO_2	MeO	Ms(Ac)N	H
f	$CH(OMe)_2$	NO_2	MeO	Ms(Ac)N	H
g	Me	H	MeO	MeO	H
h	Me	NO_2	MeO	MeO	H
i	Me	NO_2	MeO	MeO	NO_2
j	CHO	NO_2	MeO	MeO	H
k	CH_2OH	NO_2	MeO	MeO	H
l	$CH(OMe)_2$	NO_2	MeO	MeO	H
m	Me	NO_2	MeO	MeO	Cl
n	$CHCl_2$	NO_2	MeO	MeO	H
o	$CHCl_2$	NO_2	MeO	MeO	Cl
p	CHO	NO_2	MeO	MeO	Cl
q	$CH(OMe)_2$	NO_2	MeO	MeO	Cl



	R^1	R^2	R^3	R^4	R^5
7					
a	Me	H	MsHN	H	H
b	$CH(OMe)_2$	NH_2	MeO	H	CO_2Me
c	$CH(OMe)_2$	NH_2	MeO	H	H
d	$CH(OMe)_2$	NHTs	MeO	H	Ts
e	$CH(OMe)_2$	NH_2	MeO	Cl	H
f	$CH(OMe)_2$	NTs_2	MeO	H	Ts

As before, reaction of **6c** with copper(II) nitrate in acetic anhydride brought about two desired changes, nitration at C-5, and further protection of the 7-amino substituent proceeded in 59% yield, giving quinoline **6d**. Earlier experiments with similar quinolines, but without this double protection of an amino substituent, had shown that oxidation of the 4-methyl, following the protocol[32] (I_2/*t*-BuI/$FeCl_2$/TFA/DMSO) which had proved useful[27] in other related situations, had been totally

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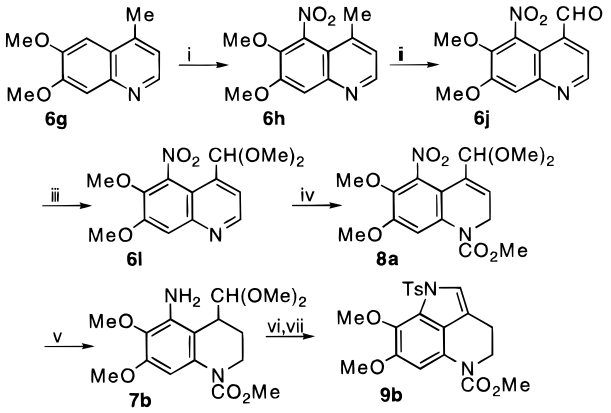
Scheme 2[a]

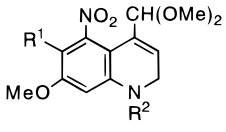


[a] Reagents: (i) fuming HNO_3, −30 °C; (ii) I_2, DMSO, TFA, *t*-BuI, $FeCl_2$, 80 °C; (iii) MeOH, HCl, reflux; (iv) BH_3·THF, −78 °C then REDAL, −78 °C then $ClCO_2Me$; (v) H_2, Pd−C, EtOH; (vi) aqueous 1 N HCl, THF, 55 °C; (vii) Bu_4NHSO_4, NaOH, TsCl.

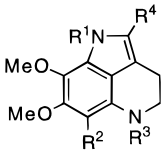
unsuccessful; however, oxidation of **6d** produced aldehyde **6e**, albeit in only 54% yield, accompanied by starting material from which it was very difficult to separate. A small quantity was characterized; it was also shown that it could be protected as its acetal **6f**.

In view of the practical problems encountered in handling quinolines **6a**−**f** and also because at this point it had become clear[11,18−20,25] that nitrogen substituents could be introduced with displacement of methoxide in late intermediates for the synthesis of these alkaloids, we turned to the use of 6,7-dimethoxy-4-methylquinoline (**6g**), easily produced from reaction of 4-aminoveratrole with methyl vinyl ketone and ferric chloride. Nitration of **6g** proceeded regioselectively, at <−40 °C, to give the 5-nitro derivative **6h** in 63% yield (reaction at 0 °C caused 5,8-dinitration giving **6i**) and this, in turn, could be oxidized to aldehyde **6j**.

Our plans now required reduction of the nitro group and the heterocyclic ring without reduction of the aldehyde group. A second consideration was control over the substitution of the two nitrogen atoms for the various target natural products. We devised several variants whereby these aims could be achieved.



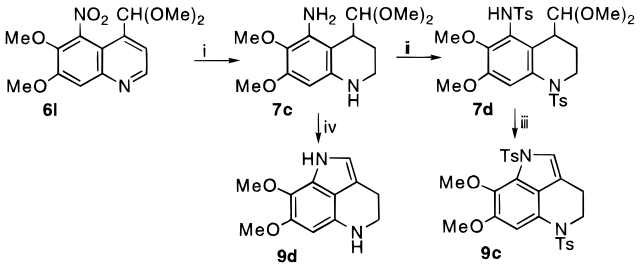
8	R^1	R^2
a	MeO	CO_2Me
b	TsO	Me
c	MeO	Me



9	R^1	R^2	R^3	R^4
a	H	H	CO_2Me	H
b	Ts	H	CO_2Me	H
c	Ts	H	Ts	H
d	H	H	H	H
e	H	H	BOC	H
f	Ts	H	BOC	H
g	Ts	H	H	H
h	Me	H	BOC	H
i	Me	H	H	H
j	H	H	Me	H
k	Ts	H	Me	H
l	Me	H	BOC	Cl
m	CHO	Cl	CHO	H
n	H	Cl	CHO	H
o	Me	Cl	CHO	H
p	Me	Cl	H	H

Treatment of the nitro-aldehyde with sodium borohydride simply gave the alcohol **6k**. Protection of the aldehyde functionality as acetal **6l** and exposure to

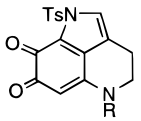
Scheme 3[a]



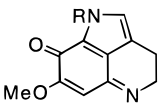
[a] Reagents: (i) $NiCl_2$, $NaBH_4$, MeOH; (ii) TsCl, Et_3N then NaOMe, MeOH, 50 °C; (iii) aqueous 1 N HCl, THF, 80 °C; (iv) aqueous 1 N HCl, THF, 40 °C.

borane and then REDAL followed by quenching with methyl chloroformate[33] produced the 1,2-dihydroquinoline **8a**. Catalytic reduction of **8a** gave an unstable amine-acetal **7b**, now at the appropriate oxidation level for ring closure to an indole, which was simply achieved in dilute hydrochloric acid in THF at 55 °C giving **9a**, characterized as its *N*-tosyl derivative **9b**, the overall yield from **6j** being 7% for the five steps, summarized in Scheme 2.

Reduction of both nitro group and heterocyclic ring in **6l**, in one pot, to produce **7c** was achieved with a large excess of a combination of sodium borohydride and nickel chloride. Initially, we were cautious over the handling of this electron-rich benzene, and the indole which would be obtained from it, and we took the precaution of converting it into its bis-*N*-tosyl derivative **7d** before proceeding. Then, as before, mild dilute acid treatment of **7d** effected acetal hydrolysis and ring closure to give **9c** in 19% yield for a four-step sequence, summarized in Scheme 3.



10	R
a	Ts
b	CO_2Me
c	Me



11	R
a	Ts
b	H

Reaction of the doubly protected tricycles **9b** and **9c** with BBr_3 and then immediate oxidation with CAN, without purification, gave us the *o*-quinones **10a** (92%) and **10b** (70%). Methanolysis of **10a** in the presence of K_2CO_3 gave the iminoquinone **11a**, though in very low yield (see later for an efficient synthesis of **11b**).

Subsequently, we found that hydrolysis of **7c** *without* prior *N*-protection produced the unprotected indole **9d** in 64% yield and that it could be handled, with care, and characterized. Even more extraordinary, we discovered that protection of the aldehyde function was unnecessary, for exposure of nitro-aldehyde **6j** to a large excess of $NiCl_2/NaBH_4$, followed by $(BOC)_2O$ gave the monoprotected tricyclic indole **9e** in 19% yield without isolation of intermediates. Base-promoted indole *N*-tosylation of this (→ **9f**) and then removal of the BOC gave the alternatively protected **9g**, which has been converted in other work[25] into **11a**, while base-promoted indole *N*-methylation (→ **9h**) and then deprotection gave **9i** efficiently.

The obvious route to the preparation of tricycles with a methyl group on the other ring nitrogen seemed to be

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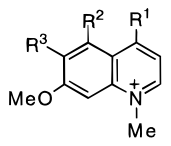


12	R^1	R^2	R^3
a	$CH(OMe)_2$	NO_2	O^-
b	$CH(OMe)_2$	NO_2	MeO (with I^-)
c	CHO	NO_2	MeO (with BF_4^-)
d	Me	H	MeO (with I^-)
e	Me	NO_2	MeO (with I^-)

a quinoline-*N*-quaternization at an early stage, to be followed by ring reduction, expected to be easier than for the neutral molecules. However, reaction of nitro-acetal **6l** with iodomethane under normal conditions led to a zwitterionic product, **12a** in which *O*-demethylation had occurred, as well as the desired *N*-methylation. The structure of this unexpected product was secured by borohydride reduction to an unstable dihydroquinoline characterized as its *O*-tosyl derivative **8b**. That it is the 6-methoxyl which had suffered demethylation was deduced from an NMR study of **8b** in which an NOE effect was found between the remaining 7-methoxyl hydrogens and the aromatic proton at C-8. Intrigued by the demethylation process we carried out two model *N*-methylations: both **6g** and **6h** underwent reaction with iodomethane in a normal fashion. It seems that the presence of both a 5-nitro group and a 4-substituent larger than methyl are required to promote the demethylation. From reaction at 30 °C, the normal methiodide **12b** could be obtained. Quaternization of **6j** could be achieved with trimethyloxonium borofluoride producing **12c** which was used without purification.

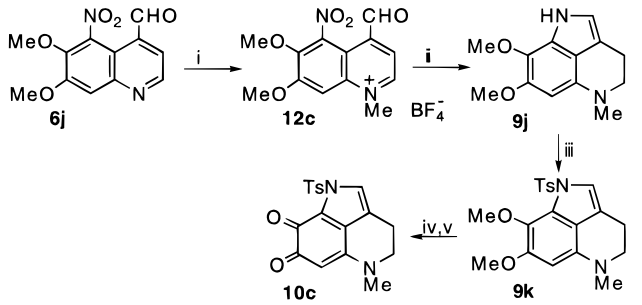
Reduction of salt **12b** with $NaBH_4$ produced the dihydroquinoline **8c**, whereas the use of the $NiCl_2/NaBH_4$ combination on salt **12c** gave tricyclic indole **9j**, in 12% yield, converted into its indole *N*-tosyl derivative **9k**. As before, de-*O*-methylation and then ceric ammonium nitrate (CAN) oxidation produced a tricyclic *o*-quinone **10c** (Scheme 4).

Several of the pyrrolo[4,3,2-*de*]quinoline-containing alkaloids have a chlorine substituent at C-6. It seemed possible that electrophilic chlorination of a suitably protected 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline might take place at that position, being an activated benzene ring position. This was attempted using **9h**, but chlorination occurred instead at C-2, the pyrrole ring α-position, forming **9l**. This meant that it would be necessary to carry the chlorine through the sequence from the beginning, so the nitroquinoline **6h** was reacted with *N*-chlorosuccinimide giving **6m** accompanied by minor amounts of side-chain-chlorinated quinolines **6n** and **6o**. The chloronitroquinoline **6m** was oxidized in the usual way giving aldehyde **6p**, protected as acetal **6q**, and then reduced to the aminotetrahydroquinoline **7e** in 28% overall yield from **6h**, the scene now being set, we assumed, for ring closure to a tricyclic chloroindole.

It was a suprise to find that mild acidic treatment of **7e** gave iminoquinone **11b** in 64% yield. This serendiptiously now provides an excellent six-step route to this key compound (see below) from the simple, starting quinoline, **6g**. We explain this result by postulating an electrophilic protonation of the electron-rich benzene ring, either before or after pyrrole ring formation (Scheme 5 shows a sequence assuming this to take place before pyrrole formation).

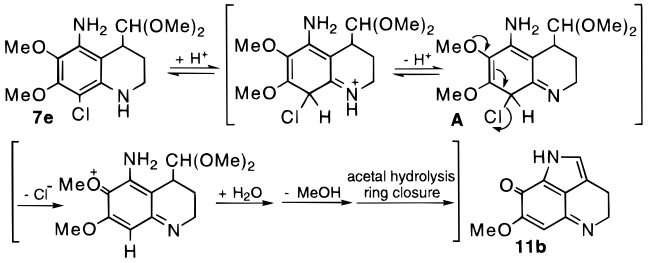
On the basis of this rationalization, we argued that reducing the nucleophilic character of the benzene ring might prevent the loss of halogen and this we sought to do by formylation of both amine groups in **7e**. Treatment with Ac_2O/HCO_2H produced a mixture of doubly formylated products in which, in addition, ring closure to the

Scheme 4[a]

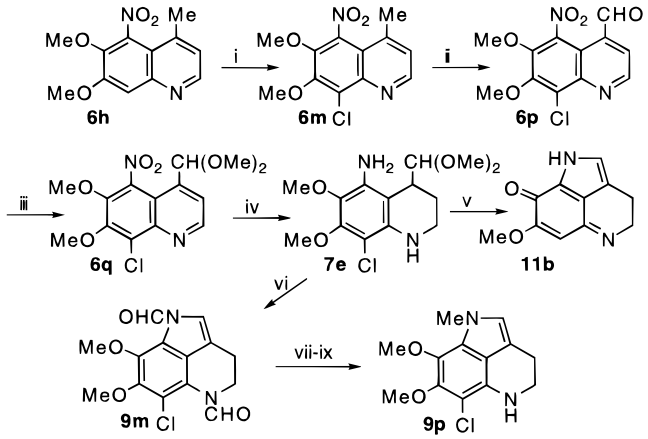


[a] Reagents: (i) Me_3OBF_4, CH_2Cl_2; (ii) $NiCl_2$, $NaBH_4$, MeOH; (iii) TsCl, Bu_4NHSO_4, NaOH; (iv) BBr_3, CH_2Cl_2, −78 °C; (v) air.

Scheme 5

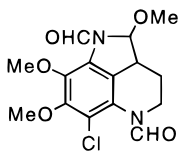


Scheme 6[a]



[a] Reagents: (i) NCS, DMF, 60 °C; (ii) I_2, DMSO, TFA, *t*-BuI, $FeCl_2$, 80 °C; (iii) MeOH, HCl, reflux; (iv) $NiCl_2$, $NaBH_4$, MeOH; (v) aqueous 1 N HCl, THF, 40 °C; (vi) HCO_2H, Ac_2O; (vii) aqueous NaOH, CH_2Cl_2; (viii) MeI, NaH; (ix) aqueous NaOH, reflux.

target systems had occurred: **9m** and **13** were isolated in 54 and 10% yields, respectively. It was further shown that the latter could be easily transformed into the former by refluxing in formic acid.



13

Selective hydrolysis of the indole *N*-formyl (→ **9n**) and then indole *N*-methylation produced **9o**, stronger alkaline hydrolysis of which gave **9p**; transformations in the chloro series are summarized in Scheme 6.

Synthesis of Marine Alkaloids. The indole **9i** has been converted by ceric ammonium nitrate (CAN) oxidation to the corresponding iminoquinone (60%) followed by displacement of the methoxyl with ammonium chlo-

ride (98%) giving makaluvamine A, **3b**, and this was then dehydrogenated (41%) with palladium on charcoal giving makaluvamine B, **3c**.[26] Comparably, indole **9j** was oxidized with CAN then reacted with ammonia affording makaluvamine C, **3d** (reported[26] 26% overall yield included a reduction of a precursor lactam to generate **9j**). Makaluvamine D, **3e**, was produced from indole **9d** by CAN oxidation (51%),[19] producing **11b** which was then reacted with tyramine (92%),[26] or from **11a**, as its toluenesulfonate salt (91%).[25] A precursor which was used for an electrochemical closure giving discorhabdin C, **4** (24%), resulted from reaction of **11b**, produced again by CAN oxidation of **9d**, and then methoxyl displacement in this case with 3,5-dibromotyramine[26] or from tosyl-protected iminoquinone **11a** directly.[21] The tosyl-protected *o*-quinone **10c** upon sodium hydroxide hydrolysis gave damirone B, **2b**, indole *N*-methylation of which with iodomethane and base gave damirone A, **2a**.[22] Finally, boron tribromide de-*O*-methylation (78%) and then air oxidation (64%) of **9p** produced batzelline C, **2c**; CAN oxidation followed by displacement of methoxyl with ammonia (64%) gave isobatzelline C, **3a**.[19]

Experimental Section

General. Proton and carbon nuclear magnetic resonance spectra were recorded in $CDCl_3$ unless otherwise specified. For infrared spectra, only structurally significant peaks are listed. UV spectra were determined in 95% EtOH unless otherwise stated. Melting points are uncorrected. Tetrahydrofuran was dried over sodium/benzophenone and then distilled under an atmosphere of dry N_2, or anhydrous commercial solvent was used. Dichloromethane was distilled from CaH_2. TLC and column chromatography was carried out using SiO_2. Organic extracts were dried over anhydrous Na_2SO_4 or $MgSO_4$, and dried solutions were evaporated under reduced presure with a rotatory evaporator.

4-(Mesyloxy)-3-(methanesulfonamido)nitrobenzene (5a). MsCl (7.5 g, 65 mmol) was added slowly to a solution of 2-amino-4-nitrophenol (5 g, 32.5 mmol) in pyridine (65 mL) at 0 °C. After 30 min the reaction mixture was stirred for 4 h at rt and then poured onto ice and the resulting precipitate filtered, washed several times with H_2O and Et_2O, and dried *in vacuo* at 50 °C to give **5a** (9.15 g, 91%). Mp 179−182 °C (CH_2Cl_2−MeOH). IR (KBr): 3267, 1532, 1351, 1337. ^{1}H-NMR (200 MHz, DMSO-d_6) 3.16 (s, 3H); 3.62 (s, 3H); 7.70 (d, J = 9.0, 1H); 8.06 (dd, J = 9.0 and 2.8, 1H); 8.38 (d, J = 2.8, 1H); 10.12 (bs, 1H). ^{13}C-NMR (50.3 MHz, DMSO-d_6) 37.8 (q); 40.5 (q); 108.7 (d); 110.8 (d); 123.8 (d); 130.8 (s); 131.1 (s); 148.4 (s). MS (EI) 312 (M + 2, 3); 311 (M + 1, 3); 310 (M^+, 19); 230 (84); 153 (100).

4-(Mesyloxy)-3-(methanesulfonamido)aniline (5b). 5a (5 g, 16.1 mmol) was dissolved in DMF (25 mL) and hydrogenated at 100 psi over 10% Pt/C (0.5 g) at 20 °C for 3 h. The mixture was filtered through Celite and concentrated to give a dark red gum which was crystallized from CH_2Cl_2−Et_2O to yield **5b** (4.2 g, 93%). Mp 139−142 °C. IR (KBr) 3475, 3375, 3295, 1328, 1151. ^{1}H-NMR (300 MHz, DMSO-d_6) 3.02 (s, 3H); 3.35 (s, 3H); 5.45 (bs, 2H); 6.35 (dd, J = 8.8 and 2.6, 1H); 6.71 (d, J = 2.6, 1H); 7.02 (d, J = 8.8, 1H); 9.09 (bs, 1H). ^{13}C-NMR (50.3 MHz, DMSO-d_6) 38.8 (q); 40.8 (q); 117.9 (d); 120.4 (d); 123.8 (d); 131.7 (s); 144.3 (s); 146.0 (s). MS (EI) 280 (M^+, 5); 201 (100); 123 (74).

6-(Mesyloxy)-7-(methanesulfonamido)-4-methylquinoline (6a). Sodium *m*-nitrobenzenesulfonate (2.55 g, 11.3 mmol) was added to a solution of **5b** (3.17 g, 11.3 mmol) in AcOH (150 mL) under N_2. The mixture was warmed at 85 °C, and methyl vinyl ketone (0.8 g, 11.3 mmol) was added during 2 min. The reaction mixture was stirred at reflux for 4 h. The solvent was removed *in vacuo*, and to the solid residue excess saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2, and the organic extract was washed with brine, dried, and concentrated to give an oil (2.62 g) which was purified by column chromatography, eluting with CH_2Cl_2−MeOH (98:2) to give **6a** (0.89 g, 24%). Mp 117−121 °C (CH_2Cl_2/*i*-Pr_2O). IR (KBr) 3298, 1308. ^{1}H-NMR (200 MHz) 2.69 (s, 3H); 3.19 (s, 3H); 3.41 (s, 3H); 7.24 (d, J = 4.4, 1H); 7.98 (s, 1H); 8.33 (s, 1H); 8.80 (d, J = 4.4, 1H). ^{13}C-NMR (75 MHz) 18.4 (q); 36.0 (q); 39.8 (q); 117.9 (d); 122.0 (d); 125.2 (s); 132.0 (s); 139.3 (s); 145.2 (s); 146.2 (s); 151.0 (d). MS (EI) 330 (M^+, 39); 251 (94); 173 (100); 145 (90) Anal. Calcd for $C_{12}H_{14}N_2O_5S_2$: C, 43.63; H, 4.24; N, 8.48. Found: C, 43.76; H, 4.42; N, 8.10.

7-[(Methanesulfonyl)acetylamino]-6-(mesyloxy)-4-methyl-5-nitroquinoline (6b). To a solution of **6a** (150 mg, 0.4 mmol) in AcOH (3 mL) cooled at −78 °C and under nitrogen, $Cu(NO_3)_2 \cdot 3H_2O$ (0.11 g, 0.59 mmol) in AcOH (6 mL) was added during 6 min. The reaction mixture was stirred at rt for 30 min and 1 h at 80 °C; during this time the color of the reaction mixture changed to green. The reaction mixture was poured over ice and extracted with CH_2Cl_2, the extract was washed with aqueous 2 N NaOH and then brine, and then dried and concentrated to give crude material (158 mg) which was purified by column chromatography, eluting with C_6H_{14}−CH_2Cl_2 (3:7−1:9) to give **6b** (77 mg, 40%). Mp 153−158 °C (CH_2Cl_2−*i*Pr_2O). IR (KBr) 3428, 1722, 1547, 1363. ^{1}H-NMR (300 MHz) 2.13 (3H, s); 2.79 (3H, s); 3.46 (s, 3H); 3.51 (s, 3H); 7.51 (d, J = 4.4, 1H); 8.36 (s, 1H); 8.93 (d, J = 4.4, 1H). ^{13}C-NMR (75 MHz) 18.9 (q); 23.8 (q); 39.6 (q); 43.0 (q); 118.6 (d); 125.4 (d); 130.1 (s); 137.6 (s); 142.5 (s); 145.2 (s); 153.4 (d); 170.3 (s). MS (EI) 417 (M^+, 0.1); 376 (8); 375 (42); 329 (57); 296 (100); 280 (53); 201 (44); 267 (35). Anal. Calcd for $C_{14}H_{15}N_3O_8S_2$: C, 40.28; H, 3.62; N, 10.07; S, 15.38. Found: C, 40.37; H, 3.92; N, 9.78; S, 15.19.

3-(Methanesulfonamido)-4-methoxynitrobenzene (5c). MsCl (6.8 g, 59.5 mmol) was added drop by drop to a solution of 2-methoxy-5-nitroaniline (10 g, 59.5 mmol) in pyridine (30 mL) cooled at 0 °C under N_2. After 30 min the reaction mixture was stirred for 4 h at rt. The white suspension obtained was poured onto ice and filtered. The solid residue was washed with H_2O and Et_2O and dried *in vacuo* at 50 °C to yield **5c** (14.3 g, 98%). Mp 162−166 °C (CH_2Cl_2−MeOH)). IR (KBr) 1596, 1508, 1340. ^{1}H-NMR (200 MHz, DMSO-d_6) 3.05 (s, 3H); 3.96 (s, 3H); 7.28 (d, J = 8.8, 1H); 8.10 (dd, J = 8.8 and 2.8, 1H); 9.45 (d, J = 2.8, 1H). ^{13}C-NMR (50.3 MHz, DMSO-d_6) 40.1 (q); 57.0 (q); 112.0 (d); 118.5 (d); 122.2 (d); 127.1 (s); 140.7 (s); 157.0 (s). MS (EI) 246 (M^+, 19); 167 (100); 121 (37); 79 (24).

3-(Methanesulfonamido)-4-methoxyaniline (5d). 5c (7 g, 28.4 mmol) dissolved in DMF (43 mL) was hydrogenated at 100 psi over 10% Pt/C (0.7 g) at 20 °C for 4 h. The mixture was filtered through Celite and concentrated to give the crude material as a solid which was crystallized from CH_2Cl_2−Et_2O to yield **5d** (5.8 g, 95%). Mp 123−126 °C (CH_2Cl_2−Et_2O). IR (KBr) 1732, 1589, 1416. ^{1}H-NMR (200 MHz) 2.90 (s, 3H); 3.67 (s, 3H); 4.75 (bs, 2H); 6.37 (dd, J = 8.6 and 2.0, 1H); 6.58 (d, J = 2.0, 1H); 6.76 (d, J = 8.6, 1H) 8.56 (bs, 1H). ^{13}C-NMR (50.3 MHz, DMSO-d_6) 40.0 (q); 56.6 (q); 111.6 (d); 111.7 (s); 113.6 (d); 126.6 (s); 142.9 (d); 143.7 (s). MS (EI) 216 (M^+, 100); 201 (72); 123 (48); 110 (63); 92 (45).

1,2,3,4-Tetrahydro-7-(methanesulfonamido)-6-methoxy-4-methylquinoline (7a) and 7-(Methanesulfonamido)-6-methoxy-4-methylquinoline (6c). Sodium *m*-nitrobenzensulfonate (14.1 g, 62.5 mmol) was added to a solution of **5d** (9 g, 41.7 mmol) in AcOH (560 mL) under N_2. The mixture was warmed to 85 °C, and methyl vinyl ketone (2.9 g, 41.7 mmol) was added during 5 min. The reaction was refluxed for 5 h. The solvent was evaporated, excess saturated aqueous $NaHCO_3$ added, and then organic material extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to give a crude product (9.8 g) which was purified by column chromatography. On elution with CH_2Cl_2 and CH_2Cl_2−MeOH (99:1), **7a** was obtained (1.3 g, 12%). Mp 88−90 °C (Me_2CO-*i*Pr_2O). IR (KBr) 3407, 3268, 1511, 1326. ^{1}H-NMR (300 MHz) 1.28 (d, J = 6.9, 3H); 1.60−1.71 (m, 1H); 1.90−2.03 (m, 1H); 2.90−2.94 (m, 1H); 2.95 (s, 2H); 3.16−3.33 (m, 2H); 3.80 (s, 3H); 6.65 (s, 1H); 6.74 (s, 1H). ^{13}C-NMR (54 MHz) 22.6 (q); 29.6 (t); 29.9 (d); 38.5 (q); 38.8 (t); 56.1 (q); 107.7 (d); 111.4 (d); 123.8 (s); 124.4 (s); 138.1 (s); 141.9 (s). MS (EI) 270 (M + 1, 65); 269 (M^+, 0.3); 255 (100); 256 (14); 164 (42); 149

(39). Anal. Calcd for $C_{14}H_{18}N_3O_3S$: C, 53.31; H, 6,71; N, 10,-36. Found: C, 53.10; H, 6.84; N, 10.18.

Further elution (CH_2Cl_2−MeOH; 98:2−96:4) gave **6c** (6.2 g, 56%). Mp 171−173 °C (Me_2CO−iPr_2O): IR (KBr): 3025, 1503, 1430, 1321. ^{1}H-NMR (200 MHz, DMSO-d_6) 2.64 (s, 3H); 3.10 (s, 3H); 4.00 (s, 3H); 7.26 (d, J = 4.4, 1H); 7.36 (s, 1H); 7.87 (s, 1H); 8.57 (d, J = 4.4, 1H); 9.27 (bs, 1H). ^{13}C-NMR (50.3 MHz, DMSO-d_6) 18.6 (q); 40.0 (q); 56.4 (q); 102.7 (d); 120.1 (d); 121.6 (d); 125.7 (s); 130.6 (s); 142.7 (s); 143.7 (s); 148.4 (d); 150.1 (s). MS (EI) 266 (M^+, 1.5); 187 (20); 157 (2); 81 (52); 69 (100). Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.32; H, 5.33; N, 10.50; S, 12.05.

7-[(Methanesulfonyl)acetylamino]-6-methoxy-4-methyl-5-nitroquinoline (6d). To a solution of **6c** (2.8 g, 10.7 mmol) in AcOH (70 mL) at −78 °C and under N_2 was added a suspension of $Cu(NO_3)_2 \cdot 3H_2O$ (3.4 g, 14.1 mmol) in AcOH (140 mL). After 5 min the mixture was stirred for 40 min at rt and 1 h at 80 °C. The solvent was evaporated, excess saturated aqueous $NaHCO_3$ was added, and then the solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to afford crude material (4.7 g) as a solid which was purified by column chromatography. On elution with C_6H_{14}−CH_2Cl_2 (3:7 to 2:8) **6d** (2.2 g, 59%) was obtained. Mp 225−230 °C (Me_2CO−iPr_2O). IR (KBr) 1717, 1542, 1360. ^{1}H-NMR (300 MHz) 2.05 (3H, s); 2.76 (s, 3H); 3.49 (s, 3H); 4.14 (s, 3H); 7.43 (d, J = 4.4, 1H); 7.50 (s, 1H); 8.75 (d, J = 4.4, 1H). ^{13}C-NMR (75 MHz) 18.7 (q); 23.4 (q); 42.6 (q); 56.9 (q); 104.6 (d); 120.0 (s); 124.8 (d); 130.7 (s); 134.4 (s); 143.5 (s); 144.5 (s); 150.6 (d); 153.2 (s); 170.7 (s). MS (EI) 353 (M^+, 5); 338 (16); 293 (82); 184 (65); 232 (91); 214 (100). Anal. Calcd for $C_{14}H_{15}N_3O_6S$: C, 47.58; H, 4.28; N, 11.89; S, 9.07. Found: C, 47.15; H, 4.42; N, 12.12; S, 9.16.

7-[(Methanesulfonyl)acetylamino]-4-formyl-6-methoxy-5-nitroquinoline (6e) and 7-[(Methanesulfonyl)acetylamino]-4-(dimethoxymethyl)-6-methoxy-5-nitroquinoline (6f). A mixture of **6d** (1 g, 2.8 mmol), TFA (2.2 g,19.1 mmol), I_2 (0.9 g, 3.6 mmol), *t*-BuI (2.3 g, 12.3 mmol), and $FeCl_2 \cdot 4H_2O$ (catalytic) in dry DMSO (25 mL) was stirred at 80 °C for 16 h under N_2. After this time EtOAc was added, and the mixture was washed several times with H_2O and with saturated aqueous $Na_2S_2O_4$. The organic layer was dried and evaporated to give crude material (1.6 g) which was purified by column chromatography, eluting with C_6H_{14}−CH_2Cl_2 (3:7 to 2:8) giving **6e** (540 mg, 54%). Mp 144−147 °C (MeCO−*i*-Pr_2O). IR (KBr): 1710, 1550. ^{1}H-NMR (300 MHz) 2.06 (s, 3H); 3.49 (s, 3H); 4.18 (s, 3H); 7.97 (d, J = 4.2, 1H); 8.85 (s, 1H); 9.20 (d, J = 4.2, 1H); 10.40 (s, 1H). ^{13}C-NMR (75 MHz, CD_3-OD) 23.6 (q); 43.0 (q); 57.5 (q); 106.0 (d); 124.4 (s); 126.1 (s); 130.3 (d); 135.0 (s); 136.2 (s); 150.8 (d); 151.5 (s); 156.2 (s); 170.1 (s); 192.6 (d). MS (EI) 367 (M^+, 4); 228 (53); 307 (100).

Trimethyl orthoformate (25 mg, 234 mmol) was added to a solution of **6e** (540 mg, 1.5 mmol) in absolute MeOH (15 mL) with *p*-toluenesulfonic acid (catalytic), and the mixture was refluxed under N_2 for 48 h. The solvent was evaporated, and the residue was purified by column chromatography. On elution with CH_2Cl_2 **6f** was obtained (480 mg, 41%). Mp 174−178 °C (Me_2CO−iPr_2O). IR (KBr): 1719, 1546, 1365, 1167. ^{1}H-NMR (300 MHz) 2.06 (s, 3H); 3.39 (s, 6H); 3.48 (s, 3H); 4.11 (s, 3H); 5.82 (s, 1H); 7.76 (d, J = 4.4, 1H); 7.87 (s, 1H); 8.90 (d, J = 4.4, 1H). ^{13}C-NMR (300 MHz) 23.61 (q); 42.88 (q); 53.06 (q); 53.11 (q); 57.14 (q); 100.31 (d); 104.51 (s); 105.50 (d); 122.71 (d); 124.80 (s); 128.16 (s); 141.34 (s); 150.50 (d); 150.72 (s); 153.43 (s); 170.45 (s). MS (EI) 413 (M^+, 7); 353 (100); 292 (64); 244 (56); 214 (55). Anal. Calcd for $C_6H_{19}N_3O_8S \cdot {}^1/_4$ Me_2CO: C, 47.01; H, 4.82; N, 9.82; S, 7.49. Found: C, 47.17; H, 4.80; N, 10.10; S, 7.50.

6,7-Dimethoxy-4-methylquinoline (6g). $FeCl_3$ (2.71 g, 10.0 mmol) was dissolved in glacial AcOH (30 mL) with warming to 60 °C. 4-Aminoveratrole (1.55 g, 10.1 mmol) was added followed, after 5 min, by methyl vinyl ketone (0.87 mL, 10.5 mmol) added dropwise over 5 min. The reaction mixture was refluxed for 1 h. The solvent was removed *in vacuo*, and the residue was made alkaline with aqueous NaOH (50% wt/vol). The aqueous phase was removed *in vacuo*, and the residue was extracted with CH_2Cl_2 (6 × 50 mL). The combined organic extracts were washed with aqueous K_2CO_3 (10% wt/vol), dried, and concentrated to give the crude product which was recrystallized from Et_2O to give a brown solid (1.35 g, 66%). Mp 112−112.5 °C. UV 216 (4.16), 220 (4.21), 240 (4.48), 316 (3.90), 330 (4.05); IR (film) 1618, 1590, 1503; ^{1}H-NMR (300 MHz) 2.73 (s, 3H); 4.09 (s, 6H); 7.20 (s, 1H); 7.21 (d, J = 4.7, 1H); 7.59 (s, 1H); 8.62 (d, J = 4.7, 1H). ^{13}C-NMR (75 MHz) 18.8 (q); 56.0 (q); 101.5 (d); 108.3 (d); 120.4 (d); 123.5 (s); 142.5 (s); 144.8 (s); 147.7 (d); 149.4 (s); 152.0 (s). MS (CI) 204 (M + 1, 100). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.45; N, 6.9. Found: C, 71.0; H, 6.45; N, 6.8.

6,7-Dimethoxy-4-methyl-5-nitroquinoline (6h). 6g (4.4 g, 21.6 mmol) was added over 1 h, in portions, to fuming HNO_3 (68 mL) and cooled to between −50 °C and −40 °C under argon. The mixture was left to stir for 25 min, keeping the temperature below −30 °C. The reaction mixture was then poured onto ice and the temperature maintained between −20 °C to 0 °C while neutralizing the acid with aqueous NaOH (50% wt/vol, 160 mL). The mixture was rigorously extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous K_2CO_3 (10% wt/vol), dried, and concentrated to give a brown solid (3.43 g, 63%). Mp 128 °C. UV 216 (4.13), 220 (4.18), 224 (4.20), 228 (4.26), 232 (4.33), 236 (4.36), 280 (3.46), 318 (3.50), 330 (3.61). IR (film) 1618, 1582, 1447. ^{1}H-NMR (300 MHz) 2.63 (s, 3H); 4.07 (s, 3H); 4.13 (s, 3H); 7.29 (d, J = 4.7, 1H); 7.83 (s, 1H); 8.73 (d, J = 4.7, 1H). ^{13}C-NMR (75 MHz) 18.4 (q); 56.4 (q); 62.7 (q); 111.7 (d); 114.9 (s); 123.6 (d); 140.9 (s); 141.1 (s); 142.4 (s); 145.8 (s); 150.1 (d); 153.6 (s). MS (EI) 248 (M^+, 100). HRMS: calcd for $C_{12}H_{12}N_2O_4$ 248.0797, found 248.0807. Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.87; N, 11.29. Found: C, 58.0; H, 4.93; N, 11.29.

6,7-Dimethoxy-4-methyl-5,8-dinitroquinoline (6i). 6g (500 mg, 2.02 mmol) was dissolved in concd H_2SO_4 (10 mL) and cooled to 0 °C, and then concd HNO_3 (30 mL) was added dropwise then the mixture was stirred for 1 h. The mixture was made basic by the careful addition of aqueous NaOH (50% wt/vol), filtered through Celite, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give the title compound as a yellow solid (295 mg, 50%). Mp 151−153 °C. UV 220 (4.47), 236 (4.58), 282 (4.01), 326 (3.94); IR (film) 1586, 1534, 1490, 1357. ^{1}H-NMR (300 MHz) 2.63 (s, 3H); 4.12 (s, 3H); 4.17 (s, 3H); 7.39 (d, J = 4.5, 1H); 8.84 (d, J = 4.5, 1H). MS (EI) 293 (M^+, 74), 276 (41), 263 (4), 248 (5), 231 (11), 58 (50), 43 (100). HRMS: calcd for $C_{12}H_{11}N_3O_6$ 293.0648, found 293.0651.

4-Formyl-6,7-dimethoxy-5-nitroquinoline (6j). To **6h** (6.1 g, 23.3 mmol) in DMSO (102 mL) were added TFA (2.23 mL, 29 mmol), *t*-BuI (0.61 mL, 5.12 mmol), I_2 (5.94 g, 23.4 mmol), and $FeCl_2$ (276 mg, 1.38 mmol), and the reaction mixture was heated at 80−85 °C for 5 h. The DMSO was removed *in vacuo*, and the resulting crude red oil was washed with aqueous $Na_2S_2O_3$ (20% wt/vol) and then with aqueous K_2CO_3 (10% wt/vol) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed again with thiosulfate and carbonate solutions, dried, and concentrated to give **6h** as a yellow solid (4.71 g, 73%). Mp 120−121°C. UV 218 (4.38), 236 (4.49), 292 (3.67), 320 (3.81), 336 (3.92). IR (film) 1706, 1619, 1537. ^{1}H-NMR (300 MHz) 4.14 (s, 3H); 4.16 (s, 3H); 7.77 (m, 2H); 9.09 (d, J = 4.4, 1H); 10.26 (s, 1H). ^{13}C-NMR (75 MHz) 56.6 (q); 63.0 (q); 111.5 (s); 112.4 (d); 122.0 (d); 137.5 (s); 139.8 (s); 144.9 (s); 146.3 (s); 150.4 (d); 154.8 (s); 189.4 (d). MS (CI) 280 (M + 18, 100), 263 (M + 1, 52). HRMS: calcd for $C_{12}H_{10}N_2O_5$ 262.0590, found 262.0589. Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 55.0; H, 3.84; N, 10.7. Found: C, 55.1; H, 3.90; N, 10.7.

4-(Hydroxymethyl)-6,7-dimethoxy-5-nitroquinoline (6k). To **6j** (100 mg, 0.38 mmol) in MeOH (10 mL) was added $NaBH_4$ (100 mg, 2.64 mmol) in portions at 20 °C. After 1 h the reaction was quenched with H_2O and partitioned between EtOAc and aqueous K_2CO_3 (10% wt/vol). The combined organic extracts were dried and concentrated to yield **6k** as a light brown solid (80 mg, 80%). Mp 120−121 °C. UV 220 (4.42), 236 (4.56), 272 (3.84), 318 (3.86), 330 (3.97); IR (film) 3442, 1583, 1532, 1472. ^{1}H-NMR (300 MHz) 1.84 (bs, 1H); 4.06 (s, 3H); 4.12 (s, 3H); 4.99 (s, 2H); 7.74 (s, 1H); 7.77 (d, J = 4.5, 1H); 8.73 (d, J = 4.5, 1H). ^{13}C-NMR (75 MHz) 56.5 (q); 59.3 (t); 62.8 (q); 111.7 (d); 112.64 (s); 118.7 (d); 140.2 (s); 142.8 (s); 144.5 (s); 145.2 (s); 150.3 (d); 153.6 (s). MS (EI) 264 (M^+,

8), 248 (2), 230 (22), 218 (72), 203 (100), 188 (58), 160 (33). HRMS: calcd for $C_{12}H_{12}N_2O_5$ 264.0746, found 264.0742.

6,7-Dimethoxy-4-(dimethoxymethyl)-5-nitroquinoline (6l). To **6j** (0.90 g, 3.44 mmol) in MeOH (100 mL) was added HCl in Et_2O (5 mL, 1 M, 5 mmol), and the reaction was refluxed for 65 h. The solvent was removed *in vacuo*, and the residue was partitioned between EtOAc and aqueous K_2CO_3 (10% wt/vol). The organic phases were dried and concentrated to give **6l** as a yellow solid (0.99 g, 93%). Mp 118 °C. UV 220 (4.39), 238 (4.54), 282 (3.72), 336 (3.95). IR (film) 1584, 1538. ^{1}H-NMR (300 MHz) 3.43 (s, 6H); 4.12 (s, 3H); 4.15 (s, 3H); 5.64 (s, 1H); 7.93 (d, J = 4.9, 1H); 7.99 (s, 1H); 8.91 (d, J = 4.9, 1H). ^{13}C-NMR (75 MHz) 54.3 (q); 56.8 (q); 63.2 (q); 100.5 (d); 112.9 (d); 113.5 (s); 119.6 (d); 140.9 (s); 141.0 (s); 144.4 (s); 146.7 (s); 150.5 (d); 153.9 (s). MS (EI) 308 (M^+, 25), 277 (53), 246 (47), 231 (37), 217 (18), 75 (100). HRMS: calcd for $C_{14}H_{16}N_2O_6$ 308.1008, found 308.1014. Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.5; H, 5.23; N, 9.08. Found C, 54.3; H, 5.20; N, 9.01.

1,2-Dihydro-6,7-dimethoxy-1-(methoxycarbonyl)-4-(dimethoxymethyl)-5-nitroquinoline (8a). To **6l** (236 mg, 0.76 mmol) in THF (10 mL) under argon cooled to −78 °C was added BH_3−THF (4 mL, 1 M in THF), and the mixture was stirred at −78 °C for 30 min. REDAL (70% solution in PhMe, 1.2 mL, 4.08 mmol) was added dropwise. The color of the reaction changed from a yellow to a deep red. The reaction was stirred at −78 °C for 40 min before MeOCOCl (4 mL, 52 mmol) was added all at once. The reaction changed from a deep red solution to yellow. The reaction was then stirred at rt for 20 h before quenching with H_2O and then filtered through Celite to remove the coarser aluminum salts. The organic phase was washed with H_2O, dried, and concentrated to give the crude product. The material was purified by flash column chromatography (petroleum ether (40−60)−EtOAc (1:1)) to give **8a** as a yellow oil (160 mg, 57%, three steps). UV 218 (4.64), 240 (4.90). IR (film) 1713, 1613, 1537. ^{1}H-NMR (200 MHz) 3.26 (s, 6H); 3.83 (s, 3H); 3.95 (s, 3H); 3.97 (s, 3H); 4.31 (d, J = 4.0, 2H); 5.07 (s, 1H); 6.48 (t, J = 4.0, 1H); 7.42 (bs, 1H). MS (CI) 386 (M + 18, 17), 367 (4), 337 (100), 309 (14), 279 (19), 249 (15), 219 (21); HRMS: calcd for $C_{16}H_{20}N_2O_8$ 368.1220, found 368.1224.

1,3,4,5-Tetrahydro-7,8-dimethoxy-5-(methoxycarbonyl)-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]quinoline (9b). **8a** (140 mg, 0.38 mmol) in absolute EtOH (20 mL) was hydrogenated at 56 psi over 5% Pt/C (100 mg) at 20 °C for 24 h. The reaction mixture was filtered through Celite and concentrated to give crude **7b**. This material was not further purified but dissolved in THF (5 mL), aqueous HCl (1 N, 5 mL) was added and the reaction was heated (50−55 °C) for 24 h. The reaction was quenched with aqueous NaOH (3 N) and extracted with EtOAc. The organic extracts were dried and concentrated to give crude indole **9a**. This material, without further purification, was dissolved in CH_2Cl_2 (3 mL), tetrabutylammonium hydrogen sulfate (12 mg, 34 mmol), powdered NaOH (200 mg, 5 mmol), and TsCl (300 mg, 1.57 mmol) in CH_2Cl_2 (1 mL) were added, the reaction was stirred at 20 °C for 3 h, H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic extract were dried and concentrated to give the crude material which was purified by flash column chromatography (petroleum ether (40−60)−EtOAc (1:1)) to give **9b** as an oil (21 mg, 0.049 mmol, 13% (three steps)). UV 216 (4.33), 232 (4.44), 280 (4.11). IR (film) 1709, 1618, 1443. ^{1}H-NMR (200 MHz) 2.39 (s, 3H); 2.80 (t, J = 5.9, 2H); 3.82 (s, 3H); 3.99 (t, J = 5.9, 2H), 3.88 (s, 6H); 7.34−7.25 (m, 4H); 7.87 (d, J = 8.3, 2H). MS (CI) 448 (M + 18, 38), 431 (M + 1, 23), 277 (100). HRMS: calcd for $C_{21}H_{26}N_3O_6S$ 448.1542, found 448.1663.

5-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(dimethoxymethyl)quinoline (7c). To **6l** (184 mg, 0.597 mmol) and $NiCl_2$ (1.7 g, 7.13 mmol) in MeOH (20 mL) was added $NaBH_4$ (1.6 g, 42.4 mmol) rapidly in portions with no external cooling. The temperature in the reaction vessel rose to about 50 °C. After 5 min the reaction was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried and concentrated and then redissolved in $CHCl_3$, and the solution was dried and concentrated to yield **7c** as a red oil (145 mg, 86%). UV 220 (4.42), 246 (4.67), 298 (4.22). IR (film) 3403, 3351, 1612, 1505. ^{1}H-NMR (300 MHz) 1.67 (m, 1H); 2.11 (m, 1H); 3.16 (m, 1H); 3.37 (s, 3H); 3.43 (s, 3H); 3.20−3.50 (m, 2H); 3.77 (s, 3H); 3.80 (s, 3H); 4.48 (d, J = 8.6, 1H); 5.61 (s, 1H). MS (EI) 282 (M^+, 29), 267 (9), 252 (8), 237 (13), 218 (12), 207 (100), 203 (18), 192 (27), 75 (28). HRMS: calcd for $C_{14}H_{22}N_2O_4$ 282.1580, found 282.1579.

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(dimethoxymethyl)-1-(4-methylbenzenesulfonyl)-5-[bis(4-methylbenzenesulfonyl)amino]quinoline (7f). A mixture of diamine **7c** (311 mg, 1.10 mmol) in triethylamine (6 mL) with *p*-toluenesulfonyl chloride (1.56 g, 8.2 mmol) and imidazole (20 mg, 0.3 mmol) was stirred for 18 h. The reaction was quenched with water and extracted with CH_2Cl_2. The dried organic extract was concentrated to give an oil which was purified by flash column chromatography (petroleum ether (40−60)−EtOAc (2:1)) to give the **7f** as a white solid (552 mg, 67%). Mp 119−123 °C. UV 236 (4.67). IR (film) 3063, 2948, 2840, 1598, 1491, 1455. ^{1}H-NMR (300 MHz) 1.72 (m, 1H); 2.14 (m, 1H); 2.44 (s, 6H); 2.51 (s, 3H); 3.11, 3.04 (2 × s, 2 × 3H); 3.26 (q, J = 7.2, 1H); 3.83, 3.51 (2 × s, 2 × 3H); 4.0−3.5 (2 × m, 2H); 4.39 (d, J = 5.9, 1H); 7.37−7.27 (3 × d, J = 8.4, 3 × 2H); 7.48 (d, J = 8.4, 2H); 7.64 (s, 1H); 7.75 (d, J = 8.4, 2H); 8.31 (d, J = 8.4, 2H). FABMS 744 (M^+, 25), 714 (37), 684 (7), 589 (62), 558 (100), 527 (42), 515 (87), 434 (19), 403 (68), 247 (76), 217 (60), 205 (80); HRMS: calcd for $C_{35}H_{40}N_2O_{10}S_3$ 744.1845, found 744.1831.

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(dimethoxymethyl)-1-(4-methylbenzenesulfonyl)-5-(4-methylbenzenesulfonylamino)quinoline (7d). To **7f** (552 mg, 0.743 mmol) in MeOH (30 mL), NaOMe (1.5 g, 27.5 mmol) was added and the mixture heated at 50 °C for 66 h. After dilution with H_2O, extraction with CH_2Cl_2, drying and concentration yielded **7d** as a yellow oil (308 mg, 70%): UV (EtOH) 220 (4.48). IR (film) 3251, 1599. ^{1}H-NMR (300 MHz) 1.60 (m, 1H); 1.85 (m, 1H); 2.29 (s, 3H); 2.33 (s, 3H); 2.85 (s, 3H); 3.06 (s, 3H); 3.13 (m, 1H); 3.37 (s, 3H); 3.37−3.80 (m, 2H); 3.80 (s, 3H); 4.38 (d, J = 5.9, 1H); 7.19−7.14 (m, 4H); 7.39 (d, J = 8.3, 2H); 7.45 (s, 1H); 7.69 (d, J = 8.3, 2H). FABMS 590 (M^+, 31), 559 (21), 436 (16), 404 (100), 361 (35), 249 (36), 217 (22), 205 (31); HRMS: calcd for $C_{28}H_{34}N_2O_8S_2$ 590.1756, found 590.1775.

1,3,4,5-Tetrahydro-7,8-dimethoxy-1,5-bis(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]quinoline (9c). A mixture of **7d** (308 mg, 0.522 mmol) and aqueous HCl (1 N, 9 mL) in THF (9 mL) was heated at 80 °C for 41 h. The reaction was quenched with aqueous NaOH (3 N, 3.5 mL) and then extracted with CH_2Cl_2. The organic extracts were dried concentrated to give a crude oil which was purified by flash column chromatography (petroleum ether (40−60)−EtOAc (1:1)) to yield **9c** as a white solid (132 mg, 48%). Mp 70−72 °C: UV 230 (4.56), 276 (4.06), 286 (4.06). IR (film) 1617, 1597, 1500. ^{1}H-NMR (300 MHz) 2.41 (s, 6H); 2.47 (m, 2H); 3.92, 3.95 (2 × s, 2 × 3H); 3.97 (m, 2H); 7.19 (d, J = 8.3, 2H); 7.20 (s, 1H); 7.27 (d, J = 8.3, 2H); 7.34 (s, 1H); 7.53 (d, J = 8.3, 2H); 7.84 (d, J = 8.3, 2H). FABMS 526 (M^+, 53), 495 (2), 371 (100), 341 (2), 217 (40), 205 (35). HRMS: calcd for $C_{26}H_{26}N_2O_6S_2$ 526.1232, found 526.1224.

1,3,4,5-Tetrahydro-7,8-dimethoxypyrrolo[4,3,2-*de*]quinoline (9d). The acetal **7c** (100 mg) was reacted with 1 N aqueous HCl (1.5 mL) in THF (1.5 mL) at 40 °C for 1 h. After evaporation of THF the solution was made basic and extracted with CH_2Cl_2 to afford **9d** as an oil (50 mg, 64%). UV 232 (4.31), 268 (4.06). IR (film) 3353, 2932, 2835, 1619. ^{1}H-NMR (300 MHz) 2.99 (t, J = 5.4, 2H); 3.50 (t, J = 5.4, 2H); 3.88, 3.90 (2 × s, 2 × 3H); 6.03 (s, 1H), 6.66 (bs, 1H); 7.89 (bs, 1H). FABMS 526 (M^+, 53), 495 (2), 371 (100), 341 (2), 217 (40), 205 (35). MS (EI) 218 (M^+, 33), 203 (50). HRMS: calcd for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1055.

1,3,4,5-Tetrahydro-1,5-bis(4-methylbenzenesulfonyl)-pyrrolo[4,3,2-*de*]quinoline-7,8-dione (10a). To a solution of **9c** (130 mg, 0.247 mmol) in CH_2Cl_2 (2.5 mL) under argon with 4 Å sieves at −78 °C was added dropwise BBr_3 (0.5 mL, 1 M in CH_2Cl_2), and then the temperature was allowed to rise to −20 °C over 50 min. The reaction was quenched with aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a red oil (130 mg) which was not purified further but oxidized in MeCN (2 mL) with CAN (370 mg, 0.675 mmol) in H_2O (2 mL) at rt for 10 min. After dilution with H_2O, extraction with CH_2Cl_2, drying, and evaporation gave **10a** as an orange oil (113

mg, 92%). UV 232 (4.25), 310 (3.70), 362 (3.48). IR (film) 1687, 1651, 1598. ^{1}H-NMR (300 MHz) 2.45 (s, 3H); 2.47 (s, 3H); 2.90 (t, J = 6.0, 2H); 4.13 (t, J = 6.0, 2H); 6.34 (s, 1H); 7.42−7.34 (m, 4H); 7.59 (s, 1H); 7.79 (d, J = 8.4, 2H); 8.10 (d, J = 8.4, 2H). FABMS 497 (M + 1, 100), 465 (6), 343 (52), 289 (38), 242 (53). HRMS: calcd for $C_{24}H_{21}N_2O_6S_2$ 497.0841, found 497.0852.

1,3,4,5-Tetrahydro-5-(methoxycarbonyl)-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]quinoline-7,8-dione (10b). *O*-Demethylation of **9b** (22 mg, 0.052 mmol) was achieved in dry CH_2Cl_2 (1 mL) under argon in the presence of 4 Å sieves and at −78 °C by reaction with BBr_3 (0.1 mL, 1 M in CH_2Cl_2), and then the temperature was allowed to rise to −25 °C over 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 and the dried extract evaporated to give a red oil (15 mg) which without further purification was dissolved in MeCN (1 mL) and oxidized with CAN (67 mg, 0.122 mmol) in H_2O (1 mL) at rt for 10 min. The mixture was diluted with H_2O and extracted with CH_2Cl_2 giving **10b** as an orange oil which solidified upon storage to give a red solid (14 mg, 70%). Mp 114−119 °C. UV 238 (4.25), 314 (3.88), 358 (3.67). IR (film) 2956, 1729, 1686, 1649, 1600, 1441, 1376, 1329, 1212, 1193, 1179, 1094. ^{1}H-NMR (300 MHz) 2.46 (s, 3H); 2.85 (t, J = 6.0, 2H); 3.90 (s, 3H); 4.13 (t, J = 6.0, 2H); 6.58 (s, 1H); 7.37 (d, J = 8.4, 2H); 7.62 (s, 1H); 8.13 (d, J = 8.4, 2H). FABMS 401 (M + 1, 100), 247 (35). HRMS: calcd for $C_{19}H_{17}N_2O_6S$ 401.0807, found 401.0794.

1,3,4,5-Tetrahydro-7-methoxy-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]quinolin-8-one (11a). To **10a** (120 mg, 0.24 mmol) in CH_2Cl_2−MeOH (1:1) (10 mL) was added K_2CO_3 (30 mg, 0.22 mmol), and then the mixture was stirred for 30 min, the solution decanted, and the solvent evaporated. The residue was extracted with $CHCl_3$ and the organic extract concentrated to give a crude oil which was purified by flash column chromatography (CH_2Cl_2−MeOH (99:1)) to give **11a** as a red oil (8 mg, 9%). UV (EtOH) 234 (4.38), 320 (3.88), 386 (3.80). IR (film) 1670, 1643, 1589, 1525. ^{1}H-NMR (300 MHz) 2.47 (s, 3H); 2.83 (t, J = 6.0, 2H); 3.93 (s, 3H); 4.13 (t, J = 6.0, 2H); 6.25 (s, 1H); 6.68 (s, 1H); 7.38 (d, J = 8.4, 2H); 7.82 (d, J = 8.4, 2H). MS (CI) 357 (M + 1, 39), 203 (100). HRMS: calcd for $C_{18}H_{17}N_2O_4S$ 357.0909, found 357.0913.

1,3,4,5-Tetrahydro-5-(*tert*-butyloxycarbonyl)-7,8-dimethoxypyrrolo[4,3,2-*de*]quinoline (9e). To nitro-aldehyde **6j** (115 mg, 0.44 mmol) in methanol (15 mL) was added $NiCl_2$ (1.35 g, 5.72 mmol). After 5 min, $NaBH_4$ (1.32 g, 35.2 mmol) was added rapidly with no external cooling. The mixture was allowed to stir for 5 min and was then diluted with H_2O. The reaction was extracted rigorously with EtOAc, and then the combined organic extracts were dried and concentrated. The resulting residue was extracted with $CHCl_3$ and the organic extract again dried and concentrated to yield a red oil which was not purified further but dissolved in CH_2Cl_2 (5 mL) and reacted with $(BOC)_2O$ (150 mg, 0.69 mmol) at rt for 15 h. The solvent was removed and the crude residue purified by flash column chromatography (C_6H_{14}−EtOAc (3:2)) to yield **9e** as an oil (27 mg, 19%). UV 230 (4.27), 286 (3.91). IR (film) 3347, 1697, 1514. ^{1}H-NMR (300 MHz) 1.61 (s, 9H); 2.95 (t, J = 5.6, 2H); 3.95 (s, 3H); 3.98 (s, 3H); 4.05 (t, J = 5.6, 2H); 6.78 (bs, 1H); 7.25 (bs, 1H); 8.38 (bs, 1H). ^{13}C-NMR (75 MHz) 22.9 (t); 28.5 (q); 45.4 (t); 57.8 (q); 61.0 (q); 81.1 (s); 100.3 (d); 110.6 (s); 116.4 (d); 117.3 (s); 128.2 (s); 128.3 (s); 130.7 (s); 147.9 (s); 153.8 (s) MS (EI) 318 (M^+, 29), 262 (100), 247 (93), 203 (48). HRMS: calcd for $C_{17}H_{22}N_2O_4$ 318.1580, found 318.1585.

1,3,4,5-Tetrahydro-5-(*tert*-butyloxycarbonyl)-7,8-dimethoxy-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]-quinoline (9f). 9e (180 mg, 0.57 mmol) in THF (1 mL) was added to a suspension of oil-free NaH (34 mg, 0.85 mmol) at rt and the mixture stirred for 45 min, refluxed for 15 min, and cooled. TsCl (150 mg, 0.77 mmol) was added and after 14 h at room temperature the mixture diluted with H_2O and extracted with CH_2Cl_2. The organic extracts were dried concentrated to give an oil which was purified by flash column chromatography (C_6H_{14}−EtOAc (2:1)) to yield **9f** as an oil (90 mg, 34%). UV 242 (4.35), 282 (4.35). IR (film) 1698, 1502. ^{1}H-NMR (300 MHz) 1.61 (s, 9H); 2.39 (s, 3H); 2.91 (t, J = 5.5, 2H); 3.91 (s, 6H); 4.00 (t, J = 5.5, 2H); 7.26 (d, J = 8.3, 2H); 7.30 (s, 1H); 7.32 (s, 1H); 7.88 (d, J = 8.3, 2H). ^{13}C-NMR (75 MHz) 21.6 (q); 22.6 (t); 28.5 (q); 44.6 (t); 57.0 (q); 61.0 (q); 81.5 (s); 102.9 (d); 114.7 (s); 119.1 (s); 120.2 (d); 126.4 (s); 127.7 (d); 128.7 (s); 129.6 (d); 132.7 (s); 136.3 (s); 144.2 (s); 151.4 (s); 153.3 (s). MS (CI) 473 (MH^+, 17), 417 (36), 373 (65), 319 (44), 263 (56), 219 (100). HRMS: calcd for $C_{24}H_{28}N_2O_6S$ 472.1668, found 472.1669.

1,3,4,5-Tetrahydro-7,8-dimethoxy-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]quinoline (9g). 9f (17 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.1 mL) at rt for 90 min. The mixture was diluted with CH_2Cl_2 and made basic with $NaHCO_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated to give **9g** as an oil (12 mg, 80%). UV 218 (3.58), 244 (4.48), 278 (4.29). IR (film) 3384, 1621, 1596. ^{1}H-NMR (300 MHz) 2.36 (s, 3H); 2.90 (t, J = 5.8, 2H); 3.39 (t, J = 5.8, 2H); 3.84 (s, 3H); 3.87 (s, 3H); 6.14 (s, 1H); 7.21 (s, 1H); 7.23 (d, J = 8.3, 2H); 7.90 (d, J = 8.3, 2H). ^{13}C-NMR (75 MHz) 21.6 (t); 22.6 (t); 42.8 (t); 56.9 (q); 61.2 (q); 93.2 (d); 114.9 (s); 115.3 (s); 118.8 (d); 127.0 (s); 127.8 (d); 129.5 (s); 129.6 (d); 136.4 (s); 136.8 (s); 144.0 (s); 152.6 (s). MS (EI) 372 (M^+, 15), 217 (100). HRMS: calcd for $C_{19}H_{20}N_2O_4S$ 372.1144, found 372.1144.

1,3,4,5-Tetrahydro-5-(*tert*-butyloxycarbonyl)-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline (9h). To **9e** (180 mg, 0.57 mmol) in THF (1 mL) was added, oil-free NaH (34 mg, 0.85 mmol) and the whole was stirred at rt for 45 min, refluxed for 15 min, and cooled. MeI (0.5 mL, 8.1 mmol) was added, and the mixture was stirred for 14 h, diluted carefully with H_2O, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give an oil which was purified by flash column chromatography (C_6H_{14}−EtOAc (3:1)) to yield **9h** as an oil (105 mg, 56%). UV 220 (4.19), 236 (4.41), 294 (4.12). IR (film) 1698, 1511. ^{1}H-NMR (300 MHz) 1.62 (s, 9H); 2.95 (t, J = 5.6, 2H); 3.95 (s, 9H); 4.00 (t, J = 5.6, 2H); 6.56 (s, 1H); 7.19 (bs, 1H). ^{13}C-NMR (75 MHz) 22.8 (t); 28.5 (q); 34.7 (q); 45.3 (t); 57.8 (q); 62.0 (q); 81.0 (s); 100.2 (d); 109.3 (s); 118.0 (s); 122.1 (d); 128.0 (s); 128.4 (s); 131.8 (s); 148.5 (s); 153.7 (s). MS (EI) 332 (M^+, 14), 276 (58), 261 (92), 217 (48). HRMS: calcd for $C_{18}H_{24}N_2O_4$ 332.1736, found 332.1736.

1,3,4,5-Tetrahydro-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline (9i). 9h (30 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.1 mL), and the mixture was stirred at rt for 90 min, diluted with CH_2Cl_2, and made basic with aqueous $NaHCO_3$. The organic layer was dried and evaporated to give **9i** as an oil (16 mg, 80%). UV 234 (4.10), 290 (3.74). IR (film) 3364, 1691, 1634. ^{1}H-NMR (300 MHz) 2.94 (t, J = 5.8, 2H); 3.42 (t, J = 5.8, 2H); 3.86 (bs, 1H); 3.86 (s, 9H); 5.99 (s, 1H); 6.43 (bs, 1H). MS (EI) 232 (M^+, 60), 217 (100), 202 (42). HRMS: calcd for $C_{13}H_{16}N_2O_2$ 232.1225, found 232.1221.

7-Methoxy-4-(dimethoxymethyl)-1-methyl-5-nitro-6-oxidoquinolinium (12a). The nitroquinoline **6l** (0.573 g, 1.86 mmol) was heated in MeCN (15 mL) with MeI (6 mL, 96.3 mmol) at 50 °C for 44 h. The reaction mixture was cooled to 0 °C to complete precipitation of an orange solid which was was filtered, washed with Et_2O, and dried to yield **12a** (0.35 g, 61%). Mp > 230 °C. UV (H_2O) 228 (4.57), 270 (4.31), 376 (4.09). IR (KBr) 1566, 1467, 1453. ^{1}H-NMR (300 MHz, DMSO-d_6) 3.32 (s, 6H); 4.11 (s, 3H); 4.54 (s, 3H); 5.56 (s, 1H); 7.26 (s, 1H); 7.83 (d, J = 6.3, 1H); 8.64 (d, J = 6.3, 1H). FABMS 309 (M + 1, 100), 293 (3), 277 (10), 261 (11), 232 (15). HRMS: calcd for $C_{14}H_{17}N_2O_6$ 309.1087, found 309.1086.

1,2-Dihydro-7-methoxy-4-(dimethoxymethyl)-1-methyl-6-[(4-methylbenzenesulfonyl)oxy]-5-nitroquinoline (8b). To the zwitterion **12a** (155 mg, 0.50 mmol) in cold MeOH/H_2O (1:1) (30 mL) was added $NaBH_4$ (190 mg, 5.0 mmol) all at once and the reaction stirred for 1 h. The MeOH was removed *in vacuo*, saturated aqueous $NaHCO_3$ was added, and then organic material was extracted with $CHCl_3$. The combined organic extracts were dried concentrated to give a red solid which was unstable with respect to reoxidation to starting material. The crude solid was dissolved in CH_2Cl_2−Et_3N (1:1) (6 mL), TsCl (287 mg, 1.50 mmol) was added, and the mixture was stirred for 18 h, quenched with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The organic extracts were dried and concentrated, leaving an oil which was purified

by flash column chromatography (petroleum ether (40−60)−EtOAc (1:1)) to give **8b** as an orange solid (79 mg, 34%). Mp 127−128.5 °C. UV 236 (4.35), 282 (3.65). IR (film) 1607, 1535, 1370. ^{1}H-NMR (300 MHz) 2.50 (s, 3H); 2.90 (s, 3H); 3.22 (s, 6H); 3.77 (s, 3H); 3.81 (d, J = 5.0, 2H); 4.96 (s, 1H); 6.26 (s, 1H); 6.27 (t, J = 5.0, 1H); 7.37 (d, J = 8.3, 2H); 7.84 (d, J = 8.3, 2H). FABMS 464 (M^+, 48), 463 (82), 433 (67), 309 (100). HRMS: calcd for $C_{21}H_{23}N_2O_8S$ 463.1175, found 463.1170.

6,7-Dimethoxy-4-(dimethoxymethyl)-1-methyl-5-nitroquinolinium Iodide (12b). **6l** (50 mg, 0.16 mmol) in MeCN (1.3 mL) with MeI in the presence of 4 Å sieves under argon was kept at 30 °C for 42 h. The solvent was removed *in vacuo* and the residue was washed with Et_2O to remove unreacted starting material. The residual solid was dried *in vacuo*, to yield **12b** as an orange solid (31 mg, 43%). Mp >230 °C. UV (H_2O) 222 (4.51), 246 (4.36), 358 (3.99). IR (KBr) 3415, 3000, 2948, 1618, 1549, 1501. ^{1}H-NMR (300 MHz, Me_2CO-d_6) 3.52 (s, 6H); 4.26 (s, 3H); 4.56 (s, 3H); 5.11 (s, 3H); 5.75 (s, 1H); 8.38 (s, 1H); 8.47 (d, J = 6.3, 1H); 9.94 (d, J = 6.3, 1H). FABMS 323 (M^+, 15), 309 (100), 277 (8), 261 (13), 248 (6), 232 (14), 218 (10). HRMS: calcd for $C_{15}H_{19}N_2O_6$ 323.1243, found 323.1252.

6,7-Dimethoxy-1,4-dimethylquinolinium Iodide (12d). Quaternization of **6g** (200 mg, 0.99 mmol) was achieved in MeCN (7 mL) with MeI (1.7 mL, 27.2 mmol) at 40 °C for 63 h. A pale yellow precipitate formed which was filtered, washed with CH_2Cl_2, and dried at the pump to yield **12d** as a yellow solid (250 mg, 72%). Mp 211−212 °C. UV (H_2O) 220 (4.38), 246 (4.33), 346 (4.05). IR (KBr) 3508, 2978, 1626, 1577, 1513, 1491, 1443, 1285, 1231, 1213, 1039. ^{1}H-NMR (300 MHz, DMSO-d_6) 2.93 (s, 3H); 4.07 (s, 3H); 4.14 (s, 3H); 4.51 (s, 3H); 7.61 (s, 2H); 7.81 (d, J = 6.2, 1H); 9.04 (d, J = 6.2, 1H). FABMS 218 (M^+, 100). HRMS: calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1186.

6,7-Dimethoxy-1,4-dimethyl-5-nitroquinolinium Iodide (12e). Quaternization of **6h** (200 mg, 0.76 mmol) was effected in MeCN (7 mL) with MeI (1.7 mL, 27.2 mmol) at 40 °C for 63 h. The precipitate which formed was filtered, washed with CH_2Cl_2, and dried to yield salt **12e** as a brown solid (112 mg, 56%). Mp > 230 °C. UV (H_2O) 226 (4.37), 270 (3.92), 350 (3.85). IR (KBr) 3436, 3050, 1620, 1590, 1524, 1504, 1282, 1213. ^{1}H-NMR (300 MHz, DMSO-d_6) 2.69 (s, 3H); 4.05 (s, 3H); 4.28 (s, 3H); 4.60 (s, 3H); 7.90 (s, 1H); 8.02 (d, J = 6.1, 1H); 9.32 (d, J = 6.1, 1H). FABMS 263 (M^+, 100). HRMS: calcd for $C_{13}H_{15}N_2O_4$ 263.1032, found 263.1030.

1,2-Dihydro-6,7-dimethoxy-4-(dimethoxymethyl)-1-methyl-5-nitroquinoline (8c). Salt **12b** (300 mg, 0.67 mmol) in MeOH (20 mL) at 0 °C was reduced with $NaBH_4$ (0.25 g, 6.7 mmol) added in portions over 1.5 h. The mixture was then stirred for 1 h, solvent removed *in vacuo*, and the solid residue was partitioned between EtOAc and aqueous K_2CO_3 (10% wt/vol). The organic extracts were dried and concentrated to give **8c** as an unstable red oil (200 mg, 92%). UV 218 (4.38), 222 (4.40), 236 (4.49), 272 (3.92), 332 (3.72). IR (film) 1611, 1534, 1499. ^{1}H-NMR (300 MHz) 2.83 (s, 3H); 3.25 (s, 6H); 3.70 (d, J = 7.6, 2H); 3.84 (s, 3H); 3.91 (s, 3H); 4.98 (s, 1H); 6.27 (m, 2H). MS (CI) 325 (M + 1, 12), 309 (19), 293 (7), 254 (40), 237 (52), 208 (100), 154 (50).

1,3,4,5-Tetrahydro-7,8-dimethoxy-5-methylpyrrolo[4,3,2-*de*]quinoline (9j) and 1,3,4,5-Tetrahydro-7,8-dimethoxy-5-methyl-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]-quinoline (9k). To Me_3OBF_4 (180 mg, 1.20 mmol) suspended in dry CH_2Cl_2 (8.5 mL) with 4 Å sieves under argon and cooled to 0 °C was added **6l** (191 mg, 0.73 mmol) in CH_2Cl_2 (3 mL), dropwise. The mixture was stirred for 22 h at room temperature, the solvent removed *in vacuo*, and then the residue redissolved in MeOH (25 mL). $NiCl_2$ (4.28 g, 18.0 mmol) was added and after 5 min $NaBH_4$ (4.54 g, 120 mmol) was added rapidly in portions with no external cooling. After 5 min the reaction was diluted with H_2O and extracted with EtOAc. The organic extracts were dried, concentrated, redissolved in $CHCl_3$, redried, and evaporated to yield an oil which could be purified by flash column chromatography (petroleum ether (40−60)−EtOAc (1:1)) to yield the indole **9j** as an oil (20 mg, 12%). UV 232 (4.56), 290 (4.15). IR (film) 3400, 3368, 1621, 1520. ^{1}H-NMR (300 MHz) 2.97 (s, 3H); 3.07 (t, J = 5.3, 2H); 3.30 (t, J = 5.3, 2H); 3.95 (s, 3H); 3.97 (s, 3H); 6.03 (s, 1H); 6.69 (s, 1H); 7.89 (bs, 1H). FABMS 232 (M^+, 61), 217 (100). HRMS: calcd for $C_{13}H_{16}N_2O_2$ 232.1212, found 232.1212.

The crude indole **9j** in CH_2Cl_2 (3 mL) was reacted without further purification, with Bu_4NHSO_4 (10 mg, 28 mmol), powdered NaOH (200 mg, 5 mmol), and TsCl (400 mg, 2.01 mmol) at rt for 3 h. H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried and concentrated to yield an oil which was purified by flash column chromatography (CH_2Cl_2−MeOH) (99:1)) to yield the tosylated indole **9k** as an oil (39 mg, two steps 14%). UV 232 (4.47), 286 (4.02). IR (film) 1617, 1507. ^{1}H-NMR (300 MHz) 2.37 (s, 3H); 2.92 (s, 3H); 2.98 (t, J = 5.9, 2H); 3.23 (t, J = 5.9, 2H); 3.86 (s, 3H); 3.91 (s, 3H); 6.12 (s, 1H); 7.21 (s, 1H); 7.25 (d, J = 8.4, 2H); 7.89 (d, J = 8.4, 2H). MS (EI) 386 (M^+, 3), 232 (58), 217 (100), 124 (65), 91 (53). HRMS: calcd for $C_{20}H_{22}N_2O_4S$ 386.1300, found 386.1307.

1,3,4,5,7,8-Hexahydro-5-methyl-1-(4-methylbenzenesulfonyl)pyrrolo[4,3,2-*de*]quinoline-7,8-dione (10c). De-*O*-methylation of **9k** (15 mg, 0.04 mmol) was achieved in dry CH_2Cl_2 (1.5 mL) with 4 Å sieves under argon at −78 °C with BBr_3 (0.2 mL of a 1 M solution in CH_2Cl_2) added dropwise. The mixture was allowed to warm up to −30 °C over 1.5 h and then maintained at −30 to −20 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a red oil which was purified by flash column chromatography (CH_2Cl_2−MeOH (95:5)) to yield **10c** as a red oil which solidified upon storage (5 mg, 37%). Mp 174−176 °C dec. UV 238 (4.26), 334 (3.95), 515 (3.11). IR (film) 1681, 1607. ^{1}H-NMR (300 MHz) 2.45 (s, 3H); 2.94 (t, J = 6.7, 2H); 3.08 (s, 3H); 3.61 (t, J = 6.7, 2H); 5.34 (s, 1H); 7.35 (d, J = 8.4, 2H); 7.56 (s, 1H); 8.14 (d, J = 8.4, 2H). MS (CI) 357 (M + 1, 42). HRMS: calcd for $C_{18}H_{17}N_2O_4S$ 357.0909, found 357.0927.

5-(*tert*-Butyloxycarbonyl)-2-chloro-1,3,4,5-tetrahydro-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline (9l). The BOC-protected pyrroloindole **9h** (20 mg, 0.06 mmol) was reacted with *N*-chlorosuccinimide (10 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) at 0 °C for 10 min. The mixture was diluted with CH_2Cl_2, washed with aqueous KCO_3, dried, and evaporated leaving **9l** (17 mg, 77%) as an oil: UV 224 (4.54). IR (film) 3382, 2933, 1702, 1159. ^{1}H-NMR (300 MHz) 1.57 (s, 9H); 2.84 (t, *J* 5.6, 2H); 3.87 (s, 3H); 3.90 (s, 6H); 3.99 (t, *J* 5.6, 2H); 7.17 (bs, 1H). MS (CI) 367 (M + 1, 100), 311 (98), 267 (32). HRMS: calcd for $C_{18}H_{23}{}^{35}ClN_2O_4$ 367.1344, found 366.1344.

8-Chloro-6,7-dimethoxy-4-methyl-5-nitroquinoline (6m), 4-(Dichloromethyl)-6,7-dimethoxy-5-nitroquinoline (6n), and 8-Chloro-4-(dichloromethyl)-6,7-dimethoxy-5-nitroquinoline (6o). The nitroquinoline **6h** (3.00g, 12.1 mmol) in DMF (38 mL) was heated at 60 °C while NCS (1.8 g, 13.6 mmol) was added in portions (3 × 0.6 g) at 20 min intervals. After 2 h a further portion of NCS (0.4 g, 3.17 mmol) was added and the reaction heated for a further 45 min. After cooling, the mixture was diluted with CH_2Cl_2 and washed thoroughly with H_2O. The organic phase was dried and concentrated to give crude material which was purified by flash column chromatography (CH_2Cl_2) to give **6o** as an oil (0.2 g, 5%). UV 218 (4.34), 246 (4.47), 320 (3.81). IR (film) 1536, 1404. ^{1}H-NMR (300 MHz) 4.14 (s, 6H); 7.12 (s, 1H); 8.33 (d, J = 4.7, 1H); 9.18 (d, J = 4.7, 1H). MS (EI) 350 (M^+, 50). HRMS: calcd for $C_{12}H_9N_2O_4{}^{35}Cl_3$ 349.9628, found 349.9624, and **6n** as an oil (0.4 g, 10%). UV (EtOH) 220 (4.13), 248 (4.37), 304 (3.75), 342 (3.96). IR (film) 1623, 1535. ^{1}H-NMR (300 MHz) 4.07 (s, 3H); 4.10 (s, 3H); 7.08 (s, 1H); 7.75 (s, 1H); 8.14 (d, J = 4.9, 1H); 8.96 (d, J = 4.9, 1H). ^{13}C-NMR (75 MHz) 56.7 (q); 62.9 (q); 64.8 (d); 109.9 (s); 111.9 (d); 121.1 (d); 139.5 (s); 142.8 (s); 144.2 (s); 145.4 (s); 150.0 (d); 154.3 (s). MS (EI) 316 (M^+, 60), 281 (32), 245 (38). HRMS: calcd for $C_{12}H_{10}N_2O_4{}^{35}Cl_2$ 316.0018, found 316.0018, and **6m** as a solid (1.88 g, 55%). Mp 81−83 °C. UV 224 (4.38), 240 (4.57), 290 (3.85). IR (Film) 2947, 1606, 1538. ^{1}H-NMR (75 MHz) 2.61 (s, 3H); 4.10 (s, 6H); 7.34 (d, J = 4.3, 1H); 8.88 (d, J = 4.3, 1H). ^{13}C-NMR (75 MHz) 18.7 (q); 61.4 (q); 63.1 (q); 112.0 (s); 117.6 (s); 125.5 (d); 129.8 (s); 141.9 (s); 145.7 (s); 150.4 (d); 151 (s). MS (EI) 282 (M^+, 100). HRMS: calcd for $C_{12}H_{11}N_2O_4{}^{35}Cl$ 282.0407, found 282.0410.

8-Chloro-4-formyl-6,7-dimethoxy-5-nitroquinoline (6p). The chloroquinoline **6m** (5.0 g, 17.7 mmol) was oxidized in

DMSO (75 mL) with a combination of TFA (1.70 mL, 22 mmol), *t*BuI (0.46 mL, 3.90 mmol), I_2 (4.52 g, 17.8 mmol), and $FeCl_2$ (210 mg, 1.05 mmol) at 80−85 °C for 5 h. The solvent was removed *in vacuo*, and the resulting oil was washed with aqueous $Na_2S_2O_3$ (20% wt/vol) and then with aqueous K_2CO_3 (10% wt/vol) and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give **6p** as a solid (3.98 g, 76%). Mp 131.9−133.9 °C: UV 218 (4.32), 240 (4.49), 300 (3.79), 330 (3.75). IR (film) 2952, 1713, 1535. ^{1}H-NMR (300 MHz) 4.10 (s, 3H); 4.14 (s, 3H); 7.84 (d, J = 6.3, 1H); 9.19 (d, J = 6.3, 1H); 10.20 (s, 1H). ^{13}C-NMR (75 MHz) 61.6 (q); 63.4 (q); 114.5 (s); 123.8 (d); 131.5 (s); 138.5 (s); 142.4 (s); 148.3 (s); 150.8 (d); 152.3 (s); 188.6 (d). MS (EI) 296 (M^+, 43), 250 (100). HRMS: calcd for $C_{12}H_9N_2O_5{}^{35}Cl$ 296.0200, found 296.0208.

8-Chloro-6,7-dimethoxy-4-(dimethoxymethyl)-5-nitroquinoline (6q). The chloro-aldehyde **6p** (3g, 10.1 mmol) was heated at reflux in methanol (300 mL) with 1 M HCl in Et_2O (14.7 mL, 14.7 mmol) for 48 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and aqueous K_2CO_3 (10% wt/vol). The organic extracts were dried and evaporated to give **6q** as a solid (2.9 g, 84%). Mp 79.5−81 °C. UV (EtOH) 216 (3.98), 242 (4.41), 302 (3.88), 330 (383). IR (film) 1600, 1105. ^{1}H-NMR (300 MHz) 3.38 (s, 6H); 4.10 (s, 3H); 4.12 (s, 3H); 5.61 (s, 1H); 7.93 (d, J = 4.5, 1H); 9.06 (d, J = 4.5, 1H). ^{13}C-NMR (75 MHz) 54.0 (2 × q); 61.4 (q); 63.2 (q); 100.0 (d); 116.2 (s); 121.4 (d); 130.9 (s); 139.6 (s); 141.6 (s); 142.5 (s); 147.4 (s); 150.4 (d); 151.2 (s). MS (CI) 100 (MH^+, 100), 311 (18), 296 (10). HRMS: calcd for $C_{14}H_{15}N_2O_6{}^{35}Cl$ 342.0619, found 342.0622.

5-Amino-8-chloro-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(dimethoxymethyl)quinoline (7e). The chloro-acetal **6q** (300 mg, 0.88 mmol) was reduced in MeOH (30 mL) by adding first $NiCl_2$ (1.26 g, 5.28 mmol) and then, after 5 min, $NaBH_4$ (1.06 g, 28.2 mmol) in portions as rapidly as possible. After 20 min the reaction was quenched with H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give **7e** as an oil (222 mg, 80%). UV 228 (4.45), 308 (3.63). IR (film) 1603, 1102. ^{1}H-NMR (300 MHz) 1.60 (m, 1H); 2.13 (m, 1H); 3.23 (m, 1H); 3.41 (m, 2H); 3.37 (s, 3H); 3.44 (s, 3H); 3.81 (s, 3H); 3.92 (s, 3H); 4.40 (bs, 3H); 4.47 (d, J = 8.7, 1H). ^{13}C-NMR (75 MHz) 22.2 (t); 34.6 (d); 37.5 (t); 51.2 (q); 56.7 (q); 60.6(q); 60.8 (q); 101.0 (s); 102.6 (s); 107.4 (d); 132.3 (s); 137.0 (s); 139.6 (s); 148.3 (s). MS (EI) 316 (M^+, 53), 286 (14), 271 (30), 241 (100). HRMS: calcd for $C_{14}H_{21}N_2O_4{}^{35}Cl$ 316.1190, found 316.1200.

1,3,4,8-Tetrahydro-7-methoxypyrrolo[4,3,2-*de*]quinolin-8-one (11b). Amine **7e** (100 mg, 0.32 mmol) heated in aqueous HCl (1 N, 1 mL) and THF (1 mL) at 40 °C for 30 min. The mixture was cooled, and the solvent was evaporated leaving a residue which was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extracts were dried and concentrated to give **11b** as an oil (41 mg, 64%). UV 240 (3.69), 306 (4.09), 400 (3.12). IR (KBr disc) 1659, 1567. ^{1}H-NMR (200 MHz) 2.78 (t, J = 7.9, 2H); 3.84 (s, 3H); 4.19 (t, J = 7.9, 2H); 6.14 (s, 1H); 6.92 (s, 1H); 10.40 (bs, 1H). ^{13}C-NMR (75 MHz) 18.8 (t); 51.4 (t); 56.9 (q); 106.8 (d); 117.5 (s); 121.8 (s); 123.1 (d); 124.3 (s); 156.9 (s); 158.8 (s); 171.5 (s). MS (EI) 202 (M^+, 40), 187 (12). HRMS: calcd for $C_{11}H_{10}N_2O_2$ 202.0742, found 202.0742.

6-Chloro-1,5-diformyl-1,3,4,5-tetrahydro-7,8-dimethoxypyrrolo[4,3,2-*de*]quinoline (9m) and 6-Chloro-1,5-diformyl-1,2,2a,3,4,5-hexahydro-2,7,8-trimethoxypyrrolo-[4,3,2-*de*]quinoline (13). Reaction of **7e** (500 mg, 1.58 mmol) with Ac_2O (3 mL) and formic acid (1.5 mL) at rt for 48 h followed by evaporation of excess reactant *in vacuo* gave a crude residue which was purified by flash column chromatography to give **9m** as a solid (262 mg, 54%). Mp 79.5−81 °C. UV 220 (4.23), 250 (4.38), 278 (4.18), 320 (3.86). IR (film) 1702, 1674. ^{1}H-NMR (200 MHz) 2.93 (t, J = 5.7, 2H); 3.97 (s, 3H); 4.08 (s, 3H); 4.10 (t, J = 5.7, 2H); 7.56 (s, 1H); 9.05 (s, 1H); 9.71 (s, 1H). ^{13}C-NMR (75 MHz) 22.5 (t); 40.2 (t); 61.1 (q); 61.6 (q); 114.0 (s); 116.7 (d); 117.3 (s); 121.5 (s); 124.6 (s); 125.6 (s); 139.4 (s); 148.0 (s); 158.8 (d); 162.2 (d). MS (CI) 326 (M + 18, 51), 309 (MH^+, 100), 281 (24). HRMS: calcd for $C_{14}H_{13}N_2O_4{}^{35}Cl$ 308.0564, found 308.0569, and then **13** as an oil (54 mg, 10%). UV 246 (4.46). IR (film) 1681, 1603. ^{1}H-NMR (200 MHz) 1.98 (m, 1H); 2.23 (m, 1H); 3.24 (m, 1H); 3.55 (s, 3H); 3.79 (m, 1H); 3.96 (m, 1H); 3.95 (s, 3H); 3.96 (s, 3H); 5.91 (d, J = 6.1, 1H); 9.08 (s, 1H); 9.26 (s, 1H); 9.71 (s, 1H). ^{13}C-NMR (75 MHz) 21.5 (t); 40.0 (d); 41.5 (t); 58.0 (q); 60.9 (q); 61.1 (q); 90.3 (d); 114.5 (s); 122.2 (s); 129.3 (s); 129.8 (s); 139.8 (s); 151.3 (s); 161.8 (d); 162.8 (d). MS (CI) 341 (MH^+, 36), 281 (52), 247 (100). HRMS: calcd for $C_{15}H_{17}N_2O_5{}^{35}Cl$ 340.0826, found 340.0818.

6-Chloro-5-formyl-1,3,4,5-tetrahydro-7,8-dimethoxypyrrolo[4,3,2-*de*]quinoline (9n). **9m** (250 mg, 0.81 mmol) was hydrolyzed in CH_2Cl_2/MeOH (4 mL, 1:1) with aqueous NaOH (10% wt/vol) (2 mL) at rt for 1 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic extracts were dried and evaporated to give **9n** as a solid (180 mg, 82%). Mp 214−216. UV 232 (4.58), 292 (4.11). IR (KBr disc) 3435, 1649. ^{1}H-NMR (200 MHz) 2.97 (t, J = 5.7, 2H); 3.96 (s, 3H); 4.08 (s, 3H); 4.13 (t, J = 5.7, 2H); 6.93 (bs, 1H); 8.26 (bs, 1H); 9.12 (s, 1H). ^{13}C-NMR (75 MHz) 22.6 (t); 40.8 (t); 61.2 (q); 61.6 (q); 109.7 (s); 110.5 (s); 118.7 (d); 119.4 (s); 124.4 (s); 126.2 (s); 137.3 (s); 144.8 (s); 162.7 (d). MS (CI) 280 (MH^+, 100). HRMS: calcd for $C_{13}H_{13}N_2O_3{}^{35}Cl$ 280.0615, found 280.0617.

6-Chloro-5-formyl-1,3,4,5-tetrahydro-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline (9o). *N*-Methylation of **9n** (150 mg, 0.54 mmol) was achieved in THF (2 mL) by addition dropwise to a suspension of oil-free NaH (39 mg, 1 mmol) in THF (2 mL), stirring at rt for 30 min, and then refluxing for 15 min. After cooling, MeI (0.4 mL) was added and the reaction stirred at rt for 20 h. The solvent was removed and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was dried and concentrated to give **9o** as a solid (89 mg, 56%). Mp 138−140 °C. UV 240 (475), 298 (4.34). IR (film) 2936, 1680. ^{1}H-NMR (200 MHz) 2.92 (t, J = 5.7, 2H); 3.95 (s, 3H); 3.98 (s, 3H); 4.03 (s, 3H); 4.09 (t, J = 5.7, 2H); 6.69 (s, 1H); 9.08 (s, 1H). ^{13}C-NMR (75 MHz) 34.8 (q); 22.5 (t); 40.7 (t); 61.5 (q); 62.0 (q); 109.0 (s); 120.1 (s); 124.5 (s); 124.6 (d); 126.4 (s); 138.4 (s); 145.3 (s); 162.7 (d). MS (EI) 294 (M^+, 100), 279 (40), 251 (61). HRMS: calcd for $C_{14}H_{15}N_2O_3{}^{35}Cl$ 294.0771, found 294.0775.

6-Chloro-1,3,4,5-tetrahydro-7,8-dimethoxy-1-methylpyrrolo[4,3,2-*de*]quinoline (9p). Hydrolysis of **9o** (50 mg, 0.17 mmol) at reflux with aqueous NaOH (2.5 N) for 24 h was followed by removal of solvent, and then the residue was dissolved in CH_2Cl_2 which was dried and evaporated to give **9p** as a foam (45 mg, 100%). UV 238 (4.56), 286 (3.96), 312 (3.97). IR (film) 3372, 2839. ^{1}H-NMR (200 MHz) 2.98 (t, J = 5.8, 2H); 3.51 (t, J = 5.8, 2H); 3.95 (s, 9H); 4.31 (bs, 1H); 6.55 (s, 1H). ^{13}C-NMR (75 MHz) 22.7 (t); 34.6 (q); 43.2 (t); 61.5 (q); 62.3 (q); 99.8 (s); 109.2 (s); 115.8(s); 121.8 (d); 126.4 (s); 132.8 (s); 133.6 (s); 145.4 (s). MS (EI) 266 (M^+, 100), 251 (72). HRMS: calcd for $C_{13}H_{15}N_2O_2{}^{35}Cl$ 266.0822, found 266.0817.

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Supporting Information Available: ^{1}H NMR spectra for compounds **5a**−**d**, **6a**−**m**,**p**,**q**, **7a**,**c**−**f**, **8a**−**c**, **9b**−**p**, **10a**−**c**, **11a**,**b**, **12a**,**b**,**d**,**e**, and **13**, ^{13}C NMR spectra for compounds **5a**−**d**, **6a**−**h**,**j**−**m**,**p**,**q**, **7a**,**f**, **9e**−**h**,**m**−**p**, **11b**, and **13** (83 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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