Synthetic Studies of the Pyrroloquinoline Nucleus of the Makaluvamine Alkaloids. Synthesis of the Topoisomerase II Inhibitor Makaluvamine D

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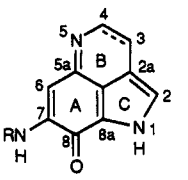
Abstract: A new synthesis of the pyrrolo[4,3,2-*de*]quinoline system characteristic of a class of marine alkaloids which includes the prianosins, discorhabdins, and other antineoplastic agents has been developed. The approach is exemplified in a total synthesis of makaluvamine D, a topoisomerase II inhibitor isolated from the sponge *Zyzzya* cf. *marsailis*. The route begins with a Fischer indole synthesis employing (2,3-dimethoxyphenyl)hydrazine (**29**) and dihydrofuran, and the resulting tryptophol **32** is protected as its ditosylate **34**. Nitration at C4 of the indole, followed by reduction and cyclization, affords the tricycle **41**, which is oxidized to the iminoquinone **42** with ceric ammonium nitrate. Replacement of the C7 methoxy substituent of the pyrroloquinoline by tryptamine could only be effected via the salt **42** and, after cleavage of the *N*-tosyl group followed by treatment with trifluoroacetic acid, gives makaluvamine D (**3**), which was isolated as its trifluoroacetate **48**. Exposure of iminoquinone **42** to sodium azide unexpectedly produced the fully unsaturated pyrroloquinoline **44**.

Introduction

A new class of highly cytotoxic metabolites based on the pyrrolo-[4,3,2-*de*]quinoline skeleton **1** has emerged from screening of marine sources for antineoplastic agents.[1] These include the prianosins,[2] discorhabdins,[3] damirones,[4] batzellines, and isobatzellines,[5] all isolated from sponges, and wakayin, isolated from the Fijian ascidian *Clavelina* sp.[6] Several additional members of the pyrroloiminoquinone family have recently been discovered by Ireland in the Fijian sponge *Zyzzya* cf. *marsailis*.[7] These substances, named makaluvamines, have been found to possess striking and potentially valuable biological properties, including inhibition of the function of mammalian topoisomerase II. They also exhibit potent in vitro cytotoxicity toward the human colon tumor cell line HCT 116. The novel molecular framework represented by these marine alkaloids together with the promising indication of a new lead into cancer chemotherapy has prompted intense interest in the synthesis of these sensitive structures. Thus far, two routes to discorhabdin C (**2**) have been reported,[8] and other novel but as yet incomplete approaches to the prianosin family have been disclosed.[9] Herein, we describe a new route to the pyrroloquinoline nucleus of these marine metabolites and we apply it to the synthesis of makaluvamine D (**3**), a pyrroloiminoquinone bearing a tyramine side chain at C7. Our route employs a novel variant of the Fischer indole synthesis and a subsequent nitration to introduce the N5 nitrogen substituent. The annulation sequence to **3** proceeds in the order A–C–B and in this respect is similar to that utilized by Yamamura[8a] and Kita[8b] in their syntheses of discorhabdin C. Elevation to the oxidation level of the iminoquinone nucleus present in **3** is accomplished with ceric ammonium nitrate.



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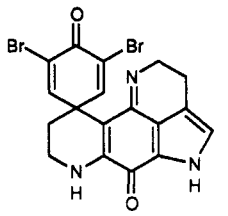

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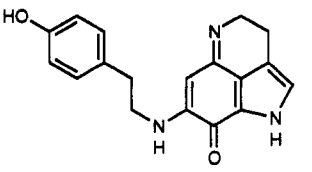

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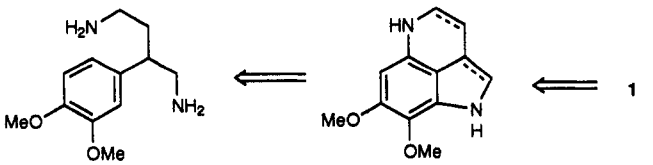
Results and Discussion

The strategy initially explored for construction of the tricyclic system of **3** envisioned simultaneous closure of rings B and C by



4 **5**

* Abstract published in *Advance ACS Abstracts*, February 1, 1994.

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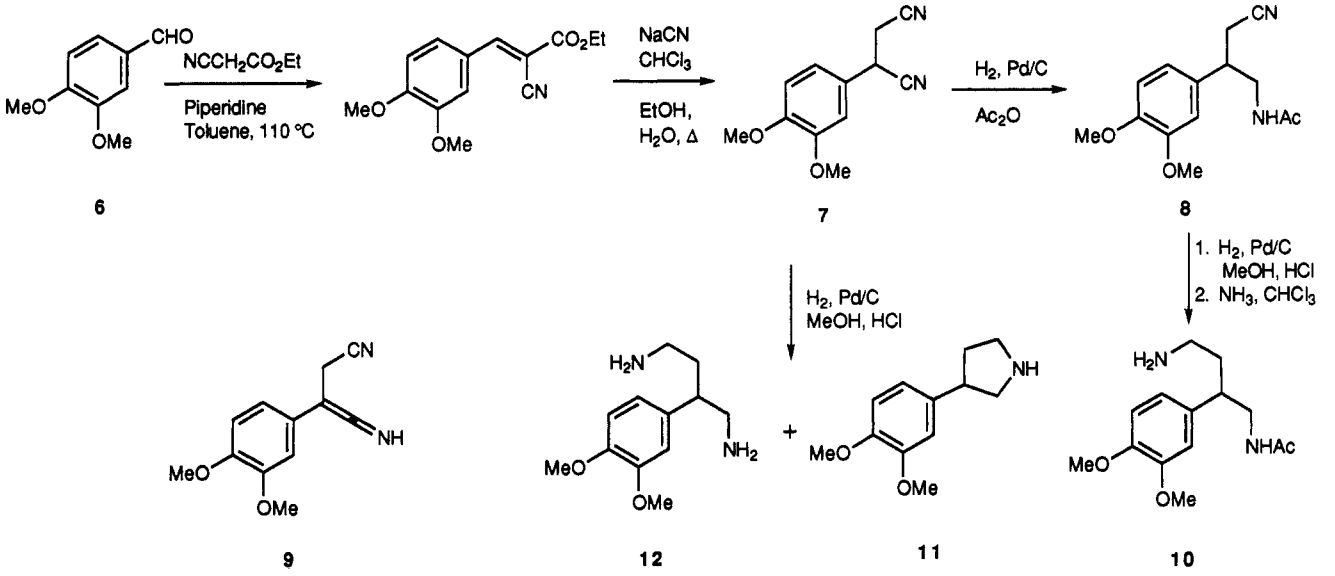
Scheme 1

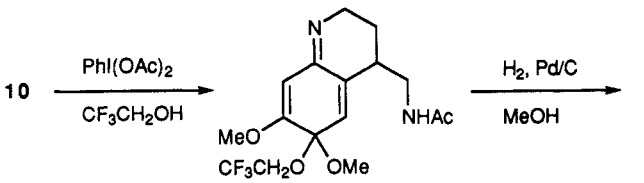


6 7 8 9 12 11 10

double cyclization of an aromatic diamine such as **4**. The feasibility of this approach clearly hinged upon several delicate maneuvers which included oxidation, but not overoxidation, of the two amino functions. Also, the correct orientation of electrophilic attack on the activated benzene nucleus was required to produce the desired substitution pattern of **5**. Although this plan was not successful, it did afford a novel entry into certain quinoline derivatives.

The requisite 2-aryl-1,4-diaminobutane **4** was synthesized from 3,4-dimethoxybenzaldehyde (**6**), via the succinonitrile **7**. The latter was obtained by the method of Crider,[10] in which Knoevenagel condensation of **6** with ethyl cyanoacetate is followed by simultaneous hydrocyanation and decarboxylation. Hydrogenation of **7** over a palladium catalyst in acetic acid resulted in a surprisingly selective reduction of the benzylic cyano function to give the monoamide **8** in 76% yield. A minor product (10%) isolated from the reduction–acetylation proved to be the diamide. It is probable that the selectivity observed in the hydrogenation of **7** has its origin in the greater ease of tautomerization of the benzylic nitrile to ketenimine **9**. Further hydrogenation of **8**, in this instance using methanolic HCl as the solvent, furnished **10** in excellent yield. However, when hydrogenation of **7** was carried out in this solvent system, the 3-arylpyrrolidine **11** was the principal product, accompanied by the diamine **12**. Thus, although controlled saturation of both nitrile groups of **7** required two steps, it did permit convenient differentiation of the resultant amino functions. (See Scheme 1.)

Of several methods explored for oxidative cyclization of **10** and **12**, iodobenzene diacetate in 2,2,2-trifluoroethanol[11] appeared to be the most promising. In fact, **10** was found to undergo smooth oxidative cyclization with this system to yield **13**, in which solvent had entered the product to afford a stereoisomeric mixture of iminoquinone acetals.[12] The ^{19}F-NMR spectrum (triplet, J_{FH} 9 Hz) and mass spectrum, which showed loss of the 2,2,2-trifluoroethoxy substituent (m/z 264), permitted confident assignment of structure to this material. The structure of **13** was further supported by hydrogenation to the tetrahydroquinoline **14**. The latter upon treatment with *p*-toluenesulfonyl chloride afforded a crystalline sulfonamide **15**, whose constitution was fully confirmed by X-ray analysis.



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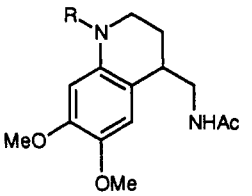

14, R = H
15, R = Ts

In the hope that **14** could be induced to cyclize to the tricyclic nucleus **1**, it is oxidized with ceric ammonium nitrate (CAN) to the unstable iminoquinone **16**. However, upon exposure to basic reagents such as sodium hydride which were intended to promote intramolecular nucleophilic addition of the acetamide anion to the iminoquinone, only the quinoline **18** was obtained. The latter is believed to arise by formation of the enolate **17** and subsequent dehydrogenative aromatization. An alternative strategy designed to enhance the acidity of the side chain amide proton via a sulfonamide was briefly explored from **19**, the product of acidic hydrolysis of **14**. Unfortunately, sulfonation of **19** was not selective, delivering both the monobenzenesulfonamides **20** and **21** as well as the bis derivative **22**. Furthermore, although **20** underwent efficient oxidation with CAN to an iminoquinone analogous to **16**, the outcome upon treatment of this species with base was again formation of a quinoline, in this instance **23**. (See Scheme 2.) Finally, in a move intended to enhance the electrophilicity of the iminoquinone system by quaternization at the nitrogen atom, **16** was reacted with methyl chloroformate. Although activation occurred to form transiently **24**, the result was the chloro-substituted tetrahydroquinoline **25** rather than cyclization to a pyrroloquinoline.

Our failure to effect closure to the five-membered ring C present in the core structure of **3** forced reconsideration of a strategy based on this A–B–C approach. The alternative sequence in which the pyrroloquinoline system was elaborated from an indole nucleus seemed initially unattractive since the required 3-alkyl-

(10) Crider, A. M.; Hemdi, T. F.; Hassan, M. N.; Fahn, S. *J. Pharm. Sci.* **1984**, *73*, 1585.
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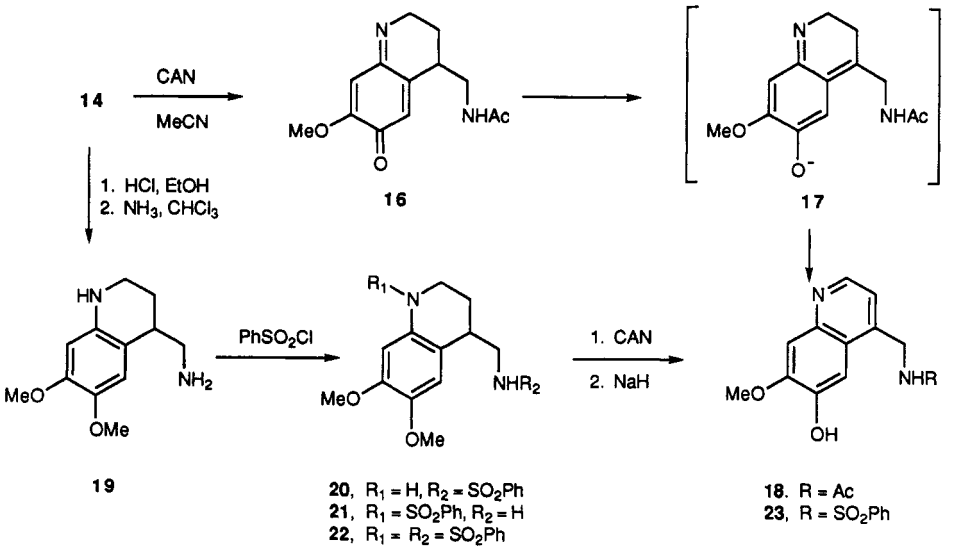
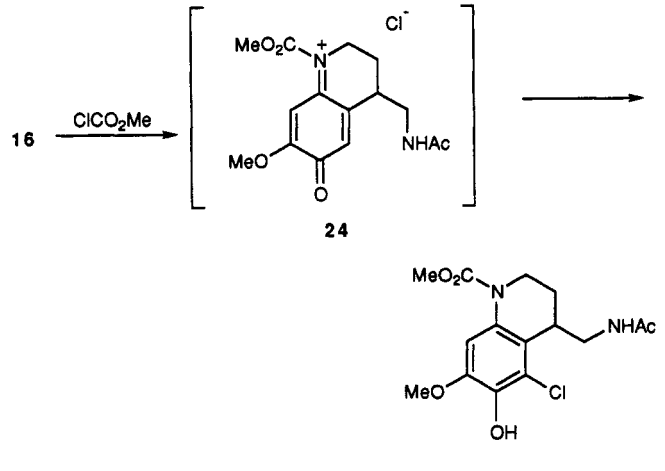
Scheme 2



6,7-dimethoxyindole precursor appeared to be relatively inaccessible. In fact, although both the Yamamura[8a] and Kita[8b] syntheses of discorhabdin C (**2**) used this A–C–B route, their pathways required considerable functional group manipulation in order to set the stage for closure to the tricyclic nucleus. On the other hand, a Fischer indolization which simultaneously installed a two-carbon side chain[13] would obviate the need for lengthy synthetic maneuvers at the indole 3-position and could lead in reasonably direct fashion to a precursor for cyclization to **3**. This tactic therefore became the focal point of our plan.



The starting point for this route to **1** was 2,3-dimethoxybenzoic acid (**26**) which was converted to urethane **27** in quantitative yield using Yamada's modification[14] of the Curtius rearrangement.[15] Basic hydrolysis of **27** afforded 2,3-dimethoxyaniline (**28**) in 95% yield. The latter was nitrosated, and the crude diazonium salt was reduced with stannous chloride to afford crystalline (3,4-dimethoxyphenyl)hydrazine (**29**).[16] This hydrazine was condensed with dihydrofuran following a protocol developed by McKittrick[17] and produced a 1:1 mixture of the tetrahydrofuran **30** and the hydrazone **31**, the latter as an E/Z mixture. The mixture was subjected to Fischer indolization conditions with zinc chloride to yield the expected tryptophol **32** accompanied by the 4-methoxyindole derivative **33**. The latter, which is the result of the so-called "abnormal Fischer indolization"[18] from ipso substitution was always a byproduct even though many variations of the Fischer synthesis were explored with the mixture of **30** and **31**. The removal of **33** from the desired product **32** proved difficult, and to avoid losses during purification, the mixture of **32** and **33** was directly sulfonated with excess *p*-toluenesulfonyl chloride. The bis sulfonyl derivative **34** was produced in good yield and after separation from **35** was readily converted to azide **36**. Reduction of **36** with triphenylphosphine[19] afforded the tryptamine derivative **37**, which, it was hoped, would undergo oxidative cyclization to the tricyclic pyrroloquinoline nucleus **1**. However, treatment of **37** with iodobenzene diacetate as well as other mild oxidants resulted in intractable tars. (See Scheme 3.)

The disappointing outcome with **37** necessitated revision of the planned route to **3** which, while preserving the A–C–B ring construction sequence, closed the tricyclic system at C4–N5 rather than at C5a of the aromatic ring. This new strategy therefore required introduction of a nitro substituent at C4 of the indole nucleus,[20] a transformation which was achieved by treating **34** with acetyl nitrate[21] in the presence of acetic anhydride at low temperature. Although this reaction gave a ca. 1:1 mixture of the 4-nitroindole **38** and its 2-nitro isomer **39**, these substances were separable by chromatography. They were easily distinguished by means of their ^{1}H-NMR spectra, **38** displaying isolated (singlet) proton signals whereas **39** had ortho coupled benzenoid protons. The site of nitration in **38** was further confirmed by locating the single benzenoid proton at C5 through a 5% nuclear Overhauser enhancement with the adjacent methoxy protons. Competing nitration at C2 of the indole nucleus was unexpected with **34**, where a highly activated benzenoid ring is present, but careful analysis of the progress of the reaction showed that **38** and **39** were formed at comparable rates under all nitration conditions investigated and that no selectivity was possible. The nitro group of **38** was cleanly reduced to an amine by hydrogenation over Adams' catalyst, but due to the air-sensitive nature of the aminoindole **40**, the latter was treated immediately with

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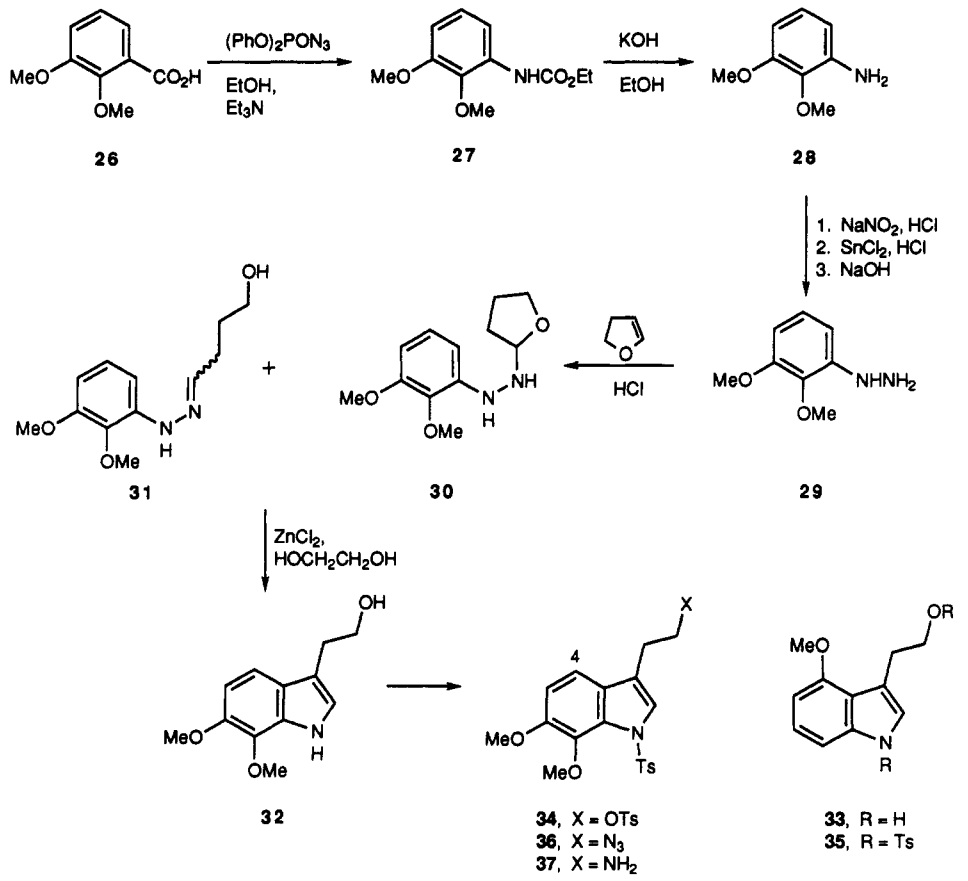
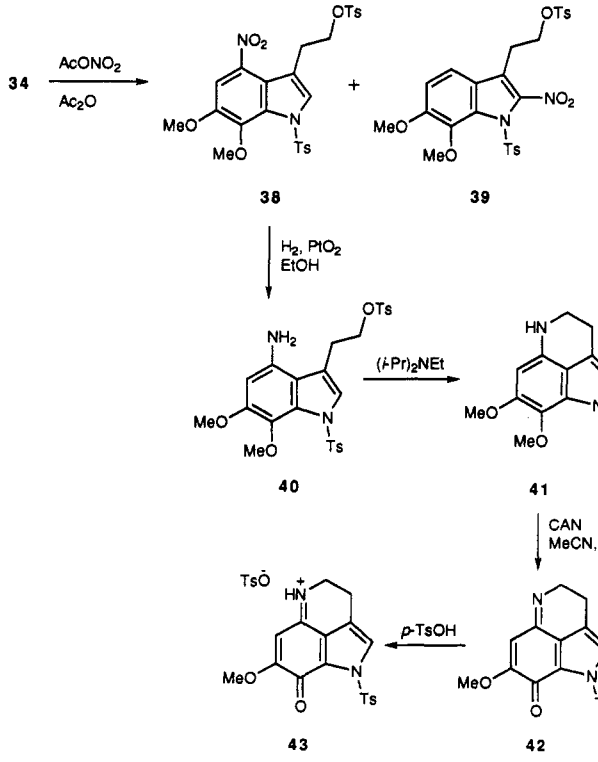
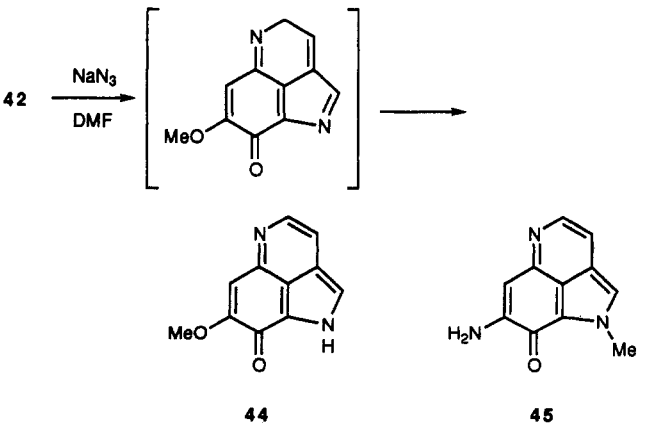
Scheme 3



N,*N*-diisopropylethylamine to give the desired tricycle **41** in 85% yield based on **38**.

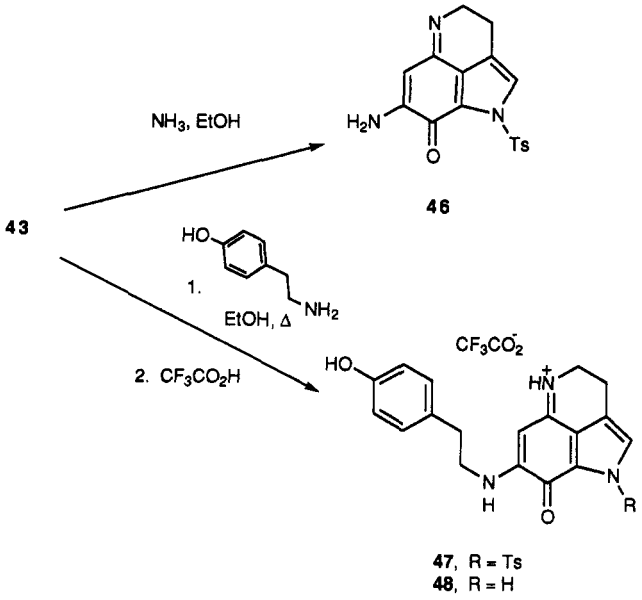


With the indole nucleus of **41** protected as its *N*-tosyl derivative, oxidation of the electron-rich para-disubstituted benzenoid ring to a quinonoid system was expected to be facile. In fact, a similar conversion was effected in Yamamura's synthesis of discorhabdin C,[8a] although the product was not characterized. In the event, oxidation of **41** with ceric ammonium nitrate proceeded smoothly to give the yellow iminoquinone **42** in 60% yield. This substance is a presumed (but unisolated) intermediate in Kita's synthesis of discorhabdin C,[8b] and the acquisition of **42**, which in our hands was sufficiently stable as the free base for characterization, constitutes a formal synthesis of **2**. The stability of **42** is considerably improved as its imine salt, and for this reason it was preserved as its tosylate **43**.



An assumption underlying our approach to **3** was that, with an iminoquinone such as **42**, replacement of the methoxy group at C7 by an amine substituent would be straightforward. Indeed, the published syntheses of **2** not only lent credence to this supposition but gave an explicit protocol for the transformation. It therefore came as a surprise to discover that **42** was inert to ammonia and primary amines, including tyramine, even under forcing conditions. Furthermore, it was found that treatment of

42 with azide, a normally potent nucleophile which was expected to effect substitution at C7, gave the aromatized system **44**, resulting from elimination of the *N*-tosyl residue. Although this unanticipated result affords a potential entry to the fully unsaturated pyrroloquinoline nucleus found, for example, in makaluvamine B (**45**), it blocks access to the broader group of iminoquinones such as **3** which bear an amine substituent at C7. Fortunately, the tosylate **43** was much more cooperative, reacting rapidly with ammoniacal ethanol to furnish **46** in high yield. Condensation of **43** with tyramine was similarly productive, yielding initially **47**. More prolonged exposure to tyramine in refluxing ethanol removed the *N*-tosyl substituent from **47** and led to makaluvamine D (**3**). The latter was isolated and characterized as its trifluoroacetate **48**, which was identical by comparison of its ^1H and ^{13}C NMR spectra, IR spectrum, and mass spectrum with a sample of natural makaluvamine D trifluoroacetate supplied by Professor Ireland.



47, R = Ts
48, R = H

In summary, a new route to the pyrroloiminoquinone system **1** characteristic of the makaluvamines and related marine alkaloids has been opened. The synthesis of makaluvamine D (**3**) required eight steps from the known hydrazine **29**.[16] An important finding from this study is that the nitrogen atom of the iminoquinone moiety must be protonated for substitution of a methoxy group at C7 by an amine to take place.

Experimental Section

Solvents were purified and dried prior to use by distillation from an appropriate drying agent. Tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl under an argon atmosphere. Methylene chloride, pyridine, and triethylamine were distilled from calcium hydride under an argon atmosphere. Bulk solvents for chromatography were distilled through glass prior to use. Starting materials were obtained from commercial sources and, unless stated otherwise, used without further purification.

Solvents were removed at water aspirator pressure by rotary evaporation, and residual solvent was removed by vacuum pump at less than 1.0 Torr. Glassware and syringes were dried in an oven at 165 °C overnight and cooled in a desiccator over $CaSO_4$ prior to use. Alternatively, flasks were flame-dried under a stream of argon.

Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm). Flash chromatography was performed with E. Merck silica gel 60 (230–400 mesh ASTM). Radial chromatography was carried out on individually prepared rotors with layer thicknesses of 1, 2, or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, CA.

Melting points were determined using a Büchi melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet Model 5DXB FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM300 or AM400 spectrometer; chemical shifts are expressed as parts per million downfield from tetramethylsilane. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were determined on a Kratos MS-50 spectrometer. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

4-Acetamido-3-(3,4-dimethoxyphenyl)butyronitrile (8). To a Parr reaction vessel were added **7**[10] (235 mg, 1.1 mmol), acetic anhydride (9 mL), sodium acetate (89 mg, 1.1 mmol) and 10% palladium on carbon (125 mg). The mixture was shaken under hydrogen at 46 psi at 25 °C for 6 h, after which TLC indicated complete reaction. The catalyst was removed by filtration over Celite, and the mixture was concentrated under reduced pressure. Chromatography (silica gel 60, ethyl acetate–methanol–chloroform 1:1:8) gave 218 mg (76%) of **8** as an oily wax: IR (neat) 3369, 3296, 2944, 2246, 1655, 1516, 1270, 1137, 1031 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8 Hz, 1H), 6.81 (d, J = 2 Hz, 1H), 6.77 (dd, J = 2, 7 Hz, 1H), 5.81 (bt, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.73 (m, 1H), 3.39 (m, 1H), 3.18 (m, 1H), 2.66 (m, 2H), 1.95 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 149.2, 148.5, 131.4, 119.2, 118.2, 111.5, 110.3, 55.9, 55.8, 43.5, 41.4, 23.0, 22.3; MS m/z 262 (M^+), 203 (100), 190 (54), 175 (14), 91 (8), 72 (26); HRMS m/z obsd 262.1317 (M^+), calcd for $C_{14}H_{18}N_2O_3$ 262.1317.

Further elution gave 34 mg (10%) of (±)-1,4-di-*N*-acetyl-2-(3,4-dimethoxyphenyl)-1,4-diaminobutane as a colorless wax: IR (KBr) 3329, 2964, 1649, 1629, 1529, 1246, 1144, 1025 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 8 Hz, 1H), 6.71 (d, J = 2 Hz, 1H), 6.69 (s, 1H), 6.28 (bt, 1H), 6.02 (bt, 1H), 3.87 (3, 3H), 3.86 (s, 3H), 3.63 (m, 1H), 3.16 (m, 3H), 2.75 (m, 1H), 1.92 (s, 3H), 1.91 (s, 3H), 1.77 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 149.1, 147.9, 134.4, 119.5, 111.3, 110.4, 55.9, 55.8, 44.9, 43.1, 37.8, 33.2, 23.2(2); MS m/z 308 (M^+), 249 (81), 190 (69), 177 (100); HRMS m/z obsd 308.1736 (M^+), calcd for $C_{16}H_{24}N_2O_4$ 308.1736.

1-Acetamido-4-amino-2-(3,4-dimethoxyphenyl)butane (10). A mixture of **8** (1.0 g, 3.8 mmol), absolute methanol (38 mL), concentrated hydrochloric acid (0.6 mL), and 10% palladium on carbon (0.5 g) was stirred under a hydrogen atmosphere at 25 °C for 20 h. The mixture was filtered over Celite, and the solvent was removed at reduced pressure to give 1.1 g (96%) of the hydrochloride salt of **10**. This was suspended in chloroform, cooled to 0 °C, and treated with excess 1% ammoniacal chloroform. The precipitated ammonium chloride was removed by filtration. Chromatography of the concentrate (silica gel 60, 20% methanol in 1% ammoniacal chloroform) afforded 0.89 g (89%) of **10** as a colorless oil: IR (neat) 3296, 2931, 1649, 1516, 1264, 1025 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 8 Hz, 1H), 6.72 (dd, J = 2, 8 Hz, 1H), 6.68 (d, J = 2 Hz, 1H), 5.59 (bt, 1H), 3.87 (s, 6H), 3.69 (m, 1H), 3.17 (m, 1H), 2.81 (m, 1H), 2.61 (m, 2H), 1.88 (s, 3H), 1.73 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.9, 149.1, 147.8, 134.7, 119.6, 111.3, 110.4, 55.8(2 OMe), 45.1, 42.9, 39.9, 37.5, 23.2; MS m/z 266 (M^+), 207 (100), 178 (87), 165 (49), 91 (29), 77 (27), 73 (53); HRMS m/z obsd 266.1630 (M^+), calcd for $C_{14}H_{22}N_2O_3$ 266.1630. Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.14; H, 8.51; N, 9.85. Found: C, 59.05; H, 8.24; N, 9.57.

1,4-Diamino-2-(3,4-dimethoxyphenyl)butane (12). A suspension of **7** (100 mg, 0.46 mmol) and 10% palladium on carbon (50 mg) in methanol was treated with concentrated hydrochloric acid (155 μL, 2 mmol) and stirred under an atmosphere of hydrogen for 22 h. The catalyst was removed by filtration over Celite, and the solvent was evaporated in vacuo. The solid residue was treated with 1% ammoniacal chloroform at 0 °C, and the ammonium chloride was removed by filtration. Chromatography of the concentrate (silica gel 60, 20% methanol in 1% ammoniacal chloroform) yielded 24.4 mg (24%) of **12** as a colorless oil: IR (neat) 3356 (b), 2937, 1589, 1516, 1264, 1144, 1031 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 8 Hz, 1H), 6.74 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.88 (m, 2H), 2.64 (m, 3H), 2.31 (bs, 4H), 1.82 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 149.1, 147.8, 134.4, 119.6, 111.4, 110.5, 55.8 (2), 48.2, 45.8, 39.1, 35.7; MS m/z 224 (M^+), 207 (13), 195 (82), 178 (100), 152 (22); HRMS m/z obsd 224.1525 (M^+), calcd for $C_{12}H_{20}N_2O_2$ 224.1525. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.09; H, 9.10; N, 12.22.

There was also obtained 41.5 mg (44%) of (±)-3-(3,4-dimethoxyphenyl)pyrrolidine (**11**) as a colorless oil: IR (neat) 3402 (b), 2950, 1520, 1423, 1257, 1144, 1025 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 6.80 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.36 (dd, J = 8 Hz, 1H), 3.11 (m, 3H), 3.00 (bs, 1H), 2.85 (dd, J = 8 Hz, 1H), 2.23 (m, 1H), 1.85 (m, 1H);

^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.8, 147.3, 136.4, 118.8, 111.1, 110.5, 55.8, 55.7, 54.9, 47.1, 45.1, 34.4; MS *m/z* 207 (M^+, 100), 178 (26), 165 (21), 164 (36), 147 (30); HRMS *m/z* obsd 207.1259 (M^+), calcd for $C_{12}H_{17}NO_2$ 207.1259.

4-(Acetamidomethyl)-6,7-dimethoxy-6-(2,2,2-trifluoroethoxy)-2,3,4,6-tetrahydroquinoline (13). A solution of **10** (43 mg, 0.16 mmol) in 2,2,2-trifluoroethanol (2.5 mL) was treated with iodobenzene diacetate (103 mg, 0.32 mmol), and the solution was stirred at 25 °C under argon for 23 h. The mixture was concentrated, and the residue was purified by chromatography (silica gel 60, ethyl acetate–methanol–chloroform 1.5:1.5:7) to yield 42.0 mg (72%) of **13** as an unstable, waxy solid: IR (neat) 3289, 2937, 1656, 1630, 1284, 1210, 1164 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, diastereomeric mixture) δ 5.95, 5.90 (d, 1H), 5.87 (s, 1H), 3.99 (m, 2H), 3.84 (m, 2H), 3.78 (s, 3H), 3.40 (m, 1H), 3.30 (s, 3H), 2.75 (m, 1H), 2.01 (s, 3H), 1.90 (m, 1H), 1.69 (m, 1H); ^{19}F-NMR (280 MHz, $CDCl_3$) δ −6.45 (t, *J* = 9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$, diastereomeric mixture) δ 174.8, 170.6, 170.4, 159.5, 159.4, 157.5, 131.6, 131.2, 129.4, 129.0, 121.9, 103.3, 94.8, 94.7, 61.7, 61.6, 61.3, 55.6, 51.5, 51.4, 46.5, 46.3, 41.5, 41.1, 35.6, 35.2, 24.7, 23.2, 23.0, 21.5; MS *m/z* 332 (–OMe), 264 (–OCH_2CF_3, 56), 260 (73), 217 (32), 205 (32), 192 (100).

4-(Acetamidomethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (14). A mixture of **13** (85 mg, 0.23 mmol) and 10% palladium on carbon (45 mg) in absolute methanol (1.5 mL) was stirred for 6 h at 25 °C under a hydrogen atmosphere. The catalyst was removed by filtration over Celite, and the concentrate was purified by chromatography (silica gel 60, ethyl acetate–methanol–chloroform 1:1:8) to give 45.0 mg (73%) of **14** as a waxy solid: IR (neat) 3355, 2930, 1649, 1509, 1370, 1237, 1151, 958, 858, 819 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.11 (s, 1H), 5.60 (bt, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.48 (t, *J* = 6 Hz, 2H), 3.26 (m, 2H), 2.94 (quin, *J* = 6 Hz, 1H), 1.99 (s, 3H), 1.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.3, 148.8, 141.3, 139.1, 113.3, 112.5, 99.5, 56.8, 55.7, 44.5, 38.6, 34.9, 25.1, 23.4; MS *m/z* 264 (M^+), 205 (34), 192 (100), 190 (17), 161 (21); HRMS *m/z* obsd 264.1474 (M^+), calcd for $C_{14}H_{20}N_2O_3$ 264.1474. Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.58; H, 7.61; N, 10.33.

4-(Acetamidomethyl)-6,7-dimethoxy-1-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroquinoline (15). To a solution of **14** (18 mg, 0.07 mmol) in dry pyridine (0.3 mL) at 0 °C was added a solution of *p*-toluenesulfonyl chloride (13 mg, 0.07 mmol) in methylene chloride (0.1 mL) under argon, and the solution was stirred for 15.5 h at 0 °C. The mixture was diluted with chloroform (7 mL) and transferred to ice-cold saturated aqueous sodium bicarbonate (2.5 mL). The aqueous layer was extracted with chloroform (4 × 2.5 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. Removal of the solvent and purification by chromatography (silica gel 60, ethyl acetate–methanol–chloroform 1:1.5:7.5) gave 24.0 mg (84%) of **15** as a tan solid: mp 168 °C; IR (KBr) 3396, 3250, 3077, 2938, 1636, 1511, 1443, 1343, 1271, 1224, 1160, 859, 680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8 Hz, 2H), 7.28 (s, 1H), 7.22 (d, *J* = 2 Hz, 2H), 6.65 (s, 1H), 5.56 (bt, *J* = 6 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (m, 1H), 3.72 (m, 1H), 3.35 (m, 1H), 2.95 (m, 1H), 2.83 (m, 1H), 2.39 (s, 3H), 1.91 (s, 3H), 1.53 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 147.5, 146.8, 143.8, 136.0, 130.0, 129.6 (2 Ar), 127.3 (2 Ar), 122.6, 110.6, 108.7, 55.9, 55.8, 44.4, 44.3, 34.7, 24.1, 23.2, 21.5; MS *m/z* 418 (M^+), 264 (11), 207 (19), 204 (19), 195 (80), 190 (28), 178 (100), 164 (22), 152 (30), 91 (40).

Compound **15** crystallized from 5% aqueous methanol in space group *Pbca* (no. 61) with *a* = 19.929(6) Å, *b* = 23.169(5) Å, *c* = 9.234(4) Å, *z* = 8, and d_{calc} = 1.304 g/cm^3. The intensity data were measured on a Rigaku AFC6R diffractometer (Mo Kα (λ_1 = 0.71069 Å) radiation). Of the 3417 reflections collected, 1587 were considered to be observed [$I > 3.00\sigma(I)$]. The structure was solved by direct methods, and the final discrepancy indices were R = 0.048 and R_w = 0.054.

4-(Acetamidomethyl)-7-methoxy-2,3,4,6-tetrahydroquinolin-6-one (16). To a solution of **14** (13 mg, 0.05 mmol) in acetonitrile (0.3 mL) at 0 °C was added a solution of ceric ammonium nitrate (57 mg, 0.10 mmol) in water (0.1 mL). After 1 h at 0 °C the mixture was diluted with chloroform (1 mL) and carefully treated with saturated aqueous sodium bicarbonate until neutral, and the layers were separated. The aqueous layer was washed with chloroform (7 × 1 mL), and the combined organic extracts were concentrated to give 12.3 mg (~100%) of **16** as a bright yellow oil that was not purified due to its instability: IR (neat) 3309, 1656, 1636, 1556, 1510 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 6.24 (s, 1H), 5.92 (bt, 1H), 4.09 (m, 2H), 3.78 (s, 3H), 3.49 (quin, *J* = 7 Hz, 1H), 3.41 (quin, *J* = 7 Hz, 1H), 2.85 (quin, *J* = 6 Hz, 1H), 2.02 (s, 3H), 1.97 (m, *J* = 6 Hz, 1H), 1.75 (m, *J* = 6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.73 (C=O), 154.3 (C=N).

4-(Acetamidomethyl)-6-hydroxy-7-methoxyquinoline (18). To a solution of **14** (21 mg, 0.08 mmol) in acetonitrile (0.5 mL) at 0 °C was added a solution of ceric ammonium nitrate (177 mg, 0.32 mmol) in water (0.4 mL). The bright yellow mixture was stirred for 2 h, poured into chloroform (3 mL), and treated with saturated aqueous sodium bicarbonate (35 drops) and water (30 drops). The mixture was extracted with chloroform (4 × 5 mL), and the combined organic washings were passed through a plug of anhydrous sodium sulfate. Removal of the solvent gave 20 mg of a 2:1 mixture of **18** and **16**. The crude material was dissolved in chloroform (2.5 mL) and was stirred under an atmosphere of oxygen for 18 h. Concentration and purification by radial chromatography (Chromatotron, 1-mm rotor, 20% methanol–chloroform) afforded 18 mg (90%) of **18** as a wax: IR (KBr) 3283, 2930, 1649, 1516, 1483, 1264, 1032, 852 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD) δ 8.49 (d, *J* = 5 Hz, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 5 Hz, 1H), 4.70 (s, 2H), 3.99 (s, 3H), 2.04 (s, 3H); ^{13}C-NMR (75 MHz, CD_3OD) δ 173.4, 153.4, 149.2, 147.7, 145.3, 144.1, 123.9, 118.8, 107.8, 105.8, 56.4, 41.2, 22.5; MS *m/z* 246 (M^+, 96), 203 (67), 176 (100); HRMS *m/z* obsd 246.1004 (M^+), calcd for $C_{13}H_{14}N_2O_3$ 246.1004. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.52; H, 5.60; N, 11.11.

4-(Aminomethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (19). A mixture of **14** (20 mg, 0.076 mmol) in ethanol (2 mL) and 3 M aqueous hydrochloric acid (3 mL) was heated to reflux for 17 h and concentrated. The residue was suspended in chloroform (2 mL) and was treated with an excess of 1% ammoniacal chloroform at 0 °C. The resulting ammonium chloride was removed by filtration, and the concentrate was purified by chromatography (silica gel 60, 5% methanol in 1% ammoniacal chloroform) to afford 13 mg (78%) of **107** as a tan oil: IR (neat) 3369, 2931, 2851, 1616, 1514, 1463, 1230, 1138, 1031, 859 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.10 (s, 1H), 3.78 (s, 6H), 3.22 (m, 2H), 2.89 (m, 2H), 2.69 (m, 1H), 1.93 (m, 2H), 1.25 (bs, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.5, 141.2, 138.9, 113.9, 113.5, 99.4, 56.8, 55.7, 47.7, 38.7, 38.3, 24.7; MS *m/z* 222 (M^+), 192 (100), 161 (20), 160 (17); HRMS *m/z* obsd 222.1368 (M^+), calcd for $C_{12}H_{18}N_2O_2$ 222.1368.

Sulfonation of 19. To a solution of **19** (19 mg, 0.08 mmol) in dry pyridine (0.3 mL) at 0 °C under argon was added a solution of benzenesulfonyl chloride (14 mg, 0.08 mmol) in dry methylene chloride (0.1 mL) during 20 min, and the solution was stirred for 24 h. The mixture was concentrated and purified by chromatography (silica gel 60, 10% methanol–ammoniacal chloroform) to afford 4.3 mg (15%) of **20** as a foam: IR (neat) 3276, 2931, 2851, 1616, 1516, 1450, 1323, 1158, 726 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 (m, *J* = 1, 2, 7 Hz, 2H), 7.54 (m, 3H), 6.44 (s, 1H), 6.07 (s, 1H), 4.60 (bt, *J* = 6 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.15 (m, 4H), 2.87 (bm, 1H), 1.91 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 149.2, 141.4, 139.9, 139.3, 132.6, 129.2 (2), 126.9 (2), 113.2, 111.3, 99.5, 56.8, 55.7, 48.1, 38.3, 35.0, 24.6; MS *m/z* 362 (M^+), 192 (100), 161 (7); HRMS *m/z* obsd 362.1300 (M^+), calcd for $C_{18}H_{22}N_2O_4S$ 362.1300.

There was also obtained 11.5 mg (40%) of (±)-4-(aminomethyl)-1-*N*-(phenylsulfonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (**21**) as a foam: IR (neat) 3389, 2937, 1609, 1509, 1450, 1343, 1164 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.40 (m, 3H), 6.60 (s, 1H), 3.97 (m, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.66 (m, 1H), 2.63 (m, 2H), 2.40 (m, 1H), 1.56 (bm, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.5, 146.9, 139.4, 132.8, 130.1, 128.9 (2), 127.3 (2), 123.3, 110.5, 109.1, 56.0 (2 OMe), 46.8, 44.9, 37.9, 23.9; MS *m/z* 362 (M^+), 204 (16), 192 (100), 190 (69); HRMS *m/z* obsd 362.1300 (M^+), calcd for $C_{18}H_{22}N_2O_4S$ 362.1300.

In addition, a third component of the reaction mixture was obtained as 15.3 mg (39%) of (±)-4-((benzenesulfonamido)methyl)-1-*N*-(phenylsulfonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (**22**): IR (neat) 3283, 2937, 1616, 1513, 1330, 1164 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.55 (m, 6H), 7.40 (m, 4H), 6.46 (s, 1H), 4.25 (bt, *J* = 6 Hz, 1H), 3.89 (s, 3H), 3.82 (m, 1H), 3.77 (s, 3H), 3.66 (m, 1H), 2.89 (m, 1H), 2.69 (m, 2H), 1.47 (m, 2H); MS *m/z* 502 (M^+), 361 (10), 204 (70), 192 (94), 190 (56), 77 (100); HRMS *m/z* obsd 502.1232 (M^+), calcd for $C_{24}H_{26}N_2O_6S$ 502.1232.

***N*-(Ethoxycarbonyl)-3,4-dimethoxyaniline (27).** To a solution of **26** (5.35 g, 29.4 mmol) in dry tetrahydrofuran (100 mL) under argon were added diphenylphosphoryl azide (9.7 g, 35.2 mmol), absolute ethanol (13.5 g, 0.3 mol), and dry triethylamine (3.57 g, 35.2 mmol). The mixture was stirred for 1.5 h at 60 °C, cooled to ambient temperature, diluted with ethyl acetate (300 mL), and washed with saturated aqueous sodium

bicarbonate (4 × 50 mL), water (3 × 50 mL), and saturated aqueous sodium chloride (3 × 20 mL). The organic layer was separated and was dried over anhydrous sodium sulfate. The concentrate was purified by chromatography (silica gel 60, 60% ether–hexane) to give 6.23 g (94%) of **27** as colorless crystals: mp 47.0–48.0 °C (ether–hexane); IR (neat) 3429, 1736, 1602, 1530, 1231, 1052, 779 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8 Hz, 1H), 7.26 (s, 1H), 7.02 (t, J = 8 Hz, 1H), 6.62 (dd, J = 1, 8 Hz, 1H), 4.24 (q, J = 7 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.33 (t, J = 7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 153.5, 152.0, 136.9, 132.2, 124.2, 110.9, 106.4, 61.1, 60.6, 55.8, 14.5; MS m/z 225 (M^+, 100), 138 (28), 95 (10), 92 (15); HRMS m/z obsd 225.1001 (M^+), calcd for $C_{11}H_{15}NO_4$ 225.1001.

2,3-Dimethoxyaniline (28). To a suspension of powdered potassium hydroxide (2.81 g, 50 mmol) in absolute ethanol (25 mL) was added **27** (1.13 g, 5 mmol). The mixture was refluxed for 4 h, cooled to room temperature, concentrated, and diluted with diethyl ether (50 mL). The ethereal solution was washed with saturated aqueous sodium chloride (3 × 25 mL) and dried over anhydrous sodium sulfate. Removal of the solvent afforded 0.73 g (95%) of **28** as an orange oil that was homogeneous by ^{1}H- and ^{13}C-NMR: IR (neat) 3467, 3370, 2937, 1617, 1496, 1317, 1271, 1131, 1005, 785 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.84 (t, J = 8 Hz, 1H), 6.38 (dd, J = 1, 8 Hz, 1H), 6.33 (dd, J = 1, 8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.83 (bs, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.9, 140.6, 135.6, 124.1, 108.7, 102.2, 59.7, 55.6; MS m/z 153 (M^+, 100), 138 (14), 95 (32), 84 (41); HRMS m/z obsd 153.0790 (M^+), calcd for $C_8H_{11}NO_2$ 153.0790.

(2,3-Dimethoxyphenyl)hydrazine (29). To a solution of **28** (3.8 g, 24.8 mmol) in 6 M aqueous hydrochloric acid (10 mL) at 0 °C was added a solution of sodium nitrite (1.9 g, 28.7 mmol) in water (5.4 mL) during 30 min, and the yellow mixture was stirred for 1.5 h. To this mixture was added dropwise a solution of stannous chloride (33.0 g, 146 mmol) in concentrated hydrochloric acid (30.0 mL) during 2 h. After stirring for 1 h the mixture was poured into 10 M aqueous sodium hydroxide (80 mL) at 0 °C, and the solids were filtered and washed with benzene (5 × 50 mL). The gray solid residue was suspended in water (30 mL) and extracted with diethyl ether (5 × 100 mL), and the combined benzene and diethyl ether extracts were dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave the crude product, which was recrystallized from diethyl ether to yield 3.05 g (73%) of **29** as a pale yellow solid: mp 78–81 °C (lit.[16] 78–82 °C); IR (neat) 3335, 2937, 1603, 1503, 1477, 1264, 772 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.00 (t, J = 8 Hz, 1H), 6.65 (dd, J = 1, 8 Hz, 1H), 6.43 (dd, J = 1, 8 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.3, 145.3, 134.8, 124.4, 140.5, 103.0, 60.0, 55.8; MS m/z 168 (M^+), 153 (33), 138 (100), 95 (63).

Condensation of 29 with Dihydrofuran. A stream of hydrogen chloride gas was bubbled through a solution of **29** (1.50 g, 8.9 mmol) in absolute methanol (20 mL) at 0 °C for 1 min, and the solution was concentrated. The residual hydrochloride salt was taken up in tetrahydrofuran (22 mL) and water (2.2 mL) at 0 °C and to this solution was added dropwise 2,3-dihydrofuran (0.81 mL, 10.7 mmol). After stirring for 18 h at 4 °C the mixture was cooled to 0 °C and diluted with diethyl ether (40 mL). The layers were separated, and the yellow organic layer was washed with saturated aqueous sodium chloride (1 × 5 mL) and dried over anhydrous magnesium sulfate. Concentration of the solution followed by chromatography (silica gel 60, 5% methanol–chloroform) gave 1.80 g (85%) of an approximately 1:1 mixture of **30** and **31** as an amber-colored oil. The following spectral data is for a homogeneous sample of **30** obtained by collection of the more highly retained chromatographic fractions: IR (neat) 3329, 2937, 1603, 1476, 1264, 1125, 773, 732 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 5 Hz, 1H), 6.98 (m, 2H), 6.40 (dd, J = 1, 8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.72 (t, J = 6 Hz, 2H), 2.41 (td, J = 5, 7 Hz, 2H), 1.84 (quin, J = 7 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.4, 141.8, 139.1, 133.5, 124.6, 106.1, 102.8, 62.3, 60.2, 55.7, 29.4, 28.9; MS m/z 238 (M^+), 168 (10), 153 (10), 138 (55), 95 (33), 77 (100); HRMS m/z obsd 238.1317 (M^+), calcd for $C_{12}H_{18}N_2O_3$ 238.1317.

3-(2-Hydroxyethyl)-6,7-dimethoxyindole (32) and 3-(2-Hydroxyethyl)-4-methoxyindole (33). A mixture of **30** and **31** (2.24 g, 8.3 mmol) and anhydrous zinc chloride (2.6 g, 19.1 mmol) in ethylene glycol (30 mL) was degassed by evacuating the flask and back-filling with argon (3×). The suspension was stirred at 160 °C for 1.5 h. The dark red mixture was poured onto a mixture of ice (30 mL) and 10% hydrochloric acid (20 mL) and was stirred for 15 min. The resulting brown solution was extracted with ether (3 × 20 mL) and ethyl acetate (3 × 20 mL). The combined organic layers were washed with 10% hydrochloric acid (2 × 20 mL) and saturated aqueous sodium chloride (2 × 20 mL) and dried over anhydrous magnesium sulfate. Concentration of the solution and chromatography (silica gel 60, 80% ether–hexane) gave 586 mg (32%) of an approximately 1.7:1 mixture of **32** and **33** as an oil. The following spectral data is for a homogeneous sample of **32** obtained by collection of the more highly retained chromatographic fractions: IR (neat) 3409, 2937, 1629, 1510, 1257, 1091, 1038, 792 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (bs, 1H), 7.25 (d, J = 9 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 6.85 (d, J = 9 Hz, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.89 (t, J = 6 Hz, 2H), 3.98 (td, J = 2, 6 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.2, 134.5, 131.0, 124.2, 122.8, 113.7, 112.5, 108.2, 62.5, 60.8, 57.4, 28.8; MS m/z 221 (M^+), 206 (12), 190 (68), 160 (100); HRMS m/z obsd 221.1052 (M^+), calcd for $C_{12}H_{15}NO_3$ 221.1052.

A solution of **32** and **33** (459 mg, 2.2 mmol) and *p*-toluenesulfonyl chloride (1.7 g, 8.9 mmol) in dry tetrahydrofuran (3 mL) under argon was cooled to 0 °C, treated with sodium hydride (895 mg, 22.1 mmol, 60% dispersion in mineral oil), and slowly warmed to ambient temperature during 5 days. The mixture was diluted with diethyl ether (5 mL) and water (1 mL), and the aqueous layer was extracted with diethyl ether (6 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (2 × 5 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent and chromatography of the residual oil (silica gel 60, 60% ether–hexane) gave 689 mg (58%) of a mixture of **34** and the tosylate of **33** as an oil. Further purification of the mixture gave pure **34** as a waxy solid: IR (neat) 2937, 1596, 1503, 1357, 1177, 1091, 905, 812 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 7.46 (t, J = 1 Hz, 1H), 7.23 (m, 4H), 7.03 (d, J = 9 Hz, 1H), 6.85 (d, J = 9 Hz, 1H), 4.26 (t, J = 7 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.01 (td, J = 1, 7 Hz, 2H), 2.41 (s, 3H), 2.35 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.7, 144.8, 144.2, 136.7, 132.6, 129.7 (2), 129.5 (2), 128.6, 127.7 (2), 127.3 (2), 127.0, 126.4, 125.8, 114.8, 113.6, 109.8, 68.9, 60.5, 56.6, 24.8, 21.5 (2); MS m/z 529 (M^+), 331 (13), 246 (12), 202 (54), 138 (29), 91 (100); HRMS m/z obsd 529.1228 (M^+), calcd for $C_{26}H_{27}NO_7S_2$ 529.1228. Anal. Calcd for $C_{26}H_{27}NO_7S_2$: C, 58.96; H, 5.14; N, 2.64. Found: C, 58.99; H, 5.30; N, 2.45.

In addition, pure **35** was isolated as a waxy solid: IR (neat) 2950, 1596, 1503, 1363, 1177, 978, 898, 819 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H), 7.21 (d, J = 1 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 2H), 6.50 (d, J = 8 Hz, 1H), 4.27 (t, J = 6 Hz, 2H), 3.72 (s, 3H), 3.07 (td, J = 1, 6 Hz, 2H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 153.9, 144.9, 144.4, 136.7, 135.1, 132.5, 129.9 (2), 129.4 (2), 127.5 (2), 126.2 (2), 125.5, 123.3, 119.5, 117.0, 106.6, 103.4, 69.8, 55.1, 26.8, 21.5 (2); MS m/z 499 (M^+), 327 (23), 172 (100), 91 (81); HRMS m/z obsd 499.1123 (M^+), calcd for $C_{25}H_{25}NO_6S_2$ 499.1123.

1-*N*-(*p*-Tolylsulfonyl)-3-(2-azidoethyl)-6,7-dimethoxyindole (36). A mixture of **34** (55 mg, 0.104 mmol) and sodium azide (136 mg, 2.08 mmol) in dry *N*,*N*-dimethylformamide (0.5 mL) was stirred at 50 °C for 45 min under argon. The mixture was diluted with diethyl ether (20 mL) and filtered through Celite. The filtrate was washed with water (3 × 3 mL) and saturated aqueous sodium chloride (1 × 3 mL) and dried over anhydrous magnesium sulfate. Concentration followed by chromatography of the residual oil (silica gel 60, 40% ethyl acetate–hexane) afforded 34 mg (82%) of **36** as a glass: IR (film) 2938, 2100, 1603, 1503, 1357, 1257, 1091, 806 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8 Hz, 2H), 7.59 (s, 1H), 7.22 (d, J = 8 Hz, 2H), 7.13 (d, J = 9 Hz, 1H), 6.90 (d, J = 9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.58 (t, J = 7 Hz, 2H), 2.94 (t, J = 7 Hz, 2H), 2.34 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.7, 144.0, 136.8, 136.7, 129.5 (2), 128.8, 127.2 (3), 125.6, 116.4, 113.5, 109.9, 60.5, 56.6, 50.6, 24.7, 21.5; MS m/z 400 (M^+, 100), 245 (44), 189 (78), 160 (72), 129 (30), 91 (84); HRMS m/z obsd 400.1205 (M^+), calcd for $C_{19}H_{20}N_4O_4S$ 400.1205.

1-*N*-(*p*-Tolylsulfonyl)-3-(2-aminoethyl)-6,7-dimethoxyindole (37). To a solution of **36** (33 mg, 0.082 mmol) in tetrahydrofuran (0.5 mL) were added triphenylphosphine (24 mg, 0.091 mmol) and water (2 drops), and the mixture was stirred for 17 h at ambient temperature. Concentration followed by chromatography of the residual oil (silica gel 60, 5% methanol–chloroform to 10% methanol–1% ammoniacal chloroform) gave 27 mg (88%) of **37** as a colorless oil: IR (neat) 3370 (b), 2944, 1596, 1503, 1350, 1257, 1171, 1091, 806 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8 Hz, 2H), 7.75 (s, 1H), 7.21 (d, J = 8 Hz, 2H), 7.15 (d, J = 9 Hz, 1H), 6.87 (d, J = 9 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.05 (t, J = 7 Hz, 2H), 2.83 (t, J = 7 Hz, 2H), 2.34 (s, 3H), 2.21 (bs, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.6, 144.0, 136.8 (2), 129.5 (2), 128.8,

127.6, 127.2 (2), 125.2, 117.7, 113.9, 109.7, 60.5, 56.6, 41.2, 28.6, 21.5; MS m/z 374 (M^+), 190 (100); HRMS m/z obsd 374.1300 (M^+), calcd for $C_{19}H_{22}N_2O_4S$ 374.1300.

1-*N*-(*p*-Tolylsulfonyl)-3-(2-*p*-((tolylsulfonyl)oxy)ethyl)-4-nitro-6,7-dimethoxyindole (38). Acetyl nitrate was prepared by adding 70% aqueous nitric acid (1 mL) to acetic anhydride (6.6 mL) at −10 °C and stirring the mixture for 1 h. A solution of **32** (30 mg, 0.057 mmol) in acetic anhydride (1 mL) was cooled to −45 °C, treated with the acetyl nitrate solution (14 drops), and then warmed to −20 °C during 2 h. The yellow mixture was diluted with chloroform (5 mL), washed with saturated aqueous sodium bicarbonate (1 × 2 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by chromatography of the residue (silica gel 60, 40% ethyl acetate–hexane) gave 14.6 mg (45%) of **38** as a yellow solid: mp 141.0–142.0 °C (ethyl acetate–hexane); IR (neat) 2951, 1510, 1357, 1178, 1104, 978, 905, 812, 666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.73 (d, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.58 (s, 1H), 7.30 (d, J = 8 Hz, 2H), 7.18 (d, J = 8 Hz, 2H), 4.21 (t, J = 6 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.17 (t, J = 6 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.2, 144.9, 144.5, 141.3, 136.9, 136.5, 132.7, 132.0, 129.8 (2), 129.7 (2), 127.9, 127.7 (2), 127.1 (2), 120.3, 113.3, 107.5, 69.7, 60.8, 56.8, 27.5, 21.6, 21.5; MS m/z 574 (M^+), 246 (10), 155 (27), 91 (100); HRMS m/z obsd 574.1079 (M^+), calcd for $C_{26}H_{26}N_2O_9S_2$ 574.1079. Anal. Calcd for $C_{26}H_{26}N_2O_9S_2$: C, 54.35; H, 4.56; N, 4.88. Found: C, 54.05; H, 4.58; N, 4.78.

There was also obtained 12.8 mg (39%) of 1-*N*-(*p*-tolylsulfonyl)-2-nitro-3-(2-*p*-((tolylsulfonyl)oxy)ethyl)-6,7-dimethoxyindole (**39**) as a yellow solid: IR (neat) 2951, 1510, 1357, 1178, 1104, 978, 905, 812, 666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 3H), 7.26 (d, J = 8 Hz, 2H), 7.04 (d, J = 8 Hz, 1H), 4.35 (t, J = 6 Hz, 2H), 3.95 (s, 3H), 3.56 (s, 3H), 3.25 (t, J = 6 Hz, 2H), 2.50 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.5, 145.1, 142.5, 137.9, 136.5, 132.1, 129.9 (2), 129.4 (2), 128.4 (2), 127.6 (2), 126.0, 123.5, 118.2 (2), 112.1 (2), 68.7, 60.1, 56.5, 25.2, 21.7, 21.6.

6,7-Dimethoxy-5-*N*'-(*p*-tolylsulfonyl)pyrrolo[4,3,2-*de*]-1,2,3-trihydroquinoline (41). A suspension of platinum(IV) oxide hydrate (37.6 mg, 0.153 mmol) in absolute ethanol (1 mL) was stirred under an atmosphere of hydrogen for 30 min and then was diluted with absolute ethanol (14 mL). To this black suspension was added a solution of **38** (44.1 mg, 0.077 mmol) in tetrahydrofuran (1 mL), and the mixture was stirred for 30 min under a hydrogen atmosphere. The colorless suspension was filtered through a cotton plug, and the filtrate was concentrated to give crude **40** as a colorless solid. This material was taken up into dry chloroform (15 mL) and *N*,*N*-diisopropylethylamine (32.7 mg, 0.253 mmol), and the solution was heated under argon at 60 °C for 29 h and then refluxed for 24 h. The mixture was cooled to room temperature, diluted with methylene chloride (30 mL), washed with saturated aqueous sodium bicarbonate (1 × 10 mL), and dried over anhydrous sodium sulfate. Concentration followed by chromatography of the residual oil (silica gel 60, 80% ether–hexane) gave 24.2 mg (85%) of **41** as a colorless foam: IR (film) 3389, 2938, 1623, 1509, 1357, 1171, 1098, 739, 673 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.17 (t, J = 1 Hz, 1H), 6.10 (s, 1H), 3.85 (bs, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.37 (t, J = 6 Hz, 2H), 2.87 (td, J = 1, 6 Hz, 2H), 2.34 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.6, 143.9, 136.7, 136.4, 129.5 (2), 127.7 (2), 127.1, 127.0, 118.7, 115.3, 114.8, 93.2, 61.1, 56.9, 42.7, 22.5, 21.6; MS m/z 372 (M^+), 219 (35), 218 (38), 217 (100), 203 (25); HRMS m/z obsd 372.1144 (M^+), calcd for $C_{19}H_{20}N_2O_4S$ 372.1144.

7-Methoxy-5-*N*'-(*p*-tolylsulfonyl)pyrrolo[4,3,2-*de*]-2,3,6-trihydroquinolin-6-one (42) and Tosylate (43). A mixture of **41** (21 mg, 0.056 mmol) in acetonitrile (0.8 mL) was cooled to 0 °C and treated dropwise with a solution of ceric ammonium nitrate (61 mg, 0.111 mmol) in water (0.48 mL). After stirring at 0 °C for 1 h, the mixture was diluted with methylene chloride (5 mL). The organic layer was washed with dilute aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The drying agent was removed by filtration, anhydrous *p*-toluenesulfonic acid (19.0 mg, 0.111 mmol), was added to the filtrate, and the mixture was allowed to stand for 2 h at room temperature. The solvent was removed under reduced pressure to give 42.2 mg of **43** as a dark yellow solid: IR (neat) 3436, 2921, 2851, 1696, 1654, 1559, 1449, 1384, 1319, 1220, 1178, 1120, 1094, 1035, 1009 cm^{-1}; UV–vis (MeOH) 222 (λ_{max}), 314 (sh) nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.62 (s, 1H), 7.35 (d, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 6.98 (s, 1H), 4.11 (t, J = 7 Hz, 2H), 3.92 (s, 3H), 3.04 (t, J = 7 Hz, 2H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.9, 162.5, 160.0, 147.4, 141.8, 140.3, 132.5, 130.1 (2), 129.2 (2), 128.8 (2), 127.0, 125.8 (2), 124.5, 123.9, 116.7, 97.9, 44.1, 29.6, 21.8, 21.2, 17.5; FAB-HRMS m/z obsd 357.0907 (M^+), calcd for $C_{18}H_{17}N_2O_4S$ 357.0909. A sample of **43** was chromatographed (silica gel 60, 10% methanol–methylene chloride) to give pure **42** as an unstable yellow glass: IR (neat) 2924, 1668, 1619, 1576, 1463, 1377, 1184, 1118, 1005, 812 cm^{-1}; UV–vis (MeOH) 222 (λ_{max}), 305 (sh) nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8 Hz, 2H), 7.52 (s, 1H), 7.31 (d, J = 8 Hz, 2H), 6.11 (s, 1H), 4.18 (t, J = 7 Hz, 2H), 3.79 (s, 3H), 2.78 (t, J = 7 Hz, 2H), 2.41 (s, 3H).

7-Methoxypyrrolo[4,3,2-*de*]quinolin-6-one (44). To a solution of **42** (6.1 mg, 0.03 mmol) in dimethylformamide (2 mL) was added sodium azide (70.2 mg, 1.08 mmol) at room temperature. The solution was stirred for 4 h and concentrated under reduced pressure. The residue was purified by chromatography (10% methanol–methylene chloride) to give 3.3 mg (55%) of **44** as an unstable yellow solid: IR (neat) 3500–3300, 2919, 2815, 1656, 1582, 1543, 1470, 1331, 1284, 1251, 1191, 1091, 1025 cm^{-1}; UV–vis (MeOH) 212 (λ_{max}), 427 (sh) nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 6 Hz, 1H), 7.92 (s, 1H), 7.70 (d, J = 6 Hz, 1H), 6.99 (s, 1H), 4.02 (s, 3H); HRMS m/z obsd 200.0586 (M^+), calcd for $C_{11}H_8N_2O_2$ 200.0586.

7-Amino-5-*N*'-(*p*-tolylsulfonyl)pyrrolo[4,3,2-*de*]-2,3,6-trihydroquinolin-6-one (46). To a solution of **43** (20.0 mg, 0.027 mmol) in absolute ethanol (6 mL) was added ammonium hydroxide solution (0.25 mL). The mixture was refluxed for 3 h. After concentration, the residue was purified by chromatography (silica gel 60, 10% methanol–methylene chloride) to give 17.4 mg (91%) of **46** as a red solid: IR (neat) 2958, 2925, 2856, 1732, 1683, 1651, 1600, 1559, 1552, 1532, 1446, 1378, 1332, 1279, 1178, 1098, 1037, 731, 667 cm^{-1}; UV–vis (MeOH) 236 (λ_{max}), 335 (sh) nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8 Hz, 2H), 7.62 (s, 1H), 7.38 (d, J = 8 Hz, 2H), 6.51 (s, 1H), 3.91 (t, J = 7 Hz, 2H), 2.93 (t, J = 7 Hz, 2H), 2.45 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.4, 156.8, 154.3, 147.6, 145.5, 132.1, 130.2 (2), 129.0 (2), 128.2, 123.3, 118.3, 89.6, 42.2, 22.0, 18.2; FAB-HRMS m/z obsd 342.0911 ($M^+ + H$), calcd for $C_{17}H_{16}N_3O_4S$ 342.0912.

Makaluvamine D Trifluoroacetate (48). To a solution of **43** (20.0 mg, 0.027 mmol) in absolute ethanol (6 mL) was added tyramine (11.0 mg, 0.080 mmol). The mixture was refluxed for 8 h and then stirred for 19 h at room temperature. After concentration, the residue was purified by chromatography (silica gel 60, chloroform–methanol–trifluoroacetic acid (100:10:0.1)) to give 10.4 mg (91%) of **48** as a red solid: IR (KBr) 3440, 2927, 1683, 1637, 1559, 1442, 1210, 1138, 843, 804, 725 cm^{-1}; UV–vis (MeOH) 244 (λ_{max}), 348 (sh) nm; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.13 (s, 1H), 10.74 (br d, 1H), 8.96 (br t, 1H), 7.31 (s, 1H), 7.04 (d, J = 8 Hz, 2H), 6.69 (d, J = 8 Hz, 2H), 5.54 (d, J = 2.5 Hz, 1H), 3.80 (t, J = 7 Hz, 2H), 3.45 (m, 2H), 2.87 (t, J = 7 Hz, 2H), 2.78 (t, J = 7 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 167.4, 157.0, 155.9, 152.9, 129.5 (2), 128.1, 126.8, 123.7, 122.5, 118.6, 115.2 (2), 84.1, 45.0, 42.3, 32.3, 18.1; FAB-HRMS m/z obsd 308.1399 (M^+), calcd for $C_{18}H_{18}N_3O_2$ 308.1399. These data were identical to those measured on a sample of natural makaluvamine D trifluoroacetate.

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Supplementary Material Available: Tables listing torsion angles, positional parameters, intramolecular distances, crystal data, and ORTEP for **15** (9 pages). This material is contained in many 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.