Efficient Syntheses of the Marine Alkaloids Makaluvamine D and Discorhabdin C: The 4,6,7-Trimethoxyindole Approach

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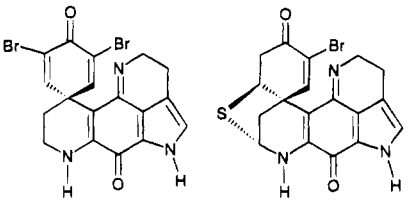
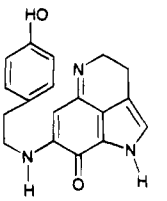
A new and efficient synthesis of the tricyclic quinonimine **20** as its trifluoroacetate **23** has been developed starting from the commercially available 2,4,5-trimethoxybenzaldehyde and proceeding *via* the hitherto unknown 4,6,7-trimethoxyindole (**7**). Quinonimine **23** is the late stage key intermediate in several previously reported syntheses of the biologically active pyrrolo[4,3,2-*de*]-quinoline marine alkaloids discorhabdin C (**1**) and makaluvamine D (**3**).

In recent years, much attention has been focused upon the isolation and structure determination of biologically active materials from marine sources. One of the most interesting classes of compounds is the structurally varied group of alkaloids containing the pyrrolo[4,3,2-*de*]quinoline nucleus. These include the discorhabdins,[1] prianosins,[2] damirones,[3] batzellins,[4] isobatzellins,[5] makaluvamines,[6] and wakayin.[7] Many of these compounds, including discorhabdin C (**1**), prianosin A (**2**), and makaluvamine D (**3**), show significant anticancer activity, although their very limited availability has precluded thorough pharmacological evaluations. For this reason, as well as the fact of their novel structures, they have become prime synthetic targets in a number of laboratories. Since 1991, three syntheses[8] of discorhabdin C (**1**) and two syntheses[8b,9] of makaluvamine D (**3**) have been reported, all of which proceed at a late stage by way of the common tricyclic quinonimine **20**. We now report a new and considerably improved synthesis of this key intermediate starting with a commercially available starting material and affording imine **20** as a stable salt **23** in a yield over 3-fold that of any previously achieved.



1, Discorhabdin C **2**, Prianosin A



3, Makaluvamine D

Results and Discussion

Our synthesis started with the commercially available 2,4,5-trimethoxybenzaldehyde, which was converted in four steps to the previously unknown 4,6,7-trimethoxyindole (**7**) in 52% overall yield. Thus, following the general Rees–Moody protocol,[10] 2,4,5-trimethoxybenzaldehyde was condensed with methyl azidoacetate[11] to afford the stable yellow azidocinnamate **4**, thermolysis of which in refluxing xylene cleanly afforded methyl 4,6,7-trimethoxyindole-2-carboxylate (**5**). Although alkaline hydrolysis of **5** led uneventfully to the corresponding acid **6**, decarboxylation of the latter by the usual copper–quinoline procedure gave a dark product which was difficult to work up and purify. In contrast, when acid **6** was thermolyzed without solvent under reduced pressure in the presence of barium oxide, pure 4,6,7-trimethoxyindole (**7**) sublimed out as a white solid. The decarboxylation could be carried out on quantities as large as 10 g without loss of yield.

Reaction of 4,6,7-trimethoxyindole with oxalyl chloride in THF–ether gave the 3-glyoxalyl chloride, which reacted with dibenzylamine to give the highly crystalline amide **8**. Reduction of the latter with lithium aluminum hydride in ether–THF afforded the corresponding *N,N*-dibenzyltryptamine **9** in virtually quantitative yield.

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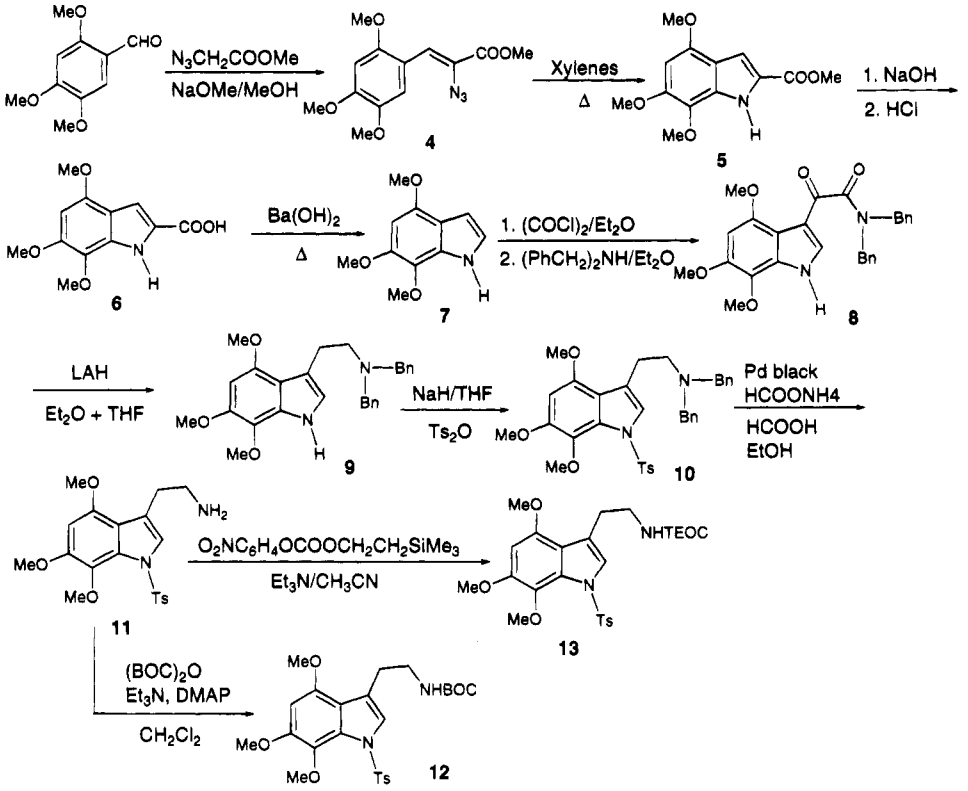
Scheme 1



Deactivation of the indole system of tryptamine **9** by N-tosylation was unexpectedly troublesome. Thus, incomplete reaction and byproduct formation were observed when **9** was treated with tosyl chloride and aqueous potassium hydroxide under phase-transfer conditions. Better results were obtained using tosyl chloride and sodium hydride in DMF, but almost quantitative yields to tosyl derivative **10** resulted when the tosyl chloride was replaced by tosic anhydride.

Reductive debenzylation of **10** was sluggish and incomplete using palladium on charcoal as the catalyst. In contrast, transfer hydrogenolysis using ammonium formate/formic acid in the presence of palladium black efficiently afforded the free tryptamine **11**, which was directly converted into either the corresponding BOC protected amine **12**, or the TEOC protected amine **13** (Scheme 1).

An unexpected problem was encountered in the oxidative conversion of **12** and **13** into the corresponding quinones (**14** and **15**). Thus, the reaction of **12** and **13** with ceric ammonium nitrate (CAN) under the standard conditions for such reactions (aqueous acetonitrile) afforded unidentified complex mixtures of products. Better results were obtained using CAN in methylene chloride in the presence of tetrabutylammonium nitrate as a phase-transfer catalyst. Under these conditions, the amide **13** gave the desired quinone **15** in low yield, along with the nitroindole **16** as the major product. The unexpected nitration was not promoted by the amide-bearing side-chain, since *N*-(*p*-toluenesulfonyl)-4,6,7-trimethoxyindole (**17**) also afforded a mixture of the corresponding quinone **18** and the nitroindole **19**.

After considerable experimentation, it was found that the nitration reaction could be largely suppressed by using CAN and tetrabutylammonium hydrogen sulfate as the phase-transfer agent. Under these conditions both the BOC quinone **14** and the TEOC quinone **15** could be prepared in good yields (72% and 78%, respectively, Scheme 2).

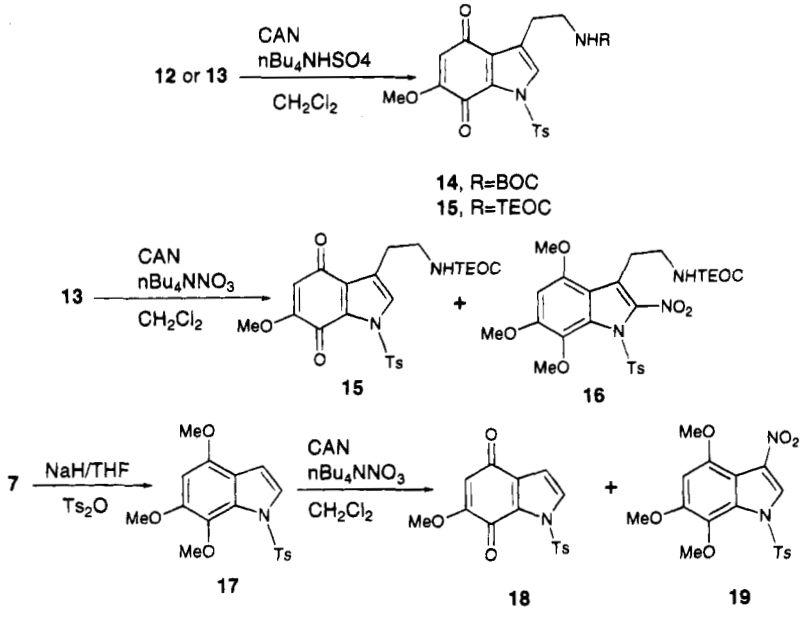
The spectroscopic properties of the TEOC quinone **15** were identical to those reported by Kita. Moreover, reaction of **15** with tosic acid followed by reaction with 3,5-dibromotyramine under the conditions described in the literature[8a] afforded the substituted quinonimine **21**, identical in its properties with those described. Since the oxidation of compound **21** to discorhabdin C has been reported, our synthesis of **15** and **21** constitutes a new and efficient discorhabdin C synthesis.

The highly crystalline BOC quinone **14** was readily deprotected by trifluoracetic acid in methylene chloride. The initial product was shown by NMR to be the trifluoracetate salt of the tryptamine quinone **22**. When this salt was dissolved in chloroform, it slowly underwent dehydration to the corresponding crystalline, chloroform-insoluble quinonimine salt **23**. The overall yield of **23** from **14** was 92%. Conversion of the salt **23** to makaluvamine D (**3**) was effected by reaction with tyramine as described by White[8b] for the corresponding tosylate salt. The properties of the resulting makaluvamine D trifluoroacetate were in excellent agreement with those reported (Scheme 3).

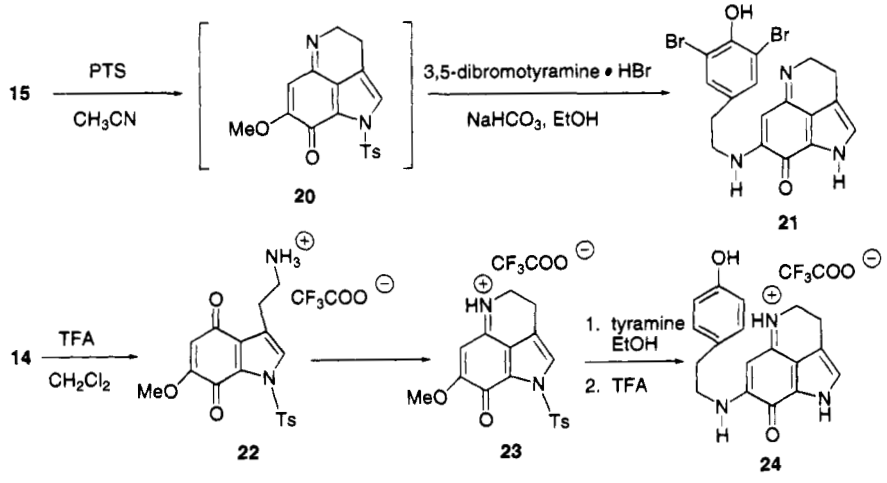
Conclusion

The commercially available 2,4,5-trimethoxybenzaldehyde has been converted into the indolequinones **14** and **15** in yields (28% and 26%, respectively) considerably higher than those previously attained. Consequently, an efficient synthesis of makaluvamine D (**3**) from **14** is now available, as well as an improved route to discorhabdin C (**1**) from **15**.

Scheme 2



Scheme 3



Experimental Section

General. Melting points were determined on a MEL-TEMP-II (Laboratory Devices) apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR were recorded at 360 and 90.6 MHz, respectively, in the indicated solvents using a Bruker AM 360 instrument. Chemical shifts are reported in ppm relative to residual nondeuterated solvent. Low- and high-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact using VG Auto Spec spectrometer. Elemental analyses were determined by Atlantic Microlab Inc., Norcross, GA.

Methyl 2,4,5-trimethoxy-α-azidocinnamate (4). A solution of sodium methoxide (25% w, 115 mL, 532 mmol) in MeOH (187 mL) was cooled to −8 °C under N_2. A solution of 2,4,5-trimethoxybenzaldehyde (25 g, 128 mmol) and methyl azidoacetate (59 g, 513 mmol) in a mixture of MeOH (50 mL) and anhydrous THF (100 mL) was added dropwise with stirring to the methoxide solution, maintaining the temperature at −8 °C for 45 min. The mixture was stirred for an additional 2 h while the temperature was maintained below 5 °C. The resulting hetereogenous mixture was poured over ice (1 kg) and stirred manually. The precipitate which separated was filtered, washed with water, and dried over $CaCl_2$ in a vaccum desiccator. The product thus obtained was dissolved in EtOAc (600 mL) and dried (Na_2SO_4). Removal of solvent from the dried extract afforded practically pure methyl 2,4,5-trimethoxy-α-azidocinnamate (**4**) as bright yellow crystals (27.6 g, 74%), mp 119 °C (dec). ^{1}H-NMR ($CDCl_3$): δ 3.85 (s, 3H), 3.89 (s, 6H), 3.92 (s, 3H), 6.48 (s, 1H), 7.37 (s, 1H), 7.91 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 52.6, 55.9, 56.4, 56.5, 96.2, 113.4, 113.8, 119.4, 122.3, 142.5, 151.4, 153.5, 164.4. MS *m/z* (relative intensity): 265 (M − N_2, 28), 250 (52), 233 (45), 218 (100), 206 (71), 190 (55), 176 (24), 162 (20), 117 (19).

Methyl 4,6,7-Trimethoxyindole-2-carboxylate (5). Methyl 2,4,5-trimethoxy-α-azidocinnamate (23.2 g, 79 mmol) was added slowly to boiling xylenes (500 mL) with stirring over a period of 3 h using a solid addition funnel. (The azido cinnamate was added slowly into refluxing xylenes, monitoring the gas evolution very carefully to avoid a build up of excess of azide in the solution.)

The evolution of N_2 was observed using a gas bubbler. The reaction mixture was refluxed for 2 h after the evolution of nitrogen had ceased. It was cooled, and the solvent was completely removed to afford the crude product. This was crystallized from MeOH to give pure white, crystalline, methyl 4,6,7-trimethoxyindole-2-carboxylate (**5**) (20.7 g, 99%), mp 122 °C. ^{1}H-NMR ($CDCl_3$): δ 3.91 (s, 9H), 3.94 (s, 3H), 6.26 (s, 1H), 7.26 (d, 1H, J = 2.3Hz), 9.04 (bs, 1H). ^{13}C-NMR ($CDCl_3$): δ 51.8, 55.6, 57.5, 61.1, 90.7, 107.2, 114.8, 125.6, 128.7, 132.6, 149.6, 150.5, 162.1. MS *m/z* (relative intensity): 265 (M^+, 61), 250 (37), 233 (30), 218 (100), 204 (8), 190 (49), 162 (11), 117 (12). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.74; H, 5.73; N, 5.32.

4,6,7-Trimethoxyindole-2-carboxylic Acid (6). Methyl

4,6,7-trimethoxyindole-2-carboxylate (20.5 g, 77 mmol) was added to a 2 N solution of sodium hydroxide (400 mL), and the suspension was heated until it became a clear solution. Then it was refluxed for 30 min, cooled to room temperature, and acidified with 6 N HCl. The precipitate was filtered, washed with water (500 mL), and dried over $CaCl_2$ in a vaccum desiccator. It was crystallized from MeOH to provide the pure acid (**6**) as white crystals (19.3 g, 98%), mp 190 °C. ^{1}H-NMR (DMSO-d_6): δ 3.73 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 6.38 (s, 1H), 6.98 (d, 1H, J = 2.2 Hz), 11.52 (s, 1H) and 12.64 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ 55.5, 57.3, 60.7, 90.9, 105.8, 114.1, 127.2, 128.8, 132.7, 149.1, 149.5, 162.3. MS *m/z* (relative intensity): 251 (M^+, 67), 236 (62), 218 (100), 190 (64), 144 (19), 117 (20). HRMS: calcd for $C_{12}H_{13}NO_5$ 251.079 373, found 251.079 650.

4,6,7-Trimethoxyindole (7). 4,6,7-Trimethoxyindole-2-carboxylic acid **6** (5 g, 20 mmol) was intimately ground with barium oxide (0.46 g, 3 mmol), and the mixture was heated under water aspirator vaccum in a Kughelrohr apparatus using a bunsen flame. The pure 4,6,7-trimethoxyindole sublimed out at ~15 mm of vaccum. Recrystallization from methylene chloride–hexane afforded analytically pure white crystals of 4,6,7-trimethoxyindole (**7**) (3 g, 73%), mp 107 °C. ^{1}H-NMR ($CDCl_3$): δ 3.92 (s, 9H), 6.29 (s, 1H), 6.56 (t, 1H, J = 2.4 Hz), 7.02 (t, 1H, J = 2.4 Hz), 8.31 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 55.7, 57.9, 61.0, 90.9, 100.2, 114.6, 122.3, 129.4, 131.1, 147.0, 148.9. MS *m/z* (relative intensity): 207 (M^+, 82), 192 (100), 176 (6), 164 (13), 149 (51), 133 (33), 120 (36), 104 (15), 91 (41), 63 (22). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.74; H, 6.33; N, 6.76. Found: C, 63.57; H, 6.31; N, 6.88.

***N,N*-Dibenzyl-4,6,7-trimethoxyindole-3-glyoxamide (8).** A solution of 4,6,7-trimethoxyindole (**7**) (5.0 g, 24.2 mmol) in anhydrous ether (300 mL) was cooled to 0 °C under N_2. A solution of oxalyl chloride (3.9 g, 30.7 mmol) in the same solvent (50 mL) was added to this over a period of 10 min. After being stirred for 2 h at 0 °C, the reaction mixture was warmed to room temperature, dibenzylamine (16.7 g, 84.8 mmol) was added to this over a period of 15 min, and the resulting mixture was stirred for an additional 2 h at rt. After filtration the solid product was repeatedly extracted with boiling water (1 L), filtered, and dried in a vacuum desiccator over $CaCl_2$.

Crystallization of the crude product from EtOAc gave analytically pure yellow crystals of **8** (10.3 g, 93%), mp 163–4 °C. ^{1}H-NMR ($CDCl_3$): δ 3.72 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.44 (s, 2H), 4.57 (s, 2H), 6.35 (s, 1H), 7.23–7.33 (m, 10H), 7.81 (d, 1H, J = 2.3Hz), 9.67 (bs, 1H). ^{13}C-NMR ($CDCl_3$): δ 45.9, 50.6, 56.3, 57.3, 61.2, 93.7, 110.1, 116.1, 127.5, 127.9, 128.2, 128.4, 128.6, 128.7, 128.8, 129.2, 132.7, 134.9, 135.4, 136.3, 148.4, 149.9, 169.0, 185.6. MS *m/z* (relative intensity): 458 (M^+, 33), 357 (75), 315 (8), 234 (71), 196 (100), 161 (6), 132 (17), 118 (7), 106 (40). Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.71; H, 5.72; N, 6.11. Found: C, 70.53; H, 5.77; N, 6.11.

***N,N*-Dibenzyl-4,6,7-trimethoxytryptamine (9).** A solution of glyoxamide **8** (5 g, 10.9 mmol) in anhydrous THF (75 mL) was slowly added to a suspension of LAH (3.32 g, 87.4 mmol) in anhydrous ether (200 mL) maintained under N_2. The reaction mixture was refluxed for 8 h. It was cooled to 0 °C, and a saturated Na_2SO_4 solution was slowly added to destroy excess LAH. Inorganic salts were allowed to settle down and removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL), washed with water (4 × 50 mL), and dried (Na_2SO_4). Removal of solvent from the dried extract furnished the pure product **9** as colorless thick oil (4.6 g, 98%). ^{1}H-NMR ($CDCl_3$): δ 2.77 (t, 2H, J = 8 Hz), 3.03 (t, 2H, J = 8 Hz), 3.66 (s, 7H), 3.88 (s, 3H), 3.89 (s, 3H), 6.14 (s, 1H), 6.68 (d, 1H, J = 2 Hz), 7.18–7.36 (m, 10H), 8.00 (bs, 1H). ^{13}C-NMR ($CDCl_3$): δ 24.3, 54.8, 55.3, 57.7, 58.1, 60.7, 89.9, 113.7, 115.0, 120.1, 126.4, 127.9, 128.5, 128.9, 131.6, 140.1, 146.5, 150.1. MS *m/z* (relative intensity): 430 (M^+, 9), 221 (11), 210 (100), 181 (13), 161 (6), 134 (5), 118 (9). HRMS: calcd for $C_{27}H_{30}N_2O_3$ 430.225 643, found 430.226 130.

1-(*p*-Toluenesulfonyl)-4,6,7-trimethoxy-*N,N*-dibenzyltryptamine (10). A solution of *N,N*-dibenzyltryptamine **9** (6.6 g, 15.3 mmol) in anhydrous THF (75 mL) was added to a suspension of NaH (3.3 g, 137 mmol) in the same solvent (25 mL) maintained under N_2 over a period of 15 min. The mixture was stirred for 1 h at room temperature and then cooled to 0 °C. A solution of *p*-toluenesulfonic anhydride (6.19 g, 19.0 mmol) in the same solvent (50 mL) was slowly added to this, and the reaction mixture was further stirred for 1 h at 0 °C and an additional 1 h at rt. Excess NaH was destroyed by slow addition of absolute ethanol. The solvent was then completely removed, and water (75 mL) was added to the residue. Extraction with CH_2Cl_2 (3 × 50 mL) and removal of the solvent from the dried (Na_2SO_4) extract provided the crude product as a yellow oil. It was crystallized from absolute EtOH to afford pure white crystals of **10** (8.8 g, 98%), mp 96–97 °C. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.77 (t, 2H, J = 7.7 Hz), 2.97 (t, 2H, J = 7.7 Hz), 3.60 (s, 3H), 3.66 (s, 4H), 3.75 (s, 3H), 3.83 (s, 3H), 6.23 (s, 1H), 7.19 (d, 2H, J = 8.3 Hz), 7.23–7.37 (m, 11H), 7.73 (d, 2H, J = 8.3 Hz). ^{13}C-NMR ($CDCl_3$): δ 21.5, 24.7, 54.1, 55.2, 56.9, 58.38, 60.6, 92.7, 116.6, 118.9, 124.1, 126.6, 127.2, 128.1, 128.7, 129.4, 129.7, 131.0, 137.0, 140.0, 143.8, 149.5, 150.3. MS *m/z* (relative intensity): 584 (M^+, 0.6), 548 (1), 428 (17), 351 (12), 319 (11), 210 (100), 190 (31), 161 (13), 139 (13), 118 (18). Anal. Calcd for $C_{34}H_{36}N_2O_5S$: C, 69.83; H, 6.21; N,4.79. Found: C, 69.96; H, 6.28; N, 4.85.

1-(*p*-Toluenesulfonyl)-4,6,7-trimethoxytryptamine (11). To a solution of **10** (2.16 g, 3.71 mmol) in absolute EtOH (300 mL) were added ammonium formate (3.6 g, 57 mmol) and Pd black (0.8 g), and the reaction mixture was refluxed under N_2 for 12 h. It was brought to room temperature and another batch of ammonium formate (3.6 g, 57 mmol) and Pd black (0.8 g) was added to this, with stirring. (Caution! Nitrogen atmosphere needed during this addition to prevent fire.) This was followed by the addition of formic acid (88%, 2 mL), and the reaction mixture was refluxed for another 12 h. The reaction mixture was then cooled and filtered through Celite 545 to remove the catalyst and insoluble salts. The filtrate was concentrated, water (20 mL) was added to the residue, and the solution was made alkaline by adding aqueous $NaHCO_3$. The product was extracted with $CHCl_3$ (3 × 100 mL), and the combined extract was washed with brine (3 × 50 mL). Removal of solvent from the dried (Na_2SO_4) extract gave the debenzylated product **11** as a gum which was used as such for the next reaction. ^{1}H-NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.90–2.93 (m, 2H), 2.98–3.01 (m, 2H), 3.72 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.32 (s, 1H), 7.20 (d, 2H, J = 8.2 Hz), 7.39 (s, 1H), 7.72 (d, 2H, J = 8.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 21.5, 30.5, 42.0, 55.6, 56.9, 60.6, 92.9, 116.2, 117.9, 124.3, 127.2, 129.5, 136.8, 143.9, 149.7, 150.5.

4,6,7-Trimethoxy-3-[2-[(*tert*-butoxycarbonyl)amino]-ethyl]-1-(*p*-toluenesulfonyl)indole (12). A solution of crude tryptamine **11** from **10** (2.16 g, 3.71 mmol) in methylene chloride (60 mL) was treated with 4-(dimethylamino)pyridine (ca. two to three crystals) followed by triethylamine (0.75 g, 7.42 mmol), under N_2, at 0 °C. A solution of BOC anhydride (1.62 g, 7.42 mmol) in methylene chloride (15 mL) was then added dropwise. The mixture was stirred at 0 °C for 5 h and warmed to rt and stirred at rt for another 2 h. After concentration *in vacuo*, the residue was purified by chromatography (EtOAc/hexane, 1:1) to give **12** as white shining crystals (1.56 g, 83% from **10**), mp 155 °C. ^{1}H-NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.34 (s, 3H), 2.94 (t, 2H, J = 6.5 Hz), 3.42 (q, 2H, J = 6.3 Hz), 3.75 (s, 3H), 3.85 (s, 6H), 4.68 (bs, 1H), 6.34 (s,1H), 7.21 (d, 2H, J = 8 Hz), 7.39 (s, 1H), 7.73 (d, 2H, J = 8 Hz). ^{13}C-NMR ($CDCl_3$): δ 21.5, 27.1, 28.4, 40.8, 55.6, 56.9, 60.7, 79.5, 92.9, 116.1, 117.7, 124.5, 127.3, 129.9, 131.1, 136.7, 144.0, 149.6,1 50.6, 155.9. MS *m/z* (relative intensity): 504 (M^+, 6), 404 (14), 293 (20), 275 (24), 250 (18), 232 (15), 220 (100), 190 (36), 161 (28), 146 (14). Anal. Calcd for $C_{25}H_{32}N_2O_7S$: C, 59.51; H, 6.39; N, 5.55. Found: C, 59.47; H, 6.47; N, 5.50.

4,6,7-Trimethoxy-3-[2-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]ethyl]-1-(*p*-toluenesulfonyl)indole (13). A solution of crude tryptamine **11** from **10** (2.16 g, 3.71 mmol), Et_3N (1.1 mL, 7.84 mmol), and (trimethylsilyl)ethyl *p*-nitro-

phenyl carbonate[12] (1.1 g, 3.9 mmol) in anhyd CH_3CN (80 mL) was refluxed under N_2 for 8 h. The solvent was removed, and the residue was poured over crushed ice. The product was extracted with $CHCl_3$ (3 × 75 mL) and the extract was washed with 1 N NaOH (5 × 75 mL) followed by water (3 × 75 mL). Removal of solvent from the dried (Na_2SO_4) extract afforded the crude product which was purified by chromatography over silica gel (230–400 mesh) using EtOAc:hexane (1:2) as eluent to furnish pure **13** as a colorless thick oil (1.42 g, 70% from **10**). ^{1}H-NMR ($CDCl_3$): δ 0.02 (s, 9H), 0.96 (t, 2H, J = 9 Hz), 2.33 (s, 3H), 2.94 (t, 2H, J = 6.6 Hz), 3.46 (dd, 2H, J_1 = 12 Hz, J_2 = 6 Hz), 3.73 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4,13 (t, 2H, J = 9 Hz), 4.81 (bs, 1H, NH), 6.34 (s, 1H), 7.20 (d, 2H, J = 8.3 Hz), 7.39 (s, 1H), 7.72 (d, 2H, J = 8.3 Hz). ^{13}C-NMR ($CDCl_3$): δ −1.5, 17.7, 21.5, 27.2, 41.2, 55.6, 56.9, 60.7, 62.8, 92.8, 116.1, 117.5, 124.5, 127.2, 129.5, 129.9, 131.0, 136.7, 143.9, 149.5, 150.6, 156.7. MS *m/z* (relative intensity): 548 (M^+, 12), 430 (10), 394 (22), 366 (15), 321 (15), 306 (11), 275 (39), 232 (26), 220 (100), 204 (17), 190 (33), 175 (12), 161 (14). HRMS: calcd for $C_{26}H_{36}N_2O_7SiS$ 548.201 252, found 548.203 742.

6-Methoxy-3-[2-*tert*-butoxycarbonyl)amino]ethyl]-1-(*p*-toluenesulfonyl)indole-4,7-dione (14). To a solution of carbamate **12** (1.00 g, 1.98 mmol) in CH_2Cl_2 (120 mL) was added tetrabutylammonium hydrogen sulfate (1.35 g, 3.96 mmol) and the resulting mixture stirred for 5 min. Then solid ceric ammonium nitrate (1.08 g, 3.96 mmol) was added, and the suspension was stirred for 5 min. One drop of water was added, and the reaction mixture was stirred for 5 min. After every 5 min a drop of water was added, and the progress of the reaction was monitored by TLC. It required six drops of water and 35 min stirring for the reaction to go to completion (controlled addition of water is crucial since excess of water can lead to side products). The mixture was then filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with ether (5 × 100 mL), and the combined ether extract was washed with water (75 mL x 3) and brine (75 mL) and dried (Na_2SO_4). Ether was evaporated, and the yellow solid residue was recrystallized from ether–hexanes to afford pure **14** (525 mg), mp 152 °C dec. The mother liquor was then concentrated and the residue dissolved in minimum amount of CH_2Cl_2 and passed through a pad of silica gel using ether as eluent. Removal of solvent and crystallization furnished second a crop of **14** (150 mg), making the total yield 72%. ^{1}H-NMR ($CDCl_3$): δ 1.41 (s, 9H), 2.42 (s, 3H), 2.96 (t, 2H, J = 6.8 Hz), 3.39 (q, 2H, J = 6 Hz), 3.77 (s, 3H), 4.72 (bs, 1H), 5.70 (s, 1H), 7.33 (d, 2H, J = 8 Hz), 7.67 (s, 1H), 8.04 (d, 2H, J = 8 Hz). ^{13}C-NMR ($CDCl_3$): δ 22.0, 26.2 28.6, 31.2 40.5, 57.1, 79.6, 107.0, 123.2, 128.9, 129.5, 129.6, 129.9, 133.9, 146.5, 156.2, 159.8, 184.2, 207.2. Anal. Calcd for $C_{23}H_{26}N_2O_7S$: C, 58.22; H, 5.52; N, 5.90. Found: C, 58.12; H, 5.57; N, 5.91.

6-Methoxy-3-[2-[[[2-(trimethylsilyl)ethoxy]carbonyl]-amino]ethyl]-1-(*p*-toluenesulfonyl)indole-4,7-dione (15). The carbamate **13** (1.25, 2.3 mmol) was similarly oxidized to the quinone **15** following the above procedure, and the pure quinone **15** was isolated as a yellow glassy solid (0.92 g. 78%). ^{1}H-NMR ($CDCl_3$): δ 0.02, 0.96 (t, 2H, J = 8.4 Hz), 2.42 (s, 3H), 2.96 (t, 2H, J = 6.5 Hz), 3.43 (dd, 2H, J_1 = 12 Hz, J_2 = 6.5 Hz), 3.77 (s, 3H), 4.12 (t, 2H, J = 8.4 Hz), 4.87 (bs, 1H), 5.71 (s, 1H), 7.33 (d, 2H, J = 8.3 Hz), 7.67 (s, 1H), 8.03 (d, 2H, J = 8.3 Hz). ^{13}C-NMR ($CDCl_3$): δ −1.4, 17.7, 21.7, 25.8, 29.7, 40.7, 56.8, 62.9, 106.7, 122.8, 128.6, 129.3, 129.4, 129.7, 132.0, 133.6, 146.2, 156.8, 159.6, 169.1, 184.0.

Oxidation of 13 with CAN/nBu_4NNO_3. To a solution of carbamate **13** (0.137 g, 0.025 mmol) in CH_2Cl_2 (20 mL) was added tetrabutylammonium nitrate (0.152 g, 0.05 mmol) and the resulting mixture stirred for 5 min at rt. Ceric ammonium nitrate (0.274 g, 0.05 mmol) was added to this, and stirring was continued. The progress of the reaction was monitored by TLC. After the mixture was stirred for 35 min, TLC showed complete disappearance of the starting material and the presence of two products. The reaction mixture was filtered and concentrated to afford the crude product which was chromatographed over silica gel using EtOAc:hexanes (1:2) to provide the products **16** (0.072 g, 49%) and **15** (0.03 g, 23%).

(12) Rosowsky, A.; Wright, J. E. *J. Org. Chem.* **1983**, *48*, 1539.

16. ^{1}H NMR ($CDCl_3$): δ 0.02 (s, 9H), 0.97 (t, 2H, J = 8.5 Hz), 2.45 (s, 3H), 3.25 (t, 2H, J = 6.5 Hz), 3.35 (s, 3H), 3.5–3.7 (m, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 4.13 (t, 2H, J = 8.5 Hz), 5.09 (bs, 1H), 6.40 (s, 1H), 7.36 (d, 2H, J = 8.3 Hz), 8.22 (d, 2H, J = 8.3 Hz). ^{13}C-NMR ($CDCl_3$): δ −1.5, 17.7, 21.7, 26.5, 40.7, 55.9, 56.6, 60.0, 63.0, 94.2, 106.5, 115.6, 126.1, 128.4, 129.3, 132.1, 133.5, 136.5, 144.9, 153.0, 155.1, 156.9. MS *m/z* (relative intensity): 593 (M^+, 0.2), 548 (1), 439 (4), 394 (4), 306 (9), 278 (51), 229 (31), 186 (33), 147 (100), 139 (60), 109 (39).

***N*-(*p*-Toluenesulfonyl)-4,6,7-trimethoxyindole (17).** A solution of 4,6,7-trimethoxyindole (**7**) (2 g, 9.7 mmol) in anhydrous THF (10 mL) was slowly added to a suspension of NaH (1 g, 41.6 mmol) in the same solvent (20 mL) maintained under N_2 and stirred at rt for 1 h. A solution of *p*-toluenesulfonic anhydride (3.94 g, 12.1 mmol) in THF (15 mL) was added to this, and the reaction mixture was stirred for 1 h. Excess NaH was destroyed by slow addition of absolute ethanol, and the solvent was evaporated under reduced pressure. The residue was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic extract was washed with water (2 × 25 mL) and dried (Na_2SO_4). Removal of solvent afforded the crude product which was purified by flash chromatography over a column of silica gel using CH_2Cl_2: hexanes (1:4) as eluent to give pure *N*-(*p*-toluenesulfonyl)-4,6,7-trimethoxyindole (**17**) (3.2 g, 92%), mp 169 °C. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.37 (s, 1H), 6.66 (d, 1H, J = 3.8 Hz), 7.21 (d, 1H, J = 8.2 Hz), 7.61 (d, 1H, J = 3.8 Hz), 7.75 (d, 1H, J = 8.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 21.6, 55.8, 56.8, 57.0, 60.8, 92.9, 103.9, 117.2, 126.6, 127.4, 129.01, 129.52, 131.1, 136.7, 144.1, 148.4, 150.7. MS *m/z* (relative intensity): 361 (M^+, 28), 240 (11), 206 (100), 191 (26), 178 (24), 163 (51), 146 (42.1), 131 (22), 120 (25). Anal. Calcd for $C_{18}H_{19}NO_5S$: C, 59.84; H, 5.26; N, 3.88. Found: C, 59.64; H, 5.30; N, 3.94.

Oxidation of 17 with CAN/nBu_4NNO_3. To a solution of *N*-(*p*-toluenesulfonyl)-4,6,7-trimethoxyindole (**17**) (0.1 g, 0.28 mmol) in CH_2Cl_2 (5 mL) were added tetrabutylammonium nitrate (0.17 g, 0.56 mmol) and ceric ammonium nitrate (0.3 g, 0.55 mmol), and the reaction mixture was stirred for 1 h at rt. Water (5 mL) was added to this, and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined extract was washed with water (3 × 15 mL) and dried (Na_2SO_4). The crude product obtained after removal of solvent was subjected to flash chromatography over silica gel using CH_2Cl_2:hexanes (1:2) to afford the expected quinone **18** (0.03 g, 33%) and the nitro compound **19** (0.055 g, 49%).

18. Mp: 152 °C. ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 3H), 3.78 (s, 3H), 5.75 (s, 1H), 6.71 (d, 1H, J = 3.2 Hz), 7.34 (d, 1H, J = 8.3 Hz), 7.82 (d, 1H, J = 3.2 Hz), 8.05 (d, 1H, J = 8.3 Hz). ^{13}C-NMR ($CDCl_3$): δ 21.8, 56.8, 106.3, 107.9, 128.1, 129.3, 129.8, 130.8, 131.8, 133.5, 146.3, 159.9, 169.1, 182.5. MS *m/z* (relative intensity): 331 (M^+, 4), 267 (7), 176 (70), 162 (7), 148 (43), 120 (100), 106 (132). Anal. Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.95; N, 4.23. Found: C, 57.48; H, 3.91; N, 4.09.

19. Mp: 143 °C dec. ^{1}H-NMR ($CDCl_3$): δ 2.47 (s, 3H), 3.46 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 6.43 (s, 1H), 7.39 (d, 2H, J = 8 Hz), 7.60 (s, 1H), 8.30 (d, 1H, J = 8 Hz). ^{13}C-NMR ($CDCl_3$): δ 21.7, 56.03, 56.8, 60.2, 94.2, 111.8, 115.2, 128.7, 129.4, 129.8, 132.3, 134.2, 136.5, 145.1, 151.8, 155.5. MS *m/z* (relative intensity): 406 (M^+, 9), 391 (11), 362 (10), 268 (11), 252 (65), 237 (100), 221 (21), 207 (24), 191 (29), 177 (15), 163 (23.7). HRMS: calcd for $C_{18}H_{18}N_2O_7S$ 406.083 473, found 406.082 943.

7-[[2-(3,5-Dibromo-4-hydroxyphenyl)ethyl]amino]-1,3,4,8-tetrahydropyrrolo[4,3,2-*de*]quinolin-8-one (21). To a solution of **15** (0.06 g, 0.12 mmol) in CH_3CN (5 mL) was added *p*-toluenesulfonic acid (0.11 g, 0.58 mmol), and the reaction mixture was stirred for 5 h under N_2 at rt. Then $NaHCO_3$ (0.15 g) and molecular sieves were added and the reaction mixture was stirred for 10 min at rt. After removal of the solvent, the residue was extracted into CH_2Cl_2 (3 × 5 mL). The organic extract was dried (Na_2SO_4) and concentrated, and the residue was dissolved in absolute EtOH (5 mL). This solution was added to a stirred suspension of 3,5-dibromotyramine hydrobromide (0.13 g, 0.35 mL) and

$NaHCO_3$ (0.06, 0.71 mmol) in absolute EtOH (2 mL). The reaction mixture was refluxed for 3 h under N_2 and then evaporated. The residue obtained was purified by radial chromatography using CH_2Cl_2:MeOH:Et_3N (90:10:1) to afford pure **21** (0.019 g, 35.4%). ^{1}H-NMR (CD_3OD): δ 2.73 (t, 2H, J = 7.1 Hz), 2.91 (t, 2H, J = 7.6 Hz), 3.44 (t, 2H, J = 7.2 Hz), 3.85 (t, 2H, J = 7.5 Hz), 5.30 (s, 1H), 7.10 (s, 1H), 7.20 (s, 2H).

Trifluoroacetate of 7-Methoxy-5-*N*'-(*p*-toluenesulfonyl)pyrrolo[4,3,2-*de*]-2,3,6-dihydroquinolin-6-one (23). To a stirred solution of the BOC-quinone **14** (0.15 g, 0.316 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of TFA/CH_2Cl_2 (1:1) (2.5 mL), dropwise, at rt. The mixture was stirred at rt for 2 h and was evaporated *in vacuo*. Traces of trifluoroacetic acid were removed *in vacuo* by coevaporation with CH_2Cl_2 (3 × 3 mL) to give a greenish yellow trifluoroacetate of the free amine **22** (0.155 g, 100%). ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.15 (br, 2H), 3.37 (br, 2H), 3.74 (s, 3H), 5.61 (bs, 3H), 5.69 (s, 1H), 7.30 (d, 2H, J = 8 Hz), 7.76 (s, 1H), 7.98 (d, 2H), J = 8 Hz). **22** was dissolved in chloroform, and on standing overnight, the cyclized product was formed and was separated by filtration to afford yellow crystalline **23** (0.137 g, 92%), mp 167–168 °C dec. ^{1}H-NMR (CD_3COCD_3): δ 2.43 (s, 3H), 3.27 (t, 2H, J = 7.3 Hz), 3.81 (s, 3H), 4.10 (t, 2H, J = 7.3 Hz), 5.8 (s, 1H), 7.47 (d, 2H, J = 8 Hz), 7.96 (s, 1H), 8.06 (d, 2H, J = 8 Hz). ^{13}C-NMR (CD_3COCD_3): δ 21.5, 24.41, 47.55, 57.29, 107.34, 121.01, 129.18, 129.89, 130.64, 131.12, 131.29, 134.8, 147.38, 160.91, 169.47, 184.85.

Makaluvamine D Trifluoroacetate 24. To a solution of tyramine (73 mg, 0.5319 mmol) in absolute ethanol (20 mL) was added a solution of **23** (100 mg, 0.212 mmol) in the same solvent (15 mL). The mixture was refluxed for 8 h and then stirred at rt for another 8 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography [silica gel, chloroform–methanol–trifluoroacetic acid (100:10:0.1)] to give **24** as a dark red solid (0.076 g, 85%). ^{1}H NMR (DMSO-d_6): 2.78 (t, 2H, J = 7 Hz), 2.86 (t, 2H, J = 7 Hz), 3.46 (m, 2H), 3.82 (t, 2H, J = 7 Hz), 5.46 (d, 1H, J = 3.6 Hz), 6.68 (d, 2H, J = 7.6 Hz), 7.03 (d, 2H, J = 7.6 Hz), 7.32 (d, 1H, 2.3 Hz), 8.99 (t, 1H, J = 6 Hz), 10.45 (brd, 1H), 13.08 (s, 1H). ^{13}C NMR (DMSO-d_6): 18.1, 32.3, 42.4, 45.0, 84.0, 115.2, 118.6, 122.5, 123.7, 126.9, 128.2, 129.5, 153.0, 155.9, 157.0, 167.4. ^{1}H NMR (CD_3OD): 2.87 (t, 2H, J = 7.2 Hz), 2.93 (t, 2H, J = 7.5 Hz), 3.53 (t, 2H, J = 7.2 Hz), 3.83 (t, 2H, J = 7.5 Hz), 5.37 (s, 1H), 6.71 (d, 2H, J = 8.3 Hz), 7.05 (d, 2H, J = 8.3 Hz), 7.13 (s, 1H). ^{13}C NMR (CD_3OD): 168.5, 159.6, 157.4, 155.0, 130.8, 129.9, 127.2, 126.9, 123.9, 120.2, 116.5, 85.2, 46.5, 44.1, 34.4, 30.4. These values are virtually identical with those reported earlier.[8b]

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **4**, **6**, **9**, **11**, **13**, **14**, **15**, **19**, **23**, and **24** are available (20 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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