Iodine(III)-Mediated Generation of Nitrogen-Tethered Orthoquinol Acetates for the Construction of Oxygenated Indole, Quinoline, and Phenanthridine Alkaloid Motifs

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Functionalized indole and quinoline derivatives are conveniently prepared from nitrogen-tethered 2-methoxyphenols via phenyliodine(III) diacetate mediated oxidative acetoxylation, followed by a fluoride- or base-induced intramolecular nucleophilic addition reaction. This regioselective Michael-type addition step is further discussed in view of the rearrangement of orthoquinol acetate intermediates into paraquinol acetates that is sometimes observed in situ. Application of this methodology to the synthesis of a functionalized phenanthridine, and its potential for the construction of polyoxygenated lycorine-type alkaloid skeleta are here described.

Introduction

The unique polycyclic structures and potentially useful pharmacological properties of *Amaryllidaceae* alkaloids continue to fuel numerous synthetic studies.[1−7] The lycorine-type alkaloids, which are characterized by the presence of the ABCD tetracyclic α-lycorane core (**1**), represent an important subclass of this family of natural products (Figure 1). Among them, lycorine (**2**) was the first *Amaryllidaceae* alkaloid isolated in 1877 from *Narcissus pseudonarcissus*.[8] It is the bioactive principle that is the most frequently isolated from ornamental plants of the *Amaryllidaceae* family, and it displays analgesic,[9] antiviral,[10] and antineoplastic activities,[11−13] as well as insect antifeedant activities.[14,15] It is known to inhibit protein and DNA syntheses and was also found to inhibit mouse tumor cell apoptosis induced by polymorphonuclear leukocyte-derived calprotectin (EC_{50} = 0.1−0.5 μg/mL).[16] The nonchiral benzannulated anhydrolycorinium chloride (**3a**, R = H) is effective in vivo against murine P-388 lymphocytic leukemia,[17] and ungeremine (**3b**, R = OH) is active against some types of carcinoma.[18] The indolic 3,4-dehydroanhydrolycorine (**4a**, X = H, H) and hippadine (**4b**, X = O) are both biosynthetically derived from 2-*epi*-lycorine,[19] and **4b** reversibly inhibits fertility in male rats.[20,21] The structurally related

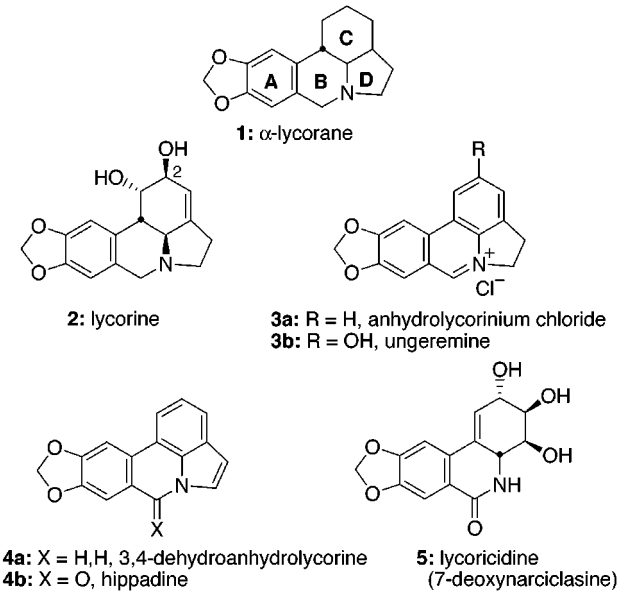

Figure 1.

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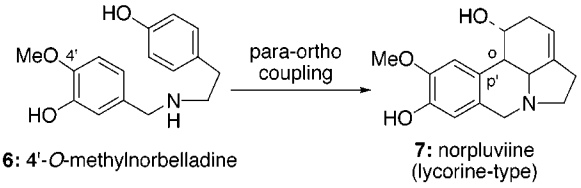
Scheme 1



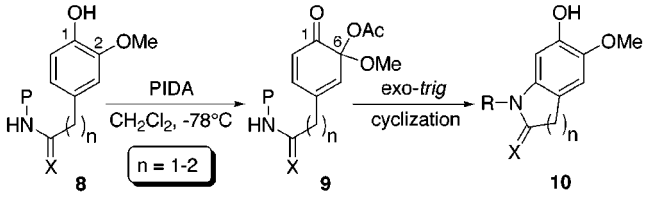
ABC tricyclic lycoricidine (**5**) exhibits in vitro antiviral activity against RNA-containing flaviviruses and bunyaviruses,[10] as well as antitumoral activity against Ehrlich carcinoma.[22]

This structural diversity in bioactive *Amaryllidaceae* alkaloids has provided organic chemists with attractive targets for the development of various synthetic methodologies.[23−30] Considerable efforts have been directed toward the elaboration of the ABCD tetracyclic skeleton of alkaloids **2**−**4**. In most cases, introduction of the oxygenated functions on cycle C was carried out after construction of the α-lycorane core **1**.

All of these lycorine-type alkaloids are biosynthetically derived from a common diphenolic precursor identified as 4′-*O*-methylnorbelladine (**6**), which presumably undergoes a one-electron oxidative para-ortho phenolic coupling in route to the lycorine-type norpluviine (**7**) (Scheme 1).[31]

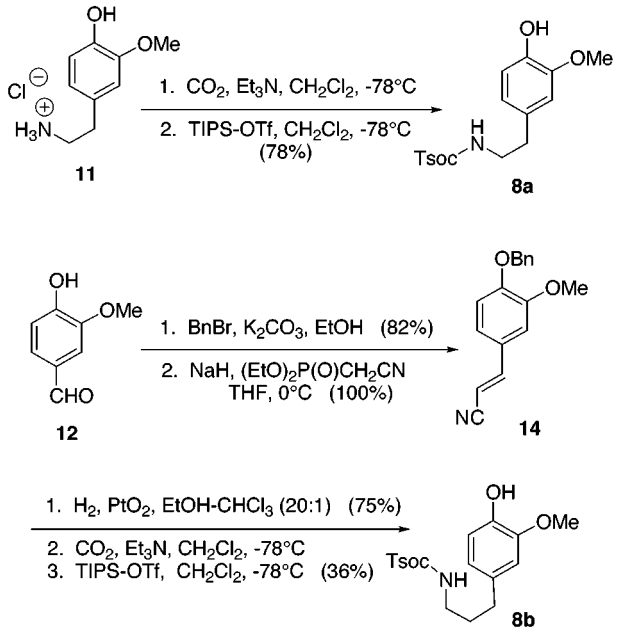
The synthetic utility of such radical coupling reactions is, however, poor because of the lack of regiochemical control and competing polymerization processes.[32−34] A two-electron oxidative activation of a nitrogen-linked diphenol such as **6** or an analogue thereof could provide a solution to this synthetic challenge. Our investigations on orthoquinone monoketal chemistry for the synthesis of polyoxygenated benzannulated heterocyclic systems led us to consider nitrogen heterocyclization as a potentially useful alternative route. In this context, oxidative acetoxylation of 2-alkoxyarenols allows the transformation of functionalized arenols (i.e., hydroxylated arenes) into orthoquinol acetates (i.e., 6-acetoxy-6-alkoxycyclohexa-2,4-dienones). Their conjugated enone system can be exploited to induce intramolecular nucleophilic addition reactions in a regiocontrolled manner. We already applied this strategy for exo-*trig*[35] selective oxygen heterocyclization using phenyliodine(III) diacetate (PIDA)[36]

Scheme 2



X = H,H or O; P = acyl or alkyl group; R = H, acyl or alkyl group

Scheme 3



as a convenient alternative to the use of metal-based oxidizing reagents such as $Pb(OAc)_4$[37,38] and $Tl(NO_3)_3$.[39] We discuss here nitrogen versions of these heterocyclizations (Scheme 2). Elaboration of various benzannulated nitrogen-containing five- and six-membered rings, i.e., indolines and tetrahydroquinolines, is described in full detail. Application of this novel methodology to the synthesis of a lycoricidine analogue and of lycorine-type advanced intermediates is also presented.

Results and Discussion

Phenols **8a**−**e** were prepared in good yields from commercially available 2-methoxyphenols. The *N*-Tsoc-protected amino phenol **8a** was synthesized in one step from 3-*O*-methyldopamine hydrochloride **11** in 78% yield (Scheme 3).[40] The introduction of the tri-*iso*-propylsilyloxycarbonyl protective group C(O)OSi(*i*-Pr)$_3$ (Tsoc) does not require preliminary phenol protection,[41] and was chosen by analogy with our work on silylated oxygen-tethered 2-methoxyphenols used in PIDA-mediated acetoxylation.[36] The synthesis of phenol **8b** began with

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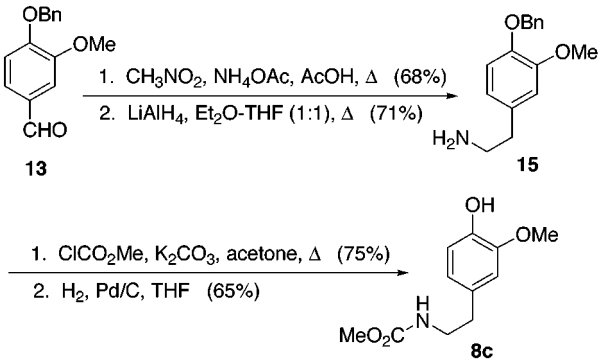
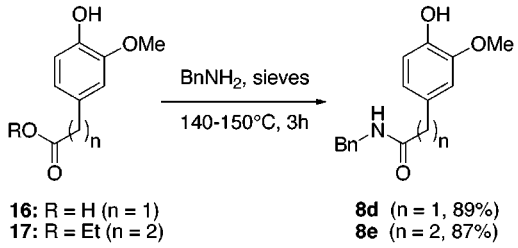
(41) Lipshutz, B. H.; Papa, P.; Keith, J. M. *J. Org. Chem.* **1999**, *64*, 3792−3793.

Scheme 4



Scheme 5



benzylation of vanillin (**12**). The aldehyde function of the resulting benzyl ether (**13**) was reacted with the anion derived from diethyl cyanomethylphosphonate to furnish the α,β-unsaturated nitrile **14** in 82% yield from **12** (Scheme 3). Treatment with hydrogen in EtOH−$CHCl_3$ (20:1) in the presence of Adam's catalyst[42] gave the corresponding phenolic primary amine,[43] which was submitted to Lipshutz's procedure[41] to give the *N*-silylated carbamate phenol **8b** in 27% yield from **14** (Scheme 3).

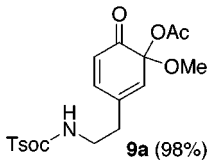
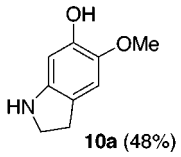
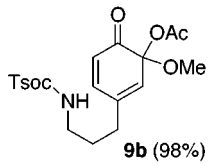
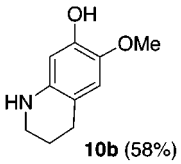
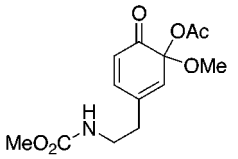
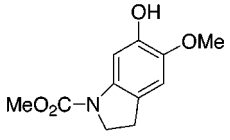
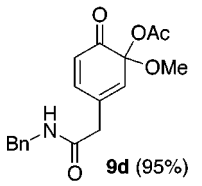
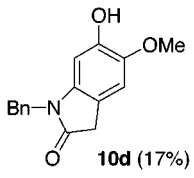
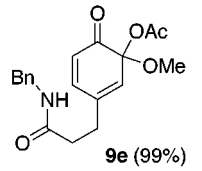
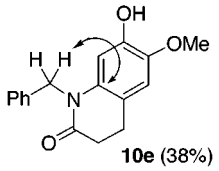
Phenol **8c** was prepared in order to probe the capacity of its carbamate nitrogen atom to perform the desired heterocyclization. Henry condensation between the aldehyde group of benzylated vanillin (**13**) and nitromethane in the presence of ammonium acetate in refluxing acetic acid furnished the corresponding nitrostyrene (Scheme 4). Reduction of this compound with $LiAlH_4$ in refluxing Et_2O/THF (1:1) gave rise to the primary amine **15** in 48% yield from **13**. Reaction of this free amine in refluxing acetone with methyl chloroformate (4 equiv) and anhydrous potassium carbonate (6 equiv)[44] furnished a carbamate derivative, which was submitted to standard debenzylation in THF to give phenol **8c** in 49% yield from **15**.

Finally, the two *N*-benzylated amido phenols **8d** and **8e** were prepared in good yields by direct condensation of homovanillic acid (**16**) or ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (**17**),[36] in the presence of 4 Å molecular sieves[45] in neat benzylamine at 140−150 °C[46] (Scheme 5).

All of the nitrogen-tethered 2-methoxyphenols **8a**−**e** were submitted to PIDA-mediated oxidative acetoxylation, in methylene chloride at −78 °C, according to our previously reported procedure.[36] The corresponding orthoquinol acetates **9a**−**e** were obtained in excellent yields (Table 1).[40] In contrast to the use of metal-based oxidizing systems, the iodobenzene and acetic acid byproducts are conveniently removed by drying under vacuum, and no spent toxic salts are generated. Of particular note is the fact that similar PIDA oxidations of free amino-tethered phenols **11** and debenzylated **15** gave rise to intractable mixtures. Protection of the appended amino group thus proved to be crucial to the success of these dearomatizing acetoxylations. The nature of the amino protective group influenced the propensity with which annulation could be promoted, and different condition sets had to be selected to carry out regioselective cyclizations to indoline and tetrahydroquinoline compounds **10a**−**e** (Table 1).[40]

We already reported that oxygen-tethered orthoquinol acetates can be stored as dry oils for several days at −20 °C without any noticeable degradation.[36] A similar behavior was observed with the nitrogen versions, but the orthoquinonoid species **9c**−**e** that bear a methyl carbamate or a benzyl amide were somewhat less stable in

Table 1. Nitrogen Benzannulation of Orthoquinol Acetates into Indoline and Quinoline Derivatives

Starting phenol	*a* → Orthoquinol acetate	*b* → indoline or quinoline
8a	 **9a** (98%)	 **10a** (48%)
8b	 **9b** (98%)	 **10b** (58%)
8c	 **9c** (92%)	 **10c** (32%)
8d	 **9d** (95%)	 **10d** (17%)
8e	 **9e** (99%)	 **10e** (38%)

[a] PIDA (1.0 equiv), CH_2Cl_2, −78 °C. [b] Exo-*trig* cyclization.

(42) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241−4250.
(43) Elorriaga, C.; Cortes Fernandez, M. A.; Fernandez Alvarez, E.; Nieto Lopez, O.; Piedrafita, F. J. *An. Quím., Ser. C* **1987**, *83*, 70−76.
(44) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *12*, 1051−1054.
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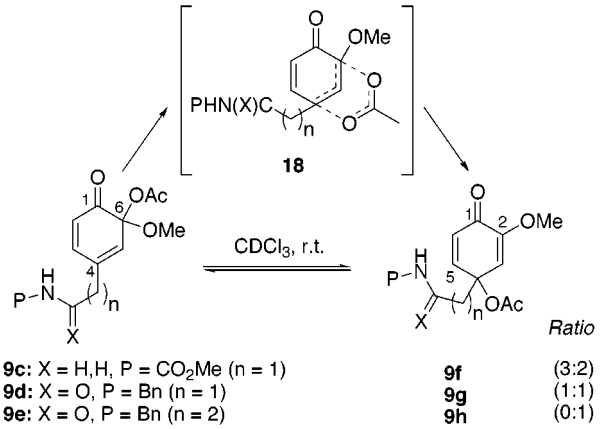
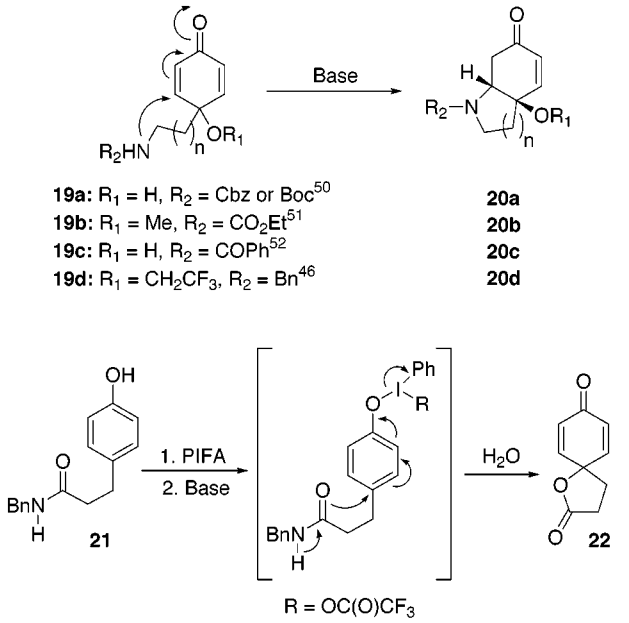
Scheme 6



solution. For example, proton NMR monitoring of **9e** in a $CDCl_3$ solution (ca. 0.4 M) indicated that this monoketal intermediate began to evolve over prolonged periods of time at room temperature. After 3 days at ambient temperature, **9e** was completely and cleanly transformed into a new compound that was then identified as the cyclohexa-2,5-dienone **9h** (Scheme 6). Despite very similar spin systems, compounds **9e** and **9h** could be distinguished on the basis of certain carbon chemical shifts. For example, the carbonyl carbon-1 of the cyclohexa-2,4-dienone **9e** resonates at 191.5 ppm, whereas carbon-1 of the 2,5-dienone counterpart **9h** is expectedly shifted upfield by about 11 ppm. The ketal carbon-6 of **9e** resonating at 92.9 ppm is converted into the methyl enol ether carbon-2, which gives a downfield signal at 151.2 ppm. Structure **9h** was further confirmed by establishing proton−proton and proton−carbon connectivities by two-dimensional NMR experiments (see Experimental Section). A [3,3] sigmatropic shift of the acetate group can be invoked to explain the transformation of the 2,4-dienone derivative **9e** into the apparently more thermodynamically stable 2,5-counterpart **9h** (Scheme 6). Similar rearrangements have been observed for orthoquinol acetates **9c** and **9d** in the course of their ^1H and ^{13}C NMR analyses. Reaction equilibria led to mixtures of 2,4- and 2,5-dienone derivatives, which suffered degradation after 3 days.

Orthoquinol acetates were consequently submitted to the cyclization conditions immediately after preparation. The silylated amines **9a**/**b** were treated with tetrabutylammonium fluoride (TBAF) in THF to afford the benzannulated indoline **10a** and tetrahydroquinoline **10b** (Table 1). The carbamate **9c** was instead deprotonated to induce cyclization. Various bases such as Na_2CO_3 in THF, K_2CO_3 in refluxing CH_3CN, NaH in THF, and tetramethylpiperidine in THF were tried without any success, but treatment with lithium hexamethyldisilazane (LHMDS) in THF gave the indoline **10c** in 32% yield. At this point, it was not clear whether this moderate cyclization yield was due to the relative instability of the orthoquinol acetate **9c** or to the lower nucleophilic force of the carbamate nitrogen when compared to that of the transient amino anion in **9a**/**b**. Amide nitrogen heterocyclization was next investigated with the aim of preparing functionalized 2-oxindoles and oxoquinolines, which constitute potentially useful pharmacophores.[47−49] As in the case of the carbamate **9c**, cyclization of the benzylated amido orthoquinol acetates **9d**/**e** was base-induced. Potassium *tert*-butoxide in refluxing THF (ca. 70 °C) was, in this case, identified as the best system to induce the desired benzannulation. The 2-oxindole **10d** and the 3,4-dehydro-2-oxoquinoline **10e** were obtained in unoptimized yields of 17% and 38%, respectively. These moderate yields of heterocyclizations and the observation of acetate shifts (vide supra) led us to wonder about the nature of the cyclohexadienone (2,4- vs 2,5-) intermediates really involved in the cyclization process. Nitrogen-tethered cyclohexa-2,5-dienones **19a**−**d**, also generated by iodine(III)-mediated oxidations of *p*-phenols, are indeed known to undergo intramolecular Michael-type nitrogen additions leading to the formation of hydroindolenones and hydroquinolenones **20a**−**d** (Scheme 7).[46,50−52]

Scheme 7



The cyclohexa-2,5-dienone **9h** was submitted to the cyclization conditions set up for the orthoquinol acetate **9e**. Refluxing at 70 °C in THF for 1.5 days did not promote any cyclization, whereas more drastic conditions, i.e., 150 °C for 3 h, induced the formation of the desired benzannulated target **10e**, which was isolated in 36% yield. This result demonstrated that the conditions proposed in our methodology clearly involved cyclohexa-2,4-dienone entities. The regiochemistry of all cyclized products was readily determined by the observation of two aromatic singlets in their ^1H NMR spectrum. The cyclic connectivity at the nitrogen atom of the amide function was further confirmed on structure **10e** by the detection of a diagnostic three-bond response in its long-range C−H correlation 2D map. The methylene hydrogen atoms of the benzyl group were nicely correlated with the nitrogen-bearing quaternary carbon atom resonating at 133.7 ppm (Table 1). Assignment of this carbon signal

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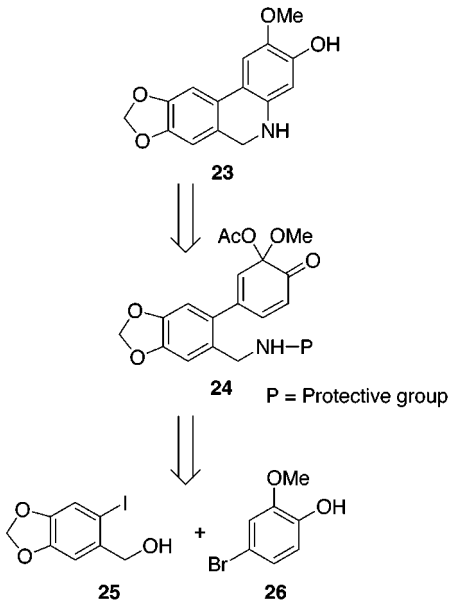
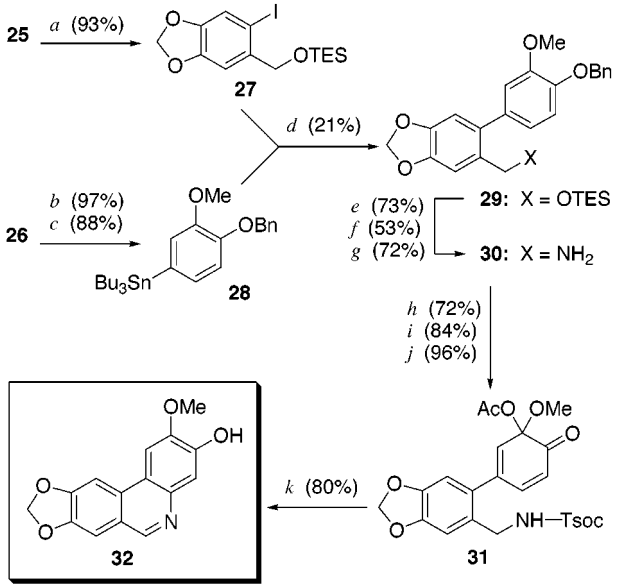
Scheme 8



Scheme 9[a]



[a] Reagents: (*a*) TES-OTf, Et_3N, CH_2Cl_2; (*b*) BnBr, K_2CO_3, EtOH; (*c*) *t*-BuLi, Et_2O, Bu_3SnCl, −78 °C; (*d*) $Pd(PPh_3)_4$, Na_2CO_3, toluene, Δ; (*e*) TBAF, THF; (*f*) $Zn(N_3)_2$·2Pyr, DEAD, PPh_3, THF/CH_2Cl_2 (4:1); (*g*) PPh_3, H_2O, THF; (*h*) CO_2, Et_3N, CH_2Cl_2, −78 °C, then TIPS-OTf; (*i*) H_2, Pd/C, THF; (*j*) PIDA, CH_2Cl_2, −78 °C; (*k*) TBAF, THF.

was deduced from its two-bond correlation with the hydrogen atom ortho to the phenol. Similar NMR data were obtained with indoline **10c** and oxindole **10d**. These structural determinations are important since the nucleophilicity of an amide oxygen is known to compete with that of the nitrogen atom (Scheme 7).[46,52] In most cases, both PIDA- and phenyliodine(III) bis(trifluoroacetate) PIFA-mediated oxidation of amido *p*-phenols furnish *O*-spirocyclohexa-2,5-dienones (e.g., **21** → **22**, Scheme 7).[46,53] Only the use of imidate groups results in nitrogen attack at the para-substituted electrophilic site[46] of the phenoxenium-type intermediate.[54] In our work, temporary introduction of the acetate group allows us to prepare the arene ring to undergo benzannulation without spiroannulation. Direct PIFA-mediated oxidation of phenol **8e** under Kita's conditions[53] afforded unidentified complex mixtures. The methoxy group in the 2-position of the starting phenols acts as an orienting group for the oxidative acetoxylation.[55] Orthoquinol acetates derived from either *N*-Tsoc-protected amines, benzylated amides, or carbamates all furnished exo-*trig* benzannulation products.

This azacyclization methodology led us to envisage the synthesis of the benzannulated tetracycle **23** (Scheme 8), a possible advanced synthetic intermediate of lycoricidine (**5**) (Figure 1). The retrosynthetic analysis was based on the regiocontrolled nitrogen-benzannulation of an orthoquinol acetate of type **24**. A Stille coupling reaction, involving two compounds derived from readily available synthons **25**[56] and **26**,[57] was selected for the biaryl carbon−carbon bond formation (Scheme 8).

The 5-(hydroxymethyl)-6-iodo-1,3-benzodioxole (**25**)[56] was protected with triethylsilyl trifluoromethanesulfonate (TES-OTf) to furnish the iodocompound **27** in 93% yield (Scheme 9). The tin derivative **28** was obtained in two steps from 4-bromo-2-methoxyphenol (**26**).[57] Benzylation[58] of **26** was followed by a treatment with *tert*-butyllithium (1.5 M in pentane, 1.05 equiv) and tributyltin chloride in Et_2O at −78 °C to afford **28** in 85% overall yield from **26**. The Stille coupling of **27** with **28** was carried out in refluxing toluene for 4 days in the presence of sodium carbonate (7 equiv) and a catalytic amount of palladium tetrakis(triphenylphosphine). The resulting *O*-silylated biaryl **29** (21% yield, not optimized) was then submitted to a TBAF-mediated desilylation, followed by a Mitsunobu reaction with $Zn(N_3)_2$·2Pyr (0.75 equiv) in the presence of diethyl azodicarboxylate (DEAD, 1.5 equiv) and PPh_3 (1.5 equiv)[59] to give the corresponding azide. Reduction of this compound under standard conditions (PPh_3, H_2O, THF, 4 days)[60] then afforded amine **30** in 28% overall yield from **29**. The primary amine **30** was protected as its *N*-Tsoc carbamate and debenzylated prior to PIDA-mediated oxidative acetoxylation. The orthoquinol acetate **31** was thus obtained in 58% yield from amine **30**. Of particular note is the fact that only the cyclohexa-2,4-dienone was experimentally observed, as in the case of the other *N*-Tsoc phenols **8a** and **8b** (vide supra). Subsequent TBAF-mediated deprotection−cyclization sequence furnished an off-white solid (80% yield) that was identified as the phenanthridine derivative **32**. The 6-exo-*trig* heterocylization was readily confirmed by the observation of two additional aromatic singlets and the disappearance of the orthoquinol acetate conjugated ethylenic signals in the ^1H NMR spectrum. We attempted to prevent in situ the oxidizing aromatization of the dihydrophenanthridine **23** into the phenanthridine **32** by adding 2,6-di-*tert*-butyl-4-methoxyphenol (1 equiv) into the reaction medium, but **32** was again formed in a very

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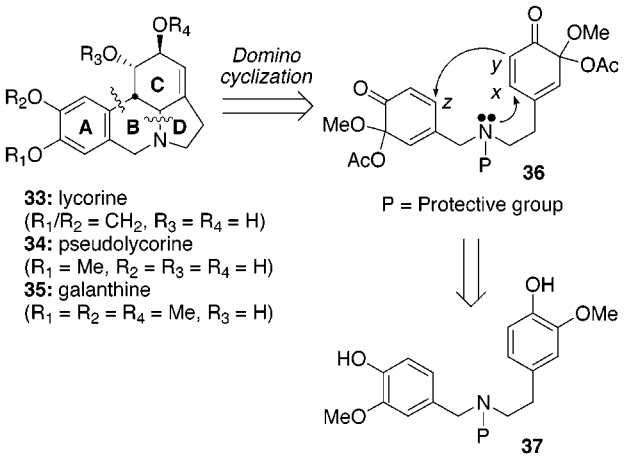
Scheme 10

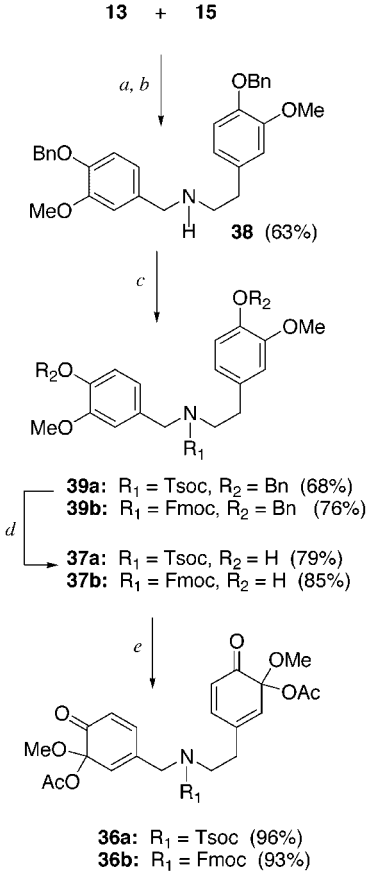


good yield. Further investigation is in progress to identify conditions that will allow one to stop the reaction at the dihydrophenanthridine stage. Nevertheless, the methodology described offers a new entry into hydroxylated analogues of fully aromatized benzo[*c*]phenanthridine alkaloids, such as trisphaeridine (not shown).[61]

Application of this methodology to natural products synthesis is also being explored for the construction of the lycorine-type polycyclic alkaloid skeleton. A *domino* reaction relying on ionic bond formations is thus here selected over radical processes. Conceptually, the ABCD tetracyclic *Amaryllidaceae* alkaloids such as **33**−**35** can be accessed via formation of both nitrogen−carbon (N−C*x*) and carbon−carbon (C*y*−C*z*) core bonds in a single operation from an adequately functionalized bis(ortho-quinone monoketal) such as the *N*-protected bis(ortho-quinol acetate) **36** (Scheme 10). Of particular note is the fact that the starting diphenol **37**, which is intended for a synthetic two-electron oxidative activation, is a structural analogue of the *Amaryllidaceae* biosynthetic precursor **6** (Scheme 1).

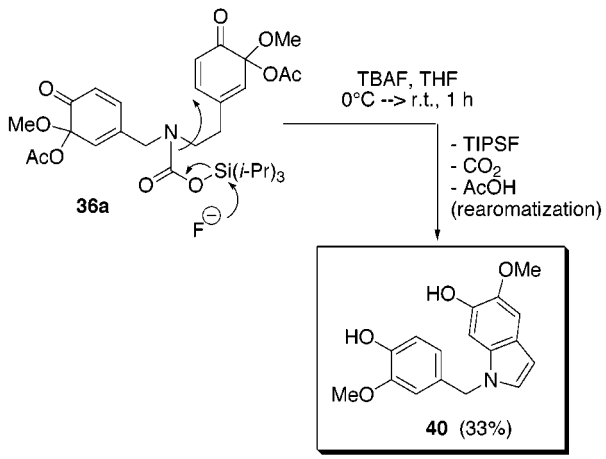
Various protective groups have been envisaged for the advanced diphenolic intermediate **37**. The synthesis of two variants **37a** and **37b** was achieved as depicted in Scheme 11. The known secondary amine **38**[62] was prepared in 63% yield by reductive amination of the benzylated vanillin **13** and the primary amine **15** in methanol in the presence of sodium borohydride.[62] As previously observed with the model compounds (vide supra), direct PIDA-mediated oxidative acetoxylation of the nonprotected amino diphenol **37** (P = H) gave intractable mixtures. Both amino protective groups Tsoc[41] and Fmoc[63,64] were selected to resist oxidation in an acidic medium and to evaluate two different modes of deprotection leading to induction of cyclization. The Tsoc group can be chemoselectively cleaved by a source of fluoride ions,[41] and the Fmoc group necessitates a base treatment to unveil the nucleophilic power of its linked nitrogen atom.[65] Both Tsoc- and Fmoc-carbamate derivatives

Scheme 11[a]



[a] Reagents: (*a*) 4 Å MS, MeOH, Δ; (*b*) $NaBH_4$, MeOH; (*c*) CO_2, Et_3N, CH_2Cl_2, −78 °C, then TIPS-OTf, or Fmoc-Cl, 10% Na_2CO_3, THF; (*d*) H_2, Pd/C, THF; (*e*) PIDA, CH_2Cl_2, −78 °C.

Scheme 12



39a/**b** were obtained in good yields (68% and 76%, respectively). Debenzylation by hydrogenolysis afforded the phenols **37a** and **37b**, which were submitted to the oxidative acetoxylation to furnish the desired bis(ortho-quinol acetates) **36a** and **36b** in excellent yields.

Desilylation of the *N*-Tsoc carbamate **36a** was performed using a commercial 1.0 M solution of TBAF (1.1 equiv) in THF. The indole **40** was isolated in a yield of 33% (Scheme 12). The deprotection−heterocyclization sequence was thus successful, but the system failed to convert itself to the desired tetracycle. Departure of the acetate group seemingly competed with trapping of the

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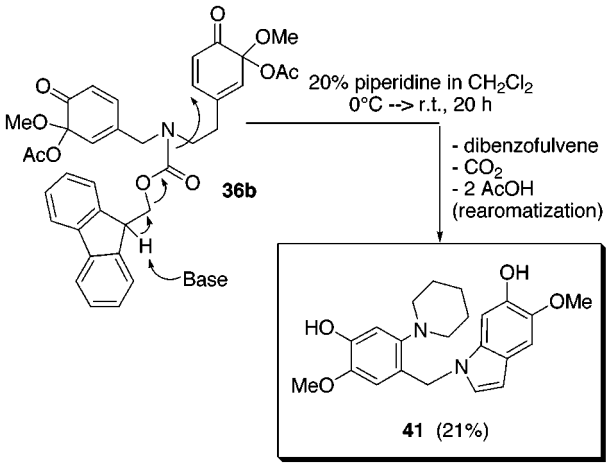
Scheme 13



second orthoquinol acetate moiety by the transient enolate. We presumed that an indoline structure is initially made, as in the conversion of **9a** into **10a** (Table 1), but an apparent intramolecular oxido-reductive process, probably driven by the complete aromatization of the system, led to the formation of the indole **40**.

We were somewhat worried about this result evidencing a certain lack of reactivity between the two *y* and *z* carbon centers. We then turned to our second *N*-protected bis(orthoquinol acetate) **36b**. Upon treatment with 20% piperidine in dichloromethane at 0 °C,[64] the Fmoc protective group of **36b** was easily cleaved, and further stirring at room temperature for 20 h afforded compound **41** in 21% yield (Scheme 13). Here again, the nitrogen−carbon bond formation was effective, but the departure of the acetate group still did not allow the required carbon−carbon linkage. An overoxidized indolic five-membered ring was obtained but aromatizaton of the second orthoquinol acetate moiety was this time preceded by the introduction of a piperidine unit at the targeted *z*-carbon center. Although the desired in situ carbon−carbon bond formation has not yet been achieved, the feasability of trapping the electrophilic site of this orthoquinonoid species via a Michael addition has been demonstrated. In view of these promising synthesis inquiries, we are now working at identifying adequate reaction conditions and substrate arrangements that will fully open this intramolecular Michael addition route to the ABCD tetracyclic core of lycorine-type alkaloids.

Conclusions

In summary, the present work has demonstrated the synthetic utility of nitrogen-tethered orthoquinol acetates in nitrogen heterocyclization chemistry for the elaboration of various benzannulated nitrogen-containing five- and six-membered rings. These orthoquinonoid species are conveniently prepared by PIDA-mediated oxidative acetoxylation and regioselectively benzannulated by intramolecular Michael-type addition reactions. This two-step methodology was here applied to the construction of nitrogen-containing polycyclic skeleta such as polyoxygenated phenanthridine derivatives. Bis(orthoquinol acetate) intermediates were also revealed as potentially useful electrophiles for the construction of lycorine-type ABCD tetracycles.

Experimental Section

General. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone under N_2 immediately before use. CH_2Cl_2 was distilled from CaH_2 prior to use. Moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under N_2. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40−63 μm silica gel and the indicated solvents. Melting points are uncorrected. NMR spectra of samples in the indicated solvent were run at 200, 250, or 400 MHz. Carbon multiplicities were determined by DEPT135 experiments. Diagnostic correlations were obtained by two-dimensional HMQC and HMBC experiments run on a 400-DPX spectrometer. Electron impact mass spectra (EIMS) were obtained at 50−70 eV. Electron impact and liquid secondary ion mass spectrometry low and high resolution (EIMS, and LSIMS, HRMS) were obtained from the mass spectrometry laboratory at the CESAMO, Université Bordeaux 1. Combustion analyses were performed by Laboratoires Wolff, Clichy, France.

4-Benzyloxy-3-methoxybenzaldehyde (13). To a stirred solution of vanillin **12** (20 g, 0.131 mol) in absolute EtOH (120 mL) were added K_2CO_3 (19.9 g, 0.144 mol) and benzyl bromide (15.7 mL, 0.131 mol), and the mixture was maintained under a nitrogen atmosphere overnight. The solution was filtered through Celite, washed with CH_2Cl_2 (3 × 100 mL), and then concentrated under vacuum. The oily residue was dissolved in 200 mL of CH_2Cl_2, washed with 5% NaOH solution, dried over K_2CO_3, concentrated, and crystallized from EtOH to furnish pure **13** as white fine crystals (26.2 g, 82%): mp 61−62 °C (lit.[66] mp 62−63 °C); IR (KBr) 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.86 (s, 3H), 5.17 (s, 2H), 6.94 (d, J = 8.2 Hz, 1H), 7.27−7.43 (m, 7H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 190.6, 153.2, 149.7, 135.7, 129.9, 128.4, 127.9, 126.9, 126.3, 112.0, 108.9, 70.4, 55.6; EIMS *m*/*z* (rel intensity) 242 (M^+, 100), 151 (12), 91 (100).

4-Benzyloxy-3-methoxy-β-cyanostyrene (14). A stirred ice-cold suspension of NaH (1.19 g, 24.8 mmol) in 50 mL of dry THF, maintained under a nitrogen atmosphere, was treated with diethyl (cyanomethyl)-phosphonate (4.39 g, 24.8 mmol, Aldrich). When the evolution of hydrogen was over (ca. 20 min), a solution of benzylated vanillin **13** (5.00 g, 20.7 mmol) in 15 mL of dry THF was added dropwise, and the resulting mixture was stirred at 0 °C for 1.5 h. The reaction mixture was then filtered through a pad of TLC-grade silica gel and washed several times with Et_2O. Evaporation of the solvents afforded **14** as a white solid, which was used without any further purification (5.47 g, quantitative yield): mp 74−75 °C; IR (KBr) 2208, 1622 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.89 (s, 3H), 5.18 (s, 2H), 5.71 (d, J = 16.5 Hz, 1H), 6.85−6.97 (m, 3H), 7.27 (d, J = 16.5 Hz, 1H), 7.33−7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.7, 149.9, 149.6, 136.1, 128.4, 127.9, 127.0, 126.7, 121.6, 118.4, 113.1, 109.2, 93.5, 70.5, 55.8; EIMS *m*/*z* (rel intensity) 266 (MH^+, 6), 265 (M^+, 21), 174 (2), 91 (100); HRMS (EI) calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1098.

***N*-Tsoc-4-hydroxy-3-methoxyphenylpropylamine (8b).** A stirred suspension of cyanostyrene **14** (2.15 g, 8.11 mmol) in absolute EtOH (40 mL) and $CHCl_3$ (2 mL) containing PtO_2 (215 mg, 10 wt %) was placed under H_2 (balloon) at room temperature and under atmospheric pressure. After 20 h, the mixture was filtered through Celite and washed with MeOH. Evaporation of the solvents, followed by filtration through a pad of silica afforded 4-hydroxy-3-methoxyphenylpropylamine[43] as a white solid, which was further dried in vacuo and then crystallized from CH_2Cl_2/MeOH (1.10 g, 75%): mp 134−135 °C; IR (KBr) 3520 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 1.85−1.92 (m, 2H), 2.48−2.55 (m, 2H), 2.76−2.83 (m, 2H), 3.73 (s, 3H), 6.56 (dd, J = 1.5, 8.1 Hz, 1H), 6.68−6.76 (m, 2H), 8.85 (bs, 2H); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 147.7, 144.9, 131.6, 120.5, 115.6, 112.7, 55.8, 46.4, 31.7, 27.5; LSIMS *m*/*z* (rel intensity) 183 (10), 182 (MH^+, 11), 181 (M^+, 31), 166 (12), 137

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(100). A stirred suspension of this aminophenol (597 mg, 3.30 mmol) and Et_3N (1.38 mL, 9.89 mmol) in dry CH_2Cl_2 (20 mL) was cooled at −78 °C. Dry ice (7.26 g, ca. 50 equiv) was added in one portion. After stirring at −78 °C for 1 h, TIPS-OTf (885 μL, 3.30 mmol) was added dropwise via syringe. After 5 min, the mixture was allowed to warm to room temperature and was stirred for 30 min. The mixture was then poured into a separatory funnel containing H_2O (20 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL); the combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine (2 × 15 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded an orange oil, which was purified by column chromatography, eluting with hexanes/Et_2O (1:1), to give **8b** as a pale yellow oil (452 mg, 36%): IR (NaCl) 3551, 3388, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (d, J = 6.9 Hz, 18H), 1.28 (h, J = 6.9 Hz, 3H), 1.71−1.85 (m, 2H), 2.51−2.59 (m, 2H), 3.08−3.21 (m, 2H), 3.83 (s, 3H), 4.92 (bs, 1H), 5.94 (bs, 1H), 6.60−6.66 (m, 2H), 6.80 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.0, 146.4, 143.7, 133.3, 120.7, 114.3, 111.0, 55.7, 40.6, 32.6, 31.7, 17.7, 11.9; EIMS *m/z* (rel intensity) 382 (MH^+, 2), 381 (M^+, 6), 338 (100), 137 (20).

2-(4-Benzyloxy-3-methoxyphenyl)ethylamine (15).[66] A mixture of NH_4OAc (3.82 g, 49.6 mmol), nitromethane (5.9 mL, 108.5 mmol), and benzylated vanillin **13** (15 g, 62.0 mmol) in AcOH (150 mL) was refluxed for 4 h. Upon cooling, the reaction deposited 9.7 g of 4-benzyloxy-3-methoxy-β-nitrostyrene as yellow crystals; the mother liquor was collected, concentrated, and crystallized from MeOH, giving another 2.3 g of yellow powder (12.0 g, 68%): mp 124−125 °C (lit.[66] mp 126−128 °C); IR (KBr) 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.91 (s, 3H), 5.20 (s, 2H), 6.89−7.09 (m, 3H), 7.32−7.42 (m, 5H), 7.52 (d, J = 13.4 Hz, 1H), 7.93 (d, J = 13.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 151.7, 149.8, 139.2, 135.9, 135.0, 128.6, 128.1, 127.1, 124.3, 122.9, 113.2, 110.6, 70.6, 55.9; EIMS *m/z* (rel intensity) 285 (M^+, 100), 147 (20), 91 (100). To a stirred solution of this nitrostyrene (2.0 g, 7.02 mmol) in 50 mL of anhydrous Et_2O/THF (1:1) was slowly added $LiAlH_4$ (0.8 g, 21.05 mmol). The solution was refluxed for 2 h and then stirred overnight at room temperature. To this solution were added water (2 mL), 15% NaOH (2 mL), and then water (6 mL), and the solution was stirred 30 min before filtering. The phases were separated, and the aqueous layer was extracted with ether (3 × 20 mL); the ether washes were combined and concentrated. The oily residue was dissolved in 10% HCl (3 mL) and washed with ether (10 mL); the aqueous layer was made basic and extracted with ether (2 × 20 mL). These two ether washes were combined and washed with water and brine before drying over K_2CO_3. Removal of the solvent produced the titled compound **15**[66] as an orange oil (1.28 g, 71%): IR (NaCl) 3367 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.32 (bs, 2H), 2.69 (bt, J = 7.0 Hz, 2H), 2.93 (bt, J = 7.0 Hz, 2H), 3.87 (s, 3H), 5.12 (s, 2H), 6.64−6.83 (m, 3H), 7.28−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 149.6, 146.6, 137.2, 132.7, 128.4, 127.7, 127.2, 120.6, 114.2, 112.6, 71.1, 55.9, 43.3, 39.1; EIMS *m/z* (rel intensity) 257 (M^+, 42), 137 (100), 91 (100).

Methyl 4-Hydroxy-3-methoxyphenylethylcarbamate (8c). To a stirred solution of the primary amine **15** (1.15 g, 4.47 mmol) in acetone (25 mL) was added powdered K_2CO_3 (3.70 g, 26.85 mmol) in one portion, followed by dropwise addition of methyl chloroformate (1.38 mL, 17.90 mmol). The mixture was heated on reflux for 20 h, after which time the solvent was evaporated, and the residue was treated with 4% methanolic sodium hydroxide (25 mL) at room temperature for 1.5 h. Evaporation of MeOH furnished an aqueous phase, which was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (2 × 15 mL), dried over Na_2SO_4, filtered, and evaporated. The resulting brown oil was submitted to column chromatography, eluting with CH_2Cl_2/AcOH/MeOH (200:6:0.5), to afford methyl 4-benzyloxy-3-methoxyphenylethylcarbamate as an off-white solid (1.06 g, 75%): mp 65−68 °C; IR (KBr) 3345, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.72 (bt, J = 7.0 Hz, 2H), 3.39 (bq, J = 7.0 Hz, 2H), 3.64 (s, 3H), 3.87 (s, 3H), 4.85 (bs, 1H), 5.12 (s, 2H), 6.65 (dd, J = 1.8, 8.2 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 7.26−7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 156.8, 149.5, 146.6, 137.1, 131.7, 128.3, 127.6, 127.1, 120.5, 114.0, 112.3, 70.9, 55.8, 51.8, 42.1, 35.5; EIMS *m/z* (rel intensity) 338 (MNa^+, 100), 316 (MH^+, 44), 315 (M^+, 96), 284 (6); HRMS (LSIMS) calcd for $C_{18}H_{21}NO_4$ 315.1470, found 315.1471. Debenzylation of this material (990 mg, 3.14 mmol) in 40 mL of dry THF was carried out under H_2 (balloon) overnight at room temperature in the presence of 10 wt % Pd/C as a catalyst (100 mg). The reaction mixture was filtered through Celite, and the solid was washed with acetone. Evaporation of the combined filtrates and washings afforded a crude oil, which was purified by column chromatography, eluting with hexanes/Et_2O (1:4), to give **8c** as a pale yellow oil (459 mg, 65%): IR (NaCl) 3510, 3382, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.72 (bt, J = 7.0 Hz, 2H), 3.39 (bq, J = 7.0 Hz, 2H), 3.65 (s, 3H), 3.84 (s, 3H), 4.91 (bs, 1H), 5.94 (bs, 1H), 6.63−6.68 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.0, 146.6, 144.2, 130.4, 121.2, 114.4, 111.2, 55.7, 51.9, 42.3, 35.6; EIMS *m/z* (rel intensity) 226 (MH^+, 7), 225 (M^+, 46), 194 (7), 151 (24), 150 (99), 137 (100); HRMS (LSIMS) calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0997.

***N*-Benzyl-4-hydroxy-3-methoxyphenylacetamide (8d).** A mixture of homovanillic acid **16** (500 mg, 2.75 mmol) and benzylamine (360 μL, 3.30 mmol) was heated at 140−150 °C in the presence of 4 Å molecular sieves for 3 h under N_2 atmosphere, after which time it was diluted with 30 mL of CH_2Cl_2, filtered, and evaporated to afford a brown oil. Purification by column chromatography, eluting with CH_2Cl_2/MeOH (20:1), gave **8d** as a pale yellow foam (662 mg, 89%): mp 83−84 °C; IR (KBr) 3506, 3368, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.53 (s, 2H), 3.83 (s, 3H), 4.40 (d, J = 5.9 Hz, 2H), 5.94 (bs, 2H), 6.68−6.76 (m, 2H), 6.86 (d, J = 7.8 Hz, 1H), 7.15−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.4, 146.9, 144.9, 138.1, 128.5, 127.4, 127.3, 126.3, 122.2, 114.8, 111.7, 55.8, 43.4, 43.3; EIMS *m/z* (rel intensity) 273 (2), 272 (MH^+, 19), 271 (M^+, 67), 137 (100), 91 (58).

***N*-Benzyl-4-hydroxy-3-methoxyphenylethylamide (8e).** A mixture of ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate **17**[36] (1.00 g, 4.46 mmol) and benzylamine (536 μL, 4.91 mmol) was heated at 140−150 °C for 3 h under N_2 atmosphere, after which time it was diluted with 40 mL of CH_2Cl_2, filtered, and evaporated to afford a brown oil. Purification by column chromatography, eluting with CH_2Cl_2/MeOH (20:1), gave **8e** as a pale yellow oil (1.10 g, 87%): IR (NaCl) 3546, 3359, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.45−2.53 (m, 2H), 2.86−2.94 (m, 2H), 3.75 (s, 3H), 4.36 (d, J = 5.6 Hz, 2H), 6.35 (bs, 1H), 6.44 (bt, J = 5.6 Hz, 1H), 6.62−6.69 (m, 2H), 6.82 (d, J = 8.1 Hz, 1H), 7.10−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 172.3, 146.5, 143.9, 137.9, 132.3, 128.3, 127.3, 127.1, 120.5, 114.4, 111.2, 55.6, 43.2, 38.4, 31.2; LSIMS *m/z* (rel intensity) 308 (MNa^+, 43), 287 (20), 286 (MH^+, 100), 285 (M^+, 72); HRMS (LSIMS) calcd for $C_{17}H_{20}NO_3$ 286.1442, found 286.1443.

Preparation of Orthoquinol Acetates (9a−e). A solution of the phenols **8a−e** (ca. 250 mg, 1.0 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of PIDA (1.0 equiv) in 5 mL of dry CH_2Cl_2 at −78 °C. The reaction mixture immediately became bright yellow. After 1 h, TLC monitoring [CH_2Cl_2/MeOH (20:1)] indicated complete consumption of the starting material. The mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (2 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature. The residue was further dried under high vacuum overnight to give the corresponding orthoquinol acetate **9a−e** as a bright yellow oil, which was used without further purification.

***N*-Tsoc-6-acetoxy-4-(2-aminoethyl)-6-methoxycyclohexa-2,4-dienone (9a).**[40] Bright yellow oil (98%). IR (NaCl) 3394, 1750, 1682, 1672 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.03 (d, J = 6.7 Hz, 18H), 1.25 (h, J = 6.7 Hz, 3H), 2.05 (s, 3H), 2.37−2.43 (m, 2H), 3.03−3.19 (m, 1H), 3.33−3.50 (m, 1H), 3.41 (s, 3H), 4.94−5.00 (m, 1H), 5.93 (bs, 1H), 6.10 (d, J = 9.9 Hz, 1H), 6.76 (dd, J = 2.2, 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.5, 169.6, 154.8, 141.9, 135.5, 131.0, 126.3, 92.8, 51.2, 38.9, 35.2, 20.5, 17.7, 11.9; EIMS *m/z* (rel intensity) 425 (M^+, 1),

382 (16), 324 (100), 137 (56); HRMS (EI) calcd for $C_{21}H_{35}NO_6Si$ 425.2233, found 425.2229.

***N*-Tsoc-6-acetoxy-4-(3-aminopropyl)-6-methoxycyclohexa-2,4-dienone (9b).** Bright yellow oil (98%). IR (NaCl) 3372, 1750, 1702, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (d, J = 6.7 Hz, 18H), 1.24 (h, J = 6.9 Hz, 3H), 1.65−1.79 (m, 2H), 2.09 (s, 3H), 2.28 (bt, J = 7.6 Hz, 2H), 3.05−3.26 (m, 2H), 3.44 (s, 3H), 4.91 (bs, 1H), 5.93 (d, J = 2.1 Hz, 1H), 6.11 (d, J = 10.2 Hz, 1H), 6.77 (dd, J = 2.1, 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 191.5, 169.5, 155.0, 142.1, 137.7, 129.3, 125.8, 92.9, 51.1, 40.1, 29.6, 22.6, 20.4, 17.7, 11.9; LSIMS *m*/*z* (rel intensity) 462 (MNa^+, 29), 438 (14), 396 (13), 380 (19).

6-Acetoxy-6-methoxy-4-(2-methoxycarbonylamino-ethyl)-cyclohexa-2,4-dienone (9c). Orange oil (92%). A 3:2 mixture of **9c** and **9f** was obtained after 1 day, and degradation was further observed. IR (NaCl) 3372, 1750, 1692, 1676 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.96 (s, 3H), 2.02 (s, 3H), 2.35 (bt, J = 6.4 Hz, 4H), 3.05−3.22 (m, 4H), 3.36 (s, 3H), 3.37 (s, 3H), 3.55 (s, 3H), 3.59 (s, 3H), 5.06 (bs, 1H), 5.16 (bs, 1H), 5.73 (d, J = 2.4 Hz, 1H), 5.89 (s, 1H), 6.05 (d, J = 10.1 Hz, 1H), 6.20 (d, J = 10.1 Hz, 1H), 6.72 (dd, J = 1.8, 10.1 Hz, 1H), 6.83 (dd, J = 2.4, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 191.4, 180.2, 169.7, 169.1, 156.8, 156.7, 151.1, 148.2, 141.9, 135.4, 130.7, 127.7, 126.0, 113.9, 92.7, 77.3, 54.8, 51.8, 51.2, 39.9, 38.6, 36.1, 35.0, 21.3, 20.3; LSIMS *m*/*z* (rel intensity) 306 (MNa^+, 100), 284 (MH^+, 9), 268 (6), 252 (10), 224 (27).

6-Acetoxy-4-benzylcarbamoylmethyl-6-methoxycyclohexa-2,4-dienone (9d). Bright yellow oil (95%). IR (NaCl) 3318, 1745, 1671, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.98 (s, 3H), 3.16 (d, J = 3.7 Hz, 2H), 3.42 (s, 3H), 4.25 (dd, J = 5.5, 14.6 Hz, 1H), 4.42 (dd, J = 6.3, 14.6 Hz, 1H), 6.08 (bs, 1H), 6.10 (d, J = 9.8 Hz, 1H), 6.70 (bs, 1H), 6.77 (dd, J = 2.2, 9.8 Hz, 1H), 7.16−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 191.0, 170.2, 168,4, 141.8, 137.9, 133.0, 132.5, 128.3, 127.6, 127.2, 126.4, 92.7, 51.3, 43.4, 42.3, 20.3. Evolution of orthoquinol acetate **9d** in the NMR tube ($CDCl_3$ as solvent) at room temperature was monitored by ^1H NMR. A 1:1 mixture of **9d** and **9g** was obtained after 3 days, and degradation was further observed. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.87 (s, 3H), 194 (s, 3H), 2.69 (s, 2H), 3.12 (d, J = 3.3 Hz, 2H), 3.37 (s, 3H), 3.51 (s, 3H), 3.62−3.78 (m, 2H), 4.34 (d, J = 5.9 Hz, 2H), 5.99 (d, J = 2.7 Hz, 1H), 6.03−6.08 (m, 1H), 6.14 (d, J = 10.0 Hz, 1H), 6.73 (dd, J = 2.1, 10.0 Hz, 1H), 6.86 (bs, 2H), 7.05 (dd, J = 2.7, 10.1 Hz, 1H), 7.16−7.29 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.1, 180.3, 173.9, 170.2, 169.3, 168.7, 166.9, 150.7, 147.6, 141.8, 137.9, 137.7, 132.9, 132.4, 128.4, 128.3, 127.4, 127.3, 127.2, 127.1, 126.2, 113.8, 92.7, 76.2, 54.8, 51.3, 46.2, 43.3, 42.1, 21.2, 20.5, 20.3.

6-Acetoxy-4-(2-benzylcarbamoyl-ethyl)-6-methoxycyclohexa-2,4-dienone (9e). Bright yellow oil (99%). IR (NaCl) 3338, 1750, 1674, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.00 (s, 3H), 2.29−2.37 (m, 2H), 2.50−2.57 (m, 2H), 3.38 (s, 3H), 4.33 (d, J = 5.9 Hz, 2H), 5.95 (d, J = 2.0 Hz, 1H), 6.00 (d, J = 10.0 Hz, 1H), 6.45 (bs, 1H), 6.70 (d, J = 2.0, 10.0 Hz, 1H), 7.18−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 191.5, 171.1, 169.5, 142.3, 138.0, 137.4, 129.6, 128.4, 127.5, 127.2, 125.7, 92.9, 51.2, 43.3, 34.9, 30.6, 20.3. Evolution of orthoquinol acetate **9e** in the NMR tube ($CDCl_3$ as solvent) at room temperature was monitored by ^1H NMR. The conversion to the 4-acetoxy-4-(2-benzylcarbamoyl-ethyl)-2-methoxycyclohexa-2,5-dienone **9h** was complete after 3 days. Evaporation of the solvent afforded an orange oil: IR (NaCl) 3368, 1758 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.99 (s, 3H), 2.09−2.37 (m, 2H), 2.45 (bt, J = 7.4 Hz, 1H), 2.84 (bt, J = 7.4 Hz, 1H), 3.54 (s, 3H), 4.31 (bt, J = 5.9 Hz, 2H), 5.67 (d, J = 2.6 Hz, 1H), 6.15 (d, J = 10.2 Hz, 1H), 6.64 (bs, 1H), 6.75 (d, J = 2.6, 10.2 Hz, 1H), 7.04−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 180.6, 171.4, 169.2, 151.2, 137.8, 128.4, 128.3, 127.9, 127.5, 127.3, 127.2, 114.3, 78.2, 54.7, 43.4, 34.2, 29.8, 20.6; EIMS *m*/*z* (rel intensity) 343 (M^+, 0.5), 285 (99),283 (8),150 (62), 137 (52), 91 (100).

7-Hydroxy-6-methoxy-1,2,3,4-tetrahydroquinoline (10b). To a stirred ice-cold solution of **9b** (110 mg, 0.25 mmol) in dry THF (5 mL) was added dropwise a commercial solution of TBAF (1 M in THF, 1.1 equiv). The reaction mixture immediately became darker. After 30 min, the ice bath was removed, and the reaction was stirred at room temperature for 1 h. Progression of the reaction was monitored by the disappearance of the orthoquinol acetate, as indicated by TLC [hexanes/Et_2O (1:1) and then CH_2Cl_2/MeOH (20:1)]. The mixture was diluted with EtOAc (30 mL), poured into ice-cold water (10 mL), extracted with EtOAc (2 × 15 mL), washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature. The resulting dark oily residue was purified by column chromatography, eluting with CH_2Cl_2/MeOH (100:1), to afford **10b** as an orange oil (26 mg, 58%): IR (NaCl) 3406 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.86−1.98 (m, 2H), 2.68 (bt, J = 6.3 Hz, 2H), 3.21−3.26 (m, 2H), 3.79 (s, 3H), 4.28 (bs, 2H), 6.19 (s, 1H), 6.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.6, 139.3, 138.4, 112.9, 101.9, 56.8, 42.1, 26.4, 22.5; LSIMS *m*/*z* (rel intensity) 180 (MH^+, 54), 179 (M^+, 100), 178 (41), 164 (26); HRMS (LSIMS) calcd for $C_{10}H_{13}NO_2$ 179.0946, found 179.0945.

***N*-Methoxycarbonyl-6-hydroxy-5-methoxy-2,3-dihydroindole (10c).** To a stirred solution of **9c** (100 mg, 0.35 mmol) in dry THF (5 mL) cooled at −8 °C was added dropwise a commercial solution of LHMDS (1.0 M in THF, 2.0 equiv). After stirring for 1 h at −8 °C, the mixture was allowed to warm to room temperature for 30 min, and was then diluted with EtOAc (30 mL) and water (10 mL). After separation, the aqueous phase was extracted with EtOAc (20 mL), and the organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to furnish a dark oily residue, which was purified by column chromatography, eluting with CH_2Cl_2/MeOH (40:1), to afford **10c** as amber crystals (25.2 mg, 32%): mp 153−155 °C; IR (KBr) 3322, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.02 (bt, J = 8.6 Hz, 2H), 3.83 (s, 6H), 3.88−4.06 (m, 2H), 5.75 (bs, 1H), 6.69 (s, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.9, 142.3, 121.3, 114.4, 111.2, 107.9, 102.7, 56.5, 52.5, 47.8, 27.8; EIMS *m*/*z* (rel intensity) 225 (8), 224 (MH^+, 42), 223 (M^+, 100), 208 (17); HRMS (LSIMS) calcd for $C_{11}H_{13}NO_4$ 223.0844, found 223.0845.

***N*-Benzyl-6-hydroxy-5-methoxy-2-oxindole (10d).** To a stirred solution of **9d** (75 mg, 0.23 mmol) in dry THF (10 mL) was added KO*t*-Bu (28 mg, 0.25 mmol) in one portion. After refluxing overnight, the reaction mixture was diluted with EtOAc (50 mL) and water (15 mL); the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated to afford 26 mg of crude product. Purification by column chromatography, eluting with CH_2Cl_2/MeOH (50:1), furnished **10d** as a dark oil (10.6 mg, 17%): IR (NaCl) 3376, 1664 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 3.49 (s, 2H), 3.83 (s, 3H), 4.41 (d, J = 6.1 Hz, 2H), 6.78 (s, 1H), 6.79 (s, 1H), 7.25−7.35 (m, 5H), 7.49 (s, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 173.7, 146.9, 144.8, 138.2, 128.6, 127.5, 126.5, 122.3, 114.8, 111.7, 55.9, 43.5, 29.7; LSIMS *m*/*z* (rel intensity) 292 (MNa^+, 5), 272 (100), 271 (54), 270 (MH^+, 9), 269 (M^+, 5), 254 (5).

***N*-Benzyl-7-hydroxy-6-methoxy-3,4-dihydro-2-oxoquinoline (10e).** To a stirred solution of **9e** (50 mg, 0.146 mmol) in dry THF (10 mL) was added KO*t*-Bu (18 mg, 0.160 mmol) in one portion. After refluxing overnight, the reaction mixture was diluted with EtOAc (50 mL) and water (15 mL); the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale orange oily crude product. Purification by column chromatography, eluting with CH_2Cl_2/MeOH (50:1), furnished **10e** as an off-white solid (16 mg, 38%): mp 134−135 °C; IR (KBr) 3404, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.72−2.79 (m, 2H), 2.86−2.94 (m, 2H), 3.85 (s, 3H), 5.12 (s, 2H), 6.55 (s, 1H), 6.67 (s, 1H), 7.19−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.3, 144.6, 142.0, 136.9, 133.7, 128.7, 127.0, 126.4, 117.5, 110.8, 103.6, 56.3, 46.2, 32.2, 25.2; LSIMS *m*/*z* (rel intensity) 306 (MNa^+, 45), 285 (31), 284 (MH^+, 75), 283 (M^+, 100), 268 (22), 252 (29); HRMS (LSIMS) calcd for $C_{17}H_{17}NO_3$ 283.1208, found 283.1210.

5-(Triethylsilyloxymethyl)-6-iodo-1,3-benzodioxole (27). To a stirred ice-cold suspension of 5-(hydroxymethyl)-6-iodo-1,3-benzodioxole **25**[56] (3.00 g, 10.8 mmol) in dry CH_2Cl_2 (55 mL) were added dropwise Et_3N (1.8 mL, 12.9 mmol) and TES-

OTf (2.68 mL, 11.9 mmol). After 10 min, the ice bath was removed and the mixture was stirred for 3.5 h at room temperature. The solution was then washed with 1 M H_3PO_4 (20 mL), water (20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to give 4.26 g of crude product. Purification by column chromatography, eluting with pentanes, afforded **27** as a colorless oil (3.95 mg, 93%): IR (NaCl) 1480, 1241, 940 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.68 (q, J = 7.3 Hz, 6H), 1.01 (t, J = 7.3 Hz, 9H), 4.54 (s, 2H), 5.93 (s, 2H), 7.07 (s, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.3, 147.1, 136.5, 117.8, 108.0, 101.3, 83.1, 68.8, 6.7, 4.4; EIMS *m/z* (rel intensity) 393 (MH^+, 11), 392 (M^+, 40), 363 (77), 236 (100); Anal. Calcd for $C_{14}H_{21}IO_3Si$: C, 42.86; H, 5.40; I, 32.35; O, 12.23; Si, 7.16. Found: C, 42.49; H, 5.18; I, 32.80.

3-Methoxy-4-benzyloxytributyltinbenzene (28). To a stirred solution of 4-bromo-2-methoxyphenol **26**[57] (6.00 g, 29.4 mol) in absolute EtOH (150 mL) were added K_2CO_3 (8.12 g, 58.8 mol) and benzyl bromide (6.99 mL, 58.8 mol), and the mixture was maintained under a nitrogen atmosphere overnight. The solution was filtered through Celite, washed with CH_2Cl_2 (3 × 30 mL), and then concentrated under vacuum. The oily residue was dissolved in 100 mL of CH_2Cl_2 and washed with 1 M H_3PO_4 (30 mL) and brine (2 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent furnished a yellow oil, which was submitted to column chromatography, eluting with hexanes/Et_2O (4:1), to give pure 3-methoxy-4-benzyloxybromobenzene[58] as a white solid (8.42 g, 97%): mp 49−51 °C (lit.[58] mp 61.0−61.2 °C); IR (KBr) 1578, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.85 (s, 3H), 5.10 (s, 2H), 6.72 (d, J = 8.5 Hz, 1H), 6.94 (dd, J = 2.3, 8.5 Hz, 1H), 6.98 (d, J = 2.3 Hz, 1H), 7.24−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 150.5, 147.4, 136.7, 128.6, 127.9, 127.3, 123.3, 115.5, 115.4, 113.4, 71.2, 56.1; EIMS *m/z* (rel intensity) 294, 292 (M^+, 68, 67), 213 (3), 203 (7), 201 (11), 91 (100). A stirred solution of this material (2.41 g, 8.22 mmol) in dry Et_2O (60 mL) was cooled at −78 °C and treated dropwise with a solution of *t*-BuLi (1.5 M in pentane, 1.05 equiv). After stirring for 45 min, tributyltin chloride (2.45 mL, 9.05 mmol) was added dropwise, and the mixture was allowed to warm to room temperature. Stirring at room temperature was maintained overnight. The mixture was then evaporated and directly submitted to column chromatography, eluting with pentanes/Et_2O (25:1), to afford **28** as a pale yellow oil (3.63 g, 88%): IR (NaCl) 1498, 1256, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, J = 7.1 Hz, 9H), 1.26−1.43 (m, 12H), 1.58−1.71 (m, 6H), 3.89 (s, 3H), 5.16 (s, 2H), 6.74 (d, J = 8.5 Hz, 1H), 6.87−6.92 (m, 2H), 7.29−7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.6, 148.1, 137.2, 128.4, 127.9, 127.7, 127.2, 121.4, 120.7, 114.1, 70.9, 55.9, 27.8, 26.8, 17.5, 13.5; EIMS *m/z* (rel intensity) 503 (M^+, 0.02), 446 (0.75), 91 (90), 57 (100).

***O*-Triethylsilyl-2-(4-benzyloxy-3-methoxyphenyl)-4,5-methylenedioxybenzyl alcohol (29).** A stirred solution of **27** (6.68 g, 13.28 mmol) and **28** (5.20 g, 13.28 mmol) in dry toluene (80 mL) was refluxed for 4 days in the presence of 10 wt % $Pd(PPh_3)_4$ as a catalyst (1.53 g) and Na_2CO_3 (9.85 g, 92.96 mmol), until TLC monitoring [hexanes/Et_2O (9:1)] indicated complete consumption of the starting materials. The resulting dark mixture was then diluted with EtOAc (50 mL) and an aqueous KF solution (40 mL), before stirring at room temperature for 30 min. The two layers were then separated, and the organic phase was extracted with EtOAc (4 × 30 mL), washed with water until pH 7, dried over Na_2SO_4, filtered, and evaporated to furnish a dark brown oil (10.20 g). Purification by column chromatography, eluting with hexanes/Et_2O (9:1), gave **29** as a colorless oil (1.35 g, 21%): IR (NaCl) 1482, 1239, 936 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.62 (q, J = 7.3 Hz, 6H), 0.97 (t, J = 7.3 Hz, 9H), 3.92 (s, 3H), 4.54 (s, 2H), 5.22 (s, 2H), 5.98 (s, 2H), 6.76 (s, 1H), 6.81 (dd, J = 2.0, 8.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 7.27−7.53 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.1, 147.2, 146.8, 146.3, 137.1, 134.1, 133.9, 132.2, 128.4, 127.7, 127.2, 121.4, 113.6, 113.2, 109.7, 108.2, 100.9, 71.0, 62.5, 55.9, 6.7, 4.4; LSIMS *m/z* (rel intensity) 501 (MNa^+, 10), 479 (MH^+, 35), 478 (M^+, 100), 449 (5), 387 (10), 347 (23); HRMS (LSIMS) calcd for $C_{28}H_{34}O_5Si$ 478.2175, found 478.2175.

2-(4-Benzyloxy-3-methoxyphenyl)-4,5-methylenedioxybenzylamine (30). To a stirred ice-cold solution of commercial TBAF (1 M in THF, 2.0 equiv) in dry THF (3 mL) was added dropwise a solution of **29** (817 mg, 2.03 mmol) in dry THF (5 mL). After 10 min, the ice bath was removed, and the reaction mixture was stirred at room temperature overnight. The mixture was then quenched by adding dropwise 20 mL of a 1:1 mixture of ice-cold water and 1 M H_3PO_4, and diluted with EtOAc (30 mL). After extraction with EtOAc (3 × 15 mL), the combined organic layers were washed with brine (4 × 15 mL), dried over Na_2SO_4, filtered, and evaporated to give an oily beige residue, which was subjected to column chromatography, eluting with hexanes/Et_2O (4:1) to remove impurities and then hexanes/Et_2O (1:1), to afford 2-(4-benzyloxy-3-methoxyphenyl)-4,5-methylenedioxybenzyl alcohol as an off-white gum (541 mg, 73%): IR (KBr) 3554, 1484, 1241, 934 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.43 (bs, 1H), 3.88 (s, 3H), 4.47 (s, 2H), 5.18 (s, 2H), 5.96 (s, 2H), 6.76 (s, 1H), 6.80 (dd, J = 2.0, 8.2 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 7.00 (s, 1H), 7.27−7.51 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.0, 147.3, 146.8, 146.6, 137.0, 134.9, 133.6, 131.7, 128.4, 127.7, 127.2, 121.3, 113.5, 113.2, 109.9, 108.7, 101.0, 71.0, 62.7, 55.9; LSIMS *m/z* (rel intensity) 387 (MNa^+, 13), 365 (MH^+, 24), 364 (M^+, 100), 347 (47), 273 (34). A stirred solution of this alcohol (532 mg, 1.46 mmol) and PPh_3 (574 mg, 2.19 mmol) in dry THF (6 mL) and dry CH_2Cl_2 (1.5 mL) was treated with ZnN_6·2Pyr[59] (337 mg, 1.10 mmol). The reaction mixture was cooled to 0 °C, and DEAD (345 μL, 2.19 mmol) was added dropwise. After stirring overnight at room temperature, the mixture was filtered through Celite, and the filtrate was evaporated to give an oil, which was purified by column chromatography, eluting with hexanes/Et_2O (9:1), to afford 2-(4-benzyloxy-3-methoxyphenyl)-4,5-methylenedioxybenzyl azide as a white solid (301 mg, 53%): mp 107−108 °C; IR (KBr) 2092, 1488, 1249, 940 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.90 (s, 3H), 4.17 (s, 2H), 5.20 (s, 2H), 6.00 (s, 2H), 6.77 (dd, J = 2.0, 8.2 Hz, 1H), 6.79 (s, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.89 (s, 1H), 6.93 (d, J = 8.2 Hz, 1H), 7.32−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.2, 147.5, 147.4, 146.9, 137.0, 136.2, 133.2, 128.5, 127.8, 127.2, 126.2, 121.4, 113.6, 113.2, 110.3, 109.4, 101.3, 71.0, 55.9, 52.6; LSIMS *m/z* (rel intensity) 412 (MNa^+, 22), 390 (MH^+, 8), 389 (M^+, 31), 347 (27), 270 (100). To a stirred solution of this azide (293 mg, 0.75 mmol) in dry THF (6 mL) were successively added PPh_3 (296 mg, 1.13 mmol) and distilled water (68 μL, 68 mmol). The resulting solution was stirred at room temperature for 4 days and then concentrated under reduced pressure to afford a residue, which was dissolved in EtOAc (30 mL). The organic layer was extracted with 1 M HCl aqueous solution (3 × 10 mL), and the pH of the aqueous layer was adjusted to 12 with KOH pellets. After extraction with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give the primary amine **30** as a colorless oil (197 mg, 72%): IR (NaCl) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (bs, 2H), 3.69 (s, 2H), 3.87 (s, 3H), 5.17 (s, 2H), 5.92 (s, 2H), 6.73−6.94 (m, 5H), 7.27−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.9, 147.0, 146.6, 145.7, 136.8, 134.2, 133.9, 128.2, 127.5, 127.0, 121.1, 113.4, 112.9, 109.9, 108.1, 100.7, 70.7, 55.7, 43.7; LSIMS *m/z* (rel intensity) 386 (MNa^+, 16), 365 (10), 364 (MH^+, 41), 363 (M^+, 82), 347 (85), 272 (38), 256 (100); HRMS (LSIMS) calcd for $C_{22}H_{21}NO_4$ 363.1470, found 363.1464.

4-(*N*-Tsoc-2-aminomethyl-4,5-methylenedioxyphenyl)-6-acetoxy-6-methoxycyclohexa-2,4-dienone (31). A stirred solution of amine **30** (190 mg, 0.52 mmol) and Et_3N (219 μL, 1.57 mmol) in dry CH_2Cl_2 (10 mL) was cooled at −78 °C. Dry ice (1.15 g, ca. 50 equiv) was added in one portion. After stirring at −78 °C for 1 h, TIPS-OTf (140 μL, 0.52 mmol) was added dropwise via syringe. After 5 min, the mixture was allowed to warm to room temperature and was stirred for 30 min. The mixture was then diluted with CH_2Cl_2 (30 mL) and poured in a separatory funnel containing H_2O (20 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL); the combined organic layers were washed with

saturated $NaHCO_3$ (20 mL) and brine (2 × 20 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded a pale yellow oil, which was purified by column chromatography, eluting with pentanes/Et_2O (2:1), to give *N*-Tsoc-2-(4-benzyloxy-3-methoxyphenyl)-4,5-methylenedioxybenzylamine as a colorless oil (212 mg, 72%): IR (NaCl) 3381, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.09 (d, J = 7.3 Hz, 18H), 1.30 (h, J = 7.3 Hz, 3H), 3.87 (s, 3H), 4.22 (d, J = 5.8 Hz, 2H), 4.99 (bt, J = 5.8 Hz, 1H), 5.17 (s, 2H), 5.93 (s, 2H), 6.71−6.94 (m, 5H), 7.27−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 154.7, 149.0, 147.2, 146.8, 146.3, 136.9, 134.7, 133.5, 129.5, 128.3, 127.7, 127.1, 121.2, 113.4, 112.8, 109.9, 108.2, 100.9, 70.8, 55.7, 42.7, 17.6, 11.8; LSIMS *m*/*z* (rel intensity) 586 (MNa^+, 31), 564 (MH^+, 37), 563 (M^+, 40), 520 (34), 347 (61), 256 (100). Debenzylation of this material (202 mg, 0.36 mmol) in 15 mL of dry THF was carried out under H_2 (balloon) overnight at room temperature in the presence of 10 wt % Pd/C as a catalyst (20 mg). The reaction mixture was filtered through Celite, and the solid was washed with acetone. Evaporation of the combined filtrates and washings afforded a crude oil, which was purified by column chromatography, eluting with pentanes/Et_2O (4:1), to give *N*-Tsoc-2-(4-hydroxy-3-methoxyphenyl)-4,5-methylenedioxybenzylamine as a colorless oil (142 mg, 84%): IR (NaCl) 3402, 3362, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (d, J = 7.0 Hz, 18H), 1.26 (h, J = 7.0 Hz, 3H), 3.85 (s, 3H), 4.21 (d, J = 5.9 Hz, 2H), 4.91 (bt, J = 5.9 Hz, 1H), 5.95 (s, 2H), 5.96 (bs, 1H), 6.70−6.92 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.8, 146.9, 146.4, 146.3, 144.9, 135.1, 132.5, 129.6, 121.9, 114.3, 111.9, 110.2, 108.4, 101.1, 55.8, 42.9, 17.7, 11.9; LSIMS *m*/*z* (rel intensity) 496 (MNa^+, 12), 474 (MH^+, 7), 473 (M^+, 7), 430 (19), 272 (5), 257 (21), 225 (100); HRMS (LSIMS) calcd for $C_{25}H_{36}NO_6Si$ 474.2311, found 474.2308. A solution of this phenol (44 mg, 0.09 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of PIDA (1.0 equiv) in 2 mL of dry CH_2Cl_2 at −78 °C. The reaction mixture immediately became bright yellow. After 1 h, TLC monitoring [hexanes/Et_2O (1:1)] indicated complete consumption of the starting material. The mixture was diluted with 20 mL of CH_2Cl_2, poured into ice-cold saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (2 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature. The residue was further dried under high vacuum overnight to give the corresponding orthoquinol acetate **31** as an orange oil (96%), which was used without further purification: IR (NaCl) 3412, 1740, 1696, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.03 (d, J = 7.0 Hz, 18H), 1.24 (h, J = 7.0 Hz, 3H), 2.13 (s, 3H), 3.49 (s, 3H), 4.14 (bt, J = 5.8 Hz, 2H), 5.36 (bt, J = 5.8 Hz, 1H), 5.95 (s, 2H), 6.08 (d, J = 2.1 Hz, 1H), 6.17 (d, J = 10.1 Hz, 1H), 6.66 (s, 1H), 6.85 (dd, J = 2.1, 10.1 Hz, 1H), 6.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 191.1, 170.2, 154.8, 147.7, 146.9, 143.0, 137.9, 132.7, 131.2, 130.6, 125.6, 109.8, 108.4, 101.4, 92.9, 51.5, 42.7, 20.6, 17.7, 12.0.

3-Hydroxy-2-methoxy-8,9-methylenedioxyphenanthridine (32). To a stirred ice-cold solution of **31** (50 mg, 0.094 mmol) in dry THF (1 mL) was added dropwise a commercial solution of TBAF (1 M in THF, 1.1 equiv). After 10 min, the ice bath was removed, and the reaction was stirred at room temperature for 1 h. Progression of the reaction was monitored by the disappearance of the orthoquinol acetate, as indicated by TLC [hexanes/Et_2O (1:1) and then CH_2Cl_2/MeOH (20:1)]. The mixture was diluted with EtOAc (20 mL), poured into ice-cold water (10 mL), extracted with EtOAc (2 × 15 mL), washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature. The resulting brown oily residue was purified by column chromatography, eluting with CH_2Cl_2/MeOH (100:1, followed by 50:1), to afford **32** as an off-white solid (20.2 mg, 80%): mp 259−260 °C; IR (KBr) 3554, 1484, 1241, 934 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.00 (s, 3H), 6.22 (s, 2H), 7.33 (s, 1H), 7.52 (s, 1H), 7.94 (s, 1H), 8.25 (s, 1H), 8.91 (s, 1H), 9.78 (bs, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 151.1, 149.4, 149.0, 148.5, 147.0, 140.2, 129.7, 121.8, 117.9, 112.8, 105.1, 103.1, 102.0, 100.1, 56.3; LSIMS *m*/*z* (rel intensity) 292 (MNa^+, 12), 270 (MH^+, 100), 269 (M^+, 43), 255 (29), 254 (19); HRMS (LSIMS) calcd for $C_{15}H_{12}NO_4$ 270.0766, found 270.0766.

***N*-(4-Benzyloxy-3-methoxybenzyl)-4-benzyloxy-3-methoxyphenylethylamine (38).**[62] A solution of benzylated vanillin **13** (3.00 g, 12.4 mmol) and primary amine **15** (3.19 g, 12.4 mmol) in dry MeOH (40 mL) was refluxed for 3 h in the presence of 4 Å molecular sieves. Filtration, followed by evaporation, furnished the expected imine as an orange oil (5.77 g, 97% crude yield). This material was submitted to $NaBH_4$ reduction (1.09 g, 28.8 mmol) in MeOH (60 mL) at room temperature. After stirring overnight, evaporation of the solution gave a solid residue, which was redissolved in CH_2Cl_2 (80 mL), washed with H_2O (3 × 20 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded an off-white solid, which was purified by column chromatography, eluting with pure EtOAc in order to remove impurities, and then with EtOAc/EtOH (1:1) to obtain **38** as an off-white solid (3.77 g, 65%): mp 94−95 °C (lit.[62] mp 106.5−107.5 °C); IR (KBr) 3366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (bs, 1H), 2.72−2.76 (m, 2H), 2.82−2.87 (m, 2H), 3.70 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 5.10 (s, 2H), 5.11 (s, 2H), 6.63−6.85 (m, 6H), 7.22−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 149.5, 149.4, 146.9, 146.4, 137.2, 137.1, 133.2, 133.0, 128.3, 127.6, 127.1, 120.4, 120.0, 113.9, 113.7, 112.3, 111.6, 70.9, 70.8, 55.8, 53.4, 50.3, 35.6; EIMS *m*/*z* (rel intensity) 483 (M^+, 2), 227 (57), 91 (100).

***N*-(4-Hydroxy-3-methoxybenzyl)-*N*-(Tsoc)-4-hydroxy-3-methoxyphenylethylamine (37a).** A stirred solution of the secondary amine **38** (745 mg, 1.54 mmol) and Et_3N (215 μL, 1.54 mmol) in dry CH_2Cl_2 (15 mL) was cooled at −78 °C. Dry ice (3.4 g, ca. 50 equiv) was added in one portion. After 1 h of stirring at −78 °C, TIPS-OTf (414 μL, 1.54 mmol) was added dropwise via syringe. After 5 min, the mixture was allowed to warm to room temperature and was stirred for 30 min. The mixture was then poured in a separatory funnel containing H_2O (10 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL); the combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (2 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded an orange oil, which was purified by column chromatography, eluting with pentanes/EtOAc (6:1), to give *N*-(4-benzyloxy-3-methoxybenzyl)-*N*-(Tsoc)-4-benzyloxy-3-methoxyphenylethylamine **39a** (1:1 mixture of two isomers) as a colorless oil (721 mg, 68%): IR (NaCl) 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.11 (d, J = 7.3 Hz, 18H), 1.17 (d, J = 7.3 Hz, 18H), 1.27−1.48 (m, 6H), 2.70−2.82 (m, 4H), 3.35−3.48 (m, 4H), 3.85 (s, 6H), 3.86 (s, 6H), 4.32 (s, 2H), 4.34 (s, 2H), 5.14 (s, 4H), 5.15 (s, 4H), 6.58−6.90 (m, 12H), 7.26−7.46 (m, 20H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.3, 154.6, 149.8, 149.5, 149.4, 147.3, 147.2, 146.5, 146.4, 137.2, 137.1, 137.0, 136.9, 132.4, 132.1, 131.3, 131.1, 128.3, 127.6, 127.1, 120.6, 120.5, 119.9, 119.3, 114.2, 114.1, 113.7, 113.4, 112.4, 112.3, 111.2, 110.5, 71.0, 70.9, 70.8, 55.8, 55.7, 55.6, 51.2, 50.4, 48.7, 48.3, 34.5, 33.6, 17.9, 17.8, 12.0; LSIMS *m*/*z* (rel intensity) 706 (MNa^+, 21), 685 (24), 684 (MH^+, 54), 683 (M^+, 45), 640 (73), 227 (100); HRMS (LSIMS) calcd for $C_{41}H_{53}NO_6Si$ 684.3720, found 684.3711. Debenzylation of this material (700 mg, 1.02 mmol) in 10 mL of dry THF was carried out under H_2 (balloon) overnight at room temperature in the presence of 10 wt % Pd/C as a catalyst (70 mg). The reaction mixture was filtered through Celite, and the solid was washed with acetone. Evaporation of the combined filtrates and washings afforded a pale yellow oil, which was purified by column chromatography, eluting with pentanes/EtOAc (3:1), to give **37a** (1:1 mixture of two isomers) as a colorless oil (408 mg, 79%): IR (NaCl) 3417, 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.09 (d, J = 7.3 Hz, 18H), 1.14 (d, J = 7.0 Hz, 18H), 1.26−1.44 (m, 6H), 2.63−2.78 (m, 4H), 3.32−3.42 (m, 4H), 3.82 (s, 6H), 3.83 (s, 6H), 4.32 (s, 4H), 5.68 (s, 1H), 5.70 (s, 1H), 5.78 (s, 1H), 5.79 (s, 1H), 6.57−6.87 (m, 12H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.4, 154.7, 146.8, 146.4, 146.3, 145.0, 144.9, 144.1, 143.9, 131.0, 130.7, 130.1, 129.8, 121.3, 121.2, 120.8, 120.2, 114.4, 114.2, 114.1, 113.9, 111.3, 111.2, 110.4, 109.5, 55.8, 55.7, 51.3, 50.6, 48.8, 48.3, 34.6, 33.6, 17.9, 17.8, 12.1; LSIMS *m*/*z* (rel intensity) 526 (MNa^+, 31), 505 (31), 504 (MH^+, 89), 503 (M^+,

25), 460 (100); HRMS (LSIMS) calcd for $C_{27}H_{41}NO_6Si$ 504.2793, found 504.2781.

***N*-(4-Hydroxy-3-methoxybenzyl)-6-hydroxy-5-methoxyindole (40).** To a stirred ice-cold solution of orthoquinol acetate **36a** (150 mg, 0.24 mmol) in dry THF (5 mL) was added dropwise a commercial solution of TBAF (1 M in THF, 1.1 equiv). The reaction mixture immediately became darker. After 20 min, the ice bath was removed, and the reaction was stirred at room temperature for another 20 min. Progression of the reaction was monitored by the disappearance of the orthoquinol acetate, as indicated by TLC [hexanes/Et_2O (1:4)]. The mixture was diluted with EtOAc (50 mL), washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature. The resulting brown residue was purified by column chromatography, eluting with hexanes/Et_2O (1:1), to afford the indole derivative **40** as a dark oil (23.9 mg, 33%): IR (NaCl) 3535, 3456, 1588 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 3.79 (s, 3H), 3.87 (s, 3H), 5.21 (s, 2H), 6.34 (dd, J = 0.7, 3.2 Hz, 1H), 6.67 (dd, J = 2.0, 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 0.7 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 7.09 (s, 1H), 7.16 (d, J = 3.2 Hz, 1H);^{13}C NMR (acetone-d_6, 62.9 MHz) δ 148.3, 146.8, 144.5, 144.2, 132.2, 130.5, 127.3, 122.1, 120.7, 115.7, 111.7, 103.0, 101.4, 96.6, 56.6, 56.1, 50.4; EIMS *m*/*z* (rel intensity) 301 (1), 300 (MH^+, 11), 299 (M^+, 60), 163 (93), 137 (100); HRMS (EI) calcd for $C_{17}H_{17}NO_4$ 299.1157, found 299.1156.

***N*-(4-Hydroxy-3-methoxybenzyl)-*N*-(Fmoc)-4-hydroxy-3-methoxyphenylethylamine (37b).** To a stirred ice-cold suspension of the secondary amine **38** (500 mg, 1.03 mmol) in dry THF (5 mL) and 10% aqueous Na_2CO_3 (250 μL) was added dropwise a solution of 9-fluorenylmethylchloroformate (320.5 mg, 1.24 mmol) in dry THF (5 mL). After stirring at 0 °C for 5 h, the resulting mixture was then diluted with H_2O (30 mL) and extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with H_2O (3 × 10 mL), dried over $MgSO_4$, and evaporated to afford an orange syrup, which was purified by column chromatography, eluting with hexanes/Et_2O (1:2), to give *N*-(4-benzyloxy-3-methoxybenzyl)-*N*-(Fmoc)-4-benzyloxy-3-methoxyphenylethylamine **39b** as a 1:1 carbamate rotameric mixture (554 mg, 76%, off-white foam): IR (KBr) 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.49 (bt, J = 7.1 Hz, 2H), 2.81 (bt, J = 7.1 Hz, 2H), 3.25 (bt, J = 7.1 Hz, 2H), 3.50 (bt, J = 7.1 Hz, 2H), 3.86 (s, 6H), 3.88 (s, 6H), 4.24−4.32 (m, 6H), 4.54−4.67 (m, 4H), 5.16 (s, 4H), 5.18 (s, 4H), 6.41−6.86 (m, 12H), 7.23−7.79 (m, 36H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.4, 155.9, 149.7, 149.5, 147.4, 146.6, 143.9, 141.3, 137.2, 137.0, 132.2, 130.7, 128.4, 128.3, 127.7, 127.6, 127.5, 127.2, 127.1, 126.9, 124.7, 120.6, 120.1, 119.9, 119.3, 114.3, 113.8, 112.5, 111.76, 110.87, 71.1, 71.0, 67.23, 66.67, 55.9, 50.56, 50.4, 49.0, 47.8, 47.45, 47.3, 34.01, 33.8; LSIMS *m*/*z* (rel intensity) 728 (MNa^+, 14), 706 (MH^+, 6), 705 (M^+, 10), 527 (2), 482 (2), 227 (100). Debenzylation of this material (434 mg, 0.61 mmol) in 25 mL of dry THF was carried out under H_2 (balloon) overnight at room temperature in the presence of 10 wt % Pd/C as a catalyst (50 mg). The reaction mixture was filtered through Celite, and the solid was washed with acetone. Evaporation of the combined filtrates and washings afforded a pale yellow oil, which was purified by column chromatography, eluting with hexanes/Et_2O (2:1), to give **37b** as a colorless oil (274 mg, 85%) that was immediately submitted to the PIDA-oxidation/cyclization sequence.

***N*-(4-Hydroxy-5-methoxy-2-piperidinobenzyl)-6-hydroxy-5-methoxyindole (41).** To a stirred ice-cold solution of orthoquinol acetate **36b** (444 mg, 0.69 mmol) in dry CH_2Cl_2 (7 mL) was added dropwise piperidine (1.4 mL, 20 equiv), over 10 min. After 1 h, the ice bath was removed, and the reaction was allowed to warm to room temperature and was stirred overnight. Evaporation of the solvent, followed by column chromatography, eluting with CH_2Cl_2/MeOH (100:1), afforded compound **41** as a dark green oil (54 mg, 21%): IR (NaCl) 3518, 3446, 1594 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 1.58−1.63 (m, 2H), 1.76−1.81 (m, 4H), 2.83−2.88 (m, 4H), 3.61 (s, 3H), 3.87 (s, 3H), 5.29 (s, 2H), 6.33 (d, J = 3.0 Hz, 1H), 6.55 (s, 1H), 6.77 (s, 1H), 6.93 (s, 1H), 7.07 (s, 1H), 7.11 (s, 1H), 7.18 (d, J = 3.0 Hz, 1H), 7.55 (s, 1H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 147.3, 147.2, 144.8, 144.5, 144.2, 132.4, 127.3, 124.9, 121.9, 112.9, 108.7, 102.9, 101.2, 96.8, 56.6, 56.4, 55.5, 45.6, 27.4, 24.9 LSIMS *m*/*z* (rel intensity) 405 (MNa^+, 5), 383 (MH^+, 5), 382 (M^+, 9), 381 (7), 220 (100); HRMS (LSIMS) calcd for $C_{22}H_{26}N_2O_4$ 382.1892, found 382.1892.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **8a**−**e**, **9a**−**h**, **10a**−**e**, **13**−**15**, **27**, **29**−**32**, **37a**, **38**, **39a**−**b**, **40**, and **41** and $^1H-^1H$ COSY (**41**), HMQC (**41**), HMBC 2D maps (**10e** and **41**). This material is available free of charge via the Internet at http://pubs.acs.org.

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