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Radical dearomatization of benzene leading to phenanthridine and phenanthridinone derivatives related to (±)-pancratistatin

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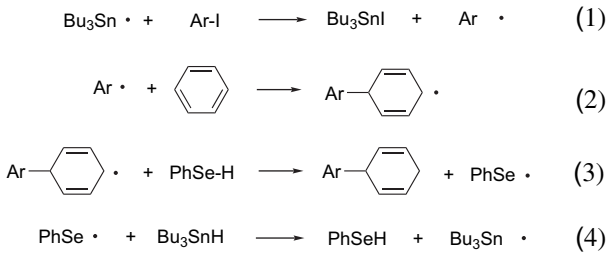
Abstract—The synthesis of the phenanthridinone nucleus common to the *Amaryllidaceae* series of natural products is achieved by a sequence involving tributylstannane-mediated, benzeneselenol-catalyzed addition of *ortho*-nitrogen functionalized aryl radicals to benzene, yielding aryl-substituted cyclohexadienes. These cyclohexadienes may be manipulated by oxidative ring closure sequences to generate functionalized phenanthridines. Beginning from 2-hydroxy-6-iodopiperonic acid a key intermediate in the Danishefsky synthesis of (±)-pancratistatin is achieved in two steps.

1. Introduction

Aryl radicals add rapidly to arenes to give cyclohexadienyl radicals substituted with aryl groups at the 6-position (Scheme 1).[1] Under typical preparative radical chain conditions the cyclohexadienyl radical is insufficiently reactive to propagate the radical chain by hydrogen atom abstraction from stannane or silane hydrogen atom donors and the eventual outcome is the formation of rearomatized biaryls.[2] Similarly the intramolecular version of this reaction, cyclization of an aryl radical onto an arene, is marked by the formation of fully re-oxidized products.[3] This breakdown in propagation typically results in poor conversion of the substrate and/or the need for excessive quantities of radical 'initiator'. Indeed, the azo-type initiators are now seen to serve the important function of oxidant for the cyclohexadienyl radical in addition to their more obvious planned function.[4] On the other hand, we have shown how the inclusion of a catalytic quantity of benzeneselenol in the stannane-mediated radical addition of aryl iodides to benzene, and other heterocycles, enables smooth trapping of the cyclohexadienyl radical by the selenol, leading to the isolation of aryl-substituted cyclohexadienes.[5] Although the Sn–H and Se–H bond dissociation energies are very similar,[6] the selenol traps alkyl radicals some 500 times faster than the stannane,[7] because of the operation of a polarity effect.[8]

The four-propagation step chain sequence is completed by regeneration of the selenol by reaction of the selenyl radical with the stannane (Scheme 1).[9]



Scheme 1. Mechanism of dearomatizing aryl radical addition to arenes.

The chemistry is rendered practical by the rapid in situ reduction of diphenyl diselenide to benzeneselenol by the stannane, which enables the direct handling of the air sensitive selenol to be avoided (Scheme 2).[9]

Scheme 2. In situ selenol generation.

The chemistry is particularly attractive when the aryl iodide is functionalized with a nucleophile at the *ortho*-position, thereby permitting the ring closing desymmetrization of the product cyclohexadiene.[10,11] We have employed this chemistry in syntheses of carbazomycin B (Scheme 3),[12] and of Kelly's β-sheet initiator (Scheme 4).[13]

Keywords: Radical; Arylation; Cyclohexadienyl; Dearomatization; Phenanthridinone.
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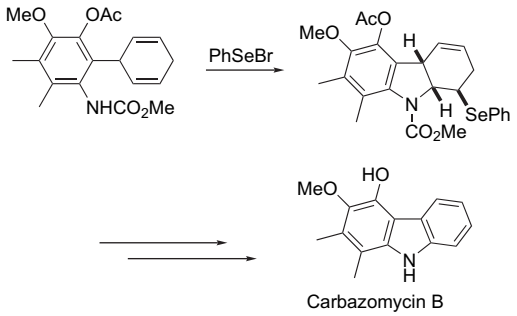
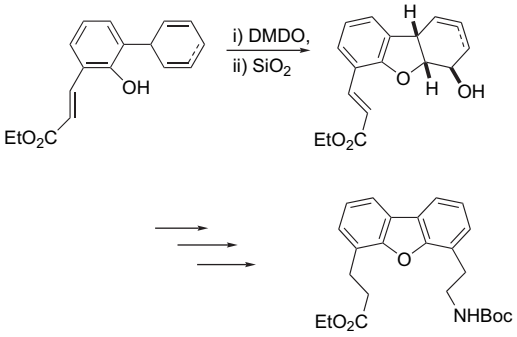
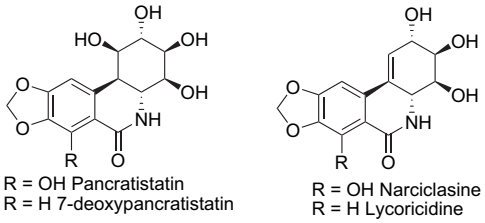


Scheme 3. Synthesis of carbazomycin B.



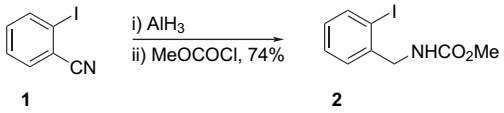
Scheme 4. Synthesis of a β-sheet initiator.

With a view to probing further the scope of the reductive radical arylation reaction and to exploiting more fully the potential of the aryl cyclohexadiene products we turned our attention to the preparation of phenanthridinone derivatives as found in the antineoplastic *Amaryllidaceae* natural products pancratistatin and lycoricidine and their analogs. The biological activity and densely arrayed functionality of these molecules have combined to make them the targets of numerous, successful synthetic endeavors since their discovery.[14–18] Moreover, it is especially noteworthy in the context of the present work that cyclohexadienes featured prominently in the original synthesis of (±)-pancratistatin by Danishefsky[15a] and in the very extensive work by Hudlicky group when they were generated, moreover, by dearomatization of arenes.[19] We report here on our work in this area, including an improved preparation of an intermediate in the Danishefsky synthesis of (±)-pancratistatin.



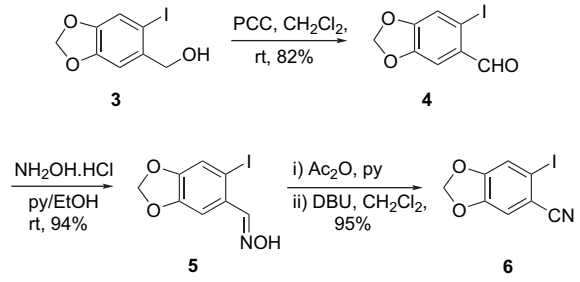
2. Results and discussion

We began our investigation by accessing the suitability of a series of *ortho*-functionalized aryl iodides for the key radical step, whose *ortho*-substituent should be convertible under mild conditions to a nucleophilic nitrogen species suitable for cyclization onto the cyclohexadiene formed in the dearomatization step. Thus, reduction of commercial *o*-iodobenzonitrile **1** with aluminum hydride,[20] followed by protection of the resulting amine with methyl chloroformate gave the iodo carbamate **2** (Scheme 5).[21]



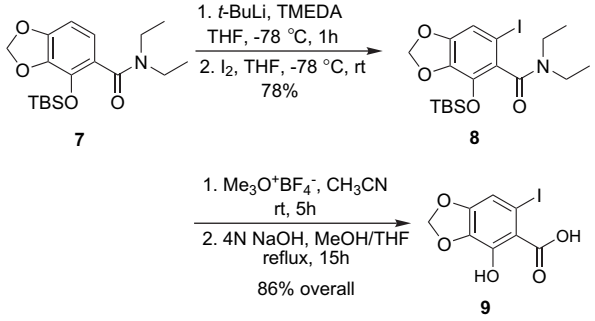
Scheme 5. Preparation of iodide **2**.

Iodide **3**, obtained from piperonyl alcohol with iodine and silver trifluoroacetate according to a literature procedure,[22] was converted to iodopiperonal **4** with PCC, and to the corresponding nitrile **6** by dehydration of oxime **5** (Scheme 6).



Scheme 6. Preparation of iodide **6**.

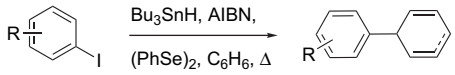
Finally, *ortho*-metallation of amide **7**, prepared by the Danishefsky route from resorcinol,[15a] and quenching with iodine gave the *o*-iodobenzamide **8**,[23] which could be hydrolyzed to the corresponding *des*-silyl acid **9** following conversion to the intermediate ester with trimethyloxonium tetrafluoroborate, and, then, heating with methanolic sodium hydroxide (Scheme 7).[24]

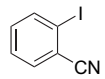
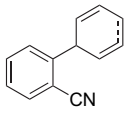
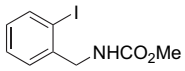
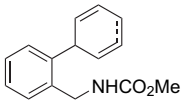
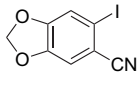
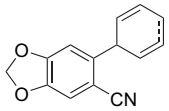
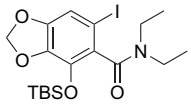
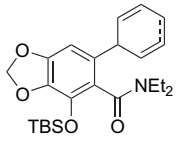
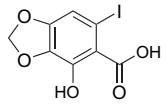
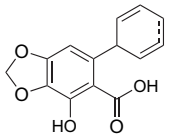
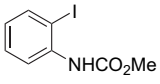
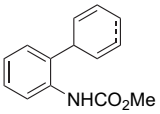
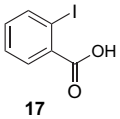
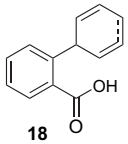


Scheme 7. Preparation of iodides **8** and **9**.

With these iodides in hand, the dearomatizing radical addition to benzene was investigated. These reactions were carried out according to a standard protocol involving the dropwise addition of tributyltin hydride and the initiator AIBN to a mixture of diphenyl diselenide and the substrate in benzene at reflux under argon, leading to the results outlined in Table 1, entries 1–5. As is typical for this type of addition[5a,10,12,13] the products were obtained as mixtures of 1,3- and 1,4-dienes in which the latter predominated, reflecting the known propensity of cyclohexadienyl radicals for kinetic trapping at the internal position.[25] The most

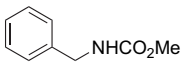
Table 1. Aryl radical addition to benzene

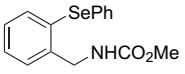


	Substrate	Product	% Yield ratio (1,4-/1,3)
1	 **1**	 **10**	44% (6/1)
2[b]	 **2**	 **11**	0%
3	 **6**	 **12**	44% (3/1)
4	 **8**	 **13**	Traces
5	 **9**	 **14**	30% (>10/1)
6	 **15**	 **16**	41% (3/2)[a]
7	 **17**	 **18**	54% (10/1)[a]

[a] Reproduced from Ref. 10.
[b] Compounds **19** and **20** were also isolated from this reaction in 30 and 32% yield, respectively.

satisfactory results were obtained with the two nitriles **1** and **6** both of which gave 44% yields of the benzene adducts (Table 1, entries 1 and 3). These yields while only moderate are typical for additions of this kind[5a,10,12,13] and, given the significant increase in complexity obtained and the simplicity of the starting materials, are acceptable for our purposes. The mass balance is typically made up of the deiodinated substrate and of the biaryl formally derived by oxidation of the cyclohexadiene: despite our best efforts over a number of years we have been unable to suppress formation of by-products of this type.[5a,10,12,13] The failure of the radical derived from the iodobenzyl carbamate **2** (Table 1, entry 2) was surprising, with carbamates having been previously shown to be compatible with the method (Table 1, entry 6)[10] Two major products **19** and **20** were isolated from this reaction in 30 and 32% yield, respectively, in addition to 35% of the recovered substrate. The formation of the *des*-iodo product **19** by intramolecular hydrogen atom transfer from the NH group to the aryl radical was excluded as a major pathway through an experiment employing *N*-deuterio **2** as substrate, when only 5% incorporation of deuterium into the *ortho*-position of **19** was observed. It is clear that most of the benzeneselenol is removed from this reaction mixture through the formation of selenide **20**. This results in a breakdown of the propagation cycle (Scheme 1), allowing an increase in stannane concentration as the addition proceeds, and ultimately results in the formation of the reduction product **19**. It is not clear why selenide **20** is formed in such high yield from substrate **2**, but it may be the result of hydrogen bonding of benzeneselenol to the carbamate, which facilitates a nucleophilic aromatic substitution reaction. Understandably in view of the obvious steric hindrance and the potential for intramolecular 1,5-hydrogen atom transfer from the amide group, only trace amounts of the adduct from the reaction between iodide **8** and benzene were obtained (Table 1, entry 4), with the major product **7** (64%) being that of simple reduction. This problem was remedied by use of the corresponding acid **9**, which reproducibly gave yields of 30% of the adduct **14** (Table 1, entry 5). Higher yields had been previously obtained with *o*-iodobenzoic acid (Table 1, entry 7),[10] but we were unable to improve on this yield despite repeated attempts. Nevertheless, it is interesting to note that the formation of **14** (Table 1, entry 5) took place with high regioselectivity in the hydrogen atom transfer step and afforded a product almost free of the minor, conjugated, isomeric diene. This unusually high regioselectivity in the quenching step was previously seen in the formation of **18** from *o*-iodobenzoic acid (Table 1, entry 7).[10]

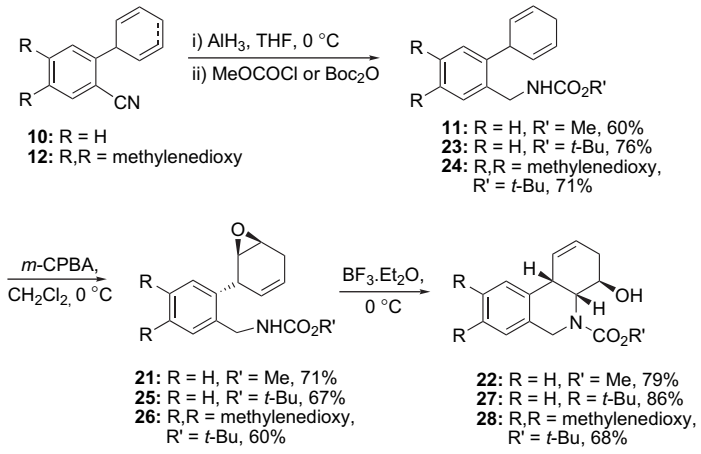

19


20

Turning to the desymmetrization step adduct **10** was converted to carbamate **11** by reduction with aluminum hydride,[20] and subsequent reaction with methyl chloroformate (Scheme 8).[26] Treatment with a controlled amount of *m*-CPBA subsequently afforded the mono epoxide **21** in 71%, which underwent the desired cyclization on exposure to boron trifluoride etherate[27] giving the phenanthridine derivative **22** in 79% yield (Scheme 8). The relative stereochemistry of **22**, with its *cis*-fused ring junction, was confirmed by X-ray crystallographic analysis.[†] An analogous series of experiments was also conducted on the corresponding *t*-butyl carbamates, and in the methylenedioxy series beginning from adduct **12**, with parallel results (Scheme 8).

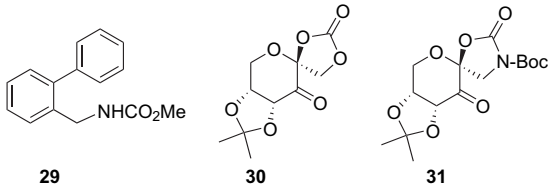
The asymmetric epoxidation of cyclohexadiene **11** with Jacobsen's catalyst[28] was attempted, but the only product

[†] CCDC 298768 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



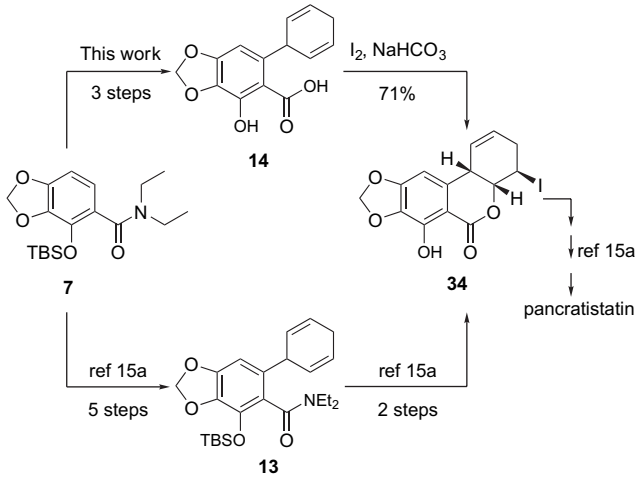
Scheme 8. Cyclization by epoxidation.

obtained was the biaryl system **29**.[29] A range of stoichiometric oxidants and additives was assayed in this catalytic protocol, including *N*-methyl morpholine *N*-oxide, sodium hypochlorite, iodosobenzene, and 4-phenylpyridine *N*-oxide, but we were unable to suppress the aromatization, which is, perhaps, not too surprising in view of the presence of the doubly allylic benzylic C–H bond in the substrate. Epoxidation of **11** with Shi catalyst **30** and dimethyl dioxirane did afford **21** in 48% yield, but in racemic form, consistent with the known substrate range of this system.[30] On the other hand, the more recent catalyst **31** developed by Shi group for *cis*-olefins gave **21** in 40% yield and 30% ee as determined by chiral HPLC methods.[31] In view of the poor enantioselectivity obtained with this system, no further investigations into enantioselective epoxidations were conducted although it is possible that other systems reported to bring about the enantioselective epoxidation of *cis*-alkenes, and which have appeared in the literature since this work was completed, may achieve the desired result.[32]

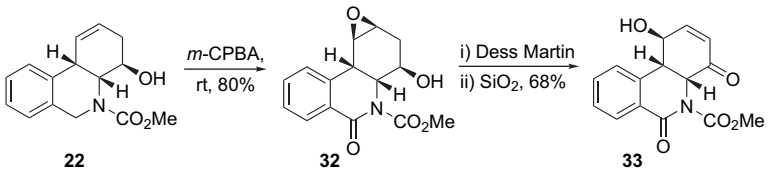


In exploring the further functionalization of the phenanthridine derivative **22**, an unexpected benzylic oxidation was encountered. Thus, treatment of **22** with excess *m*-CPBA in dichloromethane at room temperature gave not the expected simple epoxidation product but that of concomitant benzylic oxidation, the amide **32**, in 80% yield (Scheme 9). This interesting reaction has precedent in the work of Ma and co-workers who achieved the analogous oxidation of a series of cyclic and acyclic alkylarenes, including the transformation of ethylbenzene to acetophenone, with *m*-CPBA, for which they postulated a mechanism involving hydrogen atom abstraction and trapping of the benzylic radical by air.[33] Dess Martin oxidation[34] of **32** gave the corresponding ketone, which on passage over silica gel, afforded the anticipated hydroxyenone **33** in 68% yield, in which the enone ring derives its carbon skeleton from a benzene ring, of which every carbon has been modified.

Iodolactonization[35] of adduct **14** provided lactone **34**, a key intermediate in Danishefsky's synthesis of (±)-pancratistatin,[15a] in 71% yield (Scheme 10). In his synthesis Danishefsky constructed cyclohexadiene **13** from amide **7**,



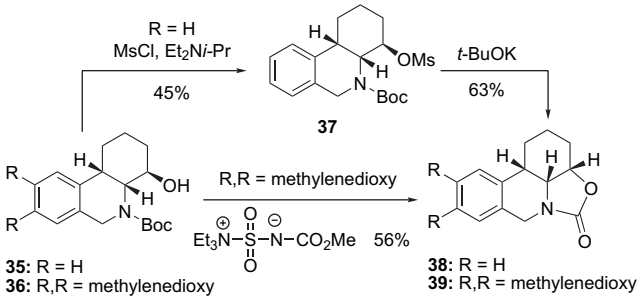
Scheme 10. Improved synthesis of a key intermediate in the Danishefsky (±)-pancratistatin synthesis.



Scheme 9. Functionalization of the 'benzene' ring.

and following removal of the silyl ether subjected it to iodolactonization to arrive at **34**. In that pioneering synthesis a sequence of five steps, including a tributyltin hydride mediated radical elimination reaction, were required to obtain **13** from **7**, and the complete sequence from **7** to iodolactone **34** was achieved in seven steps and 12.7% overall yield. The sequence of reactions that we describe here (Scheme 7, Table 1, and Scheme 10) proceeds from **7** to **34** in four steps and 14.3% overall yield, provides a convenient short cut in the original synthesis, and serves to highlight the advantages of the dearomatizing aryl radical addition to benzene as a means of aryl cyclohexadiene formation.

Finally, we note an interesting cyclization giving rise to the 7-oxa-γ-lycorane skeleton. Thus, catalytic hydrogenation of both **27** and **28** provided the dihydro analogs **35** and **36**, respectively, in excellent yield. The desmethylenedioxy system **35** was converted to the corresponding mesylate **37** by standard methods (Scheme 11). Interestingly enough this compound resisted all our attempts to bring about elimination of the mesyl group, with the major product being the oxazolidinone **38** resulting from displacement of the mesylate with inversion by the carbamate group. An analogous result was obtained on attempted elimination of water from **36** with the Burgess reagent,[36] when **39** was formed in 56% yield (Scheme 11).



Scheme 11. Formation of the 7-oxa-γ-lycorane skeleton.

3. Conclusion

The efficiency of the benzeneselenol-catalyzed, tributylstannane-mediated addition of aryl iodides to benzene depends strongly on the nature of the *ortho*-substituent. For reasons that are not yet clear, little or no addition takes place with an *o*-(methoxycarbonylaminomethyl) substituent, as in **2**, whereas the closely analogous *o*-(methoxycarbonylamino) group, as in **15**, is satisfactory. An *o*-cyano group functions well (**1** and **6**) and may be subsequently converted to the desired *o*-(methoxycarbonylaminomethyl) substituent by reduction with aluminum hydride followed by methyl chloroformate, without detriment to the 1,4-cyclohexadiene functionality. Further manipulations then lead rapidly to a variety of phenanthridine and phenanthridinone derivatives.

4. Experimental

4.1. General

All solvents were dried and distilled by standard techniques. All experiments were carried out in an atmosphere of dry nitrogen or argon. Extracts were dried over sodium sulfate and concentrated under reduced pressure at room temperature. Unless otherwise stated ^{1}H and ^{13}C NMR spectra were carried out at 400 and 100 MHz, respectively, in $CDCl_3$ solution. Chemical shifts are given in parts per million downfield from tetramethylsilane. Microanalyses were carried out by Midwest Microlabs, Indianapolis, IN. Mass spectra were recorded in the Research Resources Laboratory at UIC.

4.1.1. Methyl (2-iodobenzyl)carbamate (2). $LiAlH_4$ (173 mg, 4.6 mmol) was suspended in THF (8 mL), cooled to 0 °C, stirred vigorously, and treated with concentrated sulfuric acid (127 μL, 2.3 mmol). This mixture was stirred for 1 h at 0 °C, before a solution of 2-iodobenzonitrile (500 mg, 2.2 mmol) in THF (8 mL) was added dropwise. Stirring was continued for 1 h before the reaction was stopped by the addition of ethanol (10 mL) at 0 °C, followed by few drops of 2 N NaOH. The suspension was diluted with EtOAc (50 mL), filtered, and concentrated to provide a brown residue, which was taken directly to the next step. This residue was dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C, then treated with Et_3N (750 μL, 5 mmol) and methyl chloroformate (394 μL, 5 mmol). The resultant solution was stirred for 6 h, diluted with CH_2Cl_2 (50 mL), and washed with saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The dichloromethane layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 20% EtOAc in hexanes) to afford carbamate **2** (456 mg, 74%) as a white solid. Mp 77 °C (lit.[21] mp 74 °C); ^{1}H NMR: δ 3.68 (s, 3H), 4.37 (d, J=6.2 Hz, 2H), 5.25 (br s, 1H), 6.97 (t, J=8.0 Hz, 1H), 7.30–7.39 (m, 2H), 7.81 (d, J=7.7 Hz, 1H); ^{13}C NMR: δ 49.7, 52.3, 98.8, 128.5, 129.3, 129.5, 139.4, 140.5, 156.9.

4.1.2. 6-Iodo-1,3-benzodioxole-5-methanol (3). To a solution of piperonyl alcohol (5.15 g, 34 mmol), CF_3CO_2Ag (9.7 g, 44 mmol), and dry $CHCl_3$ (90 mL) at −5 °C was added I_2 (11.1 g, 44 mmol) in one portion. The resulting yellow mixture was maintained at −5 °C for 10 min, whereupon it was filtered. The filtrate was washed with 20% aqueous sodium thiosulfate (3x50 mL), dried, and concentrated. Recrystallization from chloroform afforded iodide **3** (6.1 g, 66%) as white needles. Mp 110–111 °C (lit.[22a] mp 106–107 °C); ^{1}H NMR (500 MHz): δ 2.06 (t, J=6.0 Hz, 1H), 4.57 (d, J=6.0 Hz, 2H), 6.0 (s, 2H), 6.98 (s, 1H), 7.26 (s, 1H); ^{13}C NMR (125 MHz): δ 69.2, 85.4, 101.7, 109.0, 118.5, 136.2, 147.9, 148.6.

4.1.3. 6-Iodo-1,3-benzodioxole-5-carbaldehyde (4). To a solution containing iodide **3** (6.1 g, 22.2 mmol) and dry CH_2Cl_2 (300 mL) at 0 °C was added PCC (9.6 g, 44 mmol). The mixture was allowed to warm to room temperature and was stirred for 5 h at 25 °C. The reaction mixture was concentrated to one third of its original volume and filtered through silica gel column (eluent: 30% EtOAc in hexanes) to give **4** as a pale yellow solid (5.7 g, 94%). Mp 110–112 °C; ^{1}H NMR (500 MHz): δ 6.08 (s, 2H), 7.32 (s, 1H), 7.35 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (125 MHz): δ 93.3, 102.7, 108.8, 119.4, 129.5, 149.2, 153.5, 194.5. Anal. Calcd for $C_8H_5O_3I$: C, 34.81; H, 1.83. Found: C, 34.56; H, 1.70.

4.1.4. 6-Iodo-1,3-benzodioxole-5-carbaldoxime (5). A solution of aldehyde **4** (5.7 g, 20.7 mmol) in 1:1 pyridine (20 mL) and ethanol (20 mL) was treated with hydroxylamine hydrochloride (2.2 g, 31.1 mmol) and stirred at room temperature. After 8 h, the resulting solution was diluted with EtOAc (80 mL) and washed with saturated aqueous NH_4Cl solution (50 mL), followed by brine (50 mL). The organic layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 30% EtOAc in hexanes) to afford oxime **5** (5.9 g, 94%) as a white solid. Mp 148 °C; ^{1}H NMR (500 MHz, CD_3OD): δ 6.0 (s, 2H), 7.24 (s, 1H), 7.26 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 87.2, 102.2, 105.6, 118.08, 128.0, 148.7, 149.7, 151.8. Anal. Calcd for $C_8H_6NO_3I$: C, 33.01; H, 2.08. Found: C, 33.12; H, 2.15.

4.1.5. 6-Iodo-1,3-benzodioxole-5-carbonitrile (6). A solution of oxime **5** (5.9 g, 19.4 mmol) and DMAP (236 mg, 1.9 mmol) in pyridine (50 mL) was treated with Ac_2O (2.7 mL, 29 mmol), and stirred at room temperature for 10 h. After complete consumption of **5**, DBU (3.5 mL, 23 mmol) was added to the reaction mixture, and stirring continued for 6 h during the course of which further DBU (2×1.7 mL) was added. The mixture was diluted with dichloromethane (70 mL), and washed with saturated NH_4Cl (2×40 mL) and brine. The dichloromethane layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 20% EtOAc in hexanes) to afford nitrile **6** (5.03 g, 95%) as pale yellow solid. Mp 127–29 °C; ^{1}H NMR (500 MHz): δ 6.09 (s, 2H), 7.01 (s, 1H), 7.28 (s, 1H); ^{13}C NMR (125 MHz): δ 89.8, 102.9, 113.0, 113.1, 119.2, 119.5, 148.3, 152.0. Anal. Calcd for $C_8H_4NO_2I$: C, 35.19; H, 1.48; N, 5.13; I, 46.48. Found: C, 35.10; H, 1.46; N, 4.96; I, 46.19.

4.1.6. *N*,*N*-Diethyl-4-(*tert*-butyldimethylsiloxy)-6-iodo-1,3-benzodioxole-5-carboxamide (8). In a dry flask, amide **7**[15a] (3.0 g, 8.54 mmol) was dissolved in THF (80 mL), and cooled to −78 °C. To this solution was added TMEDA (1.94 mL, 12.8 mmol), and *n*-BuLi (6.82 mL, 17.1 mmol, 2.0 M in hexanes). The resulting deep brown mixture was stirred at −78 °C for 1 h before I_2 (4.34 g, 17.1 mmol) in THF (20 mL) was added, and the reaction mixture allowed warm to room temperature overnight with stirring. The reaction mixture was quenched with saturated NH_4Cl, and the THF was removed in vacuo. The resulting residue was dissolved in EtOAc (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (30 mL) and dried. Purification by chromatography over silica gel (eluent: 12% EtOAc in hexanes) afforded **8** as yellow oil (3.2 g, 78%). ^{1}H NMR: δ 0.17 (s, 3H), 0.22 (s, 3H), 0.92 (s, 9H), 1.1 (t, J=7.2 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H), 3.1–3.21 (m, 3H), 3.79–3.88 (m, 1H), 5.91 (s, 1H), 5.94 (s, 1H), 6.9 (s, 1H); ^{13}C NMR: δ −4.6, −4.1, 12.6, 13.8, 18.3, 25.7 (3C), 39.3, 43.1, 82.3, 101.4, 112.7, 130.5, 136.9, 137.6, 149.3, 167.5; ESIHRMS Calcd for $C_{18}H_{28}INO_4Si$ $[M+H]^+$: 478.0911, found: 478.0917.

4.1.7. 4-Hydroxy-6-iodo-1,3-benzodioxole-5-carboxylic acid (9). To a stirred solution of benzamide **8** (220 mg, 0.46 mmol) in CH_3CN (5 mL) was added Na_2HPO_4 (98 mg, 0.69 mmol), followed by trimethyloxonium tetrafluoroborate (205 mg, 1.4 mmol). The reaction was stirred at room temperature for 5 h after which the reaction was quenched by slow addition of saturated aqueous sodium bicarbonate solution (5 mL). The resulting mixture was stirred for 7 h at room temperature, and then diluted with EtOAc (25 mL), followed by water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×15 mL). The combined organic layer was dried and concentrated. The residue was dissolved in MeOH/THF (5 mL, 1/1) mixture, treated with 4 N NaOH (3 mL) and heated to reflux for 15 h. The reaction mixture was neutralized with 6 N HCl followed by removal of the methanol in vacuo. The resulting residue was dissolved in EtOAc (25 mL) and water (15 mL), and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 70% EtOAc in hexanes) to afford **9** (122 mg, 86%) as white solid. Mp 147–148 °C; ^{1}H NMR: δ 6.0 (s, 2H), 7.14 (s, 1H); ^{13}C NMR: δ 85.4, 102.8, 112.8, 115.2, 136.4, 146.5, 152.3, 170.1; ESIHRMS Calcd for $C_8H_5IO_5$ $[M-H]^-$: 306.9103, found: 306.9105.

4.2. General procedure for radical addition to benzene

A dry flask was charged with aryl iodide (6.1 mmol) and diphenyl diselenide (380 mg, 1.22 mmol), fitted with a reflux condenser, and flushed with argon. Dry, degassed benzene (122 mL, 0.05 M) was added; the resulting solution was heated to reflux. A solution of AIBN (100 mg, 0.61 mmol) and tributyltin hydride (7.3 mmol, 1.96 mL) in dry degassed benzene (18 mL) was added via syringe pump at rate of 1.5 mL h^{-1}. On completion of the addition, the reaction mixture was refluxed for 1 h, then cooled to room temperature and the solvent removed in vacuo. The residue was taken up in acetonitrile (200 mL) and washed with (4×25 mL) hexane. The acetonitrile phase was concentrated and purified by silica gel chromatrography (eluent: EtOAc in hexanes) to yield the adducts.

4.2.1. 2-(2,5-Cyclohexadienyl)benzonitrile (10). Yield 44%; yellow oil; IR (neat): 2221, 2360, 2817, 2867, 3029 cm^{-1}; ^{1}H NMR (500 MHz): δ 2.78 (m, 2H), 4.43 (br t, J=7.5 Hz, 1H), 5.69–5.72 (br d, J=9.0 Hz, 2H), 5.89–5.92 (br d, J=10.5 Hz, 2H), 7.30 (t, J=7.3 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.53 (t, J=7.9 Hz, 1H), 7.62 (d, J=7.7 Hz, 1H); ^{13}C NMR (125 MHz): δ 25.7, 40.2, 125.1, 125.3, 126.2, 126.8, 126.9, 129.4, 132.9, 132.91, 133.0, 133.1, 148.6; EIHRMS Calcd for $C_{13}H_{11}N$ $[M-H]^+$: 180.0813, found: 180.0747. The product was contaminated with an inseparable minor isomer (1,3-cyclohexadien-5-yl)-benzonitrile, which accounted for 14% of the mass as determined by NMR. This isomer was characterized by ^{1}H NMR (500 MHz): δ 2.34 (dddd, J=17.6 Hz, J=11.8 Hz, J=4.1 Hz, J=2.2 Hz, 1H), 2.67 (dddd, J=17.6 Hz, J=9.5 Hz, J=4.8 Hz, J=1.8 Hz, 1H), 4.05–4.10 (br t, J=10.0 Hz, 1H), 5.76–5.79 (m, 2H), 5.9–6.1 (m, 1H), 6.13–6.17 (m, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.53 (t, J=7.9 Hz, 1H), 7.62 (d, J=7.7 Hz, 1H); ^{13}C NMR (125 MHz): δ 30.8, 37.7, 111.6, 117.9, 123.9, 125.1, 125.9, 126.8, 127.5, 128.4, 128.7, 133.0, 148.9.

4.2.2. 6-(2,5-Cyclohexadienyl)-1,3-benzodioxole-5-carbonitrile (12). Yield 44%; white solid; mp 101 °C; ^{1}H

NMR (500 MHz): δ 2.73–2.76 (m, 2H), 4.36–4.40 (m, 1H), 5.66 (ddt, *J*=10.0 Hz, *J*=5.5 Hz, *J*=1.5 Hz, 2H), 5.89 (ddt, *J*=10.5 Hz, *J*=5.5 Hz, *J*=1.5 Hz, 2H), 6.02 (s, 2H), 6.79 (s, 1H), 6.97 (s, 1H); ^{13}C NMR (125 MHz): δ 25.7, 39.8, 102.2, 109.5, 111.0, 118.1, 123.8, 125.2, 125.7, 126.5, 127.4, 145.5, 146.3, 152.0. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92. Found: C, 74.46; H, 4.99. The product was contaminated with an inseparable minor isomer, 6-(1,3-cyclohexadien-1-yl)-1,3-benzodioxole-5-carbonitrile, which accounted for 25% of the mass as determined by NMR and which was characterized by the following resonances: ^{1}H NMR (500 MHz): δ 2.29 (dddd, *J*=17.6 Hz, *J*=11.1 Hz, *J*=4.4 Hz, *J*=2.3 Hz, 1H), 2.65 (dddd, *J*=17.6 Hz, *J*=9.5 Hz, *J*=4.7 Hz, *J*=1.8 Hz, 1H), 4.01 (br t, *J*=9.5 Hz, 1H), 5.71 (dd, *J*=9.0 Hz, *J*=4.0 Hz, 1H), 5.76 (dt, *J*=9.5 Hz, *J*=4.5 Hz, 1H), 5.96–5.99 (m, 1H), 6.03 (s, 2H), 6.06–6.14 (m, 1H), 6.98 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (125 MHz): δ 30.8, 37.3, 103.3, 108.8, 113.3, 118.1, 125.0, 125.1, 126.3, 128.6, 128.7, 145.6, 145.3, 151.7.

4.2.3. 4-Hydroxy-6-(2,5-cyclohexadien-1-yl)-1,3-benzodioxole-5-carboxylic acid (14). Yield 30%; white solid; mp 152 °C; ^{1}H NMR: δ 2.71–2.76 (m, 2H), 4.96–5.0 (m, 1H), 5.69–5.74 (m, 2H), 5.82–5.87 (m, 2H), 6.05 (s, 2H), 6.61 (s, 1H); ^{13}C NMR: δ 25.7, 36.7, 102.5, 103.8, 106.9, 124.2, 128.3, 128.5, 130.3, 133.1, 145.8, 146.8, 153.4, 173.6; ESIHRMS Calcd for $C_{14}H_{12}O_5$ $[M-H]^-$: 259.0606, found: 259.0599.

4.2.4. Methyl benzylcarbamate (19). This compound was isolated in 30% yield from the attempted addition of **2** to benzene. White solid; mp 57–58 °C (lit.[37] mp 59–61 °C); ^{1}H NMR: δ 3.70 (s, 3H), 4.38 (d, *J*=5.9 Hz, 2H), 5.03 (br s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR: δ 45.0, 52.2, 127.2, 127.4, 127.5, 128.4, 128.6, 138.6, 157.2.

4.2.5. Methyl 2-phenylselenobenzylcarbamate (20). This compound was isolated in 32% yield from the attempted addition of **2** to benzene. Colorless oil; ^{1}H NMR: δ 3.65 (s, 3H), 4.46 (d, *J*=6.1 Hz, 2H), 5.05 (br s, 1H), 7.18 (t, *J*=7.5 Hz, 1H), 7.23–7.51 (m, 8H); ^{13}C NMR: δ 45.4, 52.2, 127.2, 127.8, 128.4, 128.5, 128.6, 128.9, 129.5 (2C), 130.3, 132.0, 135.6, 140.5, 156.9; EIHRMS Calcd for $C_{15}H_{15}NO_2Se$ $[M]^+$: 321.0268, found: 321.0257.

4.2.6. Methyl 2-(2,5-cyclohexadien-1-yl)benzylcarbamate (11). $LiAlH_4$ (250 mg, 6.6 mmol) was suspended in THF (8 mL), cooled to 0 °C, stirred vigorously, and treated with concentrated sulfuric acid (182 μL, 3.3 mmol). This mixture was stirred for 1 h at 0 °C, before a solution of diene **10** (570 mg, 3.14 mmol) in THF (7 mL) was added dropwise. Stirring was continued for 1 h before the reaction was stopped by the addition of ethanol (10 mL) at 0 °C, followed by few drops of 2 N NaOH. The suspension was diluted with EtOAc (50 mL), filtered, and concentrated to provide a brown residue, which was taken directly to the next step. This residue was dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C, and then treated with Et_3N (750 μL, 5 mmol) and methyl chloroformate (386 μL, 5 mmol). The resultant solution was stirred for 6 h, diluted with CH_2Cl_2 (50 mL), and washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The dichloromethane layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 20% EtOAc in hexanes) to afford carbamate **11** (459 mg, 60%) as a white solid. Mp 81–83 °C; ^{1}H NMR (500 MHz): δ 2.75–2.79 (m, 2H), 3.68 (s, 3H), 4.21 (m, 1H), 4.47 (d, *J*=5.5 Hz, 2H), 4.92 (br s, 1H), 5.69 (ddt, *J*=10.0 Hz, *J*=5.0 Hz, *J*=1.0 Hz, 2H), 5.83–5.85 (m, 2H), 7.19–7.29 (m, 4H); ^{13}C NMR (125 MHz): δ 25.7, 38.1, 42.5, 52.2, 123.8, 124.8, 127.7, 127.9, 128.2, 128.8, 129.1, 129.8, 135.3, 143.0, 156.7; ESIHRMS Calcd for $C_{15}H_{17}NO_2$ $[M+Na]^+$: 266.1157, found: 266.1161.

4.2.7. *tert*-Butyl 2-(2,5-cyclohexadien-1-yl)benzylcarbamate (23). This carbamate was prepared from **10** analogously to **11**, except that the methyl chloroformate was replaced by Boc_2O. It was obtained as a colorless oil in 76% yield. IR (neat): 1168, 1511, 1694, 2976, 3340 cm^{-1}; ^{1}H NMR: δ 1.46 (s, 9H), 2.74–2.78 (m, 2H), 4.23 (br t, *J*=8.5 Hz, 1H), 4.42 (d, *J*=5.3 Hz, 2H), 4.72 (br s, 1H), 5.68 (br d, *J*=10.0 Hz, 2H), 5.82–5.85 (m, 2H), 7.17–7.27 (m, 4H); ^{13}C NMR: δ 25.7, 28.4 (3C), 37.8, 42.1, 79.5, 123.9, 126.6, 127.9, 128.1, 128.5, 128.9, 129.6, 130.0, 135.6, 143.1, 155.5; ESIHRMS Calcd for $C_{18}H_{23}NO_2$ $[M+Na]^+$: 308.1627, found: 308.1625.

4.2.8. *tert*-Butyl 6-(2,5-cyclohexadien-1-yl)-1,3-benzodioxole-5-ylmethylcarbamate (24). This carbamate was prepared from **12** in the same manner as **23** was obtained from **10**. It was obtained in 71% yield as a white solid. Mp 106 °C; ^{1}H NMR: δ 1.44 (s, 9H), 2.71–2.73 (m, 2H), 4.13 (m, 1H), 4.23 (d, *J*=5.1 Hz, 2H), 4.74 (br s, 1H), 5.59 (br d, *J*=10.1 Hz, 2H), 5.79 (br d, *J*=10.1 Hz, 2H), 5.89 (s, 2H), 6.72 (s, 1H), 6.73 (s, 1H); ^{13}C NMR: δ 25.7, 28.4 (3C), 37.4, 41.9, 79.4, 100.9, 108.6, 109.6, 123.7, 125.2, 128.2, 128.7, 129.9, 136.9, 146.0, 147.3, 155.5. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04. Found: C, 69.35; H, 6.99.

4.3. General procedure for the epoxidation of dienes

3-Chloroperoxybenzoic acid (230 mg, 1.03 mmol) was added portionwise to a stirred solution of the diene (0.94 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After 2 h, the reaction mixture was diluted with dichloromethane (40 mL) and washed with saturated aqueous sodium bicarbonate (3×25 mL). The dichloromethane layer was dried, concentrated, and purified by chromatography on silica gel (eluent: EtOAC in hexanes) to afford the epoxide.

4.3.1. Methyl 2-(2-cyclohexen-5,6-epoxy-1-yl)benzylcarbamate (21). Yield 71%; white solid; mp 87–88 °C; ^{1}H NMR (500 MHz): δ 2.61–2.70 (m, 2H), 3.15 (m, 1H), 3.36 (m, 1H), 3.70 (s, 3H), 4.09 (m, 1H), 4.48 (d, *J*=6.5 Hz, 2H), 4.96 (br s, 1H), 5.53–5.60 (m, 2H), 7.22–7.35 (m, 4H); ^{13}C NMR (125 MHz): δ 24.9, 37.5, 42.7, 51.1, 52.3, 54.8, 121.5, 125.6, 127.2, 128.2, 128.8, 129.2, 136.0, 138.8, 156.7; ESIHRMS Calcd for $C_{15}H_{17}NO_3$ $[M+H]^+$: 260.1287, found: 260.1288.

4.3.2. *tert*-Butyl 2-(2-cyclohexen-5,6-epoxy-1-yl)benzylcarbamate (25). Yield 67%; white solid; mp 88 °C; IR (neat): 1167, 1248, 1519, 1699, 2359, 2977, 3354 cm^{-1}; ^{1}H NMR: δ 1.45 (s, 9H), 2.60–2.69 (m, 2H), 3.15 (d, *J*=4 Hz, 1H), 3.35 (m, 1H), 4.10 (m, 1H), 4.44 (d, *J*=5 Hz, 2H), 4.79 (br s, 1H), 5.54–5.58 (m, 2H), 7.21–7.22

(m, 4H); ^{13}C NMR: δ 25.1, 28.4 (3C), 37.5, 42.3, 51.9, 54.9, 79.7, 121.5, 125.7, 127.4, 128.1, 128.8, 129.2, 136.4, 138.8, 155.6; ESIHRMS Calcd for $C_{18}H_{23}NO_3$ [M+Na]$^+$: 324.1576, found: 324.1574.

4.3.3. *tert*-Butyl 6-(2-cyclohexen-5,6-epoxy)-[1,3]benzodioxole-5-ylmethyl)carbamate (26). Yield 60%; white solid; mp 143 °C; ^{1}H NMR: δ 1.44 (s, 9H), 2.60–2.69 (m, 2H), 3.08 (m, 1H), 3.31 (m, 1H), 4.01 (m, 1H), 4.30 (d, J=5.2 Hz, 2H), 4.80 (br s, 1H), 5.46–5.50 (m, 2H), 5.90 (s, 2H), 6.66 (s, 1H), 6.83 (s, 1H); ^{13}C NMR: δ 25.0, 28.3 (3C), 37.2, 42.4, 51.8, 54.9, 79.7, 101.2, 108.7, 109.3, 121.5, 125.9, 130.0, 132.1, 146.7, 147.3, 155.5. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71. Found: C, 66.24; H, 6.70.

4.4. General procedure for cyclization to the tricyclic skeleton

A solution of epoxide (1.0 mmol) in CH_2Cl_2 (4 mL) was treated with $BF_3\cdot Et_2O$ (0.4 mmol, 118 μL) at −10 °C and stirred for 20 min, before the addition of saturated aqueous sodium bicarbonate (10 mL) and dichloromethane (40 mL). The dichloromethane layer was dried, concentrated, and purified by chromatography over silica gel (eluent: EtOAc in hexanes).

4.4.1. [(±)-4*S*,4a*S*,10b*R*] Methyl 4-hydroxy-4,4a,6,10b-tetrahydro-3*H*-phenanthridine-5-carboxylate (22). Yield 79%; colorless oil; IR (neat): 1242, 1456, 1698, 2360, 3479 cm^{-1}; ^{1}H NMR: δ 1.95 (br s, 1H), 2.17–2.23 (m, 1H), 2.52–2.58 (m, 1H), 3.63 (m, 1H), 3.78 (s, 3H), 4.31–4.50 (m, 3H), 4.75–5.08 (m, 1H), 5.74 (m, 1H), 6.14 (m, 1H), 7.09–7.32 (m, 4H); ^{13}C NMR: δ 35.7, 38.2, 43.5, 53.1, 56.1, 66.5, 125.3, 126.2, 126.3, 127.1, 127.3, 127.6, 131.4, 136.8, 158.4; EIHRMS Calcd for $C_{15}H_{17}NO_3$ [M]$^+$: 259.1208, found: 259.1204.

4.4.2. [(±)-4*S*,4a*S*,10b*R*] *tert*-Butyl 4-hydroxy-4,4a,6,10b-tetrahydro-3*H*-phenanthridine-5-carboxylate (27). Yield 86%; colorless oil; IR (neat): 1419, 1683, 2977, 3426 cm^{-1}; ^{1}H NMR: δ 1.45 (s, 9H), 2.15–2.21 (m, 1H), 2.52–2.58 (m, 1H), 3.55 (m, 1H), 3.74 (m, 1H), 4.43–4.98 (m, 3H), 5.76 (m, 1H), 6.14 (m, 1H), 7.11–7.26 (m, 4H); ^{13}C NMR: δ 28.4 (3C), 36.3, 38.5, 44.0, 55.7, 66.9, 80.7, 125.5, 126.1, 126.3, 127.0, 127.1, 127.7, 131.7, 137.0, 157.6; ESIHRMS Calcd for $C_{18}H_{23}NO_3$ [M+Na]$^+$: 324.1576, found: 324.1566.

4.4.3. [(±)-4*S*,4a*S*,10b*R*] *tert*-Butyl 4-hydroxy-4,4a,6,10b-tetrahydro-3*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylate (28). Yield 68%; colorless oil; ^{1}H NMR: δ 1.45 (s, 9H), 2.03 (m, 1H), 2.50–2.55 (m, 1H), 2.67 (br s, 1H), 3.56 (m, 1H), 3.61 (m, 1H), 4.25–4.84 (m, 3H), 5.73 (m, 1H), 5.90 (s, 1H), 5.93 (s, 1H), 6.02 (m, 1H), 6.56 (s, 1H), 6.69 (s, 1H); ^{13}C NMR: δ 28.4 (3C), 34.5, 36.2, 42.3, 55.7, 66.7, 80.7, 100.9, 106.3, 107.3, 124.2, 126.5, 126.8, 130.3, 145.9, 146.7, 157.4; ESIHRMS Calcd for $C_{19}H_{23}NO_5$ [M+Na]$^+$: 368.1468, found: 368.1475.

4.4.4. Methyl 2-phenylbenzylcarbamate (29). To a solution of diene **11** (70 mg, 0.27 mmol) and (*R*,*R*)-(−)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (7 mg, 0.01 mmol) in CH_2Cl_2 (0.6 mL) was added NaOCl (1 mL) buffered to pH 11.3. The reaction mixture was stirred at room temperature for 4 h, then was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2×20 mL). The aqueous layer was back extracted with CH_2Cl_2 (10 mL). The combined organic layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 25% EtOAc in hexanes) to yield **29** (40 mg, 58%) as a colorless oil. IR (neat): 1251, 1527, 1708, 3023, 3332 cm^{-1}; ^{1}H NMR: δ 3.6 (s, 3H), 4.33 (d, J=6.0 Hz, 2H), 4.76 (br s, 1H), 7.23–7.46 (m, 9H); ^{13}C NMR: δ 42.9, 52.1, 127.3, 127.4, 127.7, 128.4, 128.9, 129.0, 130.2, 135.7, 140.7, 141.6, 156.9; ESIHRMS Calcd for $C_{15}H_{15}NO_2$ [M+H]$^+$: 242.1175, found: 242.1170.

4.4.5. [(±)-1*R*,2*S*,4S,4a*S*,10b*R*] Methyl 1,2-epoxy-4-hydroxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-one-5-carboxylate (32). A solution of 3-chloroperoxybenzoic acid (255 mg, 1.2 mmol) and alcohol **22** (100 mg, 0.38 mmol) in dry CH_2Cl_2 (5 mL), was stirred at room temperature for 24 h, then diluted with dichloromethane (30 mL), washed with saturated aqueous sodium bicarbonate (3×25 mL), and brine (25 mL). The dichloromethane layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 70% EtOAc in hexanes) to afford epoxide **32** as a white foam (89 mg, 80%). ^{1}H NMR: δ 2.09 (dd, J=15.6 Hz, J=9.3 Hz, 1H), 2.37–2.44 (m, 1H), 3.25 (br s, 1H), 3.29 (t, J=4.2 Hz, 1H), 3.63–3.68 (m, 1H), 3.91 (s, 3H), 3.91 (m, 1H), 4.10–4.14 (m, 1H), 4.70 (dd, J= 10.8 Hz, 5.1 Hz, 1H), 7.40 (t, J=7.5 Hz, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.59 (t, J=6.5 Hz, 1H), 8.1 (d, J=8.6 Hz, 1H); ^{13}C NMR: δ 33.1, 36.2, 51.4, 54.5, 54.6, 56.8, 64.2, 124.3, 127.4, 128.6, 130.4, 133.8, 136.8, 156.3, 162.5; ESIHRMS Calcd for $C_{15}H_{15}NO_5$ [M+Na]$^+$: 312.0842, found: 312.0847.

4.4.6. [(±)-1*R*,4*S*,4a*S*,10b*R*] Methyl 1-hydroxy-4,6-dioxo-4,4a,6,10b-tetrahydro-1*H*-phenanthridine-5-carboxylate (33). Dess–Martin periodinane (88 mg, 0.21 mmol) was added to a solution of epoxide **32** (50 mg, 0.17 mmol) in dry CH_2Cl_2 (3 mL) and stirred for 4 h. When the reaction was complete, saturated aqueous sodium thiosulfate (15 mL) was added, and the reaction mixture stirred for 0.5 h, before it was poured into saturated aqueous sodium bicarbonate. The dichloromethane layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 3% MeOH in CH_2Cl_2) to afford hydroxyenone **33** (33 mg, 68%) as a white solid. Mp 98 °C; IR (neat): 1376, 1598, 1689, 1762, 3413 cm^{-1}; ^{1}H NMR (CD_3OD): δ 4.02 (s, 3H), 4.1 (m, 1H), 5.28 (dd, J=5.5, J=2.6 Hz, 1H), 5.82 (d, J=4.9 Hz, 1H), 5.92 (d, J=9.9 Hz, 1H), 7.01 (dd, J=10.0 Hz, 5.3 Hz, 1H), 7.41 (t, J=7.6 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 8.06 (d, J=7.9 Hz, 1H); ^{13}C NMR (CD_3OD): δ 44.8, 53.3, 59.1, 63.3, 124.4, 127.6, 128.8, 128.9, 129.6, 133.7, 136.8, 146.3, 154.1, 163.1, 193.4; ESIHRMS Calcd for $C_{15}H_{13}NO_5$ [M+Na]$^+$: 310.0686, found: 310.0690.

4.4.7. [(±)-(4*S*,4a*S*,10b*R*)] 3,4,4a,10b-Tetrahydro-4-iodo-7-hydroxy-6*H*-[1,3]benzodioxolo[5,6-*c*]benzopyran-6-one (34). A solution of **14** (20 mg, 0.076 mmol) in THF (3 mL) was treated with $NaHCO_3$ (13 mg, 0.15 mmol), then I_2 (23 mg, 0.09 mmol), and stirred at room temperature

for 15 h. Saturated $Na_2S_2O_3$ solution (10 mL) was then added and the mixture was extracted with EtOAc (3×10 mL). The aqueous layer was washed with EtOAc (15 mL), and the combined organic layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 30% EtOAc in hexanes) to provide iodolactone **34** (30 mg, 71%) as a white solid. Mp 179 °C (lit.[26] mp 177 °C); ^{1}H NMR: δ 2.63–2.72 (m, 1H), 3.30–3.37 (m, 1H), 4.06–4.10 (m, 1H), 4.57–4.60 (m, 1H), 4.90–4.92 (m, 1H), 5.46–5.50 (m, 1H), 5.69–5.73 (m, 1H), 6.09 (s, 2H), 6.46 (s, 1H), 10.86 (s, 1H); ^{13}C NMR: δ 19.6, 30.8, 35.6, 77.7, 100.4, 102.7, 103.0, 124.2, 124.3, 133.5, 137.9, 145.8, 154.5, 168.0; EIHRMS Calcd for $C_{14}H_{11}IO_5$ $[M]^+$: 385.9651, found: 385.9663.

4.4.8. [(±)-4*R*,4a*R*,10b*R*] *tert*-Butyl 4-hydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylate (35). A solution of alcohol **27** (237 mg, 0.78 mmol) in methanol (4 mL) was stirred with 10% Pd–C (80 mg) under 1 atm of H_2 for 3 h, then was filtered through Celite® and purified by chromatography over silica gel (eluent: 30% EtOAc in hexanes) to yield **35** (77 mg, 95%) as a colorless oil. ^{1}H NMR: δ 1.25–1.27 (m, 2H), 1.45 (s, 9H), 1.56–1.59 (m, 1H), 1.67–1.76 (m, 1H), 1.96–1.99 (m, 1H), 2.30 (br s, 1H), 2.47 (dd, J=13.5 Hz, J=2.8 Hz, 1H), 3.30 (m, 2H), 4.25 (m, 1H), 4.45 (d, J=16.8 Hz, 1H), 4.70 (d, J=16.9 Hz, 1H), 7.11–7.29 (m, 4H); ^{13}C NMR: δ 19.6, 26.7, 28.4 (3C), 35.4, 37.4, 44.3, 58.3, 69.3, 80.5, 125.4, 126.1, 126.5, 126.8, 133.2, 135.2, 157.2; EIHRMS Calcd for $C_{18}H_{25}NO_3$ $[M]^+$: 303.1834, found: 303.1848.

4.4.9. [(±)-4*R*,4a*R*,10b*R*] *tert*-Butyl 4-hydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylate (36). Analogous to the conversion of **27** to **35**, hydrogenation of alcohol **28** gave **36** in 95% yield as colorless oil. IR (neat): 1251, 1689, 2933, 3428 cm^{-1}; ^{1}H NMR: δ 1.22–1.30 (m, 2H), 1.44 (s, 9H), 1.49–1.56 (m, 2H), 1.96–1.98 (m, 1H), 2.31–2.34 (d, J=11.2 Hz, 1H), 2.60 (br s, –OH, 1H), 3.18 (m, 1H), 3.30 (m, 1H), 4.19 (m, 1H), 4.32 (d, J=13.2 Hz, 1H), 4.59 (d, J=13.0 Hz, 1H), 5.90 (s, 1H), 5.91 (s, 1H), 6.57 (s, 1H), 6.74 (s, 1H); ^{13}C NMR: δ 19.5, 27.2, 28.5 (3C), 35.3, 37.2, 44.3, 58.2, 69.1, 80.5, 100.9, 105.6, 106.5, 126.3, 128.6, 145.9, 146.8, 157.1; EIHRMS Calcd for $C_{19}H_{25}NO_5$ $[M]^+$: 347.1733, found: 347.1723.

4.4.10. [(±)-4*R*,4a*R*,10b*R*] *tert*-Butyl 4-methanesulfonyloxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylate (37). Alcohol **35** (92 mg, 0.3 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and cooled to 0 °C. To this solution was added Hunig's base (79 μL, 0.45 mmol) and methanesulfonyl chloride (37 μL, 0.45 mmol). The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was diluted with dichloromethane (30 mL) and washed with saturated NH_4Cl (20 mL) and brine (20 mL). The dichloromethane layer was extracted, dried, and purified by chromatography over silica gel (20% EtOAc in hexanes) to provide mesylate **37** (52 mg, 45%) as a colorless oil, which was used immediately in the next step. ^{1}H NMR (500 MHz): δ 1.24–1.27 (m, 1H), 1.50 (s, 9H), 1.60–1.73 (m, 3H), 2.03–2.2 (m, 1H), 2.47–2.50 (m, 1H), 2.97 (s, 3H), 3.41 (m, 1H), 4.38–4.41 (m, 1H), 4.51–4.59 (m, 2H), 4.82–4.86 (m, 1H), 7.15–7.28 (m, 4H).

4.4.11. [(±)-3a*S*,11b*R*,11c*R*] 4-Oxa-1,2,3,3a,4,5,11b,11c-octahydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-5-one (38). Mesylate **37** (19 mg, 0.05 mmol) dissolved in DMF (0.5 mL) was treated with potassium *tert*-butoxide (6 mg, 0.055 mmol) and heated to 65 °C for 6 h. The reaction mixture was diluted with EtOAc (30 mL), washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL). The organic layer was dried, concentrated, and purified by chromatography over silica gel (20% EtOAc in hexanes) to provide **38** (7 mg, 63%) as a colorless oil. IR (neat): 1308, 1751, 1800, 2940 cm^{-1}; ^{1}H NMR: δ 1.37–1.43 (m, 1H), 1.44–1.50 (m, 1H), 1.60–1.72 (m, 1H), 1.78–1.86 (m, 2H), 2.10–2.13 (m, 1H), 2.90 (dt, J=12.4 Hz, J=4.8 Hz, 1H), 3.98 (dd, J=7.6 Hz, 4.0 Hz, 1H), 4.35 (d, J=13.2 Hz, 1H), 4.75 (d, J=13.3 Hz, 1H), 4.80 (q, J=7.6 Hz, 1H), 7.15–7.26 (m, 4H); ^{13}C NMR: δ 15.3, 26.5, 28.5, 37.7, 43.1, 53.3, 74.1, 126.8, 127.0, 127.1, 129.3, 130.3, 136.6, 158.4; ESIHRMS Calcd for $C_{14}H_{15}NO_2$ $[M+H]^+$: 230.1181, found: 230.1173.

4.4.12. [(±)-3a*S*,11b*R*,11c*R*] 4-Oxa-1,2,3,3a,4,5,11b,11c-octahydro-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one (39). A solution of alcohol **36** (40 mg, 0.12 mmol) in benzene (3 mL) was treated with methyl *N*-(triethylammoniosulfonyl)carbamate[38] (30 mg, 0.17 mmol) and heated to reflux. After 12 h, the reaction was diluted with EtOAc (25 mL) and washed with saturated aqueous NH_4Cl solution, followed by brine. The organic layer was dried, concentrated, and purified by chromatography over silica gel (eluent: 40% EtOAc in hexanes) to provide the oxazolidinone **39** as a colorless oil (18 mg, 56%). IR (neat): 1201, 1484, 1751, 2936 cm^{-1}; ^{1}H NMR: δ 1.35–1.45 (m, 2H), 1.61–1.81 (m, 3H), 2.05–2.08 (m, 1H), 2.77 (dt, J=12.4 Hz, J=4.8 Hz, 1H), 3.93 (dd, J=7.5 Hz, J=4.3 Hz, 1H), 4.23 (d, J=16.2 Hz, 1H), 4.62 (d, J=16.3 Hz, 1H), 4.77 (q, J=7.6 Hz, 1H), 5.93 (s, 2H), 6.58 (s, 1H), 6.59 (s, 1H); ^{13}C NMR: δ 19.2, 26.4, 28.9, 37.7, 43.2, 53.3, 74.1, 101.2, 106.3, 108.7, 123.3, 129.8, 146.8, 146.9, 158.2; ESIHRMS Calcd for $C_{15}H_{15}NO_4$ $[M+H]^+$: 274.1079, found: 274.1077.

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