Formal Total Synthesis of (±)-γ-Lycorane and (±)-1-Deoxylycorine Using the [4+2]-Cycloaddition/Rearrangement Cascade of Furanyl Carbamates

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The total syntheses of γ-lycorane and (±)-1-deoxylycorine were accomplished using an intramolecular Diels−Alder cycloaddition of a furanyl carbamate as the key step. The initially formed [4+2]-cycloadduct undergoes nitrogen-assisted ring opening followed by deprotonation/reprotonation of the resulting zwitterion to give a rearranged hexahydroindolinone. The stereochemical outcome of the IMDAF cycloaddition has the side arm of the tethered alkenyl group oriented *syn* with respect to the oxygen bridge. The key intermediate used in both syntheses corresponds to hexahydroindolinone **20**. Removal of the *t*-Boc group in **20** followed by reaction with 6-iodobenzo[1,3]dioxole-5-carbonyl chloride afforded enamide **22**. Treatment of this compound with $Pd(OAc)_2$ employing the Jeffrey modification of the Heck reaction provided the galanthan tetracycle **24** in good yield. Compound **24** was subsequently converted into (±)-γ-lycorane using a four-step procedure to establish the *cis*-B,C-ring junction. A radical-based cyclization of the related enamide **33** was used for the synthesis of 1-deoxylycorine. Heating a benzene solution of **33** with AIBN and *n*-Bu_3SnH at reflux gave the tetracyclic compound **38** possessing the requisite *trans* fusion between rings B and C in good yield. After hydrolysis and oxidation of **38** to **40**, an oxidative decarboxylation reaction was used to provide the C_2–C_3–C_{12} allylic alcohol unit characteristic of the lycorine alkaloids. The resulting enone was eventually transformed into (±)-1-deoxylycorine via known synthetic intermediates.

The amaryllidaceae alkaloids constitute an important class of naturally occurring compounds.[1] The lycorine-type alkaloids, which are characterized by the presence of the galanthan ring system, represent a significant subclass within the amaryllidaceae family.[2] This group of compounds has attracted the attention of synthetic chemists due to the interesting biological properties of some of its members.[3] Several of these alkaloids possess antineoplastic and antimicotic activities, while others are known to exhibit insect antifeedant activity.[1] Lycorine (**1**) was first isolated in 1877 and was shown to be a powerful inhibitor of growth and cell division in higher plants and also to possess antiviral activity.[4,5] The tetracyclic pyrrolo[*d*,*e*]phenanthridine (galanthan) skeleton has been of considerable interest to organic chemists ever since the structure of lycorine was established by Uyeo and Wildman in 1955.[6] While many lycorine-type alkaloids possess a *trans*-B,C-ring juncture (e.g., lycorine (**1**), 1-deoxylycorine (**2**), and α-lycorane (**3**)), compounds with a *cis*-B,C-ring juncture such as that found in γ-lycorane (**4**) are also known (see also fortucine (**5**) and siculinine (**6**)).[7] Despite the apparent absence of useful pharmaceutical properties, γ-lycorane (**4**) has become a popular target for illustrating potential new strategies for the synthesis of this family of alkaloids.[8]

Among the many approaches to the lycorine class of alkaloids,[9] the Diels−Alder cycloaddition reaction has played a key role in the preparation of the C-ring of these

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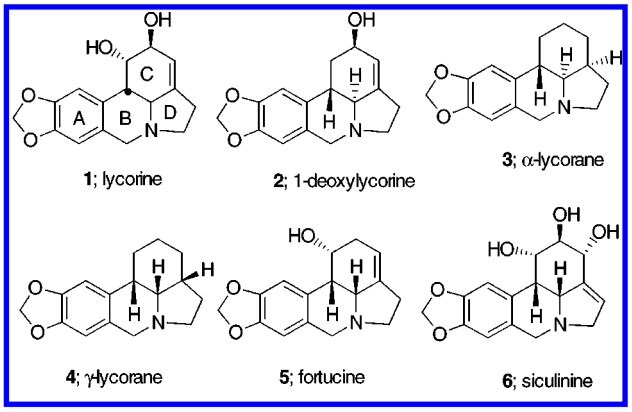
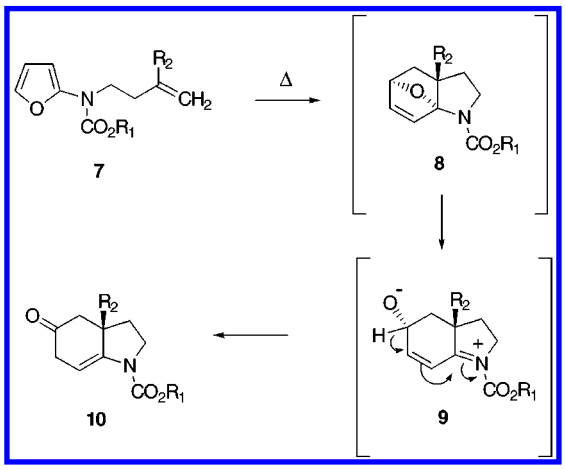
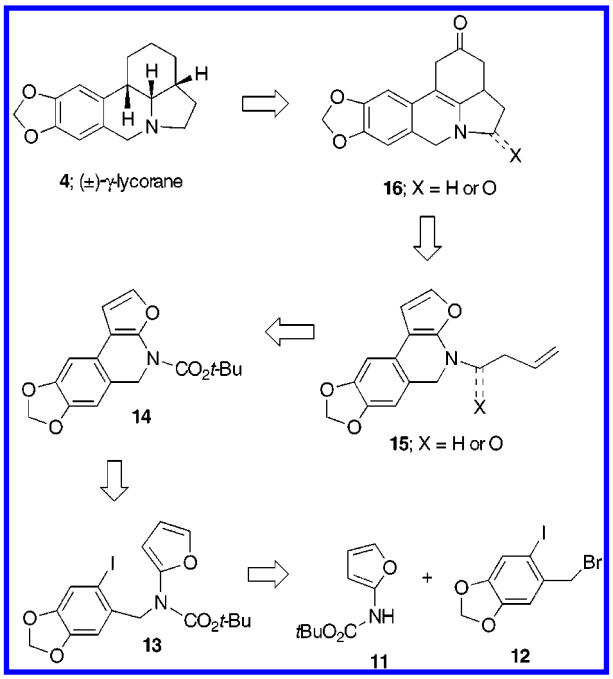


natural products.[10,11] Application of the intramolecular Diels−Alder reaction to the construction of azapolycyclic compounds has been practiced for more than two decades,[12,13] and interest in this methodology has been reinforced over the past several years.[14] Heterocycles such as furan, thiophene, and pyrrole undergo Diels−Alder reactions despite their stabilized 6-π aromatic electronic configuration.[15] The furan ring generally shows low reactivity toward unactivated dienophiles, and the competing retro-Diels−Alder reaction often becomes a problem from a synthetic point of view.[15] However, placement of the furan ring and the dienophile in the same molecule can often circumvent these problems.[16] Several years ago we began a synthetic program to provide general access to a variety of alkaloids by [4+2]-cycloaddition chemistry of furanyl carbamates.[17] Our synthetic strategy directed toward the lycorine-type alkaloids was to take advantage of an intramolecular Diels−Alder reaction of an alkenyl-substituted furanyl carbamate derivative (IMDAF),[16] as had been outlined in earlier reports from these laboratories.[18] In our approach to the hexahydroindoline skeleton, we chose to explore the ring-opening reaction of an aza-substituted oxabicyclo[2.2.1]heptene derivative. Oxabicyclic compounds are known to be valuable intermediates[19] for the synthesis of a variety of molecules of biological interest.[20] We found that the [4+2]-oxabicyclic adduct **8**, initially formed from the intramolecular Diels−Alder cycloaddition of a suitably substituted furanyl carbamate such as **7**, underwent a nitrogen-assisted ring opening. A subsequent hydrogen shift of the resulting zwitterion **9** gave

Scheme 1



Scheme 2



the hexahydroindolinone ring system **10** (Scheme 1). To highlight the method, we applied the synthetic strategy to the synthesis of (±)-γ-lycorane (**4**). This cycloaddition approach may also prove to be useful for the synthesis of more complex lycorine-type alkaloids possessing the *cis*-B,C-ring juncture (i.e., **5** and **6**). In the present paper we document the results of these studies.

Results and Discussion

Our initial retrosynthetic approach to (±)-γ-lycorane (**4**), as briefly outlined in Scheme 2, was to utilize a Pd(0)-catalyzed Heck cyclization of carbamate **13** to produce the cyclic aminofuran **14**. Removal of the *t*-Boc group of **14** followed by reaction with either a butenyl halide or the corresponding acid chloride was expected to give the desired cyclization precursor **15**. Thermolysis of **15** should provide the cyclic enamino ketone **16**, which would then be processed to γ-lycorane. Indeed, the requisite furanyl carbamate **14** could be prepared in 57% yield by treating carbamate **11** with the iodo-substituted benzyl bromide **12** in the presence of base. Heck cyclization of the resulting aryl iodide **13** occurred smoothly and

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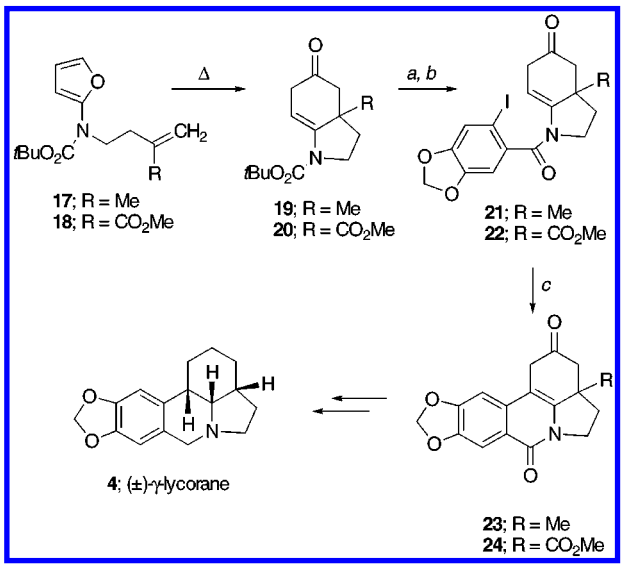
produced **14** in 75% yield. Unfortunately, all attempts to convert **14** into **15** failed to give any characterizable product. The hydrolytic lability of the intermediate N−H amine most likely interferes with both the alkylation and acylation steps.

In view of this disappointing result, we decided to approach the synthesis of **16** via an alternative strategy wherein a Pd(0)-induced cyclization of an iodoaryl amide became the key B-ring assembly step. The Heck reaction of vinyl or aryl halides with alkenes catalyzed by palladium is well recognized as a powerful tool for carbon−carbon bond formation.[22] In recent years the intramolecular version of the palladium-catalyzed arylation of alkenes has also emerged as a potent method for the construction of a variety of complex nitrogen heterocycles.[23] Although intramolecular Heck cyclizations generally show a preference for the *exo* mode of cyclization,[24] recent results by Rigby and co-workers show that the judicious choice of the Pd(0)-mediated cyclization conditions can lead to products derived from either a 6-*endo* pathway or a 5-*exo* mode.[25] For example, hydroindolone substrates afforded products derived from a 5-exocyclic mode of addition under "standard" Heck conditions,[22] while *endo* addition products were isolated using the Jeffrey catalyst system ($Pd(OAc)_2$, Bu_4NCl, KOAc, DMF).[26]

The potential of this methodology for the synthesis of various lycorine alkaloids prompted us to first carry out some model studies to probe the likelihood of Heck cyclization for B-ring assemblage. Initial feasibility studies were conducted with hexahydroindolinone **19** derived from the thermolysis of furanyl carbamate **17**. Acid hydrolysis of **19** followed by conversion of the resulting imine into enamide **21** proceeded in 72% overall yield. By following the Rigby protocol,[25] we found that treatment of **21** using the Jeffrey palladium catalyst provided only pentacycle **23** derived from the 6-*endo* mode of addition in 66% yield. The *endo*-selective cyclization pathway was extended to the more highly functionalized hexahydroindolinone **22**. In a similar fashion, reaction of the carbomethoxy-substituted enamide **22**, derived from hexahyroindolinone **20**, under the Jeffrey palladium cyclization conditions produced the galanthan derivative **24** in 68% yield (Scheme 3).

The synthesis of (±)-γ-lycorane (**4**) from **24** was completed by conversion to its thioketal derivative **25** and subsequent Ra-nickel reduction to **26** in 78% overall yield. Substrate **26** was hydrolyzed to the corresponding carboxylic acid **27**, which was decarboxylated using a modification of the Barton−McCombie deoxygenation reaction.[27] This was accomplished by converting carboxylic acid **27** into the corresponding *N*-hydroxy-2-thiazoline thione ester **28** via a DCC/DMAP coupling. Heating ester **28** in benzene at 80 °C with slow addition of a solution of 2,2′-azobis(isobutyronitrile) (AIBN) and tributyltin hydride afforded the decarboxylated benzopyridone **29** in 71% overall yield (Scheme 4).

Scheme 3[a]



[a] Reagents: (a) HCl, CH_2Cl_2; (b) pyridine, 6-iodobenzo[1,3]dioxole-5-carbonyl chloride; (c) $Pd(OAc)_2$, $[(Bu)_4N]^+Cl^-$, KOAc, DMF.

A major difficulty with any approach to the γ-lycorane ring system has been in the control of stereochemistry at the B,C-ring juncture. Our initial approach to (±)-lycorane (**4**) involved the catalytic reduction of **29** to **30**. Since **30** had already been converted to **4**, this would constitute a formal total synthesis of this alkaloid. Unfortunately, all of our attempts to hydrogenate the tetrasubstituted π-bond of enamide **29** under a variety of catalytic hydrogenation conditions proceeded only in very poor yield.

Because of the low yield associated with the catalytic hydrogenation reaction, we decided to alter our approach toward (±)-γ-lycorane (**4**). We decided that the simplest adjustment of our synthetic scheme would be first to reduce the amido carbonyl group with LAH and then carry out a subsequent enamine reduction using $NaCNBH_3$ in the presence of HCl/MeOH. We were pleased to find that this set of reducing conditions afforded (±)-γ-lycorane (**4**) in 74% yield as a single diastereomer.[28] Presumably, the initially formed enamine derived from reduction of the carbonyl group was protonated on the β-face, and the resulting iminium ion **31** reacted further with hydride from the least crowded face to produce (±)-γ-lycorane (**4**).

After the successful synthesis of (±)-γ-lycorane (**4**), we turned our attention to construction of the more complicated 1-deoxylycorine (**2**) system using the IMDAF-rearrangement strategy. As outlined in Scheme 5, we envisioned that the galanthan skeleton **32**, containing the

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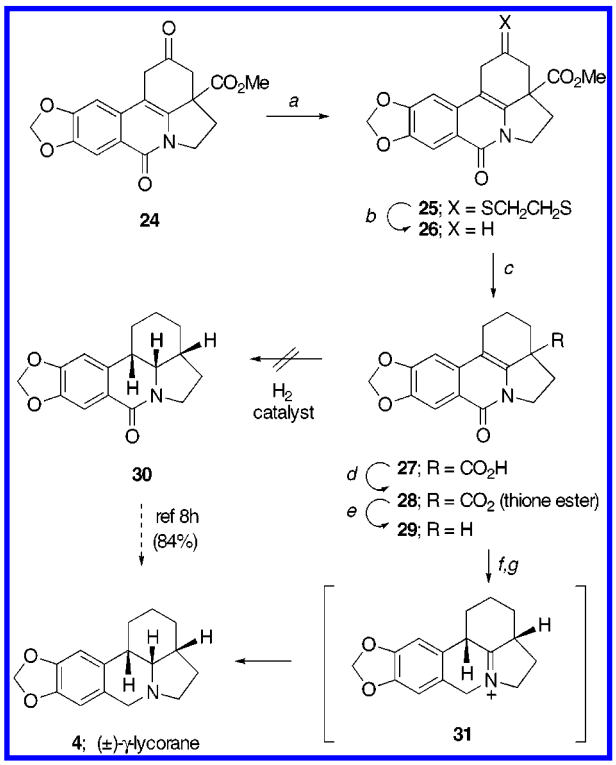
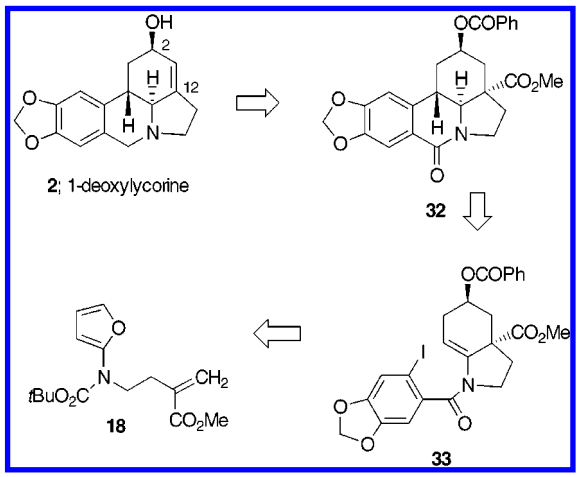
(28) The spectral data for **4** were consistent with those reported in ref 8c.

Scheme 4[a]



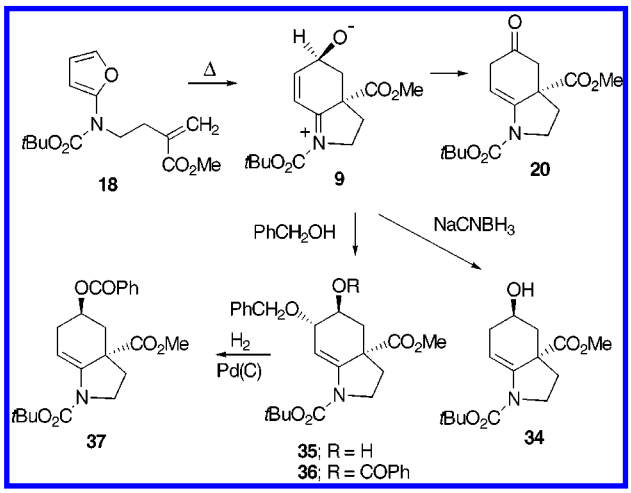
[a] Reagents: (a) $HSCH_2CH_2SH$, Δ; (b) Ra-Ni; (c) NaOH, MeOH, H_2O; (d) DCC, DMAP, $HONC_4H_4S_2$; (e) Bu_3SnH, AIBN, C_6H_6; (f) $LiAlH_4$, THF; (g) $NaCNBH_3$, HCl, MeOH.

Scheme 5



anti stereochemistry between the C_{12}-ester and the C_2-benzoate, could be produced from the IMDAF reaction of furanyl carbamate **18**. We had previously demonstrated that the thermolysis of **18** in methanol afforded mostly a *trans*-methoxy-substituted alcohol (vide infra).[18] Our intention was to use this unique cycloaddition as a key step in the synthesis of deoxylycorine, thereby avoiding additional steps to install the C-ring oxygen functionality late in the synthesis. With 1-deoxylycorine (**2**) as the target, cyclization of aryl iodide **33** across the enamide π-bond would be carried out using free radical conditions. Although precedence for the formation of a *trans*-B,C-ring junction in a radical cyclization of an achiral substrate related to **33** is available from independent work of Rigby[29] and Schultz,[9f] our approach to 1-deoxylycorine (**2**) has two novel synthetic aspects: (1) the [4+2]-cycloaddition of a furanyl carbamate to create

Scheme 6



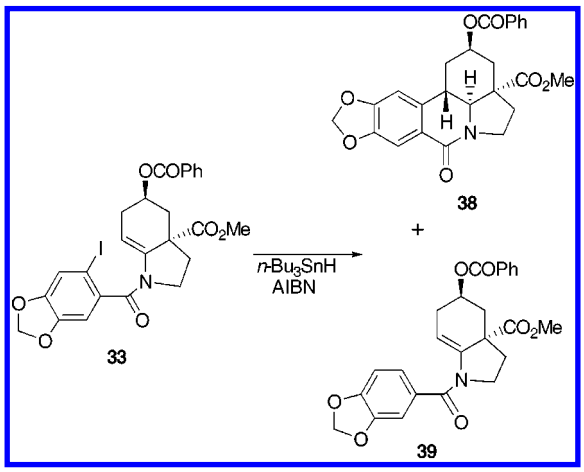
the C,D-rings of the galanthan skeleton and to control the 2-hydroxy stereochemistry and (2) use of an oxidative decarboxylation reaction of the C_{12}-ester group as a way to introduce the C_2–C_3–C_{12} allylic alcohol unit characteristic of the lycorine alkaloids.

As delineated in our synthetic plan (Scheme 3), thermolysis of carbamate **18** afforded the rearranged hexahydroindolinone **20** in 87% yield. This reaction has been proposed to proceed via zwitterion **9**, which undergoes a subsequent deprotonation/reprotonation to give **20**.[17] Unfortunately, all of our attempts to selectively reduce the keto group in **20** with a variety of hydride reducing agents invariably led to a mixture (ca. 1:1) of diastereomeric alcohols which proved to be extremely difficult to separate. It occurred to us that we might circumvent this troublesome stereochemical issue if we could induce a conjugate 1,4-reduction of iminium ion **9** with $NaCNBH_3$ (Scheme 6). Earlier results in our laboratory had demonstrated that the IMDAF cycloaddition proceeds by a transition state where the side arm of the tethered alkenyl group is oriented *exo* with respect to the oxygen bridge.[18] Products resulting from an *endo* side arm transition state were neither detected nor isolated. As a consequence of this preferred *exo* orientation, the carbomethoxy and alkoxy groups are disposed in an *anti* relationship. Thus, trapping of the vinylogous iminium ion **9** in a 1,4-conjugate fashion should produce alcohol **34**. Unfortunately, all of our attempts to obtain a sample of **34** by conjugate reduction of **9** proceeded only in poor yield (ca. 15%), and we eventually chose to abandon this approach.

We next investigated the thermolysis of **18** (65 °C) using benzyl alcohol as the solvent and were pleased to find that benzyl ether **35** was obtained as the major diastereomer (80%) in 62% overall yield. The structure of the *trans*-alcohol **35** was based on a comparison of NMR signals of the C_5,C_6-hydrogens with the related methoxy ether synthesized in this laboratory whose structure had been confirmed by X-ray crystallography.[18] Mechanistically, this result can be explained in terms of selective trapping of the zwitterion intermediate **9** with the solvent from the α-face. Apparently, the preferred mode of attack takes place on the side opposite the alcohol functionality that corresponds to the less congested face of the π-bond. This selective trapping of

(29) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975.

Scheme 7

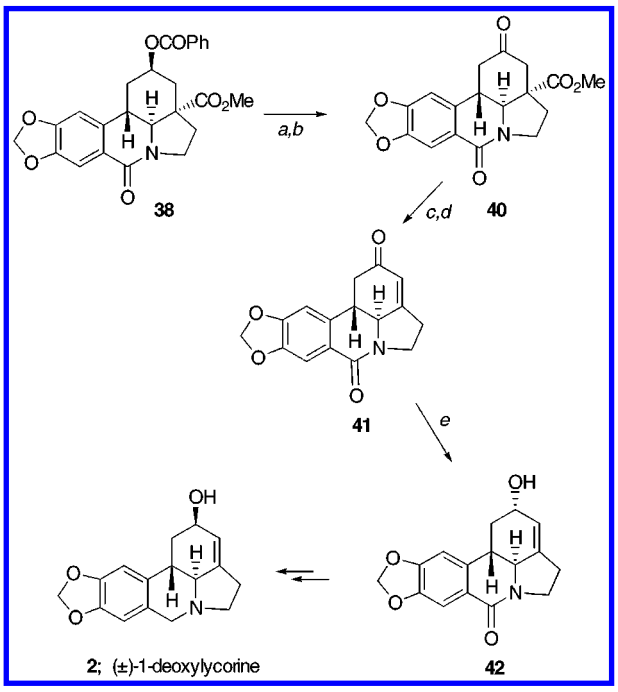


iminium ion **9** to give *trans*-alcohol **35** was a welcome discovery. The previous need for selective reduction of the keto group in **20** was now eliminated, since this single step equipped our system with the desired regio- and stereochemistry. Subsequent protection of alcohol **35** using DCC/DMAP provided the benzoate ester **36** in 90% yield. Catalytic hydrogenolysis of the benzyl ether functionality with Pd/C afforded **37** in 85% yield, which turned out to be identical to the benzoate ester obtained from the small quantity of *trans*-alcohol **34** that we had previously prepared from **18**. Deprotection of the *tert*-butyl carbamate functionality and acylation with 6-iodobenzo[1,3]dioxole-5-carbonyl chloride provided us with the radical cyclization precursor **33** in 81% yield.

Exposure of **33** to *n*-Bu_3SnH in benzene at reflux in the presence of AIBN afforded the anticipated tetracyclic product **38** in 51% yield, exhibiting the crucial *trans*-B,C-ring fusion (Scheme 7). The *trans* stereochemistry was confirmed in part by a large coupling (J = 13.2 Hz) between H_{15} and H_{16}. The relative stereochemistry between the remaining centers was unequivocally assigned by a single X-ray analysis that clearly fixes the *cis* relationship of the carbomethoxy and neighboring hydrogen.[30] The formation of the *trans*-B,C- and *cis*-C,D-ring fusion is consistent with SYBYL force field calculations, which suggest that this stereochemistry corresponds to the most stable isomer, and is also in agreement with the earlier literature reports of Rigby[29] and Schultz.[9f] Compound **38** was also accompanied by a somewhat lesser quantity (46%) of the reduced amide **39**. Enamide **39** might be formed by direct reduction of the radical derived from **33** or by way of an intramolecular α-amidoyl to aryl 1,5-hydrogen atom transfer followed by reduction.[31] Efforts to suppress the formation of **39** by changing the reaction conditions proved futile.

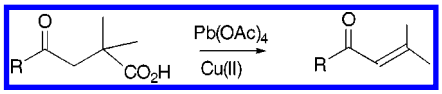
Oxidative decarboxylation of carboxylic acid derivatives is a classical procedure in synthetic organic chemistry and is well-known in scope and mechanism.[32] This reaction is best achieved by treatment of the acid with lead tetraacetate in the presence of a catalytic amount of copper(II) acetate. The latter served to trap the radical

Scheme 8[a]



[a] Reagents: (a) $NaOCH_3$, CH_3OH; (b) Dess−Martin oxidation; (c) NaOH, MeOH, H_2O; (d) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine; (e) $NaBH_4$, MeOH.

intermediate and so bring about elimination, possibly through a six-membered transition state. We reasoned that the most straightforward synthesis of 1-deoxylycorine from **38** would involve deprotection of the benzoyl ester followed by an oxidative decarboxylation. However, all of our attempts to promote this sequence of reactions were unsuccessful. Various conditions were investigated to effect the oxidative decarboxylation of the alcohol derived from **38,** but only complex mixtures of products were obtained. Having been thwarted in attempts to use benzoate ester **38** as a precursor to 1-deoxylycorine, we turned our attention to a procedure developed by McMurry and Blaszczak[33] that made use of γ-keto acids for the oxidative decarboxylation reaction.



These workers made the interesting discovery that when a carboxy group was located in a position γ to a second carbonyl group, α,β-unsaturated carbonyl compounds were readily formed. This procedure provides an easy route to some molecules that otherwise would be difficult to access. Indeed, we found that this reaction scheme does proceed in good yield and can be applied toward the synthesis of 1-deoxylycorine. The application of this method required the hydrolysis/oxidation of **38** to **40**, which occurred in 89% overall yield (Scheme 8). The oxidative decarboxylation reaction of **40** using $Pb(OAc)_4$ and $Cu(OAc)_2$ then gave enone **41** as the sole product in 70% yield. Thus, the key oxidative decarboxylation step worked quite well when a keto group was present in the γ position. Reduction of **41** with $NaBH_4$ provided the crystalline 2-*epi*-1-deoxylycorin-7-one **42** (80% yield), which had previously been converted into (±)-1-

(30) We have deposited atomic coordinates for compound **38** with the Cambridge Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Rd., CB2 1EZ, U.K.

(31) Snieckus, V.; Cuevas, J. C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.

(32) Sheldon, R. A.; Kochi, J. K. *Org. React. (N.Y.)* **1972,** *19*, 279.

(33) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.

deoxylycorine.[9f,34] The spectroscopic data of **42** were identical to those reported in the literature.[9f] Thus, the conversion of **41** to **42** represents the final step of a formal total synthesis of (±)-1-deoxylycorine (**2**).

In summary, a new strategy for the synthesis of the amaryllideace alkaloid family has been developed based in part on an intramolecular Diels−Alder reaction of a furanyl carbamate for initial construction of the hexahydroindolinone core. By using either a 6-*endo* Heck cyclization or a 6-*endo* free radical closure, either the *cis*-B,C- or *trans*-B,C-ring junction could be prepared. The IMDAF cycloaddition−rearrangement cascade was successfully used in the total synthesis of (±)-γ-lycorane and (±)-1-deoxylycorine. We plan to use this and related methodology in approaches to other alkaloidal targets.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

***tert*-Butyl N-(6-Iodo-1,3-benzodioxolo-5-ylmethyl)-*N*-(2-furyl)carbamate (13).** A solution containing 0.38 g (2 mmol) of furan-2-ylcarbamic acid *tert*-butyl ester (**11**),[18] 0.6 g (4 mmol) of K_2CO_3, 0.3 g (7 mmol) of powdered NaOH, and 0.14 g (0.4 mmol) of tetrabutylammonium hydrogen sulfate in 20 mL of benzene was heated at reflux for 30 min. Solid 5-(bromomethyl)-6-iodo-1,3-benzodioxole[35] was added in one portion, and the mixture was heated at reflux for an additional 1 h. The mixture was cooled to rt, quenched with 20 mL of water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to afford 0.88 g (95%) of **13** as a colorless oil: IR (neat) 2975, 1716, 1609, 1474 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 4.70 (s, 2H), 5.95 (s, 3H), 6.30 (dd, 1H, J = 2.0 and 0.8 Hz), 6.87 (s, 1H), 7.15 (dd, 1H, J = 2.0 and 0.8 Hz), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 49.7, 82.3, 101.3, 103.1, 106.3, 107.1, 107.2, 122.9, 123.9, 138.2, 145.8, 145.9, 147.5, 151.8. Anal. Calcd for $C_{17}H_{18}INO_5$: C, 46.07; H, 4.09; N, 3.16. Found: C, 46.26; H, 4.17; N, 2.95.

***tert*-Butyl 5*H*-3,7,9-Trioxa-4-azadicyclopenta[*a*,*g*]naphthalene-4-carbamate (14).** A solution containing 0.5 g (1.2 mmol) of iodide **13**, 0.6 g (6 mmol) of KOAc, 0.6 g (2 mmol) of *tert*-butylammonium chloride, and 0.1 g (0.4 mmol) of palladium acetate in 40 mL of freshly distilled DMF was heated to 100 °C for 1.5 h. The reaction mixture was cooled to rt, quenched with water, and extracted with ethyl acetate. The combined organic layers were washed several times with water, then dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.21 g (57%) of **14** as a white solid: mp 89−91 °C; IR (neat) 2976, 1709, 1624, 1510, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.52 (s, 9H), 4.82 (s, 2H), 5.94 (s, 2H), 6.56 (d, 1H, J = 2.0 Hz), 6.69 (s, 1H), 6.78 (s, 1H), 7.17 (d, 1H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 57.2, 81.9, 85.8, 101.8, 108.2, 109.3, 111.1, 118.7, 133.4, 138.4, 147.7, 148.1, 148.8, 153.9; HRMS calcd for $C_{17}H_{17}NO_5$ 315.1107, found 315.1092.

6-Iodobenzo[1,3]dioxole-5-carbaldehyde. To a solution containing 8.0 g (29 mmol) of 6-iodo-1,3-benzodioxole-5-methanol[35] and 300 mL of CH_2Cl_2 at 0 °C was added 12.4 g (58 mmol) of pyridinium chlorochromate. The mixture allowed to warm to rt and stirred at 25 °C for an additional 3 h. The mixture was chromatographed on a silica gel column and recrystallized from ethyl acetate/pentane to give 7.5 g (94%) of the title compound as a white solid: mp 112−113 °C; IR (KBr) 1758, 1666, 1602, 1488, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.08 (s, 2H), 7.33 (s, 1H), 7.36 (s, 1H), 9.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 93.6, 102.9, 109.1, 119.6, 129.8, 149.4, 153.8, 194.7. Anal. Calcd for $C_8H_5O_3I$: C, 34.81; H, 1.83. Found: C, 34.80; H, 1.87.

6-Iodobenzo[1,3]dioxole-5-carboxylic Acid. To a solution containing 9.6 g (56 mmol) of silver nitrate in 100 mL of H_2O at rt was added 4.5 g (113 mmol) of powdered NaOH. The mixture was allowed to stir at 25 °C for 45 min, and then 7.4 g (27 mmol) of the above aldehyde in 15 mL of EtOH was added. The solution was stirred for 2.5 h and filtered through a pad of Celite. The aqueous layer was extracted with ether and acidified using a 3 M HCl solution. Filtration of the aqueous layer provided a white solid which was taken up in ether and dried over $MgSO_4$. Removal of the solvent under reduced pressure provided 7.0 g (89%) of the title compound as a white solid: mp 216−217 °C; IR (KBr) 2911 (br), 1694, 1616, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.40 (br s, 1H), 6.12 (s, 2H), 7.31 (s, 1H), 7.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 84.9, 102.6, 110.2, 119.9, 129.1, 147.8, 150.5, 167.0. Anal. Calcd for $C_8H_5O_4I$: C, 32.90; H, 1.73. Found: C, 32.93; H, 1.79.

To a solution containing 5.0 g (17.1 mmol) of the above carboxylic acid in 150 mL of benzene were added 4.3 g (34.2 mmol) of oxalyl chloride and 4 drops of DMF. The solution was allowed to stir at rt for 5 h and concentrated under reduced pressure to give 4.8 g (90%) of 6-iodo-benzo[1,3]dioxole-5-carbonyl chloride. The acid chloride was used in the next step without further purification.

1-(6-Iodobenzo[1,3]dioxole-5-carbonyl)-3a-methyl-1,2,3,-3a,4,6-hexahydroindol-5-one (21). To a solution containing 2.0 g (8 mmol) of *tert*-butyl-3a-methyl-5-oxo-2,3,3a,4,5,6-hexahydroindol-1-carboxylate (**19**)[18] in 100 mL of CH_2Cl_2 was added 20 mL of a 3 M HCl solution. The mixture was stirred at rt for 12 h, quenched with a 50% NaOH solution, and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to provide 3a-methyl-2,3,3a,4,6,7-hexahydroindol-5-one imine as a colorless oil which rapidly decomposed upon standing: IR (neat) 2961, 1709, 1652, 1303 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 3H), 1.79−1.91 (m, 2H), 2.48−2.54 (m, 4H), 2.59−2.69 (m, 1H), 2.80−2.86 (m, 1H), 3.69−3.78 (m, 1H), 3.89−3.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 26.8, 30.5, 39.4, 40.2, 54.5, 58.6, 178.4, 208.6; HRMS calcd for $C_9H_{13}NO$ 151.0997, found 151.1005.

To a solution containing 1.2 g (8 mmol) of the above imine in 125 mL of CH_2Cl_2 at 0 °C was added 1.3 g (16 mmol) of freshly distilled pyridine. To this mixture was added 4.9 g (16 mmol) of 6-iodobenzo[1,3]dioxole-5-carbonyl chloride over a 5 min period. After being stirred at rt for 10 h, the reaction mixture was quenched with 50 mL of H_2O and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 2.4 g (72%) of **21** as a white solid: mp 193−194 °C; IR (KBr) 2904, 1790, 1724, 1610, 1504 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 3H), 1.77−1.91 (m, 2H), 2.50 (d, 1H, J = 14.4 Hz), 2.56 (d, 1H, J = 14.4 Hz), 3.01 (d, 2H, J = 3.6 Hz), 3.40−3.64 (m, 1H), 3.79−4.13 (m, 1H), 5.98 (s, 2H), 6.60 (s, 1H), 7.18 (s, 1H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 36.5, 38.0, 38.6, 44.4, 47.6, 50.1, 53.6, 103.2, 103.9, 104.4, 108.2, 113.0, 119.6, 122.9, 126.1, 145.1, 149.4, 149.8, 153.5, 169.4, 210.4. Anal. Calcd for $C_{17}H_{16}NO_4I$: C, 48.02; H, 3.79; N, 3.29. Found: C, 47.95; H, 3.77; N, 3.23.

3a-Methyl-3,3a,4,5-tetrahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-2,7-dione (23). To a solution containing 0.15 g (0.4 mmol) of iodide **21** in 3 mL of dry DMF in a sealed tube were added 8 mg (0.03 mmol) of $Pd(OAc)_2$, 0.2 g (0.7 mmol) of tetrabutylammonium chloride, and 0.19 g (2 mmol) of KOAc. The mixture was deoxygenated under

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(35) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *19*, 6959.

vacuum, sealed under argon, and heated at 100 °C for 12 h. The solution was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 0.5 g (66%) of **23** as a yellow solid: mp 214−215 °C; IR (KBr) 2925, 1733, 1669, 1640, 1479 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 3H), 2.14−2.19 (m, 1H), 2.20−2.24 (m, 1H), 2.65 (d, 1H, J = 14.4 Hz), 2.84 (d, 1H, J = 14.4 Hz), 3.36 (d, 1H, J = 21.4 Hz), 3.48 (d, 1H, J = 21.4 Hz), 4.03−4.14 (m, 1H), 4.46 (dd, 1H, J = 12.4 and 8.4 Hz), 6.09 (s, 2H), 6.77 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4, 36.5, 37.9, 43.9, 46.2, 52.8, 100.1, 102.1, 106.6, 121.5, 134.0, 143.8, 147.5, 152.4, 160.0, 207.8. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.87; H, 5.32; N, 4.53.

1-(6-Iodobenzo[1,3]dioxole-5-carbonyl)-5-oxo-1,2,3,4,5,6-hexahydroindole-3a-carboxylic Acid Methyl Ester (22). A solution of 0.1 g (0.34 mmol) of 2-[2-(*tert*-butoxycarbonylfuran-2-ylamino)ethyl]acrylic acid methyl ester[18] (**18**) in 10 mL of benzene was heated at 150 °C for 12 h in a sealed tube under an argon atmosphere. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.09 g (87%) of 5-oxo-2,3,5,6-tetrahydro-4*H*-indole-1,3a-dicarboxylic acid 1-*tert*-butyl ester 3a-methyl ester (**20**) as a yellow solid.[18] To a solution containing 3.8 g (13 mmol) of **20** and 5 mL of CH_2Cl_2 was added 20 mL of a 25% TFA/CH_2Cl_2 solution. The mixture was stirred at rt for 1 h and was concentrated under reduced pressure. The crude residue was diluted with 25 mL of CH_2Cl_2 and cooled to 0 °C, and 12 mL (86 mmol) of triethylamine was added. To the resultant residue was added dropwise a solution of 4.4 g (14 mmol) of 6-iodobenzo[1,3]dioxole-5-carbonyl chloride in 10 mL of CH_2Cl_2. The solution was allowed to stir for 4 h, the mixture was quenched with 50 mL of $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to provide 4.7 g (78%) of amide **22** as a white solid: mp 176−177 °C; IR (KBr) 1725, 1669, 1641, 1488, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.90−1.98 (m, 1H), 2.43 (d, 1H, J = 16.0 Hz), 2.57 (dd, 1H, J = 12.4 and 6.4 Hz), 2.99 (d, 1H, J = 16.0 Hz), 3.05 (dd, 1H, J = 22.8 and 5.6 Hz), 3.22 (dd, 1H, J = 22.8 and 2.0 Hz), 3.52 (t, 1H, J = 8.8 Hz), 3.75 (s, 3H), 3.77−3.90 (m, 1H), 6.06 (s, 2H), 6.79 (s, 1H), 6.95 (d, 1H, J = 2.8 Hz), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 37.0, 48.1, 50.6, 53.1, 53.2, 102.3, 107.3, 107.9, 118.8, 118.9, 136.8, 138.3, 148.8, 149.2, 168.5, 172.5, 206.5. Anal. Calcd for $C_{18}H_{16}NO_6I$: C, 46.08; H, 3.44; N, 2.99. Found: C, 45.86; H, 3.41; N, 2.95.

2,7-Dioxo-2,3,4,5-tetrahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic Acid Methyl Ester (24). To a solution containing 2.0 g (4 mmol) of iodide **22** in 30 mL of dry DMF were added 0.38 g (1.7 mmol) of $Pd(OAc)_2$, 2.4 g (8 mmol) of tetrabutylammonium chloride, and 2.3 g (23 mmol) of KOAc. The mixture was deoxygenated and heated at 100 °C for 1 h. The reaction was cooled to rt, quenched with 10 mL of H_2O, and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.95 g (66%) of **24** as a white solid: mp 229−230 °C; IR (neat) 1730, 1673, 1616, 1481, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.10−2.19 (m, 1H), 2.51 (d, 1H, J = 15.6 Hz), 2.91 (dd, 1H, J = 12.8 and 6.0 Hz), 3.17 (d, 1H, J = 16.0 Hz), 3.44 (s, 2H), 3.68 (s, 3H), 4.21 (ddd, 1H, J = 16.8, 11.2, and 6.4 Hz), 4.45 (dd, 1H, J = 12.2 and 8.4 Hz), 6.08 (d, 1H, J = 11.2 Hz), 6.09 (d, 1H, J = 1.2 Hz), 6.79 (s, 1H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.1, 36.6, 48.6, 49.0, 54.3, 54.7, 101.2, 103.1, 106.3, 107.3, 122.9, 134.4, 137.8, 148.9, 153.3, 160.7, 172.8, 205.9. Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.19; H, 4.47; N, 4.07.

7-Oxo-2-dithia-[4,5]spiro-2,3,4,5-tetrahydro-1*H*,7*H*-[1,3]-dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic Acid Methyl Ester (25). To a solution containing 0.2 g (0.6 mmol) of ketone **24** in 20 mL of dry CH_2Cl_2 were added 0.3 g (3.0 mmol) of 1,2-ethanedithiol and 0.3 g (2.3 mmol) of boron trifluoride etherate. The mixture was stirred at rt for 24 h and quenched with 10 mL of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.2 g (85%) of **25** as a white solid: mp 270−271 °C; IR (neat) 2980, 1726, 1676, 1616, 1482 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.14 (dt, 1H, J = 12.0 and 8.4 Hz), 2.23 (d, 1H, J = 14.0 Hz), 2.60 (dd, 1H, J = 12.4 and 5.6 Hz), 3.22 (d, 1H, J = 14.0 Hz), 3.34−3.46 (m, 6H), 3.67 (s, 3H), 3.90 (dt, 1H, J = 11.8 and 5.6 Hz), 4.32 (dd, 1H, J = 12.2 and 8.0 Hz), 6.08 (s, 2H), 6.91 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.9, 38.8, 39.2, 40.1, 46.0, 47.5, 53.2, 54.5, 64.9, 100.7, 102.1, 106.4, 108.3, 121.9, 133.9, 137.4, 147.4, 152.3, 160.2, 174.3. Anal. Calcd for $C_{20}H_{19}NO_5S_2$: C, 57.54; H, 4.59; N, 3.35. Found: C, 57.35; H, 4.65; N, 3.33.

7-Oxo-2,3,4,5-tetrahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic Acid Methyl Ester (26). To a solution containing 0.6 g (1.5 mmol) of thioketal **25** in 100 mL absolute ethanol was added 2 g of Ra/Ni. The suspension was heated at reflux for 4 h, cooled to rt, and filtered through Celite with 200 mL of ethanol. The solid was recrystallized from ethyl acetate to give 0.46 g (93%) of **26** as a white solid: mp 214−215 °C; IR (neat) 2949, 1728, 1678, 1619, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46−1.53 (m, 1H), 1.67−1.79 (m, 1H), 1.99−2.08 (m, 1H), 2.09−2.17 (m, 1H), 2.48−2.54 (m, 1H), 2.56 (dd, 1H, J = 12.0 and 5.6 Hz), 2.65 (dt, 1H, J = 12.8 and 3.2 Hz), 2.74 (dd, 1H, J = 16.4 and 6.4 Hz), 3.68 (s, 3H), 3.91 (ddd, 1H, J = 18.0, 12.0, and 5.6 Hz), 4.33 (dd, 1H, J = 12.4 and 8.4 Hz), 6.07 (s, 2H), 6.92 (s, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 22.0, 31.9, 36.4, 45.9, 52.9, 53.6, 100.6, 101.9, 106.2, 108.2, 121.9, 135.0, 138.4, 147.4, 152.0, 160.1, 174.2. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.98; H, 5.30; N, 4.20.

7-Oxo-2,3,4,5-tetrahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic Acid (27). To a solution containing 0.2 g (0.6 mmol) of ester **26** in 3 mL of methanol was added 20 mL of a 3 M NaOH. The reaction was heated to 50 °C for 4 h, cooled to rt, and acidified with 3 M HCl. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give 0.19 g (98%) of **27** as a white solid which was used without further purification: mp 228−229 °C; IR (neat) 3420, 2955, 1675, 1600 cm^{-1}; ^1H NMR (DMSO, 400 MHz) δ 1.43 (t, 1H, J = 12.0 Hz), 1.53−1.62 (m, 1H), 1.98−2.06 (m, 2H), 2.37−2.45 (m, 3H), 2.65 (dd, 1H, J = 16.8 and 6.8 Hz), 3.69 (ddd, 1H, J = 12.0, 11.8, and 5.6 Hz), 4.09 (dd, 1H, J = 12.0 and 8.8 Hz), 6.12 (d, 2H, J = 1.6 Hz), 7.03 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (DMSO, 100 MHz) δ 19.9, 21.3, 30.3, 35.1, 45.6, 52.8, 100.7, 101.9, 104.6, 106.7, 120.7, 134.5, 139.3, 146.7, 151.5, 158.5, 174.6. Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.16; H, 4.83; N, 4.47. Found: C, 65.08; H, 4.67; N, 4.32.

1,2,3,3a,4,5-Hexahydro[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one (29). To a solution of 0.2 g (0.6 mmol) of carboxylic acid **27** in 20 mL of CH_2Cl_2 were added 0.16 g (0.8 mmol) of DCC, 0.11 g (0.8 mmol) of 3-hydroxy-4-methyl-2(3*H*)-thiazoethione, and 0.02 g (0.2 mmol) of DMAP. The reaction mixture was allowed to stir at rt for 6 h and filtered through a pad of silica gel with ethyl acetate. The organic layer was concentrated under reduced pressure, and the resulting thione ester **28** was diluted with 25 mL of benzene. To this solution were added 0.03 g (0.2 mmol) of AIBN and 0.5 g (1.7 mmol) of tributyltin hydride, and the mixture was heated at reflux for 2 h. The reaction was allowed to cool to rt, and the solvent was removed under reduced pressure. The organic residue was partitioned between acetonitrile and hexane, and the acetonitrile layer was washed with hexane. The combined acetonitrile layers were concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.13 g (73%) of **29** as a white solid: mp 151−152 °C; IR (neat) 3065, 3020, 1680, 1483, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29−1.39 (m, 1H), 1.70 (dd, 1H, J = 12.0 and 8.4 Hz), 1.74−1.83 (m, 1H), 2.18−2.25 (m, 2H), 2.40 (ddd, 1H, J = 12.0, 6.4, and 5.6 Hz), 2.46−2.52

(m, 1H), 2.70 (dd, 1H, J = 16.0 and 6.8 Hz), 3.00−3.05 (m, 1H), 3.82 (ddd, 1H, J = 12.0, and 11.8, and 5.6 Hz), 4.37 (dd, 1H, J = 12.0 and 8.4 Hz), 6.06 (s, 2H), 6.89 (s, 1H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 23.0, 28.3, 31.3, 40.5, 47.1, 100.2, 101.8, 106.2, 106.7, 121.3, 135.4, 141.4, 146.8, 151.9, 160.2. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.15; H, 5.59; N, 5.14.

(±)-γ-Lycorane (4). To a solution of 0.03 g (0.12 mmol) of pyridone **29** in 20 mL of THF was added 0.01 g (0.3 mmol) of $LiAlH_4$, and the reaction was heated at reflux for 1 h. The solution was cooled to rt, quenched with 0.5 mL of water and then 1 mL of a 3 M NaOH solution, and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. To the crude organic residue were added 10 mL of methanol, a crystal of bromocresol green, and 0.01 g (0.2 mmol) of $NaCNBH_3$. To this solution was added 3 M methanolic/HCl until a yellow color persisted, and the solution was allowed to stir at rt for 4 h. The reaction mixture was quenched by the addition of 2 mL of 3 M KOH solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to provide 0.022 g (74%) of γ-lycorane (**4**): IR (CCl_4) 2930, 1505, 1480, 1320, 1245, 1230, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) 1.23−1.54 (m, 4H), 1.58−1.80 (m, 3H), 1.94−2.07 (m, 1H), 2.08−2.23 (m, 2H), 2.36 (dd, 1H, J = 5.0 and 4.0 Hz), 2.73 (ddd, 1H, J = 11.5, 5.0 and 1.0 Hz), 3.20 (d, 1H, J = 14.0 Hz), 3.37 (ddd, 1H, J = 9.0, 9.0 and 3.5 Hz), 4.05 (d, 1H, J = 14.0 Hz), 5.88 (br s, 2H), 6.49 (s, 1H), 6.61 (s, 1H); ^{13}C NMR δ 25.2, 29.2, 30.4, 31.7, 37.3, 39.4, 53.7, 57.1, 62.8, 100.6, 106.2, 108.3, 127.3, 133.1, 145.6, 146.0. The spectral data are in agreement with those reported in the literature.[8c]

5-Hydroxy-2,3,4,5-tetrahydro-4*H*-indole-1,3a-dicarboxylic Acid 1-*tert*-Butyl Ester 3a-Methyl Ester (34). To a solution of 1.0 g (3.4 mmol) of carbamate **18** in 50 mL of THF was added 0.9 g (13 mmol) of $NaCNBH_3$. After being heated at reflux for 24 h, the reaction mixture was quenched with 5 mL of H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.15 g (15%) of the *trans*-alcohol **34** as a clear oil: IR (neat) 3443, 1730, 1708, 1671, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.69−1.78 (m, 1H), 2.01 (ddd, 1H, J = 17.1, 9.0, and 3.2 Hz), 2.18−2.23 (m, 2H), 2.57 (dd, 1H, J = 12.0 and 3.6 Hz), 2.64 (br s, 1H), 3.39 (dt, 1H, J = 11.2 and 3.6 Hz), 3.58−3.62 (m, 1H), 3.67 (s, 3H), 3.68−3.71 (m, 1H), 3.90−3.92 (m, 1H), and 5.97 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 33.7, 34.3, 41.1, 46.6, 52.8, 52.9, 65.4, 80.4, 104.4, 137.3, 152.6, 174.7; HRMS calcd for $C_{15}H_{23}NO_5$ 297.1576, found 297.1578.

Another minor product isolated from the silica gel column contained 0.3 g (30%) of 4-*(tert*-butoxycarbonylfuran-2-ylamino)-2-methylbutyric acid methyl ester as a colorless oil: IR (neat) 2982, 1741, 1704, 1610, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.48−1.50 (m, 1H), 1.85−1.93 (m, 1H), 2.05−2.14 (m, 1H), 2.67−2.71 (m, 2H), 2.79−2.85 (m, 1H), 3.61−3.69 (m, 2H), 3.74 (s, 3H), 6.02 (br s, 1H), 6.34 (dd, 1H, J = 2.8 and 2.4 Hz), 7.18−7.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 28.3, 28.6, 30.2, 38.9, 45.9, 52.8, 81.9, 111.3, 117.7, 138.6, 148.0, 172.8; HRMS calcd for $C_{15}H_{23}NO_5$ 297.1576, found 297.1574.

6-Benzyloxy-5-hydroxy-2,3,5,6-tetrahydro-4*H*-indole-1,3a-dicarboxylic Acid *N*-tert-Butyl Ester 3a-Methyl Ester (35). A solution of 1.0 g (3.4 mmol) of furanyl carbamate **18** in 20 mL of benzyl alcohol was heated at 65 °C for 4 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.8 g (62%) of *trans*-alcohol **35** as a colorless oil: IR (neat) 3480, 1730, 1709, 1666, 1388 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 1.62 (t, 1H, J = 12.4 Hz), 1.71−1.81 (m, 1H), 2.23 (dd, 1H, J = 12.6 and 6.0 Hz), 2.42 (br s, 1H), 2.58 (dd, 1H, J = 12.4 and 4.0 Hz), 3.46 (dt, 1H, J = 11.6 and 6.0 Hz), 3.65−3.69 (m, 1H), 3.70 (s, 3H), 3.85−3.90 (m, 1H), 4.12 (dd, 1H, J = 7.4 and 3.2 Hz), 4.51 (d, 1H, J = 11.2 Hz), 4.73 (m, 1H), 6.31 (br s, 1H), 7.31−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 34.2, 38.9, 47.0, 52.9, 69.3, 69.9, 77.4, 80.9, 81.9, 103.5, 127.8, 128.1, 128.6, 138.8, 141.1, 152.3, 174.0. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.48; H, 7.25; N, 3.47. Found: C, 65.37; H, 7.18; N, 3.31.

In addition to the *trans*-alcohol, a smaller quantity (0.15 g, 20%) of the *cis*-isomer was also obtained as a colorless oil: IR (neat) 3530, 1730, 1709, 1666, 1388 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.67 (t, 1H, J = 12.4 Hz), 1.76−1.84 (m, 1H), 2.27 (dd, 1H, J = 12.4 and 6.0 Hz), 2.43 (dd, 1H, J = 12.0 and 3.6 Hz), 2.82 (br s, 1H), 3.41 (dt, 1H, J = 11.4 and 6.0 Hz), 3.66−3.67 (m, 1H), 3.69 (s, 3H), 3.74−3.80 (m, 1H), 4.12 (m, 1H), 4.48−4.54 (m, 1H), 4.70−4.79 (m, 1H), 6.44 (br s, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 33.8, 36.9, 46.6, 52.9, 66.7, 71.6, 73.0, 77.5, 81.1, 103.4, 128.1, 128.2, 128.7, 138.3, 142.4, 152.5, 174.0; HRMS calcd for $C_{22}H_{29}NO_6$ 403.1995, found 403.2003.

6-Benzoyloxy-5-(1-phenylmethanoyloxy)-2,3,4,5-tetrahydro-4*H*-indole-1,3a-dicarboxylic Acid 1-*tert*-Butyl Ester 3a-Methyl Ester (36). To a solution of 0.47 g (1.2 mmol) of *trans*-alcohol **35** in 30 mL of CH_2Cl_2 were added 0.2 g (1.6 mmol) of benzoic acid, 0.3 g (1.4 mmol) of 1,3-dicyclohexylcarbodiimide, and 0.04 g (0.3 mmol) of 4-(dimethylamino)pyridine. The reaction was allowed to stir at rt for 6 h, and the white precipitate that formed was removed by filtration. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 0.53 g (90%) of **36** as a white foam: IR (neat) 2929, 1710, 1649, 1449, 1388 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 9H), 1.69−1.79 (m, 2H), 2.31 (dd, 1H, J = 12.0 and 6.0 Hz)), 2.82 (dd, 1H, J = 12.0 and 4.0 Hz), 3.53 (td, 1H, J = 11.2 and 6.0 Hz), 3.69−3.74 (m, 1H), 3.80 (s, 1H), 4.51 (dd 1H, J = 7.2 and 4.0 Hz), 4.58−4.68 (m, 2H), 5.43 (ddd, 1H, J = 12.0, 7.2 and 4.8 Hz), 6.35 (br s, 1H), 7.21−7.30 (m, 5H), 7.41−7.45 (m, 2H), 7.52−7.58 (m, 1H), 8.00 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 34.2, 37.3, 47.2, 49.8, 52.9, 53.2, 69.6, 72.3, 81.0, 103.9, 128.1, 128.4, 128.5, 129.9, 130.4, 131.0, 133.2, 138.8, 141.8, 152.3, 166.0, 173.4; HRMS calcd for $C_{29}H_{33}NO_7$-Li 514.2417, found 514.2433.

5-Benzoyloxy-2,3,4,5-tetrahydro-4*H*-indole-1,3a-dicarboxylic Acid 1-*tert*-Butyl Ester 3a-Methyl Ester (37). To a solution of 0.05 g (0.1 mmol) of the above benzoate **36** in 15 mL of ethanol and 5 mL of THF in a high-pressure bottle under argon was added 0.05 g of 5% Pd on carbon. The mixture was shaken on a Parr hydrogenation apparatus under a 20 psi hydrogen atmosphere for 12 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to afford 0.035 g (85%) of **37** as a white solid: mp 124−125 °C; IR (neat) 2927, 1721, 1687, 1456, 1388 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.69 (t, 1H, J = 12.0 Hz), 1.78 (ddd, 1H, J = 12.4, 12.2, and 8.8 Hz), 2.25 (ddd, 1H, J = 14.0, 8.4, and 3.2 Hz), 2.31 (dd, 1H, J = 12.8 and 6.0 Hz), 2.78 (dd, 1H, J = 12.0 and 4.0 Hz), 2.86 (dt, 1H, J = 17.6 and 4.8 Hz), 3.47 (ddd, 1H, J = 17.2, 11.2, and 6.0 Hz), 3.67 (dd, 1H, J = 10.0 and 8.8 Hz), 3.76 (s, 3H), 5.20−5.30 (m, 1H), 6.08 (br s, 1H), 7.42 (t, 2H, J = 7.6 Hz), 7.53−7.56 (m, 1H), 8.00−8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 30.1, 34.4, 37.5, 46.7, 52.5, 53.0, 68.7, 80.6, 103.7, 128.5, 129.8, 130.5, 133.1, 137.5, 152.6, 166.1, 174.1. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.85; H, 6.64; N, 3.38.

A sample of **37** was also prepared from alcohol **34**. To a solution of 0.1 g (0.3 mmol) of *trans*-alcohol **34** in 10 mL of CH_2Cl_2 were added 0.08 g (0.4 mmol) of DCC, 0.05 g (0.4 mmol) benzoic acid, and 0.01 g (0.01 mmol) of DMAP. The reaction mixture was allowed to stir for 6 h at rt and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.13 g (93%) of **37**, which was identical in all respects with a sample obtained from the catalytic reduction of **36**.

5-Benzoyloxy-1-(6-iodobenzo[1,3]dioxole-5-carbonyl)-1,2,3,4,5,6-hexahydroindole-3a-carboxylic Acid Methyl Ester (33). A 0.1 g (0.25 mmol) sample of **37** in 5 mL of a 25% TFA/CH_2Cl_2 solution was stirred at rt for 6 h and concentrated under reduced pressure. The crude residue was diluted with

10 mL of CH_2Cl_2 and cooled to 0 °C, and 1.5 g (1.5 mmol) of triethylamine was added. To this mixture was added 0.09 g (0.3 mmol) of 6-iodobenzo[1,3]dioxole-5-carbonyl chloride. The solution was allowed to stir for 10 h and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to provide 0.12 g (81%) of amide **33** as a white solid: mp 86−87 °C; IR (neat) 2953, 1719, 1636, 1478, 1419 cm^{-1}; ^1H NMR (DMSO, 50 °C, 400 MHz) δ 1.78 (dd, 1H, J = 12.4 and 12.0 Hz), 1.86−1.94 (m, 1H), 2.28−2.34 (m, 2H), 2.65 (d, 1H, J = 12.0 Hz), 2.82 (d, 1H, J = 17.6 Hz), 3.30−3.32 (m, 2H), 3.74 (s, 3H), 5.20 (br s, 1H), 6.10 (s, 2H), 6.52 (br s, 1H), 6.91 (br s, 1H), 7.39 (s, 1H), 7.53 (dd, 2H, J = 7.6 and 7.2 Hz), 7.66 (dd, 1H, J = 7.6 and 7.2 Hz), 7.96 (d, 2H, J = 7.6 Hz); ^{13}C NMR (DMSO, 50 °C, 100 MHz) δ 29.3, 33.7, 36.3, 48.3, 51.9, 52.6, 59.5, 67.9, 80.9, 101.9, 106.9, 117.8, 128.5, 129.0, 129.6, 133.2, 136.6, 137.5, 147.9, 148.3, 165.0, 166.9, 173.0. Anal. Calcd for $C_{25}H_{22}NO_7I$: C, 52.19; H, 3.85; N, 2.43. Found: C, 52.09; H, 3.79; N, 2.36.

2-Benzoyloxy-12b,12c-dimethyl-7-oxo-2,3,4,5,12b,12c-hexahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]-phenanthridine-3a-carboxylic Acid Methyl Ester (38). To a solution of amide **33** in 50 mL of benzene were added 0.01 g (0.1 mmol) of AIBN and 0.1 g (0.3 mmol) of tributyltin hydride. The mixture was heated at reflux for 2 h, and the solvent was removed under reduced pressure. The organic residue was partitioned between acetonitrile and hexane, and the acetonitrile layer was washed with hexane. The combined acetonitrile layers were concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.06 g (51%) of **38** as a white solid: mp 171−172 °C; IR (neat) 2926, 1720, 1650, 1604, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33−1.38 (m, 2H), 2.03−2.15 (m, 2H), 2.34 (dt, 1H, J = 13.6 and 4.8 Hz), 2.57 (ddd, 1H, J = 12.4, 12.4, and 4.8 Hz), 3.15 (ddd, 1H, J = 13.0, 12.8, and 4.8 Hz), 3.34 (ddd, 1H, J = 12.0, 12.0, and 5.6 Hz), 3.78 (s, 3H), 4.01 (d, 1H, J = 13.2 Hz), 4.17 (d, 1H, J = 12.0 and 8.0 Hz), 5.39−5.45 (m, 1H), 6.00 (d, 1H, J = 1.2 Hz), 6.07 (d, 1H, J = 1.2 Hz), 6.66 (s, 1H), 7.46 (dd, 2H, J = 8.0 and 7.6 Hz), 7.49 (s, 1H), 7.57−7.61 (m, 1H), 8.02−8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 29.6, 34.9, 36.8, 44.4, 51.3, 53.3, 62.7, 68.7, 101.9, 104.2, 108.8, 125.1, 128.7, 129.8, 130.1, 133.5, 136.2, 147.0, 150.9, 162.8, 166.0, 175.5. Anal. Calcd for $C_{25}H_{23}NO_7$: C, 66.81; H, 5.16; N, 3.12. Found: C, 66.72; H, 5.12; N, 3.08.

The minor product isolated from the silica gel chromatography column contained 0.045 g (46%) of 1-(benzo[1,3]dioxole-5-carbonyl)-5-benzoyloxy-1,2,3,4,5,6-hexahydroindole-3a-carboxylic acid methyl ester (**39**) as a white solid: mp 60−61 °C; IR (neat) 2955, 1720, 1633, 1437, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34−1.44 (m, 2H), 1.71 (dd, 1H, J = 12.4 and 12.2 Hz), 1.82−1.89 (m, 1H), 2.12−2.26 (m, 1H), 2.44−2.52 (m, 1H), 2.68−2.78 (m, 1H), 2.80 (dd, 1H, J = 12.0 and 3.6 Hz), 3.67 (ddd, 1H, J = 12.0, 11.2, and 6.8 Hz), 3.85 (s, 3H), 5.23−5.26 (m, 1H), 6.01 (s, 2H), 6.81 (s, 1H, J = 8.0 Hz), 7.08 (br s, 1H), 7.14 (d, 1H, J = 7.2 Hz), 7.43 (dd, 2H, J = 8.0 and 7.8 Hz), 7.56 (dd, 1H, J = 7.8 and 7.2 Hz), 8.01 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.9, 30.3, 34.3, 37.6, 52.9, 53.2, 68.4, 101.5, 101.7, 107.6, 108.4, 108.9, 120.7, 122.5, 128.6, 129.8, 130.4, 133.3, 138.1, 147.6, 149.4, 166.1, 174.0. Anal. Calcd for $C_{25}H_{23}NO_7$: C, 66.81; H, 5.16; N, 3.12. Found: C, 66.75; H, 5.24; N, 3.17.

12b,12c-Dimethyl-2,7-dioxo-2,3,4,5,12b,12c-hexahydro-1*H*,7*H*-[1,3]-dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic Acid Methyl Ester (40). To a solution containing 0.15 g (0.3 mmol) of ester **38** in 15 mL of methanol was added 0.18 g (3.3 mmol) of NaOH. The mixture was heated at 60 °C for 4 h, cooled to rt, and quenched with 10 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude alcohol was taken up in 20 mL of CH_2Cl_2, and 0.17 g (0.4 mmol) of Dess−Martin reagent[36] was added. The mixture was allowed to stir for 3 h at rt and quenched with 10 mL of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.1 g (89%) of **40** as a white solid: mp 219−220 °C; IR (neat) 2889, 1736, 1648, 1607, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94 (ddd, 1H, J = 12.4, 12.4, and 8.0 Hz), 2.29 (dd, 1H, J = 18.6 and 13.6 Hz), 2.59 (d, 1H, J = 15.6 Hz), 2.77 (dd, 1H, J = 12.8 and 5.6 Hz), 2.92 (d, 1H, J = 3.6 Hz), 2.97 (d, 1H, J = 3.6 Hz), 3.35 (ddd, 1H, J = 13.4, 13.2, 4.0 Hz), 3.42 (ddd, 1H, J = 11.6, 11.6, and 6.0 Hz), 3.72 (s, 3H), 3.92 (d, 1H, J = 13.2 Hz), 4.24 (dd, 1H, J = 12.0 and 8.0 Hz), 6.02 (s, 2H), 6.61 (s, 1H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.3, 37.2, 37.7, 44.7, 47.2, 51.7, 53.4, 63.6, 102.1, 104.3, 109.0, 124.6, 134.2, 147.4, 151.1, 161.9, 174.7, 206.5. Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 62.81; H, 4.97; N, 3.99.

12b,12c-Dimethyl-4,5,12b,12c-tetrahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-2,7-dione (41). To a solution of 0.05 g (0.12 mmol) of ester **40** in 0.5 mL of methanol was added 10 mL of a 3 M NaOH solution. The mixture was heated to 50 °C for 4 h and then acidified by the addition of 3 M HCl. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide the corresponding carboxylic acid, which was used in the next step without further purification. The crude carboxylic acid was taken up in 15 mL of benzene, and 0.06 g (0.35 mmol) of copper(II) acetate and 0.1 mL (1.3 mmol) of pyridine were added. The solution was stirred until the it turned green, and then 0.15 g (0.35 mmol) of lead(IV) acetate was added. The reaction mixture was stirred at rt for 30 min and then heated at reflux for 3 h. The mixture was diluted with CH_2Cl_2 and washed with 2 M HCl and a saturated $NaHCO_3$ solution, and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.02 g (70%) of **41** as a white solid: mp 193−194 °C; IR (neat) 2915, 1653, 1605, 1477, 1364 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (dd, 1H, J = 16.8 and 13.6 Hz), 3.01−3.09 (m, 3H), 3.26 (ddd, 1H, J = 12.8 and 4.0 Hz), 3.86−3.93 (m, 1H), 3.97−4.02 (m, 1H), 4.20 (d, 1H, J = 12.4 Hz), 6.04−6.06 (m, 3H), 6.62 (s, 1H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.9, 38.4, 40.9, 43.6, 61.3, 102.1, 103.8, 109.1, 123.3, 125.3, 129.0, 134.7, 147.4, 151.2, 164.2, 197.1. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.83; H, 4.63; N, 4.95. Found: C, 67.71; H, 4.57; N, 4.86.

2-Hydroxy-12b,12c-dimethyl-1,2,4,5,12b,12c-hexahydro-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-7-one (42). To a solution of 0.01 g (0.04 mmol) of ketone **41** in 10 mL of methanol was added 5 mg (0.13 mmol) of $NaBH_4$ dissolved in 0.5 mL of H_2O at rt. The reaction mixture was allowed to stir at rt for 1 h, quenched with 5 mL of H_2O, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.008 g (80%) of **42**: mp 193−194 °C; IR ($CHCl_3$) 3600, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52 (ddd, 1H, J = 12.5, 12.5, and 9.5 Hz), 1.76 (d, 1H, J = 6.8 Hz), 2.75 (m, 4H), 3.73 (m, 1H), 3.82 (m, 1H), 3.89 (d, 1H, J = 12.0 Hz), 4.67 (m, 1H), 5.66 (m, 1H), 6.02 (s, 2H), 6.72 (s, 1H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 32.2, 40.0, 43.3, 60.2, 68.6, 101.6, 103.4, 108.3, 122.7, 125.3, 135.9, 140.3, 146.6, 150.7, 163.2. The spectral data are in agreement with those reported in the literature.[9f]

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for new compounds lacking analyses together with an ORTEP drawing for compond **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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