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Synthesis of Some Members of the Hydroxylated Phenanthridone Sub-class of the *Amaryllidaceae* Alkaloid Family

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Abstract

The total synthesis of several members of the hydroxylated phenanthridone sub-class of the *Amaryllidaceae* alkaloid family has been carried out. (±)-Lycoricidine and (±)-7-deoxypancratistatin were assembled through a one-pot Stille/intramolecular Diels-Alder cycloaddition cascade to construct the core skeleton. The initially formed [4+2]-cycloadduct undergoes nitrogen-assisted ring opening followed by a deprotonation/reprotonation of the resulting zwitterion to give a rearranged hexahydroindolinone on further heating at 160 °C. The stereochemical outcome of the IMDAF cycloaddition has the side arm of the tethered vinyl group oriented *exo* with respect to the oxygen bridge. The resulting cycloadduct was used for the stereocontrolled installation of the remaining functionality present in the C-ring of the target molecules. Key features of the synthetic strategy include (1) a lithium-hydroxide induced tandem hydrolysis/decarboxylation/elimination sequence to introduce the required π -bond in the C-ring of (±)-lycoridine; and (2) conversion of the initially formed Diels-Alder adduct into an aldehyde intermediate which then undergoes a stereospecific decarbonylation reaction mediated by Wilkinson's catalyst to set the *trans* B-C ring junction of (±)-7-deoxypancratistatin.

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 (1), represent a significant sub-class 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 (Figure 1).³ Several of these alkaloids possess antineoplastic and antimicrobial activities while others are known to exhibit insect antifeedant activity.¹

Lycorine (2) 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 (2), 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); siculinine (6)).⁷ The history of the related hydroxylated phenanthridones of the *Amaryllidaceae* group, their biological profiles and various syntheses have been reviewed on several occasions,⁸ most recently by Hudlicky and Rinner in 2005.⁹ Lycoricidine (7),¹⁰ the structurally related narciclasine (8),¹¹ as well as pancratistatin (9)¹² and 7-deoxypancratistatin (10)¹³ are popular synthetic targets primarily because their heterocyclic framework provides a means to demonstrate the utility of new synthetic strategies.⁹ In addition, the narcissus alkaloids are available only in small quantities from natural sources¹⁴ and their use as therapeutic agents¹⁵ depends on their ready availability.

Among the many approaches to the *Amaryllidaceae* alkaloids,^{9,16} the Diels-Alder cycloaddition reaction has played a key role in the preparation of the C-ring of these natural products.^{17,18} Application of the intramolecular Diels-Alder reaction for the construction of aza-polycyclic compounds has been practiced for more than two decades^{19,20} and interest in this methodology has been reinforced over the past several years.²¹ Heterocycles such as furan, thiophene, and pyrrole undergo Diels-Alder reactions despite their stabilized 6- π aromatic electronic configuration.²² 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.²² However, placement of the furan ring and the dienophile in the same molecule can often circumvent these problems.^{23,24} Our synthetic strategy directed towards the hydroxylated phenanthridone type alkaloids was to take advantage of the intramolecular Diels-Alder reaction of an alkenyl substituted 2-amidofuran (IMDAF), as had been outlined in earlier reports from this laboratory.²⁵ Our retrosynthetic analysis of (\pm)-lycoricidine (**7**) is shown in Scheme 1 and makes use of a tandem cascade sequence consisting of a Stille coupling²⁶ followed by a spontaneous intramolecular [4+2]-cycloaddition of an amidofuran. The resulting cycloadduct **13** is then used for the stereocontrolled installation of the other functionality present in the C-ring of (\pm)-lycoricidine. The carbomethoxy substituent would be utilized as the critical control element not only to facilitate the [4+2]-cycloaddition but also to provide a handle for the introduction of the required π -bond and to set the stereochemistry at the C_{4a}-ring junction. In the present paper we document the results of our studies making use of this methodology.²⁷

Results and Discussion

Model Studies

As a prelude to the total synthesis of (\pm)-lycoricidine (**7**), we initially set out to prepare the core hydroxylated phenanthridone skeleton in order to test the viability of our approach as well as to probe specific reactions to be used in a total synthesis effort. With this in mind, we first investigated the thermolysis of the prototypic system **15** prepared according to the sequence of reactions outlined in Scheme 2.

The thermolysis of 2-amidofuran **15** at 160 °C resulted in a major reorganization that gave rise to dihydrophenanthridine-dione **18** in 70% yield. When the thermolysis was carried out at 80 °C, we were pleased to discover that the desired Diels-Alder cycloadduct **16** was formed in quantitative yield. This IMDAF cycloaddition proceeded by a transition state where the side arm of the tethered vinyl group is oriented *exo* with respect to the oxygen bridge.²⁴ Consequently, the carbomethoxy group and oxy bridge in the product are disposed in an *anti* relationship. Further heating of cycloadduct **16** at 160 °C resulted in a smooth reorganization to afford the rearranged product **18** in high yield. This reaction cascade can be accounted for by a nitrogen-assisted ring opening of **16** to give zwitterion **17** as a transient intermediate. A subsequent deprotonation/reprotonation of **17** accounts for the formation of **18**.

In our planned approach toward (\pm)-lycoricidine (**7**), we needed to install the other functional groups present on the C-ring with the correct stereochemistry. The first step in our conceived synthesis of (\pm)-lycoricidine (**7**) requires a stereochemically controlled dihydroxylation of the π -bond present in the Diels-Alder cycloadduct. This tactic was easily tested using the readily available cycloadduct **16**. Treatment of **16** with catalytic OsO₄ in the presence of 4-methylmorpholine-*N*-oxide furnished the desired diol **19** in 95% yield (Scheme 4). The dihydroxylation reaction occurred exclusively from the less hindered *exo* face. In our attempts to convert diol **19** into the corresponding acetonide, a rather unusual acid-catalyzed rearrangement occurred when the reaction was performed in methanol containing a trace amount of *p*-toluenesulfonic acid. The major and unexpected product obtained from this reaction (81% yield) was identified as enone **20** on the basis of its spectral data. This unusual

reorganization can be rationalized by the cascade pathway proposed in Scheme 5. We assume that the first step proceeds by an acid-catalyzed oxabicyclic ring opening which is assisted by the electron pair of the amido nitrogen. A subsequent deprotonation would generate enol **22** which might very well transfer the Boc group on the adjacent carbamate, followed by loss of water to produce **23** as a transient species. This step is not essential for the overall reaction to occur since some variation in timing is certainly possible. Addition of methanol to the highly reactive imino functionality present in **23** would lead to *t*-butyl vinyl carbonate **24**. Hydrolysis of the acid sensitive carbonate with simultaneous elimination of water accounts for the formation of the observed product **20**.

As a consequence of the acid lability of diol **19** we decided to replace the Boc with a benzyl group in order to avoid the acid-catalyzed cascade reaction encountered with **19**. The synthesis of the *N*-benzyl cycloadduct **25** proceeded along similar lines to that described above. In this case, the methyl acrylate moiety was introduced by means of a Stille coupling²⁶ using methyl 2-tri-*n*-butyl stannylacrylate.²⁸ The optimal conditions for this reaction were eventually determined to be those described by Baldwin.²⁹ The expected cross-coupled amidofuran, however, was not isolated as it spontaneously underwent an intramolecular [4+2]-cycloaddition to furnish cycloadduct **25** in 55% overall yield for the two-step cascade. The increased reactivity of the *N*-benzyl amidofuran (55 °C) when compared to the Boc analogue (80 °C) is probably related to a higher lying HOMO of the furanyl 4 π -system. The subsequent dihydroxylation reaction proceeded as expected with exclusive *exo*-stereoselectivity to give diol **26** (Scheme 6). In order to minimize acid degradation pathways, we chose to induce the opening of the oxabicyclic ring prior to the protection of the C₃,C₄-hydroxyl groups. The expected *N*-acyliminium ion was generated by treating **26** with BF₃·OEt₂ and the incipient cation was reduced *in situ* using Et₃SiH to give triol **27** in 74% yield. The presence of the angular carbomethoxy group directs the hydride delivery from the less hindered β -face and sets the correct stereochemistry at C_{4a} that is needed for (\pm)-lycoridine (**7**). Selective esterification of the C₂ hydroxyl group with AcCl/Net₃ followed by protection of the remaining two hydroxyl groups with 2,2-dimethoxy-propane in the presence of *p*-TsOH provided acetonide **28** whose structure was unequivocally established by X-ray crystallography. The acetoxy group present in compound **28** was hydrolyzed with NaOMe and the resulting alcohol was then treated with NaH followed by the addition of CS₂ and MeI to afford the corresponding xanthate. Heating the xanthate in 1,2-dichlorobenzene for 12 h afforded the expected olefin **29** derived from a Chugaev elimination³⁰ in 92% yield.

Since the β -face of the double bond in compound **29** is blocked by the bulky acetonide, the dihydroxylation reaction was expected to take place from the less hindered α -face, *syn* to the carbomethoxy group, thereby setting the correct stereochemistry of the C₂-hydroxyl group needed for an eventual synthesis of (\pm)-lycoridine (**7**). Indeed, when **29** was treated with OsO₄/NMO, the desired diol **30** was formed as a transient species but underwent spontaneous cyclization with the adjacent carbomethoxy group to deliver γ -lactone **31** (Scheme 7). A subsequent mesylation reaction afforded mesylate **32** in 74% yield for the two-step sequence starting from **29**. With compound **32** in hand, we hoped that we could induce a domino fragmentation cascade which would involve (a) lactone hydrolysis using LiOH to deliver the carboxylate anion; and (b) a subsequent decarboxylation/elimination of the mesylate group to introduce the critical double bond in the C-ring.³¹ Gratifyingly, this desired cascade proceeded quite smoothly and afforded the allylic alcohol **35** in near quantitative yield. This reaction presumably proceeds by an initial opening of the lactone ring with hydroxide to give carboxylate anion **33**. A subsequent decarboxylation would generate anion **34** which, in turn, would induce the elimination of the mesylate anion ultimately affording the observed alcohol **35**.

(±)-Lycoricidine

Having been encouraged by the preliminary cycloaddition experiments involving furanyl carbamate **15**, we turned our attention to the preparation of amidofuran **40** which we hoped to use for the eventual synthesis of (±)-lycoricidine (**7**). The synthesis of **40** began by coupling the known acid chloride **36**³² with the lithiated carbamate **37b** derived by treating furanyl-2-ylcarbamic acid *tert*-butyl ester (**37a**) with *n*-BuLi. Removal of the Boc-protecting group from the resulting carbamate **38** with Mg(ClO₄)₂ afforded NH amide **39** in 75% yield and this was followed by reaction with NaH and *p*-methoxybenzyl chloride to give **11** in 83% yield.³³ The methyl acrylate moiety was introduced by means of a Stille coupling²⁶ using methyl 2-tri-*n*-butyl-stannylacrylate (**12**)²⁸ (Scheme 8). The optimal conditions for this reaction were eventually determined to be those described by Corey which utilized a combination of CuCl/Pd(0)/LiCl for the key coupling.³⁴ The use of DMSO with rigorous exclusion of oxygen and moisture at 60 °C gave the best results. The expected cross-coupled amidofuran **40**, however, was not isolated as it spontaneously underwent an intramolecular [4+2]-cycloaddition to furnish cycloadduct **13** in 82% overall yield for the two-step cascade. The increase in reactivity of **40** when compared to the related furanyl carbamates²⁴ (>150 °C) is due to the placement of the carbonyl center within the dienophilic tether as well as the presence of the carbomethoxy group which lowers the LUMO energy of the π -bond thereby facilitating the cycloaddition. Dramatic effects on the rate of the Diels-Alder reaction were previously noted to occur when an amido group was used to anchor the diene and dienophile.³⁵ Our ability to isolate oxabicyclic adduct **13** is presumably a result of the lower reaction temperature employed (*i.e.*, 60 °C) as well as the presence of the amido carbonyl group, which diminishes the basicity of the nitrogen atom thereby retarding the ring cleavage/rearrangement reaction generally encountered with these systems.²⁴

With the rapid construction of the lycoricidine framework in hand, installation of the other functional groups present on the C-ring with the correct relative stereochemistry was investigated. To continue the synthesis, cycloadduct **13** was transformed to diol **41** by reaction with catalytic OsO₄ in the presence of 4-methyl-morpholine-*N*-oxide. The dihydroxylation reaction occurred exclusively from the less hindered *exo* face producing **41** in 98% yield (Scheme 9). Having introduced the correct *cis*-stereochemistry of the hydroxyl groups at the C₃,C₄ positions, we then proceeded to set the stereochemistry at the C_{4a} position, insert the remaining α -hydroxyl group at C₂ and ultimately introduce the required π -bond. All of these operations were facilitated by making use of the available carbomethoxy group (*vide infra*). First, diol **41** was converted to the corresponding acetonide **42** in 80% yield by treatment with 2,2-dimethoxypropane and catalytic pyridinium *p*-toluenesulfonate. The uniquely functionalized oxabicyclic adduct **42** contains a “masked” *N*-acyliminium ion which can be released by treatment with a Lewis acid such as TMSOTf. When the resulting ring-opened iminium ion was treated with Zn(BH₄)₂,³⁶ alcohol **14** was obtained with complete diastereoselectivity in 74% yield.

What was required for the end game leading to (±)-lycoricidine (**7**) was to invert the stereochemistry of the C₂-hydroxyl group, remove the carbomethoxy moiety and generate a double bond between the C₁-C_{10b} position of the C-ring. To this end, compound **14** was treated with NaH followed by the addition of CS₂ and MeI to give the corresponding xanthate ester which, upon heating at reflux in 1,2-dichlorobenzene for 12 h, afforded the expected olefin **43** derived from a Chugaev elimination³⁰ in 94% yield (Scheme 10). Since the β -face of the π -bond of **43** was blocked by the bulky acetonide, a dihydroxylation reaction was expected to take place from the less hindered α -face (*syn* to the carbomethoxy group), thereby setting the correct stereochemistry of the C₂-hydroxyl group. Indeed, when **43** was treated with OsO₄/NMO, the desired diol **44** was formed as a transient species but underwent spontaneous cyclization with the adjacent carbomethoxy group to deliver γ -lactone **45**. A subsequent

mesylation reaction afforded mesylate **46** in 76% yield for the two-step sequence starting from **43**. The γ -lactonization of **44** to **45** permits the selective activation of the C₁-hydroxyl group. The PMB group was removed by the reaction of **46** with PdCl₂ in the presence of acetic acid³⁷ to furnish the deprotected amide in 65% yield. Gratifyingly, the reaction of this amide with LiOH in aqueous THF induced the tandem hydrolysis/decarboxylation/elimination sequence,³¹ previously encountered with the model substrate **32**, to furnish allylic alcohol **47** in 93% yield. Finally, deprotection of the acetonide with TFA afforded (\pm)-lycoricidine (**7**) in 90% yield.

(\pm)-7-Deoxypancratistatin

The potent antiviral properties associated with the hydroxylated phenanthridone 7-deoxypancratistatin (**10**)³⁸ coupled with its limited availability from natural resources and decreased toxicity relative to pancratistatin (**9**)³⁹ have prompted significant efforts toward its total synthesis.⁴⁰ The main challenge towards designing any synthetic strategy toward deoxypancratistatin lies in the control of the *trans*-fused B-C ring junction (C_{4a}, C_{10b}) and with the stereocontrolled installation of continuous hydroxy functionalities located around the perimeter of the C ring moiety. The *trans* B-C ring junction is believed to be critical for its anticancer activity¹⁵ but is much more difficult to generate than the thermodynamically more stable *cis* ring junction.⁸ For example, Rigby and co-workers have observed a decided preference for the *cis* fusion in the related pancratistatin intermediate **49** which was readily formed by epimerization of the less stable *trans* isomer **48** at room temperature (Scheme 11).⁴¹

Our plan for the synthesis of 7-deoxypancratistatin (**10**) was to convert alcohol **14**, which had previously been used as an intermediate in the total synthesis of (\pm)-lycoricidine (**7**), into the corresponding aldehyde **50**. We reasoned that the *trans* B-C ring junction could be established through a RhCl(PPh₃)₃ promoted decarbonylation reaction of this aldehyde.⁴² Under the influence of transition metal compounds, aldehydes are known to readily undergo decarbonylation and produce the corresponding saturated hydrocarbons.⁴² Rhodium complexes such as Wilkinson's catalyst RhCl(PPh₃)₃ are most often employed in both stoichiometric and catalytic reactions to effect the decarbonylation.^{42,43} The earlier seminal studies by Walborsky^{42b} demonstrated that the decarbonylation reaction using Wilkinson's catalyst proceeds with retention of configuration and this finding has been used by others in complex natural product synthesis.⁴³ With this in mind, we set out to convert the carbomethoxy group present in **14** to the corresponding aldehyde. Our first attempt to prepare aldehyde **50** involved the reduction of **14** with DIBAL. However, the expected aldehyde (or alcohol) was not produced but instead amine **51** was obtained in high yield as the exclusive product (Scheme 12). The increased reactivity of the amido carbonyl group over the ester toward DIBAL reduction is probably related to a significant decrease in the strain energy of ring B by changing the hybridization from sp² to sp³ at the C₆ position.⁴⁴ This undesired reduction could be circumvented by converting the ester group into the corresponding acid chloride after protecting the free OH group as the benzyl ether. Selective reduction of the acid chloride with Zn(BH₄)₂ followed by a subsequent oxidation of the resulting alcohol using Ley's procedure⁴⁵ afforded the desired aldehyde **50**. When a solution of **50** and RhCl(PPh₃)₃ was heated in benzonitrile at reflux, the decarbonylation reaction proceeded to give the desired *trans*-fused lactam **52** in 63% yield.

With the rapid construction of the *trans*-fused lactam in hand, installation of the other functional groups present on the C-ring with the correct relative stereochemistry was next investigated. What was required for the end game was to introduce a C₁-hydroxyl group and also to invert the stereochemistry at the C₂-position. To this end, a transient double bond between C₁ and C₂ was installed by carrying out a debenzylolation under hydrogenolysis conditions followed by

a Chugaev elimination³⁰ of the xanthate ester which proceeded in 85% overall yield (Scheme 13). Since the presence of the bulky acetonide moiety partially blocked the β -face of the π -bond of **53**, dihydroxylation occurred preferentially from the less hindered α -face to furnish two easily separable diol isomers (3:1) in almost quantitative yield. A subsequent regioselective inversion of the stereochemistry at the C₁-hydroxyl group of the major diol **54** was achieved through a three-step sequence.^{12c} Treatment of diol **54** with thionyl chloride followed by oxidation of the resulting sulfite with NaIO₄ in the presence of catalytic RuCl₃ furnished sulfate **55** in 82% yield.⁴⁶ Reaction of sulfate **55** with cesium benzoate followed by acid hydrolysis resulted in the formation of triol **56** in 75% yield. The final ester hydrolysis and amide deprotection proceeded uneventfully to furnish 7-deoxypancratistatin (**10**) in 80% yield.

In conclusion, we have developed a new type of cross-coupling/cycloaddition cascade which has been successfully utilized in the total synthesis of several members of the hydroxylated phenanthridone sub-class of the *Amaryllidaceae* alkaloid family. These alkaloids were assembled by a one-pot Stille/intramolecular Diels-Alder cycloaddition cascade to construct the core skeleton. The resulting cycloadduct was then used for the stereocontrolled installation of the other functionality present in the C-ring of the target molecules. Key features of the synthetic strategy include (1) a lithium hydroxide induced tandem hydrolysis/decarboxylation/elimination sequence to introduce the required π -bond in the C-ring of (\pm)-lycoridine; and (2) conversion of the initially formed Diels-Alder adduct into an aldehyde intermediate which is then induced to undergo a stereospecific decarbonylation reaction using Wilkinson's catalyst to set the *trans* B-C ring junction of (\pm)-7-deoxypancratistatin. We plan to use this and related cascade methodology in approaches to other natural product targets, the results of which will be disclosed in due course.

Experimental Section

2-[2-(*tert*-Butoxycarbonyl-furan-2-yl-aminocarbonyl)phenyl]acrylic Acid Methyl Ester (**15**)

To a suspension of 0.40 g (1.9 mmol) of 2-(1-methoxycarbonylvinyl)-benzoic acid⁴⁷ in 4 mL of CH₂Cl₂ at rt was added dropwise 0.25 mL (2.9 mmol) of oxalyl chloride and several drops of DMF as a catalyst. The reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure. The residue was taken up in 4 mL of THF and was used for the next step without further purification. In a separate flask containing 0.39 g (2.1 mmol) of furan-2-yl-carbamic acid furan-2-*tert*-butyl ester (**37a**) and 5 mL of THF at 0 °C was added 0.9 mL (2.3 mmol) of *n*-BuLi (2.5 M in hexane). After stirring for 20 min, the solution was added dropwise to the above acid chloride solution at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, diluted with H₂O, and extracted with EtOAc. The combined organic extracts were washed with H₂O, brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.46 g (64%) of amidofuran **15**; IR (neat) 1748, 1724, 1238, and 1153 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.28 (s, 9H), 3.75 (s, 3H), 5.86 (s, 1H), 6.23 (d, 1H, *J* = 3.0 Hz), 6.39 (s, 1H), 6.57 (s, 1H), 7.30 (d, 1H, *J* = 7.8 Hz), 7.33 (s, 1H), 7.39 (t, 1H, *J* = 7.8 Hz), 7.46 (t, 1H, *J* = 7.8 Hz), and 7.55 (d, 1H, *J* = 7.8 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ 27.7, 52.3, 84.2, 106.4, 111.5, 128.0, 128.1, 129.5, 130.6, 130.9, 135.5, 136.1, 140.4, 140.8, 143.8, 151.4, 166.3, and 170.9.

2,4a-Epoxy-6-oxo-2,4a-dihydro-1*H*,6*H*-phenanthridine-5,10*b*-dicarboxylic Acid 5-*tert*-Butyl Ester 10*b*-Methyl Ester (**16**)

A solution containing 0.43 g (1.2 mol) of amidofuran **15** in 2 mL of toluene was heated at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give cycloadduct **16** in 98% yield as a white solid; mp 133–134 °C; IR (neat) 1735, 1684, 1369, 1256, and 1150 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.58 (s, 9H), 2.53 (dd, 1H, *J* = 12.0 and 4.8 Hz), 2.80 (d, 1H, *J* = 12.0 Hz), 3.60, (s, 3H), 4.95 (dd, 1H, *J* = 4.8

and 1.8 Hz), 6.35 (d, 1H, J = 5.4 Hz), 6.50 (dd, 1H, J = 5.4 and 1.8 Hz), 7.33 (d, 1H, J = 7.8 Hz), 7.40 (dt, 1H, J = 7.8 and 1.2 Hz), 7.53 (dt, 1H, J = 7.8 and 1.2 Hz), and 8.20 (dd, 1H, J = 7.8 and 1.2 Hz); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 28.0, 41.8, 53.1, 54.9, 75.7, 84.8, 97.4, 126.4, 128.3, 128.6, 129.8, 133.8, 134.3, 136.1, 139.8, 152.1, 162.5, and 171.4; Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.61; H, 5.78; N, 3.81.

2,6-Dioxo-2,3-dihydro-1*H*,6*H*-phenanthridine-5,10*b*-dicarboxylic Acid 5-*tert*-butyl Ester 10*b*-Methyl Ester (18)

In a sealed tube was added 0.03 g (0.09 mmol) of cycloadduct **16** and 1.5 mL of benzene. The mixture was purged with argon, sealed, and heated at 160 °C for 4 h. After cooling to rt, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.03 g (80%) of **18** as a clear oil; IR (neat) 1766, 1733, 1244, and 1147 cm^{-1} ; ^1H -NMR (CDCl_3 , 600 MHz) δ 1.59 (s, 9H), 2.77 (d, 1H, J = 15.0 Hz), 3.13 (d, 1H, J = 3.9 Hz), 3.59 (d, 1H, J = 15.0 Hz), 3.64 (s, 3H), 5.61 (t, 1H, J = 3.9 Hz), 7.28 (dd, 1H, J = 7.8 and 1.5 Hz), 7.48 (td, 1H, J = 7.8 and 1.5 Hz), 7.60 (td, 1H, J = 7.8 and 1.5 Hz), 8.21 (dd, 1H, J = 7.8 and 1.5 Hz); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 27.8, 37.8, 47.0, 50.3, 53.9, 85.4, 111.0, 124.9, 126.7, 128.9, 129.5, 132.4, 134.1, 137.6, 151.3, 160.6, 170.4, and 203.5.

4*a*-Methoxy-4,6-dioxo-4,4*a*,5,6-tetrahydro-1*H*-phenanthridine-10*b*-carboxylic Acid Methyl Ester (20)

To a solution containing 0.05 g (0.14 mmol) of cycloadduct **16** in a 2 mL of a 2:1:1 -mixture of THF/ H_2O /*t*-BuOH) was added 0.03 g (0.23 mmol) of NMO (*N*-methyl morpholine-*N*-oxide) and catalytic OsO_4 . After stirring for 1 h at rt, the mixture was diluted with H_2O and extracted with CH_2Cl_2 . The combined organic extracts were washed with H_2O , brine, and dried over MgSO_4 . Concentration under reduced pressure provided the expected diol **19** in 95% yield as a clear oil which was used in the next step without further purification; ^1H -NMR (CDCl_3 , 400 MHz) δ 1.48 (s, 9H), 2.48 (dd, 1H, J = 13.2 and 6.8 Hz), 3.06 (d, 1H, J = 13.2 Hz), 3.57 (s, 3H), 4.06 (d, 1H, J = 6.0 Hz), 4.40 (d, 1H, J = 6.4 Hz), 4.92 (d, 1H, J = 6.0 Hz), 7.09 (s, 1H), 7.16 (d, 1H, J = 7.6 Hz), 7.40 (dt, 1H, J = 7.6 and 1.2 Hz), 7.52 (dt, 1H, J = 7.6 and 1.2 Hz), 8.15 (d, 1H, J = 7.6 Hz); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 27.8, 39.4, 53.2, 53.7, 71.8, 75.8, 77.4, 83.8, 93.9, 126.7, 127.0, 128.3, 128.9, 133.8, 140.4, 152.6, 164.0, and 170.9.

The crude diol **19** was taken up in 1.5 mL of 2,2-dimethoxypropane and catalytic *p*-toluene sulfonic acid was added. The mixture was stirred at rt for 30 min, quenched with a saturated NaHCO_3 solution, and extracted with EtOAc. The organic extracts were washed with H_2O , brine, and dried over MgSO_4 . After concentration under reduced pressure, the residue was subjected to preparative TLC to give 0.032 g (81%) of **20** as a white solid; mp 200–202 °C; IR (neat) 1734, 1677, and 1056 cm^{-1} ; ^1H -NMR (CDCl_3 , 600 MHz) δ 3.03 (s, 3H), 3.21 (dt, 1H, J = 18.0 and 2.4 Hz), 3.41 (dd, 1H, J = 18.0 and 6.0 Hz), 3.54 (s, 3H), 6.14 (dd, 1H, J = 10.2 and 2.4 Hz), 7.02 (ddd, 1H, J = 10.2, 6.0, and 2.4 Hz), 7.33 (brs, 1H), 7.45 (d, 1H, J = 7.8 Hz), 7.48 (t, 1H, J = 7.8 Hz), 7.62 (dt, 1H, J = 7.8 and 1.2 Hz), and 8.11 (d, 1H, J = 7.8 Hz); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 32.9, 50.4, 53.5, 83.5, 125.8, 125.9, 127.9, 128.6, 128.7, 133.4, 136.7, 147.1, 163.7, 170.7, and 188.7; Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.22; H, 4.98; N, 4.57.

5-Benzyl-2,4*a*-Epoxy-6-oxo-2,4*a*,5,6-tetrahydro-1*H*-phenanthridine-10*b*-carboxylic Acid Methyl Ester (25)

To a solution containing 4.0 g (9.9 mmol) of *N*-benzyl-*N*-furan-2-yl-2-iodo-benzamide⁴⁷ and 5.2 g (14 mmol) of methyl 2-tri-*n*-butyl stannylacrylate²⁸ in 40 mL of DMF under argon atmosphere was added 1.2 g (0.99 mmol) of $\text{Pd}(\text{PPh}_3)_4$ and 0.57 g (3.0 mmol) of CuI. The reaction mixture was stirred at rt for 20 min, followed by the addition of 2.3 g (15 mmol) of CsF. After stirring at rt for 30 min, the reaction mixture was heated at 55 °C for 8 h. The mixture

was cooled to rt, diluted with EtOAc and H₂O, and filtered over a pad of Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H₂O, brine, and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 1.9 g (55%) of cycloadduct **25** as white solid; mp 183.5–185 °C; IR (neat) 1736, 1664, 1398, 1347, and 1257 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 2.60 (dd, 1H, *J* = 11.4 and 4.8 Hz), 2.84 (d, 1H, *J* = 11.4 Hz), 3.45 (s, 3H), 4.39 (d, 1H, *J* = 15.6 Hz), 4.89 (dd, 1H, *J* = 4.8 and 1.8 Hz), 5.58 (d, 1H, *J* = 15.6 Hz), 6.13 (d, 1H, *J* = 5.4 Hz), 6.56 (dd, 1H, *J* = 5.4 and 1.8 Hz), 7.25 (t, 1H, *J* = 7.2 Hz), 7.32–7.44 (m, 6H), 7.52 (dt, 1H, *J* = 7.2 and 1.8 Hz), and 8.27 (dd, 1H, *J* = 7.2 and 1.8 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ 42.0, 49.0, 52.6, 54.2, 74.6, 100.5, 126.9, 127.1, 127.3, 128.2, 128.3, 128.6, 129.5, 133.0, 133.1, 138.6, 139.3, 139.6, 164.4, and 171.4; Anal. Calcd for C₂₂H₁₉NO₄: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.19; H, 5.22; N, 3.91.

5-Benzyl-2,4a-epoxy-3,4-dihydroxy-1-6-oxo-2,4a,5,6-tetrahydro-1H-phenanthridine-10b-carboxylic Acid Methyl Ester (26)

To a solution containing 1.0 g (2.8 mmol) of cycloadduct **25** in 40 mL of acetone and 4 mL of H₂O at rt was added 0.54 g (4.6 mmol) of NMO (*N*-methyl morpholine *N*-oxide) and catalytic OsO₄. The mixture was stirred at rt for 12 h, diluted with H₂O, and extracted with CH₂Cl₂. The organic extracts were washed with H₂O, brine, and dried over MgSO₄. Concentration under reduced pressure furnished diol **26** as a white solid in 98% yield; IR (neat) 3384, 1733, 1654, and 1242 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 2.40 (dd, 1H, *J* = 12.8 and 6.4 Hz), 3.01 (d, 1H, *J* = 12.8 Hz), 3.15 (d, 1H, *J* = 6.0 Hz), 3.33 (d, 1H, *J* = 5.6 Hz), 3.63 (s, 3H), 3.95 (t, 1H, *J* = 6.0 Hz), 4.04 (t, 1H, *J* = 5.6 Hz), 4.27 (d, 1H, *J* = 6.4 Hz), 5.21 (d, 1H, *J* = 16.0 Hz), 5.45 (d, 1H, *J* = 16.0 Hz), 7.17 (d, 1H, *J* = 7.6 Hz), 7.18–7.23 (m, 1H), 7.29–7.35 (m, 4H), 7.40 (dt, 1H, *J* = 7.6 and 0.8 Hz), 7.53 (dt, 1H, *J* = 7.6 and 1.2 Hz), and 8.18 (dd, 1H, *J* = 8.0 and 1.2 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ 39.2, 48.6, 53.4, 55.6, 73.0, 73.5, 77.2, 96.5, 126.0, 126.1, 126.2, 126.6, 128.3, 128.7, 129.3, 133.6, 139.5, 140.3, 165.8, and 171.6.

5-Benzyl-2,3,4-trihydroxy-6-oxo-2,3,4,4a,5,6-hexahydro-1H-phenanthridine-10b-carboxylic Acid Methyl Ester (27)

To a suspension containing 1.8 g (0.49 mmol) of diol **26** in 100 mL of CH₂Cl₂ at –78 °C was added 7.8 mL (4.9 mmol) of Et₃SiH, followed by the slow addition of 3.1 mL (2.5 mmol) of BF₃·Et₂O. After stirring for 1 h, the reaction mixture was allowed to warm to rt and was stirred until the color of the reaction mixture turned into green (*ca* 20 min). The reaction mixture was quenched with a saturated NH₄Cl solution and extracted with CHCl₃. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.26 g (74%) of triol **27** as a clear oil; IR (neat) 3383, 1729, and 1634 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 2.16 (t, 1H, *J* = 12.8 Hz), 2.62 (dd, 1H, *J* = 12.8 and 4.0 Hz), 3.43 (s, 3H), 3.98–4.03 (m, 1H), 4.09 (d, 1H, *J* = 10.4 Hz), 4.15 (t, 1H, *J* = 2.8 Hz), 4.72 (dd, 1H, *J* = 10.4 and 3.6 Hz), 4.95 (d, 1H, *J* = 16.0 Hz), 5.25 (d, 1H, *J* = 16.0 Hz), 7.19–7.40 (m, 7H), 7.55 (dt, 1H, *J* = 7.6 and 1.2 Hz), and 8.09 (dd, 1H, *J* = 7.6 and 1.2 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ 33.4, 47.5, 50.4, 52.9, 62.4, 66.9, 67.8, 72.8, 124.6, 126.8, 127.0, 128.4, 128.5, 128.9, 129.1, 132.6, 139.5, 141.2, 166.8, and 172.2; HRMS Calcd for [(C₂₂H₂₃NO₆) + H]⁺ 398.1598. Found: 398.1594.

12-Acetoxy-7-benzyl-16,16-dimethyl-6-oxo-7,8,11,12,13,14-hexahydro-6H-15,17-dioxo-7-aza-cyclopenta[a]phenanthrene-9-carboxylic Acid Methyl Ester (28)

To a solution containing 0.90 g (2.3 mmol) of triol **27** in 20 mL CH₂Cl₂ at 0 °C was added 0.9 mL (12 mmol) of pyridine, followed by the addition of 0.17 mL (2.4 mmol) of acetyl chloride in 2 mL of CH₂Cl₂. The reaction mixture was stirred at 0 °C for 20 min, quenched with a saturated NaHCO₃ solution and extracted with CHCl₃. The organic extracts were dried over

MgSO₄ and concentrated under reduced pressure. The residue was taken up in 10 mL of THF and was concentrated under reduced pressure in order to completely remove pyridine. The residue was dissolved in 3 mL of DMF, followed by the addition of 1.0 mL of 2,2-dimethoxypropane and a catalytic amount of *p*-toluene sulfonic acid was added. The reaction mixture was stirred at rt for 12 h, quenched with a saturated NaHCO₃ solution and extracted with EtOAc. The combined organic layers were washed with H₂O, brine and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.78 g (71%) of ketal **28** as a white solid: mp 206.5–207.5 °C; IR (neat) 1739, 1654, 1239, and 1060 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.37 (s, 3H), 1.40 (s, 3H), 2.14 (s, 3H), 2.22 (dd, 1H, *J* = 13.2 and 12.0 Hz), 2.79 (dd, 1H, *J* = 13.2 and 4.8 Hz), 3.34 (s, 3H), 4.04 (d, 1H, *J* = 8.8 Hz), 4.55 (t, 1H, *J* = 4.4 Hz), 4.89 (d, 1H, *J* = 15.6 Hz), 4.95 (dd, 1H, *J* = 8.8 and 5.2 Hz), 5.26 (dt, 1H, *J* = 12.0 and 4.4 Hz), 5.44 (d, 1H, *J* = 15.6 Hz), 7.19–7.41 (m, 6H), 7.48 (dt, 1H, *J* = 7.6 and 1.2 Hz), 7.56 (dt, 1H, *J* = 7.6 and 1.6 Hz), and 8.19 (dd, 1H, *J* = 7.6 and 1.6 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ 21.4, 26.6, 28.5, 31.4, 46.5, 50.6, 53.0, 63.6, 67.4, 74.0, 75.0, 110.5, 124.6, 126.9, 128.0, 128.4, 128.6, 129.0, 129.3, 132.6, 139.4, 140.0, 166.0, 170.4, and 171.6; Anal. Calcd for C₂₇H₂₉NO₇: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.50; H, 6.17; N, 2.88.

7-Benzyl-16,16-dimethyl-6-oxo-7,8,13,14-hexahydro-6H-15,17-dioxo-7-aza-cyclopenta[*a*]phenanthrene-9-carboxylic Acid Methyl Ester (29)

To a solution of 0.70 g (1.5 mmol) of ketal **28** in 10 mL of THF at rt was added 0.22 g (3.8 mmol) of NaOMe in several portions. After stirring for 20 min, the mixture was quenched with a saturated NH₄Cl solution, and extracted with EtOAc. The organic extracts were washed with H₂O, brine, and dried over MgSO₄. Concentration under reduced pressure gave the corresponding alcohol derived from acetate hydrolysis in quantitative yield which was used in the next step without further purification; ¹H-NMR (CDCl₃, 400 MHz) δ 2.08 (dd, 1H, *J* = 13.4 and 10.4 Hz), 2.38 (brs, 1H), 2.84 (dd, 1H, *J* = 13.4 and 5.2 Hz), 3.31 (s, 3H), 4.02–4.12 (m, 2H), 4.49 (t, 1H, *J* = 5.6 Hz), 4.87 (d, 1H, *J* = 15.6 Hz), 4.89 (dd, 1H, *J* = 8.8 and 5.6 Hz), 5.46 (d, 1H, *J* = 15.6 Hz), 7.19–7.32 (m, 5H), 7.43 (d, 1H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 7.6 Hz), 7.56 (td, 1H, *J* = 7.6 and 1.4 Hz), and 8.18 (dd, 1H, *J* = 7.6 and 1.4 Hz).

To a solution containing 0.45 g (1.0 mmol) of the above alcohol in 18 mL of THF was added 0.08 g (2.1 mmol) of NaH (60% dispersion in mineral) at 0 °C. After stirring for 10 min, the mixture was warmed to rt and was stirred for an additional 30 min. The mixture was cooled to 0 °C, and 0.25 mL (4.2 mmol) of CS₂ was added. The solution was stirred for 1 h at this temperature and then 0.5 mL (8.3 mmol) of methyl iodide was added. After stirring for 10 min, the mixture was warmed to rt and was stirred for an additional 30 min. The solution was quenched with a saturated NH₄Cl solution and extracted with EtOAc. The combined organic extracts were washed with H₂O and brine, and dried over MgSO₄. After concentration under reduced pressure, the residue was taken up in 20 mL of 1,2-dichlorobenzene and was heated at reflux for 12 h. After cooling to room temperature, the mixture was subjected to flash silica gel chromatography to give 0.4 g (92%) of alkene **29** as a pale yellow oil; IR (neat) 1734, 1654, and 1210 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.41 (s, 3H), 1.43 (s, 3H), 3.24 (s, 3H), 3.97 (d, 1H, *J* = 9.0 Hz), 4.79 (d, 1H, *J* = 15.6 Hz), 4.81–4.83 (m, 1H), 4.50 (t, 1H, *J* = 8.4 Hz), 5.58 (d, 1H, *J* = 15.6 Hz), 6.20 (dd, 1H, *J* = 10.2 and 3.0 Hz), 6.43 (d, 1H, *J* = 10.2 Hz), 7.21 (t, 1H, *J* = 7.2 Hz), 7.25–7.33 (m, 4H), 7.47–7.50 (m, 2H), 7.57 (t, 1H, *J* = 7.2 Hz), and 8.22 (d, 1H, *J* = 7.8 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ 24.8, 27.4, 46.3, 52.6, 53.1, 64.2, 72.2, 73.0, 109.4, 124.4, 126.5, 127.0, 127.8, 28.5, 128.6, 129.8, 129.9, 130.0, 132.3, 138.1, 140.4, 166.5, and 170.7; HRMS Calcd for [(C₂₅H₂₅NO₅) + H]⁺: 420.1806. Found: 420.1804.

7-Benzyl-12-hydroxy-16,16-dimethyl-8,12,13,14-tetrahydro-7H-15,17-dioxo-7-aza-cyclopenta[a]phenanthren-6-one (35)

To a solution of 0.30 g (0.7 mmol) of ketal **29** in 15 mL of acetone and 1.5 mL of H₂O was added 0.12 g (1.0 mmol) of NMO (*N*-methyl morpholine-*N*-oxide) and catalytic OsO₄. The mixture was stirred at rt for 12 h, quenched with a saturated Na₂S₂O₃ solution, and extracted with EtOAc. The combined organic layers were washed with H₂O and brine, dried over MgSO₄, and concentrated under reduced pressure. To the residue was added 20 mL of THF, 0.5 mL (3.5 mmol) of Et₃N, and 0.14 mL (1.8 mmol) of mesyl chloride. The mixture was stirred at room temperature for 12 h, quenched with a saturated NaHCO₃ solution, and extracted with EtOAc. The organic extracts were washed with H₂O, brine and dried over MgSO₄. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.26 g (74%) of mesylate **32** as a white solid; mp 231–232 °C; IR (neat) 1793, 1653, 1361, and 1182 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.35(s, 3H), 1.51 (s, 3H), 3.23 (s, 3H), 4.32 (d, 1H, *J* = 5.2 Hz), 4.48–4.54 (m, 2H), 4.70 (d, 1H, *J* = 16.8 Hz), 5.16 (d, 1H, *J* = 3.6 Hz), 5.44 (d, 1H, *J* = 16.8 Hz), 5.71 (s, 1H), 7.20–7.32 (m, 5H), 7.54–7.58 (m, 2H), 7.80–7.91 (m, 1H), and 8.33–8.36 (m, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 25.6, 27.7, 39.7, 47.1, 50.7, 65.9, 73.2, 74.5, 79.4, 81.1, 113.1, 126.4, 126.5, 127.2, 128.9, 129.7, 130.1, 130.2, 131.2, 132.8, 138.6, 165.2, and 170.1; Anal. Calcd for C₂₅H₂₅NO₈S: C, 60.11; H, 5.04; N, 2.80. Found: C, 59.87; H, 4.99; N, 2.85.

To a solution of 0.15 g (0.3 mmol) of the above mesylate **32** in 6 mL of THF was added a solution of 0.05 g (1.2 mmol) of LiOH in 1 mL of H₂O. The mixture was stirred at rt for 20 min and then heated at 60 °C for 10 min. After cooling to room temperature, the mixture was diluted with a saturated NH₄Cl solution and EtOAc. The organic extracts was washed with H₂O, brine, and dried over MgSO₄. Concentration under reduced pressure afforded 0.1 g (90%) of alcohol **35** as a white solid; mp 246–247 °C; IR (neat) 3398.2 and 1627 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.28 (s, 3H), 1.56 (s, 3H), 2.65 (brs, 1H), 3.95 (t, 1H, *J* = 7.6 Hz), 4.23 (dt, 1H, *J* = 8.0 and 2.4 Hz), 4.28–4.36 (m, 2H), 4.87 (d, 1H, *J* = 14.8 Hz), 5.56 (d, 1H, *J* = 14.8 Hz), 6.55 (t, 1H, *J* = 2.8 Hz), 7.19–7.35 (m, 5H), 7.39 (dt, 1H, *J* = 7.6 and 1.2 Hz), 7.48 (dt, *J* = 7.6 and 1.2 Hz), and 8.30 (dd, 1H, *J* = 7.6 and 1.2 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ 24.7, 27.3, 47.8, 59.7, 72.6, 79.8, 79.9, 111.7, 121.7, 125.7, 126.3, 127.3, 128.3, 128.5, 128.6, 128.9, 129.5, 131.8, 132.6, 137.8, and 162.7; Anal. Calcd for C₂₃H₂₃NO₄: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.20; H, 6.10; N, 3.77.

6-Iodo-benzo[1,3]dioxole-5-carboxylic Acid Furan-2-yl Amide (39)

To a solution of 4.5 g (25 mmol) of furan-2-yl-carbamic acid 2-*tert*-butyl ester (**37a**)⁴⁸ in 40 mL of THF at 0 °C was added 11 mL (27 mmol) of a 2.5 M *n*-BuLi in hexane solution. The reaction mixture was stirred for 20 min and was then added dropwise through a cannula to a solution containing 6.4 g (21 mmol) of 6-iodo-benzo[1,3]-dioxole-5-carbonyl chloride (**36**)⁴⁹ in 40 mL of THF at 0 °C. The resulting solution was stirred at 0 °C for 20 min, diluted with 200 mL of H₂O, and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried over MgSO₄ and concentrated under reduced pressure to afford carbamate **38** as a brown oil.

To this oil was added 50 mL of CH₃CN and 1.9 g (6.2 mmol) of Mg(ClO₄)₂. The reaction mixture was heated to 50 °C for 1 h, cooled to room temperature, diluted with 300 mL of H₂O, and extracted with EtOAc. The combined organic layers were washed with H₂O, brine and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was recrystallized from EtOAc to give 3.4 g (46%) of the titled compound **39** as a white solid. The filtrate was subjected to silica gel chromatography to give an additional 2.1 g for an overall yield of 75%; mp 192–193 °C; IR (neat) 3228, 1660, 1531, 1476, and 1243 cm⁻¹; ¹H-NMR (acetone-*d*₆, 600 MHz) δ 6.12 (s, 2H), 6.40 (d, 1H, *J* = 2.4 Hz), 6.46 (t, 1H, *J* = 2.4 Hz), 7.10

(s, 1H), 7.23 (dd, 1H, $J = 2.4$ and 1.2 Hz), 7.36 (s, 1H), and 10.07 (brs, 1H); ^{13}C -NMR (acetone- d_6 , 150 MHz) δ 82.5, 95.5, 97.8, 103.5, 109.6, 112.2, 119.8, 136.4, 147.5, 149.2, 150.7, and 165.5; Anal. Calcd for $\text{C}_{12}\text{H}_8\text{INO}_4$: C, 40.36; H, 2.26; N, 3.92. Found: C, 40.51; H, 2.12; N, 3.93.

6-Iodo-benzo[1,3]dioxole-5-carboxylic Acid Furan-2-yl-(4-methoxy-benzyl)-Amide (11)

To a solution of 0.70 g (1.9 mmol) of the above amide **39** in 8 mL of DMF at 0°C was added 0.09 g (2.3 mmol) of NaH (60% in mineral oil) in several portions. After stirring for 10 min, the reaction mixture was warmed to room temperature and was stirred for an additional 30 min. The reaction mixture was cooled to 0°C and 0.4 mL (2.8 mmol) of 4-methoxybenzyl chloride was added dropwise. After stirring for 15 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched with H_2O and extracted with EtOAc. The combined extracts were washed with H_2O , brine, and dried over MgSO_4 . After concentration under reduced pressure, the residue was subjected to silica gel chromatography to give 0.7 g (83%) of iodide **11** as a white solid: mp $119.5\text{--}120.5^\circ\text{C}$; IR (neat) 1671, 1610, 1512, 1478, and 1237 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz) δ 3.79 (s, 3H), 4.90 (s, 2H), 5.76 (d, 1H, $J = 3.2$ Hz), 5.91 (s, 2H), 6.07 (dd, 1H, $J = 3.2$ and 2.4 Hz), 6.62 (s, 1H), 6.83 (d, 2H, $J = 8.8$ Hz), 7.08 (s, 1H), 7.08–7.10 (brm, 1H), and 7.29 (d, 2H, $J = 8.8$ Hz); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 51.1, 55.4, 82.2, 102.0, 105.8, 108.0, 111.1, 113.9, 118.7, 128.8, 130.6, 135.7, 140.0, 147.3, 147.8, 148.7, 159.3, and 170.3; Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{INO}_5$: C, 50.33; H, 3.38; N, 2.93. Found: C, 50.21; H, 3.34; N, 2.81.

5-(4-Methoxy-benzyl)-2,4a-epoxy-6-oxo-2,4a,5,6-tetrahydro-1H-[1,3]dioxolo-[4,5-]phenanthridine-11b-carboxylic Acid Methyl Ester (13)

A Schlenk tube charged with 0.3 g (6.3 mmol) of LiCl was dried with a flame under vacuum. Upon cooling, 0.12 g (0.10 mmol) of $\text{Pd}(\text{PPh}_3)_4$, and 0.5 g (0.5 mmol) of CuCl were added and the mixture was degassed 3 times under vacuum using an argon purge. To this mixture was added 8.4 mL of anhydrous DMSO, 0.5 g (1.0 mmol) of iodide **11**, and 0.47 g (1.3 mmol) of methyl 2-tri-*n*-butyl stannylacrylate.²⁸ The resulting mixture was vigorously degassed by several freeze-thaw cycles (-78°C to 25°C). After stirring at room temperature for 1 h, the reaction mixture was heated at 60°C for 20 h. The mixture was then cooled to room temperature, diluted with 200 mL of EtOAc, 50 mL of a saturated NaHCO_3 solution, 150 mL of H_2O , and filtered over a celite pad. The organic layer was separated, washed with H_2O and brine, and dried over MgSO_4 . After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography with a hexane/EtOAc/ Et_3N mixture to give 0.37 g (82%) of **13** as a pale yellow oil: IR (neat) 1733, 1655, 1513, 1447, 1383, and 1249 cm^{-1} ; ^1H -NMR (CDCl_3 , 600 MHz) δ 2.51 (dd, 1H, $J = 12.0$ and 4.8 Hz), 2.76 (d, 1H, $J = 12.0$ Hz), 3.46 (s, 3H), 3.79 (s, 3H), 4.32 (d, 1H, $J = 15.6$ Hz), 4.87 (dd, 1H, $J = 4.8$ and 1.5 Hz), 5.43 (d, 1H, $J = 15.6$ Hz), 6.01 (s, 2H), 6.14 (d, 1H, $J = 5.4$ Hz), 6.54 (dd, 1H, $J = 5.4$ and 1.5 Hz), 6.73 (s, 1H), 6.85 (d, 2H, $J = 8.4$ Hz), 7.32 (d, 2H, $J = 8.4$ Hz), and 7.67 (s, 1H); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 42.1, 48.4, 52.7, 54.3, 55.4, 74.4, 100.5, 102.1, 107.7, 108.9, 113.9, 121.6, 128.6, 130.7, 133.4, 134.7, 139.4, 147.9, 151.5, 158.8, 163.9, and 171.6; HRMS Calcd for $[(\text{C}_{24}\text{H}_{21}\text{NO}_7) + \text{H}]^+$: 436.1391. Found: 436.1395.

4-(4-Methoxy-benzyl)-3b,12-epoxy-2,2-dimethyl-5-oxo-3a,4,5,11,12,12a-hexahydro-3bH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[a,h]phenanthrene-10b-carboxylic Acid Methyl Ester (42)

To a solution of 0.90 g (2.1 mmol) of alkene **13** in 30 mL of CH_3CN and 3 mL of H_2O was added 0.4 g (4.4 mmol) of 4-methyl-morpholine-*N*-oxide and a catalytic amount of OsO_4 . The reaction mixture was stirred at room temperature overnight and was then diluted with 200 mL of H_2O and extracted with CH_2Cl_2 . The organic extracts were washed with H_2O , brine, and

dried over MgSO_4 . Removal of the solvent afforded diol **41** which was immediately taken up in 2 mL of DMF and 4 mL of 2,2-dimethoxypropane and 0.1 g (0.4 mmol) of pyridinium *p*-toluenesulfonate was added. The reaction mixture was stirred at room temperature overnight, quenched with a saturated NaHCO_3 solution, and extracted with EtOAc. The organic layer was washed with H_2O , brine, and dried over MgSO_4 . After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to afford 0.9 g (80%) of **42** as a pale yellow oil: IR (neat) 1731, 1655, 1513, 1484, 1448, and 1246 cm^{-1} ; ^1H -NMR (CDCl_3 , 600 MHz) δ 1.19 (s, 3H), 1.37 (s, 3H), 2.26 (dd, 1H, $J = 12.6$ and 6.0 Hz), 2.92 (d, 1H, $J = 12.6$ Hz), 3.56 (s, 3H), 3.77 (s, 3H), 4.14 (d, 1H, $J = 4.8$ Hz), 4.30 (d, 1H, $J = 6.6$ Hz), 4.42 (d, 1H, $J = 5.4$ Hz), 5.18 (d, 1H, $J = 15.6$ Hz), 5.37 (d, 1H, $J = 15.6$ Hz), 6.00 (s, 2H), 6.50 (s, 1H), 6.80 (d, 2H, $J = 8.4$ Hz), 7.23 (d, 2H, $J = 8.4$ Hz), and 7.61 (s, 1H); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 25.1, 25.8, 39.2, 46.9, 53.4, 54.9, 55.5, 74.9, 80.6, 82.6, 96.5, 102.1, 105.5, 108.5, 112.6, 113.4, 120.9, 128.2, 132.2, 135.6, 147.8, 152.0, 158.1, 164.7, and 171.4; HRMS Calcd for $[(\text{C}_{27}\text{H}_{27}\text{NO}_9) + \text{H}]^+$: 510.1759. Found: 510.1756.

12-Hydroxy-4-(4-methoxy-benzyl)-2,2-dimethyl-5-oxo-3a,4,5,11,12,12a-hexahydro-3bH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10b-carboxylic Acid Methyl Ester (14)

To a solution of 0.20 g (0.4 mmol) of acetonide **42** in 6 mL of CH_2Cl_2 at -78°C was added 3.1 mL (0.8 mmol) of a 0.25 M solution of $\text{Zn}(\text{BH}_4)_2$ in Et_2O ,³⁶ and 0.14 mL (0.8 mmol) of TMSOTf, respectively. After stirring for 20 min at -78°C , the reaction mixture was allowed to warm to room temperature and was stirred for an additional 4 h. The mixture was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 . The combined organic extracts were washed with H_2O , brine, and dried over MgSO_4 . After removing the solvent under reduced pressure, the residue was dissolved in 5 mL of THF, and this was followed by the addition of 0.4 mL (0.4 mmol) of TBAF (1.0 M in THF) at room temperature. After stirring for 5 min, the mixture was diluted with a saturated NH_4Cl solution and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and dried over MgSO_4 . After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to afford 0.15 g (74%) of alcohol **14** as a white solid: mp $204.5\text{--}205.5^\circ\text{C}$; IR (neat) 3396, 1728, 1639, 1512, 1456, and 1244 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz) δ 1.39 (s, 3H), 1.43 (s, 3H), 2.04 (dd, 1H, $J = 13.6$ and 10.4 Hz), 2.24 (d, 1H, $J = 8.8$ Hz), 2.69 (dd, 1H, $J = 13.6$ and 5.2 Hz), 3.32 (s, 3H), 3.77 (s, 3H), 4.02 (d, 1H, $J = 8.8$ Hz), 4.02–4.08 (m, 1H), 4.47 (dd, 1H, $J = 5.2$ and 4.4 Hz), 4.73 (d, 1H, $J = 15.6$ Hz), 4.88 (dd, 1H, $J = 8.4$ and 5.6 Hz), 5.37 (d, 1H, $J = 15.6$ Hz), 6.03 (d, 1H, $J = 1.2$ Hz), 6.04 (d, 1H, $J = 1.2$ Hz), 6.80 (d, 2H, $J = 8.8$ Hz), 6.86 (s, 1H), 7.23 (d, 2H, $J = 8.8$ Hz), and 7.59 (s, 1H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 26.4, 28.4, 35.4, 45.9, 50.2, 52.8, 55.4, 63.8, 65.6, 74.8, 75.9, 102.1, 105.1, 108.8, 109.9, 113.7, 123.7, 129.1, 132.2, 135.3, 147.9, 151.3, 158.6, 165.6, and 172.; Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_9$: C, 63.4; H, 5.71; N, 2.74. Found: C, 63.0; H, 5.60; N, 2.70.

4-(4-Methoxy-benzyl)-2,2-dimethyl-5-oxo-3a,4,5,12a-tetrahydro-3bH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10b-carboxylic Acid Methyl Ester (43)

To a solution of 0.40 g (0.7 mmol) of alcohol **14** in 7 mL of THF was added 0.09 g (2.2 mmol) of NaH (60% in mineral oil) at 0°C . After stirring for 10 min, the mixture was warmed to room temperature and was stirred for an additional 30 min. The solution was cooled to 0°C , and 0.26 mL (4.4 mmol) of CS_2 was added and the mixture was stirred for 1 h at this temperature and then 0.5 mL (8.8 mmol) of MeI was added. After stirring for 10 min, the mixture was warmed to room temperature and was stirred for an additional 20 min. The solution was quenched with a saturated NH_4Cl solution and then extracted with EtOAc. The combined organic extracts were washed with H_2O , brine, and dried over MgSO_4 . After concentration under reduced pressure, the residue was dissolved in 20 mL of 1,2-dichlorobenzene and was

heated at reflux for 12 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.34 g (94%) of alkene **43** as a pale yellow oil; IR (neat) 1733, 1650, 1512, 1275, 1244, 1210 and 1037 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.43 (s, 3H), 1.44 (s, 3H), 3.25 (s, 3H), 3.77 (s, 3H), 3.91 (d, 1H, *J* = 9.0 Hz), 4.68 (d, 1H, *J* = 15.6 Hz), 4.81 (dt, 1H, *J* = 7.2 and 1.8 Hz), 4.99 (dd, 1H, *J* = 9.0 and 7.2 Hz), 5.49 (d, 1H, *J* = 15.6 Hz), 6.05 (s, 2H), 6.18 (dd, 1H, *J* = 9.6, and 1.8 Hz), 6.26 (dd, 1H, *J* = 9.6 and 1.2 Hz), 6.80 (d, 2H, *J* = 9.0 Hz), 6.93 (s, 1H), 7.23 (d, 2H, *J* = 9.0 Hz), and 7.64 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 24.8, 27.5, 45.6, 52.5, 53.1, 55.5, 64.3, 72.2, 72.9, 102.1, 105.0, 109.4, 109.5, 113.9, 124.7, 126.6, 129.1, 130.2, 132.7, 133.8, 147.8, 151.2, 158.6, 165.9, and 170.8; HRMS Calcd for [(C₂₇H₂₇NO₈) + H]⁺: 494.1809. Found: 494.1805.

Methanesulfonic Acid 4-(4-Methoxy-benzyl)-2,2-dimethyl-5,10*b*-dioxo-3*a*,3*b*,4, 5,10*b*, 11,12,12*a*-octahydro-1,3,7,9,12-pentaoxa-4-aza-dicyclopenta[*a,h*]phenanthren-11-yl Ester (46)

To a solution of 0.25 g (0.5 mmol) of alkene **43** in 8 mL of acetone and 0.8 mL of H₂O was added 0.08 g (0.7 mmol) of 4-methylmorpholine-*N*-oxide and a catalytic amount of OsO₄. The reaction mixture was stirred at room temperature for 12 h, quenched with a saturated Na₂S₂O₃ solution and extracted with EtOAc. The combined organic layer was washed with H₂O, brine, and dried over MgSO₄. After concentration under reduced pressure, the residue was dissolved in 10 mL of THF and a catalytic amount of NaOMe was added. After stirring for 20 min, the mixture was quenched with 50 mL of H₂O and extracted with EtOAc. The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. To the resulting residue was added 20 mL of THF, 0.4 mL (3.1 mmol) of Et₃N, and 0.12 mL (1.5 mmol) of MsCl. The mixture was stirred at room temperature for 6 h and was then quenched with a saturated NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with H₂O, brine, and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.22 g (76%) of **46** as a white solid: mp 179–180 °C; IR (neat) 1788, 1653, 1608, 1508, 1245, 1179, and 1037 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.35 (s, 3H), 1.52 (s, 3H), 3.22 (s, 3H), 3.76 (s, 3H), 4.27 (d, 1H, *J* = 5.4 Hz), 4.48–4.51 (m, 2H), 4.57 (d, 1H, *J* = 16.2 Hz), 5.12 (d, 1H, *J* = 3.6 Hz), 5.37 (d, 1H, *J* = 16.2 Hz), 5.63 (s, 1H), 6.04 (s, 1H), 6.06 (s, 1H), 6.82 (d, 2H, *J* = 8.4 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 7.31 (s, 1H), and 7.75 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 25.7, 27.7, 39.7, 46.3, 50.8, 5.4, 66.0, 73.2, 74.3, 79.4, 81.4, 102.4, 106.6, 109.8, 113.1, 114.3, 125.4, 126.2, 127.7, 130.7, 148.7, 151.5, 158.8, 164.6, and 170.1; Anal. Calcd for C₂₇H₂₇NO₁₁S: C, 56.54; H, 4.74; N, 2.44. Found: C, 56.29; H, 4.55; N, 2.18

Methanesulfonic Acid 2,2-Dimethyl-5,10*b*-dioxo-3*a*,3*b*,4,5,10*b*,11,12,12*a*-octahydro-1,3,7,9,12-pentaoxa-4-aza-dicyclopenta[*a,h*]phenanthren-11-yl Ester

To a solution of 0.07 g (0.12 mmol) of mesylate **46** in 1.0 mL of EtOAc was added 1.0 mL of CH₃COOH and 0.04 g (0.24 mmol) of PdCl₂. The resulting suspension was stirred under a hydrogen atmosphere (80 psi) overnight. The mixture was diluted with EtOAc and filtered over a celite pad. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.04 g (65%) of the titled compound as a white solid: mp 240–241 °C; IR (neat) 1793, 1678, 1180 and 1035 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.42 (s, 3H), 1.56 (s, 3H), 3.25 (s, 3H), 4.04 (d, 1H, *J* = 6.8 Hz), 4.22 (t, 1H, *J* = 6.4 Hz), 4.73 (dd, 1H, *J* = 5.6 and 4.4 Hz), 5.24 (d, 1H, *J* = 4.4 Hz), 5.59 (s, 1H), 5.98 (brs, 1H), 6.05 (d, 1H, *J* = 1.2 Hz), 6.08 (d, 1H, *J* = 1.2 Hz), 7.28 (s, 1H), and 7.69 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 26.0, 28.0, 39.8, 50.6, 60.1, 60.6, 73.7, 79.7, 81.8, 102.6, 107.3, 109.4, 114.3, 124.8, 127.1, 148.8, 152.0, 164.4, and 169.6; HRMS Calcd for [(C₁₉H₁₉NO₁₀S) + H]⁺: 454.0802. Found: 454.0803.

12-Hydroxy-2,2-dimethyl-3*b*,4,12,12*a*-tetrahydro-3*aH*-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthren-5-one (47)**

To a solution containing 5 mg (0.01 mmol) of the above compound in 2 mL of THF was added a solution of 2 mg (0.1 mmol) of LiOH in 0.5 mL of H₂O. The reaction mixture was stirred at room temperature for 20 min and then heated to 60 °C for 10 min. After cooling to room temperature, the mixture was diluted with a saturated NH₄Cl solution and EtOAc was added. The organic layer was washed with H₂O, brine, and dried over MgSO₄. Concentration under reduced pressure afforded 3.4 mg (93%) of alcohol **47** as a white solid whose spectral properties were identical to that reported in the literature⁵⁰: IR (neat) 3350, 1653, 1475, 1257, 1059, and 1035 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.38 (s, 3H), 1.53 (s, 3H), 1.64 (brs, 1H), 4.13–4.15 (m, 3H), 4.38–4.40 (m, 1H), 6.03 (d, 1H, *J* = 1.8 Hz), 6.04 (d, 1H, *J* = 1.8 Hz), 6.25 (brs, 1H), 7.04 (s, 1H), and 7.60 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 24.9, 27.2, 56.2, 73.2, 79.1, 79.7, 101.6, 102.2, 107.9, 111.7, 121.0, 124.1, 127.8, 128.5, 148.9, 152.1, and 162.6.

(±)-Lycoricidine (7)

To a flask containing 3 mg (0.01 mmol) of alcohol **47** at 0 °C was added 0.3 mL of cold (–20 °C) TFA. After stirring for 40 min, the solution was diluted with 2 mL of cold dioxane and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.3 mg (90%) of (±)-lycoricidine (**7**) as a white solid whose spectral properties were identical to those reported in the literature⁵⁰: ¹H-NMR (methanol-*d*₄, 400 MHz) δ 3.89–3.92 (m, 2H), 4.24 (ddd, 1H, *J* = 4.8, 2.0, and 1.6 Hz), 4.37 (ddd, 1H, *J* = 8.0, 2.4, and 1.6 Hz), 6.04 (d, 1H, *J* = 1.2 Hz), 6.05 (d, 1H, *J* = 1.2 Hz), 6.16 (m, 1H), 7.15 (s, 1H), and 7.38 (s, 1H).

12-Benzyloxy-4-(4-methoxy-benzyl)-2,2-dimethyl-5-oxo-3*a*,4,5,11,12,12*a*-hexahydro-3*bH*-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10*b*-carbaldehyde (50)**

To a solution of 1.6 g (3.0 mmol) of alcohol **14** in 60 mL DMF at 0 °C was added 0.16 g (4.0 mmol) of NaH (60% dispersion in mineral oil). After stirring for 10 min, the reaction mixture was warmed to rt and was stirred for an additional 30 min. The reaction mixture was cooled to 0 °C and 0.5 mL (4.3 mmol) of benzyl bromide was added dropwise. After stirring for 20 min, the reaction mixture was warmed to rt and was stirred for an additional 5 h. The mixture was quenched with a saturated NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with H₂O, brine, and dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 1.7 g (91%) of 12-benzyloxy-4-(4-methoxy-benzyl)-2,2-dimethyl-5-oxo-3*a*,4,5,11,12,12*a*-hexahydro-3*b**H*-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10*b*-carboxylic acid methyl ester as a colorless oil; IR (neat) 1731, 1648, 1512, 1453, 1244, and 1035 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.39 (s, 3H), 1.42 (s, 3H), 2.09 (t, 1H, *J* = 12.4 Hz), 2.59 (dd, 1H, *J* = 12.4 and 4.4 Hz), 3.19 (s, 3H), 3.70 (dt, 1H, *J* = 12.4 and 4.4 Hz), 3.76 (s, 3H), 3.93 (d, 1H, *J* = 8.8 Hz), 4.46 (t, 1H, *J* = 4.4 Hz), 4.67 (s, 2H), 4.78 (d, 1H, *J* = 15.6 Hz), 4.86 (dd, 1H, *J* = 8.8 and 4.4 Hz), 5.31 (d, 1H, *J* = 15.6 Hz), 6.03 (d, 1H, *J* = 1.2 Hz), 6.04 (d, 1H, *J* = 1.2 Hz), 6.79 (d, 2H, *J* = 8.8 Hz), 6.85 (s, 1H), 7.22 (d, 2H, *J* = 8.8 Hz), 7.28–7.38 (m, 5H), and 7.57 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 26.7, 28.6, 32.0, 45.9, 50.3, 52.6, 55.4, 63.9, 71.0, 71.4, 74.4, 75.0, 102.1, 105.0, 108.8, 110.2, 113.6, 123.7, 128.3, 128.4, 129.2, 132.2, 135.0, 137.7, 147.9, 151.3, 158.5, 165.5, and 171.6.

To a solution of 1.7 g (2.8 mmol) of the above benzyl ether in 30 mL of THF and 15 mL of MeOH was added a solution of 1.2 g (28 mmol) of LiOH in 15 mL of H₂O. The reaction mixture was heated at reflux for 12 h. After cooling to rt, the mixture was acidified to pH of 3 with 3*N* HCl and was extracted with EtOAc. The organic extracts were dried over MgSO₄ and concentrated under reduced pressure. To the residue was added 10 mL of CH₂Cl₂, followed by the addition of 0.4 mL (4 mmol) of (COCl)₂ and several drops of DMF as a catalyst. The

resulting mixture was stirred at rt for 2 h, and then concentrated under reduced pressure. The residue was taken up in 5 mL of CH₂Cl₂ and was concentrated under reduced pressure in order to completely remove the excess HCl and oxalyl chloride. The residue was taken up in 15 mL of CH₂Cl₂, cooled to 0 °C, and then 22 mL (5.6 mmol) of Zn(BH₄)₂ (0.25 M in Et₂O) was added. After stirring for 20 min, the reaction mixture was warmed to rt and was stirred for an additional 6 h. The solution was quenched with a saturated NH₄Cl solution, and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated under reduced pressure to 50 mL. To this crude solution was added 1.4 g 4 Å molecular sieves and 0.5 g (4.2 mmol) of NMO (*N*-methyl morpholine-*N*-oxide), followed by the addition of 0.05 g (0.14 mmol) of TPAP in several portions. The mixture was stirred at rt for 3 h, and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was subjected to flash silica gel chromatography to give 1.2 g (77%) of aldehyde **50** as a pale yellow oil; IR(neat) 1719, 1648, 1610, 1511, 1453, 1269, 1245, and 1036 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.35 (s, 3H), 1.45 (s, 3H), 1.98 (dd, 1H, *J* = 12.6 and 10.8 Hz), 2.69 (dd, 1H, *J* = 12.6 and 5.4 Hz), 3.73–3.76 (m, 1H), 3.77 (s, 3H), 4.25–4.27 (m, 2H), 4.49 (dd, 1H, *J* = 9.0 and 5.4 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.79 (d, 1H, *J* = 15.6 Hz), 5.44 (d, 1H, *J* = 15.6 Hz), 6.04 (d, 1H, *J* = 0.9 Hz), 6.06 (d, 1H, *J* = 0.9 Hz), 6.70 (s, 1H), 6.81 (d, 2H, *J* = 8.7 Hz), 7.22 (d, 2H, *J* = 8.7 Hz), 7.29–7.36 (m, 5H), 7.68 (s, 1H), 9.40 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 26.4, 28.3, 29.1, 45.9, 52.9, 55.4, 62.8, 71.1, 72.0, 74.1, 74.6, 102.3, 104.6, 109.5, 110.3, 114.0, 124.6, 128.2, 128.7, 128.9, 131.6, 131.7, 137.9, 148.6, 152.1, 158.7, 165.0, 197.9.

12-Hydroxy-4-(4-methoxy-benzyl)-2,2-dimethyl-3a,4,5,11,12,12a-hexahydro-3bH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*] phenanthrene-10b-carboxylic Acid Methyl Ester (51)

To a solution of 0.05 g (0.1 mmol) of alcohol **14** in a mixture containing 2 mL of CH₂Cl₂ and 1 mL of THF at –78 °C was added dropwise 0.4 mL (0.4 mmol) of DIBAL (1.0 M in CH₂Cl₂). The reaction mixture was stirred at this temperature for 1 h and was quenched by the addition of 0.4 g of powdered Na₂SO₄·10H₂O and 0.4 g Celite. The reaction mixture was warmed to rt, stirred for an additional 20 min, and filtered through a pad of anhydrous MgSO₄. The filtrate was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.04 g (91%) of **51** as a colorless oil; IR (neat) 3400, 1727, 1511, 1487, 1240, and 1039 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.40 (s, 3H), 1.53 (s, 3H), 1.97 (dd, 1H, *J* = 13.2 and 10.4 Hz), 2.23 (d, 1H, *J* = 8.4 Hz), 2.66 (dd, 1H, *J* = 13.2 and 5.0 Hz), 2.83 (d, 1H, *J* = 8.8 Hz), 3.27 (d, 1H, *J* = 13.6 Hz), 3.30 (d, 1H, *J* = 15.6 Hz), 3.64 (s, 3H), 3.70 (d, 1H, *J* = 15.6 Hz), 3.79 (s, 3H), 4.14–4.20 (m, 1H), 4.42 (d, 1H, *J* = 13.6 Hz), 4.56 (dd, 1H, *J* = 5.6 and 4.4 Hz), 4.92 (dd, 1H, *J* = 8.8 and 5.6 Hz), 5.89 (d, 1H, *J* = 1.4 Hz), 5.90 (d, 1H, *J* = 1.4 Hz), 6.34 (s, 1H), 6.81 (d, 2H, *J* = 8.8 Hz), 6.89 (s, 1H), and 7.24 (d, 2H, *J* = 8.8 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ 26.4, 28.5, 37.2, 51.8, 52.5, 55.4, 56.9, 57.3, 66.4, 67.0, 76.1, 76.6, 101.1, 105.9, 107.5, 109.1, 113.8, 128.8, 129.7, 130.5, 132.6, 146.3, 146.8, 158.6, and 174.3.

12-Benzyloxy-4-(4-methoxy-benzyl)-2,2-dimethyl-3b,4,10b,11,12,12a-hexahydro-3aH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthren-5-one (52)

To a solution of 1.2 g (2.1 mmol) of aldehyde **50** in 50 mL of benzonitrile was added 2.9 g (3.2 mmol) of RhCl(PPh₃)₃. The mixture was heated at reflux in a preheated oil bath for 24 h. After cooling to room temperature, the mixture was subjected to flash silica gel chromatography to give 0.73 g (63%) of amide **52** as a pale yellow oil; IR (neat) 1647, 1512, 1457, 1245, and 1040 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.37(s, 3H), 1.40 (s, 3H), 1.86 (q, 1H, *J* = 12.6 Hz), 2.42 (dt, 1H, *J* = 12.6 and 3.6 Hz), 2.63 (td, 1H, *J* = 12.6 and 3.6 Hz), 3.65–3.72 (m, 2H), 4.20 (dd, 1H, *J* = 8.4 and 4.8 Hz), 4.36 (t, 1H, *J* = 4.8 Hz), 4.72 (s, 2H), 4.88 (d, 1H, *J* = 15.6 Hz), 5.27 (d, 1H, *J* = 15.6 Hz), 6.02 (s, 1H), 6.78(s, 1H), 6.80 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 7.29–7.32 (m, 1H), 7.34–7.39 (m, 4H), and 7.61 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 26.6, 27.5, 28.3, 36.4, 46.0, 55.5, 62.7, 71.2, 73.5, 74.8, 76.6, 101.9, 104.1, 109.0, 110.3,

114.0, 123.5, 128.1, 128.2, 128.3, 128.8, 132.4, 134.9, 138.0, 147.2, 151.3, 158.5, and 165.7; HRMS Calcd for $[(C_{32}H_{33}NO_7) + H]^+$ 544.2330, Found: 544.2320.

4-(4-Methoxy-benzyl)-2,2-dimethyl-3b,4,10b,12a-tetrahydro-3aH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[a,h]phenanthren-5-one (53)

To a solution of 0.30 g (0.55 mmol) of **52** in 8 mL of de-gassed EtOAc was added 0.15 g of Pearlman's catalyst (20% Pd(OH)₂ on carbon). The reaction mixture was stirred at rt under a H₂ balloon for 6 h, filtered through a pad of celite, concentrated under reduced pressure and the residue was taken up in 15 mL of THF. To the above solution at 0 °C was added 0.07 g (1.6 mmol) of NaH (60% dispersion in mineral oil) in several portions. After stirring for 10 min, the cooling bath was removed and the solution was stirred at rt for 40 min. The reaction mixture was cooled to 0 °C and 85 μ L (3.3 mmol) of CS₂ was added. After stirring at 0 °C for 1 h, 0.2 mL (6.6 mmol) of methyl iodide was added and the resulting mixture was stirred at 0 °C for 10 min and then at rt for 8 h. The reaction mixture was quenched with a saturated NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with H₂O, brine, and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was taken up in 20 mL of o-dichloro-benzene and was heated at reflux for 24 h. After cooling to rt, the reaction mixture was subjected to flash silica gel chromatography to give 0.21 g (85%) of alkene **53** as a white solid; mp 171–173 °C; IR (neat) 2924, 1645, 1511, 1456, 1246, and 1038 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.34 (s, 6H), 3.46 (dd, 1H, *J* = 11.6 and 3.0 Hz), 3.64 (dd, 1H, *J* = 11.6 and 9.0 Hz), 3.77 (s, 3H), 4.37 (dd, 1H, *J* = 9.0 and 7.0 Hz), 4.59–4.62 (m, 1H), 4.95 (d, 1H, *J* = 15.6 Hz), 5.40 (d, 1H, *J* = 15.6 Hz), 6.03 (s, 2H), 6.09 (dt, 1H, *J* = 10.0 and 3.0 Hz), 6.32 (d, 1H, *J* = 10.0 Hz), 6.81 (d, 2H, *J* = 8.8 Hz), 6.90 (s, 1H), 7.25 (d, 2H, *J* = 8.8 Hz), and 7.65 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 25.4, 27.7, 38.7, 45.9, 55.4, 60.9, 72.0, 75.0, 101.9, 103.9, 109.3, 109.4, 113.8, 123.8, 126.2, 128.1, 128.4, 132.7, 133.8, 147.0, 151.2, 158.4, and 165.6; HRMS Calcd for $[(C_{25}H_{25}NO_6) + H]^+$: 436.1755. Found: 436.1757.

11,12-Dihydroxy-4-(4-Methoxy-benzyl)-2,2-dimethyl-3b,4,10b,11,12,12a-hexahydro-3aH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[a,h]phenanthren-5-one (54)

To a solution of 0.15 g (0.34 mmol) of **53** in 20 mL of acetone and 2 mL of H₂O was added NMO (*N*-methyl morpholine-*N*-oxide) and catalytic OsO₄. The mixture was stirred at rt for 24 h and then quenched with a saturated Na₂S₂O₃ solution in EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.11 g (68%) of diol **54** as a pale yellow oil; IR (neat) 3401, 1642, 1610, 1511, 1462, 1247, and 1036 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.24 (s, 3H), 1.51 (s, 3H), 2.60 (d, 1H, *J* = 2.0 Hz), 3.01 (dd, 1H, *J* = 14.8 and 7.2 Hz), 3.23 (s, 1H), 3.73 (ddd, 1H, *J* = 10.8, 5.2, and 2.0 Hz), 3.77 (s, 3H), 3.85 (dd, 1H, *J* = 14.8 and 7.2 Hz), 4.22 (dd, 1H, *J* = 10.8 and 7.2 Hz), 4.30 (dd, 1H, *J* = 7.2 and 5.2 Hz), 4.38 (t, 1H, *J* = 7.2 Hz), 4.67 (d, 1H, *J* = 15.2 Hz), 5.29 (d, 1H, *J* = 15.2 Hz), 6.01 (d, 1H, *J* = 1.2 Hz), 6.02 (d, 1H, *J* = 1.2 Hz), 6.80 (d, 1H, *J* = 8.8 Hz), 7.24 (s, 1H), 7.26 (d, 1H, *J* = 8.8 Hz), and 7.60 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 25.6, 28.1, 41.9, 46.9, 55.4, 57.8, 69.5, 70.7, 75.0, 77.1, 101.8, 106.0, 108.2, 110.6, 113.8, 122.1, 128.7, 131.6, 134.6, 147.3, 151.7, 158.7, and 165.0; HRMS Calcd for $[(C_{25}H_{27}NO_8) + H]^+$: 470.1809. Found: 470.1808.

Preparation of Hexacyclic Cyclosulfate (55)

To a solution of 0.05 g (0.11 mmol) of diol **54** in 3 mL of CH₂Cl₂ at 0 °C was added 62 μ L (0.44 mmol) of Et₃N and 12 μ L (0.17 mmol) of SOCl₂. After stirring at 0 °C for 5 min, the cooling bath was removed and the reaction mixture was stirred at rt for 40 min. The mixture was quenched with a saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic layer was washed with H₂O, brine, and dried over MgSO₄. After removal of the solvent

under reduced pressure, the residue was taken up in 4 mL of CH₃CN, followed by the addition of 2.2 mg of RuCl₃·3H₂O (0.01 mmol). A solution of 0.05 g (0.22 mmol) of NaIO₄ in 1.0 mL of H₂O was added. The mixture was stirred at rt for 12 h, diluted with EtOAc and H₂O. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.05 g of sulfate **55** (82%) as a white solid; mp 218–220 °C; IR (neat) 1648, 1511, 1460, 1396, 1248, and 1212 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.25(s, 3H), 1.56 (s, 3H), 3.47 (dd, 1H, *J* = 14.4 and 8.8 Hz), 3.77 (s, 3H), 3.81 (dd, 1H, *J* = 14.4 and 7.2 Hz), 4.53 (t, 1H, *J* = 7.2 Hz), 4.60 (dd, 1H, *J* = 9.6 and 7.2 Hz), 4.69 (d, 1H, *J* = 15.2 Hz), 4.83 (dd, 1H, *J* = 9.6 and 7.2 Hz), 5.23–5.29 (m, 2H), 6.07 (s, 2H), 6.81 (d, 2H, *J* = 8.8 Hz), 6.94 (s, 1H), 7.23 (d, 2H, *J* = 8.8 Hz), 7.64 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 25.4, 27.9, 38.8, 47.1, 55.5, 56.8, 74.0, 81.6, 82.9, 102.4, 105.4, 108.9, 112.2, 114.0, 122.1, 128.7, 130.0, 148.4, 152.3, 159.0, and 164.0; Anal. Calcd for C₂₅H₂₅NO₁₀S: C, 56.49; H, 4.74; N, 2.64. Found: C, 56.78; H, 4.75; N, 2.64.

2,3,4-Trihydroxy-5-(4-methoxy-benzyl)-6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-*h*]phenanthridine-1-carboxylic Acid Phenyl Ester (**56**)

To a solution of 0.02 g (0.04 mmol) of sulfate **55** in 1.5 mL of DMF at rt was added 9 mg (0.07 mmol) of benzoic acid and 0.02 g (0.06 mmol) of CS₂CO₃. After cooling to rt, 2 mL of THF and 3 mL of a 40% H₂SO₄ solution was added and the mixture was heated at 80 °C for 6 h, then cooled to room temperature, and diluted with H₂O and EtOAc. The combined organic layer was washed with a saturated NaHCO₃ solution, brine, and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 16 mg (75%) of **56** as a white solid; mp 230–231 °C; IR (neat) 3420, 1714, 1602, 1509, 1463, 1270, and 1034 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 2.68 (d, 1H, *J* = 4.2 Hz), 3.04 (d, 1H, *J* = 4.2 Hz), 3.37 (brs, 1H), 3.65 (dd, 1H, *J* = 13.8, and 4.2 Hz), 3.79 (s, 3H), 3.96–4.30 (m, 3H), 4.95 (d, 1H, *J* = 16.2 Hz), 5.36 (d, 1H, *J* = 16.2 Hz), 5.62 (t, 1H, *J* = 3.6 Hz), 5.93 (d, 1H, *J* = 0.9 Hz), 5.95 (d, 1H, *J* = 0.9 Hz), 6.57 (s, 1H), 6.85 (d, 2H, *J* = 9.0 Hz), 7.31 (d, 2H, *J* = 8.4 Hz), 7.40 (t, 2H, *J* = 8.4 Hz), 7.57 (t, 1H, *J* = 8.4 Hz), 7.68 (s, 1H), and 7.80 (d, 2H, *J* = 9.0 Hz); ¹³C-NMR (DMSO-*d*₆, 150 MHz) δ 38.9, 45.1, 55.0, 57.1, 67.4, 67.5, 70.4, 72.0, 101.7, 103.4, 107.7, 113.6, 123.8, 127.5, 128.6, 129.5, 129.7, 133.0, 133.4, 133.5, 146.3, 150.5, 157.6, 164.3, and 165.4.

(±)-7-Deoxypancratistatin (**10**)

To a solution of 13 mg (0.02 mmol) of ester **56** in 2 mL of THF at 25 °C was added 4 mg (0.06 mmol) of NaOMe. The reaction mixture was stirred at 25 °C for 6 h and then the mixture was quenched with a saturated NH₄Cl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was taken up in 3 mL of de-gassed THF followed by the addition of 0.05 g (0.08 mmol) of Pearlman's catalyst (20% Pd(OH)₂ on carbon). The mixture was stirred under a H₂ atmosphere at rt overnight, filtered through celite and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 6 mg (80%) of (±)-7-deoxypancratistatin (**10**) as a colorless oil¹³; ¹H-NMR (DMSO-*d*₆, 600 MHz) δ 2.98 (dd, 1H, *J* = 12.3 and 2.1 Hz), 3.67–3.76 (m, 2H), 3.82–3.86 (m, 1H), 3.94–4.00 (m, 1H), 4.30–4.35 (m, 1H), 4.79 (d, 1H, *J* = 7.4 Hz), 5.00–5.10 (m, 2H), 5.36 (d, 1H, *J* = 4.0 Hz), 6.08 (s, 2H), 6.85 (s, 1H), 6.91 (s, 1H), and 7.31 (s, 1H); ¹³C-NMR (DMSO-*d*₆, 150 MHz) δ 40.1, 50.4, 68.7, 70.2, 70.3, 73.3, 101.5, 105.5, 106.7, 123.8, 135.3, 145.8, 150.5, and 164.0.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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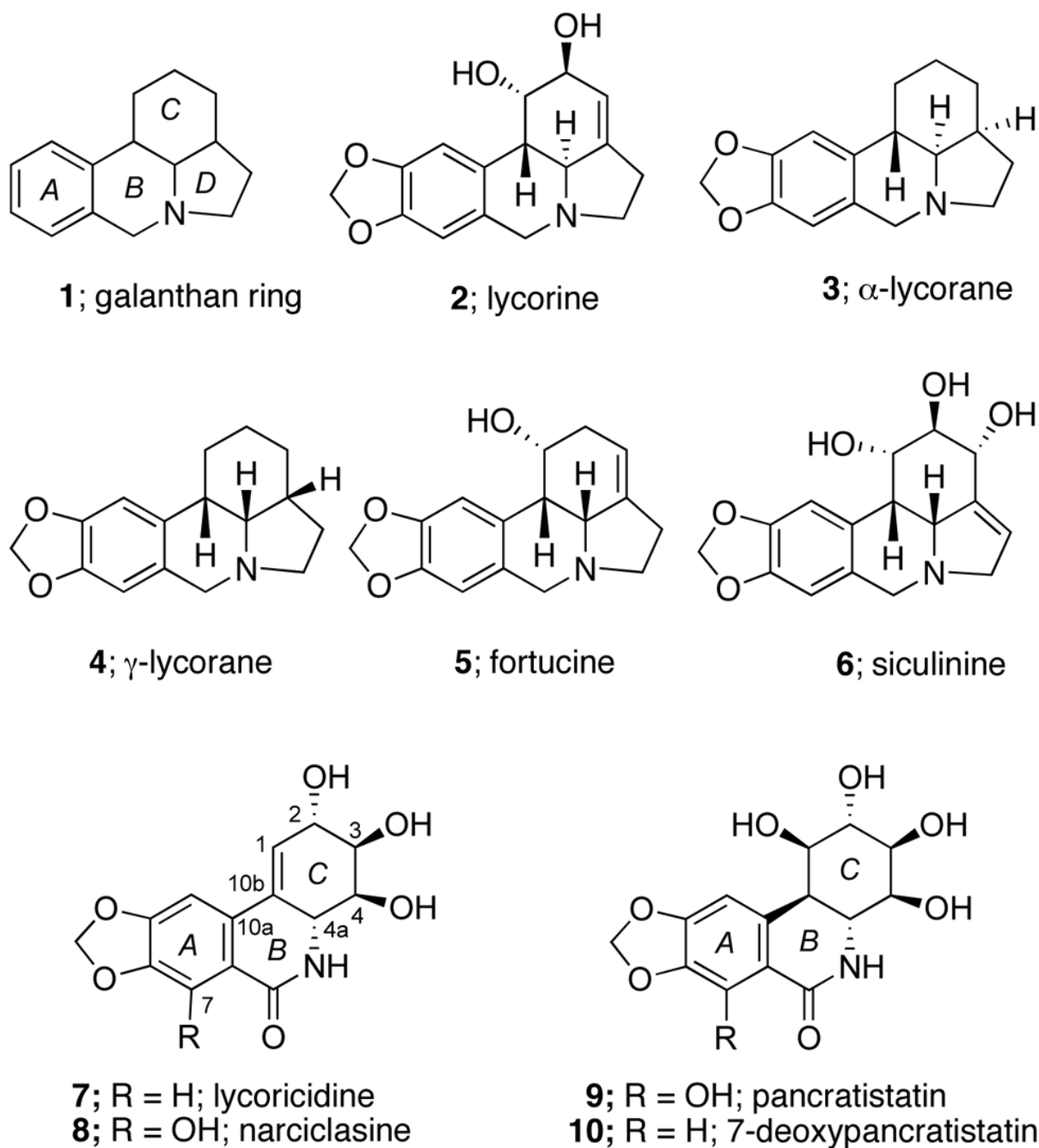
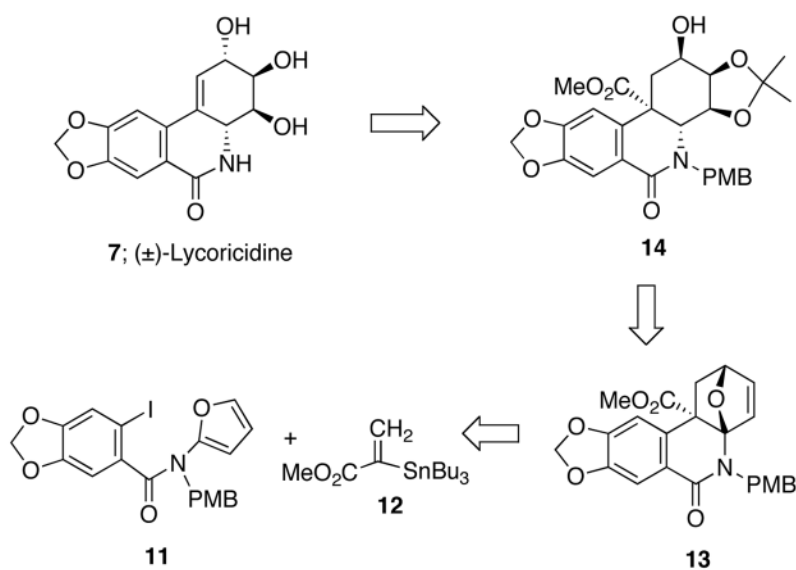
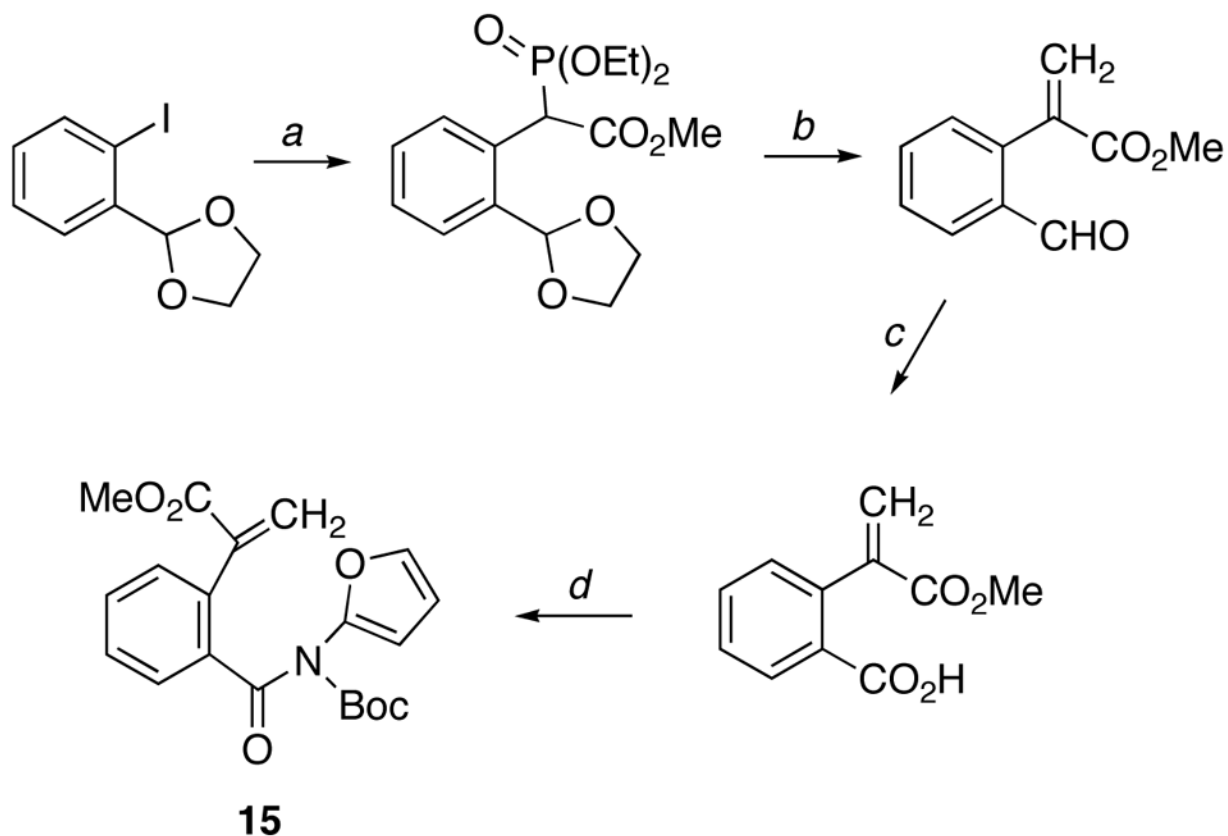


Figure 1.
Some Representative Lycorine-type Alkaloids

**Scheme 1.**

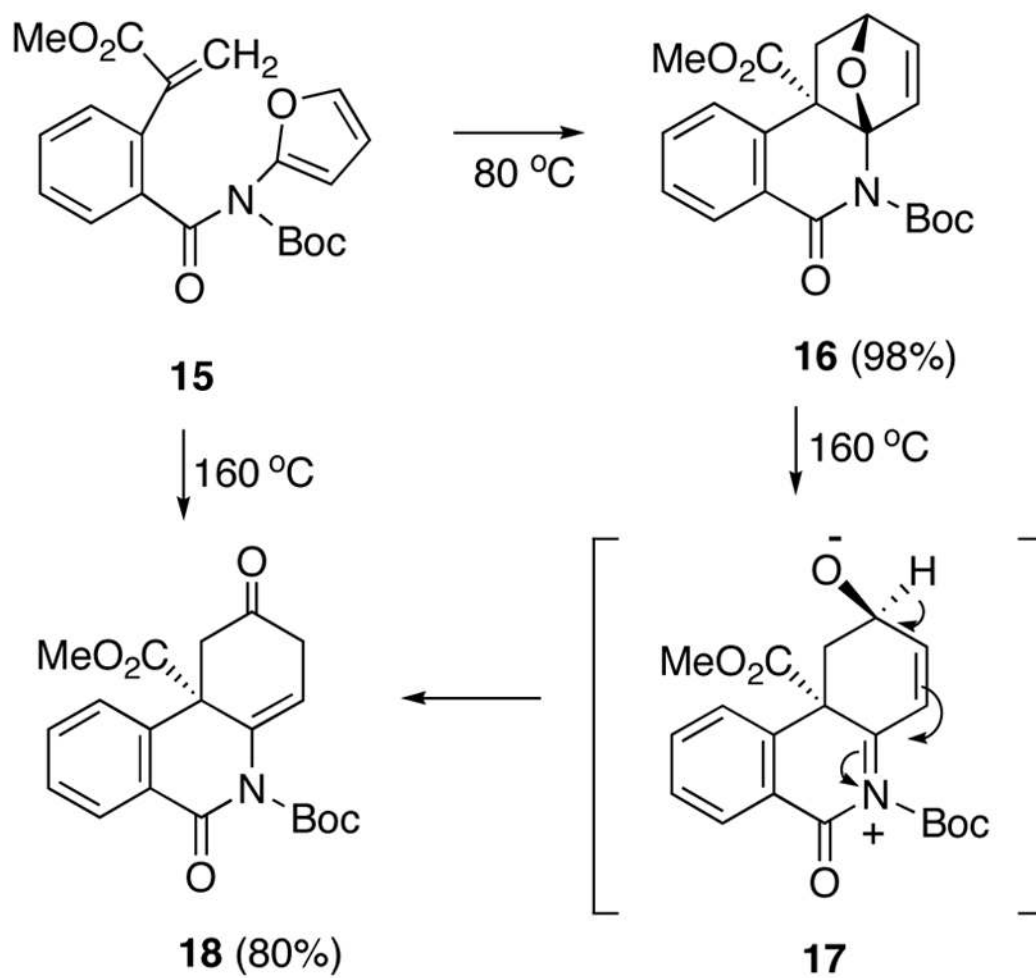
Key Disconnections for the Synthesis of (±)-Lycoricidine



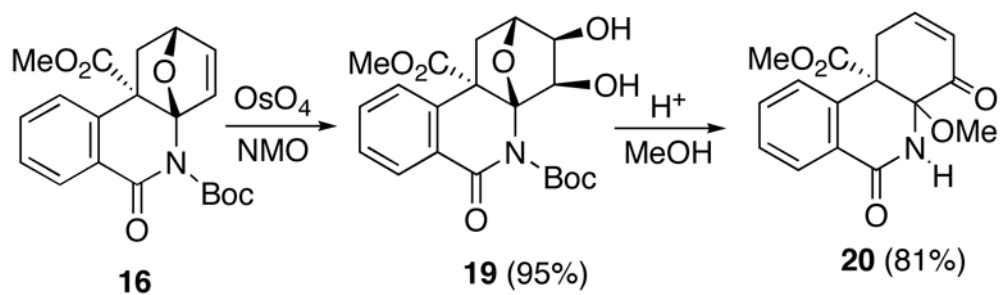
Reagents: (a) $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OEt})_2$, NaH, CuI, DMF, 100 °C, 61%; (b) NaH, CH_2O , THF, 25 °C, 83%; (c) NaClO_2 , H_2O_2 , NaH_2PO_4 , acetone, 10 °C, 93%; (d) $(\text{COCl})_2$, CH_2Cl_2 , $n\text{-BuLi}$, BocNHfuran, 65% (2 steps).

Scheme 2. Synthesis of a Model 2-Amidofuran

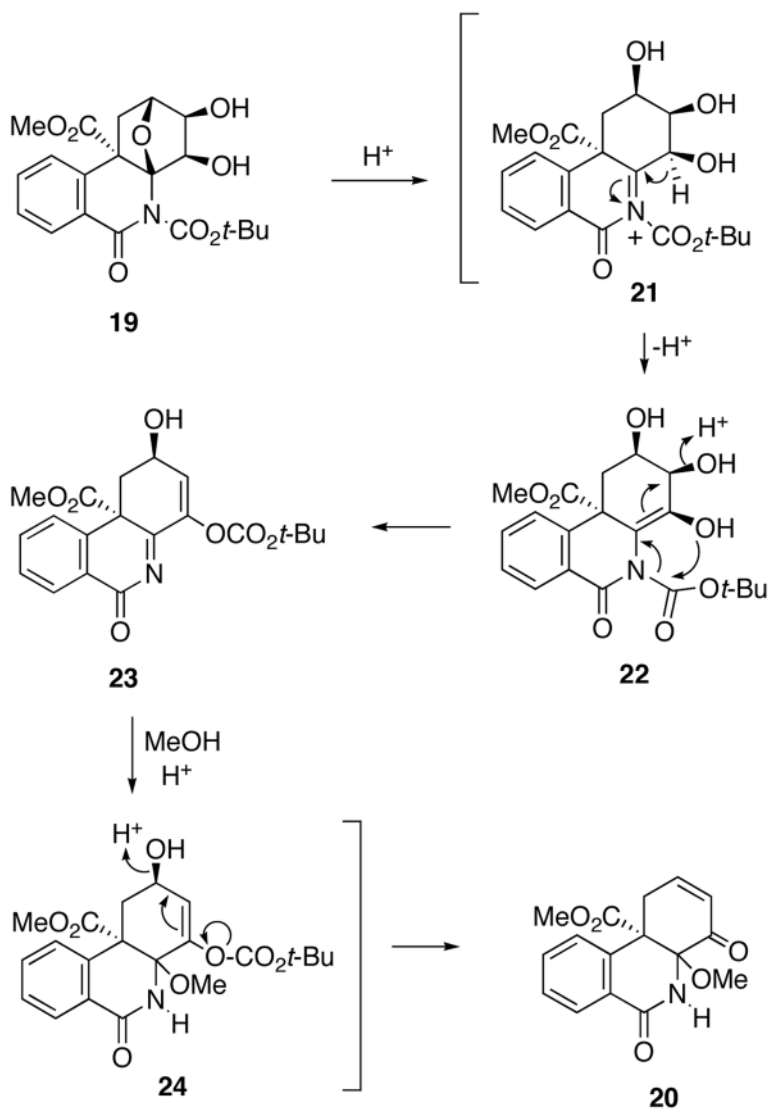
Reagents: (a) $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OEt})_2$, NaH, CuI, DMF, 100°C, 61%; (b) NaH, CH_2O , THF, 25 °C, 83%; (c) NaClO_2 , H_2O_2 , NaH_2PO_4 , acetone, 10 °C, 93%; (d) $(\text{COCl})_2$, CH_2Cl_2 , $n\text{-BuLi}$, BocNHfuran, 65% (2 steps).



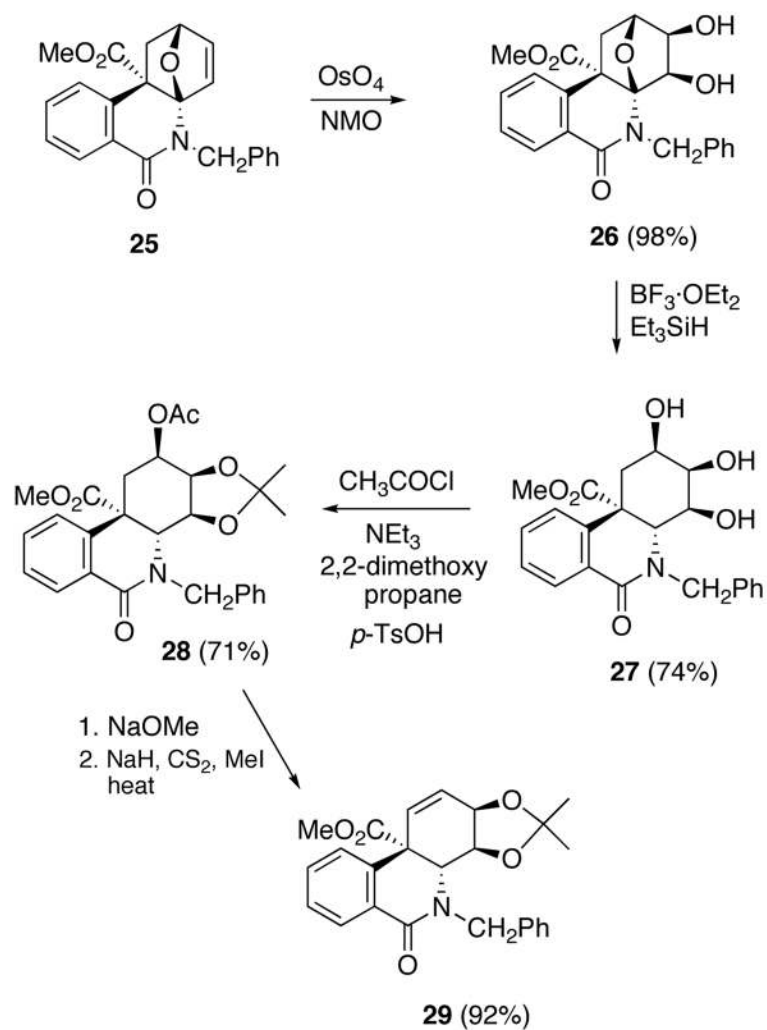
Scheme 3.
Cycloaddition/Rearrangement Cascade



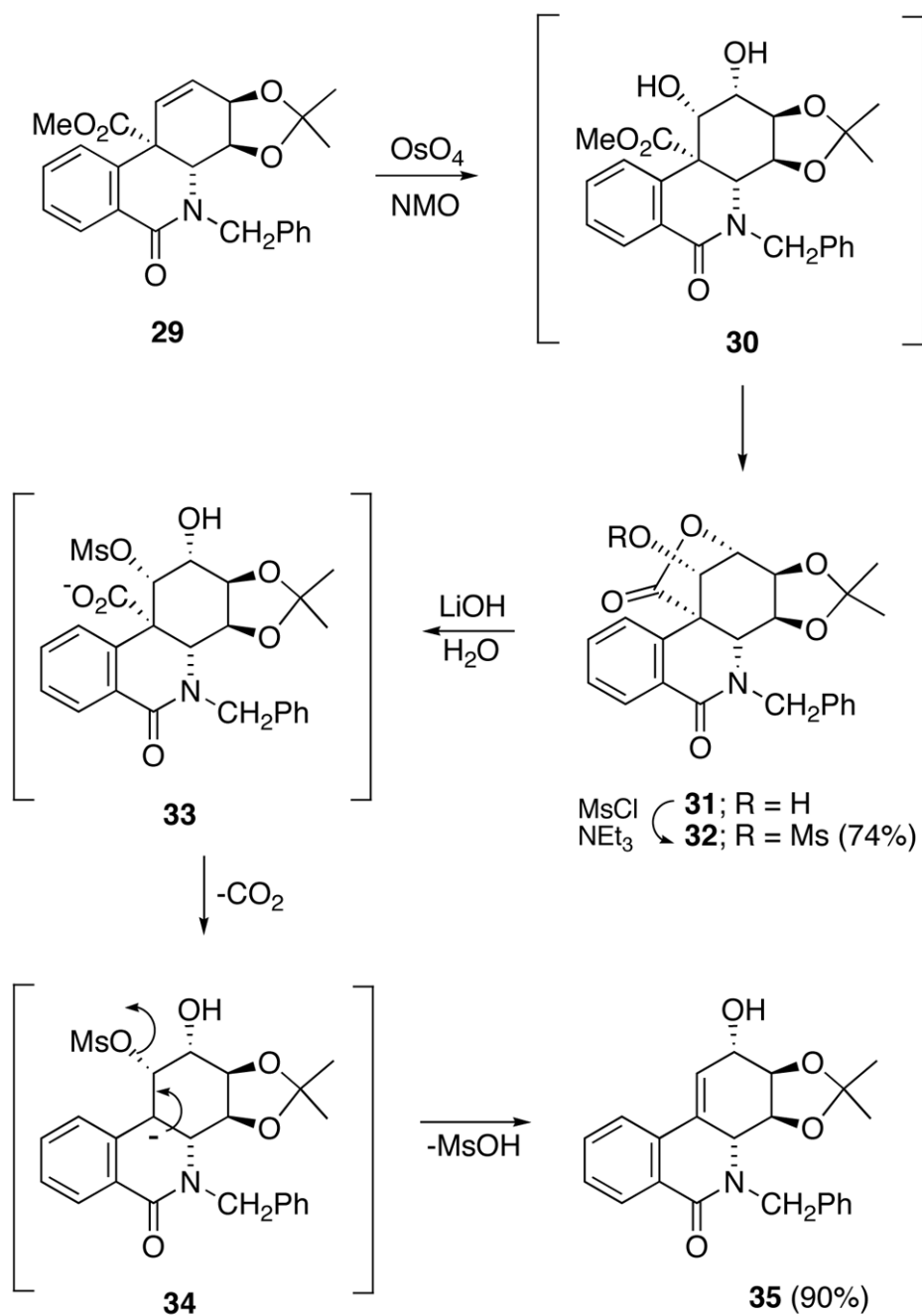
Scheme 4.
An Unusual Acid-Catalyzed Rearrangement



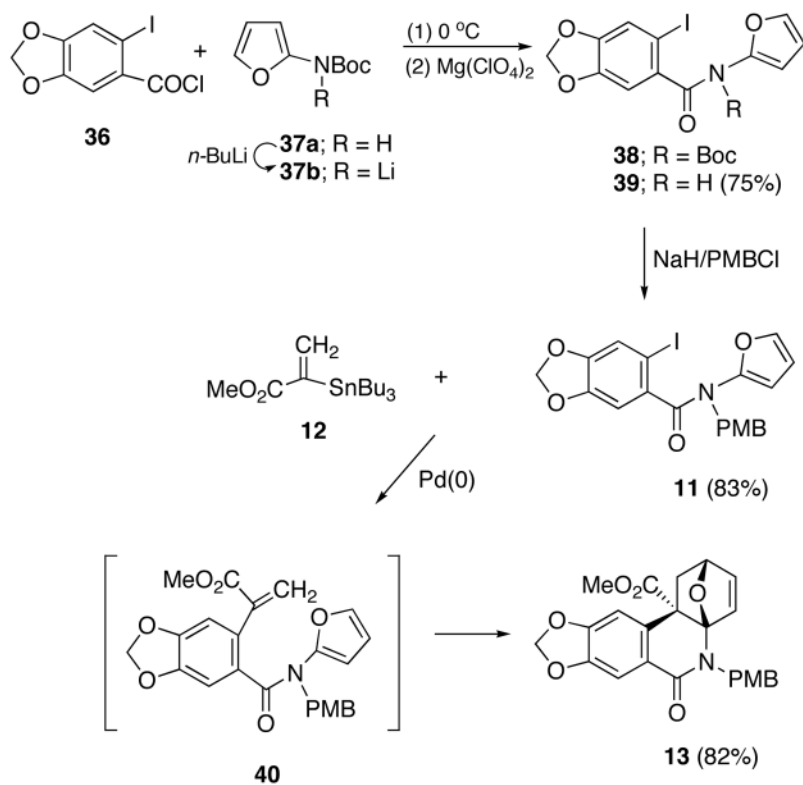
Scheme 5.
A Proposed Mechanism for the Rearrangement



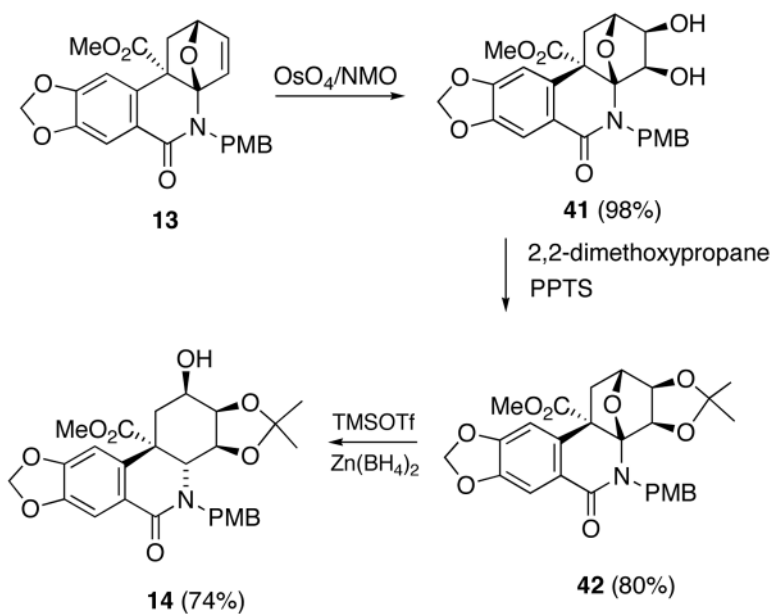
Scheme 6.
Dihydroxylation of the IMDAF Cycloadduct



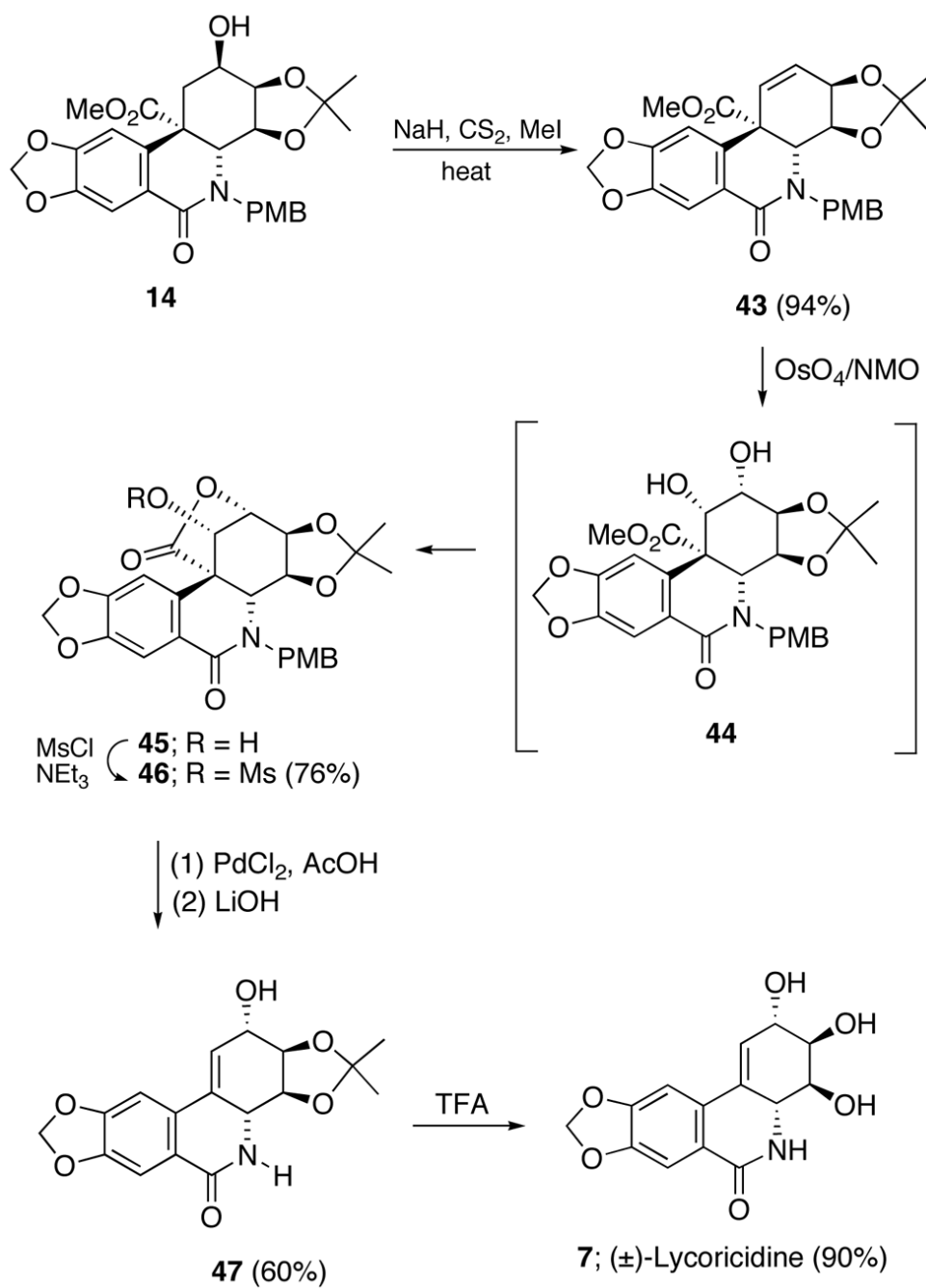
Scheme 7.
Decarboxylation/Elimination Sequence



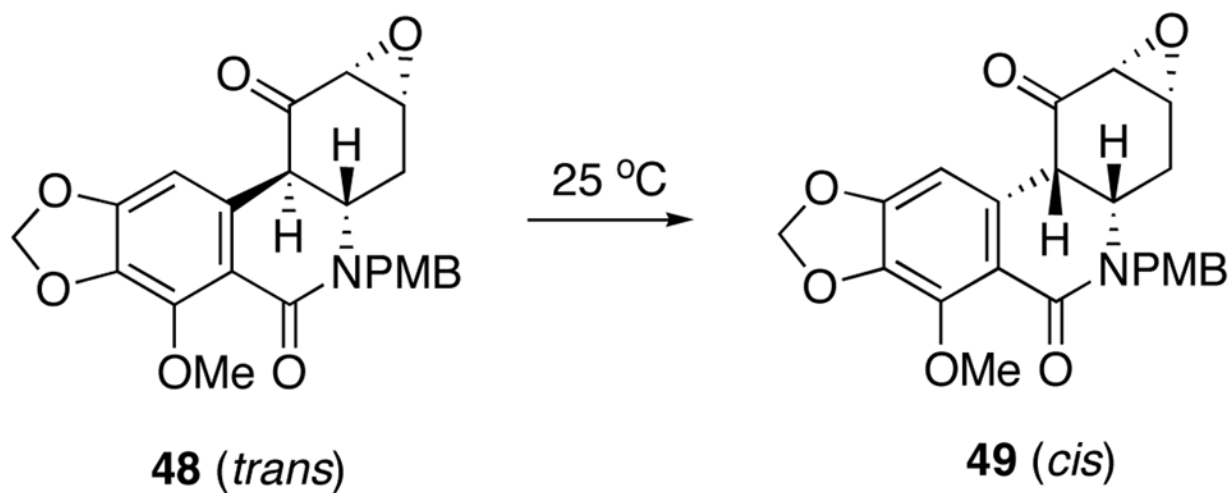
Scheme 8.
Intramolecular Diels-Alder Reaction



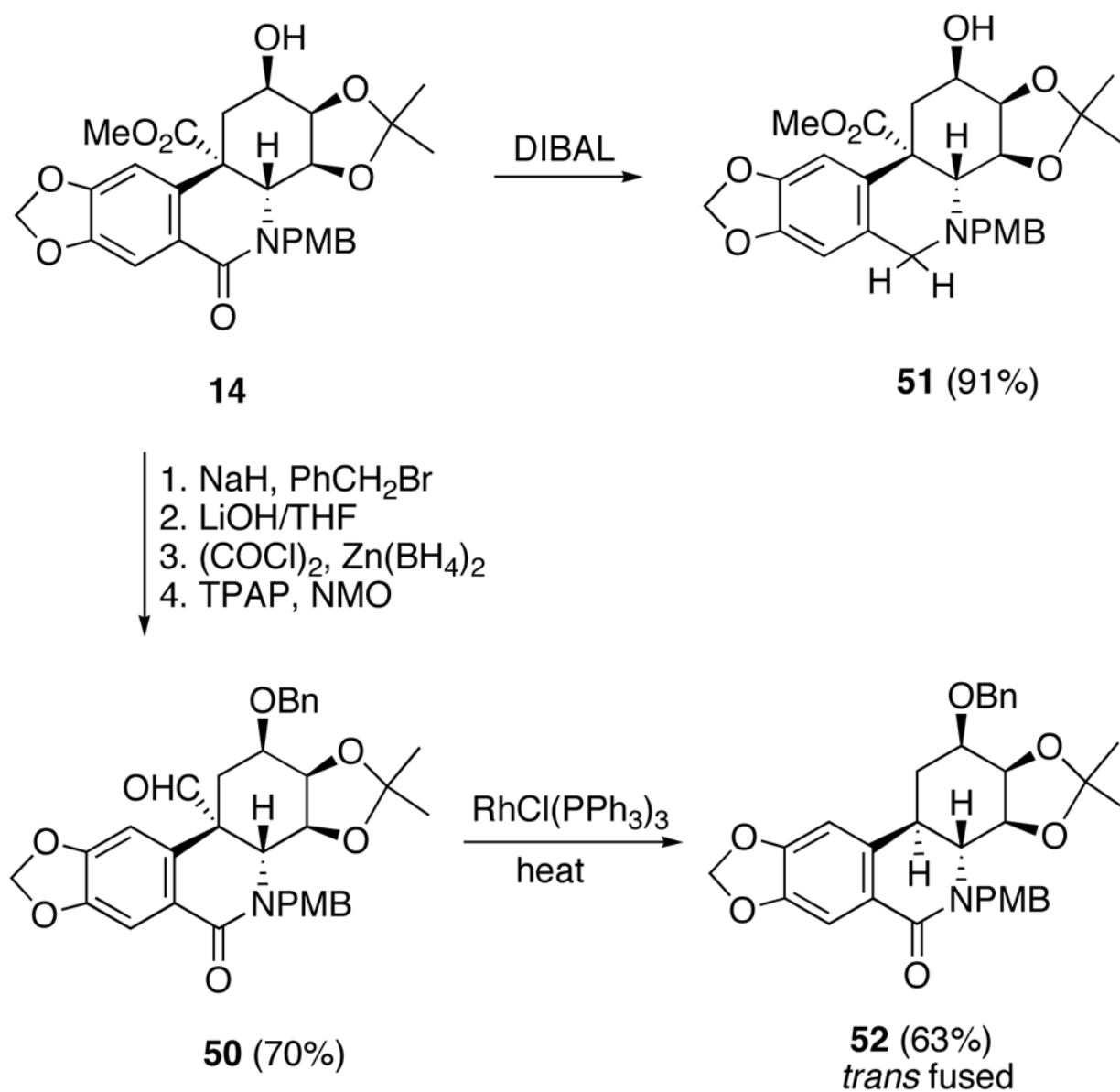
Scheme 9.
Stereocontrolled Reduction of *N*-Acyliminium Ion Precursor



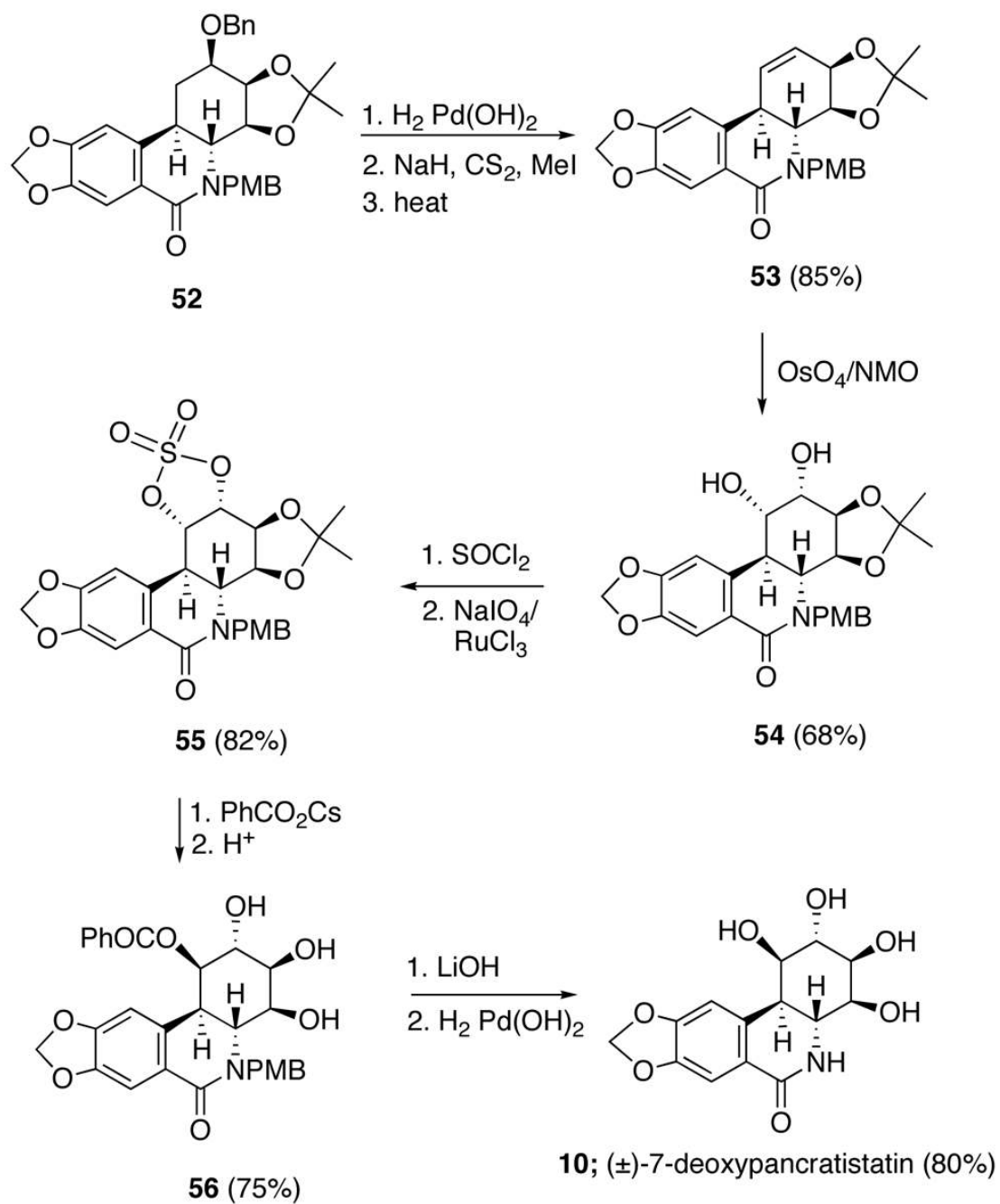
Scheme 10.
Final Steps in the Synthesis of (±)-Lycoricidine



Scheme 11.
Preference for the *cis*-Isomer



Scheme 12.
Use of Wilkinson's Catalyst to Control Stereochemistry



Scheme 13.
Synthesis of (±)-7-Deoxypancratistatin