Intramolecular Cycloaddition Reactions of Dienyl Nitroso Compounds: Application to the Synthesis of Mitomycin K

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Abstract: The total synthesis of mitomycin K has been achieved. The key reaction produced pyrrolo[1,2-*a*]indole **25** from dienyl nitrobenzenemethanol **23** by a process involving two internal photochemical redox transformations and a [4 + 2] cycloaddition.

Background

Recently, the isolation of two aziridine-containing natural products termed FR 900482 (**1**)[1] and FR 66979 (**2**)[2] was described. Both compounds, which are produced by cultures of *Streptomyces sandaensis* 6897, exhibit potent antitumor properties. Although structures **1** and **2** lack the quinone nucleus of a mitomycin (**3**, Figure 1), they share the aziridine functionality and the (carbamoyloxy)methyl group. Furthermore, there is now increasing evidence[3] supporting the hypothesis[4] that the mechanism of action of **1** and **2** parallels that of the mitomycines.[5-7] The possibility that the two series of natural products might be related by a common biosynthetic intermediate has been proposed and has formed the basis for a synthetic approach to **1**.[8]

Various approaches to the synthesis of **1** have been published.[9,10] The only total synthesis is that of Fukuyama and colleagues.[11] Our own laboratory has recently reported a synthesis of a dimethyl ether methyl ester analog of **1**.[12] The key element in this work was a Diels–Alder reaction of the arylnitroso dienophile **4** and the oxygenated diene **5** (Scheme I). After elaboration of the resultant benzoxazine cycloaddition adduct **6**, an intramolecular

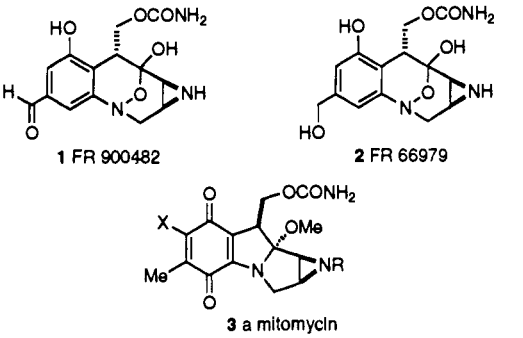
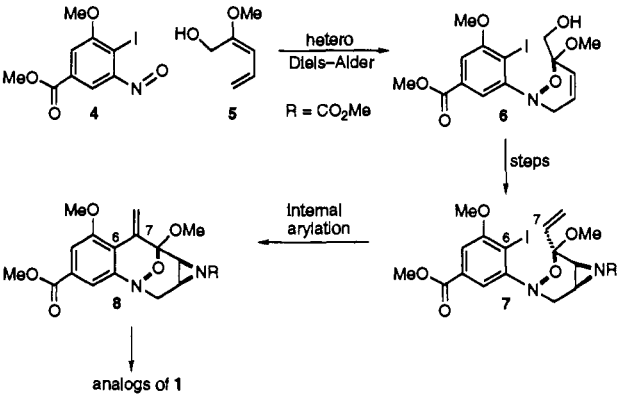


Figure 1.

Scheme I



arylation reaction was used to form the 1,5-epoxybenzazocine ring system (**7** → **8**, Scheme I).

Prior to the development of our successful method, a scheme involving an intramolecular cycloaddition reaction was explored.[13] The lure of the intramolecular route was that it could produce **10** directly (Figure 2), thereby obviating the steps required to install the C-6–C-7 bond (see structure **7**, Scheme I, for numbering). Of course we were mindful that the projected reaction presented serious and interesting questions of regiochemistry. With a C-1 tether fastening the diene to the heterodienophile in the generalized structure **9**, the cycloaddion could produce either a bridged adduct (cf. **10**) or a fused structure (cf. **11**). For the chemistry to prove successful in reaching the FR series (cf. **1** or **2**), it would be necessary for the cycloaddition to lead to **10**. However, in the event that the reaction favored the formation of the fused adduct (cf. **11**), it seemed that reductive transformation of the oxazine ring to a pyrrolo[1,2-*a*]indole system

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(1) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108.

(2) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145.

(3) Woo, J.; Sigurdsson, S. Th.; Hopkins, P. B. *J. Am. Chem. Soc.* **1993**, *115*, 1199.

(4) Fukuyama, T.; Goto, S. *Tetrahedron Lett.* **1989**, *30*, 6491.

(5) For work related to the mechanism of bioactivation, see: (a) Iyer, V. N.; Szybalski, W. *Science (Washington, D.C.)* **1964**, *145*, 55. (b) Szybalski, W.; Iyer, V. N. *Fed. Proc.* **1964**, *23*, 946. (c) Moore, H. *Science (Washington, D.C.)* **1977**, *197*, 527. (d) Egbertson, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2204. (e) Kohn, H.; Hong, Y. P. *Ibid.* **1990**, *112*, 4596. (f) Schiltz, P.; Kohn, H. *J. Am. Chem. Soc.* **1992**, *114*, 7958 and references cited therein.

(6) For DNA and related alkylation studies, see: (a) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G.; nakanishi, K. *Science (Washington, D.C.)* **1987**, *235*, 1204. (b) Tomasz, M.; Lipman, R.; Chowdary, D.; McGuiness, B. F.; Nakanishi, K. *J. Am. Chem. Soc.* **1988**, *110*, 5892. (c) Teng, S. P.; Woodson, S. A.; Crothers, D. M. *Biochemistry* **1989**, *28*, 3901. (d) Cera, C.; Egbertson, M.; Teng, S. P.; Crothers, D. M.; Danishefsky, S. J. *Ibid.* **1989**, *28*, 5665. (e) Li, V.-S.; Kohn, H. *J. Am. Chem. Soc.* **1991**, *113*, 275. (f) Bizanek, R.; McGuiness, B. F.; Nakanishi, K.; Tomasz, M. *Biochemistry* **1992**, *31*, 3084. (g) Kohn, H.; Li, V.-S.; Tang, M.-s. *J. Am. Chem. Soc.* **1992**, *114*, 5501 and references cited therein.

(7) For the total synthesis of a mitomycin, see: (a) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115. (b) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, *18*, 4295. (c) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549. For the total synthesis of mitomycins via isomitomycin A, see: (d) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881. (e) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303.

(8) Dmitrienko, G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705.

(9) Yasuda, N.; Williams, R. M. *Tetrahedron Lett.* **1989**, *30*, 3397.

(10) Jones, R. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 1144.

(11) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.

(12) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094.

(13) (a) McClure, K. F.; Benbow, J. W.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 8185. (b) For a previous communication describing the application of this chemistry to the synthesis of mitomycin K, see: Benbow, J. W.; Schulte, G. K.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 915.

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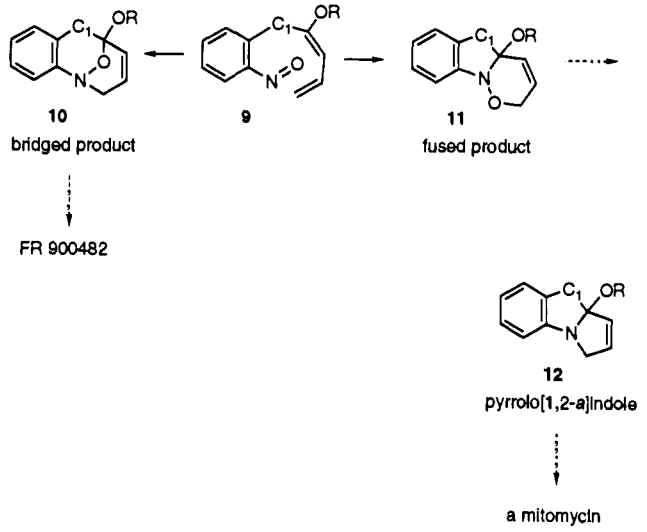
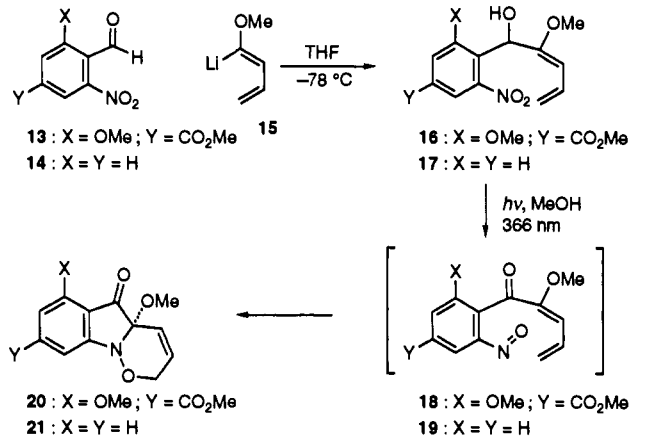


Figure 2.

Scheme II

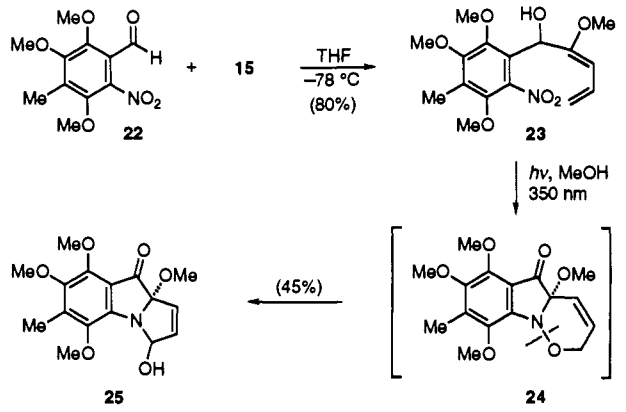


(see **11** → **12**, Figure 2) would be possible. In such a case, this chemistry could be applied to a synthesis of a mitomycin. In this paper, we detail the way in which the intramolecular cycloaddition chemistry, originally intended to lead to **1** or **2**, was in fact adapted for a synthesis of the highly functionalized mitomycin K.

Discussion of Results

Our research began with the assemblage of dienyl nitroso systems as substrates for intramolecular cycloaddition reactions. *In focusing on compounds* ***9****, we anticipated the possibility of unveiling the nitroso function with the diene already present via a photochemically driven redox reaction of an o-nitrobenzyl alcohol prototype.*[14] Reaction of *o*-nitrobenzaldehydes **13** and **14** with (1-methoxy-1,3-butadienyl)lithium[15] (**15**) provided carbinols **16** and **17**. Photolysis of the photosensitive *o*-nitrobenzyl groups then led to compounds **20** and **21** presumably via the intermediate dienyl nitroso systems **18** and **19** (Scheme II). Thus, cycloaddition had occurred at room temperature to give, perhaps not surprisingly,[16] exclusively the fused mode adducts.[17] The structure of the former was rigorously demonstrated to be as shown by a single-crystal X-ray determination.[18] The structure of the latter followed from the close similarity of its ^{1}H NMR spectrum with that of **20**.

Scheme III



Given this finding, it seemed reasonable to incorporate the "pre-mitomycin" functionality on the aromatic ring. Accordingly, addition of the butadienyl anion **15** to 2,3,5-trimethoxy-4-methyl-6-nitrobenzaldehyde (**22**) gave the nitro diene **23** (Scheme III). Interestingly, the photolysis of **23** gave very little of the expected oxazine **24**. In its stead, the pyrroloindoxyl derivative **25** was isolated as the major product. Initially, the difference in the photolysis outcome of substrates **20** (or **21**) versus **22** was observed under identical conditions (250 nm; Hg/Vycor filter). Subsequently, for preparative purposes, in the case of **22**, photolysis conditions were modified (Rayonet system; 350 nm). Higher conversions to **25** were achieved using the more specific wavelength. Although not established as an obligatory intermediate in the production of **25**, the small amount of oxazine **24** isolated from the same reaction was independently converted to **25**.

Initially, it was felt that the hemiaminal of **25** could be deoxygenated in preference to the C-9a methoxyaminal following procedures used for the reduction of carbinolamines. Unfortunately, these conditions failed to accomplish this. Also, protocols involving acylation of the hemiaminal hydroxyl followed by reduction were accompanied by elimination of the angular methoxy at C-9a, resulting in what was deemed to be a ring C pyrrole.

With the hope that the system might enjoy greater stability if the C-1–C-2 double bond were functionalized, compound **25** was treated with osmium tetraoxide. The reaction was stereospecific, resulting in formation of the diol derived from attack of the reagent from the concave face of structure **25** (Scheme IV).[19] Compound **26** is the undesired diol isomer from the standpoint of forming the aziridine by sequences involving the incorporation of a nitrogen functionality by S_N2 displacement reactions.

Knowledge of the facial bias of system such as **25** thus provided the incentive to explore reactions that would deliver the nitrogen required for the aziridine in the step to functionalize the olefin. It was anticipated that this reaction might show the same facial

(14) Applications of *o*-nitrobenzyl protective groups have been reviewed as part of the general practice of photosensitive protective groups; see: (a) Amit, B.; Zehavi, U.; Patchornik, A. *Isr. J. Chem.* **1974**, *12*, 103. (b) Sammes, P. G. *Q. Rev. Chem. Soc.* **1970**, *24*, 34.

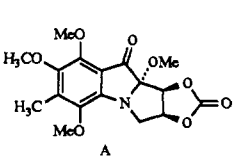
(15) (a) Everhardus, R. H.; Gräfing, R.; Brandsma, L. *Recl. Trav. Chim. Pay-Bas* **1978**, *97*, 69. (b) Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1989**, *111*, 1577.

(16) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: New York, 1990; p 140 ff.

(17) For an example of an intramolecular Diels–Alder reaction with the potential of forming either the bridged or fused adduct, in which the bridged product was formed in preference to the fused one, see: Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245.

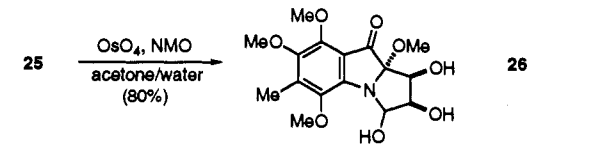
(18) Experimental details, Pluto drawings, and tables containing fractional coordinates, temperature factors, bond distances and angles, and torsional angles for the X-ray crystallographic analysis of **20** were previously published as supplementary material; see ref 13a.

(19) The stereochemical assignment was based on the X-ray crystallographic determination of the cyclic carbonate **A**. Details of the crystallographic analysis are available as supplementary material.

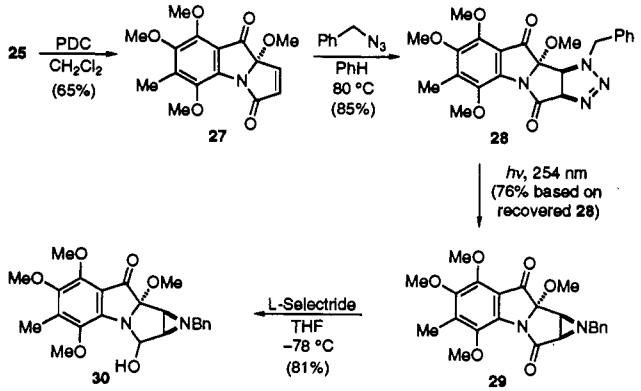


A

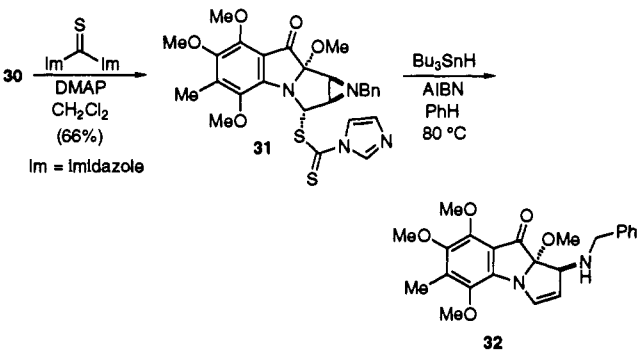
Scheme IV



Scheme V



Scheme VI



selectivity as the osmylation, thereby incorporating the nitrogen with the proper relative stereochemistry for the aziridine. As nitrene equivalents for direct aziridination are generally impractical in these pursuits, the 1,3-dipolar cycloaddition reactions of alkyl azides were examined.

Accordingly, compound **25** was oxidized (PDC) to afford a 65% yield of imide **27** (Scheme V). Following the close precedent provided by Franck[20] on a less substituted 3*H*-pyrrolo[1,2-*a*]-indol-3-one, imide **27** was converted to triazoline **28** with benzyl azide at 80 °C in benzene. Irradiation of **28** (254 nm; Vycor filter) provided a 9:1 mixture (^{1}H NMR) of aziridine **29** and the starting triazoline in 76% yield. Aziridine **29** underwent reduction with L-Selectride to afford a 81% yield of carbinolamine **30**.

Reaction of **30** with 1,1′-(thiocarbonyl)diimidazole in the presence of DMAP afforded thionothiaimidazolide **31** in 66% yield. The curious transformation of **30** → **31** presumably proceeds through rearrangement of the initial thionoimidazolide into the corresponding thiol ester (Scheme VI). The latter apparently undergoes acyl exchange under the conditions of the reaction to produce **31**. The structure of **31** was then confirmed by X-ray crystal analysis.[21] Unfortunately, Barton deoxygenation[22] of **31** led to what appeared to be[23] allylic amine **32** via a fragmentation pathway.

Given the likely propensity of β-aziridino radicals toward fragmentation, the deoxygenation of a triazoline substrate was investigated. In addition, the triazoline was now prepared with an azide source that might more readily lead to an *N*-methylaziridine. Thus, reaction of imide **27** with (phenylthio)methyl azide[24] gave a 90% yield of triazoline **33** (Scheme VII). Reduction of **33** with L-Selectride gave carbinolamine **34**, which upon acylation with 1,1′-(thiocarbonyl)diimidazole in the presence of DMAP provided thionothiaimidazolide **35** in 50% overall yield. Fortunately, reductive cleavage of the thionothiaimidazolide linkage of **35** could now be carried out through the agency of tri-*n*-butyltin hydride, thereby affording the deoxygenated compound **36** (52%). This, however, was not accomplished without the concomitant formation of small amounts (13%) of the fragmentation product **37**. Thus, while triazoline **35** was indeed less susceptible to cleavage than aziridine **31**, the fragmentation pathway could not be entirely eliminated. Interestingly, the fragmentation of triazoline **35**, unlike *N*-benzylaziridine **31**, did not terminate with an alkyl-substituted amine. Possibly, concurrently with the loss of nitrogen, the thiophenyl group was extruded, and the resultant imine was hydrolyzed to give **37**.

Photolytic conversion of triazoline **36** to aziridine was accomplished in 48% yield by irradiation at 254 nm (Vycor filter). The remainder of the material was quite polar and resisted characterization. It should be noted that the yields of the triazoline → aziridine transformation were lower than those of the corresponding benzyl cases. However, this yield loss was acceptable since the resultant aziridine **38** was converted in 70% yield to the desired *N*-methylaziridine derivative **39** through the action of Raney nickel.

With this chemistry successfully accomplished, we defined as our specific target mitomycin K (Figure 3). As a new member in a rapidly growing series of mitomycins, mitomycin K has a methylene group at C-9 unlike the more traditional congeners (cf. **3**).[25] The presence of this exo olefin poses still another locus of potential structural vulnerability and may confer electrophilicity to the compound even in the absence of reductive activation by virtue of its conjugation with the quinone.

The program for installation of C-10 was launched by reaction of **39** with ((trimethylsilyl)methyl)lithium (Scheme VIII).[26] This process proceeded quite cleanly to give rise to a 90% yield of the adduct **40** as a single stereoisomer. The transformation of **40** to quinone **41** proved more challenging. Reaction of **40** with silver(II) dipicolinate[27] afforded **41**, but in only 16% yield. Attempts to improve this step (CAN; DDQ, Fremy salt) gave, at best, single-digit yields of **41**. To improve on this synthesis, it would be necessary to go back to the beginning and use a variant of **22** in which the 3 and 6 oxygens of the benzylaldehyde were protected differently. In this way, phenolic variants of **40** might become accessible for smoother production of **41**.

In the last step of the synthesis, quinone **41** responded to the action of PPTS in methylene chloride to provide an 81% yield of the racemic mitomycin K (mp 123–125 °C). *The IR, ^{1}H NMR, and ^{13}C NMR spectra of the racemic synthetic mitomycin K were identical with those from a sample procured by partial synthesis via the naturally occurring N-methylmitomycin A.*[28]

(20) Siuta, G. J.; Franck, R. W.; Kempton, R. J. *J. Org. Chem.* **1974**, *39*, 3739.

(21) Details for the X-ray crystallographic analysis are available upon request from the Director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, G-B Cambridge, CB21EW UK, on quoting the full journal citation in footnote 13b.

(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.

(23) A ^{1}H NMR spectrum and a low-resolution MS consistent with **32** were obtained.

(24) (a) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2483. (b) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648.

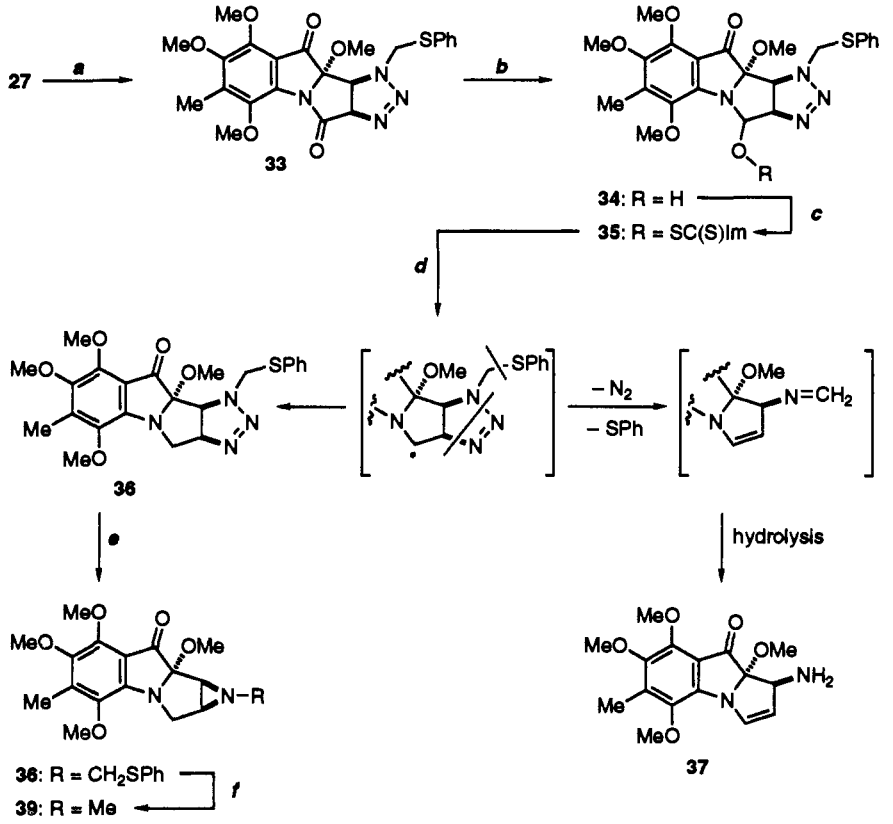
(25) (a) Kono, M.; Kasai, M.; Shirahata, K. *Synth. Commun.* **1989**, *19*, 2041. (b) Urakawa, C.; Tsuchiya, H.; Nakano, K. *J. Antibiot.* **1981**, *34*, 1152.

(26) (a) Ager, D. J. *Synthesis* **1984**, 384. (b) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

(27) Kloc, K.; Mlochowski, J.; Syper, L. *Chem. Lett.* **1980**, 725.

(28) Egbertson, S. Part I: Studies Concerning the Reductive Activation of Mitomycins. Ph.D. Thesis, Yale University, May, 1989.

Scheme VII[a]



[a] (a) $PhSCH_2N_3$, PhH, 80 °C, 90%. (b) L-Selectride, THF, −78 °C, 77%.

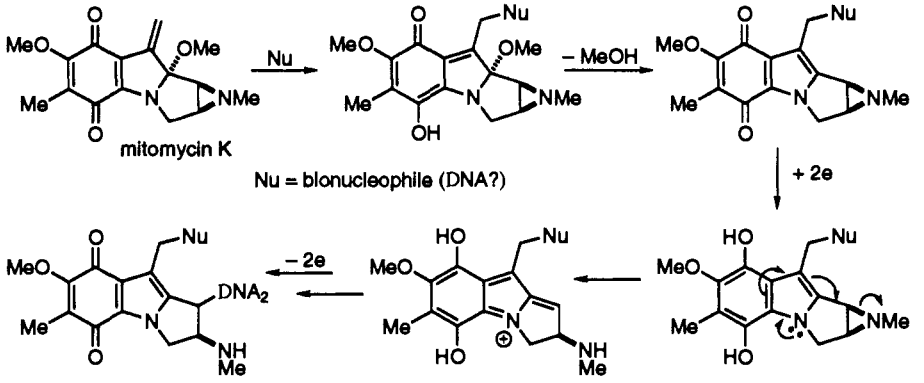
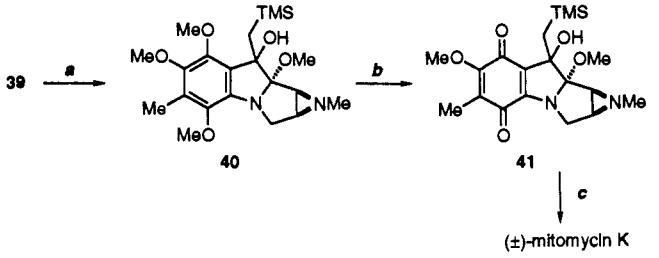


Figure 3.

Scheme VIII[a]



[a] (a) ((Trimethylsilyl)methyl)lithium, THF, −10 °C, 90%. (b) Silver(II) dipicolinate, NaOAc, CH_3CN/H_2O, 8–16%. (c) PPTS, CH_2Cl_2, 81%. (c) 1,1′-(Thiocarbonyl)diimidazole, DMAP, CH_2Cl_2, 35 °C, 65%. (d) Bu_3SNH, AIBN, PhH, 80 °C, 52% of **36** and 13% of **37**. (e) 254 nm, Hg lamp/Vycor filter, PhH in quartz tube, 48%. (f) Raney nickel, acetone, 60 °C, 70%.

Conclusions

A highly concise synthesis of the densely functionalized mitomycin K has been accomplished. Obviously, the low yield for the oxidation of **39** to quinone **40** in the latter stages of the synthesis was disappointing. Undoubtedly, this transformation would benefit greatly from the incorporation of an aromatic ring with differentiated and more readily deprotectable oxygen substituents.

This low yield notwithstanding, some rather novel and interesting chemistry was developed in our synthesis. Most notable in this regard is the one-step conversion of nitrobenzenemethanol derivative **23** to pyrroloindolone **25**. As perhaps the most rapid known assembly of an angularly functionalized pyrrolo[1,2-*a*]-indole system, this remarkable transformation begins with a photochemical redox generation of a dienyl nitroso system, which undergoes a [4 + 2] cycloaddition and subsequent rearrangement. Another noteworthy feature of this chemistry is the sensitivity to the photocleavage of the N–O bond of systems such as **11** to subtle variations in functional groups on the aromatic ring (compare the reactions of **16**, **17**, and **23**).

Also to be emphasized is the protocol developed to prepare the *N*-methylaziridine. The use of (phenylthio)methyl azide in a

1,3-dipolar cycloaddition with imide **27** provided a triazoline (**28**), which could be converted to an *N*-methylaziridine. The difference in the performances of compounds **31** and **35** with respect to the deoxygenation verses the deoxygenation and fragmentation was a key element in the successful application of this new method to the case at hand. It is our expectation that this chemistry will facilitate the study of the chemical behavior and the mechanism of action of decarbamoyloxy mitomycins.

Experimental Section

Melting points were determined using a Thomas-Hoover melting-point apparatus and are uncorrected. Ultraviolet (UV) spectra were obtained using a Varian Cary 219 spectrophotometer. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1420 spectrometer and a Nicolet SX FTIR spectrometer. Low-resolution mass spectra were obtained using a Hewlett-Packard HP-5989A MS Engine mass spectrometer; high-resolution mass spectra were obtained using a Kratos MS80RFA mass spectrometer. Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker WM-250 spectrometer. X-ray crystallographic diffraction measurements were made on a four-circle Rigaku AFC5S fully automated diffractometer, and the structure solutions were accomplished using a Digital VAX station II. Combustion analyses were performed by Robertson Laboratory, Inc., Madison, NJ.

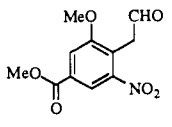
The continuous wave IR spectra were calibrated to 1601 cm^{-1} using a polystyrene film standard. IR intensities are expressed subjectively as strong (s), medium (m), and weak (w). NMR chemical shifts are given in parts per million (ppm) downfield from an internal tetramethylsilane (TMS) standard or relative to internal $CHCl_3$. Proton NMR (^1H NMR) are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), number of protons, and coupling constant(s) in hertz. When appropriate, the multiplicities are preceded by br, indicating that the signal was broad. Except for those high-resolution mass spectra indicated as requiring fast atom bombardment (FAB) ionization, all mass spectra were achieved by electron ionization (EI).

Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Methylene chloride, benzene, triethylamine, pyridine, and acetonitrile were distilled under a nitrogen atmosphere from calcium hydride. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under an inert atmosphere and stored over 3- or 4-Å molecular sieves. Solutions of *tert*-butyllithium in pentane were titrated regularly before use with 2,5-dimethoxybenzyl alcohol at 0 °C in THF.[29]

Chromatographic purifications were performed with EM Science (E. Merck) 230–400-mesh silica gel. Reactions and chromatography fractions were monitored and analyzed by thin-layer chromatography (TLC) using EM Science (E. Merck) 250-μm 60 F_{254} silica plates.

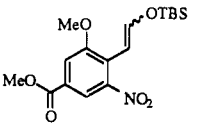
Synthesis of Aldehyde 13. Aldehyde **13** was prepared by Leimgruber–Batcho homologation[30] of 3-methoxy-4-methyl-5-nitrobenzoic acid methyl ester followed by silyl enol ether formation and ozonolysis. The experimental procedure for this process is described below.

3-Methoxy-5-nitro-4-(2-oxoethyl)benzoic Acid Methyl Ester. To a stirred solution of 3-methoxy-4-methyl-5-nitrobenzoic acid methyl ester[31] (7.61 g, 33.8 mmol) in 76 mL of *N,N*-dimethylformamide (DMF) was added *N,N*-dimethylformamide dimethyl acetal (22.4 mL, 169 mmol) at room temperature. The mixture was then heated at 100 °C for 3 h, diluted



with 200 mL of water, and extracted several times with benzene. The benzene extracts were washed several times with water and dried over $MgSO_4$. Filtration and concentration *in vacuo* provided the crude enamine as a deep red oil. Hydrolysis to the aldehyde was achieved by dissolving the crude enamine in 300 mL of THF and 50 mL of water followed by the addition of 30 mL of 1.0 N HCl. The resulting mixture was stirred for 30 min at room temperature before diluting with water and extracting the mixture several times with CH_2Cl_2. The extracts were washed with water and dried over $MgSO_4$. Filtration and removal of the solvent gave the crude aldehyde. Purification by flash column chromatography (1:1 Et_2O/hexanes) gave 7.8 g (91%) of the aldehyde as a colorless solid: mp 95–96 °C; R_f = 0.21 (1:1 Et_2O/hexanes); IR ($CHCl_3$) 1730 (s), 1540 (s), 1360 (m), 1310 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 3.98 (s, 3 H), 4.16 (s, 2 H), 7.80 (d, 1 H, J = 1.4 Hz), 8.27 (d, 1 H, J = 1.4 Hz), 9.77 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 40.68, 52.74, 56.74, 115.06, 117.65, 122.17, 130.91, 150.26, 58.46, 164.75, 196.04; MS (EI, 20 eV) m/z (M^+) 253 (11), 208 (100), 150 (78). Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.41; H, 4.43; N, 5.27.

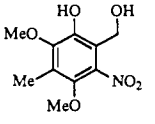
(*E*)-4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethenyl]-3-methoxy-5-nitrobenzoic Acid Methyl Ester. To a stirred solution of 3-methoxy-5-nitro-4-(2-oxoethyl)benzoic acid methyl ester (8.69 g, 34.0 mmol) and Et_3N (14.5 mL, 0.1 mol) in 86 mL of CH_2Cl_2 was added *tert*-butyldimethylsilyl chloride (10.0 g, 66 mmol) in one portion at room temperature. The resulting mixture was stirred for 2 h at room temperature



under a N_2 atmosphere. The reaction was then quenched with 300 mL of saturated aqueous $NaHCO_3$, and the mixture was extracted several times with CH_2Cl_2 (4 × 100 mL). The combined extracts were washed with water and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude silyl enol ether. Purification by flash column chromatography (1:9 EOAc/hexanes) gave 10.9 g (87%) of the silyl enol ether as a light yellow solid: mp 82–85 °C; R_f = 0.46 (1:1 Et_2O/hexanes); IR ($CHCl_3$) 2960 (w), 1730 9s), 1640 (m), 1610 (w), 1540 (s), 1310 (s), 1250 (s), 1160 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) *E*/*Z* ratio (94:6) δ 0.22 (s, 6 H), 0.95 (s, 9 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.10 (d, 1 H, J = 11.8 Hz), 7.55 (d, 1 H, J = 11.8 Hz), 7.64 (d, 1 H, J = 1.4 Hz), 7.90 (d, 1 H, J = 1.4 Hz); MS (EI, 20 eV) m/z (M^+) 367 (1), 350 (53), 310 (93), 251 (33), 207 (61), 75 (100). Anal. Calcd for $C_{17}H_{25}NO_6Si$: C, 55.57; H, 6.86; N, 3.81. Found: C, 55.33; H, 6.86; N, 3.74.

4-Formyl-3-methoxy-5-nitrobenzoic Acid Methyl Ester (13). Ozone gas was bubbled through a cold (–78 °C), yellow solution of (*E*)-4-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethenyl]-3-methoxy-5-nitrobenzoic acid methyl ester (1.5 g, 4.1 mmol) in 15 mL of MeOH/CH_2Cl_2 (1:2) until the solution appeared faintly blue. A stream of N_2 gas was then bubbled through the reaction mixture until the blue color had dissipated. To this now colorless, stirred solution was added dropwise ca. 2 mL of Me_2S at –78 °C. The mixture was then slowly warmed to room temperature and stirred overnight (8 h). Concentration *in vacuo* provided the crude aldehyde as a lightly colored solid. Purification by flash column chromatography (1:1 Et_2O/hexanes) or recrystallization (EtOAc) gave 850 mg (88%) of pure **13** as a colorless solid: mp 113–115 °C; IR ($CHCl_3$) 1730 (s), 1710 (s), 1540 (s), 1460 (m), 1300 (s), 1250 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.00 (s, 6 H), 7.89 (d, 1 H, J = 1 Hz), 8.15 (d, 1 H, J = 1 Hz), 10.39 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 53.10, 56.99, 116.46, 116.87, 124.34, 134.66, 148.20, 159.31, 164.07, 187.27; MS (EI, 20 eV) m/z (M^+) 239 (13), 209 (100), 166 (21), 139 (26). Anal. Calcd for $C_{10}H_9NO_6$: C, 50.22; H, 3.79; N, 5.86. Found: C, 50.01; H, 3.66; N, 5.57.

Synthesis of Aldehyde 22. 2-Hydroxy-3,5-dimethoxy-4-methyl-6-nitrobenzenemethanol. A solution of 2.68 g (12.6 mmol) of 2,4-dimethoxy-3-methyl-5-nitrophenol[32] in 25 mL of *tert*-butyl alcohol was treated sequentially with 5.0 mL (15.0 mmol) of a 3.0 N aqueous KOH solution and 15.3 mL (18.9 mmol) of a 37% aqueous formaldehyde solution. The



resulting red–orange solution was heated at gentle reflux for 12 h and then cooled to room temperature. The solution was concentrated *in vacuo*

(29) Winkle, M. R.; Lansinger J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

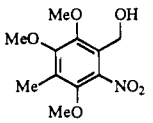
(30) For a review of the Leimgruber–Batcho indole synthesis, see: Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.

(31) Harris, C. M.; Kibby, J. J.; Fehlner, J. R.; Raabe, A. B.; Barber, T. A.; Harris, T. M. *J. Am. Chem. Soc.* **1979**, *101*, 437.

(32) Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835.

to one-quarter of the original volume, diluted with EtOAc (50 mL), and acidified to pH = 3 with 10% aqueous HCl. The layers were separated, and the organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (180 g of SiO_2; 40% EtOAc/hexanes) to provide 2.62 g (86%) of the diol as a light yellow solid: mp 85–87 °C; R_f = 0.42 (50% EtOAc/hexanes); IR (CH_2Cl_2) ν 3580, 3510, 2945, 1538, 1462, 1415, 1373, 1197, 1120, 1090, 1010 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 2.46 (t, 1 H, J = 6.5 Hz), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.69 (d, 2 H, J = 6.4 Hz), 6.55 (s, 1 H); MS (EI, 20 eV) m/z 243, 225, 196, 179, 151, 109, 83; high-resolution MS m/z calcd for $C_{10}H_{13}NO_6$ (M^+) 243.0743, found 243.0746. Anal. Calcd for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.36; H, 5.35; N, 5.70.

2,3,5-Trimethoxy-4-methyl-6-nitrobenzenemethanol. A solution of 2.52 g (10.4 mmol) of 2-hydroxy-3,5-dimethoxy-4-methyl-6-nitrobenzenemethanol in 52 mL of DMF was treated sequentially with 1.58 g (11.4 mmol) of solid K_2CO_3, and this mixture was stirred for 1 h to produce a red–orange suspension. To this suspension was added 1.77 g (12.5 mmol)



of methyl iodide, and stirring was continued for 12 h. The solids were dissolved in water (10 mL), and saturated aqueous NH_4Cl (15 mL) was added. This mixture was extracted with EtOAc (80 mL), and the organic layer was washed with brine (2 × 50 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (180 g of SiO_2; 25% EtOAc/hexanes) to provide 2.17 g (81%) of the methyl ether as a thick oil: R_f = 0.44 (40% EtOAc/hexanes); IR (neat) ν 3460 (br), 2950, 1535, 1465, 1409, 1375, 1338, 1260, 1123, 1100, 1050, 1019, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 2.36 (t, 1 H, J = 6.8 Hz), 3.83 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.59 (d, 2 H, J = 6.8 Hz); MS (EI, 20 eV) m/z 257, 240, 206, 181, 166, 151, 124, 108, 91; high-resolution MS m/z calcd for $C_{11}H_{15}NO_6$ (M^+) 257.0899, found 257.0911. Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.44. Found: C, 51.37; H, 5.77; N, 5.33.

2,3,5-Trimethoxy-4-methyl-6-nitrobenzaldehyde (22). To a vigorously stirred suspension of 2.07 g (8.05 mmol) of 2,3,5-trimethoxy-4-methyl-6-nitrobenzenemethanol and 4.00 g of Celite in 53 mL of CH_2Cl_2 was added 2.60 g (12.1 mmol) of pyridinium chlorochromate. After 6 h of being stirred, the solids were removed by filtration through a layered pad of Celite/SiO_2/Florisil and the solids were washed thoroughly with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (100 g of SiO_2; 35% EtOAc/hexanes) to provide 1.92 g (94%) of aldehyde **22** as an orange solid: mp 90–92 °C; R_f = 0.35 (16% $CHCl_3$/34% EtOAc/50% hexanes); IR (CH_2Cl_2) ν 2950, 2890, 1698, 1600, 1549, 1470, 1387, 1335, 1260, 1138, 1098, 1057, 990, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 3.99 (s, 3 H), 10.24 (s, 1 H); MS (EI, 20 eV) m/z 255, 238, 208, 195, 179, 166, 137, 109, 91; high-resolution MS m/z calcd for $C_{11}H_{13}NO_6$ (M^+) 255.0743, found 255.0747. Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.63; H, 5.08; N, 5.45.

General Procedure for the Addition of (1-Methoxy-1,3-butadienyl)-lithium (15) to *O*-Nitrobenzaldehyde, 4-Formyl—3-methoxy-5-nitrobenzoic Acid Methyl Ester (13), and 2,3,5-Trimethoxy-4-methyl-6-nitrobenzaldehyde (22). To a cold (–78 °C), stirred solution of 1.2 molar equiv of 1-methoxy-1,3-butadiene (0.5 M in THF) was added dropwise 1.1 molar equiv of *tert*-butyllithium as a solution in pentane under a N_2 atmosphere. The resulting brown solution was then allowed to warm to ca. –20 °C over ca. 30 min. After an additional 30 min at this temperature, the mixture was cooled back to –78 °C and then added dropwise via cannula to a previously cooled (–78 °C), stirred solution of nitrobenzaldehyde in THF (0.5 M). The resulting mixture was stirred for 20 min at –78 °C and warmed to 0 °C, and the reaction was quenched with an equal volume of saturated aqueous NH_4Cl. The aqueous mixture was then warmed to room temperature and extracted several times with EtOAc. The combined extracts were washed with water and brine and dried over anhydrous K_2CO_3. Filtration and concentration *in vacuo* gave the crude diene adducts **16**, **17**, and **23**.

(*E*)-(±)-4-(1-Hydroxy-2-methoxy-2,4-pentadienyl)-3-methoxy-5-nitrobenzoic Acid Methyl Ester (16). The crude adduct was purified by flash column chromatography (2:4:4 Et_2O/PhH/hexanes) and then by a second column (45:55 Et_2O/hexanes), providing **16** as a light yellow solid (56%): mp 97–98 °C; UV (MeOH) λ_{max} nm (ϵ) 242 (22 350), 297 (2900), 305 (3000); IR ($CHCl_3$) 3540 (w), 1730 9s), 1540 (s), 1300 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.50 (s, 3 H), 3.96 (s, 3 H), 3.99 (s, 3 H), 4.16 (d, 1 H, J = 11 Hz), 4.93 (dd, 1 H, J = 10, 1.7 Hz), 5.09 (dd, 1 H, J = 16.6, 1.7 Hz), 5.41 (d, 1 H, J = 11 Hz), 6.28 (d, 1 H, J = 11 Hz), 6.71 (ddd, 1 H, J = 16.6, 11, 10 Hz), 7.77 (d, 1 H, J = 1.3 Hz), 7.99 (d, 1 H, J = 1.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.77, 55.03, 56.97, 65.57, 102.91, 113.80, 115.44, 117.86, 127.91, 131.04, 150.85, 156.19, 158.19, 164.72 (one coincidental resonance in the aromatic region); MS (EI, 20 eV) m/z (M^+) 323 (14), 274 (12), 260 (18), 99 (100); high-resolution MS m/z calcd for $C_{15}H_{17}NO_7$ (M^+) 323.1005, found 323.1007.

(*E*)-(±)-α-(1-Methoxy-1,3-butadienyl)-2-nitrobenzenemethanol (17). The crude adduct was purified by flash column chromatography (3:7 Et_2O/hexanes), providing **17** as a light yellow solid (84%): mp 67–69 °C; UV (MeOH) λ_{max} nm (ϵ) 242 (19 800), 369 (700); IR ($CHCl_3$) 3550 (w), 1640 (s), 1520 (s), 1340 (s), 1210 (m), 1140 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.77 (d, 1 H, J = 7.1 Hz), 3.58 (s, 3 H), 5.00 (dd, 1 H, J = 10.2, 1.7 Hz), 5.15 (dd, 1 H, J = 16.8, 1.1 Hz), 5.52 (d, 1 H, J = 10.8 Hz) , 6.35 (d, 1 H, J = 7.1 Hz), 6.63 (ddd, 1 H, J = 16.8, 10.8, 10.2 Hz), 7.43 (td, 1 H, J = 7.7, 1.1 Hz), 7.59 (td, 1 H, J = 7.7, 1.3 Hz), 7.72 (dd, 1 H, J = 7.7, 1.1 Hz), 7.86 (dd, 1 H, J = 7.7, 1.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 54.97, 67.00, 103.84, 114.55, 124.14, 128.28, 129.02, 130.49, 132.52, 135.46, 148.69, 155.57; MS (EI, 20 eV) m/z (M^+) 235 (13), 146 (43), 130 (100), 99 (64), 68 (58). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.24; H, 5.47; N, 5.86.

(±)-(*E*)-2,3,5-Trimethoxy-α-(1-methoxy-1,3-butadienyl)-4-methyl-6-nitrobenzenemethanol (23). The crude adduct was purified by flash column chromatography (20% Et_2OAc/hexanes) to provide **23** as a brown oil (86%): R_f = 0.51 (40% EtOAc/hexanes); IR (neat) ν 3495, 3082, 3005, 2950, 2840, 1647, 1600, 1540, 1467, 1410, 1380, 1258, 1225, 1159, 1122, 1102, 1060, 960, 900, 765 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.22 (s, 3 H), 3.58 (s, 3 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 4.13 (d, 1 H, J = 9.1 Hz), 4.93 (dd, 1 H, J = 10.5, 1.8 Hz), 5.08 (dd, 1 H, J = 16.6, 1.8 Hz), 5.37 (d, 1 H, J = 10.5 Hz), 5.88 (d, 1 H, J = 9.1 Hz), 6.57 (dt, 1 H, J = 16.6, 10.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 9.6, 54.9, 60.0, 61.1, 62.5, 66.1, 102.5, 113.9, 124.7, 127.2, 130.6, 141.3, 146.4, 147.6, 153.4, 156.2; MS (EI, 20 eV) m/z 339, 262, 232, 204, 176, 149, 136, 99; high-resolution MS m/z calcd for $C_{16}H_{21}NO_7$ (M^+) 339.1318, found 339.1325. Anal. Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.38; H, 6.11; N, 4.03.

General Procedure for the Photochemical Generation of the [1,2]-Oxazino[2,3-*a*]indolone Structures 20 and 21. A stirred solution of the nitro diene in MeOH (0.01 M), which had been degassed with N_2, was irradiated with a Hanovia medium-high pressure lamp (PC 451050/7825-34) through a Pyrex filter at room temperature under an N_2 atmosphere. The reaction was monitered by thin-layer chromatography (TLC) until completion. Concentration of the reaction mixture gave the crude oxazines.

(±)-4a,5-Dihydro-4a,6-dimethoxy-5-oxo-2*H*-[1,2]oxazino[2,3-*a*]indole-8-carboxylic Acid Methyl Ester (20). The crude material was purified by flash column chromatography (6:4 Et_2O/hexanes), providing **20** as a light yellow solid (60%). Crystals suitable for X-ray analysis of **20** could be obtained by slow evaporation of a benzene solution at 23 °C:[33] mp 177–179 °C dec; R_f = 0.31 (8:2 Et_2O/hexanes); UV (MeOH) λ_{max} nm (ϵ) 215 (12 500), 234 (11 400), 301 (3100), 367 (600); IR ($CHCl_3$) 3020 (m), 1720 (s), 1620 (m), 1600 (s), 1340 (s), 1260 (s), 1230 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.41 (s, 3 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 4.20 (dd, 1 H, J = 16.6, 4.7 Hz), 4.44 (br d, 1 H, J = 16.6 Hz), 5.88 (br d, 1 H, J = 10.5 Hz), 6.18 (dd, 1 H, J = 10.5, 4.7 Hz), 7.19 (d, 1 H, J = 1 Hz), 7.56 (d, 1 H, J = 1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.56, 52.83, 56.38, 61.75, 90.94, 105.79, 107.52, 114.17, 121.70, 130.27, 139.59, 157.76, 158.49, 165.67, 189.89; MS (EI, 20 eV) m/z (M^+) 305 (26), 276 (76), 246 (69), 99 (100). Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.02; H, 5.95; N, 4.59. Found: C, 59.28; H, 4.94; N, 4.44.

(±)-2,4a-Dihydro-4a-methoxy-5*H*-[1,2]oxazino[2,3-*a*]indol-5-one (21). The crude material was purified by flash column chromatography (35:65 Et_2O/hexanes) to yield **21** as a yellow oil (75%): IR ($CHCl_3$) 1720 (s), 1610 (s), 1470 (m), 1450 (m), 1320 (m), 1300 (m), 1140 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.43 (s, 3 H), 4.18 (ddd, 1 H, J = 16.6, 4.7, 1.8 Hz), 4.37 (dt, 1 H, J = 16.6, 1.8 Hz), 5.88 (dt, 1 H, J = 10.6, 1.8 Hz), 6.18 (ddd, 1 H, J = 10.6, 4.7, 1.8 Hz), 7.15 (t, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.68 (t, 1 H, J = 8.0 Hz), 7.73 (d, 1 H, J =

(33) Details of the X-ray crystallographic analysis of compound **20** are available as supplementary material.

8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.57, 61.17, 90.65, 114.99, 121.93, 123.24, 123.66, 125.20, 130.44, 137.23, 156.69, 192.36; MS (EI, 20 eV) m/z (M^+) 217 (19), 188 (100), 157 (53), 130 (86). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.4. Found: C, 66.27; H, 4.97; N, 6.34.

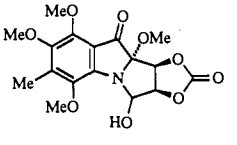
Procedure for the Photochemical Generation of the [1,2]Oxazino[2,3-*a*]indolone Structure 24 and Pyrrolo[1,2-*a*]indolone 25. A solution of 0.260 g (380 mmol) of the nitro diene in 76 mL of THF was degassed for 30 min with a stream of argon. The stirred solution was irradiated in a Rayonet system with four 350-nm lamps for 15 h. The resulting orange solution was concentrated, and the residue was purified by flash chromatography (25 g SiO_2; 50% EtOAc/hexanes) to provide 0.037 g (15%) of **24** (R_f = 0.47) and 0.111 g (45%) of **25** (R_f = 0.47).

(±)-2,4a-Dihydro-4a,6,7,9-tetramethoxy-8-methyl-5*H*-[1,2]oxazino-[2,3-*a*]indol-5-one (24): UV (CH_3OH) λ_{max} nm (ϵ) 214 (18 976), 239 (21 536), 288 (8132), 367 (3057), 382 (3057); IR (neat) ν 2942, 2840, 1724, 1650, 1597, 1485, 1403, 1290, 1152, 1112, 1090, 1032, 988, 950, 860, 790 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 3.43 (s, 3 H), 3.80 (s, 3 H), 3.91 (s, 3 H), 3.99 (s, 3 H), 4.18–4.30 (m, 2 H), 5.82 (dt, 1 H, J = 10.3, 1.9 Hz), 6.24 (ddd, 1 H, J = 10.3, 4.4, 1.9 Hz); MS (EI, 20 eV) m/z 321, 279, 234, 167, 149, 99. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.67; H, 5.91; N, 4.26.

(±)-3,9a-Dihydro-3-hydroxy-5,7,8,9a-tetramethoxy-6-methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (25): R_f = 0.23 (40% EtOAc/hexanes); IR (neat) ν 3420, 3153, 3920, 3815, 1713, 1598, 1470, 1400, 1282, 1080, 1028, 1010, 975, 930, 811, 740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 3.34 (s, 3 H), 3.41 (br d, 1 H, J = 4.8 Hz), 3.74 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 5.58 (br d, 1 H, J = 4.8 Hz), 5.99 (d, 1 H, J = 5.6 Hz), 6.07 (dd, 1 H, J = 5.6, 1.7 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 194.2, 149.7, 147.4, 146.3, 142.4, 137.5, 135.3, 129.1, 114.8, 104.0, 92.2, 61.7, 60.8, 59.3, 51.8, 10.4; MS (EI, 20 eV) m/z 322, 278, 263, 234, 210, 182, 137, 109; high-resolution MS m/z calcd for $C_{16}H_{19}NO_6$ (M^+) 312.1213, found 321.1195. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.57; H, 6.02; N, 4.25.

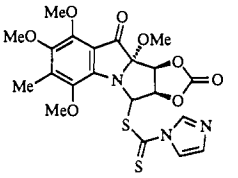
(±)-(1aα,2aα,9aα)-1,2,3,9a-Tetrahydro-1,2,3-trihydroxy-5,7,8,9a-tetramethoxy-6-methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (26). A solution of 0.400 g (1.25 mmol) of aminal **25** and 0.219 g (1.87 mmol) of *N*-methylmorpholine *N*-oxide in an 8:1 mixture of acetone/water (25 mL) was stirred as a solution of osmium tetraoxide (0.196 M in THF, 0.636 mL, 0.125 mmol) was added dropwise. After 16 h, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and this mixture was stirred for 15 min prior to extraction with EtOAc (3 × 40 mL). The organic layers were washed with brine (20 mL), and the combined aqueous layers were back-extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (40 g of SiO_2; 80% EtOAc/hexanes) to provide 0.354 g (80%) of a 6:1 mixture of triols (^{1}H NMR, major δ 5.12/minor δ 5.41). **Major diastereomer**: R_f = 0.12 (75% EtOAc/hexanes); IR (neat) ν 3410, 2980, 2980, 2935, 2830, 1715, 1603, 1483, 1450, 1402, 1280, 1268, 1115, 1091, 911, 741 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.12 (dd, 1 H, J = 6.1, 3.7 Hz), 4.35 (m, 1 H), 4.29 (t, 1 H, J = 3.7 Hz), 4.02 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.72 (d, 1 H, J = 3.7 Hz), 3.24 (s, 3 H), 2.86 (d, 1 H, J = 2.9 Hz), 2.74 (d, 1 H, J = 6.1 Hz), 2.28 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.5, 151.5, 146.5, 145.4, 141.4, 137.8, 116.2, 100.5, 92.5, 79.1, 75.0, 61.9, 60.9, 60.3, 50.7, 10.7; MS (EI, 20 eV) m/z (rel. intensity) 355 (44), 312 (4), 266 (100), 252 (38), 208 (13), 192 (9), 162 (4), 129 (4), 83 (8); high-resolution MS m/z calcd for $C_{16}H_{21}NO_8$ (M^+) 355.1267, found 355.1280.

Synthesis of Compound A. (±)-(3aα,10aα,10bα)-3a,4,10a,10b-Tetrahydro-4-hydroxy-6,8,9,10a-tetramethoxy-7-methyl-2-oxo-1,3-dioxolo-[4′,5′:3,4]pyrrolo[1,2-*a*]indol-10(1*H*)-one. To a solution of 0.330 g (0.930 mmol) of **26** and a catalytic amount of *N*,*N*-dimethylaminopyridine in 18.6 mL of CH_2Cl_2 was added 0.166 g (1.02 mmol) of 1,1′-carbonyldiimidazole. After 3 h, the mixture was concentrated to one-quarter



volume and this solution was partitioned between EtOAc/water (40 mL). The organic phase was washed with brine (15 mL), and the combined aqueous layers were back-extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (30 g of SiO_2; 50% EtOAc/hexanes) to provide 0.251 g (71%) of the cyclic carbonate: R_f = 0.40 (75% EtOAc/hexanes); IR ν 3445, 3000, 2940, 2840, 1805, 1715, 1600, 1482, 1398, 1280, 1083, 980, 768, 740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.96 (d, 1 H, J = 5.3 Hz), 5.25 (AB q, 2 H, J_{AB} = 6.2 Hz, $\Delta\nu$ = 12.4 Hz), 4.03 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.30 (s, 3 H), 2.69 (d, 1 H, J = 5.3 Hz), 2.26 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190.7, 152.4, 147.5, 145.9 (OCO_2, one aromatic C), 140.2, 139.1, 113.6, 102.8, 90.3, 87.6, 84.2, 62.0, 60.9, 59.7, 51.4, 10.6; MS (EI, 20 eV) m/z (rel. intensity) 381 (4), 334 (5), 107 (1), 85 (42), 83 (66); high-resolution MS m/z calcd for $C_{17}H_{19}NO_9$ (M^+) 386.1060, found 386.1063.

(±)-(3aα,10aα,10bα)-3a,4,10a,10b-Tetrahydro-6,8,9,10a-tetramethoxy-7-methyl-2,10(1*H*)-dioxo-1,3-dioxolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4-yl Ester of 1*H*-Imidazole-1-carbodithioic Acid. To a solution of 108 mg (0.284 mmol) of the aminal and a catalytic amount of *N*,*N*-dimethylaminopyridine in 5.7 mL of CH_2Cl_2 was added 303 mg (1.70 mmol) of 1,1′-(thiocarbonyl)diimidazole. After being stirred for 14 h, this mixture was



partitioned between EtOAc/water (50 mL) and the organic layer was washed with brine (20 mL). The combined aqueous layers were back-extracted with EtOAc, and the organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (20 g of SiO_2; 50% EtOAc/hexanes) to provide 93 mg (67%) of the thiothionoimidazolide as a yellow foam: R_f = 0.23 (60% EtOAc/hexanes): IR (neat) ν 3105, 2980, 2960, 2928, 2822, 1815, 1718, 1600, 1479, 1400, 1370, 1280, 1145, 1088, 1050, 1002, 833, 732 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (s, 1 H), 7.79 (s, 1 H), 7.17 (s, 1 H), 6.76 (s, 1 H), 5.30 (AB q, 2 H, J_{AB} = 6.4 Hz, $\Delta\nu$ = 46.9 Hz), 4.04 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.29 (s, 3 H), 2.26 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 194.5, 188.7, 151.6, 147.7, 146.5, 145.0, 140.0, 139.5, 135.3, 132.1, 117.4, 113.7, 103.3, 88.4, 83.4, 75.6, 62.0, 60.9, 60.5, 51.9, 10.6. Anal. Calcd for $C_{21}H_{21}N_3O_8S_2$: C, 49.70; H, 4.17; N, 8.28. Found: C, 49.45; H, 4.40; N, 7.99.

(±)-(3aα,10aα,10bα)-3a,4,10a,10b-Tetrahydro-6,8,9,10a-tetramethoxy-7-methyl-2-oxo-1,3-dioxolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-10(1*H*)-one (A). To a solution of 138 mg (0.272 mmol) of the thiothionoimidazolide and 3.70 mg (0.0272 mmol) of AIBN in 5.45 mL of degassed benzene was added 0.220 mL (0.816 mmol) of tri-*n*-butyltin hydride. This was placed in a sand bath at 80 °C, and after 20 min at reflux, the solution was cooled to room temperature. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (30 g of SiO_2; 40% EtOAc/hexanes) to provide 71 mg (72%) of compound A as a yellow crystalline solid: mp 154–156 °C; R_f = 0.18 (60% EtOAc/hexanes); IR (CH_2Cl_2) ν 2990, 2978, 2842, 1810, 1712, 1600, 1479, 1450, 1402, 1275, 1149, 1085, 1023, 795, 740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.31 (dd, 1 H, J = 6.4, 4.2 Hz), 5.08 (d, 1 H, J = 6.4 Hz), 4.66 (d, 1 H, J = 14.8 Hz), 4.02 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.71 (dd, 1 H, J = 14.8, 4.2 Hz), 3.26 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190.8, 152.5, 148.0, 147.3, 145.2, 140.2, 138.78, 113.8, 102.6, 84.6, 82.9, 61.9, 60.9, 59.1, 52.7, 51.7, 10.5; MS (EI, 20 eV) m/z (rel. intensity) 365 (100), 350 (44), 306 (13), 276 (16), 236 (5); high-resolution MS m/z calcd for $C_{17}H_{19}NO_8$ (M^+) 365.1111, found 365.1120. Anal. Calcd for $C_{17}H_{19}NO_8$: C, 55.89; H, 5.24; N, 3.83. Found: C, 55.76; H, 5.08; H, 3.61.

(±)-5,7,8,9a-Tetramethoxy-6-methyl-2*H*-pyrrolo[1,2-*a*]indole-3,9-(9a*H*)-dione (27). To a solution of 0.400 g (1.25 mmol) of aminal **26** in 50 mL of CH_2Cl_2 was added 4.00 g of Celite, and the resulting suspension was stirred vigorously as 4.70 g (1.25 mmol) of pyridinium dichromate was added in one portion. This mixture was stirred for 24 h, and the solids were removed by filtration through a layered pad of silica gel/Celite. The solids were thoroughly washed with EtOAc, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (40 g of SiO_2; 40% EtOAc/hexanes) to provide 0.278 g (70%) of the α,β-unsaturated amide **27** as an off-white solid: mp 110–111.5 °C; R_f = 0.47 (50% EtOAc/hexanes); IR (CH_2Cl_2) ν 3000, 2940, 2835, 1725, 1595, 1470, 1451, 1405, 1290, 1202, 1142, 1118, 1089, 1005, 938, 837 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (d, 1 H, J = 5.8 Hz), 6.33 (d, 1 H, J = 5.8 Hz), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.81 (s, 3 H), 3.41

(s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 188.6, 172.2, 149.3, 147.7, 146.4, 146.0, 137.5, 136.1, 131.3, 119.8, 98.3, 61.9, 60.8, 59.0, 52.2, 11.0; high-resolution MS m/z calcd for $C_{16}H_{18}NO_6$ (M + H^+) 320.1170, found 320.1188. Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.98; H, 5.32; N, 4.30.

(±)-(3aα,10aα,10bα)-1,3a,10a,10b-Tetrahydro-6,8,9,10a-tetramethoxy-7-methyl-1-(phenylmethyl)-1,2,3-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indole-4,10-dione (28). A solution of 0.160 g (0.502 mmol) of the α,β-unsaturated amide **27** and 0.668 g (5.02 mmol) of benzyl azide in 1.70 mL of benzene was heated at 80 °C for 62 h. The solution was cooled to room temperature and concentrated *in vacuo*, and the residue was purified by flash chromatography (40 g of SiO_2; 35% EtOAc/hexanes) to provide 0.194 g (85%) of **28** as a thick oil: R_f = 0.35 (30% EtOAc/30% $CHCl_3$/40% hexanes); IR (CH_2Cl_2) ν 2995, 2915, 2813, 1735, 1717, 1577, 1478, 1402, 1293, 1210, 1145, 1102 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.71 (d, 1 H, J = 9.1 Hz), 4.93 (AB, 2 H, J_{AB} = 14.8 Hz, $\Delta\nu$ = 191.3 Hz), 4.04 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 3.71 (d, 1 H, J = 9.1 Hz), 3.26 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190, 167.6, 149.4, 147.0, 144.1, 139.3, 136.2, 133.7, 129.5 (*Ph*CH_2 Cs)), 128.7 (2 *Ph*CH_2 Cs), 128.2, 117.8, 98.4, 85.9, 62.0, 61.0, 60.8, 60.1, 53.7, 52.2, 11.2; MS (FAB–NOBA) m/z (rel. intensity) 453 (100), 452 (33), 425 (16), 333 (6), 320 (51), 289 (14), 265 (30), 250 (15), 165 (7); high-resolution MS m/z calcd for $C_{23}H_{25}N_4O_6$ (M + H^+) 453.1776, found 453.1792. Anal. Calcd for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.35; N, 12.38. Found: C, 59.71; H, 5.39; N, 11.86.

(±)-(1aα,8aα,8bα)-1a,2,8a,8b-Tetrahydro-4,6,7,8a-tetramethoxy-5-methyl-1-(phenylmethyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2,8(1*H*)-dione (29). A solution of 0.176 g (0.389 mmol) of *N*-benzyltriazoline **28** in a 2.5:1 mixture of benzene/piperylene (7.0 mL) was placed in a quartz tube and degassed with a steady stream of argon. This solution was irradiated with a 254-nm Hanovia MP (Hg) lamp using a Vycor filter for 12 h. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography (20 g of SiO_2; 35% EtOAc/hexanes) to provide 0.125 g (76%) of a light yellow oil which was a 9:1 mixture of aziridine/triazoline (^{1}H NMR). Of this material, 0.032 g was removed and resubjected to the above procedure to provide an analytically pure sample of **29**: R_f = 0.40 (50% EtOAc/hexanes); IR ($CHCl_3$) ν 3010, 3000, 2935, 2830, 1715 (br), 1593, 1478, 1450, 1401, 1288, 1270, 1142, 1080, 1031, 1005 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.81 (s, 3 H), 3.64 (AB, 2 H, J_{AB} = 13.8 Hz, $\Delta\nu$ = 18.7 Hz), 3.40 (s, 3 H), 3.07 (d, 1 H, J = 4.0 Hz), 2.87 (d, 1 H, J = 4.0 Hz), 2.28 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.8, 170.6, 149.0, 147.0, 144.7, 137.8, 137.6, 136.5, 128.4 (2 *Ph*CH_2 Cs), 127.7 (2 *Ph*CH_2 Cs), 127.5, 118.4, 95.7, 62.1, 60.8, 60.1, 59.2, 52.1, 43.5, 40.5, 11.0; MS (FAB–NOBA) m/z (rel. intensity) 425 (47), 424 (30), 393 (6), 333 (12), 307 (11), 289 (10), 2454 (11), 220 (5), 165 (7); high-resolution MS m/z calcd for $C_{23}H_{25}N_2O_6$ (M + H^+) 425.1713, found 425.1744. Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.88; H, 5.74; N, 6.50.

(±)-(1aα,8aα,8bα)-1a,2,8a,8b-Tetrahydro-2-hydroxy-4,6,7,8a-tetramethoxy-5-methyl-1-(phenylmethyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8(1*H*)-one (30). To a solution of 0.093 g (0.219 mmol) of **29** in 4.40 mL of THF at −78 °C was added 0.274 mL (0.274 mmol) of a 1.0 M solution of lithium tri-*sec*-butylborohydride in THF. After 2 h at −78 °C, the excess hydride was quenched by the addition of 2.0 mL of saturated aqueous NH_4Cl and the resulting suspension was warmed to room temperature. The solids were dissolved in water, and the mixture was extracted with EtOAc (2 × 15 mL). The organic layers were washed with brine, and the combined aqueous layers were back-extracted with EtOAc (10 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (20 g of SiO_2; 50% EtOAc/hexanes) to provide 0.076 g (81%) of aminal **30** as a yellow oil: R_f = 0.23 (60% EtOAc/hexanes); IR ($CHCl_3$) ν 3480 (br), 3010, 3000, 2815, 2813, 1708, 1600, 1480, 1450, 1395, 1279, 1147, 1085, 1015 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21 (m, 3 H), 7.17 (m, 2 H), 5.52 (br s, 1 H), 3.91 (s, 3 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.39 (AB, 2 H, J_{AB} = 13.7 Hz, $\Delta\nu$ = 62.9 Hz), 3.29 (s, 3 H), 2.79 (d, 1 H, J = 3.9 Hz, 2.65 (br s, 1 H), 2.65 (d, 1 H, J = 3.9 Hz), 2.23 (s, 3 H); MS (FAB–NOBA) m/z (rel. intensity) 426 (37), 409 (6), 395 (19), 365 (4), 307 (18), 289 (12), 245 (267), 176 (11); high-resolution MS m/z calcd for $C_{23}H_{26}N_2O_6$ (M^+) 426.1792, found 426.1751. Anal. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.14; N, 6.57. Found: C, 64.49; H, 6.26; N, 6.40.

(±)-(1aα,2aα,8aα,8bα)-1,1a,2,8,8a,8b-Hexahydro-4,6,7,8a-tetramethoxy-5-methyl-8-oxo-1(phenylmethyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-2-yl Ester of 1*H*-Imidazole-1-carbodithioic Acid (31). To a solution of 64 mg (0.150 mmol) of aminal **30** and 9 mg (0.075 mmol) of *N*,*N*-dimethylaminopyridine in 3.0 mL of CH_2Cl_2 was added 134 mg (0.751 mmol) of 1,1′-(thiocarbonyl)diimidazole. This solution was stirred at room temperature for 48 h, and then the solvent was removed *in vacuo*. The residue was purified by flash chromatography (20 g of SiO_2; 45% EtOAc/hexanes) to provide 55 mg (66%) of thioimidazolide **31** as a bright yellow solid which produced yellow cubes upon recrystallization from chloroform: mp 141–143 °C dec; R_f = 0.30 (60% EtOAc/hexanes); IR ($CDCl_3$) ν 3010, 2998, 2930, 2825, 1710, 1602, 1472, 1467, 1450, 1406,1 1369, 1275, 1240, 1225, 1147, 1100, 1058, 1010, 837 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.52 (s, 1 H), 7.82 (s, 1 H), 7.22 (m, 3 H), 7.14 (s, 1 H), 7.12 (m, 2 H), 6.27 (s, 1 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.47 (AB, 2 H, J_{AB} = 13.7 Hz, $\Delta\nu$ = 85.2 Hz), 3.25 (s, 3 H), 2.93 (d, 1 H, J = 4.0 Hz), 2.80 (d, 1 H, J = 4.0 Hz), 2.24 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.7, 193.4, 149.0, 147.0, 145.8, 140.4, 138.0, 137.2, 135.4, 131.7, 128.2 (2 *Ph*CH_2 Cs), 127.6 (2 *Ph*CH_2 Cs), 127.2, 117.4, 115.2, 100.5, 74.2, 61.8, 60.8, 60.3, 59.4, 51.6, 49.4, 45.7, 10.5; MS (FAB–NOBA) m/z (rel. intensity) 553 (3), 552 (3), 409 (55), 378 (30), 307 (15), 287 (46), 257 (6), 220 (8), 165 (6); high-resolution MS m/z calcd for $C_{27}H_{29}N_4O_5S_2$ (M + H^+) 553.1582, found 553.1616.

(±)-(3aα,10aα,10bα)-1,3a,10a,10b-Tetrahydro-6,8,9,10a-tetramethoxy-7-methyl-1-[(phenylthio)methyl]-1,2,3-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indole-4,10-dione (33). A solution of 1.24 g (3.89 mmol) of **27** and 6.41 g (38.9 mmol) of (phenylthio)methyl azide in 3.90 mL of benzene was heated at 80 °C for 48 h. After being cooled to room temperature, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (170 g of SiO_2; 40% EtOAc/hexanes) to provide 1.70 g (90%) of ((phenylthio)methyl)triazoline **33** as an orange oil: R_f = 0.50 (60% EtOAc/hexanes); IR ($CHCl_3$) ν 3043, 3000, 3940, 2838, 1720 (br), 1580, 1480, 1450, 1440, 1407, 1292, 1270, 1195, 1150, 1100, 1010, 986, 944, 748, 698 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.28 (m, 3 H), 5.89 (d, 1 H, J = 9.4 Hz), 5.38 (AB, 2 H, J_{AB} = 14.6 Hz, $\Delta\nu$ = 154.5 Hz), 4.47 (d, 1 H, J = 9.4 Hz), 4.00 (s, 3 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.27 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190.3, 166.5, 149.3, 146.9, 144.0, 139.0, 135.6, 133.0. 131.1 (2 *Ph*CH_2 Cs), 128.9 (2 *Ph*CH_2 Cs), 127.4, 117.4, 98.4, 87.0, 61.8, 60.6, 59.8, 58.7, 55.6, 52.1, 11.0; MS (FAB–NOBA) m/z (rel. intensity) 485 (87), 457 (26), 347 (30), 320 (54), 319 (43), 304 (35), 288 (17), 266 (27), 250 (12), 192 (12), 165 (8); high-resolution MS m/z calcd for $C_{23}H_{25}N_4O_6S$ (M + H^+) 485.1497, found 485.1524. Anal. Calcd for $C_{23}H_{24}N_4O_6S$: C, 57.01; H, 4.99; N, 11.56. Found: C, 56.78; H, 4.96; N, 11.27.

(±)-(3aα,4α,10aα,10bα)-3a,4,10a,10b-Tetrahydro-4-hydroxy-6,8,9,-10a-tetramethoxy-7-methyl-1-[(phenylthio)methyl]-1,2,3-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-10(1*H*)-one (34). A solution of 1.68 g (3.47 mmol) of **33** in 69.4 mL of THF at −78 °C was treated with 4.34 mL (4.34 mmol) of a 1.0 M solution of lithium tri-*sec*-butylborohydride in THF. After 2 h at −78 °C, the excess hydride was quenched by the addition of saturated aqueous NH_4Cl (3 mL) and the resulting suspension was warmed to room temperature. The solids were dissolved in water (10 mL), and the mixture was extracted with EtOAc (2 × 15 mL). The organic layers were back-extracted with EtOAc (15 mL), and the organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (170 g of SiO_2; 40% EtOAc/hexanes) to provide 1.27 g (75%) of aminal **34** as a bright yellow oil: R_f = 0.19 (50% EtOAc/hexanes); IR (neat) ν 3440 (br), 3050, 2990, 2935, 2830, 1709, 1601, 1483, 1402, 1282, 1240, 1142, 1085, 1040, 1009, 808, 750 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (m, 2 H), 7.24 (m, 3 H), 5.67 (br dd, 1 H, J = 5.8, 1.6 Hz), 5.54 (d, 1 H, J = 14.5 Hz), 5.37 (dd , 1 H, J = 10.0, 1.6 Hz), 4.78 (d, 1 H, J = 14.5 Hz), 4.40 (d, 1 H, J = 10.0 Hz), 3.98 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.28 (s, 3 H), 3.04 (br d, 1 H, J = 5.8 Hz), 2.19 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 193.9, 146.7, 146.6, 145.3, 140.4, 138.5, 133.0, 132.0 (2 *Ph*CH_2 C-1s), 128.8 (2 *Ph*CH_2 C-1), 127.5, 114.1, 104.2, 94.9, 90.5, 63.3, 61.6, 60.7, 59.6, 55.4, 51.2, 10.4; MS (FAB–NOBA) m/z (rel. intensity) 487 (12), 349 (18), 317 (10), 307 (13), 289 (14), 266 (24), 252 (6), 192 (3), 165 (5); high-resolution MS m/z calcd for $C_{23}H_{27}N_4O_6S$ (M + H^+) 487.1653, found 487.1628. Anal. Calcd for $C_{23}H_{26}N_4O_6S$: C, 56.78; H. 5.39; N, 11.51. Found: C, 56.60; H, 5.60; N, 11.22.

(±)-(3aα,4α,10aα,10bα)-1,3a,4,10a,10b-Hexahydro-7-methyl-10-oxo-1-[(phenylthio)methyl]-1,2,3-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4-yl Ester of 1*H*-Imidazole-1-carbodithioic Acid (35). A solution of 1.25 g (2.57 mmol) of hydroxytriazoline **34**, 0.313 g (2.57 mmol) of *N*,*N*-dimethylaminopyridine, and 2.29 g (13.9 mmol) of 1,1′-(thiocarbonyl)diimidazole in 51.4 mL of CH_2Cl_2 was heated at gentle reflux for 37 h. The solution

was cooled to room temperature and concentrated *in vacuo*, and the residue was purified by flash chromatography (300 g of SiO_2; 50% EtOAc/hexanes) to provide 0.891 g (57%) of (thiocarbonyl)imidazolide **35** as a bright yellow oil: R_f = 0.31 (60% EtOAc/hexanes); IR (CH_2Cl_2) ν 3000, 2960, 2940, 2838, 1715, 1505 1488, 1470, 1452, 1407, 1372, 1290, 1245, 1230, 1108, 1061, 1012, 951, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.52 (br s, 1 H), 7.83 (br s, 1 H), 7.38 (m, 2 H), 7.25 (m, 3 H), 7.18 (br s, 1 H), 6.73 (s, 1 H), 5.55 (d, 1 H, J = 10.0 Hz), 5.16 (AB, 2 H, J_{AB} = 14.5 Hz, $\Delta\nu$ = 196.1 Hz), 4.43 (d, 1 H, J = 10.0 Hz), 3.99 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.27 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.1, 192.3, 146.8, 146.0, 145.3, 140.3, 139.1, 135.2, 132.7, 132.1 (2 *Ph*CH_2 Cs), 131.7, 129.0 (2 *Ph*CH_2 Cs), 127.8, 117.4, 114.2, 105.3, 96.0, 75.0, 62.6, 61.7, 60.8, 60.5, 55.4, 51.8, 10.5; MS (FAB–NOBA) m/z (rel. intensity) 469 (20), 378 (8), 332 (5), 304 (100), 289 (9), 258 (4), 165 (3). Anal. Calcd for $C_{27}H_{28}N_6O_5S_3$: C, 52.92; H, 4.61; N, 13.72. Found: C, 53.20; H, 4.90; N, 13.49.

(±)-(3aα,10aα,10bα)-1,3a,10a,10b-Tetrahydro-6,8,9,10a-tetramethoxy-7-methyl-1-[(phenylthio)methyl]-1,2,3-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-10-one (36) and (±)-*trans*-1-Amino-1,9a-dihydro-5,7,8,9a-tetramethoxy-6-methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (37). To a solution of 0.343 g (2.57 mmol) of (thiocarbonyl)imidazolide **35** and 3.41 g (11.73 mmol) of tri-*n*-butylstannane in 6.90 mL of degassed benzene (argon) was added a catalytic amount (15 mg) of azobis(isobutyronitrile). This mixture was placed in a bath which had been preheated to 80 °C, and after 10 min, the reaction was cooled to room temperature and the solvent removed *in vacuo*. The residue was purified by flash chromatograph (50 g of SiO_2; 20% EtOAc/hexanes) to provide 0.084 g (52%) of the reduced triazoline **36**. Further chromatography with 80% EtOAc/hexanes provided 0.015 g (13%) of the fragmentation product **37**. **36**: R_f = 0.40 (40% EtOAc/hexanes); IR (CH_2Cl_2) ν 3000, 2940, 2830, 1709, 1601, 1485, 1450, 1402, 1282, 1140, 1110, 1088, 1028, 1008, 937, 800 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (m, 2 H), 7.25 (m, 3 H), 5.27 (ddd, 1 H, J = 10.0, 7.8, 1.9 Hz), 5.15 (AB, 2 H, J_{AB} = 14.4 Hz, $\Delta\nu$ = 191.4 Hz), 4.45 (dd, 1 H, J = 13.3, 1.9 Hz), 4.26 (d, 1 H, J = 10.0 Hz), 3.97 (s, 3 H), 3.95 (dd, 1 H, J = 13.3, 7.8 Hz), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.23 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 194.4, 148.7, 146.5, 144.7, 140.3, 138.3, 133.3, 132.3 (2 *Ph*CH_2 C-1s), 129.0 (2 *Ph*CH_2 Cs), 127.7, 114.5, 104.5, 87.7, 63.6, 61.7, 60.8, 59.1, 55.6, 52.1, 51.4, 10.4; MS (FAB–NOBA) m/z (rel. intensity) 471 (45), 470 (19), 333 (100), 307 (20), 305 (29), 289 (22), 274 (20), 236 (14), 177 (8), 165 (6); high-resolution MS m/z calcd for $C_{23}H_{27}N_4O_5S$ ($M + H^+$) 471.1704, found 471.1710. Anal. Calcd for $C_{23}H_{26}N_4O_5S$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.63; H, 5.51; N, 11.71. **37**: R_f = 0.09 (40% EtOAc/hexanes); IR (neat) ν 3400, 3330, 2994, 2940, 2838, 1711, 1603, 1485, 1451, 1404, 1285, 1093, 1032, 769 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.74 (dd, 1 H, J = 3.9, 1.0 Hz), 5.38 (dd, 1 H, J = 3.9, 2.5 Hz), 3.98 (s, 3 H), 3.90 (dd, 1 H, J = 2.5, 1.0 Hz), 3.82 (s, 3 H), 3.74 (s, 3 H), 3.27 (s, 3 H), 2.21 (s, 3 H), 1.35 (br s, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.0, 149.4, 146.7, 145.9, 141.3, 137.8, 134.3, 116.1, 115.9, 103.0, 61.9 (2 O*C*H_3), 60.8, 59.2, 51.3, 10.3; MS (EI, 20 ev) m/z (rel. intensity) 320 (31), 305 (69), 277 (12), 250 (100), 234 (57), 220 (56), 149 (29), 129 (5); high-resolution MS m/z calcd for $C_{16}H_{20}N_2O_5$ (M^+) 320.1373, found 320.1387.

(±)-(1aα,8aα,8bα)-1a,2,8a,8b-Tetrahydro-4,6,7,8a-tetramethoxy-5-methyl-1-[(phenylthio)methyl]azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8(1*H*)-one (38). A Pyrex tube was charged with a solution of 84 mg of (0.179 mmol) of triazoline **36** in 72 mL of benzene, and this solution was degassed with a steady stream of argon. The material was irradiated with a 254-nm Hanovia (HG) lamp through a Vycor filter. After 8 h of irradiation, the solution was concentrated *in vacuo* and the residue was purified by flash chromatography (10 g of SiO_2, 20% EtOAc/hexanes) to provide 37 mg (47%) of aziridine **38** as an orange oil: R_f = 0.20 (33% CH_2Cl_2/benzene); IR (neat) ν 3042, 2980, 2930, 2880, 2812, 1705, 1600, 1480, 1402, 1275, 1141, 1100, 1005, 740, 648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (m, 3 H), 7.10 (m, 2 H), 4.06 (d, 1 H, J = 12.3 Hz), 3. 85 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.90–3.70 (m, 2 H), 3.46 (dd, 1 H, J = 4.4, 1.8 Hz), 3.26 (s, 3 H), 2.78 (d, 1 H, J = 4.4 Hz), 2.36 (dd, 1 H, J = 4.4, 1.8 Hz), 2.22 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.3, 152.4, 146.6, 144.3, 137.2, 136.0, 129.6 (2 *Ph*CH_2 Cs), 128.6 (2 *Ph*CH_2 Cs), 126.3, 114.8, 100.5, 61.5, 60.9, 59.8, 58.6, 51.4, 50.5, 46.0, 44.9, 10.4; MS (EI, 20 eV) m/z (rel. intensity) 442 (14), 334 (21), 305 (16), 276 (5), 123 (7), 110 (16); high-resolution MS m/z calcd for $C_{23}H_{26}N_2O_5S$ (M^+) 442.1564, found 442.1591.

(±)-(1aα,8aα,8bα)-1a,2,8a,8b-Tetrahydro-4,6,7,8a-tetramethoxy-1,5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8(1*H*)-one (39). To a solution of 37 mg (0.083 mmol) of *N*-((phenylthio)methyl)aziridine **38** in 2.5 mL of reagent grade acetone was added an excess of active Raney nickel catalyst (prewashed to pH = 7 with water and stored under EtOH). This mixture was stirred vigorously at reflux for 30 min and cooled to room temperature. The catalyst was removed by filtration through a short plug of Celite, and the solids were washed thoroughly with EtOAc. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (7.0 g of SiO_2; 40% EtOAc/hexanes) to provide 20 mg (72%) of *N*-methylaziridine **39**: R_f = 0.48 (50% EtOAc/hexanes); IR ($CHCl_3$) ν 2990, 2959, 2930, 2860, 1708, 1601, 1485, 1450, 1405, 1375, 1280, 1146, 1098, 1067, 1005, 912 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.00 (s, 3 H), 3.95 (d, 1 H, J = 12.1 Hz), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.49 (dd, 1 H, J = 12.1, 1.9 Hz), 3.24 (s, 3 H), 2.43 (d, 1 H, J = 4.4 Hz), 2.27 (dd, 1 H, J = 4.4, 1.9 Hz), 2.19 (s, 3 H), 2.16 (s, 3 H); ^{13}C ($CDCl_3$) δ 195.9, 152.3, 146.7, 144.5, 140.1, 137.3, 114.9, 100.1, 61.7, 60.8, 58.5, 51.2, 51.0, 47.8, 46.5, 44.0, 10.4; MS (EI, 20 eV) m/z (rel. intensity) 334 (42), 319 (7), 291 (6), 276 (5), 233 (3), 107 (3), 85 (47), 83 (71); high-resolution MS m/z calcd for $C_{17}H_{22}N_2O_5$ 334.1530, found 334.1550.

(±)-(1aα,8aα,8aα,8bα)-1,1a,2,8,8a,8b-Hexahydro-4,6,7,8a-tetramethoxy-1,5-dimethyl-8-[(trimethylsilyl)methyl]azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8-ol (40). To a solution of 26 mg (0.077 mmol) of ketone **39** in 3.83 mL of THF at –10 °C was added 1.15 mL (1.15 mmol) of a 1.0 M solution of ((trimethylsilyl)methyl)lithium in THF. After 10 min at –10 °C, the excess reagent was quenched by the addition of saturated aqueous NH_4Cl and the mixture was warmed to room temperature. The solids were dissolved in water, and this mixture was extracted with EtOAc (2 × 15 mL). The organic layers were washed with brine, and the combined aqueous layers were back-extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (7.0 g of SiO_2; 15% EtOAc/hexanes) to provide 28 mg (88%) of **40**: R_f = 0.47 (40% EtOAc/hexanes); IR ν 3440 (br), 3005, 2942, 2890, 2865, 2820, 1600, 1472, 1450, 1418, 1373, 1242, 1217, 1138, 1093, 1080, 1065, 1007, 994, 855 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.45 (d, 1 H, J = 1.6 Hz), 3.91 (s, 3 H), 3.73 (s, 3 H), 3.65 (s, 2 H), 3.65 (s, 3 H), 3.34 (s, 3 H), 2.40 (dd, 1 H, J = 4 .5, 1.8 Hz), 2.35 (d, 1 H, J = 4.5 Hz), 2.29 (s, 3 H), 2.12 (s, 3 H), 1.82 (AB, 2 H, J_{AB} = 13.9 Hz, $\Delta\nu$ = 45.5 Hz), –0.08 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 146.3, 145.8, 139.4, 137.9, 128.5, 125.8, 107.4, 85.3, 61.2, 60.4, 58.3, 54.0, 50.1, 48.3, 46.8, 43.7, 23.0, 9.3, 0.7; MS (EI, 20 eV) m/z (rel. intensity) 422 (37), 392 (100), 360 (27), 302 (27), 271 (20); high-resolution MS m/z calcd for $C_{21}H_{34}N_2O_5Si$ (M^+) 422.2238, found 422.2242.

(±)-(1aα,8aα,8aα,8bα)-1,1a,2,8,8a,8b-Hexahydro-8-hydroxy-6,8a-dimethoxy-1,5-dimethyl-8-[(trimethylsilyl)methyl]azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione (41). A solution of 19.5 mg (0.0462 mmol) of **40** and 38 mg (0.462 mmol) of sodium acetate in a 5:1 mixture of CH_3CN/water (1 mL) was prepared. This was stirred vigorously as 87 mg (0.231 mmol) of the silver(II) dipicolinate complex was added in three portions over 40 min. After being stirred for 1 h, the mixture was diluted with water (1 mL) and the solids were removed by filtration through a Celite pad. The solids were washed thoroughly with $CHCl_3$, and the filtrate was partitioned between water/$CHCl_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (7.0 g of SiO_2; 40% EtOAc/hexanes) to provide a slightly impure sample of mitomycin K (1 mg, 7%) as a bluish-purple solid and 2.8 mg (16%) of quinone **41** as a cherry-red oil: R_f = 0.22 (50% EtOAc/hexanes); IR (neat) ν 3440, 3040, 2950 1732, 1690, 1648, 1580, 1430, 1380, 1297, 1243, 1101, 1082, 1029, 863, 849, 740, 699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.08 (s, 3 H), 3.96 (s, 1 H) , 3.88 (d, 1 H, J = 12.7 Hz), 3.60 (dd, 1 H, J = 12.7, 2.0 Hz), 3.34 (s, 3 H), 2.43 (dd, 1 H, J = 4.4, 2.0 Hz), 2.32 (s, 3 H), 2.29 (d, 1 H, J = 4.4 Hz), 1.84 (s, 3 H), 1.63 (AB, 2 H, J_{AB} = 14.1 Hz, $\Delta\nu$ = 111.2 Hz), 0.05 (s, 9 H); MS (EI, 20 eV) m/z (rel. intensity) 392 (14), 377 (66), 361 (100), 319 (77), 289 (35), 262 (22), 185 (9), 149 (16), 84 (28); high-resolution MS m/z calcd for $C_{19}H_{28}N_2O_5Si$ (M^+) 392.1768, found 392.1787.

(±)-(1aα,8aα,8bα)-1,1a,2,8,8a,8b-Hexahydro-6,8a-dimethoxy-1,5-dimethyl-8-methyleneazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione (Mitomycin K). To a solution of 2.8 mg (0.0071 mmol) of quinone **41** in 1.0 mL of CH_2Cl_2 was added 0.5 mg (0.002 mmol) of PPTS, and the solution was stirred for 1 h. Concentration *in vacuo* and separation by flash chromatography (3.5 g of SiO_2; 40% EtOAc/hexanes) provided 1.7 mg (81%) of mitomycin K as a bluish-purple solid: R_f = 0.27 (50% EtOAc/hexanes): mp 123–125 °C; IR (CH_2Cl_2) 3040, 2940, 2920, 2846, 1649, 1628, 1610, 1550, 1431, 1360, 1300, 1210, 1137, 1060, 983, 900, 850, 812, 742, 708 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 (s, 1 H),

5.45 (s, 1 H), 4.09 (s, 3 H), 4.08 (d, 1 H, J = 12.9 Hz), 3.42 (dd, 1 H, J = 12.9, 1.8 Hz), 3.06 (s, 3 H), 2.28 (d, 1 H, J = 4.6 Hz), 2.33–2.21 (m, 1 H), 2.21 (s, 3 H), 1.86 (s, 3 H); MS (EI, 20 eV) m/z (rel. intensity) 302 (100), 287 (99), 271 (28), 256 (21), 242 (11), 228 (17), 213 (10), 190 (14), 146 (6), 131 (6), 106 (7), 82 (21); high-resolution MS m/z calcd for $C_{16}H_{18}N_2O_4$ (M^+) 302.1267, found 302.1276.

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Supplementary Material Available: Exerimental details, Pluto drawings, and tables containing fractional coordinates, temperature factors, bond distances and angles, and torsional angles for the X-ray crystallographic analysis of compound **A** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.