Total Synthesis of a Mitosene

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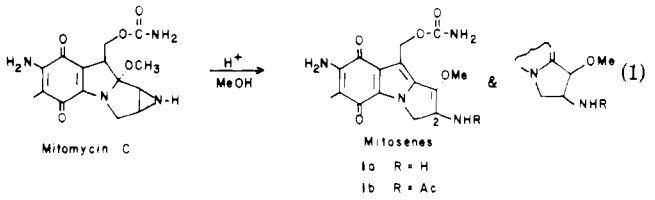
The total synthesis of a mitosene (a chemical degradation product of mitomycin C) is described. The synthesis begins with hydroxyproline and uses a Huisgen pyrrole synthesis to form a pyrrolizidine system. The carbocyclic ring is made through Dieckmann cyclization. Adjusting the oxidation states of the various atoms follows conventional lines. The synthesis requires 19 steps and proceeds in 1% overall yield. The regiochemical and stereochemical features of the synthetic reactions involving C_1 and C_2 are discussed and related to the ring-opening reactions of mitomycin C.

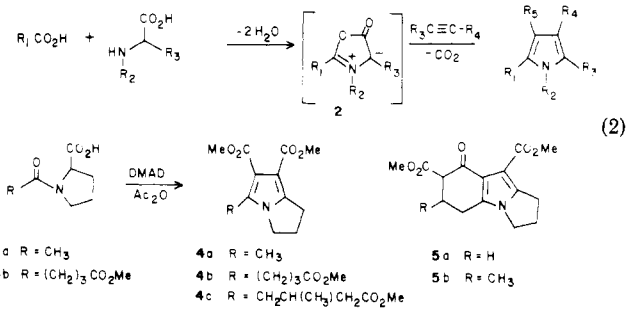
Three years ago, we reported[1] the total synthesis of a mitosene (1), a chemical degradation product of mitomycin



C. Since that time, interest in the clinical use, pharmacology, and chemistry of mitomycin C has increased substantially. Clinical studies have shown this agent to have broad antitumor activity against many adenocarcinomas and squamous cell carcinomas, and the drug is now widely used in emerging and current regimens of cancer treatment.[2] Pharmacologic studies have recently demonstrated that the drug is selectively toxic to hypoxic tumor cells,[2c-e] an observation with significant implications for cancer treatment. Chemical studies[3] are resurrecting questions concerning the mechanism of aziridine opening and its relevance to the mechanism of action of mitomycin C. Because our synthetic work has uncovered information that bears on these latter issues, reporting the experimental details is likely to be of more than exclusively synthetic interest, and we take the time here to do so.

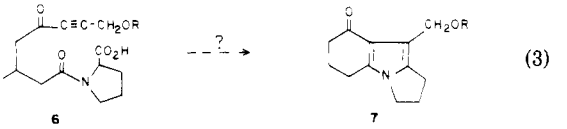
Only a single synthesis of the actual mitomycins has been achieved, that due to Kishi[4] in 1977. By that time, considerations of toxicity had forced the mitomycins into clinical desuetude in the U.S., and synthetic attention, which had generated some 20 other published approaches, migrated elsewhere. Ironically, none of these methods led to a mitomycin or even a degradation product thereof, even though most were directed at the synthesis of the sturdier mitosenes rather than the delicate natural products. These approaches are adequately described elsewhere;[5] here we note only that without exception, an intact, aromatic, six-membered ring is used as a starting material.

If the problem of mitosene synthesis be perceived as one of constructing a pentasubstituted pyrrole, the Huisgen[6] pyrrole synthesis emerges as a promising strategy (eq 2).



In this, an amino acid, acylating agent, and acetylene are combined (frequently all at once) to give the pyrrole by way of the intermediate munchnone (**2**).

The pyrrolizidine skeleton **4a** was also obtained by Huisgen[7] from proline, acetic anhydride, and dimethyl acetylene dicarboxylate (DMAD), and Hershensen[8] described not only the preparation of **4b** but also its Dieckmann cyclization to **5a**. Though we had already prepared **5b** from **4c** in model studies our intent had been to avoid intermolecular C–C bond formation altogether through the tactic suggested in eq 3. Unfortunately, the requisite **6**



could not be prepared, and a return to the alternate strategy was required.

(1) Rebek, J., Jr.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173-1177.

(2) (a) Carter, S. K.; Crooke, S. T. "Mitomycin C: Current Status and New Developments"; Academic Press: New York, 1979. (b) Ogawa, M.; Rozencweig, M.; Staquet, M. J. "Mitomycin C: Current Impact on Cancer Chemotherapy"; Excerpta-Medica: Amsterdam, 1982. (c) Kennedy, K. A.; Rockwell, S.; Sartorelli, A. C. *Cancer Res.* **1980**, *40*, 2356-2360. (d) Teicher, B. A.; Lazo, J. S.; Sartorelli, A. C. *Ibid.* **1981**, *41*, 73. (e) Kennedy, K. A.; Sligar, S. G.; Polomski, L.; Sartorelli, A. C. *Biochem. Pharmacol.* **1982**, *31*, 2011-2016. (f) denHartigh, J.; McVie, J. G.; vanOort, W. J.; Pinedo, H. *Cancer Res.* **1983**, *43*, 5017-5021. (g) Underberg, W. J. M.; Lingeman, H. *J. Pharm. Sci.* **1983**, *72*, 549-553.

(3) (a) Tomasz, M.; Lipman, R. *Biochemistry* **1981**, *20*, 5056-5061. (b) Kohn, H.; Zein, N. *J. Am. Chem. Soc.* **1983**, *105*, 4105-4106. (c) Iyengar, B. S.; Remers, W. A.; Bradner, W. T., in press. (d) Tomasz, M.; Lipman, R. *J. Am. Chem. Soc.* **1979**, *101*, 6063-6067. (e) Hornemann, U.; Iguchi, K.; Keller, P. J.; Vu, H. M.; Kozlowski, J. F.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 5026-33. (f) Bean, M.; Kohn, H. *Ibid.* **1983**, *48*, 5033-5041. (g) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1982**, *23*, 677-680.

(4) Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835-4836. Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *Ibid.* **1977**, *99*, 8115-8116. Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295-4298.

(5) For reviews of early approaches, when these structures were becoming victims of runaway methodology, see: Takahashi, K.; Kametani, T. *Heterocycles* **1979**, *13*, 411-467. Kametani, T.; Takahashi, K. *Ibid.* **1978**, *9*, 293-351. Franck, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1-45. For leading references regarding more recent approaches, see: Coates, R. M.; MacManus, P. A. *J. Org. Chem.* **1982**, *47*, 4822-4824. Luly, J. R.; Rapoport, H. *Ibid.* **1984**, *49*, 1671-1672. Corey, R. M.; Ritchie, R. B. *J. Chem. Soc., Chem. Commun.* **1983**, 1244-1245. Akiba, M.; Ikuta, S.; Takada, T. *Ibid.* **1983**, 817-818. Naruta, Y.; Arita, Y.; Nasai, N.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 1859-1862. Kozuka, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2922-2927.

(6) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *2*, 565.

(7) Huisgen, R.; Gotthard, H.; Bayer, H. O.; Schafer, F. C. *Chem. Ber.* **1970**, *103*, 2611-2624.

(8) Hershenson, F. M. *J. Org. Chem.* **1976**, *40*, 1260-1264. Rebek, J., Jr.; Gehret, J.-C. *Tetrahedron Lett.* **1977**, 3027-3030. Hershenson, F. M. *J. Heterocycl. Chem.* **1979**, *16*, 1093-1095.

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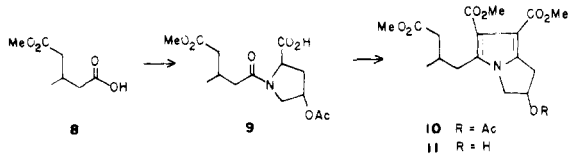
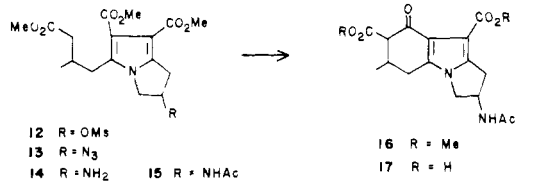
Specifically, optically active hydroxyproline was coupled to the monoester 8 by using a mixed anhydride procedure, and the initial product was acylated (Ac_2O) on workup. The mixture of diastereomers 9 thus obtained was treated with DMAD in hot Ac_2O to give 10, one diastereomer of which crystallized after chromatography (eq 4). Metha-



(4)

nolysis gave the alcohols 11, and again one isomer crystallized. As this was derived from the oily isomer of 10, both diastereomers of 11 could be had in a pure state; however, it proved more practical to use the mixture for the total synthesis.

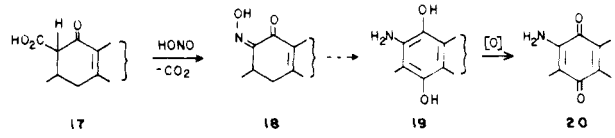
A single diastereomer of the alcohol 11 was converted uneventfully to the acetamido derivative 15 by way of the usual intermediates (eq 5). This substance had what was



(5)

then believed to be the correct absolute configuration[9] at C_3 for the natural products and some efforts were expanded in converting it to a mitosene. On treatment with KO-*t*-Bu 15 cyclized cleanly to the ketone 16. Careful saponification gave the diacid 17, the presence of which was established by its reconversion to 16 with CH_2N_2.

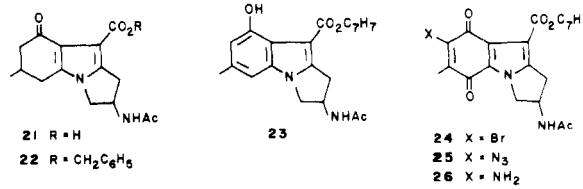
A number of more or less direct schemes to use the β-keto acid function of 17 to generate an aminoquinone were attempted (eq 6). Nitrosation[10a] led to the spec-



(6)

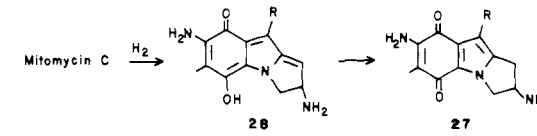
tacular color changes expected for the aromatization of the ring. The oxime 18 is an isomer of the desired 19, a reasonably low energy mechanism can be formulated for the rearrangement, and air oxidation of 19 to the quinone 20 is not without precedent. Thin-layer chromatograms of the reaction did show a number of colored products, but none of the desired (purple) aminoquinone was obtained. A stepwise, lengthier approach proved successful and generalizable.

Decarboxylation of 17 took place readily, but the resulting acid 21 failed to undergo aromatization with DDQ.



Rather, its benzyl ester 22, prepared via a mixed anhydride procedure, was readily dehydrogenated to the indole 23. With Br_2, under carefully controlled conditions,[10b] the requisite oxidation state was obtained in the form of the bromoquinone 24. Nitrogen was again introduced as azide, and the resulting 25 was finally converted to the aminoquinone 26 with dithionite.

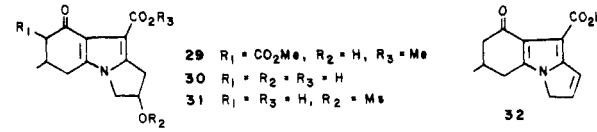
At the time, the preparation of this substance merely demonstrated the feasibility of an approach which constructed, rather than purchased, the six-membered ring. Unexpectedly, such structures have also appeared during the hydrolysis of mitomycin C under reducing conditions (eq 7). Thus 27 was isolated by Tomasz[3a] and has recently



(7)

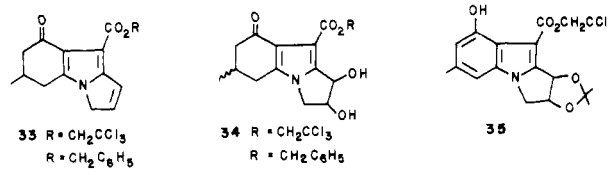
been shown by Kohn[3b] to result from protonation of the intermediate 28 at C_1.

The rapid access to a mitosene, even an optically active one such as 26, had not, however, addressed the problems of functionalizing C_1, and when the reports of such procedures were published by Kametani,[11] they were acted upon quickly. These failed. Instead, a return to the alcohol 11 was indicated. Dieckmann cyclization and then hydrolysis/decarboxylation gave the acid 30 from which the mesylate 31 was prepared. As this substance proved



to be the pivotal intermediate in our synthesis, some considerable effort was expended in its characterization. The diastereomers of 10 were separated, taken through the sequence, and shown to give enantiomeric olefins 32 on elimination (NaOMe/MeOH). Thus from the crystalline acetate 10, the derived olefin 37 showed $[\alpha]^{25}_D$ +47.0° while the corresponding value from the crystalline alcohol 11 was −45.0°. When the mixture of diastereomers of 10 was carried through the sequence, an enantiomeric excess of 25% was indicated by the rotation (+12.2°).

The cost of functionalizing C_1 had been the loss of chirality; we neither anticipated nor found any useful asymmetric induction by the remote methyl group in subsequent reactions. Moreover, initial experiments with reagents intended to just distinguish C_1 from C_2 of the alkene were discouraging. For example, the esters 33,



obtained by the mixed anhydride procedure, gave an unfortunate mixture of regioisomers with IN_3[12] and no characterizable products at all on oxyamination.[13] Conventional, OsO_4-mediated hydroxylation proved a satis-

(9) This has recently been revised. Schirahata, K.; Hirayama, N. *J. Am. Chem. Soc.* **1983**, *105*, 7199–7200. The correct structure is shown in eq 1.

(10) (a) Geissman, T. *J. Org. Chem.* **1946**, *11*, 737–740 (coupling with diazonium salts likewise led to products unsuited for conversion to aminoquinones). (b) For a similar transformation, see: Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305–4308.

(11) Kametani, T.; Takahashi, K.; Kigawa, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 28–31.

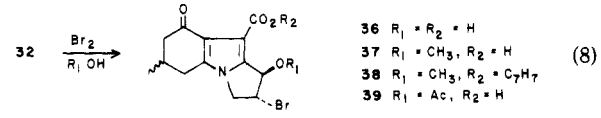
(12) Hirata, T.; Yamada, Y.; Matsui, M. *Tetrahedron Lett.* **1969**, 4107–4109.

(13) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3597–3598. We thank Professor Sharpless for experimental advice concerning the use of these reagents.

factory method and the *cis*-1,2-diol **34** was obtained in this way in moderate yield. While the stereochemistry is unambiguous, the mixture of diastereomers obtained thwarted our attempts to interpret the coupling constants involving the protons on C_1, C_2, and C_3.

The acetonide was prepared, from which **35** was obtained on DDQ dehydrogenation. This substance and its subsequent transformation products had much-simplified NMR spectra showing coupling constants involving the proton at C_1 in the 5.9–6.2-Hz range. In addition, acetylation of **34** gave *cis*-1,2-diacetates from which a number of derivatives could be prepared; these all showed coupling constants between 5.7 and 6.0 Hz.

For purposes of comparison, the requisite authentic trans compounds could be obtained from the olefin 33 through bromination (eq 8). In wet THF the bromohydrin



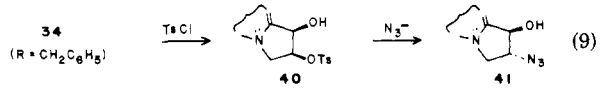
(8)

36 was obtained whereas in MeOH the ether **37** was produced. The diastereomers of **36** showed $J = 4.7$ and 5.0 Hz for the proton at C_1 while in **37** this proton appeared as a singlet in either diastereomer. Indeed, most of the the derivatives of **37** subsequently prepared showed very small couplings ($J < 1$ Hz) between the trans 1,2 H nuclei.

The regiochemistry shown is anticipated on mechanistic grounds and parallels the ring opening of mitomycins by nucleophiles exclusively at C_1. Spectroscopic evidence provides indirect support for these assignments; conversion of the acids to the benzyl esters **38** and **39** results in *upfield* shifts of the proton at C_1 as well as the methoxyl of **38** and the acyl methyl of **39**.

These manipulations revealed that considerable steric effects existed between the carboxyl function and substituents at C_1. Interactions between groups at these positions are similar to the peri interactions of naphthalene, and even though the bonds that such substituents make to the pyrrolizidine skeleton are not parallel, some steric problems can be expected. Their manifestation at the carboxyl function was the difficulty encountered in conventional esterification procedures applied to the acid when any substituent was present at C_1. Indeed, the only good method found for the preparation of the benzyl esters involved the S_N2 reaction of the carboxylate with benzyl bromide. Doubtless the keto function in the carbocycle also contributed to this behavior.

A qualitative measure of the congestion at C_1 caused by the presence of the esters at C_{10} was provided by the sluggish osmylation reactions of **33** and even its unwillingness to add Br_2. Moreover, reaction of **34** with tosyl chloride, even under forcing conditions, gave only the C_2 tosylate **40** (eq 9). This reaction proved useful since it



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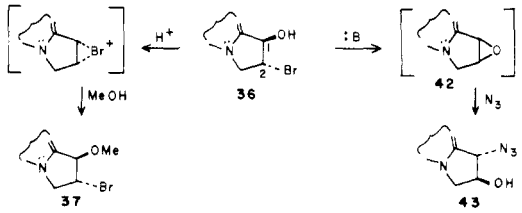
led to an azide derivative at C_2 (**41**), the NMR spectra of which was in agreement with that observed by Remers[14] for a similar 1-hydroxy-2-azidomitosene. For purposes of total synthesis, however, the low yields involved rendered this approach impractical.

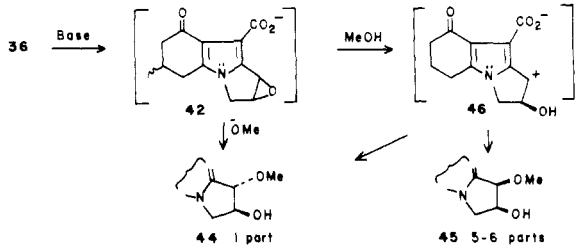
Despite these *steric* factors, the substitution reactions at C_1 are enforced by powerful *electronic* effects. The bromohydrin **36** provides a case in point (eq 10). With



(10)

acidic catalysis in the presence of MeOH, **37** was again obtained, while with NaN_3 the C_1 azide **43** was the product. The former likely arises by return of **36** to the bromonium ion, whereas the probable provenance of the latter is the epoxide **42**. In either case the opening of the three-membered intermediate occurs exclusively at C_1. The structure of **43** was deduced from its NMR characteristics which were easily distinguished from those of the isomer **41**.

These substances gave us a considerable first-hand experience with the relative reactivities of C_1 and C_2 mitosene derivatives but even so the stereochemical course of some of these reactions was unanticipated. Specifically, the treatment of **36** with NaOMe/MeOH (eq 11) gave a mixture of monomethyl esters, and while the methoxyl was found only at C_1, *the major product was the cis isomer 45*!



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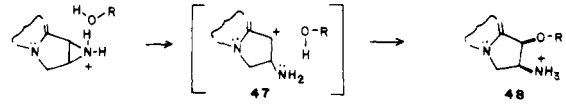
The regiochemistry of this process requires the intermediacy of the elusive epoxide **42**, but its preferential cis opening requires some explanation. The product cis/trans ratio was found to be inversely proportional to base concentration, a fact which suggests an S_N2 component which gives **44** directly from **42**. The cis ether, however, can only arise by capture of the zwitterion **46**. Formation of this species is unusually favorable in the case at hand since the positive charge enjoys electrostatic as well as resonance stabilization. Nonetheless, its lifetime must be short. Its generation involves solvation—probably even protonation—of the emerging alkoxide ion, a feature which predisposes it to capture by one of these same solvent molecule. A longer lived species would be expected to lose its solvation history and lead to products which reflect, say, steric effects instead.

The stereochemical course of aziridine opening in the mitomycins themselves suggests that this notion may be generalizable. An unusually high fraction of cis solvolysis products have been observed and commented upon without persuasive explanation. In these cases (eq 12) ring-



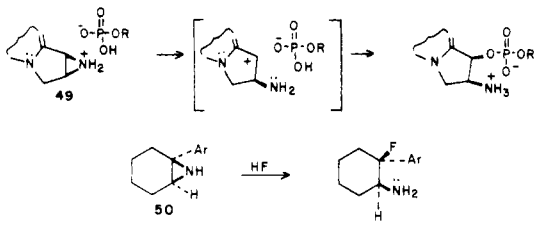
(12)

opening proceeds after protonation of the nitrogen, and solvation of the ammonium ion is likely to bias subsequent events. Capture of the ion **47** by *solvent* may also involve a general base catalysis by the amine function here, but only if the lifetime of **47** is short. If another protonation of the nitrogen of this ion be permitted, the solvents associated with such positive charge would show much attenuated nucleophilicity, and the likelihood of cis product

(14) Remers, W. A.; Roth, R. H.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 2910–2917.

formation would be diminished.

In the case of charged yet weak nucleophile such as phosphates, prior association of the charges as in **49** (eq 13) also leads to an in situ nucleophile available for cis

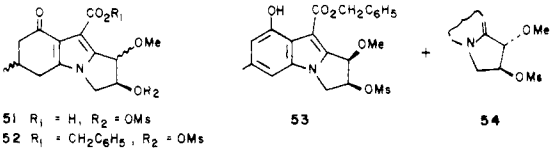


(13)

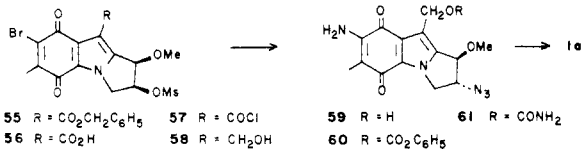
attack. The alkylation of such nucleophiles by mitomycin C, recently studied by Tomasz,[3d] wherein cis/trans product ratios of 4 to 9 are observed are in accord with this reasoning. Additional support is provided by the H–F opening of the aziridine **50** which also gives the cis product.[15]

That conventional, S_N2-type aziridine opening also contributes to products in the mitomycin series was established by Hornemann.[16] Using good nucleophiles such as xanthates, trans opening becomes the major, if not exclusive, pathway. In addition, other nucleophiles of the sort that are unlikely to be involved in solvation, e.g., purine bases, also give trans products in this reaction.[17] The relevance of these stereochemical issues to the mechanism of action of the mitomycins is, at best, obscure. A systematic study of the cis/trans ratio with a number of nucleophiles and conditions has yet to be performed but would be desirable.

At any rate, the regio- and stereochemistry of the MeOH/MeONa product of **36** ultimately led to the total synthesis of a mitosene. Identification of these products rested on their NMR spectra which showed the characteristically high (4–6 Hz) couplings for the cis isomer while the trans isomer gave a singlet for the C_1 proton. In practice, the product mixture was mesylated, esterified, and then oxidized to afford the isomers **53** and **54** in high yield.



Bromination of the phenol **53** afforded the quinone **55**, from which the benzyl ester could be cleaved by hydrogenolysis with Pd/C. Under conditions of high catalyst



concentration and short reaction time, simultaneous hydrogenolysis of the C–Br bond can be limited to <5%. The quinone function, however, was always reduced and oxidative workup ($FeCl_3$) was required. Conversion to the acyl chloride ($SOCl_2$) **57** followed by reduction ($NaBH_4$) gave the alcohol **58**. Again, oxidative workup was required to regenerate the quinone, but Fremy's salt proved more satisfactory for this purpose.

When a solution of **58** and excess NaN_3 was gradually heated to 90° in wet DMF, changes in color developed which we readily diagnosed through our experience with model systems. The yellow bromoquinones (e.g., **55**) could be converted to the characteristically orange azide quinones under relatively mild conditions (30 min, 30°). Under more vigorous heating (2 h, 60°) in this solution, the excess azide ion acts as an effective reducing agent, and the purple aminoquinones are generated. Further studies on **52** had established that substitution of the 2 mesylate with N_3^- occurred much more slowly (12 h, 90°). Thus, conversion of **58** to the desired **59** merely involved monitoring the color changes as the solution was maintained at 90° overnight.

The remaining steps of the synthesis posed little in the way of problems. Indeed, any number of groups had converted the primary alcohol of related substances to the corresponding carbamates by using phenyl chloroformate followed by ammonolysis.[18] These procedures indeed led from **59** to **61**. Final reduction of the azide was accomplished with $(C_6H_5)_3P$ in pyridine and aqueous ammonia.[19]

Material obtained in this way showed the usual coupling constant associated with 1,2 trans stereochemistry but showed the TLC behavior that had been attributed to the cis isomer of **1a**. This assignment had originally been made by Stevens[20] during his studies of the hydrolysis of mitomycin C, but since it and its acylated derivative **1b** appear elsewhere in the literature,[21] we felt obliged to reinvestigate the hydrolysis of the natural product. Under the conditions previously described (Dowex/MeOH), mitomycin C gave us a mixture of *cis*- and *trans*-1-methoxymitosenes which could be separated by preparative TLC (MeCN/Me_2CO/*n*-BuOH; 3:1:1). The higher R_f (0.15) component proved identical with our synthetic material and is the trans isomer **1a**, whereas the lower R_f (0.08) component showed the NMR spectrum anticipated for the cis isomer. The original assignments of Steven's are therefore reversed and the correction of this error has already appeared in a recent mechanistic study of mitomycin hydrolysis.[3c]

Conclusions

The synthesis of a mitosene has been achieved from hydroxyproline in 19 steps and ~1% overall yield. The stereochemistry of aziridine and epoxide opening in these systems has been examined by using high-resolution NMR. Our assignments are in accord with a very recent and detailed analysis of coupling constants in these molecules provided by Hornemann,[3e] to which the specialist reader is referred.

Experimental Section

***N*-(4-Carbomethoxy-3-methylbutyroyl)-4-acetoxy-L-proline (9).** A solution of compound 8 (36.0 g, 0.225 mol obtained from methanolysis of the cyclic anhydride) in 400 mL of THF and 32.8 mL of Et_3N (0.236 mol) was prepared and cooled to −10 °C under nitrogen with vigorous stirring. This was treated with isobutyl chloroformate (30.4 mL, 0.236 mol), and immediately a white solid formed. To this mixture was added 4-hydroxy-L-proline (29.48 g, 0.225 mol) dissolved in 80 mL of H_2O to which 32.8 mL (0.236 mol) of triethylamine had been added. The mixture was stirred at room temperature for 3 h at which time

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the THF and water were removed at reduced pressure. After all the volatiles were removed, 250 mL of acetic anhydride and 22 mL of pyridine were added, and the mixture was stirred overnight at 65–70 °C. The volatiles were removed and 10% HCl was added followed by extraction with (4 × 100 mL) ethyl acetate. The organic phase was washed with 10% HCl and brine and then dried over Na_2SO_4. Evaporation gave 67.60 g (95.4%) of **9**: IR $\lambda_{max}^{CDCl_3}$ 3450 (m), 2941, 1750 (s), 1620 (m), 1640 (m), 1445 (m) cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.05 (d, 3 H), 2.30–2.50 (br m, 6 H), 3.60 (s, 3 H), 3.70 (m, 2 H), 4.60 (t, 1 H), 5.40 (m, 1 H), 9.75 (br s, 1 H).

Dimethyl 2(*R*)-Acetoxy-2,3-dihydro-5-(3-carbomethoxy-2-methylpropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (10). Acetoxy acid **9** (59.0 g, 0.187 mol) was dissolved in 400 mL of Ac_2O and stirred at 60 °C for .25 h and then at 80 °C for 0.5 h. The solution was treated with distilled dimethyl acetylenedicarboxylate (36.8 mL, 0.299 mol) and then heated slowly to 135 °C whereupon the evolution of CO_2 was observed. The solution was heated for 3 h and cooled to room temperature, and the volatiles were removed at the water pump. The remaining DMAD was removed by Kugelrohr distillation at reduced pressure. The thick black oil was chromatographed on 600 g of silica gel with anhydrous ether. DMAD was eluted with the solvent front and the product was collected in two 1-L fractions. The ether was evaporated to give 59.6 g (82%) of a mixture of solid and oil. The solid was separated and washed with cold ether and 15.3 g were isolated (mp 91–92 °C). The white solid was one pure diastereomer (designated **10a**) by NMR and the mixture consisting mainly of oil was enriched in the second oily isomer (designated **10b** by NMR): TLC (R_f) 0.56, ethyl acetate; 0.73, acetone; 0.47 ether:acetone (2:1). **10a**: IR λ_{max}^{KBr} 2960 (m), 1735 (m), 1725 (m), 1705 (s), 1536 (m), 1460 (w), 1435 (m), 1245 (m), 1190 (s) and 1160 (w) cm^{-1}; $\lambda_{max}^{CHCl_3}$ 282.9 nm (ϵ 2339, log ϵ 3.369); NMR (100 MHz, $CDCl_3$) δ 1.00 (d, 3 H), 2.10 (s, 3 H), 2.25–2.30 (m, 3 H), 2.65–2.75 (m, 2 H), 3.24, 3.57 (m, 2 H, AB, J_{BX} = 3 H, J_{AX} = 6 Hz, J_{AB} = 18 Hz), 3.61 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.94, 4.23 (m, 2 H, A′B′ $J_{B'X'}$ = 3 Hz, $JA_{'B'}$ = 12 Hz), 5.64–5.80 (m, 1 H); H_{AB} refer to C_1 and $H_{A'B'}$ refer to C_3 with the designation H_4 and H_B arbitrary; mass spectrum (15 eV), *m/e* (relative intensity) 395 M^+, 303 (100). An analytical sample of **10a** was prepared by recrystallization from ether: $[\alpha]^{25}_D$ +42.0° (*c* 2.0, MeOH); *m/e* calcd for $C_{19}H_{25}NO_8$ 395.1580, found 395.1590. Anal. Calcd for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.79; H, 6.53; N, 3.59.

Dimethyl 2,3-Dihydro-2(*R*)-hydroxy-5-(3-carbomethoxy-2-methylpropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (11). A solution of crystalline acetate **10a** (3.95 g, 10.0 mol) in 50 mL of dry MeOH was stirred at room temperature under N_2. Sodium methoxide in MeOH (2% solution, 0.70 g, 13.0 mol) was added at room temperature and this mixture was stirred for 1 h. The reaction mixture was quenched by addition of 100 mL of 50% HOAc and the volatiles were removed at reduced pressure. Extraction into EtOAc (2 × 250 mL) followed by washing with 3 × 100 mL of H_2O and then evaporation gave 3.30 g (94%) of oily alcohol **11a**: TLC (R_f) 0.35, ethyl acetate; 0.66, acetone; 0.34 ether:acetone (2:1); IR $\lambda_{max}^{CHCl_3}$ 3470 (br, m), 2970 (m), 1710 (s), 1400 (m), 1200 (br), 1100 (m) cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.00 (d, 3 H), 2.34 (m, 3 H), 2.7 (m, 2 H), 3.15–3.25 (m, 2 H), 3.52 (s, 3 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 5.00 (m, 1 H); $[\alpha]^{25}_D$ +12.8° (*c* 2.94 $CHCl_3$), +31.0° (*c* 2.81, MeOH).

Hydrolysis of Acetate Mixture. A mixture of diastereomeric acetates **10** (enriched in the oily isomer **10b**, 28.6 g, 72.5 mmol) was treated as above and then quenched with 200 mL of 50% HOAc. Evaporation of the volatiles and workup as above followed by chromatography on 600 g of silica gel with hexane:EtOAc (1:2) gave 13.36 g (52%) of a mixture of oil and solid from which 5.99 g of a single solid isomer was obtained (**11b**) by recrystallization from hexane:EtOAc (mp 84–85 °C) and 7.37 g of an oil enriched in the oily alcohol **11a**. In practice, the isomers are not separated and are used as a mixture in subsequent reactions. Typical yields on 79.0 g (200 mmol) of starting material is 50.0 g (71%): IR λ_{max}^{KBr} 3520 (s), 2970 (m), 1710 (s), 1470 (s), 1435 (m), 1310 (s) cm^{-1}; $\lambda_{max}^{CHCl_3}$ **11b** 283.7 nm (ϵ 2170.9, log ϵ 3.337); NMR **11b** (100 MHz, $CDCl_3$) δ 1.00 (d, 3 H), 2.20–2.30 (m, 3 H), 2.7 (m, 2 H), 3.07, 3.26 (m, 2 H, AB, J_{Bx} = 3 Hz, J_{AX} = 6 Hz, J_{AB} = 19 Hz), 3.55 (s, 3 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 3.96, 4.07 (m, 2 H, A′B′, $J_{B'X'}$ = 5 Hz, $J_{A'B}$ = 12 Hz), 5.00 (m, 1 H); mass spectrum (15 eV), *m/e* (relative intensity) 353 M^+ (52.3), 354 (16.0), 322 (39.1), 321 (100), 252 (66.5), 248 (64). An analytical sample of **11a** was prepared by recrystallization from cyclohexane–ether: $[\alpha^{25}D$ +22.1° (*c* 1.5, MeOH), −4.9° (*c* 1.5, $CHCl_3$); *m/e* calcd for $C_{17}H_{23}NO_7$ 353.1474, found 353.1469. Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.74; H, 6.73; N, 3.98.

Dimethyl 2,3-Dihydro-2(*R*)-[(methylsulfonyl)oxy]-5-(3-carbomethoxy-2-methylpropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (12). Compound **11a** (3.28 g, 9.3 mmol) was dissolved in 90 mL of dry THF and cooled to 0 °C under N_2. While stirring vigorously, Et_3N (5.0 mL, 3.6 mmole) was added, followed by dropwise addition of $MeSO_2Cl$ (3.0 mL, 3.9 mmol). The resulting suspension was stirred at 0 °C for 30 min and then at room temperature for 40 min, after which time 30 mL of water and 30 mL of 10% HCl was added. Extraction into $CHCl_3$ (4 × 50 mL), drying (Na_2SO_4), and evaporation afforded 3.8 g (95%) of an almost colorless oil: $\lambda_{max}^{CHCl_3}$ 3020, 2950, 1736, 1720, 1700, 1575, 1532, 1178 cm^{-1}; NMR (90 MHz $CDCl_3$) δ 0.94 (d, 3 H), 2.27 (br m, 3 H), 2.56–2.71 (m, 2 H), 3.09 (s, 3 H), 3.36–3.44 (m, 2 H), 3.61 (s, 3 H), 3.77 (s, 3 H), 3.61 (s, 3 H), 4.20–4.33 (m, 2 H), 5.62–5.87 (m, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 431 (25), 399 (90), 326 (100), 304 (25); $[\alpha]^{25}_D$ +28.6° (*c* 2.50, MeOH); *m/e* calcd for $C_{18}H_{25}NSO9$ 431.1227, found 431.1250.

Dimethyl 2(*S*)-Azido-2,3-dihydro-5-(3-carbomethoxy-2-methylpropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (13). A solution of **12** (5.5 g, 12.7 mmol) in 70 mL of DMF was treated with 2.5 g of NaN_3 in 12 mL of H_2O. The mixture was kept at 90–100 °C overnight and then was cooled to room temperature and poured into 100 mL of H_2O. This was extracted with EtOAc (4 × 50 mL) and the pooled organic phase was washed with water and brine, dried, and evaporated to give 5.4 g of **13** as a yellow oil. Chromatography of 120 g of silica gel with ether gave 4.5 g of an almost colorless oil (93%): IR $\lambda_{max}^{CDCl_3}$ 2950, 2100, 1735, 1716, 1695, 1530, 1570, 1304 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.94 (d, 3 H), 2.10–2.37 (m, 3 H), 2.58–2.80 (m, 2 H); 3.17–3.29 (m, 2 H, AB, J_{BX} = 4 Hz, J_{AX} = 6 Hz, J_{AB} = 18 Hz), 3.57 (s, 3 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.08 4.21 (m, 2 H, A′B′, J_{BX} = 4 Hz, J_{AX} = 6 Hz, J_{AB} = 12 Hz), 4.50–4.80 (m, 1 H); mass spectrum (15 eV), *m/e* (relative intensity) 378 (30), 346 (90), 318 (40), 273 (60), 249 (100); $[\alpha]^{25}_D$ +3.44° (*c* 2.82, MeOH); *m/e* calcd for $C_{17}H_{22}N_4O_6$ 378.1539, found 378.1534.

Dimethyl 2(*S*)-Amino-2,3-dihydro-5-(3-carbomethoxy-2-methylpropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (14). A solution of **13** (4.4 g, 11.6 mmol) in 150 mL of EtOH was treated with 10% Pd or C and the mixture was hydrogenated at 1 atm H_2 for 24 h. The solution was filtered through Celite and the ethanol was removed in vacuo. The remaining oil was dissolved in 50 mL of EtOAc and was extracted into 3% HCl (4 × 40 mL). The acidic phase was washed with chloroform until colorless, then treated with 10% NaOH solution to pH >11, and then extracted with $CHCl_3$ (5 × 50 mL). The chloroform layer was washed with water and brine, dried, and then evaporated to yield 3.5 g (85%) of **14** as a clear oil: IR $\lambda_{max}^{CHCl_3}$ 3390, 2950, 1700, 1730, 1740, 1585, 1540 cm^{-1}; NMR (100-MHz, $CDCl_3$) δ 0.95 (d, 3 H), 1.73 (br, m, 2 H), 2.24 (br, m, 3 H), 2.48–2.92 (br, m, 3 H), 3.09–3.72 (br, m 3 H), 3.56 (s, 3 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 3.94–4.20 (m, 1 H); mass spectrum (15 eV), *m/e* (relative intensity) 352 (50), 320 (100), 251 (30), 247 (50); $[\alpha]^{25}_D$ −0.74° (*c* 2.7, MeOH); *m/e* calcd for $C_{17}H_{24}N_2O_6$ 352.1634, found 353.1619.

Dimethyl 2(*S*)-Acetamido-2,3-dihydro-5-(3-carbomethoxy-2-methylpropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (15). Compound **14** (34 g, 9.6 mmol) in 30 mL of Ac_2O was allowed to stir at room temperature for 2 h. Evaporation of the volatiles by Kugelrohr distillation at reduced pressure gave 3.7 g (98%) of a colorless oil: IR $\lambda_{max}^{CDCl_3}$ 3445, 3360, 2950, 1730, 1720, 1715, 1660, 1650, 1570, 1535 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 0.96 (d, 3 H), 1.98 (s, 3 H), 2.19 (br, m, 3 H), 2.65 (br, m, 2 H), 2.89–3.29 (m, 2 H, AB, J_{BX} = 4 Hz, J_{AX} = 8 Hz, J_{AB} = 17 Hz), 3.81–4.13 (m, 2 H, A′B′, $J_{B'X}$ = 4 Hz, $J_{A'X}$ = 7 Hz, $J_{A'B'}$ = 12 Hz), 4.80–5.16 (m, 1 H), 6.76–7.04 (br, 1 H); mass spectrum (70 ev), *m/e* (relative intensity) 394 (55), 362 (50), 335 (40), 303 (100); $[\alpha]^{25}_D$ −35.3° (*c* 3.0, MeOH); *m/e* calcd for $C_{19}H_{26}N_2O_7$ 394.1740, found 394.1750.

Dimethyl 2(*S*)-Acetamido-2,3,5,6,7,8-hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-7,9-dicarboxylate (16). Cyclization of 15. To a solution of freshly sublimed potassium *tert*-butoxide (540 mg, 4.82 mmol) in 54 mL of dry THF was added

15 (466 mg, 1.18 mmol) in 15 mL of THF under N_2 at 0 °C. This was allowed to warm to room temperature over 30 min. A suspension of a light yellow solid formed, which was stirred at room temperature for another 30 min. To the mixture was added 20 mL of 3% HCl under cooling, which dissolved the solid and formed an orange-yellow solution. This was extracted with $CHCl_3$, dried over Na_2SO_4, and then evaporated under reduced pressure. The resulting yellow oil was chromatographed on 30 g of silica gel (hexane:acetone, 2:1). Recrystallization from EtOAc afforded 278 mg (65%) of pure 16: mp 185–186 °C; λ_{max}^{KBr} 3350, 3005, 2950, 1730, 1660, 1540 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.08 (d, 3 H), 2.04 (s, 3 H), 2.20–2.80 (m, 3 H), 2.98, 3.22 (m, 2 H, AB, J_{BX} = 4 Hz, J_{AX} = 7 Hz, J_{AB} = 18 Hz), 3.79, 4.05 (m, 2 H, A'B', $J_{B'X}$ = 3 Hz, $J_{A'X}$ = 6 Hz), 3.68 (s, 3 H), 3.71 (s, 3 H), 4.83–5.20 (m, 1 H), 7.3–7.6 (br, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 362 (100), 330 (92), 271 (88), 203 (85); $[\alpha]^{25}_D$ +41.2° (*c* 2.0, $CDCl_3$); *m/e* calcd for $C_{18}H_{22}N_2O_6$ 362.1478, found 362.1463. Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.54; H, 6.11; N, 7.65.

2(*S*)-Acetamido-2,3,5,6,7,8-hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (21). A suspension of keto diester acetamide 16 (600 mg, 1.66 mmol) in 4 mL of methanol and 15 mL of water was treated dropwise with 18 mL of 2% NaOH under cooling. The solution was stirred overnight at room temperature and then was acidified with concentrated HCl at 0 °C to pH ≤1. A white precipitate formed which was collected by filtration. This was recrystallized from MeOH to give 430 mg (88.5%) of white needles: mp 266–267 °C dec; λ_{max}^{KBr} 3500, 3290, 2945, 2930, 1700, 1686, 1660, 1620, 1545, 1290, 920 cm^{-1}; NMR (90 MHz, $CDCl_3$–Me_2SO-d_6) δ 1.19 (d, 3 H), 1.90 (s, 3 H), 2.33–2.70 (m, 5 H), 3.08, 3.40 (m, 2 H, AB, J_{BX} = 5 Hz, J_{AX} = 7 Hz, J_{AB} = 18 Hz), 3.83, 4.58 (m, 2 H, A'B', $J_{B'X}$ = 4 Hz, $J_{A'X}$ = 6 Hz, $J_{A'B'}$ = 12 Hz, 4.72–5.11 (m, 1 H), 8.18–8.51 (br, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 290 (72), 272 (100), 230 (50), 213 (60), 189 (60), 165 (25); $[\alpha]^{25}_D$ −20.3° (*c* 0.6, DMF); *m/e* calcd for $C_{15}H_{18}N_2O_4$ 290.1266, found 290.1256. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.23; N, 9.65. Found: C, 62.06; H, 6.35; N, 0.54.

Benzyl 2(*S*)-Acetamido-2,3,5,6,7,8-hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (22). A solution of 21 (390.5 mg, 1.34 mmol) in 80 mL of anhydrous THF was heated under N_2 at 60 °C. Addition of trifluoroacetic anhydride (0.37 mL, 2.6 mmole) and stirring at 60 °C for 5 min was followed by addition of 0.32 mL (3.09 mmol) of benzyl alcohol. After 1 h, the solution was cooled to room temperature and then poured into 60 mL of saturated $NaHCO_3$ solution. This was extracted into $CHCl_3$ (3 × 40 mL). The organic phase was washed with brine, dried, and evaporated to give a residue. Recrystallization from EtOAc gave 407 mg (79%) of white solid: mp 199–200 °C; IR $\lambda_{max}^{CHCl_3}$ 2950, 1707, 1670, 1658, 1540 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.08 (d, 3 H) 2.02 (s, 3 H, $NCOCH_3$), 1.83–2.73 (m, 5 H), 2.93, 3.23 (m, 2 H), AB, J_{BX} = 4 Hz, J_{BX} = 7.5 Hz, J_{AB} = 18 Hz, 3.67, 4.02 (m, 2 H, A'B', $J_{B'X}$ = 3 Hz, $J_{A'X}$ = 6 Hz, $J_{A'B'}$ = 12 Hz), 4.98 and 5.21 (AB quartet, J = 13 Hz), 7.28 (br s, 5 H), 6.99–7.41 (br, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 380 (75), 321 (10), 289 (20), 272 (100); $[\alpha]^{25}_D$ −49° (*c* 0.7, $CHCl_3$); *m/e* calcd for $C_{22}H_{24}N_2O_4$ 380.1726, found 380.1745. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.41; H, 6.49; N, 7.34.

Benzyl 2(*S*)-Acetamido-2,3-dihydro-8-hydroxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (23). To 350 mg (0.92 mmol) of 22 in 180 mL of EtOAc was added in a dropwise manner a solution of 238 mg (1.05 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in 3 mL of ethyl acetate. The reaction was monitored by TLC, and at the completion the solution was cooled to room temperature and diluted with 150 mL of EtOAc. The organic phase was washed with saturated $NaHCO_3$ until the aqueous phase was colorless (6 × 50 mL). The organic phase was dried and after the solvent was removed, the residue was recrystallized from MeOH to give 250 mg (72%) of a white solid: mp 214–215 °C; λ_{max}^{KBr} 3290, 3030, 2902, 1680, 1660, 1540, 1200 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6, 90 MHz) δ 1.90 (s, 3 H), 2.34 (s, 3 H), 3.06, 3.44 (m, 2 H, AB, J_{BX} = 4 Hz, J_{AX} = 8 Hz, J_{AB} = 17 Hz), 3.89, 4.14 (m, 2 H, A'B', $J_{B'X}$ = 4 Hz, $J_{A'X}$ = 7 Hz, $J_{A'B}$ = 18 Hz), 4.81–5.13 (m, 1 H), 5.27 (s, 2 H), 6.37 (br s, 1 H), 6.53 (br s, 1 H), 7.33 (br s, 5 H), 7.90–8.13 (br, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 378 M^+ (90), 319 (60), 287 (70), 228 (100); $[\alpha]^{25}_D$ −77.1° (*c* 0.55, DMF); *m/e* calcd for $C_{22}H_{22}N_2O_4$ 378.1579, found 378.1562. Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.93; N, 7.46.

Benzyl 2(*S*)-Acetamido-7-bromo-2,3,5,8-tetrahydro-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (24). To a chilled solution of 23 (600 mg, 1.50 mmol) in 30 mL of THF and 8 mL of water was added 30 mL of 0.2 M acetate buffer. Bromine (0.4 mL, 8.0 mmol, 5.3 equiv) was added with vigorous stirring, and immediately upon the addition, the colorless solution turned orange-yellow. The reaction mixture was allowed to stir for 1 h and then was treated with 150 mL of saturated $NaHCO_3$ solution. This was extracted with $CHCl_3$ (3 × 60 mL). The organic phase was washed with 60 mL of 5% sodium bisulfite solution, dried, and then evaporated to yield a yellow-orange solid. Recrystallization from EtOAc gave 550 mg (73%) of a brilliant yellow solid: mp 184–186 °C dec; IR λ_{max}^{KBr} 3350, 2950, 1738, 1720, 1677, 1660, 1650, 1530 cm^{-1}; UV $\lambda_{max}^{CHCl_3}$ 294 nm (ϵ 15397, log ϵ 4.187), 334 nm (ϵ 3928, log ϵ = 3.594), 430 nm (ϵ 1492, log ϵ 3.174); NMR (90 MHz, $CDCl_3$) 2.08 (s, 3 H), 2.10 (s, 3 H), 2.88–3.68 (m, 2 H), 4.12–4.31 (m, 2 H), 5.24 and 4.96 (AB quartet, 2 H J = 12 Hz), 5.00–5.20 (m, 1 H), 2.8 (s, 5 H), 7.22–7.41 (br, 1 H); mass spectrum (70 ev), *m/e* (relative intensity) 471, 469 (20), 379, 381 (65), 363, 361 (70), 321, 319 (25), 307, 305 (100), 279, 277 (40); $[\alpha]^{25}_D$ −60° (*c* 0.15, $CHCl_3$); *m/e* calcd for $C_{22}H_{19}N_2O_5$ 470.0477, found 470.0443. Anal. Calcd for $C_{22}H_{19}N_2O_5Br$: C, 56.07; H, 4.21; N, 5.94. Found: C, 56.16; H, 4.21; N, 5.86.

Benzyl 2(*S*)-Acetamido-7-azido-2,3,5,8-tetrahydro-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (25). Compound 24 (25 mg, 0.053 mmol) was dissolved in 4 mL of MeCN and 1 mL of EtOH with heating. The mixture was cooled to room temperature and a large excess of NaN_3 (250 mg) dissolved in 3 mL of water was added dropwise. The color immediately changed from a yellow to a dark red. After being stirred at room temperature for 1 h, the reaction mixture was diluted with 10 mL of H_2O and then extracted with $CHCl_3$ (4 × 15 mL). The pooled organic phases were dried and then evaporated to give 21 mg (90%) of a red oil which was stored in the dark until used; IR $\lambda_{max}^{CHCl_3}$ 3353, 3000, 2103, 1725, 1678, 1663, 1640, 1590, 1538, 1130, 1268 cm^{-1}; UV $\lambda_{max}^{CHCl_3}$ 314 nm (ϵ 7826, log ϵ 3.89), 340 nm (ϵ 3365, log ϵ 3.52), 470 nm (ϵ 543, log ϵ 2.73); NMR (100 MHz, $CDCl_3$) 1.84 (s, 3 H), 2.06 (s, 3 H), 2.94, 3.27 (m, 2 H, AB, J_{BX} = 3 Hz, J_{AX} = 6 Hz, J_{AB} = 18 Hz), 4.23 (br d, 2 H), 4.90 and 5.26 (AB quartet, 2 H, J = 12 Hz) 5.00–5.20 (br, 1 H), 7.28 (s, 5 H), 7.17–7.51 (br, 1 H); mass spectrum (15 ev), *m/e* 405 ($M^+ - N_2$), 346, 314, 240; $[\alpha]^{25}$d −20° (*c* 0.15, $CHCl_3$); *m/e* calcd for $C_{22}H_{17}N_5O_5$ ($M^+ - N_2$) 405.1324, found 405.1326.

Benzyl 2(*S*)-Acetamido-7-amino-2,3,5,8-tetrahydro-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (26). Compound 25 (110 mg, 0.26 mmol) was dissolved in 8 mL of EtOH and 6 mL of Me_2CO. This solution was stirred at room temperature under N_2 and treated dropwise with freshly prepared 4% aqueous sodium dithionite until colorless. (A white solid formed during the addition of dithionite, and water was added dropwise to dissolve it). The mixture was stirred at 90–100 °C for 7 h and the reaction was complete when all the material showed purple TLC. The reaction mixture was cooled to room temperature and was added to 15 mL of H_2O. This was extracted into EtOAc (5 × 15 mL). The combined organic phases were washed with brine, dried, and then evaporated. Chromatography on 200 mg of silica gel (hexane/EtOAc) and then recrystallization from MeOH gave 34 mg (33%) of a purple solid whose melting point was indeterminate: IR λ_{max}^{KBr} 3470, 3320, 2930, 1728, 1718, 1680, 1661, 1625, 1600, 1580, 1300, 1270 cm^{-1}; UV λ_{max}^{MeOH} 312 nm (ϵ 16747, log ϵ 4.230), 269 nm (ϵ 11870, log ϵ 4.074), 530 nm (ϵ 1463, log ϵ 3.165); NMR (90 MHz, $CDCl_3$, Me_2SO-d_6) δ 1.80 (s, 3 H), 1.90 (s, 3 H), 2.97, 3.31 (m, 2 H, AB, J_{BX} = 5 Hz, J_{AX} = 8 Hz, J_{AB} = 17 Hz), 4.16–4.39 (m, 2 H, A'B', $J_{B'X}$ = 5 Hz, $J_{A'X}$ = 7 Hz, $J_{A'B}$ = 14 Hz), 4.76–5.11 (m, 1 H), 5.22 (s, 2 H), 5.72 (br, 2 H), 7.11–7.47 (m, 5 H), 7.92–8.22 (br, 1 H); mass spectrum (15 ev), *m/e* (relative intensity) 407 M^+ (70), 348 (30), 316 (100), 298 (50); *m/e* calcd for $C_{22}H_{21}N_3O_5$ 407.1481, found 407.1465. Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.19; N, 10.31. Found: C, 64.68; H, 5.40; H, 10.20.

Dimethyl 2,3,5,6,7,8-Hexahydro-2(*R*)-hydroxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-7,9-dicarboxylate (29). Cy-

clization of Oily Isomer 11a. A solution of potassium *tert*-butoxide (freshly sublimed, 7.750 g, 60.20 mmol, 4.5 equiv) in 500 mL of distilled THF was prepared and stirred at room temperature under nitrogen. The oily isomer **11a** dried by Kugelrohr evaporation of its benzene solution (5.43 g, 15.39 mmol) was dissolved in 55 mL of THF and added to the base. Within 0.5 min a light yellow suspension formed which was stirred at room temperature for an additional 0.5 h. The mixture was added to 10% HCl at 0 °C formed a yellow solution. This was extracted with 3 × 150 mL of $CHCl_3$ and dried. Removal of the solvent gave a yellow oil which crystallized from EtOAc to yield 1.801 g of white solid **29a**; mp 193–195 °C. The mother liquor was chromatographed on silica gel with hexane:acetone and gave an additional 0.936 g (total yield 56.1%): TLC (R_f) 0.10, ethyl acetate; 0.48, acetone, 0.29, ether:acetone (2:1); NMR (90 MHz, $CDCl_3$) δ 1.95 (d, 3 H), 2.60–2.80 (m, 3 H), 3.10–3.20 (m, 2 H), 3.70 (br s, 6 H), 4.00–4.20 (m, 2 H), 5.05 (m, 1 H); $[\alpha]^{25}_D$ +91.2 (*c* 1.5, C_3H_6O), +98.8 (*c* 1.5, MeOH).

Cyclization of Solid Isomer 11b. The same procedure was employed as described above using 5.36 g of **11b**. Recrystallization from EtOAc gave 2.80 g of **29b** from the first crop; mp 201–203 °C. The remainder was chromatographed on silica gel with hexane:acetone (2:1) and gave an additional 0.50 g (total yield 67.7%): TLC (R_f), same as above; λ_{max}^{KBr} 3480 (m), 2960 (2), 1730 (s), 1616 (m), 1475 (w), 1310 (w) cm^{-1}; $\lambda_{max}^{CHCl_3}$ 298.0 nm (ϵ 2536.1, log ϵ = 3.404); NMR (100 MHz, $CDCl_3$, C_3D_6O) δ 1.05 (d, 3 H), 2.60–2.80 (m, 3 H), 3.11–3.26 (m, 2 H, AB, J_{BX} = 1 Hz, J_{AX} = 6 Hz, J_{AB} = 15 Hz), 3.68 (s, 3 H), 3.72 (s, 3 H), 3.92, 4.16 (m, 2 H, A'B', $J_{B'X'}$ = 3 Hz, $J_{A'X}$ = 6 Hz, $J_{A'B'}$ = 17 Hz), 5.05 (m, 1 H); mass spectrum (70 ev), *m/e* (relative intensity) 321 M^+ (45), 322 (9), 290 (39), 289 (50), 262 (30), 234 (10), 230 (51), 221 (89), 215 (11), 163 (59), 135 (100). An analytical sample was prepared by recrystallization from EtOAc: mp 204–206 °C; $[\alpha]^{25}_D$ −38.2° (*c* 1.5, C_3H_6O), −36.4° (*c* 1.5, MeOH); *m/e* calcd for $C_{16}H_{19}NO_6$ 321.1212, found 321.1207. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.72; H, 6.11; N, 4.33. The same procedure was employed as above on a mixture of diastereomeric alcohols on a 18.51-g (51.41 mmol) scale. Recrystallizatiom from EtOAc gave 12.50 g (75.8%) of **29**.

Hydrolysis of 29a. 2,3,5,6,7,8-Hexahydro-2(*R*)-hydroxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid, Keto Monoacid Alcohol (30a). A solution of keto diester alcohol **29a** (2.21 g, 7.00 mmol) in 85 mL of MeOH and 200 mL of water was treated dropwise with 4.75 equiv of NaOH (1.33 g/60 mL H_2O). The solution was stirred overnight at room temperature, and then was acidified by dropwise addition of 6 N H_2SO_4 at 0 °C. Within 1 h a white suspension formed. Filtration of the suspension gave, after drying, 1.629 g of white solid, mp 250–254 °C. [Reesterification of this solid with diazomethane gave the starting material (by TLC and NMR); however, the TLC and NMR of the solid is not that of the starting material nor the 9-carboxylic acid but is consistent with the hydrolyzed 7,9-dicarboxylic acid (cf. 17). The solid product was decarboxylated to **30a** by heating in MeOH. In practice, the dicarboxylic acid is used directly to prepare the C-2 mesylate and suffers decarboxylation at C-7 upon workup.] The filtrate was concentrated at the water aspirator and extracted with ethyl acetate (5 × 100 mL) and dried. Removal of the solvent gave an additional 0.216 g of a white solid, **30a**, which was recrystallized from ether/ethyl acetate: mp 263–264 °C; the total yield was 91.4%; TLC (R_f) **30a**, 0.11, EtOAc; 0.55, acetone; 0.42, ether:acetone (2:1); λ_{max}^{KBr} 3150 (br, s), 2950 (br, w), 1735 (s), 1675 (s), 1590 (s), 1475 (m), 1140 (m), 1055 (s), 950 (br, m), 780 (s); $\lambda_{max}^{CHCl_3}$ 303.5 nm (ϵ 2216, log ϵ 3.327); NMR (90 MHz, C_3D_6O) 1.15 (d, 3 H), 2.35–2.55 (m, 5 H), 2.90–3.40 (m, 2 H), 3.75–4.25 (m, 2 H), 4.90–5.10 (m, 1 H); mass spectrum (15 eV), *m/e* (relative intensity) 249 M^+ (100), 231 (27), 207 (30), 205 (28), 163 (27); $[\alpha]^{25}_D$ +53.9° (*c* 1.4 MeOH).

Hydrolysis of 29b. Preparation of Keto Monoacid Alcohol 30b. The same procedure was employed as given above. Recrystallization from ether:EtOAc gave **30b**: mp 249–251 °C (98%); NMR (100 MHz, C_3D_6O) δ 1.15 (d, 3 H), 2.35–2.55 (m, 5 H), 3.01, 3.28 (m, 2 H, AB, J_{BX} = 3.0 Hz, J_{AX} = 5.5 Hz, J_{AB} = 15 Hz), 3.86, 4.18 (m, 2 H, A'B', $J_{B'X'}$ = 2.5 Hz, $J_{A'X'}$ = 5.4 Hz, $J_{A'B'}$ = 12.8 Hz), 4.90–5.10 (m, 1 H); *m/e* calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.0994; $[\alpha]^{25}_D$ −7.6° (*c* 1.5, MeOH). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.52; H, 6.23; N, 5.46.

Hydrolysis of Mixture of Diastereomers. The same procedure could be performed on a mixture of diastereomeric alcohols on a 12.82-g (40.00 mmol) scale, giving 11.13 g of **30** (95.6%).

2,3,5,6,7,8-Hexahydro-2(*R*)-[(methylsulfonyl)oxy]-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (31a). Compound **30a** (1.383 g, 4.75 mmol) was dissolved in 150 mL of dry THF containing 10 mL of MeCN at 60 °C, cooled to 0 °C, and rapidly treated with Et_3N (4.62 mL, 33.25 mmol) followed by 2.5 mL of mesyl chloride. The resulting suspension was stirred at 0 °C for 1 min and at room temperature for 0.5 h. Water and $CHCl_3$ were added, and the organic phase was extracted with 10% HCl, saturated NaCl, and dried. Evaporation afforded a solid, 1.284 g (82.7%), which was recrystallized from ether and EtOAc: mp 206–208 °C; TLC (R_f) 0.20, ethyl acetate; IR $\lambda_{max}^{CDCl_3}$ 3390 (m), 2941 (s), 1709 (m), 1595 (s), 1460 (d, m), 1360 (m), 1205 (s) cm^{-1}; NMR (100 MHz, C_3D_6O) δ 1.25 (d, 3 H), 2.40–2.60 (m, 5 H), 3.08 (s, 3 H), 3.40–3.50 (m, 2 H), 4.16 (m, 2 H), 4.16 (m, 2 H), 5.64–5.80 (m, 1 H); mass spectrum (70 eV), *m/e* 327 M^+, 285, 331, 213; $[\alpha]^{25}_D$ +55.1° (*c* 1.5, C_3H_6O).

Preparation of Keto Acid Mesylate 31b. The same procedure was employed as above, giving 79% **31b**: mp 182–184 °C; $\lambda_{max}^{CHCl_3}$ 303.0 nm (ϵ 2844.9, log ϵ 3.454); IR and NMR spectral data of **31b** same as **31a**; $[\alpha]^{25}_D$ −6.6° (*c* 1.5, C_3H_6O); *m/e* calcd for $C_{14}H_{17}NO_6S$ 327.0776, found 327.0772. Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.37; H, 5.23; N, 4.28. Found: C, 51.21; H, 5.28; N, 4.24.

5,6,7,8-Tetrahydro-6-methyl-8-oxo-3*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (32a). Compound **31a** (490 mg, 1.50 mmol) was dissolved in 40 mL of MeOH and cooled to 0 °C. A 2% solution of NaOMe in MeOH was added at 0 °C (2.5 equiv, 10.2 mL) and brought to reflux under nitrogen. The mixture slowly turned yellow and was stirred for 4 h at reflux and then quenched with 20 mL of 10% HCl at 0 °C. The volatiles were removed on a water aspirator, $CHCl_3$ was added, and the solution was washed with brine. The organic phase was dried and evaporated to afford a light yellow solid, which, after silica gel chromatography, gave 215 mg (69%) of a light tan solid: mp 217–220 °C; TLC (R_f) 0.18, EtOAc; 0.64, acetone; 0.46, ether:acetone (2:1); 0.39, hexane:ether (1:1); IR $\lambda_{max}^{CHCl_3}$ 1705 (br, m), 1470 (s) cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.45 (d, 3 H), 2.40–2.90 (m, 5 H), 4.42 (br, s, 2 H), 6.45–6.60 (1 H, dt, J = 6.0, 2.0 Hz, H-1), 6.85–7.00 (1 H, dt, J = 6.0, 2.0 Hz, H-2); mass spectrum (15 eV), *m/e* 231 M^+, 213, 189; $[\alpha]^{25}_D$ +47.2 (*c* 0.72, $CHCl_3$); *m/e* calcd for $C_{13}H_{13}NO_3$ 231.0896, found 231.0894. Compound **32b** was prepared from **31b** (0.44 g, 1.35 mmol) by the same procedure as above. The melting point and IR, NMR, and mass spectra were identical, but $[\alpha]^{25}D$ −45.0° (*c* 0.72, $CHCl_3$).

β,β,β-Trichloroethyl 5,6,7,8-Tetrahydro-6-methyl-8-oxo-3*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (33, R = CH_2CCl_3). Compound **32** (3.404 g, 14.74 mmol) was esterified by using CCl_3CH_2OH (2.83 mL, 29.48 mmol) and trifluoroacetic anhydride (4.16 mmol, 29.48 mmol). Workup of the reaction mixture and chromatography on 500 g of silica gel with hexanes:acetone (4:1) and elution of the product with 1:1 hexanes:acetone gave after crystallization from Et_2O:EtOAc 2.41 g (45%) of a white solid: mp 152–153 °C; IR $\lambda_{max}^{CHCl_3}$ 3010 (w), 2980 (w), 1730 (s), 1665 (m), 1580 (w), 1460 (w), 1365 (w), 1295 (m), 1115 (m), 1090 (m); NMR (90 MHz, $CDCl_3$) δ 1.15 (br d, 3 H), 2.20–2.90 (m, 5 H), 4.50–4.60 (br s, 2 H), 4.92 (s, 2 H), 6.80–6.90 (m, 1 H), 7.10–7.30 (m, 1 H); mass spectra (70 eV), *m/e* (relative intensity) 361 (85), 316 (68), 214 (100), 188 (50); *m/e* calcd for $C_{15}H_{14}NO_3Cl_3$ 361.0039, found 360.0994.

Benzyl 5,6,7,8-Tetrahydro-6-methyl-8-oxo-3*H*-pyrrolo-[1,2-*a*]indole-9-carboxylate (33, R = $CH_2C_6H_5$). Compound **32** (0.55 g, 2.38 mmol) was esterified in the usual manner with benzyl alcohol (0.49 mL, 4.77 mmol) and $(CF_3CO)_2O$ (1.90 mL, 4.77 mmol). Workup and chromatography gave 0.40 g (53%): IR $\lambda_{max}^{CHCl_3}$ 3010 (m), 2920 (m), 1710 (s), 1660 (s), 1580 (m), 1460 (s), 1430 (m), 1380 (m), 1320 (m), 1290 (s), 1130 (s), 1090 (s), 970 (w), 940 (w); NMR (300 MHz, $CDCl_3$) δ 1.15 (d, 3 H, J = 6 Hz), 2.20–2.90 (m, 5 H), 4.30–4.50 (m, 2 H, H-3), 5.32 (s, 2 H), 6.5–6.58 (dt, 1 H, J = 2 Hz, 2 Hz, 6 Hz), 6.90–6.98 (dt, 1 H, J = 2 Hz, 2 Hz, 6 Hz), 7.30–7.60 (m, 5 H); mass spectra (15 eV), *m/e* (relative intensity) 321 (50), 278 (15), 214 (100), 186 (95); *m/e* calcd for $C_{20}H_{19}NO_3$ 321.1365; found 321.1363.

β,β,β-Trichloroethyl *cis*-1,2-Dihydroxy-2,3,5,6,7,8-hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (34, R = CH_2CCl_3). The cis diol was prepared by using two hydroxylation procedures. The procedure using H_2O_2 is described below. Compound **33**, a mixture of C-6 isomers (300 mg, 0.83 mmo), was dissolved in 12 mL of THF, 6 mL of water, and 2 mL of *tert*-butyl alcohol at room temperature. To this stirred solution was added 0.2 mL of 30% H_2O_2 (1.74 mmol). The original tan solution changed to light orange-yellow and after 15 min, 0.2 mL of 2.5% OsO_4/*t*-BuOH (0.019 mmol) was added. The mixture was stirred at room temperature with careful monitoring by TLC in EtOAc. After 2 h, 0.2 mL of 30% H_2O_2 was added, and a momentary decolorization was observed; after another 1 h an additional 0.15 mL was added (total of 0.5 mL of 30% H_2O_2) and the reaction was complete by TLC. After stirring for a total of 3 h, 50 mg of sodium bisulfite in 5 mL of H_2 was added, and stirring was continued for 5 min at room temperature. The quenched mixture was added to 100 mL of EtOAc, washed with 5 × 20 mL of H_2O, and then dried over Na_2SO_4. The solvent was removed and a glassy solid formed which was crystallized from ether to give 200 mg (60%): mp 179–181 °C; IR $\lambda_{max}^{CHCl_3}$ 3450 (br s), 2920 (s), 1735 (s), 1670 (s), 1590 (w), 1455 (m), 1300 (m), 1120 (s); NMR (300 MHz, $CDCl_3$) mixture of diastereomers δ 1.15 (d, 3 H, *J* = 6.0 Hz, C-6), 2.37–2.81 (m, 5 H), 3.88–4.14 (m, 2 H, H-3), 4.83–4.88 (m, 1 H, H-2), 4.91-4.96 (AB, 2 H), 5.29–5.33 (d, 2 H), coupling constants not determined due to mixture of isomers present; mass spectrum (15 eV), *m/e* (relative intensity) 395, 397 (30), 247 (100), 219 (20), 203 (50); *m/e* calcd for $C_{15}H_{16}NO_5Cl_3$ 395.0094, found 395.0093.

Benzyl *cis*-1,2-Dihydroxy-2,3,5,6,7,8-hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (34, R = $CH_2C_6H_5$). Of *N*-methylmorphine *N*-oxide (450 mg, 261 mmol) was dissolved in *tert*-butyl alcohol:THF:H_2O (4:12:4) containing 50 μL of 2.5% OsO_4 in *tert*-butyl alcohol (0.0498 mmol). To this mixture was added 600 mg (1.87 mmol) of the benzyl ester olefin (mixture of isomers) dissolved in 10 mL of THF. The reaction mixture was stirred at room temperature for 48 h after which the dark brown mixture was quenched by adding 2.0 g of sodium bisulfite in 10 mL of H_2O and stirred for 20 min at room temperature. The mixture was added to 150 mL of $CHCl_3$ and washed with 1 × 35 mL of H_2O, 3 × 30 mL of 10% HCl and then dried. The solvent was removed and the crude residue was chromatographed on 200 g of silica gel with 4:1 Et_2O:EtOAc. The product was eluted with 1:1 Et_2O:EtOAc and 464.0 mg (76%) was isolated: IR $\lambda_{max}^{CHCl_3}$ 3200–3400 (br, m), 3010 (m), 2960 (m), 1710 (s), 1665 (s), 1455 (s), 1300 (s), 1070 (m); NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 3 H), 2.20–2.80 (m, 5 H), 4.72 (br s, 1 H, OH), 3.85–4.00 (m, 2 H, H-3), 4.70–4.75 (m, 2 H, H-2), 5.10–5.20 (d, 1 H, mixture of isomers, H-1), 5.35 (s, 2 H), 7.20–7.60 (m, 5 H); mass spectrum (70 eV), *m/e* 355 (20), 264 (15), 248 (100), 246 (50), 230 (10), 203 (30); *m/e* calcd for $C_{20}H_{21}NO_5$ 355.1420, found 355.1421.

Preparation of the Phenol Trichloroethyl Ester Acetonide 35. Compound **34** (R = CH_2CCl_3) (300 mg, 0.75 mmol) was dissolved in 10 mL of distilled acetone and to this was added 10 mg of *p*-toluenesulfonic acid. After 5 min, 0.25 mL (1.50 mmol) of 2,2-dimethoxypropane was added. This was stirred at room temperature for 10 min, after which TLC showed complete formation of a new product. Acetone was removed at the water aspirator and the concentrate was diluted with 100 mL of EtOAc and washed with saturated $NaHCO_3$ (3 × 25 mL) and H_2O. The organic phase was dried and after removal of the volatiles in vacuo the residue was chromatographed on 100 g of silica gel with hexane:EtOAc (4:1). The product was eluted with (1:1–2:1) EtOAc:hexane and crystallized from ether to give 180 mg (55%) of the acetonide. This material (150 mg, 0.34 mmol) was dissolved in 30 mL of EtOAc and dehydrogenated with 80 mg (0.35 mmol) of DDQ in 2 mL of ethyl acetate. The mixture was stirred at reflux, and at completion (as observed by TLC) the mixture was cooled to room temperature and then diluted with 60 mL of EtOAc. This was washed with saturated $NaHCO_3$ until the organic phase was colorless. After removal of the solvent the residue was crystallized from MeOH to give 110 mg of a semisolid which was homogeneous by TLC: IR $\lambda_{max}^{CHCl_3}$ 3250 (w), 1670 (s), 1550 (m), 1570 (m), 1410 (m), 1120 (s), 1130 (s); NMR (300 MHz, $CDCl_3$) δ 1.338 (s, 3 H), 1.431 (s, 3 H), 2.405 (s, 3 H, C-6), 4.171–4.241 (m, 2 H, H-3), 4.852, 5.176 (AB, 2 H, $\Delta\nu_{AB}$ = 97.4 Hz, *J* = 11.95 Hz), 5.385–5.425 (m, 1 H, H-2), 5.884 (d, 1 H, *J* = 6.25 Hz, H-1), 6.589 (s, 2 H, H-5, H-7); mass spectra (70 eV), *m/e* (relative intensity) 433, 435 (50), 418, 420 (10), 287 (100); *m/e* calcd for $C_{18}H_{18}NO_5Cl_3$ 433.0251, found 433.0239.

***trans*-2-Bromo-2,3,5,6,7,8-hexahydro-1-hydroxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (36).** Compound **32** (3.00 g, 13.0 mmol, ca. 1:1 mixture of isomers at C-6) was dissolved in 70 mL of THF at room temperature. To the solution was added 81.3 mL of 0.16 M Br_2/H_2O solution (8 μL/mL, 13.0 mmol) in 15-mL aliquots at 15-min intervals. After addition of the bromine water, TLC indicated that the reaction was complete. The reaction mixture was added to 250 mL of EtOAc and was washed with saturated sodium bisulfite (2 × 75 mL) and H_2O (3 × 50 mL). The organic phase was dried and upon removal of the solvent a white solid was deposited. This was filtered and washed with ether/ethyl acetate and weighed 2.71 g. The mother liquor was chromatographed on 250 g of hexane:EtOAc (4:1), and the product was eluted with hexane:EtOAc (1:1) and gave 450 mg (total yield 74.3%). An analytical sample was prepared by recrystallization from Et_2O/EtOAc: mp 179–181 °C dec; IR $\lambda_{max}^{CHCl_3}$ 3400 (br, m), 1670 (m), 1595 (s), 1500 (w), 1440 (s), 1400 (m), 1320 (w), 1040 (m), 920 (m); NMR (300 MHz, $CDCl_3$) mixture of isomers at C_6, δ 1.176–1.196 (d, 3 H, *J* = 5.9 Hz, C-6), 2.277–2.803 (m, 5 H), 4.083–4.181 (m, 1 H, H-3), 4.557–4.657 (m, 2 H, H-2, H-3′), 5.142 and 5.179 (br s, 1 H each diastereomer C-1, OH), 5.438 (d, one isomer at C-6, *J* = 5.0 Hz H-1, these doublets are ca. 1:1 and represent 1 H at C-1), 14.18 (s, C-9 CO_2H, these singlets are ca. 1:1 and represent 1 H); *m/e* calcd for $C_{13}H_{14}NO_4Br$ 327.0106, found 327.0108; mass spectrum (15 eV), *m/e* (relative intensity) 327, 329 M^+ (50), 309, 311 (100), 281, 283, 267, 269, 258, 260, 230 (70). Anal. Calcd for $C_{13}H_{14}NO_4Br$: C, 47.72; H, 4.31; N, 4.28. Found: C, 47.68; H, 4.33; N, 4.20.

***trans*-2-Bromo-2,3,5,6,7,8-hexahydro-1-methoxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (37).** To a suspension of 347 mg (1.50 mmol) of **32** (mixture of isomers at C-6) in 20 mL of freshly distilled MeOH was added 150 μL of bromine (3.0 mmol) dropwise over 15 min, and the mixture was stirred at room temperature. (Bromine can also be added as a solution in methanol with a concentration from 0.02 M (1.0 μL/mL) to 0.10 M (5.0 μL/mL) using 2.0 equiv. However, a higher concentration of Br_2 results in extensive decarboxylation.) After TLC, EtOAc (R_f) ~0.8), indicated complete conversion to the product (ca. 1 h), the solution was added to 120 mL of EtOAc. The solution was washed with saturated sodium bisulfite (2 × 75 mL), water (2 × 50 mL), and 2% HCl (2 × 50 mL). The solvent was dried, evaporated, and gave 342 mg (68%) of **37** as a white solid: mp 172–173 °C; IR $\lambda_{max}^{CHCl_3}$ 3200 (br w), 1715 (m), 1608 (s), 1470 (m), 1455 (s), 1085; NMR (300 MHz, $CDCl_3$), mixture of isomers at C-6, δ 1.221 (d, 3 H), 2.327–2.908 (m, 5 H), 3.502 (s, 3 H), 4.087–4.130 and 4.113–4.157 (two overlapping doublets, AB, 1 H, *J* = 12.9 Hz, H-3), 4.591–4.682 (m, 1 H, H-3′), 4.737 (apparent doublet *J* = 4.41 Hz, H-2), 5.232, 5.243 (two apparent singlets, isomers at C-6, 1 H, H-1); mass spectrum (15 eV), *m/e* (relative intensity) 341, 343 (15), 326 (s), 310, 312 (25), 300, 302 (15), 231 (100), 214 (90), 188 (50); *m/e* calcd for $C_{14}H_{16}NO_4Br$ 341.0263, found 341.0255.

Benzyl *trans*-2-Bromo-2,3,5,6,7,8-hexahydro-1-methoxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (38). To a solution of **37** (445 mg, 1.30 mmol), a mixture of isomers at C-6, dissolved in 25 mL of freshly distilled acetone was added 400 mg of anhydrous K_2CO_3 followed by three crystals of 18-crown-6. The reaction mixture was stirred and heated to reflux under nitrogen, and 250 μL (2.24 mmol) of benzyl bromide was added. After heating at reflux for 18 h, a fine suspension (KBr) was observed in the flask. The solvent was removed, and the product mixture was treated with 100 mL of EtOAc. The organic solution was washed with saturated $NaHCO_3$ (3 × 25 mL) and H_2O (2 × 25 mL). The solvent was dried and after concentration in vacuo the residue was chromatographed on 200 g of silica gel (60–200 mesh) with hexane/EtOAc. Benzyl bromide was eluted with hexane:EtOAc (3:1) and the product with hexane:EtOAc (1:1), giving 425 mg (75.5%) of a light tan solid: mp 140–141 °C dec; IR $\lambda_{max}^{CHCl_3}$ 2940 (w), 1720 (m), 1665 (s), 1480 (m), 1450 (m), 1410 (m), 1350 (m), 1305 (m), 1290 (m), 1130 (m), 1085 (s); NMR (300 MHz, $CDCl_3$), mixture of isomers at C-6, δ 1.152 (d, 3 H, *J* = 6.3

Hz), 2.276–2.774 (m, 5 H), 3.176 and 3.186 (s, 3 H ca. 1:1 isomers at C-6, OCH_3), 4.051–4.093 and 4.072–4.115 (two overlapping doublets, 1 H, $J_{3,3'}$ = 12.73 Hz, H-3), 4.537–4.620 (m, 1 H, H-3'), 4.654–4.670 (d, 1 H, J = 4.6 Hz, H-2), 4.910–4.912 and 4.931–4.933 (two doublets, 1 H, isomers at C-6, J = 0.4 Hz, H-1), 5.291, 5.363 and 5.299, 5.372 (two sets of overlapping AB, 2 H, $\Delta\nu_{AB}$ = 10.9 Hz, J = 12.5 Hz), 7.305–7.510 (m, 5 H); mass spectrum (15 eV), m/e (relative intensity) 431, 433 (70), 400, 402 (10), 325, 327 (80), 217 (100, 188 (50); m/e calcd for $C_{21}H_{22}NO_4Br$ 433.0712, found 433.0713.

***trans*-1-Acetoxy-2-bromo-2,3,5,6,7,8-hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (39).** Compound **36** (270 mg, 0.82 mmol) was dissolved in 15 mL of Ac_2O and 2 crystals of (dimethylamino)pyridine were added. The solution was stirred at room temperature for 3 h after which time the solvent was removed in vacuo. The residue was dissolved in 75 mL of EtOAc and then washed with saturated $NaHCO_3$ (3 × 30 mL) and H_2O (3 × 25 mL). After drying and removal of the solvent the residue was chromatographed on 100 g of silica gel with hexane/EtOAc. The product was eluted with hexane:EtOAc (1:1) and gave 180 mg (60%) of a white solid: mp 170–174 °C dec; IR $\lambda_{max}^{CHCl_3}$ 2600–2700 (br, m), 1750 (s), 1608 (s), 1520 (w), 1475 (s), 1455 (s), 1420 (m), 1380 (m), 1365 (m), 1020 (m); NMR (300 MHz, $CDCl_3$) δ 1.231 (d, 3 H, J = 6.2 Hz), 2.092 (s, 3 H), 2.365–2.942 (m, 5 H), 4.204–4.274 (dd, 1 H, $J_{2,3}$ = 1.0 Hz, $J_{3,3'}$ = 12.9 Hz, H-3), 4.611–4.704 (m, 1 H, H-3'), 4.751–4.777 (apparent dt, 1 H, H-2), 6.418–6.431 and 6.422–6.435 (overlapping doublets, 1 H, J = 3.84 Hz, H-1); mass spectrum (15 eV) m/e (relative intensity) 369, 371 (10), 309, 311 (70), 289 (80), 272 (85), 247 (70), 231, 213 (100); m/e calcd for $C_{15}H_{16}NO_5{}^{81}Br$ 371.0191, found 371.0192.

Benzyl *cis*-2,3,5,6,7,8-Hexahydro-1-hydroxy-6-methyl-2-[(*p*-tolylsulfonyl)oxy]-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (40). Compound **34**, R = $CH_2C_6H_5$ (297.5 mg, 0.84 mmol), was tosylated by using 15 mL of pyridine and 312 mg (1.68 mmol) of *p*-TsCl for 16 h at room temperature. The product was decolorized with charcoal and chromatographed on silica. The product was eluted with 4:1 Et_2O/EtOAc. This gave 133 mg (32%); elution with EtOAc recovered 125 mg (29%) of the starting material: IR $\lambda_{max}^{CHCl_3}$ 3300–3500 (br, m), 2920 (m), 1700 (m), 1610 (s), 1460 (m), 1180 (m); NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 3 H), 2.15–2.80 (m, 5 H), 2.43 (s, 3 H), 4.00 (br s, 1H-OH), 4.10–4.20 (m, 2 H, H-3), 5.18–5.22 (m, 4 H, H-1, H-2, C-9-$OCH_2C_6H_5$), 7.20–7.40 (m, 5 H), 7.80, 7.84 (4 H, AB, $\Delta\nu_{AB}$ = 40 Hz, J = 9 Hz).

Benzyl *trans*-2-Azido-2,3,5,6,7,8-hexahydro-1-hydroxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (41). To a solution of 104 mg (0.21 mmol) of compound **40** in 12 mL of DMF was added 1.0 g of NaN_3 in 1.0 mL of H_2O. After being stirred at 85–90 °C for 3 h, the reaction mixture was cooled to room temperature and added to 60 mL of EtOAc. It was washed with H_2O (3 × 15 mL) and then dried. The residue which formed after the solvent was removed was chromatographed on 60 g of silica gel with Et_2O/EtOAc (1:1) and gave 40 mg (50.1%) of a crystalline solid: IR $\lambda_{max}^{CHCl_3}$ 3400 (br m), 2990, 2920 (m), 2105 (s), 1708 (s), 1665 (s), 1560 (m), 1450 (m), 1360 (m), 1305 (m), 1080 (m). NMR (300 MHz, $CDCl_3$) 1.20 (d, 3 H), 2.20–2.80 (m, 5 H), 3.65–3.80 (AB, 1 H, H-3), 4.25–4.40 (AB, 1 H, H-3), 4.55–4.62 (m, 1 H, H-2), 5.20–5.26 (d, 1 H, H-1 mixture of isomers), 5.28 (br s, 2 H), 7.25–7.60 (m, 5 H); mass spectrum (15 ev), m/e (relative intensity) 380 M^+ (10), 334 (80), 325 (60), 235 (100), 228 (90), 200 (50); m/e calcd for $C_{20}H_{20}N_4O_4$ 380.1484, found 380.1494.

***trans*-1-Azido-2,3,5,6,7,8-hexahydro-2-hydroxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (43).** To a solution of **36** (mixture of isomers at C-6) (327 mg, (1.00 mmol) dissolved in 15.0 mL of DMF was added 1.00 g of NaN_3 dissolved in 3.0 mL of water. The mixture was heated from room temperature to 70 °C and was kept at this temperature for 8 h. The reaction mixture was added to 200 mL of EtOAc and was washed with H_2O (3 × 50 mL). This was reextracted with $CHCl_3$ (2 × 50 mL) and the pooled organic phases were dried and concentrated to give a crude solid which was chromatographed on 100 g of silica gel with hexane/EtOAc. The product was eluted with hexane:EtOAc (1:1) and gave 200 mg (69%) of **43**: IR $\lambda_{max}^{CHCl_3}$ 3350–3500 (br m), 2980 (m), 2105 (s), 1720 (s), 1605 (s), 1460 (s), 1420 (w), 1375 (s), 1220 (m), 1150 (w), 1120 (m), 1045 cm^{-1}; NMR (300 MHz, $CDCl_3$), isomers at C-6, δ 1.205–1.225 and 1.211–1.231 (d, 3 H, J = 6.02 Hz, C-6), 2.327–2.964 (m, 5 H), 3.916–3.956 and 3.947–3.987 (d, 1 H, two overlapping sets of doublets, $J_{3,3'}$ = 12.06 Hz, H-3), 4.122–4.178 and 4.164–4.218 (dd, 1 H, two overlapping sets of doublet of doublets, $J_{2,3'}$ = 4.30 Hz, $J_{3,3'}$ = 12.04 Hz, H-3'), 4.685–4.699 (d, 1 H, $J_{2,3'}$ = 4.30 Hz, H-2), 5.271 and 5.288 (s, 1 H, two singlets isomers at C-6, H-1), 5.225 (br s, 1 H, C_2-OH) and 14.329 (s, 1 H, CO_2H, C-9); mass spectrum (15 ev), m/e (relative intensity) 290 (50), 249 (100), 244 (100), 231 (50), 203 (20); m/e calcd for $C_{13}H_{14}N_4O_4$ 290.1015, found 290.1026.

***cis*- and *trans*-2,3,5,6,7,8-Hexahydro-2-hydroxy-1-methoxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (44 and 45).** A suspension of **36**, isomers at C-6 (3.270 g, 10.0 mmol), dissolved in 75 mL of freshly distilled MeOH was treated at room temperature with 3.0% NaOMe/MeOH solution (0.56 M) in 2.0-equiv aliquots at 15-min intervals. A total of 8.0 equiv (80.0 mmol, 143 mL) was required, and upon completion the mixture was quenched by being added to 100 mL of 10% HCl. The volatiles were removed and the crude solid remaining was taken up in 250 mL of EtOAc. The organic phase was washed with 2% HCl (2 × 50 mL) and H_2O (2 × 50 mL), and the aqueous phases were reextracted with 3 × 50 mL of EtOAc. The combined organic phases were dried and concentrated to give 2.23 g (80%) of **44/45** as a cis/trans mixture (84.4:15.6) as determined by NMR, mp 182–184 °C. The cis/trans mixture was not separable as the C_1-OMe C_2-OH derivative and was used directly in the following procedure; R_f 0.25 (EtOAc); IR $\lambda_{max}^{CDCl_3}$ (cis/trans 5:1) 3300–3700 (br w), 2500–2800 (br m), 1705 (s), 1605 (s), 1475 (s), 1460 (s), 1415 (m), 1425 (m), 1380 (w), 1340 (w), 1210 (m), 1180 (w), 1160 (w), 1115 (s), 1100 (s), 1065 (m), 1075 (w) cm^{-1}; NMR (300 MHz cis/trans isomers at C-6), δ 1.200–1.221 (d, 3 H, J = 6.07 Hz, C-6), 2.314–2.910 (m, 5 H), 3.423 and 3.426 (two singlets, isomers at C-6 H-1 OCH_3 trans), 3.572 and 3.574 (two singlets, isomers at C-6, H-1 OCH_3 cis), ratio of cis/trans 5.6:1, 3.657–3.749 (m, 1 H, H-3), 4.135–4.260 (m, 1 H, H-3'), 4.689–4.798 (m, 1 H, H-2), 4.870 and 4.880 (two singlets, C-1 trans), 4.925–4.943 and 4.932–4.950 (two overlapping doublets, $J_{1,2}$ = 5.26 Hz, H-1 cis); mass spectrum (15 ev) m/e (relative intensity) 279 (15), 259 (100) and 241 (70); m/e calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1105. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.05; H, 6.21; N, 5.00.

***cis*-2,3,5,6,7,8-Hexahydro-2-[(methylsulfonyl)oxy]-1-methoxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (51).** The mixture **44/45** (2.23 g, 7.99 mol), isomeric at C-6 and C-1,2, cis/trans (~6:1), was dissolved in 100 mL of dry THF and 4.4 mL of Et_3N and the solution was cooled to 0 °C. Mesyl chloride (2.46 mL, 31.97 mmol) was added, and the reaction mixture was warmed to room temperature over 0.5 h. The reaction was quenched by the addition of 50 mL of H_2O followed by 200 mL of $CHCl_3$. The $CHCl_3$ phase was washed with 10% HCl (2 × 50 mL) and H_2O (2 × 50 mL), dried, and evaporated in vacuo. Crystallization from hexane/EtOAc gave 1.78 g (cis:trans 9:1). The mother liquor was chromatographed on 200 g of silica gel and the pure cis product was eluted with 60% EtOAc/hexane (200 mg), mp 175–178 °C dec. An additional 120 mg of a cis/trans mixture was obtained (total yield 74%): R_f EtOAc cis 0.55, trans 0.45; IR $\lambda_{max}^{CHCl_3}$ (cis) 2920 (m), 2500–2800 (br m), 1705 (s), 1605 (s), 1465 (s), 1420 (m), 1355 (s), 1175 (s), 1120 (s), 1065 (m), 1025 (m), 970 (s), 900 (w), 860 (w) cm^{-1}; NMR (300 MHz, $CDCl_3$) **51** (cis), isomers at C-6, δ 1.227–1.283 (two overlapping doublets, 3 H, C-6), 2.308–2.916 (m, 5 H), 3.220 and 3.223 (two singlets, isomers at C-6, 3 H, OSO_2CH_3), 3.493 and 3.497 (two singlets, isomers at C-6, 3 H, OCH_3), 4.038–4.133 (two overlapping dd, 1 H, H-3), 4.304–4.366 and 4.337–4.399 (two overlapping dd, 1 H, $J_{2,3'}$ = 7.7 Hz, $J_{3,3'}$ = 11.0 Hz, H-3'), 5.167–5.184 and 5.173–5.189 (two overlapping doublets, 1 H, $J_{1,2}$ = 5.0 Hz, H-1) and 5.376–5.469 (m, 1 H, H-2); mass spectrum (15 ev), m/e (relative intensity) 357 M^+ (5), 326 (20), 278 (20), 231 (100), 213 (20); m/e calcd for $C_{15}H_{19}NO_7S$ 357.0882, found 357.0892. Anal. Calcd for $C_{15}H_{19}NO_7S$: C, 50.41; H, 5.36; N, 3.92. Found: C, 50.49; H, 5.39; N, 3.88.

Benzyl *cis*-2,3,5,6,7,8-Hexahydro-2-[(methylsulfonyl)oxy]-1-methoxy-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (52). A solution of **51** (1.90 g, 5.32 mmol), isomeric at C-6 and C-1,2 cis:trans (9:1), in 90 mL of freshly distilled acetone was stirred at room temperature under N_2 with 1.75 g of anhydrous K_2CO_3 and 100 mg of 18-crown-6. This suspension was heated

to reflux and then treated dropwise with 0.90 mL (7.5 mmol) of benzyl bromide. The reaction mixture was stirred at reflux for 18 h and then was cooled to room temperature. The volatiles were evaporated, and the solid remaining was taken up in 250 mL of EtOAc. This solution was washed with saturated $NaHCO_3$ (3 × 40 mL), 2.5 N NaOH (2 × 20 mL), 2% HCl (2 × 50 mL), and H_2O (2 × 30 mL). The solvent was dried, removed in vacuo, and gave, after crystallization from EtOAc, 1.72 g of a (7.5:1) cis:trans mixture. The mother liquors were chromatographed on 200 g of silica gel with hexane:EtOAc and 305 mg of the pure cis isomer **52** was isolated: mp 156–158 °C (total yield 85.2%); IR $\lambda_{max}^{CHCl_3}$ 3000 (w), 2960 (m), 1718 (s), 1655 (s), 1560 (w), 1515 (w), 1465 (m), 1455 (s), 1430 (m), 1365 (s), 1345 (s), 1300 (s), 1220 (s), 1180 (s), 1135 (m), 1115 (w), 1080 (w), 1060 (w), 1025 (m), 970, 880 (w); NMR (300 MHz, $CDCl_3$), mixture of isomers at C-6, δ 1.135–1.165 (two overlapping d, C-6), 2.326–2.785 (m, 5 H), 3.160 (s, 3 H, OSO_2CH_3), 3.222 and 3.222 (two singlets, 3 H, isomers at C-6 (1.3:1) OCH_3), 4.013–4.096 (m, 1 H, H-3), 4.237–4.324 (m, 1 H, H-3′), 4.939 and 4.960 (two doublets, 3 H, isomers at C-6, $J_{1,2}$ = 5.05 Hz, H-1), 5.267–5.336 (m, 1 H, H-2), 5.324 (s, 2 H, $CO_2CH_2C_6H_5$), 7.311–7.505 (m, 5 H); mass spectrum (15 ev), *m/e* (relative intensity) 447 (80), 416 (10), 341 (80), 310 (60), 216 (100), 188 (20); *m/e* calcd for $C_{22}H_{25}NO_7S$ 447.1352, found 447.1335. Anal. Calcd for $C_{22}H_{25}NO_7S$: C, 59.05; H, 5.63; N, 3.13. Found: C, 58.87; H, 5.80; N, 3.12.

Benzyl *cis*-2,3-Dihydro-8-hydroxy-2-[(methylsulfonyl)oxy]-1-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (53). Substance **52** (1.72 g, 3.85 mmol), isomeric at C-6 and C-1,2, cis:trans (7.5:1), in 125 mL of EtOAc was aromatized with 960 mg of DDQ (4.33 mmol). Workup in the usual manner with saturated $NaHCO_3$ gave 1.26 g of a white solid (cis:trans 8.1:1). The remainder was chromatographed (MPLC with hexane:Et_2O) and gave 60 mg of the pure cis isomer **53**, mp 171–172 °C, 30 mg of the trans isomer **54**, mp 145–146 °C, and 60 mg of a mixture (total yield 82.3%): R_f (Et_2O) cis 0.80, trans 0.70; IR $\lambda_{max}^{CHCl_3}$ **53** 3200–3400 (br m), 1660 (s), 1560 (m), 1500 (w), 1460 (m), 1410 (m), 1350 (s), 1290 (w), 1185 (m), 1150 (s), 1135 (m), 1110 (m), 1070 (w), 980 (s), 920 (w), 870 (w), 850 (w); UV λ_{max}^{MeOH} 280 nm sh (log ε 3.73), 315 (log ε 3.91); NMR (300 MHz, $CDCl_3$) **53** δ 2.402 (s, 3 H, C-6), 3.176 (s, 3 H OSO_2CH_3), 3.215 (s, 3 H, OCH_3), 4.178 (dd, 1 H, $J_{2,3}$ = 7.94 Hz, $J_{3,3'}$ = 10.68 Hz, H-3), 4.511 (dd, 1 H, $J_{2,3'}$ = 7.63 Hz, $J_{3,3'}$ = 10.69 Hz, H-3′), 5.058 (d, 1 H, $J_{1,2}$ = 5.05 Hz, H-1), 5.338–5.440 (m, 1 H, H-2), 5.364 and 5.412 (AB q, $\Delta\nu_{AB}$ = 14.71 Hz, J_{AB} = 11.90 Hz, $CO_2CH_2C_6H_5$), 6.572 and 6.588 (two singlets, 2 H, H-5, 7), 7.369–7.482 (m, 5 H), 10.727 (s, 1 H, Ar OH); IR $\lambda_{max}^{CHCl_3}$ **54** 3200 (m), 2980 (m), 1660 (s), 1570 (m), 1500 (w), 1460 (m), 1420 (w), 1355 (s), 1320 (m), 1260 (m), 1190 (s), 1145 (s), 1135 (s), 975 (s), 930 (s); NMR (300 MHz, $CDCl_3$) **54** δ 2.395 (s, 3 H, C-6), 3.052 (s, 3 H, OSO_2CH_3), 3.208 (s, 3 H, OCH_3), 4.253 (d, 1 H, $J_{3,3'}$ = 12.88 Hz, H-3), 4.484 (dd, 1 H, $J_{2,3'}$ = 4.08 Hz, $J_{3,3'}$ = 12.88 Hz, H-3′), 4.967 (s, 1 H, H-1), 5.317 and 5.429 (AB q, $\Delta\nu_{AB}$ = 33.7 Hz, J_{AB} = 12.0 Hz), 5.515 (d, 1 H, H-2), 6.579 (s, 2 H, H-65, 7), 7.385–7.476 (m, 5 H), 10.692 (s, 1 H, Ar OH); $[\alpha]^{25}_D$ of **53** *cis*-4.7° (*c* 0.35, $CHCl_3$); mass spectrum (70 eV), *m/e* (relative intensity) 445 (100), 335, 337; *m/e* calcd for $C_{22}H_{23}NO_7S$ 445.1195, found 445.1200. Anal. Calcd for $C_{22}H_{23}NO_7S$: C, 59.32; H, 5.20; N, 3.14. Found: C, 59.60; H, 5.33; N, 3.10.

Benzyl *cis*-7-Bromo-2,3,5,8-tetrahydro-2-[(methylsulfonyl)oxy]-1-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (55). Compounds **53**/**54** (cis:trans 8.1:1; 1.26 g, 2.83 mmol) were dissolved in 65 mL of THF and 15 mL of H_2O and then treated with 5 mL of HOAc and 1.5 g of NaOAc. The reaction mixture was treated dropwise with 1.90 mL (33.9 mmol) of Br_2. The solution was stirred at room temperature for 0.5 h and then was added to 175 mL of EtOAc. The organic phase was washed with saturated sodium bisulfite (2 × 35 mL), saturated $NaHCO_3$ (4 × 20 mL), 2% HCl (3 × 20 mL), and H_2O (2 × 20 mL). The solvent was dried and then removed in vacuo to give 1.06 g of a brilliant yellow solid. Recrystallization from EtOH gave cis:trans 7.5:1. The mother liquor was chromatographed on 100 g of silica gel and the product was eluted with hexane/EtOAc (1:1) to give 0.15 g of the pure cis isomer **55**: mp 169–171 °C (total yield 79.6%); IR $\lambda_{max}^{CHCl_3}$ 3050 (w), 2960 (w), 1730 (s), 1665 (m), 1650 (s), 1590 (m), 1350 (s), 1360 (s), 1315 (s), 1270 (s), 1210 (w), 1185 (s), 1140 (s), 1105 (s), 1070 (s), 1035 (s), 980 (s); UV λ_{max}^{MeOH} 207 nm (log ε 4.370), 236 (log ε 4.274), 287 (log ε 4.126), 315 (lot ε 3.629), 410 (log ε 3.027); NR (300 MHz, $CDCl_3$) **55** δ 2.249 (s, 3 H, C-3), 3.173 (s, 3 H, OSO_2CH_3), 3.304 (s, 3 H, OCH_3), 4.328 (dd, 1 H, $J_{2,3}$ = 7.56 Hz, $J_{3,3'}$ = 12.43 Hz, H-3), 4.804 (dd, 1 H, $J_{2,3'}$ = 7.56 Hz, $J_{3,3'}$ = 12.42 Hz, H-3′), 5.006–5.024 (d, 1 H, $J_{1,2}$ = 5.40 Hz, H-1), 5.371 (s, 2 H, $CO_2CH_2C_6H_5$), 5.411 (dt, 1 H, $J_{1,2}$ = 5.40 Hz, $J_{2,3}$ = $J_{2,3'}$ = 7.56 Hz, H-2), 7.334–7.508 (m, 5 H); mass spectrum (70 ev), *m/e* (relative intensity) 537, 539 M^+, 447, 449, 431, 433 (100); *m/e* calcd for $C_{22}H_{20}NO_8S^{81}Br - OCHC_6H_5$ 432.9654, found 432.9656. Anal. Calcd for $C_{22}H_{20}NO_8SBr$: C, 49.08; H, 3.74; N, 2.60. Found: C, 49.11; H, 3.74; N, 2.48.

***cis*-7-Bromo-2,3,5,8-tetrahydro-2-[(methylsulfonyl)oxy]-1-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylic Acid (56).** Compound **55** (798 mg, 1.46 mmol) was dissolved in 50 mL of EtOAc and 5 mL of Me_2CO. To the solution was added 600 mg of 10% Pd/C and the suspension was vigorously stirred under H_2. The reaction was monitored by TLC in EtOAc and was filtered when TLC indicated that the bromohydroquinone benzyl ester was completely converted (30 min) to the hydroquinone acid (R_f 0.10, EtOAc). To the filtrate was added 30 mL of EtOAc followed by 50 mL of 2% HCl containing 1.0 g of ferric chloride. The solution was stirred rapidly at room temperature for 1.5 h and then was washed with H_2O (2 × 30 mL). The product was extracted into saturated $NaHCO_3$ (3 × 25 mL), and the aqueous phase was carefully acidified and extracted until colorless with $CHCl_3$ (4 × 50 mL). The solvent was dried and then concentrated to give a crude orange-yellow solid which was recrystallized from EtOH and Et_2O to give 450 mg (70%). A 300-MHz NMR spectrum of the product showed the pure cis isomer with >95% C-7 Br: mp 179–180 °C dec; IR λ_{max}^{KBr} **56** 290–3200 (br, m), 2950 (m), 1730 (s), 1660 (s), 1640 (s), 1590 (w), 1550 (w), 1510 (m), 1380 (m), 1360 (m), 1270 (w), 1190 (s), 1145 (s), 1115 (w), 1075 (m), 1040 (m), 985 (s), 890 (w), 855 (w); UV λ_{max}^{MeOH} 425 nm (ε 2280, log ε 3.36), 350 (ε 2850, log ε = 3.46), 287 (log ε 4.06), 231 (log ε 4.16); NMR (300 MHz, $CDCl_3$) **56** δ 2.323 (s, 3 H, C-6), 3.218 (s, 3 H, OSO_2CH_3), 3.591 (s, 3 H, OCH_3), 4.375 (dd, 1 H, $J_{2,3}$ = 8.18 Hz, $J_{3,3'}$ = 12.40 Hz, H-3), 4.839 (dd, 1 H, $J_{2,3'}$ = 7.37 Hz, $J_{3,3'}$ = 12.40 Hz, H-3′), 5.299 (d, 1 H, $J_{1,2}$ = 5.20 Hz, H-1), 5.417 (ddd, $J_{1,2}$ = 5.20 Hz, $J_{2,3}$ = 8.20 Hz, $J_{2,3'}$ = 7.40 Hz, H-2); mass spectrum (70 ev), *m/e* (relative intensity) 447, 449 (20), 416, 418 (15), 335, 337 (40), 321, 323 (100); *m/e* calcd for $C_{15}H_{14}NO_8SBr$ 446.9624, found 446.9623. Anal. Calcd for $C_{15}H_{14}NO_8SBr$: C, 40.19; H, 3.15; N, 3.12. Found: C, 40.14; H, 3.15; N, 3.10.

***cis*-7-Bromo-2,3-dihydro-2-[(methylsulfonyl)oxy]-9-(hydroxymethyl)-1-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (58).** A solution of bromoquinone acid cis methoxy mesylate **56** (402 mg, 0.90 mmol) in 15 mL of distilled thionyl chloride was stirred under an atmosphere of nitrogen overnight. The orange red solution gradually changed to a deep yellow over the 16-h period. The thionyl chloride was carefully removed under reduced pressure and the residual yellow solid was dissolved in 25 mL of freshly distilled THF. Rapid TLC elution in EtOAc indicated the complete conversion of the acid (R_f 0.4) to the acid chloride (R_f 0.7). To the solution was added 1.00 g of sodium borohydride in 10 mL of distilled THF and the suspension was stirred at room temperature for 4 h. The reaction was quenched by the addition of 0.167 M KH_2PO_4 (30 mL) and then was oxidized with 0.167 M KH_2PO_4 containing 1.00 g of Fremy's radical. The mixture was treated with 100 mL of EtOAc and then was washed with H_2O (2 × 20 mL), saturated $NaHCO_3$ (3 × 30 mL), 2.5 N NaOH (2 × 10 mL), and 1% HCl (50 mL). The organic phase was dried and evaporated to give a yellow residue which was chromatographed on 150 g of silica gel with CH_2Cl_2/EtOAc. The product was eluted with CH_2Cl_2/EtOAc (1:1) and gave 205 mg of **58**: mp 185–187 °C dec; IR λ_{max}^{KBr} 3300–3600 (br, m), 2940 (m), 1650 (s), 1585 (w), 1490 (m), 1360 (s), 1310 (w), 1185 (s), 1145 (s), 1070 (m), 1035 (w), 980 (s), 925 (w), 880 (m); UV λ_{max}^{MeOH} 425 nm (ε 2240, log ε 3.35), 348 (ε 3951 ε 3.59), 285.5 (log ε 4.09), 229 (log ε 4.16); NMR (300 MHz, $CDCl_3$) δ 2.66 (s, 3 H, C-6), 3.182 (s, 3 H, OSO_2CH_3), 3.503 (s, 3 H, OCH_3), 4.420 (dd, 1 H, $J_{2,3}$ = 5.95 Hz, $J_{3,3'}$ = 13.07 Hz, H-3), 4.656 (dd, 1 H, $J_{2,3'}$ = 6.45 Hz, $J_{3,3'}$ = 13.07 Hz, H-3′), 4.733 and 4.769 (AB q, 2 H $\Delta\nu_{AB}$ = 10.74 Hz, J_{AB} = 14.00 Hz, H-10), 4.911 (d, 1 H, $J_{1,2}$ = 5.05 Hz, H-1) and 5.532 (ddd, 1 H, $J_{1,2}$ = 5.05 Hz, $J_{2,3}$ = 5.95, $J_{2,3}$;

= 6.45 Hz, H-2); mass spectrum (70 ev), *m/e* (relative intensity) 433, 435 (15), 355, 357 (20), 322, 321 (40), 306, 308 (100); *m/e* calcd for $C_{15}H_{16}NO_7SBr$ 434.9810, found 434.9812.

***trans*-7-Amino-2-azido-2,3-dihydro-9-(hydroxymethyl)-1-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (59).** To a solution of **58** (190 mg, 0.44 mmol) in 20 mL of DMF was added 1.25 g of NaN_3 dissolved in 2.5 mL of H_2O. The yellow solution was heated from room temperature to 95 °C over 1 h. At 40–45 °C the solution changed to a deep orange (azidoquinone) and at 80 °C the solution was a deep purple (aminoquinone, one spot on TLC). The reaction mixture was stirred at 95 °C for 12 h, after which the mixture was cooled to room temperature and TLC indicated the reaction was complete (Et_2O) R_f 0.6; (EtOAc) R_f 0.9. The reaction mixture was added to 150 mL of EtOAc and was washed with H_2O (3 × 50 mL) and 10% HCl (2 × 25 mL). The solvent was dried and then concentrated to give a purple residue which was chromatographed on 125 g of silica gel with CH_2Cl_2/EtOAc. The product was eluted with CH_2Cl_2:EtOAc (2:1) and gave 110 mg (78%) of **59** as a dark purple solid: mp 210–212 °C (N_2 evolution); IR λ_{max}^{KBr} 2920 (w), 2105 (s), 1670 (m), 1600 (m), 1500 (w), 1440 (w), 1390 (w), 1080 (w); UV λ_{max}^{MeOH} 520 nm (ε 504.3, log ε 2.70), 350 sh (ε 2738 log ε = 3.44), 306 (ε 9006, log ε = 3.95), 247 (ε 13 545, log ε = 4.132), 214 (ε 9800, log ε = 3.99); NMR (300 MHz, $CDCl_3$) δ 1.856 (s, 3 H, C-6), 3.431 (s, 3 H, OCH_3), 4.275 (dd, $J_{2,3}$ = 1.71 Hz, $J_{3,3'}$ = 13.48 Hz, H-3), 4.470–4.533 (dd, 1 H, $J_{2,3'}$ = 5.46 Hz, $J_{3,3'}$ = 13.50 Hz, H-3′), 4.572 (dd, 1 H, $J_{2,3'}$ = 5.45 Hz, $J_{2,3}$ = 1.71 Hz, H-2), 4.593 (s, 1 H, H-1), 4.578 (s, 2 H, H-10), 4.958 (br s, 2 H, NH_2); mass spectrum (15 ev), *m/e* (relative intensity) 317 M^+ (80), 302 (100), 247 (70); *m/e* calcd for $C_{14}H_{15}N_5O_4$ 317.1124, found 317.1131.

***trans*-7-Amino-2-azido-2,3-dihydro-9-(hydroxymethyl)-1-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione Phenyl Carbonate 60.** Compound **59** (80 mg, 0.25 mmol) was dissolved in 12 mL of pyridine and was stirred at 0 °C. To the solution was added 100 μL of phenyl chloroformate; this was stirred at 0 °C for 15 min and then warmed to room temperature over 1 h. TLC indicated that the reaction was complete (R_f Et_2O 0.70), and the solution was added to 75 mL of ethyl acetate. This was washed with 10% HCl (5 × 20 mL) and H_2O (2 × 20 mL) and then dried. The solvent was removed and the residue was chromatographed on 100 g of silica gel. The excess phenyl chloroformate was removed with hexane, and the product was eluted with Et_2O:CH_2Cl_2 (1:1) and gave 70 mg (65%) of **60** as a purple solid: mp 155–157 °C; IR λ_{max}^{KBr} 2980 (w), 2110 (s), 1730 (s), 1670 (w), 1610 (s), 1570 (w), 1505 (m), 1495 (m), 1385 (m), 1365 (m), 1100 (w), 1030 (s), 930 (m); UV λ_{max}^{MeOH} 522 nm (ε 846, log ε 2.93), 350 nm sh (ε 3675, log ε = 3.57), 304 nm (ε 13 135, log ε 4.12), 246 nm (ε 22 050, log ε 4.34), 207 nm (ε 20 560, log e 4.31); NMR (300 MHZ, $CDCl_3$) δ 1.858 (s, 3 H, C-6), 3.483 (s, 3 H, OCH_3), 4.312 (d, 1 H, $J_{3,3'}$ = 11.47 Hz, H-3), 4.530 (dd, 1 H, $J_{2,3'}$ = 5.62 Hz, $J_{3,3'}$ = 11.72 Hz, H-3′), 4.569 (br d, 1 H, $J_{2,3'}$ = 5.61 Hz, H-2), 4.741 (d, 1 H, $J_{1,2}$ = 1.01 Hz, H-1), 4.970 (br, s 2 H, NH_2), 5.497 (s, 2 H, CH_2O), 7.181–7.415 (m, 5 H); mass spectrum, *m/e* (relative intensity) 437 M^+ (55), 300 (100), 272 (30), 240 (60); *m/e* calcd for $C_{21}H_{19}N_5O_6$ 437.1335, found 437.1336.

***trans*-7-Amino-2-azido-2,3-dihydro-9-(hydroxymethyl)-1-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione Carbamate (61).** Phenyl carbonate **60** (45 mg, 0.10 mmol) was dissolved in 10.0 mL of CH_2Cl_2 and was added to 15.0 mL of anhydrous ammonia in a dry ice/2-propanol bath. Upon the addition, the red-purple phenyl carbonate changed to a brilliant blue-purple. After 30 min at −78 °C, the bath was removed and the solution was allowed to stand for 3 h. The solvent was then removed and the crude purple solid remaining was chromatographed on 75 g of silica gel with CH_2Cl_2/EtOAc. The product was eluted to give 26 mg of **61** (75%): mp 225–228 °C; IR λ_{max}^{KBr} 3480 (br, w), 3300 (s), 2920 (m), 2110 (s), 1725 (s), 1670 (m), 1602 (vs), 1580 (w), 1505 (m), 1440 (w), 1385 (m), 1350 (w), 1330 (s), 1260 (w), 1090 (s), 750 (m), 525 (m) 455 (m); UV λ_{max}^{MeOH} 525 nm (ε 900, log ε = 2.95), 347 nm (ε 4100, log ε 3.61, 305 nm (log ε 4.08), 245 nm (ε 21 500, log ε 4.39), 208 nm (ε 19000, log ε 4.28); NMR (300 MHz, Me_2CO-d_6) δ 1.860 (s, 3 H, C-6), 4.308 (dd, 1 H, $J_{2,3}$ = 1.47 Hz, $J_{3,3'}$ = 13.67 Hz, H-3), 4.501 (dd, 1 H, $J_{2,3'}$ = 5.37 Hz, $J_{3,3'}$ = 13.67 Hz, H-3′), 4.665 (br dt, 1 H, $J_{1,2}$ = 1.22 Hz, $J_{2,3}$ = 1.47 Hz, $J_{2,3'}$ = 5.37 Hz, H-2), 4.764 (d, 1 H, $J_{1,2}$ = 1.22 Hz, H-1), 5.283 and 5.324 (AB q; $\Delta\nu_{AB}$ = 12.3 Hz, J_{AB} = 13.18 Hz, OCH_2O), 5.387–5.568 (br s, 4 H, NH_2 and CH_2OCONH_2); mass spectrum, *m/e* (relative intensity) 360 M^+ (40), 318 (60), 272 (90), 262 (10), 258 (100); *m/e* calcd for $C_{15}H_{16}N_6O_5$ 360.1182, found 360.1186.

Preparation of *trans*-2,7-Diamino-1-methoxymitosene (1a) Followed by Acetylation to *trans*-7-Amino-2-acetamido-1-methoxymitosene (1b). Compound **60** (20 mg, 0.055 mmol) was dissolved in 4 mL of pyridine at room temperature and to this was added 1.0 mL of 57% NH_4OH followed by 150 mg of triphenylphosphine. The mixture was stirred at room temperature for 36 h. R_f EtOAc (**60**) 0.35, R_f (**1a**) 0.05, R_f (**1a**) CH_3CN/*n*-butanol/acetone (3:1:1) 0.15. The volatiles were removed at reduced pressure and the remaining residue was redissolved in 4 mL of MeOH and 0.5 mL of Ac_2O was added at 0 °C. Conversion of the C_2 amine to the corresponding amide **1b** was indicated by TLC; R_f CH_3CN/*n*-butanol/acetone (3:1:1) 0.75. After evaporation the residue was dissolved in 20 mL of EtOAc and then washed with H_2O (15 mL). The solvent was dried and concentrated and the purple product was chromatographed on 20 g of silica gel. The amide was eluted with EtOAc/acetone (1:1) and gave 7 mg of **1b** as a purple solid: IR λ_{max}^{KBr} 3410 (br w), 3300–3400 (br s), 2950 (m), 2920 (m), 1730 (s), 1665 (s), 1600 (s), 1495 (m), 1460 (w), 1385 (m), 1325 (m), 1180 (w), 1120 (w), 1090 (m), 745 (s), 690 (m), 590 (m) cm^{-1}; UV λ_{max}^{MeOH} 524 nm (ε 1200, log ε 3.08), 350 sh (ε 5100, log ε 3.71), 305 (ε 15 500, log ε 4.19), 248 (ε 21 000, log ε 4.32), 209 (ε 15 100, log ε 4.18); NMR (300 MHz, $CDCl_3$:C_3D_6O) δ 1.813 (s, 3 H), 1.973 (s, 3 H), 3.492 (s, 3 H), 4.221 (dd, ABX, 1 H, $J_{2,3}$ = 1.61 Hz, $J_{3,3'}$ = 13.54 Hz, H-3), 4.479 (dd, 1 H, ABX, $J_{2,3'}$ = 6.06 Hz, $J_{3,3'}$ = 13.54 Hz, H-3′), 4.632 (d, 1 H, $J_{1,2}$ = 1.21 Hz, H-1), 4.912–4.931 (m, 1 H, H-2), 5.271 (s, 2 H CH_2OCONH_2), 5.20–5.40 (br m, 4 H, NH_2 and -CH_2OCONH_2); mass spectrum, *m/e* (relative intensity) 376 M^+ (<1), 334 (10), 315 (15), 302 (20), 273 (90), 258 (25), 242 (100).

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