Routes to Mitomycins. Chirospecific Synthesis of Aziridinomitosenes

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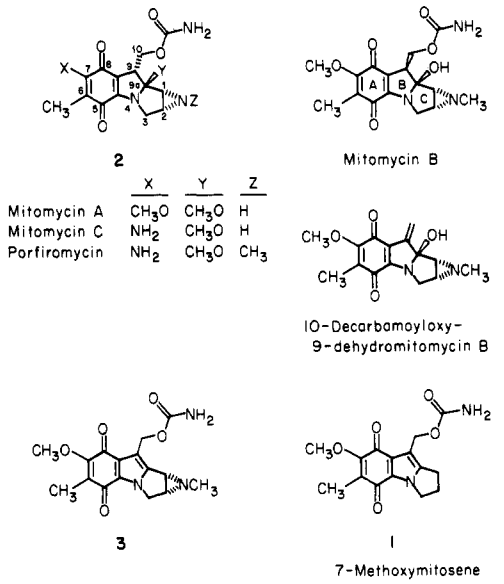
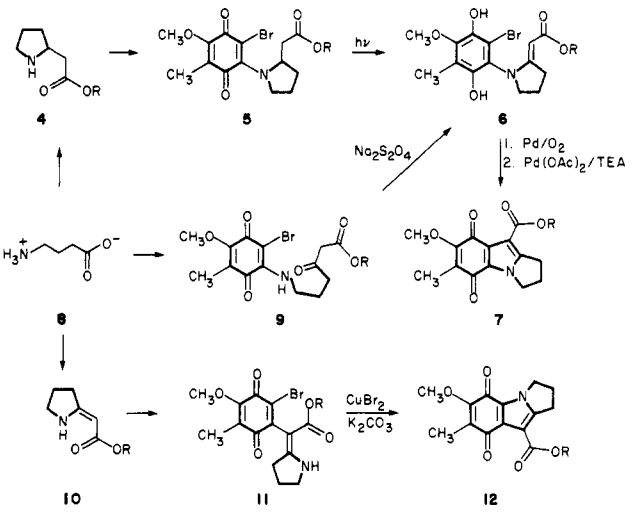
The syntheses of ethyl (1*R*,2*R*)-1,2-(*N*-benzylaziridino)-7-methoxy-6-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (**59**) and a regioisomeric aziridinoindoloquinone **60** are presented. Aziridine ring closure on a tricyclic indoloquinone nucleus and on monocyclic pyrrolidine derivatives was unsuccessful but did succeed with the acyclic educt. Thus the synthesis of the target aziridinomitosene was achieved by aziridine ring closure on the asymmetric 2-amino-3-hydroxy-4-azidobutanoate **49** followed by homologation and reductive ring closure to the bicyclic aziridinopyrrolidine **54**. Subsequent reduction, regiospecific addition to 2,3-dibromo-5-methoxy-6-methylbenzoquinone (**27**), photochemical rearrangement, oxidation, and palladium-catalyzed ring closure afforded the (*R*,*R*)-aziridinomitosene **59**. Regioisomeric aziridinoindoloquinone **60** was obtained directly by the addition of bicyclic aziridine **54** to dibromoquinone **27** followed by copper(II)-catalyzed ring closure.

In earlier reports,[1] we described high yield syntheses of 7-methoxymitosene (**1**), an analogue of the mitomycin antitumor antibiotics **2**,[2] which possesses significant antibacterial activity.[3] Two routes used to obtain a key intermediate in these syntheses, indoloquinone **7**, as well as the route used to obtain its regioisomer **12**, are summarized in Scheme I.

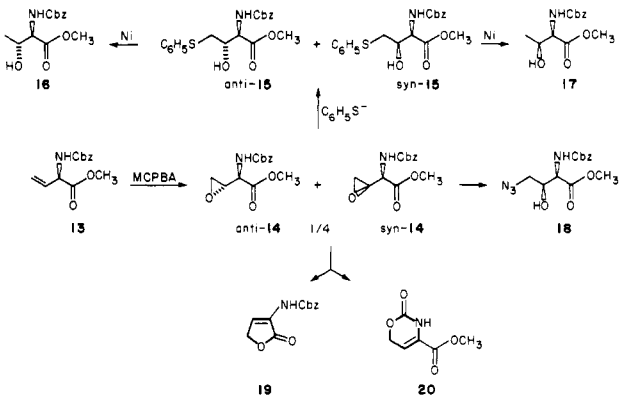


We next focused on the chirospecific synthesis of the corresponding aziridinomitosene **3** because it retains much of the strong antitumor antibiotic activity of the parent compound[4] and because degradation of mitomycin B or *N*-methylmitomycin A represents the only method reported for the preparation of this ring system. Analysis of Scheme I suggests that a derivative of γ-aminobutyric acid (**8**, GABA) would be a versatile educt for such a synthesis. Specifically, the use of an appropriate asymmetric α-amino-β-hydroxy GABA derivative in conjunction with the methods outlined in Scheme I might provide the option of forming the aziridine ring at the acyclic stage, at the pyrrolidine stage, or after the tricyclic pyrrolo-

Scheme I. Routes to Mitosene Precursor 7 and Analogue 12



Scheme II. Synthetic Plan. Stereochemistry of Vinylglycine Epoxidation. Epoxide Opening with Azide



indoloquinone nucleus is formed. It should be noted, however, that the only successful aziridine closure on a substituted 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole has resulted from a trans-1-amino-2-halo system;[5] several trans-1-activated-2-amino systems have been prepared,[6] but no aziridinomitosenes have been reported from this substitution pattern.

(1) (a) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671. (b) Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859. (c) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2404. (d) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745.

(2) The pertinent mitomycin literature is noted in ref 1 and 26.

(3) Allen, G. R.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877; *J. Org. Chem.* **1965**, *30*, 2897.

(4) (a) Kinoshita, S.; Uzu, K.; Nakano, K.; Shimizu, M.; Takahashi, T.; Matsui, M. *J. Med. Chem.* **1971**, *14*, 103. (b) Kinoshita, S.; Uzu, K.; Nakano, K.; Takahashi, T. *Ibid.* **1971**, *14*, 109. (c) Patrick, J. P.; Williams, R. P.; Meyer, W. E.; Fulmor, W.; Cosulich, D. B.; Broschard, R. W.; Webb, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1889.

(5) Hirata, T.; Yamada, Y.; Matsui, M. *Tetrahedron Lett.* **1969**, 4107. No yield was reported.

(6) (a) Remers, W. A.; Roth, R. H.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 2910. (b) Kametani, T.; Kigawa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1607; (c) *Heterocycles* **1979**, *12*, 685; (d) **1980**, *14*, 799.

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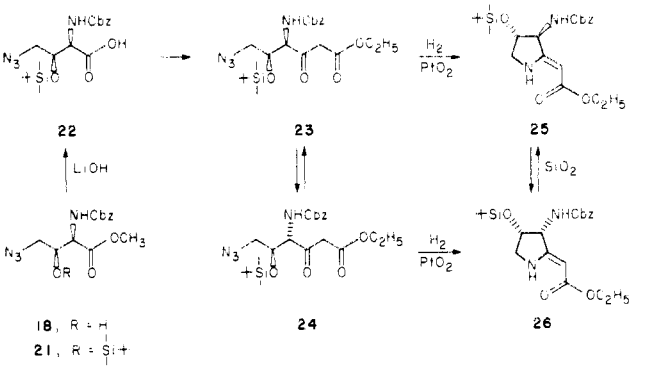
Low-yield isolation from natural product degradation[7] and lengthy racemic syntheses[8] have been the primary sources of *syn*-2,4-diamino-3-hydroxybutanoic acid. A new route clearly was needed, and we turned to the chiral pool. We obtained the appropriate derivative by functionalizing D-vinylglycine, an asymmetric educt with the correct absolute stereochemistry readily available from D-methionine[9] (Scheme II). Modification of the previously reported procedure led to an acceptable and reproducible yield of this vinylglycine on a synthetically useful scale. Azide opening of epoxidized D-vinylglycine should be an effective way to introduce the terminal nitrogen as well as the asymmetric C3 alcohol. Therefore vinylglycine **13** was epoxidized with an excess of *m*-chloroperoxybenzoic acid (MCPBA) and gave a 1/4 ratio (HPLC, NMR) of anti and syn epoxides **14**. Separation of the epoxides was achieved by MPLC. That the major diastereomer has the desired syn configuration was proved by treating the mixture with sodium thiophenoxide and desulfurizing the resulting adducts **15** with Raney nickel to the corresponding allothreonine **16** and threonine **17** derivatives (Scheme II) in a 1/4 ratio. Independent synthesis followed by comparison of HPLC retention times and NMR spectra confirmed the steric assignments. We and others[10] have also seen syn selectivity in nitrile oxide additions to vinylglycine derivatives but not to this extent. Perhaps hydrogen bonding of the MCPBA to nitrogen in a manner similar to that reported in acyclic allylic alcohols[11] may be operating.

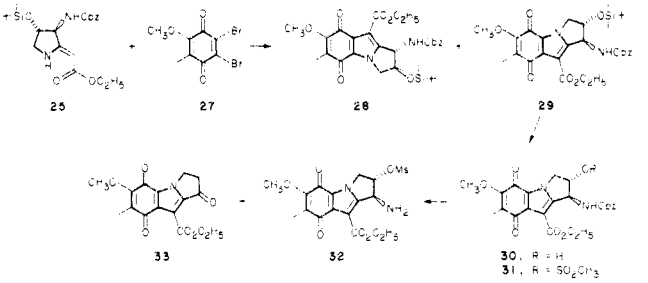
Initial attempts at opening the diastereomeric mixture of epoxides with azide ion led to the formation of side products **19** and **20**, the result of base-catalyzed eliminative ring opening and ring closing (Scheme II). Use of methanol, the solvent of choice in sodium thiophenoxide epoxide opening, gave almost exclusively **19** and **20** in the azide reaction, and similar results were obtained in DMF or aqueous dioxane. The success of thiophenoxide/methanol over azide/methanol can be rationalized in terms of enhanced nucleophilicity.[12] Adding ammonium chloride to the reaction mixture, however, resulted in smooth azide opening, and azido alcohol **18** could be isolated in a 91% yield from syn epoxide **14**. Protection of the alcohol as the *tert*-butyldimethylsilyl (TBDMS) ether proceeded well and subsequent methyl ester hydrolysis provided acid **22** in 80% yield from azido alcohol ester **18**.

Homologation of acid **22** to β-keto ester **23** using the "neutral magnesium malonate" method[13] afforded a 26% chromatographed yield of **23** and its anti-diastereomer **24** as an inseparable mixture. Since critical NMR analysis at this stage was difficult, the equilibration of **23** and **24** was not studied by this method; that *anti*-**24** is the major diastereomer was ascertained indirectly by reduction and cyclization to vinylogous carbamates **25** and **26**, present in a 15/85 ratio by NMR analysis. After separation, analysis of the individual components showed the major diastereomer **26** to be syn with a C3H–C4H coupling constant of 9 Hz while the anti minor diastereomer **25** had a 4.6 Hz coupling.[14] The $CDCl_3$ solution of *syn*-**26** 1 week later showed 81% *anti*-**25** content by HPLC analysis. The equilibration can be carried out preparatively more quickly by treating a chloroform solution of **26** with activated silica gel (Scheme III). Seeking a higher yielding synthesis of β-keto esters **23** and **24**, the basic magnesium salt of ethyl hydrogen malonate[15] was investigated. An 88% yield of crude **23**/**24** was obtained, which was reduced and cyclized as before to give **25** and **26** in 57% overall yield from **22**.

Scheme III. Elaboration of Azido Alcohol 18 to Pyrrolidinylideneacetate



Scheme IV. Synthesis of Asymmetric Indoloquinones. Attempted Aziridine Ring Closure on the Tricyclic System



The cupric bromide catalyzed addition–cyclization[1b] was employed to gain quick entry into the asymmetric pyrroloindoloquinone ring system. Treatment of pyrrolidine **25** with dibromoquinone **27**, potassium carbonate, and cupric bromide in acetonitrile at 50 °C (Scheme IV) afforded a 94% yield of indoloquinone regioisomers **28** and **29** as a 5/95 mixture, respectively, separable by preparative HPLC. A series of aziridine ring closure conditions were then applied to this 1,2-substituted pyrroloindoloquinone nucleus. However, as had been seen on a similar system,[6a] all attempts at closing the aziridine ring failed. The synthetic strategy entailed activation of the alcohol followed by deprotection of the amine, with the expectation that the free amine would cyclize to the aziridine. Cleavage of the silyl ether with tetrabutylammonium fluoride followed by mesylation afforded **31**. However, removal of the benzyl carbamate by transfer hydrogenolysis did not produce the aziridine but afforded a mixture of the amino mesylate **32** and ketone **33**. Formation of ketone **33** can be rationalized by a syn elimination of methanesulfonic acid, followed by hydrolysis of the resulting enamine.

A similar elimination has been encountered with a fused cyclopentane ring.[16] Formation of this ketone results from the inability to attain a transition state where the substituents are trans antiperiplanar. With fused five-mem-

(7) (a) Reiner, R.; Eugster, C. H. *Helv. Chim. Acta* **1967**, *50*, 128. (b) Goth, H.; Gagneux, A. R.; Eugster, C. H.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 137.

(8) Sicher, J.; Rajsner, M.; Rudinger, J.; Eckstein, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1959**, *24*, 3719.

(9) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817.

(10) Wade, P. A.; Singh, S. M.; Pillay, M. K. *Tetrahedron* **1984**, *40*, 601.

(11) Narula, A. S. *Tetrahedron Lett.* **1983**, *24*, 5421.

(12) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", Harper and Row; New York, 1976; pp 187–188.

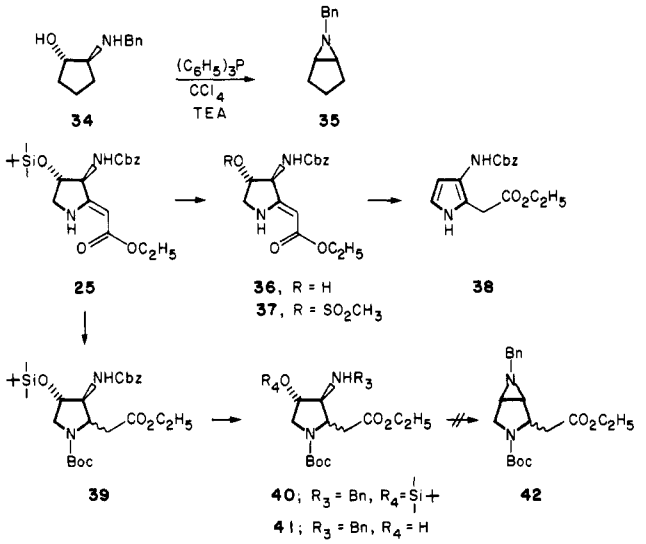
(13) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.

(14) Schoenleber, R. W.; Kim, Y.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 2645.

(15) (a) Ireland, R. E.; Marshall, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 2909. (b) Bram, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1964**, 945.

(16) Hassner, A.; Heathcock, C. *Tetrahedron* **1964**, *20*, 1037.

Scheme V. Attempted Aziridine Ring Closure on Pyrrolidinylidene and Pyrrolidine Rings

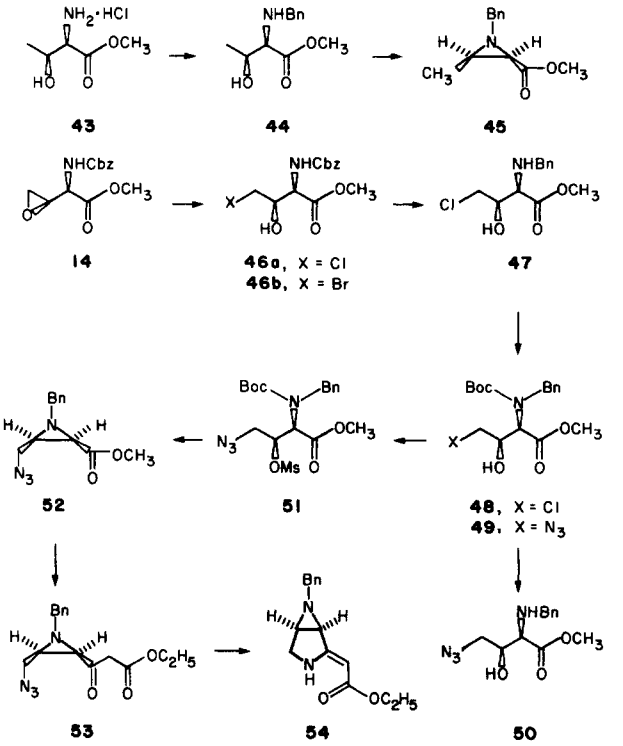


bered rings this stereochemical arrangement leading to the aziridine is not possible, thus syn elimination overwhelms ring closure. Supporting this hypothesis is a study that has shown syn elimination to be more favorable in five-membered than six-membered rings due to the coplanar transition state available for the five- but not the six-membered rings.[17] Thus, there are two substantial forces disfavoring the aziridine ring closure.

Since aziridine formation was unsuccessful on the tricyclic pyrroloindoloquinone, ring closure was next examined on a more flexible monocyclic system. Synthesis of the 6-azabicyclo[3.1.0]hexane ring system was investigated in model studies. 6-Azabicyclo[3.1.0]hexane has previously been synthesized from *trans*-2-aminocyclopentanol by heating the dry hydrochloride,[18] and by treatment with chlorosulfonic acid followed by base.[19] Alternative routes to aziridines from amino alcohols utilizing reagents formed from triphenylphosphine and CCl_4, Cl_2, or Br_2 have been reported recently.[20,21] Reaction conditions are mild and yields generally high; therefore these reagents were investigated for aziridine ring closure. Triphenylphosphine and CCl_4 have been recently utilized to close an aziridine ring on a pyrrolidinone ring system.[22] Since *N*-alkylaziridines are markedly more stable than their hydrido, sulfonyl, or acyl counterparts,[23] *trans*-α-(benzylamino)cyclopentanol was used as a substrate. Treatment with triphenylphosphine and CCl_4 led to the desired bicyclic system in a 79% yield (Scheme V).

Aziridine ring closure was now examined on the unsaturated pyrrolidine **25**. Ring closure was pursued by cleavage of the silyl ether with tetrabutylammonium fluoride to afford alcohol **36**. However mesylate **37**, generated from **36** with methanesulfonyl chloride and TEA, was not stable and readily eliminated methanesulfonic acid to give pyrrole **38** (Scheme V).

Scheme VI. Aziridine Ring Closure of D-Threonine Derivative. Synthesis of Bicyclic Aziridine 54



To suppress this ready aromatization to the pyrrole, the vinylogous carbamate of **25** was reduced with sodium cyanoborohydride. Protection of the pyrrolidine nitrogen with di-*tert*-butyldicarbonate afforded homoproline **39** as a mixture of diastereomers. Removal of the benzyl carbamate by transfer hydrogenolysis followed by reductive alkylation with benzaldehyde and sodium cyanoborohydride afforded the exo *N*-benzyl derivative **40**. Now cleavage of the silyl ether afforded the desired amino alcohol substrate **41** for reaction with triphenylphosphine-/CCl_4. However, ring closure could not be affected with this substrate under conditions effectively employed in the synthesis of 6-benzyl-6-azabicyclo[3.1.0]hexane (**35**). Reaction at room temperature for 16 h led to a quantitative yield of recovered educt **41**, and at higher temperatures only slow decomposition of **41** was observed. Reactions with triphenylphosphine and bromine gave similar results. The *tert*-butylcarbamate was cleaved with trifluoroacetic acid (TFA) to give a less hindered system. Again, no reaction occurred at room temperature with triphenylphosphine and CCl_4, and upon reflux, only decomposition products were observed (Scheme V).

The inability to close the strained aziridine on a conformationally restrained pyrrolidine ring perhaps could be overcome by first forming the aziridine ring on an acyclic precursor, then closing the pyrrolidine ring. Threonine was selected as a valid model for developing aziridine ring closure conditions, and esterification[24] of D-threonine followed by reductive alkylation with benzaldehyde and sodium cyanoborohydride afforded the *N*-benzylamino alcohol **44** (Scheme VI). Reaction with triphenylphosphine/CCl_4 gave aziridine **45** in 89% yield. From this it appeared that the appropriate azide analogue of **45** could indeed lead to the desired functionalized bicyclic system by homologation to a β-keto ester followed by reduction of the azide.

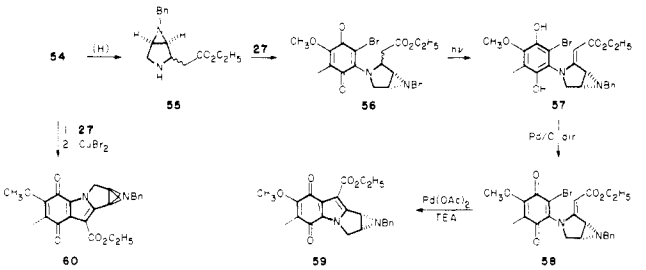
(17) Depuy, C. H.; Thurn, R. D.; Morris, G. F. *J. Am. Chem. Soc.* **1962**, *84*, 1314.
(18) Fanta, P. E. *J. Chem. Soc.* **1957**, 1441.
(19) Fanta, P. E.; Smat, R. J.; Krikau, J. R. *J. Heterocycl. Chem.* **1968**, 419.
(20) Appel, R.; Kleinstuck, R. *Chem. Ber.* **1974**, *107*, 5.
(21) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185.
(22) Kametani, T.; Kigawa, Y.; Ihara, M. *Tetrahedron* **1979**, *35*, 313.
(23) (a) Deyrup, J. A. In "Heterocyclic Compounds"; Hassner, A., Ed.; Wiley-Interscience: New York, 1983. (b) Dermer, O. C.; Ham, G. E. "Ethyleneimine and Other Aziridines"; Academic Press: New York, 1969.
(24) Morell, J. L.; Fleckenstein, P.; Gross, E. J. *J. Org. Chem.* **1977**, *42*, 355.

To synthesize the bicyclic aziridine, we treated the epoxide **14** with methanolic HCl to afford the ring-opened chlorohydrin **46a** in 68% yield (Scheme VI). Ring opening with HBr gave higher yields; however, the lability of the bromide to subsequent reductive conditions restricted its use. The regio- and stereochemistry of the ring opening was proved by conversion of the diastereomeric mixture of bromides **46b** to a previously prepared mixture of azide diastereomers **18** by reaction with sodium azide. Transfer hydrogenolysis of chlorohydrin **46a** with cyclohexene and 10% Pd/C followed by reductive alkylation with benzaldehyde and sodium cyanoborohydride afforded a 69% yield of *syn*-*N*-benzylchlorohydrin **47** separable from its anti diastereomer by chromatography. Direct azide displacement on chloride **47** was unsuccessful until the amine was protected as its *tert*-butyl carbamate, and then reaction with sodium azide in DMF proceeded to afford azide **49** in 72% yield for the two steps. Cleavage of the *tert*-butyl carbamate gave the deprotected azido benzylamino alcohol **50**.

To form the aziridine, **50** was treated with triphenylphosphine/CCl_4 under the same conditions used to form aziridine **45** from threonine derivative **44**, but no reaction occurred. Repeating the reaction at reflux for 60 h again led to no product. Similar lack of reactivity was found for *N*-benzylchlorohydrin analogue **47**. This difference in reactivity between the *N*-benzylthreonine and its 4-azido and 4-chloro analogues was puzzling. We concluded that prior activation of the hydroxyl group was necessary and proceeded by conversion of **49** to mesylate **51**. Removal of the *tert*-butyl carbamate with TFA followed by refluxing the crude product with diisopropylethylamine in acetonitrile afforded aziridine **52** in a 70% yield from **49**. The cis stereochemistry of the aziridine ring can be seen by analysis of one of the coupling constants of the ring protons (d, 2.4 ppm, J = 6.5 Hz). Homologation of the ester of **52** to the β-keto ester **53** was conveniently achieved in 90% yield by reaction with the enolate of ethyl acetate, generated from LDA in THF. Although the NMR spectrum is complex due to keto–enol equilibria, only the cis aziridine was present by analysis of the coupling constants of the upfield aziridine ring protons. Reduction of the azide with PtO_2 and hydrogen in ethanol then afforded crystalline bicyclic aziridine **54** in 78% yield after chromatography.

Aziridinopyrrolidine **54** was now ready for incorporation into a mitosene following the high-yield procedures recently described.[1] The key steps in these syntheses are a photochemical dismutation followed by palladium-catalyzed cyclization. Thus **54** was reduced with sodium cyanoborohydride to the aziridinohomoproline **55** as a mixture of diastereomers. Amination of dibromoquinone **27** with **55** followed the literature precedent[1] and gave a single regioisomer, **56**, in 94% yield. Photochemical oxidation–reduction to hydroquinone **57**, oxidation of **57** to quinone **58**, and palladium-catalyzed ring closure afforded the aziridinomitosene derivative **59** (Scheme VII). Highest yields for the three steps (**56** → **57** → **58** → **59**, 58%) were obtained in dry methanol by using a visible lamp as the light source; a more intense lamp (450-W Hanovia) gave lower yields. The structure of tetracycle **59** is supported by comparison of NMR spectral data with that of mitomycin C.[25] Most diagnostic is the doublet of the C1 aziridine ring proton of **59** at 3.5 ppm (J = 4.9 Hz) compared to a doublet at 3.1 ppm (J = 4.5 Hz) for mitomycin C. The upfield chemical shift is indicative of an aziridine ring,[23] and its assignment is further supported by comparison of coupling constants observed for other cis-1,2-disubstituted mitosene derivatives.[26]

Scheme VII. Photochemical Route to Aziridinoindoloquinone 59. Cupric Bromide and Palladium Acetate Catalyzed Ring Closures for the Syntheses of Regioisomeric Aziridinoindoloquinones 59 and 60



Addition of unsaturated aziridinopyrrolidine **54** to dibromoquinone **27** followed by cupric bromide catalyzed ring closure[1] afforded the tetracyclic aziridinoindoloquinone ring system in a 93% yield (Scheme VII). In parallel with previous observations, two regioisomeric products are formed in a 95/5 ratio with the unnatural regioisomer **60** as the major isomer. Isomitosene **60** is the first aziridinoindoloquinone with this regiochemistry. The ratio of the regioisomers was determined by comparison of the peak heights of the two methyl ether singlets in the NMR spectrum and by reverse-phase HPLC.

Thus the problem of introduction of the aziridine ring with the correct absolute stereochemistry has been effectively solved.[27] Experiments now in hand are directed to introduction of various substituents on the aziridine nitrogen and of the methoxyl group at C9a.

Experimental Section

Solvents and reagents were distilled as follows: methanol from magnesium methoxide, acetonitrile and dichloromethane from phosphorous pentoxide, tetrahydrofuran (THF) from sodium/benzophenone, dimethylformamide (DMF) from calcium hydride and then activated neutral alumina, triethylamine (TEA) from tosyl chloride and then calcium hydride, and mesyl chloride neat.

Melting points are uncorrected. IR spectra were determined in $CHCl_3$, and ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ with Me_4Si as an internal reference unless otherwise noted; $CHCl_3$ (7.26 ppm) was used as a reference for silyl ether containing compounds. Mass spectra and elemental analyses were supplied by the Analytical Laboratory, College of Chemistry, University of california, Berkeley.

High-pressure liquid chromatography (HPLC) was done with the following stainless steel columns: A, Altex 3.2 × 250 mm, 5-μm LiChrosorb Si60, normal phase (NP) silica gel; B, Whatman 9.4 × 500 mm, 10-μm Partisil, NP silica gel; C, Merck 4.6 × 250 mm, 10-μm LiChrosorb Si60, NP silica gel; D, Altex 4.6 × 250 mm, 10-μm, Ultrapacked ODS, reverse phase (RP) silica gel; E, Altex 3.2 × 250 mm, 5-μm Ultrasphere ODS, reverse phase silica gel. Column chromatography was performed with Kieselgel 60 (0.040–0.063 mm, EM Reagents). Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck). The following chromatography solvent systems were used: a, ethyl acetate/hexanes; b, ethyl acetate/isooctane; c, ether/hexanes; d, ether/isooctane; e, chloroform/methanol; f, acetonitrile/water.

(25) Lown, J. W.; Begleiter, A. *Can. J. Chem.* **1974**, *52*, 2331.

(26) (a) Bean, M.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 5033 and references therein. (b) Rebek, J.; Shaber, S. H.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164.

(27) There now exists some uncertainty about the absolute stereochemistries in the mitomycin series as has been recently well pointed out (Hornemann, U.; Heins, M. J. *J. Org. Chem.* **1985**, *50*, 1301). Thus the absolute configurations of the natural materials may be the inverse of those depicted. We are now addressing this question via synthesis of (1*S*,2*S*)-7-methoxy-1,2-(*N*-methylaziridino)mitosene (**3**).

Photochemical reactions were performed with a 600-W, 120-V projector lamp through Pyrex at a distance of 25 cm. Unless otherwise noted, reactions were conducted under a nitrogen atmosphere with magnetic stirring at room temperature, and final product solutions were dried over $MgSO_4$, filtered, and rotary evaporated.

***N*-[(Benzyloxy)carbonyl]-D-vinylglycine Methyl Ester (13).** The procedure previously reported[9] was used with a few modifications. The sulfoxide precursor in a round-bottom flask[28] was added to a preheated ($T_{air\ bath}$ = 185 °C) Kugelrohr distillation apparatus. Rapid oscillation (~100 cpm) was immediately initiated, and the pressure was quickly brought to ~0.3 mm. A room temperature air bath was used for cooling the receiver. After 3–4 h, the distillate was removed and chromatographed on SiO_2 (solvent a, 1/9). In this way, **13** could be obtained optically pure in 65% yield.

Methyl (2*R*,3*R*)-2-[[(Benzyloxy)carbonyl]amino]-3,4-epoxybutanoate (*syn*-14) and Methyl (2*R*,3*S*)-2-[[(Benzyloxy)carbonyl]amino]-3,4-epoxybutanoate (*anti*-14). To a stirred solution of **13** (6.92 g, 27.8 mmol) in dichloromethane (250 mL) was added *m*-chloroperbenzoic acid (23.7 g, 137 mmol). After 82 h the mixture was filtered through a glass filter, the solids were extracted with dichloromethane, and the combined organic phase was cooled to 0 °C and washed with 10% Na_2SO_3 (115 mL). The mixture was again filtered, and the organic phase was washed sequentially with 10% Na_2SO_3 (115 mL), 10% $NaHCO_3$ (2 × 70 mL), and water (70 mL). Drying and evaporating gave epoxide **14** as an oil (7.26 g, 99%; 4/1 syn/anti by HPLC): HPLC (column A; solvent d, 3/7; 1 mL/min) *syn*-**14**, t_R 12.0 min; *anti*-**14**, t_R 13.7 min.

Medium-pressure liquid chromatography using 200 g of Kieselgel 60, solvent d (2/3) at a flow rate of 30 mL/min, and multiple 1-g injections of the 4/1 mixture gave 4.54 g (62%) of *syn*-**14**.

syn-**14**: NMR δ 2.67, 2.79 (2 m, 2 H, OCHCH_2), 3.46 (m, 1 H, OCH), 3.82 (s, 3 H, OCH_3), 4.72 (dd, 1 H, NCH, J = 1, 9 Hz), 5.13 (s, 2 H, CH_2Ar), 5.33 (brd, 1 H, NH, J = 9 Hz), 7.4 (s, 5 H, Ar H). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. Found: C, 58.8; H, 5.7; N, 5.3.

anti-**14**: ^{1}H NMR (enriched *anti*-**14**) δ 2.79 (m, 2 H, OCHCH_2), 3.23 (m, 1 H, OCH), 3.81 (s, 3 H, OCH_3), 4.50 (dd, 1 H, NCH, J = 5, 7 Hz), 5.12 (s, 2 H, CH_2Ar), 5.55 (brd, 1 H, NH, J = 7), 7.4 (s, 5 H, Ar H).

Epoxide Opening with Thiophenoxide. Synthesis of Methyl (2*R*,3*R*)- and (2*R*,3*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-hydroxy-4-(phenylthio)butanoate (15). To anhydrous methanol (10 mL) was added sodium metal (87 mg, 3.8 mmol) with stirring under N_2. When solution was achieved, thiophenol (450 mg, 4.1 mmol) was added in one portion. After 30 min, **14** (100 mg, 0.38 mmol) in methanol (10 mL) was added, and the solution was refluxed for 22.5 h. The solvent was evaporated, and the residue was partitioned between chloroform (30 mL) and water (10 mL), the organic phase was washed (2 × 8 mL water), dried, and evaporated, and the residue was vacuum-dried: 133 mg (93%); NMR δ 2.8–3.2 (m, 2 H), 3.75 (s, 3 H), 4.0–4.2 (2 brs, 1 H), 4.5 (d, 1 H), 5.11, 5.13 (2 s, 2 H), 5.5–5.8 (2 d, 1 H), 7.3 (m, 10 H). Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.8; H, 5.6; N, 3.7. Found: C, 60.5; H, 5.7; N, 3.6.

***N*-[(Benzyloxy)carbonyl]-D,L-allothreonine Methyl Ester (16).** Through a 0 °C stirred suspension of D,L-allothreonine (150 mg, 1.26 mmol) in methanol (10 mL) was bubbled anhydrous HCl gas for 20 min. The solution was warmed to room temperature and stirred for 12 h. Evaporation provided the ester hydrochloride (215 mg, 98%) and to 169 mg (1.00 mmol) of this solid in water (10 mL) were added benzyl chloroformate (211 mg of 89% CbzCl, 1.10 mmol) and $NaHCO_3$ (185 mg, 2.20 mmol) with stirring. After 22 h, the mixture was extracted with ether (3 × 10 mL), and the combined extract was washed with water (7 mL) and dried. Filtration and evaporation provided **16** (249 mg, 93%): NMR δ 1.20 (d, 3 H, OCHCH_3, J = 6.4 Hz), 2.8 (1 H, OH), 3.77 (s, 3 H, OCH_3), 4.14 (m, 1 H, OCH), 4.44 (dd, 1 H, NCH, J = 4, 8 Hz), 5.12 (s, 2 H, CH_2), 5.71 (brd, 1 H, NH, J = 8 Hz), 7.35 (s, 5 H, Ar H); t_R (column E; solvent f, 1/1; 1 mL/min) 10.8 min.

***N*-[(Benzyloxy)carbonyl]-L-threonine methyl ester (L-17)** was prepared by the same procedures used to make **16**: NMR δ 1.24 (d, 3 H, OCHCH_3, J = 6.2 Hz), 2.12 (d, 1 H, OH, J = 5 Hz), 3.76 (s, 3 H, OCH_3), 4.31, 4.35 (2, brm, 1 H each, OCH, NCH), 5.13 (s, 2 H, CH_2), 5.61 (brd, 1 H, NH, J = 8 Hz), 7.36 (s, 5 H, Ar H); t_R (column E; solvent f, 1/1; 1 mL/min) 12.4 min.

Desulfurization of 15. A mixture of **15** (20 mg, 0.05 mmol) and W2-Raney Nickel (100 mg, pretreated by refluxing with acetone for 1 h) was refluxed in methanol (0.5 mL) for 12 h. The mixture was cooled and filtered. HPLC as above showed clean conversion of **15** to **16** and **17** in a 1/4 ratio, respectively.

Epoxide Opening with Sodium Azide. Synthesis of Lactone 19, Cyclic Carbamate 20, and Alcohols 18. A. Sodium Azide/Methanol. To a stirred solution of epoxides **14** (56 mg, 0.21 mmol) in anhydrous methanol (10 mL) under N_2 was added sodium azide (14 mg, 0.22 mmol). The mixture was refluxed for 4.5 h, the solvent was evaporated, the residue was partitioned between water (10 mL) and chloroform (5 mL), the aqueous layer was extracted with chloroform (4 × 5 mL), and the combined organic phase was washed with water (4 mL). Drying and evaporating provided an oily solid, which was triturated with hexane and then was recrystalized (ether/hexane) to give **20** (16 mg, 48%): mp 117–119 °C; R_f (solvent e, 98.5/1.5) 0.15; NMR δ 3.87 (s, 3 H, CO_2CH_3), 4.99 (d, 2 H, OCH_2, J = 3.8 Hz), 6.06 (dt, 1 H, C=CH, J = 1.8, 3.8 Hz), 7.05 (brs, 1 H, NH). Anal. Calcd for $C_6H_7NO_4$: C, 45.9; H, 4.5; N, 8.9. Found: C, 45.7; H, 4.5; N, 8.8.

B. Sodium Azide/Dioxane/Water. To a stirred solution of epoxides **14** (48 mg, 0.18 mmol) in dioxane (4.8 mL)/water (2.4 mL) under N_2 was added sodium azide (12 mg, 0.18 mmol). After 1 h of reflux, extraction with chloroform (4 × 4 mL) gave a combined organic extract, which was washed with water (3 mL), dried, and evaporated to a colorless oil (31 mg). Chromatography on 4.5 g of SiO_2 (solvent e, 99/1) provided **19** (2 mg, 5%), **14** (2 mg, 4%), **20** (2.5 mg, 9%), and alcohols **18** (2.5 mg, 5%). **19**: R_f (SiO_2; solvent e, 98.5/1.5) 0.34; NMR δ 4.88 (d, 2 H, ring CH_2, J = 2 Hz), 5.21 (s, 2 H, CH_2 Ar), 7.0, 7.2 (2 m, 1 H each, C=CH, NH), 7.38 (s, 5 H, Ar H); IR (Nujol) 3378, 1770, 1745, 1667, 1553, 1357, 1321, 1232, 1065, 1042, 799, 766, 727 cm^{-1}. **20**: R_f 0.15, identical to material characterized above.

C. Sodium Azide/Methanol/Ammonium Chloride. To a stirred solution of *syn*-**14** (4.00 g, 15.1 mmol) in methanol (70 mL) under N_2 was added sodium azide (2.42 g, 37.2 mmol) and ammonium chloride (1.45 g, 27.1 mmol). After refluxing for 2 h, the solvent was evaporated, and the residue was extracted with hot $CHCl_3$. The extract was filtered and evaporated to a light yellow oil. Chromatography (solvent e, 97/3) provided 4.22 g (91%) of **18**: NMR δ 2.80 (d, 1 H, OH, J = 5.2 Hz), 3.40 (d, 2 H, CH_2N_3, J = 6.2 Hz), 3.78 (s, 3 H, CO_2CH_3), 4.27 (brm, 1 H, C*H*OH), 4.46 (brd, 1 H, C*H*NH, J = 8.8 Hz), 5.13 (s, 2 H, CH_2 Ar), 5.65 (brd, 1 H, NH), 7.36 (s, 5 H, Ar H); IR 3731, 3030, 2128, 1757, 1730, 1515, 1205 cm^{-1}; t_R (column c; solvent e, 99.75/0.25; 1.5 mL/min) 22.5 min.

Methyl (2*R*,3*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-azidobutanoate (21). A solution of alcohol **18** (3.69 g, 12.0 mmol), *tert*-butyldimethylsilyl chloride (8.97 g, 59.5 mmol), and imidazole (8.09 g, 118.8 mmol) in DMF (12 mL) was stirred at room temperature for 70 h. The solvent was evaporated by Kugelrohr distillation [50 °C (0.5–1.0 mm)], and the residue was partitioned between water (30 mL) and dichloromethane (60 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL), and the combined organic layer was washed with water (10 mL), dried, and evaporated to afford **21**. Chromatography (solvent e, 99/1) gave ether **21** as a colorless oil: 4.13 g (82%); NMR δ 0.004, 0.096 (s + s, 3 H each, $Si(CH_3)_2$), 0.84 (s, 9 H, $C(CH_3)_3$), 3.34 (m, 2 H, N_3CH_2), 3.75 (s, 3 H, OCH_3), 4.29 (ddd, 1 H, CHOSi), 4.52 (dd, 1 H, CHN, J = 1.5, 9.8 Hz), 5.15 (s, 2 H, CH_2 Ar), 5.37 (brd, 1 H, NH), 7.40 (m, 5 H, Ar H); IR 3534, 2907, 2119, 1761, 1629, 1425, 1203, 1111, 1071, 1018, 845 cm^{-1}.

(2*R*,3*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-azidobutanoic Acid (22). To a stirred solution of **21** (1.7 g, 4.12 mmol) in dioxane (182 mL, from sodium benzophenone ketyl) at 0 °C was added aqueous LiOH (0.4 M, 60 mL, 24 mmol) dropwise over the course of 10 min under N_2. The ice bath was removed for 4 h and was then reapplied 10 min

(28) For best results, a minimum flask surface area/mass of sulfoxide ratio of 55 cm^2/g should be used.

before adding 0.1 M H_3PO_4 dropwise with stirring until the pH was 4.0 (approximately 265 mL of acid required). The mixture was then extracted with dichloromethane (100 mL and then 3 × 30 mL), and the combined organic phase was washed with water (35 mL) and dried then evaporated to give **22** as a white solid (1.7 g, 100%). A small portion was recrystallized from ethyl acetate/hexane for analysis; prolonged heating should be avoided since it leads to the cyclization–elimination product **19**.

22: mp 146–147 °C; NMR δ 0.06, 0.12 (s + s, 3 H each, Si(CH_3)$_2$), 0.86 (s, 9 H, C(CH_3)$_3$), 3.36 (m, 2 H, CH_2N_3), 4.35 (m, 1 H, OCH), 4.54 (brd, 1 H, C*H*NH, *J* = 9 Hz), 5.16 (s, 2 H, CH_2 Ar), 5.41 (brd, 1 H, NH, *J* = 9 Hz), 7.38, (s, 5 H, Ar H); IR 3546, 2137, 1733, 1508, 1255, 1205, 1115, 929 cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_4O_5Si$: C, 52.9; H, 6.9; N, 13.7. Found: C, 52.9; H, 6.9; N, 13.3.

Ethyl (3*R*,4*S*)-[3-[[(Benzyloxy)carbonyl]amino]-4-[(*tert*-butyldimethylsilyl)oxy]-(*Z*)-2-pyrrolidinylidene]-acetate (26) and Ethyl (3*S*,4*S*)-[3-[[(Benzyloxy)carbonyl]-amino]-4-[(*tert*-butyldimethylsilyl)oxy]-(*Z*)-2-pyrrolidinylidene]acetate (25). To a flame-dried flask containing a solution of **22** (740 mg, 1.81 mmol) in dry THF (15 mL) was added carbonyl diimidazole (320 mg, 1.97 mmol) with stirring. After 18 h, isopropyl magnesium bromide in THF (10.9 mL of 0.80 M solution, 8.72 mmol) was added dropwise to a separate dry flask containing a 0 °C stirred solution of ethyl hydrogen malonate (590 mg, 4.47 mmol) in THF (5 mL) under N_2. After 10 min the cold bath was removed, and 75 min later a 40 °C water bath was applied for 15 min. After both solutions were cooled to 0 °C, the imidazolide solution was added dropwise to the rapidly stirred malonate anion solution over the course of 10 min. The cold bath was then removed and the mixture gradually became heterogeneous over the course of 21 h, at which time 0.1 M HOAc (60 mL) was added. After the mixture was extracted with ether (2 × 30 mL), the combined organic phase was washed sequentially with 0.1 M HOAc (10 mL), 10% $NaHCO_3$ (20 mL), and brine (20 mL). Drying and evaporating provided crude **23/24** as an oil (0.76 g, 88%).

The crude mixture (660 mg) was dissolved in absolute ethanol (30 mL), PtO_2 (33 mg) was added with stirring, and hydrogen was passed over the mixture for 12 h, at which time the mixture was filtered and evaporated to an oil (0.60 g). Chromatography (solvent d, 2/3) provided **26** contaminated with a trace of **25** (287 mg, 48%) and **25** contaminated with a trace of **26** (102 mg, 17%). The enriched sample of **26** was used in the equilibration study below. Anal. Calcd for $C_{22}H_{34}N_2O_5Si$: C, 60.8; H, 7.9; N, 6.4. Found: C, 61.1; H, 7.9; N, 6.4.

26: NMR δ 0.04 (s, 6 H, Si(CH_3)$_2$), 0.86 (s, 9 H, C(CH_3)$_3$), 1.24 (t, 3 H, CH_3 *J* = Hz), 3.26 (dd, 1 H, NHCH*H*, *J* = 6.8, 9.5 Hz), 3.60 (br dd, 1 H, *J* = 6.8, 9.5 Hz), 4.09 (q, 2 H, CH_2CH$_3$, *J* = 7 Hz), 4.25 (m, 1 H, SiOCH), 4.60 (brs, 1 H, each, N*H*CHC=C*H*, both exchangeable with D_2O), 4.87 (br d, 1 H, *J* = 9 Hz), 5.13 (m, 2 H, CH_2 Ar), 7.35 (s, 5 H, Ar He, 7.54 (br s, 1 H, NH). After 1 week, an NMR spectrum was obtained of the same solution. Deuterium exchange of the 4.87 ppm absorption had taken place with epimerization to predominantly **25** (**25/26**, 88/12).

25: NMR δ 0.04 (s, 6 H, Si(CH_3)$_2$), 0.85 (s, 9 H, C(CH_3)$_3$), 1.24 (t, 3 H, CH_3, *J* = 7 Hz), 3.38 (dd, 1 H, NHC*H*HCH, *J* = 2, 11 Hz, converted to d, *J* = 11 Hz, in D_2O), 3.63 (dd, 1 H, *J* = 3.8, 11 Hz), 4.10 (q, 2 H, CH_2CH$_3$, *J* = 7 Hz), 4.35 (br dd, 1 H, SiOCH), 4.63 (s, 1 H, NHCHC=C*H*, exchanged with D_2O), 4.78 (dd, 1 H, *J* = 4.6, 9.5 Hz, converted to d, *J* = 9.5 Hz, by irradiation of 4.35 ppm resonance), 5.14 (br m, 3 H, CH_2 Ar, $NHCO_2$), 7.36 (s, 5 H, Ar H), 7.61 (br s, 1 H); IR 3356, 2976, 1724, 1664, 1613, 1515, 1242, 1149, 1114, 1046, 1005 cm^{-1}.

Equilibration of Vinylogous Carbamates 25 and 26. A portion of the enriched sample of **26** (245 mg) was stirred in chloroform (15 mL) with silica gel (2.45 g, activated at 180 °C for 24 h) for 28 h at which time the silica was filtered off and reextracted with chloroform. Evaporation provided 224 mg (91%) of **26** and **25** in a 1/4 ratio: HPLC (column A; solvent b, 1/4; 1 mL/min) **26**, t_R 6.52 min; **25**, t_R 8.25 min.

Ethyl (1*S*,2*S*)-1-[[(Benzyloxy)carbonyl]amino]-2-[(*tert*-butyldimethylsilyl)oxy]-6-methoxy-7-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (29) and Ethyl (1*S*,2*S*)-1-[[(Benzyloxy)carbonyl]amino]-2-[(*tert*-butyldimethylsilyl)oxy]-6-methoxy-7-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (28). To a stirred solution of **25** (56 mg, 0.129 mmol) in acetonitrile (1.5 mL) were added dibromoquinone **27** (60 mg, 0.19 mmol, 150 M %), cupric bromide (3.6 mg, 0.016 mmol), and potassium carbonate (89 mg, 0.64 mmol, finely powdered, anhydrous). The mixture was heated at 50 °C for 16 h, then cooled, diluted with $CHCl_3$ (3 mL), filtered, and evaporated to an oil. Chromatography (solvent d, 3/2) afforded **29** contaminated with 5% of **28**: 69 mg (93%); mp 167–169 °C. Anal. Calcd for $C_{30}H_{38}N_2O_5Si$: C, 61.8; H, 6.6; N, 4.8. Found: C, 61.5; H, 6.5; N, 4.5.

HPLC (column B; solvent d, 3/7; 6 mL/min) gave base line separation of **28** and **29**.

28: t_R (column A; solvent d, 3/7; 1 mL/min) 29.4 min; NMR δ 0.06, 0.09 (2 s, 6 H, Si(CH_3)$_2$), 0.85 (s, 9 H, C(CH_3)$_3$), 1.27 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 1.94 (s, 3 H, Ar CH_3), 4.06 (s, 3 H, OCH_3), 4.14–4.40 (m, 4 H, CH_2CH$_3$, NCH$_2$), 4.92 (m, 1 H), 5.13 (s, 2 H, Ar CH_2), 5.38 (m, 2 H), 7.35 (m, 5 H, Ar H).

29: t_R (column A; solvent d, 3/7; 1 mL/min) 34.8 min; NMR δ 0.07, 0.10 (2 s, total 6 H, Si(CH_3)$_2$), 0.86 (s, 9 H, C(CH_3)$_3$), 1.29 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 2.00 (s, 3 H, CH_3), 3.98 (s, 3 H, OCH_3), 4.17–4.42 (m, 4 H, CH_2CH$_3$, NCH$_2$), 4.92 (br m, 1 H), 5.14 (s, 2 H, CH_2 Ar), 5.37 (br m, 2 H), 7.35 (m, 5 H, Ar H).

Ethyl (1*S*,2*S*)-1-[[(Benzyloxy)carbonyl]amino]-2-hydroxy-6-methoxy-7-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (30). Tetrabutylammonium fluoride in water (153 mg of a 35% aqueous solution, 0.205 mmol) was made anhydrous by evaporation with benzene (3 × 10 mL) and then acetonitrile (3 × 10 mL). The residue was dissolved in THF (5 mL) and added over a 5-min period to a −48 °C solution of **29** (60 mg, 0.103 mmol) in THF (10 mL). After 1 h at −48 °C, TLC (solvent e, 95/5) showed complete conversion of **29** (yellow, R_f 0.81) to **30** (yellow, R_f 0.40). Acetic acid (1 M, 3 mL) was added, and the reaction mixture was warmed to room temperature and partitioned between H_2O (10 mL) and $CHCl_3$ (15 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL), and the combined organic phase was washed with 10% $NaHCO_3$ (10 mL) and then H_2O (10 mL) and dried. Evaporation of the solvent followed by chromatography (solvent e, 97/3) afforded **30** as a yellow solid: 48 mg (100%); mp 76–78 °C; NMR δ 1.15 (t, 3 H, CH_2CH_3, *J* = 7.2 Hz), 1.87 (s, 3 H, CH_3), 3.93–4.05 (m, 4 H, OCH_3, OH), 4.12–4.45 (m, 4 H, CH_2CH$_3$, NCH$_2$), 4.98 (br m, 1 H, CHOH), 5.15 (dd, 2 H, OCH_2 Ar, *J* = 12.2, 21.5 Hz), 5.30 (m, 1 H, C*H*NH), 6.82 (br m, 1 H, NH), 7.35 (m, 5 H, Ar H). Anal. Calcd for $C_{24}H_{24}N_2O_8$: C, 61.5; H, 5.2; N, 6.0. Found: C, 61.2; H, 5.1; N, 5.9.

Ethyl (1*S*,2*S*)-1-[[(Benzyloxy)carbonyl]amino]-2-(mesyloxy)-6-methoxy-7-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (31). To a stirred solution of **30** (17 mg, 0.036 mmol) in dichloromethane (10 mL) were added TEA (73 mg, 0.72 mmol) and methanesulfonyl chloride (50 mg, 0.44 mmol), and the reaction mixture was stirred for 1 h at room temperature and then poured into ice–water (5 mL). The mixture was washed with 0.1 M HCl (5 mL), 10% $NaHCO_3$ (10 mL), and H_2O (5 mL) and dried. Evaporation followed by chromatography (solvent e, 97/3) afforded **31** (18 mg, 91%) as a yellow oil: NMR δ 1.26 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 1.90 (s, 3 H, CH_3), 2.72 (s, 3 H, SO_2CH_3), 3.91 (s, 3 H, OCH_3), 4.22 (m, 2 H, OCH_2CH$_3$), 4.46 (dd, 1 H, NC*H*H, *J* = 5.0, 14.1 Hz), 4.63 (dd, 1 H, NCH*H*, *J* = 0.8, 14.1 Hz), 5.07 (dd, 2 H, Ar CH_2, *J* = 12.2, 26.1 Hz), 5.31 (m, 1 H, C*H*NH), 5.63 (m, 1 H, C*H*OSO$_2$CH$_2$), 6.44 (br d, NH, *J* = 5.3 Hz), 7.27 (m, 5 H, Ar H).

Ethyl 6-Methoxy-7-methyl-2,3,5,8-tetrahydro-1,5,8-trioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (33) and Ethyl (1*S*,2*S*)-1-Amino-2-(mesyloxy)-6-methoxy-7-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (32). To a stirred solution of **31** (13 mg, 0.024 mmol) in absolute ethanol (5 mL) were added 10% Pd/C (5 mg) and 1,4-cyclohexadiene (0.10 mL, 1.06 mmol), and the reaction mixture was refluxed for 14 h, cooled, filtered, and poured into CH_2Cl_2 (10 mL). The solution was extracted with 10% $NaHCO_3$ (2 × 10 mL) and then H_2O (10 mL) and dried. Evaporation followed by chromatography (solvent b, 1/4) gave **33** (3.3 mg, 44%) as a yellow solid. Continued elution with solvent b (1/1) gave **32** (4.0 mg, 41%) as a yellow oil.

33: mp 163–165 °C; R_f (solvent e, 95/5) 0.29; NMR δ 1.42 (t, 3 H, OCH_2CH_3, *J* = 7.1 Hz), 2.04 (s, 3 H, CH_3), 3.20 (m, 2 H,

$COCH_2$), 4.05 (s, 3 H, OCH_3), 4.44 (q, 2 H, OCH_2CH_3, J = 7.1 Hz), 4.63 (m, 2 H, NCH_2); mass spectrum, *m/e* (relative intensity) 318 (M + 1, 20), 317 (M^+, 100), 272 (89), 271 (94), 256 (99), 243 (26); mass spectrum, calcd for $C_{16}H_{15}NO_6$ *m/e* 317.0903, found *m/e* 317.0899.

32: NMR δ 1.44 (t, 3 H, OCH_2CH_3, J = 7.1 Hz), 2.03 (s, 3 H, CH_3), 3.20 (s, 3 H, SO_2CH_3), 3.65 (m, 2 H, NH_2), 3.99 (s, 3 H, OCH_3), 4.39 (q, 2 H, OCH_2CH_3, *J* = 7.1 Hz), 4.55 (dd, 1 H, NC*H*H, *J* = 5.4, 13.9 Hz), 4.65 (dd, 1 H, NCH*H*, *J* = 3.4, 13.9 Hz), 4.79 (d, 1 H, C*H*NH_2, *J* = 5.8 Hz), 5.61 (m, 1 H, $CHOSO_2$).

6-Benzyl-6-azabicyclo[3.1.0]hexane (35). To a stirred solution of triphenylphosphine (740 mg, 2.82 mmol) in acetonitrile (80 mL) was added carbon tetrachloride (4 mL, 41 mmol). The solution gradually turned yellow over a period of 0.5 h, at which time *trans*-2-(benzylamino)cyclopentanol[29] (174 mg, 0.91 mmol) was added in a solution of TEA (0.40 mL, 2.88 mmol) and chloroform (40 mL) over 5 min. The reaction mixture was allowed to stir for 19 h. Removal of the solvent followed by chromatography (solvent c, 2/3) gave the aziridine **35** (125 mg, 79%) as an oil. Kugelrohr distillation [50 °C (0.01 mm)] afforded an analytical sample: NMR δ 1.48–2.02 (m, 6 H, $CH_2CH_2CH_2$), 2.05 (s, 2 H, CHNCH), 3.41 (s, 2 H, CH_2 Ar), 7.28 (m, 5 H, Ar H); ^{13}C NMR δ 139.78, 128.07, 127.20, 126.47, 61.40, 45.13, 27.44, 21.05; mass spectrum, *m/e* (relative intensity) 174 (M + 1, 6), 173 (M^+, 46), 91 (77), 82 (75), 55 (100). Anal. Calcd for $C_{12}H_{15}N$: C, 83.2; H, 8.7; N, 8.1. Found: C, 83.2; H, 8.7; N, 8.1.

***trans*-Ethyl (3*S*,4*S*)-[3-[[(Benzyloxy)carbonyl]amino]-4-hydroxy-(*Z*)-2-pyrrolidinylidene]acetate (36).** Tetrabutylammonium fluoride in water (343 mg of 35% aqueous solution, 0.46 mmol) was made anhydrous by chasing on a rotary evaporator with benzene (3 × 15 mL) and then acetonitrile (3 × 15 mL). The residue was dissolved in THF (10 mL) and added to a stirred solution of **25** (100 mg, 0.23 mmol) in THF (10 mL). After 5 min TLC (solvent e, 9/1) showed conversion of **25** (R_f 0.91) to **36** (R_f 0.47). Evaporation and chromatography of the residue (solvent e, 95/5) afforded **36**: 64 mg (87%); mp 130–132 °C; NMR δ 1.23 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 2.5 (br s, 1 H, OH, exchanged with D_2O), 3.49 (dd, 1 H, NHC*H*H, *J* = 2.1, 11.6 Hz), 3.65 (dd, 1 H, NCH*H*, *J* = 3.4, 11.6 Hz), 4.10 (q, 2 H, CH_2CH_3, *J* = 7.1 Hz), 4.38 (m, 1 H, C*H*OH), 4.65 (s, 1 H, C=CH, exchanged with D_2O), 4.75 (m, 1 H, C*H*$NHCO_2CH_2$ Ar, D_2O treatment simplified to br d, *J* = 4.5 Hz), 5.14 (s, 2 H, CH_2 Ar), 5.46 (br d, 1 H, NHCO, *J* = 8.7 Hz), 7.37 (s, 5 H, Ar H), 7.57 (br s, 1 H, NH). Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 60.0; H, 6.3; N, 8.7. Found: C, 59.9; H, 6.3; N, 8.6.

Ethyl 3-[[(Benzyloxy)carbonyl]amino]-2-pyrroleacetate (38). To a stirred solution of **36** (43 mg, 0.13 mmol) in dichloromethane (2 mL) at 0 °C were added a solution of TEA (54.2 mg, 0.54 mmol) in dichloromethane (2 mL) and then methanesulfonyl chloride (38.4 mg, 0.34 mmol). The reaction mixture was allowed to warm to room temperature and stirred an additional 1 h, and then it was partitioned between ice–water (25 mL) and dichloromethane. The organic layer was washed with 10% $NaHCO_3$ (10 mL) and then H_2O (10 mL), dried, evaporated, and chromatographed (solvent e, 97/3) to afford pyrrole **38** (31 mg, 76%) as a red oil: NMR δ 1.26 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 3.58 (s, 2 H, $CH_2CO_2CH_2CH_3$), 4.16 (q, 2 H, CH_2CH_3, *J* = 7.1 Hz), 5.17 (s, 2 H, OCH_2 Ar), 6.05–6.63 (m, 3 H), 7.37 (m, 5 H, Ar H), 8.60 (br s, 1 H); mass spectrum, *m/e* (relative intensity) 303 (M + 1, 6), 302 (M^+, 33), 211 (100), 167 (48), 121 (82), 91 (93); mass spectrum, calcd for $C_{16}H_{18}N_2O_4$ *m/e* 302.1266, found *m/e* 302.1271.

Ethyl (2*R*,3*S*,4*S*)- and (2*S*,3*S*,4*S*)-[1-[(*tert*-Butyloxy)carbonyl]-3-[[(benzyloxy)carbonyl]amino]-4-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]acetate (39). To a solution of **25** (1.02 g, 2.35 mmol) in ethanol (100 mL) containing a trace of bromocresol green was slowly added sodium cyanoborohydride (148 mg, 2.36 mmol) with rapid stirring. A solution of 0.2 M HCl was added dropwise over the course of 11 h to maintain an acidic pH as indicated by the yellow color. The reaction mixture was diluted with dichloromethane (150 mL) and washed with 10% $NaHCO_3$ (50 mL), then the aqueous phase was extracted with dichloromethane (50 mL), and the combined organic phase was dried and evaporated to an oil (1.03 g, 100%), which was heated with di-*tert*-butyl dicarbonate (6.13 g, 28.1 mmol) at 55 °C for 16 h. The reaction mixture was cooled, Kugelrohr distilled [50 °C (0.01 mm) to remove the excess di-*tert*-butyl dicarbonate, and chromatographed (solvent d, 2/3) to afford **39** (1.12 g, 89%) as a mixture of diastereomers. NMR showed substantial broadening due to rotational isomers of the *tert*-butyl carbamate: δ 0.04, 0.06 (2 s, total 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.21 (br t, 3 H, CH_2CH_3), 1.44 (s, 9 H, $OC(CH_3)_3$), 2.8–4.5 (br m, 10 H), 5.10 (s, 2 H, CH_2 Ar), 7.34 (s, 5 H, Ar H). Anal. Calcd for $C_{27}H_{44}N_2O_7Si$: C, 60.4; H, 8.3; N, 5.2. Found: C, 60.3; H, 8.3; N, 5.4.

Ethyl (2*R*,3*S*,4*S*)- and (2*S*,3*S*,4*S*)-[1-[(*tert*-Butyloxy)carbonyl]-3-(benzylamino)-4-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]acetate (40). A mixture of ammonium formate (300 mg, 4.76 mmol), 10% Pd/C (100 mg), and **39** (500 mg, 0.93 mmol) was refluxed in methanol (25 mL) for 1 h. The mixture was cooled to room temperature and filtered, the catalyst was washed well with methanol, and the filtrate was evaporated. Chromatography (solvent d, 4/1) of the residue afforded the primary amine as a clear oil (350 mg, 93%). To a stirred solution of the amine (279 mg, 0.69 mmol) in dichloromethane (15 mL) were added benzaldehyde (147 mg, 1.39 mmol) and 1.0 g of crushed activated 4-Å molecular sieves. After 0.5 h, sodium cyanoborohydride (87.2 mg, 1.39 mmol) was added in two portions. The mixture was stirred for 3 h at room temperature with dropwise addition of glacial acetic acid to maintain an acidic pH, and it was filtered and carefully partitioned between 10% $NaHCO_3$ (25 mL) and dichloromethane (25 mL). The aqueous layer was extracted with dichloromethane (15 mL), and the combined organic phase was dried, evaporated, and chromatographed (solvent d, 15/85) to afford **40** (258 mg, 76%) as a clear oil: NMR δ 0.07, 0.08 (2 s, total 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.22 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 1.45 (s, 9 H, $OC(CH_3)_3$), 2.5–4.3 (m, 12 H), 7.22–7.32 (m, 5 H, Ar H). Anal. Calcd for $C_{26}H_{44}N_2O_5Si$: C, 63.4; H, 9.0; N, 5.7. Found: C, 63.0; H, 8.8; N, 5.6.

Ethyl (2*R*,3*S*,4*S*)- and (2*S*,3*S*,4*S*)-[1-(*tert*-Butyloxy)carbonyl]-3-(benzylamino)-4-hydroxy-2-pyrrolidinyl]acetate (41). Tetrabutylammonium fluoride in water (822 mg of a 35% aqueous solution, 1.10 mmol) was made anhydrous by chasing on a rotary evaporator with acetonitrile (4 × 15 mL). The residue was dissolved in THF (15 mL) and added to a stirred solution of **40** (254 mg, 0.52 mmol) in THF (25 mL) at 0 °C. The reaction mixture was stirred for 0.5 h, poured into ice–water (50 mL), and extracted with dichloromethane (2 × 50 mL), and then the combined organic extracts were dried, evaporated, and chromatographed (solvent d, 2/3) to afford **41** as a clear oil: 170 mg (87%); NMR δ 1.24 (t, 3 H, CH_2CH_3, *J* = 7.1 Hz), 1.45 (s, 9 H, $C(CH_3)_3$), 2.33–3.27 (m, 6 H), 3.30 (dd, 1 H, NC*H*H, *J* = 3.8, 12.3 Hz), 3.55–3.97 (m, 3 H), 4.02 (br m, 1 H), 4.12 (q, 2 H, CH_2CH_3, *J* = 7.1 Hz), 7.29 (m, 5 H, Ar H); mass spectrum, *m/e* (relative intensity) 379 (M + 1, 1), 378 (M^+, 2), 321 (13), 277 (15), 219 (16), 150 (19), 146 (29), 106 (63), 91 (100); mass spectrum, calcd for $C_{20}H_{30}N_2O_5$ *m/e* 378.2155, found *m/e* 378.2151.

Methyl D-*N*-Benzylthreoninate (44). To a stirred solution of methyl D-threoninate hydrochloride (**43**)[24] (1.04 g, 6.13 mmol) in glacial acetic acid (3 mL) and dichloromethane (5 mL) were added benzaldehyde (1.30 g, 12.3 mmol) and crushed activated 4-Å molecular sieves (1.0 g). After the mixture was stirred for 1 h, sodium cyanoborohydride (0.77 g, 12.3 mmol) was added in portions with ice cooling. After 4 h, TLC (solvent e, 95/5) showed conversion to **44** (R_f = 0.35), and the reaction mixture was filtered and carefully partitioned between 10% $NaHCO_3$ (50 mL) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (50 mL), and the combined organic extracts were dried, filtered, evaporated, and dried on a Kugelrohr apparatus [50 °C (0.01 mm). Chromatography (solvent e, 97/3) afforded **44** as a clear oil: 0.78 g (57%); NMR δ 1.19 (d, 3 H, CH_3, *J* = 6.2 Hz), 2.5–3.0 (br m, 2 H, NH, OH), 3.04 (d, 1 H, CHN, *J* = 7.4 Hz), 3.64–3.85 (m, 6 H), 7.29 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.5; H, 7.7; N, 6.3. Found: C, 64.2; H, 7.7; N, 6.4.

Methyl (2*R*,3*R*)-1-Benzyl-3-methyl-2-aziridinecarboxylate (45). To a stirred solution of triphenylphosphine (1.75 g, 6.67 mmol) in acetonitrile (35 mL) was added carbon tetrachloride (10 mL). The solution turned yellow over a period of 0.5 h, at which time **44** (0.50 g, 2.24 mmol) was added dropwise in a solution

(29) Barr, A. A.; Frencel, I.; Robinson, J. B. *Can. J. Chem.* **1977**, *55*, 4180.

of TEA (1.0 mL, 7.20 mmol) and acetonitrile (15 mL). The reaction mixture was stirred for 16 h at room temperature. Removal of the solvent, followed by chromatography (solvent d, 2/3) of the residue afforded aziridine **45**: 0.41 g (89%); NMR δ 1.29 (d, 3 H, CH_3, J = 5.6 Hz), 2.02 (m, 1 H, CH_3CH), 2.25 (d, 1 H, CHCO, J = 6.8 Hz), 3.60 (dd, 2 H, CH_2Ar, J = 13.6, 17.6 Hz), 3.73 (s, 3 H, OCH_3), 7.37 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.4; N, 6.8. Found: C, 69.9; H, 7.3; N, 6.8.

Methyl (2*R*,3*R*)- and (2*R*,3*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-hydroxy-4-chlorobutanoate (46a). To a solution of **14** (11.2 g, 0.042 mol; 4/1 syn/anti mixture of diastereomers) in methanol (110 mL) at 0 °C was added dropwise a saturated solution of HCl in methanol (23 mL). The solution was warmed to room temperature and stirred an additional 0.5 h, then neutralized by careful addition of $NaHCO_3$, and partioned between H_2O (300 mL) and $CHCl_3$ (100 mL). The aqueous phase was extracted with chloroform (3 × 50 mL), and the combined organic extracts were dried, filtered, evaporated, and chromatographed (solvent d, 1/1) to afford chloride **46a** (8.7 g, 68%) as a mixture of diastereomers. Recrystallization from $CHCl_3$/isooctane gave white needles: mp 90–91 °C; NMR δ 2.90 (br d, 1 H, OH), 3.52 (dd, 1 H, C*H*HCl, J = 8.0, 11.3 Hz), 3.63 (m, 1 H, CH*H*Cl), 3.78 (s, 3 H, OCH_3), 4.37 (br m, 1 H, C*H*OH), 4.57 (br dd, 1 H, C*H*NH, J = 2, 9 Hz), 5.13 (s, 2 H, CH_2 Ar), 5.62 (br d, 1 H, NH, J = 9 Hz), 7.39 (s, 5 H, Ar H). Anal. Calcd for $C_{13}H_{16}NO_5Cl$: C, 51.7; H, 5.3; N, 4.6. Found: C, 51.7; H, 5.3; N, 4.6.

Methyl (2*R*,3*R*)- and (2*R*,3*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-hydroxy-4-bromobutanoate (46b). To a solution of **14** (1.15 g, 4.3 mmol; 4/1 syn/anti mixture of diastereomers) in methanol (12 mL) at 0 °C was added dropwise a 59% (w/w) solution of HBr in methanol (2.5 mL). The solution was warmed to room temperature and stirred an additional 1 h. Isolation as for chloro compound **46a** afforded **46b** (1.24 g, 83%) as a mixture of diastereomers. Recrystallization from a $CHCl_3$/isooctane mixture gave white needles: mp 91–93 °C; NMR δ 2.80 (br s, 1 H, OH), 3.39 (dd, 1 H, C*H*HBr, J = 8.3, 10.5 Hz), 3.52 (m, 1 H, CH*H*Br), 3.78 (s, 3 H, OCH_3), 4.40 (br m, 1 H, C*H*OH), 4.61 (br dd, 1 H, C*H*NH, J = 2, 9 Hz), 5.13 (s, 2 H, CH_2 Ar), 5.63 (br d, 1 H, NH), 7.44 (s, 5 H). Anal. Calcd for $C_{13}H_{16}NO_5Br$: C, 45.1; H, 4.7; N, 4.0. Found: C, 45.1; H, 4.7; N, 4.0.

Methyl (2*R*,3*R*)-2-(Benzylamino)-3-hydroxy-4-chlorobutanoate (47). A mixture of **46a** (3.45 g, 11.4 mmol), cyclohexene (8.0 g, 97.4 mmol), glacial acetic acid (1.38 g, 23.0 mmol), and 10% Pd/C (0.70 g) was refluxed in methanol (50 mL) with stirring for 0.5 h. The mixture was cooled and filtered, the catalyst was washed well with methanol, and the combined filtrate and washings were evaporated and dried on a Kugelrohr apparatus [50 °C (0.01 mm)] for 4 h to give the acetate salt (2.55 g, 98%) as a yellow oil. To a stirred solution of the salt (2.55 g, 11.2 mmol) in glacial acetic acid (10 mL) and methanol (75 mL) were added benzaldehyde (2.38 g, 22.4 mmol) and activated 4-Å molecular sieves (10 g). After 10 min, sodium cyanoborohydride (1.41 g, 22.4 mmol) was slowly added over the course of 10 min, and the reaction mixture was stirred for 0.5 h, filtered, and partitioned between 10% $NaHCO_3$ (200 mL) and $CHCl_3$ (75 mL). The aqueous layer was extracted with chloroform (3 × 50 mL), and the combined organic extracts were dried, filtered and evaporated. Chromatography (solvent d, 2/3) afforded *syn*-**47** (198 g, 69%) and *anti*-**47** (0.51 g, 18%).

syn-**47**: R_f (solvent c, 7/3) 0.40; NMR δ 2.3–2.6 (br s, 2 H, NH, OH), 3.47 (d, 1 H, C*H*NH, J = 4.8 Hz), 3.62 (d, 2 H, CH_2Cl, J = 5.6 Hz), 3.76, 3.69–3.97 (s and m, 6 H, OCH_3, CH_2 Ar, C*H*OH), 7.41 (m, 5 H, Ar H); mass spectrum, m/e (relative intensity) 259 (M^+, 0.4), 257 (M^+, 1.4), 198 (52), 179 (46), 178 (67), 106 (46), 92 (60), 91 (100), 65 (64). Anal. Calcd for $C_{12}H_{16}NO_3Cl$: C, 55.9; H, 6.3; N, 5.4. Found: C, 56.1; H, 6.3; N, 5.4.

anti-**47**: R_f (solvent c, 7/3) 0.29; NMR δ 2.3–2.6 (br s, 2 H, NH, OH), 3.52 (d, 1 H, C*H*NH, J = 4.8 Hz), 3.60–4.38 (m, 8 H), 7.38 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{16}NO_3Cl$: C, 55.9; H, 6.3; N, 5.4. Found: C, 55.8; H, 6.3; N, 5.5.

Methyl (2*R*,3*R*)-2-[Benzyl[(*tert*-butyloxy)carbonyl]amino]-3-hydroxy-4-chlorobutanoate (48). A mixture of *syn*-**47** (800 mg, 3.1 mmol) and di-*tert*-butyl dicarbonate (5.0 g, 22.9 mmol) was stirred at 50 °C for 10 h. After cooling, the mixture was Kugelrohr distilled [50 °C (0.01 mm)], and the residue was chromatographed (solvent d, 2/3) to afford carbamate **48** as a clear oil: 1.07 (96%); R_f (solvent c, 7/3) 0.52; NMR δ 1.49 (s, 9 H, $C(CH_3)_3$), 3.48 (m, 1 H), 3.62 (s, 3 H, OCH_3), 4.27 (br m, 1 H), 4.42 (br m, 2 H), 4.62 (d, 1 H, C*H*H Ar, J = 15.3 Hz), 5.46 (br d, 1 H), 7.31 (m, 5 H, Ar H). Anal. Calcd for $C_{17}H_{24}NO_5Cl$: C, 57.1; H, 6.8; N, 3.9. Found: C, 56.8; H, 6.8; N, 3.9.

Methyl (2*R*,3*S*)-2-[Benzyl[(*tert*-butyloxy)carbonyl]amino]-3-hydroxy-4-azidobutanoate (49). A mixture of **48** (1.44 g, 4.02 mmol) and freshly activated sodium azide[30] (0.79 g, 12.2 mmol) was heated in DMF (70 mL) at 75 °C for 12 h. The mixture was cooled, poured into H_2O (100 mL), and extracted with ether (3 × 50 mL). The combined ether extracts were dried, filtered, and evaporated. Chromatography (solvent d, 3/7) afforded **49** as a clear oil: 1.10 g (75%); NMR δ 1.52 (s, 9 H, $C(CH_3)_3$), 3.12 (br m, 1 H), 3.39 (dd, 1 H, C*H*H, J = 6.1, 12.5 Hz), 3.65 (s, 3 H, OCH_3), 4.04 (d, 1 H, CHN, J = 5.7), 4.24–4.42 (br m, 2 H), 4.56 (d, 1 H, C*H*H, J = 15.1 Hz), 5.03 (br s, 1 H), 7.37 (m, 5 H, Ar H); IR (CCl_4) 2105, 1750, 1545, 1252, 1162 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_4O_5$: C, 56.0; H, 6.6; N, 15.4. Found: C, 56.0; H, 6.7; N, 15.0.

Methyl (2*R*,3*S*)-2-[Benzyl[(*tert*-butyloxy)carbonyl]amino]-3-(mesyloxy)-4-azidobutanoate (51). To a stirred solution of **49** (310 mg, 0.85 mmol) in dichloromethane (15 mL) at 0 °C were added TEA (1.20 mL, 8.65 mmol) and methanesulfonyl chloride (0.66 mL, 8.53 mmol). The mixture was warmed to room temperature and stirred an additional 0.5 h, then poured into 10% $NaHCO_3$ (20 mL), and extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried, evaporated, and chromatographed (solvent d, 1/1) to afford mesylate **51** as a colorless oil: 351 mg (93%); R_f (solvent c, 7/3) 0.45; NMR δ 1.48 (s, 9 H, $C(CH_3)_3$), 2.92–5.45 (m, 12 H), 7.38 (m, 5 H, Ar H). Anal. Calcd for $C_{18}H_{26}N_4O_7S$: C, 48.9; H, 5.9; N, 12.7. Found: C, 49.4; H, 6.1; N, 12.5.

Methyl (2*R*,3*R*)-1-Benzyl-3-(azidomethyl)-2-aziridinecarboxylate (52). To a stirred solution of **51** (1.25 g, 2.82 mmol) in dichloromethane (75 mL) at 0 °C was added trifluoroacetic acid (30 mL) over the course of 10 min. The reaction mixture was warmed to room temperature and stirred an additional 1 h, then the solvent and excess trifluoroacetic acid were evaporated, and the residue was dried in vacuo. The residue, dissolved in acetonitrile (50 mL), was refluxed with diisopropylethylamine (1.96 mL, 11.25 mmol) for 4 h, then cooled to room temperature, and partitioned between H_2O (50 mL) and chloroform (50 mL). The aqueous layer was extracted with chloroform (2 × 50 mL), and the combined organic extracts were dried and evaporated. Chromatography (solvent, d, 3/7) of the residue gave aziridine **52** as a colorless oil: 0.49 g (70%); R_f (solvent c, 7/3) 0.53; NMR δ 2.22 (q, 1 H, CH_2CH, J = 6.4 Hz), 2.40 (d, 1 H, CHCO, J = 6.5 Hz), 3.41 (dd, 1 H, N_3CHH, J = 6.3, 13.1 Hz), 3.57 (dd, 1 H, N_3CHH, J = 6.4, 13.1 Hz), 3.66 (s, 2 H, CH_2 Ar), 3.75 (s, 3 H, OCH_3), 7.35 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.5; H, 5.7; N, 22.7. Found: C, 58.4; H, 5.7; N, 22.7.

Ethyl (1*R*,5*R*)-[6-Benzyl-3,6-diazabicyclo[3.1.0]-(*Z*)-2-hexanylidene]acetate (54). To a stirred solution of diisopropylamine (2.75 mL, 19.62 mmol) in THF (100 mL) at 0 °C was added *n*-BuLi (8.23 mL of a 2.30 M solution, 18.93 mmol). The reaction mixture was stirred for 0.5 h and then cooled to −78 °C. Ethyl acetate (1.93 mL, 19.76 mmol) was added dropwise, and 0.5 h later, **52** (1.17 g, 4.75 mmol) was added dropwise in THF, keeping the temperature below −70 °C throughout. After 4 h at −78 °C, a solution of ammonium chloride (2.0 g) in H_2O (10 mL) was added, and the reaction mixture was partitioned between H_2O (200 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (2 × 50 mL) and the combined organic extracts were dried and evaporated to an oil. Chromatography (solvent d, 2/3) afforded β-keto ester **53** (1.28 g, 89%) as a colorless oil. To a stirred solution of **53** (1.28 g, 4.23 mmol) in absolute ethanol (100 mL) was added PtO_2 (60 mg), and 1 atm of hydrogen was passed over the reaction mixture until TLC (solvent c, 7/3) showed complete conversion of **53** (R_f 0.65) to **54** (R_f 0.20) within 2 h. The reaction mixture was filtered, evaporated,

(30) Smith, P. A. S. "Organic Reactions"; Wiley: New York, 1946; Vol. 3, p 382.

and chromatographed (solvent d, 3/2) to afford **54**: 0.83 g (76%); mp 115–117 °C; NMR δ 1.28 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 2.71 (m, 2 H, CH_2CH, CCHN), 3.58 (m, 4 H, cH_2 Ar, CH_2N), 4.10 (q, 2 H, CH_2CH_3, J = 7.1), 4.81 (s, 1 H, C=CH), 7.32 (m, 5 H, Ar H); IR 3400, 3160, 3030, 2985, 1720, 1620, 1260 cm^{-1}; $[\alpha]^{23}_D$ +2.1° (c 0.014, CH_3OH). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.7; H, 7.0; N, 10.8. Found: C, 69.6; H, 7.0; N, 10.7.

Ethyl (1*S*,2*S*,5*R*)- and (1*S*,2*R*,5*R*)-6-Benzyl-3,6-diazabicyclo[3.1.0]hexane-2-acetate (55). To a solution of **54** (125 mg, 0.48 mmol) in ethanol (10 mL), containing a trace of bromocresol green was added sodium cyanoborohydride (150 mg, 2.39 mmol), and glacial acetic acid was added dropwise over the course of 4 h to maintain an acidic pH as indicated by the yellow color of the bromocresol green. The reaction mixture was diluted with dichloromethane (50 mL) and washed with 10% $NaHCO_3$ (20 mL), the aqueous phase was extracted with dichloromethane (20 mL), and the combined organic extracts were dried, filtered, and evaporated to an oil. Chromatography (solvent e, 95/5) afforded **55** as a colorless oil: 112 mg, 89%, mixture of diastereomers: NMR δ 1.21 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 2.07 (br s, 1 H, NH), 2.29–2.62 (m, 4 H), 2.74 (dd, 1 H, NHCHH, J = 1.6, 12.3 Hz), 3.09 (d, 1 H, NHCHH, J = 12.3 Hz), 3.29 (m, 2 H), 3.61 (m, 1 H), 4.08 (m, 2 H, CH_2CH_3), 7.35 (m, 5 H, Ar H).

Quinones 56. To a stirred solution of **55** (110 mg, 0.42 mmol) in benzene (15 mL) were added dibromoquinone **27** (159 mg, 0.51 mmol) and potassium carbonate (120 mg, 0.87 mmol). After 65 h in the dark, the mixture was filtered and evaporated. Chromatography, eluting with benzene, gave recovered dibromoquinone **27**, and, eluting with solvent d (2/3), gave **56** as a purple oil: 192 mg (93%); R_f (solvent c, 7/3) 0.57; NMR δ 1.17 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 1.87 (s, 3 H, CH_3), 2.53 (m, 2 H), 2.85 (m, 1 H), 3.28 (d, 1 H, J = 13.3 Hz), 3.43 (dd, 1 H), 3.62 (d, 1 H, J = 13.3 Hz), 3.75–4.03 (m, 3 H), 4.04 (s, 3 H, OCH_3), 4.68 (d, 1 H, J = 13.2 Hz), 5.22 (br m, 1 H), 7.39 (m, 5 H). Anal. Calcd for $C_{23}H_{25}N_2O_5Br$: C, 56.5; H, 5.1; N, 5.7. Found: C, 57.0; H, 5.1; N, 5.7.

Ethyl (1*R*,2*R*)-1,2-(*N*-Benzylaziridino)-7-methoxy-6-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]-indole-9-carboxylate (59). A solution of **56** (29 mg, 0.059 mmol) in methanol was degassed with argon and irradiated in an argon atmosphere for 2 h with a visible lamp (Pyrex filtered). The solvent was then evaporated and the residue dissolved in ethyl acetate and stirred in the dark, open to the air, with 10% Pd/C (15 mg). After 21 h the mixture was filtered, the catalyst was washed with ethyl acetate, and the combined filtrate and washings were evaporated to an oil. Chromatography (solvent c, 2/3) afforded **58** (17.5 mg, 61%) as a purple oil: R_f (solvent c, 7/3) 0.42; NMR δ 1.21 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 1.97 (s, 3 H, CH_3), 2.71 (m, 1 H), 3.38–3.61 (m, 2 H), 3.91–4.20 (m, 8 H), 4.59 (d, 1 H, J = 16.7 Hz), 7.40 (m, 5 H, Ar H); mass spectrum, m/e (relative intensity) 490, 488 (29, 40, M + 2 with ^{81}Br, M + 2 with ^{79}Br), 486 (7, M+, ^{79}Br), 397 (50), 395 (28), 334 (35); mass spectrum, calcd for $C_{23}H_{23}N_2O_5$ ^{79}Br m/e 486.0788, found m/e 486.0789. The intermediate **58** (17.5 mg, 35.8 μmol) was dissolved in acetonitrile (2 mL), and the solution was added to $Pd(OAc)_2$ (2 mg, 8.9 mmol) in acetonitrile (1 mL) with stirring. TEA (20 μL, 0.144 mmol) was added, and the mixture was stirred for 12 h and then partitioned between water (15 mL) and dichloromethane (15 mL). The aqueous layer was extracted with dichloromethane (15 mL), and the combined organic extracts were dried, evaporated, and chromatographed (solvent c, 3/2; then solvent e, 98/2) to give **59** as a yellow solid: 14 mg (96%); mp 187–190 °C; NMR δ 1.23 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 1.92 (s, 3 H, CH_3), 3.17 (br t, 1 H, CH_2CHN, J = 4.3 Hz), 3.45 (d, 1 H, CCHN, J = 4.9 Hz), 3.67 (dd, 2 H, CH_2 Ar, J = 13.7, 24.5 Hz), 4.06 (s, 3 H, OCH_3), 4.17–4.36 (m, 3 H, CH_2CH_3, NCHH), 4.45 (d, 1 H, NCHH, J = 14.0 Hz), 7.33 (m, 5 H, Ar H); $[\alpha]^{23}_D$ −66° (c 0.013, $CHCl_3$. Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 68.0; H, 5.5; N, 6.9. Found: C, 67.7; H, 5.3; N, 6.7.

Ethyl (1*R*,2*R*)-1,2-(*N*-Benzylaziridino)-6-methoxy-7-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]-indole-9-carboxylate (60). To a stirred solution of dibromoquinone **27** (61.3 mg, 0.198 mmol) and unsaturated pyrrolidine **54** (34 mg, 0.132 mmol) in acetonitrile (3 mL) were added K_2CO_3 (91 mg, 0.66 mmol) and $CuBr_2$ (3.5 mg, 0.016 mmol). After 16 h at 50 °C, the mixture was cooled, poured into water (20 mL), and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried and evaporated, and the residue was chromatographed (solvent e, 97/3) to afford a mixture of **59** and **60** as a yellow solid: 50 mg (93%); mp 187–191 °C dec; NMR (analysis of the methyl ether resonances of **59** and **60**, 4.06 and 3.94 ppm, respectively, showed a ratio of 5/95) δ 1.25 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 2.00 (s, 3 H, CH_3), 3.18 (br t, 1 H, CH_2CHN, J = 4.3 Hz), 3.48 (d, 1 H, CCHN, J = 4.9 Hz), 3.67 (s, 2 H, CH_2 Ar), 3.94 (s, 3 H, OCH_3), 4.19–4.36 (m, 3 H, CH_2CH_3, NCHH), 4.45 (d, 1 H, NCHH, J = 13.9 Hz), 7.33 (m, 5 H, Ar H); HPLC (59/60, 5/95 column D; solvent f, 2/3; 2 mL/min) **60**, t_R 21.2 min, **59**, t_R 25.6 min. Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 68.0; H, 5.4; N, 6.9. Found: C, 67.6; H, 5.4; N, 6.8.

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[3,3] Sigmatropic Rearrangements of Benzyl Vinyl Ethers. Model Studies Directed toward the Total Synthesis of Cephalotaxine[1]

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Model studies directed toward the synthesis of cephalotaxine are described. Thermolysis of 11 gave 14 rather than 12.

Cephalotaxine (1), the major alkaloid of the genus *Cephalotaxus*, has attracted considerable interest both due to its unique structure and because of the promising antitumor activity of several ester derivatives of 1.[3]

We have recently been exploring a new approach for the synthesis of cephalotaxine. The key step in this approach involves the [3,3] sigmatropic rearrangement of a benzyl vinyl ether[4] such as **2** to give **3**. Elaboration of **3** to 1 would

(1) Synthesis Via Sigmatropic Rearrangements. 8. For previous papers in this series see: Raucher, S.; Lawrence, R. F. *Tetrahedron* **1983**, *39*, 3731.

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(3) Reviews: (a) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158. (b) Smith, C. R., Jr.; Mirolajczak, K. L.; Powell, R. G. In: "Antitumor Agents Based on Natural Product Models"; Academic Press: New York, 1980; Chapter 11. For an extensive list of references concerning *Cephalotaxus* alkaloids see the footnotes in: (c) Hiranuma, S.; Shibata, M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 5321.

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