Chiral Aziridinyl Radicals: An Application to the Synthesis of the Core Nucleus of FR-900482

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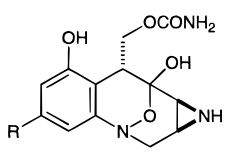
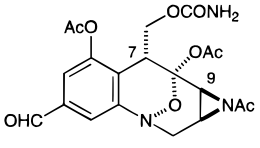
An asymmetric route to the core nucleus of the antitumor agent FR-900482 utilizes the cyclization of an aziridinyl radical into a functionalized indole nucleus. The route employs a selective Polonovski reaction and the Hootelé-Dmitrienko rearrangement to install two oxygen atoms.

In 1987, FR-900482 (**1a**), a mitomycin-like antitumor agent,[1,2] was isolated[3] from *Streptomyces sandaensis* and characterized[4,5] by the Fujisawa Laboratories. FR-900482, which is a 2:1 mixture (β:α ether bridge) of stereoisomers at neutral pH and almost exclusively the β-isomer in acidic medium, had its spectral properties investigated as the product of triacetylation, FK-973 (**2**). An X-ray analysis of FK-973 secured the relative stereochemistry while biosynthetic studies demonstrated that the nonaromatic portion of FR-900482 was derived from D-glucosamine, thereby establishing the absolute stereochemistry.[6] Two years later, FR-66979 (**1b**) was isolated from the same culture broth and was determined to have similar activity to FR-900482.[7] FR-66979 was prepared from FR-900482 by catalytic hydrogenation. FK-973 was found to be more effective than mitomycin C (**3**) in certain tumor screens.[8,9] FR-900482, FR-66979, and FK-973 behave similarly to mitomycin C in that they cross-link DNA.[10] The site of cross-linking has been determined for FR-900482 and FR-66979 by the isolation of bis-guanosine adducts derived from 5′-CpG sites.[11−14]

The unique structure of FR-900482 has prompted a number of model studies directed toward its synthesis.[15−23]



1a, R=CHO
b, R=CH_2OH



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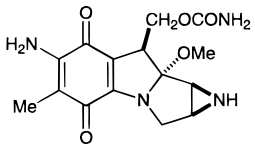

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Of these efforts, only Rapoport's approach addressed the preparation of chiral products derived from enantiomerically-pure starting material and Sulikowski's recent contribution explored the viability of a reagent-controlled asymmetric synthesis. The total synthesis of (±)-FR-900482 was first accomplished by Fukuyama in 1992[24] and later by Danishefsky.[25] More recently, Terashima et al. reported the total synthesis of natural (+)-FR-900482 using L-diethyl tartrate as the chiral pool.[26−28]

Our approach to FR-900482 is outlined in Scheme 1. The late intermediate **4** was viewed as arising from dihydroindole **5** by a double oxidation. To accomplish this goal, oxidation of **5** to an indole would have to be avoided. Drawing upon our earlier study[29] involving the generation of carbon-centered aziridinyl radicals and their intramolecular addition to an indole nucleus, indole **6** was selected as a suitable substrate. Previous cyclizations of this type had been conducted on indoles bearing electron-withdrawing groups at the 3-position wherein dimerization of the highly stabilized radical had occurred.[29−31] Two points were at issue: would an alkyl

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(1) Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 600.
(2) Hirai, O.; Shimomura, K.; Mizota, T.; Matsumoto, S.; Mori, J.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 607.
(3) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589.
(4) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 594.
(5) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108.
(6) Fujita, T.; Takase, S.; Otsuka, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 392.
(7) Terano, H.; Takese, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145.
(8) Shimomura, K.; Manda, T.; Mukumoto, S.; Masuda, K.; Nakamura, T.; Mizota, T.; Matsumoto, S.; Nishigaki, F.; Oku, T.; Mori, J.; Shibayama, F. *Cancer Res.* **1988**, *48*, 1166.
(9) Masuda, K.; Nakamura, T.; Mizota, T.; Mori, J.; Shimomura, K. *Cancer Res.* **1988**, *48*, 5172.
(10) Masuda, K.; Nakamura, T.; Shimomura, K.; Shibata, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 1497.
(11) Woo, J.; Sigurdsson, S. T.; Hopkins, P. B. *J. Am. Chem. Soc.* **1993**, *115*, 1199.
(12) Williams, R. M.; Rajski, S. R. *Tetrahedron Lett.* **1993**, *34*, 7023.
(13) Huang, H.; Pratum, T. K.; Hopkins, P. B. *J. Am. Chem. Soc.* **1994**, *116*, 2703.
(14) Huang, H.; Rajski, S. R.; Williams, R. M.; Hopkins, P. B. *Tetrahedron Lett.* **1994**, *35*, 9669.
(15) Yasuda, N.; Williams, R. M. *Tetrahedron Lett.* **1989**, *30*, 3397.
(16) Jones, R. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 1144.
(17) McClure, K. F.; Benbow, J. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 8185.
(18) McClure, K. F.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 850.
(19) Dmitrienko, G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705.
(20) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094.
(21) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169.
(22) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.
(23) Lim, H.-J.; Sulikowski, G. A. *Tetrahedron Lett.* **1996**, *37*, 5243.
(24) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.
(25) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722.
(26) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3471.
(27) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3475.
(28) Katoh, T.; Yoshino, T.; Nagata, Y.; Nakatani, S.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3479.
(29) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962.
(30) Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768.

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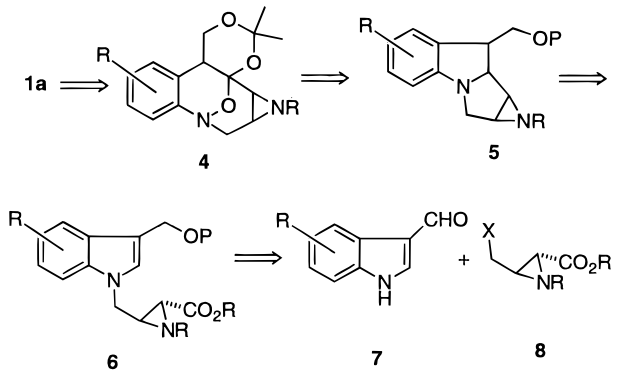
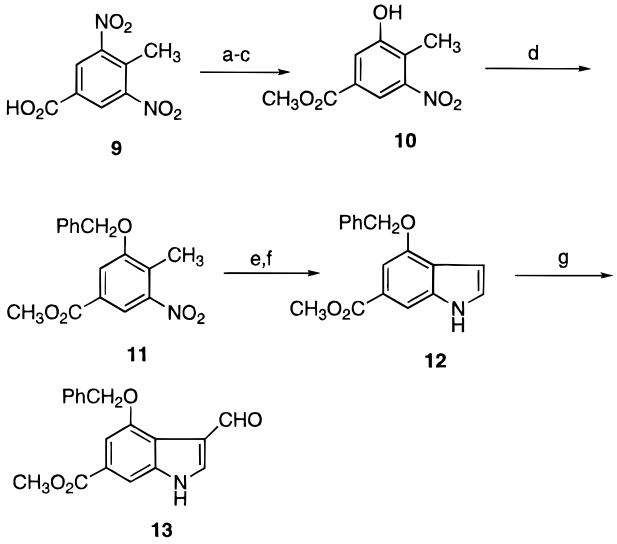
Scheme 1



Scheme 2

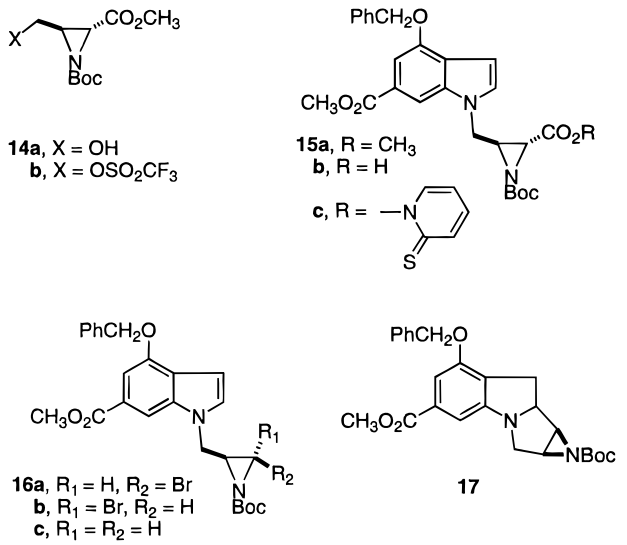


a) $(NH_4)_2S$, C_2H_5OH, Δ. b) $NaNO_2$, aq. H_2SO_4, 0 °C; Δ. c) CH_3OH, H_2SO_4, Δ. d) $PhCH_2Cl$, K_2CO_3, DMF, 100 °C. e) pyrrolidine, DMF dimethyl acetal, 110 °C. f) NH_2NH_2, Ni(R), THF-CH_3OH. g) $POCl_3$, DMF, 0 °C; H_2O.

substituent at the 3-position of the indole ring permit reductive cyclization and would the gramine-like structure of indole **6** survive the reaction conditions? Ready access to 3-formylindoles and the availability of a suitable electrophilic, enantiomerically-pure aziridine-2-carboxylate made this approach attractive. Moreover, the route would flout conventional wisdom by incorporation of "reactive" aziridine functionality at an early stage of the synthetic scheme.

In their study directed toward an asymmetric synthesis of FR-900482, Jones and Rapoport[16] employed as a starting material methyl 3-hydroxy-4-methyl-5-nitrobenzoate (**10**) prepared from 3,5-dinitro-*p*-toluic acid by successive sodium dithionite reduction, diazotization,[32] and esterification. In our hands, the dithionite reduction proved troublesome. Modification of the reported[33] Zinin reduction (ammonium sulfide) of toluic acid **9** provided the intermediate *m*-anthranilic acid in 71% yield. *o*-Nitrotoluene **11** was converted to the indole **12** in 56% yield by the Batcho–Leimgruber procedure.[34] Vilsmeier–Haack formylation afforded the target aldehyde **13** with the proviso that hydrolysis of the intermediate iminium salt was conducted in water rather than aqueous alkali to minimize ester hydrolysis.[35]

To test whether or not reductive radical cyclization could be conducted in the absence of an electron-withdrawing group at the 3-position of the indole nucleus, indole **12** was alkylated as previously described[29] with the triflate **14b**, whose genesis was D-isoascorbic acid.[36] The resultant ester **15a**, prepared in 44% yield, was saponified selectively to the monocarboxylic acid **15b** with excess LiOH without affecting the aromatic carbomethoxy group (84%). Thiohydroxamate ester formation was accomplished by the Barton–Samadi procedure[37] which utilizes 2,2′-dithiobis(pyridine *N*-oxide) and n-Bu_3P. Rather than employ a direct decarboxylation–cyclization protocol whose shortcoming has been addressed previously,[29] a two-step procedure was employed.

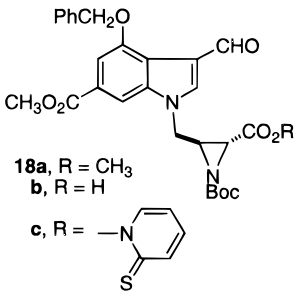


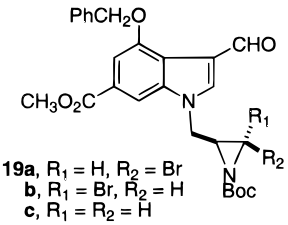
Visible light photolysis (W-lamp) of thiohydroxamic acid anhydride **15c** in neat $BrCCl_3$ afforded a mixture of cis and trans bromoaziridines **16a** and**16b** (3.3:1, respectively) in 53% yield. The presence of pyridine was necessary to scavenge HBr, which is capable of cleaving the aziridine ring.[29] The major isomer was assigned the cis stereochemistry based upon a coupling constant of 5.3 Hz for the vicinal aziridine hydrogens; the minor isomer displayed $J = 1.7$ Hz for the same signals. The isolation of the bromoaziridines as a mixture was of little consequence because both isomers were amenable to the subsequent reductive cyclization. Accordingly, a toluene solution of n-Bu_3SnH and 1,1′-azobis(cyclohexylcarbonitrile) (ACCN) was added via syringe pump to a mixture of bromoaziridines **16a** and **16b** in refluxing toluene to afford a 4:1 mixture of tetracycle **17** and uncyclized aziridine **16c** in 57% yield. The dilution technique was required to maximize the **17**:**16c** ratio. Rewardingly, the benzylic radical obtained by cyclization was sufficiently reactive to abstract a hydrogen atom from n-Bu_3SnH and sustain a chain process as opposed to dimerization, which had been observed when an electron-withdrawing group

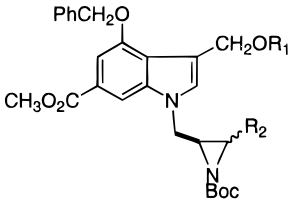
(31) Ziegler, F. E.; Harran, P. G. *Tetrahedron Lett.* **1993**, *34*, 4505.
(32) Nielson, O. B. T.; Bruun, H.; Bretting, C.; Feit, P. W. *J. Med. Chem.* **1975**, *18*, 41.
(33) The molar ratio of ammonium sulfide to 3,5-dinitro-*p*-toluic acid was increased from 1:1 to 3:1. Barben, I. K.; Suschitzky, H. *J. Chem. Soc.* **1960**, 672.
(34) Batcho, A. D.; Leimgruber, W. *Organic Syntheses*; John Wiley: New York, 1985; Vol. 63, p 214.
(35) James, P. N.; Snyder, H. R. *Organic Syntheses*; John Wiley: New York, 1963; Coll. Vol. IV, p 539.
(36) Dunigan, J.; Weigel, L. *J. Org. Chem.* **1991**, *56*, 6225.
(37) Barton, D. H. R.; Samadi, M. *Tetrahedron* **1992**, *48*, 7083.

was present at the benzylic site.[29] Although the stereochemistry of tetracycle **17** was not readily derived from the ^{1}H NMR spectrum, the methine hydrogens are most likely syn to one another as has been observed in previous cyclizations of this type.[29−31]

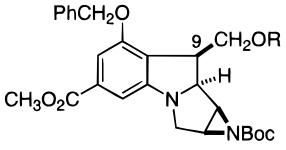
Having established the viability of the reductive cyclization in the absence of an electron-withdrawing group, the cyclization of a potentially labile indole-3-methanol was explored. The alkylation of indole-3-carboxaldehyde **13** with triflate **14b** was improved (66% yield) over the alkylation of indole **12** by rapid isolation of the triflate, which proved to be more stable than had been anticipated.[38] Ester **18a** was readily converted into a 3.8:1 mixture of aziridinyl bromides **19a** and **19b** in 69% yield by the standard protocol. The cis stereoisomer again prevailed over its trans counterpart. Not only did coupling constants (J = 4.9 and 1.8 Hz, respectively) of the vicinal aziridine methine hydrogens support the assignment, but also the cis isomer **19a** displayed an NOE between these two hydrogens (∼12%) while the trans isomer **19b** showed no NOE.





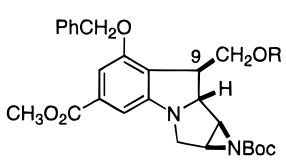


20a, R_1 = H, R_2 = Br
b, R_1 = TBDMS, R_2 = Br
c, R_1 = TBDMS, R_2 = H
d, R_1 = R_2 = H

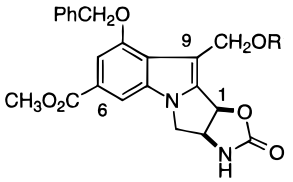


21a, R = TBDMS
b, R = H

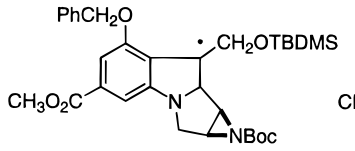
Reduction of the mixture of aldehydes **19a** and **19b** was readily achieved with $NaBH_4$ in CH_3OH to produce indole-3-methanols **20a**, which were directly silylated to form the TBDMS ethers **20b**. Attempts to purify silyl ether **20b** by SiO_2 chromatography gave complex mixtures with only 6% recovery of the silyl ether. In spite of the lability of the silyl ether toward chromatography, reductive cyclization in toluene (bath temperature 116 °C) proved successful. No dimer was detected nor was any reduced uncyclized product **20c** isolated although it had been detected spectroscopically. Chromatography separated oxazolidinone **23** (2.2%) from the diastereomeric silyl ethers **21a** and **22a**. The latter silyl ethers were separated as their alcohols **21b** (51%) and **22b** (∼5%)[39] after desilylation with tetra-*n*-butylammonium fluoride (TBAF).



22a, R = TBDMS
b, R = H
c, R = $COCH_3$



23 R = TBDMS



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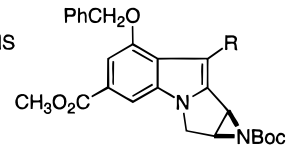


25a, R = $CH_2OTBDMS$
b, R = CH_2OH
c, R = CHO

The ^{1}H NMR spectrum of oxazolidinone **23**, which is the product of a net, nonreductive process, revealed an exchangeable proton with a concentration dependent chemical shift and a doublet at δ = 6.13 (J = 7.9 Hz) corresponding to the methine hydrogen at C_1.[40] Although the cyclization was run under a N_2 atmosphere, no effort was made to degas the solvent. Surrepticious oxygen could oxidize radical **24** to the indole **25a** followed by nitrogen-assisted cleavage of the aziridine at the C_1 site. Readdition of the Boc carbonyl oxygen followed by loss of the *tert*-butyl group would lead to oxazolidinone. This mode of aziridine ring opening is critical in the nucleophilic attack on the reduced, activated forms of FR-900482[11] and mitomycin C.[41] Alternatively, the appearance of nonreduced products in the presence of n-Bu_3SnH in radical reactions is not uncommon. At least two studies have invoked an $S_{NR}1$ mechanism to explain the oxidation of radicals in the absence of oxygen. The stannane serves as a base in the formation of a radical anion from the radical. Subsequent electron transfer affords the nonreduced product.[42−44]

The stereochemistry of the major, cyclized alcohol **21b** and the minor, cyclized alcohol **22b** were determined by NOE difference experiments and coupling constants obtained from their derived TBDMS ether **21a** and acetate **22c**, respectively. Silyl ether **21a** showed strong enhancement of the C_9-H (13.4%)[45] and C_1-H (9.3%) upon irradiation of the C_{9a}-H (Figure 1). This cis−cis arrangement places the silyloxymethyl group and the aziridine proximate to one another on the concave face of the nitrogen-bearing [3.3.0] ring system. Irradiation of the C_1-H caused enhancement (4.9%) of one of the C_{10}-H hydrogens but no enhancement of C_9-H. Although C_1-H and C_9-H are cis to one another, they are remotely situated on the convex face of the ring system. On the

(38) We thank Mr. Mikhail Berlin of this laboratory for this observation.

(39) The yield of alcohol **22b** is the average obtained by combining the products of several runs.

(40) Mitomycin numbering is used throughout the text for mitomycin-like structures. FR-900482 numbering is employed for related oxygen-bridged structures. These numbers may not agree with compound names appearing in the Experimental Section.

(41) For leading references see, Tomasz, M.; Chawla, A. K.; Lipman, R. *Biochemistry* **1988**, *27*, 3182.

(42) Antonio, Y.; De La Cruz, M. E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15.

(43) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119.

(44) Moody, C. J.; Norton, C. L. *Tetrahedron Lett.* **1995**, *36*, 9051.

(45) The heads of arrows in Figure 1 are the observed hydrogen atoms; the tails are irradiated.

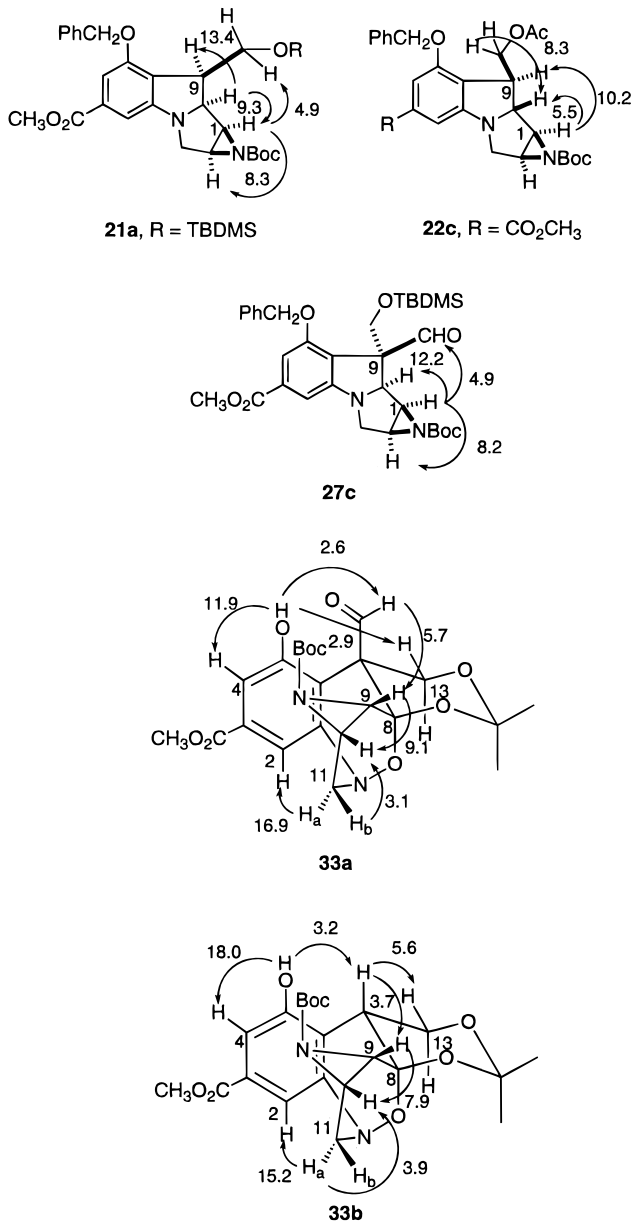


Figure 1. NOE studies.

other hand, acetate **22c** displayed a strong NOE (10.2%) between these two hydrogen atoms that are cis but proximately located on the concave face. No NOE is observed between the trans hydrogens at C_9 and C_{9a}, although the trans pair at C_1 and C_{9a} shows an enhancement of 5.5%. The proximity of one of the C_{10} methylene hydrogen atoms and the C_{9a}-H is revealed by an 8.3% NOE. These two structures, **21a** and **22c**, bear the same relative stereochemistry between C_1 and C_9 and differ only at the C_{9a} center. The coupling constant for C_9-H/C_{9a}-H (J = 9.8 Hz) in silyl ether **21a** and J = 6.3 Hz in acetate **22c** supported the respective cis and trans stereochemical assignments. The C_1-H/C_{9a}-H coupling constant (J = 1.8 Hz) in silyl ether **21a** was consistent with coupling constants of analogs in this series;[29] however, the lack of coupling at this site in acetate **22c**, while consistent with a trans relationship, cannot be construed as supporting evidence.[46] Nonetheless, these assignments would be supported by subsequent X-ray and chemical correlation studies.

(46) Harran, P. G., Ph. D. Thesis, Yale University, 1995.

A more efficient route to alcohol **21b** may be imagined by reductive cyclization of indole-3-methanol **20d.** This pathway resulted in the isolation of a mixture (5.5:1) of the desired, cyclized alcohol **21b** and reduced, uncyclized alcohol **20a**, respectively, in 53% yield. The inability to separate effectively these alcohols established the longer silylation route as the more prudent choice.

With the successful formation of the tetracyclic aziridinol **21b**, attention was directed toward the incorporation of the two oxygen atoms at C_{9a}, which bears the basic nitrogen. Any oxidation of **21b** to a tetrasubstituted iminium salt would result in facile aromatization to indole **25b**—a dead end. To preclude aromatization, a formyl group was installed at C_9 of tetracycle **21b** to permit controlled oxidation.[47] The presence of the aziridine ring would prohibit enamine formation by deprotonation of the iminium salt at C_1.

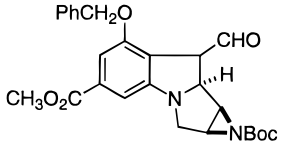
To this end, oxidation of alcohol **21b** to aldehyde **26** was explored. When Swern oxidation conditions[48] were employed, aldehyde **25c** was a minor, but nonetheless, undesirable byproduct. Tetra-*n*-butylammonium perruthenate[49,50] oxidation gave aldehyde **25c** as the major product. Dess−Martin periodinane, particularly aged samples,[51,52] proved to be a satisfactory oxidant. Because aldehyde **26** was also susceptible to aerial oxidation to indole **25c**, aldehyde **26** was directly condensed with aqueous formalin[53] in the presence of $NaHCO_3$ to afford a single aldol product in 86% yield after radial chromatography. The ^{1}H NMR spectrum of aldol **27a** displayed an exchangeable hydrogen at δ 2.77 (J = 9.8 and 4.2 Hz) that was coupled to each of the methylene hydrogen atoms at δ 3.56 and 4.41, respectively. The resonance at δ 3.56, in addition to being coupled to its geminal partner, was also weakly coupled (J = 1 Hz) to the aldehyde hydrogen. This coupling pattern argued on behalf of a hydrogen bond between the hydroxyl group and the aldehyde group.

Although much effort would be expended in locating a suitable protecting group for the hydroxyl group of aldol **27a**, our initial choice was to prepare the TBDMS silyl ether. From a practical viewpoint, the silylation was conducted on the aldol product prior to its purification by radial chromatography. In addition to the expected silyl ether **27c**, silyl ether **27d**, which was higher in mass than **27c** by 30 units, was also isolated. The ^{1}H NMR spectrum of **27d**, with an additional AB pattern (δ 4.02, 4.76; J = 5.2 Hz) revealed it to be a simple formaldehyde homolog of **27c**. The bis-formaldehyde adduct **27b** was never isolated upon radial chromatography. Its transient stability may have been due to its existence as the cyclized hemiacetal.

The stereochemistry of silyl ether **27c** was revealed by NOE difference studies (Figure 1). Irradiation of the C_1-H caused enhancement of the C_2-H (8.2%), the C_{9a}-H (12.2%), and the aldehyde hydrogen (4.9%). The second NOE placed the C_2-H and C_{9a}-H in a cis relationship as

(47) For an example of nucleophilic oxygen capture by an iminium salt during oxidation see, Bartlett, M. F.; Lambert, B. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1964**, *86*, 729.
(48) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(49) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(50) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.
(51) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *43*, 4155.
(52))For a recent modification of the original procedure and an understanding of the mechanism see, Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(53) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626.

was observed for silyl ether **21a**. The C_1-H/CHO NOE (4.9%), the same magnitude as the C_1-H/C_{10}-H NOE in silyl ether **21a**, and the lack of an NOE between the aldehyde hydrogen and C_{9a}-H, set the trans relationship between the C_1-H and the aldehyde group. The C_1-H/aldehyde enhancement is not unusual; a similar NOE has been observed[5] between the C_7-H and C_9-H in FK-973 and the structurally related diastereomer of FR-900482. From a mechanistic perspective, be it kinetic or thermodynamic, the stereochemical arrangement at C_9 in silyl ether **27c** is what would be expected from the aldol condensation. Kinetic control would argue for the electrophile formaldehyde to react with the enolate of aldehyde **26** on the uncongested convex α-face; thermodynamically, the smaller, sp^2-hybridized formyl group would occupy the concave face of the tetracyclic ring system of aldol **27a** and the sp^3-hybridized hydroxymethyl group would be favored on the convex face. The relative stereochemistry of C_1 and C_9 would be confirmed on a later substrate after introduction of the two oxygen atoms.



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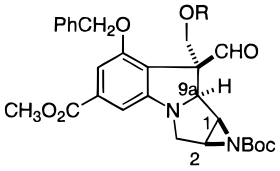
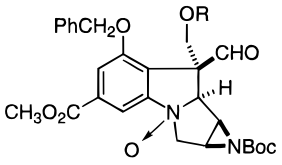
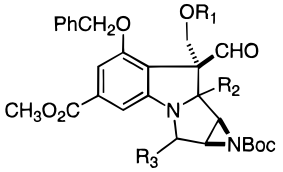


27a, R = H
b, R = CH_2OH
c, R = TBDMS
d, R = $CH_2OTBDMS$
e, R = $COCH_3$
f, R = CO_2CH_2Ph
g, R = CH_2OCH_3
h, R = CO_2CH_3



28a, R = TBDMS
b, R = $COCH_3$
c, R = CO_2CH_2Ph



29a, R_1 = TBDMS, R_2 = OH, R_3 = H
b, R_1 = TBDMS, R_2 = H, R_3 = OH
c, R_1 = $COCH_3$, R_2 = OH, R_3 = H
d, R_1 = $COCH_3$, R_2 = H, R_3 = OH
e, R_1 = CO_2CH_2Ph, R_2 = OH, R_3 = H
f, R_1 = CO_2CH_2Ph, R_2 = H, R_3 = OH

When the minor alcohol **22b** was oxidized to an aldehyde and subjected to an aldol condensation with formalin, no trace of aldol product **27a** could be isolated or detected by ^{1}H NMR. If major alcohol **21b** and minor alcohol **22b** had the same relative stereochemistry at C_1-H and C_{9a}-H, then the same aldol product, namely alcohol **27a**, would have been expected from both diastereomers. This chemical experiment supported the structural assignments for alcohols **21b** and **22b** that were made through spectroscopic studies.

The oxidants $Hg(OAc)_2$[54–56] and Pt/O_2[57] proved unsuccessful in the oxidation of silyl ether **27c**. In a synthetic study conducted in the mitomycin series, wherein the C_9 position bore a hydrogen and an aziridine ring was not present, Danishefsky and Feigelson[58] observed that a Polonovski reaction[59] led to aromatization (via C_{9a} iminium salt) and C_3 oxidation in near equal amounts. This observation notwithstanding, treatment of silyl ether **27c** to m-CPBA provided amine oxide **28a** as a single diastereomer (^{1}H NMR) presumably with the oxygen atom cis to the C_{9a}-H. Exposure of the amine oxide to acetic anhydride in THF at 0 °C gave rise to a chromatographically inseparable 2.7:1 mixture (33%) of *tert*-carbinolamine **29a** and the amine oxide precursor, amine **27c**, respectively, 40% yield of *sec*-carbinolamine **29b**, and a trace of aromatic substitution product **31a**.[60] As planned, acetate added to the regioisomeric iminium salts and was exchanged for a hydroxyl group during aqueous workup.

The ^{1}H NMR spectrum of *tert*-carbinolamine **29a** was devoid of a C_{9a}-H signal. The C_1-H (δ = 3.22, J = 4.4 Hz) resonance was now coupled only to C_2-H and no longer coupled to two vicinal hydrogens as in amine **27c**. On the other hand, *sec*-carbinolamine **29b** displayed a C_{9a}-H (δ = 4.54, J = 2.1 Hz) and a single C_3-H (δ = 4.91 (d, J = 3.7 Hz)), coupled only to the exchangeable hydroxyl proton at δ 1.96. Amine **27c** was not present due to incomplete oxidation but rather an undefined reduction process. When the more reactive trifluoroacetic anhydride was used, a complex reaction mixture was produced; no carbinolamines were detected. The interpretation of the selectivity in the Polonovski reaction at the time was that the silyloxy group was providing sufficient steric bulk to bias the formation of *sec*-carbinolamine over the tertiary isomer. Accordingly, the efficacy of a seemingly smaller protecting group, acetyl, was explored.

Acetate **27e**, prepared from aldol **27a** with Ac_2O/DMAP/pyr, was converted to amine oxide **28b** with m-CPBA in near quantitative yield. Rewardingly, Polonovski rearrangement led to the formation of *tert*-carbinolamine **29c** (59%) and *sec*-carbinolamine **29d** (8%). The ^{1}H NMR spectra of these isomers displayed similar patterns to the products of the silyl series; combustion analysis and/or mass spectroscopy confirmed the incorporation of a single oxygen in each isomer.

With the selectivity problem solved, interpolation of oxygen in the C_{9a}–N bond was required. This procedure was first employed in FR-900482 studies by Dmitrienko[19] and recently by Sulikowski.[23] The process may involve oxidation of a carbinolamine to its *N*-oxide[61] followed by spontaneous ring-opening and addition of the newly-formed hydroxylamine oxygen to the resultant carbonyl group. Ironically, an analogous sequence of events was unknowingly uncovered by Polonovski in an investigation of the *N*-oxides of Calabar bean alkaloids and correctly interpreted by Hootelé[62] as the rearrangement product. Oxidation of carbinolamine **29c** with m-CPBA led directly to the ring-expanded acetate **30a**, whose structure was

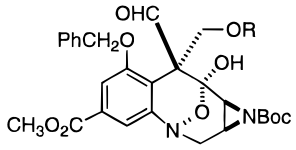
(54) Leonard, N. J.; Miller, L. A.; Thomas, P. D. *J. Am. Chem. Soc.* **1956**, *78*, 3463.
(55) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109.
(56) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116.
(57) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458.
(58) Danishefsky, S. J.; Feigelson, G. B. *Heterocycles* **1987**, *25*, 301.
(59) Grierson, D. In *Organic Reactions*; L. A. Paquette, Ed.; John Wiley: New York, 1990; Vol. 39, p 85.
(60) All the *sec*- and *tert*-carbinolamines encountered in this study were mainly single stereoisomers, and no stereochemical assignments were made.
(61) An alternative mechanism is the oxidation of the ring-opened ketoamine intermediate that might exist in low concentration.
(62) Hootelé, C. *Tetrahedron Lett.* **1969**, 2713.

confirmed by single crystal X-ray analysis.[63] The ^{1}H NMR of the acetate indicated a single stereoisomer unlike the 2:1 mixture present in FR-900482. The solution and solid state structures need not be the same stereoisomer in respect to the ether bridge. The X-ray structure confirmed the relative stereochemistry at C_1 and C_9 of acetate **27e**. This evidence, along with the NOE studies conducted on silyl ether **27c**, confirmed the stereochemistry of aldol product **27a**.

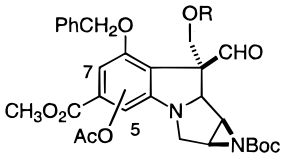
Although the acetyl protecting group proved beneficial for the Polonovski reaction, the group could not be removed effectively from acetate **30a** under a variety of conditions. Reagents as diverse as Na_2CO_3/MeOH, n-Bu_3SnOMe,[64] Otera's catalyst,[65] and p-TsOH/MeOH caused decomposition of the substrate. When acetate **30a** was dissolved in MeOH-d_4/Na_2CO_3 and monitored by ^{1}H NMR, only the resonance of sodium acetate (δ 1.89) could be identified! In light of the sensitivity of acetate **30a** toward these varied conditions, a protecting group that could be removed under neutral or weakly acidic conditions was considered. The carbobenzoxy protecting group was chosen, in spite of its seemingly greater bulk than the acetyl group.

Direct acylation of alcohol **27c** with carbobenzoxy chloride (CbzCl) in the presence of i-Pr_2NEt failed to effect acylation, and the addition of DMAP to the reaction mixture did not improve matters. However, treatment of the alcohol with 1,1′-carbonyldiimidazole in CH_3CN afforded the imidazolide which, in situ, was solvolyzed by the addition of benzyl alcohol and DMAP to provide benzyl carbonate **27f** in 68% yield. Amine oxide formation occurred without incident (98% yield), and subsequent rearrangement afforded a separable mixture of carbinolamines **29e** and **29f** in a 13:1 ratio (68%).[66] Rewardingly, the Polonovski reaction conducted on benzyl carbonate **27f** proved more selective than the reaction performed on acetate **27e**.

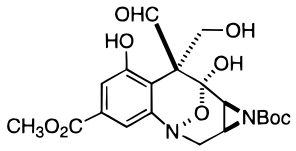
During the course of this investigation, we also had the opportunity to explore the Polonovski reaction on the silyloxymethyl ether **27d**, methoxymethyl ether **27g**, and carbomethoxy derivative **27h**. The *tert*:*sec*-carbinolamine ratio for the nonacyl protected substrates, **27c** (1.0:1.8), **27d** (1.4:1.0), and **27g** (1.2:1.0), was not selective. In addition, trace amounts of the acetoxy, aromatic substitution products **31a**−**c**[67] were also produced from their respective substrates. However, the amine oxide of carbomethoxy derivative **27h** gave a 6:1 ratio (tertiary:secondary) in 70% yield. None of the acyl derivatives gave products of aromatic substitution. These data do not support a steric argument for the regioselectivity in the Polonovski reaction. A possible explanation for the selectivity observed with the acyl series is that the carbonyl of the protecting group, which is situated cis to the C_{9a}-H, is participating as an internal base, albeit through a seven-membered transition state, in the elimination process and thereby accelerating the formation of the tetrasubstituted iminium ion at the expense of its regioisomer and aromatic substitution products. This argument implies kinetic formation of the iminium salts.



30a, R = $COCH_3$
b, R = CO_2CH_2Ph



31a, R = TBDMS
b, R = CH_2OTBDMS
c, R = MOM



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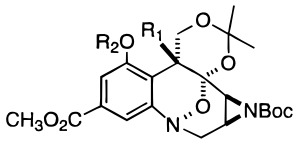
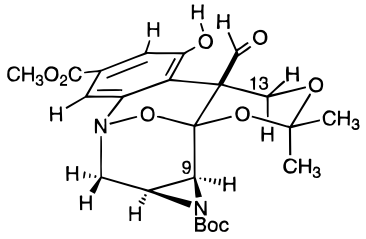


33a, R_1 = CHO, R_2 = H
b, R_1 = R_2 = H
c, R_1 = CHO, R_2 = TBDMS
d, R_1 = CHO, R_2 = $COCH_3$



34

Hootelé−Dmitrienko rearrangement of carbinolamine **29e** was performed in the usual way without incident to afford hemiketal **30b**. Hydrogenolysis of both benzyl groups of **30b** proceeded in high yield to afford triol **32**. The reduction was conducted in the presence of HOAc (10% Pd/C, EtOH, rt) to maintain the pH below 7. Although the triol was stable and could be purified by flash chromatography, prolonged exposure to SiO_2 caused decomposition. No attempt was made to effect selective debenzylation; however, hydrogenation of a sample of **30b** obtained directly from ring expansion did indicate that carbonate debenzylation was faster than liberation of the phenol. The ^{1}H NMR spectrum of the triol revealed the three hydroxyl protons at δ 8.26, 7.61, and 4.42 (dd, J = 11.2, 1.4 Hz) upon exchange with CH_3OH-d_4. The hydroxyl of the hydroxymethyl group (δ 4.42) was coupled to each of the adjacent methylene protons, one of which (δ 4.10) appeared as a triplet of doublets (J = 11.2, 1.9 Hz). The deuterium exchange reduced this pattern to a doublet of doublets with the same coupling constants, indicating that geminal coupling and W-coupling remained. These data support intramolecular hydrogen bonding of the aldol structure. At this juncture there was no direct evidence to permit the assignment of the stereochemistry of the ether bridge. Because the triol is a single isomer, its stereochemistry was assumed to be the same as that of the acetate **30a**, upon which the X-ray determination was conducted.

Triol **32** was readily converted to its acetonide **33a** which provided stability and rigidity to the molecule. The geometry of the ether bridge in the acetonide need not be the same as is present in the triol. However, the rigidity imparted to the molecule by the dioxane ring permitted an extensive NOE study that mapped the hydrogen atom contiguity (Figure 1) and consequently

(63) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(64) Farina, V.; Huang, S. *Tetrahedron Lett.* **1992**, *33*, 3979.
(65) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
(66) This ratio varied between 8:1 and 13:1.
(67) The site of substitution, C_5 or C_7, was not determined.

permitted the assignment of the stereochemistry of the ether bridge. Irradiation of the phenolic hydrogen enhanced the C_4 aromatic hydrogen, the equatorial C_{13}-H of the dioxane ring, and the aldehyde hydrogen. The issue of the ether bridge was resolved in favor of the α-configuration when irradiation of the aldehyde hydrogen gave an enhancement (5.7%) of the aziridine hydrogen at C_9. This is the same relationship that exists between one of the side chain methylene hydrogens and the C_1 aziridine hydrogen in silyl ether **21a** and aldehyde **27c**. If the ether bridge of **33a** were of the *β*-configuration (**34**), then the aldehyde hydrogen would be remote from the C_9-H and an NOE would not be expected. On the other hand, an NOE would have been anticipated between the proximate C_9-H and the axial C_{13}-H of the dioxane ring; however, no enhancement was observed. The aldehyde hydrogen showed W-coupling ($J = 1.2$ Hz) to the axial dioxane hydrogen, C_{13}-H, although the observation did not assist in distinguishing between structures **33a** and **34**. The lack of coupling of C_{11}-H_a to C_{10}-H distinguished this signal from C_{11}-H_b. A subsequent irradiation related the proximity of C_{11}-H_a to C_2-H.

With the structure of aldehyde **33a** established, attention was directed toward its decarbonylation in anticipation of the remaining functional group manipulations. The only stereochemical issue in FR-900482 is the trans relationship between the side chain and the aziridine ring. This relationship is present in aldehyde **33a**, which requires decarbonylation to occur with retention of configuration. Two procedures meet this requirement. Schaffner[68] has shown that photodecarbonylation of chiral *β*,*γ*-unsaturated aldehydes proceeds with retention of configuration.[69] Likewise, the seminal studies of Walborsky[70] demonstrated that stoichiometric decarbonylation with Wilkinson's catalyst, $(Ph_3P)_3RhCl$, also meets this requirement.[71,72]

The substrates reported by Schaffner contained limited functionality although one of them, α-naphthylisobutyraldehyde, was structurally related to aldehyde **33a**. The aldehyde was converted to its TBDMS derivative **33c** to minimize any adverse effects of the free phenolic group during photolysis. A degassed methanol solution of the silyl ether was photolyzed (450-W Hanovia Hg lamp, Pyrex filter) for 2 h. ^{1}H NMR analysis of the reaction mixture was not encouraging because, in addition to the presence of starting material, four additional aldehyde hydrogen signals were observed; no evidence of decarbonylation products could be detected. Owing to the complexity of the reaction mixture, attention was directed to the use of $(Ph_3P)_3RhCl$.

The rate of stoichiometric decarbonylation with Wilkinson's "catalyst" decreases in the order primary > secondary > tertiary. These data argue that steric factors are important. Accordingly, studies were conducted on the free phenol **33a** in either xylene or benzonitrile at 130 °C in the presence of 2.2 equiv of $(Ph_3P)_3RhCl$. Rewardingly, the desired decarbonylated product **33b** was obtained; unfortunately, the reaction proved to be capricious. No seemingly identical set of reaction conditions in regard to sample or reagent source, solvent preparation, atmosphere, concentration, or reaction time gave the same result. Changes in reaction temperature, the use of oxygen-free or oxygen-containing atmospheres and degassed or non-degassed solvent, addition of the reagent at reflux, or addition of incremental Ph_3P failed to give consistent results.[73]

The mass spectrum of decarbonylation product **33b** indicated the loss of 28 mass units relative to aldehyde **33a**. The ^{1}H NMR spectrum of **33b** was devoid of an aldehyde signal, and the appearance of the new methine hydrogen at δ 3.46 that was coupled to the C_{13} equatorial proton at δ 4.43 ($J = 6.0$ Hz) and the obscured C_{13} axial proton at δ 3.81−3.89 (11.1 Hz) supported the assignment. Amongst the NOEs present in acetal **33b** (Figure 1), the 3.7% enhancement between C_7-H and C_9-H confirmed that decarbonylation occurred with retention of configuration. A similar NOE was observed between these hydrogens in the isomer of FR-900842 that has the same α-bridge as acetal **33b**.[5]

This study has demonstrated that aziridinyl radicals may be employed as reactive intermediates in an asymmetric synthesis of the core nucleus of FR-900482. We are currently exploring alternative decarbonylation routes to the synthesis of the core nucleus **33b** whose remaining functionality should be able to be manipulated to lead to the synthesis of FR-900482 itself.[24,25,27]

Experimental Section

Unless otherwise noted, all anhydrous reactions were conducted in oven-dried glassware under N_2. THF was distilled from sodium benzophenone ketyl; CH_2Cl_2, benzene, toluene, triethylamine, pyridine, and $CBrCl_3$ were distilled from CaH_2. Other solvents and reagents were used as received. 1,1′-Azobis(cyclohexanecarbonitrile) (ACCN), obtained from Polysciences, Inc., was recrystallized from ethanol−water. $(Ph_3P)_3RhCl$ (98%) was obtained from Acros. Thiohydroxamic acid anhydrides were prepared in aluminum foil-covered flasks and were degassed (freeze-pump-thaw, 3×) in the dark. Photolyses were conducted in Pyrex tubes with a 500-W tungsten halogen lamp (Norelco or Sylvania). Work-up means the organic phase was dried over $MgSO_4$, filtered, and evaporated in vacuo. All reactions were conducted at room temperature unless stated otherwise.

Flash chromatography (SiO_2) was conducted as described by Still.[74] CH_2Cl_2 prep means that CH_2Cl_2 was used for preparing the column and for loading the sample; elution was conducted with the respective solvent systems. Since some of the advanced intermediates were unstable to extended contact with silica gel, their purification was conducted on short columns that allowed rapid elution. Radial chromatography was conducted on a Chromatotron 7924 T.

Melting points are uncorrected. Optical rotations and IR spectra were recorded in $CHCl_3$ (1% EtOH). Unless stated otherwise, product ratio were obtained by ^{1}H NMR. ^{1}H NMR (300 MHz, 7.24 ppm) and ^{13}C NMR (75.5 MHz, 77.0 ppm) were recorded in $CDCl_3$. $\langle J \rangle$ is used to indicate an average coupling constant from chemically nonequivalent hydrogens with comparable coupling constants. ^{13}C NMR* indicates that the number of observed signals due to signal overlap is less than the number of chemically nonequivalent carbons present in the compound.

Methyl 3-(Benzyloxy)-4-methyl-5-nitrobenzoate (11). To a solution of phenol **10** (25.27 g, 0.1197 mol) in DMF (200

(68) Baggiolini, E.; Hamlow, H. P.; Schaffner, K. *J. Am. Chem. Soc.* **1970**, *92*, 4906.

(69) For a recent synthetic application of photodecarbonylation see, MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

(70) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.

(71) Regeneration of $(Ph_3P)_3RhCl$ from $(Ph_3P)_2RhCl(CO)$, the product of decarbonylation, has been described: O'Connor, J. M.; Ma, J. *Inorg. Chem.* **1993**, *32*, 1866.

(72) For a review on decarbonylation with $(Ph_3P)_3RhCl$ see, Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157.

(73) The decarbonylation conditions reported in the Experimental Section were inconsistently reproducible.

(74) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

mL) were added K_2CO_3 (16.57 g, 0.1198 mol) and benzyl chloride (16.0 mL, 0.139 mol). The deep-red reaction mixture was heated at 100 °C for 5.5 h. The majority of the DMF was removed in vacuo at 70 °C. The residue was partitioned between EtOAc (200 mL) and water (150 mL), and the aqueous phase was extracted with EtOAc (200 mL, 2x). The combined organic extracts were washed with brine and worked up. Baseline material was removed with a short SiO_2 column (CH_2Cl_2). Recrystallization (EtOAc, hexanes) afforded 24.76 g of a pale yellow solid: mp 83.7−84.2 °C; IR 1724 cm^{-1}; ^1H NMR δ 8.07 (d, J = 1.1 Hz, 1H), 7.76 (d, J = 1.1 Hz, 1 H), 7.47−7.32 (m, 5 H), 5.17 (s, 2 H), 3.93 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR δ 165.1, 157.5, 150.9, 135.6, 129.0, 128.7, 128.4, 127.5, 127.3, 117.3, 115.1, 71.1, 52.6, 12.3; LRMS (CI) m/z $(M + H)^+$ = 302.20. Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.56; H, 5.01; N, 4.62. A second crop provided 5.74 g. The mother liquor was concentrated and purified by flash chromatography (4% EtOAc/hexanes) followed by recrystallization to afford an additional material (1.86 g; 90% combined yield).

Methyl 4-(Benzyloxy)-1*H*-indole-6-carboxylate (12). To a solution of nitrotoluene **11** (29.00 g, 0.0962 mol) in DMF (60.0 mL) was added freshly distilled pyrrolidine (12.0 mL, 0.144 mol) and *N*,*N*-dimethylformamide dimethyl acetal (19.0 mL of 94% purity, 0.134 mol). The dark, red-colored reaction mixture was heated at 110 °C for 3.5 h followed by concentration of the solution with a rotary evaporator. CH_3OH (350 mL) and CH_2Cl_2 (15 mL) were added to the residue, and the solution was stored at 6 °C for 12 h. The garnet-colored precipitate was filtered, carefully washed with cold CH_3OH, and freed of solvent under high vacuum. A 10:1 mixture of pyrrolidino styrene and *N*,*N*-dimethylamino styrene was obtained (23.24 g, 64%): ^1H NMR (pyrrolidino styrene) δ 8.08 (d, J = 13.2 Hz, 1 H), 7.97 (d, J = 1.6 Hz, 1 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.50−7.35 (m, 5 H), 5.44 (d, J = 13.2 Hz, 1 H), 5.16 (s, 2 H), 3.88 (s, 3 H), 3.18−3.14 (m, 4 H), 1.90−1.85 (m, 4 H).

Raney nickel (1 mL of 50% slurry in pH 9.0 water) was added to a 1:1 THF/CH_3OH (300 mL) solution of nitrostyrenes (21.50 g, 0.0566 mol) at room temperature. Hydrazine hydrate (5 mL, 55%) was added dropwise as the exothermic reaction mixture, accompanied by vigorous evolution of gas, was stirred. When the evolution of gas subsided (1.3 h), an additional 5 mL of hydrazine hydrate was added, and the reaction mixture was warmed to 43 °C. Over the next 3 h two additional portions of hydrazine hydrate (4 mL, 1 mL) were added, and the reaction mixture was stirred until gas evolution ceased. The Raney nickel was filtered on a pad of Celite and washed with CH_2Cl_2. The filtrate was worked up. Flash chromatography of the residue (30% EtOAc/hexanes) afforded indole **12** as a white solid (14.06 g, 88%): mp 165.0−166.8 °C (THF, hexanes); IR 3479, 1709 cm^{-1}; ^1H NMR δ 8.42 (br s, 1 H), 7.84 (s, 1 H), 7.52 (d, J = 7.03 Hz, 2 H), 7.45−7.24 (m, 5 H), 6.75 (br s, 1 H), 5.26 (s, 2 H), 3.92 (s, 3 H); ^{13}C NMR (CD_2Cl_2, δ = 53.80) 168.2, 152.2, 137.6, 136.7, 128.8, 128.2, 127.9, 126.5, 125.0, 122.9, 108.0, 101.5, 100.5, 70.3, 52.2; LRMS (CI) m/z $(M + H)^+$ = 282.20. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.77; H, 5.42; N, 4.99.

Methyl 4-(Benzyloxy)-3-formyl-1*H*-indole-6-carboxylate (13). $POCl_3$ (6.00 mL, 64.4 mmol) was added dropwise to stirred DMF (50 mL, 0 °C). After the addition was complete, the mixture was stirred for an additional 45 min. To the vigorously stirred solution was cannulated a THF (300 mL) solution of indole **12** (14.79 g, 52.57 mmol) over 7 min. The reaction mixture attained a yellow color, and within minutes a heavy precipitate formed. The cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. Addition of water dissolved the precipitate. After 5 h of stirring, the solution was diluted with EtOAc and washed with water (3×), 1% $NaHCO_3$ solution, and brine and then worked up. Recrystallization of the crude material from THF/ether afforded a pale yellow solid (15.01 g, 92%): mp 221.4−222.0 °C; IR 3455, 1713, 1662 cm^{-1}; ^1H NMR (DMSO-d_6, δ = 2.47) 12.57 (br s, 1 H), 10.30 (s, 1 H), 8.25 (s, 1 H), 7.79 (s, 1 H), 7.54 (d, J = 7.7 Hz, 2 H), 7.43−7.32 (m, 4 H), 5.30 (s, 2 H), 3.84 (s, 3 H); ^{13}C NMR (DMSO-d_6, δ = 39.5) 186.0, 166.5, 152.4, 137.1, 136.8, 132.7, 128.5, 128.0, 127.6, 124.7, 119.5, 118.2, 108.5, 103.2, 69.7, 52.1; LRMS (CI) m/z $(M + H)^+$ = 310.15. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.90; H, 4.93; N, 4.49.

Methyl (2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-[4-(benzyloxy)-6-(methoxycarbonyl)-1*H*-indolyl]methyl]aziridine-2-carboxylate (15a). Alkylation of indole **12** (2.50 g, 8.89 mmol) with aziridinol **14a** (1.03 g, 4.45 mmol) was conducted as previously described for 3-cyanoindole.[29] The crude material was purified by flash chromatography (30−40% ether/hexanes) to afford an impure white solid (0.96 g, 44% yield). The impurity was removed by a second flash chromatography (CH_2Cl_2) to afford diester **15a**: mp 120.0−121.0 °C (ether, hexanes); $[\alpha]^{20}_D$ = +19.9 (*c*, 0.476, $CHCl_3$); IR 1745, 1724, 1711 cm^{-1}; ^1H NMR δ 7.79 (s, 1 H), 7.50 (d, J = 7.5 Hz, 2 H), 7.43−7.30 (m, 3 H), 7.30 (s, 1 H), 7.25 (d, J = 3.0 Hz, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 5.24 (s, 2 H), 4.36 (dd, J = 15.0, 4.0 Hz, 1 H), 4.19 (dd, J = 15.0, 6.0 Hz, 1 H), 3.92 (s, 3 H), 3.72 (s, 3 H), 3.22−3.17 (m, 1 H), 2.86 (d, J = 2.3 Hz, 1 H), 1.34 (s, 9 H); ^{13}C NMR δ 167.9, 167.5, 157.6, 152.0, 137.0, 136.7, 129.5, 128.4, 127.8, 127.4, 124.4, 123.2, 105.7, 101.4, 100.2, 82.2, 69.9, 52.6, 51.9, 46.7, 41.9, 38.9, 27.6; LRMS (CI) m/z $(M + H)^+$ = 495.30. Anal. Calcd for $C_{27}H_{30}N_2O_7$: C, 65.58; H, 6.11; N, 5.66. Found: C, 65.67; H, 6.15; N, 5.57.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-[4-(benzyloxy)-6-(methoxycarbonyl)-1*H*-indolyl]methyl]aziridine-2-carboxylic Acid (15b). Ester **15a** (503.7 mg, 1.018 mmol) was saponified as previously reported (ester **5a**[29]) except that the basic aqueous solution was not washed with CH_2Cl_2 to avoid formation of an emulsion. The acid was obtained as a white solid (412.0 mg, 84%): mp 155.5−158.0 °C dec (EtOAc/hexanes); $[\alpha]^{27}_D$ = +22.6 (*c*, 0.860, $CHCl_3$); IR 2745−3413 (br), 1733, 1713 cm^{-1}; ^1H NMR δ 7.79 (s, 1 H), 7.50 (d, J = 7.5 Hz, 2 H), 7.42−7.26 (m, 4 H), 7.23 (d, J = 3.1 Hz, 1 H), 6.70 (d, J = 3.1 Hz, 1 H), 5.24 (s, 2 H), 4.39 (dd, J = 15.0, 4.0 Hz, 1 H), 4.24 (dd, J = 15.0, 5.8 Hz, 1 H), 3.91 (s, 3 H), 3.20−3.16 (m, 1 H), 2.86 (d, J = 2.5 Hz, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 171.8, 168.1, 157.7, 152.1, 137.1, 136.8, 129.5, 128.5, 127.9, 127.4, 124.5, 123.4, 105.9, 101.7, 100.4, 82.8, 70.1, 52.1, 46.7, 42.6, 38.6, 27.7; LRMS (CI) m/z $(M + H)^+$ = 481.40. Anal. Calcd for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 64.90; H, 5.89; N, 5.76.

(2*R*,3*S*)- and (2*S*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-[4-(benzyloxy)-6-(methoxycarbonyl)-1*H*-indolyl]methyl]-2-bromoaziridine (16a; 16b). The decarboxylative bromination of acid **15b** (690.0 mg, 1.436 mmol) was conducted according to the procedure described (acid **5b**[29]). Without removing the $CBrCl_3$, the reaction mixture was submitted to flash chromatography (5−10% EtOAc/hexanes) to afford a mixture of *cis*-bromoaziridine **16a** and *trans*-bromoaziridine **16b** (**16a**/**16b** = 3.3). An additional flash chromatography ($CHCl_3$) removed 2,2′-dipyridyl disulfide along with partial separation of the two diastereomers (390.0 mg, 53% combined yield). **16a** (white solid): mp 83.0−86.0 °C (ether/hexanes); $[\alpha]^{22}_D$ = +29.4 (*c*, 0.850, $CHCl_3$); IR 1732, 1710 cm^{-1}; ^1H NMR δ 7.88 (s, 1 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.42−7.31 (m, 5 H), 6.72 (d, J = 3.3 Hz, 1 H), 5.26 (s, 2 H), 4.67 (d, J = 5.3 Hz, 1 H), 4.47 (dd, J = 15.1, 5.3 Hz, 1 H), 4.39 (dd, J = 15.1, 5.9 Hz, 1 H), 3.93 (s, 3 H), 2.86−2.80 (m, 1 H), 1.36 (s, 9 H); ^{13}C NMR δ 167.9, 158.2, 152.1, 137.1, 136.8, 129.5, 128.5, 127.8, 127.4, 124.5, 123.5, 105.9, 101.7, 100.4, 83.3, 70.1, 51.9, 46.4, 41.2, 40.4, 27.6; LRMS (EI) m/z $(M)^+$ = 514.45, 516.45. Anal. Calcd for $C_{25}H_{27}N_2O_5Br$: C, 58.26; H, 5.28; N, 5.44. Found: C, 58.34; H, 5.33; N, 5.39. **16b** (colorless oil): IR 1712 (br) cm^{-1}; ^1H NMR δ 7.77 (s, 1 H), 7.50 (d, J = 7.9 Hz, 2 H), 7.42−7.30 (m, 4 H), 7.18 (d, J = 3.5 Hz, 1 H), 6.70 (d, J = 3.5 Hz, 1 H), 5.25 (s, 2 H), 4.34 (app d, J = 4.8 Hz, 2 H), 4.04 (d, J = 1.7 Hz, 1 H), 3.93 (s, 3 H), 3.05 (app td, $\langle J \rangle$ = 4.8, 1.7 Hz, 1 H), 1.42 (s, 9 H); ^{13}C NMR δ 167.9, 156.4, 152.2, 137.1, 136.9, 129.5, 128.5, 127.9, 127.5, 124.8, 123.4, 105.6, 101.8, 100.5, 83.4, 70.1, 52.0, 46.1, 44.1, 36.8, 27.9; HRMS (EI) calcd for M^+ $C_{25}H_{27}N_2O_5Br$: 514.1103, found 514.1097.

Methyl (1a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-1-(*tert*-butyloxycarbonyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (17) and (2*S*)-1-(*tert*-Butyloxycarbonyl)-2-[1-[4-(benzyloxy)-6-(methoxycar-

bonyl)1*H*-indolyl]methyl]aziridine (16c). A toluene (6.7 mL) solution of 1,1′-azo(biscyclohexylcarbonitrile) (ACCN) (37.2 mg, 0.152 mmol) and *n*-Bu_3SnH (272 μL, 0.981 mmol) was added dropwise to a refluxing toluene (23.0 mL) solution of bromoaziridines **16a** and **16b** (390.0 mg, 0.757 mmol) over 30 min. The reaction mixture was heated for 2.25 h, cooled to room temperature and directly submitted to flash chromatography (0−20% EtOAc/hexanes) to give a mixture (4:1) of tetracycle **17** and reduced, uncyclized aziridine **16c** (188.7 mg, 57% combined yield). The two compounds were separated by flash chromatography (CH_2Cl_2). **16c** (white foam): IR 1711 (br) cm^{-1}; ^1H NMR δ 7.81 (s, 1 H), 7.51 (d, J = 7.0 Hz, 2 H), 7.42−7.29 (m, 5 H), 6.70 (d, J = 3.3 Hz, 1 H), 5.25 (s, 2 H), 4.34 (dd, J = 14.8, 4.1 Hz, 1 H), 4.13 (dd, J = 14.8, 6.4 Hz, 1 H), 3.92 (s, 3 H), 2.78−2.74 (m, 1 H), 2.34 (d, J = 6.2 Hz, 1 H, C*H*$_2$NBOC), 2.00 (d, J = 3.6 Hz, 1 H, C*H*$_2$NBOC), 1.36 (s, 9 H); ^{13}C NMR δ 168.0, 161.5, 152.1, 137.2, 136.9, 129.7, 128.5, 127.8, 127.4, 124.3, 123.4, 106.0, 101.5, 99.9, 81.6, 70.1, 51.9, 48.2, 36.4, 29.8, 27.7; LRMS (EI) m/z M^+ = 436.40; HRMS (EI) calcd for M^+ $C_{25}H_{28}N_2O_5$: 436.1998, found 436.1995. **17** (white foam): $[\alpha]^{24}_D$ = +67.8 (*c*, 0.545, $CHCl_3$); IR 1713 cm^{-1}; ^1H NMR δ 7.46−7.30 (m, 5 H), 7.07 (d, J = 0.8 Hz, 1 H), 6.81 (d, J = 0.8 Hz, 1 H), 5.12 (d, J = 11.9 Hz, 1 H), 5.07 (d, J = 11.9 Hz, 1 H), 4.20 (ddd, J = 10.3, 4.7, 1.5 Hz, 1 H, CH_2NCHCH_2), 3.86 (s, 3 H), 3.60 (d, J = 12.4 Hz, 1 H), 3.38−3.30 (m, 2 H), 3.19−3.10 (m, 3 H), 1.37 (s, 9 H); ^{13}C NMR δ 167.4, 161.1, 155.5, 154.5, 137.1, 131.0, 128.4, 127.8, 127.3, 122.9, 105.4, 104.4, 81.2, 69.9, 64.5, 52.6, 51.9, 45.5, 43.3, 28.5, 27.9; HRMS (EI) calcd for M^+ $C_{25}H_{28}N_2O_5$: 436.1998, found 436.1991.

Methyl (2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-[4-(benzyloxy)-3-formyl-6-(methoxycarbonyl)-1*H*-indolyl]methyl]aziridine-2-carboxylate (18a). To a DMF (38.0 mL) solution of indole **13** (1.96 g, 6.34 mmol) was added dropwise $NaN(TMS)_2$ (6.41 mL of 1.0 M/THF, 6.41 mmol), and then the reaction mixture was stirred for 1.5 h at room temperature. Meanwhile, freshly distilled trifluoromethanesulfonic acid anhydride (1.25 mL, 7.43 mmol) was added dropwise over a few minutes to a cooled (−30 °C) CH_2Cl_2 (22.0 mL) solution of aziridinol **14a** (1.555 g, 6.721 mmol) and pyridine (0.60 mL, 7.41 mmol). The reaction mixture was stirred for 50 min at −30 °C, and the cold bath was removed. The reaction mixture was partitioned between CH_2Cl_2 and water (150 mL each), and the organic phase was thoroughly dried over $MgSO_4$ (7 min), filtered, and evaporated in vacuo (room temperature). The crude triflate was dissolved in CH_2Cl_2 (26.0 mL), cooled to −30 °C, and cannulated into the indole anion solution that had been cooled to −30 °C. The reaction mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. The mixture was diluted with EtOAc (200 mL) and washed with water (50 mL, 6×) to remove the DMF. The aqueous phase was back-extracted with EtOAc (50 mL), and the combined organic extracts were washed with brine and worked up. Flash chromatography of the crude solid (preabsorbed on SiO_2; 2% $CH_3OH/CHCl_3$) afforded recovered indole **13** (278.0 mg, 14%) and impure alkylated indole which was resubmitted to flash chromatography (30−40% EtOAc/hexanes) to afford ester **18a** as a white solid (2.20 g, 66%): mp 118.0−119.5 °C (ether); $[\alpha]^{25}_D$ = +27.4 (*c*, 2.00, $CHCl_3$); IR 1746, 1727 cm^{-1}; ^1H NMR δ 10.42 (s, 1 H), 8.02 (s, 1 H), 7.81 (s, 1 H), 7.48−7.31 (m, 6 H), 5.26 (d, 2 H), 4.47 (dd, J = 14.9, 3.6 Hz, 1 H), 4.15 (dd, J = 14.9, 6.6 Hz, 1 H), 3.92 (s, 3 H), 3.72 (s, 3 H), 3.23−3.18 (m, 1 H), 2.89 (d, J = 2.7 Hz, 1 H), 1.32 (s, 9 H); ^{13}C NMR δ 187.4, 167.2, 167.1, 157.2, 153.1, 137.5, 136.1, 133.6, 128.7, 128.2, 127.6, 125.9, 120.4, 118.9, 106.4, 104.2, 82.6, 70.5, 52.8, 52.2, 47.6, 41.2, 38.8, 27.6; LRMS (CI) m/z $(M + H)^+$ = 523.25. Anal. Calcd for $C_{28}H_{30}N_2O_8$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.42; H, 5.84; N, 5.43.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-[4-(benzyloxy)-3-formyl-6-(methoxycarbonyl)-1*H*-indolyl]methyl]aziridine-2-carboxylic Acid (18b). Ester **18a** (6.38 g, 12.2 mmol) was saponified as described except that less LiOH (0.536 g, 22.0 mmol) was used, and the basic aqueous solution was not washed with CH_2Cl_2 to avoid formation of emulsion.[29] Acid **18b** was obtained as a white solid (5.94 g, 96%): mp 194−195 °C dec (EtOAc/ hexanes); IR 1729, 1716 cm^{-1}; ^1H NMR (DMSO-d_6, δ = 2.49) 13.52 (br s, 1 H), 10.31 (s, 1 H), 8.34 (s, 1 H), 8.00 (s, 1 H), 7.54 (d, J = 7.0 Hz, 2 H), 7.44−7.32 (m, 4 H), 5.35 (s, 2 H), 4.74 (dd, J = 14.7, 3.2 Hz, 1 H), 4.26 (dd, J = 14.7, 7.5 Hz, 1 H), 3.87 (s, 3 H), 3.12−3.06 (m, 2 H), 1.19 (s, 9 H); ^{13}C NMR* (DMSO-d_6, δ = 39.5) 185.7, 168.4, 166.5, 157.5, 152.4, 137.4, 136.7, 135.3, 128.5, 128.0, 127.6, 124.9, 119.8, 117.5, 107.5, 103.8, 80.9, 69.9, 52.2, 47.2, 41.3, 27.3; HRMS (FAB) calcd for $(M + H)^+$ $C_{27}H_{29}N_2O_8$: 509.1924, found 509.1925.

(2*R*,3*S*)- and (2*S*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-[4-(benzyloxy)-3-formyl-6-(methoxycarbonyl)-1*H*-indolyl]methyl]-2-bromoaziridine (19a; 19b). Decarboxylative bromination of thiohydroxamate **18c** (1.10 g, 2.16 mmol) was conducted as described except that the thiohydroxamic acid anhydride formation was conducted for 3.5 h.[29] Without removing the $CBrCl_3$, the reaction mixture was submitted to flash chromatography (10−30% EtOAC/hexanes) to afford a mixture of bromoaziridines **19a** and **19b** (3.8:1.0, 853.7 mg, 73%). An additional flash chromatography of the mixture (4% EtOAc/$CHCl_3$) effected the partial separation of the two diastereomers wherein early and late fractions afforded pure material. **19a** (white foam): $[\alpha]^{23}_D$ = +9.8 (*c*, 1.63, $CHCl_3$); IR 1733, 1714 cm^{-1}; ^1H NMR δ 10.45 (s, 1 H), 8.13 (s, 1 H), 7.91 (s, 1 H), 7.50 (s, 1 H), 7.47 (dd, J = 8.0, 1.2 Hz, 2 H), 7.45−7.33 (m, 3 H), 5.28 (s, 2 H), 4.70 (d, J = 4.9 Hz, 1 H), 4.53 (dd, J = 14.9, 4.9 Hz, 1 H), 4.38 (dd, J = 14.9, 6.7 Hz, 1 H), 3.94 (s, 3 H), 2.90−2.84 (m, 1 H), 1.32 (s, 9 H); ^{13}C NMR δ 187.4, 167.1, 157.8, 153.2, 137.5, 136.1, 133.6, 128.7, 128.2, 127.6, 125.9, 120.5, 119.0, 106.5, 104.2, 83.7, 70.6, 52.3, 47.3, 40.7, 39.8, 27.6; LRMS (CI) m/z $(M + H)^+$ = 543.25, 545.25. Anal. Calcd for $C_{26}H_{27}N_2O_6Br$: C, 57.47; H, 5.01; N, 5.16. Found: C, 57.58; H, 5.04; N, 5.12. **19b**: mp 114.8−116.8 °C (CH_2Cl_2/hexanes); IR ($CDCl_3$) 1727, 1717 cm^{-1}; ^1H NMR δ 10.44 (s, 1 H), 7.96 (s, 1 H), 7.82 (s, 1 H), 7.51 (s, 1 H), 7.49−7.34 (m, 6 H), 5.29 (s, 1 H), 4.49 (dd, J = 15.0, 3.7 Hz, 1 H), 4.29 (dd, J = 15.0, 5.9 Hz, 1 H), 4.05 (d, J = 1.8 Hz, 1 H), 3.96 (s, 3 H), 3.09−3.05 (m, 1 H), 1.39 (s, 9 H); ^{13}C NMR δ 187.4, 167.1, 156.0, 153.2, 137.4, 136.1, 133.7, 128.7, 128.2, 127.6, 126.1, 120.4, 118.9, 106.2, 104.2, 83.7, 70.6, 52.3, 47.0, 43.2, 36.3, 27.8; HRMS (EI) calcd for $(M)^+$ $C_{26}H_{27}N_2O_6Br$: 542.1052, found 542.1051.

Methyl (1a*S*,8*R*,8a*S*,8b*R*)- and Methyl (1a*S*,8*R*,8a*R*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-(hydroxymethyl)-1-(*tert*-butyloxycarbonyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (21b; 22b), and Methyl (3a*S*,10b*S*)-2,3,3a,10b- Tetrahydro-9-(benzyloxy)-10-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxo-4*H*-oxazolo[3′,4′:5,4]pyrrolo[1,2-*a*]indole-7-carboxylate (23). Sodium borohydride (98.0 mg, 2.59 mmol) was added to a MeOH solution (18.0 mL, 0 °C) of bromoaziridines **19a** and **19b** (4:1, 1.023 g, 2.193 mmol). The reaction mixture was stirred for 15 min, quenched with acetone, and partitioned between EtOAc (50 mL) and water (20 mL) containing 2 mL of saturated NH_4Cl solution. The organic phase was washed with water, and the combined aqueous phase was back extracted with EtOAc. The combined organic extracts were then washed with brine and worked up: ^1H NMR (major isomer) δ 7.88 (s, 1 H), 7.50−7.38 (m, 5H), 7.36 (s, 1 H), 7.30 (s, 1 H), 5.27 (s, 2 H), 4.74 (br s, 2 H), 4.66 (d, J = 5.3 Hz, 1 H, CHBr), 4.44−4.32 (m, 2 H, NCH_2), 3.94 (s, 3 H), 2.86−2.80 (m, 2 H, CH_2CH, OH), 1.37 (s, 9 H).

Imidazole (178.7 mg, 2.625 mmol) and TBDMSCl (363.0 mg, 2.336 mmol) were added to a CH_2Cl_2 (18 mL) solution of the crude indole methanols **20a**. The reaction mixture was stirred for 40 min, the white suspension was filtered, and the filtrate was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo.

To a toluene (42.0 mL) solution of the crude silyloxy ethers **20b** and ACCN (98.0 mg, 0.401 mmol) was added 1 mL of a toluene (6 mL) solution of *n*-Bu_3SnH (640 μL, 2.37 mmol). The silyloxy ether solution was heated in an oil bath (116 °C), and the rest of the *n*-Bu_3SnH solution was added via a syringe pump over 65 min. The reaction mixture was heated for an additional 1 h, cooled to room temperature, and submitted to flash chromatography (0−10% EtOAc/hexanes) to give an impure silyloxy ethers **21a**. Further elution with ether fol-

lowed by EtOAc gave a yellow solid, which upon trituration with ether, afforded oxazolidone **23** as a white solid (25.4 mg, 2.2%): mp 279.0−280.5 °C dec (CH_2Cl_2/ether); $[\alpha]^{26}_D = +138.8$ (*c*, 0.640, $CHCl_3$); IR 3461, 3251 (br), 1757, 1710 cm^{-1}; ^1H NMR δ 7.60 (d, $J = 0.9$ Hz, 1 H), 7.47 (d, $J = 8.1$ Hz, 2 H), 7.41−7.32 (m, 3 H), 7.22 (d, $J = 0.9$ Hz, 1 H), 6.40 (br s, 1 H, exchangeable), 6.13 (d, $J = 7.9$ Hz, 1 H, C*H*OCONH), 5.30−5.05 (m, 5 H), 4.24 (dd, $J = 11.0, 5.9$ Hz, 1 H), 4.17 (dd, $J = 11.0, 2.4$ Hz, 1 H), 3.90 (s, 3 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR δ 167.6, 159.1, 153.5, 137.5, 136.8, 133.0, 128.5, 127.9, 127.3, 125.2, 124.0, 113.0, 106.7, 101.3, 75.8, 70.1, 59.5, 58.8, 52.0, 51.2, 26.1, 18.6, −5.4, −5.7; HRMS (FAB) calcd for $(M - H)^+$ $C_{28}H_{33}N_2O_6Si$: 521.2104, found 521.2108. Anal. Calcd for $C_{28}H_{34}N_2O_6Si$: C, 64.34; H, 6.56; N, 5.36. Found: C, 64.41; H, 6.52; N, 5.40.

To a THF (12.0 mL) solution of crude silyl ether **21a**[75] was added tetra-*n*-butylammonium fluoride (TBAF, 1.3 mL of 1.0 M/THF). The mixture was stirred 12 h and then poured into a mixture of EtOAc (80 mL), H_2O (40 mL), and saturated NH_4Cl (20 mL). The organic layer was washed with brine and worked up. Flash chromatography (30−50% EtOAc/hexanes) afforded diastereomeric alcohols **22b** (∼5%)[39] and **21b** (450 mg, 51% for four steps). Additional flash chromatography of **22b** (Florisil; CH_2Cl_2 prep; 20−30% EtOAc/hexanes) afforded a white foam: $[\alpha]^{27}_D = -47.5$ (*c*, 1.05, $CHCl_3$); IR 3512 (br), 1713 cm^{-1}; ^1H NMR δ 7.41−7.32 (m, 5 H), 7.19 (s, 1 H), 6.99 (s, 1 H), 5.12 (d, $J = 11.2$ Hz, 1 H), 5.06 (d, $J = 11.2$ Hz, 1 H), 4.00−3.58 (m, 5 H), 3.87 (s, 3 H), 3.30−3.17 (m, 3 H), 2.71 (dd, $J = 7.6, 4.2$ Hz, 1 H), 1.44 (s, 9 H); ^{13}C NMR δ 166.8, 160.1, 156.7, 154.8, 135.9, 132.3, 128.7, 128.4, 127.7, 124.4, 108.5, 106.3, 81.7, 70.6, 70.3, 64.8, 55.2, 52.1, 48.1, 47.7, 45.3, 27.9; HRMS (EI) calcd for $(M)^+$ $C_{26}H_{30}N_2O_6$: 466.2104, found 466.2102. **21b**: mp 177.3−177.7 °C (EtOAc); $[\alpha]^{25}_D = +86.8$ (*c*, 0.644, $CHCl_3$); IR 3504 (br), 1714 cm^{-1}; ^1H NMR δ 7.43−7.29 (m, 5 H), 7.07 (s, 1 H), 6.80 (s, 1 H), 5.09 (d, $J = 11.3$ Hz, 1 H), 5.04 (d, $J = 11.3$ Hz, 1 H), 4.41−4.34 (m, 1 H), 4.28 (dd, $J = 10.2, 2.0$ Hz, 1 H), 4.11−4.00 (m, 1 H), 3.85 (s, 3 H), 3.85−3.77 (m, 1 H), 3.61 (d, $J = 12.4$ Hz, 1 H), 3.36−3.27 (m, 3 H), 3.17 (dd, $J = 4.7, 1.9$ Hz, 1 H), 1.38 (s, 9 H); ^{13}C NMR δ 167.1, 161.3, 155.5, 154.9, 136.3, 131.4, 128.6, 128.1, 127.7, 122.3, 104.8, 104.0, 82.0, 70.3, 67.0, 61.0, 52.0, 51.8, 44.4, 43.0, 42.5, 27.8; LRMS (EI) m/z $(M)^+ = 466.50$. Anal. Calcd for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.83; H, 6.54; N, 5.94.

Methyl (1a*S*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-1-(*tert*-butyloxycarbonyl)-8-formyl-8-(hydroxymethyl)azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (27a). A CH_2Cl_2 (17.0 mL) solution of Dess−Martin periodinane (430.0 mg, 1.014 mmol) was rapidly added to a CH_2Cl_2 (10.0 mL) solution of alcohol **21b** (362.0 mg, 0.7759 mmol). The reaction mixture was stirred for 45 min and diluted with ether (150 mL), and the resulting cloudy solution was washed with a mixture of H_2O (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and saturated aqueous $Na_2S_2O_3$ (1.5 mL) to give a clear solution. The solvent was removed in vacuo, and the residue was used in the next reaction. For the purpose of identification, a sample of the ether solution was worked up to give crude aldehyde **26**: ^1H NMR δ 9.97 (d, $J = 3.1$ Hz, 1 H), 7.40−7.30 (m, 5 H), 7.14 (s, 1 H), 6.88 (s, 1 H), 5.14 (d, $J = 11.9$ Hz, 1 H), 5.07 (d, $J = 11.9$ Hz, 1 H), 4.38 (dd, $J = 11.1, 1.8$ Hz, 1 H, CH_2NCH), 4.10 (dd, $J = 11.1, 3.1$ Hz, 1 H), 3.87 (s, 3 H), 3.66 (d, $J = 12.5$ Hz, 1 H), 3.31 (dd, $J = 12.5, 1.7$ Hz, 1 H), 3.23 (dd, $J = 4.7, 1.7$ Hz, 1 H, CH_2CH) 3.13 (dd, $J = 4.7, 1.8$ Hz, 1 H), 1.35 (s, 9 H).

The resulting undried, crude aldehyde **26** was dissolved in CH_2Cl_2/MeOH (1:1; 16.0 mL) and treated with 37% aqueous formaldehyde (2.2 mL, 27.1 mmol) and $NaHCO_3$ (32.0 mg, 0.381 mmol). The reaction mixture was stirred for 2 h, diluted with CH_2Cl_2, and washed with 3% NH_4Cl. The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was passed through a small amount of SiO_2 to remove any trace of baseline material and then purified by radial chromatography ($CHCl_3$ for loading sample; 35% EtOAc/hexanes) to afford aldol **27a** as a white foam (324.0 mg, 86%): $[\alpha]^{25}_D = +66.5$ (*c*, 0.480, $CHCl_3$); IR 3565, 1715 cm^{-1}; ^1H NMR δ 10.11 (d, $J = 1.0$ Hz, 1 H), 7.39−7.29 (m, 5 H), 7.11 (s, 1 H), 6.89 (s, 1 H), 5.10 (d, $J = 12.1$ Hz, 1 H), 5.05 (d, $J = 12.1$ Hz, 1 H), 4.41 (dd, $J = 11.4, 4.2$ Hz, 1 H, CH_2OH), 4.37 (d, $J = 1.9$ Hz, 1 H, CH_2NCH), 3.87 (s, 3 H), 3.68 (d, $J = 12.5$ Hz, 1 H), 3.56 (app td, $\langle J \rangle = 10.4, 1.0$ Hz, 1 H, CH_2OH), 3.31 (dd, $J = 12.5, 1.7$ Hz, 1 H), 3.26 (dd, $J = 4.7, 1.7$ Hz, 1 H), 3.05 (dd, $J = 4.7, 1.9$ Hz, 1 H, CHCHN-BOC), 2.77 (dd, $J = 9.8, 4.2$ Hz, 1 H, OH), 1.36 (s, 9 H); ^{13}C NMR δ 203.9, 166.8, 160.1, 157.7, 155.1, 136.0, 133.4, 128.6, 128.0, 127.0, 118.8, 104.9, 104.7, 81.9, 70.9, 70.0, 64.4, 61.3, 52.2, 51.7, 42.9, 42.4, 27.7; LRMS (CI) m/z $(M)^+ = 495.15$. Anal. Calcd for $C_{27}H_{30}N_2O_7$: C, 65.58; H, 6.11; N, 5.66. Found: C, 65.49; H, 6.14; N, 5.61.

Methyl (1a*S*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (27c) and Methyl (1a*S*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[[[[(*tert*-butyldimethylsilyl)oxy]methyl]oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (27d). Imidazole (92.6 mg, 1.36 mmol), TBDMSCl (206.3 mg, 1.369 mmol), and DMAP (19.4 mg, 0.159 mmol) were added to a CH_2Cl_2 (5.2 mL) solution of crude (prior to chromatography) aldol **27a** that was prepared from alcohol **21b** (175.9 mg, 0.3770 mmol) by the procedure described above. The reaction mixture was stirred for 3 h, filtered, and concentrated. The residue was submitted to flash chromatography (7−15% EtOAc/hexanes) to obtain silyl ethers **27c** (white foam; 158.6 mg, 69%) and **27d** (white foam; 33.8 mg, 14%). **27c**: $[\alpha]^{26}_D = +90.0$ (*c*, 0.690, $CHCl_3$); IR 1716 cm^{-1}; ^1H NMR δ 10.06 (s, 1 H), 7.39−7.26 (m, 5 H), 7.09 (s, 1 H), 6.85 (s, 1 H), 5.10 (d, $J = 11.8$ Hz, 1 H), 5.04 (d, $J = 11.8$ Hz, 1 H), 4.26 (d, $J = 1.9$ Hz, 1 H), 3.22 (d, $J = 9.9$ Hz, 1 H), 3.94 (d, $J = 9.9$ Hz, 1 H), 3.87 (s, 3 H), 3.64 (d, $J = 12.4$ Hz, 1 H), 3.31 (dd, $J = 12.4, 1.8$ Hz, 1 H), 3.22 (dd, $J = 4.6, 1.8$ Hz, 1 H), 3.12 (dd, $J = 4.6, 1.9$ Hz, 1 H), 1.35 (s, 9 H), 0.72 (s, 9 H), −0.08 (s, 3 H), −0.21 (s, 3 H); ^{13}C NMR δ 200.8, 167.0, 160.4, 157.9, 155.1, 136.4, 132.8, 128.5, 127.9, 127.0, 119.8, 104.4, 104.3, 81.6, 71.3, 69.8, 63.7, 62.7, 52.1, 51.7, 43.0, 42.7, 27.7, 25.6, 18.0, −5.6, −5.8; HRMS (CI) calcd for $(M)^+$ $C_{33}H_{44}N_2O_7Si$: 608.2918, found 608.2929. **27d**: IR 1717 cm^{-1}; ^1H NMR δ 10.04 (s, 1 H), 7.38−7.28 (m, 5 H), 7.12 (s, 1 H), 6.88 (s, 1 H), 5.11 (d, $J = 12.2$ Hz, 1 H), 5.06 (d, $J = 12.2$ Hz, 1 H), 4.80 (d, $J = 5.2$ Hz, 1 H), 4.76 (d, $J = 5.2$ Hz, 1 H), 4.23 (d, $J = 1.8$ Hz, 1 H), 4.12 (d, $J = 9.8$ Hz, 1 H), 4.02 (d, $J = 9.8$ Hz, 1 H), 3.87 (s, 3 H), 3.66 (d, $J = 12.5$ Hz, 1 H), 3.32 (dd, $J = 12.5, 1.2$ Hz, 1 H), 3.23 (dd, $J = 4.2, 1.2$ Hz, 1 H), 3.10 (dd, $J = 4.2, 1.8$ Hz, 1 H), 1.35 (s, 9 H), 0.80 (s, 9 H), −0.03 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR δ 200.6, 167.0, 160.3, 157.7, 155.0, 136.3, 133.0, 128.5, 127.9, 127.0, 119.8, 104.9, 104.5, 90.4, 81.8, 71.8, 69.9, 68.5, 60.7, 52.2, 51.9, 42.9, 42.6, 27.8, 25.6, 18.0, −5.16; HRMS (CI) calcd for $(M)^+$ $C_{34}H_{46}N_2O_8Si$: 638.3023, found 638.3031.

Methyl (1a*S*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[(acetyloxy)methyl]-1-(*tert*-butyloxycarbonyl)-8-formylazirino[2′,3′:3,4]pyrrolo[1,2- *a*]indole-5-carboxylate (27e). Pyridine (36 μL, 0.44 mmol), acetic anhydride (43 μL, 0.46 mmol), and DMAP (2.0 mg, 0.016 mmol) were added to a CH_2Cl_2 (2 mL) solution of alcohol **27a** (110.0 mg, 0.2224 mmol). The reaction mixture was stirred for 1 h and then partitioned between CH_2Cl_2 and 3% NH_4Cl solution. The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography of the residue (20−30% EtOAc/hexanes) afforded acetate **27e** as a white foam (110.0 mg, 92%): mp 128.8−129.0 °C (EtOAc/hexanes; white chunky solid); $[\alpha]^{19}_D = +68.0$ (*c*, 0.550, $CHCl_3$); IR 1720 cm^{-1}; ^1H NMR δ 10.04 (s, 1 H), 7.37−7.25 (m, 5 H), 7.12 (s, 1 H), 6.88 (s, 1 H), 5.12 (d, $J = 11.9$ Hz, 1 H), 5.07 (d, $J = 11.9$ Hz, 1 H), 4.70 (d, $J = 11.2$ Hz, 1 H, CH_2OAc), 4.50 (d, $J = 11.2$ Hz, 1 H), 4.07 (d, $J = 1.9$ Hz, 1 H), 3.88 (s, 3 H), 3.67 (d, $J = 12.5$ Hz,

(75) A sample of the silyl ether mixture was purified by radial chromatography (CH_2Cl_2) to afford **21a** upon which the NOE studies were conducted: ^1H NMR (500.1 MHz; C_6D_6, $\delta = 7.19$) 7.25−7.16 (m, 7H), 4.93 (dd, $J = 10.0, 4.7$ Hz, 1 H, CH_2O), 4.69 (dd, $J = 11.2, 10.0$ Hz, 1 H, CH_2O), 4.55 (d, $J = 10.8$ Hz, 1 H), 4.51 (d, $J = 10.8$ Hz, 1 H), 4.02 (dd, $J = 9.8, 1.8$ Hz, 1 H, CH_2NCH), 3.82−3.77 (m, 1 H, $CHCH_2O$), 3.59 (s, 3 H), 3.45 (d, $J = 12.4$ Hz, 1 H), 3.32 (dd, $J = 4.4, 1.8$ Hz, 1 H, NCHCHNBoc), 2.78−2.74 (m, 2 H), 1.22 (s, 9 H), 1.04 (s, 9 H), 0.20 (s, 3 H), 0.15 (s, 3 H).

1 H), 3.30 (dd, J = 12.5, 1.8 Hz, 1 H), 3.24 (dd, J = 4.7, 1.8, 1 H), 3.09 (dd, J = 4.7, 1.9 Hz, 1 H), 1.90 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR δ 199.6, 170.8, 166.8, 160.1, 157.8, 155.2, 136.1, 133.4, 128.6, 127.9, 127.0, 118.5, 104.9, 104.4, 81.9, 71.7, 70.0, 64.4, 59.7, 52.2, 51.8, 42.7, 42.2, 27.7, 20.8; LRMS (EI) m/z $(M)^+$ = 536.55. Anal. Calcd for $C_{29}H_{32}N_2O_8$: C, 64.91; H, 6.01; N, 5.22. Found: C, 64.87; H, 6.01; N, 5.24.

Methyl (1a*S*,8*R*,8a*S*,8b*S*)-1,1a,2,8,8a,8b-Hexahydro-8-[(acetyloxy)methyl]-7-(benzyloxy)-1-(*tert*-butyloxycarbonyl)-8-formylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate 3-Oxide (28b). To a CH_2Cl_2 (3.0 mL) solution of amine **27e** (148.0 mg, 0.2758 mmol) at 0 °C was added *m*-chloroperbenzoic acid (m-CPBA, 96% pure, 54.5 mg, 0.303 mmol), and the reaction mixture was stirred vigorously for 1.8 h. Additional m-CPBA (2.8 mg, 0.016 mmol) was added, and 10 min later the solution was submitted directly to flash chromatography (CH_2Cl_2 prep; EtOAc; 30% CH_3OH/EtOAc) to give amine oxide **28b** as a white foam, containing a trace of impurity believed to be its diastereomer (149.4 mg, 98%): IR 1727 cm^{-1}; ^{1}H NMR δ 10.09 (s, 1 H), 7.82 (s, 1 H), 7.65 (s, 1 H), 7.40−7.30 (m, 5 H), 5.20 (s, 1 H), 5.09 (d, J = 11.2 Hz, 1 H, CH_2OAc), 4.79 (d, J = 2.8 Hz, 1 H), 4.72 (d, J = 13.3 Hz, 1 H), 4.47 (d, J = 11.2 Hz, 1 H), 4.30 (dd, J = 13.3, 2.9 Hz, 1 H), 3.90 (s, 3 H), 3.64 (dd, J = 5.5, 2.9 Hz, 1 H), 3.55 (dd, J = 5.5, 2.8 Hz, 1 H), 1.96 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR* δ 196.4, 170.4, 165.0, 158.9, 155.4, 155.2, 134.9, 128.8, 128.5, 127.2, 122.8, 113.5, 111.6, 88.9, 83.1, 73.3, 70.9, 62.9, 60.1, 52.6, 42.5, 41.2, 27.6, 20.8; HRMS (FAB) calcd for $(M + H)^+$ $C_{29}H_{33}N_2O_9$: 553.2186, found 553.2187.

Methyl (1a*S*,8*S*,8b*S*)-1,1a,2,8,8a,8b-Hexahydro-8-[(acetyloxy)methyl]-7-(benzyloxy)-1-(*tert*-butyloxycarbonyl)-8-formyl-8a-hydroxyazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (29c) and Methyl (1a*R*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-8-[(acetyloxy)methyl]-7-(benzyloxy)-1-(*tert*-butyloxycarbonyl)-8-formyl-2-hydroxyazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (29d). Acetic anhydride (65 μL, 0.69 mmol) was added to a THF (3.6 mL) solution of amine oxide **28b** (112.0 mg, 0.2027 mmol) at 0 °C, and the reaction mixture was stored at 0 °C for 40 h. Water (1.0 mL) was added, and the solution was stirred for 20 min. The reaction mixture was partitioned between CH_2Cl_2 and 3% NH_4Cl solution. The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography (CH_2Cl_2 prep; 20−30% EtOAc/hexanes) afforded a mixture of regioisomeric alcohols. Radial chromatography of the mixture gave *tert*-carbinolamine **29c** (66.4 mg, 59%) and *sec*-carbinolamine **29d** (8.4 mg, 8%) containing a trace of what might be its C_2 anomer. **29c**: $[\alpha]^{21}_D$ = −8.1 (*c*, 0.552, $CHCl_3$); IR 3568, 3328 (br), 1749, 1718 cm^{-1}; ^{1}H NMR δ 9.93 (s, 1 H), 7.36−7.29 (m, 5 H), 7.15 (s, 1 H), 6.83 (s, 1 H), 5.13−5.09 (m, 3 H), 4.74 (d, J = 11.7 Hz, 1 H), 3.94 (s, 1 H, OH), 3.87 (s, 3 H), 3.66 (d, J = 12.5 Hz, 1 H), 3.45 (dd, J = 12.5, 1.5 Hz, 1 H), 3.31 (dd, J = 4.4, 1.5 Hz, 1 H), 3.17 (d, J = 4.4 Hz, 1 H), 1.78 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR δ 199.2, 170.4, 166.8, 159.4, 155.0, 154.5, 136.1, 133.3, 128.6, 128.0, 127.2, 117.5, 105.4, 103.8, 102.4, 82.2, 70.2, 62.8, 61.6, 52.3, 50.8, 45.7, 41.2, 27.7, 20.7; LRMS (CI) m/z $(M + H)^+$ = 553.65. Anal. Calcd for $C_{29}H_{32}N_2O_9$: C, 63.03; H, 5.84; N, 5.07. Found: C, 62.96; H, 5.87; N, 5.00. **29d**: IR (CCl_4) 3612, 1749, 1726 cm^{-1}; ^{1}H NMR (CD_2Cl_2, δ = 5.32) 10.01 (s, 1 H), 7.42−7.33 (m, 5 H), 7.18 (s, 1 H), 7.08 (s, 1 H), 5.26 (d, J = 3.4 Hz, 1 H, NCHOH), 5.10 (s, 2 H, OCH_2Ph), 4.68 (d, J = 11.2 Hz, 1 H), 4.48 (d, J = 11.2 Hz, 1 H), 4.42 (d, J = 1.9 Hz, 1 H), 3.87 (s, 3 H), 3.39 (d, J = 4.4 Hz, 1 H), 3.25 (dd, J = 4.4, 1.9 Hz, 1 H), 2.63 (d, J = 3.4 Hz, 1 H, OH), 1.91 (s, 3 H), 1.37 (s, 9 H); HRMS (CI) calcd for $(M + H)^+$ $C_{29}H_{33}N_2O_9$: 553.2186, found 553.2194.

Methyl (1a*S*,8*R*,9*S*,9a*S*)-1,1a,2,8,9,9a-Hexahydro-8-[(acetyloxy)methyl]-7-(benzyloxy)-1-(*tert*-butyloxycarbonyl)-8-formyl-9-hydroxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocin-5-carboxylate (30a). To a CH_2Cl_2 (3 mL) solution of *tert*-carbinolamine **29c** (70.0 mg, 0.127 mmol) at 0 °C was added m-CPBA (75% pure, 35.7 mg, 0.155 mmol) over 0.5 min, and the reaction mixture was stirred vigorously for 1.5 h. The resulting orange solution was submitted directly to rapid flash chromatography (CH_2Cl_2 prep; 20−33% EtOAc/hexanes) to give a faint yellow solid. Recrystallization from EtOAc/hexanes gave white plates (50.0 mg, 69%) upon which a single crystal X-ray analysis was conducted. **30a**: mp (darkens at 175 °C, tarry through 235 °C, no distinct dec pt); $[\alpha]^{20}_D$ = −44.9 (*c*, 0.356, $CHCl_3$); IR 3289 (br), 1720 cm^{-1}; ^{1}H NMR δ 9.84 (s, 1 H), 7.39−7.30 (m, 6 H), 7.15 (d, J = 1.2 Hz, 1 H), 6.35 (s, 1 H, OH), 5.50 (d, J = 12.8 Hz, 1 H), 5.17 (s, 2 H), 4.48 (d, J = 12.8 Hz, 1 H), 3.90 (s, 3 H), 3.89 (dd, J = 14.6, 2.1 Hz, 1 H), 3.76 (d, J = 14.6 Hz, 1 H), 2.98 (d, J = 6.8 Hz, 1 H), 2.75 (dd, J = 6.8, 2.1 Hz, 1 H), 1.91 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR δ 198.8, 174.4, 166.3, 159.8, 155.4, 150.0, 135.2, 131.1, 128.7, 128.4, 127.5, 116.7, 113.1, 107.3, 93.3, 82.6, 70.9, 61.1, 58.0, 52.4, 52.0, 42.5, 32.0, 27.7, 21.1.

Methyl (1a*S*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[[(benzyloxycarbonyl)oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (27f). 1,1′-Carbonyldiimidazole (150.0 mg, 0.9251 mmol) was added to an CH_3CN (12.0 mL) solution of alcohol **27a** (385.0 mg, 0.7785 mmol), and the reaction mixture was stirred for 3.5 h. Benzyl alcohol (600 μL, 5.80 mmol) and DMAP (60.0 mg, 0.491 mmol) were added, and the reaction mixture was heated at 63 °C for 3.0 h. The solvent was removed, and the residue was submitted to flash chromatography (CH_2Cl_2 prep; 10−25% EtOAc/hexanes) to give a pale yellow foam containing traces of an impurity (349.0 mg, 71%). This material was suitable for further experiments. A sample of **27f** was purified by radial chromatography (3% EtOAc/CH_2Cl_2) for characterization purposes: $[\alpha]^{23}_D$ = +36.0 (*c*, 0.540, $CHCl_3$); IR 1742, 1720 cm^{-1}; ^{1}H NMR δ 10.02 (s, 1 H), 7.38−7.26 (m, 10 H), 7.10 (s, 1 H), 6.87 (s, 1 H), 5.11−5.02 (m, 4 H), 4.78 (d, J = 10.9 Hz, 1 H), 4.58 (d, J = 10.9 Hz, 1 H), 4.13 (d, J = 1.9 Hz, 1 H), 3.88 (s, 3 H), 3.66 (d, J = 12.6 Hz, 1 H), 3.29 (dd, J = 12.6, 1.8 Hz, 1 H), 3.23 (dd, J = 4.7, 1.8 Hz, 1 H), 3.08 (dd, J = 4.7, 1.9 Hz, 1 H), 1.35 (s, 9 H); ^{13}C NMR* δ 199.2, 166.8, 160.1, 157.8, 155.3, 154.8, 136.1, 135.0, 133.6, 128.6, 128.4, 128.3, 127.9, 127.0, 117.9, 105.0, 104.5, 82.0, 71.4, 70.0, 69.7, 67.8, 59.6, 52.2, 51.7, 42.7, 42.1, 27.7; LRMS (EI) m/z $(M)^+$ = 628.60. Anal. Calcd for $C_{35}H_{36}N_2O_9$: C, 66.87; H, 5.77; N, 4.46. Found: C, 66.90; H, 5.83; N, 4.40.

Methyl (1a*S*,8*R*,8a*S*,8b*S*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[[(benzyloxycarbonyl)oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate 3-Oxide (28c). The oxidation of amine **27f** (408.0 mg, 0.6490 mmol) was conducted according to the procedure described for amine **27e** to afford slightly impure amine oxide as a white foam (410.9 mg, ∼98%), which was suitable for the next reaction. **28c**: IR 1728 cm^{-1}; ^{1}H NMR δ 10.10 (s, 1 H), 7.82 (s, 1 H), 7.63 (s, 1 H), 7.36−7.32 (m, 10 H), 5.17−5.09 (m, 5 H), 4.80 (d, J = 2.7 Hz, 1 H), 4.73 (d, J = 13.3 Hz, 1 H), 4.61 (d, J = 10.6 Hz, 1 H), 4.29 (dd, J = 13.3, 2.8 Hz, 1 H), 3.90 (s, 3 H), 3.63 (dd, J = 5.4, 2.8 Hz, 1 H), 3.54 (dd, J = 5.4, 2.7 Hz, 1 H), 1.32 (s, 9 H); ^{13}C NMR* δ 195.6, 165.0, 158.9, 155.5, 155.3, 154.3, 135.1, 134.93, 134.86, 128.8, 128.5, 128.4, 127.2, 122.2, 113.7, 111.4, 88.2, 83.2, 72.7, 70.9, 70.0, 66.4, 59.5, 52.7, 42.1, 40.9, 27.6; HRMS (FAB) calcd for $(M + H)^+$ $C_{35}H_{37}N_2O_{10}$: 645.2448, found 645.2449.

Methyl (1a*S*,8*S*,8b*S*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[[(benzyloxycarbonyl)oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formyl-8a-hydroxyazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (29e) and Methyl (1a*R*,8*R*,8a*S*,8b*R*)-1,1a,2,8,8a,8b-Hexahydro-7-(benzyloxy)-8-[[(benzyloxycarbonyl)oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formyl-2-hydroxyazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-5-carboxylate (29f). Acetic anhydride (210 μL, 2.23 mmol) was added to a THF (12.0 mL) solution of amine oxide **28c** (410.9 mg, 0.6374 mmol) at 0 °C and was stored for 24 h (0 °C). Water (1 mL) was added, and the mixture was stirred for 10 min. The solution was partitioned between CH_2Cl_2 and 3% NH_4Cl solution, and the organic phase was dried with Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography (20−30% EtOAc/hexanes; for the first 30 min, the column was eluted by gravity to allow the hydrolysis of the intermediate acetate on silica gel) gave a mixture of isomeric carbinolamines **29e** and **29f** as a white foam (**29e**:**29f** =13:1 by ^{1}H NMR; 302.0 mg, 73%) which was submitted to the ring expansion step without further purification. For the purpose

of characterization, the isomers were separated by radial chromatography (10% acetone/$CHCl_3$). **29e**: IR 3566, 1752 cm^{-1}; ^1H NMR δ 9.89 (s, 1 H), 7.35−7.25 (m, 8 H), 7.16−7.14 (m, 2 H), 7.13 (s, 1 H), 6.81 (s, 1 H), 5.12 (d, J = 11.3 Hz, 1 H), 5.09 (d, J = 11.6 Hz, 1 H), 5.03 (d, J = 11.6 Hz, 1 H), 4.96 (s, 2 H), 4.86 (d, J = 11.3 Hz, 1 H), 3.89 (s, 3 H), 3.64 (d, J = 12.5 Hz, 1 H), 3.61 (s, 1 H, OH), 3.44 (dd, J = 12.5, 1.7 Hz, 1 H), 3.30 (dd, J = 4.4, 1.7 Hz, 1 H), 3.16 (dd, J = 4.4 Hz, 1 H), 1.35 (s, 9 H); ^{13}C NMR* δ 199.0, 166.7, 159.4, 155.1, 154.5, 136.1, 134.8, 133.4, 128.6, 128.5, 128.2, 128.0, 127.2, 117.1, 105.5, 103.9, 102.3, 82.3, 70.2, 69.8, 65.2, 62.8, 52.2, 50.7, 45.8, 41.2, 27.7; HRMS (FAB) calcd for $(M)^+$ $C_{35}H_{36}N_2O_{10}$: 644.2370, found 644.2370. **29f**: IR (CCl_4) 3609, 1751, 1726 cm^{-1}; ^1H NMR (500 MHz; CD_2Cl_2, δ = 5.30) 9.97 (s, 1 H), 7.38−7.26 (m, 10 H), 7.16 (d, J = 0.9 Hz, 1 H), 7.09 (d, J = 0.9 Hz, 1 H), 5.22 (d, J = 3.5 Hz, 1 H, HOC*H*), 5.08 (d, J = 11.5 Hz, 1 H), 5.05 (d, J = 11.5 Hz, 1 H), 5.69 (d, J = 11.5 Hz, 2 H), 4.70 (d, J = 10.9 Hz, 1 H), 4.60 (d, J = 10.9 Hz, 1 H), 4.42 (d, J = 2.1 Hz, 1 H, HOCHNC*H*), 3.86 (s, 3 H), 3.36 (d, J = 4.3 Hz, 1 H), 3.21 (dd, J = 4.3, 2.1 Hz, 1 H), 2.54 (d, J = 3.5 Hz, 1 H, OH), 1.35 (s, 9 H); ^{13}C NMR (125.7 MHz; CD_2Cl_2, δ = 54.00)* 199.6, 166.9, 159.9, 156.3, 155.3, 155.0, 136.8, 135.8, 134.5, 129.1, 129.0, 128.6, 127.7, 118.9, 106.4, 105.3, 87.7, 82.9, 71.4, 70.7, 70.4, 68.5, 60.0, 52.8, 47.4, 41.5, 38.7; HRMS (EI) calcd for $(M)^+$ $C_{35}H_{36}N_2O_{10}$: 644.2370, found 644.2366.

Methyl (1a*S*,8*R*,9*S*,9a*S*)-1,1a,2,8,9,9a-Hexahydro-7-(benzyloxy)-8-[[(benzyloxycarbonyl)oxy]methyl]-1-(*tert*-butyloxycarbonyl)-8-formyl-9-hydroxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxylate (30b). A mixture of carbinolamines **29e** and **29f** (**29e**:**29f** = 13:1, 145.0 mg, 0.2089 mmol) was oxidized according to the procedure described for carbinolamine **29c**. The resulting orange solution was directly submitted to rapid flash chromatography on a short column (CH_2Cl_2 prep; 25−33% EtOAc/hexanes) to give **30b** as a yellow foam (112.0 mg, 81%): $[\alpha]^{23}_D$ = −75.2 (*c*, 0.770, $CHCl_3$); IR 3309 (br), 1719 cm^{-1}; ^1H NMR δ 9.84 (s, 1 H), 7.38−7.25 (m, 11 H), 7.15 (d, J = 1.0 Hz, 1 H), 6.30 (s, 1 H, OH), 5.40 (d, J = 12.9 Hz, 1 H), 5.15 (d, J = 12.1 Hz, 1 H), 5.14 (s, 2 H), 5.07 (d, J = 12.1 Hz, 1 H), 4.68 (d, J = 12.9 Hz, 1 H), 3.90 (dd, J = 14.6, 2.0 Hz, 1 H), 3.89 (s, 3 H), 3.78 (d, J = 14.6 Hz, 1 H), 3.00 (d, J = 6.8 Hz, 1 H), 2.76 (dd, J = 6.8, 2.0 Hz, 1 H), 1.33 (s, 9 H); ^{13}C NMR* δ 198.6, 166.2, 159.7, 157.0, 155.5, 150.0, 135.3, 134.6, 131.2, 128.7, 128.4, 128.3, 128.0, 127.5, 116.3, 113.1, 107.3, 93.3, 82.6, 71.0, 70.3, 64.9, 58.1, 52.3, 52.0, 42.5, 32.0, 27.7; HRMS (FAB) calcd for $(M + H)^+$ $C_{35}H_{37}N_2O_{11}$: 661.1397, found 661.2406.

Methyl (1a*S*,8*R*,9*S*,9a*S*)-1,1a,2,8,9,9a-Hexahydro-1-(*tert*-butyloxycarbonyl)-8-formyl-7,9-dihydroxy-8-(hydroxymethyl)-3,9-epoxy-3 H**-azirino[2,3-*c*][1]benzazocine-5-carboxylate (32).** A mixture of HOAc (60 μL), 10% Pd/C (43.8 mg), and benzyl carbonate **30b** (112.0 mg, 0.1695 mmol) in EtOH (8.0 mL) was stirred under a hydrogen atmosphere for 30 min. The catalyst was filtered, and the solvent was removed in vacuo. Flash chromatography of the residue (CH_2Cl_2 prep; 30−40% EtOAc/hexanes) on a short column with rapid elution afforded triol **32** as an off-white foam (68.0 mg, 92%): $[\alpha]^{23}_D$ = +10.8 (*c*, 0.460, $CHCl_3$); IR 3257 (br), 1720, 1706 cm^{-1}; ^1H NMR δ 10.19 (d, J = 1.9 Hz, 1 H), 8.26 (br s, 1 H, OH), 7.61 (br s, 1 H, OH), 7.14 (d, J = 1.1 Hz, 1 H), 7.03 (d, J = 1.1 Hz, 1 H), 4.66 (dd, J = 11.2, 1.4 Hz, 1 H, CH_2OH), 4.42 (dd, J = 11.2, 1.4 Hz, 1 H, C*H*$_2$O*H*), 4.10 (app td, $\langle J \rangle$ = 11.2, 1.9 Hz, 1 H, C*H*$_2$OH), 3.97 (dd, J = 14.7, 1.9 Hz, 1 H), 3.90 (s, 3 H), 3.78 (d, J = 14.7 Hz, 1 H), 3.07 (d, J = 6.7 Hz, 1 H), 2.81 (dd, J = 6.7, 1.9 Hz, 1 H), 1.33 (s, 9 H); ^{13}C NMR δ 206.2, 166.8, 160.1, 153.4, 149.4, 130.9, 114.9, 112.1, 110.9, 94.5, 83.0, 64.5, 55.6, 52.7, 52.3, 42.9, 32.7, 27.7; HRMS (FAB) calcd for $(M + H)^+$ $C_{20}H_{25}N_2O_9$: 437.1560, found 437.1561.

Methyl (4a*R*,10a*S*,11a*S*,11b*S*)-4,4a,10,10a,11,11b-Hexahydro-11-(*tert*-butyloxycarbonyl)-4a-formyl-5-hydroxy-2,2-dimethyl-9,11b-epoxyazirino[2,3-*c*]-1,3-dioxino[4,5-*e*][1]benzazocine-7-carboxylate (33a). To a CH_2Cl_2 (3 mL) solution of triol **32** (65 mg, 0.15 mmol) was added 2,2-dimethoxypropane (70 μL, 0.57 mmol) and *p*-TsOH·H_2O (2.6 mg, 0.014 mmol). The mixture was stirred for 20 min, diluted with CH_2Cl_2, and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (CH_2Cl_2 prep; 20−25% EtOAc/hexanes) of the residue afforded acetonide **33a** as a colorless oil (50.0 mg, 70%): $[\alpha]^{19}_D$ = +45.7 (*c*, 1.224, $CHCl_3$); IR 3235 (br), 1721cm^{-1}; ^1H NMR δ 10.11 (d, J = 1.2 Hz, 1 H), 8.15 (s, 1 H, OH), 7.16 (d, J = 1.4 Hz, 1 H), 7.03 (d, J = 1.4 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.09 (dd, J = 12.0, 1.2 Hz, 1 H, C*H*$_2$O), 3.96 (dd, J = 14.7, 2.1 Hz, 1 H), 3.89 (s, 3 H), 3.79 (d, J = 14.7 Hz, 1 H), 3.08 (d, J = 6.7 Hz, 1 H), 2.80 (dd, J = 6.7, 2.1 Hz, 1 H), 1.58 (s, 3 H), 1.54 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR δ 201.6, 166.9, 160.0, 154.4, 148.7, 130.5, 116.4, 111.9, 111.4, 100.8, 93.4, 83.0, 60.5, 52.5, 51.8, 50.3, 43.4, 32.3, 29.3, 27.6, 24.9; LRMS (CI) m/z $(M + H)^+$ = 477.45; HRMS (FAB) calcd for $(M + H)^+$ $C_{20}H_{23}N_2O_9$: 477.1873, found 477.1876.

Methyl (4a*R*,10a*S*,11a*S*,11b*S*)-4,4a,10,10a,11,11b-Hexahydro-11-(*tert*-butyloxycarbonyl)-5-hydroxy-2,2-dimethyl-9,11b-epoxyazirino[2,3-*c*]-1,3-dioxino[4,5-*e*][1]benzazocine-7-carboxylate (33b). Tris(triphenylphosphine)rhodium chloride (20.4 mg, 0.0220 mmol; stored under nitrogen but weighed in the air) and xylene (1.7 mL, reagent grade, used as received) were added to aldehyde **33a** (5.1 mg, 0.011 mmol). The heterogeneous mixture was purged with N_2 for 3 min and lowered into a preheated oil-bath (130 °C). After heating began, the mixture became homogeneous, and within a few minutes a precipitate appeared. The dark-red heterogeneous reaction mixture was heated for 3.75 h and cooled, and the solvent was removed in vacuo. Flash chromatography of the residue (0−10% EtOAc/hexanes) afforded the decarbonylated product **33b** containing Ph_3P-derived impurities. An additional flash chromatography (CH_2Cl_2 prep; 15−25% EtOAc/hexanes) gave pure **33b** as a colorless oil film (3.7 mg, 77%): IR 3295 (br), 1717 cm^{-1}; ^1H NMR δ 7.04 (d, J = 1.2 Hz, 1 H, C_6-H), 6.97 (d, J = 1.2 Hz, 1 H), 6.23 (br s, 1 H, OH), 4.43 (dd, J = 11.7, 6.0 Hz, 1 H, $CH_2O(C_{13}$-$H_{eq})$), 3.89−3.81 (m, 2 H), 3.85 (s, 3 H), 3.65 (d, J = 14.6 Hz, 1 H, NCH_2), 3.46 (dd, J = 11.1, 6.0 Hz, 1 H, C*H*CH_2O), 3.07 (d, J = 6.6 Hz, 1 H), 2.70 (dd, J = 6.6, 1.8 Hz, 1 H), 1.58 (s, 3 H), 1.50 (s, 3 H), 1.33 (s, 9 H); ^{13}C NMR (125.7 MHz) δ 166.7, 160.7, 154.0, 149.0, 129.2, 118.4, 112.1, 110.7, 100.1, 92.5, 82.1, 58.8, 52.3, 52.2, 44.4, 33.5, 32.3, 30.2, 27.8, 24.4; HRMS (FAB) calcd for $(M + H)^+$ $C_{22}H_{29}N_2O_8$: 449.1924, found 449.1925.

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Supporting Information Available: Copies of ^1H NMR spectra of compounds **16b**, **16c**, **17**, **18b**, **19b**, **22b**, **27c**, **27d**, **27g**, **27h**, **28b**, **28c**, **29a**/**27c** mixture, **29b**, **29d**, **29e**, **29f**, **30a**, **30b**, **31a**, **32**, **33a**, and **33b**, and ^{13}C NMR spectra for compounds **28b**, **28c**, and **33b** are provided. Experimental procedures are available for compounds **27g**, **27h**, **29a**, **29b**, and **31a** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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