Synthesis of Strychnine and the Wieland-Gumlich Aldehyde

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Abstract: The tetracyclic amine **9** was converted through several steps into secondary amine **13** and acetylated with (phenylthio)acetic acid activated by bis(2-oxo-3-oxazolidinyl)phosphinic acid to give amide **15**. Treatment of **15** with sodium hydride in tetrahydrofuran at 25 °C resulted in rapid conversion into a single diastereomer, **16**. This same conjugate addition has been conducted at the sulfoxide oxidation level and also with a chiral sulfoxide to provide optically active compounds (Scheme VI). Conversion of sulfoxide **19** into dione **27** followed by ketalization and reduction gave tertiary amine **34**. Deprotection and oxidation with mercuric acetate gave the core strychnine skeleton **36**. The β-aminoacrylate double bond in **36** was reduced to give **39** followed by epimerization to give **40**. Ester **40** was protected as the sulfonamide derivative **44**, and the ester was reduced to give **45**. Alcohol **45** undergoes normal acid hydrolysis to give hemiketal **47** (Scheme X). The Wieland-Gumlich aldehyde **48** was converted into the relay compound by the route shown in Scheme XI, thus providing a convenient correlation and short route to **47**. Hemiketal **47** was converted into ketone **52** and treated with $(EtO)_2P(O)CH_2CN/KN(SiMe_3)_2/THF$ at 25 °C to give the two geometrical isomers **53** (*E*) and **54** (*Z*) (overall 72%) in a ratio of 3:2. The incorrect stereoisomer could be recycled by irradiation in benzene to give a mixture of **53** and **54**. Reduction of **53** gave the required allylic alcohol **55**. Desilylation of **55** gave diol **56**. The synthesis of strychnine and the Wieland-Gumlich aldehyde was completed by selective silylation of the allylic hydroxyl group in **56** and oxidation to give the unstable aldehyde **58**. Desilylation of **58** gave the protected Wieland-Gumlich aldehyde **49**, which was deprotected by treatment with sodium anthracenide to give **48**. The conversion of **48** into strychnine was reported by Robinson in 1953.

Introduction

Strychnine (**1**) has a long and interesting history. It was first isolated in 1818 from *Strychnos nux vomica* L. and was shown to be a poison.[1] It acts on the spinal axis, eventually leading to paralysis of the respiratory system and asphyxiation.[2] While in its day it was a popular poison, it is not particularly toxic. Doses of approximately 100 mg are required to kill an adult, although some resistance can be achieved by accumulative smaller doses. The only recorded apparent beneficial medicinal property is as an appetite stimulant.[3] Strychnine has recently been shown to interact with the glycine receptor site, thus preventing the flux of glycine and disruption of nerve-cell signaling.[4]

The elucidation of the structure of strychnine by classical degradation was an enormous feat spread over some 40 years and only made possible because of the availability of large quantities of strychnine. The most notable experimental contributions were made by Leuch and Robinson.[5] In 1946, Robinson proposed the correct structure for strychnine, and the following year, Woodward independently suggested the same structure.[6] Woodward's work was based upon a brilliant analysis of the published degradational literature. The only way to verify the proposed structure was by total synthesis. At this stage (1948) in the development of organic synthesis, it was not at all obvious how one would accomplish this ambitious task. While there were some notable synthetic achievements, particularly in the area of biomimetic (then called biogenetic) organic synthesis, the planned and logical construction of a molecule of the complexity of strychnine was considered to be beyond the scope of existing knowledge. Woodward's unique achievement in confirming the structure of strychnine by total synthesis (1953) not only was the first total synthesis of a complicated natural product but began the era of modern organic synthesis.[7] Since 1953, there have been extensive synthetic efforts devoted to indole alkaloids but the original Woodward report still stands apart as the only synthesis of strychnine.[8]

While there are a number of routes to the strychnine core skeleton, they all lack the requisite functionality for the construction of the seven-membered allylic ether ring. The Wood-

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(1) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323.
(2) Franz, D. N. *The Pharmacological Basis of Therapeutics*; Gilman, A. G., Goodman, L. S., Gilman, A., Eds.; Macmillan: New York, 1980.
(3) Creasey, W. A. *The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; Interscience: New York, 1983, p 800.
(4) Grenningloh, G.; Rienitz, A.; Schmitt, B.; Methfessel, C.; Zensen, M.; Beyreuther, K.; Gundelfinger, E. D.; Betz, H. *Nature* **1987**, *328*, 215. Snell, L. D.; Johnson, K. M. *Eur. J. Pharmacol.* **1988**, *151*, 165. Kleckner, N. W.; Dingledine, R. *Science* **1988**, *241*, 835.
(5) For numerous references to the degradation of strychnine prior to the correct structure see: Holmes, H. L. The Strychnos Alkaloids. Manske, R. H. F., Holmes, H. L., Ed.; In *The Alkaloids*; Academic Press: New York, 1950; Vol. I, p 375. Leuchs, H. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 1588. Holmes, H. L.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 903.
(6) Holmes, H. L. The Strychnos Alkaloids Part II. In *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1952; Vol. II, p 3513. Holmes, H. L.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 908. Openshaw, H. T.; Robinson, R. *Nature* **1946**, *157*, 438. Woodward, R. B.; Brehm, W. J.; Nelson, A. L. *J. Am. Chem. Soc.* **1947**, *69*, 2250. Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107.
(7) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.
(8) For the most recent published synthetic approaches, see: Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085. Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696. Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624. Legseir, B.; Henin, J.; Massiot, G.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573. Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodriquez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267. Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. Kraus, G. A.; Bougie, D. *Synlett* **1992**, 279. Teuber, H-J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1992**, 461. There are numerous other reports of synthetic endeavors, and these are referred to in the following: Massiot, G.; Delaude, C. African Strychnos Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 34, p 211. Bosch, J.; Bonjoch, J. Pentacyclic Strychnos Alkaloids. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1988; Vol. 1, 31. Enantioselective Total Synthesis of Strychnine. Knight, S. D.; Overman, L. E.; Pairaudean, G. *J. Am. Chem. Soc.* Submitted for publication.

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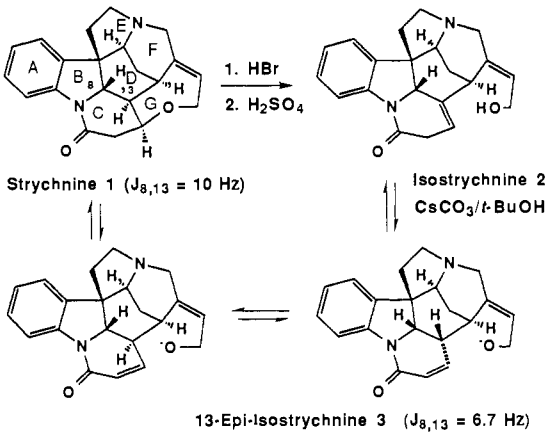
Scheme I



ward synthesis solved this problem by using the Leuchs–Prelog degradation of strychnine into isostrychnine (**2**) and its conversion back into strychnine.[9] Treatment of isostrychnine with ethanolic potassium hydroxide at 80 °C produces strychnine in very low yield (5–8%). The majority of the material appears to be converted into the so-called isostrychninic acids derived from hydroxide cleavage of the lactam and subsequent β-elimination and epimerization at C-13. This is hardly surprising since one of the classical degradation reactions of strychnine involved treatment with sodium hydroxide to give isostrychninic acid.[10] In view of this poor conversion, we decided to look at more "modern" bases in the hope that the isostrychnine–strychnine conversion could be made into an efficient process. Somewhat surprisingly, this proved to be completely unsuccessful. Treatment of **2** with a wide variety of bases (*t*-BuOH/*t*-BuOK, DBU/ROH, and etc.) under equilibration conditions (proton source available) produced little, if any, strychnine. The only interesting result was the observation that treatment of isostrychnine (**2**) with cesium carbonate in *tert*-butyl alcohol heated at reflux gave the 13-*epi* compound **3** (Scheme I).

The assignment of configuration at C-13 is based upon the C-8,13 vicinal ^{1}H NMR coupling constant. When C-8,13 is trans (as in strychnine), the vicinal coupling is 10 Hz, whereas in **3**, $J_{8,13}$ is 6.7 Hz, indicating a cis relationship. Treatment of pure (HPLC) isostrychnine with ethanolic potassium hydroxide gave approximately 10% strychnine.

The retrosynthetic analysis shown in Scheme II should allow us to examine the stereospecificity of the Wadsworth–Emmons reaction of **5** to construct the α,β-unsaturated ester **4**. The crucial carbon–carbon bond should be formed by oxidation of the tertiary amine **7** to give the iminium ion **6**.[11] There are three possible iminium ions (see Scheme VIII), and the desired one is the least strained. It was anticipated that the nine-membered ring intermediate **7** (stemmadenine-type) should be available by intramolecular conjugate addition of the heteroatom-stabilized amide enolate anion **8**. In turn, we knew from our research on vinblastine that the required nine-membered ring intermediates are readily available from the chloroformate-induced fragmentation of the tetracyclic amine **9**.[12] The tetracyclic amine **9** is the starting material for both the synthesis of vinblastine and strychnine. It is available in large quantities by Pictet–Spengler condensation of tryptamine with dimethyl 2-ketoglutarate to give the lactam **9a**. Conversion of **9a** into the thiolactam **9b** (Lawesson's reagent) followed by Raney nickel desulfurization provides the tetracyclic amine **9** (Scheme III).[13]

Nine-Membered Ring Intermediates

The tetracyclic amine **9** was treated with β,β,β-trichloroethyl chloroformate in dichloromethane to give a mixture of the α-chloro ester **10**, the α,β-unsaturated ester **11**, and a small amount (ca. 5%) of an unidentified compound that appeared to be an adduct formed by reaction of **10** with the intermediate iminium ion.[14] The ratio of **10**:**11** varies with the reaction scale and, on a large scale, is approximately 4:3 (40% and 27%, respectively). While it is possible to treat the crude product mixture of **10** and **11** with sodium methoxide in methanol and convert **10** into **11**, in practice it is better to separate **10** and **11** by chromatography. Treatment of pure **10** with sodium methoxide in methanol at 25 °C for 0.5 h gave **11** in 98% yield (Scheme IV).

In order that the subsequent conjugate addition chemistry depicted in Scheme V work successfully, it was found to be necessary to protect the indole nitrogen atom with an electron-withdrawing group. Treatment of **11** with methyl chloroformate under standard phase-transfer conditions gave the derivative **12** (86%). The β,β,β-trichloroethyl carbamate group was removed by treatment of **12** with zinc dust in acetic acid to provide the secondary amine **13** (82%). The amine **13** was acetylated with (phenylthio)acetic acid activated by bis(2-oxo-3-oxazolidinyl)phosphinic acid to give amide **15** (71%).[15] Oxidation of **15** using *m*-chloroperoxybenzoic acid gave the derived sulfoxide **18**. The ^{1}H NMR spectra of the carbamates **10**, **11**, **12**, **13**, **15**, and **18** were complicated by both carbamate resonance and slow conformational changes in the nine-membered ring.[16] Consequently, it was difficult to obtain good ^{1}H NMR spectra even at 100 °C. The diamine **14** was completely characterized.

Formation of the F-Ring of Strychnine from Nine-Membered Ring Intermediates by Intramolecular Conjugate Addition: Racemic Series

We anticipated that the amide enolate anion **15a** derived from **15** should undergo intramolecular conjugate addition to the proximate α,β-unsaturated ester, forming the F-ring of strychnine (Scheme V).

Treatment of **15** with sodium hydride in tetrahydrofuran at 25 °C resulted in rapid conversion into a single diastereomer, **16** (65%, structure by X-ray crystallography).[17] A small amount of deprotection of the indole nitrogen atom occurred to give **16a** (6%, see experimental). On a larger scale, we observed the formation of a third compound, which is assigned as the –SPh epimer **17**. This is of no consequence because the CH–SPh group is destined to eventually become a carbonyl group. The stereochemical outcome of the intramolecular Michael reaction must result from axial protonation of the ester enolate to give **16** as the kinetic product. As will be seen later, the thermodynamic equilibration for the compounds **39** and **40** prefers the ester to be on the β-face (Scheme IX).

Oxidation of **16** with *m*-chloroperoxybenzoic acid gave the derived sulfoxide **19** (97%) as a mixture of diastereomers. Both sulfoxides could be further oxidized to a single sulfone, **19a** (see Experimental Section). An improvement in the overall yield of **19** was readily made by changing the order of the sequence from

(9) Prelog, V.; Battergay, J.; Taylor, W. I. *Helv. Chim. Acta* **1948**, *31*, 2244. Leuchs, H.; Schulte, H. *Ber. Dtsch. Chem. Ges.* **1942**, *75B*, 573 and 1522.

(10) Leuchs, H.; Schulte, H. *Ber. Dtsch. Chem. Ges.* **1943**, *76B*, 1038. Oesterlin, M.; Imoudsky, G. *Ber. Dtsch. Chem. Ges.* **1943**, *76B*, 172.

(11) This type of dehydrogenation has been used for the synthesis of *Aspidosperma* and *Strychnos* alkaloids. See: Camerman, A.; Camerman, N.; Kutney, J. P.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, 637. Crawley, G. C.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1971**, 685.

(12) Magnus, P.; Stamford, A.; Ladlow, M. *J. Am. Chem. Soc.* **1990**, *112*, 8210.

(13) Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* **1989**, *28*, 951.

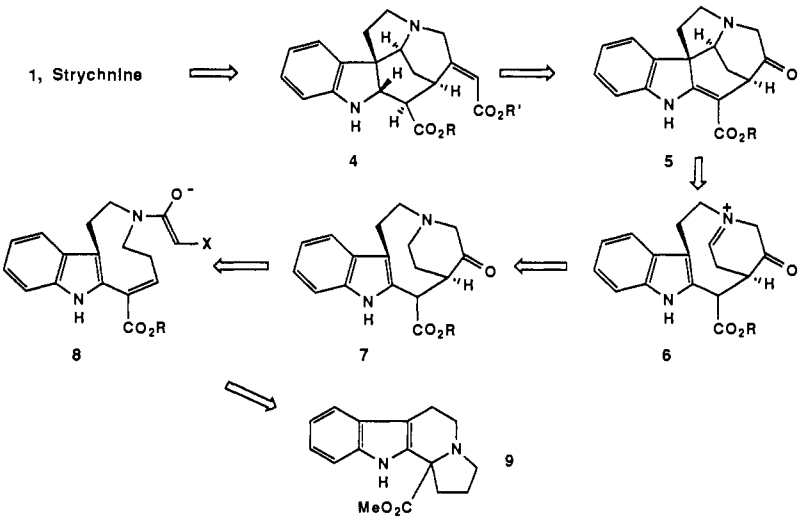
(14) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403.

(15) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bibao, A. *Synthesis* **1980**, 547.

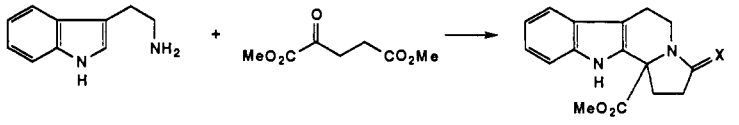
(16) Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C-S. *J. Chem. Soc., Chem. Commun.* **1989**, 518.

(17) The structures of **16**, **23**, **29**, **30**, **41**, **46**, and **50** were confirmed by single-crystal X-ray crystallography, and the information pertaining to this is available in the supplementary material.

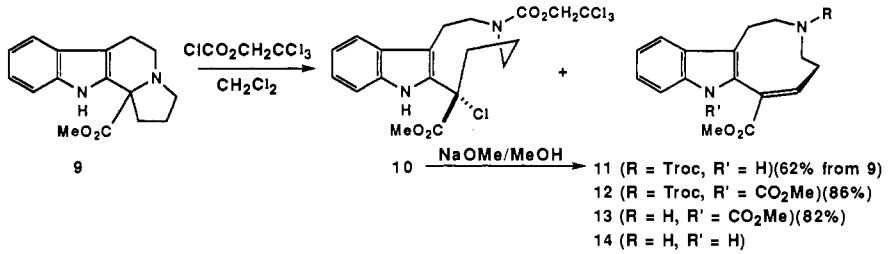
Scheme II



Scheme III



Scheme IV



15 to **19**. Oxidation of **15** with *m*-chloroperoxybenzoic acid gave the sulfoxide **18** (95%), which, when added to a suspension of sodium hydride in tetrahydrofuran at 0 °C, gave the diastereomeric sulfoxides **19** in excellent yield (98%). Prolonged exposure of **19** to the above reaction conditions resulted in equilibration with the –S(O)Ph epimer **17a**.

Before describing the subsequent transformations of **19**, it should be noted that it is not at all obvious how the sequence of transformations from the tetracyclic amine **9**, via **10**, **11**, **12**, **13**, **15**, and **18**, could be adapted into an enantiospecific synthesis of **19**, since **11**, **12**, **13** and **15** cannot be resolved. A solution to this dilemma is shown in Scheme VI.

Formation of the F-Ring of Strychnine from Nine-Membered Ring Intermediates by Intramolecular Conjugate Addition: Optically Active Series

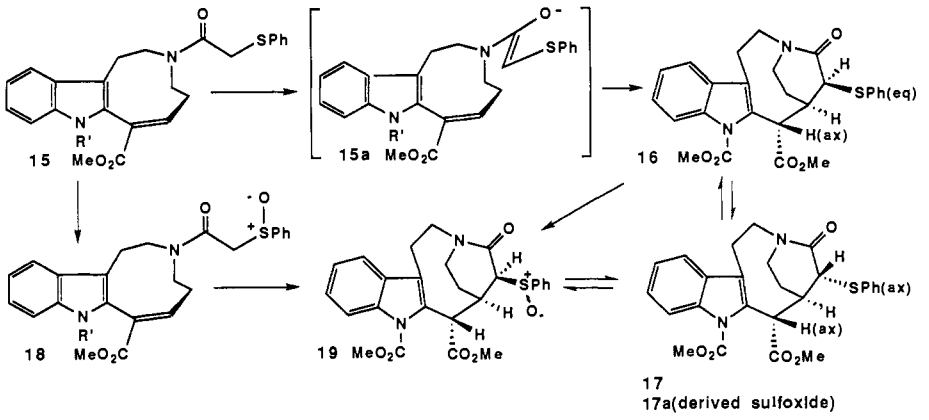
Acetylation of **13** with (+)-(*R*)-(*p*-tolylsulfinyl)acetic acid[18] activated by bis(2-oxo-3-oxazolidinyl)phosphinic acid gave the amide **20** (83%). Treatment of **20** with sodium hydride at 0 °C in tetrahydrofuran gave four diastereomers: **21** (13%), **22** (21%), **23** (36%), and **24** (6%). Fortunately, they were readily separable, and **23** gave crystals suitable for X-ray crystallography.[17] The structures shown for **23** and **24** (Scheme VI) represent the correct absolute configuration. Since the structure of **23** was unambiguously determined, it remained to establish the stereochemical relationship of the other diastereomers. Treatment of **23** with diazabicyclo[5.4.0.]undec-5-ene (DBU) gave an equilibrium mixture of **23** and **24**, thus showing that they are epimers at the C–S(O)Tol-*p* bond. Oxidation of **23** with *m*-chloroperoxybenzoic acid gave the sulfone **23a**, which is the mirror image of the sulfone **22a** derived from **22**. Similarly, **21**, on treatment with DBU, gave an equilibrium mixture of **21** and **22**. The derived sulfone **21a** is the mirror image of **24a**. Finally, treatment of the separated sulfones **22a** and **24a** with DBU gave the sulfones **21a** and **23a**, respectively. The sulfones **21a** and **24a** are enantiomers, as are **22a** and **23a**.

These experiments established that **21** and **22** are in the same absolute stereochemical series and **23** and **24** are in the mirror image series. Consequently, we could combine **21** and **22** (combined yield 34%) and **23** and **24** (combined yield 41%). While we have converted **23** and **24** into the hydroxyethylidene derivative **31** (racemic series, Scheme VII), no further work was conducted in this series because we were able to correlate an advanced synthetic intermediate with an optically active degradation product from strychnine.

(18) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613. Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227. Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105.

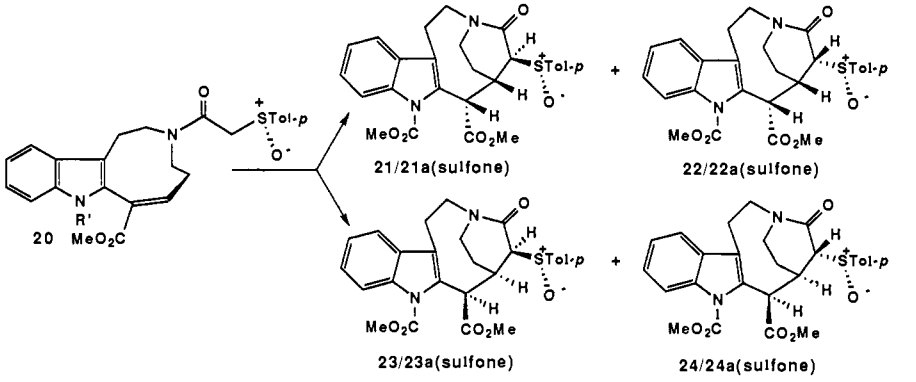
(19) We have used the Pummerer rearrangement in a number of indole–alkaloid syntheses. See: Magnus, P.; Katoh, T.; Matthews, I.; Huffman, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 6707. Magnus, P.; Gallagher, T.; Brown, P. *J. Am. Chem. Soc.* **1984**, *106*, 2105. Gallagher, T.; Huffman, J. C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

Scheme V[a]

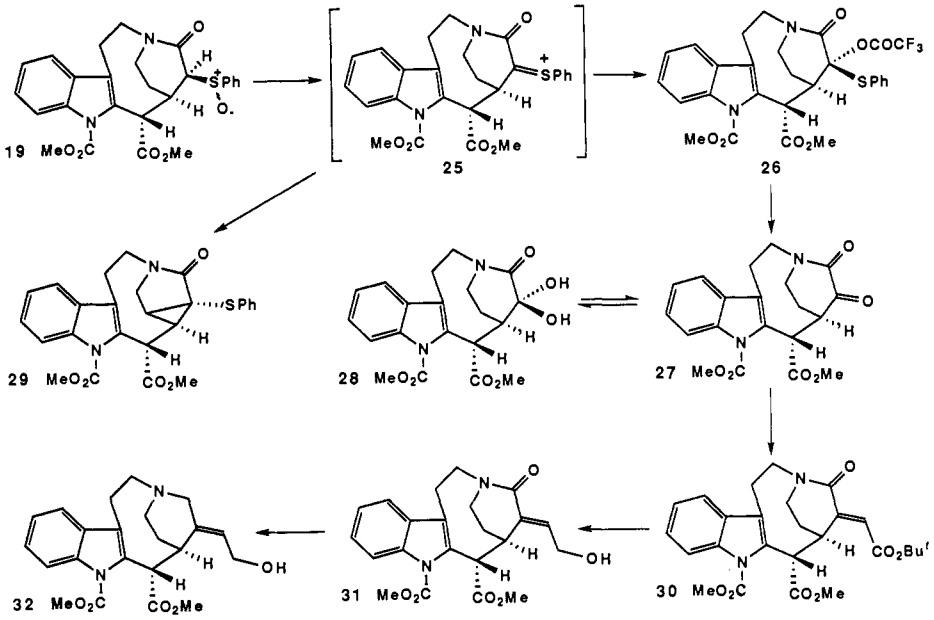


[a] R′ = CO_2Me.

Scheme VI. Optically Active Series



Scheme VII

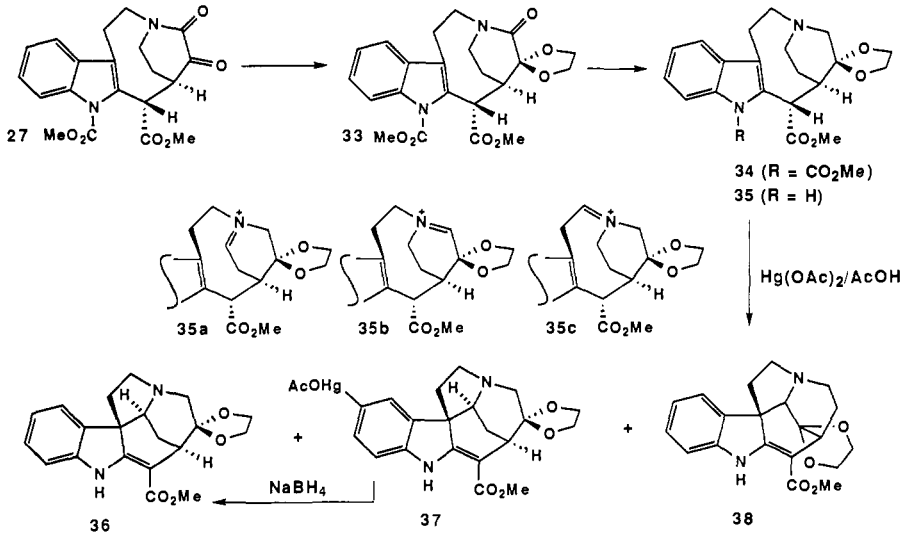


Stereospecific Synthesis of the Hydroxyethylidene Functionality

The initial plan was to convert the sulfoxides **19** via Pummerer rearrangement[19] into the α-keto lactam **27** and examine its conversion into the α,β-unsaturated ester **30**. If successful, it was hoped that we could reduce the amide functionality to give **32**, and examine its dehydrogenation to form the D-ring of strychnine (Scheme VII).

The sulfoxides **19** readily underwent Pummerer rearrangement to give the unstable α-phenylthio trifluoroacetate **26**. While we could isolate **26** and it was completely characterized, on a large scale, the crude product was used directly in the next step. Mercuric ion assisted hydrolysis of **26** gave the dione **27**, which (by ^1H NMR) was in equilibrium with the hydrate **28**. Treatment of the mixture **27/28** with the Wadsworth–Emmons reagent $Na^+ {}^-CHP(O)(OEt)_2CO_2Bu^t$ in dimethoxymethane at −40 °C gave the α,β-unsaturated ester **30** (84% from **19**). The stereochemistry of the newly introduced double bond was confirmed by X-ray crystallography.[17] We could not detect any other stereoisomers. While we could reduce **30** to the hydroxyethylidene functionality

Scheme VIII



32 ($NaBH_4$ on a derived mixed anhydride), we could not reduce the amide to give **32** without 1,4-reduction. Consequently, while this route provided a stereospecific solution to the hydroxyethylidene problem, it could not be incorporated into the synthesis of strychnine.

During the course of examining the Pummerer reaction, it was decided to conduct this transformation at higher temperatures in the ambitious hope that the intermediate sulfonium ion **25** might lose a proton to give the iminium ion **25a** which could lead to ring closure.[20] Heating the α-phenylthio trifluoroacetate at 200 °C resulted in a very clean conversion into the cyclopropane **29**! Apparently, the sulfonium ion **25** had undergone an unprecedented "homo-Pummerer" reaction.[21] The structure of **29** was confirmed by X-ray crystallography.[17]

Formation of the D-Ring of Strychnine by Tertiary Amine Oxidation

The dione **27** proved to be very resistant to the normal acid-catalyzed ketalization conditions (p-TsOH/$HOCH_2CH_2OH$/xylene at reflux for 4–5 days) to give the ketal **33** in low yield (ca. 40%). Presumably, while **27** will readily hydrate to give the glycol analogue of **28**, the next dehydration step would produce an oxonium ion adjacent to an amide carbonyl group. This is clearly a high-energy situation and causes the acid-catalyzed ketalization to be a difficult reaction. A simple solution to this problem is to take advantage of the ready hydration of **27** and use 2-bromoethanol in the presence of a base to effect the ketalization.[22] Treatment of **27** with 2-bromoethanol/DBU/toluene at 25 °C for 1 h gave the required ketal **33** (81%). The amide carbonyl group was reduced using BH_3·THF to provide the crucial precursor **34** (100%) to the ring D compounds.

While we examined the oxidation of **34** using the usual reagents[23] that are associated with the conversion of a tertiary amine into an iminium ion, namely, mercuric acetate (trifluoroacetate) and platinum oxide, it quickly became apparent that the indole protecting group (CO_2Me) reduced the nucleophilicity of the indole ring and prevented trapping of the iminium ion **35a**. The only products that could be observed were proton loss from **35a** to give the enamine and possibly traces of the desired transannular cyclization.[24] The β-aminoacrylate chromophore was readily detected by the characteristic fluorescence due to the UV absorption at 325 nm.

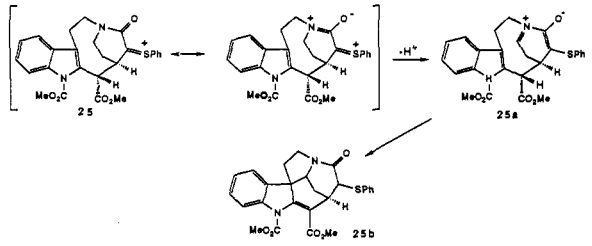
Treatment of **34** with sodium bicarbonate in methanol resulted in deprotection to the free indole **35** (72%) and, surprisingly, a small amount of the cyclized compound **36** (11%). This unexpected product presumably arose because of the presence of adventitious oxygen, but the result was not reproducible even when air was deliberately allowed into the reaction mixture. It was found that treatment of **35** with mercuric acetate/acetic acid for 60 h gave **36** (46%), the mercurated adduct **37** (6%), and the regioisomer **38** (3%). The mercurated indoline was reduced with sodium borohydride to give **36** (100%). The best yield of the pentacyclic amine **36** has been as high as 65% (including the material from reduction of **37**), but on average, it is 50% (Scheme VIII).

The dehydrogenation of **35** can, in principle, give rise to three iminium ions: the desired iminium ions **35a**, **35b**, and **35c**. The exocyclic iminium ion **35c** is considerably more strained than either **35a** or **35b** (MM2), but there is little, if any, difference in strain energy between **35a** and **35b**. The iminium ion **35b** is adjacent to the electron-deficient ketal and consequently would be expected to be a higher energy intermediate than **35a**.

Formation of the C-Ring of Strychnine with Incorrect Stereochemistry at C-13

The β-aminoacrylate double bond in **36** is resistant to a large number of reducing agents, but under strongly acidic conditions

(20) The Pummerer sulfonium ion intermediate **25** can, in principle, lose a proton to give the iminium ion **25a**, which should undergo transannular cyclization to give **25b**. It would be expected that the generation of **25a** would be a high-energy process and require high temperatures.

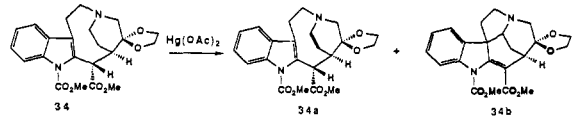


(21) For a review on homoenolization, see: Werstiuk, N. *Tetrahedron* **1983**, *39*, 205.

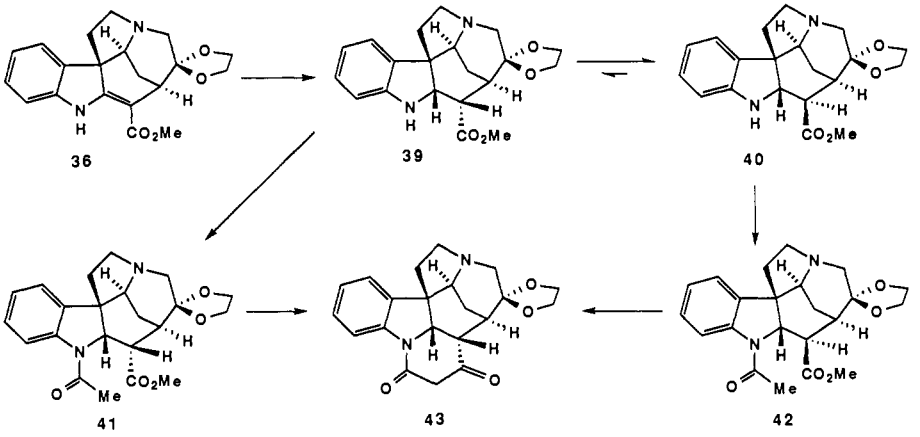
(22) Newkome, G. R.; Sauer, J. D.; McClure, G. L. *Tetrahedron Lett.* **1973**, *13*, 1599.

(23) Hudlicky, M. *Oxidations in Organic Chemistry*, ACS Monograph 186; American Chemical Society: Washington, DC, 1990; p 240.

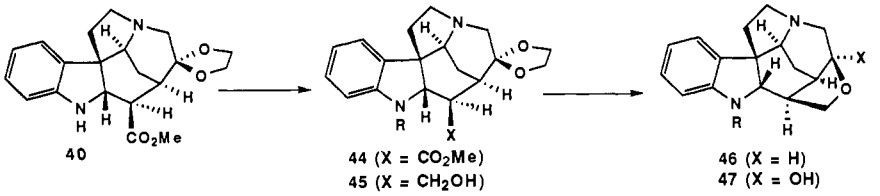
(24) The reaction of **34** with mercuric acetate was extremely slow and gave a small amount of enamine **34a** and traces of the cyclized product **34b**.



Scheme IX



Scheme X[a]



[a] R = $SO_2C_6H_4OMe$-*p*.

(concentrated H_2SO_4/MeOH), zinc dust reduces **36** to give **39** (88%). The stereochemistry assigned to **39** is based upon the vicinal coupling $J_{6,6a}$ = 4.5 Hz and the subsequent X-ray structure of the derived acetate **41**.[17] The 6α-carbomethoxy group in **39** is readily epimerized by treatment with sodium hydride in methanol to give **40** (100%). Characteristically, the vicinal coupling in the trans 6β-carbomethoxy derivative (natural strychnine stereochemistry) is larger, $J_{6,6a}$ = 9.9 Hz. Treatment of either **41** or **42** with sodium hydride in refluxing tetrahydrofuran gave the same β-keto amide **43** (98%), $J_{6,6a}$ = 6.8 Hz (Scheme IX). Since we have established that the thermodynamically preferred stereochemistry in **43** (see also Scheme I, 13-*epi*-isostrychnine **3**) is the opposite from that required in strychnine and the original isostrychnine–strychnine conversion could not be improved, this route was not pursued further.

Synthesis of the Relay Hemiketal 47 with Correct Stereochemistry at C-13

In order to permanently lock the stereochemistry at C-13, the epimeric ester **40** was first protected as the sulfonamide derivative **44** and the ester reduced using lithium borohydride to give **45**. The compound **45**, as directly isolated from the borohydride reduction, was still complexed with a boron hydride species. If this material is subjected to acid hydrolysis (neat $HClO_4$), the only compound formed is the reduced tetrahydrofuran derivative **46** (structure by X-ray crystallography).[17] Presumably, the intermediate oxonium ion in the ketal hydrolysis is reduced by the proximate N–BH_3 species. If the boron hydride complex of **45** is decomposed by treatment with diethanolamine, the uncomplexed alcohol **45** undergoes normal acid hydrolysis to give hemiketal **47** (Scheme X).

At this stage of the synthesis, we planned to examine the ring opening of hemiketal **47** to give a hydroxy ketone derivative and its subsequent conversion into strychnine. Rather than synthesize the hemiketal **47** from tryptamine (Scheme III), we decided to study the conversion of strychnine into **47**. Not only would this save a great deal of work, strychnine is one-third the price of tryptamine!

Conversion of Strychnine into the Hemiketal Relay 47

The first step in this correlation involves the conversion of strychnine into the Wieland–Gumlich aldehyde **48**.[25] The indoline nitrogen atom was protected as the (*p*-methoxyphenyl)sulfonyl derivative **49** (97%). Treatment of **49** with the standard catalytic osmylation conditions [OsO_4 (catalytic)/*N*-methylmorpholine *N*-oxide/THF/*t*-BuOH][26] proceeded in good yield (70–80%) to give the rearranged glycoside derivative **50** (structure by X-ray crystallography).[17] It proved to be surprisingly difficult to reduce the lactol **50** to the tetrol **51** in a reproducible manner. Lithium borohydride in tetrahydrofuran proved to be the best conditions and gave **51** in modest, isolated yields (43–56%). The last step of this sequence involves the oxidative cleavage of the vicinal triol side chain to arrive at the relay hemiketal **47**. Treatment of **51** with periodic acid in trifluoroacetic acid/MeOH/H_2O cleanly provided the relay **47** (55–61%) (Scheme XI). While some of the isolated yields in this sequence are modest, it does allow gram quantities of **47** to be made in three steps from the protected Wieland–Gumlich aldehyde (WGA) **48**. Furthermore, conversion of WGA into **47** may be carried out with only one chromatographic purification at the final stage. In this way, **47** is obtained in 40% overall yield from **48**.

Conversion of the Relay 47 into the Wieland–Gumlich Aldehyde and Strychnine

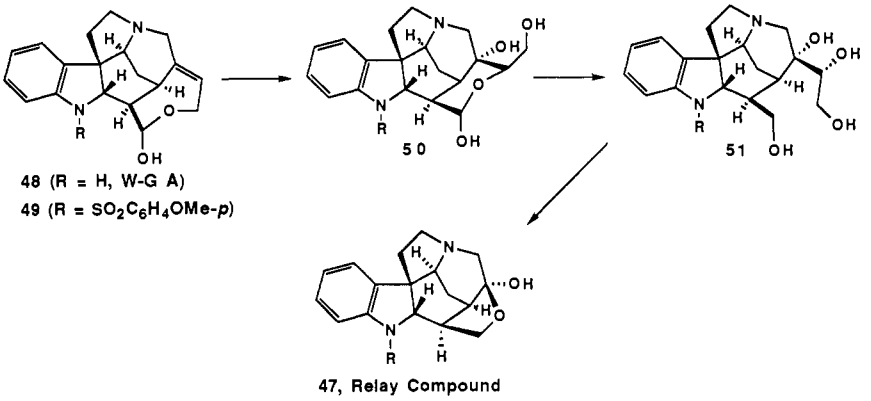
The first, and most crucial step, is the conversion of the hemiketal **47** into a ring-opened keto alcohol derivative, **52**. It was decided that a bulky silylating reagent would be the most likely species to irreversibly trap the open form **47a**.[27] Treatment of **47** with triisopropylsilyl triflate/DBU/CH_2Cl_2 from 0 to 25 °C gave the ketone **52** (69%). Treatment of **52** with $(EtO)_2P(O)CH_2CN$/$KN(SiMe_3)_2$/THF at 25 °C gave the two geometrical

(25) Wieland, H.; Gumlich, W. *Liebigs Ann. Chem.* **1932**, *494*, 191. Wieland, H.; Kaziro, K. *Liebigs Ann. Chem.* **1933**, *506*, 60. Deyrup, J. A.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1962**, *45*, 2266. Hymon, J. R.; Schmid, H.; Karrer, P.; Boller, A.; Els, H.; Fahrni, P.; Fürst, A. *Helv. Chim. Acta* **1969**, *52*, 1564. Anet, F. A. L.; Robinson, R. *J. Chem. Soc.* **1955**, 2253.

(26) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

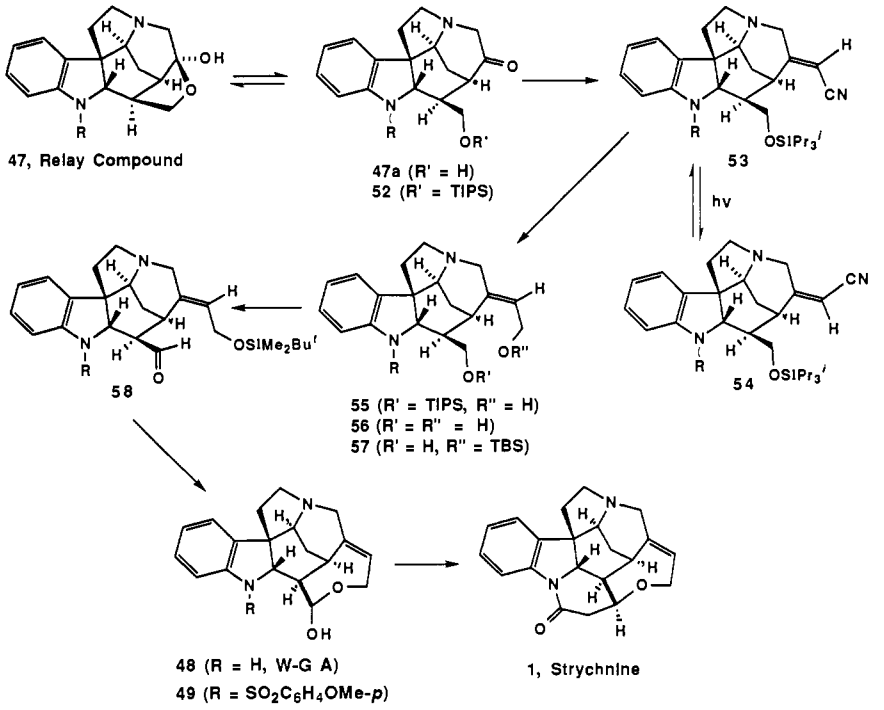
(27) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

Scheme XI[a]



[a] R = $SO_2C_6H_4OMe$-*p*.

Scheme XII[a]



[a] R = $SO_2C_6H_4OMe$-*p*.

isomers **53** (*E*) and **54** (*Z*) (overall 72%) in a ratio of 3:2. The two isomers were readily separated, and the incorrect stereoisomer could be recycled by irradiation (tungsten) in benzene to give a mixture of **53** and **54**. This enabled the yield of **53** to be raised to 52% after one cycle. Reduction of **53** using diisobutylaluminum hydride (workup) followed by sodium borohydride gave the required allylic alcohol **55** (31% for the two steps). Desilylation of **55** by treatment with 2 N HCl/MeOH gave the diol **56** (81%). The diol **56** was also made by reduction of **49** with diisobutylaluminum hydride in 90% yield.

The synthesis of strychnine and the Wieland–Gumlich aldehyde was completed by the following sequence. Selective silylation of the allylic hydroxyl group in **56** was accomplished by treatment with *t*-$BuMe_2SiOTf/DBU/CH_2Cl_2$ at −20 °C to give **57**. Oxidation of **57** with SO_3·pyridine/Me_2SO/Et_3N gave the unstable aldehyde **58** (42% for the two steps). Desilylation of **58** using the pyridine–HF complex gave the protected Wieland–Gumlich aldehyde **49** (60%), which was deprotected by treatment with sodium anthracenide[28] to give **48** (85%). The conversion of **48** into strychnine was reported by Robinson in 1953, and accordingly, treatment of **48** with $CH_2(CO_2H)_2/NaOAc/Ac_2O$ gave strychnine (**1**) (70%) (Scheme XII).[29]

While the latter steps allowed the completion of the synthesis of strychnine, we were not satisfied with the lack of stereocontrol in the conversion of the ketone **52** into the α,β-unsaturated cyanide **53**. As a consequence, we briefly examined an alternative approach. Treatment of the relay compound **47** with lithium 2-(phenylthio)acetylide/THF/−10–0 °C gave the adduct **59** (40–50%), which upon mild acidic hydrolysis gave phenyl thioester **60** (85%). When the activated ester **60** was treated with NaH/THF/−20 to −15 °C, the β-lactone **61** was formed and subsequently converted more slowly into the lactone **62** (70%). The tertiary alcohol in **62** could be acetylated using isopropenyl acetate/PTSA to give **63** (80%), but all attempts to convert it into the α,β-unsaturated lactone **64** were unsuccessful (Scheme XIII).

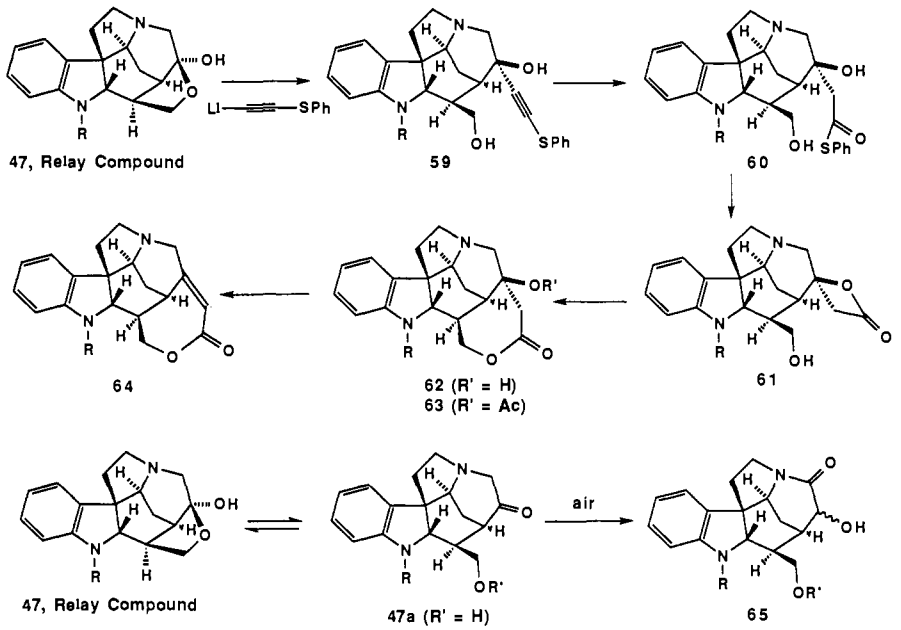
It is worth noting that attempts to convert the hemiketal relay compound **47** directly into lactone **64** using Wittig-type chemistry

(28) Quaal, K. S.; Sungchul, J.; Kim, Y. M.; Closson, W. D.; Zubieta, J. A. *J. Org. Chem.* **1978**, *43*, 1311.

(29) Anet, F. A. L.; Robinson, R. *Chem. Ind.* **1953**, 245.

(30) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850. Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 349.

Scheme XIII[a]



[a] R = $SO_2C_6H_4OMe$-*p*.

($(EtO)_2P(O)CH_2COCl$ or Ph_3PCCO) were unsuccessful.[30] The only product that could be isolated was the air oxidation adduct **65**.[31] Even if air was carefully excluded, none of the desired lactone **64** was formed.

Summary

Overall, the synthesis of strychnine and the Wieland–Gumlich aldehyde is reduced to the stereochemical problem of converting the ketone **52** into the hydroxyethylidene derivative **55** in a stereospecific manner. While the route shown in Scheme XII is successful and does allow the incorrect stereoisomer **54** to be recycled, it would be more satisfactory to have a completely stereospecific route. The conversion of **57** via the aldehyde **58** into the Wieland–Gumlich aldehyde does provide a better conclusion for the final steps because it avoids the isostrychnine into strychnine conversion and proceeds in reasonable yields.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer either neat or in $CHCl_3$, as indicated. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3B UV/vis spectrophotometer in the indicated solvents. ^1H NMR spectra were recorded on a GE 300-MHz spectrometer in the indicated solvent and are reported in ppm downfield from TMS. Elemental analyses were performed by Midwest Microlab in Indianapolis, IN. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Preparative layer chromatography was performed using Merck 60H F_{254} silica gel, glass-supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel.

Air- and moisture-sensitive reactions were performed under usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C, then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use. Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and benzene were distilled from calcium hydride under argon.

β,β,β-Trichloroethyl 7-Chloro-7-(methoxycarbonyl)-1,2,3,4,5,6,7,8-octahydroazonino[5,4-*b*]indole-3-carboxylate (10) and β,β,β-Trichloroethyl 7-(Methoxycarbonyl)-1,2,3,4,5,8-hexahydroazonino[5,4-*b*]indol-3-carboxylate (11). To a solution of the amine **9** (2.991 g, 0.011 mmol) in dichloromethane (40 mL) at 25 °C was added β,β,β-trichloroethyl chloroformate (2.814 g, 0.0133 mmol), and the solution was stirred at 25 °C for 40 h. The mixture was concentrated in vacuo and the residue adsorbed onto silica gel (25 g). The preadsorbed mixture was applied to a silica gel column and the column eluted with dichloromethane followed by dichloromethane/EtOAc (5:1) to give the chloro ester **10** (4.2 g, 79.2%) and the α,β-unsaturated ester **11** (0.45 g, 10%). On a large scale, the ratio of **10**:**11** changes. For example, starting with **9** (49 g) in dichloromethane (3 L), we obtained **10** (43.58 g, 50%) and **11** (22.24 g, 27%).

For the Chloroester 10: colorless oil; IR ($CHCl_3$) 3465, 1720, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.85 and 8.78 (2s), 7.61–7.57 (m), 7.44 (1H, d, J = 8 Hz), 7.27–7.13 (m), 5.26 (d, J = 12 Hz), 4.99 (J_{AB} = 12 Hz), 4.85 (m), 4.74 (d, J = 11.5 Hz), 4.63 (d, J = 11.5 Hz), 4.55 (t, J = 3.8 Hz), 4.50 (d, J = 3.8 Hz), 4.14 (d, J = 7.2 Hz), 3.81 (d, J = 3.8 Hz), 3.18–3.09 (m), 2.90–2.65 (m), 1.85 (dd, J = 15 and 2 Hz), 1.90–1.80 (m), 1.60 and 1.45 (m); carbamate resonance causes extensive line broadening and, in some instances, doubling of signals making integration difficult; HRMS calcd for $C_{19}H_{20}Cl_4N_2O_4$ 482.0151, found 482.0149. Anal. Calcd for $C_{19}H_{20}Cl_4N_2O_4$: C, 47.33; H, 4.18; N, 5.18. Found: C, 47.10; H, 4.05; N, 4.97.

For the α,β-Unsaturated ester 11: colorless foam; IR ($CHCl_3$) 3465, 1745, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30–8.27 (1H, 2s), 7.58–7.05 (5H, m), 4.75 (2H, 2s), 3.72 and 3.70 (3H, 2s), 3.60–3.48 (4H, m), 3.10–3.00 (2H, m), 2.25 (2H, m); carbamate resonance causes extensive line broadening and, in some instances, doubling of signals; HRMS calcd for $C_{19}H_{19}Cl_3N_2O_4$ 444.0381, found 444.0385.

Conversion of the Chloro Ester 10 into the α,β-Unsaturated Ester 11. To a solution of the chloro ester **10** (13.44 g, 28 mmol) in methanol (600 mL) was added a freshly prepared solution of sodium methoxide (2 M, 70 mL, 140 mmol), and the mixture was stirred at 25 °C for 0.5 h. The mixture was neutralized with aqueous $KHSO_4$ and extracted with dichloromethane (2 × 250 mL). The aqueous phase was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (2 × 100 mL). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo to give **11** (12.30 g, 98.5%) in greater than 95% purity (NMR) for direct use in the next step.

β,β,β-Trichloroethyl 7,8-Bis(methoxycarbonyl)-1,2,3,4,5,8-hexahydroazonino[5,4-*b*]indol-3-carboxylate (12). To a mechanically stirred solution of **11** (7.40 g, 16.60 mmol) in dichloromethane (150 mL) at 0 °C was added dropwise (0.75 h) aqueous sodium hydroxide (50%, 150 mL). Benzyltriethylammonium chloride (0.5 g) was added followed by syringe-pump addition of methyl chloroformate [15.4 mL in CH_2Cl_2 (50 mL)] over a period of 3 h, maintaining the temperature at 0 °C. After an additional 2 h at 0 °C, the mixture was diluted with dichloromethane (500 mL) followed by brine (300 mL). The aqueous layer was separated

(31) Leuchs, H.; Reich *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2417. Leuchs, H.; Bendixsohn, W. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 1443. Kotake, M.; Mitsuwa, T. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 231.

and extracted with dichloromethane (2 × 250 mL). The combined organic layers were washed with 10% aqueous citric acid (200 mL) and brine (200 mL) and dried ($MgSO_4$). Evaporation in vacuo gave **12** (7.20 g, 86%) as a foam: IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (dt), 7.51 (m), 7.38–7.16 (m), 5.02 (d, J = 12 Hz), 4.80 (d, J = 11.3 Hz), 4.66 (d, J = 12 Hz), 4.43 (d, J = 12.5 Hz), 4.05–3.95 (m), 3.94 (3H, s), 3.71 (s), 3.24–3.04 (4H, m), 2.36–2.19 (1H, m), 2.85–2.65 (2H, m); carbamate resonance causes extensive line broadening and, in some instances, doubling of signals; HRMS calcd for $C_{21}H_{21}Cl_3N_2O_6$ 502.0465, found 502.0460.

7,8-Bis(methoxycarbonyl)-1,2,3,4,5,8-hexahydroazonino[5,4-*b*]indole (13). To a solution of **12** (2.00 g, 3.972 mmol) in tetrahydrofuran (80 mL) was added acetic acid (20 mL) followed by activated zinc dust (2.60 g). The mixture was stirred at 25 °C for 10 h, and the milky solution was decanted from the zinc metal residues. The zinc residues were washed with tetrahydrofuran (300 mL), and the combined solution was concentrated (ca. 100 mL). The concentrate was cooled to 0 °C, neutralized with saturated aqueous Na_2CO_3 (150 mL), and extracted with dichloromethane (3 × 100 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give **13** (1.071 g, 82.2%). Because of the carbamate resonance problems, the derivative **14** was characterized. A small portion of **13** was hydrolyzed with aqueous sodium hydroxide to give **14**: mp 200 °C dec; IR ($CHCl_3$) 3465, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, b s), 7.52 (1H, d, J = 9 Hz), 7.37 (1H, d, J = 9 Hz), 7.29 (1H, t), 7.21 (1H, d, J = 8 Hz), 7.15 (1H, t), 3.78 (3H, s), 3.20–2.98 (6H, m), 2.36 (2H, m). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.36; H, 6.70; N, 10.03.

7,8-Bis(methoxycarbonyl)-3-((phenylthio)acetyl)-1,2,3,4,5,8-hexahydroazonino[5,4-*b*]indole (15). To a solution of the amine **13** (12.5 g, 38.1 mmol) in dichloromethane (200 mL) under argon at 0 °C was added (phenylthio)acetic acid (6.41 g, 38.1 mmol) followed by triethylamine (10.6 mL). The solution was stirred for 5 min and solid bis(2-oxo-3-oxazolidinyl)phosphinic acid (9.70 g, 38.1 mmol) added in one portion. After 1.5 h, the mixture was diluted with dichloromethane (200 mL) followed by 2 N hydrochloric acid (200 mL). The organic layer was washed with water (400 mL), dried ($MgSO_4$), and evaporated in vacuo to give **15** (18 g, crude). The amide was purified by chromatography over silica gel eluting with EtOAc/CH_2Cl_2 (9:1) to give **15** (13.0 g, 71%): IR (CH_2Cl_2) 1725, 1640 cm^{-1}; LRMS (M^+) m/e 478, $C_{26}H_{26}N_2O_5S$ 478. The ^1H NMR was severely broadened by two sets of carbamate resonance.

7α,8-Bis(methoxycarbonyl)-4-oxo-5β-(phenylthio)-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole (16). The α,β-unsaturated ester **15** (196 mg, 0.41 mmol) in dry tetrahydrofuran (5 mL) was treated with excess sodium hydride (30 mg, 1.2 mmol) at 25 °C. The mixture was stirred at 25 °C for 10 min and the reaction quenched with ethyl acetate (30 mL)/water (3 mL). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give **16**. Purification by chromatography over silica gel eluting with dichloromethane/petroleum ether (5:1) gave **16** (127 mg, 65%) and the deprotected compound **16a** (10 mg, 6%). On a larger scale, the initial product **16** was partially converted into the thiophenyl epimer **17**.

16: mp 230–231 °C (methanol); IR (CH_2Cl_2) 1735, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, d, J = 8 Hz), 7.64 (2H, d, J = 8 Hz), 7.52 (1H, d, J = 9 Hz), 7.48–7.22 (5H, m), 4.44 (1H, dd, J = 5 Hz), 4.52 (1H, d, J = 1 Hz), 3.94 (3H, s), 3.79 (1H, d, J = 3.5 Hz), 3.67 (1H, b s), 3.59 (3H, s), 3.43 (1H, m), 3.28 (1H, m), 2.80 (1H, d, J = 18 Hz), 2.52 (2H, m), 1.78 (1H, m), 1.57 (1H, m). Anal. Calcd for $C_{26}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.86. Found: C, 65.35; H, 5.48; N, 5.94. **16** was further characterized by single-crystal X-ray crystallography.

16a: mp 237–238 °C (methanol); IR (CH_2Cl_2) 3420, 1725, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.6 (1H, b s), 7.56 (1H, d, J = 1 Hz), 7.45–7.1 (8H, m), 4.45 (1H, dd, J = 4 Hz), 4.52 (1H, d, J = 2 Hz), 4.48 (1H, d, J = 2Hz), 3.80 (3H, s), 3.30 (2H, m), 3.04 (1H, b s), 2.90 (1H, d, J = 5 Hz), 2.60 (1H, b s), 2.65 (1H, b), 1.60 (2H, m). Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.54; H, 5.75; N, 6.66. Found: C, 68.24; H, 5.65; N, 6.81.

7,8-Bis(methoxycarbonyl)-3-[(phenylsulfinyl)acetyl]-1,2,3,4,5,8-hexahydroazonino[5,4-*b*]indole (18). To a solution of the amide **15** (0.50 g, 1.05 mmol) in dichloromethane (40 mL) at 0 °C was added sodium bicarbonate (1 g) followed by *m*-chloroperoxybenzoic acid (237 mg, 1.1 mmol). The mixture was stirred at 0 °C for 30 min and quenched with aqueous sodium bisulfite (10 mL). The solution was extracted with dichloromethane (2 × 10 mL), dried (Na_2SO_4), and evaporated in vacuo to give **18** (494 mg, 95%). This material was used directly in the next step, without further purification.

7α,8-Bis(methoxycarbonyl)-4-oxo-5β-(phenylsulfinyl)-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole (19). To a suspension of sodium hydride (0.880 g, 30.4 mmol) in dry tetrahydrofuran (50 mL) at 0 °C was added a solution of **18** (5.0 g, 10.12 mmol) in tetrahydrofuran (250 mL) slowly over 0.75 h. The mixture was stirred at 0 °C for 1 h and quenched with ethyl acetate/water (200 mL, 10:1). The solution was extracted with ethyl acetate (3 × 200 mL), and the combined extracts were washed with saturated aqueous ammonium chloride (200 mL) and brine (200 mL), dried (Na_2SO_4), and evaporated in vacuo to give **19** (4.90 g, 98%) as a mixture of two diastereomeric sulfoxides. The sulfoxides **19** can be used directly in the next step. On a small scale, they were separated by chromatography over silica gel.

Less polar sulfoxide: mp 250–252 °C dec (methanol); IR ($CHCl_3$) 1735, 1655, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.2 (1H, d, J = 6 Hz), 8.05 (1H, d, J = 6 Hz), 7.54 (5H, m), 7.2 (1H, t, J = 7 Hz), 7.15 (1H, t, J = 7 Hz), 4.3 (1H, b m), 4.15 (1H, d, J = 3 Hz), 4.0 (3H, s), 3.78 (3H, s), 3.6 (1H, d, J = 1 Hz), 3.3 (2H, m), 2.8 (1H, d, J = 7 Hz), 2.5 (2H, m), 1.85 (1H, m), 1.7 (1H, m); HRMS calcd for $C_{26}H_{26}N_2O_6S$ 494.1511, found 494.1504.

More polar sulfoxide: mp 242–244 °C dec (methanol). Treatment of **16** (140 mg, 0.29 mmol) in dichloromethane (5 mL) with *m*-chloroperoxybenzoic acid (53 mg, 1.05 equiv) gave the diastereomeric sulfoxides **19** (137 mg, 97%). Further oxidation of **19** with *m*-chloroperoxybenzoic acid converted the two sulfoxides into the same sulfone **19a**. The derived sulfone **19a** has mp 249–250 °C. Anal. Calcd for $C_{26}H_{26}N_2O_7S$: C, 61.17; H, 5.13; N, 5.49. Found: C, 60.71; H, 5.18; N, 5.33.

(+)-7,8-Bis(methoxycarbonyl)-3-[((4-methylphenyl)sulfinyl)acetyl]-1,2,3,4,5,8-hexahydroazonino[5,4-*b*]indole (20). To a solution of amine **13** (1.06 g, 3.2 mmol) in dichloromethane (10 mL) under argon at 0 °C was added (+)-((4-methylphenyl)sulfinyl)acetic acid (643 mg, 3.2 mmol) followed by triethylamine (0.9 mL). The solution was stirred for 5 min and solid bis(2-oxo-3-oxazolidinyl)phosphinic acid (825 mg, 3.2 mmol) added in one portion. After 1 h, the mixture was diluted with dichloromethane (20 mL) followed by 2 N hydrochloric acid (20 mL). The organic layer was washed with water (40 mL), dried ($MgSO_4$), and evaporated in vacuo to give **20** (2.3 g, crude). The amide was purified by chromatography over silica gel eluting with EtOAc/CH_2Cl_2 (9:1) to give **20** (1.36 g, 83%): IR (CH_2Cl_2) 1725, 1640, 1440, 1360, 1320, 1240 cm^{-1}; the ^1H NMR was severely broadened by two sets of carbamate resonance; HRMS calcd for $C_{27}H_{28}N_2O_6S$ 508.1668, found 508.1674.

7α,8-Bis(methoxycarbonyl)-4-oxo-5β-[(4-methylphenyl)sulfinyl]-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole (21, 22, 23, and 24). To a suspension of sodium hydride (0.497 g, 20.7 mmol) in dry tetrahydrofuran (40 mL) at 0 °C was added a solution of **20** (2.0 g, 3.9 mmol) in tetrahydrofuran (75 mL) slowly over 0.75 h. The mixture was stirred at 0 °C for 1 h and quenched with ethyl acetate/water (100 mL, 9:1). The solution was extracted with ethyl acetate (3 × 75 mL), and the combined extracts were washed with saturated aqueous ammonium chloride (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated in vacuo to give a mixture of **21–24**. The mixture was separated by HPLC to give, in order of elution, **23** (713 mg, 35.6%), **21** (269 mg, 13.4%), **22** (419 mg, 20.9%), and **24** (124 mg, 6.2%), total 76.1%.

Least polar sulfoxide 23: R_f 0.56 (CH_2Cl_2/MeOH, 19:1); mp 244 °C (EtOAc/petroleum ether); IR (CH_2Cl_2) 2950, 1730, 1650, 1440, 1360, 1330, 1220, 1130, 1080, 1040, 905, 800, 730 cm^{-1}; $[\alpha]^{20}_D$ −13.7° (*c*, 5.4 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.51 (1H, dd, J = 7.1 and 1.7 Hz), 7.41–7.27 (4H, m), 4.39 (1H, ddd, J = 13.4, 4.6, and 1.7 Hz), 3.97 (3H, s), 3.94–3.87 (2H, m), 3.76 (1H, ddd, J = 14.1, 10.7, and 5.5 Hz), 3.63 (3H, s), 3.62 (1H, d, J = 4.5 Hz), 3.08 (1H, ddd, J = 14.9, 12.4, and 4.4 Hz), 2.79 (1H, d, J = 14 Hz), 2.67–2.55 (2H, m), 2.44 (3H, s), 2.46–2.36 (1H, m), 1.60–1.48 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.47 (t), 21.51 (q), 22.28 (t), 36.95 (d), 46.06 (t), 47.39 (d), 49.34 (t), 52.29 (q), 53.60 (q), 76.10 (d), 115.67 (d), 118.13 (d), 119.78 (s), 123.22 (d), 124.66 (d), 125.23 (d), 128.62 (s), 129.93 (d), 132.42 (s), 135.45 (s), 138.71 (s), 142.39 (s), 151.55 (s), 167.82 (s), 170.66 (s). Anal. Calcd for $C_{27}H_{28}N_2O_6S$: C, 63.76; H, 5.55; N, 5.51; S, 6.30. Found: C, 63.67; H, 5.55; N, 5.53; S, 6.27. **23** was further characterized by single-crystal X-ray crystallography.

Sulfoxide 21: R_f 0.44 (CH_2Cl_2/MeOH, 19:1); IR (CH_2Cl_2) 2957, 1739, 1655, 1479, 1460, 1443, 1368, 1331, 1123, 1136, 1086, 808 cm^{-1}; $[\alpha]^{20}_D$ −23.3° (*c* 3.3 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08

(1H, d, J = 8.8 Hz), 7.64 (2H, d, J = 8.2 Hz), 7.51 (1H, dd, J = 7.4 and 1.6 Hz), 7.39–7.26 (4H, m), 4.49 (1H, dd, J = 13.2 and 4.0 Hz), 3.99 (3H, s), 3.86 (1H, t, J = 3.3 Hz), 3.84–3.76 (1H, m), 3.69–3.65 (1H, m), 3.60 (1H, d, J = 4.6 Hz), 3.57 (3H, s), 3.08 (1H, ddd, J = 14.9, 13.0, and 5.1 Hz), 2.78 (1H, d, J = 13.7 Hz), 2.61 (1H, dt, J = 13.0 and 3.3 Hz), 2.43 (3H, s), 2.49–3.37 (1H, m), 2.31–2.19 (1H, m), 1.61–1.49 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.64 (t), 21.43 (q), 22.27 (t), 38.54 (d), 45.81 (t), 47.98 (d), 48.89 (t), 52.23 (q), 53.67 (q), 75.35 (d), 115.66 (d), 118.26 (d), 120.20 (s), 123.29 (d), 124.36 (d), 125.21 (d), 128.69 (s), 129.96 (d), 131.94 (s), 135.10 (s), 139.48 (s), 142.12 (s), 151.91 (s), 167.60 (s), 170.89 (s); HRMS calcd for $C_{27}H_{28}N_2O_6S$ 508.1668, found 508.1716.

Sulfoxide 22: R_f 0.36 (CH_2Cl_2/MeOH, 19:1); IR (CH_2Cl_2) 3050, 2980, 1735, 1640, 1420, 1360, 1330, 1250, 1130, 1035, 890 cm^{-1}; $[\alpha]^{20}_D$ +114.2° (c 2.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, d, J = 8.3 Hz), 7.91 (2H, d, J = 8.2 Hz), 7.49 (1H, d, J = 7.9 Hz), 7.39–7.27 (4H, m), 4.28–4.19 (2H, m), 4.10 (1H, d, J = 3.7 Hz), 3.99 (3H, s), 3.74 (3H, s), 3.58 (1H, d, J = 1.6 Hz), 3.84–3.76 (1H, m), 3.69–3.65 (1H, m), 3.60 (1H, d, J = 4.6 Hz), 3.57 (3H, s), 3.18–3.32 (2H, m), 2.78 (1H, d, J = 14.9 Hz), 2.39 (3H, s), 2.56–2.39 (1H, m), 1.88–1.74 (1H, m), 1.66–1.54 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.73 (t), 21.30 (q), 26.97 (t), 37.04 (d), 45.25 (d), 45.80 (t), 48.49 (t), 52.35 (q), 53.48 (q), 74.51 (d), 115.50 (d), 117.96 (d), 119.46 (s), 123.07 (d), 125.09 (d), 126.53 (d), 128.43 (s), 129.27 (d), 133.06 (s), 135.43 (s), 141.51 (s), 141.58 (s), 151.40 (s), 169.41 (s), 171.00 (s); HRMS calcd for $C_{27}H_{28}N_2O_6S$ 508.1668, found 508.1676.

Most polar sulfoxide 24: R_f 0.25 (CH_2Cl_2/MeOH, 19:1); IR (CH_2Cl_2) 2960, 1735, 1650, 1485, 1455, 1432, 1360, 1334, 1124, 1137, 1076, 810 cm^{-1}; $[\alpha]^{20}_D$ −17.3° (c 3.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, d, J = 8.8 Hz), 7.67 (2H, d, J = 8.1 Hz), 7.54 (1H, dd, J = 7.4 and 1.6 Hz), 7.39–7.31 (4H, m), 4.45 (1H, dd, J = 13.1 and 4.2 Hz), 3.95 (3H, s), 3.86 (1H, t, J = 3.3 Hz), 3.85–3.69 (1H, m), 3.70–3.60 (1H, m), 3.62 (1H, d, J = 4.5 Hz), 3.57 (3H, s), 3.10 (1H, ddd, J = 14.7, 13.1, and 5.0 Hz), 2.76 (1H, d, J = 13.7 Hz), 2.65 (1H, dt, J = 13.0 and 3.3 Hz), 2.44 (3H, s), 2.50–2.35 (1H, m), 2.30–2.15 (1H, m), 1.62–1.50 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.81 (t), 21.47 (q), 22.30 (t), 38.61 (d), 45.88 (t), 48.17 (d), 48.90 (t), 52.26 (q), 53.71 (q), 75.40 (d), 116.06 (d), 118.29 (d), 120.25 (s), 123.22 (d), 124.37 (d), 125.24 (d), 128.75 (s), 130.07 (d), 131.78 (s), 135.21 (s), 139.45 (s), 142.17 (s), 151.87 (s), 167.56 (s), 170.78 (s); HRMS calcd for $C_{27}H_{28}N_2O_6S$ 508.1668, found 508.1718.

Treatment of **21** with diazabicyclo[5.4.0]undec-5-ene (DBU) in dichloromethane produced an equilibrium mixture of **21** and **22**. Similarly, treatment of **23** gave an equilibrium mixture of **23** and **24**. Oxidation of **21** (MCPBA) gave the derived sulfone **21a**. Similarly, **22** gave **22a**, **23** gave **23a**, and **24** gave **24a**. The ^{1}H NMR spectra of **21a** and **24a** are identical, as are those of **22a** and **23a**. Treatment of **22a/24a** with DBU gave **21a/23a**, respectively.

21a/24a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 7.7 Hz), 8.06 (2H, d, J = 8.1 Hz), 7.51 (1H, dd, J = 8.8 and 1.6 Hz), 7.40–7.26 (2H, m), 7.36 (2H, d, J = 8.1 Hz), 4.49–4.41 (1H, m), 4.39–4.30 (1H, m), 4.25 (1H, d, J = 3.8 Hz), 3.99 (3H, s), 3.86–3.82 (1H, m), 3.70 (3H, s), 3.35–3.21 (2H, m), 2.88–2.78 (1H, m), 2.53–2.41 (2H, m), 2.44 (3H, s), 1.93–1.65 (2H, m).

22a/23a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, d, J = 7.5 Hz), 7.86 (2H, d, J = 8.8 Hz), 7.53 (1H, dd, J = 8.5 and 1.4 Hz), 7.42–7.28 (2H, m), 7.40 (2H, d, J = 8.8 Hz), 4.52–4.40 (1H, m), 4.23 (1H, t, J = 2.7 Hz), 4.06–3.98 (1H, m), 4.01 (3H, s), 3.95–3.84 (1H, m), 3.62 (3H, s), 3.49 (1H, d, J = 5.2 Hz), 3.04 (1H, ddd, J = 16.2, 11.1, and 5.1 Hz), 2.85–2.79 (1H, m), 2.66 (1H, dt, J = 13.0 and 3.2 Hz), 2.50–2.35 (2H, m), 2.47 (3H, s), 1.58–1.44 (1H, m).

7α,8-Bis(methoxycarbonyl)-4-oxo-5β-(phenylthio)-5α-(trifluoroacetoxy)-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole (26). To a mixture of the diastereomeric sulfoxides **19** (137 mg, 0.277 mmol) in dichloromethane (2 mL) at 0 °C was added 2,6-di-*tert*-butyl-4-methylpyridine (10 mg) followed by trifluoroacetic anhydride (200 μL, 5 equiv). The mixture was stirred at 0 °C for 15 min, then diluted with dichloromethane (30 mL), and washed with aqueous $NaHCO_3$ solution (30 mL). The organic layer was dried (MgSO4) and evaporated in vacuo to give a yellow oil. Purification by PLC eluting with dichloromethane gave **26** (67 mg, 41%): mp 187–190 °C (EtOAc/hexane); IR (CH_2Cl_2) 1795, 1735, 1675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, d, J = 5 Hz), 7.54 (1H, d, J = 5 Hz), 7.45–7.22 (7H, m), 4.3 (2H, b), 3.97 (3H, s), 3.90 (1H, d, J = 3 Hz), 3.84 (1H, m), 3.58 (3H, s), 3.20 (1H, m), 2.80 (1H, d, J = 5 Hz), 2.56 (2H, m), 2.18 (1H, m), 1.58 (1H, m). Anal. Calcd for $C_{28}H_{25}N_2O_7SF_3$: C, 56.94; H, 4.27; N, 4.74. Found: C, 56.95; H, 4.20; N, 4.84. Trifluoroacetate **26** is very labile toward hydrolysis, and therefore, on a large scale, it was converted directly into the dione **27** (see below).

To a solution of the sulfoxides **19** (10.22 g, 20.7 mmol) at 0 °C in dichloromethane (150 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (1.4 g, 6.8 mmol) followed by the dropwise addition of trifluoroacetic anhydride (14.8 mL, 105 mmol) over a period of 10 min. After 3 h, the mixture was worked up as above to give crude **26** (13.8 g, 12.18 g is the theoretical yield). The crude material was used directly in the next stage.

7α,8-Bis(methoxycarbonyl)-4,5-dioxo-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indoles 27/28. The crude trifluoroacetate **26** (13.8 g) in tetrahydrofuran (500 mL) and water (200 mL) was treated with yellow mercuric oxide (14.2 g) and calcium carbonate (11.8 g). The mixture was raiply stirred at 25 °C for 12 h and then filtered through Celite. The Celite was washed with tetrahydrofuran (500 mL) and dichloromethane (500 mL) and dried ($MgSO_4$). Evaporation of the filtrate in vacuo gave the crude dione **27** (15.18 g), which was used directly in the subsequent stages.

On a small scale, the dione was purified by chromatography over silica gel eluting with dichloromethane to give **27**. The dione **27** exists in equilibrium with its hydrate **28**, approximately 2:3. **27/28** mp 109–111 °C (EtOAc/hexane); IR ($CHCl_3$) 3420, 2950, 1740, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz), 8.13 (d, J = 8.4 Hz), 7.57 (d, J = 7.5 Hz), 7.52 (d, J = 7.5 Hz), 7.44–7.25 (2H, m), 4.54 (ddd, J = 13.4, 5.1, 0.6 Hz), 4.42 (ddd, J = 13.4, 4.8, 0.4 Hz), 4.19 (d, J = 4.1 Hz), 3.87 (m), 4.01 (s), 3.97 (s), 3.84–3.36 (m), 3.67 (s), 3.62 (s), 3.49 (m), 3.26 (m), 2.95 (d, J = 15.5 Hz), 2.83 (d, J = 14.1 Hz), 2.80–2.34 (m), 2.20–1.88 (m); HRMS calcd for $C_{20}H_{20}N_2O_6$ 384.1321, found 384.1318.

(*E*)-7α,8-Bis(methoxycarbonyl)-4-oxo-5-[(*tert*-butoxycarbonyl)-methylidene]-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole (30). To a solution of the crude dione **27** (15.1 g) in dimethoxyethane (300 mL) at −40 °C was added a solution of $Na^+{}^-CHP(O)(OEt)_2CO_2Bu^t$ (prepared from $CH_2P(O)(OEt)_2CO_2Bu^t$ (5.22 g)/NaH (0.68 g)/dimethoxyethane (200 mL) at 0 °C and then cooled to −40 °C). The mixture was stirred at −40 °C for 1 h and the reaction quenched by the addition of aqueous ammonium chloride solution (200 mL); the mixture was extracted with ethyl acetate (3 × 200 mL). The dried ($MgSO_4$) extract was evaporated in vacuo, and the residue was purified by chromatography over silica gel eluting with EtOAc/CH_2Cl_2 (4:1) to give ester **30** (8.42 g, 84% from **19**): mp 182–183 °C (EtOAc/hexane); IR (CH_2Cl_2) 2940, 1740, 1720, 1645 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 7.2 Hz), 7.55 (1H, dd, J = 7.6 and 1.5 Hz), 7.37 (1H, dt, J = 7.5 and 1.5 Hz), 7.30 (1H, dt, J = 7.5 and 1.5 Hz), 6.36 (1H, s), 5.08 (1H, t, J = 4.4 Hz), 4.50 (1H, ddd, J = 13.2, 4.2, and 1.2 Hz), 4.00 (3H, s), 3.78 (1H, d, J = 4.3 Hz), 3.61 (3H, s), 3.30 (1H, ddd, J = 13.7, 10.4, and 5.7 Hz), 3.13 (1H, ddd, J = 14.9, 12.3, and 5.1 Hz), 2.87 (1H, ddd, J = 13.7, 2.4, and 1.2 Hz), 2.61 (1H, dt, J = 13.1 and 2.6 Hz), 2.43 (1H, ddd, J = 13.8, 10.5, and 4.2 Hz), 1.82 (1H, m), 1.74 (1H, m), 1.57 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.35, 24.88, 28.05, 37.44, 45.58, 47.54, 48.00, 52.04, 53.50, 81.05, 115.63, 118.11, 119.70, 121.70, 123.09, 125.00, 128.63, 133.17, 135.40, 151.21, 151.55, 164.56, 170.47, 170.67. Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.40; H, 6.31; N, 5.80. **30** was further characterized by single-crystal X-ray crystallography.

Cyclopropane Adduct 29. The trifluoroacetate **26** (20 mg) and 2,6-di-*tert*-butyl-4-methylpyridine (10 mg) in toluene were heated at 200 °C (sealed tube) for 3 h. The mixture was cooled to room temperature and directly applied to a preparative silica gel plate. Elution with CH_2Cl_2/EtOAc (9:1) gave **29** (11.5 mg, 71%): mp 245–247 °C (acetone/hexane); IR (CH_2Cl_2) 1735, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 6.0 Hz), 7.45 (1H, d, J = 6.0 Hz), 7.45–7.15 (7H, m), 4.05 (1H, dd, J = 4.0 Hz), 4.02 (3H, s), 3.98 (1H, d, J = 4.0 Hz), 3.64 (3H, s), 3.32 (1H, dd, J = 5.0 Hz), 3.05 (1H, dt), 2.85 (2H, m), 2.58 (1H, dt), 2.18 (1H, d, J = 6.0 Hz), 2.00 (1H, dd, J = 3 Hz). Anal. Calcd for $C_{26}H_{24}N_2O_5S$: C, 65.53; H, 5.08; N, 5.88. Found: C, 65.33; H, 4.95; N, 5.75. **29** was further characterized by single-crystal X-ray crystallography.

7α,8-Bis(methoxycarbonyl)-4,5-dioxo-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole 5-(Ethylene acetal) (33). To a solution of the crude dione **27** (7.8 g, from 4.74 g of sulfoxide **19**) in toluene (300 mL) was added 2-bromoethanol (7.07 mL, 4.9 equiv) followed by DBU (10.6 mL, 3.5 equiv) at 25 °C. The mixture was stirred at 25 °C for 1 h and quenched with water (100 mL). The toluene layer was washed with 1 N hydrochloric acid (2 × 100 mL) and saturated sodium bicarbonate solution (100 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue

was chromatographed over silica gel eluting with ethyl acetate to give **33** (3.33 g, 81% from **19**): mp 215–216 °C dec (EtOAc/petroleum ether); IR (CH_2Cl_2) 2940, 2900, 1730, 1660, 1450, 1360, 1330, 1200, 1135, 1020, 940 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, dd, J = 7.4 and 0.5 Hz), 7.51 (1H, dd, J = 7.4 and 0.5 Hz), 7.35 (1H, dt, J = 7.3 and 1.4 Hz), 7.28 (1H, dt, J = 7.3 and 1.4 Hz), 4.45–4.27 (3H, m), 4.12–3.97 (2H, m), 3.95 (3H, s), 3.87 (1H, d, J = 4.5 Hz), 3.60 (3H, s), 3.62–3.51 (1H, m), 3.38 (1H, t, J = 5.2 Hz), 3.26 (1H, ddd, J = 14.8, 12.7, and 4.9 Hz), 2.78 (1H, d, J = 12.8 Hz), 2.56 (1H, dt, J = 12.9 and 2.9 Hz), 2.41 (1H, ddd, J = 14.0, 11.2, and 3.3 Hz), 2.09–1.97 (1H, m), 1.42 (1H, dddd, J = 13.7, 11.0, 5.7, and 0.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.42 (t), 21.76 (t), 42.00 (d), 44.78 (d), 45.81 (t), 49.62 (t), 52.23 (q), 53.44 (q), 65.22 (t), 65.98 (t), 106.88 (s), 115.63 (d), 118.18 (d), 120.35 (s), 123.20 (d), 125.10 (d), 128.79 (s), 133.36 (s), 135.41 (s), 151.71 (s), 170.50 (s), 170.90 (s); HRMS calcd for $C_{22}H_{24}N_2O_7$ 428.1577, found 428.1567. Anal. Calcd for $C_{22}H_{24}N_2O_7$: C, 61.68; H, 5.65; N, 6.54. Found: C, 61.24; H, 5.72; N, 6.44.

7α,8-Bis(methoxycarbonyl)-5-oxo-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole Ethylene acetal (34). To a solution of **33** (0.50 g, 1.167 mmol) in tetrahydrofuran (30 mL) at 25 °C was added BH_3·THF complex (3.5 mL). The mixture was stirred at 25 °C for 1 h, and quenched with ethyl acetate (50 mL) and saturated aqueous sodium chloride (50 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give **34** (0.482, 100%): IR (CH_2Cl_2) 2900, 2820, 1730, 1365, 1330, 1200, 1135, 1115, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 8.2 Hz), 7.50 (1H, ddd, J = 7.7, 1.3, and 0.6 Hz), 7.32 (1H, ddd, J = 8.5, 7.2, and 1.3 Hz), 7.27 (1H, dt, J = 7.7 and 1.1 Hz), 4.34–4.28 (1H, m), 4.22 (1H, d, J = 4.7 Hz), 4.14–4.08 (1H, m), 4.04–3.98 (2H, m), 3.96 (3H, s), 3.60 (3H, s), 3.34 (1H, dd, J = 13.8 and 2.2 Hz), 3.25 (1H, dd, J = 14.5 and 3.5 Hz), 3.19 (1H, d, J = 13.8 Hz), 3.07 (1H, t, J = 5.1 Hz), 2.91–2.86 (1H, m), 2.81–2.70 (2H, m), 2.58 (1H, t, J = 6.0 Hz), 1.93 (1H, t, J = 11.6 Hz), 1.69–1.62 (1H, m), 1.34 (1H, dddd, J = 14.2, 10.8, 6.8, and 1.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.16 (t), 25.20 (t), 38.74 (d), 44.76 (d), 45.27 (t), 51.99 (q), 53.30 (q), 54.38 (t), 54.80 (t), 64.35 (t), 64.80 (t), 111.62 (s), 115.62 (d), 118.10 (d), 120.42 (s), 122.92 (d), 124.41 (d), 129.06 (s), 134.47 (s), 135.47 (s), 152.00 (s), 173.30 (s); HRMS calcd for $C_{22}H_{26}N_2O_6$ 414.1784, found 414.1786.

7α-(Methoxycarbonyl)-5-oxo-1,4,5,6β,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole Ethylene acetal (35). A solution of **34** (4.50 g, 10.86 mmol) in methanol (450 mL) containing sodium bicarbonate (4.50 g, 42.45 mmol) was heated at reflux for 16 h. The mixture was cooled to 25 °C and evaporated in vacuo to dryness. The residue was dissolved in ethyl acetate (200 mL) and water (50 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo to give **35** (93% crude). Purification by chromatography over silica gel eluting with ethyl acetate gave **35** (2.784 g, 71.9%) and **36** (0.416 g, 10.8%). The crude product could be used directly in the next stage. **35**: IR (CH_2Cl_2) 3443, 3048, 2954, 2890, 1729, 1606, 1461, 1437, 1373, 1337, 1246, 1194, 1170, 1114, 1046, 1022, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, b s), 7.53 (1H, d, J = 7.8 Hz), 7.35 (1H, d, J = 7.8 Hz), 7.16 (1H, dt, J = 8.7 and 1.3 Hz), 7.09 (1H, dt, J = 7.8 and 0.9 Hz), 4.39 (1H, d, J = 3.6 Hz), 4.04–3.96 (4H, m), 3.91–3.87 (1H, m), 3.76 (3H, s), 3.36 (1H, b d, J = 13.8 Hz), 3.21–3.14 (2H, d, J = 13.6 Hz), 2.90–2.58 (6H, m), 2.00–1.85 (1H, b s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.84 (t), 24.47 (t), 42.39 (d), 43.44 (d), 45.45 (t), 52.45 (q), 54.43 (t), 55.34 (t), 64.52 (t), 110.83 (d), 111.59 (s), 112.70 (s), 118.01 (d), 119.18 (d), 121.56 (d), 127.45 (s), 131.80 (s), 135.25 (s), 176.02 (s); HRMS calcd for $C_{20}H_{24}N_2O_4$ 356.1736, found 356.1735.

6-(Methoxycarbonyl)-12-oxo-1,2,3aβ,4,5β,7-hexahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole Ethylene acetal (36). To a solution of **35** (420 mg, 1.18 mmol) in acetic acid (30 mL) at 25 °C was added mercuric acetate (750 mg, 2.36 mmol), and the mixture was stirred at 25 °C for 60 h. The solution was evaporated in vacuo and the residue extracted with ethyl acetate (3 × 50 mL). The extract was washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give the crude product mixture. Purification by chromatography over silica gel eluting with EtOAc/MeOH (3:1) gave **36** (190 mg, 46%), **37** (26 mg, 6%), and **38** (14 mg, 3%). Treatment of **37** with sodium borohydride in methanol gave **36** (>95%).

36: mp 190–195 °C (EtOAc/petroleum ether); IR (CH_2Cl_2) 3430, 3370, 2940, 2880, 1670, 1600, 1455, 1150, 1110, 1080, 1030, 1005, 965, 880 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 203 (13 200), 229.5 (10 000), 293.8 (9500), 323.3 (12 900); ^1H NMR (500 MHz, $CDCl_3$) δ 8.85 (1H, b s), 7.18 (1H, dt, J = 7.3 and 0.5 Hz), 7.13 (1H, td, J = 7.7 and 1.2 Hz), 6.90 (1H, td, J = 7.5 and 1.2 Hz), 6.81 (1H, dt, J = 7.7 and 0.8 Hz), 4.13–4.08 (1H, m), 4.04–3.92 (4H, m), 3.78 (3H, s), 3.14 (1H, b s), 3.12 (1H, ddd, J = 11.5, 9.9, and 6.7 Hz), 2.99 (1H, d, J = 13.1 Hz), 2.91 (1H, ddd, J = 11.6, 6.9, and 3.1 Hz), 2.74 (1H, ddd, J = 13.1, 9.8, and 7.0 Hz), 2.64 (1H, d, J = 13.1 Hz), 2.37 (1H, dt, J = 13.5 and 3.3 Hz), 1.88 (1H, ddd, J = 13.2, 6.7, and 3.1 Hz), 1.33 (1H, ddd, J = 13.5, 3.5, and 3.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.43 (t), 36.37 (d), 43.25 (t), 51.21 (q), 53.07 (t), 53.57 (t), 57.36 (s), 59.07 (d), 64.53 (t), 64.68 (t), 99.61 (s), 107.24 (s), 109.63 (d), 120.11 (d), 121.02 (d), 127.69 (d), 135.00 (s), 144.31 (s), 168.27 (s), 169.60 (s); HRMS calcd for $C_{20}H_{22}N_2O_4$ 354.1580, found 354.1578.

38: IR (CH_2Cl_2) 3368, 3045, 2953, 1674, 1603, 1463, 1160, 1144, 1102 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 203 (11 000), 230 (9000), 295 (8000), 325 (12 000); ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (1H, b s), 7.07–7.12 (2H, m), 6.87 (1H, td, J = 8.0 and 0.8 Hz), 6.78 (1H, d, J = 8.0 Hz), 4.10–3.95 (2H, m), 3.78–3.71 (5H, m), 3.64 (1H, d, J = 2.0 Hz), 3.05–2.87 (5H, m), 2.47 (1H, td, J = 12.9 and 4.7 Hz), 2.27 (1H, ddd, J = 13.1, 9.0, and 3.7 Hz), 1.88–1.77 (1H, m), 1.70 (1H, d, J = 13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.65 (t), 36.44 (d), 43.89 (t), 44.35 (t), 51.14 (q), 54.43 (t), 58.72 (s), 64.48 (t), 65.09 (t), 65.55 (d), 95.89 (s), 108.57 (s), 109.89 (d), 119.12 (d), 121.16 (d), 127.19 (d), 136.60 (s), 144.40 (s), 168.40 (s), 170.95 (s); HRMS calcd for $C_{20}H_{22}N_2O_4$ 354.1580, found 354.1571.

6α-(Methoxycarbonyl)-12-oxo-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole Ethylene acetal (39). To a solution of **36** (1.25 g, 3.53 mmol) in methanol (90 mL) and concentrated sulfuric acid (10 mL) was added zinc dust (16.15 g, 247 mmol), and the mixture was heated at reflux for 0.5 h. The mixture was filtered, and the zinc residues were washed with ethyl acetate (3 × 100 mL). The filtrate was slowly added to a mixture of ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo to give **39** (1.108 g, 88.2%): IR ($CHCl_3$) 3392, 2954, 2893, 1735, 1607, 1486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05–7.01 (2H, m), 6.77 (1H, td, J = 7.3 and 0.7 Hz), 6.58 (1H, d, J = 7.7 Hz), 4.21 (1H, d, J = 4.5 Hz), 4.05–4.02 (2H, m), 3.98–3.91 (3H, m), 3.79 (3H, s), 3.22–3.16 (1H, m), 3.01–2.94 (3H, m), 2.88 (1H, dd, J = 5.1 and 3.1 Hz), 2.73 (1H, d, J = 13.2 Hz), 2.70–2.69 (1H, m), 2.31 (1H, ddd, J = 13.8, 7.1, and 3.1 Hz), 2.21–2.13 (2H, m), 2.06 (1H, ddd, J = 14.0, 4.1, and 2.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.94, 32.73, 38.81, 42.25, 51.82, 52.26, 53.80, 54.96, 64.13, 64.28, 64.77, 65.01, 109.23, 109.76, 119.67, 122.29, 127.75, 136.10, 149.15, 174.25; HRMS calcd for $C_{20}H_{24}N_2O_4$ 356.1736, found 356.1733.

6α-(Methoxycarbonyl)-12-oxo-7-acetyl-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole Ethylene acetal (41). To a solution of **39** (190 mg, 0.53 mmol) in acetic anhydride (20 mL) was added sodium acetate (2.0 g), and the resulting mixture was stirred at 25 °C for 12 h. The mixture was evaporated in vacuo, and the residue was washed with saturated aqueous $NaHCO_3$ (10 mL), extracted with ethyl acetate (2 × 10 mL), dried ($MgSO_4$), and evaporated to give crude **41**. Purification by chromatography over silica gel eluting with EtOAc/MeOH (9:1) gave **41** (160 mg, 75%): mp 170–171 °C (EtOAc/petrol); IR (CH_2Cl_2) 2955, 1731, 1658, 1597, 1484, 1463, 1437, 1398, 1251, 1164, 1121, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, b s), 7.23–7.03 (3H, m), 4.33 (1H, b s), 4.01–3.67 (6H, m), 3.55 (1H, b s), 3.40 (3H, s), 3.26–3.15 (1H, m), 3.04 (1H, b d, J = 12.1 Hz), 2.89–2.81 (1H, m), 2.44–2.39 (1H, m), 2.35 (3H, s), 2.32–2.23 (1H, m), 2.17 (1H, dt, J = 13.7 Hz), 1.95 (1H, b s), 1.90–1.81 (1H, m); the ^1H NMR was severely broadened by amide resonance; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 23.4, 36.9, 43.49, 44.9, 51.7, 53.39, 55.9, 59.9, 64.66, 64.79, 66.4, 107.37, 120.9, 124.4, 127.6, 135.8, 141.6, 168.6, 171.7; HRMS calcd for $C_{22}H_{26}N_2O_5$ 398.1841, found 398.1847. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.10; H, 6.48; N, 6.89. **41** was further characterized by single-crystal X-ray crystallography.

6β-(Methoxycarbonyl)-12-oxo-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole Ethylene acetal (40). To a solution of **39** (75 mg, 0.21 mmol) in methanol (10 mL) was added sodium hydride (14 mg), and the solution was heated at reflux for 2 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give a residue which was purified by chromatography over silica gel to give **40** (75 mg, 100%): IR ($CHCl_3$) 3425, 1729, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07–7.06 (2H, m), 6.72 (1H, td, J = 7.3 and 0.7 Hz), 6.58 (1H, d, J = 7.7 Hz), 4.24 (1H, b s), 4.07 (1H, d, J = 9.9 Hz), 3.95–3.81 (4H, m), 3.74 (3H, s), 3.51 (1H, t, J = 2.8 Hz), 3.26–3.17 (1H, m), 2.99 (1H, d, J = 13.8 Hz), 2.99–2.90 (1H, m), 2.52 (2H, d, J = 13.5 Hz), 2.63–2.41 (1H, m), 2.34–2.28 (2H, m), 1.79–1.70 (1H, m), 1.66 (1H, dt, J = 14.0 and 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.05,

37.23, 41.18, 50.03, 51.39, 53.09, 53.22, 55.89, 59.03, 60.08, 64.14, 64.45, 108.29, 108.85, 118.26, 121.72, 127.75, 131.50, 148.69, 173.97; HRMS calcd for $C_{20}H_{24}N_2O_4$ + H^+ 357.1814, found 357.1836.

β-Keto Amide 43. To a solution of **41** (260 mg, 0.65 mmol) in tetrahydrofuran (50 mL) was added sodiun hydride (47 mg, 1.96 mmol), and the mixture was heated at reflux for 8 h. A further portion of sodium hydride (47 mg) was added and the mixture heated at reflux for 8 h. The solution was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give **43** (237 mg, 98%): mp 204–207 °C (EtOAc/MeOH); IR (CH_2Cl_2) 3050, 2960, 2880, 1725, 1680, 1484, 1401 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, d, J = 8.0 Hz), 7.27–7.23 (1H, m), 7.20 (1H, dd, J = 7.5 and 1.3 Hz), 7.15 (1H, td, J = 7.4 and 1.0 Hz), 4.58 (1H, d, J = 6.8 Hz), 4.10–4.03 (2H, m), 4.02–3.96 (2H, m), 3.67 (1H, d, J = 15.7 Hz), 3.45 (1H, d, J = 15.7 Hz), 3.22 (1H, ddd, J = 12.0, 10.1, and 7.1 Hz), 3.04 (1H, ddd, J = 12.0, 7.2, and 2.6 Hz), 3.00 (1H, dd, J = 4.3 and 1.9 Hz), 2.92 (1H, d, J = 12.8 Hz), 2.91–2.89 (1H, m), 2.66 (1H, d, J = 12.8 Hz), 2.50 (1H, ddd, J = 14.0, 7.1, and 2.6 Hz), 2.45 (1H, b s), 2.37 (1H, ddd, J = 14.0, 10.0, and 7.3 Hz), 2.11 (1H, ddd, J = 14.4, 4.3, and 3.0 Hz), 1.49 (1H, ddd, J = 14.5, 3.7, and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 33.6, 40.2, 46.1, 51.1, 51.4, 52.8, 54.8, 64.2 (2C), 65.2, 66.1, 107.9, 116.2, 122.4, 125.6, 128.5, 137.4, 140.0, 162.5, 203.2; HRMS calcd for $C_{21}H_{22}N_2O_4$ 366.1579, found 366.1571.

6β-(Methoxycarbonyl)-12-oxo-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole Ethylene acetal (44). To a solution of ester **40** (100 mg, 0.28 mmol) in dichloromethane (1.5 mL) containing $EtNPr^i_2$ (65 μL) was added 4-methoxybenzenesulfonyl chloride (160 μL of a solution of 193 mg in CH_2Cl_2 (400 μL)) and 4-(dimethylamino)pyridine (100 μL of a solution of 13 mg in CH_2Cl_2 (260 μL)) at 0 °C. After 4 h, a further portion of (4-methoxybenzenesulfonyl chloride (180 μL of the above solution) was added and the mixture stirred at 25 °C for 20 h. The mixture was quenched with water (5 mL) and the mixture extracted with chloroform (2 × 5 mL). The extract was washed with aqueous $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), and evaporated in vacuo to give **44** (120 mg, 81%). Generally, purification was not required and the material was used directly in the next step. **44**: IR ($CHCl_3$) 1734, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 8.0 Hz), 7.61 (2H, d, J = 8.8 Hz), 7.23 (1H, t, J = 8.0 Hz), 7.10 (1H, t, J = 8.0 Hz), 6.98 (1H, d, J = 7.5 Hz), 6.84 (2H, d, J = 8.8 Hz), 4.57 (1H, d, J = 7.0 Hz), 3.94–3.81 (4H, m), 3.78 (3H, s), 3.74 (3H, s), 3.17 (1H, b s), 3.03–2.92 (2H, m), 2.74–2.67 (2H, m), 2.38–2.28 (3H, m), 1.50–1.36 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.65, 37.06, 45.59, 51.22, 51.91, 52.61, 53.86, 54.26, 55.54, 63.10, 64.36, 64.88, 69.32, 106.94, 113.93, 117.67, 122.04, 125.46, 128.25, 129.23, 129.66, 137.95, 140.86, 163.24, 172.95; HRMS calcd for $C_{27}H_{30}N_2SO_7$ 526.1774, found 526.1762.

6β-(Hydroxymethyl)-12-oxo-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole Ethylene acetal (45). To a solution of the ester **44** (85 mg, 0.161 mmol) in tetrahydrofuran (4 mL) was added lithium borohydride (485 μL of a 2 M solution in THF), and the mixture was stirred at 50 °C for 10 h. A further portion of lithium borohydride (600 μL) was added and stirring continued for 9 h. Diethanolamine (500 mg) in tetrahydrofuran (1 mL) was added to the mixture at 50 °C followed by methanol (3 mL) 1 h later. The mixture was cooled to 25 °C, diluted with water (5 mL), and extracted with chloroform (2 × 5 mL). The dried ($MgSO_4$) extract was evaporated in vacuo, and the residue was purified by PLC eluting with EtOAc/MeOH (4:1) to give **45** (54 mg, 67%): IR ($CHCl_3$) 3479, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 7.9 Hz), 7.52 (2H, d, J = 8.9 Hz), 7.29 (1H, td, J = 7.8 and 1.0 Hz), 7.17 (1H, td, J = 7.9 and 1.0 Hz), 7.07 (1H, d, J = 7.5 Hz), 6.80 (2H, d, J = 8.9 Hz), 4.19 (1H, d, J = 10.3 Hz), 4.13–3.94 (6H, m), 3.78 (3H, s), 3.45 (1H, b s), 3.29 (1H, t, J = 2.5 Hz), 3.03–2.96 (1H, m), 2.92 (1H, d, J = 12.3 Hz), 2.64–2.56 (1H, m), 2.38 (1H, dt, J = 13.8 and 3.6 Hz), 2.29 (2H, d, J = 12.3 Hz), 1.96 (1H, d, J = 3.0 Hz), 1.85–1.79 (1H, m), 1.43 (1H, dt, J = 13.8 and 2.7 Hz), 1.18–1.10 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.37, 38.34, 43.15, 48.19, 53.03, 53.73, 55.53, 55.61, 62.54, 62.95, 64.00, 65.29, 71.46, 108.46, 113.90, 119.44, 122.08, 126.18, 128.11, 129.54, 130.08, 139.15, 140.68, 163.22; HRMS (M + 1) calcd for $C_{26}H_{31}N_2SO_6$ 499.1903, found 499.1938.

6β,12β-(Methyleneoxa)-12α-hydroxy-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (47). Acetal **45** (100 mg, 0.20 mmol) was dissolved in neat perchloric acid (500 μL) and the solution stirred at 25 °C for 24 h. The mixture was poured onto solid $NaHCO_3$ and diluted with water (5 mL). The solution was extracted with chloroform (5 × 10 mL), and the extract was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give crude **47**. Purification by PLC eluting with $CHCl_3$/MeOH (4:1) gave **47** (50 mg, 55%): IR ($CHCl_3$) 3360, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, d, J = 8.0 Hz), 7.60 (2H, d, J = 8.9 Hz), 7.27 (1H, td, J = 8.4 and 1.0 Hz), 7.08 (1H, td, J = 7.5 and 0.4 Hz), 6.96. (1H, d, J = 7.3 Hz), 6.85 (2H, d, J = 8.9 Hz), 4.30 (1H, d, J = 9.0 Hz), 4.16 (1H, dd, J = 9.0 and 3.5 Hz), 3.80 (3H, s), 3.59 (1H, d, J = 3.3 Hz), 3.52 (1H, d, J = 3.3 Hz), 3.28–3.14 (2H, m), 3.02 (1H, d, J = 14.7 Hz), 2.85 (1H, d, J = 14.8 Hz), 2.79–2.74 (1H, m), 2.45-2.40 (1H, m), 1.99 (1H, dt, J = 14.6 and 3.9 Hz), 1.67–1.52 (2H, m), 0.56 (1H, dd, J = 12.6 and 5.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.32, 40.83 (d), 42.93, 48.97, 51.82, 52.67, 53.61, 55.58, 58.00, 69.96, 74.31, 105.26 (d), 114.15 (d, 2C), 116.26 (d), 122.81 (d), 124.91 (d), 128.36 (s), 128.92 (d), 129.17 (d, 2C), 134.23 (s), 141.50 (s), 163.48 (s); HRMS calcd for $C_{24}H_{26}N_2SO_5$ 454.1562, found 454.1564.

If the above acid cleavage of the ketal is carried out on material from the lithium borohydride reduction step but without the diethanolamine workup process, the reduction product **46** (R = $SO_2C_6H_4OMe$-*p*) is formed: mp 174–175 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (1H, d, J = 8.2 Hz), 7.59 (2H, d, J = 9.0 Hz), 7.25 (1H, td, J = 7.3 and 1.2 Hz), 7.06 (1H, td, J = 7.5 and 0.9 Hz), 6.92. (1H, d, J = 7.5 Hz), 6.83 (2H, d, J = 9.0 Hz), 4.32 (1H, d, J = 11.0 Hz), 4.11 (1H, dd, J = 10.0 and 2.5 Hz), 3.78 (3H, s), 3.69 (1H, dd, J = 9.0 and 3.5 Hz), 3.59 (1H, d, J = 3.5 Hz), 3.57 (1H, d, J = 3.7 Hz), 3.31–3.25 (1H, m), 3.19 (1H, t, J = 8.7 Hz), 2.96 (1H, dd, J = 15.7 and 2.8 Hz), 2.86 (1H, d, 2.8 Hz), 2.65–2.62 (1H, m), 2.58–2.53 (1H, m), 1.85 (1H, dt, J = 14.7 and 4.0 Hz), 1.58–1.50 (1H, m), 1.47 (1H, dt, J = 14.7 and 2.0 Hz), 0.52 (1H, dd, J = 12.6 and 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.15, 32.40, 43.33, 47.85, 48.31, 53.55, 53.78, 55.57, 58.24, 70.24, 75.72, 78.89, 114.09, 116.39, 122.68, 124.81, 128.64, 128.79, 129.19, 134.98, 141.66, 163.41; HRMS calcd for $C_{24}H_{26}N_2SO_4$ 438.1613, found 438.1635. **46** was further characterized by single-crystal X-ray crystallography.

(*p*-Methoxyphenyl)sulfonyl Derivative of the Wieland–Gumlich Aldehyde 49. The Wieland–Gumlich aldehyde **48** (as a chloroform solvate) (7.75 g, 0.025 mol) in dichloromethane (190 mL) and diisopropylethylamine (5 mL) at 0 °C was treated dropwise with a solution of *p*-methoxybenzenesulfonyl chloride (7.7 g, 1.5 equiv in CH_2Cl_2 (20 mL)) and 4-(dimethylamino)pyridine (100 mg). The mixture was stirred for 1 h at 0 °C, warmed to 25 °C, and stirred for a further 2 h. The solution was poured into saturated aqueous $NaHCO_3$ solution and extracted with chloroform (3 × 100 mL). The extract was dried (Na_2SO_4) and evaporated in vacuo to give a residue which was chromatographed over silica gel eluting with $CHCl_3$/MeOH (9:1) to give **49** (8.4 g, 97%): mp 178–182 °C (softens at 155 °C) (EtOH/water); $[\alpha]^{23}_D$ –28.1° (*c* 1.4 in MeOH); IR ($CHCl_3$) 2593, 1590, 1491, 1347, 1261, 1013, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, d, J = 8.0 Hz), 7.61 (2H, d, J = 8.9 Hz), 7.29 (1H, t, J = 7.4 Hz), 7.14 (1H, t, J = 7.4 Hz), 7.01 (1H, d, J = 7.5 Hz), 6.81 (2H, d, J = 8.9 Hz), 5.88–5.82 (2H, m), 4.82 (1H, dd, J = 15.0 and 3.5 Hz), 4.08 (1H, d, J = 11.1 Hz), 3.92–3.80 (2H, m), 3.79 (3H, s), 3.68 (1H, d, J = 14.9 Hz), 3.40 (1H, s), 3.14–2.98 (1H, m), 2.70 (1H, d, J = 15.1 Hz), 2.67–2.46 (1H, m), 2.20 (1H, dt, J = 14.4 and 3.9 Hz), 1.66–1.60 (1H, m), 1.37–1.18 (2H, m), 0.32 (1H, dd, J = 13.0 and 5.8 Hz); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 25.09, 28.27 (d), 29.62, 39.74, 48.63, 50.76, 52.75, 53.65, 55.51, 60.10, 66.19, 94.39 (d), 114.03 (d, 2C), 118.75 (d), 122.47 (d), 125.71 (d), 128.26 (d), 128.43 (d), 129.18 (d, 2C), 130.29 (s), 135.68 (s), 139.80 (s), 141.02 (s), 163.29 (s); HRMS calcd for $C_{26}H_{28}N_2O_5S$ 480.1719, found 480.1709. Anal. Calcd for $C_{26}H_{28}N_2O_5S$: C, 64.98; H, 5.87; N, 5.83. Found: C, 64.43; H, 6.09; N, 5.66.

Glycoside Derivative 50. A solution of **49** (8.2 g, 0.017 mol) in *tert*-butyl alcohol (150 mL), tetrahydrofuran (175 mL), and water (28 mL) was treated with *N*-methylmorpholine *N*-oxide (10 g, 5 equiv) followed by a 10 mol % solution of osmium tetroxide (10 mL, aqueous) at 25 °C. After 2 h, saturated aqueous Na_2SO_3 solution (30 mL) was added to the mixture and the solution stirred for 10 min. The mixture was evaporated in vacuo to approximately 70 mL and the product crystallized. The mixture was filtered, and the precipitate was washed with water and dried in vacuo to give **50** (6.27 g, 72%): mp 257–259 °C (MeOH); $[\alpha]^{23}_D$ –27.5° (*c* 0.68 in MeOH): IR (Nujol mull) 3192, 1586, 1495, 1472, 1355, 1256, 1158, 1113, 1089, 1049, 1009, 970, 763, 668, 584 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.60 (1H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.9 Hz), 7.24 (1H, td, J = 7.5 and 1.1 Hz), 7.14 (1H, td, J = 7.5 and 1.1 Hz), 7.05 (1H, d, J = 7.6 Hz), 6.84 (2H, d, J = 8.9 Hz), 5.77 (1H, s), 3.92 (1H, d, J = 9.1 Hz), 3.83 (1H, dd, J = 7.6 and 3.5 Hz), 3.76 (1H, dd, J = 11.4 and 3.5 Hz), 3.70 (3H, s), 3.54 (1H, dd, J = 11.2 and 7.6 Hz), 3.16–3.10 (1H, m), 2.83–2.72 (1H, m), 2.68 (1H, d, J = 13.3

Hz), 2.46 (1H, ddd, J = 12.3, 4.3, and 3.6 Hz), 2.34 (1H, d, J = 13.3 Hz), 2.32 (1H, dd, J = 13.7 and 3.6 Hz), 2.07–1.98 (1H, m), 1.69 (1H, dd, J = 8.9 and 4.9 Hz), 1.13–0.92 (3H, m); ^{13}C NMR (APT) (75 MHz, CD_3OD) δ 21.54, 32.34 (d), 44.30, 49.45, 53.93, 53.67, 54.60, 56.25, 60.73, 63.41, 70.00, 73.08, 76.19, 92.76 (d), 115.34 (d, 2C), 120.27 (d), 123.65 (d), 127.81 (d), 129.32 (d), 130.74 (d, 2C), 131.01 (s), 140.35 (s), 141.82 (s), 165.24 (s); HRMS calcd for $C_{26}H_{30}N_2O_7S$ 514.1774, found 514.1772. Anal. Calcd for $C_{26}H_{30}N_2O_7S$: C, 60.68; H, 5.88; N, 5.44. Found: C, 60.41; H, 6.24; N, 5.42. Crystals suitable for X-ray crystallography were grown from MeOH/EtOH.

Tetrol 51. To a solution of **50** (5.0 g, 9.72 mmol) in tetrahydrofuran (500 mL) was added lithium borohydride (100 mL of a 2.0 M solution in THF), and the mixture was heated at reflux for 16 h. The solution was cooled to 0 °C and treated with methanol (40 mL) followed by 2 M hydrochloric acid (30 mL). When the effervescence ceased, the mixture was evaporated in vacuo and the residue partitioned between saturated $NaHCO_3$ (100 mL) and chloroform (100 mL). The aqueous layer was extracted with chloroform (3 × 100 mL), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give a residue, which was dissolved in ethanol (200 mL) containing diethanolamine (4 mL) and heated at reflux for 1.5 h. The mixture was cooled to 25 °C and evaporated in vacuo to give a residue. The residue was partitioned between water (100 mL) and chloroform (100 mL) and the chloroform layer washed with saturated aqueous NH_4Cl solution. The aqueous layer was further extracted with chloroform (3 × 100 mL), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give a residue. The residue was chromatographed over silica gel eluting with chloroform/MeOH (3:1) increasing to neat MeOH to give the tetrol **51** (2.82 g, 56%): amorphous solid; IR (Nujol mull) 3345, 1544, 1497, 1479, 1414, 1348, 1310, 1263, 1160, 1091, 1047, 836, 805, 760, 667, 585 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.57 (1H, d, J = 8.0 Hz), 7.44 (2H, d, J = 9.0 Hz), 7.25–7.18 (1H, m), 7.14–7.02 (2H, m), 6.83 (2H, d, J = 9.0 Hz), 5.77 (1H, s), 4.18 (1H, dd, J = 11.9 and 4.1 Hz), 4.01 (1H, dd, J = 11.4 and 2.5 Hz), 3.89 (1H, d, J = 12.1 Hz), 3.75 (1H, dd, J = 7.4 and 2.6 Hz), 3.69 (3H, s), 3.62 (1H, dd, J = 11.4 and 7.5 Hz), 3.26–3.22 (1H, m), 3.12 (1H, d, J = 13.9 Hz), 2.85–2.70 (1H, m), 2.62-2.44 (2H, m), 2.16 (1H, d, J = 13.5 Hz), 2.20–2.03 (1H, m), 1.82–1.67 (1H, m), 1.26–1.08 (3H, m), 1.00–0.87 (1H, m); ^{13}C NMR (APT) (75 MHz, CD_3OD) δ 27.21, 34.33 (d), 43.50, 50.65, 54.14, 54.27, 56.24, 57.25, 62.85, 63.56, 64.10, 74.02, 76.77, 76.91, 115.29 (d, 2C), 119.90 (d), 123.75 (d), 127.54 (d), 129.32 (d), 130.72 (d, 2C), 131.20 (s), 140.37 (s), 141.40 (s), 165.24 (s); HRMS calcd for $C_{26}H_{32}N_2O_7S$ 516.1930, found 516.1926.

Conversion of the Tetrol 51 into the Relay 47. The tetrol **51** (5.7 g, crude from 4.96 g of **48**) in methanol (110 mL), water (110 mL), and trifluoroacetic acid (20 mL) was treated with periodic acid (5 g) and the mixture stirred at 25 °C for 3 h. The mixture was concentrated in vacuo to 150 mL, cooled to −10 °C, and treated with saturated $NaHCO_3$ solution (100 mL) and chloroform (100 mL). The organic layer was separated and the aqueous phase extracted with chloroform (4 × 100 mL). The dried (Na_2SO_4) extracts were evaporated in vacuo, and the residue was preadsorbed on silica gel and applied to a silica gel column. Elution of the silica gel column with chloroform/methanol (25:1 increasing to 20:1) gave the relay compound **47** (2.11 g, 40%, from 4.96 g of **48**).

6β-[((Triisopropylsilyl)oxy)methyl]-12-oxo-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (52). To a solution of the ketal **47** (145 mg, 0.319 mmol) in dichloromethane (5 mL) at 0 °C was added triisopropylsilyl triflate (103 μL, 1.2 equiv) and DBU (62 μL, 1.3 equiv), and the mixture was warmed to 25 °C. After 0.5 h, the mixture was partitioned between chloroform (10 mL) and aqueous $NaHCO_3$ solution (10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo and the residue purified by chromatography over silica gel eluting with $CHCl_3$/MeOH (40:1) to give **52** (134 mg, 69%): colorless foam, unstable; IR ($CHCl_3$) 2943, 2866, 1712, 1665, 1596, 1498, 1461, 1356, 1309, 1263, 1162, 1094, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 8.0 Hz), 7.52 (2H, d, J = 9.0 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.13 (1H, t, J = 7.5 Hz), 7.02 (1H, d, J = 7.0 Hz), 6.79 (2H, d, J = 9.0 Hz), 4.29 (1H, dd, J = 10.3 and 3.7 Hz), 4.00 (1H, t, J = 10.1 Hz), 3.77 (3H, s), 3.60 (1H, d, J = 16.6 Hz), 3.47 (1H, d, J = 11.5 Hz), 3.10 (1H, t, J = 8.9 Hz), 3.01–2.95 (1H, m), 2.82 (1H, d, J = 16.6 Hz), 2.41 (1H, dt, J = 10.7 and 6.8 Hz), 2.27 (1H, dt, J = 14.5 and 3.6 Hz), 1.91–1.79 (1H, m), 1.65 (1H, d, J = 14.5 Hz), 1.29–0.93 (23H, m), 0.47 (1H, dd, J = 7.8 and 5.5 Hz); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 11.29 (d, 3C), 17.97 (q, 6C), 25.55, 40.28, 40.70, 49.07, 53.55, 54.03, 55.50, 59.29, 60.58, 61.93, 66.50, 114.03 (d, 2C), 118.65 (d), 122.18 (d), 125.59 (d), 128.50 (d), 129.07 (d, 2C), 130.39 (s), 135.87 (s), 140.97 (s), 163.29 (s), 211.21 (s); HRMS calcd for $C_{33}H_{46}N_2O_5SSi$ 610.2897, found 610.2887.

(*E*)- and (*Z*)-6β-[((Triisopropylsilyl)oxy)methyl]-12-(2-cyanomethylidene)-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (53 and 54). To a solution of solid potassium hexamethyldisilazide (450 mg) in tetrahydrofuran (20 mL) was added dimethyl (cyanomethyl)phosphonate (0.421 mL) dropwise at 25 °C, and the solution was stirred for 20 min. A solution of ketone **52** (1.22 g, 2.0 mmol) in tetrahydrofuran (20 mL) was added dropwise over 5 min and the mixture stirred at 25 °C for 42 h. The mixture was quenched with saturated NH_4Cl solution (20 mL) and the mixture partitioned between water (50 mL) and chloroform (50 mL). The chloroform layer was separated and the aqueous layer extracted with chloroform (4 × 50 mL). The combined dried (Na_2SO_4) extracts were evaporated in vacuo, and the residue was preadsorbed onto silica gel and chromatographed over silica gel eluting with $CHCl_3$/MeOH (99:1 increasing to 50:1) to give **54** (370 mg, 29%), recovered **52** (153 mg), and **53** (549 mg, 43%).

***E*-Isomer 53**: mp 239–241 °C ($CHCl_3$/hexane); $[\alpha]^{23}_D$ +61.6° (c 0.34 in MeOH); IR ($CHCl_3$) 2942, 2865, 2221, 1596, 1497, 1461, 1353, 1262, 1161, 1091, 1027, 731, 671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 7.8 Hz), 7.44 (2H, d, J = 8.9 Hz), 7.30 (1H, td, J = 7.8 and 1.1 Hz), 7.18 (1H, td, J = 7.8 and 1.1 Hz), 7.00 (1H, d, J = 7.0 Hz), 6.78 (2H, d, J = 8.9 Hz), 5.32 (1H, d, J = 1.5 Hz), 4.39 (1H, dd, J = 10.6 and 3.1 Hz), 3.77 (3H, s), 3.63 (1H, d, J = 10.4 Hz), 3.55–3.40 (3H, m), 3.32–3.28 (1H, m), 2.96–2.84 (2H, m), 2.61–2.51 (1H, m), 2.00 (1H, dt, J = 13.8 and 3.4 Hz), 1.95–1.86 (1H, m), 1.67–1.58 (1H, m), 1.28–0.95 (23H, m); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 12.00 (d, 3C), 18.11 (q, 6C), 27.84, 34.41 (d), 42.90, 49.94, 53.27, 53.88, 55.56, 56.72, 62.67, 62.72, 71.27, 96.60 (d), 113.97 (d, 2C), 115.60 (s), 119.45 (d), 122.08 (d), 126.44 (d), 128.44 (d), 129.36 (d, 2C), 130.21 (s), 138.53 (s), 140.51 (s), 161.84 (s), 163.28 (s); HRMS (M + 1) calcd for $C_{35}H_{48}N_3O_4SSi$ 634.3135, found 634.3146. Anal. Calcd for $C_{35}H_{47}N_3O_4SSi$: C, 66.31; H, 7.47; N, 6.63. Found: C, 65.92; H, 7.39; N, 6.39.

***Z*-Isomer 54**: colorless foam; IR ($CHCl_3$) 2942, 2865, 2217, 1595, 1497, 1460, 1355, 1262, 1161, 1091, 1026, 921, 756, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 8.0 Hz), 7.62 (2H, d, J = 8.9 Hz), 7.28 (1H, t, J = 7.6 Hz), 7.14 (1H, t, J = 7.6 Hz), 6.98 (1H, d, J = 8.6 Hz), 6.79 (2H, d, J = 8.9 Hz), 5.43 (1H, s), 4.45 (1H, dd, J = 11.1 and 4.5 Hz), 3.93 (1H, d, J = 16.7 Hz), 3.77 (3H, s), 3.51 (1H, s), 3.47 (1H, t, J = 11.1 Hz), 3.37 (1H, d, J = 10.8 Hz), 3.13 (1H, d, J = 16.7 Hz), 3.06 (1H, s), 2.99 (1H, ddd, J = 11.3, 8.3, and 4.4 Hz), 2.49 (1H, dt, J = 11.3 and 7.5 Hz), 2.06 (1H, dt, J = 14.0 and 3.6 Hz), 1.94–1.80 (1H, m), 1.52–1.43 (1H, m), 1.21–0.96 (22H, m), 0.68 (1H, ddd, J = 13.6, 7.8, and 4.7 Hz); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 11.88 (d, 3C), 18.04 (q, 6C), 25.68, 33.37 (d), 41.60, 49.10, 52.54, 53.32, 53.45, 55.59, 60.66, 62.36, 69.01, 97.01 (d), 114.09 (d, 2C), 116.00 (s), 118.94 (d), 122.16 (d), 125.98 (d), 128.53 (d), 129.26 (d, 2C), 130.15 (s), 137.06 (s), 140.81 (s), 162.90 (s), 163.39 (s); HRMS (M + 1) calcd for $C_{35}H_{48}N_3O_4SSi$ 634.3135, found 634.3146.

Photoequilibration of 53 and 54. A solution of **54** (30 mg) in benzene (40 mL) at 25 °C was irradiated with a 250-W tungsten lamp for 2 h to give a mixture of **54** and **53** (3:2).

(*E*)-6β-[((Triisopropylsilyl)oxy)methyl]-12-(2-hydroxyethylidene)-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (55). A solution of **53** (500 mg, 0.79 mmol) in dichloromethane (25 mL) was treated with DIBAL (2.5 mL, 1.0 M in CH_2Cl_2) at 25 °C for 20 min. The mixture was cooled to −15 °C and treated with 2 N HCl (5 mL). The mixture was poured into saturated aqueous $NaHCO_3$ solution (5 mL) and Rochelle salt solution (5 mL) was added. The mixture was extracted with chloroform (5 × 5 mL), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give a residue. The residue was dissolved in methanol (30 mL) and treated with sodium borohydride (60 mg) at 25 °C for 0.5 h. The mixture was quenched with saturated aqueous NH_4Cl solution and the mixture extracted with chloroform (4 × 10 mL). The dried (Na_2SO_4) extract was evaporated in vacuo to give a residue which was preadsorbed onto silica gel and chromatographed over silica gel eluting with chloroform/MeOH (20:1 increasing to 15:1) to give **55** (156 mg, 31%): mp 250–251.5 °C ($CHCl_3$/hexane); $[\alpha]^{23}_D$ +27.2° (c 0.82 in MeOH); IR ($CHCl_3$) 3222, 2942, 2864, 1596, 1495, 1461, 1354, 1265, 1161, 1092, 1013, 759, 672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 7.9 Hz), 7.43 (2H, d, J = 8.9 Hz), 7.29 (1H, t, J = 8.9 Hz), 7.18 (1H, t, J = 7.3 Hz), 7.00 (1H, d, J = 7.4 Hz), 6.78 (2H, d, J = 8.9 Hz), 5.86 (1H, t, J = 7.0 Hz), 4.54 (1H, dd, J = 11.2 and 3.3 Hz), 4.25 (1H, dd, J = 12.6 and 8.1 Hz), 3.89 (1H, dd, J = 12.6 and 6.8 Hz), 3.77 (3H, s), 3.50–3.36 (3H,

m), 3.32–3.28 (1H, m), 3.25–3.15 (1H, m), 2.91–2.78 (1H, m), 2.74 (1H, d, J = 13.3 Hz), 1.96 (1H, dt, J = 13.4 and 3.4 Hz), 1.90–1.80 (1H, m), 1.52–1.44 (1H, m), 1.31–0.96 (24H, m); ^{13}C NMR (PT) (75 MHz, $CDCl_3$) δ 11.93 (d, 3C), 17.98 (q, 6C), 27.47, 28.01 (d), 43.00, 49.43, 52.94, 53.90, 55.55, 57.09, 57.72, 62.87, 63.18, 71.97, 113.97 (d, 2C), 119.31 (d), 122.13 (d), 126.34 (d), 127.26 (d), 128.23 (d), 129.33 (d, 2C), 130.24 (s), 137.53 (s), 139.11 (s), 140.52 (s), 163.25 (s); HRMS (M + 1) calcd for $C_{35}H_{51}N_2O_5SSi$ 639.3292, found 639.3288. Anal. Calcd for $C_{35}H_{50}N_2O_5SSi$: C, 65.79; H, 7.89; N, 4.38. Found: C, 65.15; H, 7.91; N, 4.41.

(*E*)-6β-(Hydroxymethyl)-12-(2-hydroxyethylidene)-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (56). To a solution of the silyl alcohol **55** (90 mg, 0.14 mmol) in methanol (10 mL) at 25 °C was added 2 N HCl (2 mL), and the mixture was stirred for 15 h. The mixture was evaporated in vacuo and the residue partitioned between saturated aqueous $NaHCO_3$ (10 mL) and chloroform (10 mL). The aqueous layer was extracted with choroform (4 × 10 mL), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give a white foam. Crystallization from $CHCl_3$/hexane gave **56** (63 mg, 81%; it contained 0.6 equiv of $CHCl_3$): mp 244–246 °C ($CHCl_3$/hexane); $[\alpha]^{23}_D$ +37.3° (*c* 0.55 in MeOH); IR ($CHCl_3$) 3320, 3237, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 7.9 Hz), 7.49 (2H, d, J = 8.8 Hz), 7.30 (1H, t, J = 7.3 Hz), 7.18 (1H, t, J = 7.3 Hz), 7.04 (1H, d, J = 7.9 Hz), 6.81 (2H, d, J = 8.8 Hz), 5.80 (1H, t, J = 7.2 Hz), 4.25 (1H, dd, J = 12.1 and 8.6 Hz), 4.15 (1H, dd, J = 11.8 and 2.9 Hz), 3.91–3.77 (3H, m), 3.77 (3H, s), 3.44 (1H, d, J = 14.3 Hz), 3.36 (1H, b s), 3.11 (1H, d, J = 2.8 Hz), 2.90–2.83 (2H, m), 2.61–2.53 (1H, m), 1.93 (1H, dt, J = 13.6 and 3.1 Hz), 1.84–1.78 (1H, m), 1.52 (1H, dt, J = 13.6 and 2.2 Hz), 1.20–1.10 (2H, m); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ 27.56, 29.27 (d), 42.92, 48.81, 52.82, 53.60, 55.53, 56.68, 57.55, 61.87, 62.90, 71.79, 114.01 (d, 2C), 118.98 (d), 122.21 (d), 125.87 (d), 126.33 (d), 128.22 (d), 129.31 (d, 2C), 129.84 (s), 138.68 (s), 138.70 (s), 140.26 (s), 163.30 (s); HRMS, calcd for $C_{26}H_{30}N_2O_5S$ 482.1875, found 482.1865.

Treatment of **49** (480.1 mg, 1.0 mmol) in dichloromethane (10 mL) at –78 °C with DIBAL (6.0 equiv of a 1 M solution in CH_2Cl_2) for 15 min and then warming to 25 °C for 2 h gave, after the usual workup, **56** (434 mg, 90%).

(*E*)-6β-(Hydroxymethyl)-12-[2-((*tert*-butyldimethylsilyl)oxy)ethylidene]-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (57). To a solution of the diol **56** (48.2 mg, 0.10 mmol) in dichloromethane (2 mL) at –20 °C was added dropwise DBU (0.5 equiv) followed by *tert*-butyldimethylsilyl triflate (TBDMSOTf) (0.1 equiv). Further quantities of TBDMSOTf in 0.1-equiv portions were added until 0.8 equiv were added. A further portion of DBU (0.25 equiv) and TBDMSOTf (0.3 equiv) were added, and TLC (silica gel, $CHCl_3$/MeOH (4:1)) indicated complete reaction. The mixture was quenched by addition of water (2 mL), the dichloromethane layer was dried (Na_2SO_4) and evaporated in vacuo, and the residue was puified by PLC (silica gel) eluting with $CHCl_3$/2% MeOH to give **57** (36 mg, 60%): mp 173–174 °C (from EtOAc/petroleum ether); $[\alpha]^{23}_D$ +37.3° (*c* 1.0 in EtOAc); IR ($CHCl_3$) 3427, 1596, 1497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 7.9 Hz), 7.51 (2H, d, J = 8.9 Hz), 7.28 (1H, t, J = 7.4 Hz), 7.17 (1H, t, J = 7.4 Hz), 7.01 (1H, d, J = 7.4 Hz), 6.80 (2H, d, J = 8.9 Hz), 5.65 (1H, t, J = 7.0 Hz), 4.32 (1H, dd, J = 12.1 and 8.2 Hz), 4.13–4.02 (2H, m), 3.83 (1H, d, J = 10.2 Hz), 3.79 (3H, s), 3.63 (1H, dd, J = 11.7 and 8.0 Hz), 3.40 (1H, d, J = 13.9 Hz), 3.32 (1H, b s), 3.08 (1H, d, J = 3.1 Hz), 2.93–2.83 (2H, m), 2.59–2.51 (1H, m), 1.91 (1H, dt, J = 13.4 and 3.4 Hz), 1.87–1.79 (1H, m), 1.52 (1H, dt, J = 13.4 and 2.4 Hz), 1.25–1.05 (2H, m), 0.90 (9H, s), 0.09 (6H, s); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ –5.30 (q), –5.04 (q), 18.32 (s), 25.87 (q, 3C), 27.70, 29.76 (d), 43.24, 48.95, 52.96, 53.89, 55.52, 57.77, 58.15, 62.24, 63.13, 72.06, 113.91 (d, 2C), 119.19 (d), 122.05 (d), 124.51 (d), 126.16 (d), 128.07 (d), 129.40 (d, 2C), 130.25 (s), 139.17 (s), 139.61 (s), 140.51 (s), 163.19 (s); HRMS calcd for $C_{32}H_{44}N_2O_5SSi$ 596.2740, found 596.2740.

(*E*)-6β-Formyl-12-[2-((*tert*-butyldimethylsilyl)oxy)ethylidene]-7-((4-methoxyphenyl)sulfonyl)-1,2,3aβ,4,5β,6,6a,7-octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole (58). To a solution of **57** (200 mg, 0.335 mmol) in dimethyl sulfoxide (2 mL) at 25 °C were added triethylamine (1.4 mL) and SO_3·pyridine complex (900 mg). The mixture was stirred at 25 °C for 4 h, quenched with saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with chloroform (4 × 10 mL). The extract was dried ($NaSO_4$) and evaporated in vacuo to give a residue that was purified by PLC eluting with $CHCl_3$/MeOH (9:1) to give the aldehyde **58** (140 mg, 70%): $[\alpha]^{23}_D$ +50.0° (*c* 1.0 in EtOAc); IR ($CHCl_3$) 2931, 2856, 1723, 1596, 1497, 1460, 1357, and 1261 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (1H, d, J = 2.4 Hz), 7.70 (1H, d, J = 7.9 Hz), 7.60 (2H, d, J = 8.9 Hz), 7.30 (1H, dt, J = 7.0 and 1.0 Hz), 7.17 (1H, dt, J = 7.2 and 0.7 Hz), 7.04 (1H, d, J = 7.4 Hz), 6.87 (2H, d, J = 9.0 Hz), 5.54 (1H, t, J = 5.5 Hz), 4.46 (1H, d, J = 9.0 Hz), 4.30–4.18 (1H, m), 4.08 (1H, ddd, J = 13.5, 5.2, and 1.9 Hz), 3.82 (3H, s), 3.50–3.46 (1H, m), 3.41 (1H, b s), 3.12 (1H, d, J = 3.7 Hz), 3.02–2.92 (1H, m), 2.88 (1H, d, J = 14.0 Hz), 2.77–2.71 (1H, m), 2.67–2.60 (1H, m), 2.01 (1H, dt, J = 13.6 and 3.3 Hz), 1.91 (1H, dt, J = 9.8 and 3.0 Hz), 1.58 (1H, dt, J = 13.6 and 2.6 Hz), 1.39–1.23 (1H, m), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (APT) (75 MHz, $CDCl_3$) δ –5.17 (q, 2C), 18.29 (s), 25.91 (q, 3C), 27.10, 30.03 (d), 44.34, 52.47, 53.94, 55.62, 56.84, 58.23, 59.84, 62.83, 68.62, 114.17 (d, 2C), 117.98 (d), 122.13 (d), 125.97 (d), 127.81 (d), 128.60 (d), 129.36 (d, 2C), 129.74 (s), 133.45 (s), 137.67 (s), 139.95 (s), 163.45 (s), 202.37 (d); HRMS calcd for $C_{32}H_{42}N_2O_5SSi$ 594.2584, found 594.2540.

Deprotection of 58 To Give the Protected Wieland–Gumlich Aldehyde 49. The aldehyde **58** (20 mg, 0.033 mmol) in pyridine (250 μL) at 0 °C was treated with pyridine·HF complex (20 μL, 20.0 equiv) for 2 h. The mixture was evaporated in vacuo and the residue dissolved in chloroform (2 mL) and washed with brine. The dried (Na_2SO_4) extract was evaporated in vacuo and the residue purified by PLC eluting with $CHCl_3$/MeOH (4:1) to give **49** (9.7 mg, 60%).

Conversion of 49 into the Wieland–Gumlich Aldehyde 48. To a solution of **49** (115.5 mg, 0.240 mmol) in degassed dimethoxyethane (20 mL) at –30 °C was added dropwise a solution of sodium anthracenide in dimethoxyethane (2.0 mL of a solution made from sodium (230 mg) and anthracene (1.78 g) in DME (20 mL)). After 3.5 h, a further portion (4 mL) of the sodium anthracenide solution was added and the mixture stirred at 25 °C for 10 h. The mixture was quenched with saturated $NaHCO_3$ solution (1 mL) and solid K_2CO_3 (6 g). After stirring the mixture for 6 h at 25 °C, the mixture was filtered and the solid washed with chloroform. The chloroform washings were dried (Na_2SO_4) and evaporated in vacuo to give a residue which was purified by PLC eluting with $CHCl_3$/MeOH (5:1) containing 5% NH_4OH to give **48** (90%). Treatment of **48** (200 mg) with malonic acid (1.0 g) and anhydrous NaOAc (1.0 g) in acetic anhydride (2.0 mL) heated at reflux for 2 h gave, after workup, strychnine (**1**) (70%).[28]

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Supplementary Material Available: Details of the X-ray structure determination of **16**, **23**, **30**, **41**, **46**, and **50** and tables of fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond lengths, and bond angles (111 pages). Ordering information is given on any current masthead page.