Stereocontrolled Total Synthesis of (+)-Paraherquamide B[⊥]

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Received August 7, 1995[⊗]

Abstract: The convergent stereocontrolled, asymmetric total synthesis of (+)-paraherquamide B is described. Key features of this synthesis include (1) an improved procedure to effect reduction of unprotected oxindoles to indoles; (2) a complex application of the Somei/Kametani coupling reaction; (3) a high-yielding and entirely stereocontrolled intramolecular S_N2' cyclization reaction that constructs the core bicyclo[2.2.2] ring system; (4) a mild Pd(II)-mediated cyclization reaction that constructs a complex tetrahydrocarbazole; and (5) the chemoselective reduction of a highly hindered tertiary lactam in the presence of an unhindered secondary lactam, utilizing precoordination of the more reactive secondary lactam to triethylaluminum.

Introduction

The paraherquamides are complex, heptacyclic, toxic mold metabolites with potent anthelmintic activity isolated from various *Penicillium* sp. The parent and most potent derivative, paraherquamide A (**1**), was first isolated from *Penicillium parherquei* in 1980 by Yamazaki.[1] The simplest member, paraherquamide B (**2**), plus five other structurally related paraherquamides C−G (**3**−**9**) were isolated from *Penicillium charlesii* (*fellutanum*) (ATCC 20841) in 1990 at Merck & Co.[2,3] and concomitantly at SmithKline Beecham.[4] More recently three additional related compounds were discovered by the same group at SmithKline.[5] Interest in the paraherquamides has come from the finding that this class of alkaloids displays potent anthelmintic and antinematodal properties.[6,7]

There are essentially three classes of broad-spectrum anthelmintics currently in use: the benzimidazoles, the levamisoles/morantels, and the avermectins/milbemycins. Unfortunately, the first two groups have lost much of their utility due to the recent appearance of drug resistance built up by the helminths.[7a,8] More recently drug resistance to the avermectins has been observed in various parasites.[9] The paraherquamides represent an entirely new structural class of antiparasitic agents, which promise to play a significant role in the near future. The relatively low culture yields of paraherquamide obtained for biological study have slowed the development and potential commercialization of these agents (Figure 1).

As part of our ongoing efforts to elucidate the biosynthesis of the core bicyclo[2.2.2] ring system of the related alkaloids the brevianamides,[10] we have applied methodology originally developed for the stereocontrolled total synthesis of (−)-brevianamide B[11] to complete the first stereocontrolled total synthesis of (+)-paraherquamide B (**12**);[12] the results of this study are described in full herein.

The paraherquamides are structurally very similar to brevianamides A and B (**17** and **16**)[13] and marcfortines A−C (**13**−**15**)[14] with respect to the common core bicyclo[2.2.2] ring system that is derived from the cycloaddition of an isoprene unit across the amino acid α-carbons. This close structural similarity might imply a related biogenesis, and the structural features of these substances shall be described briefly from this standpoint. The paraherquamides and brevianamides A and B (**17** and **16**) appear to be derived from the condensation of tryptophan and proline, while the marcfortines are formed from the condensation of tryptophan and pipecolic acid. The origin of the methyl group in the pyrrolidine ring of paraherquamides A and C−E and VM55595-7 could in principle come from the methylation of proline, but it seems more likely that this amino acid residue is derived from isoleucine. The very low fermentation yield of paraherquamide B may be a manifestation of poor incorporation of cyclo-L-trp-L-pro into the subsequent biosynthetic machinery

[⊥] Dedicated to Professor Ei-ichi Negishi on the occasion of his 60th birthday.

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[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.

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(4) Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot.* **1991**, *44*, 492.

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(9) (a) Van Wyk, J. A.; Malan, F. S. *Vet. Rec*. **1988**, *123*, 226. (b) Echevarria, F. A. M.; Trindade, N. P. *Vet. Rec.* **1989**, *124*, 147.

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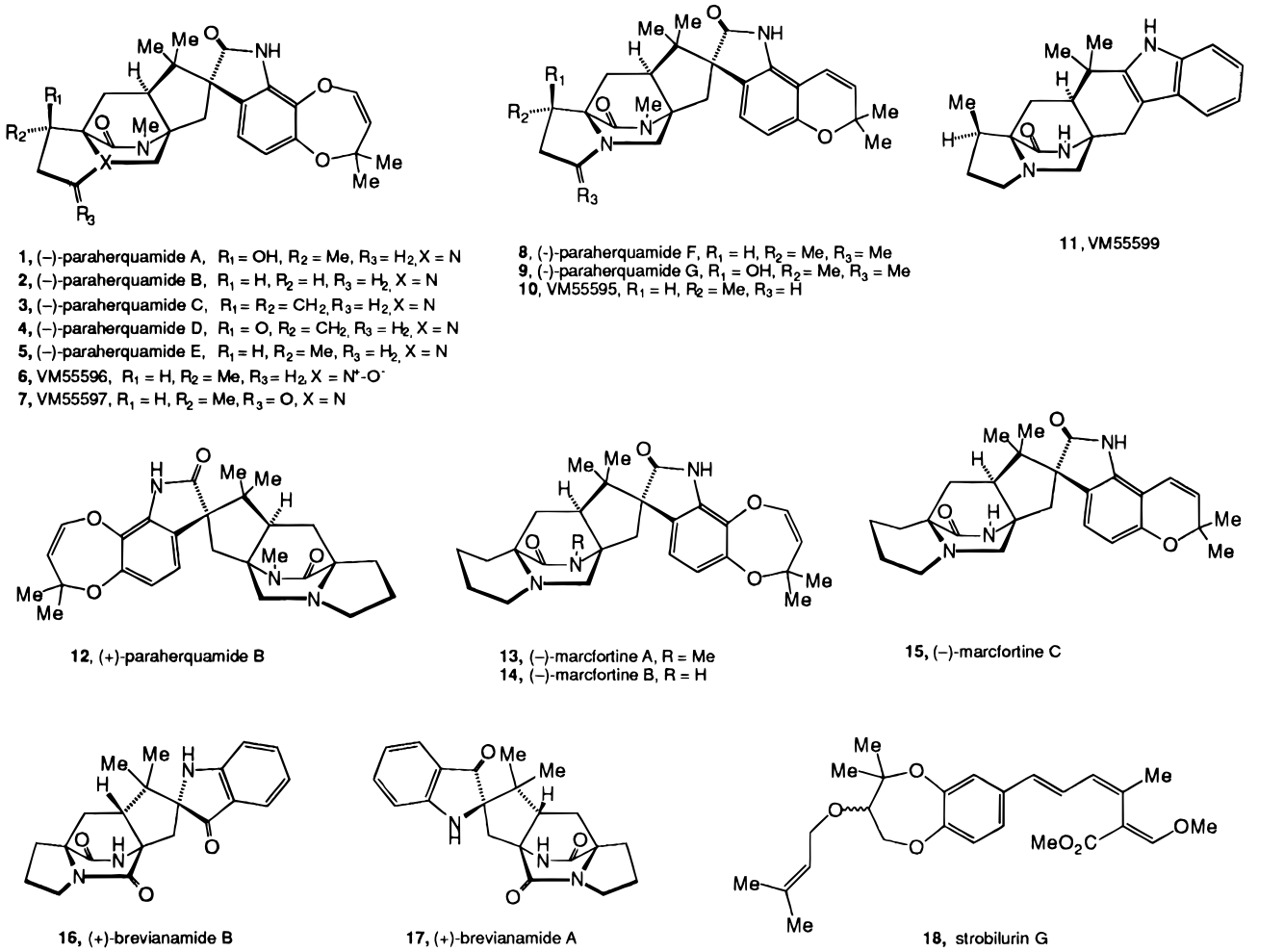

Figure 1.

or may be the result of inefficient demethylation of the isoleucine-derived amino acid precursor.

The oxidation state of the amino acid-derived dioxopiperazine moiety remains unchanged in the case of the brevianamides, but for the paraherquamides and the marcfortines the tertiary amide residue is enzymatically reduced to a monooxopiperazine, a process that is known.[15] The tryptophan-derived indolyl side chain of the paraherquamides and marcfortines is oxidized to spiro-oxindoles while the indolyl side chain of the brevianamides oxidize to spiro-indoxyls. The paraherquamides, marcfortines, and brevianamides all incorporate one isoprene unit that forms the bridging bicyclo[2.2.2] ring structure. The paraherquamides and marcfortines differ from the brevianamides in that a second isoprene unit coupled with an oxidized form of tryptophan gives the dioxepin (or pyran) moiety. This is one of the most interesting and unique features of these compounds. The *gem*-dimethyl dioxepin ring found in paraherquamides A−E (**1**−**5**) and marcfortines A and B (**13** and **14**) is a unique ring system among natural products. A similar structural feature was discovered in the antifungal natural product strobilurin G (**18**),[16] but this dioxepin moiety lacks the double bond found in the other metabolites (Figure 1).

As outlined in Scheme 1, a convergent synthesis of the enantiomer of paraherquamide B (**12**)[17] was envisioned to contain four key carbon−carbon bond-forming reactions. The first task would involve the construction of a suitably α-alkylated proline derivative.[11] The second important coupling would be the Somei/Kametani-type alkylation[18] of a suitably protected gramine derivative (**20**) and the requisite piperazinedione (**19**). The third and perhaps most crucial C−C bond-forming reaction, providing the core bicyclo[2.2.2] ring system, was a stereofacially controlled intramolecular S_N2' cyclization reaction that sets the stereochemistry at C-20 (paraherquamide numbering) and concomitantly installs the isopropenyl group that will be utilized in the fourth C−C bond-forming reaction. This isopropenyl group, in turn, would be conscripted for an olefin−cation cyclization to provide the heptacyclic tetrahydrocarbazole. Standard procedures to effect this transformation involve strong protic acids,[11,19] and there was reason for concern about the reactivity of the more highly oxygenated indole (**22**) as a practical synthetic precursor to **23**. The penultimate step, a regio- and stereofacially controlled oxidative spirocyclization reaction, must be accomplished to construct the desired spiro-oxindole. A number of these transformations were explored during the course of the investigations on the synthesis of (−)-brevianamide B,[11] including a simple oxindole model study,[11c] which set a firm foundation for addressing some of the

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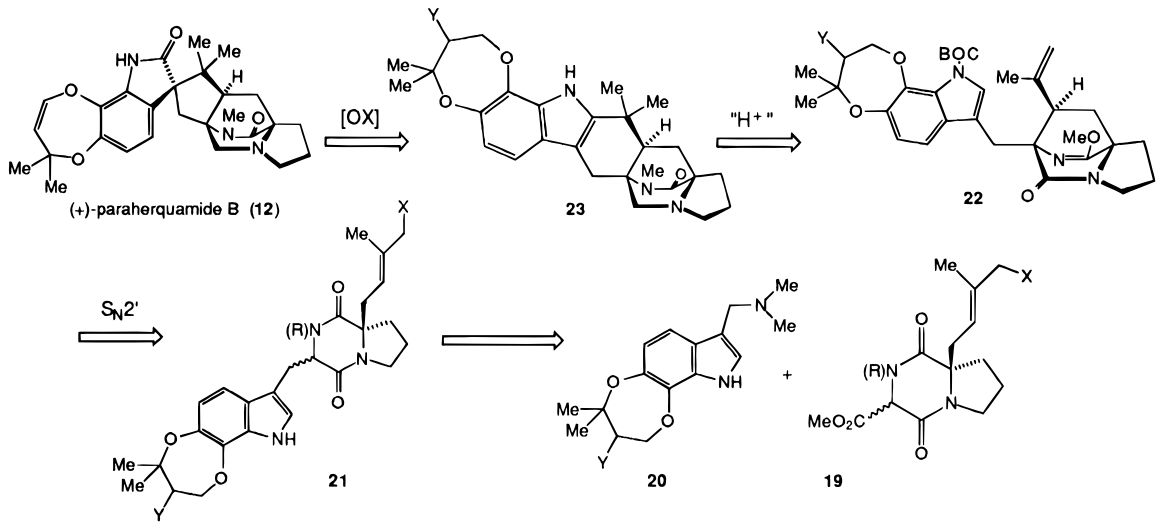
(16) Fredenhagen, A.; Hug, P.; Peter, H. H. *J. Antibiot.* **1990**, *48*, 661.

(17) The enantiomer of the natural product was selected as the target due to the large relative cost difference between (*S*)- and (*R*)-proline.

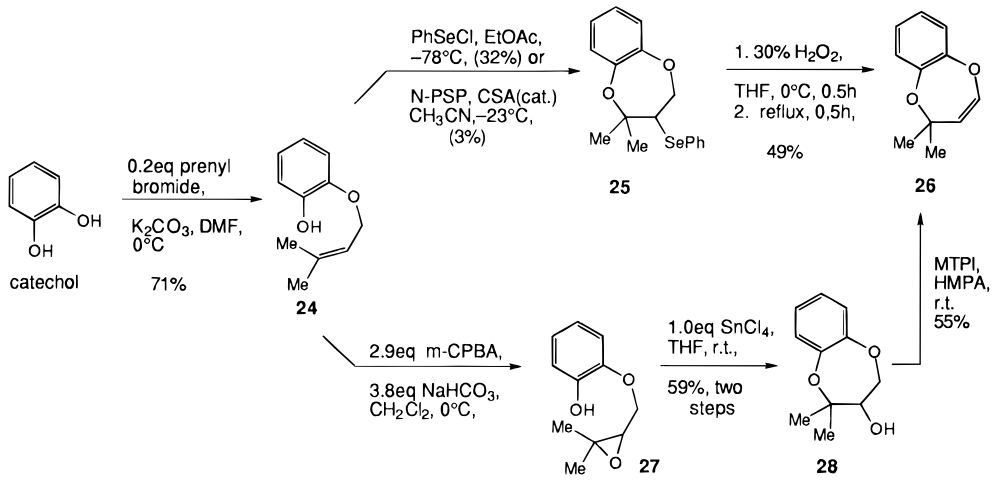
(18) (a) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941. (b) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974.

(19) (a) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564. (b) Guller, R.; Dobler, M.; Borschberg, H.-J. *Helv. Chim. Acta* **1991**, *74*, 1636. (c) Darbre, T.; Nussbaumer, C.; Borschberg, H.-J. *Helv. Chim. Acta* **1984**, *67*, 1040. (d) Delpech, B.; Khuong-Huu, Q. *J. Org. Chem.* **1978**, *43*, 4898.

Scheme 1



Scheme 2



stereochemical and regiochemical issues that would be faced in attacking the paraherquamide ring system.

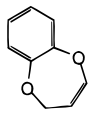
Results and Discussion

Construction of the Dioxepinooxindole Ring System. The prenylated catechol ring system of the paraherquamides is an unusual oxidative cyclization product that previously has not been observed to occur in metabolites of mixed biogenetic origin. Although the parent 2*H*-1,5-benzodioxepin has been synthesized previously,[20] to the best of our knowledge there has been no reported synthesis of the corresponding isoprenyl dioxepin ring system of paraherquamide. The synthesis of this ring system was explored in a simple model study employing prenylated catechol **24** (Scheme 2).[21] It was speculated that the requisite 7-*endo-tet* cyclization reaction would be facilitated by a stabilized tertiary carbocation provided by the prenyl substituent.

The first attempt at effecting this cyclization reaction employed a phenylselenoetherification.[22] Following a procedure of Clive,[23] **24** cyclized to **25** with either PhSeCl or *N*-phenylselenophthalimide (N-PSP),[24] although in very low yield. The main byproducts came from the electrophilic addition across the double bond, electrophilic aromatic substitution of the phenyl ring by the phenyl selenide, and phenolic attack at the methylene producing the six-membered-ring product. The selenide **25** was treated with H_2O_2 and the resulting selenoxide thermally eliminated providing the unique dioxepin **26** in 49% yield.

Due to the low yield of the phenylselenoetherification, an alternative procedure involving epoxidation followed by a Lewis acid-mediated ring closure was investigated.[25] The prenylated catechol **24** was epoxidized with buffered *m*-CPBA to provide epoxide **27**, which was treated with stannic chloride to give the dioxepin **28**. A major side product in this reaction was a ketone,

(20) Guillaumet, G.; Coudert, G.; Loubinnoux, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 64.



2H-1,5-benzodioxepin

(21) Williams, R. M.; Cushing, T. D. *Tetrahedron Lett.* **1990**, *31*, 6325.

(22) (a) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097. (b) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784. (c) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049−1132.

(23) (a) Clive, D. J. L.; Chiiattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1977**, 725. See also: (b) Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, *50*, 4977. (c) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429.

(24) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

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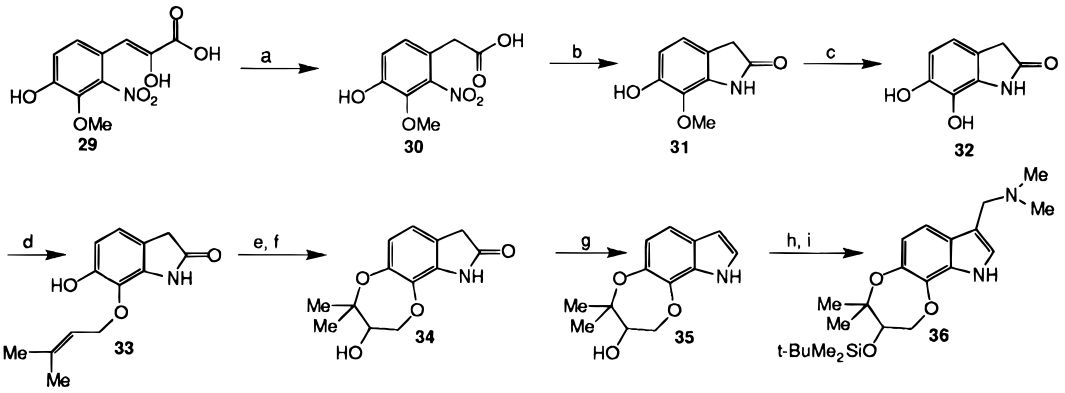
Scheme 3[a]



[a] Reagents and conditions: (a) 4.0 equiv of NaOH, 1.0 equiv of 30% H_2O_2, 81−93%; (b) H_2, Pd/C, AcOH, 92%; (c) 2.5 equiv of BBr_3, CH_2Cl_2, −78 °C, 99%; (d) 1.2 equiv of prenyl bromide, 1.1 equiv of K_2CO_3, DMF, 0 °C to room temperature, 52%; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (f) 1.2 equiv of $SnCl_4$, THF, 64%; (g) 1.6 equiv of $NaBH_4$, 3.5 equiv of $BF_3{\cdot}OEt_2$, THF, 44−50%; (h) *t*-$BuMe_2SiCl$, im, DMF, 40 °C, 83%; (i) CH_2O, $HNMe_2$, AcOH, H_2O, 99%.

resulting from a 1,2 hydride shift.[26] A number of methods were explored to effect the dehydration of the secondary alcohol of dioxepin **28**; the best result was realized with methyltriphenoxyphosphonium iodide (MTPI) in HMPA to provide **26**.[27]

With a proven method accessible for the construction of the dioxepin ring system, attention was focused on constructing the requisite gramine derivative. Oxygenated indoles are notoriously unstable and undergo facile autoxidation,[28] photooxidation,[29] dimerization, and polymerization.[30] In light of this problematic reactivity, our plan called for formation of the dioxepin ring system prior to indole (gramine) formation. The approach employed involved the formation of a suitably substituted oxindole (essentially a protected indole), followed by the construction of the dioxepin and final elaboration into the gramine derivative.

The known pyruvic acid **29** (Scheme 3)[31] (prepared in five steps from vanillin) was oxidatively decarboxylated[32] to afford the phenylacetic acid **30**, which was reductively cyclized to give the required oxindole **31**[33] in nearly quantitative yield.

At this point, a method was needed to differentiate between the two phenolic substituents for the prenylation reaction. A number of attempted selective protecting group strategies were explored, but nothing satisfactory was found; it was thus decided to forgo any protecting group for the 6-hydroxy position. Oxindole **31** was cleanly demethylated upon treatment with (clear) boron tribromide. The resulting oxindole **32** was subjected to the prenylation conditions, and the desired alkylated product **33** was obtained in 52% yield.[34,35] Both of the methods discussed above for the formation of the seven-membered ring were examined. The phenylselenoetherification procedure failed on this substrate, and only products resulting from electrophilic aromatic substitution were formed.

The alternative epoxidation/Lewis acid-mediated cyclization again proved to be successful on this substrate. The epoxidation reaction (*m*-CPBA) had to be buffered with $NaHCO_3$, to prevent the formation of the six-membered-ring tertiary alcohol. In most cases, the reaction was worked up and taken on to the next step without purification (the labile epoxide tended to cyclize to the six-membered tertiary alcohol upon contact with silica gel). The incipient epoxide product was directly treated with $SnCl_4$ in THF to provide the desired seven-membered-ring alcohol **34** (64% overall yield from **33**).

N-Alkylated oxindoles have been reported to be reduced to indoles by the use of DIBAL or $LiAlH_4$;[36] however, in the case of unsubstituted oxindoles, this reduction either fails or requires

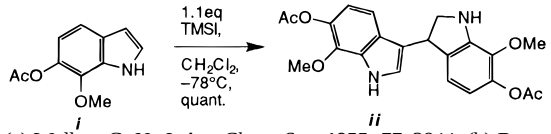
(26) For a related observation, see: Taylor, S. T.; Davisson, M. E.; Hissom, B. R., Jr.; Brown, S. J.; Pristach, H. A.; Schramm, S. B.; Harvey, S. M. *J. Org. Chem.* **1987**, *52*, 425.

(27) Hutchins, R. O.; Hutchins, M. G.; Milewski, C. A. *J. Org. Chem.* **1972**, *37*, 4191.

(28) Houlihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles, Part one, The Chemistry of Heterocycles;* John Wiley & Sons, Inc.: New York, 1972.

(29) (a) Chan, A. C.; Hilliard, P. R., Jr. *Tetrahedron Lett*. **1989**, *30*, 6483. (b) d'Ischia, M.; Prota, G. *Tetrahedron* **1987**, *43*, 431.

(30) This difficulty was observed in a short synthesis of the known 6-acetoxy-7-methoxyindole (**i**). The unstable substance **i** was treated with TMSI, producing the dimer **ii** as the sole product.



i *ii*

See: (a) Walker, G. N. *J. Am. Chem. Soc.* **1955**, *77*, 3844. (b) Burton, H.; Duffield, J. A.; Prail, P. F. G. *J. Chem. Soc.* **1950**, 1062. (c) Beer, R. J. S.; Mcgrath, L.; Robertson, A.; Woodier, A. B. *J. Chem. Soc.* **1949**, 2061. (d) Beer, R. J S.; Clarke, K.; Khorana, H. G.; Robertson, A. *J. Chem. Soc.* **1948**, 2223. (e) Chan, A. C.; Hilliard, P. R., Jr. *Tetrahedron Lett*. **1989**, *30*, 6483. (f) d'Ischia, M.; Prota, G. *Tetrahedron* **1987**, *43*, 431. (g) Deibel, R. M. B.; Chedekel, M. R. *J. Am. Chem. Soc*. **1984**, *106*, 5884. (h) Heacock, R. A. *Chem. Rev*. **1959**, *59*, 181.

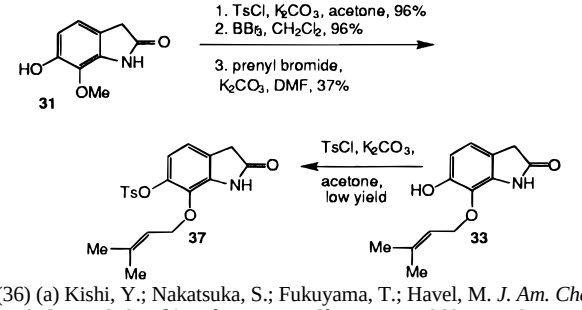
(31) (a) Beer, R. J. S.; Clarke, K.; Davenport, H. F.; Robertson, A. *J. Chem. Soc*. **1951**, 2029. (b) Bennington, F.; Morin, R. D.; Clark, L. C., Jr. *J. Org. Chem.* **1959**, *24*, 917.

(32) Kosuge, T.; Ishida, H.; Inabe, A.; Nukaya, H. *Chem. Pharm. Bull.* **1985**, *33*, 1414.

(33) This material has interesting chemical and physical characteristics. The solvent must be removed immediately after the hydrogenolysis to prevent the white product from turning to a black sludge. This oxindole **31** would also change from a white color to a metallic gray simply by drying on the vacuum pump. These decomposition properties are no doubt due to the autoxidation of the indole tautomer form.

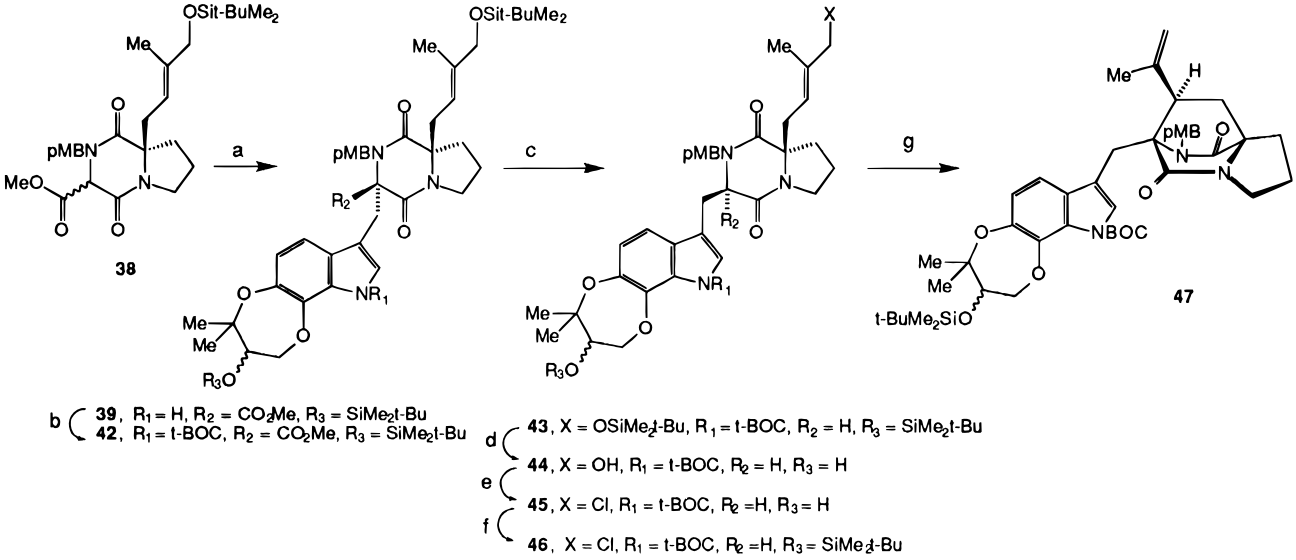
(34) The undesired regioisomer was obtained in less than 1% yield, and the bis-alkylated material was produced in only 8.3% yield. This selectivity is presumably a manifestation of the domination of inductive effects of the amide functionality directing the alkylation to the 7-position.

(35) The structure of compound **33** was confirmed by simply tosylating **33** and comparing the product (**37**) to the same substance prepared from **31**. The two independently synthesized products were identical in every way.



(36) (a) Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc*. **1973**, *95*, 6494. (b) Robinson, B. *Chem. Rev*. **1969**, *69*, 785.

Scheme 4[a]



[a] Reagents and conditions: (a) **36**, 0.5 equiv of PBu_3, MeCN, 51%; (b) DMAP, Et_3N, BOC_2O, CH_2Cl_2, 90%; (c) 5 equiv of LiCl, 1.5 equiv of H_2O, HMPA, 100 °C, 66%; (d) 3.0 equiv of *n*-Bu_4NF, THF, 79%; (e) 1.9 equiv of LiCl, 4.0 equiv of collidine, 4.0 equiv of MsCl, DMF, 86%; (f) *t*-$BuMe_2SiOTf$, 2,6-lutidine,CH_2Cl_2, 76%; (g) 10 equiv of NaH, benzene, 11%.

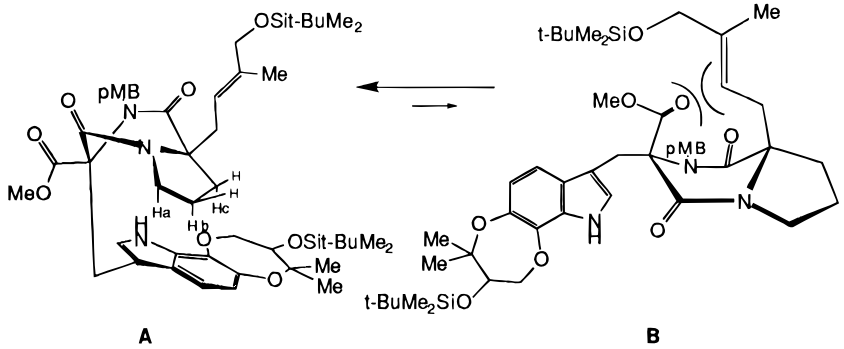


Figure 2.

more vigorous conditions. In 1972 it was reported[37] that substituted and unsubstituted oxindoles could be reduced to the corresponding indole in high yields with borane in THF at 0 °C. Oxindole **34** was subjected to these conditions (1.0 M BH_3/THF, Aldrich), but with no reaction. However, when oxindole **34** was treated with 1.6 equiv of $NaBH_4$ and 3.5 equiv of BF_3·OEt_2 in THF for 1 day (0 °C to room temperature), the desired indole **35** was obtained in 43−50% yield. The indole **35** was treated with a warm solution of TBDMSCl and imidazole in DMF, to provide the required O-silylated indole, which was easily converted to the gramine **36** through the well-known Mannich procedure (Scheme 3).

Construction of the Bicyclo[2.2.2] Ring System. To probe the stability of the dioxepin−indole in subsequent transformations, a model study involving the previously synthesized racemic piperazinedione **38**[38] was investigated (Scheme 4). Indole **36** was condensed with the piperazinedione **38** following the Somei/Kametani conditions[18] to give the desired *syn* product **39** (a racemic mixture of two diastereomers) in 51% yield. The relative stereochemistry of this substance was evident by an examination of the ^1H NMR spectrum. There is a large upfield shift of the proline ring protons of **39** (δ Ha, Hb, Hc; 0.03−0.19 (m), 0.43−0.52 (m), 0.62−0.72 (m) ppm). It is well-known that N-alkylated piperazinediones prefer to adopt a boat-like conformation due to the planar geometry of the amides and A-1,3 steric interactions of *N*-alkyl residues. This forces the substituents on the amino acid α-carbons to adopt either pseudoaxial or pseudoequatorial dispositions. In conformer **B** (Figure 2) the carbomethoxy group is sterically congested by the bulky isopentenyl group, favoring the alternate boat conformer (**A**), which positions the indole ring under the piperazinedione, positioning the two pyrrolidine protons Ha and Hb directly over the shielding cone of the aromatic indole ring system; the corresponding *anti*-isomer cannot adopt this type of conformation. Furthermore, a consideration of the mechanism of the Somei/Kametani reaction[18] supports the expectation that the *syn*-isomer (**39**) should be the major product. The gramine derivative (**36**) reacts with tributylphosphine to form a bulky (tributylphosphino)indole intermediate that can only approach from the less congested face of the piperazinedione enolate, away from the isopentenyl moiety.

A similar phenomenon was observed when **39** was subjected to the decarbomethoxylation procedure (LiCl, H_2O, HMPA) directly. The two main products isolated were the *syn*-isomer **40** and the *anti*-isomer **41**, in a ratio of 3.3:1.0 (Figure 3). These stereochemical assignments were made by comparing the ^1H NMR spectral data of **40** and **41**. There was a pronounced upfield shift of three pyrrolidine ring protons in compound **41**, a shift that is not observed for diastereomer **40**.

Piperazinedione **39** was first converted to the BOC-protected indole **42**, which was subsequently subjected to a decarbomethoxylation reaction supplying the *syn*-diastereomer **43** as

(37) Sirowej, H.; Khan, S. A.; Plieninger, H. *Synthesis* **1972**, 84.

(38) Williams, R. M.; Glinka, T. *Tetrahedron Lett.* **1986**, *27*, 3581.

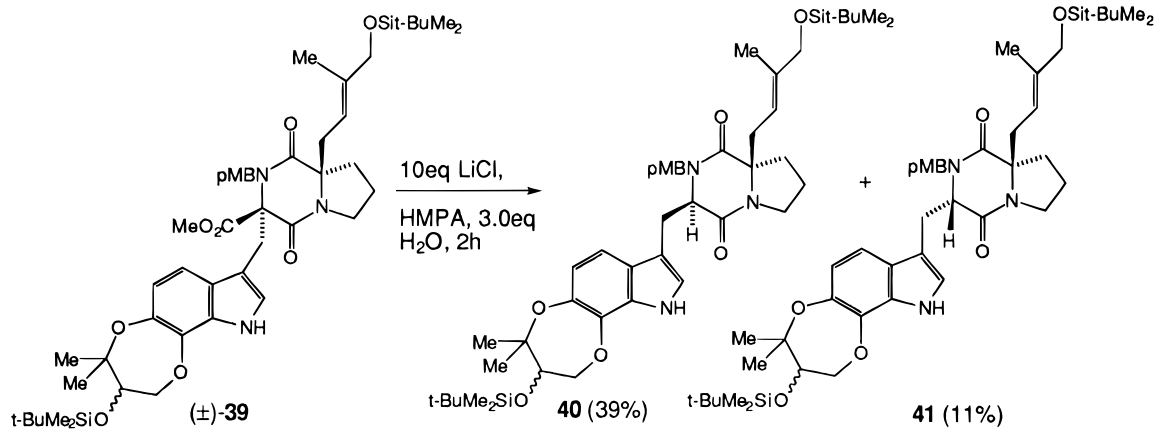
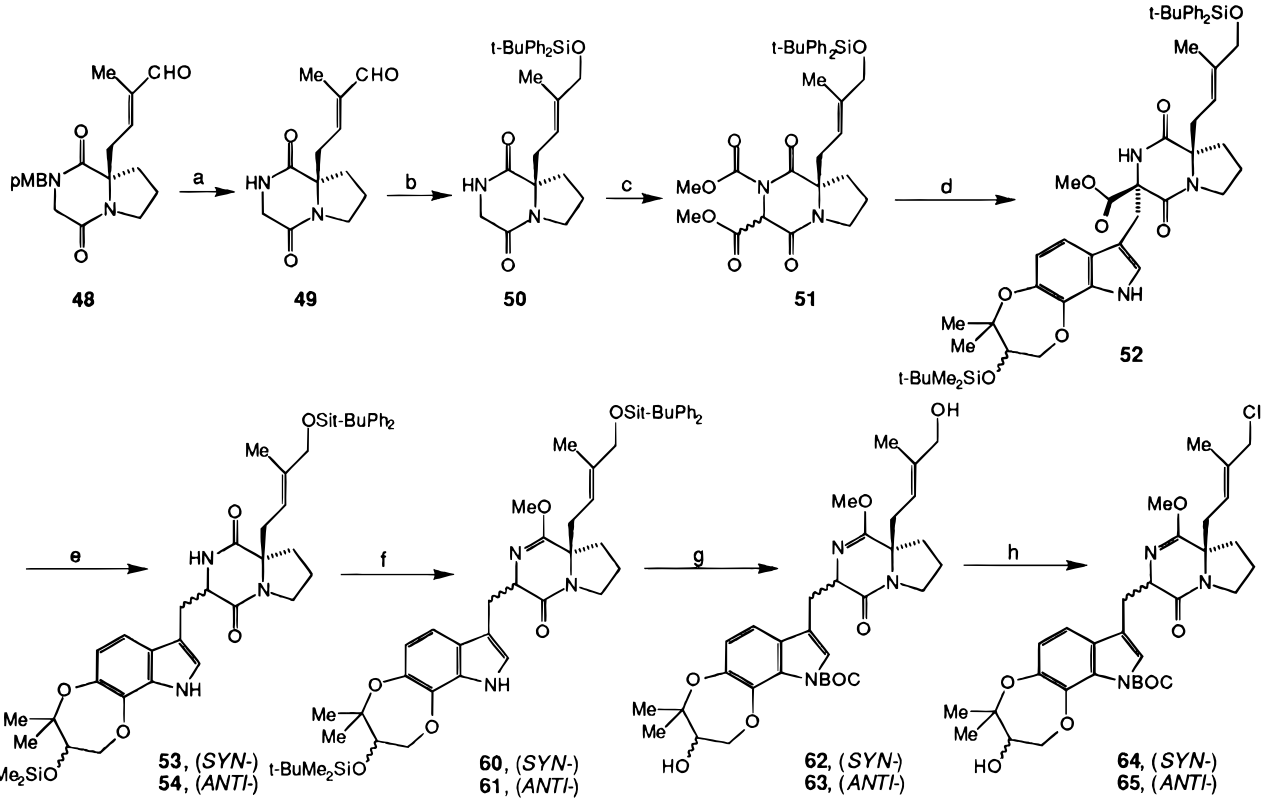


Figure 3.

Scheme 5[a]



[a] Reagents and conditions: (a) 3.8 equiv of CAN (0.33 M), 2:1 CH_3CN/H_2O, 2 h, 79%; (b) (i) 2 equiv of $NaBH_4$, EtOH; (ii) *t*-$BuPh_2SiCl$, im, DMF, 75%; (c) (i) 1.0 equiv of *n*-BuLi, 1.1 equiv of MeOCOCl, −78 °C; (ii) 2.2 equiv of $LiN(SiMe_3)_2$, 1.1 equiv of MeOCOCl, THF, −100 °C, 93%; (d) **36**, 0.5 equiv of PBu_3, CH_3CN, reflux, 73%; (e) LiCl, HMPA, 100 °C (*syn*/*anti* 3:1), 89%; (f) Me_3OBF_4, Na_2CO_3, CH_2Cl_2 (*syn*, 81%; *anti*, 62−71%); (g) (i) BOC_2O, DMAP, Et_3N, CH_2Cl_2; (ii) *n*-Bu_4NF, THF (*syn*, 90%; *anti*, 85%); (h) NCS, Me_2S (*syn*, 74−81%; *anti*, 86%).

the major product. Compound **43** (the minor, *anti*-diastereomer was not utilized) was desilylated to provide the diol **44**, which was converted to the allylic chloride **45**. Careful treatment of **45** with *t*-$BuMe_2SiOTf$, to prevent transesterification of the BOC groups,[39] gave the desired product **46** in 76% yield. Allylic chloride **46** was subjected to 10 equiv of NaH in refluxing benzene, but the reaction proved extremely sluggish. After 5 days, the desired product **47** was obtained in a poor 11% yield (19% based on recovered **46**; accompanied by extensive decomposition). The *syn*-isomer **47** was the only stereoisomer formed in this reaction; the corresponding *anti*-isomer was not detected. While this reaction demonstrated the potential viability of the stereoselective intramolecular S_N2' reaction, work on the racemic model system was halted, due to the low yield in this key transformation coupled with perceived difficulties associated with removing the *N*-*p*-methoxybenzyl group.

Total Synthesis of (+)-Paraherquamide B. Starting from the known piperazinedione **48** (prepared in eight steps from (S)-proline),[11] the enal **49** was obtained in 79% yield by treatment of **48** with a 0.33 M solution of ceric ammonium nitrate (Scheme 5).[40] The resulting product (**49**) was reduced with $NaBH_4$ and protected with *t*-$BuPh_2SiCl$ in a two-step process to give the silyl ether **50** in 75% yield. Compound **50** was then subjected to a two-step, one-pot acylation providing the required substrate **51** in 93% yield. The crude material was a mixture of epimers in a ratio of approximately 4:1 (*syn:anti*). Interestingly this mixture had a tendency to epimerize during column chroma-

(39) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.

(40) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

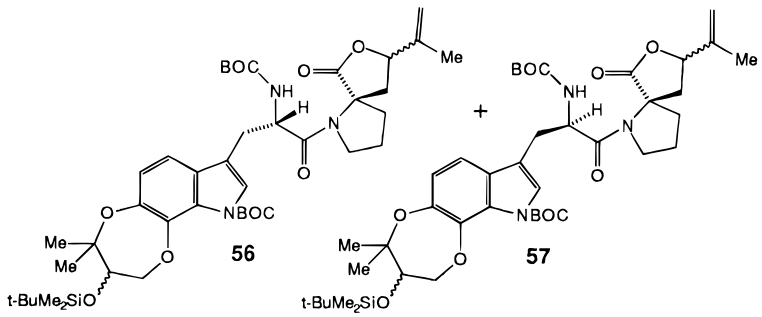
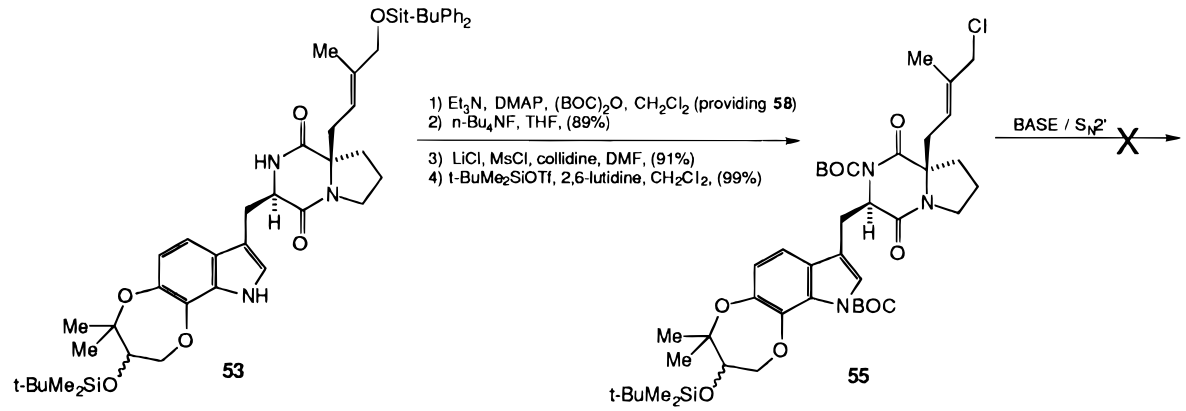


Figure 4.

Scheme 6



tography, resulting in an increase in the proportion of the *syn*-isomer. The two products were combined and condensed with the gramine **36** providing the indole **52** in 73% yield as a mixture of two diastereomers (epimeric at the secondary alcohol stereogenic center). Interestingly, the imidic carbamate group was also cleaved in the course of this reaction. Compound **52** was subjected to the decarbomethoxylation procedure, affording a 3:1 mixture of **53** (*syn*) and **54** (*anti*) in 89% combined yield.

The lactam **53** could be converted to the *N*-BOC-protected allylic chloride **55** in four steps and in good overall yield (Scheme 6), but numerous attempts to effect the S_N2' reaction on this substrate failed. These reactions were capricious and were accompanied by the occasional appearance of the spirolactones **56** and **57**, formed in low yield <5% (Figure 4). It seems likely that the failure of **55** to cyclize in the desired fashion can be attributed to nonbonding interactions between the *tert*-butoxycarbonyl group and the pendant dioxepin indole.[41,42]

These observations dictated that a suitable amide protecting group would have to be selected that was less electron withdrawing and less sterically demanding than both the *tert*-butoxycarbonyl and the *p*-methoxybenzyl groups. The loss of the lactam methoxycarbonyl group in the alkylation of **51** with the gramine **36** was presumably due to N → N acyl transfer to dimethylamine, a byproduct of the Somei/Kametani reaction. This appears to be a general reaction that was used to selectively deprotect the *N*-*tert*-butoxycarbonyl group of **58** without deblocking the *N*-*tert*-BOC-protected indole. Thus, refluxing a solution of **58** and Me_2NH in CH_3CN furnished compound **59** in 92% yield[43] (Scheme 7).

The strategy planned for the reduction of the tertiary amide called for the protection of the secondary lactam as a lactim ether,[44] and this group seemed suitable for use earlier in the synthesis and appeared compatible with the S_N2' cyclization. Thus, *syn*-isomer **53** was treated with 20 equiv (optimum) of Na_2CO_3 and 5 equiv of Me_3OBF_4 in dichloromethane for 4 h, to yield 81% of compound **60**. Even though the next two reactions could be carried out in a stepwise fashion, it proved most convenient to convert **60** directly to the protected diol **62** in a one-pot, two-step sequence. Diol **62** was then subjected to the chlorination procedure successfully used in the conversion of diol **44** to the allylic chloride **45**. Unfortunately, under these conditions, the reaction failed and the lactim ether was cleanly deblocked back to the lactam. This problem was finally solved by following the procedure of Corey,[45] which called for the addition of compound **62** to a mixture of *N*-chlorosuccinimide and dimethyl sulfide, which yielded the chloride **64** in 81% yield.

Allylic chloride **64** was reprotected with *t*-$BuPh_2SiOTf$ to provide **66** in 77−82% yield. The stage was now set to effect the S_N2' reaction. Compound **66** was refluxed in benzene with 20 equiv of sodium hydride, resulting in a very clean and high-yielding cyclization reaction furnishing the desired product **68** in 93% yield (Scheme 8).

(41) The formation of the two spiro compounds **56** and **57** is presumably due to the increased electrophilicity of the N-acylated amide. Apparently, trace moisture in the reaction mixture caused the production of hydroxide, which then hydrolyzed the reactive amide bond. The resulting carboxylic acid cyclized in an S_N2' fashion, furnishing the spiro lactones.

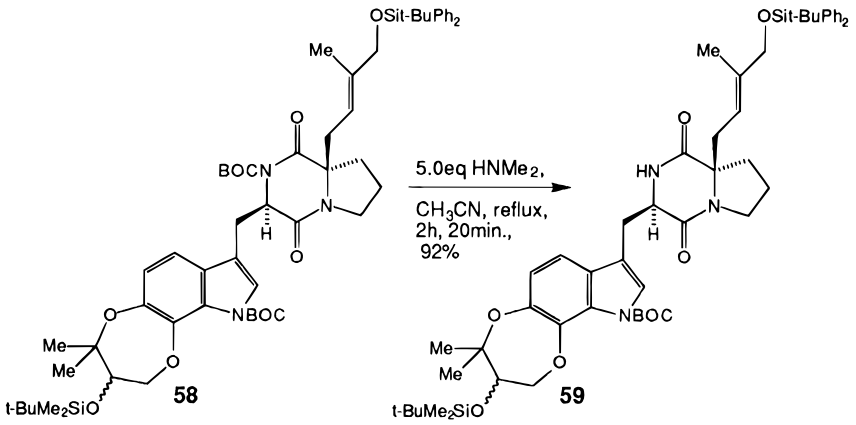
(42) (a) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228. (b) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(43) This result is noteworthy, especially in light of a report that *tert*-butoxycarbonyl-protected amides are cleaved to the *tert*-butoxycarbonyl-protected amines with DEAEA (2-(*N*,*N*-diethylamino)ethylamine) in CH_3CN at room temperature; see: Grehn, L.; Gummarsonn, K.; Ragnarsson, U. *Acta Chem. Scand. B* **1987**, *41*, 18. However, the substrates examined in that report were all open-chain amides. Interestingly it is known that BOC-protected lactams can be cleaved by base but it is the amide bond that is broken as was observed on substrate **55**. Recently it has been reported that $Mg(OMe)_2$ will also cleave lactam carbamates including BOC-protected lactams; see: Wei, Z.-Y.; Knaus, E. E.; *Tetrahedron Lett.* **1994**, *35*, 847.

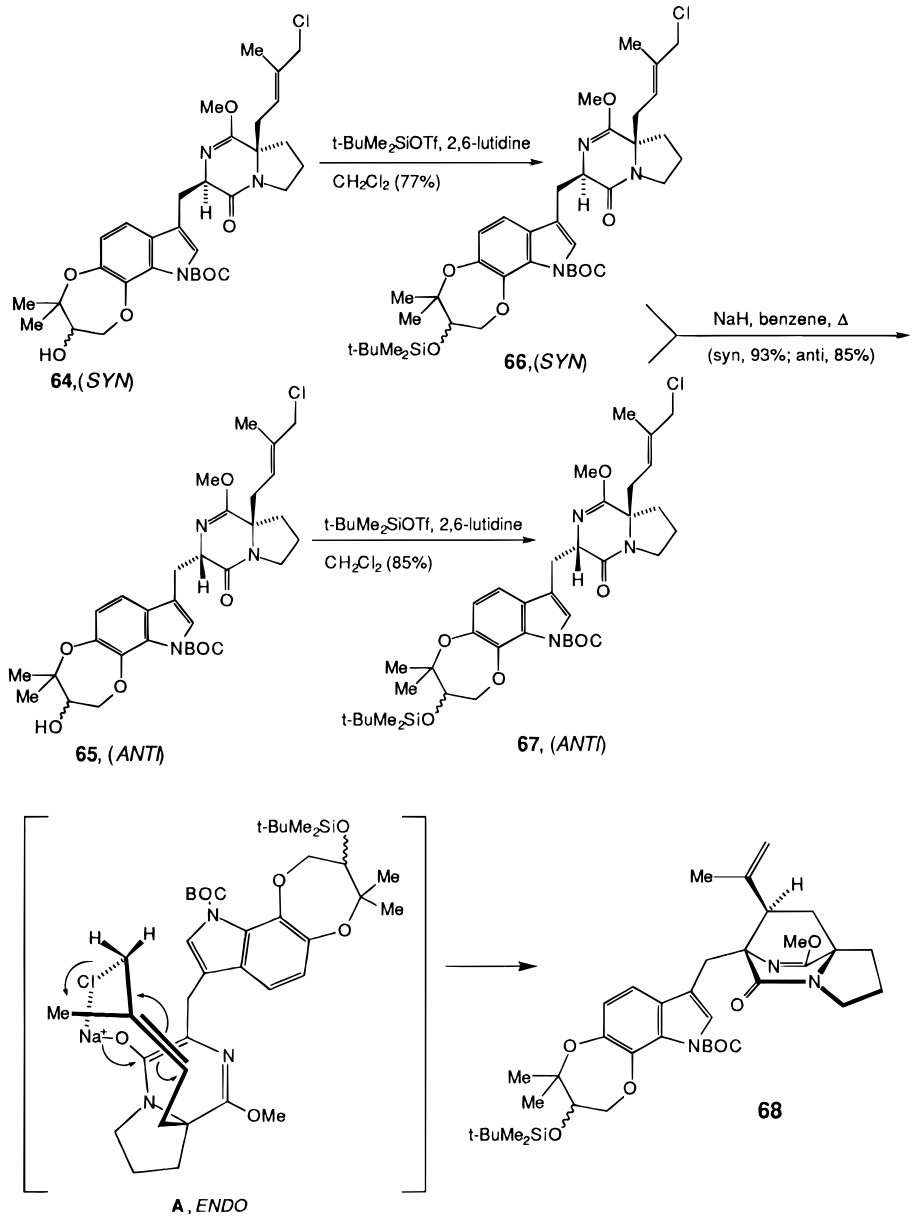
(44) Williams, R. M.; Brunner, E. J.; Sabol, M. R. *Synthesis* **1988**, 963.

(45) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339.

Scheme 7



Scheme 8



This last series of reactions was also carried out in parallel on the *anti*-isomer **54**. Following the same sequence (five steps) we obtained the fully protected chloride **67** in good yield. The chloride **67** was then refluxed in benzene with the required amount of sodium hydride to yield the same product (**68**, 85% yield) as that obtained from **66**. The yields of **68** from both routes were very high, and the undesired *anti*-diastereomer was not detected. The high degree of facial selectivity observed in the cyclizations to **68** and **47** is quite interesting and warrants some comments. It is generally accepted that S_N2' reactions

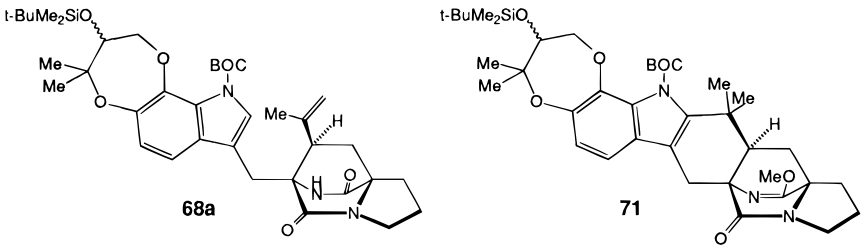


Figure 5.

favor a *syn* orientation[46] (i.e., the incoming nucleophile attacks the π-electrons from the same face as the departing leaving group, polarizing the π-system in the proper orientation for a "backside" displacement on the C−Cl bond). Alternatively, a frontier molecular orbital analysis has indicated[46a] that the stabilization imparted by a $HOMO_{Nuc}-LUMO_{allylic}$ interaction is greater for the *syn* overlap. While the greatest level of diastereoselectivity was observed with a nonpolar aprotic solvent (benzene), a fairly significant change in the relative amounts of the *syn*- and *anti*-diastereomers can be realized by simply changing the solvent to a more polar solvent such as DMF.[11] In the present system, additional stabilization for the *endo* transition state may be due to the formation of a tight contact ion pair between the chlorine atom and sodium atom of the enolate species (see **A**, Scheme 8) in the transition state for the formation of the C−C bond.[47] The poor ligating solvent benzene is not capable of effectively solvating the enolate cation nor the developing chloride anion in the transition state. It is reasonable that this type of association favors the rotamer that positions the allylic chloride moiety over the enolate, resulting in the desired *syn* stereochemistry.

With the bicyclo[2.2.2] ring system constructed in a reliable and high-yielding sequence, attention was turned to the final C−C bond-forming reaction on the indole. Due to the strongly acidic conditions that were used previously for a related cyclization reaction in the brevianamide synthesis, it was assumed that the silyl ether, the *tert*-butoxycarbonyl protecting group, and the lactim ether would be removed during this cyclization reaction. Subjecting compound **68** to the standard conditions (dilute, aqueous HCl in dioxane at 10 °C)[11,19,48] resulted in extensive decomposition, and none of the desired cyclized product was ever detected. The reaction conditions were extensively varied using different acids and temperatures, but the only recognizable products were those stemming from the loss of protecting groups. The problem might be attributed to the enhanced basicity of the indole at the 2-position (indole numbering) caused by the electron-donating oxygen atoms in the aromatic ring. If protonation at the 2-position is kinetically competitive with olefin protonation, cyclization would be precluded.

A search of the literature revealed a 1982 Trost and Fortunak paper[49] wherein $PdCl_2$ and $AgBF_4$ were utilized to effect the Heck-type cyclialkylations of various isoquinuclidine model compounds. Compound **68** was exposed to these conditions, affording the heptacycle **69** in 63−82% yields. During the course of the reaction, the lactim ether moiety was cleaved, restoring the free, secondary amide.[50] The main byproduct of this reaction was the uncyclized free lactam **68a** (Figure 5), which curiously did not cyclize to **69** when subjected to the same conditions. It was also observed that the lactim ether protected heptacycle **71** could not be deblocked to the free lactam **69** with $PdCl_2$ and $AgBF_4$ alone, implying that the cleavage of the lactim ether is due to the tetrafluoroboric acid produced in the cyclization, and that the cyclization occurs *prior* to lactim ether cleavage.

Trost and Fortunak speculated[49] that the cyclization mechanism was either a Heck-type arylation or the electrophilic aromatic substitution of a palladium-complexed olefin, and there was evidence to support both mechanistic possibilities. It is possible that the palladium chloride and the silver tetrafluoroborate react to form a powerful Lewis acid, since an incubation period involving these two reagents is needed prior to the introduction of the substrate. It was reported[49] that there is no reaction with other mixed-metal systems involving palladium chloride (e.g., boron trifluoride, aluminum chloride, stannous chloride, stannic chloride, titanium trichloride). The enhanced basicity (nucleophilicity) at the 2-position of indole **68** renders this substance perfectly disposed to undergo a Heck-type arylation reaction.

There are several reports of methods that will selectively reduce a tertiary amide in the presence of a secondary amide.[51] The secondary lactam of **69** was protected as the lactim ether **71** and treated with diborane; however, the spectral characteristics of the major products isolated were consistent with reduction of both the tertiary amide and the lactim ether. In 1991 Martin *et al.*[52] successfully used alane to reduce a tertiary amide in the presence of an oxindole (secondary amide) relying on the known rate difference for reduction between these two groups.[53] However, initial experiments with this reagent gave poor results, with the secondary amide undergoing reduction along with the tertiary amide. Compound **69** (and **71**) is sufficiently twisted such that the *gem*-dimethyl groups effectively block the β-face of the tertiary amide (Figure 6),

(46) (a) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359. (b) Magid, R. A. *Tetrahedron* **1980**, *36*, 1901.

(47) The idea that the stereochemical outcome of an intramolecular enolate alkylation is determined by chelation in the transition state was recently demonstrated by Denmark and Henke, who observed a marked preference for a "closed" transition state (coordination of the cationic counterion to an enolate and the developing alcohol) resulting in a *syn* product. For example, the highest *syn:anti* ratio (89:11) was obtained in toluene and the lowest *syn:anti* ratio (2:98) was obtained with a crown ether. These observations parallel the facial selectivities described herein and in ref 11 on the intramolecular S_N2' reaction; see: (a) Denmark, S. A.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177. (b) Denmark, S. A.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8022.

(48) (a) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786. (b) Guller, R.; Borschberg, H.-J. *Tetrahedron Lett* **1994**, *35*, 865.

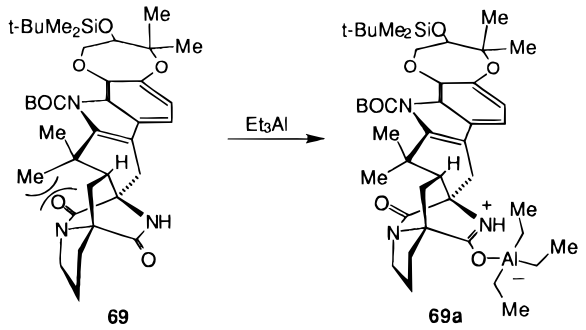
(49) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7.

(50) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (c) Cava, M. P.; Kevinson, M. I. *Tetrahedron* **1985**, *41*, 5061 and literature cited therein.

(51) In a recently reported synthesis of gelsemine, a tertiary lactam was reduced in the presence of a secondary lactam with DIBAH. However, this reagent failed on substrates **69**; see: Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765.

(52) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161.

(53) (a) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927. (b) Marlett, E. M.; Park, W. S.; *J. Org. Chem.* **1990**, *55*, 2968. (c) Jorgenson, M. J. *Tetrahedron Lett.* **1962**, 559. (d) Another very recent synthesis of gelsemine reported the reduction of the same gelsemine precursor (as in ref 51) with AlH_3. Newcombe, N. J.; Fang, Y.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767.



69 69a

Figure 6.

leaving the α-face relatively unencumbered. However, a modification of the alane procedure[52] proved satisfactory for this transformation. The piperazinedione **69** was pretreated with $AlEt_3$, with the expectation that this Lewis acid would form a complex with the more exposed secondary lactam (**69a**, Figure 6) and leave the tertiary lactam accessible for reduction.

Following 10 min of precomplexation with $AlEt_3$, 5 equiv of AlH_3-Me_2NEt complex was added, followed by quenching with $NaCNBH_3$, acetic acid, and methanol to provide the desired amine **70** in 63% yield. Compound **70** was smoothly alkylated with methyl iodide, affording the N-methylated product **72** in 95−98% yield. Compound **72** was subsequently deblocked with 80 equiv of TFA in CH_2Cl_2 to yield the penultimate heptacycle **73** in 97% (Scheme 9).

The stage was now set for the final transformations involving the oxidative pinacol-type rearrangement and dehydration. Due to the difficulties encountered in the attempted cationic cyclization on the indole (cf. **68** → **69**), there was concern about the reactivity of the indole ring toward the electrophilic reagents that would be utilized in the oxidative pinacol-type reaction. There was the possibility that the electron-donating oxygen atoms on the indole ring would hinder the acid-catalyzed rearrangement of, for example, an intermediate chloroindolenine,[54] similarly to the way that strong acid hindered the cationic cyclization.[55] When compound **73** was treated with *tert*-butyl hypochlorite and triethylamine, there was an almost an instantaneous reaction resulting in the total disappearance of starting material and the appearance of two new components (≈1:2 ratio as evidenced by ^{1}H NMR analysis) that were presumed to be the expected diastereomeric chloroindolenines. When this mixture was subjected to the standard rearrangement procedure employing a refluxing solution of acetic acid, water, and methanol, these substances slowly decomposed (many bands in the PTLC).[56]

Since the tertiary amine of **73** might react with the chlorinating reagent and was thus considered to be a possible culprit in these oxidations, an attempt to effect the pinacol-type rearrangement before the amide reduction step was investigated. Thus, piperazinedione **69** was readily deblocked with TFA to provide the amide **76** in 95% yield (Scheme 10). This substance was treated with *t*-BuOCl and Et_3N in the same manner as before, producing two products **77**/**78** (≈1:4 ratio). Using a milder $MeOH/H_2O/AcOH$ system (stirring at room temperature), an oxindole compound **79** was formed in 29% yield. Although this result was encouraging, this substance appeared to possess the incorrect relative stereochemistry at the spiro-ring juncture. This assignment was supported by comparing the ^{1}H NMR spectra of **79** and an authentic sample of (−)-paraherquamide B (**1**). The *gem*-dimethyl signals of **79** were shifted upfield, indicating that one methyl group is in the shielding cone of the oxindole carbonyl.

After a careful reexamination of the decomposition products obtained from the attempted pinacol-type rearrangement of **73**, it was determined that there were mainly two decomposition pathways, and that they were in direct competition with the desired process. These two pathways involve the intermediacy of an oxonium-stabilized tertiary carbocation (at C-3 of the indole) that decomposes to quinone-type products. Additionally, products were isolated whose spectral characteristics were consistent with an elimination process followed by nucleophilic reaction with the solvent at the tryptophan benzylic carbon.

In the classical pinacol rearrangement there is a distinct carbonium ion intermediate, but recent studies have shown that this may in fact be more of a concerted process[57] and, furthermore, that the nature of the solvent can have an impact on which of the two processes, concerted or stepwise, will predominate. There have been conflicting reports in the literature on whether this type of rearrangement is, at all times, stereospecific.[58,59] A detailed study[59c] involving the isolation and separation of the two diastereomeric chloroindolenines derived from yohimbine demonstrated that this reaction can be entirely stereospecific. Alternatively, by increasing the solvating power of the reaction medium, each of these chloroindolenines formed two rearranged products, indicating that the reaction went (at least in part) by way of a carbocationic intermediate. This is consistent with the observed production of **79** from **77** and **78**. A less polar solvent system should minimize the side reactions involving carbocation intermediates and, at the same time, should increase the stereospecific nature of the pinacol-type rearrangement. Thus, treatment of **73** with *t*-BuOCl and Et_3N in CH_2Cl_2 provided the two chloroindolenines **74** and **75** (≈2.25:1 ratio, respectively). The solvent was removed, and the crude reaction mixture was refluxed with a solution of 95% THF, 4% H_2O, and 1% TFA, giving a 62% yield of oxindole products (43% of the desired **80** and 19% the epi product **81**).[60] The C-3-epi-isomer (**81**) was easily distinguishable from the desired isomer (**80**) by the upfield shift of the *gem*-dimethyl signals in the ^{1}H NMR spectrum. The relative amounts of products (**80** and **81**) indicate that the cyclization was stereospecific under these conditions. It was thus deduced that an increase in the ratio of the desired oxindole **80** to the undesired

(54) (a) Gaskell, A. J.; Radunz, H. -E.; Winterfeldt, E. *Tetrahedron Lett.* **1970**, 5361. (b) Winterfeldt, E.; Gaskell, A. J.; Korth, T.; Radnuz, H.-E.; Walkowiak, M. *Chem. Ber.* **1969**, *102*, 3558. (c) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*, 529.

(55) Concern about this possible difficulty was somewhat ameliorated by the knowledge of an alternative procedure that employed OsO_4−pyridine. See: (a) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 4583. (b) Takayama, H.; Odaka, H.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1990**, *38*, 5483. (c) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327. (d) Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661. See also: (e) Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381.

(56) Similar problems were observed during the total synthesis of isopteropodine and pteropodine; see: Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557. In this system, the solution involved treating the chloroindolenines with silver perchlorate in methanolic perchloric acid. This method was attempted on substrate **73**, but unfortunately it failed to produce any desired product.

(57) Osamura, Y.; Nakamura, K. *J. Am. Chem. Soc.* **1993**, *115*, 9112.

(58) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

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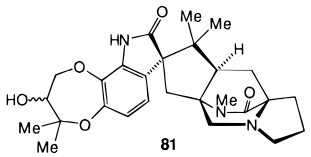
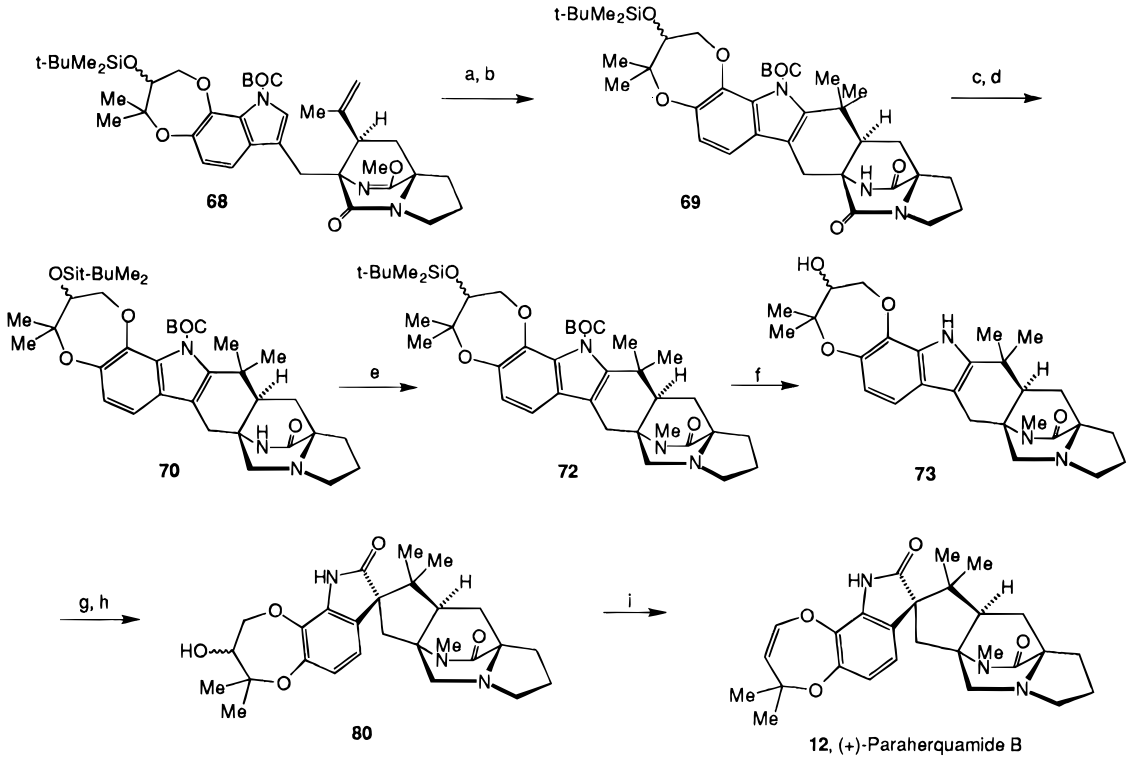
(60)



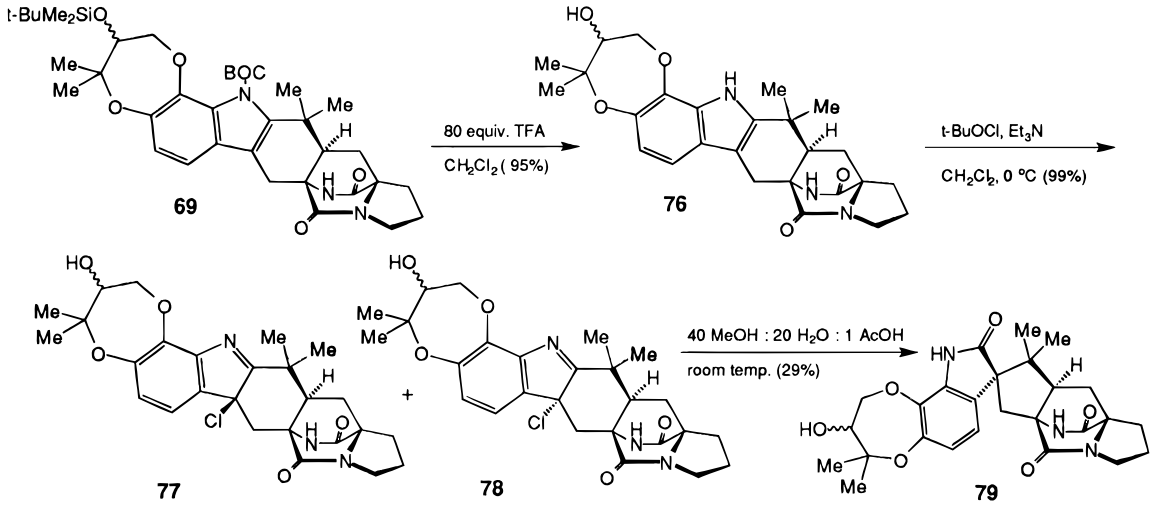
81

Scheme 9[a]

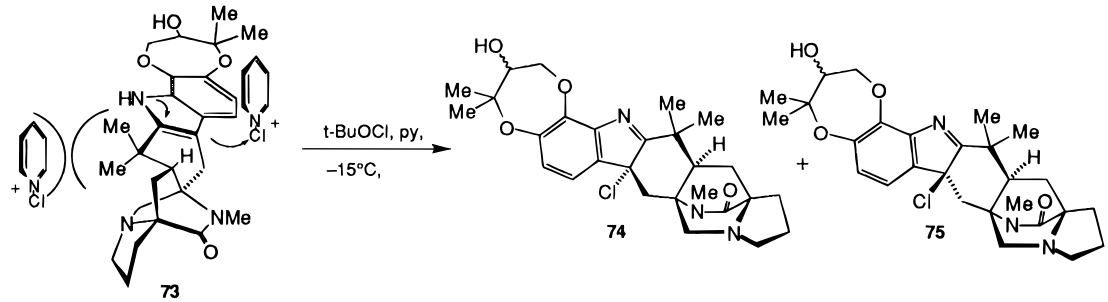


[a] Reagents and conditions: (a) $PdCl_2$, $AgBF_4$, MeCN; (b) $NaBH_4$ (63−82% from **68**); (c) 1.1 equiv of Et_3Al, 5.0 equiv of AlH_3−DMEA, THF, toluene; (d) 2.0 equiv of $NaCNBH_3$, AcOH, MeOH (65% from **69**); (e) 2.5 equiv of NaH, 2.0 equiv of MeI, DMF (98%); (f) 80 equiv of TFA, CH_2Cl_2 (96%); (g) *t*-BuOCl, pyridine, −15 °C; (h) 90% THF, 10% H_2O, pTsOH (76%); (i) MTPI, DMPU (79%).

Scheme 10



Scheme 11



isomer **81** could be achieved simply by finding a method that would increase the ratio of chloroindolenines (**74**:**75**). The α-face of **73** is considerably more hindered than the *β*-face, a supposition that was supported by the difficulties encountered in the reduction of **71** and **69**. Increasing the steric bulk of the chlorinating agent should favor attack on the *β*-face of **73**, thus

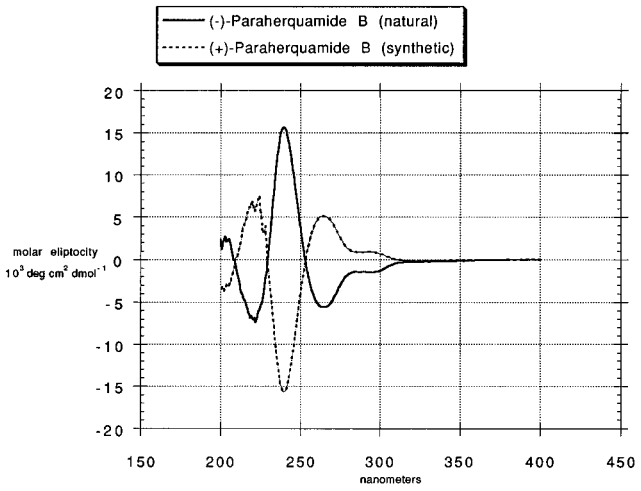


Figure 7.

providing a greater relative amount of chloroindolenine **74**. When **73** was treated with *t*-BuOCl in pyridine instead of triethylamine, the desired chloroindolenine **74** was produced in a much more stereoselective fashion. It can be speculated that *tert*-butyl hypochlorite forms a bulky complex with pyridine, delivering the chlorine more selectively to the least hindered α-face of **73** (only a small amount, ≈5%, of the undesired isomer **75** was formed under these conditions (Scheme 11)).

Employing a minor modification of the solvent system, the crude mixture of **74**/**75** was refluxed with a solution of 90% tetrahydrofuran, 10% H_2O containing 15 equiv of *p*-toluenesulfonic acid to give the desired oxindole **80** in 76% yield (from **73**), with only 4% of the undesired **81** being formed.

The stereospecific conversion of the chloroindolenines into the corresponding oxindoles requires that the water molecule attack the imine from the same face as the chlorine atom. *Anti* attack on the imine is not as likely because of certain stereoelectronic effects.[59c] The addition of water to the β-face of **74** situates the six-membered ring adjacent to the indole ring in a stable chair conformation that would also place the C−Cl bond and the migrating $(CH_3)_2CC$ group in an unfavorable *syn* alignment. Conversely, the addition of water to the α-face of compound **75** would result in an unfavorable boat conformation that would also place the C−Cl bond and the migrating $(CH_3)_2$-CC group in an unfavorable *syn* alignment. Thus, the major isomer **74** must either (1) suffer kinetically controlled attack by water on the same face of **74** as the chlorine atom, which aligns the migrating group and the C−Cl bond in a stereoelectronically favorable *anti* orientation, or (2) undergo reversible attack by water from either face, with only the correct carbinolamine, which aligns the migrating group and the C−Cl bond in a stereoelectronically favorable *anti* orientation, rearranging irreversibly to the oxindole.

The final dehydration reaction (MTPI, DMPU, 18 h) on the alcohol **80** produced (+)-paraherquamide B (**12**) in 79% yield (Scheme 9). This substance proved to be identical to the natural product by comparison of the ^1H and ^{13}C NMR spectra, mobility on TLC, IR spectra, mass spectra, and UV spectra. Comparison of the CD spectra of the natural (−)-paraherquamide B (**2**) and the synthetic (+)-paraherquamide B (**12**) (Figure 7) confirmed the expected enantiomeric relationship between these two products.

Conclusion

The first stereocontrolled, asymmetric total synthesis of (+)-paraherquamide B has been completed. The synthesis is convergent, starting from (S)-proline and vanillin with an overall yield of 1.4% from (S)-proline.

Key features of this synthesis include (1) a new method to effect reduction of unprotected oxindoles to indoles; (2) a complex application of the Somei/Kametani reaction that concomitantly effected a desired decarbomethoxylation; (3) a high-yielding and entirely stereocontrolled intramolecular S_N2' cyclization reaction; (4) a mild Pd(II)-mediated cyclization reaction that concomitantly deblocked a lactim ether protecting group; and (5) the chemoselective reduction of a highly hindered tertiary lactam in the presence of an unhindered secondary lactam, utilizing precoordination of the more reactive secondary lactam to triethylaluminum.

Experimental Section

General information. Melting points were determined in open-ended capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either a Bruker WP-270SY 270 MHz or a Bruker AC300P 300 MHz NMR spectrometer. Chemical shifts are reported in ppm relative to $CHCl_3$ at δ 7.24 or TMS at δ 0.0. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer. Mass spectra were obtained on a V. G. Micromass Ltd. Model 16F spectrometer. The CD spectrum was obtained on a Jasco J710 spectropolarimeter. High-resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry Department of Chemistry, University of Nebraska−Lincoln, Lincoln, NE. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. Optical rotations were recorded on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm using a 1.0 dm cell of 1.0 mL total volume.

Column chromatography and flash column chromatography were performed with silica gel grade 60 (230−400 mesh). Radial chromatography was performed with a Harrison Research Chromatotron Model 7924 using E. Merck silica gel 60 PF-254 containing gypsum; 1, 2, 4, and 8 mm plates were used as needed. Preparatory thin layer chromatography (PTLC) was carried out with Merck Kieselgel 60 F_{254} precoated glass plates (either 0.25 or 0.50 mm); visualization was carried out with ultraviolet light and/or heating with a solution of 5−7% phosphomolybdic acid; staining with I_2; vanillin; or Dragendorf.

All solvents were commercial grade and were distilled and dried as follows: tetrahydrofuran (THF) from sodium benzophenone ketyl; diethyl ether from sodium benzophenone ketyl; carbon tetrachloride from calcium hydride; dioxane from sodium; benzene from sodium benzophenone ketyl; dichloromethane from calcium hydride; acetonitrile from P_2O_5. DMF was dried and stored over 3 Å molecular sieves, as were benzene and toluene. HMPA was dried and stored over 4 Å molecular sieves. Dimethyl sulfide, 2,6-lutidine, triethylamine, and pyridine were all distilled prior to use. Phenylselenium chloride was purified by sublimation. *N*-Chlorosuccinimide (NCS) was recrystallized from benzene. LiCl was dried and stored in the oven. All other reagents were commercial grade and used without further treatment. Abbreviations are used throughout: *N*,*N*-dimethylformamide (DMF); acetic acid (AcOH); di-*tert*-butyl dicarbonate ($(BOC)_2O$); methyltriphenoxyphosphonium iodide (MTPI); ethyl acetate (EtOAc); *m*-chloroperbenzoic acid (*m*-CPBA); (*N*,*N*-dimethylamino)pyridine (DMAP); hexamethylphosphoramide (HMPA); ceric ammonium nitrate (CAN); methanesulfonyl chloride (MsCl); *N*-chlorosuccinimide (NCS); trifluoroacetic acid (TFA); dimethylethylamine (DMEA); imidazole (im); 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).

2-[(3-Methyl-2-butenyl)oxy]phenol (24). To a stirred, cold (0 °C), dark solution of catechol (2.07 g, 18.8 mmol, 5.0 equiv) in DMF (65 mL) in a reaction vessel that had been flushed with Ar was added anhydrous K_2CO_3 (0.520 g, 3.76 mmol, 1.0 equiv). After 5 min, prenyl bromide (0.441 mL, 3.76 mmol, 1.0 equiv) was added dropwise. The reaction mixture was kept at 0 °C for ∼6 h and stirred at room temperature for an additional 18 h. The mixture was then poured into a separatory funnel, diluted with H_2O (100 mL), and extracted five times with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by radial chromatography (eluted with 1% ethyl acetate/hexanes) to give 479 mg (71%) of **24** as a colorless oil. An analytical sample was obtained by PTLC on silica gel (eluted with hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.74 (3H, s), 1.80 (3H, s), 4.57 (2H, d, J = 6.8 Hz), 5.49 (1H, m), 5.70 (1H, s, D_2O exch), 6.82−6.92 (4H, m). IR (NaCl, neat): 3533, 2932, 1612, 1502, 1467, 1385, 1259, 1221, 1106, 997, 743 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 178 (11), 161 (11), 110 (78), 69 (67), 32 (100). Microanalysis calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92 Found: C, 73.88; H, 8.00.

(±)-3,4-Dihydro-2,2-dimethyl-3-(phenylseleno)-2*H*-benzodioxepin (25). A solution of phenylselenium chloride (117.8 mg, 0.615 mmol, 1.05 equiv) in EtOAc (4.1 mL, 0.15 M) was slowly added (∼1 mmol/h) to a stirred solution of **24** (104.4 mg, 0.58 mmol, 1.0 equiv) in EtOAc (3.90 mL, 0.15 M) at −75 °C under Ar. This mixture was allowed to warm to room temperature and was stirred for a total of 17 h. The solution was poured into a separatory funnel and washed twice with H_2O and once with brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by PTLC (eluted with 1:3 hexanes/benzene) to afford 62.1 mg (32%) of **25**. An analytical sample was obtained by PTLC (eluted with hexanes, and then distilled under reduced pressure).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.28 (3H, s), 1.76 (3H, s), 3.62 (1H, dd, J = 3.4, 10.3 Hz), 4.17 (1H, dd, J = 10.3, 12.6 Hz), 4.40 (1H, dd, J = 3.5, 12.6 Hz), 6.94−6.98 (4H, m), 7.30−7.34 (3H, m), 7.59−7.62 (2H, m). IR (NaCl, neat): 2986, 1491, 1256, 1088, 1000 cm^{-1}. HRMS (EI): *m/e* 334.0473 ($C_{17}H_{18}O_2Se$ requires 334.0472).

2,2-Dimethyl-2*H*-1,5-benzodioxepin (26). To a stirred solution of **25** (61.7 mg, 0.185 mmol, 1.0 equiv) in THF (3 mL) was added H_2O_2 (0.21 mL, 0.5 mmol, 10 equiv) at 0 °C. The resulting solution was stirred for 0.5 h and then brought to reflux temperature for 0.5 h. The mixture was poured into a separatory funnel, diluted with water, and extracted with ether. The ethereal solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by PTLC (eluted with 1:3 hexanes/EtOAc) to afford 16.0 mg (49%) of **26** as a pale yellow oil (see data below).

Compound **26** was also obtained from **28** as follows: To a solution of **28** (76.2 mg, 0.39 mmol, 1.0 equiv) in HMPA (2 mL) under N_2 at room temperature was added MTPI (291.5 mg, 0.64 mmol, 1.6 equiv) all at once. After being stirred for 1 day, the mixture was poured into a separatory funnel containing 1 M NaOH and was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation gave a crude yield of 163.5 mg. The crude product was purified by radial chromatography (eluted with 1:10 EtOAc/hexanes, then 1:5 EtOAc/hexanes) to afford 46 mg (66%) of **26**.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.42 (6H, s), 4.81 (1H, d, J = 7.8 Hz), 6.30 (1H, d, J = 7.8 Hz), 6.95−7.06 (4 H, m). IR (neat): 2978, 1654, 1587, 1495, 1311, 1242, 750 cm^{-1}. HRMS (EI): *m/e* 176.0835 ($C_{11}H_{12}O_2$ requires 176.0837).

(±)-2-[(3,3-Dimethyloxiranyl)methoxy]phenol (27). To a solution of **24** (1.31 g, 7.35 mmol, 1.0 equiv) in CH_2Cl_2 (40.0 mL) under N_2 at 0 °C was added $NaHCO_3$ (803 mg, 9.56 mmol, 1.3 equiv) followed by *m*-CPBA (1.27 g, 7.35 mmol, 1.0 equiv). After 1.5 h additional $NaHCO_3$ (812 mg, 9.66 mmol, 1.21 equiv) and *m*-CPBA (1.26 g, 7.35 mmol, 0.99 equiv) were added. This mixture was kept stirring at 0 °C for 2 h, when more $NaHCO_3$ (778 mg, 9.27 mmol, 1.3 equiv) and *m*-CPBA (1.12 g, 6.49 mmol, 0.88 mmol) were added. After 2 h, the cold mixture was filtered to remove the solids. The filtrate was washed three times with 10% $Na_2S_2O_3$ and three times with brine, dried over $MgSO_4$, and evaporated to dryness to afford 1.41 g (99%) of **27**. An analytical sample was recrystallized from toluene to give a glassy solid, mp 36−37 °C.

^{1}H NMR (270 MHz) ($CDCl_3$): δ TMS 1.37 (3H, s), 1.41 (3H, s), 3.18 (1H, dd, J = 4.2, 6.3 Hz), 4.07 (1H, dd, J = 6.4, 11.0 Hz), 4.28 (1H, dd, J = 4.2, 11.0 Hz), 5.78 (1H, s, D_2O exch), 6.81−6.97 (4H, m). IR (NaCl, neat): 3413, 2966, 1590, 1502, 1267, 744 cm^{-1}. Microanal. Calcd for $C_{11}H_{14}O_4$: C, 68.02; H, 7.26. Found: C, 67.91; H, 7.39.

(±)-3,4-Dihydro-2,2-dimethyl-2*H*-1,5-benzodioxepin-3-ol (28). A flame-dried flask, flushed with Ar, was charged with dry THF (85.4 mL). Tin tetrachloride (0.85 mL, 7.3 mmol, 1.0 equiv) was then added dropwise in 5 min. After 10 min a solution of **27** (1.41 g, 7.26 mmol, 1.0 equiv) in dry THF (13.8 mL) was added slowly (dropwise) to the mixture. The reaction mixture was stirred at room temperature for 20 min, poured into saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by radial chromatography (eluted with 1:7 EtOAc/hexanes) to afford 842 mg (60% or 59% for two steps) of **28** as an oil. An analytical sample was obtained by PTLC (eluted with 5:1 EtOAc/hexanes, and then distilled under reduced pressure).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.20 (3H, s), 1.53 (3H, s), 2.96 (1H, d, J = 11.3 Hz, D_2O exch), 3.58 (1H, ddd, J = 1.1, 4.0, 11.3 Hz), 4.08 (1H, dd, J = 1.1, 12.6 Hz), 4.20 (1H, dd, J = 4.0, 12.6 Hz), 6.98−7.02 (4H, m). IR (NaCl, neat): 3448, 2978, 1596, 1490, 1261 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 194 (41), 176 (19), 136 (57), 121 (100), 59 (63). HRMS (EI) *m/e* 194.0943 ($C_{11}H_{14}O_3$ requires 194.0943).

4-Hydroxy-3-methoxy-2-nitrophenylacetic Acid (30). To a flask containing **29** (101 g, 397 mmol, 1.0 equiv) at 0 °C was added a solution of NaOH (63.5 g, 1.59 mol, 4.0 equiv) in H_2O (1.4 L). After 10 min, hydrogen peroxide (49.5 mL, 437 mmol, 1.1 equiv, 30% solution in water) was added dropwise. The deep purple solution slowly turned brown during the addition. The mixture was allowed to reach room temperature and stirred for 24 h. The reaction mixture was then acidified with concentrated HCl until pH ≈ 3, during which CO_2 was released and a fine yellow crystalline product precipitated. The mixture was filtered, washed with cold H_2O, and dried to yield 72.6 g (81%) of **30**. An analytical sample was recrystallized from H_2O to give bright yellow needles, mp 161−162 °C (when the reaction was carried out with 11.9 g of the phenylacetic acid, the yield was 93%).

^{1}H NMR (300 MHz) (acetone-d_6): δ TMS 2.83 (2H, br s, D_2O exch), 3.62 (2H,s), 3.91 (3H, s), 7.10 (2H, s). IR (KBr): 3488, 2958, 2641, 1668, 1533, 1399, 1344, 1296, 1225, 1051, 825 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 228 (M^+, 0.7), 227 (5.8), 166 (10.0), 106 (13.6), 44 (100). Microanal. Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.16. Found: C, 47.56; H, 4.06; N, 6.25.

1,3-Dihydro-6-hydroxy-7-methoxy-2*H*-indol-2-one (31). A mixture of **30** (23.0 g, 101 mmol, 1.0 equiv) in glacial acetic acid (100 mL) and Pd/C (10%, 1.5 g) was hydrogenated at 40 psi of H_2 in an oil bath (80 °C) for 5 h. The mixture was immediately filtered through a Celite plug and washed with a small amount of warm AcOH. The flask was kept under suction (cold) until a large quantity of white product had precipitated. This was filtered to collect the product, when an additional quantity of product precipitated under suction. This was collected, and the two crops of white flakes were combined and dried under reduced pressure to yield 17.2 g (95%) of **31**. An analytical sample was recrystallized from H_2O to give white crystals, mp 210−211 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 3.50 (2H, d, J = 1.0 Hz), 3.87 (3H, s), 5.49 (1H, s, D_2O exch), 6.60 (1H, d, J = 8.1 Hz), 6.86 (1H, d, J = 8.0 Hz), 7.94 (1H, s, D_2O exch). IR (KBr): 3287, 3014, 2953, 1686, 1633, 1504, 1466, 1315, 1163, 637 cm^{-1}. Microanal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.05; N, 7.60.

1,3-Dihydro-7-methoxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one. To a stirred mixture of **31** (321.6 mg, 1.795 mmol, 1.0 equiv) in acetone (7 mL) at 0 °C under Ar were added K_2CO_3 (740.5 mg, 5.358 mmol, 2.98 equiv) and *p*-toluenesulfonyl chloride (376.4 mg, 1.974 mmol, 1.1 equiv). The mixture was stirred for 5 h at 0 °C and 1 h at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed three times with 1 M NaOH and once with brine, dried over $MgSO_4$, and concentrated to dryness. The product, 572.3 mg (96%), was obtained as a rust-colored, amorphous solid.

^{1}H NMR (270 MHz) ($CDCl_3$): δ 2.47 (3H, s), 3.52 (2H, s), 3.81 (3H, s), 6.70 (1H, d, J = 8.2 Hz), 6.86 (1H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.1 Hz), 7.79 (2H, d, J = 8.3 Hz), 7.85 (1H, s, D_2O exch). IR (KBr): 3172 (br), 1709, 1616, 1496, 1458, 1371, 1338, 1175, 1093, 1050, 1000, 848, 815, 728, 662, 548, cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 333 (5.0), 269 (1.4), 178 (40), 91 (77), 28 (100).

1,3-Dihydro-7-hydroxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one. Boron tribromide (1.1 mL, 1.1 mmol, 2.0 equiv, 1 M/CH_2Cl_2) was added to a stirred mixture of 1,3-dihydro-7-methoxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one obtained above (181.5 mg, 0.54 mmol, 1.0 equiv) in CH_2Cl_2 (4.3 mL) under Ar, at −78 °C. The mixture was stirred for 8 h and stored at −20 °C for 12 h. The mixture was poured into ice/

water, stirred for 0.5 h, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness to give 164.7 mg (95%) of a red solid.

^{1}H NMR (270 MHz) (acetone-d_6): δ TMS 2.45 (3H, s), 3.43 (2H, d, J = 0.8 Hz), 6.61 (1H, d, J = 8.1 Hz), 6.71 (1H, d, J = 8.1 Hz), 7.46 (2H, d, J = 8.6 Hz), 7.79 (2H, d, J = 8.3 Hz), 8.50 (1H, s, D_2O exch), 9.28 (1H, s, D_2O exch). IR (NaCl, neat): 3259 (br), 2921, 1698, 1365, 1175, 1142, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 319 (3.4), 278 (6.0), 246 (6.7), 163 (49), 139 (73), 91 (100).

1,3-Dihydro-7-[(3-methyl-2-butenyl)oxy]-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one (37). To a stirred solution of 1,3-dihydro-7-hydroxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one obtained above (159.4 mg, 0.49 mmol, 1.0 equiv) in DMF (1.5 mL) at 0 °C was added K_2CO_3 (103.5 mg, 0.75 mmol, 1.5 equiv) followed by prenyl bromide (0.09 mL, 0.75 mmol, 1.5 equiv). After 4 h the mixture was poured into water, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated to dryness. The product was purified by radial chromatography (eluted with 3:2 hexanes/EtOAc) to afford 71.9 mg (37%) of **37** as a red solid.

^{1}H NMR (270 MHz) ($CDCl_3$): δ TMS 1.58 (3H, s), 1.70 (3H, s), 2.45 (3H, s), 3.52 (2H, s), 4.47 (2H, d, J = 7.3 Hz), 5.35 (1H, t, J = 7.3 Hz), 6.74 (1H, d, J = 8.2 Hz), 6.87 (1H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.3 Hz), 8.61 (1H, s, D_2O exch). IR (NaCl, neat): 3194 (br), 1714, 1627, 1464, 1376, 1196, 1175, 837, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 387 (16), 319 (16), 164 (37), 91 (91), 67 (100).

1,3-Dihydro-6,7-dihydroxy-2*H*-indol-2-one (32). Boron tribromide (800 mL, 800 mmol, 2.5 equiv, 1M/CH_2Cl_2) was added dropwise to a stirred mixture of **31** (57.3 g, 320 mmol, 1.0 equiv)) in CH_2Cl_2 (640 mL) under N_2 at −78 °C. The reaction mixture was stirred at −78 °C for 8 h and was then poured into a large (4 L) beaker containing 1.5 L of ice/water, stirred for 10 min, and filtered to remove undissolved product. The remaining liquid was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to yield the pure product **32**, which was combined with the filter cake, total yield 52.3 g (99%). An analytical sample was recrystallized from H_2O (three times) to give a faint pink crystalline solid, mp 245 °C dec.

^{1}H NMR (300 MHz) (DMSO-d_6): δ TMS 3.32 (2H, s), 6.36 (1H, d, J = 7.9 Hz), 6.48 (1H, d, J = 2.9 Hz), 8.80 (2H, br s, D_2O exch), 10.0 (1H, br s, D_2O exch). IR (KBr): 3366−3123 (br), 1672, 1649, 1618, 1359, 1265, 1178, 786 cm^{-1}. Microanal. Calcd for $C_8H_7NO_3$: C, 58.18; N, 4.27; N, 8.48. Found: C, 58.34; H, 4.44; N, 8.25.

1,3-Dihydro-6-hydroxy-7-[(3-methyl-2-butenyl)oxy]-2*H*-indol-2-one (33). To a stirred solution of 6,7-dihydroxyoxindole (**32**) (19.0 g, 115 mmol, 1.0 equiv) in DMF (230 mL) at 0 °C under Ar was added K_2CO_3 (15.9 g, 115 mmol, 1.0 equiv). After 8 min prenyl bromide (14.8 mL, 127 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 6.5 h, poured into a separatory funnel, diluted with H_2O, and extracted with ether. The ethereal solution was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The product was purified by column chromatography (eluted with 3:1 hexanes/EtOAc, then 1:1 hexanes/EtOAc) to yield 14.5 g (54%) of **33**. An analytical sample was recrystallized from toluene to give a red-white solid, mp 111 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.65 (3H, s), 1.80 (3H, s), 3.50 (2H, s), 4.47 (1H, d, J = 7.4 Hz), 5.50−5.55 (1H, m), 5.57 (1H, s, D_2O exch), 6.59 (1H, d, J = 8.1 Hz), 6.84 (1H, d, J = 8.0 Hz), 7.77 (1H, s, D_2O exch). IR (KBr): 3367, 3192, 2971, 1694, 1664, 1635, 1461, 1356, 1286, 1199, 1047 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.16; H, 6.52; N, 6.07.

(±)-1,3-Dihydro-7-[(3,3-dimethyloxiranyl)methoxy]-6-hydroxy-2*H*-indol-2-one. To a stirred solution of **33** (14.5 g, 62.1 mmol, 1.0 equiv) in CH_2Cl_2 (620 mL) were added $NaHCO_3$ (5.7 g, 68.3 mmol, 1.1 equiv) and *m*-CPBA (10.7 g, 62.1 mmol, 1.0 equiv). The mixture was stirred for 1 h, and an additional amount of each reagent was added, $NaHCO_3$ (5.7 g, 68.3 mmol, 1.1 equiv) and *m*-CPBA (10.7 g, 62.1 mmol, 1.0 equiv). The mixture was stirred for an additional 1 h, and a third portion each of $NaHCO_3$ (5.7 g, 68.3 mmol, 1.1 equiv) and *m*-CPBA (10.7 g, 62.1 mmol, 1.0 equiv) was added. The resulting mixture was stirred for 3 h, while the temperature was maintained at 0 °C. The reaction mixture was filtered into a flask containing 10% $Na_2S_2O_3$ and 10% $NaHCO_3$. The organic layer was isolated, diluted with CH_2Cl_2, and washed with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ and finally with brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried in vacuo to yield 17 g of the product, which was used directly for the next step. An analytical sample was recrystallized from toluene to give a white solid, mp 122−123 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.38 (3H, s), 1.42 (3H, s), 3.25 (1H, dd, J = 2.9, 8.5 Hz), 3.47−3.49 (2H, m), 3.80 (1H, dd, J = 8.5, 12.0 Hz), 4.54 (1H, dd, J = 2.9, 12.0 Hz), 6.25 (1H, s, D_2O exch), 6.58 (1H, d, J = 8.1 Hz), 6.84 (1H, d, J = 8.1 Hz), 8.44 (1H, s, D_2O exch). IR (KBr): 3495, 3146, 2982, 1717, 1694, 1635, 1501, 1466, 1321, 1187, 1047, 861 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.70; H, 6.15; N, 5.66.

(±)-3,4,8,10-Tetrahydro-3-hydroxy-4,4-dimethyl-2*H*,9*H*-[1,4]dioxepino[2,3-*g*]indol-9-one (34). $SnCl_4$ (9.6 mL, 81.8 mmol, 1.2 equiv) was slowly added dropwise to a flame-dried flask, which had been flushed with Ar and charged with dry THF (960 mL). After 10 min a solution of (±)-1,3-dihydro-7-[(3,3-dimethyloxiranyl)methoxy]-6-hydroxy-2*H*-indol-2-one obtained above (17 g, 62 mmol, 1.0 equiv) in THF (73 mL) was added dropwise to the reaction vessel and stirred for 2 h. Approximately one-half of the solvent was removed under reduced pressure and the remaining solution poured into a separatory funnel containing saturated $NaHCO_3$ and H_2O (∼50:50), which was then exhaustively extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give a dark crude product. The product was purified by column chromatography (eluted with 1:2 hexanes/EtOAc) to yield 10 g (64% for two steps) of **34**. An analytical sample was recrystallized from toluene to give a yellow crystalline solid, mp 194 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.24 (3H, s), 1.54 (3H, s), 2.94 (1H, d, J = 11.2 Hz, D_2O exch), 3.51 (2H, s), 3.63 (1H, ddd, J = 1.0, 4.0, 11.2 Hz), 4.12 (1H, dd, J = 1.0, 12.4 Hz), 4.24 (1H, dd, J = 4.0, 12.5 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.83 (1H, d, J = 7.9 Hz), 7.64 (1H, s, D_2O exch). IR (KBr): 3460, 3320, 3169, 2982, 1711, 1682, 1461, 1327, 1216, 1047 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.08; N, 5.61. Found: C, 62.28; H, 6.21; N, 5.56.

(±)-3-Hydroxy-4,4-dimethyl-3,4,dihydro-2*H*,10*H*-[1,4]dioxepino-[2,3-*g*]indole (35). To a stirred solution of **34** (11.2 g, 44.8 mmol, 1.0 equiv) in THF (225 mL) under Ar at 0 °C was added BF_3·OEt_2 (19.3 mL, 157 mmol, 3.5 equiv). After 10 min, $NaBH_4$ (2.71 g, 71.8 mmol, 1.6 equiv) was added at once, and the mixture was stirred for 8 h at 0 °C and then at room temperature for 40 h. The reaction was completed by the slow addition of water (1 L) and was stirred for 0.5 h. HCl (concentrated) was added until pH = 1, and the mixture was stirred for an additional 0.5 h. The mixture was treated with 1 M NaOH until pH = 14 and stirred for 0.5 h. The mixture was poured into a separatory funnel and extracted with EtOAc/ether. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave 10 g of a crude solid. The product was purified by column chromatography (eluted with 2:1 hexanes/EtOAc) to yield 4.5 g (43%) of **35**. An analytical sample was recrystallized from benzene to afford a white crystalline solid, mp 202−205 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.22 (3H, s), 1.56 (3H, s), 3.03 (1H, d, J = 11.4 Hz, D_2O exch), 3.63 (1H, ddd, J = 4.0, 0.9, 11.3 Hz), 4.19 (1H, dd, J = 0.9, 12.3 Hz), 4.31 (1H, dd, J = 4.0, 12.3 Hz), 6.49 (1H, dd, J = 2.2, 3.1 Hz), 6.78 (1H, d, J = 8.4 Hz), 7.16−7.19 (2H, m), 8.29 (1H, s, D_2O exch). IR (KBr): 3340, 2984, 1580, 1504, 1444, 1338, 1224, 1133, 1057, 814, 753 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.16; H, 6.63; N, 5.79.

(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-3,4-dihydro-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole. To a stirred solution of **35** (11.6 g, 49.7 mmol, 1.0 equiv) in DMF (124 mL) at room temperature under N_2 was added *tert*-butyldimethylsilyl chloride (15.0 g, 99.4 mmol, 2.0 equiv) immediately followed by imidazole (23.7 g, 348 mmol, 7.0 equiv). The solution was slowly heated to 40 °C, stirred overnight, poured into a separatory funnel, and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed and the crude solid purified by column chromatography (eluted with 5:1 hexanes/EtOAc) to yield 14.2 g (82%) of

the product. An analytical sample was recrystallized from cyclohexane to give a white solid, mp 118−119 °C.

^{1}H NMR (300 Hz) ($CDCl_3$): δ TMS 0.14 (6H, s), 0.89 (9H, s), 1.12 (3H, s), 1.48 (3H, s), 3.88 (1H, dd, J = 9.2, 11.5 Hz), 3.98 (1H, dd, J = 3.2, 9.2 Hz), 4,22 (1H, dd, J = 3.2, 11.5 Hz), 6.48 (1H, dd, J = 2.2, 3.1 Hz), 6.76 (1H, d, J = 8.4 Hz), 7.14 (2H, ddd, J = 2.4, 3.4, 3.5 Hz), 8.21 (1H, s, D_2O exch). IR (neat): 3412, 2936, 1500, 1438, 1234, 1093, 833 cm^{-1}. Microanal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.66; H, 8.41; N, 4.03. Found: C, 65.59; H, 8.20; N, 3.90.

(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-8-[(*N*,*N*-dimethylamino)methyl]-3,4-dihydro-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]-indole (36). To a flask charged with acetic acid (136 mL) under Ar were added formaldehyde (3.4 mL, 45 mmol, 1.1 equiv, 37%/H_2O) and dimethylamine (20.5 mL, 163 mmol, 4.0 equiv, 40% solution in H_2O) followed by (±)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-3,4,dihydro-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole obtained above (14.2 g, 40.9 mmol, 1.0 equiv) over a 10 min period. The reaction mixture was stirred for 1 day when 10% K_2CO_3 was added until pH ≈ 8; then 2 M NaOH was added. The mixture was extracted with ether/EtOAc, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, leaving 17.3 g (quantitative) of the pure product **36**. An analytical sample was recrystallized from toluene to give a white flaky solid, mp 152 °C.

^{1}H NMR (300 Hz) ($CDCl_3$): δ TMS 0.15 (6H, s), 0.90 (9H, s), 1.13 (3H, s), 1.48 (3H, s), 2.28 (6H, s), 3.58 (2H, s), 3.58 (2H, s), 3.88 (1H, dd, J = 9.2, 11.4 Hz), 3.98 (1H, dd, J = 3.2, 9.1 Hz), 4.21 (1H, dd, J = 3.2, 11.5 Hz), 6.76 (1H, d, J = 8.4 Hz), 8.44 (1H, s, D_2O exch). IR (NaCl, neat): 2932, 1502, 1458, 1360, 1251, 1218, 1093, 837, 777 cm^{-1}. Microanal. Calcd for $C_{22}H_{36}N_2O_3Si$: C, 65.31; H, 8.97; N, 6.92. Found: C, 65.09; H, 8.77; N, 6.73.

(±)-6(*R*)-(2*E*)-Methyl 3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazine-3-carboxylate (39). To a stirred solution of **38** (23.0 mg, 0.043 mmol, 1.0 equiv) in CH_3CN (0.3 mL) and PBu_3 (5.4 μL, 0.022 mmol, 0.5 equiv) was added a solution of **36** (19.3 mg, 0.048 mmol, 1.1 equiv) in CH_3CN (0.3 mL). The mixture was refluxed for 5.5 h and stirred at room temperature overnight. The reaction mixture was then diluted with ether, washed with water, dilute HCl, and brine, and dried over $MgSO_4$. The solvent was removed and the crude oily solid purified by PTLC on silica gel (eluted with 1:4 EtOAc/hexanes) to yield 19.8 mg (51%) of **39**. An analytical sample was recrystallized from cyclohexane to give a white crystalline solid, mp 168−168.5 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (a racemic mixture of two diastereomers): δ TMS 0.00 (6H, s), 0.01 (6H, s), 0.13 (6H, s), 0.14 (6H, s), 0.034−0.19 (2H, m), 0.43−0.52 (2H, m), 0.62−0.72 (2H, m), 0.84 (9H, s), 0.85 (9H, s), 0.86 (9H, s), 0.88 (9H, s), 1.05 (3H, s), 1.1 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 1.537 (3H, s), 1.544 (3H, s), 1.33−1.67 (2H, m), 2.14−2.25 (2H, m), 2.52−2.60 (2H, m), 2.87−3.03 (2H, m), 3.27 (6H, s), 3.36−3.52 (2H, m), 3.66 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.66 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.75 (6H, s), 3.77−3.96 (12H, m), 4.14−4.20 (2H, m), 5.25−5.31 (2H, m); 5.48 (2H, $^1/_2$ ABq, J = 14.6 Hz), 6.70−6.89 (8H, m), 7.15−7.22 (6H, m), 8.29 (1H, s, D_2O exch), 8.32 (1H, s, D_2O exch). IR (NaCl, neat): 3303, 2954, 2856, 1752, 1660, 1512, 1447, 1251, 1098, 1049, 837, 777 cm^{-1}. Microanal. Calcd for $C_{48}H_{71}N_3O_9Si_2$: C, 64.76; H, 8.04; N, 4.72. Found: C, 64.95; H, 8.09; N, 4.53.

[(±)-[3α,8a*β*(*E*)]]-8-[[2-[(4-Methoxyphenyl)methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-g]indole (40). [(±)-[3*β*,8aα(*E*)]]-8-[[2-[(4-Methoxyphenyl)methyl]-8a-[4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]-methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole (41). A dry flask containing **39** (24.4 mg, 0.027 mmol, 1.0 equiv) and lithium chloride (11.6 mg, 0.27 mmol, 10 equiv) under N_2 was charged with HMPA (0.21 mL) and water (1.5×10^{-3} mL, 0.082 mmol, 3.0 equiv). This mixture was heated to 100−105 °C for 2 h. The resulting solution was diluted with 1:1 EtOAc/hexanes and washed with water (5×) and brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness. The product was purified by PTLC on silica gel (eluted with 1:3 EtOAc/hexanes) to yield 8.9 mg (39%) of **40** (oil) and 2.7 mg (12%) of **41** (oil). Total yield: 51%.

^{1}H NMR (300 MHz) ($CDCl_3$) (a racemic mixture of two diastereomers) (**40**): δ 0.036 (12H, s), 0.12 (6H, s), 0.13 (6H, s), 0.84 (9H, s), 0.87 (9H, s), 0.88 (9H, s), 0.882 (9H, s), 1.10 (3H, s), 1.11 (3H, s), 1.458 (9H, s), 1.463 (3H, s), 1.72−2.04 (10H, m), 2.12−2.23 (2H, m), 3.24−3.51 (8H, m), 3.72 (3H, s), 3.73 (3H, s), 3.79−3.82 (6H, m), 3.83 (2H, s), 3.86 (2H, s), 4.15−4.20 (4H, m), 5.15 (1H, $^1/_2$ ABq, J = 14.2 Hz), 5.20 (1H, $^1/_2$ ABq, J = 14.2 Hz), 5.28 (1H, m), 5.45 (1H, m), 6.67−6.71 (4H, m), 6.76 (2H, d, J = 8.5 Hz), 6.81−6.90 (6H, m), 7.16 (2H, d, J = 8.5 Hz), 8.12 (2H, s, D_2O exch). IR (*syn*) (NaCl, neat): 2920, 1655, 1508, 1449, 1250, 1220, 1091, 838 cm^{-1}.

^{1}H NMR (300 MHz) ($CDCl_3$) (a racemic mixture of two diastereomers) (**41**): δ −0.18 (12H, s), 0.12 (6H, s), 0.13 (6H, s), 0.26−0.41 (2H, m), 0.47−0.58 (2H, m), 0.62−0.72 (2H, m), 0.84 (18H, s), 0.87 (9H, s), 0.89 (9H, s), 1.06 (3H, s), 1.10 (3H, s), 1.44 (6H, s), 1.47 (3H, s), 1.48 (3H, s), 1.63−1.67 (2H, m), 2.10−2.17 (2H, m), 2.44−2.52 (2H, m), 2.89−3.05 (2H, m), 3.20−3.28 (2H, m), 3.40−3.52 (4H, m), 3.71−3.97 (16H, m), 4.08 (2H, br s), 4.14−4.21 (2H, m), 5.05 (2H, br s), 5.56 (1H, $^1/_2$ ABq, J = 14.2 Hz), 5.57 (1H, $^1/_2$ ABq, J = 14.5 Hz), 6.71 (1H, d, J = 8.6 Hz), 6.73 (1H, d, J = 8.6 Hz), 6.83−6.88 (6H, m), 7.14 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 8.6 Hz), 7.22−7.23 (4H, m), 8.34 (2H, s, D_2O exch). IR (*anti*) (neat): 2932, 1649, 1508, 1455, 1250, 1220, 1103, 838 cm^{-1}. HRMS (EI) (*anti*): 831.46765 ($C_{46}H_{69}N_3O_7Si_2$ requires 831.4674).

[(±)-[3α,8aα(*E*)]]-1,1-Dimethylethyl 8-[[3-(Methoxycarbonyl)-2-[(4-methoxyphenyl)methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (42). To a stirred solution of **39** (260.0 mg, 0.292 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C under Ar were added DMAP (35.7 mg, 0.292 mmol, 1.0 equiv) and Et_3N (0.041 mL, 0.29 mmol, 1.0 equiv). After 5 min $(BOC)_2O$ (191.2 mg, 0.876 mmol, 3.0 equiv) was added in one portion. The resulting solution was stirred for 20 h, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude solid was purified by radial chromatography (eluted with 1:5 EtOAc/hexanes) to yield 260.4 mg (90%) of **42** as a white crystalline solid, mp 74−75 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ −0.01 (6H, s), 0.00 (6H, s), 0.113 (6H, s), 0.12 (6H, s), 0.58−0.68 (2H, m), 0.80−0.92 (38H, m), 1.06 (6H, s), 1.45−1.63 (2H, m), 1.47 (6H, s), 1.53 (6H, s), 1.60 (18H, s), 1.59−1.81 (2H, m), 2.22−2.34 (2H, m), 2.60 (2H, dd, J = 8.1, 15.0 Hz), 2.91−3.08 (2H, m), 3.26 (6H, s), 3.26−3.42 (2H, m), 3.56 (1H, $^1/_2$ ABq, J = 14.8 Hz), 3.59 (1H, $^1/_2$ ABq, J = 14.8 Hz), 3.71−3.80 (4H, m), 3.74 (6H, s), 3.83 (2H, s), 3.84 (2H, s), 3.90−3.97 (4H, m), 4.13−4.17 (2H, m), 3.32 (2H, m), 5.34 (1H, $^1/_2$ ABq, J = 14.8 Hz), 5.42 (1H, $^1/_2$ ABq, J = 14.8 Hz), 6.75−6.79 (4H, m), 6.88 (1H, d, J = 8.4 Hz), 6.89 (1H, d, J = 8.4 Hz), 7.03 (2H, s), 7.12−7.20 (6H, m). IR (NaCl, neat): 2943, 1752, 1660, 1507, 1496, 1464, 1463, 1404, 1365, 1251, 1153, 1109, 1082, 837, 772 cm^{-1}. HRMS (EI): 989.5249 ($C_{53}H_{79}N_3O_{11}Si_2$ requires 989.5253).

[(±)-[3*β*,8a*β*(*E*)]]-1,1-Dimethylethyl 8-[[8a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)-methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (*syn*-43). [(±)-[3α,8a*β*(*E*)]]-1,1-Dimethylethyl 8-[[8a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]-octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]-dioxepino[2,3-*g*]indole-10-carboxylate (anti-43). A flask containing **42** (126.6 mg, 0.128 mmol, 1.0 equiv) and LiCl (27.1 mg, 0.64 mmol, 5.0 equiv) under N_2 was charged with HMPA (0.78 mL) and H_2O (3.4 $\times 10^{-3}$ mL, 1.9 $\times 10^{-4}$ mmol, 1.5 equiv). The solution was heated (100−105 °C) for 1.25 h and then poured into water and extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated, leaving a crude oily solid. The product

was purified by radial chromatography (eluted with 1:5 EtOAc/hexanes) to yield 79.2 mg (66%) of *syn*-**43** (an analytical sample was obtained by PTLC, eluted with 1:5 EtOAc/hexanes, to give an oil) and 3.1 mg (2.6%) of the *anti*-isomer (oil).

^{1}H NMR (300 MHz) ($CDCl_3$) (*syn*-**43**): δ 0.026 (6H, s), 0.32 (6H, s), 0.127 (6H, s), 0.14 (6H, s), 0.867 (9H, s), 0.873 (9H, s), 0.878 (9H, s), 0.883 (9H, s), 1.10 (6H, s), 1.48 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 1.57 (3H, s), 1.610 (9H, s), 1.613 (9H, s), 1.83−1.96 (6H, s), 2.22−2.35 (4H, m), 2.46 (2H, dd, J = 6.0, 15.0 Hz), 3.11−3.21 (2H, m), 3.31−3.85 (2H, m), 3.37 (1H, ^{1}/2ABq, J = 14.5 Hz), 3.48 (1H, ^{1}/$_2$ ABq, J = 14.6 Hz), 3.71 (3H, s), 3.72 (3H, s), 3.76−3.98 (8H, m), 3.99 (2H, m), 4.02 (2H, s), 4.15−4.21 (4H, m), 5.17 (1H, ^{1}/$_2$ ABq, J = 14.5 Hz), 5.20 (1H, ^{1}/$_2$ ABq, J = 14.6 Hz), 5.35 (1H, m), 5.48 (1H, m), 6.62−6.70 (6H, m), 6.79 (2H, m), 6.91 (2H, d, J = 8.3 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 8.3 Hz), 7.22 (1H, s), 7.23 (1H, s). IR (NaCl, neat) (*syn*): 2932, 1755, 1661, 1455, 1367, 1250, 1156, 1114,1091, 838 cm^{-1}. HRMS (EI) (*syn*): 931.51955 ($C_{51}H_{77}N_3O_9Si_2$ requires 931.5198). Microanal. Calcd for $C_{51}H_{77}N_3O_9Si_2$: C, 65.70; H, 8.32; N, 4.51. Found: C, 65.37; H, 8.37; N, 4.54.

^{1}H NMR (300 MHz) ($CDCl_3$) (*anti*): δ −0.02 (6H, s), −0.01 (6H, s), 0.03−0.22 (2H, m), 0.12 (6H, s), 0.13 (6H, s), 0.146−0.62 (4H, m), 0.84 (9H, s), 0.85 (9H, s), 0.87 (18H, s), 1.05 (3H, s), 1.07 (3H, s), 1.43 (3H, s), 1.47 (3H, s), 1.49 (3H, s), 1.52 (3H, s), 1.55 (9H, s), 1.60 (9H, s), 1.80−1.91 (2H, m), 2.19−2.22 (2H, m), 2.50−2.61 (2H, m), 3.09−3.23 (2H, m), 3.29−3.52 (4H, m), 3.63−3.96 (18H, m), 4.13−4.20 (4H, m), 5.04−5.10 (1H, m), 5.28−5.32 (1H, m), 5.48 (1H, ^{1}/$_2$ ABq, J = 14.3 Hz), 5.52 (1H, ^{1}/$_2$ ABq, J = 14.3 Hz), 6.71−6.90 (6H, m), 7.04−7.22 (8H, m). IR (NaCl, neat) (*anti*: 3295 (br), 1753, 1657, 1510, 1447, 1249, 1152, 1090, 1034, 836, 773 cm^{-1}.

1,1-Dimethylethyl 8-[[8a-[4-Hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-hydroxy-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (44). To a stirred solution of **43** (36.3 mg, 0.04 mmol, 1.0 equiv) under N_2 in THF (1.0 mL) was added *n*-Bu_4NF (0.12 mL, 0.12 mmol, 3.0 eq, 1.0M/THF). The solution was heated (∼40 °C) for 3 h. At this time the solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The residue was purified by PTLC on silica gel (eluted with EtOAc) to yield 24.9 mg (79%) of **44**.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.19 (3H, s), 1.22 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 1.56 (3H, s), 1.57 (3H, s), 1.59 (9H, s), 1.60 (9H, s), 1.72−2.21 (12H, m), 2.71 (2H, br s, D_2O exch), 3.18−3.49 (4H, m), 3.51 (2H, ^{1}/$_2$ ABq, J = 14.5 Hz), 3.56 (1H, s, D_2O exch), 3.61 (1H, s, D_2O exch), 3.72 (3H, s), 3.74 (3H, s), 3.75−3.94 (6H, s), 4.18−4.30 (4H, s), 4.26−4.27 (4H, m), 4.44 (2H, m), 5.25 (2H, ^{1}/$_2$ ABq, J = 14.5 Hz), 5.25 (2H, ^{1}/$_2$ ABq, J = 14.4 Hz), 6.70 (2H, d, J = 8.7 Hz), 6.77 (2H, d, J = 8.6 Hz), 6.83 (2H, d, J = 8.6 Hz), 6.927 (1H, d, J = 8.4 Hz), 6.932 (1H, d, J = 8.3 Hz), 7.03 (2H, d, J = 8.6 Hz), 7.12 (1H, d, J = 8.3 Hz), 7.15 (1H, d, J = 8.4 Hz), 7.21 (1H, s), 7.23 (1H, s). IR (NaCl, neat): 3422, 2976, 1753, 1649, 1513, 1496, 1457, 1371, 1333, 1251, 1153, 1033, 733 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 703 (M^+, 8), 604 (37), 603 (100). HRMS (EI): 703.3461 ($C_{39}H_{49}N_3O_9$ requires 703.3472).

1,1-Dimethylethyl 8-[[8a-[4-Chloro-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-hydroxy-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (45). To **44** (24.9 mg, 0.035 mmol, 1.0 equiv) in DMF (0.35 mL) at 0 °C under Ar were added dry LiCl (2.9 mg, 0.07 mmol, 1.9 equiv) and collidine (7 μL, 0.05 mmol, 1.5 equiv). After stirring for 10 min, methanesulfonyl chloride (4 μL, 0.05 mmol, 1.5 equiv) was added dropwise. The ice bath was removed and the mixture stirred at room temperature for 24 h. At this time additional collidine (2.5 equiv) and methanesulfonyl chloride (2.5 equiv) were added, and the mixture was stirred for 2 h. It was then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The product was purified by PTLC on silica gel (eluted with 2:1 EtOAc/hexanes) to yield 21.9 mg (86%) of **45** as an oil.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.22 (3H, s), 1.23 (3H, s), 1.57 (3H, s), 1.58 (3H, s), 1.62 (9H, s), 1.63 (9H, s), 1.66 (3H, s), 1.73 (3H, s), 1.83−1.93 (8H, m), 2.05−2.37 (4H, m), 3.06 (2H, dd, J = 3.8, 11.4 Hz), 3.35−3.42 (6H, m, 1H, D_2O exch), 3.46−3.69 (4H, m), 3.75 (3H, s), 3.77 (3H, s), 3.86−3.94 (2H, m), 3.96 (2H, s), 4.02 (2H, s), 4.21−4.29 (6H, m), 5.20−5.29 (3H, m), 5.53 (1H, m), 6.69−6.81 (6H, m), 6.94−6.99 (4H, m), 7.18−7.21 (4H, m). IR (NaCl, neat): 3433, 2976, 1752, 1654, 1513, 1496, 1453, 1371, 1251, 1153 cm^{-1}.

1,1-Dimethylethyl 8-[[8a-[4-Hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (46). To a solution of **45** (28.2 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) at 0 °C under Ar was added *tert*-butyldimethylsilyl triflate (9.0 μL, 0.04 mmol, 1.2 equiv) followed immediately by 2,6-lutidine (6.0 μL, 0.047 mmol, 1.4 equiv). The mixture was stirred for 2 h, then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by radial chromatography (eluted with 1:1 EtOAc/hexanes) to yield 24.9 mg (76%) of **46** as an oil.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 0.12 (6H, s), 0.13 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.08 (3H, s), 1.10 (3H, s), 1.48 (6H, s), 1.61 (9H, s), 1.63 (9H, s), 1.69 (3H, s), 1.79 (3H, s), 1.82−2.03 (8H, m), 2.16−2.24 (4H, m), 3.19 (2H, dd, J = 7.2, 8.5 Hz), 3.25−3.39 (4H, m), 3.49 (1H, ^{1}/$_2$ ABq, J = 14.5 Hz), 3.65 (1H, ^{1}/$_2$ ABq, J = 14.5 Hz), 3.72 (3H, s), 3.76 (3H, s), 3.79−3.99 (8H, m), 4.15−4.22 (4H, m), 5.19−5.28 (4H, m), 5.49 (2H, m), 6.67−6.81 (6H, m), 6.92 (4H, dd, J = 1.9, 8.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.20 (1H, s), 7.24 (1H, s). IR (NaCl, neat): 2932, 1752, 1654, 1512, 1491, 1447, 1365, 1251, 1153, 1088, 837 cm^{-1}.

[(±)-[3α,8aα,10(R*)]]-1,1-Dimethylethyl 8-[[Tetrahydro-2-[(4-methoxyphenyl)methyl]-10-(1-methylethenyl)-1,4-dioxo-6*H*-3,8a-ethanopyrrolo[1,2-*a*]pyrazin-3(4*H*)-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (47). To **46** (24.0 mg, 0.028 mmol, 1.0 equiv) in a flask equipped with a magnetic stir bar were added NaH (12.3 mg, 0.3 mmol, 10.8 equiv) and benzene (3.5 mL). The flask was fitted with a condenser and gently refluxed for 59 h (additional benzene (1.5 mL) was added during this time). The solution was stirred at room temperature for 8 days, after which NaI (10.8 mg, 0.072 mmol, 2.5 equiv) was added. The mixture was then stirred at reflux temperature for an additional 2 days. The resulting mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by PTLC on silica gel (eluted with 1:1 hexanes/EtOAc) to afford 2.5 mg (11% or 19% based on recovered **46**) of **47** as an amorphous yellow solid.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 0.12 (6H, s), 0.14 (6H, s), 0.882 (9H, s), 0.885 (9H, s), 1.10 (3H, s), 1.13 (3H, s), 1.48 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 1.56 (3H, s), 1.59 (18H, s), 1.80 (2H, dd, J = 5.7, 13.3 Hz), 1.90 (2H, dd, J = 13.2 Hz), 2.03−2.08 (4H, m), 2.22 (2H, dd, J = 10.4, 13.4 Hz), 2.85−2.98 (4H, m), 3.08 (2H, ^{1}/$_2$ ABq, J = 17.1 Hz), 3.29 (2H, ^{1}/$_2$ ABq, J = 17.6 Hz), 3.56−3.62 (4H, m), 3.72 (3H, s), 3.73 (3H, s), 3.74−3.83 (2H, dd, J = 9.4, 12.5 Hz), 3.91−3.96 (2H, m), 4.18 (2H, dd, J = 3.6, 12.2 Hz), 4.28 (1H, ^{1}/$_2$ ABq, J = 15.9 Hz), 4.37 (1H, ^{1}/$_2$ ABq, J = 15.9 Hz), 4.54−4.74 (6H, m), 6.62−6.75 (8H, m), 6.89−6.94 (2H, m), 6.99−7.04 (2H, m), 7.25 (1H, s), 7.28 (1H, s). IR (NaCl, neat): 2932, 1687, 1365, 1251, 1158, 1088 cm^{-1}. HRMS (EI): 799.4252 ($C_{45}H_{61}N_3O_8Si$ requires 799.4228).

(*R*)-(*E*)-8a-[3-Methyl-4-oxo-2-buten-yl]hexahydropyrrolo[1,2-*a*]-pyrazine-1,4-dione (49). To a stirred solution of **48** (17.25 g, 48.45 mmol, 1.0 equiv) in a 2:1 solution of CH_3CN (343 mL) and H_2O (171 mL) was added, in one portion, CAN (93 g, 170 mmol, 3.8 equiv). After stirring for 2 h, the orange solution was poured into a large separatory funnel and exhaustively extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography (eluted with 95:4:1 CH_2Cl_2/MeOH/AcOH) to yield 9.0 g (79%) of **49** as a yellow oil. An analytical sample was obtained by PTLC (silica gel, eluted with 1:1 hexanes/EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.76 (3H, s), 1.99−2.10 (2H, br s), 2.17−2.26 (2H, m), 2.78 (1H, dd, J = 7.3, 14.5 Hz), 2.90 (1H,

dd, J = 8.0, 14.8 Hz), 3.54−3.63 (1H, m), 3.84 (1H, dt, J = 12.3, 8.4 Hz), 3.95 (1H, d $^1/_2$ ABq, J = 3.4, 17.6 Hz), 4.10 (1H, $^1/_2$ ABq, J = 17.6 Hz), 6.55 (1H, t, J = 7.2 Hz), 7.96 (1H, br s, D_2O exch), 9.45 (1H, s). IR (NaCl, neat): 3246, 1684, 1448, 1326, 1107 cm^{-1}. $[\alpha]^{25}_D$ = −1.51/1.92 × 10^{-2})° = −78.4° (CH_2Cl_2, c = 0.164). Microanal. Calcd: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.88; H, 6.66; N, 11.71. HRMS (EI): 236.1155 ($C_{12}H_{16}N_2O_3$ requires 236.11609).

(*R*)-(*E*)-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]hexahydro-2*H*-pyrrolo[1,2-*a*]pyrazine-1,4-dione (50). To a stirred solution of **49** (9.0 g, 37 mmol, 1.0 equiv) in absolute ethanol (742 mL) at room temperature was added $NaBH_4$ (2.85 g, 75.5 mmol, 2.0 equiv). After 2 h the excess hydride was quenched with water (500 mL) and the pH adjusted to 3−4 by the slow addition of 1 M HCl. Fifteen minutes later, the water and ethanol were removed under reduced pressure and the crude residue was dried in vacuo overnight. The resulting mass (10.87 g) was triturated (1:4 CH_3OH/CH_2Cl_2) and filtered to remove the salts. The remaining solution was concentrated to yield 9.1 g of the crude allylic alcohol, which was immediately utilized for the next step without additional purification. The crude allylic alcohol (9.1 g, 38 mmol, 1.0 equiv) was dissolved in DMF (191 mL) under Ar, and to this mixture was added imidazole (11.9 g, 175.3 mmol, 4.6 equiv) followed by *tert*-butyldiphenylsilyl chloride (12.9 mL, 49.5 mmol, 1.3 equiv). After 2 days the reaction mixture was diluted with water (1 L) and extracted with a 1:1 solution of hexanes and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude solid was recrystallized (ethyl acetate, two crops) to give 10.5 g of the product. The remaining mother liquor was chromatographed (eluted with EtOAc) to give 3.0 g of the pure product. Total yield of **50**: 13.5 g (75% from the enone, two steps). An analytical sample was recrystallized from acetone to provide a white crystalline solid, mp 132 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.03 (9H, s), 1.54 (3H, s), 1.92−2.19 (4H, m), 2.49 (1H, dd, J = 8.6, 14.1 Hz), 2.58 (1H, dd, J = 7.5, 14.1 Hz), 3.44−3.53 (1H, m), 3.73 (1H, d $^1/_2$ ABq, J = 4.1, 16.9 Hz), 3.78−3.85 (1H, m), 4.01 (2H, s), 4.06 (1H, $^1/_2$ ABq, J = 16.9 Hz), 5.56−5.62 (1H, m), 6.38 (1H, d, J = 3.7 Hz, D_2O exch), 7.32−7.43 (6H, m), 7.62 (4H, dd, J = 1.8, 7.6 Hz). IR (NaCl, neat): 3232 (br), 2930, 2857, 1664, 1446, 1435, 1113, 822, 733, 702 cm^{-1}. $[\alpha]^{25}_D$ = −63.3° ($CDCl_3$, c = 0.0822). Microanal. Calcd for $C_{28}H_{36}N_2O_3Si$: C,70.55; H, 7.61; N, 5.88. Found C, 70.60; H, 7.56; N, 5.91.

[(R)-[3α*β*,8a*β*(*E*)]]-Methyl 8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-2-(methoxycarbonyl)-1,4-dioxopyrrolo[1,2-*a*]pyrazine-3-carboxylate (51). To a stirred solution of **50** (8.12 g, 17.0 mmol, 1.0 equiv) in THF (208 mL) at −78 °C, was added a solution of *n*-BuLi (10.65 mL, 17.03 mmol, 1.0 equiv, 1.6 M/hexanes) dropwise. After 25 min methyl chloroformate (1.45 mL, 18.7 mmol, 1.1 equiv) was added dropwise to the reaction mixture and stirred for 25 min. The solution was then transferred via cannula to a cold (−100 °C) flask charged with $LiN[Si(CH_3)_3]_2$ (37.47 mL, 37.47 mmol, 2.2 equiv, 1.0 M/THF) and methyl chloroformate (1.45 mL, 18.7 mmol, 1.1 equiv). The resulting solution was stirred for 45 min, diluted with EtOAc, and washed with saturated aqueous NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluted with 2:1 hexanes/EtOAc) to yield 9.4 g (93%) of **51** (as a mixture of two diastereomers, *anti*/*syn*). An analytical sample (oil) was obtained by PTLC (eluted with 2:1 hexanes/EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.04 (9H, s), 1.40 (3H, s), 1.86−2.03 (2H, m), 2.12−2.31 (2H, m), 2.55 (1H, d, J = 7.4 Hz), 3.43−3.52 (2H, m), 3.74−3.82 (1H, m), 3.83 (3H, s), 3.88 (3H, s), 4.03 (2H, br s), 5.48−5.53 (2H, m), 7.34−7.41 (6H, m), 7.57−7.66 (4H, m). IR (NaCl, neat): 2960, 1790, 1740, 1681, 1430, 1366, 1272, 1223, 1109, 735, 705 cm^{-1}. Microanal. Calcd for $C_{32}H_{40}N_2O_7Si$: C, 68.06; H, 7.14; N, 4.96. Found: C, 67.87; H, 7.27; N, 4.77.

[3*β*,8a*β*(*E*)]-Methyl 3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazine-3-carboxylate (52). To a flask containing **51** (5.89 g, 14.56 mmol, 1.0 equiv) and **36** (8.64 g, 14.56 mmol, 1.1 equiv) were added CH_3CN (291 mL) and tributylphosphine (1.82 mL, 7.28 mmol, 0.5 equiv). The resulting mixture was gently refluxed for 3.5 h and then stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 9.56 g (73%) of **52**. An analytical sample was purified by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes) to give a white crystalline solid, mp 106−108 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.10 (6H, s), 0.115 (3H, s), 0.12 (3H, s), 0.87 (9H, s), 0.88 (9H, s), 1.02 (18H, s), 1.096 (3H, s), 1.10 (3H, s), 1.45 (3H, s), 1.46 (3H, s), 1.54 (6H, s), 1.60−1.88 (6H, m), 2.02−2.11 (2H, m): 2.92 (2H, dd, J = 7.1, 14.4 Hz), 2.44 (2H, dd, J = 8.1, 14.5 Hz), 3.32−3.44 (4H, m), 3.60 (3H, s), 3.62 (3H, s), 3.72−3.93 (8H, m), 3.98 (4H, br s), 4.18 (2H, dd, J = 2.9, 8.4 Hz), 5.43 (2H, m), 6.38 (1H, s, D_2O exch), 6.41 (1H, s, D_2O exch), 6.74 (1H, d, J = 8.5 Hz), 6.75 (1H, d, J = 8.5 Hz), 6.89 (1H, d, J = 2.3 Hz), 6.92 (1H, d, J = 2.3 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.33−7.41 (12H, m), 7.61−7.63 (8H, m), 8.43 (1H, d, J = 2.9 Hz, D_2O exch), 8.64 (1H, d, J = 1.9 Hz, D_2O exch.). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 4.8, 4.2, 9.5, 17.9, 19.2, 19.3, 19.5, 20.3, 25.7, 26.8, 28.0, 28.3, 29.7, 33.7, 35.6, 46.1, 46.2, 53.3, 66.9, 68.0, 71.6, 76.3, 80.7, 80.8, 108.2, 112.9, 117.1, 117.9, 118.0, 123.5, 123.6, 125.5, 127.6, 129.1, 129.2, 129.6, 133.6, 135.5, 138.8, 141.6, 141.8, 161.4, 169.7, 170.5, 170.6. IR (NaCl, neat): 3281 (br), 2954, 2932, 2856, 1747, 1670, 1665, 1649, 1431, 1251, 1224, 1109, 1088, 733, 706 cm^{-1}. HRMS (EI): 893.4457 ($C_{50}H_{67}N_3O_8Si_2$ requires 893.4467). Microanal. Calcd for $C_{50}H_{67}N_3O_8Si_2$: C, 67.16; H, 7.55; N, 4.70. Found: C, 66.93; H, 7.36; N, 4.51.

[3*β*,8a*β*(*E*)]-8-[[8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole (53). [3α,8a*β*(*E*)] 8-[[8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole (54). A flask containing **52** (9.56 g, 10.7 mmol, 1.0 equiv) and LiCl (2.26 g, 53.45 mmol, 5.0 equiv) under Ar was charged with HMPA (82 mL) and water (0.29 mL, 16.0 mmol, 1.5 equiv). This mixture was gently heated (100−105 °C) for 9 h and then diluted with 1:1 hexanes/EtOAc. The resulting solution was washed with water. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 5.90 g (66%) of **53** (two diastereomers; an analytical sample was recrystallized from CCl_4, mp (*syn*) 167−168 °C) and 2.10 g (23%) of **54** (two diastereomers); an analytical sample was obtained by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes, mp (*anti*) 95−99 °C, white crystalline solid). Total combined yield: 8.00 g (89%).

^{1}H NMR (300 MHz) ($CDCl_3$) (**53**, mixture of two diastereomers): δ TMS 0.12 (6H, s), 0.13 (6H, s), 0.90 (18H, s), 1.0 (18H, s), 1.126 (3H, s), 1.13 (3H, s), 1.48 (6H, s), 1.64 (6H, s), 1.94−2.06 (6H, m), 2.20−2.24 (2H, m), 2.36−2.46 (2H, m), 2.60−2.72 (2H, m), 2.98 (2H, dd, J = 11.6, 14.1 Hz), 3.44−3.57 (4H, m), 3.88 (2H, dd, J = 6.7, 9.2 Hz), 3.97 (2H, dd, J = 3.1, 9.1 Hz), 4.02−4.06 (2H, m), 4.10 (4H, s), 4.17−4.25 (4H, m), 5.58 (2H, m), 5.68 (2H, br s, D_2O exch), 6.75 (2H, d, J = 8.5 Hz), 6.86 (1H, d, J = 2.2 Hz), 6.88 (1H, J = 2.2 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.26−7.44 (12H, m), 7.60−7.64 (8H, m), 8.04 (1H, s, D_2O exch), 8.06 (1H, s, D_2O exch).

The analytical samples of the *syn*-diastereomers were separable by PTLC.

^{1}H NMR (300 MHz) ($CDCl_3$) (**53a**, less polar): δ TMS 0.12 (3H, s), 0.13 (3H, s), 0.88 (9H, s), 1.03 (9H, s), 1.11 (3H, s), 1.46 (3H, s), 1.63 (3H, s), 1.92−2.04 (3H, m), 2.18−2.23 (1H, m), 2.39 (1H, dd, J = 7.2, 14.2 Hz), 2.64 (1H, dd, J = 8.7, 14.2 Hz), 2.99 (1H, dd, J = 11.4, 14.2 Hz), 3.42−3.46 (1H, m), 3.51 (1H, dd, J = 2.7, 14.2 Hz), 3.85 (1H, dd, J = 9.2, 11.3 Hz), 3.94 (1H, dd, J = 3.0, 9 Hz), 3.99−4.06 (1H, m), 4.08 (2H, s), 4.11−4.15 (1H, m), 4.19 (1H, dd, J = 3.0, 11.3 Hz), 5.58 (1H, t, J = 7.8 Hz), 5.76 (1H, d, J = 2.7 Hz, D_2O exch), 6.73 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 2.1 Hz), 7.11 (1H, d, J = 8.5 Hz), 7.26−7.42 (6H, m), 7.57−7.63 (4H, m), 8.15 (1H, s, D_2O exch).

^{1}H NMR (300 MHz) ($CDCl_3$) (**53b**, more polar): δ TMS 0.12 (3H, s), 0.14 (3H, s), 0.88 (9H, s), 1.03 (9H, s), 1.11 (3H, s), 1.46 (3H, s), 1.62 (3H, s), 1.91−2.04 (3H, m), 2.18−2.22 (1H, m), 2.36 (1H, dd, J

= 7.3, 14.2 Hz), 2.60 (1H, dd, *J* = 8.6, 14.3 Hz), 2.97 (1H, dd, *J* = 11.3, 14.2 Hz), 3.41−3.44 (1H, m), 3.50 (1H, dd, *J* = 3.1, 14.2 Hz), 3.86 (1H, dd, *J* = 9.3, 11.3 Hz), 3.95 (1H, dd, *J* = 3.0, 9.1 Hz), 3.99−4.03 (1H, m), 4.08 (2H, s), 4.14−4.16 (1H, m), 4.20 (1H, dd, *J* = 2.9, 11.6 Hz), 5.56 (1H, t, *J* =7.5 Hz), 5.72 (1H, d, *J* = 2.6 Hz, D_2O exch), 6.73 (1H, d, *J* = 8.4 Hz), 6.84 (1H, d, *J* = 2.1 Hz), 7.11 (1H, d, *J* = 8.4 Hz), 7.26−7.42 (6H, m), 7.57−7.62 (4H, m), 8.07 (1H, s, D_2O exch). IR (NaCl, neat) (*syn*): 3274 (br), 2929, 2858, 1666, 1651, 1453, 1428, 1250, 1224, 1112, 1052, 858, 838, 777 cm^{-1}. Microanal. Calcd for $C_{49}H_{65}N_3O_6Si_2$ (*syn*): C, 68.94; H, 7.84; N, 5.02. Found: C, 69.06; H, 7.76; N, 5.03.

^1H NMR (300 MHz) ($CDCl_3$) (**54**, mixture of two diastereomers): *δ* TMS 0.14 (6H, s), 0.16 (6H, s), 0.90 (18H, s), 1.04 (9H, s), 1.045 (9H, s), 1.09 (3H, s), 1.13 (3H, s), 1.47 (6H, s), 1.53 (3H, m), 1.54 (3H, m), 1.97−2.17 (8H, m), 2.47−2.62 (4H, m), 2.78−2.88 (2H, m), 3.54−3.65 (4H, m), 3.82−3.99 (6H, m), 4.02 (4H, s), 4.21 (2H, dd, *J* = 3.1, 11.0 Hz), 4.35−4.39 (2H, m), 5.52−5.54 (2H, m), 5.69 (2H, br s, D_2O exch), 6.60 (2H, d, *J* = 8.4 Hz), 6.63 (2H, d, *J* = 8.4 Hz), 6.89 (2H, d, *J* = 2.1 Hz), 6.98 (2H, d, *J* = 8.4 Hz), 7.36−7.42 (10H, m), 7.62−7.69 (8H, m), 8.08 (2H, br s, D_2O exch). IR (NaCl, neat) (*anti*): 3289 (br), 2929, 2855, 1666, 1444, 1428, 1254, 1222, 1111, 857, 836, 704 cm^{-1}. Mass spectrum (EI) (*anti*): *m/e* (relative intensity) 833 (M^+, 0.1), 512 (6.4), 361 (26), 360 (100), 199 (47). Microanal. Calcd for $C_{48}H_{65}N_3O_6Si_2$ (*anti*): C, 68.94; H, 7.84; N, 5.02. Found: C, 68.76; H, 7.60; N, 4.82.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (58). To a stirred solution of **53** (310 mg, 0.37 mmol, 1.0 equiv) at 0 °C under Ar in CH_2Cl_2 (7.4 mL) were added Et_3N (0.1 mL, 0.74 mmol, 2.0 equiv) and DMAP (90.7 mg, 0.74 mmol, 2.0 equiv). After 5 min, $(BOC)_2O$ (486.2 mg, 2.2 mmol, 6.0 equiv) was added in one portion. The resulting solution was stirred for 8.5 h, poured into water, and extracted with EtOAc. The organic layer was washed with 10% $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 EtOAc/hexanes) to yield 375 mg (97%) of **58** as an amorphous solid.

^1H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): *δ* 0.12 (6H, s), 0.13 (6H, s), 0.879 (9H, s), 0.880 (9H, s), 1.01 (18H, s), 1.05 (3H, s), 1.07 (3H, s), 1.14 (9H, s), 1.18 (9H, s), 1.55 (6H, s), 1.47 (6H, s), 1.57 (18H, s), 1.88−2.16 (6H, m), 2.17−2.26 (2H, m), 2.28−2.36 (2H, m), 2.50 (2H, dd, *J* = 8.1, 14.5 Hz), 3.22 (2H, m), 3.32−3.45 (4H, m), 3.71−3.81 (2H, m), 3.84−3.96 (4H, m), 4.00 (4H, br s), 4.13−4.18 (2H, m), 5.02−5.07 (2H, m), 5.42 (1H, t, *J* = 7.3 Hz), 5.53 (1H, t, *J* = 7.5 Hz), 6.91 (2H, d, *J* = 8.3 Hz), 7.16 (1H, d, *J* = 8.0 Hz), 7.19 (1H, d, *J* = 8.2 Hz),7.22 (1H, s), 7.24 (1H, s), 7.30−7.40 (12H, m), 7.57−7.61 (8H, m). IR (NaCl, neat): 2932, 1752, 1730, 1660, 1371, 1251, 1153, 1109, 1088, 706 cm^{-1}. HRMS (EI): 1035.5481 ($C_{58}H_{81}N_3O_{10}Si_2$ requires 1035.5461).

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-hydroxy-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate. To a stirred solution of **53** (511 mg, 0.61 mmol, 1.0 equiv) at 0 °C under Ar in CH_2Cl_2 (12.2 mL) were added DMAP (149.4 mg, 1.2 mmol, 2.0 equiv) and Et_3N (0.17 mL, 1.2 mmol, 2.0 equiv). After 5 min, $(BOC)_2O$ (801.0 mg, 3.67 mmol, 6.0 equiv) was added in one portion. The resulting solution was stirred for 2.7 h, and reaction was found to be complete by TLC analysis; during this period, the reaction temperature slowly reached 15 °C. The reaction flask was then charged with THF (12 mL) and the CH_2Cl_2 removed by evaporation (until the volume of the flask was approximately 12 mL). The solution was stirred at room temperature and *n*-Bu_4NF (1.96 mL, 1.96 mmol, 3.2 eq, 1.0 M/THF) added quickly. After 22 h, additional *n*-Bu_4NF (1.0 mL, 1.0 mmol, 1.6 equiv, 1.0 M/THF) was added to the reaction flask and stirred for 24 h. The reaction was complete by TLC and was poured into water and extracted with EtOAc. The organic layer was washed with 10% $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with EtOAc) to yield 369 mg (89%) of the diol (obtained as a pale yellow, amorphous solid).

^1H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): *δ* 1.21 (3H, s), 1.24 (3H, s), 1.29 ((9H, s), 1.35 (9H, s), 1.47 (6H, s), 1.52 (6H, s), 1.56 (18H, s), 1.63−2.21 (14H, m), 3.21−3.38 (8H, m), 3.54 (1H, br s, D_2O exch), 3.58 (1H, br s, D_2O exch), 3.81−3.87 (6H, m, 2H D_2O exch), 4.22 (4H, d, *J* = 8.0 Hz), 4.62 (1H, t, *J* = 8.4 Hz), 4.96−5.01 (2H, m), 5.07 (1H, t, *J* = 7.2 Hz), 6.90 (1H, d, *J* = 8.4 Hz), 6.91 (1H, d, *J* = 8.4 Hz), 7.13 (1H, d, *J* = 8.4 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.22 (1H, s), 7.23 (1H, s). IR (NaCl, neat): 3436, 2978, 1755, 1649, 1367, 1249, 1149, 732 cm^{-1}.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-chloro-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate. To a stirred solution of the diol obtained above (50.0 mg, 0.0725 mmol, 1.0 equiv) in DMF (0.73 mL) at 0 °C under Ar were added collidine (0.014 mL, 0.11 mmol, 1.5 equiv) and LiCl (5.27 mg, 0.12 mmol, 1.7 equiv). After 15 min, MsCl (8.4 *μ*L, 0.11 mmol, 1.5 equiv) was added and the reaction mixture allowed to reach room temperature in the course of 16 h. At this time an additional amount (1.0 equiv) of each reagent was added in the same manner as above. After 8.5 h there was little change by TLC, so a large excess of MsCl (0.06 mL, 0.775 mmol, 10.7 equiv) was added at 0 °C and stirred for ∼12 h until only the desired product was apparent by TLC. The solution was diluted with 1:1 hexanes/EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated, under reduced pressure. The residue was purified by radial chromatography, 1:1 EtOAc/hexanes, to yield 45.5 mg (91%) of the product allylic chloride (obtained as a foamy glass).

^1H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): *δ* 1.18 (3H, s), 1.20 (3H, s), 1.24 (9H, s), 1.30 (9H, s), 1.51 (3H, s), 1.54 (3H, s), 1.58 (18H, s), 1.64 (3H, s), 1.66 (3H, s), 1.74−2.18 (10H, m), 2.27 (2H, dd, *J* = 8.1, 15.0 Hz), 3.02 (2H, br s, D_2O exch), 3.19 (2H, dd, *J* = 7.2, 14.8 Hz), 3.27−3.44 (4H, m), 3.56 (2H, br s), 3.81−3.89 (2H, m), 3.91 (2H, s), 3.94 (2H, s), 4.18−4.30 (4H, m), 4.99−5.06 (2H, m), 5.21 (1H, t, *J* = 8.3 Hz), 5.38−5.43 (1H, m), 6.93 (2H, d, *J* = 8.3 Hz), 7.17 (1H, d, *J* = 8.3 Hz), 7.20 (1H, d, *J* = 8.3 Hz), 7.21 (1H, s), 7.24 (1H, s). IR (NaCl, neat): 3384, 2920, 1750, 1736, 1657, 1367, 1250, 1149 cm^{-1}.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-chloro-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (55). To a stirred solution of the allylic chloride obtained above (96.2 mg, 0.37 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) under Ar were added 2,6-lutidine (0.016 mL, 0.14 mmol, 0.38 equiv) and *tert*-butyldimethylsilyl triflate (0.03 mL, 0.14 mmol, 0.38 equiv). After 1 h an additional amount (0.5 equiv) of the two reagents was added. The mixture was stirred for 1 h, and another portion (0.5 equiv) of each reagent was added. The solution was stirred for 75 min and was then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 EtOAc/hexanes) to yield 106.5 mg (99%) of **55** as a white crystalline solid, mp 70−73 °C.

^1H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): *δ* 0.10 (3H, s), 0.11 (6H, s), 0.12 (3H, s), 0.877 (18H, s), 1.04 (3H, s), 1.06 (3H, s), 1.22 (9H, s), 1.29 (9H, s), 1.44 (3H, s), 1.46 (3H, s), 1.58 (18H, s), 1.62 (3H, s), 1.65 (3H, s), 1.76−2.13 (10H, m), 2.22 (2H, dd, *J* = 8.4, 14.8 Hz), 3.19 (2H, dd, *J* = 7.1, 14.7 Hz), 3.26−3.42 (4H, m), 3.68−3.78 (2H, m), 3.81−3.87 (4H, m), 3.90 (2H, s), 3.94 (2H, s), 4.10−4.17 (2H, m), 5.00−5.05 (2H, m), 5.22 (1H, t, *J* = 7.6 Hz), 5.41 (1H, t, *J* = 7.6 Hz), 6.91 (2H, d, *J* = 8.3 Hz), 7.14 (1H, d, *J* = 8.3 Hz), 7.16 (1H, d, *J* = 8.3 Hz), 7.21 (1H, s), 7.24 (1H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): *δ* −5.0, −4.1, −4.0, 14.3, 17.8, 18.3, 19.7, 19.8, 25.6 27.3, 27.4, 27.9, 28.5, 29.6, 30.1, 34.5, 34.7, 36.1, 45.2, 45.32, 51.3, 51.4, 60.5, 68.1, 68.2, 70.9, 70.9, 75.7, 80.2, 83.1, 84.2, 84.2, 113.6, 113.8, 114.1, 114.2, 120.0, 120.1, 122.6, 122.7, 126.9, 127.1, 127.8, 127.9, 129.0, 135.6, 135.8, 140.43, 146.3, 146.4, 148.3, 148.4, 150.3, 150.5, 164.4, 164.5, 168.6, 168.7. IR (NaCl, neat): 2936, 1754, 1729, 1663, 1496, 1456, 1370,

1248, 1152, 1086, 838 cm^{-1}. HRMS (EI): 815.3973 ($C_{42}H_{62}N_3O_9SiCl$ requires 815.3944).

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (59). To a flask fitted with a reflux condenser was added **58** (799 mg, 0.771 mmol, 1.0 equiv) followed by CH_3CN (15.4 mL) and dimethylamine (0.53 mL, 3.85 mmol, 5.0 equiv, 40% solution in water). The resulting solution was refluxed for 2 h and 20 min. The solvent was removed under reduced pressure and the residue purified by radial chromatography (eluted with 1:2 EtOAc/hexanes) to yield 657 mg (92%) of **59**. An analytical sample was obtained by PTLC, on silica gel (eluted with 1:2 EtOAc/hexanes) (foamy oil).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.14 (6H, s), 0.23 (6H, s), 0.88 (18H, s), 1.01 (18H, s), 1.10 (6H, s), 1.48 (6H, d), 1.59 (18H, s), 1.62 (6H, s), 1.98−2.05 (6H, m), 2.07−2.19 (2H, m), 2.37−2.47 (2H, m), 2.64−2.75 (2H, m), 2.94 (2H, dd, J = 11.6, 14.1 Hz), 3.41−3.47 (4H, m), 3.82 (2H, dd, J = 9.6, 12.2 Hz), 3.93−4.03 (4H, m), 4.07 (4H, br s), 4.10−4.15 (2H, m), 4.20 (2H, dd, J = 2.7, 12.4 Hz), 5.56−5.61 (2H, m), 5.78 (1H, d, J = 3.0 Hz, D_2O exch), 5.81 (1H, d, J = 2.8 Hz, D_2O exch), 6.877 (1H, d, J = 8.4 Hz), 6.884 (1H, d, J = 8.4 Hz), 7.09 (2H, d, J = 8.4 Hz), 7.20−7.40 (14H, m), 7.56 − 7.61 (8H, m). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −5.0, −4.1, 13.7, 14.0, 17.8, 18.6, 18.8, 19.1, 19.6, 22.5, 25.7, 26.7, 28.0, 28.4, 28.4, 31.4, 31.6, 31.7, 34.9, 35.8, 44.81, 57.5, 67.5, 68.2, 71.0, 75.8, 76.6, 77.0, 77.4, 80.3, 83.3, 83.1, 113.3, 114.6, 116.6, 120.1, 126.3, 126.3, 127.5 127.6, 128.1, 128.2, 128.4, 128.4, 128.6, 133.1, 133.2, 135.4, 139.2, 140.5, 140.6, 146.4, 146.5, 148.4, 164.4, 169.6, 169.7. IR (NaCl, neat): 3246, 2960 2861, 1750, 1676, 1662, 1430, 1366, 1252, 1159, 1109, 1090 cm^{-1}. HRMS (EI): 935.48955 ($C_{53}H_{73}N_3O_8Si_2$ requires 935.4936). Microanal. Calcd for $C_{53}H_{73}N_3O_8Si_2$: C, 67.57; H, 7.96; N, 4.54. Found: C, 67.62; H, 7.94; N, 4.32.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (60). To a stirred solution of **53** (3.87 g, 4.63 mmol, 1.0 equiv) in CH_2Cl_2 (46 mL) under Ar at 0 °C was added Na_2CO_3 (9.8 g, 92.6 mmol, 20.0 equiv). After 10 min, Me_3OBF_4 (3.42 g, 23.15 mmol, 5.0 equiv) was added in one portion. The mixture was stirred for 4.0 h at room temperature, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (eluted with 1:2 hexanes/EtOAc; then 1:1 hexanes/EtOAc) to yield 3.20 g (81%) of **60**. An analytical sample was obtained by PTLC on silica gel (eluted with EtOAc) (isolated as a white solid, mp 74−76 °C).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.120 (12H, s), 0.875 (18H, s), 1.02 (18H, s), 1.06 (3H, s), 1.07 (3H, s), 1.45 (12H, s), 1.65−2.08 (14H, m), 3.07−3.15 (2H, m), 3.26 (2H, dd, J = 6.2, 12.6 Hz), 3.32−3.40 (2H, m), 3.61 (6H, s), 3.70−3.86 (2H, m), 3.91−3.95 (4H, m), 3.99 (2H, s), 4.15 (2H, dd, J = 3.6, 11.7 Hz), 4.36−4.40 (2H, m), 5.37−5.44 (2H, br m), 6.69 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 1.7 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.26−7.41 (12H, m), 7.58−7.62 (8H, m), 8.06 (2H, s, D_2O exch). IR (NaCl, neat): 3292, 2932, 1687, 1643, 1447, 1251, 1218, 1109, 837 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 849 (M^+, 8.9), 361 (26), 360 (95), 167 (100). Microanal. Calcd for $C_{49}H_{67}N_3O_6Si_2$: C, 69.02; H, 7.94; N, 4.94. Found: C, 69.02; H, 7.88; N, 4.79.

[3α,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (61). To a stirred solution of **54** (8.47 g,10.13 mmol, 1.0 equiv) in CH_2Cl_2 (101 mL) at 0 °C under Ar was added Na_2CO_3 (21.26 g, 202.6 mmol, 20.0 equiv). After 15 min Me_3OBF_4 (7.49 g, 50.64 mmol, 5.0 equiv) was added in one portion. The mixture was stirred for 5 min, the ice bath was removed, and the reaction mixture was stirred for 4.5 h. The mixture was then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 5.30 g (62%) of **61**. [The yield of **61** was 365 mg (71%) from 508 mg of **54**.] An analytical sample was obtained by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes and obtained as a white crystalline solid, mp 54−58 °C).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.13 (3H, s), 0.14 (9H, s), 0.89 (18H, s), 1.03 (9H, s), 1.04 (9H, s), 1.087 (3H, s), 1.093 (3H, s), 1.28−1.43 (4H, m), 1.48 (6H, s), 1.50 (6H, s), 1.79−1.89 (4H, m), 2.24−2.38 (4H, m), 3.22−3.42 (6H, m), 3.60 (3H, s), 3.62 (3H, s), 3.68−3.76 (2H, m), 3.79−3.87 (2H, m), 3.94 (2H, d, J = 3.4 Hz), 3.97 (4H, br s), 4.15−4.20 (2H, m), 4.26−4.32 (2H, m), 5.41 (2H, t, J = 7.8 Hz), 6.701 (1H, d, J = 8.5 Hz), 6.703 (1H, d, J = 8.4 Hz), 6.96 (1H, d, J = 2.6 Hz), 6.97 (1H, d, J = 2.6 Hz), 7.28 (2H, d, J = 8.5 Hz), 7.32−7.44 (12H, m), 7.60−7.64 (8H, m), 7.97 (2H, br s, D_2O exch). IR (NaCl, neat): 3304, 2930, 1695, 1645, 1447, 1249, 1221, 836 cm^{-1}. HRMS (EI): 849.4550 ($C_{49}H_{67}N_3O_6Si_2$ requires 849.4568). Microanal. Calcd for $C_{49}H_{67}N_3O_6Si_2$: C, 69.22; H, 7.94; N, 4.94. Found: C, 59.06; H, 8.04; N, 4.89.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-hydroxy-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (62). To stirred solution of **60** (5.45 g, 6.41 mmol, 1.0 equiv) in CH_2Cl_2 (32 mL) under Ar at 0 °C were added Et_3N (0.89 mL, 6.41 mmol, 1.0 equiv) and DMAP (783.1 mg, 6.41 mmol, 1.0 equiv). After 10 min $(BOC)_2O$ (4.20 g, 19.2 mmol, 3.0 equiv) was added in one portion. The reaction mixture was stirred for 6 h and diluted with THF (45 mL). The remaining CH_2Cl_2 was removed by evaporation under reduced pressure (until the volume in the flask was 45 mL). The flask was charged with *n*-Bu_4NF (19.2 mL, 19.2 mmol, 3.0 equiv, 1.0 M/THF), and the mixture was stirred at room temperature for approximately 12 h. The solution was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes; then 2:1 EtOAc/hexanes) to yield 3.45 g (90%) of **62**. [The yield of **62** was 243 mg (97%) from 355 mg of **60**.] An analytical sample was obtained by PTLC on silica gel (eluted with 2:1 EtOAc/hexanes) to afford a white solid, mp 72−85 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.18 (6H, s), 1.52 (3H, s), 1.53 (3H, s), 1.56 (3H, s), 1.57 (21H, s), 1.61−2.07 (10H, m), 2.14 (2H, dd, J = 8.6, 14.5 Hz), 2.85 (2H, br s, D_2O exch), 2.92−3.01 (2H, m), 3.18−3.35 (6H, m), 3.56 (2H, br s, D_2O exch), 3.62 (3H, s), 3.64 (3H, s), 3.88 (4H, br s), 3.91−4.00 (2H, m), 4.25 (4H, br s), 4.30−4.39 (2H, m), 4.98−5.01 (2H, m), 6.87 (1H, d, J = 8.3 Hz), 6.88 (1H, d, J = 8.3 Hz), 7.16 (1H, d, J = 8.3 Hz), 7.17 (1H, d, J = 8.3 Hz), 7.34 (1H, s), 7.35 (1H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 13.4, 19.5, 19.7, 23.5, 23.6, 25.1, 25.3, 27.9, 30.3, 30.5, 34.4, 34.8, 35.1, 35.3, 43.4, 43.6, 52.6, 52.7, 62.0, 62.4, 65.3, 65.4, 67.7, 67.8, 70.6, 75.4, 82.6, 82.6, 114.5, 114.7, 116.8, 116.9, 118.2, 118.3 119.0, 119.1, 126.3, 128.0, 128.1, 129.9 130.0, 138.6, 138.7, 140.7, 146.2, 148.5, 161.32, 161.5, 168.5, 168.7 IR (NaCl, neat): 3390 (br), 2976, 1752, 1692, 1632, 1491, 1453, 1371, 1251, 1158, 733 cm^{-1}. Microanal. Calcd for $C_{32}H_{43}N_3O_8$: C, 64.30; H, 7.25; N, 7.03. Found: C, 64.12; H, 7.41; N, 6.88. HRMS (EI): m/e 597.3065 ($C_{32}H_{43}N_3O_8$ requires 597.3050).

[3α,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-hydroxy-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (63). To a stirred solution of **61** (5.30 g, 5.65 mmol, 1.0 equiv) under Ar in CH_2Cl_2 (1.5 mL) at 0 °C were added Et_3N (0.79 mL, 5.65 mmol, 1.0 equiv) and DMAP (689.7 mg, 5.65 mmol, 1.0 equiv). After 5 min $(BOC)_2O$ (3.70 g, 16.94 mmol, 3.0 equiv) was added in one portion. The reaction mixture was stirred for 4.5 h and diluted with THF (40 mL). The remaining CH_2Cl_2 was removed under reduced pressure (until the reaction volume was 40 mL). The flask was charged with *n*-Bu_4NF (17.0 mL, 17.0 mmol, 3.0 equiv, 1.0 M/THF), and the mixture was stirred at room temperature for ∼12 h. The solution was diluted with water and extracted with EtOAc.

The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography (eluted with EtOAc) to yield 3.16 g (85%) of **63** as a white, amorphous solid, mp 72−80 °C [The yield of **63** was 179 mg (98%) with 260 mg of **61**].

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.16 (3H, s), 1.18 (3H, s), 1.51 (3H, s), 1.52 (3H, s), 1.55 (6H, s), 1.57 (18H, s), 1.60−2.14 (10H, m, 2H D_2O exch), 2.22−2.37 (4H, m), 3.06−3.18 (3H, m, 1H D_2O exch), 3.26−3.36 (5H, m, 1H D_2O exch), 3.55 (3H, s), 3.56 (2H, br s), 3.60 (3H, s), 3.63−3.72 (2H, m), 3.89 (4H, m), 4.18−4.23 (2H, m), 4.25 (4H, br s), 5.21−5.27 (2H, m), 6.857 (1H, d, J = 8.3 Hz), 6.861 (1H, d, J = 8.3 Hz), 7.22 (2H, d, J = 8.3 Hz), 7.24 (2H, s). IR (NaCl, neat): 3401 (br), 2976, 1747, 1692, 1632, 1496, 1436, 1371, 1251, 1158, 733 cm^{-1}. HRMS (EI): 597.3050 ($C_{32}H_{43}N_3O_8$ requires 597.3050).

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (64). Dimethyl sulfide (0.67 mL, 9.13 mmol, 8.0 equiv) was added dropwise to a stirred solution of NCS (1.22 g, 9.13 mmol, 8.0 equiv) in CH_2Cl_2 (51 mL) at 0 °C under Ar. The resulting mixture was stirred for 10 min and then cooled to −23 °C. After 10 min, **62** (682.4 mg, 1.14 mmol, 1.0 equiv) was added to the flask in one portion and stirring continued for 6 h. At this time the reaction flask was placed in a freezer (−35 °C) for 16 h, followed by an additional 10 h of stirring at −23 °C. The mixture was then diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 hexanes/EtOAc) to yield 565.8 mg (81%) of **64** as a white amorphous solid. [The yield of **64** was 2.12 g (37% or 74% based on recovered **62**) with 5.60 g of **62**.] An analytical sample was obtained by PTLC on silica gel (eluted with 2:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.17 (6H, s), 1.52 (6H, s), 1.57 (18H, s), 1.65 (6H, s), 1.73−2.20 (10H, m), 2.84 (2H, dd, J = 9.0, 14.4 Hz), 3.06 (1H, br s, D_2O exch), 3.10 (1H, br s, D_2O exch), 3.26−3.36 (4H, m), 3.55−3.58 (4H, m), 3.62 (3H, s), 3.63 (3H, s), 3.91 (4H, s), 3.95−4.05 (2H, m), 4.24−4.25 (4H, m), 4.30−4.36 (2H, m), 5.28 (2H, m), 6.88 (2H, d, J = 8.3 Hz), 7.14 (1H, d, J = 8.3 Hz), 7.15 (1H, d, J = 8.3 Hz), 7.376 (1H, s), 7.384 (1H, s). IR (NaCl, neat): 3403, 2979, 1750, 1716, 1642, 1348, 1154 cm^{-1}. HRMS (EI): 615.2709 ($C_{32}H_{42}N_3O_7Cl$ requires 615.2711). Microanal. Calcd for $C_{32}H_{42}N_3O_7Cl$: C, 62.38; H, 6.87; N, 6.82. Found: C, 62.53; H, 6.86; N, 6.67.

[3α,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]-indole-10-carboxylate (65). To a stirred solution of NCS (5.67 g, 42.4 mmol, 8.0 equiv) at 0 °C under Ar in CH_2Cl_2 (206 mL) was added dimethyl sulfide (3.12 mL, 42.4 mmol, 8.0 equiv) dropwise. After 0.5 h the mixture was cooled (−23 °C) and stirred for an additional 0.5 h. At this time the lactim ether−diol **63** (3.17 g, 5.30 mmol, 1.0 equiv) was added [approximately 3 g was added as a solid; the remaining amount was added as a solution in CH_2Cl_2 (30 mL) via cannula]. The white mixture was stirred for 12 h, diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluted with 2:1 hexanes/EtOAc; then 1:1 hexanes/EtOAc) to afford 2.80 g (86%) of **65** as a glass.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.17 (3H, s), 1.18 (3H, s), 1.52 (3H, s), 1.54 (3H, s), 1.57 (18H, s), 1.65 (6H, s), 1.71−1.92 (8H, m), 2.24−2.39 (4H, m), 3.03−3.19 (4H, m, 2H D_2O exch), 3.28−3.37 (4H, m), 3.56 (3H, s), 3.60 (3H, s), 3.59−3.75 (4H, m), 3.89 (4H, s), 4.21−4.29 (6H, m), 5.35 (2H, t, J = 7.5 Hz), 6.86 (1H, d, J = 8.3 Hz), 6.87 (1H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.22 (1H, s), 7.27 (1H, s). IR (NaCl, neat): 3412 (br), 2976, 1752, 1698, 1638, 1365, 1251, 1158 cm^{-1}. HRMS (EI): 615.2714 ($C_{32}H_{42}N_3O_7Cl$ requires 615.2711).

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (66). To a stirred solution of **64** (3.55 g, 5.76 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) at 0 °C under Ar was added 2,6-lutidine (0.74 mL, 6.34 mmol, 1.1 equiv) followed by *tert*-butyldimethylsilyl triflate (1.08 mL, 6.34 mmol, 1.1 equiv). After 3 h an additional amount (1.1 equiv) of each reagent was added to the reaction flask; after stirring for 2 h, an additional amount (1.1 equiv) of each reagent was added. The mixture was stirred for 1 h, diluted with EtOAc, washed four times with water and once with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (eluted with 1:1 hexanes/EtOAc) to yield 3.23 g (77%) of **66** as an amorphous, white solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 hexanes/EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.88 (18H, s), 1.06 (6H, s), 1.47 (6H, s), 1.59 (18H, s), 1.65 (6H, s), 1.78−1.98 (8H, s), 2.02−2.12 (2H, m), 2.86 (2H, dd, J = 9.0, 14.6 Hz), 3.31−3.34 (2H, m), 3.33 (2H, dd, J = 4.0, 13.6 Hz), 3.62 (3H, s), 3.64 (3H, s), 3.71−3.79 (2H, m), 3.73 (1H, dd, J = 4.2, 9.8 Hz), 3.77 (1H, dd, J = 4.4, 9.7 Hz), 3.92 (4H, s), 3.94−4.01 (4H, m), 4.15 (2H, dd, J = 3.8, 12.4 Hz), 4.32−4.37 (2H, m), 5.28−5.30 (2H, m), 6.87 (2H, d, J = 8.3 Hz), 7.12 (1H, d, J = 8.3 Hz), 7.13 (1H, d, J = 8.3 Hz), 7.38 (2H, s). IR (NaCl, neat): 2930, 1750, 1691, 1652, 1494, 1424, 1366, 1248, 1159, 1088 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 729 (M^+, 4.2), 731 (M + 2, 2.1), 629 (9.4), 361 (24.1), 360 (100), 167 (94.8), 57.2 (63). Microanal. Calcd for $C_{38}H_{56}N_3O_7SiCl$: C, 62.49; H, 7.73; N, 5.75. Found: C, 62.57; H, 7.71; N, 5.55.

[3α,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (67). To a stirred solution of **65** (2.73 g, 4.43 mmol, 1.0 equiv) under Ar at 0 °C in CH_2Cl_2 (18 mL) was added 2,6-lutidine (0.57 mL, 4.87 mmol, 1.1 equiv) followed by *tert*-butyldimethylsilyl triflate (0.87 mL, 4.87 mmol, 1.1 equiv). After 1 h, 1.1 equiv of each reagent was added and stirred for 3 h. The solution was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 2.76 g (85%) of **67** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.87 (18H, s), 1.05 (3H, s), 1.06 (3H, s), 1.47 (6H, s), 1.50−1.53 (2H, m), 1.58 (18H, s), 1.65 (6H, s), 1.72−1.91 (6H, m), 2.21−2.37 (4H, m), 3.06−3.19 (2H, m), 3.28−3.36 (4H, m), 3.56 (3H, s), 3.60 (3H, s), 3.63−3.87 (4H, m): 3.89 (4H, s), 3.93 (2H, dd, J = 3.9, 9.8 Hz), 4.13−4.18 (2H, m), 4.22−4.35 (2H, m), 5.30−5.40 (2H, m), 6.85 (1H, d, J = 8.3 Hz), 6.86 (1H, d, J = 8.3 Hz), 7.19−7.26 (4H, m). IR (NaCl, neat): 2949, 1751, 1693, 1652, 1493, 1424, 1369, 1250, 1156, 1086 cm^{-1}. Microanal. Calcd for $C_{38}H_{56}N_3O_7SiCl$: C, 62.49; H, 7.73; N, 5.75. Found: C, 62.29; H, 7.61; N, 5.76. HRMS (EI): 729.3555 ($C_{38}H_{56}N_3O_7SiCl$ requires 729.3576).

1,1-Dimethylethyl 8-[[7,8-Dihydro-1-methoxy-10-(1-methylethenyl)-4-oxo-6*H*-3,8a-ethanopyrrolo[1,2-*a*]pyrazin-3(4*H*)-yl]]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (68). To a stirred solution of **66** (1.43 g, 1.96 mmol, 1.0 equiv) in benzene (300 mL) was added NaH (939 mg, 39.16 mmol, 20.0 equiv, freshly washed in pentane). This mixture was gently stirred at reflux temperature for 8.25 h, diluted with EtOAc, and washed with water and dilute HCl. The organic layer was isolated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:3 EtOAc/hexanes) to yield 1.26 g of **68** (93%). [The yield of **68** was 2.52 g (86%) from 3.10 g of **66**.]

To a stirred solution of **67** (1.60 g, 2.19 mmol, 1.0 equiv) in benzene (313 mL) was added NaH (1.05 g, 43.8 mmol, 20.0 equiv, freshly washed in pentane). This mixture was gently stirred at reflux temperature for 5.5 h and stirred at room temperature overnight. At this time, a small sample was removed, washed with water, and extracted with EtOAc. A crude proton NMR (in $CDCl_3$) indicated that the reaction was complete. The remaining mixture was diluted with EtOAc and washed with water. The organic layer was washed with

brine, dried over Na_2SO_4, and concentrated under reduced pressure. The two samples were combined and purified by radial chromatography (eluted with 1:3 EtOAc/hexanes) to yield 1.29 g of **68** (85%). An analytical sample was obtained by PTLC on silica gel (eluted with 1:3 EtOAc/hexanes); the product was obtained as a white solid, mp 105−108 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.872 (9H, s), 0.875 (9H, s), 1.06 (3H, s), 1.07 (3H, s), 1.46 (6H, s), 1.58 (18H, s), 1.61 (3H, s), 1.64 (3H, s), 1.72−2.03 (8H, m), 2.25−2.42 (2H, m), 2.47 (2H, dd, J = 5.1, 9.7 Hz), 2.54 (2H, dd, J = 5.8, 9.7 Hz), 3.05 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.07 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.31−3.53 (6H, m), 3.57 (3H, s), 3.64 (3H, s), 3.73−3.89 (2H, m), 3.94 (2H, dd, J = 3.7, 9.7 Hz), 4.17 (2H, dd, J = 3.1, 11.6 Hz), 4.62 (1H, s), 4.75 (1H, s), 4.78 (1H, s), 4.85 (1H, s), 6.82 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.38 (1H, d, J = 8.4 Hz), 7.44 (1H, s), 7.52 (1H, s). IR (NaCl, neat): 2935, 1752, 1684, 1637, 1496, 1418, 1365, 1350, 1250, 1220, 1156, 1083 cm^{-1}. HRMS (EI): *m/e* 693.3834 ($C_{38}H_{55}N_3O_7Si$ requires 693.3809). Microanal. Calcd for $C_{38}H_{55}N_3O_7Si$: C, 65.77; H, 7.99; N, 6.05. Found: C, 65.85; H, 7.99; N, 5.91.

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-9,17-dioxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*] carbazole-16-carboxylate (69). To a flask charged with $PdCl_2$ (827.9 mg, 4.67 mmol, 3.0 equiv) and $AgBF_4$ (605.3 mg, 3.11 mmol, 2.0 equiv) was added dry CH_3CN (50 mL). The mixture was stirred for 6.5 h, when a solution of **68** (1.08 g, 1.56 mmol, 1.0 equiv) in CH_3CN (5.0 mL) was syringed into the flask. The reaction mixture was stirred for 48 h, and EtOH (55 mL) was added, followed by small portions of $NaBH_4$ (590 mg, 15.6 mmol, 10.0 equiv) at 0 °C. The addition was complete in 0.5 h, and the mixture was stirred for an additional 0.5 h. The black mixture was filtered to remove palladium and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with dilute aqueous HCl (0.01 M) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 25:25:1 CH_2Cl_2/Et_2O/MeOH) to afford 676.3 mg (63%) of **69** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 25:25:1 CH_2Cl_2/Et_2O/MeOH).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.081 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.08 (3H, s), 1.17 (3H, s), 1.26 (3H, s), 1.27 (3H, s), 1.34 (3H, s), 1.35 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 1.56 (9H, s), 1.58 (9H, s), 1.81−1.90 (2H, m), 1.96−2.06 (6H, m), 2.20 (2H, dd, J = 10.3, 13.5 Hz), 2.52−2.60 (4H, m), 2.78 (2H, dt, J = 6.5, 12.9 Hz), 3.36−3.49 (2H, m), 3.51−3.57 (2H, m), 3.63−3.84 (4H, m), 3.88−3.92 (2H, m), 4.04−4.16 (2H, m), 6.24 (1H, s, D_2O exch), 6.26 (1H, s, D_2O exch), 6.78 (1H, d, J = 8.3 Hz), 6.80 (1H, d, J = 8.5 Hz), 6.98 (1H, d, J = 8.2 Hz), 6.99 (1H, d, J = 8.4 Hz). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −5.2, −5.1, −5.0, −4.5, −4.3, 17.6. 18.7, 19.3, 19.7, 19.9, 24.3,.25.5, 25.6, 26.9, 26.2, 27.2, 27.8, 27.9, 28.3, 28.5, 29.1, 31.1, 36.2, 43.8, 50.5, 50.6, 53.3, 54.8, 55.7, 59.4, 60.2, 60.2, 66.3, 67.6, 71.1, 72.7, 75.9, 78.0, 80.5, 84.1, 84.3, 108.3, 112.4, 112.5, 113.6, 117.9, 118.5, 124.6, 124.9, 128.7, 128.9, 129.4, 137.7, 138.3, 139.4, 139.6, 143.0, 143.2, 152.9, 153.0, 168.3, 174.1. IR (neat): 3214, 2928, 2856, 1745, 1556, 1496, 1443, 1368, 1252, 1233, 1154, 1141, 1091, 1052, 994, 859, 838, 777, 733. Microanal. Calcd for $C_{37}H_{53}N_3O_7Si$: C, 65.36; H, 7.86; N, 6.18. Found: C, 65.18; H, 7.77; N, 6.18. MS (EI): *m/e* (relative intensity) 679 (M^+, 0.3), 580 (20.4), 579 (51), 73 (100). HRMS (EI): *m/e* 679.3661 ($C_{37}H_{53}N_3O_7Si$ requires 679.3653).

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-17-methoxy-9-oxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylate (71). To a stirred solution of **69** (26.1 mg, 0.38 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) under Ar at 0 °C was added Na_2CO_3 (81.0 mg, 0.76 mmol, 20.0 equiv). After 10 min Me_3OBF_4 (28.3 mg, 0.191 mmol, 5.0 equiv) was added in one portion. The mixture was stirred for 4 h at room temperature, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 1:2 hexanes/EtOAc) to afford 19.6 mg (74%) of **71** as a white amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ TMS 0.10−0.15 (12H, m), 0.89 (9H, s), 0.90 (9H, s), 1.09 (6H, s), 1.26 (3H, s), 1.29 (3H, s), 1.33 (3H, s), 1.36 (3H, s), 1.46 (3H, s), 1.48 (3H, s), 1.58 (9H, s), 1.60 (9H, s), 1.76−2.51 (10H, m), 2.23−2.31 (2H, m), 2.60−2.70 (2H, m), 3.027 (1H, $^1/_2$ ABq, J = 16.4 Hz), 3.032 (1H, $^1/_2$ ABq, J = 16.4 Hz), 3.31−3.41 (2H, m), 3.46−3.54 (2H, m), 3.68 (2H, dd, J = 9.1, 12.1 Hz), 3.77 (6H, s), 3.87−3.94 (2H, m), 3.90 (2H, $^1/_2$ ABq, J = 16.3 Hz), 4.08 (2H, dd, J = 3.5, 11.9 Hz), 6.79 (1H, d, J = 8.3 Hz), 6.80 (1H, d, J = 8.3 Hz), 7.063 (1H, d, J = 8.3 Hz), 7.061 (1H, d, J = 8.3 Hz). IR (NaCl, neat): 2952, 2886, 1745, 1683, 1640, 1496, 1412, 1355, 1252, 1232, 1156, 1140, 1111, 1090, 1052, 992, 838, 770 cm^{-1}. HRMS (EI): *m/e* 693.3810 ($C_{38}H_{55}N_3O_7Si$ requires 693.3810).

3-(Hydroxy)-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-9,17-dioxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino-[2,3-*a*]indolizino[6,7-*h*]carbazole (76). To a stirred solution of **69** (150 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (4.4 mL) under N_2 at 0 °C was added TFA (1.4 mL, 17.8 mmol, 80 equiv) dropwise. The reaction mixture was allowed to reach room temperature overnight. The solution was concentrated and the residue taken up in EtOAc. The resulting solution was washed with 10% Na_2CO_3 and brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by radial chromatography (eluted with EtOAc) to yield 102 mg (95%) of **76**. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes) as a white amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.06 (3H, s), 1.08 (3H, s), 1.18 (3H, s), 1.20 (3H, s), 1.23 (3H, s), 1.29 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 1.79−2.04 (8H, m), 2.17 (2H, td, J = 5.1, 11.9 Hz), 2.43 (1H, m), 2.43 (1H, $^1/_2$ ABq, J = 15.5 Hz), 2.51 (1H, dd, J = 4.8, 10.2 Hz), 2.59 (1H, $^1/_2$ ABq, J = 15.5 Hz), 2.78 (2H, dt, J = 6.5, 12.9 Hz), 3.21 (1H, br s, D_2O exch), 3.33−3.41 (3H, m), 3.41−3.56 (3H, m), 3.60 (1H, br s, D_2O exch), 3.70 (1H, $^1/_2$ ABq, J = 15.4 Hz), 3.78 (1H, $^1/_2$ ABq, J = 15.4 Hz), 4.12 (2H, dd, J = 8.4, 12.0 Hz), 4.25 (2H, td, J = 4.0, 12.2 Hz), 6.65 (2H, s, D_2O exch), 6.72 (1H, d, J = 8.3 Hz), 6.73 (1H, d, J = 8.3 Hz), 7.02 (1H, d, J = 7.9 Hz), 7.05 (1H, d, J = 8.1 Hz), 7.98 (1H, s, D_2O exch), 8.10 (1H, s, D_2O exch). IR (NaCl, neat): 3308, 1684, 1679, 1402, 1367, 1232, 1044, 733 cm^{-1}. HRMS (EI): *m/e* 465.2248 ($C_{26}H_{31}N_3O_5$ requires 465.2264).

14-Deoxy-29-demethyl-24,25-dihydro-25-hydroxy-12-oxo-17-nor-paraherquamide (79). To a stirred mixture of **76** (16.5 mg, 0.035 mmol, 1.0 equiv) in CH_2Cl_2 (0.7 mL) at 0 °C under N_2 was added Et_3N (4.6 μL, 0.04 mmol, 1.1 equiv) followed by *t*-BuOCl (5.4 μL, 0.04 mmol, 1.1 equiv). After 0.5 h, the resulting clear, yellow solution was concentrated to dryness (the flask being kept cold). The residue was immediately subjected to a solution of MeOH/H_2O/AcOH (40:20:1) and stirred under N_2 at room temperature for 0.5 h. The solution was diluted with saturated $NaHCO_3$, and the organic layer was washed three times with saturated $NaHCO_3$, washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 20:1 CH_2Cl_2/MeOH) to yield 5.0 mg (29%) of **79** as an amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.46 (3H, s), 0.48 (3H, s), 0.93 (6H, s), 1.22 (3H, s), 1.23 (3H, s), 1.45 (3H, s), 1.51 (3H, s), 1.65−2.09 (14H, m), 2.71−2.79 (2H, m), 2.87 (2H, td, J = 3.2, 9.3 Hz), 3.40−4.99 (2H, m), 3.56−3.66 (6H, m, 2H D_2O exch), 4.08−4.26 (4H, m), 6.56 (1H, d, J = 8.1 Hz), 6.61 (1H, d, J = 8.1 Hz), 6.80 (1H, d, J = 7.7 Hz), 6.82 (1H, d, J = 7.8 Hz), 6.96 (1H, s, D_2O exch), 7.09 (1H, s, D_2O exch), 8.03 (1H, s, D_2O exch), 8.11 (1H, s, D_2O exch). IR (NaCl, neat): 3411, 3237, 1698, 1632, 1496, 1404, 1333, 1213, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 481 (M^+, 23.9), 412 (15.2), 249 (12.7), 220 (100), 149 (60.6). HRMS (EI): *m/e* 481.2194 ($C_{26}H_{31}N_3O_6$ requires 481.2213).

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-17-oxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylate (70). To a stirred solution of **69** (164 mg, 0.24 mmol, 1.0 equiv) in THF (4.9 mL) at −78 °C under Ar was added Et_3Al (0.14 mL, 0.26 mmol, 1.1 equiv, 1.9 M in toluene)

dropwise. After 10 min the solution was warmed to 0 °C and AlH_3•-DMEA (6.0 mL, 1.20 mmol, 5.0 equiv, 0.2 M in toluene) was added dropwise. The ice bath was removed and the solution stirred for 1 h and 20 min at room temperature. At this time MeOH (4.7 mL) and AcOH (0.31 mL) were syringed into the flask, followed by $NaCNBH_3$ (179 mg, 2.85 mmol, 11.9 equiv). This mixture was stirred for 10 min, and the solvent was removed under reduced pressure and replaced with ethyl acetate. The resulting solution was washed with $NaHCO_3$ (saturated) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:1 hexanes/EtOAc) to yield 102 mg (65%) of **70** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.085 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.12 (3H, s), 1.15 (3H, s), 1.23 (3H, s), 1.24 (3H, s), 1.36 (3H, s), 1.37 (3H, s), 1.45 (6H, s), 1.59 (9H, s), 1.61 (9H, s), 1.88−1.92 (6H, s), 1.97−2.10 (2H, m), 2.17−2.26 (2H, m), 2.54−2.63 (2H, m), 2.70 (2H, $^1/_2$ ABq, J = 15.5 Hz), 2.829 (1H, $^1/_2$ ABq, J =15.4 Hz), 2.835 (1H, $^1/_2$ ABq, J = 15.6 Hz), 3.06−3.09 (2H, m), 3.45−3.49 (4H, m), 3.67−3.85 (4H, m), 3.90 (2H, dd, J = 3.4, 8.7 Hz), 4.09−4.18 (4H, m), 6.03 (2H, s, D_2O exch), 6.78 (1H, d, J = 8.3 Hz), 6.79 (1H, d, J = 8.3 Hz), 6.89 (2H, d, J = 8.3 Hz). IR (NaCl, neat): 3227, 2928, 1746, 1683, 1597, 1371, 1254, 1233, 1154, 1138, 1090, 836 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 665 (M^+, 0.3), 565 (30.6), 521 (40.1), 164 (100). Microanal. Calcd for $C_{37}H_{55}N_3O_6Si$: C, 66.73; H, 8.32; N, 6.31. Found: C, 66.50; H, 8.18; N, 6.33. HRMS (EI): *m/e* 665.38365 ($C_{37}H_{55}N_3O_6Si$ requires 665.3860).

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15,18-pentamethyl-17-oxo-11*H*,-16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino-[6,7-*h*]carbazole-16-carboxylate (72). To a stirred solution of **70** (147.5 mg, 0.22 mmol, 1.0 equiv) in DMF (2.2 mL) under Ar at 0 °C was added NaH (13.3 mg, 0.55 mmol, 2.5 equiv). After 5 min, MeI (27.6 μL, 0.44 mmol, 2.0 equiv) was syringed in dropwise. The mixture was stirred for 4 h, when a small amount of water and mercaptoethanol (21.6 μL) were added. After a few minutes, the mixture was diluted with water and extracted with 1:1 hexanes/EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 hexanes/EtOAc) to yield 146.9 mg (98%) of **72** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.089 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.13 (3H, s), 1.15 (3H, s), 1.25 (6H, s), 1.36 (3H, s), 1.37 (3H, s), 1.46 (6H, s), 1.59 (9H, s), 1.61 (9H, s), 1.86−2.06 (10H, m), 2.09−2.20 (6H, m), 2.61−2.70 (2H, m), 2.747 (1H, $^1/_2$ ABq, J = 15.4 Hz), 2.754 (1H, $^1/_2$ ABq, J = 15.4 Hz), 2.30−3.05 (2H, m), 3.05 (6H, s), 3.14 (2H, $^1/_2$ ABq, J = 15.4 Hz), 3.39 (2H, d, J = 10.5 Hz), 3.74−3.85 (2H, m), 3.89−3.93 (2H, m), 4.07−4.18 (2H, m), 6.797 (1H, d, J = 8.3 Hz), 6.804 (1H, d, J = 8.3 Hz), 6.93 (2H, d, J = 8.3 Hz). IR (NaCl, neat): 2921, 1747, 1665, 1496, 1371, 1251, 1235, 1158, 1142, 1108, 1093, 837, 755 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 679 (M^+, 2.1), 579 (4.2), 520 (4.2), 178 (100). Microanal. Calcd for $C_{38}H_{57}N_3O_6Si$: C, 67.12; H, 8.45; N, 6.18. Found: C, 67.33; H, 8.27; N, 6.44. HRMS (EI): *m/e* 679.4008 ($C_{38}H_{57}N_3O_6Si$ requires 679.4017).

3-Hydroxy-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15,18-pentamethyl-17-oxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole (73). To a stirred solution of **72** (294.7 mg, 0.43 mmol, 1.0 equiv) in CH_2Cl_2 (8.7 mL) at 0 °C under Ar was added TFA (2.77 mL, 34.7 mmol, 80.0 equiv) dropwise. The solution was stirred for 15 h, the temperature being maintained at 15 °C. At this time the solution was concentrated under reduced pressure, diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with EtOAc) to yield 194.8 mg (96%) of **73** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.21 (3H, s), 1.23 (3H, s), 1.29 (3H, s), 1.32 (3H, s), 1.42 (3H, s), 1.45 (3H, s), 1.54 (6H, s), 1.88−2.00 (10H, m), 2.07−2.22 (6H, m), 2.63−2.72 (2H, m), 2.79 (1H, $^1/_2$ ABq, J = 15.1 Hz), 2.80 (1H, $^1/_2$ ABq, J = 15.1 Hz), 3.01−3.07 (4H, m, 2H D_2O exch), 3.07 (6H, s), 3.17 (1H, $^1/_2$ ABq, J = 15.1 Hz), 3.19 (1H, $^1/_2$ ABq, J = 15.4 Hz), 3.37−3.43 (2H, m), 3.62 (2H, br s), 4.20 (2H, dd, J = 4.4, 12.3 Hz), 4.29 (1H, dd, J = 4.0, 12.3 Hz), 4.31 (1H, dd, J = 4.0, 12.3 Hz), 6.750 (1H, d, J = 8.4 Hz), 6.753 (1H, d, J = 8.3 Hz), 7.01 (2H, d, J = 8.4 Hz), 8.01 (2H, s, D_2O exch). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 14.0, 20.8, 22.6, 23.9, 24.4, 24.5, 24.7, 25.1, 27.7, 27.9, 30.2, 30.3, 31.3, 34.4, 45.9, 54.3, 57.4, 60.0, 60.2, 64.0, 71.0, 75.5, 76.6, 77.0, 77.4, 79.5, 104.6, 112.2, 116.17, 116.22, 125.0, 129.2, 137.2, 140.4, 141.6, 171.0, 174.3. IR (NaCl, neat): 3324, 2954, 1654, 1507, 1474, 1365, 1235, 1071, 1049, 908, 733 cm^{-1}. Microanal. Calcd for $C_{27}H_{35}N_3O_4Si$: C, 69.65; H, 7.58; N, 9.02. Found: C, 69.54; H, 7.66; N, 8.89. Mass spectrum (EI): *m/e* (relative intensity) 465 (M^+, 9.7), 406 (14.5), 287 (11.8), 178 (100). HRMS (EI): *m/e* 465.2625 ($C_{27}H_{35}N_3O_4Si$ requires 465.2628).

14-Deoxy-24,25-dihydro-25-hydroxy-17-norparaherquamide (80). To a stirred solution of **73** (99 mg, 0.21 mmol, 1.0 equiv) in pyridine (4 mL) at −15 °C under Ar was added *t*-BuOCl (37 μL, 0.32 mmol, 1.5 equiv). After 2 h the solvent was removed under reduced pressure to give 106 mg (quantitative) of the crude chloroindolenines (**74**/**75** as a mixture of epimers). The majority of the crude chloroindolenines, **74**/**75** (71 mg, 0.14 mmol, 1.0 equiv), was dissolved in THF (10 mL) and water (1 mL), and *p*-toluenesulfonic acid monohydrate (135 mg, 0.41 mmol, 15 equiv) was added. The resulting yellow solution was stirred at reflux temperature for 20 min and diluted with EtOAc and aqueous K_2CO_3. The organic layer was isolated, washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 20:1 CH_2Cl_2/MeOH) to yield (from the chloroindolenines) 52 mg (76%) of **80** and 2.7 mg (4%) of **81**.

^{1}H NMR (300 MHz) ($CDCl_3$) (**80** mixture of two diastereomers): δ TMS 0.80 (3H, s), 0.83 (3H, s), 1.08 (3H, s), 1.10 (3H, s), 1.22 (3H, s), 1.26 (3H, s), 1.50 (3H, s): 1.52 (3H, s), 1.40−1.60 (8H, m), 1.77−1.93 (8H, m), 2.05−2.21 (2H, m), 2.55−2.71 (4H, m), 3.02−3.10 (4H, m), 3.06 (6H, s), 3.63 (4H, br s, 2H D_2O exch), 4.05−4.24 (4H, m), 6.60 (1H, d, J = 8.1 Hz), 6.62 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 8.1 Hz), 6.79 (1H, d, J = 8.2 Hz), 7.42 (1H, s, D_2O exch), 7.45 (1H, s, D_2O exch). IR (NaCl, neat): 3333, 2974, 2933, 1703, 1651, 1646, 1631, 1456, 1395, 1323, 1200, 1046, 903, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 481 (M^+, 0.7), 422 (20.7), 421 (15), 135 (48), 133 (100). HRMS (CI): *m/e* 481 ($C_{27}H_{35}N_3O_5$ requires 481.2578), [M + H] 482.2645 ($C_{27}H_{36}N_3O_5$ requires 482.2655).

^{1}H NMR (500 MHz) ($CDCl_3$) (**81** mixture of two diastereomers): δ TMS 0.53 (3H, s), 0.56 (3H, s), 0.84 (3H, s), 0.86 (3H, s), 1.22 (3H, s), 1.25 (3H, s), 1.50 (3H, s), 1.52 (3H, s), 1.41−1.73 (8H, m), 1.83−1.90 (8H, m), 2.09−2.13 (2H, m), 2.28−2.41 (6H, m), 2.51−2.58 (2H, m), 3.00 (3H, s), 3.01 (3H, s), 3.63 (2H, br s), 3.78 (1H, D_2O exch), 3.81 (1H, s D_2O exch), 4.05−4.24 (4H, m), 6.60 (2H, d, J = 8.0 Hz), 6.62 (2H, d, J = 7.4 Hz), 7.42 (2H, s, D_2O exch). IR (NaCl, neat): 3271, 2924, 2854, 1714, 1644, 1496, 1464, 1393, 1375, 1211, 1142, 1066 cm^{-1}.

(+)-Paraherquamide B (12). To a stirred solution of **80** (22.5 mg, 0.047 mmol, 1.0 equiv) in DMPU (500 μL) under Ar at room temperature was added MTPI (90 mg, 0.20 mmol, 4.0 equiv). After 16 h KOH (10 mL, 1 M) was added, and the mixture was stirred for an additional 10 min. The pH was adjusted to 2 (addition of HCl) and the mixture extracted with EtOAc. The mixture was diluted with 1:1 hexanes/EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 20:1 CH_2Cl_2/MeOH) to afford 17.1 mg (79%) of (+)-paraherquamide B (**12**) as a white, amorphous solid. This material proved to be identical to an authentic sample of natural (−)-paraherquamide B by ^{1}H NMR, ^{13}C NMR, TLC mobility, IR, mass spectrum, and UV (see text for CD spectrum, Figure 7).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 0.82 (3H, s), 1.09 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.64 (1H, dd, J = 9.7, 12.4 Hz), 1.73−1.92 (4H, m), 1.82 (1H, $^1/_2$ ABq, J = 15.5 Hz), 2.16 (1H, dd, J = 8.6, 17.8 Hz), 2.54−2.59 (1H, m), 2.61 (1H, $^1/_2$ ABq, J = 11.1 Hz), 2.66 (1H, $^1/_2$ ABq, J = 15.5 Hz), 3.03−3.10 (2H, m), 3.05 (3H, s), 3.60 (1H, $^1/_2$

ABq, $J = 11.1$ Hz), 4.87 (1H, d, $J = 7.7$ Hz), 6.30 (1H, d, $J = 7.7$ Hz), 6.64 (1H, d, $J = 8.2$ Hz), 6.78 (1H, d, $J = 8.2$ Hz), 8.5 (1H, br s, D_2O exch). ^{13}C NMR (75.5 MHz) ($CDCl_3$): δ 20.7 (q), 23.8 (q), 26.2 (q), 28.2 (q), 28.8 (t), 29.8 (t), 29.9 (q), 37.2 (t), 46.1 (s), 52.8 (d), 53.8 (t), 59.5 (t), 63.0 (s), 65.2 (s), 67.4 (s), 79.7 (s), 115.0 (d), 117.2 (d), 120.3 (d), 125.3 (s), 132.5 (s), 135.3 (s), 139.0 (d), 146.0 (s), 172.9 (s), 183.1 (s). IR (NaCl, neat): 3190, 2974, 2933, 1703, 1697, 1651, 1631, 1503, 1456, 1328, 1195, 1046 728 cm^{-1}. UV: λ_{max} 226 nm ($\epsilon = 30\,200$). $[\alpha]^{25}_D = (+0.4/7.75 \times 10^{-3})° = +51.6°$ ($CHCl_3$, $c = 0.008$). Mass spectrum (EI): *m/e* (relative intensity) 463 (M^+, 0.5), 404 (15.6), 135 (41.5), 133 (100). HRMS (EI): *m/e* 463.2456 ($C_{27}H_{33}N_3O_4$ requires 463.2471).

Spiro Product 56. ^1H NMR (300 MHz) (acetone-d_6) (mixture of two diastereomers): δ TMS 0.21 (12H, s), 0.93 (18H, s), 1.13 (6H, s), 1.41 (18H, s), 1.48 (6H, s), 1.62 (18H, s), 1.82 (6H, s), 1.88−2.15 (6H, m), 2.54 (2H, t, $J = 11.3$ Hz), 2.81−2.83 (4H, m), 3.02−3.06 (4H, m), 3.36−3.42 (2H, m), 3.62−3.64 (2H, m), 3.88 (2H, dd, $J = 9.3$, 12.2 Hz), 3.99 (2H, dd, $J = 3.5$, 9.3 Hz), 4.21 (2H, dd, $J = 3.5$, 12.2 Hz), 4.61−4.83 (4H, m), 4.96 (2H, br s), 5.07 (2H, br s), 5.94 (2H, d, $J = 8.5$ Hz, D_2O exch), 6.92 (2H, d, $J = 8.3$ Hz), 7.25 (2H, d, $J = 8.3$ Hz), 7.41 (2H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −4.9 (q), −4.0 (q), 16.5 (q), 17.9 (s), 18.4 (q), 24.1 (t), 25.7 (q), 28.0 (q), 28.3 (q), 28.6 (q), 29.4 (t), 29.7 (d), 35.6 (t), 36.6 (t), 47.9 (t), 51.7 (d), 66.6 (s), 70.9 (t), 75.9 (d), 76.6 (s), 79.8 (d), 80.4 (s), 83.1 (s), 113.7 (d), 113.9 (t), 114.6 (s), 120.3 (d), 126.4 (d), 127.9 (s), 129.3 (s), 140.4 (s), 141.8 (s), 146.6 (s), 148.5 (s), 155.0 (s), 169.7 (s), 176.6 (s). IR (NaCl, neat): 2932, 1780, 1752, 1714, 1649, 1496, 1425, 1365, 1251, 1229, 1158, 1088 cm^{-1}.

Spiro Product 57. ^1H NMR (300 MHz) (acetone-d_6) (mixture of two diastereomers): δ TMS 0.21 (12H, s), 0.94 (18H, s), 1.14 (6H, s), 1.41 (18H, s), 1.47 (6H, s), 1.62 (18H, s), 1.80 (6H, s), 1.96−2.07 (6H, m), 2.58 (2H, t, $J = 11.3$ Hz), 2.84 (4H, br s), 2.98−3.13 (4H, m), 3.48−3.50 (2H, m), 3.51−3.52 (2H, m), 3.88 (2H, dd, $J = 9.3$, 12.1 Hz), 4.00 (2H, dd, $J = 3.4$, 9.1 Hz), 4.22 (2H, dd, $J = 3.4$, 12.2 Hz), 4.72 (2H, dd, $J = 6.6$, 15.0 Hz), 4.84 (2H, dd, $J = 6.3$, 10.7 Hz), 4.96 (2H, br s), 5.08 (2H, br s), 5.95 (2H, d, $J = 8.6$ Hz, D_2O exch), 6.91 (2H, d, $J = 8.3$ Hz), 7.23 (2H, d, $J = 8.3$ Hz), 7.38 (2H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −4.9 (q), −4.0 (q), 16.5 (q), 17.9 (s), 18.8 (q), 24.1 (t), 25.7 (q), 28.0 (q), 28.3 (q), 29.0 (t), 29.7 (d), 35.6 (t), 36.7 (t), 48.0 (t), 52.4 (d), 66.7 (s), 71.0 (t), 75.8 (d), 76.6 (s), 79.8 (d), 80.4 (s), 83.1 (s), 113.6 (d), 113.8 (t), 114.7 (s), 120.0 (d), 126.1 (d), 127.8 (s), 129.3 (s), 140.4 (s), 141.7 (s), 146.4 (s), 148.6 (s), 155.0 (s), 169.8 (s), 175.7 (s). IR (neat): 2926, 1783, 1754, 1715, 1652, 1494, 1457, 1367, 1250, 1160, 1087 cm^{-1}.

Acknowledgment. This work was supported in part by the National Institutes of Health (Grant CA 43969) and the National Science Foundation (CHE 9320010). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and The Colorado State University Agricultural Experiment Station (USDA SAES Western Project W-122) for partial support of this work. Mass spectra were obtained on instruments supported by the National Institutes of Health Shared Instrumentation Grant GM49631. We would like to thank Dr. Chris Rithner of Colorado State University for technical assistance with several 2D NMR experiments. Narashima Sreerama and Prof. Robert W. Woody (Department of Biochemistry and Molecular Biology, Colorado State University) are gratefully acknowledged for help in obtaining CD spectra. We would also like to acknowledge Dr. Dusan Stanojevic and Prof. Gregory L. Verdine (Department of Chemistry, Harvard University) for their assistance in obtaining CD spectra of paraherquamide B. We are grateful to Dr. John Ondeyka of Merck & Co. for furnishing NMR spectra of natural paraherquamide B. J.F.S.-C. thanks the Conselleria de Educacio i Ciencia de la Generalitat Valenciana (Spain) for a fellowship. We also wish to acknowledge Renee Gallegos (Colorado State University), Felix Sancenon (University of Valencia), and M. Eugenia Martinez (University of Valencia) for valuable assistance in isolating natural (−)-paraherquamide B from *P. fellutanum*. Mr. Dan Bond is gratefully acknowledged for providing synthetic chemical technical assistance.

JA952666C