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Synthesis of 8-Desbromohinckdentine A[1]

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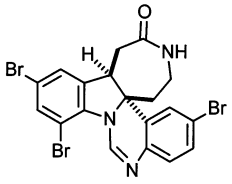
Abstract: Hinckdentine A is an alkaloid isolated from the bryozoan *Hincksinoflustra denticulate*. This natural product contains a novel and unique 11b,12,13,14,15,16-hexahydroazepino[4′,5′:2,3]indolo[1,2-*c*]quinazoline ring system that has not previously been synthesized. We have synthesized 8-desbromohinckdentine A from a 2-aryl indole by first preparing the quaternary center of the natural product and then building the seven-membered lactam and dihydropyrimidine rings onto this intermediate to form the framework of hinckdentine A.

Introduction

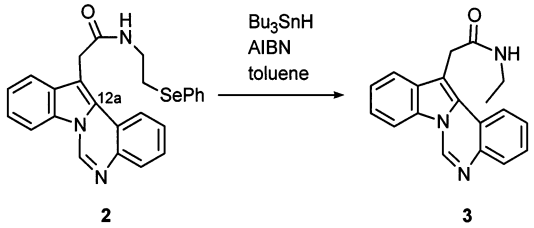
Hinckdentine A was isolated from the bryozoan *Hincksinoflustra denticulate*, which was collected from the eastern coast of Tasmania.[2] Its structure and the absolute configuration were determined by single-crystal X-ray methods.[2] The natural product contains a novel and unique 11b,12,13,14,15,16-hexahydroazepino[4′,5′:2,3]indolo[1,2-*c*]quinazoline ring system, a challenging synthetic target, that has not yet been successfully synthesized. The biological activity of hinckdentine A has apparently not been determined and is consequently not described in the literature,[2] but biologically important dihydrotryptamine and dihydropyrimidine units are contained within the framework of the natural product.



1

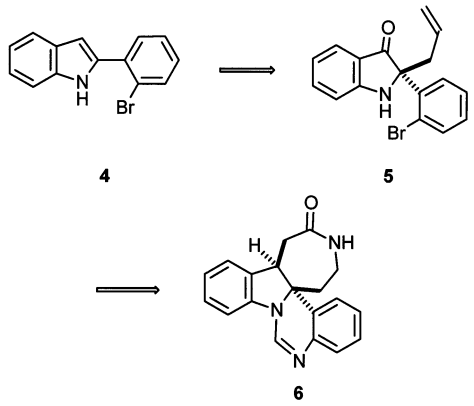
The indolo[1,2-*c*]quinazoline ring system was first prepared in 1956 by Kiang and co-workers.[3] Cava and Billimoria[4a] have reviewed the chemistry of indoloquinazolines, which are uncommon in nature. Moreover, they have published an interesting approach to the synthesis of hinckdentine A,[4b] in which they attempted to use an intramolecular radical cyclization to the 12a position of an indolo[1,2-*c*]quinazoline as the key step (Scheme 1). A study of the Diels−Alder reaction between indoles and phenylsulfonylbuta-1,3-dienes has been investigated with the synthesis of hinckdentine A in mind.[5]

Scheme 1



2 **3**

Scheme 2



4 **5** **6**

We planned to synthesize hinckdentine A from a 2-aryl indole by first preparing the quaternary center of the natural product, the key structural feature. Intermediate **5** provides a platform onto which the seven-membered lactam and dihydropyrimidine rings can be built to form the framework of hinckdentine A as shown in Scheme 2.

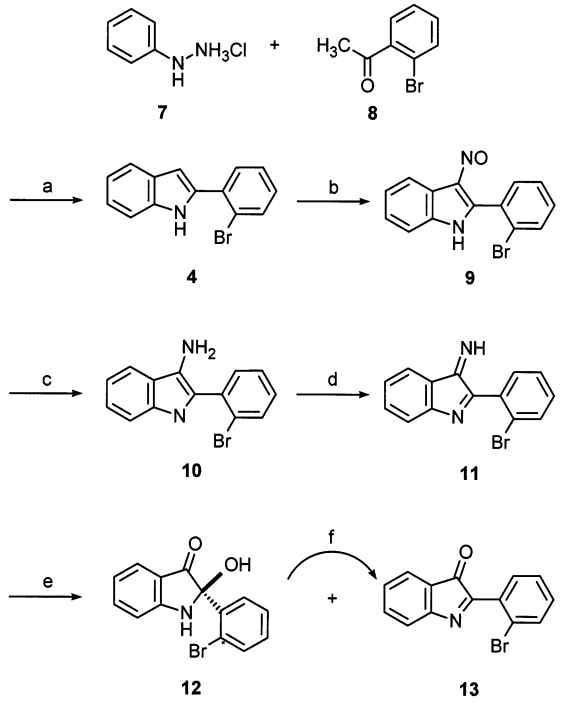
Results and Discussion

The starting material for our synthesis, 2-(2-bromophenyl)-indole **4**, was prepared by the Fischer indole synthesis from

(1) This work was presented in preliminary form: Liu, Y.; McWhorter, W. W., Jr. *Abstracts of Papers*, 224th National Meeting of the American Chemical Society, Boston, MA, August 17−22, 2002, American Chemical Society, Washington, DC (ORGN 807).
(2) Blackman, A. J.; Hambly, T. W.; Picker, K.; Taylor, W. C.; Thirasasana, N. *Tetrahedron Lett.* **1987**, *28*, 5561.
(3) Kiang, A. K.; Mann, F. G.; Prior, A. F.; Topham, A. *J. Chem. Soc.* **1956**, 1319.
(4) (a) Billimoria, A. D.; Cava, M. P. *Heterocycles* **1996**, *42*, 453. (b) Billimoria, A. D.; Cava, M. P. *J. Org. Chem.* **1994**, *59*, 6777.
(5) Barnwell, N.; Beddoes, R. L.; Mitchell, M. B.; Joule, J. A. *Heterocycles* **1994**, *37*, 175.

10.1021/ja021380m CCC: $25.00

Scheme 3 [a]



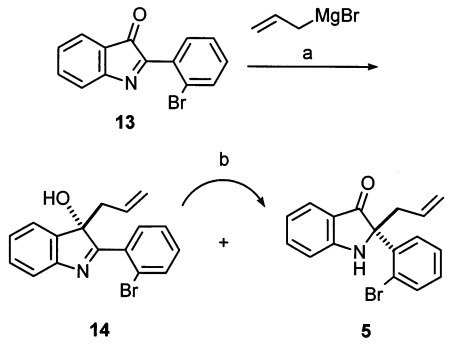
[a] Reagents and conditions: (a) polyphosphoric acid, 120 °C, 4 h (78%); (b) $NaNO_2$, HOAc, room temperature, 3 h (97%); (c) $Na_2S_2O_4$, NaOH, H_2O, EtOH, reflux, 24 h (94%); (d) PbO_2, benzene, reflux, 24 h (98%); (e) 1 N HCl (aq), toluene, room temperature, 12 h (42% **12** and 56% **13**); (f) reduced pressure, 105 °C, 4 h (99%).

phenylhydrazine hydrochloride and 2-bromoacetophenone.[6] Indole **4** can be oxidized to the indolenine **13** in one step using singlet oxygen,[7] but this procedure is not suitable for the preparation of large amounts of indolenine. We found that the four-step, high yielding procedure[8] shown in Scheme 3 was suitable for the preparation of 2-(2-bromophenyl)-3*H*-indol-3-one **13** in multigram quantities. This procedure[8] yields a mixture of both **12** and **13**, but we found that heating this mixture under vacuum at 105 °C yielded exclusively **13**.

We initially anticipated, on the basis of the results of Marchetti and co-workers,[9] that we would be able to add an allyl anion to indolenine **13** to directly obtain indolone **5**, which contains the quaternary center of hinckdentine A. In fact, when we added allylmagnesium bromide to indolenine **13**, we obtained indolol **14** (IR OH 3296, 3212 cm^{-1}) containing a trace of indolone **5** (Scheme 4). Indolol **14** was cleanly converted to indolone **5** (IR C═O 1675 cm^{-1}) by means of a pinacol-like rearrangement under acidic conditions.[10] There are a few examples of this type of rearrangement in the literature in which migration is reported to take place under basic or thermal conditions.[11] This rearrangement is more well known when the migrating group is tethered to the indole at the 2 position and has been used to prepare a variety of spirocyclic alkaloids.[12]

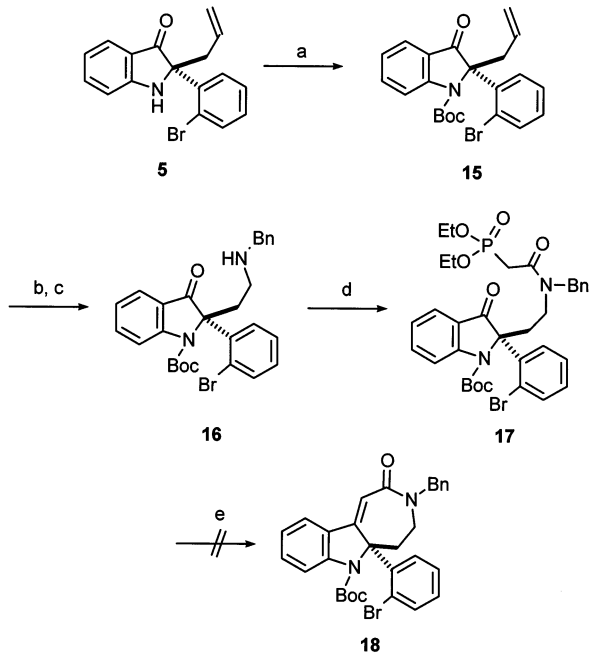
At this point, we considered three possibilities for the construction of the seven-membered lactam ring.

Scheme 4 [a]



[a] Reagents and conditions: (a) THF, room temperature, 2 h (89% **14** and 3% **5**); (b) 88% HCO_2H, toluene, reflux, 30 min (96%).

Scheme 5 [a]

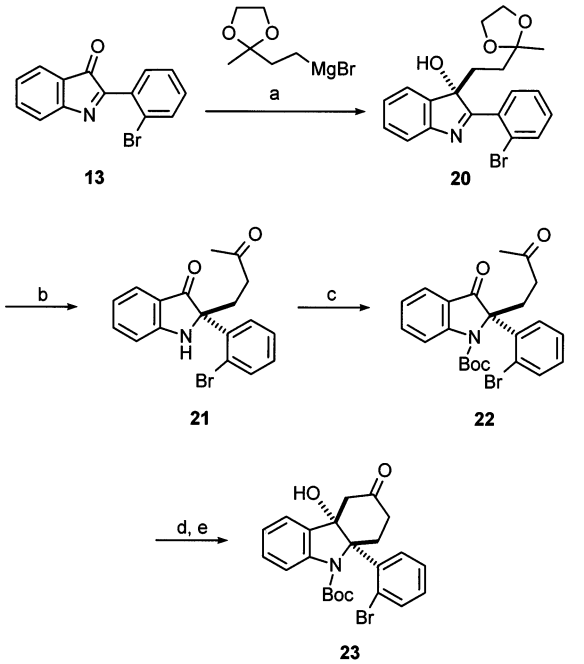


[a] Reagents and conditions: (a) Boc_2O, DMAP, CH_3CN, room temperature, 17 h (96%); (b) O_3, MeOH, −78 °C, then Me_2S, −78 °C to room temperature; (c) $BnNH_2$, HOAc, $NaBH_3CN$, MeOH/THF, room temperature, 16 h (71% for b and c); (d) diethylphosphonoacetic acid, HATU, DIEA, CH_2Cl_2, 0 °C to room temperature, 24 h (91%); (e) NaH, THF, room temperature, 17 h.

First, we attempted to form the seven-membered lactam by means of an intramolecular Horner−Wadsworth−Emmons reaction (Scheme 5). The secondary amine of indolone **5** was protected with a Boc group[13] to yield **15**. The terminal olefin of **15** was cleaved by ozonolysis to yield the corresponding aldehyde, which was in turn converted to the benzylamine **16** by a reductive amination. Benzylamine **16** was coupled[14] with diethyl phosphonoacetic acid to yield diethylphosphonate **17**. Our efforts to carry out the intramolecular Horner−Wadsworth−Emmons reaction using NaH in THF at room temperature for 24 h or LDA in THF at −78 °C followed by warming to room temperature led only to recovered starting material, while the

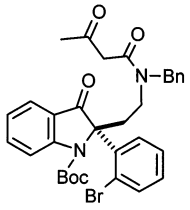
(6) Dalton, L.; Humphrey, G. L.; Cooper, M. M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2417.
(7) Ling, K.-Q. *Synth. Commun.* **1995**, *25*, 3831.
(8) Richman, R. J.; Hassner, A. *J. Org. Chem.* **1968**, *33*, 2548.
(9) Berti, C.; Greci, L.; Marchetti, L. *J. Chem. Soc., Perkin Trans. 2* **1979**, 233.
(10) Liu, Y.; McWhorter, W. W. *J. Org. Chem.* **2003**, *68*, 2618−2622.
(11) (a) Lednicer, D.; Emmert, D. E. *J. Heterocycl. Chem.* **1970**, 575. (b) Robinson, B.; Uppal Zubair, M. *Pak. J. Sci. Ind. Res.* **1976**, *19*, 214.
(12) For examples: (a) Witkop, B.; Patrick, J. B. *J. Am. Chem Soc.* **1951**, *73*, 2188. (b) Hutchison, A. J.; Kishi, Y. *J. Am. Chem Soc.* **1979**, *101*, 6786. (c) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am Chem. Soc.* **1990**, *112*, 808. (d) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564.
(13) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand. B* **1986**, *40*, 745.
(14) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

Scheme 6 [a]



[a] Reagents and conditions: (a) THF, room temperature, 1 h (88%); (b) 88% HCO_2H, toluene, reflux, 30 min (89%); (c) Boc_2O, DMAP, CH_3CN, room temperature, 17 h (96%); (d) LDA, THF, −78 °C, 5 min; (e) HOAc, THF, −78 °C to room temperature (54% for d and e).

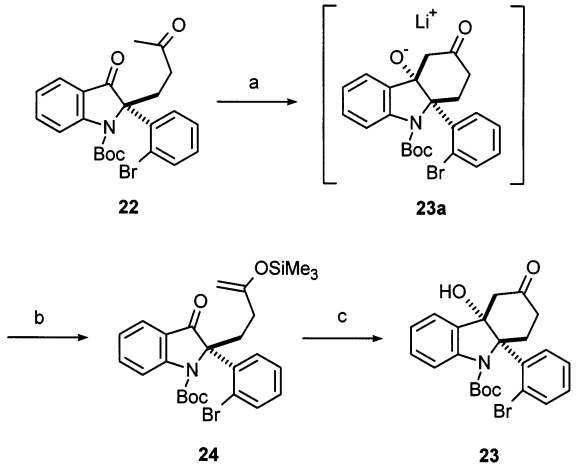
use of NaH in THF at reflux for 16 h or *n*-BuLi in THF at −78 °C followed by warming to room temperature led to consumption of **17** without formation of any α,β-unsaturated lactam **18**. It is apparently difficult for this resonance stabilized, bulky phosphonate anion to attack the sterically hindered ketone. Although the amine of **17** is acylated with a Boc protecting group, resonance deactivation of the ketone may also play a role in the failure of this reaction. We also attempted a similar ring closure reaction of **19** and found it to be unsuccessful.



Our second plan for the formation of the lactam ring is shown in Schemes 6 and 8. The Grignard reagent, prepared from 2-methyl-2-(β-bromoethyl)-1,3-dioxolane,[15] was added to indolenine **13** to yield **20**, which was rearranged and deprotected under acidic conditions to yield indolone **21**. As before, the amine of **21** was protected with a Boc group[13] to yield **22**. Acylation of the amine also enhances the electrophilicity of the carbonyl of the indolone. We have extensively investigated the intramolecular aldol condensation of **22** to form **23**. All conditions, which lead to the formation of the thermodynamic enolate or enol under basic or acidic conditions, yielded a retro-Michael reaction product with loss of methyl vinyl ketone, indolone **21**, recovered starting material, or destruction of the

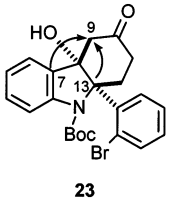
(15) (a) Ponaras, A. A. *Tetrahedron Lett.* **1976**, *17*, 3105. (b) Hsung, R. P. *Synth. Commun.* **1990**, *20*, 1175−1179.

Scheme 7 [a]



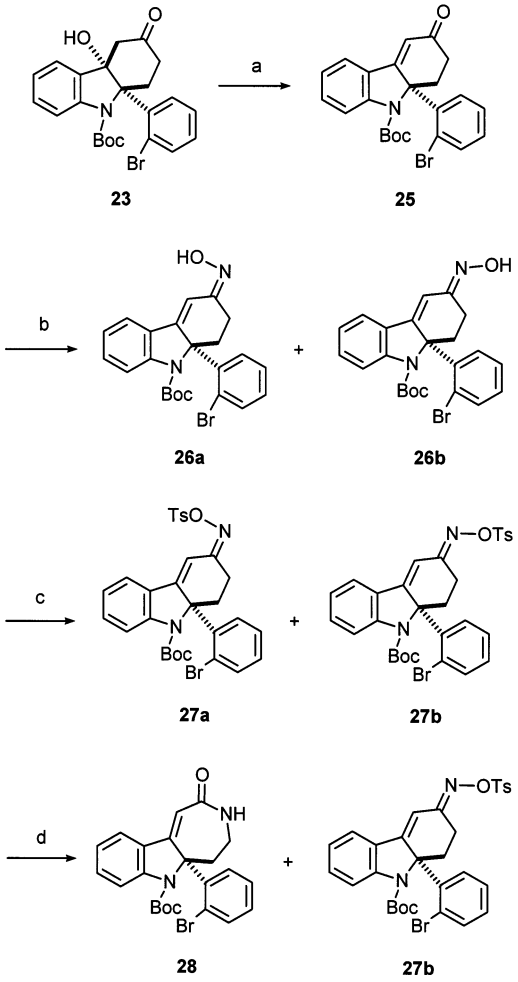
[a] Reagents and conditions: (a) LDA, THF, −78 °C, 5 min; (b) Me_3SiCl, THF, −78 °C to room temperature (78%); (c) silica gel, CH_2Cl_2/MeOH (4/1), room temperature, 16 h (25%).

starting material. When indolone **22** was deprotonated kinetically at −78 °C using LDA in THF,[16] we could detect by thin-layer chromatography (TLC) clean formation of the aldol product **23** without the presence of starting material **22**. The reaction is apparently cleanly quenched on a very small scale on the TLC plate. Extensive efforts to duplicate this quench on a larger scale led to the discovery of our best conditions: adding the cold reaction mixture to a −78 °C solution of 5 equiv of acetic acid in THF. Under these conditions, we obtained a 54% yield of the stable aldol product **23** and 39% recovery of **22**. This represents our best result in carrying out this reaction, as the ratio of aldol **23** to starting material **22** was often lower. We believe that substantial starting material **22** was recovered upon protonation of the intermediate alkoxide **23a** because protonation of the carbonyl group of the intermediate, which leads to retro aldol reaction to yield **22**, is competitive with protonation of the hindered tertiary alkoxide, which leads to aldol **23**. Protonation on the carbonyl group followed by reversion to starting material **22** is also strongly favored entropically as models show the 2-bromophenyl group to be in a much more sterically demanding environment in aldol **23** than it occupies in indolone **22**. When we attempted to trap the alkoxide intermediate using trimethylsilyl chloride,[17] we observed only the formation of silyl enol ether **24** (Scheme 7). The silyl enol ether **24** could be converted to the aldol **23** in low yield by stirring it with silica gel in a mixture of methanol and CH_2Cl_2. The relatively clean detection of aldol **23** on the TLC plate indicates that formation of aldol **23** can be favored by quenching the intermediate on the mildly acidic, proton rich silica gel surface, but these quenching conditions are difficult to reproduce on the scales necessary for a successful synthesis of hinckdentine A.



The structure of aldol **23** was confirmed by NMR experiments and subsequent transformations. The HMBC experiment ex-

Scheme 8 [a]

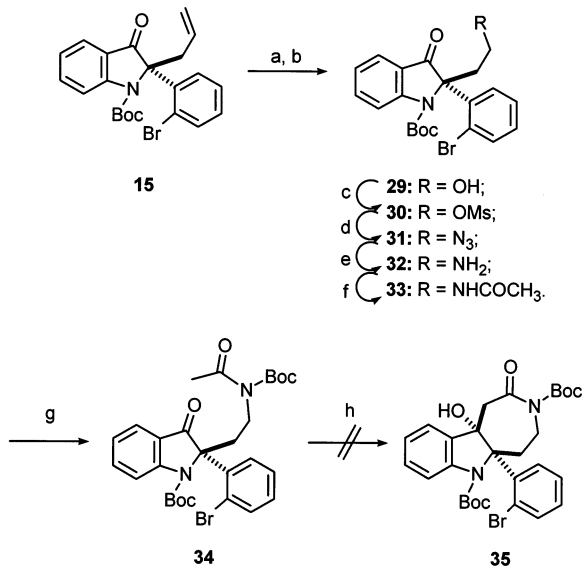


[a] Reagents and conditions: (a) MsCl, pyridine, 0 °C to room temperature, 20 h (76%); (b) $HONH_3Cl$, pyridine, room temperature, 3.5 h (55% **26a** and 45% **26b**); (c) TsCl, pyridine, room temperature; (d) EtOH, 78 °C (19% **28** from **25**).

hibited a three bond correlation of the quaternary carbon (C.13) to one of the protons on C.9 and a three bond correlation of C.7 to the same proton on C.9, indicating that the six-membered ring had been closed. When the aldol product was treated with mesyl chloride in pyridine,[18] the α,β-unsaturated ketone **25** was formed (Scheme 8). Ketone **25** was converted to a 6:1 mixture of oximes **26a** and **26b** by treatment with hydroxylamine hydrochloride in ethanol in the presence of pyridine and water. Treatment of **25** with hydroxylamine hydrochloride in pyridine resulted in a 55:45 mixture of **26a** and **26b**. The Beckmann rearrangement of α,β-unsaturated oximes **26a** and **26b** is precedented to yield the desired α,β-unsaturated lactam **28** through the *p*-toluenesulfonates **27**.[19] The 55:45 mixture of **26a** and **26b** was converted to the corresponding oxime toluene *p*-sulfonates **27a** and **27b** with tosyl chloride in pyridine. This reaction mixture could not be analyzed by TLC because **27a** and **27b** apparently react on the silica gel surface, but the NMR

(16) Gaudemar-Bardone, F.; Gaudemar, M. *Synthesis* **1979**, 463.
(17) Palomo, C.; Aizpurua, J. M.; Aurrekoetxea, N.; Lopez, M. C. *Tetrahedron Lett.* **1991**, *32*, 2525.
(18) Semeria, D.; Philippe, M.; Delaumeny, J.-M.; Sepulchre, A.-M.; Gero, S. D. *Synthesis* **1983**, 710.
(19) (a) Lyga, J. W. *J. Heterocycl. Chem.* **1996**, *33*, 1631. (b) Fleming, I.; Woodward, R. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1653.

Scheme 9 [a]



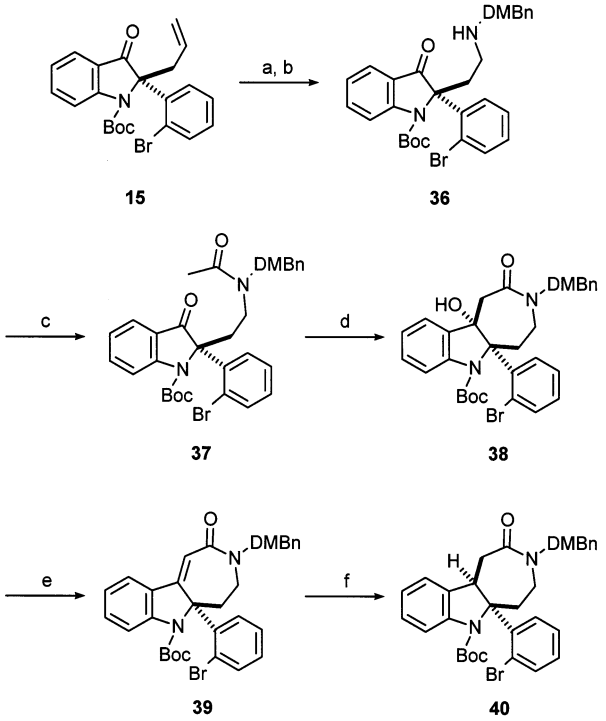
[a] Reagents and conditions: (a) O_3, EtOH, −78 °C, 1 h; (b) $NaBH_4$, THF/EtOH, −78 °C to room temperature (98% for a and b); (c) MsCl, pyridine, room temperature, 2 h (88%); (d) NaN_3, DMF, 100 °C, 12 h (97%); (e) H_2, Pd/C, EtOAc, room temperature, 18 h (99%); (f) Ac_2O, pyridine, room temperature, 20 h (98%); (g) Boc_2O, DMAP, CH_3CN, room temperature, 17 h (96%); (h) LDA, THF, −78 °C, 5 min, then HOAc, THF, −78 °C to room temperature.

of the crude product showed the formation of two oxime toluene *p*-sulfonates together with a small amount of Beckmann rearrangement product **28**. When crude **27** was warmed in ethanol at 78 °C, the Beckmann rearrangement product **28** was obtained in 19% yield. A small amount of one of the oxime toluene *p*-sulfonates, literature[19] precedent suggests **27b**, remained unreacted. Ketone **25** and several byproducts that are not rearrangement products were detected in this reaction mixture. The structure assignments of **26a**, **26b**, and **27a** are based on our assignment of structure **27b** to the unrearranged oxime toluene *p*-sulfonate and the observation that a sample of pure **26a** was converted into **27a**. The acidic conditions employed by Fleming and Woodward[19b] to bring about the Beckmann rearrangement were at best very low yielding and brought about loss of the Boc protecting group. When a mixture of **26a** and **26b** was treated under the conditions of Lyga,[19a] Beckmann rearrangement was not observed. Simultaneous to our investigation of this synthetic sequence, we were investigating a third approach to the lactam ring which proved to be more convenient than this route involving the aldol condensation followed by the Beckmann rearrangement.

Our third and most successful effort to prepare the lactam ring involved direct formation of this ring by means of an aldol condensation. We initially sought to use the Boc group to protect the acetamide of **34** during the aldol condensation. Boc protected amide **34** was prepared from **15** as shown in Scheme 9. The terminal olefin of **15** was cleaved by ozonolysis, and the intermediate oxidation products were directly reduced with $NaBH_4$[20] to yield alcohol **29**. Alcohol **29** was converted to mesylate **30**. The mesylate was displaced with azide anion, and azide **31** was reduced to amine **32**.[21] Amine **32** was acylated,

(20) For an example of this reaction sequence, see: Meyers, A. I.; Reuman, M.; Gabel, R. A. *J. Org. Chem.* **1981**, *46*, 783.
(21) For a recent example of this reaction sequence, see: WO 0224705.

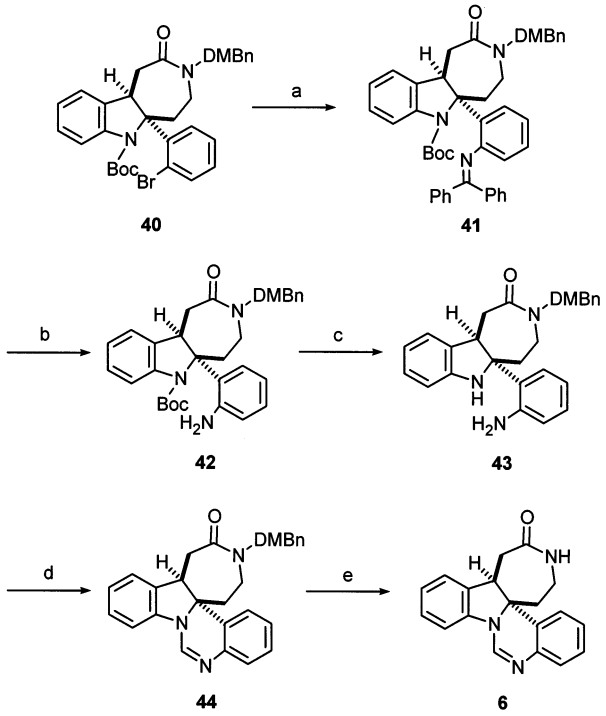
Scheme 10 [a]



DMBn: 2,4-dimethoxybenzyl

[a] Reagents and conditions: (a) O_3, MeOH, −78 °C, then Me_2S, −78 °C to room temperature; (b) 2,4-dimethoxybenzylamine, HOAc, $NaBH_3CN$, MeOH/THF, room temperature, 16 h (60% for a and b); (c) Ac_2O, pyridine, 0 °C to room temperature, 20 h (91%); (d) LDA, THF, −78 °C, 5 min, then HOAc, THF, −78 °C to room temperature (92%); (e) MsCl, pyridine, 0 °C to room temperature, 20 h (96%); (f) Mg turnings, MeOH, room temperature, 24 h (79%).

Scheme 11 [a]



DMBn: 2,4-dimethoxybenzyl

[a] Reagents and conditions: (a) $Ph_2C{=}NH$, *t*-BuONa, $Pd(DPPF)_2Cl_2$, DPPF, toluene, 140 °C, 48 h (62%); (b) 2 N HCl (aq), THF, room temperature, 5 h (97%); (c) 20% TFA in CH_2Cl_2, 0 °C to room temperature, 8 h (95%); (d) 1:1 HCO_2H (96%)/2-propanol, 75 °C, 4 h (72%); (e) HCO_2H (96%), 100 °C, 2 h (93%).

first to yield **33**, and a second time to yield **34**. Although there is good literature precedent,[22] we were unsuccessful in bringing about the formation of aldol **35**. Amide **34** was consumed, but cyclization products could not be detected.

As a result, we decided to replace the Boc protecting group of **34** with a benzyl protecting group (Scheme 10). We chose the 2,4-dimethoxybenzyl protecting group[23] because it can be more readily removed under milder conditions from a lactam than an unsubstituted benzyl protecting group. As before, the terminal olefin of **15** was cleaved by ozonolysis, and the resulting aldehyde was converted to benzylamine **36**. Amine **36** was acetylated under standard conditions to yield **37**. Deprotonation of acetamide **37** at −78 °C with LDA[16] followed by quenching with acetic acid in THF at −78 °C resulted in formation of aldol **38** in 92% yield. Aldol **38** was treated with mesyl chloride in pyridine[18] to yield the α,β-unsaturated amide **39**, which was in turn reduced to lactam **40** using magnesium in methanol.[24]

The framework of hinckdentine A **6** is constructed from **40** as shown in Scheme 11. Palladium-catalyzed amination of **40** using benzophenone imine yielded **41** in 62% yield.[25] The conditions used to bring about amination of **40** are extremely powerful because the bromine of **40** is in a very sterically congested environment due to the enormous orthosubstituent on the aromatic ring. It should be noted that we required a higher reaction temperature (140 °C) than is reported in the literature[25,26] to successfully bring about this transformation. We examined a number of aromatic amination conditions and catalysts before finding the ones that gave a successful result. The diphenylmethylidene protecting group of **41** is cleaved using 2 N aqueous HCl in THF[26] to yield **42**, and the Boc protecting group was cleaved using trifluoroacetic acid in CH_2Cl_2 to give aniline **43**. Condensation of **43** with formic acid in 1:1 formic acid/2-propanol at 75 °C resulted in formation of the pyrimidine ring containing **44**. When the condensation was attempted in formic acid at 100 °C,[3] the dimethoxybenzyl protecting group was removed prior to complete formation of the pyrimidine ring, and the resulting unprotected diamine displayed poor solubility in formic acid such that the formation of the pyrimidine ring proceeded sluggishly in low yield. The dimethoxybenzyl protecting group was cleaved from **44** in formic acid at 100 °C to yield the framework of hinckdentine A **6**.[27] The observed coupling constants between the hydrogens of C.12 and C.11b (J = 6.3 and 3.1 Hz) are very nearly identical to those observed with hinckdentine A (J = 6.2 and 3.0 Hz)[1] and indicate that

(22) For examples, see: (a) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Marzocchi, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213.

(23) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681.

(24) (a) Brettle, R.; Shibib, S. M. *Tetrahedron Lett.* **1980**, *21*, 2915. (b) Brettle, R.; Shibib, S. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2912.

(25) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827.

(26) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

(27) The reaction sequences shown in Schemes 10 and 11 were first carried out with a benzyl protecting group instead of a 2,4-dimethoxybenzyl protecting group, but despite extensive experimentation, conditions could not be found which allowed the benzyl group to be removed to yield **6**.

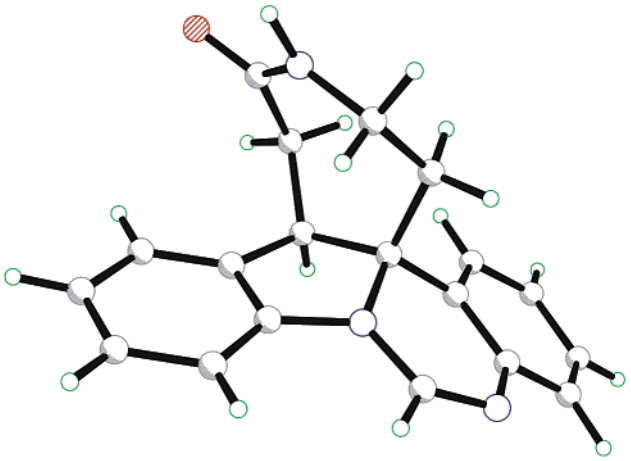
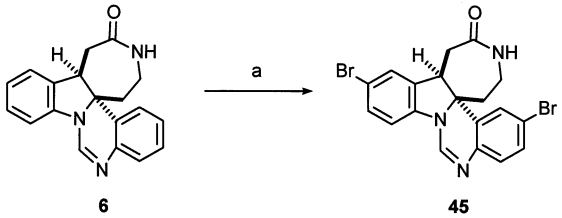


Figure 1. Crystal structure of the hinckdentine framework.

Scheme 12 [a]



[a] Reagents and conditions: (a) Br_2, HCO_2H, room temperature, 48 h (92%).

the magnesium in methanol reduction has fixed the correct relative stereochemistry between the quaternary center and C.11b. Crystalline **6** was submitted to X-ray analysis, and the results (Figure 1) clearly show that the stereochemical relationships of **6** correspond to those of hinckdentine A **1**.

Although we had originally planned to modify our synthesis of the hinckdentine A framework to allow introduction of bromine at an earlier stage, with a successful synthesis of the hinckdentine framework **6** realized, we decided to study the direct bromination of this structure. One can argue on the basis of known brominations of 3,4-dihydroquinazolines[28] and indolines[29] that it is possible to brominate the dihydroindolo[1,2-*c*]quinazoline ring system of **6** at the 2, 8, and 10 positions. Biosynthetically, bromine is probably introduced at a late stage of the biosynthesis of hinckdentine A.[30] Bromination of **6** with bromine in ethanol or chloroform at 60 °C resulted in the sluggish formation of a mixture of monobrominated and dibrominated products. A trace amount of tribrominated products could be detected by LC-MS. Bromination in 96% formic acid (Scheme 12),[31] methanesulfonic acid, or trifluoromethanesulfonic acid at room temperature for 48 h furnished cleanly a single dibrominated product **45** whose structure was elucidated with ^{1}H NMR, ^{1}H−^{1}H COSY NMR, and X-ray crystallography (Figure 2). This bromination reaction can be accelerated by the addition of iodine and iron powder or by heating at 60 °C.

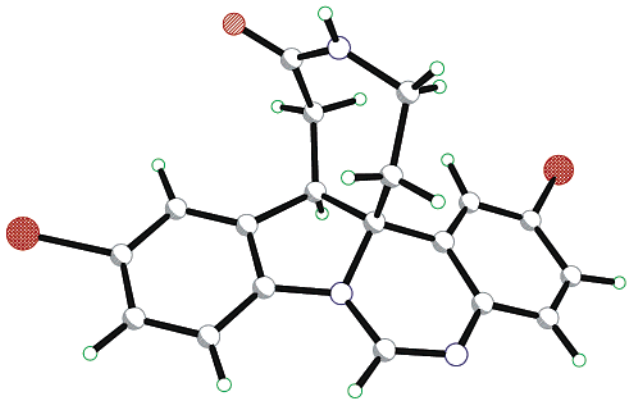


Figure 2. Crystal structure of 8-desbromohinckdentine A.

Further bromination of **45** required much harsher reaction conditions. We found that tribrominated products were formed when a mixture of 98% sulfuric acid and fuming sulfuric acid (1:1) was used as the solvent,[32] but this harsh reaction condition resulted in the formation of other side products. Bromination of **45** with 1,3-dibromo-5,5-dimethylhydantoin/CF_3SO_3H in CH_2Cl_2[33] at room temperature resulted in a mixture of tribrominated and tetrabrominated as well as more highly brominated products, all of which were isomeric mixtures. Hinckdentine A **1** may have been present in this mixture, but we were unable to chromatographically separate all of the isomeric bromides. The formation of many tribromination products with little selectivity after the clean formation of dibrominated **45** surprised us. We had expected primarily products derived from the bromination of positions 4 and 8.

Conclusion

We have produced the first synthesis of the hinckdentine A framework **6** using a 19 step reaction sequence from readily available starting materials. We first formed the quaternary center of hinckdentine A using an uncommon pinacol-like rearrangement of an indolol **14** to yield key intermediate **5**. The lactam was built onto this intermediate using a reaction sequence that featured an efficient seven-membered ring-forming intramolecular aldol condensation as the key step. The α,β-unsaturated lactam **39** was reduced to the corresponding saturated lactam **40** with complete stereocontrol. The dihydropyrimidine ring was prepared by means of a reaction sequence in which the remarkable palladium-catalyzed amination of arylbromide **40** is the key step. This reaction sequence also includes the clean condensation of formic acid with diamine **43** to yield the framework of the natural product. With the framework of hinckdentine A **6** in hand, we investigated the bromination of this structure and found that we could efficiently introduce bromine at the 2 and 10 positions to yield 8-desbromohinckdentine A.

Experimental Section

General. Proton and ^{13}C magnetic resonance spectra were recorded on a 400 MHz/100 Hz Bruker spectrometer and are reported in ppm on the δ scale. Infrared spectra (IR), ultraviolet spectra (UV), high-resolution mass spectra (HRMS), and combustion analyses were

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determined by the Analytical Chemistry Department of Pharmacia. Anhydrous THF was distilled prior to use from sodium metal/benzophenone. Acetonitrile and methanol were dried over 3A/4A molecular sieves. Diisopropylamine and *N*,*N*-diisopropylethylamine were distilled from calcium hydride prior to use. Pyridine was dried by reflux and distillation over KOH. Toluene was distilled from sodium metal prior to use. Anhydrous benzene was purchased from Aldrich in Sure-Seal bottles. All other commercially available solvents and reagents were used without further purification. All moisture-sensitive reactions were conducted under N_2. Brine refers to a saturated aqueous sodium chloride solution. Solvent removal was accomplished by a rotary evaporator operating at house vacuum (40−50 Torr). Column chromatography was performed with silica gel 60 (EM Science, 230−400 mesh ASTM).

2-(2-Bromophenyl)indole (4). 2-Bromoacetophenone (50.0 g, 251.19 mmol) and phenylhydrazine hydrochloride (54.5 g, 376.90 mmol) were mixed with polyphosphoric acid (780 g), and the mixture was heated with stirring. The temperature of the reaction mixture was kept at 100−110 °C for 4 h. It was poured into ice water (2.4 L) and extracted with EtOAc (8 × 200 mL). The combined extracts were dried over Na_2SO_4. The dried extracts were concentrated, and the crude product was chromatographed (SiO_2, 10:1 hexane/EtOAc to yield **4** (53.3 g, 78%). ^{1}H NMR ($CDCl_3$): δ 6.85 (dd, J = 2.1 and 0.8 Hz, 1H), 7.17 (ddd, J = 7.5, 7.0, and 1.0 Hz, 1H), 7.22−7.28 (2H), 7.42 (ddd, J = 7.6, 7.5, and 1.3 Hz, 1H), 7.46 (dd, J = 8.1 and 0.8 Hz, 1H), 7.64 (dd, J = 7.9 and 1.7 Hz, 1H), 7.68−7.73 (2H), 8.68 (br s, 1H, NH); ESI-MS *m*/*z* 272 (MH^+). Anal. Calcd for $C_{14}H_{10}BrN$: C, 61.79; H, 3.70; N, 5.15. Found: C, 61.48; H, 3.52; N, 5.16.

2-(2-Bromophenyl)-3-nitrosoindole (9). To a magnetically stirred solution of **4** (48.0 g, 176.37 mmol) in acetic acid (1000 mL) was added sodium nitrite (30 g, 434.78 mmol) slowly and portionwise during 2.5 h. The reaction mixture was stirred for an additional 30 min and then poured into 2.5 L of water. The precipitate was collected by filtration and dried under reduced pressure to afford a yellow solid **5** (51.5 g, 97%). ^{1}H NMR (CD_3OD): δ 7.39−7.45 (3H), 7.48−7.57 (3H), 7.75 (dd, J = 8.1 and 1.0 Hz, 1H), 8.18 (d, J = 7.3 Hz, 1H); HRMS calcd for $C_{14}H_{10}BrN_2O$ (MH^+) 300.9977, found 300.9966. Anal. Calcd for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found: C, 55.26; H, 2.99; N, 9.19.

3-Amino-2-(2-bromophenyl)indole (10). To a solution of **9** (36.0 g, 119.54 mmol) in ethanol (250 mL) were added sodium hydrosulfite (30 g, 172.30 mmol) and 2 N NaOH solution (250 mL). The reaction mixture was heated to reflux. An additional 30 g (172.30 mmol) of sodium hydrosulfite was added portionwise during 24 h. The reaction mixture was cooled to room temperature, and the solids were collected by filtration. The solids were washed with water (4 × 25 mL) and dried under reduced pressure for 14 h to yield **10** (32.26 g, 94%). ^{1}H NMR ($CDCl_3$): δ 7.15 (ddd, J = 7.5, 7.1, and 1.0 Hz, 1H), 7.22−7.28 (2H), 7.36 (d, J = 8.1 Hz, 1H), 7.41 (ddd, J = 7.6, 7.5, and 1.3 Hz, 1H), 7.59−7.63 (2H), 7.73 (dd, J = 8.1 and 1.0 Hz, 1H), 7.82 (br s, 1H, NH); HRMS calcd $C_{14}H_{12}BrN_2$ (MH^+) 287.0184, found 287.0178.

2-(2-Bromophenyl)-3-imino-indole (11). To a solution of **10** (25.6 g, 89.15 mmol) in benzene was added lead(IV) oxide (86 g, 359.55 mmol). After being refluxed for 24 h, the reaction mixture was filtered, and the filtrate was concentrated. Chromatography of the concentrated crude product (SiO_2, 3:1 hexane/EtOAc) afforded **11** (24.91 g, 98%). ^{1}H NMR ($CDCl_3$): δ 7.36−7.62 (7H), 7.76 (d, J = 7.9 Hz, 1H); HRMS calcd $C_{14}H_{10}BrN_2$ (MH^+) 285.0028, found 285.0014.

2-(2-Bromophenyl)-2-hydroxy-1,2-dihydro-3*H*-indol-3-one (12) and 2-(2-Bromophenyl)-3*H*-indol-3-one (13). To a solution of **11** (25.5 g, 89.43 mmol) in toluene (250 mL) was added a 2 N HCl aqueous solution (250 mL). After being stirred for 12 h, the reaction mixture was diluted with EtOAc (400 mL) and washed with water (400 mL). The aqueous phase was extracted with EtOAc (6 × 150 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 9:2 hexane/EtOAc) to afford **12** (11.42 g, 42%) and **13** (14.33 g, 56%). **12**, ^{1}H NMR ($CDCl_3$): δ 7.34−7.41 (2H), 7.47 (ddd, J = 7.6, 7.5, and 1.3 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.59−7.65 (3H), 7.74 (dd, J = 7.9 and 1.3 Hz, 1H); HRMS calcd $C_{14}H_{11}BrNO_2$ (MH^+) 302.9895, found 287.9895. **13**, ^{1}H NMR ($CDCl_3$): δ 7.34−7.41 (2H), 7.47 (ddd, J = 7.6, 7.5, and 1.3 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.59−7.65 (3H), 7.74 (dd, J = 8.1 and 1.0 Hz, 1H); HRMS calcd $C_{14}H_9BrNO$ (MH^+) 285.9868, found 285.9877. Anal. Calcd for $C_{14}H_8BrNO$: C, 58.77; H, 2.82; N, 4.90. Found: C, 58.71; H, 2.82; N, 4.86.

Dehydration of 12 to 13. Compound **12** (11 g, 36.17 mmol) was placed in a flask and heated in a 110 °C oil bath under reduced pressure for 4 h to furnish **13** (10.25 g, 99%).

3-Allyl-2-phenyl-3*H*-indol-3-ol (14). Indolone **13** (8.58 g, 30 mmol) was dissolved in dry THF (600 mL). At room temperature, a solution of allylmagnesium bromide in ethyl ether/THF (0.10 M, 330 mL, 33 mmol, made by dilution of 1.0 M ethyl ether solution with THF) was added in a slow dropwise fashion. After being stirred for 2 h, the reaction mixture was concentrated to a small volume, diluted with EtOAc (400 mL), and washed with 10% aqueous NH_4Cl solution (300 mL). The aqueous wash was extracted with EtOAc (4 × 80 mL). The combined EtOAc extracts were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed (SiO_2, hexane/EtOAc) to afford product **14** (8.76 g, 89%) together with a minor amount of **5** (295 mg, 3%). **14**, IR: 3296 (br), 3212 (br), 3072, 3009, 2977, 2926, 2905, 1638, 1617, 1589, 1569, 1467, 916, 908, 902 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 1H, OH), 2.53 (dd, J = 14.0 and 7.9 Hz, 1H), 2.75 (dd, J = 14.0 and 6.8 Hz, 1H), 5.09 (dd, J = 17.0 and 1.5 Hz, 1H), 5.14 (dd, J = 10.2 and 1.5 Hz, 1H), 5.67 (dddd, J = 17.0, 10.2, 7.9, and 6.8 Hz, 1H), 7.30−7.36 (2H), 7.41−7.47 (3H), 7.66 (d, J = 7.7 Hz, 1H), 7.74 (dd, J = 8.0 and 1.1 Hz, 1H), 7.78 (dd, J = 7.7 and 1.7 Hz, 1H); HRMS calcd $C_{17}H_{15}BrNO$ (MH^+) 328.0337, found 328.0329. Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.27; H, 4.28; N, 4.28.

2-Allyl-2-(2-bromophenyl)-1,2-dihydro-3*H*-indol-3-one (5). To a solution of **14** (8.53 g, 26 mmol) in toluene (100 mL) was added 88% aqueous formic acid (20 mL). After being stirred and refluxed for 30 min, the reaction mixture was cooled to room temperature and carefully poured into a saturated Na_2CO_3 solution (300 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 × 80 mL). The combined organic solution layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 10:1 hexane/EtOAc) to afford **5** (8.19 g, 96%). IR: 3345, 3301, 3076, 3058, 3006, 2979, 2903, 1675, 1618, 1586, 1490, 1467, 1330, 1318, 1301, 1286, 1272, 935, 928, 910 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.90 (dd, J = 14.0 and 7.1 Hz, 1H), 3.30 (dd, J = 14.0 and 7.3 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 5.18 (dd, J = 17.0 and 1.3 Hz, 1H), 5.37 (dddd, J = 17.0, 10.0, 7.3, and 7.1 Hz, 1H), 5.95 (br, 1H, NH), 6.84 (dd, J = 7.7 and 7.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 7.17 (ddd, J = 7.8, 7.5, and 1.5 Hz, 1H), 7.31 (ddd, J = 7.9, 7.3, and 1.2 Hz, 1H), 7.47 (ddd, J = 8.3, 7.0, and 1.3 Hz, 1H), 7.64−7.69 (3H). ^{13}C NMR ($CDCl_3$): δ 41.9, 72.1, 112.6, 119.3, 120.0, 121.4, 123.2, 125.0, 127.9, 129.7, 129.7, 131.9, 135.6, 137.7, 138.0, 160.3, 201.6. HRMS calcd $C_{17}H_{15}BrNO$ (MH^+) 328.0337, found 328.0340. Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.17; H, 4.30; N, 4.08.

***tert*-Butyl 2-Allyl-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (15).** To a magnetically stirred solution of **5** (5.64 g, 17.18 mmol) and 4-(dimethylamino)pyridine (8.4 g, 68.75 mmol) in acetonitrile (300 mL) was added a solution of di(*tert*-butyl) dicarbonate (12.39 g, 56.76 mmol) in acetonitrile (100 mL). After being stirred for 17 h under N_2, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between EtOAc (300 mL) and saturated NH_4Cl solution (300 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 10:1 hexane:EtOAc) to afford **15**

(7.07 g, 96%). IR: 3073, 3004, 2977, 2927, 1710, 1607, 1465, 1392, 1360, 1277, 1254, 1157, 1143, 1009, 997, 920, 760, 748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (s, 9H), 3.18 (dd, J = 12.7 and 6.6 Hz, 1H), 3.46 (br m, 1H), 4.95 (dd, J = 10.0 and 1.9 Hz, 1H), 5.13 (dd, J = 17.0 and 1.9 Hz, 1H), 5.43 (dddd, J = 16.8, 10.1, 7.9, and 6.6 Hz, 1H), 7.15−7.22 (2H), 7.41 (ddd, 8.1, 7.8, and 1.3 Hz, 1H), 7.54 (dd, J = 7.8 and 1.3 Hz, 1H), 7.65−7.70 (2H), 7.74 (d, J = 7.7 Hz, 1H), 8.31 (broad s, 1H); HRMS calcd $C_{22}H_{23}BrNO_3$ (MH^+) 428.0862, found 428.0859. Anal. Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.85; H, 5.28; N, 3.33.

***tert*-Butyl 2-[2-(Benzylamino)ethyl]-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (16).** Olefin **15** (1.52 g, 3.54 mmol) was dissolved in methanol (40 mL) and cooled to −78 °C under N_2. O_3, from an ozone generator, was bubbled through the reaction mixture until a faint blue color appeared in the reaction mixture. Complete consumption of starting material was confirmed by thin-layer chromatography (4:1 hexane/EtOAc). After the mixture was bubbled with N_2 for 15 min, methyl sulfide (2.5 mL, 34 mmol) was added, and the reaction mixture was allowed to warm to room temperature during 1.5 h. This solution was concentrated and diluted with a mixed solvent of 1:1 MeOH/THF (60 mL), and the resulting solution was cooled to 0 °C. Benzylamine (1.90 g, 17.7 mmol) followed by acetic acid (2.23 mL, 39 mmol) was added to the reaction mixture which was stirred at 0 °C for 30 min. $NaCNBH_3$ (460 mg, 7.32 mmol) was added, and the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 6 h. Another portion of $NaCNBH_3$ (220 mg, 3.5 mol) was added, and the reaction mixture was stirred for an additional 10 h. The reaction mixture was concentrated and diluted with water (100 mL) and extracted with EtOAc (4 × 50 mL). The combined extracts were washed with saturated Na_2CO_3 solution, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 6:5 hexane/EtOAc) to afford **16** (1.32 g, 71%). IR: 3335, 3079, 3062, 3026, 3000, 2975, 2931, 2871, 2852, 1712, 1605, 1591, 1495, 1473, 1466, 1393, 1366, 1265, 1252, 1164, 771, 755, 747, 699 cm^{-1}. ^1H NMR (CD_3OD): δ 1.23 (s, 9H), 2.41 (ddd, J = 11.7, 11.4, and 4.6 Hz, 1H), 2.56 (ddd, J = 11.7, 11.4, and 4.6 Hz, 1H), 2.68 (ddd, J = 11.7, 11.4, and 4.6 Hz, 1H), 2.98 (ddd, J = 11.7, 11.4, and 4.6 Hz, 1H), 3.72 (s, 2H), 7.22−7.33 (7H), 7.48 (ddd, J = 7.8, 6.7, and 1.3 Hz, 1H), 7.57 (dd, J = 7.8 and 1.3 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.75−7.81 (2H), 8.26 (broad s, 1H); HRMS calcd $C_{28}H_{30}BrN_2O_3$ (MH^+) 521.1440, found 521.1433. Anal. Calcd for $C_{28}H_{29}BrN_2O_3$: C, 64.49; H, 5.61; N, 5.37. Found: C, 64.62; H, 5.58; N, 5.00.

***tert*-Butyl 2-(2-{Benzyl[(diethoxyphosphoryl)acetyl]amino}ethyl)-2-(2- bromophenyl)-3-oxoindoline-1-carboxylate (17).** To a solution of **16** (260 mg, 0.5 mmol), diethylphosphonoacetic acid (98 mg, 0.5 mmol), and *N*,*N*-diisopropylethylamine (129.3 mg, 1.0 mmol) in methylene chloride (20 mL) was added HATU (190 mg, 0.5 mmol). After being stirred at room temperature for 24 h, the reaction mixture was concentrated under reduced pressure and then diluted with EtOAc (50 mL). The EtOAc solution was washed with saturated NH_4Cl solution (30 mL). The aqueous wash was extracted with EtOAc (3 × 10 mL), and the combined EtOAc layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to furnish the crude product which was purified by chromatography (SiO_2, 1.5:9.5 hexane/EtOAc) to afford **17** (318 mg, 91%). IR: 3075, 3055, 2980, 2932, 1712, 1676, 1605, 1591, 1554, 1474, 1466, 1394, 1361, 1251, 1202, 1163, 1054, 1026, 972, 769, 757 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.21−1.26 (12H), 1.35 (dt, J = 7.0 and 2.8 Hz, 3H), 2.66 (m, 0.5H), 2.74 (m, 0.5H), 2.78 (m, 0.5H), 2.92−3.06 (3.5H), 3.19 (m, 0.5H), 3.58 (m, 0.5H), 4.10−4.24 (4H), 4.54 (d, J = 17.2 Hz, 0.5H), 4.58 (s, 1H), 4.70 (d, J = 17.2 Hz, 0.5H), 7.10−7.34 (7H), 7.40 (m, 1H), 7.51 (dd, J = 8.2 and 8.1 Hz, 1H), 7.58 (d, J = 7.1 Hz, 0.5H), 7.67 (dd, J = 8.4 and 7.3 Hz, 1H), 7.72 (dd, J = 8.2 and 7.7 Hz, 1H), 7.81 (d, J = 6.9 Hz, 0.5H), 8.17−8.23 (1H); HRMS calcd $C_{34}H_{41}BrN_2O_7P$ (MH^+) 699.1835, found 699.1841. Anal. Calcd for $C_{34}H_{40}BrN_2O_7P$: C, 58.37; H, 5.76; N, 4.00. Found: C, 58.05; H, 5.91; N, 3.93.

2-(2-Bromophenyl)-3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3*H*-indol-3-ol (20). To a solution of indolone **13** (6 g, 20.97 mmol) in dry THF (900 mL) stirred magnetically at room temperature under N_2 was added dropwise a solution of 3,3-ethylenedioxylbutylmagnesium bromide (∼1.0 M, 25−30 mL) that was freshly prepared according to the literature[15] procedure. Complete consumption of starting material was confirmed by thin-layer chromatography (2:1 hexane/EtOAc). After being stirred for 1 h, the reaction mixture was concentrated under reduced pressure, then diluted with EtOAc (200 mL) and washed with 10% NH_4Cl solution (200 mL). The aqueous wash was extracted with EtOAc (4 × 50 mL). The combined EtOAc solutions were washed with brine, dried over Na_2SO_4, and concentrated. The residual crude product was purified by chromatography (SiO_2, 4:1 hexane/EtOAc) to furnish **20** (8.41 g, 88%). ^1H NMR ($CDCl_3$): δ 1.24 (s, 3H), 1.52−1.67 (2H), 1.96 (ddd, J = 13.8, 10.3, and 5.4 Hz, 1H), 2.10 (ddd, J = 13.7, 10.4, and 5.9 Hz, 1H), 3.08 (br s, 1H, OH), 3.78−3.93 (4H), 7.30−7.35 (2H), 7.41−7.47 (3H), 7.64 (d, J = 7.5 Hz, 1H), 7.74 (dd, J = 8.1 and 1.2 Hz, 1H), 7.84 (d, J = 7.7 and 1.7 Hz, 1H); HRMS calcd $C_{20}H_{21}BrNO_3$ (MH^+) 402.0705, found 402.0697.

2-(2-Bromophenyl)-2-(3-oxobutyl)-1,2-dihydro-3*H*-indol-3-one (21). To a solution of **20** (8.33 g, 20.7 mmol) in toluene (200 mL) was added 88% formic acid (40 mL), and the reaction mixture was refluxed for 30 min. After being cooled to room temperature, the reaction mixture was poured into saturated Na_2CO_3 solution (400 mL) slowly and carefully and extracted with EtOAc (4 × 100 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. Chromatographic purification of the crude product (SiO_2, 4:1 hexane/EtOAc) afforded **21** (6.60 g, 89%). IR: 3363, 3064, 3023, 2933, 1710, 1694, 1646, 1615, 1567, 1487, 1468, 754, 733 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.06 (s, 3H), 2.24 (m, 1H), 2.42−2.57 (2H), 2.82 (m, 1H), 6.10 (br s, 1H, NH), 6.83−6.89 (2H), 7.17 (ddd, J = 7.9, 7.5, and 1.7 Hz, 1H), 7.30 (ddd, J = 8.4, 7.3, and 1.5 Hz, 1H), 7.50 (ddd, J = 7.7, 7.1, and 1.5 Hz, 1H), 7.61 (dd, J = 7.9 and 1.7 Hz, 1H), 7.65 (dd, J = 7.9 and 1.2 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H); HRMS calcd $C_{18}H_{17}BrNO_2$ (MH^+) 358.0443, found 358.0443. Anal. Calcd for $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91. Found: C, 60.71; H, 4.51; N, 3.92.

***tert*-Butyl 2-(2-Bromophenyl)-3-oxo-2-(3-oxobutyl)indoline-1-carboxylate (22).** To a magnetically stirred solution of **21** (5.64 g, 15.8 mmol) and 4-(dimethylamino)pyridine (8.4 g, 68.75 mmol) in acetonitrile (300 mL) was added a solution of di-*tert*-butyl dicarbonate (12.39 g, 56.76 mmol) in acetonitrile (100 mL). After being stirred for 17 h under N_2, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between EtOAc (300 mL) and saturated NH_4Cl solution (300 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 9:2 hexane/EtOAc) to afford **22** (6.93 g, 96%). IR: 3006, 2985, 2971, 2933, 1709, 1604, 1592, 1461, 1273, 1167, 1160, 762, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (s, 9H), 2.03 (s, 3H), 2.24−2.32 (2H), 2.74 (m, 1H), 2.97 (m, 1H), 7.18−7.25 (2H), 7.42 (dd, J = 7.3 and 6.7 Hz, 1H), 7.53 (dd, J = 7.9 and 1.5 Hz, 1H), 7.70−7.78 (3H), 8.33 (br s, 1H); HRMS calcd $C_{23}H_{25}BrNO_4$ (MH^+) 458.0967, found 458.0971. Anal. Calcd for $C_{23}H_{24}BrNO_4$: C, 60.27; H, 5.28; N, 3.06. Found: C, 60.39; H, 5.36; N, 3.02.

***tert*-Butyl 9a-(2-Bromophenyl)-4a-hydroxy-3-oxo-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxylate (23).** A solution of dry diisopropylamine (536 mg, 5.03 mmol) in dry THF (50 mL) was cooled to −78 °C, and a solution of butyllithium in hexane (1.6 M, 3.06 mL, 4.9 mol) was added. After being stirred for 10 min at −78 °C under N_2, a solution of **22** (1.87 g, 4.08 mmol) in THF (40 mL) that had been cooled to −78 °C was added to the lithium diisopropylamide/THF solution. After the complete consumption of starting material, which was confirmed by thin-layer chromatography (2:1 hexane/EtOAc), the reaction mixture was poured into a solution of acetic acid (1.17 mL, 20.4 mmol) in THF (90 mL) at −78 °C. The resulting mixture was partitioned between water (200 mL) and EtOAc (200 mL), and

the aqueous layer was neutralized with saturated Na_2CO_3 solution and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 8.7:2.3 hexane/EtOAc) to afford **23** (1.01 g, 54%) and recovered **22** (729 mg, 39%). IR: 3551, 3441, 3065, 2974, 2929, 1705, 1603, 1482, 1464, 1392, 1372, 1315, 1290, 1249, 1163, 1105, 1083, 1065, 1024, 759, 731 cm^{-1}. ^1H NMR (CD_3OD) δ 1.14 (s, 9H), 1.33−1.68 (br s, 1H), 1.94 (ddd, J = 18.5, 14.7, and 3.1 Hz, 1H), 2.36 (br d, J = 19.3 Hz, 1H), 2.80 (d, J = 15.1 Hz, 1H), 2.85 (br s, 1H), 3.28 (br s, 1H), 7.06 (dd, J = 7.5 and 7.5 Hz, 1H), 7.17 (dd, J = 7.5 and 7.3 Hz, 1H), 7.27 (dd, J = 7.7 and 1.0 Hz, 1H), 7.32 (ddd, J = 8.5, 7.2, and 1.4 Hz, 1H), 7.41 (br s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.77 (br s, 1H), 8.00 (br s, 1H); HRMS calcd $C_{23}H_{24}BrN_2O_4$ (M^+) 457.0889, found 457.0886. Anal. Calcd for $C_{23}H_{24}BrNO_4$: C, 60.27; H, 5.28; N, 3.06. Found: C, 60.46; H, 5.39; N, 3.02.

***tert*-Butyl 2-(2-Bromophenyl)-3-oxo-2-{3-[(trimethylsilyl)oxy]but-3-enyl}indoline-1-carboxylate (24).** A solution of dry diisopropylamine (536 mg, 5.03 mmol) in dry THF (50 mL) was cooled to −78 °C, and a solution of butyllithium in hexane (1.6 M, 3.06 mL, 4.9 mol) was added. After being stirred for 10 min at −78 °C under N_2, a solution of **22** (1.87 g, 4.08 mmol) in THF (40 mL) was added to the resulting lithium diisopropylamide/THF solution. After the complete consumption of starting material, which was confirmed by thin-layer chromatography (2:1 hexane/EtOAc), a solution of chlorotrimethylsilane in THF (1.0 M, 4.49 mL, 4.49 mmol) was added in the reaction mixture. After the formation of **24** was confirmed by thin-layer chromatography (2:1 hexane/EtOAc), the reaction mixture was poured into 20% aqueous NH_4Cl solution (200 mL), and the resulting mixture was extracted with EtOAc (4 × 80 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The crude was purified by chromatography (SiO_2, 10:1 hexane/EtOAc) to afford **24** (1.69 g, 78%). IR: 3072, 3061, 2973, 2964, 2932, 1761, 1711, 1633, 1606, 1467, 1392, 1366, 1363, 1251, 1163, 1159, 1090, 1060, 1052, 1033, 928, 868, 846, 744 cm^{-1}. ^1H NMR (C_6D_6): 0.12 (s, 9H, $SiMe_3$), 1.15 (s, 9H), 2.09 (ddd, J = 13.5, 12.8, and 4.7 Hz, 1H), 2.19 (ddd, J = 13.5, 12.8, and 4.7 Hz, 1H), 2.94 (ddd, J = 13.1, 12.8, and 4.7 Hz, 1H), 3.07 (m, 1H), 3.97 (d, J = 1.0 Hz, 1H), 4.07 (d, J = 1.0 Hz, 1H), 6.59 (ddd, J = 7.6, 7.5, and 1.5 Hz, 1H), 6.68 (dd, J = 7.7 and 7.6 Hz, 1H), 6.87 (dd, J = 7.6 and 7.3 Hz, 1H), 7.19−7.23 (2H), 7.58 (d, J = 7.1 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 8.71 (br s, 1H); ESI-MS m/z 530 (MH^+); HRMS calcd for $C_{23}H_{24}BrNO_4Si$ ($M - SiMe_3 + H^+$) 457.0889, found 457.0886.

Preparation of 23 from 24. To a solution of **24** (1.60 g, 3 mmol) in a mixed solvent of 4:1 methylene chloride/methanol (50 mL) was added 230−400 mesh ASTM silica gel (10 g). The mixture was evaporated under reduced pressure and kept at room temperature for 16 h. Chromatography of the mixture (SiO_2, 7:3 hexane/EtOAc as mobile phase) afforded **23** (344 mg, 25%).

***tert*-Butyl 9a-(2-Bromophenyl)-3-oxo-1,2,3,9a-tetrahydro-9*H*-carbazole-9-carboxylate (25).** A solution of **23** (630 mg, 1.37 mmol) in dry pyridine (20 mL) was stirred at 0 °C, and methansulfonyl chloride (785 mg, 6.85 mmol) was added. After being stirred at 0 °C for 30 min, the reaction mixture was allowed to warm and was stirred at room temperature for 20 h. The reaction mixture was poured into NH_4Cl solution (200 mL), acidified with 2 N HCl solution to pH = 2, and extracted with EtOAc (4 × 60 mL). The combined extracts were washed with saturated Na_2CO_3 solution (2 × 20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 3.4:1 hexane/EtOAc) to afford **25** (460 mg, 76%). IR: 3073, 3045, 3018, 2985−2928 (br), 2887, 2853, 1708, 1663, 1656, 1620, 1600, 1393, 1366, 1270, 1247, 1229, 1200, 1161, 1007, 928, 880, 763, 759 cm^{-1}. UV λ_{max} 255 (12 700), 299 (7620), 385 (6780) nm. ^1H NMR ($CDCl_3$): δ 1.47 (s, 9H), 2.31 (m, 1H), 2.55−2.59 (2H), 3.90 (br d, J = 13.7 Hz, 1H), 6.29 (s, 1H), 7.11−7.16 (2H), 7.35 (ddd, J = 7.6, 7.1, and 1.5 Hz, 1H), 7.47 (ddd, J = 7.8, 7.3, and 1.2 Hz, 1H), 7.55 (dd, J = 7.9 and 1.5 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.87−7.94 (2H); HRMS calcd $C_{23}H_{23}BrNO_3$ (MH^+) 440.0862, found 440.0863. Anal. Calcd for $C_{23}H_{22}BrNO_3$: C, 62.74; H, 5.04; N, 3.18. Found: C, 61.60; H, 5.05; N, 3.06.

***tert*-Butyl 9a-(2-Bromophenyl)-3-(hydroxyimino)-1,2,3,9a-tetrahydro-9*H*-carbazole-9-carboxylate (26).** A suspension of **25** (400 mg, 0.908 mmol) in EtOH (20 mL) was heated at 50 °C until a complete solution was obtained. Pyridine (2 mL) and aqueous hydroxylamine solution (4.0 M, 273 μL, 1.09 mmol) were added sequentially, and the reaction mixture was refluxed for 30 min. After being cooled to room temperature, the reaction mixture was poured into ice-cold water (150 mL) and extracted with EtOAc (4 × 50 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed with (SiO_2, 3.4:1 hexane/EtOAc) to afford **26a** (322 mg, 78%) and **26b** (53.8 mg, 13%). **26b** is more polar than **26a**. **26b** rapidly equilibrates at room temperature to a mixture of **26a** and **26b**. **26a**, ^1H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.01 (ddd, J = 13.1, 13.1, and 6.2 Hz, 1H), 2.62 (ddd, J = 13.1, 13.1, and 6.2 Hz, 1H), 2.89 (dd, J = 18.5 and 6.2 Hz, 1H), 3.81 (dd, J = 18.5 and 4.5 Hz, 1H), 6.49 (s, 1H), 7.06−7.12 (2H), 7.29−7.34 (2H), 7.51−7.55 (2H), 7.82−7.86 (2H); HRMS calcd $C_{23}H_{24}BrN_2O_3$ (MH^+) 455.0970, found 455.0974. Anal. Calcd for $C_{23}H_{23}Br\,N_2O_3$: C, 60.67; H, 5.09; N, 6.15. Found: C, 60.63; H, 5.46; N, 5.78. **26b**, ^1H NMR ($CDCl_3$) partial data, δ 7.02 (s, 1H); HRMS calcd $C_{23}H_{24}BrN_2O_3$ (MH^+) 455.0970, found 455.0978. Anal. Calcd for $C_{23}H_{23}BrN_2O_3$: C, 60.67; H, 5.09; N, 6.15. Found: C, 60.63; H, 5.51; N, 5.75.

Preparation of 26 in Pyridine. Hydroxylamine hydrochloride (116 mg, 1.67 mmol) was added to a solution of **25** (487 mg, 1.11 mmol) in pyridine (5 mL), and the resulting mixture was stirred at room temperature for 3.5 h. The reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was a 55:45 mixture of **26a** and **26b** and was clean when analyzed by NMR. It was used without purification.

***tert*-Butyl 5a-(2-Bromophenyl)-2-oxo-3,4,5,5a-tetrahydroazepino-[4,5-*b*]indole-6(2*H*)-carboxylate (28).** To a solution of **26** (101 mg, 0.221 mmol) in anhydrous pyridine was added tosyl chloride (62.4 mg, 0.327 mmol). The reaction mixture was stirred at room temperature for 17 h, and then it was partitioned between EtOAc (25 mL) and saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, and the organic layer was washed with H_2O (25 mL), dried over $MgSO_4$, filtered, and concentrated to yield **27** [olefinic proton signals for **27a**, ^1H NMR ($CDCl_3$) δ 6.41 (s, 1H), and **27b**, ^1H NMR ($CDCl_3$) δ 6.86 (s, 1H)]. Crude **27** (111 mg) was heated in EtOH (5 mL) for 3 h. The reaction mixture was concentrated, and the residue was chromatographed (SiO_2, 4:1 hexane/EtOAc followed by 1:1 hexane/EtOAc followed by 1:2 hexane/EtOAc) to yield **28** (18.6 mg) in 19% yield. IR: 3138, 3098, 3052, 2976, 2895, 2867, 1725, 1710, 1676, 1646, 1615, 1604, 1475, 1390, 1378, 1374, 1297, 1253, 1248, 1231, 1206, 1165, 757, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.16 (s, 9H), 2.57 (dd, J = 13.1 and 7.9 Hz, 1H), 2.65 (dd, J = 14.6 and 11.1 Hz, 1H), 2.90 (ddd, J = 13.1, 11.0, and 10.8 Hz, 1H), 3.89 (br s, 1H), 5.98 (s, 1H), 6.43 (d, J = 2.9 Hz, 1H), 7.06 (dd, J = 7.9 and 7.9 Hz, 1H), 7.15 (dd, J = 8.3 and 8.3 Hz, 1H), 7.32 (dd, J = 7.7 and 7.7 Hz, 1H), 7.36 (dd, J = 7.8 and 7.8 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 8.00 (br s, 1H); HRMS calcd $C_{23}H_{24}BrN_2O_3$ (MH^+) 455.0971, found 455.0960. Anal. Calcd for $C_{23}H_{23}BrN_2O_3$: C, 60.67; H, 5.09; N, 6.15. Found: C, 60.26; H, 5.26; N, 5.78.

***tert*-Butyl 2-(2-Bromophenyl)-2-(2-hydroxyethyl)-3-oxoindoline-1-carboxylate (29).** Olefin **15** (2.66 g, 6.21 mmol) was dissolved in ethanol (100 mL) and cooled to −78 °C under N_2. O_3, from an ozone generator, was bubbled through the reaction mixture until a faint blue color appeared in the reaction mixture. Complete consumption of starting material was confirmed using thin-layer chromatography (4:1 hexane/EtOAc). After being bubbled with N_2 for 15 min, the reaction mixture was diluted with THF (50 mL), and $NaBH_4$ (235 mg, 6.21

mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. An additional portion of $NaBH_4$ (235 mg, 6.21 mmol) was added to the reaction mixture, and it was stirred for another 5 h. The reaction mixture was concentrated, diluted with saturated NH_4Cl solution (100 mL), and extracted with EtOAc (4 × 50 mL). The combined extracts were washed with saturated Na_2CO_3 solution (2 × 10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 2:1 hexane/EtOAc) to afford **29** (2.63 g, 98%). IR: 3429 (br), 2976, 2932, 2888, 1710, 1607, 1592, 1467, 1393, 1367, 1324, 1305, 1266, 1253, 1164, 1069, 1054, 1038, 1023, 773, 756, 747 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (s, 9H), 2.77 (ddd, J = 13.3, 6.8 and 6.8 Hz, 1H), 2.95 (m, 1H), 3.55−3.67 (2H), 7.18−7.21 (2H), 7.42 (ddd, J = 7.7, 7.5, and 1.3 Hz, 1H), 7.53 (dd, J = 7.9 and 1.3 Hz, 1H), 7.68−7.73 (2H), 7.78 (dd, J = 7.7 and 0.8 Hz, 1H), 8.32 (br s, 1H); HRMS calcd $C_{21}H_{23}BrNO_4$ (MH^+) 432.0811, found 432.0808. Anal. Calcd for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.51; H, 5.33; N, 3.37.

***tert*-Butyl 2-(2-Bromophenyl)-2-{2-[(methylsulfonyl)oxy]ethyl}-3-oxoindoline-1-carboxylate (30).** A solution of **29** (2.50 g, 5.78 mmol) in dry pyridine (50 mL) was stirred at 0 °C, and methanesulfonyl chloride (1.06 g, 9.25 mmol) was added. After being stirred at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was poured into saturated NH_4Cl solution (150 mL), acidified with 2 N HCl solution to pH = 2, and extracted with EtOAc (4 × 50 mL). The combined extracts were washed with saturated Na_2CO_3 solution (2 × 10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 8:3 hexane/EtOAc) to afford **30** (2.60 g, 88%). IR: 3075, 3023, 2977, 2934, 2906, 1711, 1605, 1467, 1393, 1366, 1361, 1267, 1252, 1199, 1177, 773, 757 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27 (s, 9H), 2.79 (s, 3H), 2.97 (ddd, J = 13.9, 6.2, and 6.2 Hz, 1H), 3.15 (m, 1H), 4.08−4.23 (2H), 7.20−7.25 (2H), 7.43 (ddd, J = 7.7, 7.7, and 1.5 Hz, 1H), 7.55 (dd, J = 7.9 and 1.3 Hz, 1H), 7.63 (dd, J = 8.0 and 1.0 Hz, 1H), 7.73 (ddd, J = 7.9, 7.5, and 1.5 Hz, 1H), 8.05 (dd, J = 7.7 and 0.6 Hz, 1H), 8.34 (br s, 1H); HRMS calcd $C_{22}H_{25}BrNO_6S$ (MH^+) 510.0586, found 510.0605.

***tert*-Butyl 2-(2-Azidoethyl)-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (31).** To a solution of **30** (2.5 g, 4.9 mmol) in DMF (50 mL) was added sodium azide (2.55 g, 39.2 mmol), and the reaction mixture was heated at 95 °C for 20 h. After being cooled to room temperature, the reaction mixture was partitioned between water (200 mL) and EtOAc (200 mL), and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 10:31 hexane/EtOAc) to afford **31** (2.17 g, 97%). IR: 3082, 3061, 3005, 2995, 2980, 2959, 2930, 2145, 2094, 2091, 1711, 1603, 1468, 1391, 1364, 1361, 1265, 1250, 1164, 1155, 772, 761, 755, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (s, 9H), 2.75 (ddd, J = 13.1, 7.5 and 7.5 Hz, 1H), 2.95 (m, 1H), 3.18 (t, J = 7.3 Hz, 1H), 7.19−7.25 (2H), 7.43 (ddd, J = 7.7, 7.5, and 1.5 Hz, 1H), 7.54 (dd, J = 7.9 and 1.3 Hz, 1H), 7.65 (dd, J = 8.1 and 1.3 Hz, 1H), 7.73 (ddd, J = 7.9, 7.3, and 1.5 Hz, 1H), 7.79 (ddd, J = 7.7, 1.5, and 0.8 Hz, 1H), 8.33 (br s, 1H); HRMS calcd $C_{21}H_{22}BrN_4O_3$ (MH^+) 457.0876, found 457.0890.

***tert*-Butyl 2-(2-Aminoethyl)-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (32).** A solution of **31** (2 g, 4.37 mmol) in EtOAc (100 mL) was stirred at room temperature under H_2 (atmospheric pressure) for 18 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The residue was diluted with a mixture of methylene chloride (100 mL) and a saturated solution of NH_3 in MeOH (40 mL) and evaporated again. The crude product was purified by chromatography (SiO_2, 10:1 CH_2Cl_2/MeOH) to afford **32** (1.87 g, 99%). IR: 3381, 3312, 3188, 3062, 2976, 2932, 2910, 2971, 1710, 1604, 1467, 1392, 1366, 1361, 1265, 1251, 1161, 770, 756 cm^{-1}. ^1H NMR (CD_3OD): δ 1.25 (s, 9H), 2.41 (ddd, J = 11.8, 11.0, and 3.9 Hz, 1H), 2.52 (ddd, J = 11.8, 11.0, and 3.9 Hz, 1H), 2.61 (ddd, J = 11.8, 11.0, and 3.9 Hz, 1H), 2.92 (ddd, J = 11.8, 11.0, and 3.9 Hz, 1H), 7.25−7.30 (2H), 7.50 (ddd, J = 7.8, 7.5, and 0.8 Hz, 1H), 7.57 (dd, J = 7.9 and 1.3 Hz, 1H), 7.71−7.83 (3H), 8.29 (d, J = 7.1 Hz, 1H); HRMS calcd $C_{21}H_{24}BrN_2O_3$ (MH^+) 431.0970, found 431.0970.

***tert*-Butyl 2-[2-(Acetylamino)ethyl]-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (33).** A solution of **32** (1.70 g, 3.94 mmol) in dry pyridine (50 mL) was stirred at 0 °C, and acetic anhydride (2.01 g, 19.70 mmol) was added. After being stirred at 0 °C for 30 min, the reaction mixture was allowed to warm to room temperature and was stirred for 20 h. The reaction mixture was poured into saturated NH_4Cl solution (150 mL), acidified with 2 N HCl solution to pH = 2, and extracted with EtOAc (4 × 50 mL). The combined extracts were washed with saturated Na_2CO_3 solution (2 × 10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 5:6 hexane/EtOAc) to afford **33** (1.83 g, 98%). IR: 3294, 3090, 2977, 2950, 1710, 1676, 1662, 1656, 1645, 1606, 1467, 1433, 1392, 1365, 1360, 1266, 1252, 1162, 768, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (s, 9H), 1.88 (s, 3H), 2.69 (ddd, J = 13.3, 6.6, and 6.6 Hz, 1H), 2.92 (ddd, J = 13.3, 6.6 and 6.6 Hz, 1H), 3.12−3.27 (2H), 5.32 (br s, 1H, NH), 7.17−7.24 (2H), 7.41 (ddd, J = 7.7, 7.5, and 1.5 Hz, 1H), 7.53 (ddd, J = 7.9 and 1.3 Hz, 1H), 7.70−7.75 (2H), 7.78 (ddd, J = 7.7, 1.3, and 0.6 Hz, 1H), 8.35 (br s, 1H); HRMS calcd $C_{23}H_{26}BrN_2O_4$ (MH^+) 473.1076, found 473.1084. Anal. Calcd for $C_{23}H_{25}BrN_2O_4$: C, 58.36; H, 5.32; N, 5.92; Found: C, 58.31; H, 5.38; N, 5.77.

***tert*-Butyl 2-{2-[Acetyl(*tert*-butoxycarbonyl)amino]ethyl}-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (34).** To a magnetically stirred solution of **33** (1.75 g, 3.70 mmol) and 4-(dimethylamino)-pyridine (2.26 g, 18.50 mmol) in acetonitrile (100 mL) was added a solution of di-*tert*-butyl dicarbonate (3.23 g, 14.80 mmol) in acetonitrile (50 mL). After being stirred for 17 h under N_2, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between EtOAc (100 mL) and saturated NH_4Cl solution (120 mL). The aqueous phase was extracted with EtOAc (3 × 40 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 10:1 hexane:EtOAc) to afford **34** (2.04 g, 96%). IR: 3008, 2977, 2933, 1734, 1714, 1694, 1607, 1467, 1449, 1392, 1308, 1265, 1221, 1198, 1167, 764, 748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27 (s, 9H), 1.48 (s, 9H), 2.47 (s, 3H), 2.56 (ddd, J = 12.3, 12.3, and 4.8 Hz, 1H), 2.82 (ddd, J = 12.3, 12.3, and 4.8 Hz, 1H), 3.37 (ddd, J = 12.9, 12.3, and 4.8 Hz, 1H), 3.82 (ddd, J = 12.9, 12.3, and 4.8 Hz, 1H), 7.17−7.21 (2H), 7.42 (ddd, J = 7.1, 7.6, and 1.5 Hz, 1H), 7.52 (dd, J = 7.9 and 1.3 Hz, 1H), 7.70 (ddd, J = 7.8, 7.3, and 1.3 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 8.35 (br s, 1H); HRMS calcd $C_{28}H_{34}BrN_2O_6$ (MH^+) 573.1600, found 573.1609. Anal. Calcd for $C_{28}H_{33}BrN_2O_6$: C, 58.64; H, 5.80; N, 4.88; Found: C, 58.33; H, 5.90; N, 4.79.

***tert*-Butyl 2-(2-Bromophenyl)-2-{2-[(2,5-dimethoxybenzyl)amino]-ethyl}-3-oxo-2,3-dihydro-1*H*-indole-1-carboxylate (36).** Olefin **15** (11.3 g, 26.38 mmol) was dissolved in methanol (280 mL) and cooled to −78 °C under N_2. O_3, from an ozone generator, was bubbled through the reaction mixture until a faint blue color appeared in the reaction mixture. Complete consumption of starting material was confirmed using thin-layer chromatography (4:1 hexane/EtOAc). After the mixture was bubbled with N_2 for 15 min, methyl sulfide (19.4 mL, 263.8 mmol) was added, and the reaction mixture was allowed to warm to room temperature during 1.5 h. This solution was concentrated and diluted with methanol/THF (1:1, 400 mL), and the resulting solution was cooled to 0 °C. 2,4-Dimethoxybenzylamine (22.0 g, 131.9 mmol) followed by acetic acid (17.4 g, 290 mmol) was added to the reaction mixture, which was stirred at 0 °C for 30 min. $NaCNBH_3$ (3.29 g, 52.36 mmol) was added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 6 h. An additional portion of $NaCNBH_3$ (1.68 g, 26.7 mmol) was added to the reaction mixture that was stirred for another 10 h. The reaction mixture was concentrated, diluted with water (300 mL), and extracted with EtOAc (4 × 100 mL).

The combined extracts were washed with saturated Na_2CO_3 solution (2 × 50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 6:5 hexane/EtOAc) to afford **36** (9.14 g, 60%). IR: 3073, 2974, 2934, 2834, 1710, 1608, 1589, 1506, 1467, 1392, 1365, 1362, 1288, 1252, 1207, 1157, 1098, 1069, 1036, 835, 770, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (s, 9H), 2.39 (ddd, J = 11.1, 10.6, and 5.5 Hz, 1H), 2.50 (ddd, J = 11.1, 10.6, and 4.8 Hz, 1H), 2.65 (ddd, J = 12.9, 10.6, and 5.5 Hz, 1H), 2.93 (ddd, J = 11.1, 10.6, and 4.8 Hz, 1H), 3.53 (d, J = 13.0 Hz, 1H), 3.57 (d, J = 13.0 Hz, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 6.37−6.41 (2H), 6.99 (d, J = 8.1 Hz, 1H), 7.16−7.19 (2H), 7.39 (ddd, J = 7.9, 7.3, and 1.3 Hz, 1H), 7.52 (dd, J = 7.9 and 1.3 Hz, 1H), 7.68 (ddd, J = 7.9, 7.3, and 1.3 Hz, 1H), 7.71−7.73 (2H), 8.31 (br s, 1H); HRMS calcd $C_{30}H_{34}BrN_2O_5$ (MH^+) 581.1652, found 581.1660. $C_{30}H_{33}BrN_2O_5$: C, 61.97; H, 5.72; N, 4.82. Found: C, 61.92; H, 5.83; N, 4.83.

***tert*-Butyl 2-{2-[Acetyl(2,4-dimethoxybenzyl)amino]ethyl}-2-(2-bromophenyl)-3-oxoindoline-1-carboxylate (37).** A solution of **36** (9.0 g, 15.5 mmol) in dry pyridine (100 mL) was stirred at 0 °C, and acetic anhydride (7.92 g, 77.5 mmol) was added. After being stirred at 0 °C for 30 min, the reaction mixture was allowed to warm to room temperature and was stirred for 20 h. The reaction mixture was poured into saturated NH_4Cl solution (400 mL), acidified with 2 N HCl solution to pH = 2, and extracted with EtOAc (4 × 150 mL). The combined extracts were washed with saturated Na_2CO_3 solution (2 × 50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 3:2 hexane/EtOAc) to afford **37** (8.79 g, 91%). IR: 3073, 3000, 2974, 2933, 2836, 1711, 1645, 1609, 1589, 1507, 1467, 1392, 1360, 1291, 1265, 1250, 1209, 1158, 1121, 1072, 1033, 838, 757 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.23 (br s, 9H), 2.04 (s, 1.2H), 2.15 (s, 1.8H), 2.54 (ddd, J = 11.8, 11.4, and 3.7 Hz, 0.6H), 2.73 (ddd, J = 12.2, 12.2, and 4.6 Hz, 0.6H), 2.77 (ddd, J = 12.0, 12.0, and 4.6 Hz, 0.4H), 2.88−3.03 (1.4H), 3.17 (m, 0.4H), 3.53 (ddd, J = 13.1, 11.4, and 4.6 Hz, 0.6H), 3.76 (s, 1.8H), 3.78 (s, 1.8H), 3.78 (s, 1.2H), 3.79 (s, 1.2H), 4.25 (d, J = 16.2 Hz, 0.6H), 4.36 (d, J = 16.4 Hz, 0.6H), 4.45 (d, J = 14.1 Hz, 0.4H), 4.53 (d, J = 14.7 Hz, 0.4H), 6.35 (dd, J = 8.3 and 2.3 Hz, 0.6H), 6.39−6.42 (1.4H), 6.84 (d, J = 8.3 Hz, 0.6H), 7.14−7.28 (2.4H), 7.40−7.45 (1H), 7.50 (dd, J = 7.9 and 1.3 Hz, 0.6H), 7.54 (dd, J = 7.9 and 1.2 Hz, 0.4H), 7.62−7.75 (2.4H), 7.91 (d, J = 7.9 Hz, 0.6H), 8.30 (br s, 1H); HRMS calcd $C_{32}H_{36}BrN_2O_6$ (MH^+) 623.1757, found 623.1772. Anal. Calcd for $C_{32}H_{35}BrN_2O_6$: C, 61.64; H, 5.66; N, 4.49; Found: C, 61.64; H, 5.84; N, 4.51.

***tert*-Butyl 5a-(2-Bromophenyl)-3-(2,4-dimethoxybenzyl)-10b-hydroxy-2-oxo-2,3,4,5,5a,10b-hexahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (38).** A solution of dry diisopropylamine (1.83 g, 18.1 mmol) in dry THF (200 mL) was cooled to −78 °C, and a solution of butyllithium in hexane (1.6 M, 10.43 mL, 16.68 mmol) was added. After being stirred for 10 min at −78 °C under N_2, a solution of **37** (8.68 g, 13.90 mmol) in THF that had been cooled to −78 °C was added to the lithium diisopropylamide/THF solution. After the complete consumption of starting material, which was confirmed by thin-layer chromatography (1:2 hexane/EtOAc), the reaction mixture was poured into a solution of acetic acid (4.2 g, 69.5 mmol) in THF (200 mL) at −78 °C. The resulting mixture was concentrated under reduced pressure, and the residue was partitioned between water (200 mL) and EtOAc (200 mL). The aqueous layer was neutralized with saturated Na_2CO_3 solution and extracted with EtOAc (4 × 40 mL). The combined extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 3:8 hexane/EtOAc) to afford **38** (7.99 g, 92%). IR: 3562, 3550, 3543, 3373, 3066, 3056, 2998, 2971, 2933, 2835, 1732, 1727, 1701, 1627, 1615, 1590, 1504, 1466, 1461, 1372, 1369, 1289, 1252, 1207, 1164, 1159, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12 (s, 9H), 1.53 (br s, 1H), 2.82 (br m, 1H), 3.20 (br s, 1H), 3.25 (br s, 1H), 3.38 (d, J = 17.6 Hz, 1H), 3.53 (d, J = 17.6 Hz, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 4.13 (d, J = 15.3 Hz, 1H), 4.54 (d, J = 15.3 Hz, 1H), 6.22 (s, 2H), 6.35 (s, 1H), 7.14 (dd, J = 7.3 and 7.3 Hz, 1H), 7.19 (dd, J = 7.3 and 7.3 Hz, 1H), 7.40−7.45 (2H), 7.50 (d, J = 6.8 Hz, 1H), 7.56 (d, J = 6.8 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 8.13 (d, J = 6.8 Hz, 1H); HRMS calcd $C_{32}H_{36}BrN_2O_6$ (MH^+) 623.1757, found 623.1771. Anal. Calcd for $C_{32}H_{35}BrN_2O_6$: C, 61.64; H, 5.66; N, 4.49. Found: C, 61.49; H, 5.80; N, 4.54.

***tert*-Butyl 5a-(2-Bromophenyl)-3-(2,4-dimethoxybenzyl)-2-oxo-3,4,5,5a-tetrahydroazepino[4,5-*b*]indole-6(2*H*)-carboxylate (39).** A solution of **38** (7.89 g, 12.65 mmol) in dry pyridine (150 mL) was stirred at 0 °C, and methansulfonyl chloride (7.25 g, 63.25 mmol) was added. After being stirred at 0 °C for 30 min, the reaction mixture was allowed to warm to room temperature and was stirred for 20 h. The reaction mixture was poured into saturated NH_4Cl solution (400 mL), acidified with 6 N HCl solution to pH = 2, and extracted with EtOAc (4 × 150 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (2 × 60 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (SiO_2, 6:5 hexane/EtOAc) to afford **39** (7.36 g, 96%). IR: 2976, 2933, 2835, 1706, 1653, 1618, 1588, 1506, 1475, 1379, 1367, 1291, 1262, 1250, 1208, 1160, 1093, 1068, 1033, 1020, 844, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (br s, 9H), 2.15 (dd, J = 14.9 and 6.7 Hz, 1H), 3.49 (dd, J = 14.9 and 6.8 Hz, 1H), 3.66 (m, 1H), 3.82 (s, 3H), 3.91 (s, 3H), 4.09 (m, 1H), 4.15 (d, J = 14.7 Hz, 1H), 4.71 (d, J = 14.7 Hz, 1H), 6.35 (s, 1H), 6.46 (dd, J = 8.4 and 2.5 Hz, 1H), 6.50 (d, J = 2.1 Hz, 1H), 7.10−7.14 (2H), 7.19 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 7.6 and 7.6 Hz, 1H), 7.42 (dd, J = 7.6 and 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 8.13 (br, 1H); HRMS calcd $C_{32}H_{34}BrN_2O_5$ (MH^+) 605.1652, found 605.1636. Anal. Calcd for $C_{32}H_{33}BrN_2O_5$: C, 63.47; H, 5.49; N, 4.63; Found: C, 63.06; H, 5.61; N, 4.48.

***tert*-Butyl 5a-(2-Bromophenyl)-3-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,5a,10b-hexahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (40).** To a solution of **39** (6.28 g, 10.37 mmol) in MeOH (180 mL) were added magnesium turnings (2.48 g, 103.7 mmol), and the reaction mixture was stirred at room temperature under N_2. After an induction period, a very vigorous exothermic reaction ensued, which was controlled using an ice-water bath. After being stirred for 24 h, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (200 mL), and washed with 20% NH_4Cl solution (200 mL). The aqueous wash was extracted with EtOAc (3 × 40 mL), and the combined EtOAc layers were washed with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (20 mL). After being dried over Na_2SO_4, the EtOAc solution of the crude product was filtered and concentrated. The crude product was purified by chromatography (SiO_2, 7:4 hexane/EtOAc) to furnish **40** (4.98 g, 79%). IR: 3095−3018, 2998−2903, 2880, 2833, 1701, 1626, 1586, 1498, 1490, 1467, 1440, 1386, 1359, 1285, 1268, 1258, 1239, 1207, 1179, 1168, 1158, 1081, 1043, 1030, 836, 765, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.09 (br s, 9H), 1.43 (br, 1H), 2.62 (br, 1H), 3.00−3.37 (4H), 3.72 (s, 3H), 3.79 (s, 3H), 4.19 (m, 1H), 4.24 (d, J = 15.1 Hz, 1H), 4.60 (d, J = 15.1 Hz, 1H), 6.24 (d, J = 7.5 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.43 (m, 1H), 7.08 (dd, J = 7.4 and 7.4 Hz, 1H), 7.18 (dd, J = 7.4 and 7.4 Hz, 1H), 7.29−7.42 (3H), 7.50 (d, J = 6.6 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.97 (br, 1H); HRMS calcd $C_{32}H_{36}BrN_2O_5$ (MH^+) 607.1808, found 607.1813. Anal. Calcd for $C_{32}H_{35}BrN_2O_5$: C, 63.26; H, 5.81; N, 4.61; Found: C, 63.66; H, 5.95; N, 4.62.

***tert*-Butyl 3-(2,4-Dimethoxybenzyl)-5a-{2-[(diphenylmethylene)-amino]phenyl}-2-oxo-2,3,4,5,5a,10b-hexahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (41).** A pressure tube was charged with **40** (3.76 g, 6.19 mmol), benzophenone imine (1.46 g, 8.05 mmol), $Pd(DPPF)_2Cl_2$ (22.7 mg, 0.031 mmol), DPPF (25.5 mg, 0.046 mmol), sodium *tert*-butoxide (833 mg, 8.67 mmol), and dry toluene (20 mL) and purged with argon gas. The pressure tube was sealed and heated in a 140 °C bath for 24 h. After being cooled to room temperature, the reaction mixture was chromatographed (SiO_2, 8:3 hexane/EtOAc) to afford **41** (2.72 g, 62%). IR: 3060, 2995, 2972, 2932, 1694, 1630, 1615, 1590, 1570, 1504, 1482, 1459, 1366, 1317, 1289, 1256, 1207, 1157, 1132,

749, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 9H), 2.90−3.35 (6H), 3.70 (s, 3H), 3.77 (s, 3H), 4.10 (d, J = 15.4 Hz, 1H), 4.46 (br s, 1H), 4.59 (d, J = 15.4 Hz, 1H), 6.18 (dd, J = 8.5 and 2.4 Hz, 1H), 6.26 (d, J = 8.5 Hz, 1H), 6.27 (br s, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.82−6.98 (4H), 7.06−7.47 (13H); HRMS calcd $C_{45}H_{46}N_3O_5$ (MH^+) 708.3437, found 708.3433.

***tert*-Butyl 5a-(2-Aminophenyl)-3-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,5a,10b-hexahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (42).** To a solution of **41** (1.19 g, 1.68 mmol) in THF (60 mL) was added 2 N aqueous HCl solution (3 mL). After being stirred at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure, then diluted with EtOAc (100 mL) and washed with saturated Na_2CO_3 (50 mL) solution. The aqueous wash was extracted with EtOAc (3 × 20 mL), and the combined EtOAc layers were dried over Na_2SO_4 and concentrated. The crude product was chromatographed (SiO_2, 7:4 hexane/EtOAc as mobile phase) to furnished **42** (1.47 g, 97%). IR: 3477, 3359, 3218, 3069, 3036, 3000, 2971, 2932, 2835, 1695, 1627, 1615, 1591, 1502, 1480, 1456, 1378, 1366, 1318, 1313, 1289, 1258, 1207, 1158, 1091, 1079, 1036, 837, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15 (s, 9H), 2.43 (br s, 1H), 2.94−3.07 (2H), 3.17 (dd, J = 15.6 and 6.6 Hz, 1H), 3.29 (dd, J = 15.6 and 10.0 Hz, 1H), 3.41 (br s, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.26 (d, J = 15.1 Hz, 1H), 4.30 (d, J = 5.2 Hz, 1H), 4.58 (d, J = 15.1 Hz, 1H), 6.23 (dd, J = 8.3 and 2.4 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.44 (br s, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 7.7 and 7.5 Hz, 1H), 7.09−7.17 (2H), 7.24 (d, J = 7.7 Hz, 1H), 7.32 (dd, J = 7.7 and 7.7 Hz, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H); HRMS calcd $C_{32}H_{38}N_3O_5$ (MH^+) 544.2811, found 544.2828. Anal. Calcd for $C_{32}H_{37}N_3O_5$: C, 70.70; H, 6.86; N, 7.73; Found: C, 70.40; H, 7.01; N, 7.26.

5a-(2-Aminophenyl)-3-(2,4-dimethoxybenzyl)-3,4,5,5a,6,10b-hexahydroazepino[4,5-*b*]indol-2(1*H*)-one (43). To a magnetically stirred solution of **42** (1.32 g, 2.4 mmol) in methylene chloride (40 mL) was added trifluoroacetic acid (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 14 h. The reaction mixture was partitioned between ice-cold 2 N NaOH (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined EtOAc extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 6:5 hexane/EtOAc) to afford **43** (1.02 g, 95%). IR: 3322, 3046, 3000, 2955, 2934, 2835, 1644, 1638, 1611, 1589, 1505, 1484, 1456, 1324, 1289, 1257, 1208, 1035, 834, 827, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.72 (dd, J = 15.0 and 8.5 Hz, 1H), 2.43 (dd, J = 15.0 and 8.1 Hz, 1H), 2.86 (dd, J = 15.2 and 2.1 Hz, 1H), 3.08 (dd, J = 15.2 and 8.1 Hz, 1H), 3.51 (dd, J = 14.9 and 7.7 Hz, 1H), 3.69 (m, 1H), 3.71 (s, 3H), 3.78 (s, 3H), 4.28 (br d, J = 7.3 Hz, 1H), 4.34 (d, J = 14.6 Hz, 1H), 4.68 (d, J = 14.6 Hz, 1H), 6.24 (dd, J = 8.3 and 2.3 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.76−6.81 (3H), 6.90 (dd, J = 7.4 and 7.3 Hz, 1H), 7.10−7.16 (3H), 7.37 (d, J = 7.5 Hz, 1H); HRMS calcd $C_{27}H_{30}N_3O_3$ (MH^+) 444.2287, found 444.2292. Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47; Found: C, 73.15; H, 6.72; N, 9.04.

14-(2,4-Dimethoxybenzyl)-11b,12,15,16-tetrahydroazepino[4′,5′:2,3]indolo[1,2-*c*]quinazolin-13(14*H*)-one (44). To a solution of **43** (992 mg, 2.24 mmol) in 2-propanol (20 mL) was added formic acid (20 mL). The reaction mixture was stirred at 75 °C for 4 h. After being cooled to room temperature, the reaction mixture was poured into saturated Na_2CO_3 solution (300 mL) and extracted with EtOAc (4 × 100 mL). The combined EtOAc solutions were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, EtOAc) to afford **44** (730 mg, 72%). IR: 3053, 3036, 2996, 2939, 2835, 1611, 1581, 1554, 1506, 1489, 1468, 1456, 1287, 1263, 1256, 1232, 1207, 1123, 1034, 832, 812, 765, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (dd, J = 14.3 and 8.7 Hz, 1H), 2.08 (dd, J = 14.3 and 8.7 Hz, 1H), 3.04 (dd, J = 15.6 and 8.3 Hz, 1H), 3.28 (dd, J = 15.6 and 8.3 Hz, 1H), 3.54 (dd, J = 15.8 and 6.2 Hz, 1H), 3.60 (s, 3H), 3.62 (d, J = 12.7 and 3.1 Hz, 1H), 3.77 (s, 3H), 4.12 (br, 1H), 4.27 (d, J = 14.5 Hz, 1H), 4.57 (d, J = 14.5 Hz, 1H), 6.25 (dd, J = 8.3 and 2.3 Hz, 1H), 6.33 (d, J = 2.3 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 7.12−7.21 (2H), 7.24 (dd, J = 7.3 and 7.1 Hz, 1H), 7.30−7.41 (4H), 7.57 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H); HRMS calcd $C_{28}H_{28}N_3O_3$ (MH^+) 454.2131, found 454.2114. Anal. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.26; Found: C, 73.56; H, 6.17; N, 9.02.

11b,12,15,16-Tetrahydroazepino[4′,5′:2,3]indolo[1,2-*c*]quinazolin-13(14*H*)-one (6). A solution of **44** (670 mg, 1.48 mmol) in formic acid (10 mL) was heated in a 100 °C bath for 2 h. After being cooled to room temperature, the reaction mixture was poured into saturated Na_2CO_3 solution (150 mL) and extracted with EtOAc (4 × 60 mL). The combined EtOAc solutions were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 10:1 EtOAc/MeOH) to afford **6** (417 mg, 93%). IR: 3200, 3085, 3065, 2945, 2881, 1663, 1273, 1233, 767, 748 cm^{-1}. UV λ_{max} 237 (12 400), 339 (14 500), 352 (9030) nm. ^1H NMR ($CDCl_3$): δ 1.90 (ddd, J = 14.9, 8.7, and 1.6 Hz, 1H), 2.15 (ddd, J = 14.9, 8.7, and 1.6 Hz, 1H), 2.98 (dddd, J = 14.9, 8.7, 3.9, and 1.6 Hz, 1H), 3.11 (dddd, J = 14.9, 8.7, 5.4, and 1.6 Hz, 1H), 3.40 (ddd, J = 16.0, 6.3, and 1.5 Hz, 1H), 3.53 (dd, J = 16.0 and 3.1 Hz, 1H), 4.14 (br dd, J = 6.3 and 3.1 Hz, 1H), 5.71 (br s, 1H), 7.07−7.14 (2H), 7.22−7.30 (2H), 7.35−7.39 (3H), 7.42 (d, J = 7.5 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 35.6, 36.9, 37.0, 46.3, 66.2, 108.8, 122.9, 124.4, 125.6, 126.0, 126.4, 129.2, 129.2, 129.8, 130.3, 140.4, 140.8, 142.1, 173.3; HRMS calcd $C_{19}H_{18}N_3O$ (MH^+) 304.1450, found 304.1449. Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.12; H, 5.65; N, 13.79.

2,10-Dibromo-11b,12,15,16-tetrahydroazepino[4′,5′:2,3]indolo-[1,2-*c*]quinazolin-13(14*H*)-one (45). To a solution of **6** (50 mg, 0.165 mmol) in formic acid (4 mL) was added bromine (1055 mg, 6.6 mmol), and the reaction mixture was stirred at room temperature for 48 h (caution: pressure may develop). The reaction mixture was evaporated under reduced pressure, and the residue was partitioned between 2 N NaOH solution (50 mL) and EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (SiO_2, 10:1 EtOAc/MeOH) to afford **45** (70 mg, 92%). IR: 3340, 3066, 3020, 2978, 2946, 2926, 2847, 1680, 1662, 1638, 1601, 1574, 1543, 1481, 1464, 1315, 1265, 1235, 1205, 1068, 1063, 834, 811 cm^{-1}. UV λ_{max} 245 (11 200), 347 (18 500), 360 (12 500) nm. ^1H NMR ($CDCl_3$): δ 1.89 (dd, J = 15.1 and 8.4, 1H), 2.16 (dd, J = 14.6 and 8.4 Hz, 1H), 3.02 (ddd, J = 14.9, 8.4, and 4.0 Hz, 1H), 3.15 (ddd, J = 14.9, 8.4, and 5.6 Hz, 1H), 3.38 (dd, J = 16.0 and 6.2 Hz, 1H), 3.49 (dd, J = 16.0 and 2.9 Hz, 1H), 4.11 (br dd, J = 6.2 and 2.9 Hz, 1H), 6.06 (br s, 1H), 7.05 (d, J = 6.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 7.44 (s, 1H), 7.49 (dd, J = 8.4 and 1.9 Hz, 1H), 7.56 (s, 1H), 8.01 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 34.9, 36.3, 36.7, 45.6, 66.0, 110.0, 116.7, 118.9, 125.5, 127.2, 128.4, 131.4, 132.0, 132.1, 139.2, 140.0, 172.1 (two aromatic C's are missing); HRMS calcd $C_{19}H_{16}Br_2N_3O$ (MH^+) 459.9661, found 459.9657. Anal. Calcd for $C_{19}H_{15}Br_2N_3O$: C, 49.49; H, 3.28; N, 9.11. Found: C, 49.40; H, 3.40; N, 8.74.

Bromination of 2,10-Dibromo-11b,12,15,16-tetrahydroazepino-[4′,5′:2,3]indolo[1,2-*c*]quinazolin-13(14*H*)-one (45). To a solution of **45** (60 mg) and 1,3-dibromo-5,5-dimethylhydantoin in methylene chloride was added trifluoromethanesulfonic acid. After being stirred at room temperature for 64 h, the reaction mixture was portioned between 2 N NaOH solution (50 mL) and EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was analyzed with LC-MC, and the LC-MC analysis indicated that the crude contains dibrominated, tribrominated, tetrabrominated, as well as more highly brominated products, all as isomeric mixtures.

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Supporting Information Available: ^{1}H NMR spectra of **4**, **9**, **10**, **11**, **12**, **13**, **14**, **5**, **15**, **16**, **17**, **20**, **21**, **22**, **23**, **24**, **25**, **26a**, **26a/26b**, **28**, **29**, **30**, **31**, **32**, **33**, **34**, **36**, **37**, **38**, **39**, **40**, **41**, **42**, **43**, **44**, **6**, and **45**, ^{13}C NMR spectra of **6** and **45** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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