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Reactions of Indole Derivatives with Oxiranes and Aziridines on Silica. Synthesis of β-Carbolin-1-one Mimic of Pancratistatin

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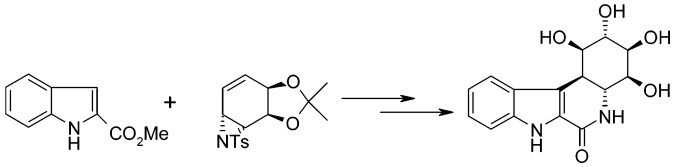

Indole and several indoles functionalized at C-2 were condensed with oxiranes, vinyloxiranes, aziridines, and vinylaziridines in the solid state on the surface of silica. The yields of these reactions were compared to those obtained from Lewis acid-catalyzed ring-opening reactions performed in solution and found to be superior in each case. The solid-phase aziridine opening constituted a key step in the synthesis of the β-carbolin-1-one mimic of pancratistatin. Methyl 2-indolecarboxylate was found to react on the silica gel surface with *N*-tosylvinylaziridine in 68% yield. A nine-step synthesis of the pancratistatin mimic has been attained. The additional key transformation in this synthesis involved silica gel-catalyzed opening of an epoxide and hydrolysis of an acetonide. Detailed experimental procedures and full characterization are reported for all new compounds.

Introduction

Amaryllidaceae constituents pancratistatin (**1**) and narciclasine (**2**) are the most potent anticancer agents isolated from *Pancratium litorale* and *Narcissus poeticus,* respectively.[1] Both compounds have been tested against human cancer cell lines[2] and P388 lymphocytic leukemia with GI_{50} values on the order of 0.02 μg/mL.[3] Their structures continue to elicit the interest of the synthetic community, and many strategically diverse syntheses have been reported.[4,5] Although little is known about the precise mode of action of these compounds, a great deal of effort has been expended in the preparation and biological evaluation of unnatural and truncated derivatives of Amaryllidaceae constituents, including those related to the congeners lacking the 7-hydroxy group, namely 7-deoxypancratistatin (**3**) and lycoricidine (**4**),[6] Figure 1.

For the most part, the activities of unnatural derivatives were 10- to 100-fold lower than those of the natural products.[6a,b,d] The strategy toward developing a better analogue through rational study of structure−activity

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(1) Narciclasine is isolated from the daffodil (*Narcissus poeticus*): (a) Ceriotti, G. *Nature* **1967**, *11*, 595. Pancratistatin was first isolated by Pettit from *Hymenocallis littoralis*, the Hawaiian plant formerly known as *Pancratium littorale*. (b) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693. (c) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995.

(2) Cancer types: P388 (lymphocytic leukemia); human lines BX-PC-3 (pancreas adenocarcinoma); MCF-7 (breast adenocarcinoma); KM20L2 (colon adenocarcinoma); SF268 (CNS gliobaltoma); NCI-H460 (lung large cell), and DU-145 (prostate carcinoma).

(3) GI_{50} may be defined as the in μg/mL cell solution necessary to stop the growth of 50% of the cancer cells. For studies detailing the biological activity of Amaryllidaceae constituents, see: (a) Fitzgerald, D. B.; Hartwell, J. L.; Leiter, J. *J. Nat. Cancer Inst.* **1958**, *20*, 763. (b) Ceriotti, G. *Nature* **1967**, *11*, 595. (c) Carrasco, L.; Fresno, M.; Vazquez, D. *FEBS Lett.* **1975**, *52*, 236. (d) Jimenez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *55*, 53. (e) Jimenez, A.; Santos, A.; Alsonso, G.; Vazquez, D. *Biochim. Biophys. Acta* **1976**, *425*, 342. (f) Pettit, G. R.; Gaddamidi, D. L.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995. (g) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kefauver, D. F.; Pettit, G. R.; Groszek, G.; Hollingshead, M.; Kirsi, J. J.; Shannon, W. M.; Schubert, E. M.; DaRe, J.; Urgarkar, B.; Ussery, M. A.; Phelan, M. J. *J. Nat. Prod.* **1992**, *55*, 1569.

(4) For reviews of synthetic approaches, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A. R., Ed.; Academic: New York, 1987; Vol. 40, p 251. (b) Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, p 109. (c) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, 1998; Vol. 51, p 323. (d) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606. (e) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365.

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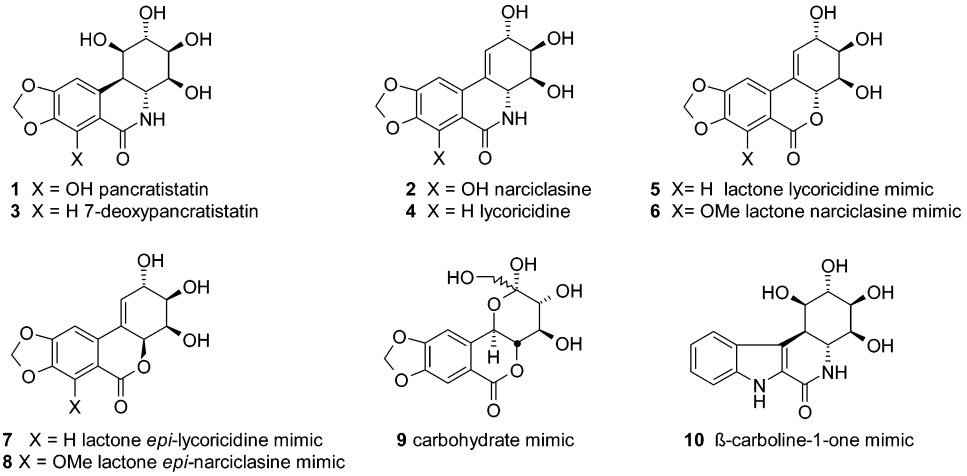

FIGURE 1. Amaryllidaceae constituents and some unnatural mimics.

relationship is hampered by the almost complete lack of understanding of the mode of action of **1** and **2**. A limited study conducted with narciclasine indicated that the mode of action may be connected to the inhibition of protein synthesis by interference with RNA transcription at the ribosomal level.[7] Narciclasine appears to inhibit transfer of the 60S subunit at the 3′ end of the peptidyl transfer center. Pettit devoted considerable effort to the synthesis of pancratistatin-based prodrugs[8] and more bioavailable analogues[9] as well as the chemical conversion of the more abundant member, **2**, into pancratistatin.[10] Thus, at this point we are only able to speculate about the exact mode of interaction of these compounds at the cellular level.

Their structural motifs, however, do permit some degree of speculation. The aminoinositol moiety of **1** and the conduramine unit in **2** are no doubt the structural elements responsible for the antiviral activities reported for these compounds.[3g] On the other hand, the oxygenated phenanthridone unit may be involved in DNA intercalation; this statement would be supported by the observation that the *cis*-fused derivatives of **1** are inactive[11] perhaps because their three-dimensional structures are more concave. Another structural element affecting the levels of activity is the donor−acceptor hydrogen bond pairing found in the 7-hydroxyl derivatives: the enolized β-acylamide moiety of **1** and **2** is responsible for a 10-fold increase in activity over **3** and **4**.[12] Successful binding to DNA domains could be invoked to explain this difference. Until a complete study of the mode of action emerges the efforts toward a more bioavailable or more potent analogue will be guided solely by intuition. Recently, a lactone-containing mimic of **3**, compound **9**, was synthesized,[6c] but no biological data have been reported for this compound. However, a recent disclosure of Chapleur[13] provided further insight into the importance of the amide functionality. Lactone analogues of lycoricidine (Figure 1, **5** and **7**) and narciclasine (Figure

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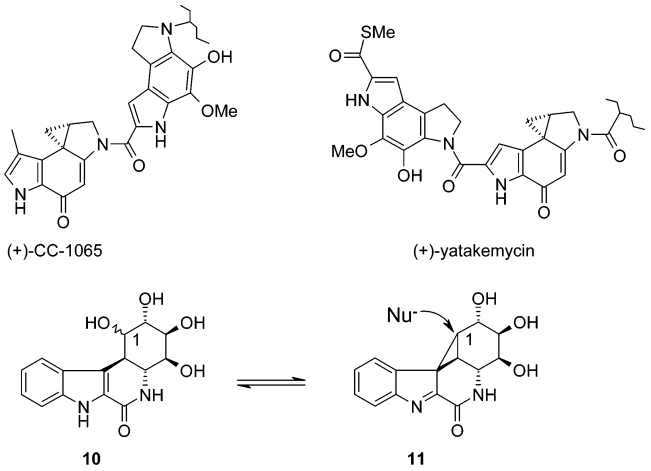

FIGURE 2. Cyclopropylindolenine generation from β-carbolin-1-one mimics and structural comparison to DNA-binding cyclopropylquinoids.

1, **6** and **8**) have been synthesized and shown to be completely inactive in screening against cancer cell lines, suggesting that the amide moiety is essential for activity.

We became interested in the synthesis of indole-containing analogues of **1** on the basis of several ideas. First, indoles found in agents such as CC-1065[14] or yatakemycin[15] generate reactive cyclopropylquinoid species that covalently attach to AT-rich regions of DNA. Second, the design of indole mimics of **1**, such as **10**, permits the preparation of cyclopropylindolenines **11**, which could trigger interactions similar to those observed for CC-1065 type compounds, as shown in Figure 2.

Third, serotonin-regulating activites have been associated with compounds that display the β-carbolin-1-one or constrained tryptamine motifs, both of which are found in **10**. The indole mimic has been compared to pancratistatin in modeling of the electrostatic potential energy surface and was shown to have significant structural and electrostatic overlap with the natural product except for the benzene portion of the indole region.[16] In this paper, we report the details of a nine-step synthesis of **10** along with a study of the silica surface catalysis in the reaction of indole derivatives with strained three-membered heterocycles.

Results and Discussion

Reactions of indole with electrophiles at C-3 under Lewis or protic acid catalysis are well documented,[17] although strongly acidic conditions lead to the formation of indirubin, indigo, and other dimers. Under weakly acidic conditions, i.e., 10% HOAc aq, indole reacts with cyclic imines in high yield as demonstrated in the synthesis of aspidosperma alkaloids by Wenkert.[18] Lewis acid catalysis by lanthanides (In or Sc) permits the synthesis of tryptamines and tryptophols through the opening of aziridines (or Mannich products) and epoxides, respectively.[19] Silica gel[20] and alumina[21] have been widely used as both acid or surface catalysts, and in general, the use of such catalysts leads to either milder conditions or rate acceleration or both. In addition, zeolite catalysts used in conjunction with transition metals have recently been shown[22] to promote electrophilic substitution reactions between indole and aldehydes. A silica gel-supported ionic liquid catalyst system has also been shown to facilitate oxime-carbonyl transformations under relatively mild conditions.[23] A recent report from Baskaran decribes the opening of *N*-tosylaziridines by various nucleophiles catalyzed by phosphomolybdic acid on a silica gel surface,[24] although no example of this reaction employing aromatic nucleophiles is offered in this paper.

We chose to investigate a series of epoxides and aziridines in their reactivity toward indole, indole-2-methylcarboxylate, and indole-3-methylcarboxylate as such reactions would lead to the above-mentioned tryptamine or tryptophol derivatives. The reactions were performed by adsorbing a solution of both reactants in methylene chloride on previously activated silica gel, evaporating to dryness, and heating the solid mixture under argon atmosphere at 70 °C for 15−48 h. In all cases, a 3-fold excess of the indole nucleophile was added to the epoxide or aziridine. Considering the success of the recently reported $InCl_3/CH_2Cl_2$ solution catalysis[25] and silica surface catalysis, we developed a hybrid $InCl_3$/silica catalyst system in which 5% (by weight) $InCl_3$ was added to silica gel before the standard activation protocol. We hoped initially that the reactions could be performed at room temperature; however, heating was required in order to effect opening of azirdines and epoxides in the presence $InCl_3$ on silica. The products derived from the $InCl_3$-treated silica gel contained a significant amount of impurities in both the aziridine and epoxide series. The reactivity of an alternative $InCl_3$/silica surface (entry **d** in Table 1) was examined by pretreating silica gel with 10% aq $InCl_3$ prior to the standard activation protocol and the yield found to be equal to that for 5% $InCl_3$-doped silica surface reactions in the case of epoxide **14**. Our results demonstrate that the mildest and the most

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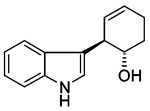
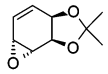
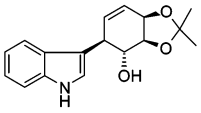
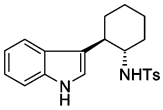
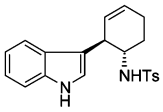
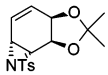
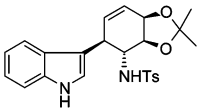
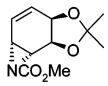
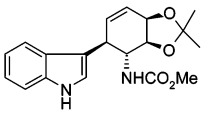
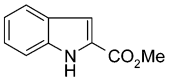
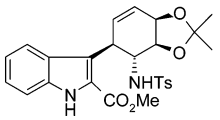
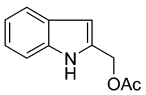
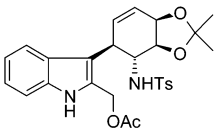
TABLE 1. Reaction of Epoxides and Aziridines with Indole on Silica and in Solution

Electrophile*	Condensation product	Yield**
 13	 19	**a) 32%** b) 22% c) 51%
 14	 20	**a) 51%** b) 8% c) 17% d) 17%
 15	 21	**a) 38%** b) <5% c) 26%
 16	 22	**a) 76%** b) 25% c) 66%
 17	 23	**a) 48%** b) 8% c) 31% d) – e) 70%; rt, TLC plate
 18	 24	**a) 29%** b) not determined c) not determined

* Electrophiles **13**−**18** were prepared according to literature procedures. References may be found in the Supporting Information. ** Yields are isolated: (a) silica gel surface at 70 °C; (b) 0.1 equiv of $InCl_3$ in CH_2Cl_2; (c) $InCl_3$-doped silica at 70 °C; (d) 10% aq $InCl_3$-treated silica at 70 °C; (e) rt, TLC plate silica.

TABLE 2. Reaction of 2-substituted Indoles with Aziridine 17

Indole nucleophile	Condensation product	Yield*
 25	 27	**a) 68%** b) NR c) NR
 26	 28	**a) 24%** b) NR c) not determined

* Yields are isolated: (a) silica gel surface at 70 °C; (b) 0.1 equiv of $InCl_3$ in CH_2Cl_2; (c) $InCl_3$-doped silica at 70 °C.

efficient method for the ring-opening catalysis in the presence of several indole nucleophiles is the silica-surface reaction (entry **a** in Tables 1 and 2). The results of these experiments are shown in Tables 1 and 2.

We were initially concerned about the possibility of vinyl epoxide opening at the distal olefinic center via an S_N2' mechanism (producing **20-alt** in Figure 3), rather than the expected 1,2-opening resulting from an S_N2-like mechanism. A detailed NMR study demonstrated that the opening of vinyl epoxide **14** occurred in a 1,2-fashion to yield compound **20**. The sequence 3.54−3.89−4.22−4.76 ppm, revealed by the coupling constants seen in the ^1H NMR spectrum, supports the connectivity assignment in **20**. The proton at 3.54 ppm is adjacent to the indole ring because it couples with three carbons of the indole moiety. One can easily make three arguments for assignment of structure **20**, as opposed to **20-alt**: (i) the proton at 3.89 ppm displays two large couplings, 9.0 and 10.0 Hz; therefore, it is axial and its vicinal protons at 3.54 and 4.22 ppm are also axial, which would imply a *trans* relationship of the protons in the acetonide moiety in **20-alt**; (ii) the chemical shifts of the protons at 4.22 and 4.76 ppm and their coupling constant of 6.6 Hz are expected for the acetonide moiety represented in **20**; (iii) the proton at 1.45 ppm displays an NOE with the protons at 4.76, but not with that at 3.89 ppm.

Synthesis of β-Carbolin-1-one Mimic. The initial strategy for the synthesis of **10** was pursued with the well-documented premise in mind that indoles substituted at C-3 readily participate in the Pictet−Spengler reaction at C-2.[26] Thus, compound **24**, prepared by the silica gel-promoted condensation of *N*-carbomethoxyaziridine **18** and indole, was subjected to the modified conditions of Banwell[27] in an attempt to generate the β-carbolin-1-one nucleus as shown in Scheme 1. However, in our hands, treatment of **24** with 5 equiv of triflic anhydride and 3 equiv of DMAP in methylene chloride failed to effect the desired closure to **30**, possibly because of the reactive nature of the indole nitrogen toward triflic anhydride, the product of which would contribute toward deactivating the nucleophilicity at the indole C-2 position. An additional competitive reaction pathway that was observed under forcing conditions was the aromatization of the aminocyclitol portion in compound **24**.

Our preliminary silica-surface reactions established that *N*-tosylaziridines are superior electrophiles to *N*-carbomethoxy- or *N*-Boc-protected aziridines toward indole nucleophiles. The initial ring-opening experiments simply involved pouring a solution in methylene chloride of both indole nucleophile and aziridine electrophile onto an analytical TLC plate and allowing the plate to stand at rt for 12 h. The silica gel containing the adsorbed

(26) For comprehensive reviews of the Pictet−Spengler reaction, see: (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151. (b) Abramovitch, R. D.; Spenser, I. D. *Adv. Heterocycl. Chem.* **1964**, *3*, 79. (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. For applications of the Pictet−Spengler cyclization in the synthesis of natural products, see: (d) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead *J. Am. Chem. Soc.* **1956**, *78*, 2023. (e) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4894. (f) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428. (g) Zhao, S.; Liao, X.; Wang, T.; Flippen-Anderson, J.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 6279. (h) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929. (i) For a discussion of the mechansim of the Pictet−Spengler reaction in 3-substituted indoles, see: Harley-Mason, J.; Kaplan, M. *J. Chem. Soc., Chem. Commun.* **1967**, 915.

(27) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551.

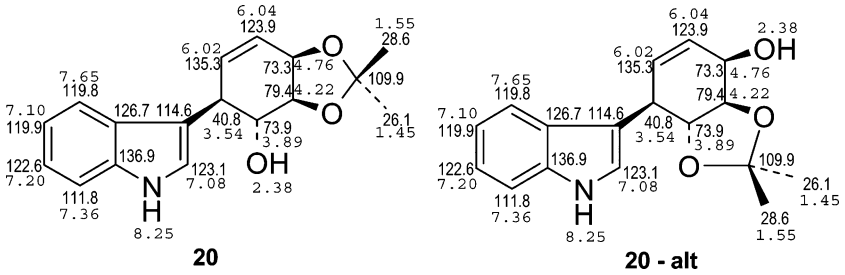
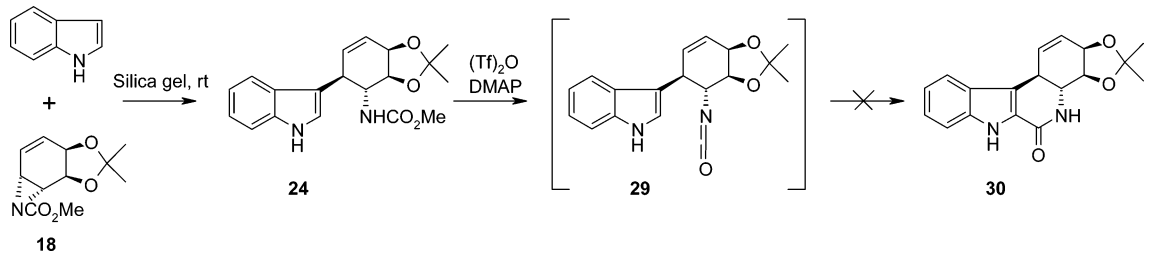
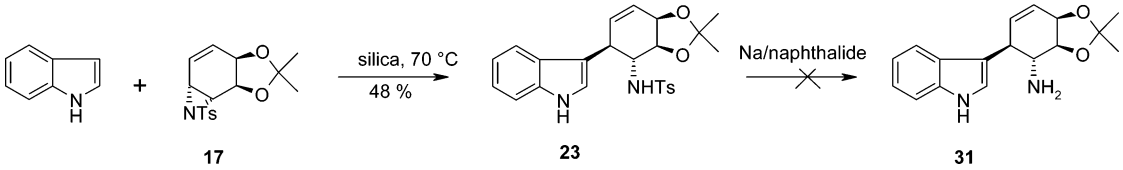


FIGURE 3. ^{1}H and ^{13}C chemical shift assignments in **20**.

SCHEME 1



SCHEME 2



reaction mixture was transferred to a flash silica gel column and eluted to provide the condensation product in 70% yield. Changing to flash chromatography grade silica and heating the adsorbed mixture of reactants to 70 °C provided 48% isolated yield of **23**.

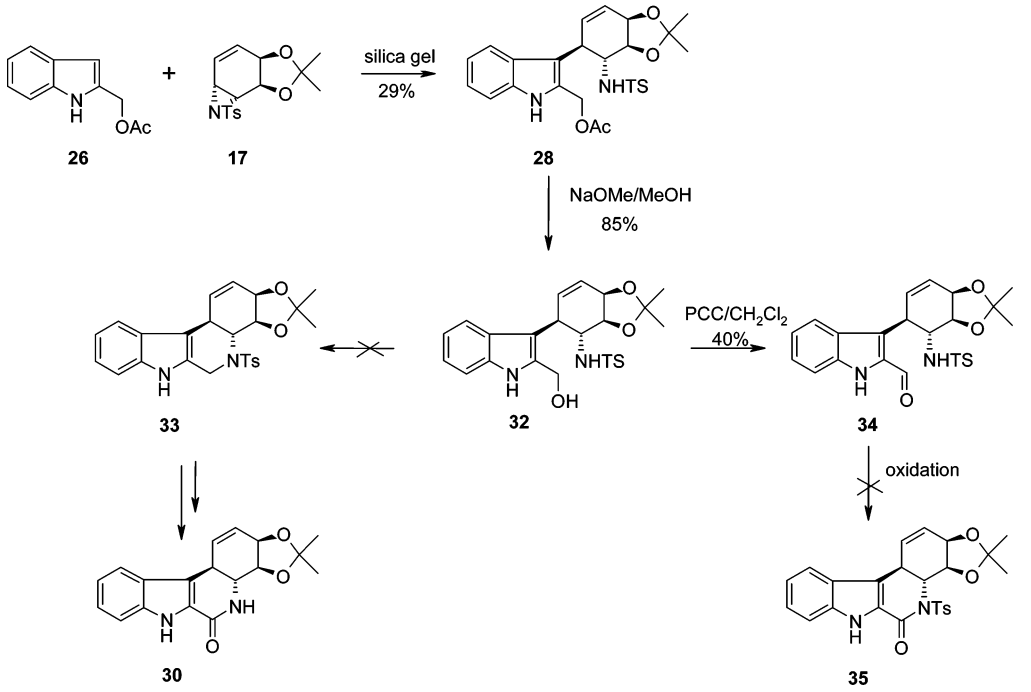
Encouraged by the results of silica catalysis in the condensation of indole with tosylaziridines and the high yield of tosyl amide **23** (entry **e** in Table 1), we attempted its reductive deprotection to **31**, Scheme 2. Only partial reduction of the indole nucleus was observed, and the free amine **31** was not obtained.

We next examined the reactions of a 2-substituted indole, acetate **26**, with aziridine **17** in the presence of silica gel at room temperature, providing tosylamide **28** in a modest, unoptimized, yield of 29% (Scheme 3). The free alcohol **32**, obtained by treatment of acetate **28** with sodium methoxide in methanol, was then subjected to pyridinium chlorochromate (PCC). Aldehyde **34** was isolated and subjected to a variety of oxidizing conditions. PCC was employed in an attempt to oxidize any hemiaminals formed from the closure of the tosyl amide onto the aldehyde, thus driving the equilibrium toward the desired amide. Unfortunately, treatment of **34** with PCC returned the starting material unchanged. When treated with sodium hypochlorite, aldehyde **34** was converted to the corresponding carboxylic acid, however without subsequent ring closure to the lactam. Under more vigorous oxidizing conditions, i.e., Jones reagent, decomposition of the starting material was observed. Since it has been shown that tosylamides of type **33** are easily oxidized to imides, which are readily detosylated under mild conditions such as sodium naphthalide,[5w] such an approach would allow the installation of the C-6 carbonyl. We also attempted the closure of **32** to **33** under a variety of conditions but without success. The failure of these compounds to form the phenanthridone indicates that atropisomers exist in this series and are sterically indisposed to the ring closure, in analogy with the established precedent for such isomerism.[5b,d]

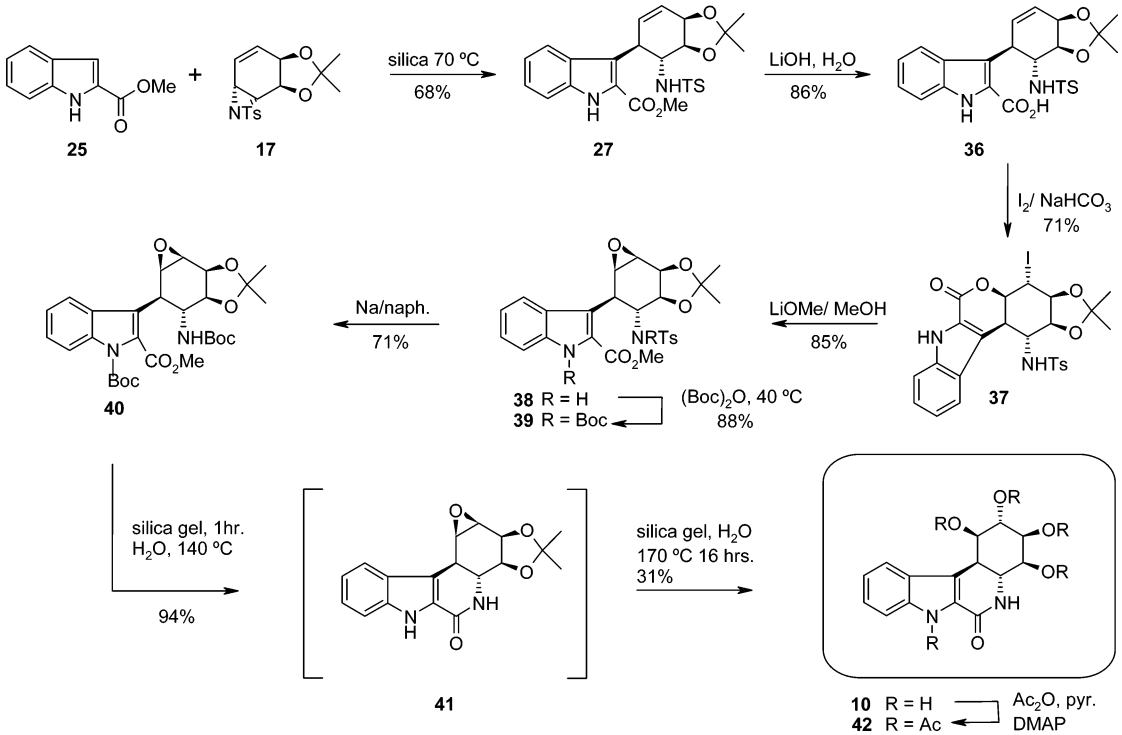
To circumvent problems with the formation of the phenanthridone amide bond, indole-2-methylcarboxylate **25** was used as shown in Scheme 4. We were delighted that indole-2-methyl ester condensed with tosylaziridine **17** and provided tosylamide **27** in good yields when adsorbed on silica and heated at 70 °C for 48 h. This result was especially surprising in view of the fact that Lewis acid catalysis in solution did not produce significant amounts of **27**. We attributed the low reactivity to the decreased electron density at C-3 because of the fully conjugated vinylogous urethane moiety in indole-2-carboxylate. To avoid indole oxidation during functionalization of the cyclohexene, ester **27** was hydrolyzed to its acid with LiOH and immediately subjected to the modified Danishefsky iodolactonization conditions reported by Jung[28] to produce iodolactone **37**, Scheme 4. This material was converted to methyl ester **38**, and both nitrogen atoms were protected as Boc-carbamates **39**, rendering the tosylamide moiety more reactive toward its reductive removal. We were not able to effect selective acylation of the tosylamide nitrogen under neutral or basic conditions because of similar acidity and nucleophilicity of the indole and tosylamide nitrogen atoms. We originally attempted to selectively protect the *N*-tosyl as its carbamate in ester **27** early in the synthesis. When **27** was subjected to

(28) Jung, M.; Ham, J.; Song, J. *Org. Lett.* **2002**, *4*, 2763.

SCHEME 3



SCHEME 4



standard carbamate protection conditions (NEt_3/Boc_2O, 2 equiv), the indolyl nitrogen was selectively protected in favor of the more deactivated *N*-tosyl species; higher temperatures (>50 °C) led to the aromatization of the aminocyclitol moiety. A solution to these selectivity and thermal stability issues was realized by treatment of methyl ester **38** with 2.5 equiv of sodium hydride followed by neat Boc-anhydride at 40 °C for 48 h. The corresponding bis-protected material **39** was cleanly detosylated upon treatment with Na/naphthalide to provide bis-Boc derivative **40**.

The Boc-amide **40** was adsorbed on silica suspended in distilled water and heated at 140 °C for 1 h in a capped thick-walled tube. These conditions resulted in smooth deprotection of both Boc-groups via a thermal retro-ene reaction and the intramolecular closure to β-carbolin-1-one **41**. Further heating at 170 °C for 16 h resulted in the opening of the epoxide as well as the hydrolysis of the acetonide to provide **10** in 31% overall yield. The last sequence of reactions is noteworthy for several reasons. First, the conditions of the reaction are essentially neutral. Second, under such conditions, epoxides or

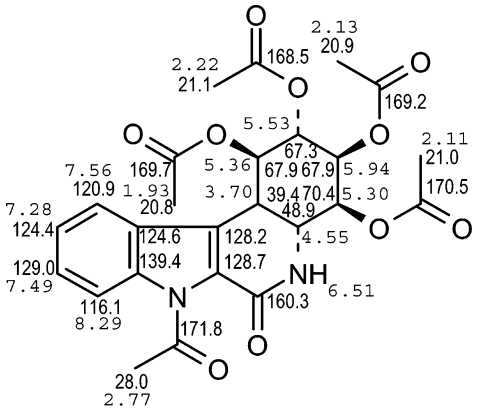


FIGURE 4. ^{1}H and ^{13}C chemical shift assignment in tetraacetate **42**.

acetonides would not be expected to hydrolyze. Third, these conditions are similar, at least as far as pH is concerned, to those consisting of 5% aqueous sodium benzoate reported for hydrolysis of acetonide in D-*chiro*-inositol synthesis.[29] The dilute aqueous solution of sodium benzoate is nearly neutral, but the isolation of products is complicated by the presence of benzoic acid and its salts. Under such conditions epoxides are difficult to hydrolyze as well. We attribute the success of this sequence entirely to the previously reported rate accelerations observed for reactions conducted on silica or alumina surfaces.[20−24]

Tetrol **10** was isolated by filtering the silica slurry, washing the residual silica copiously with methanol, and evaporating the filtrate to dryness. The material, insoluble in most solvents except for methanol and acetone, was converted to its tetraacetate **42** (pyr, Ac_2O, DMAP), which was then characterized by HMBC, HMQC, and NOE NMR techniques. The assignment of the ^{1}H and the ^{13}C chemical shifts in **42** is given in Figure 4.

All of the intermediates in the synthesis of **10** have been screened in a panel of human cancer lines and were found to be moderately active. The results of the screening were reported in the preliminary communication.[16] We were surprised to find that the most active compound was the iodolactone **37**—its activity against pancreatic adenocarcinoma BXPC-3 was at 1.9 μg/mL about 100-fold less than that of pancratistatin. It is active also against breast adenocarcinoma MCF-7 (4.3 μg/mL) and P388 lymphocytic leukemia (11.7 μg/mL). It is interesting to note that certain iodolactones have been identified as antineoplastic agents in breast tumors where they are synthesized enzymatically.[30] Iodine-rich diet was linked to lower coincidence of breast cancers. The iodolactone **37** was essentially inactive against colon adenocarcinoma (KM20L2), whereas epoxides **38** and **41** show reasonable activity against this particular cell line. This difference seems to indicate that a different mechanism may be expected to operate at the cellular level for these compounds as it might be envisioned that the iodolactone would be converted in vivo to the epoxy carboxylate such as **38**, which was found to be inactive. This is a promising result that merits further investigation and analogue development.

Conclusion

The enhanced reactivity of indoles with aziridines and epoxides on silica surface bodes well for further applications to synthesis of indole derivatives. The investigations of the β-carbolin-1-one mimic of pancratistatin provided further insight into the biological activity of Amaryllidaceae constituents. It is noteworthy that its synthesis represents to date the shortest approach to compounds containing an aminoinositol motif attached to an aromatic nucleus. Further modifications of the pancratistatin pharmacophore should address changes in the aromatic portion only, as it now appears that both the aminoinositol and the enolized acylamide moieties are essential for high levels of activity. Progress in the development of analogues and the results of their screening will be reported in due course.

Experimental Section

2-(1*H*-Indol-3-yl)cyclohex-3-enol (19). Indole (367 mg, 3.12 mmol, 3 equiv) and vinyl epoxide **13** (100 mg, 1.04 mmol, 1.0 equiv) were heated on a previously activated silica gel surface (1.0 g) at 70 °C for 27 h as described in the general procedure (Supporting Information). The silica gel supporting the reaction mixture was cooled to rt and chromatographed directly on flash silica (hexanes/ethyl acetate; gradient elution, 4:1 to 1:1), providing the title compound as an off-white crystalline solid (68 mg, 32%). The crystalline material was recrystallized from methylene chloride/pentane to obtain product of higher purity: R_f 0.5 (hexanes−ethyl acetate, 1:1); mp (sealed tube) 121−122 °C; IR (film) ν 3543, 3410, 3056, 3022, 2922, 1618, 1456, 1433, 1339, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.15 (m, 1H), 7.00 (m, 2H), 5.77 (m, 1H), 5.66 (dd, J = 9.7, 1.2 Hz, 1H), 3.91 (ddd, J = 10.3, 7.3, 2.9 Hz, 1H), 3.48, (m, 1H), 2.2 (m, 2H), 1.98 (m, 1H), 1.84 (bs, 1H), 1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 129.0, 127.4, 127.0, 122.9, 122.6, 120.0, 119.8, 117.2, 111.7, 72.3, 43.4, 29.4, 24.8; HRMS (EI) calcd for $C_{14}H_{15}NO$ 213.1153, found 213.1148.

5-(1*H*-Indol-3-yl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxol-4-ol (20). Indole (211 mg, 1.8 mmol, 3 equiv) and vinyl epoxide **14** (100 mg, 0.60 mmol, 1.0 equiv) were heated at 70 °C on a previously activated silica gel surface (600 mg) for 20 h as described in the general procedure (Supporting Information). The reaction mixture on silica gel was purified by chromatography on flash silica gel (hexanes/ethyl acetate; gradient elution, 4:1 to 1:1), providing a foamy solid (86 mg, 51%): R_f 0.28 (pentane/ethyl acetate, 1:1); $[\alpha]^{28}_{D}$ +35.45 (*c* 0.35, MeOH); IR (film) ν 3407, 2927, 1456,1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.12 (m, 1H), 7.05−6.95 (m, 2H), 5.93 (s, 2H), 4.66 (d, J = 6.2 Hz, 1H), 4.12 (m, 1H), 3.80 (t, J = 9.3 Hz, 1H), 3.45 (d, J = 9.8 Hz, 1H), 2.21 (bs, 1H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 135.6, 126.8, 123.9, 123.2, 122.7, 119.9, 119.8, 114.5, 111.0, 79.4, 74.0, 73.2, 40.9, 28.7, 26.2; HRMS (EI) calcd for $C_{17}H_{19}NO_3$ 285.1364, found 285.1364.

***N*-[2-(1*H*-Indol-3-yl)cyclohexyl]-4-methylbenzenesulfonamide (21).** Indole (95 mg, 0.81 mmol, 3 equiv) and *N*-tosylaziridine **15** (68 mg, 0.27 mmol, 1.0 equiv) were heated on a previously activated silica gel surface (800 mg) at 70 °C for 22 h according to the general procedure. The silica gel containing the adsorbed reaction mixture was loaded onto a chromatography column, and the condensation product was purified by flash chromatography (hexanes/ethyl acetate 4:1),

(29) Mandel, M.; Hudlicky, T.; Kwart, L. D.; Whited, G. M. *J. Org. Chem.* **1993**, *58*, 2331.

(30) Torremante, P. *Dtsch. Med. Wochenschr.* **2004**, 641. We thank Dr. Med. Pompilio Torremante for communicating these facts to us and providing his paper on the subject.

affording **21** as a white foam (38 mg, 38%): R_f 0.22 (hexanes/ethyl acetate, 2:1); IR (film) ν 3404, 2930, 1598, 1457, 1316, 1157, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.27 (m, 2H), 7.16 (m, 3H), 6.90 (m, 3H), 6.75 (d, J = 2.5 Hz, 1H), 4.51 (d, J = 3.3 Hz, 1H), 3.17 (m, 1H), 2.65 (dt, J = 11.2, 3.5 Hz, 1 H), 2.50 (m, 1H), 2.33 (s, 3H), 1.95 (m, 1H), 1.75 (m, 3H), 1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.0, 136.9, 136.5, 129.4, 126.9, 126.4, 122.2, 122.1, 119.4, 116.7, 111.7, 57.5, 42.0, 35.1, 33.7, 26.4, 25.3, 21.8; HRMS (EI) calcd for $C_{21}H_{24}N_2O_2S$ 368.1558, found 368.1553.

***N*-[2-(1*H*-Indol-3-yl)cyclohex-3-enyl]-4-methylbenzenesulfonamide (22).** Indole (141 mg, 1.2 mmol, 3 equiv) and vinyl aziridine **16** (100 mg, 0.40 mmol, 1.0 equiv) were heated on a previously activated silica gel surface (1.0 g) at 70 °C for 20 h as described in the general procedure. The silica gel supporting the starting materials was directly loaded onto a flash silica gel column and the condensation product purified by flash chromatography (hexanes/ethyl acetate; gradient elution, 4:1 to 2:1), providing the tosyl derivative **22** as an off-white solid (112 mg, 76%): R_f 0.2 (pentane/ethyl acetate, 3:1); mp 158−160 °C; IR (film) ν 3406, 3285, 3027, 2924,2860, 1598, 1493, 1457, 1420, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.35−7.20 (m, 2 H), 7.17−7.10 (m, 2H), 7.0 (d, J = 8.0 Hz, 2H), 6.97 (m, 1H), 6.82 (s, 2H), 5.88 (m, 1H), 5.65 (d, J = 9.5 Hz, 1H), 4.85 (d, J = 5.3 Hz, 1H), 3.50 (s, 2H), 2.33 (s, 3H), 2.20 (s, 2H), 2.05−1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.1, 137.0, 129.7, 128.1, 127.6, 127.2, 123.3, 122.4, 119.7, 119.4, 166.5, 111.5, 53.4, 39.9, 26.3, 22.8, 21.9; HRMS (EI) calcd for $C_{21}H_{22}N_2O_2S$ 366.1401, found 366.1398.

3-Indolyl-1*H*-3-(2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-[1,3]dioxolyl)-4-tosylamine (23). Indole (73 mg, 0.621 mmol, 2.0 equiv) and vinyl aziridine **17** (100 mg, 0.311 mmol, 1.0 equiv) were allowed to react on a previously activated silica gel surface (1.0 g) at 70 °C for 17 h as described in the general procedure. The silica gel supporting the adsorbed reaction mixture was loaded onto a flash silica column and eluted with hexanes/ethyl acetate; 4:1 to 2:1, to give the title compound as a brown crystalline solid (130 mg, 48%): R_f 0.26 (hexanes/ethyl acetate, 1:1); $[\alpha]^{19}_D$ +59 (c 0.99, $CHCl_3$); IR (film) ν 3389, 3039, 2985, 2931, 1718, 1621, 1599, 1458, 1375, 1246, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.30−7.15 (m, 4H), 7.10 (m, 1H), 6.97 (m, 2 H), 6.83 (d, J = 7.5 Hz, 2 H), 5.93 (s, 2H), 5.12 (d, J = 7.3 Hz, 1H), 4.65 (m, 1H), 4.19 (m, 1H), 3.75 (dd, J = 17, 8.4 Hz, 1H), 3.49 (d, J = 9.8 Hz, 1H), 2.26 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 138.3, 136.8, 135.9, 129.0, 126.8, 126.6, 123.6, 123.5, 122.2, 119.7, 119.3, 114.1, 110.1, 72.7, 57.5, 39.4, 28.4, 26.4, 21.8; HRMS (EI) calcd for $C_{24}H_{26}N_2O_4S$ 438.16158, found 438.16114. Anal. Calcd for $C_{24}H_{26}N_2O_4S\cdot H_2O$: C, 63.14; H, 6.18. Found: C, 63.32; H, 5.95.

3-Indolyl-1*H*-3-(2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-[1,3]dioxole)-4-methylcarbamate (24). To a solution of indole (0.97 g, 8.29 mmol, 1.6 equiv) and vinyl aziridine **18** (1.0 g, 5.18 mmol, 1.0 equiv) in 20 mL of methylene chloride was added a catalytic amount of $InCl_3$ (115 mg, 0.52 mmol, 0.1 equiv). The solution was stirred at rt until total consumption of starting material was observed by TLC (24 h). The solvent was removed under reduced pressure and the residue purified by flash chromatography (gradient elution, hexanes/ethyl acetate, 5:1 to 3:1), affording 390 mg of the condensation product (22%): R_f 0.21 (hexanes/ethyl acetate, 2:1); IR ν 3334, 1704, 1532 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (bs, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1 H), 7.40 (t, J = 7.9 Hz, 1H), 7.32 (m, 2H), 6.28 (d, J = 9.9 Hz, 1H), 6.18 (dt, J = 10.2, 3.5 Hz, 1H), 4.93 (t, J = 5.0 Hz, 1H), 4.83 (m, 1H), 4.63 (bs, 1H), 4.10 (bs, 1H), 4.01 (t, J = 9.1 Hz, 1H), 3.68 (bs, 3H), 1.77 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 136.9, 136.7, 127.0, 122.8, 122.6, 122.1, 119.1, 115.1, 111.6, 109.8, 76.8, 72.8, 60.5, 55.8, 51.9, 38.3, 28.5, 26.2; HRMS (EI) calcd for $C_{19}H_{22}O_4N_2$ 342.1580, found 342.1580.

2-Methyl{1*H*-3-(2,2-Dimethyl-3a,4,5,7a-tetrahydrobenzo-[1,3]dioxolyl)-4-tosylamine}-3-indolylcarboxylate (27). To a solution of indole-2-carboxylic acid methyl ester **25** (6.0 g, 34 mmol) and vinyl aziridine **17** (3.1 g, 9.5 mmol) in methylene chloride (100 mL) was added dry silica gel (approximately 50 g; 250−400 mesh). The solvent was removed under reduced pressure and the adsorbed material was heated to 70 °C for 48 h under argon atmosphere. After the material was cooled to room temperature, the silica was loaded on a chromatography column, and the reaction mixture was purified by flash column chromatography (hexanes/ethyl acetate 3:1), affording coupled product **27** as yellow oil (3.2 g; 6.4 mmol; 68%): R_f 0.20 (hexanes/ethyl acetate, 1:1); $[\alpha]^{28}_D$ −15.5 (c 1.05 $CHCl_3$); IR ν 3327, 2986, 1692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (bs, 1 H), 7.62 (d, J = 8.2 Hz, 2 H), 7.18−7.34 (m, 3 H), 7.06 (t, J = 7.0 Hz, 1 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.02−6.14 (m, 2 H), 5.22 (d, J = 8.2 Hz, 1 H), 4.72 (m, 1 H), 4.41 (d, J = 9.9 Hz, 1 H), 4.14 (dd, J = 9.6, 5.8 Hz, 1 H), 3.94 (s, 3 H), 3.80 (q, J = 9.9 Hz, 1 H), 2.25 (s, 3 H), 1.55 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 141.8, 139.0, 136.2, 135.7, 128.8, 126.3, 126.1, 123.8, 123.6, 122.4, 122.2, 120.8, 112.2, 110.1, 79.3, 72.8, 58.5, 52.4, 38.5, 28.4, 26.4, 21.7; HRMS (EI) calcd for $C_{26}H_{28}SN_2O_6$ 496.1668, found 496.1668.

2-Methyl{1*H*-3-(2,2-Dimethyl-3a,4,5,7a-tetrahydrobenzo-[1,3]dioxolyl)-4-tosylamine}-3-indolylacetate (28). Acetic acid 1*H*-indol-2-ylmethyl ester **26** (315 mg, 1.82 mmol 1.2 equiv) and *N*-tosylaziridine **17** (490 mg, 1.52 mmol, 1.0 equiv) were dissolved in 2 mL of freshly distilled methylene chloride and the silica gel containing the adsorbed starting materials poured over silica gel (1.0 g) in a 50 mL round-bottomed flask. The solvent was evaporated under reduced pressure, and the silica was allowed to stand at rt for a period of 16 h. The silica gel containing the crude reaction mixture was poured onto a flash silica gel column and the condensation product purified by flash chromatography (gradient elution, hexanes/ethyl acetate 5:1 to 1:1) affording the title compound as a tan solid (189 mg, 24%): R_f 0.2 (hexanes/ethyl acetate, 1:1); $[\alpha]^{23}_D$ = +58.7 (c 0.985, $CHCl_3$); IR (film) ν 3341, 2984, 2932, 1725, 1598, 1494, 1457, 1372, 1324, 1244, 1218, 1155; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (bs, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.19 (m, 2H), 7.07 (d, J = 8.5 Hz, 2H), 7.00 (t, J = 6.7 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.07, (dt, J = 10.0, 3.6 Hz, 1H), 5.94 (d, J = 9.7 Hz, 1H), 5.17 (d, J = 13.3 Hz, 1H), 5.09 (d, J = 13.1 Hz, 1H), 4.71 (m, 2H), 4.17 (dd, J = 9.5, 5.9 Hz, 1H), 3.76 (m, 1H), 3.53 (m, 1H), 2.25 (s, 3H), 2.14 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 141.9, 138.2, 136.2, 136.0, 130.2, 128.7, 126.2, 126.1, 123.7, 122.9, 120.2, 119.8, 113.5, 111.5, 110.1, 78.7, 72.8, 57.5, 57.3, 38.8, 28.3, 26.3, 21.6, 21.2; HRMS (EI) calcd for $C_{27}H_{30}N_2O_6S$ 510.1846, found 510.1824.

5-(1*H*-2-Carboxyindol-3-yl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxol-4-tosylamine (34). To a solution of acetate **28** (70 mg; 0.14 mmol) in 5 mL of methanol was added a solution of sodium methoxide in methanol (1.0 M; 68 μL, 0.069 mmol). The solution turned yellow immediately. The reaction mixture was stirred at rt until complete consumption of the starting material (15 min). The reaction was quenched with aq NH_4Cl (5 mL), and 15 mL of water was added to the reaction mixture. The contents of the reaction were transferred to a separatory funnel and extracted with ethyl acetate (6 × 20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent removed in vacuo affording alcohol **32** (62 mg, 97%), which was used in the subsequent reaction without purification.

To a solution of alcohol **32** (50 mg, 0.106 mmol) in 10 mL of dichloroethane was added PCC (46 mg, 0.212 mmol, 2 equiv). The solution was stirred at rt until total consumption of the starting material occurred (1 h). The solvent was removed under reduced pressure and the residue purified by flash column chromatography (hexanes/ethyl acetate, 2:1) affording the title compound **34** (21 mg, 40%): R_f 0.35 (hexanes/ethyl acetate 1:1); IR (neat) ν 3428, 1644 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 9.95, (s, 1H), 8.96 (bs, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.33 (ddd, J = 9.3, 6.7, 0.9 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.10 (m, 3H), 6.83 (d, J = 7.9 Hz, 2H), 6.12 (ddd, J = 9.6, 6.4, 4.8 Hz, 1H), 6.01 (d, J = 10.5 Hz, 1H), 5.39 (d, J = 8.2 Hz, 1H), 4.76 (t, J = 4.8 Hz, 1H), 4.22 (dd, J = 9.3, 5.8 Hz, 1H), 4.05 (d, J = 10.5 Hz, 1 H), 3.92 (m, 1H), 2.26 (s, 3H), 1.54 (s, 3H), 1.42 (s, 3H); HRMS (EI) calcd for $C_{25}H_{26}O_3N_2S$ 466.1562, found 466.1575.

3-Indolyl-2-{1*H*-3-(2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxolyl)-4-tosylamine}carboxylic Acid (36). To a solution of methyl ester **27** (700 mg; 1.41 mmol) in 15 mL of THF was added a solution of lithium hydroxide (2.50 g; 60 mmol) in water (15 mL). The resulting heterogeneous reaction mixture was stirred for 14 h at rt. The layers were separated and the aqueous phase acidified with 1 M HCl to a pH of approximately 4 before the water layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford 620 mg (86%) of acid **36** as a pale yellow oil. The title compound was used in the subsequent reaction without further purification.

1-Iodo-2(*S*),3(*S*)-hexahydro-2,3-dimethylbenzodioxol-5(*R*)-[3-indolyl]-5(*R*)-toluenesulfonamide (37). To a solution of acid **36** (1.72 g; 3.57 mmol) in THF (40 mL) was added $NaHCO_3$ (3.00 g; 35.7 mmol), followed by iodine (3.62 g; 14.3 mmol). The resulting reaction mixture was stirred at rt until complete consumption of the starting material (16 h). The reaction mixture was poured into a saturated aqueous solution of $Na_2S_2O_3$ (200 mL) and stirred for 30 min to destroy the excess iodine. The aqueous layer was extracted with ethyl acetate (4 × 50 mL), the combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was purified by recrystallization from hexanes/ethyl acetate affording pure iodolactone **37** (1.54 g; 2.53 mmol; 71%): R_f 0.45 (hexanes/ethyl acetate 1:1); mp 224−225 °C dec (ethyl acetate); $[\alpha]^{22}_D$ +6.22 (*c* 0.201, acetone); IR ν 3303, 2962, 2923, 1713 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.55 (d, J = 8. 1 Hz, 1 H), 7.18 (m, 2 H), 6.93 (m, 2 H), 6.72 (d, J = 8.0 Hz, 2 H), 5.05 (t, J = 3.8 Hz, 1 H), 4.81 (s, 1H), 4.59 (t, J = 5.6 Hz, 1 H), 4.53 (t, J = 5.1 Hz, 1 H), 4.32 (dd, J = 8.2, 5.3 Hz, 1 H), 3.70 (dd, J = 12.0, 8.6 Hz, 1 H), 3.54 (dd, J = 12.1, 3.5 Hz, 1 H), 3.35 (s, 3H), 2.20 (s, 3 H), 1.33 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.1, 142.2, 138.9, 138.7, 128.6, 126.1, 125.6, 125.4, 123.0, 121.6, 121.3, 120.8, 112.7, 110.2, 85.8, 79.5, 78.7, 55.7, 35.0, 28.5, 27.4, 24.9, 24.1, 20.4; HRMS (EI) calcd for $C_{25}H_{25}O_6N_2SI$ 608.0110, found 608.0502.

***N*-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4-dihydroxy-5,6-(isopropylidenedioxy)cyclohex-1-yl]-5-toluenesulfonamide-3-indolyl-2-methyl Ester (38).** To a solution of LiOMe in methanol, freshly prepared by dissolving lithium wire (11 mg; 1.6 mmol) in methanol (2 mL), was added a solution of iodolactone **37** (200 mg; 0.33 mmol) in methanol (5 mL). The reaction mixture was allowed to stir at room temperature until total consumption of the starting material (16 h). The reaction was quenched with 10 mL of NH_4Cl_{aq}, water (10 mL) was added, and the solution was extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/ethyl acetate 9:1) to provide the desired ester **38** (143 mg; 0.28 mmol; 85%) as a colorless oil: R_f 0.20 (chloroform/ methanol, 4:1); $[\alpha]^{20}_D$ +69 (*c* 0.82, CH_3OH); IR ν 3318, 3267, 2989, 1689 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.5 (bs, 1H), 7.93 (d, J = 8.3 Hz, 1 H), 7.21 (m, 2 H), 6.99 (m, 2 H), 6.92 (d, J = 8.2 Hz, 2 H), 6.69 (d, J = 8.1 Hz, 2 H), 5.15 (d, J = 8.3 Hz, 1H), 4.68 (dd, J = 7.5, 3.0 Hz, 1 H), 4.27 (d, J = 11.7 Hz, 1 H), 4.08 (t, J = 8.1 Hz, 1 H), 3.92 (s, 3H), 3.50 (t, J = 3.6 Hz, 1 H), 3.33 (m, 1 H), 2.20 (s, 3 H). 1.55 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.2, 142.9, 139.5, 138.0, 129.6, 127.4, 126.4, 125.8, 123.6, 121.1, 120.8, 113.5, 110.9, 81.1, 74.9, 58.2, 57.1, 53.4, 36.7, 27.6, 25.6, 21.6; HRMS (EI) calcd for $C_{26}H_{28}N_2O_7S$ 498.1915, found 498.1437.

***N*-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4-epoxy-5,6-(isopropylidenedioxy)cyclohex-1-yl]-5-*tert*-butoxycarbonyl-3-indolyl-2-(1-*tert*-butoxycarbonyl)carboxylic Acid Methyl Ester (40).** To a suspension of ester **38** (530 mg, 1.03 mmol) in THF (3 mL) was added NaH (60% suspension in mineral oil; 104 mg, 2.58 mmol). After the hydrogen formation ceased, $(Boc)_2O$ was added (6.0 g, 28 mmol). The resulting reaction mixture was heated to 40 °C until the starting material was completely consumed (16 h). The mixture was poured into a saturated solution of aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (hexanes/ethyl acetate 9:1 to 2:1) affording the bis-Boc-protected tosylate **39** (642 mg, 0.90 mmol, 88%) as a pale yellow oil as a mixture of atropoisomers: R_f 0.65 (hexanes/ethyl acetate 1:1); $[\alpha]^{20}_D$ 32.8 (c 1.01, $CHCl_3$); IR ν 3338, 2983, 1734, 1156 cm^{-1}. The epoxide **39** was used directly in the subsequent reaction.

To a solution of tosylate **39** (662 mg; 0.93 mmol) in dry DME (8 mL) was added a solution of sodium naphthalide (0.54 M) at −65 °C until the characteristic deep blue-green color persisted. The reaction mixture was stirred an additional 10 min at this temperature before it was quenched with a saturated solution of aqueous NH_4Cl (20 mL) and warmed to rt. Water was added (50 mL), and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 5:1 to 1:1) to afford detosylated material (370 mg; 0.66 mmol; 71%) as pale, yellow oil: R_f 0.20 (hexane/ethyl acetate, 1:1); $[\alpha]^{20}_D$ −8.8 (c 1.1, $CHCl_3$); IR ν cm^{-1}; 3354, 2981, 1727 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.14 (bs, 1 H), 7.99 (d, J = 8.2 Hz, 1 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.23 (t, J = 7.7 Hz, 1 H), 4. 60 (m, 2 H), 4.14 (bs, 2 H), 3.87 (s, 3 H) 3. 87 (bs, 1 H), 3.51 (bs, 1 H), 3.42 (d, J = 3.5 Hz, 1 H), 1.56 (s, 9 H), 1.53 (s, 3 H), 1.33 (s, 3 H), 1.06 (bs, 6 H), 0.86 (bs, 3 H); HRMS (EI) calcd for $C_{29}H_{38}N_2O_6$ 558.2566, found 558.2591.

(1*R*,2*R*,3*S*,4*S*,4a*S*)-12c-Hexahydro-1,2-epoxy-3,4-benzodioxolylindolyl[2,3-*c*]-6(5*H*)-quinolinone (41). To a solution of bis-Boc derivative **40** (100 mg; 0.18 mmol) in CH_2Cl_2 (5 mL) was added silica gel (500 mg; 200−400 mesh). The solvent was removed under reduced pressure, and the adsorbed material was suspended in water (10 mL) and heated to 140 °C in a sealed tube until total consumption of the starting material (1.5 h). The reaction mixture was cooled to rt; the silica gel was removed by filtration and washed with warm ethyl acetate (5 × 5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 × 5 mL). The combined organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (chloroform/methanol, 19:1 to 9:1) affording epoxyacetonide **41** as pale yellow crystals (55 mg, 0.17 mmol, 94%):

R_f 0.80 (chloroform/methanol, 9:1); $[\alpha]^{23}_D$ +4.12 (*c* 0.21 $CHCl_3$); mp >250 °C; IR ν 3375, 2919, 2522, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.34 (bs, 1 H); 7.75 (d, J = 8.1 Hz, 1 H), 7.43 (d, J = 8.3 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 5.69 (bs, 1 H), 4.63 (dd, J = 6.9, 3.5 Hz, 1 H), 4.31 (d, J = 3.7 Hz, 1 H), 4.06 (dd, J = 9.9, 7.1 Hz, 1 H), 3.91 (t, J = 11.3 Hz, 1 H), 3.60 (t, J = 3.6 Hz, 1 H), 3.47 (d, J = 12.8 Hz, 1 H), 1.45 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 137.7, 127.5, 125.7, 124.9, 121.6, 118.1, 113.3, 113.2, 110.5, 76.1, 72.9, 54.9, 53.1, 50.8, 35.6, 27.9, 25.8; HRMS (EI) calcd for $C_{18}H_{18}N_2O_4$ 326.1274, found 326.1263.

(1*R*,2*S*,3*S*,4*S*,4a*S*)-12c-Hexahydro-1,2,3,4-tetraolindolyl-[2,3-*c*]-6(5*H*)-quinolinone (10). To a solution of epoxide **40**

(55 mg; 0.17 mmol) in ethyl acetate (8 mL) was added silica gel (500 mg; 200−400 mesh). The solvent was removed under reduced pressure, and the adsorbed material was suspended in water (8 mL) and heated to 170 °C in a sealed tube for 13 h. The reaction mixture was cooled to rt, the water was removed by azeotropic distillation with benzene under reduced pressure, and the remaining residue was subjected to purification by flash column chromatography (chloroform/methanol 9:1 to 4:1) affording the indole mimic **10** as a yellow crystalline solid (16 mg; 0.053 mmol; 31%): R_f 0.20 (chloroform/methanol 4:1); $[\alpha]^{22}_D$ +25 (c 0.40, MeOH); IR ν 3270, 2922, 1644 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 6.58 (s, 1 H), 5.43 (d, J = 3.4 Hz, 1 H), 5.14 (m, 2 H), 4.08 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 138.2, 128.8, 125.1, 124.6, 122.6, 120.3, 120.2, 113.4, 74.5, 71.8, 70.9, 70.3, 53.7, 39.4; HRMS (EI) calcd for $C_{15}H_{16}N_2O5$ 304.1059, found 304.1055.

(1*R*,2*S*,3*S*,4*S*,4a*S*)-12c-Hexahydro-1,2,3,4-tetraacetateindolyl[2,3-*c*]-6(5*H*)-quinolinone (42). To a solution of tetrol **10** (20 mg, 0.082 mmol) in pyridine (3 mL) were added acetic anhydride (3 mL) and a catalytic amount of DMAP. The solution was stirred at rt for 48 h (until total consumption of the starting material as determined by TLC) before the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 2:1) to afford pure pentaacetate **42** as yellow oil (31 mg, 72%): R_f 0.20 (hexanes/ethyl acetate, 1:1); $[\alpha]^{23}_D$ +151 (c 0.65, acetone); IR ν 2926, 1755, 1669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.6 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 1 H), 7.41 (t, J = 7.8 Hz, 1 H), 7.20 (t, J = 7.6 Hz, 1 H), 6.33 (s, 1 H), 5.85 (m, 1 H), 5.44 (t, J = 2.8 Hz, 1 H), 5.29 (t, J = 2.7 Hz, 1 H), 5.21 (dd, J = 11.1, 3.4 Hz, 1 H), 4.46 (t, J = 12.0 Hz, 1 H), 3.62 (dd, J = 12.9, 3.1 Hz, 1 H), 2.68 (s, 3 H), 2.14 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.6, 169.8, 168.7, 160.3, 139.6, 129.1, 128.8, 128.4, 124.8, 124.6, 121.0, 116.4, 70.6, 68.1, 67.9, 67.4, 49.2, 39.6, 28.1, 21.2, 21.1, 21.0, 21.0; HRMS (EI) calcd for $C_{25}H_{26}N_2O_{10}$ 514.1800, found 514.1576.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra are available for compounds **10**, **19**−**23**, **37**, **38**, **41**, and **42**. ^{1}H NMR spectra are available for compounds **24**, **27**, **28**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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