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Synthesis of Indole Analogues of the Natural Schweinfurthins

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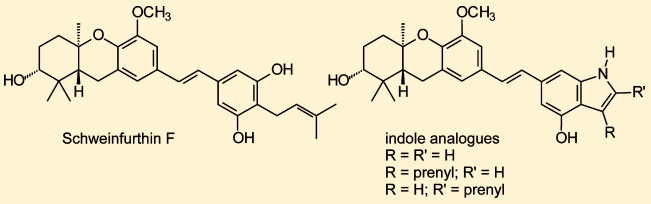
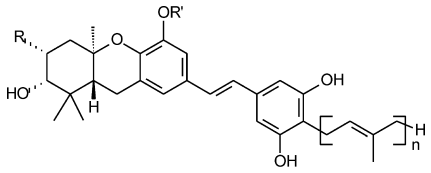
Supporting Information

ABSTRACT: An interest in the schweinfurthins, natural stilbenes with significant antiproliferative activity, has prompted efforts to prepare a set of indole analogues. To approach the desired compounds through a Horner–Wadsworth–Emmons condensation, new indole derivatives bearing a phosphonomethyl substituent in the B-ring were required. The parent indole system with the necessary substitution pattern was obtained through Stobbe condensation and cyclization. A prenyl substituent was incorporated at the C3 position of a 4,6-disubstituted indole through a highly regioselective electrophilic aromatic substitution reaction, while metalation and alkylation provided the C2-prenylated indole. After introduction of the phosphonate group through classical reactions, the new indole phosphonates were found to undergo the desired condensation with nonracemic aldehydes representing the schweinfurthin left half. This approach provides facile access to new heteroaromatic analogues of the natural schweinfurthins and should be applicable to many other natural stilbenes as well.



INTRODUCTION

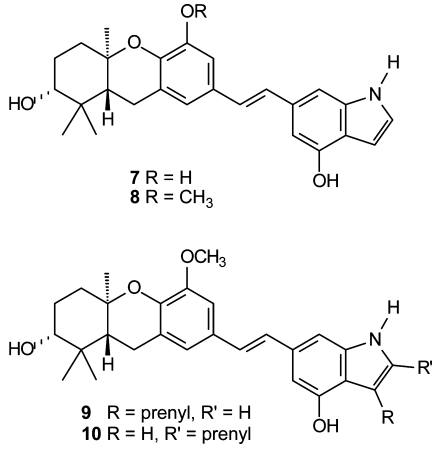
The schweinfurthins (Figure 1), a small group of rare natural products,[1,2] display a novel pattern of differential activity in the National Cancer Institute (NCI) 60 cell line screen. Their activity pattern suggests that these compounds act on a novel target or through a new mechanism,[1] and thus, they can be viewed as potential leads for further drug development. To alleviate the scarcity of these natural products, to access novel analogues, and to explore the limits of the pharmacophore, we have undertaken the synthesis of both natural schweinfurthins and a range of analogues.[3−9] After an analysis of new compounds of potential interest, we considered the possibility of incorporating an indole into the stilbene system. The indole substructure is so common in both natural products and pharmaceutical agents that it often is considered a privileged scaffold.[10,11] Incorporation of an indole motif might afford analogues with comparable or improved activity while at the same time increasing their bioavailability.[12,13] Furthermore, the D-ring resorcinol of the natural schweinfurthins may limit their stability, and proper placement of an indole system might improve the chemical stability as well. On the basis of this rationale, the synthesis of indole analogues of the schweinfurthins became a goal of our program.



1 R = OH, R' = H, n = 2 Schweinfurthin A
2 R = OH, R' = CH_3, n = 2 Schweinfurthin B
3 R = H, R' = CH_3, n = 1 Schweinfurthin F
4 R = H, R' = H, n = 1 Schweinfurthin G
5 R = H, R' = H, n = 2 3-Deoxyschweinfurthin A
6 R = H, R' = CH_3, n = 2 3-Deoxyschweinfurthin B

Figure 1. Some natural schweinfurthins (**1**–**4**) and synthetic analogues (**5** and **6**).

There are multiple ways that an indole moiety could be superimposed upon the D-ring of the natural schweinfurthins. The pattern pursued in this study views the indole nitrogen as a replacement for one of the resorcinol oxygens and incorporates the remainder of the indole ring as a substituent at the position para to the stilbene olefin (Figure 2). These structures would exploit the known flexibility of the para position toward modification with preservation of biological activity.[4,7,8] Furthermore, the preparation of intermediates leading to



7 R = H
8 R = CH_3

9 R = prenyl, R' = H
10 R = H, R' = prenyl

Figure 2. First-generation indole targets.

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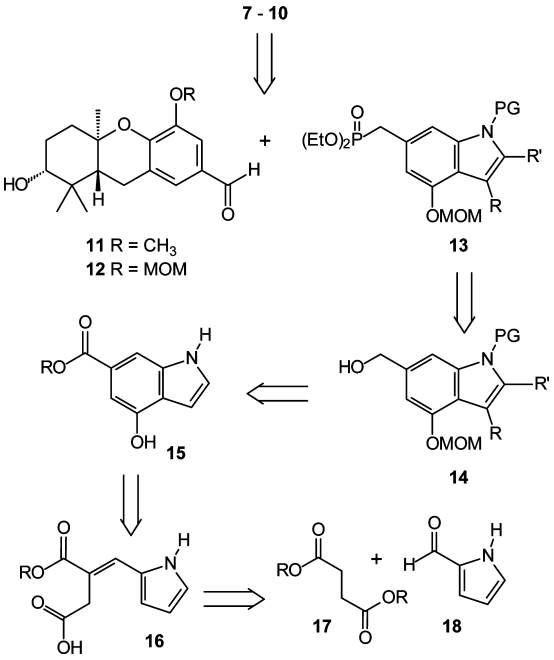
structures **7** and **8** might be readily modified to allow addition of isoprenoid substituents to the five-membered ring via electrophilic aromatic substitution (which is favored at C3 of indole itself[14] and would lead to compound **9**) or via anion chemistry (which can be directed to C2 in N-substituted indoles and would provide compound **10**).[15,16] Because compounds **9** and **10** both represent modest deviations from the natural products in terms of the position of the prenyl group, both series were of interest, and a strategy that could diverge to both isomers at a later stage would be particularly attractive.

Our foray into schweinfurthin studies began with synthesis of schweinfurthin C,[17] and that early effort established the strategy of a late stage Horner–Wadsworth–Emmons (HWE) condensation for construction of the *trans*-stilbene olefin. To take advantage of intermediates already in hand from previous research, especially the now readily available *R,R,R*-aldehydes **11** and **12** that carry all of the schweinfurthin stereogenic centers (Scheme 1), would require an indole phosphonate such

Scheme 1. Retrosynthetic Analysis

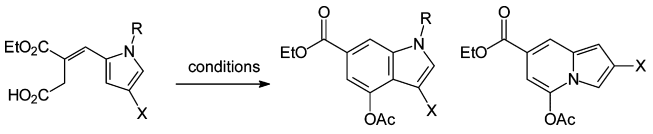


as compound **13**. In view of the vast number of known indoles, it was somewhat surprising to find that apparently only C2[18] and C3[19] phosphonomethyl compounds have been prepared. On the basis of the assumption that phosphonate **13** could be prepared from the corresponding alcohol **14**, which in turn should be available from ester **15**, routes to these two potential intermediates were considered. The presence of the "benzylic" alcohol of compound **14** might not be tolerated by many of the classical methods[20] for de novo indole synthesis because of their reliance on acidic conditions, and the recent Kraus indole synthesis appears to be better suited for the preparation of 2-substituted or 2,3-disubstituted compounds.[21,22] However, the preparation of substituted indole **15** through an approach based on Stobbe condensation of succinate diester **17** and pyrrole-2-carboxaldehyde (**18**) followed by cyclization of the intermediate acid **16** has been reported.[23] While the initial report did not provide a complete characterization of the product, a more recent study from the Vedejs laboratories placed this approach on a solid foundation and proved that it does afford the desired substitution pattern.[24] Therefore, we began an effort to obtain the targeted schweinfurthin analogues by preparing several indoles using this strategy.

RESULTS AND DISCUSSION

The Stobbe condensation of diethyl succinate with aldehyde **18** smoothly gave half-ester **19** as expected.[24] Without extensive purification, this material was treated with a 6:1 mixture of acetic anhydride and acetic acid in refluxing toluene to induce cyclization (Scheme 2). These conditions resulted in the

Scheme 2. Cyclization To Give Indoles and Indolizines



19 R = H, X = H	Ac_2O, AcOH, toluene	**20** R = H, X = H (74%)	**21** X = H (1%)
22 R = H, X = Br	Ac_2O, AcOH, THF	**23** R = H, X = Br (trace)	**24** X = Br (79%)
25 R = MOM, X = Br	Ac_2O, KOAc	**26** R = MOM, X = Br (79%)	
27 R = MOM, X = H	Ac_2O, KOAc	**28** R = MOM, X = H (82%)	

formation of the acetate-protected indole **20** (74%) accompanied by small amounts of indolizine **21** (~1%), also as expected,[24] while a parallel reaction in THF at reflux gave a less favorable product ratio (42% and 19%, respectively). Attempts to extend this approach to brominated pyrrole **22**, which might be useful for elaboration of the final products through halogen–metal exchange or cross-coupling reactions,[25] were more complex. While the desired half-ester **22** was readily prepared by a Stobbe condensation, subjecting compound **22** to the standard cyclization conditions gave only trace amounts of the desired indole **23** and instead afforded indolizine **24** as the major product. Compound **24** is highly fluorescent and might be useful for the synthesis of new types of fluorescent schweinfurthin analogues.[26] However, for the immediate goal, N-protection of the pyrrole aldehyde would circumvent this issue, as observed with *N*-methylpyrrole.[27] Because previous syntheses of schweinfurthin analogues employed MOM-protected phenols, half-ester **25** was prepared by Stobbe condensation of the MOM-protected aldehyde. In this case, cyclization under the standard conditions afforded only the desired indole product **26**. In a similar sense, after pyrrole aldehyde **18** was protected as its MOM derivative, cyclization of the Stobbe product **27** gave only the desired indole **28**. Because a late-stage deprotection of the indole MOM group ultimately proved to be more difficult than expected (vide infra), compound **18** also was protected as its tosyl derivative. In this case, however, the attempted Stobbe condensation proved to be problematic, so introduction of this group at this stage of the sequence was not pursued further.

After hydrolysis of the acetate group of indole **20**, treatment of the resulting phenol **29** with NaH and MOMCl in THF gave the desired MOM-protected indole **30** along with a significant amount of a C-alkylated product, tentatively assigned as the C5-substituted indole **31** (Scheme 3). Addition of DMF to the solvent system improved the ratio of desired to undesired product from ~1.3:1 to ~9:1. The reduction of ester **30** proceeded in quantitative yield, but attempts at conversion to the phosphonate were somewhat frustrating. The reaction proceeded via the corresponding bromide, although the

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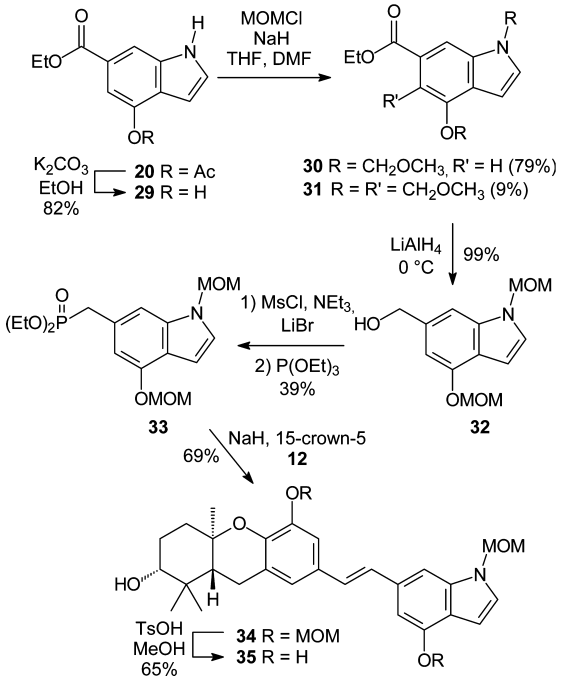
Scheme 3. Synthesis and HWE Condensation of Indole Phosphonate 33



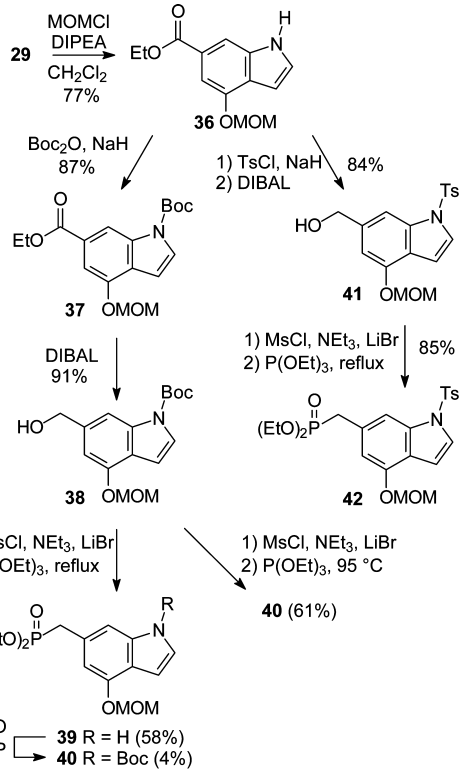
Arbuzov reaction of that bromide with $(EtO)_3P$ in refluxing toluene gave the desired phosphonate **33** in modest yield.

The HWE coupling of hexahydroxanthene aldehyde **12**[28] with phosphonate **33** smoothly gave the protected analogue **34**. Unfortunately, the attempted hydrolysis of the three MOM groups by treatment with TsOH/MeOH gave compound **35**, in which both of the phenolic MOM groups had been cleaved but the indole nitrogen was still protected. Attempts to remove this remaining MOM group under more vigorous conditions[29−31] proved unsuccessful, resulting only in decomposition.

To circumvent this difficult hydrolysis, a new strategy based upon early formation of a differentially protected indole was explored. Selective MOM protection of phenol **29** gave indole **36** (Scheme 4), and different N-protecting groups then could be introduced easily. For example, treatment of compound **36** with base and Boc_2O gave carbamate **37**, and selective reduction of the ethyl ester gave primary alcohol **38** in good yield. Under standard conditions for formation of the phosphonates [i.e., initial formation of the mesylate followed by treatment with LiBr and then neat $(EtO)_3P$ at reflux], formation of the C−P bond was accompanied by cleavage of the Boc group[32] to afford phosphonate **39** as the major product. The Boc group was easily reinstalled through treatment of phosphonate **39** with Boc_2O to give phosphonate **40**, which could also be obtained more directly from alcohol **38** in a reasonable yield (61%) when the Arbuzov reaction was conducted at a lower temperature (~95 °C) instead of reflux (~165 °C). Alternatively, a tosylate protecting group could be installed through treatment of indole **36** with TsCl and base, and the intermediate carboxylic acid ester was reduced selectively to give alcohol **41** in good yield. The tosyl group proved to be stable toward the standard conditions for formation of the phosphonate, and compound **42** was obtained smoothly.

Of the new indole phosphonates **39**, **40**, and **42**, the HWE condensation of compound **39** with an aldehyde representing

Scheme 4. Synthesis of New Indole Phosphonates



the schweinfurthin left half would be most advantageous because it would avoid an N-deprotection step of the product at a later stage. In the limited number of condensations between an indole phosphonate and an aldehyde, an N-protected indole was always employed.[33−36] Nevertheless, because aldehyde **12** has been used in similar HWE reactions,[3,6,13] condensations between this aldehyde and phosphonate **39** were attempted. At best just trace amounts of a possible stilbene product were observed in this case, even though *p*-methoxybenzaldehyde reacted smoothly with phosphonate **39**.[37] The attempted condensation of aldehyde **12** with phosphonate **40** also was problematic. In this case, little or no condensation was observed, and TLC analysis suggested that Boc cleavage had taken place instead. Fortunately, the HWE condensation of phosphonate **42** with aldehyde **12** at reflux gave a mixture of stilbene products in very good total yield (Scheme 5). Somewhat to our surprise, analysis of the ^1H and ^{13}C NMR spectra showed that the major product **43** carried a tosylate as an A-ring ester, while the minor product **44** did not have an A-ring tosylate but already had undergone cleavage of the *N*-tosyl group. The hindered tosylate ester **43** proved to be resistant to standard hydrolysis,[38−45] but reduction with $LiAlH_4$[46,47] converted the major HWE product **43** to the minor product **44** in low yield. Final hydrolysis of the MOM groups gave stilbene **7**, the first schweinfurthin G analogue that incorporates an indole system.

To prepare the analogous schweinfurthin F analogue, phosphonate **42** was allowed to react with aldehyde **11**[3] and base (Scheme 6). When the reaction was conducted at reflux in THF, the only stilbene product (56%) again reflected transfer of the tosyl group from the indole nitrogen to the A-ring alcohol. Treatment of this hindered tosylate ester with $LiAlH_4$ did afford the free alcohol **46** in modest yield. Compound **46**

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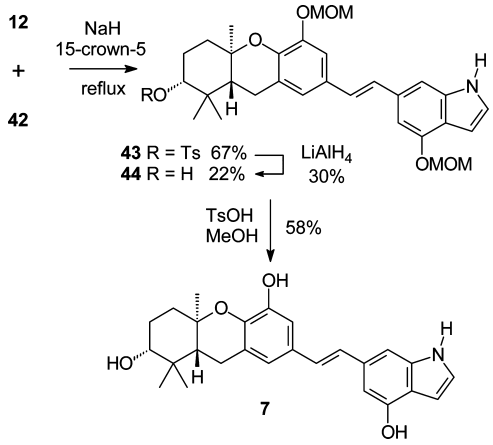
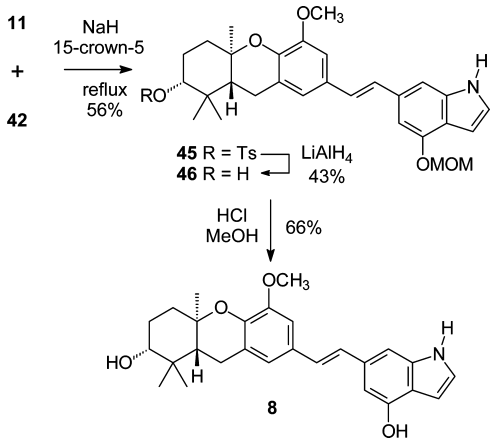
Scheme 5. Synthesis of an Indole Analogue of Schweinfurthin G



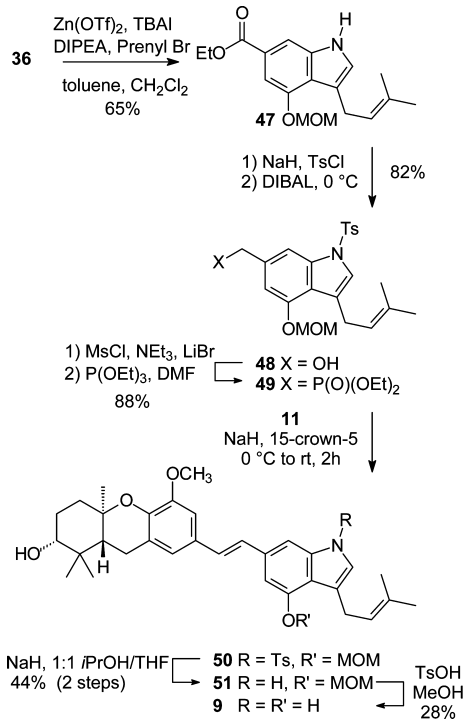
Scheme 6. Synthesis of an Indole Analogue of Schweinfurthin F



underwent hydrolysis of the phenolic MOM group under standard conditions to afford schweinfurthin F analogue **8**.

Because the natural schweinfurthins contain an isoprene chain as a D-ring substituent, installation of an isoprenoid chain on the indole would afford analogues more closely parallel to the natural products. Our original plan had been to incorporate this chain in a regiospecific manner through halogen−metal exchange on a protected indole derived from bromide **26**, but this sequence would become unappealing if the MOM hydrolysis were problematic or the S_N2' product was formed during alkylation with prenyl bromide.[48−52] An attractive alternative might be based on an extension of the methodology of Ganesan,[53] which relies upon $Zn(OTf)_2$ activation of an allylic halide to bring about only C3 alkylation through electrophilic aromatic substitution. Among the attractive features of the original study, alkylation of indole itself with prenyl halides generally gave only the C3-alkylated product, proceeded in ∼60% yield, and did not give the S_N2' reaction products (i.e., "reverse prenyl" substituents) that are frequently observed with other methods.[48,49] However, it was unclear whether this approach could be applied to access the substituted indole required here, where both C6 and C4 groups that might impact reactivity were required. In particular, a C6 ethoxycarbonyl group would add an electron-withdrawing substituent system, while reduction of this group to the corresponding alcohol might invite polymerization reactions in view of the known reactivity of benzyl alcohol under these conditions.[53] Furthermore, a MOM substituent at the C4 position might compete with an isoprenoid halide for complexation with the $Zn(OTf)_2$ or introduce a degree of steric hindrance at the C3 position. Nevertheless, the brevity of this approach led us to study the process with indole **36**. To our delight, the reaction of **36** with prenyl bromide in the presence of $Zn(OTf)_2$ gave the desired product **47** in 65% yield (Scheme 7). This yield is comparable to those obtained on indole itself,[53] despite the presence of the B-ring substituents.

Scheme 7. Synthesis of Prenylated Indole Schweinfurthin 9



Once ester **47** was in hand, the remaining steps in the sequence proceeded in a fashion parallel to those employed to prepare the earlier analogues. Protection of the indole nitrogen as the tosylate proceeded smoothly. Then, after selective reduction of the carboxylic acid ester with DIBAL, the resulting alcohol **48** was readily converted to phosphonate **49**. HWE condensation of **49** with aldehyde **11** afforded a mixture of *N*-tosyl intermediate **50** and free indole **51**. After partial purification, treatment with NaH in a mixture of THF and *i*-PrOH afforded only compound **51**. Final hydrolysis of the MOM group proceeded in low yield but did afford the desired target compound, schweinfurthin F analogue **9**.

To access compound **10** from an intermediate already in hand, indole **41** was protected as its silyl ether **52**, which was then treated with *n*-BuLi and prenyl bromide (Scheme 8). Despite the presence in the B-ring of two substituents that might participate in directed ortho metalation,[54] this sequence gave a single product identified as the C2-alkylated indole **53**. After deprotection to give alcohol **54** and the formation of phosphonate **55** through standard reactions, condensation of **55** with aldehyde **11** provided a mixture of the new stilbenes **56** and **57**. After partial purification, treatment with 2-propanol and base completed conversion to compound **57**, and final deprotection gave the desired schweinfurthin analogue **10**.

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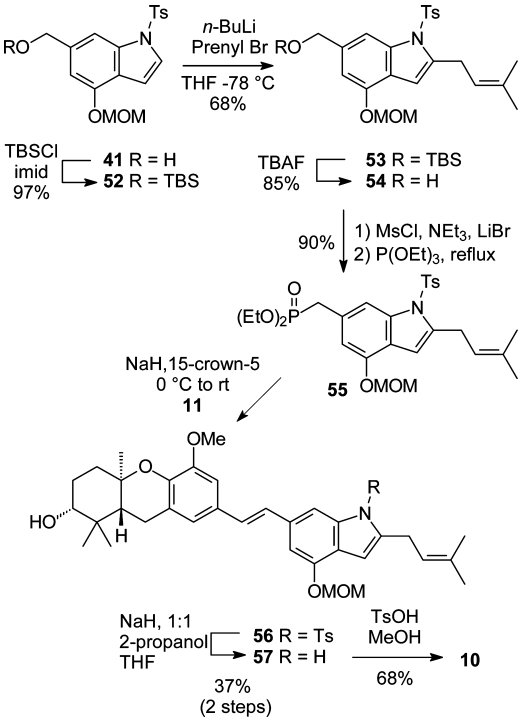
Scheme 8. Synthesis of Prenylated Indole Schweinfurthin 10



In preliminary bioassays, compounds **7**−**10** were tested for their activities against the SF-295 cell line, which is one of those more sensitive to the natural schweinfurthins.[1] These new schweinfurthin analogues did show activity in these assays, with EC_{50} values ranging from ∼200 nM to 2.5 μM (Table 1).[37]

Table 1. Preliminary Bioassays in the SF-295 Cell Line

compound	EC_{50} (μM)
7	0.2
8	2.5
9	0.2
10	2.2

Because the more active compounds showed potencies comparable to those of some of the natural schweinfurthins, preparation of additional indole analogues as well as more extensive testing in the NCI 60 cell line assay would be warranted.

CONCLUSION

We have developed a strategy for the synthesis of indole analogues of the natural schweinfurthins. This effort included the preparation of several new indoles by cyclization after a Stobbe condensation, which ultimately led to the preparation of the first indoles bearing a phosphonomethyl substituent in the indole B-ring. These B-ring phosphonates were then used in HWE reactions with the complex aldehydes **11** and **12** and underwent these condensations smoothly as long as the indole nitrogen was securely protected. With a tosyl group on the indole nitrogen, an unexpected transfer of the tosyl group to an unprotected alcohol was observed. While this transfer undoubtedly could be avoided through the use of an alcohol protecting group, instead, because this transfer also deprotected the indole nitrogen, the tosylate ester was isolated and cleaved to the free alcohol, which allowed the preparation of indole analogues of the schweinfurthin G and F cores. These studies also have shown that the $Zn(OTf)_2$-mediated alkylation of a 4,6-disubstituted indole is a facile way to introduce a prenyl substituent at C3 of this indole system, which in turn allowed preparation of a schweinfurthin F analogue complete with a side chain. With this more hindered prenyl indole, HWE condensation did afford the desired stilbene without transfer of the tosyl group, and basic cleavage of the *N*-tosyl group was more efficient. Finally, a C2-prenylated indole was obtained through metalation and alkylation of a tosyl indole intermediate, allowing divergent use of intermediate **36** to obtain either the C2- or C3-alkylated compounds. Together these studies have afforded four new indole analogues (**7**−**10**) of the natural schweinfurthins, and they define procedures that could be used to prepare analogues of many other natural stilbenes, including resveratrol,[55] the chiricanines,[56] the arachidins and arahypins,[57] and the pawhuskins.[58] Further research on the biological activities of the new schweinfurthin analogues is underway and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. THF was freshly distilled from sodium/benzophenone, while CH_2Cl_2 and Et_3N were freshly distilled from CaH_2. All of the reactions in nonaqueous solvents were conducted in oven-dried glassware under a positive pressure of argon with magnetic stirring. All commercial reagents were used without further purification unless otherwise stated. NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C or higher with $CDCl_3$ as the solvent and $(CH_3)_4Si$ (^1H, 0.00 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards, unless otherwise noted. High-resolution mass spectra were run with magnet detection, unless another method is noted. Elemental analyses were performed by a commercial facility.

General Procedure for Stobbe Condensations: 2-(1*H*-Pyrrol-2-ylmethylene)succinic Acid 1-Ethyl Ester (19). According to the procedure of Vedejs[24] but in THF (60 mL) instead of benzene, NaH (4.2 g, 105 mmol, 60% dispersion in oil) was added slowly to aldehyde **18** (5.01 g, 52.6 mmol) and diethyl succinate (13.3 mL, 80.2 mmol) at 0 °C. The reaction mixture was allowed to stir overnight and warm to rt. The reaction mixture was cooled to 0 °C, and the reaction was quenched by addition of water; Et_2O was added, and the mixture was extracted with 5% KOH. The combined aqueous layers were acidified with HCl (6 M) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to afford acid **19** (11.2 g, 96%) as a red-brown solid. ^1H NMR ($(CD_3)_2CO$, 400 MHz): δ 10.83 (br s, 1H), 10.63 (br s, 1H), 7.75 (s, 1H), 7.07−7.06 (m, 1H), 6.61−6.59 (m, 1H), 6.30−6.27 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($(CD_3)_2CO$, 100 MHz): δ 172.4, 168.5, 131.8, 128.8, 123.1, 119.2, 114.4, 111.9, 61.3, 34.4, 14.9. HRMS (TOF MS EI) *m*/*z*: calcd for $C_{11}H_{13}NO_4$ (M^+), 223.0845; found, 223.0851.

4-Acetoxy-1*H*-indole-6-carboxylic Acid Ethyl Ester (20) and 5-Acetoxyindolizine-7-carboxylic Acid Ethyl Ester (21). To acid **19** (17.1 g, 76.7 mmol) in toluene (800 mL) were added Ac_2O (48 mL, 506 mmol) and glacial AcOH (4.62 mL, 80.5 mmol), and the reaction mixture was heated to reflux. The next day the reaction mixture was allowed to cool to rt, and the reaction was quenched by addition of K_2CO_3(sat). The mixture was washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (0 to 50% ethyl acetate in hexanes) afforded indole **20** (14.0 g, 74%) as a light-brown solid and indolizine **21** (201 mg, 1%) as a yellow-brown oil.

Data for indole **20**: ^1H NMR: δ 8.98 (br s, 1H), 7.95 (s, 1H), 7.53 (s, 1H), 7.20−7.18 (m, 1H), 6.40 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ 169.5, 167.0, 142.8, 136.7, 127.9, 124.8, 124.2, 112.6, 111.8, 99.4, 60.9, 20.9, 14.3. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.97; H, 5.31; N, 5.61.

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Data for indolizine **21**: ^{1}H NMR: δ 8.14 (s, 1H), 7.33−7.31 (m, 1H), 6.94 (d, J = 1.4 Hz, 1H), 6.90 (dd, J = 3.9, 2.8 Hz, 1H), 6.79 (dd, J = 4.0, 1.2 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 166.9, 165.6, 138.8, 133.4, 120.2, 119.2, 115.7, 110.5, 105.6, 99.0, 60.9, 20.6, 14.3. HRMS (TOF MS EI) m/z: calcd for $C_{13}H_{13}NO_4$ (M^+), 247.0845; found, 247.0849.

Alternative Route to Indole 20 and Indolizine 21. To acid **19** (1.00 g, 4.48 mmol) in THF were added Ac_2O (5.4 mL, 57.5 mmol) and glacial AcOH (2.2 mL, 5.76 mmol), and the reaction mixture was heated to reflux. The next day the reaction mixture was allowed to cool to rt, poured into Et_2O and water, washed with $NaHCO_3$(sat), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (15 to 50% Et_2O in hexanes) afforded indole **20** (461 mg, 42%) and indolizine **21** (212 mg, 19%).

2-(4-Bromo-1*H*-pyrrol-2-ylmethylene)succinic Acid 1-Ethyl Ester (22). According to the general procedure, a solution of 4-bromopyrrole-2-carboxaldehyde (502 mg, 2.89 mmol) and diethyl succinate (0.72 mL, 4.29 mmol) in THF (4 mL) at 0 °C was treated with NaH (266 mg, 6.65 mmol, 60% dispersion in oil). Standard workup and final purification by flash column chromatography (30 to 40% ethyl acetate in hexanes) afforded acid **22** (316 mg, 36%) as a light-brown solid. ^{1}H NMR ($(CD_3)_2CO$): δ 10.87 (br s, 1H), 7.67 (s, 1H), 7.14 (dd, J = 2.9, 1.4 Hz, 1H), 6.63−6.62 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.65 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($(CD_3)_2CO$): δ 172.2, 167.9, 130.7, 129.3, 122.5, 121.5, 115.0, 98.8, 61.3, 34.1, 14.5. HRMS (TOF MS EI) m/z: calcd for $C_{11}H_{12}BrNO_4$ (M^+), 300.9950; found, 300.9954.

5-Acetoxy-2-bromoindolizine-7-carboxylic Acid Ethyl Ester (24). To acid **22** (811 mg, 2.68 mmol) in THF were added glacial AcOH (0.19 mL, 3.3 mmol) and Ac_2O (3.2 mL 33.8 mmol), and the solution was heated at reflux overnight. After the reaction mixture was allowed to cool to rt, the reaction was quenched by addition of Na_2CO_3(sat), and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (20% Et_2O in hexanes) afforded indolizine **24** (687 mg, 79%). ^{1}H NMR: δ 8.00 (d, J = 1.4 Hz, 1H), 7.32 (dd, J = 1.5, 0.5 Hz, 1H), 6.96 (d, J = 1.4 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 166.6, 165.1, 138.1, 133.3, 120.6, 118.6, 110.3, 107.2, 105.4, 99.4, 61.2, 20.6, 14.3. Anal. Calcd for $C_{13}H_{12}BrNO_4$: C, 47.88; H, 3.71; N, 4.29. Found: C, 48.10; H, 3.73; N, 4.22.

2-(4-Bromo-1-methoxymethyl-1*H*-pyrrol-2-ylmethylene)-succinic Acid 1-Ethyl Ester (25). To 4-bromo-1*H*-pyrrole-2-carboxaldehyde (1.84 g, 10.6 mmol) in 10:1 THF/DMF (55 mL) at 0 °C was added NaH (525 mg, 7.5 mmol, 60% dispersion in oil), and the reaction mixture was allowed to stir for 5 min. To the resulting solution was added MOMCl (0.97 mL, 12.8 mmol), and the reaction mixture was allowed to stir for 2 h. The reaction was then quenched by addition of NH_4Cl(sat), and the mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (25% Et_2O in hexanes) afforded the protected aldehyde (1.97 g, 86%) as a white solid. ^{1}H NMR: δ 9.53 (d, J = 1.0 Hz, 1H), 7.13 (dd, J = 1.7, 1.0 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 5.62 (s, 2H), 3.31 (s, 3H). ^{13}C NMR: δ 179.0, 131.8, 130.1, 125.8, 98.0, 78.4, 56.3. HRMS (EI) m/z: calcd for $C_7H_8BrNO_2$ (M^+), 216.9738; found, 216.9740. According to the general procedure, the MOM-protected bromopyrrole aldehyde (1.01 g, 4.63 mmol) in THF (9 mL) at 0 °C was treated with diethyl succinate (1.2 mL, 1.54 mmol) followed by NaH (310 mg, 7.75 mmol). Standard workup and final purification by flash column chromatography (25 to 40% ethyl acetate in hexanes) afforded acid **25** (425 mg, 27%) as a brown-yellow solid. ^{1}H NMR: δ 7.77 (s, 1H), 6.92 (d, J = 1.4 Hz, 1H), 6.61 (d, J = 1.1 Hz, 1H), 5.23 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.68 (s, 2H), 3.26 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 175.4, 167.6, 128.3, 128.2, 125.2, 122.1, 116.6, 97.9, 78.1, 61.5, 56.0, 34.0, 14.2. Anal. Calcd for $C_{13}H_{16}BrNO_5$: C, 45.10; H, 4.66; N, 4.05. Found: C, 45.19; H, 4.69; N, 3.93.

4-Acetoxy-3-bromo-1-methoxymethyl-1*H*-indole-6-carboxylic Acid Ethyl Ester (26). To acid **25** (1.084 g, 3.13 mmol) in Ac_2O (20 mL) was added KOAc (0.49 g, 5.0 mmol), and the reaction mixture was heated to reflux for 1 h and then allowed to cool to rt. The solution was diluted with ethyl acetate, washed with Na_2CO_3(sat), water, and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (20% ethyl acetate in hexanes) afforded indole **26** (911 mg, 79%) as a brown solid. ^{1}H NMR: δ 8.14 (d, J = 1.2 Hz, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.33 (s, 1H), 5.45 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.28 (s, 3H), 2.43 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 179.9, 166.2, 142.9, 137.1, 130.8, 126.1, 123.1, 115.2, 110.8, 88.2, 77.7, 61.2, 56.4, 21.0 14.4. Anal. Calcd for $C_{15}H_{16}BrNO_5$: C, 48.67; H, 4.36; N, 3.78. Found: C, 48.84; H, 4.60; N, 3.58.

2-(1-Methoxymethyl-1*H*-pyrrol-2-ylmethylene)succinic Acid 1-Ethyl Ester (27). A solution of *N*-MOM-pyrrole-2-carboxaldehyde (100 mg, 0.72 mmol) and diethyl succinate (145 mg, 0.84 mmol) in THF at 0 °C was treated with KO*t*-Bu (120 mg, 1.07 mmol). The solution was allowed to warm to rt overnight and the next day was heated to reflux for 1 h. After the solution was cooled to 0 °C, the reaction was quenched by addition of water, and the mixture was diluted with Et_2O and extracted with 5% KOH. The combined aqueous extracts were acidified (6 M HCl) and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated in vacuo. Final purification by flash column chromatography (30% ethyl acetate in hexanes) afforded acid **27** (60 mg, 31%) as a yellow solid. ^{1}H NMR: δ 7.87 (s, 1H), 6.93 (dd, J = 2.7, 1.5 Hz, 1H), 6.67−6.66 (m, 1H), 6.29−6.27 (m, 1H), 5.29 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.72 (s, 2H), 3.25 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 176.1, 168.1, 129.3, 127.7, 126.2, 120.0, 115.6, 110.1, 78.0, 61.3, 55.7, 34.2, 14.2. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41. Found: C, 58.49; H, 6.43.

4-Acetoxy-1-methoxymethyl-1*H*-indole-6-carboxylic Acid Ethyl Ester (28). To acid **27** (333 mg, 1.25 mmol) in Ac_2O (10 mL) was added KOAc (153 mg, 1.56 mol), and the solution was heated at reflux until the reaction was complete as judged by TLC analysis. The solution was allowed to cool to rt and then poured into $NaHCO_3$(sat) and diluted with Et_2O. Once bubbling had ceased, the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with $NaHCO_3$(sat), water, and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (40% ethyl acetate in hexanes) afforded indole **28** (298 mg, 82%) as a brown-yellow solid. ^{1}H NMR: δ 8.14 (dd, J = 1.0, 1.0 Hz, 1H), 7.60 (d, J = 1.1 Hz, 1H), 7.31 (d, J = 3.3 Hz, 1H), 6.46 (dd, J = 3.3, 0.8 Hz, 1H), 5.47 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.25 (s, 3H), 2.40 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 169.0, 166.6, 143.0, 137.2, 131.2, 125.9, 124.9, 113.4, 110.3, 99.7, 77.5, 60.9, 56.0, 22.0, 14.3. HRMS (TOF MS EI) m/z: calcd for $C_{15}H_{17}NO_5$ (M^+), 291.1107; found, 291.1104.

4-Hydroxy-1*H*-indole-6-carboxylic Acid Ethyl Ester (29). To a solution of acetate **20** (201 mg, 0.81 mmol) in EtOH (20 mL) was added K_2CO_3 (210 mg, 1.52 mmol), and the resulting mixture was heated to reflux for 90 min. The reaction mixture was cooled to 0 °C, filtered through Celite, and then concentrated in vacuo. The resulting residue was dissolved in Et_2O and extracted with 2 N NaOH. The aqueous extracts were acidified, extracted with Et_2O, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% Et_2O in hexanes) afforded phenol **29** (136 mg, 82%) as a light-brown solid. ^{1}H NMR ($(CD_3)_2CO$): δ 10.5 (br s, 1H), 8.60 (br s, 1H), 7.76 (dd, J = 1.2, 1.2 Hz, 1H), 7.42 (dd, J = 3.2, 2.5 Hz, 1H), 7.18 (d, J = 1.3 Hz, 1H), 6.67 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 167.8, 150.9, 138.2, 127.2, 125.5, 122.8, 107.0, 104.5, 100.1, 60.9, 14.7. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.49; N, 6.66.

4-Methoxymethoxy-1-methoxymethyl-1*H*-indole-6-carboxylic Acid Ethyl Ester (30) and 4-Methoxymethoxy-1,5-bis-(methoxymethyl)-1*H*-indole-6-carboxylic Acid Ethyl Ester (31). To a stirring suspension of NaH (800 mg, 20 mmol, 60% dispersion in oil) in a 6:1 mixture of THF and DMF (35 mL) at 0 °C was added

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indole **29** (1.61 g, 7.86 mmol) as a THF solution. Next, MOMCl (1.5 mL, 20 mmol) was added dropwise, and the reaction mixture was allowed to stir for 50 min. The reaction was quenched by addition of water, and the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (25 to 50% Et_2O in hexanes) afforded indoles **30** (1.82 g, 79%) and **31** (227 mg, 9%).

Data for compound **30**: ^{1}H NMR: δ 7.94 (dd, J = 0.9, 0.9 Hz, 1H), 7.47 (d, J = 1.1 Hz, 1H), 7.25 (d, J = 3.3 Hz, 1H), 6.69 (dd, J = 3.2, 0.8 Hz, 1H), 5.47 (s, 2H), 5.38 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 3.55 (s, 3H), 3.25 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 167.3, 150.0, 137.1, 129.8, 125.4, 124.0, 106.8, 104.6, 100.2, 94.7, 77.4, 60.8, 56.2, 55.9, 14.4. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53. Found: C, 61.59; H, 6.62.

Data for compound **31**: ^{1}H NMR: δ 7.82 (d, J = 0.6 Hz, 1H), 7.25 (d, J = 3.3 Hz, 1H), 6.68 (dd, J = 3.3, 0.8 Hz, 1H), 5.46 (s, 2H), 5.28 (s, 2H), 4.93 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.66 (s, 3H), 3.39 (s, 3H), 3.22 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 168.4, 150.0, 136.7, 130.1, 126.9, 124.6, 121.1, 109.1, 100.9, 99.5, 77.4, 65.7, 61.0, 58.0, 57.4, 56.0, 14.3. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.40; H, 7.00; N, 4.00.

(4-Methoxymethoxy-1-methoxymethyl-1*H*-indol-6-yl)-methanol (32). To ester **30** (668 mg, 2.28 mmol) in THF at 0 °C was added $LiAlH_4$ (190 mg, 5.0 mmol), and the resulting mixture was allowed to stir for 2 h. The reaction was then quenched by addition of water, and the mixture was acidified and extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% ethyl acetate in hexanes) afforded alcohol **32** (566 mg, 99%) as a white solid. ^{1}H NMR: δ 7.17 (s, 1H), 7.09 (d, J = 3.3 Hz, 1H), 6.80 (d, J = 0.9 Hz, 1H), 6.63 (dd, J = 3.2, 0.7 Hz, 1H), 5.39 (s, 2H), 5.32 (s, 2 H), 4.75 (s, 2H), 3.53 (s, 3H), 3.22 (s, 3H), 2.02 (br s, 1H). ^{13}C NMR: δ 150.7, 137.9, 136.6, 127.3, 119.9, 103.7, 102.8, 99.8, 94.7, 77.5, 66.1, 56.1, 55.8. HRMS (EI) m/z: calcd for $C_{13}H_{17}NO_4$ (M^+), 251.1158; found, 251.1152.

(4-Methoxymethoxy-1-methoxymethyl-1*H*-indol-6-ylmethyl)phosphonic Acid Diethyl Ester (33). To a solution of alcohol **32** (12 mg, 0.048 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added Et_3N (0.05 mL, 0.38 mmol) and MsCl (0.02 mL, 0.24 mmol), and the reaction was allowed to warm to rt. The following day the reaction was quenched by addition of NH_4Cl(sat), and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in acetone (5 mL) at rt, and LiBr (33 mg, 0.38 mmol) was added. The reaction mixture was allowed to stir overnight and then poured into Et_2O. The reaction was quenched by addition of water, and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in $P(OEt)_3$ (0.5 mL) and toluene (3 mL), and the solution was heated at reflux overnight. The following day the solution was allowed to cool to rt and poured into Et_2O. The reaction was then quenched by addition of water, and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (80% ethyl acetate in hexanes) afforded phosphonate **33** (7 mg, 39% yield) as an oil. ^{1}H NMR: δ 7.12 (d, J = 3.2 Hz, 1H), 7.07 (dd, J = 3.2 Hz, 1.0 Hz, 1H), 6.75 (dd, J = 1.7, 1.3 Hz, 1H), 6.61 (dd, J = 3.2 Hz, 0.7 Hz, 1H), 5.40 (s, 2H), 5.32 (s, 2H), 4.06−3.96 (m, 4H), 3.53 (s, 3H), 3.25 (d, J_{HP} = 21.3 Hz, 2H), 3.23 (s, 3H), 1.26 (td, J = 7.1, 0.3 Hz, 6H). ^{13}C NMR: δ 150.4 (d, J_{CP} = 2.8 Hz), 138.0 (d, J_{CP} = 3.0 Hz), 127.0 (d, J_{CP} = 1.2 Hz), 126.4 (d, J_{CP} = 9.2 Hz), 119.3 (d, J_{CP} = 2.9 Hz), 106.5 (d, J_{CP} = 5.9 Hz), 105.5 (d, J_{CP} = 7.7 Hz), 99.7 (d, J_{CP} = 1.5 Hz), 94.7, 77.4, 62.0 (d, J_{CP} = 6.6 Hz, 2C), 56.1, 55.8, 34.2 (d, J_{CP} = 138 Hz), 16.3 (d, J_{CP} = 6.1 Hz, 2C). ^{31}P NMR: δ 27.4. HRMS (EI) m/z: calcd for $C_{17}H_{26}NO_6P$ (M^+), 371.1498; found, 371.1497.

5-Methoxymethoxy-7-[2-(4-methoxymethoxy-1-methoxymethyl-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-ol (34). To a suspension of NaH (45 mg, 1.13 mol, 60% dispersion in oil) in THF at 0 °C was added phosphonate **33** (37 mg, 0.10 mmol) as a THF solution followed by aldehyde **12**[28] (17.6 mg, 0.052 mmol) as a THF solution, and the reaction mixture was allowed to warm slowly to rt. The following day the reaction was quenched by addition of water, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50 to 70% ethyl acetate in hexanes) afforded stilbene **34** (16 mg, 55%) as an oil. ^{1}H NMR: δ 7.24 (s, 1H), 7.16 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 3.2 Hz, 1H), 7.03−6.97 (m, 4H), 6.62 (d, J = 3.2 Hz, 1H), 5.44 (s, 2H), 5.39 (s, 2H), 5.25 (d, J = 6.5 Hz, 1H), 5.21 (d, J = 6.6 Hz, 1H), 3.57 (s, 3H) 3.55 (s, 3H), 3.47−3.42 (m, 1H), 3.27 (s, 3H), 2.75−2.72 (m, 2H), 2.13−2.08 (m, 1H), 1.91−1.64 (m, 5H), 1.25 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H). ^{13}C NMR: δ 150.8, 146.2, 143.6, 138.2, 133.5, 129.5, 127.7, 127.0, 125.5, 123.1, 121.9, 120.1, 113.4, 102.9, 102.5, 100.0, 95.9, 94.8, 78.0, 77.6, 76.9, 56.2, 56.2, 55.9, 46.8, 38.4, 37.7, 28.3, 27.3, 23.2, 19.9, 14.3. HRMS (EI) m/z: calcd for $C_{32}H_{41}NO_7$ (M^+), 551.2883; found,, 551.2891.

7-[2-(4-Hydroxy-1-methoxymethyl-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-2,5-diol (35). To MOM-protected compound **34** (16 mg, 0.029 mmol) in MeOH (3 mL) was added TsOH (80 mg, 0.42 mmol), and the solution was allowed to stir at rt. The next day the reaction was quenched by addition of NH_4Cl(sat), and the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% ethyl acetate in hexanes) afforded schweinfurthin analogue **35** (9 mg, 67%) as a yellow oil. ^{1}H NMR (CD_3OD): δ 7.16 (d, J = 3.3 Hz, 1H), 7.11 (m, 1H), 6.98 (d, J = 16.0 Hz, 1H), 6.91 (d, J = 16.4 Hz, 1H), 6.86 (d, J = 1.9 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 6.73 (d, J = 1.0 Hz, 1H), 6.55 (dd, J = 3.3, 0.7 Hz, 1H), 5.47 (s, 2H), 3.40−3.35 (m, 1H), 3.25 (s, 3H), 2.75−2.71 (m, 2H), 2.09−2.04 (m, 1H), 1.85−1.63 (m, 4H), 1.24 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 151.6, 147.0, 142.1, 140.1, 134.9, 131.4, 128.6, 128.4, 128.0, 124.0, 120.3, 120.2, 111.1, 103.3, 102.2, 100.5, 78.8, 78.3, 78.2, 56.0, ~49 (obscured by solvent), 39.5, 38.9, 29.0, 27.9, 24.0, 20.3, 14.8. HRMS (EI) m/z: calcd for $C_{28}H_{33}NO_5$ (M^+), 463.2359; found, 463.2353.

Preparation of 4-Methoxymethoxy-1*H*-indole-6-carboxylic Acid Ethyl Ester (36). To a suspension of phenol **29** (1.18 g, 5.74 mmol) in CH_2Cl_2 (100 mL) at rt were added DIPEA (4.0 mL, 23.0 mmol) and MOMCl (0.7 mL, 9.2 mmol), and the reaction mixture was allowed to stir overnight. The reaction was quenched by addition of water, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (15 to 25% ethyl acetate in hexanes) afforded indole **36** (1.10 g, 77%) as a light-yellow solid. ^{1}H NMR: δ 8.95 (br s, 1H), 7.89 (dd, J = 1.0, 1.0 Hz, 1H), 7.43 (d, J = 1.1 Hz, 1H), 7.26 (dd, J = 3.1, 2.5 Hz, 1H), 6.69 (m, 1H), 5.38 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.54 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 167.7, 149.9, 136.5, 126.4, 124.7, 123.0, 108.4, 103.8, 100.0, 94.7, 60.8, 56.2, 14.3. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.83; H, 6.12; N, 5.42.

4-Methoxymethoxyindole-1,6-dicarboxylic Acid 1-*tert*-Butyl Ester 6-Ethyl Ester (37). To a solution of indole **36** (1.00 g, 4.01 mmol) in THF (20 mL) at 0 °C were added NaH (200 mg, 5 mmol, 60% dispersion in oil) and Boc_2O (960 mg, 4.40 mmol). An additional aliquot of THF was added (8 mL), and after 1 h, the reaction was quenched by addition of NH_4Cl(sat). After the mixture was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Final purification of the resulting material by flash column chromatography (12.5 to 15% Et_2O in hexanes) afforded indole **37** (1.23 g, 87%). ^{1}H NMR: δ 8.54 (br s, 1H), 7.67 (d, J = 3.7 Hz, 1H),

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7.57 (d, J = 1.2 Hz, 1H), 6.74 (dd, J = 3.7, 0.7 Hz, 1H), 5.36 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.53 (s, 3H), 1.70 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 167.0, 149.8, 149.4, 135.7, 127.5, 127.4, 125.4, 111.6, 107.5, 104.2, 94.8, 84.4, 60.9, 56.3, 28.1 (3C), 14.4. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.00; H, 6.68; N, 4.02.

6-Hydroxymethyl-4-methoxymethoxyindole-1-carboxylic Acid *tert*-Butyl Ester (38). To ester **37** (434 mg, 1.24 mmol) in THF (30 mL) at 0 °C was added DIBAL (4.1 mL, 1 M in THF). When judged complete by TLC analysis, the reaction was quenched by addition of NH_4Cl(sat), and the mixture was poured into ethyl acetate, acidified, and then extracted with ethyl acetate. The combined organic extracts were washed with $NaHCO_3$(sat) and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (25% ethyl acetate in hexanes) afforded alcohol **38** (345 mg, 91%) as a colorless oil. ^{1}H NMR: δ 7.84 (s, 1H), 7.48 (d, J = 3.8 Hz, 1H), 6.93 (d, J = 0.9 Hz, 1H), 6.67 (dd, J = 3.8, 0.7 Hz, 1H), 5.30 (s, 2H), 4.75 (s, 2H), 3.51 (s, 3H), 2.16 (br s, 1H), 1.66 (s, 9H). ^{13}C NMR: δ 150.3, 149.7, 138.7, 136.6, 124.8, 121.0, 108.0, 106.3, 104.1, 94.7, 83.7, 66.0, 56.1, 28.1 (3C). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.30; H, 7.13; N, 4.56.

(4-Methoxymethoxy-1*H*-indol-6-ylmethyl)phosphonic Acid Diethyl Ester (39) and 6-(Diethoxyphosphorylmethyl)-4-methoxymethoxyindole-1-carboxylic Acid *tert*-Butyl Ester (40). To LiBr (450 mg, 5.18 mmol) and NEt_3 (0.43 mL, 3.09 mmol) in THF at 0 °C was added benzylic alcohol **38** (312 mg, 1.02 mmol) as a THF solution. The solution was stirred for 5 min, and then MsCl (0.16 mL, 2.07 mmol) was added dropwise. The reaction mixture was allowed to stir for 1 h, and more LiBr (400 mg, 4.61 mmol) was added. After the reaction was judged complete by TLC analysis it was quenched by addition of $NaHCO_3$(sat), and the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. To the resulting residue was added $P(OEt)_3$ (4 mL), and the solution was heated at reflux overnight. The next day the solution was allowed to cool to rt and then poured into water and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50 to 70% ethyl acetate in hexanes) afforded indole phosphonate **40** (18 mg, 4%) as an oil and the parent indole phosphonate **39** (194 mg, 58%) as an oil.

Data for phosphonate **39**: ^{1}H NMR: δ 9.61 (s, 1H), 7.05 (d, J = 2.9 Hz, 1H), 6.99 (t, J = 2.3 Hz, 1H), 6.66 (s, 1H), 6.54, (t, J = 2.2 Hz, 1H), 5.29 (s, 2H), 4.44–3.96 (m, 4H), 3.50 (s, 3H), 3.21 (d, J_{PH} = 21.1 Hz, 2H), 1.24 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 150.2 (d, J_{CP} = 2.7 Hz), 137.7 (d, J_{CP} = 2.9 Hz), 124.8 (d, J_{CP} = 9.4 Hz), 123.5, 118.2 (d, J_{CP} = 2.7 Hz), 107.1 (d, J_{CP} = 7.4 Hz), 105.6 (d, J_{CP} = 5.8 Hz), 98.7, 94.7, 62.1 (d, J_{CP} = 6.8 Hz, 2C), 55.9, 33.9 (d, J_{CP} = 138 Hz), 16.2 (d, J_{CP} = 6.1 Hz, 2C). ^{31}P NMR: δ 28.2. HRMS (EI) m/z: calcd for $C_{15}H_{22}NO_5P$ (M^+), 327.1236; found, 327.1229.

Boc Protection of Phosphonate 39. To phosphonate **39** (194 mg, 0.593 mmol) in CH_2Cl_2 (10 mL) were added DMAP (8 mg, 0.065 mmol) and Boc_2O (150 mg, 0.69 mmol). The reaction was allowed to stir for 2 h and then checked by TLC analysis. After an additional amount of Boc_2O was added (50 mg, 0.23 mmol), the reaction was allowed to proceed for another hour. The reaction was quenched by addition of water, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (80% ethyl acetate in hexanes) afforded Boc-protected indole **40** (183 mg, 72%), whose ^{1}H and ^{13}C NMR spectra were consistent with those of the material prepared via the route below.

Preparation of Phosphonate 40 at Reduced Temperature. To alcohol **38** (147 mg, 0.48 mmol) in THF (10 mL) were added LiBr (250 mg, 2.9 mmol) and NEt_3 (0.2 mL, 1.4 mmol), and the solution was cooled to 0 °C and then allowed to stir. After 10 min, MsCl (0.08 mL, 2.07 mmol) was added dropwise, and the reaction mixture was allowed to stir for 2 h. The reaction was then quenched by addition of NH_4Cl(sat), and the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. To the residue was added $P(OEt)_3$, and the resulting solution was heated to 95 °C and allowed to stir overnight. The next day the solution was allowed to cool to rt and then concentrated in vacuo. Final purification by flash column chromatography (1.5% EtOH in Et_2O) afforded phosphonate **40** (125 mg, 61%) as an oil. ^{1}H NMR: δ 7.78 (br s, 1H), 7.48 (d, J = 3.5 Hz, 1H), 6.88 (m, 1H), 6.66 (d, J = 3.7 Hz, 1H), 5.30 (s, 2H), 4.09–4.00 (m, 4H), 3.51 (s, 3H), 3.26 (d, J_{PH} = 21.6 Hz, 2H), 1.66, (s 9H), 1.27 (t, J = 7.1 Hz, 6H). ^{13}C NMR: δ 150.0 (d, J_{CP} = 2.9 Hz), 149.6, 128.7 (d, J_{CP} = 9.5 Hz), 124.6, 120.3, 110.7 (d, J_{CP} = 7.9 Hz), 108.9 (d, J_{CP} = 5.7 Hz), 104.0 (d, J_{CP} = 1.6 Hz), 94.7, 83.6, 62.0 (d, J_{CP} = 6.6 Hz, 2C), 56.3, 34.3 (d, J_{CP} = 138 Hz), 28.1 (3C), 16.3 (d, J_{CP} = 6.3 Hz, 2C). ^{31}P NMR: δ 27.3. HRMS (EI) m/z: calcd for $C_{20}H_{30}NO_7P$ (M^+), 427.1760; found, 427.1757.

[4-Methoxymethoxy-1-(toluene-4-sulfonyl)-1*H*-indol-6-yl]-methanol (41). To indole **36** (805 mg, 3.23 mmol) in THF (30 mL) at 0 °C was added NaH (170 mg, 4.2 mmol, 60% dispersion in oil) followed after 10 min by TsCl (700 mg, 3.61 mmol). After 30 min, DIBAL (1.45 mL, 8.1 mmol) was added, and the mixture was allowed to stir for an additional 30 min. The reaction was then quenched by addition of NH_4Cl(sat), and the mixture was poured into ethyl acetate, acidified, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% ethyl acetate in hexanes) afforded benzylic alcohol **41** (1.02 g, 87% overall yield). ^{1}H NMR ($(CD_3)_2CO$): δ 7.84 (d, J = 8.3 Hz, 2H), 7.78 (s, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.22, (d, J = 8.5 Hz, 2H), 6.99 (s, 1H), 6.81 (dd, J = 3.7, 0.7 Hz, 1H), 5.27 (s, 2H), 4.78 (s, 2H), 4.53 (br s, 1H), 3.41 (s, 3H), 2.23 (s, 3H). ^{13}C NMR: δ 151.2, 146.0, 141.8, 136.9, 135.8, 130.7 (2C), 127.5 (2C), 126.0, 121.5, 107.2, 106.7, 105.9, 95.2, 65.0, 56.2, 21.3. HRMS (EI) m/z: calcd for $C_{18}H_{19}NO_5S$ (M^+), 361.0984; found, 361.0992.

[4-Methoxymethoxy-1-(toluene-4-sulfonyl)-1*H*-indol-6-ylmethyl]phosphonic Acid Diethyl Ester (42). To alcohol **41** (118 mg, 0.33 mmol) in THF (10 mL) at 0 °C were added LiBr (226 mg, 2.62 mmol) and NEt_3 (0.18 mL, 1.30 mmol). The reaction was allowed to stir for 5 min, and then MsCl (0.06 mL, 0.78 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, and after 3 h, the reaction was quenched by addition of $NaHCO_3$(sat). The mixture was then extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in $P(OEt)_3$ (3 mL) and heated to reflux. The next day the reaction mixture was allowed to cool to rt, poured into water, and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (2.5 to 3% EtOH in Et_2O) afforded phosphonate **42** (133 mg, 85%) as a white solid. ^{1}H NMR: δ 7.78 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 2.8 Hz, 1H), 7.44 (dd, J = 3.7, 0.9 Hz, 1H), 7.22, (d, J = 8.0 Hz, 2H), 6.86 (m, 1H), 6.73 (d, J = 3.7 Hz, 1H), 5.25 (s, 2H), 4.05–3.95 (m, 4H), 3.47 (s, 3H), 3.25 (d, J_{PH} = 21.5 Hz, 2H), 2.33 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR: δ 150.2 (d, J_{CP} = 2.9 Hz), 144.8, 136.1 (d, J_{CP} = 3.1 Hz), 135.1, 129.7 (2C), 129.3 (d, J_{CP} = 9.2 Hz), 126.8 (2C), 125.0 (d, J_{CP} = 1.4 Hz), 120.6 (d, J_{CP} = 3.1 Hz), 109.3 (d, J_{CP} = 6.0 Hz), 108.6 (d, J_{CP} = 7.5 Hz), 105.8 (d, J_{CP} = 1.5 Hz), 94.6, 62.0 (d, J_{CP} = 6.7 Hz, 2C), 56.2, 34.2 (d, J_{CP} = 138.1 Hz), 21.5, 16.3 (d, J_{CP} = 6.1 Hz, 2C). ^{31}P NMR: δ 27.3. HRMS (EI) m/z: calcd for $C_{22}H_{28}NO_7PS$ (M^+), 481.1324; found, 481.1315.

Toluene-4-sulfonic Acid 5-Methoxymethoxy-7-[2-(4-methoxymethoxy-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-yl Ester (43) and 5-Methoxymethoxy-7-[2-(4-methoxymethoxy-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-ol (44). To phosphonate **42** (40 mg, 0.83 mmol) and aldehyde **12**[28] (18 mg, 0.54 mmol) in THF (3 mL) at rt were added NaH (60 mg, 1.5 mmol, 60% dispersion in oil) and 15-

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crown-5 (3 drops), and the resulting solution was heated to reflux. After 30 min, the reaction mixture was allowed to cool to rt, and the reaction was quenched by addition of NH_4Cl(sat). The mixture was then diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (20 to 40% ethyl acetate in hexanes) afforded tosylate **43** (24 mg, 67%) along with alcohol **44** (5 mg, 22%).

Data for tosylate **43**: ^{1}H NMR: δ 8.24 (br s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.14−7.11 (m, 3H), 6.98−6.92 (m, 4H), 6.63 (m, 1H), 5.38 (s, 2H), 5.23 (d, J = 6.6 Hz, 1H), 5.19 (d, J = 6.6 Hz, 1H), 4.33 (dd, J = 10.6, 4.8 Hz, 1H), 3.57 (s, 3H), 3.53 (s, 3H), 2.69−2.66 (m, 2H), 2.45 (s, 3H), 2.10−2.04 (m, 1H), 1.82−1.60 (m, 4H), 1.22 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H). ^{13}C NMR: δ 150.8, 146.1, 144.7, 143.3, 137.7, 134.3, 133.1, 129.8 (3C), 127.9, 127.7 (2C), 126.5, 123.5, 122.6, 121.7, 119.1, 113.4, 104.1, 101.9, 100.1, 95.9, 94.8, 88.4, 76.0, 56.2, 56.2, 47.0, 38.2, 37.4, 27.0, 25.8, 23.1, 21.6, 19.8, 15.1. HRMS (TOF MS ES) m/z: calcd for $C_{37}H_{44}NO_8S$ ([M + H]$^+$), 662.2788; found, 662.2797.

Data for alcohol **44**: ^{1}H NMR: δ 8.30 (br s, 1H), 7.15−7.11 (m, 3H), 7.05−6.92 (m, 4H), 6.64 (m, 1H), 5.39 (s, 2H), 5.24 (d, J = 6.4 Hz, 1H), 5.20 (d, J = 6.5 Hz, 1H), 3.57 (s, 3H), 3.35 (s, 3H), 3.43 (dd, J = 11.5, 3.8 Hz, 1H), 2.75−2.71 (m, 2H), 2.11−2.04 (m, 1H), 1.90−1.54 (m, 5H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 150.8, 146.1, 143.6, 137.7, 133.2, 129.6, 127.8, 126.7, 123.5, 123.2, 121.9, 119.1, 113.5, 104.1, 102.0, 100.1, 96.0, 94.8, 78.0, 76.9. 56.2, 56.2, 46.8, 38.4, 37.7, 28.3, 27.3, 23.2, 19.9, 14.2. HRMS (EI) m/z: calcd for $C_{30}H_{37}NO_6$ (M$^+$), 507.2621; found, 507.2620.

Reduction of Tosylate 43. To MOM-protected tosylate **43** (19.0 mg, 0.03 mmol) in THF (3 mL) at 0 °C was added $LiAlH_4$ (14 mg, 0.40 mmol), and the reaction mixture was allowed to warm to rt overnight. The following morning the reaction was quenched by addition of NH_4Cl(sat), and the mixture was diluted with water and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Final purification by preparative TLC (70% ethyl acetate in hexanes) afforded the desired indole **44** (4.4 mg, 30%) along with recovered starting material (2.7 mg, 14%). The ^{1}H NMR spectrum was consistent with that of the material prepared above.

7-[2-(4-Hydroxy-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-2,5-diol (7). To a methanol solution of protected indole **44** (6 mg, 0.012 mmol) at 0 °C was added TsOH (25 mg, 0.145 mmol). The reaction was allowed to stir overnight and then quenched by addition of water, and the mixture was extracted with ethyl acetate. The combined organic extracts were dried (Mg_2SO_4), filtered, and concentrated in vacuo. Final purification of the residue by preparative TLC (70% ethyl acetate in hexanes) afforded schweinfurthin analogue **7** (2.9 mg, 58%). ^{1}H NMR (CD_3OD): δ 7.09 (d, J = 3.3 Hz, 1H), 7.00 (s, 1H), 6.95 (d, J = 16.2 Hz, 1H), 6.87 (d, J = 16.2 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 1.6 Hz, 1H), 6.66 (d, J = 1.0 Hz, 1H), 6.50 (dd, J = 3.2, 0.9 Hz, 1H), 3.43 (dd, J = 11.5, 3.8 Hz, 1H), 2.74−2.71 (m, 2H), 2.09−2.04 (m, 1H), 1.83−1.63 (m, 4H), 1.24 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 151.2, 147.0, 141.9, 139.8, 133.9, 131.5, 128.9, 127.2, 124.4, 124.0, 120.2, 119.3, 111.0, 103.8, 101.8, 99.7, 78.8, 78.2, 39.5, 38.9, 29.0, 27.9, 24.0, 20.3, 14.9. HRMS (EI) m/z: calcd for $C_{26}H_{29}NO_4$ (M$^+$), 419.2097; found, 419.2096.

Toluene-4-sulfonic Acid 5-Methoxy-7-[2-(4-methoxymethoxy-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-yl Ester (45). To aldehyde **11**[3,28] (63 mg, 0.21 mmol) and phosphonate **42** (156 mg, 0.32 mmol) in THF (5 mL) at rt were added NaH (80 mg, 2.0 mmol, 60% dispersion in oil) and 15-crown-5 (3 drops). The reaction mixture was slowly heated to reflux for 40 min and then allowed to cool to rt. After the reaction was quenched by addition of $NaHCO_3$(sat), the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (30% ethyl acetate in hexanes) afforded tosylate **45** (73 mg, 56%). ^{1}H NMR: δ 8.25 (br s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.14 (s, 1H), 7.12 (dd, J = 3.2, 2.4 Hz, 1H), 7.03 (d, J = 16.2 Hz, 1H), 6.99 (d, J = 1.1 Hz, 1H), 6.95 (d, J = 16.3 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 6.65−6.63 (m, 1H), 5.39 (s, 2H), 4.36−4.31 (m, 1H), 3.89 (s, 3H), 3.57 (s, 3H), 2.70−2.67 (m, 2H), 2.45 (s, 3H), 2.14−2.09 (m, 1H), 2.01−1.96 (m, 1H), 1.87−1.68 (m, 3H), 1.56 (br s, 1H), 1.23 (s, 3H), 0.91 (m, 6H). ^{13}C NMR: δ 150.8, 148.9, 144.6, 142.0, 137.7, 134.3, 133.1, 129.8 (2C), 129.6, 127.8, 127.7 (2C), 126.8, 123.6, 122.0, 120.1, 119.2, 107.0, 104.0, 102.0, 100.1, 94.8, 88.5, 76.0, 56.2, 56.0, 47.0, 38.2, 37.3, 27.1, 25.7, 23.1, 21.6, 19.7, 15.1. HRMS (TOF MS ES) m/z: calcd for $C_{36}H_{42}NO_7S$ ([M + H]$^+$), 632.2682; found, 632.2684.

Toluene-4-sulfonic Acid 5-Methoxy-7-[2-(4-methoxymethoxy-1*H*-indol-6-yl)vinyl]-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-yl Ester (46). To tosylate **45** (73 mg, 0.12 mmol) in THF (3 mL) was added $LiAlH_4$ (45 mg, 1.18 mmol), and the reaction mixture was allowed to stir overnight. The reaction then was quenched by addition of NH_4Cl(sat), and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (30 to 50% ethyl acetate in hexanes) yielded alcohol **46** (24 mg, 43%). ^{1}H NMR: δ 8.25 (br s, 1H), 7.15 (s, 1H), 7.12 (dd, J = 3.1, 2.5 Hz, 1H), 7.04 (d, J = 16.2 Hz, 1H), 7.00 (s, 1H), 6.97 (d, J = 16.2 Hz, 1H), 6.91 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.63 (m, 1H), 5.39 (s, 2H), 3.90 (s, 3H), 3.58 (s, 3H), 3.45−3.40 (m, 1H), 2.74−2.71 (m, 2H), 2.15−2.10 (m, 1H), 1.90−1.80 (m, 2H), 1.74−1.50 (m, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 150.8, 148.9, 142.3, 137.7, 133.2, 129.4, 127.6, 127.0, 123.5, 122.6, 120.2, 119.1, 106.9, 104.0, 102.0, 100.1, 94.8, 78.0, 77.0, 56.2, 56.0, 46.8, 38.4, 37.7, 28.3, 27.3, 23.2, 19.9, 14.3. HRMS (EI) m/z: calcd for $C_{29}H_{35}NO_5$ (M$^+$), 477.2515; found, 477.2512.

6-[2-(7-Hydroxy-4-methoxy-8,8,10a-trimethyl-(5*R*,8a*R*,10a*R*)-5,7,8,8a,9a,10a-hexahydro-6*H*-xanthen-2-yl)-vinyl]-1*H*-indol-4-ol (8). To MOM-protected indole **46** (16.0 mg, 0.033 mmol) in MeOH (3 mL) was added HCl (0.15 mL, 6 M), and the reaction mixture was stirred in a warm water bath for 8.5 h. The reaction was then quenched by dropwise addition of $NaHCO_3$(sat), and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered through basic alumina, and the filtrate was concentrated in vacuo. Final purification by preparative TLC (70% ethyl acetate in hexanes) afforded indole **8** (9 mg, 62%). ^{1}H NMR: δ 8.2 (br s, 1H), 7.13 (dd, J = 3.1, 2.5 Hz, 1H), 7.07 (s, 1H), 7.00 (d, J = 16.2 Hz, 1H), 6.94 (d, J = 16.4 Hz, 1H), 6.90 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 1.7 Hz, 1H), 6.77 (d, J = 0.9 Hz, 1H), 6.59−6.57 (m, 1H), 5.22 (br s, 1H), 3.90 (s, 3H), 3.43 (dd, J = 11.5, 3.7 Hz, 1H), 2.75−2.72 (m, 2H), 2.16−2.10 (m, 1H), 1.90−1.80 (m, 2H), 1.75−1.60 (m, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 149.0, 148.9, 142.4, 138.0, 133.4, 129.4, 127.3, 127.2, 123.5, 122.7, 120.4, 117.4, 106.9, 103.1, 102.1, 99.2, 78.1, 77.0, 56.0, 46.8, 38.4, 37.6, 28.3, 27.4, 23.2, 19.9, 14.3. HRMS (EI) m/z: calcd for $C_{27}H_{31}NO_4$ (M$^+$), 433.2253; found, 433.2245.

4-Methoxymethoxy-3-(3-methylbut-2-enyl)-1*H*-indole-6-carboxylic Acid Ethyl Ester (47). To indole **36** (1.00 g, 4.01 mmol), TBAI (739 mg, 2.00 mmol), and $Zn(OTf)_2$ (878 mg, 2.41 mmol) in a 9:2 mixture of toluene and CH_2Cl_2 (22 mL) at rt was added DIPEA (0.77 mL, 4.41 mmol). After the reaction mixture was allowed to stir for 10 min, prenyl bromide (298 mg, 2.00 mmol) was added dropwise. After 3 h, the reaction was quenched by addition of NH_4Cl(sat), and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (10 to 15% ethyl acetate in hexanes) afforded prenylated indole **47** (415 mg, 65%) along with recovered starting material **36** (540 mg). ^{1}H NMR: δ 8.47 (br s, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.34 (d, J = 1.1 Hz, 1H), 6.96 (m, 1H), 5.46 (m, 1H), 5.35 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.65 (d, J = 6.6 Hz, 2H), 3.53 (s, 3H), 1.74 (d, J = 1.0 Hz, 3H), 1.72 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 167.6, 151.4, 137.4, 131.5, 124.6, 123.8, 123.7, 121.3, 116.7,

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108.2, 102.8, 94.2, 60.7, 56.2, 25.7, 25.4, 17.7, 14.4. HRMS (EI) *m*/*z*: calcd for $C_{18}H_{23}NO_4$ (M^+), 317.1627; found, 317.1631.

[4-Methoxymethoxy-3-(3-methylbut-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indol-6-yl]methanol (48). To indole **47** (315 mg, 0.99 mmol) in THF at 0 °C was added NaH (50 mg, 1.25 mmol, 60% dispersion in oil), and the reaction mixture was allowed to stir for 10 min. After TsCl (230 mg, 1.21 mmol) was added, the solution was stirred for 30 min, and then DIBAL (0.71 mL, 4.0 mmol) was added dropwise. After an additional 30 min, the reaction was quenched by addition of NH_4Cl(sat), and the mixture was acidified with HCl and extracted with ethyl acetate. The combined organic extracts were washed with Na_2CO_3(sat) and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Purification by flash column chromatography (34% ethyl acetate in hexanes) afforded benzylic alcohol **48** (348 mg, 82%). ^{1}H NMR: δ 7.71 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.13 (m, 1H), 6.85 (d, J = 0.6 Hz, 1H), 5.41−5.39 (m, 1H), 5.22 (s, 2H), 4.71 (s, 2H), 3.51 (d, J = 7.1 Hz, 2H), 3.46 (s, 3H), 2.37 (br s, 1H), 2.30 (s, 3H), 1.76 (d, J = 0.8 Hz, 3H), 1.68 (s, 3H). ^{13}C NMR: δ 151.8, 144.6, 139.1, 137.0, 135.2, 132.9, 129.7 (2C), 126.6 (2C), 122.7, 121.9, 121.8, 120.2, 105.9, 105.7, 94.1, 65.5, 56.1, 25.7, 25.6, 21.4, 17.7. HRMS (EI) *m*/*z*: calcd for $C_{23}H_{27}NO_5S$ (M^+), 429.1610; found, 429.1609.

[4-Methoxymethoxy-3-(3-methylbut-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indol-6-ylmethyl]phosphonic Acid Diethyl Ester (49). To alcohol **48** (332 mg, 0.77 mmol) in THF (15 mL) at 0 °C were added LiBr (537 mg, 6.18 mmol) and NEt_3 (0.43 mL, 3.09 mmol). The solution was stirred for 5 min, and then MsCl (0.18 mL, 2.32 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, and after 2 h, the reaction was quenched by addition of $NaHCO_3$ (sat). The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Without further purification, the resulting residue was dissolved in $P(OEt)_3$ (3 mL) and heated to reflux. The next day the solution was allowed to cool to rt and then poured into water and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash column chromatography (2% EtOH in Et_2O) afforded indole phosphonate **49** (374 mg, 88%) as a waxy white solid. ^{1}H NMR: δ 7.75 (d, J = 8.4 Hz, 2H), 7.57 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.10, (d, J = 1.1 Hz, 1H), 6.80 (m, 1H), 5.41−5.36 (m, 1H), 5.23 (s, 2H), 4.00 (m, 4H), 3.51−3.47 (m, 5H), 3.22 (d, J_{PH} = 21.5 Hz, 2H), 2.33 (s, 3H), 1.77 (s 3H), 1.68 (s, 3H), 1.25 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 151.6 (d, J_{CP} = 2.9 Hz) 144.8, 137.1 (d, J_{CP} = 3.1 Hz), 135.4, 133.0, 129.7 (2C), 129.2 (d, J_{CP} = 9.3 Hz), 126.8 (2C), 122.7 (d, J_{CP} = 1.6 Hz), 121.8, 121.7 (d, J_{CP} = 1.8 Hz), 119.7 (d, J_{CP} = 3.2 Hz), 108.9 (d, J_{CP} = 5.9 Hz), 108.7 (d, J_{CP} = 7.6 Hz), 94.3, 62.1 (d, J_{CP} = 6.7 Hz, 2C), 56.1, 34.2 (d, J_{CP} = 138.3 Hz), 25.7, 25.6, 21.4, 17.7, 16.3 (d, J_{CP} = 6.0 Hz, 2C). ^{31}P NMR: δ 26.9. HRMS (EI) *m*/*z*: calcd for $C_{27}H_{36}NO_7PS$ (M^+), 549.1950; found, 549.1959.

5-Methoxy-7-{2-[4-methoxymethoxy-3-(3-methylbut-2-enyl)-1*H*-indol-6-yl]vinyl}-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-ol (51). To aldehyde **11** (44 mg, 0.15 mmol) and phosphonate **49** (100 mg, 0.18 mmol) in THF (4 mL) at 0 °C were added NaH (80 mg, 2.0 mmol, 60% dispersion in oil) and 15-crown-5 (2 drops), and the reaction mixture was allowed warm to rt. After 2 h, the reaction was quenched by addition of NH_4Cl(sat), and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Purification by flash column chromatography (50% ethyl acetate in hexanes) afforded a mixture of the *N*-Ts compound **50** and free indole **51** (55 mg) as an oil. This material was dissolved in a mixture of THF and *i*-PrOH (5 mL, 1:1 mixture) at 0 °C, NaH (150 mg, excess) was added, and the reaction mixture was allowed to warm to rt. The following day the reaction was quenched by addition of water, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% ethyl acetate in hexanes) afforded indole **51** (35 mg, 44% for two steps) as an oil. ^{1}H NMR: δ 7.95 (br s, 1H), 7.07 (s, 1H), 6.99−6.98 (m, 2H), 6.92−6.90 (m, 2H), 6.87 (m, 1H), 6.81 (s, 1H), 5.51−5.46 (m, 1H), 5.36 (s, 2H), 3.90 (s, 3H), 3.62 (d, J = 7.0 Hz, 2H), 3.57 (s, 3H), 3.43 (dd, J = 11.6, 3.8 Hz, 1H), 2.74−2.71 (m, 2H), 2.15−2.10 (m, 1H), 1.89−1.56 (m, 11H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 152.1, 148.9, 142.3, 138.6, 133.0, 131.2, 129.4, 127.6, 126.8, 124.1, 122.6, 120.9, 120.2, 117.5, 116.7, 106.9, 103.8, 100.9, 94.3, 78.0, 77.0, 56.1, 56.0, 46.8, 38.4, 37.7, 28.3, 27.3, 25.7, 25.6, 23.2, 19.8, 17.7, 14.3. HRMS (EI) *m*/*z*: calcd for $C_{34}H_{43}NO_5$ (M^+), 545.3141; found, 545.3135.

6-[2-(7-Hydroxy-4-methoxy-8,8,10a-trimethyl-(5*R*,8a*R*,10a*R*)-5,7,8,8a,9,10a-hexahydro-6*H*-xanthen-2-yl)-vinyl]-3-(3-methylbut-2-enyl)-1*H*-indol-4-ol (9). To compound **51** (31 mg, 0.057 mmol) in MeOH (2 mL) at rt was added TsOH (75 mg, 0.39 mmol), and the reaction flask was wrapped in foil. After 10 h, the reaction was quenched by addition to $NaHCO_3$(sat), and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with Na_2CO_3(sat) and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% ethyl acetate in hexanes) afforded stilbene **9** (8 mg, 28%) as a light-yellow oil. ^{1}H NMR: δ 7.90 (br s, 1H), 6.99−6.96 (m, 3H), 6.89−6.85 (m, 3H), 6.74 (s, 1H), 5.91 (br s, 1H), 5.54 (m, 1H), 3.90 (s, 3H), 3.58 (d, J = 6.6 Hz, 2H), 3.44 (dd, J = 11.6, 3.7 Hz, 1H), 2.75−2.72 (m, 2H), 2.16−2.10 (m, 1H), 1.90−1.55 (m, 5H), 1.84 (s, 3H), 1.82 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 150.1, 148.9, 139.2, 135.1, 133.6, 129.8, 129.4, 127.3, 127.1, 125.1, 122.6, 121.0, 120.3, 116.4, 115.2, 106.9, 102.8, 102.8, 78.1, 56.0, 46.8, 38.4, 37.7, 28.3, 27.4, 25.8, 25.7, 23.2, 19.8, 17.7, 14.3. HRMS (EI) *m*/*z*: calcd for $C_{32}H_{39}NO_4$ (M^+), 501.2879; found, 501.2874.

6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxymethoxy-1-(toluene-4-sulfonyl)-1*H*-indole (52). To alcohol **41** (1.09 g, 3.01 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added imidazole (502 mg, 7.53 mmol) and TBSCl (500 mg, 3.31 mmol), and then the solution was allowed to warm to rt. The next day the reaction was quenched by addition of NH_4Cl(sat), and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (8% ethyl acetate in hexanes) afforded silyl ether **52** (1.39 g, 97%). ^{1}H NMR: δ 7.75 (d, J = 8.4 Hz, 2H), 7.63 (m, 1H), 7.45 (d, J = 3.7 Hz, 1H), 7.20, (dd, J = 8.5, 0.6 Hz, 2H), 6.88 (m, 1H), 6.73 (dd, J = 3.7, 0.8 Hz, 1H), 5.24 (s, 2H), 4.81 (s, 2H), 3.47 (s, 3H), 2.33 (s, 3H), 0.97 (s, 9H), 0.12 (s, 6H). ^{13}C NMR: δ 150.3, 144.8, 139.8, 136.1, 135.3, 129.8 (2C), 128.8 (2C), 124.9, 120.7, 105.8, 105.9, 104.9, 94.7, 65.2, 56.1, 25.9 (3C), 21.5, 18.3, −5.2 (2C). HRMS (EI) *m*/*z*: calcd for $C_{24}H_{33}NO_5SSi$ (M^+), 475.1849; found, 475.1856.

6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxymethoxy-2-(3-methylbut-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indole (53). To silyl-protected indole **52** (724 mg, 1.52 mmol) in THF were added a few 4 Å molecular sieves, and the mixture was cooled to −78 °C. After *n*-BuLi (0.75 mL, 2.3 M in hexanes) was added, the mixture was stirred for 20 min, and then prenyl bromide (420 mg, 2.82 mmol) was added. The next day the reaction was quenched by addition of NH_4Cl(sat), and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (5% ethyl acetate in hexanes) afforded prenyl indole **53** (560 mg, 68%) as well as recovered starting material **52** (76 mg, 10%). ^{1}H NMR: δ 7.91 (d, J = 0.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.99 (s, 1H), 6.52 (d, J = 0.8 Hz, 1H), 5.47 (m, 1H), 5.31 (s, 2H), 4.90 (s, 2H), 3.74 (d, J = 7.2 Hz, 2H), 3.55 (s, 3H), 2.40 (s, 3H), 1.86 (s, 3H), 1.71 (s, 3H), 1.05 (s, 9H), 0.20 (s, 6H). ^{13}C NMR: δ 149.5, 144.5, 139.9, 138.7, 138.6, 136.5, 134.5, 129.7 (2C), 126.3 (2C), 119.8, 119.6, 106.5, 106.3, 105.3, 94.8, 65.5, 56.0, 27.9, 25.9 (3C), 25.7, 21.4, 18.3, 17.7, −5.2 (2C). HRMS (EI) *m*/*z*: calcd for $C_{29}H_{41}NO_5SSi$ (M^+), 543.2475; found, 543.2476.

[4-Methoxymethoxy-2-(3-methylbut-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indol-6-yl]methanol (54). To silyl ether **53** (682 mg, 1.26 mmol) in THF (20 mL) at rt was added TBAF (1.88 mL, 1.0 M

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in THF). After 2 h, the reaction was quenched by addition of water, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Purification by flash column chromatography (30 to 45% ethyl acetate in hexanes) afforded alcohol **54** (461 mg, 85%). ^{1}H NMR: δ 7.84 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.93 (s, 1H), 6.44 (s, 1H), 5.38 (m, 1H), 5.24 (s, 2H), 4.74 (s, 2H), 3.64 (d, J = 7.1 Hz, 2H), 3.46 (s, 3H), 2.60 (br s, 1H), 2.31 (s, 3H), 1.78 (s, 3H), 1.61 (s, 3H). ^{13}C NMR: δ 149.5, 144.6, 140.1, 138.5, 138.1, 136.2, 134.7, 129.7 (2C), 126.2 (2C), 119.9, 119.5, 107.2, 106.7, 105.2, 94.5, 65.7, 56.1, 27.8, 25.7, 21.4, 17.6. HRMS (TOF MS EI) m/z: calcd for $C_{23}H_{27}NO_5S$ (M^+), 429.1610; found, 429.1622.

[4-Methoxymethoxy-2-(3-methylbut-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indol-6-ylmethyl]phosphonic Acid Diethyl Ester (55). To benzylic alcohol **54** (333 mg, 0.78 mmol) in THF were added LiBr (540 mg, 6.20 mmol) and NEt_3 (0.44 mL, 3.10 mmol), and the solution was cooled to 0 °C. After 15 min, MsCl (0.19 mL, 2.46 mmol) was added dropwise, and the reaction was allowed to stir and slowly warm to rt. After 2 h, when the reaction was complete as judged by TLC analysis, it was quenched by addition of water, and the mixture was extracted with Et_2O. The organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. To the resulting residue was added $P(OEt)_3$ (3 mL), and the solution was heated at reflux overnight. The next day the solution was allowed to cool to rt and then poured into water and extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50 to 70% ethyl acetate in hexanes) afforded indole phosphonate **55** (384 mg, 90%). ^{1}H NMR: δ 7.82 (d, J = 2.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.87 (s, 1H), 6.43 (s, 1H), 5.40−5.35 (m, 1H), 5.25 (s, 2H), 4.07−3.94 (m, 4H), 3.64 (d, J = 7.2 Hz, 2H), 3.48 (s, 3H), 3.26 (d, J_{PH} = 21.3 Hz, 2H), 2.34 (s, 3H), 1.78 (s, 3H), 1.62 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H). ^{13}C NMR: δ 149.3 (d, J_{CP} = 3.1 Hz) 144.6, 140.0 (d, J_{CP} = 1.9 Hz), 138.5 (d, J_{CP} = 3.1 Hz), 136.2, 134.7, 129.9 (2C), 128.1 (d, J_{CP} = 9.3 Hz), 126.3 (2C), 119.5, 119.4 (d, J_{CP} = 3.1 Hz), 109.9 (d, J_{CP} = 7.4 Hz), 109.5 (d, J_{CP} = 6.1 Hz), 105.2, 94.8, 62.2 (d, J_{CP} = 6.9 Hz, 2C), 56.2, 34.2 (d, J_{CP} = 137.7 Hz), 27.8, 25.6, 21.4, 17.7, 16.2 (d, J_{CP} = 5.9 Hz, 2C). ^{31}P NMR: δ 27.3. HRMS (EI) m/z: calcd for $C_{27}H_{36}NO_7PS$ (M^+), 549.1950; found, 549.1943.

5-Methoxy-7-{2-[4-methoxymethoxy-2-(3-methylbut-2-enyl)-1*H*-indol-6-yl]vinyl}-1,1,4a-trimethyl-(2*R*,4a*R*,9a*R*)-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-2-ol (57). To phosphonate **55** (74 mg, 0.14 mmol) and aldehyde **11** (30 mg, 0.10 mmol) in THF (2 mL) at 0 °C were added NaH (50 mg, 1.25 mmol, 60% dispersion in oil) and 15-crown-5 (3 drops). After the reaction mixture was allowed to stir for 4 h, the reaction was quenched by addition of NH_4Cl(sat), and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Purification by flash column chromatography (50% ethyl acetate in hexanes) afforded a mixture of *N*-tosyl indole **56** and unprotected indole **57**. To the mixed residue in 1:1 THF/*i*-PrOH (3 mL) at 0 °C was added NaH (120 mg, 3.0 mmol), and the reaction mixture was allowed to warm to rt overnight. The next day the reaction was quenched by addition of NH_4Cl(sat), and the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% ethyl acetate in hexanes) afforded indole **57** (20 mg, 37% for two steps) as an oil. ^{1}H NMR: δ 7.92 (br s, 1H), 7.08 (m, 1H), 7.02 (d, J = 16.1 Hz, 1H), 6.96 (m, 1H), 6.94 (d, J = 16.1 Hz, 1H), 6.89 (m, 1H), 6.86 (m, 1H), 6.31 (m, 1H), 5.40 (m, 1H), 5.36 (s, 2H), 3.90 (s, 3H), 3.56 (s, 3H), 3.49−3.39 (m, 3H), 2.74−2.71 (m, 2H), 2.18−2.10 (m, 1H), 1.90−1.60 (m, 5H), 1.79 (s, 3H), 1.74 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H). ^{13}C NMR: δ 150.1, 148.9, 142.3, 138.3, 137.5, 134.6, 132.1, 129.5, 127.8, 126.4, 122.6, 120.1, 120.1, 119.9, 107.1, 106.9, 103.5, 102.3, 95.0, 78.1, 77.0, 56.1, 56.0, 46.8, 38.4, 37.7, 28.3, 27.4, 27.1, 25.7, 23.2, 19.9, 17.8, 14.3. HRMS (EI) m/z: calcd for $C_{34}H_{43}NO_5$ (M^+), 545.3141; found, 545.3135.

6-[2-(7-Hydroxy-4-methoxy-8,8,10a-trimethyl-(5*R*,8a*R*,10a*R*)-5,7,8,8a,9,10a-hexahydro-6*H*-xanthen-2-yl)-vinyl]-2-(3-methylbut-2-enyl)-1*H*-indol-4-ol (10). To compound **57** (8 mg, 0.015 mmol) in MeOH (0.8 mL) in a foil-wrapped flask was added TsOH (25 mg, 0.13 mmol), and the reaction mixture was allowed to stir at rt. After 10 h, the reaction was quenched by addition of $NaHCO_3$(sat), and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by radial chromatography (50% ethyl acetate in hexanes) afforded compound **10** (5 mg, 68%) as a light-yellow oil. ^{1}H NMR (CD_3OD): δ 6.99 (d, J = 16.4 Hz, 1H), 6.95 (m, 2H), 6.90 (d, J = 16.2 Hz, 1H), 6.82 (m, 1H), 6.63 (s, 1H), 6.17 (s, 1H), 5.46−5.41 (m, 1H), 3.85 (s, 3H), 3.44 (d, J = 7.3 Hz, 2H), 3.37 (dd, J = 10.8, 3.9 Hz, 1H), 2.76−2.73 (m, 2H), 2.07−2.02 (m, 1H), 1.85−1.60 (m, 4H), 1.79 (s, 3H), 1.75 (s, 3H), 1.23 (s, 3H), 1.11 (s, 3H), 0.88 (s, 3H). ^{13}C NMR: δ 150.5, 150.1, 143.2, 140.1, 139.4, 134.3, 132.9, 131.4, 129.3, 126.6, 124.0, 122.2, 121.4, 119.4, 108.0, 103.4, 102.0, 96.7, 78.7, 78.1, 56.4, ~49 (obscured by solvent), 39.5, 38.9, 29.0, 28.0, 27.9, 25.9, 24.1, 20.2, 17.8, 14.9. HRMS (TOF MS ES) m/z: calcd for $C_{32}H_{39}NO_4$ ([M + H]$^+$), 502.2957; found, 502.2956.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): DFW is a co-founder and holds an equity interest in Terpenoid Therapeutics, Inc.

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