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Synthesis of Indole Analogues of the Natural Schweinfurthins

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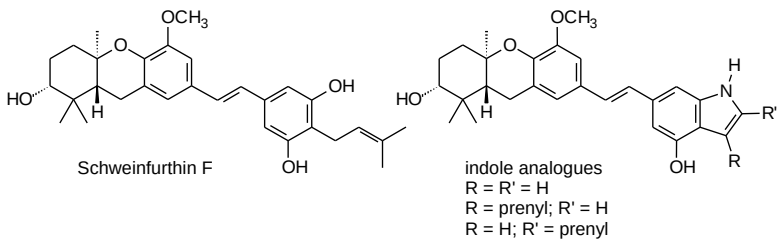
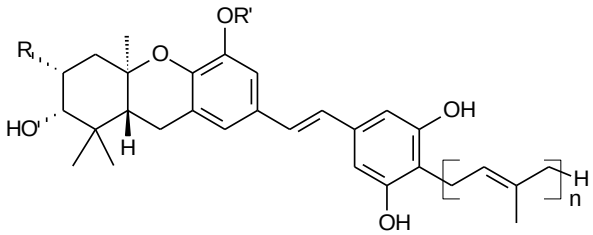


Abstract.

An interest in the schweinfurthins, natural stilbenes with significant anti-proliferative activity, has prompted efforts to prepare a set of indole analogues. To approach the desired compounds through a Horner-Wadsworth-Emmonds 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 a Stobbe condensation and cyclization. A prenyl substituent was incorporated at the C-3 position of a 4,6-disubstituted indole through a highly regioselective electrophilic aromatic substitution reaction, while metalation and alkylation provided the C-2 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 gives 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's (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 these compounds 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 in 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 bioavailability.[12,13] Furthermore, the D-ring resorcinol of the natural schweinfurthins may limit the schweinfurthins' stability, and proper placement of an indole system might improve the chemical stability as well. Based on this rationale, 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' = H, n = 2 3-Deoxyschweinfurthin B

Figure 1. Some natural schweinfurthins (**1** – **4**) and some synthetic analogues (**5**, **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 would view the indole nitrogen as a replacement for one of the resorcinol oxygens, and incorporate the remainder of the indole ring as a substituent on the position para to the stilbene olefin (Figure 2). These structures would exploit the known flexibility of the para position to modification with preservation of biological activity.[4,7,8] Furthermore, preparation of intermediates leading to structures **7** and **8** might be readily modified to allow addition of isoprenoid substituents to the 5-membered ring, via electrophilic aromatic substitution (which is favored at C-3 of indole itself[14] and would lead to compound **9**) or via anion chemistry (which can be directed to C-2 in *N*-substituted indoles and would provide compound **10**).[15,16] Because both compounds **9** and **10** 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.

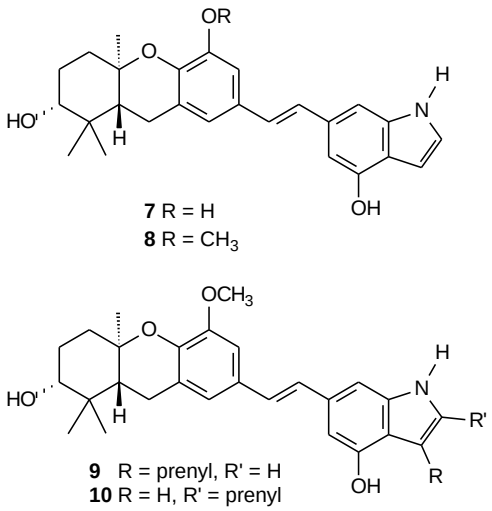
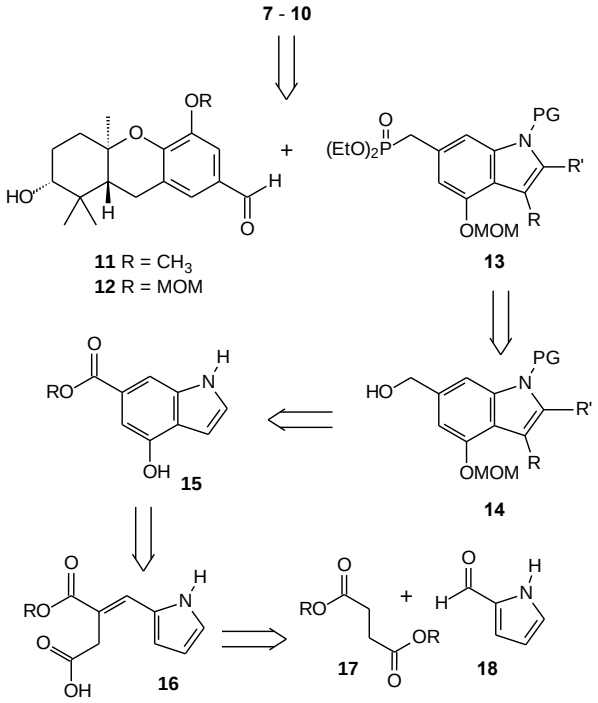


Figure 2. First generation indole targets.

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 as compound **13**. Given the vast number of known indoles it was somewhat surprising to find that apparently only C-2[18] and C-3[19] phosphonomethyl compounds have been prepared. Based on the assumption that phosphonate **13** could be prepared from the corresponding alcohol **14**, which in turn should be available from the 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 preparation of 2-substituted or 2,3-disubstituted compounds.[21,22] However, preparation of the substituted indole **15** has been reported through an approach based on a Stobbe condensation of a succinate diester (**17**) and 2-pyrrole carboxaldehyde (**18**) followed by cyclization of the intermediate acid **16**.[23] While the initial report did not provide a complete characterization of the product, a more recent study from the Vedejs labs 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 with preparation of several indoles based on this strategy.

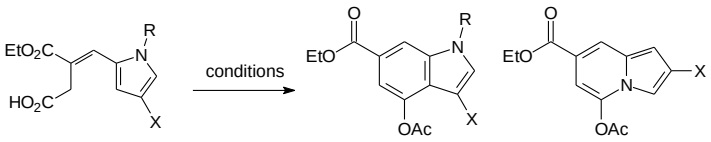


Scheme 1. Retrosynthetic analysis.

Results and Discussion.

The Stobbe condensation of diethyl succinate with 2-pyrrole carboxaldehyde (**18**) smoothly gave the half ester **19** as expected.[24] Without extensive purification, this material was treated with a mixture of acetic anhydride and acetic acid (6:1) in refluxing toluene to induce cyclization (Scheme 2). These conditions resulted in formation of the acetate-protected indole **20** (74%) accompanied by small amounts of the 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 the 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, treatment of compound **22** under standard cyclization conditions gave only trace amounts of the desired indole **23** and afforded the indolizine **24** as the major product

instead. Compound **24** is highly fluorescent and might be useful for 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*-methyl pyrrole.[27] Because previous syntheses of schweinfurthin analogues employed MOM-protected phenols, the 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 the pyrrole **18** was protected as its MOM derivative **27**, cyclization of the Stobbe product now gave only the desired indole **28**. Because a late stage deprotection of the indole MOM group ultimately proved more difficult than expected (*vide infra*), pyrrole aldehyde **18** also was protected as its tosyl derivative. However, in this case attempted Stobbe condensation proved problematic, so introduction of this group at this stage of the sequence was not pursued further.

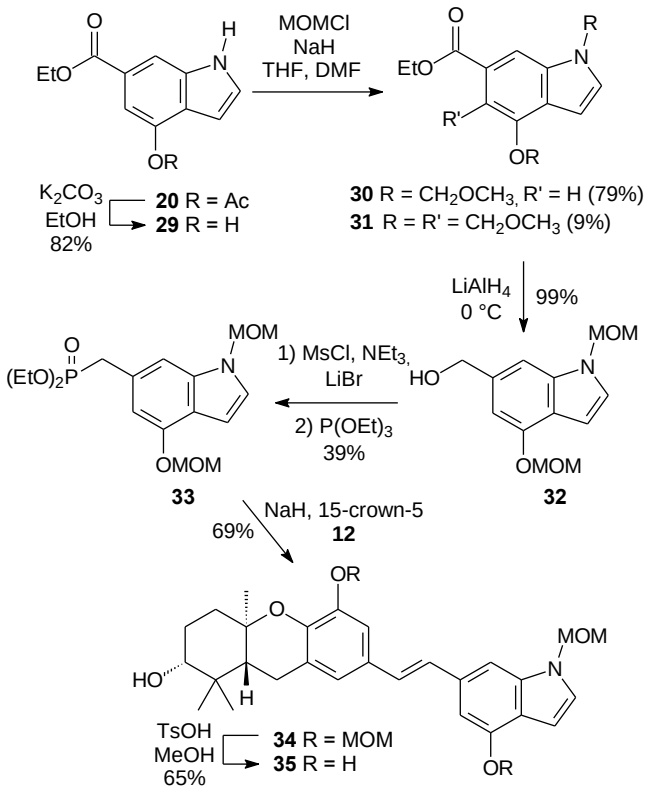


19 R = H, X = H — Ac_2O, AcOH, toluene — **20** R = H, X = H (74%) — **21** X = H (1%)
22 R = H, X = Br — Ac_2O, AcOH, THF — **23** R = H, X = Br (trace) — **24** X = Br (79%)
25 R = MOM, X = Br — Ac_2O, KOAc — **26** R = MOM, X = Br (79%)
27 R = MOM, X = H — Ac_2O, KOAc — **28** R = MOM, X = H (82%)

Scheme 2. Cyclization to indoles and indolizines

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 C-5 isomer **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. 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 Arbuzov reaction of that bromide with $(EtO)_3P$ in refluxing toluene gave the desired phosphonate **33** in modest yield.

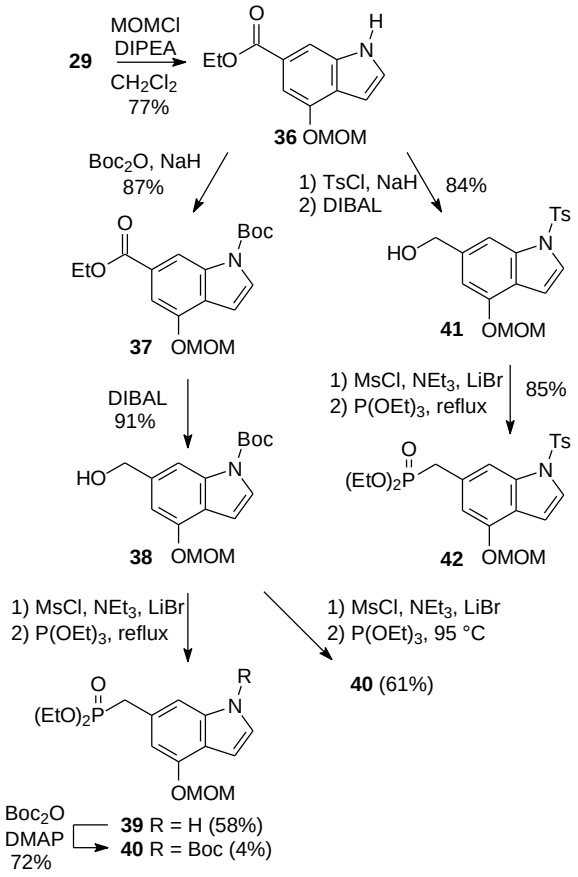


Scheme 3. Synthesis and HWE condensation of indole phosphonate **33**.

The HWE coupling of the hexahydroxanthene aldehyde **12**[28] with phosphonate **33** smoothly gave the protected analogue **34**. Unfortunately, attempted hydrolysis of the three MOM groups by treatment with TsOH/MeOH gave compound **35**, where 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, and gave only decomposition.

To circumvent this difficult hydrolysis, a new strategy based upon early formation of a differentially protected indole was explored. Selective MOM protection of the phenol **29** gave

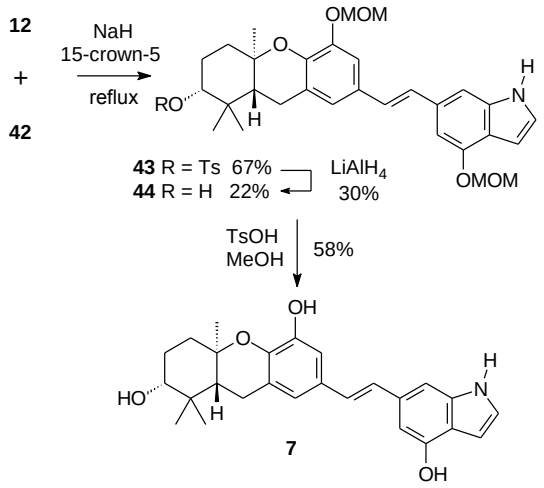
indole **36** (Scheme 4) and different *N*-protecting groups then could be introduced easily. For example, treatment of compound **36** with base and Boc_2O gave the carbamate **37**, and selective reduction of the ethyl ester gave the primary alcohol **38** in good yield. Under standard conditions for 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 re-installed through treatment of phosphonate **39** with Boc_2O to give phosphonate **40**, or phosphonate **40** could be obtained more directly from the alcohol **38** in a reasonable yield (61%) if the Arbuzov reaction were 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 the alcohol **41** in good yield. The tosyl group proved stable to standard conditions for formation of the phosphonate, and compound **42** was obtained smoothly.



Scheme 4. Synthesis of new indole phosphonates.

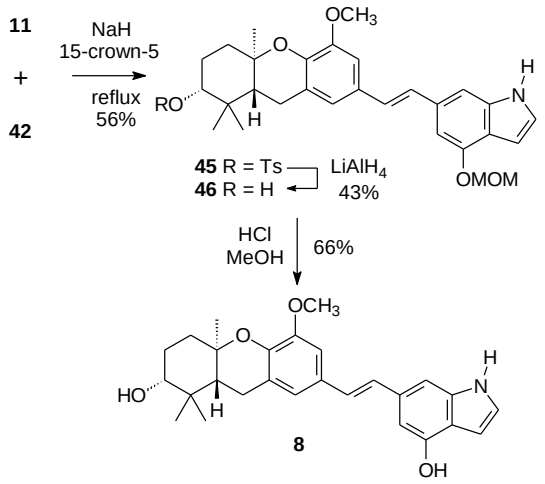
Of the new indole phosphonates **39**, **40**, and **42**, the HWE condensation of compound **39** with an aldehyde representing the schweinfurthin left half would be most advantageous because it would avoid an *N*-deprotection step of the product at a later stage. In the limited number of condensations between an indole phosphonate and an aldehyde, an *N*-protected indole always was employed.[33-36] Nevertheless, because aldehyde **12** has been used in similar HWE reactions,[3,6,13] condensations were attempted between this aldehyde and phosphonate **39**. 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] 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 ^{1}H 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 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 the stilbene **7**, the first schweinfurthin G analogue that incorporates an indole system.



Scheme 5. Synthesis of an indole analogue of schweinfurthin G.

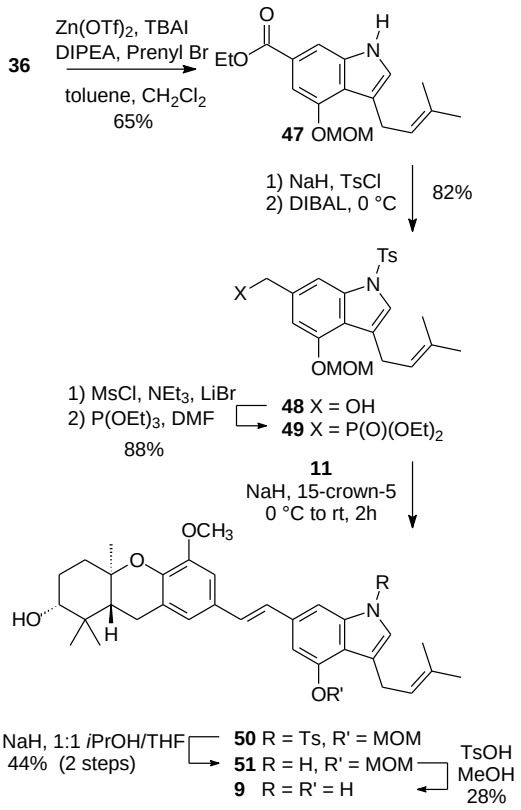
To prepare the analogous schweinfurthin F analogue, phosphonate **42** was allowed to react with aldehyde **11**[3] and base (Scheme 6). When the reaction was conducted at reflux in THF, the only stilbene product (56%) again reflected transfer of the tosyl group from the indole nitrogen to the A-ring alcohol. Treatment of this hindered tosylate ester with $LiAlH_4$ did afford the free alcohol **46** in modest yield. Compound **46** undergoes hydrolysis of the phenolic MOM group under standard conditions to afford the schweinfurthin F analogue **8**.



Scheme 6. Synthesis of an indole analogue of schweinfurthin F.

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 C-3 alkylation through electrophilic aromatic substitution. Among the attractive features of the original study, alkylation of indole itself with prenyl halides generally gave only the C-3 alkylated product, proceeded in ~60% yield, and did not give the products of S_N2' reaction (i.e. "reversed" 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 C-6 and C-4 groups that might impact reactivity were required. In particular, a C-6 ethoxycarbonyl group would add an electron withdrawing substituent system, while reduction of this group to the corresponding

alcohol might invite polymerization reactions given the known reactivity of benzyl alcohol under these conditions.[53] Furthermore, a MOM substituent at the C-4 position might compete with an isoprenoid halide for complexation with the $Zn(OTf)_2$ or introduce a degree of steric hindrance to the C-3 position. Nevertheless, the brevity of this approach led us to study the process with indole **36**. To our delight, the reaction of indole **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.

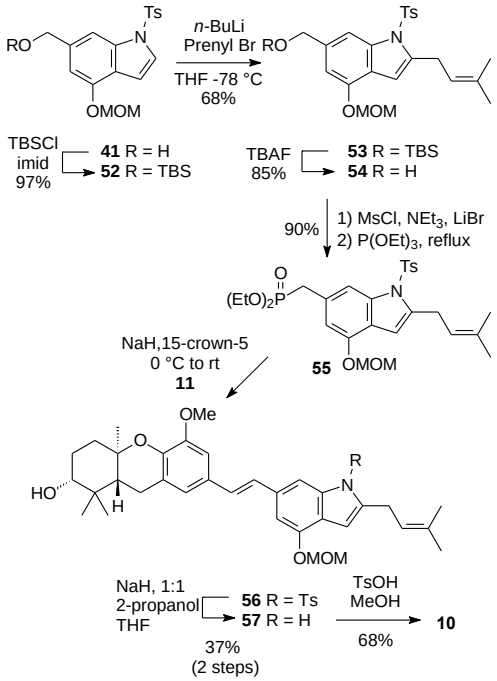


Scheme 7. Synthesis of the prenylated indole schweinfurthin **9**.

Once ester **47** was in hand, the remaining steps in the sequence proceeded in a fashion parallel to those employed for preparation of 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**. An

HWE condensation with aldehyde **11** afforded a mixture of *N*-tosyl intermediate **50** and the 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, the schweinfurthin F analogue **9**.

To access compound **10** from an intermediate already in hand, indole **41** was protected as its silyl ether **52**, and then treated with *n*-BuLi and prenyl bromide. Despite the presence in the B-ring of two substituents that might participate in directed ortho metallation,[54] this sequence gave a single product identified as the C-2 alkylated indole **53**. After deprotection to the alcohol **54**, and formation of the phosphonate **55** through standard reactions, condensation of phosphonate **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**.



Scheme 8. Synthesis of the prenylated indole schweinfurthin **10**.

In preliminary bioassays, compounds **7**–**10** were tested for their activity 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}'s ranging from ~200 nM to 2.5 μM (Table 1).[37] Because the more active compounds show potency comparable to some of the natural schweinfurthins, preparation of additional indole analogues as well as more extensive testing in the 60 cell line assay of the National Cancer Institute would be warranted.

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

Table 1. Preliminary bioassays in the SF-295 cell line

In conclusion, we have developed a strategy for synthesis of indole analogues of the natural schweinfurthins. This effort included preparation of several new indoles by cyclization after a Stobbe condensation, and ultimately led to preparation of the first indoles bearing a phosphonomethyl substituent in the indole B-ring. These B-ring phosphonates have been used in HWE reactions with the complex aldehydes **11** and **12**, and undergo these condensations smoothly as long as the indole nitrogen is 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 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 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 to C-3 of the indole system, which in turn allowed preparation of a schweinfurthin F analogue complete

with a side chain. In this more hindered prenyl indole, an HWE condensation at room temperature did afford the desired stilbene without transfer of the tosyl group, and reductive cleavage of the *N*-tosyl group was more efficient. Finally, a C-2 prenylated indole was obtained through metalation and alkylation of a tosyl indole intermediate, which allows divergent use of intermediate **35** to obtain either the C-2 or C-3 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 activity 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 reactions in non-aqueous 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 solvent and $(CH_3)_4Si$ (^1H, 0.00 ppm) or $CDCl_3$ (^{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.

2-(1*H*-Pyrrol-2-ylmethylene)-succinic acid 1-ethyl ester (19). General Procedure for Stobbe Condensations. According to the procedure of Vedejs[24] but in THF (60 mL) instead of benzene, NaH (4.2 g, 105 mmol, 60% dispersion oil) was added slowly to aldehyde **18** (5.01 g, 52.6 mmol) and diethylsuccinate (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, quenched by addition of water and Et_2O was added and then 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 ($MgSO_4$), filtered, and the solvent was removed *in vacuo* to afford acid **19** (11.2 g, 96%) as a red-brown solid: ^{1}H 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 ($(CD_3)_2CO$, 400 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-Acetoxy-indolizine-7-carboxylic acid ethyl ester (21). To acid **19** (17.1 g, 76.7 mmol) in toluene (800 mL) was added Ac_2O (48 mL, 506 mmol) and glacial AcOH (4.62 mL, 80.5 mmol) and the reaction was heated to reflux. The next day the reaction mixture was allowed to cool to rt, quenched by addition of K_2CO_3 (sat), 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. For indole **20**: ^{1}H 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 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.

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 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 was 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-bromo-2-pyrrolecarboxaldehyde (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 oil). Standard work-up 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-bromo-indolizine-7-carboxylic acid ethyl ester (24). To acid **22** (811 mg, 2.68 mmol) in THF was 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. The reaction mixture was then allowed to cool to rt, quenched by addition of Na_2CO_3 (sat), and 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 oil) and the reaction was allowed to stir for 5 min. To the resulting solution was added MOMCl (0.97 mL, 12.8 mmol) and the reaction was allowed to stir for 2 h and then quenched by addition of NH_4Cl (sat), diluted with water, and extracted with Et_2O. The combined organic extracts were washed with water and the 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}HMR 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 work-up 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 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 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-2-pyrrolecarboxaldehyde (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 one h. The solution was cooled to 0 °C, quenched by addition of water, diluted with Et_2O, and extracted with 5% KOH. The combined aqueous extracts were acidified (6M 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 chromatograph (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 and 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 2N NaOH. The aqueous extracts were acidified and 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 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 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%). 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. 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, 2 H), 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 mixture was then quenched by addition of water, 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 was 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 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, LiBr (33 mg, 0.38 mmol) was added, and the reaction mixture was allowed to stir overnight. The following day the reaction mixture was poured into Et_2O, quenched by addition of 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*. 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, poured into Et_2O, and then quenched by addition of 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 (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 Hz, 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 was allowed to warm slowly to rt. The following day the reaction mixture was quenched by addition of 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 (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 solution was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with ethyl acetate. The combined organics 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 the 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 was 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 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-Methoxymethoxy-indole-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 was 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 mixture was quenched by addition of NH_4Cl (sat) and 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), 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 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-methoxymethoxy-indole-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, 1M in THF). When judged complete by TLC analysis, the reaction was quenched by addition of NH_4Cl (sat), 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 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.

Preparation of (4-Methoxymethoxy-1*H*-indol-6-ylmethyl)-phosphonic acid diethyl ester (39) and 6-(Diethoxy-phosphorylmethyl)-4-methoxymethoxy-indole-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 the 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), 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.

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) was 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 mixture was quenched by addition of water and 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 the Boc-protected indole **40** (183 mg, 72%) with ^{1}H and ^{13}C NMR spectra consistent with 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) was added LiBr (250 mg, 2.9 mmol) and NEt_3 (0.2 mL, 1.4 mmol), the solution was cooled to 0 °C, and then was 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), 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 reaction was allowed to stir for an additional 30 min. It then was quenched by addition of NH_4Cl (sat), 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 was 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 was allowed to warm to rt

and after 3 h it was quenched by addition of $NaHCO_3$ (sat) and 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 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.

Preparation of 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 was added NaH (60 mg, 1.5 mmol, 60% dispersion in oil) and 15-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 quenched by addition of NH_4Cl (sat), 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 the tosylate **43** (24 mg, 67%) along with the alcohol **44** (5 mg, 22%). 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.

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 the 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), 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 spectra was consistent with that of 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, then quenched by addition of water and 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 was 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), it 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 the 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 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 the 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 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 the MOM-protected indole **46** (16.0 mg, 0.033 mmol) in MeOH (3 mL) was added HCl (0.15 mL, 6M). The reaction was stirred in a warm water bath for 8.5 h, quenched by dropwise addition of $NaHCO_3$ (sat), and then 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 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-methyl-but-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 mixture was quenched by addition of NH_4Cl (sat) 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 (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 δ 167.6, 151.4, 137.4, 131.5, 124.6, 123.8, 123.7, 121.3, 116.7, 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-methyl-but-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 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), 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-methyl-but-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 was 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 was allowed to warm to rt, and after 2 h it was quenched by addition of $NaHCO_3$ (sat.) 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*. 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-methyl-but-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 was added NaH (80 mg, 2.0 mmol, 60% dispersion oil) and 15-crown-5 (2 drops), and the reaction mixture was allowed warm to rt. After 2 hrs it was quenched by addition of NH_4Cl (sat) and 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 mixture was quenched by addition of 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 (50% ethyl acetate in hexanes) afforded indole **51** (35 mg, 44% for 2 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-methyl-but-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 extracted with ethyl acetate. The combined organic extracts were washed with Na_2CO_3 (sat), brine, and dried ($MgSO_4$), 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*-Butyl-dimethyl-silanyloxymethyl)-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 was 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 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 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*-Butyl-dimethyl-silanyloxymethyl)-4-methoxymethoxy-2-(3-methyl-but-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indole (53). To the silyl-protected indole **52** (724 mg, 1.52 mmol) in THF was added a few 4 Å molecular sieves and the mixture was cooled to –78 °C. After *n*-BuLi (0.75 mL, 2.3M 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 mixture was quenched by

addition of NH_4Cl (sat), and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrated was concentrated *in vacuo*. Final purification by flash column chromatography (5% ethyl acetate in hexanes) afforded the 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-methyl-but-2-enyl)-1-(toluene-4-sulfonyl)-1*H*-indol-6-yl]-methanol (54). To the silyl ether **53** (682 mg, 1.26 mmol) in THF (20 mL) at rt was added TBAF (1.88 mL, 1.0 M in THF). After 2 h the reaction was quenched by addition of 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*. 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 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) calcd *m/z* for $C_{23}H_{27}NO_5S$ (M^+) 429.1610; found 429.1622.

[4-Methoxymethoxy-2-(3-methyl-but-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 was

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 by TLC analysis, it was quenched by addition of water and 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-methyl-but-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 was added NaH (50 mg, 1.25 mmol, 60% dispersion oil) and 15-crown-5 (3 drops). The reaction mixture was allowed to stir for 4 h, then quenched by addition of NH_4Cl (sat) 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*. Purification by flash column chromatography (50% ethyl acetate in hexanes) afforded a mixture of *N*-tosyl indole **56** and the unprotected indole **57**. To the mixed residue in 1:1 THF and *i*-PrOH (3 mL) at 0 °C was added NaH (120 mg, 3.0 mmol) and the reaction mixture allowed to warm to rt overnight. The next day the reaction mixture was quenched by addition of NH_4Cl (sat), diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, and dried ($MgSO_4$), 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 the 2 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-methyl-but-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 was allowed to stir at rt. After 10 h the reaction was quenched by addition of $NaHCO_3$ (sat) 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 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.

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Supporting Information Available: The ^{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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