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Synthesis and Structure Activity Relationships of Schweinfurthin Indoles

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Abstract

As part of a program to explore the biological activity of analogues of the natural schweinfurthins, a set of compounds has been prepared where an indole system can be viewed as a substitution for the resorcinol substructure of the schweinfurthin's D-ring. Twelve of these schweinfurthin indoles have been prepared and evaluated in the 60 cell line screen of the National Cancer Institute. While a range of activity has been observed, it is now clear that schweinfurthin indoles can demonstrate the intriguing pattern of activity associated with the natural stilbenes. In the best cases, these indole analogues display both potency and differential activity across the various cell lines comparable to the best resorcinol analogues.

Keywords

Schweinfurthin; indole; stilbene analogues; SAR

1. Introduction

Extracts of the plant *Macaranga schweinfurthii*[1–3] and other *Macaranga* species[4–6] have yielded a small set of natural stilbenes referred to collectively as the schweinfurthins. The tetracyclic members of this family, represented by schweinfurthins A (**1**), B (**2**), F (**3**), and G (**4**) (Figure 1), have shown intriguing results in the National Cancer Institute's 60 cell line screen, including potent anti-proliferative effects, good differential activity, and a pattern of activity against different cell types that suggests a novel mechanism of action. While efforts to secure more material from the natural source have met with limited success, a program to synthesize these natural products has been more rewarding. Our synthesis efforts have

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Supplementary data

Supplementary data (including NMR spectra and complete bioassay data) associated with this article can be found, in the online version, at

determined the absolute stereochemistry of the natural products,[7] provided access to most of the tetracyclic examples in the correct natural stereochemistry,[8–11] and afforded a host of analogues designed to gather information on structure-activity relationships[12–15] and to afford fluorescent[16] or biotinylated[17] probes. From the results of these studies it is now clear that: a) the C-3 hydroxyl group is not essential for activity; b) compounds with a free phenol at C-5 show greater activity than the corresponding methoxy compounds, although both are active; c) methylation of one D-ring phenol improves chemical stability but does not diminish activity greatly; and, d) the para position on the D-ring is tolerant of a variety of substituents. Integration of all of these factors led us to an interest in compounds where the entire D-ring was replaced with an indole motif.

The indole system is found in an enormous variety of natural products and many bioactive agents, and it is sometimes considered to be a privileged scaffold for drug development.[18,19] If one were to view the indole nitrogen as a replacement for one D-ring phenol, analogues to schweinfurthin F (or G) could take on the general structure **5** (or **6**, Figure 2). Given the inherent flexibility for substituents at the para position noted above, isoprenoid substituents might be appended at either of the two positions on the 5-membered ring (as shown in structures **7** and **8**). If such target compounds were to be prepared through a late-stage formation of the central olefin, as has been the case with so many of the schweinfurthins, then advanced intermediates bearing the substitution pattern of structures **9** or **10** would be attractive. While there are many routes to various indoles,[20] strategies for preparation of the desired substitution pattern are much more limited. We recently reported preparation[21,22] of compound **9** through a variation of the procedures refined by Vedejs.[23] This specific intermediate was used to assemble indoles **5** and **6**, and similar phosphonate intermediates were used to make compounds **7** and **8**.[21,22] In this manuscript, we report the preparation of complementary aldehydes of the general structure **10**, synthesis of a variety of methylated analogues, and the biological activity of twelve of these schweinfurthin indoles in the NCI's 60 cell line screen.

2. Chemical Synthesis

Most of the new compounds prepared here can be viewed as analogues of schweinfurthin F (**3**)[5] or 3-deoxyschweinfurthin B[14] which carries a geranyl group on the D-ring in place of the prenyl group of schweinfurthin F. This choice was made as a compromise between synthetic expediency and the known activity of these parent compounds. The first of the new compounds prepared was the geranylated indole **18** (Scheme 1). Reaction of the MOM-protected compound **11**[21] with geranyl bromide gave the 3-geranyl derivative **12**, as expected from the parallel reaction of prenyl bromide.[22] After protection of the indole nitrogen (**12**) through reaction with tosyl chloride, reduction with DIBALH gave the primary alcohol **13**, and conversion to the phosphonate **14** proceeded under standard conditions. An HWE condensation with aldehyde **15**[14,8] gave the desired stilbene **16** as a single *E*-olefin isomer,[24] and removal of the tosyl group by treatment with $LiAlH_4$ gave the free indole **17**. Hydrolysis of the MOM group gave the target compound **18** in modest yield.

Because methylation of one D-ring phenol improves the chemical stability of the schweinfurthins, determination of the impact of methylation in the indole subsystem was the

next objective. With compound **6** already in hand, the two isomeric monomethyl compounds **19** and **20**, as well as the dimethyl compound **21**, became the next targets (Figure 3).

Preparation of the *O*-methyl compound **19** began with treatment of compound **22** with K_2CO_3 and limited methyl iodide to obtain the methyl ether **23** (Scheme 2). Protection of the indole nitrogen and reduction gave the expected alcohol **24** smoothly, and this product could be converted to the phosphonate **25** under standard conditions. An HWE condensation with aldehyde **15** and *in situ* cleavage of the tosyl group gave the first of the methylated analogues, compound **19**.

Preparation of the *N*-methyl compound **20** began in a similar fashion (Scheme 3). Treatment of the MOM protected indole **11** with base and methyl iodide gave the expected product **27**. However, after attempted conversion of compound **27** to the corresponding phosphonate proved difficult, the complementary HWE condensation was pursued. Therefore compound **27** was oxidized to the corresponding aldehyde **28** and phosphonate **29**[7] was used to assemble the central olefin. This HWE condensation proceeded smoothly to afford the desired stilbene **30**. Treatment of this compound with TsOH in methanol under standard conditions gave the desired stilbene **20**.

A similar strategy was employed to prepare the dimethyl compound **21** (Scheme 4). Complete methylation of indole **22** was followed by a standard reduction-oxidation sequence on indole **31** to obtain aldehyde **32**. Because hydrolysis of the MOM group from the C-2 alcohol had proven slow with compound **30**, phosphonate **29** was treated with TsOH/EtOH to remove the MOM group prior to the HWE condensation. Reaction of aldehyde **32** with phosphonate **33** proceeded in modest yield, but gave the desired target **21** directly.

To allow a second comparison of the impact of hydrogen (**5**), prenyl, and geranyl substituents in an *O*-methyl series, compounds **38** and **43** were prepared (Scheme 5). For the geranyl series, reaction of indole **23** with geranyl bromide in the presence of $Zn(OTf)_2$[25] gave the geranylated indole **34**. After introduction of the tosyl protecting group, reduction of the ester gave the primary alcohol **35**. In this series, formation of the phosphonate **36** proceeded smoothly under standard conditions, and condensation with aldehyde **15** gave the desired stilbene **37**. Final deprotection gave the geranylated target **38** in modest yield. Preparation of the prenyl analogue proceeded through a parallel series of reactions in comparable yields, through intermediates **39, 40**, and **41**. In this case, after the HWE condensation of compounds **41** and **15**, deprotection was conducted without isolation of the intermediate **42**, to afford the prenyl compound **43**.

Finally, because the C-ring phenols tend to be more active that the corresponding methoxy compounds in other schweinfurthin studies, two analogues of schweinfurthin G (**4**) were prepared (**47** and **50**). For the first of these targets (Scheme 6), the tricyclic alcohol **44** was converted to the phosphonate **45**.[8] Condensation with aldehyde **32** gave the desired stilbene, and final hydrolysis of the A-ring MOM group gave the desired phenol **47**.

Because phosphonate **41** already was in hand, compound **50** was prepared from the right half phosphonate and a left half aldehyde (Scheme 7). To exclude the possibility of tosyl transfer to an A-ring hydroxyl group,[21] the protected aldehyde **48**[11] was used. This HWE condensation proceeded smoothly and the resulting stilbene was treated with base *in situ* to remove the tosyl group and afford compound **49**. Final hydrolysis of the MOM protecting groups gave the desired analogue **50**.

With this set of new compounds complete, these eight schweinfurthin indoles (**18–21, 38, 43, 47**, and **50**), together with the four previously prepared (**5–8**), were examined for their biological activity in the 60 cell line assay.

3. Biological Results and Discussion

Twelve indole schweinfurthins were tested in the 60 cell line bioassay. Each compound maintains the hexahydroxanthene A-B-C ring system found in the natural products schweinfurthin F (**3**) and G (**4**), along with the *R,R,R*-stereochemistry, to focus on the impact of the indole substructure on bioactivity. Key aspects of the data generated through these assays are summarized in Table 1. Because the set of assay data is quite substantial, any number of comparisons might be made, but some central conclusions are summarized below.

Compound **5** can be considered parallel to schweinfurthin G with a 4-hydroxyindole system replacing the resorcinol unit found in the natural material, while compound **6** bears the same relationship to schweinfurthin F. As shown in Table 1, both compounds showed significant activity in the 60 cell line screen, with mean GI_{50}'s of 570 and 1020 nM (vs. 110 and 780 nM for schweinfurthin G and F, respectively) as well as differential activity of 3.29 and 2.02 $\log_{10}$ units (vs. 3.12 and 2.79). Visual inspection of the activity profiles was consistent with schweinfurthin-like activity, given that the CNS and leukemia subpanels were particularly sensitive while the ovarian subpanel was relatively resistant. Perhaps more importantly, comparison of the mean GI_{50} data from all the tested cell lines with a Pearson correlation shows good correlations to the natural schweinfurthins. The activity of compound **5**, which carries a C-ring hydroxyl group, correlates very well with schweinfurthin G (0.83), while the activity of compound **6**, which bears a C-ring methoxy group, correlates nearly as well with schweinfurthin F (0.61). This confirms that the new indoles demonstrate schweinfurthin-like behavior, and indicates that modification of the right-half resorcinol to an indole motif is a well-tolerated change.

The early results summarized above encouraged efforts to prepare additional analogues, including some with isoprenoid side chains that more closely resemble natural schweinfurthins. Compound **7** bears a prenyl substituent at C-2 of the indole ring, while compound **8** carries a prenyl substituent at C-3 and compound **18** carries a geranyl substituent at the same site. All three compounds showed differential activity of three $\log_{10}$ units or more, and their activity correlated well with that of the natural schweinfurthins. However, compound **8** showed the greatest potency, with a mean GI_{50} of 390 nM.

In past studies we have shown that monomethylation of the D-ring resorcinol increased chemical stability with a minimal impact on potency.[7,13] Therefore, we prepared the *O*- and *N*-methylindoles as shown in compounds **19** and **20**, as well as the *N*-,*O*-dimethyl compound **21**. All three compounds showed activity in the 60 cell line screen, but only compound **19** had a mean GI_{50} below 1 μM. To explore this activity further, both the 3-geranyl (**38**) and 3-prenyl (**43**) derivatives of compound **19** were prepared and tested for their activity. Both of these compounds showed activity but only the prenyl compound **43** displayed a sub-micromolar mean GI_{50}.

Finally, because the C-ring hydroxyl group of schweinfurthin G appears to confer somewhat greater activity than the C-ring methoxy group of schweinfurthin F, and this pattern was observed again with compounds **5** and **6**, the C-ring phenols **47** and **50** were prepared. Both compounds showed sub-micromolar mean GI_{50}'s and differential activity of more than three orders of magnitude. Addition of the C-3 prenyl substituent to the indole system in this case does not appear to enhance substantially either the potency or the differential activity in this pairwise comparison.

Mean GI_{50} values provide a useful comparison of these indole schweinfurthins, and differential activity is a useful indication of selective activity. However, activity in a single cell line also is a valid comparator and Table 1 includes the GI_{50} values for the SF-295 cell line, as run within the NCI 60 screen. This is a human-derived glioblastoma cell line, and one of those most sensitive to the schweinfurthins. In this set of 12 compounds, four (**8, 43, 47**, and **50**) displayed mean GI_{50} values of 50 nM or less against this specific cell line, values that are comparable to those of schweinfurthins F and G.

4. Conclusions

A number of new schweinfurthin indoles have been prepared, including compounds that bear geranyl or prenyl groups at C-2 or C-3 of the indole system, as well as compounds that have been selectively methylated on the indole nitrogen or a phenolic hydroxyl group. Twelve such compounds have been tested for biological activity in the NCI's 60 cell line screen and all of them showed activity. The best compounds display GI_{50}s comparable to those of the natural schweinfurthins, show a range of activity of ~3 orders of magnitude between the most sensitive and the most resistant cell lines, and display a schweinfurthin-like pattern of activity that suggest they possess a similar mechanism of action. Taken together, these data suggest that an indole moiety is a viable replacement for the resorcinol-based D-ring of the natural schweinfurthins.

5. Experimental Section

5.1 General Experimental Conditions

Tetrahydrofuran 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.

5. 2 Geranylated indole 12

To indole **11**[21] (1.11 g, 4.44 mmol), TBAI (820 mg, 2.22 mmol), and $Zn(OTf)_2$ (968 mg, 2.66 mmol) in toluene (15 mL) at rt was added DIPEA (0.86 mL, 4.88 mmol) and the reaction mixture was allowed to stir for 15 min. Geranyl bromide (481 mg, 2.22 mmol) was added dropwise, the reaction was allowed to proceed for 3 h and then quenched by addition of NH_4Cl (satd.) and extracted with Et_2O. The combined organic layers were washed with H_2O, dried (Na_2SO_4), concentrated, and purified by column chromatography (17.5 to 20% EtOAc in hexanes) to afford geranylated indole **12** (524 mg, 62%) as a colorless oil along with recovered starting material **11** (553 mg): ^1H NMR δ 8.72 (br s, 1H), 7.81 (d, *J* = 0.9 Hz, 1H), 7.35 (d, *J* = 0.9 Hz, 1H), 6.96–6.95 (m, 1H), 5.51–5.46 (m, 1H), 5.35 (s, 2H), 5.14–5.10 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.67 (d, *J* = 7.1 Hz, 2H), 3.53 (s, 3H), 2.16–2.03 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H) 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 167.7, 151.3, 137.3, 135.1, 131.2, 124.3, 124.3, 123.9, 123.5, 121.2, 116.4, 108.3, 102.6, 94.1, 60.7, 56.1, 39.6, 26.6, 25.6, 25.2, 17.6, 15.9, 14.3. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.43; H, 8.19, N, 3.77.

5.3 Alcohol 13

To indole **12** (397 mg, 1.04 mmol) in THF at 0 °C was added NaH (55 mg, 1.38 mmol, 60% dispersion in oil) and the solution was allowed to stir for 10 min. Tosyl chloride (235 mg, 1.23 mmol) was added and the solution was allowed to warm to rt. When the reaction was judged complete by TLC analysis the reaction mixture was cooled to 0 °C, then DIBALH (0.54 mL, 2.63 mmol) was added. After 30 min the solution was quenched by addition of NH_4Cl (satd.), poured into EtOAc, acidified, and extracted with EtOAc. The combined organic extracts were washed with Na_2CO_3 (satd.), brine, dried ($MgSO_4$), and filtered, and then concentrated in vacuo. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded benzylic alcohol **13** (366 mg, 71%) as an oil: ^1H NMR δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.61 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.13 (s, 1H), 6.86 (s, 1H), 5.44–5.39 (m, 1H), 5.22 (s, 2H), 5.14–5.10 (m, 1H), 4.71 (s, 2H), 3.53 (d, *J* = 7.0 Hz, 2H), 3.47 (s, 3H), 2.31–2.29 (m, 4H), 2.14–2.05 (m, 4H), 1.69–1.68 (m, 6H), 1.61 (s, 3H); ^{13}C NMR δ 151.9, 144.6, 139.1, 137.1, 136.6, 135.3, 131.5, 129.7 (2C), 126.6 (2C), 124.1, 122.7, 121.9, 121.7, 120.3, 106.0, 105.8, 94.2, 65.5, 56.1, 39.6, 26.6, 25.6, 25.5, 21.4, 17.6, 16.1. Anal. Calcd for $C_{28}H_{35}NO_5S$: C, 67.58; H, 7.09; N, 2.81. Found: C, 67.81; H, 7.19, N, 2.83.

5.4 Phosphonate 14

To alcohol **13** (366 mg, 0.74 mmol) in THF (20 mL) was added LiBr (510 mg 5.87 mmol) and Et_3N (0.41 mL, 2.94 mmol) and the solution was cooled to 0 °C. After 20 min, MsCl (0.14 mL, 1.8 mmol) was added dropwise. The reaction was allowed to stir and slowly warm to rt. When complete by TLC analysis it was quenched by addition of $NaHCO_3$ (satd.) and extracted with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The resulting residue was dissolved in

DMF (3 mL) and $P(OEt)_3$ (0.4 mL) was added and the solution was heated at reflux overnight. The next day the solution was allowed to cool to rt, then poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash column chromatography (2.5% EtOH in Et_2O) afforded phosphonate **14** (320 mg, 70%) as a light yellow oil: ^{1}H NMR δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.59–7.58 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 1.1 Hz, 1H), 6.82–6.80 (m, 1H), 5.43–5.38 (m, 1H), 5.23 (s, 2H), 5.15–5.11 (m, 1H), 4.06–3.95 (m, 4H), 3.52 (d, *J* = 7.2 Hz, 2H), 3.47 (s, 3H), 3.22 (d, J_{PH} = 21.5 Hz, 2H), 2.32 (s, 3H), 2.14–2.07 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H) 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR δ 151.6 (d, J_{CP} = 2.8 Hz) 144.4, 137.1 (d, J_{CP} = 2.9 Hz), 136.5, 135.3, 131.4, 129.6 (2C), 129.2 (d, J_{CP} = 9.3 Hz), 126.7 (2C), 124.0, 122.7 (d, J_{CP} = 1.6 Hz), 121.7, 121.6, 119.7 (d, J_{CP} = 3.2 Hz), 108.9 (d, J_{CP} = 5.6 Hz), 108.7 (d, J_{CP} = 7.7 Hz), 94.3, 61.9 (d, J_{CP} = 6.7 Hz, 2C), 56.0, 39.5, 34.1 (d, J_{CP} = 138.1 Hz), 26.5, 25.5, 25.4, 21.3, 17.5, 16.2 (d, J_{CP} = 6.0 Hz, 2C), 15.9; ^{31}P NMR δ 26.9; HRMS (EI) calcd for $C_{32}H_{44}NO_7PS$ (M^+) 617.2576; found 617.2562.

5.5 Indole 16

To phosphonate **14** (84 mg, 0.14 mmol) and aldehyde **15**[8] (32 mg, 0.10 mmol) in THF (5 mL) at rt was added NaH (60 mg, 1.50 mmol, 60% dispersion in oil) followed by 15-crown-5 (3 drops). The reaction mixture was allowed to stir for 90 min, then quenched by addition of Na_2CO_3 (satd.), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated in vacuo. Final purification by flash column chromatography (35 to 40% EtOAc in hexanes) afforded compound **16** (53%, 43 mg): ^{1}H NMR δ 7.75–7.73 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 7.04–7.02 (m, 3H), 6.94–6.93 (m, 1H), 6.91–6.90 (m, 1H), 5.44–5.40 (m, 1H), 5.28, (s, 2H), 5.15–5.11 (m, 1H), 3.93 (s, 3H), 3.53–3.51 (m, 2H), 3.51 (s, 3H), 3.46–3.42 (m, 1H), 2.75–2.73 (m, 2H), 2.33 (s, 3H), 2.17–2.08 (m, 5H), 1.92–1.60 (m, 5H), 1.70 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 152.0, 149.0, 144.6, 142.7, 137.5, 136.7, 135.7, 135.3, 131.5, 129.7 (2C), 128.9, 128.5, 126.7, 126.7 (2C), 124.1, 123.1, 122.6, 122.1, 121.7, 120.5, 120.3, 106.9, 105.9, 104.8, 94.3, 78.0, 77.0, 56.2, 56.0, 46.8, 39.7, 38.4, 37.7, 28.3, 27.3, 26.6, 25.7, 25.6, 23.1, 21.5, 19.8, 17.7, 16.1, 14.2; HRMS (EI) calcd for $C_{46}H_{57}NO_7S$ (M^+) 767.3856; found 767.3853.

5.6 Indole 17

To the schweinfurthin analogue **16** (43 mg, 0.056 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (45 mg, 1.06 mmol) and then the mixture was allowed to warm to rt. The following day, the reaction mixture was quenched by addition of NH_4Cl (satd.), poured into H_2O, and extracted with EtOAc. 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 (30 to 40% EtOAc in hexanes) afforded indole **17** (27 mg, 78%) as a light yellow oil: ^{1}H NMR δ 7.92 (br s, 1H), 7.07–7.06 (m, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.95 (d, *J* = 16.3 Hz, 1H), 6.92, (d, *J* = 0.7 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 1.4 Hz, 1H), 6.81–6.80 (m, 1H), 5.53–5.47 (m, 1H), 5.36 (s, 2H), 5.16–5.10 (m, 1H), 3.90 (s, 3H), 3.64 (d, *J* = 7.3 Hz, 2H) 3.57 (s, 3H), 3.45–3.40 (m, 1H), 2.74–2.71 (m, 2H), 2.11–2.04, (m, 6H), 1.89–1.84 (m, 2H), 1.72 (d, *J* = 0.6 Hz, 3H), 1.72–1.57 (m, 2H), 1.69 (d, *J* = 0.8 Hz, 3H), 1.60 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 152.2,

148.9, 142.3, 138.6, 135.0, 133.0, 131.3, 129.4, 127.6, 126.7, 124.4, 123.8, 122.6, 121.0, 120.2, 117.6, 116.7, 106.9, 103.8, 100.9, 94.3, 78.1, 77.0, 56.0, 56.0, 46.8, 39.8, 38.4, 37.7, 28.3, 27.3, 26.7, 25.7, 25.5, 23.2, 19.8, 17.7, 16.0, 14.3; HRMS (EI) calcd for $C_{39}H_{51}NO_5$ (M^+) 613.3767; found 613.3754.

5.7 Analogue 18

To the protected indole **17** (21 mg, 0.034 mmol) in MeOH (2 mL) was added TsOH (40 mg, 0.21 mmol) in two proportions 3 h apart, and the solution was allowed to stir. The next day the solution was quenched by addition of $NaHCO_3$ (satd.), diluted with H_2O and extracted with EtOAc. The combined organics extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% EtOAc in hexanes) afforded schweinfurthin analogue **18** (7 mg, 36%) as a light yellow oil: ^{1}H NMR (CD_3OD) δ 6.96–6.93 (m, 3H), 6.92–6.91 (m, 1H), 6.85–6.84 (m, 1H), 6.73 (d, *J* = 0.9 Hz, 1H), 6.61–6.60 (m, 1H), 5.54–5.49 (m, 1H), 5.16–5.11 (m, 1H), 3.61 (d, *J* = 7.1 Hz, 2H), 3.38–3.33 (m, 1H), 3.25 (s, 3H), 2.74–2.71 (m, 2H), 2.15–2.01 (m, 5H), 1.83–1.59 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (CD_3OD) δ 153.2, 150.1, 143.2, 140.7, 135.4, 133.6, 132.1, 131.4, 129.2, 126.9, 125.8, 125.6, 124.0, 121.8, 121.4, 118.0, 116.6, 108.0, 103.8, 101.4, 78.7, 77.1, 56.4, ~49*, 40.9, 39.5, 38.9, 29.0, 27.9, 27.7, 26.4, 26.0, 24.1, 20.2, 17.8, 16.1, 14.9; HRMS (EI) calcd for $C_{37}H_{47}NO_4$ (M^+) 569.3505 found 569.3504. *Obscured by solvent

5.8 Preparation of the methylated indole 23 and the dimethylated indole 31

Following Vedejs[23] procedure, to phenol **22** (1.05 g, 5.12 mmol) in DMF (28 mL) was added K_2CO_3 (2.12 g, 15.4 mmol), the reaction mixture was cooled to 0 °C, and after 20 min MeI (0.32 mL, 5.12 mmol) was added dropwise. The reaction was maintained at 0 °C overnight, then quenched by addition of 1M HCl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and then concentrated in vacuo. Final purification by flash column chromatography (20 to 25% EtOAc in hexanes) afforded methoxyindole **23** (824 mg, 73%) as a white solid: ^{1}H NMR δ 8.66 (br s, 1H), 7.85 (t, *J* = 0.9 Hz, 1H), 7.26 (dd, *J* = 3.3, 2.5 Hz, 1H), 7.22 (d, *J* = 1.0 Hz, 1H), 6.70–6.68 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 167.8, 152.7, 136.2, 125.9, 124.9, 122.3, 107.5, 100.2, 99.9, 60.8, 55.4, 14.4; HRMS (EI) calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895; found 219.0904.

Also recovered was the dimethylated indole **31** (31 mg, 3%) as a white solid: ^{1}H NMR δ 7.77 (t, *J* = 0.9 Hz, 1H), 7.21 (d, *J* = 1.0 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.60 (dd, *J* = 3.1, 0.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 3H), 3.83 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 167.7, 152.7, 137.1, 130.3, 124.4, 122.7, 105.8, 99.6, 98.7, 60.8, 55.4, 33.2, 14.5; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ (M^+) 233.1052; found 233.1056.

5.9 Benzylic indole alcohol 24

To indole **23** (436 mg, 1.99 mmol) in THF (10 mL) at 0 °C was added NaH (100 mg, 2.5 mmol, 60% dispersion in oil), followed by TsCl (430 mg, 2.25 mmol). Once the reaction was judged complete by TLC analysis, DIBALH (1.07 mL, 6.0 mmol) was added dropwise.

After 1 h the reaction mixture was quenched by addition of NH_4Cl (satd.), diluted with EtOAc, acidified with 1M HCl to dissolve the solids, and extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ (satd.), brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated in vacuo. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded alcohol **24** (533 mg, 81%) as a white solid: ^{1}H NMR δ 7.72 (d, *J* = 8.4, Hz, 2H), 7.57 (s, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.72 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.67 (s, 1H), 4.74 (s, 2H), 3.85 (s, 3H), 2.32 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR δ 153.0, 144.9, 139.2, 135.8, 135.0, 129.8 (2C), 126.7 (2C), 124.9, 120.4, 105.9, 104.7, 102.7, 65.8, 55.3, 21.4; HRMS (EI) calcd for $C_{17}H_{17}NO_4S$ (M^+) 331.0878; found 331.0873.

5.10 Phosphonate 25

To benzylic alcohol **24** (517 mg, 1.56 mmol) in THF (15 mL) was added LiBr (1.09 g, 12.5 mmol) and the solution was cooled to 0 °C. Next Et_3N (0.87 mL, 6.2 mmol) and, after 10 min, MsCl (0.36 mL, 1.73 mmol) were added and the reaction mixture was allowed to stir for 2.5 h. The reaction mixture was quenched by addition of NH_4Cl (satd.) 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. After the resulting oil was dissolved in DMF (6mL) and $P(OEt)_3$ (2 mL) was added, the solution was heated at reflux. The next day the reaction was allowed to cool to rt and poured into Et_2O, washed with H_2O, brine, dried ($MgSO_4$), and filtered and then the filtrate was concentrated in vacuo. Final purification by flash column chromatography (2.5 to 3% MeOH in Et_2O) afforded phosphonate **25** (529 mg, 75%) as a light yellow solid: ^{1}H NMR δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 2.9 Hz, 1H), 7.42 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 3.6 Hz, 1H), 6.65 (s, 1H), 4.03–3.93 (m, 4H), 3.88 (s, 3H), 3.25 (d, J_{HP} = 21.5 Hz, 2H), 2.33 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR δ 152.8 (d, J_{CP} = 2.8 Hz), 144.8, 136.0 (d, J_{CP} = 3.1 Hz), 135.3, 129.7 (2C), 129.4 (d, J_{CP} = 9.2 Hz), 126.7 (2C), 124.8 (d, J_{CP} = 1.7 Hz), 120.0 (d, J_{CP} = 3.3 Hz), 107.7 (d, J_{CP} = 7.9 Hz), 106.0 (d, J_{CP} = 1.7 Hz), 105.6 (d, J_{CP} = 5.7 Hz), 62.1 (d, J_{CP} = 6.7 Hz, 2C), 55.4, 34.4 (d, J_{CP} = 138.3 Hz), 21.4, 16.3 (d, J_{CP} = 5.9 Hz, 2C); ^{13}P δ 26.2; HRMS (EI) calcd for $C_{21}H_{26}NO_6PS$ (M^+) 451.1218; found 451.1216.

5.11 Schweinfurthin analogue 19

To aldehyde **15** (40 mg, 0.13 mmol) and phosphonate **25** (72 mg, 0.16 mmol) in THF (1.2 mL) was added NaH (50 mg, 1.25 mmol, 60% dispersion in oil) and 15-crown-5 (3 drops). After 1 h the reaction was quenched by addition of NH_4Cl (satd.) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and then concentrated in vacuo. Purification by flash column chromatography (35% EtOAc in hexanes) afforded a mixture of tosyl protected indole **26** and the free indole **19** (36 mg). The resulting mixture in THF (5 mL) was added dropwise to a solution of NaH (115 mg, 2.88 mmol, 60% dispersion in oil) in 2-propanol (2 mL). The solution was allowed to stir overnight and then quenched by addition of H_2O and extracted with EtOAc. 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 (40% EtOAc in hexanes) afforded schweinfurthin analogue **19** (23 mg, 39% for 2 steps) as a colorless oil: ^{1}H NMR δ 8.17 (br s, 1H), 7.12–7.10 (m, 2H), 7.06 (d, *J* = 16.3, Hz, 1H), 6.99 (d, *J* =

16.3 Hz, 1H), 6.91–6.89 (m, 2H), 6.74 (s, 1H), 6.63 (t, *J* = 2.4 Hz, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 3.44 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.76–2.73 (m, 2H), 2.16–2.11 (m, 1H), 1.90–1.56 (m, 5H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 153.5, 149.1, 142.5, 137.6, 133.3, 129.6, 128.0, 127.0, 123.3, 122.8, 120.4, 118.7, 107.1, 103.5, 100.4, 97.9, 78.2, 56.2, 55.5, 47.0, 38.6, 37.8, 28.5, 27.5, 23.4, 20.0, 14.4; HRMS (EI) calcd for $C_{28}H_{33}NO_4$ (M^+) 447.2410; found 447.2413.

5.12 Alcohol 27

To indole **11** (202 mg, 0.81 mmol) in THF (10 mL) at 0 °C was added NaH (49 mg, 1.2 mmol, 60% dispersion in mineral oil) followed after 5 min by MeI (0.06 mL, 0.96 mmol), and the reaction mixture was allowed to stir for 2 h. After $LiAlH_4$ (92 mg, 2.42 mmol) was added, the reaction mixture was allowed to stir for 1 h and then quenched with NH_4Cl (satd.) and extracted with EtOAc. 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 (40% EtOAc in hexanes) afforded benzylic alcohol **27** (146 mg, 81%, 2 steps) as a light yellow solid: ^{1}H NMR δ 6.96 (s, 1H), 6.91 (d, *J* = 3.2 Hz, 1H), 6.70 (s, 1H), 6.53 (d, *J* = 3.1 Hz, 1H), 5.27 (s, 2H), 4.69 (s, 2H), 3.65 (s, 3H), 3.48 (s, 3H), 2.68 (br s 1H); ^{13}C NMR δ 150.3, 138.1, 135.7, 127.8, 118.9, 102.6, 102.2, 97.9, 94.4, 65.8, 56.0, 32.8; HRMS (EI) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1052; found 221.1042.

5.13 Aldehyde 28

To alcohol **27** (73 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) at rt was added MnO_2 (430 mg, 4.9 mmol) and the resulting mixture was allowed to stir for 4 h, then filtered through celite, and washed with EtOAc. The solvent was removed in vacuo to afford aldehyde **28** (58 mg, 80%) as a light yellow solid: ^{1}H NMR δ 9.98 (s, 1H), 7.55 (s, 1H), 7.27 (s, 1H), 7.19 (d, *J* = 2.9 Hz, 1H), 6.65 (d, *J* = 2.8 Hz, 1H), 5.38, (s, 2H), 3.85 (s, 3H), 3.54 (s, 3H); ^{13}C NMR δ 192.2, 150.7, 137.4, 131.8, 131.7, 124.8, 108.5, 102.0, 99.2, 94.5, 56.2, 33.2; HRMS (EI) calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895; found 219.0889.

5.14 Stilbene 30

To aldehyde **28** (11 mg, 0.05 mmol) and phosphonate **29** (27 mg, 0.06 mmol) in THF (1.5 mL) at rt was added NaH (40 mg, 1.0 mmol, 60% dispersion in oil). After the reaction mixture was allowed to stir for 6 h, it was quenched by addition of NH_4Cl (satd.) and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (50% Et_2O in hexanes) afforded stilbene **30** (19 mg, 71%) as a light yellow oil: ^{1}H NMR δ 7.11 (d, *J* = 16.1 Hz, 1H), 7.10 (s, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 6.56 (d, *J* = 3.0 Hz, 1H), 5.39 (s, 2H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 3.92 (s, 3H), 3.72 (s, 3H), 3.57 (s, 3H), 3.42 (s, 3H), 3.29 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.74–2.71 (m, 2H), 2.17–2.12 (m, 1H), 1.87–1.57 (m, 4H), 1.25 (s, 3H), 1.10 (s, 3H), 0.92 (s, 3H); ^{13}C NMR δ 150.7, 148.9, 142.3, 138.4, 132.7, 129.3, 128.2, 127.7, 126.8, 122.6, 120.2, 119.5, 106.7, 102.3, 101.5, 98.4, 96.1, 94.8, 84.0, 76.9, 56.1, 55.7, 55.6, 47.0, 38.2, 37.6, 33.0, 29.7, 25.3, 23.1, 19.8, 15.1; HRMS (EI) calcd for $C_{32}H_{41}NO_6$ (M^+) 535.2934; found 535.2919.

5.15 Indole 20

To stilbene **30** (19 mg 0.035 mmol) in a 1:1 mixture of THF and MeOH (2 mL) was added TsOH (30 mg, 0.16 mmol) and the resulting solution was allowed to stir at rt overnight. It was then quenched by addition of $NaHCO_3$ (satd.) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and then concentrated in vacuo. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded analogue **20** (8 mg, 51%) as a light yellow oil: ^{1}H NMR δ 7.05 (d, *J* = 16.1 Hz, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.97 (d, *J* = 16.5 Hz, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.50 (d, *J* = 3.1 Hz, 1H), 5.24 (br s, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.44 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.75–2.72 (m, 2H), 2.17–2.11 (m 1H), 1.90–1.55 (m, 5H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 148.9, 148.9, 142.3, 138.8, 132.9, 129.3, 128.2, 127.5, 127.0, 122.6, 120.3, 117.8, 106.6, 101.6, 101.5, 97.4, 78.0, 56.0, 46.7, 38.4, 37.6, 33.1, 29.7, 28.2, 27.3, 19.8, 14.3; HRMS (EI) calcd for $C_{28}H_{33}NO_4$ (M^+) 447.2410; found 447.2422.

5.16 *N, O*-Dimethylindole 31

To indole **22** (500 mg, 2.43 mmol) in a mixture of THF and DMF (5:1) at 0 °C was added NaH (224 mg, 5.6 mmol, as a 60% dispersion in oil), followed after 20 min by MeI (0.34 mL, 5.35 mmol). The reaction was allowed to stir for 3 h, then quenched by addition of NH_4Cl (satd.), and finally extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded indole **31** (460 mg, 81%) as a white solid with ^{1}H and ^{13}C NMR spectra identical to those of material obtained above.

5.17 Aldehyde 32

To indole **31** (54 mg, 0.24 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (28 mg, 0.73 mmol), and the reaction was allowed to warm to rt over 50 min. It was then quenched by addition by NH_4Cl (satd.) and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The resulting residue was then dissolved in CH_2Cl_2 (10 mL) and MnO_2 (315 mg, 3.62 mmol) was added. After the reaction mixture was allowed to stir for 4 h, it was filtered through celite and the solvent was removed in vacuo to afford aldehyde **32** (38 mg, 84%, for 2 steps) as a light yellow solid: ^{1}H NMR δ 9.98 (s, 1H), 7.48 (s, 1H), 7.17 (d, *J* = 2.9 Hz, 1H), 7.05 (s, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 4.00 (s, 3H), 3.85 (s, 3H); ^{13}C NMR δ 192.2, 153.5, 137.0, 132.0, 131.4, 124.2, 109.3, 99.4, 97.1, 55.4, 33.2; HRMS (EI) calcd for $C_{11}H_{11}NO_2$ (M^+)189.0790; found 189.0787.

5.18 Phosphonate 33

To phosphonate **29**[8] (81 mg, 0.17 mmol) in EtOH (3 mL) was added TsOH (80 mg, 0.42 mmol) and the reaction flask was wrapped in foil. The reaction mixture was allowed to stir for 2 days, then quenched by addition of $NaHCO_3$ (satd.), and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and then concentrated in vacuo. Final purification by flash column chromatography (3% EtOH in

Et_2O) afforded phosphonate **33** (62 mg, 85%) as a colorless oil: ^{1}H NMR δ 6.66–6.65 (m, 1H), 6.64–6.62 (m, 1H), 4.07–3.99 (m, 4H), 3.83 (s, 3H), 3.39 (dd, J = 11.5, 3.9 Hz, 1H), 3.05 (d, J_{HP} = 21.1 Hz, 2H), 2.69–2.66 (m, 2H), 2.13–2.09 (m, 1H), 1.90–1.59 (m, 5H), 1.26 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.22 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR δ 148.6 (d, J_{CP} = 3.1 Hz), 141.5 (d, J_{CP} = 3.6 Hz), 122.7 (d, J_{CP} = 7.5 Hz), 122.6 (d, J_{CP} = 3.1 Hz), 122.0 (d, J_{CP} = 9.2 Hz), 111.8 (d, J_{CP} = 5.9 Hz), 77.9, 77.7, 62.1 (d, J_{CP} = 6.8 Hz), 62.0 (d, J_{CP} = 6.7 Hz), 46.6, 38.3, 37.6, 33.1 (d, J_{CP} = 138.1 Hz), 28.2, 27.3, 23.0, 19.7, 16.4 (d, J_{CP} = 6.1 Hz), 16.4 (d, J_{CP} = 6.2 Hz), 14.2; ^{31}P NMR δ 27.1; HRMS (EI) calcd for $C_{22}H_{35}O_6P$ (M^+) 426.2171 found 426.2177.

5.19 Analogue 21

To phosphonate **33** (31 mg, 0.073 mmol) and aldehyde **32** (12 mg, 0.063 mmol) in THF (1 mL) was added NaH (40 mg, 1.0 mmol, 60% dispersion in oil) and 15-crown-5 (1 drop). The solution was allowed to stir overnight, then quenched by addition of NH_4Cl (satd.) and finally extracted with EtOAc. 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 (45% EtOAc in hexanes) afforded analogue **21** (15 mg, 51%) as a yellow oil: ^{1}H NMR δ 7.11 (d, J = 16.1 Hz, 1H), 7.04–6.99 (m, 2H), 6.96 (d, J = 3.2 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 1.5 Hz, 1H), 6.75 (s, 1H), 6.55 (d, J = 2.9 Hz, 1H), 4.02 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.44 (dd, J = 11.7, 4.0 Hz, 1H), 2.75–2.72 (m, 2H), 2.17–2.12 (m, 1H), 1.90–1.60 (m, 5H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 153.3, 148.9, 142.3, 138.3, 132.6, 129.4, 128.0, 127.9, 126.6, 122.6, 120.2, 118.8, 106.7, 101.8, 98.5, 97.2, 78.0, 77.0, 56.0, 55.3, 46.7, 38.4, 37.6, 33.1, 28.3, 27.4, 23.2, 19.8, 14.3; HRMS (EI) calcd for $C_{29}H_{35}NO_4$ (M^+) 461.2566; found 461.2569.

5.20 Geranyl indole 34

According to the procedure of Zhu and Ganesan,[25] to indole **23** (824 mg, 3.76 mmol), TBAI (663 mg, 1.80 mmol), and $Zn(OTf)_2$ (745 mg, 2.05 mmol) were allowed to react in a mixture of toluene (16 mL), and CH_2Cl_2 (2 mL) and DIPEA (0.66 mL, 3.76 mmol). After stirring for 15 min, geranyl bromide (371 mg, 1.71 mmol) was added dropwise and after an additional 2.5 h the reaction mixture was quenched by addition of NH_4Cl (satd.) and finally extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and then concentrated in vacuo. Final purification by flash column chromatography (17% EtOAc in hexanes) afforded the geranylated indole **34** (325 mg, 53%) as a colorless oil along with recovered starting indole (436 mg): ^{1}H NMR δ 8.18 (br s, 1H), 7.74 (d, J = 0.9 Hz, 1H), 7.15 (d, J = 1.0 Hz, 1H), 6.94–6.93 (m, 1H), 5.49–5.44 (m, 1H), 5.15–5.10 (m, 1H), 4.39 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.64 (d, J = 7.2 Hz, 2H), 2.14–2.04 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 167.7, 154.5, 137.1, 135.3, 131.3, 124.7, 124.7, 123.5, 123.2, 120.9, 117.2, 107.4, 99.8, 60.7, 55.3, 39.7, 26.7, 25.7, 25.3, 17.7, 16.0, 14.4; HRMS (EI) calcd for $C_{22}H_{29}NO_3$ (M^+) 355.2147; found 355.2152.

5.21 Benzylic alcohol 35

To indole **34** (325 mg, 0.91 mmol) in THF (10 mL) at 0 °C was added NaH (44 mg, 1.1 mmol, 60% dispersion in oil) followed by TsCl (183 mg, 0.96 mmol). When the reaction was judged complete by TLC, DIBALH (0.53 mL, 2.97 mmol) was added dropwise. After an additional h the solution was quenched by addition of NH_4Cl (satd.), diluted with EtOAc, acidified with 1M HCl to dissolve the solids, and finally extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$ (satd.), brine, dried ($MgSO_4$), and filtered and then concentrated in vacuo. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded alcohol **35** (273 mg, 64%) as a colorless oil: ^{1}H NMR δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.09 (s, 1H), 6.62 (s, 1H), 5.41–5.37 (m, 1H), 5.15–5.11 (m, 1H), 4.71 (s, 2H), 3.79 (s, 3H), 3.50 (d, *J* = 7.0 Hz, 2H), 2.74 (br s, 1H), 2.26 (s, 3H), 2.14–2.04 (m, 4H), 1.67 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 154.6, 144.5, 139.0, 136.9, 136.5, 135.2, 131.4, 129.6 (2C), 126.5 (2C), 124.0, 123.1, 121.7, 121.4, 119.8, 104.8, 102.8, 65.6, 55.1, 39.6, 26.5, 25.6, 25.5, 21.3, 17.6, 15.9; HRMS (EI) calcd for $C_{27}H_{33}NO_4S$ (M^+) 467.2130; found 467.2135.

5.22 Phosphonate 36

To benzylic alcohol **35** (269 mg, 0.58 mmol) in THF (10 mL) was added LiBr (400 mg, 4.60 mmol) and the solution was cooled to 0 °C. Next Et_3N (0.32 mL, 2.3 mmol) followed after 10 min by MsCl (0.13 mL, 1.73 mmol) were added, and the reaction mixture was allowed to stir for 2 h. The reaction mixture was then quenched by addition of NH_4Cl (satd.) 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 oil was dissolved in $P(OEt)_3$ (2 mL) and heated at reflux. The next day the reaction was allowed to cool to rt, then poured into Et_2O, washed with H_2O, brine, dried ($MgSO_4$), and filtered, and finally the filtrate was concentrated in vacuo. Final purification by flash column chromatography (2.5 to 3% MeOH in Et_2O) afforded phosphonate **36** (273 mg, 81%) as a colorless oil; ^{1}H NMR δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.07–7.06 (m, 1H), 6.62–6.61 (m, 1H), 5.41–5.36 (m, 1H), 5.15–5.11 (m, 1H), 4.02–3.96 (m, 4H), 3.84 (s, 3H), 3.49 (d, *J* = 7.2 Hz, 2H), 3.23 (d, J_{PH} = 21.4 Hz, 2H), 2.33 (s, 3H), 2.14–2.05 (m, 4H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.67 (d, *J* = 1.0 Hz, 3H), 1.62 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR δ 154.3 (d, J_{CP} = 3.0 Hz), 144.4, 137.0 (d, J_{CP} = 3.1 Hz), 136.5, 135.4, 131.4, 129.6 (2C), 129.1 (d, J_{CP} = 9.1 Hz), 126.6 (2C), 124.1, 123.1 (d, J_{CP} = 1.6 Hz), 121.6, 121.4 (d, J_{CP} = 1.3 Hz), 119.3 (d, J_{CP} = 3.2 Hz), 107.8 (d, J_{CP} = 7.9 Hz), 105.8 (d, J_{CP} = 5.5 Hz), 62.1 (d, J_{CP} = 6.6 Hz, 2C), 55.2, 39.6, 34.3 (d, J_{CP} = 138.1 Hz), 26.6, 25.6, 25.5, 21.4, 17.6, 16.3 (d, J_{CP} = 5.9 Hz, 2C), 16.0; ^{13}P NMR δ 26.2; HRMS (EI) calcd for $C_{31}H_{42}NO_6PS$ (M^+) 587.2470; found 587.2481.

5.23 Geranylated stilbene 37

To phosphonate **36** (100 mg, 0.17 mmol) and aldehyde **15** (40 mg, 0.13 mmol) in THF (1.0 mL) at 0 °C was added NaH (60 mg, 1.0 mmol, 60% oil dispersion) and 15-crown-5 (1 drop). When the aldehyde had disappeared as judged by TLC, the reaction was quenched by addition of NH_4Cl (satd.), and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), and filtered, and then concentrated in vacuo. Final purification by flash

column chromatography (30% EtOAc in hexanes) afforded analogue **37** (37 mg, 38%) as an oil which was used directly in the next step: ^{1}H NMR δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 0.9 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.09 (t, *J* = 1.1 Hz, 1H), 7.04–7.03 (m, 2H), 6.94–6.93 (m, 1H), 6.91–6.90 (m, 1H), 6.79 (s, 1H), 5.42–5.37 (m, 1H), 5.15–5.11 (m, 1H), 3.93 (s, 3H), 3.90, (s, 3H), 3.51–3.42 (m, 3H), 2.76–2.73 (m, 2H), 2.17–2.04 (m, 5H), 1.91–1.82 (m, 3H), 1.75–1.59 (m, 11H), 1.27 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 154.6, 149.0, 144.6, 142.7, 137.5, 136.6, 135.7, 135.4, 131.5, 129.7 (2C), 128.9, 128.2, 127.0, 126.7 (2C), 124.2, 123.5, 122.7, 121.8, 121.7, 120.5, 120.0, 106.9, 105.4, 101.4, 78.0, 77.1, 56.0, 55.2, 46.8, 39.7, 38.4, 37.7, 28.3, 27.3, 26.6, 25.7, 25.6, 23.2, 21.5, 19.8, 17.7, 16.0, 14.3.

5.24 Analogue 38

Stilbene **37** (37 mg, 0.05 mmol) in THF (2 mL) was added to a solution of NaH (150 mg, 3.75 mmol, 60% dispersion in oil) in 2-propanol (2 mL) and the solution was allowed to stir overnight. The reaction mixture was then quenched by addition of H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and then concentrated in vacuo. Final purification by flash column chromatography (45% EtOAc in hexanes) afforded schweinfurthin analogue **38** (17 mg, 58%, or 22% over two steps from compound **36**) as a colorless oil: ^{1}H NMR δ 7.91 (br s, 1H), 7.02–6.99 (m, 3H), 6.91–6.90 (m, 1H). 6.88–6.87 (m, 1H), 6.78 (s, 1H), 6.68 (s, 1H), 5.50–5.46 (m, 1H), 5.16–5.12 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.63 (d, *J* = 7.2 Hz, 2H), 3.46–3.41 (m, 1H), 2.75–2.71 (m, 2H), 2.16–2.06 (m, 5H), 1.90–1.61 (m, 14H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.0, 148.9, 142.3, 138.4, 135.0, 132.9, 131.3, 129.5, 127.9, 126.5, 124.5, 123.8, 122.6, 120.6, 120.2, 117.2, 117.0, 106.9, 103.3, 97.4, 78.0, 56.0, 55.1, 46.8, 39.8, 38.4, 37.7, 28.3, 27.4, 26.8, 25.7, 25.5, 23.2, 19.8, 17.7, 16.0, 14.3; HRMS (EI) calcd for $C_{38}H_{49}NO_4$ (M^+) 583.3662; found 587.2672.

5.25 Prenylated indole 39

To indole **23** (388 mg, 1.77 mmol), TBAI (360 mg, 0.98 mmol), and $Zn(OTf)_2$ (436 mg, 1.2 mmol) in a 5:1 mixture of toluene and CH_2Cl_2 (12 mL) at rt was added DIPEA (0.38 mL, 2.2 mmol) and the reaction mixture was allowed to stir for 10 min. Prenyl bromide (126 mg, 0.88 mmol) was added dropwise. After 2 h the reaction mixture was quenched by addition of NH_4Cl (satd.) and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (10 to 15% EtOAc in hexanes) afforded prenylated indole **39** (209 mg, 59%) along with recovered indole **23** (149 mg) as expected based on the literature precedent:[25] ^{1}H NMR δ 8.31 (br s, 1H), 7.74 (d, *J* = 1.0 Hz, 1H), 7.15 (d, *J* = 0.5 Hz, 1H), 6.94–6.93 (m, 1H), 5.47–5.42 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.63 (d, *J* = 7.2 Hz, 2H), 1.75 (s, 3H), 1.72 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.8, 154.4, 137.1, 131.5, 124.6, 123.7, 123.2, 120.8, 117.1, 107.4, 99.8, 60.7, 55.3, 25.7, 25.4, 17.7, 14.4; HRMS (EI) calcd for $C_{17}H_{21}NO_3$ (M^+) 287.1521; found 287.1523.

5.26 Alcohol 40

To a solution of indole **39** (18 mg, 0.06 mmol) in THF (3 mL) at rt was added NaH (5 mg, 0.13 mmol, 60% dispersion oil) and the reaction mixture was allowed to stir for 10 min. After TsCl (15 mg, 0.08 mmol) was added, the solution was stirred for 2 h and then DIBALH (0.05 mL, 0.44 mmol) was added dropwise. After an additional 30 min, the reaction was quenched with NH_4Cl (satd.), poured into EtOAc, acidified with 1M HCl, and extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ (satd.), and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (35% EtOAc in hexanes) afforded the benzylic alcohol **40** (19 mg, 76%): ^{1}H NMR δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.53 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.10 (s, 1H), 6.64 (s, 1H), 5.39–5.35 (m, 1H), 4.72 (s, 2H), 3.82 (s, 3H), 3.49 (d, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H); ^{13}C NMR δ 154.7, 144.6, 139.0, 136.9, 135.2, 132.9, 129.7 (2C), 126.6 (2C), 123.1, 121.8, 121.5, 119.8, 104.9, 102.9, 65.7, 55.2, 25.7, 25.6, 21.4, 17.7; HRMS (EI) calcd for $C_{22}H_{25}NO_4S$ (M^+) 399.1504; found 399.1508.

5.27 Phosphonate 41

To alcohol **40** (102 mg, 0.25 mmol) in THF (5 mL) at 0 °C was added LiBr (133 mg, 1.53 mmol) and Et_3N (0.11 mL, 0.79 mmol). The solution was stirred for 5 min, MsCl (0.05 mL, 0.65 mmol) was added dropwise, and the reaction was allowed to warm to rt. After 2 h it was quenched by addition of NH_4Cl (satd.), extracted with Et_2O, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. To the resulting residue was added $P(OEt)_3$ (2 mL) and the solution was heated to 130 °C and allowed to stir overnight. The next day the solution was allowed to cool to rt and the solvent was removed in vacuo. Final purification by flash column chromatography (2% EtOH in Et_2O) afforded indole phosphonate **41** (111 mg, 84%) as a colorless oil: ^{1}H NMR δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.50 (d, J_{HP} = 2.3 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 1.1 Hz, 1H), 6.62 (s, 1H), 5.40–5.34 (m, 1H), 4.06–3.92 (m, 4H), 3.84 (s, 3H), 3.48 (d, *J* = 7.1 Hz, 2H), 3.23 (d, J_{HP} = 21.5 Hz, 2H), 2.32 (s, 3H), 1.76 (s, 3H), 1.67 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR δ 154.3 (d, J_{CP} = 2.9 Hz), 144.4, 136.9 (J_{CP} = 2.9 Hz), 135.2, 132.9, 129.7 (2C), 129.1 (d, J_{CP} = 9.8 Hz), 126.7 (2C), 123.1 (d, J_{CP} = 1.7 Hz), 121.7, 121.3 (d, J_{CP} = 1.6 Hz), 119.3 (d, J_{CP} = 3.2 Hz), 107.8 (d, J_{CP} = 7.8 Hz), 105.8 (d, J_{CP} = 5.6 Hz), 62.0 (d, J_{CP} = 2.9 Hz, 2C), 55.2, 34.2 (d, J_{CP} = 138.2 Hz), 25.7, 25.6, 21.4, 17.7, 16.3 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR δ 26.2; HRMS (EI) calcd for $C_{26}H_{34}NO_6PS$ (M^+) 519.1844; found 519.1843.

5.28 Analogue 43

To phosphonate **41** (45 mg, 0.089 mmol) and aldehyde **15** (21 mg, 0.069 mmol) in THF (1mL) at 0 °C was added NaH (40 mg, 1.0 mmol, 60% dispersion oil) and 15-crown-5 (2 drops). The reaction mixture was allowed to stir for 45 min, then quenched by addition of NH_4Cl (satd.), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated in vacuo. Purification by flash column chromatography (20 to 50% EtOAc in hexanes) afforded a mixture of protected and unprotected indoles (26 mg). This mixture was treated with NaO*i*-Pr in THF (3 mL), generated *in situ* from NaH (160 mg, 4 mol, 60% dispersion oil) and *i*-

PrOH, and the reaction mixture was allowed to stir overnight. The next day the reaction mixture was quenched by addition of H_2O and extracted with EtOAc. 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 (45% EtOAc in hexanes) afforded indole **43** (13.5 mg, 38% for two steps) as a light yellow oil: ^{1}H NMR δ 7.90 (br s, 1H), 7.03 (d, *J* = 16.0 Hz, 1H), 7.01 (s, 1H), 6.96 (d, *J* = 16.2 Hz, 1H), 6.91–6.90 (m, 1H), 6.88–6.87 (m, 1H), 6.79–6.78 (m, 1H), 6.68 (s, 1H) 5.49–5.44 (m, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.46–3.41 (m, 1H), 2.75–2.72 (m, 2H), 2.17–2.10 (m, 1H), 1.91–1.59 (m, 5H), 1.75 (s, 3H), 1.73 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.0, 148.9, 142.3, 138.3, 132.9, 131.2, 129.5, 127.9, 126.5, 124.0, 122.6, 120.5, 120.2, 117.2, 117.0, 106.9, 103.3, 97.4, 78.1, 77.0, 56.0, 55.1, 46.8, 38.3, 37.7, 28.3, 27.3, 25.8, 25.6, 23.3, 19.8, 17.7, 14.3; HRMS (EI) calcd for $C_{33}H_{41}NO_4$ (M^+) 515.3036; found 515.3040.

5.29 Phosphonate 45

Through a variation of our earlier procedure, alcohol **44**[8] (204 mg, 0.66 mmol) in THF (10 mL) at 0 °C was treated with LiBr (400 mg, 4.6 mmol) and Et_3N (0.37 mL, 2.65 mmol), and then after 5 min MsCl (0.13 mL, 1.65 mmol) was added. After 90 min, the reaction mixture was 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 $P(OEt)_3$ (3 mL) and the solution was heated to reflux overnight. The next day the solution was allowed to cool to rt and then concentrated in vacuo. Final purification by flash column chromatography (2% EtOH in Et_2O) afforded phosphonate **45** (297 mg, 90%) as an oil whose ^{1}H and ^{13}C NMR spectra were consistent with those from previously prepared materials.[8]

5.30 Stilbene 46

To aldehyde **32** (15 mg, 0.08 mmol) and phosphonate **45** (48 mg, 0.10 mmol) in THF (3 mL) at 0 °C was added NaH (40 mg, 1.0 mmol, 60% dispersion oil) and 15-crown-5 (2 drops) and the reaction mixture was allowed to warm to rt. The following day the reaction mixture was quenched by addition of NH_4Cl (satd.) and extracted with EtOAc. 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% EtOAc in hexanes) afforded stilbene **46** (18 mg, 42%) as a light yellow oil: ^{1}H NMR δ 7.17 (d, *J* = 1.7 Hz, 1H), 7.08 (d, *J* = 16.8 Hz, 1H), 7.03 (s, 1H), 6.99 (d, *J* = 16.4 Hz, 1H), 6.98 (d, *J* = 1.4 Hz, 1H), 6.94 (d, *J* = 3.1 Hz, 1H), 6.73 (s, 1H), 6.54 (d, *J* = 2.9 Hz, 1H), 5.25 (d, *J* = 6.7 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.01 (s, 3H), 3.78 (s, 3H), 3.55 (s, 3H), 3.41 (s, 3H), 3.29 (dd, *J* = 11.5, 3.9 Hz, 1H), 2.75–2.72 (m, 2H), 2.13–1.97 (m, 2H), 1.80–1.57 (m, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 153.3, 146.2, 143.6, 138.3, 132.7, 129.6, 128.2, 127.8, 126.4, 123.2, 121.7, 118.9, 113.4, 101.8, 98.5, 97.3, 96.2, 95.9, 84.0, 76.9, 56.2, 55.6, 55.3, 47.1, 38.3, 37.7, 33.0, 27.3, 25.3, 23.2, 19.9, 15.1; HRMS (EI) calcd for $C_{32}H_{41}NO_6$ (M^+) 535.2934; found 535.2933.

5.31 Analogue 47

To the MOM-protected analogue **46** (18 mg, 0.034 mmol) in 1:1 MeOH:THF (0.8 mL) protected from ambient light was added TsOH (50 mg, excess) and the resulting solution was allowed to stir overnight. The reaction mixture was quenched by addition of NH_4Cl (satd.) and extracted with EtOAc. 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 (50% EtOAc in hexanes) afforded analogue **47** (9 mg, 60%) as a light green oil: ^{1}H NMR δ 7.08 (d, *J* = 16.2 Hz, 1H), 7.02 (s, 1H), 7.00–6.95 (m, 2H), 6.94 (d, *J* = 3.0 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 6.73 (s, 1H), 6.54 (d, *J* = 2.6 Hz, 1H), 5.46 (br s, 1 OH), 4.01 (s, 3H), 3.78 (s, 3H), 3.45 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.74–2.70 (m, 2H), 2.06–2.01 (m, 1H), 1.91–1.60 (m, 4H), 1.55 (br s, 1 OH), 1.26 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 153.3, 145.2, 139.7, 138.4, 132.7, 130.3, 128.3, 127.9, 126.5, 122.0, 119.2, 118.9, 119.4, 101.8, 98.5, 97.3, 77.9, 77.9, 55.3, 47.2, 38.5, 37.7, 33.0, 28.2, 27.3, 22.7, 20.2, 14.3; HRMS (EI) calcd for $C_{28}H_{33}NO_4$ (M^+) 447.2410; found 447.2404.

5.32 Stilbene 49

To phosphonate **41** (45 mg, 0.089 mmol) and aldehyde **48**[11] (25.7 mg, 0.068 mmol) in THF (3mL) at 0 °C was added NaH (50 mg, 1.25 mmol, 60% dispersion oil) and 15-crown-5 (2 drops). The reaction was allowed to warm to rt and then allowed to stir for 4 h. To the reaction mixture was added 2-propanol (3 mL) and NaH (40 mg, 1.0 mmol, 60% dispersion oil) and the solution was allowed to stir. After 20 h the reaction was quenched by addition of $NaHCO_3$ (satd.) and extracted with EtOAc. 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 (40% EtOAc in hexanes) afforded indole **49** (20 mg, 51% for 2 steps) as a light yellow oil: ^{1}H NMR δ 7.89 (br s, 1H), 7.15 (d, *J* = 1.4 Hz, 1H), 7.00 (s, 1H), 6.99 (s, 1H), 6.98–6.97 (m, 2H), 6.78 (d, *J* = 1.1 Hz, 1H), 6.68 (s, 1H), 5.49–5.44 (m, 1H), 5.25 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.97 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 3.41 (s, 3H), 3.29 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.75–2.71 (m, 2H), 2.13–1.94 (m, 2H), 1.75–1.55 (m, 3H), 1.75 (s, 3H), 1.73 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR δ 155.0, 146.2, 143.6, 138.3, 132.9, 131.2, 129.6, 128.0, 126.3, 124.7, 123.3, 121.7, 120.5, 117.2, 117.0, 113.4, 103.4, 97.4, 96.2, 95.9, 84.0, 76.9, 56.2, 55.6, 55.1, 47.1, 38.3, 37.7, 27.4, 25.8, 25.6, 25.3, 23.2, 19.9, 17.7, 14.3; HRMS (EI) calcd for $C_{36}H_{47}NO_6$ (M^+) 589.3403; found 589.3416.

5.33 Analogue 50

To protected analogue **49** (12.2 mg, 0.021 mmol) was added 1:1 THF/MeOH (2 mL) and TsOH (35 mg, 0.18 mmol) and the reaction mixture was allowed to stir overnight. The next day the reaction mixture was quenched by addition of NH_4Cl (satd.) and extracted with EtOAc. 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 (25 to 50% EtOAc in hexanes) afforded analogue **50** (6.4 mg, 62%) as an oil: ^{1}H NMR δ 7.89 (br s, 1H), 7.01 (d, *J* = 16.1 Hz, 1H), 7.00 (s, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 16.2 Hz, 1H), 6.80–6.78 (m, 2H), 6.67 (s, 1H), 5.49–5.44 (m, 2H), 3.97 (s,

3H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.45 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.78–2.63 (m, 2H), 2.06–2.00 (m, 1H), 1.93–1.58 (m, 5H), 1.75 (s, 3H), 1.73 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 155.0, 145.2, 139.7, 138.3, 132.9, 131.2, 130.3, 128.2, 126.4, 124.1, 122.0, 120.5, 119.2, 117.2, 117.1, 109.4, 103.4, 97.4, 77.9, 77.8, 55.1, 47.2, 38.5, 37.7, 28.2, 27.3, 25.8, 25.6, 22.7, 20.2, 17.7, 14.3; HRMS (EI) calcd for $C_{32}H_{39}NO_4$ (M^+) 501.2879; found 501.2881.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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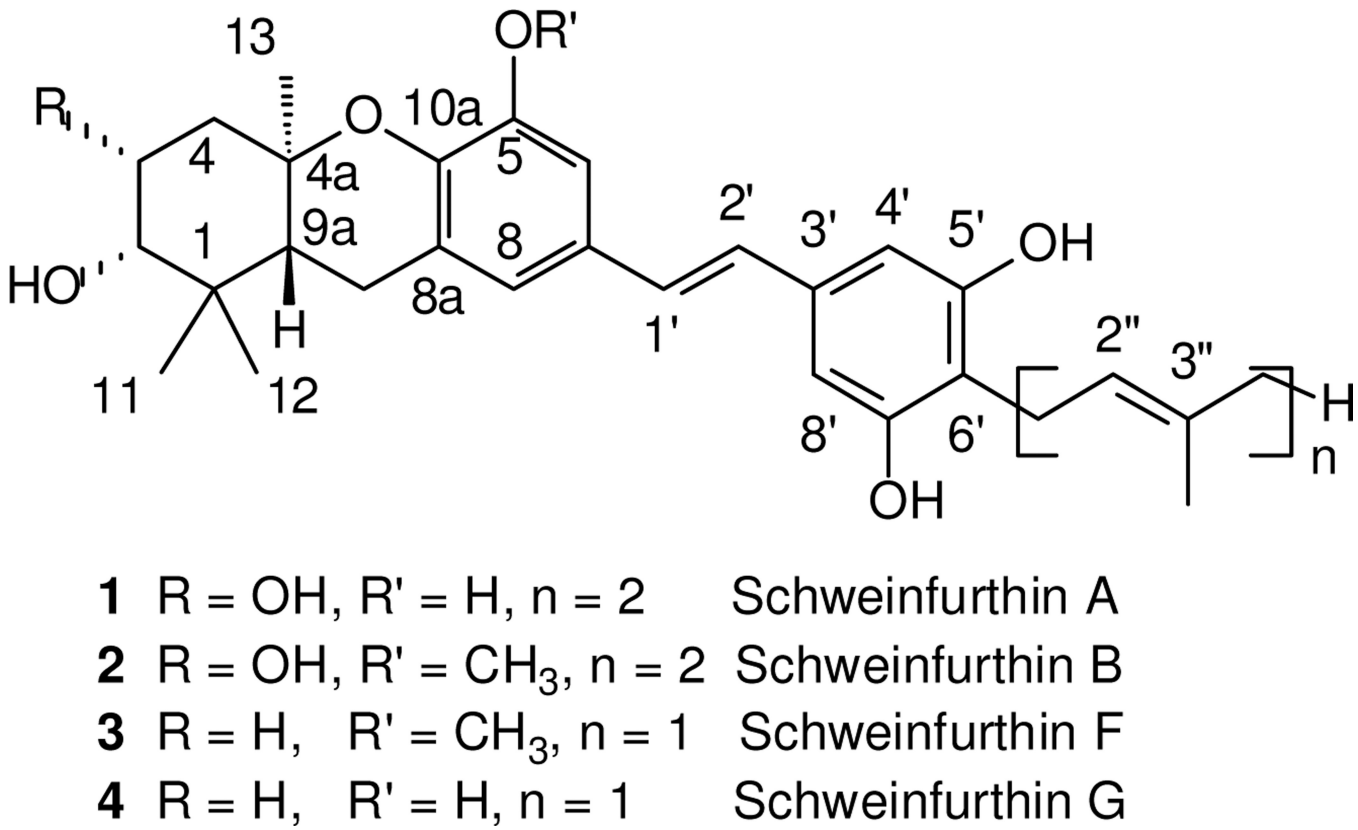
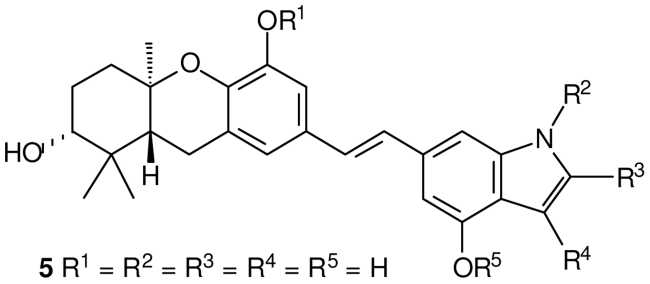
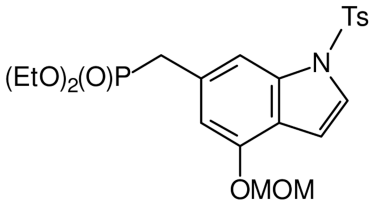


1 R = OH, R' = H, n = 2 Schweinfurthin A
2 R = OH, R' = CH_3, n = 2 Schweinfurthin B
3 R = H, R' = CH_3, n = 1 Schweinfurthin F
4 R = H, R' = H, n = 1 Schweinfurthin G

Figure 1.
Some natural schweinfurthins.



5 $R^1 = R^2 = R^3 = R^4 = R^5 = H$
6 $R^1 = CH_3$; $R^2 = R^3 = R^4 = R^5 = H$
7 $R^1 = CH_3$; R^3 = prenyl; $R^2 = R^4 = R^5 = H$
8 $R^1 = CH_3$; R^4 = prenyl; $R^2 = R^3 = R^5 = H$



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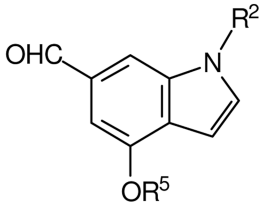


10

Figure 2.
Intermediates for assembly of schweinfurthin indoles.

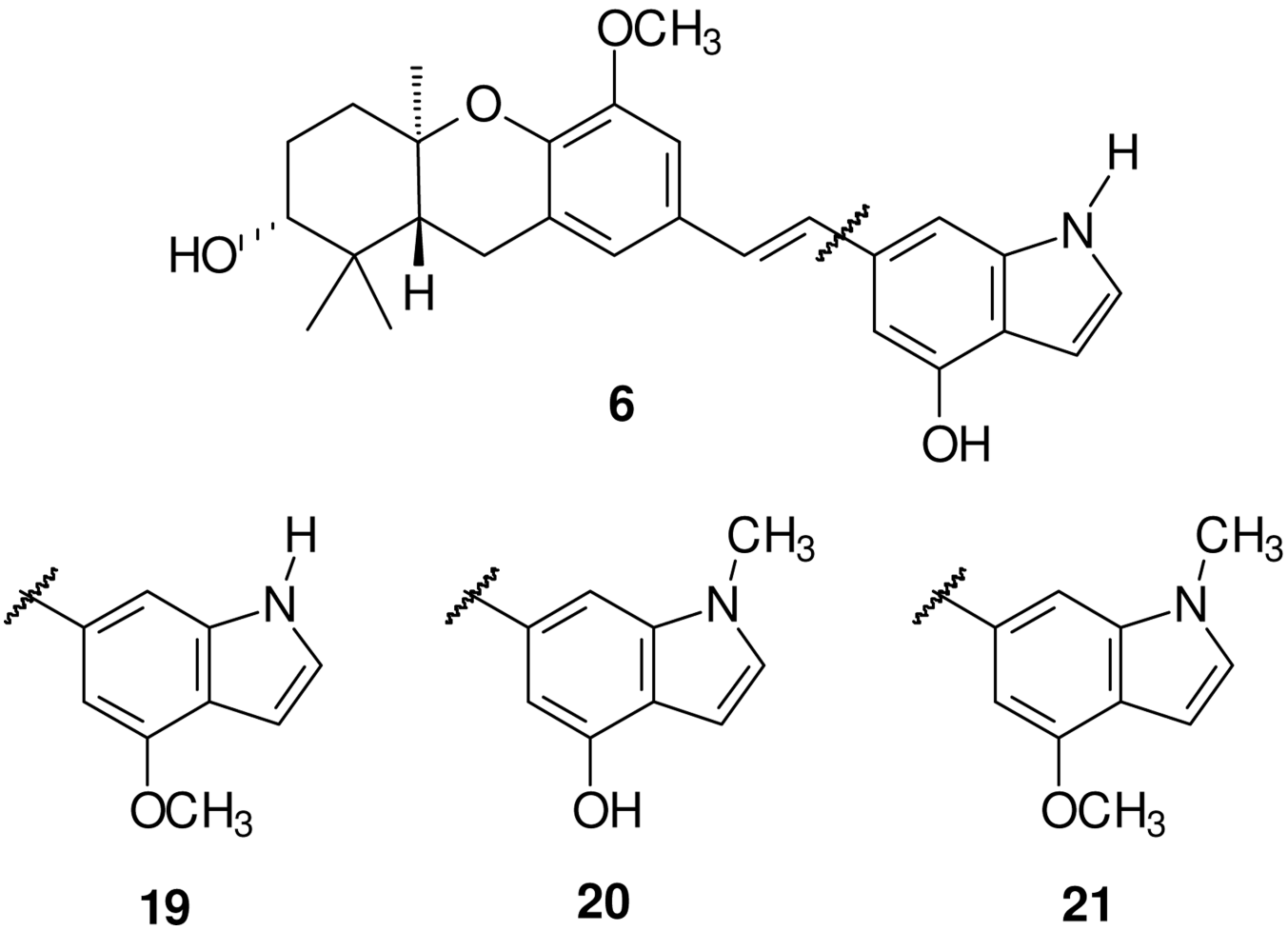
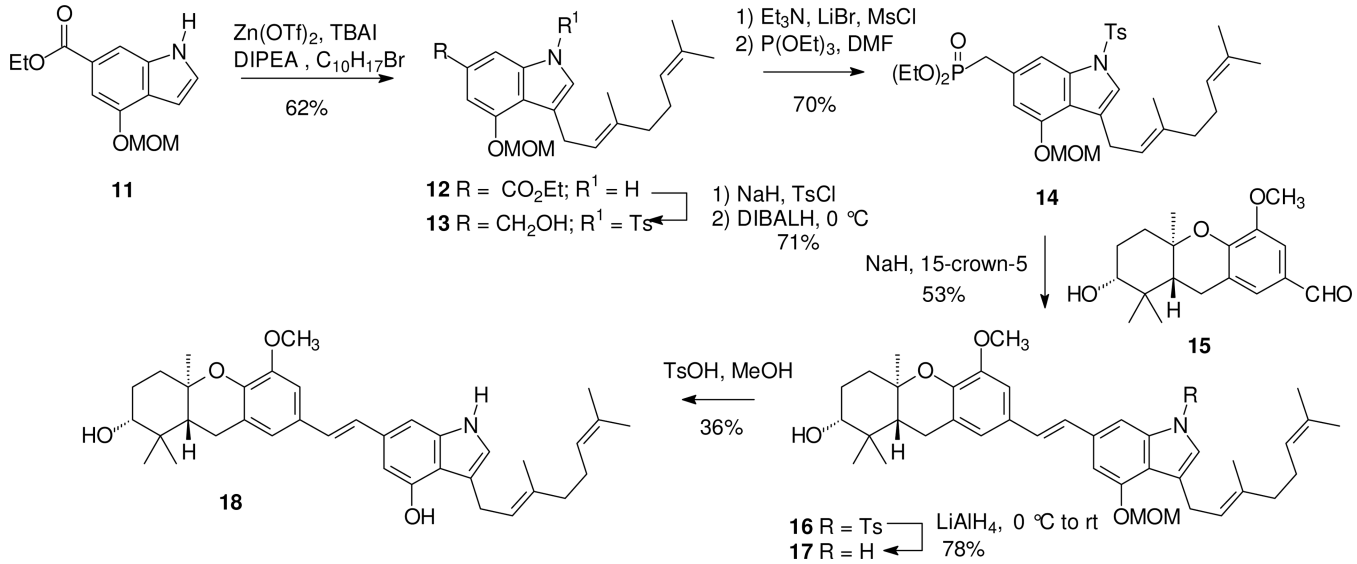
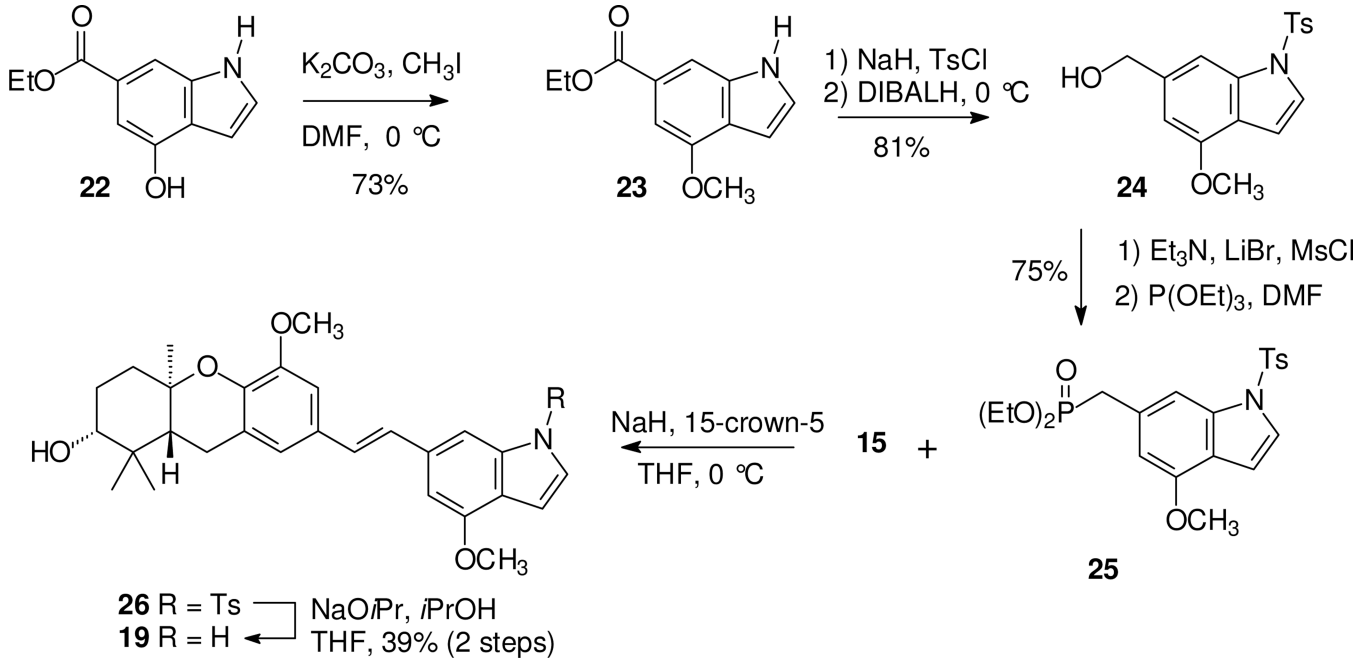


Figure 3.
Mono- and dimethylated schweinfurthin indole targets.

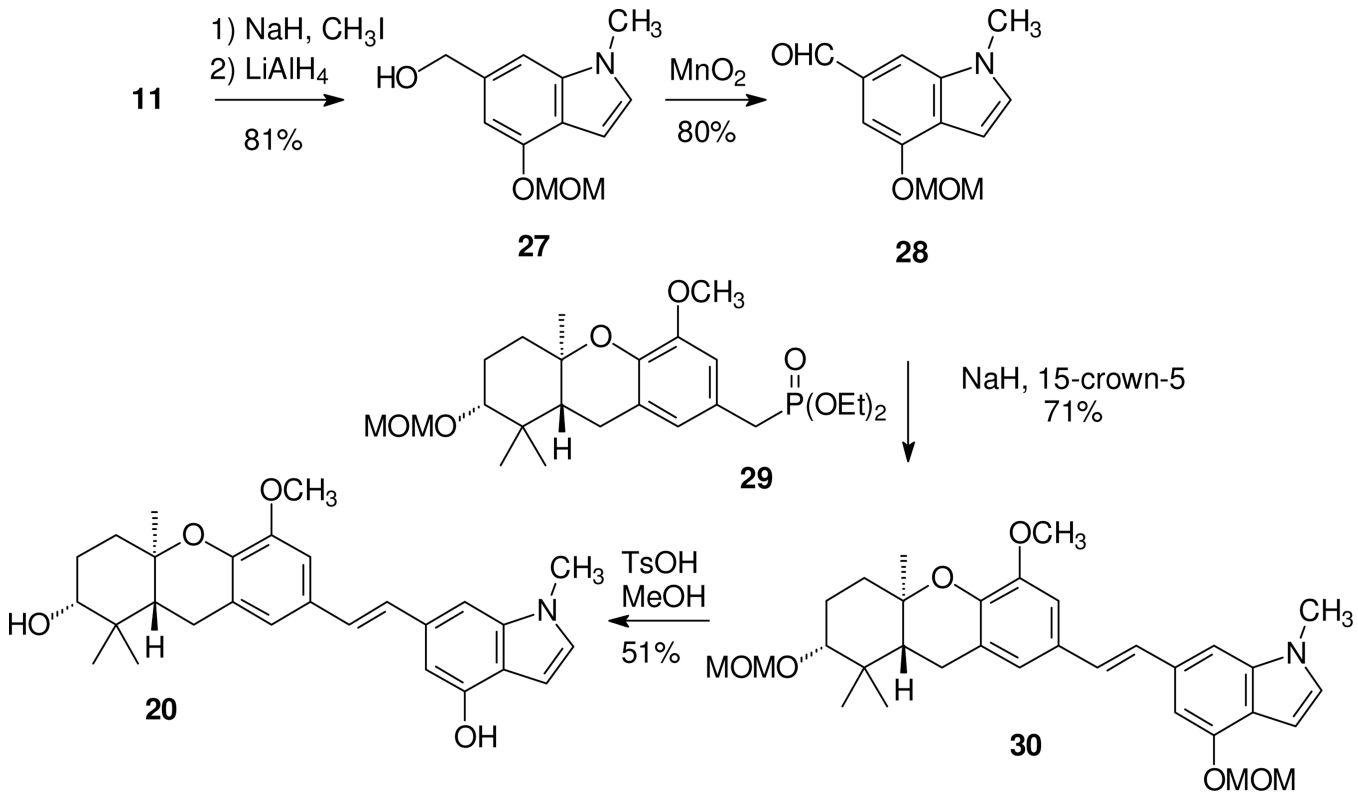


Scheme 1.

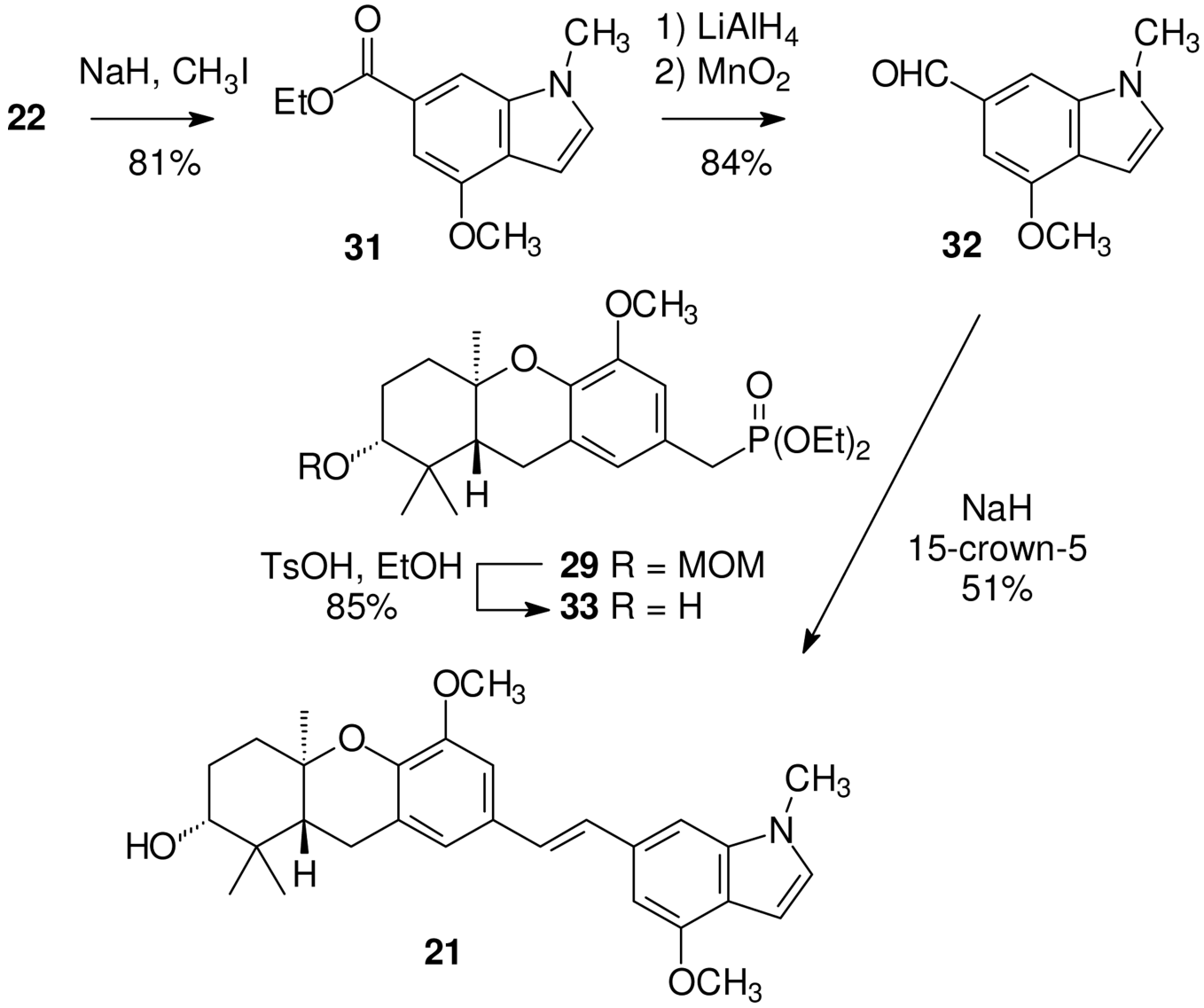
Synthesis of a geranylated schweinfurthin indole.



Scheme 2.
Synthesis of an *O*-methyl schweinfurthin indole.

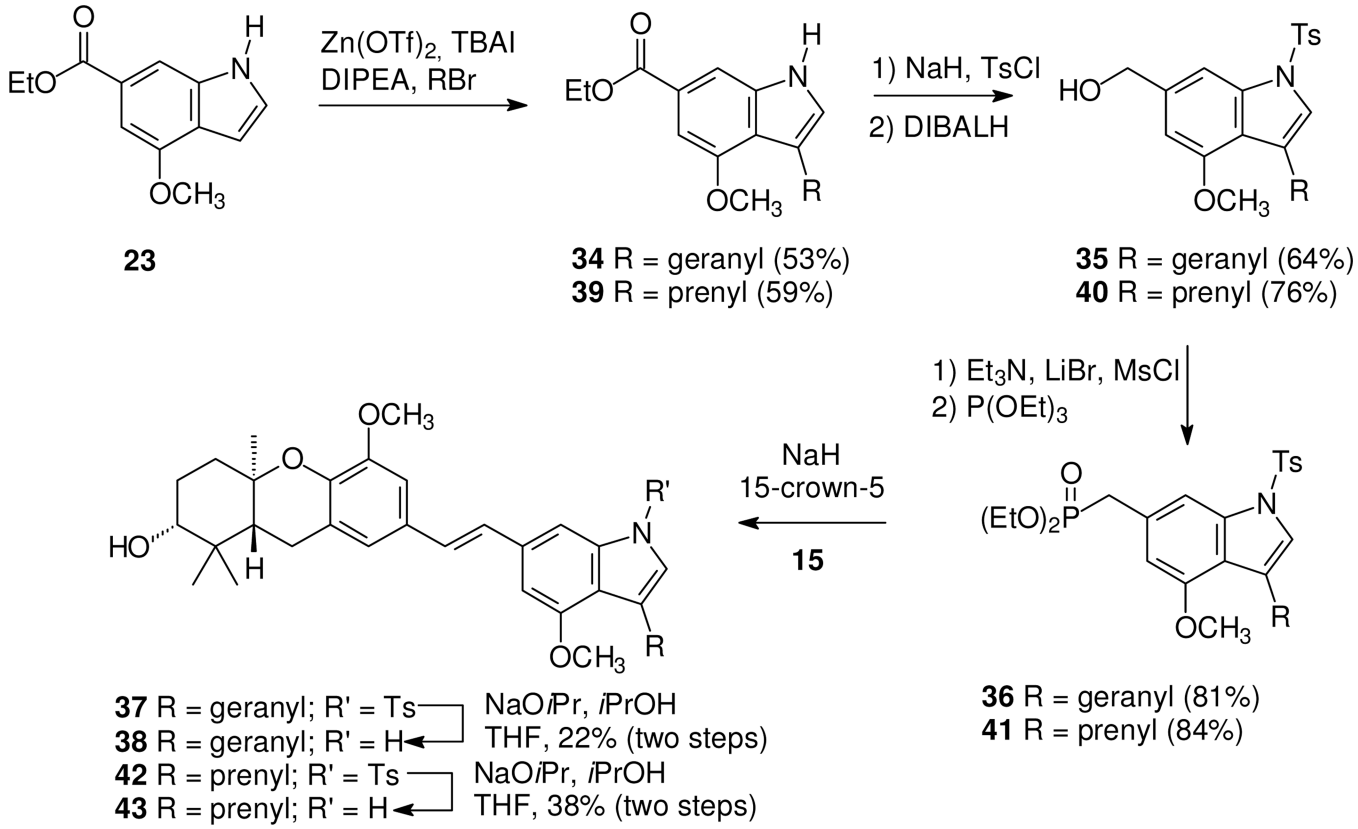


Scheme 3.
Synthesis of an *N*-methyl schweinfurthin indole.

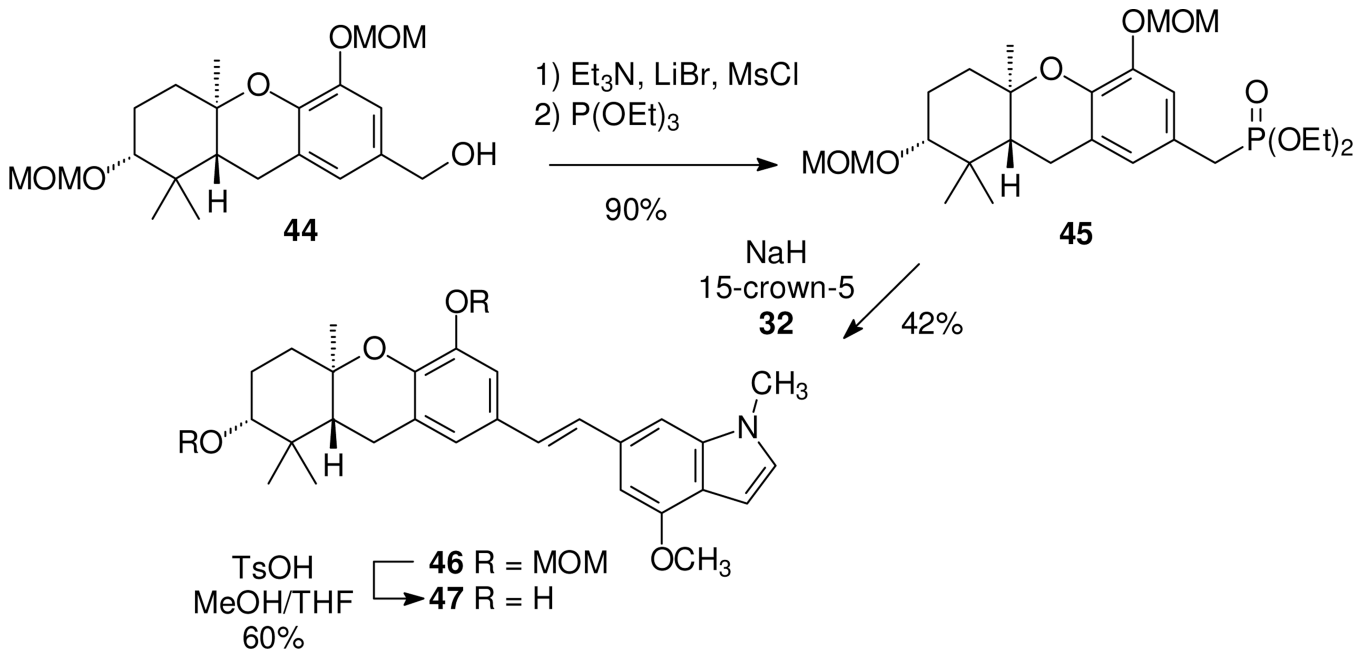


Scheme 4.

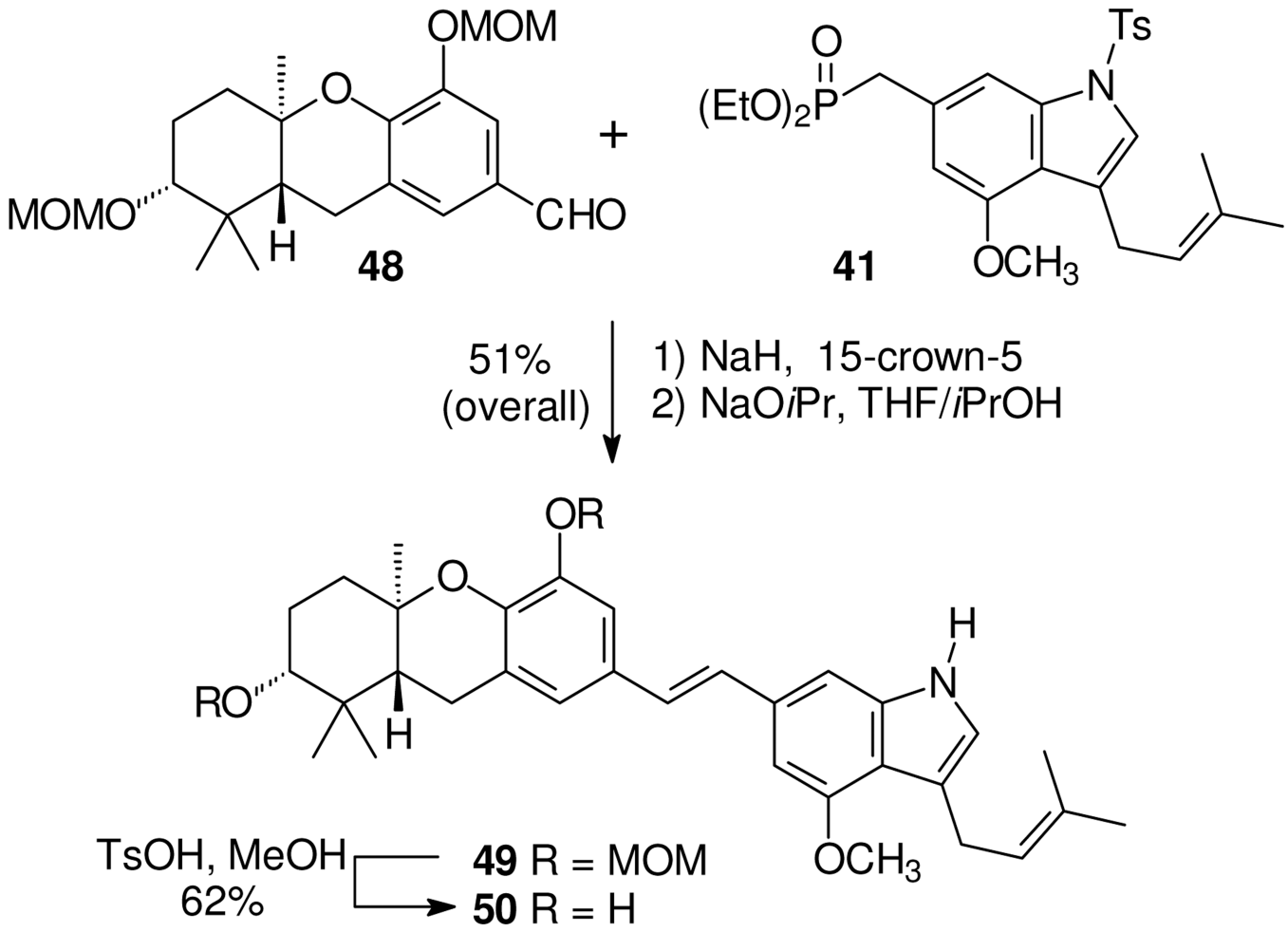
Synthesis of an *N*,*O*-dimethyl schweinfurthin indole.



Scheme 5.
Synthesis of geranyl and prenyl-substituted schweinfurthin indoles.



Scheme 6.
Synthesis of a C-5 hydroxy schweinfurthin indole.



Scheme 7.
Synthesis of a C-5 hydroxy E-ring prenyl schweinfurthin indole.

Table 1

Activity of schweinfurthin indoles in the NCI 60 cell line screen.

cmpd	NSC#	R^1	R^2	R^3	R^4	R^5	Mean GI_{50} (nM)	GI_{50}Range (log_{10} units)	*n*	SF-295 GI_{50} (nM)
5	750658	H	H	H	H	H	570	3.29	2[a]	89
6	750655	CH_3	H	H	H	H	1020	2.02	2[a]	230
7	752116	CH_3	H	prenyl	H	H	3160	3.08	2[a]	290
8	752816	CH_3	H	H	prenyl	H	390	3.00	2[a]	<21[b]
18	750656	CH_3	H	H	geranyl	H	1620	3.19	1	110
19	751060	CH_3	H	H	H	CH_3	380	2.41	1	55
20	752115	CH_3	CH_3	H	H	H	1260	2.63	2[a]	760
21	752114	CH_3	CH_3	H	H	CH_3	1260	2.61	2[a]	170
38	751061	CH_3	H	H	geranyl	CH_3	1070	2.54	1	200
43	754492	CH_3	H	H	prenyl	CH_3	430	2.38	2[a]	48
47	752817	H	CH_3	H	H	CH_3	450	3.00	2[a]	<12[b]
50	754493	H	H	H	prenyl	CH_3	580	3.26	2[a]	<23[b]
3	740544	Schweinfurthin F					780	2.79	2[a]	<36[b]
4	744343	Schweinfurthin G					110	3.12	2[a]	10

[a] Data represents the average of two independent experiments.

[b] In one experiment the GI_{50} was below the lowest concentration tested (10 nM).