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# Relevance of the C-5 position to schweinfurthin induced cytotoxicity

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ABSTRACT

The schweinfurthins are an intriguing group of anti-proliferative agents that display low nanomolar activities against several cell types, including the human-derived glioblastoma cell line SF-295, but have little impact on other cell lines even at micromolar concentrations. This activity has inspired the synthesis of seven of the natural schweinfurthins, all with the correct absolute stereochemistry, and a variety of analogues designed to probe different facets of the pharmacophore. Reported herein is the synthesis of several new schweinfurthin analogues varied at the C-5 position along with data on their biological activity in the NCI 60 cell-line assay.

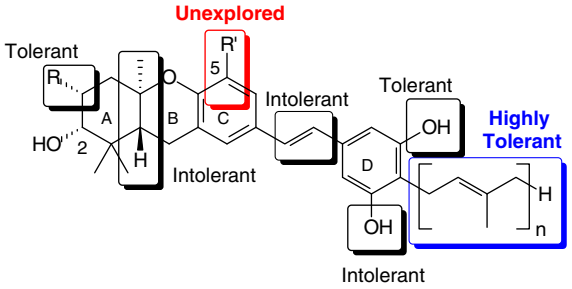


## 1. Introduction

In 1998 the structures of schweinfurthins A and B (**1** and **2**, Fig. 1) were reported as part of the National Cancer Institute's (NCI) search for anti-proliferative agents with new mechanisms of action. These compounds were isolated from an extract of *Macaranga schweinfurthii* through bioassay guided fractionation,[1] and subsequently were subjected to the NCI 60 cell-line screen. This assay revealed a unique pattern of activity which does not correlate to any known mechanism of cell growth inhibition. Several cell lines were particularly sensitive to the schweinfurthins, including the human glioblastoma line SF-295, while other cell lines (e.g., the lung cancer line A549) were only marginally affected even at elevated doses. These observations led to the hypothesis that further exploration of the schweinfurthins might uncover a new target for treatment of specific malignancies, especially for conditions with poor clinical prognoses such as glioblastoma multiforme.

At this time seven of the eleven natural schweinfurthins[1–4] have been synthesized, including specifically schweinfurthins A (**1**),[5] B (**2**),[6] C,[7] E (**3**),[6] F (**4**),[8] and G (**5**),[8] as well as vedelianin[9] (**6**). Our group also has synthesized numerous schweinfurthin analogues and in the process has gained considerable knowledge of the schweinfurthin pharmacophore. Several portions of the schweinfurthin structure have shown tolerance to modification, including the presence or absence of a hydroxyl group at C-3,[10] methylation of one D-ring phenol[11] (Fig. 1, 'tolerant'), and especially incorporation of substituents at the para position of the D-ring, including hydrogen or an alkyl, allyl, prenyl, or geranyl group ('highly tolerant').[12–15] Conversely, modification of other regions resulted in a significant loss of activity, including a *cis*-fused A/B system,[16] a *cis*-stilbene or a saturated linkage,[13] and simultaneous methylation of both D-ring phenols (Fig. 1, 'intolerant').[11]

Investigations of the schweinfurthin mechanism[17] have revealed that schweinfurthin A can phenocopy the tumor suppressor




Schweinfurthin A **1** R = OH, R' = OH, n = 2
Schweinfurthin B **2** R = OH, R' = $OCH_3$, n = 2
Schweinfurthin E **3** R = OH, R' = $OCH_3$, n = 1
Schweinfurthin F **4** R = H, R' = $OCH_3$, n = 1
Schweinfurthin G **5** R = H, R' = OH, n = 1
Vedelianin **6** R = OH, R = OH, n = 1

**Figure 1.** Key schweinfurthins and current understanding of the pharmacophore.

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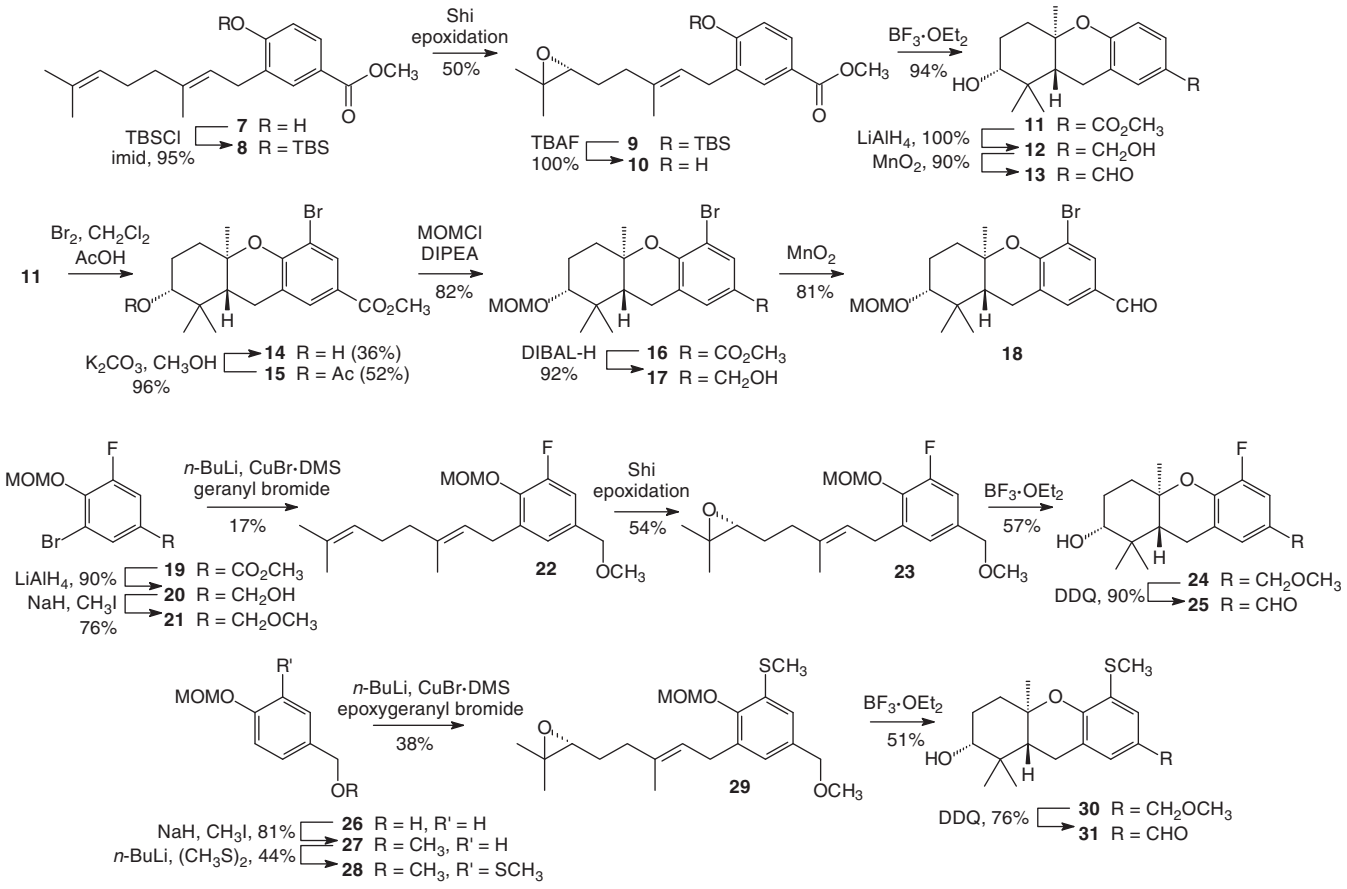
NF1 in CNS and peripheral nervous system tumor cell lines,[17a] although a proximate target has not yet been identified conclusively. Recent work by the Shair group has implicated oxysterol binding proteins in the action of schweinfurthins and other apparently similar natural products, but the evidence for schweinfurthins is less compelling than for OSW-1 and cephalostatin 1.[17b] A recent study more specific to the schweinfurthins found that the synthetic analogue 3-deoxyschweinfurthin B had a pronounced impact on isoprenoid homeostasis,[17c] but more work is clearly needed before the mechanism(s) will be understood in any detail.

An increased understanding of the pharmacophore has allowed synthesis of schweinfurthins for use as fluorescent[12,14] or biotinylated[15] probes that may allow more specific determination of the basis of schweinfurthins' cellular activity. However, one region of the schweinfurthin structure that, until now, has remained relatively unexplored is the C-5 position. Within the natural family, this position has been found only as a free phenol or a methoxy group, with the free phenol typically 2–4 fold more potent. Given this difference in potency, it appeared to be worthwhile to explore the effect that various substituents at the C-5 position might have on activity. Reported herein is the synthesis of a small set of C-5 modified schweinfurthins with an evaluation of their relative activity in the NCI's 60 cell-line assay.

## 2. Synthesis

Our strategy for schweinfurthin synthesis is based on a late stage Horner–Wadsworth–Emmons (HWE) condensation between an aryl aldehyde, usually representing the hexahydroxanthene side of the target, and a benzylic phosphonate.[10] To use this approach to obtain C-5 analogues required preparation of several key aldehydes (Scheme 1). The first aldehyde prepared carried only a hydrogen substituent at C-5. To pursue this compound, protection of the previously reported arene **7**[18] as the TBS ether afforded compound **8**, which was epoxidized under Shi conditions[19] to obtain the nonracemic compound **9**. Removal of the silyl group in epoxide **9** afforded the phenol **10**, and subsequent treatment with $BF_3{\cdot}OEt_2$ brought about cyclization to afford the hexahydroxanthene **11** in very good yield. After reduction of this methyl ester to the benzylic alcohol **12**, oxidation with $MnO_2$ gave the parent aldehyde **13**. While aldehyde **13** underwent direct bromination at the C-5 position in modest yield (23%), a longer sequence provided the MOM-protected bromide **18** in much better yield. Thus, bromination of the methyl ester **11** in methylene chloride and acetic acid provided a mixture of bromides **14** and **15**, but cleavage of the acetate could be accomplished in near-quantitative yield. After protection of the hydroxyl group of compound **14** through reaction with MOMCl, reduction provided the benzylic alcohol **17** and a final oxidation with $MnO_2$ gave the desired aldehyde **18**. This aldehyde was condensed with a 'right-half' phosphonate (vide infra) that was also MOM-protected, so a separate step was not required for the eventual removal of the C-2 MOM group.

A substantial number of important drugs bear a fluorine substituent, at least in part because fluorine's electronic properties are significantly different from hydrogen but its size is sufficiently similar that there is minimal potential for introduction of unfavorable steric interactions in a mono-fluoro compound.[20] To prepare a C-5 fluorinated schweinfurthin analogue, synthesis of the requisite aldehyde began with ester **19**, obtained in three steps from commercial 3-fluoro-4-hydroxybenzoic acid (esterification, bromination and protection as the MOM acetal).[21] After this ester was reduced to alcohol **20** it was converted to the methyl ether



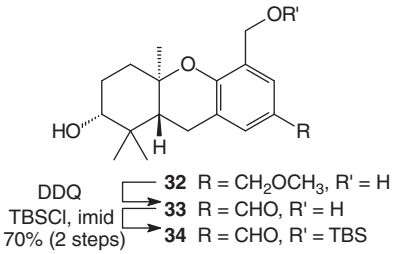

**Scheme 1.** Synthesis of four intermediate aldehydes for the 'left half' of the schweinfurthins.

**21** via a standard Williamson synthesis. Halogen metal exchange and reaction of the resulting aryl lithium intermediate with geranyl bromide provided compound **22** in low yield. Application of a Shi epoxidation furnished epoxide **23** in moderate yield and good enantiomeric excess. Cyclization of this epoxide afforded the hexahydroxanthene **24**. The benzyl methyl ether has been utilized as a latent benzaldehyde in other schweinfurthin syntheses,[5,8] and in this specific case DDQ oxidation provided aldehyde **25** cleanly in a single step from the methyl ether **24**.

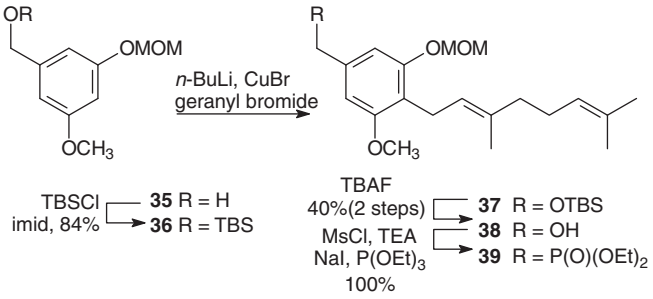
A slightly different approach based on sequential and selective directed *ortho* metallation was employed to gain access to the C-5 methylthio schweinfurthin analogue. In this case, after alcohol **26** was converted to the methyl ether **27**, deprotonation with *n*-BuLi followed by treatment with $(CH_3S)_2$ provided the thiomethyl ether **28**. A second ortho metallation and copper-mediated coupling with the known[22] epoxide of geranyl bromide provided epoxide **29**. Cyclization to compound **30** proceeded in reasonable yield, and DDQ oxidation of the benzyl methyl ether provided aldehyde **31 s**moothly without detectable oxidation of the thiomethyl group.

We also prepared compounds with carbon-containing substituents at C-5 (Scheme 2). During the course of these studies, the benzyl alcohol **32** became available through a cascade cyclization terminated by electrophilic aromatic substitution.[5] Treatment of compound **32** with DDQ preferentially oxidized the benzyl methyl ether in the presence of the free benzyl alcohol to provide aldehyde **33**, corroborating previous observations on the regioselectivity of this oxidation.[5] Protection of the benzyl alcohol as a TBS ether afforded aldehyde **34** for use as a partner in HWE reactions.

The right half of the new schweinfurthin analogues was prepared as shown in Scheme 3. Directed ortho metallation of alcohol **35**[23] occurred upon exposure to multiple equivalents of *n*-BuLi, and subsequent reaction with geranyl bromide afforded the expected geranylated arene **38** in 47% yield.[24] This approach presumably involves formation of an intermediate dianion, and was more efficient than the 34% overall yield if alcohol **35** was protected as the TBS ether **36**, alkylated to obtain compound **37**, and then deprotected to afford alcohol **38.** Conversion of benzyl alcohol **38** to the phosphonate **39** was conducted by a classical Arbuzov reaction[25] after formation of the mesylate and iodide. This provided phosphonate **39** which was used as an HWE coupling partner throughout this series.




**Scheme 2.** Synthesis of C-5 alkyl compounds.

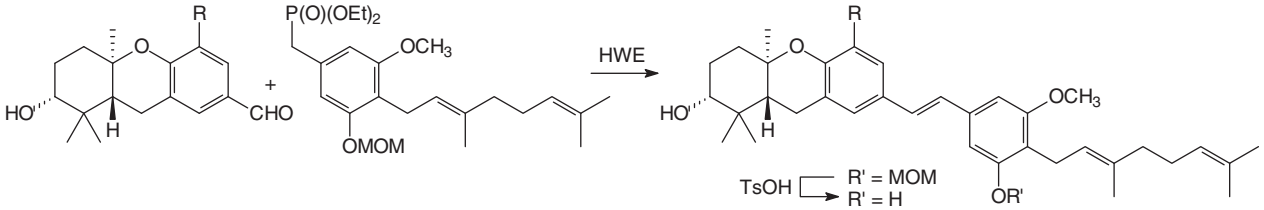



**Scheme 3.** Synthesis of phosphonate **39**.

With phosphonate **39** and a set of aldehydes now available, stilbene formation was accomplished by standard HWE olefination (Table 1). Treatment of the new aldehydes **13**, **18**, **25**, **31**, and **34**, as well as the known aldehydes **40**,[5] **41**,[8] and **42**,[10] with phosphonate **39** and base provided stilbenes **43**–**50** in moderate to high yield. Hydrolysis of the MOM acetals **43**–**49** was accomplished by exposure to methanolic *p*-TsOH to provide schweinfurthin analogues **51**–**57**.

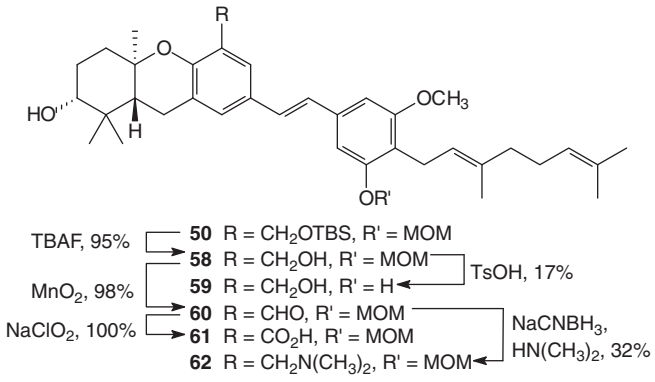
The benzylic C-5 position of compound **50** allowed the possibility of further elaboration and this intermediate was exploited to obtain several additional analogues. After cleavage of the silyl ether through treatment with TBAF, several analogues were obtained through straightforward reactions of the resulting benzyl alcohol **58** (Scheme 4). Exposure of alcohol **58** to $MnO_2$ resulted in aldehyde **60**. Further oxidation of this intermediate with sodium chlorite[26] provided the carboxylic acid **61**, while reductive amination of aldehyde **60** with $NaCNBH_3$ and dimethylamine resulted in the tertiary amine **62**. The D-ring MOM group of compound **58** could be removed via hydrolysis to afford schweinfurthin **59**, but this reaction proceeded in low yield. Given this disappointing yield, and because MOM groups might be cleaved *in vivo* during cellular assays, hydrolysis of the other MOM acetals in this small set was not pursued pending the results of bioassays on two representative

**Table 1**
HWE condensations and subsequent hydrolysis




| Entry | RCHO | R = | HWE (% Yield) | Stilbene | Hydrolysis (% Yield) | Schwein. | R = |
|---|---|---|---|---|---|---|---|
| 1 | **13** | H | 66 | **43** | 53 | **51** | H |
| 2 | **18**[a] | Br | 54 | **44**[a] | 92 | **52** | Br |
| 3 | **25** | F | 53 | **45** | 77 | **53** | F |
| 4 | **31** | $SCH_3$ | 74 | **46** | 40 | **54** | $SCH_3$ |
| 5 | **40** | $CH_2OCH_3$ | 50 | **47** | 41 | **55** | $CH_2OCH_3$ |
| 6 | **41** | OMOM | 77 | **48** | 61 | **56** | OH |
| 7 | **42** | $OCH_3$ | 90 | **49** | 92 | **57** | $OCH_3$ |
| 8 | **34** | $CH_2OTBS$ | 36 | **50** | | | |

[a] In this series, the aldehyde and stilbene bear a C-2 MOM group that is cleaved in the final hydrolysis.




**Scheme 4.**

members of this group, the alcohol **58** and the corresponding aldehyde **60**.

## 3. Biological results and discussion

Nine of these new schweinfurthin analogues have been submitted to the NCI's 60 cell-line screen,[27] compounds **51**–**58**, and **60**. The current protocol for this assay requires initial testing at a single dose, and then the more active compounds are subjected to the full 5-dose assay. Of these nine schweinfurthins, compounds **52** and **55** did not pass the single dose assay with a level of activity sufficient to justify the full screen. Given the substantial size of the bromide substituent, it may not be surprising that compound **52** showed little activity, but the limited activity of the fluoride **55** was disappointing. This may suggest that a C-5 substituent capable of hydrogen bond donation is important to activity, or that the limited ability of fluorine[28] to serve as hydrogen bond acceptor diminishes activity.

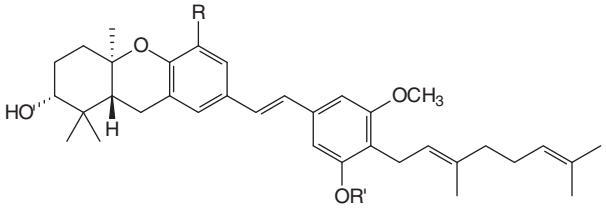
Five of the compounds that did pass this test carried one phenol and one methoxy substituent in the D-ring, and these five compounds displayed a range of activity (Table 2). Compound **56** was the most potent, with a mean $GI_{50}$ of 0.47 μM, and this compound also showed the greatest difference in activity between the most and least sensitive cell lines (2.84 log units). Reflecting the same trend as the natural products schweinfurthin A and B, introduction of a methyl ether at the C-5 position (i.e., compound **57**) resulted in about a 3-fold loss of potency as measured by the mean $GI_{50}$ values. The difference in activity is even more striking if one considers just the sensitive SF-295 and insensitive A549 cell lines. For these two cell lines, compound **56** was more than 30-fold more potent against SF-295 cells than against A549 cells, while compound **57** showed only about 13-fold greater activity in the SF-295 assay. A lesser differential activity also is observed in the full 60 cell-line data for compound **57** versus compound **56** (1.58 versus 2.84).

By some measures, compound **57** also is an interesting compound: it has a relatively low mean $GI_{50}$ (1.67 μM) and shows a 13-fold difference in activity between the SF-295 and A549 cells. However, perhaps the most surprising compound is the benzyl alcohol **58**. As noted above, because attempted hydrolysis of the D-ring MOM group in compound **58** was accompanied by extensive decomposition, both compounds **58** and **60** were submitted for this assay with the D-ring MOM group still in place. Thus there are two points of difference between compounds **58** and **57** which complicates any direct comparison of their biological activity. Nevertheless, the fact that compound **58** displays potency comparable to compound **57** and high differential activity (2.56 log units in the 60 cell assay) is intriguing. If one assumes that the D-ring MOM group is lost after cell uptake, the resulting compound would be simply isomeric to compound **56** at C-5 and it is nearly equivalent in mean $GI_{50}$. However compound **58** may be significantly more stable to metabolism. Because ortho quinone formation in the C-ring would require extensive metabolism with any carbon substituent at C-5, it may be worthwhile to explore other schweinfurthin analogues that include a C-5 hydroxymethyl group.

## 4. Conclusions

In conclusion, several C-5 modified schweinfurthin analogues have been prepared through new variations on the strategies that have been used to prepare the natural products in this family. These syntheses required sequences of varied length and gave varied yields, but averaged 11 linear steps and proceeded in an average yield of ~5%. Of the nine schweinfurthin analogues synthesized for this study and tested in the NCI 60 cell assay, only compounds **56** and **58** have in vitro potency comparable to schweinfurthin A (**1**),[1] although most of them show selectivity for inhibition of CNS tumor cell growth. From these studies, it appears that the phenol group at C-5 is one structural feature that preserves both good potency and a high differential activity. Perhaps surprisingly, incorporation of a hydroxymethyl group at this position also led

**Table 2**
Activity of schweinfurthin analogues in the NCI 60 cell line screen[27]




| Entry | Schweinfurthin | R = | R' = | Mean $GI_{50}$ (μM) | Differential (log units) | SF-295 $GI_{50}$ (μM) | A-549 $GI_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| 1 | **51**[a] | H | H | 10.15 | 1.56 | 1.66 | 13.2 |
| 2 | **53**[a] | F | H | 6.23 | 1.40 | 5.01 | 2.14 |
| 3 | **54**[a] | $SCH_3$ | H | 7.95 | 1.58 | 3.80 | 6.03 |
| 4 | **56**[b] | OH | H | 0.47 | 2.84 | 0.022 | 0.72 |
| 5 | **57**[a] | $OCH_3$ | H | 1.67 | 1.58 | 0.19 | 2.45 |
| 6 | **58**[b] | $CH_2OH$ | MOM | 1.66 | 2.56 | 0.15 | 1.41 |
| 7 | **60**[a] | CHO | MOM | 6.30 | 2.46 | 1.20 | 7.8 |

[a] Duplicate wells were run for each of these compounds in one assay.
[b] Duplicate wells were run for each of these compounds in each of two independent assays and the average value is given in this table.

to an analogue with good activity. Thus the contribution of the C-5 substituent may be more reliant on its ability to undergo hydrogen bonding than on its electronic effect on the extended $\pi$ system. It is now apparent that preservation of a C-5 substituent capable of H-bonding will be important during studies that probe other aspects of the schweinfurthin pharmacophore. Furthermore, the activity observed for compound **58**, despite the presence of a D-ring MOM acetal, suggests that this group is biodegradable upon cell uptake and/or that there is more flexibility to substituents at this position than previously recognized. Thus it is reasonable to conclude that there is still more to be learned about the activity of synthetic compounds modeled upon the natural schweinfurthins, and further studies in this vein will be forthcoming.

## 5. Experimental procedures and methods

### 5.1. General experimental conditions

Tetrahydrofuran was freshly distilled from sodium/benzophenone, while methylene chloride was distilled from calcium hydride prior to use. All other reagents and solvents were purchased from commercial sources and used without further purification. All reactions in nonaqueous solvents were conducted in flame-dried glassware under a positive pressure of argon and with magnetic stirring. All NMR spectra were obtained at 300 MHz for $^1$H, and 75 MHz for $^{13}$C 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. The $^{31}$P chemical shifts were reported in ppm relative to 85% $H_3PO_4$ (external standard). High resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Silica gel (60 Å, 0.040–0.063 mm) was used for flash chromatography.

### 5.2. Silyl ether 8

To a solution of phenol **7** (1.86 g, 6.4 mmol) in $CH_2Cl_2$ (200 mL) was added imidazole (2.19 g, 32.2 mmol), followed by TBSCl (1.15 g, 7.7 mmol) in one portion at 0 °C. The solution was allowed to stir for 12 h, and then the reaction was quenched by addition of water. The resulting solution was extracted with $CH_2Cl_2$, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (1–5% EtOAc in hexanes) produced ester **8** as an oil (2.46 g, 95%): $^1$H NMR $\delta$ 7.83 (d, $J$ = 2.2 Hz, 1H), 7.78 (dd, $J$ = 8.4, 2.2 Hz, 1H), 6.80 (d, $J$ = 8.4 Hz, 1H), 5.34–5.29 (m, 1H), 5.14–5.09 (m, 1H), 3.86 (s, 3H), 3.32 (d, $J$ = 6.8 Hz, 2H), 2.12–2.01 (m, 4H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.02 (s, 9H), 0.26 (s, 6H); $^{13}$C NMR $\delta$ 167.2, 157.8, 136.7, 132.5, 131.4, 129.6, 128.8, 124.3, 122.9, 122.0, 117.9, 51.8, 39.8, 28.5, 26.7, 25.7 (3C), 25.7, 18.3, 17.7, 16.3, −3.7 (2C). Anal. Calcd for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51. Found C, 71.44; H, 9.58.

### 5.3. Epoxide 9

To a solution of ester **8** (879 mg, 2.2 mmol), $CH_2Cl_2$ (6 mL), $CH_3CN$ (3 mL), EtOH (3 mL), and aqueous buffer (2 M $K_2CO_3$, $4 \times 10^{-3}$ M EDTA, 12 mL), and the Shi catalyst (140 mg, 0.5 mmol) was added $H_2O_2$ (30% wt. in $H_2O$, 1.2 mL, 10.6 mmol) via syringe pump (0.14 mL/h) at −10 °C. After 17 h, the reaction was quenched by addition of $Na_2SO_3$. The resulting solution was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (2–5% EtOAc in hexanes) provided recovered ester **8** (318 mg, 36%) and epoxide **9** (459 mg, 50%) as oils: $^1$H NMR $\delta$ 7.81 (d, $J$ = 2.1 Hz, 1H), 7.77 (dd, $J$ = 8.4, 2.4 Hz, 1H), 6.79 (d, $J$ = 8.2 Hz, 1H), 5.38–5.33 (m, 1H), 3.86 (s, 3H), 3.33 (d, $J$ = 6.9 Hz, 2H), 2.72 (t, $J$ = 6.4 Hz, 1H), 2.28–2.09 (m, 2H), 1.77–1.56 (m, 2H), 1.71 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.01 (s, 9H), 0.26 (s, 6H); $^{13}$C NMR $\delta$ 167.1, 157.8, 135.8, 132.2, 131.4, 128.9, 122.8, 122.5, 117.9, 64.2, 58.4, 51.9, 36.3, 28.5, 27.4, 25.7 (3C), 24.9, 18.7, 18.3, 16.3, −3.7 (2C). Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15. Found C, 69.09; H, 9.19.

### 5.4. Phenol 10

To a solution of epoxide **9** (459 mg, 1.1 mmol) in THF (20 mL) at rt was added TBAF (1 M in THF, 2.2 mL, 2.2 mmol). After 3 h, the reaction was quenched by addition of water. The resulting solution was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (10–15% EtOAc in hexanes) afforded phenol **10** (333 mg, 100%) as an oil: $^1$H NMR $\delta$ 7.81–7.77 (m, 2H), 6.84–6.81 (m, 1H), 5.36 (td, $J$ = 7.1, 1.4 Hz, 1H), 3.87 (s, 3H), 3.38 (d, $J$ = 6.9 Hz, 2H), 2.74 (t, $J$ = 6.2 Hz, 1H), 2.29–2.12 (m, 2H), 1.77 (s, 3H), 1.71–1.64 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H); $^{13}$C NMR $\delta$ 167.3, 158.7, 137.0, 131.8, 129.6, 127.2, 122.2, 122.0, 115.4, 64.4, 58.9, 51.9, 36.4, 29.1, 27.2, 24.8, 18.7, 16.2. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found C, 70.73; H, 7.96.

### 5.5. Hexahydroxanthene 11

To a solution of epoxide **10** (353 mg, 1.16 mmol) in $CH_2Cl_2$ (125 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.73 mL, 5.76 mmol). After 6 min, the reaction was quenched by addition of triethylamine (TEA, 1.5 mL). Water was added, the resulting solution was extracted with $CH_2Cl_2$, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (25% EtOAc in hexanes) afforded compound **11** (332 mg, 94%) as a white solid: $[\alpha]_D^{26.4}$ +66.8 (*c* 7.3, $CHCl_3$, 93% ee by HPLC); $^1$H NMR $\delta$ 7.82 (d, $J$ = 1.8 Hz, 1H), 7.77 (dd, $J$ = 8.4, 2.1 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 3.87 (s, 3H), 3.44 (dd, $J$ = 11.3, 4.2 Hz, 1H), 2.82–2.66 (m, 2H), 2.03 (dt, $J$ = 12.4, 3.3 Hz, 1H), 1.92–1.54 (m, 5H), 1.23 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.1, 157.3, 131.9, 129.2, 121.7, 117.0, 77.9, 76.7, 51.8, 46.7, 38.4, 37.6, 28.2, 27.3, 22.9, 20.0, 14.3; $^{13}$C NMR (75.5 MHz, acetone-$d_6$) $\delta$ 167.4, 158.7, 132.9, 129.9, 123.6, 122.8, 118.0, 78.8, 78.0, 52.2, 48.0, 39.5, 38.9, 29.4, 28.1, 23.9, 20.6, 15.2. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found C, 70.82; H, 8.10.

### 5.6. Hexahydroxanthene 12

To a solution of ester **11** (108 mg, 0.4 mmol) in THF (20 mL) at 0 °C was added $LiAlH_4$ (74 mg, 2.0 mmol). After 2 h, the reaction was quenched by addition of $H_2O$, acidified (pH 2), extracted into ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo to afford alcohol **12** (98 mg, 100%) as a white solid: $^1$H NMR $\delta$ 7.10–7.06 (m, 2H), 6.75 (d, $J$ = 8.1 Hz, 1H), 4.58 (s, 2H), 3.41 (dd, $J$ = 11.5, 4.4 Hz, 1H), 2.72 (br d, 1H), 2.69 (d, $J$ = 3.9 Hz, 1H), 2.00 (dt, $J$ = 12.3, 3.2 Hz, 1H), 1.88–1.82 (m, 1H), 1.80–1.50 (m, 4H), 1.25 (br s, 1H), 1.21 (s, 3H), 1.09 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR $\delta$ 152.8, 132.3, 129.0, 126.6, 122.0, 117.1, 78.0, 76.5, 65.3, 46.9, 38.4, 37.8, 28.3, 27.4, 23.1, 19.9, 14.3. Anal. Calcd for $C_{17}H_{24}O_3$: C, 69.84; H, 8.27. Found C, 70.16; H, 7.92.

### 5.7. Aldehyde 13

To a solution of diol **12** (98 mg, 0.35 mmol) in $CH_2Cl_2$ (25 mL) at rt was added $MnO_2$ (812 mg, 8.22 mmol). After 2 h, the reaction was diluted, filtered through a pad of celite, and the filtrate was concentrated in vacuo. Final purification by crystalization (hexanes) afforded aldehyde **13** (78 mg, 90%) as white needles: $^1$H NMR $\delta$ 9.83 (s, 1H), 7.64–7.61 (m, 2H), 6.86 (d, $J$ = 8.4 Hz, 1H), 3.45 (d, $J$ = 12.0 Hz, 1H), 2.79–2.75 (m, 2H), 2.07–2.02 (m, 1H), 1.92–1.60 (m, 5H), 1.25 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR $\delta$ 191.0, 158.9, 132.2, 129.7, 129.2, 122.5, 117.7, 78.0, 77.8,

46.6, 38.4, 37.6, 28.2, 27.3, 22.9, 20.1, 14.3; HRMS (EI) *m*/*z* calcd for $C_{17}H_{22}O_3$ ($M^+$) 274.1570, found 274.1579.

### 5.8. C5-Bromo hexahydroxanthene 14

*Method A*: To a flask containing unsubstituted hexahydroxanthene **11** (107 mg, 0.4 mmol), glacial acetic acid (1 mL), and $CH_2Cl_2$ (35 mL) was added $Br_2$ (0.02 mL, 0.4 mmol) in $CH_2Cl_2$ (1 mL) dropwise at room temperature. The solution was allowed to stir for 24 h, and then the reaction was quenched by addition of $Na_2SO_3$. Water was added and the product was extracted into $CH_2Cl_2$, dried ($MgSO_4$), and concentrated under reduced pressure. Final purification by flash chromatography produced bromide **14** as a white solid (48 mg, 36%): $^1$H NMR $\delta$ 8.03 (d, $J$ = 2.1 Hz, 1H), 7.76 (d, $J$ = 2.2 Hz, 1H), 3.88 (s, 3H), 3.44 (dd, $J$ = 11.4, 4.1 Hz, 1H), 2.78–2.75 (m, 2H), 2.17–2.10 (m, 1H), 1.94–1.55 (m, 5H), 1.24 (s, 3H), 1.11 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR $\delta$ 166.0, 154.0, 132.5, 130.7, 123.1, 122.4, 111.2, 79.0, 77.7, 52.1, 46.5, 38.4, 37.3, 28.1, 27.3, 23.3, 20.2, 14.3; HRMS (EI) *m*/*z* calcd for $C_{18}H_{23}O_4Br$ ($M^+$) 382.0780, found 382.0777. In addition the acetate-protected compound **15** was isolated as a white solid (78 mg, 52%): $^1$H NMR $\delta$ 8.04 (d, $J$ = 2.2 Hz, 1H), 7.75 (d, $J$ = 2.1 Hz, 1H), 4.66 (dd, $J$ = 11.5, 3.9 Hz, 1H), 3.88 (s, 3H), 2.78–2.75 (m, 2H), 2.18–1.37 (m, 5H), 2.09 (s, 3H), 1.37 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H); $^{13}$C NMR $\delta$ 170.6, 165.9, 153.9, 132.5, 130.6, 122.8, 122.5, 111.3, 79.0, 78.5, 52.0, 46.6, 37.4, 37.0, 27.2, 24.6, 23.1, 21.2, 20.2, 15.4; HRMS (EI) *m*/*z* calcd for $C_{20}H_{25}O_5Br$ ($M^+$) 424.0886, found 424.0889.

*Method B*: To a flask containing acetate **15** (76 mg, 0.2 mmol), and $CH_3OH$ (10 mL) was added potassium carbonate (137 mg, 1.0 mmol) at room temperature. The solution was allowed to stir for 6 h, the $CH_3OH$ was removed in vacuo and then the reaction was quenched by addition of $NH_4Cl$. The product was extracted into $CH_2Cl_2$, dried ($MgSO_4$), and concentrated under reduced pressure. Final purification by flash chromatography produced the bromide **14** as a white solid (66 mg, 96%).

### 5.9. MOM-protected bromide 16

To a flask containing alcohol **14** (174 mg, 0.5 mmol), and $CH_2Cl_2$ (10 mL) was added DIPEA (0.5 mL, 2.9 mmol) followed by MOMCl (0.08 mL, 1.1 mmol) at room temperature. The solution was allowed to stir for 24 h, and then the reaction was quenched by addition of water. The product was extracted into $CH_2Cl_2$, dried ($MgSO_4$), and concentrated under reduced pressure. Final purification by flash chromatography produced **16** as a yellow oil (185 mg, 82%): $^1$H NMR $\delta$ 8.03 (d, $J$ = 1.8 Hz, 1H), 7.76–7.75 (m, 1H), 4.78 (d, $J$ = 6.9 Hz, 1H), 4.65 (d, $J$ = 7.1 Hz, 1H), 3.88 (s, 3H), 3.41 (s, 3H), 3.28 (dd, $J$ = 11.7, 4.1 Hz, 1H), 2.80–2.68 (m, 2H), 2.12 (dt, $J$ = 12.8, 3.3 Hz, 1H), 2.05–1.97 (m, 1H), 1.85–1.51 (m, 3H), 1.25 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR $\delta$ 166.0, 154.0, 132.5, 130.7, 123.2, 122.4, 111.2, 96.2, 83.7, 78.9, 55.7, 52.0, 46.8, 38.2, 37.3, 27.4, 25.2, 23.3, 20.2, 15.1; HRMS (EI) *m*/*z* calcd for $C_{20}H_{27}O_5Br$ ($M^+$) 426.1042, found 426.1051.

### 5.10. Benzyl alcohol 17

To a flask containing ester **16** (185 mg, 0.4 mmol) and THF (10 mL) was added DIBAL-H (2.2 mL, 5.2 mmol) at 0 °C. The solution was allowed to stir for 3 h, and then the reaction was quenched by addition of saturated $NH_4Cl$. The product was extracted into ether, dried ($MgSO_4$), and concentrated under reduced pressure. Final purification by flash chromatography produced alcohol **17** (158 mg, 92%): $^1$H NMR $\delta$ 7.36 (d, $J$ = 1.8 Hz, 1H), 7.04 (d, $J$ = 1.8 Hz, 1H), 4.77 (d, $J$ = 7.1 Hz, 1H), 4.65 (d, $J$ = 6.6 Hz, 1H), 4.56 (s, 2H), 3.41 (s, 3H), 3.28 (dd, $J$ = 11.4, 4.2 Hz, 1H), 2.72 (d, $J$ = 9.5 Hz, 2H), 2.09 (dt, $J$ = 12.6, 3.0 Hz, 1H), 1.95–1.43 (m, 5H), 1.22 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR $\delta$ 149.5, 133.2, 129.9, 127.9, 123.7, 111.3, 96.2, 84.0, 77.7, 64.6, 55.7, 47.1, 38.2, 37.4, 27.4, 25.2, 23.4, 20.0, 15.1; HRMS (EI) *m*/*z* calcd for $C_{19}H_{27}O_4Br$ ($M^+$) 398.1093, found 398.1093.

### 5.11. Brominated aldehyde 18

To a flask containing benzyl alcohol **17** (76 mg, 0.2 mmol) in methylene chloride (52 mL) was added $MnO_2$ (88% precipitated active, 315 mg, 3.2 mmol). The mixture was allowed to stir for 3.25 h and then the reaction was quenched by filtration through celite. Final purification by flash chromatography produced aldehyde **18** (61 mg, 81%) as a white solid: $[\alpha]_D^{26.4}$ +75.9 (c 0.61, $CHCl_3$, 96% ee by HPLC); $^1$H NMR $\delta$ 9.71, (s, 1H), 7.81 (d, $J$ = 1.7 Hz, 1H), 7.51 (d, $J$ = 1.6 Hz, 1H), 4.71 (d, $J$ = 7.1 Hz, 1H), 4.58 (d, $J$ = 7.1 Hz, 1H), 3.34 (s, 3H), 3.22 (dd, $J$ = 11.7, 4.3 Hz, 1H), 2.77–2.65 (m, 2H), 2.07 (dt, $J$ = 12.7, 3.2 Hz, 1H), 2.01–1.45 (m, 4H), 1.20 (s, 3H), 1.03 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR $\delta$ 189.8, 155.5, 132.8, 130.8, 129.7, 123.9, 112.3, 96.2, 83.7, 79.4, 55.7, 46.8, 38.3, 37.2, 27.4, 25.2, 23.3, 20.3, 15.1. Anal. Calcd for $C_{19}H_{25}O_4Br$: C, 57.44; H, 6.34. Found C, 57.54; H, 6.37.

### 5.12. Benzyl alcohol 20

To a solution of ester **19** (254 mg, 0.9 mmol) in THF (3 mL) at 0 °C was added $LiAlH_4$ (35 mg, 0.9 mmol). After 20 min, the reaction was quenched by slow addition of saturated $NH_4Cl$. The resulting solution was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography afforded alcohol **20** (208 mg, 90%) as a colorless oil: $^1$H NMR $\delta$ 7.26–7.23 (m, 1H), 6.97 (dd, $J_{HF}$ = 11.3 Hz, $J$ = 2.0 Hz, 1H), 5.09 (s, 2H), 4.50 (s, 2H), 3.56 (s, 3H), 2.68 (br s, 1H); $^{13}$C NMR $\delta$ 156.0 (d, $J_{CF}$ = 254 Hz), 141.1 (d, $J_{CF}$ = 14.0 Hz), 138.7 (d, $J_{CF}$ = 7.0 Hz), 126.5 (d, $J_{CF}$ = 2.3 Hz), 117.8 (d, $J_{CF}$ = 3.4 Hz), 114.3 (d, $J_{CF}$ = 21.2 Hz), 98.9 (d, $J_{CF}$ = 5.6 Hz), 63.5, 57.8; $^{19}$F NMR (280 MHz, $CDCl_3$) $\delta$ −125.8. Anal. Calcd for $C_9H_{10}O_3BrF$: C, 40.93; H, 3.82. Found C, 41.17; H, 3.85.

### 5.13. Benzyl ether 21

To a solution of benzyl alcohol **20** (198 mg, 0.7 mmol) in THF (5 mL) at 0 °C was added NaH (60% wt. in mineral oil, 35 mg, 0.9 mmol) followed by iodomethane (0.06 mL, 1.0 mmol). After 10 h, the reaction was quenched by addition of water, the resulting solution was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (8% EtOAc in hexanes) afforded ether **21** (158 mg, 76%) as an oil: $^1$H NMR $\delta$ 7.25–7.24 (m, 1H), 6.98 (dd, $J_{HF}$ = 11.1 Hz, $J$ = 2.0 Hz, 1H), 5.11 (s, 2H), 4.29 (s, 2H), 3.56 (s, 3H), 3.31 (s, 3H); $^{13}$C NMR $\delta$ 155.9 (d, $J_{CF}$ = 250 Hz), 141.4 (d, $J_{CF}$ = 13.4 Hz), 136.1 (d, $J_{CF}$ = 6.7 Hz), 127.3 (d, $J_{CF}$ = 3.5 Hz), 117.8 (d, $J_{CF}$ = 3.5 Hz), 115.1 (d, $J_{CF}$ = 20.9 Hz), 99.0 (d, $J_{CF}$ = 6.1 Hz), 72.9 (d, $J_{CF}$ = 1.8 Hz), 58.3, 57.8 (d, $J_{CF}$ = 1.7 Hz); $^{19}$F NMR (280 MHz, $CDCl_3$) $\delta$ −126.1. Anal. Calcd for $C_{10}H_{12}BrF\ O_3$: C, 43.03; H, 4.33. Found C, 42.87; H, 4.33.

### 5.14. Geranylated arene 22

To a solution of ether **21** (153 mg, 0.6 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.27 mL, 0.6 mmol). After 10 min, CuBr·DMS (136 mg, 0.7 mmol) was added. After an additional 30 min, geranyl bromide (0.11 mL, 0.6 mmol) was added and after an additional 1 h, the reaction was quenched by addition of water. The resulting solution was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography afforded arene **22** (31 mg, 17%) as an oil: $^1$H NMR $\delta$ 6.94–6.79 (m, 2H), 5.21 (t, $J$ = 7.2 Hz, 1H), 5.04 (s, 2H), 5.04–5.00

(m, 1H), 4.28 (s, 2H), 3.51 (s, 3H), 3.34–3.27 (m, 2H), 3.30 (s, 3H), 2.09–1.84 (m, 4H), 1.63 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H); $^{13}$C NMR $\delta$ 155.3 (d, $J_{CF}$ = 247 Hz), 141.7 (d, $J_{CF}$ = 10.8 Hz), 136.8, 136.7, 134.4 (d, $J_{CF}$ = 6.9 Hz), 131.5, 124.2, 124.0 (d, $J_{CF}$ = 2.9 Hz), 122.0, 113.6 (d, $J_{CF}$ = 20.6 Hz), 99.1 (d, $J_{CF}$ = 6.0 Hz), 73.9 (d, $J_{CF}$ = 1.1 Hz), 58.2, 57.4 (d, $J_{CF}$ = 1.0 Hz), 39.7, 28.3 (d, $J_{CF}$ = 2.5 Hz), 27.6, 25.7, 17.7, 16.2; $^{19}$F NMR (280 MHz, $CDCl_3$): $\delta$ −130.6; HRMS (EI) $m/z$ calcd for $C_{20}H_{29}O_3F$ ($M^+$) 336.2102, found 336.2106.

### 5.15. (*R*)-Epoxide 23

To a solution of benzyl ether **22** (30 mg, 0.1 mmol) in $CH_2Cl_2$ (1 mL), $CH_3CN$ (0.5 mL), EtOH (0.5 mL), aqueous buffer (2 M $K_2CO_3$, $4 \times 10^{-3}$ M EDTA, 2 mL), and Shi catalyst (24 mg, 0.1 mmol) at 0 °C, $H_2O_2$ (30% wt. in $H_2O$, 0.05 mL, 0.44 mmol) was added over 2 h. After an additional 45 min the reaction was quenched by addition of $Na_2SO_3$. The resulting solution was extracted with $CH_2Cl_2$, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography afforded epoxide **23** (17 mg, 54%) as an oil: $^1$H NMR $\delta$ 6.91–6.82 (m, 2H), 5.26 (t, $J$ = 7.1 Hz, 1H), 5.04 (s, 2H), 4.23 (s, 2H), 3.51 (s, 3H), 3.34 (d, $J$ = 7.1 Hz, 2H), 3.30 (s, 3H), 2.64 (t, $J$ = 6.3 Hz, 1H), 2.29–1.86 (m, 4H), 1.66 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR $\delta$ 155.3 (d, $J_{CF}$ = 246 Hz), 141.7 (d, $J_{CF}$ = 12.4 Hz), 136.5 (d, $J_{CF}$ = 1.8 Hz), 135.8, 134.5 (d, $J_{CF}$ = 7.4 Hz), 124.0 (d, $J_{CF}$ = 2.8 Hz), 122.6, 113.6 (d, $J_{CF}$ = 20.4 Hz), 99.1 (d, $J_{CF}$ = 6.5 Hz), 73.9 (d, $J_{CF}$ = 1.9 Hz), 64.1, 58.4, 58.2, 57.5, 36.4, 28.4, 27.4, 24.9, 18.8, 16.2; $^{19}$F NMR (280 MHz, $CDCl_3$) $\delta$ −130.6; HRMS (EI) $m/z$ calcd for $C_{20}H_{29}O_3F$ ($M^+$) 352.2051, found 352.2048.

### 5.16. 5-Fluoro-hexahydroxanthene 24

To a solution of epoxide **23** (16 mg, 0.05 mmol) in $CH_2Cl_2$ (6 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.03 mL, 0.2 mmol). After 6 min, the reaction was quenched by addition of TEA. Water was added and the product was extracted into $CH_2Cl_2$, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography (20% EtOAc in hexanes) produced hexahydroxanthene **24** (8 mg, 57%) as a white solid: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.91–6.85 (m, 2H), 4.33 (s, 2H), 3.44 (dd, $J$ = 11.3, 6.9 Hz, 1H), 3.38 (s, 3H), 2.79–2.66 (m, 2H), 2.12–1.58 (m, 5H), 1.25 (s, 3H), 1.11 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.8 (d, $J_{CF}$ = 246 Hz), 141.0 (d, $J_{CF}$ = 11.3 Hz), 129.4 (d, $J_{CF}$ = 5.6 Hz), 124.4 (d, $J_{CF}$ = 2.8 Hz), 124.0 (d, $J_{CF}$ = 2.8 Hz), 113.4 (d, $J_{CF}$ = 18.3 Hz), 77.9, 74.1 (d, $J_{CF}$ = 1.5 Hz), 58.1, 46.7, 38.4, 37.5, 28.3, 27.3, 23.0, 22.9, 19.8, 14.3; $^{19}$F NMR ($CDCl_3$) $\delta$ −136.9; HRMS (EI) $m/z$ calcd for $C_{18}H_{25}O_3F$ ($M^+$) 308.1789, found 308.1782.

### 5.17. 5-Fluorinated aldehyde 25

To a solution of methyl ether **24** (7 mg, 0.02 mmol) in $CH_2Cl_2$ (1.0 mL) and water (0.1 mL) at rt was added DDQ (12 mg, 0.05 mmol). After 4 h, the reaction was quenched by addition of saturated $NaHCO_3$. The resulting solution was extracted with $CH_2Cl_2$, dried ($MgSO_4$), and concentrated in vacuo. Final purification by radial chromatography (40% EtOAc in hexanes) produced aldehyde **25** (6 mg, 90%) as a film: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.81 (d, $J_{HF}$ = 1.9 Hz, 1H), 7.45–7.42 (m, 2H), 3.47 (dd, $J$ = 11.7, 4.0 Hz, 1H), 2.88–2.75 (m, 2H), 2.17–1.58 (m, 5H), 1.30 (s, 3H), 1.14 (s, 3H), 0.92 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.9 (d, $J_{CF}$ = 2.0 Hz), 152.0 (d, $J_{CF}$ = 249 Hz), 147.3 (d, $J_{CF}$ = 11.0 Hz), 128.4 (d, $J_{CF}$ = 5.2 Hz), 127.8 (d, $J_{CF}$ = 2.6 Hz), 124.6 (d, $J_{CF}$ = 2.6 Hz), 113.7 (d, $J_{CF}$ = 19.5 Hz), 78.8, 77.5, 46.3, 38.3, 37.1, 28.0, 27.1, 22.7, 19.9, 14.1; $^{19}$F NMR ($CDCl_3$) $\delta$ −134.7. HRMS (EI) $m/z$ calcd for $C_{17}H_{21}O_3F$ ($M^+$) 292.1477, found 292.1478.

### 5.18. Ether 27

To a solution of alcohol **26**[29] (2.66 g, 15.8 mmol) in THF (50 mL) at 0 °C was added NaH (750 mg, 18.8 mmol, 60% dispersion oil). After 30 min, MeI (1.09 mL, 17.5 mmol) was added dropwise and the reaction mixture was allowed to stir overnight. The reaction was quenched by the addition of $NH_4Cl$ (sat), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Final purification by flash column (15–40% ethyl acetate in hexanes) afforded arene **27** (2.34 g, 81%) as a colorless oil: $^1$H NMR $\delta$ 7.25 (d, $J$ = 8.7 Hz, 2H), 7.01 (d, $J$ = 8.7 Hz, 2H), 5.15 (s, 2H), 4.38 (s, 2H), 3.46 (s, 3H), 3.35 (s, 3H); $^{13}$C NMR $\delta$ 156.7, 131.5, 129.1 (2C), 116.0 (2C), 94.3, 74.1, 57.7, 55.8; HRMS ($ESI^+$) calcd for $C_{10}H_{14}O_3$ ($M^+$) 182.0943, found 182.0949.

### 5.19. Thiol Ether 28

To a solution of arene **27** (2.34 g, 12.8 mmol) in THF (60 mL) at 0 °C was added *n*-BuLi (6.0 mL, 2.2 M in hexanes) and after 5 min dimethyldisulfide (1.23 mL, 14 mmol) was added dropwise. After 5 h the reaction mixture was quenched by addition of $NH_4Cl$ (sat), extracted with EtOAc, washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Final purification by flash column chromatography (13% EtOAc in hexanes) afforded **28** (1.29 g, 44%) as an oil: $^1$H NMR $\delta$ 7.13 (s, 1H), 7.04 (m, 2H), 5.22 (s, 2H), 4.38 (s, 2H), 3.49 (s, 3H), 3.36 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR $\delta$ 153.2, 132.2, 128.2, 125.2, 125.2, 113.9, 94.7, 74.1, 57.5, 56.0, 14.4; HRMS ($EI^+$) $m/z$ calcd for $C_{11}H_{16}O_3S$ ($M^+$) 228.0820, found 228.0822.

### 5.20. Epoxide 29

To a solution of arene **28** (829 mg, 3.63 mmol), in THF (15 mL) at to 0 °C was added *n*-BuLi (1.6 mL, 3.68 mmol). After 1 h, the solution was cooled to −20 °C and CuBr·DMS (784 mg, 3.81 mmol) was added. After an additional 1 h, epoxygeranyl bromide[22] (887 mg, 3.93 mmol) was added dropwise as a THF solution (2 mL). After 2 h, the reaction mixture was quenched by addition of $NH_4Cl$ (sat), diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered, and then concentrated in vacuo. Final purification by column chromatography (15% EtOAc in hexanes) afforded epoxide **29** (522 mg, 38%) as a light yellow oil: $^1$H NMR $\delta$ 6.99 (d, $J$ = 2.0 Hz, 1H), 6.92 (d, $J$ = 1.6 Hz, 1H), 5.36 (m, 1H), 5.03 (s, 2H), 4.37 (s, 2H), 3.63 (s, 3H), 3.43 (d, $J$ = 7.2 Hz, 2H), 3.38 (s, 3H), 2.71 (t, $J$ = 6.2 Hz, 1H), 2.43 (s, 3H), 2.04 (m, 2H), 1.73 (s, 3H), 1.69–1.62 (m, 2H), 1.28 (s, 3H), 1.25 (s, 3H); $^{13}$C NMR $\delta$ 151.6, 135.4, 134.8, 134.8, 132.6, 125.9, 123.1, 123.0, 99.2, 74.3, 64.0, 58.2, 58.0, 57.6, 36.3, 28.4, 27.3, 24.7, 18.6, 16.1, 14.8; HRMS (EI) $m/z$ calcd for $C_{21}H_{32}O_4S$ ($M^+$) 380.2120, found 380.2127.

### 5.21. Hexahydroxanthene 30

To a solution of epoxide **29** (207 mg, 0.54 mmol) in $CH_2Cl_2$ (136 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.40 mL, 3.3 mmol). After 10 min, the reaction was quenched by addition of TEA (0.3 mL), allowed to warm to room temperature, and the solvent was removed in vacuo. Final purification by flash column chromatography (25–30% EtOAc in hexanes) gave hexahydroxanthene **30** (93 mg, 51%) as an oil: $^1$H NMR $\delta$ 6.93 (d, $J$ = 1.6 Hz, 1H), 6.87 (d, $J$ = 1.6 Hz, 1H), 4.34 (s, 2H), 3.40–3.35 (m, 1H), 3.74 (s, 3H), 2.71–2.68 (m, 2H), 2.40 (s, 3H), 2.09–2.04 (m, 1H), 1.87–1.77 (m, 2H), 1.71–1.57 (m, 3H), 1.21 (s, 3H), 1.07 (s, 3H), 0.86 (s, 3H); $^{13}$C NMR $\delta$ 149.6, 129.6, 126.3, 126.2, 123.6, 121.2, 77.9, 77.2, 74.6, 57.9, 46.8, 38.3,

37.5, 28.2, 27.2, 23.1, 19.9, 14.6, 14.2; HRMS (EI) $m/z$ calcd for $C_{19}H_{28}O_3S$ ($M^+$) 336.1759, found 336. 1750.

### 5.22. Aldehyde 31

To a solution of methyl ether **30** (84 mg, 0.25 mmol) in a 9:1 mixture of $CH_2Cl_2$ and $H_2O$ (10 mL) at rt was added DDQ (79 mg, 0.35 mmol). After 20 min, the reaction was quenched by the addition of $NaHCO_3$ (sat.), diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford aldehyde **31** (61 mg, 76%) as a white solid: $^1$H NMR $\delta$ 9.82 (s, 1H), 7.48 (d, $J$ = 1.6 Hz, 1H), 7.42 (d, $J$ = 1.1 Hz, 1H), 3.45 (dd, $J$ = 11.2, 3.6 Hz, 1H), 2.80–2.76 (m, 2H), 2.45 (s, 3H), 2.16–2.10 (m, 1H), 1.94–1.81 (m, 2H), 1.76–1.56 (m, 3H), 1.27 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR $\delta$ 190.9, 155.2, 130.0, 129.5, 128.9, 123.6, 121.5, 79.1, 77.9, 46.7, 38.5, 37.5, 28.3, 27.4, 23.1, 20.4, 14.4, 14.4; HRMS (EI) $m/z$ calcd for $C_{18}H_{24}O_3S$ ($M^+$) 320.1446, found 320.1447.

### 5.23. Aldehyde 33

To a solution of methyl ether **32**[5] (350 mg, 1.1 mmol), in $CH_2Cl_2$/water (10:1) at rt was added DDQ (320 mg, 1.4 mmol). After 15 min, the reaction was quenched by addition of brine and $NaHCO_3$. The resulting solution was extracted with $CH_2Cl_2$, and the combined organic extracts were washed with a small amount of water followed by brine. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, aldehyde **33** was obtained as a faintly yellow wax that was used without further purification: $^1$H NMR $\delta$ 9.76 (s, 1H), 7.65 (d, $J$ = 1.6 Hz, 1H), 7.54 (d, $J$ = 2.0 Hz, 1H), 5.26 (s, 1H), 4.64 (d, $J$ = 13.2 Hz, 1H), 4.60 (d, $J$ = 13.6 Hz, 1H), 3.38 (dd, $J$ = 11.4, 4.2 Hz, 1H), 2.79–2.67 (m, 2H), 2.34 (br, 1H), 2.04–1.99 (m, 1H), 1.87–1.57 (m, 4H), 1.20 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); $^{13}$C NMR $\delta$ 191.2, 156.2, 131.3, 129.6, 128.6, 127.7, 122.2, 78.4, 77.5, 60.7, 46.4, 38.3, 37.5, 27.9, 27.1, 22.7, 20.2, 14.2; HRMS (EI) $m/z$ calcd for $C_{18}H_{24}O_4$ ($M^+$) 304.1675, found 304.1668.

### 5.24. Silyl Ether 34

To a solution of alcohol **33**, in $CH_2Cl_2$ at rt was added TBSCl (485 mg, 3.2 mmol) followed by imidazole (394 mg, 5.8 mmol). After 45 min, the reaction was quenched by addition of water. The resulting solution was extracted with $CH_2Cl_2$, and the combined organic extracts were washed with a small amount of water followed by brine. After which the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Final purification by column chromatography (30% EtOAc in hexanes) afforded aldehyde **34** (321 mg, 70% over 2-steps) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 9.82 (s, 1H), 7.78 (d, $J$ = 1.2 Hz, 1H), 7.55 (d, $J$ = 1.8 Hz, 1H), 4.70 (d, $J$ = 14.4 Hz, 1H), 4.62 (d, $J$ = 14.1 Hz, 1H), 3.40 (dd, $J$ = 11.4, 3.9 Hz, 1H), 2.77–2.72 (m, 2H), 2.07–2.00 (m, 1H), 1.89–1.62 (m, 4H), 1.20 (s, 3H), 1.09 (s, 3H), 0.94 (s, 9H), 0.87 (s, 3H), -0.11 (s, 6H); $^{13}$C NMR $\delta$ 191.5, 155.3, 130.1, 130.0, 128.6, 127.4, 121.6, 77.9, 77.6, 59.7, 46.4, 38.3, 37.5, 28.0, 27.1, 25.9 (3C), 22.8, 20.2, 18.4, 14.2, −5.4 (2C); HRMS (EI) $m/z$ calcd for $C_{24}H_{38}O_4Si$ ($M^+-t$Bu) 362.1869, found 362.1861.

### 5.25. Silyl ether 36

To a flask containing benzyl alcohol **35** (1.81 g, 9.2 mmol) and $CH_2Cl_2$ (150 mL) was added imidazole (3.19 g, 46.9 mmol), followed by TBSCl (1.61 g, 10.7 mmol) at room temperature. The solution was allowed to stir for 9 h, and then the reaction was quenched by addition of saturated $NH_4Cl$. The product was extracted into $CH_2Cl_2$, dried ($MgSO_4$), and concentrated under reduced pressure. Final purification by flash chromatography produced the silyl ether **36** as an oil (2.40 g, 84%): $^1$H NMR NMR $\delta$ 6.62–6.57 (m, 2H), 6.49–6.48 (m, 1H), 5.15 (s, 2H), 4.68 (s, 2H), 3.78 (s, 3H), 3.47 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR $\delta$ 160.9, 158.5, 144.4, 106.2, 105.2, 101.2, 94.7, 65.0, 56.2, 55.5, 26.2 (3C), 18.6, -5.0 (2C); HRMS (EI) $m/z$ calcd for $C_{16}H_{28}O_4Si$ ($M^+$) 312.1757, found 312.1753.

### 5.26. Geranylated benzyl alcohol 38

To a flamed dried Schlenk flask under argon, ether (30 mL) was added via syringe followed by TMEDA (3.8 mL, 25 mmol) and $n$-BuLi (12 mL, 29 mmol, 2.4 M solution in hexanes) and this solution was cooled to 0 °C. Compound **35** (2.97 g, 12.6 mmol) was dissolved in ether (20 mL) and transferred via cannula to the reaction vessel, which gave a white precipitate. After 20 min, solid CuI (2.64 g, 13.8 mmol) was added in one portion leading to an immediate color change to black. The resulting mixture was allowed to stir for 20 min and then geranyl bromide (3.3 mL, 16.3 mmol) was added dropwise over a 10 min period. The reaction mixture was allowed to stir for 4 h, and then was quenched by addition of water. The product was extracted into diethyl ether, dried ($MgSO_4$), and concentrated under reduced pressure. Final purification by column chromatography (30% EtOAc in hexanes) produced alcohol **38** (1.98 g, 47%) as an oil: $^1$H NMR $\delta$ 6.72 (s, 1H), 6.61 (s, 1H), 5.20–5.06 (m, 1H), 5.18 (s, 2H), 5.06–5.04 (m, 1H), 4.63 (s, 2H), 3.82 (s, 3H), 3.46 (s, 3H), 3.36 (d, $J$ = 6.9 Hz, 2H), 2.05–2.00 (m, 2H), 1.96–1.91 (m, 2H), 1.77 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H); $^{13}$C NMR $\delta$ 158.3, 155.6, 139.9, 134.6, 131.1, 124.4, 122.6, 118.6, 105.6, 103.3, 94.4, 65.6, 55.9, 55.7, 39.8, 26.7, 25.6, 22.3, 17.6, 16.0; HRMS (EI) $m/z$ calcd for $C_{20}H_{30}O_4$ ($M^+$) 334.2144, found 334.2141.

### 5.27. Phosphonate 39

To a solution of alcohol **38** (1.00 g, 3.0 mmol) in $CH_2Cl_2$ (200 mL) at 0 °C was added TEA (1.70 mL, 12.2 mmol), followed by MsCl (0.93 mL, 12.0 mmol). After 20 h, the reaction was quenched by addition of saturated $NH_4Cl$. The resulting solution was extracted with $CH_2Cl_2$, dried ($MgSO_4$), and concentrated in vacuo to yield the intermediate mesylate as an oil which was used without further purification.

To a solution of the crude intermediate mesylate in acetone (11 mL) in a foil-wrapped flask at rt was added sodium iodide (1.81 g, 12.1 mmol). After 30 min, the reaction was concentrated in vacuo. The residue was diluted with water and the resulting solution was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo to yield the intermediate iodide as a yellow oil, which was used without further purification.

To a flask containing the intermediate iodide, triethylphosphite (1.1 mL, 12.1 mmol) was added at rt. The solution was heated to 62 °C, and after 16 h the reaction was quenched by addition of water. The resulting solution was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. Final purification by column chromatography afforded phosphonate **39** (1.36 g, 100% for 3 steps) as a colorless oil: $^1$H NMR $\delta$ 6.65–6.64 (m, 1H), 6.55–6.54 (m, 1H), 5.19–5.14 (m, 1H), 5.16 (s, 2H), 5.09–5.04 (m, 1H), 4.08–4.00 (m, 4H), 3.81 (s, 3H), 3.45 (s, 3H), 3.33 (d, $J$ = 7.1 Hz, 2H), 3.10 (d, $J_{HP}$ = 21.5 Hz, 2H), 2.07–1.91 (m, 4H), 1.75 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.26 (t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR $\delta$ 158.0, 155.5, 134.6, 131.2, 130.0, 124.5, 122.7, 118.0 (d, $J_{CP}$ = 3.9 Hz), 108.7 (d, $J_{CP}$ = 6.6 Hz), 106.4 (d, $J_{CP}$ = 6.1 Hz), 94.4, 62.1 (d, $J_{CP}$ = 7.4 Hz, 2C), 55.9, 55.8, 39.8, 34.0 (d, $J_{CP}$ = 138.2 Hz), 26.7, 25.7, 22.2, 17.7, 16.4 (d, $J_{CP}$ = 6.1 Hz, 2C), 16.0; $^{31}$P NMR $\delta$ 27.1; HRMS (EI) $m/z$ calcd for $C_{24}H_{39}O_6P$ ($M^+$) 454.2486, found 454.2471.

### 5.28. Stilbene 43

Under the general conditions for HWE condensations (vide infra), the reaction of aldehyde **13** (36 mg, 0.1 mmol), phosphonate **39** (31 mg, 0.1 mmol), and NaH (60% wt. in mineral oil, 34 mg, 0.9 mmol) provided stilbene **43** as a white solid (49 mg, 66%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26–7.25 (m, 1H), 6.99–6.86 (m, 4H), 6.74 (d, $J$ = 8.3 Hz, 1H), 6.70 (s, 1H), 5.22 (s, 2H), 5.20–5.18 (m, 1H), 5.07 (t, $J$ = 6.7 Hz, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 3.43 (dd, $J$ = 11.8, 4.6 Hz, 1H), 3.37 (d, $J$ = 7.0 Hz, 2H), 2.76–2.66 (m, 2H), 2.07–1.48 (m, 9H), 1.78 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.23 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.1, 155.6, 152.7, 136.5, 134.4, 131.0, 129.2, 127.7, 127.2, 126.3, 125.4, 124.3, 122.5, 121.8, 118.6, 117.1, 105.2, 102.4, 94.4, 77.9, 76.5, 55.8, 55.6, 46.7, 39.7, 38.2, 37.6, 28.1, 27.2, 26.6, 25.5, 22.9, 22.3, 19.8, 17.5, 15.9, 14.1; HRMS (EI) $m/z$ calcd for $C_{37}H_{50}O_5$ ($M^+$) 574.3660, found 574.3651.

### 5.29. Schweinfurthin analogue 51

Under general conditions for the removal of MOM-ethers from protected stilbenes (vide infra), stilbene **53** (33 mg, 0.1 mmol) was treated with methanol (0.3 mL) and $p$-TsOH·$H_2O$ (56 mg, 0.3 mmol) for 2.5 h to provide analogue **51** as a clear oil (16 mg, 53%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25–6.61 (m, 7H), 5.33 (br s, 1H), 5.25 (t, $J$ = 7.0 Hz, 1H), 5.07 (t, $J$ = 6.7 Hz, 1H), 3.87 (s, 3H), 3.47–3.42 (m, 3H), 2.80–2.68 (m, 2H), 2.18–1.55 (m, 10H), 1.82 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.24 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.8, 155.5, 152.8, 138.1, 136.9, 131.7, 129.1, 128.0, 127.7, 126.0, 125.4, 123.7, 121.8, 121.6, 117.1, 114.3, 106.7, 101.1, 77.9, 77.0, 55.6, 46.7, 39.5, 38.2, 37.6, 28.1, 27.2, 26.3, 25.5, 22.9, 22.1, 19.8, 17.5, 16.0, 14.1; HRMS (EI) $m/z$ calcd for $C_{35}H_{46}O_4$ ($M^+$) 530.3398, found 530.3399.

### 5.30. C-5 Bromostilbene 44

Under the general conditions for HWE condensations, the reaction of aldehyde **18** (60 mg, 0.2 mmol), phosphonate **39** (72 mg, 0.2 mmol), and NaH (60% wt. in mineral oil, 33 mg, 0.8 mmol) provided stilbene **44** as a white solid (57 mg, 54%): $[\alpha]_D^{26.4}$ +64.2 ($c$ 0.25, $CHCl_3$, 96% ee by HPLC); $^1$H NMR $\delta$ 7.46 (d, $J$ = 1.9 Hz, 1H), 7.10 (d, $J$ = 1.6 Hz, 1H), 6.82–6.79 (m, 3H), 6.62 (s, 1H), 5.15 (s, 2H), 5.12 (t, $J$ = 7.0 Hz, 1H), 5.00 (t, $J$ = 6.4 Hz, 1H), 4.71 (d, $J$ = 6.9 Hz, 1H), 4.58 (d, $J$ = 7.0 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 3.35 (s, 3H), 3.30 (d, $J$ = 7.0 Hz, 1H), 3.22 (dd, $J$ = 11.6, 4.1 Hz, 1H), 2.81 (d, $J$ = 9.5 Hz, 2H), 2.06–1.36 (m, 9H), 1.70 (s, 3H), 1.57 (s, 3H), 1.50 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.83 (s, 3H); $^{13}$C NMR $\delta$ 158.2, 155.8, 149.5, 136.2, 134.7, 131.2, 130.3, 128.8, 127.6, 127.0, 126.5, 124.5, 123.6, 122.6, 119.1, 111.7, 105.4, 102.7, 96.2, 94.5, 83.9, 77.9, 56.0, 55.7, 55.7, 47.1, 38.8, 38.2, 37.3, 27.4, 26.7, 25.7, 25.2, 23.4, 22.5, 20.1, 17.6, 16.1, 15.1; HRMS (EI) $m/z$ calcd for $C_{39}H_{53}O_6Br$ ($M^+$) 696.3027, found 696.3098.

### 5.31. 5-Bromoschweinfurthin analogue 52

Under the general conditions for removal of MOM-acetals, the reaction of stilbene **44** (10 mg, 0.01 mmol), methanol (1.5 mL), and $p$-TsOH·$H_2O$ (11 mg, 0.06 mmol) for 96 h provided analogue **52** as a white solid (8 mg, 92%): $[\alpha]_D^{26.4}$ +29.2 ($c$ 0.27, $CHCl_3$, 96% ee by HPLC); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53–6.60 (m, 6H), 5.33 (br s, 1H), 5.25 (t, $J$ = 6.6 Hz, 1H), 5.07 (t, $J$ = 6.6 Hz, 1H), 3.87 (s, 3H), 3.48–3.38 (m, 3H), 2.79–2.70 (m, 2H), 2.14–1.35 (m, 10H), 1.82 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.8, 155.6, 149.4, 138.2, 136.5, 131.7, 130.1, 128.7, 127.1, 126.8, 126.6, 123.7, 123.3, 121.5, 114.6, 111.6, 106.9, 101.2, 77.8, 77.7, 55.6, 46.6, 39.5, 38.2, 37.3, 28.1, 27.1, 26.2, 25.5, 23.2, 22.1, 19.9, 17.5, 16.0, 14.0; HRMS (EI) $m/z$ calcd for $C_{35}H_{45}O_4Br$ ($M^+$) 608.2503, found 608.2498.

### 5.32. 5-Fluoro stilbene 45

Under the general conditions for HWE reactions, aldehyde **25** (6 mg, 0.02 mmol), phosphonate **39** (10 mg, 0.02 mmol), and NaH (60% wt. in mineral oil, 5 mg, 0.1 mmol), and purification by column chromatography (25% EtOAc in hexanes) provided stilbene **45** as a white solid (6 mg, 53%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.11–6.70 (m, 6H), 5.23 (s, 2H), 5.23–5.19 (m, 1H), 5.08 (t, $J$ = 6.7 Hz, 1H), 3.88 (s, 3H), 3.51 (s, 3H), 3.46 (dd, $J$ = 11.1, 3.6 Hz, 1H), 3.38 (d, $J$ = 6.9 Hz, 2H), 2.81–2.68 (m, 2H), 2.13–1.60 (m, 9H), 1.78 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.28 (s, 3H), 1.13 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.1, 155.7, 151.9 (d, $J_{CF}$ = 244 Hz), 140.9 (d, $J_{CF}$ = 10.3 Hz), 136.0, 134.5, 131.0, 129.0 (d, $J_{CF}$ = 8.3 Hz), 127.5, 126.8 (d, $J_{CF}$ = 2.3 Hz), 125.3, 124.3, 122.8 (d, $J_{CF}$ = 2.3 Hz), 122.4, 119.0, 111.0 (d, $J_{CF}$ = 19.0 Hz), 105.3, 102.6, 94.3, 77.7, 77.3, 55.8, 55.6, 46.6, 39.6, 38.2, 37.3, 28.1, 27.1, 26.6, 25.5, 22.8, 22.3, 19.7, 17.5, 15.9, 14.1; $^{19}$F NMR ($CDCl_3$) $\delta$ −136.8; HRMS (EI) $m/z$ calcd for $C_{37}H_{49}O_5F$ ($M^+$) 592.3566, found 592.3574.

### 5.33. 5-Fluoro schweinfurthin analogue 53

Under the general conditions for MOM hydrolysis, stilbene **45** (6 mg, 0.01 mmol), methanol (0.6 mL), and $p$-TsOH·$H_2O$ (12 mg, 0.1 mmol) were allowed to react for 24 h. Final purification by column chromatography provided analogue **53** as a white solid (4 mg, 72%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.09 (dd, $J$ = 12.1, 1.7 Hz, 1H), 6.99 (s, 1H), 6.91 (d, $J$ = 16.3 Hz, 1H), 6.84 (d, $J$ = 16.3 Hz, 1H), 6.64 (d, $J$ = 1.3 Hz, 1H), 6.60 (d, $J$ = 1.3 Hz, 1H), 5.34 (br s, 1H), 5.27–5.23 (m, 1H), 5.09–5.05 (m, 1H), 3.87 (s, 3H), 3.48–3.42 (m, 3H), 2.82–1.84 (m, 11H), 1.82 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.8, 155.6, 151.9 (d, $J_{CF}$ = 243 Hz), 141.0 (d, $J_{CF}$ = 11.3 Hz), 138.2, 136.5, 131.7, 129.0 (d, $J_{CF}$ = 7.5 Hz), 127.1, 127.1 (d, $J_{CF}$ = 2.3 Hz), 124.3 (d, $J_{CF}$ = 1.6 Hz), 123.7, 122.9 (d, $J_{CF}$ = 2.1 Hz), 121.5, 114.6, 111.0 (d, $J_{CF}$ = 19.2 Hz), 106.8, 101.2, 77.7, 77.3, 55.6, 46.6, 39.5, 38.2, 37.3, 28.1, 27.1, 26.3, 25.5, 22.8, 22.1, 19.7, 17.5, 15.9, 14.1; $^{19}$F NMR ($CDCl_3$) $\delta$ −136.8; HRMS (EI) $m/z$ calcd for $C_{35}H_{45}O_4F$ ($M^+$) 548.3304, found 548.3299.

### 5.34. Stilbene 46

Under the general conditions for HWE condensations, aldehyde **31** (23 mg, 0.07 mmol), phosphonate **39** (40 mg, 0.09 mmol), THF (0.7 mL), and NaH (50 mg, 1.25 mmol, 60% dispersion oil) were allowed to react for 18 h. Final purification by flash column chromatography (25% EtOAc in hexanes) afforded stilbene **46** (33 mg, 74%) as a colorless oil; $^1$H NMR $\delta$ 7.11 (d, $J$ = 1.7 Hz, 1H), 7.07 (d, $J$ = 1.6 Hz, 1H), 6.96 (d, $J$ = 16.3 Hz, 1H), 6.92–6.88 (m, 2H), 6.71 (s, 1H), 5.23 (s, 2H), 5.23–5.18 (m, 1H), 5.09–5.05 (m, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 3.43 (dd, $J$ = 11.5, 3.8 Hz, 1H), 3.37 (d, $J$ = 7.0 Hz, 2H), 2.74–2.70 (m, 2H), 2.45 (s, 3H), 2.11–1.57 (m, 10H), 1.78 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR $\delta$ 158.3, 155.8, 149.8, 136.5, 134.6, 131.1, 129.5, 127.7, 126.8, 126.6, 124.7, 124.4, 122.6, 122.0, 121.4, 118.9, 105.4, 102.6, 94.5, 77.8, 77.5, 55.9, 55.7, 46.8, 39.8, 38.4, 37.5, 28.2, 27.3, 26.7, 25.6, 23.1, 22.4, 20.0, 17.6, 16.0, 14.8, 14.2 HRMS (EI) $m/z$ calcd for $C_{38}H_{52}O_5S$ ($M^+$) 620.3535, found 620.3536.

### 5.35. Schweinfurthin analogue 54

Under general conditions for MOM hydrolysis, stilbene **46** (16.5 mg, 0.03 mmol), methanol (1.5 mL), and TsOH (25 mg, 0.13 mmol) were allowed to react for 18 h. Final purification by column chromatography (25% EtOAc in hexanes) afforded analogue **54** (6 mg, 40%) as an off-white solid: $^1$H NMR $\delta$ 7.11 (d, $J$ = 1.5 Hz, 1H), 7.06 (d, $J$ = 1.4 Hz, 1H), 6.95 (d, $J$ = 16.2 Hz, 1H), 6.86 (d, $J$ = 16.2 Hz, 1H), 6.64 (d, $J$ = 1.1 Hz, 1H), 6.60 (d, $J$ = 1.0 Hz, 1H), 5.26–5.23 (m, 1H), 5.08–5.04 (m, 1H), 3.86 (s, 3H), 3.47–3.41 (m, 3H), 2.74–2.71 (m, 2H), 2.45 (s, 3H), 2.10–2.03 (m, 4H), 1.90–1.63 (m, 5H), 1.81 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.0, 155.8, 153.0, 138.3, 137.2, 131.9, 129.3, 128.2, 127.9, 126.2, 125.6, 123.9, 122.0, 121.8, 117.4, 114.5, 106.9, 101.3, 78.1, 77.2, 55.8, 46.9, 39.8, 38.4, 37.8, 30.3, 28.3, 27.4, 26.5, 25.7, 23.1, 22.3, 20.0, 17.7, 16.2, 14.3; HRMS (EI) $m/z$ calcd for $C_{36}H_{48}O_4S$ ($M^+$) 576.3273, found 576.3279.

### 5.36. 5-Methoxymethyl stilbene 47

Under the general conditions for HWE condensations, aldehyde **40** (26 mg, 0.1 mmol), phosphonate **39** (42 mg, 0.1 mmol), and NaH (60% wt. in mineral oil, 48 mg, 1.2 mmol) were allowed to react. Final purification by column chromatography provided stilbene **47** (26 mg, 50%) as a solid: $[\alpha]_D^{26.4}$ +31.1 ($c$ 0.30, $CHCl_3$, 81% ee by HPLC); $^1$H NMR $\delta$ 7.30 (d, $J$ = 1.6 Hz, 1H), 7.11 (d, $J$ = 1.6 Hz, 1H), 6.89–6.64 (m, 4H), 5.15 (s, 2H), 5.19–5.10 (m, 1H), 5.02–4.97 (m, 1H), 4.38 (s, 2H), 3.79 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 3.35–3.38 (m, 3H), 2.67–2.63 (m, 2H), 2.02–1.75 (m, 5H), 1.70 (s, 3H), 1.57 (s, 3H), 1.50 (s, 3H), 1.14–1.13 (m, 4H), 1.13 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.2, 155.8, 150.4, 136.7, 134.6, 131.2, 128.9, 128.0, 127.0, 126.5 (2C), 124.5, 124.5, 122.7, 121.7, 118.7, 105.4, 102.6, 94.5, 78.1, 76.7, 69.2, 58.5, 56.0, 55.7, 46.8, 39.9, 38.7, 37.7, 28.3, 27.3, 26.8, 25.7, 23.1, 22.7, 20.2, 17.7, 16.1, 14.3; HRMS (EI) $m/z$ calcd for $C_{39}H_{54}O_6$ ($M^+$) 618.3922, found 618.3922.

### 5.37. 5-Methoxymethyl schweinfurthin analogue 55

Under the general conditions for MOM hydrolysis, stilbene **47** (34 mg, 0.1 mmol), methanol (3.0 mL), and $p$-TsOH·$H_2O$ (59 mg, 0.3 mmol) were allowed to react for 14 h. Purification by radial chromatography (20% EtOAc in hexanes) afforded analogue **55** (13 mg, 41%) as an oil: $[\alpha]_D^{26.4}$ +40.0 ($c$ 0.68, $CHCl_3$, 81% ee by HPLC); $^1$H NMR ($CDCl_3$) $\delta$ 7.31–7.01 (m, 2H), 6.90 (d, $J$ = 16.3 Hz, 1H), 6.80 (d, $J$ = 16.3 Hz, 1H), 6.58–6.46 (m, 2H), 5.29 (br s, 1H), 5.21–5.11 (m, 1H), 5.00–4.97 (m, 1H), 4.38 (s, 2H), 3.78 (s, 3H), 3.37 (s, 3H), 3.34 (d, $J$ = 6.7 Hz, 2H), 2.73–2.58 (m, 2H), 2.09–1.40 (m, 11H), 1.73 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.8, 155.5, 150.3, 138.1, 137.0, 131.7, 128.7, 128.1, 126.9, 126.3, 125.9, 124.3, 123.7, 121.6, 121.5, 114.2, 106.7, 101.1, 77.9, 77.0, 69.0, 58.3, 55.6, 46.6, 39.5, 38.2, 37.5, 28.1, 27.1, 26.3, 25.5, 22.9, 22.1, 20.0, 17.5, 16.0, 14.1; HRMS (EI) $m/e$ calcd for $C_{37}H_{49}O_5$ $(M-H)^-$ 573.3580, found 573.3560.

### 5.38. Stilbene 48

#### 5.38.1. General procedure for HWE condensations

To a suspension of NaH (85 mg, 60% oil dispersion, 2.1 mmol) and 15–crown-5 (0.01 mL, 0.05 mmol) in THF (10 mL) at 0 °C was added a solution of phosphonate **39** (65 mg, 0.14 mmol) in THF (1.5 mL). The resulting mixture was stirred for 0.5 h. and aldehyde **41** (39 mg, 0.12 mmol) in THF (0.5 mL) was then added to the cooled solution. After the reaction was allowed to warm to room temperature and stirred for 16 h, it was quenched by addition of water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), concentrated in vacuo to a yellow liquid, and purified by flash column chromatography (2:1 hexanes/EtOAc) to afford stilbene **48** (57 mg, 77%) as a colorless oil: $[\alpha]_D^{26.4}$ +38.4 ($c$ 3.74, $CHCl_3$); $^1$H NMR $\delta$ 7.13 (d, $J$ = 1.8 Hz, 1H), 6.95 (d, $J$ = 1.8 Hz, 1H), 6.94 (d, $J$ = 15.9 Hz, 1H), 6.90–6.86 (m, 1H), 6.86 (s, 1H), 6.71 (s, 1H), 5.25–5.18 (m, 5H), 5.07 (t, $J$ = 6.6 Hz,1H), 3.86 (s, 3H), 3.54 (s, 3H), 3.49 (s, 3H), 3.42 (dd, $J$ = 11.4, 3.9 Hz, 1H), 3.39 (d, $J$ = 6.9 Hz, 2H), 2.74 (s, 1H), 2.71 (d, $J$ = 2.7 Hz, 1H), 2.15–2.05 (m, 1H), 2.00–1.80 (m, 5H), 1.78 (s, 3H), 1.75–1.70 (m, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR $\delta$ 158.4, 155.9, 146.3, 143.9, 136.6, 134.7, 131.3, 129.2, 127.9, 126.9, 124.6, 123.3, 122.8, 122.1, 118.9, 113.6, 105.5, 102.7, 96.0, 94.6, 78.1, 77.1, 56.3, 56.1, 55.8, 46.9, 39.9, 38.5, 37.9, 28.4, 27.4, 26.8, 25.8, 23.3, 22.6, 20.0, 17.8, 16.2, 14.4; HRMS ($EI^+$) $m/z$ calcd for $C_{39}H_{54}O_7$ ($M^+$) 634.3870, found 634.3876.

### 5.39. 3-Deoxy-5'-*O*-methylschweinfurthin A (56)

#### 5.39.1. General Procedure for MOM hydrolysis

To a solution of stilbene **48** (54 mg, 0.09 mmol) in MeOH (10 mL) was added TsOH (80 mg, 0.47 mmol) at room temperature and the solution was stirred for 23 h. The reaction was quenched by addition of $NaHCO_3$ (sat.) and extracted with EtOAc. The organic extracts were washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. Final purification by flash column chromatography (2:1 hexanes/EtOAc) gave compound **56** (29 mg, 61%) as a white solid: $[\alpha]_D^{26.4}$ +44.7 ($c$ 1.84, $CH_3OH$); $^1$H NMR ($CD_3OD$) $\delta$ 6.89 (d, $J$ = 16.2, 1H), 6.83 (d, $J$ = 1.8 Hz, 1H), 6.79 (d, $J$ = 16.2, 1H), 6.73 (s, 1H), 6.58 (s, 2H), 5.19 (t, $J$ = 7.2 Hz, 1H), 5.05 (t, $J$ = 6.9 Hz, 1H), 3.81 (s, 3H), 3.37–3.33 (m, 1H), 3.31–3.28 (m, 2H), 2.70–2.67 (m, 2H), 2.05–2.00 (m, 2H), 1.95–1.90 (m, 2H), 1.82–1.78 (m, 2H), 1.78 (s, 3H), 1.70–1.65 (m, 3H), 1.61 (s, 3H), 1.55 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 159.9, 156.9, 147.0, 142.2, 137.8, 134.8, 131.9, 130.9, 128.9, 127.6, 125.5, 124.5, 123.9, 120.6, 117.1, 111.1, 107.1, 101.6, 78.7, 78.2, 56.1, 48.6, 41.0, 39.5, 38.9, 29.0, 27.9, 27.8, 25.9, 24.0, 23.1, 20.3, 17.7, 16.2, 14.9; HRMS ($EI^+$) $m/z$ calcd for $C_{35}H_{46}O_5$ ($M^+$) 546.3345, found 546.3340.

### 5.40. Stilbene 49

Under the general conditions for HWE condensations, aldehyde **42** (98 mg, 0.32 mmol), phosphonate **39** (172 mg, 0.38 mmol), and NaH (130 mg, 3.2 mmol, 60% in oil) were allowed to react in THF (6.2 mL) for 15 h. Final purification by column chromatography (1:1 hexanes/ethyl acetate) afforded stilbene **49** (175 mg, 90%) as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.00–6.72 (m, 6H), 5.23 (s, 2H), 5.23–5.21 (m, 1H), 5.08 (t, $J$ = 8.5 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H), 3.46–3.37 (m, 3H), 2.73 (d, $J$ = 9.2 Hz, 2H), 2.17–1.51 (m, 10H), 1.78 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.26, (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H);$^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 155.8, 148.9, 142.5, 136.5, 134.6, 131.1, 128.9, 128.0, 126.6, 124.4, 122.59, 122.56, 120.5, 118.7, 106.8, 105.3, 102.5, 94.4, 77.9, 77.1, 55.94, 55.92, 55.7, 46.7, 39.8, 38.3, 37.6, 28.2, 27.3, 26.7, 25.6, 23.1, 22.4, 19.8, 17.6, 16.0, 14.2; HRMS (ESI) $m/z$ calcd for $C_{38}H_{52}O_6$ ($M^+$) 604.3764, found 604.3754.

### 5.41. 3-Deoxy-schweinfurthin B analogue 57

Under the general conditions for MOM hydrolysis, stilbene **49** (80 mg, 0.13 mmol), MeOH (35 mL), and $p$-TsOH (75 mg, 0.42 mmol) were allowed to react for 4 days. Final purification by column chromatography (1:1 hexanes/ethyl acetate) afforded

compound **57** (68 mg, 92%) as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.00–6.60 (m, 6H), 5.28–5.24 (m, 1H), 5.07–5.05 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.43–3.37 (m, 3H), 2.73 (d, $J$ = 9.2 Hz, 2H), 2.17–1.51 (m, 10H), 1.80 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.26, (s, 3H), 1.11 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.0, 155.6, 148.8, 142.5, 137.7, 136.8, 131.7, 128.9, 128.2, 126.3, 123.9, 122.6, 121.9, 120.5, 114.7, 106.79, 106.77, 101.2, 77.9, 77.0, 55.94, 55.7, 46.7, 39.7, 38.3, 37.6, 28.2, 27.3, 26.4, 25.6, 23.1, 22.2, 19.8, 17.6, 16.1, 14.2; HRMS (ESI) $m/z$ calcd for $C_{36}H_{48}O_5$ ($M^+$) 560.3502, found 560.3481.

### 5.42. Stilbene 50

Under the general conditions for HWE condensations, aldehyde **34** (320 mg, 0.76 mmol) phosphonate **39** (560 mg, 1.23 mmol), and KHMDS (0.5 M in toluene, 5 mL, 2.5 mmol) were allowed to react in THF (10 mL) for 10 min. Final purification by column chromatography (30% EtOAc in hexanes) afforded stilbene **50** (195 mg, 36%) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.44 (d, $J$ = 0.8 Hz, 1H), 7.14 (d, $J$ = 1.6 Hz, 1H), 6.96 (d, $J$ = 16.0 Hz, 1H), 6.90 ($J$ = 16.0 Hz, 1H), 6.86 (d, $J$ = 0.8 Hz, 1H), 6.71 (d, $J$ = 0.8 Hz, 1H), 5.23 (s, 2H), 5.20 (t, $J$ = 6.8 Hz, 1H), 5.07 (t, $J$ = 6.8 Hz, 1H), 4.70 (d, $J$ = 13.6 Hz, 1H), 4.63 (d, $J$ = 13.6 Hz, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 3.43 (dd, $J$ = 11.6, 4.4 Hz, 1H), 3.37 (d, $J$ = 6.8 Hz, 2H), 2.73–2.70 (m, 2H), 2.06–1.84 (m, 8H), 1.78 (s, 3H), 1.72–1.68 (m, 2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 0.98 (s, 9H), 0.88 (s, 3H), –0.13 (s, 6H); $^{13}$C NMR $\delta$ 158.2, 155.8, 149.6, 136.8, 134.6, 131.2, 129.4, 128.8, 128.4, 126.3, 126.3, 124.4, 123.4, 122.7, 121.1, 118.6, 105.3, 102.6, 94.5, 78.0, 76.5, 60.2, 56.0, 55.7, 46.8, 39.8, 38.3, 37.8, 28.2, 27.3, 26.7, 26.0, 25.7 (3C), 23.0, 22.4, 20.1, 18.5, 17.6, 16.0, 14.2, –5.2 (2C); HRMS (EI) $m/z$ calcd for $C_{44}H_{66}O_6Si$ ($M^+$) 718.4629, found 718.4631.

### 5.43. Alcohol 58

To a solution of silyl ether **50** (195 mg, 0.27 mmol) in THF at rt was added TBAF (0.5 mL, 1 M in THF, 0.5 mmol). After 4 h, the reaction was quenched by addition of water, the resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo, which provided nonracemic alcohol **58** (193 mg, 100% yield, 89% ee by HPLC) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.27 (d, $J$ = 1.2 Hz, 1H), 7.18 (d, $J$ = 1.2 Hz, 1H), 6.97 (d, $J$ = 16.0 Hz, 1H), 6.92 (d, $J$ = 16.0 Hz, 1H), 6.84 (s, 1H), 6.71 (s, 1H), 5.23 (s, 2H), 5.22 (m, 1H), 5.08 (t, $J$ = 6.2 Hz, 1H), 4.66 (d, $J$ = 13.2 Hz, 1H), 4.59 (d, $J$ = 13.2 Hz, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 3.40–3.37 (m, 3H), 2.75–2.64 (m, 2H), 2.08–1.95 (m, 5H), 1.86–1.80 (m, 2H), 1.79 (s, 3H), 1.75–1.67 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.1, 155.7, 150.5, 136.5, 134.4, 130.9, 129.0, 128.7, 127.7, 127.2, 126.6, 124.3, 124.2, 122.6, 121.8, 118.7, 105.3, 102.6, 94.4, 77.6, 77.1, 61.8, 55.8, 55.6, 46.7, 39.7, 38.2, 37.7, 28.0, 27.2, 26.6, 25.6, 22.8, 22.4, 20.1, 17.5, 15.9, 14.2; HRMS (EI) $m/z$ calcd for $C_{38}H_{52}O_6$ ($M^+$) 604.3764, found 604.3751.

### 5.44. Schweinfurthin analogue 59

Under the general conditions for MOM hydrolysis, stilbene **58** (14 mg, 0.025 mmol), methanol (1 mL), and $p$-TsOH·$H_2O$ (68 mg, 0.37 mmol) were allowed to react for 24 h to provide analogue **59** (2 mg, 17%) as a white solid after purification by thin layer chromatography (50% EtOAc in hexanes): $^1$H NMR ($CDCl_3$) $\delta$ 7.26 (s, 1H), 7.18 (s, 1H), 6.95 (d, $J$ = 16.0 Hz, 1H), 6.86 (d, $J$ = 16.0 Hz, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 5.23 (m, 1H), 5.06 (m, 1H), 4.67 (d, $J$ = 12.4 Hz, 1H), 4.60 (d, $J$ = 12.4 Hz, 1H), 3.85 (s, 3H), 3.46–3.40 (m, 3H), 2.76 (m, 2H), 2.09–1.88 (m, 8H), 1.80 (s, 3H), 1.75–1.70 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); HRMS (EI) $m/z$ calcd for $C_{36}H_{48}O_5$ ($M^+$) 560.3502, found 560.3508.

### 5.45. Aldehyde 60

To a solution of alcohol **58** (50 mg, 0.10 mmol) in $CH_2Cl_2$ at rt was added activated $MnO_2$ (250 mg, 2.3 mmol). After 22 h at rt, the solution was diluted with ethyl acetate, filtered through celite, and concentrated in vacuo which afforded aldehyde **60** (49 mg, 98%) as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 10.41 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 6.96 (s, 2H), 6.87 (s, 1H), 6.70 (s, 1H), 5.20 (s, 2H), 5.19 (m, 1H), 5.06 (m, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 3.44 (dd, $J$ = 11.4, 3.4 Hz, 1H), 3.37 (d, $J$ = 6.8 Hz, 2H), 2.77–2.73 (m, 2H), 2.08–1.82 (m, 8H), 1.77 (s, 3H), 1.74–1.70 (m, 2H), 1.64 (s, 3H), 1.50 (s, 3H), 1.28 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 189.9, 158.2, 155.8, 155.6, 136.0, 134.6, 133.6, 131.1, 129.2, 128.0, 126.6, 124.4, 124.4, 123.8, 123.7, 122.5, 119.2, 105.4, 102.7, 94.5, 78.0, 77.7, 55.9, 55.7, 46.5, 39.7, 38.4, 37.4, 28.1, 27.2, 26.7, 25.6, 22.9, 22.4, 20.2, 17.6, 16.0, 14.2; HRMS (EI) $m/z$ calcd for $C_{38}H_{50}O_6$ ($M^+$) 602.3607, found 602.3616.

### 5.46. Acid 61

To a solution of aldehyde **60** (17 mg, 0.028 mmol) in $(CH_3)_3COH$ (1 mL) at rt was added 2-methyl-2-butene (0.3 mL). Dropwise addition of $NaH_2PO_4$ (40 mg) and $NaClO_2$ (34 mg, 0.38 mmol) as an aqueous solution (0.3 mL) resulted in a darkening of the reaction solution. After 45 min, the reaction was quenched by addition of 1 N HCl. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford acid **61** (18 mg, 100%) as a yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 8.23 (d, $J$ = 2.4 Hz, 1H), 7.55 (d, $J$ = 1.8 Hz, 1H), 7.09 (d, $J$ = 16.8 Hz, 1H), 7.05 (d, $J$ = 16.6 Hz, 1H), 6.97 (d, $J$ = 0.8 Hz, 1H), 6.79 (d, $J$ = 1.2 Hz, 1H), 5.30 (s, 2H), 5.27 (m, 1H), 5.15 (t, $J$ = 5.1 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 3.56 (m, 1H), 3.45 (d, $J$ = 7.2 Hz, 2H), 2.92–2.87 (m, 2H), 2.20–1.88 (m, 8H), 1.85 (s, 3H), 1.81–1.74 (m, 2H), 1.72 (s, 3H), 1.65 (s, 3H), 1.44 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.7, 158.3, 155.9, 151.1, 135.8, 134.7, 132.8, 131.2, 130.9, 129.5, 129.1, 126.0, 124.4, 123.4, 122.5, 119.5, 117.4, 105.6, 102.9, 94.6, 81.3, 77.2, 56.0, 55.7, 46.4, 39.8, 38.5, 37.5, 28.0, 27.1, 26.7, 25.6, 22.9, 22.4, 20.3, 17.6, 16.0, 14.2; HRMS (EI) $m/z$ calcd for $C_{38}H_{50}O_7$ ($M^+$) 618.3557, found 618.3560.

### 5.47. Amine 62

Aldehyde **60** (7.5 mg, 0.012 mmol) was dissolved in dimethylamine (2 M solution in THF, 1 mL, 2 mmol) at rt and molecular sieves were added. After 2 h, additional dimethylamine (1 mL, 2 mmol) was added along with AcOH (0.05 mL). After an additional 5 h, $NaBH(OAc)_3$ (58 mg, 0.4 mmol) was added in one portion. After 15 h, the reaction was quenched by addition of 1 N NaOH. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. Final purification by preparative thin layer chromatography on a base-washed plate (75% EtOAc and 5% TEA in hexanes) afforded amine **62** (2.5 mg, 33%) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.34 (s, 1H), 7.30 (s, 1H), 6.95 (s, 2H), 6.86 (s, 1H), 6.70 (s, 1H), 5.22 (s, 2H), 5.19 (m, 1H), 5.05 (m, 1H), 3.88 (s, 3H), 3.64 (s, 2H), 3.50 (s, 3H), 3.44 (dd, $J$ = 11.4, 7.6 Hz, 1H), 3.36 (d, $J$ = 7.6 Hz, 2H), 2.76–2.73 (m, 2H), 2.59 (s, 6H), 2.06–2.03 (m, 6H), 1.97–1.88 (m, 2H), 1.81 (s, 3H), 1.73–1.68 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.4, 156.9, 152.6, 137.3, 135.7, 132.2, 130.6, 130.3, 129.9, 129.7, 128.7, 128.6, 128.0, 125.5, 123.7, 120.2, 106.6,

103.8, 95.6, 78.9, 78.2, 71.6, 57.0, 56.8, 48.0, 43.9, 40.9 (2C), 39.5, 38.9, 29.3, 28.4, 27.8, 26.7, 24.3, 23.5, 21.3, 18.7, 17.1, 15.4; HRMS (EI) $m/z$ calcd for $C_{40}H_{57}NO_5$ ($M^+$) 631.4237, found 631.4232.

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## Supplementary data

Supplementary data (NMR spectra and complete bioassay data) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.10.034.

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