# BF$_3$·Et$_2$O Mediated Cascade Cyclizations: Synthesis of Schweinfurthins F and G

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## Abstract

The total synthesis of the natural stilbene (+)-schweinfurthin G (**8**) has been accomplished through a sequence based on an efficient cationic cascade cyclization. This cascade process is initiated by Lewis acid promoted ring opening of an epoxide and terminated through a novel reaction with a phenolic oxygen "protected" as its MOM ether. Several Lewis acids have been examined for their ability to induce this new reaction, and BF$_3$·Et$_2$O was found to be the most effective. The only major by-product under these conditions was one where the expected secondary alcohol was found as its MOM ether derivative (e.g. **30**). While this by-product could be converted to the original target compound through hydrolysis, it also could be employed as a protected alcohol to allow preparation of a benzylic phosphonate (**43**) without dehydration of the secondary alcohol. The resulting phosphonate was employed in a Horner-Wadsworth-Emmons condensation with an aldehyde representing the right half of the target compounds, an approach complementary to previous studies based on condensation of a right half phosphonate and a left half aldehyde.

## Graphical Abstract
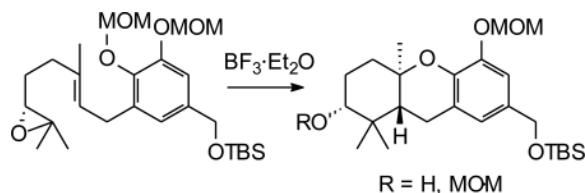


## Introduction

Carbon–carbon bond formation is the central operation of organic synthesis, and reactions that accomplish this objective while bringing added complexity to the reaction product are particularly valuable. Consideration of the range of natural products generated in plants, animals, and fungi through cationic cascade cyclizations makes clear that this process has abundant potential.[1] However, to date synthetic chemistry based on cationic cascades has been able to recapture only a fraction of the varied structures produced through biosynthesis and even the "successful" reactions often afford complex mixtures and modest yields. The

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**Supporting Information.**

Experimental paragraphs for compounds **25**, **26**, **38**, **39**, **40**, and **11**, along with complete ^{1}H and ^{13}C NMR spectra for compounds **8**, **10**, **21**, **25**, **26**, **28–32**, **34**, and **36–44**, can be found here. This material is available free of charge via the Internet at http://pubs.acs.org.

history of cationic cascade cyclizations is extensive with much attention directed towards transformations of epoxy-enes.[2] There is considerably less precedence for cationic cascade cyclizations terminated by phenolic nucleophiles. Previous work in this particular arena utilized harsh conditions to achieve cyclization and often suffered from low yields.[3]

Our interest in cationic cascade cyclizations originated in an effort to prepare some natural hexahydroxanthenes. The tetracyclic schweinfurthins A (**1**) and B (**2**), along with a simpler stilbene named schweinfurthin C (**3**), were isolated from the plant *Macaranga schweinfurthii* and were reported to have an interesting profile of anti-cancer activity (Figure 1).[4] A short time later, a fourth member of this family with a hydrated terminal olefin in the geranyl chain was isolated from the same plant and named schweinfurthin D (**4**).[5] The tetracyclic schweinfurthins are closely related to the natural product vedelianin (**5**), which bears a prenyl group on the D–ring instead of the geranyl group of the first schweinfurthins and was isolated from *M. vedeliana*.[6] Very recently several new hexahydroxanthene natural products that bear D-ring prenyl groups were isolated from *M. alnifolia* and named as schweinfurthins E–H (**6**–**9**).[7]

While the biosynthesis of the tetracyclic schweinfurthins has not been studied, both the structure of the hexahydroxanthene system and the co-occurrence of schweinfurthin A and B with schweinfurthin C strongly suggest a sequence that includes a cationic cascade cyclization. A process initiated through opening of an epoxide and terminated by reaction with a phenol would easily explain the A/B/C-ring system of schweinfurthin F and G, while a more oxidized precursor could lead to the A-ring diol schweinfurthins through a parallel process. From the standpoint of chemical synthesis, a biomimetic route to the schweinfurthins would be attractive but past examples of cascade cyclizations have emphasized use of olefins, arenes, and hydroxyl groups for termination of the cascades.[2] Phenols or protected forms of them have been less studied,[3,8] but may still offer great opportunity because they may be reasonably stable to the reaction conditions and yet serve as potent nucleophiles. The available precedents for cascade cyclizations of MOM-protected phenols were not encouraging. A paper from Kitahara and coworkers[9a] reported treatment of an epoxide bearing a remote MOM ether with picric acid and then with methanolic HCl. The desired cyclization product was obtained, but this compound was isolated in just 2% yield and the loss of a second MOM ether under the reaction conditions makes it unclear if MOM cleavage occurred prior to or during the cyclization. A more recent study of the same substrate was unable to effect cyclization with either protic or Lewis acids, and found instead only inseparable mixtures.[9b] There is a precedent for chromane formation through a cyclization of an epoxide with a MOM-protected phenol,[10] but whether this process could be extended to formation of a hexahydroxanthene was not known. In this paper, we describe the synthesis of two schweinfurthins, F (**7**) and G (**8**), and two schweinfurthin analogues, 3-deoxyschweinfurthin A (3dSA, **10**, Figure 2) and 3-deoxyschweinfurthin B (3dSB, **11**), via efficient cascade cyclizations mediated by $BF_3 \cdot Et_2O$.

## Results and Discussion

Our general, convergent approach to the schweinfurthins (**12**) takes advantage of a late stage Horner–Wadsworth–Emmons (HWE) condensation to provide the central stilbene as the

penultimate step (Scheme 1). The utility of this strategy was demonstrated first in the synthesis of schweinfurthin C (**3**).[11] The parallel coupling of a "left–half" aldehyde (**13**) and a "right–half" phosphonate (**14**) at this stage offers the opportunity to use common precursors in the synthesis of several schweinfurthins.[11] The "left–half" aldehydes were envisioned to arise from phenol terminated cationic cascade cyclizations of enantiopure epoxides **15**. The intermediate epoxides were expected to be available through Shi epoxidation[12] of a geranyl derivative (**16**) of commercially available vanillin (**17**) or through Shi epoxidation of a geranyl ester and alkylation of a vanillin derivative (**18**).[13] Several "right–half" phosphonates appropriate for this strategy are known from our previous work.[11, 14, 15]

The current studies began with the known compound bromovanillin (**18**), available through direct bromination of commercially available vanillin (**17**), and readily converted to the geranylated epoxide **19** (Scheme 2).[13] Vanillin is an especially attractive starting material for schweinfurthins with a C–ring methoxy group (e.g. schweinfurthin F), and conversion of epoxide **19** to an intermediate hexahydroxanthene has been reported using a Brönsted acid to induce cyclization.[16] While that approach allowed preparation of some key targets, in the best cases the acid-catalyzed cyclization proceeds in just 30–40% yield. A Lewis acid mediated cascade cyclization would be attractive if it allowed use of milder reaction conditions and proceeded in better yield.

Studies on the use of Lewis acids to induce a cascade reaction were performed with epoxide **19** (Figure 3) to determine the conditions necessary to enact cyclization and formation of the desired tricycle (Table 1). Several Lewis acids were examined with varying conditions of reaction times and temperatures. Upon treatment with $Ti(OiPr)_4$ no reaction was detected (Trials 1–3) and the starting epoxide could be recovered unchanged, suggesting that this Lewis acid was unable to enact cyclization in this system. In contrast, upon treatment with $TiCl_4$ (Trial 4) or $SnCl_4$ (Trial 5) no isolable compounds were obtained and no starting materials could be recovered.[17] A reaction with $MeAlCl_2$, which has been used in a number of other cationic cascades,[18] gave the desired products in modest yield (Trial 6). The use of $In(OTf)_3$ gave more promising results (Trials 7–10), including formation of significant amounts of the desired tricycle and merits further evaluation as a reagent to promote these cascade cyclizations.[19] However, reactions with $BF_3 \cdot Et_2O$ were inexpensive, convenient, and easily amenable to larger scales. They appeared to have great promise in providing tricycle **20**, and thus this Lewis acid became our immediate focus.[20] Even very brief exposure to this Lewis acid at low temperature (Trial 11) gave a yield comparable to the best obtained from reactions with protic acids. At slightly longer times (Trials 12 and 13), the yield of the tricyclic alcohol **20** improved to 64–68% and the major by-product was the tricyclic compound with an A-ring methoxymethyl (MOM) ether **21**. Thus the total yield of hexahydroxanthene was ~75% under these conditions, or nearly double the best reported from the protic acid catalyzed reactions in similar systems.[16] Further increases in reaction time did not lead to improved yields (Trials 14 and 15).

To determine if these conditions could be applied to other substrates, and to gain access to intermediates for more facile synthesis of hexahydroxanthenes with a C-ring phenol, aromatic compounds with two MOM groups were sought. Our synthesis of schweinfurthin

G (**8**) and its analogue 3dSA (**10**) proceeded from bromovanillin (**18**) through treatment with aluminum (III) chloride as a standard demethylation[21] to provide catechol **22** (Scheme 3). Protection of compound **22** as its MOM ether (**23**) followed by reduction of the aldehyde afforded the known benzylic alcohol **24**.[11] The resultant alcohol was masked as the silyl ether to give differentially protected bromide **25**. Treatment of bromide **25** with *n*–BuLi enacted halogen metal exchange and subsequent reaction with geranyl bromide installed the geranyl chain to provide compound **26** in 86% yield. A Shi epoxidation[12] of geranylated arene **26** was observed upon treatment with hydrogen peroxide in the presence of sugar catalyst **27** and acetonitrile in buffered solution to afford epoxide **28** in a modest yield but excellent enantioselectivity (*vide infra*). In addition this application of the Shi epoxidation generally results in recovery of 33–54% of the starting olefin so yields based on recovered starting material are very attractive. With epoxide **28** in hand, the stage was set for Lewis–acid mediated cascade cyclizations. Brief treatment with $BF_3 \cdot Et_2O$ afforded tricycle **29** in a 52% yield along with tricycle **30** in 30% yield, representing very efficient formation of the tricyclic system. Removal of the silyl protecting group of tricycle **29** was successful using standard conditions and oxidation gave the new "left-half" aldehyde **32**.

Formation of the A-ring MOM ethers as by-products of the cyclization of both epoxides **19** and **28** was not expected. These products can be readily explained by formation of a formal $CH_3OCH_2^+$ cation during the course of cyclization, and ultimate reaction of this cation with the nucleophilic oxygen of the C-2 hydroxyl group. However, the corresponding by-product from reaction of such a cation at the benzylic oxygen was not observed, so a more complex mechanism may be at play and further studies will be necessary to clarify this process.

Completion of the target compounds proceeded in a straightforward manner. Aldehyde **32** was employed for synthesis of schweinfurthin G (**8**) and 3dSA (**10**). In the first case, an HWE condensation of aldehyde **32** and known phosphonate **33**[14] provided the penultimate compound as stilbene **34**. Acidic hydrolysis of the three MOM ethers yielded schweinfurthin G (**8**) in 57% yield (Scheme 4). This route represents the first total synthesis of schweinfurthin G and spectral data matched that of the isolated natural product. Analysis of the product by HPLC indicated an ee of ~94%, originating in the Shi epoxidation. A similar strategy was used for the synthesis of 3–deoxyschweinfurthin A (**10**). For this target aldehyde **32** underwent a smooth HWE condensation with known phosphonate **35**[11] to afford stilbene **36**. Treatment of compound **36** with TsOH resulted in cleavage of the three MOM groups and provided the new schweinfurthin analogue **10** in a modest yield. Finally, standard cleavage of the silyl protecting group of tricycle **20** followed by $MnO_2$ oxidation to the corresponding aldehyde represents a formal synthesis of both schweinfurthin F (**7**)[12] and 3dSB (**11**).[16] Synthesis of 3dSB through this $BF_3 \cdot Et_2O$ mediated cyclization shows consistent transmission of stereochemical integrity from the epoxide through the cyclization, in parallel with our work using protic acids.[16]

In principle, the A-ring MOM compounds **21** and **30** could be hydrolyzed to the corresponding alcohols **20** and **29**, and thus recycled into the desired stilbenes. Instead we chose to take advantage of these compounds as protected A-ring alcohols and use them in a different manner. Accordingly, compound **21** was treated with TBAF to afford the benzylic

alcohol **37**, and this alcohol was converted to the corresponding phosphonate through sequential treatment with mesyl chloride, NaI, and triethyl phosphite. In contrast, if the A-ring alcohol is left unprotected, attempted reactions with triethyl phosphite resulted in dehydration. An HWE condensation of phosphonate **38** with aldehyde **39**[22] (Scheme 5), readily available by $MnO_2$ oxidation of the corresponding benzylic alcohol,[11] gave the desired stilbene **40** in a modest yield (Scheme 5). Final hydrolysis of the three MOM groups by treatment with TsOH in methanol gave the desired 3dSB (**11**). Through a parallel sequence, compound **30** was converted to the benzylic alcohol **41** and then to phosphonate **42**. In this case, the HWE condensation with aldehyde **39** gave stilbene **43** in a good yield, and final deprotection of the four MOM groups gave 3dSA (**10**) in 52% yield, along with a partial hydrolysis product (**44**) that retained the A-ring MOM group (33%). These experiments show that the adventitious formation of the A-ring MOM compound allows preparation of the benzylic phosphonate, and that condensation of this phosphonate "left half" with an aldehyde "right half" is a viable alternative to the reverse strategy (i.e. a phosphonate "right half" with an aldehyde "left half") that has been employed in all previous studies. Although the yields have not been optimized and currently are somewhat lower for this approach than for the original strategy, this allows attractive flexibility in distribution of the number of steps between the two branches of the convergent synthesis.

In conclusion, the scope of Lewis acid mediated cascade cyclizations has been expanded to include two examples of efficient epoxy-ene cyclizations mediated by brief treatment with $BF_3 \cdot Et_2O$ and terminated by reaction with a MOM-protected phenol. These cyclizations were used to provide the hexahydroxanthene core necessary for the synthesis of two schweinfurthin natural products (schweinfurthins F and G), and two parallel schweinfurthin analogues (3dSA and 3dSB). Further application of the use of Lewis acid mediated cascade cyclizations, particularly those terminated by oxygen nucleophiles, will be reported in due course.

## Experimental Section

### Benzylic silyl ethers 20 and 21

To a solution of epoxide **19** (320 mg, 0.66 mmol) in $CH_2Cl_2$ was added $BF_3 \cdot Et_2O$ (0.35 mL, 2.8 mmol) at −78 °C. The resulting solution was allowed to stir 16 minutes and triethylamine (0.5 mL, 4 mmol) was added. After an additional 10 minutes, water (75 mL) was added, the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phase was washed with water and brine, then dried ($MgSO_4$), and concentrated. Final purification by flash chromatography (15:1 to 3:1 hexanes:EtOAc) afforded the tricyclic alcohol **20** (132 mg, 48%) as a clear oil with spectral data matching previously reported data.[13,16] Also isolated as a clear oil (69 mg, 22%) was the A-ring methoxymethylether **21**: $[\alpha]^{26.4}_D$ = +8.9° (*c* 0.03, CHCl₃); ¹H NMR δ 6.70 (s, 1H), 6.64 (s, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.64 (s, 2H), 3.83 (s, 3H), 3.41 (s, 3H), 3.27 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.70–2.67 (m, 2H), 2.13 (dt, *J* = 12.7, 3.2 Hz, 1H), 1.97 (dq, *J* = 13.0, 3.7 Hz, 1H), 1.85–1.52 (m, 3H), 1.24 (s, 3H), 1.08 (s, 3H), 0.95 (s, 9H), 0.90 (s, 3H), 0.11 (s, 6H); ¹³C NMR δ 148.6, 141.4, 132.3, 122.2, 119.0, 107.4, 96.1, 84.0, 76.4,

64.9, 55.8, 55.8, 47.0, 38.3, 37.5, 27.4, 26.0 (3C), 25.2, 23.1, 19.4, 18.4, 15.1, –5.2(2C);
HRMS (EI$^+$) $m/z$ calcd for $C_{26}H_{44}O_5Si$ (M$^+$) 464.2958, found 464.2944.

### 5–((2E)–3,7–Dimethyl–6–epoxy–octa–2–enyl) –3,4–bis(O-methoxymethyl)benzyloxy–*tert*–butyldimethylsilane (28)

To a solution of olefin **26** (689 mg, 1.4 mmol) in acetonitrile (0.4 mL), $n$–butanol (10 mL) and a buffer solution (5 mL, 2 M $K_2CO_3$, 0.4 mM EDTA) at 0 °C was added the sugar catalyst **27** (95 mg, 0.4 mmol). Hydrogen peroxide (0.85 mL, 30% solution, 8.3 mmol) was added dropwise to the cooled mixture and the reaction was stirred for 22 h. The reaction was quenched by addition of $Na_2SO_3$ and extracted with EtOAc. The combined organic extracts were washed with $H_2O$ and brine, dried (MgSO$_4$), and concentrated *in vacuo* to afford a pale liquid. Final purification by flash column chromatography (8% EtOAc in hexanes) provided epoxide **28** (277 mg, 39%) as a colorless liquid: [α]$^{26.4}$$_D$ = +0.56° ($c$ 0.11, CHCl$_3$); $^1$H NMR δ 6.98 (d, $J$ = 1.8 Hz, 1H), 6.78 (d, $J$ = 1.5 Hz, 1H), 5.36 (t, $J$ = 7.2 Hz, 1H), 5.17 (s, 2H), 5.08 (s, 2H), 4.64 (s, 2H), 3.59 (s, 3H), 3.49 (s, 3H), 3.41 (d, $J$ = 6.9 Hz, 2H), 2.71 (t, $J$ = 6.3 Hz, 1H), 2.20–2.05 (m, 2H), 1.73 (s, 3H), 1.70–1.60 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR δ 149.7, 143.6, 137.6, 135.5, 135.4, 123.3, 120.5, 112.2, 99.2, 95.3, 64.8, 64.3, 58.4, 57.6, 56.2, 36.5, 28.6, 27.6, 26.0 (3C), 25.0, 18.9, 18.5, 16.3, –5.1 (2C). Anal. Calcd for $C_{27}H_{46}O_6Si \cdot$ ½ $H_2O$: C, 64.38; H, 9.40. Found: C, 64.48; H, 9.35.

### Tricycles 29 and 30

To a solution of epoxide **28** (355 mg, 0.7 mmol) in $CH_2Cl_2$ (60 mL) at –78 °C was added BF$_3$·Et$_2$O (0.36 mL, 2.8 mmol) dropwise. The reaction was stirred for 3.5 minutes and quenched by addition of triethylamine, treated with NH$_4$CL (sat.), and extracted with $CH_2Cl_2$. The combined organics were washed with $H_2O$ and brine, dried (MgSO$_4$), and concentrated *in vacuo* to give a yellow liquid. Final purification by flash column chromatography (15% EtOAc in hexanes) provided tricycles **29** (163 mg, 52%) and **30** (108 mg, 30%) as colorless oils. For compound **29**: [α]$^{26.4}$$_D$ = +38.7° ($c$ 0.02, CHCl$_3$); $^1$H NMR δ 6.91 (s, 1H), 6.75 (s, 1H), 5.17 (d, $J$ = 6.6 Hz, 1H), 5.13 (d, $J$ = 6.3 Hz, 1H), 4.61 (s, 2H), 3.50 (s, 3H), 3.39 (dd, $J$ = 11.7, 3.1 Hz, 1H), 2.71 (s, 1H), 2.70–2.66 (m, 1H), 2.10–2.00 (m, 1H), 1.80–1.65 (m, 5H), 1.22 (s, 3H), 1.09 (s, 3H), 0.94 (s, 9H), 0.87 (s, 3H), 0.10 (s, 6H); $^{13}$C NMR δ 145.9, 143.1, 134.7, 123.1, 121.5, 114.4, 96.2, 78.3, 76.7, 65.0, 56.3, 47.0, 38.6, 38.0, 28.5, 27.6, 26.3 (3C), 23.5, 20.1, 18.7, 14.5, –4.9 (2C); HRMS (EI$^+$) $m/z$ calcd for $C_{25}H_{42}O_5Si$ (M$^+$) 450.2802, found 450.2809. For compound **30**: [α]$^{26.4}$$_D$ = +9.7° ($c$ 0.05, CHCl$_3$); $^1$H NMR δ 6.91 (d, $J$ = 1.8 Hz, 1H), 6.74 (d, $J$ = 1.8 Hz, 1H), 5.17 (d, $J$ = 6.6 Hz, 1H), 5.13 (d, $J$ = 6.3 Hz, 1H), 4.77 (d, $J$ = 6.9 Hz, 1H), 4.64 (d, $J$ = 6.9 Hz, 1H), 4.62 (s, 2H), 3.50 (s, 3H), 3.41 (s, 3H), 3.25 (dd, $J$ = 11.7, 4.2 Hz, 1H), 2.71 (s, 1H), 2.69–2.66 (m, 1H), 2.12–2.04 (m, 1H), 2.02–1.94 (m, 1H), 1.80–1.65 (m, 3H), 1.23 (s, 3H), 1.08 (s, 3H), 0.94 (s, 9H), 0.89 (s, 3H), 0.09 (s, 6H); $^{13}$C NMR δ 145.9, 143.1, 132.6, 123.0, 121.4, 114.3, 96.3, 96.1, 84.2, 76.6, 64.9, 56.2, 55.7, 47.2, 38.4, 37.8, 27.5, 26.1(3C), 25.4, 23.4, 19.9, 18.6, 15.2, –5.1 (2C); HRMS (EI$^+$) $m/z$ calcd for $C_{27}H_{46}O_6Si$ (M$^+$) 494.3064, found 494.3057.

### Tricyclic alcohol 31

To a solution of tricycle **29** (112 mg, 0.25 mmol) in THF at 0 °C was added TBAF (0.3 mL, 0.3 mmol, 1 M in THF). The reaction was stirred for 2 h and quenched with $NH_4Cl$ (sat.), extracted with EtOAc, and washed with $H_2O$ and brine. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **31** (83 mg, 99%) as a white solid: $[\alpha]^{26.4}_D = +43.5°$ (*c* 0.01, $CHCl_3$); ^{1}H NMR δ 6.96 (d, *J* = 1.8 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H), 5.19 (d, *J* = 6.3 Hz, 1H), 5.15 (d, *J* = 6.6 Hz, 1H), 4.56 (s, 2H), 3.51 (s, 3H), 3.40 (dd, *J* = 11.7, 3.0 Hz, 1H), 2.72 (s, 1H), 2.70 (d, *J* = 3.0 Hz, 1H), 2.15–2.05 (m, 1H), 1.86–1.81 (m, 2H), 1.69–1.63 (m, 4H), 1.26 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 146.1, 143.7, 132.2, 123.4, 122.6, 115.1, 96.0, 78.1, 76.9, 65.4, 56.3, 46.8, 38.5, 37.9, 28.4, 27.4, 23.3, 20.0, 14.4; HRMS (EI[+]) *m/z* calcd for $C_{19}H_{28}O_5$ (M[+]) 336.1937, found 336.1932.

### Tricyclic Aldehyde 32

To a solution of alcohol **31** (19 mg, 0.06 mmol) in $CH_2Cl_2$ was added manganese dioxide (120 mg, 1.2 mmol). The resulting solution was stirred for 16.5 h and quenched by filtration through a celite pad. After the pad was rinsed with $CH_2Cl_2$ and EtOAc, the combined organic extracts were dried ($MgSO_4$) and concentrated to afford aldehyde **32** (19 mg, 100%) as a white solid: $[\alpha]^{26.4}_D = +74.8°$ (*c* 0.02, $CHCl_3$); ^{1}H NMR δ 9.79 (s, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 5.23 (d, *J* = 6.6 Hz, 1H), 5.19 (d, *J* = 6.6 Hz, 1H), 3.51 (s, 3H), 3.42 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.79 (s, 1H), 2.77 (d, *J* = 4.5 Hz, 1H), 2.16–2.10 (m, 1H), 1.91–1.84 (m, 2H), 1.74–1.60 (m, 4H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 191.0, 150.1, 146.7, 128.9, 127.3, 123.5, 115.4, 95.8, 78.5, 77.9, 56.4, 46.6, 38.6, 37.7, 28.3, 27.4, 23.2, 20.2, 14.4. Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.94; H, 8.07.

### (2*R*,4a*R*,9a*R*)–Tri(*O*-methoxymethyl)schweinfurthin G (34)

To a suspension of NaH (42 mg, 1.04 mmol, 60% oil dispersion) and 15–crown–5 (0.01 mL, 0.05 mmol) in THF at 0 °C was added a solution of phosphonate **33** (33 mg, 0.08 mmol) and aldehyde **32** (20 mg, 0.06 mmol) in THF. After the reaction was allowed to warm to room temperature and stirred for 18 h, it was quenched by addition of $H_2O$ and extracted with EtOAc. The combined organic extracts were washed with $H_2O$ 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 **34** (18 mg, 50%) as a colorless oil: ^{1}H NMR δ 7.12 (d, *J* = 2.1 Hz, 1H), 6.95–6.93 (m, 2H), 6.90 (s, 2H), 6.89 (s, 1H), 5.25–5.18 (m, 7H), 3.55 (s, 3H), 3.51 (s, 6H), 3.47–3.44 (m, 1H), 3.38 (d, *J* = 7.2 Hz, 2H), 2.74 (s, 1H), 2.71 (d, *J* = 3.0 Hz, 1H), 2.15–2.05 (m, 1H), 1.90–1.80 (m, 2H), 1.79 (s, 3H), 1.75–1.70 (m, 3H), 1.66 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 156.6 (2C), 146.9, 144.6, 137.4, 131.8, 129.8, 128.8, 127.4, 123.9, 123.5, 122.8, 120.1, 114.7, 106.7 (2C), 96.6, 95.2 (2C), 78.7, 77.8, 57.0, 56.8 (2C), 47.5, 39.1, 36.5, 30.0, 29.0, 26.6, 23.9, 23.5, 20.7, 18.6, 15.0; HRMS (EI[+]) *m/z* calcd for $C_{35}H_{48}O_8$ (M[+]) 596.3351, found 596.3349.

### (2*R*,4a*R*,9a*R*)–Schweinfurthin G (8)

To a solution of stilbene **34** (24 mg, 0.04 mmol) in MeOH was added TsOH (31 mg, 0.18 mmol) at room temperature and the solution was stirred for 19 h. The reaction was quenched

by addition of NaHCO$_3$ (sat.) and extracted with EtOAc. The combined extracts were washed with H$_2$O and brine, dried (MgSO$_4$), and concentrated *in vacuo* to afford a yellow oil. Final purification by flash column chromatography (3:2 hexanes/EtOAc) afforded stilbene **8** (11 mg, 57%) as a colorless oil: [α]$^{26.4}$$_D$ = +58.4° (*c* 0.007, CH$_3$OH); literature[7] [α]$^{22}$ = +32.4° (*c* 0.04, CH OH); both $^1$H and $^{13}$C NMR spectra matched that of the natural product;[7] HRMS (EI$^+$) *m/z* calcd for C$_{29}$H$_{36}$O$_5$ (M$^+$) 464.2563, found 464.2565. The HPLC analyses were performed on a Shimadzu LC-20AT instrument with a Chiralcel OD-H column. The enantiomeric excess for compound **8** was determined by elution with a 4:1 mixture of hexanes and 2-propanol. Retention times for the enantiomers of schweinfurthin G (**8**) were 15.2 min (3.1 %) and 17.9 min (96.9 %), respectively.

### (2*R*,4a*R*,9a*R*)–Tri(*O*-methoxymethyl)–3–deoxyschweinfurthin A (36)

To a suspension of NaH (50 mg, 1.24 mmol, 60% oil dispersion) and 15–crown–5 (0.01 mL, 0.05 mmol) in THF at 0 °C was added a solution of phosphonate **35** (37 mg, 0.08 mmol) and aldehyde **32** (25 mg, 0.08 mmol) in THF. After the reaction was allowed to warm to room temperature and stirred for 20 h, it was quenched by addition of H$_2$O and extracted with EtOAc. The combined organic extracts were washed with H$_2$O 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 **36** (33 mg, 66%) as a colorless oil: [α]$^{26.4}$$_D$ = +39.0 (*c* 0.02, CHCl$_3$); $^1$H NMR δ 7.11 (d, *J* = 2.1 Hz, 1H), 6.96–6.94 (m, 2H), 6.90 (s, 2H), 6.87–6.86 (s, 1H), 5.23–5.19 (m, 7H), 5.07–5.04 (m, 1H), 3.54 (s, 3H), 3.51–3.49 (m, 7H), 3.39 (d, *J* = 6.9 Hz, 2H), 2.73 (s, 1H), 2.71 (d, *J* = 3.2 Hz, 1H), 2.15–2.05 (m, 3H), 2.00–1.80 (m, 5H), 1.79 (s, 3H), 1.75–1.70 (m, 2H), 1.64 (s, 3H), 1.57 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR δ 156.0 (2C), 146.3, 144.0, 136.8, 134.8, 131.4, 129.2, 128.2, 126.8, 124.5, 123.3, 122.8, 122.2, 119.7, 113.7, 106.2 (2C), 96.1, 94.6 (2C), 78.1, 77.1, 56.4, 56.1 (2C), 46.9, 40.0, 38.5, 37.9, 28.4, 27.4, 26.9, 25.7, 23.4, 23.1, 20.1, 17.8, 16.2, 14.4; HRMS (EI$^+$) *m/z* calcd for C$_{40}$H$_{56}$O$_8$ (M$^+$) 664.3975, found 664.3989.

### (2*R*,4a*R*,9a*R*)–3–Deoxyschweinfurthin A (10)

To a solution of stilbene **36** (4.9 mg, 0.01 mmol) in MeOH was added TsOH (7.3 mg, 0.04 mmol) at room temperature and the solution was stirred for 24 h. The reaction was quenched by addition of NaHCO$_3$ (sat.) and extracted with EtOAc. The combined extracts were washed with H$_2$O and brine, dried (MgSO$_4$), and concentrated *in vacuo* to afford a yellow oil. After final purification by flash column chromatography (3:2 hexanes/EtOAc), stilbene **10** (2.7 mg, 69%) was obtained as a colorless oil:: $^1$H NMR (CD$_3$OD) δ 6.83 (d, *J* = 16.5 Hz, 1H), 6.81–6.80 (m, 1H), 6.73–6.72 (m, 1H), 6.71 (d, *J* = 16.2 Hz, 1H), 6.43 (s, 2H), 5.23 (t, *J* = 6.6 Hz, 1H), 5.06 (t, *J* = 6.9 Hz, 1H), 3.34–3.28 (m, 3H), 2.74–2.69 (m, 2H), 2.05–2.00 (m, 4H), 1.95–1.90 (m, 2H), 1.75 (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$_3$OD) δ 157.3 (2C), 147.0, 142.2, 137.5, 134.8, 132.0, 131.0, 128.6, 127.5, 125.5, 124.6, 124.0, 120.4, 115.9, 111.1, 105.7 (2C), 78.7, 78.2, 48.6, 41.0, 39.5, 38.9, 29.0, 27.9, 27.8, 25.9, 24.0, 23.2, 20.2, 17.7, 16.3, 14.8; HRMS (EI$^+$) *m/z* calcd for C$_{34}$H$_{44}$O$_5$ (M$^+$) 532.3189, found 532.3193.

### Alcohol 37

To a solution of silyl ether **21** (39 mg, 0.08 mmol) in THF at 0 °C was added a solution of TBAF (0.10 mL, 0.10 mmol, 1 M in THF). The resulting solution was stirred for 4 h, quenched by addition of $NH_4Cl$ (sat.), and extracted with EtOAc. The organic extracts were washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow liquid. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded alcohol **37** (20 mg, 68%) as a colorless oil: $[\alpha]^{26.4}_D$ = +34.6 (*c* 0.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.73 (d, *J* = 1.8 Hz, 1H), 6.70 (s, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.57 (s, 2H), 3.84 (s, 3H), 3.41 (s, 3H), 3.26 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.71–2.68 (m, 2H), 2.13 (dt, *J* = 12.0, 3.3 Hz, 1H), 2.02–1.94 (m, 2H), 1.85–1.75 (m, 2H), 1.24 (s, 3H), 1.07 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.9, 142.2, 132.1, 122.7, 120.5, 108.5, 96.2, 84.1, 76.8, 65.5, 56.1, 55.7, 47.1, 38.3, 37.7, 27.5, 25.4, 23.2, 19.8, 15.2; HRMS (EI[+]) *m/z* calcd for $C_{20}H_{30}O_5$ (M[+]) 350.2093, found 350.2095.

### Alcohol 41

To a solution of silyl ether **30** (76 mg, 0.15 mmol) in THF at 0 °C was added a solution of TBAF (0.18 mL, 0.18 mmol, 1 M in THF). The resulting solution was stirred for 16 h, quenched by addition of $NH_4Cl$ (sat.), and extracted with EtOAc. The organic extracts were washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow liquid. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded alcohol **41** (35 mg, 59%) as a colorless oil: $[\alpha]^{26.4}_D$ = +26.2 (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.95 (d, *J* = 1.8 Hz, 1H), 6.81–6.80 (m, 1H), 5.19 (d, *J* = 6.9 Hz, 1H), 5.15 (d, *J* = 6.3 Hz, 1H), 4.77 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.55 (s, 2H), 3.51 (s, 3H), 3.41 (s, 3H), 3.27 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.71 (s, 1H), 2.68 (d, *J* = 4.2 Hz, 1H), 2.15–2.05 (m, 1H), 2.02–1.95 (m, 1H), 1.90–1.80 (br s, 1H), 1.75–1.65 (m, 3H), 1.23 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.0, 143.8, 132.2, 123.4, 122.6, 114.9, 96.2, 95.9, 84.1, 76.8, 65.3, 56.3, 55.8, 47.1, 38.3, 37.7, 27.5, 25.3, 23.3, 19.9, 15.2; HRMS (EI[+]) *m/z* calcd for $C_{21}H_{32}O_6$ (M[+]) 380.2199, found 380.2201.

### Phosphonate 42

To a solution of alcohol **41** (38 mg, 0.10 mmol) in $CH_2Cl_2$ at 0 °C was added triethylamine (0.08 mL, 0.58 mmol). Methanesulfonyl chloride (0.05 mL, 0.64 mmol) was added dropwise and the solution was stirred for 5.5 h. The reaction was quenched by addition of $H_2O$ and extracted with $CH_2Cl_2$. The combined organic layers were washed with $NH_4Cl$ (sat.) and brine, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil, which was then dissolved in acetone and treated with sodium iodide (79 mg, 0.53 mmol) for 15 h. After the solvent was removed *in vacuo*, the red oily residue was extracted with EtOAc. The organic layers were washed with $H_2O$, $NaHCO_3$ (sat.) and then $Na_2S_2O_3$ until the reddish color dissipated. The combined aqueous layers were extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to a yellow oil which was subsequently dissolved in $P(OEt)_3$ (0.08 mL, 0.47 mmol). This solution was heated for 7 h at 80 °C and then quenched by addition of $H_2O$ and extracted with EtOAc. The organic extracts were washed with $H_2O$ and brine, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow liquid. Final purification by flash column chromatography (20–100% EtOAc in hexanes) yielded

phosphonate **42** (31 mg, 62%) as a colorless oil: $[\alpha]^{26.4}_D = +20.0$ ($c$ 0.02, CHCl$_3$); $^1$H NMR (CDCl$_3$) δ 6.86 (s, 1H), 6.74 (s, 1H), 5.17 (d, $J = 6.3$ Hz, 1H), 5.13 (d, $J = 6.6$ Hz, 1H), 4.77 (d, $J = 6.9$ Hz, 1H), 4.64 (d, $J = 6.9$ Hz, 1H), 4.07–3.99 (m, 4H), 3.49 (s, 3H), 3.41 (s, 3H), 3.27 (dd, $J = 11.4, 4.2$ Hz, 1H), 3.03 (d, $J_{PH} = 21.3$ Hz, 2H), 2.69 (s, 1H), 2.66 (d, $J = 4.2$ Hz, 1H), 2.10–2.05 (m, 1H), 2.02–1.95 (m, 1H), 1.75–1.65 (m, 3H), 1.27 (t, $J = 6.9$ Hz, 6H), 1.22 (s, 3H), 1.07 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 145.9 (d, $J_{CP} = 3.2$ Hz), 143.1, 124.9 (d, $J_{CP} = 7.6$ Hz), 123.4 (d, $J_{CP} = 2.7$ Hz), 122.2 (d, $J_{CP} = 9.2$ Hz), 117.3 (d, $J_{CP} = 6.4$ Hz), 96.2, 96.0, 84.1, 77.4, 62.2 (d, $J_{CP} = 6.9$ Hz), 62.2 (d, $J_{CP} = 6.9$ Hz), 56.2, 55.8, 47.0, 38.3, 37.8, 33.0 (d, $J_{CP} = 138.1$ Hz), 27.5, 25.4, 23.2, 19.9, 16.5 (d, $J_{CP} = 6.2$ Hz), 16.5 (d, $J_{CP} = 6.2$ Hz), 15.2; $^{31}$P NMR δ 28.1; HRMS (EI$^+$) $m/z$ calcd for C$_{25}$H$_{41}$O$_8$P (M$^+$) 500.2541, found 500.2539.

### (2*R*,4a*R*,9a*R*)–Tetra(*O*-methoxymethyl)–3–deoxyschweinfurthin A (43)

To a suspension of NaH (56 mg, 1.40 mmol, 60% oil dispersion) and 15–crown–5 (0.01 mL, 0.05 mmol) in THF at 0 °C was added a solution of phosphonate **42** (31 mg, 0.06 mmol) and aldehyde **39** (39 mg, 0.11 mmol) in THF. After the reaction was allowed to warm to room temperature and stirred for 16 h, it was quenched by addition of H$_2$O and extracted with EtOAc. The organic extracts were washed with H$_2$O and brine, dried (MgSO$_4$), concentrated *in vacuo* to a yellow liquid, and purified by flash column chromatography (10–25% EtOAc in hexanes) to afford stilbene **43** (30 mg, 67%) as a colorless oil: $[\alpha]^{26.4}_D = +42.2$ ($c$ 0.02, CHCl$_3$); $^1$H NMR (CDCl$_3$) δ 7.12 (d, $J = 1.8$ Hz, 1H), 6.95 (d, $J = 1.5$ Hz, 1H), 6.94–6.90 (m, 3H), 6.86 (d, $J = 16.2$ Hz, 1H), 5.25–5.18 (m, 7H), 5.07 (t, $J = 6.9$ Hz, 1H), 4.78 (d, $J = 6.9$ Hz, 1H), 4.65 (d, $J = 6.6$ Hz, 1H), 3.54 (s, 3H), 3.50 (s, 6H), 3.41 (s, 3H), 3.41–3.37 (m, 2H), 3.28 (dd, $J = 11.4, 4.2$ Hz, 1H), 2.73 (s, 1H), 2.70 (d, $J = 4.2$ Hz, 1H), 2.15–1.95 (m, 7H), 1.78 (s, 3H), 1.75–1.70 (m, 2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.25 (s, 3H), 1.09 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 156.1 (2C), 146.3, 144.0, 136.8, 134.8, 131.4, 129.2, 128.2, 126.7, 124.5, 123.3, 122.7, 122.2, 119.6, 113.6, 106.1 (2C), 96.3, 96.0, 94.6 (2C), 84.2, 77.1, 56.4, 56.1 (2C), 55.8, 47.2, 40.0, 38.4, 37.8, 27.7, 26.9, 25.8, 25.4, 23.3, 22.8, 20.0, 17.8, 16.2, 15.3; HRMS (EI$^+$) $m/z$ calcd for C$_{42}$H$_{60}$O$_9$ (M$^+$) 708.4237, found 708.4231.

### (2*R*,4a*R*,9a*R*)–3–Deoxyschweinfurthin A (10)

To a solution of stilbene **43** (28 mg, 0.04 mmol) in MeOH was added TsOH (43 mg, 0.25 mmol) at room temperature and the solution was stirred for 136 h. The reaction was quenched by addition of NaHCO$_3$ (sat.) and extracted with EtOAc. The organic extracts were washed with H$_2$O and brine, dried (MgSO$_4$), and concentrated *in vacuo* to afford a yellow oil. Final purification by flash column chromatography (60:40 hexanes/EtOAc) afforded the desired target 3dSA (**10**, 11 mg, 52%) as a yellow oil: $[\alpha]^{26.4}_D = +48.5$ ($c$ 0.006, CD$_3$OD); with spectral data matching that reported above. Also isolated was a partially hydrolyzed analogue bearing an A-ring MOM ether (**44,** 7 mg, 33%) as a yellow oil: $^1$H NMR (CDCl$_3$) δ 6.92 (d, $J = 2.1$ Hz, 1H), 6.87 (d, $J = 16.8$ Hz, 1H), 6.75 (d, $J = 16.2$ Hz, 1H), 6.75–6.74 (m, 1H), 6.56 (s, 2H), 5.68 (br s, 2H), 5.49 (br s, 1H), 5.28 (t, $J = 6.6$ Hz, 1H), 5.06 (t, $J = 5.4$ Hz, 1H), 4.78 (d, $J = 6.6$ Hz, 1H), 4.65 (d, $J = 7.2$ Hz, 1H), 3.45–3.42 (m, 2H), 3.42 (s, 3H), 3.29 (dd, $J = 11.4, 3.6$ Hz, 1H), 2.73–2.66 (m, 2H), 2.13–1.96 (m, 5H), 1.82 (s, 3H), 1.78–1.70 (m, 4H), 1.68 (s, 3H), 1.59 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H),

0.90 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 155.5 (2C), 145.3, 139.1, 137.2, 132.2, 129.8, 128.5, 126.3, 123.9, 122.2, 121.7, 119.7, 113.0, 109.6, 106.2 (2C), 105.8, 96.3, 84.0, 78.0, 63.9, 55.8, 47.6, 39.9, 38.4, 37.7, 27.5, 26.5, 25.8, 25.3, 22.8, 20.3, 17.9, 16.3, 15.2; HRMS (EI$^+$) *m/z* calcd for C$_{20}$H$_{30}$O$_5$ (M$^+$) 350.2093, found 350.2095.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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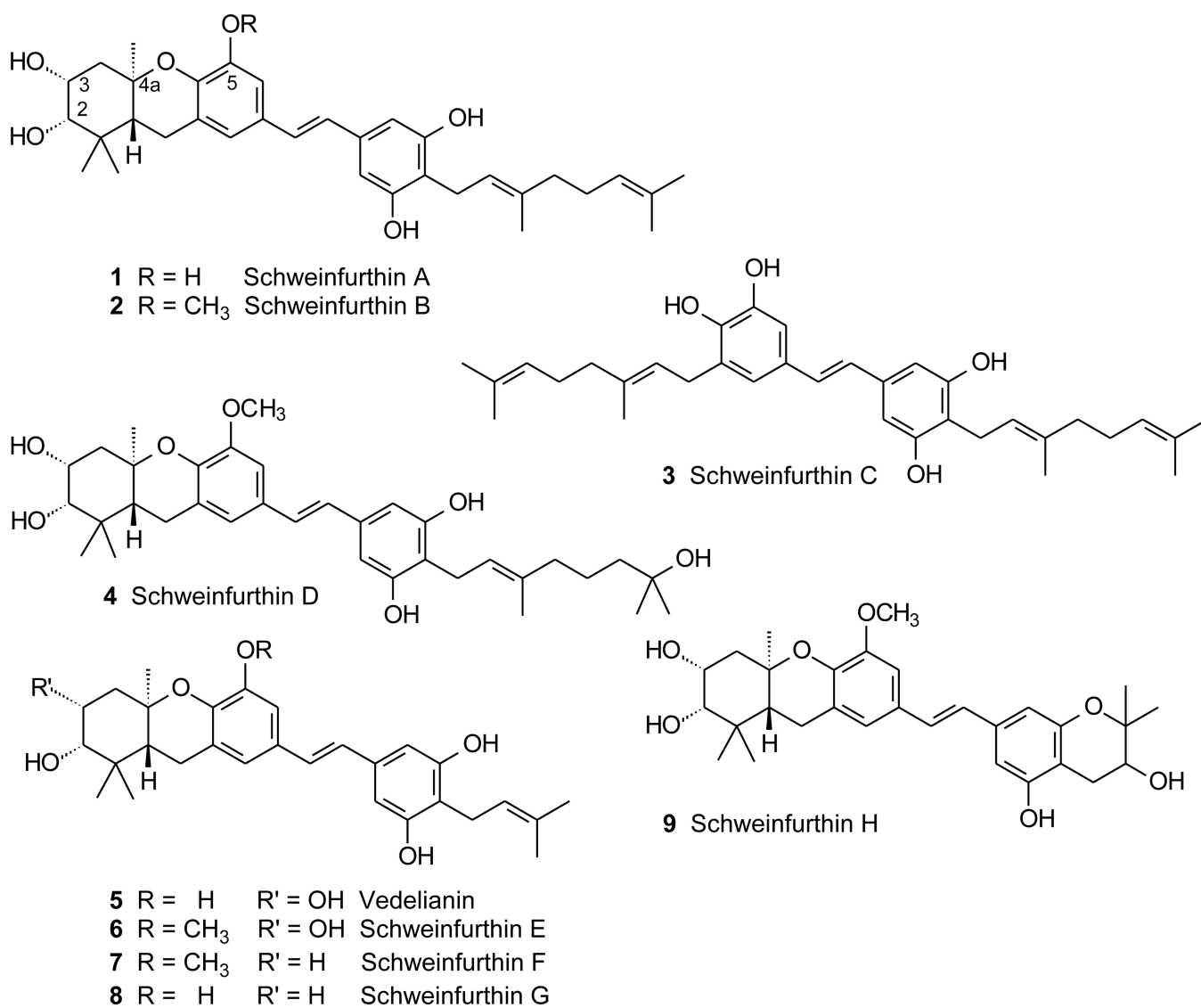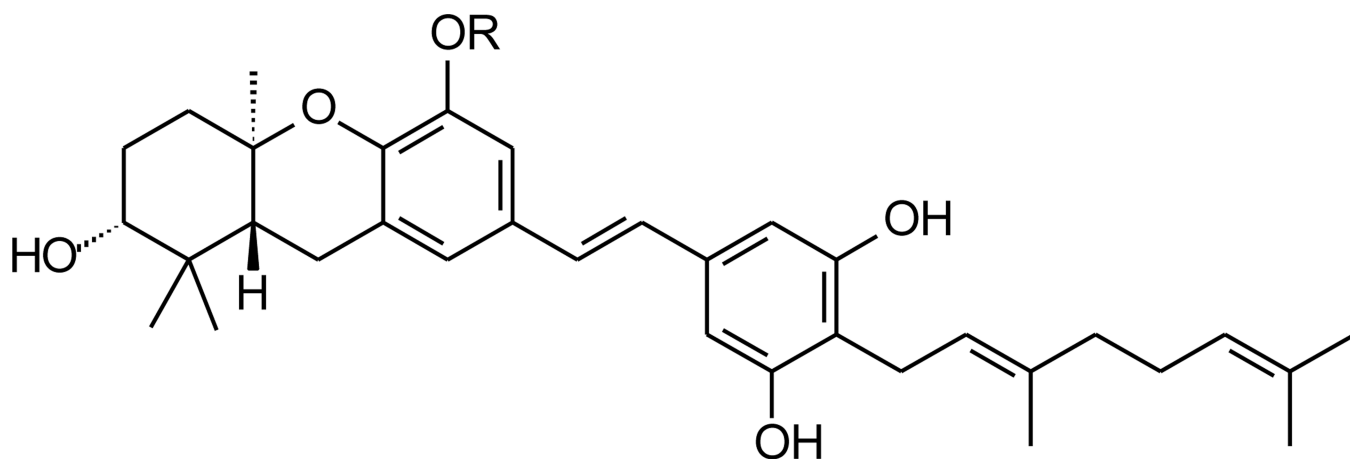
**Figure 1.**
Structures of the natural schweinfurthins and vedelianin.

**10** R = H     3-Deoxyschweinfurthin A
**11** R = CH₃  3-Deoxyschweinfurthin B
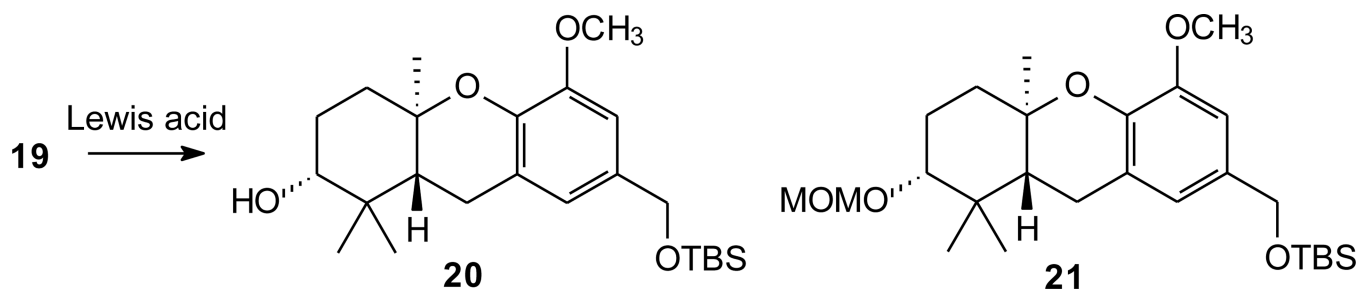
**Figure 2.**
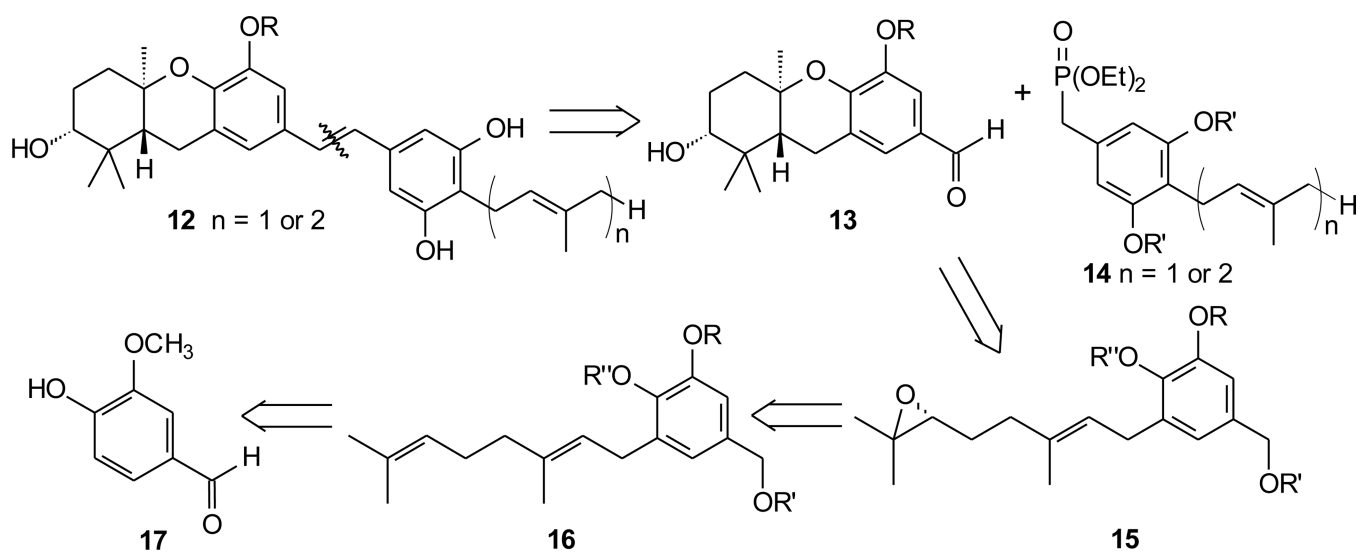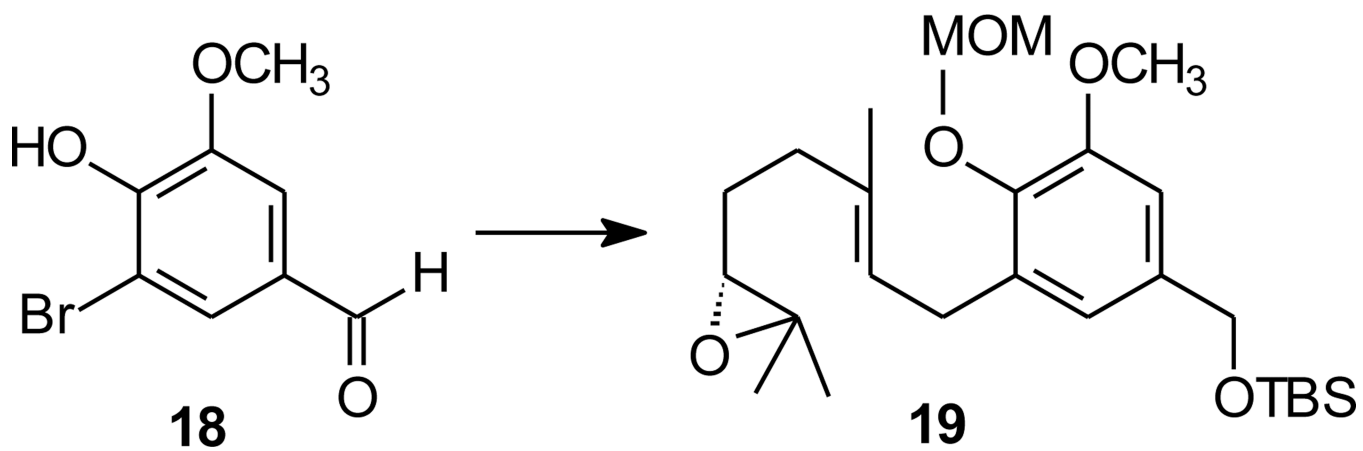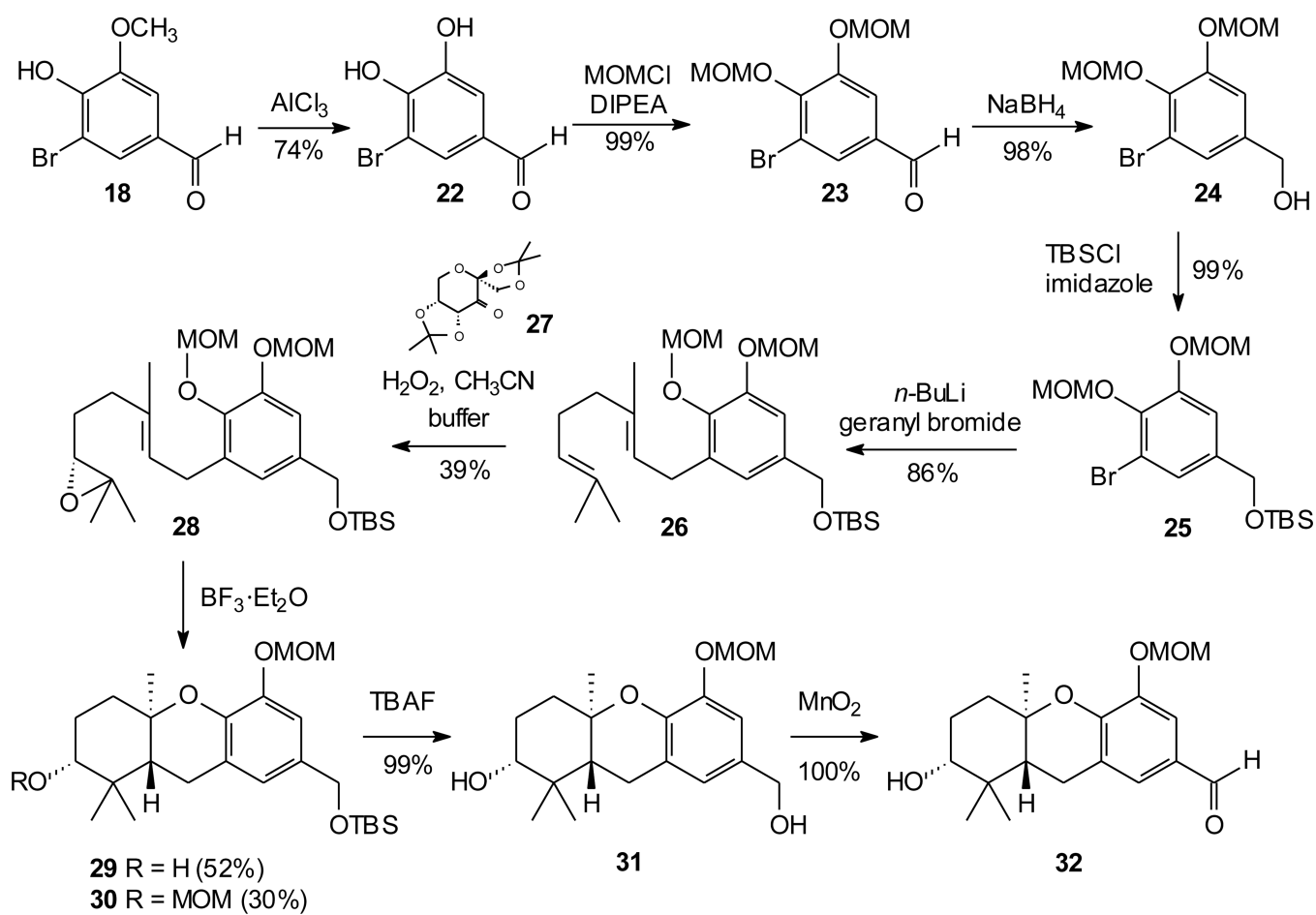Structures of schweinfurthin analogues.

**Figure 3.**
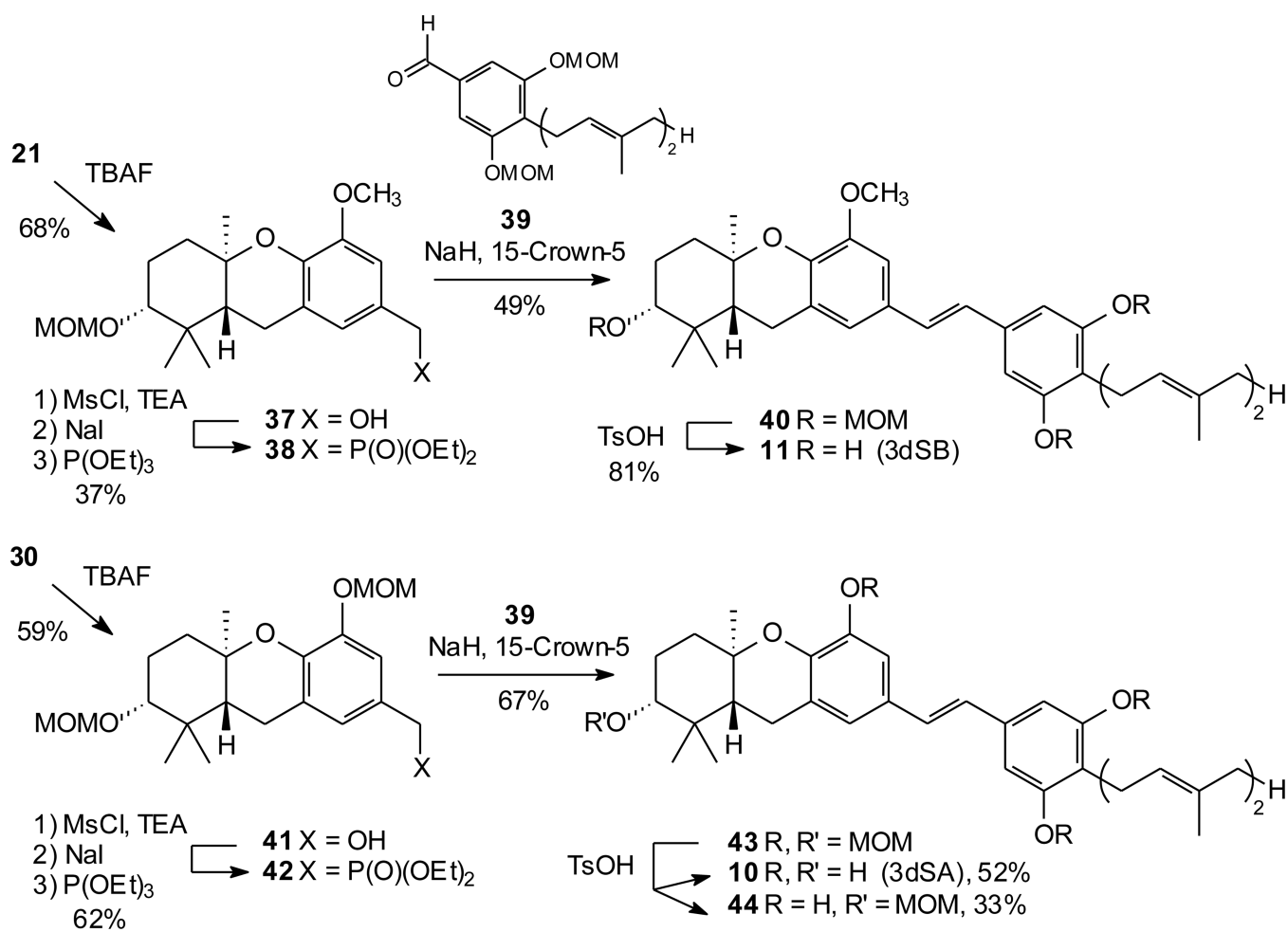Lewis acid mediated cyclization of epoxide **19**.

**Scheme 1.**
Retrosynthetic analysis of schweinfurthins.

**Scheme 2.**
Synthesis of an epoxide for preparation of schweinfurthin F.

**Scheme 3.**
Synthesis of a C-5 MOM ether and its BF$_3$·Et$_2$O mediated cyclization.

**Scheme 4.**
Synthesis of schweinfurthin G and 3dSA.

**Scheme 5.**
Synthesis of hexahydroxanthene phosphonates en route to stilbenes.

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**Table 1**

Attempted cyclizations of epoxide **19**.

| Trial # | Acid | Time (min.) | T (°C) | Distribution (by gc vs int std) | | |
|---|---|---|---|---|---|---|
| | | | | 19 | 20 | 21 |
| 1 | Ti(OiPr)$_4$ | 5 | −78 | 100 | 0 | 0 |
| 2 | Ti(OiPr)$_4$ | 5 | rt | 100 | 0 | 0 |
| 3 | Ti(OiPr)$_4$ | 1.5 | rt | 100 | 0 | 0 |
| 4 | TiCl$_4$ | 5 | −78 | 0 | 0 | 0 |
| 5 | SnCl$_4$ | 5 | −78 | 0 | 0 | 0 |
| 6 | CH$_3$AlCl$_2$ | 30 | −78 | 0 | 17[a] | 8[a] |
| 7 | In(OTf)$_3$ | 1 | rt | 0 | 65 | 0 |
| 8 | In(OTf)$_3$ | 5 | −78 | 55 | 29 | 0 |
| 9 | In(OTf)$_3$ | 5 | 0 | 0 | 60 | 2 |
| 10 | In(OTf)$_3$ | 8 | −35 | 14 | 36 | 3 |
| 11 | BF$_3$·Et$_2$O | 0.5 | −78 | 0 | 44 | 6 |
| 12 | BF$_3$·Et$_2$O | 1 | −78 | 0 | 64 | 11 |
| 13 | BF$_3$·Et$_2$O | 2 | −78 | 0 | 68[a] | 7[a] |
| 14 | BF$_3$·Et$_2$O | 4 | −78 | 0 | 49[a] | 11[a] |
| 15 | BF$_3$·Et$_2$O | 8 | −78 | 0 | 51 | 15 |

[a]Isolated yields following column chromatography.