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Exploration of Cascade Cyclizations Terminated By Tandem Aromatic Substitution: Total Synthesis of (+)-Schweinfurthin A

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Abstract

The termination of epoxide-initiated cascade cyclizations with a range of "protected" phenols is described. When the protecting group can be lost as a stabilized electrophile, the cascade process continues beyond ring closure to afford products which have undergone a tandem electrophilic aromatic substitution. A number of groups have proven viable in this process and the regiochemistry of their substitution reactions has been studied. Application of this methodology in the first total synthesis of (+)-schweinfurthin A, a potent anti-proliferative agent, has been achieved.

Keywords

cascade cyclization; tandem reaction; polyene cyclization; cascade reaction; schweinfurthin

Introduction

As the field of organic synthesis has evolved, the laboratory synthesis of ever more complex natural products has become feasible.[1–3] For such syntheses to be practical however, it is very helpful to assemble multiple bonds in a single transformation, and in this context catalytically driven tandem[4] or cascade reactions can be particularly appealing.[5–10] Epoxides have proven their utility as cascade components[6–9] and arguably one of the most powerful cascade classes is based upon epoxide initiated, cationic polyene cyclizations.[10–12] Although pioneering descriptions of such cascade cyclizations were set forth in the 1950's, [10–12] modern chemists continue to explore polyene cyclizations and recent studies have lead to many significant advances in novel modes of cascade initiation.[13–25] In contrast, very little has been done to extend cationic cascade cyclizations beyond terminal ring closure.

Our group has been interested in epoxide initiated cascade cyclizations as they pertain to the formation of hexahydroxanthenes and particularly as they apply to synthesis of the schweinfurthins.[26–31] Previous studies have shown that "MOM-protected" phenols are sufficiently nucleophilic to terminate a cascade sequence (e.g. conversion of epoxide **1** to hexahydroxanthene **2**, Scheme 1), and also have discovered that the MOM group could be transferred to the A-ring hydroxyl group during the cyclization (e.g. yielding compound **3**). [29] If transfer of the MOM group is the result of a transient electrophilic species, then one might envision other applications of this electrophile.[32] In an initial report on extension of this cascade process,[33] our lab demonstrated that a MOM group can be transferred to an adjacent aromatic ring with high efficiency. This represents a cationic cascade ultimately

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Supporting Information Available: Experimental details for all other compounds, and the ^{1}H and ^{13}C NMR spectra for compounds **15**–**21**, **23**–**27**, **29**–**51**, **59**–**75**, **77**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

terminated with a tandem electrophilic aromatic substitution reaction (e.g. cyclization of epoxide **4** to compound **5**). In this initial example, the reaction sequence continues beyond ring closure to electrophilic aromatic substitution, and a new carbon-carbon bond is the result. That tandem process allowed a highly efficient synthesis of (+)-angelichalcone.[33]

The genesis of the present work resides in the concept that a new tandem cascade sequence might be used in the synthesis of several schweinfurthins via a single late stage intermediate. This report describes: 1) issues of regioselectivity that arise during application of the MOM-based cascade cyclization/aromatic substitution process; 2) exploration of tandem cascade cyclization/aromatic substitution with other "protecting" groups; and 3) application of a new tandem cascade cyclization/aromatic substitution sequence to the formal synthesis of schweinfurthins B, E, F, and G, and the first total synthesis of (+)-schweinfurthin A.[29, 30, 34, 35]

Results and Discussion

Several schweinfurthins and numerous analogues have been prepared through synthesis,[27, 29, 30] but one of the most potent congeners[34, 35] of the natural family (schweinfurthin A, **9**) has remained elusive until now. As part of an ongoing program to determine their mode of action as antiproliferative agents,[36–38] we have attempted to optimize access to a key intermediate en route to schweinfurthin A. Previous work has utilized vanillin as an inexpensive, commercial starting material.[26, 27, 30] This reagent fits especially well into syntheses of schweinfurthin B, E, and F (**10**–**12**), where the methoxy group derived from vanillin remains on the C-5 position of the natural products, but for synthesis of schweinfurthin A or G (**9** and **13**) the use of this starting material would require demethylation early in the sequence. In an effort to develop a more versatile late-stage intermediate, a tantalizing synthetic proposal exploiting cascade cyclization terminated by electrophilic aromatic substitution[33] was envisioned to allow a diversity oriented synthesis (Scheme 2). This approach would be based upon a tandem cascade cyclization/aromatic substitution of the "MOM-protected" epoxide **6** to obtain the hexahydroxanthene **7** followed by elaboration of the benzylic position at C-5 to phenolic functionality via standard oxidation protocols. If an efficient route could be developed, the intermediate **8** would represent a single keystone intermediate which could be converted into both C-5 hydroxy- and methoxy-substituted schweinfurthins (Scheme 2) as well as new analogues.

To explore this possibility, methyl 4-hydroxybenzoate (**14**) was elaborated rapidly to the requisite *R* epoxide **15** by standard methods (Scheme 3).[39, 40] To our delight, when compound **15** was treated with $BF_3{\cdot}OEt_2$ under standard cyclization conditions, the major product obtained had undergone both cyclization and electrophilic aromatic substitution. Unfortunately, even though the hexahydroxanthene **16** was obtained in reasonable yield as a single stereo- and regioisomer, efforts directed at further elaboration met with limited success. While oxidation, hydrolysis, and substitution reactions demonstrated high regioselectivity, they uniformly favored the benzylic position para to the hexahydroxanthene oxygen, rather than the position ortho. Thus, for example, treatment of compound **16** with excess DDQ afforded the single aldehyde **17** in nearly quantitative yield.

In an effort to sway this natural selectivity through modification of steric or electronic factors, a more extended sequence was pursued. Reduction of aldehyde **17** and protection of the resulting alcohol was readily accomplished and allowed preparation of a variety of protected alcohols. Of those prepared, including the Boc derivative, the *p*-nitrobenzoate ester, the MOM acetal, and the TBS ether, only derivatives with acyl groups were found to allow preparation of the desired C-5 aldehyde. For example, after preparation of the Boc derivative **18** or the *p*-nitrobenzoate **19**, subsequent reaction with DDQ gave the desired

aldehydes **20** and **21** in ~75% yield. While this longer sequence allowed preparation of the desired aldehyde regioisomer, the incompatibility of carbonyl-containing substituents with the organolithium intermediate necessary for the synthesis of epoxide **15** rules out early introduction of these protecting groups. Given the inherent impracticality and non-ideality[41–43] of the oxidation/reduction and protection/deprotection sequences described above, it became prudent to explore alternative approaches. Based on the hypothesis that an *ortho*-selective differentiation of the benzylic positions could be accomplished if a group other than the MOM acetal were induced to undergo a cascade cyclization/electrophilic aromatic substitution, this process was examined with other phenolic substituents.

Exploration of Cascade Cyclizations Terminated with Aromatic Substitution

Because it contains unsubstituted ortho and para positions and because it is readily available,[33] 4-geranylresorcinol was used as the starting point to explore the viability of different phenolic substituents in cascade cyclization/aromatic substitution reactions. Numerous racemic epoxides bearing different groups at the phenolic oxygens (**22**–**27**) were prepared by standard methods and then treated with $BF_3{\cdot}OEt_2$ under typical cyclization conditions.[33] Because the electrophilic species generated from the previously employed MOM acetal would be stabilized by the adjacent heteroatom, other acetals of similar structures were explored first (Table 1). As one might predict, other common alkoxymethyl protecting groups undergo parallel cascade cyclization/aromatic substitution reactions. The BOM (**23**), SEM (**24**), and MEM (**25**) derivatives all favored formation of the substituted products **29a**–**31a** in yields comparable to that observed in the MOM case (**28a**).[33] All of these products were obtained as single diastereo- and regioisomers. Furthermore, when a competition reaction was conducted with a 1:1 mixture of compounds **23** and **24**, the major products were compounds **29a** and **30a**, both were found in yields comparable to those for the individual experiments, and no evidence for a crossed product was detected. The pivaloyloxymethyl (or POM) group, which features an acyloxy rather than an alkoxy substituent, was resistant to a complete cascade cyclization and the reaction of compound **26** instead gave the bridged ether **32c** as the only major product.[44–49] The surprising case in this series was the cyclization involving the 4-chlorophenoxymethyl group (**27**), which arose from commercially available α,4-dichloroanisole. This reaction provided compound **33b** as the major product and none of compound **33a** was isolated. Because all of the other substrates in Table 1 favored formation of either the a- or c-type products, this is unique among the groups surveyed. The use of secondary acetals was less productive under standard conditions,[40] and the modest mass balance reflected in the isolated yields for some of these cyclizations may result from formation of trace amounts of the b-type structure as well as any of several epoxide rearrangement pathways.[12, 31, 50]

Other common protecting groups also were explored, including the acetate (**34**), benzoate, and Boc protected compounds. In all of these cases however, the major products were the bridged A-ring ethers as shown for the acetate **35** (Figure 1).[40] This type of structure has been observed in several earlier studies and in some natural products.[44–49, 51, 52] A crystalline sample of the product **35** was subjected to X-ray diffraction analysis to assign the relative configuration unambiguously, and acetate **35** was found to have an exo (trans) structure. On this basis, the structures of the parallel products from cyclization of the benzoate and Boc derivatives were assigned analogous stereochemistry.[40,20, 53]

The tandem cascade cyclization/aromatic substitution process then was explored with various alkyl groups as the phenol substituents (**36**–**43**, Table 2). Not surprisingly, the methyl compound **36** gave bridged ether **44c** as the major product. The allyl derivative **37**, which would add stabilization to the presumed intermediate through π delocalization, proved more interesting. Exposure of the diallyl epoxide **37** to $BF_3{\cdot}OEt_2$ resulted in a mixture of

products, with the bridged ether **45c** predominating, and the cyclization/aromatic substitution product (**45a**) isolated as a minor component. This suggests that a group that could provide at least some stabilization to a formal cation is required for a tandem cascade cyclization/aromatic substitution process to occur.

To strengthen a hypothesis regarding the impact of the displaced electrophile's stability on the results of cascade cyclization/aromatic substitution reactions, several benzyl groups with varied substituents were examined. As one might expect, addition of withdrawing or donating groups to modify electron density at the benzylic position leads to stark differences in the product distribution (Table 2). With the parent system, benzyl ether **39**, standard reaction conditions afforded the product of the tandem process as the major product (**47a**), along with a significant amount of the cascade-only product **47b**. A trace of the *para*-substituted product **47d** was found in this reaction, which marks the first observation of electrophilic aromatic substitution at the para position during the cascade process. Addition of an electron-withdrawing 4-nitro substituent to the phenyl ring (**38**) resulted in an unusually complicated reaction mixture, and the bridged ether **46c** was the only significant product found. While reaction of the 2-bromophenyl derivative **40** gave a much less complicated reaction mixture, again only the bridged product (**48c**) was observed. In contrast, addition of an electron donating 4-methoxy substituent (**41**) resulted in cascade cyclization/aromatic substitution to afford the ortho product **49a**, but a significant amount of the para regioisomer **49d** also was observed. Further increasing the electron density of the aromatic system with the trimethoxybenzyl group (**42**) completely reversed the ortho regioselectivity, and only substitution at the para position was observed (**50d**) along with the cascade-only product (**50b**). Finally, the 3-furyl group was examined as a representative case of a heteroaryl system because it is found as a component of numerous natural terpenoids.[54–57] The furan derivative **43** was found to undergo cascade cyclization/aromatic substitution and afford compound **51a** as the major product. Thus it appears that a variety of neutral or electron rich arenes will afford a major product that has undergone cascade cyclization/aromatic substitution, but as the ability of the arene to stabilize a benzylic cation increases, less regioselectivity is observed. Ultimately, if there is minimal stabilization for a benzylic cation, the cascade process stops at the A-ring bridged ethers.

Based on the observations described above, at least a partial mechanistic picture of this process can be offered (Scheme 4). Initial complexation of BF_3 to the epoxide oxygen, generalized as structure **52**, could be followed by a cascade cyclization to the oxonium ion **53**.[58, 59] If loss of the primary alkyl group from the oxonium ion would afford an unstabilized carbocation (e.g. a methyl group), then the reaction may continue through the tertiary carbocation **54** instead. In this case, attack of the A-ring oxygen on the tertiary cation would explain formation of ether **55**. The bridged ether **55** would have the stereochemistry shown, as found in the diffraction analysis of compound **35**, because the C-6' stereochemistry is set in the original epoxide and the C-2' stereochemistry would be established through the chair-chair transition state[11, 12, 27] that leads to oxonium ion **53**. If oxonium ion **53** instead undergoes loss of a semi- or highly-stabilized carbocation, the adjacent arene may serve as a Lewis base and quickly trap this electrophile. This sequence would rapidly afford a π complex such as structure **56**. This branch of the reaction manifold would be consistent with the lack of cross-over products observed in earlier studies with isotopically labeled MOM groups,[33] as well as the fidelity observed in the competition experiment with compounds **23** and **24**. Rapid formation of an ipso complex would be expected for any relatively short-lived cationic species (e.g. allyl or BOM), which would lead to the proximal substitution product at C-2. In the case of longer-lived cationic species, partial diffusion would lead to formation of the distal ipso complex and subsequently substitution at C-6. Finally, in those cases where dissociation of the oxonium ion **53** gives

the longest lived cations (e.g. trimethoxybenzyl) a greater percentage of the unsubstituted hexahydroxanthene product would be more likely.

Taken together, these results indicate that the cascade cyclization/aromatic substitution is a general process for those cases where the phenolic substituent can form a reasonably stabilized carbocation. With a touch of reflection, it should be clear that this process is a powerful strategy: this tandem reaction sequence closed two rings, generated two additional stereogenic centers with complete control of the relative stereochemistry, and forged a new functionalized carbon-carbon bond in a single operation. In addition, this cascade sequence has proven its viability in forming new benzylic positions with a range of substituent groups. With this improved understanding of the scope of this process, application of a tandem cascade cyclization/aromatic substitution sequence to a schweinfurthin synthesis was reexamined.

Application to the Synthesis of Schweinfurthins A, B, E, F, and G

Application of the cascade cyclization/aromatic substitution strategy to the synthesis of key intermediates en route to schweinfurthins now could proceed as shown in Scheme 5. The expanded scope of the tandem reaction sequence was exploited to differentiate the newly generated benzylic position at C-5 from the original benzyl methyl ether at an early stage in the synthesis (*vide supra*). To accomplish this objective, a BOM acetal was chosen as the phenolic substituent, both because of its commercial availability and the assumption that the benzyl ether could be selectively cleaved by hydrogenolysis late in the synthesis. The synthetic sequence was initiated with bromination of 4-hydroxybenzoate (**58**) followed by BOM protection. Reduction of the intermediate ester and methylation all proceeded smoothly to afford arene **59** in high overall yield on a 50 gram scale. Halogen metal exchange, transmetalation, and addition of (*R*)-6,7-epoxygeranyl bromide (up to 93% ee)[28, 29] afforded epoxide **60** in excellent yield, again on a multi-gram scale. The crucial cascade cyclization/aromatic substitution proceeded smoothly to afford the desired tricycle **62** along with the unsubstituted analogue **61** (which had been obtained earlier from reaction of the corresponding MOM compound). Although compounds **61** and **62** were obtained as an inseparable mixture, each was a single regio- and diastereoisomer. Separation of these products was readily accomplished after selective hydrogenolysis, which afforded the benzylic alcohol **63** and recovered hexahydroxanthene **61**, provided the reaction was monitored frequently. With excessive hydrogen pressure or extended reaction duration, over reduction was observed.

Once alcohol **63** was in hand, installation of the requisite C-5 phenol proceeded smoothly (Scheme 5). Chemoselective oxidation of benzyl alcohol **63** to the corresponding aldehyde **64** was accomplished upon treatment with MnO_2. Subsequent Baeyer-Villiger oxidation[60] with *m*-CPBA and hydrolysis of the resultant formate provided phenol **65** in excellent yield. This reaction sequence extends cascade cyclization/aromatic substitution strategy to allow the introduction of the C-5 phenol central to the schweinfurthins. In fact, phenol **65** serves as the keystone divergent intermediate which intersects most of the previously synthesized schweinfurthins. Alkylation of phenol **65** with either methyl iodide or MOMCl proceeded with excellent selectivity to afford intermediates **66** and **67**, respectively. The synthesis of compound **66** constitutes a formal synthesis of schweinfurthins B, E, and F as well as most of the presently known schweinfurthin analogues.[27, 29, 30, 36, 38, 61–63] In a similar sense, preparation of compound **67** accomplishes a formal synthesis of schweinfurthin G.[29] More importantly, the ready availability of compound **67** has provided the means to pursue the synthesis of the parent compound in this family, (+)-schweinfurthin A.

With gram amounts of intermediate **67** now in hand, the total synthesis of (+)-schweinfurthin A was pursued (Scheme 6).[30] Intermediate **67** was oxidized with TPAP/NMO[64] to provide the new ketone **68**. Condensation of ketone **68** with benzaldehyde provided enone **69**, which was to be utilized as a latent carbonyl group.[65, 66] Reduction proceeded smoothly under Luche conditions[67] to afford alcohol **70** in excellent yield. The relative stereochemistry was assigned based on consideration of models and precedence,[30] and ultimately confirmed by comparison of the final product to natural material. Alcohol **70** was subjected to Upjohn dihydroxylation[68] to provide triol **71**. Subsequent glycolytic cleavage was accomplished in a separate step upon reaction with $NaIO_4$. This reaction was highly selective for cleavage of the exocyclic diol, and provided ketone **72** in very good yield. In comparison to the earlier synthesis of schweinfurthin B where attempted oxidation in the presence of a C-2 MOM group was too sluggish to be useful,[30] the C-2 hydroxyl group in this series greatly accelerated the desired oxidation. Diastereoselective reduction of ketone **72** provided diol **73**, where the C-2 stereochemistry could be assigned based on precedents[30, 69] and a straightforward analysis of the relevant coupling constants in the ^1H NMR spectrum. Treatment of benzyl ether **73** with DDQ provided aldehyde **74**, demonstrating once again the value of a benzyl methyl ether as a latent benzaldehyde.[30, 70, 71] Unfortunately, ensuing attempts at a direct HWE condensation of aldehyde **74** with phosphonate **76** proved troublesome. To circumvent this problem, the A-ring diol of aldehyde **74** was protected by treatment with excess MOMCl and base to afford aldehyde **75**. Subsequent attempts at the HWE condensation of aldehyde **75** with phosphonate **76**[72, 73] in the presence of KHMDS afforded stilbene **77** in moderate yield. Global hydrolysis of the MOM acetals provided schweinfurthin A in an acceptable yield. In direct NMR analyses, synthetic (+)-schweinfurthin A proved identical to an authentic sample of the natural material and displayed a specific rotation of the same sign and magnitude as that reported for the natural product ($[\alpha]25_D$ = +47 (c 1.0, EtOH) from epoxide of 90% ee; lit ($[\alpha]25_D$ = +51.8 (c 2.0, EtOH).[35] Therefore, the natural antipode of schweinfurthin A now can be assigned as (+)-(2*S*, 3*R*, 4a*R*, 9aR)-schweinfurthin A.

Conclusions

In conclusion, the scope of cascade cyclizations terminated by electrophilic aromatic substitution has been expanded to include an array of substituents that ultimately become incorporated on the arene. This tandem process appears to be general as long as the original protecting group affords an electrophile that can be viewed as a stabilized cation. The diether **16** was found to undergo a highly regioselective para oxidation upon treatment with DDQ, but migration of other stabilized motifs has allowed rapid generation of complex polycycles that lead to the ortho oxidized products. To demonstrate the potential of this approach, a cascade cyclization/aromatic substitution strategy has been used to provide a late stage schweinfurthin intermediate that represents a formal synthesis of four natural products. Furthermore, this intermediate has been elaborated to complete the first synthesis of natural (+)-schweinfurthin A, which makes the rare natural product available by synthesis. Efforts to exploit the utility of this reaction manifold in other natural product syntheses are in progress and will be reported in due course.[74–76]

Experimental Section

Epoxide 15

To a solution of the corresponding olefin[40] (6.2 g, 19 mmol) and Shi's catalyst (1.4 g, 5.0 mmol) in aq buffer (80 mL, 2 M K_2CO_3 and 4 mM EDTA) and organic phase (100 mL, 1:1:1 CH_2Cl_2/MeCN/EtOH) at 0 °C was added hydrogen peroxide (7 mL, 30%) via syringe pump over 20 h. The reaction was then quenched by addition of aq Na_2SO_3. The resulting solution was extracted with ethyl acetate, and the organic phase was washed with brine.

After the organic phase was dried ($MgSO_4$), and concentrated *in vacuo*, final purification by column chromatography (20% ethyl acetate in hexanes) afforded recovered starting material (2.8 g, 44%) and epoxide **15** (2.9 g, 44%, ee ranged from 88% – 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.11 – 7.08 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.35 (m, 1H), 5.19 (s, 2H), 4.35 (s, 2H), 3.45 (s, 3H), 3.34 (s, 3H), 3.35 (m, 2H), 2.69 (t, *J* = 6.4 Hz, 1H), 2.19 – 2.11 (m, 2H), 1.73 (s, 3H), 1.68 – 1.60 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.4, 134.8, 131.1, 130.4, 129.3, 126.6, 123.0, 113.6, 94.2, 74.3, 64.0, 58.2, 57.8, 55.8, 36.3, 28.5, 27.3, 24.7, 18.6, 16.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_4$ (M^+) 334.2144, found 334.2135.

Ether 16

To a solution of epoxide **15** (1.15 g, 3.4 mmol) in CH_2Cl_2 (350 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (2.2 mL, 20 mmol). After 9 min, the reaction was quenched by addition of excess Et_3N (5 mL). The resulting solution was concentrated *in vacuo* and the resulting oil was dissolved in ethyl acetate which was washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (30% ethyl acetate in hexanes) afforded the cyclized product without a C-5 substituent[40] (229 mg, 23%) along with ether **16** (620 mg, 54%) as a yellow oil: $[\alpha]25_D$ = +39 (c 0.9, $CHCl_3$, 82% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.97 (s, 1H), 4.40 (s, 2H), 4.30 (s, 2H), 3.38 (s, 3H), 3.34 (s, 3H), 3.09 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.85 (br, 1H), 2.66 – 2.62 (m, 2H), 1.93 – 1.89 (m, 1H), 1.72 – 1.52 (m, 4H), 1.13 (s, 3H), 0.97 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.0, 128.7, 128.5, 126.3, 125.7, 121.2, 77.1, 76.2, 74.5, 68.9, 58.1, 57.7, 46.5, 37.9, 37.5, 27.9, 27.0, 22.8, 19.8, 14.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_4$ (M^+) 334.2144, found 334.2134.

Aldehyde 17

To a solution of benzyl ether **16** (400 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) and water (1.0 mL) at rt was added DDQ (308 mg, 1.4 mmol). After 2 hr, the reaction was quenched by addition of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* afforded aldehyde **17** as orange oil which was advanced to the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.56 (d, *J* = 1.2 Hz, 1H), 4.46 (s, 2H), 3.41 (s, 3H), 3.40 (m, 1H), 2.76 – 2.71 (m, 2H), 2.25 (br, 1H), 2.01 (ddd, *J* = 12.4, 3.6, 3.6 Hz, 1H), 1.84 (dq, *J* = 12.8, 3.6 Hz, 1H), 1.73 (dd, *J* = 13.0, 3.8 Hz, 1H), 1.65 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.59 (m, 1H), 1.19 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.3, 156.1, 130.7, 128.5, 128.4, 127.0, 122.1, 78.0, 77.5, 68.7, 58.5, 46.3, 38.3, 37.4, 27.9, 27.1, 22.8, 20.2, 14.2; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1813.

Boc Carbonate 18

To a solution of the parent alcohol[40] (179 mg, 0.56 mmol) in THF in an ice bath, was added NaH (190 mg, 60% in oil, 4.8 mmol) followed by Boc_2O (153 mg, 0.70 mmol). After 12 hr, the reaction was quenched by addition of water, the resulting solution was extracted with ethyl acetate, and the organic phases were washed with brine. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (40% ethyl acetate in hexanes) afforded Boc carbonate **18** (102 mg, 43%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.17 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 1.6 Hz, 1H), 4.97 (s, 2H), 4.39 (s, 2H), 3.39 (s, 3H), 3.39 – 3.33 (m, 1H), 2.69 – 2.65 (m, 2H), 2.09 (br, 1H), 1.96 (dt, *J* = 12.8, 3.4 Hz, 1H), 1.81 (dq, *J* = 8.8, 3.6 Hz, 1H), 1.72 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.63 (dd, *J* = 12.0, 6.4 Hz, 1H), 1.58 – 1.50 (m, 1H), 1.46 (s, 9H), 1.15 (s, 3H), 1.04 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.4, 153.4, 150.7, 129.4, 127.0, 126.2, 121.6, 81.9, 77.7, 76.4, 69.0, 68.8, 58.3, 46.5, 38.2, 37.6, 28.0, 27.7 (3C), 27.2, 22.9, 19.9, 14.1; HRMS (EI) *m/z* calcd for $C_{24}H_{36}O_6$ (M^+) 420.2512, found 420.2507.

p-Nitrobenzoate 19

To a solution of the parent alcohol[40] (222 mg, 0.69 mmol) in THF (10 mL) at rt was added 4-nitrobenzoyl chloride (160 mg, 0.86 mmol) followed by py (0.12 mL, 1.5 mmol). After 3.5 hr, the reaction was quenched by addition of water and the resulting mixture was extracted with ethyl acetate. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (30% to 50% ethyl acetate in hexanes) afforded ester **19** (209 mg, 64%) as colorless oil: $[\alpha]25_D$ = +41 (c 0.6, $CHCl_3$, 82% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 8.20 – 8.05 (m, 4 H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 5.20 (s, 2H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 12.4 Hz, 1H), 3.34 (s, 3H), 3.30 – 3.27 (m, 1H), 2.65 – 2.62 (m, 2H), 1.94 – 1.91 (m, 1H), 1.78 – 1.50 (m, 4H), 1.11 (s, 3H), 1.02 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 152.0, 151.5, 136.5, 131.6 (2C), 130.8, 128.2, 127.4, 127.1, 124.3 (2C), 123.0, 78.3, 77.7, 70.0, 68.6, 58.7, 47.7, 39.2, 38.7, 28.7, 27.8, 23.9, 20.4, 14.8; HRMS (EI) *m/z* calcd for $C_{26}H_{31}NO_7$ (M^+) 469.2101, found 469.2096.

Aldehyde 20

To a solution of carbonate **18** (95 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) and water (0.5 mL) at rt was added DDQ (110 mg, 0.48 mmol). After 2 hr, the reaction was quenched by addition of $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford aldehyde **20** (71 mg, 78%) as an orange oil: $[\alpha]25_D$ = +42 (c 0.7, $CHCl_3$, 82% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 4.98 (s, 2H,), 3.44 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.75 – 2.71 (m, 2H), 2.07 – 2.04 (m, 1H), 1.48 (s, 9H), 1.25 (s, 3H), 1.07 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.8, 156.2, 153.3, 136.3, 126.8, 126.3, 124.2, 123.8, 82.4, 80.0, 77.7, 68.0, 46.3, 38.3, 37.4, 28.1, 27.7 (3C), 27.2, 22.8, 20.1, 14.2; HRMS (EI) *m/z* calcd for $C_{23}H_{32}O_6$ (M^+) 404.2199, found 404.2192.

Aldehyde 21

According to the procedure described above, compound **19** was treated with DDQ followed by standard work up. Concentration of the resulting solution afforded aldehyde **21** (140 mg, 71%) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.24 (d, *J* = 8.6 Hz, 2H), 8.18 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 5.28 (s, 2H), 3.42 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.77 – 2.74 (m, 2H), 2.05 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.04 (br, 1H), 1.89 (dq, *J* = 12.8, 3.2 Hz, 1H), 1.78 (dd, *J* = 13.2, 3.6 Hz, 1H), 1.70 (dd, *J* = 11.6 Hz, 6.4 Hz, 1H), 1.64 – 1.60 (m, 1H), 1.23 (s, 3H), 1.10 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.7, 164.4, 156.3, 150.4, 136.4, 135.3, 130.7 (2C), 126.4, 126.4, 124.2, 124.0, 123.4 (2C), 78.1, 77.5, 66.9, 46.2, 38.3, 37.4, 28.0, 27.1, 22.8, 20.1, 14.2; HRMS (EI) *m/z* calcd for $C_{25}H_{27}NO_7$ (M^+) 453.1788, found 453.1782.

BOM Epoxide 23

To the parent geranyl arene[40] (411 mg, 0.88 mmol) in CH_2Cl_2 (15 mL) at −20 °C was added *m*-CPBA (200 mg, 0.89 mmol) slowly. The reaction was allowed to stir for 1 hour and then quenched by addition of Na_2SO_3 (sat.) and extracted with CH_2Cl_2. The organic extracts were washed with 0.5 M NaOH, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (4% to 5% ethyl acetate in hexanes) afforded the external epoxide **23** (131 mg, 31%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.33 – 7.27 (m, 10H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.36 (t, *J* = 7.3 Hz, 1H), 5.29 (s, 2H), 5.24 (s, 2H), 4.72 (s, 2H), 4.71 (s, 2H), 3.32 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.22 – 2.12 (m, 2H), 1.74 (s, 3H), 1.74 – 1.61 (m, 2H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.5, 155.5, 137.2, 137.2, 134.7, 129.7, 128.4 (2C), 128.4 (2C), 127.9 (2C), 127.9 (2C), 127.8, 127.7, 123.9, 123.3, 108.8,

103.5, 92.4, 92.2, 69.9, 69.7, 64.2, 58.4, 36.3, 27.9, 27.3, 24.8, 18.7, 16.1; HRMS (EI) *m/z* calcd for $C_{32}H_{38}O_5$ (M^+) 502.2719; found 502.2716.

Benzyl Ether 29a

To epoxide **23** (121 mg, 0.24 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.15 mL, 1.19 mmol). After 8 minutes the reaction was quenched by addition of Et_3N, diluted with water, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (30% ethyl acetate in hexanes) afforded ether **29a** (75 mg, 62%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.39 – 7.21 (m, 10H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.28 (s, 2H), 4.70 (s, 2H), 4.65 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 9.9 Hz, 1H), 4.58 (s, 2H), 3.41 (dd, *J* = 11.5, 4.1 Hz, 1H), 2.67 – 2.64 (m, 2H), 2.04 – 1.97 (m, 1H), 1.85 – 1.75 (m, 2H), 1.70 – 1.56 (m, 3H), 1.20 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.4, 152.6, 139.3, 137.4, 129.8, 128.4 (2C), 128.1 (2C), 127.9 (2C), 127.7, 127.2 (2C), 127.2, 115.6, 115.0, 106.6, 92.7, 78.1, 76.4, 72.0, 69.9, 60.8, 46.7, 38.3, 37.7, 28.2, 27.3, 22.7, 20.0, 14.2; HRMS (EI) *m/z* calcd for $C_{32}H_{38}O_5$ (M^+) 502.2719; found 502.2721.

Competition experiment

To a solution of epoxide **23** (77 mg, 0.15 mmol) and epoxide **24** (85 mg, 0.16 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.20 mL, 1.6 mmol). After 10 min, the reaction was quenched by addition of Et_3N (0.4 mL), allowed to warm to rt, and then extracted with CH_2Cl_2. The organic extracts were washed with water, dried ($MgSO_4$), and filtered, and then the filtrate was concentrated *in vacuo*. Final purification by flash column chromatography (7.5% to 20% ethyl acetate in hexanes) afforded compound **29a** as a colorless oil (52 mg, 68%) and compound **30a** (58 mg, 68%) as a colorless oil.

Epoxide 34

To a solution of the geranyl arene[40] (304 mg, 0.92 mmol) in CH_2Cl_2 (40 mL) at −30 °C was added *m*-CPBA (228 mg, 77% maximum by mass, 1.0 mmol). After 1 h the reaction was quenched by addition of $NaHCO_3$ and the resulting solution was extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (8% to 25% ethyl acetate in hexanes) afforded epoxide **34** (226 mg, 71%) as colorless oil: ^{1}H NMR ($CDCl_3$) 7.17 (d, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 5.24 (td, *J* = 7.2, 1.2 Hz, 1H), 3.20 (d, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 6.2 Hz, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.20 – 2.09 (m, 2H), 1.68 (s, 3H), 1.65 – 1.59 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1, 169.9, 150.2, 150.0, 137.2, 131.8, 131.2, 122.9, 120.2, 117.0, 65.0, 59.3, 37.4, 29.3, 28.4, 25.9, 22.1, 21.8, 19.8, 17.2: HRMS (EI) *m/z* calcd for $C_{20}H_{26}O_5$ (M^+) 346.1780, found 346.1772.

Bridged Ether 35

To a solution of epoxide **34** (95 mg, 0.27 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.18 mL, 1.4 mmol). After 7 min the reaction was quenched by addition of Et_3N (0.35 mL, 2.5 mmol) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with water, 1N HCl, and brine. The organic phase was then dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (20% to 50% ethyl acetate in hexanes) afforded tricyclic ether **35** (44 mg, 46%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (d, *J* = 8.4 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 3.68 (d, *J* = 5.2 Hz, 1H), 2.45 (d, *J* = 7.6 Hz, 2H), 2.23 (s, 3H), 2.18 (s, 3H), 1.88 – 1.84 (m, 1H), 1.81 (t, *J* = 7.6 Hz, 1H), 1.66 – 1.59 (m, 1H), 1.51 – 1.45 (m, 1H), 1.39 (dd, *J* = 12.2, 4.8 Hz, 1H), 1.20 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.6,

148.8, 148.7, 131.0, 129.7, 118.6, 115.9, 86.6, 86.0, 54.2, 45.4, 38.8, 26.8, 25.8, 25.8, 23.6, 21.0, 20.8, 19.0; HRMS (EI) *m/z* calcd for $C_{20}H_{26}O_5$ (M^+) 346.1780, found 346.1790.

Methyl Ether 59

To a solution of the parent alcohol[40] (ca. 210 mmol from above) in THF (250 mL) cooled to 0 °C was added NaH (18 g, 60% in oil, 600 mmol) in small portions. After evolution of hydrogen ceased (ca. 10 min), CH_3I (17 mL, 272 mmol) was added slowly. After an additional 5 hr, the reaction was slowly quenched by addition of water. The resulting solution was extracted with ethyl acetate. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (25% ethyl acetate in hexanes) afforded compound **59** (51 g, 73% over 4 steps) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.38 – 7.37 (m, 5H), 7.24 – 7.23 (m, 2H), 5.37 (s, 2H), 4.79 (s, 2H), 4.39 (s, 2H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.95, 136.7, 133.1, 132.5, 128.2, (2C), 127.8 (2C), 127.7, 127.7, 115.7, 112.5, 92.6, 73.1, 70.0, 57.7; HRMS (EI) *m/z* calcd for $C_{16}H_{17}O_3Br$ (M^+) 336.0361, found 336.0362.

Epoxide 60

To a solution of TMEDA (3 mL, 20 mmol) in ether (40 mL) cooled in a brine bath was added BuLi (7.5 mL, 2.3 M in hexanes, 17.3 mmol). After 5 min, bromide **59** (4.86 g, 14.4 mmol) was added in ether (20 mL) via canula. After an additional 15 min, CuI (3.0 g, 16 mmol) was added as a solid in one portion, resulting in a slow blackening of the solution. After an additional 15 min at the same temperature, freshly prepared (*R*)-6,7-epoxy geranyl bromide, prepared from the corresponding alcohol (3.74g, 22 mmol, 93% ee), was added via canula as a solution in ether (5 mL). The reaction was allowed to warm slowly to rt and then was quenched by addition of NH_4Cl after an additional 4 h. The resulting mixture was extracted with ethyl acetate, and the organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (18% ethyl acetate in hexanes) afforded epoxide **60** (4.2 g, 71%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.31 – 7.22 (m, 5H), 7.13 (s, 1H), 7.09 (m, 2H), 5.38 (t, *J* = 7.2 Hz, 1H), 5.26 (s, 2H), 4.67 (s, 2H), 4.33 (s, 2H), 3.37 (d, *J* = 7.2 Hz, 2H), 3.32 (s, 3H), 2.66 (t, *J* = 6.2 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.74 (s, 3H), 1.67 – 1.60 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.3, 137.0, 134.6, 131.0, 130.1, 129.0, 128.1 (2C), 127.6 (2C), 127.4, 126.4, 122.9, 113.5, 92.0, 74.1, 69.6, 63.6, 57.8, 57.5, 36.1, 28.4, 27.1, 24.5, 18.4, 15.8; HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_4$ (M^+) 410.2457, found 410.2462.

Hexahydroxanthene 62

To a solution of epoxide **60** (774 mg, 1.89 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (1.0 mL, 8.0 mmol). After 8 min, the reaction was quenched by addition of Et_3N (2 mL), allowed to warm to rt, and concentrated *in vacuo*. Purification of the initial oil by column chromatography (30% ethyl acetate in hexanes) afforded compounds **61** and **62** as an inseparable mixture (520 mg, 1:2 **61: 62** corresponding to compound **62** (384 mg, 50%) and compound **61** (136 mg, 25%)) as a colorless oil: For compound **62**, HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_4$ (M^+) 410.2457, found 410.2450.

Benzyl Alcohol 63

A mixture of compound **61** and compound **62** (185 mg, 2:1 **62** to **61**) was dissolved in CH_3OH (0.5 mL) and 10% Pd/C (30 mg) was added. The reaction vessel was sealed and purged with H_2 at rt. A stream of H_2 then was provided to maintain 1 atm of H_2, which resulted in the slow concentration of the solution to near dryness. After 23 hr, the resulting mixture was diluted with CH_3OH, filtered through celite, and concentrated *in vacuo*. Final purification by column chromatography (50% ethyl acetate in hexanes) afforded alcohol **63**

(81 mg, 76%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.03 (m, 2H), 4.63 (d, *J* = 12.8 Hz, 1H), 4.57 (d, *J* = 12.8, 1H), 4.34 (s, 2H), 3.41 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.37 (s, 3H), 2.73 – 2.68 (m, 2H), 2.02 (dt, *J* = 12.8, 3.4 Hz, 1H), 1.88 – 1.60 (m, 4 H), 1.22 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ150.7, 129.4, 129.0, 128.5, 126.4, 121.8, 77.9, 74.5, 62.4, 58.0, 46.8, 38.4, 37.8, 28.2, 27.3, 22.9, 20.1, 14.2; ^{13}C NMR (MeOD) δ 151.3, 130.1, 130.0, 129.8, 126.8, 122.8, 78.8, 77.7, 75.8, 60.3, 57.9, 39.4, 39.0, 29.0, 27.9, 24.0, 20.3, 14.8; HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1990.

Aldehyde 64

To a solution of alcohol **63** (13 mg, 0.04 mmol) in CH_2Cl_2 at rt was added activated MnO_2 (95 mg, 0.87 mmol). After 20 h at rt, the solution was diluted with ethyl acetate, filtered through celite, and concentrated *in vacuo* which afforded aldehyde **64** (13 mg, 96%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 2H), 3.42 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.37 (s, 3H), 2.76 – 2.73 (m, 2H), 2.05 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.90 – 1.60 (m, 5H), 1.26 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.0, 155.8, 135.7, 129.5, 125.6, 125.1, 123.7, 77.8, 77.8, 74.0, 58.1, 46.4, 38.4, 37.5, 28.2, 27.2, 22.9, 20.1, 14.2; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1839.

Phenol 65

To a solution of aldehyde **64** (18 mg, 0.056 mmol) in CH_2Cl_2 (2 mL) was added *m*-CPBA (35 mg, 77% maximum, 0.14 mmol) at rt. After 2 hr, the reaction was diluted with CH_3OH (3mL) and solid K_2CO_3 (65 mg, 0.47 mmol) was added. After an additional 20 hr, the reaction was quenched by addition of 1N HCl and Na_2SO_3. The resulting mixture was neutralized by addition of $NaHCO_3$ and extracted with CH_2Cl_2. After the organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, final purification by column chromatography (30% to 50% ethyl acetate in hexanes) afforded phenol **65** (17 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.73 (d, *J* = 1.6 Hz, 1H), 6.63 (d, *J* = 1.6, 1H), 5.46 (s, 1H), 4.31 (s, 2H), 3.40 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.36 (s, 3H), 2.71 – 2.66 (m, 2H), 2.01 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.89 – 1.59 (m, 5H), 1.22 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.0, 139.6, 130.0, 121.9, 120.1, 112.0, 77.9, 77.7, 74.7, 57.9, 47.2, 38.4, 37.7, 28.2, 27.3, 22.7, 20.1, 14.3; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_4$ (M^+) 306.1831, found 306.1837.

Schweinfurthin B intermediate 66

To a solution of phenol **65** (9 mg, 0.03 mmol) in acetone (2 mL) was added K_2CO_3 (60 mg, 0.43 mmol) followed by CH_3I (0.06 mL, 0.96 mmol) and this solution was heated to reflux. After 2 hrs, the solution was allowed to cool to rt, quenched by addition of water and extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford compound **66** (9 mg, 94%) as a colorless oil in sufficient purity for further use. The ^{1}H MNR spectrum of this material was identical to that prepared via different methods.[30]

Schweinfurthin G intermediate 67

To a solution of phenol **65** (13 mg, 0.04 mmol) in CH_2Cl_2 (2mL), was added DIPEA (0.1 mL, 0.57 mmol) followed by MOMCl (0.02 mL, 0.26 mmol). After 2 h at rt, the reaction was quenched by addition of water and extracted with CH_2Cl_2. The resulting solution was washed with 1N HCl. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo* to afford compound **67** (13 mg, 89%) as a yellow oil. The ^{1}H NMR spectrum of this material was identical to that prepared via different methods;[29] $[\alpha]25_D$ = +34 (c 1.6, $CHCl_3$, 90% ee by HPLC).

Ketone 68

To a solution of hexahydroxanthene **67** (680 mg, 1.9 mmol) in CH_2Cl_2 at rt was added catalytic TPAP (73 mg, 0.21 mmol) and NMO (284 mg, 2.4 mmol). After 26 hr, the reaction mixture was diluted with ethyl acetate, filtered through celite and silica, and concentrated *in vacuo*. Final purification by column chromatography (50% ethyl acetate in hexanes) afforded ketone **68** (675 mg, 100%) as a colorless oil: $[\alpha]25_D$ = +88 (c 1.1, $CHCl_3$, 90% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 1H), 6.66 (s, 1H), 5.04 (d, *J* = 6.4 Hz, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.18 (s, 2H), 3.36 (s, 3H), 3.22 (s, 3H), 2.73 – 2.65 (m, 1H), 2.60 – 2.52 (m, 2H), 2.33 – 2.28 (m, 1H), 2.22 – 2.17 (m, 1H), 2.01 – 1.90 (m, 2H), 1.29 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 212.5, 145.3, 142.7, 129.2, 122.4, 121.5, 115.2, 95.2, 74.9, 73.8, 57.3, 55.5, 46.9, 45.8, 37.5, 34.5, 23.9, 23.1, 20.2, 18.5; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_5$ (M^+) 348.1937, found 348.1940.

Enone 69

To a solution of ketone **68** (140 mg, 0.40 mmol) in ethanol at rt was added benzaldehyde (0.2 mL, 1.7 mmol) followed by KOH (177 mg, 3.2 mmol). After 25 min, the reaction was quenched by addition of NH_4Cl, the resulting solution was extracted with ethyl acetate, and the organic extracts were washed with brine. After the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, final purification of the residue by column chromatography (25% ethyl acetate in hexanes) afforded enone **69** (148 mg, 86%) as a colorless oil: $[\alpha]25_D$ = +157 (c 1.0, CH_3OH, 90% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.32 (m, 5H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 4.32 (s, 2H), 3.49 (s, 3H), 3.50 – 3.40 (m, 1H), 3.36 (s, 3H), 2.98 (dd, *J* = 15.2, 2.8 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.34 (dd, *J* = 12.6, 5.6, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.0, 145.5, 142.8, 138.6, 135.0, 132.2, 130.0 (2C), 129.5, 128.7, 128.3 (2C), 122.6, 121.8, 115.4, 95.6, 75.4, 74.3, 57.8, 56.0, 45.7, 45.3, 41.7, 28.6, 24.2, 22.1, 19.1; HRMS (EI) *m/z* calcd for $C_{27}H_{32}O_5$ (M^+) 436.2250, found 436.2257.

Alcohol 70

To a solution of ketone **69** (115 mg, 0.26 mmol) in CH_3OH at rt was added $CeCl_3{\cdot}7H_2O$ (108 mg, 0.27 mmol) followed by $NaBH_4$ (12 mg, 0.32 mmol). After 2 hr, the reaction was quenched by addition of water and concentrated *in vacuo*. The resulting solution was extracted with ethyl acetate, and the extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (20% ethyl acetate in hexanes) afforded alcohol **70** (110 mg, 96%) as white crystals: $[\alpha]25_D$ = +62 (c 0.9, $CHCl_3$, 90% ee by HPLC); ^{1}H NMR ($CDCl_3$) δ 7.37 – 7.22 (m, 5H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.80 (m, 2H), 5.19 (d, *J* = 6.6 Hz, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 4.33 (s, 2H), 3.91 (s, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.75 – 2.70 (m, 2H), 2.29 (m, 2H), 1.92 (dd, *J* = 12.2, 5.8 Hz, 1H), 1.20 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 143.5, 138.0, 137.4, 129.2, 128.8 (2C), 128.2 (2C), 126.3, 123.9, 123.2, 122.8, 115.3, 95.6, 79.8, 78.0, 74.6, 58.0, 56.0, 47.1, 41.2, 39.7, 27.2, 23.2, 19.8, 14.2; HRMS (EI) *m/z* calcd for $C_{27}H_{34}O_5$ (M^+) 438.2406, found 438.2408.

Triol 71

To a solution of alcohol **70** (115 mg, 0.26 mmol) in dioxane (2 mL) and water (0.1 mL) at rt was added OsO_4 (0.2 mL, 0.002 M in tBuOH, 0.004 mmol) followed by NMO (68 mg, 0.58 mmol). After 17 hr, the reaction was diluted with water and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, which afforded triol **71** as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.34 – 7.26 (m, 3H), 6.86 (s, 1H), 6.75 (s, 1H), 5.07 (s, 1H), 5.03 (s, 2H), 4.64 (br s, 1H), 4.36 (br s, 1H), 4.28 (s,

2H), 3.61 (br s, 1H), 3.40 (s, 3H), 3.36 – 3.30 (m, 1H), 3.33 (s, 3H), 2.69 – 2.66 (m, 2H), 2.14 (d, *J* = 14.4 Hz, 1H), 1.94 (dd, *J* = 10.8, 7.2 Hz, 1H), 1.72 (d, *J* = 14.4 Hz, 1H), 1.26 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 143.2, 139.4, 129.1 (2C), 129.1, 128.2 (2C), 128.1, 123.2, 123.0, 115.8, 95.8, 84.8, 77.8, 76.7, 75.1, 74.5, 57.9, 56.0, 46.0, 45.5, 37.8, 30.1, 23.2, 21.7, 16.5; HRMS (EI) *m/z* calcd for $C_{27}H_{36}O_7$ (M^+) 472.2461, found 472.2467.

Ketone 72

To a solution of partially purified triol **71** (ca. 0.26 mmol) in CH_2Cl_2 (5mL) and water (0.1 mL) at rt was added $NaIO_4$ (720 mg, 3.3 mmol) and the resulting mixture was *vigorously* stirred. After 24 hr, the reaction was diluted with water and extracted with CH_2Cl_2 and the extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (30% ethyl acetate in hexanes) afforded ketone **72** (81 mg, 84% over 2 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.95 (d, *J* = 1.6 Hz, 1H), 6.80 (s, 1H), 5.18 (d, *J* = 6.4 Hz, 1H), 5.15 (d, *J* = 6.4 Hz, 1H), 4.33 (s, 2H), 4.05 (d, *J* = 3.6 Hz, 1H), 3.50 (s, 3H), 3.46 (d, *J* = 4.4 Hz, 1H), 3.38 (s, 3H), 3.03 – 2.99 (m, 2H), 2.85 (dd, *J* = 16.4, 3.6 Hz, 1H), 2.77 (m, 1H), 2.34 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.74 (s, 3H);^{13}C NMR ($CDCl_3$) δ 207.5, 146.0, 142.8, 130.2, 122.9, 122.5, 115.4, 95.8, 82.6, 78.8, 74.5, 58.1, 56.2, 52.5, 46.3, 41.5, 27.3, 23.2, 21.0, 15.1; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_6$ (M^+) 364.1886, found 364.1883.

Diol 73

To a solution of ketone **72** (81 mg, 0.22 mmol) in CH_3OH (0.3 mL) and THF (3 mL) at rt was added $NaBH_4$ (18 mg, 0.47 mmol). After 15 min, the reaction was quenched by addition of 1N HCl. The resulting solution was extracted with ethyl acetate, and the organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Immediate purification by column chromatography (80% ethyl acetate in hexanes) afforded diol **73** (78 mg, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.92 (d, *J* = 1.6 Hz, 1H), 6.77 (s, 1H), 5.18 (d, *J* = 6.0 Hz, 1H), 5.14 (d, *J* = 6.4 Hz, 1H), 4.31 (s, 2H), 4.15 (q, *J* = 3.2 Hz, 1H), 3.51 (s, 3H), 3.38 (s, 3H), 3.39 – 3.36 (m, 1H), 3.16 (brd, 1H), 2.77 – 2.69 (m, 3H), 2.42 (dd, *J* = 14.2, 3.0 Hz, 1H), 1.93 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.70 (dd, *J* = 12.2, 5.4 Hz, 1H), 1.41 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.9, 143.3, 129.1, 123.4, 123.2, 115.9, 95.9, 77.3, 76.3, 74.7, 70.8, 58.0, 56.2, 46.9, 43.3, 37.9, 28.8, 23.0, 21.5, 15.9; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_6$ (M^+) 366.2042, found 366.2041.

Aldehyde 74

To a solution of methyl ether **73** (116 mg, 0.32 mmol), in CH_2Cl_2/water (15:1) at rt was added DDQ (90 mg, 0.40 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 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 **74** (109 mg, 98%) was obtained as a faintly yellow wax that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 6.4 Hz, 1H), 5.21 (d, *J* = 6.4 Hz,1 H), 4.26 (q, *J* = 3.2 Hz, 1H), 3.56 (s, 3H), 3.40 (m, 1H), 2.86 – 2.82 (m, 2H), 2.51 (dd, *J* = 14.2, 3.0 Hz, 1H), 2.25 (m, 2H), 2.03 (dd, *J* = 14.8, 3.4, Hz, 1H), 1.78 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.47 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 149.6, 146.6, 128.8, 127.1, 123.5, 115.3, 95.7, 78.0, 77.4, 70.7, 56.3, 46.6, 43.2, 38.1, 28.9, 23.0, 21.8, 16.0; HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_6$ (M^+) 350.1729, found 350.1736.

Tris-MOM Aldehyde 75

To a solution of diol **74** (40 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) at rt was added DIPEA (0.8 mL, 7.3 mmol) followed by slow addition of MOMCl (0.2 mL, 2.6 mmol) over 20 min. After 5 hr, the reaction was quenched by addition of water, the resulting solution was extracted with CH_2Cl_2, and the organic phases were washed with 1N HCl followed by brine. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by column chromatography (45% ethyl acetate in hexanes) afforded aldehyde **75** (37 mg, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 1.2 Hz, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.70 (s, 2H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.21 (q, *J* = 3.4 Hz, 1H), 3.50 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 3.32 (d, *J* = 3.2 Hz, 1H), 2.84 – 2.81 (m, 2H), 2.50 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.91 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.78 (dd, *J* = 11.2, 6.8 Hz, 1H), 1.44 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 149.5, 146.6, 128.7, 127.1, 123.6, 115.0, 96.2, 95.9, 95.5, 82.7, 78.1, 72.9, 56.3, 56.2, 55.6, 47.1, 41.5, 38.3, 28.7, 22.9, 21.3, 16.2; HRMS (EI) *m/z* calcd for $C_{23}H_{34}O_8$ (M^+) 438.2254, found 438.2250.

Stilbene 77

To a solution of diisopropyl amine (0.05 mL, 0.36 mmol) in THF (0.3 mL) in an ice bath was added BuLi (2.4M in hexanes, 0.05 mL, 0.12 mmol). To this solution, phosphonate **76** (68 mg, 0.14 mmol) in THF (0.5 mL) was added via canula. After 5 min, aldehyde **75** (21 mg, 0.05 mmol) in THF (0.5 mL) was added via canula. After 2 hr, TLC analysis showed little reaction progress and additional base was added (KHMDS, 0.5 M in toluene, 0.3 mL, 0.15 mmol). After an additional 2 hr, the reaction was complete by TLC and the reaction was quenched by addition of NH_4Cl. The resulting solution was extracted with ethyl acetate, and the organic phases were washed with 1N HCl followed by brine. After the organic phase was dried ($MgSO_4$), and concentrated *in vacuo*, final purification by column chromatography (50% ethyl acetate in hexanes) afforded stilbene **77** (25 mg, 68%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.16 (d, *J* = 1.6 Hz, 1H), 6.96 (s, 1H), 6.94 – 6.89 (m, 4H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.25 (s, 4H), 5.23 (d, *J* = 7.2 Hz, 1H), 5.20 (t, *J* = 5.2 Hz, 1H), 5.05 (t, *J* = 5.2 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 4.20 (q, *J* = 3.2 Hz, 1H), 3.54 (s, 3H), 3.49 (s, 6H), 3.46 (s, 3H), 3.41 (s, 3H), 3.37 (d, *J* = 6.4 Hz, 2H), 3.35 (d, *J* = 3.6 Hz, 1H), 2.78 – 2.75 (m, 2H), 2.51 (dd, *J* = 14.0, 2.8 Hz, 1H), 2.06 – 1.88 (m, 6H), 1.78 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.43 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.4 (2C), 146.1, 142.9, 136.3, 134.7, 131.4, 128.7, 127.6, 126.2, 124.1, 123.2, 122.1, 121.7, 118.9, 112.3, 105.3 (2C), 95.9, 95.4, 95.3, 93.9 (2C), 82.3, 77.2, 72.9, 56.2, 56.2, 55.9 (2C), 55.6, 46.9, 41.2, 39.7, 38.1, 28.6, 26.5, 25.7, 22.9, 22.4, 21.0, 17.6, 16.2, 16.0; HRMS (EI) *m/z* calcd for $C_{44}H_{64}O_{11}$ (M^+) 768.4449, found 768.4452.

Schweinfurthin A (9)

To a solution of stilbene **77** (12 mg, 0.016 mmol) in methanol (1 mL) at rt was added TsOH (16 mg, 0.08 mmol). After 48 hr, the reaction was quenched by addition of $NaHCO_3$ and the resulting solution was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Final purification by preparative thin layer chromatography (70% ethyl acetate in hexanes) afforded schweinfurthin A (**9**, 5 mg, 58%) as a yellow wax: $[\alpha]25_D$ = +47 (c 1.0, EtOH, 90% ee by HPLC); ^{1}H NMR (MeOD) δ 6.79 (s, 1H), 6.77 (d, *J* = 16.4 Hz, 1H), 6.72 (s, 1H), 6.72 (d, *J* = 16.4 Hz, 1H), 6.44 (s, 2H), 5.24 (t, *J* = 7.2 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 3.6 Hz, 1H), 3.30 (m, 3H), 2.75 (m, 2H), 2.36 (dd, *J* = 13.8, 3.0 Hz, 1H), 2.06 – 2.02 (m, 2H), 1.96 – 1.93 (m, 3H), 1.76 (s, 3H), 1.77 – 1.73 (m, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (MeOD) δ 157.3 (2C), 147.1, 141.9, 137.5, 134.8, 132.0, 130.9, 128.6, 127.4, 125.5, 124.6, 124.2, 120.4, 115.8, 111.0, 105.6 (2C), 78.8, 78.1, 71.8, 48.9, 44.7, 41.0, 39.2, 29.4, 27.8, 25.9,

23.9, 23.2, 22.0, 17.7, 16.6, 16.3; HRMS (EI) *m/z* calcd for $C_{34}H_{44}O_6$ (M^+) 548.3138, found 548.3145.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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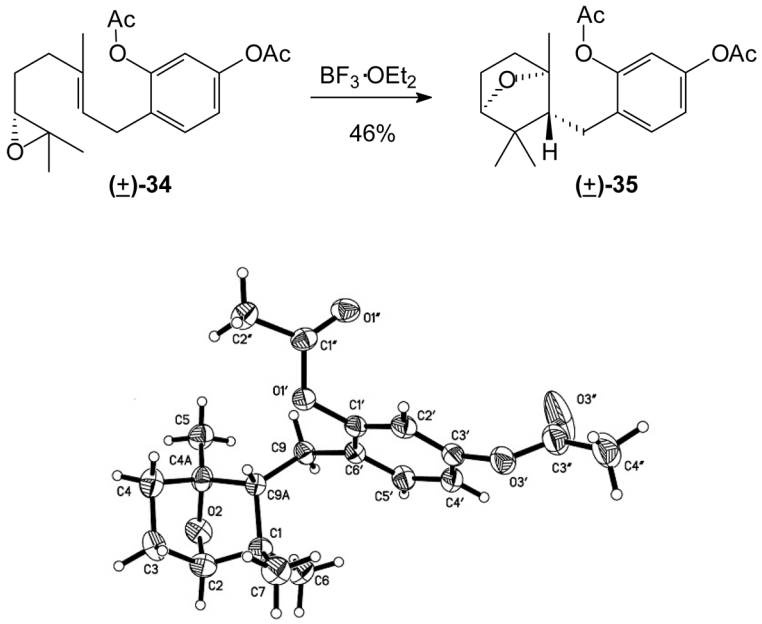
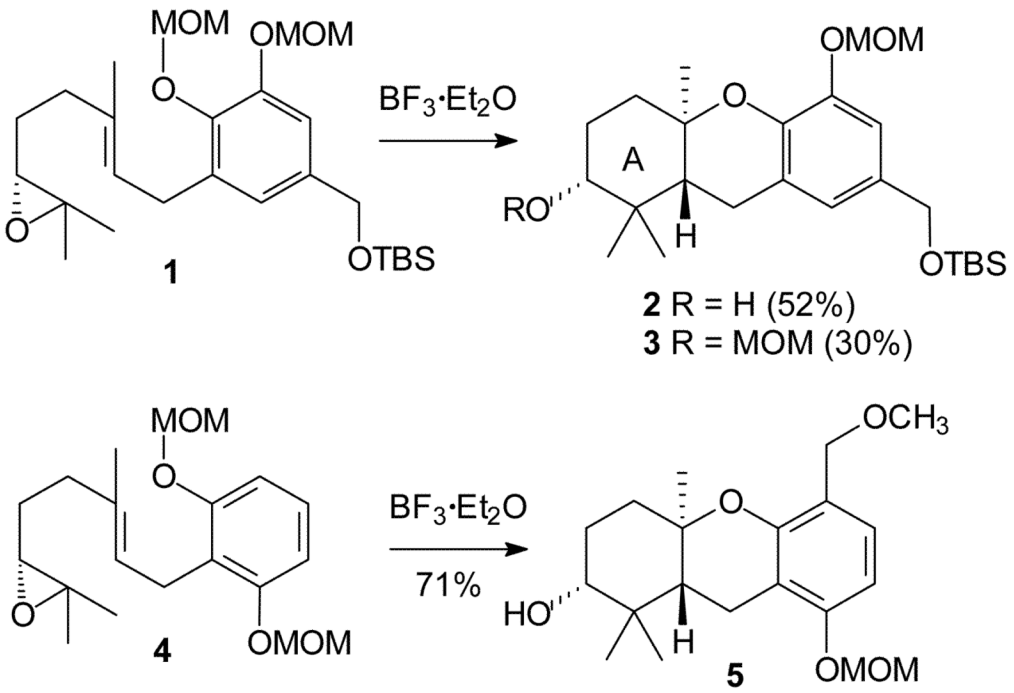
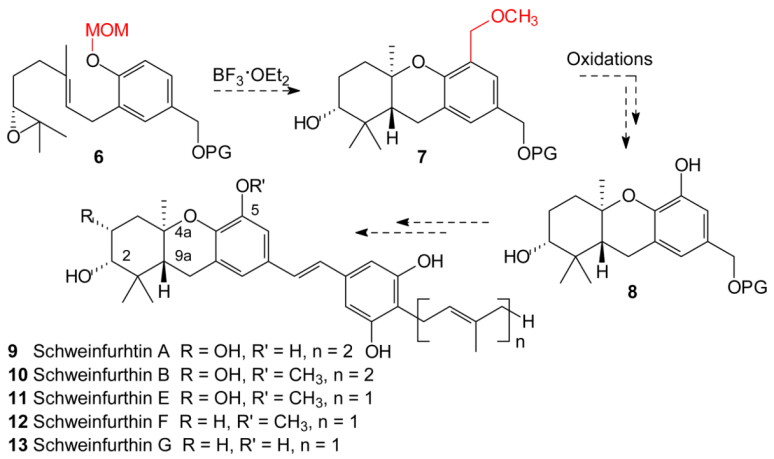


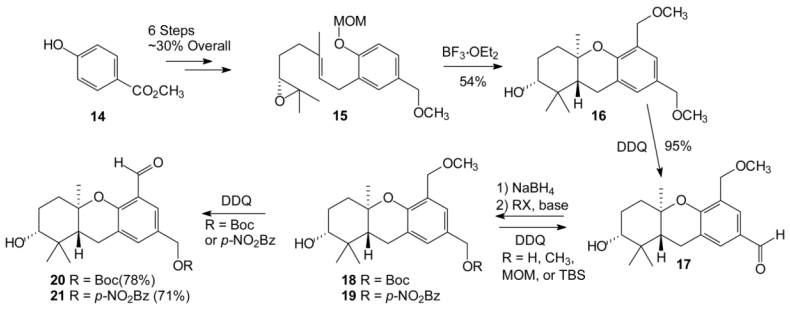
Figure 1.
ORTEP of Compound **35**.



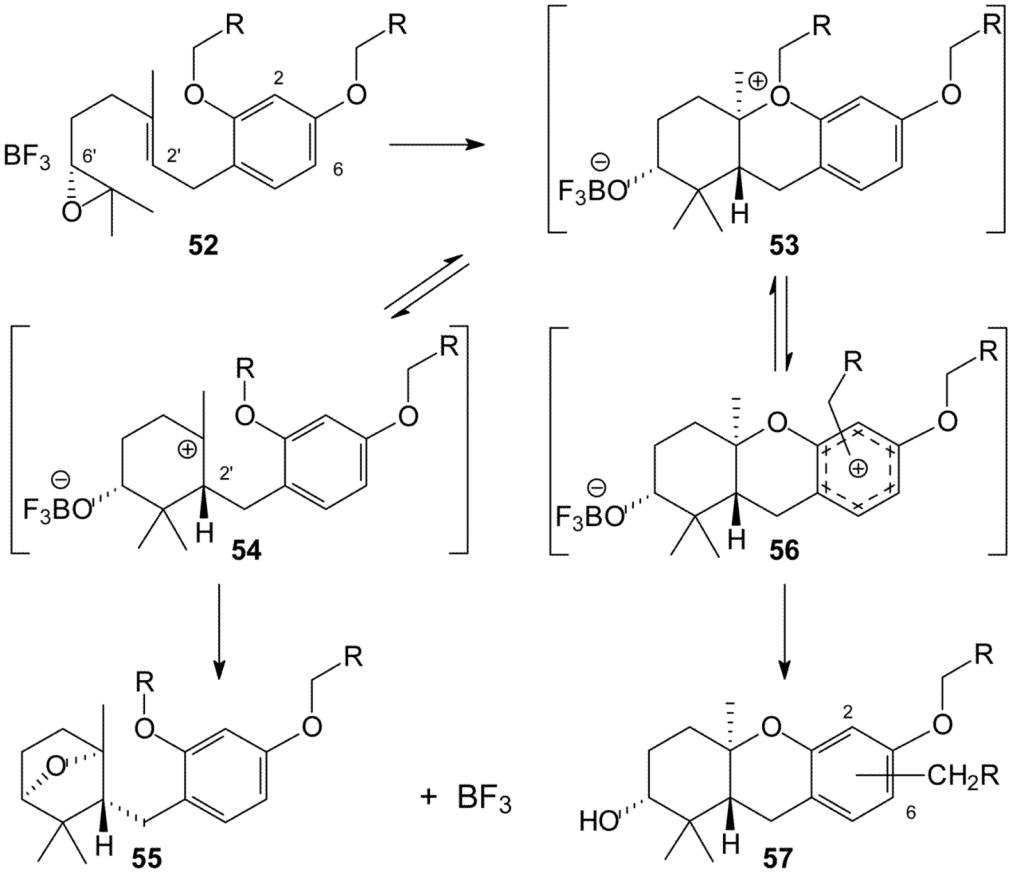
Scheme 1.
Cascade Cyclization Routes to Hexahydroxanthenes.



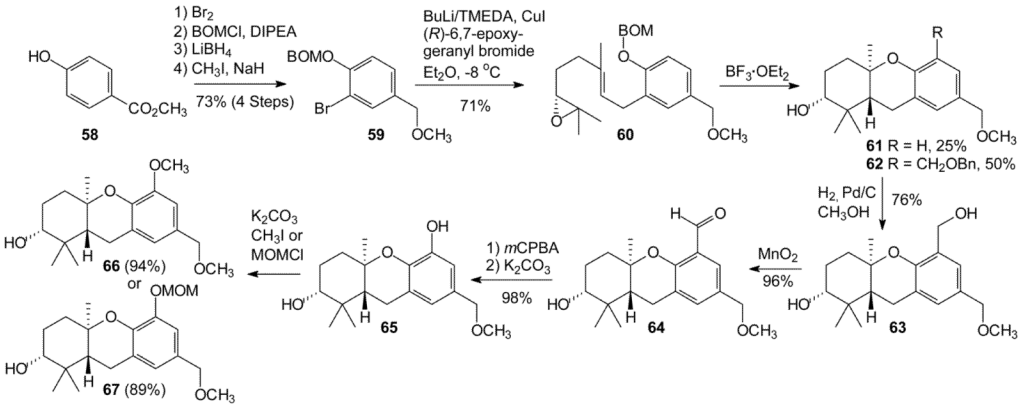
Scheme 2.
Synthetic Plan for a Divergent Route to the Schweinfurthins.



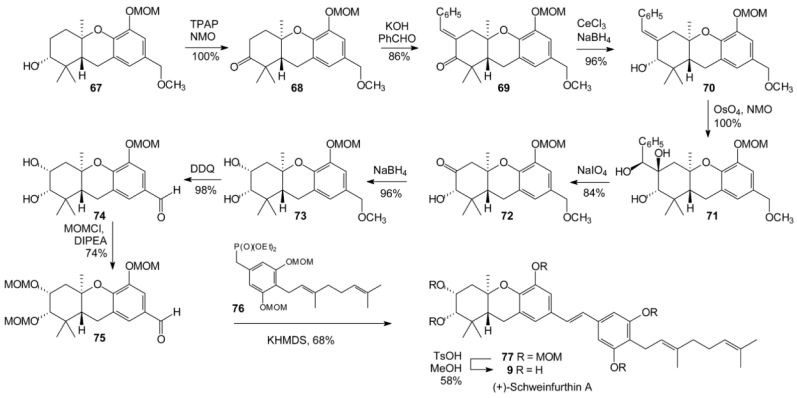
Scheme 3.
Synthesis and Regioselective Oxidation of Compound **16**.



Scheme 4.
A Possible Mechanistic Picture.



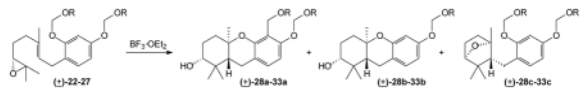
Scheme 5.
Formal Synthesis of Schweinfurthins B, E, F, and G.



Scheme 6.
Total Synthesis of (+)-Schweinfurthin A

Table 1

Cyclizations of Alkoxymethyl-substituted Phenols [a]



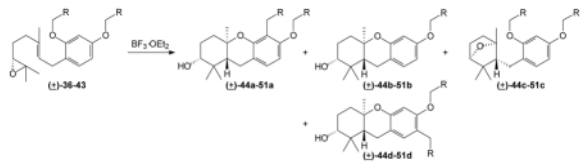
Entry	substrate (R =)	common abbreviation	A % yield[b]	b % yield[b]	c % yield[b]
1	CH_3 (**22**)	MOM	52 (**28a**)	30 (**28b**)	
2	Bn (**23**)	BOM	62 (**29a**)		
3	CH_2CH_2TMS (**24**)	SEM	57 (**30a**)		
4	$CH_2CH_2OCH_3$ (**25**)	MEM	53 (**31a**)	28 (**31b**)	
5	$C(O)C(CH_3)_3$ (**26**)	POM			47 (**32c**)
6	4-ClC_6H_4 (**27**)			56 (**33b**)	37 (**33c**)

[a] See Supporting information for experimental details.

[b] Isolated yields.

Table 2

Cascade Cyclization/Aromatic Substitution of Alkyl-substituted Phenols.[a]



Entry	Substrate (R =)	a % yield[b]	b % yield[b]	c % yield[b]	d % yield[b]
1	H (**36**)			72 (**44c**)	
2	$CH{=}CH_2$ (**37**)	8 (**45a**)		32 (**45c**)	
3	$4\text{-}NO_2C_6H_4$ (**38**)			20 (**46c**)	
4	C_6H_5 (**39**)	43 (**47a**)	18 (**47b**)		2 (**47d**)
5	$2\text{-}BrC_6H_4$ (**40**)			49 (**48c**)	
6	$4\text{-}CH_3OC_6H_4$ (**41**)	33 (**49a**)	12 (**49b**)[c]		19 (**49d**)
7	3,4,5-trimethoxyphenyl (**42**)		41 (**50b**)[d]		28 (**50d**)
8	3-furyl (**43**)	49 (**51a**)			

[a] See Supporting Information for experimental details.

[b] Isolated yields.

[c] Isolated as the A-ring PMB ether.

[d] Isolated as the A-ring alcohol (32%) and A-ring ether (9%).