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TITLE: Molecular Basis for the Toxicity of Schweinfurthins to Breast Cancer Cells

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### 13. ABSTRACT (Maximum 200 Words)

The Schweinfurthins are a small set of diprenylated stilbenes isolated from an African plant. Schweinfurthins A, and B display significant and unique activity in the NCI’s 60 cell line panel, and the breast cancer lines MCF7 and HS 578T were among the most sensitive. We have developed multiple convergent routes to this family of compounds allowing an analog retaining anticancer activity to be synthesized as a single enantiomer. We have now synthesized a series of analogs including one bearing suitable functional groups for attachment to an affinity reagent or other reagent for determination of the mechanism of action. These studies have also led to synthetic analogs with more favorable stability, improving the ability to handle these agents. Quantitative structure activity studies have advanced our understanding of the essential pharmacophore and will pave the way for design of next generation analogs targeted at increasing the potency of the Schweinfurthin family.

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Introduction:

The schweinfurthins (1-3) are a small set of diprenylated stilbenes isolated from the African plant Macaranga schweinfurthii Pax. by Beutler et al. at the National Cancer Institute.\textsuperscript{1,2} Schweinfurthins A (1), B (2), display significant activity in the NCI's 60-cell line anticancer assay with average GI\textsubscript{50}'s of less than 0.5 \textmu M. Among the most sensitive cell lines were the breast cancer lines MCF7 and HS 578T. Inspection of the spectrum of activity shows no correlation with any currently used agents suggesting that these compounds may act at a previously unrecognized target or through a novel mechanism. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis effort. An eventual asymmetric synthesis will allow assignment of the absolute stereochemistry and will provide a reliable source of schweinfurthins for further testing. Further chemical synthesis will eventually allow access to analogs designed to probe the biological activity of these compounds.

Body.

This project has been advanced considerably in this final year. We will discuss the most recent advances after a summary of the first two years has been described. Our overall strategy for the synthesis of the schweinfurthins envisioned penultimate construction of the central stilbene olefin via a Horner-Wadsworth-Emmons condensation. The project then required the synthesis of two fragments representing the left (4) and right halves (5) of the molecules. Important discoveries concerning both have been made.

Our strategy for the synthesis of the left half of the molecule has evolved to include two cationic cascade cyclization sequences. Initially we explored a route wherein stereochemical information would be transferred into the cationic sequence through the agency of a phenylselenide moiety (path A). While successful at achieving a diastereoselective cascade cyclization,\textsuperscript{3} this intermediate proved intransigent to further modification consistent with our synthetic plans and we opted to explore a more biomemetic route. In this route an epoxide would
initiate the cationic sequence allowing direct installation of one of the A-ring hydroxyl groups in this process (path B).

Using this second route we have synthesized 3-deoxyschweinfurthin B (6) and numerous analogs in enantioenriched form. The parent stilbene 6 of this series was found to have biological activity comparable to the natural products, and an examination of structure versus activity on this series has led to an appreciation of the role of the right half hydroxyl groups in the activity of these molecules. We have also used this left half to synthesize an active analog (13) with appropriate functionalization for attachment of affinity reagents. This will allow us to initiate a search for the biological target(s) of this family of potential breast cancer drug leads.

<table>
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<tr>
<th>Compound</th>
<th>R</th>
<th>R’</th>
<th>R”</th>
<th>Mean GI₅₀</th>
<th>Differential activity</th>
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<tbody>
<tr>
<td>6</td>
<td>OH</td>
<td>Geranyl</td>
<td>OH</td>
<td>0.2 µM</td>
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</tr>
<tr>
<td>7</td>
<td>OCH₃</td>
<td>Geranyl</td>
<td>OCH₃</td>
<td>6.6 µM</td>
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<tr>
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<td>F</td>
<td>Geranyl</td>
<td>F</td>
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<tr>
<td>9</td>
<td>H</td>
<td>Geranyl</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>16 µM</td>
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<td>H</td>
<td>3.8 µM</td>
<td>yes</td>
</tr>
<tr>
<td>13</td>
<td>OH</td>
<td>Geranyl-OH</td>
<td>OH</td>
<td>1.0 µM</td>
<td>yes</td>
</tr>
</tbody>
</table>

Another important outcome of this SAR study is the finding of significant correlated activity in the phenol derivative 12. Our collaborators had noted a disposition towards degradation in the natural products, and we surmised this would be due to oxidative lability of the resorcinol moiety. While the right half is clearly crucial to activity it appears that only one hydroxyl is absolutely required. This discovery should greatly facilitate further advances due to the increased stability.

**Recent Advances**

With this interesting structure-activity data in hand the next step was to achieve an enantioselective synthesis using our established route to secure samples of both enantiomers of 3-deoxyschweinfurthin B (6). After some experimentation it was discovered that allowing the
intermediate diol 14 to react with the appropriate enantiomer of camphorsulfonic acid under mixed anhydride esterification conditions allowed a kinetic resolution of the diol to be achieved. This has allowed both enantiomers of the arene 14 to be produced in >99% ee and subsequently both enantiomers of 3-deoxyschweinfurthin B (6) were synthesized and submitted to NCI for biological testing.

Intriguingly both enantiomers show strong anticancer activity (R,R,R-6a : mean \( G_{50} = 0.62 \mu M \), S,S,S-6b : mean \( G_{50} = 1.0 \mu M \)). However the R,R,R isomer showed a high degree of correlation with the natural products, whereas the S,S,S isomer did not. This suggests that these agents may well act via two different mechanisms of action. From this point our attention will be focused on the R,R,R isomer as the most favorable for accessing the natural product stereochemistry.

With all of these positive results we were now in the position to reexamine our synthetic efforts with an eye toward a more efficient synthesis. Our initial route to the right half phosphonate 5 at 8 steps and 34% overall yield seemed reasonable, but we wondered whether it might be possible to avoid the benzylic alcohol protection. After some exploration of conditions, direct alkylation of the benzylic alcohol 16 afforded the phosphonate 5 in 6 steps at comparable yields. This shortens the sequence to compounds 5 to just 6 steps.

Likewise the successful synthesis of the left half tricyclic aldehyde relied on a rather cumbersome protection deprotection sequence (See references 3 and 4, appendix). In this sequence a silyl ether was installed on the phenolic hydroxyl of bromide 19 only to be replaced with an ethoxyethyl (EE) group and then eventually reinstalled. This was an expeditious route and allowed us to avoid problems of retro-Brooke rearrangement of the silyl ether at one stage and the problems inherent in the resident asymmetric center in the EE protecting group at later stages.

Prior to our recent work on this we had found that the retro-Brooke rearrangement could be avoided by use of a Stille coupling of a geranyl stannane and the aryl bromide 19, however the desire to avoid the use of toxic stannanes led us to further exploration. Tactics involving the protection of both hydroxyl groups as methoxymethyl (MOM) ethers seemed a good place to start. Treatment of the aryl bromide with Hunig’s Base and MOMCI gave a very high yield of the bis MOM protected arene which was then subjected to the halogen metal exchange conditions. The resulting geranylated arene 21 is then dihydroxylated asymmetrically and converted into the epoxide 23. Absolute stereochemistry of the newly formed asymmetric center was determined by
The H-NMR analysis of the ester 25 according to the methods of Trost and Mosher. Treatment with trifluoroacetic acid induces cationic cascade cyclization to afford the protected tricycle 24.

This route to the protected tricycle 24 proceeds in 8 steps and 17% overall yield from vanillin. With comparable yields and 8 steps versus 14 in the original synthesis, this route is much more efficient to reach the tricycle stage. This second generation synthesis of the tricyclic hexahydroxanthene core will greatly facilitate further development of the schweinfurthin family as anticancer therapeutics.

Finally, we have carried out quantitative structure activity relationship (QSAR) studies on the analogs with right half modifications synthesized to date. After searching for correlations with several common molecular descriptors calculated in silico (PM3 level of theory) we found a significant correlation ($r^2 = 0.72$, GI50 against HS 578T breast cancer cell line) with the Q-Plus (partial charge on the most positive atom in the molecule). The most positively charged atom
turned out to be the right half resorcinol hydroxyl hydrogen. This information is currently being used to design more potent analogs which should greatly improve the utility of these agents as drug leads and as biological probes.

Key Accomplishments.

- Second generation synthesis of the 3-deoxyschweinfurthin family has been achieved allowing much more facile access to these agents.
- The synthetic route has been expanded to establish an enantioselective synthesis and both enantiomers of the most active compound have been synthesized by a kinetic resolution approach and tested for anticancer activity.
- Analogs of 3-deoxyschweinfurthin B have been synthesized and QSAR studies carried out allowing identification of a strategy for improving potency in the family.
- An analog showing improved stability has been synthesized and shown to retain considerable activity.
- An analog with suitably placed functionality to attach an affinity reagent or for yeast three hybrid assays has been synthesized and shown to retain significant and differential bioactivity.

Reportable Outcomes.


Conclusions.

We have developed a second generation synthesis to both intermediates required for our synthetic efforts. These new routes allow increased efficiency in producing analogs and in producing quantities available for further exploration. We have synthesized both enantiomers of the most active compound 3-deoxyschweinfurthin B and this has allowed us to determine that the RRR enantiomer has more highly correlated activity to that of the natural schweinfurthins. QSAR studies on analogs of this agent have given insight into the functionality essential to the activity of these agents. We have achieved the synthesis of analogs with greater stability and with functional groups suitable for attachment to affinity reagents both of which retain significant and correlated activity. Future efforts will focus on using our results to increase the potency of this family of potential anticancer agents further, as well as synthesizing quantities of affinity reagents for determination of the mechanism of action of these agents.

References.

Appendices.


A Cascade Cyclization Approach to Schweinfurthin B

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ABSTRACT

A strategy for synthesis of the hexahydroxanthene moiety of the natural products schweinfurthin A, B, and D is described. The relative stereochemistry in the key cationic cyclization step is established through the preference of the phenylselenide substituent for an equatorial orientation.

The schweinfurthins (Figure 1, 1−4) are a small set of doubly prenylated stilbenes isolated from the African plant Macaranga schweinfurthii Pax. by Beutler et al. at the National Cancer Institute. Schweinfurthins A (1), B (2), and D (4) display significant activity in the NCI's 60-cell line anticancer assay with GI50 values less than 0.5 μM.1,2 Their profile of activity does not match that of any clinically used anticancer agent, which suggests that these compounds may act either by a novel mechanism or at an unknown site. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis that ultimately should allow assignment of the schweinfurthins' absolute stereochemistry and provide a reliable source for further biological testing.

We have demonstrated the feasibility of a convergent approach to the schweinfurthins through synthesis of schweinfurthin C (3), the inactive congener.3 In that synthesis, the central stilbene olefin was prepared by a Horner-Wadsworth-Emmons condensation of a benzylic phosphonate (compound 5) and a complementary aldehyde. The phosphonate was prepared in eight steps from commercially available 3,5-dihydroxybenzoic acid (6) employing a directed ortho metalation for introduction of the geranyl substituent. Phosphonate 5 also could be used to advantage in preparation of the more complex schweinfurthins, provided preparation

Figure 1. Structures of the schweinfurthins.

Scheme 1. Retrosynthetic Analysis of Schweinfurthin B

Scheme 2. Initial Synthesis of Hydroxyselenide 16

Figure 2. Possible transition states for cyclization of hydroxyselenide 8.

of a tricyclic aldehyde (7, Scheme 1) could be achieved. The methylated version of this tricyclic aldehyde was targeted initially because the requisite phenolic methyl ether could be carried along the sequence from the aromatic starting material, bromovanillin 9.

One approach to the hexahydroxanthene core could be based on an acid-catalyzed cyclization to assemble both the A- and B-rings on an aromatic C-ring in a single reaction. Previous reports on cyclizations of geranylated phenols are known, but often the cyclizations occurred in low yield with numerous byproducts observed. We hypothesized that a substituent $\alpha$ to the incipient carbocation could help stabilize the terminal cation, thereby possibly increasing the yield and providing an opportunity for stereocontrol. There is substantial precedent for stabilization of adjacent cations by phenylthio substituents, and some precedent for stabilization by phenylselenyl groups. As shown in Figure 2, one transition state would place the phenylselenide substituent in an equatorial position with a pseudochair conformation in the incipient B-ring, while the other would require an axial phenylselenide group with a pseudoboat conformation. The use of hydroxyselenides for similar reactions has been described in two seminal papers by Kametani et al., though application to enantiopure material was not attempted. With this aim in mind, racemic $\beta$-hydroxyselenide 8 was viewed as a cyclization precursor that would allow evaluation of the viability of such an approach.

The synthesis began with preparation of the known benzaldehyde derivative 10 (Scheme 2) from commercially available vanillin. Reduction of the aldehyde and subsequent protection of the alcohol as the triethylsilyl ether afforded

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the fully protected arene 12, and halogen—metal exchange followed by reaction with geranyl bromide allowed installation of the geranyl chain in 74% yield. An mCPBA epoxidation of compound 13 initially afforded a 1:1 mixture of the regioisomeric 6,7- and 2,3-epoxides in 55% yield along with the diepoxide (7%). Even though careful column chromatography could separate the two regioisomers, the low yield of the desired product was unattractive. When the ortho carbon has been observed in similar examples, cf.: (b) Branchaud, B. P.; Blanchette, H. S. Ed.; Jai Press: Greenwich, CT, 1992; Vol 2., pp 299-376. For more recent (10) When treated with n-butyllithium, both compound 18 and the TIPS protecting group were cleaved upon silica gel column chromatography. A second synthetic strategy was developed to address this problematic deprotection issue. Because the silyl ether could be readily removed, it appeared attractive to protect the phenolic functionality as a silyl ether as well. However, introduction of the phenolic silyl ether would have to follow the alkylation step in the synthetic sequence, because migration of the silyl group from the oxygen to the adjacent ortho carbon has been observed in similar reactions. 11 Therefore, an ethoxyethyl-protected phenol was envisioned for the sequence up to and including the alkylation step, at which point it would be removed and a silyl ether installed in its place. 11

Direct protection of the phenol as the ethoxyethyl ether was not successful under acidic conditions, so an indirect route was employed. The known alcohol 17,12 also available from vanillin, was disilylated and then selectively cleaved to the free phenol 19 by treatment with 1.0 equiv of tetrabutylammonium fluoride 13 (Scheme 3). An acid-catalyzed reaction of compound 19 with ethyl vinyl ether gave the fully protected aryl bromide 20. This intermediate can be prepared in multigram quantities in an overall yield of 68% from vanillin without need for a chromatographic separation. Application of the halogen—metal protocol and reaction with geranyl bromide afforded the analogous geranylated arene, which upon acidic workup gave the free phenol 21. After silylation of the free phenol, the material was subjected to oxidation, and epoxide opening analogous to that used on arene 13 delivered the protected α-hydroxyselelenide 24. The deprotected target 16 could be obtained in 84% yield by treatment of the disilylated material with excess TBAF.

(10) When treated with n-butyllithium, both compound 18 and the TIPS analogue show a 1,3 O—C silyl migration in the only isolable products. (11) The EE group was not carried throughout the sequence to avoid introduction of diasteromers and because the phenolic EE group was readily cleaved upon silica gel column chromatography.


To induce the desired cationic cyclization, the tertiary alcohol 16 was treated with acid under various conditions. Treatment of compound 16 with TFA afforded a single hexahydroxanthene system as the labile trifluoroacetate 25. Purification of this product by column chromatography gave both the trifluoroacetate 25 and the parent alcohol 26 in 43% combined yield.

The relative stereochemistry of the hexahydroxanthene was assigned after extensive NMR spectroscopy on the trifluoroacetate 25. Analysis of the coupling constants observed for the C-2 hydrogen (schweinfurthin numbering) suggested an axial disposition and hence an equatorial orientation for the phenylselenide group. The bridgehead methine hydrogen (C-9a) also appeared to be in an axial orientation on the basis of analysis of the coupling constants with the benzylic hydrogens at C-9. In this case, a COSY spectrum nicely displayed the H-9ax, H-9eq, H-9a spin system, indicative of a trans-decalin skeleton. Furthermore, the chemical shifts of the methyl groups compared favorably to those reported for a related trans-fused system but did not agree with those of a related cis-fused structure. Finally, a NOESY spectrum revealed correlations (Figure 3) of the bridgehead methyl group with axial hydrogens at C-3 and C-9 and to the axial methyl group at C-1. On the other face of the molecule, complementary correlations were observed between the equatorial methyl group at C-1 and the axial hydrogen at C-9a, as well as from the axial hydrogen at C-2 to both the C-1 equatorial methyl group and the C-9 equatorial hydrogen.

The NMR data make clear that the phenylselenide substituent was successful in providing a single diastereomer of the hexahydroxanthene and may facilitate the cyclization. The equatorial disposition of the phenylselenide moiety in the final product is encouraging in that this single substituent appears to effectively govern the stereochemistry of the bridgehead centers, as expected from consideration of the transition states (Figure 2).

Preparation of the tricycle 26 should allow elaboration of racemic schweinfurthin B after introduction of the A-ring hydroxyl groups and coupling with phosphonate 5. Alternatively, now that the viability of this cyclization strategy has been shown, preparation of the epoxide 23 in nonracemic form should allow preparation of nonracemic schweinfurthin B (2). Our efforts to prepare the nonracemic epoxide, as well as to complete preparation of the natural products themselves, will be reported in due course.

Acknowledgment. Financial support from the DOD Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds 16–26. This material is available free of charge via the Internet at http://pubs.acs.org.

Synthesis of nonracemic 3-deoxyschweinfurthin B has been accomplished through a synthetic sequence including a key cascade cyclization of an epoxy olefin. The intermediate epoxide could be prepared as a single enantiomer through an AD-mix-a (or AD-mix-b) oxidation, and the stereochemistry of the epoxide has been shown to control formation of the two additional stereogenic centers created through the cyclization. Synthetic 3-deoxyschweinfurthin B was found to have potent differential activity in the National Cancer Institute's 60 cell line anticancer assay. This represents the first synthesis of the tetracyclic schweinfurthin skeleton, validating our overall synthetic strategy and providing the first schweinfurthin analogue with activity slightly greater than those of the natural products.

At this time, the small family of natural products known as the schweinfurthins is composed of four compounds (Figure 1, 1–4) isolated from the African plant Macaranga schweinfurthii Pax at the National Cancer Institute. Schweinfurthins A (1), B (2), and D (4) display significant activity in the National Cancer Institute's (NCI's) 60 cell line anticancer assay with mean GI₅₀ values <1 μM. Their biological activity has attracted interest because some central nervous system, renal, and breast cancer cell lines are among the types most sensitive to these compounds. Furthermore, the spectrum of their anticancer activity shows no correlation with any currently used agent and suggests that these compounds may be acting at a previously unrecognized target or through a novel mechanism. Repeated attempts to isolate larger samples of the schweinfurthins from the natural source have met with limited success, and the absolute stereochemistry of these natural products has yet to be determined. For these reasons, as well as their interesting biological activity, we have undertaken an effort directed at total synthesis of the schweinfurthins. An asymmetric synthesis would be particularly attractive because it would allow assignment of the absolute stereochemistry of the natural products and could provide a reliable source of natural schweinfurthins and synthetic analogues for further biological testing.

Our retrosynthetic analysis of schweinfurthin B (Figure 2) calls for an approach where the central stilbene olefin would be constructed in the penultimate step. This...
approach is highly convergent and should allow facile access to analogues for structure–activity studies. We already have demonstrated that a Horner–Wadsworth–Emmons (HWE) condensation can be used to introduce the stilbene olefin through synthesis of the simplest member of the family, schweinfurthin (Scheme 3), and the “right-half” phosphonate (5) employed in that endeavor can be conserved for synthesis of schweinfurthins A and/ or B. All of the tetracyclic schweinfurthins require a dihydroxylated “left-half” core represented in the aldehyde 6. A synthetic approach to phenyl selenide 7 (Scheme 1), which can be viewed as an advanced precursor to this aldehyde, has been reported in a previous paper. Schweinfurthin B (2) was chosen as the initial target so recourse could be made to commercial vanillin as a starting material. This would forego the need for an orthogonal protection of the aryl oxygens because the regiochemistry of the required methyl ether is secured.

Our initial route to racemic hexahydroxanthene 7 involved epoxidation of the geranyl arene 9, available from vanillin in 60% yield over seven steps. The epoxide 10 was opened to phenyl selenide 11, which, after deprotection and acid-catalyzed cationic cascade cyclization, afforded a single racemic diastereomer of the trans fused tricycle 7. Completion of the natural product from this point would require selenoxide elimination, dihydroxylation of the resulting olefin, and an HWE condensation of the aldehyde with the phosphonate encompassing schweinfurthin’s right half (vide supra). In the event, oxidation of racemic phenyl selenide 7 with m-CPBA and thermal elimination of the resulting selenoxide gave the olefin 13 (Scheme 2) in moderate yield. Despite some literature precedent for similar oxidation/elimination reactions under mild reaction conditions, it was necessary to subject this system to a more forceful protocol. In this case, the decreased flexibility of the tricyclic system may make it difficult to achieve the syn conformation of the selenoxide and the adjacent hydrogen necessary for elimination.

With olefin 13 in hand, introduction of the diol moiety through an osmium-mediated dihydroxylation reaction was examined. Inspection of a molecular model of olefin 13 showed that both faces might be somewhat inaccessible, and that if reaction occurred it would most likely take place from the undesired face of the olefin trans to the angular methyl group. Despite this analysis, there is literature precedent for dihydroxylation in similar systems, and both diastereomers of the cis-diol would be of use from a structure–activity standpoint. Unfortunately, treatment of olefin 13 with catalytic or stoichiometric osmium tetroxide or potassium osmate failed to give any detectable dihydroxylation products in our hands. 

![FIGURE 2. Retrosynthetic analysis.](image)

**SCHEME 1**

![SCHEM 2](image)

**SCHEME 2**


(7) It was found that yields increased for the elimination when going from the original conditions of Reich (refluxing dichlormethane) to benzene and finally toluene.


Synthesis of Nonracemic 3-Deoxyschweinfurthin B

The risk of an adverse stereochemical outcome of the dihydroxylation and the difficult oxidation observed in practice made it necessary to seek alternative methodology for introduction of functionality in the A ring of the tricycle. The pioneering work of van Tamelen and Corey on biogenic cyclization of oxidesulfane and, subsequently on acid-catalyzed cyclization of synthetic equivalents, suggested that a nonracemic epoxide (Figure 3) could serve as a viable substrate for cyclization.

Perusal of the literature shows numerous examples of proline and Lewis acid-catalyzed epoxypolyene cyclizations. In this system, a pseudo-chair-chair-like transition state center was assigned tentatively as the risk of an adverse stereochemical outcome of the resulting tricycle, as shown. This strategy could lead directly to 3-deoxyschweinfurthin B, and in principle further elaboration of the A-ring could lead to the natural product.

There is considerable literature precedent for regio-selective dihydroxylation of the terminal olefin in geraniol (Figure 4). The terminal methyl groups are found as a singlet with a chemical shift of 1.16 ppm in ester 16 and selective dihydroxylation of the terminal olefin in geraniol (Figure 4). The terminal methyl groups are found as a singlet with a chemical shift of 1.16 ppm in ester 16 and it appeared that the steric encumbrance and regiocontrol. The resulting diol might then be converted to the epoxide via the secondary mesylate, to intersect the route already developed or bring new functionality into the tricyclic system. Our delight, treatment of diene 9 with AD-mix-α in the presence of methanesulfonamide gave the desired diol 14 in 68% yield and 83% ee (Scheme 3). Use of the pictorial device suggested by Sharpless et al. for the facial selectivity of the attack indicated that an (S)-alcohol should be expected at the newly created asymmetric center.

While the stereochemistry at the new stereogenic center was assigned tentatively to S, a spectroscopic method to support an assignment was pursued. In this case, separate samples of the enantiomeric diol 14 were treated with the (S)- and (R)-enantiomers of O-methylmandelic acid under standard mixed anhydride coupling conditions. After isolation of the major diastereomer from each reaction, compounds 15 and 16, respectively, the 1H NMR spectra were examined for chemical shift differences in accordance with the model of Trost et al. Significant shifts were noted for two sets of easily identifiable hydrogens in the two diastereomers (Figure 4). The terminal methyl groups are found as a singlet with a chemical shift of 1.16 ppm in ester 16 and are shifted to 0.94 ppm in isomer 15. In contrast, the olefinic hydrogen is shifted from 5.27 ppm in compound 15 to a more upfield 5.00 ppm in the isomer 16. Both of these changes are consistent with expectations based on placing the more upfield hydrogens in the shielding region of the phenyl ring when viewed in an extended Newman projection format as required by the Trost model. On this basis, the new asymmetric center in diol 14 was assigned the S configuration.

FIGURE 3. Proposed path of epoxide cyclization.

SCHEME 3
Treatment of diol 14 with mesyl chloride and base, followed by in situ nucleophilic displacement of the resulting mesylate by the tertiary alkoxide, did in fact deliver the nonracemic epoxide 17 in good yield (Scheme 4). Deprotection of epoxide 17 to the diol 18 followed by treatment with trifluoroacetic acid to induce cyclization gave the expected tricycle as the trifluoroacetate ester, and subsequent hydrolysis gave the benzyl alcohol 19 as a single diastereomer. That the secondary alcohol of compound 19 is indeed in an equatorial disposition is evidenced by the large coupling constant \( \text{J}(^1\text{H},^3\text{J}_{ax}) = 11.9 \text{ Hz} \) observed in the \(^1\text{H} \) NMR spectrum. Manganese dioxide oxidation cleanly affords aldehyde 20, and condensation with phosphonate 5 under modified Horner–Wadsworth–Emmons conditions\(^ {17} \) gave the protected stilbene 21 in high yield, all without recourse to protection of the secondary alcohol. Final deprotection of the MOM ethers upon treatment with camphorsulfonic acid gave enantioenriched 3-deoxyschweinfurthin B (22) in good yield.\(^ {18} \)

After the viability of this strategy had been demonstrated with enantioenriched epoxide 17, application of this approach to enantiopure material was pursued. The initial studies with a phenyl selenide cyclization precursor had been made with the assumption that this large substituent could ultimately be used to transfer absolute stereocontrol through a cationic cyclization manifold. There was some reason, however, to question this hypothesis. It had been noted in reactions of episulfonium ions that there is potential for the positive charge to be carried by either center of the three-membered ring intermediate.\(^ {19} \) In contrast there is literature precedent for faithful transmission of stereochemical information through the epoxide cyclization transition state,\(^ {20} \) but to determine the stereointegrity of this specific case, a resolution of the enantiomeric material was required. Our experience with the Trost–Mosher esters 15 and 16 indicated this should be straightforward. To this end a large-scale esterification was conducted (Scheme 5), and the resulting material was readily partitioned into major (15) and minor diastereomers by flash chromatography. Hydrolysis of the major ester 15 was accomplished upon treatment with sodium hydroxide in ethanol to afford diol \((S)-14\) as a single enantiomer.\(^ {21} \)

The diol \((S)-14\) then was subjected to the same protocols developed for the epoxide cyclization which led to tricyclic material in the enantiomeric series. Treatment with mesyl chloride followed by internal displacement mediated by potassium carbonate gave the epoxide \((R)-17\) in moderate yield. Removal of the silyl ether protecting groups and subsequent cyclization with trifluoroacetic acid gave, as expected, the tricyclic diol \((R,R,R)-19\) in reasonable yield. This diol could be subjected to benzyl oxidation with manganese dioxide to afford the aldehyde \((R,R,R)-20\).

The aldehyde \((R,R,R)-20\) displayed a specific rotation of \(+159^\circ\). Two other samples of optically active compound 20 also were available: one with a rotation of \(+97.8^\circ\) for material synthesized from diol 14 with an enantiomeric excess of 64\% \([\alpha]_D = -6.1^\circ\), and another with a rotation of \(+112^\circ\) from diol 14 with an enantiomeric excess of 74\% \([\alpha]_D = -7.0^\circ\). On the basis of the rotation of the enantiopure aldehyde \((R,R,R)-20\), these values would correspond to ee's of 63\% and 72\%, respectively, indicating that this cascade cyclization is stereospecific within

\( ^{17} \) Baker, R.; Siu, R. J. Synthesis 1981, 117.


Synthesis of Nonracemic 3-Deoxyschweinfurthin B

**SCHEME 5**

![Scheme 5](image)

**SCHEME 6**

![Scheme 6](image)

the error of these measurements. It should be noted that oxidation of compound 9 with the AD-mix-β reagent affords the diol (R)-14 in similar yield and enantiopurity (Scheme 6). The tricyclic aldehyde (S,S,S)-20 has been synthesized from diol (R)-14 via this route as well, thus providing access to either enantiomer of compound 22.

Enantioenriched compound 22 was tested at the NCI in the 60 cell line anticancer assay, and was found to have a mean GI<sub>50</sub> of 0.21 μM, slightly lower than those of any of the natural schweinfurthins. The finding of more potent activity in this analogue is significant and makes this compound an interesting addition to a family which warrants further study. Furthermore, the viability of the epoxide cyclization suggests that the biosynthesis of the natural schweinfurthins may follow a similar reaction manifold. In that context, the very recent report of the natural product 23, identical to 3-deoxyschweinfurthin B except for the D-ring prenyl substituent that replaces the geranyl group of schweinfurthin B, is intriguing and strongly suggests that 3-deoxyschweinfurthin B may someday be found as a natural product.

In conclusion, a cascade cyclization of an epoxy olefin has been used to prepare the carbon skeleton of the hexahydroxanthene unit found in schweinfurthins A, B, and D. Furthermore, an aldehyde derived from this tricyclic compound has been condensed with the right-half synthon reported earlier to afford the complete schweinfurthin skeleton in a product that can be viewed as 3-deoxyschweinfurthin B. This work represents the first synthesis of a tetracyclic schweinfurthin analogue and, with absolute stereochemistry derived from an AD-mix reagent, can afford the final product as a single enantiomer. These efforts validate the strategies we have developed for the synthesis of this family of natural products. Application of these strategies to preparation of the natural compounds, as well as the results of bioassays conducted on various synthetic materials, will be reported in due course.

**Experimental Section**

**Olefin 13.** To a solution of the alcohol 7 (32 mg, 0.07 mmol) in THF (5 mL) at -10 °C was added m-CPBA (24 mg, 0.1 mmol, 70% technical grade). The resulting solution was stirred for 40 min and transferred into a solution of diisopropylamine

(30 µL, 0.22 mmol) in toluene (30 mL) at reflux. After 3 h the mixture was allowed to cool to rt and quenched by addition of 10% aqueous sodium sulfite. The mixture was extracted with EtOAc, and the organic phase was washed with brine, dried (MgSO₄), and concentrated in vacuo to give a yellow oil. Final purification by flash chromatography (silica gel 60, 230-400 mesh) afforded the mandelate ester 15 (3.65 g, 82%) as a clear oil: 1H NMR (CDCl₃) δ 7.46 (dd, J = 7.9, 1.8 Hz, 2H), 7.40-7.22 (m, 3H), 6.72 (s, 1H), 6.64 (s, 1H), 5.27 (t, J = 8.0 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 3.77 (s, 3H), 3.43 (s, 3H), 3.33 (d, J = 7.9 Hz, 2H), 1.96 (t, J = 8.0 Hz, 2H), 1.78-1.61 (m, 3H), 1.64 (s, 3H), 1.00 (s, 9H), 0.94 (s, 15H), 0.18 (s, 6H), 0.09 (s, 6H). 13C NMR δ 170.4, 149.7, 141.3, 136.5, 135.0, 133.7, 129.7 (2C), 127.2 (2C), 123.1, 119.0, 107.3, 82.6, 80.7, 72.3, 65.0, 57.3, 54.7, 35.0, 28.5, 26.1 (3C), 25.0 (3C). 25.9, 24.6, 18.9, 18.4, 16.3, -3.9 (2C), -5.1 (2C). HRMS (ESI) m/z calcd for C₂₉H₂₄O₄Si₂Na (M + Na)⁺ 723.4088, found 723.4090.

(R)-Methylmandelate 16. In a manner identical to that described above for the preparation of ester 15, the diol 14 (35 mg, 0.27 mmol), EDC (14 mg, 0.06 mol), and DMAP (0.08 mmol) were allowed to react with (R)-(+)-methylmandelic acid (12 mg, 0.07 mmol). Standard workup and final purification by column chromatography (silica gel 60, 230-400 mesh) afforded the triol 16 (11.6 mg, 82%) as a clear oil along with the (R,R)-diastereomer (total yield of 100%). A diastereomeric ratio of 54:16, corresponding to an initial ee of 66% for compound 14, was determined by integration of signals at 5.00 and 5.27 ppm in the 1H NMR spectrum of the isolated mixture. Data for diastereomer 16: 1H NMR δ 7.46 (d, J = 8.7 Hz, 2H), 7.36-7.28 (m, 3H), 6.73 (s, 1H), 6.57 (s, 1H), 5.00 (s, 1H), 2.15-2.04 (m, 2H), 1.55-1.45 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 0.99 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.09 (s, 6H). 13C NMR δ 170.9, 149.7, 141.3, 136.5, 135.0, 133.7, 129.7 (2C), 127.2 (2C), 123.1, 119.0, 107.3, 82.6, 72.3, 65.0, 57.3, 54.7, 35.4, 35.3, 33.8, 32.8, 26.1 (3C), 25.6, 24.8, 18.9, 18.4, 16.2, -3.9 (2C), -5.1 (2C). HRMS (ESI) m/z calcd for C₂₉H₂₂N₄O₄Si, Na⁺ 506.1851, found 506.1853.

Aldehyde 20. To a solution of benzylic alcohol 19 (251 mg, 0.82 mmol) in CH₂Cl₂ (30 mL) was added MnO₂ (1.71 g, 19.6 g/mol).
Synthesis of Nonracemic 3-Deoxyschweinfurthin B

3-Deoxydimethylmethyleneschweinfurthin B (21). A suspension of NaH (29 mg, 1.2 mmol) and 15-crown-5 (4 µL, 0.02 mmol) in THF (1.6 mL) was cooled to -5 °C. To this was added aldehyde 20 (10 mg, 0.03 mmol) and phosphonate 5 (22 mg, 0.05 mmol) in THF (2 mL). The mixture was allowed to warm to rt and stirred for a total of 18 h. Water was added dropwise, and the solution was allowed to stir for 1 h. The resulting organic phase was washed with brine, dried over MgSO4, and concentrated in vacuo. Final purification by column chromatography (3:1 hexane/EtOAc) gave the aldehyde (RRR)-20 as a white solid (24 mg, 0.04 mmol) in MeOH (2 mL). The solution was allowed to stir for 20 h and then heated to 60 °C for an additional 5 h. The reaction was quenched by addition of sat NaHCO3 and extracted with ethyl acetate, and the organic phase was washed with brine and dried over MgSO4. Concentration in vacuo gave a yellow solid. Final purification by flash chromatography (2:1 to 1:1 hexanes/EtOAc) afforded the aldehyde (RRR)-20 as a white solid (74 mg, 62%).

Aldehyde (R,R,R)-20. To a solution of benzyl alcohol (R,R,R)-20 (118 mg, 0.4 mmol) in CH2Cl2 (15 mL) was added MnO2 (954 mg, 11.0 mmol) as a single aliquot. The resulting suspension was allowed to stir for 19 h and then filtered through Celite, and the residue was concentrated in vacuo to give a colorless oil. Final purification by flash chromatography (3:1 hexane/EtOAc) gave the aldehyde (R,R,R)-20 as a white solid (74 mg, 62%): [α]D = +159 (c 0.012, CHCl3); the spectral data were identical to those of the enantioenriched diol 19.

3-(3',7'-Dimethyl-2-octen-6'(R),7'-diol)-(4-tert-butyldimethylsiloxyl)-5-methoxybenzoxylotert-butyldimethylsilane (RB-14). To a solution of mandelate ester 21 (203 mg, 0.29 mmol) in EtOH (10 mL) was added NaOH (0.63 mL, 6.65 mmol,aq, 1 M). After 5 h at rt, HCI (0.63 mL, 0.063 mmol,aq, 1 M) was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with water and brine, then dried (MgSO4), and concentrated in vacuo to give a slightly yellow oil. Purification by column chromatography (1:1 hexane/EtOAc) afforded the diol (S)-14 (132 mg, 83%) as a colorless oil: [α]23°D = -9.6 (c 0.03, CHCl3); spectral data were identical to those of the enantioenriched diol 14.

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Supporting Information Available: General experimental procedures and 1H and 13C NMR spectra for compounds 13, 15, 16, and 18–22 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Total synthesis of pawhuskin C: a directed ortho metalation approach

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Abstract — The total synthesis of the opioid modulator pawhuskin C has been accomplished in eight steps from methyl 3,5-dihydroxybenzoate. The key step in this sequence is a directed ortho metalation reaction conducted without protection of a benzylic alcohol and thus presumed to involve a formal dianion intermediate.

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Earlier this year, Belofsky et al. reported isolation of a small set of natural opioid receptor modulators named pawhuskin A–C (1–3, Fig. 1) from Dalea purpurea, a plant once used by Plains Indians in North America. These compounds are prenylated stilbenes and as such display structural similarity to the schweinfurthins, a family of natural products with anticancer activity. Indeed pawhuskin C (3) includes a geranylated resorcinol also found in three of the natural schweinfurthins as well as the synthetic analogue 3-deoxyschweinfurthin B (4, Fig. 2). As an initial step toward the pawhuskin family of natural products, the phosphonate 5 was identified as a synthon for the right half of compound 3. A first generation synthesis of phosphonate 5 was disclosed in connection with the total synthesis of schweinfurthin C, and allowed use of a late stage Horner–Wadsworth–Emmons (HWE) condensation to establish the central

Figure 1. The pawhuskins.

Keywords: Pawhuskin; Directed ortho metalation.

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Figure 2. Retrosynthetic analysis.
stilbene olefin. While a similar strategy might be used to prepare pawhuskin C, a more efficient synthesis of the phosphonate intermediate 5 would make this route more attractive.

The initial route to phosphonate 5 (Scheme 1) commenced with the commercial resorcinol 6. The resorcinol hydroxyl groups were protected as methoxymethyl (MOM) ethers followed by reduction of the ester to give benzyl alcohol 7. Protection of the benzyl alcohol as a silyl ether gave arene 8. This compound was subjected to directed ortho metalation (DoM) conditions followed by lithium-copper exchange and alklylation to install the geranyl chain and set the entire carbon skeleton for the right half of pawhuskin C in silyl ether 9. Removal of the silyl ether and functional group manipulation at the benzyl position afforded the required phosphonate 5 in eight steps and 34% overall yield from ester 6.

This series of reactions gives access to the desired reagent 5, but a more efficient synthesis would be attractive. Studies by several groups suggested that this route could be improved through use of DoM methodology to generate a formal dianion. Specifically, if the bis-MOM ether 7 could be regioselectively metalated at the C-4 position without introduction of the silyl ether protecting group, both the silylation and the later deprotection could be avoided. There is some literature precedent, which suggested that a selective DoM reaction could be accomplished. Treatment of the dimethoxy compound 12 with nBuLi in hexanes affords the product of metalation at the C-2 position, compound 13 (Scheme 2, path a), whereas use of nBuLi with TMEDA and lithium-copper exchange gives the product where metalation has been directed to the C-4 position 14 (path b).

It might be possible to alkylate the dimethoxy compound 12 with geranyl bromide, and subsequently cleave the methyl ethers to phenols. However, we chose instead to explore alkylation of the protected resorcinol 7 because the MOM ethers would be easier to remove. After some experimentation (Table 1), it was found that reaction of the MOM protected resorcinol 7 with sBuLi and TMEDA, followed by treatment with copper bromide–dimethyl sulfide and geranyl bromide at -20 °C, gave the alkylated benzylic alcohol 10 in yields comparable to those observed with the protected analogue 8 (Scheme 3). This route allows access to the phosphonate 5 in just six steps and 37% yield. This represents several improvements over the first generation route, notably in the removal of a protection/deprotection sequence. This strategy saves significant time and effort, while also allowing use of the less toxic CuBr reagent in place of the CuCN used in the first generation approach.

To complete the synthesis of pawhuskin C, the known benzaldehyde 15 (Scheme 4) was treated with phosphonate 5 and sodium hydride in the presence of catalytic 15-crown-5 to initiate an HWE condensation and afford the stilbene 16 in good yield. This stilbene bearing four MOM protecting groups was subjected to acidic hydro-
Table 1. Conditions explored for dianion DoM reaction of arene 7 and geranyl bromide (RX) in the presence of TMEDA (2 equiv)

<table>
<thead>
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<th>Trial</th>
<th>Base, equiv, addition T</th>
<th>CuBr-DMS (equiv, 7)</th>
<th>Addition T for RX</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nBuLi, 2.5 equiv, -20 °C</td>
<td>-</td>
<td>-78 °C</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>nBuLi, 2.5 equiv, -20 °C</td>
<td>2.0 equiv, -20 °C</td>
<td>-78 °C</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>KH (excess), nBuLi, 3.3 equiv, -78 °C</td>
<td>-</td>
<td>-78 °C</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>KH (excess), nBuLi, 2.7 equiv, -20 °C</td>
<td>-</td>
<td>-78 °C</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>KH (excess), nBuLi, 3.0 equiv, -20 °C</td>
<td>-</td>
<td>-20 °C</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>KH (excess), nBuLi, 3.0 equiv, -20 °C</td>
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<td>-20 °C</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>nBuLi, 3.3 equiv, -20 °C</td>
<td>2.0 equiv, -20 °C</td>
<td>-20 °C</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>sBuLi, 2.4 equiv, -20 °C</td>
<td>2.0 equiv, -20 °C</td>
<td>-20 °C</td>
<td>63</td>
</tr>
</tbody>
</table>

Acknowledgements

We thank Professor Gil Belofsky (University of Tulsa) for providing an authentic sample of pawhuskin C. Financial support from the Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423) and the University of Iowa Graduate College is gratefully acknowledged.

References and notes


10. [4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-dimethoxymethoxyphenyl]-methanol (10). sec-BuLi (8.0 mL, 1.00 M in hexanes) was added dropwise to a solution of benzylic alcohol 7 (772 mg, 3.37 mmol) and TMEDA (1.10 mL, 7.28 mmol) in THF (20 mL) at −20 °C. After this solution was stirred for 1 h at −20 °C, CuBr as its DMS complex (1.39 mg, 6.76 mmol) was added in one portion and the mixture was stirred for 1 h at −20 °C. Geranyl bromide (0.75 mL, 3.77 mmol) was added dropwise and the reaction mixture was stirred for 2 h at −20 °C. The reaction was quenched by addition of 1 N HCl, the aqueous layer was neutralized to pH 7 with 1 N HCl, and then was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated in vacuo. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded compound 10 (773 mg, 63%) as a clear yellow oil.

11. Tetra-MOM ether 16. A suspension of NaH (36 mg, 1.5 mmol) and 15-crown-5 (4 μL, 0.02 mmol) in THF (10 mL) was cooled to 0°C. Aldehyde 15 (32 mg, 0.14 mmol) and phosphonate 5 (94 mg, 0.19 mmol) in THF (2 mL) were added, and the mixture was allowed to warm to rt and stirred for a total of 18 h. Water was added dropwise, and the solution was extracted with EtOAc. The resulting organic phase was washed with brine, dried over MgSO₄, and concentrated in vacuo. Final purification by column chromatography (4:1 hexanes/EtOAc) gave the stilbene 16 (60 mg, 77%) as a clear oil: 1H NMR (CDCl₃) δ 7.33–7.32 (m, 1H), 7.15–7.08 (m, 2H), 7.03–6.88 (m, 4H), 5.24 (s, 2H), 5.23 (s, 2H), 5.22–5.19 (m, 1H), 5.11–5.04 (m, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.50 (s, 6H), 3.40 (d, J = 7.2 Hz, 2H), 2.08–2.01 (m, 2H), 1.98–1.93 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H); 13C NMR (CDCl₃) δ 155.9 (2C), 147.4, 146.8, 136.4, 134.6, 132.2, 131.2, 127.7, 127.7, 124.4, 122.6, 121.0, 119.8, 116.6, 114.3, 106.1 (2C), 95.4, 95.4, 94.5 (2C), 56.2, 56.2, 56.0 (2C), 39.8, 26.7, 25.6, 22.7, 17.6, 16.1; HRMS calcd for C₃₂H₄₁O₃ (M+H)⁺ 557.3114, found 557.3130.

12. Pawhuskin C (3). To a solution of stilbene 16 (60 mg, 0.11 mmol) in MeOH (10 mL) was added a catalytic amount of camphorsulfonic acid, and the resulting solution was stirred at rt for 24 h. The reaction was quenched by addition of satd NaHCO₃, extracted with ethyl acetate, and the organic phase was washed with brine and dried (MgSO₄). Concentration in vacuo, followed by final purification by column chromatography (1:1, hexanes/ethyl acetate) afforded pawhuskin C (3, 21 mg, 51%) as a yellow solid; all spectral characteristics matched the published data.¹

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Abstract: Synthesis and bioactivity of several enatioenriched schweinfurthins B analogs is described. All of the target stilbenes contain a common left half hexahydroxanthene ring system and an aromatic right half with varied substituents. The synthesis involves penultimate Horner-Wadsworth-Emmons coupling of one of several right-half phosphonates with the aldehyde comprising the left-half of 3-deoxyschweinfurthin B. We describe the synthesis of the requisite phosphonates, and the respective stilbenes, as well as the cytotoxicity profiles of these new compounds in the National Cancer Institute’s 60 cell-line anticancer screen. Several of these analogs displayed differential cytotoxicity well-correlated with the natural products. Together, these assay results indicate the importance of at least one free hydroxyl group on the aromatic D-ring of this system for differential cytotoxicity.
Introduction

The schweinfurthins are a small set of natural stilbenes isolated from the African tree Macaranga schweinfurthii at National Cancer Institute (NCI) in the late 1990's.\(^1\) These compounds were isolated through bioassay guided fractionation as part of the Developmental Therapeutics Program at NCI, and three of the four were found to have significant and differential cytotoxicity in the NCI's 60 cell-line anticancer screen. Schweinfurthin A (1) and schweinfurthin B (2, Figure 1) presented mean GI\(_{50}\)’s of 0.36 and 0.81 \(\mu\)M respectively and schweinfurthin D (4) was found to be equipotent with schweinfurthin B (2).\(^1\) The fourth member of this family, schweinfurthin C (3), lacks the left-half hexahydroxanthene core and displayed little differential activity and considerably reduced cytotoxicity in initial screens. Vedelianin (5), a closely related natural product, has been shown to have cytotoxic activity similar to schweinfurthin A (1).\(^2\)

![Figure 1. The schweinfurthin family and related natural products.](image-url)
To prioritize their investigations, the NCI utilizes a bioinformatics algorithm known as COMPARE to search for correlations between patterns of cytotoxic activity in the 60 cell-line assays.\(^3\) Compounds which act on the same molecular targets typically display a higher degree of correlation across the various cell lines and sub-panels of the screen. The schweinfurthins differential activity presented with CNS, renal, leukemia, and some breast cancer cell lines showing high susceptibility, while many ovarian, melanoma, and lung cancer lines were resistant. The specific pattern was not correlated to any compound in the NCI standard agents database by COMPARE analysis and this could indicate that these cytotoxins act via a novel cellular pathway or target.\(^4\) Because of their intriguing bioactivity as well as our ongoing interest in chemotherapeutic chemistry\(^5\) and prenylated aromatics in general,\(^6\) we undertook an effort to explore some structure activity relationships in the schweinfurthin family.

Our synthetic strategy involves a late stage introduction of the central stilbene olefin via a Horner-Wadsworth-Emmons (HWE) olefination (Figure 2). It was envisioned that this would allow maximum convergence and facilitate introduction of changes in the right-half architecture to identify the relevant pharmacophore(s) therein. Early work on the simplest member of the family, schweinfurthin C, required synthesis of the right half phosphonate \(^6\) which also could serve as a synthon for schweinfurthins A and B. This reduced the problem of preparation of a tetracyclic schweinfurthin to synthesis of the left half hexahydroxanthene as in aldehyde 7.

We targeted schweinfurthin B initially to derive the C-ring, including the methoxy substituents, from vanillin (8). Two routes involving cationic cascade cyclization to effect the formation of the A and B rings of the tricyclic system have been explored
(Figure 3). With the substantial literature precedents for the diastereoselectivity of such processes the primary issue became one of introducing the initial stereocenter to allow substrate control through the cascade manifold and to ensure proper relative stereochemistry. The first such process employed a phenylselenide substituent (i.e. compound 9) to direct

The diastereoselective cascade, ultimately leading to tricyclic olefin 10. After some experimentation a pathway involving a more biomimetic cyclization of epoxide 11 was found to afford tricyclic aldehyde 12. The epoxide 11 is available via an AD-mix α oxidation as an enantioenriched mixture with 68% ee, and all of the analogs synthesized here have a similar enantiopurity.
To complete synthesis of a tetracyclic schweinfurthins, aldehyde 12 was condensed with the natural right half synthon, phosphonate 6. Final deprotection of the resulting stilbene afforded 3-deoxyschweinfurthin B (13). This result confirmed the overall synthetic plan and represented the first synthesis of an oxygenated tetracyclic schweinfurthin. Synthetic 3-deoxyschweinfurthin B was tested in the 60 cell-line assay and to our great satisfaction was found to have activity (0.20 μM) very comparable to that of the natural products. Even more importantly the differential activity across the cell-lines was correlated with the natural schweinfurthins A/B? (correlation coefficient = 0.75, Figure 4), suggesting that the synthetic compound was operating at the same, and as yet unknown, molecular or cellular target. Thus the opportunity to explore the effect of right half modifications on the bioactivity and physical properties of the schweinfurthins was
presented. In addition to this structure activity information, such studies might help to identify and overcome a tendency toward decomposition noted during the isolation of the tetracyclic natural products and observed with the synthetic 3-deoxyschweinfurthin B as well. The origin of this lability was presumed to be the resorcinol moiety and that assumption might be verified through the synthesis of analogues. Finally, preparation of a series of analogues might allow identification of a point to introduce functionality that ultimately would allow mechanism of action studies.12

Figure 4. Mean graph comparison of 3-deoxyschweinfurthin B (13) and schweinfurthin B (2). Deviations from the mean in log units against each cell line measured in the NCI 60 cell-line assay at the GI50 level, data is presented so that positive deviations indicate more potent cytotoxicity. Approximate regions of several sub-panels are indicated. Complete 60 cell-line data is presented in the supplemental material.

Chemical Synthesis

Dimethoxy-3-deoxyschweinfurthin B (17) was selected as the first target of these studies. A path to the requisite phosphonate 16 commenced with the commercial benzyl
alcohol 14 (Scheme 1). Alkylation of this alcohol by treatment with 2-3 equivalents of strong base and subsequent reaction of the presumed dianion intermediate with geranyl bromide gave the geranylated arene 15 in modest yield. While modest in this case, the yield from this approach is comparable to those where the benzylic alcohol was protected, and this strategy leads to considerable savings in time and materials.

Subsequent introduction of the phosphonate via Arbuzov reaction of the iodide, itself the result of displacement of the mesylate, smoothly gave the desired benzylic phosphonate 16 in 4 steps and 16% overall yield. Modified HWE coupling of phosphonate 16 with aldehyde 12 afforded the desired dimethoxy-3-deoxyschweinfurthin B (17) in modest yield.

Scheme 1.
Using very similar chemistry phosphonates 20 and 21 were synthesized (Scheme 2). Thus known methoxymethyl protected benzylic alcohols 18 and 19 were subjected to a three step protocol including preparation of the mesylates, conversion to
the corresponding iodides, and Arbuzov reactions. The desired phosphonates 20 and 21 were isolated in satisfactory yields.

\[
\text{HO-}
\begin{array}{c}
\text{R} \\
\text{R'}
\end{array}
\text{R} \xrightarrow{1) \text{MsCl, TEA}} \xrightarrow{2) \text{Nal, acetone}} \xrightarrow{3) \text{P(OEt)}_3} \text{P} \xrightarrow{\text{(EtO)}_2} \text{R}
\]

\[18 \text{ R} = \text{OMOM}, \text{R'} = \text{OMOM} \quad 19 \text{ R} = \text{OMOM}, \text{R'} = \text{H} \]
\[20 \text{ R} = \text{OMOM}, \text{R'} = \text{OMOM} \quad 21 \text{ R} = \text{OMOM}, \text{R'} = \text{H} \]

54% 83%

Scheme 2.

The phosphonate 26 (Scheme 3), which lacks both of the resorcinol hydroxyl groups was obtained by alkylation of the organolithium reagent derived by halogen metal exchange of known aryl bromide 22. The resulting geranylated arene 23 was then allowed to react with fluoride ion to remove the silyl ether protecting group and afford benzylic alcohol 24. A parallel series of three steps was used to convert alcohol 24 to the phosphonate 26 in excellent yield.

\[\text{nBuLi, geranyl bromide} \quad \text{TBSO} \quad \text{Br} \quad -78 \degree C \quad 70\% \]

\[\text{TBSO} \quad \text{R} \quad \text{TBAF} \quad 77\% \]

\[1) \text{MsCl, TEA} \quad 2) \text{Nal, acetone} \quad \text{P(OEt)}_3, \text{reflux} \]
\[24 \text{ R} = \text{OH} \quad 25 \text{ R} = \text{I} (76\% \text{ 2 steps}) \quad 26 \text{ R} = \text{P(O)(OEt)}_2 (97\%) \]

Scheme 3.

Difluorophosphonate 29 was synthesized from the commercial difluoro benzylic alcohol 27 (Scheme 4). Treatment of this alcohol under the optimized DoM conditions, and alkylation of the resulting dianion, afforded the arene 28 in moderate yield. A two
step reaction sequence involving transformation into the benzylic bromide and Arbuzov reaction with triethylphosphite gave the desired phosphonate 29.

Scheme 4

To obtain the terminally functionalized phosphonate 35, the requisite allyl bromide 31 was synthesized from the known silyl ether 30 by treatment with PBr₃. The benzylic alcohol 18 (Scheme 5) then was treated with KH followed by DoM and alkylation with the allylic bromide 31 to afford arene 32. The standard sequence of transformations, from the benzylic alcohol to the iodide followed by displacement with triethylphosphite, gave the protected phosphonate 34. This was subjected to reaction with TBAF under standard conditions to effect removal of the silyl ether and afford the desired phosphonate 35 in excellent yield.

Scheme 5.
With a representative group of phosphonates in hand, exploration of the required HWE couplings was initiated. Phosphonates 20, 21, 26, 29, 35 and the commercial phosphonate 36 were allowed to react with aldehyde 12 (Scheme 6, Table 1) under conditions parallel to those employed to synthesize dimethoxy-3-deoxyschweinfurthin B (17, *vide supra*). These reactions afforded the expected stilbenes 37-42 in moderate to excellent yields. These HWE couplings have been found reliable in the presence of the unprotected A-ring hydroxyl group, thus avoiding potentially problematic protection/deprotection sequences. Finally, the stilbenes 37, 38, and 41 were treated with camphorsulfonic acid (CSA) in methanol\textsuperscript{19} to free the resorcinol hydroxyl groups (Scheme 7, Table 2) and afford the desired compounds 43-45.

<table>
<thead>
<tr>
<th>Phosphonate</th>
<th>Substituents</th>
<th>Stilbene</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>( R = R' = \text{OMOM} ), ( R'' = H )</td>
<td>37</td>
<td>91%</td>
</tr>
<tr>
<td>21</td>
<td>( R = \text{OMOM} ), ( R' = R'' = H )</td>
<td>38</td>
<td>62%</td>
</tr>
<tr>
<td>26</td>
<td>( R = R' = H ), ( R'' = \text{C}<em>{10}\text{H}</em>{17} )</td>
<td>39</td>
<td>55%</td>
</tr>
<tr>
<td>29</td>
<td>( R = R' = F ), ( R'' = \text{C}<em>{10}\text{H}</em>{17} )</td>
<td>40</td>
<td>85%</td>
</tr>
<tr>
<td>35</td>
<td>( R = R' = \text{OMOM} ), ( R'' = \text{C}<em>{10}\text{H}</em>{16}\text{OH} )</td>
<td>41</td>
<td>60%</td>
</tr>
<tr>
<td>36</td>
<td>( R = R' = R'' = H )</td>
<td>42</td>
<td>90%</td>
</tr>
</tbody>
</table>

Table 1.

Scheme 6.

Scheme 7.
**Results and Discussion**

The seven target schweinfurthin analogs 17, 39, 40, 42-45 were tested at the NCI in the 60 cell line cytotoxicity screen. Every compound tested showed some cytotoxic effects (Table 3), with mean GI$_{50}$’s ranging from 42 μM for the difluoro analog 40, to 1.0 μM for the analog with the modified geranyl chain 45. Of special significance however was the pattern of activity for the compounds tested.

Our initial hypothesis was that the pharmacophore for differential activity in this family resided within the left half of the molecule. [?This seems reasonable based on the activity differences within the natural members of the family with schweinfurthin C (3) bearing an identical right half resorcinol substructure displaying essentially no differential correlated cytotoxicity whereas the hexahydroxanthenes schweinfurthin A (1) and B (2) show highly differential activity against the various cell lines.?] The dimethoxy derivative 17 was targeted with the hope that it would be more stable and still retain the cytotoxic profile of the family. Unfortunately, this proved not to be the case.

### Table 2. Results and Discussion

<table>
<thead>
<tr>
<th>Protected Stilbene</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>R = R' = OMOM, R'' = H</td>
<td>93%</td>
</tr>
<tr>
<td>38</td>
<td>R = OMOM, R' = R'' = H</td>
<td>63%</td>
</tr>
<tr>
<td>41</td>
<td>R = R' = OMOM, R'' = C$<em>{10}$H$</em>{16}$OH</td>
<td>42%</td>
</tr>
</tbody>
</table>

### Table 3. Cytotoxic activity of the schweinfurthin analogs at the GI$_{50}$ level and the correlation matrix for the 60 cell-line assay for the entire schweinfurthin family date.
Instead, dimethoxy-3-deoxyschweinfurthin B (17) was 10 fold less cytotoxic than the parent 3-deoxyschweinfurthin B. More intriguing was the differential cytotoxicity displayed by this analog (Figure 5). While displaying some differential activity across the tested cell lines, the pattern was not as well correlated with the natural product (correlation coefficient = 0.42 vs. 2) as was that of 3-deoxyschweinfurthin B (correlation coefficient = 0.75 vs. 2, Table 4). Clearly this result shows that methylation of the phenols is not well-tolerated but these findings also raise a question of how they function within the pharmacophore.

![Figure 5](image)

**Figure 5.** Mean graph comparison of 3-deoxyschweinfurthin B (13) and dimethoxy-3-deoxyschweinfurthin B (17). Deviations from the mean in log units against each cell line measured in the NCI 60 cell-line assay at the GI50 level, data is presented so that positive deviations indicate more potent cytotoxicity. Complete 60 cell line data is available in the supplemental material.

To probe the activity of other H-bond acceptors in the D-ring, the difluorinated compound 40 was tested. This compound was found to have the weakest antitumor activity of all the analogs tested so far, as well as a total lack of correlation to the activity.
of the natural products (correlation coefficient = -0.17 vs. 2). The results of these two
assays highlight the importance of this right half substructure to differential activity. A
further test of this theory involved compounds 39 and 42, both of which lack the
resorcinol oxygens. Both compounds show very weak cytoxicity (mean GI<sub>50</sub>'s of 19 and
15 µM respectively), and virtually no correlation to the natural product (correlation
coefficients 0.05 and 0.29 respectively vs. 2).

Once the importance of the hydroxyl hydrogen was identified, implicating this
substructure as a hydrogen bond donor in the pharmacophore, it was intriguing to
ascertain the requirements for the geranyl chain. Schweinfurthin D (4) which shows
similar cytotoxicity to schweinfurthin B (2) possesses a hydrated terminal olefin that
would seem to indicate a region with some tolerance to modification. This would be of
crucial importance in efforts to attach an active schweinfurthin to an affinity reagent or
other probe for studies aimed at elucidation of their cellular target(s). As a first step
towards deciphering the role of the geranyl chain it seemed appropriate to test if simple
deletion of this substructure would affect the activity.

Compound 43, lacking the geranyl chain, was shown to be ~30 times less active
(mean GI<sub>50</sub> = 7.8 µM) than 3-deoxyschweinfurthin B (13). It does however show some
degree of correlation in pattern of differential activity (correlation coefficient = 0.46 vs.
2) with the natural product. This result reveals the opportunity to install other motifs at
this position with a goal of finding a potential affinity probe. Compound 43 still does
show the same propensity towards degradation as the other stilbenes bearing the
resorcinol hydroxyl groups. Because a formal deletion of one of the D-ring hydroxyl
groups might be expected to improve the phenol 44 was tested and found to be two-fold
more cytotoxic than resorcinol 43 (mean GI\textsubscript{50} = 3.8 \mu M). Even more importantly, phenol 44 was found to have differential activity highly correlated with that of the natural product (correlation coefficient = 0.72).

Based on these results a partial pharmacophore could be recognized. At least one of the D-ring hydroxyl groups was crucial to activity, whereas the geranyl chain was a clearly amenable to some modification. In order to test our hypothesis of using the terminus of the geranyl system as a point of attachment to some form of affinity reagent, it would be necessary to append some form of reactive functional group to this position. This was realized in the analog 45 which contains an allylic alcohol at the trans position of the geranyl chain terminus. Gratifyingly this compound showed very good activity. It was essentially equipotent with schweinfurthin B (mean GI\textsubscript{50} = 1.0 \mu M) and this activity was highly correlated to the natural product (correlation coefficient = 0.78 vs. 2).

Conclusions

The schweinfurthin family of natural products offers a rare opportunity in the field of cytotoxic natural products. Their profile of activity across the NCI 60 cell line assay indicates these agents may act at a novel and as yet untapped mechanism of action against the susceptible tumor cell lines. The current studies encourage further testing of these compounds by making available synthetic analogs with high activity and more favorable chemical properties than the natural products. Finding highly correlated activity in the phenol analog 44 should lead to much less labile schweinfurthins and to more predictable supplies of these agents for the next stages of testing. Synthetic analog 45 which displays highly correlated and potent activity is suitable for studies leading to
the attachment of affinity reagents to probe the mechanism of action of this family of cytotoxins. Further work in these areas will be disclosed in due course.

**Experimental**

[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-dimethoxy-phenyl]-methanol (15) nBuLi (0.87 mL, 2.15 M in hexanes) was added dropwise to a solution of benzylic alcohol 14 (105 mg, 0.62 mmol) and TMEDA (0.28 mL, 1.9 mmol) in THF (10 mL) at -20 °C. After the solution was stirred at -20 °C for 1 h, CuBr as its DMS complex (255 mg, 1.24 mmol) was added in one portion and the solution was stirred for 1 h at -20 °C. Geranyl bromide (0.15 mL, 0.76 mmol) in THF (5 mL) was added via syringe and the reaction mixture was stirred for 2 h at -20 °C. The reaction was quenched by addition of 1N NH₄Cl, the aqueous layer was neutralized to pH 7 with 1N HCl, and this layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (20% EtOAc in hexanes) afforded alcohol 15 (76 mg, 40%) as a clear oil. $^1$H NMR $\delta$ 6.54 (s, 2H), 5.17-5.12 (tm, $J = 7.1$ Hz, 1H), 5.07-5.02 (tm, $J = 6.9$ Hz, 1H), 4.63 (s, 2H), 3.80 (s, 6H), 3.31 (d, $J = 7$ Hz, 2H), 2.04-1.89 (m, 4H), 1.74 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H); $^{13}$C NMR $\delta$ 160.3 (2C), 141.8, 136.8, 133.2, 126.6, 124.8, 119.9, 104.7 (2C), 68.0, 57.9 (2C), 41.9, 28.9, 27.8, 24.2, 19.8, 18.1. Anal. Calcd for C$_{19}$H$_{28}$O$_3$: C, 74.96; H, 9.27. Found: C, 74.82; H, 9.34.

[4-(3,7-dimethyl-octa-2,6-dienyl)-3,5-dimethoxy-benzyl]-phosphonic acid diethyl ester (16) Methanesulfonyl chloride (0.15 mL, 1.94 mmol) was added dropwise to a solution of alcohol 15 (181 mg, 0.59 mmol) and Et$_3$N (0.3 mL 1.9 mmol) in CH$_2$Cl$_2$ (5
mL) and the solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of H2O, and extracted with EtOAc. The combined organic layers were washed with NH4Cl (sat), brine, dried (MgSO4), and concentrated in vacuo. The resulting residue and NaI (310 mg, 2.06 mmol) were stirred in acetone (8 mL) for 24 h. The reaction mixture was concentrated in vacuo to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO3 and then with Na2S2O3 until the color faded, it was extracted with ether and the combined organic layers were dried (MgSO4) and concentrated in vacuo. The resulting yellow oil was added to triethyl phosphite (1.5 mL) and the mixture was heated at 100 °C for 20 h. After the solution was allowed to cool to rt, it was poured into ether (5 mL). The mixture was extracted with ether, dried (MgSO4), and concentrated in vacuo. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate 16 (73 mg, 40%) as a light yellow oil: 1H NMR δ 6.49 (d, J = 2.4 Hz, 2H), 5.18–5.13 (tm, J = 7.3 Hz, 1H), 5.07–5.02 (tm, J = 6.8 Hz, 1H), 4.09–3.98 (m, 4H), 3.80 (s, 6H), 3.31 (d, J = 7.0 Hz, 2H), 3.11 (d, JPH = 21.5 Hz, 2H), 2.06–1.94 (m, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.56 (s, 3H), 1.27 (tm, J = 7.0 Hz, 6H); 13C NMR δ 160.9 (d, JCP = 3.1 Hz, 2C), 137.5, 134.1, 132.9 (d, JCP = 9.0 Hz), 127.5, 125.7 (d, JCP = 2.9 Hz), 120.1 (d, JCP = 3.4 Hz), 108.6 (d, JCP = 6.7 Hz, 2C), 65.1 (d, JCP = 6.7 Hz, 2C), 58.7 (2C), 42.8, 37.1 (d, JCP = 137.3 Hz), 29.7, 28.6, 24.9, 20.6, 19.4 (d, JCP = 6.0 Hz, 2C), 18.9; 31P NMR δ +26.4; HRMS (El) calcd for C23H37O5PNa [M+ + Na], 447.2276; found 447.2265.

**Dimethoxy-3-deoxy Schweinfurthin B (17).** A solution of phosphonate 16 (20 mg, 0.04 mmol) and aldehyde 12 (10 mg, 0.03 mmol) in THF (1.5 mL) was added to a suspension
of NaH (29 mg, 0.71 mmol, 60% suspension in oil) and 15C5 (4 µL, 22 nmol) in THF (2.5 mL) at 0 °C. The resulting mixture was allowed to come to rt and stir for 20 hours. The solution was quenched with water, extracted (ether), and the combined organic layers were washed with brine. The residual organic layer was dried (MgSO₄), and concentrated in vacuo to give a yellow oil. Final purification by column chromatography (1:1 hexanes:EtOAc) afforded the target schweinfurthin analog 17 (6.4 mg, 37%) as a clear oil: \(^1\)H NMR δ 6.95 - 6.88 (m, 4H), 6.67 (s, 2H), 5.19 (t, \(J = 6.8\) Hz, 1H), 5.07 (t, \(J = 5.7\) Hz, 1H), 3.90 (s, 3H), 3.87 (s, 6H), 3.46 - 3.44 (m, 2H), 3.36 - 3.33 (m, 1H), 2.75 - 2.72 (m, 2H), 2.21 - 1.75 (m, 9H), 1.77 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H); HREIMS calcd for \(C_{37}H_{50}O_{5}\) (M⁺) 574.3658, found 574.3651.

(3,5-bis-Methoxymethoxy-benzyl)-phosphonic acid diethyl ester (20).

Methanesulfonyl chloride (1.4 mL, 18.1 mmol) was added dropwise to a stirred solution of alcohol 18 (881 mg, 3.9 mmol) and Et₃N (2.2 mL 15.76 mmol) in CH₂Cl₂ (150mL). The solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of water, and extracted with EtOAc. The combined organic layers were washed with NH₄Cl (sat), brine, dried (MgSO₄), and concentrated in vacuo. The yellow residue was treated with NaI (2.33 g, 15.6 mmol) in acetone (20 mL) for 24 h at rt. The reaction mixture was concentrated in vacuo to a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO₃ and then with Na₂S₂O₃ until the color faded, it was extracted with ether and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Final purification of the residue by flash column chromatography (30% EtOAc in hexanes) afforded compound iodide (1.12 g, 84%) as a yellow oil: \(^1\)H NMR δ 6.73 (d, \(J = 2.2\) Hz,
2H), 6.63 (t, J = 2.2 Hz, 1H), 5.2 (s, 4H), 4.4 (s, 2H), 3.5 (s, 6H); \(^{13}\)C NMR δ 158.5 (2C), 141.5, 110.3 (2C), 104.7, 94.7 (2C), 56.3 (2C), 5.5; HRMS (El) calcd for C\(_{11}\)H\(_{15}\)O\(_{4}\)I [M\(^+\)], 338.0015; found 338.0016. A stirred solution of this iodide (1.11g, 3.3 mmol) in triethyl phosphite (2.5 mL) was heated at reflux for 9 h, then it was allowed to cool to rt and poured into ether (8 mL). The resulting mixture was extracted with ether, dried (MgSO\(_4\)) and concentrated in vacuo. Final purification of the residue by flash chromatography (gradient, 30–80% EtOAc in hexanes) afforded phosphonate 20 (734 mg, 64%) as a light yellow oil: \(^1\)H NMR δ 6.58–6.55 (m, 3H), 5.06 (s, 4H), 3.97 (m, 4H), 3.39 (s, 6H), 3.01 (d, \(J_{\text{PH}} = 21.6\) Hz, 2H), 1.20 (tm, \(J = 7.1\) Hz, 6H); \(^{13}\)C NMR δ 158.2 (d, \(J_{\text{CP}} = 3.2\) Hz, 2C), 133.8 (d, \(J_{\text{CP}} = 8.8\) Hz), 111.2 (d, \(J_{\text{CP}} = 6.5\) Hz, 2C), 103.5 (d, \(J_{\text{CP}} = 3.4\) Hz), 94.4 (2C), 62.1 (d, \(J_{\text{CP}} = 6.6\) Hz, 2C), 55.9 (2C), 33.9 (d, \(J_{\text{CP}} = 138.1\) Hz), 16.3 (d, \(J_{\text{CP}} = 6.1\) Hz, 2C); \(^{31}\)P NMR δ + 25.7. Anal. Calcd for C\(_{15}\)H\(_{25}\)O\(_{7}\)P: C, 51.72; H, 7.23. Found: C, 51.55; H, 7.27.

(3-Methoxymethoxy-benzyl)-phosphonic acid diethyl ester (21) Methanesulfonyl chloride (1.0 mL, 12.9 mmol) was added dropwise to a solution of alcohol 19 (500 mg, 2.97 mmol) and Et\(_3\)N (0.5 mL 3.6 mmol) in CH\(_2\)Cl\(_2\) (10 mL) and the solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of H\(_2\)O, and extracted with EtOAc. The combined organic layers were washed with NH\(_4\)Cl (sat), brine, dried (MgSO\(_4\)), and concentrated in vacuo. The resulting yellow residue was treated with NaI (1 g, 3.6 mmol) in acetone (15 mL) for 24 h at rt. This reaction mixture was concentrated in vacuo to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO\(_3\) and then with Na\(_2\)S\(_2\)O\(_3\) until the color faded, it was extracted with ether and the combined organic
layers were dried (MgSO₄) and concentrated in vacuo. The resulting yellow oil was added to triethyl phosphate (4 mL) and the solution was heated at 100 °C for 20 h. After the solution was allowed to cool to rt, it was poured into ether (10 mL). The mixture was extracted with ether, dried (MgSO₄), and concentrated in vacuo. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate 21 (709 mg, 83%) as a light yellow oil: ¹H NMR δ 7.20 (tr, J = 7.9 Hz, 1H), 7.08-6.89 (m, 3H), 5.17 (s, 2H), 4.15-3.97 (m, 4H), 3.44 (s, 3H), 3.11 (d, JₚH = 21.6 Hz, 2H), 1.27-1.22 (m, 6H); ¹³C NMR δ 157.1 (d, JCP = 3.2 Hz), 132.9 (d, JCP = 8.9 Hz), 129.2 (d, JCP = 3.1 Hz), 123.1 (d, JCP = 6.5 Hz), 117.5 (d, JCP = 6.5 Hz), 114.5 (d, JCP = 3.5 Hz), 94.1, 61.8 (d, JCP = 6.7 Hz, 2C), 55.6, 33.4 (d, JCP = 137.2 Hz), 16.1 (d, JCP = 6.0 Hz, 2C); ³¹P NMR δ +25.8. Anal. Calcd for C₁₃H₂₁O₅P: C, 54.16; H, 7.34. Found: C, 53.98; H, 7.35.

tert-Butyl-[4-(3,7-dimethyl-octa-2,6-dienyl)-benzyloxy]-dimethyl-silane (23) nBuLi (7.90 mL, 2.5 M in hexane, 19.8 mmol) was added dropwise to a stirred solution of aryl bromide 22 (3.13 g, 10.4 mmol) in THF (15 mL) over 15 min at −78 °C. The reaction mixture was allowed to stir for 2 h at −78 °C. Geranyl bromide (2.5 mL, 12.6 mmol) was added dropwise and the reaction mixture was stirred for 2 h at −78 °C. The reaction mixture was allowed to warm to rt, was quenched by addition of H₂O, and then was extracted with ether. The combined organic layers were washed with NH₄Cl (sat), brine, dried (MgSO₄), and concentrated in vacuo. Final purification of the residue by flash column chromatography (hexanes) afforded compound 23 (2.61 g, 70%) as a light yellow oil: ¹H NMR δ 7.24-7.19 (m, 2H), 7.14-7.12 (m, 2H), 5.43-5.38 (tm, J = 7.4 Hz, 1H), 5.20-5.15 (tm, J = 7.5 Hz, 1H), 4.77 (s, 2H), 3.41 (d, J = 7.4 Hz, 2H), 2.19-2.09 (m, 4H), 1.77 (s, 3H), 1.75 (s, 3H), 1.67 (s, 3H), 1.01 (s, 9H), 0.16 (s, 6H); ¹³C NMR δ 140.6,
140.0, 136.3, 131.6, 128.4 (2C), 126.4 (2C), 124.5, 123.4, 65.1, 39.9, 34.1, 26.8, 26.2
(3C), 25.9, 18.6, 17.9, 16.3, -5.0 (2C). Anal. Calcd for C_{23}H_{38}OSi: C, 77.01; H, 10.68.
Found: C, 77.08; H, 10.69.

[4-(3,7-Dimethyl-octa-2,6-dienyl)-phenyl]-methanol (24) TBAF (26.0 mL, 1.0 M in
THF, 26.0 mmol) was added dropwise to a stirred solution of protected alcohol 23 (2.56
 g, 7.14 mmol) in THF (20 mL). The solution was stirred for 2 h at 0 °C and then was
allowed to warm to rt over 5 h. The reaction was quenched by addition of NH_{4}Cl (sat),
and extracted with EtOAc. The combined organic layers were washed with brine, dried
(MgSO_{4}), and concentrated in vacuo. Final purification of the residue by flash column
chromatography (20% EtOAc in hexanes) afforded compound 24 (1.35 g, 77%) as a light
yellow oil: \textsuperscript{1}H NMR \delta 7.28-7.24 (m, 2H), 7.18-7.15 (m, 2H), 5.35–5.30 (tm, J = 7.2 Hz,
1H), 5.12–5.08 (tm, J = 6.7 Hz, 1H), 4.63 (s, 2H), 3.35 (d, J = 7.3 Hz, 2H), 2.12–2.02 (m,
4H), 1.70 (s, 1H exchanges with D_{2}O), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); \textsuperscript{13}C NMR
\delta 141.6, 138.5, 136.5, 131.7, 128.7 (2C), 127.4 (2C), 124.4, 123.1, 65.4, 39.9, 34.1, 26.8,
26.0, 17.9, 16.3; HRMS (El) calcd for C_{17}H_{24}O [M+], 244.1827; found 244.1832 .

1-(3,7-Dimethyl-octa-2,6-dienyl)-4-iodomethyl-benzene (25) Methanesulfonyl
chloride (1.8 mL, 23.3 mmol) was added dropwise to a stirred solution of alcohol 24
(1.27 g, 5.22 mmol) and Et_{3}N (3 mL 21.5 mmol) in CH_{2}Cl_{2} (20 mL) at 0 °C over 2 h. The
reaction mixture was allowed to warm to rt over 5 h. After the reaction was quenched by
addition of water, it was extracted with EtOAc. The combined organic layers were
washed with NH_{4}Cl (sat), brine, dried (MgSO_{4}), and concentrated in vacuo. The
resulting yellow residue was treated with NaI (3.51 g, 23.4 mmol) in acetone (20 mL) at
rt for 24 h. The reaction mixture was concentrated in vacuo to afford a red solid, which
was dissolved in EtOAc. After the resulting solution was washed once with NaHCO₃ and then with Na₂S₂O₃ until the color faded, the aqueous layer was extracted with ether and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Final purification of the residue by flash column chromatography (20% EtOAc in hexanes) afforded compound 25 (1.44 g, 78%) as a yellow oil: ¹H NMR δ 7.30-7.24 (m, 2H), 7.11-7.08 (m, 2H), 5.35-5.30 (tm, J = 7.2 Hz, 1H), 5.14-5.09 (tm, J = 6.6 Hz, 1H), 4.47 (s, 2H), 3.33 (d, J = 7.2 Hz, 2H), 2.14-2.03 (m, 4H), 1.71 (s, 6H), 1.61 (s, 3H); ¹³C NMR δ. 141.9 (2C), 136.8, 131.7, 129.0 (2C), 128.9 (2C), 124.4, 122.8, 39.9, 34.1, 26.8, 26.0, 17.9, 16.3, 6.4; HRMS (El) calcd for C₁₇H₂₃[C–1], 227.1800; found 227.1801.

Diethyl[4-(3,7-dimethyl-oct-2,6-dienyl)-benzyl]phosphonate (26) A stirred solution of iodide 25 (1.35 g, 3.82 mmol) in triethyl phosphite (25 mL) was heated at reflux for 4 h, and then allowed to cool to rt. Excess triethyl phosphite was removed by vacuum distillation and the resulting yellow oil was purified by flash chromatography (30% EtOAc in hexanes) to afford phosphonate 26 (1.34 g, 97%) as a light yellow oil: ¹H NMR δ 7.22-7.18 (m, 2H), 7.12-7.09 (m, 2H), 5.33–5.30 (tm, J = 7.2 Hz, 1H), 5.11–5.08 (tm, J = 6.6 Hz, 1H), 4.06-4.00 (m, 4H), 3.32 (d, J = 7.2 Hz, 2H), 3.11 (d, JₚH = 21.3 Hz, 2H), 2.12–2.05 (m, 4H), 1.69 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.24 (t, J = 7.2 Hz, 6H); ¹³C NMR δ 140.6 (d, JₚC = 3.8 Hz), 136.5, 131.7, 129.8 (d, JₚC = 6.5 Hz, 2C), 128.9 (d, JₚC = 9.3 Hz), 128.7 (d, JₚC = 3.1 Hz, 2C), 124.5, 123.1, 62.2 (d, JₚC = 6.8 Hz, 2C), 39.9, 34.4, 32.6 (d, JₚC = 138.2 Hz), 26.8, 26.0, 17.9, 16.6 (d, JₚC = 6.1 Hz, 2C), 16.3; ³¹P NMR δ +26.6. Anal. Calcd for C₂₁H₃₃O₃P: C, 69.21; H, 9.13. Found: C, 69.09; H, 9.16.

[4-(3,7-Dimethyl-oct-2,6-dienyl)-3,5-difluoro-phenyl]-methanol (28) A solution of benzylic alcohol 27 (67 mg, 0.46 mmol) and TMEDA (0.21 mL, 1.4 mmol) in THF (10
mL) was cooled to −20 °C. After nBuLi (0.64 mL, 2.15 M in hexanes) was added dropwise and the solution was stirred at −20 °C for 1 h, CuBr as its DMS complex (192 mg, 0.93 mmol) was added in one portion and the solution was stirred for 1 h at −20 °C. A solution of geranyl bromide (0.11 mL, 0.55 mmol) in THF (5 mL) was added to the reaction mixture via syringe at −20 °C and the solution was stirred for 2 h. The reaction was quenched by addition of 1N NH₄Cl, the aqueous layer was neutralized to pH 7 with 1N HCl, and then was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc in hexanes) afforded alcohol 28 (68 mg, 53%) as a clear oil: ¹H NMR δ 6.91–6.83 (dm, J_HF = 7.5 Hz, 2H), 5.23–5.19 (tm, J = 7.3 Hz, 1H), 5.08–5.03 (tm, J = 6.8 Hz, 1H), 4.65 (d, J = 5.6 Hz, 2H, becomes a singlet at D₂O wash), 3.36 (d, J = 7.2 Hz, 2H), 2.07–1.96 (m, 4H), 1.75 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H); ¹³C NMR δ 161.6 (dd, J_CF = 246.9, 9.6 Hz, 2C), 141.2 (t, J_CF = 9.0 Hz), 136.8, 131.7, 124.3, 120.7, 116.4 (t, J_CF = 20.9 Hz), 109.4 (dd, J_CF = 26.6, 8.9 Hz, 2C), 54.4 (t, J_CF = 2.1 Hz), 39.8, 26.7, 25.9, 21.5 (t, J_CF = 2.5 Hz), 17.9, 16.2; HRMS (EI) calcd for C₁₇H₂₂F₂O [M⁺], 280.1639; found 280.1639.

[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-difluoro-benzyl]-phosphonic acid diethyl ester (29) PBr₃ (0.03 mL, 0.32 mmol) was added dropwise to a solution of alcohol 28 (180 mg, 0.64 mmol) in ether (10 mL) and the solution was stirred for 7 h at 0 °C. The reaction mixture was poured into ice water, extracted with ether, and washed with brine. The combined organic layer was dried (MgSO₄), and concentrated in vacuo. The resulting yellow oil was added to triethyl phosphite (3 mL) and sodium iodide (62 mg, 0.41 mmol), and the mixture was heated at 100 °C for 30 h. After this solution was
allowed to cool to rt, it was poured into ether (10 mL) and washed with sodium thiosulfate. The mixture was extracted with ether, dried (MgSO₄), and concentrated in vacuo. The initial yellow oil was purified by flash chromatography (gradient, 30–80% EtOAc in hexanes) to afford phosphonate 29 (153 mg, 60%) as a light yellow oil: ¹H NMR δ 6.84–6.77 (m, 2H), 5.22–5.17 (tm, J = 6.4 Hz, 1H), 5.08–5.03 (tm, J = 6.9 Hz, 1H), 4.11–4.00 (m, 4H), 3.35–3.32 (dm, J = 7.2 Hz, 2H), 3.11–3.04 (dm, J_PH = 21.7 Hz, 2H), 2.07–1.92 (m, 4H), 1.74 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.31–1.24 (tm, J = 7.1 Hz, 6H); ¹³C NMR δ 161.4 (ddd, J_CF = 245.7, 10.0 Hz, J_CP = 3.5 Hz, 2C), 136.8, 132.0–131.6 (m), 131.7, 124.3, 120.7, 116.0 (td, J_CF = 20.3 Hz, J_CP = 3.5 Hz), 112.9–112.5 (m, 2C), 65.5 (d, J_CP = 6.75 Hz, 2C), 39.8, 33.5 (dd, J_CP = 139.2 Hz, J_CF = 1.9 Hz), 26.7, 25.9, 21.4 (t, J_CF = 1.7 Hz), 17.9, 16.6 (d, J_CP = 6.00 Hz, 2C), 16.1; ³¹P NMR δ +24.8 (t, J_PF = 2.3 Hz). Anal. Calcd for C₂₁H₃₁F₂O₃P: C, 62.99; H, 7.80. Found: C, 63.22; H, 7.98.

{4-[8-(tert-butyl-diphenyl-silanyloxy)-3,7-dimethyl-octa-2,6-dienyl]-3,5-bis-methoxymethoxy-phenyl}-methanol (32) PBr₃ (0.7 mL, 7.4 mmol) was added dropwise to a solution of alcohol 30 (521 mg, 1.27 mmol) in ether (10 mL) and the solution was stirred for 7 h at 0 °C. The reaction mixture was poured into ice water, extracted with ether, and washed with brine. The combined organic layer was dried (MgSO₄), and concentrated in vacuo to give a yellow residue, bromide 31. A solution of benzylalcohol 18 (305 mg, 1.34 mmol) in THF (5 mL) was added to a stirred suspension of KH (87 mg, 2.2 mmol) in THF (10 mL) and the reaction mixture was stirred for 1 h at 0 °C. After TMEDA (0.4 mL, 2.7 mmol) was added, the solution was cooled to −20 °C, then nBuLi (1.87 mL, 2.15 M in hexanes) was added dropwise and the solution was stirred at −20 °C for 1 h. CuBr as its DMS complex (556 mg, 2.7 mmol) was added in
one portion and the solution was stirred for 1 h at -20 °C. Bromide 31 in THF (5 mL) was added to the reaction mixture via syringe at -20 °C. After 2 h, the reaction was quenched by addition of 1N NH₄Cl, and the aqueous layer was neutralized to pH 7 with 1N HCl, and extracted with EtOAc. The combined organic layer was washed with brine, dried (MgSO₄), and concentrated in vacuo. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded compound 32 (341 mg, 43% from alcohol 30) as a clear oil: ¹H NMR δ 7.70–7.67 (m, 4H), 7.43–7.35 (m, 6H), 6.79 (s, 2H), 5.43–5.39 (tm, J= 7.0 Hz, 1H), 5.26–5.19 (m, 5H), 4.62 (s, 2H), 4.03 (s, 2H), 3.47 (s, 6H), 3.40 (d, J = 9 Hz, 2H), 2.19–1.96 (m, 4H), 1.81 (s, 3H), 1.59 (s, 3H), 1.06 (s, 9H); ¹³C NMR δ 156.0 (2C), 140.2, 135.8 (4C), 134.8, 134.2 (2C), 134.1, 129.7 (2C), 127.8 (4C), 124.6, 122.9, 119.6, 106.7 (2C), 94.6 (2C), 69.3, 65.7, 56.2 (2C), 39.8, 27.1 (3C), 26.4, 22.8, 19.5, 16.3, 13.7. Anal. Calcd for C₃₇H₇₀O₆Si: C, 71.81; H, 8.14. Found: C, 71.72; H, 7.98.

tert-Butyl-[8-(4-iodomethyl-2,6-bis-methoxymethoxy-phenyl)-2,6-dimethyl-octa-2,6-dienyloxy]-diphenyl-silane (33) Methanesulfonyl chloride (0.1 mL, 1.3 mmol) was added dropwise to a stirred solution of alcohol 32 (364 mg, 0.62 mmol) and Et₃N (0.2 mL 1.4 mmol) in CH₂Cl₂ (5 mL) and the solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of H₂O, and extracted with EtOAc. The combined organic layers were washed with NH₄Cl (sat) and brine, dried (MgSO₄), and concentrated in vacuo. The resulting yellow residue was allowed to react with NaI (132 mg, 0.886 mmol) in acetone (8 mL) for 24 h at rt. The reaction mixture was concentrated in vacuo to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO₃ and then with
Na$_2$S$_2$O$_3$ until the color faded, it was extracted with ether and the combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded the iodide 33 (347 mg, 77%) as a yellow oil: $^1$H NMR $\delta$ 7.77–7.72 (m, 4H), 7.49–7.38 (m, 6H), 6.84 (s, 2H), 5.48–5.44 (tm, $J = 6.6$ Hz, 1H), 5.29–5.19 (tm, $J = 6.0$ Hz, 1H), 5.20 (s, 4H), 4.43 (s, 2H), 4.08 (s, 2H), 3.50 (s, 6H), 3.41 (d, $J = 7.1$ Hz, 2H), 2.30–2.01 (m, 4H), 1.85 (s, 3H), 1.63 (s, 3H), 1.11 (s, 9H); $^{13}$C NMR $\delta$ 155.8 (2C), 138.1, 135.7 (4C), 134.9, 134.1 (2C), 134.0, 129.7 (2C), 127.8 (4C), 124.5, 122.6, 120.2, 108.6 (2C), 94.6 (2C), 69.2, 56.2 (2C), 39.8, 27.0 (3C), 26.3, 22.9, 19.5, 16.3, 13.7, 6.7; HRMS (EI) calcd for C$_{37}$H$_{49}$O$_5$Si [M$^+$], 728.2394; found 728.2395.

{4-[8-(tert-Butyl-diphenyl-silanyloxy)-3,7-dimethyl-octa-2,6-dienyl]-3,5-bis-methoxymethoxy-benzyl]-phosphonic acid diethyl ester (34) A solution of iodide 33 (68 mg, 0.093 mmol) and sodium iodide (39 mg, 0.26 mmol) in triethyl phosphite (1.5 mL) was heated at 100 °C for 20 h, allowed to cool to rt, and poured into ether (5 mL). The resulting mixture was extracted with ether, dried (MgSO$_4$), and concentrated in vacuo. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate 34 (63.5 mg, 92%) as light yellow oil: $^1$H NMR $\delta$ 7.70–7.67 (m, 4H), 7.42–7.34 (m, 6H), 6.70 (d, $J_{HP} = 2.3$ Hz, 2H), 5.42–5.39 (tm, $J = 5.7$ Hz, 1H), 5.21–5.17 (tm, $J = 7.0$ Hz, 1H), 5.17 (s, 4H), 4.10–4.00 (m, 6H), 3.45 (s, 6H), 3.37 (d, $J = 7.0$ Hz, 2H), 3.09 (d, $J_{PH} = 21.5$ Hz, 2H), 2.14–1.95 (m, 4H), 1.80 (s, 3H), 1.58 (s, 3H), 1.28 (tm, $J = 7.08$ Hz, 6H), 1.06 (s, 9H); $^{13}$C NMR $\delta$ 155.8 (d, $J_{CP} = 3.2$ Hz, 2C), 135.8 (4C), 134.7, 134.1 (2C), 134.0, 130.5 (d, $J_{CP} = 9.0$ Hz), 129.7 (2C), 127.7 (4C), 124.7, 123.0, 118.9 (d, $J_{CP} = 3.9$ Hz), 109.8 (d, $J_{CP} = 6.6$ Hz, 2C), 94.6 (2C), 69.2, 62.3
(d, $J_{CP} = 6.7$ Hz, 2C), 56.2 (2C), 39.8, 34.1 (d, $J_{CP} = 138.3$ Hz), 27.0 (3C), 26.5, 22.7, 19.5, 16.6 (d, $J_{CP} = 5.8$ Hz, 2C), 16.3, 13.6; $^{31}$P NMR $\delta$ +26.2. Anal. Calcd for C$_{41}$H$_{59}$O$_8$PSi: C, 66.64; H, 8.05. Found: C, 66.58; H, 8.32.

[4-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-3,5-bis-methoxymethoxy-benzyl]-phosphonic acid diethyl ester (35) TBAF (0.3 mL, 1M in THF, 0.3 mmol) was added to a solution of phosphonate 34 (55.1 mg, 0.075 mmol) in THF (3 mL) and the solution was stirred for 3 h at rt. The reaction was quenched by addition of water and EtOAc, and then extracted with EtOAc. The combined organic layer was washed with brine, dried (MgSO$_4$), and concentrated in vacuo. Final purification of the residue by flash column chromatography (gradient, 60–100% EtOAc in hexanes) afforded compound 35 (36 mg, 96%) as a clear oil: $^1$H NMR $\delta$ 6.66 (broad s, 2H), 5.30–5.24 (m, 1H), 5.13–5.06 (m, 5H), 4.04–3.97 (m, 4H), 3.83 (s, 2H), 3.42 (s, 6H), 3.32 (d, $J = 7.0$ Hz, 2H), 3.04 (d, $J_{PH} = 21.5$ Hz, 2H), 2.07–1.95 (m, 4H), 1.73 (s, 3H), 1.53 (s, 3H), 1.24 (t, $J = 6.8$ Hz, 6H); $^{13}$C NMR $\delta$ 155.8 (d, $J_{CP} = 3.4$ Hz, 2C), 135.1, 134.1, 130.4 (d, $J_{CP} = 9.1$ Hz), 125.9, 123.4, 119.1 (d, $J_{CP} = 3.9$ Hz), 109.9 (d, $J_{CP} = 6.6$ Hz, 2C), 94.7 (2C), 68.9, 62.3 (d, $J_{CP} = 6.7$ Hz, 2C), 56.2 (2C), 39.5, 34.0 (d, $J_{CP} = 138.3$ Hz), 26.1, 22.7, 16.6 (d, $J_{CP} = 6.1$ Hz, 2C), 16.2, 13.8; $^{31}$P NMR $\delta$ +26.2; HRMS (El) calcd for C$_{25}$H$_{41}$O$_8$P [M$^+$], 500.2539; found 500.2531.

7-[2-(3,5-bis-Methoxymethoxy-phenyl)-vinyl]-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (37) To a stirred suspension of NaH (30 mg, 1.3 mmol) and 15C5 (5 µL, 3 mol %) in THF (5 mL) was added phosphonate 20 (25 mg, 0.12 mmol) and aldehyde 12 (20 mg, 0.066 mmol) at 0 ºC. The reaction mixture was allowed to warm to rt over 10 h. The reaction was quenched by addition of water, and
extracted with EtOAc. After the combined organic layers were washed with brine, dried (MgSO₄), and concentrated *in vacuo*, final purification by flash column chromatography (50% EtOAc in hexanes) afforded compound 37 (30 mg, 91%) as a clear oil: $^1$H NMR δ 7.00 (d, $J = 17.1$ Hz, 1H), 6.90–6.85 (m, 5H), 6.64 (t, $J = 2.1$ Hz, 1H), 5.20 (s, 4H), 3.90 (s, 3H), 3.51 (s, 6H), 3.46–3.42 (m, 1H), 2.76–2.74 (m, 1H), 2.73–2.71 (m, 1H), 2.17–2.11 (m, 1H), 1.91–1.81 (m, 2H), 1.75–1.54 (m, 2H), 1.27 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR δ 158.7 (2C), 149.2, 143.0, 140.1, 129.6, 128.9, 126.2, 122.8, 120.9, 107.8 (2C), 107.3, 104.1, 94.7 (2C), 78.2, 77.3, 55.3 (2C), 56.2, 46.9, 38.6, 37.9, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (El) calcd for C$_{29}$H$_{38}$O$_{7}$ [M$^+$], 498.2618; found 498.2608.

5-Methoxy-7-[2-(3-methoxymethoxy-phenyl)-vinyl]-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (38). To a stirred suspension of NaH (27 mg, 0.68 mmol) and 15C5 (5 µL, 3 mol %) in THF was added phosphonate 21 (50 mg, 0.173 mmol) and aldehyde 12 (20 mg, 0.066 mmol) at 0 °C and the reaction mixture was allowed to warm to rt over 10 h. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (50% EtOAc in hexanes) afforded compound 38 (18 mg, 62%) as a clear oil: $^1$H NMR δ 7.29–6.87 (m, 8H), 5.21 (s, 2H), 3.90 (s, 3H), 3.51 (s, 3H), 3.46–3.39 (m, 1H), 2.74–2.72 (m, 2H), 2.16–1.59 (m, 5H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR δ 157.8, 149.2, 142.9, 139.5, 129.8, 129.3, 129.0, 126.3, 122.9, 120.9, 120.3, 115.3, 113.9, 107.2, 94.7, 78.2, 77.3, 56.3, 46.9, 38.6, 37.9, 29.9, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (ES$^+$) calcd for C$_{27}$H$_{34}$O$_{7}$ (M+H)$^+$, 439.2484; found 439.2475.
7-{2-[4-(3,7-Dimethyl-octa-6,7-dienyl)-phenyl]-vinyl}-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (39). To a suspension of NaH (64 mg, 1.6 mmol, 60% in mineral oil) in THF (17 mL) at 0 °C was added a mixture of phosphonate 26 (56 mg, 0.15 mmol) and aldehyde 12 (28 mg, 0.09 mmol) in THF (3 mL). After 5 min 15C5 (10 μL) was added and the reaction was allowed to warm to rt and stir for 19 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine and dried (MgSO₄). Concentration in vacuo afforded a yellow oil and final purification by column chromatography (1:1 hexanes:EtOAc) gave the stilbene 39 (26 mg, 55%) as a clear oil: ¹H NMR δ 7.40 (m, 2H), 7.16 (m, 2H), 6.95 – 6.94 (m, 2H), 6.89 – 6.88 (m, 2H), 5.34 (td, J = 7.3, 1.0 Hz, 1H), 5.11 (t, J = 6.7 Hz, 1H), 3.89 (s, 3H), 3.43 (dd, J = 11.7, 4.0 Hz, 1H), 3.35 (d, J = 7.3 Hz, 2H), 2.74 – 2.71 (m, 2H), 2.16 – 2.04 (m, 5H), 1.90 – 1.81 (m, 2H), 1.80 – 1.70 (m, 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 148.9, 142.5, 140.9, 136.3, 135.2, 131.4, 129.1 (2C), 128.6, 127.8, 126.2, 126.2 (2C), 124.2, 122.8, 122.6, 120.4, 106.9, 78.0, 77.0, 56.0, 46.7, 39.7, 38.4, 37.6, 33.9, 28.3, 27.3, 26.6, 25.7, 23.1, 19.8, 17.7, 16.1, 14.3; HREIMS calcd for C₃₅H₄₆O₃ (M⁺) 514.3447, found 514.3447.

7-{2-[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-difluoro-phenyl]-vinyl}-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (40) To a stirred suspension of NaH (30 mg, 1.3 mmol) and 15C5 (5 μL, 3 mol %) in THF (5 mL) was added phosphonate 29 (71 mg, 0.177 mmol) and aldehyde 12 (20 mg, 0.066 mmol) at 0 °C and the solution was allowed to warm to rt over 10 h. The reaction was quenched by addition of water and then was extracted with EtOAc. The combined organic layers were washed
with brine, dried (MgSO₄), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (50% EtOAc in hexanes) afforded compound 40 (30.9 mg, 85%) as a clear oil: ¹H NMR δ 6.99–6.79 (m, 6H), 5.26–5.22 (tm, J = 7.0 Hz, 1H), 5.09–5.04 (tm, J = 6.8 Hz, 1H), 3.9 (s, 3H), 3.47–3.42 (m, 1H), 3.37–3.35 (dm, J = 7.2 Hz, 2H), 2.77–2.74 (m, 1H), 2.73–2.70 (m, 1H), 2.18–1.82 (m, 7H), 1.76 (s, 3H), 1.72–1.69 (m, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 163.4–160.0 (dd, JCF = 241.8 Hz, JCF = 9.8 Hz, 2C), 149.3, 143.4, 137.9, 136.8, 131.7, 130.5, 124.5 (t, JCF = 9.5 Hz), 124.3, 123.0, 121.1, 120.8, 115.9 (t, JCF = 23.4 Hz), 110.0, 108.7 (dd, JCF = 26.6 Hz, JCF = 8.6 Hz, 2C), 107.3, 78.2, 77.4, 56.3, 47.0, 39.8, 38.6, 37.9, 28.5, 27.6, 26.7, 25.8, 23.4, 21.6 (t, JCF = 2.0 Hz), 20.1, 17.8, 16.2, 14.5; HRMS (El) calcd for C₃₅H₄₄O₄F₂[M⁺], 550.3259; found 550.3256.

7-{2-[4-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-3,5-bis-methoxymethoxy-phenyl]-vinyl}-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (41) To a suspension of NaH (12 mg, 0.3 mmol) and 15C5 (5 μL, 3 mol %) in THF (5mL) was added phosphonate 35 (34 mg, 0.068 mmol) and aldehyde 12 (16 mg, 0.053 mmol) at 0 °C and the reaction mixture was allowed to warm to rt over 10 h. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated *in vacuo*. Purification of the resulting oil by flash column chromatography (50% EtOAc in hexanes) afforded compound 41 (20.5 mg, 60%) as a clear oil: ¹H NMR δ 6.99–6.87 (m, 6H), 5.37–5.33 (tm, J = 6.0 Hz, 1H), 5.24–5.18 (m, 5H), 3.95 (s, 2H), 3.91 (s, 3H), 3.52–3.39 (m, 9H), 2.74–2.72 (m, 1H), 2.72–2.70 (m, 1H), 2.17–1.98 (m, 5H), 1.90–1.57 (m, 10H), 1.26 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 156.1 (2C), 149.2, 142.8, 137.0, 134.9,
5-Methoxy-1,1,4a-trimethyl-7-styryl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (42)
To a suspension of NaH (26 mg, 1 mmol) and 15C5 (5 ρL, 3 mol %) in THF (5 mL) was added phosphonate 36 (25 mg, 0.12 mmol) and aldehyde 12 (15.8 mg, 0.05 mmol) at 0 °C and the reaction mixture was stirred for 10 h at rt. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO$_4$), and concentrated in vacuo. Final purification of the residue by flash column chromatography (35% EtOAc in hexanes) afforded compound 42 (17 mg, 90%) as a clear oil: $^1$H NMR δ 7.50–7.47 (m, 2H), 7.37–7.34 (m, 2H), 7.26–7.20 (m, 1H), 6.98 (d, $J$ = 8.5 Hz, 2H), 6.91–6.87 (m, 2H), 3.90 (s, 3H), 3.46–3.41 (m, 1H), 2.77–2.75 (m, 1H), 2.72–2.68 (m, 2H), 2.16–2.11 (m, 1H), 1.90–1.81 (m, 2H), 1.74–1.55 (m, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR δ 149.2, 142.9, 137.9, 129.2, 128.9 (2C), 128.8, 127.4, 126.5, 126.4 (2C), 122.9, 120.8, 107.2, 78.2, 77.3, 56.3, 47.0, 38.6, 37.9, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (EI) calcd for C$_{29}$H$_{54}$O$_8$ [M$^+$], 650.3819; found 650.3812.

5-[2-(7-Hydroxy-4-methoxy-8,8,10a-trimethyl-5,7,8,8a,9,10a-hexahydro-6H-xanthen-2-yl)-vinyl]-benzene-1,3-diol (43) To a stirred solution of stilbene 37 (30 mg, 0.06 mmol) in methanol (5 mL) was added CSA (20 mg, 0.09 mmol) and the solution was allowed to stir 10 h at 50 °C. The reaction mixture was allowed to cool to rt, concentrated in vacuo, and the residue was dissolved in EtOAc and water. The mixture was extracted with ether, washed with brine, dried (MgSO$_4$), and concentrated in vacuo.
Final purification of the residue by flash column chromatography (60% EtOAc in hexanes) afforded compound 43 (23 mg, 93%) as a clear oil: $^1$H NMR (CDCl$_3$/CD$_3$OD) $\delta$ 7.06–6.88 (m, 4H), 6.58 (d, $J$ = 2.0 Hz, 2H), 6.31 (t, $J$ = 2.0 Hz, 1H), 3.97 (s, 3H), 3.75–3.68 (m, 1H), 2.96–2.81 (m, 2H), 2.20–1.68 (m, 5H), 1.33 (s, 3H), 1.16 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (CDCl$_3$/CD$_3$OD) $\delta$ 157.7 (2C), 148.3, 142.0, 139.4, 128.8, 128.0, 125.9, 122.3, 120.3, 106.6, 104.3 (2C), 101.2, 77.0, 76.7, 55.1, 46.9, 37.8, 37.2, 27.2, 26.2, 22.5, 18.9, 13.4; HRMS (EI) calcd for C$_{25}$H$_{30}$O$_5$ [M$^+$], 410.2093; found 410.2093.

7-[2-(3-Hydroxy-phenyl)-vinyl]-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (44) CSA (17 mg, 0.073 mmol) was added to a stirred solution of stilbene 38 (16 mg, 0.036 mmol) in methanol (5 mL) and the reaction mixture was allowed to stir for 15 h at rt. The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc and water. The mixture was extracted with ether, the organic layer was washed with brine, dried (MgSO$_4$), and concentrated in vacuo.

Purification of the residue by flash column chromatography (60% EtOAc in hexanes) afforded compound 44 (9 mg, 63%) as a clear oil: $^1$H NMR $\delta$ 7.26–7.19 (m, 1H), 7.06–6.85 (m, 6H), 6.73–6.70 (m, 1H), 5.05 (s, 1H, exchangeable with D$_2$O), 3.83 (s, 3H), 3.46–3.43 (m, 1H), 2.75–2.66 (m, 2H), 2.18–1.61 (m, 5H), 1.49 (br. s, 1H, exchangeable with D$_2$O), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR $\delta$ 156.1, 149.2, 142.9, 139.6, 130.0, 129.4, 129.0, 126.1, 122.9, 120.9, 119.3, 114.4, 112.9, 107.2, 78.3, 77.4, 56.2, 46.9, 38.6, 37.8, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (EI) calcd for C$_{25}$H$_{30}$O$_4$ (M$^+$), 395.2222; found 395.2237.

2-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-5-[2-(7-hydroxy-4-methoxy-8,8,10a-trimethyl-5,7,8,8a,9,10a-hexahydro-6H-xanthen-2-yl)-vinyl]-benzene-1,3-diol (45)
CSA (20 mg, 0.09 mmol) was added to a stirred solution of stilbene 41 (17 mg, 0.026 mmol) in methanol (5 mL) and the reaction mixture was allowed to stir for 15 h at 50 °C. The reaction mixture was allowed to cool to rt, and concentrated *in vacuo* and the residue was dissolved in EtOAc and water. The mixture was extracted with ether, the organic layer was washed with brine, dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (80% EtOAc in hexanes) afforded compound 45 (6 mg, 42%) as a clear oil: ¹H NMR δ 6.94–6.73 (m, 4H), 6.49 (s, 2H), 5.40 (s, 2H, exchangeable with D₂O), 5.31–5.29 (m, 2H), 4.01 (s, 2H), 3.89 (s, 3H), 3.45–3.43 (m, 3H), 2.74–2.72 (m, 1H), 2.72–2.70 (m, 1H), 2.37–2.12 (m, 5H), 1.91–1.57 (m, 10H), 1.46 (s, 1H, exchangeable with D₂O), 1.26 (s, 2H), 1.12 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 155.2 (2C), 149.2, 142.9, 139.2, 137.6, 136.5, 129.0 (2C), 125.8, 125.0, 122.9, 122.7, 120.8, 112.6, 107.2, 106.4 (2C), 78.1, 69.1, 56.2, 47.0, 39.4, 38.6, 37.9, 28.4, 27.6 (2C), 25.1, 23.4, 22.7, 20.1, 15.8, 14.5, 13.9; HRMS (EI) calcd for C₃₅H₄₆O₆ [M⁺], 561.3216; found 561.3214.

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